Synthesis of an antibacterial oligopeptide library

Von der Naturwissenschaftlichen Fakultät der
Gottfried Wilhelm Leibniz Universität Hannover

zur Erlangung des Grades
Doktor der Naturwissenschaften (Dr. rer. nat.)

genehmigte Disseration
von
Tim Seedorf, M. Sc.

2023

Referent:	Prof. Dr. rer. nat. Andreas Kirschning
Korreferent:	Prof. Dr. rer. nat. Mark Brönstrup
Tag der Promotion:	30.06.2023

„Wir können allen Feinden einer sich mühsam zur richtigen Erkenntnis durchringenden Wissenschaft, allen Kurpfuschern und Scharlatanen keinen größeren Dienst erweisen und […] der gesamten leidenden Menschheit keinen größeren Schaden zufügen, als wenn wir müßig und feig die Hände in den Schoß legen würden. Nur dadurch, daß wir diese Probleme anpacken, ergibt sich überhaupt erst die Möglichkeit, daß sie gelöst werden.“

Prof. Dr. Gerhard Domagk, *Angewandte Chemie* **1935**, *48*(42), 657-676.

Kurzzusammenfassung

Tim Seedorf

Synthesis of an antibacterial oligopeptide library

Schlagwörter: Antibiotika, Cystobactamide, Myxovalargin A, Totalsynthese, Medizinalchemie, Struktur-Aktivitäts-Beziehung (SAR), Festphasensynthese

Die Oligopeptide Cystobactamid und Myxovalargin A sind Naturstoffe, die aus Myxobakterien stammen. Beide Sekundärmetabolite weisen hohe antibakterielle Wirkung auf und befinden sich auf unterschiedlichen Stufen der präklinischen Antibiotikaentwicklung. In der vorliegenden Arbeit wurden Synthesen dieser Naturstoffe und ihrer Analoga zur Etablierung ihrer Totalsynthese bzw. der Optimierung ihres antibakteriellen Profils durchgeführt.

Cystobactamide stellen eine neue Antibiotikaklasse dar. Seit ihrer Entdeckung wurden durch Naturstoffisolation und Totalsynthese Struktur-Aktivitäts-Beziehungen (SAR) aufgestellt. In dieser Arbeit wurden die SAR-Studien durch Synthese einer Wirkstoffbibliothek vertieft und das antibakterielle Profil gegenüber Vertretern aller ESKAPE-Pathogene durch Strukturvereinfachung, Bioisosterie und neuartige Strukturmotive optimiert.

Myxovalargin A zeigt Wirkung gegen Tuberkulose. Unzureichender Zugang durch Fermentation verhinderte für lange Zeit die Aufklärung der absoluten Stereokonfiguration. Dafür wurden in dieser Arbeit synthetische Studien zur Totalsynthese von Myxovalargin A durchgeführt mit dem langfristigen Ziel, den Weg zu einem medizinalchemischen Projekts zu ebnen. Eine Kombination aus Fest- und Flüssigphasensynthese ermöglichte die Bereitstellung großer Fragmente des Naturstoffs.

Abstract

Tim Seedorf

Synthesis of an antibacterial oligopeptide library

Schlagwörter: antibiotics, Cystobactamids, Myxovalargin A, total synthesis, medicinal chemistry, structure-activity-relationship (SAR), solid-phase-synthesis

The oligopeptides cystobactamid and Myxovalargin A are natural products produced by myxobacteria. Both secondary metabolites exhibit high antibacterial activity and are currently in different stages of preclinical antibiotic development. In the present work syntheses of these natural products and their analogs were performed to establish their total synthesis and to optimize their antibacterial profile, respectively.

Cystobactamids represent a new class of antibiotics. Since their discovery structure-activity-relationships (SAR) were stated through natural product isolation and totalsynthesis. In this work the SAR studies were extended by synthesis of an agent library und the antibacterial profile was optimized against representatives of all ESKAPE pathogens utilizing structural simplification, bioisosterism and novel structural motifs.

Myxovalargin A exhibits biological activity against tuberculosis. Insufficient access through fermentation prevented the elucidation of the absolute stereoconfiguration for a long time. Therefore, synthetic studies towards the total synthesis of Myxovalargin A were performed in this work with the long term aim to pave the way for a medicinal chemistry program. A combination solid and liquid phase synthesis enabled the provision of advanced fragments of the natural product.

Table of Content

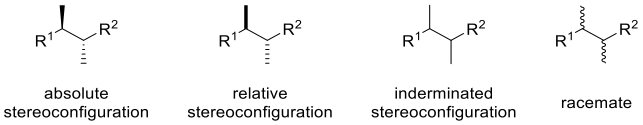
List of abbreviations

Ac	acetyl
ADC	arginine decarboxylase
ADME	absorption, distribution, metabolism and excretion
Alloc	allyloxycarbonyl
aq.	aqueous
Ar	aryl
ATP	adenosine triphosphate
BGC	biosynthetic gene cluster
brsm	based on recovered starting material
bs	broad singlet
Boc	*tert*-butyloxycarbonyl
BPO	benzoyl peroxide
CDI	1,1‘-carboyldiimidazole
CIP	ciprofloxacin
CoA	coenzyme A
conc.	concentrated
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DIC	Diisopropylcarbodiimide
DIPEA	*N*,*N*‘-diisopropylethylamine
DMSO	dimethylsulfoxide
DVB	divinylbenzene
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
equiv.	equivalents
ESI	electron spray ionization
ESKAPE	*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeroginosa*, *Enterobacter spp*.
Et	ethyl
FA	formic acid
Fmoc	fluorenylmethoxycarbonyl
HFIP	1,1,1,3,3,3-hexafluor-2-propanol
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1*H*-1,2,3-benzotriazol-1-ole
HRMS	high resolution mass spectrometry
IBX	2-iodoxybenzoic acid
*i*Pr	isopropyl
LAH	lithium aluminium hydride
m	multiplet
*m*CPBA	*meta*-chloroperoxybenzoic acid
MDR	multiple drug resistance
Me	methyl
MIC	minimal inhibitory concentration
MS	molecular sieves
Ms	mesyl
MW	microwave irradiation
*n*Bu	*n*-butyl
nc	no conversion

nd	not determined
NMM	*N*-methylmorpholine
NMP	*N*-methyl-2-pyrrolidone
NRPS	nonribosomal peptide synthetase
oct	octet
Oxyma	ethyl (*2Z*)-2-cyano-2-(hydroxyimino)acetate
p	pentet
PABA	*para*-aminobenzoic acid
Pbf	2,2,4,6,7-Pentamethyldihydrobenzofuran-5-sulfonyl
PDR	pan drug resistance
PG	protecting group
Ph	phenyl
PNBA	*para*-nitrobenzoic acid
RP	reverse-phase
rt	room temperature
s	singlet
SAR	structure-activity-relationship
sat.	saturated
sept	septet
SPS	solid phase synthesis
Su	succinimidyl
t	triplet
*t*Bu	*tert*-butyl
TEMPO	2,2,6,6-tetramethylpiperidinyloxyl
TFA	trifluoroacetic acid
THF	tetrahydrofurane
TLC	thin layer chromatography
TMS	trimethylsiyl
Ts	tosyl
US	ultrasonic irradiation
XDR	extensive drug resistance

Preliminary remarks

The stereochemistry in this work is differentiated by the following definition: wedged bond display absolute stereoconfiguration, while bars indicate relative stereoconfiguration. Undefined stereoconfiguration is shown with single bounds. Wavy bonds represent a racemate.



The atom numbering for NMR signal assigning does not follow the IUPAC rules.

Parts of the research of this work have already been published:

[1] Natural and Synthetic Oligoarylamides: Privileged Structures for Medical Applications, T. Seedorf, A. Kirschning, D. Solga, *Chem. Eur. J.* **2021**, 27, 7321-7339.

[2] The Myxobacterial Antibiotic Myxovalargin: Biosynthesis, Structural Revision, Total Synthesis, and Molecular Characterization of Ribosomal Inhibition, T. O. Koller, U. Scheid, T. Kösel, J. Herrmann, D. Krug, H. I. M. Boshoff, B. Beckert, J. C. Evans, J. Schlemmer, B. Sloan, D. M. Weiner, L. E. Via, A. Moosa, T. R. Ioerger, M. Graf, B. Zinshteyn, M. Abdelshahid, F. Nguyen, S. Arenz, F. Gille, M. Siebke, T. Seedorf, O. Plettenburg, R. Green, A.-L. Warnke, J. Ullrich, R. Warrass, C. E. Barry 3rd, D. F. Warner, V. Mizrahi, A. Kirschning, D. N. Wilson, R. Müller, *J. Am. Chem. Soc.* **2023**, *145*, 2, 851-863.

1 Introduction

As the threat of multiple drug resistance (MDR) steadily exacerbates, the WHO constantly updates a priority list of pathogens to promote comprehensive global research and development of novel antibiotics since 2017. This list includes nosocomial ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeroginosa* and *Enterobacter spp*.) pathogens and addresses tuberculosis causing pathogen *Mycobacterium tuberculosis* separately, stressing its medical relevance as top infectious killer.[1] Since that until mid of 2021, global approval of only 12 new antibiotic drugs was successful with solely one agent belonging to a new antibacterial class. Candidates in clinical development are insufficiently differentiated, especially against critical pathogens. Therefore, the discovery of novel antibacterial lead structures is an urgent need.[2] This work contributes to the development of two novel oligopeptidic antibiotics with activity against WHO-listed priority pathogens. On the one hand, cystobactamids represent a new antibiotic class with high activity against ESKAPE pathogens (chapter 2). On the other hand, myxovalargin was revealed as potential antibiotic against *Mycobacterium tuberculosis* (chapter 3).

1.1 Multiple drug resistance – a long known threat

The history of antibiotics from discovery to application, over the "golden age" until the recent lack of novel antibiotics along with bacterial resistance is stressed in a vast number of students presentations, theses, publications, reviews, conference talks and popular scientific articles.

However, somehow it seems humanity is unable to apprehend its own alert and further to take appropriate actions:[3] In 1935 prontosil was discovered as antibiotic and allowed the systematic therapy of infectious diseases.[4] Later in the 1930s the first sulfonamide resistance emerged and was identified as such.[5] In 1945 FLEMING already concluded in his Nobel lecture: "it's not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them […] there is the danger that the ignorant man may easily under-dose himself and, by exposing his microbes to non-lethal quantities of the drug, make them resistant."[6] In 1955 multiple drug resistance (MDR) of the tuberculosis causing *Mycobacterium tuberculosis* was reported for the first time.[7] In 1963 an early review was published, in which MDR and its infective heredity was still described as "interesting problem".[8] At least since 1982, headlines changed: "Microbial resistance to antibiotics – an evolving and persistent problem"[9] and even before the turn of the millennium society was advised to consider the (mis)use of antibiotics to may reverse the problem of MDR.[10] Already

in 2004 scientists realized that "[…] antimicrobial resistance is not new […]".[5] Five years later, in 2009, the European Centre for Disease Prevention and Control (ECDC) together with the European Medicines Agency (EMA) eventually confessed that it is "time to react".[11] However, in 2014, a soon arising "post-antibiotic era" was predicted by the WHO,[12] which still concerned the scientific community as lethal threat in 2022.[13] Beyond that, the terms extensive drug resistance (XDR) and pan drug resistance (PDR) start to supersede MDR.[14]

The list of admonishing publications could be extended by numerous examples. MDR is well understood.[13] The answer to this threat is known for a long time, but economic, social, political, jurisdictional as well as communicative hurdles demonstrate the underlying cross-disciplinary complexity.[2,3] This work offers to take over responsibility from a scientific, and more precisely, synthetic, forward looking point of view.

1.2 Structure-activity-relationship in drug design

Scientists developed multiple ways to design drugs. Dependent on the information available about the active agent and the molecular target, this goal is achieved with more or less obstacles. Innovations like 3D X-ray or NMR analysis of biomolecular structures, docking tools and other computer aided methodologies accelerated the drug discovery over the past decades and contribute to a rational drug design.[15] A very basic, but fundamental approach for drug design – regardless of the availability of other methodologies – is the experimental investigation of the relationship between the chemical constitution and physiological action of a potential drug. The structure-activity-relationship (SAR) approach is even applicable when the molecular target or the binding-site within the target is unknown. Iterative modification of the active compound by synthesis and subsequent biological profiling affords data from which principles are deduced.[16] Thus, SAR is located at the intersection of chemistry, biology, and statistics (Figure 1).[17]

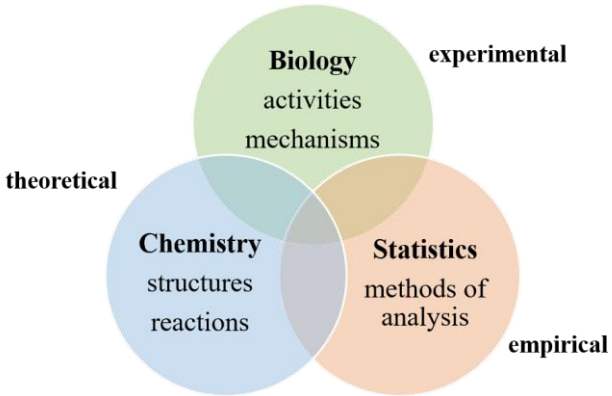


Figure 1: SAR connects chemistry, biology, and statistics.[17]

The key of mechanistic SAR investigations is to find the rate-determining event in the mechanism of action and its most relevant structural feature in the chemical agent, which, in turn, can be altered in assumption of mechanistic similarity of the substitute (Figure 2).[17]

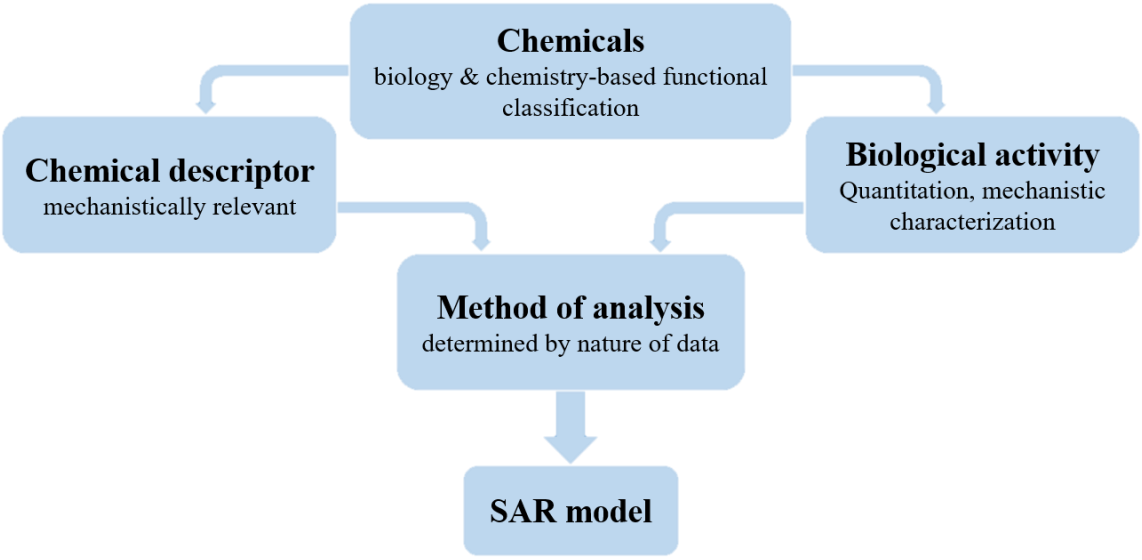


Figure 2: Progress and relations in the development of mechanistic SARs.[17]

Nevertheless, a generalization is often difficult, as certain compounds with high constitutional similarity differ significantly in biological action. Others have only little in common in terms of constitution but are physiologically almost indistinguishable. The physiological activity is no defined variable and represents not only the on-target efficiency, but displays an ensemble of all interactions within the living organism.[16] Therefore drug design based on SAR can be employed to enhance biological activity and physicochemical characteristics simultaneously or successively. In medicinal chemistry the idea of finding structure-activity-relationships is as pivotal as obvious and SAR can be explored in infinite complexity with constantly growing technology. However, the capability of synthesis is underlying.[18] Natural products with biological activity of interest constantly serve as starting points for SAR studies.[19]

1.3 Myxobacteria as a source of new antibiotics

Myxobacteria are ubiquitous in soils of different properties and proved as excellent source for secondary metabolites with striking structural diversity and biological activity (antibacterial, antifungal, anti-cancerous, antiparasitic, immunomodulatory) not covered by isolates from other bacterial sources like *Actinomycetes*, *Bacillus* or *Pseudomonas*. These natural products appear with a variety of chemical scaffolds synthesized from PKS, NRPS or ribosomally and also terpenes are reported. Sequences of monomeric building blocks lead to modular natural

products that may undergo further modifications during or after scaffold synthesis. The discovery of new secondary metabolites isolated from myxobacteria, understanding their mode of action and optimization of such drug candidates is a powerful tool in combating MDR. Within the plethora of structural diversity peptidic structures are commonly found in myxobacterial secondary metabolites.[20] The oligopeptides cystobactamid (chapter 2) and myxovalargin (chapter 3) embody two novel isolates that raised attention in the preclinical development of new antibiotics.

2 Cystobactamids

Cystobactamids represent a new class of antibiotics. The natural products were isolated first from the myxobacteria *Cystobacter velatus* Cbv34 and show antibacterial activity against GRAM-negative and -positive bacteria. Cystobactamids are NRPS derived aromatic oligoarylamides. Cystobactamid **919-2** was one of the first isolates (Figure 3). The hexapeptide consists of the unnatural amino acid β-methoxy-L-asparagine as a linker, which is flanked by two aromatic peptide fragments: The western fragment comprises one *para*-aminobenzoic acid (PABA) and one *para*-nitrobenzoic acid (PNBA), whereas the eastern fragment consists of three PABA moieties. The five aromatic building blocks can be designated A-E consecutively from the *N*- to the *C*-terminus. In addition, rings D and E are decorated with isoproxy and hydroxy groups.[21,22] Cystobactamids represent a novel compound class within the group of oligoarylamides[23] comprising the diversely occurring, privileged building block PABA, which is known as eligible architecture for modifications in drug design.[24]

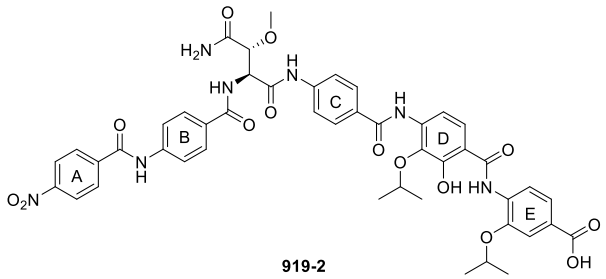


Figure 3: Structure of cystobactamid **919-2**.

Structurally similar natural products with antibacterial activity against GRAM-negative bacteria were reported. Coralmycins may differ in the alkoxy and hydroxy substitution pattern of rings D and E or possess different stereoisomers of the central amino acids, e.g. Coralmycin B (**1**).[25] Therefore they can be seen as cystobactamid analogs.[26] In contrast, Albicidin (**2**) isolated from *Xanthomonas albilineans*, which is unrelated to myxobacteria, consists of β-L-cyanoalanine as

linker, which is also found in cystobactamids, and also differs in the substitution pattern of rings D and E. Additionally, Albicidin (**2**) contains a *para*-hydroxy coumaric acid with a methyl group in the 3-position instead of the PNBA unit of cystobactamids (Figure 4).[27]

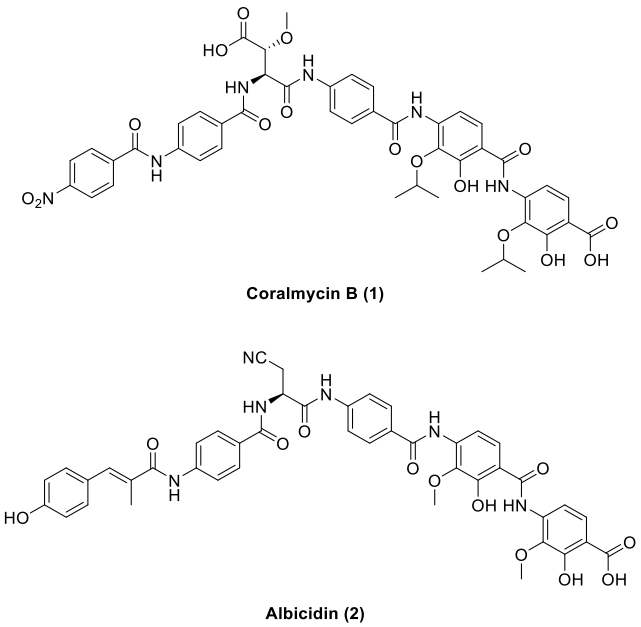


Figure 4: Structures of Coralmycin B (**1**) and Albicidin (**2**).

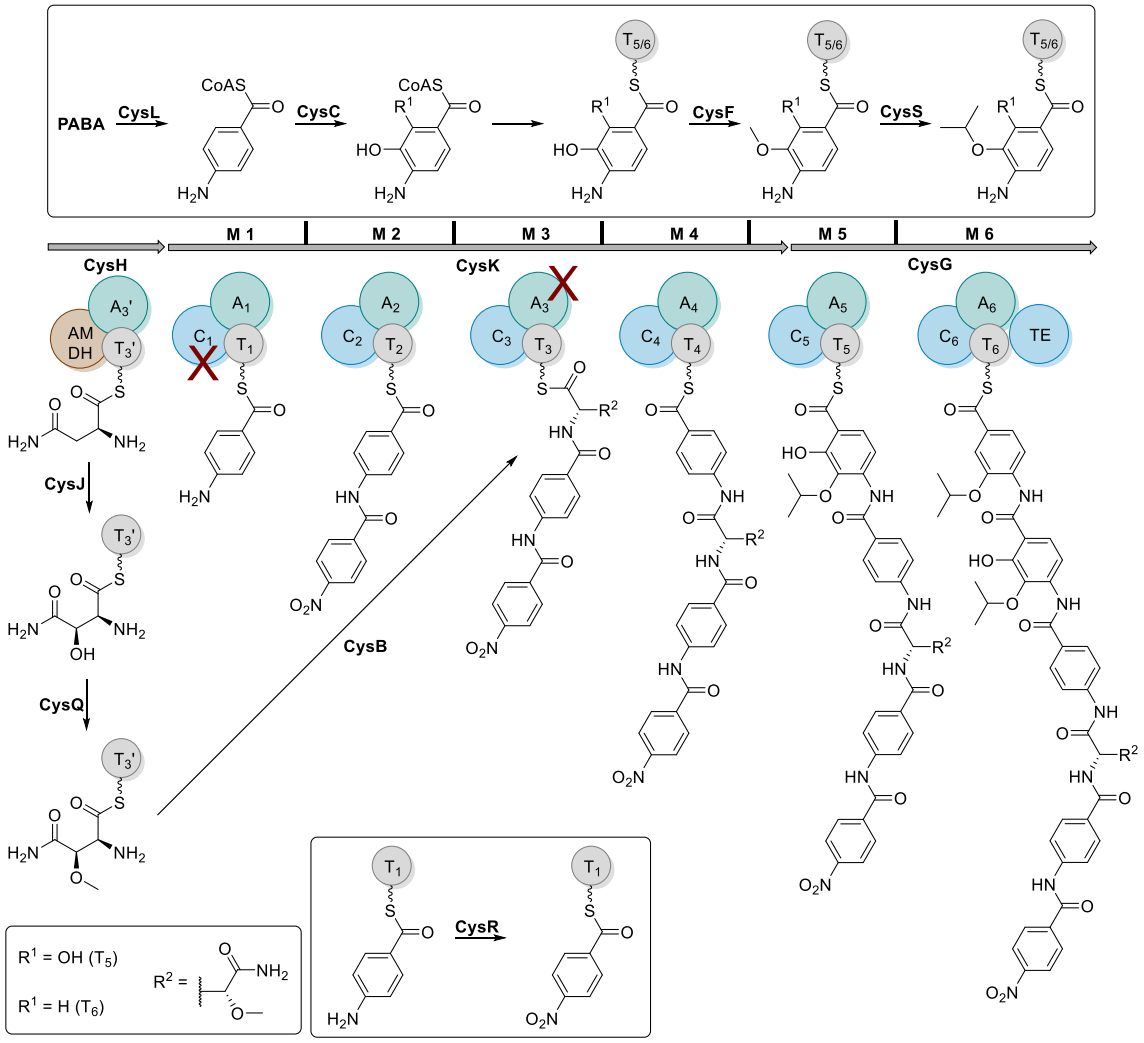
2.1 Mode of action

Cystobactamids were found to target bacterial type IIA topoisomerases with limited cross-resistance to known gyrase inhibitors.[21] Type IIA topoisomerases represent a favorable target in drug design since their exclusive appearance in bacteria and their crucial role in the replication process. Two representatives of this enzyme class are the gyrase responsible for intramolecular negative supercoiling during replication and the topoisomerase IV catalyzing intermolecular decatenation after replication.[28] Biochemical assays indicated the gyrase as main target besides topoisomerase IV with **919-2** showing higher activity than the fluoroquinolone antibiotic CIP. The ATP-dependent negative DNA supercoiling catalyzed by the gyrase is suggested to be inhibited by binding of cystobactamids to the GyrA-DNA interphase like quinolones. Increased ATP concentrations led not to decreased activity of cystobactamids, excluding the ATP-binding pocket as alternative target.[21] Structurally related natural product Albicidin (**2**) was confirmed as gyrase poison by not only inhibiting the catalytic cycle, but consequently also inducing cell death. Mechanistic studies revealed albicidins bind both the gyrase and the cleaved DNA, resulting in a lock of the catalytic cycle.[29] The trimeric eastern part of Albicidin (**2**) is responsible for the specific enzyme binding. The dimeric western part intercalates into the DNA. The linker acts as hinge region while it interacts with the water

shell of a Mg^{2+} ion, which is considered to fix the inhibitor. It is hypothesized that albicidins first intercalate and finally prohibit religation of the DNA strands.[29] The assumption that structurally similar cystobactamids act, in the same manner, is not far to seek. This unique mode of action within the class of topoisomerase inhibitors highlights the potential of oligoarylamides like albicidins or cystobactamids as response to the emerging lack of drugs against MDR pathogens.

2.2 Biosynthesis

Heterologous expression of the cystobactamid biosynthetic gene cluster in *Myxococcus xanthus* was reported and resulted in a revised biosynthesis model depicted in Scheme 1.[21,30] CysK consists of four modules. Module 1 accepts only PABA units, that are activated by CysL to form CoA-bound PABA. Oxygenation of the *N*-terminus to the NO_2 group is accomplished by CysR in trans or after the final product is released. A second PABA building block is incorporated by module 2 (CysK). CysH-bound L-asparagine is hydroxylated by CysJ. *O*-Methylation is catalyzed by CysQ to form the most prominent linker β-methoxy-L-asparagine. An aminomutase dehydratase domain on CysH is involved in the biosynthesis of other linker moieties. CysB shuttles the linker from the independent CysH to the assembly line on CysK to elongate the peptide chain. An additional PABA moiety is added to module 4. CysC is expected to oxidize CoA-bound PABA building blocks before loading to modules 5 and 6 of CysG. Alkylation of the free phenols is performed by SAM-dependent CysF to form the corresponding methoxy moieties. Cobalamin-dependent radical-SAM enzyme CyS is responsible for the tailoring methyl group alkylation steps. Besides the isolation of **919-2** a variety of cystobactamids were isolated since their discovery. Only a small number of natural cystobactamids possess worthwhile antibacterial activity. A selective biosynthesis of these desired natural products through heterologous expression is not yet established.[30] Therefore, synthetic approaches are necessary to develop novel cystobactamids, improve their antibacterial profile and provide sufficient quantities.



Scheme 1: Biosynthesis model of cystobactamid **919-2**; domains: AMDH = aminomutase dehydratase, A = adenylation, C = condensation, T = thiolation, TE = thioesterase, red cross: inactive domain.

2.3 Structure-activity-relationship studies

Until today several naturally occuring cystobactamids have been reported. The natural products differ in their linker structure and their functionality pattern of rings D and E (Figure 5).[26,30]

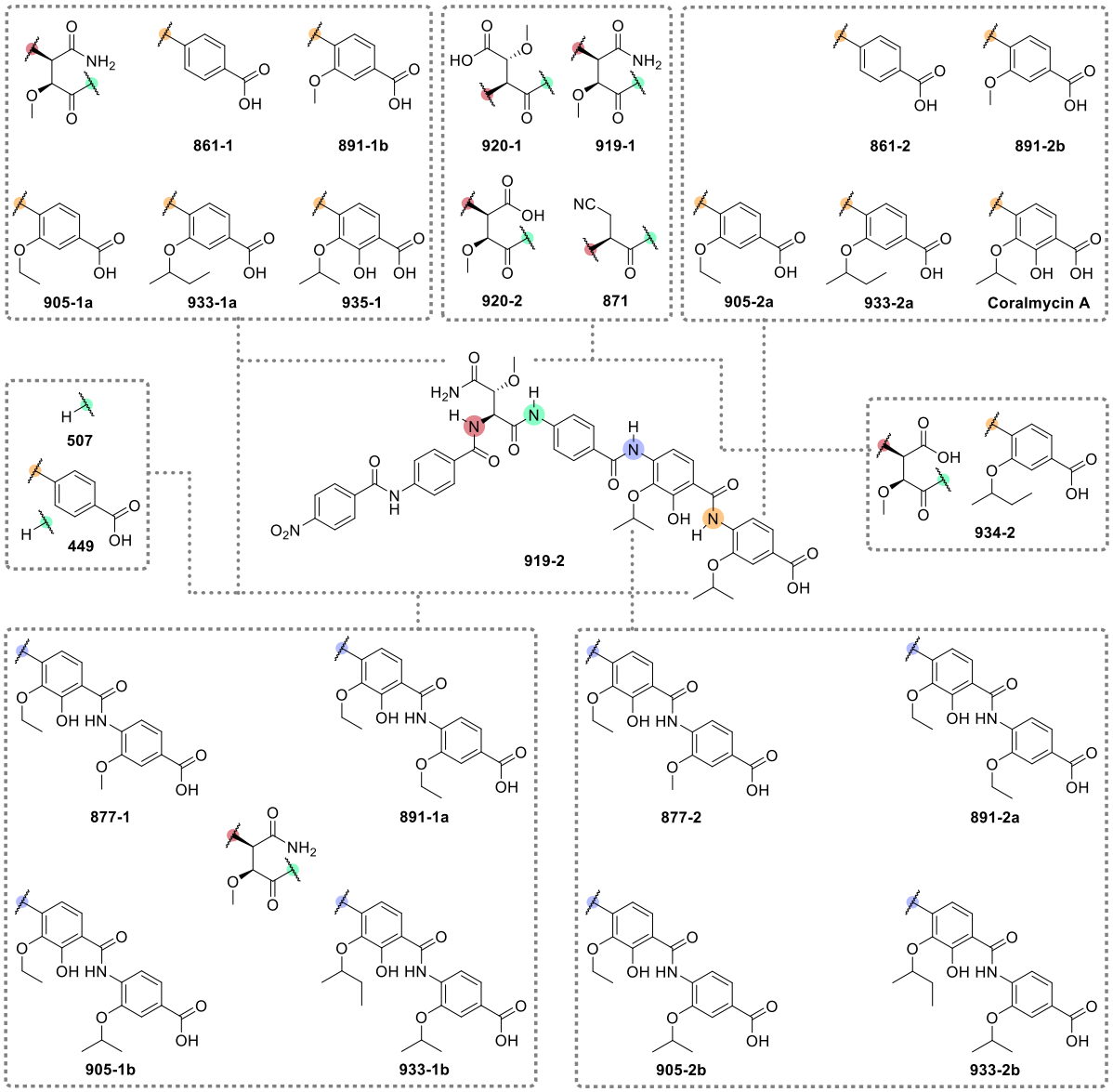


Figure 5: Structures of natural cystobactamids.

Synthetic programs were started to get access to novel cystobactamids with simplified structures, bioisosters or novel structural motifs. Today, several total syntheses of natural and unnatural cystobactamids are reported.[21,31,32,33] Comparison of native and synthetic cystobactamids on their antibacterial potential provided information about the structure-activity-relationship (SAR). In a first SAR study of the natural products only cystobactamids **919-2** and **861-2** with β-methoxy-L-asparagine as linker showed sufficient antibacterial activity, whereas **861-2** is superior to **919-2**.[26]

Generally, cystobactamids require the core structure of a hexapeptide. Truncated analogs, lacking rings A, AB or E lost their antibacterial activity (Figure 6 & Figure 7).[32,33] This is plausible, when taking the mode of action of albicidins into consideration, in which the western fragment is responsible for DNA intercalation.[29] While Nature leaves the western fragment untouched, total synthesis allows the modification of the *N*-terminal flank of the linker. Early investigations – with **861-2** as reference compound – revealed the CN group of **CN861** as suitable substitute for the NO_2 group (Figure 6). Efforts were made towards amide replacements by bioisosters. Urea linkages between the aromatic units were tested and tolerated between rings A and B. On the other hand, a triazole connecting rings C and D led to retained antibacterial activity and potentially circumvents the previously reported resistance factor AlbD.[33,34,35] Different ring A analogs were tested in combination with the triazole moiety between rings C and D. However, **CN861** remained the most potent derivative (Figure 6).

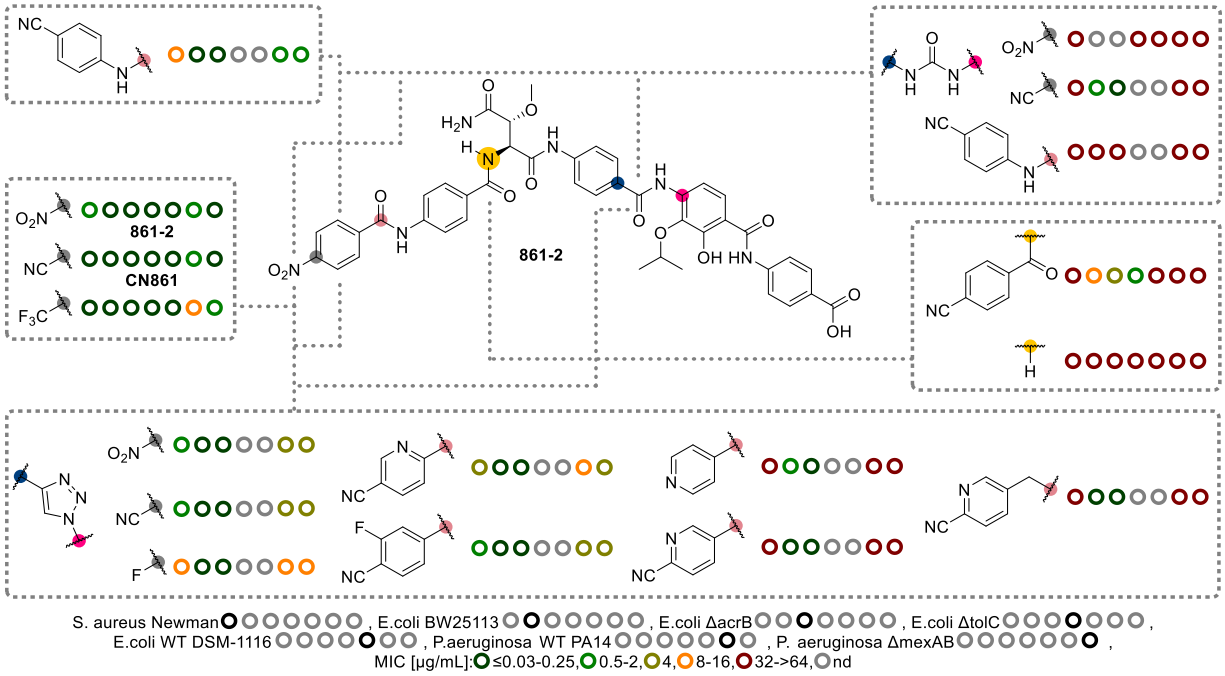


Figure 6: Overview of selected structural modifications of cystobactamid **861-2** for SAR investigations[32,34]; MICs against selected Gram-negative and -positive bacterial strains.

In parallel, numerous variations were investigated using the simplified L-asparagine as linker (Figure 7). *N*-Terminal electron-donating groups or heterocyclic benzene substituents retained antibacterial activity. The combination of structural motifs of both natural products cystobactamids and Albicidin (**2**) afforded active compounds. The *para*-hydroxylated coumaric acid derived western fragment was successfully integrated into the cystobactamid structure. Exchange of the *N*-terminal OH group to the CN group increased the antibacterial activity.[33] Other modified linkages between rings A and B were not beneficial. Furthermore, the limited

variability of the eastern fragment was confirmed. Variations on ring D were not tolerated. Alkoxylated ring E derivates were active, but not superior. The studies demonstrated that the *C*-terminal benzoic acid is essential for activity. While modifications like the incorporation of a heterocyclic benzene substitute or additional residues on the PABA ring retained antibacterial activity, the exchange or deletion of the acidic moiety resulted in a loss of activity. Elongation of the amide linkage between D and E by simultaneously breaking the conjugated system also led to inactive analogs. Generally, substantial changes in the architecture were not tolerated. Ultimately, the promising beneficial modifications could not compete with **CN861** on a broader panel of pathogens.[33] Extensive SAR studies of albicidins are reported. The structural similarity to the cystobactamids may suggest the transfer of SAR results between the two antibiotics. Nevertheless, up to date the transferability is still not obvious and remains complicated. On the other hand, structural optimization of cystobactamids and Albicidin **(2)** leads to blurred borders between the two natural products.

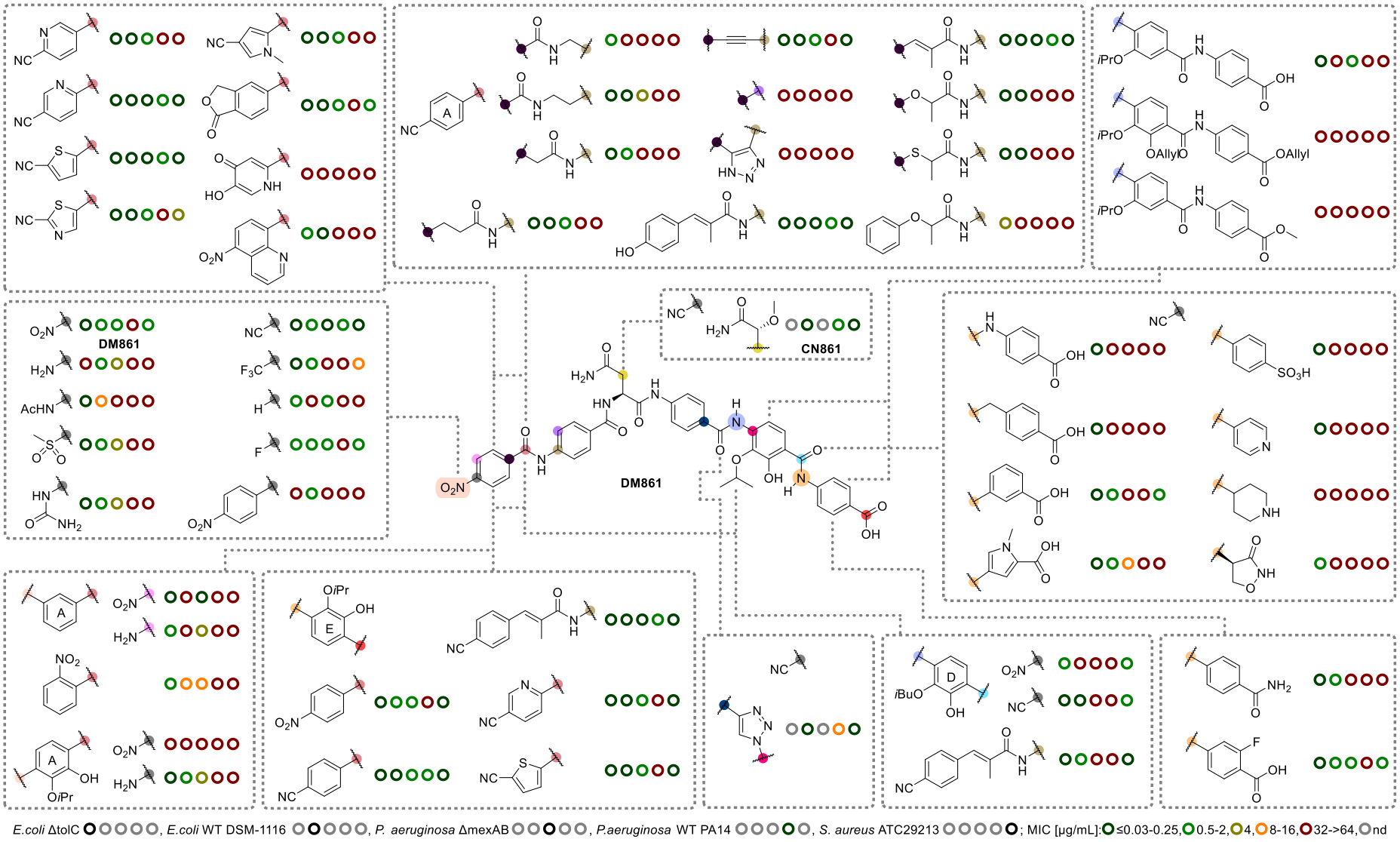
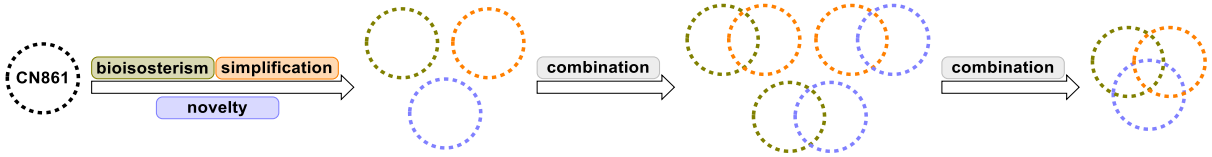


Figure 7: Overview of selected structural modifications of cystobactamid **DM861** for SAR investigations[33]; MICs against selected GRAM-negative and -positive bacterial strains.

2.4 Project aims

Former studies revealed the existence of naturally occurring cystobactamid derivatives with diverse structural motifs. However, neither the isolation of sufficient quantities nor the discovery of an analog with superior antibacterial activity was feasible.[26,30] Since the establishment of a convenient total synthesis the way for a medicinal chemistry program was paved.[32] Initial studies with synthetic cystobactmids gave first insights into the SAR.[32–34]

In this work, the synthesis of a library of novel cystobactamids with enhanced antibacterial potential against nosocomial ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeroginosa* and *Enterobacter spp*.) pathogens was aimed with focus on WHO priority list leader pathogen *A. baumannii* (priority 1, critical).[1] Detailed SAR investigations should support the rational design of superior analogs. Concepts like bioisosterism and simplification were planned to serve as tools for the modification proposals. Novel structural features were sought to contribute to an increased antibacterial activity and facilitate the patenting of the new potential antibiotics. Stepwise combination of promising motifs unveils the impact of each structural feature and may eventuate in a new lead structure (Scheme 2).



Scheme 2: Schematic plan for the SAR investigations towards novel highly potent cystobactamid antibiotics from diversity to a new combinatorial lead structure.

Within the OpCyBac project, different approaches were followed to obtain a large number of new cystobactamid analogs with different modifications. The constant exchange of information between the academic and industrial partners, and the use of shared databases enabled the rapid synthesis of novel analogs. Therefore, the resources of all involved collaborators were directly utilized as needed. As a result, some of the cystobactamids described in this work seem to stand alone. However, all analogs fit into a series of compounds for SAR studies within the OpCyBac project.[36]

2.5 Results and discussion

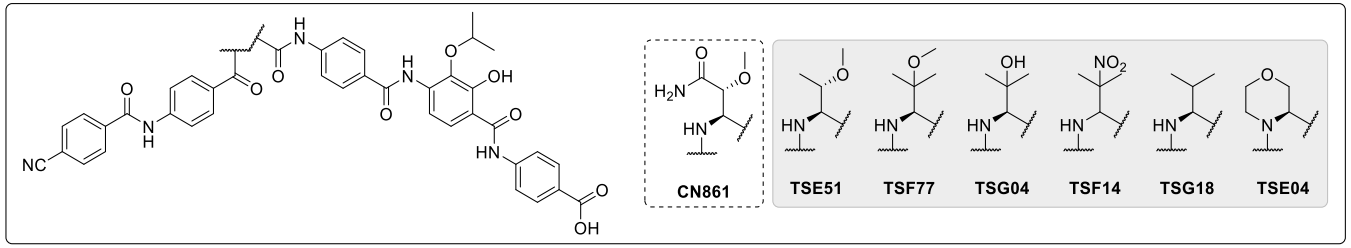
2.5.1 Structure-activity-relationship

Modified analogs were synthesized for the optimization of the current front runner **CN861**. For the evaluation of the novel antibiotics MICs were determinated against selected strains of the ESKAPE pathogens in the MÜLLER group at Helmholtz Institute for Pharmaceutical Research Saarland, Germany. Comparison of the results in regard to the chemical structures gave insights into the SAR of cystobactamids.[36]

2.5.1.1 New central amino acids

The central amino acid of cystobactamids represents a unique structural feature haboured between the aromatic PABA derived flanks leading to the hypothesis that the central fragment acts as key element reminiscenting of a hinge region. Therefore, SAR investigations were planned to acquire deeper insights in the relevance of the central amino acid and further to improve the antibacterial profile. To date only natural occuring linker are known except of **CNDM861**, a cystobactamid including asparagine as central amino acid. This simplified analog of **CN861** proved to be active in IC_{50} assays against bacterial gyrases, but could not compete with its parental derivative in MIC assays.[33,36] However, the antibacterial activity is sufficient, while the synthetic access was simplified by deleting one stereocenter. Inspired by this simplification approach a series of novel cystobactamids with new central amino acids were synthesized and tested (Table 1). **TSE51** containing methylated allothreonine and therefore lacking the primary amide in the side chain circumvents the amphoteric character auf **CN861**. The antibacterial activity was increased on all strains and the spectrum was broadened compared to **CN861**. The series was continued with **TSF77**. Although an additional methyl group was installed, simplification was achieved by deleting the stereocenter in the β-position. **TSF77** possesses similiar MIC values as **TSF51**. The corresponding free alcohol **TSG04** was even able to combat *E. cloacae* and *E. aerogenes*. 3-Nitrovaline was incorporate as linker in **TSF14** and showed superior activity on nearly all strains, even though no stereo information is found in this analog. The even more simplified analog **TSG18** habouring L-valine as central amino acid shows promising MICs, albeit some data is missing to generalize the results. Additionally, rigidified morpholine analog **TSE04** was synthesized, but showed only decreased activity on most tested strains. With the simplification of the linker the activity of cystobactamids was substancially optimized.

Table 1: MIC values (µg/mL) for synthetic cystobactamids with novel central amino acids compared to CN861 and CIP. a) BAA-1710; b) (S83L, D87N, S80I, ΔmarR, ΔacrR); c) (waaC::Tn30); d) (QnrA1); e) ΔmexAB; f) BAA-2468; g) PAO1 instead of PA14; color code for activity: green = good, orange = moderate, red = insufficient.



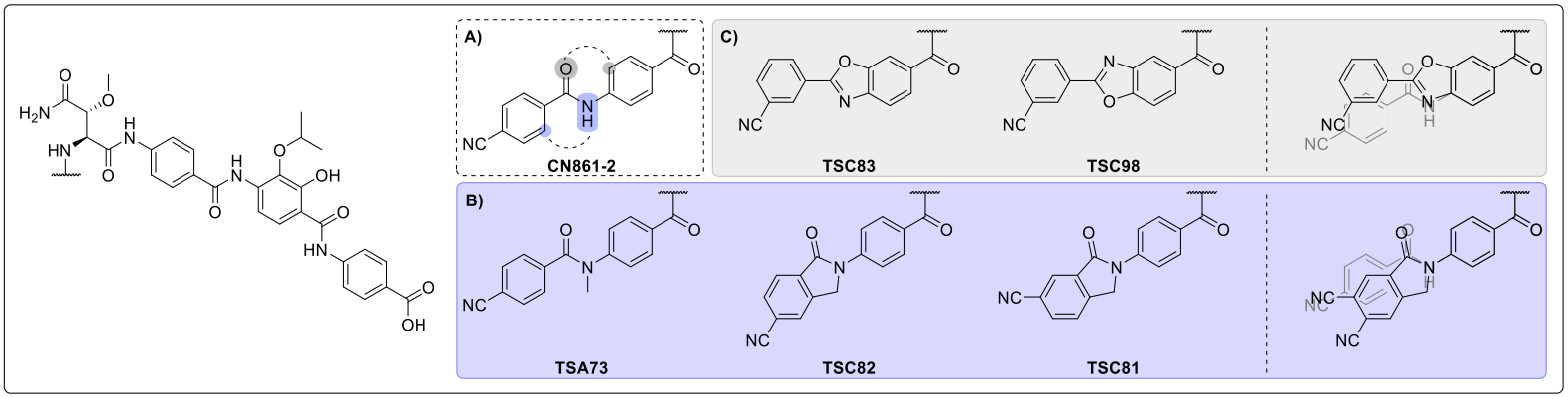
	A. baumannii					*E. coli*		*S. aureus*	*K. pneumoniae*			*P. aeruginosa*		*E. cloacae*	*E. aerogenes*	*E. faecium*
	DSM-30008	ATCC[a)]	CIP-105742	CIP-107292	R835	LM705[b)]	ATCC-25922	ATCC-29213	CIP-104298	KP10581[c)]	R1525[d)]	PA14	PA14[e)]	ATCC[f)]	CIP 106754	DSM-17050(VRE)
CIP	0.1	>6.4	0.05	>6.4	>6.4	>6.4	0.01	0.8	0.05	>6.4	>6.4	0.125	0.01	>6.4	>6.4	3.2
CN861	1	8	0.25	>64	64	0.64	0.25	0.125	16	2	16	16	0.5	32	4	nd
TSE51	<0.03	0.25	<0.03	1	2	0.25	<0.03	<0.03	16	0.25	32	16	1	0.5	2	>64
TSF77	≤0.03	0.125	nd	0.25	2	2	≤0.03	0.25	nd	0.06	>64	nd	nd	4	16	nd
TSG04	nd	0.05	nd	3	nd	0.25	<0.001	<0.003	nd	0.025	nd	4[g)]	nd	0.2	1	<0.003
TSF14	0.03	0.38	<0.0038	0.5	0.5	1	<0.06	<0.06	<0.3	0.25	1.25	1	8	2	2	<0.06
TSG18	nd	0.05	nd	2	nd	0.5	<0.001	<0.03	nd	0.2	nd	>64[g)]	nd	0.5	3	<0.01
TSE04	8	>8	4	>8	>8	>64	1	0.5	32	0.25	>64	>64	8	64	>64	2

2.5.1.2 New western fragments

In a previous work of the BRÖNSTRUP group various modifications on the western fragment were investigated.[33] The amide linkage between rings A and B was elongated by one or two methylene groups, deleted or replaced by a methacrylamide inspired by Albicidin (**2**). Only the methacrylamide derivative possessed sufficient antibacterial activity. These results affirmed that the spatial requirement of the western fragment is limited or, on the other hand, the amide motif is neccessary such as for hydrogen bonding. The idea then was to stick to the amide, but to enhance the stability (Table 2). *N*-Methylated cystobactamid **TSA73** (Table 2 B) was active on nearly all tested bacterial strains, while reference compound **CN861** lacked activity on certain strains. Encouraged by this result stability was envisioned to be strenghthened by increasing rigidity. Therefore, the amide was cyclized in connection with the adjacent aromatic rings. C-C-Connection between the *N*-methyl group in **TSA73** and ring A furnished isoindolinone **TSC82** (Table 2 B). Additionally, regioisomer **TSC81** was synthesized. Superimposition of **TSC81** and **TSC82** with **CN861** illustrates the superior match between **CN861** and **TSC81** regarding the *N*-terminal CN group (Table 2 B, right). The antibacterial activities of **TSC81** and **TSC82** support this hypothesis. Although **CN861** features the lowest MIC values on a number of strains the SAR investigations towards **TSC81** led to a broadener antibacterial spectrum with good to moderate activity. C-O-Connection between the amide carbonyl O and the adjacent ring B gave access to benzoxazoles **TSC83** and **TSC98** (Table 2 C). The superimposition with **CN861** reveals a discrepancy in the spatial orientation (Table 2 C, right). Both compounds lost activity on almost all strains. It is noteworthy, that the benzoxazoles showed moderate activity against all *A. baumannii* strains comparable to the potency of the before mentioned analogs.

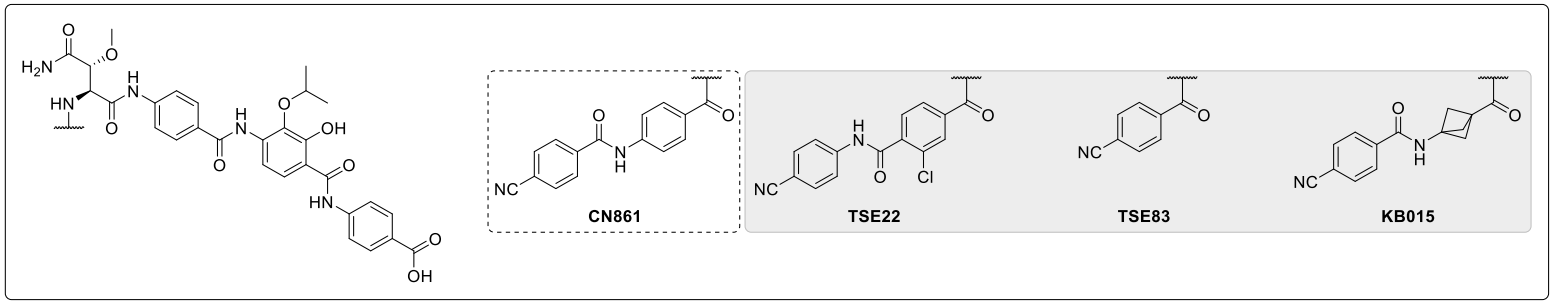
Three additional derivatives with modified western fragment were synthesized and tested (Table 3). Collaborators at HZI found the benificial effect of a chlorinated ring B, which proved to be activity enhancing.[36] The antibacterial activity with **TSE22** was increased as expected and the spectrum broadened. **TSE83** lacking ring A was inactive on the whole panel. This is in line with published data.[32] **KB015** consists of an aliphatic benzene isoster as ring B.[37] The biocyclopentane motif was considered to enhance aqueous solubility and proved active in tested derivatives.[36] Contrary to the expectations **KB015** showed no or only slight activity.

Table 2: A) SAR considerations on **CN861** for enhanced stability and rigidification, B) structures of cystobactamids with methylated amide or isoindolinone and superimposition with **CN861**, C) structures of cystobactamids with benzoxazole and superimposition with **CN861**; MIC values (µg/mL, bottom) of synthetic cystobactamids with novel western fragments compared to **CN861** and **CIP**. a) BAA-1710; b) (S83L, D87N, S80I, ΔmarR, ΔacrR); c) (waaC::Tn30); d) (QnrA1); e) ΔmexAB; f) BAA-2468; color code for activity: green = good, orange = moderate, red = insufficient.



	A. baumannii					*E. coli*		*S. aureus*	*K. pneumoniae*			*P. aeruginosa*		*E. cloacae*	*E. aerogenes*	*E. faecium*
	DSM-30008	ATCC[a)]	CIP-105742	CIP-107292	R835	LM705[b)]	ATCC-25922	ATCC-29213	CIP-104298	KP10581[c)]	R1525[d)]	PA14	PA14[e)]	ATCC[f)]	CIP 106754	DSM-17050(VRE)
CIP	0.1	>6.4	0.05	>6.4	>6.4	>6.4	0.01	0.8	0.05	>6.4	>6.4	0.125	0.01	>6.4	>6.4	3.2
CN861	1	8	0.25	>64	64	0.64	0.25	0.125	16	2	16	16	0.5	32	4	nd
TSA73	8	4	0.5	8	8	8	0.25	nd	8	4	8	4	4	64	32	nd
TSC82	0.25	2	0.125	8	8	1	0.03	0.5	4-8	4	8	32	4	>64	8	1
TSC81	0.5	2	0.25	>8	>8	1	0.03	2	>8	2	>8	>8	2	>8	8	2
TSC83	4	8	1	≥8	≥8	>64	nd	>64	>64	1	>64	>64	>64	>64	>64	>64
TSC98	>8	>8	4	>8	>8	>64	nd	>64	>64	>64	>64	>64	>64	>64	>64	>64

Table 3: Structures and MIC values (µg/mL) of synthetic cystobactamids with novel western fragments compared to **CN861** and **CIP**. a) BAA-1710; b) (S83L, D87N, S80I, ΔmarR, ΔacrR); c) (waaC::Tn30); d) (QnrA1); e) ΔmexAB; f) BAA-2468; color code for activity: green = good, orange = moderate, red = insufficient.



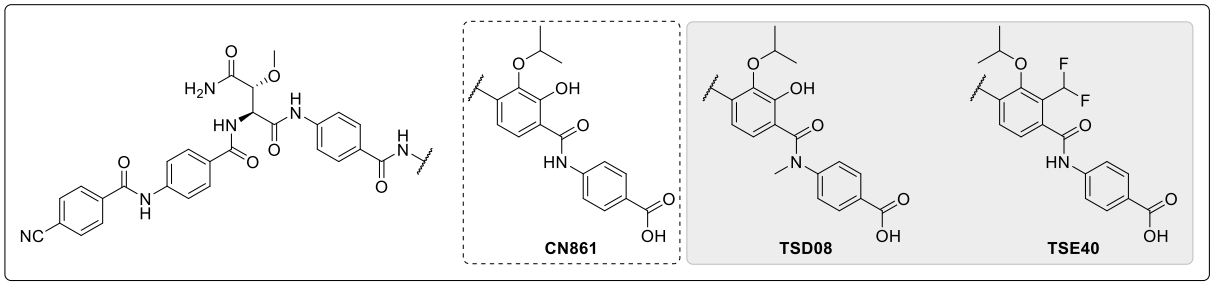
	A. baumannii					*E. coli*		*S. aureus*	*K. pneumoniae*			*P. aeruginosa*		*E. cloacae*	*E. aerogenes*	*E. faecium*
	DSM-30008	ATCC[a)]	CIP-105742	CIP-107292	R835	LM705[b)]	ATCC-25922	ATCC-29213	CIP-104298	KP10581[c)]	R1525[d)]	PA14	PA14[e)]	ATCC[f)]	CIP 106754	DSM-17050(VRE)
CIP	0.1	>6.4	0.05	>6.4	>6.4	>6.4	0.01	0.8	0.05	>6.4	>6.4	0.125	0.01	>6.4	>6.4	3.2
CN861	1	8	0.25	>64	64	0.64	0.25	0.125	16	2	16	16	0.5	32	4	nd
TSE22	1-2	3	0.5	4	3	2	0.038	1	0.5	<0.03	1	16	2	>64	4	0.125
KB015	32	>64	16	>64	>64	8	8	8	8	8	16	>64	4	32	32	16
TSE83	32	> 64	> 64	16	64	> 64	4	16	>64	8	>64	>64	>64	>64	>64	16

2.5.1.3 New eastern fragments

Two derivatives with modified eastern fragments were synthesized and tested for their antibacterial activity. Encouraged by the positive results of **TSA73**, which bears a methyl group on the amide N between rings A and B, the *C*-terminal amide was methylated in **TSD08** (Table 4). However, the methylated analog possesses only moderate activity against *A. baumannii* and sufficient activity against *E. coli*, while antibacterial capability against other GRAM-negative strains was lost. Nevertheless, **TSD08** inhibits *E. cloacae*, a strain that is barely inhibited by the before mentioned cystobactamids.

While the eastern fragment of isolated cystobactamids can differ in size of the alkoxy moieties on rings D and E, the *C*-terminal hydroxy group at ring D arised attention, since no variation was observed for this functionality to date. Phenols may serve as HBD or HBA and are consequently crucial for the on-target activity of the drugs. Furthermore, the aromatic alcohols contribute to the solubility of the drug due to their acidity and hydrophilicity. On the other hand, phenols are prone to rapid elimination during metabolism. Toxic metabolites of the alcohols can cause undesired cytotoxicity.[38] The structural flexibility of the cystobactamid phenol was investigated by the exchange of the alcohol by an difluoromethyl group (OH → CF_2H), since the surrogate can act as hydroxy bioisoster. The fluorinated C1 unit contains an acidic proton and is able to form moderately stable hydrogen-bonds. Compared to phenols the hydrophilicty of the CF_2H group is decreased, while the steric bulk and metablic stability is increased.[39] Difluormethylated **TSE40** possesses only moderate antibacterial activity against *A. baumannii* and one *E. coli* strain as well as *S. aureus* (Table 4). On all other tested strains the new analog failed, hinting on the importance of the strong HBD phenol.

Table 4: Structures and MIC values (µg/mL) of synthetic cystobactamids with novel eastern fragments compared to **CN861** and **CIP**. a) BAA-1710; b) (S83L, D87N, S80I, ΔmarR, ΔacrR); c) (waaC::Tn30); d) (QnrA1); e) ΔmexAB; f) BAA-2468; color code for activity: green = good, orange = moderate, red = insufficient.



	A. baumannii					***E. coli***		***S. aureus***	***K. pneumoniae***			***P. aeruginosa***		***E. cloacae***	***E. aerogenes***	***E. faecium***
	DSM-30008	ATCC[a)]	CIP-105742	CIP-107292	R835	LM705[b)]	ATCC-25922	ATCC-29213	CIP-104298	KP10581[c)]	R1525[d)]	PA14	PA14[e)]	ATCC[f)]	CIP 106754	DSM-17050(VRE)
CIP	0.1	>6.4	0.05	>6.4	>6.4	>6.4	0.01	0.8	0.05	>6.4	>6.4	0.125	0.01	>6.4	>6.4	3.2
CN861	1	8	0.25	>64	64	0.64	0.25	0.125	16	2	16	16	0.5	32	4	nd
TSD08	>8	>8	>8	>8	>8	1	nd	8	> 64	32	>64	>64	16	2	16	>64
TSE40	>8	>8	>8	>8	>8	>64	>8	>6.4	>64	>64	>64	>64	>64	>64	>64	>64

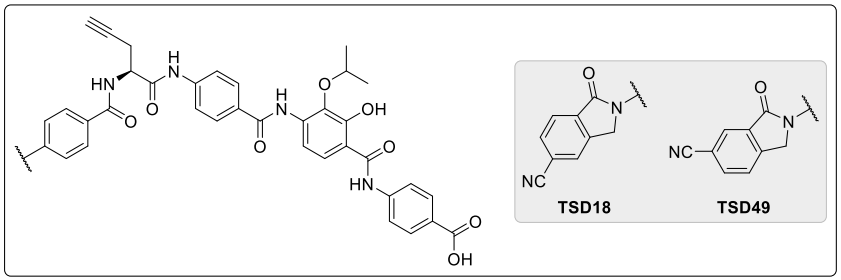
2.5.1.4 Combinatorial analogs

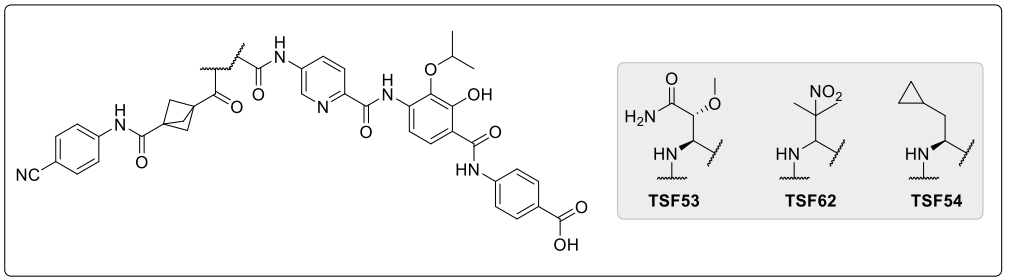
At regular intervals the new cystobactamids were evaluated and convincing structural motifs were identified. Combination of promising motifs were proposed and the syntheses were distributed within the OpCyBac consortium to utilize resources effectively for a quick acccess to novel cystobactamid analogs.[36] A variety of combinatorial derivatives were synthesized and tested as part of this work.

Two groups of combinatorial analogs were synthesized. The first generation of combinations was created to incorporate activity enhancing moieties together with structural motifs, that possibly improve ADME characteristics. Isoindolinones **TSC81** and **TSC82** passed the first MIC panel with minor increase of the antibacterial activity and are assumed to be stable compared to the natural amide at this position. Thus, the isoindolinone motifs were combined with (*S*)-2-aminopent-4-ynoic acid as linker, which was proved to enhance activity compared to the natural product.[36] However, activity for both **TSD08** and **TSD49** is only maintained on a small number of strains, while on other strains a complete loss of activity is observed (Table 5). Nevertheless, **TSD49** is able to inhibit *E. cloacae* and *E. aerogenes* in sufficient manner.

Furthermore, three different central amino acids were combined with a fixed set of western and eastern fragments. While the western fragment consists of a reversed amide and a bicyclopentane[37] structure as ring B for improved stability and solubility, respectively, ring C derived from picolinic acid (Table 5). The pyridine containing eastern fragment may contribute to an increased activity as shown before.[36,40] The original central amino acid was tested first: **TSF53** shows activity against the whole panel and only fails on *P. aeruginosa*. The antibiotical potency clearly improved compared to **CN861**, although only moderate activity was achieved against a number of strains. **TSF54** and **TSF62** are equipped with two of the most promising linkers, (*S*)-2-amino-3-cyclopropylpropanoic acid and 2-amino-3-methyl-3-nitrobutanoic acid, respectively (Table 5). Both analogs show superior activity. Nonetheless, the activity against *P. aeruginosa* is still insufficient. This series of novel cystobactamids confirmed, that the beneficial effects of selected buildings blocks can be combined to further improve the antibacterial profile, although some exceptions occured.

Table 5: Structures and MIC values (µg/mL) of synthetic cystobactamids with combined novel western fragments and central amino acids compared to **CN861** and **CIP**. a) BAA-1710; b) (S83L, D87N, S80I, ΔmarR, ΔacrR); c) (waaC::Tn30); d) (QnrA1); e) ΔmexAB; f) BAA-2468; color code for activity: green = good, orange = moderate, red = insufficient.

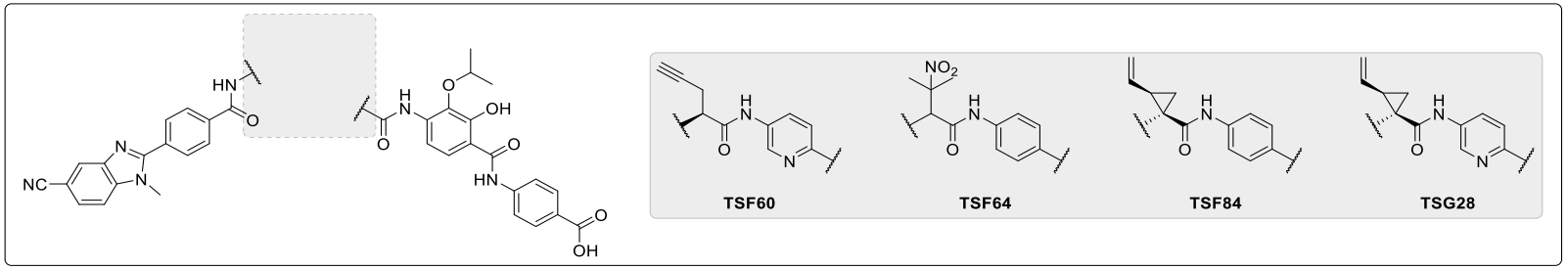




	A. baumannii				*E. coli*			*S. aureus*	*K. pneumoniae*			*P. aeruginosa*		*E. cloacae*	*E. aerogenes*	*E. faecium*
	DSM-30008	ATCC[a)]	CIP-105742	CIP-107292	R835	LM705[b)]	ATCC-25922	ATCC-29213	CIP-104298	KP10581[c)]	R1525[d)]	PA14	PA14[e)]	ATCC[f)]	CIP 106754	DSM-17050(VRE)
CIP	0.1	>6.4	0.05	>6.4	>6.4	>6.4	0.01	0.8	0.05	>6.4	>6.4	0.125	0.01	>6.4	>6.4	3.2
CN861	1	8	0.25	>64	64	0.64	0.25	0.125	16	2	16	16	0.5	32	4	nd
TSD18	0.125	2(4)	0.125	>8	8	>64	nd	>64	>64	>64	>64	>64	>64	>64	>64	>64
TSD49	0.03	0.38	0.06	4	4	0.5	≤0.03	0.5	>64	4	>64	>64	4(2)	1	2	0.125
TSF53	4	0.5	0.5	4	4	4	<0.03	1	2	0.06	4	32	2	8	8	<0.03
TSF54	<0.03	<0.03	<0.03	0.5	1	1	<0.03	<0.03	1	<0.03	1	16	2	8	8	<0.03
TSF62	0.06	<0.03	<0.03	<0.03	0.25	0.5	<0.03	2	0.5	<0.03	1	16	2	16	4	<0.03

The isoindolinones as first analogs with cyclized linkage between rings A and B laid the foundation of investigations towards new cyclized motifs as amide surrogates between the aromatic units. SAR studies revealed *N*-methylated benzimidazoles as suitable cycles.[36] A second generation of combinations were accomplished by merging the *N*-terminal benzimidazole with reliable central amino acids either with a PABA or picolinic acid moiety as ring C (Table 6). **TSF60** bearing the pyridine ring C and the before mentioned propagylic central amino acid convinces with very low MIC values against all strains, although *K. pneumoniae* R1525 (QnrA1), *P. aeruginosa* PA14 and *E. aerogenes* were not addressed. **TSF64** combining the benzimidazole motif with the racemic nitro amino acid of **TSF14** could compete with **TSF60** on all tested strains and even inhibited the critical strains *K. pneumoniae* R1525 (QnrA1), *P. aeruginosa* PA14 and *E. aerogenes* in good to moderate manner. Further improvement was achieved by introduction of (1*S*,2*R*)-1-amino-2-vinylcyclopropane-1-carboxylic acid as linker in **TSF84** and pyridyl variant **TSG28**. However, some data is missing to finally approve the compounds as superior analogs.

Table 6: Structures and MIC values (µg/mL) of synthetic cystobactamids with combined benzimidazole western fragment, central amino acids and possibly ring C pyridine compared to **CN861** and **CIP**. a) BAA-1710; b) (S83L, D87N, S80I, ΔmarR, ΔacrR); c) (waaC::Tn30); d) (QnrA1); e) ΔmexAB; f) BAA-2468; g) PAO1 instead of PA14; color code for activity: green = good, orange = moderate, red = insufficient.



	A. baumannii					*E. coli*		*S. aureus*	*K. pneumoniae*			*P. aeruginosa*		*E. cloacae*	*E. aerogenes*	*E. faecium*
	DSM-30008	ATCC[a)]	CIP-105742	CIP-107292	R835	LM705[b)]	ATCC-25922	ATCC-29213	CIP-104298	KP10581[c)]	R1525[d)]	PA14	PA14[e)]	ATCC[f)]	CIP 106754	DSM-17050(VRE)
CIP	0.1	>6.4	0.05	>6.4	>6.4	>6.4	0.01	0.8	0.05	>6.4	>6.4	0.125	0.01	>6.4	>6.4	3.2
CN861	1	8	0.25	>64	64	0.64	0.25	0.125	16	2	16	16	0.5	32	4	nd
TSF60	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	<0.03	0.5	<0.03	>64	>64	0.5	0.125	16	<0.03
TSF64	0.06	<0.03	<0.03	<0.03	<0.03	0.125	<0.03	0.125	1	0.125	2	8	1	2	4	<0.03
TSF84	≤0.03	≤0.03	nd	≤0.03	0.06	≤0.03	≤0.03	≤0.03	nd	≤0.03	0.25	nd	nd	0.25	0.5	nd
TSG28	nd	0.025	nd	0.06	nd	0.5	<0.003	<0.003	nd	0.006	nd	1[g)]	nd	0.25	1(2)	<0.003

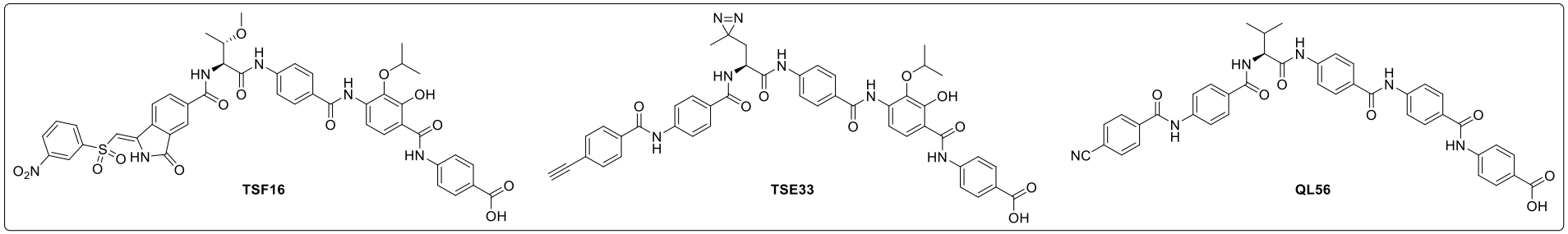
2.5.1.5 Miscellaneous analogs

In this work three additional derivatives were synthesized, that do not fit into the SAR studies described above (Table 7). **TSF16** consists of *O*-methyl-L-allothreonine, the most active linker structure at that time and an unobvious western fragment inspired by a publication of JEGANMOHAN.[41] The (*Z*)-3-methyleneisoindolin-1-one replaces the amide linkage between rings A and B. An additional sulfonyl unit ensures a more accurate positioning of the *N*-terminal electron-withdrawing group and contributes to the physico-chemical profile of the analog. Due to synthetic criteria **TSF16** was equipped with the original NO_2 group instead of the CN group of **CN861**. The isoindolinone corresponding to ring B occupies molecular space that was proven to be available in chlorinated cystobactamid **KB015**. The original amide carbonyl is missing without substitution at this position. The sum of new functionalities comprised in **TSF16** allowed no prediction wether the analog is active or not. Unfortunately, **TSF16** proved to be inactive against most tested strains.

TSE33 serves as analog for photoaffinity labeling studies and was provided to collaborators. The new cystobactamid contains an *N*-terminal alkine and a diazirine in the side chain of the central amino acid. To affirm **TSE33** to be a suitable model compound, antibacterial activity was tested against both one GRAM-negative and -positive strain (Table 7).

Besides the SAR studies for the improvement of the drug properties of cystobactamids, the synthetic access should be simplified. Encouraged by the results of simplified analog **TSG18** (c.f. chapter 2.5.1.1) first attempts towards a SPS of cystobactamids were made (c.f. chapter 2.5.3.5.6) and **QL56** with an eastern fragment consisting of only PABAs and L-valine as central amino acid was synthesized.[42] However, **QL56** was completely inactive against all tested strains, emphasizing the essential substitution pattern of ring D (Table 7).

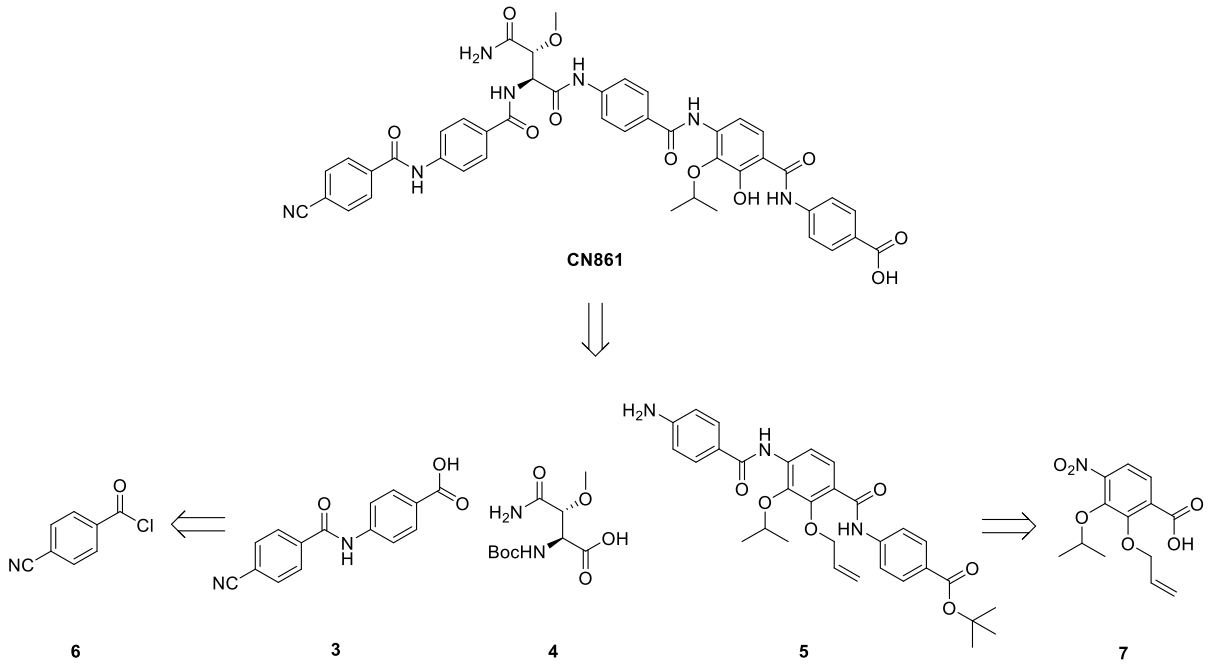
Table 7: Structures and MIC values (µg/mL) of synthetic cystobactamids with miscellaneous modifications compared to **CN861** and **CIP**. a) BAA-1710; b) (S83L, D87N, S80I, ΔmarR, ΔacrR); c) (waaC::Tn30); d) (QnrA1); e) ΔmexAB; f) BAA-2468; color code for activity: green = good, orange = moderate, red = insufficient.



	A. baumannii					***E. coli***		***S. aureus***	***K. pneumoniae***			***P. aeruginosa***		***E. cloacae***	***E. aerogenes***	***E. faecium***
	DSM-30008	ATCC[a)]	CIP-105742	CIP-107292	R835	LM705[b)]	ATCC-25922	ATCC-29213	CIP-104298	KP10581[c)]	R1525[d)]	PA14	PA14[e)]	ATCC[f)]	CIP 106754	DSM-17050(VRE)
CIP	0.1	>6.4	0.05	>6.4	>6.4	>6.4	0.01	0.8	0.05	>6.4	>6.4	0.125	0.01	>6.4	>6.4	3.2
CN861	1	8	0.25	>64	64	0.64	0.25	0.125	16	2	16	16	0.5	32	4	nd
TSF16	>8	>8	>8	>8	>8	>64	0.06	8	32	>64	>64	>64	>64	>64	>64	8
TSE33	0.125	nd	nd	nd	nd	nd	nd	0.125	nd	nd	nd	nd	nd	nd	nd	nd
QL56	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64

2.5.2 Retrosynthesis

For the syntheses of the described novel cystobactamids, the retrosynthetic approach of MOELLER et al. was utilized.[32] The strategy is depicted exemplarily for **CN861**, the current front runner (Scheme 3). The core structure can be established via successive amide couplings between protected eastern fragment **5**, protected central amino acid **4** and western fragment **3** followed by final deprotection. Besides these key retrosynthetic steps, the two aromatic fragments **3** and **5** can be divided into monomers **6** and **7** as well as PABA building blocks. If feasible, syntheses of new cystobactamids were performed in accordance to this retrosynthetic approach to take advantage of stock quantities of each fragment. However, in some cases the strategies may differ substancially and are described in the following chapters. Moreover, linker **4**[32] was replaced by a number of different amino acids during the SAR studies. A retrosynthetic analysis at this position is inexpedient.

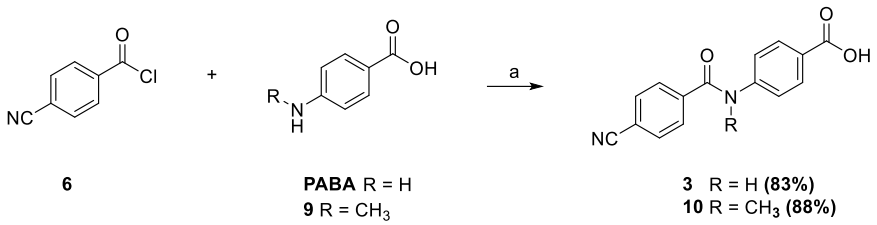


Scheme 3: Retrosynthetic strategy of cystobactamids exemplified by **CN861**.

2.5.3 Synthesis

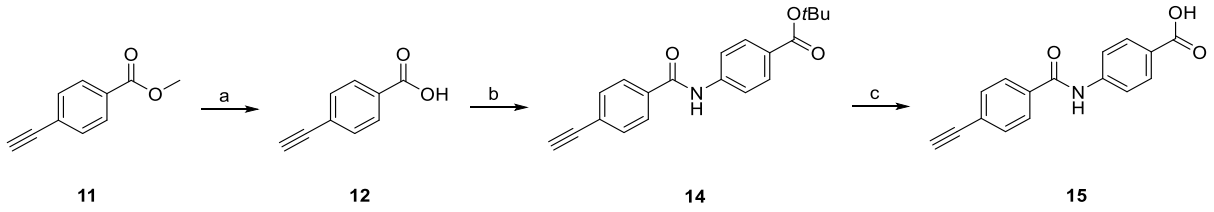
2.5.3.1 Western fragments

For the variation of the western fragment, different modifications were introduced, focusing on the linkage between the two aromatic rings. The synthesis started with the parental western fragment **3** and its *N*-methylated analog **8**. Coupling of 4-cyanobenzoyl chloride (**6**) and PABA and amine **9** formed fragments AB **3** and **10**, respectively (Scheme 4).[43]



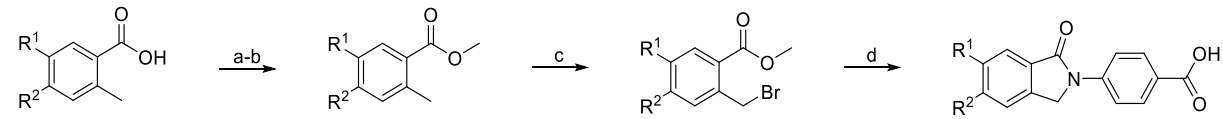
Scheme 4: Synthesis of western fragments **3** and **10**. Conditions: a) **6** 1.00 equiv., sat. $NaHCO_{3(aq.)}$/THF (1:1), rt, 3 h.

Ester **11** was saponificated with NaOH. The resulting benzoic acid **12** was coupled to *tert*-butyl 4-aminobenzoate (**13**) and saponificated to furnish western fragment **15** (Scheme 5).



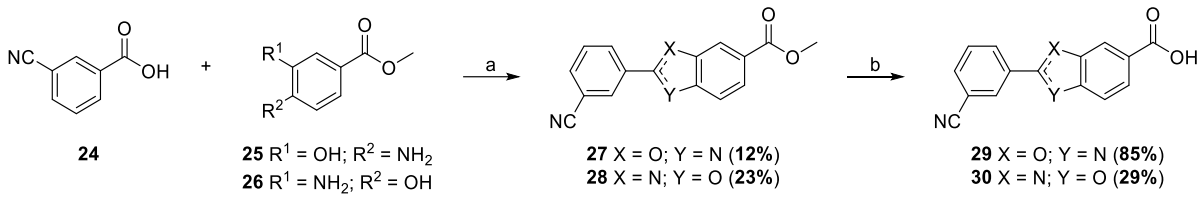
Scheme 5: Synthesis of AB fragment **15**. Conditions: a) NaOH 2.50 equiv., THF/H_2O (1:1), rt, 16 h, quant.; b) *tert*-butyl 4-aminobenzoate (**13**) 1.50 equiv., EDC·HCl 1.20 equiv., HOBt·H_2O 1.20 equiv., DMF, rt, 24 h, 69%; c) TFA, CH_2Cl_2, 0 °C to rt, 3 h, 95%.

Oxoindolinones **22** and **23** were synthesized starting from bromobenzoic acids **16** and **17**, respectively (Scheme 6). Methylation and substitution of the bromide by cyanide gave access to esters **18** and **19**. Benzylic bromination afforded bromides **20** and **21**, which could be condensated with PABA under MW irradiation.[44]



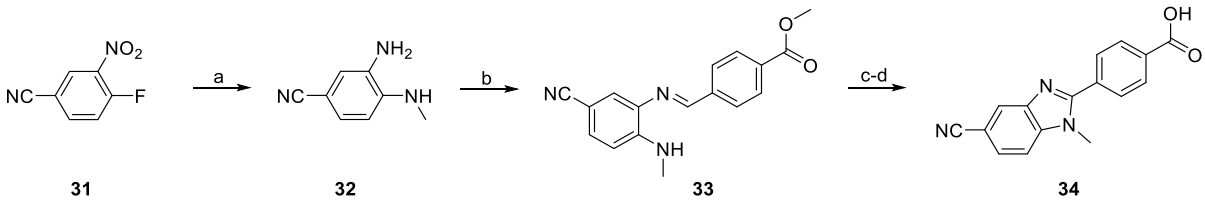
Scheme 6: Synthesis of oxoindolinones **22** and **23** as western fragments. Conditions: a) H_2SO_4/MeOH (1:20), 80 °C, 18 h; b) CuCN 1.20 equiv., NMP, 180 °C, 5 h; c) NBS 1.00 equiv., BPO 10 mol%, CCl_4, 80 °C, 18 h; d) PABA 1.30 equiv., DMF, MW irradiation, 150 °C, 5 min.

Benzoxazoles **29** and **30** were synthesized from 3-cyanobenzoic acid (**24**) and *ortho*-aminophenols **25** and **26** in the presence of $B(OH)_3$ (Scheme 7).[45] Saponification of esters **27** and **28** was accomplished with LiOH.[46]



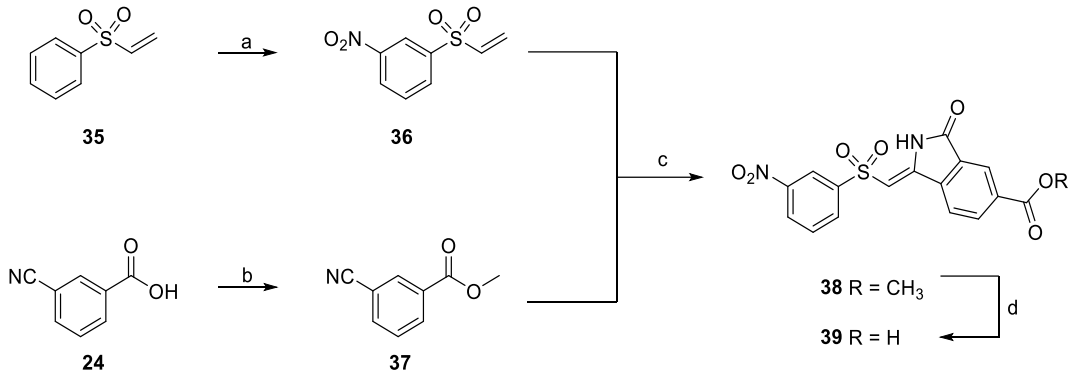
Scheme 7: Synthesis of benzoxazoles **29** and **30** as western fragments. Reaction conditions: a) **25** 1.00 equiv., $B(OH)_3$ 1.00 equiv., *p*-xylene, 160 °C, 20 h; b) LiOH 4.00 equiv., THF/MeOH/H_2O (3:1:1), rt, 3-48 h.

The benzimidazole motif as amide substitute between ring A and B originated from 4-fluoro-3-nitrobenzonitrile (**31**). The electron-withdrawing groups allowed the nucleophilic aromatic substitution of the fluoride by $MeNH_2$. Subsequent reduction gave access to diamine **32**, which was condensated with methyl 4-formylbenzoate. Imine **33** was cyclized and oxidized in the presence of iodine and NaOAc. Saponification furnished desired acid **34**.



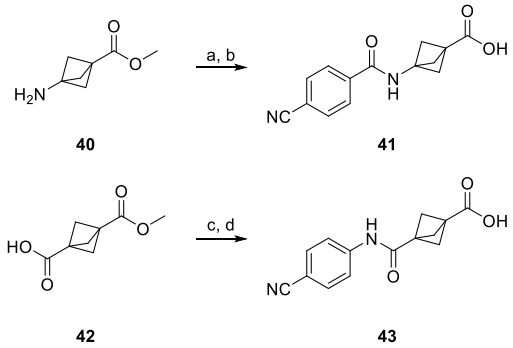
Scheme 8: Synthesis of benzimidazole **34** as western fragment. Reaction conditions: a) $MeNH_2$ 2.70 equiv., THF/EtOH, 0 °C to rt, 10 min, then Zn dust 15.0 equiv., AcOH 17.0 equiv., 40 °C, 16 h, 98%; b) methyl 4-formylbenzoate 1.00 equiv., MeOH/THF, rt, 1 h, 80%; c) I_2 1.20 equiv, NaOAc 2.00 equiv., CH_2Cl_2, rt, 4 h, 75%; d) LiOH·H_2O 8.00 equiv., H_2O/THF (1:1), rt, 18 h, 98%.

A more exotic modification was inspired by a publication by JEGANMOHAN, in which the one-pot coupling of vinyl sulfones with nitriles towards (*Z*)-sulfonylmethyleneisoindolinones are reported.[41] The described one-pot coupling of vinyl sulfones with nitriles yields (Z)-sulfonylmethyleneoxoisoindonlines. This method does not tolerate the CN group as optimized functionality at the *N*-terminus, so that the original NO_2 group was choosen as electron-withdrawing alternative. Therefore, phenyl vinylsulfone **35** was nitrated and 3-cyanobenzoic acid (**24**) methylated (Scheme 9). Under the use of $Cu(OAc)_2·H_2O$ and catalytic amounts of ruthenium and $AgSbF_6$, the nitrile was first hydrolized before coupling to the vinyl group under cyclization yielded the isoindonlinone. The electron-poor starting materials only led to a low yield of 20%. However, ester **38** was saponificated to furnish western fragment **39** in sufficient quantities.



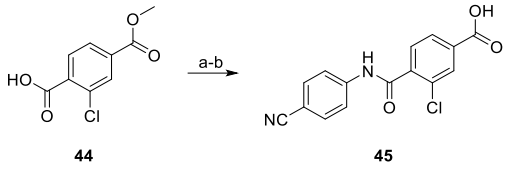
Scheme 9: Synthesis of western fragment **39** containing a (*Z*)-sulfonylmethyleneoxoisoindoline linkage. Reaction Conditions: a) H_2SO_4/HNO_3 (7:3), 0 °C, 1 h, 83%; b) MeI 1.50 equiv., K_2CO_3 1.50 equiv., DMF, rt, 14 h, 78%; c) **36** 1.20 equiv., $[RuCl_2(p\text{-cymene})]_2$ 5 mol%, $AgSbF_6$ 20 mol%, $Cu(OAc)_2 \cdot H_2O$ 2.00 equiv., AcOH, 120 °C, 3 d, 20%; d) NaOH 11.0 equiv., THF/MeOH/H_2O (1:1:1.1), rt, 19 h, 72%.

The aliphatic bicyclopentane ring system was introduced as ring B. Additionally, two variants **41** and **43** with traditional and reversed amide linkage, respectively, were synthesized following standard amide coupling protocols (Scheme 10).



Scheme 10: Synthesis of western fragments with bicylcic aliphatic benzene isosters as ring B. Reaction conditions: a) 4-cyanobenzoyl chloride **6** 1.00 equiv., THF/sat. $NaHCO_{3aq.}$ (1:1), rt, 3 h, 72%; b) LiOH 3.00 equiv., THF/H_2O (1:1), rt, 1 h, 76%; c) 4-aminobenzonitrile 1.00 equiv., **42** 1.10 equiv, $POCl_3$ 1.1 equiv, pyridine 3.00 equiv., CH_2Cl_2, 0 °C to rt, 18 h, 62%; d) $LiOH \cdot H_2O$ 8.00 equiv., THF/H_2O (1:1), rt, 5 min, 99%.

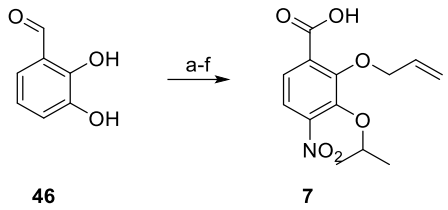
Additionally, the reversed amide motif was combined chlorinated ring B. Coupling of acid **44** with 4-aminobenzonitrile yielded western fragment **45** (Scheme 11).



Scheme 11: Synthesis of western fragment **45**. Reaction conditions: a) 4-aminobenzonitrile 1.00 equiv., HATU 1.20 equiv., pyridine 2.00 equiv., DMF, rt, 21 h, 79% brsm; b) LiOH 3.00 equiv., H_2O/THF (1:1), 0 °C to rt, 15 h, 92%.

2.5.3.2 Eastern fragments

The synthesis of the eastern fragments started with the preparation of the central ring D **7**, which originated from 2,3-dihydroxybenzaldehyde (**46**) (Scheme 12).[26]

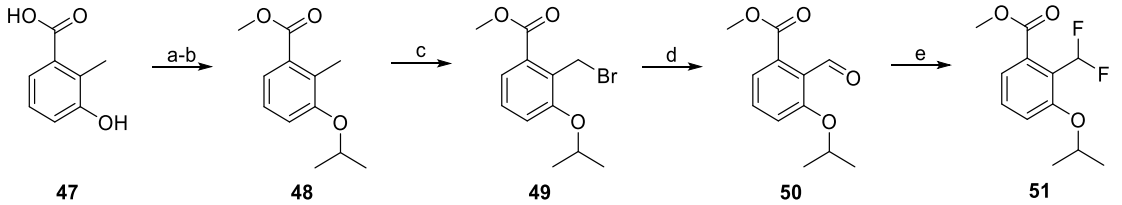


Scheme 12: Synthesis of ring D **7**. Reaction conditions: a) NaH 2.50 equiv., *i*PrOH 1.00 equiv., DMSO, rt, 3 d, 59%; b) Ac_2O 2.00 equiv., pyridine, rt, 2 h, 94%; c) fuming HNO_3 16.0 equiv., CH_2Cl_2, -40 °C, 3 h, 95%, d) LiOH 10.0 equiv., THF/H_2O (1:1), rt, 3 h, quant.; e) K_2CO_3 2.00 equiv., allyl bromide 1.50 equiv., DMF, rt, 18 h, 70%, f) $NaClO_2$ 1.10 equiv, 2-methyl-2-butene 10.0 equiv., 1 M NaH_2PO_4/*t*BuOH (1:4), rt, 3 h, quant.

2.5.3.2.1 Difluorinated Ring D

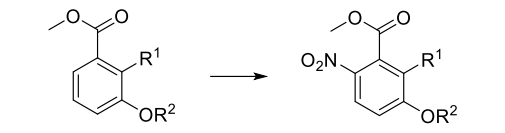
The hydroxy group of Ring D **7** was planned to be replaced by a difluoromethyl moiety. Selective fluorination reagents are available either with nucleophilic or electrophilic fluorine.[47] Trifluoromethyl groups can be utilized to act as precursor via C-F bond cleavage.[48] Furthermore, the introduction of a C1 unit „CHF_2“ is conceivable. Alternatively, difluorinated starting materials may be available. However, difluoromethylation of tetrasubstituted ring D turned out to be challenging.

Commercially avaliable 3-hydroxy-2-methylbenzoic acid (**47**) was chosen as starting material having already three aromatic positions substituted. While the hydroxy as well as the benzoic acid moieties are desired, the methyl group has to be transformed into the difluoromethyl group. Moreover, the introduction of the NO_2 moiety is required. Acid **47** was methylated with $SOCl_2$ in MeOH and alkylated subsequently (Scheme 13). Benzylic bromination of compound **48** with NBS furnished bromide **49**.[49] Oxidation to aldehyde **50** gave access to a suitable starting material for the nucleophilic difluorination.[50] DAST was utilized to obtain difluorinated compound **51**.[51]



Scheme 13: Synthesis of difluorinated ring D precursor **51**. Reaction conditions: a) $SOCl_2$ 1.70 equiv., MeOH, 80 °C, 2 h, quant.; b) *i*PrBr 1.20 equiv., NaH 1.20 equiv., DMF, rt, 20 h, 93% brsm; c) NBS 1.50 equiv., AIBN 10 mol%, CCl_4, 100 °C, 18 h, 97%; d) NMO 4.0 equiv., MeCN, rt, 20 h, 94%; e) DAST 4.00 equiv., CH_2Cl_2, rt, 18 h, 92% brsm.

Trifunctionalized building block **51** lacked the nitrogen moiety in the *para*-position of the ester. As for ring D **7**, the NO_2 group was planned to be incorporated, which could be reduced to the aniline at a later stage of the synthesis. However, it was not possible to nitrate any intermediate of this route. All tested conditions led exclusively to the NO_2 group in *ortho*-position of the ester (Scheme 14).

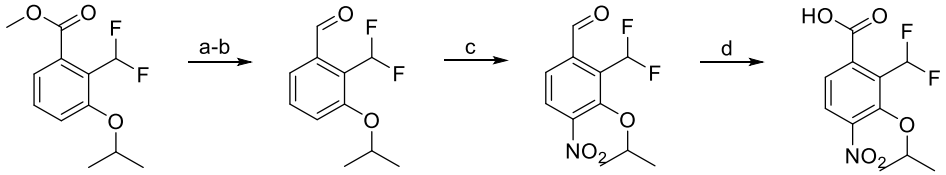


52 $R^1 = CH_3$, $R^2 = H$
49 $R^1 = CH_2Br$, $R^2 = i$Pr
50 $R^1 = CHO$, $R^2 = i$Pr
51 $R^1 = CF_2H$, $R^2 = i$Pr

53 $R^1 = CH_3$, $R^2 = H$
54 $R^1 = CH_2Br$, $R^2 = i$Pr
55 $R^1 = CHO$, $R^2 = i$Pr
56 $R^1 = CF_2H$, $R^2 = i$Pr

Scheme 14: Nitration of intermediates **49**-**52** under various conditions exclusively led to undesired regioisomers **53**-**56**.

To adjust the regioselectivity of the nitration, advanced intermediate **51** was converted to aldehyde **57** via LAH reduction and subsequent PCC oxidation. Treatment with fuming HNO_3 at low temperature yielded regioisomer **58**. Unfortunately, the undesired regioisomer was still the main product. However, the regioisomers were separable via column chromatography. Finally, tetrasubstituted aldehyde **58** was oxidized to acid **59** under PINNICK conditions (Scheme 15).

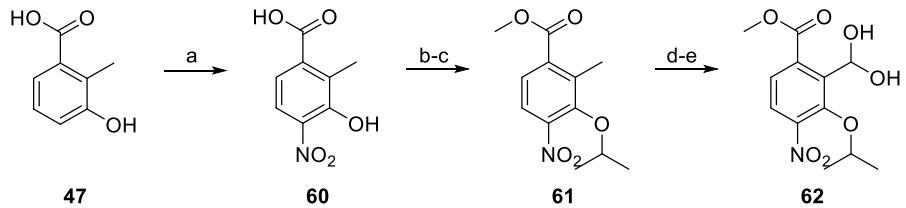


51 **57** **58** **59**

Scheme 15: Synthesis of 4-nitrobenzoic acid **59**. Reaction conditions: a) LAH 2.00 equiv., THF, rt, 4 h; b) PCC 1.50 equiv., CH_2Cl_2, rt, 1 h, 83% over two steps; c) fuming HNO_3 11.00 equiv., CH_2Cl_2, -40 °C, 3 h, 23%, d) $NaClO_2$ 1.10 equiv, 2-methyl-2-butene 10.0 equiv., 1 M NaH_2PO_4, *t*BuOH, rt, 3 h, 90%.

Although the described synthesis led to the desired product, it consists of numerous steps and the nitration yielded the wrong regioisomer as main product. Therefore, other approaches were tested in parallel and shall be presented briefly.

Thus, starting material **47** was nitrated first with $NaNO_2$ in the presence of H_2SO_4. The following steps were performed in the same manner as for compound **50**. Methylation and alkylation of compound **60** afforded toluate **61**. Unfortunately, the following bromination and subsequent oxidation only led to poor yields of hydrate **62**.

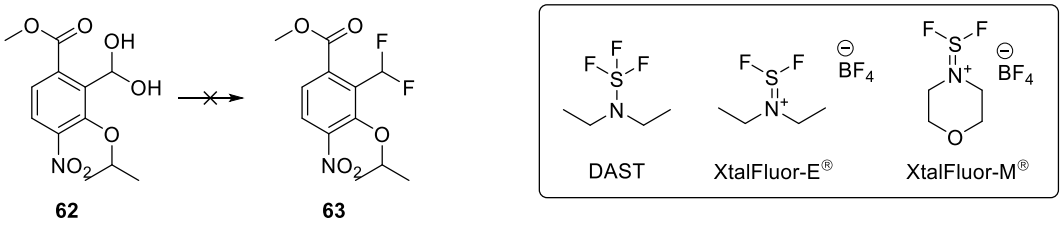


47 **60** **61** **62**

Scheme 16: Alternative starting material **62** for the difluorination. Reaction conditions: a) $NaNO_2$ 1.00 equiv., H_2SO_4 1.00 equiv., H_2O, 85 °C, 3 h, 37%; b) $SOCl_2$ 1.70 equiv., MeOH, 80 °C, 2 h, 99%; c) *i*PrBr 1.60 equiv., NaH 1.20 equiv., DMF, 70 °C, 18 h, 96%; d) NBS 1.50 equiv., AIBN 10 mol%, MeCN, 85 °C, 18 h; e) NMO 4.00 equiv., MeCN, rt, 20 h, 16% over two steps.

Difluorination is reported for aldehydes as well as for benzylic hydrates.[52] However, under the investigated conditions, no transformation of starting material **62** was observed. Unfortunately, the difluorination of compound **62** did not succeed with DAST (Table 8, entry 1). Increased reagent loading and addition of catalytic EtOH was not fruitful (entry 2). The use of XtalFluor-E® or XtalFluor-M® as alternative F-sources and higher reaction temperature also led to isolation of only starting material (entries 3-5).

Table 8: Difluorination attempts of nitrated hydrate **62** with different fluoride sources.

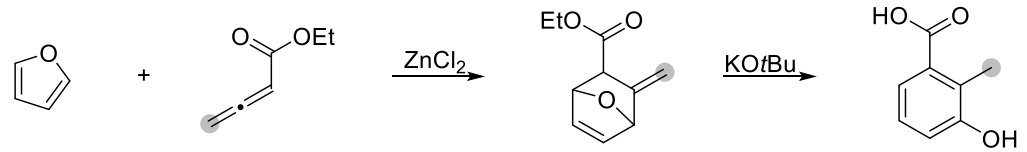


62 **63**

Entry	Solvent	F-source (equiv.)	Additive (equiv.)	T [°C]	t [h]
1	CH_2Cl_2	DAST (4.00)	-	rt	18
2	CH_2Cl_2	DAST (8.00)	EtOH (cat.)	rt	48
3	CH_2Cl_2	XtalFluor-E® (1.50)	Et_3N•3HF (2.0)	rt	20
4	DCE	XtalFluor-E® (1.50)	Et_3N•3HF (2.0)	90	20
5	DCE	XtalFluor-M® (1.50)	Et_3N•3HF (2.0)	90	20

Direct benzylic difluorination of single *ortho*-substituted toluates is reported with Selectfluor®.[53] This method could not be applied to chosen intermediates of the described synthetic route. In all cases starting material was isolated. Only traces of monofluorinated product were observed, what indicates the need of low steric hindrance.

In parallel, a fundamentally different approach was investigated. A comprehensive literature search revealed that 2-methyl-3-hydroxybenzoic acid **47** can be synthesized from allene **64** in a two-step procedure (Scheme 17).[54] A DIELS-ALDER reaction with furane leads to cycloadduct **65**, which can be aromatized under basic conditions.



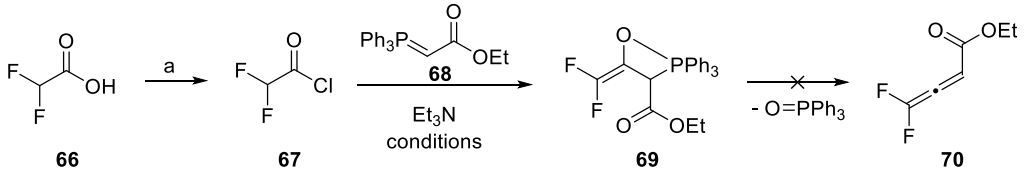
furane **64** **65** **47**

Scheme 17: Synthesis of 2-methyl-3-hydroxybenzoic acid (**47**) from allene **64**, grey = potentially difluorinated C atom.[54]

Allene **64** should be decorated with two terminal fluorine atoms. Instead of introducing fluorine into a given structure, commercially available difluoroacetic acid (**66**) was transformed into the corresponding acyl chloride **67** (Table 9).[55] The latter was intended to react with phosphonium ylide **68**, which was synthesized from ethyl 2-bromoacetate. However, desired allene (**70**) was

not obtained. In all cases, mass spectrometry indicated the formation of oxaphosphetane **69**, which was stable enough to resist elimination under the tested conditions (Table 9). The reaction temperature was screened over a broad range between -10 to 120 °C and various reaction times. Moreover, microwave or ultrasonic irradiation were unsuccesful. Even upon addition of the strong base NaH, no conversion was observed. Only under the harsh conditions of *n*BuLi, oxaphosphetane **69** was consumed. However, this only led to decomposition.

Table 9: Synthetic studies towards difluorinated allene **70** with **68**. Reaction conditions: a) PCl_5 1.10 equiv., -10-0 °C, 15 min; c) judged by LC/MS analysis; MW = microwave irradiation; US = ultrasonic irradiation.

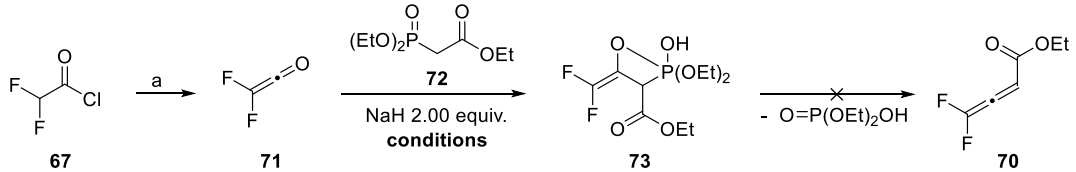


66 67 69 70

Entry	Solvent	Add. contitions	T [°C]	t [h]	Result[c)]
1	CH_2Cl_2	-	0	1	**69**
2	CH_2Cl_2	-	rt	1	**69**
3	PhMe	-	-10	1	**69**
4	PhMe	-	0	1	**69**
5	PhMe	-	80	5	**69**
6	PhMe	-	100	18	**69**
7	PhMe	-	120	18	**69**
8	PhMe	MW (< 1 W)	30	0.5	**69**
9	PhMe	MW (< 2 W)	50	0.5	**69**
10	PhMe	MW (< 10 W)	70	0.5	**69**
11	PhMe	US (~ 1 W)	≥50	0.5	**69**
12	PhMe/H_2O	US (~ 1 W)	≥50	0.5	**69**
13	PhMe	NaH	rt	2	**69**
14	PhMe	*n*BuLi	rt	0.25	-

A stepwise reaction of acyl chloride **67** to form ketene **71** first and subsequent treatment with phosphonate **72** under various conditions resulted again in formation of oxaphosphetane **73** but elimination to allene **70** failed (Table 10).[56]

Table 10: Synthetic studies towards difluorinated allene **70** with **72**. Reaction conditions: a) Et_3N 1.00 equiv., THF, -78 °C to rt; c) judged by LC/MS analysis; MW = microwave irradiation; US = ultrasonic irradiation.

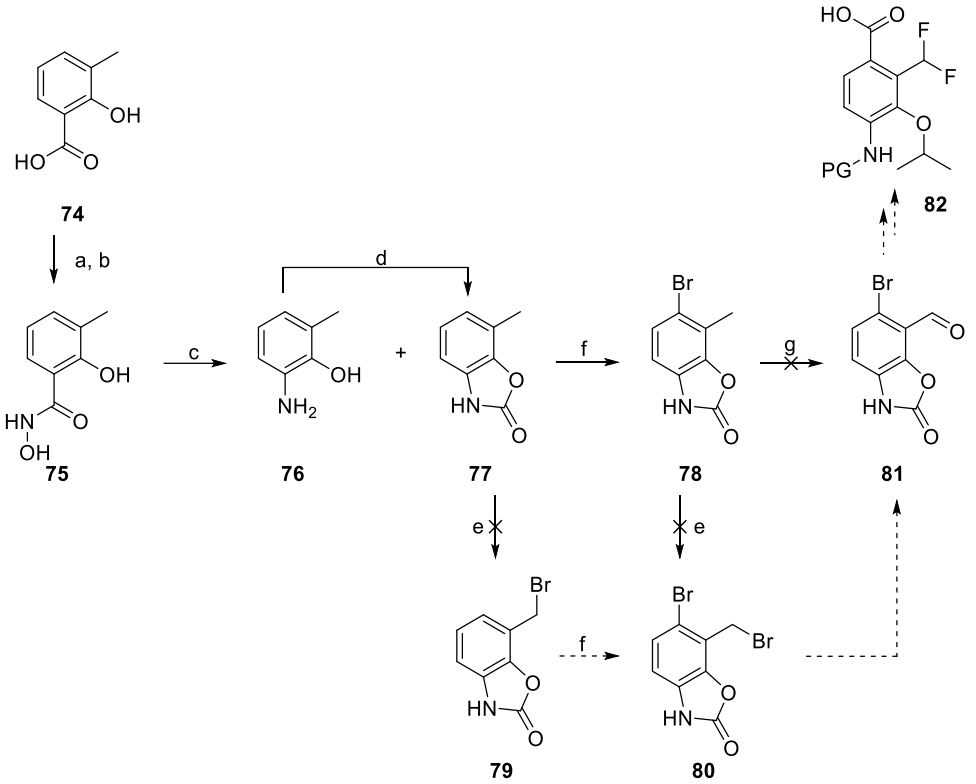


67 71 73 70

Entry	Add. conditions	T [°C]	t [h]	Result[a)]
1	-	rt	18	**73**
2	-	50	2	**73**
3	-	80	2	**73**
4	MW (300 W)	<100	0.5	**73**

In addition, 3-methylsalicylic acid (**74**), a regioisomer of **47**, was used as alternative starting material. In this apporach the benzoic acid was planned to be transformed into the aniline, while the final carboxylic acid moiety is introduced later. Therefore, acid **74** was methylated[57] and

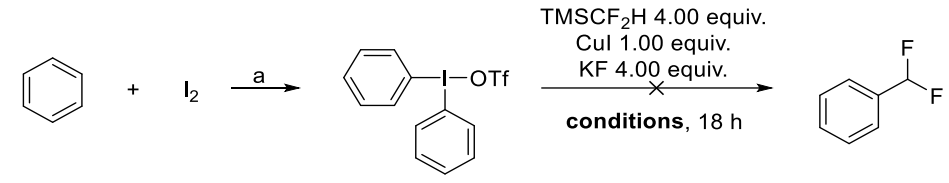
then tranformed into hydroxamic acid **75** (Scheme 18).[58] Subsequent LOSSEN rearrangement in DMF at elaborated temperatures afforded a mixture of 2-amino-6-methylphenol (**76**) and desired benzoxazolinone **77**.[59] The mixture was reacted with CDI to exclusively isolate benzoxazolinone **77**.[60] Benzylic and aromatic bromination was planned to lead to intermediate **80**. The order of the bromination sequence was investigated. While the aromatic bromination of **77** afforded bromide **78**,[61] benzylic bromination of both precursors **77** and **78** failed. Direct benzylic oxidation of **78** with IBX to aldehyde **81** was not successful.



Scheme 18: Synthetic studies towards difluorinated ring D **82**. Reaction conditions: a) conc. H_2SO_4, MeOH, reflux, 5 d, 88%, b) $H_2NOH{\cdot}HCl$ 2.00 equiv., KOH 4.00 equiv., MeOH, rt, 20 h, quant., c) K_2CO_3 3.00 equiv., DMF, 160 °C, 1 h, d) CDI 1.60 equiv., DMF, 60 °C, 2 h, 44% over three steps, e) NBS 1.50 equiv., AIBN 10 mol%, CCl_4, 100 °C, 18 h, f) NBS 1.00 equiv., THF, rt, 4 h, 77%, g) IBX 3.00 equiv., DMSO, 85 °C, 16 h.

It shall be mentioned that another approach was tested in parallel. Diaryliodonium salts are broadly established reagents for the introdution of various nucleophiles to aromatic systems. The trifluoromethylation of diaryliodonium salts with $TMSCF_3$ was reported before as well as the difluoromethylation of heterocycles.[62] In analogy salt **83** was synthesized as test substrate from benzene and iodine using *m*CPBA and *p*TsOH (Table 11). The use of $TMSCF_2H$ led not to the desired difluoromethylated benzene **84** under the tested conditions.

Table 11: Initial investigations of the difluoromethylation of diaryliodonium salt **83** under various conditions. Reaction conditions: a) *m*CPBA 1.10 equiv., *p*TsOH 5.00 equiv., CH_2Cl_2, 0 °C, 10 min, 78%.



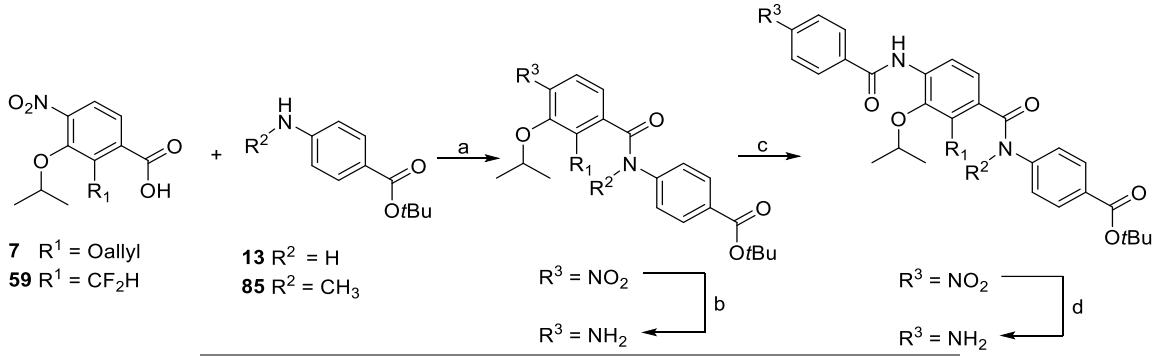
benzene **83** **84**

Entry	Solvent	Temp. [°C]
1	MeCN	rt
2	EtOAc	rt
3	EtOAc	80
4	THF	80

2.5.3.2.2 Ring couplings

Eastern fragment **5** consists of three PABA-derived monomers. Rings D **7** and **59** were first coupled to rings E **13** or **85** to afford aromatic amides **86-88** (Table 12). Reduction of the NO_2 group yielded anilines **89-91**, that were further coupled to 4-nitrobenzoyl chloride. Trimers **92-94** were reduced to western fragments **5, 95** and **96**.

Table 12: Fragment couplings towards eastern fragments **5**, **95** and **96**. Reaction conditions: a) **13** or **85** 0.95 equiv., $POCl_3$ 1.00 equiv., DIPEA 1.70 equiv., CH_2Cl_2, 0 °C, 1 h; b) Zn 15.0 equiv., AcOH 15.0 equiv., THF/EtOH, rt, 2 h; c) 4-nitrobenzoyl chloride 1.60 equiv., pyridine 4.00 equiv., CH_2Cl_2, rt, 2 h; d) see b); e) over two steps.



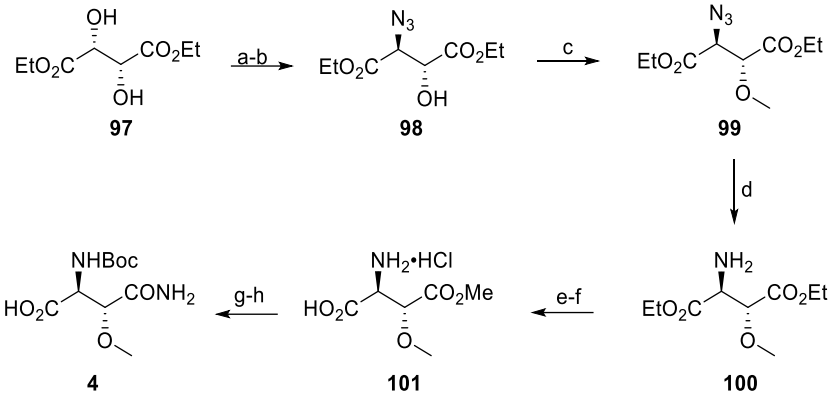
7 R^1 = Oallyl
59 R^1 = CF_2H

13 R^2 = H
85 R^2 = CH_3

Reactants	R1	R2	Compound (yield [%]) after step			
			a	b	c	d
7 + 13	OAllyl	H	**86** (79)	**89** (86)	**92**	**5** (55[e])
7 + 85	OAllyl	CH_3	**87** (79)	**90** (97)	**93** (92)	**95** (72)
59 + 13	CF_2H	H	**88**	**91** (35)	**94**	**96**

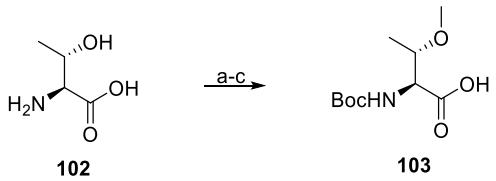
2.5.3.3 Central amino acids

The original central amino acid was synthesized from diethyl (2*R*,3*R*)-diethyltatrate (**97**) (Scheme 19).[32] Substitution with $SOCl_2$ and subsequent treatment with NaN_3 yielded azide **98**. The free alcohol was methylated with MeI to yield compound **99**. Hydration under Pd-catalysis furnished secondary amine **100**. Amino acid hydrochloride **101** was afforded by subsequent treatment with aq. HCl and dry HCl. Finally, Boc-protection and aminolysis yielded desired *N*-protected amino acid **4**.



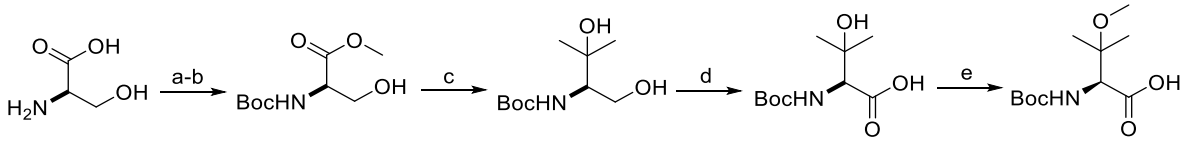
Scheme 19: Synthesis of central amino acid **4**. Reaction conditions: a) $SOCl_2$ 1.50 equiv., DMF 2 mol%; b) NaN_3 3.00 equiv., DMF, 35 °C, 20 h, 63% over two steps; c) MeI 3.30 equiv., AgO 1.00 equiv., CH_2Cl_2, rt, 20 h, 89%; d) H_2 1 atm, $Pd(OH)_2$ 1 mol%, EtOAc, rt, 10 d, 56%; e) 5 M $HCl_{(aq.)}$, 80 °C, 20 h; f) HCl, MeOH, rt, 20 h, 67% over two steps; g) Boc_2O 1.40 equiv., $NaHCO_3$ 3.00 equiv., H_2O, 0 °C to rt, 18 h; h) 28% $NH_{3(aq.)}$, rt, 4 h, 74% over two steps.

To investigate the importance of the primary amide, allothreonine was chosen as simplified analog, in which the amide is replaced by a methyl group. Therefore, L-allothreonine (**102**) was Boc-protected and methylated with an excess of MeI. Saponification furnished the desired amino acid **103**.[63,64]



Scheme 20: Synthesis of amino acid **103**. Reaction conditions: a) $NaHCO_3$ 1.50 equiv., Boc_2O 1.60 equiv., MeOH/H_2O (1:1), rt, 18 h, b) Ag_2O 5.00 equiv., MeI 16.0 equiv., MeCN, rt, 48 h, c) LiOH·H_2O 6.00 equiv., THF/H_2O (2:1), rt, 3 h, 47% over 3 steps.

Moreover, amino acid **103** should further modified by introducing a second methyl group in β-position. The aimed product could serve as building block for the cystobactamids (starting from D-serine) as well as for Myxovalargin A (**234**) (starting from L-serine, see chapter 3). Therefore, serine was esterified and Boc-protected to yield primary alcohol **104**.[65] Addition of two methyl groups furnished diol **105**, which was oxidized to carboxylic acid **106**.[66] **(*S*)-106** was methylated to give linker **107**.[67]



D-serine
L-serine

(*S*)-**104** (91%)
(*R*)-**104** (73%)

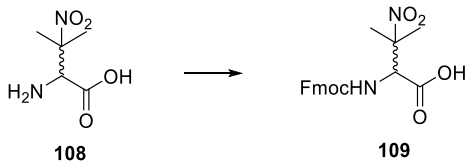
(*S*)-**105** (92%)
(*R*)-**105** (52%)

(*S*)-**106** (79%)
(*R*)-**106** (86%)

107 (51%)

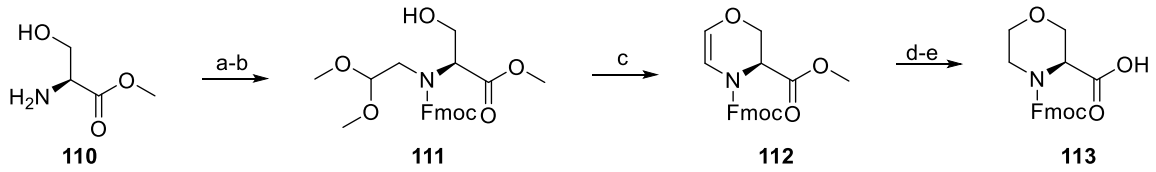
Scheme 21: Synthesis of β-hydroxyvaline **106** and β-methoxyvaline **107**. Reaction conditions: a) $SOCl_2$ 6.0 equiv., MeOH, rt, 20 h; b) Boc_2O 1.10 equiv, Et_3N 2.70 equiv., CH_2Cl_2, rt, 16 h; c) MeMgBr 6.00 equiv., Et_2O, rt, 3 h; d) $NaClO_2$ 2.00 equiv., NaOCl 2 mol%, TEMPO 10 mol%, phosphate buffer pH 7, MeCN/H_2O, 35 °C, 18 h; e) NaH 3.0 equiv., MeI 1.20 equiv., THF, rt, 19 h, 51%.

3-Nitrovaline **108**[68] was Fmoc-protected to furnish carbamate **109** (Scheme 22), which was also used in the totalsynthesis of Myxovalargin A (**234**) (see chapter 3).



Scheme 22: Fmoc-protection of 3-nitrovaline **108**. Reaction conditions: FmocCl 1.10 equiv, 10% $Na_2CO_{3(aq.)}$, 1,4-dioxane, 0 °C to rt, 18 h, 57%.

A rigidified central amino acid was synthesized by closing a morpholine ring between the amine and the side chain alcohol (Scheme 23).[69] Therefore, methyl L-serinate (**110**) was condensated with 2,2-dimethoxyacetaldehyde under reducing conditions. After subsequent Fmoc protection alcohol **111** was isolated. Refluxing this compound under acidic conditions gave access to dehydromorpholine **112**. The double bond was reduced and the methyl ester was cleaved under acidic conditions to furnish desired carboxylic acid **113**.

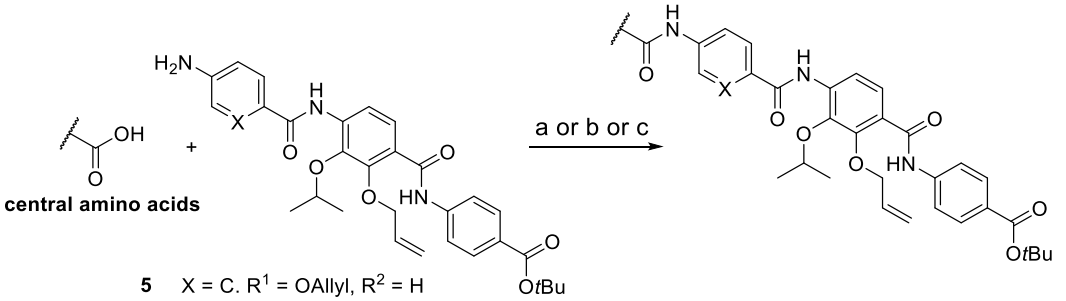


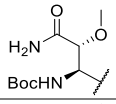
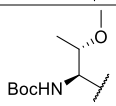
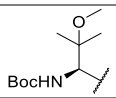
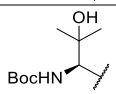
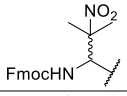
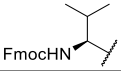
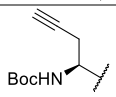
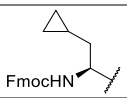
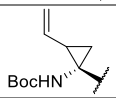
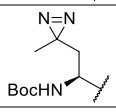
Scheme 23: Synthesis of morpholinic amino acid **113**. Reaction conditions: a) 2,2-dimethoxyacetaldehyde 1.00 equiv., Et_3N 1.00 equiv., Pd/C 10% w/w, H_2 1 atm, MeOH/H_2O, rt, 17 h; b) FmocCl 1.00 equiv., $NaHCO_3$ 2.00 equiv., EtOAc/H_2O (1:1), 0 °C to rt, 22 h, 84% over two steps; c) *p*TsOH·H_2O 10 mol%, 4Å MS, PhMe, 123 °C, 3 h, 68%; d) Pt/C, H_2, MeOH/CH_2Cl_2 (2:1), rt, 15 h, 93%; e) 5 M HCl, 1,4-dioxane, 110 °C, 16 h, 90%.

2.5.3.4 Coupling between eastern fragments and central amino acids

The first fragment couplings were performed between eastern fragments **5** and **114**[70] and the central amino acids under appropriate coupling conditions yielding intermediates LCDE **118-132**. While EEDQ as neutral coupling reagent was used in the reference,[32] T3P appeared to be suitable for the majority of amino acids during the synthetic studies. For morpholine derived acid **111** acyl chloride formation prior to coupling to amine **5** was successful (Table 13, entry 6). The fragment combinations, coupling conditions and yields are given in Table 13.

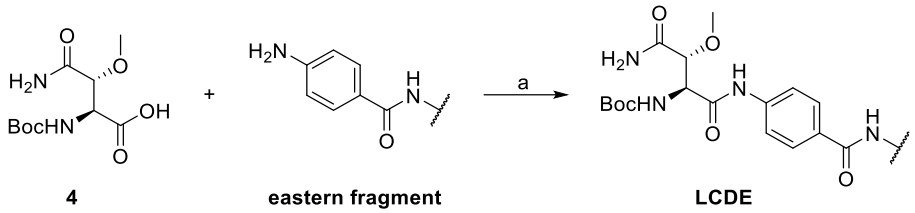
Table 13: Fragment coupling between eastern fragments and central amino acids. Reaction conditions: a) EEDQ 1.50-1.60 equiv., central amino acid 1.50-1.70 equiv., $CHCl_3$, 0 °C to rt, 16-18 h; b) T3P 1.80-4.00 equiv., pyridine 3.00-6.00 equiv., EtOAc, 0 °C to rt, 2-22 h; c) **111**, $SOCl_2$, 80 °C, 3 h, then **5**, 2,6-lutidine 4.60 equiv., CH_2Cl_2, rt, 18 h; d) isolated; e) not isolated.



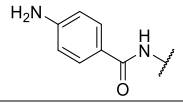
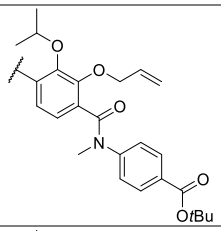
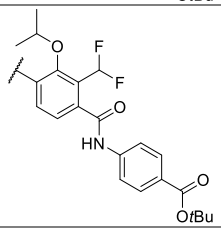
Entry	Central amino acid residue	Central amino acid	X	Eastern fragment	Coupling conditions	LCDE (yield [%][d])
1		**4**	C	**5**	a)	**120** (59)
2			N	**114**	b)	**121** (39)
3		**103**	C	**5**	a)	**122** (53)
4		**107**	C	**5**	b)	**123** (49)
5		(*S*)-**106**	C	**5**	b)	**124** (68)
6		**113**	C	**5**	c)	**125** (63)
7		**109**	C	**5**	b)	**126** (76)
8		**115**	C	**5**	b)	**127** (quant.)
9		**116**	C	**5**	b)	**128** (50)
10			N	**114**	b)	**129** (97)
11		**117**	C	**5**	a)	**130** (85)
12			N	**114**	b)	**131** (97)
13		**118**	C	**5**	b)	**132** (84)
14			N	**114**	b)	**133** (67)
15		**119**	C	**5**	a)	**134**[e]

In addition, model central amino acid β-methoxy asparagine **4** was coupled to two modified eastern fragments **95** and **96** (Table 14).

Table 14: Fragment coupling between β-methoxy asparagine **4** and different eastern fragments. Reaction conditions: a) EEDQ 1.60 equiv., β-methoxy asparagine **4** 1.70 equiv., $CHCl_3$, 0 °C to rt, 16 h; b) isolated; c) over three steps;



4 **eastern fragment** **LCDE**

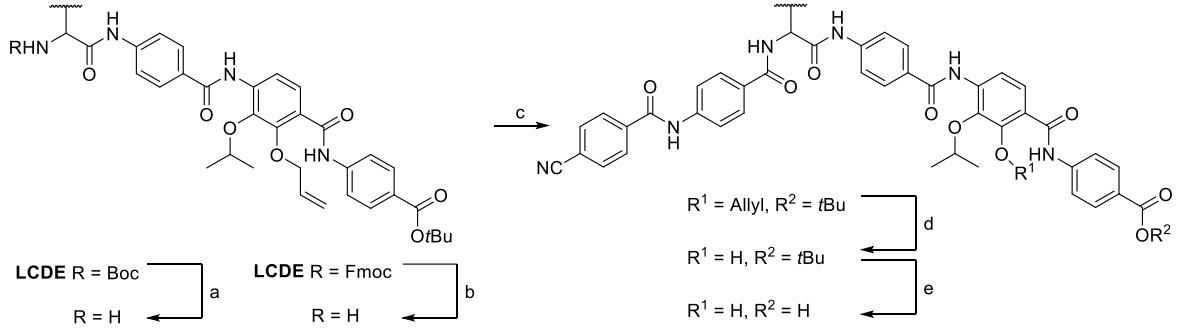
Entry	Eastern fragment residue	Eastern fragment 	LCDE (yield [%][b])
1		**95**	**135** (52)
2		**96**	**136** (33[c])

2.5.3.5 Final fragment coupling and deprotection

2.5.3.5.1 New central amino acid derivatives

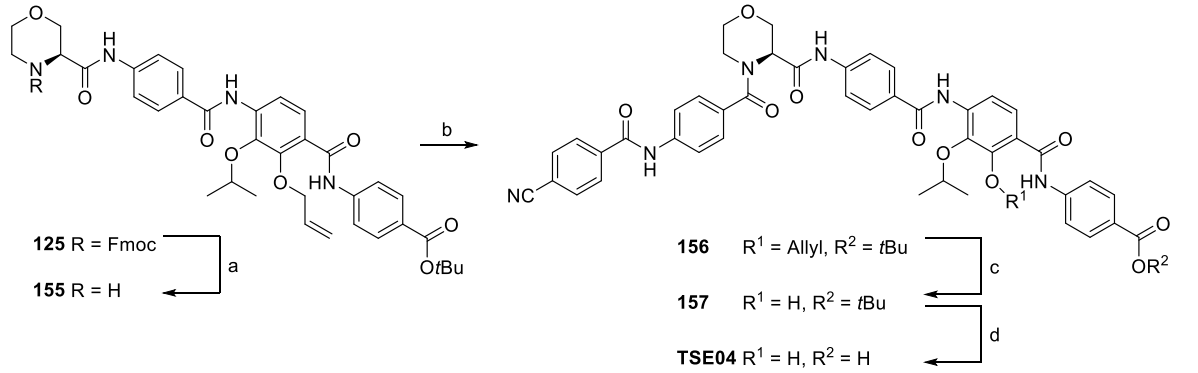
Intermediates **122-124**, **126**, **127** and **130** were deprotected at the *N*-terminus either under acidic or basic conditions for Boc- or Fmoc-removal, respectively. Amide coupling to model western fragment **3** and final deprotections gave access to new cystobactamids with different central amino acid sidechain residues (Table 15). **DK405** was resynthesized in larger quantities and provided to the OpCyBac project for more extensive studies (entry 6).

Table 15: Fragment coupling and deprotection towards cystobactamids with different central amino acids. Reaction conditions: a) 4 M HCl in 1,4-dioxane, 0 °C to rt, 15 min; b) piperidine or Et_2NH, MeCN, rt, 2-3 h; c) acid **3** 1.20-2.50 equiv., HATU 1.20-2.50 equiv., DIPEA 3.00-5.00 equiv., DMF, rt, 16-23 h; c) $Ph(PPh_3)_4$ 10 mol%, $PhNH_2$ 3.30 equiv, THF, rt, 2 h; d) TFA, 0 °C to rt, 30 min; f) over three steps.



Entry	Central amino acid residue	LCDE	Step a/b)	Step c) (yield [%])	Step d) (yield [%])	Step e) (yield [%])
1		**122**	**137**[a)]	**143** (37)	**149** (71)	**TSE51** (61)
2		**123**	**138**[a)]	**144** (52)	**150** (73)	**TSF77** (23)
3		**124**	**139**[a)]	**145** (47)	**151** (83)	**TSG04** (39)
4		**126**	**140**[b)]	**146** (77)	**152** (84)	**TSF14** (61)
5		**127**	**141**[b)]	**147** (51)[f)]	**153** (54)	**TSG18** (66)
6		**130**	**142**[b)]	**148** (90)	**154** (80)	**DK405** (88)

Morpholine analog **125** was deprotected and coupled in the same manner to form tertiary amide **156**. Deallylation and ester cleavage furnished cystobactamid **TSE04** (Scheme 24).

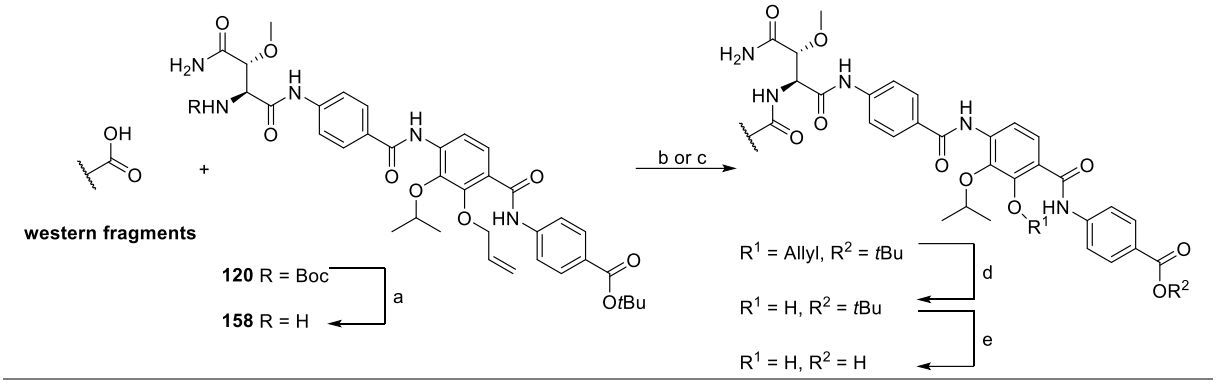


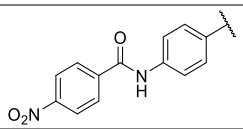
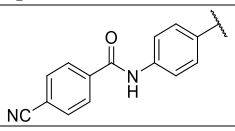
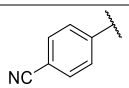
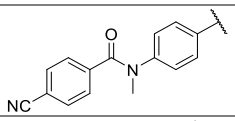
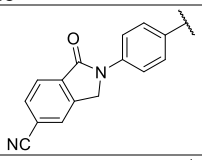
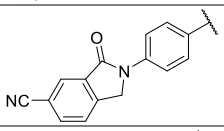
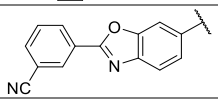
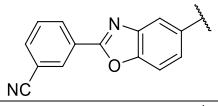
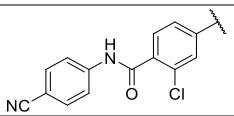
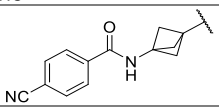
Scheme 24: Fragment coupling and deprotection towards **TSE04**. Reaction conditions: a) Et_2NH/MeCN (1:4), rt, 90 min; b) acid **3** 2.50 equiv., HATU 2.50 equiv., DIPEA 5.00 equiv., DMF, rt, 16 h, 70%; c) $Ph(PPh_3)_4$ 10 mol%, $PhNH_2$ 3.30 equiv, THF, rt, 90 min, 91%; d) TFA, 0 °C to rt, 30 min, 79%.

2.5.3.5.2 New western fragment derivatives

For the preparation of new cystobactamids varying in the western fragment, intermediate **120** was Boc-deprotected and coupled to the depicted western fragments (Table 16). While the reported coupling conditions with HATU were applicable for amides **159**, **162**, **167** and **168** (entries 1, 4, 9, 10), western fragments **22**, **23**, **29** and **30** with cyclized motifs as linkage between the two aromatic rings did not react. Formation and isolation of the acyl chlorides prior to the fragment couplings led to full conversion. Furthermore, products **160**, **163-166** (entries 2, 5-8) were precipitated under those conditions and no chromatographic purification was necessary. Compound **161** was isolated as side product at some point (entry 3). Deallylation of intermediates **159-168** to phenols **169-178** and subsequent ester cleavage furnished the corresponding cystobactamids shown in Table 16.

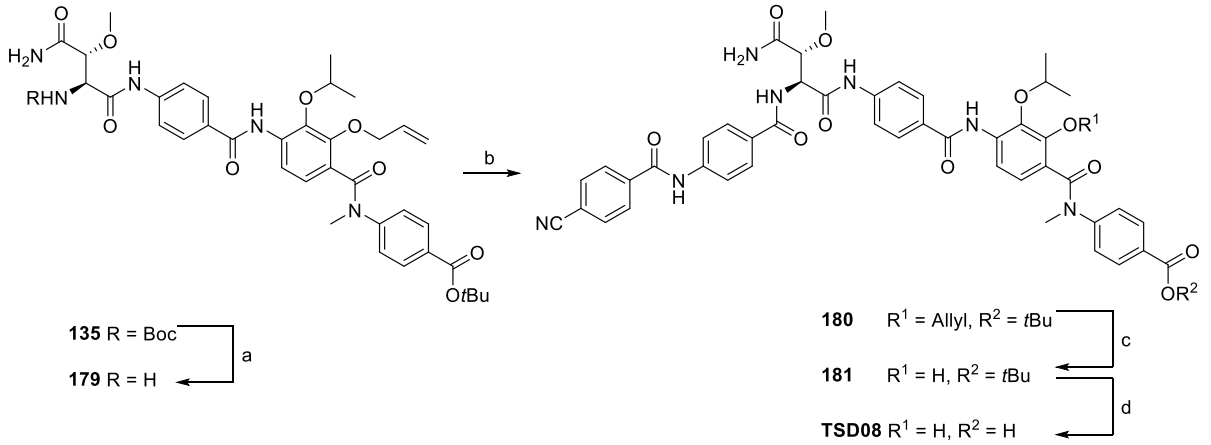
Table 16: Fragment coupling and deprotection towards cystobactamids with β-methoxy asparagine as central amino acid and modified western fragments. Reaction conditions: a) 4 M HCl in 1,4-dioxane, 0 °C to rt, 15 min; b) western fragment 1.20-2.50 equiv., HATU 1.20-2.50 equiv. DIPEA 13.0 equiv., DMF, rt, 15-20 h; c) western fragment, $SOCl_2$, 80 °C, 2 h, then **158** 1.00 equiv., NMM 2.00 equiv., CH_2Cl_2, 0 °C to rt, 16-19 h; d) $Ph(PPh_3)_4$ 10 mol%, $PhNH_2$ 3.30 equiv, THF, rt, 2-3 h; e) TFA, 0 °C to rt, 30 min; f) isolated; g) pyridine 3.00 equiv. instead of DIPEA



Entry	Western fragment residue	Western fragment 	Step b) or c) (yield [%][f])	Step d) (yield [%][f])	Step e) (yield [%][f])
1		**157**	**159**[b] (25)	**169** (62)	**861-2** (89)
2		**3**	**160**[c] (62)	**170** (75)	**CN861** (68)
3		**-**	**161**	**171** (52)	**TSE83** (68)
4		**10**	**162**[b] (26)	**172** (77)	**TSA73** (67)
5		**22**	**163**[c] (46)	**173** (73)	**TSC82** (79)
6		**23**	**164**[c] (34)	**174** (76)	**TSC81** (75)
7		**29**	**165**[c] (44)	**175** (77)	**TSC83** (70)
8		**30**	**166**[c] (49)	**176** (74)	**TSC98** (80)
9[g]		**45**	**167**[b] (60)	**177** (88)	**TSE22** (88)
10		**41**	**168**[b] (41)	**178** (47)	**KB015** (24)

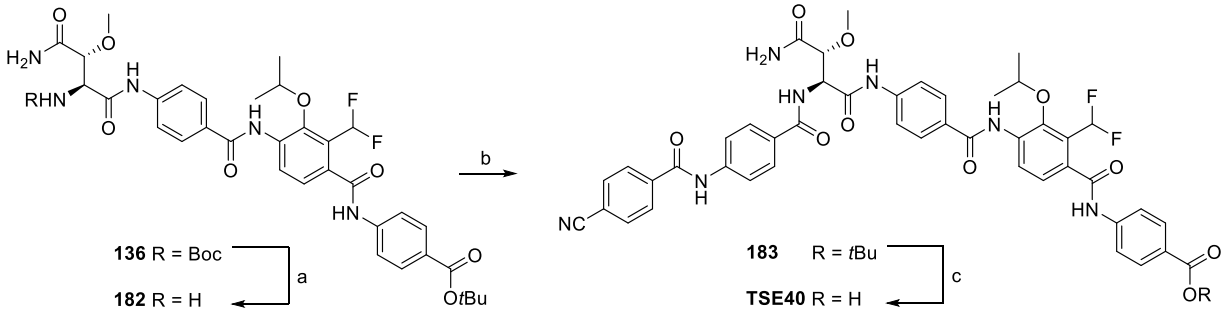
2.5.3.5.3 New eastern fragment derivatives

TSD08 bearing a methyl group on the amide between rings D and E was synthesized following the established synthetic route (Scheme 25).



Scheme 25: Fragment coupling and deprotection towards cystobactamid **TSD08**. Reaction conditions: a) 4 M HCl in 1,4-dioxane, 0 °C to rt, 15 min; b) acid **3**, $SOCl_2$, 80 °C, 3 h, then **179**, NMM 2.00 equiv., CH_2Cl_2, rt, 18 h, 46%; c) $Ph(PPh_3)_4$ 10 mol%, $PhNH_2$ 3.30 equiv, THF, rt, 2 h, 57%; d) TFA, 0 °C to rt, 30 min, 49%.

Difluorinated derivative **TSE40** was obtained in the same manner, whereas the deallylation step was not neccessary (Scheme 26).

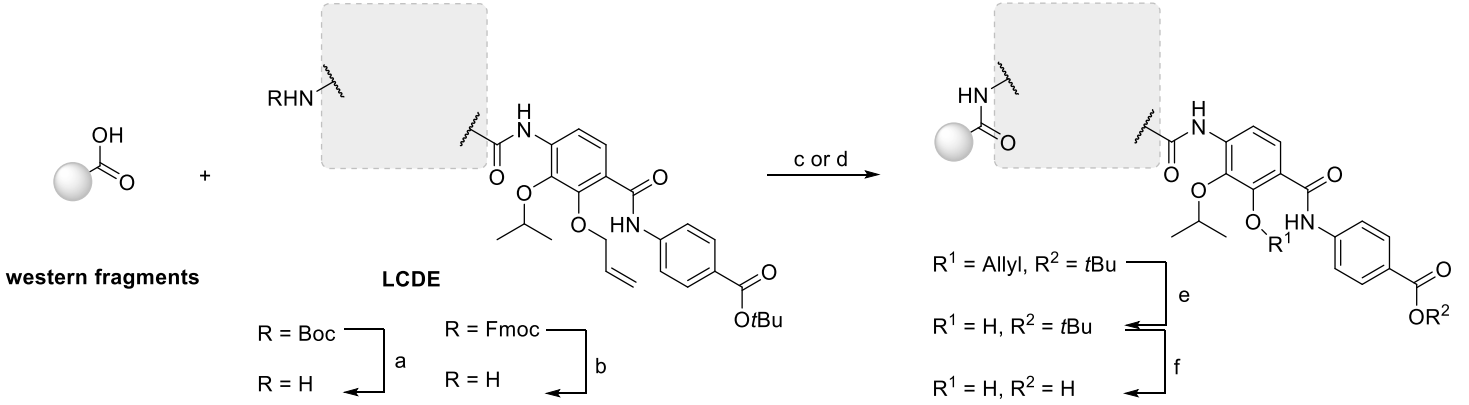


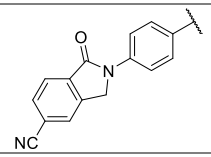
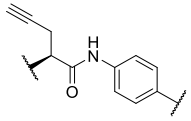
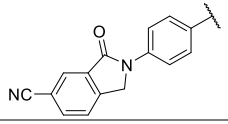
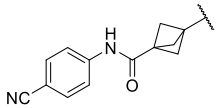
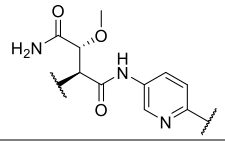
Scheme 26: Fragment coupling and deprotection towards cystobactamid **TSE40**. Reaction conditions: a) 4 M HCl in 1,4-dioxane, 0 °C to rt, 15 min; b) **3** 1.20 equiv., HATU 1.20 equiv. DIPEA 3.00 equiv., DMF, rt, 18 h, 33%; c) TFA, 0 °C to rt, 30 min73%.

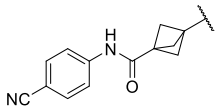
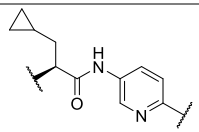
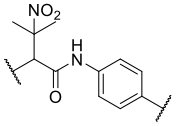
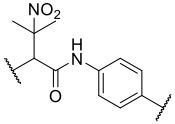
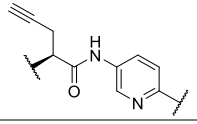
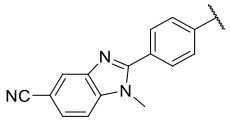
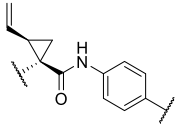
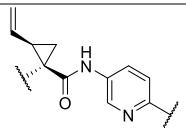
2.5.3.5.4 Combinatorial derivatives

In a second generation of novel cystobactamids, advantageous structural motifs were combined. Eight cystobactamids bearing two to three activity enhancing motifs were synthesized following the established synthetic procedures suitable for the different fragments (Table 17).

Table 17: Fragment coupling and deprotection towards cystobactamids with combined benficial strucutral motifs. Reaction conditions: a) 4 M HCl in 1,4-dioxane, 0 °C to rt, 15 min; b) piperidine, MeCN, rt, 2 h; c) western fragment 1.20-2.50 equiv., HATU 1.20-2.50 equiv. DIPEA 3.00-5.00 equiv., DMF, rt, 17-19 h; d) western fragment, $SOCl_2$, 80 °C, 2 h, then eastern fragment 1.00 equiv., NMM 2.00 equiv., CH_2Cl_2, 0 °C to rt, 18-20 h; e) $Ph(PPh_3)_4$ 10 mol%, $PhNH_2$ 3.30 equiv, THF, rt, 2-4 h; f) TFA, 0 °C to rt, 30 min; g) isolated; h) over three steps.

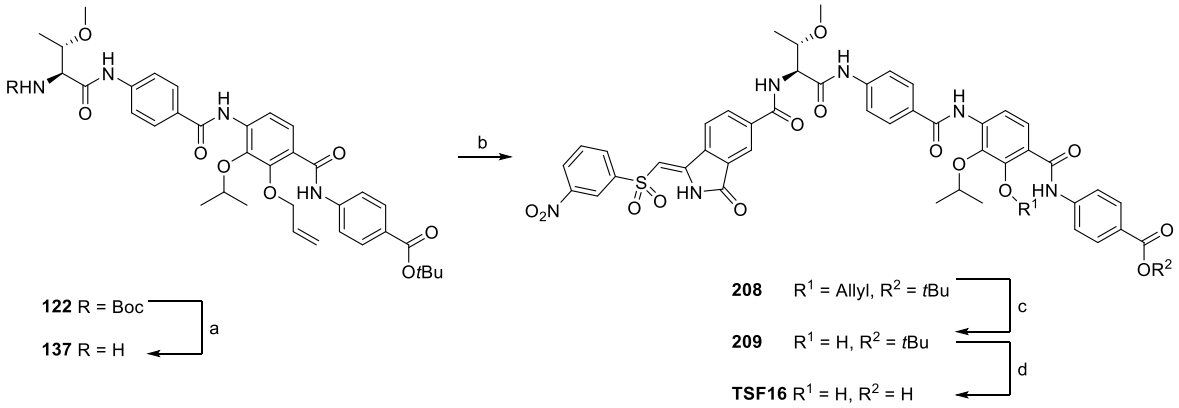


Entry	Western fragment residue	Western fragment	Central residue	LCDE	Step a) or b)	Step c) or d) (yield [%][g])	Step e) (yield [%][g])	Step f) (yield [%][g])
1		**22**		**128**	**184**[a]	**190**[b] (41)	**199** (56)	**TSD18** (78)
2		**23**				**191**[b] (64)	**200** (73)	**TSD49** (81)
3		**43**		**121**	**185**[a]	**192**[c] (72)	**201** (76)	**TSF53** (63)

4		**43**		**131**	**186**[b)]	**193**[c)] (90)	**202** (88)	**TSF54** (quant.)
5				**126**	**140**[b)]	**194**[c)] (73)	**203** (88)	**TSF62** (78)
6				**126**	**140**[b)]	**195**[c)] (66)	**204** (82)	**TSF64** (53)
7				**129**	**187**[a)]	**196**[c)] (63)	**205** (74)	**TSF60** (quant.)
8		**34**		**132**	**188**[a)]	**197**[c)]	**206** (32[h)])	**TSF84** (42)
9				**133**	**189**[a)]	**198**[c)] (66)	**207** (82)	**TSG28** (87)

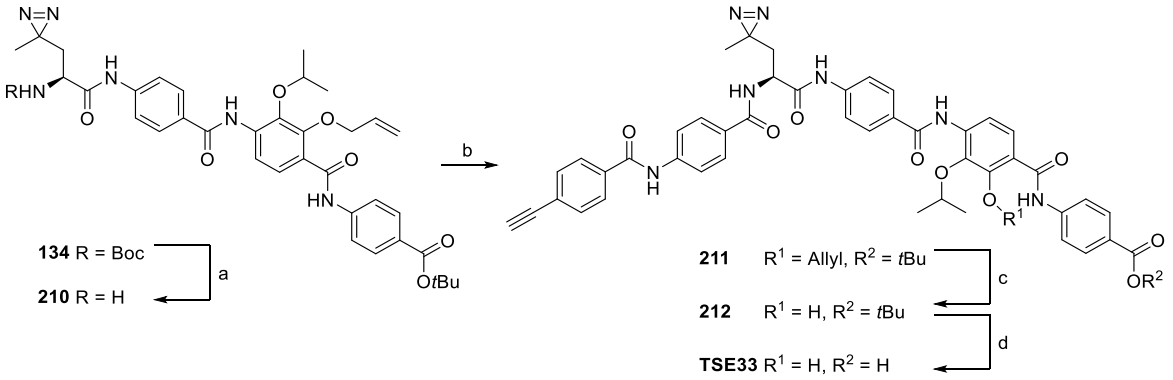
2.5.3.5.5 Miscellaneous derivatives

Unusual western fragment **39** was coupled to intermediate **137** after Boc-deprotection. **TSF16** was obtained after deallylation and ester cleavage in only 1% over three steps (Scheme 27). Side products during the reaction sequence decreased the yields and complicated the purification.



Scheme 27: Synthesis of **TSF16**. Reaction conditions: a) 4 M HCl in 1,4-dioxane, 0 °C to rt, 15 min; b) acid **39** 1.20 equiv., HATU 1.20 equiv., DIPEA 3.00 equiv., DMF, 0 °C to rt, 20 h; c) $PhNH_2$ 3.30 equiv., $Pd(PPh_3)_4$ 10 mol%, THF, rt, 90 min, d) TFA, 0 °C to rt, 30 min, 1% over three steps.

For photoaffinity labeling experiments, diazirine intermediate **134** was deprotected and coupled to compound **15** bearing a terminal alkine. Allyl deprotection and ester cleavage furnished cystobactamid **TSE33** (Scheme 28).

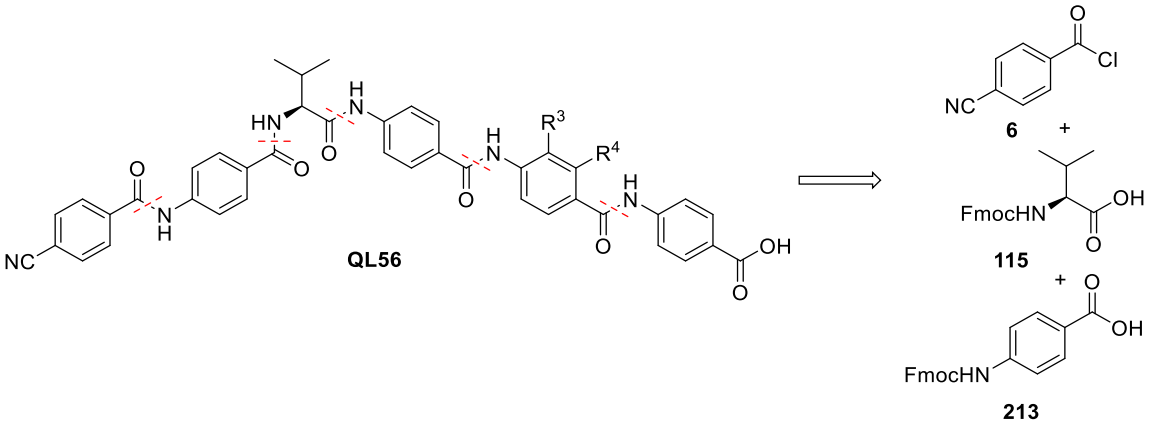


Scheme 28: Synthesis of photoaffinity label cystobactamid **TSE33**. Reaction conditions: a) 4 M HCl in 1,4-dioxane, 0 °C to rt, 15 min; b) acid **15** 1.20 equiv., HATU 1.20 equiv., DIPEA 3.00 equiv., DMF, 0 °C to rt, 20 h, 57% over three steps; c) $PhNH_2$ 3.30 equiv., $Pd(PPh_3)_4$ 10 mol%, THF, rt, 2 h, 37%, d) TFA, 0 °C to rt, 30 min, 62%.

2.5.3.5.6 Solid phase synthesis of a simplified cystobactamid derivative

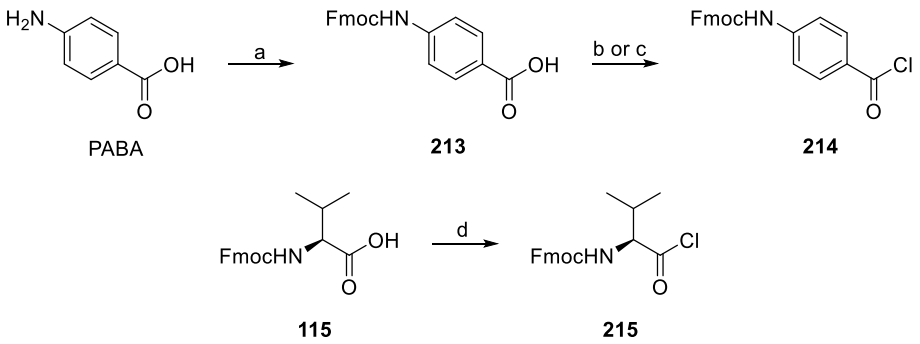
Besides the optimization of the biological profile of cystobactamids, the synthesis itself embodies an improvable topic tob e investigated. On one hand, a number of low or moderate yielding steps complicates uspscaling, which is important to provide sufficient quantities for a broad biological characterization. On the other hand, long reaction times and numerous

purification steps prolongate the synthesis. SPS is a well-established method that could possibly circumvent the mentioned drawbacks during peptide synthesis. However, cystobactamids represent peptides consisting of non-cannonical aromatic amino acids, which differ from cannonical amino acids significantly. During this project, the first SPS of the oligoarylamide natural products coralmycins was published by the PAYNE group, which incorporated also the non-aromatic amino acid asparagine in the SPS-sequence.[71] Aiming the SPS of **CN861**, a number of synthetic steps were suggested to be critical on solid phase. As in the liquid phase, the SPS was intended to be performed from *C*- to *N*-terminus. While in the established synthesis NO_2 groups are used for capping the amines, Fmoc protection in combination with an acid-labile resin is the most convenient strategy in SPS. Therefore, the synthesis of new building blocks was required. Fmoc deprotection is realized in basic milieu, in which β-methoxy asparagine **4** is prone to epimerize. Ring D bears an additional alcohol, which is originally allyl protected. The deprotection can be performed after cleavage in liquid phase or the allyl protection group can be exchanged. To overcome all the critical steps, a simplified target molecule was aimed. Cystobactamid **QL56** contains L-valine as linker, which generated promising results in SAR studies (c.f. chapter 2.5.1.1) and consists of PABA moieties without any alkoxy decoration. Retroynthetic analysis with respect to the Fmoc strategy leads to the three building blocks **6**, Fmoc- L-valine (**115**) (Scheme 29).



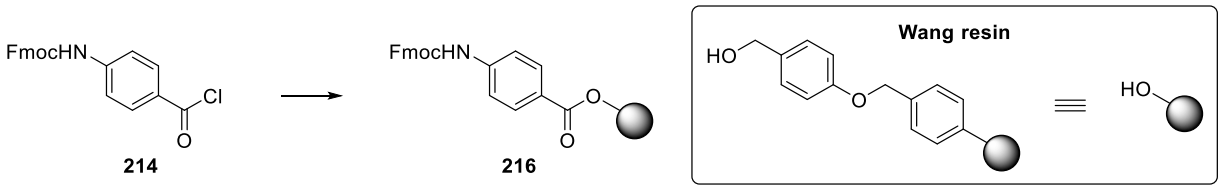
Scheme 29: Retrosynthesis for SPS of **QL56**.

Amide couplings on solid phase were intended via the acyl chlorides. Their high reactivity should ensure full conversion, to prevent the formation of side-products. Therefore, PABA was Fmoc-protected (Scheme 30). Acids **115** and **213** were transformed into acyl chlorides **214** and **215**, respectively, either with stochiometric amount or excess of $SOCl_2$ depending on wether it was used for resin loading or further coupling reactions.



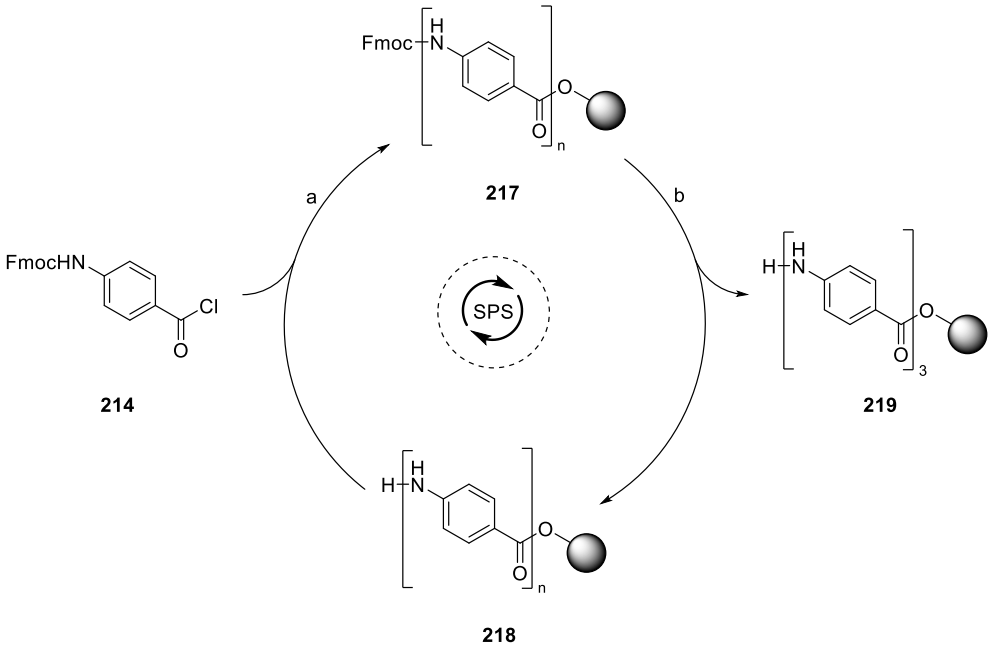
Scheme 30: Protection and activation of SPS building blocks PABA and Fmoc-L-valine (**115**). Reaction conditions: a) FmocCl 1.50 equiv., 10% $Na_2CO_{3(aq.)}$/1,4-dioxane, 0 °C to rt, 20 h, 77%; b) $SOCl_2$ 1.50 equiv., NMP, rt, 2 h, quant.; c) $SOCl_2$, 80 °C, 1 h, quant; d) $SOCl_2$ 10.0 equiv., CH_2Cl_2, 55 °C, 1 h, 97%.

The SPS of **QL56** started with the resin loading. Therefore, chloride **214** was shaken with acid-labile WANG resin in NMP (Scheme 31).



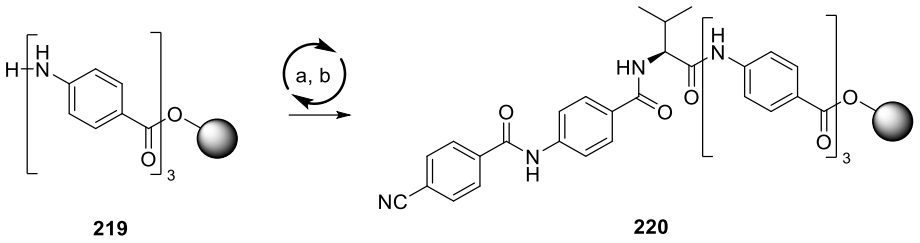
Scheme 31: Resin loading with WANG resin and acyl chloride **214**. Reaction conditions: WANG resin, **214** 10.0 equiv., NMP, rt, 18 h.

After loading on WANG resin, a deprotection/coupling-sequence which was iterated twice was performed to yield resin-bound trimer **219** (Scheme 32).



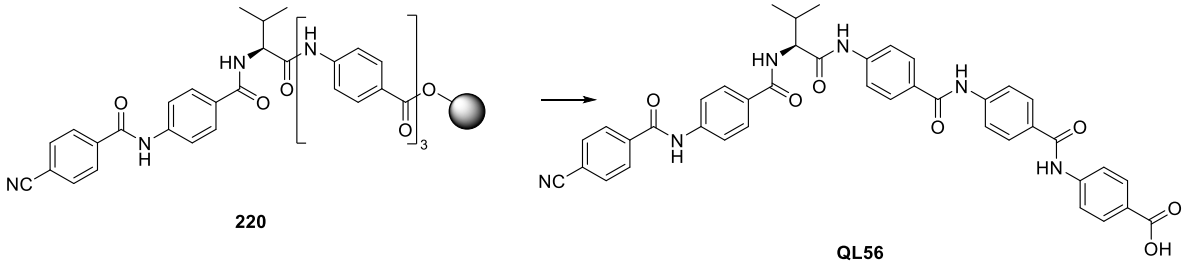
Scheme 32: SPS of trimer **219** consisting of three PABA units after 2 iterations. Conditions: a) **214** 3.00 equiv., DIPEA 6.00 equiv., CH_2Cl_2, rt, 18 h; b) piperidine/DMF (1:4), rt, 3+7 min.

Three further deprotection/coupling iterations were performed with acyl chlorides **215**, **214** and **6** to obtain resin-bound cystobactamid **220** (Scheme 33).



Scheme 33: SPS of resin-bound **220** from trimer **219**. Reaction conditions:a) i. **215**, ii. **214**, iii. **6** 3.00 equiv., DIPEA 6.00 equiv., CH_2Cl_2, rt, 18 h; b) piperidine/DMF (1:4), rt, 3+7 min.

TFA cleavage and subsequent HPLC purification furnished **QL56** in 22% over 12 steps (Scheme 34). It is noteworthy that the SPS of **QL56** proceeded smoothly without specific optimization.

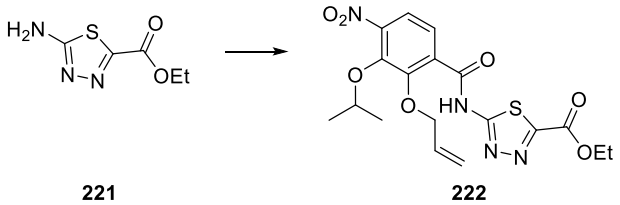


Scheme 34: Resin cleavage of **QL56**. Reaction conditions: TFA/CH_2Cl_2 (1:1), rt, 1 h, 22% over 12 steps.

Encouraged by the results of **QL56**, the SPS of **CN861** was adressed. However, first attempts to incorporate ring D into the SPS turned out not to be successful. The synthesis of Fmoc-deprotected ring D was also found to be a complicated task and the alternative NO_2 reduction on SPS was tested, but was also not successful.

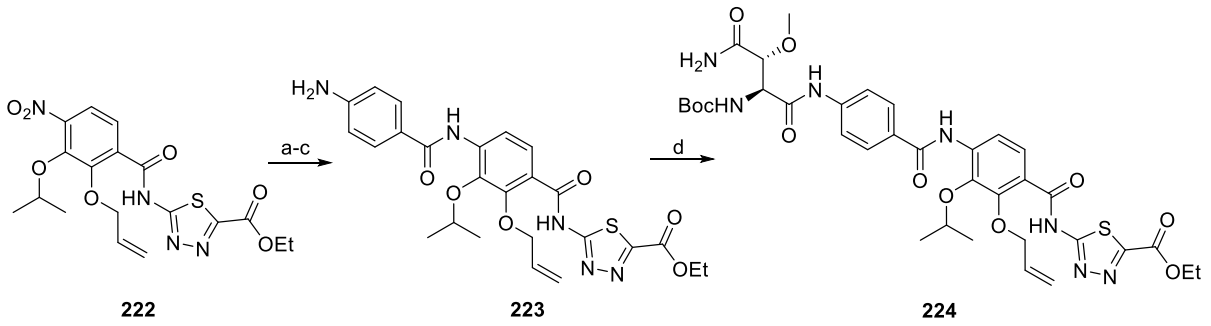
2.5.3.6 Preliminary work towards future cystobactamid derivatives

In addition to the described syntheses of the biologically evaluated cystobactamids, extensive studies on the extension of the project have already been initiated. Commercially available thiadiazole **221** was incorporated as ring E analog by coupling the free amine to ring D **7** (Scheme 35).



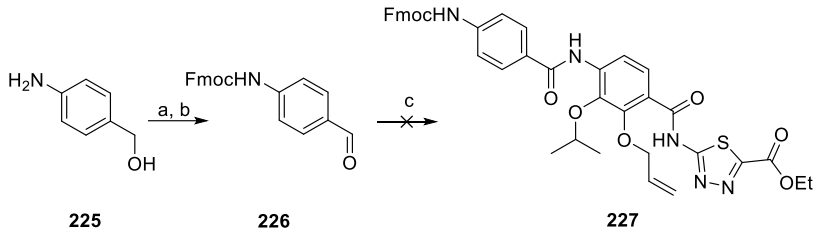
Scheme 35: Coupling between thiadiazole **221** and ring D **7**. Reaction conditions: **221** 1.10 equiv, $POCl_3$ 1.00 equiv., DIPEA 1.70 equiv., CH_2Cl_2, 0 °C, 1 h, 43%.

The ethyl ester as protecting group for the desired *C*-terminal carboxylic acid was expected to necessitate an alternative deprotection procedure as the established *tert*-butyl ester. However, the heterocycle turned out to effect the following synthetic steps so that alternative procedures were required even before the ester deprotection. Dimer **222** was chosen as model substrate to investigate the critical steps. During the NO_2 reduction with zinc in the presence of AcOH partial ester deprotection was observed. An alternative reduction procedure with $SnCl_2{\cdot}2H_2O$ was found to be suitable for this substrate, although full conversion required reaction times up to 6 d (Scheme 36). Shorter reaction times resulted in the isolation of the corresponding hydroxylamine. Coupling with 4-nitrobenzoyl chloride and subsequent NO_2 reduction furnished eastern fragment **223**, which was coupled with EEDQ to central amino acid **4** to yield intermediate **224**.



Scheme 36: Synthesis of eastern fragment **224** using alternative Sn-based NO_2 reduction and coupling to central amino acid **4**. Reaction conditions: $SnCl_2{\cdot}2H_2O$ 5.00 equiv., EtOH, rt, 4 d, 95%; b) 4-nitrobenzoyl chloride 1.60 equiv., pyridine 4.00 equiv., CH_2Cl_2, rt, 3 h, 84%; c) $SnCl_2{\cdot}2H_2O$ 5.00 equiv., EtOH, rt, 6 d, 60%; d) acid **4** 1.70 equiv., EEDQ 1.60 equiv., $CHCl_3$, rt, 24 h, 28%.

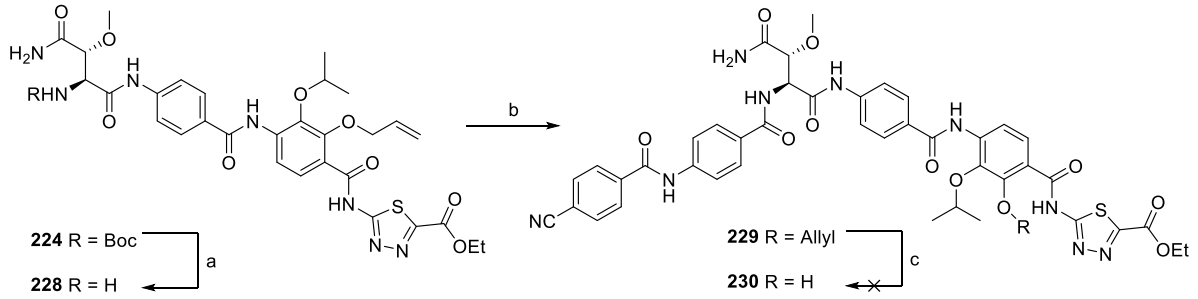
It shall be mentioned, that in parallel a different approach was investigated. Coupling of fragment DE **222** and aldehyde **226**, which was generated from alcohol **225** after Fmoc-protection and subsequent oxidation, under both reductive as well as oxidative coupling conditions should yield trimer **227** according to the literature (Scheme 37).[72] Unfortunately, trimer **227** was not isolated under the investigated conditions. Besides the recovery of aldehyde **226**, the hydroxylamine intermediate of fragment DE **222** was isolated in 54%. These findings confirm the observation of slow reduction of the NO_2 group. Interestingly, under these conditions no ethyl ester cleavage was observed.



225 226 227

Scheme 37: Alternative approach towards Fmoc-protected eastern fragment **229** via one-pot reaction between aldehyde **226** and fragment DE **222** under both oxidative and reductive conditions. Reaction conditions: a) FmocOSu 1.00 equiv., $NaHCO_3$ 2.00 equiv, H_2O/MeCN, 0 °C to rt, 18 h, 93%; b) MnO_2 10.0 equiv., THF, rt, 18 h; c) **222**, Zn 4.00 equiv., AcOH 2.00 equiv., $NaClO_3$ 1.00 equiv., EtOH/H_2O (3:1), 35 °C, 6 h.

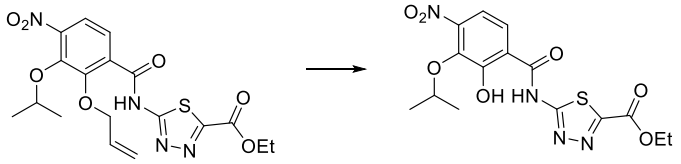
The following reactions were performed in accordance to the standard procedures towards protected intermediate **230** (Scheme 38). No conversion was observed during deallylation of compound **229** under the use of catalytic Pd^0. It was hypothesized that the sulfur containing heterocycle deactivates the catalyst. Consequently, an over-stochiometric amount of Pd^0 (1.20 equiv.) was tested but without success. The reaction mixture turned dark and an inseparable mixture of compounds was obtained, while no product formation was detected as judged by LC/MS analysis.



Scheme 38: Final fragment coupling towards cystobactamid precursor **230**. Reaction conditions: a) 4 M HCl in 1,4-dioxane, 0 °C to rt, 15 min; b) acid **3** 1.20 equiv., HATU 1.20 equiv., DIPEA 3.00 equiv., DMF, 0 °C to rt, 18 h, 58%; c) $PhNH_2$ 3.30 equiv., $Pd(PPh_3)_4$ 10 mol%, THF, rt, 90 min.

At this point, the focus was shifted back to fragment **222**, which served as model substrate. Alternative deallylation procedures were tested (Table 18). Under the standard conditions no product was isolated (entry 1). LEWIS acid mediated deallylation with $AlBr_3$ in the presence of Me_2S was not fruitful (entry 2 and 3).[73] However, under refluxing conditions using $CeCl_3 \cdot 7H_2O$ and NaI the desired alcohol **231** was formed in 95% yield (entry 4).[74] Alternatively, an oxidative one-pot deallylation via repeated dihydroxylation and periodate cleavage was performed with OsO_4 and $NaIO_4$ in the presence of NMO, but alcohol **231** was not obtained (entry 4).[75] Unfortunately, the conditions of entry 4 were not applicable to compounds with complete cystobactamid carbon backbone.

Table 18: Optimization of the deallylation of model substrate **222**.

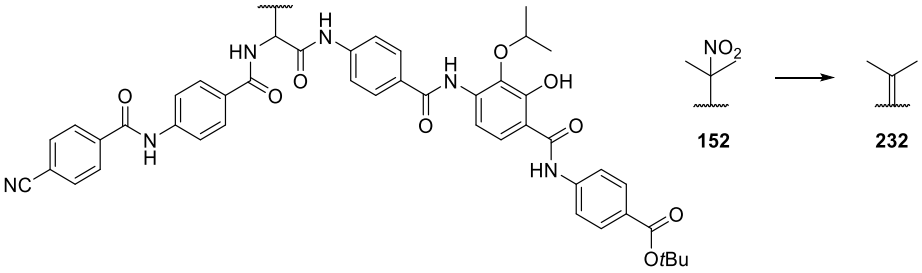


222 **231**

entry	reagents (equiv.)	solvent / conditions	Yield [%]
1	$Pd(PPh_3)_4$ (0.10) $PhNH_2$ (3.30)	THF, rt, 23 h	-
2	$AlBr_3$ (8.00)	CH_2Cl_2/Me_2S (2:1), 0 °C, 2 h	nc
3	$AlBr_3$ (8.00)	CH_2Cl_2/Me_2S (2:1), rt, 18 h	nc
4	$CeCl_3 \cdot 7H_2O$ (3.00) NaI (3.00)	MeCN, 90 °C, 6 h	95%
5	NMO (3.00) OsO_4 (0.20) $NaIO_4$ (3.00) piperidine (1.00)	1,4-dioxane/H_2O/*t*BuOH (6:3:1), 60 °C, 6 h	-

Further investigations were started using intermediate **152**, which was considered to be a suitable precursor for a NO_2 elimination.[76] The late-stage modification would lead to a rigidified cystobactamid with dehydrovaline as central amino acid. The basic conditions had to be chosen carefully. Initial attempts with LiOH resulted in amide hydrolysis, especially between the central amino acid and the eastern fragment (Table 19, entries 1 and 2). On the other hand, organic base DABCO led to no conversion of the starting material after 72 h (entry 3). In parallel, DBU was utilized as alternative base. Dehydro cystobactamid **232** was isolated after 72 h in 74% yield (entry 4). The yield was increased to 93% by shortening the reaction time to 20 h (entry 5).

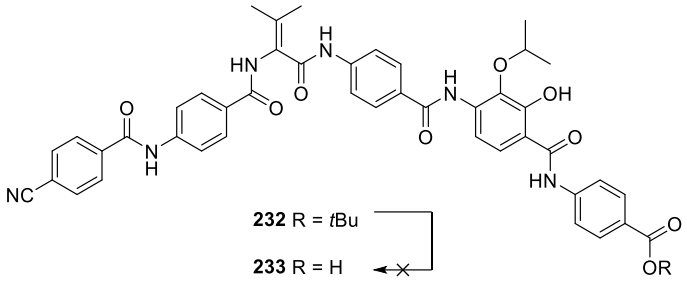
Table 19: Optimization of the NO_2 elimination of compound **152** towards cystobactamid with dehydrovaline as central amino acid.



152 **232**

Entry	Solvent	Base (equiv.)	Temp. [°C]	Time [h]	result
1	H_2O/THF	LiOH (24.0)	50	2	decomposition
2	H_2O/THF	LiOH (24.0)	0 to rt	24	amide hydrolysis
3	CH_2Cl_2	DABCO (7.0)	0 to rt	72	no conversion
4	CH_2Cl_2	DBU (3.0)	0 to rt	72	74%
5	CH_2Cl_2	DBU (3.0)	0 to rt	20	93%

Surprisingly, the final ester cleavage using TFA was unsucessful under the established conditions and neither product **233** nor the starting material could be isolated (Scheme 39).



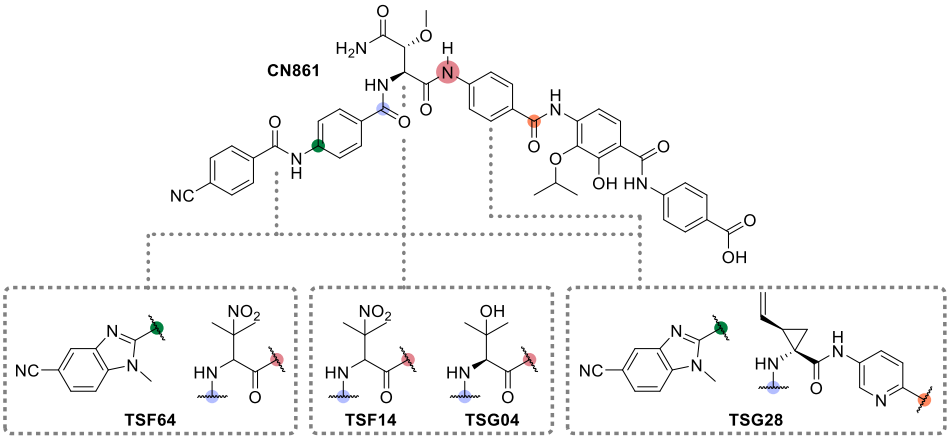
Scheme 39: Unsucessful ester cleavage towards dehydro cystobactamid **233**. Reaction conditions: TFA, 0 °C to rt, 30 min.

2.6 Conclusion and Outlook

In this work the synthesis of cystobactamids with optimized antibacterial profile was aimed. The current frontrunner **CN861**[32] served as starting point for the SAR studies. In exchange with all OpCyBac collaborators the biological data, especially MIC values, of cystobactamids were interpreted. Consequently, new structural proposals for enhanced antibacterial properties were specified. A variety of novel cystobactamids, depicted in Figure 8, were synthesized and provided to the OpCyBac consortium for antibacterial testings.With focus on the central amino acid, simplified cystobactamid analogs, e.g. **TSF14**, were found with superior activity compared to **CN861** (Scheme 40). On the other hand, amide replacements within the western fragment proved to be benificial, while modifications on the eastern fragment were hardly tolerated. Different promising motifs, found within the OpCyBac consortium, were combined successfully. In addition, the resynthesis of **861-2**, **CN861** and **DK405** in larger quantities was accomplished. The resynthesized cystobactamids were utilized as reference compounds or used for more in-depth biological profiling.

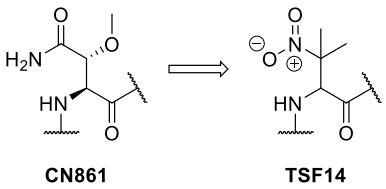
In conclusion, the OpCyBac[36] portfolio of novel cystobactamids was extended. The current frontrunner **CN861** was outraced by numerous analogs in terms of antibacterial activity. Four analogs **TSF14**, **TSF64**, **TSG04** and **TSG28** were developed with up to nanomolar activity against representitives of all ESKAPE pathogens (Table 20).

Table 20: MIC values (µg/mL) of selected cystobactamids analogs compared to **CN861** and **CIP**. a) BAA-1710; b) (S83L, D87N, S80I, ΔmarR, ΔacrR); c) (waaC::Tn30); d) (QnrA1); e) ΔmexAB; f) BAA-2468, g) PAO1 instead of PA14; color code for activity: green = good, orange = moderate, red = insufficient.



		CIP	CN861	TSF14	TSF64	TSG04	TSG28
A. baumannii	DSM3008	0.1	1	0.03	0.06	nd	nd
	ATCC[a)]	<6.4	8	0.38	<0.03	0.05	0.025
	CIP-105742	0.05	0.25	<0.0038	<0.03	nd	nd
	CIP-107292	<6.4	<64	0.5	<0.03	3	0.06
	R835	<6.4	<64	0.5	<0.03	nd	nd
E. coli	LM705[b)]	<6.4	0.64	1	0.125	0.25	0.5
	ATCC-25922	0.01	0.25	<0.06	<0.03	<0.001	<0.003
S. aureus	ATCC-29213	0.8	0.125	<0.06	0.125	<0.003	<0.003
K. pneumoniae	CIP-104298	0.5	16	<0.3	1	nd	nd
	KP10581[c)]	<6.4	2	0.25	0.125	0.025	0.006
	R1525[d)]	<6.4	16	1.25	2	nd	nd
P. aeruginosa	PA14	0.125	16	1	8	4[g)]	1[g)]
	PA14[e)]	0.01	0.5	8	1	nd	nd
E. cloacae	ATCC[f)]	<6.4	32	2	2	0.2	0.25
E. aerogenes	CIP-106754	<6.4	4	2	4	1	1(2)
E. faecium	DSM-17050(VRE)	3.2	nd	<0.06	<0.03	<0.003	<0.003

Future work should include the finalization of the analogs described in chapter 2.5.3.6. The structural evolution from **CN861** to **TSF14** comprises several structural differences. The significance of the second methyl group or the possibility of other NO_2 bioisosters remains to be clarified. Furthermore, the relevance of the stereoconfiguration within the central amino acid is yet to be solved.



Scheme 40: Structural evolution from **CN861** to **TSF14**.

With a variety of benificial motifs in hand, SAR studies can be continued. The crucial role of the central amino acid for activity was emphasized. While the antibacterial activity was enhanced significantly during this studies, other pharmacological properties (e.g. solubility) are now improvable and play a major role in the development towards a new lead structure. Therefore, SAR studies are necessary to locate structural sides mechanistically relevant for activity and consequently reveal flexibility within the cystobactamid scaffold. It is noteworthy, that organic synthesis is still the inevitable bottleneck of drug discovery.[77] First investigations of a SPS approach towards cystobactamids were accomplished and should be extended in future work to find a solution for the rapid provision of drug quantities.

This work as part of the close collaboration between academic and industrial partners within the OpCyBac project addressed a major challenge of recent drug discovery. The lack of new antibiotic classes requires hand-in-hand practice of academia and industry to efficiently overcome MDR.

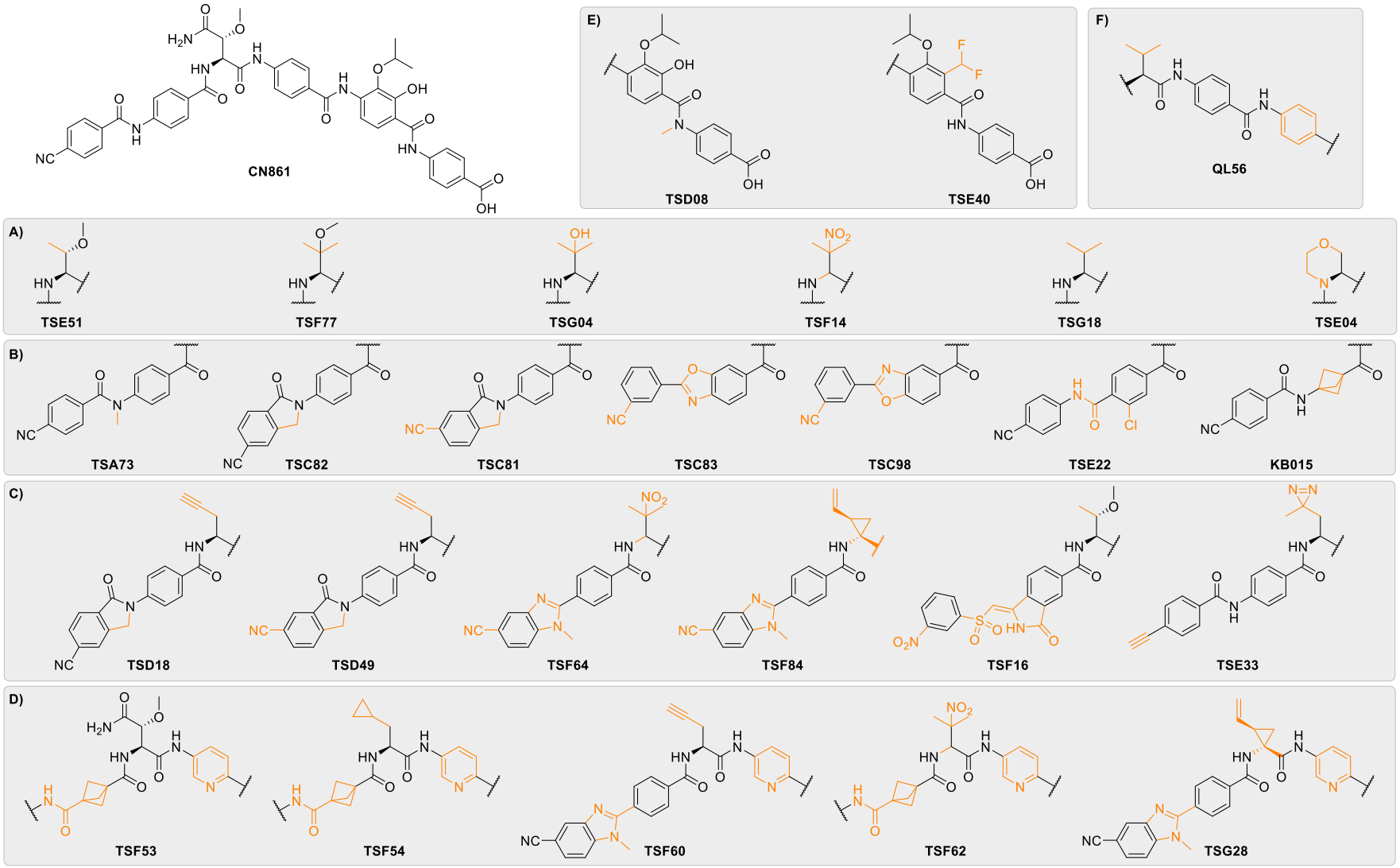


Figure 8: Overview of synthesized novel cystobactamids with modified linker (A); western fragment (B); western fragment and linker (C); western fragment, linker and ring C (D), eastern fragment (E); linker and ring D (F)

3 Myxovalargin A

Myxovalargins were first described in 1981 as an isolate of *Myxococcus fulvus* strain Mx f65. Along with the myxovalargin isolate antibacterial activity against a variety of bacteria was observed with MICs between 0.3-5 µg/mL for GRAM-positive and 6-100 µg/mL for GRAM-negative strains.[78,79] In 1987 the peptidic structure of Myxovalargin A (**234**) was suggested.[80] Later, elucidation of the biosynthesis (see chapter 3.1) and feeding experiments coupled with mass spectrometry disproved the proposed stereoconfiguration of the valines in position 7 and 10. In this work Myxovalargin A (**234**) is illustrated with the revised stereoconfiguration (Figure 9). In the course of the biosynthesis investigations the biotechnological production was optimized. In *Myxococcus fulvus* strain Mcy6431 fermantation scale was achieved to isolate Myxovalargin A (**234**) in a yield of 23.9 mg/L, allowing a detailed biological profiling of the natural product.[81]

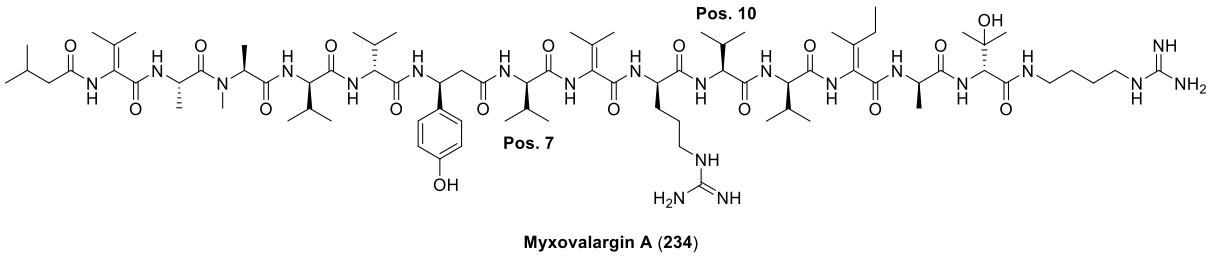


Figure 9: Structure of Myxovalargin A (**234**).

3.1 Biosynthesis

The NRPS-type biosynthesis of Myxovalargin A (**234**) (Figure 10) was studied on *Myxococcus fulvus* strain Mcy6431. The genes mxv A-E encode 14 modules that represent the essembly line. Six further genes mxv F-K are located on the BGC. The biosynthesis starts with the loading of isovaleryl-CoA by mxvB. Stepwise essembling over the 14 modules yields Myxovalargin A (**234**). The myxovalargin scaffold consists of mainly non-proteinogenic amino acid building blocks: D-valine, D-alanine, D-arginine, (*S*)-β-tyrosine, dehydrovaline, dehydroisoleucine and β-hydroxyvaline. Epimerases included in the corresponding modules are responsible for the tansformation of the proteinogenic amino acids to the D-configated amino acids. A methyltransferase on module 3 *N*-methylates the loaded alanine. (*S*)-β-Tyrosine derives from L-tyrosine catalyzed by a 2,3-aminomutase encoded by mxvJ. The dehydro amino acids as well as the β-hydroxyvaline are assumed to result from a hydroxylation/dehydration sequence by mxvH. An additional C-domain is suggested to incorporate the *C*-terminal agmatine, transformed from arginine by an ADC, and therefore terminate the biosynthesis.[81]

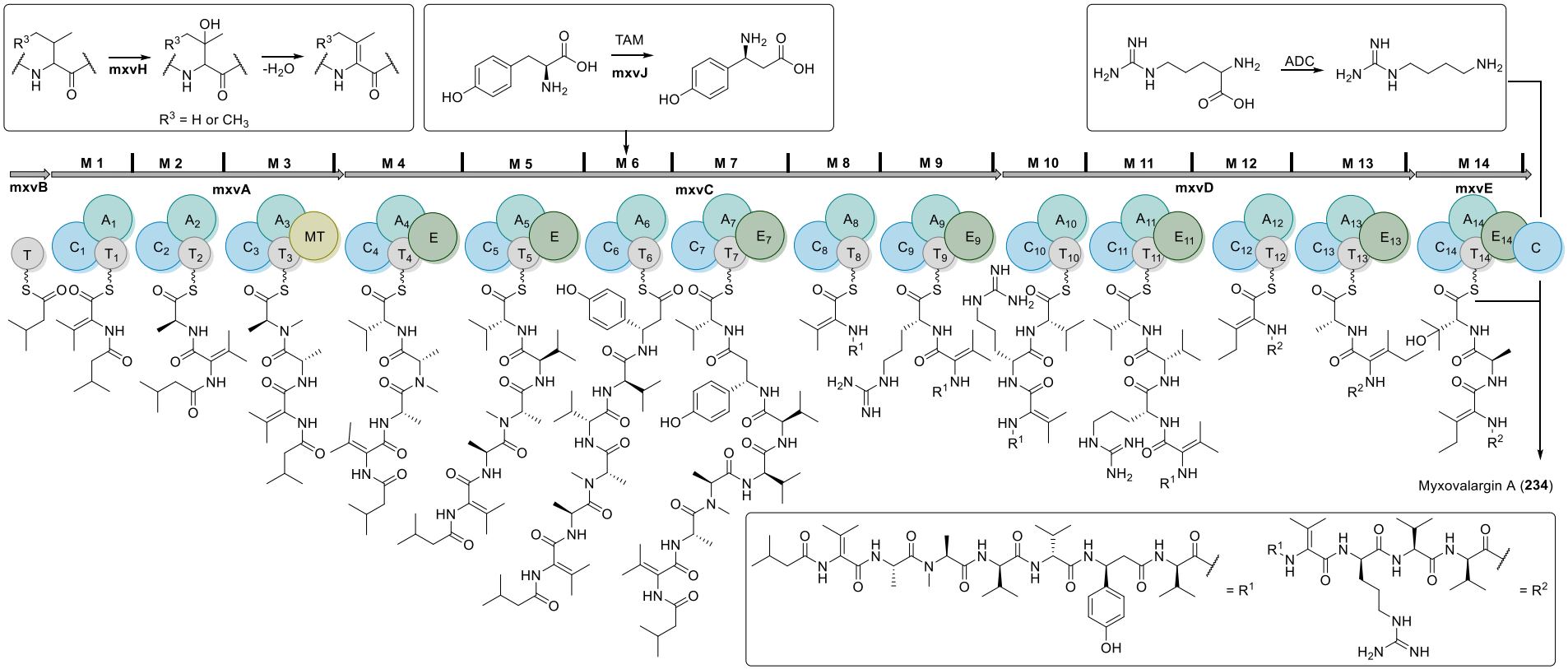


Figure 10: Biosynthesis model of Myxovalargin A (**234**). ADC = arginine decarboxylase, domains: T = thiolation, C = condensation, A = adenylation, MT = methyltransferase, E = epimerization.

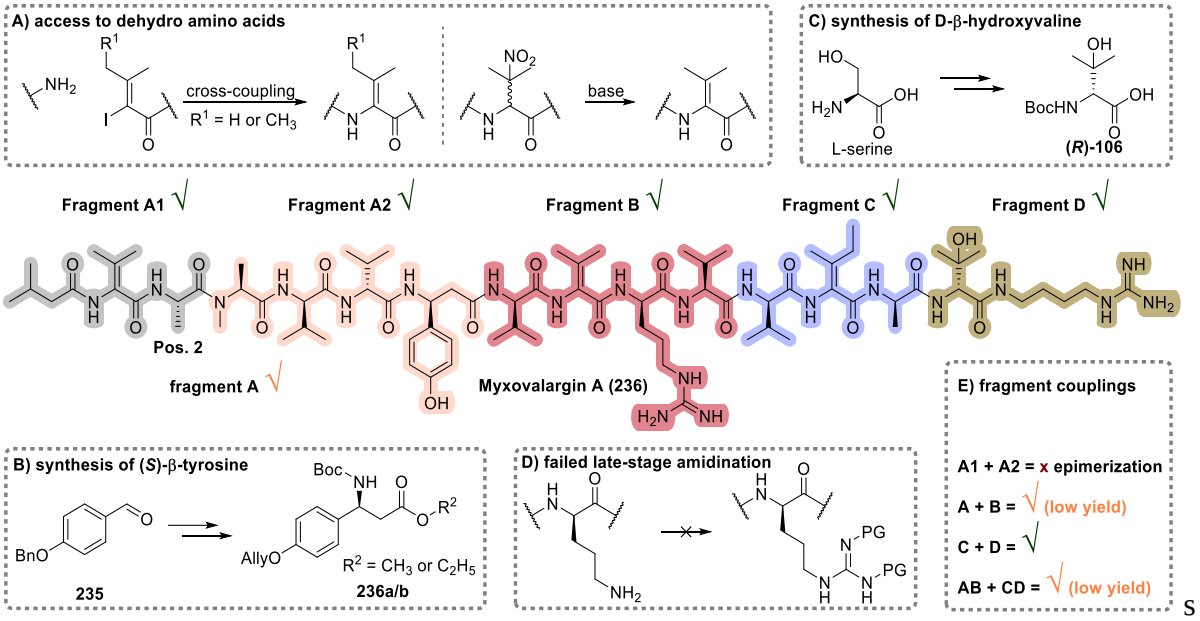
3.2 Biological activity and mode of action

Early reports on myxovalargin already demonstrated the antibacterial activity of myxovalargin against various GRAM-positive and -negative bacteria.[79,82] Later, Myxovalargin A (**234**) was found as a potent canditate for growth inhibition of *Mycobacterium tuberculosis*, a pathogen that causes tuberculosis.[83,84] The bacterial ribosome was identified as target of the natural product. Therefor, myxovalargin inhibits binding of the initiator tRNA on the large ribosomal subunit. Blocking the exit tunnel prohibits the protein biosynthesis on a late stage of the translation initiation. Pharmacokinetic properties of Myxovalargin A (**234**) were satisfying and *in vivo* efficacy was demonstrated. Unfortunately, administered Myxovalargin A (**234**) displayed toxicity in a mouse model of tuberculosis. Since the target and mode of action are known, rational design of myxovalargin analogs with reduced toxicity could help to overcome the described burden towards a new antibiotic with medicinal application. Therefore, a total synthesis program was started at an early stage to not only confirm the structure, but also provide a tool to modify the myxovalargin scaffold for improved biological properties.[81]

3.3 Preliminary studies towards the total synthesis of Myxovalargin A

The total synthesis program was initiated by GILLE and later taken up by SIEBKE and KÖSEL. The natural product – at that time with incorrect stereoconfiguration – was retrosynthetically divided into four fragments (Scheme 41, also c.f. Scheme 42). The synthesis of fragments A-D was accomplished. Therefore, syntheses for the building blocks non-proteinogenic amino acids (*S*)-β-tyrosine **236** and D-β-hydroxyvaline (*R*)-**106** were established (Scheme 41 B & C). One major challenge was the incorporation of the unnatural dehydro amino acids in fragments A-C.[85] The cross-coupling between amines and vinyl iodides gave access to the mentioned fragments (Scheme 41 A left).[86] However, low yields, limited scalability and complicated protecting group strategies hampered the synthesis of sufficient quantities. First attempts of fragment couplings were conducted and the myxovalargin backbone was obtained (Scheme 41 E). The late-stage amidination of the sidechain amine in fragment B failed (Scheme 41 D).[85] SIEBKE continued the synthetic studies towards both Myxovalargins A (**234**) with incorrect and revised stereoconfiguration. With an alternative retrosynthesis by dividing fragment A further into fragments A1 and A2 the upscaling was aimed. Utilizing β-nitrovaline as precursor for the dehydrovalines proved to be fruitful. Nitroelimination improved the overall yield and scalalibity of fragment A1 (Scheme 41 A right). On the other hand, a modified route towards

fragment A2 was established. Fragment coupling towards fragment A resulted in epimerization of alanine at position 2. The epimerization occured with all investigated conditions and fragmentations of fragment A (Scheme 41 E).[68] The synthesis of both fragments B with incorrect and revised stereoconfiguration was accomplished via an adopted synthesis from GILLE[85] and implementation of the nitroelimination with β-nitrovaline as building block (Scheme 41 A right). During the synthesis of fragment CD guanidination of fragment D and coupling of fragments C and D were not reproducable in accordance to GILLE. Modified conditions enabled the synthesis of fragmend CD. Ultimately, SIEBKE worked out that epimerization and protecting group strategy complicate the total synthesis of Myxovalargin A (**234**).[68]



Scheme 41: Preliminary studies towards the total synthesis of Myxovalargin A (**234**); √ = synthesis accomplished, √ = synthesis accomplished with need for optimization.

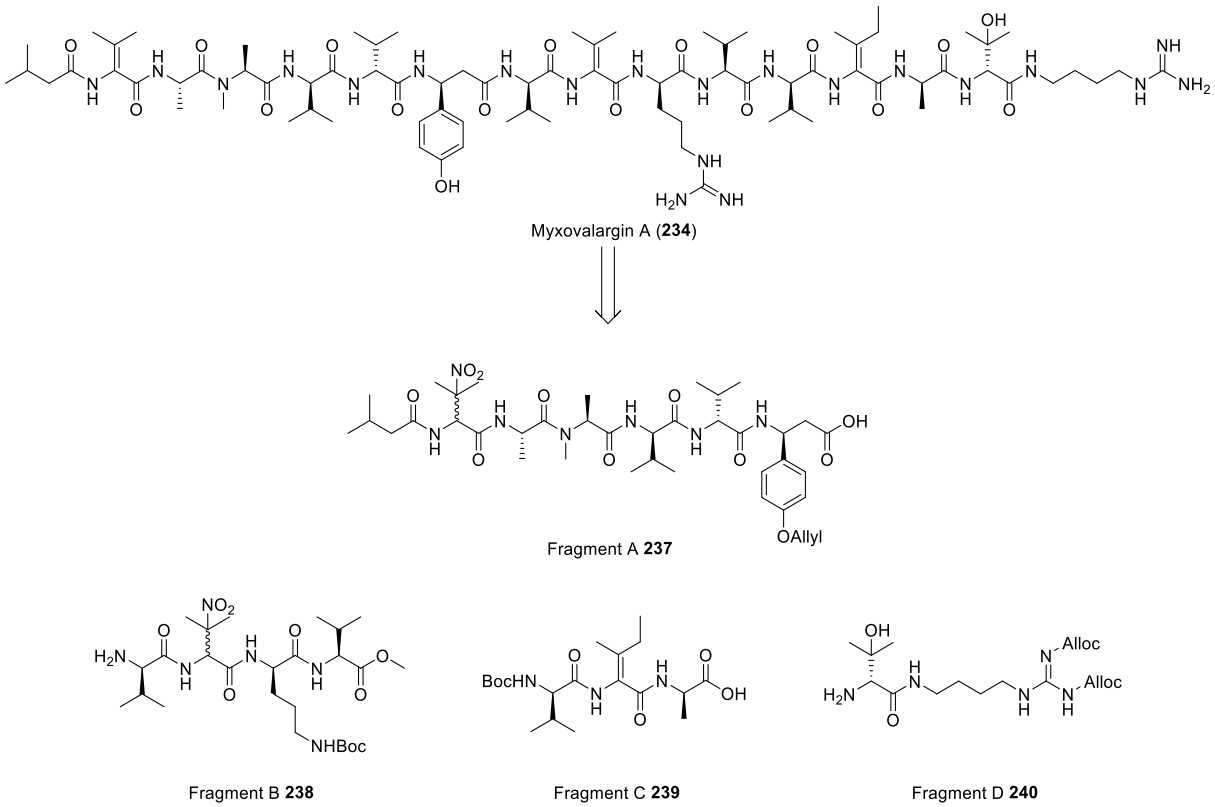
3.4 Project aims

Preliminary studies towards the total synthesis of Myxovalargin A (**234**) were performed by DR. FRANZISKA GILLE[85,86] and DR. MAIK SIEBKE[68] as described above. In this work – in cooperation with DR. TERESA KÖSEL[87] – the completion of the total synthesis was aimed to verify the postulated stereochemistry.[80] Therefore a SPS approach was considered to prevent epimerization during peptide couplings. A combination of liquid-phase synthesis and SPS seemed reasonable. Furthermore, a synthetic access to Myxovalargin A (**234**) paves the way for provision of analogs with reduced toxicity, contributing to the fight against infectious diseases like tubercolusis, the wold's top infectious killer in accordance to the WHO.[83,84]

3.5 Results and discussion

3.5.1 Retrosynthesis

The peptidic natural product Myxovalargin A (**234**) was retrosynthetically divided into four fragments A-D **237**-**240** by amide bound cleavage (Scheme 42). This fragmentation ensured the late introduction of the susceptible structural motifs like dehydro amino acids, β-hydroxyvaline or the guanidine residues.[85] However, for the SPS approach the *C*- to *N*-terminus Fmoc protecting strategy was choosen and might not follow the depicted retrosynthetic analysis. By that time, the length of the amino acid sequence from solid-phase was not predifined and might succeed in combination with liquid-phase synthesis of certain fragments.

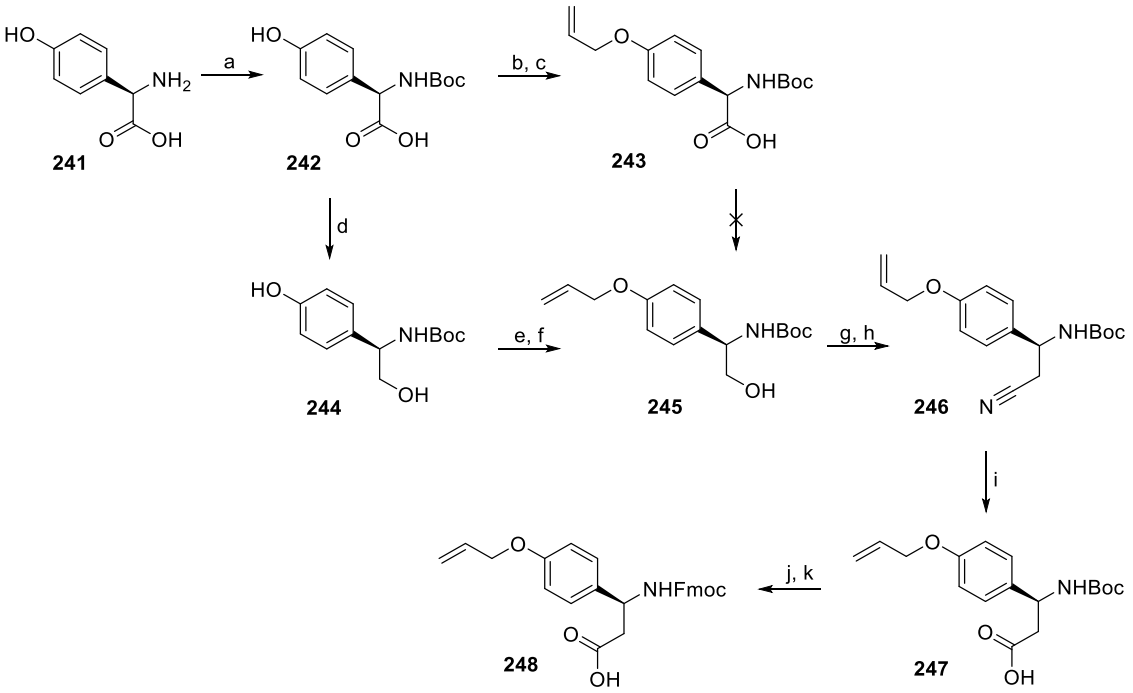


Scheme 42: Retrosynthesis of Myxovalargin A (**234**) in accordance to GILLE.[85]

3.5.2 Synthesis

3.5.2.1 -(*S*)-Fmoc-β-tyrosine

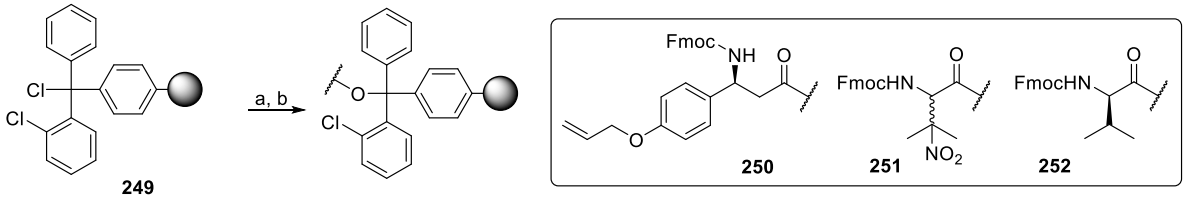
For fragment A **237** the unnatural β-tyrosine building block allyl-protected (*S*)-Fmoc-β-tyrosine (**248**) was synthesized from the non-proteinogenic (*R*)-4-hydroxyphenylglycine (**241**) (Scheme 43). Elongation of the carbonchain of **241** by one carbon atom gave access to (*S*)-Fmoc-β-tyrosine (**248**), while the stereocenter was switched formally. Boc-protection of the starting material yielded *N*-protected amino acid **242**. Allylation of the phenol and the acid and subsequent saponification furnished acid **243**, which could not be reduced to primary alcohol **245** under the tested conditions. Alternatively, acid **242** was reduced first. Diol **244** was selectively allyl protected by prior formation of the required sodium salt. Mesylation of primary alcohol **245** followed by treatment with NaCN afforded nitrile **246**, which could be saponificated to yield (*S*)-Boc-β-tyrosine **247**. At this point, it was not clearified if the synthesis of Myxovalargin A (**234**) would be achieved by batch synthesis or a new SPS approach. The SPS approach required a Fmoc protected amine. The change from the Boc to the Fmoc protecting group in (*S*)-Fmoc-β-tyrosine (**248**) was accomplished under standard conditions.



Scheme 43: Synthesis of (*S*)-Boc-β-tyrosine (**247**) and (*S*)-Fmoc-β-tyrosine (**248**). Reaction conditions: a) $NaHCO_3$ 5.00 equiv., Boc_2O 1.10 equiv, 1,4-dioxane/H_2O (1:1), rt, 20 h, quant.; b) K_2CO_3 4.00 equiv., allyl bromide 2.50 equiv., DMF, rt, 17 h; c) NaOH 2.00 equiv., MeOH, 35 °C, 2 h, 93% over two steps; d) BH_3 2.00 equiv., THF, 0 °C, 2 h, 80%; e) NaOH 1.00 equiv., MeOH, rt, 1 h; f) allyl bromide 1.20 equiv., DMF, rt, 3 h, 90% over two steps; g) MsCl 1.50 equiv., Et_3N 1.50 equiv., CH_2Cl_2, 0 °C, 1 h; h) NaCN 3.00 equiv., DMSO, 40 °C, 4 h, 59% over two steps, i) NaOH 10.0 equiv., EtOH, 90 °C, 4 h, 98%; j) TFA 50.0 equiv., CH_2Cl_2, 0 °C, 15 h; k) FmocCl 1.20 equiv, Na_2CO_3, 1,4-dioxane/H_2O (1:1), rt, 16 h, 97% over two steps.

3.5.2.2 Solid phase synthesis towards Myxovalargin A

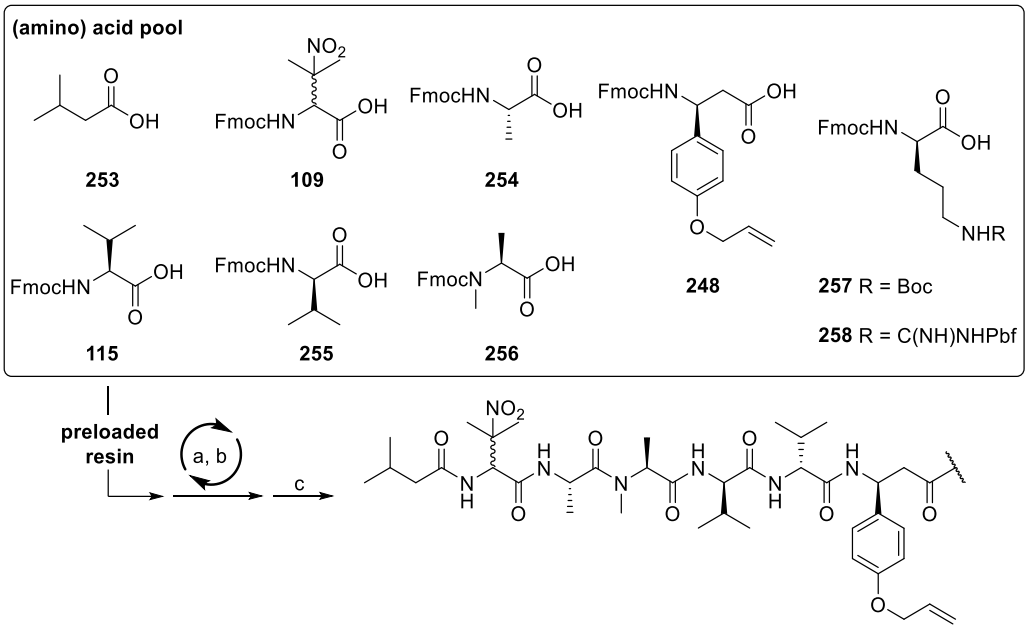
In collaboration with DR. TERESA KÖSEL[87] and the Institute for Medicinal Chemistry Helmholtz Munich[88] the SPS towards myxovalargin was investigated at a Liberty Blue™ Automated Microwave Peptide Synthesizer from CEM. Chlorotrityl resin **249** was preloaded with (*S*)-Fmoc-β-tyrosine (**248**),[87] nitrovaline **109** and Fmoc-D-valine (**255**) in batch to avoid excess of the starting material (Scheme 44).

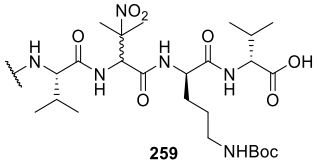
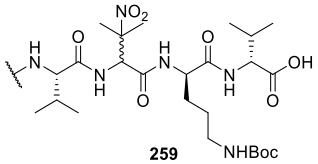
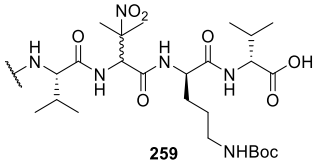
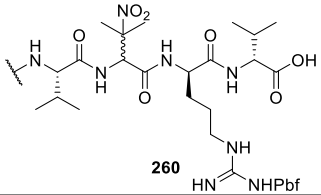
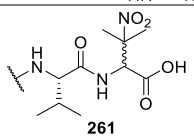


Scheme 44: Resin preloading with different amino acids. Reaction conditions: a) $SOCl_2$ 1.20 equiv., pyridine 2.40 equiv., CH_2Cl_2, 0 °C to 80 °C, 3 h; b) **109**, **248** or Fmoc-D-valine (**255**) 1.20 equiv., DIPEA 5.00 equiv., CH_2Cl_2, rt, 14 h.

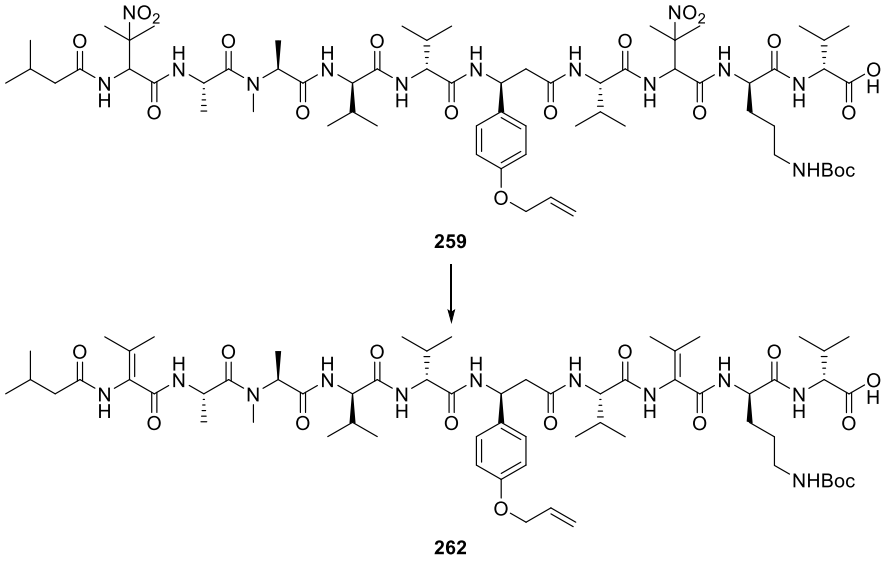
Loaded resins **250**-**252** were ready to serve as starting materials in the subsequent SPS (Table 21). First investigations aimed myxovalargin with incorrect stereochemistry. A sequence of standardized coupling and deprotection steps were accomplished with a pool of (amino) acids. Deprotection was realized with piperazine. Amide couplings were exerted with DIC and Oxyma. The corresponding peptides were released from the resin under acidic conditions. In a first attempt fragment AB was aimed. Desired product **259** was formed, but partially Boc deprotected, presumably during the acidic TFA cleavage (entry 1). Releasing final peptide **259** with FA instead caused a decreased yield (entry 2). An improvement was achieved by utilizing hexafluoroisopropanol (HFIP) as mild acid (entry 3).[89] However, the diastereomeric ratio was insufficient. Alternatively, Boc protected ornithine **257** was substituted with Pbf protected arginine **258**, but corresponding product **260** was not obtained (entry 4). By shortening the peptide sequence to avoid the critical arginine residue, loaded resin **251** was used, albeit desired peptide **261** was not isolated (entry 5). Eventually, SPS synthesis of fragment A **237** starting from loaded resin **250** succeeded in satisfactory yield (entry 6).[81]

Table 21: SPS synthesis towards myxovalargin. Reaction conditions: a) (amino) acid 5.00 equiv., DIC 5.00 equiv., Oxyma™ 5.00 equiv., DMF, 75-90 °C, 15-110 s; b) piperazine 5.00 equiv., EtOH/NMP, 75-90 °C, 15-50 s; c) 1% TFA in CH_2Cl_2, 2 min (4x); d) isolated; e) 1% FA in CH_2Cl_2, 2 min (4x) instead of c); f) HFIP/CH_2Cl_2 (1:1), rt, 3 min (4x) instead of c); g) isolated after following NO_2 elimination, see Scheme 45.



Entry	preloaded resin	(amino) acid sequence	Product residue	Yield [%][d]
1	**252**	**257**, **109**, **115**, **248**, **255**, **255**, **256**, **254**, **109**, **253**	 **259**	Partial Boc deprotection
2[e]	**252**	**257**, **109**, **115**, **248**, **255**, **255**, **256**, **254**, **109**, **253**	 **259**	16%
3[f]	**252**	**257**, **109**, **115**, **248**, **255**, **255**, **256**, **254**, **109**, **253**	 **259**	26%, d.r. = 2:1[g]
4	**252**	**258**, **109**, **115**, **248**, **255**, **255**, **256**, **254**, **109**, **253**	 **260**	-
5	**251**	**115**, **248**, **255**, **255**, **256**, **254**, **109**, **253**	 **261**	-
6	**250**	**255**, **255**, **256**, **254**, **109**, **253**	 **237**	68%

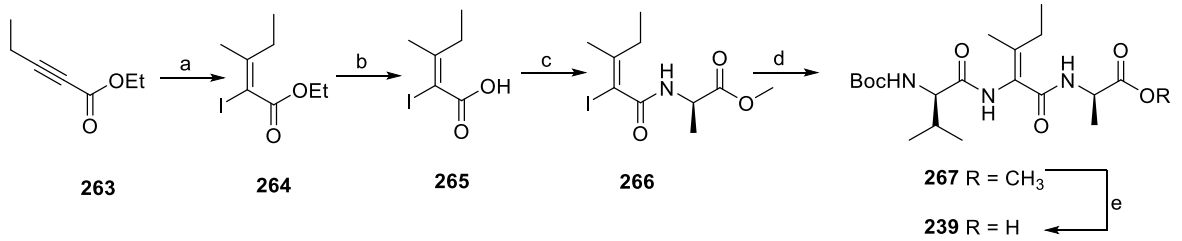
The incorporated nitrovalines should serve as precoursors for the desired dehydrovalines.[68,76] NO_2 elimination was tested with intermediate **259** (Table 21 entry 2, Scheme 45). Qualitative analysis via LC/MS revealed the consumption of starting material **259**, while product **262** was formed, confirming the basic conditions to be suitable. Nevertheless, low yields towards fragment AB **262** or the appearance of diastereomers and complicated purification contested the SPS of the large intermediate. A more promising result was achieved, when only synthesizing fragment A **237** on SPS (Table 21 entry 6).



Scheme 45: NO_2 elimination towards fragment AB **262**. Reaction conditions: LiOH 10.0 equiv., H_2O/THF (1:1), 0 °C to rt, 20 h.

3.5.2.3 Fragment C

Fragment C **239** was synthesized starting from ester **263** over four steps following the established route (Scheme 46).[68] Cuprate addition and treatment with MeLi and iodine yielded vinyl iodide **264**, which underwent saponification that gave access to carboxylic acid **265** in moderate yield. Next, amide coupling with D-alanine methyl ester hydrochloride under optimized conditions afforded vinyl iodide **266**, which was then used in the GOLDBERG coupling with *tert*-butyl (*R*)-(1-amino-3-methyl-1-oxobutan-2-yl)carbamate to furnish desired fragment C **239** after saponification.

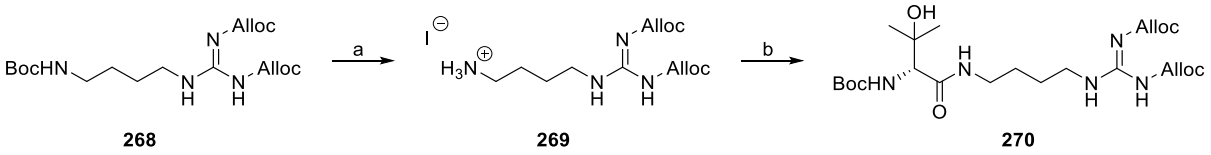


Scheme 46: Synthesis of fragment C **239**. Reaction conditions: a) MeLi 3.00 equiv., CuI 1.50 equiv., I_2 3.00 equiv., THF, -78 °C, 3 h, 94%; b) LiOH 4.00 equiv., H_2O/EtOH, 60 °C, 22 h, 57%; c) d-Ala-OCH_3·HCl 1.20 equiv.,

HOAt 1.07 equiv., PyAOP 1.07 equiv., DIPEA 5.00 equiv., DMF, 0 °C to rt, 20 h, 82%; d) *tert*-Butyl (*R*)-(1-amino-3-methyl-1-oxobutan-2-yl)carbamate 1.00 equiv., **266** 2.00 equiv., K_2CO_3 2.00 equiv, CuI 0.60 equiv., (1*R*,2*R*)-N^1,N^2-dimethylcyclohexane-1,2-diamine 4.20 equiv., 1,4-dioxane, 70 °C, 20 h, 47%; e) LiOH 10.3 equiv., H_2O, rt, 20 h, 85%.

3.5.2.4 Fragment D

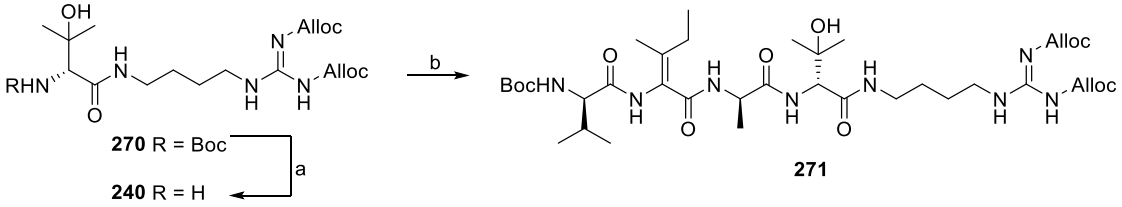
Agmatine analog **268** was treated with TMSI to form iodide salt **269**, which was coupled with amino acid (*R*)-**106** (see chapter 2.5.3.3) to fragment D precursor **270** (Scheme 47).[68]



Scheme 47: Synthesis of fragment D precursor **270**. Reaction conditions: a) TMSI 1.10 equiv., CH_2Cl_2, rt, 5 min; b) amino acid (*R*)-**106** 1.10 equiv., Oxyma 1.5 equiv., EDC·HCl 1.25 equiv., $NaHCO_3$ 5.00 equiv., CH_2Cl_2/DMF, rt, 18 h, 16% over two steps.

3.5.2.5 Fragment CD

Fragment D precursor **270** was deprotected and coupled with fragment C **239** to yield protected fragment CD **271** (Scheme 48).[68]

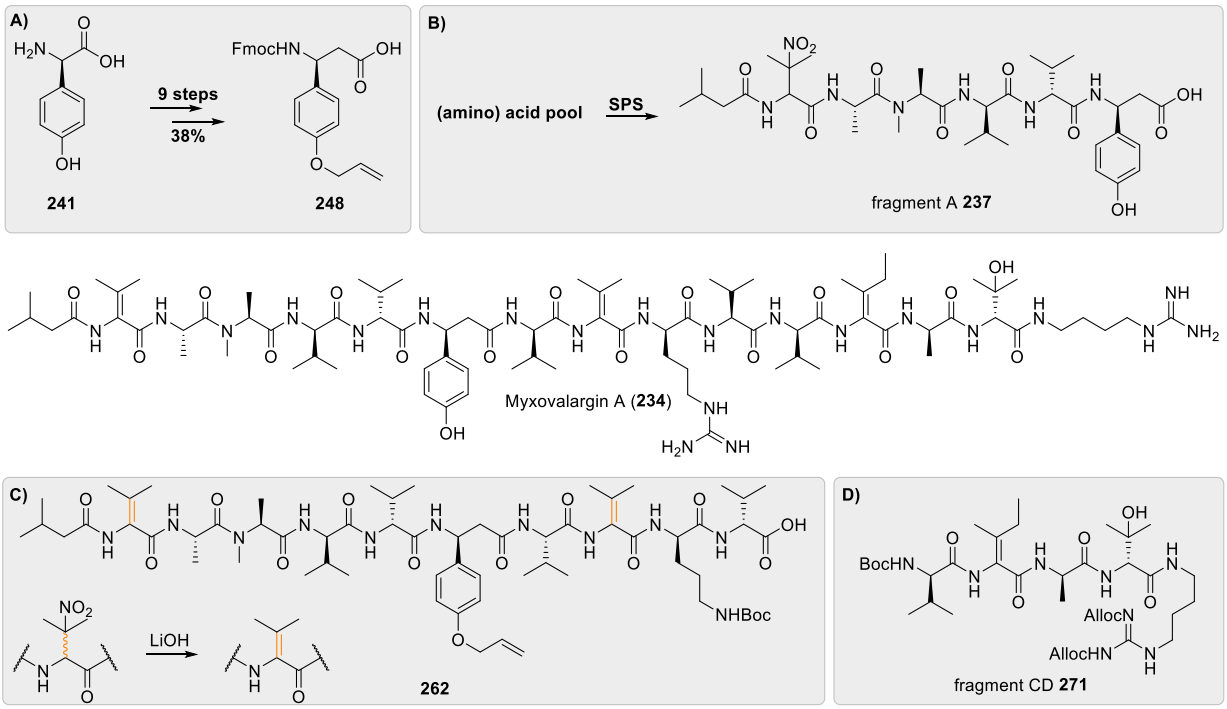


Scheme 48: Fragment coupling between fragments C **239** and D **240**. Reaction conditions: a) TFA 50.0 equiv., CH_2Cl_2, 0 °C, 2 h; b) fragment C **239** 1.50 equiv., HOAt 2.30 equiv., EDC·HCl 1.90 equiv., $NaHCO_3$ 7.00 equiv., MeCN/DMF, -15 °C to rt, 22 h, 23% over two steps.

3.6 Conclusion and outlook

In this work a new high yielding route towards β-tyrosine building block **248** was developed, allowing the synthesis of large quantities of the unnatural amino acid, which served as starting material for the SPS approach (Scheme 49 A). Following the retrosynthesis of GILLE[85] major fragments of Myxovalargin A (**234**), both with correct and incorrect stereochemistry were synthesized and provided to finalize the total synthesis. Therefore, a SPS of fragment A **237** and potentially fragment AB **259** was established to circumvent epimerization during batch synthesis of the mentioned fragments (Scheme 49 B). The NO_2 elimination of advanced intermediate **259** was demonstrated to be possible (Scheme 49 C). Furthermore, fragment CD **271** was resynthesized in sufficient quantities for subsequent synthetic investigations (Scheme 49 D). The total synthesis of Myxovalargin A (**234**) was completed during the course of this collaborative work.[81,87] For future work, the first total synthesis of Myxovalargin A (**234**)

allowed the start of medicinal chemistry programs[87] towards myxovalargin analogs. The structural modification through synthesis can be utilized to overcome the recently observed toxic effects of Myxovalargin A (**234**).[81]



Scheme 49: A) Established synthesis of (*S*)-β-tyrosine building block **248** from (*R*)-4-hydroxyphenylglycine **241**; B) Established SPS of fragment A **237** from a (amino) acid pool; C) proof-of-concept of NO_2 elimination towards fragment AB **262**; D) resynthesis of fragment CD **271**.

4 Experimental section

4.1 Materials and methods

Solvent and reagents

All non-aqueous reactions were carried out in dried glassware in dry solvents under inert conditions unless otherwise noted. Light sensitive reactions were carried out under light exclusion. Dry solvents (MeCN, DMF, Et_2O) were taken from a MBRAUN solvent purification system. THF was freshly destilled over sodium (benzophenone as indicator). Petroleum ether was destilled (60 °C). Et_3N was freshly destilled over KOH. Other commercially available (dry) solvents were purchased from MERCK or ACROS ORGANICS. Commercial reagents were used as supplied from MERCK, ACROS ORGANICS, TCI, ABCR, ALFA AESAR. Deuterated solvents were purchased from DEUTERO. $AgSbF_6$ was used from the glovebox. In addition to the synthesized building blocks, compounds **5**, **7** and **89** were also supplied from OpCyBac collaborators.

Microwave

For reactions under microwave irratiation a CEM Discover S-Class was used with a power maximum of 300 W.

Flash column chromatography

The silica gel used for manual flash column chromatography was acquired from MACHEREY-NAGEL (type 60 M, grain size 40-63 µm). Automated flash column chromatography was conducted with the flash purification system Sepacore® by BÜCHI® or Biotage® SP using prepacked cartridges (puriFlash® by INTERCHIM or chromobond® by MACHEREY-NAGEL). The eluents are given in brackets.

High performance liquid chromatography

Semi-preparateive HPLC was performed by using a WATERS Alliance 2695 HPLC-system with a 996 diode array detector (λ = 200-350 nm) and a MACHEREY-NAGEL Nucleodur C18 ISIS column (5 µm, 250 mm, diameter = 8 mm). Mass detection was conducted with a WATERS Quattro micro API mass spectrometer in negative ionization mode

Thin layer chromatography

TLCs were performed on MACHEREY-NAGEL aluminium plates coated with silica gel 60 F245. For detection UV light (254 nm) as well as $KMnO_4$, Ninhydrin, vanillin and anisaldehyde stains were used.

NMR-spectroscopy

All ^{1}H-, ^{13}C- and ^{19}F-NMR spectra were recorded at 298 K by using BRUKER Ascend 600 MHz with Avance Neo console, Ultrashield 500 MHz with Avance-III HD console, Ascend 400 MHz with Avance- III console, Ascend 400 MHz with Avance-III HD console or Ultrashield 400 MHz with Avance-I console. Chemical shifts are given in ppm relative to the residual solvent peak with multiplicities (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septet, oct = octet, m = multiplet), coupling constants and integration. For the interpretation of new compounds COSY, HSQC and HMBC spectra were recorded. TopSpin by BRUKER was used for spectrum analysis.

Mass spectrometry

High resolution mass spectrometry was performed with a MICROMASS LCT with lock-spray unit and injection via loop modus in a WATERS (Alliance 2695) HPLC device. Alternatively, a MICROMASS Q-TOF was used in combination with a WATERS Aquity UPLC device. The ionization occured through electron spray ionization. Calculated and found masses are reported.

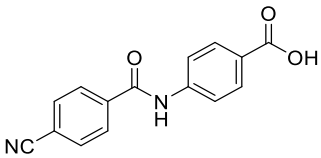
Optical rotation

The specific optical rotation [α] was measured with a polarimeter type 341 from PERKIN-ELMER at λ = 589.3 nm (sodium D line) in a 10 cm quartz cuvette. It is given in 10^{-1} cm^2 g^{-1}. The concentration c is given in 10 mg mL^{-1}.

4.2 Cystobactamids – Experimental procedures

4.2.1 Western fragments

4-(4-Cyanobenzamido)benzoic acid (**3**)

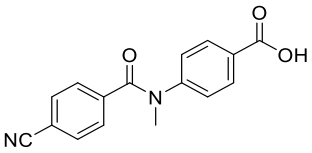


PABA (4.14 g, 30.2 mmol) was dissolved in THF (23 mL) and a sat. $NaHCO_3$ solution (23 mL) was added. The mixture was cooled to 0 °C and 4-cyanobenzoyl chloride (**6**) (5.00 g, 30.2 mmol, 1.00 equiv.) was added. The reaction mixture was stirred for 3 h at rt. A 1 M HCl solution was added and the precipitate was seperated by filtration and washed with Et_2O to furnish product **3** (6.64 g, 24.9 mmol, 83%) as colorless amorphous solid.

The analytical data are consistent with those reported in the literature.[32]

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 12.78 (s, 1H, CO_2H), 10.75 (s, 1H, NH), 8.13-8.11 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 8.05-8.03 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 7.97-7.95 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.92-7.90 (d, *J* = 8.8 Hz, 2H, H_{Ar}) ppm.

4-(4-Cyano-*N*-methylbenzamido)benzoic acid (**10**)



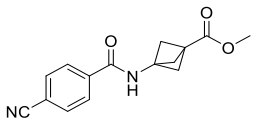
4-(Methylamino)benzoic acid (**9**) (200 mg, 1.32 mmol) was dissolved in THF (1 mL) and a sat. $NaHCO_3$ solution (1 mL) was added. The mixture was cooled to 0 °C and 4-cyanobenzoyl chloride (**6**) (219 mg, 1.32 mmol, 1.00 equiv.) was added. The reaction mixture was stirred at rt for 3 h. A 1 M HCl solution was added and the precipitate was seperated by filtration and washed with Et_2O to furnish product **10** (326 mg, 1.16 mmol, 88%) as colorless amorphous solid.

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 13.02 (s, 1H, CO_2H), 7.82-7.80 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.75-7.73 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 7.46-7.44 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 7.31-7.29 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 3.41 (s, 3H, CH_3) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 167.9 (CO), 166.5 (CO), 147.6 (C_{Ar}), 140.5 (C_{Ar}), 132.0 (C_{Ar}), 130.2 (C_{Ar}), 128.9 (C_{Ar}), 128.7 (C_{Ar}), 127.0 (C_{Ar}), 118.2 (CN), 112.1 (C_{Ar}), 37.5 (CH_3) ppm;

HRMS (ESI) calculated for $C_{16}H_{11}N_2O_3$ $[M-H]^-$: 279.0770; found: 279.0768.

Methyl 3-(4-cyanobenzamido)bicyclo[1.1.1]pentane-1-carboxylate (**272**)

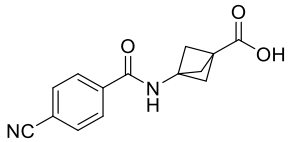


Amine **40** (53.6 mg, 0.30 mmol) was dissolved in THF (250 µL) and a sat. $NaHCO_3$ solution (250 µL) was added. The mixture was cooled to 0 °C and 4-cyanobenzoyl chloride (**6**) (50.0 mg, 0.30 mmol, 1.00 equiv.) was added. The reaction mixture was stirred at rt for 3 h. A 1 M HCl solution was added and the precipitate was seperated by filtration and washed with Et_2O to furnish product **272** (58.7 mg, 0.22 mmol, 72%) as colorless amorphous solid.

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 9.36 (s, 1H, NH), 7.99-7.94 (m, 4H, H_{Ar}), 3.63 (s, 3H, CH_3), 2.34 (s, 6H, CH_2) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 169.3 (CO), 165.2 (CO), 137.9 (C_{Ar}), 132.4 (C_{Ar}), 128.0 (C_{Ar}), 118.3 (CN), 113.8 (C_{Ar}), 53.9 (HN*C*$(CH_2)_3$), 51.6 (CH_3), 45.8 (CH_2), 35.8 (*C*CO_2Me) ppm.

3-(4-Cyanobenzamido)bicyclo[1.1.1]pentane-1-carboxylic acid (**41**)



Ester **272** (40.0 mg, 0.15 mmol) was suspended in THF (340 µL) and LiOH (1 M in H_2O, 440 µL, 0.44 mmol, 3.00 equiv.) was added. The mixture was stirred at rt for 1 h. THF was removed under reduced pressure. The aq. phase was acified with a 2 M HCl solution. The precipitate was filtered off to furnish acid **41** (28.8 mg, 0.11 mmol, 76%) as colorless amorphous solid.

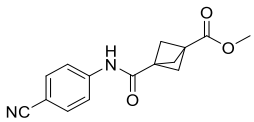
The CN group is not visible in the ^{13}C spectrum due to the small amount of analytical probe.

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 12.45 (s, 1H, CO_2H), 9.32 (s, 1H, NH), 7.99-7.96 (m, 4H, H_{Ar}), 2.29 (s, 6H, CH_2) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 170.6 (CO), 165.2 (CO), 138.0 (C_{Ar}), 132.4 (C_{Ar}), 128.0 (C_{Ar}), 113.8 (C_{Ar}), 53.7 (HN*C*$(CH_2)_3$), 45.6 (CH_2), 36.1 (*C*CO_2H) ppm.

HRMS (ESI) calculated for $C_{14}H_{11}N_2O_3$ $[M-H]^-$: 255.0770; found: 255.0762.

Methyl 3-((4-cyanophenyl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxylate (**273**)

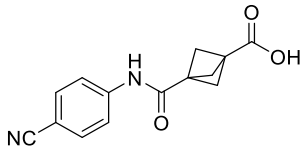


4-Aminobenzonitrile (300 mg, 2.54 mmol) and 3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (**42**) (475 mg, 2.79 mmol, 1.10 equiv.) were dissolved in CH_2Cl_2 (9 mL) and pyridine (615 µL, 7.62 mmol, 3.00 equiv.) was added. $POCl_3$ (260 µL, 2.79 mmol, 1.10 equiv.) was added at 0 °C. The mixture was stirred for 18 h while warming to rt. MeOH was added and the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (dry load, PE/EtOAc = 2:1) to furnish product **273** (423.9 mg, 1.57 mmol, 62%) as colorless amorphous solid.

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 10.04 (s, 1H, NH), 7.85-7.82 (d, *J* = 9.0 Hz, 2H, H_{Ar}), 7.79-7.76 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 3.63 (s, 3H, CH_3), 2.31 (s, 6H, CH_2) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 169.3 (CO), 168.0 (CO), 142.8 (C_{Ar}), 133.2 (C_{Ar}), 119.7 (C_{Ar}), 119.0 (CN), 105.4 (C_{Ar}), 52.0 (CH_2), 51.6 (OCH_3), 40.4 (HNC(O)*C*$(CH_2)_3$), 36.4 (*C*CO_2CH_3) ppm.

3-((4-Cyanophenyl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxylic acid (**43**)



Ester **273** (378 mg, 1.40 mmol) was dissolved in THF (8 mL) and H_2O (8 mL). $LiOH{\cdot}H_2O$ (469 mg, 11.2 mmol, 8.00 equiv.) was added and the mixture was stirred at rt for 5 min. The mixture was acidified with a 1 M HCl solution and the aq. phase was extracted with EtOAc (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish acid **43** (354 mg, 1.38 mmol, 99%) as colorless amorphous solid.

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 12.56 (s, 1H, CO_2H), 10.01 (s, 1H, NH), 7.85-7.84 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.78-7.77 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 2.27 (s, 6H, CH_2) ppm;

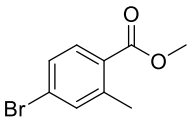
^{13}C-NMR (151 MHz, DMSO-d_6) = δ 170.7 (CO), 168.2 (CO), 142.9 (C_{Ar}), 133.1 (C_{Ar}), 119.7 (C_{Ar}), 119.0 (CN), 105.3 (C_{Ar}), 51.8 (CH_2), 40.4 (HNC(O)*C*$(CH_2)_3$), 36.4 (*C*CO_2CH_3) ppm;

HRMS (ESI) calculated for $C_{14}H_{11}N_2O_3$ $[M-H]^-$: 255.0770; found: 255.0766.

Generell procedure: Methyl esterification

A conc. H_2SO_4 solution (0.04 L/mol) was added dropwise to a mixture of the benzoic acid in MeOH (0.86 L/mol). The mixture was stirred under reflux for 18 h. The solvent was removed under reduced pressure and the residue was diluted with Et_2O. The mixture was washed with H_2O, a sat. $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Drying *in vacuo* furnished the ester.

Methyl 4-bromo-2-methylbenzoate (**274**)

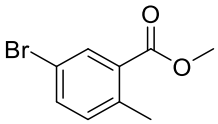


Methyl 4-bromo-2-methylbenzoate (**274**) (4.70 g, 20.5 mmol, 88%) was synthesized as brown oil from 4-bromo-2-methylbenzoic acid (**16**) (5.00 g, 23.3 mmol) following the general procedure.

The analytical data are consistent with those reported in the literature.[90]

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 7.79-7.77 (d, *J* = 8.3 Hz, 1H, H_{Ar}), 7.42 (s, 1H, H_{Ar}), 7.39-7.37 (d, *J* = 8.3 Hz, 1H, H_{Ar}), 3.88 (s, 3H, CO_2CH_3), 2.58 (s, 3H, CH_3) ppm.

Methyl 5-bromo-2-methylbenzoate (**275**)



Methyl 5-bromo-2-methylbenzoate (**275**) (5.17 g, 22.6 mmol, 97%) was synthesized as yellowish amorphous solid from 3-bromo-2-methylbenzoic acid (**17**) (5.00 g, 23.3 mmol) following the general procedure.

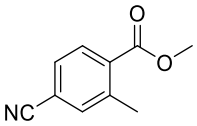
The analytical data are consistent with those reported in the literature.[91]

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 8.03 (d, *J* = 2.2 Hz, 1H, H_{Ar}), 7.51-7.48 (dd, *J* = 2.2, 8.2 Hz 1H, H_{Ar}), 7.12-7.10 (d, *J* = 8.2 Hz, 1H, H_{Ar}), 3.89 (s, 3H, CO_2CH_3), 2.53 (s, 3H, CH_3) ppm.

General procedure: S_{NAr} from bromide to nitrile

The bromide was dissolved in NMP (1.47 L/mol) and CuCN (1.20 equiv.) was added. The mixture was stirred at 180 °C for the indicated time before it was poured into cold H_2O. The precipitate was filtered and subjected to a mixture of a sat. NH_4Cl solution and EtOAc. The mixture was filtered again and the precipitate was washed with an excess of EtOAc. The aq. phase was extracted with EtOAc (3x). The combined organic phases were washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, PE/EtOAc = 10:1) to furnish the nitrile.

Methyl 4-cyano-2-methylbenzoate (**18**)



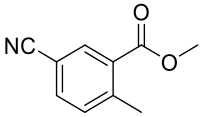
Methyl 4-cyano-2-methylbenzoate (**18**) (2.83 g, 16.2 mmol, 79%) was synthesized as colorless amorphous solid from bromide **274** (4.70 g, 20.5 mmol) following the general procedure and stirring for 5 h.

The analytical data are consistent with those reported in the literature.[92]

R_f (PE/EtOAc = 8:1) = 0.42;

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 7.98-7.96 (d, *J* = 8.2 Hz, 1H, H_{Ar}), 7.54-7.52 (d, *J* = 7.9 Hz, 2H, H_{Ar}), 3.92 (s, 3H, CO_2CH_3), 2.62 (s, 3H, CH_3) ppm.

Methyl 5-cyano-2-methylbenzoate (**19**)



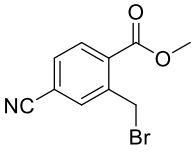
Methyl 5-cyano-2-methylbenzoate (**19**) (5.14 g, 22.4 mmol, 83%) was synthesized as colorless oil from bromide **275** (4.70 g, 20.5 mmol) following the general procedure and stirring for 18 h.

The analytical data are consistent with those reported in the literature.[93]

R_f (PE/EtOAc = 8:1) = 0.34;

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 8.21 (d, *J* = 1.6 Hz, 1H, H_{Ar}), 7.67-7.64 (dd, *J* = 1.7, 8.0 Hz, 2H, H_{Ar}), 7.38-7.36 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 3.92 (s, 3H, CO_2CH_3), 2.67 (s, 3H, CH_3) ppm.

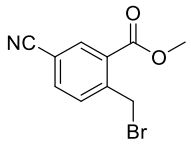
Methyl 2-(bromomethyl)-4-cyanobenzoate (**20**)



Toluate **18** (2.83 g, 16.2 mmol) was dissolved in CCl_4 (100 mL). Dibenzoyl peroxide (0.52 g, 1.62 mmol, 0.10 equiv.) was added before addition of NBS (2.88 g, 16.2 mmol, 1.00 equiv.). The mixture was stirred at 80 °C for 18 h. Further NBS (0.30 equiv.) was added and stirring at 80 °C was continued for 2 h. Again NBS (0.50 equiv.) was added and stirring was continued at 80 °C for 5 h. When TLC indicated full conversion, a sat. $NaHCO_3$ solution was added and the aq. phase was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (dry load, PE/EtOAc = 10:1) to furnish product **20** (4.51 g) as mixture, which contained impurities. The product was used in the next step without further purification.

R_f (PE/EtOAc = 8:1) = 0.49

Methyl 2-(bromomethyl)-5-cyanobenzoate (**21**)



Toluate **19** (3.25 g, 18.5 mmol) was dissolved in $CHCl_3$ (115 mL). Dibenzoyl peroxide (0.60 g, 1.85 mmol, 0.10 equiv.) was added before addition of NBS (3.30 g, 18.5 mmol, 1.00 equiv.). The mixture was stirred at 80 °C for 18 h. A sat. $NaHCO_3$ solution was added and the aq. phase was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (dry load, PE/EtOAc = 10:1) to furnish product **21** (3.28 g, 12.9 mmol, 70%) as colorless amorphous solid.

The analytical data are consistent with those reported in the literature.[94]

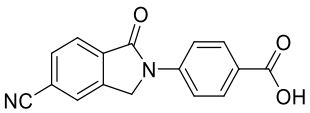
R_f (PE/EtOAc = 10:1) = 0.23;

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 8.26 (d, *J* = 1.4 Hz, 1H, H_{Ar}), 7.77-7.75 (dd, *J* = 1.6, 8.0 Hz, 2H, H_{Ar}), 7.61-7.59 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 4.95 (s, 2H, CO_2CH_3), 3.97 (s, 3H, CH_3) ppm.

General procedure: oxoisoindoline synthesis

Methyl 2-(bromomethyl) benzoate (1.00 equiv.) was dissolved in DMF (0.40 L/mol). PABA (1.30 equiv.) was added. The reaction mixture was stirred at 150 °C for 5 min under microwave irradiation. After cooling down to rt the mixture was filtered. The precipitate was washed with MeOH and dried *in vacuo* to furnish the oxoisoindoline.

4-(5-Cyano-1-oxoisoindolin-2-yl)benzoic acid (**22**)



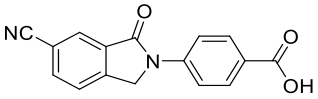
4-(5-Cyano-1-oxoisoindolin-2-yl)benzoic acid (**22**) (379 mg, 1.36 mmol, 16% over two steps) was synthesized as colorless oil from ester **20** (2.15 g, 8.44 mmol) following the general procedure.

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 12.86 (s, 1H, CO_2H), 8.24 (s, 1H, H_{Ar}), 8.08-7.97 (m, 6H, H_{Ar}), 5.15 (s, 2H, CH_2) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 166.8 (CO_2H), 165.5 (CON), 142.7 (C_{Ar}), 141.7 (C_{Ar}), 136.0 (C_{Ar}), 132.4 (C_{Ar}), 130.5 (C_{Ar}), 127.8 (C_{Ar}), 126.3 (C_{Ar}), 124.4 (C_{Ar}), 118.5 (CN), 114.6 (C_{Ar}), 50.4 (CH_2) ppm;

HRMS (ESI) calculated for $C_{16}H_9N_2O_3$ $[M-H]^-$: 277.0613; found: 277.0621.

4-(6-Cyano-1-oxoisoindolin-2-yl)benzoic acid (**23**)



4-(6-cyano-1-oxoisoindolin-2-yl)benzoic acid (**23**) (1.56 g, 5.60 mmol, 71%) was synthesized as colorless oil from ester **21** (2.00 g, 7.87 mmol) following the general procedure.

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 12.86 (s, 1H, CO_2H), 8.29 (s, *J* = 1.5, 7.9 Hz, 1H, H_{Ar}), 8.06-8.02 (m, 4H, H_{Ar}), 7.92-7.90 (dd, *J* = 0.6, 7.9 Hz, 1H, H_{Ar}), 5.20 (s, 2H, CH_2) ppm;

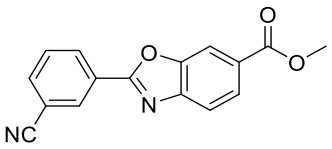
^{13}C-NMR (101 MHz, DMSO-d_6) = δ 166.8 (CO_2H), 165.3 (CON), 145.8 (C_{Ar}), 142.8 (C_{Ar}), 136.0 (C_{Ar}), 133.1 (C_{Ar}), 130.5 (C_{Ar}), 127.7 (C_{Ar}), 125.0 (C_{Ar}), 118.5 (C_{Ar}), 118.3 (CN), 111.4 (C_{Ar}), 50.8 (CH_2) ppm;

HRMS (ESI) calculated for $C_{16}H_9N_2O_3$ $[M-H]^-$: 277.0613; found: 277.0613.

General procedure: benzoxazole synthesis

Methyl aminohydroxybenzoate (1.00 equiv.), 3-cyanobenzoic acid (**24**) (1.00 equiv.) and $B(OH)_3$ (1.00 equiv.) in *p*-xylene (0.60 M) were stirred at 160 °C for 20 h. After cooling down to rt EtOAc was added and the mixture was filtered and washed with EtOAc. The filtrate was concentrated under reduced pressure. The residue was purified by short column chromatography (CH_2Cl_2) to furnish the benzoxazole.

Methyl 2-(3-cyanophenyl)benzo[*d*]oxazole-6-carboxylate (**27**)



Benzoxazole **27** (0.19 g, 0.69 mmol, 12%) was synthesized as colorless amorphous solid from methyl 4-amino-3-hydroxybenzoate (**25**) (1.00 g, 5.98 mmol) following the general procedure.

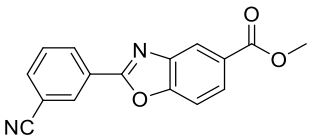
$\mathbf{R_f}$ (CH_2Cl_2) = 0.29;

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 8.58 (s, 1H, H_{Ar}), 8.52-8.50 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 8.31 (s, 1H, H_{Ar}), 8.15-8.13 (dd, *J* = 1.3, 8.3 Hz, 1H, H_{Ar}), 7.87-7.82 (t, *J* = 9.0 Hz, 2H, H_{Ar}), 7.72-7.68 (t, *J* = 7.9 Hz, 1H, H_{Ar}), 3.99 (s, 3H, CH_3) ppm;

^{13}C-NMR (101 MHz, $CDCl_3$) = δ 166.6 (CO_2), 163.2 (C=N), 150.6 (C_{Ar}), 145.7 (C_{Ar}), 135.2 (C_{Ar}), 131.9 (C_{Ar}), 131.5 (C_{Ar}), 130.2 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 126.9 (C_{Ar}), 120.2 (C_{Ar}), 117.9 (CN), 113.9 (C_{Ar}), 112.7 (C_{Ar}), 52.7 (CH_3) ppm;

HRMS (ESI) calculated for $C_{16}H_{11}N_2O_3$ $[M+H]^+$: 279.0770; found: 279.0776.

Methyl 2-(3-cyanophenyl)benzo[*d*]oxazole-5-carboxylate (**28**)



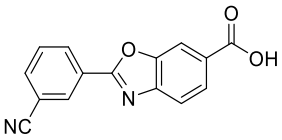
Benzoxazole **28** (187 mg, 0.67 mmol, 23%) was synthesized as colorless amorphous solid from methyl 3-amino-4-hydroxybenzoate (**26**) (500 mg, 2.99 mmol) following the general procedure.

$\mathbf{R_f}$ (CH_2Cl_2) = 0.11;

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 8.56 (t, *J* = 1.2 Hz, 1H, H_{Ar}), 8.52-8.49 (m, 2H, H_{Ar}), 8.31 (s, 1H, H_{Ar}), 8.18-8.15 (dd, *J* = 1.6, 8.6 Hz, 1H, H_{Ar}), 7.87-7.82 (dt, *J* = 1.4, 7.8 Hz, 2H, H_{Ar}), 7.71-7.68-7.64 (m, 2H, H_{Ar}), 3.98 (s, 3H, CH_3) ppm;

^{13}C-NMR (101 MHz, $CDCl_3$) = δ 166.6 (CO_2), 162.1 (C=N), 153.8 (C_{Ar}), 142.0 (C_{Ar}), 135.0 (C_{Ar}), 131.8 (C_{Ar}), 131.3 (C_{Ar}), 130.2 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 127.7 (C_{Ar}), 122.6 (C_{Ar}), 117.9 (CN), 113.8 (C_{Ar}), 110.8 (C_{Ar}), 52.6 (CH_3) ppm;

2-(3-Cyanophenyl)benzo[*d*]oxazole-6-carboxylic acid (**29**)



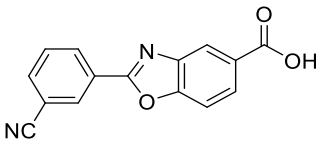
Ester **27** (184 mg, 0.66 mmol) was suspended in THF/MeOH/H_2O (3:1:1, 4 mL). $LiOH \cdot H_2O$ (111 mg, 2.65 mmol, 4.00 equiv.) was added. The mixture was stirred at rt for 3 h. A 1 M HCl solution was added. The aq. phase was extracted with EtOAc (3x). The combined organic phases were dried over $MgSO_4$, filtered, concentrated under reduced pressure and dried *in vacuo* to furnish acid **29** (149 mg, 0.56 mmol, 85%) as colorless amorphous solid.

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 13.28 (s, 1H, CO_2H), 8.61 (s, 1H, H_{Ar}), 8.54-8.52 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 8.29 (s, 1H, H_{Ar}), 8.16-8.14 (d, *J* = 7.7 Hz, 1H, H_{Ar}), 8.06-8.04 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 7.96-7.94 (d, *J* = 8.3 Hz, 1H, H_{Ar}), 7.88-7.84 (t, *J* = 7.8 Hz, 1H, H_{Ar}) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 166.7 (CO_2H), 162.9 (C=N), 150.1 (C_{Ar}), 144.9 (C_{Ar}), 135.8 (C_{Ar}), 132.8 (C_{Ar}), 132.0 (C_{Ar}), 131.5 (C_{Ar}), 130.8 (C_{Ar}), 128.6 (C_{Ar}), 127.3 (C_{Ar}), 126.5 (C_{Ar}), 120.0 (C_{Ar}), 117.9 (CN), 112.7 (C_{Ar}), 112.2 (C_{Ar}) ppm;

HRMS (ESI) calculated for $C_{15}H_7N_2O_3$ $[M-H]^-$: 263.0457; found: 263.0450.

2-(3-Cyanophenyl)benzo[*d*]oxazole-5-carboxylic acid (**30**)



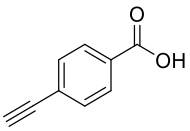
Ester **28** (184 mg, 0.66 mmol) was suspended in THF/MeOH/H_2O (3:1:1, 4 mL). $LiOH \cdot H_2O$ (111 mg, 2.65 mmol, 4.00 equiv.) was added. The mixture was stirred at rt for 3 h. A 1 M HCl solution was added. The aq. phase was extracted with EtOAc (3x). The combined organic phases were dried over $MgSO_4$, filtered, concentrated under reduced pressure and dried *in vacuo* to furnish acid **30** (50.0 mg, 0.19 mmol, 29%) as colorless amorphous solid, which contained impurities. The product was used in the next step without further purification.

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 13.15 (s, 1H, CO_2H), 8.61-8.60 (m, 1H, H_{Ar}), 8.54-8.52 (dt, *J* = 1.2, 8.0 Hz, 1H, H_{Ar}), 8.36 (m, 1H, H_{Ar}), 8.15-8.13 (m, 1H, H_{Ar}), 8.08-8.07 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 7.94-7.93 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 7.87-7.84 (t, *J* = 7.9 Hz, 1H, H_{Ar}) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 166.8 (CO_2H), 161.9 (C=N), 153.1 (C_{Ar}), 141.4 (C_{Ar}), 135.6 (C_{Ar}), 131.9 (C_{Ar}), 130.9 (C_{Ar}), 130.8 (C_{Ar}), 128.2 (C_{Ar}), 127.6 (C_{Ar}), 127.3 (C_{Ar}), 121.4 (C_{Ar}), 117.9 (CN), 112.7 (C_{Ar}), 111.3 (C_{Ar}) ppm;

HRMS (ESI) calculated for $C_{15}H_7N_2O_3$ $[M-H]^-$: 263.0457; found: 263.0444.

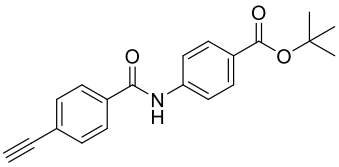
4-Ethynylbenzoic acid (**12**)



Methyl 4-ethynylbenzoate (**11**) (300 mg, 1.87 mmol) was dissolved in THF (2 mL). NaOH (187 mg, 4.68 mmol, 2.50 equiv.) in H_2O (2 mL) was added and the resulting mixture was stirred at rt for 16 h. A 1 M HCl solution was added until pH 1. The aq. phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish acid **12** (quant.) as colorless amorphous solid, which was used in the next step without further purification.

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 13.14 (bs, 1H, CO_2H), 7.94-7.92 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 7.60-7.58 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 4.44 (s, 1H, CCH) ppm.

tert-Butyl 4-(4-ethynylbenzamido)benzoate (**14**)



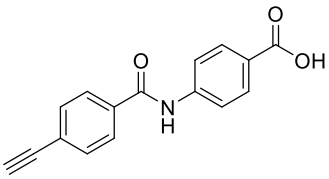
Acid **12** (249 mg, 1.70 mmol) was dissolved in DMF (5.2 mL). EDC·HCl (392 mg, 2.04 mmol, 1.20 equiv.), HOBt·H_2O (313 mg, 2.04 mmol, 1.20 equiv.) and *tert*-butyl 4-aminobenzoate (**13**) (494 mg, 2.56 mmol, 1.50 equiv.) were added subsequently. The mixture was stirred at rt for 24 h before it was poured into H_2O. The aq. phase was extracted with EtOAc (3x). The combined organic phases were washed with a sat. $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc = 6:1, 5:1) to furnish amide **14** (271 mg, 1.17 mmol, 69%) as colorless amorphous solid.

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 10.60 (s, 1H, NH), 7.99-7.97 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 7.94-7.88 (m, 4H, H_{Ar}), 7.66-7.64 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 4.43 (s, 1H, CCH), 1.55 (s, 9H, H-CH_3) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 165.1 (CO), 164.6 (CO), 143.1 (C_{Ar}), 134.6 (C_{Ar}), 131.7 (C_{Ar}), 129.9 (C_{Ar}), 128.1 (C_{Ar}), 126.2 (C_{Ar}), 125.1 (C_{Ar}), 119.5 (C_{Ar}), 83.3 (*C*CH), 82.8 (C*C*H), 80.4 (*C*(CH_3)$_3$), 27.8 (C(*C*H_3)$_3$) ppm;

HRMS (ESI) calculated for $C_{20}H_{19}NO_3Na$ $[M+Na]^+$: 344.1263; found: 344.1277.

4-(4-ethynylbenzamido)benzoic acid (**15**)



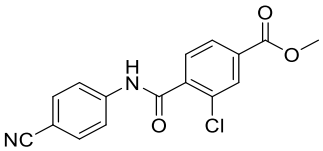
Ester **14** (264 mg, 0.82 mmol) was dissolved in CH_2Cl_2 (8.0 mL) and TFA (3.2 mL) was added at 0 °C. The mixture was stirred at rt for 3 h and afterwards diluted with Et_2O at 0 °C. The precipitate was filtered off and washed with Et_2O to furnish acid **15** (206 mg, 0.78 mmol, 95%) as colorless amorphous solid.

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 12.75 (bs, 1H, CO_2H), 10.60 (s, 1H, NH), 7.99-7.97 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 7.96-7.90 (m, 4H, H_{Ar}), 7.66-7.64 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 4.43 (s, 1H, CCH) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 166.9 (CO), 165.1 (CO), 143.1 (C_{Ar}), 134.6 (C_{Ar}), 131.8 (C_{Ar}), 130.3 (C_{Ar}), 128.1 (C_{Ar}), 125.7 (C_{Ar}), 125.1 (C_{Ar}), 119.6 (C_{Ar}), 83.3 (*C*CH), 82.8 (C*C*H) ppm;

HRMS (ESI) calculated for $C_{16}H_{10}NO_3$ $[M-H]^-$: 264.0661; found: 264.0659.

Methyl 3-chloro-4-((4-cyanophenyl)carbamoyl)benzoate (**276**)



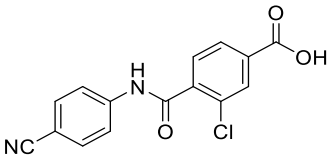
2-Chloro-4-(methoxycarbonyl)benzoic acid (**44**) (233 mg, 1.08 mmol) was dissolved in DMF (11 mL). HATU (494 mg, 1.30 mmol, 1.20 equiv.) and pyridine (175 µL, 2.17 mmol, 2.00 equiv.) were added and the resulting mixture was stirred at rt for 10 min before addition of 4-aminobenzonitrile (128 mg, 1.08 mmol, 1.00 equiv.). The mixture was stirred at rt for 21 h. Then, Et_2O was added and the mixture was washed with a 1 M HCl solution and a sat. Na_2CO_3 solution. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (dry load, PE/EtOAc = 3:1) to furnish product **276** (126 mg, 0.40 mmol, 37% or 79% brsm) as colorless amorphous solid.

The basic phase was acidified with a 2 M HCl solution and extracted with EtOAc (2x). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to recover 2-chloro-4-(methoxycarbonyl)benzoic acid (**44**) (98.0 mg, 0.46 mmol, 42%) as yellow amorphous solid.

R_f (PE/EtOAc = 2:1) = 0.31;

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 11.09 (s, 1H, NH), 8.06 (d, *J* = 1.4 Hz, 1H, H_{Ar}), 8.03-8.01 (dd, *J* = 1.5, 8.0 Hz, 1H, H_{Ar}), 7.90-7.88 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.86-7.83 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.81-7.79 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 3.91 (s, 3H, CH_3) ppm;
^{13}C-NMR (101 MHz, DMSO-d_6) = δ 164.7 (CO), 164.6 (CO), 142.7 (C_{Ar}), 140.1 (C_{Ar}), 133.4 (C_{Ar}), 132.3 (C_{Ar}), 130.4 (C_{Ar}), 130.0 (C_{Ar}), 129.5 (C_{Ar}), 128.0 (C_{Ar}), 119.7 (C_{Ar}), 118.9 (CN), 106.0 (C_{Ar}), 52.8 (CH_3) ppm;

3-Chloro-4-((4-cyanophenyl)carbamoyl)benzoic acid (**45**)

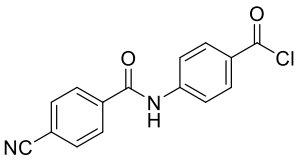


Ester **276** (124 mg, 0.39 mmol) was dissolved in THF (1.2 mL) and LiOH (1 M in H_2O, 1.20 mL, 1.20 mmol, 3.00 equiv.) was added at 0 °C. The mixture was stirred for 15 h while warming to rt. A 2 M HCl solution and EtOAc were added. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish acid **45** (109 mg, 0.36 mmol, 92%) as colorless amorphous solid.
^{1}H-NMR (400 MHz, DMSO-d_6) = δ 13.55 (bs, 1H, CO_2H), 11.07 (s, 1H, NH), 8.03 (d, *J* = 1.4 Hz, 1H, H_{Ar}), 8.01-7.98 (dd, *J* = 1.5, 7.9 Hz, 1H, H_{Ar}), 7.91-7.88 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.85-7.83 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.78-7.76 (d, *J* = 7.9 Hz, 1H, H_{Ar}) ppm;
^{13}C-NMR (101 MHz, DMSO-d_6) = δ 165.6 (CO), 164.8 (CO), 142.8 (C_{Ar}), 139.8 (C_{Ar}), 133.6 (C_{Ar}), 133.4 (C_{Ar}), 130.2 (C_{Ar}), 130.1 (C_{Ar}), 129.3 (C_{Ar}), 128.1 (C_{Ar}), 119.7 (C_{Ar}), 118.9 (CN), 105.9 (C_{Ar}) ppm;
HRMS (ESI) calculated for $C_{15}H_8ClN_2O_3$ $[M-H]^-$: 299.0223; found: 299.0216.

General procedure: synthesis of benzoyl chlorides

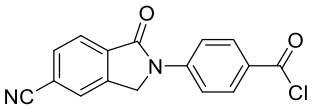
Carboxylic acids were stirred in $SOCl_2$ (0.3 M) at 80 °C for 2 h. The mixture was cooled down to rt and diluted with CH_2Cl_2. The solvent was removed under reduced pressure to furnish acyl chlorides, which were used in the next step without further purification.

4-(4-Cyanobenzamido)benzoyl chloride (**277**)



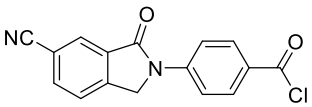
Benzoyl chloride **277** (1.05 g, 3.70 mmol, 98%) was synthesized as colorless amorphous solid from acid **3** (1.00 g, 3.76 mmol).[95]

4-(5-Cyano-1-oxoisoindolin-2-yl)benzoyl chloride (**278**)



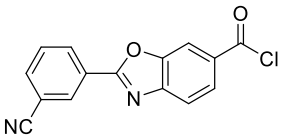
Benzoyl chloride **278** (48.1 mg, 0.16 mmol, quant.) was synthesized as colorless amorphous solid from acid **22** (45.0 mg, 0.16 mmol).

4-(6-Cyano-1-oxoisoindolin-2-yl)benzoyl chloride (**279**)



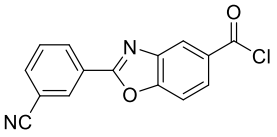
Benzoyl chloride **279** (108 mg, 0.36 mmol, quant.) was synthesized as colorless amorphous solid from acid **23** (100 mg, 0.36 mmol).

2-(3-Cyanophenyl)benzo[*d*]oxazole-6-carbonyl chloride (**280**)



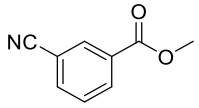
Benzoyl chloride **280** (52.6 mg, 0.19 mmol, quant.) was synthesized as colorless amorphous solid from acid **29** (50.0 mg, 0.19 mmol).

2-(3-Cyanophenyl)benzo[*d*]oxazole-5-carbonyl chloride (**281**)



Benzoyl chloride **281** (37.6 mg, 0.13 mmol, 96%) was synthesized as beige amorphous solid from acid **30** (36.8 mg, 0.14 mmol).

Methyl 3-cyanobenzoate (**37**)

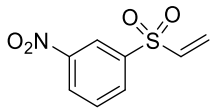


3-Cyanobenzoic acid (**24**) (200 mg, 1.36 mmol) was dissolved in DMF (3 mL) and K_2CO_3 (282 mg, 2.04 mmol, 1.50 equiv.) was added. The mixture was stirred at rt for 30 min. MeI (127 µL, 2.04 mmol, 1.50 equiv.) was added dropwise over 15 min. The mixture was stirred at rt for 14 h. Afterwards, the mixture was poured into ice water. The precipitate was filtered off and washed with H_2O to furnish ester **37** (172 mg, 1.07 mmol, 78%) as colorless amorphous solid.

The analytical data are consistent with those reported in the literature.[96]

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 8.34-8.33 (t, *J* = 1.2 Hz, 1H, H_{Ar}), 8.28-8.26 (dt, *J* = 1.2, 7.9 Hz, 1H, H_{Ar}), 7.85-7.83 (dt, *J* = 1.2, 7.8 Hz, 1H, H_{Ar}), 7.61-7.57 (t, *J* = 7.8 Hz, 1H, H_{Ar}), 3.96 (s, 3H, CH_3) ppm.

1-Nitro-3-(vinylsulfonyl)benzene (**36**)



Phenylvinylsulfone (**35**) (200 mg, 1.19 mmol) was dissolved in a mixture of conc. H_2SO_4 and fuming HNO_3 (7:3, 4 mL), at 0 °C. The mixture was stirred at 0 °C for 1 h. Afterwards, the mixture was poured into ice water. The precipitate was filtered off to furnish product **36** (209 mg, 0.98 mmol, 83%) as yellowish amorphous solid.

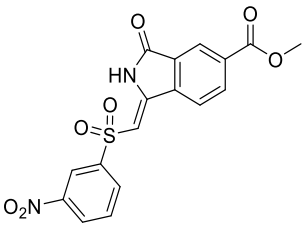
R_f (PE/EtOAc = 3:2) = 0.38;

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 8.74-8.73 (t, *J* = 1.9 Hz, 1H, H_{Ar}), 8.51-8.49 (qd, *J* = 1.0, 8.2 Hz, 1H, H_{Ar}), 8.25-8.22 (qd, *J* = 1.1, 8.2 Hz, 1H, H_{Ar}), 7.81-7.77 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 6.73-6.59 (m, 2H, CHCH_2), 6.22-6.19 (d, *J* = 9.2 Hz, 1H, C*H*CH_2) ppm;

^{13}C-NMR (101 MHz, $CDCl_3$) = δ 148.6 (C_{Ar}), 142.1 (C_{Ar}), 137.5 (CH*C*H_2), 133.5 (C_{Ar}), 131.0 (C_{Ar}), 130.4 (*C*HCH_2), 128.3 (C_{Ar}), 123.4 (C_{Ar}) ppm;

HRMS (ESI) calculated for $C_8H_7NO_4SNa$ $[M+Na]^+$: 235.9993; found: 235.9993.

Methyl (*Z*)-1-(((3-nitrophenyl)sulfonyl)methylene)-3-oxoisoindoline-5-carboxylate (**38**)



Methyl 3-cyanobenzoate (**37**) (500 mg, 3.10 mmol), 1-nitro-3-(vinylsulfonyl)benzene (**36**) (793.8 mg, 3.72 mmol, 1.20 equiv.), dichloro(*p*-cymene)ruthenium(II) dimer (95.0 mg, 0.16 mmol, 5 mol%), $Cu(OAc)_2 \cdot H_2O$ (1.24 g, 6.21 mmol, 2.00 equiv.) and $AgSbF_6$ (213 mg, 0.62 mmol, 0.20 equiv.) were evacuated and flushed with Ar (3x). AcOH (19 mL) was added and the mixture was stirred for several seconds before it was evacuated and flushed with Ar (3x). The reaction flask was sealed and the mixture was stirred at 120 °C for 3 d. After the mixture was cooled to rt, CH_2Cl_2 was added. The mixture was filtered through Celite®. The filtrate was washed with H_2O and the aq. phase was backextracted with CH_2Cl_2 (2x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The residue was recrystallized from CH_2Cl_2 and Et_2O to furnish product **38** (243 mg, 0.63 mmol, 20%) as brown amorphous solid.

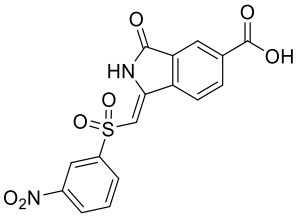
R_f (PE/EtOAc = 3:2) = 0.28;

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 10.96 (s, 1H, NH), 8.86-8.85 (t, *J* = 1.9 Hz, 1H, H_{Ar}), 8.56-8.54 (dd, *J* = 2.2, 8.2 Hz, 1H, H_{Ar}), 8.51-8.50 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 8.31-8.29 (dd, *J* = 1.4, 8.0 Hz, 1H, H_{Ar}), 8.22 (s, 1H, H_{Ar}) 8.19-8.18 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 7.99-7.96 (t, *J* = 8.1 Hz, 1H, H_{Ar}), 7.19 (s, 1H, SO_2CH), 3.90 (s, 3H, CH_3) ppm;

^{13}C-NMR (101 MHz, $CDCl_3$) = δ 167.2 (CO), 165.0 (CO), 148.2 (C_{Ar}), 143.9 (C_{Ar}), 143.3 (C_{Ar}), 149.9 (C_{Ar}), 133.9 (C_{Ar}), 133.2 (C_{Ar}), 133.1 (C_{Ar}), 131.7 (C_{Ar}), 128.9 (C_{Ar}), 128.4 (C_{Ar}), 123.7 (C_{Ar}), 123.1 (C_{Ar}), 122.0 (C_{Ar}), 101.9 (SO_2CH), 52.7 (CH_3) ppm;

HRMS (ESI) calculated for $C_{17}H_{11}N_2O_7S$ $[M-H]^-$: 387.0287; found: 387.283.

(*Z*)-1-(((3-Nitrophenyl)sulfonyl)methylene)-3-oxoisoindoline-5-carboxylic acid (**39**)

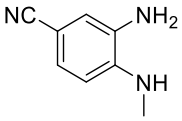


Ester **38** (218 mg, 0.56 mmol) was dissolved in THF (5.5 mL) and MeOH (5.5 mL). A 1 M NaOH solution (6.20 mL, 6.17 mmol, 11.0 equiv.) was added and the resulting mixture was stirred at rt for 19 h. The precipitate was filtered off and washed with Et_2O to furnish acid **39**

(152 mg, 0.41 mmol, 72%) as brown amorphous solid, which was used in the next step without further purification.

HRMS (ESI) calculated for $C_{16}H_9N_2O_7S$ $[M-H]^-$: 373.0130; found: 373.0129.

3-amino-4-(methylamino)benzonitrile (**32**)



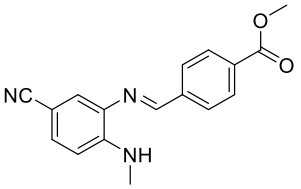
4-Fluoro-3-nitrobenzonitrile (**31**) (2.00 g, 12.0 mmol) was dissolved in THF (12 mL) and $MeNH_2$ (33% in EtOH, 10.8 mL, 32.5 mmol, 2.00 equiv.) was added dropwise at 0 °C. The mixture was stirred at rt for 15 min until the starting material was consumed. EtOH (12 mL) and zinc dust (17.0 g, 180 mmol, 15.0 equiv.) were added. AcOH (11.7 mL, 205 mmol, 17.0 equiv.) was added dropwise at 0 °C, afterwads the mixture was stirred at 40 °C for 16 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (dry load, CH_2Cl_2) to furnish diamine **32** (1.74 g, 11.9 mmol, 98%) as grey amorphous solid.

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 6.96-6.93 (dd, *J* = 2.0, 8.2 Hz, 1H, H_{Ar}), 6.76 (d, *J* = 2.0 Hz, 1H, H_{Ar}), 6.42-6.40 (d, *J* = 8.2 Hz, 1H, H_{Ar}), 5.57-5.54 (q, *J* = 4.4 Hz, 1H, NH), 4.89 (s, 2H, NH_2), 2.77-2.76 (d, *J* = 4.6 Hz, 3H, CH_3) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 141.1 (C_{Ar}), 135.1 (C_{Ar}), 123.0 (C_{Ar}), 121.1 (CN), 114.4 (C_{Ar}), 108.1 (C_{Ar}), 96.4 (C_{Ar}), 29.5 (CH_3) ppm;

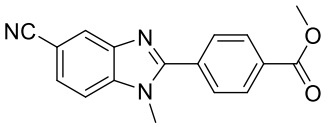
HRMS (ESI) calculated for $C_8H_9N_3Na$ $[M+Na]^+$: 170.0694; found: 170.0694.

Methyl (*E*)-4-(((5-cyano-2-(methylamino)phenyl)imino)methyl)benzoate (**33**)



Diamine **32** (1.74 g, 11.8 mmol) and methyl 4-formylbenzoate (1.94 g, 11.8 mmol, 1.00 equiv.) were dissolved in THF (21 mL) and MeOH (12 mL). The mixture was stirred at rt for 1 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (dry load, PE/EtOAc = 10:1, then CH_2Cl_2) to furnish imine **33** (2.76 g, 9.41 mmol, 80%) as yellow amorphous solid, which was directly used in the next step.

Methyl 4-(5-cyano-1-methyl-1H-benzo[*d*]imidazol-2-yl)benzoate (**282**)



Imine **33** (2.70 g, 9.20 mmol) was dissolved in CH_2Cl_2 (100 mL). I_2 (2.80 g, 11.1 mmol, 1.20 equiv.) and NaOAc (1.51 g, 18.4 mmol, 2.00 equiv.) were added subsequently and the resulting mixture was stirred at rt for 4 h. A sat. $Na_2S_2O_3$ solution was added and the aq. phase was extracted with CH_2Cl_2 (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, PE/EtOAc = 2:1, then 5% MeOH in CH_2Cl_2) to furnish benzimidazole **282** (2.02 g, 6.92 mmol, 75%) as brown amorphous solid.

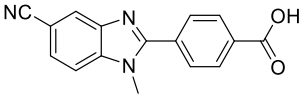
R_f (PE/EtOAc = 1:1) = 0.39;

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 8.28 (dd, *J* = 0.6, 1.5 Hz, 1H, H_{Ar}), 8.17-8.15 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 8.07-8.05 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.90-7.88 (dd, *J* = 0.6, 8.5 Hz, 2H, H_{Ar}), 7.75-7.72 (dd, *J* = 1.5, 8.4 Hz, 2H, H_{Ar}), 3.97 (s, 3H, NCH_3), 3.92 (s, 3H, OCH_3) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 165.7 (CO), 154.5 (C=N), 141.9 (C_{Ar}), 135.6 (C_{Ar}), 133.6 (C_{Ar}), 130.9 (C_{Ar}), 129.8 (C_{Ar}), 129.4 (C_{Ar}), 126.0 (C_{Ar}), 124.3 (C_{Ar}), 119.8 (CN), 112.5 (C_{Ar}), 104.4 (C_{Ar}), 52.5 (OCH_3), 32.2 (NCH_3) ppm;

HRMS (ESI) calculated for $C_{17}H_{13}N_3O_2Na$ $[M+Na]^+$: 314.0905; found: 314.0898.

4-(5-Cyano-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)benzoic acid (**34**)



Ester **282** (1.96 g, 6.18 mmol) was dissolved in THF (40 mL) and H_2O (40 mL). $LiOH{\cdot}H_2O$ (2.25 g, 53.7 mmol, 8.00 equiv.) was added and the mixture was stirred at rt for 18 h. Afterwards, the mixture was acidified with a 1 M HCl solution and the precipitate was filtered off to furnish acid **34** (1.81 g, 6.52 mmol, 97%) as beige amorphous solid.

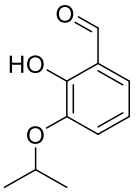
^{1}H-NMR (600 MHz, DMSO-d_6) = δ 13.28 (bs, 1H, CO_2H), 8.28 (d, *J* = 0.9 Hz, 1H, H_{Ar}), 8.15-8.13 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 8.04-8.03 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.90-7.89 (d, *J* = 0.6, 8.5 Hz, 2H, H_{Ar}), 7.75-7.73 (dd, *J* = 1.5, 8.4 Hz, 2H, H_{Ar}), 3.97 (s, 3H, CH_3) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 166.8 (CO), 154.7 (C=N), 141.7 (C_{Ar}), 139.5 (C_{Ar}), 133.1 (C_{Ar}), 132.1 (C_{Ar}), 129.7 (C_{Ar}), 129.6 (C_{Ar}), 126.0 (C_{Ar}), 124.1 (C_{Ar}), 119.8 (CN), 112.5 (C_{Ar}), 104.4 (C_{Ar}), 32.2 (NCH_3) ppm;

HRMS (ESI) calculated for $C_{16}H_{11}N_3O_2$ $[M-H]^-$: 276.0773; found: 276.0780.

4.2.2 Eastern fragments

2-Hydroxy-3-isopropoxybenzaldehyde (**283**)



Small scale

2,3-Dihydroxybenzaldehyde (**46**) (4.00 g, 29.0 mmol) was dissolved in DMSO (58 mL), and NaH (60% in mineral oil, 2.32 g, 57.9 mmol, 2.00 equiv.) was added slowly at rt. After stirring for 1 h 2-bromopropane (3.00 mL, 31.9 mmol, 1.10 equiv) was added. The reaction was stirred for 24 h at rt. Further NaH (60% in mineral oil, 580 mg, 14.5 mmol, 0.50 equiv.) and 2-bromopropane (0.54 mL, 5.8 mmol, 0.20 equiv.) were added. Afterwards, the reaction mixture was stirred for 3 d at rt. The reaction was stopped with a 1 M HCl solution. The aq. layer was extracted with Et_2O (3x). The combined organic phases were washed with brine (2x), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, PE/EtOAc = 10:1) to give product **283** (3.08 g, 17.1 mmol, 59%) as a yellow liquid.

Large scale

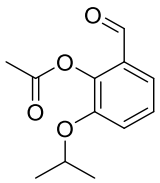
A solution of 2,3-dihydroxybenzaldehyde (**46**) (25.0 g, 181 mmol) in DMSO (150 mL) was added slowly to a suspension of NaH (60% in mineral oil, 18.1 g, 452 mmol, 2.50 equiv.) in DMSO (300 mL) at 0 °C. The reaction mixture was warmed up to rt and and stirred for 2 h. Then 2-bromopropane (17.0 mL, 181 mmol, 1.00 equiv.) was added and the resulting mixture was stirred for 5 d. The reaction was stopped by addition of a 1 M HCl solution. The aq. layer was extracted with Et_2O (3x). The combined organic phases were washed with brine (2x), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (PE/EtOAc = 10:1) to give product **283** (9.22 g, 51.2 mmol, 28%) as a yellow liquid.

The analytical data are consistent with those reported in the literature.[26]

R_f (PE/EtOAc = 9:1) = 0.51;

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 10.97 (s, 1H, CHO), 9.92 (s, 1H, OH), 7.21-7.18 (dd, *J* = 6.4, 9.1 Hz, 1H, H_{Ar}), 7.16-7.14 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 6.96-6.92 (t, *J* = 7.9 Hz, 1H, H_{Ar}), 4.62-4.56 (m, 1H, C*H*$(CH_3)_2$), 1.39-1.38 (d, *J* = 6.0 Hz, 6H, CH(C*H*$_3)_2$) ppm.

2-Formyl-6-isopropoxyphenyl acetate (**284**)

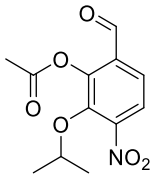


2-Hydroxy-3-isopropoxybenzaldehyde (**283**) (9.22 g, 51.2 mmol) was dissolved in pyridine (25 mL) and acetic anhydride (9.70 mL, 102 mmol, 2.00 equiv.) was added. The solution was stirred for 2.5 h at rt. The reaction mixture was acidified with a 1 M $KHSO_4$ solution at 0 °C and diluted with H_2O. The aq. phase was extracted with Et_2O (3x) and the combined organic phases were washed with a sat. $NaHCO_3$ solution (2x) and brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give the crude product **284** (11.5 g, 51.7 mmol, quant.) as an orange oil, which was used in the next step without further purification.

The analytical data are consistent with those reported in the literature.[26]

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 10.14 (s, 1H, CHO), 7.45-7-43 (dd, *J* = 1.4, 7.7 Hz, 1H, H_{Ar}), 7.32-7.28 (t, *J* = 7.9 Hz, 1H, H_{Ar}), 7.22-7-20 (dd, *J* = 1.3, 8.2 Hz, 1H, H_{Ar}) 4.59-4.53 (m, 1H, C*H*$(CH_3)_2$), 2.39 (s, 3H, CH_3), 1.35-1.34 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3)_2$) ppm.

6-Formyl-2-isopropoxy-3-nitrophenyl acetate (**285**)

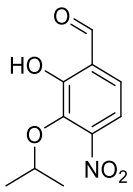


Fuming nitric acid (34.4 mL, 819 mmol, 16.0 equiv.) was stirred at -40 °C and acetate **284** (11.3 g, 51.2 mmol) in CH_2Cl_2 (73 mL) was added dropwise. The resulting reaction mixture was stirred for 3 h at -40 °C. Afterwards, the reaction mixture was diluted with H_2O. The aq. phase was extracted with CH_2Cl_2 (3x). The combined organic phases were washed with brine (2x), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give the crude product **285** (12.4 g, 46.2 mmol, 90%) as an orange oil, which was used in the next step without further purification.

The analytical data are consistent with those reported in the literature.[26]

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 10.07 (s, 1H, CHO), 7.76-7.74 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 7.69-7.67 (d, *J* = 8.5 Hz, 1H, H_{Ar}) 4.51-4.45 (m, 1H, C*H*$(CH_3)_2$), 2.44 (s, 3H, CH_3), 1.33-1.32 (d, *J* = 6.2 Hz, 6H, CH(C*H*$_3)_2$) ppm.

2-Hydroxy-3-isopropoxy-4-nitrobenzaldehyde (**286**)

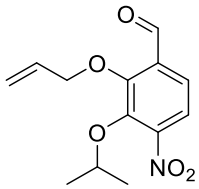


Acetate **285** (12.4 g, 46.2 mmol) was dissolved in THF (58 mL) and cooled to 0 °C. LiOH (11.1 g, 462 mmol, 10.0 equiv.) in H_2O (58 mL) was added and the resulting reaction mixture was warmed up to rt and stirred for 2 h. A 2 M HCl solution was added to the mixture until pH 1. The aq. phase was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give crude product **286** (10.2 g, quant.) as an orange oil, wich was used in the next step without further purification.

The analytical data are consistent with those reported in the literature.[26]

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 11.43 (s, 1H, CHO), 9.97 (s, 1H, OH), 7.40-7.38 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 7.25-7.22 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 4.92-4.85 (m, 1H, C*H*$(CH_3)_2$), 1.34-1.32 (d, *J* = 6.2 Hz, 6H, CH(C*H*$_3)_2$) ppm.

2-(Allyloxy)-3-isopropoxy-4-nitrobenzaldehyde (**287**)

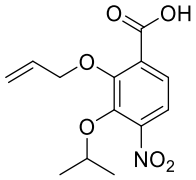


Alcohol **286** (10.2 g, 45.4 mmol) was dissolved in DMF (90 mL). K_2CO_3 (12.5 g, 90.7 mmol, 2.00 equiv.) and allyl bromide (5.88 mL, 68.0 mmol, 1.50 equiv.) were added at rt and the reaction mixture was stirred for 18 h at the same temperature. Then, H_2O was added at 0 °C. The aq. phase was extracted with Et_2O (3x) and the combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced. The residue was purified by column chromatography (PE/EtOAc = 7:1) to give crude product **287** (6.21 g, 23.4 mmol, 52%) as a yellow oil.

The analytical data are consistent with those reported in the literature.[26]

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 10.39 (s, 1H, CHO), 7.65-7.62 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 7.51-7.49 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.10-6.00 (m, 1H, C*H*CH_2), 5.41-5.37 (ddd, *J* = 1.4, 17.0 Hz, 1H, CHC*H*$_2$), 5.35-5.32 (ddd, *J* = 1.1, 10.3 Hz, 1H, CHC*H*$_2$), 4.74-4.72 (dt, *J* = 1.3, 6.1 Hz, 2H, OC*H*$_2$CH) 4.70-4.67 (m, 1H, C*H*$(CH_3)_2$), 1.33-1.31 (d, *J* = 6.2 Hz, 6H, CH(C*H*$_3)_2$) ppm.

2-(Allyloxy)-3-isopropoxy-4-nitrobenzoic acid (**7**)

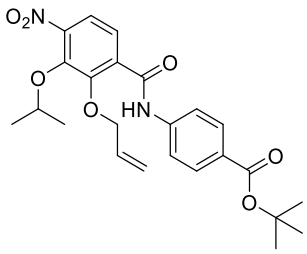


Aldehyde **287** (6.21 g, 23.4 mmol) and 2-methyl-2-butene (24.8 mL, 234 mmol, 10.0 equiv.) were dissolved in *t*BuOH (96 mL). $NaClO_2$ (2.32 g, 25.7 mmol, 1.10 equiv) in a 1 M NaH_2PO_4 solution (20 mL) was added dropwise at rt. The solution was stirred for 3 h. Then, a 1 M HCl solution was added. The aq. layer was extracted with Et_2O (3x) and the combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give the crude product **7** (6.91 g, 24.6 mmol, quant.) as a yellow amorphous amorphous solid.

The analytical data are consistent with those reported in the literature.[26]

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 7.94-7.92 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 7.59-7.57 (d, *J* = 8.7 Hz, 1H, H_{Ar}), 6.11-6.03 (m, 1H, C*H*CH_2), 5.49-5.43 (ddd, *J* = 1.1, 2.5, 17.0 Hz, 1H, CHC*H*$_2$), 5.42-5.39 (dd, *J* = 10.2 Hz, 1H, CHC*H*$_2$), 4.84-4.82 (dt, *J* = 1.1, 6.5 Hz, 2H, OC*H*$_2$CH), 4.65-4.60 (m, 1H, C*H*$(CH_3)_2$), 1.33-1.32 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3)_2$) ppm.

tert-Butyl 4-(2-(allyloxy)-3-isopropoxy-4-nitrobenzamido)benzoate (**86**)



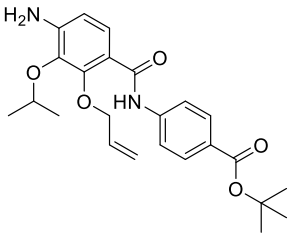
Benzoic acid **7** (2.00 g, 7.11 mmol) and *tert*-butyl 4-aminobenzoate (**13**) (1.31 g, 6.76 mmol, 0.95 equiv.) were dissolved in CH_2Cl_2 (23 mL). The solution was cooled to 0 °C and DIPEA (2.10 mL, 12.1 mmol, 1.70 equiv.) and $POCl_3$ (660 µL, 7.11 mmol, 1.00 equiv.) were added. The solution was stirred for 2 h at 0 °C. A sat. NH_4Cl solution was added and the aq. phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (dry load, hexane/EtOAc = 9:1, 5:1) to furnish amide **86** (2.42 g, 5.31 mmol, 79%) as brown amorphous solid.

The analytical data are consistent with those reported in the literature.[32]

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 10.73 (s, 1H, NH), 7.92-7.89 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.81-7.79 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.73-7.70 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 7.46-7.44 (d, *J* = 8.4 Hz,

2H, H_{Ar}), 6.01-5.90 (m, 1H, C*H*CH_2), 5.35-5.30 (m, 1H, CHC*H*$_2$), 5.19-5.16 (m, 1H, CHC*H*$_2$), 4.70-4.64 (m, 1H, C*H*$(CH_3)_2$), 4.60-4.59 (dt, *J* = 8.8 Hz, 2H, OC*H*$_2$CH), 1.54 (s, 9H, C(C*H*$_3)_3$), 1.24-1.23 (d, *J* = 8.8 Hz, 6H, CH(C*H*$_3)_2$) ppm.

tert-Butyl 4-(2-(allyloxy)-3-isopropoxy-4-aminobenzamido)benzoate (**89**)

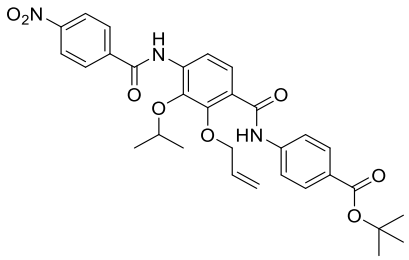


Compound **86** (2.42 g, 5.31 mmol) was dissolved in THF (9 mL) and EtOH (8 mL). Zinc dust (5.21 g, 79.6 mmol, 15.0 equiv.) was added. The mixture was cooled to 0 °C and AcOH (4.60 mL, 79.6 mmol, 15.0 equiv.) was added dropwise over 1 h. The mixture was warmed to rt. After completion of the reaction Et_2O was added and the reaction was terminated with a sat. $NaHCO_3$ solution. The mixture was filtered and the phases were separated. The aq. phase was extracted with Et_2O (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish amine **89** (1.95 g, 4.58 mmol, 86%) as yellow resin.

The analytical data are consistent with those reported in the literature.[32]

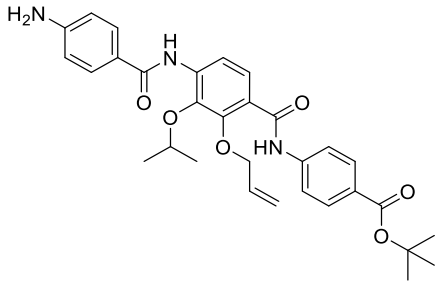
^{1}H-NMR (400 MHz, DMSO-d_6) = δ 10.23 (s, 1H, NH), 7.87-7.85 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.77-7.75 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.41-7.39 (d, *J* = 8.7 Hz, 1H, H_{Ar}), 6.57-6.55 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 6.12-6.03 (m, 1H, C*H*CH_2), 5.59 (s, 2H, NH_2), 5.48-5.43 (dd, *J* = 17.1, 1.6 Hz, 1H, CHC*H*$_2$), 5.28-5.26 (dd, *J* = 10.4, 1.2 Hz, 1H, CHC*H*$_2$), 4.62-4.60 (d, *J* = 5.6 Hz, 2H, OC*H*$_2$CH), 4.49-4.43 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 1.54 (s, 9H, C(C*H*$_3)_3$), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3)_2$) ppm.

tert-Butyl 4-(2-(allyloxy)-3-isopropoxy-4-(4-nitrobenzamido)benzamido)benzoate (**92**)



Amine **89** (1.95 g, 4.58 mmol) was dissolved in CH_2Cl_2 (13 mL) and pyridine (1.50 mL, 18.3 mmol, 4.00 equiv.) was added. 4-Nitrobenzoyl chloride (1.36 g, 7.33 mmol, 1.60 equiv.) was added in portions and the resulting mixture was stirred at rt for 2 h. A 1 M $KHSO_4$ solution was added and the aq. phase was extracted with CH_2Cl_2 (3x). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure to furnish crude product **92** (3.06 g, quant.) as yellow amorphous solid, which was used in the next step without further purification.

tert-Butyl 4-(2-(allyloxy)-4-(4-aminobenzamido)-3-isopropoxybenzamido)benzoate (**5**)



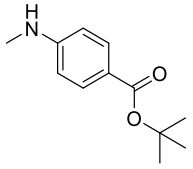
Compound **92** (2.64 g, 4.58 mmol) was dissolved in THF (8 mL) and EtOH (7 mL). Zinc dust (4.50 g, 68.7 mmol, 15.0 equiv.) was added. The mixture was cooled to 0 °C and AcOH (3.90 mL, 68.7 mmol, 15.0 equiv.) was added dropwise over 1 h. The mixture was warmed to rt. After completion of the reaction Et_2O was added and the reaction was determined with a sat. $NaHCO_3$ solution. The mixture was filtered and the phases were separated. The aq. phase was extracted with Et_2O (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude prodcut was purified by column chromatography (dry load, hexane/EtOAc = 2:1) to furnish amine **5** (1.37 g, 2.51 mmol, 55%) as yellow amorphous solid.

The analytical data are consistent with those reported in the literature.[32]

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 10.49 (s, 1H, NH), 9.05 (s, 1H, NH), 7.96-7.94 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 7.90-7.68 (m, 8H, H_{Ar}), 7.41-7.39 (d, *J* = 8.6 Hz, 1H, H-5), 6.64-6.62 (d, *J* = 8.6 Hz, 2H, NH_2), 6.05-5.97 (m, 1H, C*H*CH_2), 5.40-5.36 (dd, *J* = 1.5, 17.2 Hz, 1H, CHC*H*$_2$), 5.22-5.19 (dd, *J* = 1.2, 10.4 Hz, 1H, CHC*H*$_2$), 4.60-4.59 (d, *J* = 5.4 Hz, 2H,

OC*H*$_2$CH), 4.56-4.50 (p, *J* = 6.1 Hz, 1H, C*H*(CH$_3$)$_2$), 1.55 (s, 9H, C(C*H*$_3$)$_3$), 1.28-1.27 (d, *J* = 6.2 Hz, 6H, CH(C*H*$_3$)$_2$) ppm.

tert-Butyl 4-(methylamino)benzoate (**85**)



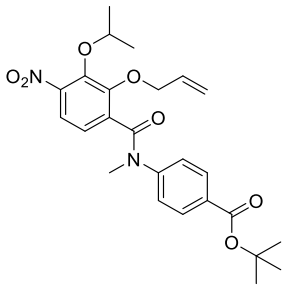
4-Methylaminobenzoic acid (0.50 g, 3.31 mmol) was dissolved in *t*BuOH (17 mL). EDC·HCl (2.22 g, 11.6 mmol, 3.50 equiv.) and DMAP (2.02 g, 16.5 mmol, 5.00 equiv.) were added and the solution was stirred at rt for 20 h. The solvent was removed under reduced pressure. The residue was purified by column chromatography (dry load, PE/EtOAc = 6:1) to furnish ester **85** (0.34 g, 1.65 mmol, 50%) as colorless oil.

The analytical data are consistent with those reported in the literature.[97]

R$_f$ (PE/EtOAc = 6:1) = 0.40;

^{1}H-NMR (400 MHz, CDCl$_3$) = δ 7.84-7.82 (d, *J* = 8.8 Hz, 2H, H$_{Ar}$), 6.57-6.55 (d, *J* = 8.8 Hz, 2H, H$_{Ar}$), 4.50 (bs, 1H, NH), 2.88 (s, 3H, CH$_3$), 1.57 (s, 9H, C(CH$_3$)$_3$) ppm.

tert-Butyl 4-(2-(allyloxy)-3-isopropoxy-*N*-methyl-4-nitrobenzamido)benzoate (**87**)



Benzoic acid **7** (484 mg, 1.72 mmol) and amine **85** (339 mg, 1.64 mmol, 0.95 equiv.) were dissolved in CH$_2$Cl$_2$ (5 mL). The solution was cooled to 0 °C and DIPEA (510 µL, 2.93 mmol, 1.70 equiv.) and POCl$_3$ (160 µL, 1.72 mmol, 1.00 equiv.) were added. The solution was stirred for 2 h at 0 °C. A sat. NH$_4$Cl solution was added and the aq. phase was extracted with CH$_2$Cl$_2$. The combined organic phases were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, PE/EtOAc = 4:1) to furnish amide **87** (639 mg, 1.36 mmol, 79%) as yellow gum.

R$_f$ (PE/EtOAc = 4:1) = 0.16;

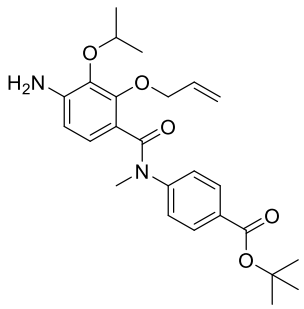
^{1}H-NMR (400 MHz, CDCl$_3$) = δ 7.79-7.77 (d, *J* = 8.2 Hz, 2H, H$_{Ar}$), 7.40-7.38 (d, *J* = 8.1 Hz, 1H, H$_{Ar}$), 7.09-7.07 (d, *J* = 8.1 Hz, 2H, H$_{Ar}$), 7.03-7.01 (d, *J* = 8.3 Hz, 1H, H$_{Ar}$), 6.07-5.97 (m,

1H, C*H*CH_2), 5.40-5.35 (dq, *J* = 1.5, 17.2 Hz, 1H, CHC*H*$_2$), 5.30-5.27 (dq, *J* = 1.4, 10.4 Hz, 1H, CHC*H*$_2$), 4.53-4.52 (d, *J* = 4.6 Hz, 2H, OCH_2), 4.29-4.23 (p, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 3.49 (s, 3H, NCH_3), 1.54 (s, 9H, $C(CH_3)_3$), 1.01 (bs, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (101 MHz, $CDCl_3$) = δ 166.8 (CO), 164.7 (CO), 149.6 (C_{Ar}), 146.7 (C_{Ar}), 146.4 (C_{Ar}), 144.8 (C_{Ar}), 137.0 (C_{Ar}), 133.2 (*C*HCH_2), 130.9 (C_{Ar}), 130.1 (C_{Ar}), 126.8 (C_{Ar}), 122.3 (C_{Ar}), 120.0 (C_{Ar}), 118.5 (CH*C*H_2), 81.6 (*C*$(CH_3)_3$), 77.4 (*C*$H(CH_3)_2$), 75.2 (OCH_2), 37.1 (NCH_3), 28.3 ($C(CH_3)_3$), 22.0 ($CH(CH_3)_2$) ppm;

HRMS (ESI): m/z calculated for $C_{25}H_{30}N_2O_7Na$ $[M+Na]^+$: 493.1951; found: 493.1956.

tert-Butyl 4-(2-(allyloxy)-4-amino-3-isopropoxy-*N*-methylbenzamido)benzoate (**90**)



Compound **87** (587 mg, 1.25 mmol) was dissolved in THF (2.1 mL) and EtOH (1.8 mL). Zinc dust (1.22 g, 18.7 mmol, 15.0 equiv.) was added. The mixture was cooled to 0 °C and AcOH (1.00 mL, 18.7 mmol, 15.0 equiv.) was added dropwise over 1 h. The mixture was warmed to rt and stirred for 1 h. After completion of the reaction Et_2O was added and the reaction was terminated with a sat. $NaHCO_3$ solution. The mixture was filtered and the phases were separated. The aq. phase was extracted with Et_2O (2x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish amine **90** (533 mg, 1.21 mmol, 97%) as colorless amorphous solid.

R_f (PE/EtOAc = 2:1) = 0.21

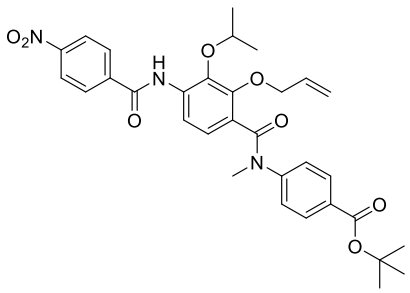
^{1}H-NMR (400 MHz, $CDCl_3$) = δ 7.77-7.75 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.06-7.04 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 6.88-6.86 (d, *J* = 8.2 Hz, 1H, H_{Ar}), 6.51-6.49 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 6.04-5.94 (m, 1H, C*H*CH_2), 5.34-5.29 (dq, *J* = 1.6, 17.2 Hz, 1H, CHC*H*$_2$), 5.23-5.19 (dq, *J* = 1.5, 10.4 Hz, 1H, CHC*H*$_2$), 4.41-4.39 (d, *J* = 5.6 Hz, 1H, OCH_2), 4.13-4.07 (p, *J* = 6.0 Hz, 1H, C*H*$(CH_3)_2$), 3.45 (s, 3H, NCH_3), 1.54 (s, 9H, $C(CH_3)_3$), 1.03-1.01 (d, *J* = 6.0 Hz, 1H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (101 MHz, $CDCl_3$) = δ 169.1 (CO), 165.2 (CO), 148.6 (C_{Ar}), 148.1 (C_{Ar}), 137.9 (C_{Ar}), 134.2 (*C*HCH_2), 131.4 (C_{Ar}), 129.6 (C_{Ar}), 129.4 (C_{Ar}), 126.3 (C_{Ar}), 123.9 (C_{Ar}), 117.3

(CHCH$_2$), 111.9 (C$_{Ar}$), 81.2 (*C*(CH$_3$)$_3$), 74.7 (*C*H(CH$_3$)$_2$), 74.5 (OCH$_2$), 37.3 (NCH$_3$), 28.3 (C(*C*H$_3$)$_3$), 22.3 (CH(*C*H$_3$)$_2$) ppm;

HRMS (ESI): m/z calculated for $C_{25}H_{32}N_2O_5Na$ $[M+Na]^+$: 463.2209; found: 463.2206.

tert-Butyl 4-(2-(allyloxy)-3-isopropoxy-*N*-methyl-4-(4-nitrobenzamido)benzamido)benzoate (**93**)



Amine **90** (200 mg, 0.45 mmol) and pyridine (150 µL, 1.82 mmol, 4.00 equiv.) was dissolved in CH_2Cl_2 (3 mL). 4-Nitrobenzoyl chloride (135 mg, 0.73 mmol, 1.60 equiv.) was added in small portions. The solution was stirred at rt für 3 h. A sat. $KHSO_4$ solution was added and the aq. phase was extracted with CH_2Cl_2 (2x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, PE/EtOAc = 3:1) to furnish amide **93** (245 mg, 0.42 mmol, 92%) as yellow amorphous solid.

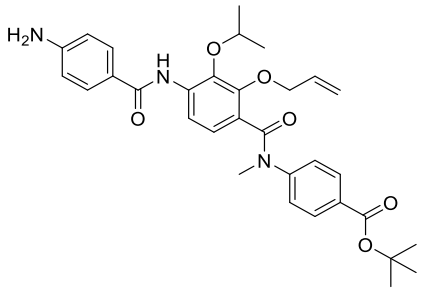
The *N*-methyl group is not visible in the ^{13}C NMR spectrum and may appear underneath the solvent peak.

R$_f$ (PE/EtOAc = 3:1) = 0.18;

^{1}H-NMR (400 MHz, DMSO-d$_6$) = δ 9.87 (s, 1H, NH), 8.36-8.34 (d, *J* = 8.8 Hz, 2H, H$_{Ar}$), 8.14-8.12 (d, *J* = 8.6 Hz, 2H, H$_{Ar}$), 7.72-7.71 (d, *J* = 6.3 Hz, 2H, H$_{Ar}$), 7.54-7.52 (d, *J* = 8.2 Hz, 1H, H$_{Ar}$), 7.24 (bs, 2H, H$_{Ar}$), 7.06-7.04 (d, *J* = 8.2 Hz, 1H, H$_{Ar}$), 6.07-5.97 (m, 1H, C*H*CH$_2$), 5.39-5.34 (dd, *J* = 1.6, 17.2 Hz, 1H, CHC*H*$_2$), 5.26-5.23 (dd, *J* = 1.5, 10.5 Hz, 1H, CHC*H*$_2$), 4.43 (bs, 2H, OCH$_2$), 4.05-4.00 (m, 1H, C*H*(CH$_3$)$_2$), 3.39 (s, 3H, NCH$_3$), 1.49 (s, 9H, C(CH$_3$)$_3$), 0.97 (bs, 6H, CH(C*H*$_3$)$_2$) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 167.1 (CO), 164.2 (CO), 163.5 (CO), 149.2 (C_{Ar}), 147.8 (C_{Ar}), 147.3 (C_{Ar}), 142.7 (C_{Ar}), 139.9 (C_{Ar}), 134.0 (C_{Ar}), 133.6 (*C*HCH$_2$), 129.1 (C_{Ar}), 129.0 (C_{Ar}), 128.9 (C_{Ar}), 126.5 (C_{Ar}), 123.7 (C_{Ar}), 122.6 (C_{Ar}), 119.8 (C_{Ar}), 117.1 (C-12), 80.7 (*C*(CH$_3$)$_3$), 75.2 (*C*H(CH$_3$)$_2$), 73.9 (OCH$_2$), 27.7 (C(*C*H$_3$)$_3$), 21.8 (CH(*C*H$_3$)$_2$) ppm;
HRMS (ESI): m/z calculated for $C_{32}H_{35}N_3O_8Na[M+Na]^+$: 612.2322; found: 612.2311.

tert-Butyl 4-(2-(allyloxy)-4-(4-aminobenzamido)-3-isopropoxy-*N*-methylbenzamido)benzoate (**95**)



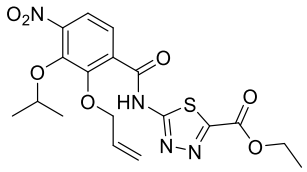
Compound **93** (239 mg, 0.40 mmol) was dissolved in THF (1 mL) and EtOH (1 mL). Zinc dust (397 mg, 6.07 mmol, 15.0 equiv.) was added. The mixture was cooled to 0 °C and AcOH (350 µL, 6.07 mmol, 15.0 equiv.) was added dropwise over 1 h. The mixture was warmed to rt and stirred for 1 h. After completion of the reaction Et_2O was added and the reaction was terminated with a sat. $NaHCO_3$ solution. The mixture was filtered and the phases were separated. The aq. phase was extracted with Et_2O (2x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc = 1:1) to furnish amine **95** (163 mg, 0.29 mmol, 72%) as colorless amorphous solid.
The *N*-methyl group is not visible in the ^{13}C NMR spectrum and may appear underneath the solvent peak.
R$_f$ (PE/EtOAc = 1:1) = 0.44;
^{1}H-NMR (400 MHz, DMSO-d_6) = δ 8.81 (s, 1H, NH), 7.79-7.69 (m, *J* = 8.6 Hz, 4H, H_{Ar}), 7.61-7.59 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.22 (bs, 2H, H_{Ar}), 7.01-6.99 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 6.87-6.85 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 6.60-6.58 (d, *J* = 8.6 Hz, 2H, NH_2) 6.06-5.96 (m, 1H, C*H*CH$_2$), 5.38-5-33 (dd, *J* = 1.7, 17.2 Hz, 1H, CHC*H*$_2$), 5.25-5.22 (dq, *J* = 1.6, 10.5 Hz, 1H, CHC*H*$_2$),

4.41-40 (d, J = 4.2 Hz, 2H, OCH_2), 4.02 (bs, 1H, CH(CH_3)$_2$), 3.38 (s, 3H, NCH_3), 1.48 (s, 9H, C(CH_3)$_3$), 0.99 (bs, 6H, CH(CH_3)$_2$) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 167.2 (CO), 164.3 (CO), 164.2 (CO), 152.5 (C_{Ar}), 147.4 (C_{Ar}), 134.8 (C_{Ar}), 134.6 (C_{Ar}), 134.1 (CHCH$_2$), 129.1 (C_{Ar}), 128.9 (C_{Ar}), 128.7 (C_{Ar}), 128.3 (C_{Ar}), 127.5 (C_{Ar}), 127.0 (C_{Ar}), 126.4 (C_{Ar}), 122.8(C_{Ar}), 120.1 (C_{Ar}), 117.1 (CHCH$_2$), 112.8(C_{Ar}), 80.7 (C(CH$_3$)$_3$), 75.1 (CH(CH$_3$)$_2$), 73.9 (OCH_2), 27.7 (C(CH$_3$)$_3$), 21.8 (CH(CH$_3$)$_2$) ppm;

HRMS (ESI): m/z calculated for $C_{32}H_{37}N_3O_6Na$ $[M+Na]^+$: 582.2580; found: 582.2585.

Ethyl 5-(2-(allyloxy)-3-isopropoxy-4-nitrobenzamido)-1,3,4-thiadiazole-2-carboxylate (**222**)



Benzoic acid **7** (208 mg, 0.74 mmol) and amine **221** (122 mg, 0.70 mmol, 0.95 equiv.) were dissolved in CH_2Cl_2 (2.2 mL). The solution was cooled to 0 °C and DIPEA (220 µL, 1.26 mmol, 1.70 equiv.) and $POCl_3$ (70 µL, 0.74 mmol, 1.00 equiv.) were added. The solution was stirred at 0 °C for 1 h. A sat. NH_4Cl solution was added and the aq. phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, PE/EtOAc = 5:1, 2:1) to furnish amide **222** (138 mg, 0.32 mmol, 43%) as colorless amorphous solid.

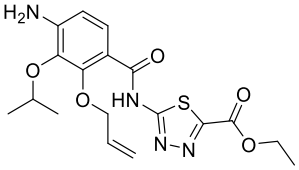
R_f (PE/EtOAc = 2:1) = 0.38;

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 13.53 (s, 1H, NH), 7.75-7.73 (d, J = 8.4 Hz, 1H, H_{Ar}), 7.54-7.51 (d, J = 8.4 Hz, 1H, H_{Ar}), 5.96-5.86 (m, 1H, CHCH$_2$), 5.32-5.27 (dq, J = 1.6, 17.2 Hz, 1H, CHCH_2), 5.18-5.15 (dq, J = 1.5, 10.4 Hz, 1H, CHCH_2), 4.73-4.67 (p, J = 6.2 Hz, 1H, CH(CH_3)$_2$), 4.58-4.56 (dt, J = 1.2, 6.9 Hz, 2H, OCH_2), 4.46-4.40 (q, J = 7.1 Hz, 2H, CH_2CH$_3$) 1.38 (t, J = 7.1 Hz, 3H, CH$_2$CH_3), 1.25-1.23 (d, J = 6.1 Hz, 6H, CH(CH_3)$_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 164.2 (CO), 161.5 (CO), 158.8 (C_{Ar}), 154.2 (C_{Ar}), 150.6 (C_{Ar}), 147.5 (C_{Ar}), 143.2 (C_{Ar}), 132.9 (C_{Ar}), 132.9 (CHCH$_2$), 123.8 (C_{Ar}), 119.2 (C_{Ar}), 118.5 (CHCH$_2$), 77.3 (CH(CH$_3$)$_2$), 74.8 (OCH_2), 62.5 (CH$_2$CH$_3$), 22.0 (CH(CH$_3$)$_2$), 14.0 (CH$_2C$H$_3$) ppm;

HRMS (ESI): m/z calculated for $C_{18}H_{20}N_4O_7SNa$ $[M+Na]^+$: 459.0950; found: 459.0951.

Ethyl 5-(2-(allyloxy)-4-amino-3-isopropoxybenzamido)-1,3,4-thiadiazole-2-carboxylate (**288**)



Compound **222** (167 mg, 0.40 mmol) was suspended in EtOH (4 mL) and $SnCl_2 \cdot 2H_2O$ (445 mg, 1.98 mmol, 5.00 equiv.) was added. The mixture was stirred at rt for 4 d. A sat. $NaHCO_3$ solution was added. The mixture was filtered and the residue was washed with EtOAc. The aq. filtrate was extracted with EtOAc (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish aniline **288** (153 mg, 0.38 mmol, 95%) as yellow amorphous solid.

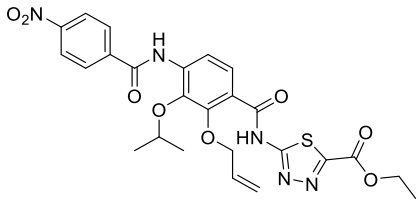
R_f (PE/EtOAc = 1:1) = 0.70;

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 11.99 (s, 1H, NH), 7.48-7.46 (d, *J* = 8.7 Hz, 1H, H_{Ar}), 6.59-6.57 (d, *J* = 8.7 Hz, 1H, H_{Ar}), 6.12-6.04 (m, 1H, C*H*CH_2), 5.91 (s, 2H, NH_2), 5.48-5.44 (dd, *J* = 1.5, 17.2 Hz, 1H, CHC*H*$_2$), 5.31-5.29 (dd, *J* = 1.4, 10.4 Hz, 1H, CHC*H*$_2$), 4.66-4.65 (d, *J* = 5.8 Hz, 1H, OC*H*$_2$CH), 4.50-4.43 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.43-4.39 (q, *J* = 7.1 Hz, 2H, C*H*$_2$CH$_3$) 1.36 (t, *J* = 7.1 Hz, 3H, CH_2C*H*$_3$), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3$)$_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 163.1 (CO), 161.6 (CO), 159.0 (C_{Ar}), 153.6 (C_{Ar}), 151.7 (C_{Ar}), 149.5 (C_{Ar}), 135.1 (C_{Ar}), 133.1 (*C*HCH_2), 126.9 (C_{Ar}), 119.0 (CH*C*H$_2$), 110.6 (C_{Ar}), 110.0 (C_{Ar}), 74.5 (*C*H$(CH_3)_2$), 74.0 (OC*H*$_2$CH), 62.3 (*C*H$_2$CH$_3$), 22.1 (CH(*C*H$_3$)$_2$), 14.0 (CH_2*C*H$_3$) ppm;

HRMS (ESI): m/z calculated for $C_{18}H_{22}N_4O_7SNa$ $[M+Na]^+$: 429.1209; found: 429.1213.

Ethyl 5-(2-(allyloxy)-3-isopropoxy-4-(4-nitrobenzamido)benzamido)-1,3,4-thiadiazole-2-carboxylate (**289**)



Amine **288** (151 mg, 0.37 mmol) and pyridine (120 µL, 1.49 mmol, 4.00 equiv.) were dissolved in CH_2Cl_2 (2.5 mL). 4-Nitrobenzoyl chloride (110 mg, 0.59 mmol, 1.60 equiv.) was added in portions. The mixture was stirred at rt for 3 h. A sat. $KHSO_4$ solution was added and the aq. phase was extracted with CH_2Cl_2 (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column

chormatography (PE/EtOAc = 2:1, 1:1) to furnish product **289** (173 mg, 0.31 mmol, 84%) as yellow amorphous solid.

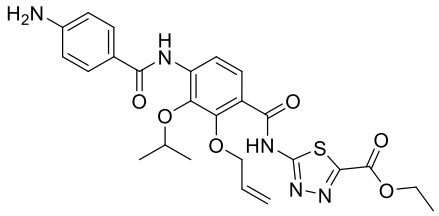
$\mathbf{R_f}$ (PE/EtOAc = 1:1) = 0.49;

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 13.09 (s, 1H, NH), 10.17 (s, 1H, NH), 8.41-8.39 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 8.22-8.20 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.77-7.76 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 7.50-7.49 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.02-5.96 (m, 1H, C*H*CH_2), 5.37-5.33 (dq, *J* = 1.6, 17.2 Hz, 1H, CHC*H*$_2$), 5.21-5.19 (dd, *J* = 1.5, 10.5 Hz, 1H, CHC*H*$_2$), 4.61-4.60 (d, *J* = 5.6 Hz, 1H, OC*H*$_2$CH), 4.54-4.47 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.45-4.41 (q, *J* = 7.1 Hz, 2H, C*H*$_2$$CH_3$) 1.38-1.35 (t, *J* = 7.1 Hz, 3H, CH_2C*H*$_3$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3$)$_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 164.6 (CO), 163.9 (CO), 161.7 (CO), 158.9 (C_{Ar}), 153.9 (C_{Ar}), 150.5 (C_{Ar}), 149.4 (C_{Ar}), 143.4 (C_{Ar}), 139.7 (C_{Ar}), 136.3 (C_{Ar}), 133.4 (*C*HCH_2), 129.2 (C_{Ar}), 124.8 (C_{Ar}), 124.1 (C_{Ar}), 123.8 (C_{Ar}), 120.0 (C_{Ar}), 118.2 (CH*C*H_2), 76.4 (*C*H$(CH_3)_2$), 74.4 (O*C*H_2CH), 62.4 (*C*$H_2$$CH_3$), 22.3 (CH(*C*$H_3$)$_2$), 14.0 ($CH_2$*C*$H_3$) ppm;

HRMS (ESI): m/z calculated for $C_{25}H_{25}N_5O_8SNa$ $[M+Na]^+$: 578.1322; found: 578.1326.

Ethyl 5-(2-(allyloxy)-4-(4-aminobenzamido)-3-isopropoxybenzamido)-1,3,4-thiadiazole-2-carboxylate (**223**)



Compound **289** (134 mg, 0.24 mmol) was suspended in EtOH (3.2 mL) and $SnCl_2 \cdot 2H_2O$ (273 mg, 1.21 mmol, 5.00 equiv.) was added. The mixture was stirred at rt for 6 d. A sat. $NaHCO_3$ solution was added. The mixture was filtered and the residue was washed with an excess of EtOAc. The aq. filtrate was extracted with EtOAc (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (dry load, PE/EtOAc = 3:2) to furnish aniline **223** (76.3 mg, 0.15 mmol, 60%) as yellow amorphous solid.

One aromatic ^{13}C-signal and two carbonyl ^{13}C-signals are not visible.

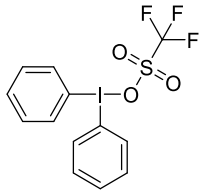
^{1}H-NMR (600 MHz, DMSO-d_6) = δ 12.92 (s, 1H, NH), 9.07 (s, 1H, NH), 8.02-8.01 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 7.70-7.68 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.50-7.48 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 6.64-6.62 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 6.04-5.97 (m, 1H, C*H*CH_2), 5.90 (s, 2H, NH_2), 5.39-5.35 (dq, *J* = 1.6, 17.2 Hz, 1H, CHC*H*$_2$), 5.23-5.20 (dd, *J* = 1.6, 10.5 Hz, 1H, CHC*H*$_2$), 4.60-4.58 (d, *J* = 5.6 Hz, 1H, OC*H*$_2$CH), 4.59-4.53 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.45-4.40 (q,

J = 7.1 Hz, 2H, C*H*$_2$CH$_3$), 1.38-1.35 (t, *J* = 7.1 Hz, 3H, CH$_2$C*H*$_3$), 1.30-1.28 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3$)$_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d$_6$) = δ 164.5 (CO), 159.0 (C$_{Ar}$), 153.8 (C$_{Ar}$), 152.7 (C$_{Ar}$), 150.2 (C$_{Ar}$), 141.0 (C$_{Ar}$), 137.7 (C$_{Ar}$), 133.4 (*C*HCH$_2$), 129.1 (C$_{Ar}$), 124.6 (C$_{Ar}$), 119.8 (C$_{Ar}$), 118.3 (CH*C*H$_2$), 117.0 (C$_{Ar}$), 112.9 (C$_{Ar}$), 76.2 (*C*H(CH$_3$)$_2$), 74.4 (O*C*H$_2$CH), 62.4 (*C*H$_2$CH$_3$), 22.3 (CH(*C*H$_3$)$_2$), 14.0 (CH$_2$*C*H$_3$) ppm;

HRMS (ESI): m/z calculated for $C_{25}H_{27}N_5O_6SNa$ $[M+Na]^+$: 548.1580; found: 548.1560.

Diphenyl-λ^3-iodaneyl trifluoromethanesulfonate (**83**)

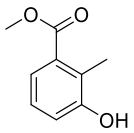


Iodine (500 mg, 1.97 mmol) and *m*CPBA (65%, 1.57 g, 5.91 mmol, 3.00 equiv.) were dissolved in CH$_2$Cl$_2$ (22 mL). The solution was cooled to 0 °C and benzene (720 µL, 8.08 mmol, 4.1 equiv.) was added. *p*TsOH (1.10 mL, 11.8 mmol, 6.00 equiv.) was added dropwise. The mixture was stirred at rt for 1 h before concentration under reduced pressure. The residue was diluted with Et$_2$O and stirred for 15 min before storage in the freezer overnight. Filtration and drying *in vacuo* furnished product **83** (1.30 g, 3.09 mmol, 78%) as beige amorphous solid.

The analytical data are consistent with those reported in the literature.[98]

^{1}H-NMR (400 MHz, DMSO-d$_6$) = δ 8.19-8.16 (d, *J* = 8.5 Hz, 4H, H$_{Ar}$), 7.72-7.68 (t, *J* = 7.2 Hz, 2H, H$_{Ar}$), 7.56-7.52 (t, *J* = 7.7 Hz, 4H, H$_{Ar}$) ppm.

Methyl 3-hydroxy-2-methylbenzoate (**52**)



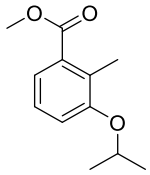
3-Hydroxy-2-methylbenzoic acid **47** (2.00 g, 13.1 mmol) was dissolved in MeOH (6 mL) and SOCl$_2$ (1.63 mL, 22.3 mmol, 1.70 equiv.) was added at 0 °C. The solution was stirred at 80 °C for 2 h. All volutiles were removed under reduced pressure to furnish ester **52** (quant.) as colorless amorphous solid, which was used in the next step without further purification

The analytical data are consistent with those reported in the literature.[99]

R$_f$ (PE/EtOAc = 7:1) = 0.22;

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 7.41-7.39 (dd, *J* = 1.0, 7.8 Hz, 1H, H_{Ar}), 7.11-7.07 (t, *J* = 7.9 Hz, 1H, H_{Ar}), 6.96-6.93 (dd, *J* = 0.8, 8.0 Hz, 1H, H_{Ar}), 4.39 (bs, 1H, OH), 3.89 (s, 3H, CO_2CH_3), 2.45 (s, 3H, CH_3) ppm.

Methyl 3-hydroxy-2-methylbenzoate (**48**)



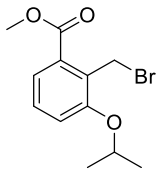
Ester **52** (2.18 g, 13.1 mmol) was dissolved in DMF (10 mL). NaH (60% in mineral oil, 631 mg, 15.8 mmol, 1.20 equiv.) was added in portions. The mixture was stirred at rt for 1 h. 2-Bromopropane (1.48 mL, 15.8 mmol, 1.20 equiv.) was added and the mixture was stirred at rt for 20 h. The reaction was stopped with a 1 M HCl solution. The aq. phase was extracted with Et_2O (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered und concentrated. The crude product was purified by column chromatography (PE/EtOAc = 7:1) to furnish product **48** (1.66 g, 7.98 mmol, 92 % brsm) as colorless oil.

$\mathbf{R}_f$ (PE/EtOAc = 7:1) = 0.66;

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 7.39-7.37 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.18-7.14 (t, *J* = 7.8 Hz, 1H, H_{Ar}), 7.00-6.99 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 4.53-4.47 (sept, *J* = 6.0 Hz, 1H, C*H*$(CH_3)_2$), 3.88 (s, 3H, CO_2CH_3), 2.41 (s, 3H, CH_3), 1.35-1.33 (d, *J* = 5.9 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (101 MHz, $CDCl_3$) = δ 168.8 (CO), 156.6 (C_{Ar}), 132.0 (C_{Ar}), 129.9 (C_{Ar}), 126.0 (C_{Ar}), 122.2 (C_{Ar}), 117.1 (C_{Ar}), 71.2 (*C*H$(CH_3)_2$), 52.1 (CO_2*C*H_3), 22.3 (CH(*C*$H_3)_2$), 13.2 (CH_3) ppm.

Methyl 2-(bromomethyl)-3-isopropoxybenzoate (**49**)



Ester **48** (1.63 g, 7.81 mmol) was dissolved in CCl_4 (40 mL). NBS (2.08 g, 11.7 mmol, 1.50 equiv.) and AIBN (0.27 g, 1.56 mmol, 0.2 equiv.) were added. The mixture was stirred at 100 °C for 16 h. The solvent was removed and the residue was diluted with EtOAc and H_2O. The aq. phase was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product

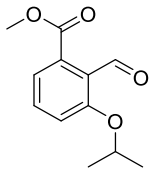
was purified by column chromatography (PE/EtOAc = 10:1) to furnish bromide **49** (2.16 g, 7.54 mmol, 97%) as yellow amorphous solid.

R_f (PE/EtOAc = 10:1) = 0.44;

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 7.49-7.46 (dd, *J* = 1.1, 7.8 Hz, 1H, H_{Ar}), 7.31-7.27 (t, *J* = 8.1 Hz, 1H, H_{Ar}), 7.07-7.05 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 5.04 (s, 2H, CH_2Br), 4.68-4.59 (sept, *J* = 6.1 Hz, 1H, $CH(CH_3)_2$), 3.93 (s, 3H, CO_2CH_3), 1.41-1.39 (d, *J* = 6.0 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (101 MHz, $CDCl_3$) = δ 167.5 (CO), 156.5 (C_{Ar}), 131.1 (C_{Ar}), 129.2 (C_{Ar}), 128.6 (C_{Ar}), 122.7 (C_{Ar}), 117.1 (C_{Ar}), 71.3 ($CH(CH_3)_2$), 52.5 (CO_2CH_3), 25.0 (CH_2Br), 22.2 ($CH(CH_3)_2$) ppm.

Methyl 2-formyl-3-isopropoxybenzoate (**50**)



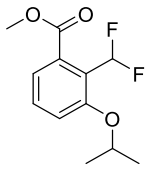
Bromide **49** (1.20 g, 4.19 mmol) was dissolved in MeCN (36 mL) and NMO (1.96 g, 16.8 mmol, 4.00 equiv.) was added. The solution was stirred at rt for 3 h. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc = 10:1) to furnish aldehyde **50** (873 mg, 3.93 mmol, 94%) as yellowish amorphous solid.[100]

R_f (PE/EtOAc = 10:1) = 0.26;

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 10.47 (s, 1H, CHO), 7.52-7.48 (t, *J* = 7.9 Hz, 1H, H_{Ar}), 7.10-7.07 (m, 2H, H_{Ar}), 4.70-4.64 (sept, *J* = 6.0 Hz, 1H, $CH(CH_3)_2$), 3.90 (s, 3H, CO_2CH_3), 1.39-1.38 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (101 MHz, $CDCl_3$) = δ 190.4 (CHO), 169.4 (CO_2CH_3), 159.6 (C_{Ar}), 134.3 (C_{Ar}), 134.1 (C_{Ar}), 125.1 (C_{Ar}), 120.1 (C_{Ar}), 116.3 (C_{Ar}), 71.9 ($CH(CH_3)_2$), 52.9 (CO_2CH_3), 22.1 ($CH(CH_3)_2$) ppm.

Methyl 2-(difluoromethyl)-3-isopropoxybenzoate (**51**)



Aldehyde **50** (299 mg, 1.35 mmol) was dissolved in CH_2Cl_2 (3.3 mL) and DAST (533 µL, 4.04 mmol, 4.00 equiv.) was added at 0 °C. The mixture was stirred at rt for 20 h. A sat.

$NaHCO_3$ solution was added at 0 °C and the aq. phase was extracted with CH_2Cl_2 (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc = 15:1) to furnish product **51** (204 mg, 0.83 mmol, 92% brsm) as yellow oil.

$\mathbf{R_f}$ (PE/EtOAc = 10:1) = 0.34;

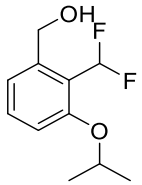
^{1}H-NMR (400 MHz, $CDCl_3$) = δ 7.44-7.40 (t, *J* = 8.0 Hz, 1H, H_{Ar}), 7.31-7.03 (t, *J* = 54.5 Hz, 1H, CHF_2), 7.22-7.20 (d, *J* = 7.7 Hz, 1H, H_{Ar}), 7.09-7.07 (d, *J* = 8.4 Hz, 1H, H_{Ar}) 4.66-4.60 (sept, *J* = 6.0 Hz, 1H, C*H*$(CH_3)_2$), 3.91 (s, 3H, CO_2CH_3), 1.37-1.36 (d, *J* = 5.9 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (101 MHz, $CDCl_3$) = δ 168.5 (CO), 156.8 (C_{Ar}), 133.0 (t, *J* = 3.5 Hz, C_{Ar}), 131.7 (t, *J* = 1.3 Hz, C_{Ar}), 122.0-121.6 (t, *J* = 21.9 Hz, C_{Ar}), 121.2 (t, *J* = 1.1 Hz, C_{Ar}), 116.7 (C_{Ar}), 113.8-109.1 (t, *J* = 237.3 Hz, CHF_2), 71.9 (*C*H$(CH_3)_2$), 52.8 (CO_2*C*H_3), 22.1 (CH(*C*$H_3)_2$) ppm;

^{19}F-NMR (376 MHz, $CDCl_3$) = δ -114.67- -114.81 (d, *J* = 54.6 Hz, 2F, CHF_2) ppm;

HRMS (ESI): m/z calculated for $C_{12}H_{14}F_2O_3Na$ $[M+Na]^+$: 267.0809; found: 267.0811.

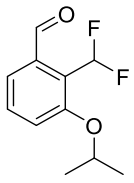
(2-(Difluoromethyl)-3-isopropoxyphenyl)methanol (**290**)



LAH (58.8 mg, 1.55 mmol, 2.00 equiv.) was suspended in THF (1.1 mL) at 0 °C. Ester **51** (189 mg, 0.78 mmol) in THF (1.5 mL) was added at 0 °C and the mixture was stirred at rt for 4 h. H_2O was added at 0 °C and the suspension was filtered through a short Celite® plug. The plug was washed with EtOAc and the aq. phase was extracted with EtOAc. The combined organic phases were washed with a 1 M HCl solution, a sat. $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish alcohol **290** (141 mg, 0.65 mmol, 84%) as colorless oil, which was used in the next step without further purification.

$\mathbf{R_f}$ (PE/EtOAc = 5:1) = 0.46.

2-(Difluoromethyl)-3-isopropoxybenzaldehyde (**57**)



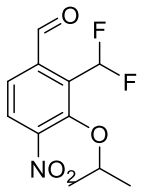
Alcohol **290** (141 mg, 0.65 mmol) was dissolved in CH_2Cl_2 (3.8 mL). Celite® (210 mg) and PCC (211 mg, 0.98 mmol, 1.50 equiv.) were added subsequently. The mixture was stirred at rt for 1 h before it was poured onto a small silica plug. Elution with PE/EtOAc (7:3) furnished aldehyde **57** (135 mg, 0.63 mmol, 96%) as a colorless oil.

$\mathbf{R_f}$ (PE/EtOAc = 5:1) = 0.69;

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 10.55-10.54 (t, *J* = 2.0 Hz, 1H, CHO), 7.64-7.62 (d, *J* = 7.7 Hz, 1H, H_{Ar}), 7.53-7.49 (t, *J* = 8.3 Hz, 1H, H_{Ar}), 7.50-7.23 (t, *J* = 54.5 Hz, 1H, CHF_2), 7.19-7.17 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 4.67-4.58 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 1.39-1.38 (d, *J* = 6.0 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (101 MHz, $CDCl_3$) = δ 191.1 (t, *J* = 4.6 Hz, CHO), 156.3 (C_{Ar}), 136.6 (C_{Ar}), 132.2 (t, *J* = 1.4 Hz, C_{Ar}), 124.4 (C_{Ar}), 120.6 (t, *J* = 1.8 Hz, C_{Ar}) 119.1 (C_{Ar}), 114.3-109.6 (t, *J* = 235.3 Hz, CHF_2), 72.3 (*C*H$(CH_3)_2$), 22.1 (CH(*C*H$_3)_2$) ppm.

2-(Difluoromethyl)-3-isopropoxy-4-nitrobenzaldehyde (**58**)



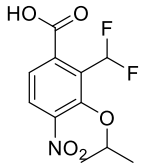
Aldehyde **57** (126 mg, 0.59 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to fuming HNO_3 (272 µL, 6.47 mmol, 11.0 equiv.) at -40 °C. The solution was stirred at -40 °C for 2 h. The mixture was diluted with H_2O and the aq. phase was extracted with CH_2Cl_2 (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc = 10:1) to furnish product **58** (35.5 mg, 0.14 mmol, 23%) as brown oil.

$\mathbf{R_f}$ (PE/EtOAc = 10:1) = 0.47;

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 10.57-10.56 (t, *J* = 1.9 Hz, 1H, CHO), 8.01-7.98 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 7.93-7.91 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 7.43-7.16 (t, *J* = 53.8 Hz, 1H, CHF_2), 4.31-4.22 (sept, *J* = 6.3 Hz, 1H, C*H*$(CH_3)_2$), 1.36-1.35 (d, *J* = 6.2 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (101 MHz, $CDCl_3$) = δ 188.7 (t, *J* = 5.1 Hz, CHO), 149.8 (t, *J* = 7.3 Hz, C_{Ar}), 147.0 (C_{Ar}), 138.8 (C_{Ar}), 132.0-131.5 (t, *J* = 24.9 Hz, C_{Ar}), 128.0 (C_{Ar}), 124.0 (C_{Ar}), 113.6-108.9 (t, *J* = 237.8 Hz, CHF_2), 81.5 (*C*H$(CH_3)_2$), 22.3 (CH(*C*H$_3)_2$) ppm;

2-(Difluoromethyl)-3-isopropoxy-4-nitrobenzoic acid (**59**)



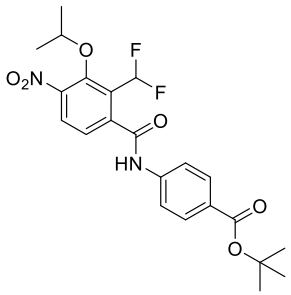
Aldehyde **58** (31.8 mg, 0.12 mmol) and 2-methyl-2-butene (130 µL, 1.22 mmol, 10.0 equiv.) were dissolved in *t*BuOH (0.5 mL). $NaClO_2$ (12.2 mg, 0.13 mmol, 1.10 equiv) in a 1 M NaH_2PO_4 solution (0.1 mL) was added dropwise at rt. The solution was stirred for 5 h. Then, a 1 M HCl solution was added. The aq. layer was extracted with Et_2O (3x) and the combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give the crude product **59** (30.4 mg, 0.11 mmol, 90%) as a yellow amorphous solid.

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 9.42 (bs, 1H, CO_2H), 7.94-7.92 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 7.68-7.66 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 7.35-7.08 (t, *J* = 53.8 Hz, 1H, CHF_2), 4.42-4.33 (sept, *J* = 6.3 Hz, 1H, C*H*$(CH_3)_2$), 1.35-1.33 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (101 MHz, $CDCl_3$) = δ 170.6 (CO), 150.4 (C_{Ar}), 146.5 (C_{Ar}), 135.3 (C_{Ar}), 130.1-129.8 (t, *J* = 23.4 Hz, C_{Ar}), 127.4 (C_{Ar}), 125.2 (C_{Ar}), 112.6-107.8 (t, *J* = 240.3 Hz, CHF_2)), 81.2 (*C*$H(CH_3)_2$), 22.1 (CH(*C*$H_3)_2$) ppm;

HRMS (ESI): m/z calculated for $C_{11}H_{10}F_2NO_5$ $[M-H]^-$: 274.0527; found: 274.0529.

tert-Butyl 4-(2-(difluoromethyl)-3-isopropoxy-4-nitrobenzamido)benzoate (**88**)

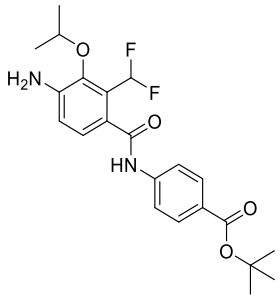


Benzoic acid **59** (293 mg, 1.07 mmol) and *tert*-butyl 4-aminobenzoate (**13**) (196 mg, 1.01 mmol, 0.95 equiv.) were dissolved in CH_2Cl_2 (5 mL). The solution was cooled to 0 °C and DIPEA (316 µL, 1.81 mmol, 1.70 equiv.) and $POCl_3$ (99 µL, 1.07 mmol, 1.00 equiv.) were added. The solution was stirred for 2 h at 0 °C. A sat. NH_4Cl solution was added and the aq. phase was extracted with CH_2Cl_2 (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc = 3:1) to furnish amide **88** (395 mg) as orange amorphous solid, which contained small impurities. The product was used in the next step without further purification.

R_f (PE/EtOAc = 5:1) = 0.37;

HRMS (ESI): m/z calculated for $C_{22}H_{24}F_2N_2O_6Na$ $[M+Na]^+$: 473.1500; found: 473.1479.

tert-Butyl 4-(4-amino-2-(difluoromethyl)-3-isopropoxybenzamido)benzoate (**91**)



Compound **88** (395 mg, 0.88 mmol) was dissolved in THF (1.5 mL) and EtOH (1.3 mL). Zinc dust (859 mg, 13.1 mmol, 15.0 equiv.) was added. The mixture was cooled to 0 °C and AcOH (0.80 mL, 13.3 mmol, 15.0 equiv.) was slowly added dropwise. The mixture was warmed to rt and stirred for 6 h, before Et_2O and a sat. $NaHCO_3$ solution were added. The mixture was filtered and the phases were separated. The aq. phase was extracted with Et_2O (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, PE/EtOAc = 2:1) to furnish aniline **91** (154 mg, 0.37 mmol, 35% over two steps) as yellowish amorphous solid.

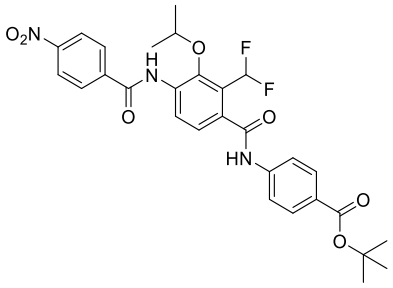
R_f (PE/EtOAc = 2:1) = 0.22;

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 10.40 (s, 1H, NH), 7.86-7.84 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.80-7.78 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.22-6.95 (t, *J* = 54.2 Hz, 1H, CHF_2), 7.13-7.09 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 6.88-6.86 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 5.44 (s, 2H, NH_2), 4.37-4.35 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 1.54 (s, 9H, C(C*H*$_3)_3$), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 166.9 (CO), 164.6 (CO), 144.6 (C_{Ar}), 143.7 (C_{Ar}), 142.1-142.0 (t, *J* = 4.9 Hz, C_{Ar}), 129.9 (C_{Ar}), 125.6 (C_{Ar}), 125.2-124.9 (t, *J* = 21.8 Hz, C_{Ar}), 124.8

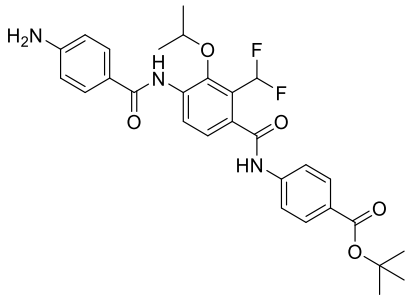
(C_{Ar}), 123.9 (C_{Ar}), 118.6 (C_{Ar}), 115.7 (C_{Ar}), 113.9-110.8 (t, J = 236.1 Hz, CHF_2), 80.2 ($C(CH_3)_3$), 75.1 ($CH(CH_3)_2$), 27.9 ($C(CH_3)_3$), 21.8 ($CH(CH_3)_2$) ppm;
HRMS (ESI) calculated for $C_{22}H_{26}F_2N_2O_4Na$ $[M+Na]^+$: 443.1758; found: 443.1756.

tert-Butyl 4-(2-(difluoromethyl)-3-isopropoxy-4-(4-nitrobenzamido)benzamido)benzoate (**94**)



4-Nitrobenzoyl chloride (107 mg, 0.57 mmol, 1.60 equiv.) was added in portions to a mixture of amine **91** (151 mg, 0.36 mmol) and pyridine (116 µL, 1.44 mmol, 4.00 equiv.) in CH_2Cl_2 (4 mL). The mixture was stirred at rt for 1 h. Then, the mixture was diluted with a 1 M $KHSO_4$ solution. The aq. phase was extracted with CH_2Cl_2 (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated to furnish crude product **94** (244 mg), which was used in the next step without further purification.

tert-Butyl 4-(4-(4-aminobenzamido)-2-(difluoromethyl)-3-isopropoxybenzamido)benzoate (**96**)

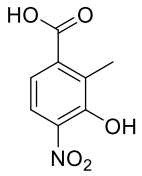


Compound **94** (205 mg, 0.36 mmol) was dissolved in THF (0.6 mL) and EtOH (0.5 mL). Zinc dust (352 mg, 5.39 mmol, 15.0 equiv.) was added. The mixture was cooled to 0 °C and AcOH (0.30 mL, 5.39 mmol, 15.0 equiv.) was slowly added dropwise. The mixture was warmed to rt

and stirred for 1 h, before Et_2O and a sat. $NaHCO_3$ solution were added. The mixture was filtered and the phases were separated. The aq. phase was extracted with Et_2O (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish aniline **96** (188 mg) as yellowish amorphous solid, which was used in the next step without further purification.

HRMS (ESI) calculated for $C_{29}H_{31}F_2N_3O_5Na$ $[M+Na]^+$: 562.2129; found: 562.2124.

3-Hydroxy-2-methyl-4-nitrobenzoic acid (**60**)



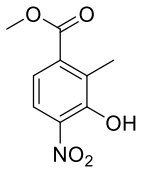
Conc. H_2SO_4 (350 µL, 6.57 mmol, 1.00 equiv.) was added to H_2O (3.3 mL) before addition of $NaNO_3$ (0.43 g, 5.02 mmol, 0.8 equiv.). 3-Hydroxy-2-methylbenzoic acid (**47**) (1.00 g, 6.57 mmol) was added and the mixture was warmed up slowly to 60 °C. The mixture was further warmed up to 85 °C and stirred at this temperature for 3 h. During the reaction additional H_2O was added to ensure stirring. The mixture was cooled to rt and the precipitate was filtered off and dried *in vacuo* to furnish product **60** (0.36 g, 1.83 mmol, 37%) as brown amorphous solid.

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 11.09 (s, 1H, CO_2H), 8.05-8.03 (d, *J* = 9.0 Hz, 1H, H_{Ar}), 7.52-7.50 (d, *J* = 9.0 Hz, 1H, H_{Ar}), 2.60 (s, 3H, CH_3) ppm;

^{13}C-NMR (101 MHz, $CDCl_3$) = δ 170.5 (CO), 154.1 (C_{Ar}), 136.7 (C_{Ar}), 125.8 (C_{Ar}), 122.0 (C_{Ar}), 121.0 (C_{Ar}), 13.2 (CH_3) ppm;

HRMS (ESI) calculated for $C_8H_6NO_5$ $[M-H]^-$: 196.0246; found: 196.0237.

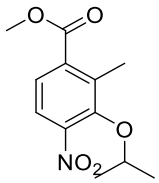
Methyl 3-hydroxy-2-methyl-4-nitrobenzoate (**291**)



Acid **60** (355 mg, 1.80 mmol) was dissolved in MeOH (3 mL) and $SOCl_2$ (210 µL, 2.88 mmol, 1.60 equiv.) was added at 0 °C. The solution was stirred at 80 °C for 1 h. All volatiles were

removed under reduced pressure to furnish ester **291** (376 mg, 1.78 mmol, 99%) as colorless amorphous solid, which was used in the next step without further purification.

Methyl 3-isopropoxy-2-methyl-4-nitrobenzoate (**61**)

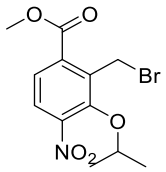


Ester **291** (370 mg, 1.75 mmol) and K_2CO_3 (248 mg, 1.80 mmol, 1.00 equiv.) were dissolved in DMF (5 mL) and 2-bromopropane (225 µL, 2.40 mmol, 1.40 equiv.) was added and the mixture was stirred at 70 °C for 16 h. After cooling down to rt the mixture was diluted with H_2O. The mixture was acidified with a 1 M HCl solution and the aq. phase was extracted with Et_2O (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated to furnish product **61** (426 mg, 1.68 mmol, 96%) as colorless oil, which was used in the next step without further purification.

R_f (PE/EtOAc = 10:1) = 0.33;

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 7.65-7.62 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 7.59-7.57 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 4.22-4.16 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 3.93 (s, 3H, CO_2CH_3), 2.52 (s, 3H, CH_3), 1.30-1.28 (d, *J* = 6.2 Hz, 6H, CH(C*H*$_3)_2$) ppm.

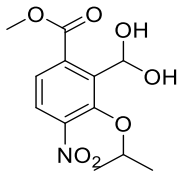
Methyl 2-(bromomethyl)-3-isopropoxy-4-nitrobenzoate (**292**)



Toluate **61** (360 mg, 1.42 mmol) was dissolved in MeCN (4 mL). NBS (304 mg, 1.71 mmol, 1.20 equiv.) and AIBN (46.7 mg, 0.28 mmol, 0.20 equiv.) were added. The mixture was stirred at 85 °C for 19 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (PE/EtOAc = 15:1) to furnish a mixture of starting material **61** and product **292**. The mixture was used in the next step without further purification.

R_f (PE/EtOAc = 10:1) = 0.30.

Methyl 2-(dihydroxymethyl)-3-isopropoxy-4-nitrobenzoate (**62**)



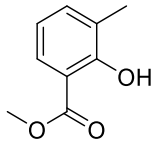
Bromide **292** (472 mg) was dissolved in MeCN (12 mL) and NMO (666 mg, 5.68 mmol, 4.00 equiv.) was added. The solution was stirred at rt for 1 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (dry load, PE/EtOAc = 10:1) to furnish hydrate **62** (62.5 mg, 0.23 mmol, 16% over two steps) as orange amorphous solid.

R_f (PE/EtOAc = 10:1) = 0.22;

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 8.13-8.11 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 7.71-7.69 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 6.79 (s, 1H, $CH(OH)_2$), 4.77-4.68 (sept, *J* = 6.1 Hz, 1H, $CH(CH_3)_2$), 3.57 (s, 3H, CO_2CH_3), 1.33-1.32 (d, *J* = 6.0 Hz, 3H, $CH(CH_3)_2$), 1.24-1.22 (d, *J* = 6.0 Hz, 3H, $CH(CH_3)_2$) ppm.

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 166.3 (CO), 147.6 (C_{Ar}), 145.5 (C_{Ar}), 135.4 (C_{Ar}), 131.0 (C_{Ar}), 127.6 (C_{Ar}), 119.4 (C_{Ar}), 102.0 ($CH(OH)_2$), 76.7 ($CH(CH_3)_2$), 56.4 (OCH_3), 22.3 ($CH(CH_3)_2$), 21.9 ($CH(CH_3)_2$) ppm;

Methyl 2-hydroxy-3-methylbenzoate (**293**)



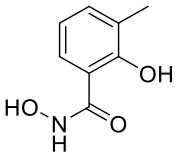
2-Hydroxy-3-methylbenzoic acid (**74**) (5.00 g, 32.9 mmol) was dissolved in MeOH (100 mL) and conc. H_2SO_4 (1 mL) was added. The solution was stirred at 80 °C for 5 d. The mixture was cooled to rt and diluted with EtOAc and a sat. $NaHCO_3$ solution. The aq. phase was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc = 15:1) to furnish ester **293** (4.79 g, 28.8 mmol, 88%) as colorless liquid.

The analytical data are consistent with those reported in the literature.[101]

R_f (PE/EtOAc = 10:1) = 0.62;

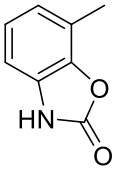
^{1}H-NMR (400 MHz, $CDCl_3$) = δ 11.01 (s, 1H, OH), 7.70-7.68 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 7.32-7.31 (d, *J* = 7.2 Hz, 1H, H_{Ar}), 6.80-6.76 (t, *J* = 7.7 Hz, 1H, H_{Ar}), 3.94 (s, 3H, CO_2CH_3), 2.27 (s, 3H, CH_3) ppm.

N,2-Dihydroxy-3-methylbenzamide (**75**)



$NH_2OH{\cdot}HCl$ (2.27 g, 32.7 mmol, 2.00 equiv.) was dissolved in MeOH (16 mL) and KOH (3.67 g, 65.3 mmol, 4.00 equiv.) in MeOH (16 mL) was added at 0 °C. After 5 min of stirring the mixture was filtered and the filtrate was added to ester **293** (2.71 g, 16.3 mmol). Additional KOH (6 pellets) was added and the solution was stirred at rt for 20 h. The mixture was concentrated under reduced pressure and the residue was dissolved in H_2O. A 2 M HCl solution was added until pH 4. The precipitate was filtered off to furnish hydroxamic acid **75** (2.74 g, quant.) as colorless amorphous solid, which was used in the next step without further purification.

7-Methylbenzo[*d*]oxazol-2(3*H*)-one (**77**)



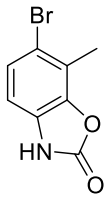
Hydroxamic acid **75** (2.39 g, 14.3 mmol) was dissolved in DMF (20 mL) and K_2CO_3 (5.92 g, 42.8 mmol, 3.00 equiv.) was added. The mixture was stirred at 160 °C for 1 h. The dark mixture was cooled to rt and the solvent was removed under reduced pressure. The residue was diluted with H_2O and CH_2Cl_2 and the aq. phase was extracted with CH_2Cl_2 (3x). The combined organic phases were washed with H_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (1% MeOH in CH_2Cl_2) to furnish a mixture of 2-amino-6-methylphenol (**76**) and product **77** (984 mg). The mixture was dissolved in DMF (21 mL) and CDI (2.07 g, 12.8 mmol, 1.60 equiv.) was added. The solution was stirred at 60 °C for 2 h. The mixture was cooled to rt and poured into H_2O (120 mL). The precipitate was filtered off and washed with H_2O to furnish product **77** (630 mg, 4.22 mmol, 30% over three steps) as red-brown amorphous solid. The filtrate was extracted with EtOAc (3x) and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc = 1:1) to furnish product **77** (305 mg, 2.04 mmol, 14% over three steps) as red-brown amorphous solid.

The analytical data are consistent with those reported in the literature.[60]

R_f (PE/EtOAc = 1:1) = 0.53;

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 11.53 (s, 1H, NH), 7.05-7.01 (m, 1H, H_{Ar}), 6.92-6.89 (m, 2H, H_{Ar}), 2.29 (s, 3H, CH_3) ppm.

6-Bromo-7-methylbenzo[*d*]oxazol-2(3*H*)-one (**78**)

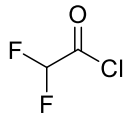


Carbamate **77** (200 mg, 1.34 mmol) and NBS (239 mg, 1.34 mmol, 1.00 equiv.) were dissolved in THF (2.4 mL). The mixture was stirred at rt for 4 h. H_2O (0.8 mL) and EtOAc (0.6 mL) were added and the precipitate was filtered off and washed with PE to furnish bromide **78** (235 mg, 1.03 mmol, 77%) as light red amorphous solid.

The analytical data are consistent with those reported in the literature.[61]

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 11.74 (s, 1H, NH), 7.37-7.35 (d, *J* = 8.3 Hz, 1H, H_{Ar}), 6.90-6.88 (d, *J* = 8.3 Hz, 1H, H_{Ar}), 2.31 (s, 3H, CH_3) ppm.

2,2-Difluoroacetyl chloride (**67**)

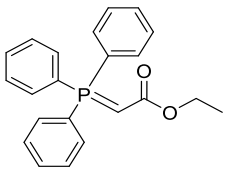


To 2,2-Difluoroacetic acid (**66**) (13.0 g, 135 mmol) was added PCl_5 (31.0 g, 149 mmol, 1.10 equiv) in small portions at -10 °C. The mixture was stirred at 0 °C for 15 min. Distillation (oil bath: 80-90 °C) furnished product **67** as clear liquid, which was collect at -78 °C and used in the next step without further purification.

The analytical data are consistent with those reported in the literature.[102]

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 6.10-5.83 (t, *J* = 53.5 Hz, 1H, CHF_2) ppm.

Ethyl 2-(triphenyl-λ^5-phosphaneylidene)acetate (**68**)



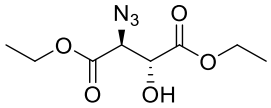
Ethyl 2-bromoacetate (10.0 g, 59.9 mmol) was added to a solution of PPh_3 (15.7 g, 59.9 mmol, 1.00 equiv.) in PhMe (100 mL). The mixture was stirred at rt for 18 h. The mixture was filtrated

and the phosphonium salt was dissolved in CH_2Cl_2. The solution was washed with a sat. Na_2CO_3 solution (3x) and brine, dried over $MgSO_4$, filtrated and concentrated under reduced pressure. Drying *in vacuo* furnished product **68** (18.4 g, 52.9 mmol, 88%) as colorless amorphous solid.

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 7.67-7.44 (m, 15H, H_{Ar}), 3.99 (bs, 2H, C*H*$_2$CH$_3$), 2.90 (bs, 1H, CH), 1.31-0.70 (m, 3H, CH$_2$C*H*$_3$) ppm.

4.2.3 Central amino acids

Diethyl (2*S*,3*R*)-2-azido-3-hydroxysuccinate (**98**)

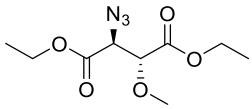


$SOCl_2$ (2.70 mL, 36.4 mmol, 1.50 equiv.) was slowly added to diethyl (2*R*,3*R*)-tartrate (**97**) (5.00 g, 24.3 mmol) at 0 °C, which was stirred. A scrubber (20% NaOH solution) was connected to the flask. DMF (0.40 mL, 0.49 mmol, 2 mol%) was added dropwise and the resulting solution was stirred for 90 min at ambient temperature, before heating to 50 °C. Stirring was continued for another 90 min at this temperature. The solution was concentrated under reduced pressure and the residue was dissolved in DMF (6 mL). The solution was added to a suspension of NaN_3 (4.73 g, 72.8 mmol, 3.00 equiv.) in DMF (7 mL) at 0 °C. The mixture was stirred for 22 h at 35 °C and was then concentrated to the half of the volume (45 °C, 10 mbar). EtOAc (12 mL) and H_2O (12 mL) were added. The aq. phase was extracted with EtOAc (5x 16 mL) and the combined organic phases were washed with a sat. $NaHCO_3$ solution (37 mL), a 5% NaCl solution (5x 37 mL) and brine (37 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give product **98** (3.54 g, 15.3 mmol, 63%) as an orange oil, which was used in the next step without further purification.

The analytical data are consistent with those reported in the literature.[32]

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 4.64-4.62 (dd, *J* = 2.7, 5.4 Hz, 1H, C*H*OH), 4.33-4.25 (m, 5H, CHN_3, OCH_2), 3.29-3.27 (d, *J* = 5.4 Hz, 1H, OH), 1.33-1.29 (m, *J* = 2.9, 7.1 Hz, 6H, CH_3) ppm.

Diethyl (2*S*,3*R*)-2-azido-3-methoxysuccinate (**99**)

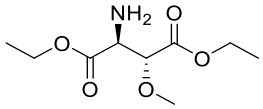


Alcohol **98** (3.54 g, 15.3 mmol) was dissolved in CH_2Cl_2 (11 mL) and Ag_2O (3.62 g, 15.6 mmol, 1.00 equiv.) was added. The solution was cooled to 0 °C and MeI (3.15 mL, 50.6 mmol, 3.30 equiv.) was added slowly. The reaction mixture was stirred at ambient temperature for 20 h. The mixture was filtered through a pad of Celite® and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure to give crude product **99** (3.36 g, 13.7 mmol, 89%), which was used in the next step without further purification.

The analytical data are consistent with those reported in the literature.[32]

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 4.34-4.21 (m, 5H, CHN_3, OCH_2), 4.18-4.17 (dd, *J* = 3.6 Hz, 1H, C*H*OCH_3), 3.55 (s, 3H, OCH_3), 1.33-1.29 (m, *J* = 7.1 Hz, 6H, CH_3) ppm.

Diethyl (2*S*,3*R*)-2-amino-3-methoxysuccinate (**100**)

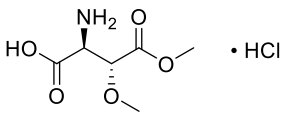


Azide **99** (3.36 g, 13.7 mmol) was dissolved in EtOAc (18 mL) and $Pd(OH)_2$ (20% on carbon (dry) with 50% H_2O, 0.20 g, 0.14 mmol, 1 mol%) was added. The suspension was stirred under H_2 atmosphere and rt for 10 d. The mixture was filtered through a pad of silica and washed with an excess of EtOAc. The eluent was concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc) to afford amine **100** (1.67 g, 7.63 mmol, 56%) as a colorless oil.

The analytical data are consistent with those reported in the literature.[32]

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 4.27-4.17 (m, 4H, OCH_2), 4.07-4.06 (d, *J* = 3.7 Hz, 1H, C*H*NH_2), 3.93-3.92 (d, *J* = 3.7 Hz, 1H, C*H*OCH_3), 3.50 (s, 3H, OCH_3), 1.31-1.25 (m, *J* = 7.1 Hz, 6H, CH_3) ppm.

(2*S*,3*R*)-2-Amino-3,4-dimethoxy-4-oxobutanoic acid HCl (**101**)



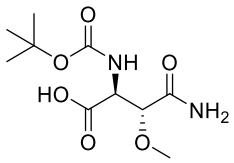
Amine **100** (1.67 g, 7.62 mmol) was suspended in a 5 M HCl solution (23.9 mL, 120 mmol, 15.7 equiv.) and the mixture was stirred at 80 °C for 24 h. All volatiles were removed under reduced pressure and boiling THF (22 mL) was added and the solid was crushed with a spatula. The mixture was stirred for 20 min. Propylene oxide (5.3 mL) was added at 0 °C and the mixture was stirred at ambient temperature for 3 h. The mixture was filtered and the precipitate

was washed with an excess of THF and dried *in vacuo*. MeOH (1.7 mL) was added before addition of dry HCl (0.8 mL AcCl in 6.0 mL MeOH at 0 °C) at 0 °C. The solution was stirred at rt for 18 h and transferred to stirring Et_2O (52 mL). The precipitate was filtered and washed with an excess of Et_2O. Drying *in vacuo* furnished product **100** (1.09 g, 5.14 mmol, 67%) as a colorless amorphous solid.

The analytical data are consistent with those reported in the literature.[32]

^{1}H-NMR (400 MHz, CD_3OD) = δ 4.50 (d, *J* = 2.7 Hz, 1H, C*H*NH_2), 4.31-4.30 (d, *J* = 2.7 Hz, 1H, C*H*OCH_3), 3.81 (s, 3H, CO_2CH_3), 3.56 (s, 3H, OCH_3) ppm.

(2*S*,3*R*)-4-Amino-2-((*tert*-butoxycarbonyl)amino)-3-methoxy-4-oxobutanoic acid (**4**)

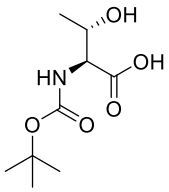


To a suspension of $NaHCO_3$ (4.73 g, 56.3 mmol, 3.00 equiv.) in H_2O (30 mL) was added salt **101** (4.00 g, 18.8 mmol) in H_2O (46 mL) dropwise at 0 °C. Boc_2O (5.73 g, 26.3 mmol, 1.40 equiv.) in THF (61 mL) was added carefully and the mixture was stirred at rt for 18 h. The mixture was washed with Et_2O (2x) and afterwards acidified with a conc. HCl solution (37%, 4.70 mL, 56.3 mmol, 3.00 equiv.) dropwise until pH 1. The mixture was extracted with CH_2Cl_2 (3x 132 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure (40 °C, minimum 100 mbar). The residue was dissolved in an aq. NH_3 solution (28%, 30.0 mL, 437 mmol, 23.30 equiv.) and stirred at rt for 4 h. The mixture was then transferred to a stirring mixture of EtOAc (500 mL) and a 1 M HCl solution (500 mL) at 0 °C. The aq. phase was extracted with EtOAc (3x 200 mL). The combined organic phases were dried over $MgSO_4$, filtered, coevaporated with toluene (3x) and dried *in vacuo* to furnish acid **4** (3.66 g, 14.0 mmol, 74%) as colorless amorphous solid.

The analytical data are consistent with those reported in the literature.[32]

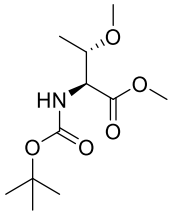
^{1}H-NMR (400 MHz, DMSO-d_6) = δ 12.70 (bs, 1H, CO_2H), 7.39-7.37 (d, *J* = 9.6 Hz, 2H, NH_2), 6.55-6.53 (d, *J* = 8.7 Hz, 1H, NH), 4.39-4.36 (dd, *J* = 8.8, 4.3 Hz, 1H, C*H*NH), 3.85-3.84 (d, *J* = 4.2 Hz, 1H, C*H*OCH_3), 3.33 (s, 3H, OCH_3), 1.38 (s, 9H, $C(CH_3)_3$) ppm.

(*tert*-Butoxycarbonyl)-L-*allo*threonine (**294**)



A mixture of $NaHCO_3$ (543 mg, 6.46 mmol, 1.50 equiv.) and Boc_2O (1.43 g, 6.55 mmol, 1.60 equiv.) in MeOH (8.5 mL) was added to a solution of L-allothreonine (**102**) (500 mg, 4.20 mmol) in H_2O (8.5 mL). The mixture was stirred at rt for 18 h and afterwards acidified with a 0.5 M HCl solution. The aq. phase was extracted with EtOAc (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish carbamate **294** (963 mg), which was used in the next step without further purification.

Methyl *N*-(*tert*-butoxycarbonyl)-*O*-methyl-L-*allo*threoninate (**295**)



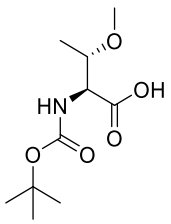
Amino acid **294** (920 mg, 4.20 mmol) was dissolved in MeCN (4.6 mL) and Ag_2O (4.86 g, 21.0 mmol, 5.00 equiv.) was added. MeI (4.20 mL, 67.2 mmol, 16.00 equiv.) was added at 0 °C and the resulting mixture was stirred at rt for 48 h. The mixture was filtered through Celite® and the plug was washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (dry load, PE/EtOAc = 8:1) to furnish product **295** (486 mg, 1.97 mmol, 47% over two steps) as colorless oil.

The analytical data are consistent with those reported in the literature.[64]

R_f (PE/EtOAc = 8:1) = 0.22;

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 5.28-5.27 (d, *J* = 7.2 Hz, 1H, NH), 4.44-4.41 (dd, *J* = 3.6, 4.9 Hz, 1H, C*H*NHBoc), 3.76 (s, 3H, CO_2CH_3), 3.64-3.62 (m, 1H, C*H*CH_3), 3.36 (s, 3H, OCH_3), 1.44 (s, 9H, $C(CH_3)_3$), 1.21-1.19 (d, *J* = 6.4 Hz, 1H, CHC*H*$_3$) ppm.

N-(*tert*-Butoxycarbonyl)-*O*-methyl-L-allothreonine (**103**)

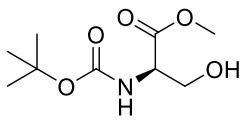


Ester **295** (479 mg, 1.94 mmol) was dissolved in THF (3.6 mL) and H_2O (1.8 mL). $LiOH \cdot H_2O$ (488 mg, 11.6 mmol, 6.00 equiv.) was added and the mixture was stirred at rt for 3 h. THF was removed under reduced pressure and the residue was acidified with a 2 M HCl solution. The aq. phase was extracted with EtOAc (3x). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure to furnish acid **103** (490 mg, quant.) as yellow oil, which was used in the next step without further purification.

The analytical data are consistent with those reported in the literature.[64]

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 8.34 (bs, 1H, CO_2H), 5.31-5.29 (d, *J* = 7.5 Hz, 1H, NH), 4.44-4.43 (m, 1H, C*H*NHBoc), 3.69 (m, 1H, C*H*CH_3), 3.38 (s, 3H, OCH_3), 1.45 (s, 9H, $C(CH_3)_3$), 1.26-1.24 (d, *J* = 6.3 Hz, 3H, CHC*H*$_3$) ppm.

Methyl (*tert*-butoxycarbonyl)-D-serinate (**(*S*)-104**)

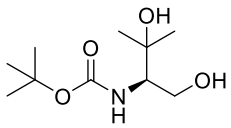


D-Serine (500 mg, 4.76 mmol) was suspended in MeOH (10 mL) and $SOCl_2$ (2.1 mL, 28.5 mmol, 6.00 equiv.) was added dropwise at 0 °C. The solution was stirred at ambient temperature for 19 h. The solvent was removed under reduced pressure and coevaporated with Et_2O (3x). The residue was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. Then Et_3N (1.80 mL, 12.8 mmol, 2.70 equiv.) and Boc_2O (1.10 g, 5.23 mmol, 1.10 equiv) were added carefully and the reaction mixture was allowed to warm to rt. The mixture was stirred for 22 h before the solvent was removed under reduced pressure. The residue was purified by column chromatography (MeOH in CH_2Cl_2 = 2%, 5%, 10%) to furnish product (*S*)-**104** (945 mg, 4.31 mmol, 91%) as a yellow oil.

The analytical data are consistent with those reported in the literature.[65]

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 5.43 (s, 1H, NH), 4.39 (m, 1H, CH), 3.99-3.88 (m, 2H, CH_2), 3.79 (s, 3H, OCH_3), 2.24 (s, 1H, OH), 1.46 (s, 9H, $C(CH_3)_3$) ppm.

tert-Butyl (*R*)-(1,3-dihydroxy-3-methylbutan-2-yl)carbamate ((*S*)-**105**)



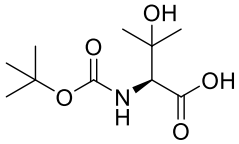
Ester (*S*)-**104** (940 mg, 4.30 mmol) was suspended in Et_2O (23 mL). MeMgBr (3 M in Et_2O, 8.60 mL, 25.7 mmol, 6.00 equiv.) was added at -78 °C. The emulsion was allowed to warm to rt and stirred at rt for 3 h. The reaction mixture was cooled to 0 °C and a sat. NH_4Cl solution

was added. The aq. phase was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish alcohol (*S*)-**105** (866 mg, 3.95 mmol, 92%) as yellow oil.

The analytical data are consistent with those reported in the literature.[66]

^{1}H-NMR (400 MHz, CD_3OD) = δ 3.82-3.79 (dd, *J* = 4.1, 11.2 Hz, 1H, CH_2), 3.62-3.57 (m, 1H, CH), 3.51-3.48 (m, 1H, CH_2), 1.45 (s, 9H, $C(CH_3)_3$), 1.23 (s, 3H, $C(CH_3)_2$), 1.15 (s, 3H, $C(CH_3)_2$) ppm.

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-hydroxy-3-methylbutanoic acid ((*S*)-**106**)

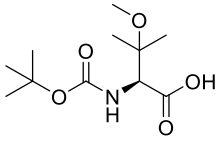


Diol (*S*)-**105** (860 mg, 3.92 mmol) was dissolved in MeCN (15 mL). Phosphate buffer (pH 7, 14 mL) and TEMPO (61.3 mg, 0.39 mmol, 0.10 equiv.) were added. The solution was warmed to 35 °C and $NaClO_2$ (2 M in H_2O, 4.00 mL, 7.84 mmol, 2.00 equiv.) and NaOCl (0.04 M in H_2O, 2.00 mL, 0.08 mmol, 2 mol%) were added simultaneously over 2 h. The mixture was stirred at 35 °C for 24 h. Citric acid (10%) was added until pH 2. The aq. phase was extracted with EtOAc (3x) and the combined organic phases were concentrated under reduced pressure. The residue was dissolved in a sat. $NaHCO_3$ solution (80 mL). The aq. phase was washed with EtOAc (2x) and afterwards treated with a 1 M H_3PO_4 solution (100 mL) until pH 2 was reached. The acidic phase was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish carboxylic acid (*S*)-**106** (719 mg, 3.08 mmol, 79%) as a colorless amorphous solid.

The analytical data are consistent with those reported in the literature.[66]

^{1}H-NMR (400 MHz, CD_3OD) = δ 4.08 (m, 1H, C*H*NH), 1.45 (s, 9H, $C(CH_3)_3$), 1.29 (s, 3H, $C(CH_3)_2$), 1.25 (s, 3H, $C(CH_3)_2$) ppm.

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-methoxy-3-methylbutanoic acid (**107**)



Tertiary alcohol **(*S*)-106** (300 mg, 1.29 mmol) in THF (2.0 mL) was added to NaH (60% in mineral oil, 154 mg, 3.86 mmol, 3.00 equiv.) in THF (2.4 mL) at 0 °C. The mixture was stirred at rt for 1 h. MeI (96 µL, 1.54 mmol, 1.20 equiv.) was added and the mixture was stirred at rt for 19 h. H_2O was added and the aq. phase was extracted with Et_2O (3x). The aq. phase was acidified with 6 M HCl until pH 2 and extracted with EtOAc (4x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH in CH_2Cl_2 = 0%, 2%) to furnish product **107** (162 mg, 0.65 mmol, 51%) as yellow gum.

R_f (3% MeOH in CH_2Cl_2) = 0.20;

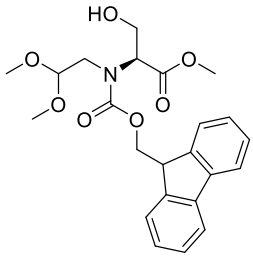
$[\alpha]_D^{21}$ = +5.8 ° (c 1.3, MeOH);

^{1}H-NMR (500 MHz, CD_3OD) = δ 4.20 (s, 1H, CH), 3.23 (s, 3H, OCH_3), 1.45 (s, 9H, $C(CH_3)_3$), 1.28 (s, 3H, $C(CH_3)_2$), 1.26 (s, 3H, $C(CH_3)_2$) ppm;

^{13}C-NMR (126 MHz, CD_3OD) = δ 174.1 (CO_2H), 157.9 (CO), 80.8 ($COCH_3$), 77.1 ($C(CH_3)_3$), 61.7 (CHNH), 50.0 (OCH_3), 28.7 ($C(CH_3)_3$), 22.7 (d, *J* = 8.0 Hz, $C(CH_3)_2$) ppm;

HRMS (ESI$^+$) calculated for $C_{11}H_{20}NO_5$ $[M-H]^-$: 246.1341; found: 246.1351.

Methyl *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-(2,2-dimethoxyethyl)-L-serinate (**111**)



Methyl L-serinate hydrochloride (**110**) (500 mg, 3.21 mmol) was dissolved in MeOH (10 mL). Et_3N (450 µL, 3.21 mmol, 1.00 equiv.), 2,2-dimethoxyacetaldehyde (60% in H_2O, 558 mg, 3.21 mmol, 1.00 equiv.) and 10% Pd/C (45.0 mg) were added subsequently. The mixtue was stirred under an H_2 atmosphere for 17 h before filtration through a short plug of Celite®. The filtrate was concentrated under reduced pressure. The crude product was dissolved in H_2O (6 mL) and $NaHCO_3$ (540 mg, 6.42 mmol, 2.00 equiv.) and FmocCl (815 mg, 3.15 mmol, 1.00 equiv.) were added. The mixture was diluted with EtOAc (7 mL) at 0 °C. After stirring for 1 h at 0 °C the mixture was warmed to rt and stirring was continued for 21 h. EtOAc was added and the phases were seperated. The organic phase was washed with a 1 M HCl solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, PE/EtOAc = 2:1) to furnish tertiary amine **111** (1.16 g, 2.69 mmol, 84%) as colorless oil.

The analytical data are consistent with those reported in the literature.[69]

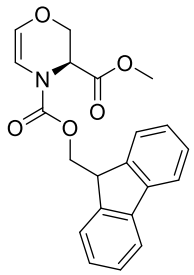
R_f (PE/EtOAc = 2:1) = 0.11;

$[\alpha]_D^{24}$ = -29.1 ° (c 1.1, $CHCl_3$);

^{1}H-NMR (400 MHz, $CDCl_3$) = δ (3:2 mixture of rotamers) 7.78-7.76 (d, *J* = 7.4 Hz, 2H, H_{Ar}), 7.61-7.60 (d, *J* = 7.3 Hz, 1H, H_{Ar}), 7.56-7.53 (m, 1H, H_{Ar}), 7.43-7.29 (m, 4H, H_{Ar}), 4.77-4.69 (m, 2H), 4.63-4.45 (m, 2H), 4.24-4.22 (m, 1H), 3.96-3.94 (m, 1H), 3.86-3.80 (m, 1H), 3.70-3.60 (m, 4H), 3.48-3.44 (m, 2.5H), 3.22-3.11 (m, 4H), 2.99-2.94 (dd, *J* = 7.3, 15.1 Hz, 0.5H) ppm;

HRMS (ESI$^+$) calculated for $C_{23}H_{27}NO_7Na$ $[M+Na]^+$: 452.1685; found: 452.1678.

4-((9*H*-Fluoren-9-yl)methyl) 3-methyl (*S*)-2,3-dihydro-4*H*-1,4-oxazine-3,4-dicarboxylate (**112**)



Alcohol **111** (459 mg, 1.07 mmol) was dissolved in PhMe (15 mL) and *p*TsOH·H_2O (20.3 mg, 0.11 mmol, 0.10 equiv.) was added. The reaction flask was equipped with a dropping funnel including MS (4Å, 5.2 g) and a condenser. The mixture was stirred at 123 °C for 3 h, before it was filtered through a short plug of $NaHCO_3$. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (PE/EtOAc = 4:1) to furnish product **112** (265 mg, 0.73 mmol, 68%) as colorless foam.

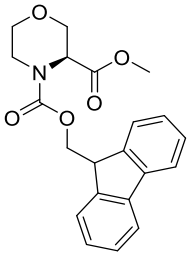
The analytical data are consistent with those reported in the literature.[69]

R_f (PE/EtOAc = 3:1) = 0.36;

^{1}H-NMR (400 MHz, $CDCl_3$) = δ (3:2 mixture of rotamers) 7.79-7.75 (t, *J* = 7.6 Hz, 2H, H_{Ar}), 7.63-7.59 (m, 1H, H_{Ar}), 7.52-7.49 (dd, *J* = 2.7, 7.2 Hz, 1H, H_{Ar}), 7.44-7.39 (q, *J* = 6.9 Hz, 2H, H_{Ar}), 7.35-7.29 (m, 2H, H_{Ar}), 6.42-6.41 (dd, *J* = 1.1, 5.0 Hz, 0.4H), 6.42-6.41 (dd, *J* = 1.1, 5.0 Hz, 0.6H), 6.02-6.01 (d, *J* = 4.9 Hz, 0.4H), 5.98-5.97 (d, *J* = 5.0 Hz, 0.6H), 4.98 (s, 0.6H), 4.70-4.67 (dd, *J* = 1.2, 10.9 Hz, 0.6H), 4.61-4.40 (m, 3H), 3.34-4.30 (t, *J* = 7.2 Hz, 0.6H), 4.23-4.22 (t, *J* = 6.1 Hz, 0.4H), 4.01-3.98 (dd, *J* = 2.8, 11.1 Hz, 0.6H), 3.89-3.86 (dd, *J* = 2.8, 11.1 Hz, 0.4H), 3.79 (s, 1.9H, CH_3), 3.71 (s, 1.1H, CH_3) ppm;

HRMS (ESI$^+$) calculated for $C_{21}H_{19}NO_5Na$ $[M+Na]^+$: 388.1161; found: 388.1161.

4-((9*H*-Fluoren-9-yl)methyl) 3-methyl (*S*)-morpholine-3,4-dicarboxylate (**296**)



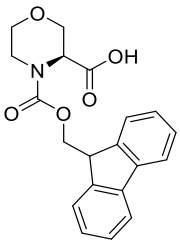
Alkene **112** (160 mg, 0.44 mmol) was dissolved in MeOH (3.1 mL) and CH_2Cl_2 (1.6 mL). Pt/C (10%, 19.7 mg) was added and the mixture was stirred at rt under an H_2 atmosphere for 15 h. The mixture was filtered through a short plug of Celite®. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (dry load, PE/EtOAc = 4:1) to furnish morpholine **296** (149 mg, 0.41 mmol, 93%) as colorless foam.The analytical data are consistent with those reported in the literature.[69]

R_f (PE/EtOAc = 3:1) = 0.28;

^{1}H-NMR (400 MHz, $CDCl_3$) = δ (mixture of rotamers) 7.78-7.75 (t, *J* = 7.0 Hz, 2H, H_{Ar}), 7.62-7.58 (m, 1H, H_{Ar}), 7.52-7.48 (t, *J* = 6.9 Hz, 1H, H_{Ar}), 7.43-7.38 (m, 2H, H_{Ar}), 7.35-7.28 (m, 2H, H_{Ar}), 4.66-4.65 (d, *J* = 2.8 Hz, 0.6H), 4.56-4.45 (m, 1.6H), 4.43-4.37 (m, 1.4H), 4.30-4.28 (m, 1.6H), 4.24-4.21 (t, *J* = 7.2 Hz, 0.5H), 3.91-3.84 (m, 1.4H), 3.78 (s, 1.5H. OCH_3), 3.73 (s, 1.5H, OCH_3), 3.69-3.65 (dd, *J* = 3.7, 11.7 Hz, 0.7H), 3.61-3.57 (dd, *J* = 3.9, 11.9 Hz, 0.5H), 3.51-3.41 (m, 1.8H), 3.32-3.25 (ddt, *J* = 3.7, 12.8 Hz, 0.5H) ppm;

HRMS (ESI$^+$) calculated for $C_{21}H_{21}NO_5Na$ $[M+Na]^+$: 390.1317; found: 390.1317.

(*S*)-4-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)morpholine-3-carboxylic acid (**113**)



Ester **296** (147 mg, 0.40 mmol) was dissolved in 1,4-dioxane (1 mL) and a 5 M HCl solution (1 mL) was added. The mixture was stirred at 110 °C for 16 h. A 5% Na_2CO_3 solution was added at rt and the aq. phase was washed with Et_2O, acidified with conc. HCl and extracted with CH_2Cl_2 (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Acid **113** (127 mg, 0.36 mmol, 90%) was obtained as colorless amorphous solid, which was used in the next step without further purification.

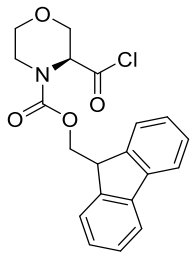
The peaks in the ^{1}H NMR spetrum are shifted compared to the literature[69], what might be caused by 1,4-dioxane impurities.

[α]$_D^{25}$ = -35.2 ° (c 1.0, CH_2Cl_2);

^{1}H-NMR (400 MHz, $CDCl_3$) = δ (mixture of rotamers) 7.78-7.76 (d, *J* = 7.6 Hz, 1H, H_{Ar}), 7.75-7.71 (t, *J* = 6.8 Hz, 1H), 7.60-7.57 (m, 1H, H_{Ar}), 7.53-7.48 (m, 1H, H_{Ar}), 7.42-7.36 (m, 2H, H_{Ar}), 7.34-7.28 (m, 2H, H_{Ar}), 4.71-4.70 (d, *J* = 3.0 Hz, 0.5H), 4.59-4.50 (m, 1.5H), 4.47-4.40 (m, 1H), 4.32-4.21 (m, 2H), 3.93-3.90 (m, 1H), 3.81-3.73 (m, 1.5H), 3.68-3.63 (m, 1H), 3.60-3.56 (dd, *J* = 4.0, 11.9 Hz, 0.5H), 3.52-3.40 (m, 1.5H), 3.31-3.23 (ddt, *J* = 3.4, 13.4 Hz, 0.5H) ppm.

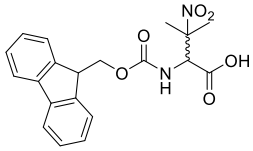
HRMS (ESI$^+$) calculated for $C_{20}H_{18}NO_5$ [M-H]$^-$: 352.1185; found: 352.1185.

(9*H*-Fluoren-9-yl)methyl (*S*)-3-(chlorocarbonyl)morpholine-4-carboxylate (**297**)



Carboxylic acid **113** (90.0 mg, 0.25 mmol) was stirred in $SOCl_2$ (1 mL) at 80 °C for 30 min. The solvent was removed under reduced pressure to furnish acyl chloride **297** (101 mg, quant.) as yellow oil, which was used in the next step without further purification.

2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methyl-3-nitrobutanoic acid (**109**)



3-Nitrovaline (**108**) (1.03 g, 6.43 mmol) was dissolved in 1,4-dioxane (30 mL) and a 10% Na_2CO_3 solution was added at 0 °C, followed by a solution of FmocCl (1.83 g, 7.07 mmol, 1.10 equiv) in 1,4-dioxane (30 mL) via a dropping funnel. The mixture was stirred for 18 h while warming to rt. Afterwards, the mixture was diluted with H_2O and Et_2O. The aq. phase was washed with Et_2O (2x), acidified with a 6 M HCl solution and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was coevaporated with PhMe (4x), MeOH (3x) and CH_2Cl_2 (4x) to furnish product **109** (1.40 g, 3.65 mmol, 57%) as colorless amorphous solid.

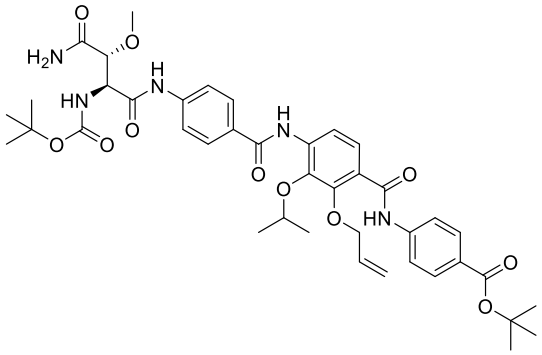
^{1}H-NMR (400 MHz, DMSO-d_6) = δ 13.40 (s, 1H, CO_2H), 8.12-8.09 (d, *J* = 9.9 Hz, 1H, NH), 7.91-7.89 (d, *J* = 7.6 Hz, 2H, H_{Ar}), 7.74-7.73 (d, *J* = 6.5 Hz, 2H, H_{Ar}), 7.44-7.40 (t, *J* = 7.4 Hz, 2H, H_{Ar}), 7.34-7.30 (dt, *J* = 1.0, 7.4 Hz, 2H, H_{Ar}), 4.99-4.97 (d, *J* = 9.9 Hz, 1H, C*H*NH), 4.42-4.38 (dd, *J* = 7.2 Hz, 1H, CH_2), 4.35-4.31 (m, 1H, CH_2), 4.27-4.23 (m, 1H, C*H*CH_2), 1.58 (s, 3H, CH_3), 1.50 (s, 3H, CH_3) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 169.8 (CO_2H), 156.6 (CON), 143.6 (d, *J* = 6.4 Hz, C_{Ar}), 140.7 (d, *J* = 1.6 Hz, C_{Ar}), 127.8 (d, *J* = 2.0 Hz, C_{Ar}), 127.1 (d, *J* = 2.1 Hz, C_{Ar}), 125.3 (d, *J* = 9.6 Hz, C_{Ar}), 120.2 (d, *J* = 3.6 Hz, C_{Ar}), 88.4 (*C*(CH_3)$_2$), 66.1 (CHNH), 59.2 (CHC*H*$_2$), 46.6 (*C*HCH_2), 24.7 (CH_3), 21.1 (CH_3) ppm;

HRMS (ESI$^+$) calculated for $C_{20}H_{19}N_2O_6$ [M-H]$^-$: 383.1243; found: 383.1244.

4.2.4 (2*S*,3*R*)-2,4-Diamino-3-methoxy-4-oxobutanoic acid derivavtives

tert-Butyl 4-(2-(allyloxy)-4-(4-((2*S*,3*R*)-4-amino-2-((*tert*-butoxycarbonyl)amino)-3-methoxy-4-oxobutanamido)benzamido)-3-isopropoxybenzamido)benzoate (**120**)



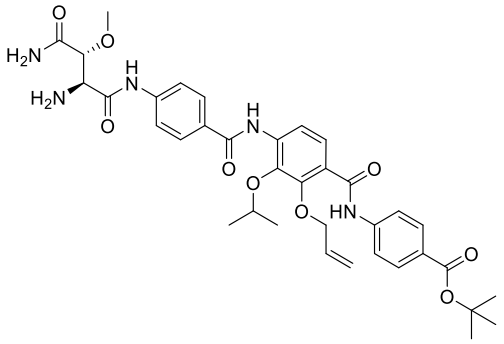
Amine **5** (628 mg, 1.15 mmol) and acid **4** (513 mg, 1.96 mmol, 1.70 equiv.) were dissolved in $CHCl_3$ (3.5 mL). A solution of EEDQ (455 mg, 1.84 mmol, 1.60 equiv.) in $CHCl_3$ (2.3 mL) was added dropwise at 0 °C. The reaction mixture was stirred while the cooling bath warmed up to rt. Stirring was continued for 20 h. The mixture was concentrated and the crude product was purified by column chromatography (dry load, wash with 20% Et_2O in CH_2Cl_2, elution with 3% MeOH in CH_2Cl_2) to furnish product **120** (538 mg, 0.68 mmol, 59%) as yellow amorphous solid.

The analytical data are consistent with those reported in the literature.[32]

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 10.53 (s, 1H, NH), 10.36 (s, 1H, NH), 9.52 (s, 1H, NH), 7.98-7.96 (m, 2H, H_{Ar}), 7.90-7.88 (m, 2H, H_{Ar}), 7.83-7.79 (m, 5H, H_{Ar}), 7.45-7.40 (m, 3H, H_{Ar}), 6.81-6.79 (d, *J* = 8.5 Hz, 1H, C*H*N*H*), 6.07-5.97 (m, 1H, C*H*CH_2), 5.40-5.35 (dd, *J* = 1.5, 17.2 Hz, 1H, CHC*H*$_2$), 5.22-5.19 (dd, *J* = 1.3, 10.5 Hz, 1H, CHC*H*$_2$), 4.61-4.60 (d, *J* = 5.5 Hz, 1H, OCH_2), 4.53-4.47 (p, *J* = 6.0 Hz, 1H, C*H*(CH_3)$_2$), 4.42-4.38 (t, *J* = 7.9 Hz, 1H, C*H*NH),

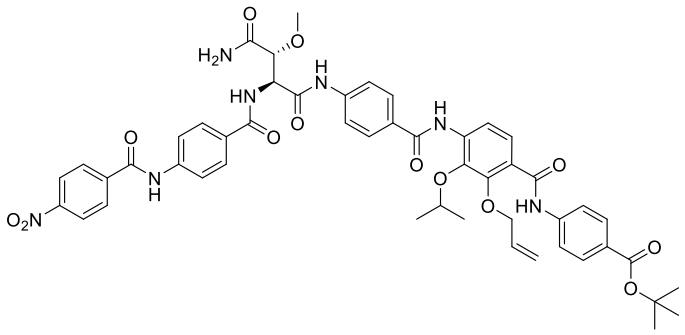
3.86-3.84 (d, J = 7.4 Hz, 1H, C*H*OCH$_3$), 3.25 (s, 3H, OCH$_3$), 1.55 (s, 9H, C(CH$_3$)$_3$), 1.38 (s, 9H, C(CH$_3$)$_3$), 1.27-1.25 (d, J = 6.1 Hz, 6H, CH(C*H*$_3$)$_2$) ppm.

tert-Butyl 4-(2-(allyloxy)-4-(4-((2*S*,3*R*)-2,4-diamino-3-methoxy-4-oxobutanamido) benzamido)-3-isopropoxybenzamido)benzoate (**158**)



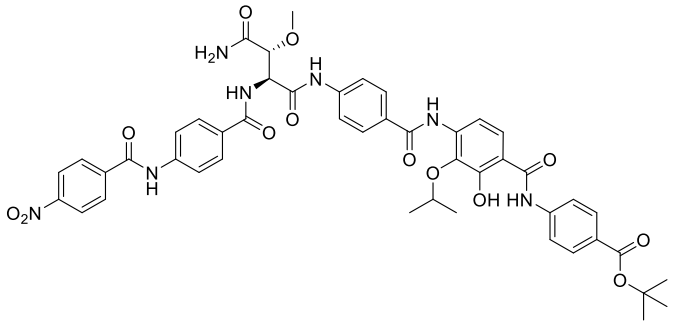
Carbamate **120** (521 mg, 0.66 mmol) was dissolved in HCl (4 M in 1,4-dioxane, 16.5 mL, 66.0 mmol, 100 equiv.) at 0 °C. The mixture was warmed up to rt and stirred for 15 min. The solution was transferred to a stirred suspension of EtOAc (290 mL) and a sat. NaHCO$_3$ solution (290 mL). The aq. phase was extracted with EtOAc (3x 145 mL) and the combined organic phases were washed with brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was used in the next step without further purification.

tert-Butyl 4-(2-(allyloxy)-4-(4-((2*S*,3*R*)-4-amino-3-methoxy-2-(4-(4-nitrobenzamido) benzamido)-4-oxobutanamido)benzamido)-3-isopropoxybenzamido)benzoate (**159**)



DIPEA (1.30 mL, 7.36 mmol, 12.7 equiv.) was added dropwise to a stirred solution of HATU (551 mg, 1.45 mmol, 2.50 equiv.) and carboxylic acid **157** (423 mg, 1.48 mmol, 2.60 equiv.) in DMF (13 mL). The solution was stirred for 30 min and was then transferred to a stirred solution of amine **158** (400.0 mg, 0.58 mmol) in DMF (8 mL). The reaction mixture was stirred at rt for 19 h. The mixture was diluted with EtOAc (420 mL) and washed with a 0.1 M HCl solution (420 mL), brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 2%, 3%, 4%) to furnish product **159** (141 mg, 0.15 mmol, 25%) as yellow amorphous solid.
The analytical data are consistent with those reported in the literature.[32]
^{1}H-NMR (500 MHz, DMSO-d_6) = δ 10.81 (s, 1H, NH), 10.56 (s, 1H, NH), 10.53 (s, 1H, NH), 9.52 (s, 1H, NH), 8.48-8.45 (d, *J* = 8.0 Hz, 1H, C*H*N*H*), 8.40-8.38 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 8.22-8.20 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 8.00-7.97 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.91-7.81 (m, 11H, H_{Ar}), 7.55-7.48 (d, *J* = 25.5 Hz, 2H, NH_2), 7.42-7.40 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.07-5.97 (m, 1H, C*H*CH_2), 5.40-5.35 (dq, *J* = 1.7, 17.4 Hz, 1H, CHC*H*$_2$), 5.22-5.19 (dq, *J* = 1.6, 10.5 Hz, 1H, CHC*H*$_2$), 4.94-4.90 (t, *J* = 8.1 Hz, 1H, C*H*NH), 4.61-4.60 (d, *J* = 5.5 Hz, 2H, OCH_2), 4.53-4.46 (p, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.10-4.08 (d, *J* = 8.1 Hz, 1H, C*H*OCH_3), 3.31 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.27-1.25 (d, *J* = 6.2 Hz, 6H, $CH(CH_3)_2$) ppm.

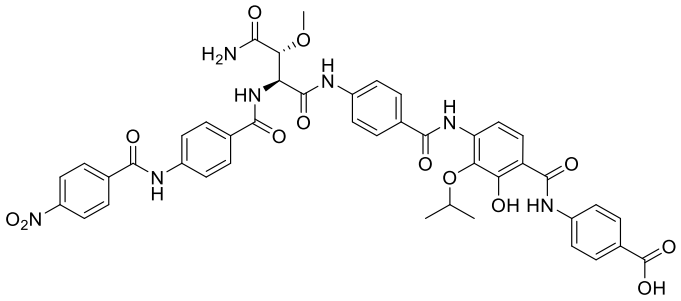
tert-Butyl 4-(4-(4-((2*S*,3*R*)-4-amino-3-methoxy-2-(4-(4-nitrobenzamido)benzamido)-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**169**)



Allyl ether **159** (136 mg, 0.14 mmol) was dissolved in THF (7 mL). Aniline (50 µL, 0.47 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (16.4 mg, 0.01 mmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 2 h. The mixture was concentrated onto silica (370 mg). The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 3%, 5%) to furnish product **169** (80.5 mg, 0.09 mmol, 62%) as beige amorphous solid.
The analytical data are consistent with those reported in the literature.[32]
^{1}H-NMR (400 MHz, DMSO-d_6) = δ 12.28 (s, 1H, OH), 10.81 (s, 1H, NH), 10.66 (bs, 1H, NH), 10.58 (s, 1H, NH), 9.40 (s, 1H, NH), 8.48-8.46 (d, *J* = 8.0 Hz, 1H, C*H*N*H*), 8.40-8.38 (d,

J = 8.9 Hz, 2H, H_{Ar}), 8.22-8.19 (d, *J* = 9.0 Hz, 2H, H_{Ar}), 7.98-7.83 (m, 13H, H_{Ar}), 7.70-7.68 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 7.55-7.48 (d, *J* = 26.6 Hz, 2H, NH_2), 4.94-4.90 (t, *J* = 8.1 Hz, 1H, C*H*NH), 4.59-4.52 (p, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.10-4.08 (d, *J* = 8.1 Hz, 1H, C*H*OCH_3), 3.31 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.27-1.26 (d, *J* = 6.2 Hz, 6H, $CH(CH_3)_2$) ppm.

4-(4-(4-((2*S*,3*R*)-4-Amino-3-methoxy-2-(4-(4-nitrobenzamido)benzamido)-4-oxobutan-amido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **861-2**

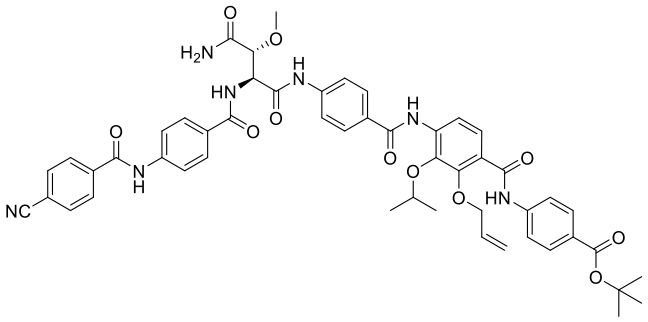


tert-Butyl ester **169** (76.7 mg, 0.08 mmol) was dissolved in precooled TFA (5 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **861-2** (64.3 mg, 0.07 mmol, 89%) as brown amorphous solid.

The analytical data are consistent with those reported in the literature.[32]

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 12.81 (bs, 1H, CO_2H), 12.29 (s, 1H, OH), 10.80 (s, 1H, NH), 10.60 (s, 1H, NH), 10.57 (s, 1H, NH), 9.40 (s, 1H, NH), 8.47-8.45 (d, *J* = 8.2 Hz, 1H, CHN*H*), 8.40-8.38 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 8.22-8.20 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.98-7.84 (m, 13H, H_{Ar}), 7.72-7.70 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 7.54-7.47 (d, *J* = 39.7 Hz, 2H, NH_2), 4.93-4.91 (t, *J* = 8.1 Hz, 1H, C*H*NH), 4.57-4.53 (p, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.10-4.09 (d, *J* = 8.1 Hz, 1H, C*H*OCH_3), 3.31 (s, 3H, OCH_3), 1.27-1.26 (d, *J* = 6.2 Hz, 6H, $CH(CH_3)_2$) ppm.

tert-Butyl 4-(2-(allyloxy)-4-(4-((2*S*,3*R*)-4-amino-2-(4-(4-cyanobenzamido)benzamido)-3-methoxy-4-oxobutanamido)benzamido)-3-isopropoxybenzamido)benzoate (**160**)

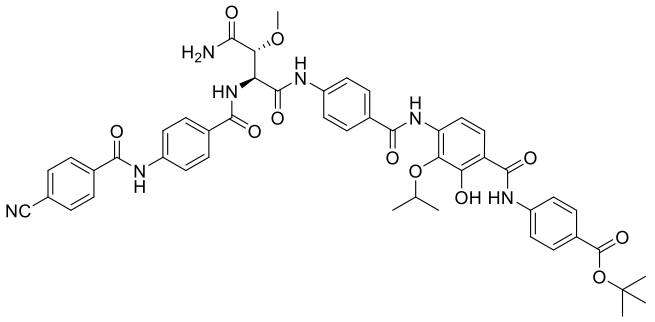


Amine **158** (88.4 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (1.3 mL) and NMM (29 µL, 0.26 mmol, 2.00 equiv.) was added. Chloride **277** (36.5 mg, 0.13 mmol, 1.00 equiv.) was added at 0 °C and the suspension was stirred for 16 h while warming to rt. The mixture was diluted with a sat. $NaHCO_3$ solution and the aq. phase was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was washed with MeOH. The precipitate was filtered off to furnish compound **160** (74.4 mg, 0.08 mmol, 62%) as colorless amorphous solid.

The analytical data are consistent with those reported in the literature.[32]

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 10.72 (s, 1H, NH), 10.56 (s, 1H, NH), 10.53 (s, 1H, NH), 9.52 (s, 1H, NH), 8.47-8.45 (d, *J* = 7.8 Hz, 1H, CHN*H*), 8.14-8.12 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 8.06-8.04 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 7.99-7.97 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.90-7.81 (m, 11H, H_{Ar}), 7.55-7.48 (d, *J* = 26.8 Hz, 2H, NH_2), 7.42-7.40 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 6.07-5.97 (m, 1H, C*H*CH_2), 5.39-5.35 (d, *J* = 17.0 Hz, 1H, CHC*H*$_2$), 5.22-5.19 (d, *J* = 10.8 Hz, 1H, CHC*H*$_2$), 4.94-4.90 (t, *J* = 8.1 Hz, 1H, C*H*NH), 4.61-4.60 (d, *J* = 4.6 Hz, 2H, OCH_2), 4.52-4.48 (p, *J* = 5.9 Hz, 1H, C*H*$(CH_3)_2$), 4.10-4.08 (d, *J* = 7.8 Hz, 1H, C*H*OCH_3), 3.32 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.27-1.25 (d, *J* = 6.0 Hz, 6H, $CH(CH_3)_2$) ppm.

tert-Butyl 4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(4-cyanobenzamido)benzamido)-3-methoxy-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**170**)



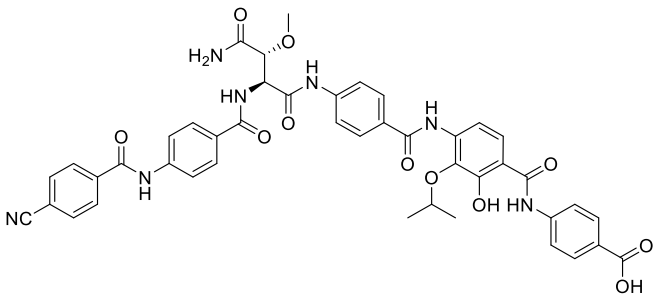
Allyl ether **160** (23.7 mg, 0.03 mmol) was dissolved in THF (1.5 mL). Aniline (8 µL, 0.08 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (2.9 mg, 2 µmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 2 h. The mixture was concentrated and the residue

was washed with Et_2O. The precipitate was filtered off to furnish product **170** (17.1 mg, 0.02 mmol, 75%) as yellow amorphous solid.

The analytical data are consistent with those reported in the literature.[32]

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 12.28 (s, 1H, OH), 10.72-10.57 (m, 3H, NH), 9.34 (s, 1H, NH), 8.47-8.45 (d, *J* = 8.1 Hz, 1H, CHN*H*), 8.14-8.12 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 8.06-8.04 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 7.96-7.83 (m, 14H, H_{Ar}), 7.55-7.48 (d, *J* = 27.0 Hz, 2H, NH_2), 4.94-4.90 (t, *J* = 8.1 Hz, 1H, C*H*NH), 4.60 (m, 1H, C*H*$(CH_3)_2$), 4.10-4.08 (d, *J* = 7.9 Hz, 1H, C*H*OCH_3), 3.31 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm.

4-(4-(4-((2*S*,3*R*)-4-Amino-2-(4-(4-cyanobenzamido)benzamido)-3-methoxy-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **CN861**

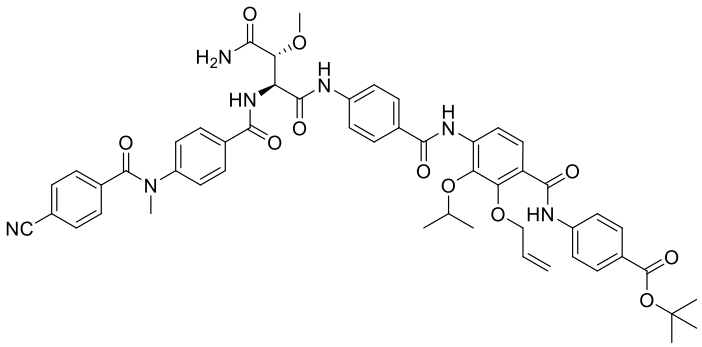


tert-Butyl ester **170** (14.1 mg, 0.02 mmol) was dissolved in precooled TFA (1 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **CN861** (9.0 mg, 0.01 mmol, 68%) as yellow amorphous solid.

The analytical data are consistent with those reported in the literature.[32]

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 12.80 (bs, 1H, CO_2H), 12.29 (s, 1H, OH), 10.72 (s, 1H, NH), 10.60 (s, 1H, NH), 10.58 (s, 1H, NH), 9.40 (s, 1H, NH), 8.47-8.45 (d, *J* = 8.1 Hz, 1H, CHN*H*), 8.14-8.12 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 8.06-8.04 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 8.00-7.80 (m, 13H, H_{Ar}), 7.72-7.70 (d, *J* = 8.8 Hz, 1H, H_{Ar}), 7.54-7.48 (d, *J* = 25.0 Hz, 2H, NH_2), 4.94-4.90 (t, *J* = 8.1 Hz, 1H, C*H*NH), 4.57-4.50 (p, *J* = 5.7 Hz, 1H, C*H*$(CH_3)_2$), 4.10-4.08 (d, *J* = 8.3 Hz, 1H, C*H*OCH_3), 3.31 (s, 3H, OCH_3), 1.27-1.26 (d, *J* = 6.0 Hz, 6H, $CH(CH_3)_2$) ppm.

tert-Butyl 4-(2-(allyloxy)-4-(4-((2*S*,3*R*)-4-amino-3-methoxy-2-(4-(*N*-methyl-4-nitrobenzamido)benzamido)-4-oxobutanamido)benzamido)-3-isopropoxybenzamido)benzoate (**162**)



DIPEA (0.20 mL, 1.01 mmol, 12.7 equiv.) was added dropwise to a stirred solution of HATU (75.8 mg, 0.20 mmol, 2.50 equiv.) and carboxylic acid **10** (57.0 mg, 0.20 mmol, 2.55 equiv.) in DMF (1.8 mL). The solution was stirred for 30 min and then transferred to a stirred solution of amine **158** (55.0 mg, 0.08 mmol) in DMF (1.0 mL). The reaction mixture was stirred at rt for 19 h. The mixture was diluted with EtOAc (58 mL) and washed with a HCl solution (0.1 M, 58 mL), brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 2%, 4%). The product fraction was washed with a K_2CO_3 solution. The organic phase was dried over $MgSO_4$, filtered, concentrated under reduced pressure and dried *in vacuo* to furnish product **162** (19.8 mg, 0.02 mmol, 26%) as yellow amorphous solid.

R_f (5% MeOH in CH_2Cl_2) = 0.37;

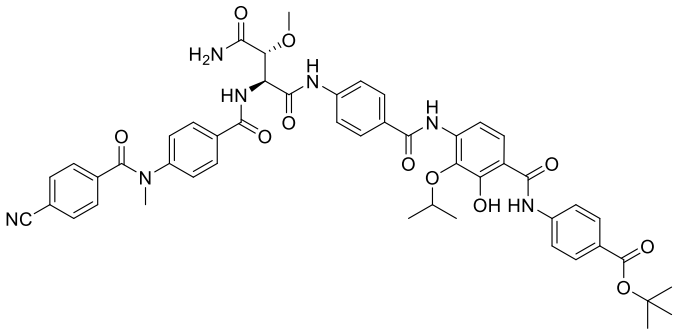
$[\alpha]_D^{23}$ = +6.00 ° (c = 0.10, MeOH);

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 10.56 (s, 1H, NH), 10.53 (s, 1H, NH), 9.52 (s, 1H, NH), 8.59-8.58 (m, 1H, CHN*H*), 7.99-7.97 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.91-7.89 (d, *J* = 9.2 Hz, 2H, H_{Ar}), 7.84-7.81 (m, 5H, H_{Ar}), 7.76-7.74 (d, *J* = 8.2 Hz, 4H, H_{Ar}), 7.52-7.46 (m, 4H, H_{Ar}, NH_2), 7.42-7.40 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 7.34-7.32 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 6.06-5.99 (m, 1H, C*H*CH_2), 5.40-5.36 (dq, *J* = 1.7, 17.2 Hz, 1H, CHC*H*$_2$), 5.22-5.19 (dq, *J* = 1.7, 10.5 Hz, 1H, CHC*H*$_2$), 4.88-4.84 (t, *J* = 8.2 Hz, 1H, C*H*NH), 4.62-4.61 (d, *J* = 5.5 Hz, 2H, OCH_2), 4.52-4.47 (p, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.07-4.06 (d, *J* = 8.1 Hz, 1H, C*H*OCH_3), 3.42 (s, 3H, NCH_3), 3.29 (s, 3H, OCH_3), 1.56 (s, 9H, $C(CH_3)_3$), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 170.8 (CO), 168.6 (CO), 167.9 (CO), 165.1 (CO), 164.6 (CO), 164.5 (CO), 164.3 (CO), 149.5 (C_{Ar}), 146.6 (C_{Ar}), 143.0 (C_{Ar}), 142.5 (C_{Ar}), 142.1 (C_{Ar}), 140.6 (C_{Ar}), 135.6 (C_{Ar}), 133.7 (*C*HCH_2), 132.0 (C_{Ar}), 131.6 (C_{Ar}), 130.1 (C_{Ar}), 129.0 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 127.1 (C_{Ar}), 126.8 (C_{Ar}), 126.0 (C_{Ar}), 123.6 (C_{Ar}), 118.9 (C_{Ar}), 118.9 (C_{Ar}), 118.8 (C_{Ar}), 118.2 (CH*C*H_2), 117.8 (CN), 112.1 (C_{Ar}), 80.3 (*C*$HOCH_3$), 79.8 (*C*$(CH_3)_3$), 76.3 (OCH_2), 74.3 (*C*$H(CH_3)_2$), 57.7 (OCH_3), 55.8 (*C*HNH), 37.5 (NCH_3), 27.9 ($C(CH_3)_3$), 22.3 ($CH(CH_3)_2$) ppm;

HRMS (ESI$^+$) calculated for $C_{52}H_{53}N_7O_{11}Na$ $[M+Na]^+$: 974.3701; found: 974.3701.

tert-Butyl 4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(4-cyano-*N*-methylbenzamido)benzamido)-3-methoxy-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**172**)



Allyl ether **162** (19.0 mg, 0.02 mmol) was dissolved in THF (1 mL). Aniline (6 µL, 0.07 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (2.3 mg, 2 µmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 2 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 2%, 3%, 5%) to furnish product **172** (14.0 mg, 0.02 mmol, 77%) as beige amorphous solid.

R_f (5% MeOH in CH_2Cl_2) = 0.16;

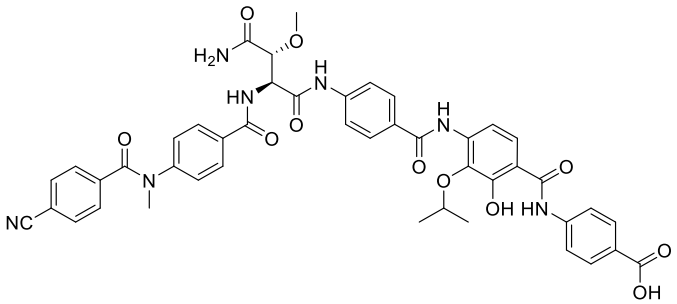
$[\alpha]_D^{25}$ = +6.9 ° (c 0.2, MeOH);

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 12.28 (s, 1H, OH), 10.56 (bs, 2H, NH), 9.38 (s, 1H, NH), 8.54-8.52 (d, *J* = 8.2 Hz, 1H, CHN*H*), 7.95-7.67 (m, 14H, $H_{Ar,}$ NH_2), 7.48-7.46 (d, *J* = 8.5 Hz, 4H, H_{Ar}), 7.33-7.32 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 4.87-4.84 (t, *J* = 8.2 Hz, 1H, C*H*NH), 4.56 (bs, 1H, C*H*$(CH_3)_2$), 4.05-4.03 (d, *J* = 8.2 Hz, 1H, C*H*OCH_3), 3.42 (s, 3H, NCH_3), 3.28 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.27-1.25 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm.

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 170.8 (CO), 168.6 (CO), 168.4 (CO), 167.9 (CO), 165.1 (CO), 164.6 (CO), 164.1 (CO), 146.6 (C_{Ar}), 142.2 (C_{Ar}), 140.6 (C_{Ar}), 136.3 (C_{Ar}), 132.0 (C_{Ar}), 131.5 (C_{Ar}), 129.9 (C_{Ar}), 129.0 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 126.8 (C_{Ar}), 122.9 (C_{Ar}), 120.6 (CN), 119.0 (C_{Ar}), 118.9 (C_{Ar}), 118.2 (C_{Ar}), 112.1 (C_{Ar}), 80.4 (*C*HOCH_3), 79.9 (*C*$(CH_3)_3$), 74.7 (*C*H$(CH_3)_2$), 57.7 (OCH_3), 55.8 (CHNH), 37.5 (NCH_3), 27.8 ($C(CH_3)_3$), 22.3 ($CH(CH_3)_2$) ppm.

HRMS (ESI) calculated for $C_{49}H_{49}N_7O_{11}Na$ $[M+Na]^+$: 934.3388; found: 934.3386.

4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(4-cyano-*N*-methylbenzamido)benzamido)-3-methoxy-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSA73**



tert-Butyl ester **172** (12.9 mg, 0.01 mmol) was dissolved in precooled TFA (1 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSA73** (8.1 mg, 0.01 mmol, 67%) as brownish amorphous solid.

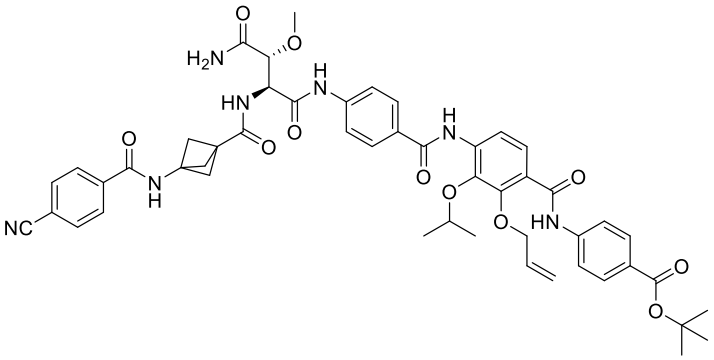
$[\alpha]_D^{25}$ = +5.3 ° (c 0.2, MeOH);

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 12.80 (s, 1H, CO_2H), 12.29 (s, 1H, OH), 10.60 (s, 1H, NH), 10.54 (s, 1H, NH), 9.39 (s, 1H, NH), 8.53-8.52 (d, *J* = 8.2 Hz, 1H, CHN*H*), 7.98-7.70 (m, 13H, H_{Ar}), 7.48-7.45 (m, 3H, H_{Ar}, $CONH_2$), 7.33-7.32 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 4.87-4.85 (t, *J* = 8.0 Hz, 1H, C*H*NH), 4.56-4.52 (p, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.05-4.04 (d, *J* = 8.2 Hz, 1H, C*H*OCH_3), 3.42 (s, 3H, NCH_3), 3.29 (s, 3H, OCH_3), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 170.8 (CO), 168.6 (CO), 168.5 (CO), 167.9 (CO), 166.8(CO), 165.1 (CO), 164.2 (CO), 154.1 (C_{Ar}), 146.6 (C_{Ar}), 142.2 (C_{Ar}), 141.9 (C_{Ar}), 140.6 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 132.0 (C_{Ar}), 131.5 (C_{Ar}), 130.2 (C_{Ar}), 128.9 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 126.8 (C_{Ar}), 126.3 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (CN), 119.0 (C_{Ar}), 118.1 (C_{Ar}), 112.4 (C_{Ar}), 112.1 (C_{Ar}), 112.1 (C_{Ar}), 79.9 (*C*HOCH_3), 74.8 (*C*H$(CH_3)_2$), 57.7 (OCH_3), 55.7 (CHNH), 37.5 (NCH_3), 22.3 (CH(*C*H$_3)_2$) ppm.

HRMS (ESI) calculated for $C_{45}H_{40}N_7O_{11}$ $[M-H]^-$: 854.2786; found: 854.2793.

tert-Butyl 4-(2-(allyloxy)-4-(4-((2*S*,3*R*)-4-amino-2-(3-(4-cyanobenzamido) bicyclo[1.1.1] pentane-1-carboxamido)-3-methoxy-4-oxobutanamido)benzamido)-3-isopropoxybenzamido) benzoate (**168**)



DIPEA (0.30 mL, 1.69 mmol, 12.7 equiv.) was added dropwise to a stirred solution of HATU (126.1 mg, 0.33 mmol, 2.50 equiv.) and carboxylic acid **41** (85.0 mg, 0.33 mmol, 2.50 equiv.) in DMF (3.0 mL). The solution was stirred for 15 min and then transferred to a stirred solution of amine **158** (91.5 mg, 0.13 mmol) in DMF (1.8 mL). The reaction mixture was stirred at rt for 20 h. The mixture was diluted with EtOAc and washed with an aq. HCl solution (0.1 M, 15 mL). The aq. phase was extracted with EtOAc and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 5%). The product fraction was washed with an aq. K_2CO_3 solution. The organic phase was dried over $MgSO_4$, filtered, concentrated under reduced pressure and dried *in vacuo* to furnish product **168** (50.6 mg, 0.06 mmol, 41%) as yellow amorphous solid.[103]

R_f (5% MeOH in CH_2Cl_2) = 0.20;

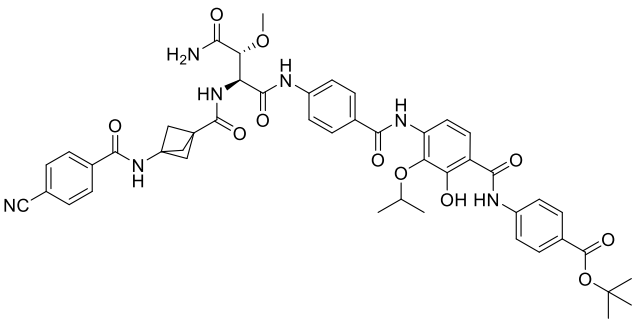
$[\alpha]_D^{19}$ = +2.50 ° (c 0.1, MeOH);

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 10.53 (s, 1H, NH), 10.52 (s, 1H, NH), 9.52 (s, 1H, NH), 9.31 (s, 1H, NH), 7.80-7.95 (m, 7H, CHN*H*, H_{Ar}), 7.90-7.88 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.84-7.79 (m, 6H, H_{Ar}), 7.44-7.40 (m, 3H, H_{Ar}, NH_2), 6.06-5.98 (m, 1H, C*H*CH_2), 5.40-5.35 (dq, *J* = 1.7, 17.2 Hz, 1H, CHC*H*$_2$), 5.22-5.19 (dq, *J* = 1.7, 10.5 Hz, 1H, CHC*H*$_2$), 4.74-4.70 (t, *J* = 8.5 Hz, 1H, C*H*NH), 4.61-4.60 (d, *J* = 5.5 Hz, 2H, OCH_2), 4.52-4.47 (p, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 3.96-3.94 (d, *J* = 8.3 Hz, 1H, C*H*OCH_3), 3.26 (s, 3H, OCH_3), 2.29 (s, 6H, CCH_2C), 1.55 (s, 9H, $C(CH_3)_3$), 1.27-1.25 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (500 MHz, DMSO-d_6) = δ 170.6 (CO), 168.5 (CO), 168.1 (CO), 165.2 (CO), 164.6 (CO), 164.5 (CO), 164.3 (CO), 149.5 (C_{Ar}), 143.0 (C_{Ar}), 142.5 (C_{Ar}), 142.1 (C_{Ar}), 140.6 (C_{Ar}), 138.1 (C_{Ar}), 135.6 (C_{Ar}), 133.7 (*C*HCH_2), 132.4 (C_{Ar}), 130.1 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.1 (C_{Ar}), 127.1 (C_{Ar}), 126.0 (C_{Ar}), 123.6 (C_{Ar}), 118.9 (C_{Ar}), 118.9 (C_{Ar}), 118.8 (C_{Ar}), 118.3 (CH*C*H_2), 117.8 (CN), 113.7 (C_{Ar}), 80.3 (*C*$HOCH_3$), 79.9 (*C*$(CH_3)_3$), 76.3 (*C*$H(CH_3)_2$), 74.3 (C-10), 59.8 (CHNH), 57.7 (OCH_3), 53.5 (*C*CH_2C), 45.3 (*C*CH_2C), 37.4 (C*C*H_2C), 27.9 ($C(CH_3)_3$), 22.3 ($CH(CH_3)_2$) ppm;

HRMS (ESI$^+$) calculated for $C_{50}H_{53}N_7O_{11}Na$ [M+Na]$^+$: 950.3701; found: 950.3703.

tert-Butyl 4-(4-(4-((2*S*,3*R*)-4-amino-2-(3-(4-cyanobenzamido)bicyclo[1.1.1]pentane-1-carboxamido)-3-methoxy-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**178**)



Allyl ether **168** (40.0 mg, 0.04 mmol) was dissolved in THF (2.3 mL). Aniline (13 µL, 0.14 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (5.0 mg, 4 µmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 2 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 5%) to furnish product **178** (17.9 mg, 0.02 mmol, 47%) as beige amorphous solid.[103]

R_f (5% MeOH in CH_2Cl_2) = 0.13;

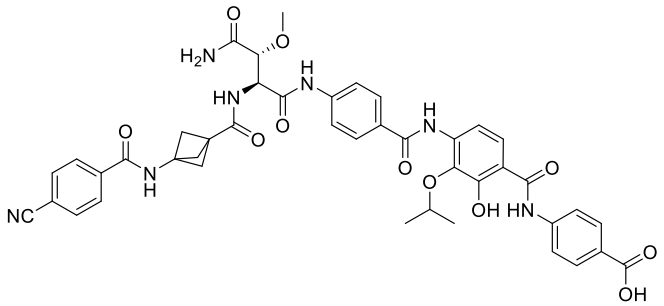
$[\alpha]_D^{23}$ = +5.0 ° (c 1.3, MeOH);

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 12.29 (s, 1H, OH), 10.62 (s, 1H, NH), 10.53 (s, 1H, NH), 9.37 (s, 1H, NH), 9.31 (s, 1H, NH), 8.00-7.91 (m, 9H, H_{Ar}), 7.86-7.79 (m, 6H, CHN*H*, H_{Ar}), 7.44-7.41 (d, *J* = 14.1 Hz, 2H, NH_2), 4.74-4.70 (t, *J* = 8.5 Hz, 1H, C*H*NH), 4.57 (bs, 1H, C*H*$(CH_3)_2$), 3.96-3.94 (d, *J* = 8.4 Hz, 1H, C*H*OCH_3), 3.26 (s, 3H, OCH_3), 2.29 (s, 6H, CCH_2C), 1.55 (s, 9H, $C(CH_3)_3$), 1.27-1.25 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (500 MHz, DMSO-d_6) = δ 170.6 (CO), 170.3 (CO), 168.5 (CO), 168.0 (CO), 165.2 (CO), 164.6 (CO), 164.1 (CO), 142.2 (C_{Ar}), 138.1 (C_{Ar}), 132.4 (C_{Ar}), 129.9 (C_{Ar}), 128.3 (C_{Ar}), 128.1 (C_{Ar}), 122.9 (C_{Ar}), 120.6 (C_{Ar}), 119.0 (C_{Ar}), 118.3 (C_{Ar}), 113.7 (C_{Ar}), 80.3 (*C*$HOCH_3$), 79.9 (*C*$(CH_3)_3$), 59.7 (CHNH), 57.7 (OCH_3), 53.5 (CCH_2C), 45.3 (*C*CH_2C), 37.4 (*C*CH_2C), 27.9 ($C(CH_3)_3$), 22.3 ($CH(CH_3)_2$) ppm;

HRMS (ESI$^+$) calculated for $C_{47}H_{49}N_7O_{11}Na$ [M+Na]$^+$: 910.3380; found: 910.3363.

4-(4-(4-((2*S*,3*R*)-4-Amino-2-(3-(4-cyanobenzamido)bicyclo[1.1.1]pentane-1-carboxamido)-3-methoxy-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **KB015**



tert-Butyl ester **178** (22.0 mg, 0.03 mmol) was dissolved in precooled TFA (1.5 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **KB015** (5.0 mg, 0.01 mmol, 24%) as brown amorphous solid.[103]

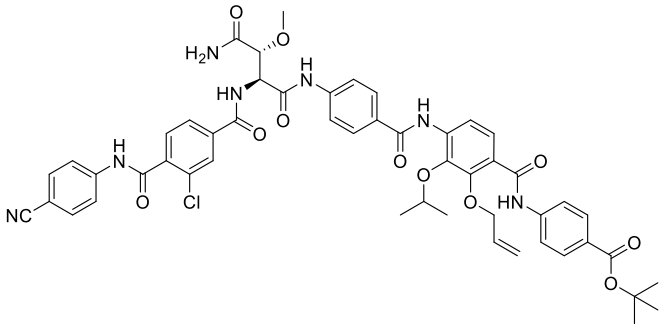
$[\alpha]_D^{22}$ = +0.6 ° (c 0.2, MeOH);

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 12.78 (s, 1H, CO_2H), 12.36 (bs, 1H, OH), 10.53 (bs, 2H, NH), 9.37 (s, 1H, NH), 9.31 (s, 1H, CHN*H*), 8.00-7.94 (m, 9H, H_{Ar}), 7.83-7.79 (m, 6H, NH, H_{Ar}), 7.43-7.41 (d, *J* = 13.6 Hz, 2H, NH_2), 4.74-4.70 (t, *J* = 8.5 Hz, 1H, C*H*NH), 4.57 (bs, 1H, C*H*$(CH_3)_2$), 3.96-3.94 (d, *J* = 8.3 Hz, 1H, C*H*OCH_3), 3.26 (s, 3H, OCH_3), 2.29 (s, 6H, CCH_2C), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 170.6 (CO), 168.5 (CO), 168.0 (CO), 165.2 (C-9), 164.1 (CO), 142.2 (C_{Ar}), 138.1 (C_{Ar}), 132.4 (C_{Ar}), 130.2 (C_{Ar}), 128.3 (C_{Ar}), 128.1 (C_{Ar}), 127.4 (C_{Ar}), 122.9 (C_{Ar}), 120.6 (C_{Ar}), 119.0 (C_{Ar}), 118.3 (C_{Ar}), 113.7 (C_{Ar}), 112.1 (C_{Ar}), 79.9 (*C*HOCH_3), 57.7 (OCH_3), 54.8 (CHNH), 53.5 (C*C*H_2C), 45.3 (*C*CH_2C), 37.4 (*C*CH_2C), 22.3 (CH(*C*$H_3)_2$) ppm;

HRMS (ESI) calculated for $C_{43}H_{40}N_7O_{11}$ $[M-H]^-$: 830.2786; found: 830.2782.

tert-Butyl 4-(2-(allyloxy)-4-(4-((2*S*,3*R*)-4-amino-2-(3-chloro-4-((4-cyanophenyl)carbamoyl) benzamido)-3-methoxy-4-oxobutanamido)benzamido)-3-isopropoxybenzamido)benzoate (**167**)



Acid **45** (26.2 mg, 0.09 mmol, 1.20 equiv.) and HATU (33.1 mg, 0.09 mmol, 1.20 equiv.) were dissolved in DMF (1.8 mL) and pyridine (18 µL, 0.22 mmol, 3.00 equiv.) was added. The

mixture was stirred at rt for 5 min and then transferred to a solution of amine **158** (50.0 mg, 0.07 mmol) in DMF (1.0 mL) at 0 °C. The resulting reaction mixture was stirred for 15 h while warming to rt. EtOAc was added and the mixture was washed with a 0.1 M HCl solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH in CH_2Cl_2 = 3%, 5%) to furnish product **167** (42.1 mg, 0.04 mmol, 60%) as colorless amorphous amorphous solid.

R_f (5% MeOH in CH_2Cl_2) = 0.25;

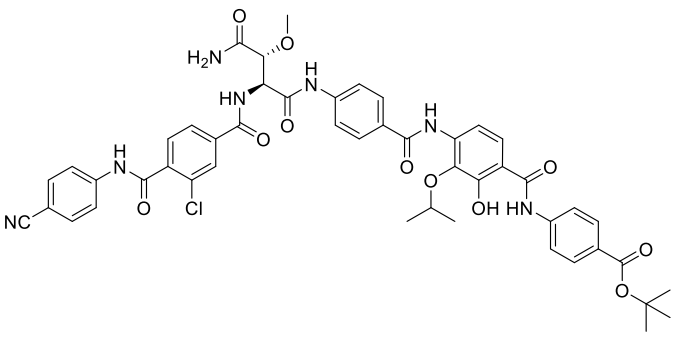
$[\alpha]_D^{26}$ = +13.9 ° (c 0.2, MeOH);

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 11.05 (s, 1H, NH), 10.58 (s, 1H, NH), 10.53 (s, 1H, NH), 9.53 (s, 1H, NH), 8.86-8.85 (d, *J* = 8.3 Hz, 1H, CHN*H*), 8.06 (d, *J* = 1.5 Hz, 1H, H_{Ar}), 8.00-7.98 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.94-7.92 (dd, *J* = 1.6, 8.0 Hz, 1H, H_{Ar}), 7.91-7.88 (m, 4H, H_{Ar}), 7.86-7.81 (m, 7H, H_{Ar}), 7.79-7.77 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.49-7.48 (d, *J* = 6.3 Hz, 2H, NH_2), 7.42-7.40 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.06-5.98 (m, 1H, C*H*CH_2), 5.39-5.35 (dq, *J* = 1.7, 15.5 Hz, 1H, CHC*H*$_2$), 5.22-5.19 (dq, *J* = 1.7, 10.5 Hz, 1H, CHC*H*$_2$), 4.98-4.94 (t, *J* = 8.3 Hz, 1H, C*H*NH), 4.61-4.60 (d, *J* = 5.5 Hz, 2H, OCH_2), 4.53-4.46 (sept, *J* = 6.1 Hz, 2H, C*H*$(CH_3)_2$), 4.08-4.07 (d, *J* = 8.2 Hz, 1H, C*H*OCH_3), 3.32 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3$)$_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 170.8 (CO), 168.3 (CO), 164.9 (CO), 164.6 (CO), 164.5 (CO), 164.3 (CO), 164.1 (CO), 149.5 (C_{Ar}), 143.0 (C_{Ar}), 142.8 (C_{Ar}), 142.6 (C_{Ar}), 142.1 (C_{Ar}), 138.7 (C_{Ar}), 136.3 (C_{Ar}), 135.6 (C_{Ar}), 133.6 (*C*HCH_2), 133.4 (C_{Ar}), 130.1 (C_{Ar}), 129.2 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 127.1 (C_{Ar}), 126.5 (C_{Ar}), 126.0 (C_{Ar}), 123.6 (C_{Ar}), 119.7 (C_{Ar}), 119.0 (C_{Ar}), 118.9 (CH*C*H_2), 118.8 (CN), 117.8 (C_{Ar}), 105.9 (C_{Ar}), 80.3 (*C*$(CH_3)_3$), 80.0 (*C*HOCH_3), 76.3 (OCH_2), 74.3 (*C*H$(CH_3)_2$), 57.9 (CHNH), 55.8 (OCH_3), 27.9 (C(*C*$H_3)_3$), 22.3 (CH(*C*$H_3)_2$) ppm;

HRMS (ESI$^+$) calculated for $C_{51}H_{50}ClN_7O_{11}Na$ $[M+Na]^+$: 994.3155; found: 994.3162.

tert-Butyl 4-(4-(4-((2*S*,3*R*)-4-amino-2-(3-chloro-4-((4-cyanophenyl)carbamoyl)benzamido)-3-methoxy-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**177**)



Allyl ether **167** (39.7 mg, 0.04 mmol) was dissolved in THF (1.8 mL). Aniline (12 µL, 0.13 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (4.7 mg, 4 µmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 2 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 5%) to furnish product **177** (33.5 mg, 0.04 mmol, 88%) as beige amorphous solid.

R_f (5% MeOH in CH_2Cl_2) = 0.16;

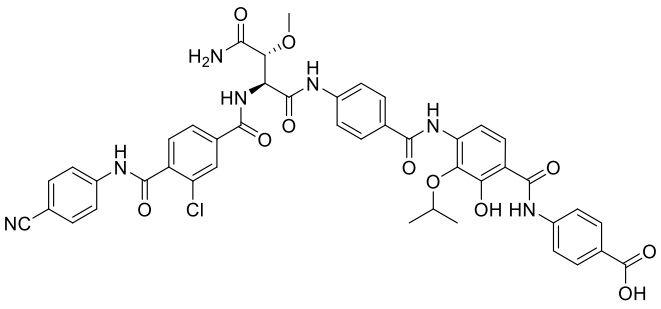
$[\alpha]_D^{25}$ = +9.4 ° (c 0.2, THF);

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 12.29 (s, 1H, OH), 11.05 (s, 1H, NH), 10.60 (bs, 2H, NH), 9.40 (s, 1H, NH), 8.86-8.85 (d, *J* = 8.3 Hz, 1H, CHN*H*), 8.06 (d, *J* = 1.5 Hz, 1H, H_{Ar}), 7.97-7.95 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.94-7.89 (m, 5H, H_{Ar}), 7.86-7.84 (m, 7H, H_{Ar}), 7.79-7.77 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.70-7.69 (d, *J* = 8.7 Hz, 1H, H_{Ar}), 7.49-7.48 (d, *J* = 7.1 Hz, 2H, NH_2), 4.97-4.95 (t, *J* = 8.3 Hz, 1H, C*H*NH), 4.58-4.52 (sept, *J* = 6.1 Hz, 2H, C*H*$(CH_3)_2$), 4.08-4.07 (d, *J* = 8.3 Hz, 1H, C*H*OCH_3), 3.32 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 170.8 (CO), 168.5 (CO), 168.3 (CO), 164.9 (CO), 164.5 (CO), 164.2 (CO), 164.1 (CO), 154.1 (C_{Ar}), 142.8 (C_{Ar}), 142.2 (C_{Ar}), 142.0 (C_{Ar}), 138.7 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 136.3 (C_{Ar}), 133.4 (C_{Ar}), 130.1 (C_{Ar}), 129.9 (C_{Ar}), 129.2 (C_{Ar}), 128.6 (C_{Ar}), 128.3 (C_{Ar}), 126.8 (C_{Ar}), 126.5 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.7 (C_{Ar}), 119.0 (C_{Ar}), 118.9 (CN), 112.4 (C_{Ar}), 112.2 (C_{Ar}), 105.9 (C_{Ar}), 80.5 (*C*$(CH_3)_3$), 80.0 (*C*HOCH_3), 74.8 (*C*H$(CH_3)_2$), 57.9 (CHNH), 55.8 (OCH_3), 27.8 ($C(CH_3)_3$), 22.3 ($CH(CH_3)_2$) ppm;

HRMS (ESI$^+$) calculated for $C_{48}H_{46}ClN_7O_{11}Na$ $[M+Na]^+$: 954.2842; found: 954.2825.

4-(4-(4-((2*S*,3*R*)-4-Amino-2-(3-chloro-4-((4-cyanophenyl)carbamoyl)benzamido)-3-methoxy-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSE22**

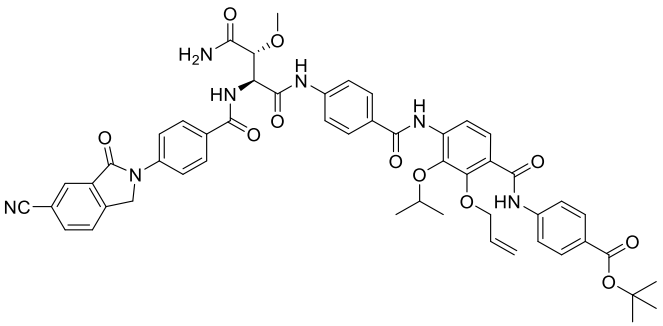


tert-Butyl ester **177** (31.3 mg, 0.03 mmol) was dissolved in precooled TFA (1.8 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSE22** (26.0 mg, 0.03 mmol, 88%) as beige amorphous solid.

$[\alpha]_D^{27}$ = +0.5 ° (c 0.1, DMSO);

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 12.82 (bs, 1H, CO_2H), 12.30 (s, 1H, OH), 11.05 (s, 1H, NH), 10.60 (bs, 2H, NH), 9.41 (s, 1H, NH), 8.86-8.85 (d, *J* = 8.3 Hz, 1H, CHN*H*), 8.06 (d, *J* = 1.5 Hz, 1H, H_{Ar}), 7.97-7.96 (dd, *J* = 2.3, 8.9 Hz, 4H, H_{Ar}), 7.94-7.93 (dd, *J* = 1.7, 8.0 Hz, 1H, H_{Ar}), 7.90-7.89 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.86-7.84 (m, 6H, H_{Ar}), 7.79-7.77 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 7.71-7.70 (d, *J* = 8.8 Hz, 1H, H_{Ar}), 7.49-7.47 (d, *J* = 7.3 Hz, 2H, NH_2), 4.97-4.95 (t, *J* = 8.3 Hz, 1H, C*H*NH), 4.58-4.52 (sept, *J* = 6.1 Hz, 2H, C*H*$(CH_3)_2$), 4.08-4.07 (d, *J* = 8.3 Hz, 1H, C*H*OCH_3), 3.32 (s, 3H, OCH_3), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3)_2$) ppm;
^{13}C-NMR (151 MHz, DMSO-d_6) = δ 170.8 (CO), 168.5 (CO), 168.3 (CO), 166.9 (CO), 164.9 (CO), 164.2 (CO), 164.1 (CO), 154.1 (C_{Ar}), 142.8 (C_{Ar}), 142.2 (C_{Ar}), 142.0 (C_{Ar}), 138.7 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 136.3 (C_{Ar}), 133.4 (C_{Ar}), 130.2 (C_{Ar}), 130.0 (C_{Ar}), 129.2 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 126.5 (C_{Ar}), 126.3 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.7 (C_{Ar}), 119.0 (C_{Ar}), 118.9 (CN), 112.5 (C_{Ar}), 112.2 (C_{Ar}), 105.9 (C_{Ar}), 80.0 (*C*$HOCH_3$), 74.9 (*C*H$(CH_3)_2$), 57.9 (CHNH), 55.8 (OCH_3), 22.3 (CH(*C*$H_3)_2$) ppm;
HRMS (ESI) calculated for $C_{44}H_{37}ClN_7O_{11}$ $[M-H]^-$:874.2240; found: 874.2239.

tert-Butyl 4-(2-(allyloxy)-4-(4-((2*S*,3*R*)-4-amino-2-(4-(6-cyano-1-oxoisoindolin-2-yl) benzamido)-3-methoxy-4-oxobutanamido)benzamido)-3-isopropoxybenzamido)benzoate (**164**)



Amine **158** (58.1 mg, 0.08 mmol) was dissolved in CH_2Cl_2 (1.0 mL) and NMM (19 µL, 0.17 mmol, 2.00 equiv.) was added. Chloride **279** (25.0 mg, 0.08 mmol, 1.00 equiv.) was added at 0 °C and the suspension was stirred for 16 h while warming to rt. The mixture was diluted with a sat. $NaHCO_3$ solution and the aq. phase was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated. The

residue was washed with MeOH. The precipitate was filtered off to furnish product **164** (27.6 mg, 0.03 mmol, 34%) as orange amorphous solid.

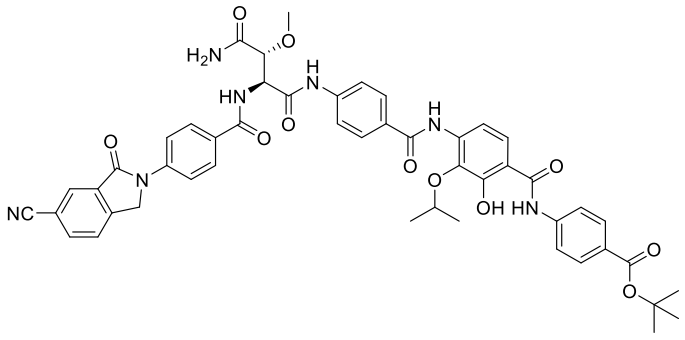
The measurement of optical rotation was not possible due to insolubility of compound **164**.

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 10.57 (s, 1H, NH), 10.53 (s, 1H, NH), 9.52 (s, 1H, NH), 8.53-8.51 (d, *J* = 8.1 Hz, 1H, CHN*H*), 8.29 (s, 1H, H_{Ar}), 8.16-8.14 (dd, *J* = 1.4, 7.9 Hz, 2H, H_{Ar}), 8.07-8.04 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.99-7.81 (m, 12H, H_{Ar}), 7.54-7.48 (d, *J* = 22.7 Hz, 2H, NH_2), 7.42-7.40 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.07-5.97 (m, 1H, C*H*CH_2), 5.40-5.34 (dq, *J* = 1.7, 17.2 Hz, 1H, CHC*H*$_2$), 5.24-5.19 (m, 3H, CHC*H*$_2$, NCH_2), 4.95-4.91 (t, *J* = 8.1 Hz, 1H, C*H*NH), 4.61-4.60 (d, *J* = 5.4 Hz, 2H, OCH_2), 4.54-4.46 (p, *J* = 6.2 Hz, 1H, C*H*$(CH_3)_2$), 4.11-4.09 (d, *J* = 8.2 Hz, 1H, C*H*OCH_3), 3.32 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.27-1.25 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (500 MHz, DMSO-d_6) = δ 170.9 (CO), 168.7 (CO), 165.3 (CO), 165.3 (CO), 164.6 (CO), 164.5 (CO), 164.3 (CO), 149.5 (C_{Ar}), 145.8 (C_{Ar}), 143.0 (C_{Ar}), 142.5 (C_{Ar}), 142.1 (C_{Ar}), 141.8 (C_{Ar}), 136.0 (C_{Ar}), 135.6 (C_{Ar}), 133.6 (*C*HCH_2), 133.2 (C_{Ar}), 130.5 (C_{Ar}), 130.1 (C_{Ar}), 129.1 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 127.6 (C_{Ar}), 127.1 (C_{Ar}), 126.0 (C_{Ar}), 124.9 (C_{Ar}), 123.6 (C_{Ar}), 118.9 (C_{Ar}), 118.9 (C_{Ar}), 118.8 (C_{Ar}), 118.5 (C_{Ar}), 118.3 (CH*C*H_2), 117.8 (CN), 111.4 (C_{Ar}), 80.3 (*C*$(CH_3)_3$), 80.0 (*C*HOCH_3), 76.3 (*C*H$(CH_3)_2$), 74.3 (OCH_2), 57.8 (OCH_3), 55.8 (CHNH), 50.8 (NCH_2), 27.9 (C(*C*$H_3)_3$), 22.3 (CH(*C*$H_3)_2$) ppm;

HRMS (ESI) calculated for $C_{52}H_{51}N_7O_{11}Na$ $[M+Na]^+$: 972.3544; found: 972.3546.

tert-Butyl 4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(6-cyano-1-oxoisoindolin-2-yl)benzamido)-3-methoxy-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**174**)

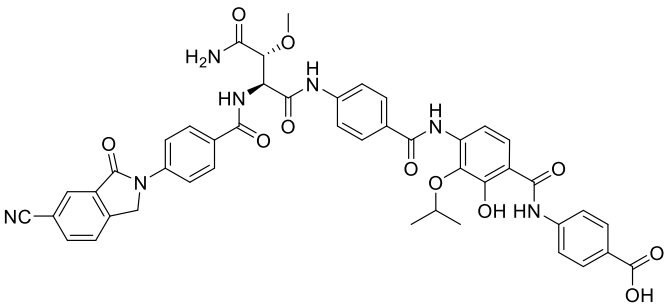


Allyl ether **164** (12.6 mg, 0.01 mmol) was dissolved in THF (1.0 mL). Aniline (4 µL, 0.04 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (1.5 mg, 1 µmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 2 h. The mixture was concentrated under reduced pressure. The crude product was washed with Et_2O. The precipitate was filtered off to furnish product **174** (9.2 mg, 0.01 mmol, 76%) as brown amorphous solid, which was used in the next step without further purification.

The measurement of optical rotation was not possible due to insolubility of compound **174**.

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 12.28 (s, 1H, OH), 10.57 (bs, 2H, NH), 9.38 (s, 1H, NH), 8.54-8.51 (d, *J* = 8.3 Hz, 1H, CHN*H*), 8.29 (s, 1H, H_{Ar}), 8.16-8.14 (dd, *J* = 1.4, 7.9 Hz, 2H, H_{Ar}), 8.07-8.04 (d, *J* = 9.0 Hz, 2H, H_{Ar}), 7.98-7.90 (m, 9H, H_{Ar}), 7.86-7.84 (m, 4H, H_{Ar}), 7.54-7.48 (d, *J* = 22.0 Hz, 2H, NH_2), 7.42-7.40 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 5.21 (s, 2H, NCH_2), 4.95-4.91 (t, *J* = 8.1 Hz, 1H, C*H*NH), 4.57 (bs, 1H, C*H*$(CH_3)_2$), 4.11-4.09 (d, *J* = 8.1 Hz, 1H, C*H*OCH_3), 3.32 (s, 3H, OCH_3), 1.55 (s, 9H, C$(CH_3)_3$), 1.27-1.25 (d, *J* = 6.1 Hz, 6H, CH(CH_3)$_2$) ppm.

4-(4-(4-((2*S*,3*R*)-4-Amino-2-(4-(6-cyano-1-oxoisoindolin-2-yl)benzamido)-3-methoxy-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSC81**



tert-Butyl ester **174** (7.5 mg, 0.01 mmol) was dissolved in precooled TFA (1 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSC81** (5.3 mg, 0.01 mmol, 75%) as colorless amorphous solid.

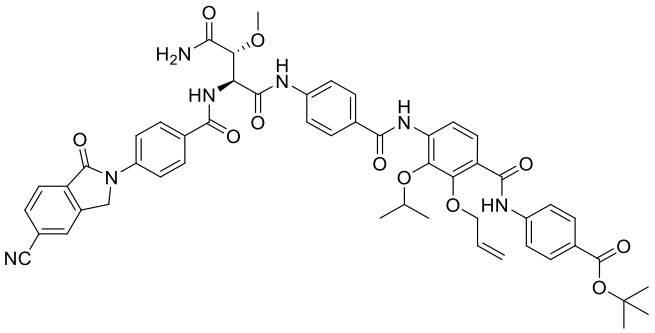
The measurement of optical rotation was not possible due to insolubility of compound **TSC81**.

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 12.82 (s, 1H, CO_2H), 12.29 (s, 1H, OH), 10.60 (s, 1H, NH), 10.59 (s, 1H, NH), 9.40 (s, 1H, NH), 8.53-8.52 (d, *J* = 8.2 Hz, 1H, CHN*H*), 8.29 (s, 1H, H_{Ar}), 8.16-8.14 (dd, *J* = 1.5, 7.9 Hz, 2H, H_{Ar}), 8.06-8.05 (d, *J* = 8.9 Hz 2H, H_{Ar}), 7.98-7.95 (m, 4H, H_{Ar}), 7.92-7.91 (d, *J* = 7.9 Hz, 2H, H_{Ar}), 7.86-7.84 (m, 4H, H_{Ar}), 7.72-7.70 (d, *J* = 8.8 Hz, 1H, H_{Ar}), 7.53-7.48 (d, *J* = 26.3 Hz, 2H, NH_2), 5.21 (s, 2H, NCH_2), 4.94-4.92 (t, *J* = 8.1 Hz, 1H, C*H*NH), 4.57-4.52 (p, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.11-4.09 (d, *J* = 8.1 Hz, 1H, C*H*OCH_3), 3.32 (s, 3H, OCH_3), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, CH(CH_3)$_2$) ppm;

^{13}C-NMR (500 MHz, DMSO-d_6) = δ 170.9 (CO), 168.7 (CO), 168.5 (CO), 166.9 (CO), 165.3 (CO), 165.3 (CO), 164.6 (CO), 154.1 (C_{Ar}), 145.8 (C_{Ar}), 142.3 (C_{Ar}), 142.0 (C_{Ar}), 141.8 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 136.0 (C_{Ar}), 133.2 (C_{Ar}), 130.2 (C_{Ar}), 129.1 (C_{Ar}), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 127.6 (C_{Ar}), 126.3 (C_{Ar}), 126.3 (C_{Ar}), 124.9 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.0 (C_{Ar}),

118.5 (C_{Ar}), 118.3 (CN), 112.4 (C_{Ar}), 112.2 (C_{Ar}), 111.4 (C_{Ar}), 80.0 (*C*HOCH$_3$), 74.9 (*C*H(CH$_3$)$_2$), 57.8 (CHNH), 55.8 (NCH$_2$), 50.8 (OCH$_3$), 22.3 (CH(*C*H$_3$)$_2$) ppm;
HRMS (ESI) calculated for $C_{45}H_{38}N_7O_{11}$ [M-H]$^-$: 852.2629; found: 852.2612.

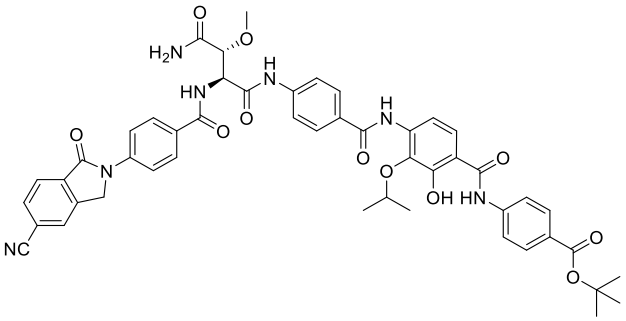
tert-Butyl 4-(2-(allyloxy)-4-(4-((2*S*,3*R*)-4-amino-2-(4-(5-cyano-1-oxoisoindolin-2-yl) benzamido)-3-methoxy-4-oxobutanamido)benzamido)-3-isopropoxybenzamido)benzoate (**163**)



Amine **158** (116 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (1.7 mL) and NMM (37 µL, 0.34 mmol, 2.00 equiv.) was added. Chloride **278** (50.0 mg, 0.17 mmol, 1.00 equiv.) was added at 0 °C and the suspension was stirred for 16 h while warming to rt. The mixture was concentrated and the residue was washed with MeOH. The precipitate was filtered off to furnish product **163** (74.4 mg, 0.08 mmol, 46%) as beige amorphous solid.
The measurement of optical rotation was not possible due to insolubility of compound **163**.
^{1}H-NMR (500 MHz, DMSO-d$_6$) = δ 10.58 (s, 1H, NH), 10.53 (s, 1H, NH), 9.52 (s, 1H, NH), 8.56-8.53 (d, *J* = 8.2 Hz, 1H, CHN*H*), 8.23 (s, 1H, H_{Ar}), 8.08-8.06 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 8.04-7.97 (m, 6H, H_{Ar}), 7.90-7.88 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.85-7.81 (m, 5H, H_{Ar}), 7.54-7.48 (d, *J* = 36.0 Hz, 2H, NH$_2$), 7.42-7.40 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.05-5.99 (m, 1H, C*H*CH$_2$), 5.40-5.35 (dq, *J* = 1.7, 17.2 Hz, 1H, CHC*H*$_2$), 5.21-5.19 (dq, *J* = 1.7, 10.5 Hz, 1H, CHC*H*$_2$), 5.16-5.15 (m, 2H, NCH$_2$), 4.95-4.92 (t, *J* = 8.2 Hz, 1H, C*H*NH), 4.61-5.60 (d, *J* = 5.4 Hz, 2H, OCH$_2$), 4.52-4.47 (sept, *J* = 6.1 Hz, 1H, C*H*(CH$_3$)$_2$), 4.11-4.09 (d, *J* = 8.1 Hz, 1H, C*H*OCH$_3$), 3.31 (s, 3H, OCH$_3$), 1.54 (s, 9H, C(CH$_3$)$_3$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3$)$_2$) ppm;
^{13}C-NMR (126 MHz, DMSO-d$_6$) = δ 170.9 (CO), 168.7 (CO), 165.5 (CO), 165.3 (CO), 164.6 (CO), 164.5 (CO), 164.3 (CO), 149.5 (C_{Ar}), 145.8 (C_{Ar}), 143.0 (C_{Ar}), 142.5 (C_{Ar}), 142.2 (C_{Ar}), 141.8 (C_{Ar}), 141.7 (C_{Ar}), 136.1 (C_{Ar}), 135.6 (C_{Ar}), 133.6 (*C*HCH$_2$), 132.4 (C_{Ar}), 130.5 (C_{Ar}), 130.1 (C_{Ar}), 129.2 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 127.7 (C_{Ar}), 127.1 (C_{Ar}), 126.0 (C_{Ar}), 124.4 (C_{Ar}), 123.6 (C_{Ar}), 118.9 (C_{Ar}), 118.9 (C_{Ar}), 118.8 (C_{Ar}), 118.5 (C_{Ar}), 118.4 (CH*C*H$_2$), 117.8 (CN), 114.5 (C_{Ar}), 80.3 (*C*(CH$_3$)$_3$), 80.0 (*C*HOCH$_3$), 76.3 (*C*H(CH$_3$)$_2$), 74.3 (OCH$_2$), 57.8 (CHNH), 55.8 (NCH$_2$), 50.4 (OCH$_3$), 27.9 (C(*C*H$_3$)$_3$), 22.3 (CH(*C*H$_3$)$_2$) ppm;

HRMS (ESI) calculated for $C_{52}H_{51}N_7O_{11}Na$ $[M+Na]^+$: 972.3544; found: 972.3550.

tert-Butyl 4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(5-cyano-1-oxoisoindolin-2-yl)benzamido)-3-methoxy-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**173**)



Allyl ether **163** (64.8 mg, 0.07 mmol) was dissolved in THF (3.0 mL). Aniline (21 µL, 0.23 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (7.8 mg, 6 µmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 2 h. The mixture was concentrated under reduced pressure. The crude product was washed with Et_2O. The precipitate was filtered off and purified by column chromatography (dry load, 5% MeOH in CH_2Cl_2) to furnish product **173** (45.3 mg, 0.05 mmol, 73%) as brown amorphous solid.

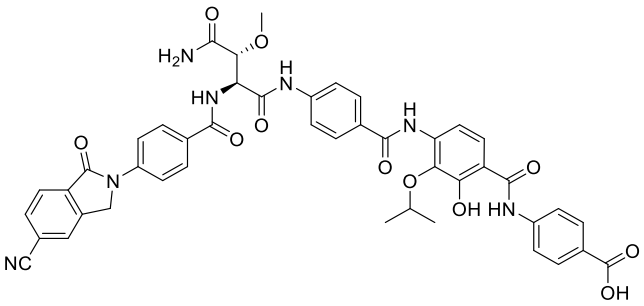
The measurement of optical rotation was not possible due to insolubility of compound **173**.

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 12.29 (s, 1H, OH), 10.59 (bs, 2H, NH), 9.40 (s, 1H, NH), 8.54-8.52 (d, *J* = 8.2 Hz, 1H, CHN*H*), 8.24 (s, 1H, H_{Ar}), 8.07-8.06 (d, *J* = 9.0 Hz, 2H, H_{Ar}), 8.03-8.02 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.99-7.92 (m, 7H, H_{Ar}), 7.86-7.84 (m, 5H, H_{Ar}), 7.70-7.69 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 7.54-7.48 (d, *J* = 26.0 Hz, 2H, NH_2), 5.17 (s, 2H, NCH_2), 4.95-4.92 (t, *J* = 8.2 Hz, 1H, C*H*NH), 4.57-4.52 (p, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.11-4.09 (d, *J* = 8.2 Hz, 1H, C*H*OCH_3), 3.31 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.27-1.26 (d, *J* = 6.2 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 170.9 (CO), 168.7 (CO), 168.5 (CO), 165.5 (CO), 165.3 (CO), 164.5 (CO), 164.2 (CO), 142.3 (C_{Ar}), 141.8 (C_{Ar}), 141.7 (C_{Ar}), 136.3 (C_{Ar}), 136.1 (C_{Ar}), 132.4 (C_{Ar}), 132.0 (C_{Ar}), 132.0 (C_{Ar}), 131.5 (C_{Ar}), 131.4 (C_{Ar}), 129.9 (C_{Ar}), 129.2 (C_{Ar}), 128.8 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 127.7 (C_{Ar}), 126.8 (C_{Ar}), 124.4 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.0 (C_{Ar}), 118.5 (C_{Ar}), 118.4 (CN), 114.5 (C_{Ar}), 80.5 (*C*$(CH_3)_3$), 80.0 (*C*HOCH_3), 74.8 (*C*H$(CH_3)_2$). 57.8 (CHNH), 55.8 (NCH_2), 50.4 (OCH_3), 27.8 (C(*C*$H_3)_3$), 22.3 (CH(*C*$H_3)_2$) ppm;

HRMS (ESI) calculated for $C_{49}H_{47}N_7O_{11}Na$ $[M+Na]^+$: 932.3231; found: 932.3213.

4-(4-(4-((2*S*,3*R*)-4-Amino-2-(4-(5-cyano-1-oxoisoindolin-2-yl)benzamido)-3-methoxy-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSC82**



tert-Butyl ester **173** (41.0 mg, 0.05 mmol) was dissolved in precooled TFA (2.5 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish product **TSC82** (30.5 mg, 0.04 mmol, 79%) as colorless amorphous solid.

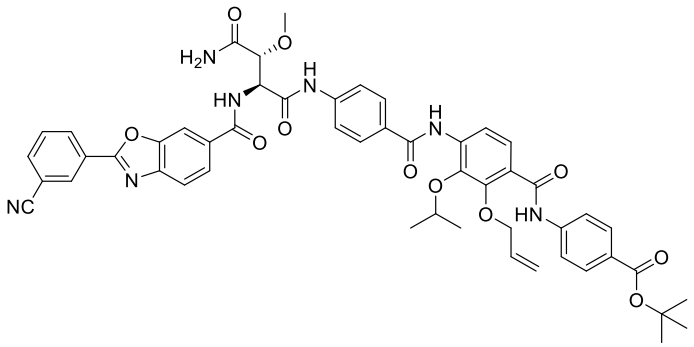
The measurement of optical rotation was not possible due to insolubility of compound **TSC82**.

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 12.82 (s, 1H, CO_2H), 12.29 (s, 1H, OH), 10.60 (s, 1H, NH), 10.59 (s, 1H, NH), 9.40 (s, 1H, NH), 8.54-8.52 (d, *J* = 8.1 Hz, 1H, CHN*H*), 8.24 (s, 1H, H_{Ar}), 8.07-8.06 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 8.06-8.05 (d, *J* = 7.8 Hz 2H, H_{Ar}), 8.03-8.02 (d, *J* = 8.9 Hz 2H, H_{Ar}), 7.99-7.95 (m, 7H, H_{Ar}), 7.86-7.84 (m, 5H, H_{Ar}), 7.72-7.70 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 7.54-7.48 (d, *J* = 32.4 Hz, 2H, NH_2), 5.17 (s, 2H, NCH_2), 4.94-4.92 (t, *J* = 8.2 Hz, 1H, C*H*NH), 4.56-4.52 (p, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.11-4.09 (d, *J* = 8.2 Hz, 1H, C*H*OCH_3), 3.31 (s, 3H, OCH_3), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 170.9 (CO), 168.7 (CO), 168.5 (CO), 166.9 (CO), 165.5 (CO), 165.3 (CO), 164.2 (CO), 154.1 (C_{Ar}), 142.2 (C_{Ar}), 141.9 (C_{Ar}), 141.8 (C_{Ar}), 141.7 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 136.1 (C_{Ar}), 132.4 (C_{Ar}), 130.2 (C_{Ar}), 129.2 (C_{Ar}), 128.5 (C_{Ar}), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 127.7 (C_{Ar}), 126.3 (C_{Ar}), 124.4 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.0 (C_{Ar}), 118.5 (C_{Ar}), 118.4 (CN), 114.5 (C_{Ar}), 112.2 (C_{Ar}), 112.2 (C_{Ar}), 80.0 (*C*HOCH_3), 74.9 (*C*H$(CH_3)_2$), 57.8 (CHNH), 55.8 (NCH_2), 50.4 (OCH_3), 22.3 (CH(*C*H$_3)_2$) ppm;

HRMS (ESI) calculated for $C_{45}H_{38}N_7O_{11}$ $[M-H]^-$: 852.2629; found: 852.2645.

tert-Butyl 4-(2-(allyloxy)-4-(4-((2*S*,3*R*)-4-amino-2-(4-(5-cyano-1-oxoisoindolin-2-yl) benzamido)-3-methoxy-4-oxobutanamido)benzamido)-3-isopropoxybenzamido)benzoate (**165**)



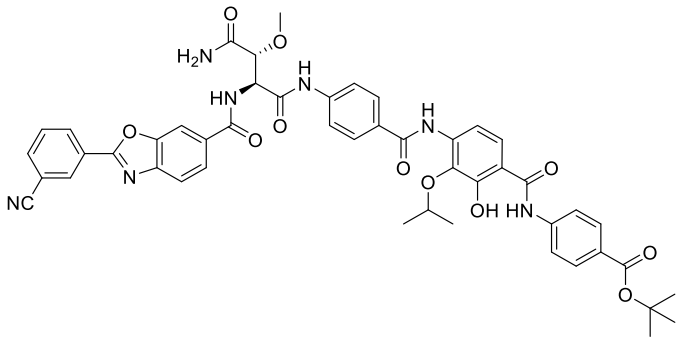
Amine **158** (97.6 mg, 0.14 mmol) was dissolved in CH_2Cl_2 (1.4 mL) and NMM (31 µL, 0.28 mmol, 2.00 equiv.) was added. Chloride **280** (40.0 mg, 0.14 mmol, 1.00 equiv.) was added at 0 °C and the suspension was stirred for 16 h while warming to rt. The mixture was concentrated and the residue was washed with MeOH. The precipitate was filtered off to furnish compound **165** (58.0 mg, 0.06 mmol, 44%) as beige amorphous solid. A small amount of a diastereomer is visible in the ^{1}H-NMR spectrum. The product was used in the next step without further purification.

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 10.60 (s, 1H, NH), 10.53 (s, 1H, NH), 9.52 (s, 1H, NH), 8.77-8.75 (d, *J* = 8.3 Hz, 1H, CHN*H*), 8.63 (dt, *J* = 0.5, 1.7 Hz, 1H, H_{Ar}), 8.56-8.54 (m, 1H, H_{Ar}), 8.31 (m, 1H, H_{Ar}), 8.16-8.14 (dt, *J* = 1.2, 7.8 Hz, 1H, H_{Ar}), 8.00-7.96 (m, 4H, H_{Ar}), 7.90-7.81 (m, 8H, H_{Ar}), 7.56-7.51 (d, *J* = 24.5 Hz, 2H, NH_2), 7.42-7.40 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.06-5.98 (m, 1H, C*H*CH_2), 5.39-5.35 (dq, *J* = 1.7, 17.2 Hz, 1H, CHC*H*$_2$), 5.22-5.19 (dq, *J* = 1.7, 10.5 Hz, 1H, CHC*H*$_2$), 4.98-4.95 (t, *J* = 8.2 Hz, 1H, C*H*NH), 4.61-5.60 (d, *J* = 5.5 Hz, 2H, OCH_2), 4.52-4.47 (p, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.13-4.12 (d, *J* = 8.2 Hz, 1H, C*H*OCH_3), 3.33 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 170.9 (CO), 168.5 (CO), 165.3 (CO), 164.6 (CO), 164.5 (CO), 164.3 (CO), 162.6 (CO), 150.1 (C_{Ar}), 149.5 (C_{Ar}), 143.9 (C_{Ar}), 143.0 (C_{Ar}), 142.5 (C_{Ar}), 142.1 (C_{Ar}), 135.7 (C_{Ar}), 135.6 (C_{Ar}), 133.6 (*C*HCH_2), 132.0 (C_{Ar}), 131.5 (C_{Ar}), 131.0 (C_{Ar}), 130.8 (C_{Ar}), 130.1 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 127.3 (C_{Ar}), 127.1 (C_{Ar}), 126.0 (C_{Ar}), 124.9 (C_{Ar}), 123.6 (C_{Ar}), 119.9 (C_{Ar}), 118.9 (C_{Ar}), 118.8 (C_{Ar}), 118.3 (CH*C*H_2), 117.8 (C_{Ar}), 112.7 (C_{Ar}), 110.5 (C_{Ar}), 80.3 (*C*$(CH_3)_3$), 80.0 (*C*HOCH_3), 76.3 (*C*H$(CH_3)_2$), 74.3 (OCH_2), 57.8 (CHNH), 56.0 (OCH_3), 27.8 (C(*C*$H_3)_3$), 22.3 (CH(*C*$H_3)_2$) ppm;

HRMS (ESI) calculated for $C_{51}H_{49}N_7O_{11}Na$ $[M+Na]^+$: 958.3388; found: 958.3367.

tert-Butyl 4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(5-cyano-1-oxoisoindolin-2-yl)benzamido)-3-methoxy-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**175**)



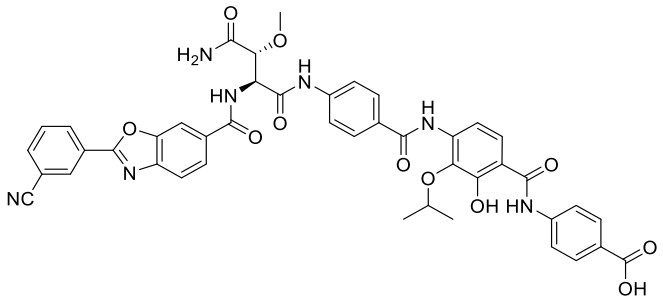
Allyl ether **165** (55.0 mg, 0.06 mmol) was dissolved in THF (2.6 mL). Aniline (18 µL, 0.19 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (6.8 mg, 6 µmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 2 h. The mixture was concentrated under reduced pressure. The crude product was washed with Et_2O. The precipitate was filtered off and purified by column chromatography (dry load, 5% MeOH in CH_2Cl_2) to furnish product **175** (40.6 mg, 0.05 mmol, 77%) as colorless amorphous solid. A small amount of a diastereomer is visible in the ^{1}H-NMR spectrum. The product was used in the next step without further purification.

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 12.28 (s, 1H, OH), 10.61 (bs, 2H, NH), 9.40 (s, 1H, NH), 8.77-8.75 (d, *J* = 8.2 Hz, 1H, CHN*H*), 8.63 (t, *J* = 1.8 Hz, 1H, H_{Ar}), 8.56-8.54 (dt, *J* = 1.1, 8.2 Hz, 1H, H_{Ar}), 8.31 (m, 1H, H_{Ar}), 8.16-8.14 (dt, *J* = 1.2, 7.8 Hz, 1H, H_{Ar}), 7.98-7.92 (m, 6H, H_{Ar}), 7.88-7.83 (m, 6H, H_{Ar}), 7.71-7.69 (d, *J* = 8.9 Hz, 1H, H_{Ar}) 7.55-7.51 (d, *J* = 22.1 Hz, 2H, NH_2), 4.98-4.95 (t, *J* = 8.2 Hz, 1H, C*H*NH), 4.56-4.52 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.13-4.11 (d, *J* = 8.2 Hz, 1H, C*H*OCH_3), 3.32 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 170.9 (CO), 168.6 (CO), 168.5 (CO), 165.3 (CO), 164.5 (CO), 164.2 (CO), 162.6 (CO), 150.1 (C_{Ar}), 143.9 (C_{Ar}), 142.2 (C_{Ar}), 142.0 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 135.7 (C_{Ar}), 132.0 (C_{Ar}), 131.6 (C_{Ar}), 131.5 (C_{Ar}), 131.0 (C_{Ar}), 130.8 (C_{Ar}), 129.9 (C_{Ar}), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 127.4 (C_{Ar}), 126.8 (C_{Ar}), 124.9 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.9 (C_{Ar}), 119.0 (C_{Ar}), 117.9 (C_{Ar}), 112.7 (C_{Ar}), 112.4 (C_{Ar}), 110.5 (C_{Ar}), 80.5 (*C*$(CH_3)_3$), 80.0 (*C*HOCH_3), 74.9 (*C*H$(CH_3)_2$), 57.8 (CHNH), 55.9 (OCH_3), 27.8 ($C(CH_3)_3$), 22.3 ($CH(CH_3)_2$) ppm;

HRMS (ESI) calculated for $C_{48}H_{45}N_7O_{11}Na$ $[M+Na]^+$: 918.3075; found: 918.3058.

4-(4-(4-((2*S*,3*R*)-4-Amino-2-(2-(3-cyanophenyl)benzo[d]oxazole-6-carboxamido)-3-methoxy-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSC83**



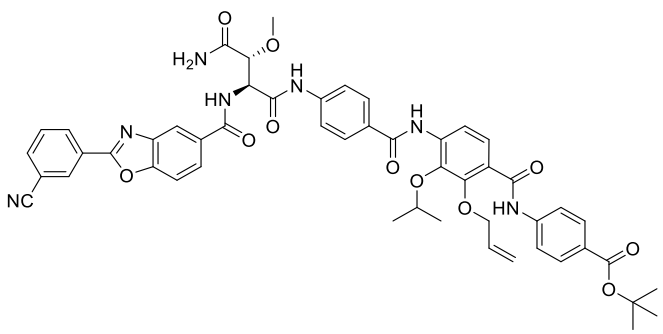
tert-Butyl ester **175** (38.0 mg, 0.04 mmol) was dissolved in precooled TFA (2.3 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish product **TSC83** (26.7 mg, 0.03 mmol, 70%, d.r. 24:1) as colorless amorphous solid.

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 12.83 (bs, 1H, CO_2H), 12.29 (s, 1H, OH), 10.61 (s, 1H, NH), 10.60 (s, 1H, NH), 9.40 (s, 1H, NH), 8.77-8.75 (d, *J* = 8.3 Hz, 1H, CHN*H*), 8.63 (t, *J* = 1.6 Hz, 1H, H_{Ar}), 8.56-8.54 (dt, *J* = 1.4, 8.0 Hz, 1H, H_{Ar}), 8.31 (m, 1H, H_{Ar}), 8.16-8.14 (dt, *J* = 1.5, 7.8 Hz, 1H, H_{Ar}), 7.98-7.95 (m, 6H, H_{Ar}), 7.88-7.83 (m, 6H, H_{Ar}), 7.72-7.70 (d, *J* = 8.9 Hz, 1H, H_{Ar}) 7.55-7.51 (d, *J* = 26.7 Hz, 2H, NH_2), 4.98-4.95 (t, *J* = 8.2 Hz, 1H, C*H*NH), 4.56-4.52 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.13-4.11 (d, *J* = 8.2 Hz, 1H, C*H*OCH_3), 3.33 (s, 3H, OCH_3), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 170.9 (CO), 168.6 (CO), 168.5 (CO), 166.9 (CO), 165.3 (CO), 164.2 (CO), 162.6 (CO), 154.1 (C_{Ar}), 150.1 (C_{Ar}), 143.9 (C_{Ar}), 142.2 (C_{Ar}), 142.0 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 135.7 (C_{Ar}), 132.0 (C_{Ar}), 131.6 (C_{Ar}), 131.0 (C_{Ar}), 130.8 (C_{Ar}), 130.2 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 127.4 (C_{Ar}), 126.3 (C_{Ar}), 124.9 (C_{Ar}), 120.7 (C_{Ar}), 119.9 (C_{Ar}), 119.0 (C_{Ar}), 117.9 (C_{Ar}), 112.7 (C_{Ar}), 112.4 (C_{Ar}), 112.2 (C_{Ar}), 110.5 (C_{Ar}), 80.0 (*C*$HOCH_3$), 74.9 (*C*H$(CH_3)_2$), 57.8 (CHNH), 56.0 (OCH_3), 22.3 (CH(*C*$H_3)_2$) ppm;

HRMS (ESI) calculated for $C_{44}H_{36}N_7O_{11}$ $[M-H]^-$: 838.2473; found: 838.2478.

tert-Butyl 4-(2-(allyloxy)-4-(4-((2*S*,3*R*)-4-amino-2-(2-(3-cyanophenyl)benzo[d]oxazole-5-carboxamido)-3-methoxy-4-oxobutanamido)benzamido)-3-isopropoxybenzamido)benzoate (**166**)



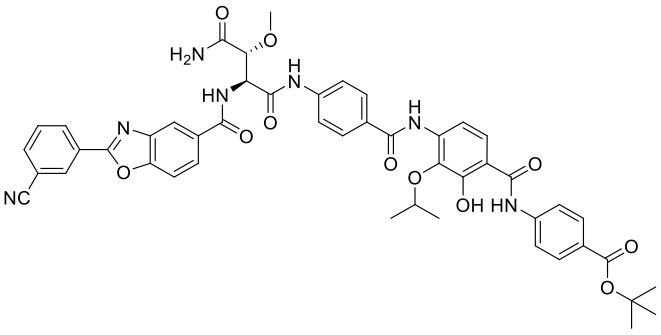
Amine **158** (89.6 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (1.3 mL) and NMM (29 µL, 0.26 mmol, 2.00 equiv.) was added. Chloride **281** (36.7 mg, 0.13 mmol, 1.00 equiv.) was added at 0 °C and the suspension was stirred for 14 h while warming to rt. The mixture was concentrated and the residue was washed with MeOH. The precipitate was filtered off and washed with Et_2O to furnish product **166** (59.4 mg, 0.06 mmol, 49%) as beige amorphous solid. The measurement of optical rotation was not possible due to insolubility of compound **166**.

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 10.58 (s, 1H, NH), 10.53 (s, 1H, NH), 9.52 (s, 1H, NH), 8.74-8.72 (d, *J* = 8.2 Hz, 1H, CHN*H*), 8.62-8.62 (dt, *J* = 0.7, 1.5 Hz, 1H, H_{Ar}), 8.55-8.53 (dt, *J* = 1.1, 8.0 Hz, 1H, H_{Ar}), 8.37 (d, *J* = 1.1 Hz, 1H, H_{Ar}), 8.16-8.13 (dt, *J* = 1.6, 7.9 Hz, 1H, H_{Ar}), 8.00-7.95 (m, 4H, H_{Ar}), 7.90-7.88 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.86-7.81 (m, 6H, H_{Ar}), 7.56-7.52 (d, *J* = 20.7 Hz, 2H, NH_2), 7.42-7.40 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.06-5.98 (m, 1H, C*H*CH_2), 5.39-5.35 (dq, *J* = 1.7, 17.2 Hz, 1H, CHC*H*$_2$), 5.22-5.19 (dq, *J* = 1.7, 10.5 Hz, 1H, CHC*H*$_2$), 4.97-4.94 (t, *J* = 8.2 Hz, 1H, C*H*NH), 4.61-4.60 (d, *J* = 5.5 Hz, 2H, OCH_2), 4.53-4.46 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.13-4.11 (d, *J* = 8.2 Hz, 1H, C*H*OCH_3), 3.33 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 170.9 (CO), 168.6 (CO), 165.5 (CO), 164.6 (CO), 164.5 (CO), 164.3 (CO), 161.8 (CO), 152.3 (C_{Ar}), 149.5 (C_{Ar}), 143.0 (C_{Ar}), 142.5 (C_{Ar}), 142.1 (C_{Ar}), 141.2 (C_{Ar}), 135.6 (C_{Ar}), 135.6 (C_{Ar}), 133.7 (*C*HCH_2), 131.9 (C_{Ar}), 131.1 (C_{Ar}), 130.9 (C_{Ar}), 130.8 (C_{Ar}), 130.1 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 127.4 (C_{Ar}), 127.1 (C_{Ar}), 126.0 (C_{Ar}), 123.6 (C_{Ar}), 119.5 (C_{Ar}), 119.0 (C_{Ar}), 118.9 (C_{Ar}), 118.8 (CH*C*H_2), 117.9 (C_{Ar}), 117.8 (C_{Ar}), 112.7 (C_{Ar}), 111.1 (C_{Ar}), 80.3 (*C*$(CH_3)_3$), 80.0 (*C*HOCH_3), 76.3 (*C*H$(CH_3)_2$), 74.3 (OCH_2), 57.8 (CHNH), 56.0 (OCH_3), 27.9 ($C(CH_3)_3$), 22.3 ($CH(CH_3)_2$) ppm;

HRMS (ESI) calculated for $C_{51}H_{49}N_7O_{11}Na$ $[M+Na]^+$: 958.3388; found: 958.3376.

tert-Butyl 4-(4-(4-((2*S*,3*R*)-4-amino-2-(2-(3-cyanophenyl)benzo[d]oxazole-5-carboxamido)-3-methoxy-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**176**)



Allyl ether **166** (56.1 mg, 0.06 mmol) was dissolved in THF (2.6 mL). Aniline (18 µL, 0.19 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (6.9 mg, 6 µmol, 0.10 equiv.) were added subsequently

and the resulting mixture was stirred at rt for 3 h. The mixture was concentrated onto silica under reduced pressure. The crude product was purified by column chromatography (dry load, 5% MeOH in CH_2Cl_2) to furnish product **176** (39.7 mg, 0.04 mmol, 74%) as yellow amorphous solid.

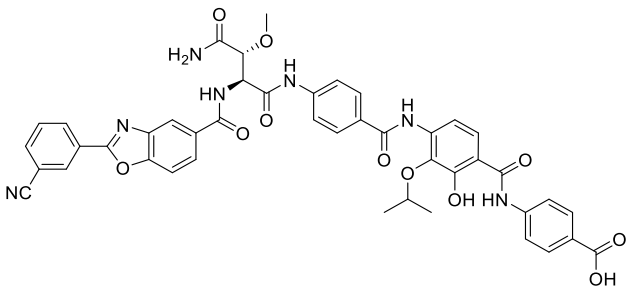
The measurement of optical rotation was not possible due to insolubility of compound **176**.

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 12.28 (s, 1H, OH), 10.61 (bs, 2H, NH), 9.40 (s, 1H, NH), 8.74-8.72 (d, *J* = 8.2 Hz, 1H, CHN*H*), 8.62 (t, *J* = 1.6 Hz, 1H, H_{Ar}), 8.55-8.53 (dt, *J* = 1.2, 8.4 Hz, 1H, H_{Ar}), 8.37 (d, *J* = 1.2 Hz, H_{Ar}), 8.15-8.14 (dt, *J* = 1.4, 7.8 Hz, 1H, H_{Ar}), 8.01-7.92 (m, 6H, H_{Ar}), 7.88-7.85 (m, 6H, H_{Ar}), 7.71-7.69 (d, *J* = 8.5 Hz, 1H, H_{Ar}) 7.56-7.52 (d, *J* = 24.0 Hz, 2H, NH_2), 4.97-4.94 (t, *J* = 8.2 Hz, 1H, C*H*NH), 4.58-4.52 (sept, *J* = 5.9 Hz, 1H, C*H*$(CH_3)_2$), 4.13-4.11 (d, *J* = 8.3 Hz, 1H, C*H*OCH_3), 3.33 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 170.9 (CO), 168.6 (CO), 168.4 (CO), 165.5 (CO), 164.5 (CO), 164.2 (CO), 161.8 (CO), 152.3 (C_{Ar}), 142.2 (C_{Ar}), 142.0 (C_{Ar}), 141.2 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 135.6 (C_{Ar}), 131.9 (C_{Ar}), 131.1 (C_{Ar}), 130.9 (C_{Ar}), 130.8 (C_{Ar}), 129.9 (C_{Ar}), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 127.4 (C_{Ar}), 126.0 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.5 (C_{Ar}), 119.0 (C_{Ar}), 117.9 (C_{Ar}), 112.7 (C_{Ar}), 112.4 (C_{Ar}), 111.1 (C_{Ar}), 80.5 (*C*$(CH_3)_3$), 80.0 (*C*HOCH_3), 74.8 (*C*H$(CH_3)_2$), 57.8 (CHNH), 56.0 (OCH_3), 27.8 ($C(CH_3)_3$), 22.3 ($CH(CH_3)_2$) ppm;

HRMS (ESI) calculated for $C_{48}H_{45}N_7O_{11}Na$ $[M+Na]^+$: 918.3075; found: 918.3070.

4-(4-(4-((2*S*,3*R*)-4-Amino-2-(2-(3-cyanophenyl)benzo[d]oxazole-5-carboxamido)-3-methoxy-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSC98**



tert-Butyl ester **176** (38.7 mg, 0.04 mmol) was dissolved in precooled TFA (2.3 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The

precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish product **TSC98** (31.0 mg, 0.04 mmol, 80%) as yellow amorphous solid.

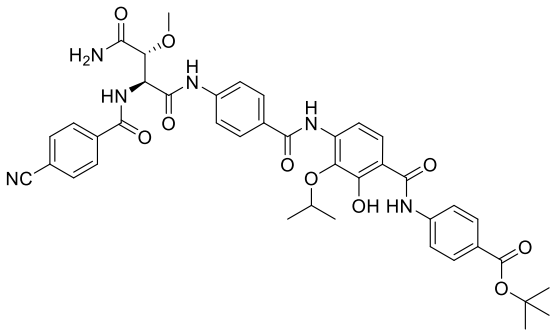
The measurement of optical rotation was not possible due to insolubility of compound **TSC98**.

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 12.82 (bs, 1H, CO_2H), 12.29 (s, 1H, OH), 10.61 (s, 1H, NH), 10.60 (s, 1H, NH), 9.41 (s, 1H, NH), 8.74-8.72 (d, *J* = 8.2 Hz, 1H, CHN*H*), 8.62 (s, 1H, H_{Ar}), 8.55-8.53 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 8.37 (d, *J* = 1.2 Hz, 1H, H_{Ar}), 8.15-8.14 (d, *J* = 7.7 Hz, 1H, H_{Ar}), 8.01-7.95 (m, 6H, H_{Ar}), 7.88-7.82 (m, 6H, H_{Ar}), 7.72-7.70 (d, *J* = 8.9 Hz, 1H, H_{Ar}) 7.56-7.52 (d, *J* = 24.5 Hz, 2H, NH_2), 4.97-4.94 (t, *J* = 8.2 Hz, 1H, C*H*NH), 4.57-4.51 (sept, *J* = 6.3 Hz, 1H, C*H*(CH_3)$_2$), 4.13-4.12 (d, *J* = 8.3 Hz, 1H, C*H*OCH_3), 3.33 (s, 3H, OCH_3), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3$)$_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 170.9 (CO), 168.6 (CO), 168.5 (CO), 166.9 (CO), 165.5 (CO), 164.2 (CO), 161.8 (CO), 154.1 (C_{Ar}), 152.3 (C_{Ar}), 142.3 (C_{Ar}), 142.0 (C_{Ar}), 141.2 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 135.6 (C_{Ar}), 131.9 (C_{Ar}), 131.1 (C_{Ar}), 130.9 (C_{Ar}), 130.8 (C_{Ar}), 130.2 (C_{Ar}), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 127.4 (C_{Ar}), 126.3 (C_{Ar}), 126.0 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.5 (C_{Ar}), 119.0 (C_{Ar}), 117.9 (C_{Ar}), 112.7 (C_{Ar}), 112.4 (C_{Ar}), 112.2 (C_{Ar}), 111.1 (C_{Ar}), 80.0 (*C*HOCH_3), 74.9 (*C*H(CH_3)$_2$), 57.8 (CHNH), 56.0 (OCH_3), 22.3 (CH(*C*H_3)$_2$) ppm;

HRMS (ESI) calculated for $C_{44}H_{36}N_7O_{11}$ $[M-H]^-$: 838.2473; found: 838.2484.

tert-Butyl 4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-cyanobenzamido)-3-methoxy-4-oxobutan amido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**171**)



Allyl ether **161** (15.7 mg, 0.02 mmol) was dissolved in THF (1 mL). Aniline (6 µL, 0.06 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (2.2 mg, 2 µmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 3 h. The mixture was concentrated onto silica under

reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 2%, 3%) to furnish product **171** (6.2 mg, 0.01 mmol, 42%) as colorless amorphous solid.

The analytical data are consistent with those reported in the literature.[32]

R_f (3% MeOH in CH_2Cl_2) = 0.22;

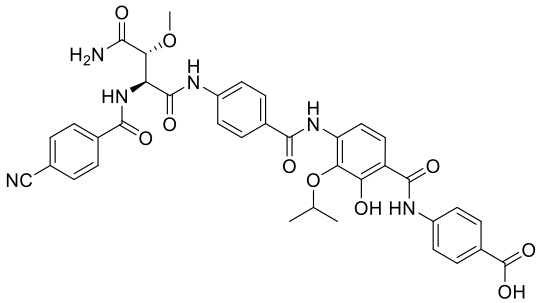
$[\alpha]_D^{23}$ = +1.2 ° (c 0.3, THF/MeOH (1:1))

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 12.29 (s, 1H, OH), 10.65 (bs, 1H, NH), 10.58 (s, 1H, NH), 9.39 (s, 1H, NH), 8.87-8.85 (d, *J* = 8.3 Hz, 1H, CHN*H*), 8.00 (s, 4H, H_{Ar}), 7.97-7.94 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.94-7.92 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.86-7.82 (m, 5H, H_{Ar}), 7.70-7.68 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 7.50-7.47 (d, *J* = 11.9 Hz, 2H, NH_2), 4.97-4.92 (t, *J* = 8.2 Hz, 1H, C*H*NH), 4.59-4.50 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.08-4.06 (d, *J* = 8.1 Hz, 1H, C*H*OCH_3), 3.31 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.27-1.25 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 170.8 (CO), 168.5 (CO), 168.3 (CO), 164.8 (CO), 164.5 (CO), 164.2 (CO), 147.7 (C_{Ar}), 142.2 (C_{Ar}), 142.0 (C_{Ar}), 137.7 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 132.5 (C_{Ar}), 129.9 (C_{Ar}), 128.6 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 126.8 (C_{Ar}), 122.8 (C_{Ar}), 120.6 (C_{Ar}), 120.2 (C_{Ar}), 119.0 (C_{Ar}), 118.3 (CN), 114.0 (C_{Ar}), 112.5 (C_{Ar}), 80.5 (*C*$(CH_3)_3$), 80.0 (*C*HOCH_3), 74.8 (*C*H$(CH_3)_2$), 57.9 (CHNH), 55.8 (OCH_3), 27.8 ($C(CH_3)_3$), 22.3 ($CH(CH_3)_2$) ppm;

HRMS (ESI) calculated for $C_{41}H_{42}N_6O_{10}Na$ $[M+Na]^+$: 801.2860; found: 801.2861.

4-(4-(4-((2*S*,3*R*)-4-Amino-2-(4-cyanobenzamido)-3-methoxy-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSE83**



Ester **171** (7.7 mg, 9 µmol) was dissolved in precooled TFA at 0 °C and the mixture was stirred for 45 min while warming to rt. Et_2O was added at 0 °C. The precipitate was filtered off and washed with an excess of Et_2O to furnish acid **TSE83** (4.6 mg, 6 µmol, 68%) as beige amorphous solid.

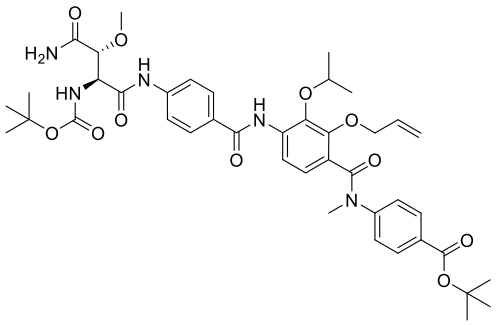
The analytical data are consistent with those reported in the literature.[32]

$[\alpha]_D^{23}$ = +2.2 ° (c 0.1, THF);

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 12.29 (bs, 2H, CO_2H, OH), 10.58 (bs, 2H, NH), 9.37 (s, 1H, NH), 8.87-8.85 (d, *J* = 8.3 Hz, 1H, CHN*H*), 8.02-7.99 (m, 4H, H_{Ar}), 7.97-7.94 (m, 4H, H_{Ar}), 7.86-7.82 (t, *J* = 8.4 Hz, 5H, H_{Ar}), 7.66 (bs, 1H, H_{Ar}), 7.50-7.47 (d, *J* = 16.3 Hz, 2H, NH_2), 4.96-4.93 (t, *J* = 8.2 Hz, 1H, C*H*NH), 4.58 (bs, 1H, C*H*$(CH_3)_2$), 4.08-4.06 (d, *J* = 8.1 Hz, 1H, C*H*OCH_3), 3.31 (s, 3H, OCH_3), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3)_2$) ppm;

HRMS (ESI) calculated for $C_{37}H_{33}N_6O_{12}$ $[M-H]^-$: 721.2258; found: 721.2258.

tert-Butyl 4-(2-(allyloxy)-4-(4-((2*S*,3*R*)-4-amino-2-((*tert*-butoxycarbonyl)amino)-3-methoxy-4-oxobutanamido)benzamido)-3-isopropoxy-*N*-methylbenzamido)benzoate (**135**)



Amine **95** (100 mg, 0.18 mmol), acid **4** (80.0 mg, 0.30 mmol, 1.70 equiv.) and EEDQ (71.0 mg, 0.29 mmol, 1.60 equiv.) were dissolved in precooled $CHCl_3$ (1 mL). The mixture was stirred for 18 h while warming to rt. The mixture was concentrated and the crude product was purified by column chromatography (dry load, wash with 20% Et_2O in CH_2Cl_2, elution with 3% MeOH in CH_2Cl_2) to furnish product **135** (75.1 mg, 0.09 mmol, 52%) as colorless amorphous solid.

$[\alpha]_D^{23}$ = -0.5 ° (c 0.1, MeOH);

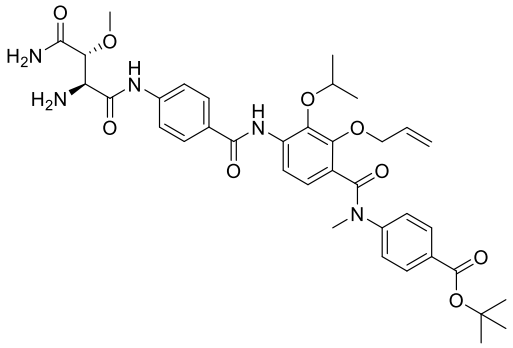
^{1}H-NMR (400 MHz, DMSO-d_6) = δ 10.33 (s, 1H, NH), 9.26 (s, 1H, NH), 7.89-7.87 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.77-7.75 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.71-7.70 (d, *J* = 7.5 Hz, 2H, H_{Ar}), 7.67-7.65 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 7.44-7.40 (d, *J* = 14.4 Hz, 2H, NH_2), 7.23 (bs, 2H, H_{Ar}), 7.04-7.02 (d, *J* = 8.3 Hz, 1H, H_{Ar}), 6.79-6.77 (d, *J* = 8.3 Hz, 1H, CHN*H*), 6.06-5.97 (m, 1H, C*H*CH_2), 5.39-5.33 (dq, *J* = 1.7, 17.2 Hz, 1H, CHC*H*$_2$), 5.26-5.23 (dq, *J* = 1.6, 10.5 Hz, 1H, CHC*H*$_2$), 4.43-4.42 (d, *J* = 4.4 Hz, 2H, OCH_2), 4.40-4.36 (t, *J* = 7.8 Hz, 1H, C*H*NH), 4.03 (bs, 1H, C*H*$(CH_3)_2$), 3.84-3.83 (d, *J* = 7.6 Hz, 1H, C*H*OCH_3), 3.38 (s, 3H, NCH_3), 3.33 (s, 3H, OCH_3), 1.48 (s, 9H, $C(CH_3)_3$), 1.37 (s, 9H, $C(CH_3)_3$), 0.98 (bs, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 170.6 (CO), 168.9 (CO), 167.2 (CO), 164.2 (CO), 164.1 (CO), 154.8 (CO), 147.6 (C_{Ar}), 147.3 (C_{Ar}), 142.1 (C_{Ar}), 141.5 (C_{Ar}), 134.2 (C_{Ar}), 134.0 (*C*HCH_2), 129.1 (C_{Ar}), 128.8 (C_{Ar}), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 126.4 (C_{Ar}), 122.7

(C_{Ar}), 118.8 (C_{Ar}), 118.4 (CH*C*H_2), 117.1 (C_{Ar}), 80.7 (*C*(CH_3)$_3$), 80.1 (*C*HOCH_3), 78.7 (*C*(CH_3)$_3$), 75.2 (*C*H(CH_3)$_2$), 73.9 (OCH_2), 57.6 (CHNH), 56.6 (OCH_3), 36.5 (NCH_3), 28.1 (C(*C*H_3)$_3$), 27.7 (C(*C*H_3)$_3$), 21.8 (CH(*C*H_3)$_2$) ppm;

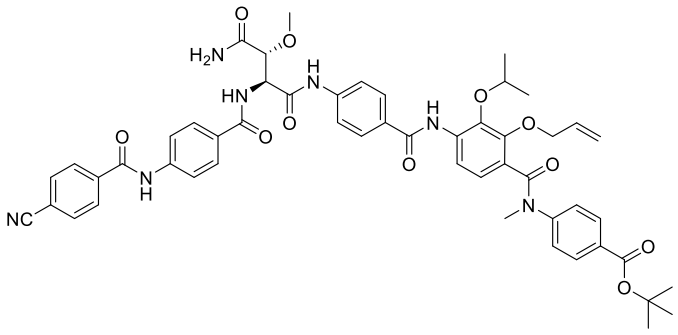
HRMS (ESI) calculated for $C_{42}H_{53}N_5O_{11}Na$ $[M+Na]^+$: 826.3639; found: 826.3648.

tert-Butyl 4-(2-(allyloxy)-4-(4-((2*S*,3*R*)-2,4-diamino-3-methoxy-4-oxobutanamido) benzamido)-3-isopropoxy-*N*-methylbenzamido)benzoate (**179**)



Carbamate **135** (71.3 mg, 0.09 mmol) was dissolved in HCl (4 M in 1,4-dioxane, 2.20 mL, 8.87 mmol, 100.0 equiv.) at 0 °C. The mixture was warmed up to rt and stirred for 15 min. The solution was transferred to a stirred suspension of EtOAc (200 mL) and a sat. $NaHCO_3$ solution (200 mL). The aq. phase was extracted with EtOAc (3x 100 mL) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was used in the next step without further purification.

tert-Butyl 4-(2-(allyloxy)-4-(4-((2*S*,3*R*)-4-amino-2-(4-(4-cyanobenzamido)benzamido)-3-methoxy-4-oxobutanamido)benzamido)-3-isopropoxy-*N*-methylbenzamido)benzoate (**180**)



Amine **179** (62.4 mg, 0.09 mmol) was dissolved in CH_2Cl_2 (1 mL) and NMM (20 µL, 0.18 mmol, 2.00 equiv.) was added. Chloride **277** (25.3 mg, 0.09 mmol, 1.00 equiv.) was added at 0 °C and the suspension was stirred for 18 h while warming to rt. The mixture was concentrated. The crude product was purified by column chromatography (dry load, 5% MeOH

in CH_2Cl_2) to furnish product **180** (39.1 mg, 0.04 mmol, 46%) as beige amorphous solid, which contained minor impurities of a diastereomer.

The *N*-methyl group is not visible in the ^{13}C NMR spectrum and may appear underneath the solvent peak.

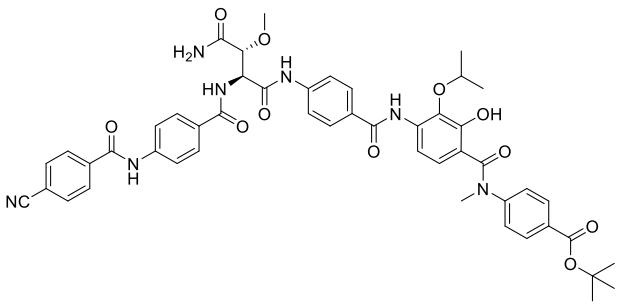
$\mathbf{R_f}$ (5% MeOH in CH_2Cl_2) = 0.54;

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 10.71 (s, 1H, NH), 10.53 (s, 1H, NH), 9.26 (s, 1H, NH), 8.45-8.43 (d, *J* = 8.1 Hz, 1H, CHN*H*), 8.13-8.12 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 8.05-8.04 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.91-7.87 (m, 5H, H_{Ar}), 7.80-7.78 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.71 (bs, 2H, H_{Ar}), 7.66-7.65 (d, *J* = 8.2 Hz, 1H, H_{Ar}), 7.53-7.47 (d, *J* = 37.9 Hz, 2H, NH_2), 7.22 (bs, 2H, H_{Ar}), 7.04-7.02 (d, *J* = 8.2 Hz, 1H, H_{Ar}), 6.05-5.98 (m, 1H, C*H*CH_2), 5.38-5.34 (dq, *J* = 1.7, 17.2 Hz, 1H, CHC*H*$_2$), 5.25-5.23 (dq, *J* = 1.7, 10.5 Hz, 1H, CHC*H*$_2$), 4.91-4.89 (t, *J* = 8.1 Hz, 1H, C*H*NH), 4.42 (bs, 2H, OCH_2), 4.08-4.07 (d, *J* = 8.1 Hz, 1H, C*H*OCH_3), 4.03 (bs, 1H, C*H*$(CH_3)_2$), 3.38 (s, 3H, NCH_3), 3.30 (s, 3H, OCH_3), 1.48 (s, 9H, $C(CH_3)_3$), 0.99 (bs, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 170.9 (CO), 168.7 (CO), 167.2 (CO), 165.4 (CO), 164.5 (CO), 164.2 (CO), 164.1 (CO), 147.6 (C_{Ar}), 147.3 (C_{Ar}), 142.0 (C_{Ar}), 141.8 (C_{Ar}), 141.5 (C_{Ar}), 138.7 (C_{Ar}), 134.2 (C_{Ar}), 134.0 (*C*HCH_2), 132.5 (C_{Ar}), 130.0 (C_{Ar}), 129.1 (C_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 128.6 (C_{Ar}), 128.6 (C_{Ar}), 128.3 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 126.4 (C_{Ar}) 122.7 (C_{Ar}), 119.6 (C_{Ar}), 118.9 (C_{Ar}), 118.3 (CH*C*H_2), 117.1 (CN), 114.0 (C_{Ar}), 80.7 (*C*$(CH_3)_3$), 80.0 (*C*HOCH_3), 75.1 (*C*H$(CH_3)_2$), 73.9 (OCH_2), 57.7 (CHNH), 55.7 (OCH_3), 27.7 ($C(CH_3)_3$), 21.8 ($CH(CH_3)_2$) ppm;

HRMS (ESI) calculated for $C_{52}H_{53}N_7O_{11}Na$ $[M+Na]^+$: 974.3701; found: 974.3693.

tert-Butyl 4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(4-cyanobenzamido)benzamido)-3-methoxy-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**181**)



Allyl ether **180** (35.9 mg, 0.04 mmol) was dissolved in THF (1.7 mL). Aniline (11 µL, 0.12 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (4.4 mg, 4 µmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 2 h. The mixture was concentrated onto silica. The

crude product was purified by column chromatography (dry load, 5% MeOH in CH_2Cl_2) to furnish product **181** (19.6 mg, 0.02 mmol, 57%) as beige amorphous solid.

R_f (5% MeOH in CH_2Cl_2) = 0.22;

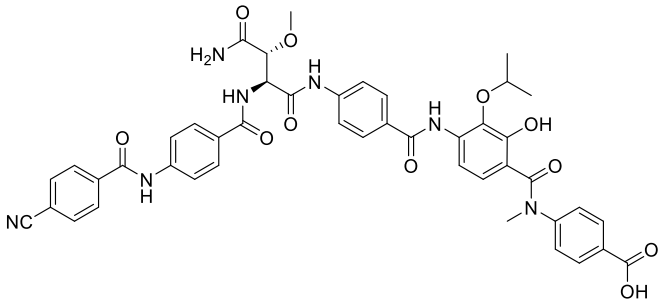
$[\alpha]_D^{21}$ = +29.2 ° (c 1.0, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 10.71 (s, 1H, OH), 10.52 (s, 1H, NH), 9.30 (s, 1H, NH), 9.28 (s, 1H, NH), 8.44-8.43 (d, *J* = 8.1 Hz, 1H, CHN*H*), 8.13-8.12 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 8.05-8.04 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.91-7.87 (m, 5H, H_{Ar}), 7.79-7.78 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.73-7.71 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.53-7.46 (d, *J* = 39.2 Hz, 2H, NH_2), 7.27-26 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.25-7.24 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.88-6.86 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 4.91-4.88 (t, *J* = 8.1 Hz, 1H, C*H*NH), 4.09-4.07 (d, *J* = 8.1 Hz, 1H, C*H*OCH_3), 4.07-4.01 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 3.37 (s, 3H, NCH_3), 3.30 (s, 3H, OCH_3), 1.49 (s, 9H, $C(CH_3)_3$), 1.02-1.01 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 170.9 (CO), 168.6 (CO), 168.0 (CO), 165.4 (CO), 164.5 (CO), 164.3 (CO), 164.0 (CO), 147.8 (C_{Ar}), 147.3 (C_{Ar}), 141.9 (C_{Ar}), 141.8 (C_{Ar}), 138.7 (C_{Ar}), 137.5 (C_{Ar}), 133.4 (C_{Ar}), 132.5 (C_{Ar}), 129.2 (C_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 128.6 (C_{Ar}), 128.3 (C_{Ar}), 126.3 (C_{Ar}), 123.0 (C_{Ar}), 121.7 (C_{Ar}), 119.6 (C_{Ar}), 118.8 (C_{Ar}) 118.3 (CN), 114.5 (C_{Ar}), 114.0 (C_{Ar}), 80.7 (*C*$(CH_3)_3$), 80.0 (*C*HOCH_3), 74.6 (*C*H$(CH_3)_2$), 57.7 (CHNH), 55.7 (OCH_3), 36.8 (NCH_3). 27.7 ($C(CH_3)_3$), 21.7 ($CH(CH_3)_2$) ppm;

HRMS (ESI) calculated for $C_{49}H_{49}N_7O_{11}Na$ $[M+Na]^+$: 934.3388; found: 934.3394.

4-(4-(4-((2*S*,3*R*)-4-Amino-2-(4-(4-cyanobenzamido)benzamido)-3-methoxy-4-oxo butanamido)benzamido)-2-hydroxy-3-isopropoxy-*N*-methylbenzamido)benzoic acid **TSD08**



tert-Butyl ester **181** (16.0 mg, 0.02 mmol) was dissolved in precooled TFA (1 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSD08** (7.4 mg, 0.01 mmol, 49%) as colorless amorphous solid.

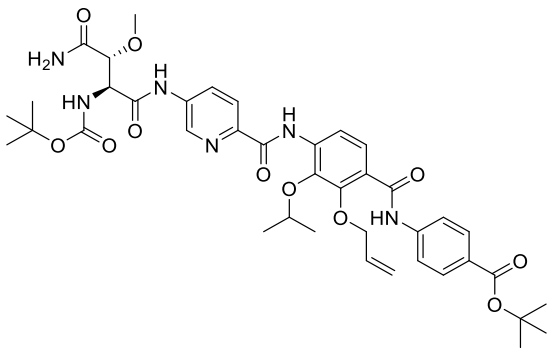
[α]$_D^{21}$ = +2.1 ° (c 0.1, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 12.89 (s, 1H, CO_2H), 10.71 (s, 1H, OH), 10.51 (s, 1H, NH), 9.31 (s, 1H, NH), 9.28 (s, 1H, NH), 8.44-8.43 (d, *J* = 8.2 Hz, 1H, CHN*H*), 8.13-8.12 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 8.05-8.04 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.91-7.87 (m, 6H, H_{Ar}), 7.79-7.76 (m, 4H, H_{Ar}), 7.53-7.46 (d, *J* = 39.0 Hz, 2H, NH_2), 7.28-27 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.23-7.22 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 6.87-6.86 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 4.91-4.88 (t, *J* = 8.1 Hz, 1H, C*H*NH), 4.08-4.04 (m, 2H, C*H*OCH_3, C*H*$(CH_3)_2$), 3.38 (s, 3H, NCH_3), 3.30 (s, 3H, OCH_3), 1.02-1.01 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 170.9 (CO), 168.6 (CO), 168.0 (CO), 166.7 (CO), 165.4 (CO), 164.5 (CO), 164.0 (CO), 147.8 (C_{Ar}), 147.3 (C_{Ar}), 141.9 (C_{Ar}), 141.8 (C_{Ar}), 138.7 (C_{Ar}), 137.5 (C_{Ar}), 133.4 (C_{Ar}), 132.5 (C_{Ar}), 129.5 (C_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 128.6 (C_{Ar}), 128.3 (C_{Ar}), 128.1 (C_{Ar}), 126.3 (C_{Ar}), 122.9 (C_{Ar}), 121.7 (C_{Ar}), 119.6 (C_{Ar}), 118.8 (C_{Ar}) 118.3 (CN), 114.6 (C_{Ar}), 114.0 (C_{Ar}), 80.0 (*C*HOCH_3), 74.6 (*C*H$(CH_3)_2$), 57.7 (CHNH), 55.7 (OCH_3), 36.7 (NCH_3). 21.7 (CH(*C*H$_3)_2$) ppm;

HRMS (ESI) calculated for $C_{45}H_{40}N_7O_{11}$ [M-H]$^-$: 854.2786; found: 854.2778.

tert-Butyl 4-(2-(allyloxy)-4-(5-((2*S*,3*R*)-4-amino-2-((*tert*-butoxycarbonyl)amino)-3-methoxy-4-oxobutanamido)picolinamido)-3-isopropoxybenzamido)benzoate (**121**)



Amine **114** (150 mg, 0.27 mmol) and acid **4** (101 mg, 0.38 mmol, 1.40 equiv.) were dissolved in EtOAc (600 µL) and pyridine (66 µL, 0.82 mmol, 3.00 equiv.) was added. T3P (50% in EtOAc, 300 µL, 0.49 mmol, 1.80 equiv.) was added at 0 °C and the mixture was stirred at 0 °C for 5 h. H_2O was added and the aq. phase was extracted with EtOAc (3x). The combined organic

phases were washed with a sat. $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (2% MeOH in CH_2Cl_2) to furnish product **121** (85.7 mg, 0.11 mmol, 39%) as colorless amorphous solid.

R_f (3% MeOH in CH_2Cl_2) = 0.20;

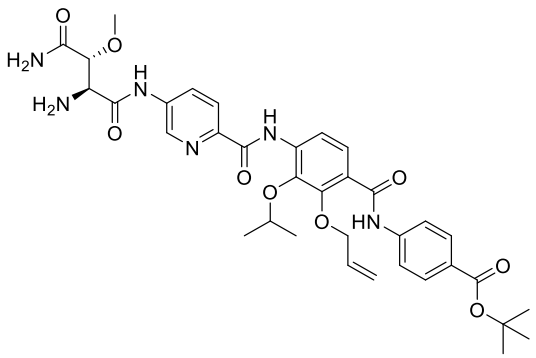
$[\alpha]_D^{22}$ = -1.1 ° (c 1.0, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 10.68 (s, 1H, NH), 10.67 (s, 1H, NH), 10.48 (s, 1H, NH), 9.01 (d, *J* = 1.8 Hz, 1H, NH), 8.35-8.34 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 8.31-8.29 (dd, *J* = 2.2, 8.6 Hz, 1H, H_{Ar}), 8.20-8.18 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 7.90-7.88 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.83-7.82 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.49-7.43 (m, 3H, NH_2, H_{Ar}), 6.87-6.85 (d, *J* = 8.2 Hz, 1H, CHN*H*), 6.05-5.99 (m, 1H, C*H*CH_2), 5.41-5.37 (dq, *J* = 1.6, 17.2 Hz, 1H, CHC*H*$_2$), 5.22-5.20 (dq, *J* = 1.7, 10.5 Hz, 1H, CHC*H*$_2$), 4.68-4.63 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.62-4.61 (d, *J* = 5.5 Hz, 2H, OCH_2), 4.45-4.42 (t, *J* = 7.7 Hz, 1H, C*H*NH), 3.89-3.88 (d, *J* = 7.2 Hz, 1H, C*H*OCH_3), 3.27 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.39 (s, 9H, $C(CH_3)_3$), 1.37-1.36 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 170.5 (CO), 169.5 (CO), 164.6 (CO), 164.3 (CO), 161.1 (CO), 154.9 (CO), 149.3 (C_{Ar}), 143.4 (C_{Ar}), 143.0 (C_{Ar}), 139.4 (C_{Ar}), 138.7 (C_{Ar}), 135.5 (C_{Ar}), 133.5 (*C*HCH_2), 130.1 (C_{Ar}), 127.3 (C_{Ar}), 126.0 (C_{Ar}), 125.8 (C_{Ar}), 124.6 (C_{Ar}), 122.9 (C_{Ar}), 118.8 (CH*C*H_2), 118.0 (C_{Ar}), 113.8 (C_{Ar}), 80.3 (*C*$(CH_3)_3$), 80.0 (*C*$HOCH_3$), 78.8 (*C*$(CH_3)_3$), 76.3 (OCH_2), 74.3 (*C*$H(CH_3)_2$), 57.7 (CHNH), 56.6 (OCH_3), 28.1 ($C(CH_3)_3$), 27.9 ($C(CH_3)_3$), 22.3 ($CH(CH_3)_2$) ppm;

HRMS (ESI) calculated for $C_{40}H_{51}N_6O_{11}$ $[M+H]^+$: 791.3616; found: 791.3621.

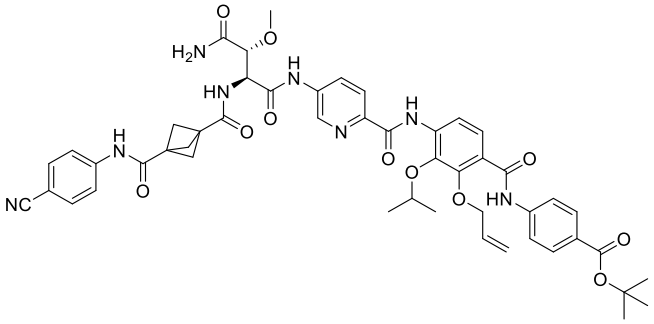
tert-Butyl 4-(2-(allyloxy)-4-(5-((2*S*,3*R*)-2,4-diamino-3-methoxy-4-oxobutanamido)picolin amido)-3-isopropoxybenzamido)benzoate (**185**)



Carbamate **121** (116 mg, 0.15 mmol) was dissolved in HCl (4 M in 1,4-dioxane, 3.70 mL, 14.6 mmol, 100 equiv.) at 0 °C. The mixture was warmed up to rt and stirred for 15 min. The

solution was transferred to a stirred suspension of EtOAc (100 mL) and a sat. $NaHCO_3$ solution (100 mL). The aq. phase was extracted with EtOAc (3x 100 mL) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was used in the next step without further purification.

tert-Butyl 4-(2-(allyloxy)-4-(5-((2*S*,3*R*)-4-amino-2-(3-((4-cyanophenyl)carbamoyl) bicyclo [1.1.1]pentane-1-carboxamido)-3-methoxy-4-oxobutanamido)picolinamido)-3-isopropoxybenzamido)benzoate (**192**)



DIPEA (80 µL, 0.45 mmol, 3.00 equiv.) was added dropwise to a stirred solution of HATU (66.6 mg, 0.18 mmol, 1.20 equiv.) and carboxylic acid **43** (44.9 mg, 0.18 mmol, 1.20 equiv.) in DMF (3.6 mL). The solution was stirred for 5 min and was then transferred to a stirred solution of amine **185** (101 mg, 0.15 mmol) in DMF (2.0 mL). The reaction mixture was stirred at rt for 19 h. The mixture was diluted with EtOAc and washed with a 0.1 M HCl solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 1%, 3%, 5%) to furnish product **192** (97.3 mg, 0.10 mmol, 72%) as yellow amorphous solid.

R_f (3% MeOH in CH_2Cl_2) = 0.17;

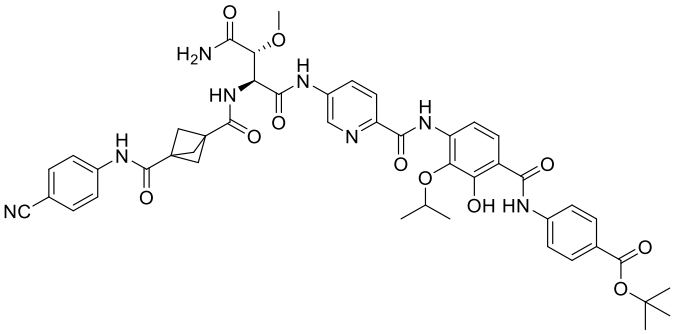
$[\alpha]_D^{21}$ = +0.8 ° (c 0.1, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 10.84 (s, 1H, NH), 10.67 (s, 1H, NH), 10.48 (s, 1H, NH), 10.01 (s, 1H, NH), 9.02-9.01 (d, *J* = 2.3 Hz, 1H, H_{Ar}), 8.35-8.34 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 8.32-8.30 (dd, *J* = 2.4, 8.6 Hz, 1H, H_{Ar}), 8.21-8.19 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 7.95-7.94 (d, *J* = 8.4 Hz, 1H, CHN*H*), 7.90-7.88 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.86-7.85 (d, *J* = 9.0 Hz, 2H, H_{Ar}), 7.83-7.82 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.79-7.77 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.49-7.45 (m, 3H, H_{Ar}, NH_2), 6.05-5.99 (m, 1H, C*H*CH_2), 5.41-5.37 (dq, *J* = 1.7, 17.2 Hz, 1H, CHC*H*$_2$), 5.22-5.20 (dq, *J* = 1.7, 10.5 Hz, 1H, CHC*H*$_2$), 4.77-4.74 (t, *J* = 8.3 Hz, 1H, C*H*NH), 4.67-4.63 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.62-4.61 (d, *J* = 5.5 Hz, 2H, OCH_2), 3.98-3.97 (d, *J* = 8.1 Hz, 1H, C*H*OCH_3), 3.28 (s, 3H, OCH_3), 2.26 (s, 6H, CCH_2C), 1.55 (s, 9H, $C(CH_3)_3$), 1.37-1.36 (dd, *J* = 1.8, 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 170.5 (CO), 169.0 (CO), 168.4 (CO), 168.4 (CO), 164.6 (CO), 164.3 (CO), 161.1 (CO), 149.3 (C_{Ar}), 143.5 (C_{Ar}), 143.0 (C_{Ar}), 142.9 (C_{Ar}), 139.5 (C_{Ar}), 139.4 (C_{Ar}), 138.6 (C_{Ar}), 135.4 (C_{Ar}), 133.5 (*C*HCH$_2$), 133.1 (C_{Ar}), 130.1 (C_{Ar}), 127.3 (C_{Ar}), 126.0 (C_{Ar}), 125.8 (C_{Ar}), 124.6 (C_{Ar}), 122.9 (C_{Ar}), 119.7 (C_{Ar}), 119.0 (C_{Ar}), 118.8 (CH*C*H$_2$), 118.0 (CN), 113.8 (C_{Ar}), 105.3 (C_{Ar}), 80.3 (*C*(CH$_3$)$_3$), 79.8 (*C*HOCH$_3$), 76.4 (OCH$_2$), 74.3 (*C*H(CH$_3$)$_2$), 57.8 (CHNH), 54.7 (OCH$_3$), 51.7 (C*C*H$_2$C), 38.9 (*C*CH$_2$C), 37.9 (*C*CH$_2$C), 27.8 (C(*C*H$_3$)$_3$), 22.3 (d, *J* = 2.2 Hz, CH(*C*H$_3$)$_2$) ppm;

HRMS (ESI): m/z calculated for $C_{49}H_{52}N_8O_{11}Na$ [M+Na]$^+$: 951.3653; found: 951.3643.

tert-Butyl 4-(4-(5-((2*S*,3*R*)-4-amino-2-(3-((4-cyanophenyl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxamido)-3-methoxy-4-oxobutanamido)picolinamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**201**)



Allyl ether **192** (93.2 mg, 0.10 mmol) was dissolved in THF (4.6 mL). Aniline (30 µL, 0.33 mmol, 3.30 equiv.) and Pd(PPh$_3$)$_4$ (11.6 mg, 0.01 mmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 3 h. The mixture was concentrated onto silica. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 2%, 5%) to furnish product **201** (68.1 mg, 0.08 mmol, 76%) as colorless amorphous solid.

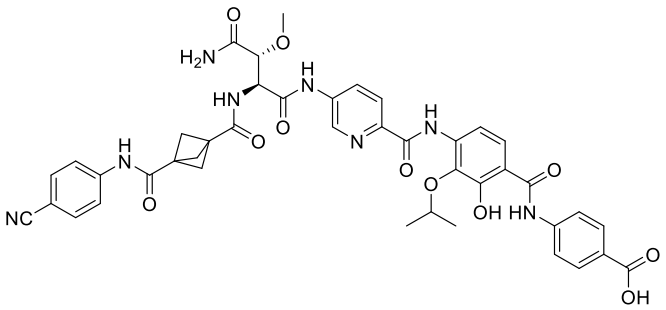
R$_f$ (5% MeOH in CH_2Cl_2) = 0.12;

[*α*]$_D^{22}$ = +0.5 ° (c 0.1, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 12.45 (s, 1H, OH), 10.85 (s, 1H, NH), 10.74 (s, 1H, NH), 10.61 (s, 1H, NH), 10.01 (s, 1H, NH), 9.01 (d, *J* = 2.4 Hz, 1H, H_{Ar}), 8.32-8.30 (dd, *J* = 2.4, 8.6 Hz, 1H, H_{Ar}), 8.20-8.19 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 8.11-8.10 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 7.95-7.91 (m, 4H, CHN*H*, H_{Ar}), 7.86-7.85 (m, 4H, H_{Ar}), 7.79-7.77 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.48-7.44 (d, *J* = 18.4 Hz, 2H, NH$_2$), 4.77-4.74 (t, *J* = 8.2 Hz, 1H, C*H*NH), 4.70-4.64 (sept, *J* = 6.1 Hz, 1H, C*H*(CH$_3$)$_2$), 3.98-3.97 (d, *J* = 8.1 Hz, 1H, C*H*OCH$_3$), 3.28 (s, 3H, OCH$_3$), 2.26 (s, 6H, CCH$_2$C), 1.55 (s, 9H, C(CH$_3$)$_3$), 1.36-1.34 (dd, *J* = 2.2, 6.1 Hz, 6H, CH(C*H*$_3$)$_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 170.5 (CO), 169.0 (CO), 168.7 (CO), 168.4 (CO), 168.4 (CO), 164.5 (CO), 161.2 (CO), 154.1 (C_{Ar}), 143.5 (C_{Ar}), 142.9 (C_{Ar}), 141.9 (C_{Ar}), 139.4 (C_{Ar}), 138.6 (C_{Ar}), 136.8 (C_{Ar}), 134.0 (C_{Ar}), 133.1 (C_{Ar}), 129.9 (C_{Ar}), 127.3 (C_{Ar}), 126.9 (C_{Ar}), 123.5 (C_{Ar}), 123.0 (C_{Ar}), 120.8 (C_{Ar}), 119.7 (C_{Ar}), 119.0 (CN), 111.6 (C_{Ar}), 108.4 (C_{Ar}), 105.3 (C_{Ar}), 80.5 (*C*(CH_3)$_3$), 79.8 (*C*HOCH_3), 74.8 (*C*H(CH_3)$_2$), 57.8 (CHNH), 54.7 (OCH_3), 51.7 (C*C*H_2C), 38.9 (*C*CH_2C), 37.9 (*C*CH_2C), 27.8 (C(*C*H_3)$_3$), 22.3 (d, *J* = 2.4 Hz, CH(*C*H_3)$_2$) ppm;
HRMS (ESI): m/z calculated for $C_{46}H_{48}N_8O_{11}Na$ $[M+Na]^+$: 911.3340; found: 911.3333.

4-(4-(5-((2*S*,3*R*)-4-Amino-2-(3-((4-cyanophenyl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxamido)-3-methoxy-4-oxobutanamido)picolinamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSF53**

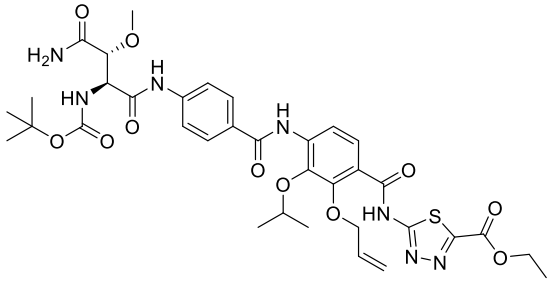


tert-Butyl ester **201** (67.6 mg, 0.08 mmol) was dissolved in precooled TFA (4 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSF53** (39.7 mg, 0.05 mmol, 63%) as yellow amorphous solid.
[*α*]$_D^{22}$ = +1.0 (c 0.1, MeOH);
^{1}H-NMR (600 MHz, DMSO-d_6) = δ 12.83 (s, 1H, CO_2H), 12.45 (s, 1H, OH), 10.85 (s, 1H, NH), 10.74 (s, 1H, NH), 10.60 (s, 1H, NH), 10.01 (s, 1H, NH), 9.01 (d, *J* = 2.4 Hz, 1H, H_{Ar}), 8.32-8.30 (dd, *J* = 2.4, 8.7 Hz, 1H, H_{Ar}), 8.20-8.19 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 8.12-8.10 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 7.98-7.96 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.95-7.94 (d, *J* = 8.4 Hz, 1H, NH), 7.92-91 (d, *J* = 9.1 Hz, 1H, H_{Ar}), 7.86-7.85 (m, 4H, H_{Ar}), 7.79-7.77 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.48-7.44 (d, *J* = 18.2 Hz, 2H, NH_2), 4.77-4.74 (t, *J* = 8.2 Hz, 1H, C*H*NH), 4.71-4.65 (sept, *J* = 6.1 Hz, 1H, C*H*(CH_3)$_2$), 3.98-3.97 (d, *J* = 8.1 Hz, 1H, C*H*OCH_3), 3.28 (s, 3H, OCH_3), 2.26 (s, 6H, CCH_2C), 1.36-1.34 (dd, *J* = 2.1, 6.1 Hz, 6H, CH(CH_3)$_2$) ppm;
^{13}C-NMR (151 MHz, DMSO-d_6) = δ 170.5 (CO), 169.0 (CO), 168.7 (CO), 168.4 (CO), 168.4 (CO), 166.9 (CO), 161.2 (CO), 154.1 (C_{Ar}), 143.5 (C_{Ar}), 142.9 (C_{Ar}), 141.9 (C_{Ar}), 139.4 (C_{Ar}), 138.6 (C_{Ar}), 136.8 (C_{Ar}), 134.0 (C_{Ar}), 133.1 (C_{Ar}), 130.2 (C_{Ar}), 127.3 (C_{Ar}), 126.3 (C_{Ar}), 123.5 (C_{Ar}), 123.0 (C_{Ar}), 120.8 (C_{Ar}), 119.7 (C_{Ar}), 119.0 (CN), 111.7 (C_{Ar}), 108.4 (C_{Ar}), 105.3 (C_{Ar}),

79.8 (*C*HOCH$_3$), 74.8 (*C*H(CH$_3$)$_2$), 57.8 (CHNH), 54.7 (OCH$_3$), 51.7 (C*C*H$_2$C), 38.9 (*C*CH$_2$C), 37.9 (*C*CH$_2$C), 22.3 (d, *J* = 2.4 Hz, CH(*C*H$_3$)$_2$) ppm;

HRMS (ESI): m/z calculated for $C_{42}H_{39}N_8O_{11}$ [M-H]$^-$: 831.2738; found: 831.2746.

Ethyl 5-(2-(allyloxy)-4-(4-((2*S*,3*R*)-4-amino-2-((*tert*-butoxycarbonyl)amino)-3-methoxy-4-oxobutanamido)benzamido)-3-isopropoxybenzamido)-1,3,4-thiadiazole-2-carboxylate (**224**)



Amine **223** (68.9 mg, 0.13 mmol), acid **4** (58.5 mg, 0.22 mmol, 1.70 equiv.) and EEDQ (51.9 mg, 0.21 mmol, 1.60 equiv.) were dissolved in precooled $CHCl_3$ (0.7 mL). The mixture was stirred for 24 h while warming to rt. The mixture was concentrated and the crude product was purified by column chromatography (dry load, wash with 20% Et_2O in CH_2Cl_2, elution with 3% MeOH in CH_2Cl_2) to furnish product **224** (28.1 mg, 0.04 mmol, 28%) as yellow amorphous solid.

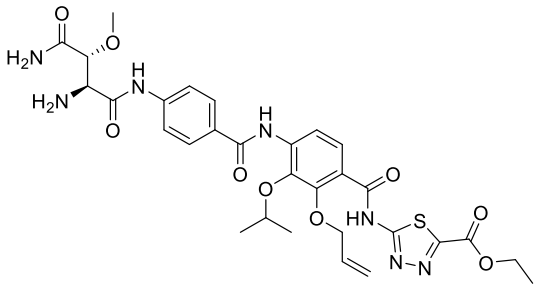
[*α*]$_D^{23}$ = -1.0 ° (c 0.1, MeOH);

^{1}H-NMR (500 MHz, DMSO-d$_6$) = δ 13.37 (s, 1H, NH), 10.37 (s, 1H, NH), 9.53 (s, 1H, NH), 7.98-7.96 (d, *J* = 8.8 Hz, 2H, H$_{Ar}$), 7.91-7.89 (d, *J* = 8.6 Hz, 1H, H$_{Ar}$), 7.81-7.80 (d, *J* = 8.7 Hz, 2H, H$_{Ar}$), 7.50-7.49 (d, *J* = 8.6 Hz, 2H, H$_{Ar}$), 7.45-7.41 (d, *J* = 17.8 Hz, 2H, NH$_2$), 6.81-6.79 (d, *J* = 8.4 Hz, 1H, NH$_{Boc}$), 6.04-5.96 (m, 1H, C*H*CH$_2$), 5.38-5.34 (dq, *J* = 1.6, 17.2 Hz, 1H, CHC*H*$_2$), 5.23-5.20 (dd, *J* = 1.6, 10.5 Hz, 1H, CHC*H*$_2$), 4.61-4.60 (d, *J* = 5.6 Hz, 1H, OC*H*$_2$CH), 4.55-4.50 (p, *J* = 6.1 Hz, 1H, C*H*(CH$_3$)$_2$), 4.45-4.39 (m, 3H, C*H*NH, C*H*$_2$CH$_3$), 3.86-3.84 (d, *J* = 7.5 Hz, 1H, C*H*OCH$_3$), 3.25 (s, 3H, OCH$_3$), 1.38-1.35 (m, 12H, C(CH$_3$)$_3$, CH$_2$C*H*$_3$), 1.28-1.27 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3$)$_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d$_6$) = δ 170.6 (CO), 168.9 (CO), 164.5 (CO), 164.3 (CO), 161.7 (CO), 158.9 (CO), 154.8 (C$_{Ar}$), 153.9 (C$_{Ar}$), 150.3 (C$_{Ar}$), 142.3 (C$_{Ar}$), 142.2 (C$_{Ar}$), 137.0 (C$_{Ar}$), 133.4 (*C*HCH$_2$), 128.4 (C$_{Ar}$), 128.3 (C$_{Ar}$), 124.3 (C$_{Ar}$), 123.5 (C$_{Ar}$), 118.9 (C$_{Ar}$), 118.5 (C$_{Ar}$), 118.2 (CH*C*H$_2$), 80.1 (*C*(CH$_3$)$_3$), 78.7 (*C*HOCH$_3$), 76.4 (*C*H(CH$_3$)$_2$), 74.5 (O*C*H$_2$CH), 62.4 (*C*H$_2$CH$_3$), 60.6 (CHNH), 57.6 (OCH$_3$), 28.1 (C(*C*H$_3$)$_3$), 22.3 (CH(*C*H$_3$)$_2$), 14.0 (CH$_2$*C*H$_3$) ppm;

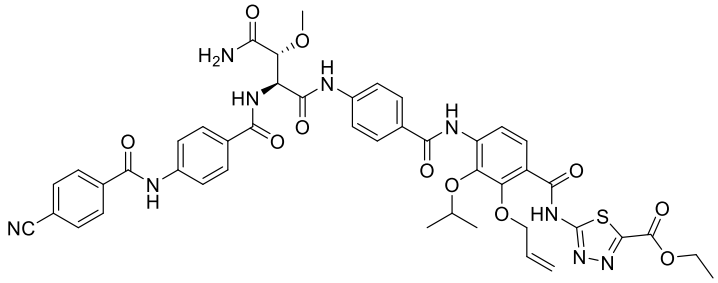
HRMS (ESI): m/z calculated for $C_{25}H_{27}N_5O_6SNa$ [M+Na]$^+$: 792.2639; found: 792.2608.

Ethyl 5-(2-(allyloxy)-4-(4-((2*S*,3*R*)-2,4-diamino-3-methoxy-4-oxobutanamido)benzamido)-3-isopropoxybenzamido)-1,3,4-thiadiazole-2-carboxylate (**228**)



Carbamate **224** (25.8 mg, 0.03 mmol) was dissolved in HCl (4 M in 1,4-dioxane, 0.80 mL, 3.27 mmol, 100 equiv.) at 0 °C. The mixture was warmed up to rt and stirred for 15 min. The solution was transferred to a stirred suspension of EtOAc (20 mL) and a sat. $NaHCO_3$ solution (20 mL). The aq. phase was extracted with EtOAc (2x) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was used in the next step without further purification.

Ethyl 5-(2-(allyloxy)-4-(4-((2*S*,3*R*)-4-amino-2-(4-(4-cyanobenzamido)benzamido)-3-methoxy-4-oxobutanamido)benzamido)-3-isopropoxybenzamido)-1,3,4-thiadiazole-2-carboxylate (**229**)



DIPEA (17 µL, 0.10 mmol, 3.00 equiv.) was added dropwise to a stirred solution of HATU (14.9 mg, 0.04 mmol, 1.20 equiv.) and carboxylic acid **3** (10.5 mg, 0.04 mmol, 1.20 equiv.) in DMF (0.8 mL). The solution was stirred for 5 min and was then transferred to a stirred solution of amine **228** (22.6 mg, 0.03 mmol) in DMF (0.5 mL). The reaction mixture was stirred at rt for 18 h. The mixture was diluted with EtOAc and washed with a 0.1 M HCl solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was

purified by column chromatography (MeOH in CH_2Cl_2 = 2%, 3%, 4%) to furnish product **229** (17.4 mg, 0.02 mmol, 58%) as colorless amorphous solid.

R_f (5% MeOH in CH_2Cl_2) = 0.25;

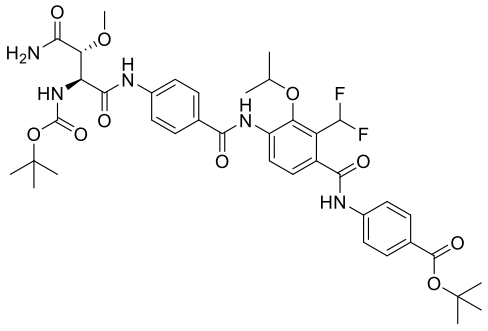
$[\alpha]_D^{25}$ = +2.1 ° (c 0.1, MeOH);

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 13.01 (s, 1H, NH), 10.72 (s, 1H, NH), 10.57 (s, 1H, NH), 9.53 (s, 1H, NH), 8.46-8.45 (d, *J* = 8.2 Hz, 1H, CHN*H*), 8.14-8.11 (m, 2H, H_{Ar}), 8.06-8.04 (m, 2H, H_{Ar}), 7.99-7.95 (m, 2H, H_{Ar}), 7.92-7.88 (m, 5H, H_{Ar}), 7.84-7.83 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.54-7.48 (m, 3H, NH_2, H_{Ar}), 6.04-5.96 (m, 1H, C*H*CH_2), 5.38-5.34 (dq, *J* = 1.6, 17.2 Hz, 1H, CHC*H*$_2$), 5.22-5.19 (dd, *J* = 1.6, 10.5 Hz, 1H, CHC*H*$_2$), 4.93-4.90 (t, *J* = 8.1 Hz, 1H, C*H*NH), 4.61-4.60 (d, *J* = 5.6 Hz, 1H, OC*H*$_2$CH), 4.56-4.48 (sept, *J* = 6.2 Hz, 1H, C*H*$(CH_3)_2$), 4.44-4.40 (q, *J* = 7.1 Hz, 2H, C*H*$_2$$CH_3$), 4.10-4.07 (m, 1H, C*H*OCH_3), 3.28 (s, 3H, OCH_3), 1.38-1.35 (t, *J* = 7.1 Hz, 3H, CH_2C*H*$_3$), 1.28-1.26 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3$)$_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 170.9 (CO), 168.7 (CO), 166.9 (CO), 165.4 (CO), 164.6 (CO), 164.5 (CO), 164.3 (CO), 150.3 (C_{Ar}), 142.8 (C_{Ar}), 142.3 (C_{Ar}), 142.2 (C_{Ar}), 141.8 (C_{Ar}), 138.7 (C_{Ar}), 133.4 (*C*HCH_2), 132.5 (C_{Ar}), 130.3 (C_{Ar}), 128.9 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 124.3 (C_{Ar}), 119.6 (C_{Ar}), 119.6 (C_{Ar}), 118.9 (C_{Ar}), 118.5 (CN), 118.3 (C_{Ar}), 118.1 (CH*C*H_2), 114.1 (C_{Ar}), 80.0 (*C*HOCH_3), 76.3 (*C*H$(CH_3)_2$), 74.4 (O*C*H_2CH), 62.4 (*C*$H_2$$CH_3$), 57.7 (O$CH_3$), 55.8 (CHNH), 22.3 (CH(*C*H$_3$)$_2$), 14.0 (CH_2*C*H$_3$) ppm;

HRMS (ESI): m/z calculated for $C_{45}H_{43}N_9O_{11}SNa$ $[M+Na]^+$: 940.2700; found: 940.2700.

tert-Butyl 4-(4-(4-((2*S*,3*R*)-4-amino-2-((*tert*-butoxycarbonyl)amino)-3-methoxy-4-oxobutan amido)benzamido)-2-(difluoromethyl)-3-isopropoxybenzamido)benzoate (**136**)



Aniline **96** (90.6 mg, 0.17 mmol), acid **4** (74.9 mg, 0.29 mmol, 1.70 equiv.) and EEDQ (66.4 mg, 0.27 mmol, 1.60 equiv.) were dissolved in precooled $CHCl_3$ (1 mL) at 0 °C. The mixture was stirred for 16 h while warming to rt. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (dry load, washing with 20% Et_2O in CH_2Cl_2, elution with 3% MeOH in CH_2Cl_2) to furnish product **136** (45.9 mg, 0.06 mmol, 33% over 3 steps) as orange amorphous solid.

R_f (3% MeOH in CH_2Cl_2) = 0.10;

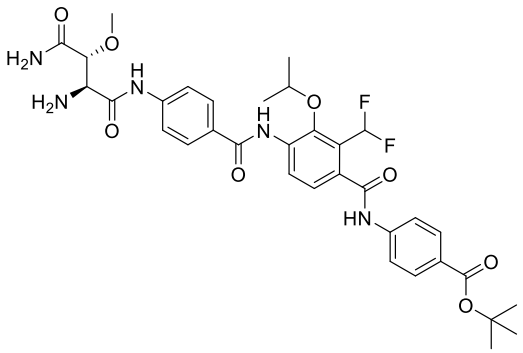
$[\alpha]_D^{25}$ = -0.5 ° (c 0.1, MeOH);

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 10.76 (s, 1H, NH), 10.35 (s, 1H, NH), 9.96 (s, 1H, NH), 8.03-8.02 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.90-7.88 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.88-7.86 (d, *J* = 8.8 Hz, 1H, H_{Ar}), 7.83-7.81 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.80-7.78 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.45-7.41 (d, *J* = 18.6 Hz, 2H, NH_2), 7.39-7.38 (d, *J* = 8.2 Hz, 1H, H_{Ar}), 7.30-7.08 (t, *J* = 53.6 Hz, 1H, CHF_2), 6.80-6.79 (d, *J* = 8.2 Hz, 1H, CHN*H*), 4.41-4.35 (m, 2H, C*H*NH, C*H*$(CH_3)_2$), 3.86-3.84 (d, *J* = 7.4 Hz, 1H, C*H*OCH_3), 3.25 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.38 (s, 9H, $C(CH_3)_3$), 1.23-1.22 (d, *J* = 6.2 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 170.6 (CO), 168.9 (CO), 166.2 (CO), 164.6 (CO), 164.6 (CO), 154.9 (CO), 150.0 (C_{Ar}), 143.2 (C_{Ar}), 142.2 (C_{Ar}), 134.2 (C_{Ar}), 133.2 (C_{Ar}), 130.0 (C_{Ar}), 129.4 (C_{Ar}), 128.6 (C_{Ar}), 128.2 (C_{Ar}), 126.1 (C_{Ar}), 124.9 (C_{Ar}), 123.3 (C_{Ar}), 118.8 (C_{Ar}), 118.7 (C_{Ar}), 113.8-110.1 (t, *J* = 236.5 Hz, CHF_2), 80.4 (2C, *C*$(CH_3)_3$), 80.1 (*C*HOCH_3), 78.7 (CHNH), 77.0 (*C*H$(CH_3)_2$), 57.6 (OCH_3), 28.1 ($C(CH_3)_3$), 27.9 ($C(CH_3)_3$), 21.9 ($CH(CH_3)_2$) ppm;

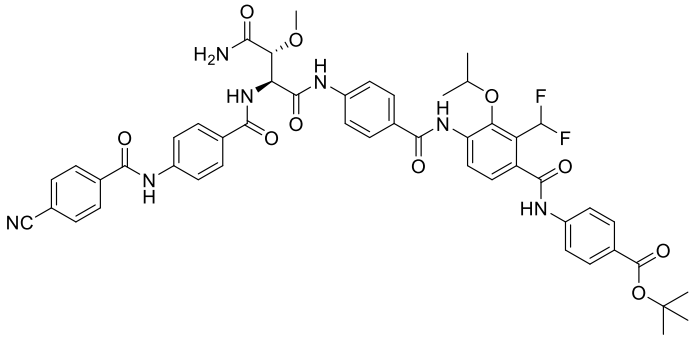
HRMS (ESI) calculated for $C_{39}H_{47}F_2N_5O_{10}Na$ $[M+Na]^+$: 806.3189; found: 806.3204.

tert-Butyl 4-(4-(4-((2*S*,3*R*)-2,4-diamino-3-methoxy-4-oxobutanamido)benzamido)-2-(difluoromethyl)-3-isopropoxybenzamido)benzoate (**182**)



Carbamate **136** (44.0 mg, 0.06 mmol) was dissolved in HCl (4 M in 1,4-dioxane, 1.40 mL, 5.61 mmol, 100 equiv.) at 0 °C. The mixture was warmed up to rt and stirred for 15 min. The solution was transferred to a stirred suspension of EtOAc (40 mL) and a sat. $NaHCO_3$ solution (40 mL). The aq. phase was extracted with EtOAc and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was used in the next step without further purification.

tert-Butyl 4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(4-cyanobenzamido)benzamido)-3-methoxy-4-oxobutanamido)benzamido)-2-(difluoromethyl)-3-isopropoxybenzamido)benzoate (**183**)



DIPEA (28 µL, 0.16 mmol, 3.00 equiv.) was added dropwise to a stirred solution of HATU (24.6 mg, 0.06 mmol, 1.20 equiv.) and carboxylic acid **3** (17.2 mg, 0.06 mmol, 1.20 equiv.) in DMF (1.4 mL). The solution was stirred for 5 min and was then transferred to a stirred solution of amine **182** (36.8 mg, 0.05 mmol) in DMF (0.8 mL). The reaction mixture was stirred at rt for 18 h. The mixture was diluted with EtOAc and washed with a 1 M HCl solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 3%, 4%, 5%) to furnish product **183** (16.9 mg, 0.02 mmol, 33% over two steps) as colorless amorphous solid.

R_f (5% MeOH in CH_2Cl_2) = 0.19;

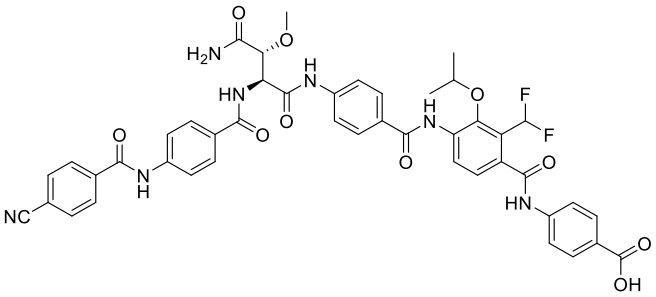
$[\alpha]_D^{23}$ = +2.4 ° (c 0.1, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 10.76 (s, 1H, NH), 10.72 (s, 1H, NH), 10.55 (s, 1H, NH), 9.97 (s, 1H, NH), 8.46-8.44 (d, *J* = 8.2 Hz, 2H, CHN*H*), 8.13-8.11 (m, 2H, H_{Ar}), 8.05-8.03 (m, 4H, H_{Ar}), 7.91-7.81 (m, 11H, H_{Ar}), 7.54-7.48 (d, *J* = 39.3 Hz, 2H, NH_2), 7.39-7.38 (d, *J* = 8.2 Hz, 1H, H_{Ar}), 7.28-7.10 (t, *J* = 53.7 Hz, 1H, CHF_2), 4.93-4.90 (t, *J* = 8.1 Hz, 1H, C*H*NH), 4.40-4.34 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.10-4.08 (d, *J* = 8.0 Hz, 1H, C*H*OCH_3), 3.31 (s, 3H, OCH_3), 1.55 (s, 9H, C(C*H*$_3)_3$), 1.23-1.22 (d, *J* = 6.2 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 170.9 (CO), 168.7 (CO), 166.2 (CO), 165.5 (CO), 164.6 (CO), 164.5 (CO), 164.5 (CO), 150.0 (C_{Ar}), 143.2 (C_{Ar}), 142.1 (C_{Ar}), 141.8 (C_{Ar}), 138.7 (C_{Ar}), 134.2 (C_{Ar}), 133.2 (C_{Ar}), 132.5 (C_{Ar}), 130.0 (C_{Ar}), 129.4 (C_{Ar}), 128.9 (C_{Ar}), 128.6 (C_{Ar}), 128.6 (C_{Ar}), 128.3 (C_{Ar}), 128.2 (C_{Ar}), 126.1, (C_{Ar}), 124.9 (C_{Ar}), 123.3 (C_{Ar}), 119.6 (C_{Ar}), 118.8 (C_{Ar}), 118.8 (C_{Ar}), 118.3 (CN), 114.1 (C_{Ar}), 113.5-110.4 (t, *J* = 237.5 Hz, CHF_2), 80.4 (*C*$(CH_3)_3$), 80.0 (*C*HOCH_3), 77.0 (*C*H$(CH_3)_2$), 57.6 (OCH_3), 55.8 (CHNH), 27.9 (C(*C*H$_3)_3$), 21.9 (CH(*C*H$_3)_2$) ppm;

HRMS (ESI) calculated for $C_{49}H_{47}F_2N_7O_{10}Na$ $[M+Na]^+$: 954.3250; found: 954.3248.

4-(4-(4-((2*S*,3*R*)-4-Amino-2-(4-(4-cyanobenzamido)benzamido)-3-methoxy-4-oxo butanamido)benzamido)-2-(difluoromethyl)-3-isopropoxybenzamido)benzoic acid **TSE40**



tert-Butyl ester **183** (14.4 mg, 0.02 mmol) was dissolved in precooled TFA (1 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSE40** (9.9 mg, 0.01 mmol, 73%) as beige amorphous solid.

[*α*]$_D^{23}$ = -0.5 ° (c 0.1, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 12.74 (bs, 1H, CO_2H), 10.76 (s, 1H, NH), 10.72 (s, 1H, NH), 10.55 (s, 1H, NH), 9.97 (s, 1H, NH), 8.46-8.44 (d, *J* = 8.2 Hz, 2H, CHN*H*), 8.13-8.12 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 8.05-8.03 (m, 4H, H_{Ar}), 7.94-7.92 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 7.91-7.89 (m, 4H, H_{Ar}), 7.88-7.86 (d, *J* = 8.3 Hz, 1H, H_{Ar}), 7.83-7.81 (m, 4H, H_{Ar}), 7.54-7.48 (d, *J* = 39.7 Hz, 2H, NH_2), 7.39-7.38 (d, *J* = 8.2 Hz, 1H, H_{Ar}), 7.28-7.10 (t, *J* = 53.7 Hz, 1H, CHF_2), 4.93-4.90 (t, *J* = 8.1 Hz, 1H, C*H*NH), 4.40-4.34 (sept, *J* = 6.2 Hz, 1H, C*H*$(CH_3)_2$), 4.10-4.08 (d, *J* = 8.0 Hz, 1H, C*H*OCH_3), 3.31 (s, 3H, OCH_3), 1.23-1.22 (d, *J* = 6.2 Hz, 6H, CH(C*H*$_3)_2$) ppm;

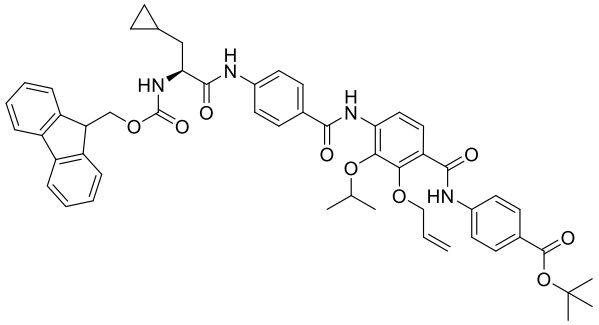
^{13}C-NMR (151 MHz, DMSO-d_6) = δ 170.9 (CO), 168.7 (CO), 166.9 (CO), 166.2 (CO), 165.5 (CO), 164.6 (CO), 164.5 (CO), 150.0 (C_{Ar}), 143.1 (C_{Ar}), 142.1 (C_{Ar}), 141.8 (C_{Ar}), 138.7 (C_{Ar}), 134.2 (C_{Ar}), 133.2 (C_{Ar}), 132.5 (C_{Ar}), 130.3 (C_{Ar}), 129.5 (C_{Ar}), 128.9 (C_{Ar}), 128.6 (C_{Ar}), 128.6 (C_{Ar}), 128.3 (C_{Ar}), 128.2 (C_{Ar}), 125.5, (C_{Ar}), 124.9 (C_{Ar}), 123.3 (C_{Ar}), 119.6 (C_{Ar}), 118.9 (C_{Ar}), 118.8 (C_{Ar}), 118.3 (CN), 114.1 (C_{Ar}), 113.5-110.4 (t, *J* = 236.5 Hz, CHF_2), 80.0 (*C*HOCH_3), 77.0 (*C*H$(CH_3)_2$), 57.6 (OCH_3), 55.8 (CHNH), 21.9 (CH(*C*H$_3)_2$) ppm;

^{19}F-NMR (376 MHz, DMSO-d_6) = δ -110.11- -110.25 (d, *J* = 53.7 Hz, 2F, CHF_2) ppm;

HRMS (ESI) calculated for $C_{45}H_{38}F_2N_7O_{10}$ $[M-H]^-$: 874.2648; found: 874.2642.

4.2.5 (*S*)-2-Amino-3-cyclopropylpropanoic acid derivatives

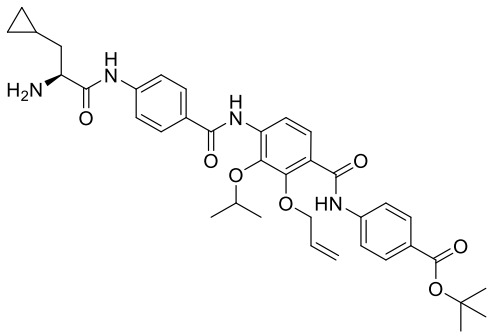
tert-Butyl (*S*)-4-(4-(4-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-cyclopropyl propanamido)benzamido)-2-(allyloxy)-3-isopropoxybenzamido)benzoate (**130**)



Amine **5** (400 mg, 0.73 mmol), acid **117** (438 mg, 1.25 mmol, 1.70 equiv.) and EEDQ (290 mg, 1.17 mmol, 1.60 equiv.) were dissolved in precooled $CHCl_3$ (3.7 mL) at 0 °C. The mixture was stirred for 19 h while warming to rt. The solution was concentrated on silica und purified by column chromatography (20% Et_2O in CH_2Cl_2, then 1% MeOH in CH_2Cl_2) to furnish carbamate **130** (547 g, 0.62 mmol, 85%) was yellow amorphous solid, which contained minor impurities. The compound was used in the next step without further purification.

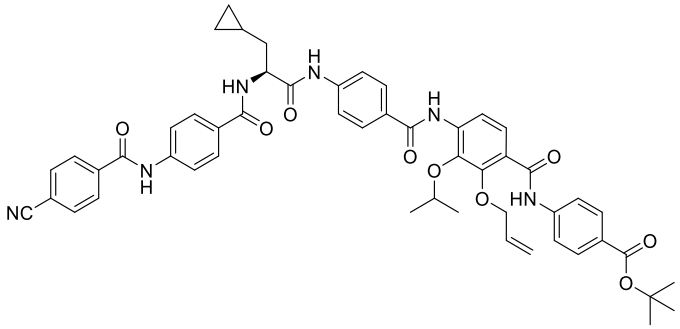
HRMS (ESI) calculated for $C_{52}H_{54}N_4O_9Na$ $[M+Na]^+$: 901.3788; found: 901.3812.

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(4-(2-amino-3-cyclopropylpropanamido)benzamido)-3-isopropoxybenzamido)benzoate (**142**)



Carbamate **130** (500 mg, 0.57 mmol) was dissolved in MeCN (5.3 mL). Et_2NH (1.3 mL) was added. The solution was stirred at rt for 30 min. The mixture was concentrated under reduced pressure. The residue was diluted with MeCN and concentrated three times. The crude product was dried *in vacuo* to furnish amine **142**, which was used in the next step without further purification.

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(4-(2-(4-(4-cyanobenzamido)benzamido)-3-cyclopropyl propanamido)benzamido)-3-isopropoxybenzamido)benzoate (**148**)



DIPEA (435 µL, 2.49 mmol, 5.00 equiv.) was added dropwise to a stirred solution of HATU (473 mg, 1.24 mmol, 2.50 equiv.) and carboxylic acid **3** (331 mg, 1.24 mmol, 2.50 equiv.) in DMF (12 mL). The solution was stirred for 30 min and was then transferred to a stirred solution of amine **142** (327 mg, 0.50 mmol) in DMF (7 mL). The reaction mixture was stirred at rt for 19 h. The mixture was diluted with EtOAc and washed with a 0.1 M HCl solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 1%, 5%) to furnish product **148** (405.2 mg, 0.45 mmol, 90%) as yellow amorphous solid.

R_f (2% MeOH in CH_2Cl_2) = 0.31;

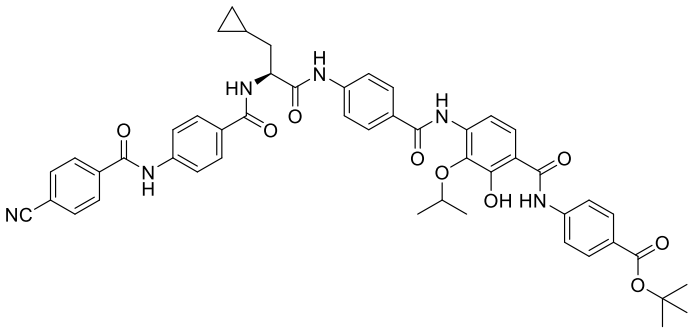
$[\alpha]_D^{22}$ = +13.6 ° (c 0.3, MeOH);

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 10.69 (s, 1H, NH), 10.53 (s, 1H, NH), 10.46 (s, 1H, NH), 9.51 (s, 1H, NH), 8.62-8.61 (d, *J* = 7.1 Hz, 1H, CHN*H*), 8.14-8.12 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 8.06-8.04 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.99-7.97 (m, 4H, H_{Ar}), 7.90-7.88 (d, *J* = 7.8 Hz, 4H, H_{Ar}), 7.84-7.80 (m, 5H, H_{Ar}), 7.42-7.40 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.05-5.99 (m, 1H, $OCH_2C\mathit{H}CH_2$), 5.39-5.36 (dq, *J* = 1.7, 17.2 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 5.21-5.19 (dq, *J* = 1.7, 10.5 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 4.71-4.67 (q, *J* = 7.5 Hz, 1H, C*H*NH), 4.61-4.60 (d, *J* = 5.4 Hz, 2H, OCH_2), 4.53-4.47 (sept, *J* = 6.1 Hz, 1H, $C\mathit{H}(CH_3)_2$), 1.96-1.92 (m, 1H, $CHC\mathit{H}_2CH$), 1.60-1.57 (m, 1H, $CHC\mathit{H}_2CH$), 1.55 (s, 9H, $C(CH_3)_3$), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, $CH(C\mathit{H}_3)_2$), 0.91-0.88 (m, 1H, $C\mathit{H}(CH_2)_2$), 0.49-0.38 (m, 2H, $CH(C\mathit{H}_2)_2$), 0.25-0.14 (m, 2H, $CH(C\mathit{H}_2)_2$) ppm;

^{13}C-NMR (500 MHz, DMSO-d_6) = δ 171.7 (CO), 166.0 (CO), 164.6 (CO), 164.5 (CO), 164.4 (CO), 164.3 (CO), 149.5 (C_{Ar}), 143.0 (C_{Ar}), 142.5 (C_{Ar}), 142.4 (C_{Ar}), 141.5 (C_{Ar}), 138.7 (C_{Ar}), 135.7 (C_{Ar}), 133.6 ($OCH_2C\mathit{H}CH_2$), 132.5 (C_{Ar}), 130.1 (C_{Ar}), 129.3 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 127.1 (C_{Ar}), 126.0 (C_{Ar}), 123.6 (C_{Ar}), 119.5 (C_{Ar}), 118.9 (C_{Ar}), 118.8 (C_{Ar}), 118.7 (C_{Ar}), 118.3 ($OCH_2CH\mathit{C}H_2$), 117.8 (CN), 114.0 (C_{Ar}), 80.3 ($\mathit{C}(CH_3)_3$), 76.2 ($\mathit{C}H(CH_3)_2$), 74.3 (OCH_2), 55.3 (CHNH), 36.3 ($CH\mathit{C}H_2CH$), 27.9 ($C(\mathit{C}H_3)_3$), 22.3 ($CH(\mathit{C}H_3)_2$), 8.2 ($\mathit{C}H(CH_2)_2$), 4.7 ($CH(\mathit{C}H_2)_2$), 4.0 ($CH(\mathit{C}H_2)_2$) ppm;

HRMS (ESI) calculated for $C_{52}H_{52}N_6O_9Na$ $[M+Na]^+$: 927.3693; found: 927.3712.

tert-Butyl (*S*)-4-(4-(4-(2-(4-(4-cyanobenzamido)benzamido)-3-cyclopropylpropanamido) benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**154**)



Allyl ether **148** (374 mg, 0.41 mmol) was dissolved in THF (18 mL). Aniline (124 µL, 1.36 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (47.7 mg, 0.04 mmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 2 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 2%, 5%) to furnish product **154** (286 mg, 0.33 mmol, 80%) as yellow amorphous solid.

R_f (2% MeOH in CH_2Cl_2) = 0.23;

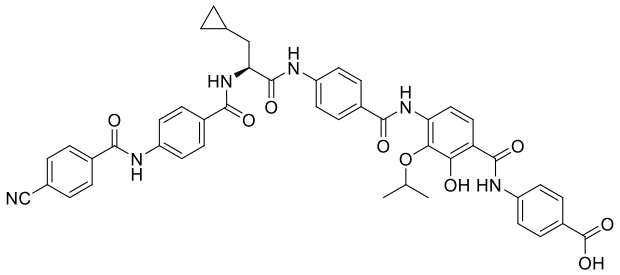
$[\alpha]_D^{22}$ = -10.2 ° (c 0.3, MeOH);

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 12.29 (s, 1H, OH), 10.69 (s, 1H, NH), 10.62 (bs, 1H, NH), 10.48 (s, 1H, NH), 9.39 (s, 1H, NH), 8.62-8.61 (d, *J* = 7.4 Hz, 1H, CHN*H*), 8.14-8.12 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 8.05-8.04 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.98-7.95 (m, 4H, H_{Ar}), 7.93-7.92 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.90-7.88 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.86-7.84 (m, 3H, H_{Ar}), 7.82-7.81 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.71-7.70 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 4.71-4.68 (q, *J* = 7.5 Hz, 1H, C*H*NH), 4.57-4.53 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 1.96-1.91 (m, 1H, CHC*H*$_2$CH), 1.60-1.58 (m, 1H, CHC*H*$_2$CH), 1.55 (s, 9H, C$(CH_3)_3$), 1.27-1.26 (dd, *J* = 1.7, 6.1 Hz, 6H, CH(C*H*$_3$)$_2$), 0.91-0.87 (m, 1H, C*H*$(CH_2)_2$), 0.49-0.38 (m, 2H, CH(C*H*$_2$)$_2$), 0.25-0.13 (m, 2H, CH(C*H*$_2$)$_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 171.7 (CO), 168.5 (CO), 166.0 (CO), 164.5 (CO), 164.4 (CO), 164.2 (CO), 154.1 (C_{Ar}), 142.5 (C_{Ar}), 142.0 (C_{Ar}), 141.5 (C_{Ar}), 138.7 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 132.5 (C_{Ar}), 129.9 (C_{Ar}), 129.3 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 126.8 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.5 (C_{Ar}), 118.8 (C_{Ar}), 118.3 (CN), 114.0 (C_{Ar}), 112.4 (C_{Ar}), 112.1 (C_{Ar}), 80.5 (*C*$(CH_3)_3$), 74.8 (*C*H$(CH_3)_2$), 55.3 (CHNH), 36.3 (CH*C*H$_2$CH), 27.8 (C(*C*H$_3$)$_3$), 22.3 (CH(*C*H$_3$)$_2$), 8.1 (*C*H$(CH_2)_2$), 4.6 (CH(*C*H$_2$)$_2$), 4.0 (CH(*C*H$_2$)$_2$) ppm;

HRMS (ESI) calculated for $C_{49}H_{48}N_6O_9Na$ $[M+Na]^+$: 887.3380; found: 887.3381.

(*S*)-4-(4-(4-(2-(4-(4-Cyanobenzamido)benzamido)-3-cyclopropylpropanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **DK405**



tert-Butyl ester **154** (250 mg, 0.29 mmol) was dissolved in precooled TFA (10 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0°C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **DK405** (205 mg, 0.25 mmol, 88%) as colorless amorphous solid.

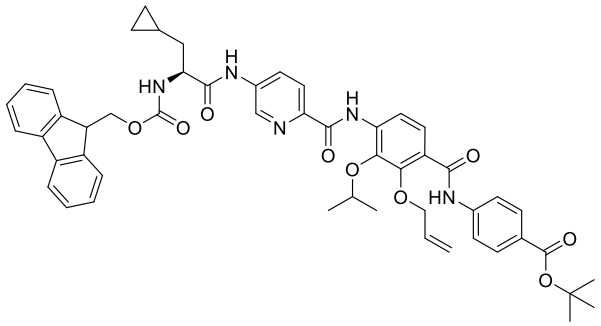
$[\alpha]_D^{22}$ = +3.8 ° (c 0.1, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 12.82 (bs, 1H, CO_2H), 12.29 (s, 1H, OH), 10.69 (s, 1H, NH), 10.60 (s, 1H, NH), 10.48 (s, 1H, NH), 9.40 (s, 1H, NH), 8.62-8.61 (d, *J* = 7.4 Hz, 1H, CHN*H*), 8.14-8.12 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 8.06-8.04 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.98-7.95 (m, 6H, H_{Ar}), 7.90-7.88 (d, *J* = 9.1 Hz, 2H, H_{Ar}), 7.86-7.84 (m, 3H, H_{Ar}), 7.82-7.81 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.72-7.70 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 4.71-4.68 (q, *J* = 6.9 Hz, 1H, C*H*NH), 4.58-4.52 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 1.96-1.91 (m, 1H, CHC*H*$_2$CH), 1.60-1.55 (m, 1H, CHC*H*$_2$CH), 1.27-1.26 (dd, *J* = 1.5, 6.1 Hz, 6H, CH(C*H*$_3$)$_2$), 0.90-0.87 (m, 1H, C*H*$(CH_2)_2$), 0.49-0.37 (m, 2H, CH(C*H*$_2$)$_2$), 0.25-0.13 (m, 2H, CH(C*H*$_2$)$_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = 171.7 (CO), 168.5 (CO), 166.9 (CO), 166.0 (CO), 164.4 (CO), 164.2 (CO), 154.1 (C_{Ar}), 142.5 (C_{Ar}), 142.0 (C_{Ar}), 141.5 (C_{Ar}), 138.7 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 132.5 (C_{Ar}), 130.2 (C_{Ar}), 129.2 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 126.3 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.5 (C_{Ar}), 118.8 (C_{Ar}), 118.3 (CN), 114.0 (C_{Ar}), 112.4 (C_{Ar}), 112.2 (C_{Ar}), 74.9 (*C*H$(CH_3)_2$), 55.3 (CHNH), 36.3 (CH*C*H$_2$CH), 22.3 (CH(*C*H$_3$)$_2$), 8.1 (*C*H$(CH_2)_2$), 4.6 (CH(*C*H$_2$)$_2$), 4.0 (CH(*C*H$_2$)$_2$) ppm;

HRMS (ESI) calculated for $C_{45}H_{39}N_6O_9$ $[M-H]^-$: 807.2779; found: 807.2767.

tert-Butyl (*S*)-4-(4-(5-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-cyclopropyl propanamido)picolinamido)-2-(allyloxy)-3-isopropoxybenzamido)benzoate (**131**)



Amine **114** (200 mg, 0.37 mmol) and amino acid **117** (180 mg, 0.51 mmol, 1.40 equiv.) were dissolved in EtOAc (800 µL) and pyridine (90 µL, 1.10 mmol, 3.00 equiv.) was added. T3P (50% in EtOAc, 392 µL, 0.66 mmol, 1.80 equiv.) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 2 h. H_2O was added and the aq. phase was extracted with EtOAc (3x). The combined organic phases were washed with a sat. $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (dry load, PE/EtOAc = 1:1) to furnish product **131** (313 mg, 0.36 mmol, 97%) as yellow amorphous solid.

R_f (PE/EtOAc = 1:1) = 0.63;

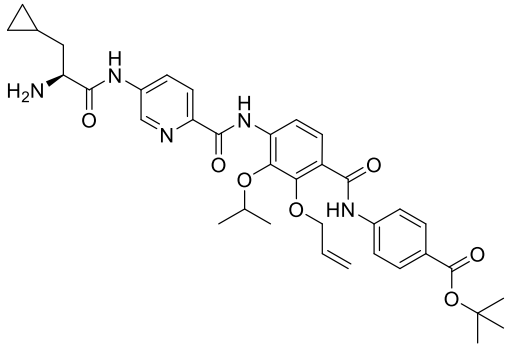
$[\alpha]_D^{21}$ = -2.7 ° (c 0.2, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 10.68 (s, 1H, NH), 10.67 (s, 1H, NH), 10.48 (s, 1H, NH), 9.02-8.98 (m, 1H, H_{Ar}), 8.35-8.33 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 8.30-8.28 (dd, *J* = 2.3, 8.6 Hz, 1H, H_{Ar}), 8.19-8.18 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 7.90-7.88 (m, 4H, H_{Ar}), 7.84-7.82 (m, 3H, H_{Ar}), 7.76-7.74 (t, *J* = 7.7 Hz, 2H, H_{Ar}), 7.49-7.47 (d, *J* = 8.6 Hz, 1H, NH), 7.43-7.40 (td, *J* = 3.3, 7.4 Hz, 2H, H_{Ar}), 7.34-7.32 (t, *J* = 7.4 Hz, 2H, H_{Ar}),6.05-5.99 (m, 1H, C*H*CH_2), 5.40-4.37 (dq, *J* = 1.6, 17.2 Hz, 1H, CHC*H*$_2$), 5.22-5.20 (dq, *J* = 1.6, 10.5 Hz, 1H, CHC*H*$_2$), 4.67-4.63 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.62-4.61 (d, *J* = 5.5 Hz, 2H, OC*H*$_2$CH), 4.34-4.23 (m, 4H, C*H*NH, C(O)OC*H*$_2$CH, C(O)OCH$_2$C*H*), 1.81-1.76 (m, 1H, NHCHC*H*$_2$), 1.55 (s, 9H, C$(CH_3)_3$), 1.48-1.44 (m, 1H, NHCHC*H*$_2$), 1.37-1.35 (dd, *J* = 6.2, 8.8 Hz, 6H, CH(C*H*$_3$)$_2$), 0.86-9.81 (m, 1H, C*H*$(CH_2)_3$), 0.47-0.37 (m, 2H, $(CH_2)_2$), 0.19-0.09 (m, 2H, $(CH_2)_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = 172.3 (CO), 164.6 (CO), 164.3 (CO), 161.1 (CO), 156.1 (CO), 149.3 (C_{Ar}), 143.8 (d, *J* = 10.8 Hz, C_{Ar}), 143.3 (C_{Ar}), 143.0 (C_{Ar}), 140.7 (C_{Ar}), 139.4 (C_{Ar}), 139.3-138.8 (d, *J* = 75.1 Hz, C_{Ar}), 135.5 (C_{Ar}), 133.5 (*C*HCH_2), 130.1 (C_{Ar}), 127.6 (d, *J* = 3.4 Hz, C_{Ar}), 127.1 (C_{Ar}), 126.0-125.8 (d, *J* = 36.8 Hz, C_{Ar}), 125.3 (C_{Ar}), 124.6 (C_{Ar}), 122.9 (C_{Ar}), 120.1 (d, *J* = 2.1 Hz, C_{Ar}), 118.8 (C_{Ar}), 118.0 (CH*C*H_2), 113.8 (C_{Ar}), 80.3 (*C*$(CH_3)_3$), 76.3 (O*C*H_2CH), 74.3 (*C*H$(CH_3)_2$), 65.7 (C(O)O*C*H_2CH), 56.2 (NHCH), 46.7 (C(O)OCH$_2$*C*H), 36.4 (NHCH*C*H_2), 27.9 (C(*C*$H_3)_3$), 22.3 (d, *J* = 9.2 Hz, CH(*C*$H_3)_2$), 7.9 (*C*H$(CH_2)_3$), 4.6 ($(CH_2)_2$), 3.9 ($(CH_2)_2$) ppm;

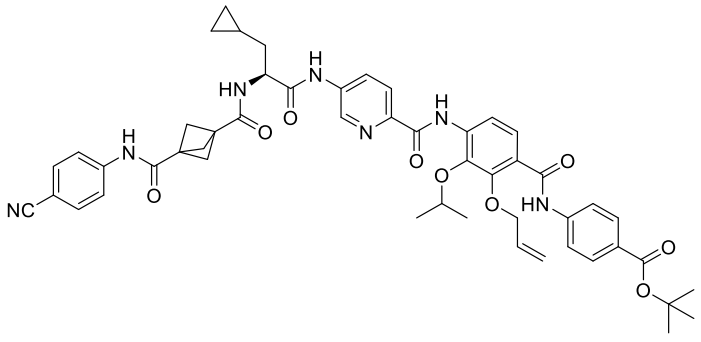
HRMS (ESI) calculated for $C_{51}H_{53}N_5O_9Na$ $[M+Na]^+$: 902.3741; found: 902.3748.

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(5-(2-amino-3-cyclopropylpropanamido)picolinamido)-3-isopropoxybenzamido)benzoate (**186**)



Carbamate **131** (305 mg, 0.35 mmol) was dissolved in MeCN (4 mL) and piperidine (1 mL) was added. The mixture was stirred at rt for 90 min, before it was concentrated under reduced pressure. The residue was coevaporated with MeCN (3x). Th crude product was used in the next step without further purification.

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(5-(2-(3-((4-cyanophenyl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxamido)-3-cyclopropylpropanamido)picolinamido)-3-isopropoxybenzamido)benzoate (**193**)



DIPEA (435 µL, 2.49 mmol, 5.00 equiv.) was added dropwise to a stirred solution of HATU (473 mg, 1.24 mmol, 2.50 equiv.) and carboxylic acid **43** (331 mg, 1.24 mmol, 2.50 equiv.) in DMF (12 mL). The solution was stirred for 30 min and was then transferred to a stirred solution of amine **186** (327 mg, 0.50 mmol) in DMF (7 mL). The reaction mixture was stirred at rt for 19 h. The mixture was diluted with EtOAc and washed with a 0.1 M HCl solution, brine, dried

over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 1%, 5%) to furnish product **193** (405 mg, 0.45 mmol, 90%) as yellow amorphous solid.

R_f (3% MeOH in CH_2Cl_2) = 0.19;

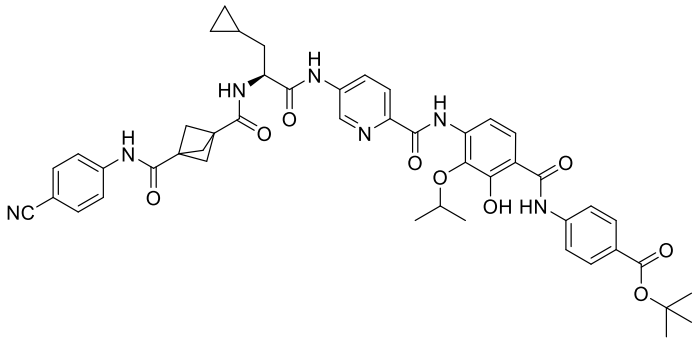
$[\alpha]_D^{21}$ = +1.3 ° (c 0.3, MeOH);

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 10.73 (s, 1H, NH), 10.68 (s, 1H, NH), 10.48 (s, 1H, NH), 9.99 (s, 1H, NH), 8.99-8.98 (d, *J* = 2.3 Hz, 1H, H_{Ar}), 8.36-8.33 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 8.31-8.28 (dd, *J* = 2.4, 8.7 Hz, 2H, H_{Ar}), 8.20-8.18 (m, 2H, NH, H_{Ar}), 7.90-7.77 (m, 8H, H_{Ar}), 7.49-7.47 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 6.07-5.97 (m, 1H, OCH_2CHCH_2), 5.41-5.36 (dq, *J* = 1.7, 17.2 Hz, 1H, OCH_2CHCH_2), 5.23-5.20 (dq, *J* = 1.7, 10.5 Hz, 1H, OCH_2CHCH_2), 4.68-4.61 (m, 3H, $CH(CH_3)_2$, OCH_2CH), 4.59-4.53 (m, 1H, CHNH), 2.28 (s, 6H, CCH_2C), 1.79-1.57 (m, 2H, $NHCHCH_2$), 1.55 (s, 9H, $C(CH_3)_3$), 1.38-1.35 (t, *J* = 6.2 Hz, 6H, $CH(CH_3)_2$), 0.85-0.73 (m, 1H, $CH(CH_2)_3$), 0.48-0.34 (m, 2H, $(CH_2)_2$), 0.22-0.06 (m, 2H, $(CH_2)_2$) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 171.8 (CO), 168.9 (CO), 168.6 (CO), 164.6 (CO), 164.3 (CO), 161.1 (CO), 149.3 (C_{Ar}), 143.3 (C_{Ar}), 143.0 (C_{Ar}), 142.9 (C_{Ar}), 139.4 (C_{Ar}), 139.3 (C_{Ar}), 138.8 (C_{Ar}), 135.5 (C_{Ar}), 133.5 (OCH_2CHCH_2), 133.1 (C_{Ar}), 130.1 (C_{Ar}), 127.1 (C_{Ar}), 126.0 (C_{Ar}), 125.8 (C_{Ar}), 124.6 (C_{Ar}), 122.9 (C_{Ar}), 119.7 (C_{Ar}), 119.0 (CN), 118.8 (C_{Ar}), 118.0 (OCH_2CHCH_2), 113.8 (C_{Ar}), 105.3 (C_{Ar}), 80.3 ($C(CH_3)_3$), 76.3 (OCH_2CH), 74.3 ($CH(CH_3)_2$), 54.2 (NHCH), 51.7 (CCH_2C), 38.9 (CCH_2C), 37.9 (CCH_2C), 36.2 ($NHCHCH_2$), 27.8 ($C(CH_3)_3$), 22.3 (d, *J* = 6.6 Hz, $CH(CH_3)_2$), 7.9 ($CH(CH_2)_3$), 4.5 ($(CH_2)_2$), 3.9 ($(CH_2)_2$) ppm;

HRMS (ESI) calculated for $C_{50}H_{53}N_7O_9Na$ $[M+Na]^+$: 918.3802; found: 918.3809.

tert-Butyl (*S*)-4-(4-(5-(2-(3-((4-cyanophenyl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxamido)-3-cyclopropylpropanamido)picolinamido)-2-hydroxy-3-isopropoxybenzamido) benzoate (**202**)



Allyl ether **193** (263 mg, 0.29 mmol) was dissolved in THF (13 mL). Aniline (88 µL, 0.97 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (33.9 mg, 0.03 mmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 4 h. The mixture was concentrated

under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 2%, 4%) to furnish product **202** (220 mg, 0.26 mmol, 88%) as yellow amorphous solid.

R_f (5% MeOH in CH_2Cl_2) = 0.31;

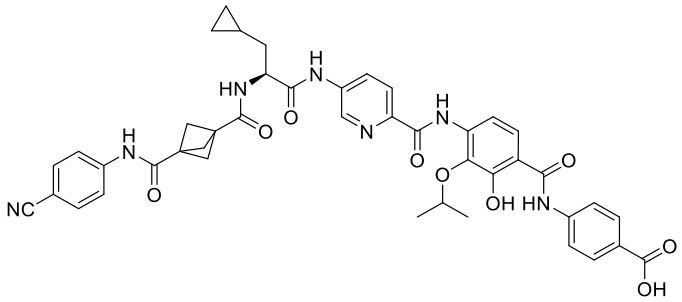
$[\alpha]_D^{22}$ = +1.4 ° (c 0.3, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 12.45 (s, 1H, OH), 10.74 (s, 1H, NH), 10.73 (s, 1H, NH), 10.61 (bs, 1H, NH), 9.99 (s, 1H, NH), 8.98 (d, *J* = 2.3 Hz, 1H, H_{Ar}), 8.31-8.29 (dd, *J* = 2.4, 8.6 Hz, 2H, H_{Ar}), 8.20-8.18 (m, 2H, NH, H_{Ar}), 8.11-8.10 (d, *J* = 8.8 Hz, 1H, H_{Ar}), 7.94-7.90 (m, 3H, H_{Ar}), 7.87-7.85 (m, 4H, H_{Ar}), 7.79-7.77 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 4.70-4.64 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.59-4.54 (m, 1H, C*H*NH), 2.28 (s, 6H, CCH_2C), 1.78-1.57 (m, 2H, NHCHC*H*$_2$), 1.55 (s, 9H, C$(CH_3)_3$), 1.36-1.33 (dd, *J* = 6.1, 9.8 Hz, 6H, CH(C*H*$_3)_2$), 0.81-0.76 (m, 1H, C*H*$(CH_2)_3$), 0.47-0.35 (m, 2H, $(CH_2)_2$), 0.21-0.07 (m, 2H, $(CH_2)_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 171.8 (CO), 168.9 (CO), 168.7 (CO), 168.6 (CO), 164.5 (CO), 161.3 (CO), 154.1 (C_{Ar}), 143.3 (C_{Ar}), 142.9 (C_{Ar}), 141.9 (C_{Ar}), 139.3 (C_{Ar}), 138.8 (C_{Ar}), 136.8 (C_{Ar}), 134.0 (C_{Ar}), 133.1 (C_{Ar}), 129.9 (C_{Ar}), 127.1 (C_{Ar}), 126.9 (C_{Ar}), 123.5 (C_{Ar}), 123.0 (C_{Ar}), 120.8 (C_{Ar}), 119.7 (C_{Ar}), 119.0 (CN), 111.6 (C_{Ar}), 108.3 (C_{Ar}), 105.3 (C_{Ar}), 80.5 (*C*$(CH_3)_3$), 74.3 (*C*H$(CH_3)_2$), 54.2 (NHCH), 51.7 (C*C*H_2C), 38.9 (*C*CH_2C), 37.9 (*C*CH_2C), 36.3 (NHCH*C*H_2), 27.8 (C(*C*$H_3)_3$), 22.3 (d, *J* = 10.3 Hz, CH(*C*$H_3)_2$), 7.9 (*C*H$(CH_2)_3$), 4.5 ($(CH_2)_2$), 3.9 ($(CH_2)_2$) ppm;

HRMS (ESI) calculated for $C_{47}H_{49}N_7O_9Na$ $[M+Na]^+$: 878.3489; found: 878.3491.

(*S*)-4-(4-(5-(2-(3-((4-Cyanophenyl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxamido)-3-cyclopropylpropanamido)picolinamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSF54**



tert-Butyl ester **202** (216 mg, 0.25 mmol) was dissolved in precooled TFA (13 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0°C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSF54** (215 mg, 0.25 mmol, quant.) as yellow amorphous solid.

$[\alpha]_D^{22}$ = +1.5 ° (c 0.2, MeOH);

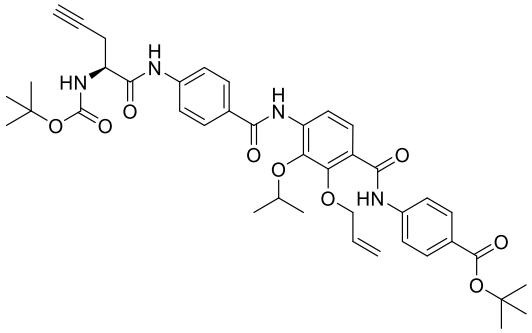
^{1}H-NMR (600 MHz, DMSO-d_6) = δ 12.83 (bs, 1H, CO_2H), 12.45 (s, 1H, OH), 10.74 (s, 1H, NH), 10.73 (s, 1H, NH), 10.61 (s, 1H, NH), 10.00 (s, 1H, NH), 8.98 (d, *J* = 2.4 Hz, 1H, H_{Ar}), 8.31-8.29 (dd, *J* = 2.3, 8.6 Hz, 2H, H_{Ar}), 8.20-8.18 (m, 2H, NH, H_{Ar}), 8.12-8.10 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 7.98-7.96 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.92-7.91 (d, *J* = 9.2 Hz, 1H, H_{Ar}), 7.87-7.85 (m, 4H, H_{Ar}), 7.79-7.77 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 4.71-4.65 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 4.57-4.54 (m, 1H, C*H*NH), 2.28 (s, 6H, CCH_2C), 1.78-1.55 (m, 2H, NHCHC*H*$_2$), 1.36-1.33 (dd, *J* = 6.1, 9.8 Hz, 6H, $CH(CH_3)_2$), 0.81-0.75 (m, 1H, C*H*$(CH_2)_3$), 0.47-0.35 (m, 2H, $(CH_2)_2$), 0.21-0.07 (m, 2H, $(CH_2)_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 171.8 (CO), 168.9 (CO), 168.7 (CO), 168.6 (CO), 166.9 (CO), 161.3 (CO), 154.1 (C_{Ar}), 143.3 (C_{Ar}), 142.9 (C_{Ar}), 141.9 (C_{Ar}), 139.3 (C_{Ar}), 138.8 (C_{Ar}), 136.8 (C_{Ar}), 134.0 (C_{Ar}), 133.1 (C_{Ar}), 130.2 (C_{Ar}), 127.1 (C_{Ar}), 126.3 (C_{Ar}), 123.5 (C_{Ar}), 123.0 (C_{Ar}), 120.8 (C_{Ar}), 119.7 (C_{Ar}), 119.0 (CN), 111.6 (C_{Ar}), 108.4 (C_{Ar}), 105.3 (C_{Ar}), 74.8 (*C*$H(CH_3)_2$), 54.2 (NHCH), 51.7 (C*C*H_2C), 38.9 (*C*CH_2C), 37.9 (*C*CH_2C), 36.3 (NHCH*C*H_2), 27.8 (C(*C*$H_3)_3$), 22.3 (d, *J* = 10.3 Hz, CH(*C*$H_3)_2$), 7.9 (*C*$H(CH_2)_3$), 4.5 (($CH_2)_2$), 3.9 (($CH_2)_2$) ppm;

HRMS (ESI) calculated for $C_{43}H_{40}N_7O_9$ $[M-H]^-$: 798.2888; found: 798.2889.

4.2.6 (*S*)-2-Aminopent-4-ynoic acid derivatives

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(4-(2-((*tert*-butoxycarbonyl)amino)pent-4-ynamido) benzamido)-3-isopropoxybenzamido)benzoate (**128**)



Amine **5** (700 mg, 1.28 mmol), acid **116** (328 mg, 1.54 mmol, 1.20 equiv.) and DIPEA (700 µL, 4.00 mmol, 3.10 equiv.) were dissolved in DMF (10 mL). T3P (50% in DMF, 1.63 g, 2.57 mmol, 2.00 equiv.) was added at 0 °C. The mixture was stirred for 21 h while warming to rt. EtOAc was added and the organic phase was washed with a 1 M HCl solution, a sat. $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The

residue was purified by column chromatography (dry load, PE/EtOAc = 3:2) to furnish product **128** (355 mg, 0.65 mmol, 50%) as yellow amorphous solid.

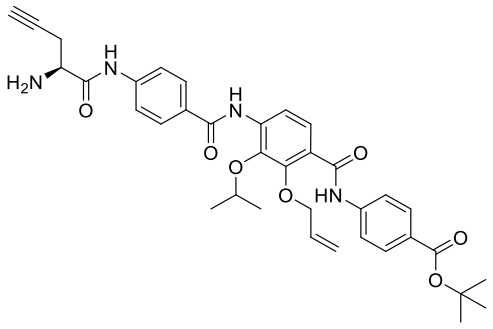
[α]$_D^{22}$ = -1.3 ° (c 1.4, MeOH);

^{1}H-NMR (400 MHz, DMSO-d$_6$) = δ 10.53 (s, 1H, NH), 10.42 (s, 1H, NH), 9.52 (s, 1H, NH), 7.99-7.97 (d, *J* = 8.8 Hz, 2H, H$_{Ar}$), 7.90-7.88 (d, *J* = 8.7 Hz, 2H, H$_{Ar}$), 7.84-7.80 (m, 3H, H$_{Ar}$), 7.79-7.77 (d, *J* = 8.5 Hz, 2H, H$_{Ar}$), 7.42-7.40 (d, *J* = 8.5 Hz, 1H, H$_{Ar}$), 7.23-7.21 (d, *J* = 7.9 Hz, 1H, NHBoc), 6.07-5.97 (m, 1H, OCH$_2$C*H*CH$_2$), 5.40-5.35 (dq, *J* = 1.7, 17.2 Hz, 1H, OCH$_2$CHC*H*$_2$), 5.22-5.18 (dq, *J* = 1.3, 10.5 Hz, 1H, OCH$_2$CHC*H*$_2$), 4.61-4.60 (d, *J* = 5.5 Hz, 2H, OC*H*$_2$CHCH$_2$), 4.54-4.45 (sept, *J* = 6.1 Hz, 1H, C*H*(CH$_3$)$_2$), 4.32-4.27 (q, *J* = 7.8 Hz, 1H, C*H*NH$_2$), 2.92-2.90 (t, *J* = 2.3 Hz, 1H, CH$_2$CC*H*), 2.65-2.56 (m, 2H, C*H*$_2$CCH), 1.55 (s, 9H, C(CH$_3$)$_3$), 1.40 (s, 9H, (CH$_3$)$_{3Boc}$), 1.27-1.25 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3$)$_2$) ppm;

^{13}C-NMR (101 MHz, DMSO-d$_6$) = 169.9 (CO), 164.6 (CO), 164.5 (CO), 164.3 (CO), 155.2 (CO), 149.5 (C$_{Ar}$), 143.0 (C$_{Ar}$), 142.5 (C$_{Ar}$), 142.1 (C$_{Ar}$), 135.6 (C$_{Ar}$), 133.6 (OCH$_2$*C*HCH$_2$), 130.1 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.5 (C$_{Ar}$), 127.1 (C$_{Ar}$), 126.0 (C$_{Ar}$), 123.6 (C$_{Ar}$), 119.0 (C$_{Ar}$), 118.8 (C$_{Ar}$), 118.8 (OCH$_2$CH*C*H$_2$), 117.8 (CN), 80.5 (*C*(CH$_3$)$_3$), 80.3 (CH$_2$*C*CH), 78.4 (*C*(CH$_3$)$_{3Boc}$), 76.2 (*C*H(CH$_3$)$_2$), 74.3 (O*C*H$_2$CH*C*H$_2$), 73.2 (CH$_2$C*C*H), 54.1 (CHNH$_2$), 28.2 ((CH$_3$)$_{3Boc}$), 27.9 (C(*C*H$_3$)$_3$), 22.3 (CH(*C*H$_3$)$_2$) 21.7 (*C*H$_2$CCH) ppm;

HRMS (ESI) calculated for C$_{41}$H$_{48}$N$_4$O$_9$Na [M+Na]$^+$: 763.3319; found: 763.3324.

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(4-(2-aminopent-4-ynamido)benzamido)-3-isopropoxy benzamido)benzoate (**184**)



Carbamate **128** (356 mg, 0.48 mmol) was dissolved in precooled HCl (4 M in 1,4-dioxane, 12.0 mL, 48.0 mmol, 100 equiv.) at 0 °C. The mixture was warmed up to rt and stirred for 15 min. The solution was transferred to a stirred suspension of EtOAc (320 mL) and a sat. NaHCO$_3$ solution (320 mL). The aq. phase was extracted with EtOAc (3x 160 mL) and the combined organic phases were washed with brine, dried over MgSO$_4$ and concentrated under reduced pressure to furnish amine **184** (248 mg, 0.39 mmol, 81%) as yellow amorphous solid.

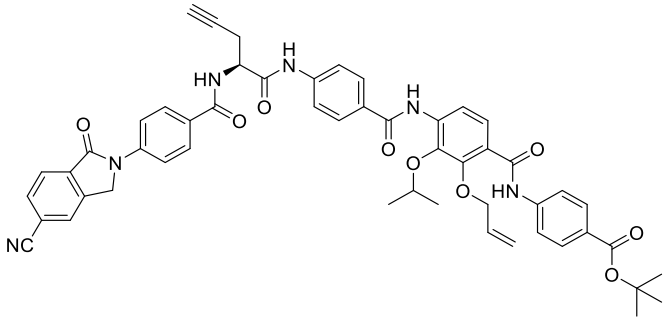
[α]$_D^{23}$ = -1.0 ° (c 0.2, MeOH);

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 10.53 (s, 1H, NH), 9.53 (s, 1H, NH), 7.99-7.97 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.90-7.88 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.84-7.80 (m, 5H, H_{Ar}), 7.41-7.39 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.06-5.98 (m, 1H, OCH_2CHCH_2), 5.40-5.35 (dq, *J* = 1.6, 17.2 Hz, 1H, OCH_2CHCH_2), 5.22-5.19 (dq, *J* = 1.3, 10.5 Hz, 1H, OCH_2CHCH_2), 4.61-4.60 (d, *J* = 5.3 Hz, 2H, OCH_2CHCH_2), 4.53-4.46 (sept, *J* = 6.1 Hz, 1H, $CH(CH_3)_2$), 3.58-3.55 (m, 1H, $CHNH_2$), 2.88-2.87 (t, *J* = 2.3 Hz, 1H, CH_2CCH), 2.59-2.51 (m, 2H, CH_2CCH), 1.55 (s, 9H, $C(CH_3)_3$), 1.27-1.25 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 166.9 (CO), 164.6 (CO), 164.5 (CO), 164.3 (CO), 149.5 (C_{Ar}), 143.0 (C_{Ar}), 142.6 (C_{Ar}), 142.0 (C_{Ar}), 135.6 (C_{Ar}), 133.7 (OCH_2CHCH_2), 130.4 (C_{Ar}), 130.1 (C_{Ar}), 128.4 (C_{Ar}), 128.4 (C_{Ar}), 127.1 (C_{Ar}), 126.0 (C_{Ar}), 123.6 (C_{Ar}), 119.0 (C_{Ar}), 118.8 (C_{Ar}), 118.7 (OCH_2CHCH_2), 117.8 (CN), 81.1 ($C(CH_3)_3$), 80.3 (CH_2CCH), 76.2 ($CH(CH_3)_2$), 74.3 (OCH_2CHCH_2), 73.2 (CH_2CCH), 54.6 ($CHNH_2$), 27.9 ($C(CH_3)_3$), 24.7 (CH_2CCH), 22.3 ($CH(CH_3)_2$) ppm;

HRMS (ESI) calculated for $C_{36}H_{41}N_4O_7$ $[M+H]^+$: 641.2975; found: 641.2982.

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(4-(2-(4-(5-cyano-1-oxoisoindolin-2-yl)benzamido)pent-4-ynamido)benzamido)-3-isopropoxybenzamido)benzoate (**190**)



Amine **184** (108 mg, 0.17 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (1.7 mL) and NMM (37 µL, 0.34 mmol, 2.00 equiv.) was added. Chloride **280** (50.0 mg, 0.17 mmol) was added at 0 °C and the suspension was stirred for 20 h while warming to rt. The solvent was removed under reduced pressure and the residue purified by column chromatography (dry load, MeOH in CH2Cl2 = 1%, 2%) to furnish product **190** (62.6 mg, 0.07 mmol, 41%) as colorless amorphous solid.

R_f (3% MeOH in CH_2Cl_2) = 0.21;

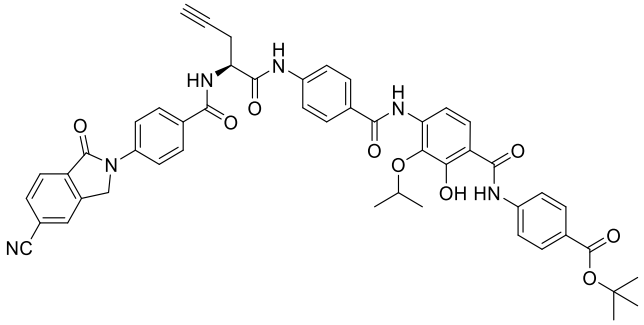
$[\alpha]_D^{22}$ = +0.35 ° (c 0.5, THF);

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 10.57 (s, 1H, NH), 10.53 (s, 1H, NH), 9.53 (s, 1H, NH), 8.85-8.83 (d, *J* = 7.5 Hz, 1H, CHN*H*), 8.24 (s, 1H, H_{Ar}), 8.07-8.02 (m, 5H, H_{Ar}), 8.00-7.98 (m, 3H, H_{Ar}), 7.90-7.88 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.84-7.80 (m, 5H, H_{Ar}), 7.41-7.40 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.06-5.98 (m, 1H, OCH_2CHCH_2), 5.39-5.35 (dd, *J* = 1.6, 17.2 Hz, 1H, OCH_2CHCH_2), 5.21-5.19 (dd, *J* = 1.4, 10.5 Hz, 1H, OCH_2CHCH_2), 5.17 (s, 2H, NCH_2), 4.84-4.79 (m, 1H, C*H*NH), 4.61-4.60 (d, *J* = 5.4 Hz, 2H, OCH_2CHCH_2), 4.53-4.46 (sept, *J* = 6.1 Hz, 1H, $CH(CH_3)_2$), 2.95-2.94 (t, *J* = 2.5 Hz, 1H, CH_2CCH), 2.85-2.74 (m, 2H, CH_2CCH), 1.55 (s, 9H, $C(CH_3)_3$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 169.7 (CO), 165.8 (CO), 165.5 (CO), 164.6 (CO), 164.5 (CO), 164.3 (CO), 149.5 (C_{Ar}), 143.0 (C_{Ar}), 142.6 (C_{Ar}), 142.1 (C_{Ar}), 141.7 (C_{Ar}), 141.7 (C_{Ar}), 136.1 (C_{Ar}), 135.6 (C_{Ar}), 133.7 (OCH_2CHCH_2), 133.4 (C_{Ar}), 130.1 (C_{Ar}), 129.3 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 128.5 (C_{Ar}), 127.7 (C_{Ar}), 127.1 (C_{Ar}), 126.0 (C_{Ar}), 124.4 (C_{Ar}), 123.6 (C_{Ar}), 119.0 (C_{Ar}), 118.9 (C_{Ar}), 118.8 (C_{Ar}), 118.5 (C_{Ar}), 118.4 (OCH_2CHCH_2), 117.8 (CN), 114.5 (C_{Ar}), 80.6 (CH_2CCH), 80.3 ($C(CH_3)_3$), 76.3 (OCH_2CHCH_2), 74.3 ($CH(CH_3)_2$), 73.2 (CH_2CCH), 53.5 (CHNH), 50.4 (NCH_2), 27.9 ($C(CH_3)_3$), 22.3 ($CH(CH_3)_2$), 21.4 (CH_2CCH) ppm;

HRMS (ESI) calculated for $C_{52}H_{48}N_6O_9Na$ $[M+Na]^+$: 923.3380; found: 923.3376.

tert-Butyl (*S*)-4-(4-(4-(2-(4-(5-cyano-1-oxoisoindolin-2-yl)benzamido)pent-4-ynamido) benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**199**)

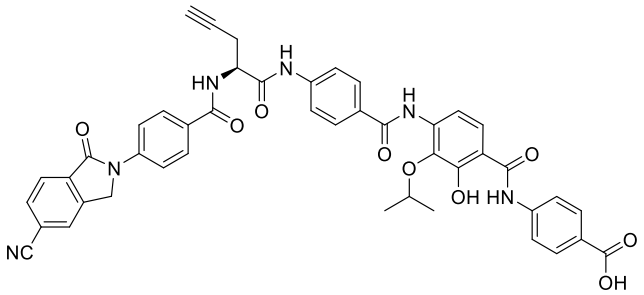


Allyl ether **190** (60.4 mg, 0.07 mmol) was dissolved in THF (3.3 mL). Aniline (20 µL, 0.22 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (7.8 mg, 7 µmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 2 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH in CH_2Cl_2 = 1%, 2%) to furnish product **199** (36.0 mg, 0.04 mmol, 56%, 90% purity) as orange amorphous solid, which contained triphenylphosphinoxide as impurity. The compound was used in the next step without further purification.

R_f (5% MeOH in CH_2Cl_2) = 0.33;

HRMS (ESI) calculated for $C_{49}H_{44}N_6O_9Na$ $[M+Na]^+$: 883.3067; found: 883.3053.

(*S*)-4-(4-(4-(2-(4-(5-Cyano-1-oxoisoindolin-2-yl)benzamido)pent-4-ynamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSD18**



tert-Butyl ester **199** (31.0 mg, 0.04 mmol) was dissolved in precooled TFA (1.8 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added and the precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSD18** (22.5 mg, 0.03 mmol, 78%) as colorless amorphous solid.

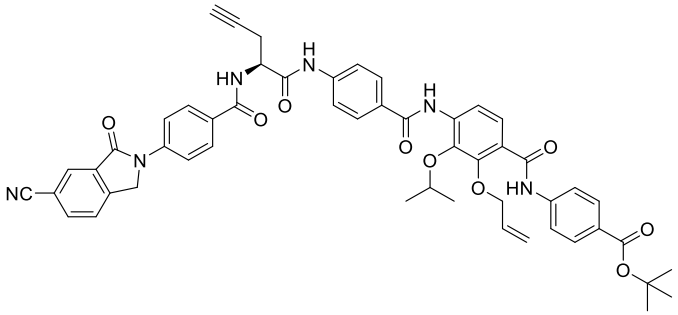
The measurement of optical rotation was not possible due to insolubility of compound **TSD18**.

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 12.82 (bs, 1H, CO_2H), 12.30 (s, 1H, OH), 10.60 (s, 1H, NH), 10.59 (s, 1H, NH), 9.41 (s, 1H, NH), 8.85-8.84 (d, *J* = 7.5 Hz, 1H, CHN*H*), 8.24 (s, 1H, H_{Ar}), 8.07-8.01 (m, 5H, H_{Ar}), 7.99-7.96 (m, 5H, H_{Ar}), 7.86-7.82 (m, 5H, H_{Ar}), 7.71-7.70 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 5.17 (s, 2H, NCH_2), 4.84-4.80 (m, 1H, C*H*NH), 4.57-4.51 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 2.94 (t, *J* = 2.5 Hz, 1H, CH_2CCH), 2.85-2.74 (m, 2H, CH_2CCH), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, CH(CH_3)$_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 169.7 (CO), 168.5 (CO), 166.9 (CO), 165.8 (CO), 165.5 (CO), 164.2 (CO), 154.1 (C_{Ar}), 142.2 (C_{Ar}), 142.0 (C_{Ar}), 141.7 (C_{Ar}), 141.7 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 136.1 (C_{Ar}), 132.4 (C_{Ar}), 130.2 (C_{Ar}), 129.3 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 127.7 (C_{Ar}), 126.3 (C_{Ar}), 124.4 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.0 (C_{Ar}), 118.5 (C_{Ar}), 118.4 (CN), 114.5 (C_{Ar}), 112.4 (C_{Ar}), 112.2 (C_{Ar}), 80.6 (CH_2CCH), 74.9 ($CH(CH_3)_2$), 73.2 (CH_2CCH), 53.5 (CHNH), 50.4 (NCH_2), 22.3 ($CH(CH_3)_2$), 21.4 (CH_2CCH) ppm;

HRMS (ESI) calculated for $C_{45}H_{35}N_6O_9$ $[M-H]^-$: 803.2466; found: 803.2458.

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(4-(2-(4-(6-cyano-1-oxoisoindolin-2-yl)benzamido)pent-4-ynamido)benzamido)-3-isopropoxybenzamido)benzoate (**191**)



Amine **184** (63.4 mg, 0.10 mmol) and NMM (22 µL, 0.20 mmol, 2.00 equiv.) were dissolved in CH_2Cl_2 (1 mL) and chloride **281** (29.4 mg, 0.10 mmol, 1.00 equiv.) was added at 0 °C. The mixture was stirred for 18 h while warming to rt. The solvent was removed under reduced pressure. The residue was washed with MeOH and the precipitate was filtered off and dried in vacuo to furnish product **191** (57.0 mg, 0.06 mmol, 64%) as beige amorphous solid.

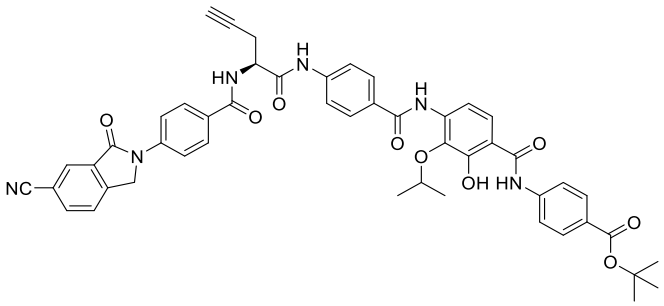
$[\alpha]_D^{23}$ = +23.8 ° (c 0.1, MeCN);

^{1}H-NMR (400 MHz, DMSO-d_6) = 10.58 (s, 1H, NH), 10.53 (s, 1H, NH), 9.53 (s, 1H, NH), 8.84-8.83 (d, *J* = 7.5 Hz, 1H, CHN*H*), 8.39 (s, 1H, H_{Ar}), 8.16-8.14 (dd, *J* = 1.5, 7.9 Hz, 1H, H_{Ar}), 8.05 (bs, 4H, H_{Ar}), 8.00-7.99 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.92-7.90 (d, *J* = 8.2 Hz, 1H, H_{Ar}), 7.90-7.88 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.84-7.81 (m, 5H, H_{Ar}), 7.41-7.40 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.06-5.98 (m, 1H, $OCH_2C\mathit{H}CH_2$), 5.39-5.35 (dq, *J* = 1.6, 17.2 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 5.21-5.19 (m, 4H, NCH_2, $OCH_2CHC\mathit{H}_2$), 4.84-4.79 (q, *J* = 7.0 Hz, 1H, C*H*NH), 4.61-4.60 (d, *J* = 5.5 Hz, 2H, $OC\mathit{H}_2CHCH_2$), 4.55-4.45 (sept, *J* = 6.1 Hz, 1H, $C\mathit{H}(CH_3)_2$), 2.94-2.93 (t, *J* = 2.6 Hz, 1H, $CH_2CC\mathit{H}$), 2.85-2.74 (m, 2H, $C\mathit{H}_2CCH$), 1.55 (s, 9H, $C(CH_3)_3$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, $CH(C\mathit{H}_3)_2$) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = 169.7 (CO), 165.8 (CO), 165.3 (CO), 164.6 (CO), 164.5 (CO), 164.3 (CO), 149.5 (C_{Ar}), 145.8 (C_{Ar}), 143.0 (C_{Ar}), 142.6 (C_{Ar}), 142.1 (C_{Ar}), 141.7 (C_{Ar}), 136.0 (C_{Ar}), 135.6 (C_{Ar}), 133.7 (C-33), 133.2 ($OCH_2\mathit{C}HCH_2$), 130.1 (C_{Ar}), 129.2 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 128.5 (C_{Ar}), 127.6 (C_{Ar}), 127.1 (C_{Ar}), 126.0 (C_{Ar}), 124.9 (C_{Ar}), 123.6 (C_{Ar}), 119.0 (C_{Ar}), 118.9 (C_{Ar}), 118.8 (C_{Ar}), 118.4 ($OCH_2CH\mathit{C}H_2$), 117.8 (CN), 111.4 (C_{Ar}), 80.6 ($CH_2\mathit{C}CH$), 80.3 ($\mathit{C}(CH_3)_3$), 76.3 ($O\mathit{C}H_2CHCH_2$), 74.3 ($\mathit{C}H(CH_3)_2$), 73.2 ($CH_2C\mathit{C}H$), 53.5 (CHNH), 50.9 (NCH_2), 27.9 ($C(\mathit{C}H_3)_3$), 22.3 ($CH(\mathit{C}H_3)_2$), 21.4 ($\mathit{C}H_2CCH$) ppm;

HRMS (ESI) calculated for $C_{52}H_{48}N_6O_9Na$ $[M+Na]^+$: 923.3380; found: 923.3359.

tert-Butyl (*S*)-4-(4-(4-(2-(4-(6-cyano-1-oxoisoindolin-2-yl)benzamido)pent-4-ynamido) benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**200**)



Allyl ether **191** (50.5 mg, 0.06 mmol) was dissolved in THF (2.5 mL). Aniline (17 µL, 0.19 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (6.5 mg, 6 µmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 3 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, 3% MeOH in CH_2Cl_2) to furnish product **200** (35.1 mg, 0.04 mmol, 73%) as yellow amorphous solid, which included small impurities. The product was used in the next step without further purification.

R_f (3% MeOH in CH_2Cl_2) = 0.26;

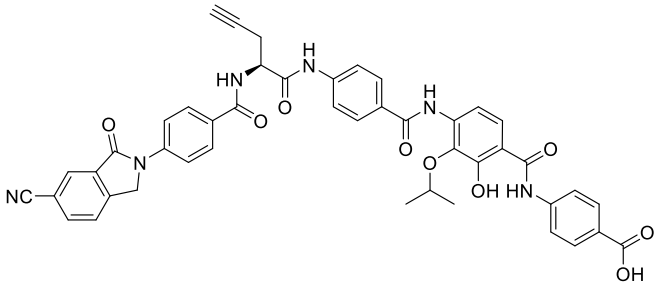
$[\alpha]_D^{23}$ = +41.0 ° (c 0.1, MeCN);

^{1}H-NMR (400 MHz, DMSO-d_6) = 12.28 (s, 1H, OH), 10.59 (bs, 2H, NH), 9.41 (s, 1H, NH), 8.85-8.83 (d, *J* = 7.5 Hz, 1H, CHN*H*), 8.29 (s, 1H, H_{Ar}), 8.16-8.14 (dd, *J* = 1.5, 7.9 Hz, 1H, H_{Ar}), 8.05 (bs, 4H, H_{Ar}), 7.98-7.95 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.94-7.90 (m, 4H, H_{Ar}), 7.86-7.84 (d, *J* = 9.0 Hz, 2H, H_{Ar}), 7.84-7.81 (d, *J* = 9.0 Hz, 2H, H_{Ar}), 7.70-7.68 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 5.22 (bs, 2H, NCH_2), 4.84-4.79 (q, *J* = 6.9 Hz, 1H, C*H*NH), 4.57-4.50 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 2.95-2.93 (t, *J* = 2.6 Hz, 1H, CH_2CCH), 2.86-2.74 (m, 2H, C*H*$_2$CCH), 1.55 (s, 9H, $C(CH_3)_3$), 1.27-1.26 (d, *J* = 6.2 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = 169.7 (CO), 168.5 (CO), 165.8 (CO), 165.3 (CO), 164.5 (CO), 164.2 (CO), 145.8 (C_{Ar}), 142.2 (C_{Ar}), 141.7 (C_{Ar}), 136.3 (C_{Ar}), 136.0 (C_{Ar}), 133.2 (C_{Ar}), 131.5 (C_{Ar}), 131.4 (C_{Ar}), 129.9 (C_{Ar}), 129.2 (C_{Ar}), 128.8 (C_{Ar}), 128.8 (C_{Ar}), 128.7 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 127.6 (C_{Ar}), 124.9 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.0 (C_{Ar}), 118.4 (C_{Ar}), 118.3 (CN), 113.8 (C_{Ar}), 111.4 (C_{Ar}), 80.6 (CH_2CCH), 80.5 ($C(CH_3)_3$), 74.8 ($CH(CH_3)_2$), 73.2 (CH_2CCH), 53.5 (CHNH), 50.9 (NCH_2), 27.8 ($C(CH_3)_3$), 22.3 ($CH(CH_3)_2$), 21.4 (CH_2CCH) ppm;

HRMS (ESI) calculated for $C_{49}H_{43}N_6O_9$ $[M-H]^-$: 859.3092; found: 859.3106.

(*S*)-4-(4-(4-(2-(4-(6-Cyano-1-oxoisoindolin-2-yl)benzamido)pent-4-ynamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSD49**



tert-Butyl ester **200** (33.5 mg, 0.04 mmol) was dissolved in precooled TFA (2 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0°C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSD49** (25.3 mg, 0.03 mmol, 81%) as yellow amorphous solid.

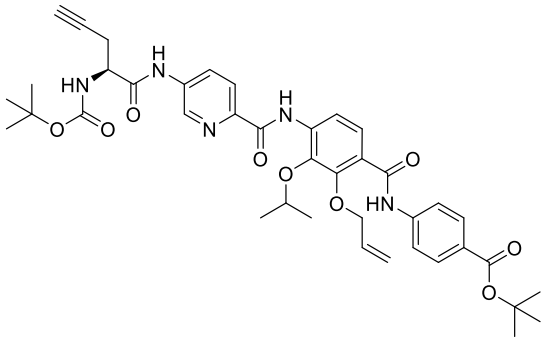
The measurement of optical rotation was not possible due to insolubility of compound **TSD49**.

^{1}H-NMR (400 MHz, DMSO-d_6) = 12.82 (s, 1H, CO_2H), 12.29 (s, 1H, OH), 10.60 (s, 1H, NH), 10.59 (s, 1H, NH), 9.41 (s, 1H, NH), 8.85-8.83 (d, *J* = 7.5 Hz, 1H, CHN*H*), 8.29 (s, 1H, H_{Ar}), 8.16-8.14 (dd, *J* = 1.5, 7.9 Hz, 1H, H_{Ar}), 8.05 (bs, 4H, H_{Ar}), 7.98-7.95 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 7.92-7.90 (d, *J* = 8.1 Hz, 2H, H_{Ar}), 7.87-7.81 (m, 6H, H_{Ar}), 7.71-7.69 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 5.21 (s, 2H, NCH_2), 4.85-4.79 (q, *J* = 7.2 Hz, 1H, C*H*NH), 4.59-4.50 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 2.95-2.93 (t, *J* = 2.5 Hz, 1H, CH_2CCH), 2.86-2.73 (m, 2H, C*H*$_2$CCH), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3$)$_2$) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = 169.7 (CO), 168.5 (CO), 166.9 (CO), 165.8 (CO), 165.3 (CO), 164.2 (CO), 154.1 (C_{Ar}), 145.8 (C_{Ar}), 142.2 (C_{Ar}), 141.7 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 136.0 (C_{Ar}), 133.2 (C_{Ar}), 130.2 (C_{Ar}), 129.2 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 127.6 (C_{Ar}), 126.3 (C_{Ar}), 124.9 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.0 (C_{Ar}), 118.4 (C_{Ar}), 118.3 (CN), 112.4 (C_{Ar}), 112.2 (C_{Ar}), 111.4 (C_{Ar}), 80.6 (CH_2*C*CH), 74.9 (*C*H$(CH_3)_2$), 73.2 (CH_2*C*CH), 53.5 (CHNH), 50.9 (NCH_2), 22.3 (CH(*C*H$_3$)$_2$), 21.4 (*C*H$_2$CCH) ppm;

HRMS (ESI) calculated for $C_{45}H_{35}N_6O_9$ $[M-H]^-$: 803.2466; found: 803.2466.

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(5-(2-((*tert*-butoxycarbonyl)amino)pent-4-ynamido) picolinamido)-3-isopropoxybenzamido)benzoate (**129**)



Amine **114**[70] (100.0 mg, 0.18 mmol) and (*S*)-2-((*tert*-butoxycarbonyl)amino)pent-4-ynoic acid (**116**) (54.6 mg, 0.26 mmol, 1.40 equiv.) were dissolved in EtOAc (400 µL) and pyridine (44 µL, 0.55 mmol, 3.00 equiv.) was added. The mixture was cooled to 0 °C and T3P (50 wt% in EtOAc, 200 µL, 0.33 mmol, 1.80 equiv.) was added dropwise. The solution was stirred at 0 °C for 4 h. After addition of H_2O, the aq. phase was extracted with EtOAc (3x). The combined organic phases were washed with a sat. $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (dry load, PE/EtOAc = 2:1) to furnish product **129** (132 mg, 0.18 mmol, 97%) as yellowish amorphous solid.

R_f (PE/EtOAc = 1:1) = 0.68;

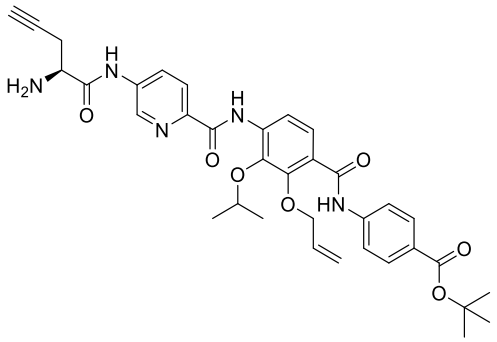
$[\alpha]_D^{22}$ = -1.1 ° (c 0.1, MeOH);

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 10.74 (s, 1H, NH), 10.68 (s, 1H, NH), 10.48 (s, 1H, NH), 8.99-8.98 (d, *J* = 2.2 Hz, 1H, H_{Ar}), 8.35-8.33 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 8.30-8.28 (dd, *J* = 2.3, 8.6 Hz, 1H, H_{Ar}), 8.20-8.19 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 7.90-7.88 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.83-7.82 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.49-7.47 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 7.32-7.31 (d, *J* = 7.8 Hz, 1H, CHN*H*), 6.06-5.98 (m, 1H, OCH_2CHCH_2), 5.41-5.36 (dq, *J* = 1.6, 17.2 Hz, 1H, OCH_2CHCH_2), 5.23-5.20 (dq, *J* = 1.6, 10.5 Hz, 1H, OCH_2CHCH_2), 4.67-4.64 (sept, *J* = 6.1 Hz, 1H, $CH(CH_3)_2$), 4.62-4.61 (d, *J* = 5.5 Hz, 2H, OCH_2CHCH_2), 4.34-4.29 (q, *J* = 7.6 Hz, 1H, CHNH), 2.93 (bs, 1H, CH_2CCH), 2.68-2.55 (m, 2H, CH_2CCH), 1.55 (s, 9H, $C(CH_3)_3$), 1.40 (s, 9H, $C(CH_3)_3$), 1.37-1.35 (dd, *J* = 2.2, 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 164.6 (CO), 164.3 (CO), 161.1 (CO), 155.2 (CO), 149.3 (C_{Ar}), 143.4 (C_{Ar}), 143.0 (C_{Ar}), 139.4 (C_{Ar}), 139.4 (C_{Ar}), 138.6 (C_{Ar}), 135.4 (C_{Ar}), 133.5 (OCH_2CHCH_2), 130.1 (C_{Ar}), 127.3 (C_{Ar}), 126.0 (C_{Ar}), 125.8 (C_{Ar}), 124.6 (C_{Ar}), 122.9 (C_{Ar}), 118.8 (C_{Ar}), 118.0 (OCH_2CHCH_2), 113.8 (C_{Ar}), 80.4 ($C(CH_3)_3$), 80.3 (CH_2CCH), 78.5 ($C(CH_3)_{3Boc}$), 76.4 ($CH(CH_3)_2$), 74.3 (OCH_2CHCH_2), 73.3 (CH_2CCH), 54.1 ($CHNH_2$), 28.2 ($(CH_3)_{3Boc}$), 27.9 ($C(CH_3)_3$), 22.3 (d, *J* = 2.3 Hz, $CH(CH_3)_2$) 21.5 (CH_2CCH) ppm;

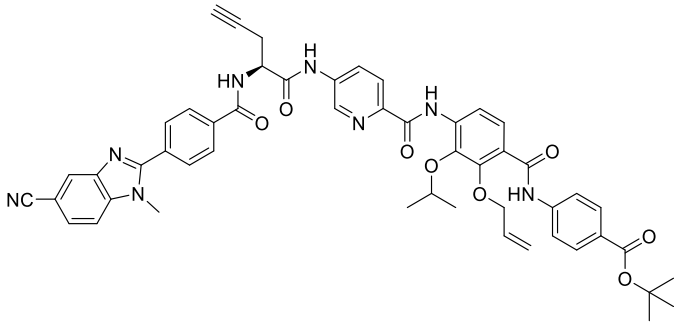
HRMS (ESI) calculated for $C_{40}H_{47}N_5O_9Na$ $[M+Na]^+$: 764.3271; found: 764.3273.

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(5-(2-aminopent-4-ynamido)picolinamido)-3-isopropoxy benzamido)benzoate (**187**)



Carbamate **129** (184 mg, 0.25 mmol) was dissolved in HCl (4 M in 1,4-dioxane, 6.20 mL, 24.8 mmol, 100 equiv.) at 0 °C. The mixture was warmed up to rt and stirred for 15 min. The solution was transferred to a stirred suspension of EtOAc (180 mL) and a sat. $NaHCO_3$ solution (180 mL). The aq. phase was extracted with EtOAc and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was used in the next step without further purification.

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(5-(2-(4-(5-cyano-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)benzamido)pent-4-ynamido)picolinamido)-3-isopropoxybenzamido)benzoate (**196**)



DIPEA (129 µL, 0.74 mmol, 3.00 equiv.) was added dropwise to a stirred solution of HATU (113 mg, 0.30 mmol, 1.20 equiv.) and carboxylic acid **34** (82.4 mg, 0.30 mmol, 1.20 equiv.) in DMF (6.0 mL). The solution was stirred for 5 min and was then transferred to a stirred solution of amine **187** (159 mg, 0.25 mmol) in DMF (3.5 mL). The reaction mixture was stirred at rt for 18 h. The mixture was diluted with EtOAc and washed with a 1 M HCl solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH in CH_2Cl_2 = 1%, 2%) to furnish product **196** (142 mg, 0.16 mmol, 63%) as yellowish amorphous solid.

R_f (3% MeOH in CH_2Cl_2) = 0.19;

$[\alpha]_D^{22}$ = +3.5 ° (c 0.1, MeOH);

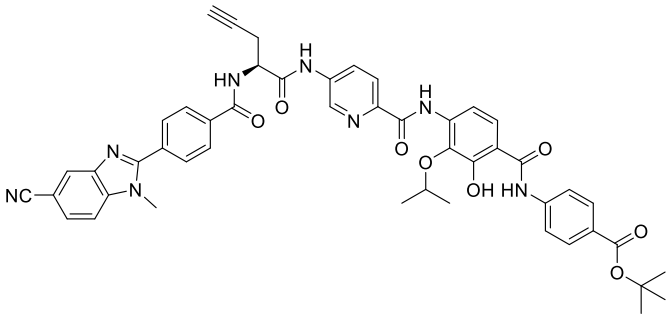
^{1}H-NMR (600 MHz, DMSO-d_6) = 10.88 (s, 1H, NH), 10.69 (s, 1H, NH), 9.48 (s, 1H, NH), 9.14-9.13 (d, *J* = 7.4 Hz, 1H, NH), 9.03-9.02 (d, *J* = 2.6 Hz, 1H, H_{Ar}), 8.35-8.32 (m, 3H, H_{Ar}),

8.28 (dd, *J* = 0.6, 1.4 Hz, 1H, H_{Ar}), 8.22-8.20 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 8.15-8.14 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 8.05-8.03 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 7.90-7.88 (m, 3H, H_{Ar}), 7.83-7.82 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.75-7.73 (dd, *J* = 1.5, 8.4 Hz, 1H, H_{Ar}), 7.49-7.48 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.05-5.99 (m, 1H, C*H*CH_2), 5.40-5.37 (dq, *J* = 1.7, 17.2 Hz, 1H, CHC*H*$_2$), 5.22-5.20 (dq, *J* = 1.6, 10.5 Hz, 1H, CHC*H*$_2$), 4.88-4.84 (m, 1H, C*H*NH), 4.68-4.63 (sept, *J* = 5.5 Hz, 1H, C*H*$(CH_3)_2$), 4.62-4.61 (d, *J* = 5.5 Hz, 2H, OC*H*$_2$CH), 3.98 (s, 3H, NCH_3), 2.98-2.97 (t, *J* = 2.6 Hz, 1H, CCH), 2.91-2.79 (m, 2H, C*H*$_2$CCH), 1.55 (s, 9H, $C(CH_3)_3$), 1.37-1.36 (dd, *J* = 3.9, 6.1 Hz, 6H, CH(C*H*$_3$)$_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = 170.0 (CO), 166.0 (CO), 164.6 (CO), 164.3 (CO), 161.1 (CO), 154.9 (NCN), 149.3 (C_{Ar}), 143.5 (C_{Ar}), 143.0 (C_{Ar}), 141.9 (C_{Ar}), 139.5 (C_{Ar}), 139.5 (C_{Ar}), 139.4 (C_{Ar}), 138.6 (C_{Ar}), 135.4 (C_{Ar}), 134.9 (C_{Ar}), 133.5 (*C*HCH_2), 132.1 (C_{Ar}), 130.1 (C_{Ar}), 129.4 (C_{Ar}), 128.0 (C_{Ar}), 127.4 (C_{Ar}), 126.0 (C_{Ar}), 125.9 (C_{Ar}), 125.8 (C_{Ar}), 124.6 (C_{Ar}), 124.1 (C_{Ar}), 122.9 (C_{Ar}), 119.9 (CN), 118.8 (C_{Ar}), 118.2 (CH*C*H$_2$), 113.8 (C_{Ar}), 112.4 (C_{Ar}), 104.3 (C_{Ar}), 80.5 (*C*$(CH_3)_3$), 80.3 (*C*CH), 76.3 (O*C*H$_2$CH), 74.3 (*C*H$(CH_3)_2$), 73.3 (C*C*H), 53.6 (CHNH), 32.2 (NCH_3), 27.9 (C(*C*H$_3$)$_3$), 22.3 (d, *J* = 3.7 Hz, CH(*C*H$_3$)$_2$), 21.2 (*C*H$_2$CCH) ppm;

HRMS (ESI) calculated for $C_{51}H_{48}N_8O_8Na$ $[M+Na]^+$: 923.3493; found: 923.3503.

tert-Butyl (*S*)-4-(4-(5-(2-(4-(5-cyano-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)benzamido)pent-4-ynamido)picolinamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**205**)



Allyl ether **196** (139 mg, 0.15 mmol) was dissolved in THF (7 mL). Aniline (47 µL, 0.51 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (17.8 mg, 0.02 mmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 2 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, 3% MeOH in CH_2Cl_2) to furnish product **205** (98.0 mg, 0.11 mmol, 74%) as colorless amorphous solid.

$[\alpha]_D^{22}$ = +1.8 ° (c 0.1, MeOH);

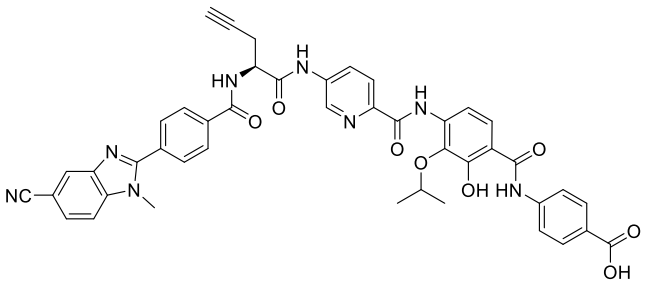
^{1}H-NMR (600 MHz, DMSO-d_6) = 12.44 (s, 1H, OH), 10.88 (s, 1H, NH), 10.75 (s, 1H, NH), 10.61 (s, 1H, NH), 9.14-9.13 (d, *J* = 7.4 Hz, 1H, NH), 9.02-9.01 (d, *J* = 2.4 Hz, 1H, H_{Ar}), 8.35-8.33 (dd, *J* = 2.4, 8.6 Hz, 1H, H_{Ar}), 8.28 (dd, *J* = 0.6, 1.4 Hz, 1H, H_{Ar}), 8.21-8.20 (d, *J* = 8.5 Hz,

1H, H_{Ar}), 8.15-8.14 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 8.11-8.10 (d, *J* = 8.7 Hz, 1H, H_{Ar}), 8.05-8.03 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 7.94-7.92 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.90-7.89 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 7.86-7.85 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.75-7.73 (dd, *J* = 1.5, 8.4 Hz, 1H, H_{Ar}), 4.88-4.84 (m, 1H, C*H*NH), 4.71-4.65 (sept, *J* = 6.2 Hz, 1H, C*H*$(CH_3)_2$), 3.98 (s, 3H, NCH_3), 2.98-2.97 (t, *J* = 2.6 Hz, 1H, CCH), 2.90-2.79 (m, 2H, CH_2CCH), 1.55 (s, 9H, C$(CH_3)_3$), 1.35-1.34 (dd, *J* = 4.4, 6.1 Hz, 6H, CH(C$H_3)_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = 170.1 (CO), 168.6 (CO), 166.0 (CO), 164.5 (CO), 161.2 (CO), 154.9 (NCN), 154.1 (C_{Ar}), 143.5 (C_{Ar}), 141.9 (C_{Ar}), 139.5 (C_{Ar}), 138.7 (C_{Ar}), 136.8 (C_{Ar}), 134.9 (C_{Ar}), 134.0 (C_{Ar}), 132.1 (C_{Ar}), 129.9 (C_{Ar}), 129.4 (C_{Ar}), 128.0 (C_{Ar}), 127.4 (C_{Ar}), 126.0 (C_{Ar}), 125.9 (C_{Ar}), 124.1 (C_{Ar}), 123.5 (C_{Ar}), 122.9 (C_{Ar}), 120.8 (C_{Ar}), 119.9 (CN), 112.4 (C_{Ar}), 111.7 (C_{Ar}), 108.4 (C_{Ar}), 104.3 (C_{Ar}), 80.5 (2C, *C*CH, *C*$(CH_3)_3$), 74.8 (*C*H$(CH_3)_2$), 73.3 (C*C*H), 53.5 (CHNH), 32.2 (NCH_3), 27.8 (C(*C*$H_3)_3$), 22.3 (d, *J* = 3.7 Hz, CH(*C*$H_3)_2$), 21.2 (*C*H_2CCH) ppm;

HRMS (ESI) calculated for $C_{48}H_{44}N_8O_8Na$ $[M+Na]^+$: 883.3180; found: 883.3184.

(*S*)-4-(4-(5-(2-(4-(5-Cyano-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)benzamido)pent-4-ynamido)picolinamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSF60**



tert-Butyl ester **205** (92.2 mg, 0.11 mmol) was dissolved in precooled TFA (5.4 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSF60** (88.6 mg, 0.11 mmol, quant.) as yellowish amorphous solid.

$[\alpha]_D^{22}$ = +2.5 ° (c 0.2, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = 12.81 (s, 1H, CO_2H), 12.45 (s, 1H, OH), 10.88 (s, 1H, NH), 10.75 (s, 1H, NH), 10.60 (s, 1H, NH), 9.15-9.13 (d, *J* = 7.4 Hz, 1H, NH), 9.02 (d, *J* = 2.6 Hz, 1H, H_{Ar}), 8.35-8.33 (dd, *J* = 2.4, 8.6 Hz, 1H, H_{Ar}), 8.29-8.28 (d, *J* = 0.9 Hz, 1H, H_{Ar}), 8.22-8.20 (d, *J* = 8.6 Hz, 1H, H_{Ar}), 8.15-8.14 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 8.12-8.10 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 8.05-8.03 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 7.98-7.96 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.92-7.89 (m, 2H, H_{Ar}), 7.86-7.85 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.75-7.73 (dd, *J* = 1.4, 8.4 Hz, 1H, H_{Ar}), 4.88-4.84 (m, 1H, C*H*NH), 4.71-4.65 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 3.98 (s, 3H, NCH_3), 2.98-2.97 (t,

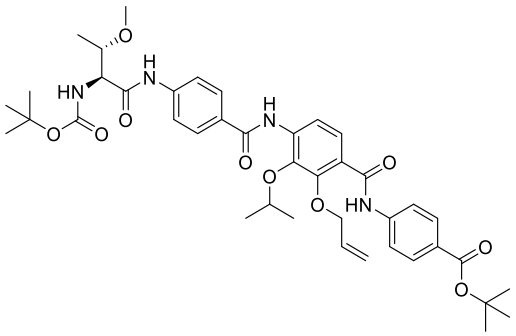
J = 2.6 Hz, 1H, CCH), 2.91-2.79 (m, 2H, C*H*$_2$CCH), 1.36-1.34 (dd, *J* = 4.4, 6.1 Hz, 6H, CH(C*H*$_3$)$_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d$_6$) = 170.1 (CO), 168.7 (CO), 166.9 (CO), 166.0 (CO), 161.2 (CO), 154.9 (NCN), 154.1 (C$_{Ar}$), 143.5 (C$_{Ar}$), 141.9 (C$_{Ar}$), 141.7 (C$_{Ar}$), 139.5 (C$_{Ar}$), 139.5 (C$_{Ar}$), 138.7 (C$_{Ar}$), 136.8 (C$_{Ar}$), 134.9 (C$_{Ar}$), 134.0 (C$_{Ar}$), 132.0 (C$_{Ar}$), 130.2 (C$_{Ar}$), 129.4 (C$_{Ar}$), 128.0 (C$_{Ar}$), 127.4 (C$_{Ar}$), 126.3 (C$_{Ar}$), 126.0 (C$_{Ar}$), 124.1 (C$_{Ar}$), 123.5 (C$_{Ar}$), 122.9 (C$_{Ar}$), 120.8 (C$_{Ar}$), 119.9 (CN), 112.5 (C$_{Ar}$), 111.7 (C$_{Ar}$), 108.4 (C$_{Ar}$), 104.4 (C$_{Ar}$), 80.5 (2C, *C*CH, *C*(CH$_3$)$_3$), 74.8 (*C*H(CH$_3$)$_2$), 73.3 (C*C*H), 53.6 (CHNH), 32.2 (NCH$_3$), 22.3 (d, *J* = 4.1 Hz, CH(*C*H$_3$)$_2$), 21.2 (*C*H$_2$CCH) ppm;

HRMS (ESI) calculated for C$_{44}$H$_{35}$N$_8$O$_8$ [M-H]$^-$: 803.2578; found: 803.2588.

4.2.7 *O*-Methyl-L-allothreonine derivatives

tert-Butyl 4-(2-(allyloxy)-4-(4-((2*S*,3*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methoxy butanamido)benzamido)-3-isopropoxybenzamido)benzoate (**122**)



Amine **5** (100 mg, 0.18 mmol), amino acid **103** (72.7 mg, 0.31 mmol, 1.70 equiv.) and EEDQ (72.5 mg, 0.29 mmol, 1.60 equiv.) were dissolved in precooled CHCl$_3$ (1 mL) at 0 °C. The mixture was stirred at 18 h while warming to rt. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (1. dry load, 20% Et$_2$O in CH$_2$Cl$_2$, 2. dry load, 1% MeOH in CH$_2$Cl$_2$) to furnish product **122** (74.3 mg, 0.10 mmol, 53%) as yellow amorphous solid, which contained small impurities. The compound was used in the next step without further purification.

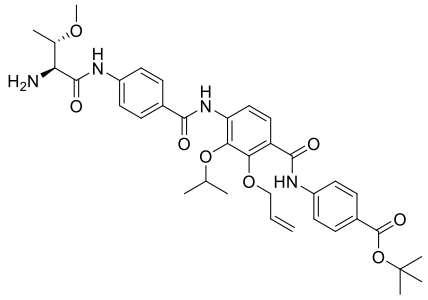
R$_f$ (1% MeOH in CH$_2$Cl$_2$) = 0.37;

^{1}H-NMR (500 MHz, DMSO-d$_6$) = δ 10.53 (s, 1H, NH), 10.33-10.25 (m, 1H, NH), 9.51-9.49 (m, 1H, NH), 7.98-7.94 (m, 2H, H$_{Ar}$), 7.90-7.88 (m, 2H, H$_{Ar}$), 7.83-7.79 (m, 5H, H$_{Ar}$), 7.42-7.40 (d, *J* = 8.4 Hz, 1H, H$_{Ar}$), 7.08-7.07 (d, *J* = 8.6 Hz, 1H, CHN*H*), 6.07-5.98 (m, 1H, C*H*CH$_2$), 5.39-5.36 (dd, *J* = 1.6, 17.2 Hz, 1H, CHC*H*$_2$), 5.21-5.19 (dd, *J* = 1.5, 10.5 Hz, 1H, CHC*H*$_2$), 4.61-4.60 (d, *J* = 5.4 Hz, 1H, OC*H*$_2$CH), 4.54-4.46 (sept, *J* = 6.1 Hz, 1H, C*H*(CH$_3$)$_2$), 4.23-4.20

(t, *J* = 8.1 Hz, 1H, C*H*NH), 3.59-3.57 (m, 1H, C*H*OCH$_3$), 3.23 (s, 3H, OCH$_3$), 1.55 (s, 9H, CCO$_2$C(C*H*$_3$)$_3$), 1.39 (s, 9H, NHCO$_2$C(C*H*$_3$)$_3$), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, H-9), 1.13-1.12 (d, *J* = 5.9 Hz, 3H, CHC*H*$_3$) ppm;

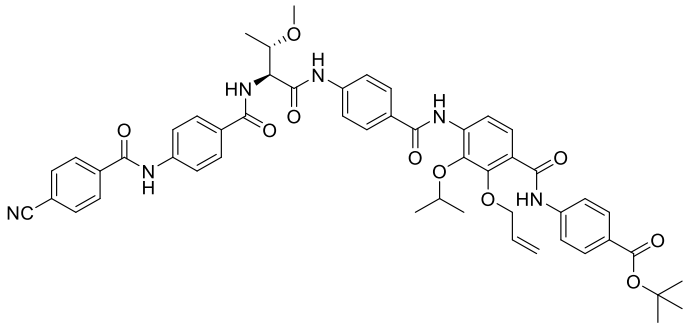
HRMS (ESI) calculated for $C_{41}H_{52}N_4O_{10}Na$ $[M+Na]^+$: 783.3581; found: 783.3583.

tert-Butyl 4-(2-(allyloxy)-4-(4-((2*S*,3*S*)-2-amino-3-methoxybutanamido)benzamido)-3-isopropoxybenzamido)benzoate (**137**)



Carbamate **122** (70.9 mg, 0.09 mmol) was dissolved in HCl (4 M in 1,4-dioxane, 2.3 mL, 9.32 mmol, 100 equiv.) at 0 °C. The mixture was warmed up to rt and stirred for 15 min. The solution was transferred to a stirred suspension of EtOAc (60 mL) and a sat. $NaHCO_3$ solution (60 mL). The aq. phase was extracted with EtOAc and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was used in the next step without further purification.

tert-Butyl 4-(2-(allyloxy)-4-(4-((2*S*,3S)-2-(4-(4-cyanobenzamido)benzamido)-3-methoxybutanamido)benzamido)-3-isopropoxybenzamido)benzoate (**143**)



DIPEA (49 µL, 0.28 mmol, 3.00 equiv.) was added dropwise to a stirred solution of HATU (42.5 mg, 0.11 mmol, 1.20 equiv.) and carboxylic acid **3** (29.8 mg, 0.11 mmol, 1.20 equiv.) in DMF (2.3 mL). The solution was stirred for 5 min and was then transferred to a stirred solution of amine **137** (61.6 mg, 0.09 mmol) in DMF (1.3 mL). The reaction mixture was stirred at rt for 16 h. The mixture was diluted with EtOAc and washed with a 1 M HCl solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, 2% MeOH in CH_2Cl_2) to furnish product **143** (31.4 mg, 0.04 mmol, 37%) as colorless amorphous solid.

R_f (2% MeOH in CH_2Cl_2) = 0.20;

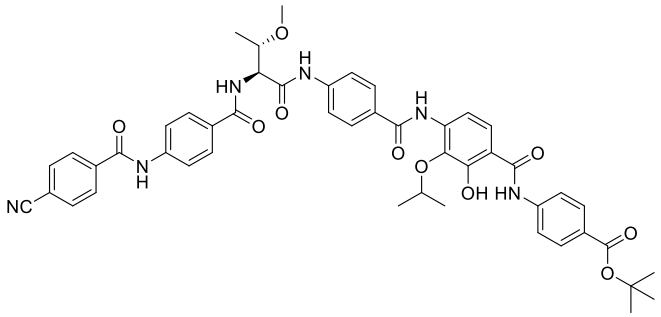
$[\alpha]_D^{23}$ = +3.3 ° (c 0.1, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = 10.69 (s, 1H, NH), 10.52 (s, 1H, NH), 10.50 (s, 1H, NH), 9.51 (s, 1H, NH), 8.53-8.52 (d, *J* = 8.3 Hz, 1H, CHN*H*), 8.13-8.12 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 8.05-8.04 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.99-7.95 (m, 4H, H_{Ar}), 7.90-7.88 (m, 4H, H_{Ar}), 7.84-7.82 (m, 4H, H_{Ar}), 7.41-7.40 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 6.05-5.98 (m, 1H, C*H*CH_2), 5.39-5.36 (dd, *J* = 1.6, 17.2 Hz, 1H, CHC*H*$_2$), 5.21-5.19 (dd, *J* = 1.3, 10.5 Hz, 1H, CHC*H*$_2$), 4.61-4.60 (d, *J* = 5.3 Hz, 2H, C*H*$_2$CH), 4.74-4.72 (t, *J* = 8.3 Hz, 1H, C*H*NH), 4.53-4.48 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 3.85-3.81 (m, 1H, C*H*CH_3), 3.29 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.27-1.25 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3$)$_2$), 1.23-1.22 (d, *J* = 6.0 Hz, 3H, CHC*H*$_3$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = 170.1 (CO), 166.0 (CO), 164.6 (CO), 164.5 (CO), 164.4 (CO), 164.3 (CO), 149.5 (C_{Ar}), 143.0 (C_{Ar}), 142.5 (C_{Ar}), 142.3 (C_{Ar}), 141.6 (C_{Ar}), 138.7 (C_{Ar}), 135.6 (C_{Ar}), 133.6 (*C*HCH_2), 132.5 (C_{Ar}), 130.1 (C_{Ar}), 129.1 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.4 (C_{Ar}), 127.1 (C_{Ar}), 126.0 (C_{Ar}), 123.6 (C_{Ar}), 119.5 (C_{Ar}), 118.9 (C_{Ar}), 118.8 (C_{Ar}), 118.8 (CH*C*H_2), 118.3 (CN), 117.8 (C_{Ar}), 114.0 (C_{Ar}), 80.3 (*C*$(CH_3)_3$), 76.3 (*C*HCH_3), 76.2 (O*C*H_2CH), 74.3 (*C*H$(CH_3)_2$), 58.5 (CHNH), 56.5 (OCH_3), 27.9 (C(*C*H_3)$_3$), 22.3 (CH(*C*H_3)$_2$), 16.2 (CH*C*H_3) ppm;

HRMS (ESI) calculated for $C_{51}H_{52}N_6O_{10}Na$ $[M+Na]^+$: 931.3643; found: 931.3643.

tert-Butyl 4-(4-(4-((2*S*,3*S*)-2-(4-(4-cyanobenzamido)benzamido)-3-methoxybutanamido) benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**149**)



Allyl ether **143** (29.0 mg, 0.03 mmol) was dissolved in THF (1.6 mL). Aniline (10 µL, 0.11 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (3.7 mg, 0.003 mmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 90 min. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 2%, 3%) to furnish product **149** (19.7 mg, 0.02 mmol, 71%) as beige amorphous solid.

In the ^{13}C NMR spectrum is one signal around 154 ppm missing due to the minimal analytical amount.

R_f (3% MeOH in CH_2Cl_2) = 0.28;

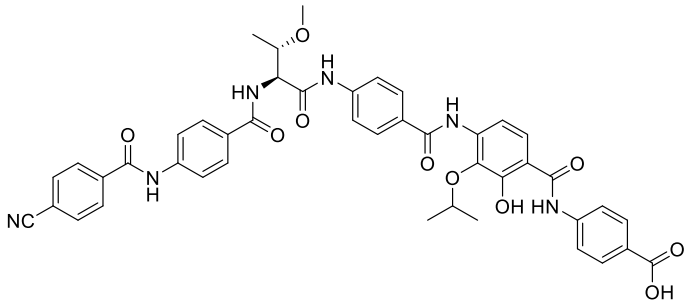
$[\alpha]_D^{25}$ = +2.3 ° (c 0.1, MeOH);

^{1}H-NMR (500 MHz, DMSO-d_6) = 12.29 (s, 1H, OH), 10.69 (s, 1H, NH), 10.61 (bs, 1H, NH), 10.52 (s, 1H, NH), 9.39 (s, 1H, NH), 8.54-8.52 (d, *J* = 8.3 Hz, 1H, CHN*H*), 8.14-8.12 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 8.05-8.04 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.96-7.92 (m, 6H, H_{Ar}), 7.89-7.84 (m, 7H, H_{Ar}), 7.72-7.70 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 4.74-4.71 (t, *J* = 8.3 Hz, 1H, C*H*NH), 4.58-4.51 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 3.85-3.80 (m, 1H, C*H*CH_3), 3.29 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$), 1.24-1.22 (d, *J* = 6.0 Hz, 3H, $CHCH_3$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 170.1 (CO), 168.5 (CO), 166.0 (CO), 164.5 (CO), 164.4 (CO), 164.2 (CO), 142.4 (C_{Ar}), 142.0 (C_{Ar}), 141.6 (C_{Ar}), 138.7 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 132.5 (C_{Ar}), 129.9 (C_{Ar}), 129.1 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (2C, C_{Ar}), 126.8 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.5 (C_{Ar}), 118.8 (C_{Ar}), 118.3 (CN), 114.0 (C_{Ar}), 112.4 (C_{Ar}), 112.1 (C_{Ar}), 80.5 (*C*$(CH_3)_3$), 76.3 (*C*HCH_3), 74.8 (*C*H$(CH_3)_2$), 58.5 (CHNH), 56.5 (OCH_3), 27.8 ($C(CH_3)_3$), 22.3 ($CH(CH_3)_2$), 16.2 ($CHCH_3$) ppm;

HRMS (ESI) calculated for $C_{48}H_{48}N_6O_{10}Na$ $[M+Na]^+$: 891.3330; found: 891.3321.

4-(4-(4-((2*S*,3*S*)-2-(4-(4-Cyanobenzamido)benzamido)-3-methoxybutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSE51**



tert-Butyl ester **149** (17.6 mg, 0.02 mmol) was dissolved in precooled TFA (1.2 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSE51** (10.1 mg, 0.01 mmol, 61%) as grey amorphous solid.

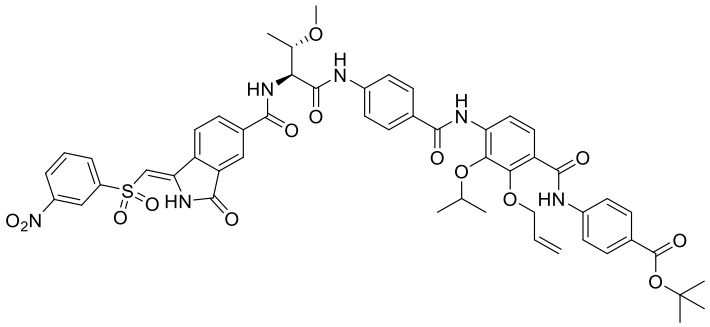
$[\alpha]_D^{25}$ = +4.2 ° (c 0.1, MeOH);

^{1}H-NMR (500 MHz, DMSO-d_6) = 12.82 (bs, 1H, CO_2H), 12.30 (s, 1H, OH), 10.69 (s, 1H, NH), 10.60 (s, 1H, NH), 10.52 (s, 1H, NH), 9.40 (s, 1H, NH), 8.54-8.52 (d, *J* = 8.4 Hz, 1H, CHN*H*), 8.14-8.12 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 8.05-8.04 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 7.98-7.95 (m, 6H, H_{Ar}), 7.89-7.84 (m, 7H, H_{Ar}), 7.72-7.70 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 4.74-4.71 (t, *J* = 8.3 Hz, 1H, C*H*NH), 4.58-4.51 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 3.85-3.80 (m, 1H, C*H*CH_3), 3.29 (s, 3H, OCH_3), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3)_2$), 1.24-1.22 (d, *J* = 6.1 Hz, 3H, CHC*H*$_3$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 170.1 (CO), 168.5 (CO), 166.9 (CO), 166.0 (CO), 164.4 (CO), 164.2 (CO), 154.1 (C_{Ar}), 142.4 (C_{Ar}), 142.0 (C_{Ar}), 141.6 (C_{Ar}), 138.7 (C_{Ar}), 137.1 (C_{Ar}), 136.3 (C_{Ar}), 132.5 (C_{Ar}), 130.2 (C_{Ar}), 129.1 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.4 (C_{Ar}), 126.3 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.5 (C_{Ar}), 118.8 (C_{Ar}), 118.3 (CN), 114.0 (C_{Ar}), 112.4 (C_{Ar}), 112.2 (C_{Ar}), 76.3 (*C*HCH_3), 74.9 (*C*H$(CH_3)_2$), 58.5 (CHNH), 56.5 (OCH_3), 22.3 (CH(*C*H$_3)_2$), 16.2 (CH*C*H$_3$) ppm;

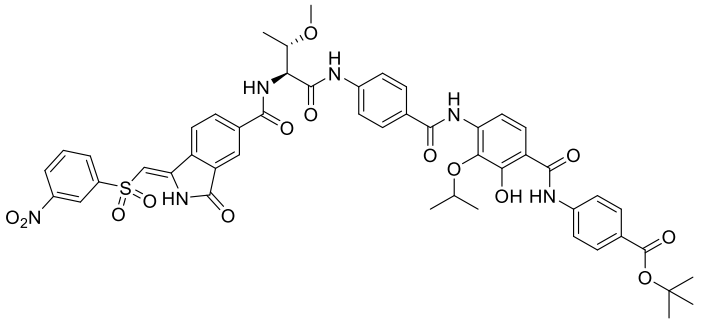
HRMS (ESI) calculated for $C_{44}H_{39}N_6O_{10}$ $[M-H]^-$: 811.2728; found: 811.2733.

tert-Butyl 4-(2-(allyloxy)-3-isopropoxy-4-(4-((2*S*,3*S*)-3-methoxy-2-((*Z*)-1-(((3-nitrophenyl)-sulfonyl)methylene)-3-oxoisoindoline-5-carboxamido)butanamido)benzamido)benzamido)-benzoate (**208**)



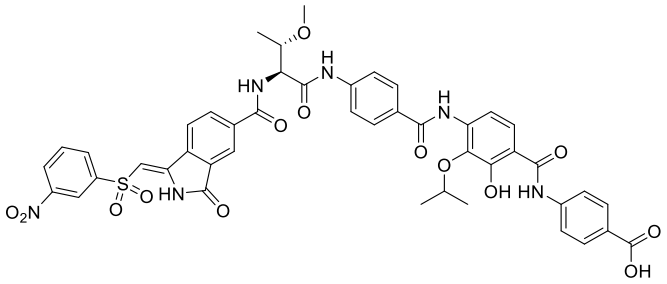
Acid **39** (63.0 mg, 0.17 mmol, 1.20 equiv.) and HATU (64.0 mg, 0.17 mmol, 1.20 equiv.) were dissolved in DMF (3.5 mL) and DIPEA (73 µL, 0.42 mmol, 3.00 equiv.) was added. The mixture stirred at rt for 5 min. Afterwards, it was transferred to a stirred solution of amine **137** (92.6 mg, 0.14 mmol) in DMF (2.0 mL) at 0 °C. The resulting mixture was stirred for 21 h while warming to rt. EtOAc was added and the organic phase was washed with a 0.1 M HCl solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (dry load, washing with 20% Et_2O in CH_2Cl_2, elution with 3% MeOH in CH_2Cl_2) to furnish product **208** (40.8 mg) as yellow oil, which contained impurities. The product was used in the next step without further purification.
HRMS (ESI) calculated for $C_{52}H_{52}N_6O_{14}S$ $[M-H]^-$: 1015.3184; found: 1015.3181.

tert-Butyl 4-(2-hydroxy-3-isopropoxy-4-(4-((2*S*,3*S*)-3-methoxy-2-((*Z*)-1-(((3-nitrophenyl)-sulfonyl)methylene)-3-oxoisoindoline-5-carboxamido)butanamido)benzamido)benzamido)-benzoate (**209**)



Ether **208** (35.7 mg, 0.04 mmol) was dissolved in THF (1.5 mL). Aniline (11 µL, 0.12 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (4.1 mg, 4 µmol, 0.10 equiv.) were added subsequently. The mixture was stirred at rt for 90 min. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (dry load, 2% MeOH in CH_2Cl_2) to furnish product **209** (21.7 mg) as yellow film, which contained impurities. The product was used in the next step without further purification.

4-(2-Hydroxy-3-isopropoxy-4-(4-((2*S*,3S)-3-methoxy-2-((*Z*)-1-(((3-nitrophenyl)sulfonyl)-methylene)-3-oxoisoindoline-5-carboxamido)butanamido)benzamido)benzamido)benzoic acid **TSF16**



Ester **209** (19.1 mg, 0.02 mmol) was dissolved in precooled TFA (1 mL). The mixture was stirred for 30 min while warming to rt. Et_2O was added at 0 °C. The solvent was removed under reduced pressure. The residue was purified by RP-HPLC ((MeCN + 1% FA) in (H_2O + 1% FA) 20-70% over 60 min, 70-90% over 5 min, 90% over 15 min) to furnish **TSF16** (2.1 mg, 0.002 mmol, 1% over 3 steps, 87% purity) as colorless amorphous solid.

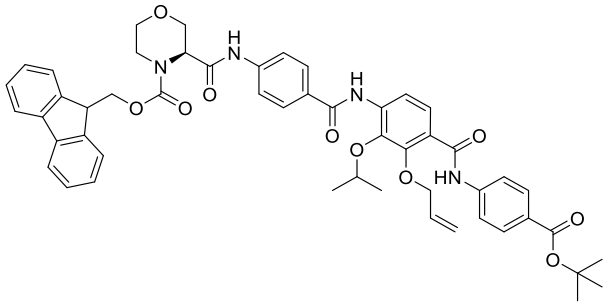
^{1}H-NMR (600 MHz, DMSO-d_6) = 12.81 (bs, 1H, CO_2H), 12.30 (s, 1H, OH), 10.88 (s, 1H, NH), 10.61 (bs, 1H, NH), 10.54 (s, 1H, NH), 9.37 (s, 1H, NH), 9.02-9.00 (d, *J* = 8.2 Hz, 1H, CHN*H*), 8.86 (t, *J* = 1.9 Hz, 1H, H_{Ar}), 8.56-8.54 (ddd, *J* = 1.0, 2.3, 8.2 Hz, 1H, H_{Ar}), 8.52-8.50 (ddd, *J* = 1.1, 1.7, 7.9 Hz, 1H, H_{Ar}), 8.39 (m, 1H, H_{Ar}), 8.26-8.25 (dd, *J* = 1.5, 8.1 Hz, 1H, H_{Ar}), 8.15-8.14 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 7.99-7.94 (m, 5H, H_{Ar}), 7.86-7.82 (m, 5H, H_{Ar}), 7.69 (bs, 1H, H_{Ar}), 7.14 (s, 1H, SO_2CH), 4.76-4.73 (t, *J* = 8.2 Hz, 1H, C*H*NH), 4.56 (bs, 1H, C*H*$(CH_3)_2$), 3.85-3.81 (m, 1H, C*H*CH_3), 3.29 (s, 3H, OCH_3), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3)_2$), 1.23-1.22 (m, 3H, CHC*H*$_3$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = 169.7 (CO), 168.4 (CO), 167.6 (CO), 166.9 (CO), 165.1 (CO), 164.1 (CO), 148.2 (C_{Ar}), 144.3 (C_{Ar}), 143.4 (C_{Ar}), 142.3 (C_{Ar}), 142.0 (C_{Ar}), 138.5 (C_{Ar}), 137.4 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 133.1 (C_{Ar}), 133.0 (C_{Ar}), 131.7 (C_{Ar}), 130.2 (C_{Ar}), 129.6 (C_{Ar}), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 126.2 (C_{Ar}), 124.1 (C_{Ar}), 122.8 (C_{Ar}), 122.6 (C_{Ar}), 122.0 (C_{Ar}), 120.6 (C_{Ar}), 118.9 (CN), 112.5 (C_{Ar}), 112.1 (C_{Ar}), 101.2 (SO_2CH), 76.1 (*C*HCH_3), 74.8 (*C*H$(CH_3)_2$), 58.6 (CHNH), 56.5 (OCH_3), 22.3 (CH(*C*H$_3)_2$), 16.2 (CH*C*H$_3$) ppm;

HRMS (ESI) calculated for $C_{45}H_{40}N_6O_{14}S$ $[M+Na]^+$: 943.2221; found: 943.2226.

4.2.8 (*S*)-Morpholine-3-carboxylic acid derivative

(9*H*-Fluoren-9-yl)methyl(*S*)-3-((4-((3-(allyloxy)-4-((4-(*tert*-butoxycarbonyl) phenyl)carb-amoyl)-2-isopropoxyphenyl)carbamoyl)phenyl)carbamoyl)morpholine-4-carboxylate (**125**)



Amine **5** (139.0 mg, 0.25 mmol) and 2,6-lutidine (136 µL, 1.17 mmol, 4.6 equiv.) were dissolved in CH_2Cl_2 (2.5 mL). Chloride **297** (94.7 mg, 0.25 mmol, 1.00 equiv.) in CH_2Cl_2 (2.5 mL) was added at 0 °C and the mixture was stirred at rt for 18 h. Afterwards the mixture was washed with a 1 M HCl solution, a 5% Na_2CO_3 solution and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (PE/EtOAc = 1:1) to furnish product **125** (142 mg, 0.16 mmol, 63%) as yellow amorphous solid.

R_f (PE/EtOAc = 1:1) = 0.26;

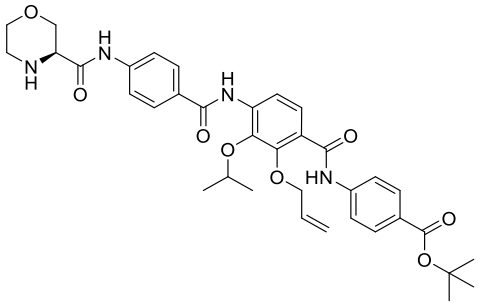
$[\alpha]_D^{25}$ = -72.0 ° (c 0.3, CH_2Cl_2);

^{1}H-NMR (400 MHz, DMSO-d_6) = (mixture of rotamers) 10.53 (s, 1H, NH), 10.45 (s, 0.5H, NH), 10.39 (s, 0.5H, NH), 9.58 (s, 0.5H, NH), 9.54 (s, 0.5H, NH), 8.05-8.03 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 7.99-7.98 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 7.92-7.88 (m, 3H, H_{Ar}), 7.84-7.80 (m, 5H, H_{Ar}), 7.76-7.74 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 7.71-7.68 (t, *J* = 7.7 Hz, 1H, H_{Ar}), 7.57-7.55 (m, 1H, H_{Ar}), 7.45-7.27 (m, 4H, H_{Ar}), 7.09-7.03 (m, 1H, H_{Ar}), 6.06-5.98 (m, 1H, $OCH_2C\mathit{H}CH_2$), 5.39-5.36 (d, *J* = 17.2 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 5.21-5.19 (d, *J* = 10.5 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 4.61 (s, 2H, $OC\mathit{H}_2CHCH_2$), 4.56-4.54 (m, 1H), 4.49 (bs, 1H, $C\mathit{H}(CH_3)_2$), 4.40-4.20 (m, 4H), 3.92-3.86 (m, 1H), 3.79-3.71 (m, 2H), 3.62-3.58 (m, 1H), 3.50-3.38 (m, 2H), 1.55 (s, 9H, $C(CH_3)_3$), 1.27-1.25 (m, 6H, $CH(C\mathit{H}_3)_2$) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = (mixture of rotamers) 169.0 (CO), 164.6 (CO), 164.6 (CO), 164.3 (CO), 156.0 (CO), 155.5 (C_{Ar}), 149.5 (C_{Ar}), 143.7 (C_{Ar}), 143.0 (C_{Ar}), 140.7 (C_{Ar}), 135.6 (C_{Ar}), 133.7 ($OCH_2\mathit{C}HCH_2$), 130.1 (C_{Ar}), 128.5 (C_{Ar}), 127.7 (C_{Ar}), 127.6 (C_{Ar}), 127.2 (C_{Ar}), 127.0 (C_{Ar}), 126.0 (C_{Ar}), 125.1 (t, *J* = 12.4 Hz, C_{Ar}), 123.6 (C_{Ar}), 120.1 (C_{Ar}), 118.8 (C_{Ar}), 118.7 ($OCH_2CH\mathit{C}H_2$), 117.8 (C_{Ar}), 80.3($\mathit{C}(CH_3)_3$), 76.3 (OCH_2CHCH_2), 74.3 ($\mathit{C}H(CH_3)_2$), 67.8-67.1, 65.9, 65.5, 59.7, 55.2, 54.6, 46.6, 46.5, 27.9 ($C(\mathit{C}H_3)_3$), 22.3 ($CH(\mathit{C}H_3)_2$) ppm;

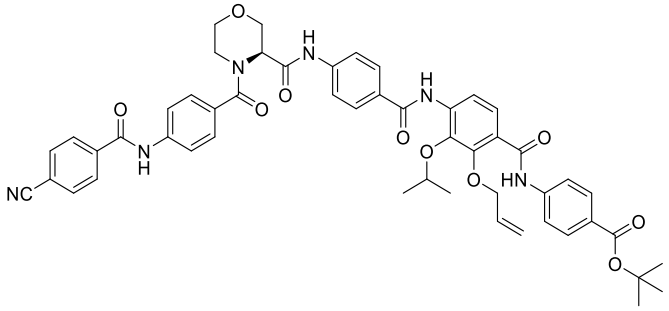
HRMS (ESI) calculated for $C_{51}H_{52}N_4O_{10}$ $Na[M+Na]^+$: 903.3581; found: 903.3572.

tert-Butyl (*S*)-4-(2-(allyloxy)-3-isopropoxy-4-(4-(morpholine-3-carboxamido)benzamido) benzamido)benzoate (**155**)



Carbamate **125** (132 mg, 0.15 mmol) was dissolved in MeCN/piperidine (4:1, 1.8 mL). The solution was stirred at rt for 90 min and then concentrated under reduced pressure. The residue was co-evaporated with MeCN (3x) to furnish crude product **155**, which was used in the next step without further purification.

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(4-(4-(4-(4-cyanobenzamido)benzoyl)morpholine-3-carboxamido)benzamido)-3-isopropoxybenzamido)benzoate (**156**)



DIPEA (88 µL, 0.50 mmol, 5.00 equiv.) was added dropwise to a stirred solution of HATU (95.7 mg, 0.25 mmol, 2.50 equiv.) and carboxylic acid **3** (67.0 mg, 0.25 mmol, 2.50 equiv.) in DMF (2.5 mL). The solution was stirred for 5 min and was then transferred to a stirred solution of amine **155** (66.3 mg, 0.10 mmol) in DMF (1.4 mL). The reaction mixture was stirred at rt for 16 h. The mixture was diluted with EtOAc and washed with a 1 M HCl solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 0.5%, 1%, 3%) to furnish product **156** (63.8 mg, 0.07 mmol, 70%) as yellow amorphous solid.

R_f (1% MeOH in CH_2Cl_2) = 0.13;

$[\alpha]_D^{27}$ = -8.0 ° (c 0.1, MeOH);

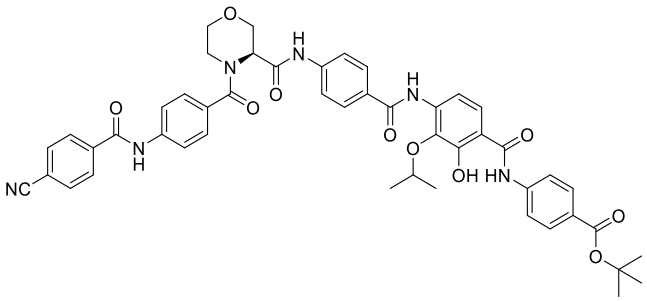
^{1}H-NMR (500 MHz, DMSO-d_6) = δ 10.67 (s, 1H, NH), 10.53 (s, 1H, NH), 10.47 (s, 1H, NH), 9.55 (s, 1H, NH), 8.12-8.11 (m, 2H, H_{Ar}), 8.05-8.04 (d, *J* = 8.2 Hz, 2H, H_{Ar}), 8.01-8.00 (m, 2H, H_{Ar}), 7.90-7.88 (m, 4H, H_{Ar}), 7.84-7.69 (m, 6H, H_{Ar}), 7.50 (bs, 1H, H_{Ar}), 7.42-7.40 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.06-5.98 (m, 1H, $OCH_2C\mathit{H}CH_2$), 5.40-5.35 (dq, *J* = 1.7, 17.2 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 5.22-5.19 (dq, *J* = 1.6, 10.5 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 5.03 (bs, 0.5H,

OC*H*$_2$CHN), 4.62-4.61 (d, *J* = 5.4 Hz, 2H, OC*H*$_2$CHCH$_2$), 4.53-4.46 (sept, *J* = 6.1 Hz, 1H, C*H*(CH$_3$)$_2$), 4.43-4.40 (m, 1H, OCH$_2$C*H*N), 4.35-4.18 (m, 0.5H, OC*H*$_2$CHN), 3.96-3.80 (m, 3H, OC*H*$_2$CH$_2$N, OC*H*$_2$CHN), 3.54-3.42 (m, 2H, OCH$_2$C*H*$_2$N), 1.55 (s, 9H, C(CH$_3$)$_3$), 1.27-1.26 (d, *J* = 6.0 Hz, 6H, CH(C*H*$_3$)$_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d$_6$) = δ 170.7 (CO), 168.7 (CO), 164.6 (CO), 164.5 (CO), 164.4 (CO), 164.3 (CO), 149.5 (C$_{Ar}$), 143.0 (C$_{Ar}$), 142.6 (C$_{Ar}$), 142.1 (C$_{Ar}$), 140.2 (C$_{Ar}$), 138.7 (C$_{Ar}$), 135.6 (C$_{Ar}$), 133.7 (OCH$_2$*C*HCH$_2$), 132.5 (C$_{Ar}$), 130.1 (C$_{Ar}$), 128.6 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.1 (C$_{Ar}$), 127.2 (C$_{Ar}$), 126.0 (C$_{Ar}$), 123.6 (C$_{Ar}$), 119.9 (C$_{Ar}$), 119.0 (C$_{Ar}$), 118.8 (C$_{Ar}$), 118.3 (OCH$_2$CH*C*H$_2$), 117.8 (CN), 114.0 (C$_{Ar}$), 80.3 (*C*(CH$_3$)$_3$), 76.2 (O*C*H$_2$CHCH$_2$), 74.3 (*C*H(CH$_3$)$_2$), 67.9 (OCH$_2$*C*HN), 65.6 (O*C*H$_2$CH$_2$N), 53.3 (O*C*H$_2$CHN), 45.5 (OCH$_2$*C*H$_2$N), 27.9 (C(*C*H$_3$)$_3$), 22.3 (CH(*C*H$_3$)$_2$) ppm;

HRMS (ESI) calculated for C$_{51}$H$_{50}$N$_6$O$_{10}$Na [M+Na]$^+$: 929.3486; found: 929.3494.

tert-Butyl (*S*)-4-(4-(4-(4-(4-(4-cyanobenzamido)benzoyl)morpholine-3-carboxamido) benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**157**)



Allyl ether **156** (60.9 mg, 0.07 mmol) was dissolved in THF (3 mL). Aniline (20 µL, 0.22 mmol, 3.30 equiv.) and Pd(PPh$_3$)$_4$ (7.8 mg, 7 µmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 90 min. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH$_2$Cl$_2$ = 2%, 3%) to furnish product **157** (53.0 mg, 0.06 mmol, 91%) as yellow amorphous solid.

R$_f$ (3% MeOH in CH$_2$Cl$_2$) = 0.51;

[α]$_D^{27}$ = -10.6 ° (c 0.2, THF);

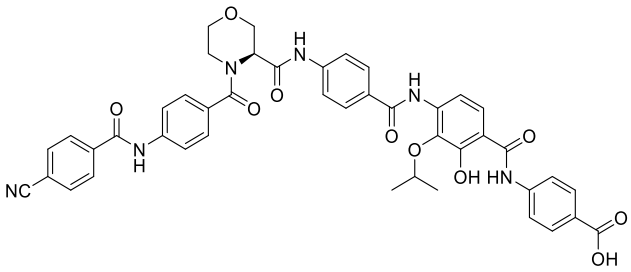
^{1}H-NMR (600 MHz, DMSO-d$_6$) = 12.28 (s, 1H, OH), 10.67-10.20 (m, 3H, NH), 9.43 (s, 1H, NH), 8.11 (bs, 2H, H$_{Ar}$), 8.05-8.04 (d, *J* = 7.9 Hz, 2H, H$_{Ar}$), 7.98 (bs, 2H, H$_{Ar}$), 7.94-7.92 (d, *J* = 8.8 Hz, 2H, H$_{Ar}$), 7.90-7.73 (m, 7H, H$_{Ar}$), 7.70-7.68 (d, *J* = 8.8 Hz, 1H, H$_{Ar}$), 7.50-7.38 (m, 2H, H$_{Ar}$), 5.03 (bs, 0.5H, OC*H*$_2$CHN), 4.58-4.52 (sept, *J* = 6.1 Hz, 1H, C*H*(CH$_3$)$_2$), 4.43-4.18

(m, 1.5H, OCH_2CHN), 3.98-3.80 (m, 3H, OCH_2CH_2N, OCH_2CHN), 3.54-3.50 (m, 2H, OCH_2CH_2N), 1.55 (s, 9H, $C(CH_3)_3$), 1.27-1.26 (d, J = 5.7 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 170.7 (CO), 168.7 (CO), 168.4 (CO), 164.5 (CO), 164.4 (CO), 164.2 (CO), 154.2 (C_{Ar}), 142.2 (C_{Ar}), 142.0 (C_{Ar}), 140.2 (C_{Ar}), 138.7 (C_{Ar}), 137.0 (C_{Ar}), 136.4 (C_{Ar}), 132.5 (C_{Ar}), 131.5 (C_{Ar}), 131.4 (C_{Ar}), 130.5 (C_{Ar}), 129.9 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 128.1 (C_{Ar}), 126.8 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.9 (C_{Ar}), 118.9 (C_{Ar}), 118.3 (CN), 114.0 (C_{Ar}), 112.5 (C_{Ar}), 112.2 (C_{Ar}), 80.5 ($C(CH_3)_3$), 74.8 ($CH(CH_3)_2$), 67.9 (OCH_2CHN), 66.0 (OCH_2CH_2N), 53.3 (OCH_2CHN), 45.5 (OCH_2CH_2N), 27.8 ($C(CH_3)_3$), 22.3 ($CH(CH_3)_2$) ppm;

HRMS (ESI) calculated for $C_{48}H_{46}N_6O_{10}Na$ $[M+Na]^+$: 889.3173; found: 889.3176.

(*S*)-4-(4-(4-(4-(4-(4-Cyanobenzamido)benzoyl)morpholine-3-carboxamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSE04**



tert-Butyl ester **157** (48.0 mg, 0.06 mmol) was dissolved in precooled TFA (3 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSE04** (35.4 mg, 0.04 mmol, 79%) as colorless amorphous solid.

$[\alpha]_D^{27}$ = -7.9 ° (c 0.1, MeOH);

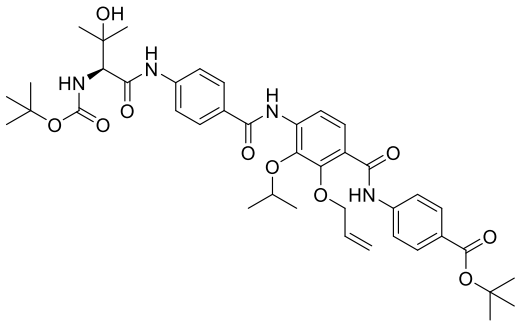
^{1}H-NMR (600 MHz, DMSO-d_6) = 12.82 (bs, 1H, CO_2H), 12.28 (s, 1H, OH), 10.67 (s, 1H, NH), 10.60 (s, 1H, NH), 10.49-10.20 (m, 1H, NH), 9.44 (s, 1H, NH), 8.11 (bs, 2H, H_{Ar}), 8.05-8.04 (d, J = 7.9 Hz, 2H, H_{Ar}), 7.98-7.96 (m, 5H, H_{Ar}), 7.89-7.73 (m, 8H, H_{Ar}), 7.71-7.69 (d, J = 8.8 Hz, 1H, H_{Ar}), 7.50-7.38 (m, 2H, H_{Ar}), 5.04 (bs, 0.7H, OCH_2CHN), 4.58-4.52 (sept, J = 6.1 Hz, 1H, $CH(CH_3)_2$), 4.41-4.17 (m, 2H, OCH_2CH_2N, OCH_2CHN, OCH_2CHN), 3.96-3.80 (m, 4.3H, OCH_2CH_2N, OCH_2CHN), 1.28-1.27 (d, J = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 170.7 (CO), 168.7 (CO), 168.5 (CO), 166.9 (CO), 164.4 (CO), 164.2 (CO), 154.1 (C_{Ar}), 142.2 (C_{Ar}), 142.0 (C_{Ar}), 140.2 (C_{Ar}), 138.7 (C_{Ar}), 137.0 (C_{Ar}), 136.4 (C_{Ar}), 132.5 (C_{Ar}), 130.2 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 128.1 (C_{Ar}), 126.3 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.9 (C_{Ar}), 118.9 (C_{Ar}), 118.3 (CN), 114.0 (C_{Ar}), 112.5 (C_{Ar}), 112.3 (C_{Ar}), 74.9 ($CH(CH_3)_2$), 67.9 (OCH_2CHN), 66.0 (OCH_2CH_2N), 53.3 (OCH_2CHN), 45.5 (OCH_2CH_2N), 22.3 ($CH(CH_3)_2$) ppm;

HRMS (ESI) calculated for $C_{44}H_{37}N_6O_{10}$ [M-H]$^-$: 809.2571; found: 809.2578.

4.2.9 (*S*)-2-Amino-3-hydroxy-3-methylbutanoic acid derivative

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(4-(2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3-methyl butanamido)benzamido)-3-isopropoxybenzamido)benzoate (**124**)



Amine **5** (200 mg, 0.37 mmol) and acid **(*S*)-106** (120 mg, 0.51 mmol, 1.40 equiv.) were dissolved in EtOAc (800 µL) and pyridine (89 µL, 1.10 mmol, 3.00 equiv.) was added. T3P (50% in EtOAc, 400 µL, 0.66 mmol, 1.80 equiv.) was added at 0 °C and the mixture was stirred for 22 h while warming to rt. H_2O was added and the aq. phase was extracted with EtOAc (3x). The combined organic phases were washed with a sat. $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (MeOH in CH_2Cl_2 = 0%, 1%) to furnish product **124** (189 mg, 0.25 mmol, 68%) as yellow amorphous solid.

R_f (3% MeOH in CH_2Cl_2) = 0.20;

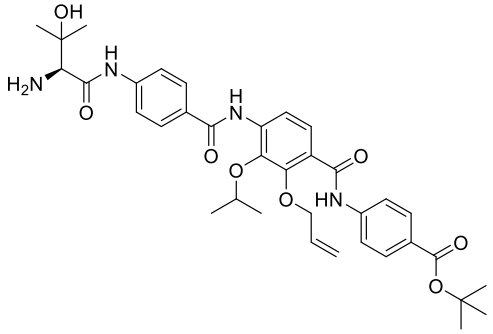
$[\alpha]_D^{22}$ = -2.7 ° (c 0.2, MeOH);

^{1}H-NMR (500 MHz, DMSO-d_6) = 10.53 (s, 1H, NH), 10.10 (s, 1H, NH), 9.51 (s, 1H, NH), 7.98-7.96 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.90-7.88 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.84-7.81 (m, 3H, H_{Ar}), 7.79-7.77 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.41-7.40 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 6.66-6.64 (d, *J* = 9.0 Hz, 1H, CHN*H*), 6.06-5.98 (m, 1H, $OCH_2C\mathit{H}CH_2$), 5.39-5.35 (dq, *J* = 1.7, 17.1 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 5.22-5.19 (dq, *J* = 1.7, 10.5 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 4.87 (s, 1H, OH), 4.61-4.60 (d, *J* = 5.5 Hz, 1H, $OC\mathit{H}_2CHCH_2$), 4.53-4.46 (sept, *J* = 6.1 Hz, 1H, $C\mathit{H}(CH_3)_2$), 4.12-4.08 (m, 1H, C*H*NH), 1.55 (s, 9H, $C(CH_3)_3$), 1.40 (s, 9H, $C(CH_3)_3$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, $CH(C\mathit{H}_3)_2$), 1.21 (s, 3H, $C(CH_3)_2$), 1.16 (s, 3H, $C(CH_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 169.8 (CO), 164.6 (CO), 164.6 (CO), 164.3 (CO), 155.4 (CO), 149.5 (C_{Ar}), 143.0 (C_{Ar}), 142.5 (C_{Ar}), 142.1 (C_{Ar}), 135.7 (C_{Ar}), 133.7 ($OCH_2\mathit{C}HCH_2$), 130.1 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 127.1 (C_{Ar}), 126.0 (C_{Ar}), 123.6 (C_{Ar}), 118.9 ($OCH_2CH\mathit{C}H_2$), 118.9 (C_{Ar}), 118.8 (C_{Ar}), 117.8 (C_{Ar}), 80.4 ($\mathit{C}(CH_3)_3$), 78.4 ($\mathit{C}(CH_3)_3$), 76.3

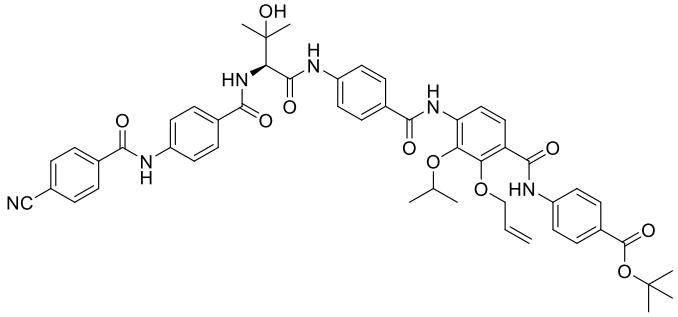
(OCH_2CHCH_2), 74.3 ($CH(CH_3)_2$), 70.8 ($COCH_3$), 63.2 (CHNH), 28.2 ($C(CH_3)_3$), 27.9 ($C(CH_3)_3$), 27.4 ($C(CH_3)_2$), 26.4 ($C(CH_3)_2$), 22.3 ($CH(CH_3)_2$) ppm;
HRMS (ESI) calculated for $C_{41}H_{52}N_4O_{10}Na$ $[M+Na]^+$: 783.3581; found: 783.3585.

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(4-(2-amino-3-hydroxy-3-methylbutanamido)benzamido)-3-isopropoxybenzamido)benzoate (**139**)



Carbamate **124** (184 mg, 0.24 mmol) was dissolved in HCl (4 M in 1,4-dioxane, 6.00 mL, 24.2 mmol, 100 equiv.) at 0 °C. The mixture was warmed up to rt and stirred for 15 min. The solution was transferred to a stirred suspension of EtOAc (160 mL) and a sat. $NaHCO_3$ solution (160 mL). The aq. phase was extracted with EtOAc and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was used in the next step without further purification.

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(4-(2-(4-(4-cyanobenzamido)benzamido)-3-hydroxy-3-methyl butanamido)benzamido)-3-isopropoxybenzamido)benzoate (**145**)



DIPEA (62 µL, 0.36 mmol, 3.00 equiv.) was added dropwise to a stirred solution of HATU (54.1 mg, 0.14 mmol, 1.20 equiv.) and carboxylic acid **3** (37.9 mg, 0.14 mmol, 1.20 equiv.) in DMF (3.0 mL). The solution was stirred for 5 min and was then transferred to a stirred solution of amine **139** (78.3 mg, 0.12 mmol) in DMF (1.7 mL). The reaction mixture was stirred at rt for 21 h. The mixture was diluted with EtOAc and washed with a 1 M HCl solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified

by column chromatography (MeOH in CH_2Cl_2 = 1%, 2%, 3%) to furnish product **145** (50.3 mg, 0.06 mmol, 47%) as colorless amorphous solid.

R_f (3% MeOH in CH_2Cl_2) = 0.19;

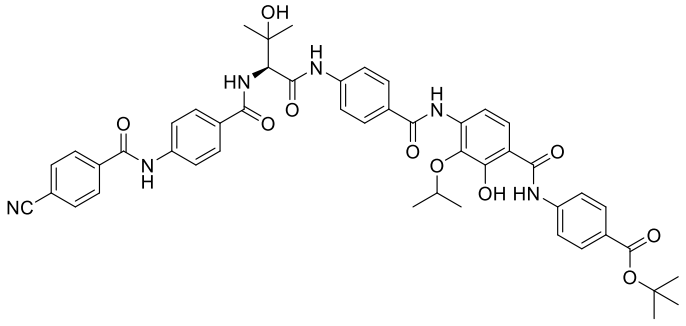
$[\alpha]_D^{23}$ = +6.0 ° (c 0.1, MeOH);

^{1}H-NMR (500 MHz, DMSO-d_6) = 10.71 (s, 1H, NH), 10.53 (s, 1H, NH), 10.28 (s, 1H, NH), 9.52 (s, 1H, NH), 8.14-8.12 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 8.08-8.06 (d, *J* = 8.9 Hz, 1H, CHN*H*), 8.06-8.04 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.99-7.97 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.96-7.95 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.92-7.88 (m, 4H, H_{Ar}), 7.83-7.80 (m, 5H, H_{Ar}), 7.41-7.40 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.05-5.97 (m, 1H, $OCH_2C\mathit{H}CH_2$), 5.39-5.35 (dq, *J* = 1.7, 17.2 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 5.21-5.18 (dq, *J* = 1.7, 10.5 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 5.07 (s, 1H, OH), 4.67-4.66 (d, *J* = 8.7 Hz, 1H, C*H*NH), 4.61-4.60 (d, *J* = 5.5 Hz, 2H, $OC\mathit{H}_2CHCH_2$), 4.53-4.46 (sept, *J* = 6.1 Hz, 1H, $C\mathit{H}(CH_3)_2$), 1.54 (s, 9H, $C(CH_3)_3$), 1.31 (s, 3H, $C(CH_3)_2$), 1.27 (s, 3H, $C(CH_3)_2$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, $CH(C\mathit{H}_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 169.4 (CO), 166.1 (CO), 164.6 (CO), 164.6 (CO), 164.5 (CO), 164.3 (CO), 149.6 (C_{Ar}), 143.0 (C_{Ar}), 142.6 (C_{Ar}), 142.1 (C_{Ar}), 141.7 (C_{Ar}), 138.7 (C_{Ar}), 135.7 (C_{Ar}), 133.7 ($OCH_2\mathit{C}HCH_2$), 132.6 (C_{Ar}), 130.1 (C_{Ar}), 129.3 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 127.1 (C_{Ar}), 126.1 (C_{Ar}), 123.7 (C_{Ar}), 119.6 (C_{Ar}), 119.0 ($OCH_2CH\mathit{C}H_2$), 118.9 (C_{Ar}), 118.3 (CN), 117.8 (C_{Ar}), 114.1 (C_{Ar}), 80.4 ($\mathit{C}(CH_3)_3$), 76.3 ($O\mathit{C}H_2CHCH_2$), 74.3 ($\mathit{C}H(CH_3)_2$), 70.9 ($\mathit{C}(CH_3)_2$), 62.3 (CHNH), 27.9 ($C(\mathit{C}H_3)_3$), 27.4 ($C(\mathit{C}H_3)_2$), 27.2 ($C(\mathit{C}H_3)_2$), 22.4 ($CH(\mathit{C}H_3)_2$) ppm;

HRMS (ESI) calculated for $C_{51}H_{52}N_6O_{10}Na$ $[M+Na]^+$: 931.3643; found: 931.3638.

tert-Butyl (*S*)-4-(4-(4-(2-(4-(4-cyanobenzamido)benzamido)-3-hydroxy-3-methylbutanamido) benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**151**)



Allyl ether **145** (47.4 mg, 0.05 mmol) was dissolved in THF (2.6 mL). Aniline (16 µL, 0.17 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (6.0 mg, 5 µmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 2 h. The mixture was concentrated under reduced

pressure. The crude product was purified by column chromatography (MeOH in CH_2Cl_2 = 1%, 2%, 3%) to furnish product **151** (37.7 mg, 0.04 mmol, 83%) as yellow amorphous solid.

R_f (3% MeOH in CH_2Cl_2) = 0.14;

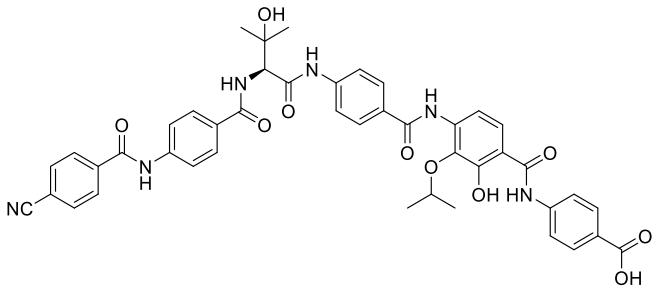
$[\alpha]_D^{23}$ = +4.9 ° (c 0.1, MeOH);

^{1}H-NMR (500 MHz, DMSO-d_6) = 12.28 (s, 1H, ArOH), 10.71 (s, 1H, NH), 10.61 (s, 1H, NH), 10.30 (s, 1H, NH), 9.40 (s, 1H, NH), 8.14-8.13 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 8.08-8.04 (m, 3H, CHN*H*, H_{Ar}), 7.97-7.90 (m, 8H, H_{Ar}), 7.86-7.81 (m, 5H, H_{Ar}), 7.71-7.69 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 5.05 (s, 1H, $C(CH_3)_2O\mathit{H}$), 4.69-4.67 (d, *J* = 8.7 Hz, 1H, C*H*NH), 4.58-4.51 (sept, *J* = 6.1 Hz, 1H, $C\mathit{H}(CH_3)_2$), 1.55 (s, 9H, $C(CH_3)_3$), 1.31 (s, 3H, $C(CH_3)_2$), 1.27-1.26 (s, 9H, $C(CH_3)_2$, $CH(C\mathit{H}_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 169.4 (CO), 168.5 (CO), 166.1 (CO), 164.5 (CO), 164.5 (CO), 164.2 (CO), 154.1 (C_{Ar}), 142.2 (C_{Ar}), 142.0 (C_{Ar}), 141.7 (C_{Ar}), 138.7 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 132.5 (C_{Ar}), 129.9 (C_{Ar}), 129.3 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 128.4 (C_{Ar}), 126.8 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.6 (C_{Ar}), 118.9 (C_{Ar}), 118.3 (CN), 114.1 (C_{Ar}), 112.4 (C_{Ar}), 80.5 ($\mathit{C}(CH_3)_3$), 74.9 ($\mathit{C}H(CH_3)_2$), 70.9 ($\mathit{C}(CH_3)_2$), 62.3 (CHNH), 27.8 ($C(\mathit{C}H_3)_3$), 27.3 ($C(\mathit{C}H_3)_2$), 27.1 ($C(\mathit{C}H_3)_2$), 22.3 ($CH(\mathit{C}H_3)_2$) ppm;

HRMS (ESI) calculated for $C_{48}H_{47}N_6O_{10}Na$ $[M-H]^-$: 867.3354; found: 867.3352.

(*S*)-4-(4-(4-(2-(4-(4-Cyanobenzamido)benzamido)-3-hydroxy-3-methylbutanamido) benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSG04**



Ester **151** (35.8 mg, 0.04 mmol) was dissolved in precooled TFA (2 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSG04** (13.0 mg, 0.02 mmol, 39%) as beige amorphous solid.

$[\alpha]_D^{23}$ = +9.5 ° (c 0.1, MeOH);

^{1}H-NMR (500 MHz, DMSO-d_6) = 12.82 (s, 1H, CO_2H), 12.29 (s, 1H, ArOH), 10.71 (s, 1H, NH), 10.60 (s, 1H, NH), 10.30 (s, 1H, NH), 9.40 (s, 1H, NH), 8.14-8.13 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 8.08-8.04 (m, 3H, CHN*H*, H_{Ar}), 7.98-7.95 (m, 5H, H_{Ar}), 7.92-7.90 (d, *J* = 8.9 Hz, 2H,

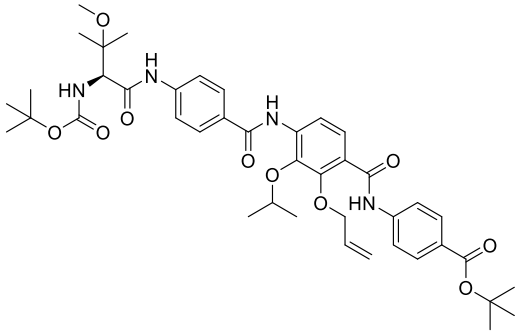
H_{Ar}), 7.86-7.81 (m, 5H, H_{Ar}), 7.72-7.70 (d, *J* = 9.0 Hz, 1H, H_{Ar}), 5.05 (s, 1H, $C(CH_3)_2O\mathit{H}$), 4.69-4.67 (d, *J* = 8.7 Hz, 1H, $C\mathit{H}NH$), 4.58-4.51 (sept, *J* = 6.2 Hz, 1H, $C\mathit{H}(CH_3)_2$), 1.31 (s, 3H, $C(CH_3)_2$), 1.27-1.26 (s, 9H, $C(CH_3)_2$, $CH(C\mathit{H}_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 169.4 (CO), 168.5 (CO), 166.9 (CO), 166.1 (CO), 164.5 (CO), 164.2 (CO), 154.1 (C_{Ar}), 142.2 (C_{Ar}), 142.0 (C_{Ar}), 141.7 (C_{Ar}), 138.7 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 132.5 (C_{Ar}), 130.2 (C_{Ar}), 129.3 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 128.4 (C_{Ar}), 126.3 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.6 (C_{Ar}), 118.9 (C_{Ar}), 118.3 (CN), 114.1 (C_{Ar}), 112.4 (C_{Ar}), 112.2 (C_{Ar}), 74.9 ($\mathit{C}H(CH_3)_2$), 70.9 ($\mathit{C}(CH_3)_2$), 62.3 (CHNH), 27.3 ($C(\mathit{C}H_3)_2$), 27.1 ($C(\mathit{C}H_3)_2$), 22.3 ($CH(\mathit{C}H_3)_2$) ppm;

HRMS (ESI) calculated for $C_{44}H_{39}N_6O_{10}$ $[M-H]^-$: 811.2728; found: 811.2729.

4.2.10 (*S*)-2-Amino-3-methoxy-3-methylbutanoic acid derivative

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(4-(2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-methyl butanamido)benzamido)-3-isopropoxybenzamido)benzoate (**123**)



Amine **5** (100 mg, 0.18 mmol) and acid **107** (63.5 mg, 0.26 mmol, 1.40 equiv.) were dissolved in EtOAc (400 µL) and pyridine (44 µL, 0.55 mmol, 3.00 equiv.) was added. T3P (50% in EtOAc, 200 µL, 0.33 mmol, 1.80 equiv.) was added at 0 °C and the mixture was stirred at 0 °C for 3 h. H_2O was added and the aq. phase was extracted with EtOAc (3x). The combined organic phases were washed with a sat. $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (dry load, PE/EtOAc = 2:1) to furnish product **123** (70.2 mg, 0.09 mmol, 49%) as brown amorphous solid.

R_f (PE/EtOAc = 1:1) = 0.54;

$[\alpha]_D^{22}$ = -15.2 ° (c 0.1, MeOH);

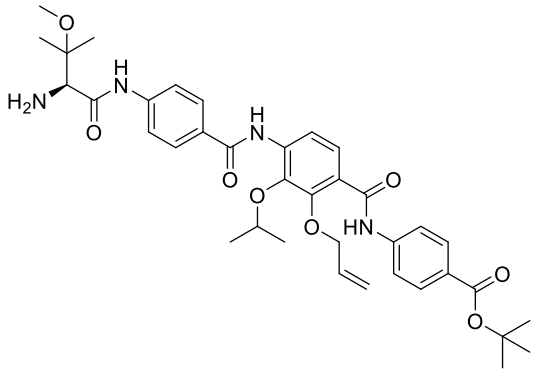
^{1}H-NMR (500 MHz, DMSO-d_6) = 10.53 (s, 1H, NH), 10.16 (s, 1H, NH), 9.51 (s, 1H, NH), 7.98-7.97 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.90-7.88 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.84-7.81 (m, 3H, H_{Ar}), 7.79-7.78 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.41-7.40 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 6.76-6.74 (d, *J* = 8.7 Hz,

1H, CHN*H*), 6.05-5.99 (m, 1H, OCH_2CHCH_2), 5.39-5.38 (dd, *J* = 1.6, 17.2 Hz, 1H, OCH_2CHCH_2), 5.21-5.19 (dd, *J* = 1.4, 10.5 Hz, 1H, OCH_2CHCH_2), 4.61-4.60 (d, *J* = 5.4 Hz, 1H, OCH_2CHCH_2), 4.53-4.47 (sept, *J* = 6.2 Hz, 1H, $CH(CH_3)_2$), 4.31-4.30 (d, *J* = 9.0 Hz, 1H, CHNH), 3.17 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.40 (s, 9H, $C(CH_3)_3$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$), 1.19 (s, 6H, $C(CH_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 169.4 (CO), 164.6 (CO), 164.5 (CO), 164.3 (CO), 155.4 (CO), 149.5 (C_{Ar}), 143.0 (C_{Ar}), 142.5 (C_{Ar}), 142.0 (C_{Ar}), 135.6 (C_{Ar}), 133.6 (OCH_2CHCH_2), 130.1 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 127.1 (C_{Ar}), 126.0 (C_{Ar}), 123.6 (C_{Ar}), 118.9 (OCH_2CHCH_2), 118.8 (C_{Ar}), 118.8 (C_{Ar}), 117.8 (C_{Ar}), 80.5 ($C(CH_3)_3$), 78.5 ($C(CH_3)_3$), 76.2 (OCH_2CHCH_2), 76.0 ($COCH_3$), 74.3 ($CH(CH_3)_2$), 59.7 (CHNH), 49.2 (OCH_3), 28.1 ($C(CH_3)_3$), 27.9 ($C(CH_3)_3$), 22.3 ($CH(CH_3)_2$), 22.1 ($C(CH_3)_2$) ppm;

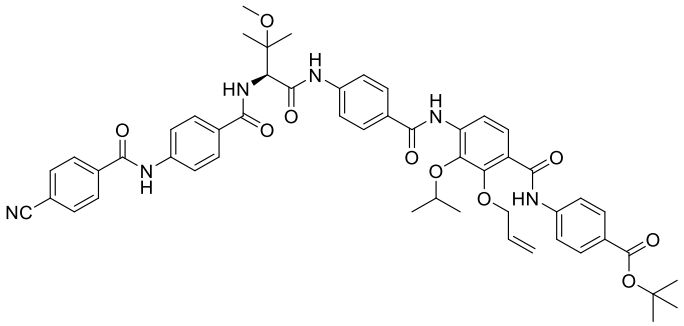
HRMS (ESI) calculated for $C_{42}H_{54}N_4O_{10}Na$ $[M+Na]^+$: 797.3738; found: 797.3726.

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(4-(2-amino-3-methoxy-3-methylbutanamido)benzamido)-3-isopropoxybenzamido)benzoate (**138**)



Carbamate **123** (65.0 mg, 0.08 mmol) was dissolved in HCl (4 M in 1,4-dioxane, 2.10 mL, 9.32 mmol, 100 equiv.) at 0 °C. The mixture was warmed up to rt and stirred for 15 min. The solution was transferred to a stirred suspension of EtOAc (60 mL) and a sat. $NaHCO_3$ solution (60 mL). The aq. phase was extracted with EtOAc and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was used in the next step without further purification.

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(4-(2-(4-(4-cyanobenzamido)benzamido)-3-methoxy-3-methylbutanamido)benzamido)-3-isopropoxybenzamido)benzoate (**144**)



DIPEA (44 µL, 0.25 mmol, 3.00 equiv.) was added dropwise to a stirred solution of HATU (38.3 mg, 0.10 mmol, 1.20 equiv.) and carboxylic acid **3** (26.8 mg, 0.10 mmol, 1.20 equiv.) in DMF (2.1 mL). The solution was stirred for 5 min and was then transferred to a stirred solution of amine **138** (56.6 mg, 0.08 mmol) in DMF (1.2 mL). The reaction mixture was stirred at rt for 21 h. The mixture was diluted with EtOAc and washed with a 1 M HCl solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH in CH_2Cl_2 = 1%, 2%, 3%) to furnish product **144** (40.3 mg, 0.04 mmol, 52%) as colorless amorphous solid.

R_f (3% MeOH in CH_2Cl_2) = 0.27;

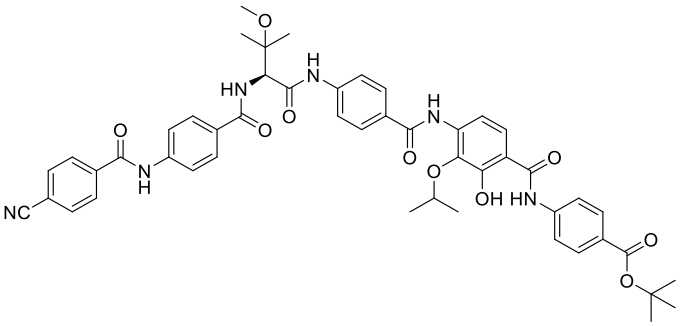
$[\alpha]_D^{22}$ = +5.4 ° (c 0.1, MeOH);

^{1}H-NMR (500 MHz, DMSO-d_6) = 10.71 (s, 1H, NH), 10.53 (s, 1H, NH), 10.33 (s, 1H, NH), 9.52 (bs, 1H, NH), 8.14-8.12 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 8.07-8.04 (m, 3H, NH, H_{Ar}), 7.99-7.97 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.96-7.94 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.91-7.88 (m, 3H, H_{Ar}), 7.84-7.80 (m, 5H, H_{Ar}), 7.41-7.40 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.06-5.98 (m, 1H, OCH_2CHCH_2), 5.39-5.35 (dq, *J* = 1.7, 17.2 Hz, 1H, OCH_2CHCH_2), 5.22-5.19 (dq, *J* = 1.7, 10.5 Hz, 1H, OCH_2CHCH_2), 4.89-4.87 (d, *J* = 8.7 Hz, 1H, C*H*NH), 4.61-4.60 (d, *J* = 5.5 Hz, 1H, OCH_2CHCH_2), 4.53-4.46 (sept, *J* = 6.1 Hz, 1H, $CH(CH_3)_2$), 3.23 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.31 (s, 6H, $C(CH_3)_2$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 169.1 (CO), 166.2 (CO), 164.6 (CO), 164.5 (CO), 164.4 (CO), 164.3 (CO), 149.5 (C_{Ar}), 143.0 (C_{Ar}), 142.5 (C_{Ar}), 142.0 (C_{Ar}), 141.7 (C_{Ar}), 138.7 (C_{Ar}), 135.6 (C_{Ar}), 133.7 (OCH_2CHCH_2), 132.5 (C_{Ar}), 130.4 (C_{Ar}), 130.1 (C_{Ar}), 129.2 (C_{Ar}), 128.6 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 127.1 (C_{Ar}), 126.0 (C_{Ar}), 123.6 (C_{Ar}), 119.5 (C_{Ar}), 119.0 (OCH_2CHCH_2), 118.9 (C_{Ar}), 118.8 (C_{Ar}), 118.3 (CN), 117.8 (C_{Ar}), 114.0 (C_{Ar}), 80.5 ($C(CH_3)_3$), 76.2 (OCH_2CHCH_2), 76.1 ($COCH_3$), 74.3 ($CH(CH_3)_2$), 60.4 (CHNH), 49.3 (OCH_3), 27.9 ($C(CH_3)_3$), 22.3 ($CH(CH_3)_2$), 21.7 ($C(CH_3)_2$) ppm;

HRMS (ESI) calculated for $C_{52}H_{54}N_6O_{10}Na$ $[M+Na]^+$: 945.3799; found: 945.3806.

tert-Butyl (*S*)-4-(4-(4-(2-(4-(4-cyanobenzamido)benzamido)-3-methoxy-3-methylbutanamido) benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**150**)



Allyl ether **144** (38.5 mg, 0.04 mmol) was dissolved in THF (2 mL). Aniline (13 µL, 0.14 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (4.8 mg, 4 µmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 2 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH in CH_2Cl_2 = 1%, 2%, 3%) to furnish product **150** (27.0 mg, 0.03 mmol, 73%) as colorless amorphous solid.

R_f (3% MeOH in CH_2Cl_2) = 0.18;

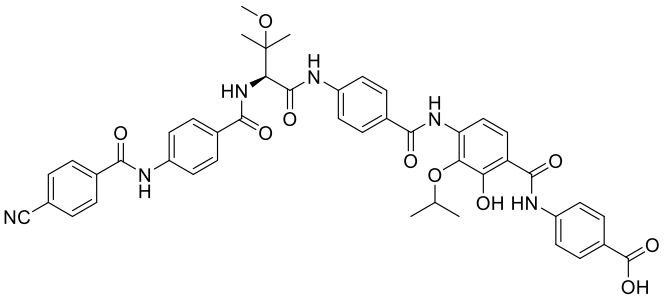
$[\alpha]_D^{22}$ = -3.8 ° (c 0.1, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = 12.29 (s, 1H, OH), 10.70 (s, 1H, NH), 10.60 (bs, 1H, NH), 10.35 (s, 1H, NH), 9.39 (bs, 1H, NH), 8.14-8.13 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 8.07-8.04 (m, 3H, NH, H_{Ar}), 7.96-7.89 (m, 8H, H_{Ar}), 7.86-7.81 (m, 5H, H_{Ar}), 4.89-4.88 (d, *J* = 8.9 Hz, 1H, C*H*NH), 4.55 (bs, 1H, C*H*$(CH_3)_2$), 3.23 (s, 3H, OCH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.31 (s, 6H, $C(CH_3)_2$), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = 169.1 (CO), 168.4 (CO), 166.2 (CO), 164.6 (CO), 164.4 (CO), 164.1 (CO), 142.1 (C_{Ar}), 141.7 (C_{Ar}), 138.7 (C_{Ar}), 136.3 (C_{Ar}), 132.5 (C_{Ar}), 131.5 (C_{Ar}), 131.4 (C_{Ar}), 129.9 (C_{Ar}), 129.2 (C_{Ar}), 128.8 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 122.9 (C_{Ar}), 120.6 (C_{Ar}), 119.5 (C_{Ar}), 118.9 (C_{Ar}), 118.3 (CN), 114.0 (C_{Ar}), 80.5 (*C*$(CH_3)_3$), 76.1 (*C*OCH_3), 74.9 (*C*H$(CH_3)_2$), 60.4 (CHNH), 49.3 (OCH_3), 27.8 (C(*C*$H_3)_3$), 22.3 (CH(*C*$H_3)_2$), 21.7 (C(*C*$H_3)_2$) ppm;

HRMS (ESI) calculated for $C_{49}H_{50}N_6O_{10}Na$ $[M+Na]^+$: 905.3486; found: 905.3470.

(*S*)-4-(4-(4-(2-(4-(4-Cyanobenzamido)benzamido)-3-methoxy-3-methylbutanamido) benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSF77**



Ester **150** (25.0 mg, 0.03 mmol) was dissolved in precooled TFA (1.5 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSF77** (5.3 mg, 0.01 mmol, 23%) as beige amorphous solid.

$[\alpha]_D^{22}$ = +0.8 ° (c 0.1, MeOH);

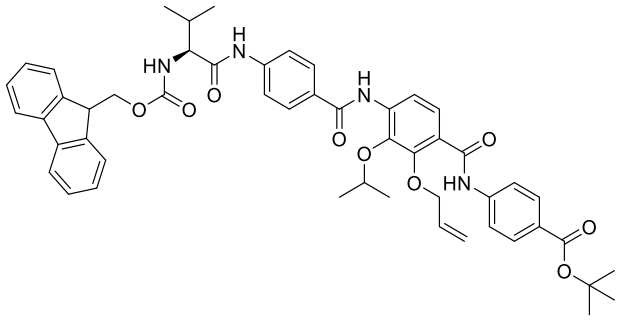
^{1}H-NMR (500 MHz, DMSO-d_6) = 12.82 (s, 1H, CO_2H), 12.29 (s, 1H, OH), 10.71 (s, 1H, NH), 10.60 (s, 1H, NH), 10.35 (s, 1H, NH), 9.40 (s, 1H, NH), 8.14-8.12 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 8.07-8.04 (m, 3H, NH, H_{Ar}), 7.98-7.94 (m, 6H, H_{Ar}), 7.91-7.89 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.86-7.81 (m, 5H, H_{Ar}), 7.71-7.70 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 4.89-4.87 (d, *J* = 8.9 Hz, 1H, C*H*NH), 4.58-4.51 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 3.23 (s, 3H, OCH_3), 1.31 (s, 6H, $C(CH_3)_2$), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 169.1 (CO), 168.5 (CO), 166.9 (CO), 166.2 (CO), 164.4 (CO), 164.2 (CO), 154.1 (C_{Ar}), 142.1 (C_{Ar}), 142.0 (C_{Ar}), 141.7 (C_{Ar}), 138.7 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 132.5 (C_{Ar}), 130.2 (C_{Ar}), 129.2 (C_{Ar}), 128.6 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 126.3 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.5 (C_{Ar}), 118.9 (C_{Ar}), 118.3 (CN), 114.0 (C_{Ar}), 112.4 (C_{Ar}), 112.2 (C_{Ar}), 76.1 (*C*OCH_3), 74.9 (*C*H$(CH_3)_2$), 60.4 (CHNH), 49.3 (OCH_3), 22.3 (CH(*C*$H_3)_2$), 21.7 (C(*C*$H_3)_2$) ppm;

HRMS (ESI) calculated for $C_{45}H_{41}N_6O_{10}$ $[M-H]^-$: 825.2884; found: 825.2889.

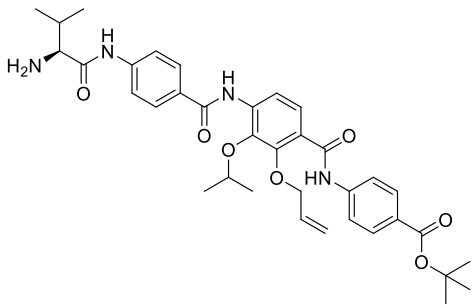
4.2.11L-Valine derivative

tert-Butyl (*S*)-4-(4-(4-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutanamido) benz-amido)-2-(allyloxy)-3-isopropoxybenzamido)benzoate (**127**)



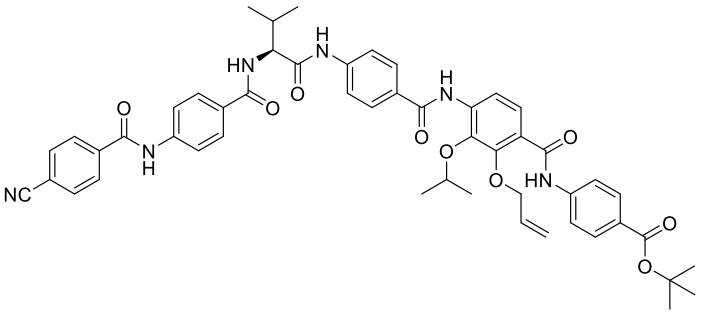
Amine **5** (200 mg, 0.37 mmol) and Fmoc-L-valine (**115**) (174 mg, 0.51 mmol, 1.40 equiv.) were dissolved in EtOAc (800 µL) and pyridine (180 µL, 2.20 mmol, 6.00 equiv.) was added. T3P (50% in EtOAc, 900 µL, 1.47 mmol, 4.00 equiv.) was added dropwise at 0 °C. The mixture was stirred for 4 h while warming to rt. The mixture was diluted with EtOAc and the organic phase was washed with 1 M HCl solution, sat. $NaHCO_3$ solution, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (dry load, 40% EtOAc in hexane) to furnish product **127** (324 mg, quant.) as yellowish amorphous solid, which was directly used in the next step.

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(4-(2-amino-3-methylbutanamido)benzamido)-3-isopropoxy benz-amido)benzoate (**141**)



Carbamate **127** (324 mg, 0.37 mmol, 1.00 equiv.) was dissolved in MeCN (4 mL) and piperidine (1 mL) was added. The mixture was stirred at rt for 3 h, before it was concentrated under reduced pressure. The residue was coevaporated with MeCN (3x) to furnish amine **141**, which was used in the next step without further purification.

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(4-(2-(4-(4-cyanobenzamido)benzamido)-3-methylbutanamido) benz-amido)-3-isopropoxybenzamido)benzoate (**147**)



Acid **3** (136 mg, 0.51 mmol, 1.40 equiv.) and HATU (195 mg, 0.51 mmol, 1.40 equiv.) were dissolved in DMF (9 mL) and DIPEA (200 µL, 1.10 mmol, 3.00 equiv.) was added. The mixture was stirred for 5 min before it was transferred to a stirred solution of amine **141** (236 mg, 0.37 mmol, 1.00 equiv.) in DMF (5 mL). The resulting mixture was stirred at rt for 23 h. EtOAc was added and the organic phase was washed with 0.1 M HCl solution, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (2% MeOH in CH_2Cl_2) to furnish product **147** (168 mg, 0.19 mmol, 51% over three steps) as yellowish amorphous solid.

R_f (3% MeOH in CH_2Cl_2) = 0.36;

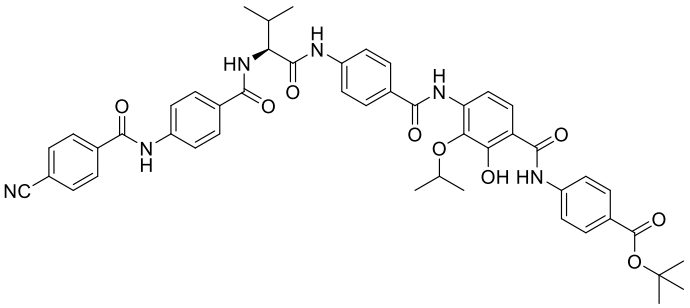
[α]$_D^{22}$ = +5.5 ° (c 0.1, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 10.69 (s, 1H, NH), 10.53 (s, 1H, NH), 10.52 (s, 1H, NH), 9.52 (s, 1H, NH), 8.49-8.47 (d, *J* = 8.1 Hz, 1H, CHN*H*), 8.14-8.12 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 8.05-8.04 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.99-7.96 (m, 4H, H_{Ar}), 7.90-7.88 (m, 4H, H_{Ar}), 7.84-7.81 (m, 5H, H_{Ar}), 7.41-7.40 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.05-5.98 (m, 1H, $OCH_2C\mathit{H}CH_2$), 5.39-5.35 (dq, *J* = 1.6, 17.2 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 5.21-5.19 (dq, *J* = 1.6, 10.5 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 4.61-4.60 (d, *J* = 5.5 Hz, 1H, $OC\mathit{H}_2CHCH_2$), 4.53-4.47 (sept, *J* = 6.1 Hz, 1H, $OC\mathit{H}(CH_3)_2$), 4.45-4.42 (t, *J* = 8.3 Hz, 1H, C*H*NH), 2.28-2.20 (m, 1H, $C\mathit{H}(CH_3)_2$), 1.55 (s, 9H, $C(CH_3)_3$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, $OCH(C\mathit{H}_3)_2$), 1.04-0.99 (dd, *J* = 6.7 Hz, 6H, $CH(C\mathit{H}_3)_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 171.2 (CO), 166.2 (CO), 164.6 (CO), 164.5 (CO), 164.4 (CO), 164.3 (CO), 149.5 (C_{Ar}), 143.0 (C_{Ar}), 142.5 (C_{Ar}), 142.1 (C_{Ar}), 141.5 (C_{Ar}), 138.7 (C_{Ar}), 135.7 ($OCH_2\mathit{C}HCH_2$), 133.6 (C_{Ar}), 132.5 (C_{Ar}), 130.1 (C_{Ar}), 129.3 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 127.1 (C_{Ar}), 126.0 (C_{Ar}), 123.6 (C_{Ar}), 119.5 (C_{Ar}), 118.9 ($OCH_2CH\mathit{C}H_2$), 118.8 (C_{Ar}), 118.7 (C_{Ar}), 118.3 (CN), 117.8 (C_{Ar}), 114.0 (C_{Ar}), 80.3 ($\mathit{C}(CH_3)_3$), 76.2 (OCH_2CHCH_2), 74.8 ($OCH(CH_3)_2$), 60.3 (CHNH), 30.0 ($\mathit{C}H(CH_3)_2$), 27.9 ($C(\mathit{C}H_3)_3$), 22.3 ($OCH(\mathit{C}H_3)_2$), 19.3 ($CH(\mathit{C}H_3)_2$), 19.2 ($CH(\mathit{C}H_3)_2$) ppm;

HRMS (ESI$^+$) calculated for $C_{51}H_{52}N_6O_9Na$ $[M+Na]^+$: 915.3693; found: 915.3715.

tert-Butyl (*S*)-4-(4-(4-(2-(4-(4-cyanobenzamido)benzamido)-3-methylbutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**153**)



Allyl ether **147** (152 mg, 0.17 mmol, 1.00 equiv.) was dissolved in THF (9 mL). Aniline (50.0 µL, 0.56 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (20.0 mg, 0.02 mmol, 10 mol%) were added and the mixture was stirred at rt for 2 h. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (dry load, 3% MeOH in CH_2Cl_2) to obtain a brown amorphous solid (169 mg), which was stirred in CH_2Cl_2. The mixture was filtered and the precipitate was washed with CH_2Cl_2 to furnish product **153** (78.4 mg, 0.09 mmol, 54%) as beige amorphous solid.

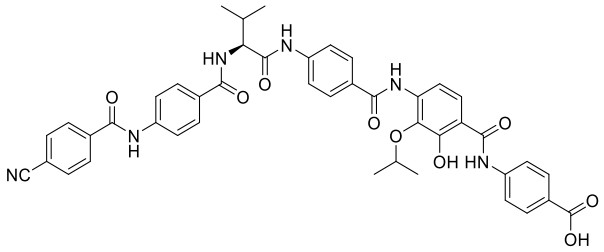
$[\alpha]_D^{22}$ = +7.8 ° (c 0.2, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 12.29 (s, 1H, OH), 10.69 (s, 1H, NH), 10.61 (s, 1H, NH), 10.54 (s, 1H, NH), 9.39 (s, 1H, NH), 8.49-8.48 (d, *J* = 8.1 Hz, 1H, CHN*H*), 8.14-8.12 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 8.05-8.04 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.97-7.96 (m, 4H, H_{Ar}), 7.93-7.92 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.89-7.88 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.86-7.82 (m, 5H, H_{Ar}), 7.71-7.70 (d, *J* = 8.7 Hz, 1H, H_{Ar}), 4.58-4.52 (sept, *J* = 6.1 Hz, 1H, OC*H*$(CH_3)_2$), 4.45-4.42 (t, *J* = 8.3 Hz, 1H, C*H*NH), 2.26-2.21 (m, 1H, C*H*$(CH_3)_2$), 1.55 (s, 9H, C$(CH_3)_3$), 1.27-1.26 (dd, *J* = 1.2, 6.1 Hz, 6H, OCH(C*H*$_3)_2$), 1.04-0.99 (dd, *J* = 6.7 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 171.2 (CO), 168.5 (CO), 166.2 (CO), 164.5 (CO), 164.4 (CO), 164.2 (CO), 154.1 (C_{Ar}), 142.2 (C_{Ar}), 142.0 (C_{Ar}), 141.5 (C_{Ar}), 138.7 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 132.5 (C_{Ar}), 129.9 (C_{Ar}), 129.3 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 126.8 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.5 (C_{Ar}), 118.8 (C_{Ar}), 118.3 (CN), 114.0 (C_{Ar}), 112.4 (C_{Ar}), 112.2 (C_{Ar}), 80.5 (*C*$(CH_3)_3$), 74.8 (O*C*H$(CH_3)_2$), 60.3 (CHNH), 30.0 (*C*H$(CH_3)_2$), 27.8 (C(*C*H$_3)_3$), 22.3 (OCH(*C*H$_3)_2$), 19.3 (CH(*C*H$_3)_2$), 19.2 (CH(*C*H$_3)_2$) ppm;

HRMS (ESI$^+$) calculated for $C_{48}H_{47}N_6O_9$ $[M-H]^-$: 851.3405; found: 851.3419.

(*S*)-4-(4-(4-(2-(4-(4-Cyanobenzamido)benzamido)-3-methylbutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSG18**



Ester **153** (34.7 mg, 0.04 mmol, 1.00 equiv.) was dissolved in precooled TFA (2 mL) at 0 °C. The mixture was stirred for 30 min while warming to rt. Et_2O was added at 0 °C. The precipitate was filtered off and washed with an excess of Et_2O to furnish **TSG18** (21.4 mg, 0.03 mmol, 66%) as beige amorphous solid.

$[\alpha]_D^{22}$ = +5.7 ° (c 0.1 MeOH);

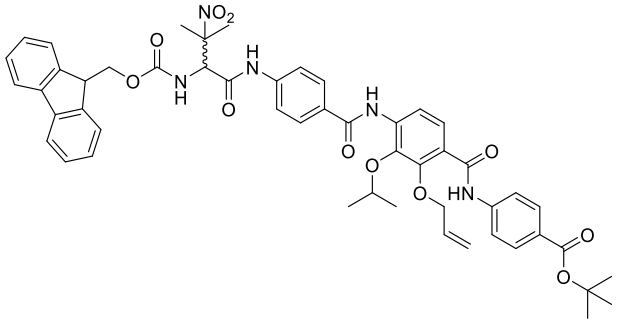
^{1}H-NMR (500 MHz, DMSO-d_6) = δ 12.82 (s, 1H, CO2H), 12.30 (s, 1H, OH), 10.69 (s, 1H, NH), 10.60 (s, 1H, NH), 10.54 (s, 1H, NH), 9.40 (s, 1H, NH), 8.49 (d, *J* = 8.0 Hz, 1H, CHN*H*), 8.14-8.12 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 8.06-8.04 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.97-7.95 (m, 6H, H_{Ar}), 7.89-7.82 (m, 7H, H_{Ar}), 7.72-7.70 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 4.59-4.51 (sept, *J* = 6.1 Hz, 1H, OC*H*$(CH_3)_2$), 4.46-4.42 (t, *J* = 8.4 Hz, 1H, C*H*NH), 2.28-2.19 (sept, *J* = 6.7 Hz, 1H, C*H*$(CH_3)_2$), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, OCH(C*H*$_3)_2$), 1.04-0.99 (dd, *J* = 6.7, 18.5 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 171.2 (CO), 168.5 (CO), 166.9 (CO), 166.2 (CO), 164.4 (CO), 164.2 (CO), 154.1 (C_{Ar}), 142.2 (C_{Ar}), 142.0 (C_{Ar}), 141.5 (C_{Ar}), 138.7 (C_{Ar}), 138.6 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 132.5 (C_{Ar}), 130.2 (C_{Ar}), 129.3 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 126.3 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.5 (C_{Ar}), 118.8 (C_{Ar}), 118.3 (CN), 114.0 (C_{Ar}), 112.4 (C_{Ar}), 112.2 (C_{Ar}), 74.8 (O*C*H$(CH_3)_2$), 60.3 (CHNH), 30.0 (*C*H$(CH_3)_2$), 22.3 (OCH(*C*H$_3)_2$), 19.3 (CH(*C*H$_3)_2$), 19.2 (CH(*C*H$_3)_2$) ppm;

HRMS (ESI$^+$) calculated for $C_{44}H_{39}N_6O_9$ $[M-H]^-$: 795.2779; found: 795.2773.

4.2.12 (*S*)-2-Amino-3-methyl-3-nitrobutanoic acid derivatives

tert-Butyl 4-(4-(4-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-methyl-3-nitrobutanamido) benzamido)-2-(allyloxy)-3-isopropoxybenzamido)benzoate (**126**)



Amine **5** (100 mg, 0.18 mmol) and β-nitrovaline **109** (98.6 mg, 0.26 mmol, 1.40 equiv.) were dissolved in EtOAc (400 µL) and pyridine (45 µL, 0.55 mmol, 3.00 equiv.) was added. T3P (50% in EtOAc, 200 µL, 0.33 mmol, 1.80 equiv.) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 2 h. H_2O was added and the aq. phase was extracted with EtOAc (3x). The combined organic phases were washed with a sat. $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (dry load, PE/EtOAc = 2:1) to furnish product **126** (127 mg, 0.14 mmol, 76%) as yellowish amorphous solid.

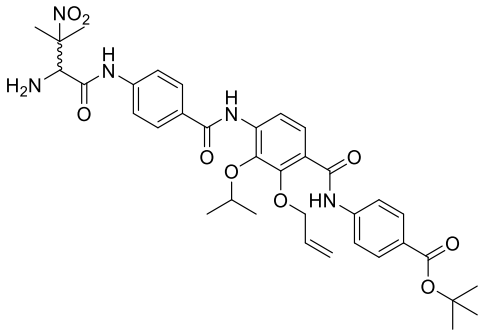
R_f (PE/EtOAc = 1:1) = 0.35;

^{1}H-NMR (500 MHz, DMSO-d_6) = 10.73 (s, 1H, NH), 10.53 (s, 1H, NH), 9.56 (s, 1H, NH), 8.26-8.24 (d, *J* = 8.6 Hz, 1H, CHN*H*), 8.01-7.98 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.90-7.88 (m, 4H, H_{Ar}), 7.84-7.75 (m, 7H, H_{Ar}), 7.43-7.39 (m, 3H, H_{Ar}), 7.34-7.29 (m, 2H, H_{Ar}), 6.06-5.98 (m, 1H, C*H*(CH_2)), 5.39-5.35 (dq, *J* = 1.6, 17.2 Hz, 1H, CHC*H*$_2$), 5.21-5.17 (m, 2H, CHC*H*$_2$, C*H*NH), 4.61-4.60 (d, *J* = 5.5 Hz, 2H, ArOC*H*$_2$), 4.54-4.45 (sept, *J* = 6.1 Hz, 1H, C*H*(CH_3)$_2$), 4.42-4.36 (m, 1H, C*H*CH_2O), 4.29-4.23 (m, 2H, CHC*H*$_2$O), 1.67 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.55 (s, 9H, C(CH_3)$_3$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3$)$_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 166.8 (CO), 164.6 (CO), 164.5 (CO), 164.2 (CO), 156.2 (CO), 149.5 (C_{Ar}), 143.7 (C_{Ar}), 143.7 (C_{Ar}), 143.0 (C_{Ar}), 142.7 (C_{Ar}), 141.4 (C_{Ar}), 140.7 (C_{Ar}), 135.6 (C_{Ar}), 133.7 (*C*HCH_2), 130.1 (C_{Ar}), 129.1 (C_{Ar}), 128.5 (C_{Ar}), 127.7 (d, *J* = 2.5 Hz, C_{Ar}), 127.2 (C_{Ar}), 127.1 (d, *J* = 7.6 Hz, C_{Ar}), 126.0 (C_{Ar}), 125.4 (d, *J* = 11.3 Hz, C_{Ar}), 123.6 (C_{Ar}), 120.1 (d, *J* = 2.6 Hz, C_{Ar}), 119.4 (C_{Ar}), 119.1 (C_{Ar}), 118.8 (C_{Ar}), 117.8 (CH*C*H_2), 89.0 (*C*(CH_3)$_2$), 80.3 (*C*(CH_3)$_3$), 76.3 (*C*H(CH_3)$_2$), 74.3 (ArOCH_2), 66.2 (*C*HCH_2O), 60.5 (CHNH), 46.6 (CH*C*H_2O), 27.9 (C(*C*H_3)$_3$), 23.2 (CH_3), 22.3 (CH(*C*H_3)$_2$) ppm;

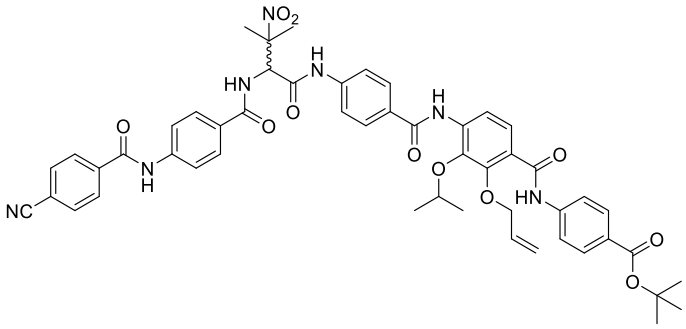
HRMS (ESI) calculated for $C_{51}H_{53}N_5O_{11}Na$ $[M+Na]^+$: 934.3639; found: 934.3634.

tert-Butyl 4-(2-(allyloxy)-4-(4-(2-amino-3-methyl-3-nitrobutanamido)benzamido)-3-isopropoxybenzamido)benzoate (**140**)



Carbamate **126** (400 mg, 0.44 mmol) was dissolved in a mixture of piperidine (1.3 mL) and MeCN (5.3 mL). The mixture was stirred at rt for 2 h, before it was concentrated under reduced pressure and coevaporated with MeCN (3x) to furnish amine **140** as yellow amorphous solid, which was used in the next step without further purification.

tert-Butyl 4-(2-(allyloxy)-4-(4-(2-(4-(4-cyanobenzamido)benzamido)-3-methyl-3-nitrobutanamido) benzamido)-3-isopropoxybenzamido)benzoate (**146**)



DIPEA (230 µL, 1.32 mmol, 3.00 equiv.) was added dropwise to a stirred solution of HATU (200 mg, 0.53 mmol, 1.20 equiv.) and carboxylic acid **3** (140 mg, 0.53 mmol, 1.20 equiv.) in DMF (11 mL). The solution was stirred for 5 min and then transferred to a stirred solution of amine **140** (303 mg, 0.44 mmol) in DMF (6 mL) at 0 °C. The reaction mixture was stirred at 20 h while warming to rt. The mixture was diluted with EtOAc and washed with a 1 M HCl solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (2% MeOH in CH_2Cl_2) to furnish product **146** (315 mg, 0.34 mmol, 77%) as orange amorphous solid.

R_f (3% MeOH in CH_2Cl_2) = 0.19;

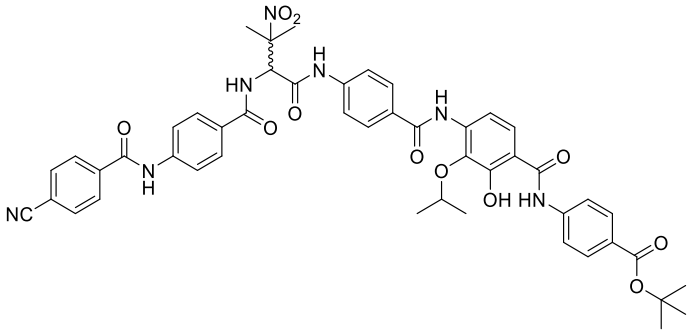
^{1}H-NMR (500 MHz, DMSO-d_6) = δ 10.71 (s, 1H, NH), 10.70 (s, 1H, NH), 10.53 (s, 1H, NH), 9.56 (s, 1H, NH), 8.78-8.76 (d, *J* = 9.2 Hz, 1H, CHN*H*), 8.14-8.12 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 8.06-8.04 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 8.00-7.98 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.96-7.95 (d, *J* = 8.8 Hz,

2H, H_{Ar}), 7.91-7.88 (m, 4H, H_{Ar}), 7.84-7.79 (m, 5H, H_{Ar}), 7.41-7.40 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 6.05-5.98 (m, 1H, OCH_2CHCH_2), 5.71-5.69 (d, *J* = 9.3 Hz, 1H, CHNH), 5.39-5.35 (dq, *J* = 1.6, 17.2 Hz, 1H, OCH_2CHCH_2), 5.21-5.19 (dq, *J* = 1.5, 10.5 Hz, 1H, OCH_2CHCH_2), 4.61-4.60 (d, *J* = 5.4 Hz, 2H, OCH_2CHCH_2), 4.52-4.45 (sept, *J* = 6.1 Hz, 1H, $CH(CH_3)_2$), 1.76 (s, 3H, $C(CH_3)_2$), 1.69 (s, 3H, $C(CH_3)_2$), 1.55 (s, 9H, $C(CH_3)_3$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 168.6 (CO), 166.8 (CO), 166.7 (CO), 164.6 (CO), 164.5 (CO), 164.2 (CO), 149.5 (C_{Ar}), 143.0 (C_{Ar}), 142.6 (C_{Ar}), 141.9 (C_{Ar}), 141.5 (C_{Ar}), 138.6 (C_{Ar}), 135.6 (C_{Ar}), 133.7 (OCH_2CHCH_2), 132.5 (C_{Ar}), 130.1 (C_{Ar}), 129.1 (C_{Ar}), 128.9 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 127.6 (C_{Ar}), 127.2 (C_{Ar}), 126.0 (C_{Ar}), 123.6 (C_{Ar}), 119.9 (C_{Ar}), 119.5 (C_{Ar}), 119.4 (C_{Ar}), 118.8 (OCH_2CHCH_2), 117.8 (CN), 114.1 (C_{Ar}), 89.0 ($C(CH_3)_2$), 80.3 ($C(CH_3)_3$), 76.2 (OCH_2CHCH_2), 74.3 ($CH(CH_3)_2$), 58.5 (CHNH), 27.9 ($C(CH_3)_3$), 23.2 ($C(CH_3)_2$), 22.9 ($C(CH_3)$), 22.3 ($CH(CH_3)_2$) ppm;

HRMS (ESI) calculated for $C_{51}H_{51}N_7O_{11}Na$ $[M+Na]^+$: 960.3544; found: 960.3557.

tert-Butyl 4-(4-(4-(2-(4-(4-cyanobenzamido)benzamido)-3-methyl-3-nitrobutanamido) benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**152**)

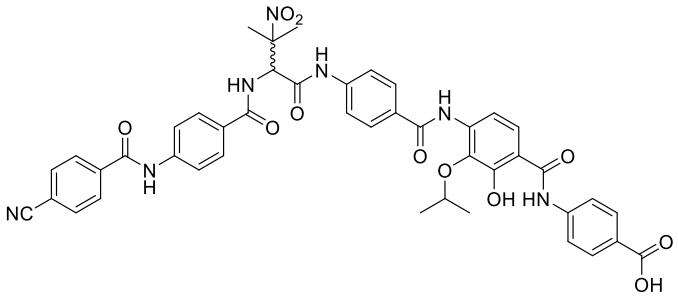


Allyl ether **146** (56.8 mg, 0.06 mmol) was dissolved in THF (2.7 mL). Aniline (18 µL, 0.20 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (7.0 mg, 6 µmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 90 min. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, 2% MeOH in CH_2Cl_2) to furnish product **152** (57.3 mg, 0.05 mmol, 84%) as yellow amorphous solid, which had a purity of 80% due to the presence of triphenylphosphin oxide impurities. The product was used in the next step without further purification.

$\mathbf{R}_f$ (3% MeOH in CH_2Cl_2) = 0.19;

HRMS (ESI) calculated for $C_{48}H_{46}N_7O_{11}$ $[M-H]^-$: 896.3255; found: 896.3212.

4-(4-(4-(2-(4-(4-Cyanobenzamido)benzamido)-3-methyl-3-nitrobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSF14**



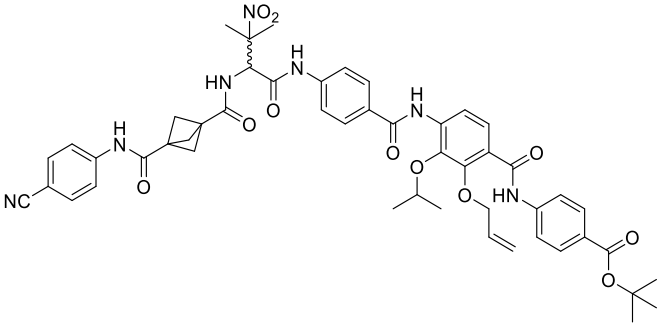
tert-Butyl ester **152** (19.8 mg, 0.02 mmol) was dissolved in precooled TFA (1.1 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSF14** (11.4 mg, 0.01 mmol, 61%) as colorless amorphous solid.

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 12.82 (s, 1H, CO_2H), 12.28 (s, 1H, OH), 10.71 (bs, 2H, NH), 10.60 (s, 1H, NH), 9.44 (s, 1H, NH), 8.78-8.76 (d, *J* = 9.3 Hz, 1H, CHN*H*), 8.14-8.12 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 8.06-8.04 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.98-7.94 (m, 6H, H_{Ar}), 7.92-7.89 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.86-7.84 (m, 3H, H_{Ar}), 7.82-7.80 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.70-7.68 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 5.71-5.69 (d, *J* = 9.3 Hz, 1H, C*H*NH), 4.57-4.50 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 1.76 (s, 3H, C(C*H*$_3$)), 1.70 (s, 3H, C(C*H*$_3$)), 1.27-1.25 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 168.5 (CO), 166.9 (CO), 166.8 (CO), 166.7 (CO), 164.5 (CO), 164.2 (CO), 154.1 (C_{Ar}), 142.0 (C_{Ar}), 141.9 (C_{Ar}), 141.6 (C_{Ar}), 138.6 (C_{Ar}), 137.0 (C_{Ar}), 136.4 (C_{Ar}), 132.5 (C_{Ar}), 130.2 (C_{Ar}), 129.1 (C_{Ar}), 128.9 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.3 (C_{Ar}), 126.3 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.6 (C_{Ar}), 119.4 (C_{Ar}), 118.3 (CN), 114.1 (C_{Ar}), 112.5 (C_{Ar}), 112.3 (C_{Ar}), 89.0 (*C*$(CH_3)_2$), 74.9 (*C*H$(CH_3)_2$), 58.5 (CHNH), 23.2 (C(*C*$H_3)_2$), 22.9 (C(*C*$H_3)_2$), 22.3 (CH(*C*$H_3)_2$) ppm;

HRMS (ESI) calculated for $C_{44}H_{38}N_7O_{11}$ $[M-H]^-$: 840.2629; found: 840.2632.

tert-Butyl 4-(2-(allyloxy)-4-(4-(2-(3-((4-cyanophenyl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxamido)-3-methyl-3-nitrobutanamido)benzamido)-3-isopropoxybenzamido)benzoate (**194**)



DIPEA (35 µL, 0.20 mmol, 3.00 equiv.) was added dropwise to a stirred solution of HATU (30.2 mg, 0.08 mmol, 1.20 equiv.) and carboxylic acid **43** (20.3 mg, 0.08 mmol, 1.20 equiv.) in DMF (1.6 mL). The solution was stirred for 5 min and then transferred to a stirred solution of amine **140** (45.6 mg, 0.07 mmol) in DMF (1.0 mL) at 0 °C. The reaction mixture was stirred for 18 h while warming to rt. The mixture was diluted with EtOAc and washed with a 1 M HCl solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH in CH_2Cl_2 = 1%, 2%) to furnish product **194** (45.0 mg, 0.05 mmol, 73%) as beige amorphous solid.

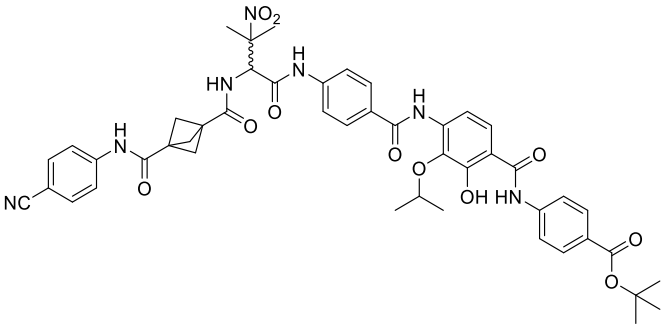
R_f (3% MeOH in CH_2Cl_2) = 0.20;

^{1}H-NMR (600 MHz, DMSO-d_6) = 10.70 (s, 1H, NH), 10.53 (s, 1H, NH), 9.98 (s, 1H, NH), 9.56 (s, 1H, NH), 8.40-8.38 (d, *J* = 9.9 Hz, 1H, CHN*H*), 8.00-7.99 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.90-7.88 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.87-7.85 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.84-7.77 (m, 7H, H_{Ar}), 7.41-7.40 (d, *J* = 8.4 Hz, 1H, H_{Ar}), 6.05-5.98 (m, 1H, C*H*CH_2), 5.48-5.47 (d, *J* = 9.6 Hz, 1H, C*H*NH), 5.39-5.35 (dq, *J* = 1.6, 17.2 Hz, 1H, CHC*H*$_2$), 5.21-5.19 (dq, *J* = 1.6, 10.5 Hz, 1H, CHC*H*$_2$), 4.61-4.60 (d, *J* = 5.4 Hz, 2H, OC*H*$_2$CH), 4.52-4.46 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 2.32 (s, 6H, CCH_2C), 1.68 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = 169.3 (CO), 168.5 (CO), 166.4 (CO), 166.1 (CO), 164.6 (CO), 164.2 (CO), 149.5 (C_{Ar}), 143.0 (C_{Ar}), 142.9 (C_{Ar}), 142.6 (C_{Ar}), 135.6 (C_{Ar}), 133.6 (*C*HCH_2), 133.1 (C_{Ar}), 130.1 (C_{Ar}), 129.1 (C_{Ar}), 128.4 (C_{Ar}), 127.2 (C_{Ar}), 126.0 (C_{Ar}), 123.6 (C_{Ar}), 119.7 (C_{Ar}), 119.6 (C_{Ar}), 119.4 (C_{Ar}), 119.1 (CN), 118.8 (C_{Ar}), 117.8 (CH*C*H_2), 105.3 (C_{Ar}), 88.9 (*C*$(CH_3)_2$), 80.3 (*C*$(CH_3)_3$), 76.2 (OCH_2), 74.3 (*C*H$(CH_3)_2$), 57.6 (CHNH), 51.8 (CCH_2C), 40.3 (*C*CH_2C), 38.0 (*C*CH_2C), 27.9 ($C(CH_3)_3$), 22.9 ($CH(CH_3)_2$), 22.7 ($CH(CH_3)_2$), 22.3 ($C(CH_3)_2$) ppm;

HRMS (ESI) calculated for $C_{50}H_{53}N_7O_{11}Na$ $[M+Na]^+$: 950.3701; found: 950.3692.

tert-Butyl 4-(4-(4-(2-(3-((4-cyanophenyl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxamido)-3-methyl-3-nitrobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**203**)



Allyl ether **194** (43.2 mg, 0.05 mmol) was dissolved in THF (2.1 mL). Aniline (14 µL, 0.15 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (5.4 mg, 5 µmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 2 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 1%, 3%) to furnish product **203** (36.5 mg, 0.04 mmol, 88%) as yellowish amorphous solid.

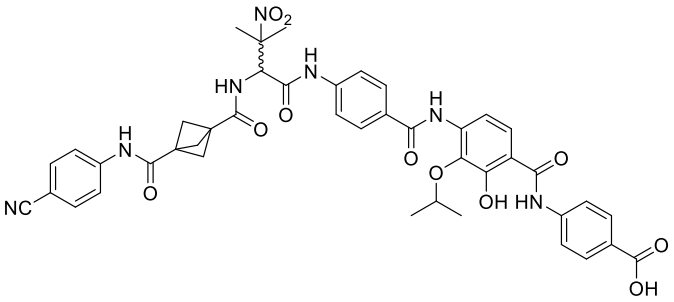
R_f (3% MeOH in CH_2Cl_2) = 0.14;

^{1}H-NMR (600 MHz, DMSO-d_6) = 12.28 (s, 1H, OH), 10.71 (s, 1H, NH), 10.62 (bs, 1H, NH), 9.98 (s, 1H, NH), 9.41 (s, 1H, NH), 8.40-8.39 (d, *J* = 9.6 Hz, 1H, CHN*H*), 7.97-7.96 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.93-7.91 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.87-7.84 (m, 5H, H_{Ar}), 7.81-7.79 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.79-7.77 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.66 (bs, 1H, H_{Ar}), 5.48-5.47 (d, *J* = 9.6 Hz, 1H, C*H*NH), 4.56 (bs, 1H, C*H*$(CH_3)_2$), 2.32 (s, 6H, CCH_2C), 1.68 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.55 (s, 9H, $C(CH_3)_3$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, $CH(CH_3)_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = 169.3 (CO), 168.5 (CO), 168.4 (CO), 166.4 (CO), 164.6 (CO), 164.1 (CO), 142.9 (C_{Ar}), 141.5 (C_{Ar}), 136.9 (C_{Ar}), 136.5 (C_{Ar}), 133.1 (C_{Ar}), 129.9 (C_{Ar}), 129.2 (C_{Ar}), 128.3 (C_{Ar}), 122.9 (C_{Ar}), 120.5 (C_{Ar}), 119.7 (C_{Ar}), 119.5 (C_{Ar}), 119.0 (CN), 112.6 (C_{Ar}), 112.2 (C_{Ar}), 105.3 (C_{Ar}), 88.9 (*C*$(CH_3)_2$), 80.4 (*C*$(CH_3)_3$), 57.6 (CHNH), 51.8 (CCH_2C), 40.4 (*C*CH_2C), 38.0 (*C*CH_2C), 27.8 ($C(CH_3)_3$), 22.9 ($CH(CH_3)_2$), 22.7 ($CH(CH_3)_2$), 22.3 ($C(CH_3)_2$) ppm;

HRMS (ESI) calculated for $C_{47}H_{49}N_7O_{11}Na$ $[M+Na]^+$: 910.3388; found: 910.3389.

4-(4-(4-(2-(3-((4-Cyanophenyl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxamido)-3-methyl-3-nitrobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSF62**



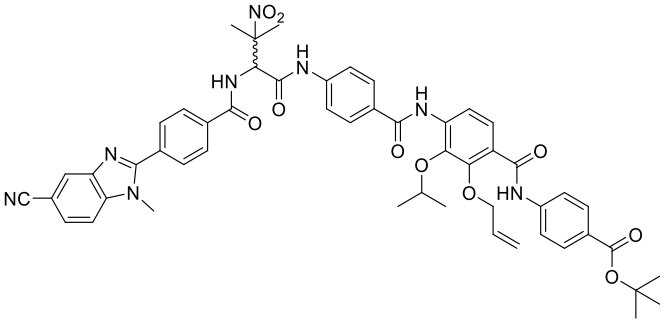
tert-Butyl ester **203** (35.1 mg, 0.04 mmol) was dissolved in precooled TFA (2 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSF62** (25.5 mg, 0.03 mmol, 78%) as colorless amorphous solid.

^{1}H-NMR (600 MHz, DMSO-d_6) = 12.82 (s, 1H, CO_2H), 12.29 (s, 1H, OH), 10.71 (s, 1H, NH), 10.60 (s, 1H, NH), 9.98 (s, 1H, NH), 9.43 (s, 1H, NH), 8.40-8.38 (d, *J* = 9.9 Hz, 1H, CHN*H*), 7.98-7.96 (m, 4H, H_{Ar}), 7.87-7.85 (m, 5H, H_{Ar}), 7.81-7.80 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.79-7.77 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.70-7.68 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 5.48-5.47 (d, *J* = 9.6 Hz, 1H, C*H*NH), 4.57-4.51 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 2.32 (s, 6H, CCH_2C), 1.68 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = 169.3 (CO), 168.5 (CO), 168.5 (CO), 166.9 (CO), 166.4 (CO), 164.1 (CO), 154.1 (C_{Ar}), 142.9 (C_{Ar}), 141.9 (C_{Ar}), 141.5 (C_{Ar}), 137.0 (C_{Ar}), 136.4 (C_{Ar}), 133.1 (C_{Ar}), 130.2 (C_{Ar}), 129.1 (C_{Ar}), 128.4 (C_{Ar}), 126.3 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.7 (C_{Ar}), 119.5 (C_{Ar}), 119.0 (CN), 112.5 (C_{Ar}), 112.3 (C_{Ar}), 105.3 (C_{Ar}), 88.9 (*C*$(CH_3)_2$), 74.9 (*C*H$(CH_3)_2$), 57.6 (CHNH), 51.8 (C*C*H_2C), 40.4 (*C*CH_2C), 38.0 (*C*CH_2C), 22.9 (CH(*C*$H_3)_2$), 22.7 (CH(*C*$H_3)_2$), 22.3 (C(*C*$H_3)_2$) ppm;

HRMS (ESI) calculated for $C_{43}H_{41}N_7O_{11}$ $[M-H]^-$: 830.2786; found: 830.2771.

tert-Butyl 4-(2-(allyloxy)-4-(4-(2-(4-(5-cyano-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)benzamido)-3-methyl-3-nitrobutanamido)benzamido)-3-isopropoxybenzamido)benzoate (**195**)



DIPEA (35 µL, 0.20 mmol, 3.00 equiv.) was added dropwise to a stirred solution of HATU (30.2 mg, 0.08 mmol, 1.20 equiv.) and carboxylic acid **34** (22.0 mg, 0.08 mmol, 1.20 equiv.) in DMF (1.6 mL). The solution was stirred for 5 min and then transferred to a stirred solution of amine **140** (45.6 mg, 0.0.7 mmol) in DMF (1.0 mL) at 0 °C. The reaction mixture was stirred for 17 h while warming to rt. The mixture was diluted with EtOAc and washed with a 1 M HCl solution, brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH in CH_2Cl_2 = 1%, 3%) to furnish product **195** (41.7 mg, 0.04 mmol, 66%) as orange amorphous solid.

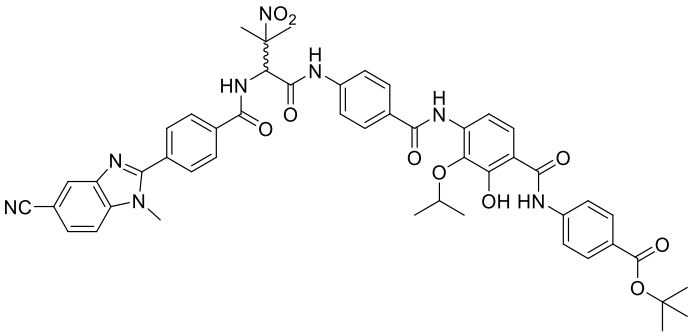
R_f (3% MeOH in CH_2Cl_2) = 0.15;

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 10.72 (s, 1H, NH), 10.52 (bs, 1H, NH), 9.56 (s, 1H, NH), 9.14-9.13 (d, *J* = 9.2 Hz, 1H, NH), 8.28 (s, 1H, H_{Ar}), 8.11-8.10 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 8.03-8.02 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 8.00-7.99 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.90-7.88 (m, 3H, H_{Ar}), 7.83-7.79 (m, 5H, H_{Ar}), 7.75-7.73 (dd, *J* = 1.5, 8.4 Hz, 1H, H_{Ar}), 7.41-7.40 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.05-5.98 (m, 1H, $OCH_2C\mathit{H}CH_2$), 5.75-5.73 (d, *J* = 9.2 Hz, 1H, C*H*NH), 5.39-5.35 (dq, *J* = 1.7, 17.2 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 5.21-5.19 (dq, *J* = 1.5, 10.5 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 4.61-4.60 (d, *J* = 5.5 Hz, 1H, $OC\mathit{H}_2CHCH_2$), 4.52-4.46 (sept, *J* = 9.2 Hz, 1H, $C\mathit{H}(CH_3)_2$), 3.97 (s, 3H, NCH_3), 1.78 (s, 3H, $C(C\mathit{H}_3)$), 1.72 (s, 3H, $C(C\mathit{H}_3)$), 1.55 (s, 9H, $C(C\mathit{H}_3)_3$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, $CH(C\mathit{H}_3)_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 166.9 (CO), 166.2 (CO), 164.6 (CO), 164.5 (CO), 164.2 (CO), 154.9 (NCN), 149.5 (C_{Ar}), 142.6 (C_{Ar}), 141.9 (C_{Ar}), 140.4 (C_{Ar}), 139.5 (C_{Ar}), 135.6 (C_{Ar}), 134.9 (C_{Ar}), 133.6 ($OCH_2\mathit{C}HCH_2$), 132.2 (C_{Ar}), 130.1 (C_{Ar}), 129.3 (C_{Ar}), 129.1 (C_{Ar}), 128.4 (C_{Ar}), 128.4 (C_{Ar}), 127.2 (C_{Ar}), 127.0 (C_{Ar}), 126.7 (C_{Ar}), 126.0 (C_{Ar}), 126.0 (C_{Ar}), 125.4 (C_{Ar}), 124.2 (C_{Ar}), 119.8 (CN), 119.6 (C_{Ar}), 118.8 ($OCH_2CH\mathit{C}H_2$), 117.8 (C_{Ar}), 112.4 (C_{Ar}), 104.3 (C_{Ar}), 89.0 ($\mathit{C}(CH_3)_2$), 80.3 ($\mathit{C}(CH_3)_3$), 76.2 ($O\mathit{C}H_2CHCH_2$), 74.3 ($\mathit{C}H(CH_3)_2$), 58.5 (CHNH), 32.2 (NCH_3), 27.9 ($C(\mathit{C}H_3)_3$), 23.4 ($C(\mathit{C}H_3)_2$), 22.8 ($CH(\mathit{C}H_3)_2$), 22.3 ($CH(\mathit{C}H_3)_2$) ppm;

HRMS (ESI) calculated for $C_{52}H_{52}N_8O_{10}Na$ $[M+Na]^+$: 971.3704; found: 971.3693.

tert-Butyl 4-(4-(4-(2-(4-(5-cyano-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)benzamido)-3-methyl-3-nitrobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**204**)



Allyl ether **195** (40.0 mg, 0.04 mmol) was dissolved in THF (1.9 mL). Aniline (13 µL, 0.14 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (4.9 mg, 4 µmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 2 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 1%, 2%, 3%) to furnish product **204** (31.3 mg, 0.03 mmol, 82%) as yellow amorphous solid.

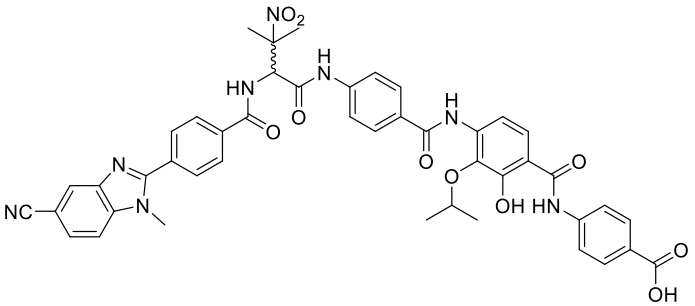
R_f (3% MeOH in CH_2Cl_2) = 0.20;

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 12.28 (s, 1H, OH), 10.73 (s, 1H, NH), 10.61 (bs, 1H, NH), 9.43 (bs, 1H, NH), 9.14-9.13 (d, *J* = 9.2 Hz, 1H, NH), 8.28 (s, 1H, H_{Ar}), 8.11-8.10 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 8.03-8.02 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.98-7.97 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.93-7.92 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.90-7.89 (d, *J* = 8.7 Hz, 1H, H_{Ar}), 7.86-7.82 (m, 5H, H_{Ar}), 7.75-7.73 (dd, *J* = 1.5, 8.4 Hz, 1H, H_{Ar}), 7.70-7.64 (m, 1H, H_{Ar}), 5.75-5.74 (d, *J* = 9.2 Hz, 1H, C*H*NH), 4.55 (m, 1H, C*H*$(CH_3)_2$), 3.97 (s, 3H, NCH_3), 1.78 (s, 3H, C(C*H*$_3$)), 1.72 (s, 3H, C(C*H*$_3$)), 1.55 (s, 9H, C(C*H*$_3$)$_3$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3$)$_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 168.4 (CO), 166.9 (CO), 166.6 (CO), 164.6 (CO), 164.1 (CO), 154.9 (NCN), 141.9 (C_{Ar}), 141.6 (C_{Ar}), 139.5 (C_{Ar}), 134.9 (C_{Ar}), 132.2 (C_{Ar}), 129.9 (C_{Ar}), 129.3 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 125.9 (C_{Ar}), 124.2 (C_{Ar}), 122.9 (C_{Ar}), 120.6 (C_{Ar}), 119.9 (CN), 119.6 (C_{Ar}), 112.4 (C_{Ar}), 112.3 (C_{Ar}), 89.0 (*C*$(CH_3)_2$), 80.5 (*C*$(CH_3)_3$), 74.7 (*C*H$(CH_3)_2$), 58.5 (CHNH), 32.2 (NCH_3), 27.8 (C(*C*H$_3$)$_3$), 23.3 (C(*C*H$_3$)$_2$), 22.8 (CH(*C*H$_3$)$_2$), 22.3 (CH(*C*H$_3$)$_2$) ppm;

HRMS (ESI) calculated for $C_{49}H_{48}N_8O_{10}Na$ $[M+Na]^+$: 931.3391; found: 931.3417.

4-(4-(4-(2-(4-(5-Cyano-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)benzamido)-3-methyl-3-nitrobutanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSF64**



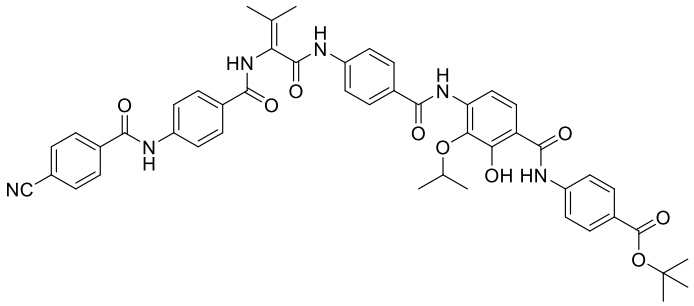
tert-Butyl ester **204** (30.1 mg, 0.03 mmol) was dissolved in precooled TFA (1.7 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSF64** (14.9 mg, 0.02 mmol, 53%) as colorless amorphous solid.

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 12.82 (bs, 1H, CO_2H), 12.28 (s, 1H, OH), 10.74 (s, 1H, NH), 10.60 (s, 1H, NH), 9.44 (s, 1H, NH), 9.14-9.13 (d, *J* = 9.2 Hz, 1H, NH), 8.28 (s, 1H, H_{Ar}), 8.11-8.10 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 8.03-8.02 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.99-7.96 (m, 4H, H_{Ar}), 7.90-7.89 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 7.86-7.82 (m, 5H, H_{Ar}), 7.75-7.73 (dd, *J* = 1.4, 8.4 Hz, 1H, H_{Ar}), 7.70-7.68 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 5.75-5.74 (d, *J* = 9.2 Hz, 1H, C*H*NH), 4.57-4.51 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 3.97 (s, 3H, NCH_3), 1.78 (s, 3H, C(C*H*$_3$)), 1.72 (s, 3H, C(C*H*$_3$)), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3$)$_2$) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 168.5 (CO), 166.9 (CO), 166.9 (CO), 166.6 (CO), 164.2 (CO), 154.9 (NCN), 154.1 (C_{Ar}), 141.9 (C_{Ar}), 141.9 (C_{Ar}), 141.6 (C_{Ar}), 139.5 (C_{Ar}), 137.0 (C_{Ar}), 136.4 (C_{Ar}), 134.9 (C_{Ar}), 132.2 (C_{Ar}), 130.2 (C_{Ar}), 129.3 (C_{Ar}), 129.1 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 126.3 (C_{Ar}), 126.0 (C_{Ar}), 124.1 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.9 (CN), 119.6 (C_{Ar}), 112.5 (C_{Ar}), 112.4 (C_{Ar}), 112.3 (C_{Ar}), 104.3 (C_{Ar}), 89.0 (*C*$(CH_3)_2$), 74.9 (*C*H$(CH_3)_2$), 58.5 (CHNH), 32.2 (NCH_3), 23.3 (CH(*C*H_3)$_2$), 22.8 (CH(*C*H_3)$_2$), 22.3 (C(*C*H_3)$_2$) ppm;

HRMS (ESI) calculated for $C_{45}H_{39}N_8O_{10}$ $[M-H]^-$: 851.2789; found: 851.2789.

tert-Butyl 4-(4-(4-(2-(4-(4-cyanobenzamido)benzamido)-3-methylbut-2-enamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**232**)



Compound **152** (10.0 mg, 0.01 mmol) was dissolved in THF (300 µL) and DBU (5 µL, 0.03 mmol, 3.00 equiv.) was added at 0 °C. The mixture was stirred for 20 h while warming to rt. The mixture was loaded onto silica. Column chromatography (MeOH in CH_2Cl_2 = 2%, 3%) furnished product **232** (8.8 mg, 0.01 mmol, 93%) as colorless amorphous solid.

R_f (3% MeOH in CH_2Cl_2) = 0.17;

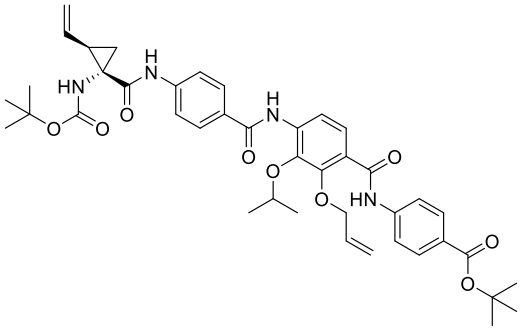
^{1}H-NMR (400 MHz, DMSO-d_6) = δ 12.30 (s, 1H, OH), 10.71 (s, 1H, NH), 10.67 (bs, 1H, NH), 10.36 (s, 1H, NH), 9.63 (s, 1H, NH), 9.37 (s, 1H, NH), 8.14-8.12 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 8.06-8.04 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 8.01-7.99 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.96-7.84 (m, 11H, H_{Ar}), 7.73-7.71 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 4.60-4.51 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 1.97 (s, 3H, C(CH_3)), 1.85 (s, 3H, C(CH_3)), 1.55 (s, 9H, C$(CH_3)_3$), 1.28-1.26 (d, *J* = 6.2 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 168.5 (CO), 164.9 (CO), 164.9 (CO), 164.6 (CO), 164.5 (CO), 164.2 (CO), 154.3 (C_{Ar}), 142.8 (C_{Ar}), 142.0 (C_{Ar}), 141.7 (C_{Ar}), 138.7 (C_{Ar}), 137.0 (C_{Ar}), 136.2 (C_{Ar}), 132.9 (C*C*NH), 132.5 (C_{Ar}), 129.9 (C_{Ar}), 128.9 (C_{Ar}), 128.6 (C_{Ar}), 128.6 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 127.0 (*C*H$(CH_3)_2$), 126.8 (C_{Ar}), 122.9 (C_{Ar}), 120.6 (C_{Ar}), 119.5 (C_{Ar}), 119.4 (C_{Ar}), 119.0 (C_{Ar}), 118.3 (CN), 114.1 (C_{Ar}), 112.4 (C_{Ar}), 80.5 (*C*$(CH_3)_2$), 74.8 (*C*H$(CH_3)_2$), 27.8 (C(*C*$H_3)_3$), 22.3 (C(*C*$H_3)_2$), 20.7 (C(*C*$H_3)_2$), 20.4 (CH(*C*$H_3)_2$) ppm;

HRMS (ESI) calculated for $C_{48}H_{45}N_6O_9$ $[M-H]^-$: 849.3248; found: 849.3250.

4.2.13(1*S*,2*R*)-1-Amino-2-vinylcyclopropane-1-carboxylic acid derivatives

tert-Butyl 4-(2-(allyloxy)-4-(4-((1*S*,2*R*)-1-((*tert*-butoxycarbonyl)amino)-2-vinylcyclopropane-1-carboxamido)benzamido)-3-isopropoxybenzamido)benzoate (**132**)



Amine **5** (200 mg, 0.37 mmol) and acid **118** (117 mg, 0.51 mmol, 1.40 equiv.) were dissolved in EtOAc (800 µL) and pyridine (90 µL, 1.10 mmol, 3.00 equiv.) was added. T3P (50% in EtOAc, 400 µL, 0.66 mmol, 1.80 equiv.) was added at 0 °C and the mixture was stirred at 0 °C for 3 h. H_2O was added and the aq. phase was extracted with EtOAc (3x). The combined organic phases were washed with a sat. $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (1% MeOH in CH_2Cl_2) to furnish product **132** (233 mg, 0.31 mmol, 84%) as yellowish amorphous solid.

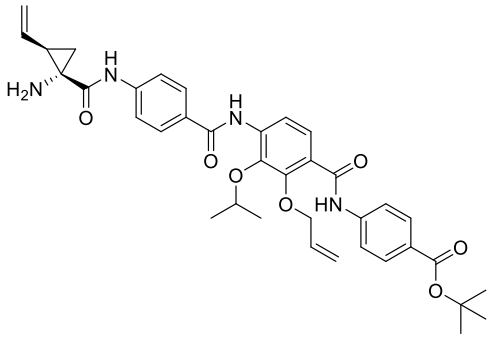
$[\alpha]_D^{23}$ = -8.2 ° (c 0.2, CH_2Cl_2);

^{1}H-NMR (600 MHz, DMSO-d_6) = 10.52 (s, 1H, NH), 9.95-9.88 (m, 1H, NH), 9.52 (s, 1H, NH), 7.97-7.95 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.90-7.88 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.85-7.78 (m, 5H, H_{Ar}), 7.51 (bs, 1H, NH), 7.41-7.40 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.05-5.99 (m, 1H, OCH_2CHCH_2), 5.65-5.53 (m, 1H, $CHCHCH_2$), 5.39-5.35 (dq, *J* = 1.6, 17.2 Hz, 1H, OCH_2CHCH_2), 5.24-5.19 (m, 2H, $CHCHCH_2$, OCH_2CHCH_2), 5.04-5.02 (dd, *J* = 1.9, 10.4 Hz, 1H, $CHCHCH_2$), 4.61-4.60 (d, *J* = 5.5 Hz, 2H, OCH_2CHCH_2), 4.53-4.47 (sept, *J* = 6.1 Hz, 1H, $CH(CH_3)_2$), 2.27-2.22 (m, 1H, CCH), 1.79-1.77 (m, 1H, CCH_2), 1.55 (s, 9H, $C(CH_3)_3$), 1.41-1.32 (m, 9H, $C(CH_3)_3$), 1.26-1.25 (dd, *J* = 1.7, 6.1 Hz, 6H, $CH(CH_3)_2$), 1.24-1.22 (m, 1H, CCH_2) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 169.9 (CO), 164.6 (CO), 164.5 (CO), 164.3 (CO), 155.6 (CO), 149.5 (C_{Ar}), 143.0 (C_{Ar}), 142.5 (C_{Ar}), 135.7 (C_{Ar}), 134.5 ($CHCHCH_2$), 133.6 (CH_2CHCH_2), 132.0 (C_{Ar}), 130.1 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 127.1 (C_{Ar}), 126.0 (C_{Ar}), 123.6 (C_{Ar}), 119.2 (C_{Ar}), 118.9 (C_{Ar}), 118.8 (C_{Ar}), 118.3 (CH_2CHCH_2), 117.8 ($CHCHCH_2$), 80.5 ($C(CH_3)_3$), 78.9 ($C(CH_3)_3$), 76.2 (CH_2CHCH_2), 74.3 ($CH(CH_3)_2$), 45.4 (C_q), 30.7 (CCH), 28.1 ($C(CH_3)_3$), 27.8 ($C(CH_3)_3$), 22.3 (d, *J* = 2.5 Hz, $CH(CH_3)_2$), 20.0 (CCH_2) ppm;

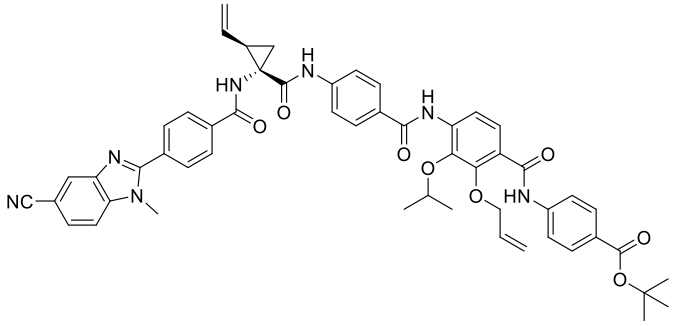
HRMS (ESI) calculated for $C_{42}H_{50}N_4O_9Na$ $[M+Na]^+$: 777.3475; found: 777.3471.

tert-Butyl 4-(2-(allyloxy)-4-(4-((1*S*,2*R*)-1-amino-2-vinylcyclopropane-1-carboxamido) benzamido)-3-isopropoxybenzamido)benzoate (**188**)



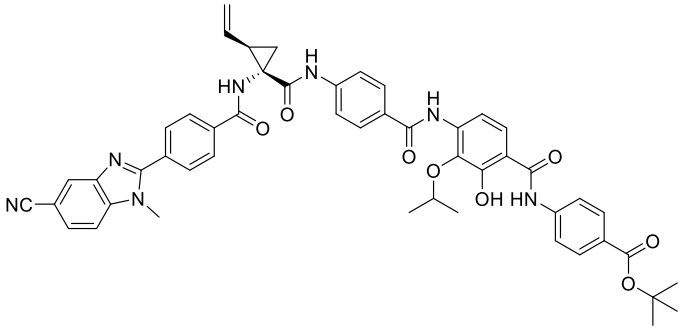
Carbamate **132** (150 mg, 0.20 mmol) was dissolved in HCl (4 M in 1,4-dioxane, 5.00 mL, 20.0 mmol, 100 equiv.) at 0 °C. The mixture was warmed up to rt and stirred for 15 min. The solution was transferred to a stirred suspension of EtOAc (135 mL) and a sat. $NaHCO_3$ solution (135 mL). The aq. phase was extracted with EtOAc (2x) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was used in the next step without further purification.

tert-Butyl 4-(2-(allyloxy)-4-(4-((1*S*,2*R*)-1-(4-(5-cyano-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)benzamido)-2-vinylcyclopropane-1-carboxamido)benzamido)-3-isopropoxybenzamido)benzoate (**197**)



DIPEA (89 µL, 0.51 mmol, 3.00 equiv.) was added dropwise to a stirred solution of HATU (77.4 mg, 0.20 mmol, 1.20 equiv.) and acid **34** (56.4 mg, 0.20 mmol, 1.20 equiv.) in DMF (4.2 mL). The solution was stirred for 5 min and then transferred to a stirred solution of amine **188** (111 mg, 0.17 mmol) in DMF (2.4 mL) at 0 °C. The reaction mixture was stirred for 18 h while warming to rt. The mixture was diluted with EtOAc and washed with a 1 M HCl solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH in CH_2Cl_2 = 1%, 2%) to furnish product **197** (83.0 mg) as beige amorphous solid, which contained minor impurities. The product was used in the next step without further purification.

tert-Butyl 4-(4-(4-((1*S*,2*R*)-1-(4-(5-cyano-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)benzamido)-2-vinylcyclopropane-1-carboxamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**206**)



Allyl ether **197** (83.0 mg, 0.09 mmol) was dissolved in THF (4.5 mL). Aniline (27 µL, 0.30 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (10.5 mg, 0.01 mmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 3 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 1%, 2%) to furnish product **206** (47.3 mg, 0.05 mmol, 32% over two steps) as yellowish amorphous solid.

R_f (3% MeOH in CH_2Cl_2) = 0.17;

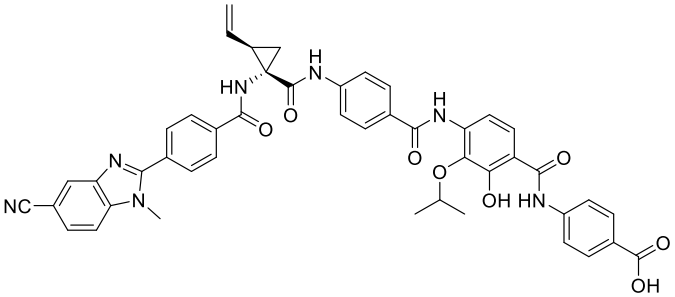
$[\alpha]_D^{22}$ = +10.8 ° (c 0.1, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = 12.28 (s, 1H, OH), 10.61 (bs, 1H, NH), 10.02 (s, 1H, NH), 9.39 (s, 1H, NH), 9.27 (s, 1H, NH), 8.29-8.28 (dd, *J* = 0.6, 1.5 Hz, 1H, H_{Ar}), 8.19-8.18 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 8.04-8.03 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.95-7.89 (m, 5H, H_{Ar}), 7.86-7.84 (m, 3H, H_{Ar}), 7.81-7.79 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.75-7.73 (dd, *J* = 1.5, 8.4 Hz, 2H, H_{Ar}), 7.68 (bs, 1H, H_{Ar}), 5.75-5.69 (m, 1H, CHC*H*CH_2), 5.34-5.31 (d, *J* = 17.1 Hz, 1H, CHCHC*H*$_2$), 5.12-5.10 (d, *J* = 10.5 Hz, 1H, CHCHC*H*$_2$), 4.55 (bs, 1H, C*H*$(CH_3)_2$), 3.97 (s, 3H, NCH_3), 1.97-1.94 (m, 1H, CCH), 1.55 (s, 9H, $C(CH_3)_3$), 1.39-1.36 (m, 1H, CCH_2), 1.26-1.25 (dd, *J* = 3.9, 6.1 Hz, 6H, $CH(CH_3)_2$), 1.23 (m, 1H, CCH_2) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 168.4 (CO), 168.3 (CO), 166.8 (CO), 164.6 (CO), 164.2 (CO), 154.9 (NCN), 142.2 (C_{Ar}), 141.9 (C_{Ar}), 139.5 (C_{Ar}), 136.9 (C_{Ar}), 136.3 (C_{Ar}), 135.1 (CH*C*HCH$_2$), 134.6 (C_{Ar}), 132.0 (C_{Ar}), 129.9 (C_{Ar}), 129.3 (C_{Ar}), 128.6 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 125.9 (C_{Ar}), 124.1 (C_{Ar}), 122.9 (C_{Ar}), 120.6 (C_{Ar}), 119.9 (C_{Ar}), 119.7 (C_{Ar}), 119.4 (CN), 117.2 (CHCH*C*H$_2$), 112.4 (C_{Ar}), 104.3 (C_{Ar}), 80.5 (*C*$(CH_3)_3$), 74.8 (*C*H$(CH_3)_2$), 42.4 (C_q), 32.2 (C*C*H), 27.8 (C(*C*$H_3)_3$), 22.3 (d, *J* = 2.5 Hz, CH(*C*$H_3)_2$), 21.6 (C*C*H_2) ppm;

HRMS (ESI) calculated for $C_{50}H_{47}N_7O_8Na$ $[M+Na]^+$: 896.3384; found: 896.3384.

4-(4-(4-((1*S*,2*R*)-1-(4-(5-Cyano-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)benzamido)-2-vinylcyclopropane-1-carboxamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSF84**



tert-Butyl ester **206** (41.4 mg, 0.05 mmol) was dissolved in precooled TFA (2.4 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSF84** (16.4 mg, 0.02 mmol, 42%) as colorless amorphous solid.

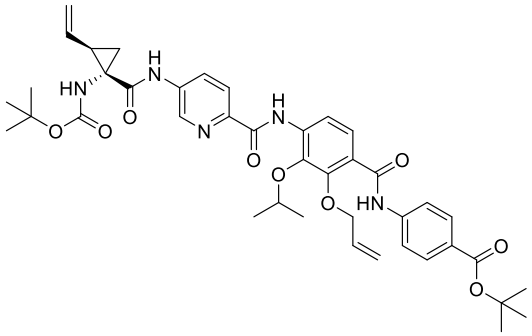
[*α*]$_D^{23}$ = +6.3 (c 0.2, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = 12.83 (bs, 1H, CO_2H), 12.28 (s, 1H, OH), 10.60 (s, 1H, NH), 10.02 (s, 1H, NH), 9.41 (s, 1H, NH), 9.27 (s, 1H, NH), 8.28 (dd, *J* = 0.6, 1.5 Hz, 1H, H_{Ar}), 8.19-8.18 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 8.04-8.02 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.97-7.96 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.95-7.94 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.91-7.89 (dd, *J* = 0.5, 8.6 Hz, 2H, H_{Ar}), 7.86-7.84 (m, 3H, H_{Ar}), 7.81-7.79 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.75-7.73 (dd, *J* = 1.5, 8.4 Hz, 2H, H_{Ar}), 7.70-7.69 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 5.75-5.69 (m, 1H, CHC*H*CH_2), 5.34-5.31 (d, *J* = 17.1 Hz, 1H, CHCHC*H*$_2$), 5.12-5.11 (d, *J* = 12.1 Hz, 1H, CHCHC*H*$_2$), 4.57-4.51 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 3.98 (s, 3H, NCH_3), 1.97-1.94 (m, 1H, CCH), 1.39-1.36 (m, 1H, CCH_2), 1.30-1.23 (m, 1H, CCH_2), 1.26-1.25 (dd, *J* = 3.8, 6.1 Hz, 6H, CH(C*H*$_3)_2$) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 168.5 (CO), 168.3 (CO), 166.9 (CO), 166.9 (CO), 164.2 (CO), 154.9 (NCN), 154.1 (C_{Ar}), 142.2 (C_{Ar}), 142.0 (C_{Ar}), 141.9 (C_{Ar}), 139.5 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 135.1 (CH*C*HCH$_2$), 134.6 (C_{Ar}), 132.0 (C_{Ar}), 130.2 (C_{Ar}), 129.3 (C_{Ar}), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 126.3 (C_{Ar}), 126.0 (C_{Ar}), 124.1 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.9 (C_{Ar}), 119.7 (C_{Ar}), 119.5 (CN), 117.0 (CHCH*C*H$_2$), 112.4 (C_{Ar}), 112.2 (C_{Ar}), 104.4 (C_{Ar}), 74.6 (*C*H$(CH_3)_2$), 42.4 (C_q), 32.2 (C*C*H), 22.3 (d, *J* = 2.3 Hz, CH(*C*H$_3)_2$), 21.6 (C*C*H$_2$) ppm;

HRMS (ESI) calculated for $C_{46}H_{39}N_7O_8$ $[M+Na]^+$: 840.2758; found: 840.2769.

tert-Butyl 4-(2-(allyloxy)-4-(5-((1*S*,2*R*)-1-((*tert*-butoxycarbonyl)amino)-2-vinylcyclopropane-1-carboxamido)picolinamido)-3-isopropoxybenzamido)benzoate (**133**)



Amine **114** (200 mg, 0.37 mmol) and acid **118** (116 mg, 0.51 mmol, 1.40 equiv.) were dissolved in EtOAc (800 µL) and pyridine (90 µL, 1.10 mmol, 3.00 equiv.) was added. T3P (50% in EtOAc, 400 µL, 0.66 mmol, 1.80 equiv.) was added at 0 °C and the mixture was stirred for 3 h while warming to rt. H_2O was added and the aq. phase was extracted with EtOAc (2x). The combined organic phases were washed with a sat. $NaHCO_3$ solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (PE/EtOAc = 1:1) to furnish product **133** (186 mg, 0.25 mmol, 67%) as yellowish amorphous solid.

R_f (2% MeOH in CH_2Cl_2) = 0.26;

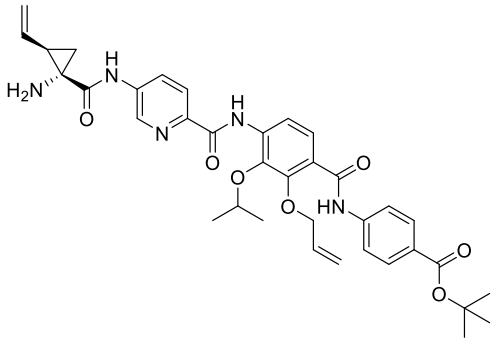
$[\alpha]_D^{22}$ = -9.6 ° (c 0.2, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = 10.70 (s, 1H, NH), 10.48 (s, 1H, NH), 10.36-10.25 (m, 1H, NH), 9.03 (bs, 1H, H_{Ar}), 8.35-8.34 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 8.18-8.16 (d, *J* = 8.8 Hz, 1H, H_{Ar}), 7.90-7.88 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.83-7.82 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.54 (bs, 0.6H, NH), 7.49-7.47 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 7.23 (bs, 0.3H, NH), 6.05-5.99 (m, 1H, OCH_2CHCH_2), 5.70-5.59 (m, 1H, $CHCHCH_2$), 5.41-5.37 (dq, *J* = 1.6, 17.2 Hz, 1H, OCH_2CHCH_2), 5.25-5.20 (m, 2H, $CHCHCH_2$, OCH_2CHCH_2), 5.06-5.04 (dd, *J* = 1.8, 10.4 Hz, 1H, $CHCHCH_2$), 4.68-4.63 (sept, *J* = 6.1 Hz, 1H, $CH(CH_3)_2$), 4.62-4.61 (d, *J* = 5.5 Hz, 2H, OCH_2CHCH_2), 2.34-2.29 (m, 1H, CCH), 1.80 (bs, 1H, CCH_2), 1.55 (s, 9H, $C(CH_3)_3$), 1.41-1.32 (m, 9H, $C(CH_3)_3$), 1.37-1.36 (dd, *J* = 2.6, 6.1 Hz, 6H, $CH(CH_3)_2$), 1.26 (bs, 1H, CCH_2) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = 169.5 (CO), 164.6 (CO), 164.3 (CO), 161.1 (CO), 155.6 (CO), 149.3 (C_{Ar}), 143.3 (C_{Ar}), 143.0 (C_{Ar}), 140.0 (C_{Ar}), 139.4 (C_{Ar}), 138.8 (C_{Ar}), 135.5 (C_{Ar}), 134.3 ($CHCHCH_2$), 133.5 (CH_2CHCH_2), 130.1 (C_{Ar}), 127.7 (C_{Ar}), 126.0 (C_{Ar}), 125.7 (C_{Ar}), 124.6 (C_{Ar}), 122.7 (C_{Ar}), 118.8 (C_{Ar}), 118.0 (C_{Ar}), 117.2 (CH_2CHCH_2), 113.8 ($CHCHCH_2$), 80.3 ($C(CH_3)_3$), 78.9 ($C(CH_3)_3$), 76.3 (CH_2CHCH_2), 74.3 ($CH(CH_3)_2$), 42.4 (C_q), 32.6 (CCH), 28.1 ($C(CH_3)_3$), 27.8 ($C(CH_3)_3$), 22.3 (d, *J* = 2.7 Hz, $CH(CH_3)_2$), 21.8 (CCH_2) ppm;

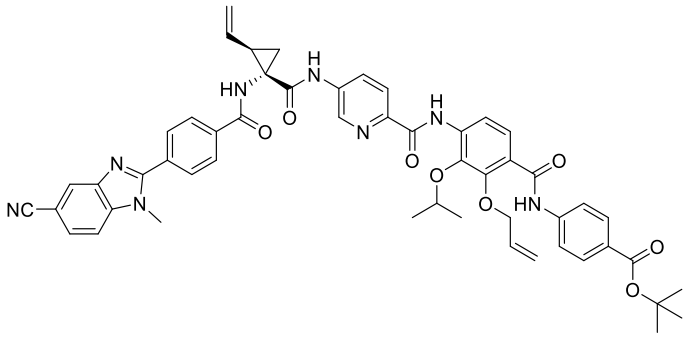
HRMS (ESI) calculated for $C_{41}H_{49}N_5O_9Na$ $[M+Na]^+$: 778.3428; found: 778.3441.

tert-Butyl 4-(2-(allyloxy)-4-(5-((1*S*,2*R*)-1-amino-2-vinylcyclopropane-1-carboxamido)picolinamido)-3-isopropoxybenzamido)benzoate (**189**)



Carbamate **133** (177 mg, 0.23 mmol) was dissolved in HCl (4 M in 1,4-dioxane, 5.90 mL, 23.4 mmol, 100 equiv.) at 0 °C. The mixture was warmed up to rt and stirred for 15 min. The solution was transferred to a stirred suspension of EtOAc (150 mL) and a sat. $NaHCO_3$ solution (150 mL). The aq. phase was extracted with EtOAc (3x) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was used in the next step without further purification.

tert-Butyl 4-(2-(allyloxy)-4-(5-((1*S*,2*R*)-1-(4-(5-cyano-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)benzamido)-2-vinylcyclopropane-1-carboxamido)picolinamido)-3-isopropoxybenzamido)benzoate (**198**)



DIPEA (123 µL, 0.70 mmol, 3.00 equiv.) was added dropwise to a stirred solution of HATU (107 mg, 0.28 mmol, 1.20 equiv.) and acid **34** (78.1 mg, 0.28 mmol, 1.20 equiv.) in DMF (6.0 mL). The solution was stirred for 5 min and then transferred to a stirred solution of amine **189** (154 mg, 0.23 mmol) in DMF (3.4 mL) at 0 °C. The reaction mixture was stirred for 18 h while warming to rt. The mixture was diluted with EtOAc and washed with a 1 M HCl solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH in CH_2Cl_2 = 1%, 2%) to furnish product **198** (142 mg, 0.16 mmol, 66%) as yellowish amorphous solid.

R_f (3% MeOH in CH_2Cl_2) = 0.25;

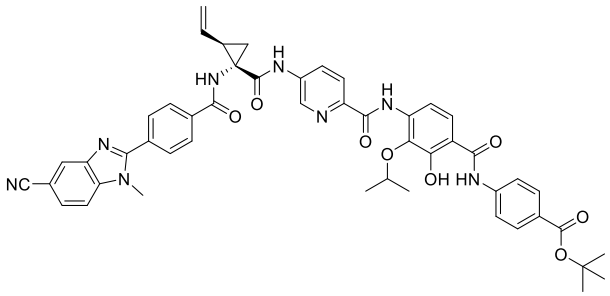
[α]$_D^{22}$ = +5.3 ° (c 0.2, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = 10.62 (s, 1H, NH), 10.48 (s, 1H, NH), 10.29 (s, 1H, NH), 9.33 (s, 1H, NH), 9.00 (d, *J* = 2.5 Hz, 1H, H_{Ar}), 8.37-8.34 (m, 2H, H_{Ar}), 8.29-8.28 (m, 1H, H_{Ar}), 8.20-8.17 (m, 3H, H_{Ar}), 8.04-8.03 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.91-7.88 (m, 3H, H_{Ar}), 7.82-7.81 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.75-7.73 (dd, *J* = 1.5, 8.4 Hz, 2H, H_{Ar}), 7.48-7.47 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 6.05-5.97 (m, 1H, OCHC*H*CH_2), 5.79-5.72 (m, 1H, CHC*H*CH_2), 5.40-5.32 (m, 2H, OCHCHC*H*$_2$, CHCHC*H*$_2$), 5.22-5.19 (dq, *J* = 1.6, 10.5 Hz, 1H, OCHCHC*H*$_2$), 5.14-5.12 (m, 1H, CHCHC*H*$_2$), 4.68-4.62 (sept, *J* = 6.0 Hz, 1H, C*H*$(CH_3)_2$), 4.61-4.60 (d, *J* = 5.5 Hz, 1H, OC*H*$CHCH_2$), 3.97 (s, 3H, NCH_3), 1.99-1.96 (m, 1H, CCH), 1.54 (s, 9H, $C(CH_3)_3$), 1.43-1.40 (m, 1H, CCH_2), 1.36-1.34 (dd, *J* = 6.3, 7.4 Hz, 6H, $CH(CH_3)_2$), 1.23 (m, 1H, CCH_2) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = 169.1 (CO), 166.9 (CO), 164.6 (CO), 164.3 (CO), 161.1 (CO), 154.9 (NCN), 149.3 (C_{Ar}), 143.4 (C_{Ar}), 143.0 (C_{Ar}), 141.9 (C_{Ar}), 140.2 (C_{Ar}), 139.5 (C_{Ar}), 139.4 (C_{Ar}), 138.7 (C_{Ar}), 135.5 (CH*C*HCH_2), 135.1 (C_{Ar}), 134.4 (C_{Ar}), 133.5 (C_{Ar}), 132.1 (C_{Ar}), 130.1 (C_{Ar}), 129.3 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 126.0 (C_{Ar}), 126.0 (C_{Ar}), 125.8 (C_{Ar}), 124.6 (C_{Ar}), 124.1 (C_{Ar}), 122.7 (C_{Ar}), 119.9 (CN), 118.8 (C_{Ar}), 118.0 (C_{Ar}), 117.4 (CHCH*C*H_2), 113.7 (C_{Ar}), 112.4 (C_{Ar}), 104.3 (C_{Ar}), 80.3 (*C*$(CH_3)_3$), 76.3 (C*H*$_2$$CHCH_2$), 74.3 (*C*$H(CH_3)_2$), 42.2 ($C_q$), 32.2 (C*C*H), 27.9 (C(*C*$H_3)_3$), 22.3 (d, *J* = 7.4 Hz, CH(*C*$H_3)_2$), 22.3 (C*C*H_2) ppm;

HRMS (ESI) calculated for $C_{52}H_{50}N_8O_8Na$ $[M+Na]^+$: 937.3649; found: 937.3690.

tert-Butyl 4-(4-(5-((1*S*,2*R*)-1-(4-(5-cyano-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)benzamido)-2-vinylcyclopropane-1-carboxamido)picolinamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**207**)



Allyl ether **197** (137 mg, 0.15 mmol) was dissolved in THF (7.5 mL). Aniline (45 µL, 0.49 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (17.3 mg, 0.02 mmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 90 min. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 2%, 3%) to furnish product **207** (107 mg, 0.12 mmol, 82%) as yellowish amorphous solid.

R_f (3% MeOH in CH_2Cl_2) = 0.15;

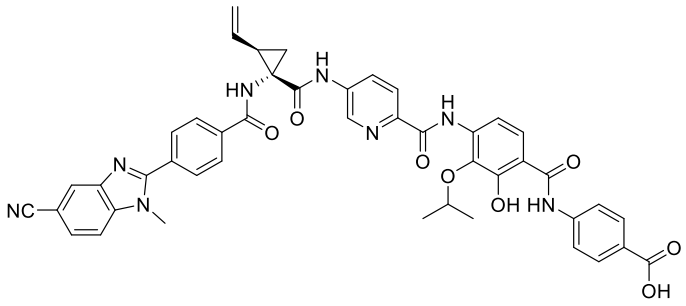
$[\alpha]_D^{22}$ = +4.2 ° (c 0.1, MeOH);

^{1}H-NMR (500 MHz, DMSO-d_6) = 12.44 (s, 1H, OH), 10.75 (bs, 1H, NH), 10.62 (bs, 1H, NH), 10.28 (s, 1H, NH), 9.33 (s, 1H, NH), 8.99-8.98 (d, *J* = 2.6 Hz, 1H, H_{Ar}), 8.38-8.36 (dd, *J* = 2.4, 8.6 Hz, 1H, H_{Ar}), 8.29-8.28 (dd, *J* = 0.6, 1.5 Hz, 1H, H_{Ar}), 8.20-8.18 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 8.18-8.16 (d, *J* = 8.8 Hz, 1H, H_{Ar}), 8.07 (bs, 1H, H_{Ar}), 8.05-8.03 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 7.93-7.88 (m, 4H, H_{Ar}), 7.85-7.84 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.75-7.73 (dd, *J* = 1.5, 8.4 Hz, 2H, H_{Ar}), 5.75-5.69 (m, 1H, CHC*H*CH_2), 5.36-5.32 (dd, *J* = 1.4, 17.1 Hz, 1H, CHCHC*H*$_2$), 5.14-5.12 (dd, *J* = 1.7, 10.4 Hz, 1H, CHCHC*H*$_2$), 4.72-4.65 (sept, *J* = 6.0 Hz, 1H, C*H*$(CH_3)_2$), 3.97 (s, 3H, NCH_3), 1.99-1.96 (m, 1H, CCH), 1.55 (s, 9H, $C(CH_3)_3$), 1.43-1.40 (m, 1H, CCH_2), 1.34-1.31 (t, *J* = 6.6 Hz, 6H, $CH(CH_3)_2$), 1.23 (m, 1H, CCH_2) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 169.1 (CO), 168.6 (CO), 166.9 (CO), 164.6 (CO), 161.2 (CO), 154.9 (NCN), 143.4 (C_{Ar}), 141.9 (C_{Ar}), 140.2 (C_{Ar}), 139.5 (C_{Ar}), 138.7 (C_{Ar}), 136.7 (C_{Ar}), 135.1 (CH*C*HCH$_2$), 134.4 (C_{Ar}), 134.0 (C_{Ar}), 132.1 (C_{Ar}), 131.5 (C_{Ar}), 131.4 (C_{Ar}), 129.9 (C_{Ar}), 129.3 (C_{Ar}), 128.8 (C_{Ar}), 128.7 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 126.0 (C_{Ar}), 124.1 (C_{Ar}), 123.6 (C_{Ar}), 122.7 (C_{Ar}), 120.7 (C_{Ar}), 119.9 (CN), 117.4 (CHCH*C*H$_2$), 112.4 (C_{Ar}), 104.4 (C_{Ar}), 80.5 (*C*$(CH_3)_3$), 74.6 (*C*H$(CH_3)_2$), 42.2 (C_q), 32.2 (C*C*H), 27.8 (C(*C*$H_3)_3$), 22.3 (d, *J* = 6.5 Hz, CH(*C*$H_3)_2$), 22.3 (C*C*H_2) ppm;

HRMS (ESI) calculated for $C_{49}H_{45}N_8O_8$ $[M-H]^-$: 873.3360; found: 873.3354.

4-(4-(5-((1*S*,2*R*)-1-(4-(5-Cyano-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)benzamido)-2-vinylcyclopropane-1-carboxamido)picolinamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSG28**



tert-Butyl ester **207** (103 mg, 0.12 mmol) was dissolved in precooled TFA (6 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSG28** (84.1 mg, 0.10 mmol, 87%) as colorless amorphous solid.

$[\alpha]_D^{21}$ = +3.4 ° (c 0.1, CH_2Cl_2/MeOH (1:1));

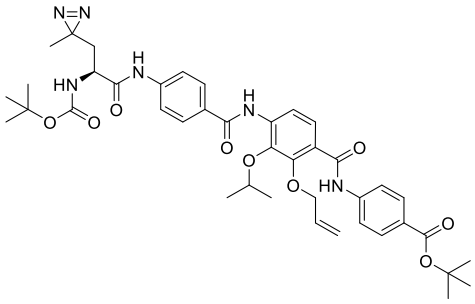
^{1}H-NMR (500 MHz, DMSO-d_6) = 12.82 (bs, 1H, CO_2H), 12.44 (s, 1H, OH), 10.76 (s, 1H, NH), 10.60 (s, 1H, NH), 10.28 (s, 1H, NH), 9.33 (s, 1H, NH), 8.99 (d, *J* = 2.4 Hz, 1H, H_{Ar}), 8.38-8.36 (dd, *J* = 2.5, 8.6 Hz, 1H, H_{Ar}), 8.29 (d, *J* = 0.9 Hz, 1H, H_{Ar}), 8.20-8.17 (m, 3H, H_{Ar}), 8.12-8.10 (d, *J* = 9.0 Hz, 1H, H_{Ar}), 8.05-8.03 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.98-7.96 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.92-7.91 (dd, *J* = 2.4, 8.8 Hz, 2H, H_{Ar}), 7.86-7.84 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.75-7.73 (dd, *J* = 1.4, 8.4 Hz, 1H, H_{Ar}), 5.79-5.72 (m, 1H, CHC*H*CH_2), 5.36-5.33 (d, *J* = 17.0 Hz, 1H, CHCHC*H*$_2$), 5.14-5.12 (d, *J* = 10.5 Hz, 1H, CHCHC*H*$_2$), 4.71-4.64 (sept, *J* = 6.1 Hz, 1H, C*H*$(CH_3)_2$), 3.97 (s, 3H, NCH_3), 1.99-1.96 (m, 1H, CCH), 1.43-1.40 (m, 1H, CCH_2), 1.34-1.32 (t, *J* = 6.5 Hz, 6H, CH(C*H*$_3)_2$), 1.34-1.15 (m, 1H, CCH_2) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = 169.1 (CO), 168.7 (CO), 166.9 (CO), 166.9 (CO), 161.3 (CO), 154.9 (NCN), 154.1 (C_{Ar}), 143.4 (C_{Ar}), 141.9 (C_{Ar}), 141.8 (C_{Ar}), 140.3 (C_{Ar}), 139.5 (C_{Ar}), 138.7 (C_{Ar}), 136.8 (C_{Ar}), 135.1 (CH*C*HCH_2), 134.4 (C_{Ar}), 133.9 (C_{Ar}), 132.1 (C_{Ar}), 130.2 (C_{Ar}), 129.3 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 126.3 (C_{Ar}), 126.0 (C_{Ar}), 124.1 (C_{Ar}), 123.5 (C_{Ar}), 122.7 (C_{Ar}), 120.8 (C_{Ar}), 119.9 (CN), 117.4 (CHCH*C*H_2), 112.4 (C_{Ar}), 111.6 (C_{Ar}), 108.3 (C_{Ar}), 104.4 (C_{Ar}), 74.7 (*C*H$(CH_3)_2$), 42.3 (C_q), 32.2 (C*C*H), 22.3 (d, *J* = 6.4 Hz, CH(*C*$H_3)_2$), 22.3 (C*C*H_2) ppm;

HRMS (ESI) calculated for $C_{45}H_{37}N_8O_8$ $[M-H]^-$: 817.2734; found: 817.2750.

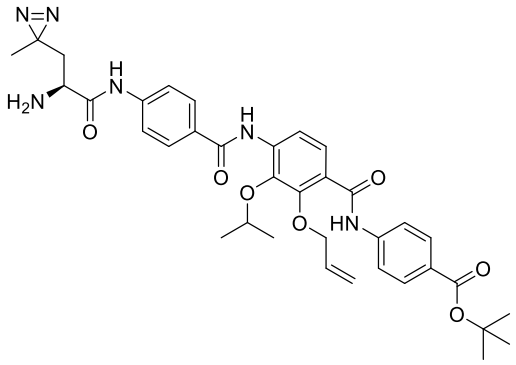
4.2.14(*S*)-2-Amino-3-(3-methyl-3*H*-diazirin-3-yl)propanoic acid derivative

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(4-(2-((*tert*-butoxycarbonyl)amino)-3-(3-methyl-3*H*-diazirin-3-yl)propanamido)benzamido)-3-isopropoxybenzamido)benzoate (**134**)



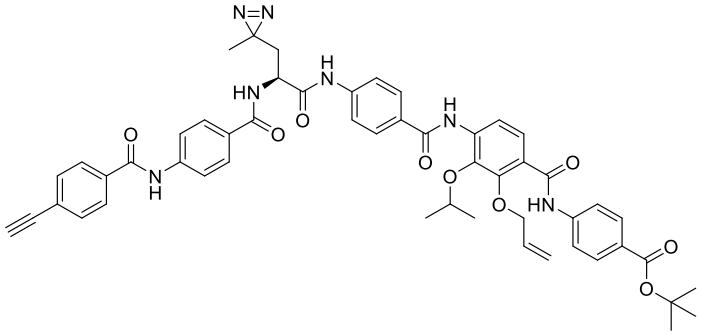
Amine **5** (200 mg, 0.37 mmol), L-photo-leucin **119** (233 mg, 0.55 mmol, 1.50 equiv.) and EEDQ (136 mg, 0.55 mmol, 1.50 equiv.) were dissolved in precooled $CHCl_3$ (2 mL) at 0 °C. The mixture was stirred at 18 h while warming to rt. Then, a 1 M HCl solution was added and the aq. phase was extracted with CH_2Cl_2 (3x). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (20% Et_2O in CH_2Cl_2) to furnish product **134** (261 mg), which contained quinoline as impurity. The crude product was used in the next step without further purification.

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(4-(2-amino-3-(3-methyl-3*H*-diazirin-3-yl)propanamido)benzamido)-3-isopropoxybenzamido)benzoate (**210**)



Carbamate **134** (261 mg, 0.34 mmol) was dissolved in HCl (4 M in 1,4-dioxane, 8.50 mL, 33.9 mmol, 100 equiv.) at 0 °C. The mixture was warmed up to rt and stirred for 15 min. The solution was transferred to a stirred suspension of EtOAc (110 mL) and a sat. $NaHCO_3$ solution (110 mL). The aq. phase was extracted with EtOAc and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was used in the next step without further purification.

tert-Butyl (*S*)-4-(2-(allyloxy)-4-(4-(2-(4-(4-ethynylbenzamido)benzamido)-3-(3-methyl-3*H*-diazirin-3-yl)propanamido)benzamido)-3-isopropoxybenzamido)benzoate (**211**)



DIPEA (0.20 mL, 1.02 mmol, 3.00 equiv.) was added dropwise to a stirred solution of HATU (155 mg, 0.41 mmol, 1.20 equiv.) and acid **15** (108 mg, 0.41 mmol, 1.20 equiv.) in DMF (8 mL). The solution was stirred for 5 min and then transferred to a stirred solution of amine **210** (228 mg, 0.34 mmol) in DMF (5 mL). The reaction mixture was stirred at rt for 20 h. The mixture was diluted with EtOAc and washed with a 1 M HCl solution, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (2% MeOH in CH_2Cl_2) to furnish product **211** (191 mg, 0.21 mmol, 61% over 3 steps) as yellow amorphous solid.

R_f (5% MeOH in CH_2Cl_2) = 0.54;

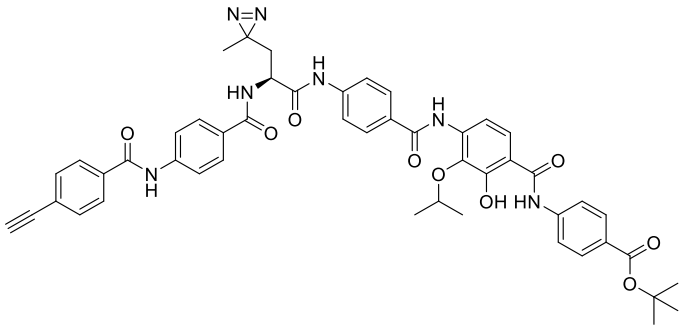
$[\alpha]_D^{29}$ = +3.6 ° (c 0.1, MeOH);

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 10.55 (s, 1H, NH), 10.53 (bs, 2H, NH), 9.53 (s, 1H, NH), 8.69-8.67 (d, *J* = 7.8 Hz, 1H, CHN*H*), 8.01-7.95 (m, 7H, H_{Ar}), 7.92-7.90 (d, *J* = 9.0 Hz, 2H, H_{Ar}), 7.90-7.88 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.84-7.82 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 7.80-7.78 (d, *J* = 8.9 Hz, 2H, H_{Ar}), 7.66-7.65 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.41-7.40 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.05-5.98 (m, 1H, $OCH_2C\mathit{H}CH_2$), 5.39-5.35 (dq, *J* = 1.7, 17.2 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 5.21-5.19 (dq, *J* = 1.6, 10.5 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 4.61-4.60 (d, *J* = 5.4 Hz, 2H, $OC\mathit{H}_2CHCH_2$), 4.54-4.47 (m, 2H, C*H*NH, $C\mathit{H}(CH_3)_2$), 4.43 (s, 1H, CCH), 2.00-1.98 (d, *J* = 7.6 Hz, 2H, $CHC\mathit{H}_2C$), 1.55 (s, 9H, $C(CH_3)_3$), 1.26-1.25 (d, *J* = 6.1 Hz, 6H, $CH(C\mathit{H}_3)_2$), 1.12 (s, 3H, CCH_3) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 170.5 (CO), 166.0 (CO), 165.0 (CO), 164.6 (CO), 164.5 (CO), 164.3 (CO), 149.5 (C_{Ar}), 143.0 (C_{Ar}), 142.6 (C_{Ar}), 142.2 (C_{Ar}), 141.9 (C_{Ar}), 135.6 (C_{Ar}), 134.6 (C_{Ar}), 133.7 ($OCH_2\mathit{C}HCH_2$), 131.7 (C_{Ar}), 130.1 (C_{Ar}), 128.8 (C_{Ar}), 128.5 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.1 (C_{Ar}), 127.1 (C_{Ar}), 126.0 (C_{Ar}), 125.0 (C_{Ar}), 123.6 (C_{Ar}), 119.5 (C_{Ar}), 119.0 ($OCH_2CH\mathit{C}H_2$), 118.9 (C_{Ar}), 118.8 (C_{Ar}), 117.8 (C_{Ar}), 83.3 (C*C*H), 82.8 (*C*CH), 80.3 ($\mathit{C}(CH_3)_3$), 76.3 ($O\mathit{C}H_2CHCH_2$), 74.3 ($\mathit{C}H(CH_3)_2$), 50.4 (CHNH), 35.8 ($CH\mathit{C}H_2C$), 27.9 ($C(\mathit{C}H_3)_3$), 24.6 (NCN), 22.3 ($CH(\mathit{C}H_3)_2$), 19.8 ($C\mathit{C}H_3$) ppm;

HRMS (ESI) calculated for $C_{52}H_{51}N_7O_9Na$ $[M+Na]^+$: 940.3646; found: 940.3656.

tert-Butyl (*S*)-4-(4-(4-(2-(4-(4-ethynylbenzamido)benzamido)-3-(3-methyl-3*H*-diazirin-3-yl)propanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoate (**212**)



Allyl ether **211** (163 mg, 0.18 mmol) was dissolved in THF (8 mL). Aniline (53 µL, 0.58 mmol, 3.30 equiv.) and $Pd(PPh_3)_4$ (20.5 mg, 0.02 mmol, 0.10 equiv.) were added subsequently and the resulting mixture was stirred at rt for 4 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (dry load, MeOH in CH_2Cl_2 = 1%, 2%) to furnish product **212** (58.1 mg, 0.07 mmol, 37%) as beige amorphous solid.

R_f (2% MeOH in CH_2Cl_2) = 0.41;

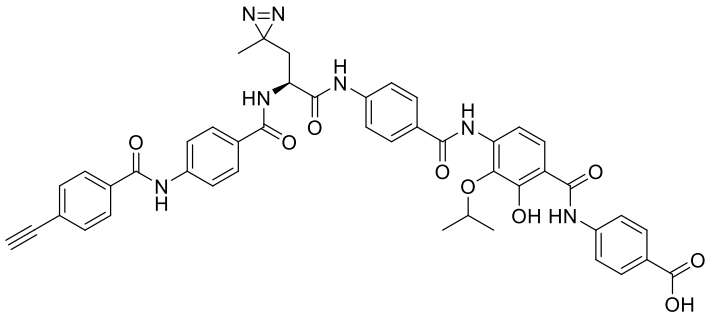
$[\alpha]_D^{30}$ = +2.3 ° (c 0.1, THF);

^{1}H-NMR (500 MHz, DMSO-d_6) = δ 12.28 (s, 1H, OH), 10.62 (bs, 1H, NH), 10.56 (s, 1H, NH), 10.54 (s, 1H, NH), 9.40 (s, 1H, NH), 8.69-8.68 (d, *J* = 7.8 Hz, 1H, CHN*H*), 8.01-7.99 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.99-7.90 (m, 7H, H_{Ar}), 7.86-7.84 (m, 2H, H_{Ar}), 7.81-7.80 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.70-7-60 (m, 4H, H_{Ar}), 7.57-7.53 (m, 1H, H_{Ar}), 4.57-4.50 (m, 2H, C*H*NH, C*H*$(CH_3)_2$), 4.43 (s, 1H, CCH), 2.00- 1.98 (d, *J* = 7.5 Hz, 2H, CHCH_2C), 1.55 (s, 9H, C$(CH_3)_3$), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, CH(CH_3)$_2$), 1.12 (s, 3H, CCH_3) ppm;

^{13}C-NMR (126 MHz, DMSO-d_6) = δ 170.5 (CO), 168.4 (CO), 166.0 (CO), 165.0 (CO), 164.6 (CO), 164.2 (CO), 142.3 (C_{Ar}), 141.9 (C_{Ar}), 136.4 (C_{Ar}), 134.6 (C_{Ar}), 132.1 (C_{Ar}), 132.0 (C_{Ar}), 131.8 (C_{Ar}), 131.5 (C_{Ar}), 131.4 (C_{Ar}), 129.9 (C_{Ar}), 128.8 (C_{Ar}), 128.8 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.4 (C_{Ar}), 128.1 (C_{Ar}), 125.0 (C_{Ar}), 122.8 (C_{Ar}), 120.6 (C_{Ar}), 119.5 (C_{Ar}), 119.0 (C_{Ar}), 83.3 (C*C*H), 82.8 (*C*CH), 80.5 (*C*$(CH_3)_3$), 74.8 (*C*H$(CH_3)_2$), 50.4 (CHNH), 35.8 (CH*C*H_2C), 27.8 (C(*C*H_3)$_3$), 24.6 (NCN), 22.3 (CH(*C*H_3)$_2$), 19.8 (C*C*H_3) ppm;

HRMS (ESI) calculated for $C_{49}H_{47}N_7O_9Na$ $[M+Na]^+$: 900.3333; found: 900.3335.

(*S*)-4-(4-(4-(2-(4-(4-Ethynylbenzamido)benzamido)-3-(3-methyl-3*H*-diazirin-3-yl)propanamido)benzamido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid **TSE33**



tert-Butyl ester **212** (52.4 mg, 0.06 mmol) was dissolved in precooled TFA (3 mL) at 0 °C with stirring. The solution was warmed up to rt over 30 min. Et_2O was added at 0 °C. The precipitate was filtered off, washed with an excess of Et_2O and dried *in vacuo* to furnish **TSE33** (30.6 mg, 0.04 mmol, 62%) as beige amorphous solid.

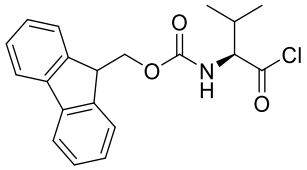
$[\alpha]_D^{25}$ = +4.0 ° (c 0.1, MeOH);

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 12.82 (s, 1H, CO_2H), 12.29 (s, 1H, OH), 10.60 (s, 1H, NH), 10.55 (s, 1H, NH), 10.54 (s, 1H, NH), 9.41 (s, 1H, NH), 8.69-8.68 (d, *J* = 7.8 Hz, 1H, CHN*H*), 8.00-7.99 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 7.98-7.95 (m, 6H, H_{Ar}), 7.92-7.91 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.86-7.84 (m, 3H, H_{Ar}), 7.81-7.80 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 7.71-7-69 (d, *J* = 8.9 Hz, 1H, H_{Ar}), 7.66-7.65 (d, *J* = 8.3 Hz, 2H, H_{Ar}), 4.56-4.53 (m, 2H, C*H*NH, C*H*$(CH_3)_2$), 4.43 (s, 1H, CCH), 2.00- 1.98 (d, *J* = 7.5 Hz, 2H, CHCH_2C), 1.27-1.26 (d, *J* = 6.1 Hz, 6H, CH(CH_3)$_2$), 1.12 (s, 3H, CCH_3) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 170.5 (CO), 168.5 (CO), 166.9 (CO), 166.0 (CO), 165.0 (CO), 164.2 (CO), 142.3 (C_{Ar}), 154.1 (C_{Ar}), 142.3 (C_{Ar}), 142.0 (C_{Ar}), 141.9 (C_{Ar}), 137.0 (C_{Ar}), 136.3 (C_{Ar}), 134.4 (C_{Ar}), 131.7 (C_{Ar}), 130.2 (C_{Ar}), 128.8 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.4 (C_{Ar}), 128.1 (C_{Ar}), 126.3 (C_{Ar}), 125.0 (C_{Ar}), 122.8 (C_{Ar}), 120.7 (C_{Ar}), 119.5 (C_{Ar}), 119.0 (C_{Ar}), 112.4 (C_{Ar}), 112.2 (C_{Ar}), 83.3 (C*C*H), 82.8 (C*C*H), 74.9 (*C*H(CH_3)$_2$), 50.4 (CHNH), 35.8 (CH*C*H$_2$C), 24.6 (NCN), 22.3 (CH(*C*H$_3$)$_2$), 19.8 (C*C*H$_3$) ppm;
HRMS (ESI) calculated for $C_{45}H_{39}N_7O_9Na$ $[M+Na]^+$: 844.2707; found: 844.2719.

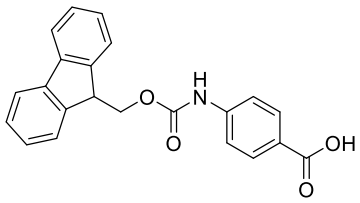
4.2.15 Solid phase synthesis of QL56

(9*H*-Fluoren-9-yl)methyl (*S*)-(1-chloro-3-methyl-1-oxobutan-2-yl)carbamate (**215**)



Fmoc-L-valine (**115**) (300 mg, 0.88 mmol) was dissolved in CH_2Cl_2 (3.7 mL) and $SOCl_2$ (700 µL, 8.83 mmol, 10.0 equiv.) was added at 55 °C. The mixture was stirred at 55 °C for 1 h. The solvent was removed under reduced pressure. The residue was coevaporated with CH_2Cl_2 to furnish chloride **215** (310 mg, 0.86 mmol, 97%) as colorless amorphous solid, which was used directly in the next step.[42]

4-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)benzoic acid (**213**)



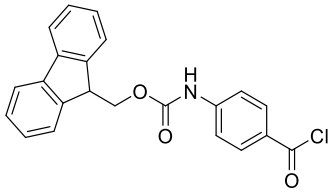
PABA (3.00 g, 21.9 mmol) was dissolved in a mixture of a 10% Na_2CO_3 solution and 1,4-dioxane (3:2, 440 mL). FmocCl (8.57 g, 32.8 mmol, 1.50 equiv.) was added in portions at 0 °C over 20 min. The mixture was stirred at rt for 20 h. H_2O was added and the precipitates were filtered off and washed with Et_2O. The filtrate was acidified with a 1 M HCl solution until pH 1. The precipitate was filtered off and washed with H_2O, Et_2O and dried in vacuo to furnish acid **213** (6.08 g, 16.9 mmol, 77%) as colorless amorphous solid.[42]
The analytical data are consistent with those reported in the literature.[104]
^{1}H-NMR (400 MHz, DMSO-d_6) = δ 12.65 (bs, 1H, CO_2H), 10.06 (bs, 1H, NH), 7.92-7.91 (d, *J* = 7.4 Hz, 2H, H_{Ar}), 7.85-7.83 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.76-7.75 (d, *J* = 7.4 Hz, 2H, H_{Ar}),

7.55-7.53 (m, 2H, H_{Ar}), 7.45-7.41 (t, *J* = 7.3 Hz, 2H, H_{Ar}), 7.38-7.34 (dt, *J* = 1.1, 7.4 Hz, 2H, H_{Ar}), 4.54-4.53 (d, *J* = 6.5 Hz, 2H, H_{Ar}), 4.34-4.31 (t, *J* = 6.6 Hz, 1H, H_{Ar}) ppm.

General information

All SPS reactions were carried out in a 20 mL syringe as peptide reactor with plunge and frit. For the SPS commercially available Wang resin (4-benzoxybenzylalcohol, polymer-bound, 100-200 mesh, 1.0-1.5 mmol/g OH loading, 1% DVB crosslinked) was used. Coupling reactions and Fmoc-deprotection reactions were monitored by the chloranil test.

(9*H*-Fluoren-9-yl)methyl (4-(chlorocarbonyl)phenyl)carbamate (**214**)



Method A

Fmoc-PABA-OH **213** was dissolved in NMP (0.8 M) and $SOCl_2$ (1.50 equiv.) was added. The mixture was stirred at rt for 2 h and used directly in the next step.[42]

Method B

Fmoc-PABA-OH **213** was dissolved in $SOCl_2$ (0.5 M). The mixture was stirred at 80 °C for 2 h. The solvent was removed under reduced pressure. The residue was dried in vacuo to furnish chloride **214** as yellow amorphous solid, which was used in the next step without further purification.[42]

General procedures

Chloranil test

Reagent A: Acetaldehyde (0.1 mL) was dissolved in DMF (0.5 mL).

Reagent B: *para*-Chloranil (10 mg) was dissolved in DMF (0.5 mL).

A sample of the resin (approx. 1 mg) was added to a test tube. Reagent A (1 drop) and reagent B (1 drop) were added. The mixture was incubated at rt for 5 min. Afterwards, the resin color was analysed:

Green = positive, free amine

Yellow = negative, no free amine

1 Resin loading

Wang resin was swollen in NMP (1.0 mL/100 mg) at rt for 30 min. Fmoc-PABA-COCl **214** (prepared with method A, 10.0 equiv.) was added. The resulting mixture was shaken at rt for 18 h. Afterwards, the loaded resin was filtered and washed with NMP (2x), MeOH (2x) and CH_2Cl_2 (2x) and dried *in vacuo*.

2 Fmoc deprotection

The resin-bound Fmoc-protected compound was shaken with piperidine/MeCN (1:4) at rt for 3 min. The resin was filtered and washed with DMF (2x), MeOH (2x) and CH_2Cl_2 (2x). The procedure was repeated, whereas shaking was conducted for 7 min. Afterwards, the resin was dried *in vacuo*. The reaction was controlled via chloranil test.

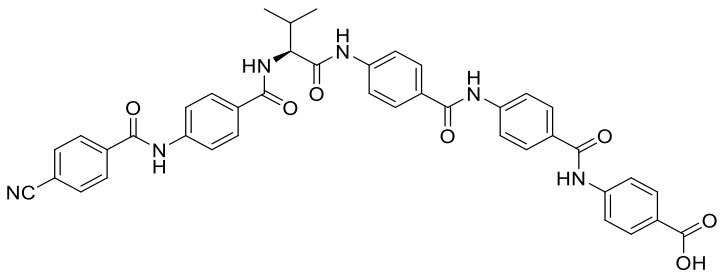
3 Amide coupling

The resin-bound amine was swollen in CH_2Cl_2 at rt for 20-30 min. Afterwards, the resin was shaken in a mixture of acyl chloride (3.00 equiv.) and DIPEA (6.00 equiv.) in CH_2Cl_2 (3.0 M) at rt for 18 h. The resin was filtered and washed with DMF (2x), MeOH (2x) and CH_2Cl_2 (2x) and dried *in vacuo*. The reaction was controlled via chloranil test.

4 Resin cleavage

The resin-bound ester was shaken in TFA/ CH_2Cl_2 (0.05 M, 1:1) at rt for 1 h. The resin was filtered and washed with CH_2Cl_2 (3x). The filtrate was concentrated under reduced pressure. The residue was washed with Et_2O, filtered and dried *in vacuo*.

(*S*)-4-(4-(4-(2-(4-(4-Cyanobenzamido)benzamido)-3-methylbutanamido)benzamido)benzamido)benzoic acid **QL56**



SPS was performed by accomplishing the following steps:

1. Procedure **1**: Wang-resin (200 mg, 0.22 mmol) .
2. Procedure **2** and **3**: Fmoc-PABA-Cl **214** (prepared with method B)
3. Repeatition of step 2.

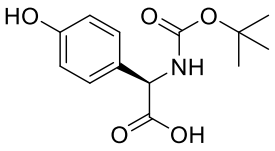
4. Produre **2** and **3**: Fmoc-l-Val-Cl **215**.
5. Produre **2** and **3**: Fmoc-PABA-Cl **214** (prepared with method B).
6. Produre **2** and **3**: 4-cyanobenzoyl chloride **6**.
7. Procedure **4**.

The crude product was purified by HPLC. The collected fractions were concentrated under reduced pressure. The residue was suspended in H_2O and incubated for 5 min in an ultrasonic bath. The precipitate was filtered off and washed with an excess of H_2O, Et_2O and a minimal amount of MeOH to furnish **QL56** (34.9 mg, 0.05 mmol, 22%) as colorless amorphous solid.[42]
$[\alpha]_D^{23}$ = +2.7 ° (c 0.1, MeOH/THF (1:1));
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.71 (bs, 1H, CO_2H), 10.69 (s, 1H, NH), 10.52 (s, 1H, NH), 10.42 (s, 1H, NH), 10.41 (s, 1H, NH), 8.49-8.47 (d, *J* = 8.1 Hz, 1H, CHN*H*), 8.14-8.12 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 8.05-8.03 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 8.00-7.91 (m, 12H, H_{Ar}), 7.89-7.88 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 7.82-7.80 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 4.46-4.43 (t, *J* = 8.3 Hz, 1H, C*H*NH), 2.27-2.20 (sept, *J* = 6.8 Hz, C*H*$(CH_3)_2$), 1.04-0.99 (d, *J* = 6.7, 21.2 Hz, 6H, CH(C*H*$_3)_2$) ppm.
^{13}C-NMR (400 MHz, DMSO-d_6): δ = 171.2 (CO), 167.1 (CO), 166.2 (CO), 165.3 (CO), 165.2 (CO), 164.4 (CO), 143.3 (C_{Ar}), 142.6 (C_{Ar}), 142.0 (C_{Ar}), 141.5 (C_{Ar}), 138.7 (C_{Ar}), 132.5 (C_{Ar}), 130.2 (C_{Ar}), 129.3 (C_{Ar}), 129.1 (C_{Ar}), 129.0 (C_{Ar}), 128.8 (C_{Ar}), 128.5 (C_{Ar}), 125.7 (C_{Ar}), 119.5 (C_{Ar}), 119.4 (C_{Ar}), 118.5 (C_{Ar}), 118.3 (CN), 115.1 (C_{Ar}), 114.0 (C-Ar), 60.3 (CHNH), 30.0 (*C*H$(CH_3)_2$), 19.3 (d, *J* = 2.4 Hz, CH(*C*$H_3)_2$) ppm.
HRMS (ESI) calculated for $C_{41}H_{33}N6O_7$ $[M-H]^-$: 721.2411; found: 721.2405.

4.3 Myxovalargin A – Experimental procedures

4.3.1 (*S*)-Fmoc-β-tyrosine

(*R*)-2-((*tert*-Butoxycarbonyl)amino)-2-(4-hydroxyphenyl) acetic acid (**242**)



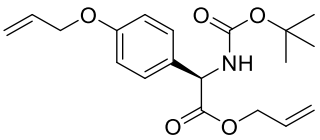
(*R*)-4-Hydroxyphenylglycine (**241**) (20.4 g, 121.7 mmol) was suspended in 1,4-dioxane/H_2O (1:1, 800 mL). $NaHCO_3$ (51.1 g, 609 mmol, 5.00 equiv.) was added before addition of Boc_2O (29.2 g, 134 mmol, 1.10 equiv) at 0 °C. The suspension was warmed to rt and stirred for 20 h. The organic solvent was removed under reduced pressure. EtOAc and a 5 M HCl solution were added. The organic phase was washed with a 5 M HCl solution, H_2O and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Drying *in vacuo* furnished crude product **242** (35.4 g, quant.) as colorless amorphous solid, which was used in the next step without further purification.

$[\alpha]_D^{21}$ = -107.7 ° (c 0.1, MeOH);

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 9.49 (bs, 1H, OH), 7.39-7.37 (d, *J* = 8.1 Hz, 1H, NH), 7.18-7.16 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 6.72-6.70 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 4.96-4.94 (d, *J* = 8.1 Hz, 1H, C*H*NH), 1.37 (s, 9H, $C(CH_3)_3$) ppm.

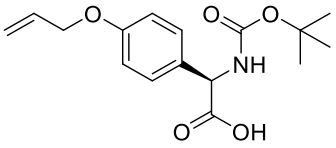
The analytical data are consistent with those reported in the literature.[105]

Allyl (*R*)-2-(4-(allyloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino) acetate (**298**)



Amino acid **242** (1.60 g, 5.98 mmol) was dissolved in DMF (12 mL) and K_2CO_3 (3.30 g, 23.9 mmol, 4.00 equiv.) was added. Allyl bromide (1.81 mL, 15.0 mmol, 2.50 equiv.) was added dropwise at 0 °C. The reaction mixture was stirred at rt for 17 h. The mixture was diluted with EtOAc (90 mL) and the organic phase was washed with H_2O (3x 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Drying *in vacuo* furnished crude product **298** (2.06 g) as yellow oil, which was used in the next step without further purification.

(*R*)-2-(4-(Allyloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino) acetic acid (**243**)



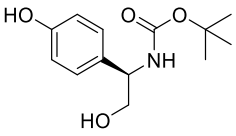
Allyl ester **298** (2.06 g, 5.93 mmol) was dissolved in MeOH (2 mL) and NaOH (0.62 g, 15.4 mmol, 2.00 equiv.) was added. The mixture was stirred at 35 °C for 2 h. H_2O (20 mL) was added and the mixture was acidified with a 6 M HCl solution. The aq. phase was extracted with EtOAc (3x 50 mL). The combined organic phases were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo* to furnish amino acid **243** (1.71 g, 5.57 mmol, 93% over 3 steps) as yellow gum.

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 12.67 (bs, 1H, CO_2H), 7.50-7.48 (d, *J* = 8.0 Hz, 1H, NH), 7.30-7.28 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 6.91-6.89 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 6.07-5.98 (m, 1H, OCH_2CHCH_2), 5.40-5.36 (dd, *J* = 1.3, 17.3 Hz, 1H, OCH_2CHCH_2), 5.26-5.23 (dd, *J* = 1.4, 10.5 Hz, 1H, OCH_2CHCH_2), 5.03-5.01 (d, *J* = 8.0 Hz, 1H, C*H*NH), 4.56-4.54 (d, *J* = 4.9 Hz, 2H, OCH_2CHCH_2), 1.38 (s, 9H, $C(CH_3)_3$) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 172.7 (CO), 157.8 (CO), 155.2 (C_{Ar}), 133.7 (OCH_2CHCH_2), 129.5 (C_{Ar}), 129.0 (C_{Ar}), 117.4 (OCH_2CHCH_2), 114.5 (C_{Ar}), 78.3 ($C(CH_3)_3$), 68.2 (OCH_2CHCH_2), 57.0 (CHNH), 28.2 ($C(CH_3)_3$) ppm;

HRMS (ESI) calculated for $C_{16}H_{21}NO_5Na$ $[M+Na]^+$: 330.1317; found: 330.1320.

tert-Butyl (*R*)-(2-hydroxy-1-(4-hydroxyphenyl)ethyl)carbamate (**244**)



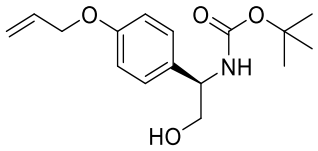
Acid **242** (33.4 g, 124 mmol) was dissolved in THF (165 mL) and BH_3 (0.9 M in THF, 276 mL, 249 mmol, 2.00 equiv.) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 2 h. The mixture was treated with H_2O and EtOAc and stirred at rt for 30 min. The aq. phase was extracted with EtOAc. The combined organic phases were washed with H_2O and brine, dried over $MgSO_4$, filtered and dried *in vacuo* to furnish diol **244** (25.2 g, 99.4 mmol, 80%) as colorless amorphous solid.

R_f (5% MeOH in CH_2Cl_2) = 0.24;

$[\alpha]_D^{22}$ = -72.7 ° (c 0.1, MeOH);

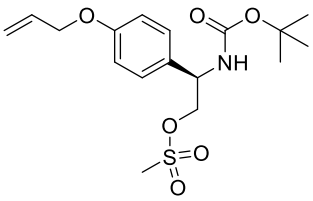
^{1}H-NMR (400 MHz, DMSO-d_6) = δ 9.20 (s, 1H, ArOH), 7.07-7.05 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 6.68-6.66 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 4.69-4.66 (t, *J* = 5.8 Hz, 1H, OH), 4.43-4.38 (q, *J* = 7.2 Hz, 1H, C*H*NH), 3.43-3.40 (m, 2H, CH_2), 1.38 (s, 9H, $C(CH_3)_3$) ppm;
^{13}C-NMR (101 MHz, DMSO-d_6) = δ 156.1 (C_{Ar}), 155.1 (CO), 132.1 (C_{Ar}), 127.8 (C_{Ar}), 114.7 (C_{Ar}), 77.5 ($C(CH_3)_3$), 65.0 (CH_2), 56.2 (CHNH), 28.3 ($C(CH_3)_3$) ppm;
HRMS (ESI) calculated for $C_{13}H_{19}NO_4Na$ $[M+Na]^+$: 276.1212; found: 276.1212.

tert-Butyl (*R*)-(1-(4-(allyloxy)phenyl)-2-hydroxyethyl)carbamate (**245**)



Diol **244** (405 mg, 1.60 mmol) was dissolved in MeOH (1.3 mL) and NaOH (0.5 M in H_2O, 3.20 mL, 1.60 mmol, 1.00 equiv.) was added. The solution was stirred at rt for 1 h. The solvent was removed under reduced pressure. The residue was dissolved in DMF (2.2 mL) before addition of allyl bromide (170 µL, 1.92 mmol, 1.20 equiv.) at 0 °C. The solution was stirred at rt for 3 h and subsequently concentrated under reduced pressure. The residue was purified by column chromatography (dry load; PE/EtOAc = 7:1, 5:1, 4:1, 3:1) to furnish primary alcohol **245** (423 mg, 1.44 mmol, 90%) as colorless amorphous solid.
R_f (PE/EtOAc = 2:1) = 0.19;
$[\alpha]_D^{21}$ = -63.0 ° (c 0.1, MeOH);
^{1}H-NMR (400 MHz, DMSO-d_6) = δ 7.19-7.18 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 7.13-7.11 (d, *J* = 8.2 Hz, 1H, NH), 6.88-6.87 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 6.07-5.98 (m, 1H, OCH_2CHCH_2), 5.41-5.35 (dq, *J* = 1.7, 17.3 Hz, 1H, OCH_2CHCH_2), 5.26-5.22 (dq, *J* = 1.6, 10.5 Hz, 1H, OCH_2CHCH_2), 4.73-4.70 (t, *J* = 5.7 Hz, 1H, OH), 4.54-4.52 (dt, *J* = 1.5, 5.2 Hz, 2H, OCH_2CHCH_2), 4.49-4.42 (q, *J* = 7.2 Hz, 1H, C*H*NH), 3.46-3.42 (m, 2H, CH_2OH), 1.36 (s, 9H, $C(CH_3)_3$) ppm;
^{13}C-NMR (101 MHz, DMSO-d_6) = δ 157.0 (C_{Ar}), 155.1 (CO), 134.0 (OCH_2CHCH_2), 133.9 (C_{Ar}), 127.9 (C_{Ar}), 117.3 (OCH_2CHCH_2), 114.2 (C_{Ar}), 77.6 ($C(CH_3)_3$), 68.1 (OCH_2CHCH_2), 64.9 (CH_2OH), 56.1 (CHNH), 28.3 ($C(CH_3)_3$) ppm;
HRMS (ESI) calculated for $C_{13}H_{19}NO_4Na$ $[M+Na]^+$: 316.1525; found: 316.1523.

(*R*)-2-(4-(Allyloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)ethyl methanesulfonate (**299**)

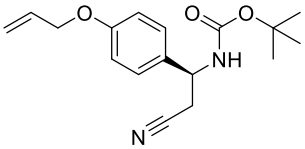


Alcohol **245** (200 mg, 0.68 mmol) was dissolved in CH_2Cl_2 (5 mL) and Et_3N (143 µL, 1.02 mmol, 1.50 equiv.) was added. The solution was cooled to 0 °C and MsCl (80 µL, 1.02 mmol, 1.50 equiv.) was added. The solution was stirred at 0 °C for 1 h before addition of a sat. NH_4Cl solution. The aq. phase was extracted with CH_2Cl_2 (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish crude product **299** (283 mg, quant.) as yellow amorphous solid, which was used in the next step without further purification.

R_f (PE/EtOAc = 2:1) = 0.42;

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 7.60-7.58 (d, *J* = 8.9 Hz, 1H, NH), 7.29-7.27 (d, *J* = 8.4 Hz, 2H, H_{Ar}), 6.94-6.92 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 6.08-5.98 (m, 1H, OCH_2CHCH_2), 5.41-5.36 (dd, *J* = 1.3, 17.2 Hz, 1H, OCH_2CHCH_2), 5.26-5.23 (dd, *J* = 1.2, 10.4 Hz, 1H, OCH_2CHCH_2), 4.84-4.79 (q, *J* = 5.6 Hz, 1H, C*H*NH), 4.56-4.54 (d, *J* = 5.1 Hz, 2H, OCH_2CHCH_2), 4.22-4.19 (m, 2H, $CHCH_2$), 3.15 (s, 3H, SCH_3), 1.37 (s, 9H, $C(CH_3)_3$) ppm.

tert-Butyl (*S*)-(1-(4-(allyloxy)phenyl)-2-cyanoethyl)carbamate (**246**)



Mesylate **299** (0.68 mmol) was dissolved in DMSO (5 mL) and NaCN (100 mg, 2.05 mmol, 3.00 equiv.) was added. The solution was stirred at 40°C for 4 h before addition of H_2O. The mixture was extracted with Et_2O (4x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc = 4:1, 2:1) to furnish nitrile **246** (121 mg, 0.40 mmol, 59%) as colorless amorphous solid.

R_f (PE/EE = 2:1) = 0.65;

$[\alpha]_D^{22}$ = -50.4 ° (c 0.1, MeOH);

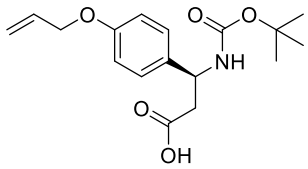
^{1}H-NMR (400 MHz, DMSO-d_6) = δ 7.67-7.65 (d, *J* = 8.8 Hz, 1H, NH), 7.27-7.25 (d, *J* = 8.5 Hz, 2H, H_{Ar}), 6.93-6.90 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 6.06-5.98 (m, 1H, OCH_2CHCH_2), 5.40-5.36 (dd, *J* = 1.3, 17.3 Hz, 1H, OCH_2CHCH_2), 5.26-5.23 (d, *J* = 10.4 Hz, 1H,

OCH_2CHCH_2), 4.82-4.80 (m, 1H, C*H*NH), 4.55-4.54 (d, *J* = 5.1 Hz, 2H, OCH_2CHCH_2), 2.86-2.82 (m, 2H, $CHCH_2$), 1.37 (s, 9H, $C(CH_3)_3$) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 157.5 (C_{Ar}), 154.7 (CO), 133.7 (OCH_2CHCH_2), 133.2 (C_{Ar}), 127.5 (C_{Ar}), 118.6 (CN), 117.4 (OCH_2CHCH_2), 114.5 (C_{Ar}), 78.3 ($C(CH_3)_3$), 68.1 (OCH_2CHCH_2), 50.3 (CHNH), 28.2 ($C(CH_3)_3$), 24.8 ($CHCH_2$) ppm;

HRMS (ESI) calculated for $C_{17}H_{22}N_2O_3Na$ $[M+Na]^+$: 325.1528; found: 325.1528.

(*S*)-3-(4-(Allyloxy)phenyl)-3-((*tert*-butoxycarbonyl)amino)propanoic acid (**247**)



Nitrile **246** (8.71 g, 28.8 mmol) was dissolved in EtOH (350 mL) and NaOH (2 M in H_2O, 144 mL, 288 mmol, 10.0 equiv.) was added. The solution was stirred at 90 °C for 4 h. After cooling down to rt the solvent was removed under reduced pressure. The residue was acidified with a 2 M HCl solution and extracted with EtOAc (4x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, concentrated under reduced pressure and dried *in vacuo* to furnish carboxylic acid **247** (9.08 g, 28.2 mmol, 98%) as colorless amorphous solid.

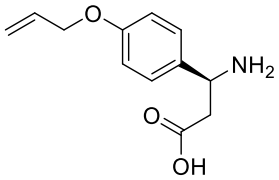
$[\alpha]_D^{24}$ = -52.6 ° (c 1.4, MeOH);

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 12.10 (bs, 1H, CO_2H), 7.36-7.34 (d, *J* = 8.7 Hz, 1H, NH), 7.21-7.19 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 6.88-6.86 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 6.07-5.98 (m, 1H, OCH_2CHCH_2), 5.41-5.35 (dq, *J* = 1.7, 17.3 Hz, 1H, OCH_2CHCH_2), 5.26-5.22 (dq, *J* = 1.6, 10.5 Hz, 1H, OCH_2CHCH_2), 4.86-4.80 (q, *J* = 7.3 Hz, 1H, C*H*NH), 4.54-4.52 (m, 2H, OCH_2CHCH_2), 2.67-2.55 (m, 2H, $CHCH_2$), 1.34 (s, 9H, $C(CH_3)_3$) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 171.9 (CO), 157.1 (C_{Ar}), 154.7 (CO), 135.4 (C_{Ar}), 133.8 (OCH_2CHCH_2), 127.5 (C_{Ar}), 117.4 (OCH_2CHCH_2), 114.3 (C_{Ar}), 77.8 ($C(CH_3)_3$), 68.1 (OCH_2CHCH_2), 50.5 (CHNH), 41.4 ($CHCH_2$), 28.3 ($C(CH_3)_3$) ppm;

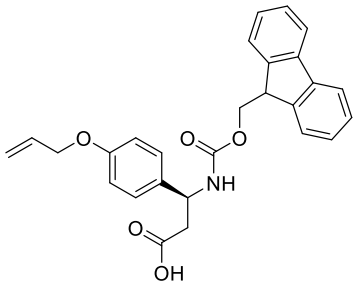
HRMS (ESI) calculated for $C_{17}H_{22}NO_5$ $[M-H]^-$: 320.1498; found: 320.1497.

(*S*)-3-(4-(Allyloxy)phenyl)-3-aminopropanoic acid (**300**)



To a solution of carbamate **247** (8.12 g, 25.3 mmol, 1.00 equiv.) in CH_2Cl_2 (300 mL) TFA (58.4 mL, 758 mmol, 30.0 equiv.) was added at 0 °C and the reaction mixture was stirred for 16 h while warming to rt. The solvent was removed under reduced pressure and the residue was used in the next step without further purification.

(*S*)-3-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-(allyloxy)phenyl)propanoic acid (**248**)



Amino acid **300** (5.59 g, 25.3 mmol) was dissolved in 1,4-dioxane (250 mL) and a 10% Na_2CO_3 solution (500 mL). FmocCl (7.84 g, 30.3 mmol, 1.20 equiv.) in 1,4-dioxane (250 mL) was added dropwise at 0 °C. The mixture was stirred at rt for 15 h. Afterwards, the mixture was diluted with H_2O and the aq. phase was washed with Et_2O (3x). The aq. phase was acidified with a 1 M HCl solution. The precipitate was filtered off. Additionally, the aq. filtrate was extracted with EtOAc (3x). The combined organic extracts were dried over $MgSO_4$, filtered, concentrated and combined with the acidic precipitate to furnish product **248** (6.70 g, 15.1 mmol, 60% over two steps) as colorless amorphous solid.

$[\alpha]_D^{24}$ = -18.5 ° (c 1.0, MeOH);

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 12.21 (bs, 1H, CO_2H), 7.89-7.84 (m, 3H, NH, H_{Ar}), 7.21-7.68-7.66 (d, *J* = 7.4 Hz, 2H, H_{Ar}), 7.43-7.21 (m, 6H, H_{Ar}), 6.89-6.87 (d, *J* = 8.7 Hz, 2H, H_{Ar}), 6.08-5.98 (m, 1H, OCH_2CHCH_2), 5.41-5.36 (dd, *J* = 1.6, 17.2 Hz, 1H, OCH_2CHCH_2), 5.26-5.23 (dd, *J* = 1.5, 10.5 Hz, 1H, OCH_2CHCH_2), 4.91-4.85 (m, 1H, C*H*NH), 4.54-4.53 (d, *J* = 5.2 Hz, 2H, OCH_2CHCH_2), 4.30-4.17 (m, 3H, OCH_2CHAr), 2.73-2.58 (m, 2H, $CHCH_2$) ppm;

^{13}C-NMR (101 MHz, DMSO-d_6) = δ 171.8 (CO), 157.2 (C_{Ar}), 155.3 (CO), 143.9 (C_{Ar}), 143.8 (C_{Ar}), 140.7 (C_{Ar}), 135.0 (C_{Ar}), 133.8 (OCH_2CHCH_2), 127.6 (C_{Ar}), 127.5 (C_{Ar}), 127.0 (C_{Ar}),

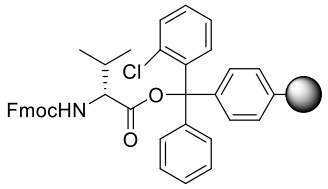
125.2-125.1 (d, J = 4.9 Hz, C_{Ar}), 120.1 (C_{Ar}), 117.4 (OCH_2CHCH_2), 114.4 (C_{Ar}), 68.1 (OCH_2CHCH_2), 65.3 (OCH_2CHC_{Ar}), 51.0 (CHNH), 46.7 (OCH_2CHC_{Ar}), 41.1 (CH_2) ppm; **HRMS (ESI)** calculated for $C_{27}H_{24}NO_5$ $[M-H]^-$: 442.1654; found: 442.1647.

4.3.2 Solid phase synthesis of fragment A

General procedure: resin preloading

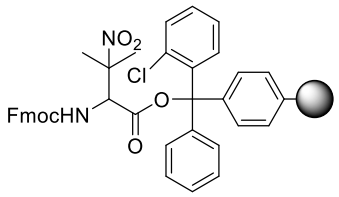
2-Chlorotrityl chloride resin **249** (1.5 mmol/g, 1.00 equiv.) was suspended in CH_2Cl_2 (10 mL/g resin). Pyridine (2.4 equiv.) and $SOCl_2$ (1.20 equiv.) were added at 0 °C. The mixture was stirred under reflux (oil bath 55 °C) for 4 h. The resin was filtrated and washed with an excess of CH_2Cl_2. The resin was dried *in vacuo* and added to a stirred solution of Fmoc-protected amino acid (1.20 equiv.) and DIPEA (5.00 equiv.) in CH_2Cl_2 (10 mL/g resin). The mixture was stirred at rt overnight. Then, the mixture was filtrated and washed with CH_2Cl_2/MeOH/DIPEA (17:2:1, 3x 20 mL), CH_2Cl_2 (3x 20 mL), DMF (2x 20 mL) and DCM (2x 20 mL). The loaded resin was dried *in vacuo*.

2-Chlorotrityl-2-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-D-valine resin (**252**)



2-Chlorotrityl-2-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-D-valine resin (**252**) (2.95 mmol) was prepared from Fmoc-D-valine **255** according to the general procedure.

2-Chlorotrityl-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-methyl-3-nitrobutanoic acid resin (**251**)



2-Chlorotrityl-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-methyl-3-nitrobutanoic acid resin (**251**) (2.17 mmol) was prepared from amino acid **109** according to the general procedure.

General procedure: peptide synthesizer

Peptides were synthesized with a LIBERTY BLUE™ Automated Microwave Peptide Synthesizer from CEM following a standard Fmoc-protocol (Table 22). A 2-chlorotrityl chloride resin (200-400 mesh, 1.50-1.90 mmol/g) from BACHEM was used. The appropriate reagents were prepared as stock solutions before they were added to the synthesizer. Standard couplings of Fmoc-protected amino acids (5.00 equiv. in regard to resin) were performed with DIC (5.00 equiv.) and Oxyma (5.00 equiv.) in DMF. The corresponding Fmoc-deprotection was conducted with 10% piperazine (w/v) in EtOH:NMP (1:9, 5.00 equiv.). As required, the reaction mixture was irradiated with microwaves. The amino acids that were used are depicted in Table 23. The specific cleavages of the final peptides are described in the respective experimental.

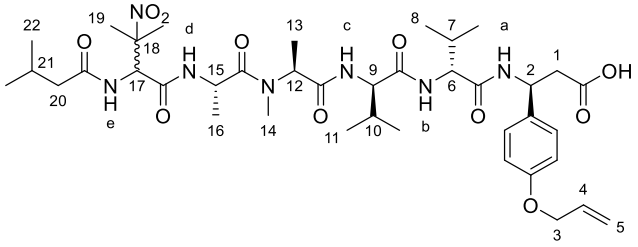
Table 22: SPS settings used for standard coupling and Fmoc-deprotection towards Myxovalargin A (**234**).

	Temp. [°C]	**Power [W]**	**Time [s]**	**ΔT [°C]**
Standard coupling	75	170	15	2
	90	30	110	1
Deprotection	75	155	15	2
	90	30	50	1

Table 23: (Amino) acids used for SPS towards Myxovalargin A (**234**).

(Amino) acid	**Reagent**
Ala	Fmoc-Ala-OH (**254**)
Arg	Fmoc-Arg(Pbf)-OH (**258**)
Val	Fmoc-Val-OH (**115**)
(*S*)-3-(4-(Allyloxy)phenyl)-3-aminopropionic acid	Fmoc-(*S*)-3-(4-(allyloxy)phenyl)aminopropanoic acid (**248**)
D-Val	Fmoc-D-Val-OH (**255**)
***N*-Me-Ala**	Fmoc-*N*-Me-Ala-OH (**256**)
2-Amino-3-methyl-3-nitrobutanioc acid	Fmoc-2-amino-3-methyl-3-nitrobutanoic acid (**109**)
3-Methylbutanoic acid	3-Methylbutanoic acid (**253**)
2-amino-5-(Boc-amino)pentanoic acid	Fmoc-2-amino-5-(Boc-amino)pentanoic acid (**257**)

(3*S*,6*R*,9*R*,12*S*,15*S*)-3-(4-(Allyloxy)phenyl)-6,9-diisopropyl-12,13,15,22-tetramethyl-18-(2-nitropropan-2-yl)-5,8,11,14,17,20-hexaoxo-4,7,10,13,16,19-hexaazatricosanoic acid (**237**)



The title compound was prepared according to the general procedure at the peptide synthesizer in a 0.5 mmol scale. Resin-bound (*R*)-3-(4-(allyloxy)phenyl)-3-aminopropanoic acid **250** (333.0 mg), Fmoc-D-Val-OH (**255**) (3.12 g), Fmoc-*N*-Me-Ala-OH (**256**) (1.50 g), Fmoc-Ala-OH (**254**) (1.43 g), Amino-3-methyl-3-nitrobutanoic acid (**109**) (1.77 g) and isovaleric acid **253**

(0.47 g) were used. After completion of the SPS, the resin was transferred to a syringe with filter. The solvent was exhausted and the resin was washed with DMF (3x 15.0 mL) and CH_2Cl_2 (3x 15.0 mL). The cleavage was performed by adding TFA (1% in CH_2Cl_2, 3 mL) to the syringe, which was shaken at rt for 2 min. Pyridine (10% in MeOH, 3.0 mL) was added to the filtrate. The cleavage, filtration and base addition were repeated (4x). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (RP-Büchi, solvent A: H_2O + 0.1% (v/v) FA, solvent B: MeOH; 15x150 mm column; tube volume: 20.0 mL; flow rate: 80.0 ml/min; gradient: (*t* [min]/solvent B [%]): 0/10, 3/10, 13/100, 15/100; t_R = 10.0 min) to furnish product **237** (272 mg, 338 μmol, 68%) as a white foam.[87,106]

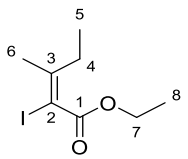
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.58-8.50 (m, 1H, NH_d), 8.38-8.36 (m, 1H, NH_a), 8.21-8.15 (m, 1H, NH_e), 7.81-7.78 (m, 1H, $NH_{b/c}$), 7.59-7.29 (m, 1H, $NH_{b/c}$), 7.20 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 6.84 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 6.06-5.97 (m, 1H, H-4), 5.39-5.34 (m, 1H, H-5), 5.25-5.22 (m, 1H, H-5), 5.14 (q, *J* = 7.6 Hz, 1H, H-2), 5.07-5.01 (m, 1H, H-12), 4.73-4.56 (m, 1H, H-15), 4.53-4.51 (m, 2H, H-3), 4.19-4.14 (m, 1H, H-6/9), 4.09 (t, *J* = 8.3 Hz, 1H, (m, 1H, H-6/9), 3.17-2.81 (2s, 3H, H-14), 2.64-2.62 (m, 2H, H-1), 2.11-1.99 (m, 2H, H-20), 1.95-1.87 (m, 3H, H-7/10/21), 1.66-1.48 (m, 6H, H-19), 1.23-1.17 (m, 6H, H-13/16), 0.86-0.71 (m, 18H, H-8/11/22) ppm;

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 172.0 (CO), 171.9 (CO), 171.7 (CO), 170.9 (CO), 170.8 (CO), 170.6 (CO), 169.7 (CO), 157.1 (C_{Ar}), 134.3 (C_{Ar}), 133.8 (C-4), 127.6 (C_{Ar}), 117.3 (C-5), 114.3 (C_{Ar}), 89.0 (C-18), 68.1 (C-3), 57.9 (C-6/9), 57.3 (C-6/9), 56.8 (C-17), 51.5 (t, C-12), 48.6 (C-2), 45.6 (C-15), 44.2 (C-20), 40.7 (C-1), 30.4 (C-14), 30.2 (C-7/10), 25.7 (C-21), 25.6 (C-7/10), 23.6 (C-19), 23.3 (C-19), 22.3 (C-19), 22.2 (C-8/11/22), 22.1 (C-8/11/22), 22.0 (C-8/11/22), 21.6 (C-19), 19.2 (C-8/11/22), 19.1 (C-8/11/22), 18.3 (C-8/11/22), 18.2 (C-8/11/22), 17.9 (C-8/11/22), 16.5 (C-16), 14.5 (C-13) ppm;

HRMS (ESI) calculated for $C_{39}H_{62}N_7O_{11}$ $[M+H]^+$: 804.4507; found 804.4502.

4.3.3 Fragment C

Ethyl (*E*)-2-iodo-3-methylpent-2-enoate (**264**)



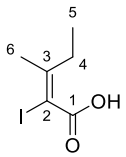
To a suspension of CuI (1.13 g, 5.90 mmol, 1.50 equiv.) in THF (37 mL) MeLi (1.6 M in Et_2O, 11.9 mmol, 3.00 equiv.) was added dropwise at 0 °C. The mixture was stirred for 30 min. The solution was cooled to -78 °C and ethyl-2-pentynoate (**263**) (0.52 mL, 4.00 mmol) was added

dropwise. The mixture was stirred for 3 h at this temperature and iodine (3.02 g, 11.9 mmol, 1.50 equiv.) in THF (11 mL) was added. After 15 min a sat. $Na_2S_2O_3$ solution and Et_2O were added. The aq. phase was extracted with Et_2O (4x) and the combined organic layers were washed with a sat. NH_4Cl solution and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish crude product **264** (1.00 g, 3.70 mmol, 94%) as an orange oil, which was used in the next step without further purification.

The analytical data are consistent with those reported in the literature.[86]

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 4.27-4.22 (q, *J* = 7.1 Hz, 2H, H-7), 2.48-2.42 (q, *J* = 7.5 Hz, 1H, H-4), 2.05 (s, 3H, H-6), 1.34-1.30 (t, *J* = 7.1 Hz, 3H, H-8), 1.10-1.07 (t, *J* = 7.5 Hz, 3H, H-5) ppm.

(*E*)-2-Iodo-3-methylpent-2-enoic acid (**265**)

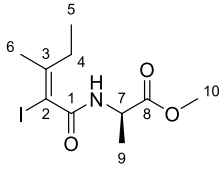


Ester **264** (1.00 g, 3.73 mmol) was dissolved in EtOH (0.9 mL, degassed) and LiOH (0.36 g, 14.9 mmol, 4.00 equiv.) in H_2O (6.5 mL, degassed) was added. The mixture was stirred at 60 °C for 22 h. Et_2O was added at rt. The aq. phase was extracted with Et_2O (2x). Then, the aq. phase was acidified by addition of a 1 M HCl solution until pH 1. The aq. phase was extracted with EtOAc (4x). The combined organic phases were washed with brine and dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product **265** (0.51 g, 2.12 mmol, 57%), which was used in the next step without further purification.

The analytical data are consistent with those reported in the literature.[86]

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 2.63-2.57 (q, *J* = 7.5 Hz, 2H, H-4), 2.13 (s, 3H, H-6), 1.13-1.09 (t, *J* = 7.5 Hz, 3H, H-5) ppm.

Methyl (*E*)-(2-iodo-3-methylpent-2-enoyl)-D-alaninate (**266**)



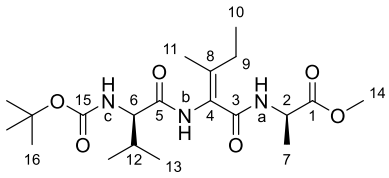
D-Alanine methylester hydrochloride (355 mg, 2.54 mmol, 1.20 equiv.), HOAt (308 mg, 2.26 mmol, 1.10 equiv) and PyAOP (1.18 g, 2.26 mmol, 1.10 equiv) were dissolved in DMF (10 mL) and carboxylic acid **265** (508 mg, 2.12 mmol) dissolved in DMF (13 mL) was added.

The solution was cooled to 0 °C and DIPEA (1.80 mL, 10.6 mmol, 5.00 equiv.) was added dropwise. The reaction mixture was stirred at rt for 20 h. Afterwards a sat. NH_4Cl solution and EtOAc were added. The aq. phase was extracted with EtOAc (6x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc = 6:1) to give product **266** (566 mg, 1.74 mmol, 82%) as a colorless solid.

The analytical data are consistent with those reported in the literature.[86]

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 6.23-6.22 (d, *J* = 4.8 Hz, 1H, NH), 4.65-4.58 (p, *J* = 7.4 Hz, 1H, H-7), 3.77 (s, 3H, H-10), 2.43-2.37 (q, *J* = 7.5 Hz, 2H, H-4), 1.98 (s, 3H, H-6), 1.56-1.44 (d, *J* = 7.2 Hz, 3H, H-9), 1.10-1.06 (t, *J* = 7.5 Hz, 3H, H-5) ppm.

Methyl ((*E*)-2-((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-3-methylpent-2-enoyl)-D-alaninate (**267**)

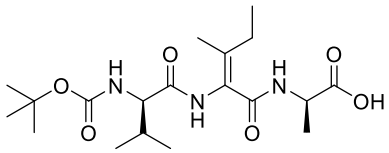


K_2CO_3 (106 mg, 0.77 mmol, 2.00 equiv.) was subjected to a reaction flask, which had been dry-heated before. Vinyl iodide **266** (250 mg, 0.77 mmol, 2.00 equiv.), *tert*-butyl (*R*)-(1-amino-3-methyl-1-oxobutan-2-yl)carbamate (83.0 mg, 0.38 mmol) and CuI (44.0 mg, 0.23 mmol, 0.6 equiv.) were added and dissolved in 1,4-dioxane (0.5 mL). Then, *trans*-*N*,*N*'-dimethylcyclohexane-1,2-diamine (250 µL, 1.58 mmol, 4.12 equiv.) was added and the resulting mixture was stirred at 70 °C for 20 h. Afterwards, a sat. NH_4Cl solution was added and the mixture was diluted with EtOAc. The aq. phase was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2/MeOH = 100:0, 100:1, 100:2) to give product **267** (74.4 mg, 0.18 mmol, 47%) as a colorless amorphous solid.

The analytical data are consistent with those reported in the literature.[86]

^{1}H-NMR (400 MHz, DMSO-d_6) = δ 8.98 (s, 1H, NH_b), 7.75-7.73 (d, *J* = 7.0 Hz, 1H, NH_a), 6.87-6.85 (d, *J* = 7.8 Hz, 1H, NH_c), 4.32-4.25 (p, *J* = 7.1 Hz, 1H, H-2), 3.79-3.75 (t, *J* = 7.6 Hz, 1H, H-6), 3.61 (s, 3H, H-14), 2.38-2.32 (q, *J* = 7.4 Hz, 2H, H-9), 2.01-1.89 (oct, *J* = 6.9 Hz, 1H, H-12), 1.66 (s, 3H, H-11), 1.38 (s, 9H, H-16), 1.27-1.25 (d, *J* = 7.2 Hz, 3H, H-7), 1.01-0.97 (t, *J* = 7.5 Hz, 3H, H-10), 0.90-0.88 (d, *J* = 6.8 Hz, 3H, H-13), 0.88-0.86 (d, *J* = 6.8 Hz, 3H, H-13) ppm.

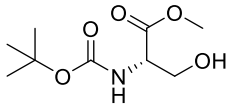
((*E*)-2-((*R*)-2-((*tert*-Butoxycarbonyl)amino)-3-methylbutanamido)-3-methylpent-2-enoyl)-D-alanine (**239**)



Methyl ester **267** (74.4 mg, 0.18 mmol) was dissolved in THF (2 mL) and LiOH (1 M in H_2O, 1.85 mL, 1.85 mmol, 10.0 equiv.) was added dropwise at 0 °C. The reaction was stirred at ambient temperature for 21 h. H_2O and Et_2O were added and the aq. phase was washed with Et_2O (2x). The aq. phase was acidified with a 1 M HCl solution and extracted with EtOAc (4x). The combined organic phases were dried over $MgSO_4$, filtrated, concentrated under reduced pressure and dried *in vacuo* to furnish acid **239** (61.4 mg, 0.15 mmol, 85%), which was used in the next step without further purification.

4.3.4 Fragment D

Methyl (*tert*-butoxycarbonyl)-L-serinate ((*R*)-**104**)

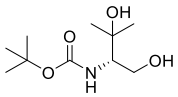


L-Serine (1.00 g, 9.52 mmol) was suspended in MeOH (20 mL) and freshly destilled $SOCl_2$ (4.10 mL, 56.6 mmol, 6.00 equiv.) was added dropwise at 0 °C. The solution was stirred at ambient temperature for 20 h. The solvent was removed under reduced pressure and coevaporated with Et_2O (3x). The residue was dissolved in CH_2Cl_2 (40 mL) and cooled to 0 °C. Then Et_3N (3.60 mL, 25.8 mmol, 2.70 equiv.) and Boc_2O (2.28 g, 10.5 mmol, 1.10 equiv) were added carefully and the reaction mixture was allowed to warm to rt. The mixture was stirred for 16 h before the solvent was removed under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/MeOH = 100:0, 100:2, 100:5) to give product (*R*)-**104** (1.52 g, 6.9 mmol, 73%) as a yellowish oil.

The analytical data are consistent with those reported in the literature.[65]

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 5.43 (s, 1H, NH), 4.39 (m, 1H, C*H*NH), 3.99-3.88 (m, 2H, CH_2), 3.79 (s, 3H, CH_3), 2.24 (s, 1H, OH), 1.46 (s, 9H, $C(CH_3)_3$) ppm.

tert-Butyl (*S*)-(1,3-dihydroxy-3-methylbutan-2-yl)carbamate ((*R*)-**105**)

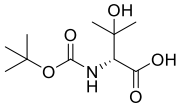


Ester (*R*)-**104** (1.51 g, 6.91 mmol) was suspended in Et_2O (37 mL). MeMgBr (3 M in Et_2O, 13.8 mL, 41.5 mmol, 6.00 equiv.) was added at -78 °C. The emulsion was allowed to warm to rt and stirred at rt for 3 h. The mixture was cooled to 0 °C and a sat. NH_4Cl solution was added. The aq. phase was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc = 3:2) to furnish diol (*R*)-**105** (784 mg, 3.58 mmol, 52%) as colorless solid.

The analytical data are consistent with those reported in the literature.[66]

^{1}H-NMR (400 MHz, CD_3OD) = δ 3.82-3.78 (dd, *J* = 4.1, 11.2 Hz, 1H, C*H*NH), 3.62-3.57 (m, 1H, CH_2), 3.51-3.48 (m, 1H, OH), 1.45 (s, 9H, $C(CH_3)_3$), 1.23 (s, 3H, $C(CH_3)_2$), 1.15 (s, 3H, $C(CH_3)_2$) ppm.

(*R*)-2-((*tert*-Butoxycarbonyl)amino)-3-hydroxy-3-methylbutanoic acid ((*R*)-**106**)

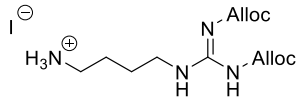


Diol (*R*)-**105** (784 mg, 3.58 mmol) was dissolved in MeCN (14 mL). Phosphate buffer (pH 7, 13 mL) and TEMPO (55.9 mg, 0.36 mmol, 0.10 equiv.) were added. The solution was warmed to 35 °C and $NaClO_2$ (2 M in H_2O, 3.60 mL, 7.15 mmol, 2.00 equiv.) and NaOCl (0.04 M in H_2O, 1.90 mL, 0.07 mmol, 2 mol%) were added simultaneously over 2 h. The mixture was stirred at 35 °C for 20 h. Citric acid (10%) was added until pH 2. The aq. phase was extracted with EtOAc (3x) and the combined organic phases were concentrated under reduced pressure. The residue was dissolved in a sat. $NaHCO_3$ solution (30 mL). The aq. phase was washed with EtOAc (2x) and treated with a 1 M H_3PO_4 solution (50 mL) until pH 2. The aq. phase was extracted with EtOAc (4x). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish carboxylic acid (*R*)-**106** (714 mg, 3.06 mmol, 86%) as a colorless amorphous solid.

The analytical data are consistent with those reported in the literature.[66]

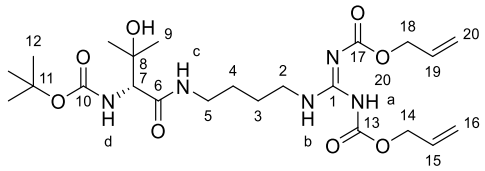
^{1}H-NMR (400 MHz, CD_3OD) = δ 4.09-4.08 (m, 1H, C*H*NH), 1.45 (s, 9H, $C(CH_3)_3$), 1.29 (s, 3H, H-4), 1.26 (s, 3H, $C(CH_3)_2$) ppm.

(*Z*)-4-(2,3-Bis((allyloxy)carbonyl)guanidino)butan-1-aminium iodide (**269**)



Carbamate **268** (1.35 g, 3.39 mmol) was dissolved in CH_2Cl_2 (34 mL). TMSI (0.53 mL, 3.72 mmol, 1.10 equiv) was added. The solution was stirred for 5 min at rt. MeOH was added and the solution was concentrated and coevaporated with CH_2Cl_2 (3x 5 mL) under reduced pressure. The orange residue was used in the next step without further purification.

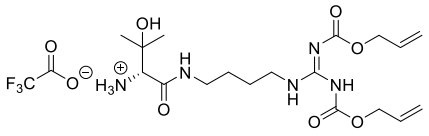
(*N*-Boc-D-3-hydroxyvalyl)-*Nθ*,*Nθ'*-bisalloc-Nα-agmatide (**270**)



Amino acid (*R*)-**106** (0.71 g, 3.06 mmol) was dissolved in CH_2Cl_2 (20 mL). Hydroiodide **269** (3.37 mmol, 1.10 equiv) in CH_2Cl_2 (20 mL) and DMF (7 mL) were added and the solution was cooled to 0 °C. Oxyma^{TM} (0.65 g, 4.60 mmol, 1.50 equiv.), EDC·HCl (0.73 g, 3.82 mmol, 1.30 equiv.) and $NaHCO_3$ (1.29 g, 15.3 mmol, 5.00 equiv.) were added and the reaction mixture was stirred for 18 h at rt. A 1 M HCl solution and EtOAc were added and the organic phase was washed with a 1 M HCl solution (2x), a sat. $NaHCO_3$ solution (2x) and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (MeOH in CH_2Cl_2 = 0 to 1.5%) to furnish fragment D **270** (244 mg, 0.48 mmol, 16%) as yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) = δ 11.70 (s, 1H, NH_a), 8.33-8.30 (t, *J* = 5.1 Hz, 1H, NH_b), 6.73 (s, 1H, NH_c), 5.99-5.85 (m, 2H, H-15/19), 5.56-5.54 (d, *J* = 8.6 Hz, 1H, NH_d), 5.32-5.26 (m, 3H, H-16/20), 5.21-5.18 (m, 1H, H-16/20), 4.63-4.62 (d, *J* = 5.8 Hz, 2H, H-14/18), 4.59-4.57 (d, *J* = 5.8 Hz, 2H, H-14/18), 4.22 (s, 1H, OH), 3.85-3.83 (d, *J* = 9.1 Hz, 1H, H-7), 3.44-3.40 (q, *J* = 6.8 Hz, 2H, H-2), 3.30-3.23 (q, *J* = 6.0 Hz, 2H, H-5), 1.60-1.55 (m, 4H, H-3/4), 1.40 (s, 9H, H-12), 1.27 (s, 3H, H-9), 1.16 (s, 3H, H-9) ppm.

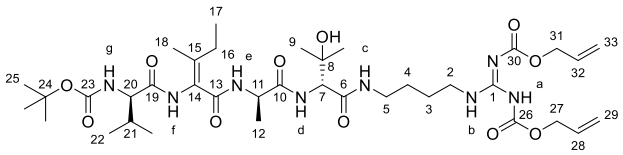
(*R*,*Z*)-7-(((Allyloxy)carbonyl)amino)-16-hydroxy-16-methyl-5,14-dioxo-4-oxa-6,8,13-triazaheptadeca-1,6-dien-15-aminium trifluoroacetate (**240**)



Boc protected amine **270** (51.6 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (1 mL) and TFA (0.40 mL, 5.0 mmol, 50.0 equiv.) was added at 0 °C. The solution was stirred at 0 °C for 2 h. All volutiles were removed under reduced pressure and the crude product was coevaporized with MeOH (2x, 0 mbar, rt) and CH_2Cl_2 (20 mbar, 40 °C). The crude product was used in the next step without further purification.

4.3.5 Fragment CD

Fragment CD (**271**)



Acid **239** (61.4 mg, 0.15 mmol, 1.50 equiv.) was dissolved in MeCN (1.0 mL) and DMF (0.5 mL) and added to salt **240** (0.10 mmol). EDC·HCl (36.8 mg, 0.19 mmol, 1.90 equiv.) and HOAt (31.5 mg, 0.23 mmol, 2.30 equiv.) in DMF (1.0 mL) were added at -15 °C dropwise over 10 min. The solution was stirred for 3 h. $NaHCO_3$ (59.1 mg, 0.70 mmol, 7.00 equiv.) was added and the mixture was stirred for 22 h at rt. The mixture was diluted with H_2O and MeOH. The solution was subjected to flash column chromatography (RP Büchi: 12x150 mm, 10 mL/min, 1 min/fraction, H_2O (1% FA)/MeOH (1% FA) = 9:1 (5 min), 9:1 → 0:1 (45 min, 0:1 (10 min)) to furnish product **271** (18.1 mg, 0.02 mmol, 23%) as colorless film.

The analytical data are consistent with those reported in the literature.[68]

^{1}H-NMR (600 MHz, DMSO-d_6) = δ 11.55 (s, 1H, NH_a), 9.26 (s, 1H, NH_f), 8.36 (t, *J* = 5.0 Hz, 1H, NH_b), 7.89-7.88 (d, *J* = 7.0 Hz, 1H, NH_e) 7.75-7.74 (d, *J* = 9.2 Hz, 1H, NH_d), 7.72-7.70 (t, *J* = 5.2 Hz, 1H, NH_c), 6.77-6.76 (d, *J* = 7.5 Hz, 1H, NH_g), 6.00-5.90 (m, 2H, H-28/32), 5.37-5.34 (d, *J* = 17.2 Hz, 1H, H-29/33), 5.28-5.26 (m, 2H, H-29/33), 5.18-5.17 (d, *J* = 10.4 Hz, 1H, H-29/33), 4.77 (bs, 1H, OH), 4.66-4.65 (d, *J* = 5.1 Hz, 1H, H-27/31), 4.49-4.48 (d, *J* = 5.2 Hz, 2H, H-27/31), 4.29-4.26 (p, *J* = 7.0 Hz, 1H, H-11), 4.22-4.21 (d, *J* = 9.2 Hz, 1H, H-7), 3.86-3.84 (t, *J* = 9.2 Hz, 1H, H-20), 3.32-3.28 (m, 2H, H-2), 3.18-3.12 (m, 1H, H-5), 3.03-2.98 (m, 1H, H-5), 2.32-2.21 (m, 2H, H-16), 1.97-1.94 (m, 1H, H-21), 1.68 (s, 3H, H-18), 1.50-1.48 (m, 2H, H-3) 1.42-1.36 (m, 12H, H-4/25), 1.24-1.23 (d, *J* = 7.3 Hz, 3H, H-12), 1.11 (s, 3H, H-9),

1.09 (s, 3H, H-9), 1.00-0.97 (t, *J* = 7.4 Hz, 3H, H-17), 0.89-0.88 (d, *J* = 6.7 Hz, 3H, H-22), 0.87-0.86 (d, *J* = 6.7 Hz, 3H, H-22) ppm;

^{13}C-NMR (151 MHz, DMSO-d_6) = δ 172.1 (C-10), 171.1 (C-19), 170.0 (C-6), 165.5 (C-13), 163.0 (C-30), 155.8 (C-23), 155.1 (C-1), 152.6 (C-26), 138.3 (C-14), 133.5 (C-32), 131.9 (C-28), 125.0 (C-15), 118.9 (C-29), 117.4 (C-33), 78.4 (C-24), 66.5 (C-27), 65.5 (C-31), 60.0 (C-7), 59.9 (C-20), 49.0 (C-11), 40.2 (C-2), 38.2 (C-5), 30.2 (C-21), 28.2 (C-25), 27.3 (C-9), 26.4 (C-16), 26.2 (C-9), 26.1 (C-4), 25.9 (C-3), 19.1 (C-22), 18.4 (C-22), 17.5 (C-12), 17.5 (C-18), 12.6 (C-17) ppm.

5 References

[1] https://www.who.int/publications/i/item/WHO-EMP-IAU-2017.12 (20.03.2023).

[2] M. S. Butler, V. Gigante, H. Sati, S. Paulin, L. Al-Sulaiman, J. H. Rex, P. Fernandes, C. A. Arias, M. Paul, G. E. Thwaites et al., *Antimicrob. Agents Chemother.* **2022**, *66*, e0199121.

[3] B. J. Langford, N. Daneman, V. Leung, J. H. C. Wu, K. Brown, K. L. Schwartz, G. Garber, *JAC Antimicrob. Resist.* **2019**, *1*, dlz059.

[4] G. Domagk, *Angew. Chem.* **1935**, *48*, 657–667.

[5] S. B. Levy, B. Marshall, *Nature medicine* **2004**, *10*, 122-129.

[6] A. Fleming, Penicillin, Nobel Lecture **1945**.

[7] E. Nassau, G. M. Hamilton, *Tubercle* **1955**, *36*, 281–282.

[8] T. Watanabe, *Bacteriol. Rev.* **1963**, *27*, 87–115.

[9] S. B. Levy, *Lancet* **1982**, *2*, 83–88.

[10] S. B. Levy, *SciAm* **1998**, *278*, 46–53.

[11] www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf (20.03.2023).

[12] S. Reardon, *Nature* **2014**.

[13] A. Catalano, D. Iacopetta, J. Ceramella, D. Scumaci, F. Giuzio, C. Saturnino, S. Aquaro, C. Rosano, M. S. Sinicropi, *Molecules* **2022**, *27*, 616.

[14] S. Karakonstantis, E. I. Kritsotakis, A. Gikas, *J. Antimicrob. Chemother.* **2020**, *75*, 271–282.

[15] S. Mandal, M. Moudgil, S. K. Mandal, *Eur. J. Pharmacol.* **2009**, *625*, 90–100.

[16] F. L. Pyman, *J. Chem. Soc., Trans.* **1917**, *111*, 1103–1128.

[17] J. D. McKinney, A. Richard, C. Waller, M. C. Newman, F. Gerberick, *Toxicol. Sci.* **2000**, *56*, 8–17.

[18] R. Guha in *Methods in Molecular Biology* (Ed.: S. Kortagere), Humana Press, Totowa, NJ, **2013**, 81–94.

[19] K. Dzobo, *Comprehensive Pharmacology* **2022**, *2*, 408–422.

[20] a) J. Herrmann, A. A. Fayad, R. Müller, *Nat. Prod. Rep.* **2017**, *34*, 135–160; b) M. A. Bhat, A. K. Mishra, M. A. Bhat, M. I. Banday, O. Bashir, I. A. Rather, S. Rahman, A. A. Shah, A. T. Jan, *Pharmaceutics* **2021**, *13*, 1265.

[21] S. Baumann, J. Herrmann, R. Raju, H. Steinmetz, K. I. Mohr, S. Hüttel, K. Harmrolfs, M. Stadler, R. Müller, *Angew. Chem. Int. Ed.* **2014**, *53*, 14605–14609.

[22] T. Planke, M. Moreno, S. Hüttel, J. Fohrer, F. Gille, M. D. Norris, M. Siebke, L. Wang, R. Müller, A. Kirschning, *Org. Lett.* **2019**, *21*, 1359–1363.

[23] T. Seedorf, A. Kirschning, D. Solga, *Eur. J. Chem.* **2021**, *27*, 7321–7339.

[24] A. Kluczyk, T. Popek, T. Kiyota, P. de Macedo, P. Stefanowicz, C. Lazar, Y. Konishi, *Curr. Med. Chem.* **2002**, *9*, 1871–1892.

[25] a) Y. J. Kim, H.-J. Kim, G.-W. Kim, K. Cho, S. Takahashi, H. Koshino, W.-G. Kim, *J. Nat. Prod.* **2016**, *79*, 2223–2228; b) B.-M. Kim, N. van Minh, H.-Y. Choi, W.-G. Kim, *Molecules* **2019**, *24*, 1390.

[26] S. Hüttel, G. Testolin, J. Herrmann, T. Planke, F. Gille, M. Moreno, M. Stadler, M. Brönstrup, A. Kirschning, R. Müller, *Angew. Chem. Int. Ed.* **2017**, *56*, 12760–12764.

[27] a) S. M. Hashimi, M. K. Wall, A. B. Smith, A. Maxwell, R. G. Birch, *Antimicrob. Agents Chemother.* **2007**, *51*, 181–187; b) J. Kretz, D. Kerwat, V. Schubert, S. Grätz, A. Pesic, S. Semsary, S. Cociancich, M. Royer, R. D. Süssmuth, *Angew. Chem. Int. Ed.* **2015**, *54*, 1969–1973.

[28] J. Hirsch, D. Klostermeier, *Nucleic Acids Res.* **2021**, *49*, 6027–6042.

[29] E. Michalczyk, K. Hommernick, I. Behroz, M. Kulike, Z. Pakosz-Stępień, L. Mazurek, M. Seidel, M. Kunert, K. Santos, H. von Moeller et al., *Nature catalysis* **2023**, *6*, 52–67.

[30] S. Groß, B. Schnell, P. A. Haack, D. Auerbach, R. Müller, *Nat. Commun.* **2021**, *12*, 1696.

[31] a) M. Moreno, W. Elgaher, J. Herrmann, N. Schläger, M. Hamed, S. Baumann, R. Müller, R. Hartmann, A. Kirschning, *Synlett* **2015**, *26*, 1175–1178; b) W. A. M. Elgaher, M. M. Hamed, S. Baumann, J. Herrmann, L. Siebenbürger, J. Krull, K. Cirnski, A. Kirschning, M. Brönstrup, R. Müller et al., *Eur. J. Chem.* **2020**, *26*, 7219–7225; c) B. Cheng, R. Müller, D. Trauner, *Angew. Chem. Int. Ed.* **2017**, *56*, 12755–12759.

[32] M. Moeller, M. D. Norris, T. Planke, K. Cirnski, J. Herrmann, R. Müller, A. Kirschning, *Org. Lett.* **2019**, *21*, 8369–8372.

[33] G. Testolin, K. Cirnski, K. Rox, H. Prochnow, V. Fetz, C. Grandclaudon, T. Mollner, A. Baiyoumy, A. Ritter, C. Leitner et al., *Chem. Sci.* **2020**, *11*, 1316–1334.

[34] T. Planke, K. Cirnski, J. Herrmann, R. Müller, A. Kirschning, *Eur. J. Chem.* **2020**, *26*, 4289–4296.

[35] a) L. Vieweg, J. Kretz, A. Pesic, D. Kerwat, S. Grätz, M. Royer, S. Cociancich, A. Mainz, R. D. Süssmuth, *J. Am. Chem. Soc.* **2015**, *137*, 7608–7611; b) L. Kleebauer, L. Zborovsky, K. Hommernick, M. Seidel, J. B. Weston, R. D. Süssmuth, *Org. Lett.* **2021**, *23*, 7023–7027.

[36] unpublished results, OpCyBac www.gesundheitsforschung-bmbf.de.

[37] P. K. Mykhailiuk, *Org. Biomol. Chem.* **2019**, *17*, 2839–2849.

[38] K. A. Scott, P. B. Cox, J. T. Njardarson, *J. Med. Chem.* **2022**, *65*, 7044–7072.

[39] C. D. Sessler, M. Rahm, S. Becker, J. M. Goldberg, F. Wang, S. J. Lippard, *J. Am. Chem. Soc.* **2017**, *139*, 9325–9332.

[40] L. Zborovsky, L. Kleebauer, M. Seidel, A. Kostenko, L. von Eckardstein, F. O. Gombert, J. Weston, R. D. Süssmuth, *Chem. Sci.* **2021**, *12*, 14606–14617.

[41] M. C. Reddy, M. Jeganmohan, *Org. Lett.* **2014**, *16*, 4866–4869.

[42] The synthesis was performed in collaboration with My Quynh La.

[43] G. Testolin, M. Brönstrup, H. P. Prochnow, J. Herrmann, R. Müller, WO2019038405 (A1), **2018**.

[44] R. Vohra, G. Dube, Z. Gan, N. Gill, X. Cui, US2009082368 (A1), **2009**.

[45] M. Terashima, M. Ishii, Y. Kanaoka, *Synthesis* **1982**, *1982*, 484–485.

[46] H. Bian, K. M. Chevalier, P. J. Connolly, C. M. Flores, S.-C. Lin, L. Liu, J. Mabus, M. J. Macielag, M. E. McDonnell, P. M. Pitis, S.-P. Zhang, Y.-M. Zhang, B. Zhu, J. Clemente, WO2010124082 A1, **2010**.

[47] K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886.

[48] F. Zhao, W. Zhou, Z. Zuo, *Adv Synth Catal* **2022**, *364*, 234–267.

[49] H. S. Lim, Y. L. Choi, J.-N. Heo, *Org. Lett.* **2013**, *15*, 4718–4721.

[50] F. Mazzini, T. Netscher, P. Salvadori, *Tetrahedron* **2005**, *61*, 813–817.

[51] G. S. Lal, G. P. Pez, R. J. Pesaresi, F. M. Prozonic, H. Cheng, *J. Org. Chem.* **1999**, *64*, 7048–7054.

[52] a) M. R. Machacek, E. T. Romeo, S. D. Kattar, M. Christopher, M. D. Altman, A. B. Northrup, J. M. Ellis, B. O. Boyle, A. Donofrio, J. Grimm et al., WO2014048065 (A1), **2013**; b) B. Wang, R. Xu, E. Wallace, F. Lightstone, Y. Yang, P. Bisignano, A. E. Maciag, D. M. Turner, D. K. Simanshu, A. H. W. Chan et al., WO2022177917 (A2), **2022**.

[53] P. Xu, S. Guo, L. Wang, P. Tang, *Angew. Chem. Int. Ed.* **2014**, *53*, 5955–5958.

[54] M. J. Kelly, EP1008583 (A1), **1999**.

[55] D. Billen, N. A. L. Chubb, D. M. Gethin, K. T. Hall, L. R. Roberts, N. D. A. Walshe, N. A. L. Chubb, D. M. Gethin, K. T. Hall, L. R. Roberts et al., US2005148649 (A1), **2004**.

[56] S. D. Andrews, A. C. Day, R. N. Inwood, *J. Chem. Soc.* **1969**, 2443–2449.

[57] U. K. Velagapudi, M.-F. Langelier, C. Delgado-Martin, M. E. Diolaiti, S. Bakker, A. Ashworth, B. A. Patel, X. Shao, J. M. Pascal, T. T. Talele, *J. Med. Chem.* **2019**, *62*, 5330–5357.

[58] N. Ohtsuka, M. Okuno, Y. Hoshino, K. Honda, *Org. Biomol. Chem.* **2016**, *14*, 9046–9054.

[59] M. S. Gerova, S. R. Stateva, E. M. Radonova, R. B. Kalenderska, R. I. Rusew, R. P. Nikolova, C. D. Chanev, B. L. Shivachev, M. D. Apostolova, O. I. Petrov, *Eur. J. Med. Chem.* **2016**, *120*, 121–133.

[60] A. Bach, D. Pizzirani, N. Realini, V. Vozella, D. Russo, I. Penna, L. Melzig, R. Scarpelli, D. Piomelli, *J. Med. Chem.* **2015**, *58*, 9258–9272.

[61] R. Mizojiri, H. Banno, M. Asano, D. Tomita, N. Nii, H. Maezaki, M. Tawada, EP3225618 (A1), **2015**.

[62] a) V. K. Pandey, P. Anbarasan, *RSC Adv.* **2016**, *6*, 18525–18529; b) R. Sakamoto, H. Kashiwagi, K. Maruoka, *Org. Lett.* **2017**, *19*, 5126–5129.

[63] E. Butler, L. Florentino, D. Cornut, G. Gomez-Campillos, H. Liu, A. C. Regan, E. J. Thomas, *Org. Biomol. Chem.* **2018**, *16*, 6935–6960.

[64] G. B. Martinez, A. Griffin, P. Charifson, K. Reddy, K. M. Kahlig, B. Marron, WO2020227101 (A1), **2020**.

[65] F. W. Foss, A. H. Snyder, M. D. Davis, M. Rouse, M. D. Okusa, K. R. Lynch, T. L. Macdonald, *Bioorg. Med. Chem.* **2007**, *15*, 663–677.

[66] J. E. Dettwiler, W. D. Lubell, *J. Org. Chem.* **2003**, *68*, 177–179.

[67] P. A. Barsanti, S. Chamoin, M. L. Doumampouom, B. H. Geierstanger, R. M. Grotzfeld, L. S. Guerro, D. B. Jones, A. Karpov, M. Lafrance, O. C. Nieto et al., WO2014151030 (A1), **2014**.

[68] M. Siebke, *Studien zur Totalsynthese von Myxovalargin und Darstellung einer Myxovalargin-Bibliothek*, Gottfried Wilhelm Leibniz Universität Hannover, **2021**.

[69] F. Sladojevich, A. Trabocchi, A. Guarna, *J. Org. Chem.* **2007**, *72*, 4254–4257.

[70] The compound was provided by Daniel Kohnhäuser and Kevin Wiederhold.

[71] P. M. E. Hawkins, D. Y. Liu, R. G. Linington, R. J. Payne, *Org. Biomol. Chem.* **2021**, *19*, 6291–6300.

[72] G. Sheng, X. Wu, X. Cai, W. Zhang, *Synthesis* **2015**, *47*, 949–954.

[73] T. J. Donohoe, A. Flores, C. J. R. Bataille, F. Churruca, *Angew. Chem. Int. Ed.* **2009**, *48*, 6507–6510.

[74] J. S. Yadav, B. V. S. Reddy, C. Madan, S. R. Hashim, *Chem. Lett.* **2000**, *29*, 738–739.

[75] P. I. Kitov, D. R. Bundle, *Org. Lett.* **2001**, *3*, 2835–2838.

[76] Y. Shiraishi, H. Yamauchi, T. Takamura, H. Kinoshita, *Bull. Chem Soc. Jpn.* **2004**, *77*, 2219–2229.

[77] D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson, A. Wood, *Nat. Chem.* **2018**, *10*, 383–394.

[78] T. Kemmer, S. Santoso, H. Steinmetz, H. Irschik, L. Witte, G. Höfle, *Int. Conf. Chem. Biotechnol. Biol. Act. Nat. Prod.* **1981**, 285–289.

[79] H. Irschik, K. Gerth, T. Kemmer, H. Steinmetz, H. Reichenbach, *J. Antibiot.* **1983**, *36*, 6–12.

[80] H. Steinmetz, H. Irschik, H. Reichenbach, *Sixth USSR-FRG Symposium on Chemistry on Peptides and Proteins (Hamburg, FRG, Sept 1-5)* **1987**, König, W., Voelter, W., Eds.; Attempto Verlag GmbH: (Tübingen, Germany), 1987; 13–18.

[81] T. O. Koller, U. Scheid, T. Kösel, J. Herrmann, D. Krug, H. I. M. Boshoff, B. Beckert, J. C. Evans, J. Schlemmer, B. Sloan et al., *J. Am. Chem. Soc.* **2023**, *145*, 851–863.

[82] H. Irschik, H. Reichenbach, *J. Antibiot.* **1985**, *38*, 1237–1245.

[83] https://www.who.int/health-topics/tuberculosis#tab=tab_1 (16.03.2023).

[84] E. Harding, *Lancet. Respir. Med.* **2020**, *8*, 19.

[85] F. Gille, *Studien zur Total- und Mutasynthese von Myxovalargin und synthetische Untersuchungen zu den Cystobactamiden*, Gottfried Wilhelm Leibniz Universität Hannover, **2016**.

[86] F. Gille, A. Kirschning, *Beilstein J. Org. Chem.* **2016**, *12*, 564–570.

[87] T. Kösel, *Development of a total synthesis of Myxovalargin A and derivatives− investigations on transformations with polymer-supported Bisazidoiodate (I)*, Gottfried Wilhelm Leibniz Universität Hannover, **2022**.

[88] The synthesis was performed in collaboration with Dr. Anna-Louisa Warnke and Prof. Dr. Oliver Plettenburg.

[89] R. Bollhagen, M. Schmiedberger, K. Barlos, E. Grell, *J. Chem. Soc., Chem. Commun.* **1994**, 2559–2560.

[90] S. S. Zimmerman, A. Khatri, E. C. Garnier-Amblard, P. Mullasseril, N. L. Kurtkaya, S. Gyoneva, K. B. Hansen, S. F. Traynelis, D. C. Liotta, *J. Med. Chem.* **2014**, *57*, 2334–2356.

[91] C. J. Saint-Louis, R. N. Shavnore, C. D. C. McClinton, J. A. Wilson, L. L. Magill, B. M. Brown, R. W. Lamb, C. E. Webster, A. K. Schrock, M. T. Huggins, *Org. Biomol. Chem.* **2017**, *15*, 10172–10183.

[92] X. Sun, J. Qiu, S. A. Strong, L. S. Green, J. W. F. Wasley, D. B. Colagiovanni, S. C. Mutka, J. P. Blonder, A. M. Stout, J. P. Richards et al., *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3671–3675.

[93] Le Wang, G. T. Wang, X. Wang, Y. Tong, G. Sullivan, D. Park, N. M. Leonard, Q. Li, J. Cohen, W.-Z. Gu et al., *J. Med. Chem.* **2004**, *47*, 612–626.

[94] K. Akira, D. Masaki, N. Hiroshi, Y. Masato, I. Naoki, T. masashi, H. Kousuke, EP3327019, **2018**.

[95] Y. Dong, X. Wang, M. Cal, M. Kaiser, J. L. Vennerstrom, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 944–948.

[96] C. A. Malapit, J. T. Reeves, C. A. Busacca, A. R. Howell, C. H. Senanayake, *Angew. Chem. Int. Ed.* **2016**, *55*, 326–330.

[97] T. Ikeda, T. Yamazaki, H. Tsuchida, EP2409977 (A1), **2010**.

[98] P. Osuský, J. Nociarová, M. Smolíček, R. Gyepes, D. Georgiou, I. Polyzos, M. Fakis, P. Hrobárik, *Org. Lett.* **2021**, *23*, 5512–5517.

[99] F. Yang, X. Jiang, J. Li, Y. Wang, Y. Liu, M. Bi, C. Wu, Q. Zhao, W. Chen, J. Yin et al., *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3141–3147.

[100] The synthesis was performed in collaboration with Norman Birke.

[101] M. A. Dean, S. R. Hitchcock, *Tetrahedron Asymmetry* **2010**, *21*, 2471–2478.

[102] D. Billen, N. A. L. Chubb, D. M. Gethin, K. T. Hall, L. R. Roberts, N. D. A. Walshe, N. A. L. Chubb, D. M. Gethin, K. T. Hall, L. R. Roberts et al., US2005148649 (A1), **2004**.

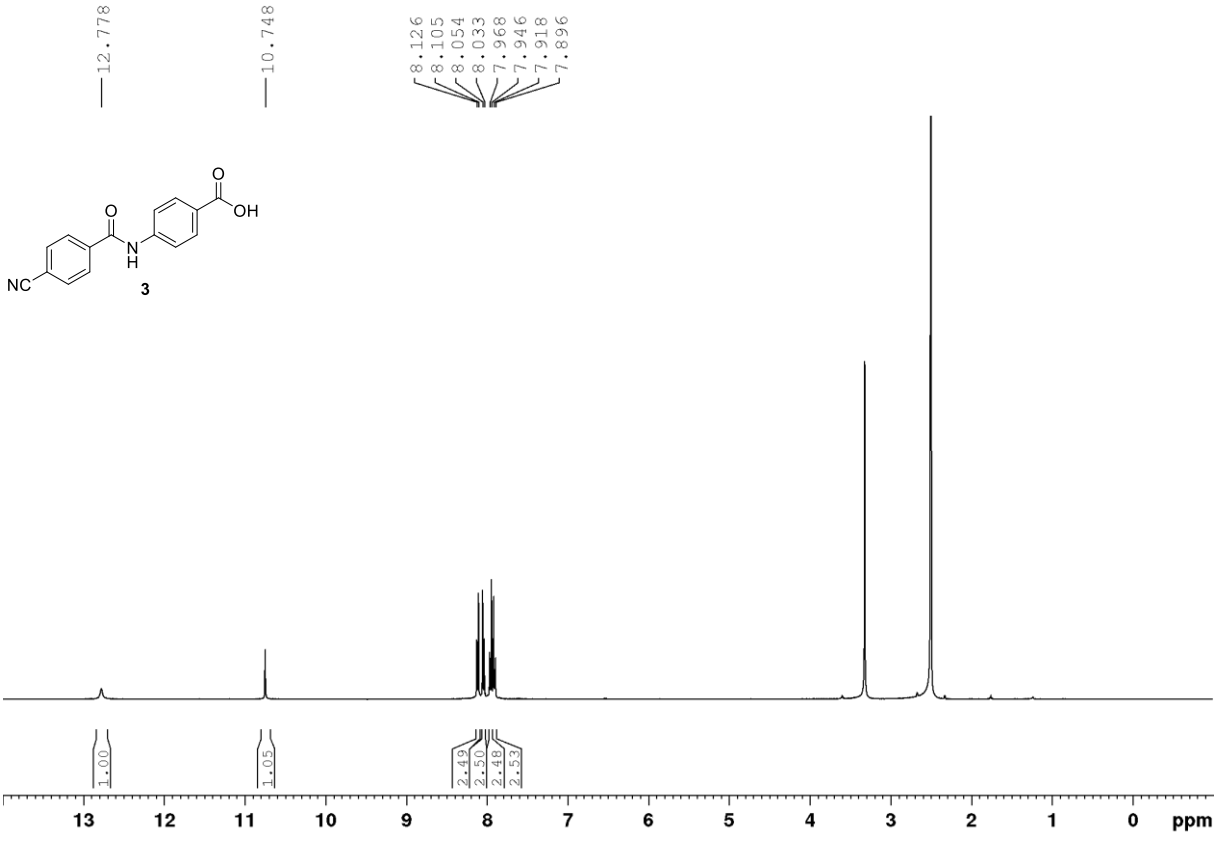
[103] The synthesis was performed in collaboration with Kevin Bajerke.

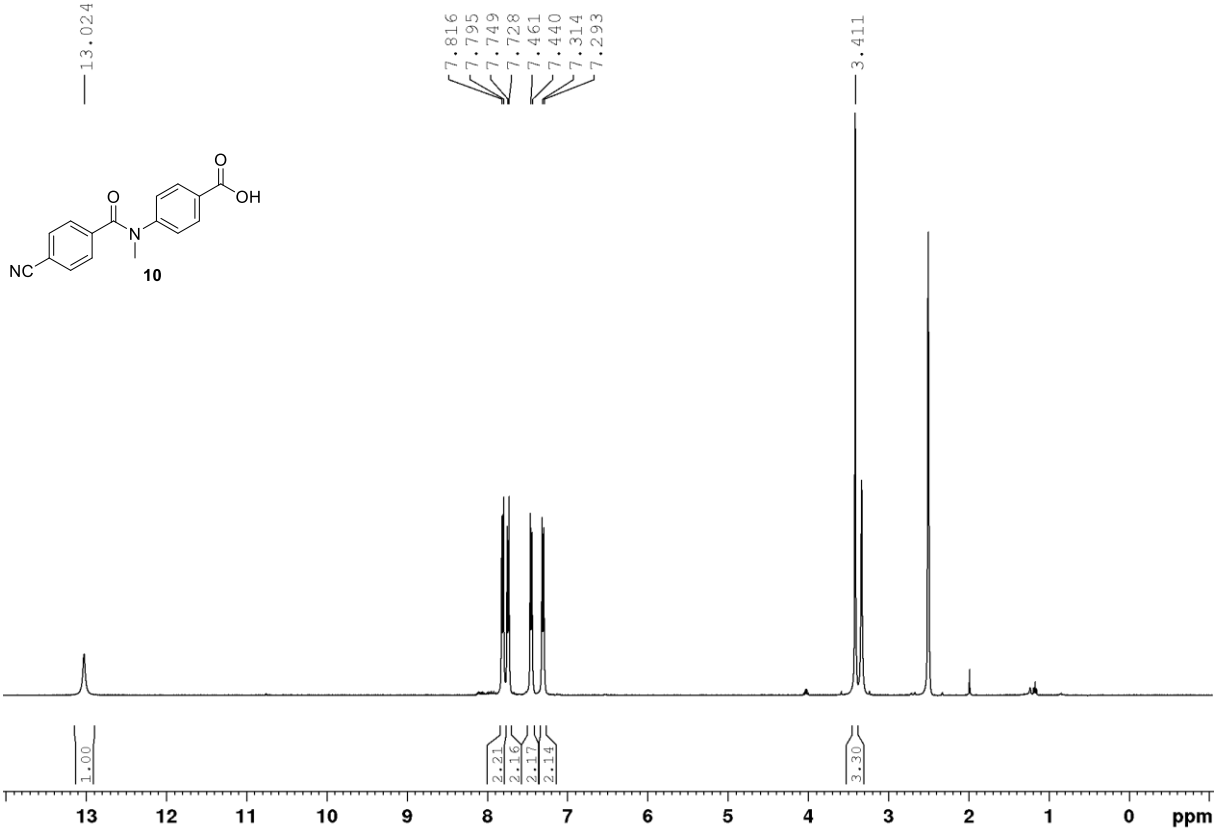
[104] L. Sinatra, J. J. Bandolik, M. Roatsch, M. Sönnichsen, C. T. Schoeder, A. Hamacher, A. Schöler, A. Borkhardt, J. Meiler, S. Bhatia et al., *Angew. Chem.* **2020**, *132*, 22681–22687.

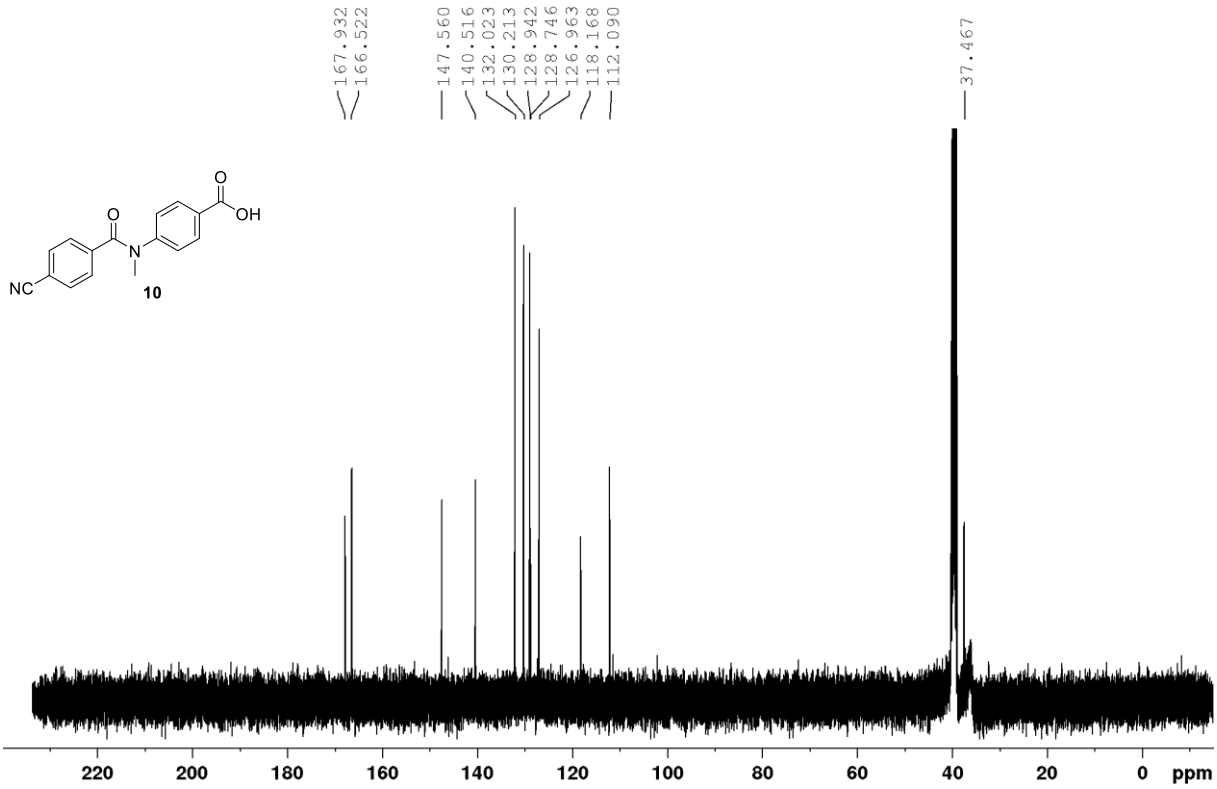
[105] G. M. Salituro, C. A. Townsend, *J. Am. Chem. Soc.* **1990**, *112*, 760–770.

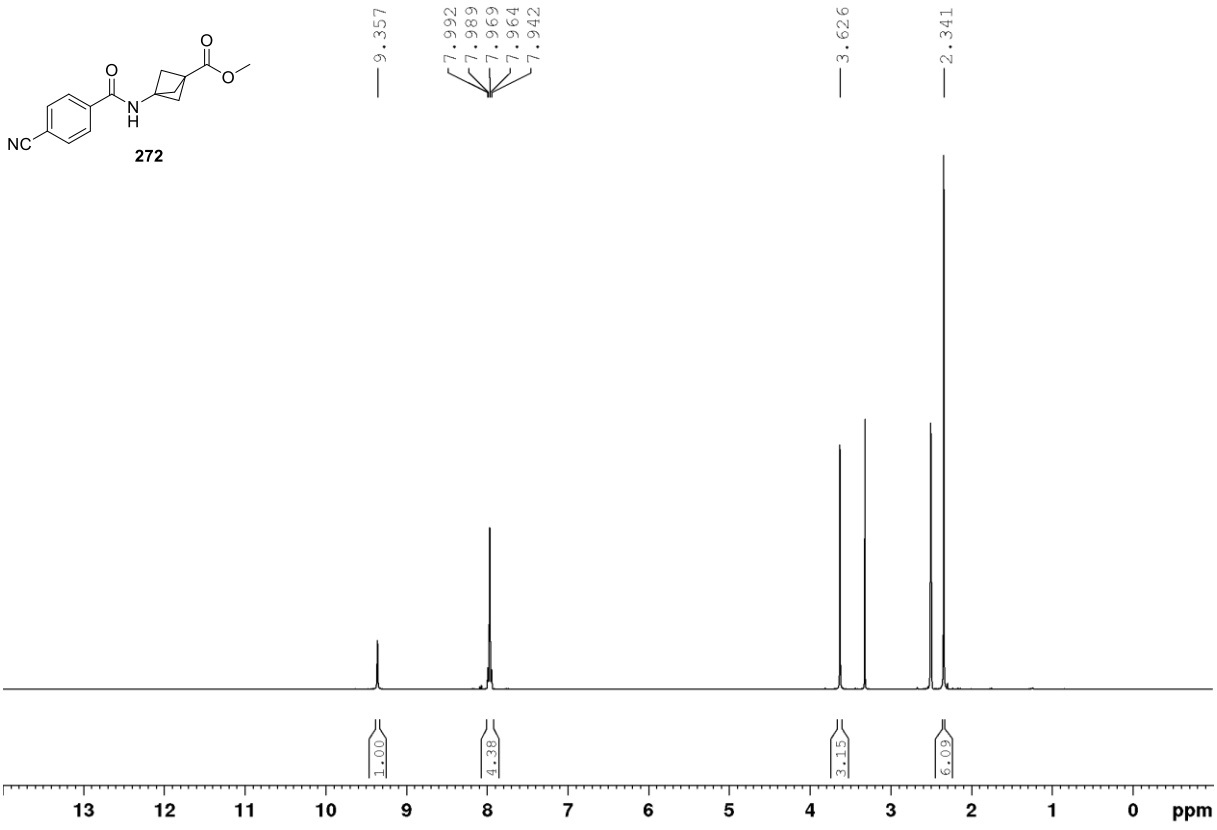
[106] The synthesis was performed in collaboration with Dr. Teresa Kösel.

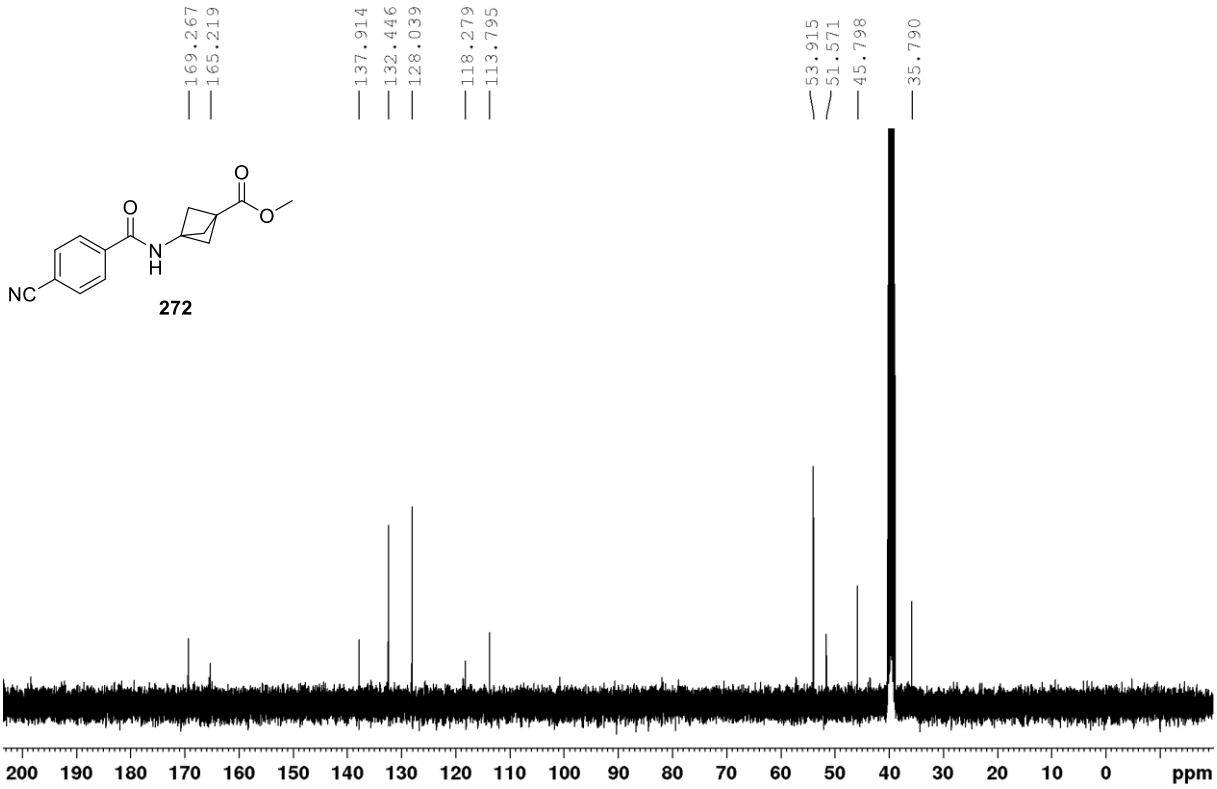
6 Appendix

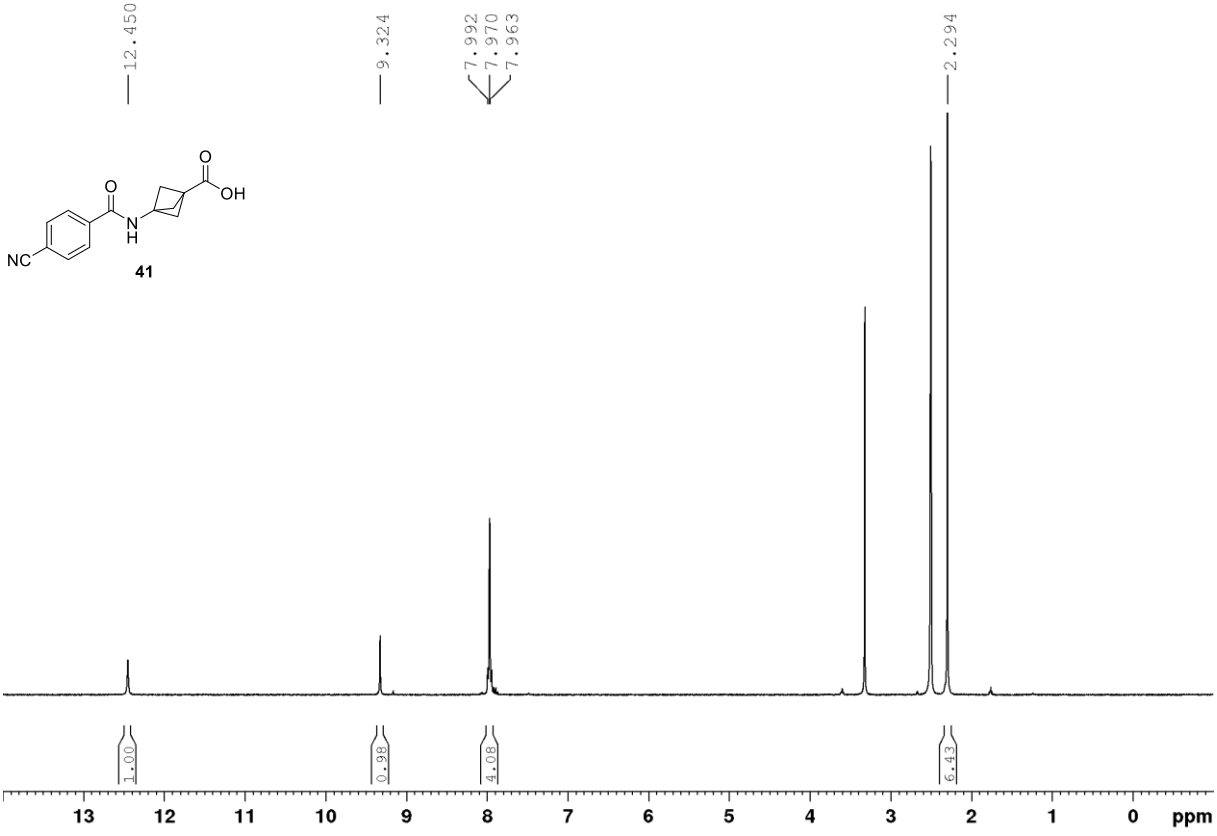

12.778
10.748
8.126
8.105
8.054
8.033
7.968
7.946
7.918
7.896
O
OH
O
N
H
NC
3
1.00
1.05
2.49
2.50
2.48
2.53
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

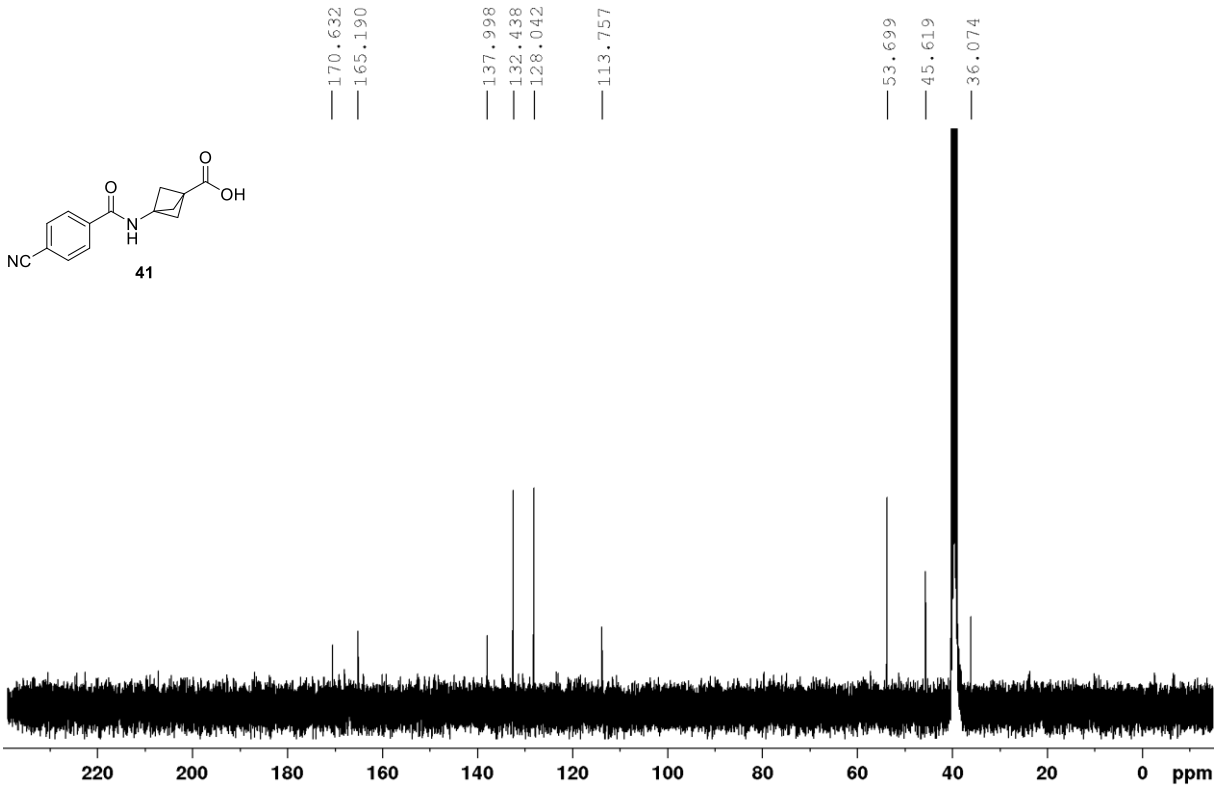

13.024
7.816
7.795
7.749
7.728
7.461
7.440
7.314
7.293
3.411
O
OH
O
N
NC
10
1.00
2.21
2.16
2.17
2.14
3.30
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

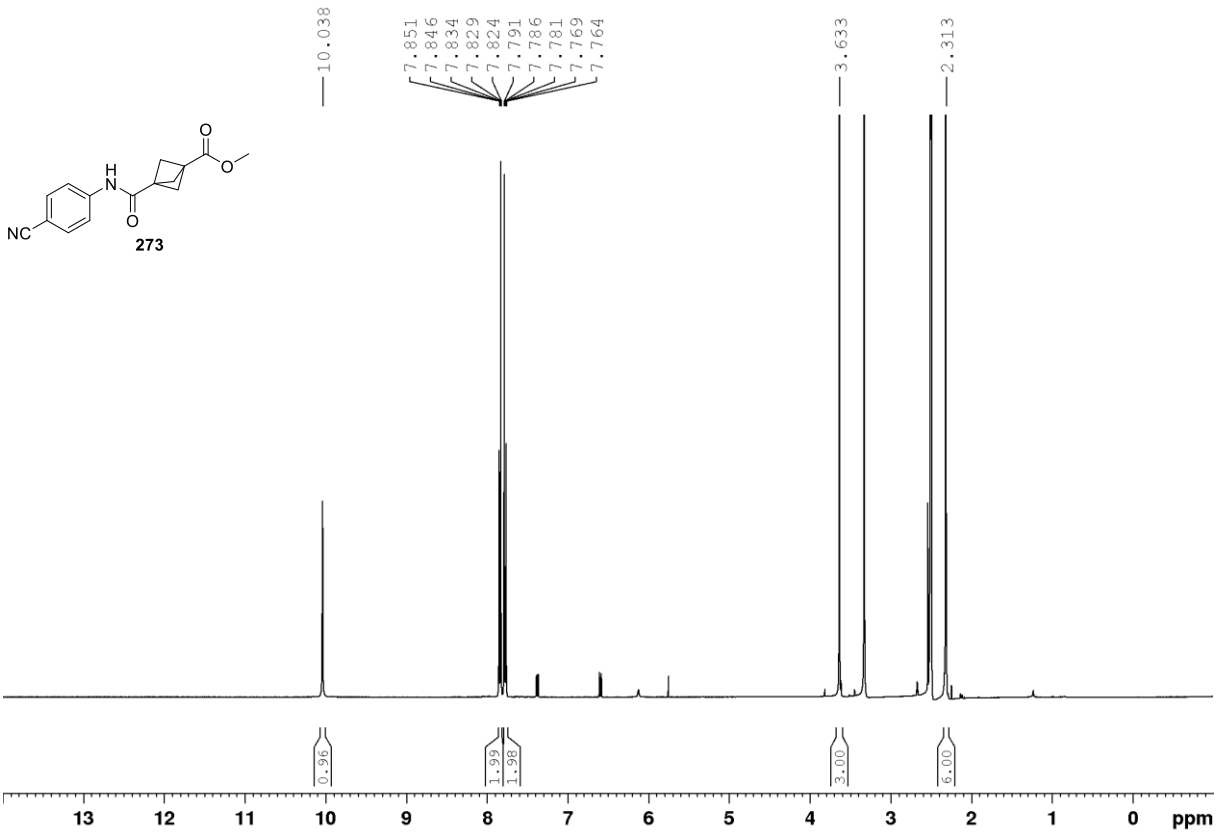

167.932
166.522
147.560
140.516
132.023
130.213
128.942
128.746
126.963
118.168
112.090
37.467
O
OH
O
N
NC
10
220
200
180
160
140
120
100
80
60
40
20
0
ppm

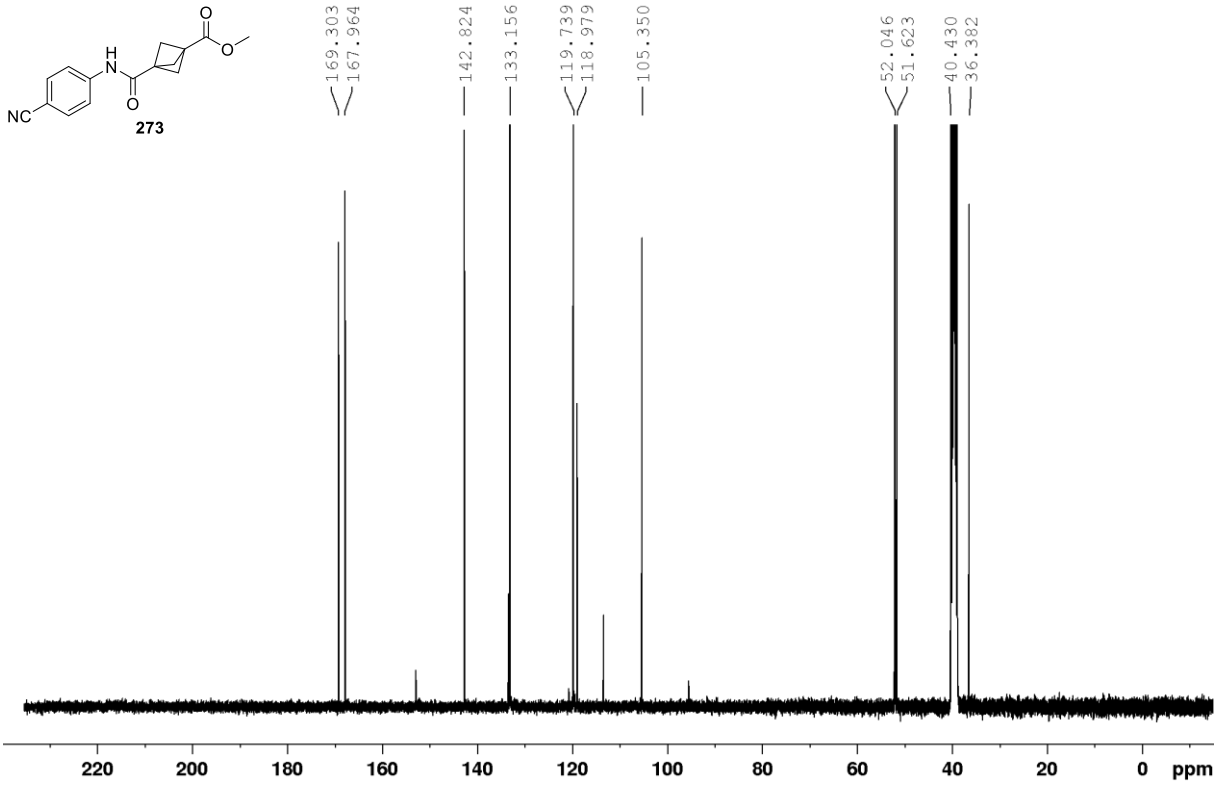

9.357
7.992
7.989
7.969
7.964
7.942
3.626
2.341
O
O
O
N
H
NC
272
1.00
4.38
3.15
6.09
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

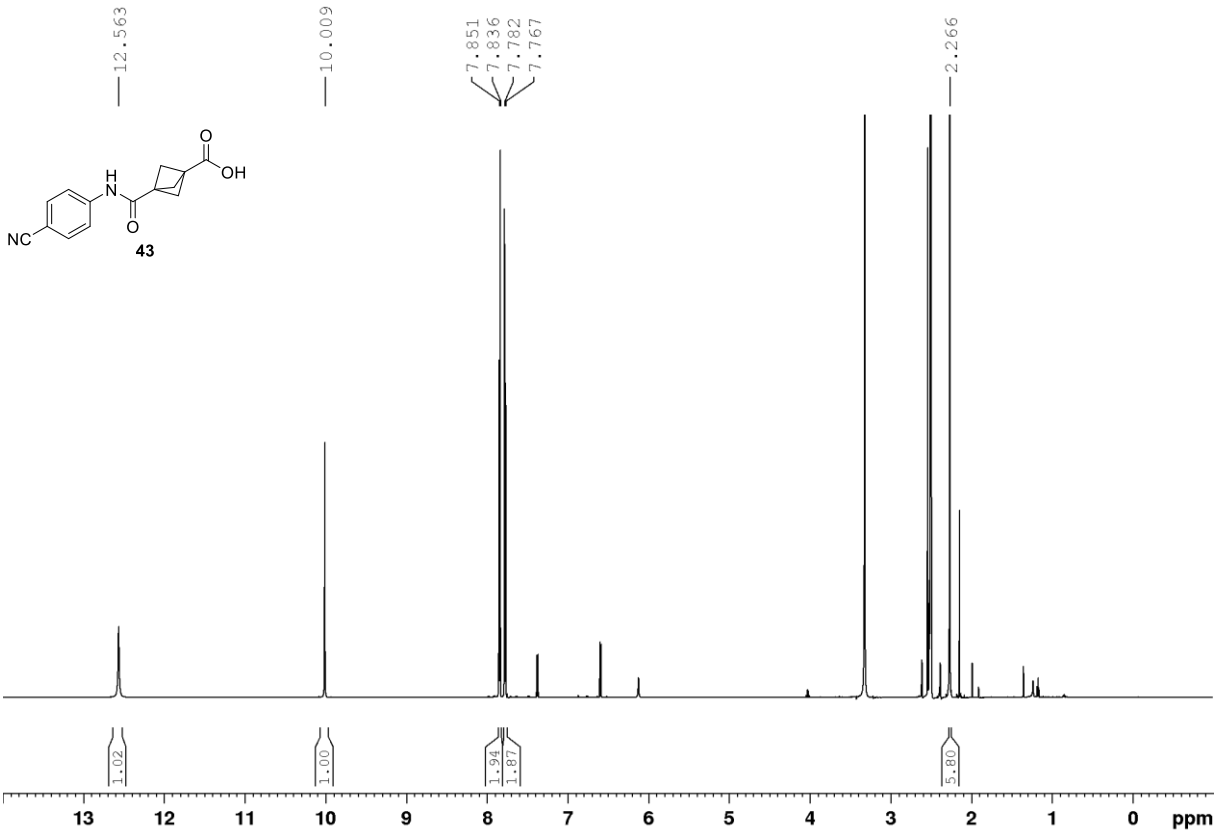

169.267
165.219
137.914
132.446
128.039
118.279
113.795
53.915
51.571
45.798
35.790
O
O
N
H
O
O
NC
272
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

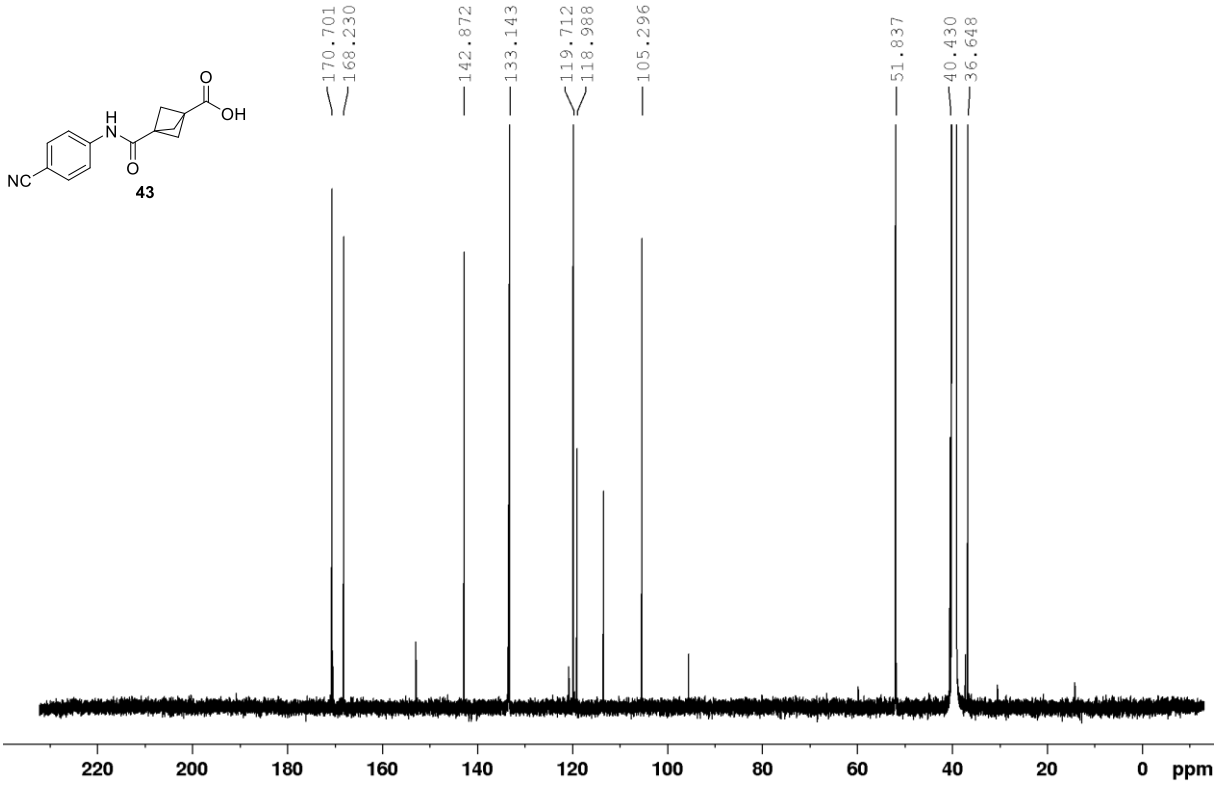

12.450
9.324
7.992
7.970
7.963
2.294
O
O
N
H
O
OH
NC
41
1.00
0.98
4.08
6.43
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

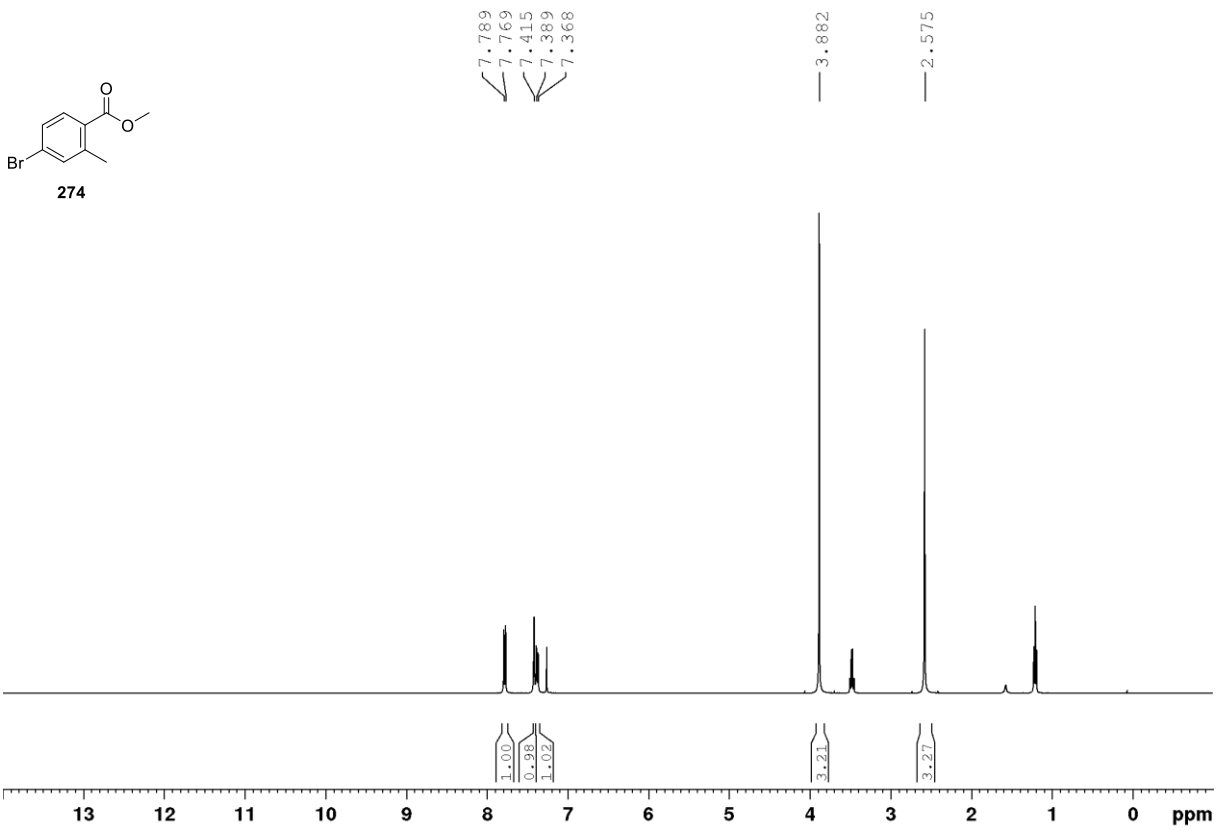

170.632
165.190
137.998
132.438
128.042
113.757
53.699
45.619
36.074
O
OH
O
N
H
NC
41
220
200
180
160
140
120
100
80
60
40
20
0
ppm

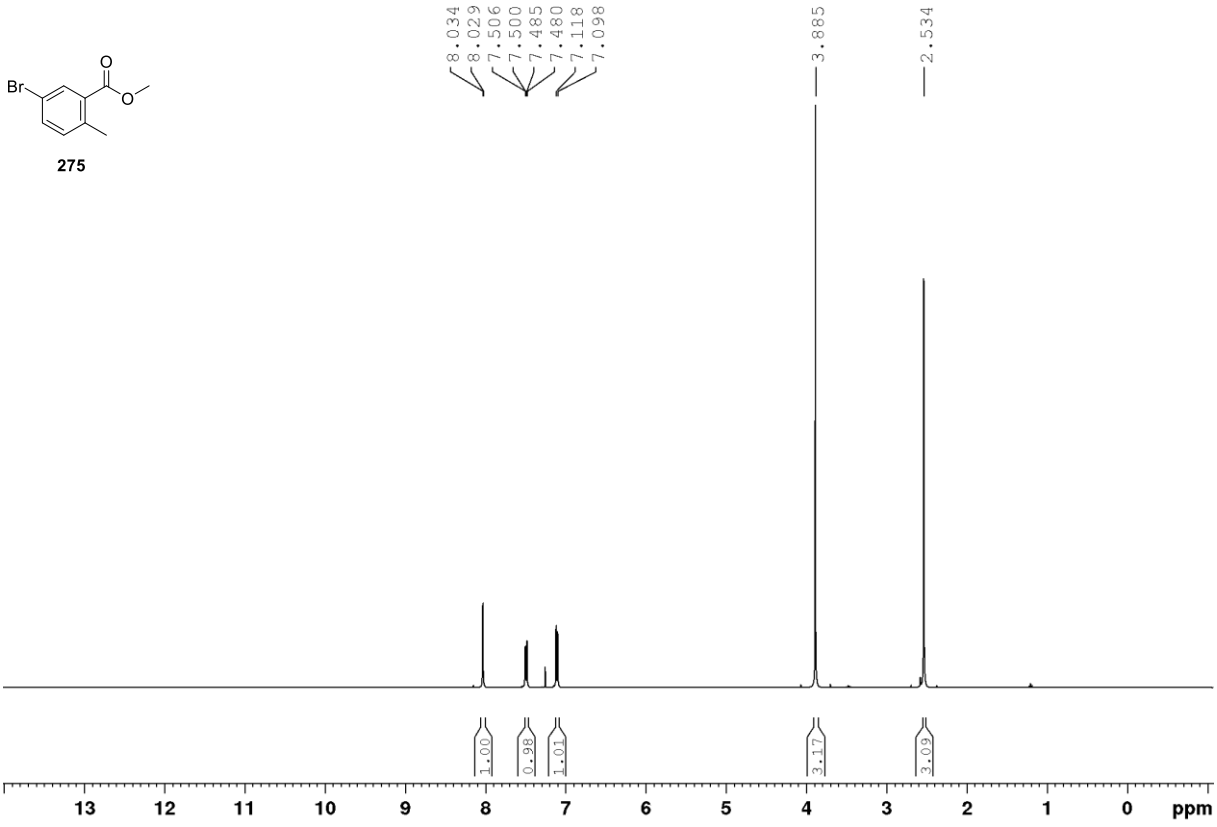

10.038
7.851
7.846
7.834
7.829
7.824
7.791
7.786
7.781
7.769
7.764
3.633
2.313
O
O
H
N
O
NC
273
0.96
1.99
1.98
3.00
6.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

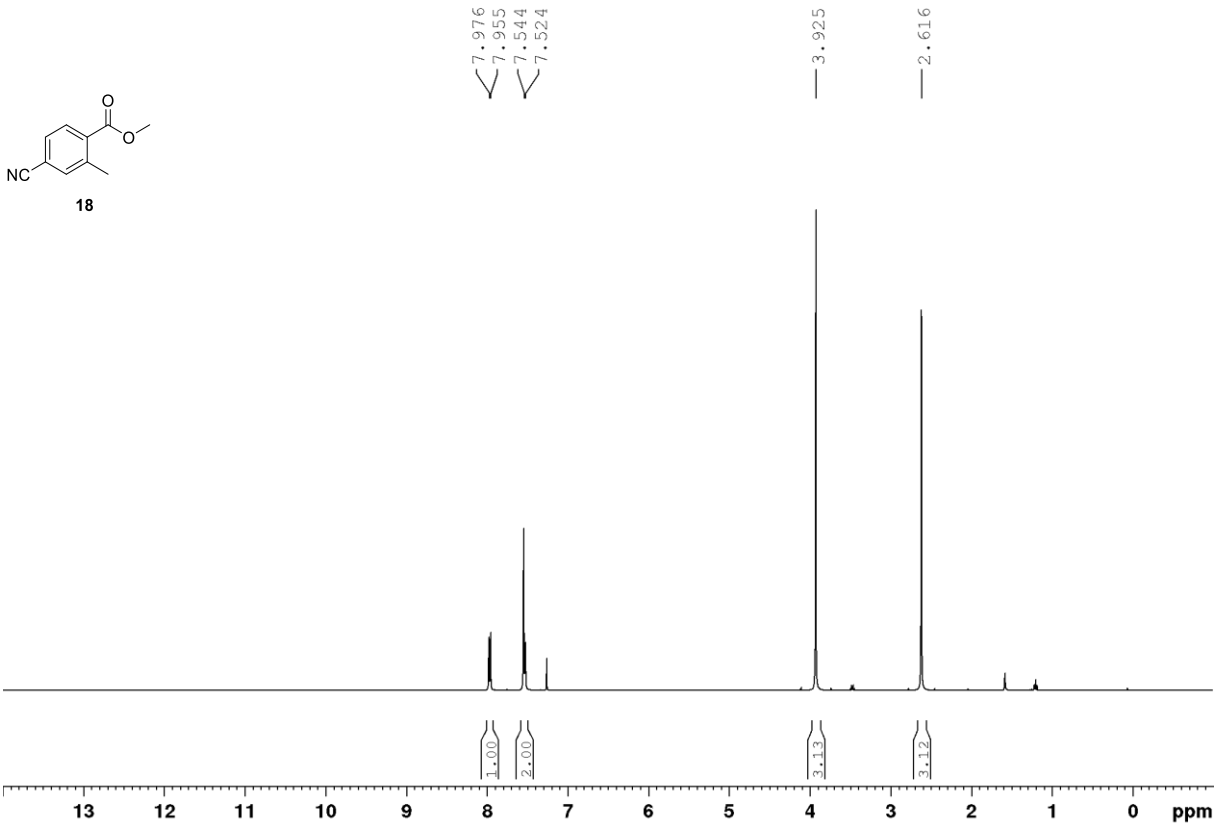

273
169.303
167.964
142.824
133.156
119.739
118.979
105.350
52.046
51.623
40.430
36.382
220
200
180
160
140
120
100
80
60
40
20
0
ppm

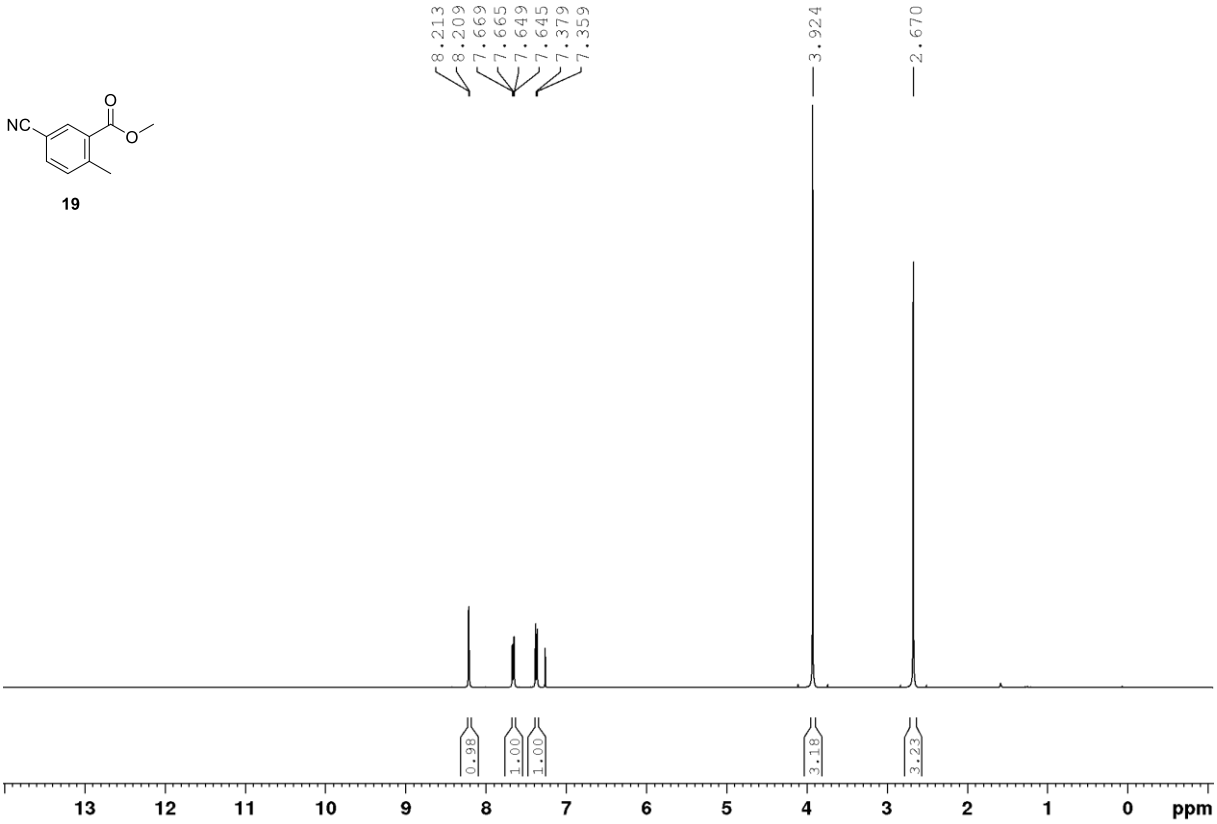

43
12.563
10.009
7.851
7.836
7.782
7.767
2.266
1.02
1.00
1.94
1.87
5.80
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

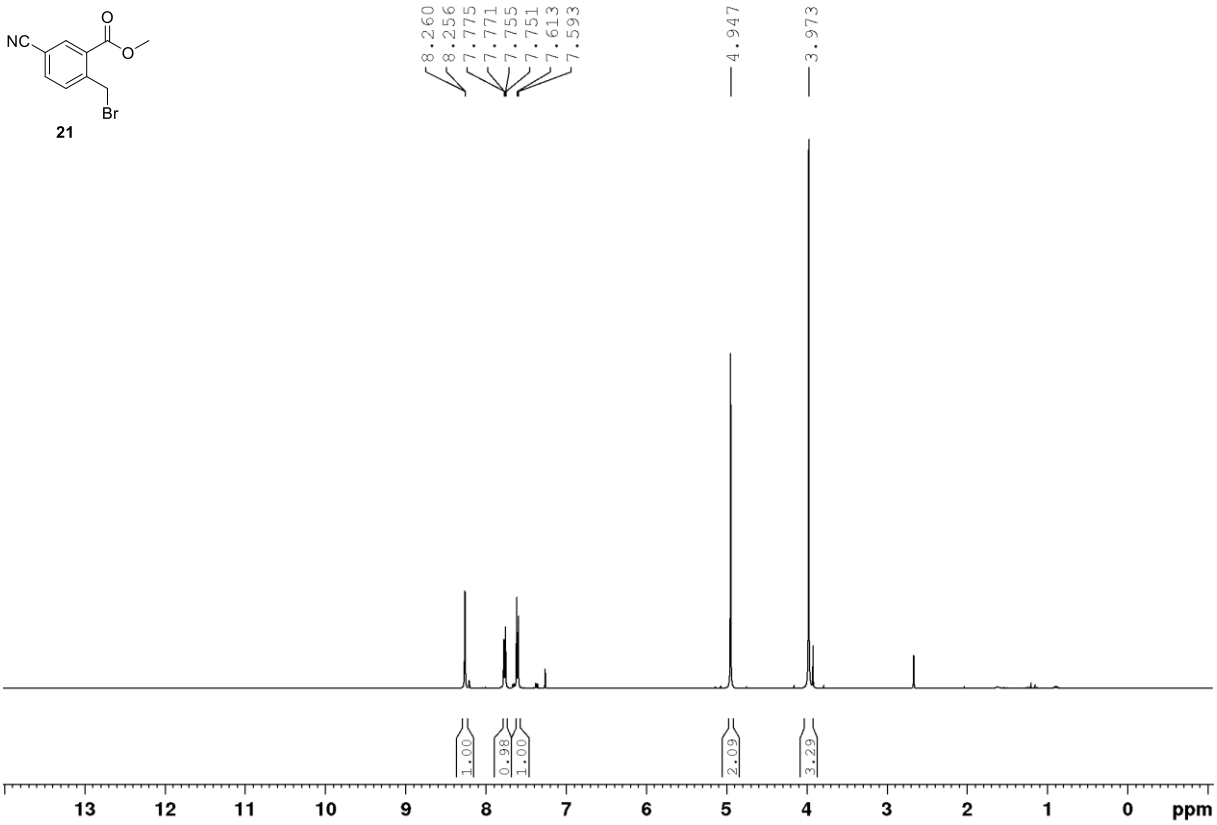

170.701
168.230
142.872
133.143
119.712
118.988
105.296
51.837
40.430
36.648
NC
43
220
200
180
160
140
120
100
80
60
40
20
0
ppm

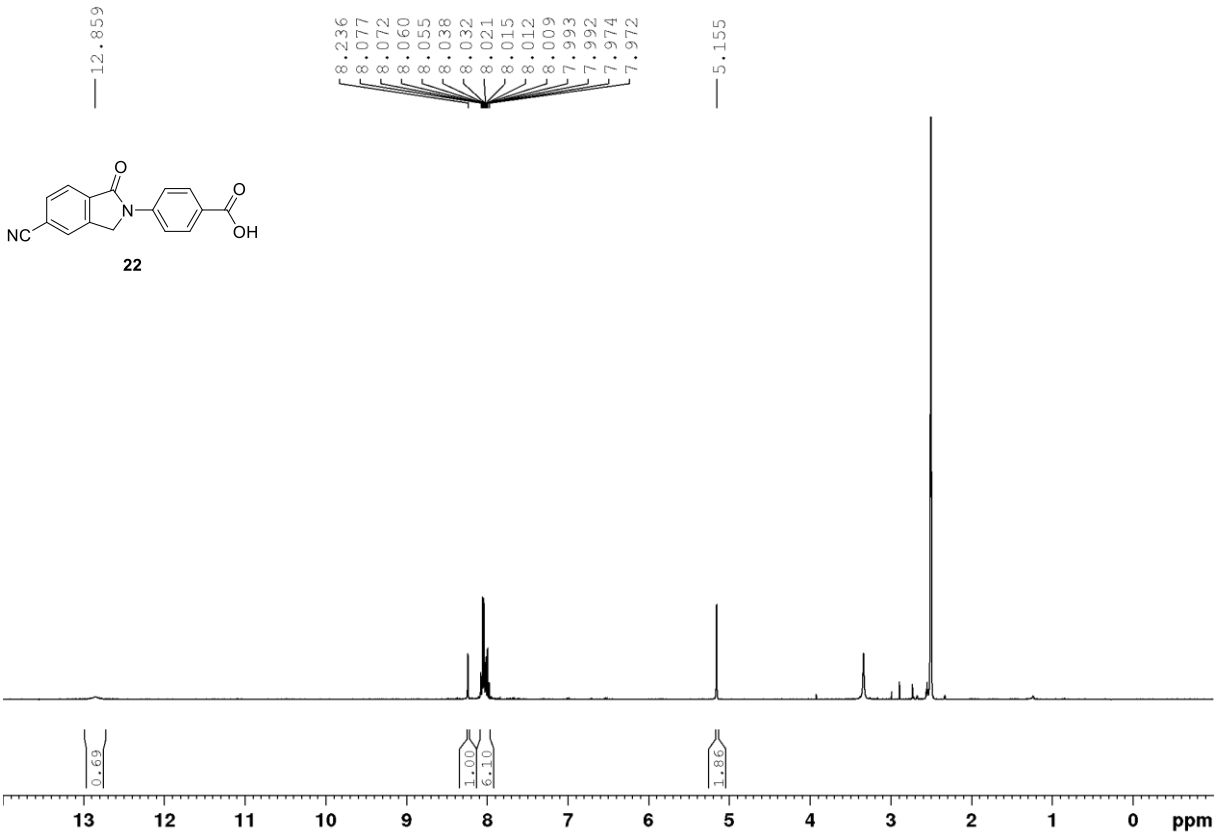

7.789
7.769
7.415
7.389
7.368
3.882
2.575
Br
274
1.00
0.98
1.02
3.21
3.27
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

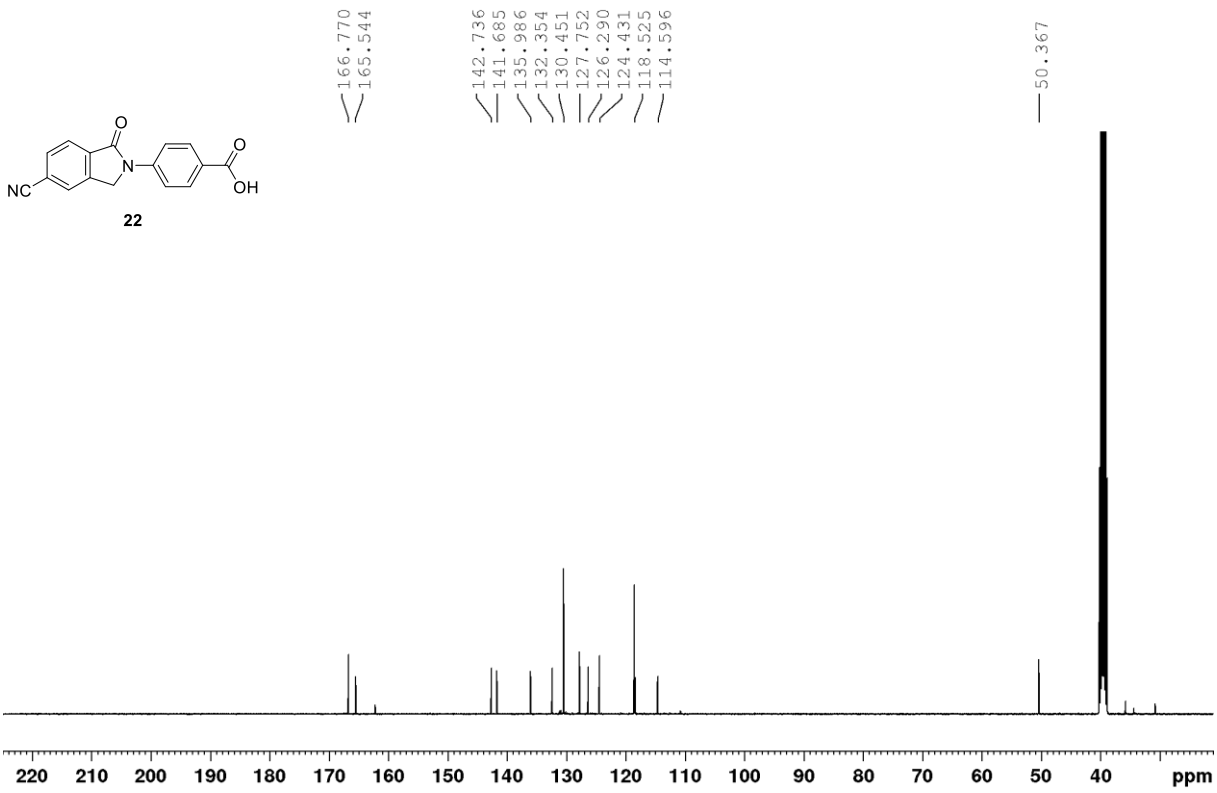

Br
O
O
275
8.034
8.029
7.506
7.500
7.485
7.480
7.118
7.098
3.885
2.534
1.00
0.98
1.01
3.17
3.09
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

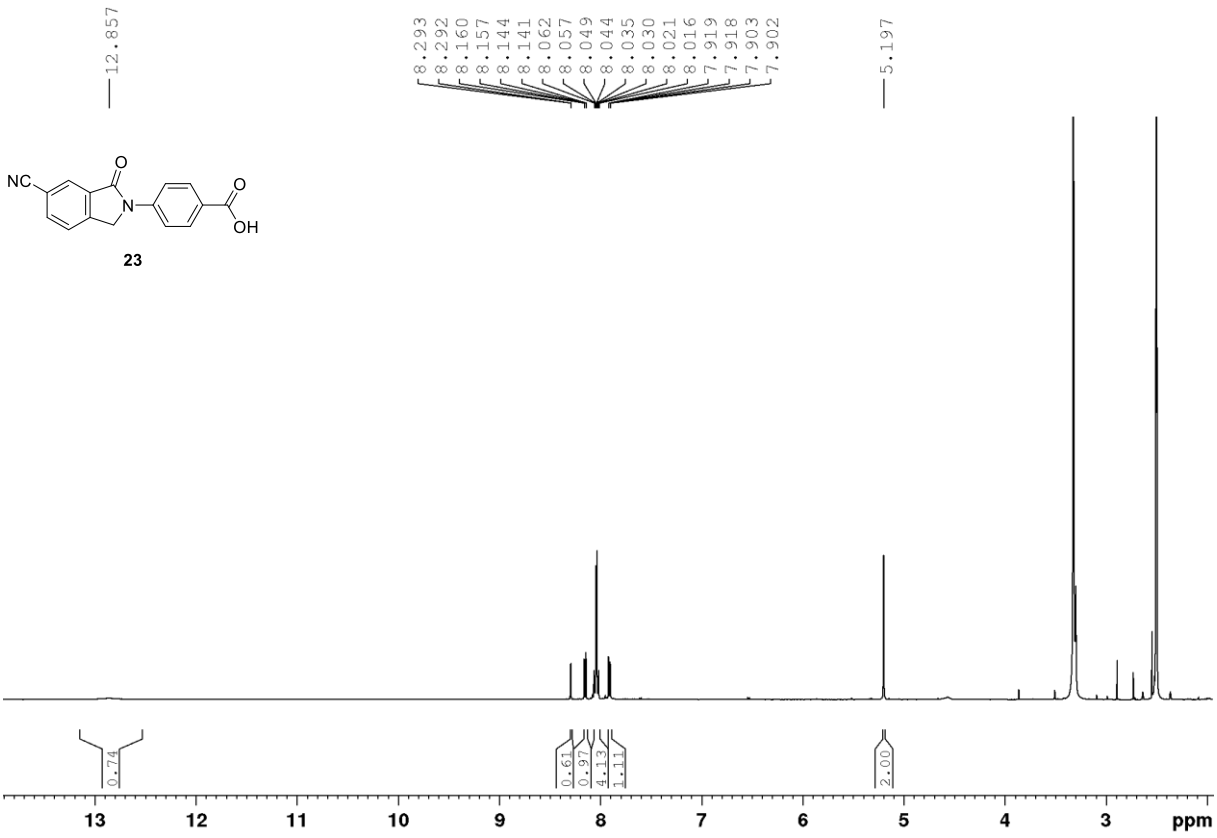

NC
O
O
18
7.976
7.955
7.544
7.524
3.925
2.616
1.00
2.00
3.13
3.12
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

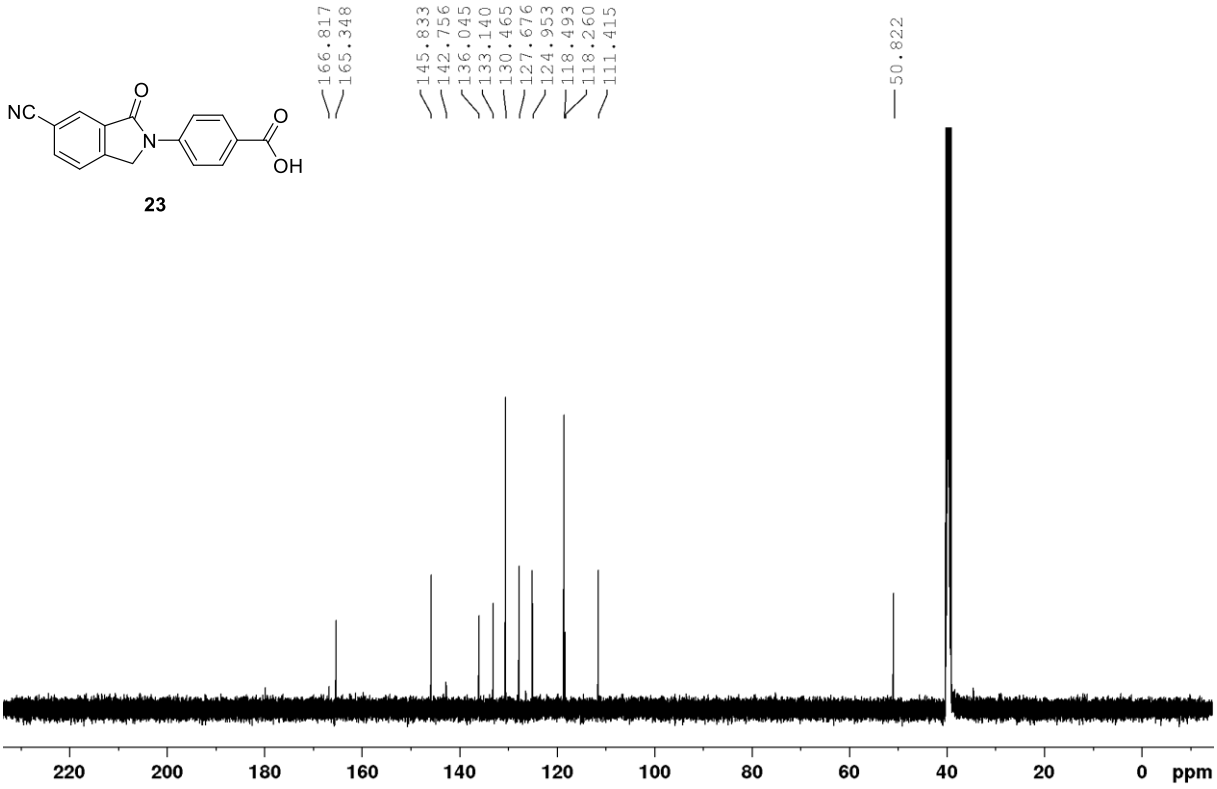

NC
O
O
19
8.213
8.209
7.669
7.665
7.649
7.645
7.379
7.359
3.924
2.670
0.98
1.00
1.00
3.18
3.23
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

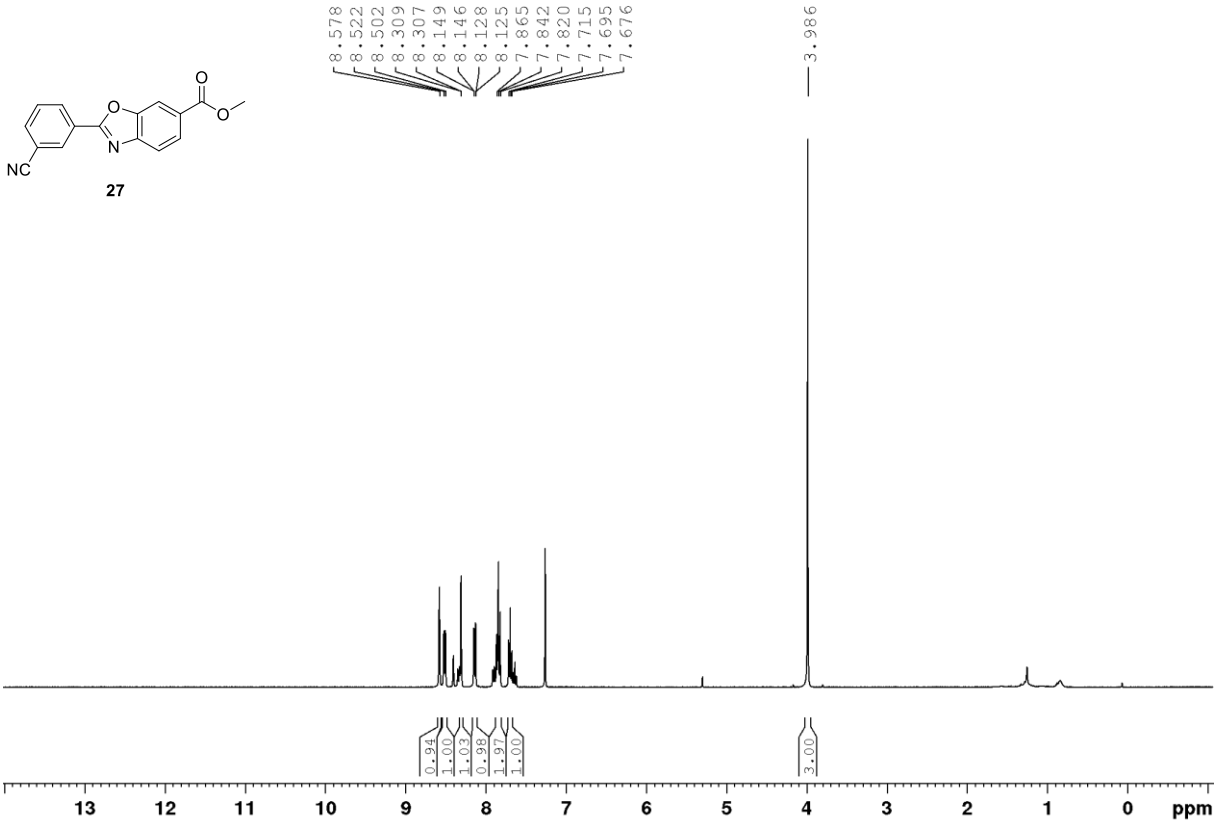

NC
O
O
Br
21
8.260
8.256
7.775
7.771
7.755
7.751
7.613
7.593
4.947
3.973
1.00
0.98
1.00
2.09
3.29
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

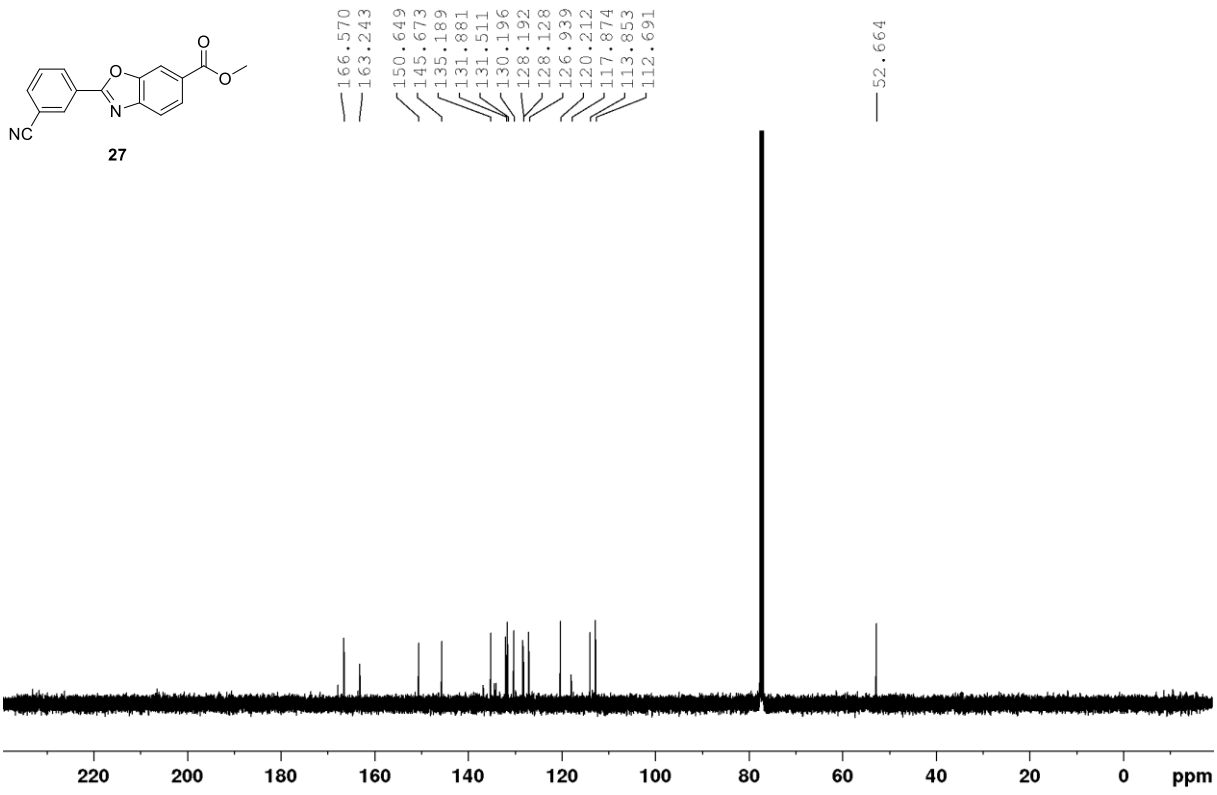

12.859
8.236
8.077
8.072
8.060
8.055
8.038
8.032
8.021
8.015
8.012
8.009
7.993
7.992
7.974
7.972
5.155
O
N
O
OH
NC
22
0.69
1.00
6.10
1.86
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

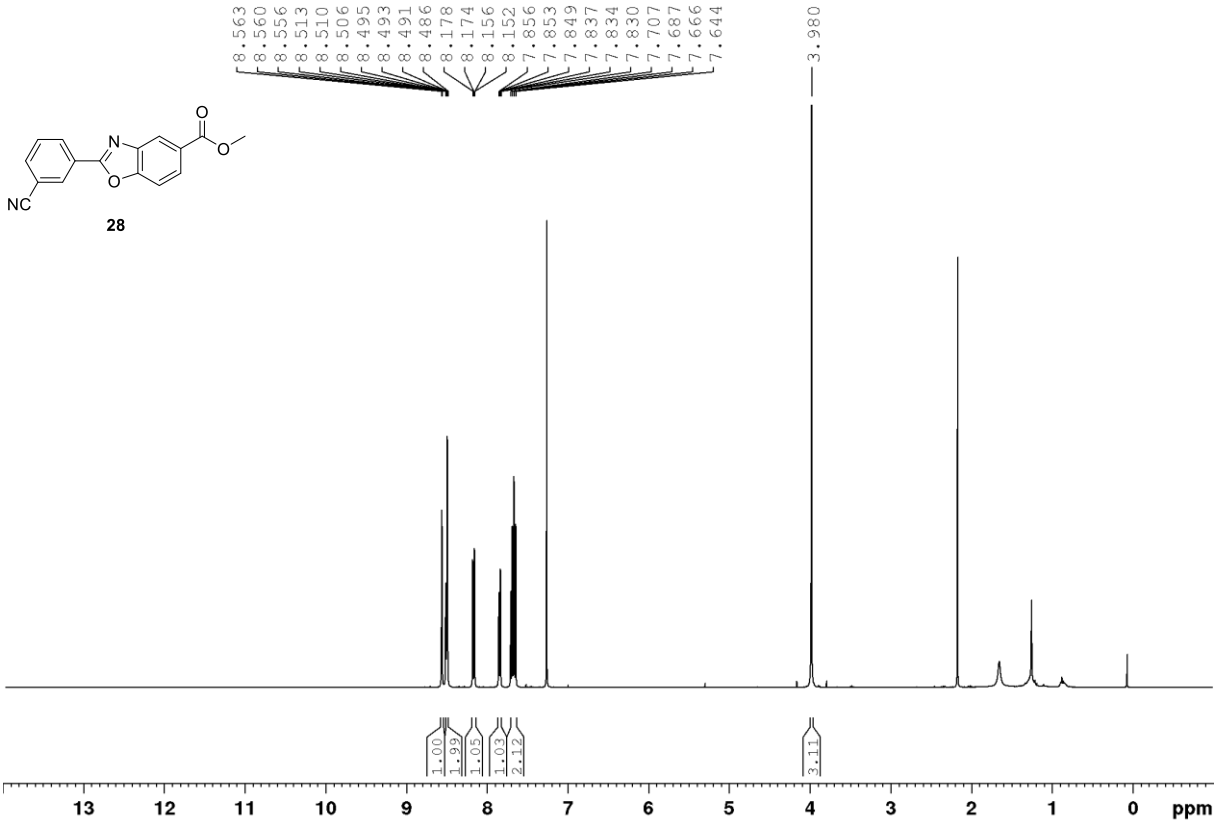

166.770
165.544
142.736
141.685
135.986
132.354
130.451
127.752
126.290
124.431
118.525
114.596
50.367
O
N
O
OH
NC
22
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm

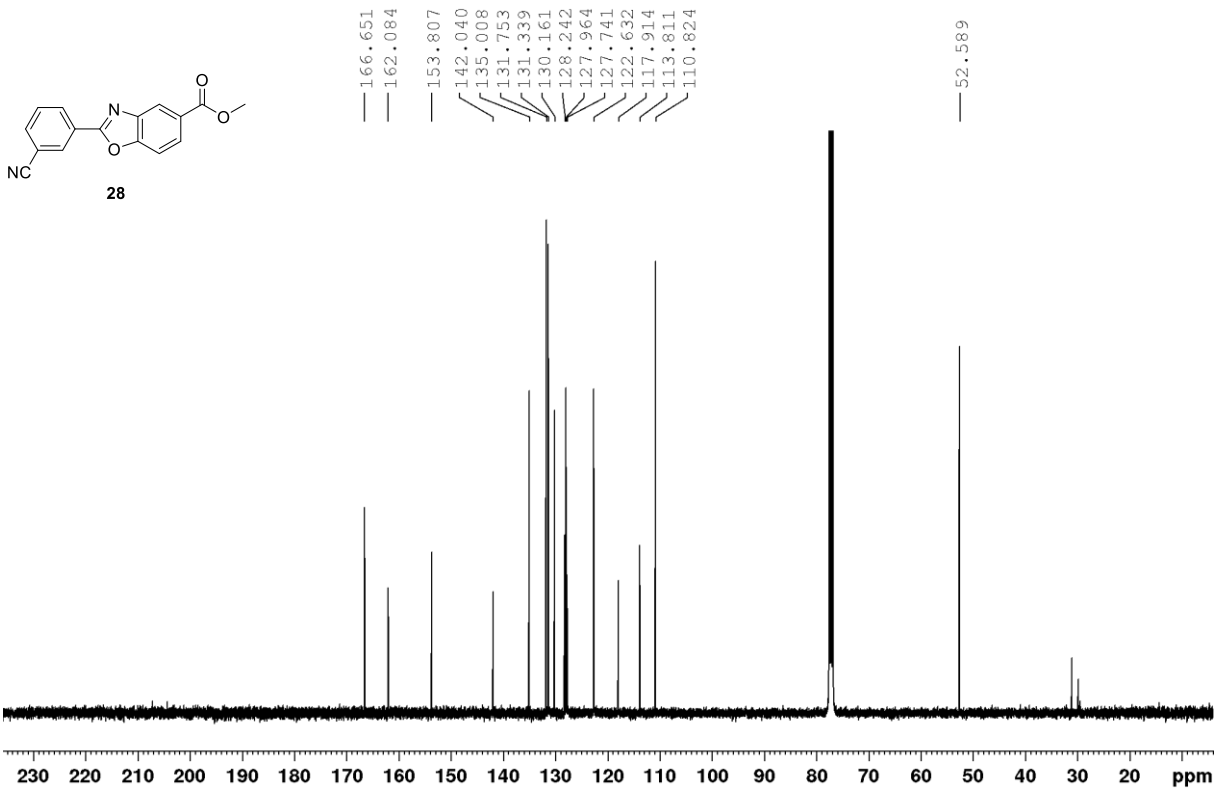

12.857
8.293
8.292
8.160
8.157
8.144
8.141
8.062
8.057
8.049
8.044
8.035
8.030
8.021
8.016
7.919
7.918
7.903
7.902
5.197
NC
O
N
O
OH
23
0.74
0.61
0.97
4.13
1.11
2.00
13
12
11
10
9
8
7
6
5
4
3
ppm

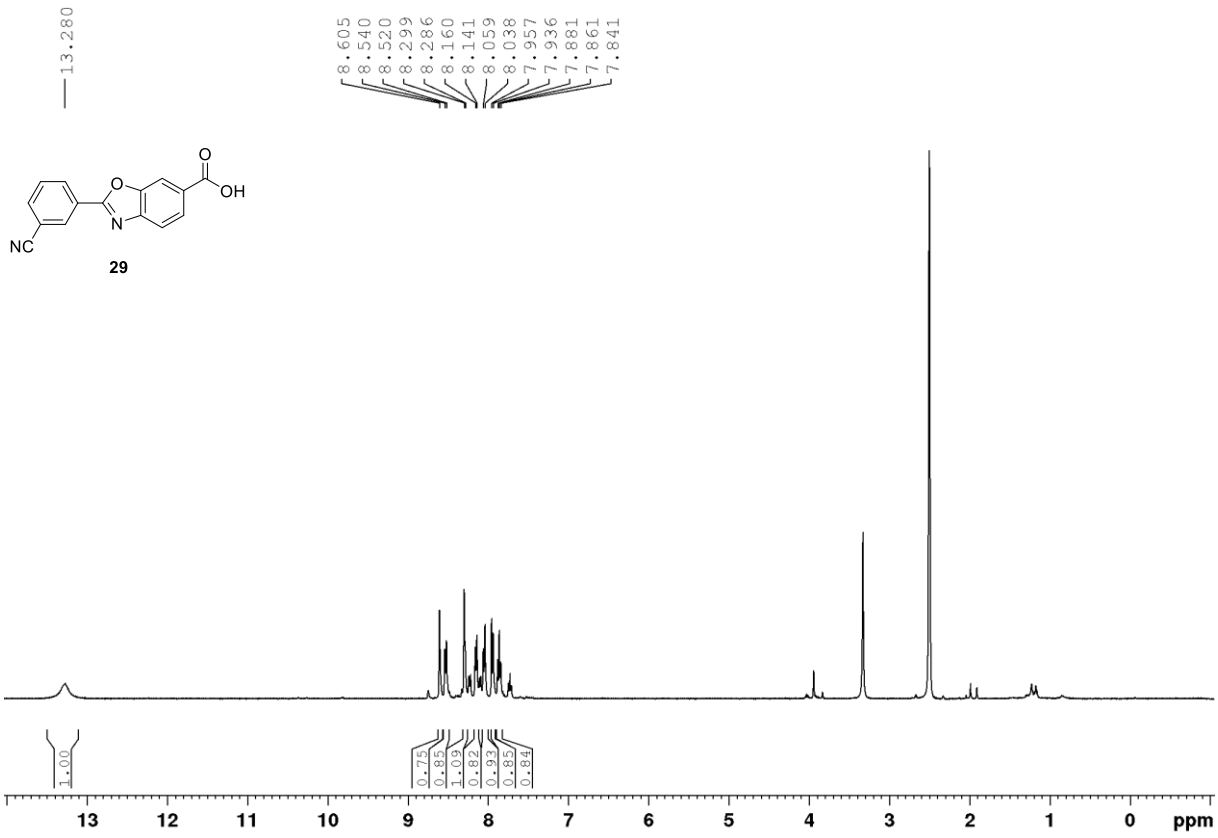

166.817
165.348
145.833
142.756
136.045
133.140
130.465
127.676
124.953
118.493
118.260
111.415
50.822
NC
O
N
O
OH
23
220
200
180
160
140
120
100
80
60
40
20
0
ppm

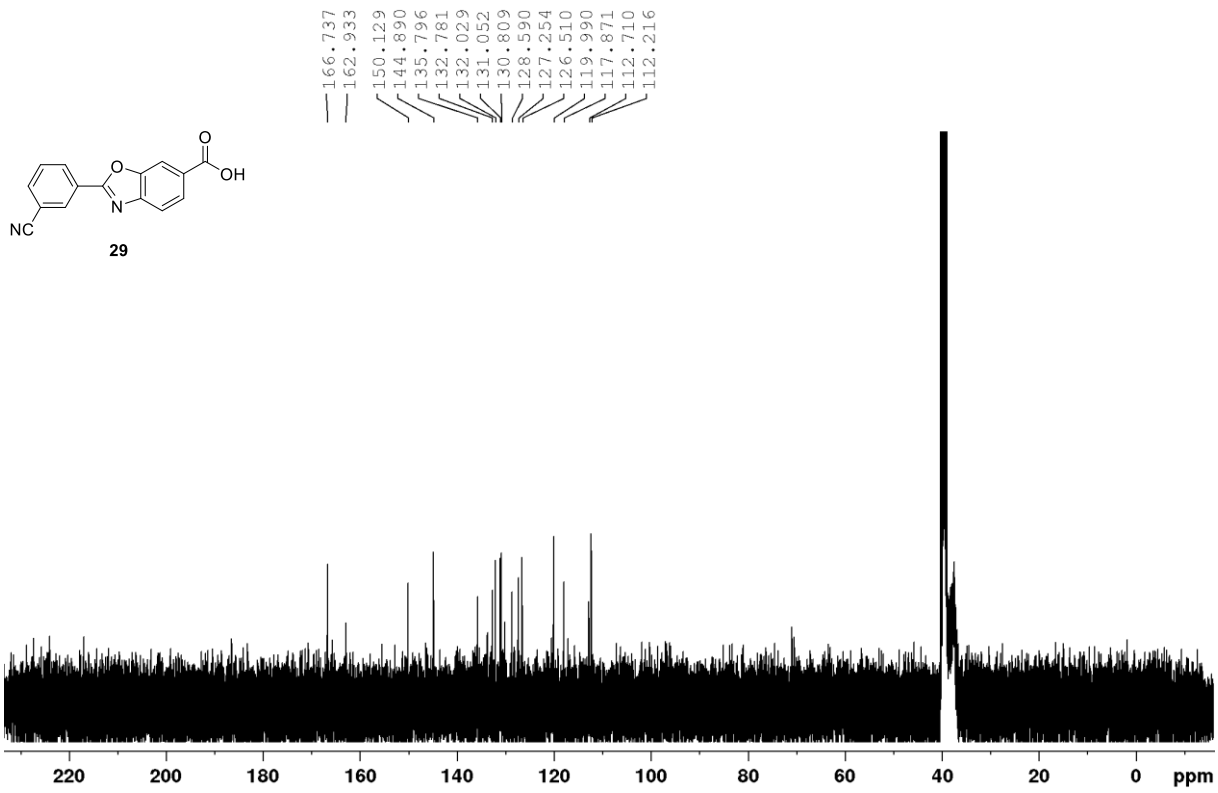

8.578
8.522
8.502
8.309
8.307
8.149
8.146
8.128
8.125
7.865
7.842
7.820
7.715
7.695
7.676
3.986
NC
27
0.94
1.00
1.03
0.98
1.97
1.00
3.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

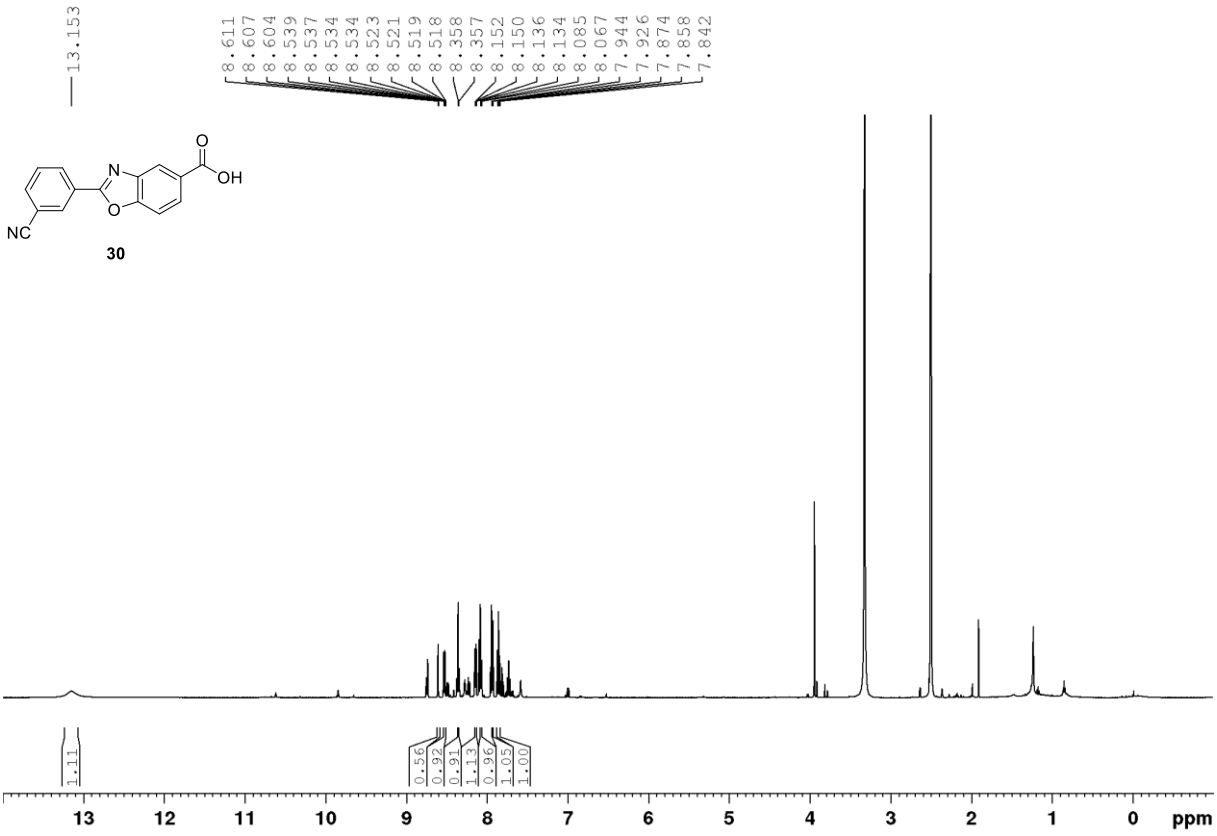

166.570
163.243
150.649
145.673
135.189
131.881
131.511
130.196
128.192
128.128
126.939
120.212
117.874
113.853
112.691
52.664
NC
27
220
200
180
160
140
120
100
80
60
40
20
0
ppm

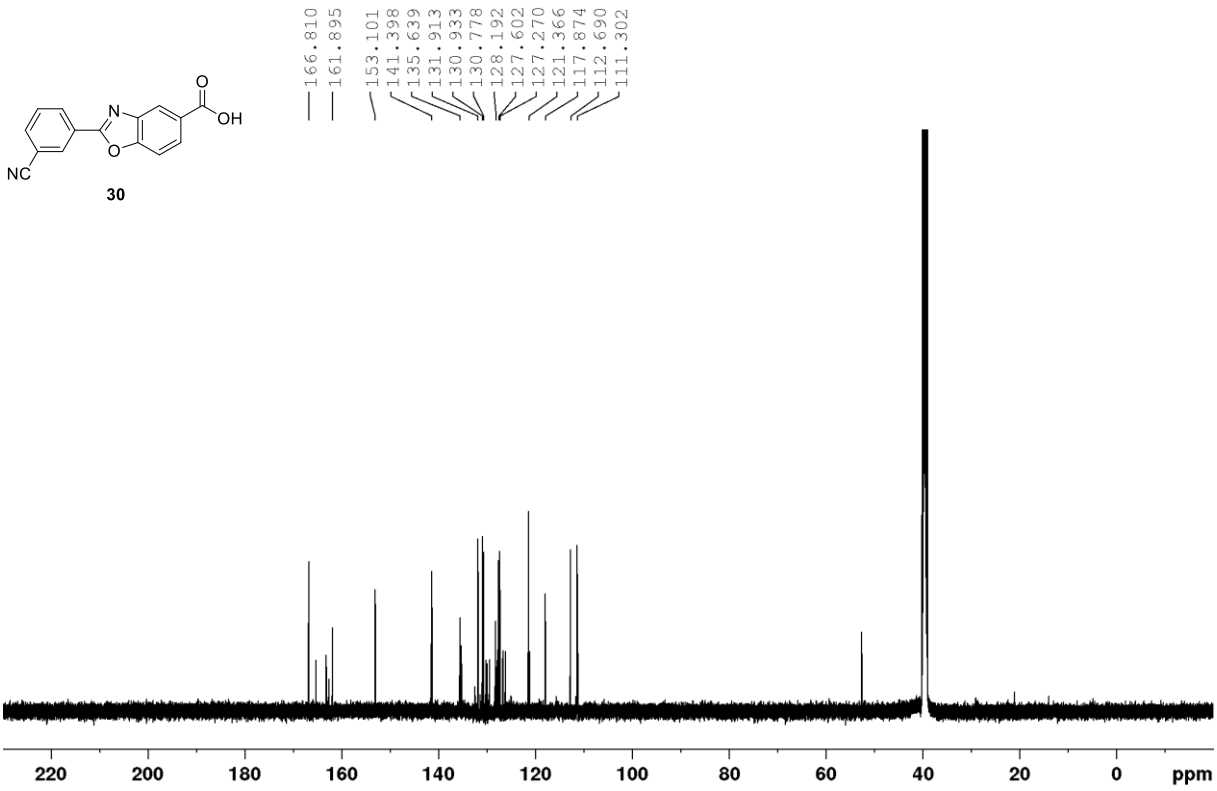

8.563
8.560
8.556
8.513
8.510
8.506
8.495
8.493
8.491
8.486
8.178
8.174
8.156
8.152
7.856
7.853
7.849
7.837
7.834
7.830
7.707
7.687
7.666
7.644
3.980
O
N
O
O
NC
28
1.00
1.99
1.05
1.03
2.12
3.11
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

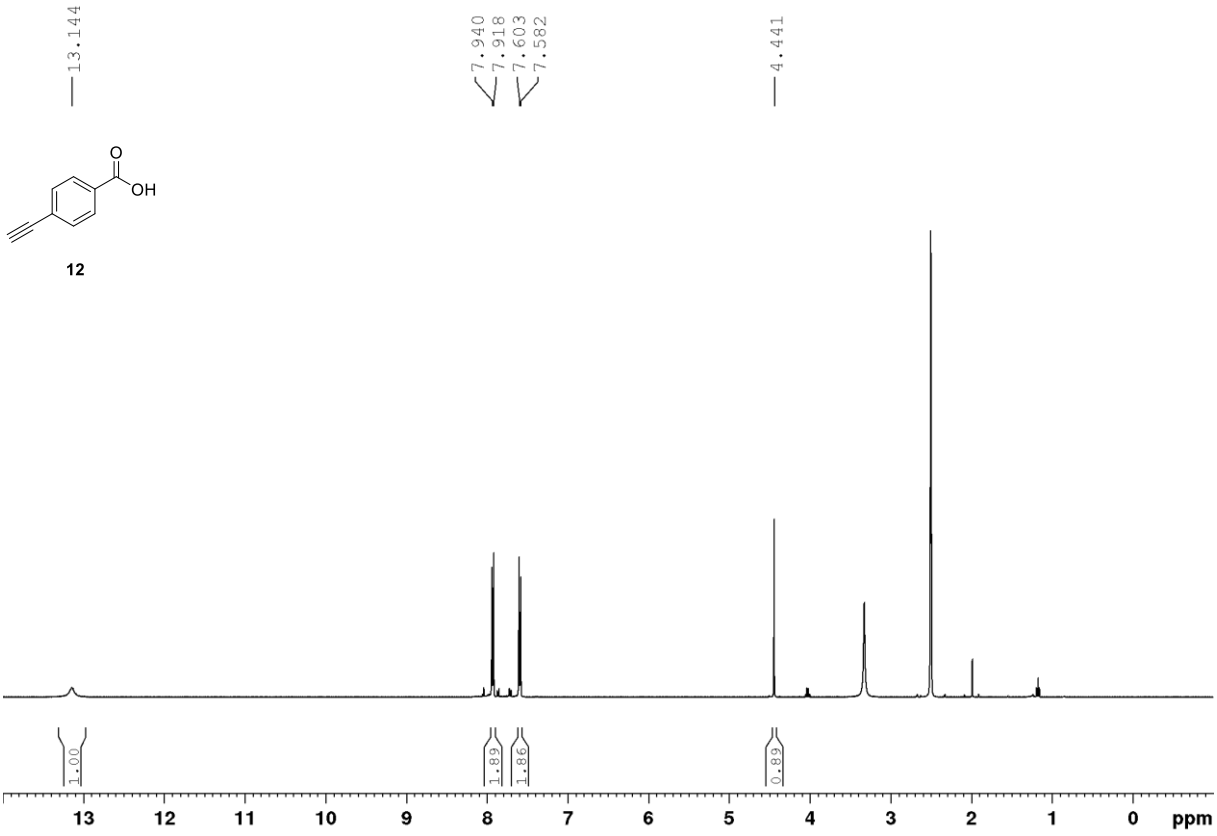

166.651
162.084
153.807
142.040
135.008
131.753
131.339
130.161
128.242
127.964
127.741
122.632
117.914
113.811
110.824
52.589
O
N
O
O
NC
28
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

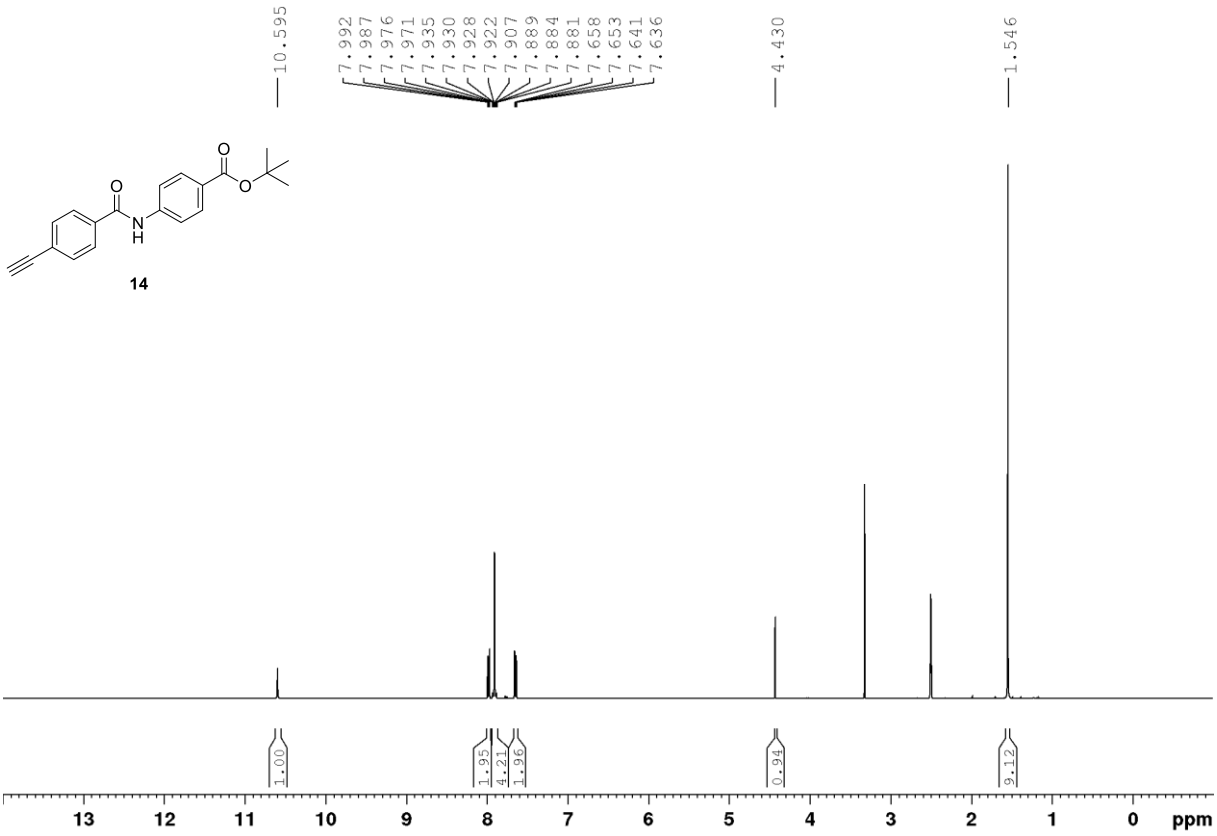

13.280
8.605
8.540
8.520
8.299
8.286
8.160
8.141
8.059
8.038
7.957
7.936
7.881
7.861
7.841
O
OH
O
N
NC
29
1.00
0.75
0.85
1.09
0.82
0.93
0.85
0.84
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

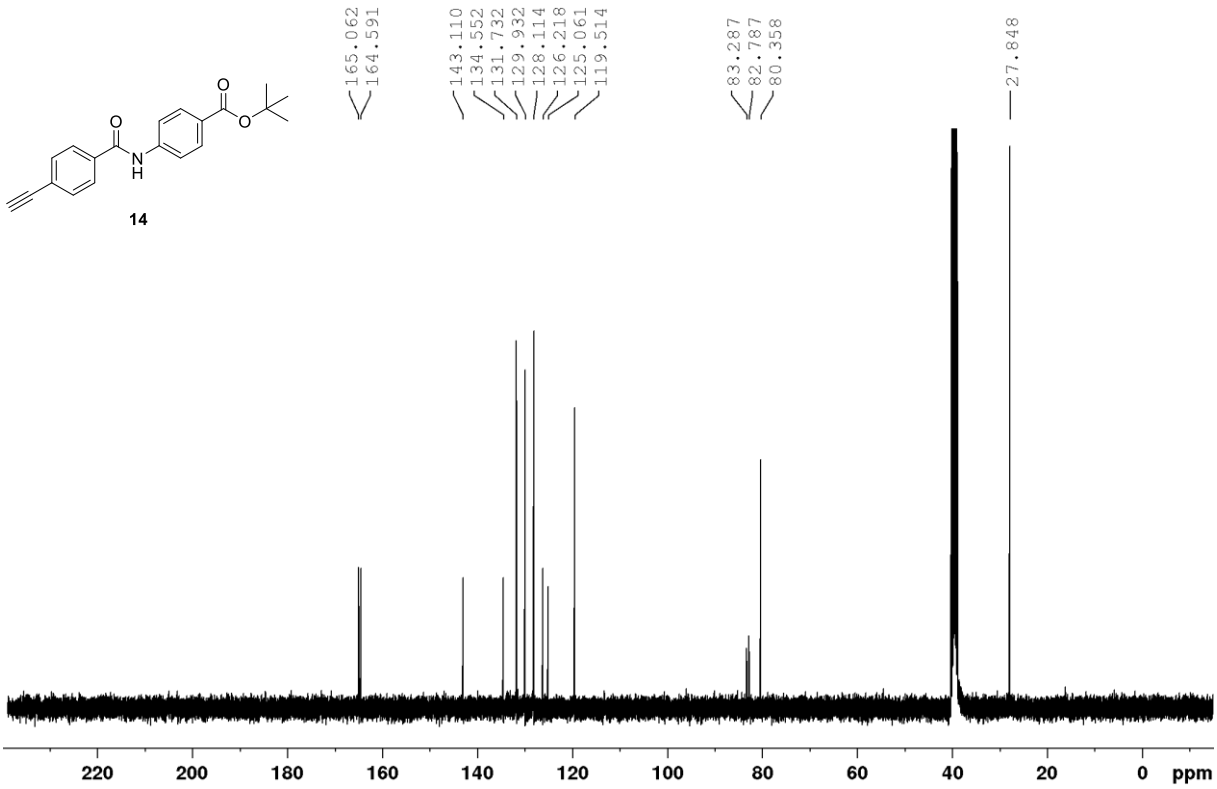

166.737
162.933
150.129
144.890
135.796
132.781
132.029
131.052
130.809
128.590
127.254
126.510
119.990
117.871
112.710
112.216
O
OH
O
N
NC
29
220
200
180
160
140
120
100
80
60
40
20
0
ppm

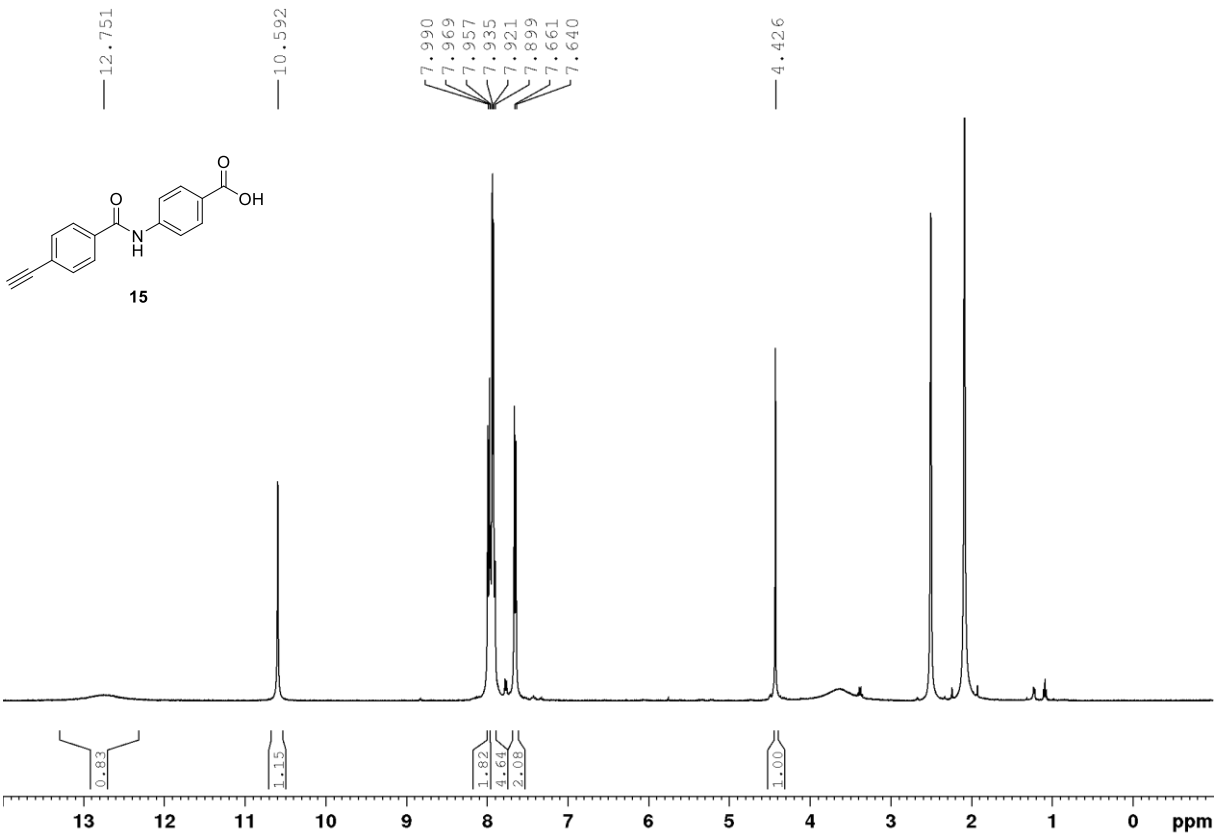

13.153
8.611
8.607
8.604
8.539
8.537
8.534
8.534
8.523
8.521
8.519
8.518
8.358
8.357
8.152
8.150
8.136
8.134
8.085
8.067
7.944
7.926
7.874
7.858
7.842
O
OH
N
O
NC
30
1.11
0.56
0.92
0.91
1.13
0.96
1.05
1.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

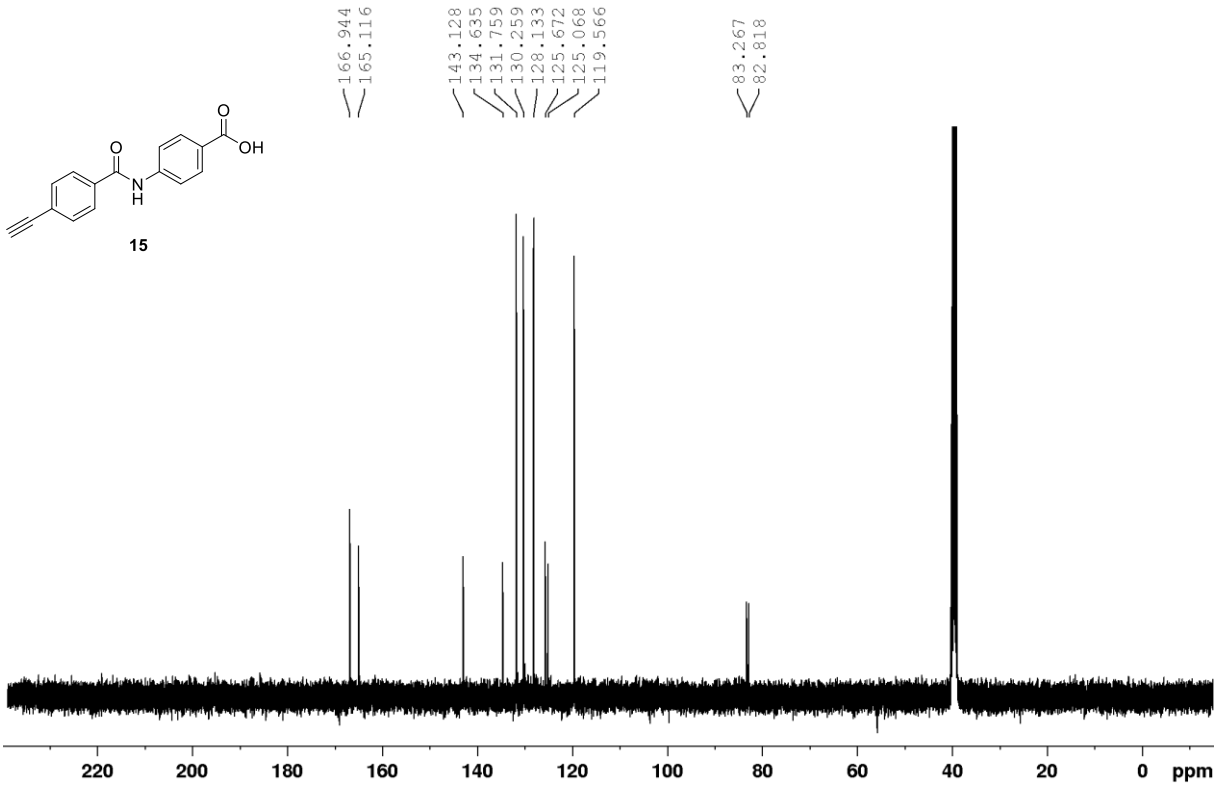

166.810
161.895
153.101
141.398
135.639
131.913
130.933
130.778
128.192
127.602
127.270
121.366
117.874
112.690
111.302
O
OH
N
O
NC
30
220
200
180
160
140
120
100
80
60
40
20
0
ppm

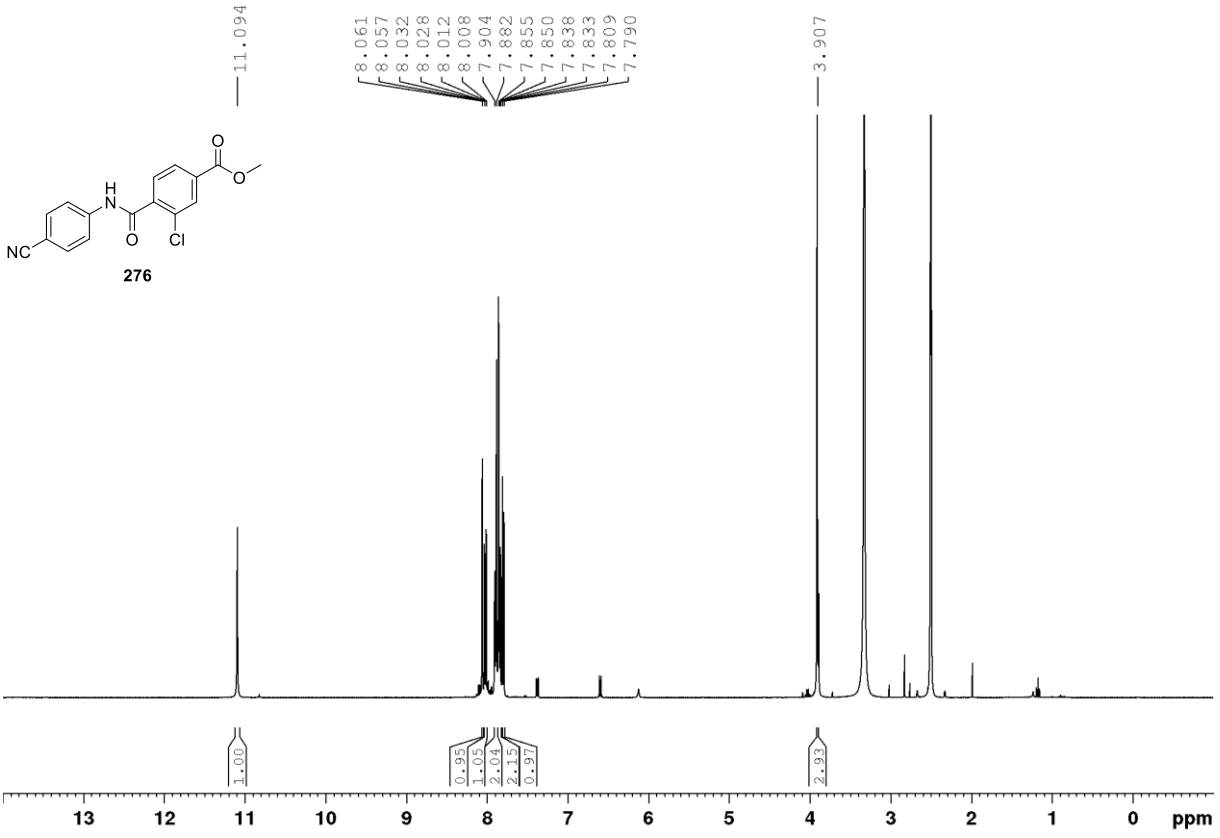

13.144
7.940
7.918
7.603
7.582
4.441
O
OH
12
1.00
1.89
1.86
0.89
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

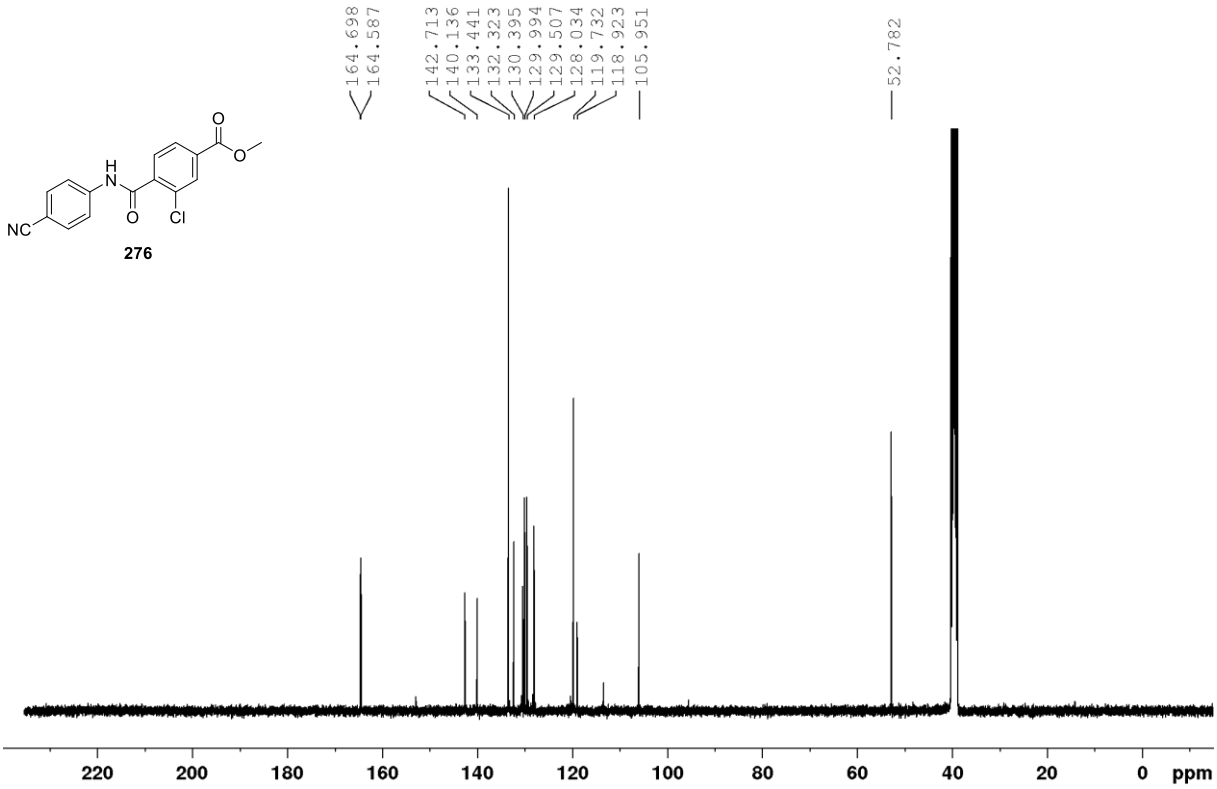

10.595
7.992
7.987
7.976
7.971
7.935
7.930
7.928
7.922
7.907
7.889
7.884
7.881
7.658
7.653
7.641
7.636
4.430
1.546
O
O
O
N
H
14
1.00
1.95
4.21
1.96
0.94
9.12
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

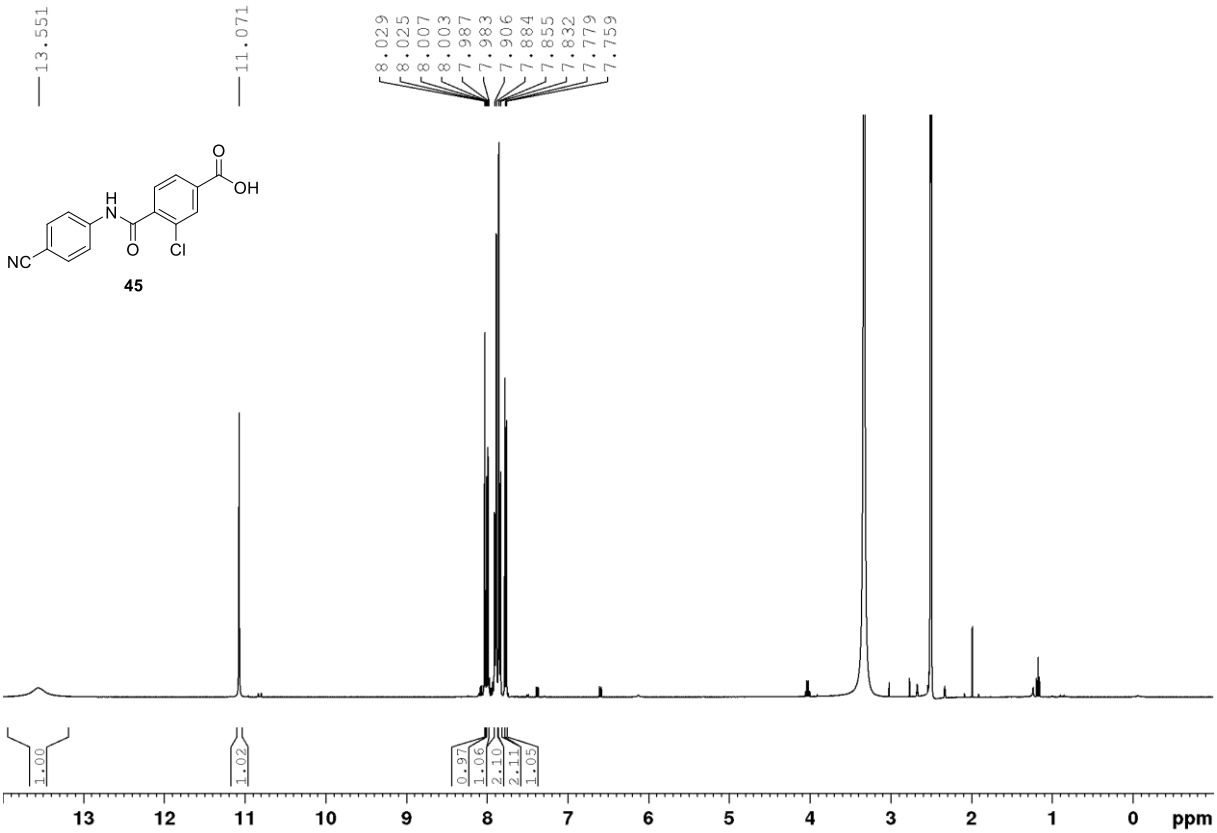

165.062
164.591
143.110
134.552
131.732
129.932
128.114
126.218
125.061
119.514
83.287
82.787
80.358
27.848
14
220
200
180
160
140
120
100
80
60
40
20
0
ppm

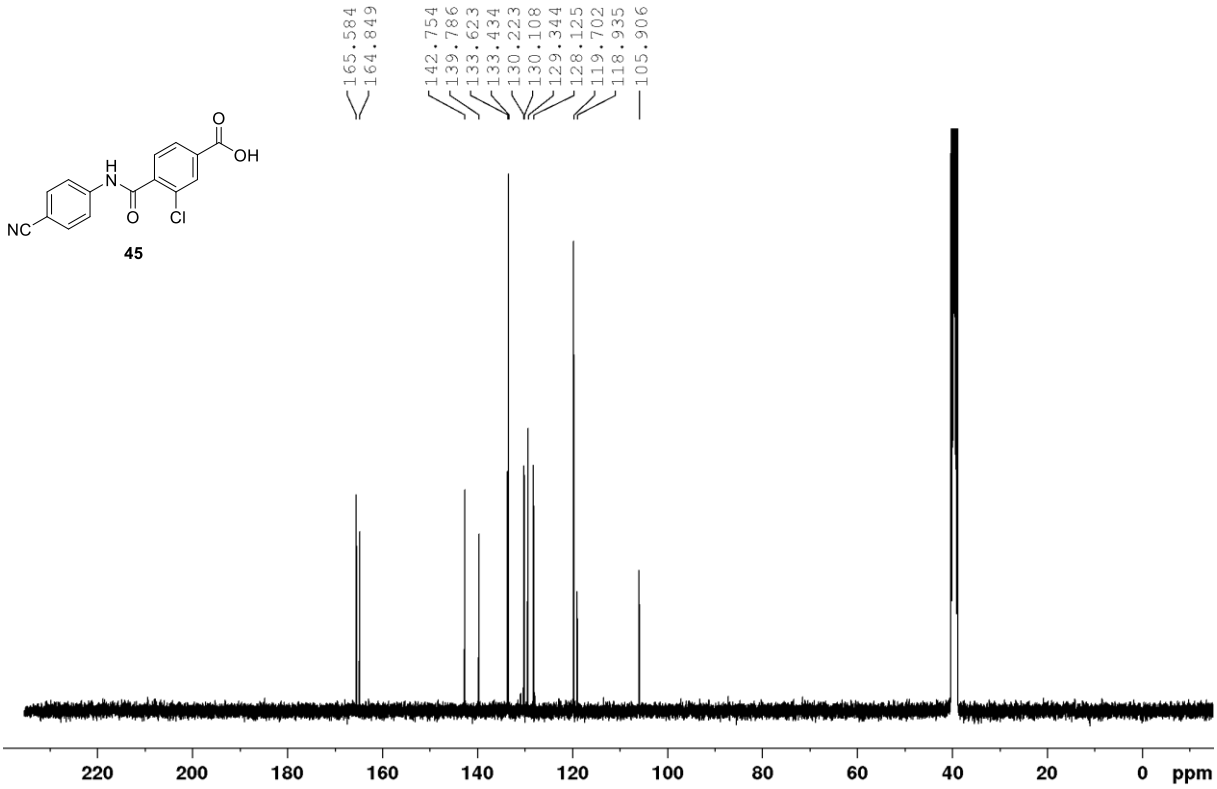

12.751
10.592
7.990
7.969
7.957
7.935
7.921
7.899
7.661
7.640
4.426
15
0.83
1.15
1.82
4.64
2.08
1.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

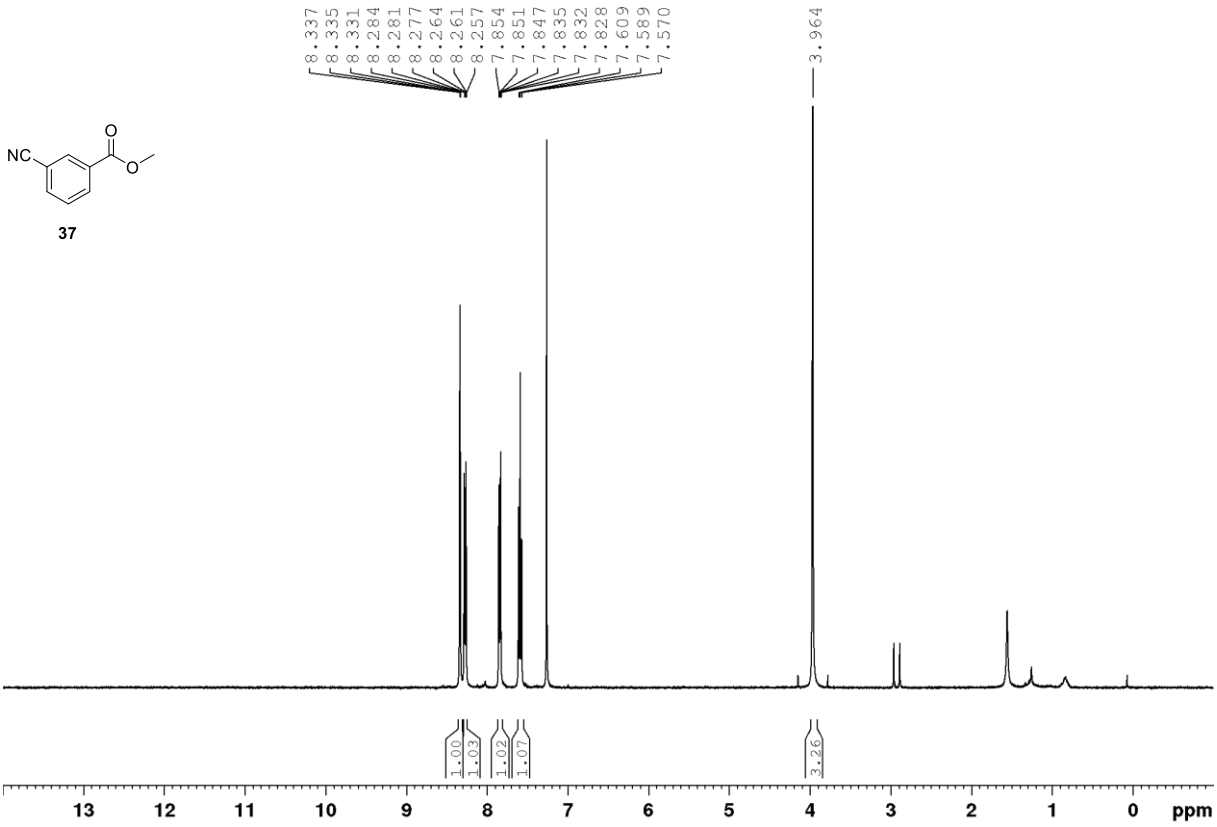

166.944
165.116
143.128
134.635
131.759
130.259
128.133
125.672
125.068
119.566
83.267
82.818
O
OH
N
H
15
220
200
180
160
140
120
100
80
60
40
20
0
ppm

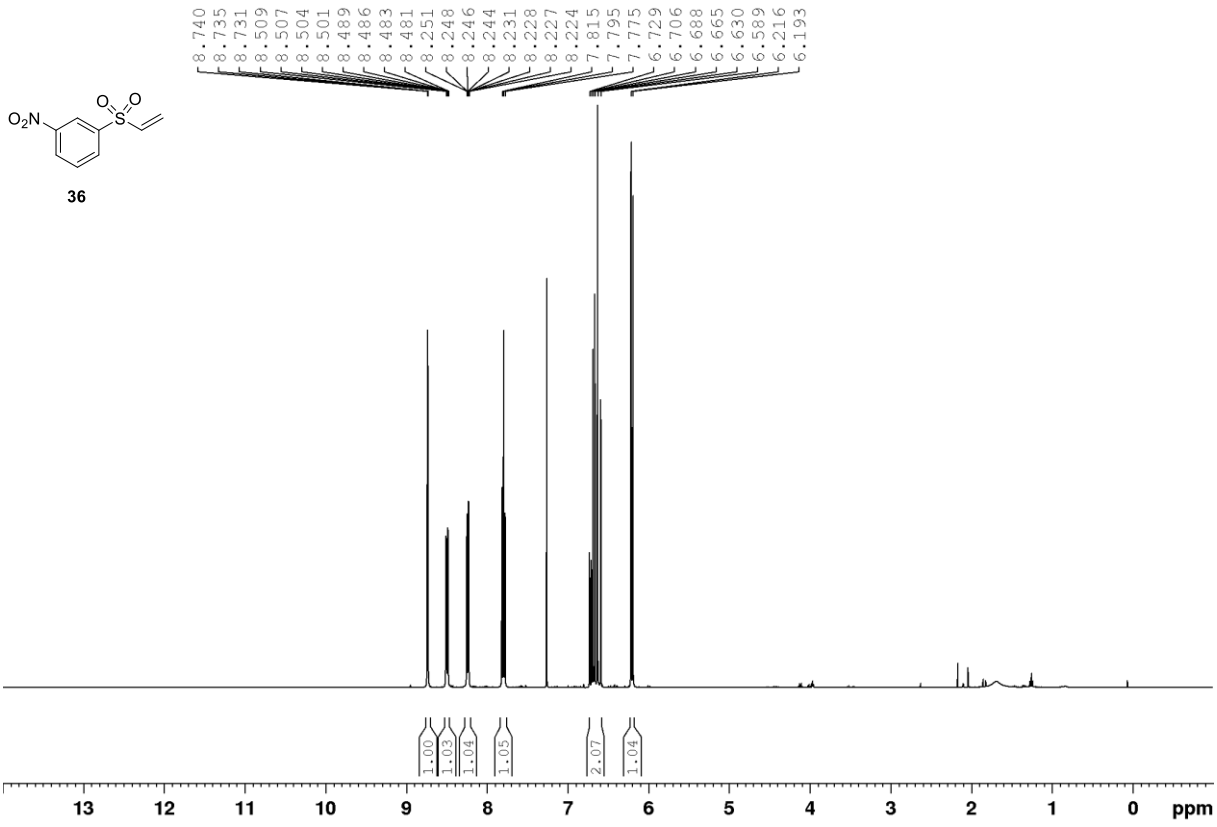

11.094
8.061
8.057
8.032
8.028
8.012
8.008
7.904
7.882
7.855
7.850
7.838
7.833
7.809
7.790
3.907
O
O
H
N
O
Cl
NC
276
1.00
0.95
1.05
2.04
2.15
0.97
2.93
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

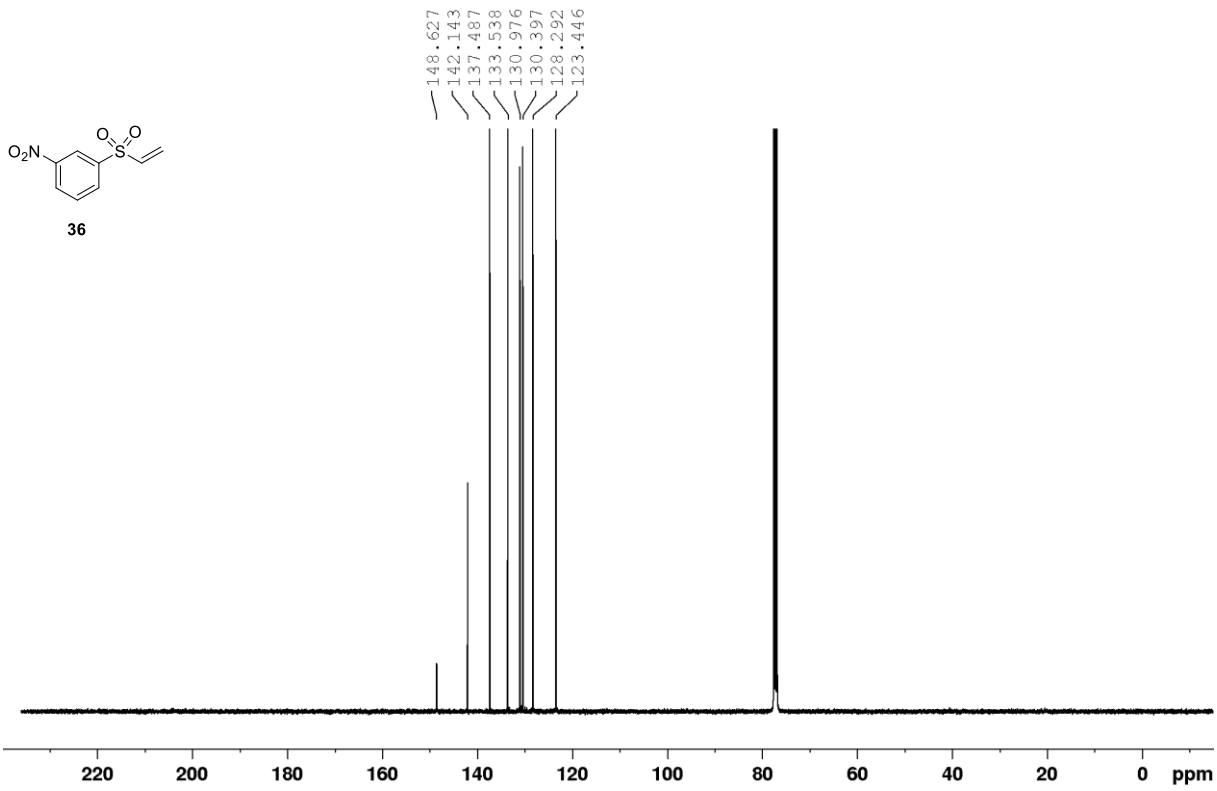

164.698
164.587
142.713
140.136
133.441
132.323
130.395
129.994
129.507
128.034
119.732
118.923
105.951
52.782
276
220
200
180
160
140
120
100
80
60
40
20
0
ppm

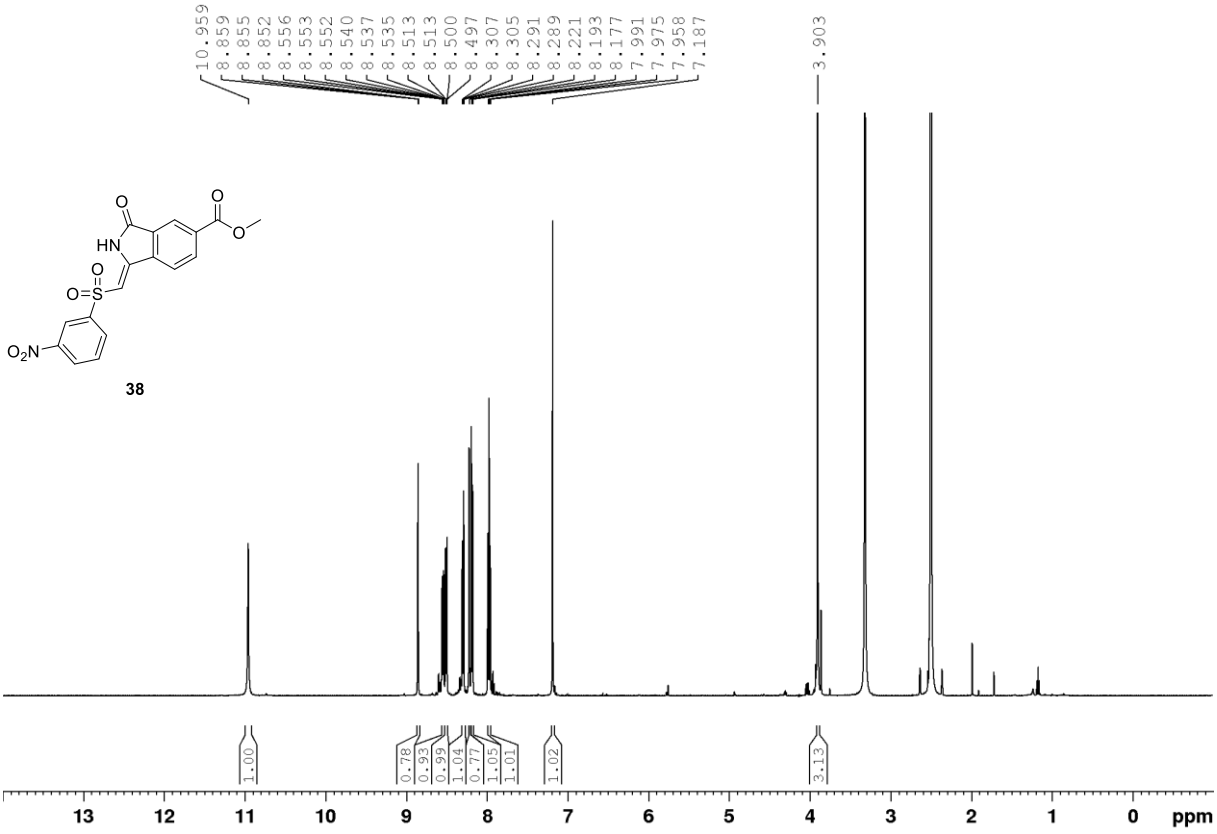

13.551
11.071
8.029
8.025
8.007
8.003
7.987
7.983
7.906
7.884
7.855
7.832
7.779
7.759
45
1.00
1.02
0.97
1.06
2.10
2.11
1.05
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

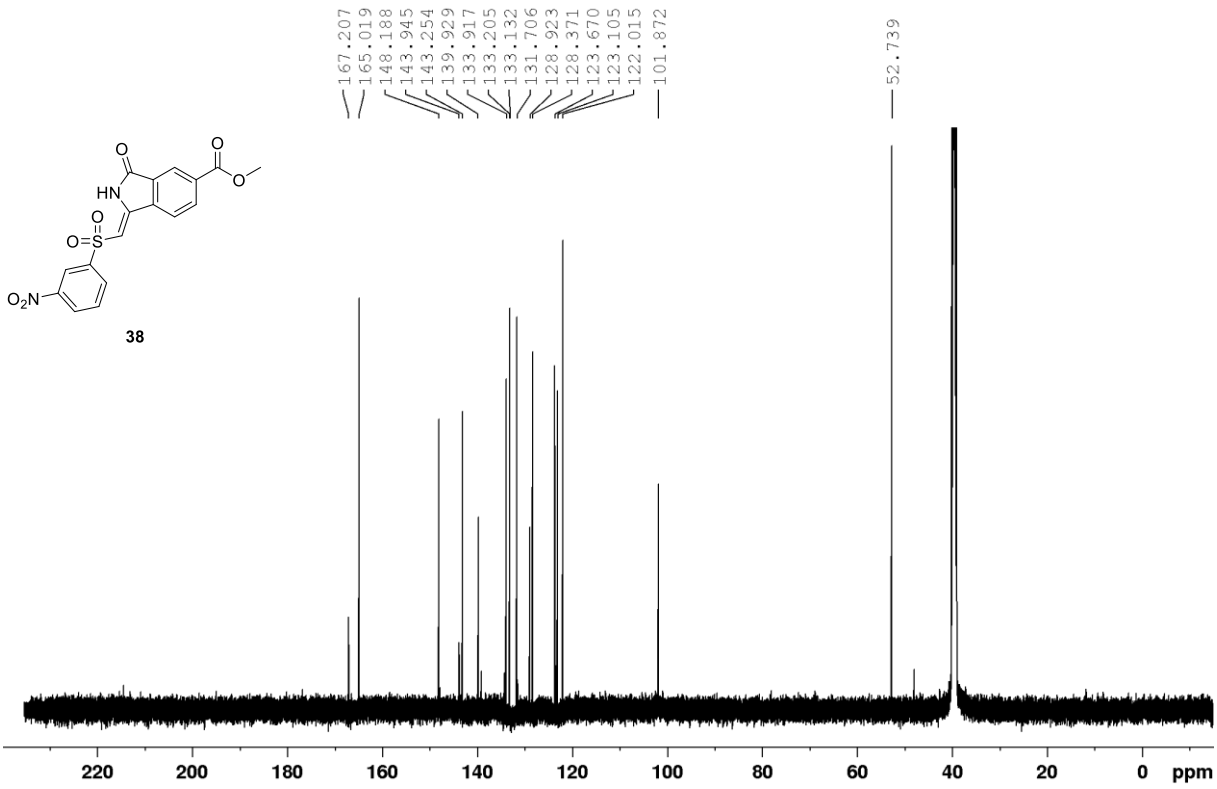

165.584
164.849
142.754
139.786
133.623
133.434
130.223
130.108
129.344
128.125
119.702
118.935
105.906
O
OH
H
N
O
Cl
NC
45
220
200
180
160
140
120
100
80
60
40
20
0
ppm

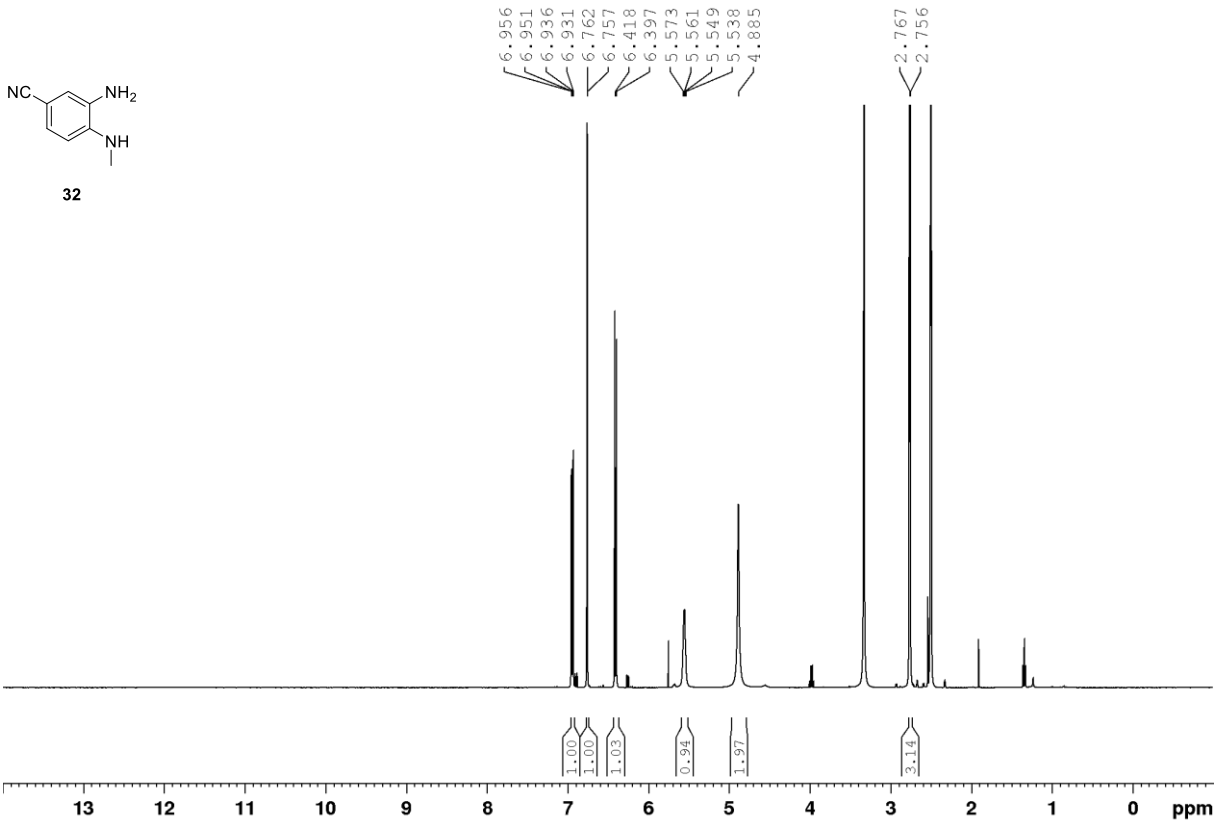

8.337
8.335
8.331
8.284
8.281
8.277
8.264
8.261
8.257
7.854
7.851
7.847
7.835
7.832
7.828
7.609
7.589
7.570
3.964
O
NC
O
37
1.00
1.03
1.02
1.07
3.26
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

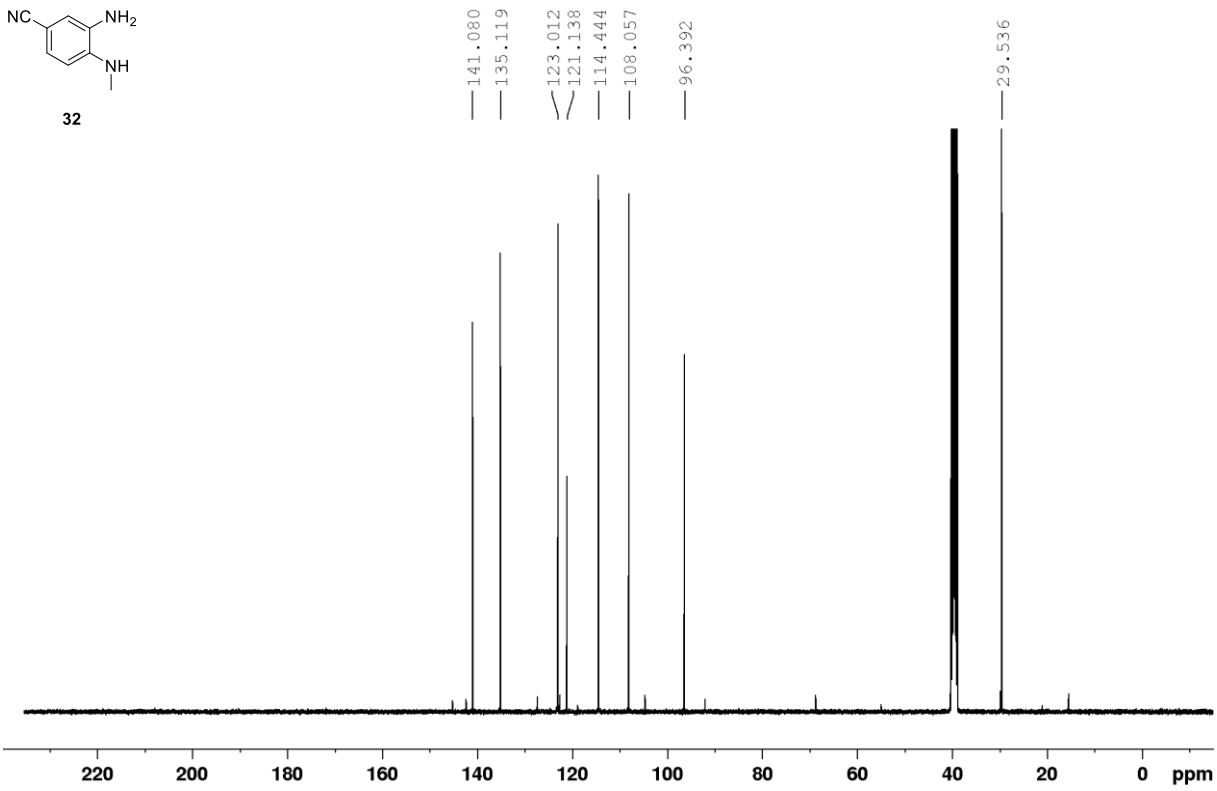

8.740
8.735
8.731
8.509
8.507
8.504
8.501
8.489
8.486
8.483
8.481
8.251
8.248
8.246
8.244
8.231
8.228
8.227
8.224
7.815
7.795
7.775
6.729
6.706
6.688
6.665
6.630
6.589
6.216
6.193
O2N
36
1.00
1.03
1.04
1.05
2.07
1.04
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

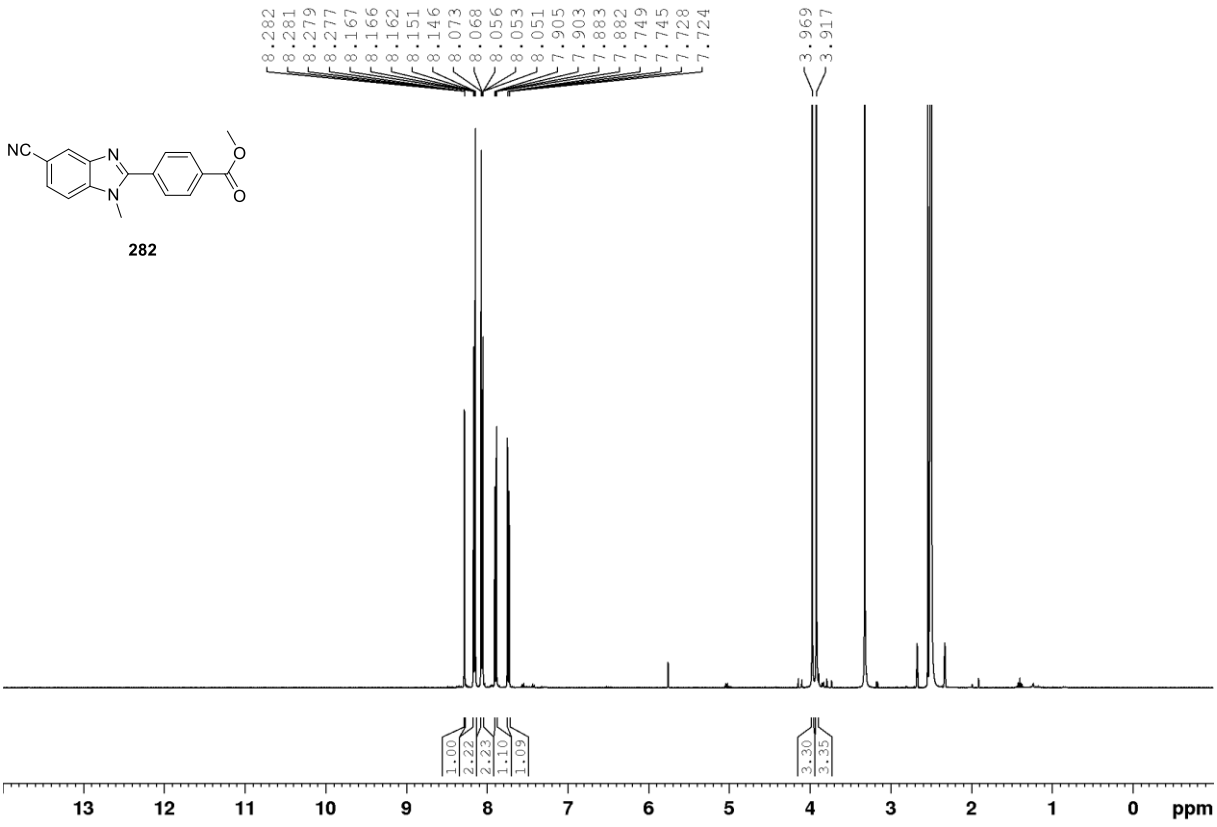

148.627
142.143
137.487
133.538
130.976
130.397
128.292
123.446
O2N
36
220
200
180
160
140
120
100
80
60
40
20
0
ppm

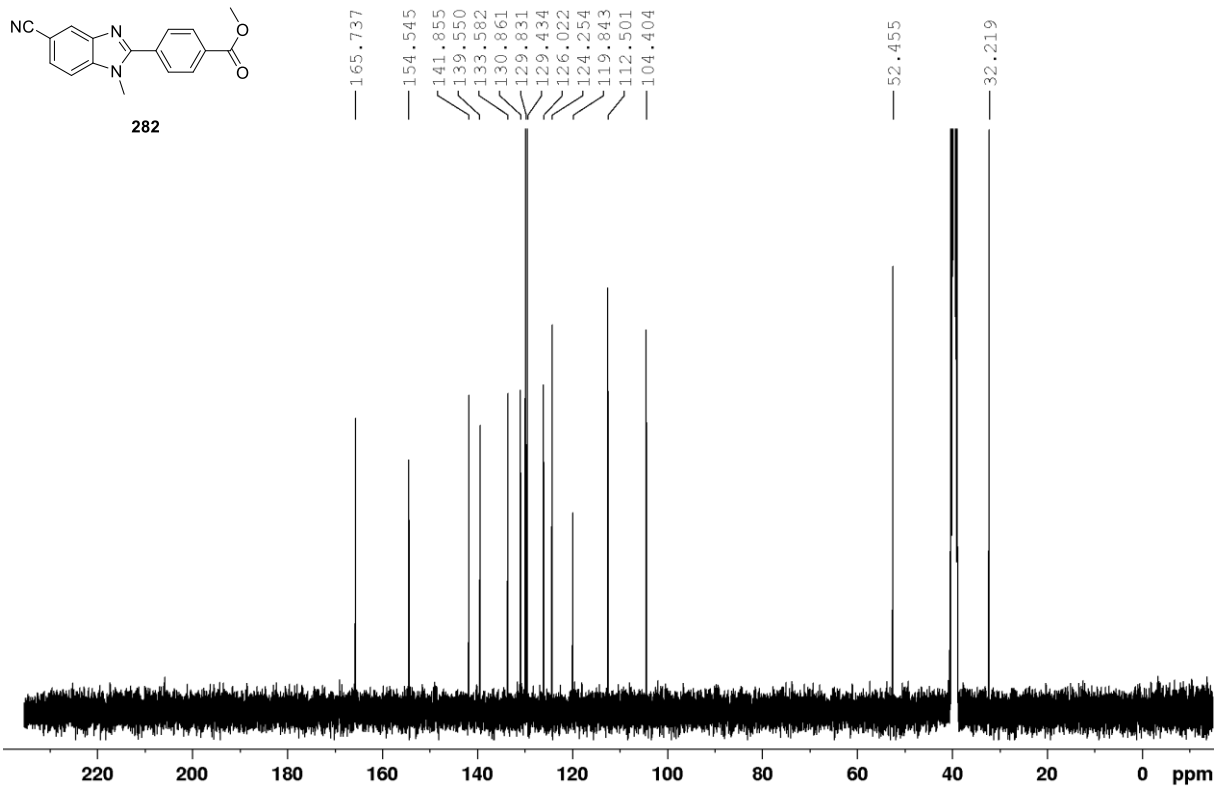

10.959
8.859
8.855
8.852
8.556
8.553
8.552
8.540
8.537
8.535
8.513
8.513
8.500
8.497
8.307
8.305
8.291
8.289
8.221
8.193
8.177
7.991
7.975
7.958
7.187
3.903
1.00
0.78
0.93
0.99
1.04
0.77
1.05
1.01
1.02
3.13
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

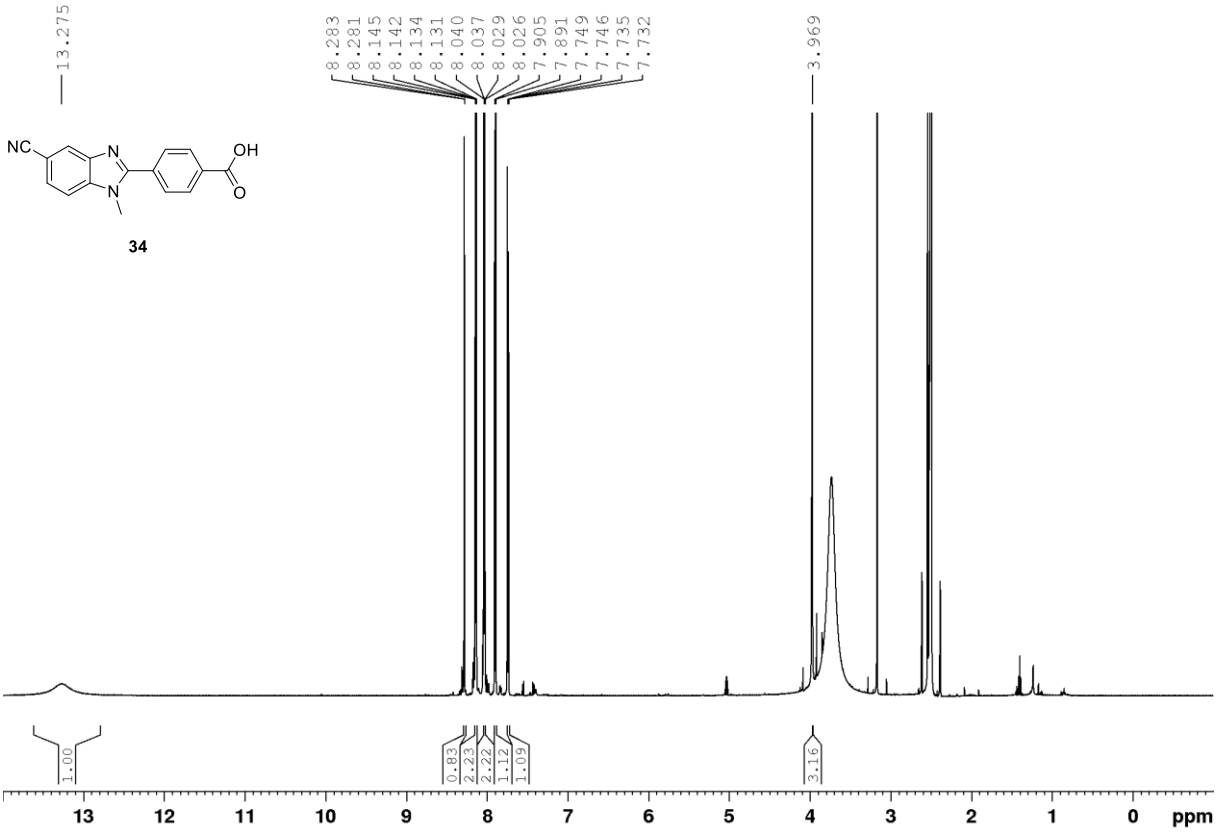

167.207
165.019
148.188
143.945
143.254
139.929
133.917
133.205
133.132
131.706
128.923
128.371
123.670
123.105
122.015
101.872
52.739
220
200
180
160
140
120
100
80
60
40
20
0
ppm

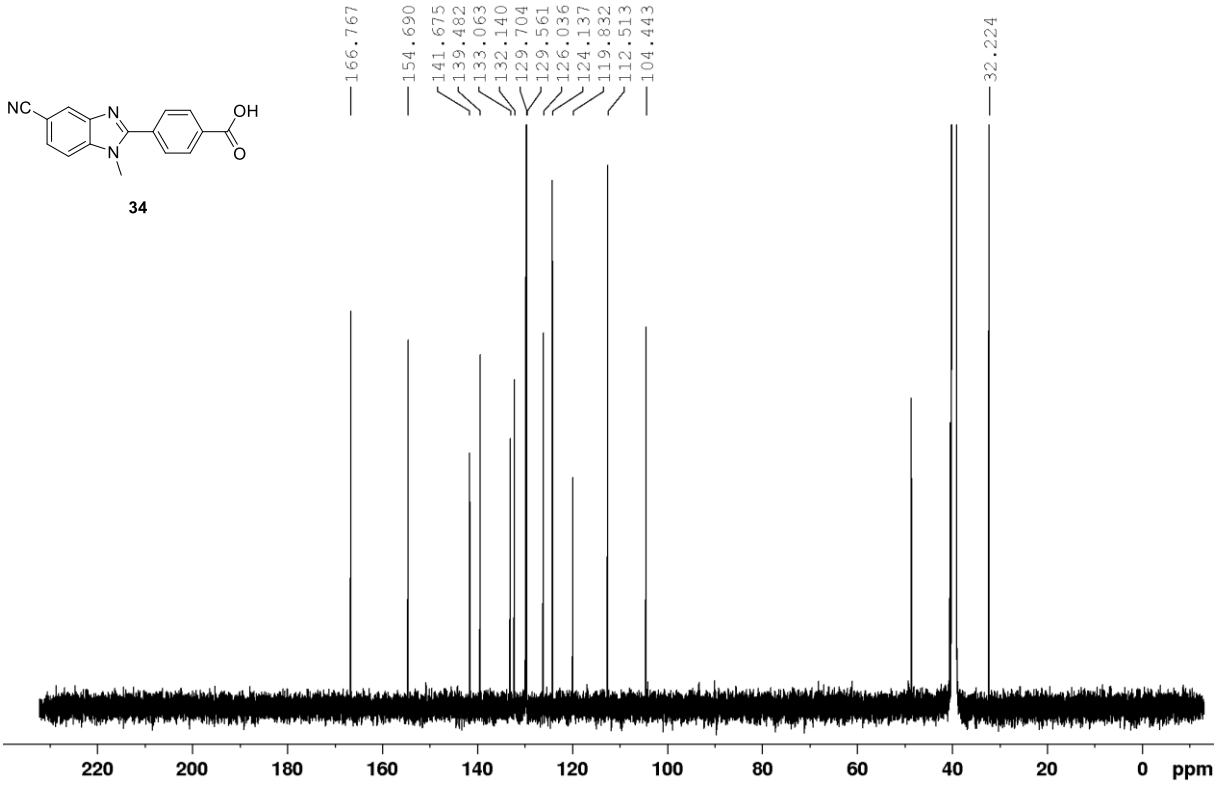

NC
NH2
NH
32
6.956
6.951
6.936
6.931
6.762
6.757
6.418
6.397
5.573
5.561
5.549
5.538
4.885
2.767
2.756
1.00
1.00
1.03
0.94
1.97
3.14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

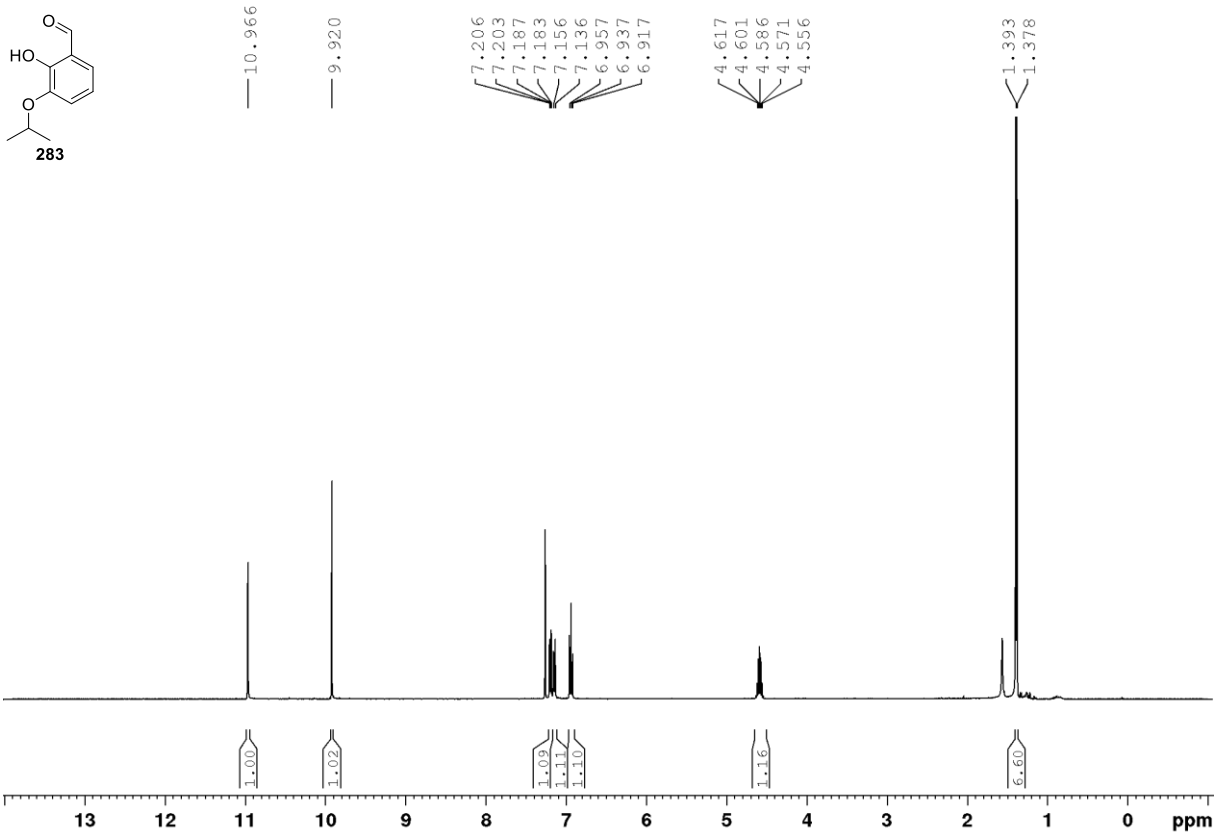

NC
NH2
NH
32
141.080
135.119
123.012
121.138
114.444
108.057
96.392
29.536
220
200
180
160
140
120
100
80
60
40
20
0
ppm

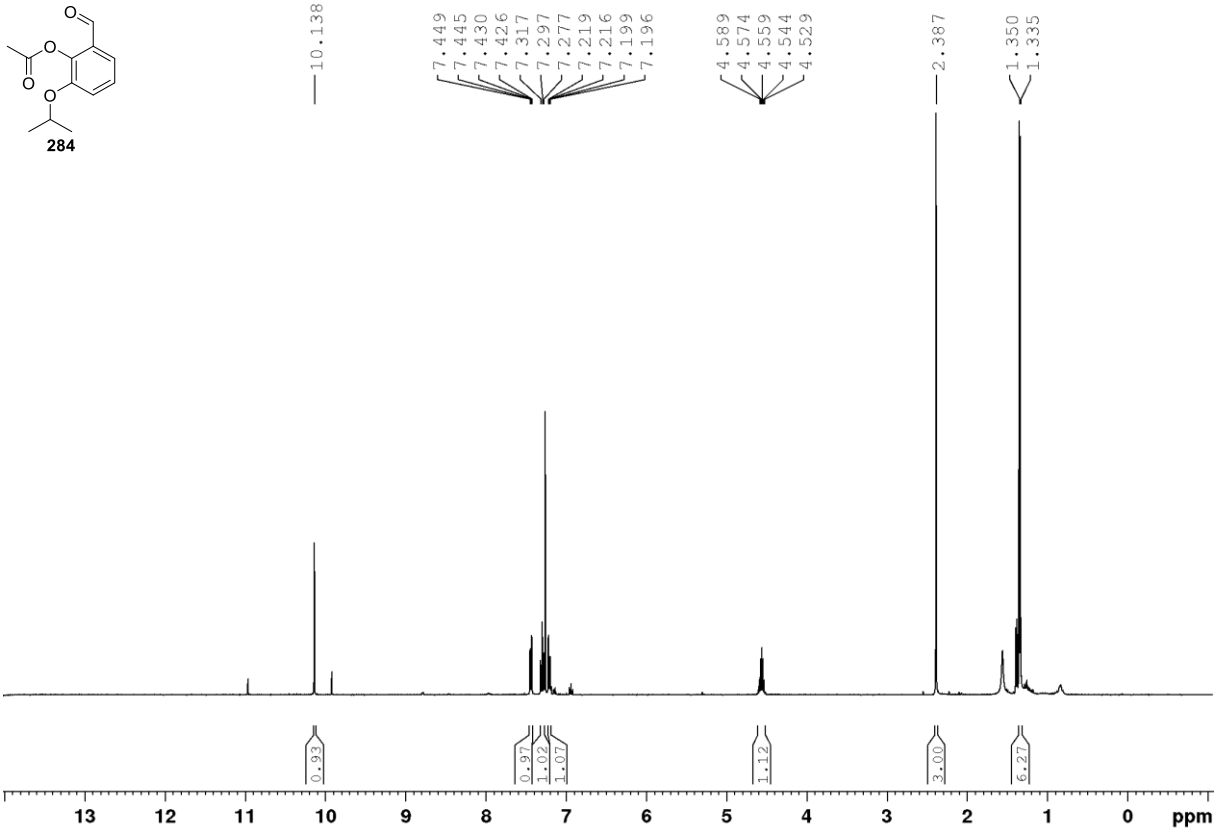

8.282
8.281
8.279
8.277
8.167
8.166
8.162
8.151
8.146
8.073
8.068
8.056
8.053
8.051
7.905
7.903
7.883
7.882
7.749
7.745
7.728
7.724
3.969
3.917
NC
O
O
N
N
282
1.00
2.22
2.23
1.10
1.09
3.30
3.35
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

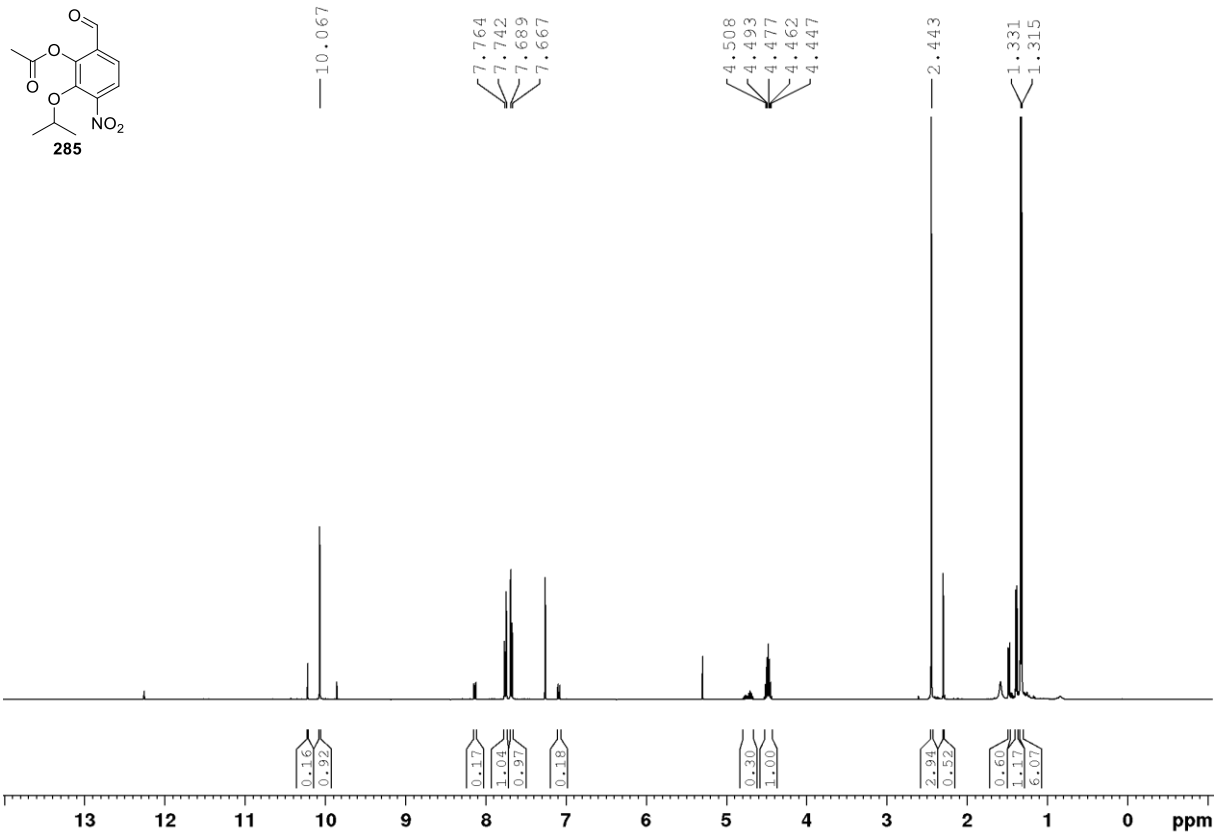

NC
O
O
N
N
282
165.737
154.545
141.855
139.550
133.582
130.861
129.831
129.434
126.022
124.254
119.843
112.501
104.404
52.455
32.219
220
200
180
160
140
120
100
80
60
40
20
0
ppm

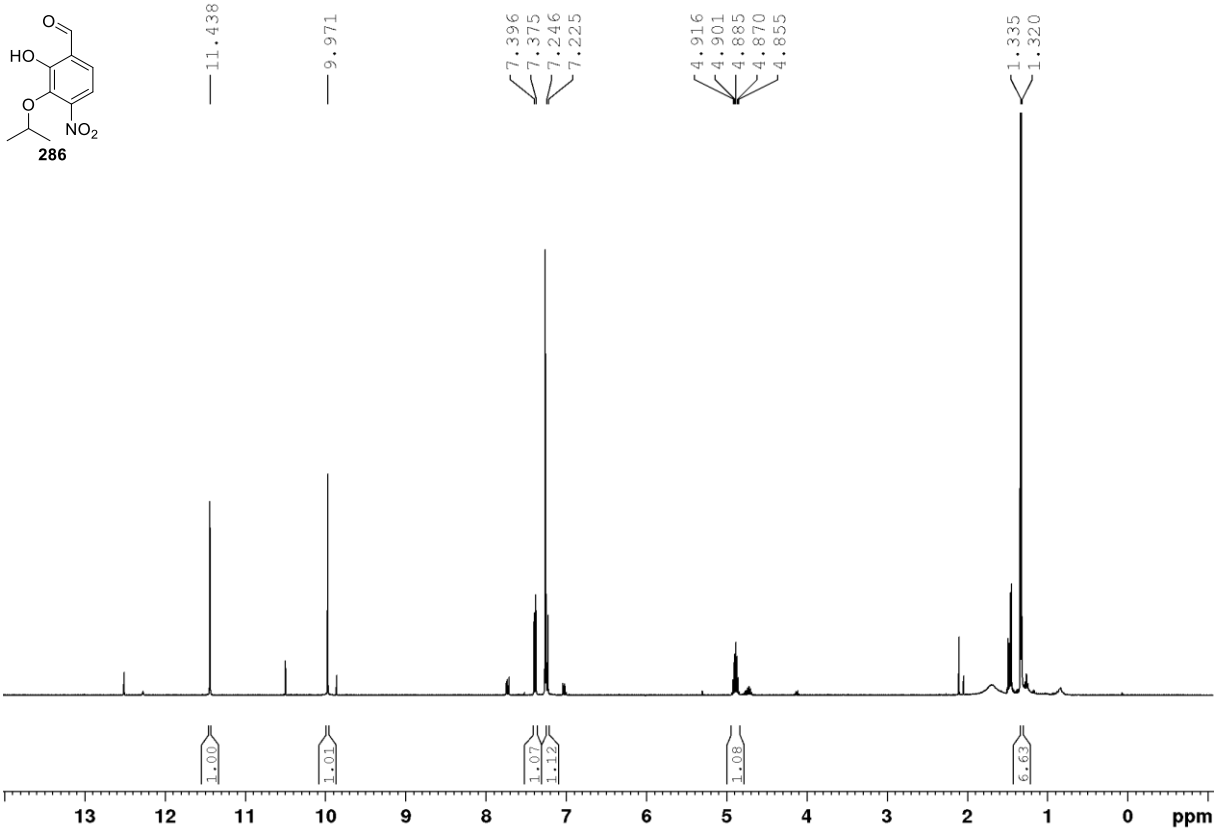

13.275
8.283
8.281
8.145
8.142
8.134
8.131
8.040
8.037
8.029
8.026
7.905
7.891
7.749
7.746
7.735
7.732
3.969
NC
OH
O
N
N
34
1.00
0.83
2.23
2.22
1.12
1.09
3.16
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

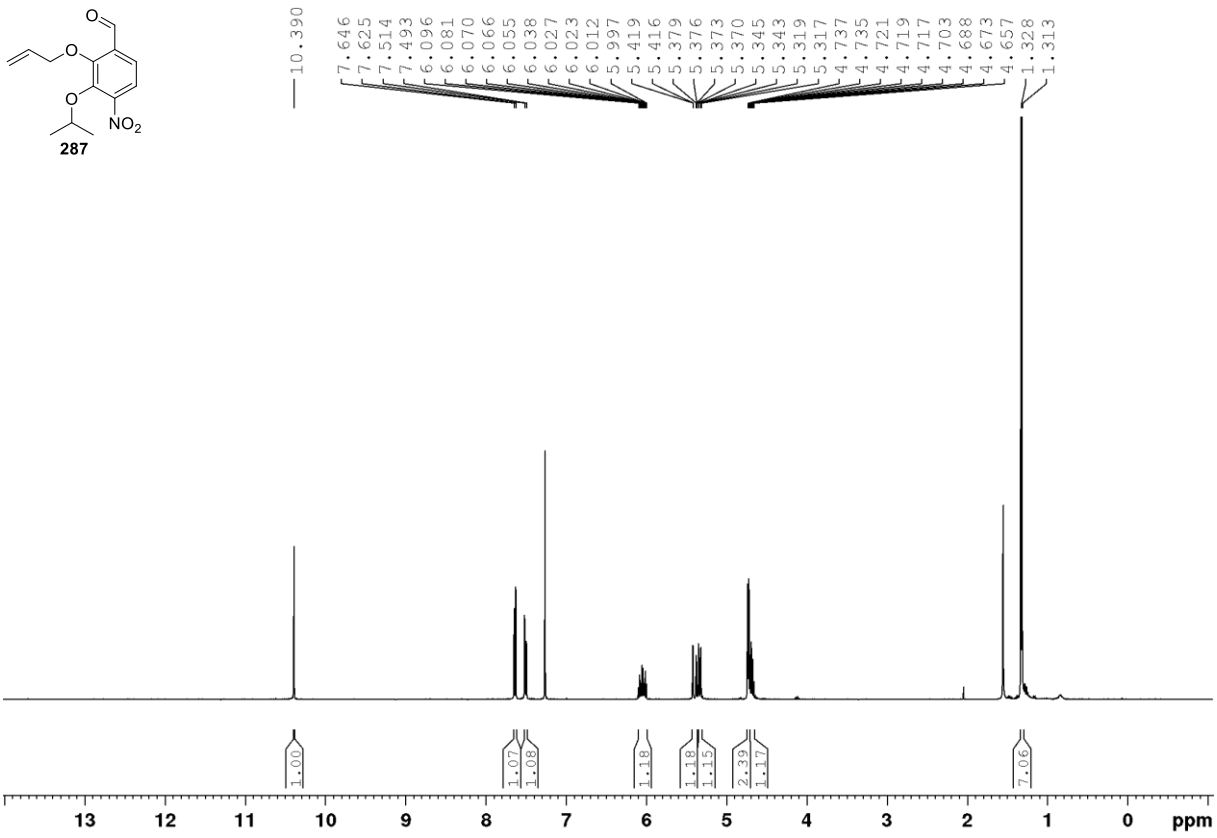

166.767
154.690
141.675
139.482
133.063
132.140
129.704
129.561
126.036
124.137
119.832
112.513
104.443
32.224
NC
OH
O
N
N
34
220
200
180
160
140
120
100
80
60
40
20
0
ppm

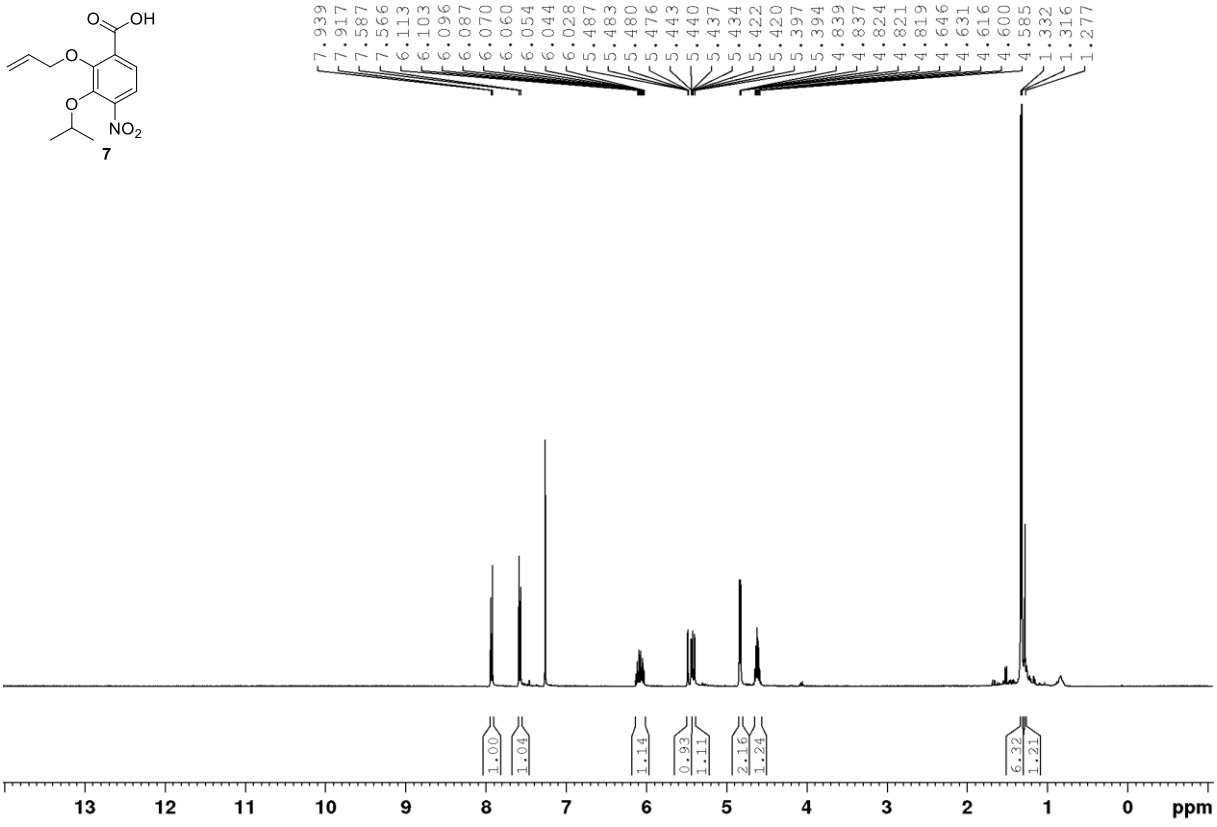

283
10.966
9.920
7.206
7.203
7.187
7.183
7.156
7.136
6.957
6.937
6.917
4.617
4.601
4.586
4.571
4.556
1.393
1.378
1.00
1.02
1.09
1.11
1.10
1.16
6.60
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

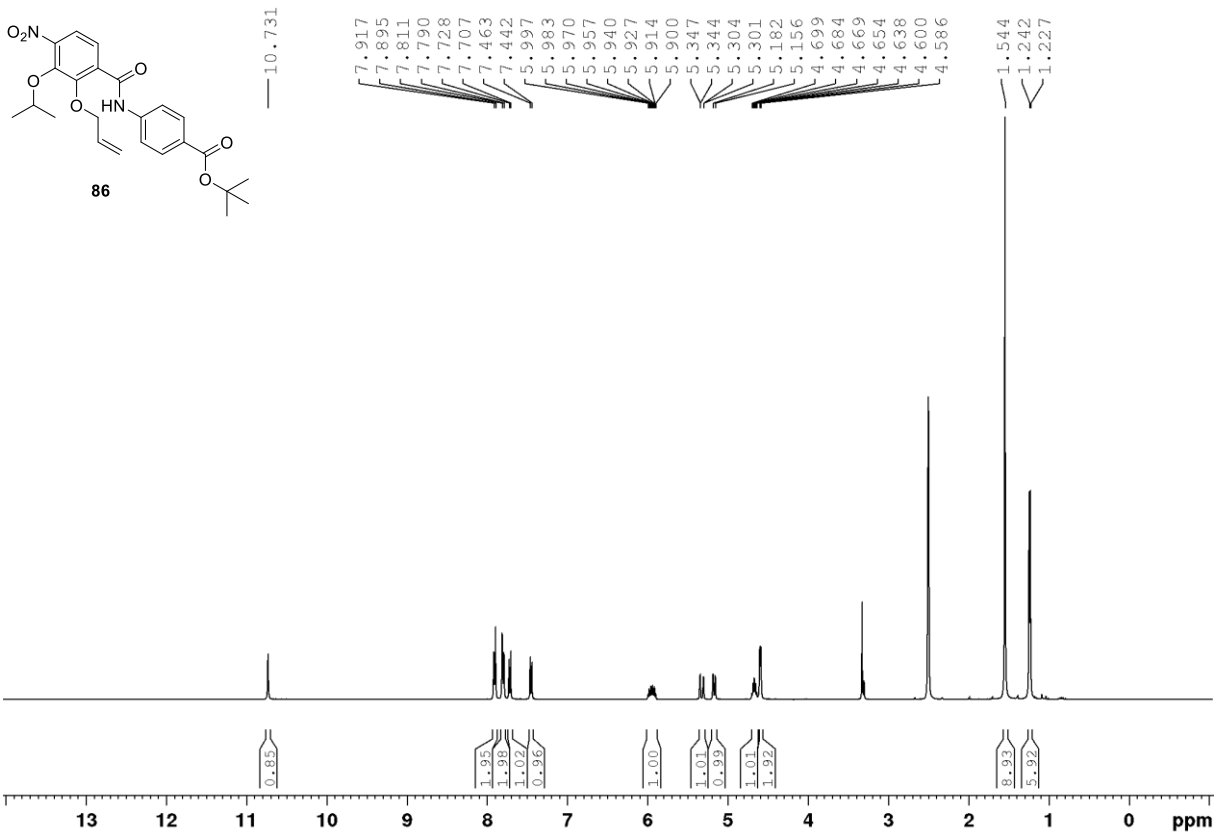

284
10.138
7.449
7.445
7.430
7.426
7.317
7.297
7.277
7.219
7.216
7.199
7.196
4.589
4.574
4.559
4.544
4.529
2.387
1.350
1.335
0.93
0.97
1.02
1.07
1.12
3.00
6.27
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

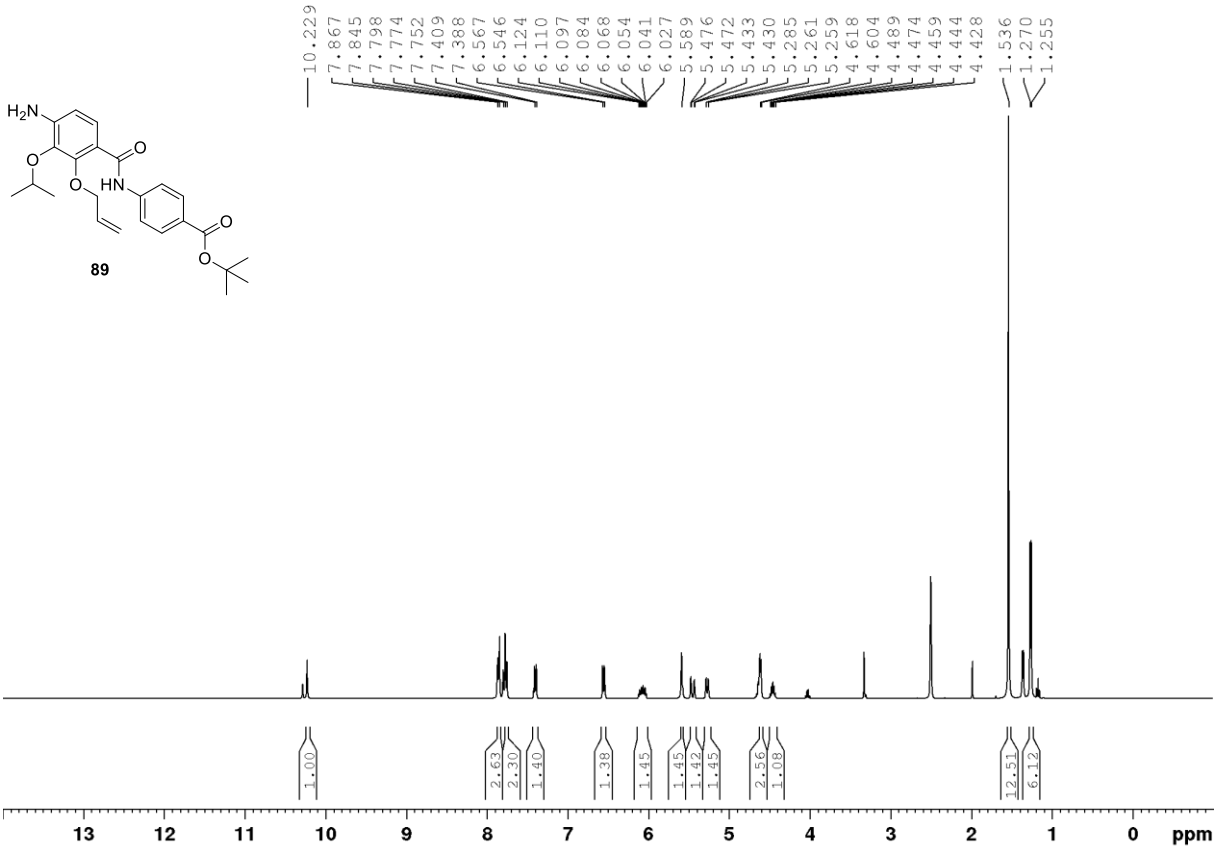

285
10.067
7.764
7.742
7.689
7.667
4.508
4.493
4.477
4.462
4.447
2.443
1.331
1.315
0.16
0.92
0.17
1.04
0.97
0.18
0.30
1.00
2.94
0.52
0.60
1.12
6.07
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

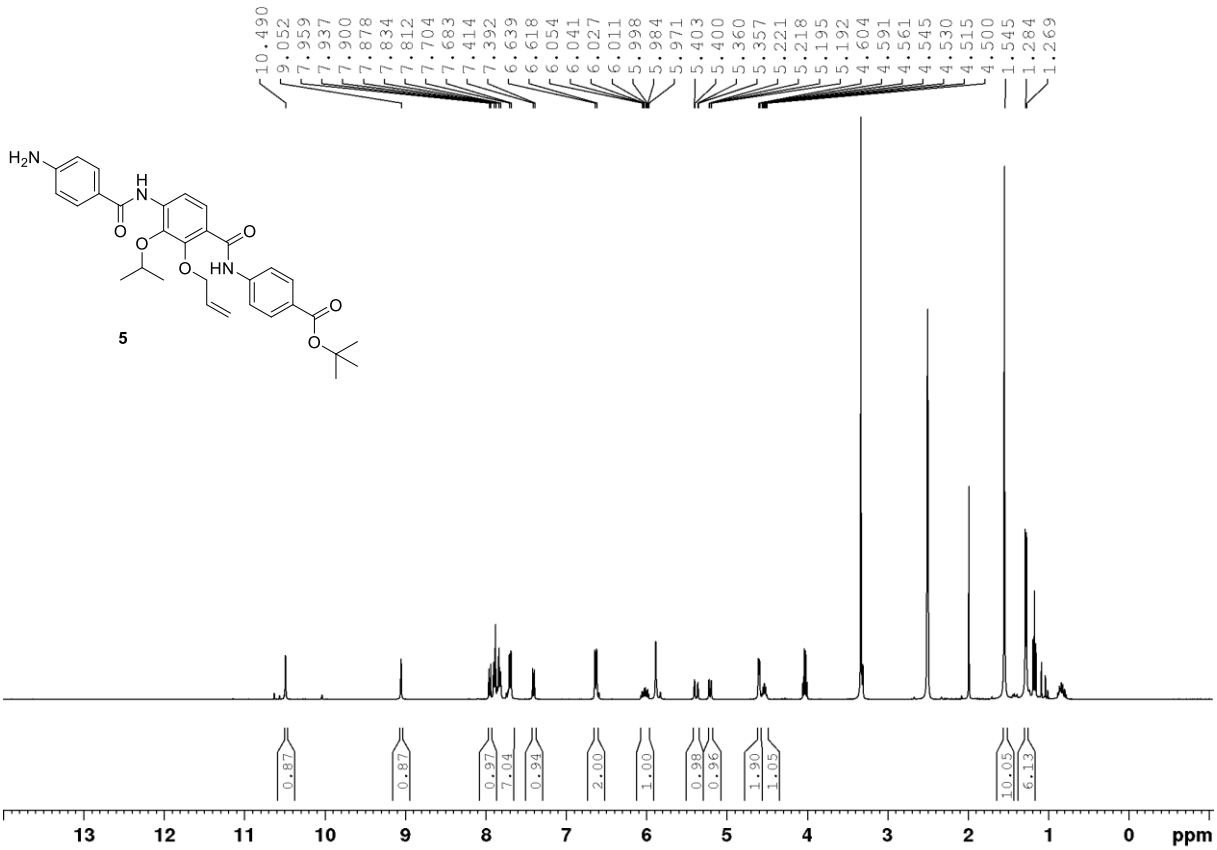

286
11.438
9.971
7.396
7.375
7.246
7.225
4.916
4.901
4.885
4.870
4.855
1.335
1.320
1.00
1.01
1.07
1.12
1.08
6.63
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

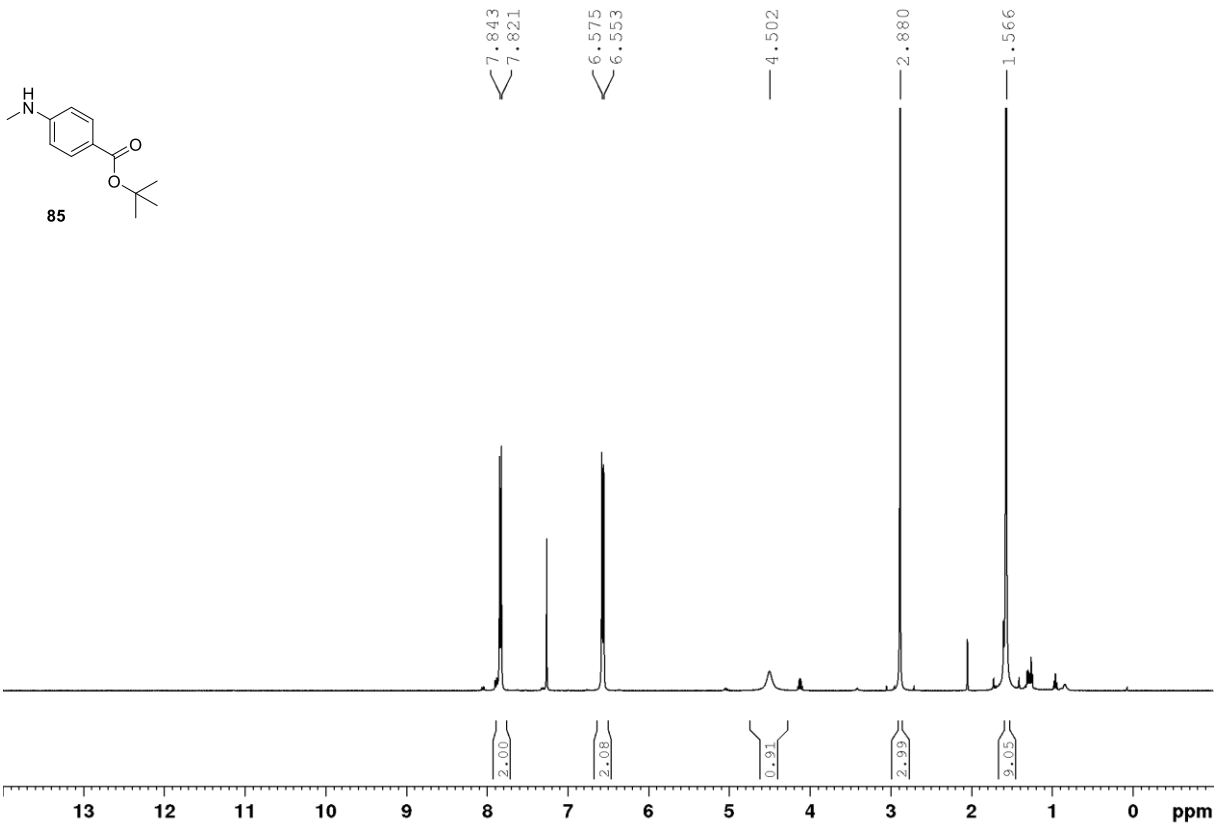

287
10.390
7.646
7.625
7.514
7.493
6.096
6.081
6.070
6.066
6.055
6.038
6.027
6.023
6.012
5.997
5.419
5.416
5.379
5.376
5.373
5.370
5.345
5.343
5.319
5.317
4.737
4.735
4.721
4.719
4.717
4.703
4.688
4.673
4.657
1.328
1.313
1.00
1.07
1.08
1.18
1.18
1.15
2.39
1.17
7.06
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

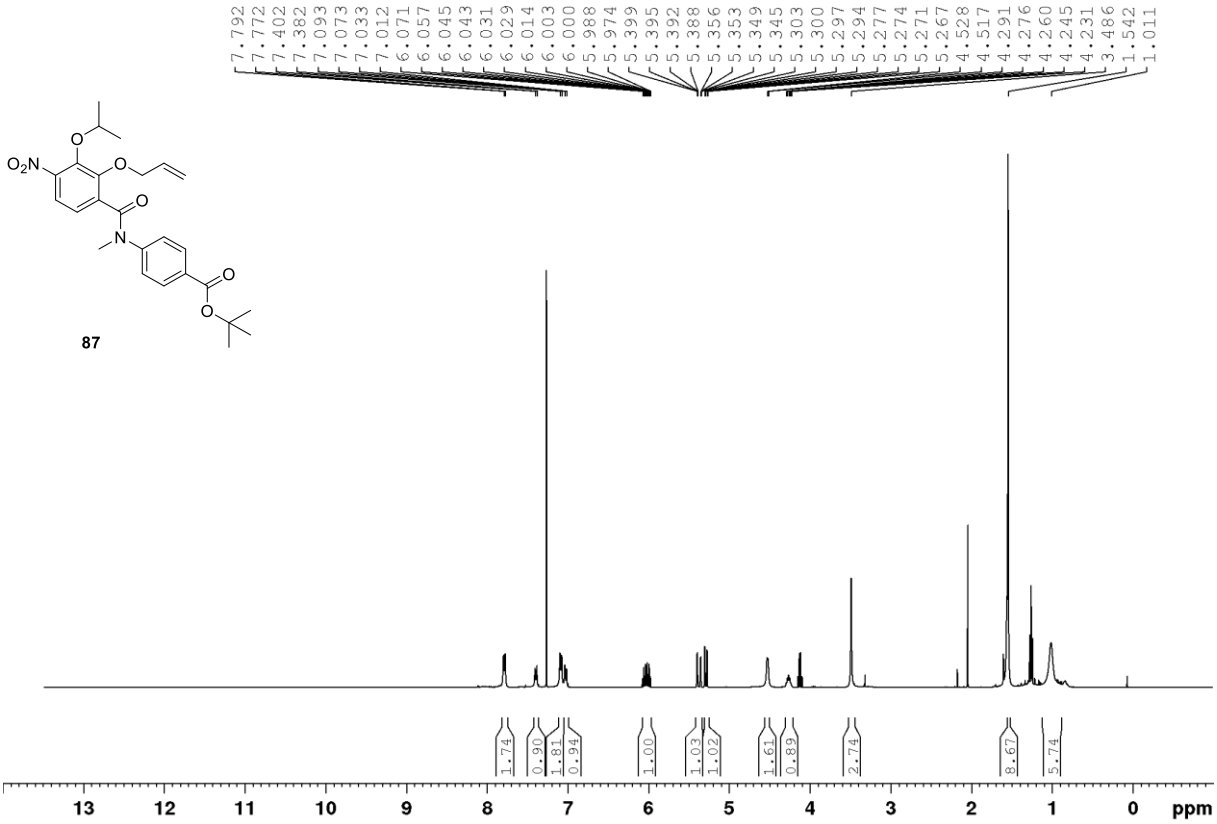

7
7.939
7.917
7.587
7.566
6.113
6.103
6.096
6.087
6.070
6.060
6.054
6.044
6.028
5.487
5.483
5.480
5.476
5.443
5.440
5.437
5.434
5.422
5.420
5.397
5.394
4.839
4.837
4.824
4.821
4.819
4.646
4.631
4.616
4.600
4.585
1.332
1.316
1.277
1.00
1.04
1.14
0.93
1.11
2.16
1.24
6.32
1.21
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


86
10.731
7.917
7.895
7.811
7.790
7.728
7.707
7.463
7.442
5.997
5.983
5.970
5.957
5.940
5.927
5.914
5.900
5.347
5.344
5.304
5.301
5.182
5.156
4.699
4.684
4.669
4.654
4.638
4.600
4.586
1.544
1.242
1.227
0.85
1.95
1.98
1.02
0.96
1.00
1.01
0.99
1.01
1.92
8.93
5.92
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

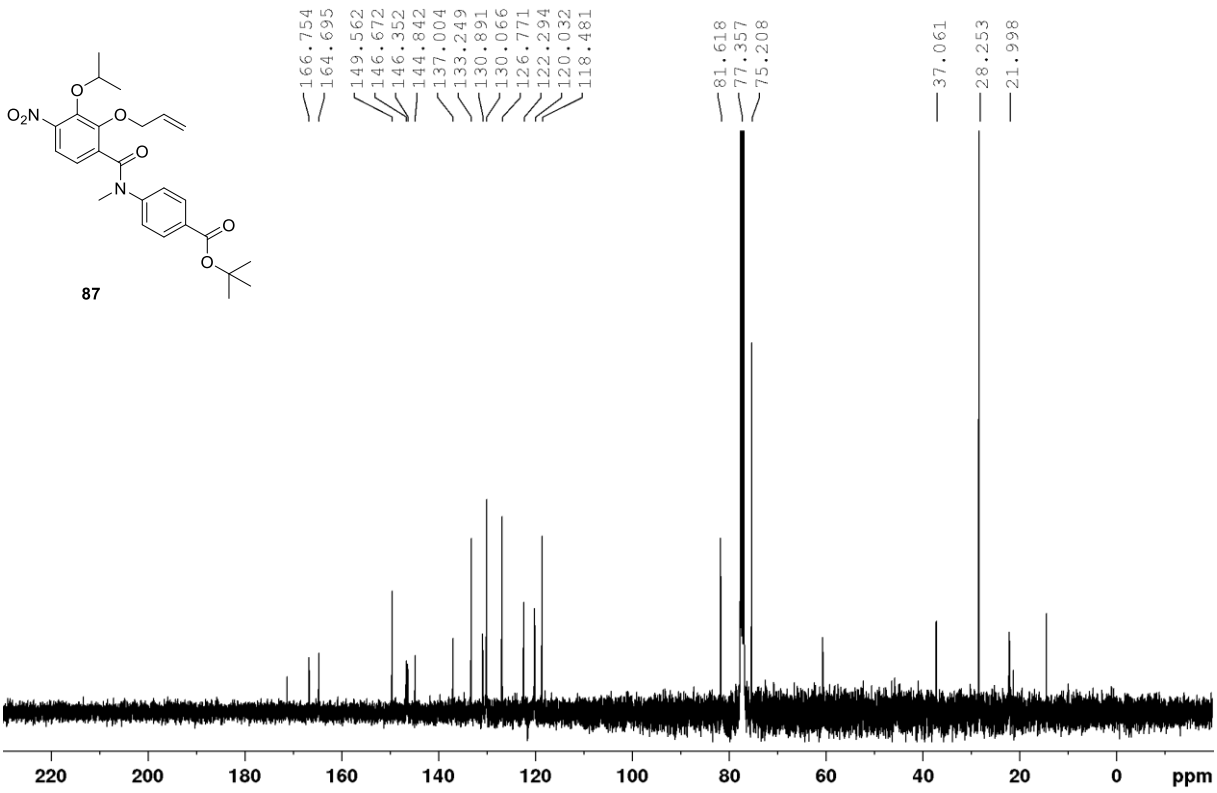

89
10.229
7.867
7.845
7.798
7.774
7.752
7.409
7.388
6.567
6.546
6.124
6.110
6.097
6.084
6.068
6.054
6.041
6.027
5.589
5.476
5.472
5.433
5.430
5.285
5.261
5.259
4.618
4.604
4.489
4.474
4.459
4.444
4.428
1.536
1.270
1.255
1.00
2.63
2.30
1.40
1.38
1.45
1.45
1.42
1.45
2.56
1.08
12.51
6.12
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm


10.490
9.052
7.959
7.937
7.900
7.878
7.834
7.812
7.704
7.683
7.414
7.392
6.639
6.618
6.054
6.041
6.027
6.011
5.998
5.984
5.971
5.403
5.400
5.360
5.357
5.221
5.218
5.195
5.192
4.604
4.591
4.561
4.545
4.530
4.515
4.500
1.545
1.284
1.269
5
0.87
0.87
0.97
7.04
0.94
2.00
1.00
0.98
0.96
1.90
1.05
10.05
6.13
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

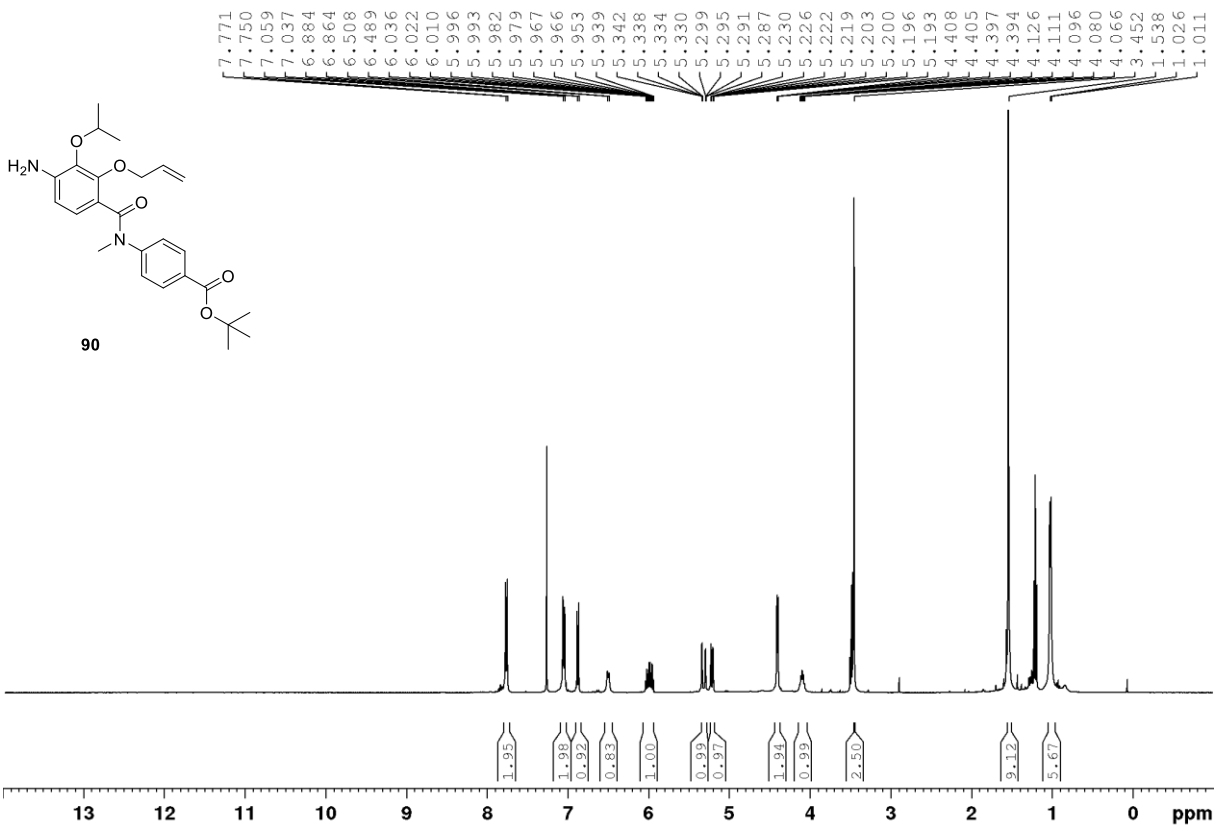

7.843
7.821
6.575
6.553
4.502
2.880
1.566
85
2.00
2.08
0.91
2.99
9.05
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

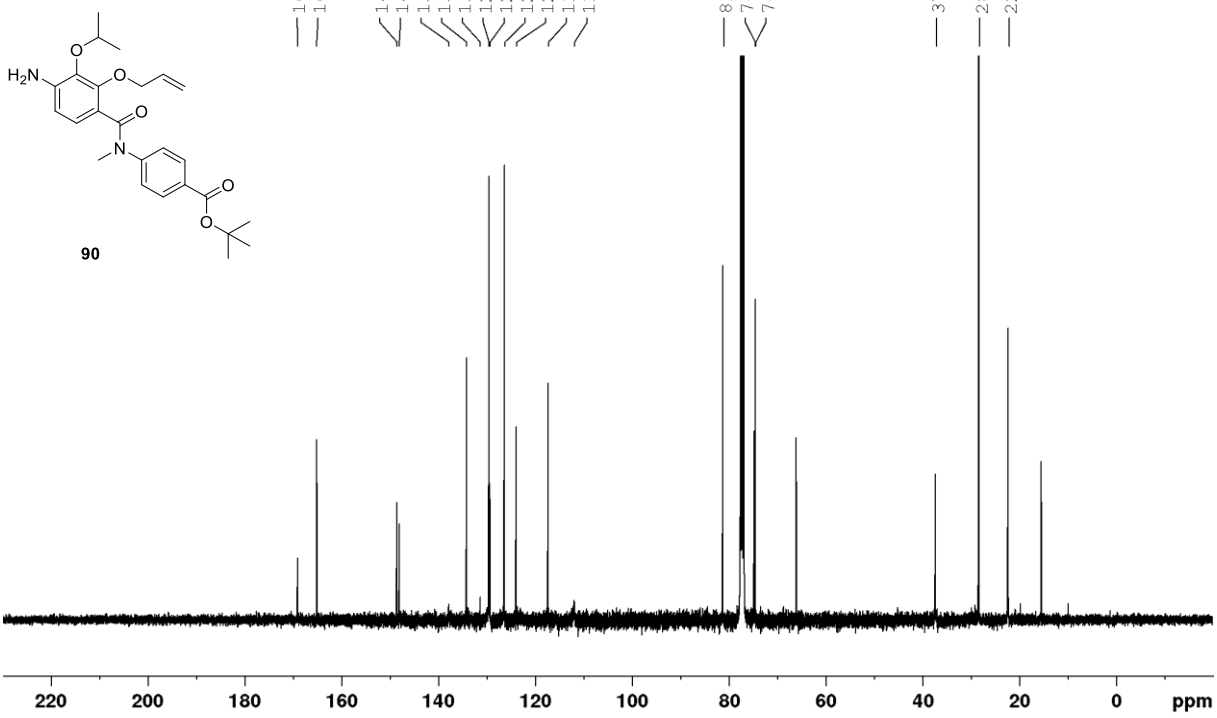

7.792
7.772
7.402
7.382
7.093
7.073
7.033
7.012
6.071
6.057
6.045
6.043
6.031
6.029
6.014
6.003
6.000
5.988
5.974
5.399
5.395
5.392
5.388
5.356
5.353
5.349
5.345
5.303
5.300
5.297
5.294
5.277
5.274
5.271
5.267
4.528
4.517
4.291
4.276
4.260
4.245
4.231
3.486
1.542
1.011
1.74
0.90
1.81
0.94
1.00
1.03
1.02
1.61
0.89
2.74
8.67
5.74
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

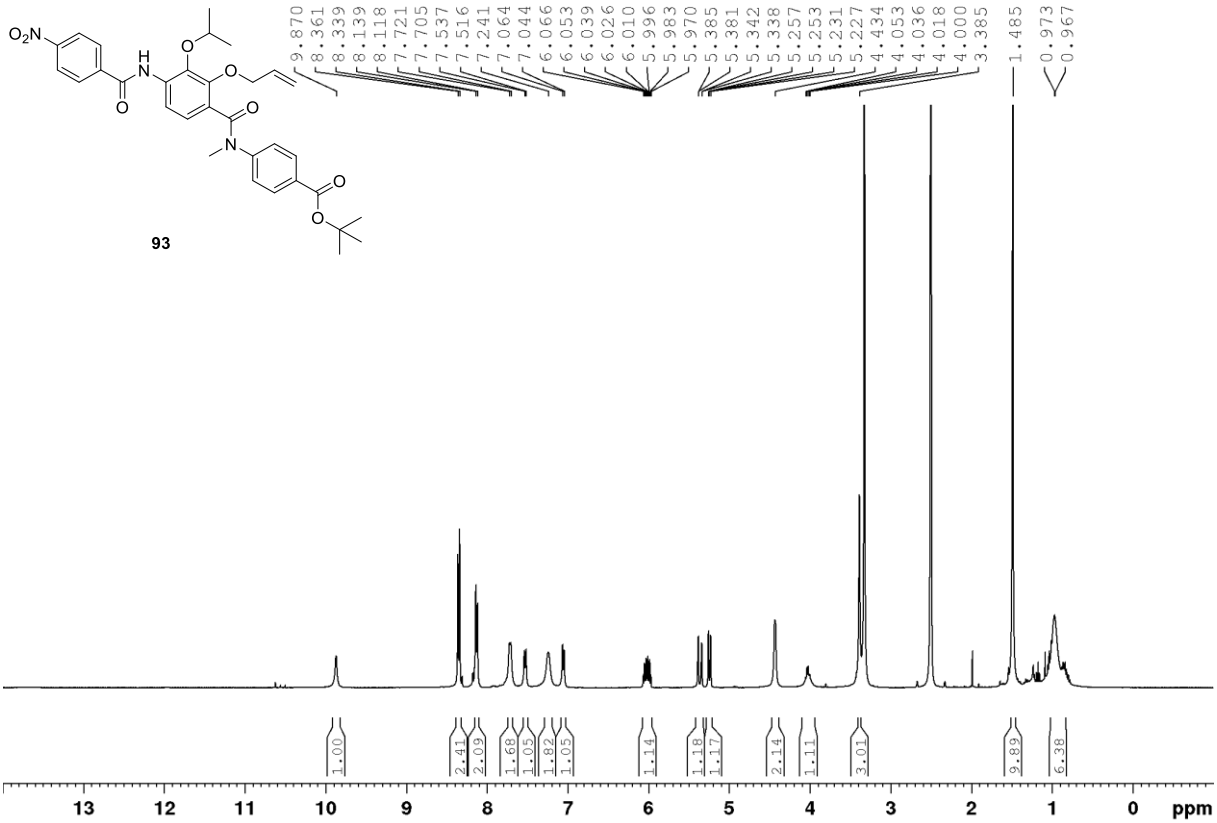
87

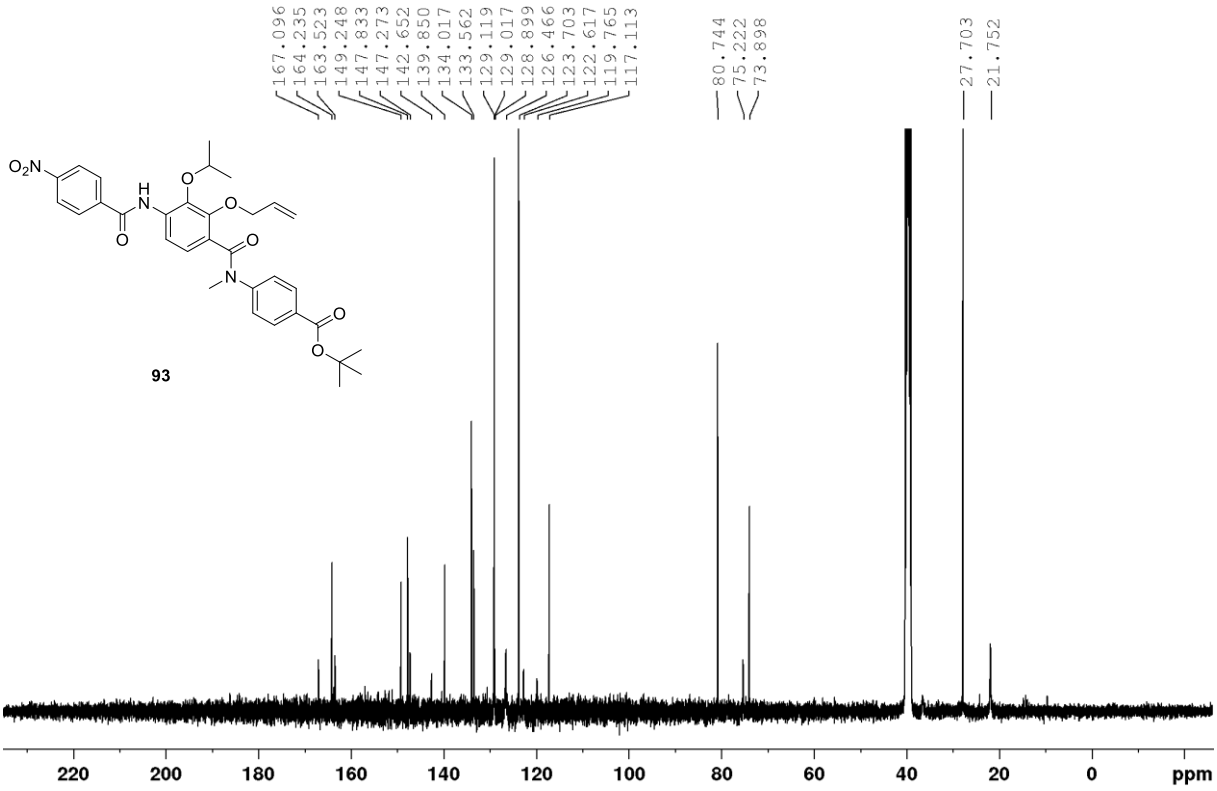

166.754
164.695
149.562
146.672
146.352
144.842
137.004
133.249
130.891
130.066
126.771
122.294
120.032
118.481
81.618
77.357
75.208
37.061
28.253
21.998
220
200
180
160
140
120
100
80
60
40
20
0
ppm

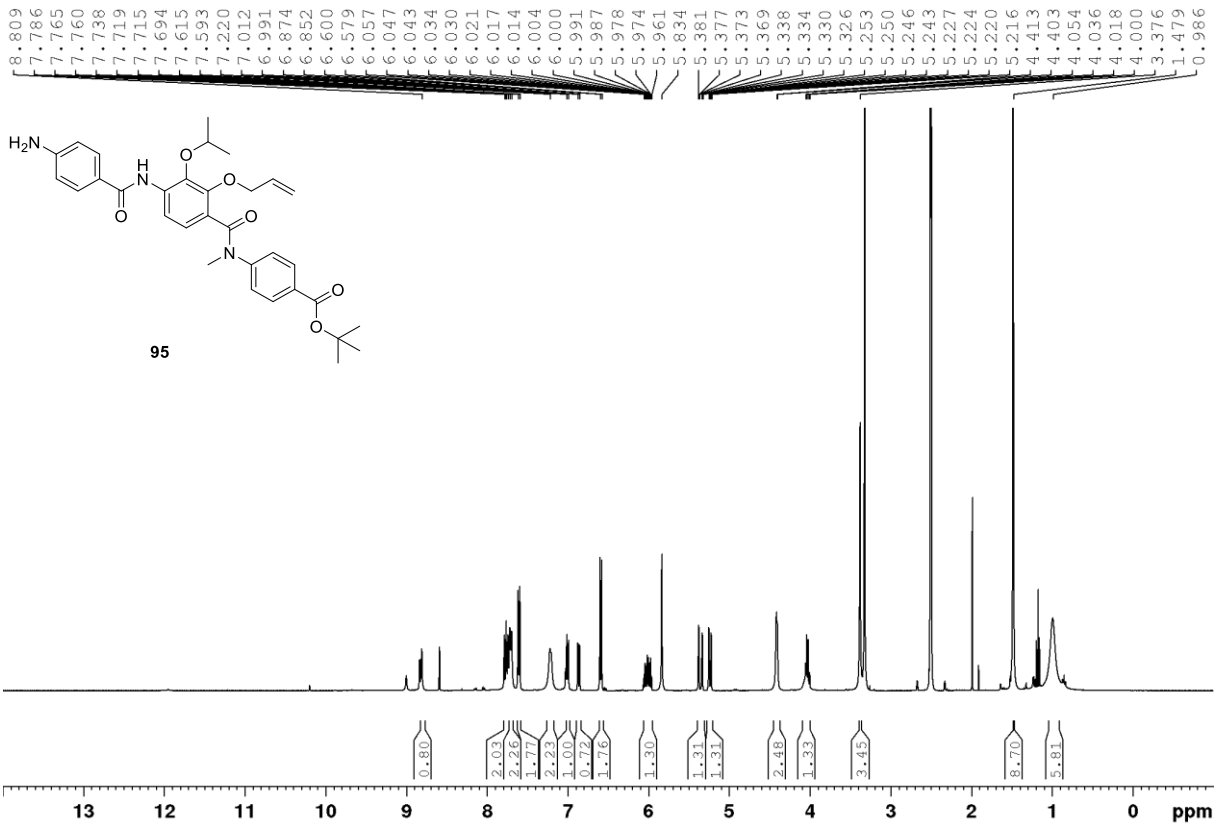
87

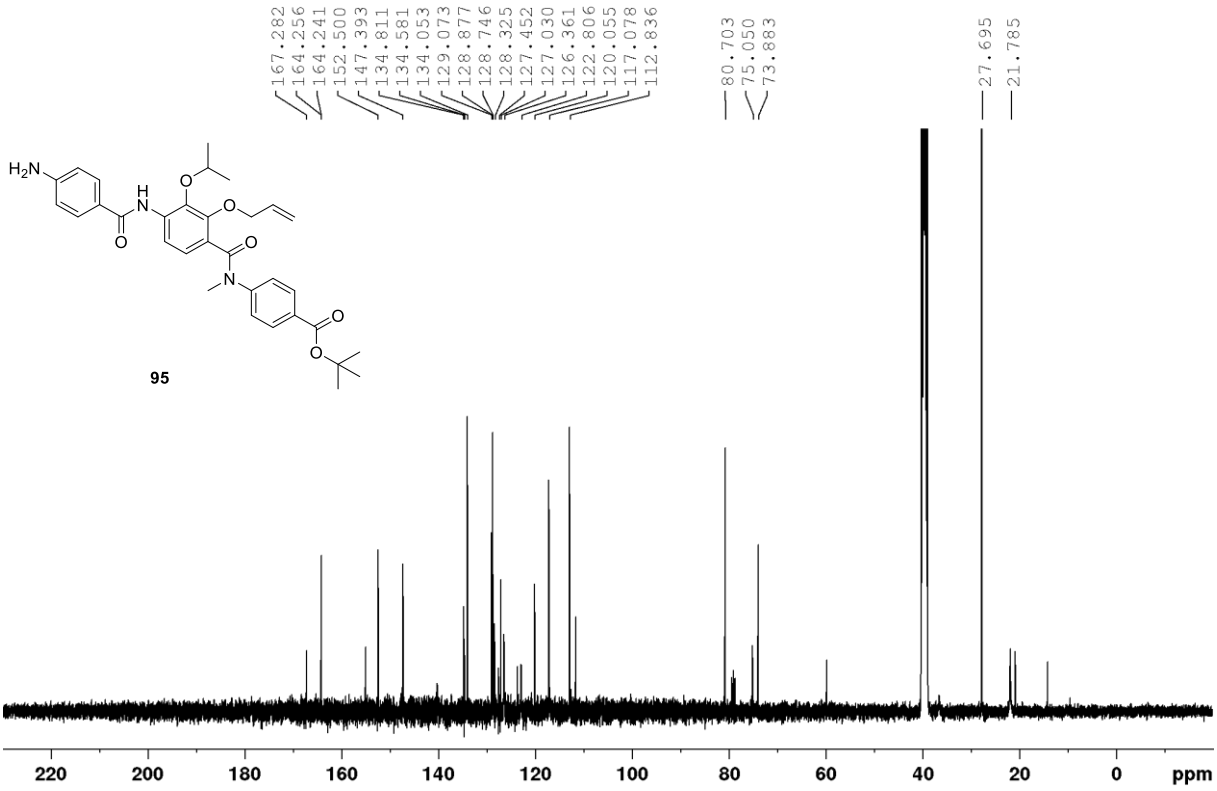

7.771
7.750
7.059
7.037
6.884
6.864
6.508
6.489
6.036
6.022
6.010
5.996
5.993
5.982
5.979
5.967
5.966
5.953
5.939
5.342
5.338
5.334
5.330
5.299
5.295
5.291
5.287
5.230
5.226
5.222
5.219
5.203
5.200
5.196
5.193
4.408
4.405
4.397
4.394
4.126
4.111
4.096
4.080
4.066
3.452
1.538
1.026
1.011
1.95
1.98
0.92
0.83
1.00
0.99
0.97
1.94
0.99
2.50
9.12
5.67
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

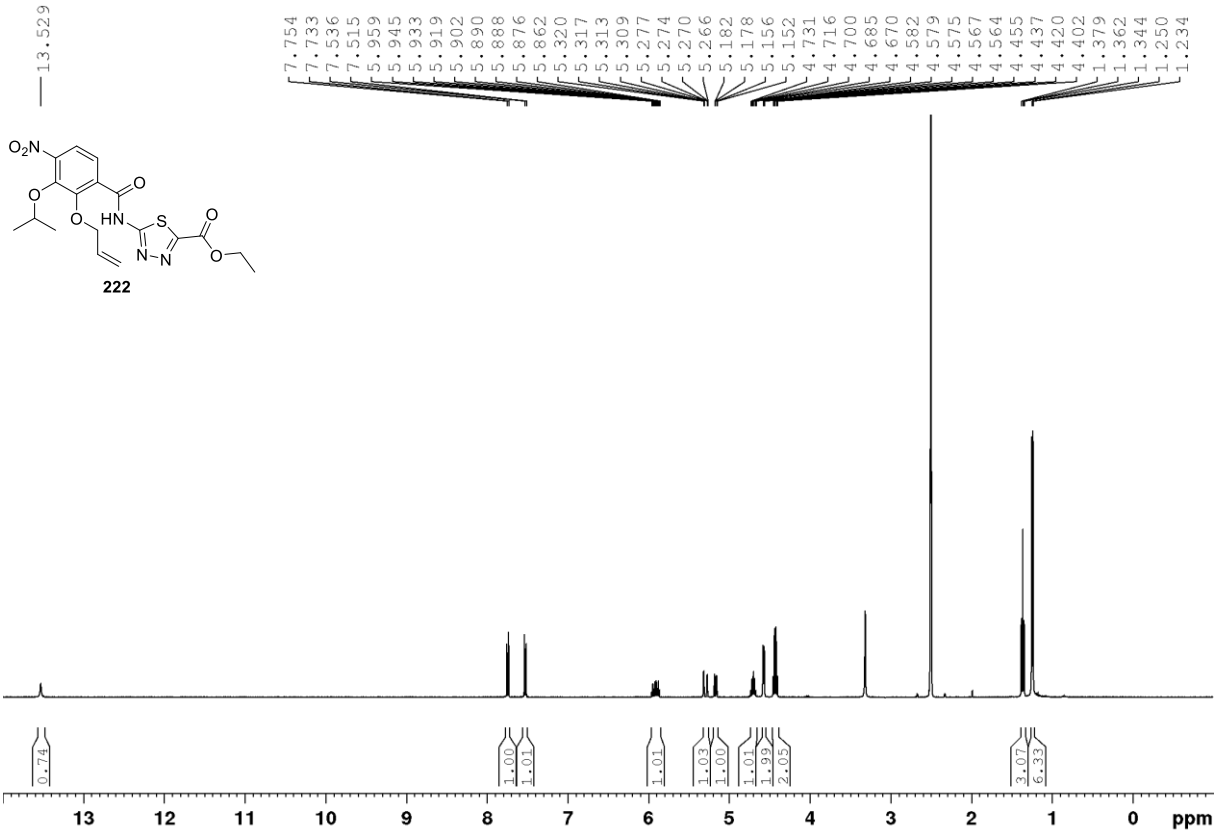

169.130
165.159
148.649
148.122
137.915
134.213
131.442
129.588
129.391
126.303
123.886
117.253
111.921
81.156
74.697
74.476
37.257
28.283
22.250
220
200
180
160
140
120
100
80
60
40
20
0
ppm

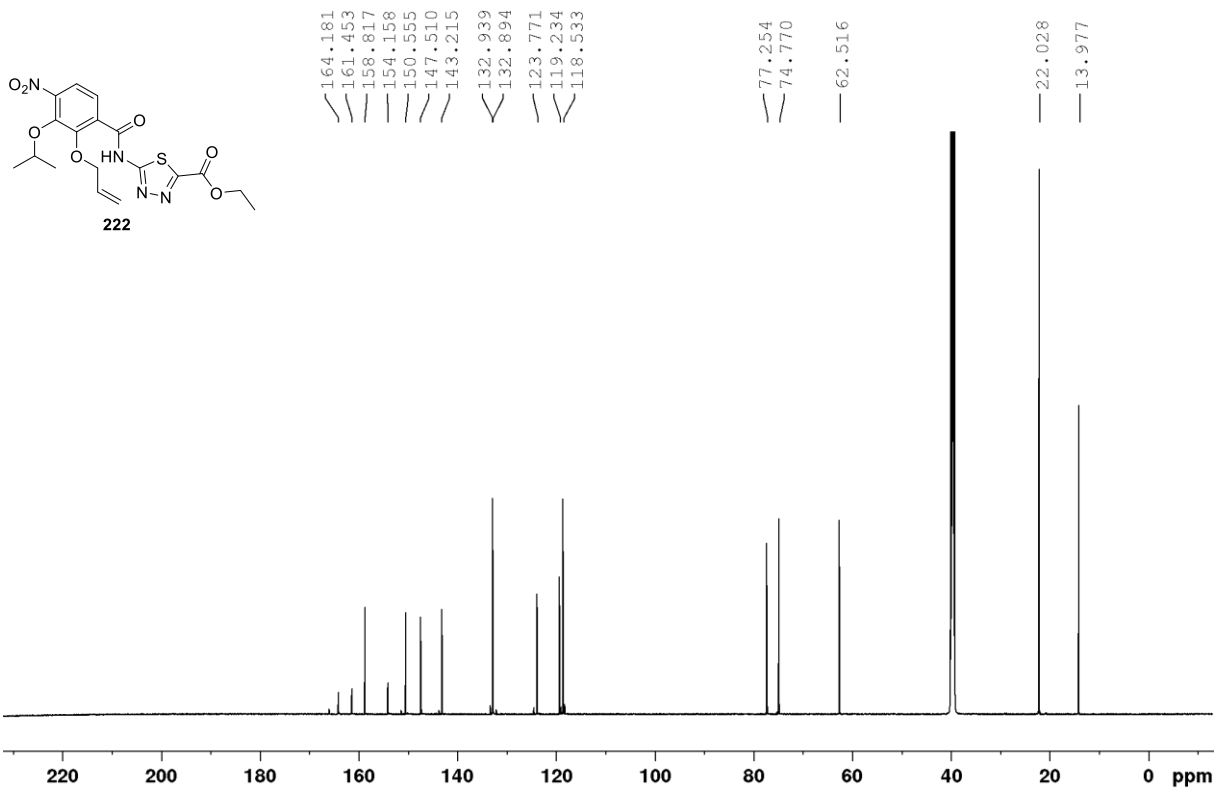

9.870
8.361
8.339
8.139
8.118
7.721
7.705
7.537
7.516
7.241
7.064
7.044
6.066
6.053
6.039
6.026
6.010
5.996
5.983
5.970
5.385
5.381
5.342
5.338
5.257
5.253
5.231
5.227
4.434
4.053
4.036
4.018
4.000
3.385
1.485
0.973
0.967
1.00
2.41
2.09
1.68
1.05
1.82
1.05
1.14
1.18
1.17
2.14
1.11
3.01
9.89
6.38
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
93

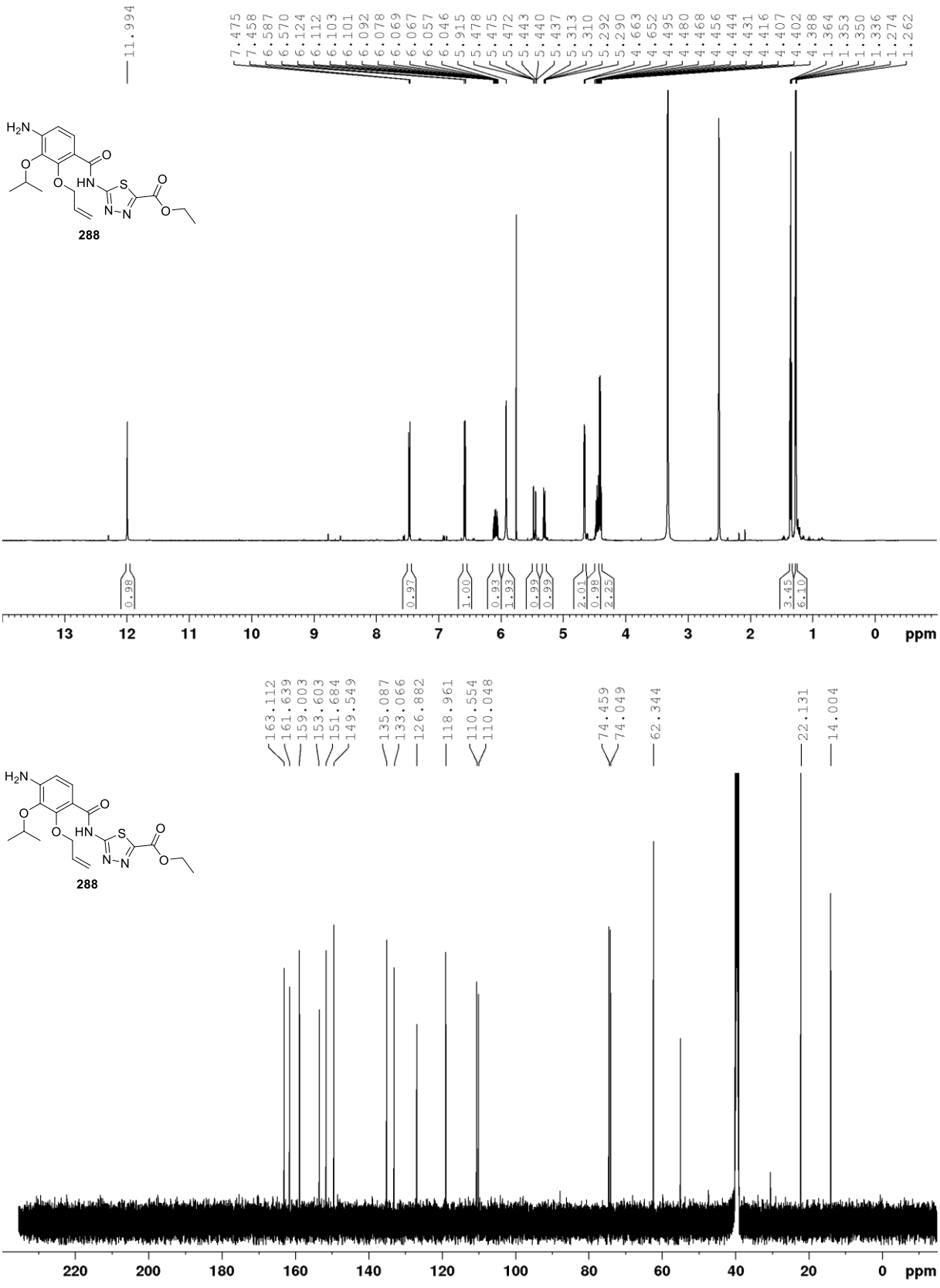

167.096
164.235
163.523
149.248
147.833
147.273
142.652
139.850
134.017
133.562
129.119
129.017
128.899
126.466
123.703
122.617
119.765
117.113
80.744
75.222
73.898
27.703
21.752
220
200
180
160
140
120
100
80
60
40
20
0
ppm
93

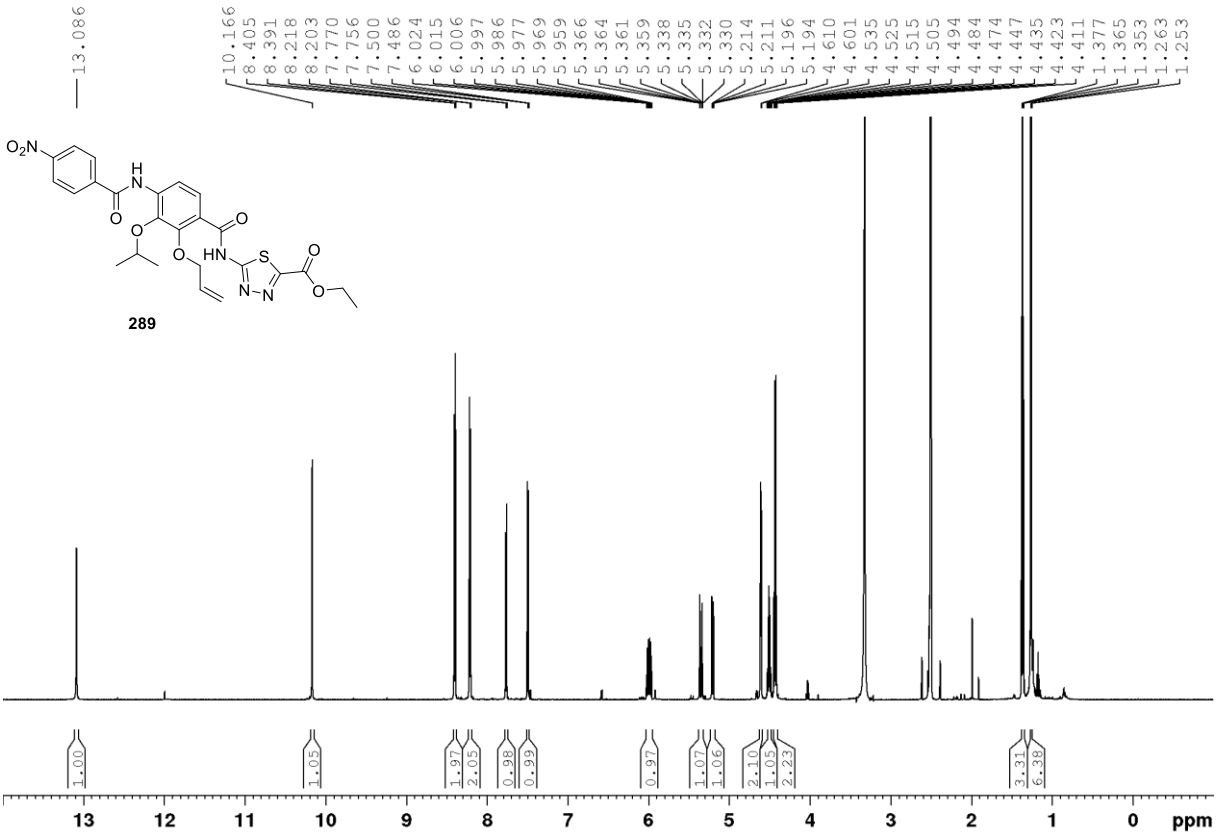

8.809
7.786
7.765
7.760
7.738
7.719
7.715
7.694
7.615
7.593
7.220
7.012
6.991
6.874
6.852
6.600
6.579
6.057
6.047
6.043
6.034
6.030
6.021
6.017
6.014
6.004
6.000
5.991
5.987
5.978
5.974
5.961
5.834
5.381
5.377
5.373
5.369
5.338
5.334
5.330
5.326
5.253
5.250
5.246
5.243
5.227
5.224
5.220
5.216
4.413
4.403
4.054
4.036
4.018
4.000
3.376
1.479
0.986
H2N
O
H
N
O
O
O
N
O
O
95
0.80
2.03
2.26
1.77
2.23
1.00
0.72
1.76
1.30
1.31
1.31
2.48
1.33
3.45
8.70
5.81
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

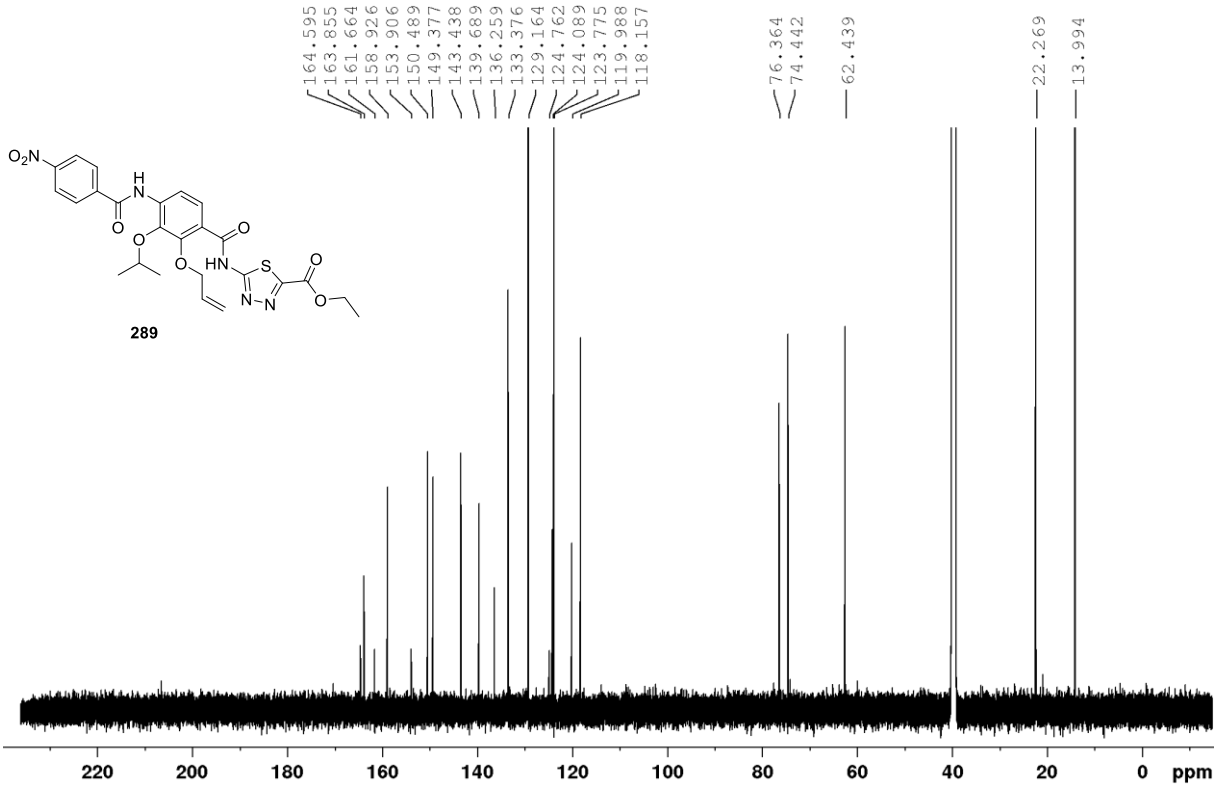

167.282
164.256
164.241
152.500
147.393
134.811
134.581
134.053
129.073
128.877
128.746
128.325
127.452
127.030
126.361
122.806
120.055
117.078
112.836
80.703
75.050
73.883
27.695
21.785
H2N
O
H
N
O
O
O
N
O
O
95
220
200
180
160
140
120
100
80
60
40
20
0
ppm

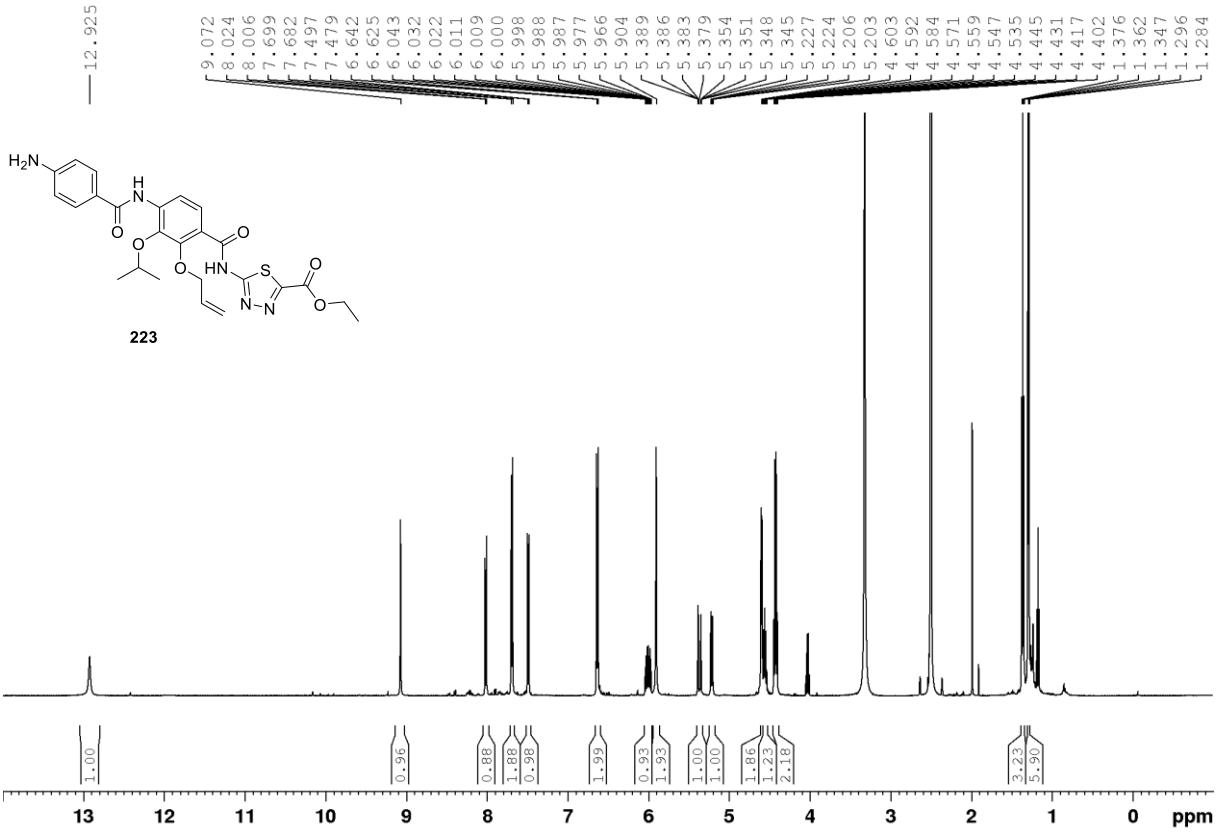

13.529
7.754
7.733
7.536
7.515
5.959
5.945
5.933
5.919
5.902
5.890
5.888
5.876
5.862
5.320
5.317
5.313
5.309
5.277
5.274
5.270
5.266
5.182
5.178
5.156
5.152
4.731
4.716
4.700
4.685
4.670
4.582
4.579
4.575
4.567
4.564
4.455
4.437
4.420
4.402
1.379
1.362
1.344
1.250
1.234
222
0.74
1.00
1.01
1.01
1.03
1.00
1.01
1.98
2.05
3.07
6.33
ppm

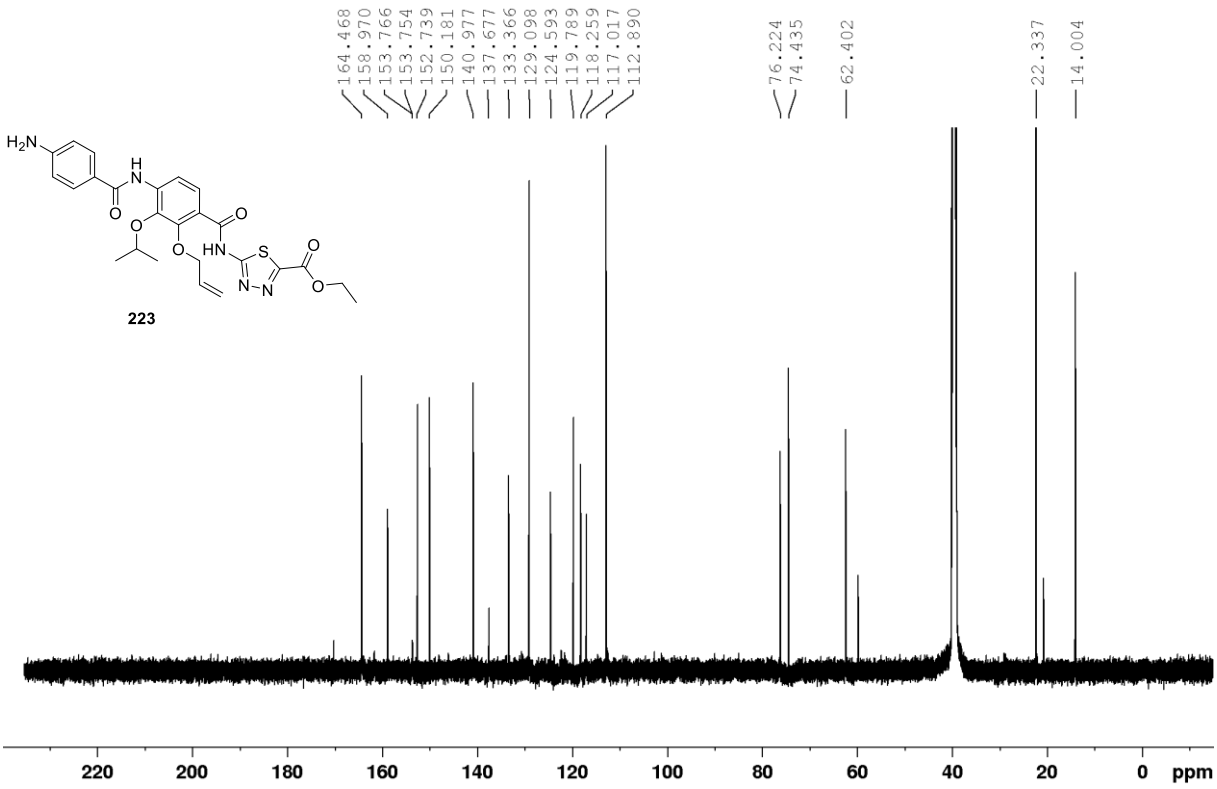

164.181
161.453
158.817
154.158
150.555
147.510
143.215
132.939
132.894
123.771
119.234
118.533
77.254
74.770
62.516
22.028
13.977
222
ppm

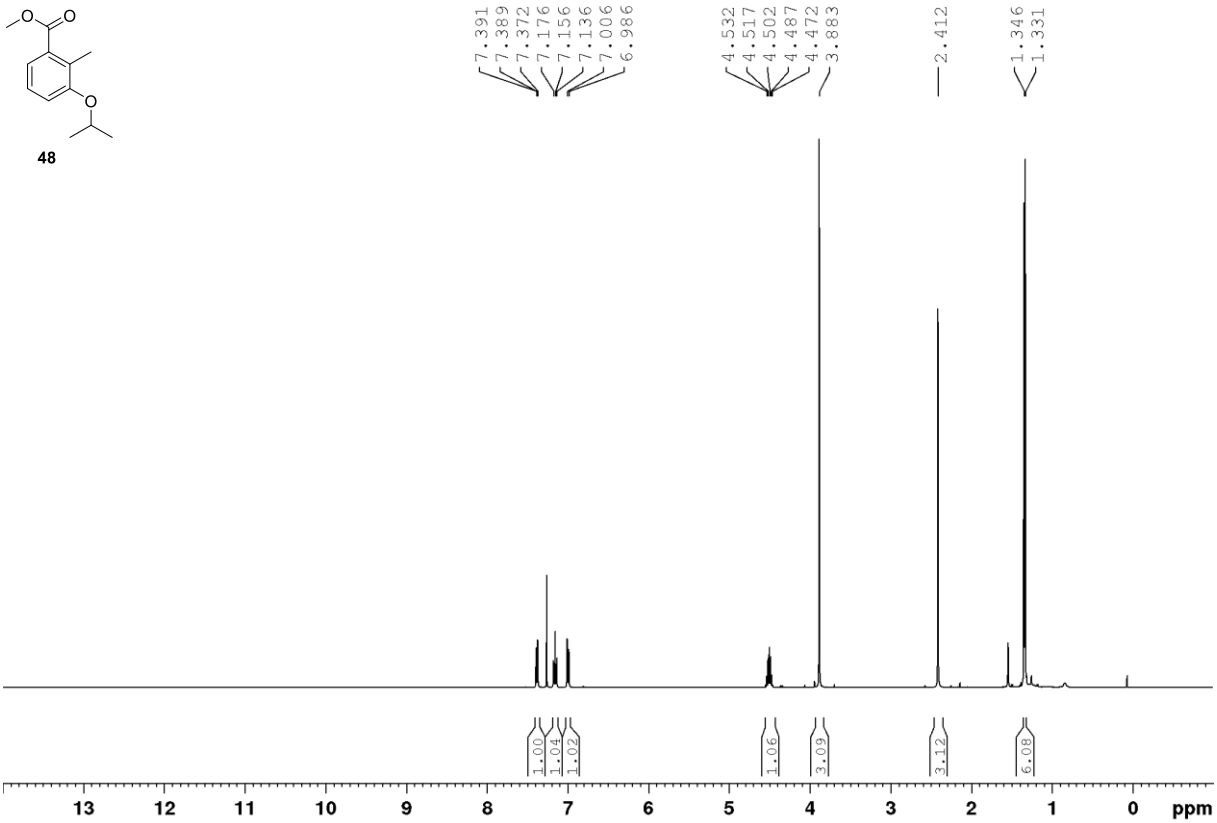

11.994
7.475
7.458
6.587
6.570
6.124
6.112
6.103
6.101
6.092
6.078
6.069
6.067
6.057
6.046
5.915
5.478
5.475
5.472
5.443
5.440
5.437
5.313
5.310
5.292
5.290
4.663
4.652
4.495
4.480
4.468
4.456
4.444
4.431
4.416
4.407
4.402
4.388
1.364
1.353
1.350
1.336
1.274
1.262
0.98
0.97
1.00
0.93
1.93
0.99
0.99
2.01
0.98
2.25
3.45
6.10
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
288
163.112
161.639
159.003
153.603
151.684
149.549
135.087
133.066
126.882
118.961
110.554
110.048
74.459
74.049
62.344
22.131
14.004
220
200
180
160
140
120
100
80
60
40
20
0
ppm
288

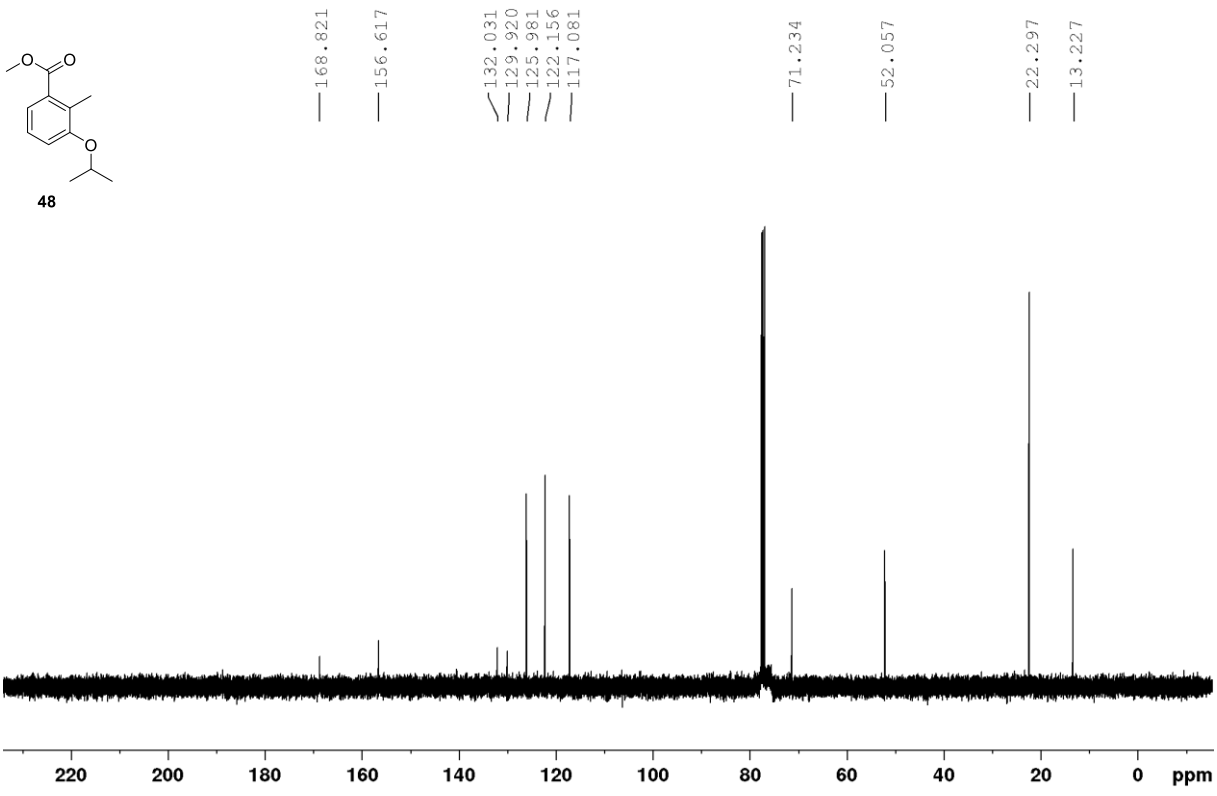

13.086
10.166
8.405
8.391
8.218
8.203
7.770
7.756
7.500
7.486
6.024
6.015
6.006
5.997
5.986
5.977
5.969
5.959
5.366
5.364
5.361
5.359
5.338
5.335
5.332
5.330
5.214
5.211
5.196
5.194
4.610
4.601
4.535
4.525
4.515
4.505
4.494
4.484
4.474
4.447
4.435
4.423
4.411
1.377
1.365
1.353
1.263
1.253
289
1.00
1.05
1.97
2.05
0.98
0.99
0.97
1.07
1.06
2.10
1.05
2.23
3.31
6.38
ppm

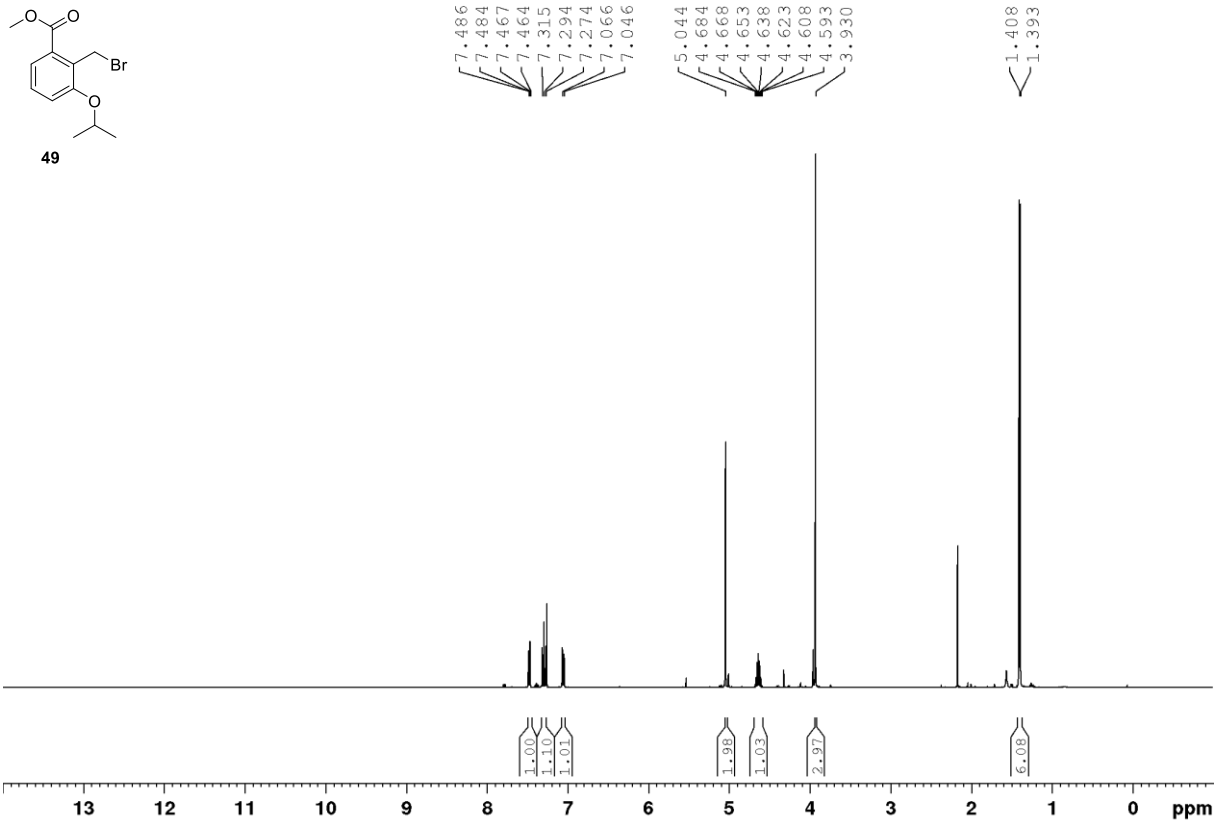

164.595
163.855
161.664
158.926
153.906
150.489
149.377
143.438
139.689
136.259
133.376
129.164
124.762
124.089
123.775
119.988
118.157
76.364
74.442
62.439
22.269
13.994
289
ppm

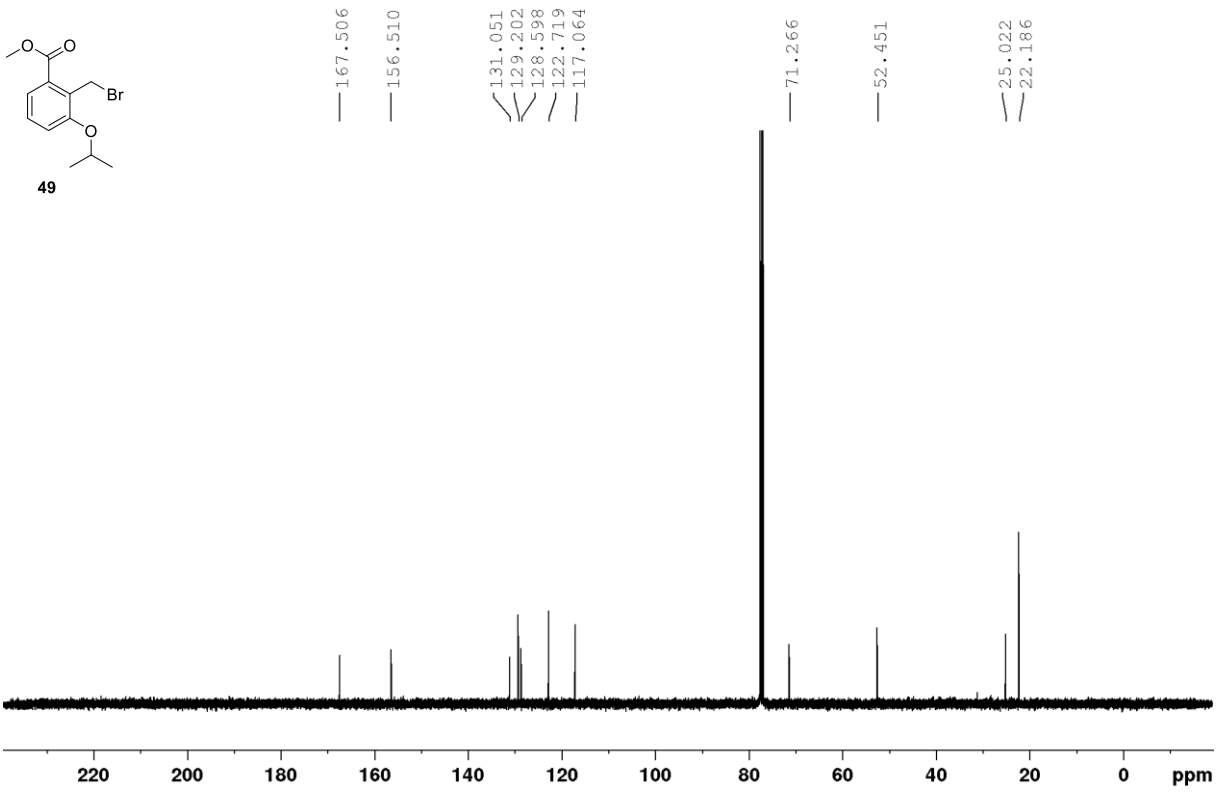

12.925
9.072
8.024
8.006
7.699
7.682
7.497
7.479
6.642
6.625
6.043
6.032
6.022
6.011
6.009
6.000
5.998
5.988
5.987
5.977
5.966
5.904
5.389
5.386
5.383
5.379
5.354
5.351
5.348
5.345
5.227
5.224
5.206
5.203
4.603
4.592
4.584
4.571
4.559
4.547
4.535
4.445
4.431
4.417
4.402
1.376
1.362
1.347
1.296
1.284
223
1.00
0.96
0.88
1.88
0.98
1.99
0.93
1.93
1.00
1.00
1.86
1.23
2.18
3.23
5.90
ppm

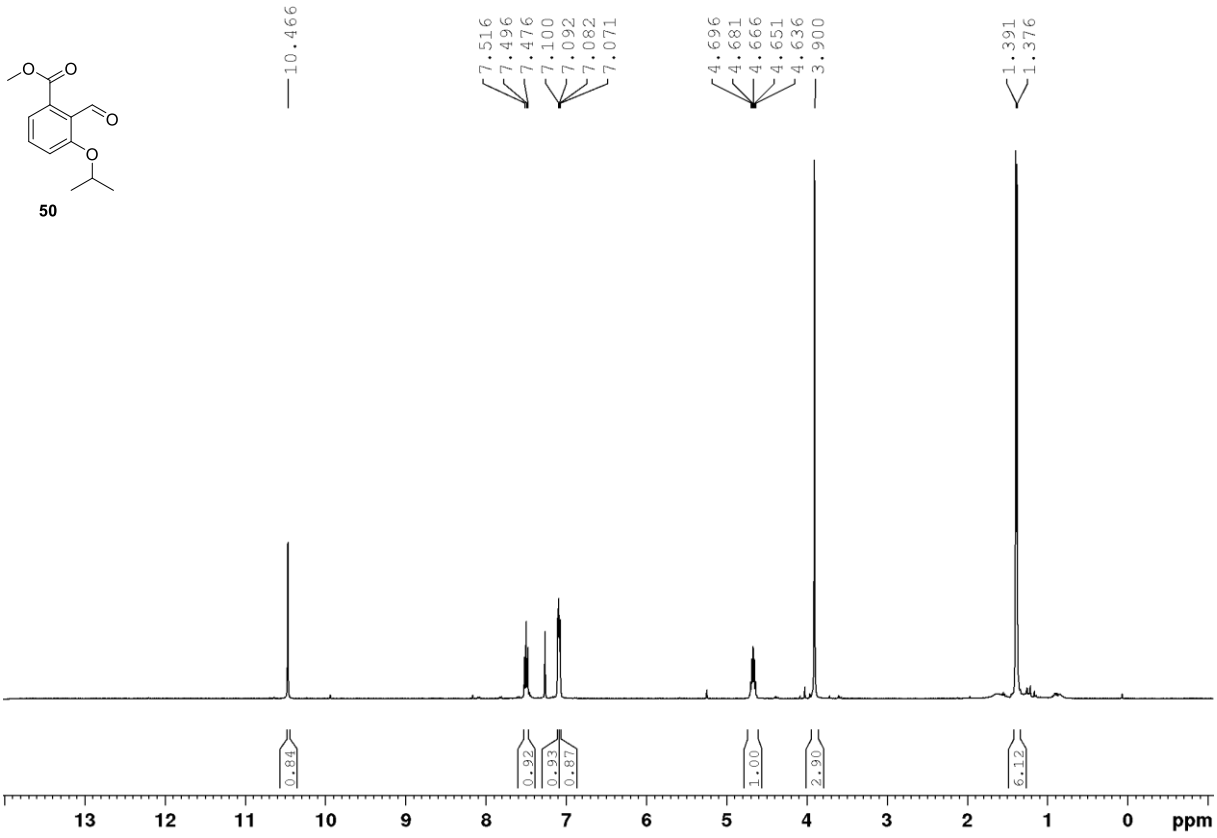

164.468
158.970
153.766
153.754
152.739
150.181
140.977
137.677
133.366
129.098
124.593
119.789
118.259
117.017
112.890
76.224
74.435
62.402
22.337
14.004
223
ppm

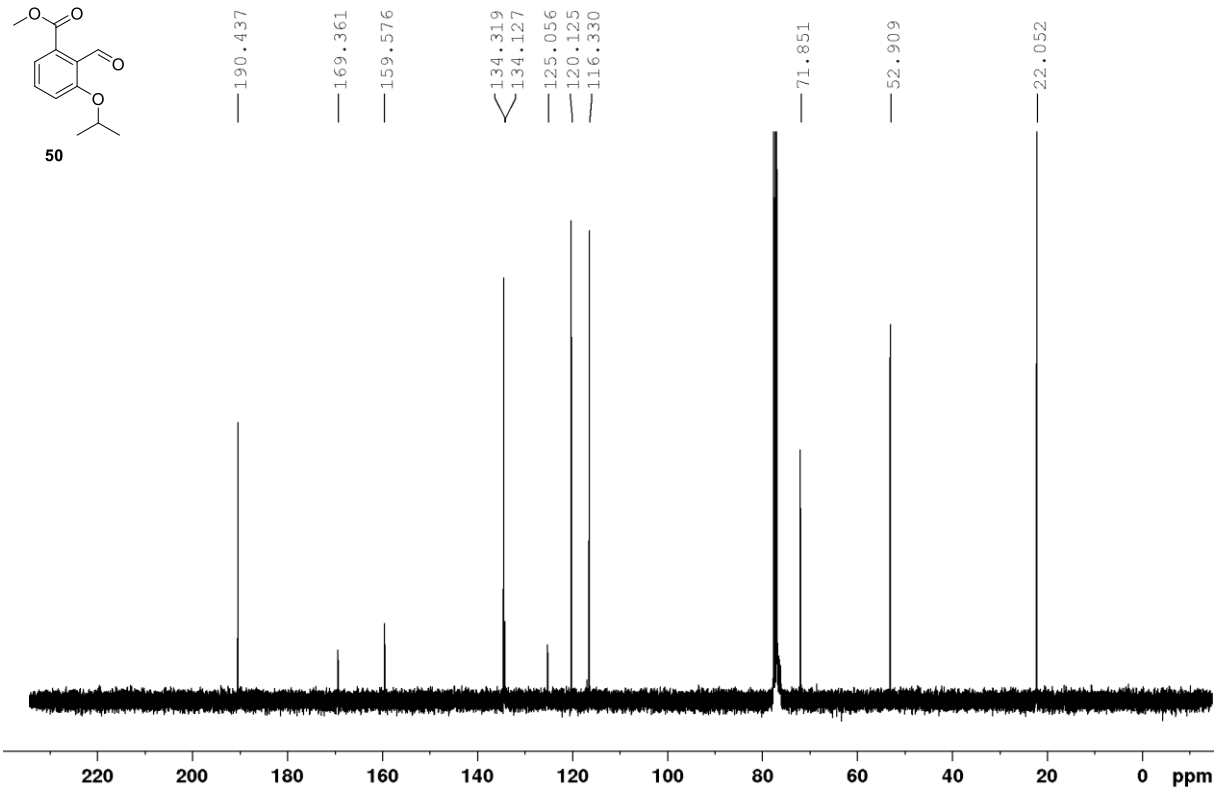

48
7.391
7.389
7.372
7.176
7.156
7.136
7.006
6.986
4.532
4.517
4.502
4.487
4.472
3.883
2.412
1.346
1.331
1.00
1.04
1.02
1.06
3.09
3.12
6.08
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

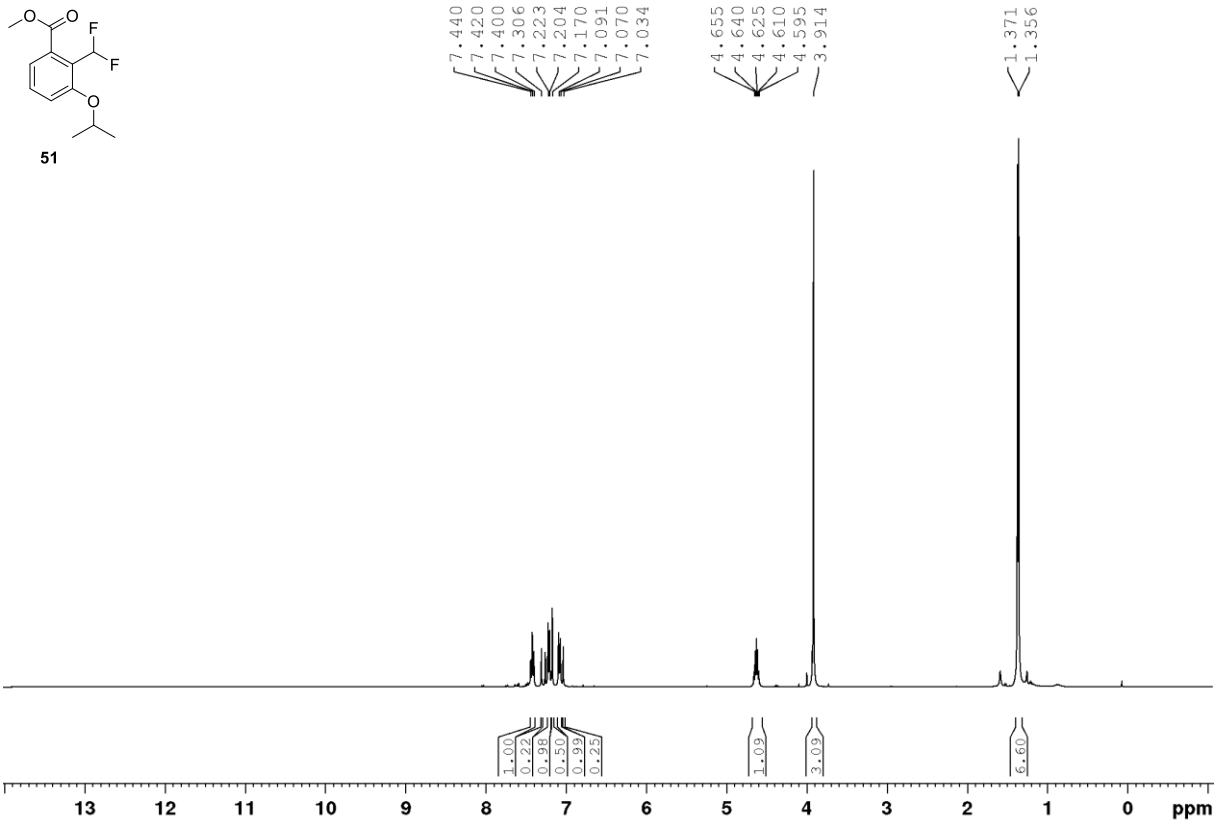

48
168.821
156.617
132.031
129.920
125.981
122.156
117.081
71.234
52.057
22.297
13.227
220
200
180
160
140
120
100
80
60
40
20
0
ppm

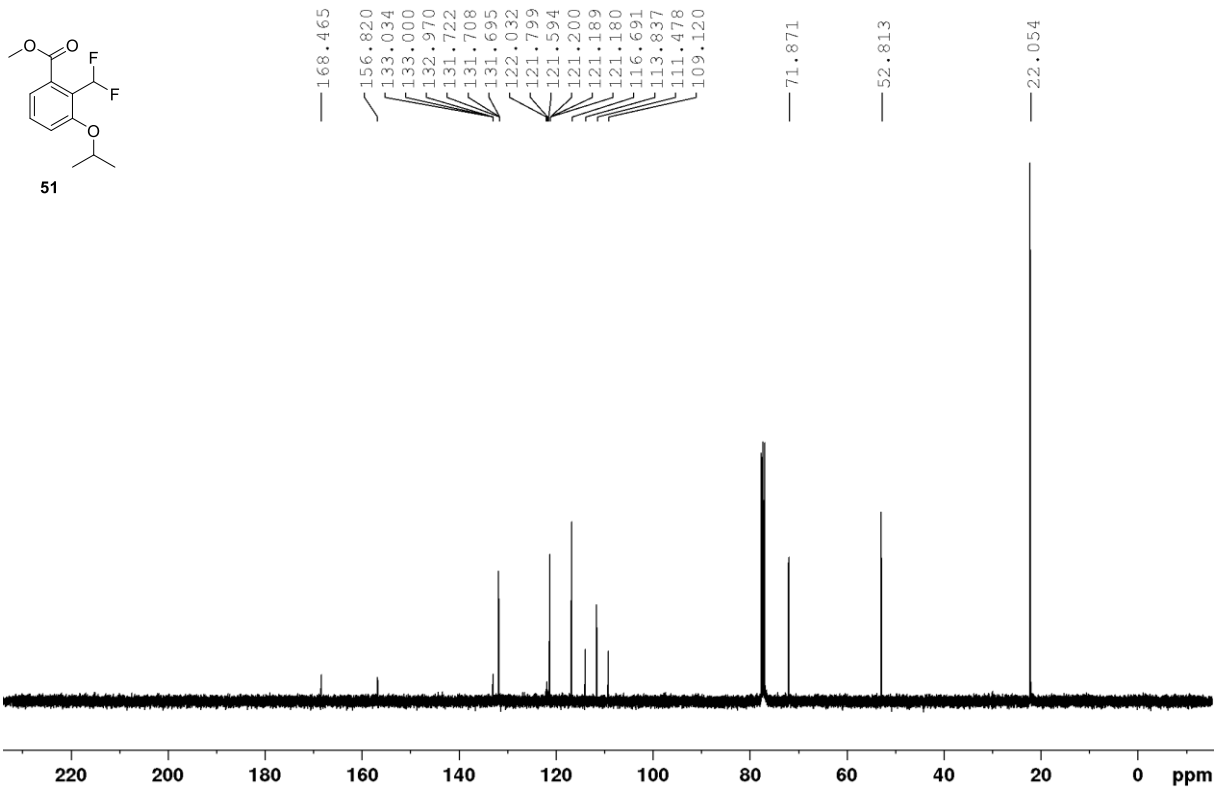

49
7.486
7.484
7.467
7.464
7.315
7.294
7.274
7.066
7.046
5.044
4.684
4.668
4.653
4.638
4.623
4.608
4.593
3.930
1.408
1.393
1.00
1.10
1.01
1.98
1.03
2.97
6.08
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

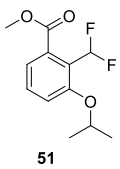

49
167.506
156.510
131.051
129.202
128.598
122.719
117.064
71.266
52.451
25.022
22.186
220
200
180
160
140
120
100
80
60
40
20
0
ppm


50
10.466
7.516
7.496
7.476
7.100
7.092
7.082
7.071
4.696
4.681
4.666
4.651
4.636
3.900
1.391
1.376
0.84
0.92
0.93
0.87
1.00
2.90
6.12
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


50
190.437
169.361
159.576
134.319
134.127
125.056
120.125
116.330
71.851
52.909
22.052
220
200
180
160
140
120
100
80
60
40
20
0
ppm

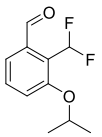

51
7.440
7.420
7.400
7.306
7.223
7.204
7.170
7.091
7.070
7.034
4.655
4.640
4.625
4.610
4.595
3.914
1.371
1.356
1.00
0.22
0.98
0.50
0.99
0.25
1.09
3.09
6.60
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


51
168.465
156.820
133.034
133.000
132.970
131.722
131.708
131.695
122.032
121.799
121.594
121.200
121.189
121.180
116.691
113.837
111.478
109.120
71.871
52.813
22.054
220
200
180
160
140
120
100
80
60
40
20
0
ppm



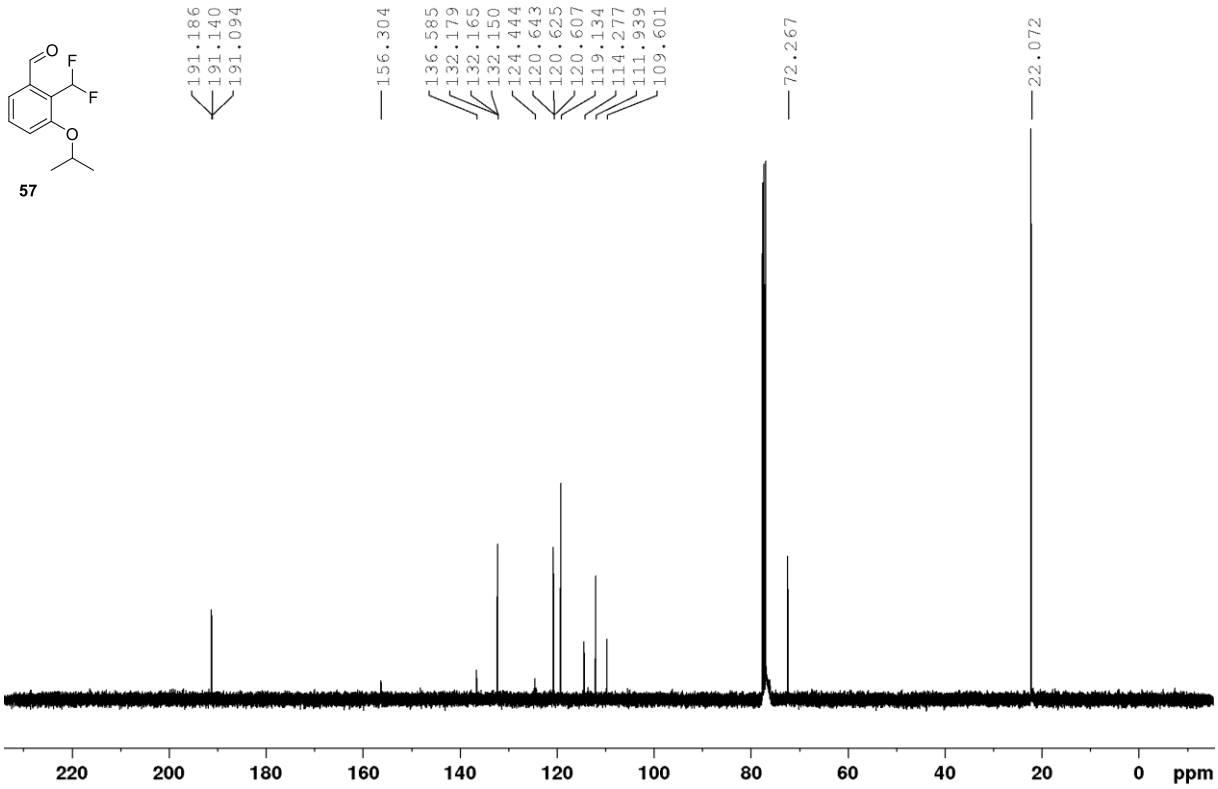
51

-114.666
-114.811
2.00
-112
-113
-114
-115
-116
-117
-118
-119
-120
ppm

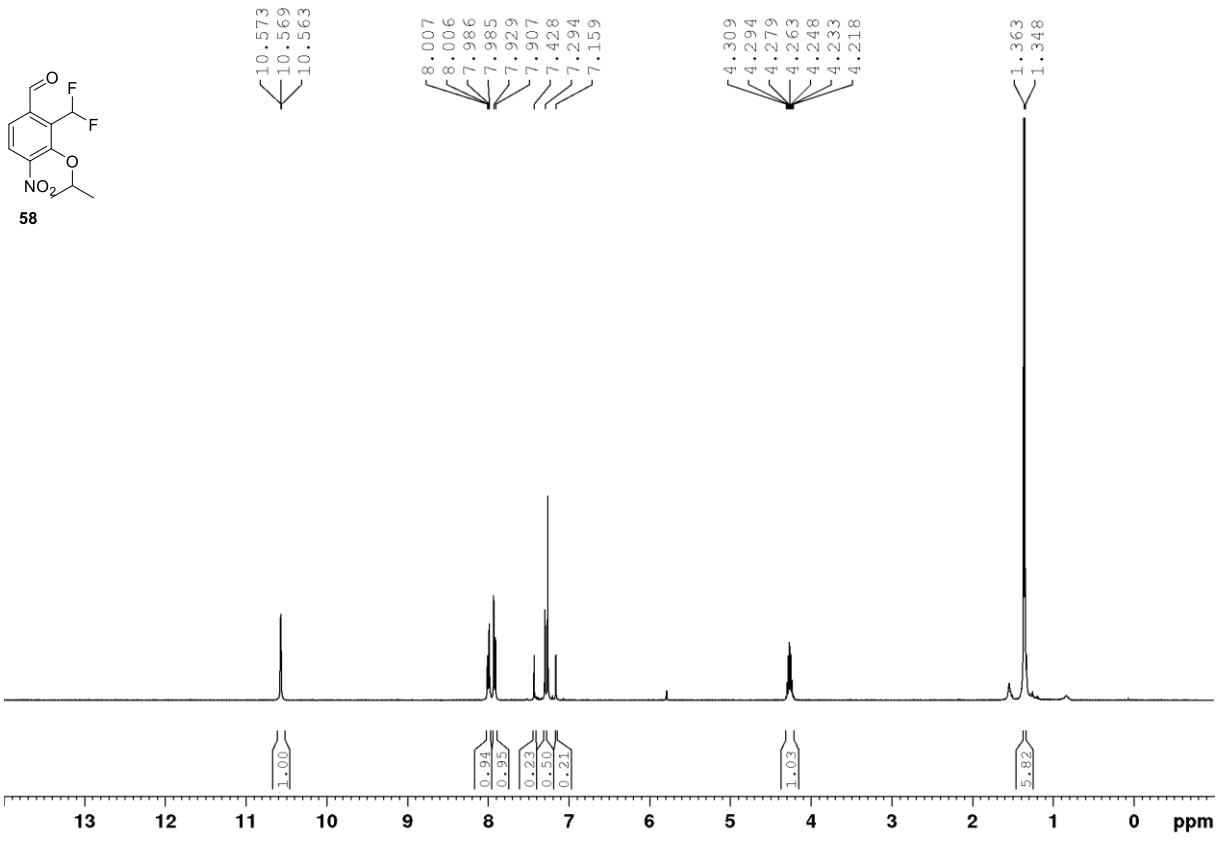


57

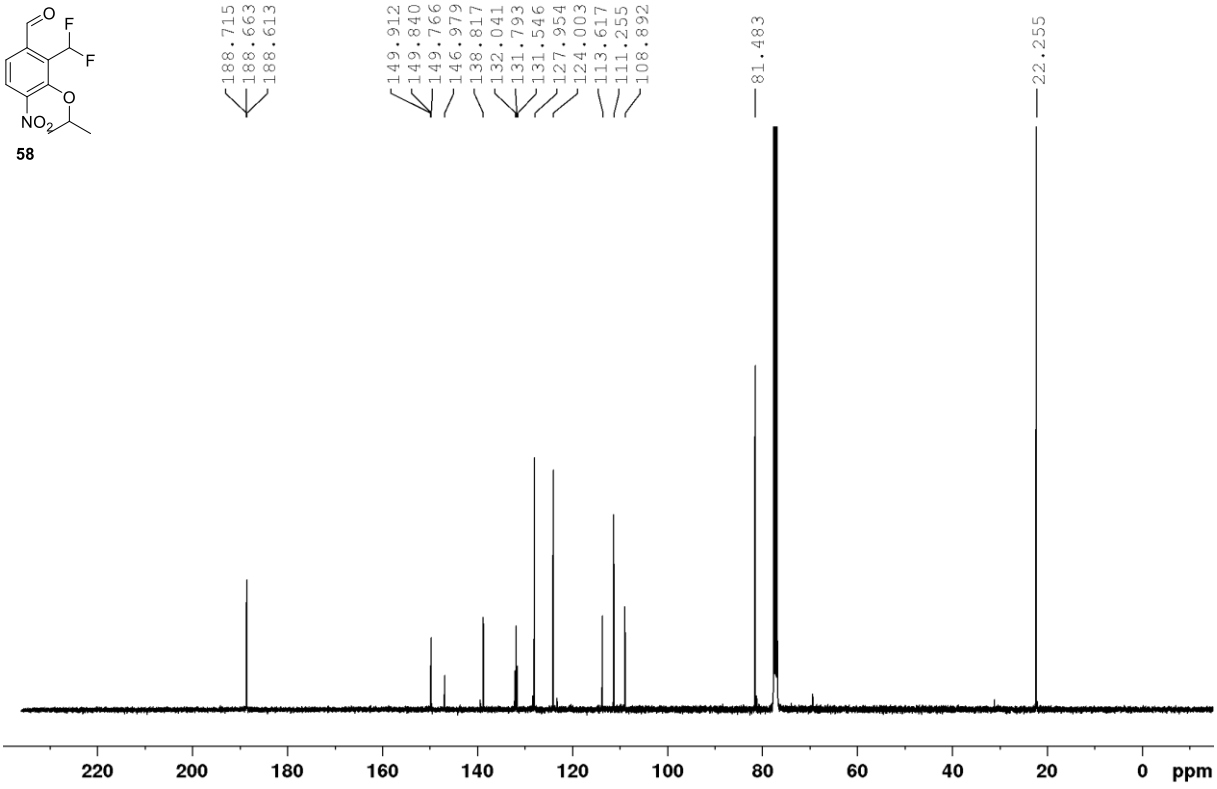
10.553
10.548
10.543
7.642
7.623
7.534
7.513
7.504
7.494
7.368
7.232
7.193
7.173
4.674
4.659
4.644
4.629
4.613
4.598
4.583
1.391
1.376
1.00
1.03
1.37
0.50
0.28
1.09
1.18
6.26
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

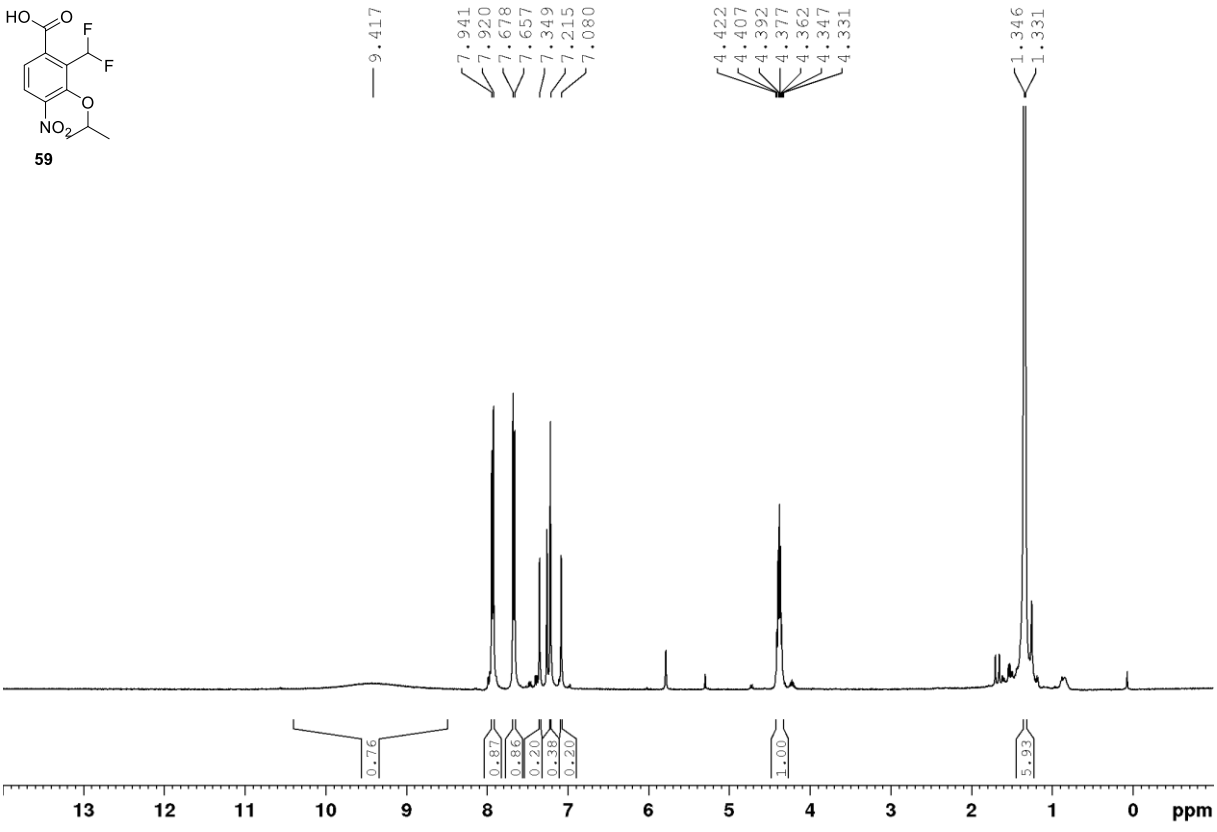

191.186
191.140
191.094
156.304
136.585
132.179
132.165
132.150
124.444
120.643
120.625
120.607
119.134
114.277
111.939
109.601
72.267
22.072
220
200
180
160
140
120
100
80
60
40
20
0
ppm

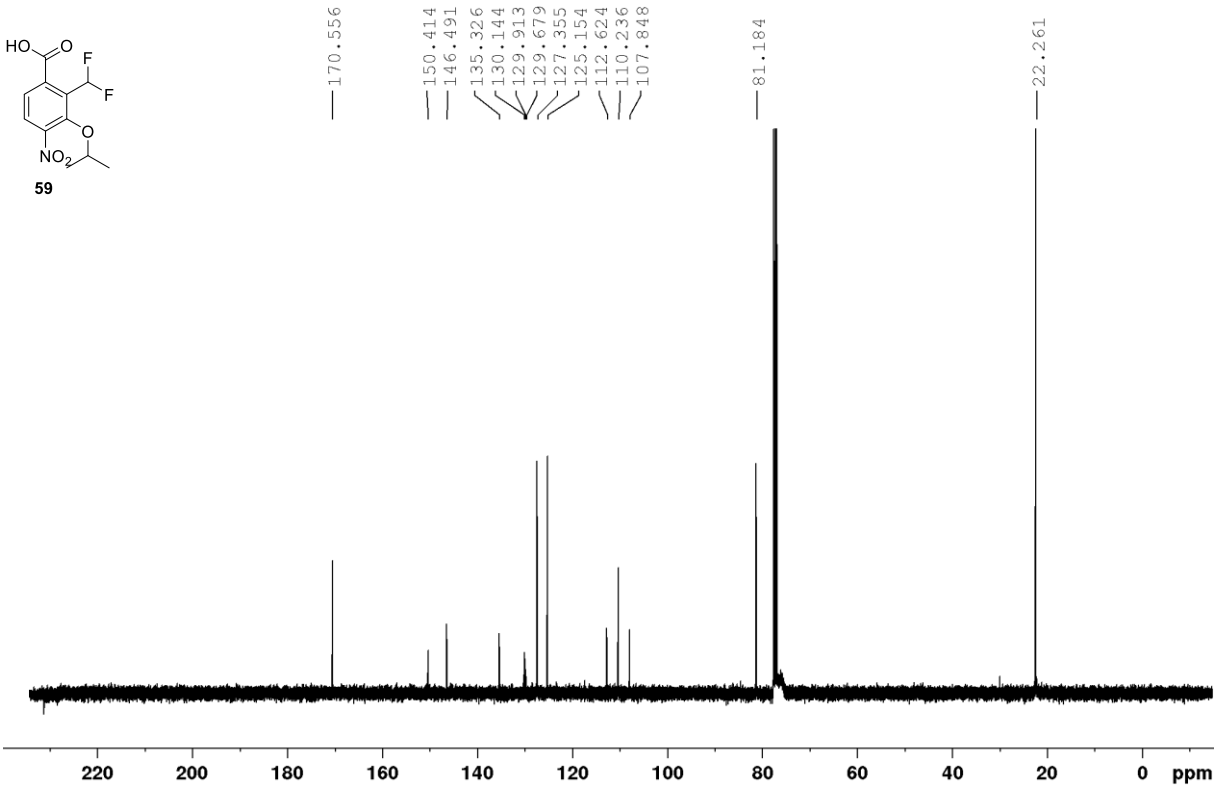
57

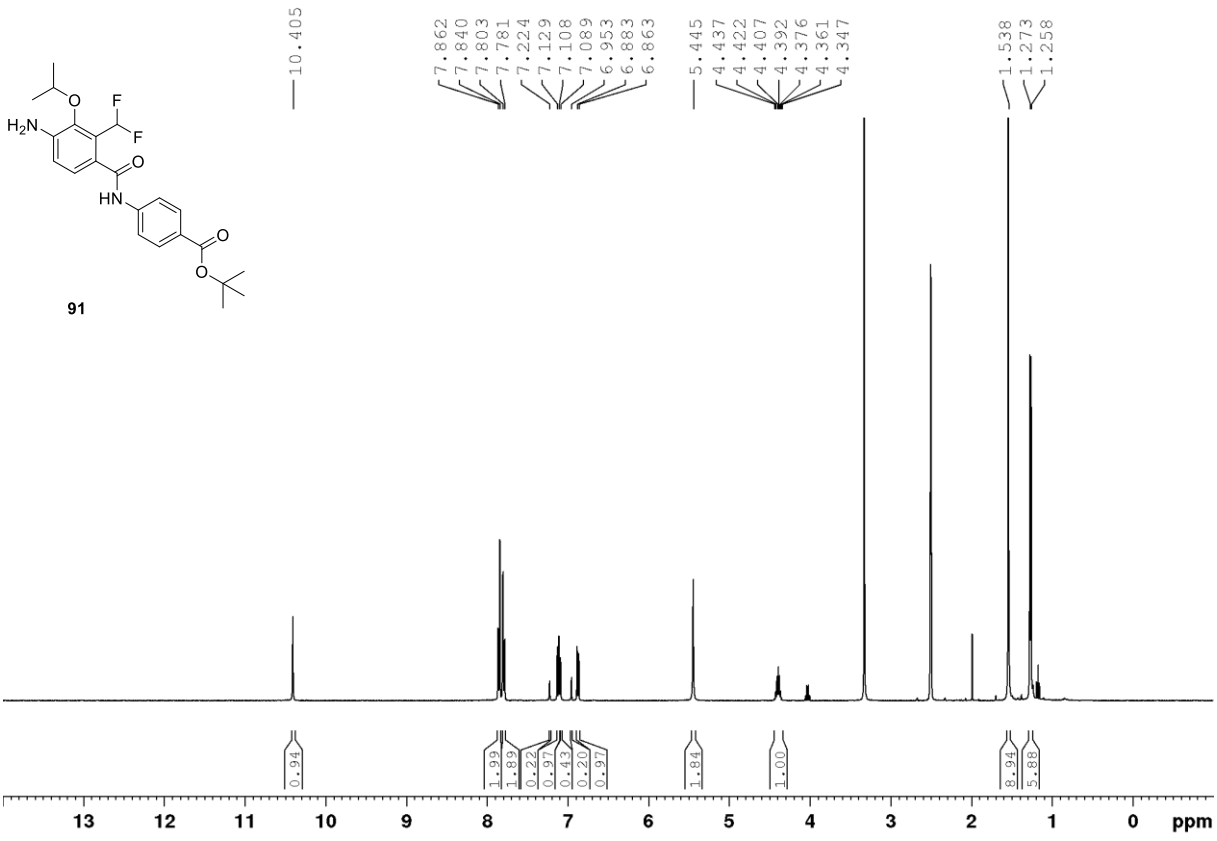

10.573
10.569
10.563
8.007
8.006
7.986
7.985
7.929
7.907
7.428
7.294
7.159
4.309
4.294
4.279
4.263
4.248
4.233
4.218
1.363
1.348
1.00
0.94
0.95
0.23
0.50
0.21
1.03
5.82
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

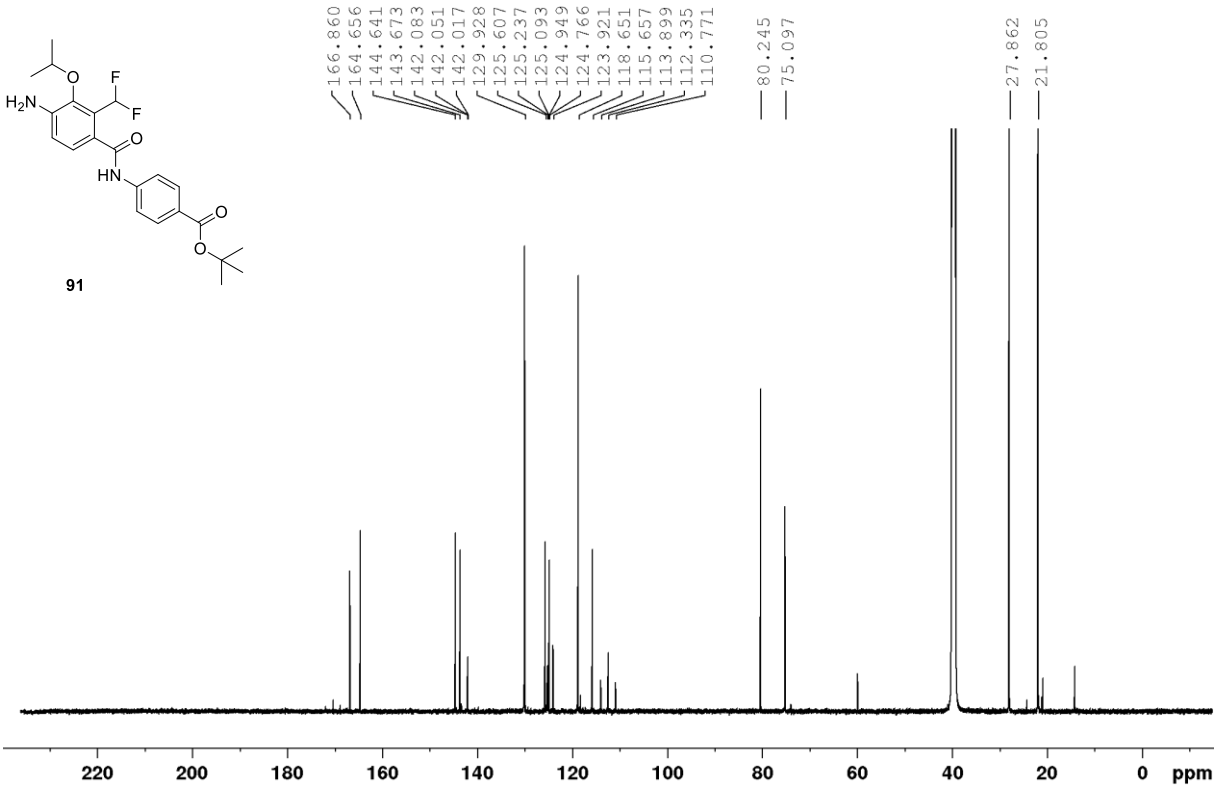
58


58
188.715
188.663
188.613
149.912
149.840
149.766
146.979
138.817
132.041
131.793
131.546
127.954
124.003
113.617
111.255
108.892
81.483
22.255
220
200
180
160
140
120
100
80
60
40
20
0
ppm

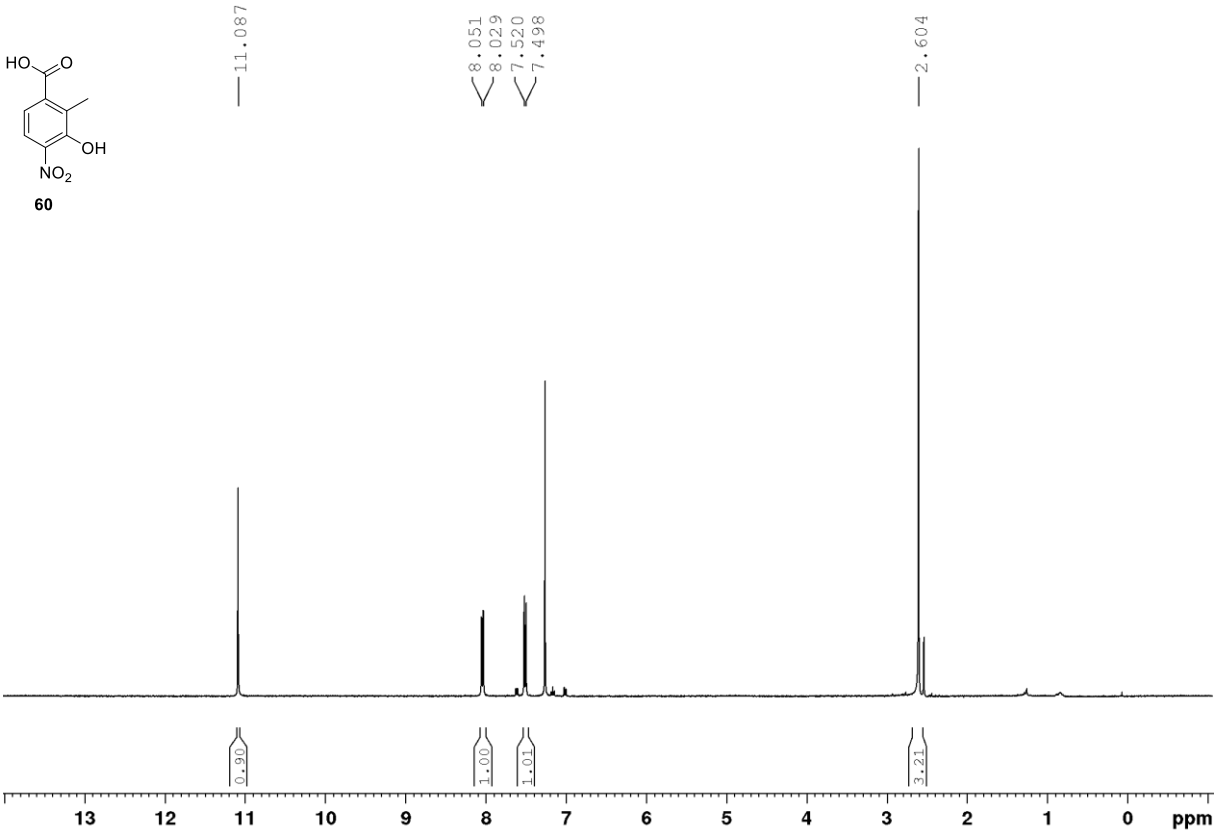

59
9.417
7.941
7.920
7.678
7.657
7.349
7.215
7.080
4.422
4.407
4.392
4.377
4.362
4.347
4.331
1.346
1.331
0.76
0.87
0.86
0.20
0.38
0.20
1.00
5.93
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


HO
O
F
F
O
NO2
59
170.556
150.414
146.491
135.326
130.144
129.913
129.679
127.355
125.154
112.624
110.236
107.848
81.184
22.261
220
200
180
160
140
120
100
80
60
40
20
0
ppm

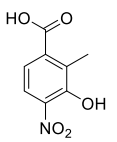

H2N
O
F
F
O
HN
O
O
91
10.405
7.862
7.840
7.803
7.781
7.224
7.129
7.108
7.089
6.953
6.883
6.863
5.445
4.437
4.422
4.407
4.392
4.376
4.361
4.347
1.538
1.273
1.258
0.94
1.99
1.89
0.22
0.97
0.43
0.20
0.97
1.84
1.00
8.94
5.88
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


166.860
164.656
144.641
143.673
142.083
142.051
142.017
129.928
125.607
125.237
125.093
124.949
124.766
123.921
118.651
115.657
113.899
112.335
110.771
80.245
75.097
27.862
21.805
220
200
180
160
140
120
100
80
60
40
20
0
ppm

91

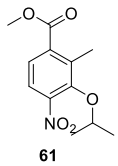

11.087
8.051
8.029
7.520
7.498
2.604
0.90
1.00
1.01
3.21
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

60



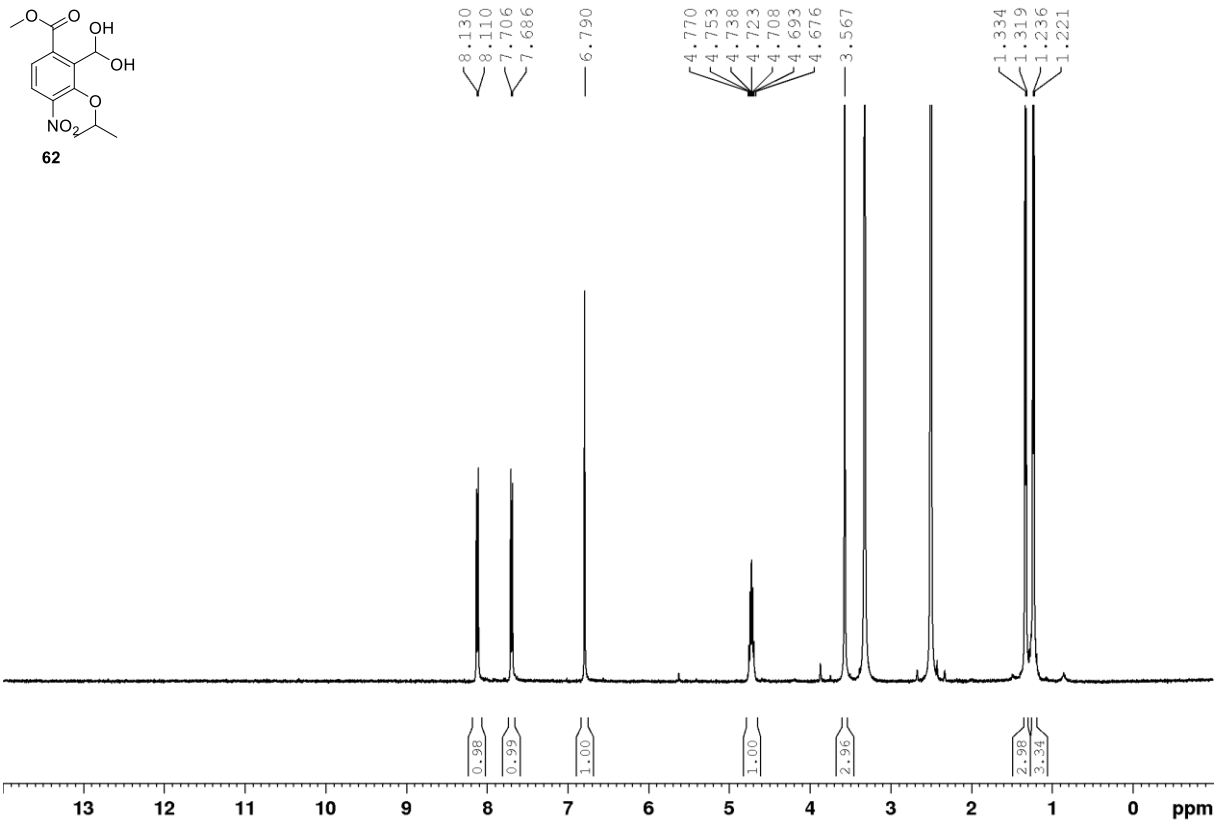
60

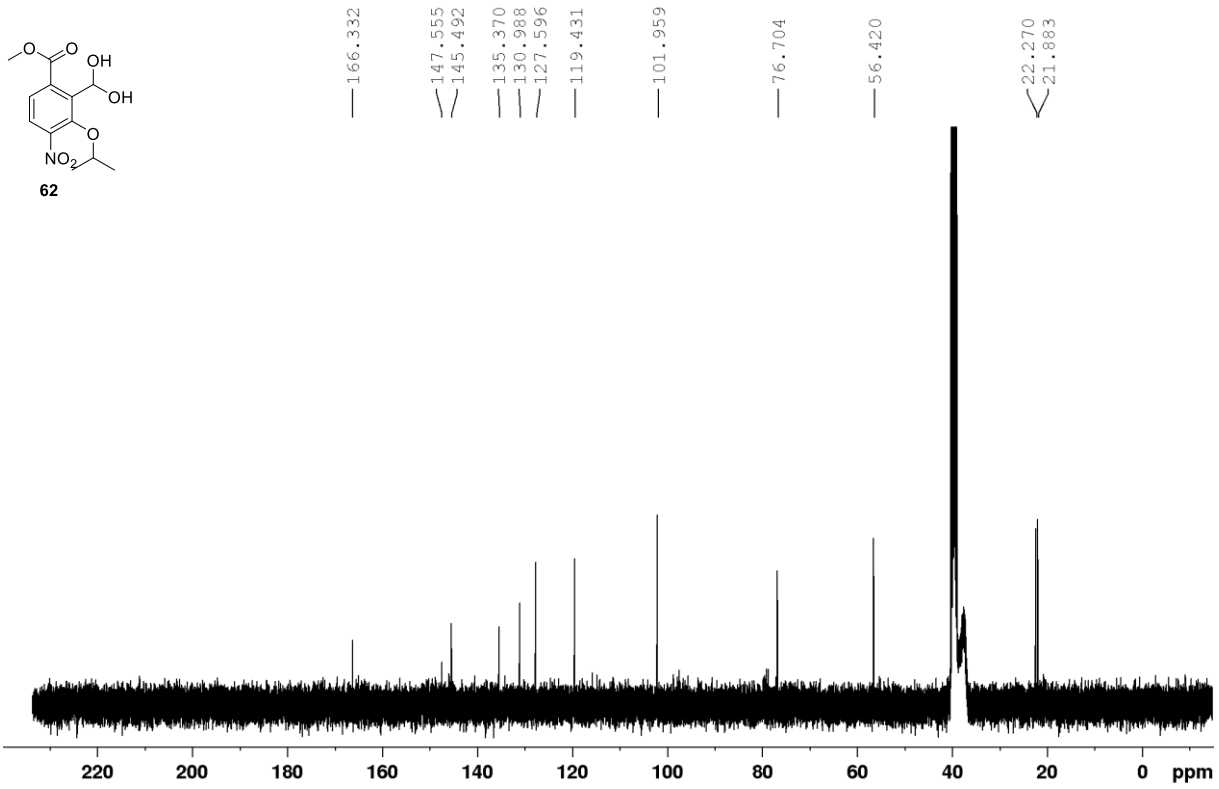
170.523
154.105
136.681
125.831
122.007
120.956
13.174
220
200
180
160
140
120
100
80
60
40
20
0
ppm

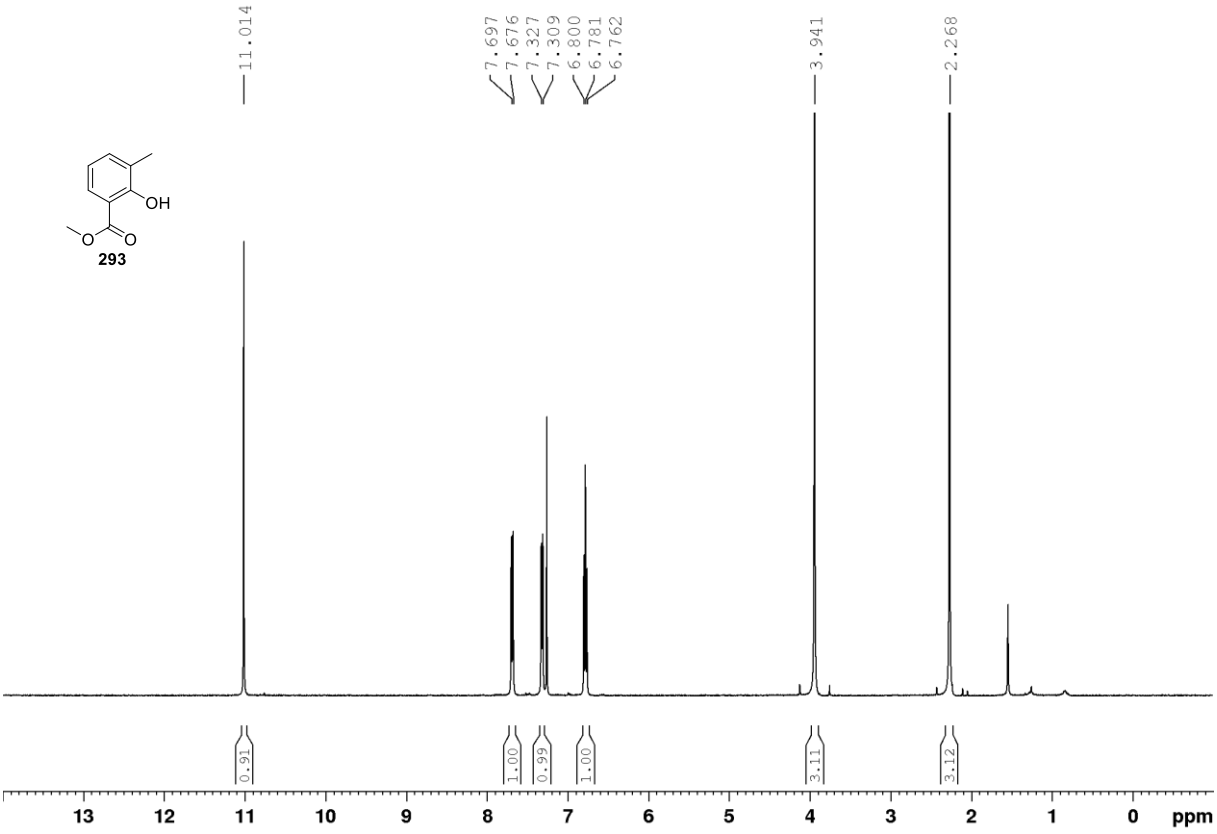


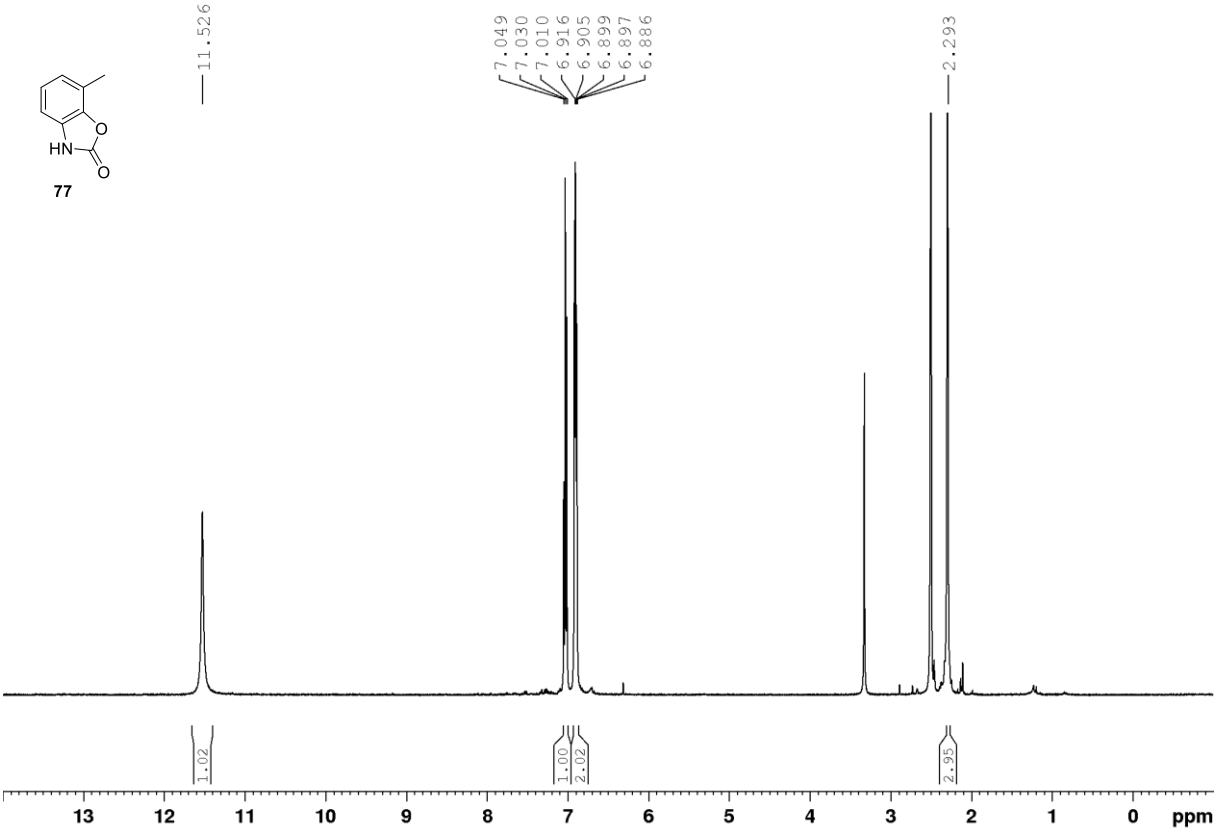
61

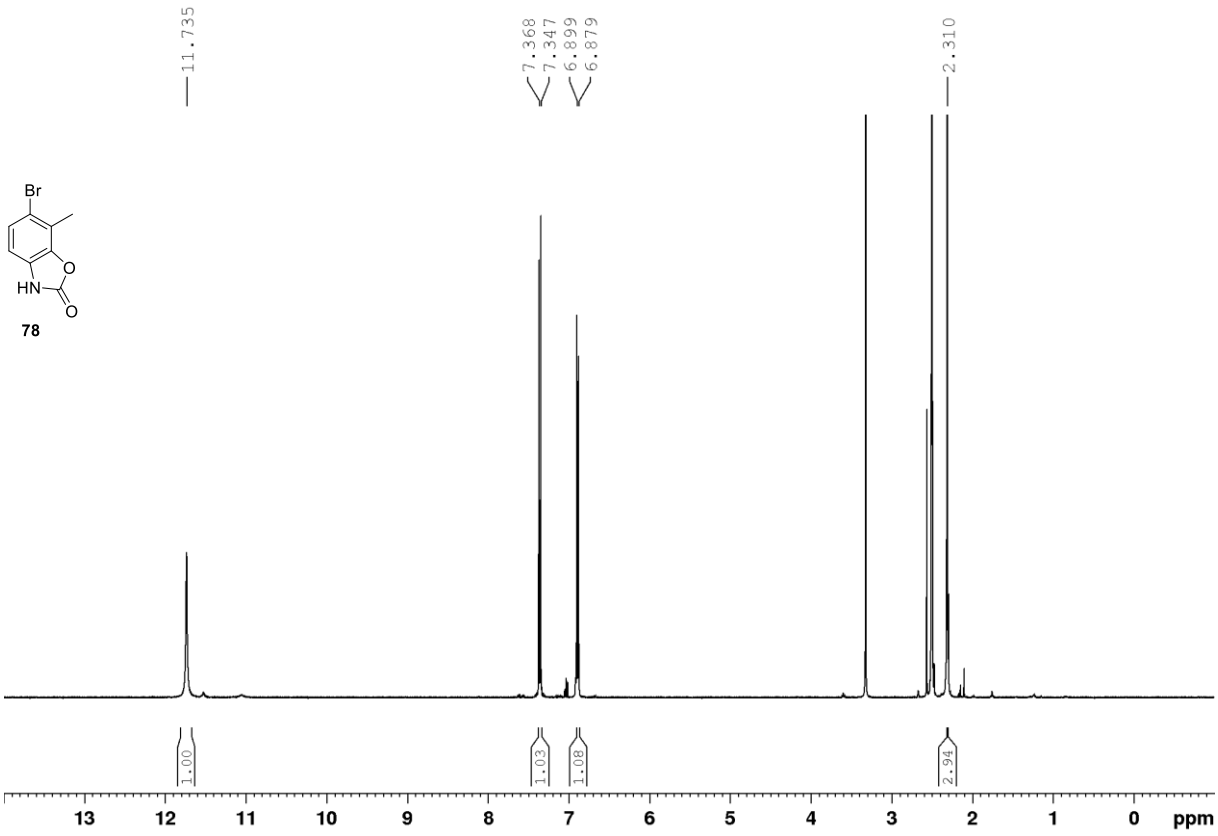
7.645
7.624
7.587
7.566
4.219
4.203
4.188
4.173
4.158
3.929
2.521
1.297
1.282
1.00
1.00
1.07
2.89
3.30
6.35
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

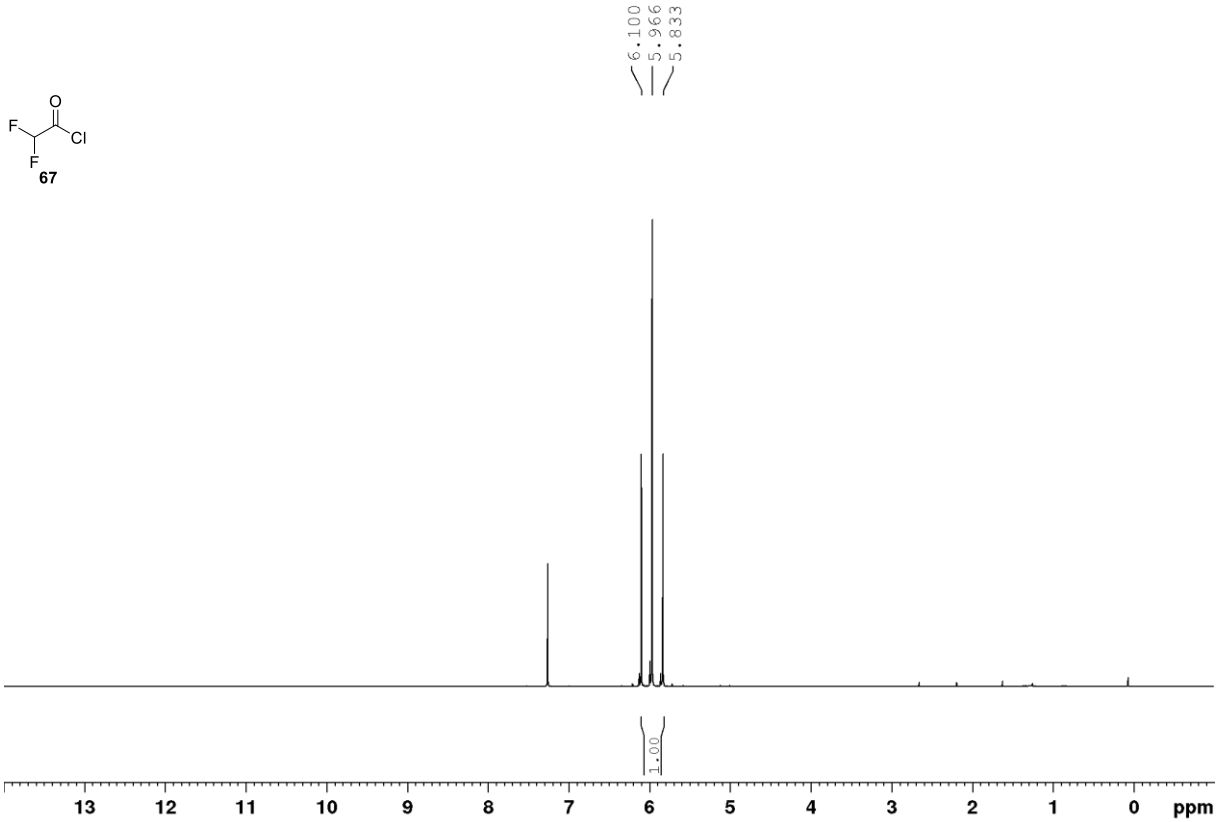

62
8.130
8.110
7.706
7.686
6.790
4.770
4.753
4.738
4.723
4.708
4.693
4.676
3.567
1.334
1.319
1.236
1.221
0.98
0.99
1.00
1.00
2.96
2.98
3.34
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

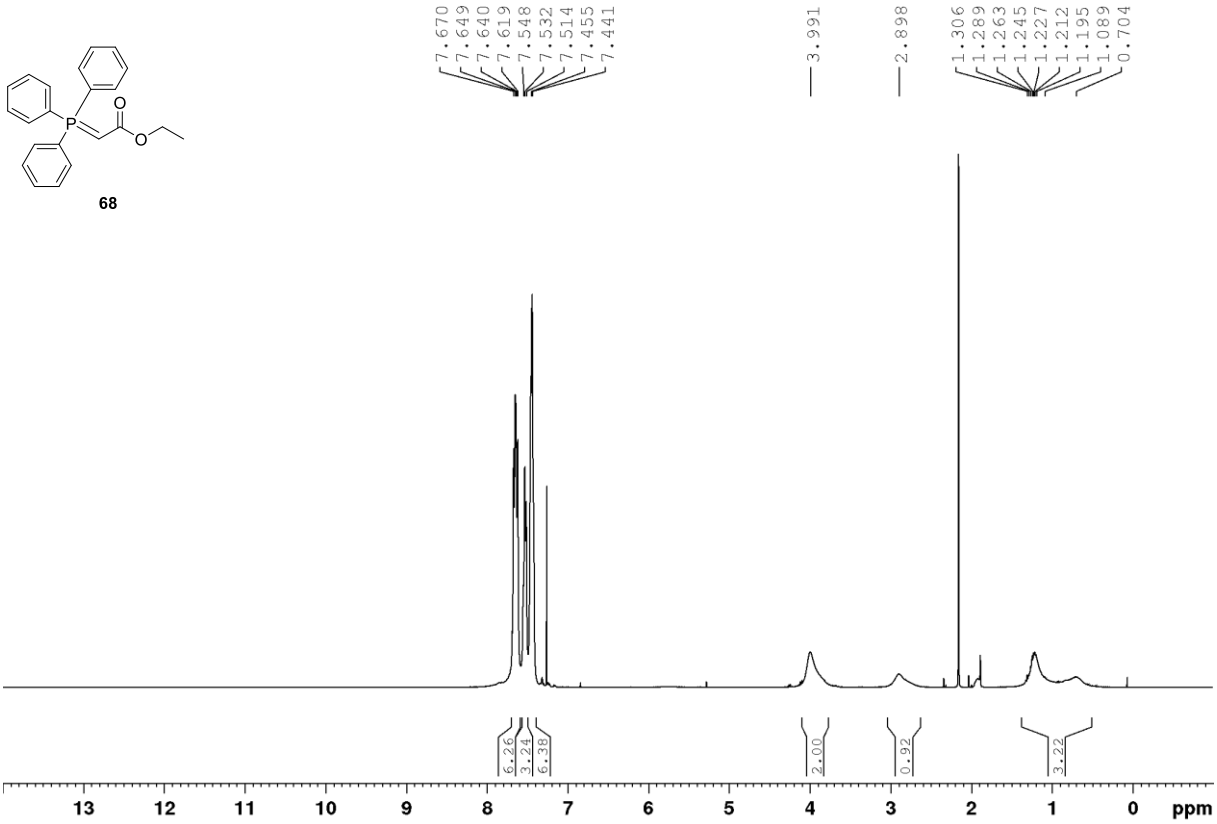

62
166.332
147.555
145.492
135.370
130.988
127.596
119.431
101.959
76.704
56.420
22.270
21.883
220
200
180
160
140
120
100
80
60
40
20
0
ppm


11.014
7.697
7.676
7.327
7.309
6.800
6.781
6.762
3.941
2.268
OH
O
O
293
0.91
1.00
0.99
1.00
3.11
3.12
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

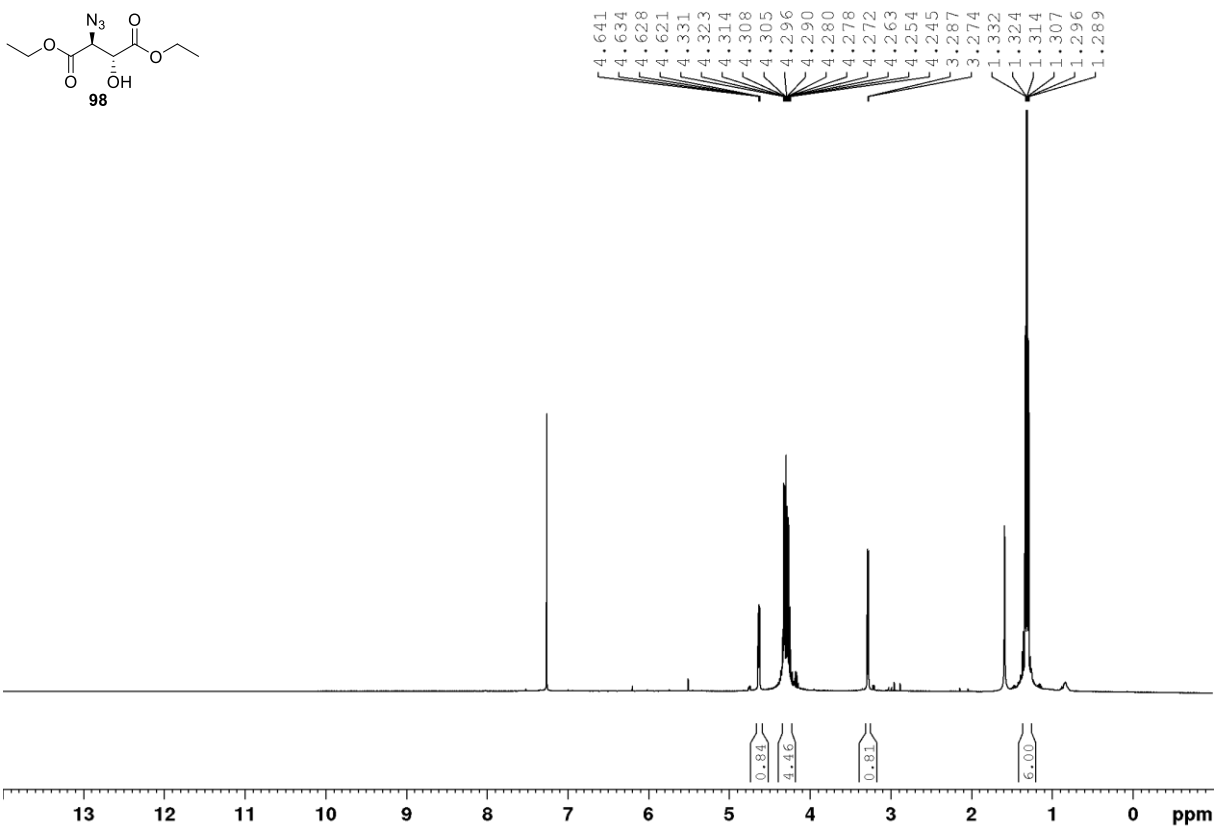

11.526
7.049
7.030
7.010
6.916
6.905
6.899
6.897
6.886
2.293
HN
O
O
77
1.02
1.00
2.02
2.95
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


11.735
7.368
7.347
6.899
6.879
2.310
Br
O
HN
O
78
1.00
1.03
1.08
2.94
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

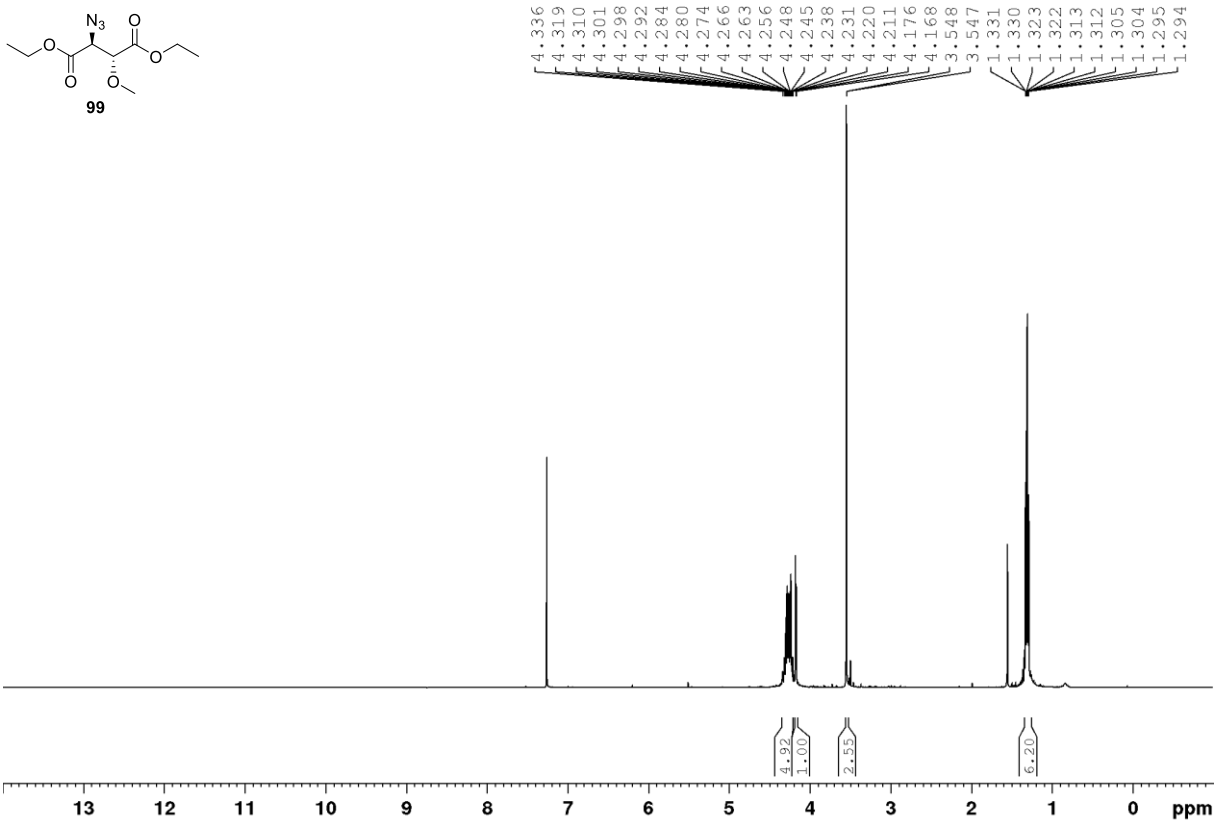

6.100
5.966
5.833
O
F
Cl
F
67
1.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

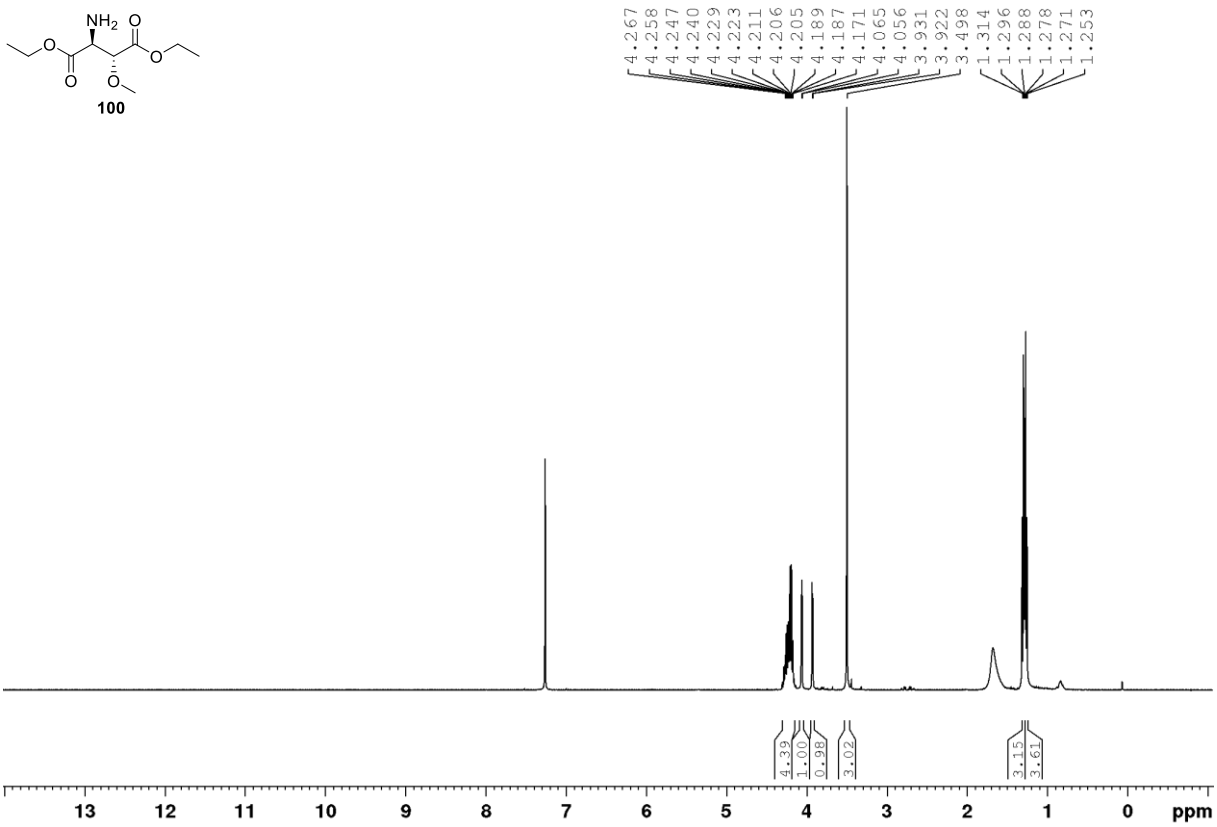

7.670
7.649
7.640
7.619
7.548
7.532
7.514
7.455
7.441
3.991
2.898
1.306
1.289
1.263
1.245
1.227
1.212
1.195
1.089
0.704
6.26
3.24
6.38
2.00
0.92
3.22
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

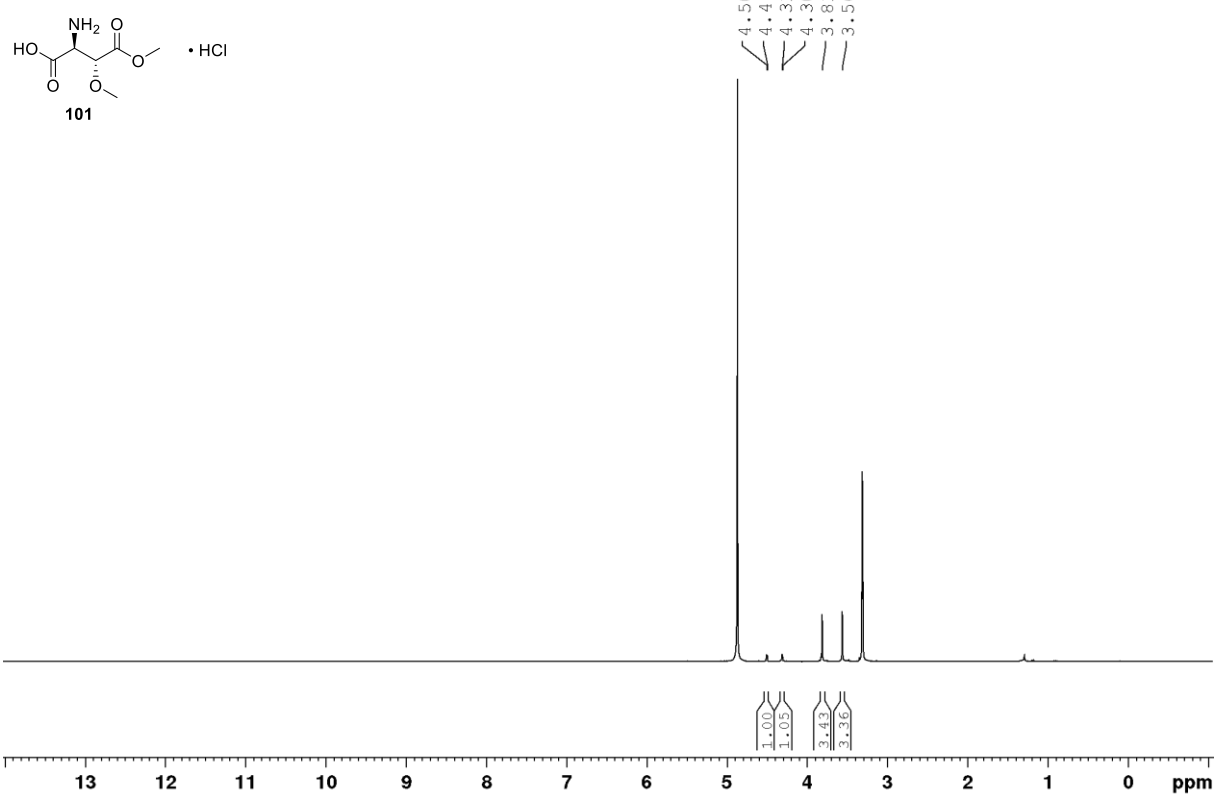
68

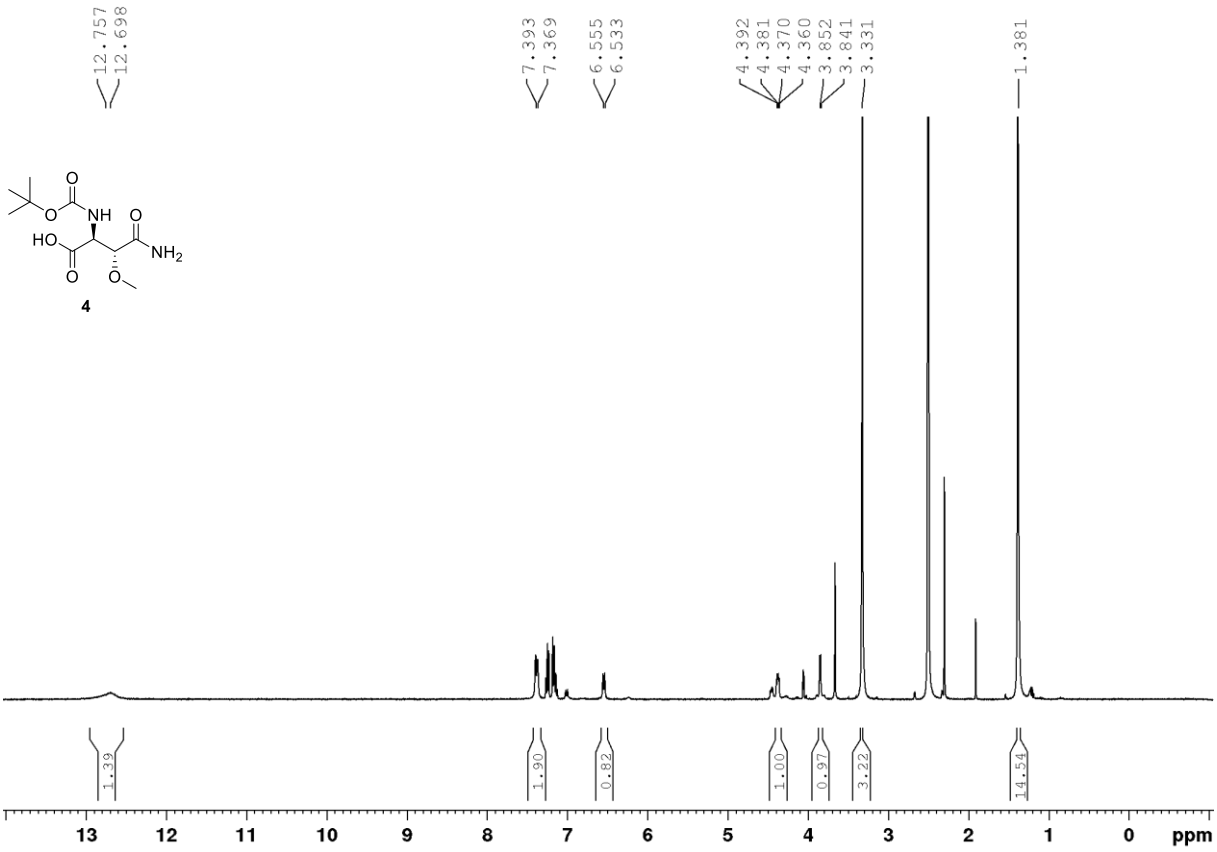

4.641
4.634
4.628
4.621
4.331
4.323
4.314
4.308
4.305
4.296
4.290
4.280
4.278
4.272
4.263
4.254
4.245
3.287
3.274
1.332
1.324
1.314
1.307
1.296
1.289
0.84
4.46
0.81
6.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

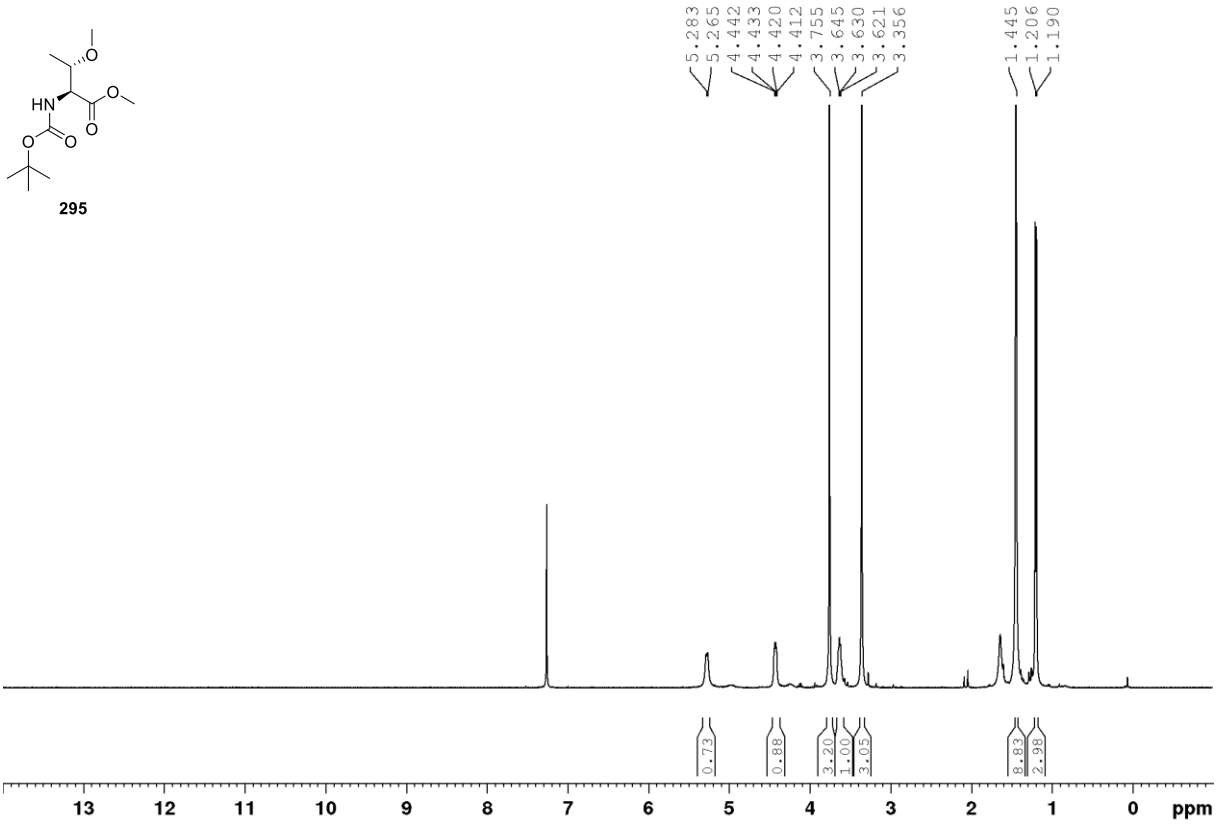
98

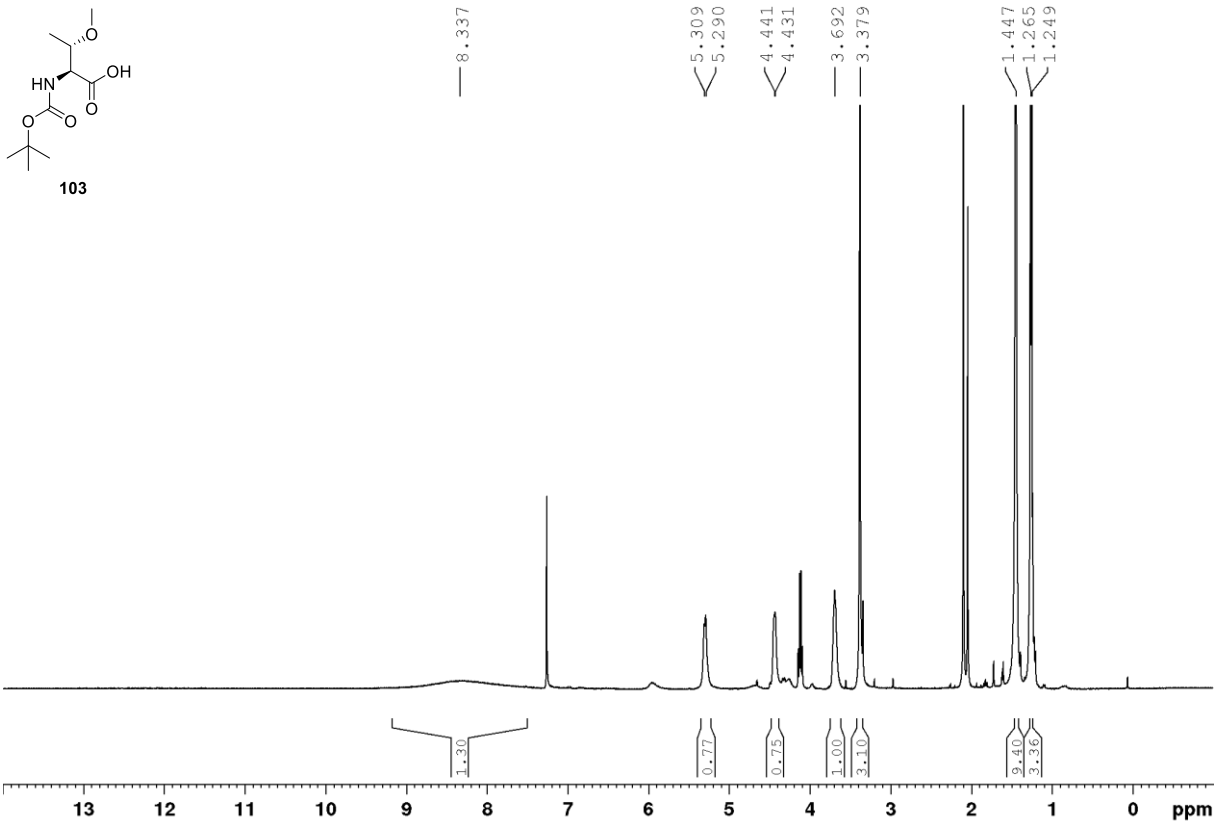

99
4.336
4.319
4.310
4.301
4.298
4.292
4.284
4.280
4.274
4.266
4.263
4.256
4.248
4.245
4.238
4.231
4.220
4.211
4.176
4.168
3.548
3.547
1.331
1.330
1.323
1.322
1.313
1.312
1.305
1.304
1.295
1.294
4.92
1.00
2.55
6.20
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

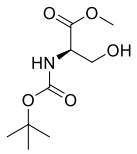

100
4.267
4.258
4.247
4.240
4.229
4.223
4.211
4.206
4.205
4.189
4.187
4.171
4.065
4.056
3.931
3.922
3.498
1.314
1.296
1.288
1.278
1.271
1.253
4.39
1.00
0.98
3.02
3.15
3.61
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


NH2
O
HO
O
O
• HCl
101
4.503
4.496
4.311
4.304
3.812
3.560
1.00
1.05
3.43
3.36
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


12.757
12.698
7.393
7.369
6.555
6.533
4.392
4.381
4.370
4.360
3.852
3.841
3.331
1.381
NH
O
HO
O
NH2
O
O
4
1.39
1.90
0.82
1.00
0.97
3.22
14.54
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

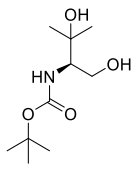

295
5.283
5.265
4.442
4.433
4.420
4.412
3.755
3.645
3.630
3.621
3.356
1.445
1.206
1.190
0.73
0.88
3.20
1.00
3.05
8.83
2.98
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


103
8.337
5.309
5.290
4.441
4.431
3.692
3.379
1.447
1.265
1.249
1.30
0.77
0.75
1.00
3.10
9.40
3.36
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm



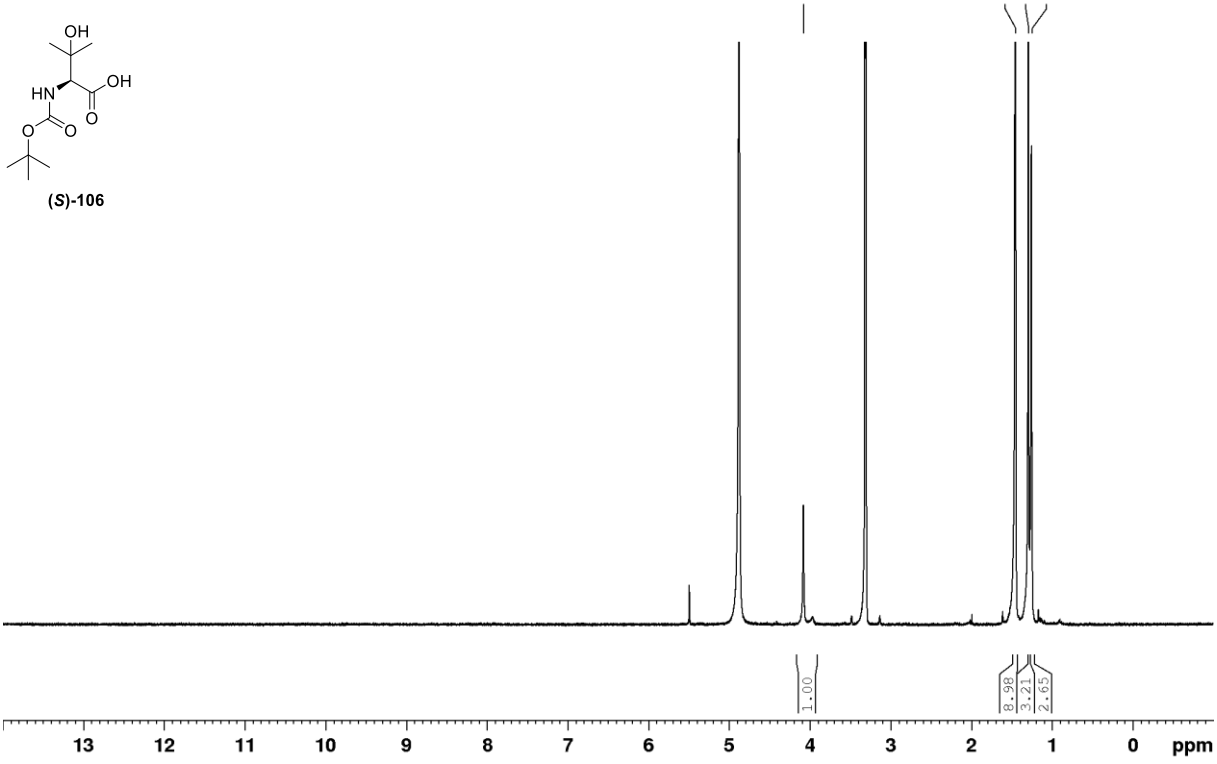
(*S*)-104

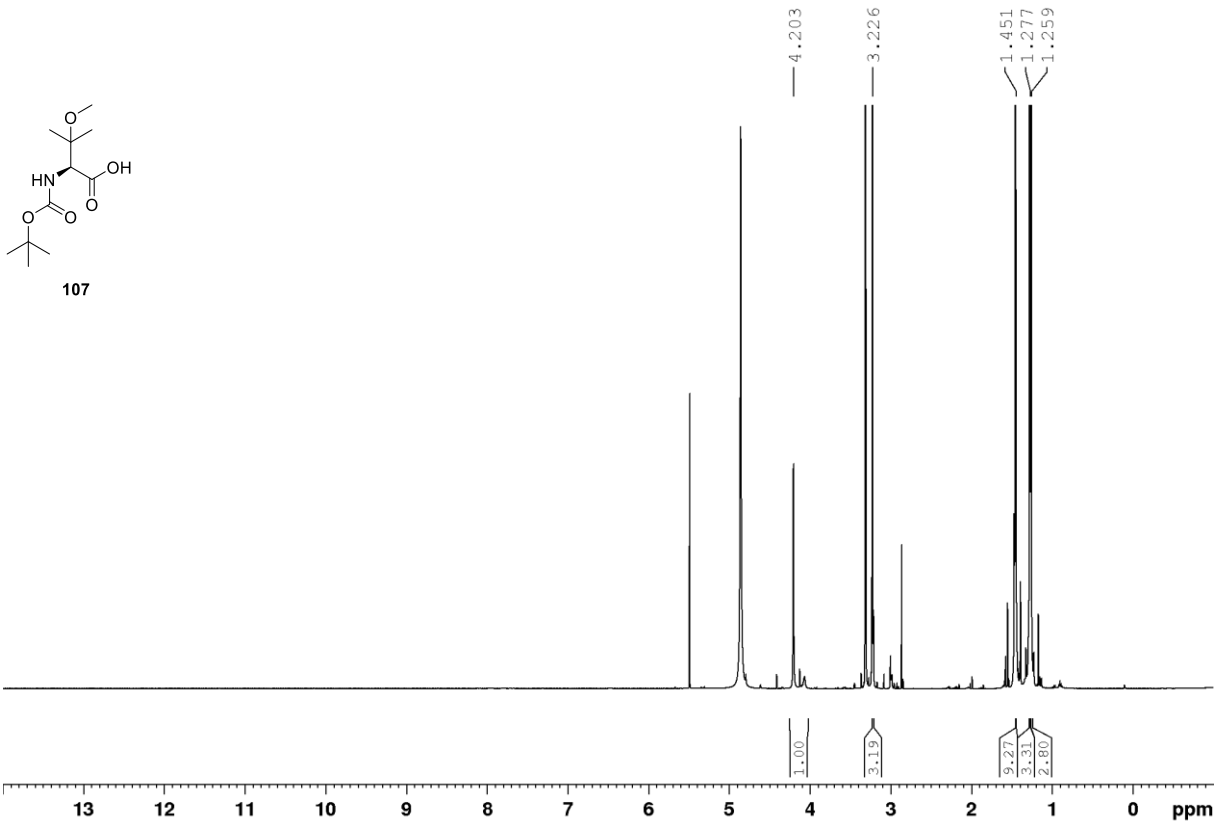
5.431
4.392
3.993
3.977
3.966
3.955
3.950
3.940
3.935
3.920
3.910
3.883
3.790
2.240
1.456
1.00
1.05
2.38
3.30
0.99
9.12
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

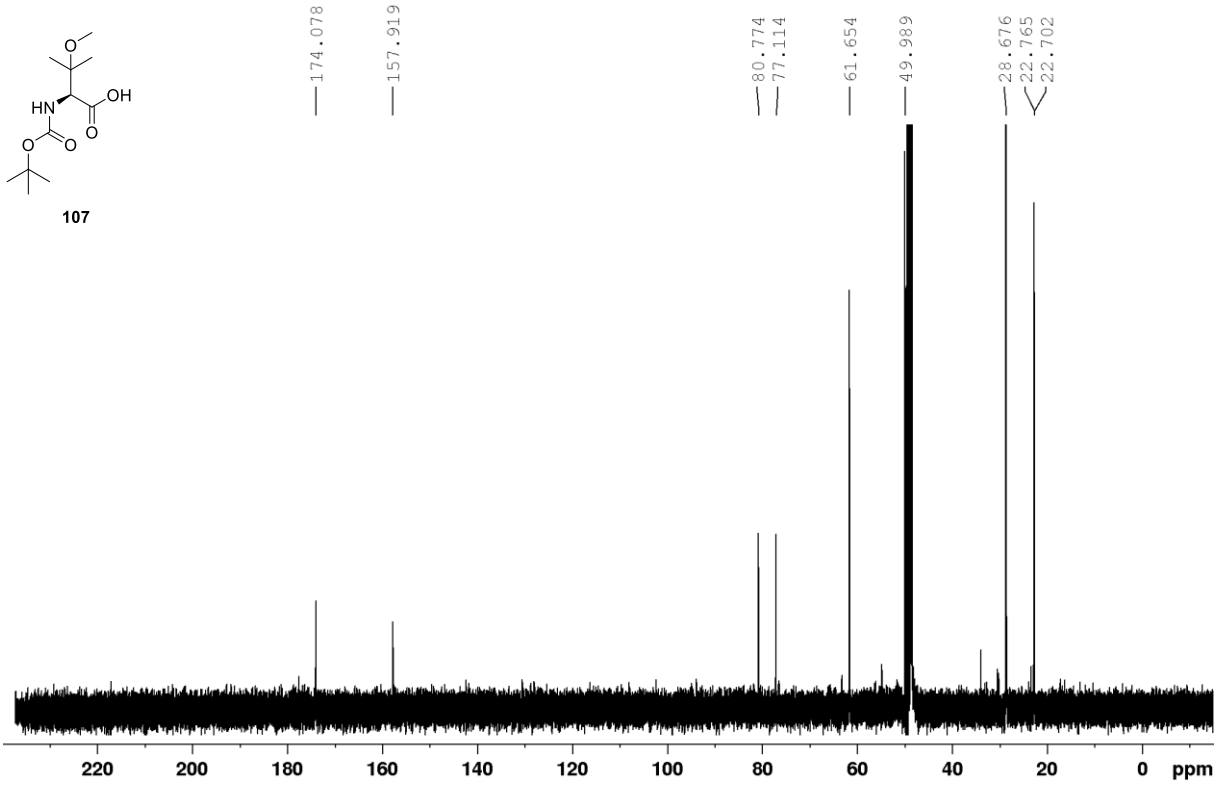


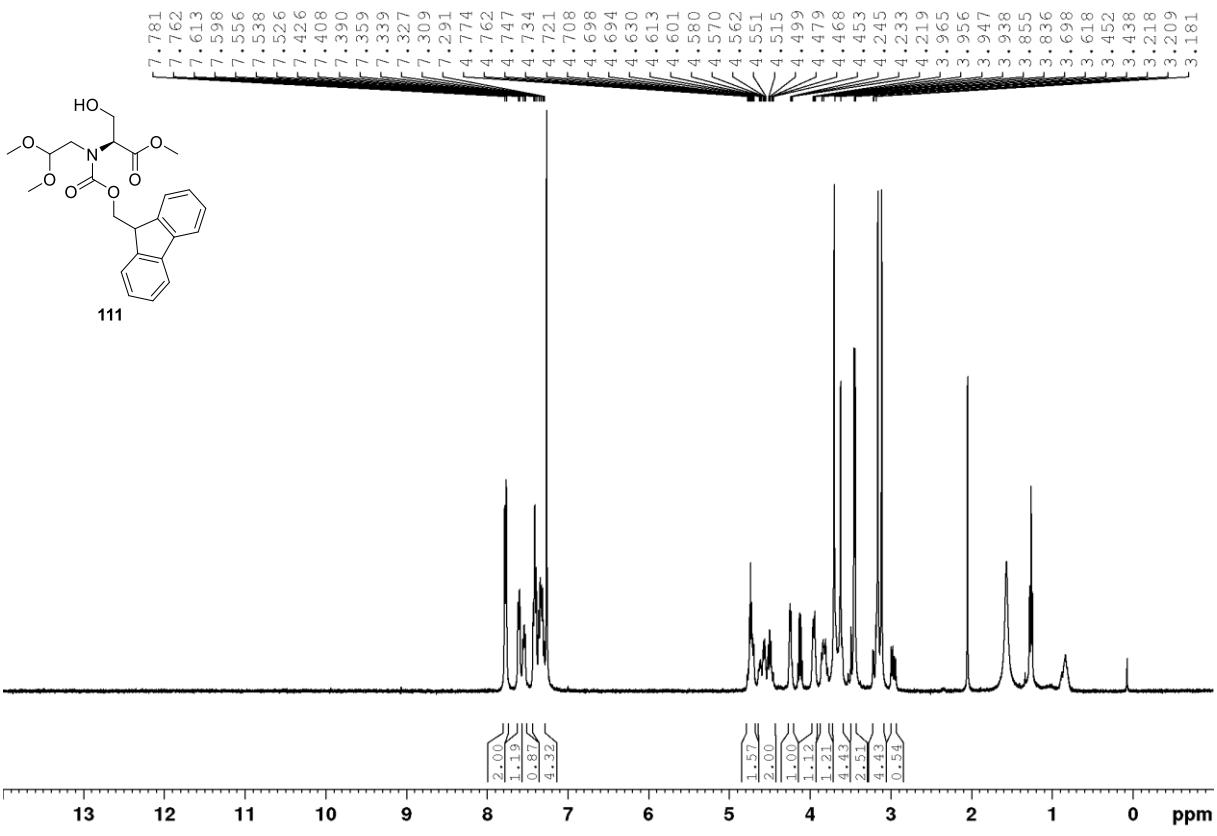
(*S*)-105

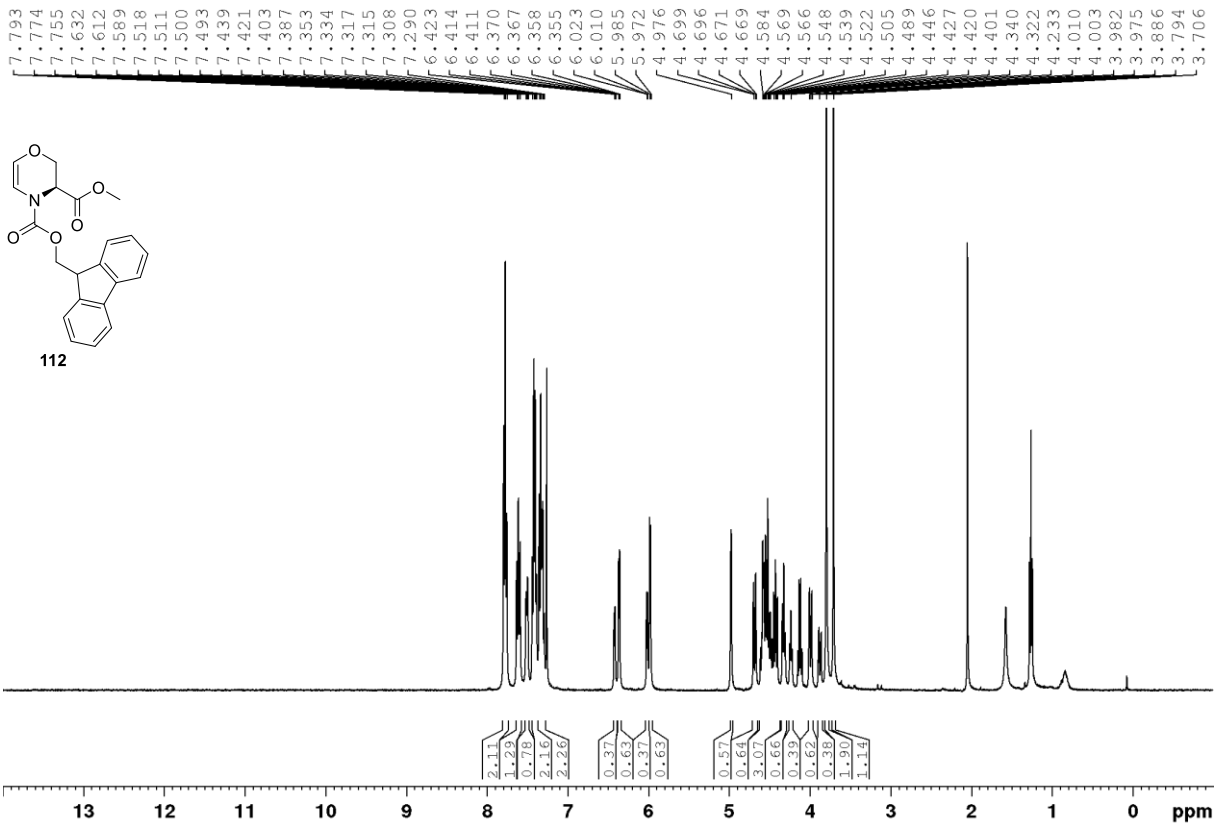
3.824
3.814
3.796
3.786
3.618
3.599
3.590
3.572
3.510
3.500
3.492
3.482
1.454
1.228
1.151
1.00
1.00
0.95
9.35
3.24
2.92
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

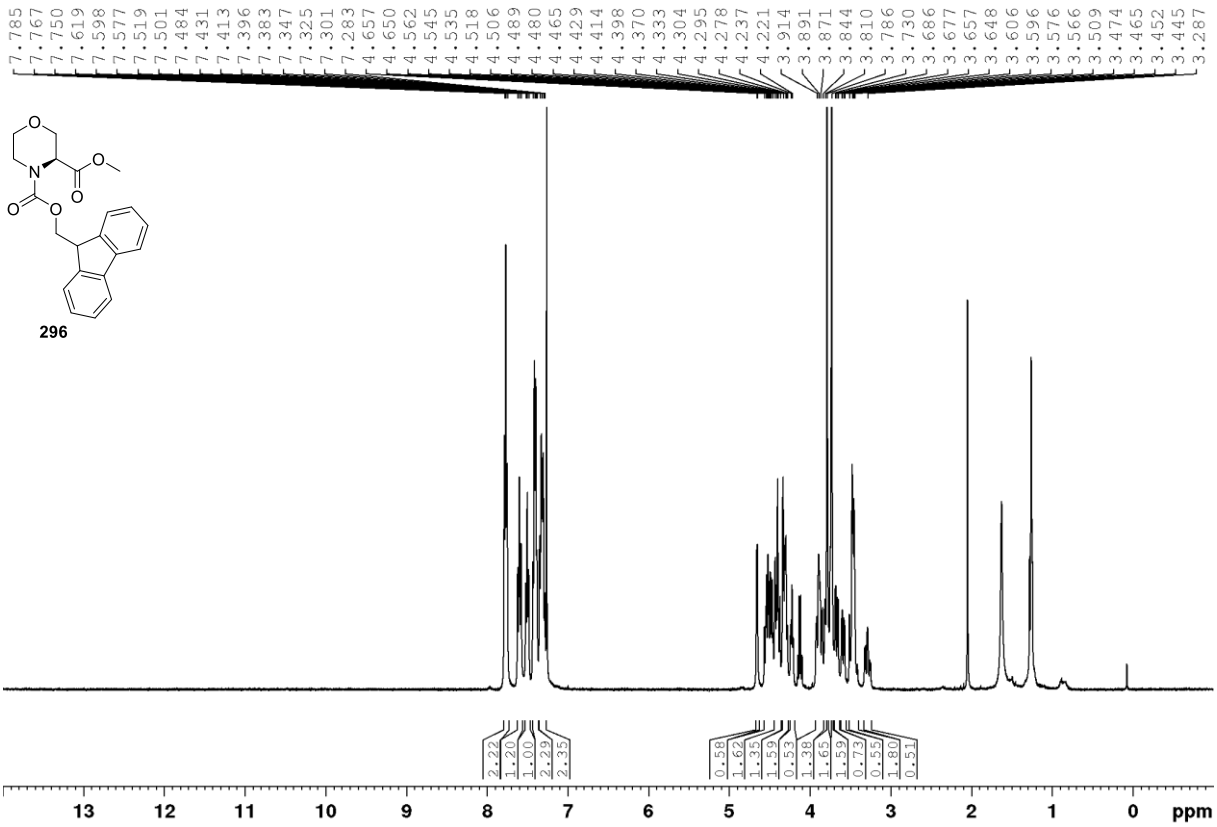

OH
HN
OH
O
O
O
(S)-106
4.079
1.454
1.293
1.254
1.00
8.98
3.21
2.65
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

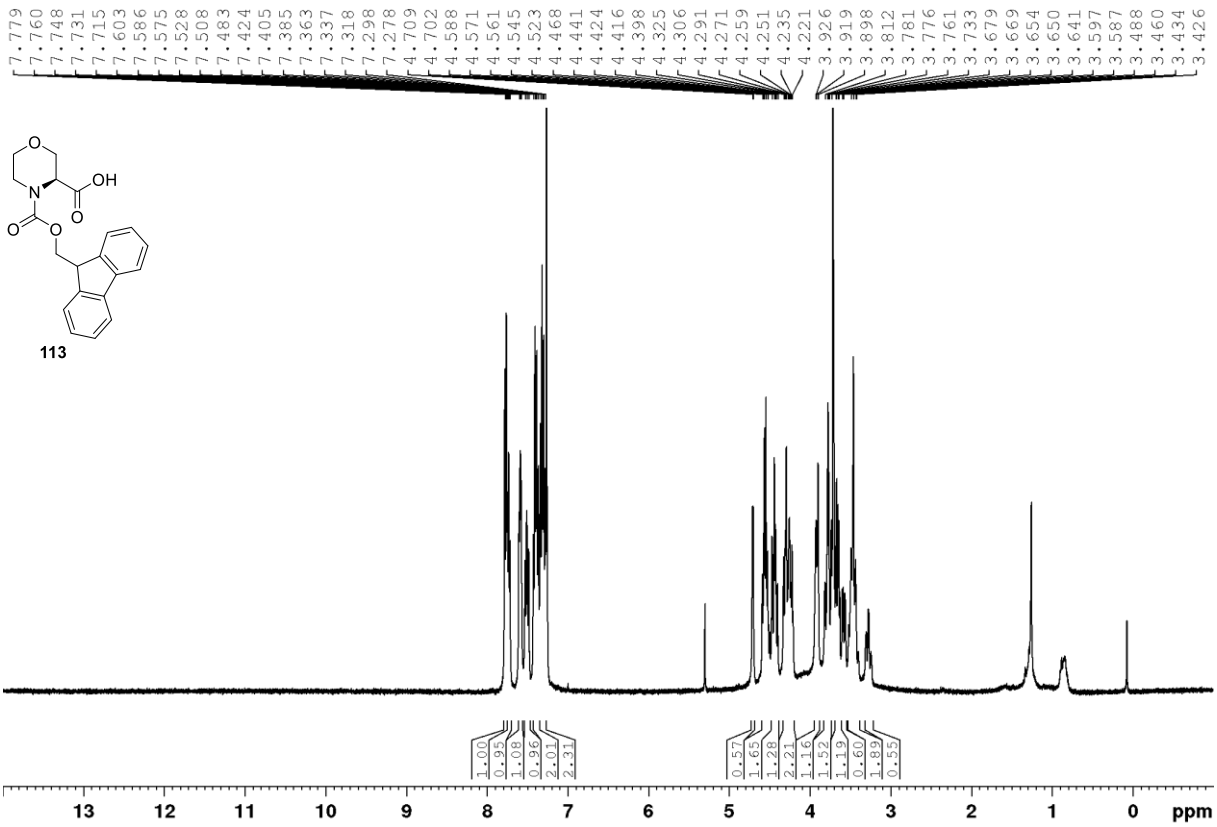

O
HN
OH
O
O
O
107
4.203
3.226
1.451
1.277
1.259
1.00
3.19
9.27
3.31
2.80
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


174.078
157.919
80.774
77.114
61.654
49.989
28.676
22.765
22.702
107
220
200
180
160
140
120
100
80
60
40
20
0
ppm

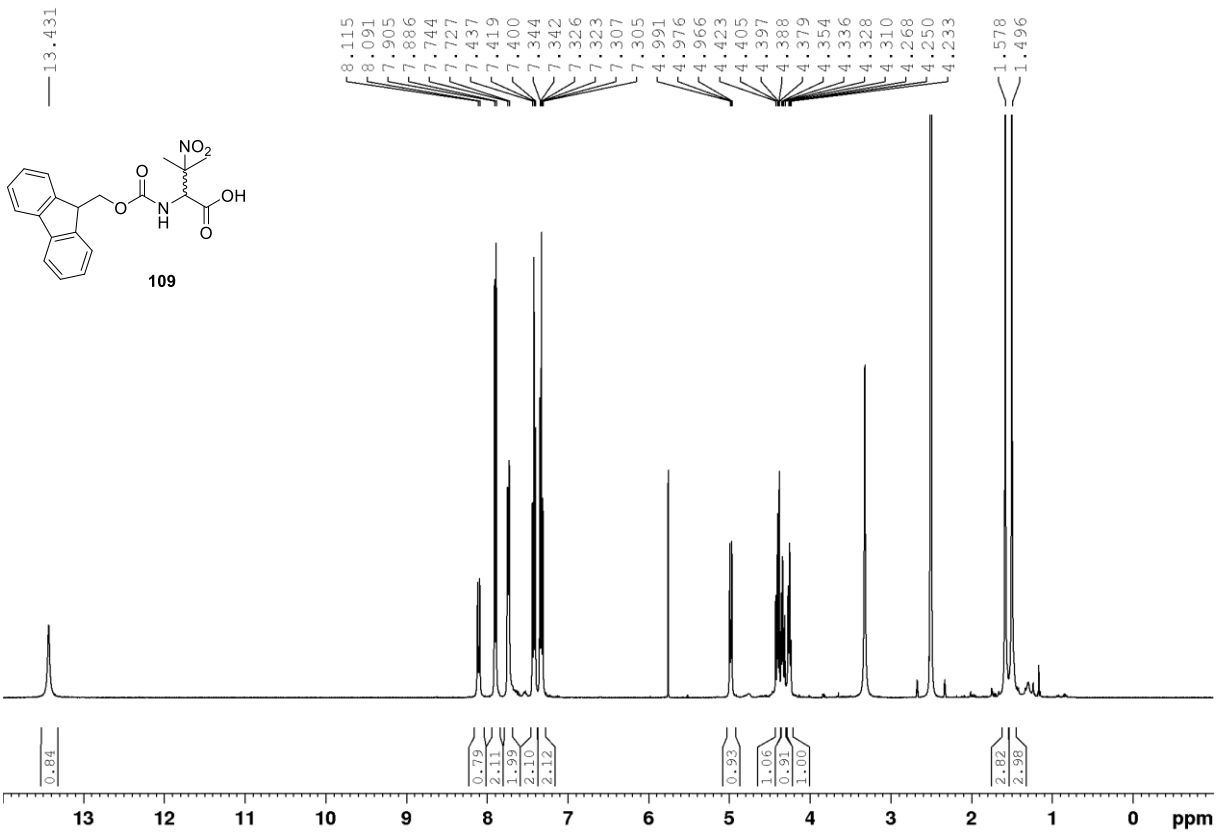

7.781
7.762
7.613
7.598
7.556
7.538
7.526
7.426
7.408
7.390
7.359
7.339
7.327
7.309
7.291
4.774
4.762
4.747
4.734
4.721
4.708
4.698
4.694
4.630
4.613
4.601
4.580
4.570
4.562
4.551
4.515
4.499
4.479
4.468
4.453
4.245
4.233
4.219
3.965
3.956
3.947
3.938
3.855
3.836
3.698
3.618
3.452
3.438
3.218
3.209
3.181
111
2.00
1.19
0.87
4.32
1.57
2.00
1.00
1.12
1.21
4.43
2.51
4.43
0.54
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


7.793
7.774
7.755
7.632
7.612
7.589
7.518
7.511
7.500
7.493
7.439
7.421
7.403
7.387
7.353
7.334
7.317
7.315
7.308
7.290
6.423
6.414
6.411
6.370
6.367
6.358
6.355
6.023
6.010
5.985
5.972
4.976
4.699
4.696
4.671
4.669
4.584
4.569
4.566
4.548
4.539
4.522
4.505
4.489
4.446
4.427
4.420
4.401
4.340
4.322
4.233
4.010
4.003
3.982
3.975
3.886
3.794
3.706
112
2.11
1.29
0.78
2.16
2.26
0.37
0.63
0.37
0.63
0.57
0.64
3.07
0.66
0.39
0.62
0.38
1.90
1.14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

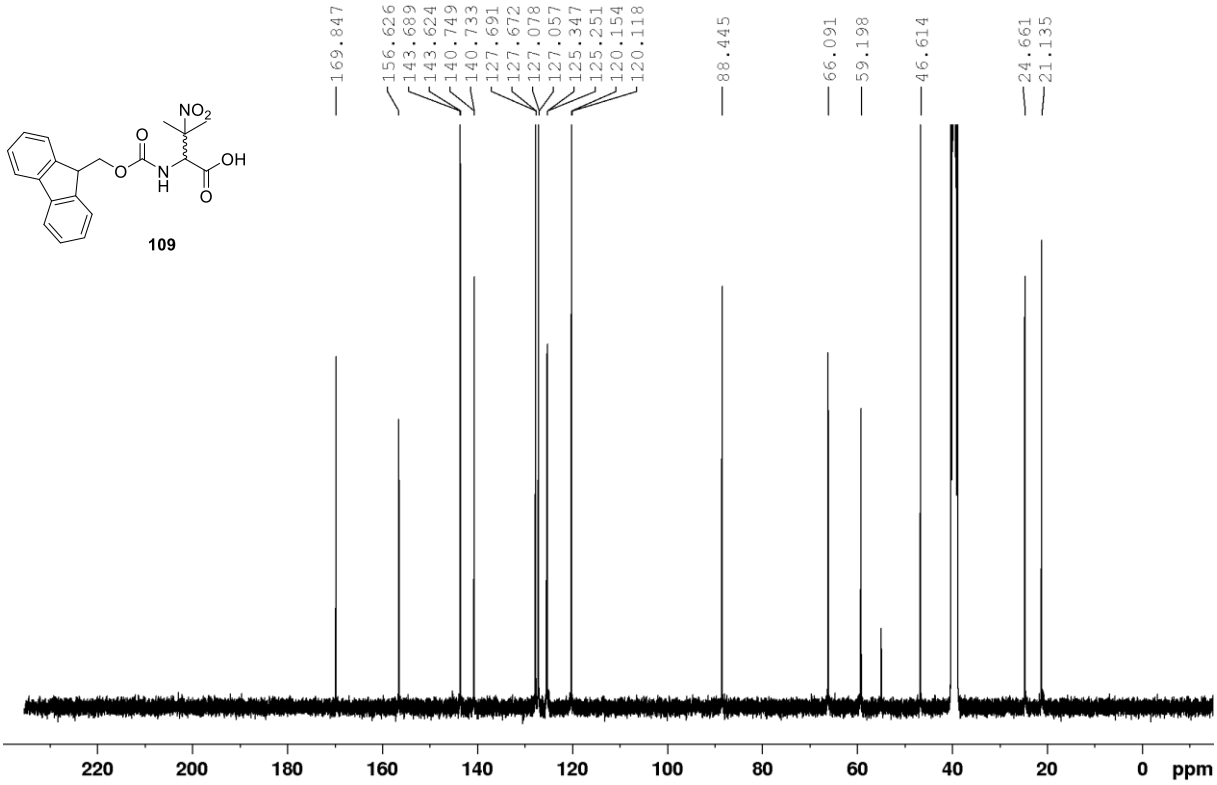

7.785
7.767
7.750
7.619
7.598
7.577
7.519
7.501
7.484
7.431
7.413
7.396
7.383
7.347
7.325
7.301
7.283
4.657
4.650
4.562
4.545
4.535
4.518
4.506
4.489
4.480
4.465
4.429
4.414
4.398
4.370
4.333
4.304
4.295
4.278
4.237
4.221
3.914
3.891
3.871
3.844
3.810
3.786
3.730
3.686
3.677
3.657
3.648
3.606
3.596
3.576
3.566
3.509
3.474
3.465
3.452
3.445
3.287
296
2.22
1.20
1.00
2.29
2.35
0.58
1.62
1.35
1.59
0.53
1.38
1.65
1.59
0.73
0.55
1.80
0.51
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

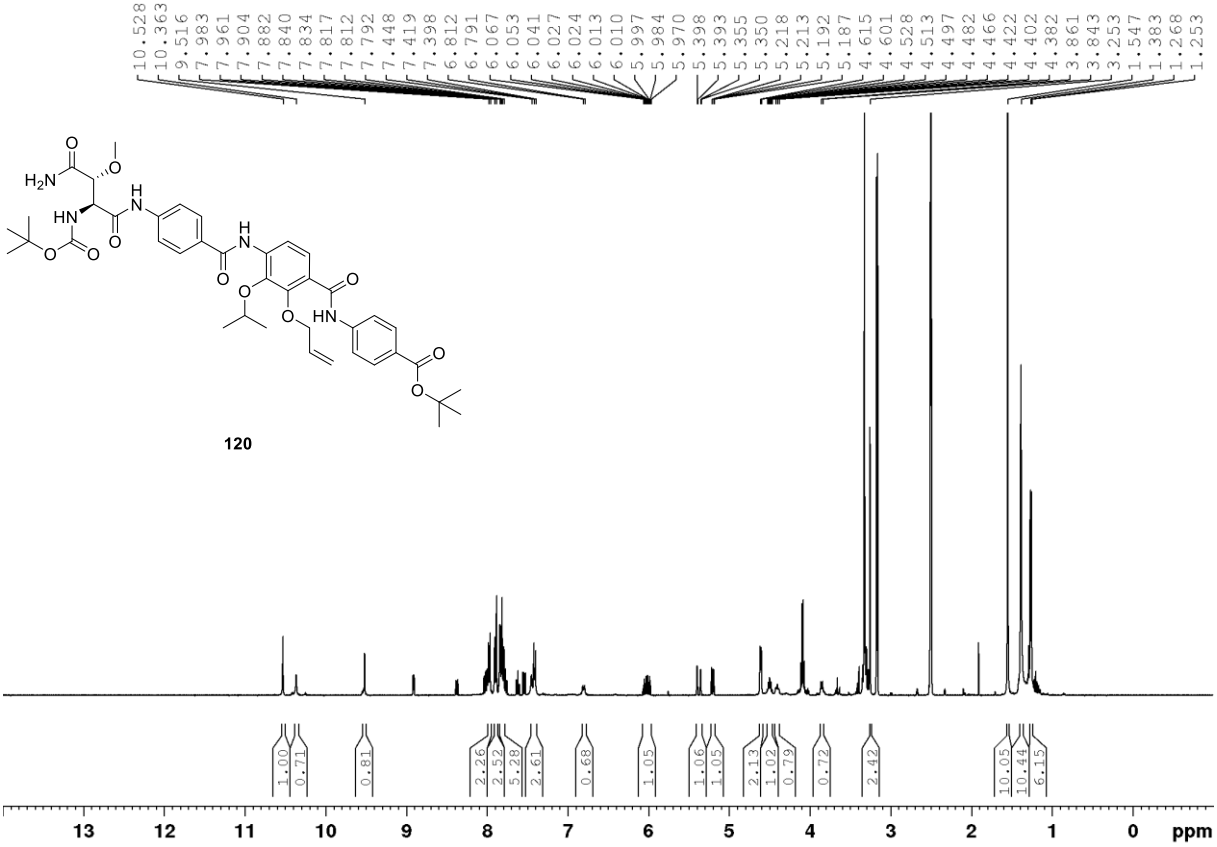

7.779
7.760
7.748
7.731
7.715
7.603
7.586
7.575
7.528
7.508
7.483
7.424
7.405
7.385
7.363
7.337
7.318
7.298
7.278
4.709
4.702
4.588
4.571
4.561
4.545
4.523
4.468
4.441
4.424
4.416
4.398
4.325
4.306
4.291
4.271
4.259
4.251
4.235
4.221
3.926
3.919
3.898
3.812
3.781
3.776
3.761
3.733
3.679
3.669
3.654
3.650
3.641
3.597
3.587
3.488
3.460
3.434
3.426
OH
O
N
O
O
O
1.00
0.95
1.08
0.96
2.01
2.31
0.57
1.65
1.28
2.21
1.16
1.52
1.19
0.60
1.89
0.55
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

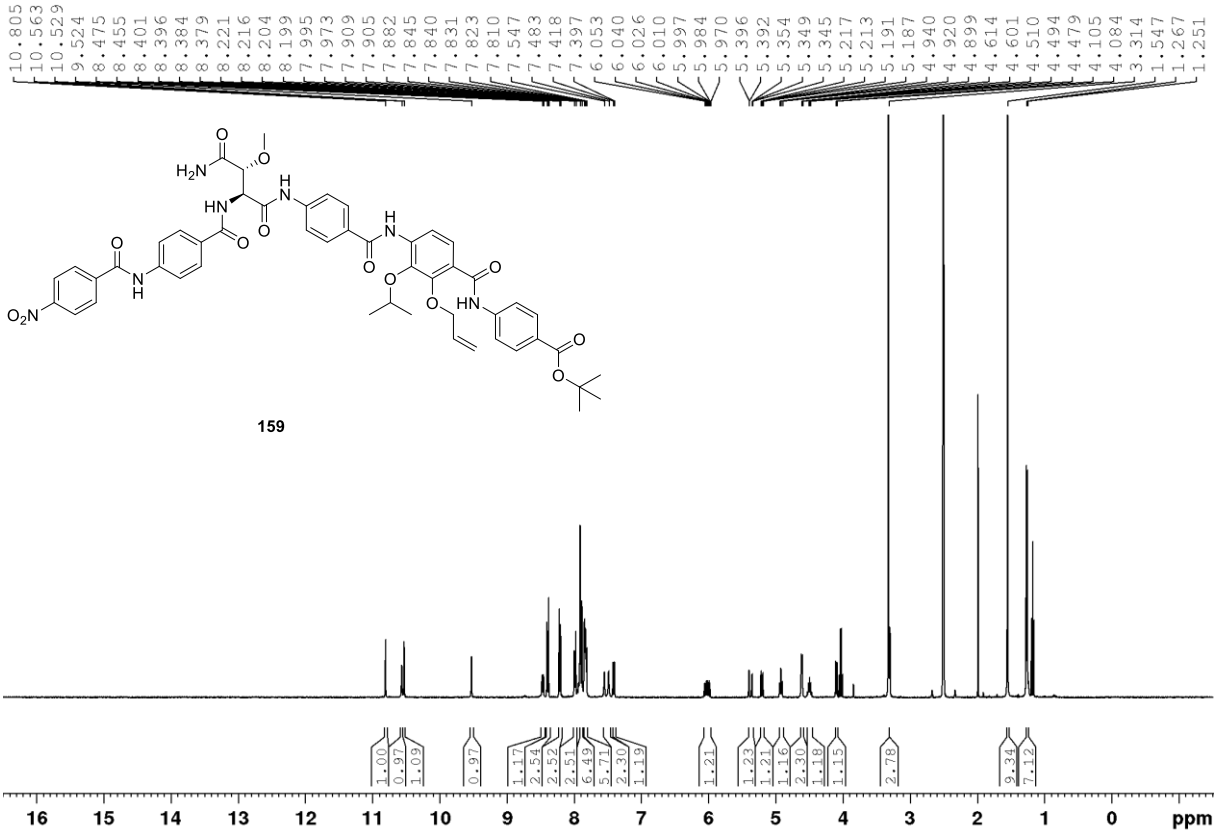
113

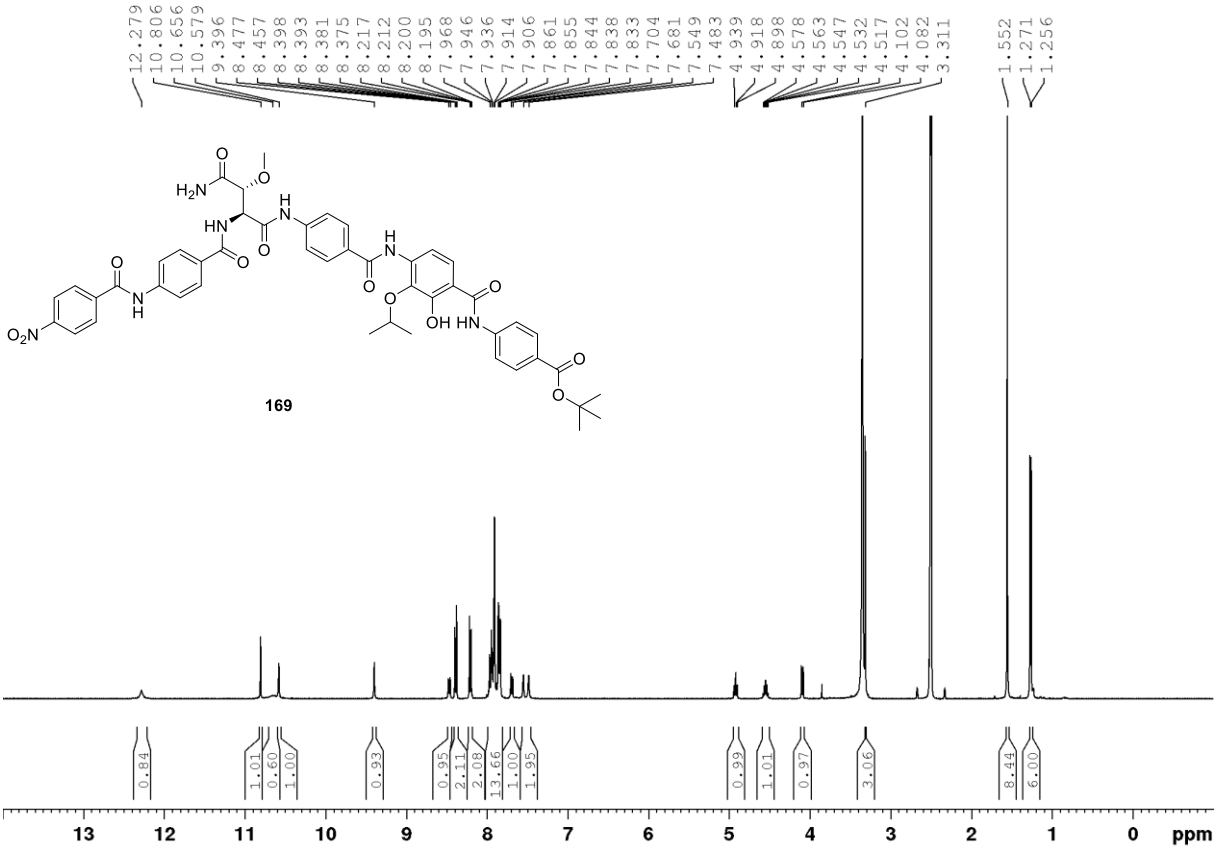

13.431
8.115
8.091
7.905
7.886
7.744
7.727
7.437
7.419
7.400
7.344
7.342
7.326
7.323
7.307
7.305
4.991
4.976
4.966
4.423
4.405
4.397
4.388
4.379
4.354
4.336
4.328
4.310
4.268
4.250
4.233
1.578
1.496
NO2
O
O
N
H
OH
O
0.84
0.79
2.11
1.99
2.10
2.12
0.93
1.06
0.91
1.00
2.82
2.98
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

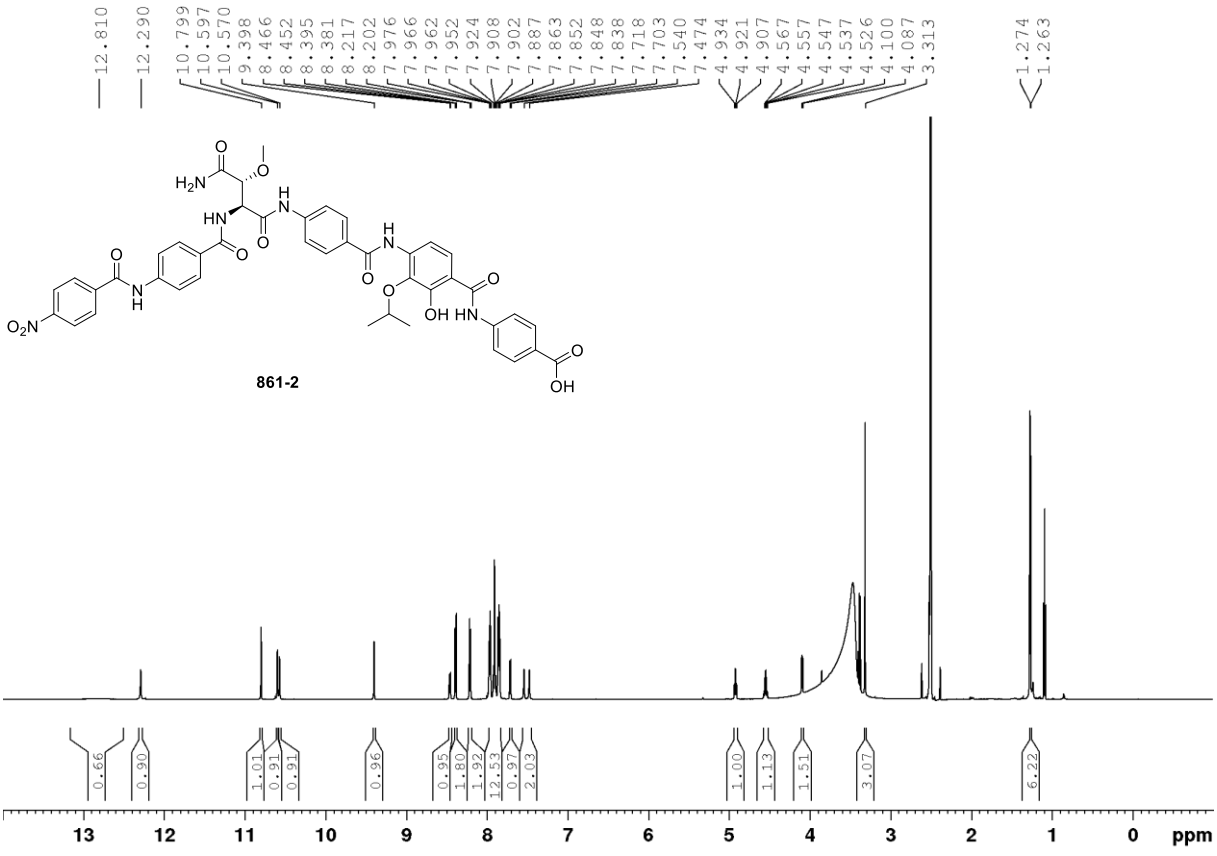
109

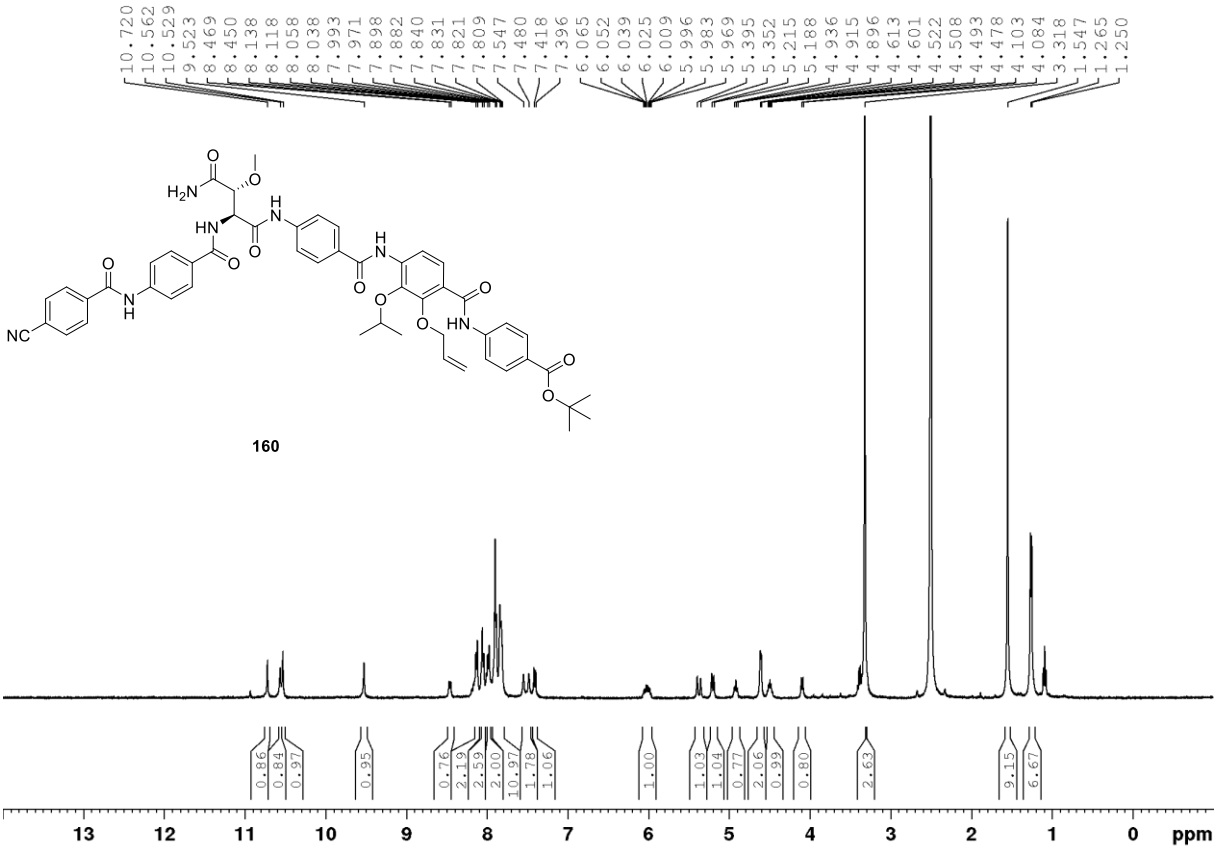

169.847
156.626
143.689
143.624
140.749
140.733
127.691
127.672
127.078
127.057
125.347
125.251
120.154
120.118
88.445
66.091
59.198
46.614
24.661
21.135
NO2
OH
109
220
200
180
160
140
120
100
80
60
40
20
0
ppm

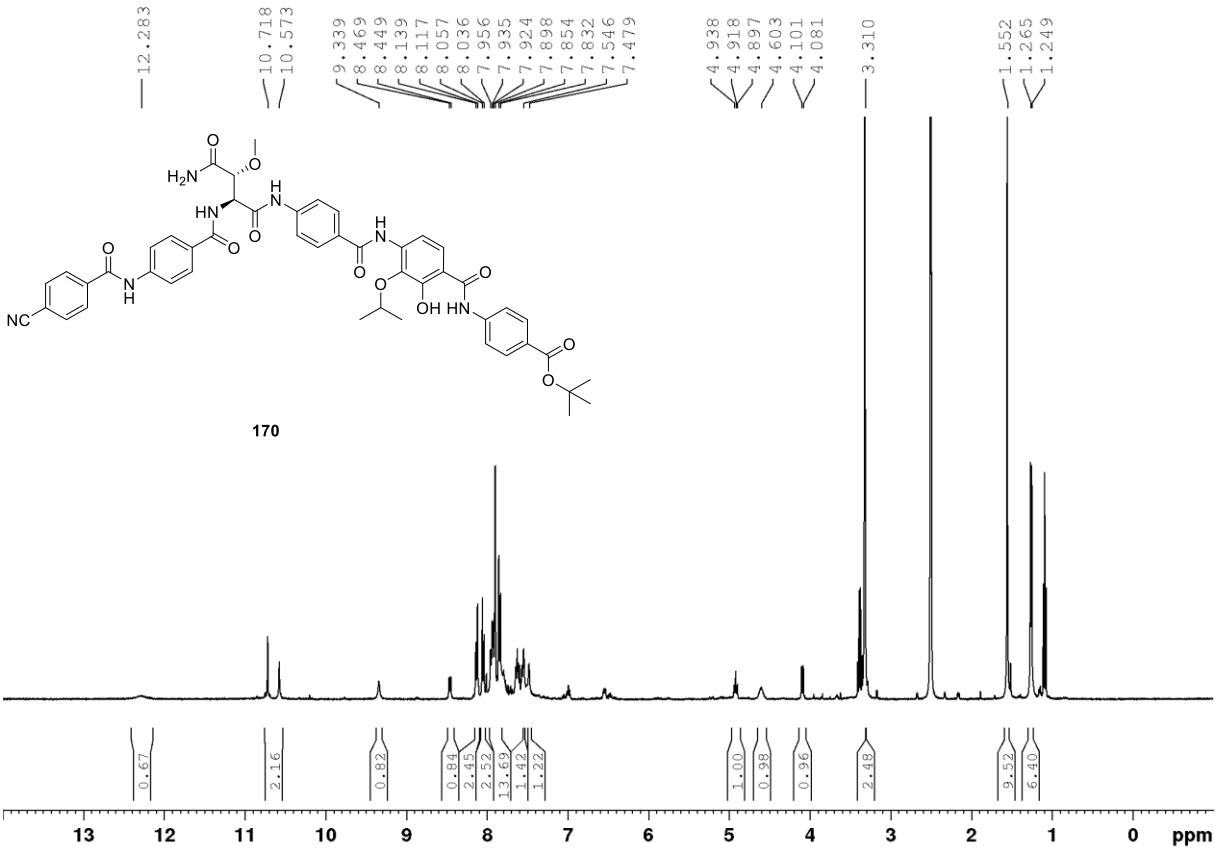

10.528
10.363
9.516
7.983
7.961
7.904
7.882
7.840
7.834
7.817
7.812
7.792
7.448
7.419
7.398
6.812
6.791
6.067
6.053
6.041
6.027
6.024
6.013
6.010
5.997
5.984
5.970
5.398
5.393
5.355
5.350
5.218
5.213
5.192
5.187
4.615
4.601
4.528
4.513
4.497
4.482
4.466
4.422
4.402
4.382
3.861
3.843
3.253
1.547
1.383
1.268
1.253
120
1.00
0.71
0.81
2.26
2.52
5.28
2.61
0.68
1.05
1.06
1.05
2.13
1.02
0.79
0.72
2.42
10.05
10.44
6.15
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

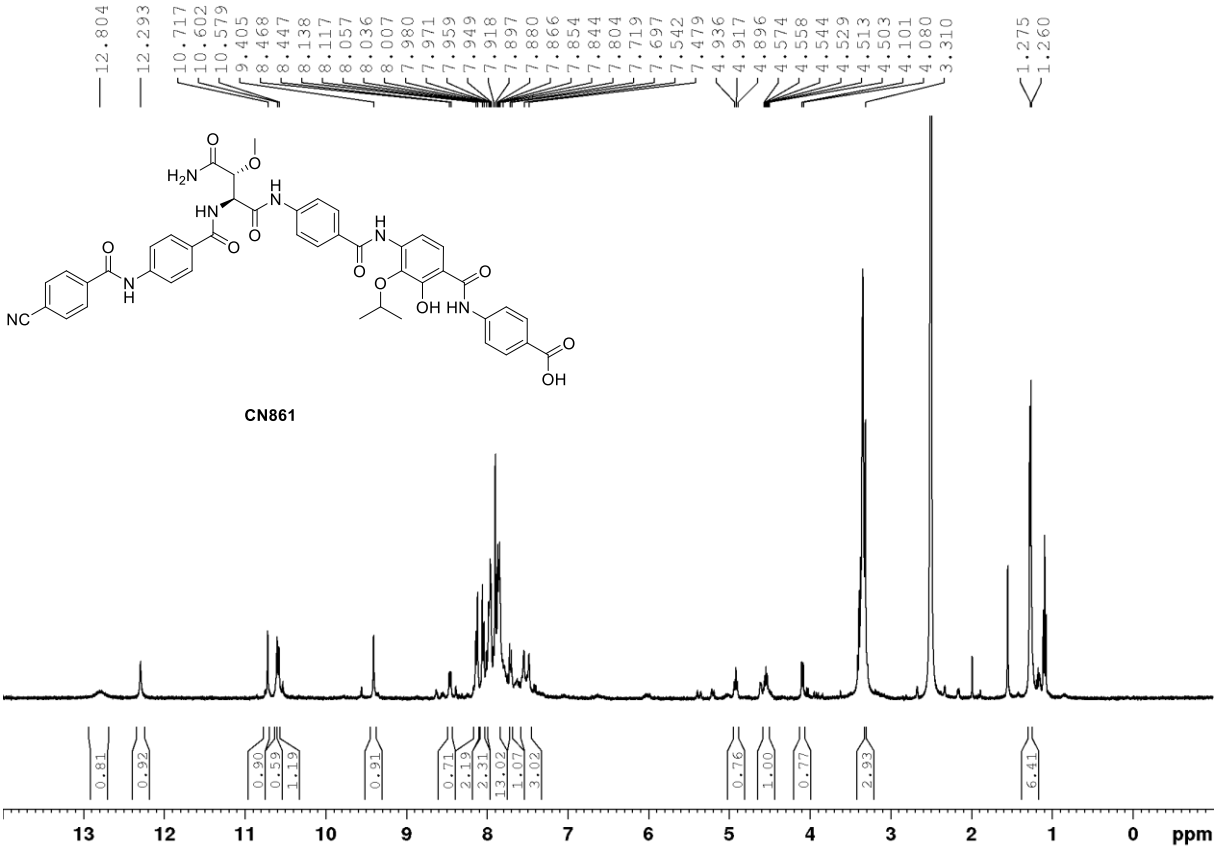

10.805
10.563
10.529
9.524
8.475
8.455
8.401
8.396
8.384
8.379
8.221
8.216
8.204
8.199
7.995
7.973
7.909
7.905
7.882
7.845
7.840
7.831
7.823
7.810
7.547
7.483
7.418
7.397
6.053
6.040
6.026
6.010
5.997
5.984
5.970
5.396
5.392
5.354
5.349
5.345
5.217
5.213
5.191
5.187
4.940
4.920
4.899
4.614
4.601
4.510
4.494
4.479
4.105
4.084
3.314
1.547
1.267
1.251
159
1.00
0.97
1.09
0.97
1.17
2.54
2.52
2.51
6.49
5.71
2.30
1.19
1.21
1.23
1.21
1.16
2.30
1.18
1.15
2.78
9.34
7.12
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

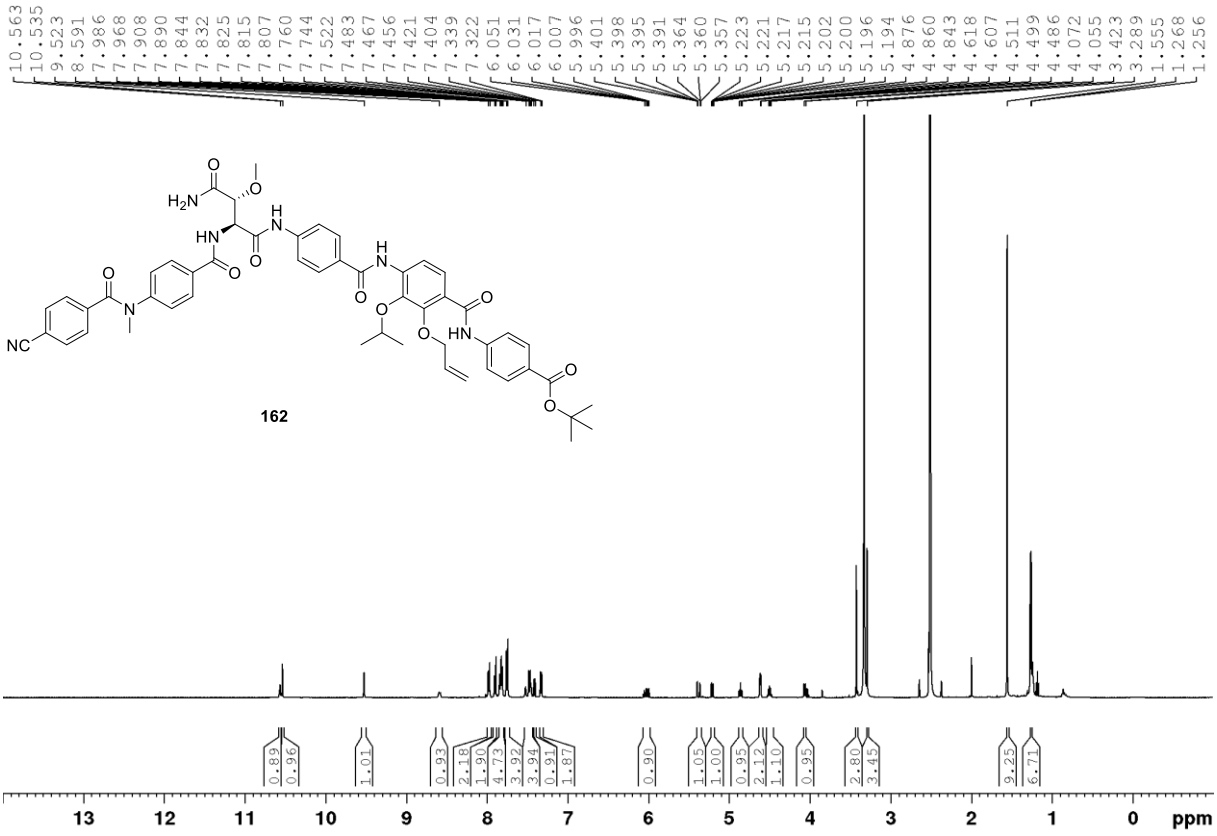

12.279
10.806
10.656
10.579
9.396
8.477
8.457
8.398
8.393
8.381
8.375
8.217
8.212
8.200
8.195
7.968
7.946
7.936
7.914
7.906
7.861
7.855
7.844
7.838
7.833
7.704
7.681
7.549
7.483
4.939
4.918
4.898
4.578
4.563
4.547
4.532
4.517
4.102
4.082
3.311
1.552
1.271
1.256
169
0.84
1.01
0.60
1.00
0.93
0.95
2.11
2.08
13.66
1.00
1.95
0.99
1.01
0.97
3.06
8.44
6.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

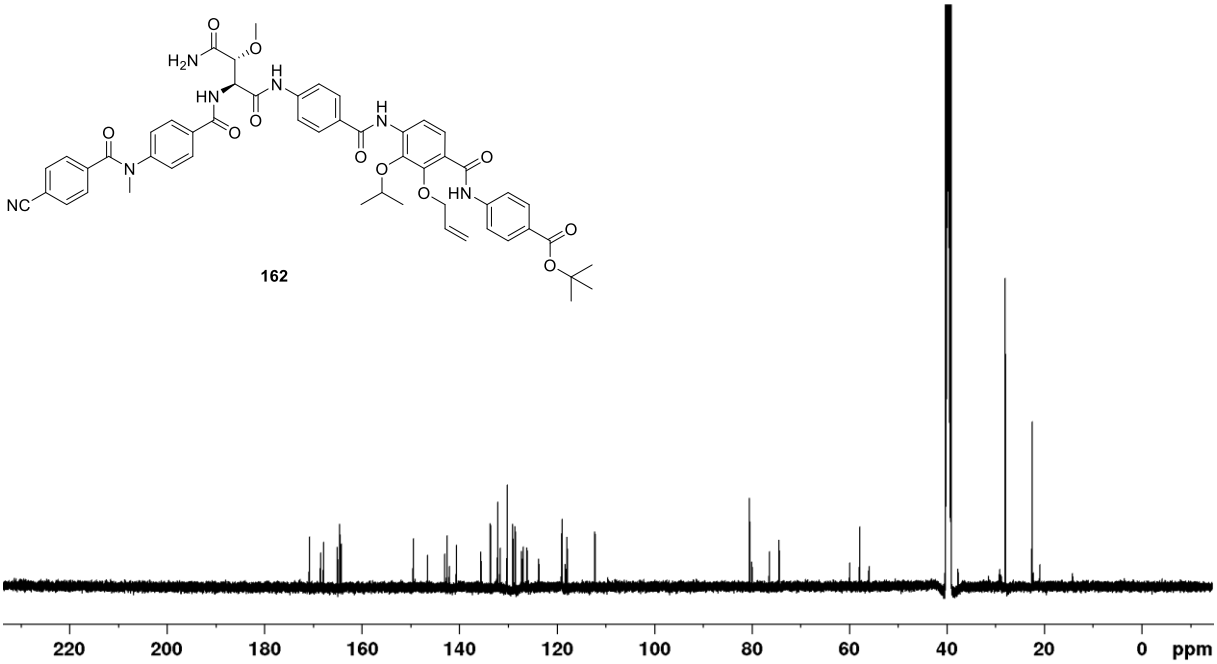

12.810
12.290
10.799
10.597
10.570
9.398
8.466
8.452
8.395
8.381
8.217
8.202
7.976
7.966
7.962
7.952
7.924
7.908
7.902
7.887
7.863
7.852
7.848
7.838
7.718
7.703
7.540
7.474
4.934
4.921
4.907
4.567
4.557
4.547
4.537
4.526
4.100
4.087
3.313
1.274
1.263
861-2
0.66
0.90
1.01
0.91
0.91
0.96
0.95
1.80
1.92
12.53
0.97
2.03
1.00
1.13
1.51
3.07
6.22
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

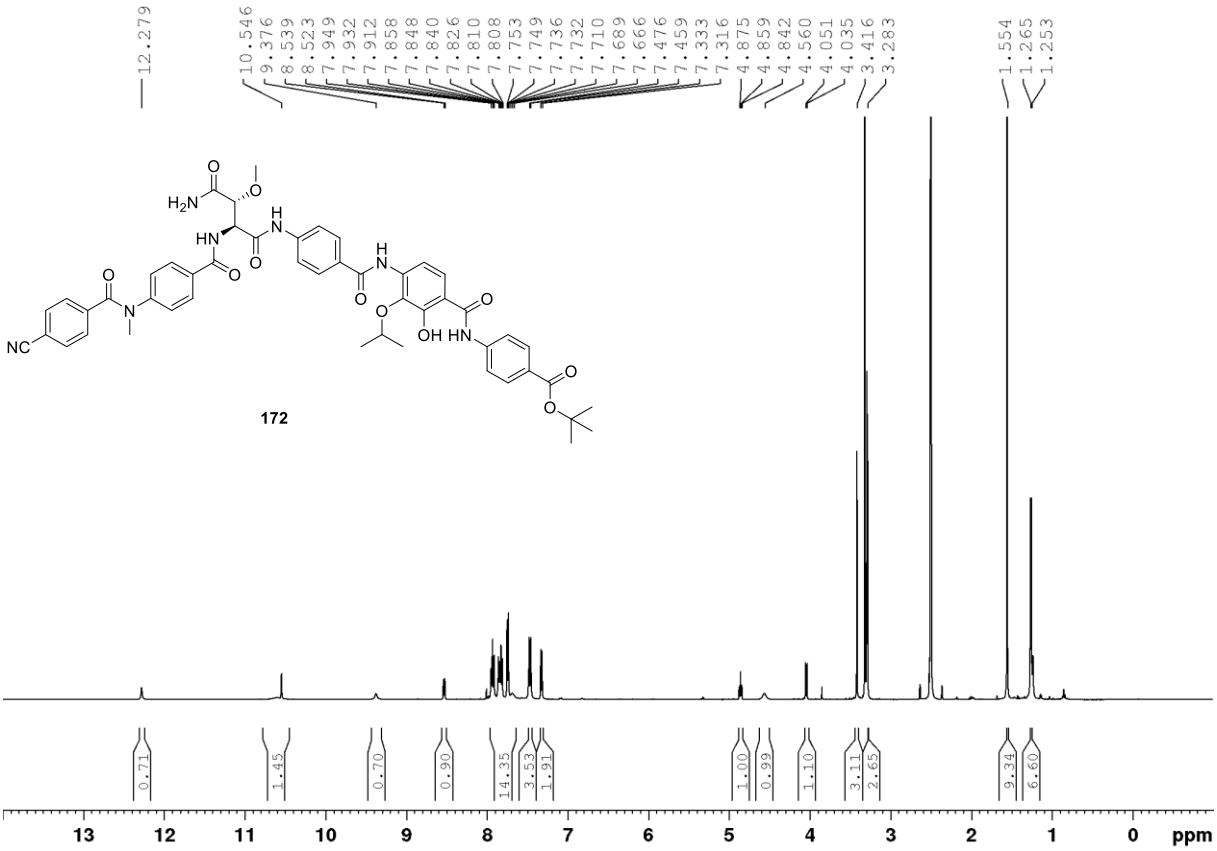

10.720
10.562
10.529
9.523
8.469
8.450
8.138
8.118
8.058
8.038
7.993
7.971
7.898
7.882
7.840
7.831
7.821
7.809
7.547
7.480
7.418
7.396
6.065
6.052
6.039
6.025
6.009
5.996
5.983
5.969
5.395
5.352
5.215
5.188
4.936
4.915
4.896
4.613
4.601
4.522
4.508
4.493
4.478
4.103
4.084
3.318
1.547
1.265
1.250
160
0.86
0.84
0.97
0.95
0.76
2.19
2.59
2.00
10.97
1.78
1.06
1.00
1.03
1.04
0.77
2.06
0.99
0.80
2.63
9.15
6.67
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


12.283
10.718
10.573
9.339
8.469
8.449
8.139
8.117
8.057
8.036
7.956
7.935
7.924
7.898
7.854
7.832
7.546
7.479
4.938
4.918
4.897
4.603
4.101
4.081
3.310
1.552
1.265
1.249
170
0.67
2.16
0.82
0.84
2.45
2.52
13.69
1.42
1.22
1.00
0.98
0.96
2.48
9.52
6.40
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

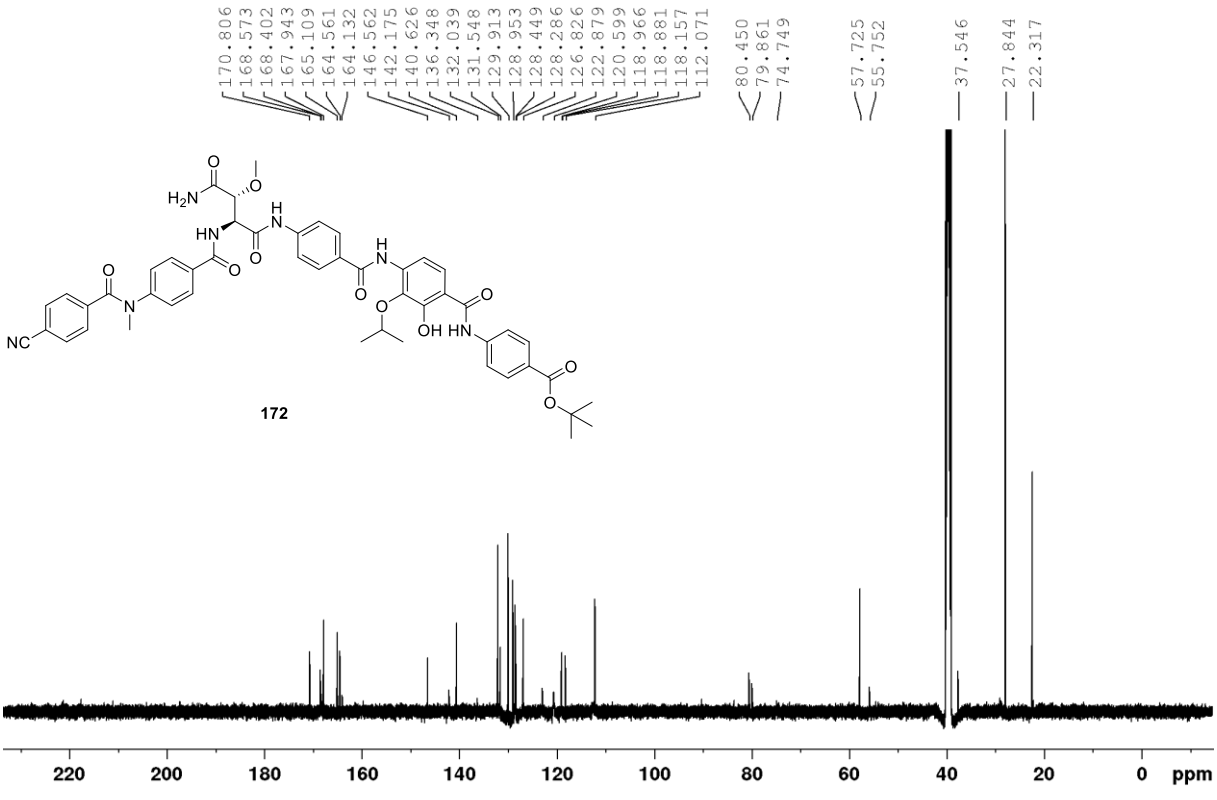

12.804
12.293
10.717
10.602
10.579
9.405
8.468
8.447
8.138
8.117
8.057
8.036
8.007
7.980
7.971
7.959
7.949
7.918
7.897
7.880
7.866
7.854
7.844
7.804
7.719
7.697
7.542
7.479
4.936
4.917
4.896
4.574
4.558
4.544
4.529
4.513
4.503
4.101
4.080
3.310
1.275
1.260
CN861
0.81
0.92
0.90
0.59
1.19
0.91
0.71
2.19
2.31
13.02
1.07
3.02
0.76
1.00
0.77
2.93
6.41
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm


10.563
10.535
9.523
8.591
7.986
7.968
7.908
7.890
7.844
7.832
7.825
7.815
7.807
7.760
7.744
7.522
7.483
7.467
7.456
7.421
7.404
7.339
7.322
6.051
6.031
6.017
6.007
5.996
5.401
5.398
5.395
5.391
5.364
5.360
5.357
5.223
5.221
5.217
5.215
5.202
5.200
5.196
5.194
4.876
4.860
4.843
4.618
4.607
4.511
4.499
4.486
4.072
4.055
3.423
3.289
1.555
1.268
1.256
0.89
0.96
1.01
0.93
2.18
1.90
4.73
3.92
3.94
0.91
1.87
0.90
1.05
1.00
0.95
2.12
1.10
0.95
2.80
3.45
9.25
6.71
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

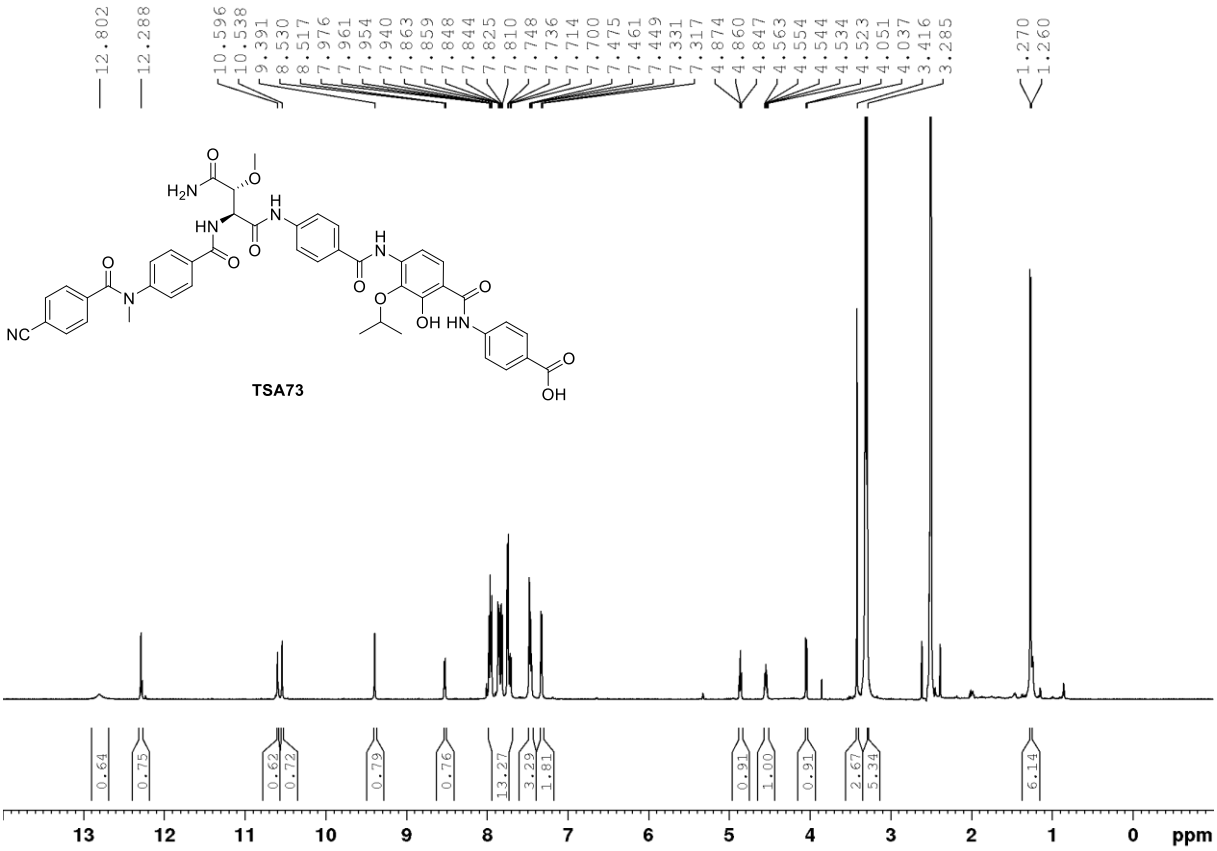

170.814
168.553
167.945
165.101
164.586
164.535
164.274
149.520
146.559
143.025
142.534
142.122
140.629
135.631
133.650
132.042
131.564
130.088
128.956
128.459
128.390
127.110
126.827
126.014
123.611
118.947
118.876
118.827
118.161
117.800
112.073
80.338
79.845
76.253
74.299
59.750
57.704
55.820
37.550
27.854
22.331
220
200
180
160
140
120
100
80
60
40
20
0
ppm

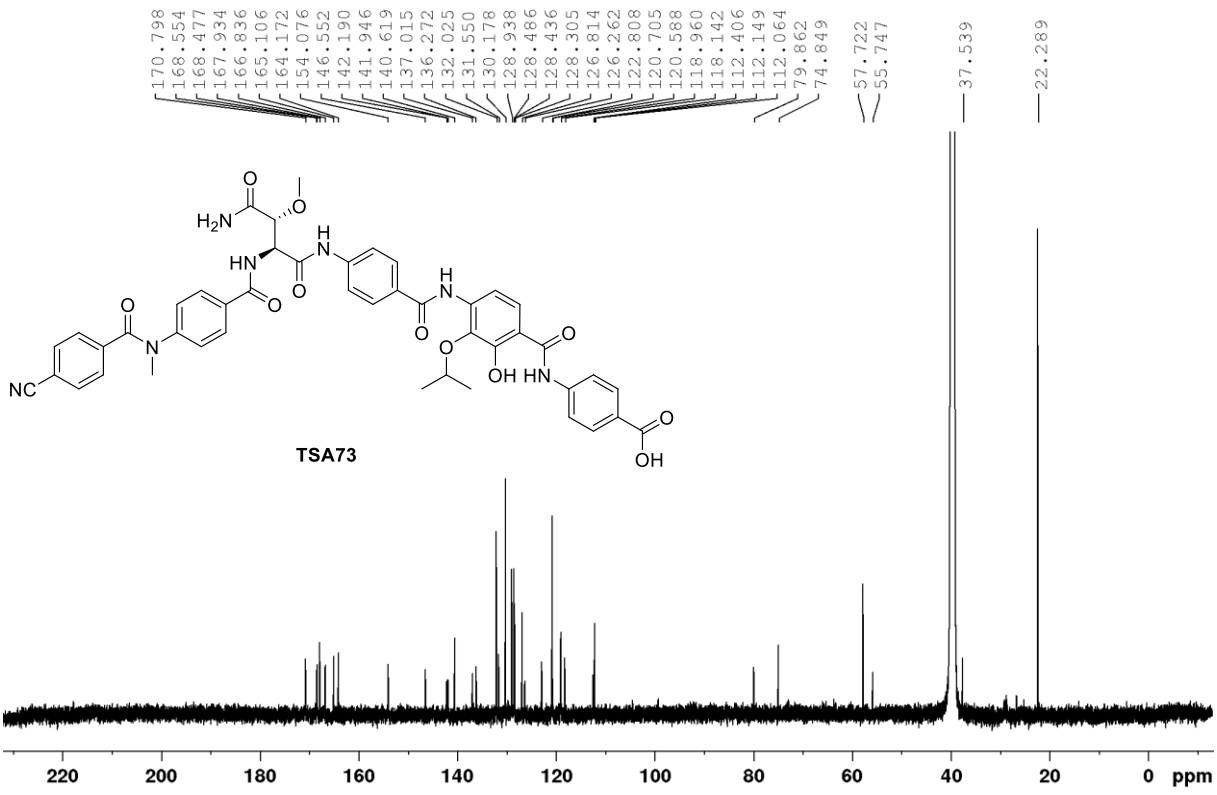

12.279
10.546
9.376
8.539
8.523
7.949
7.932
7.912
7.858
7.848
7.840
7.826
7.810
7.808
7.753
7.749
7.736
7.732
7.710
7.689
7.666
7.476
7.459
7.333
7.316
4.875
4.859
4.842
4.560
4.051
4.035
3.416
3.283
1.554
1.265
1.253
0.71
1.45
0.70
0.90
14.35
3.53
1.91
1.00
0.99
1.10
3.11
2.65
9.34
6.60
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

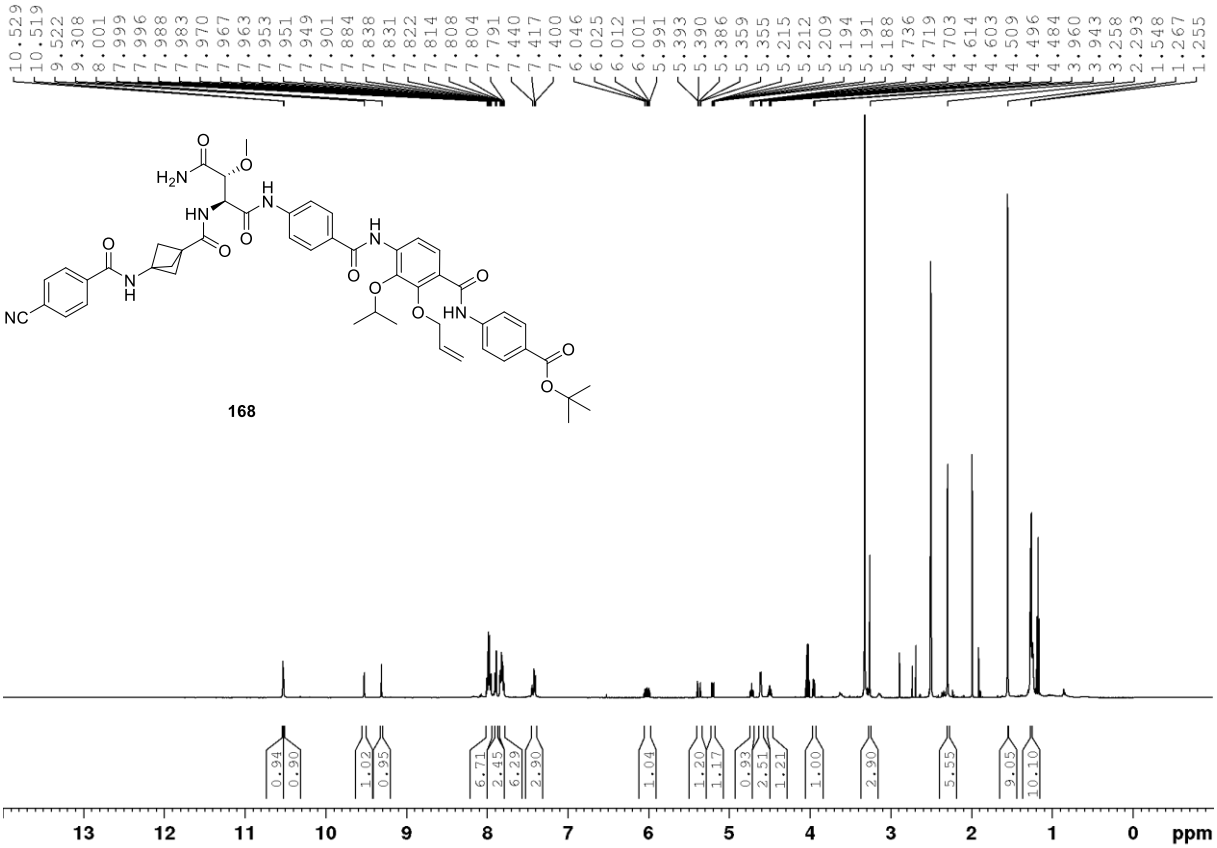
172

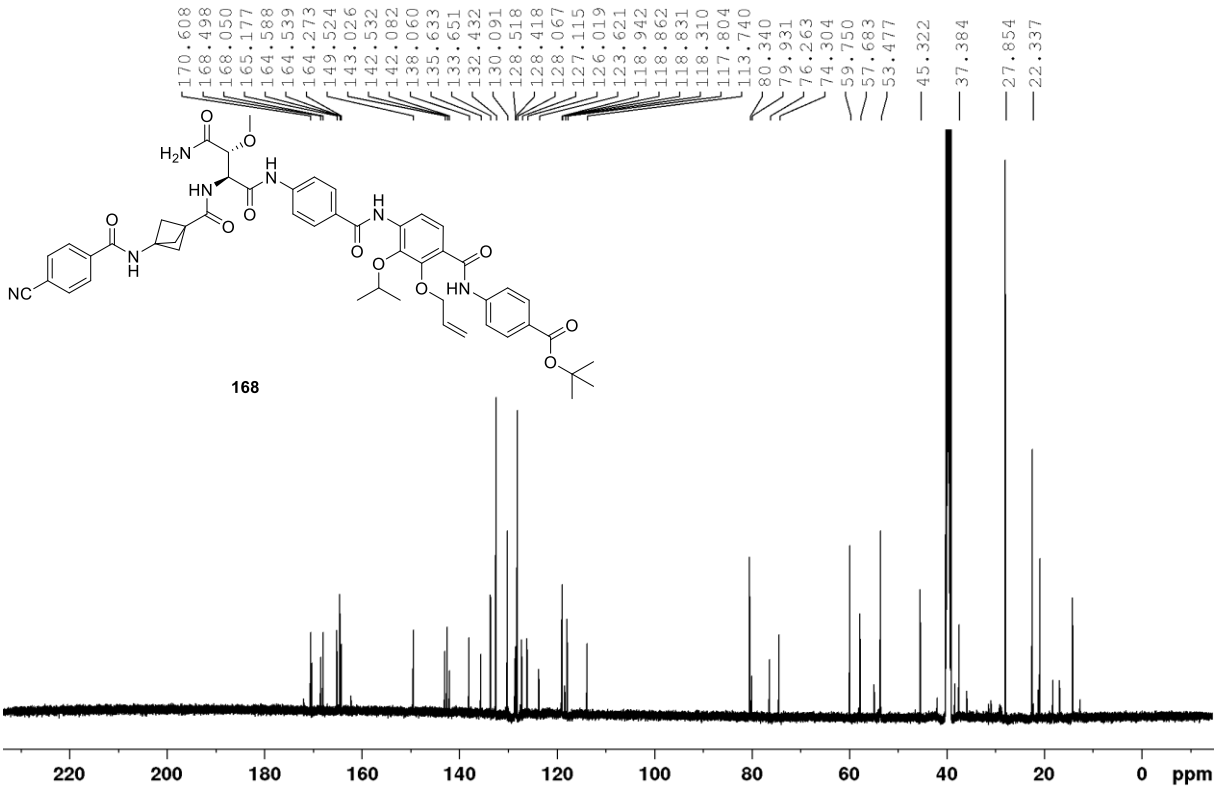

170.806
168.573
168.402
167.943
165.109
164.561
164.132
146.562
142.175
140.626
136.348
132.039
131.548
129.913
128.953
128.449
128.286
126.826
122.879
120.599
118.966
118.881
118.157
112.071
80.450
79.861
74.749
57.725
55.752
37.546
27.844
22.317
220
200
180
160
140
120
100
80
60
40
20
0
ppm

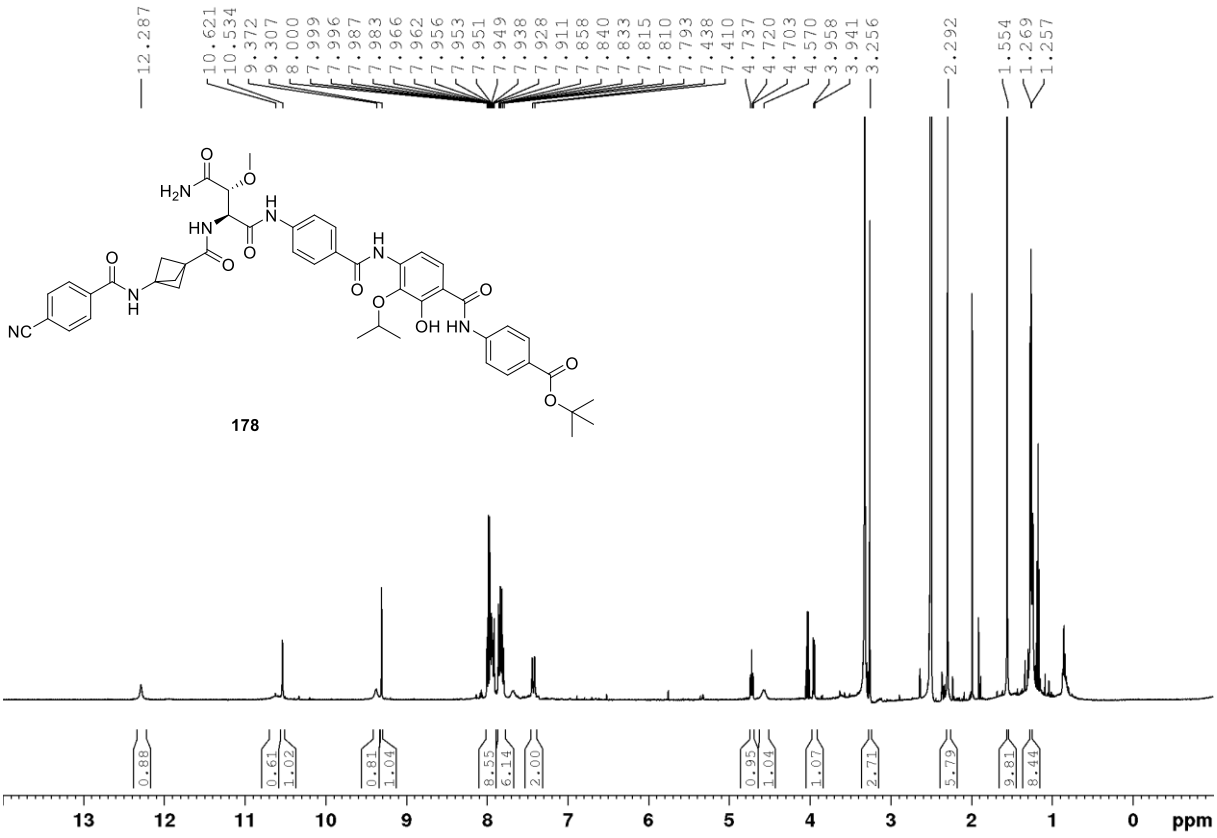
172

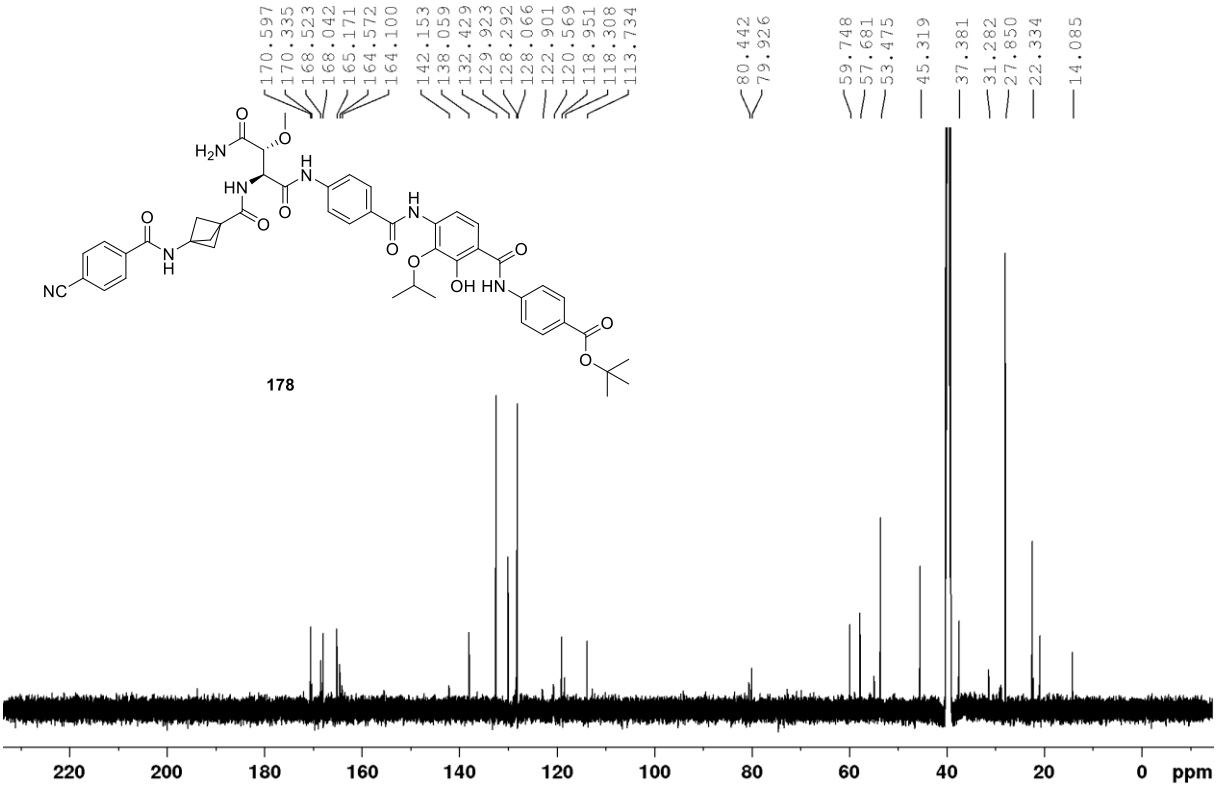

12.802
12.288
10.596
10.538
9.391
8.530
8.517
7.976
7.961
7.954
7.940
7.863
7.859
7.848
7.844
7.825
7.810
7.748
7.736
7.714
7.700
7.475
7.461
7.449
7.331
7.317
4.874
4.860
4.847
4.563
4.554
4.544
4.534
4.523
4.051
4.037
3.416
3.285
1.270
1.260
TSA73
0.64
0.75
0.62
0.72
0.79
0.76
13.27
3.29
1.81
0.91
1.00
0.91
2.67
5.34
6.14
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

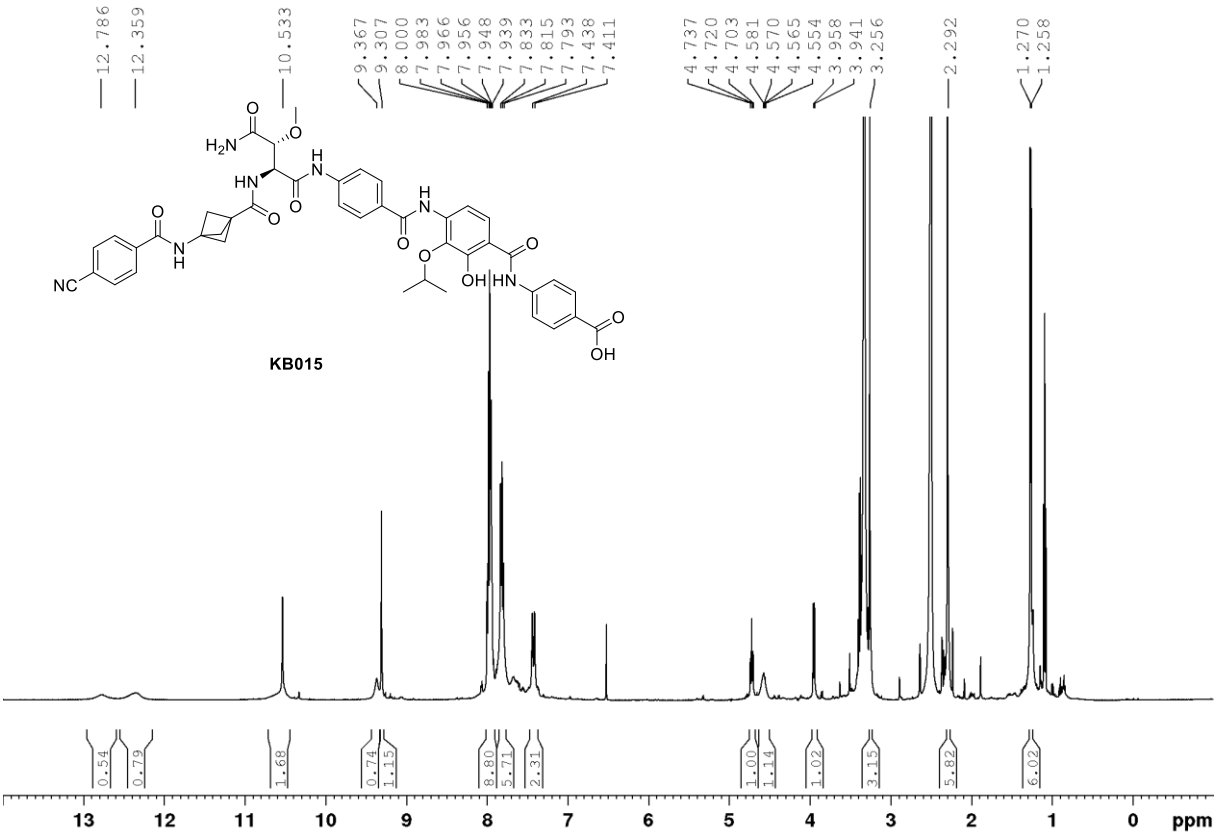

170.798
168.554
168.477
167.934
166.836
165.106
164.172
154.076
146.552
142.190
141.946
140.619
137.015
136.272
132.025
131.550
130.178
128.938
128.486
128.436
128.305
126.814
126.262
122.808
120.705
120.588
118.960
118.142
112.406
112.149
112.064
79.862
74.849
57.722
55.747
37.539
22.289
TSA73
220 200 180 160 140 120 100 80 60 40 20 0 ppm

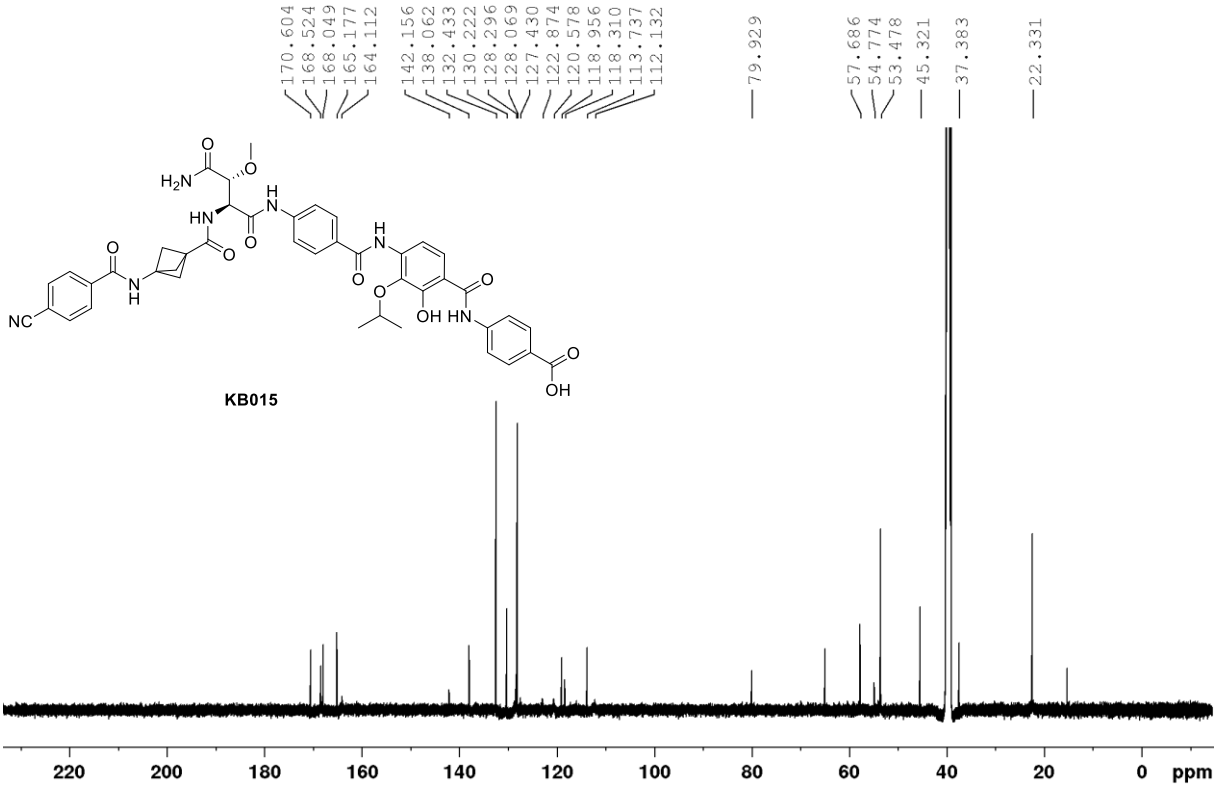

10.529
10.519
9.522
9.308
8.001
7.999
7.996
7.988
7.983
7.970
7.967
7.963
7.953
7.951
7.949
7.901
7.884
7.838
7.831
7.822
7.814
7.808
7.804
7.791
7.440
7.417
7.400
6.046
6.025
6.012
6.001
5.991
5.393
5.390
5.386
5.359
5.355
5.215
5.212
5.209
5.194
5.191
5.188
4.736
4.719
4.703
4.614
4.603
4.509
4.496
4.484
3.960
3.943
3.258
2.293
1.548
1.267
1.255
168
0.84
0.90
1.02
0.95
6.71
2.45
6.29
2.90
1.04
1.20
1.17
0.93
2.51
1.21
1.00
2.90
5.55
9.05
10.10
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

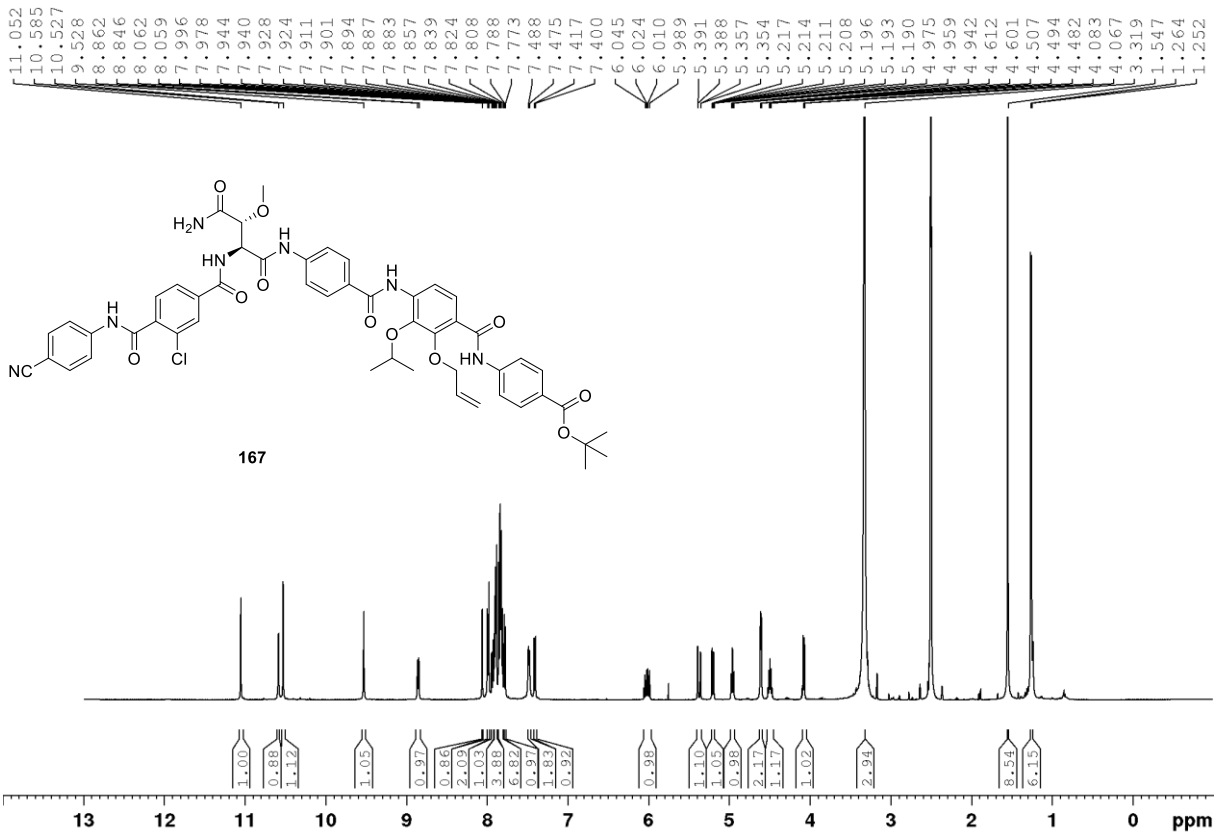

170.608
168.498
168.050
165.177
164.588
164.539
164.273
149.524
143.026
142.532
142.082
138.060
135.633
133.651
132.432
130.091
128.518
128.418
128.067
127.115
126.019
123.621
118.942
118.862
118.831
118.310
117.804
113.740
80.340
79.931
76.263
74.304
59.750
57.683
53.477
45.322
37.384
27.854
22.337
168
220
200
180
160
140
120
100
80
60
40
20
0
ppm

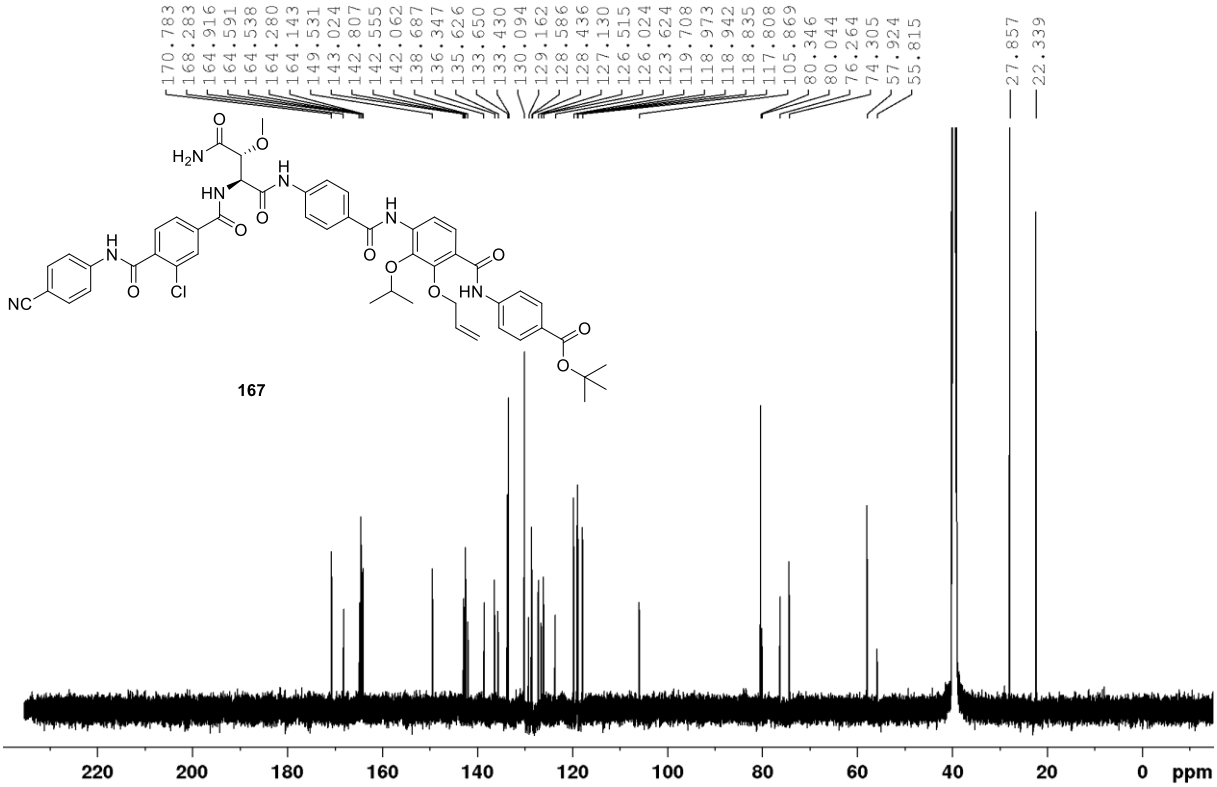

12.287
10.621
10.534
9.372
9.307
8.000
7.999
7.996
7.987
7.983
7.966
7.962
7.956
7.953
7.951
7.949
7.938
7.928
7.911
7.858
7.840
7.833
7.815
7.810
7.793
7.438
7.410
4.737
4.720
4.703
4.570
3.958
3.941
3.256
2.292
1.554
1.269
1.257
178
0.88
0.61
1.02
0.81
1.04
8.55
6.14
2.00
0.95
1.04
1.07
2.71
5.79
9.83
8.44
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

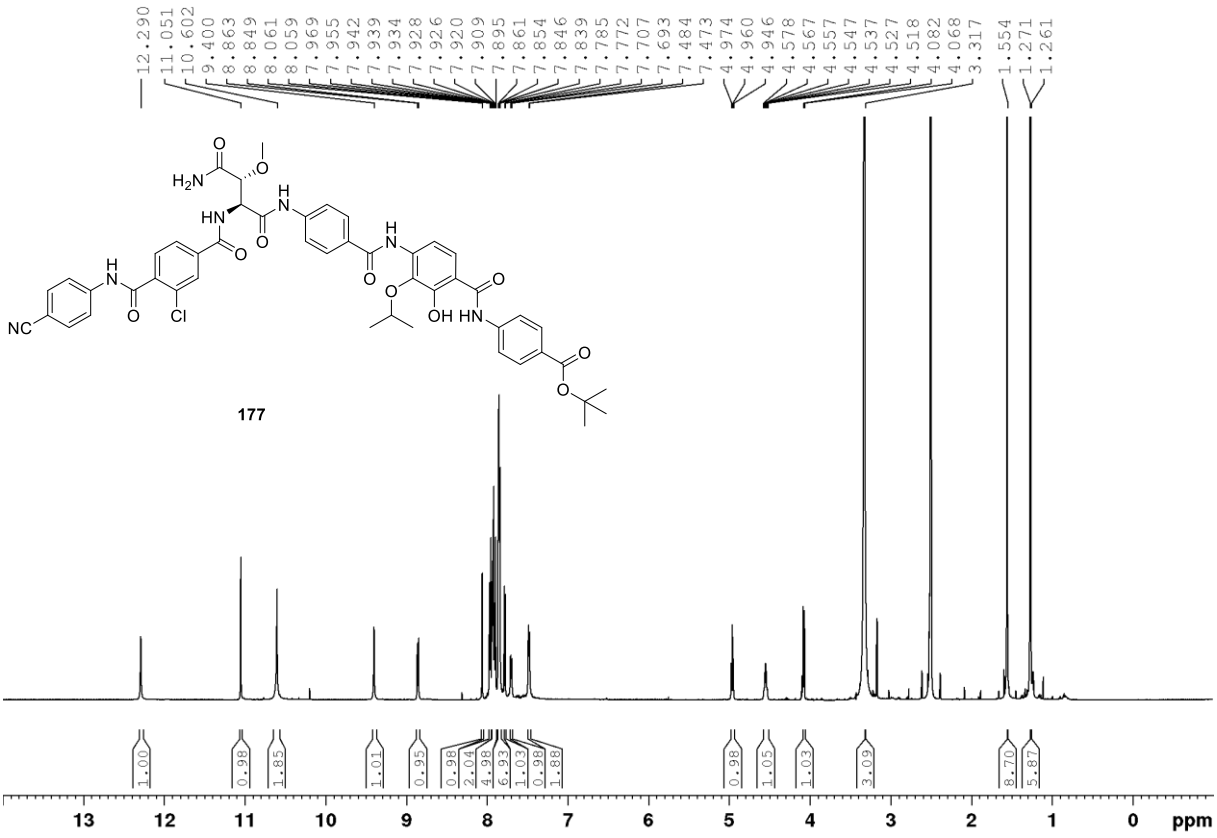

170.597
170.335
168.523
168.042
165.171
164.572
164.100
142.153
138.059
132.429
129.923
128.292
128.066
122.901
120.569
118.951
118.308
113.734
80.442
79.926
59.748
57.681
53.475
45.319
37.381
31.282
27.850
22.334
14.085
178
220
200
180
160
140
120
100
80
60
40
20
0
ppm

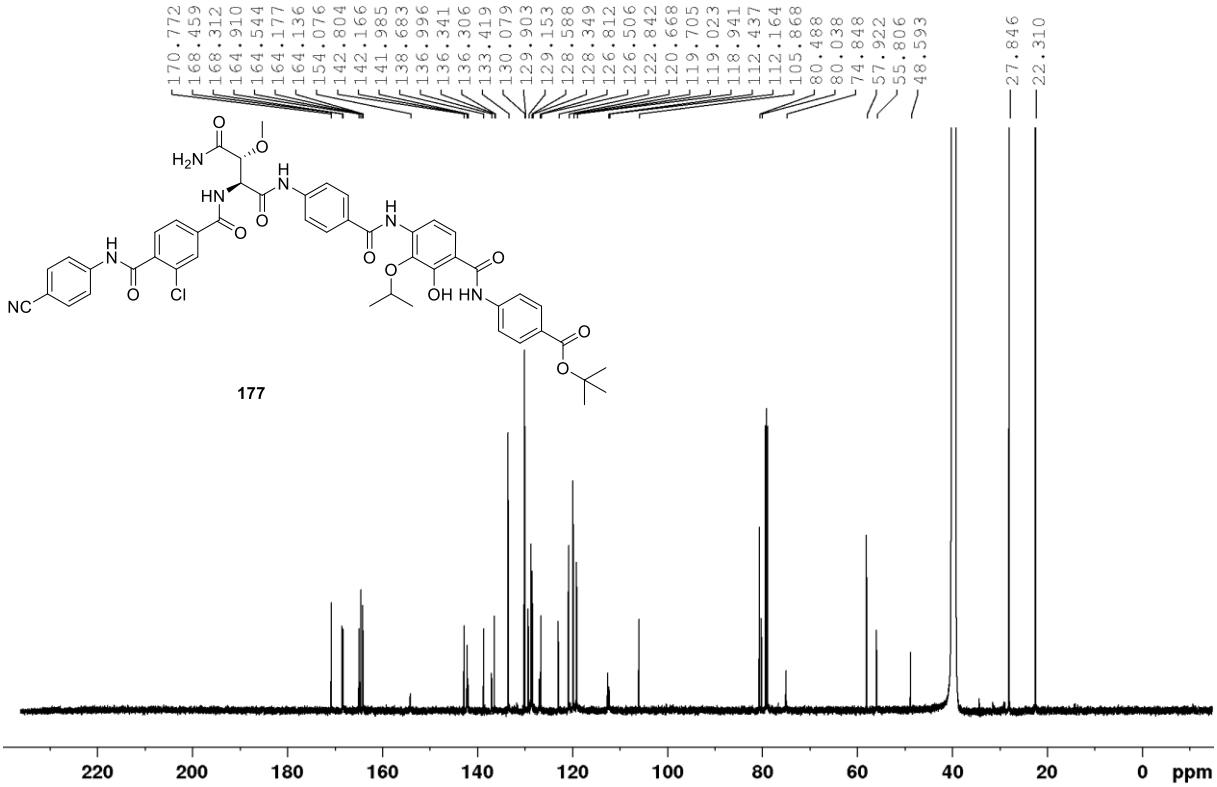

12.786
12.359
10.533
9.367
9.307
8.000
7.983
7.966
7.956
7.948
7.939
7.833
7.815
7.793
7.438
7.411
4.737
4.720
4.703
4.581
4.570
4.565
4.554
3.958
3.941
3.256
2.292
1.270
1.258
KB015
0.54
0.79
1.68
0.74
1.15
8.80
5.71
2.31
1.00
1.14
1.02
3.15
5.82
6.02
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

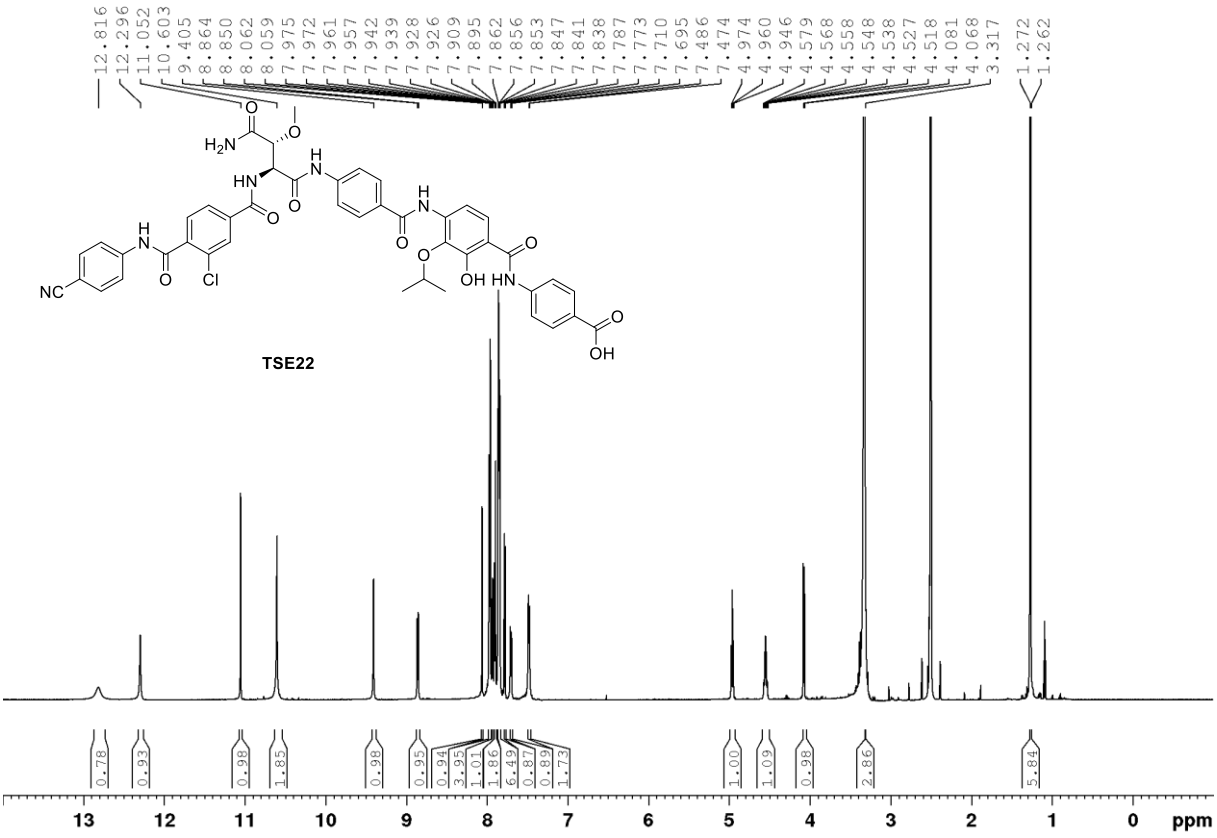

170.604
168.524
168.049
165.177
164.112
142.156
138.062
132.433
130.222
128.296
128.069
127.430
122.874
120.578
118.956
118.310
113.737
112.132
79.929
57.686
54.774
53.478
45.321
37.383
22.331
KB015
220
200
180
160
140
120
100
80
60
40
20
0
ppm

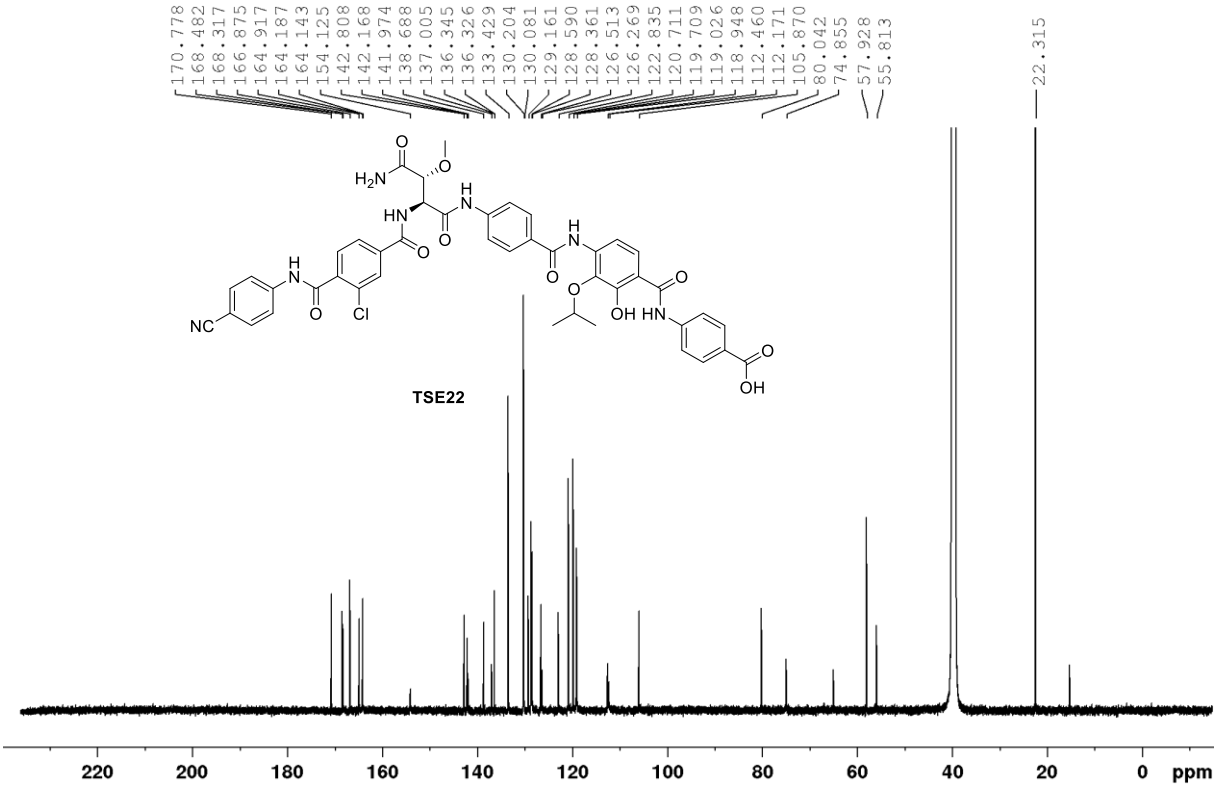

11.052
10.585
10.527
9.528
8.862
8.846
8.062
8.059
7.996
7.978
7.944
7.940
7.928
7.924
7.911
7.901
7.894
7.887
7.883
7.857
7.839
7.824
7.808
7.788
7.773
7.488
7.475
7.417
7.400
6.045
6.024
6.010
5.989
5.391
5.388
5.357
5.354
5.217
5.214
5.211
5.208
5.196
5.193
5.190
4.975
4.959
4.942
4.612
4.601
4.507
4.494
4.482
4.083
4.067
3.319
1.547
1.264
1.252
167
1.00
0.88
1.12
1.05
0.97
0.86
2.09
1.03
3.88
6.82
0.97
1.82
0.92
0.98
1.10
1.05
0.98
2.17
1.17
1.02
2.94
8.54
6.15
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

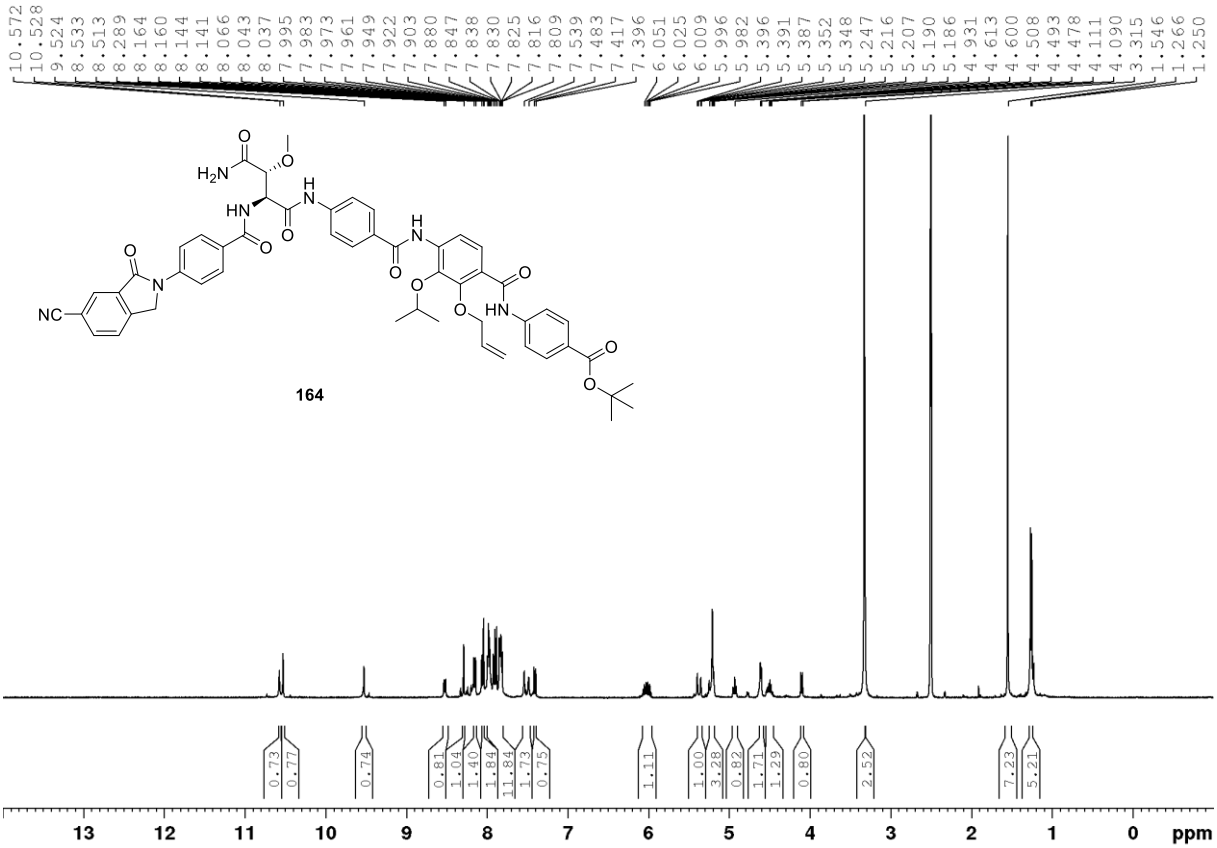

170.783
168.283
164.916
164.591
164.538
164.280
164.143
149.531
143.024
142.807
142.555
142.062
138.687
136.347
135.626
133.650
133.430
130.094
129.162
128.586
128.436
127.130
126.515
126.024
123.624
119.708
118.973
118.942
118.835
117.808
105.869
80.346
80.044
76.264
74.305
57.924
55.815
27.857
22.339
167
220
200
180
160
140
120
100
80
60
40
20
0
ppm

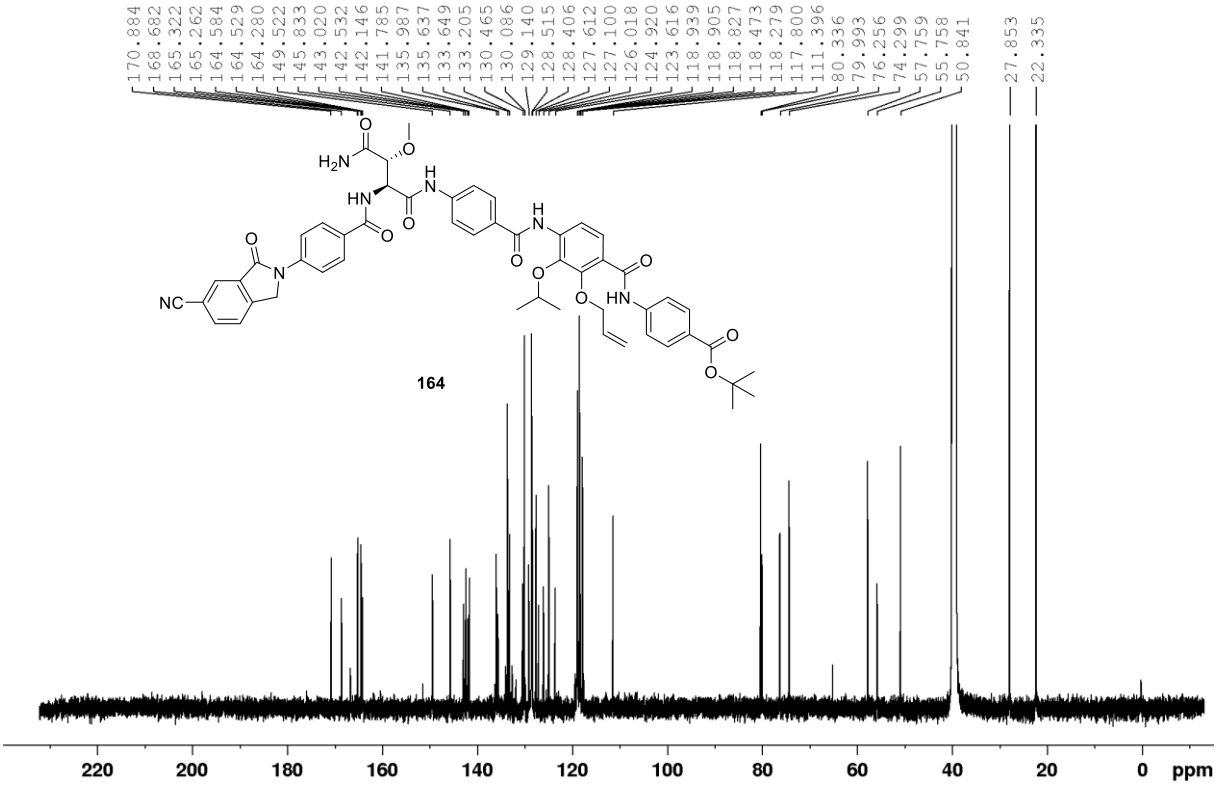

12.290
11.051
10.602
9.400
8.863
8.849
8.061
8.059
7.969
7.955
7.942
7.939
7.934
7.928
7.926
7.920
7.909
7.895
7.861
7.854
7.846
7.839
7.785
7.772
7.707
7.693
7.484
7.473
4.974
4.960
4.946
4.578
4.567
4.557
4.547
4.537
4.527
4.518
4.082
4.068
3.317
1.554
1.271
1.261
177
1.00
0.98
1.85
1.01
0.95
0.98
2.04
4.98
6.93
1.03
0.98
1.88
0.98
1.05
1.03
3.09
8.70
5.87
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

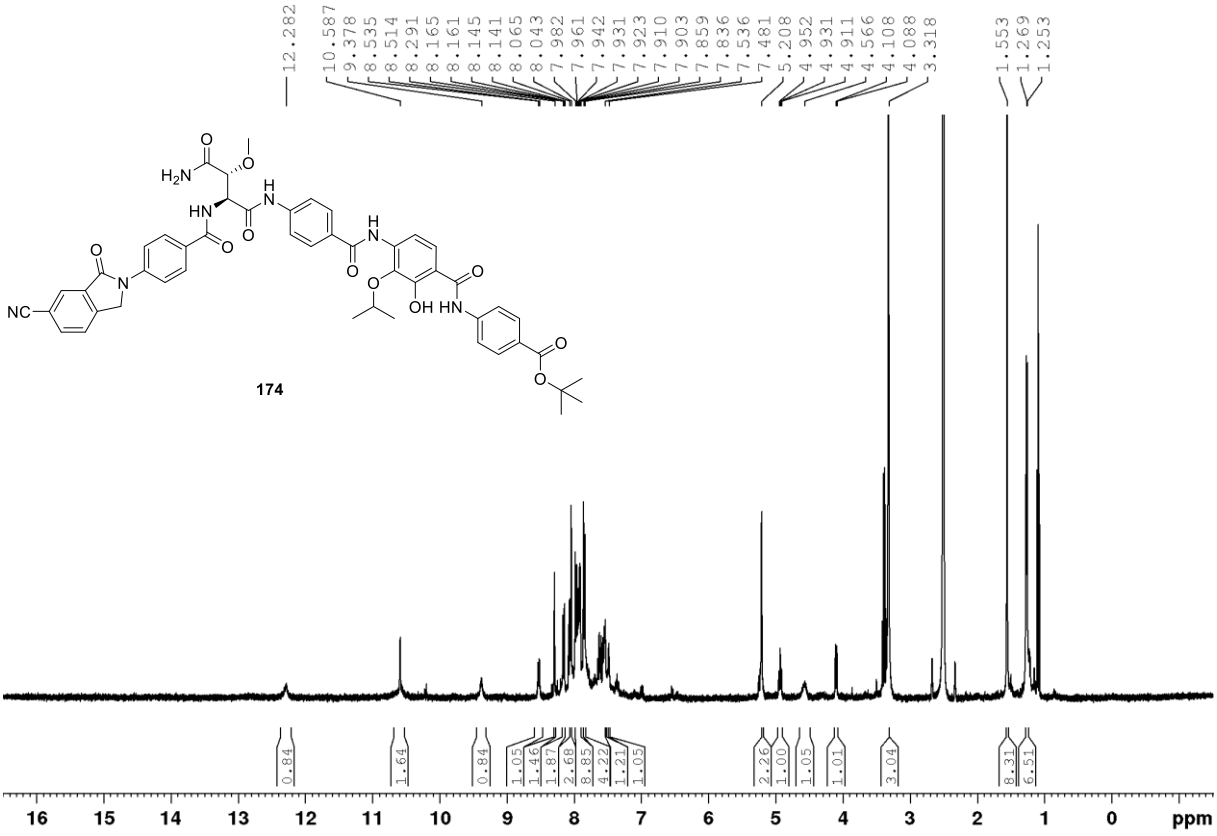

170.772
168.459
168.312
164.910
164.544
164.177
164.136
154.076
142.804
142.166
141.985
138.683
136.996
136.341
136.306
133.419
130.079
129.903
129.153
128.588
128.349
126.812
126.506
122.842
120.668
119.705
119.023
118.941
112.437
112.164
105.868
80.488
80.038
74.848
57.922
55.806
48.593
27.846
22.310
177
220
200
180
160
140
120
100
80
60
40
20
0
ppm

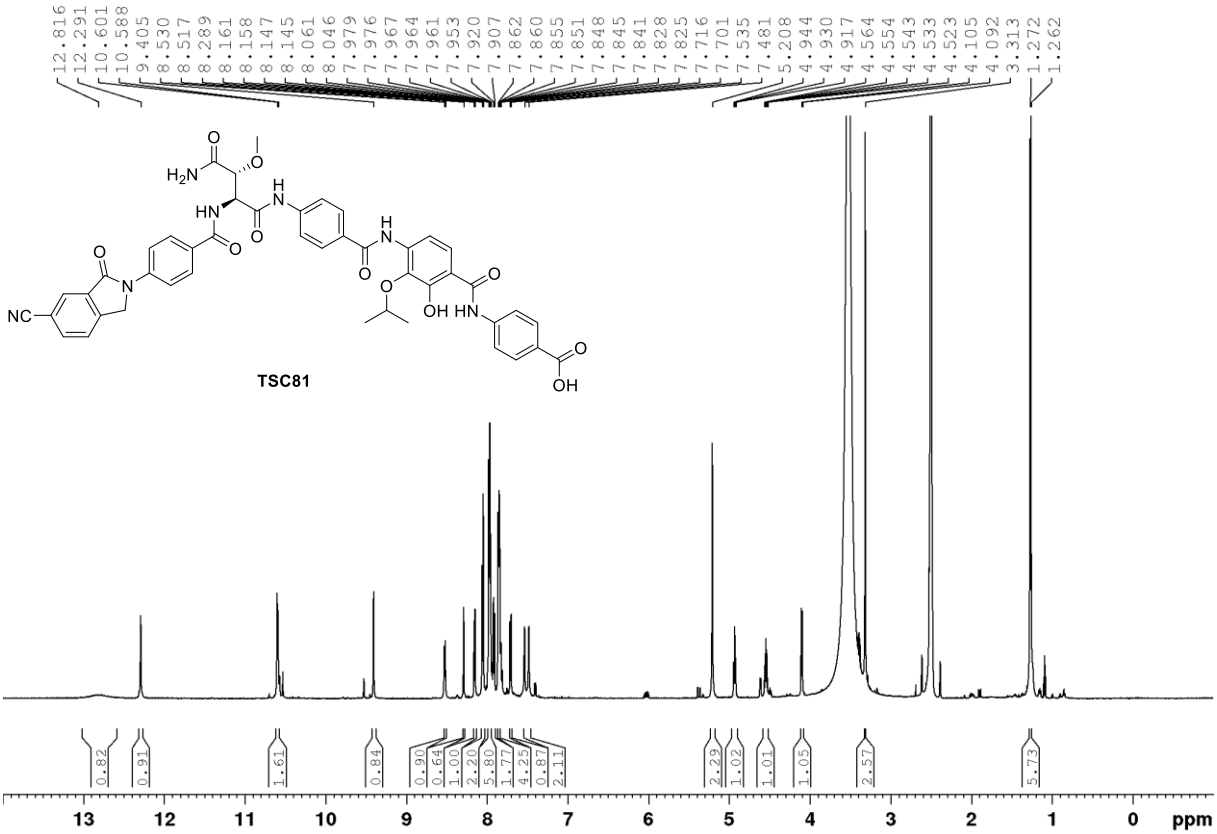

12.816
12.296
11.052
10.603
9.405
8.864
8.850
8.062
8.059
7.975
7.972
7.961
7.957
7.942
7.939
7.928
7.926
7.909
7.895
7.862
7.856
7.853
7.847
7.841
7.838
7.787
7.773
7.710
7.695
7.486
7.474
4.974
4.960
4.946
4.579
4.568
4.558
4.548
4.538
4.527
4.518
4.081
4.068
3.317
1.272
1.262
TSE22
0.78
0.93
0.98
1.85
0.98
0.95
0.94
3.95
1.01
1.86
6.49
0.87
0.89
1.73
1.00
1.09
0.98
2.86
5.84
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

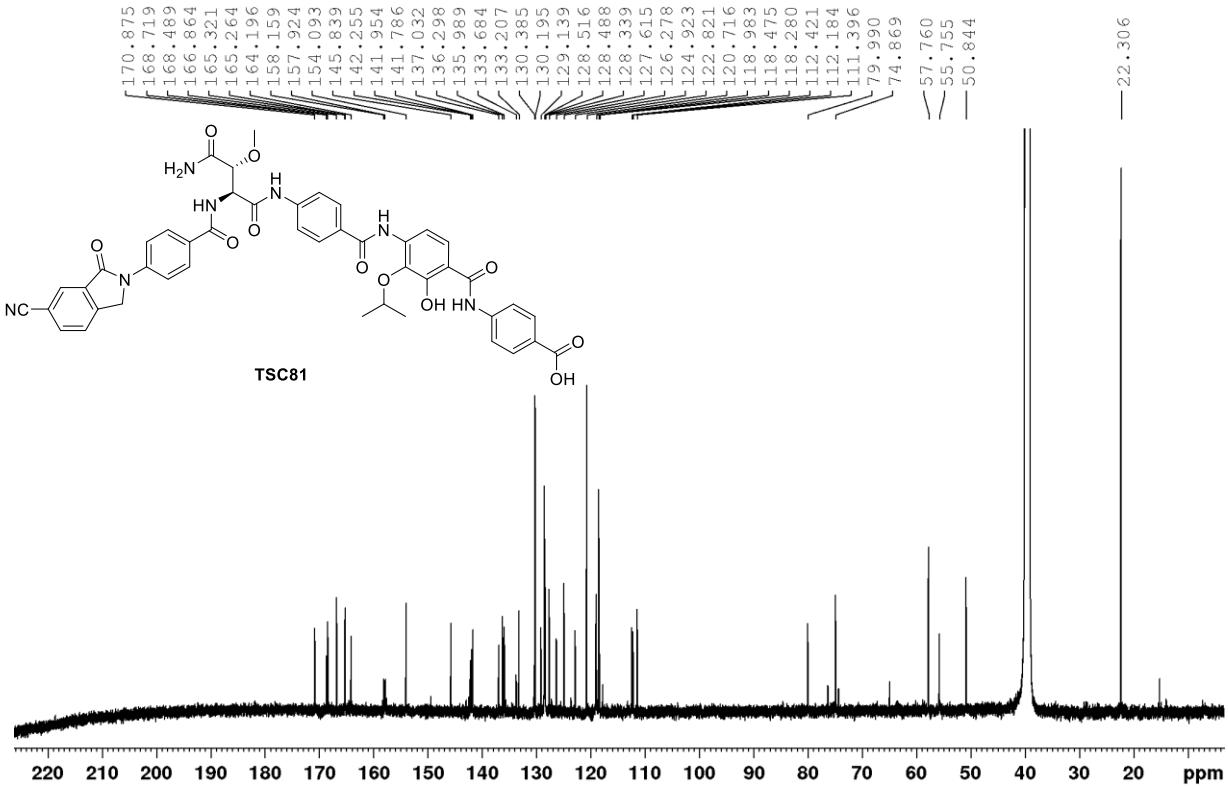

170.778
168.482
168.317
166.875
164.917
164.187
164.143
154.125
142.808
142.168
141.974
138.688
137.005
136.345
136.326
133.429
130.204
130.081
129.161
128.590
128.361
126.513
126.269
122.835
120.711
119.709
119.026
118.948
112.460
112.171
105.870
80.042
74.855
57.928
55.813
22.315
TSE22
220
200
180
160
140
120
100
80
60
40
20
0
ppm

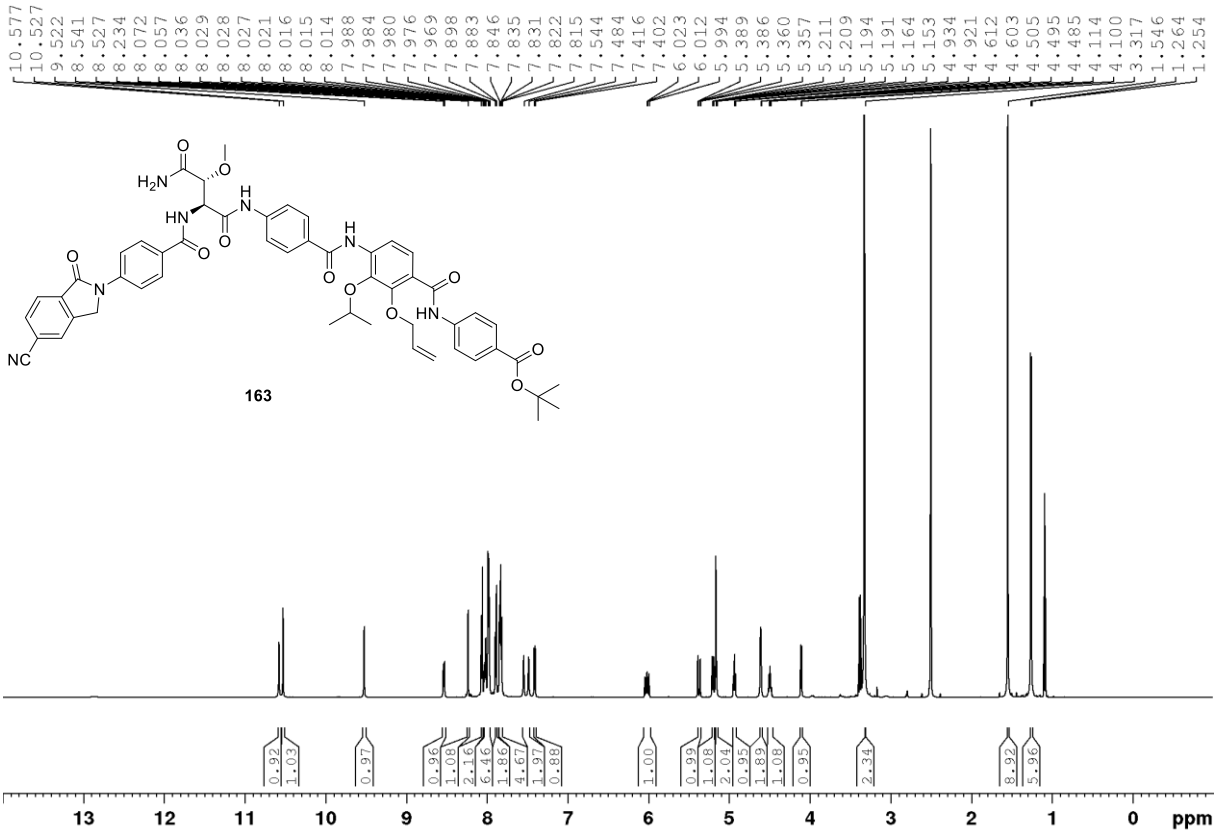

10.572
10.528
9.524
8.533
8.513
8.289
8.164
8.160
8.144
8.141
8.066
8.043
8.037
7.995
7.983
7.973
7.961
7.949
7.922
7.903
7.880
7.847
7.838
7.830
7.825
7.816
7.809
7.539
7.483
7.417
7.396
6.051
6.025
6.009
5.996
5.982
5.396
5.391
5.387
5.352
5.348
5.247
5.216
5.207
5.190
5.186
4.931
4.613
4.600
4.508
4.493
4.478
4.111
4.090
3.315
1.546
1.266
1.250
164
0.73
0.77
0.74
0.81
1.04
1.40
1.84
11.84
1.73
0.75
1.11
1.00
3.28
0.82
1.71
1.29
0.80
2.52
7.23
5.21
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

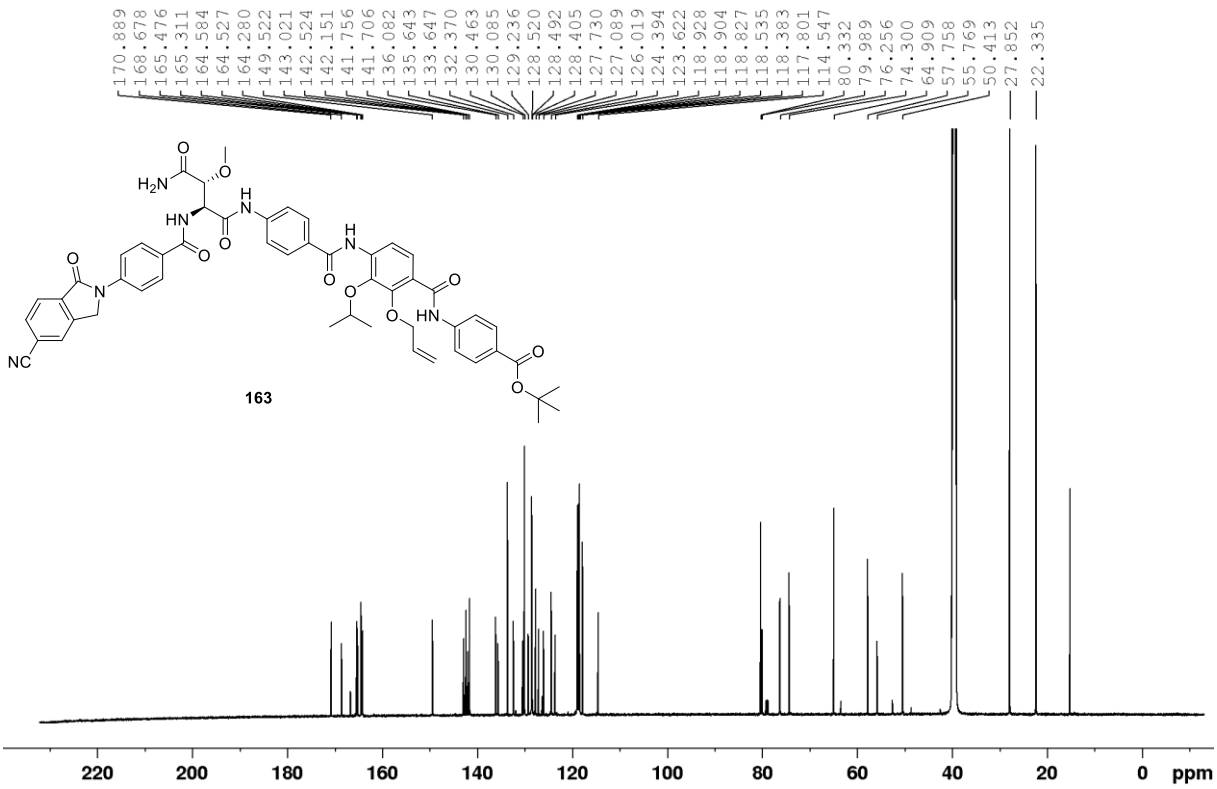

170.884
168.682
165.322
165.262
164.584
164.529
164.280
149.522
145.833
143.020
142.532
142.146
141.785
135.987
135.637
133.649
133.205
130.465
130.086
129.140
128.515
128.406
127.612
127.100
126.018
124.920
123.616
118.939
118.905
118.827
118.473
118.279
117.800
111.396
80.336
79.993
76.256
74.299
57.759
55.758
50.841
27.853
22.335
164
220
200
180
160
140
120
100
80
60
40
20
0
ppm


12.282
10.587
9.378
8.535
8.514
8.291
8.165
8.161
8.145
8.141
8.065
8.043
7.982
7.961
7.942
7.931
7.923
7.910
7.903
7.859
7.836
7.536
7.481
5.208
4.952
4.931
4.911
4.566
4.108
4.088
3.318
1.553
1.269
1.253
174
0.84
1.64
0.84
1.05
1.46
1.87
2.69
8.85
4.22
1.21
1.05
2.26
1.00
1.05
1.01
3.04
8.31
6.51
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

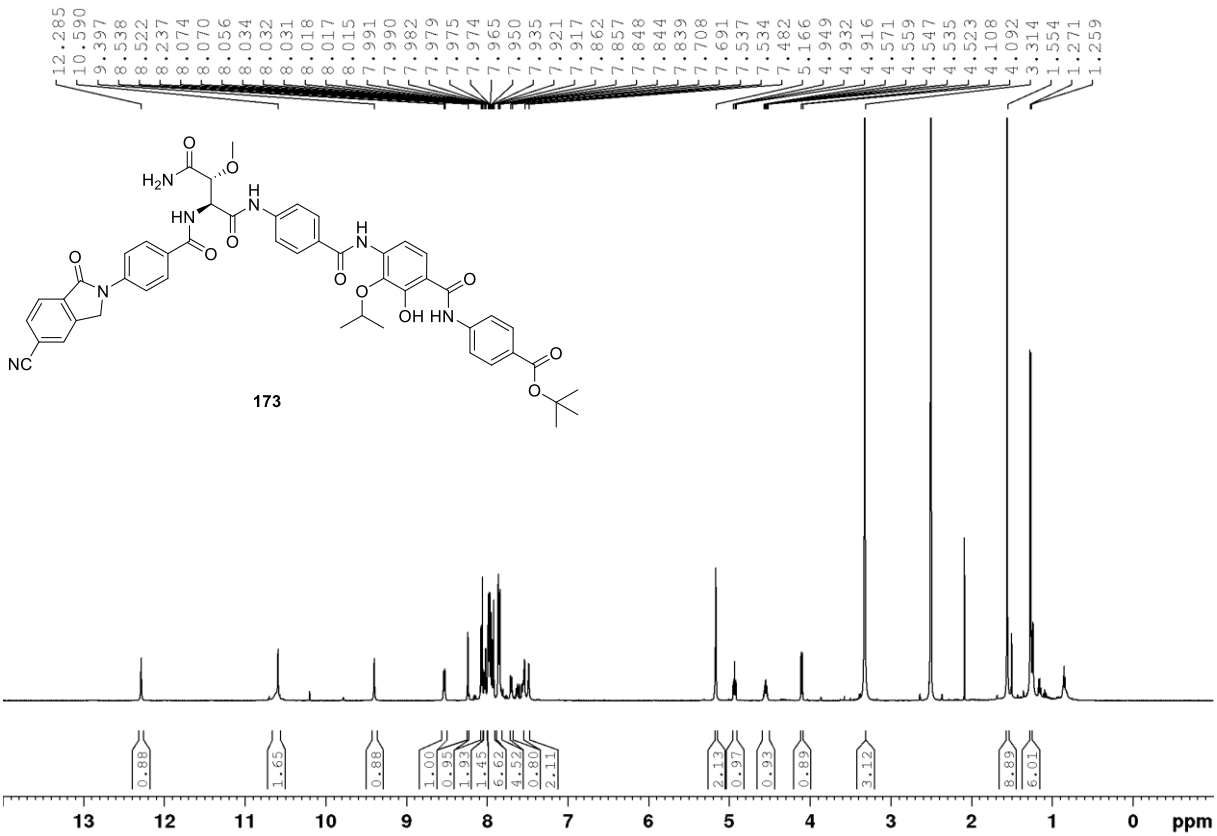

12.816
12.291
10.601
10.588
9.405
8.530
8.517
8.289
8.161
8.158
8.147
8.145
8.061
8.046
7.979
7.976
7.967
7.964
7.961
7.953
7.920
7.907
7.862
7.860
7.855
7.851
7.848
7.845
7.841
7.828
7.825
7.716
7.701
7.535
7.481
5.208
4.944
4.930
4.917
4.564
4.554
4.543
4.533
4.523
4.105
4.092
3.313
1.272
1.262
TSC81
0.82
0.91
1.61
0.84
0.90
0.64
1.00
2.20
5.80
1.77
4.25
0.87
2.11
2.29
1.02
1.01
1.05
2.57
5.73
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm


TSC81

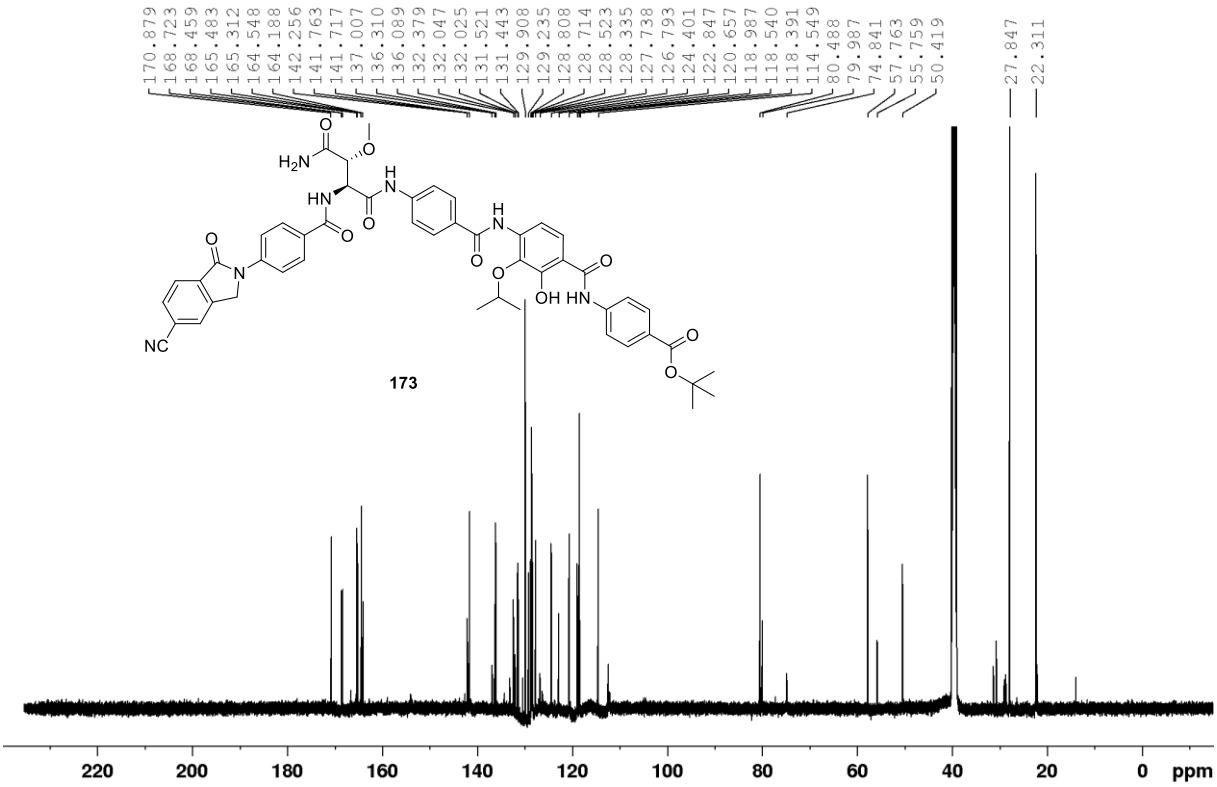

163

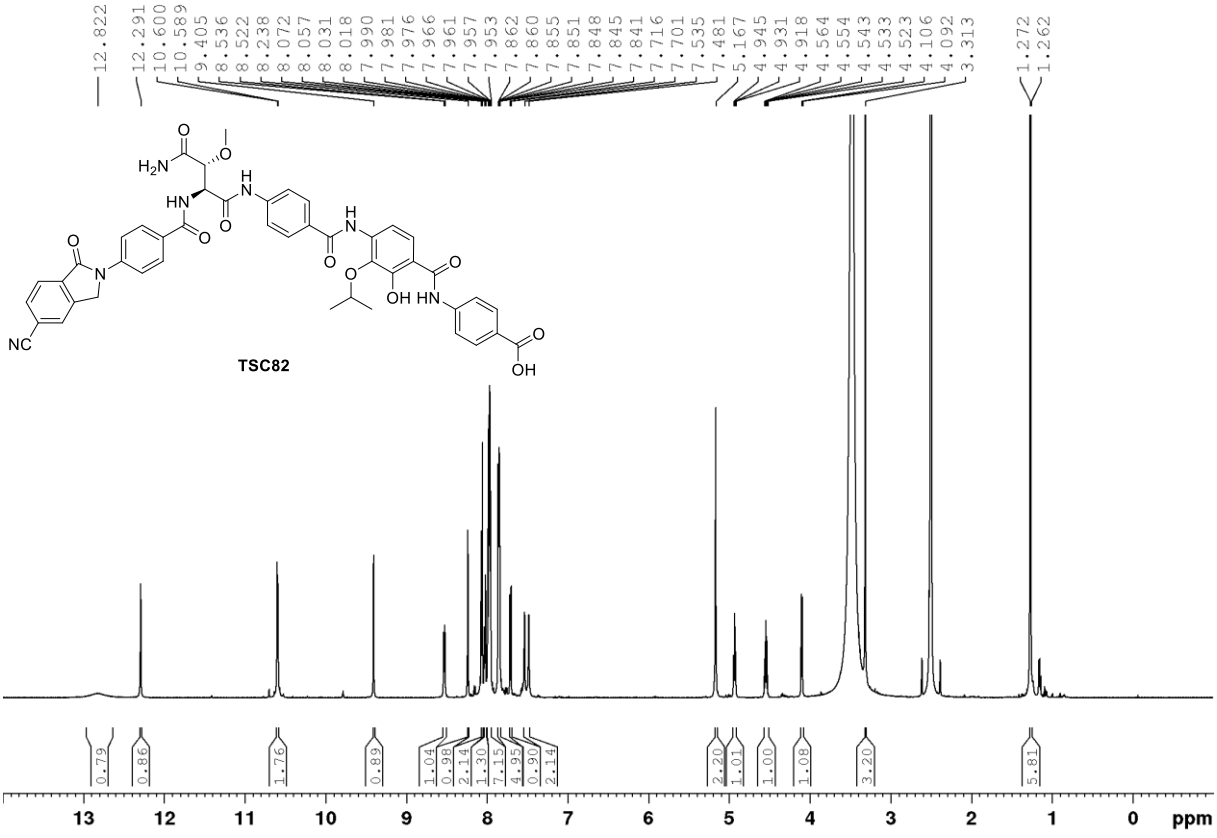

170.889
168.678
165.476
165.311
164.584
164.527
164.280
149.522
143.021
142.524
142.151
141.756
141.706
136.082
135.643
133.647
132.370
130.463
130.085
129.236
128.520
128.492
128.405
127.730
127.089
126.019
124.394
123.622
118.928
118.904
118.827
118.535
118.383
117.801
114.547
80.332
79.989
76.256
74.300
64.909
57.758
55.769
50.413
27.852
22.335
220
200
180
160
140
120
100
80
60
40
20
0
ppm

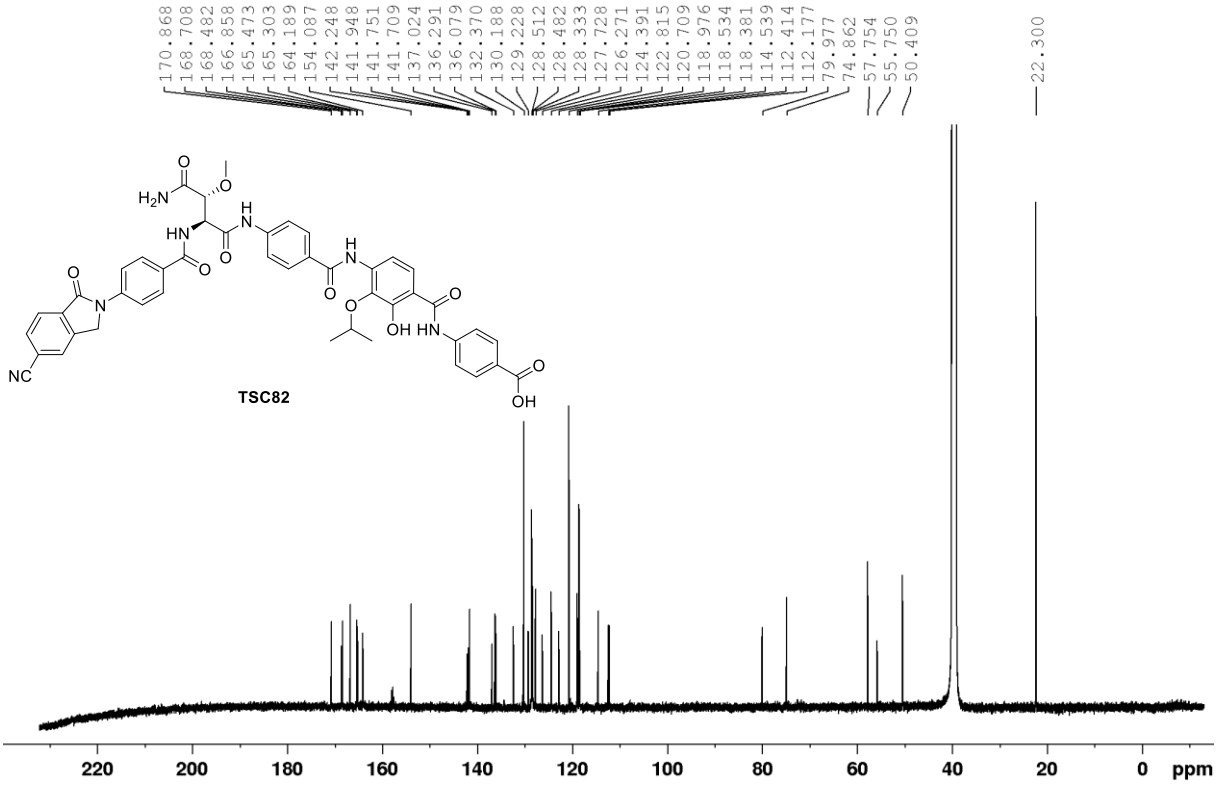
163

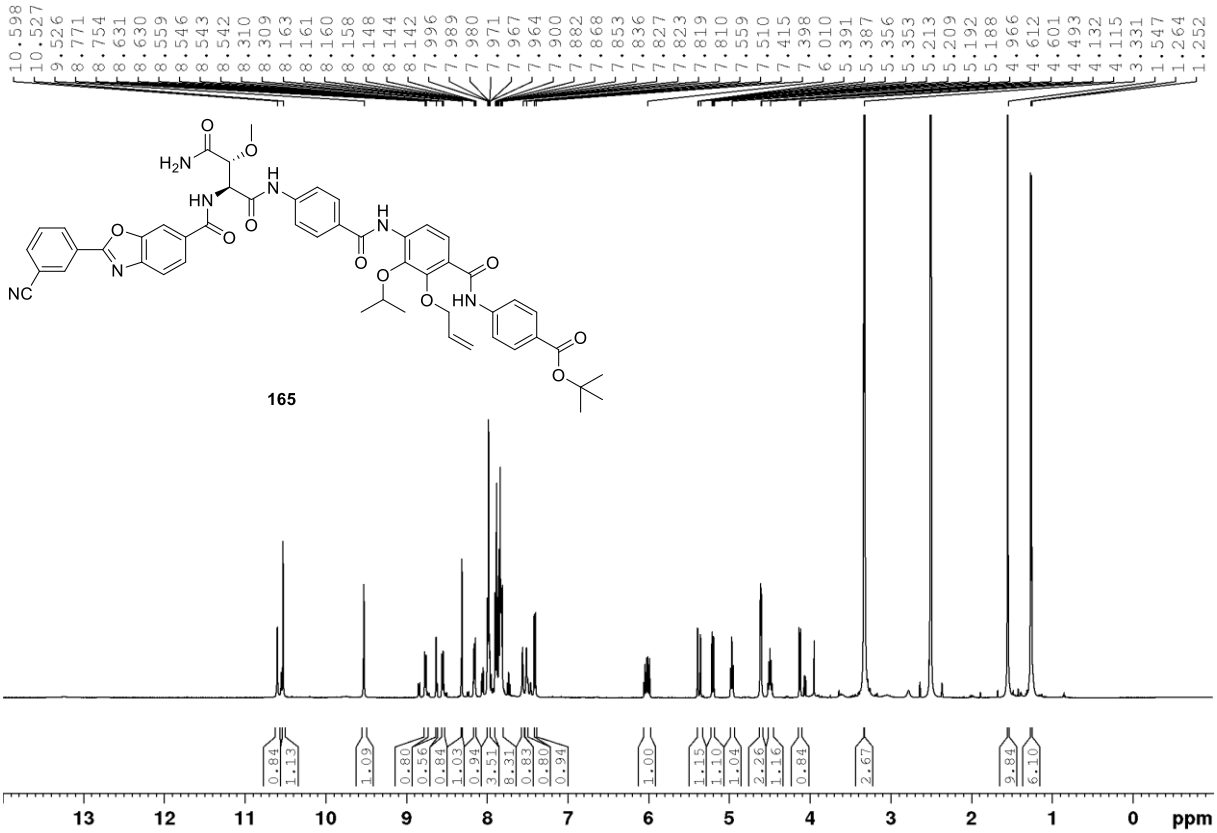

12.285
10.590
9.397
8.538
8.522
8.237
8.074
8.070
8.056
8.034
8.032
8.031
8.018
8.017
8.015
7.991
7.990
7.982
7.979
7.975
7.974
7.965
7.950
7.935
7.921
7.917
7.862
7.857
7.848
7.844
7.839
7.708
7.691
7.537
7.534
7.482
5.166
4.949
4.932
4.916
4.571
4.559
4.547
4.535
4.523
4.108
4.092
3.314
1.554
1.271
1.259
0.88
1.65
0.88
1.00
0.95
1.93
1.45
6.62
4.52
0.80
2.11
2.13
0.97
0.93
0.89
3.12
8.89
6.01
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

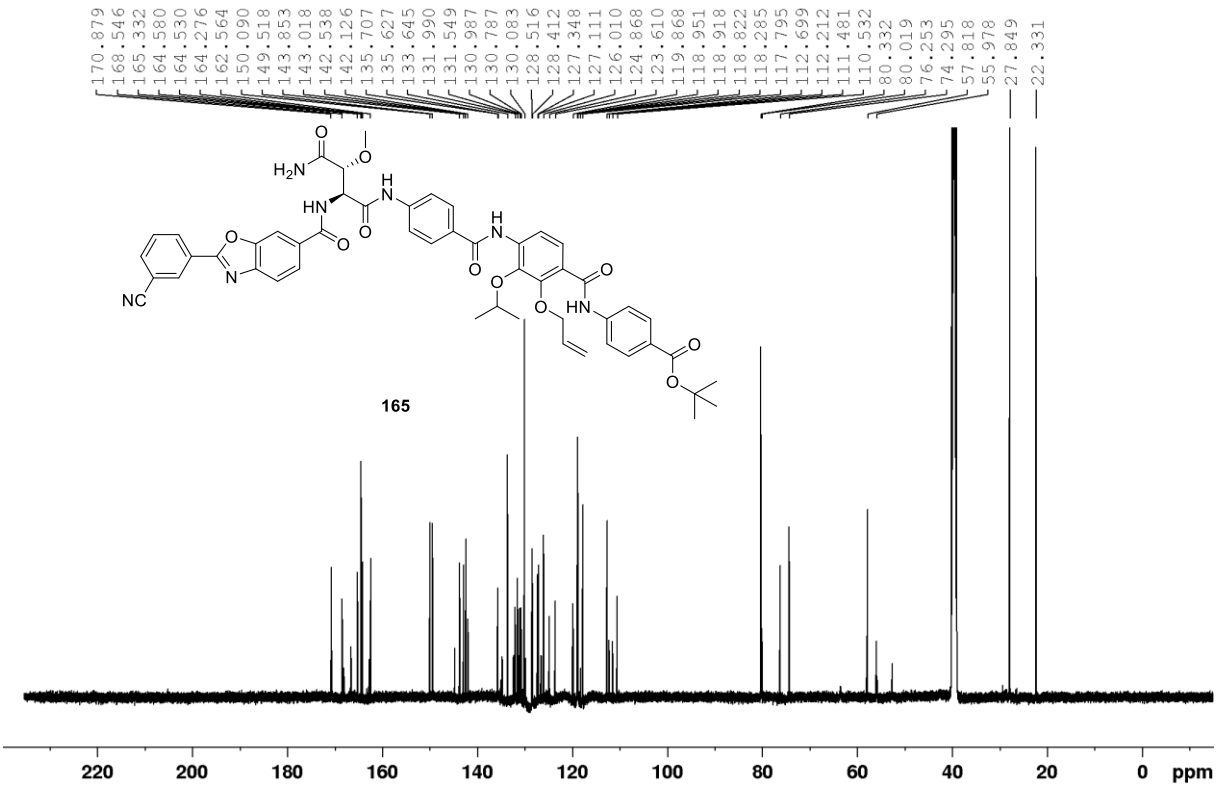
173

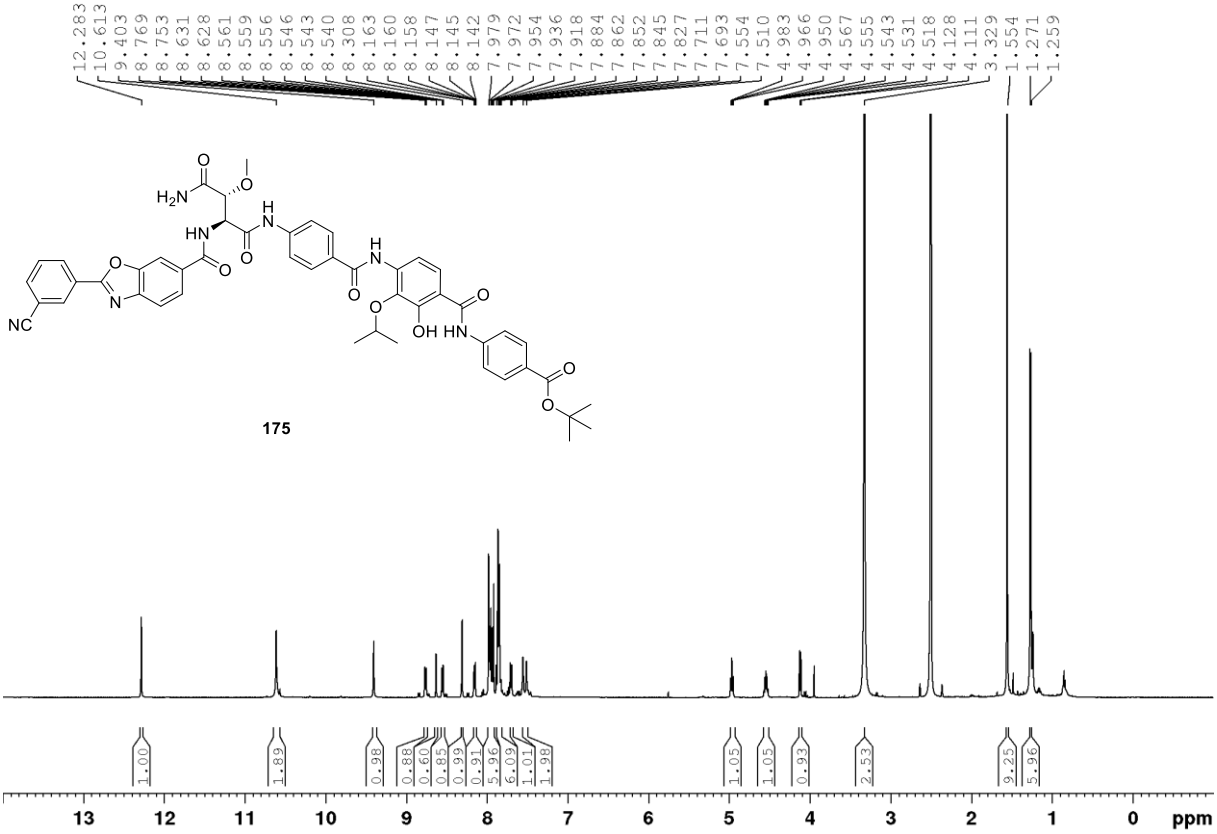

170.879
168.723
168.459
165.483
165.312
164.548
164.188
142.256
141.763
141.717
137.007
136.310
136.089
132.379
132.047
132.025
131.521
131.443
129.908
129.235
128.808
128.714
128.523
128.335
127.738
126.793
124.401
122.847
120.657
118.987
118.540
118.391
114.549
80.488
79.987
74.841
57.763
55.759
50.419
27.847
22.311
173
220
200
180
160
140
120
100
80
60
40
20
0
ppm

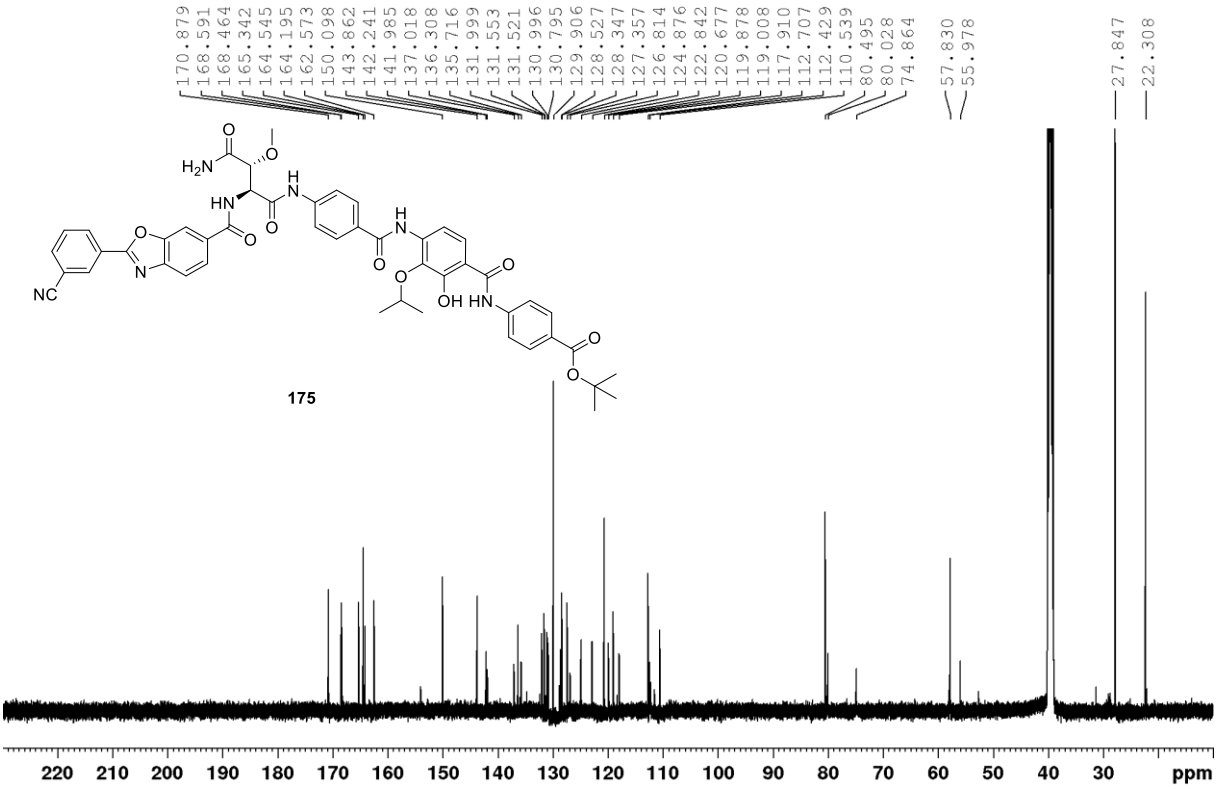

12.822
12.291
10.600
10.589
9.405
8.536
8.522
8.238
8.072
8.057
8.031
8.018
7.990
7.981
7.976
7.966
7.961
7.957
7.953
7.862
7.860
7.855
7.851
7.848
7.845
7.841
7.716
7.701
7.535
7.481
5.167
4.945
4.931
4.918
4.564
4.554
4.543
4.533
4.523
4.106
4.092
3.313
1.272
1.262
TSC82
0.79
0.86
1.76
0.89
1.04
0.98
2.14
1.30
7.15
4.95
0.90
2.14
2.20
1.01
1.00
1.08
3.20
5.81
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

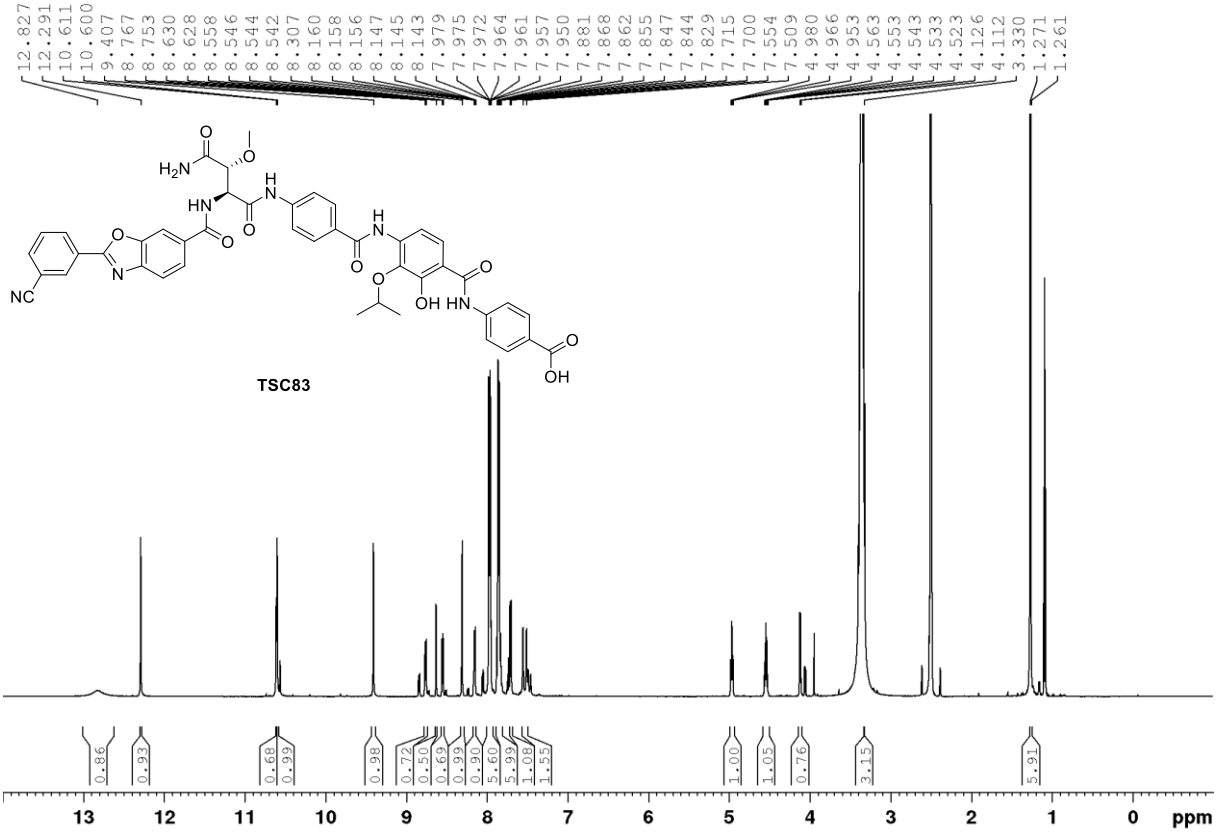

170.868
168.708
168.482
166.858
165.473
165.303
164.189
154.087
142.248
141.948
141.751
141.709
137.024
136.291
136.079
132.370
130.188
129.228
128.512
128.482
128.333
127.728
126.271
124.391
122.815
120.709
118.976
118.534
118.381
114.539
112.414
112.177
79.977
74.862
57.754
55.750
50.409
22.300
TSC82
220
200
180
160
140
120
100
80
60
40
20
0
ppm

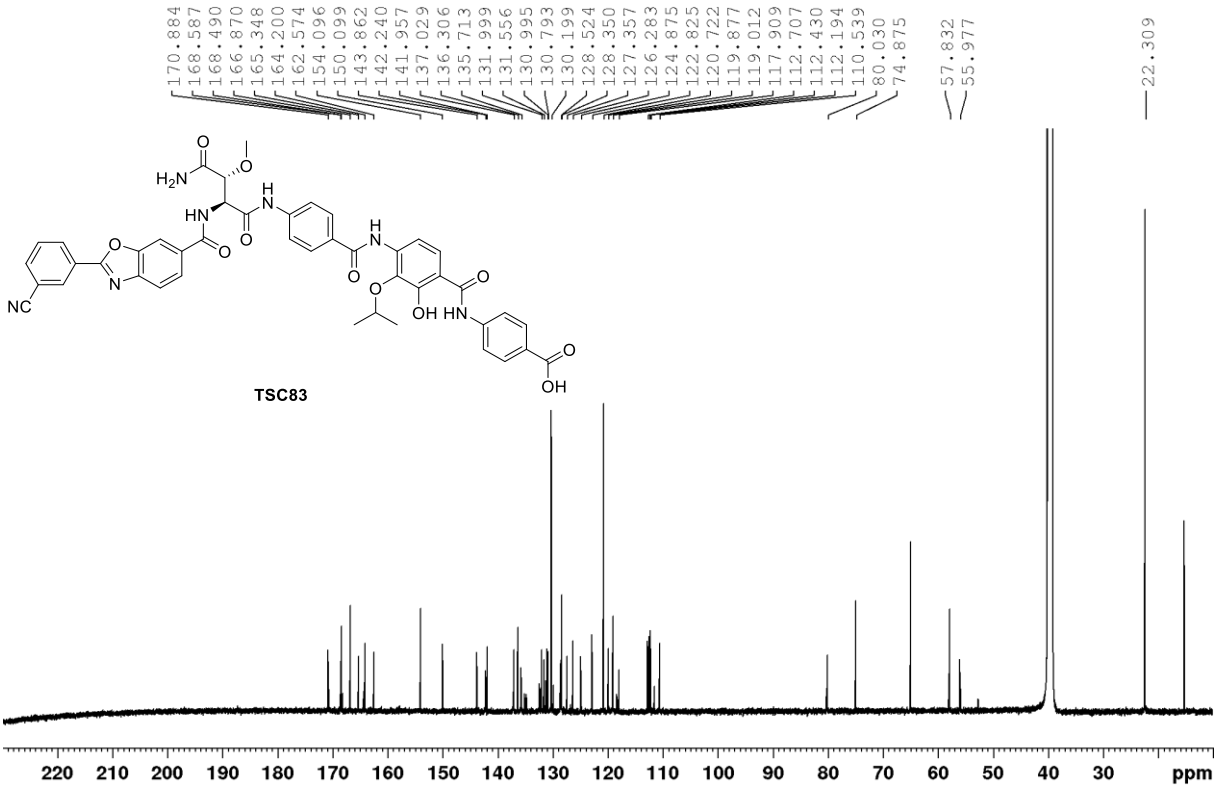

10.598
10.527
9.526
8.771
8.754
8.631
8.630
8.559
8.546
8.543
8.542
8.310
8.309
8.163
8.161
8.160
8.158
8.148
8.144
8.142
7.996
7.989
7.980
7.971
7.967
7.964
7.900
7.882
7.868
7.853
7.836
7.827
7.823
7.819
7.810
7.559
7.510
7.415
7.398
6.010
5.391
5.387
5.356
5.353
5.213
5.209
5.192
5.188
4.966
4.612
4.601
4.493
4.132
4.115
3.331
1.547
1.264
1.252
165
0.84
1.13
1.09
0.80
0.56
0.84
1.03
0.94
3.51
8.31
0.83
0.80
0.94
1.00
1.15
1.10
1.04
2.26
1.16
0.84
2.67
9.84
6.10
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

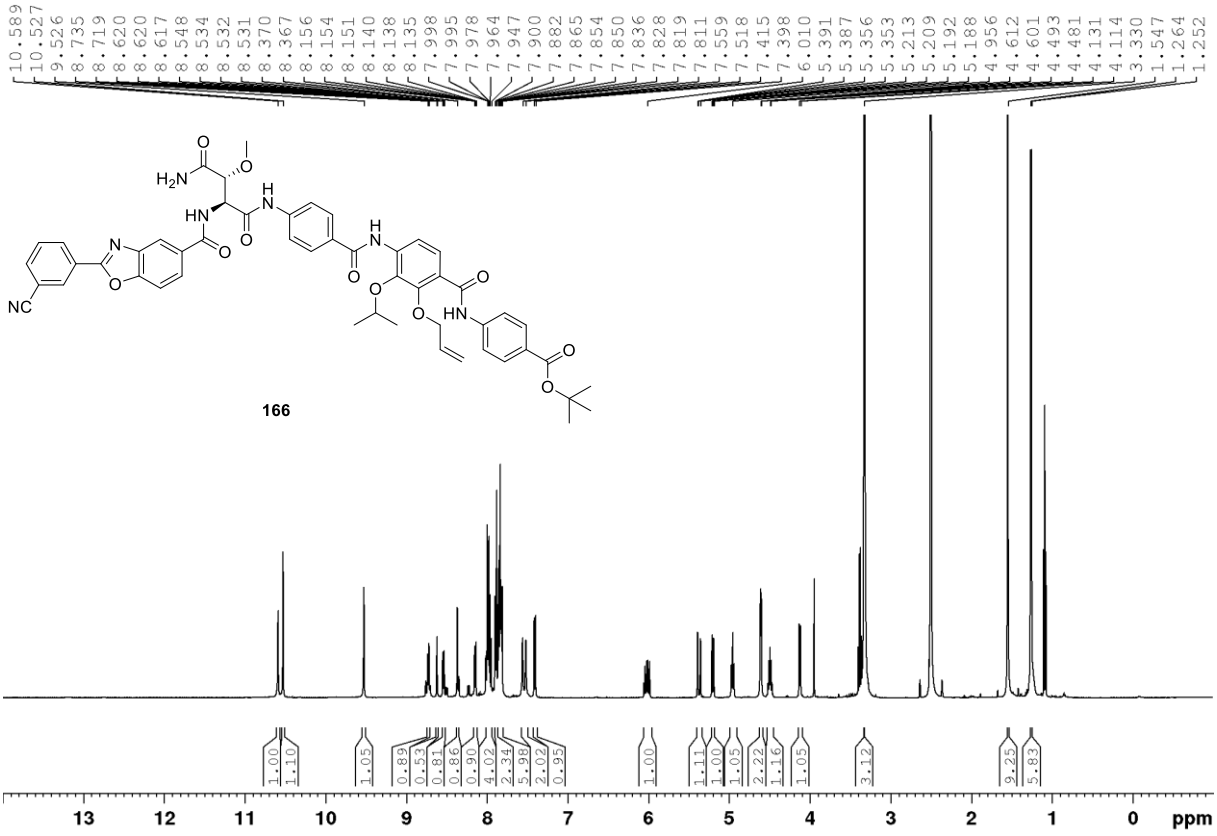

170.879
168.546
165.332
164.580
164.530
164.276
162.564
150.090
149.518
143.853
143.018
142.538
142.126
135.707
135.627
133.645
131.990
131.549
130.987
130.787
130.083
128.516
128.412
127.348
127.111
126.010
124.868
123.610
119.868
118.951
118.918
118.822
118.285
117.795
112.699
112.212
111.481
110.532
80.332
80.019
76.253
74.295
57.818
55.978
27.849
22.331
165
220
200
180
160
140
120
100
80
60
40
20
0
ppm

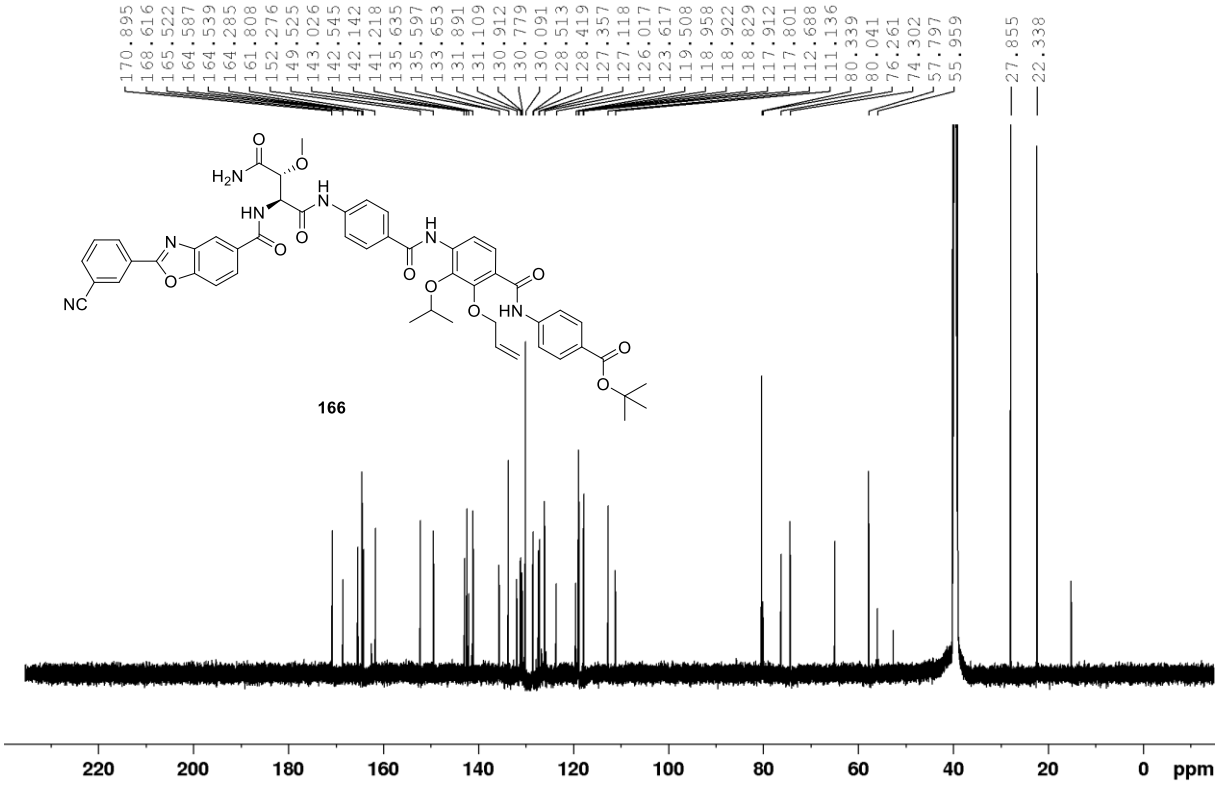

12.283
10.613
9.403
8.769
8.753
8.631
8.628
8.561
8.559
8.556
8.546
8.543
8.540
8.308
8.163
8.160
8.158
8.147
8.145
8.142
7.979
7.972
7.954
7.936
7.918
7.884
7.862
7.852
7.845
7.827
7.711
7.693
7.554
7.510
4.983
4.966
4.950
4.567
4.555
4.543
4.531
4.518
4.128
4.111
3.329
1.554
1.271
1.259
175
1.00
1.89
0.98
0.88
0.60
0.85
0.99
0.91
5.96
6.09
1.01
1.98
1.05
1.05
0.93
2.53
9.25
5.96
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

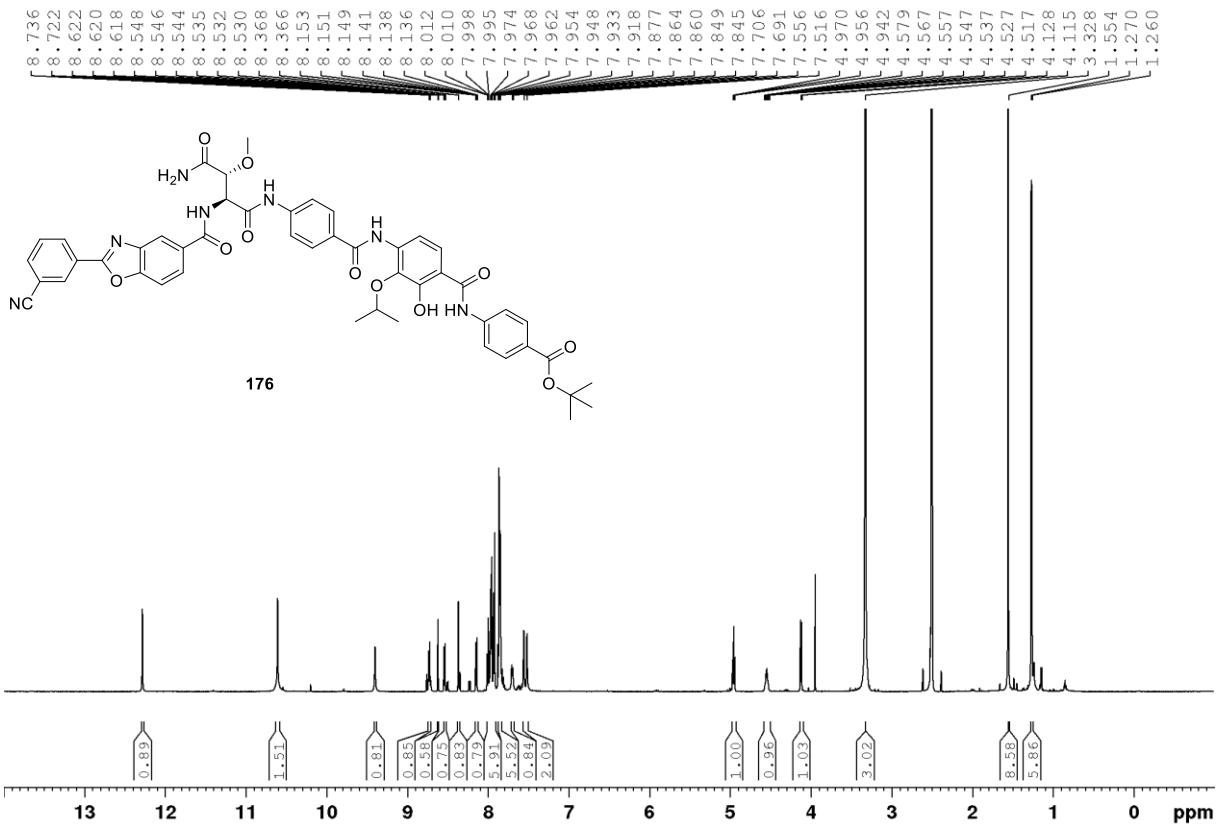

170.879
168.591
168.464
165.342
164.545
164.195
162.573
150.098
143.862
142.241
141.985
137.018
136.308
135.716
131.999
131.553
131.521
130.996
130.795
129.906
128.527
128.347
127.357
126.814
124.876
122.842
120.677
119.878
119.008
117.910
112.707
112.429
110.539
80.495
80.028
74.864
57.830
55.978
27.847
22.308
175
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm

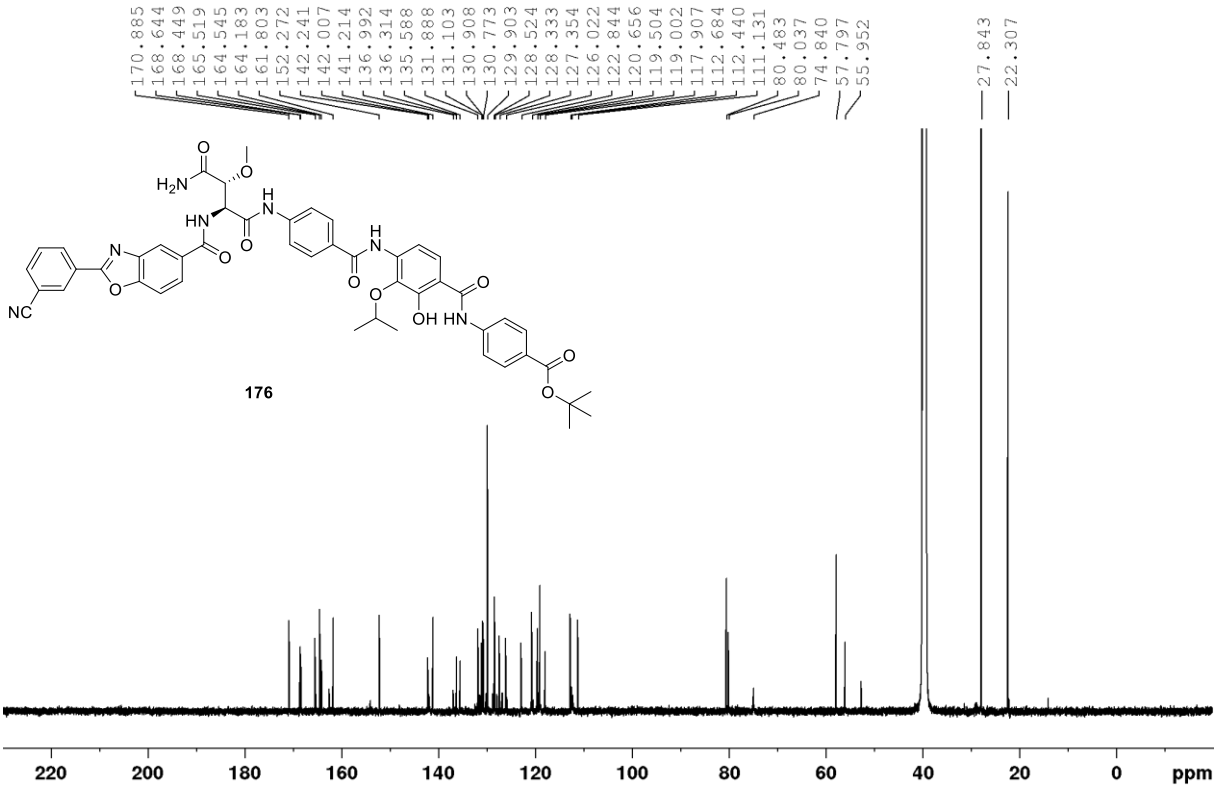

12.827
12.291
10.611
10.600
9.407
8.767
8.753
8.630
8.628
8.558
8.546
8.544
8.542
8.307
8.160
8.158
8.156
8.147
8.145
8.143
7.979
7.975
7.972
7.964
7.961
7.957
7.950
7.881
7.868
7.862
7.855
7.847
7.844
7.829
7.715
7.700
7.554
7.509
4.980
4.966
4.953
4.563
4.553
4.543
4.533
4.523
4.126
4.112
3.330
1.271
1.261
TSC83
0.86
0.93
0.68
0.99
0.98
0.72
0.50
0.69
0.99
0.90
5.60
5.99
1.08
1.55
1.00
1.05
0.76
3.15
5.91
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

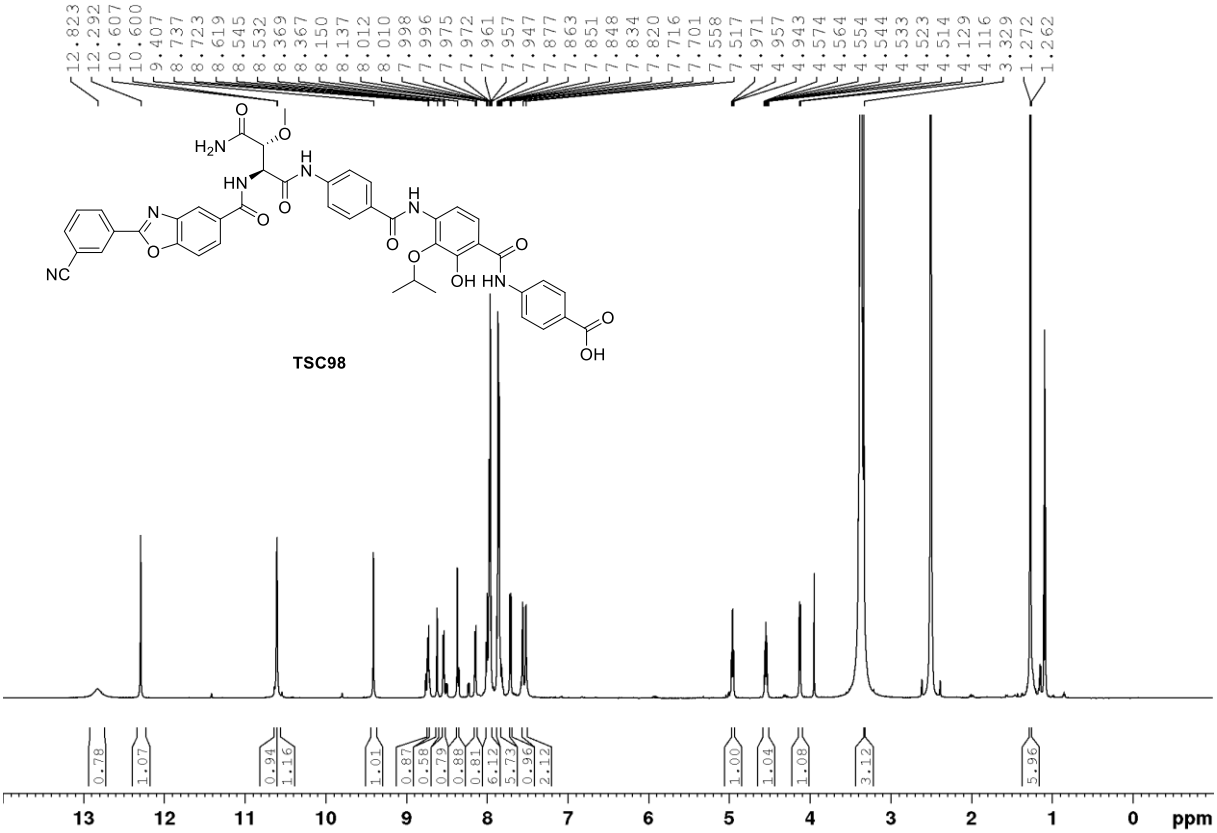

170.884
168.587
168.490
166.870
165.348
164.200
162.574
154.096
150.099
143.862
142.240
141.957
137.029
136.306
135.713
131.999
131.556
130.995
130.793
130.199
128.524
128.350
127.357
126.283
124.875
122.825
120.722
119.877
119.012
117.909
112.707
112.430
112.194
110.539
80.030
74.875
57.832
55.977
22.309
TSC83
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm

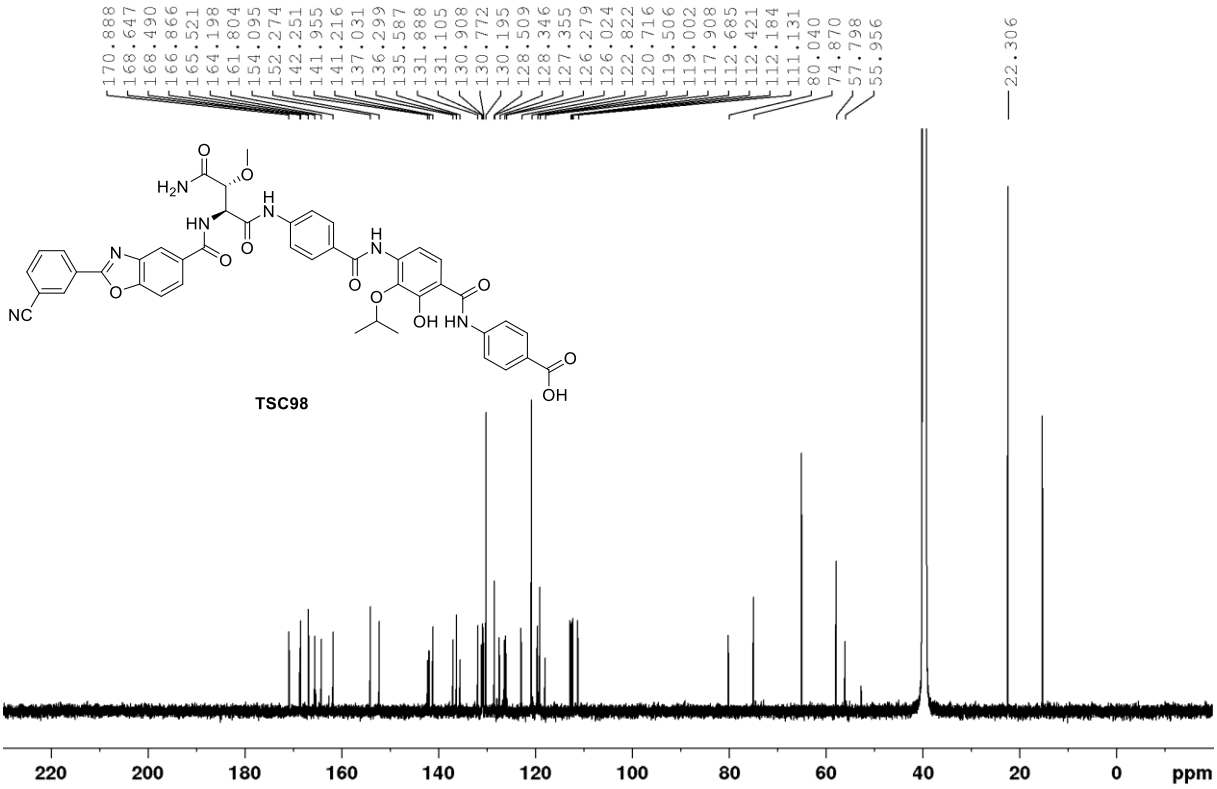

10.589
10.527
9.526
8.735
8.719
8.620
8.620
8.617
8.548
8.534
8.532
8.531
8.370
8.367
8.156
8.154
8.151
8.140
8.138
8.135
7.998
7.995
7.978
7.964
7.947
7.900
7.882
7.865
7.854
7.850
7.836
7.828
7.819
7.811
7.559
7.518
7.415
7.398
6.010
5.391
5.387
5.356
5.353
5.213
5.209
5.192
5.188
4.956
4.612
4.601
4.493
4.481
4.131
4.114
3.330
1.547
1.264
1.252
166
1.00 1.10 1.05 0.89 0.53 0.81 0.86 0.90 4.02 2.34 5.98 2.02 0.95 1.00 1.11 1.00 1.05 2.22 1.16 1.05 3.12 9.25 5.83
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

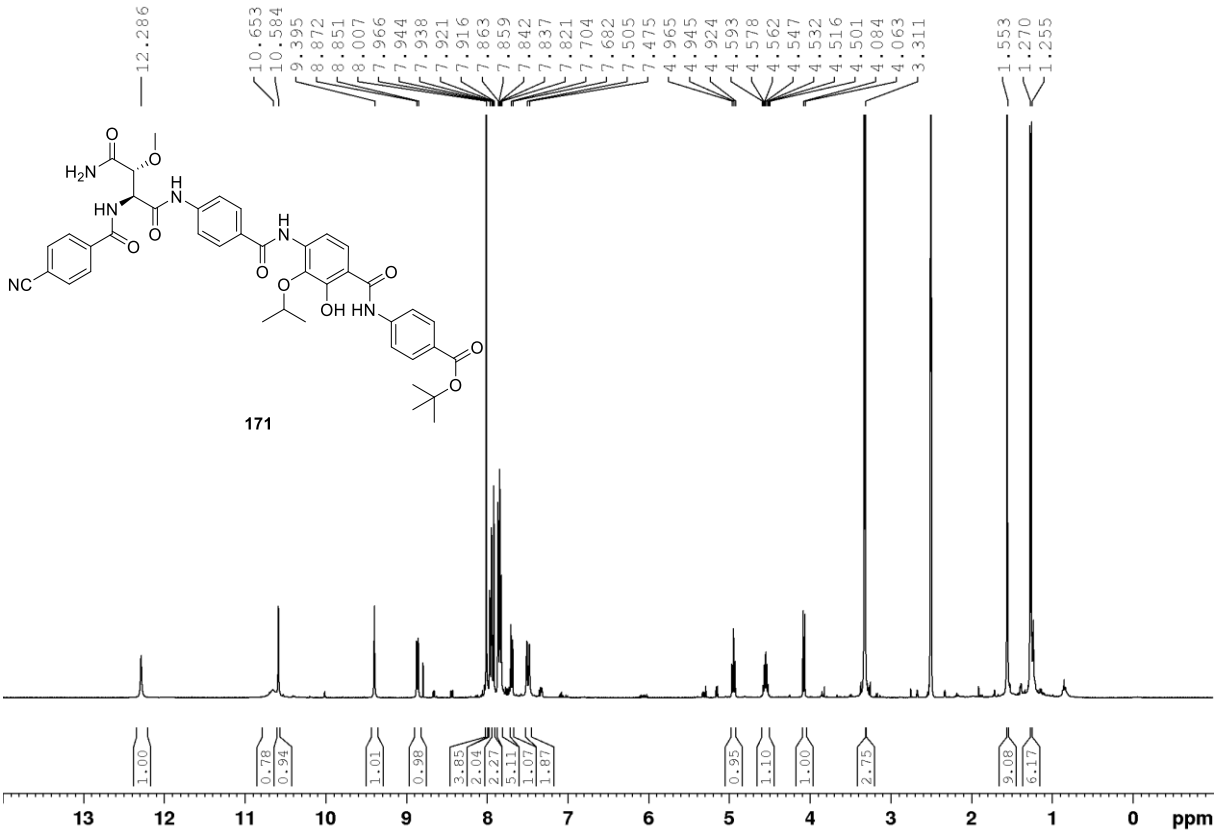

170.895
168.616
165.522
164.587
164.539
164.285
161.808
152.276
149.525
143.026
142.545
142.142
141.218
135.635
135.597
133.653
131.891
131.109
130.912
130.779
130.091
128.513
128.419
127.357
127.118
126.017
123.617
119.508
118.958
118.922
118.829
117.912
117.801
112.688
111.136
80.339
80.041
76.261
74.302
57.797
55.959
27.855
22.338
166
220
200
180
160
140
120
100
80
60
40
20
0
ppm

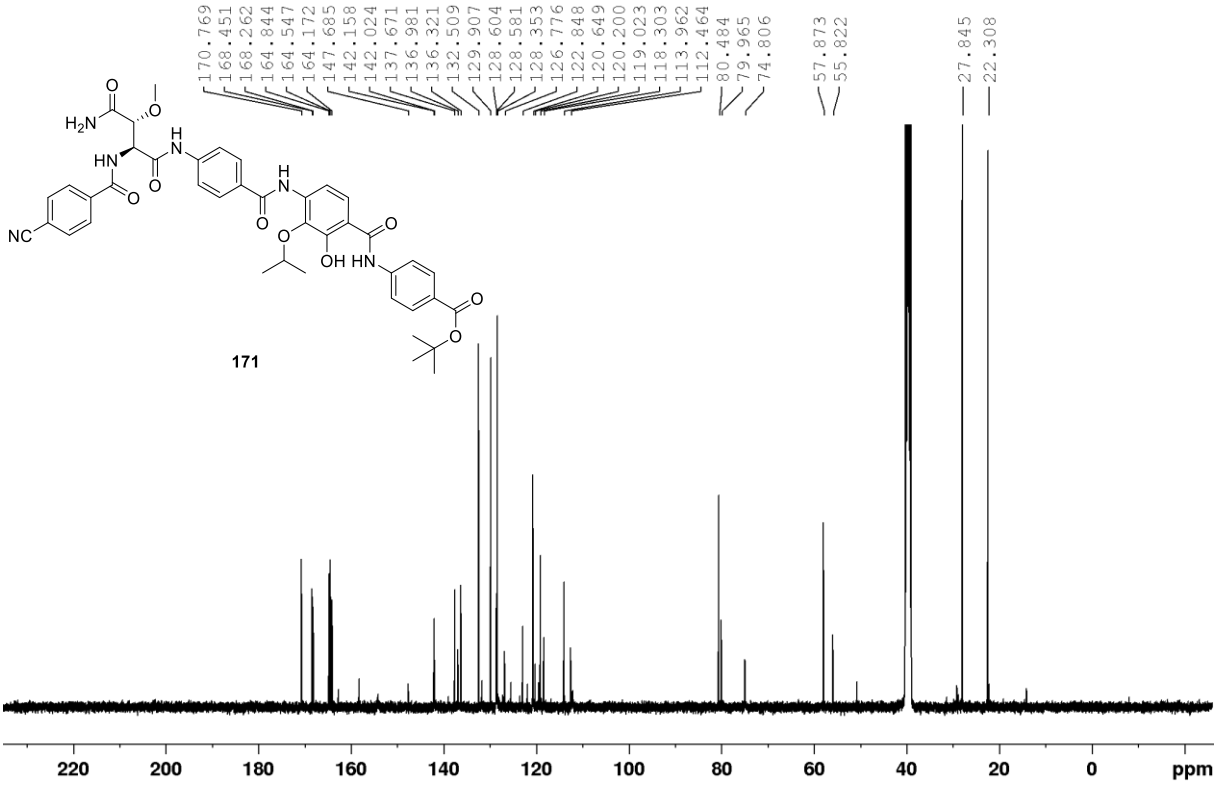

8.736
8.722
8.622
8.620
8.618
8.548
8.546
8.544
8.535
8.532
8.530
8.368
8.366
8.153
8.151
8.149
8.141
8.138
8.136
8.012
8.010
7.998
7.995
7.974
7.968
7.962
7.954
7.948
7.933
7.918
7.877
7.864
7.860
7.849
7.845
7.706
7.691
7.556
7.516
4.970
4.956
4.942
4.579
4.567
4.557
4.547
4.537
4.527
4.517
4.128
4.115
3.328
1.554
1.270
1.260
176
0.89
1.51
0.81
0.85
0.58
0.75
0.83
0.79
5.91
5.52
0.84
2.09
1.00
0.96
1.03
3.02
8.58
5.86
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

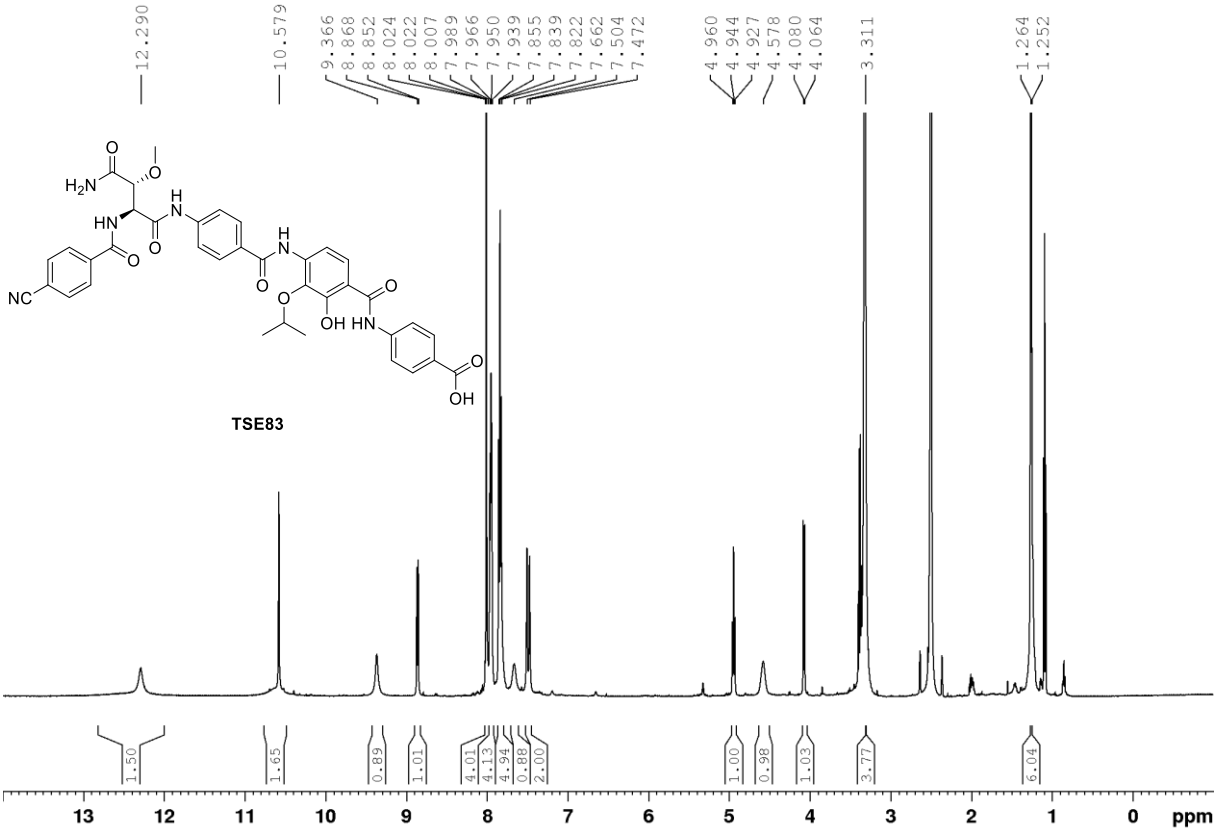

170.885
168.644
168.449
165.519
164.545
164.183
161.803
152.272
142.241
142.007
141.214
136.992
136.314
135.588
131.888
131.103
130.908
130.773
129.903
128.524
128.333
127.354
126.022
122.844
120.656
119.504
119.002
117.907
112.684
112.440
111.131
80.483
80.037
74.840
57.797
55.952
27.843
22.307
176
220
200
180
160
140
120
100
80
60
40
20
0
ppm

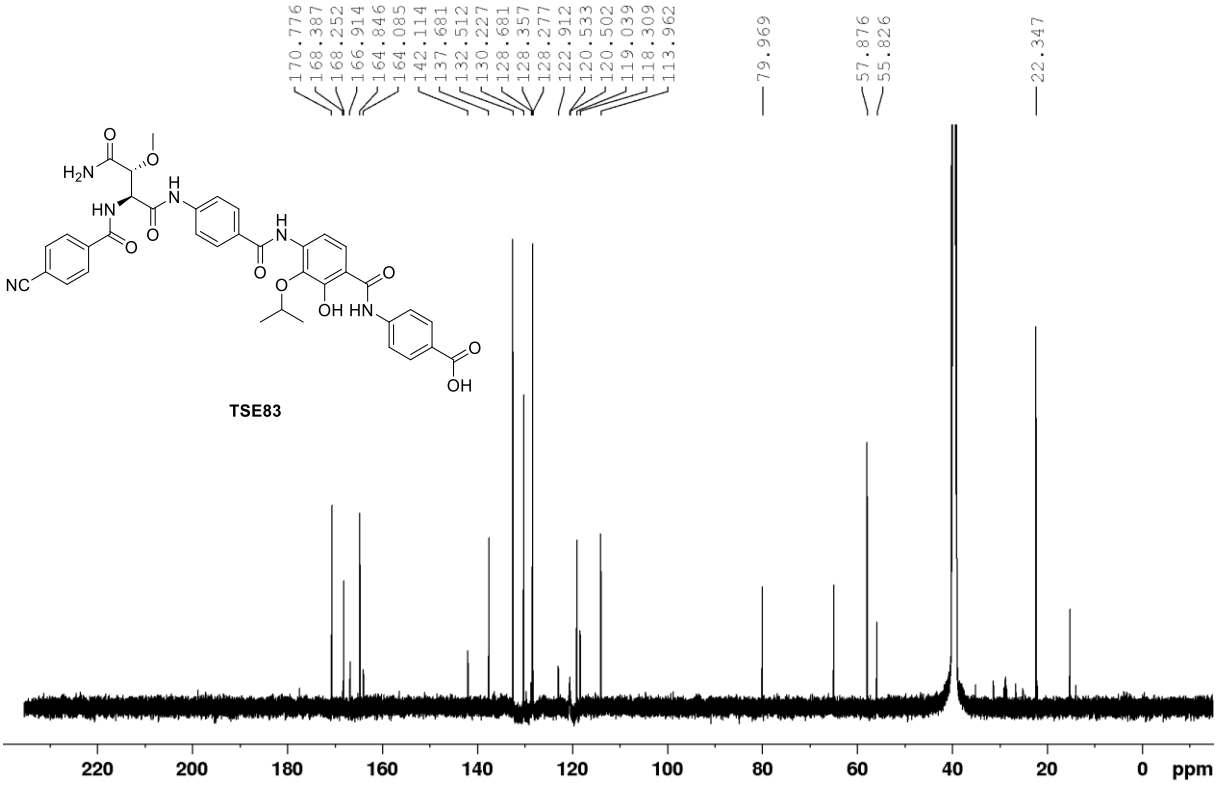

12.823
12.292
10.607
10.600
9.407
8.737
8.723
8.619
8.545
8.532
8.369
8.367
8.150
8.137
8.012
8.010
7.998
7.996
7.975
7.972
7.961
7.957
7.947
7.877
7.863
7.851
7.848
7.834
7.820
7.716
7.701
7.558
7.517
4.971
4.957
4.943
4.574
4.564
4.554
4.544
4.533
4.523
4.514
4.129
4.116
3.329
1.272
1.262
TSC98
0.78
1.07
0.94
1.16
1.01
0.87
0.58
0.79
0.88
0.81
6.12
5.73
0.96
2.12
1.00
1.04
1.08
3.12
5.96
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

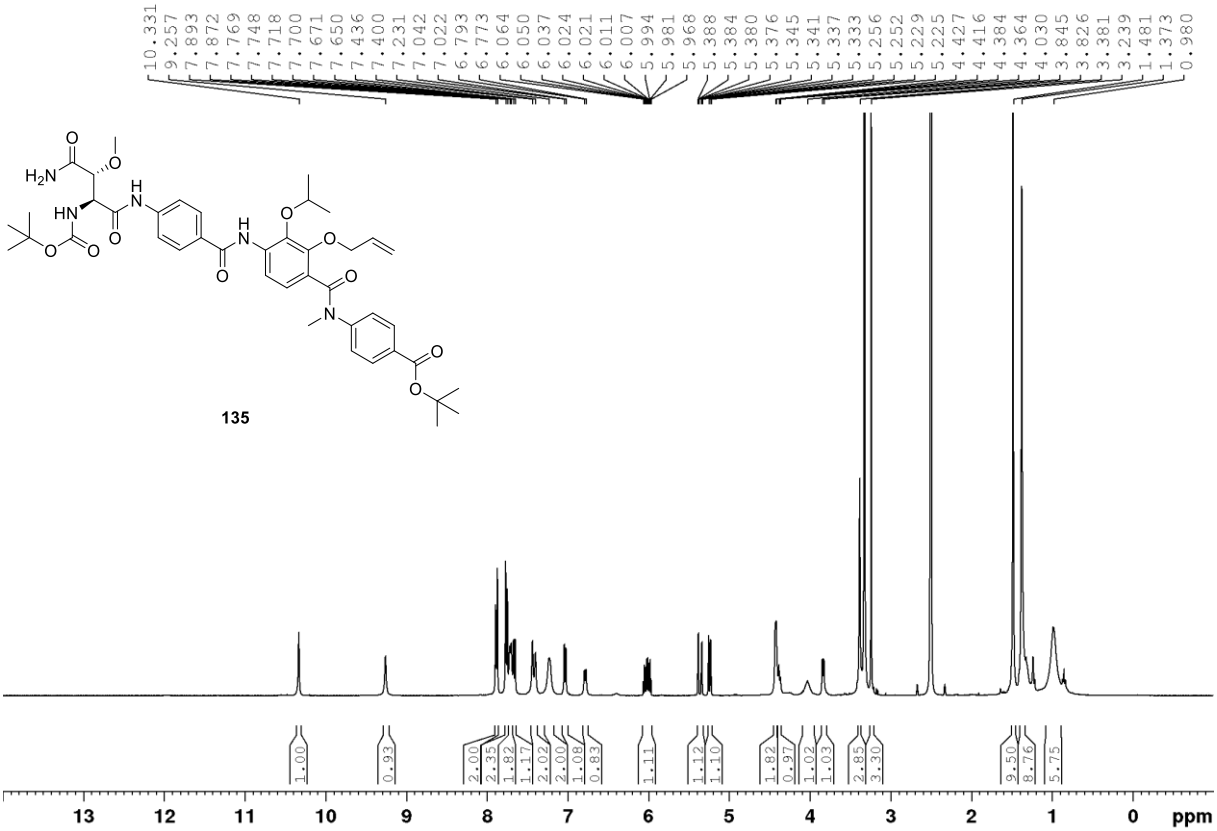

170.888
168.647
168.490
166.866
165.521
164.198
161.804
154.095
152.274
142.251
141.955
141.216
137.031
136.299
135.587
131.888
131.105
130.908
130.772
130.195
128.509
128.346
127.355
126.279
126.024
122.822
120.716
119.506
119.002
117.908
112.685
112.421
112.184
111.131
80.040
74.870
57.798
55.956
22.306
TSC98
220
200
180
160
140
120
100
80
60
40
20
0
ppm

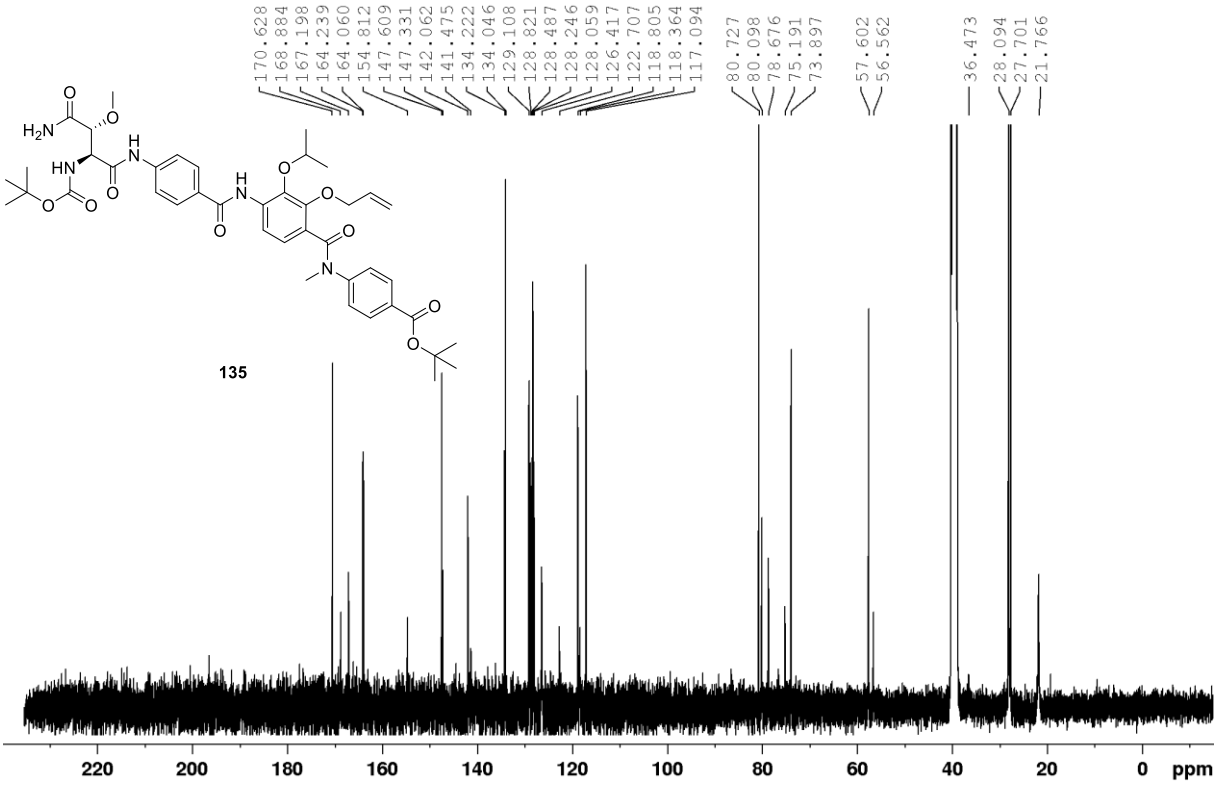

12.286
10.653
10.584
9.395
8.872
8.851
8.007
7.966
7.944
7.938
7.921
7.916
7.863
7.859
7.842
7.837
7.821
7.704
7.682
7.505
7.475
4.965
4.945
4.924
4.593
4.578
4.562
4.547
4.532
4.516
4.501
4.084
4.063
3.311
1.553
1.270
1.255
171
1.00
0.78
0.94
1.01
0.98
3.85
2.04
2.27
5.11
1.07
1.87
0.95
1.10
1.00
2.75
9.08
6.17
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

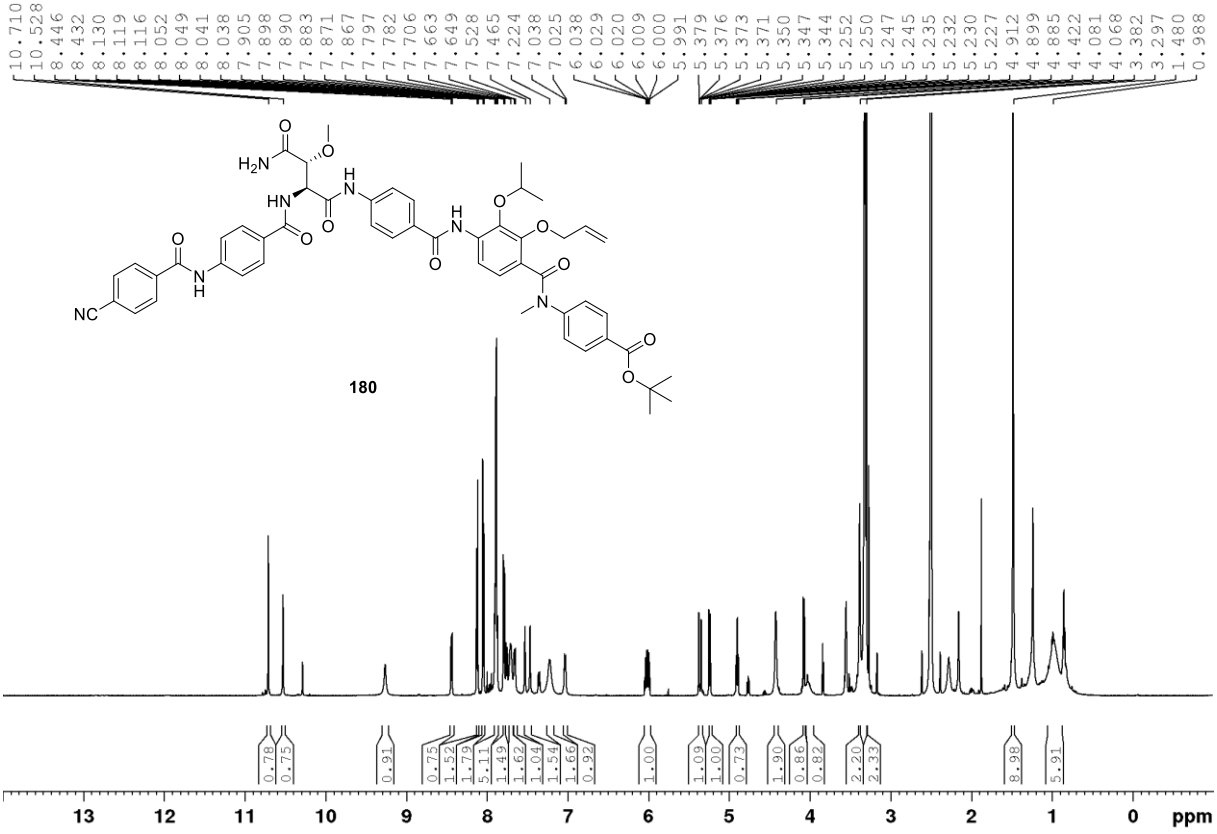

170.769
168.451
168.262
164.844
164.547
164.172
147.685
142.158
142.024
137.671
136.981
136.321
132.509
129.907
128.604
128.581
128.353
126.776
122.848
120.649
120.200
119.023
118.303
113.962
112.464
80.484
79.965
74.806
57.873
55.822
27.845
22.308
171
220
200
180
160
140
120
100
80
60
40
20
0
ppm

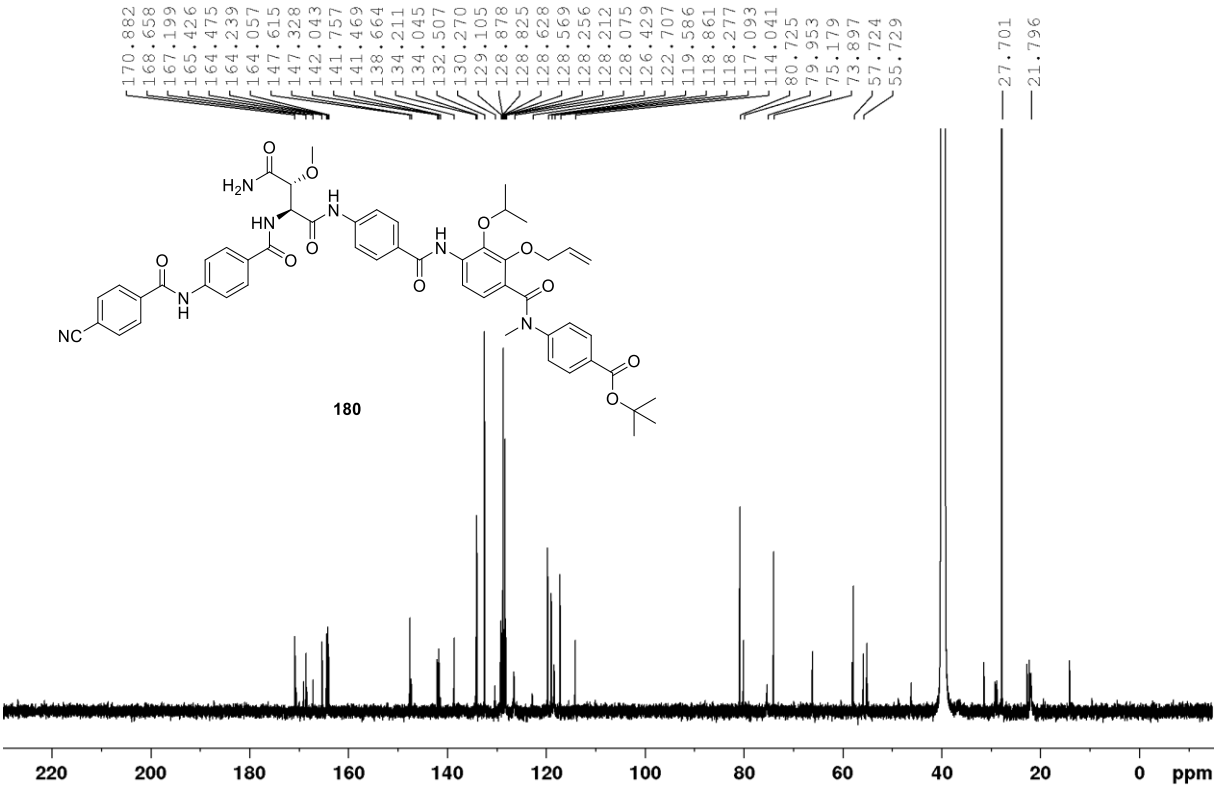

12.290
10.579
9.366
8.868
8.852
8.024
8.022
8.007
7.989
7.966
7.950
7.939
7.855
7.839
7.822
7.662
7.504
7.472
4.960
4.944
4.927
4.578
4.080
4.064
3.311
1.264
1.252
TSE83
1.50
1.65
0.89
1.01
4.01
4.13
4.94
0.88
2.00
1.00
0.98
1.03
3.77
6.04
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

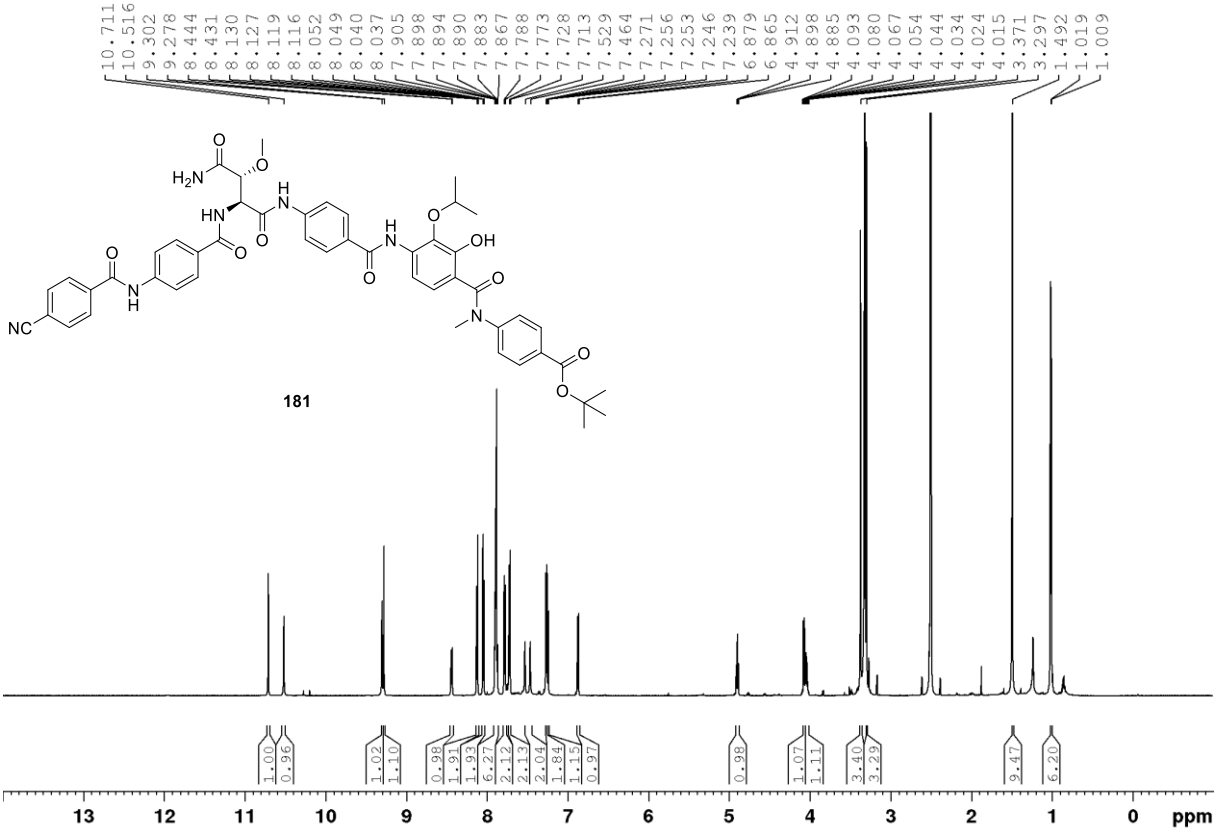

170.776
168.387
168.252
166.914
164.846
164.085
142.114
137.681
132.512
130.227
128.681
128.357
128.277
122.912
120.533
120.502
119.039
118.309
113.962
79.969
57.876
55.826
22.347
TSE83
220
200
180
160
140
120
100
80
60
40
20
0
ppm

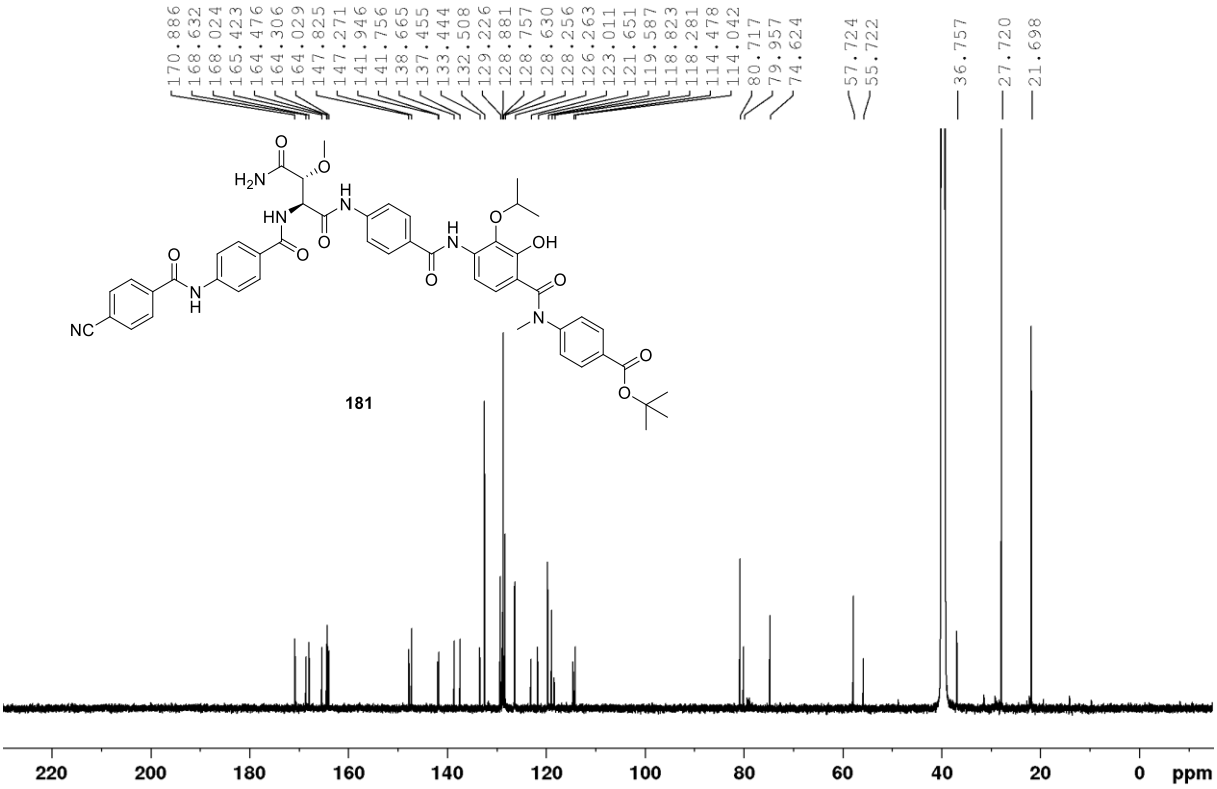

10.331
9.257
7.893
7.872
7.769
7.748
7.718
7.700
7.671
7.650
7.436
7.400
7.231
7.042
7.022
6.793
6.773
6.064
6.050
6.037
6.024
6.021
6.011
6.007
5.994
5.981
5.968
5.388
5.384
5.380
5.376
5.345
5.341
5.337
5.333
5.256
5.252
5.229
5.225
4.427
4.416
4.384
4.364
4.030
3.845
3.826
3.381
3.239
1.481
1.373
0.980
135
1.00
0.93
2.00
2.35
1.82
1.17
2.02
2.00
1.08
0.83
1.11
1.12
1.10
1.82
0.97
1.02
1.03
2.85
3.30
9.50
8.76
5.75
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

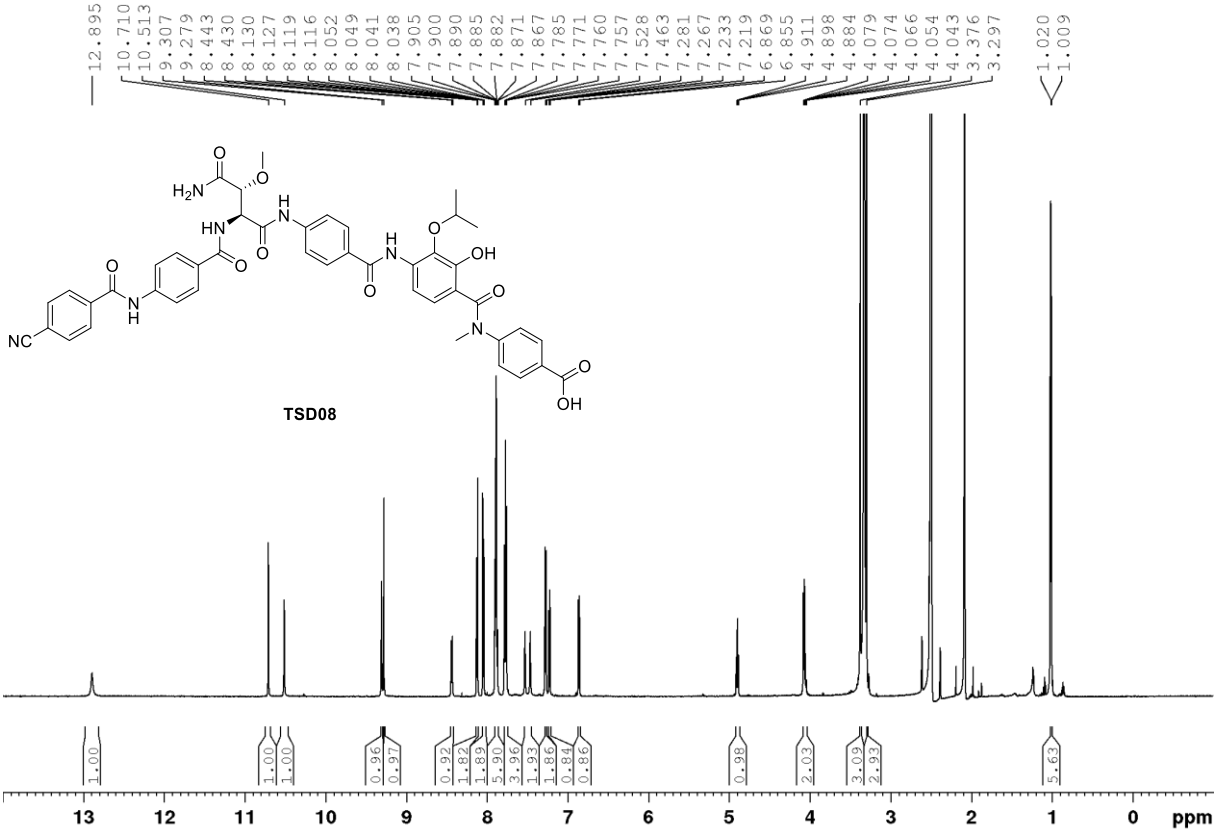

170.628
168.884
167.198
164.239
164.060
154.812
147.609
147.331
142.062
141.475
134.222
134.046
129.108
128.821
128.487
128.246
128.059
126.417
122.707
118.805
118.364
117.094
80.727
80.098
78.676
75.191
73.897
57.602
56.562
36.473
28.094
27.701
21.766
135
220
200
180
160
140
120
100
80
60
40
20
0
ppm

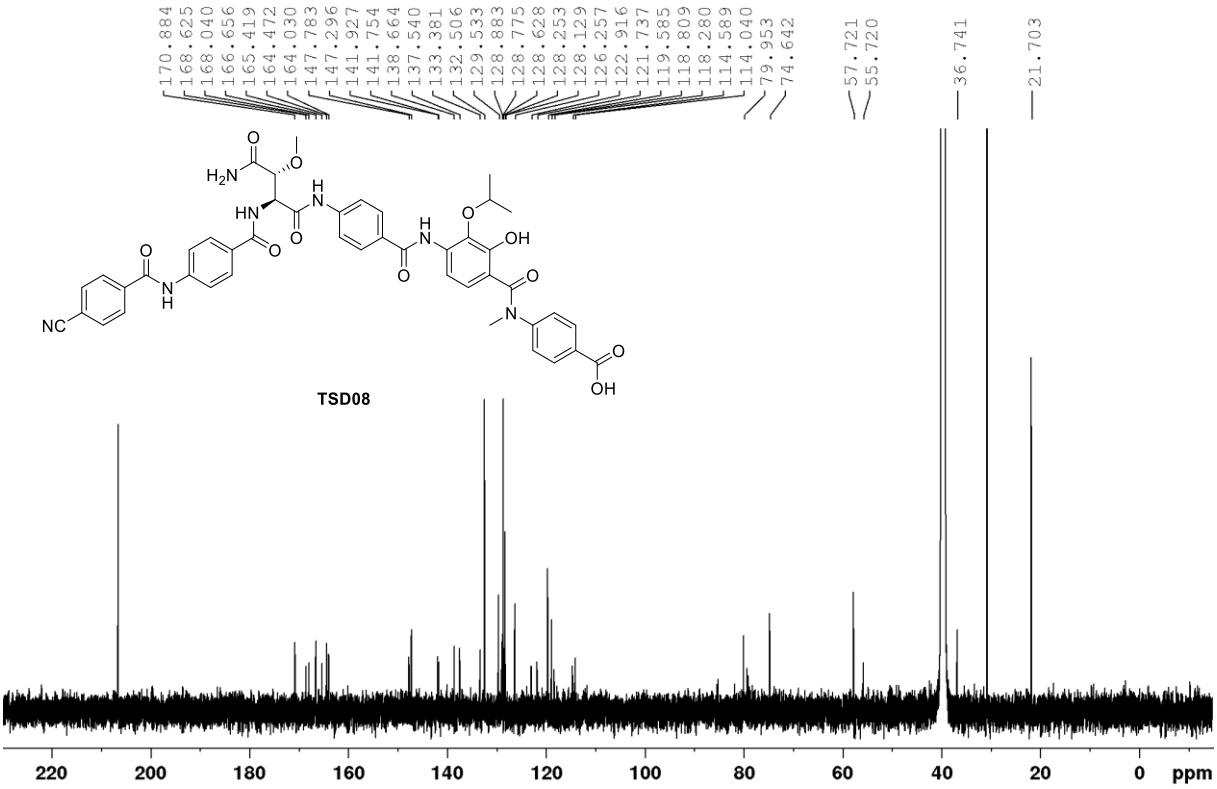

10.710
10.528
8.446
8.432
8.130
8.119
8.116
8.052
8.049
8.041
8.038
7.905
7.898
7.890
7.883
7.871
7.867
7.797
7.782
7.706
7.663
7.649
7.528
7.465
7.224
7.038
7.025
6.038
6.029
6.020
6.009
6.000
5.991
5.379
5.376
5.373
5.371
5.350
5.347
5.344
5.252
5.250
5.247
5.245
5.235
5.232
5.230
5.227
4.912
4.899
4.885
4.422
4.081
4.068
3.382
3.297
1.480
0.988
180
0.78
0.75
0.91
0.75
1.52
1.79
5.11
1.49
1.62
1.04
1.54
1.66
0.92
1.00
1.09
1.00
0.73
1.90
0.86
0.82
2.20
2.33
8.98
5.91
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

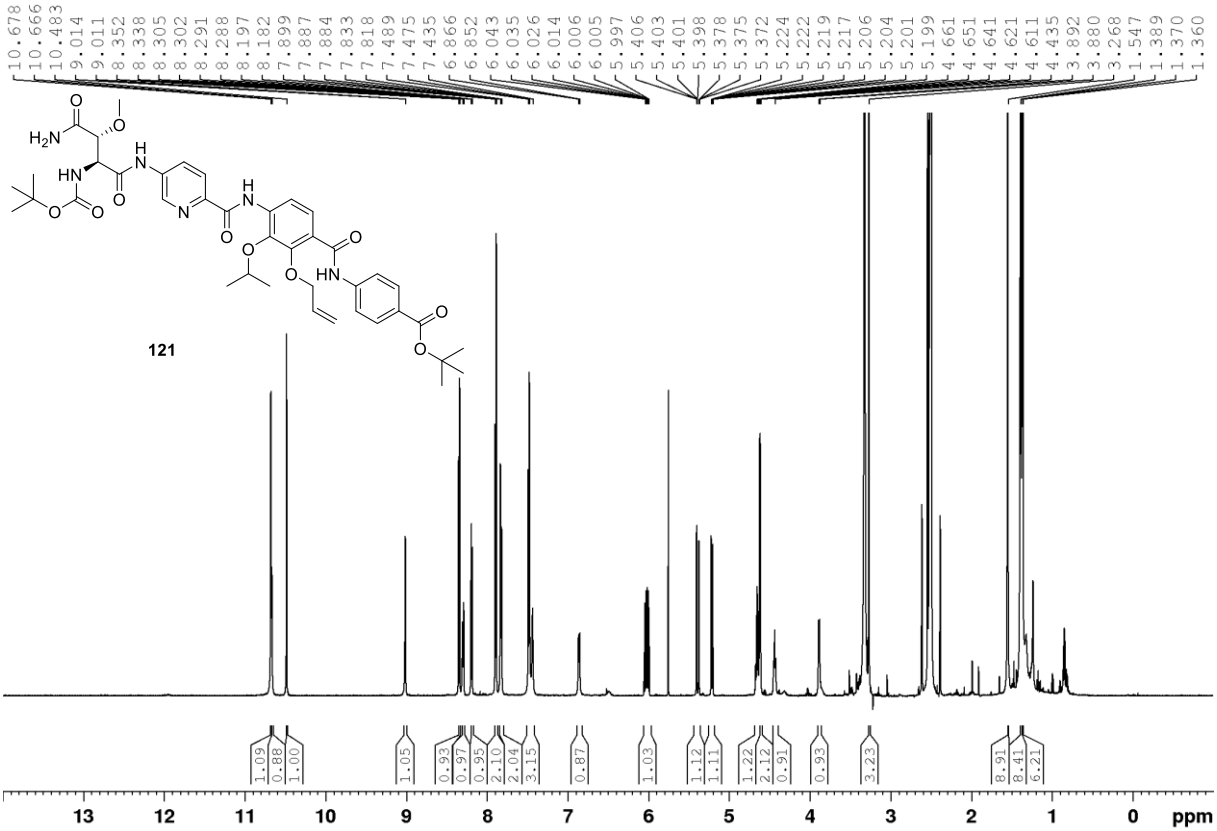

170.882
168.658
167.199
165.426
164.475
164.239
164.057
147.615
147.328
142.043
141.757
141.469
138.664
134.211
134.045
132.507
130.270
129.105
128.878
128.825
128.628
128.569
128.256
128.212
128.075
126.429
122.707
119.586
118.861
118.277
117.093
114.041
80.725
79.953
75.179
73.897
57.724
55.729
27.701
21.796
180
220
200
180
160
140
120
100
80
60
40
20
0
ppm

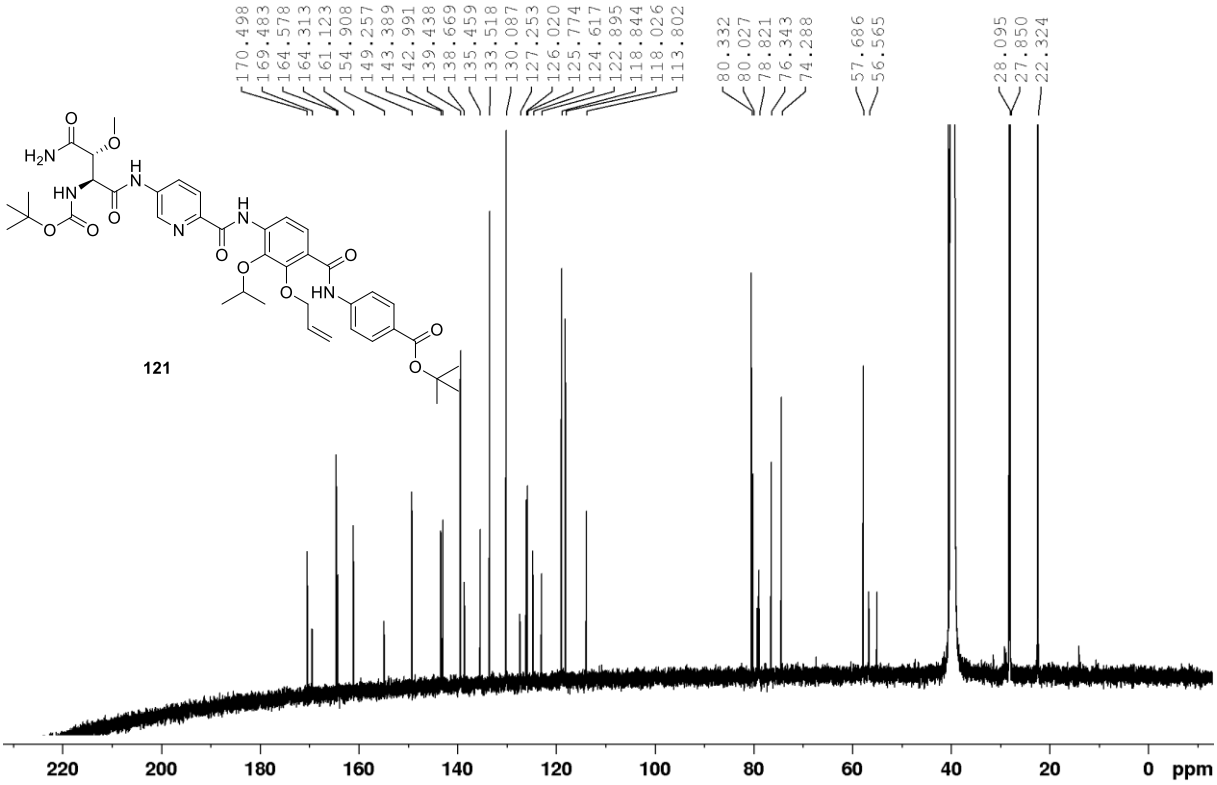

10.711
10.516
9.302
9.278
8.444
8.431
8.130
8.127
8.119
8.116
8.052
8.049
8.040
8.037
7.905
7.898
7.894
7.890
7.883
7.867
7.788
7.773
7.728
7.713
7.529
7.464
7.271
7.256
7.253
7.246
7.239
6.879
6.865
4.912
4.898
4.885
4.093
4.080
4.067
4.054
4.044
4.034
4.024
4.015
3.371
3.297
1.492
1.019
1.009
181
1.00
0.96
1.02
1.10
0.98
1.91
1.93
6.27
2.12
2.13
2.04
1.84
1.15
0.97
0.98
1.07
1.11
3.40
3.29
9.47
6.20
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

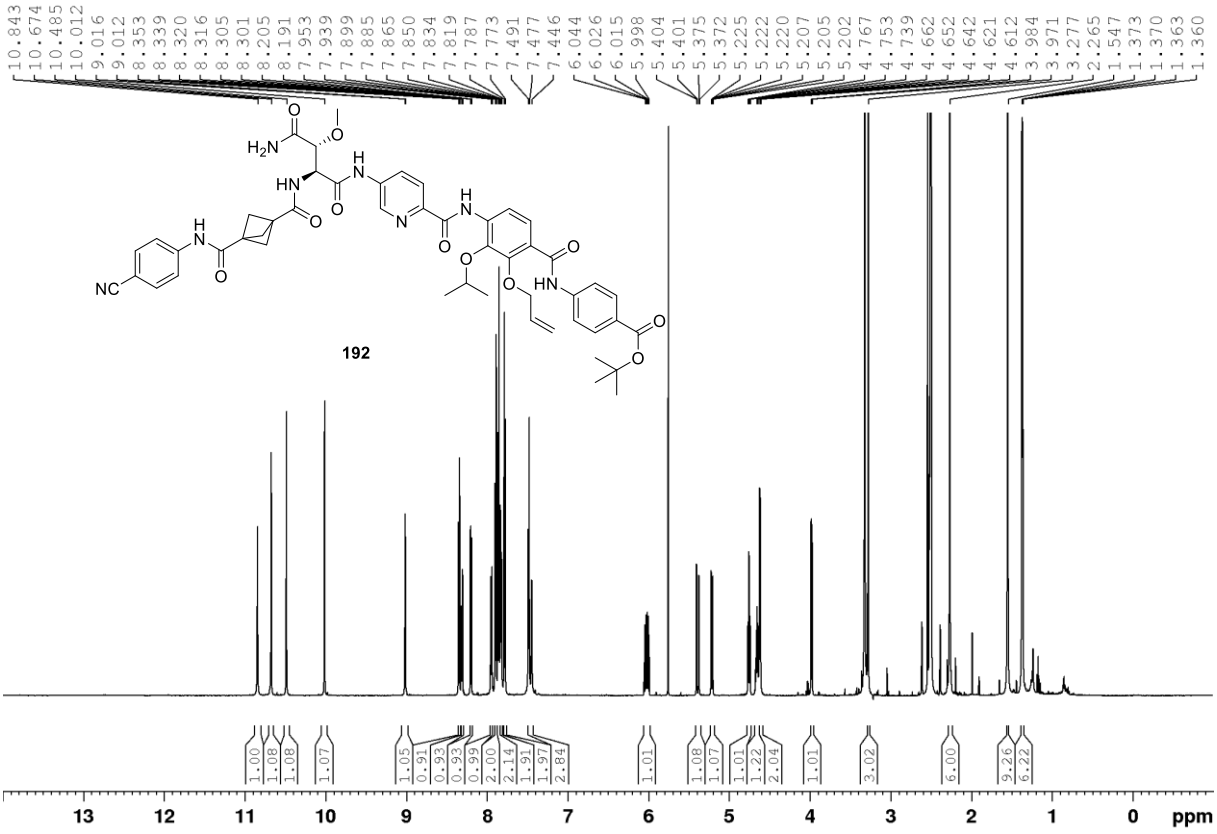

170.886
168.632
168.024
165.423
164.476
164.306
164.029
147.825
147.271
141.946
141.756
138.665
137.455
133.444
132.508
129.226
128.881
128.757
128.630
128.256
126.263
123.011
121.651
119.587
118.823
118.281
114.478
114.042
80.717
79.957
74.624
57.724
55.722
36.757
27.720
21.698
181
220
200
180
160
140
120
100
80
60
40
20
0
ppm

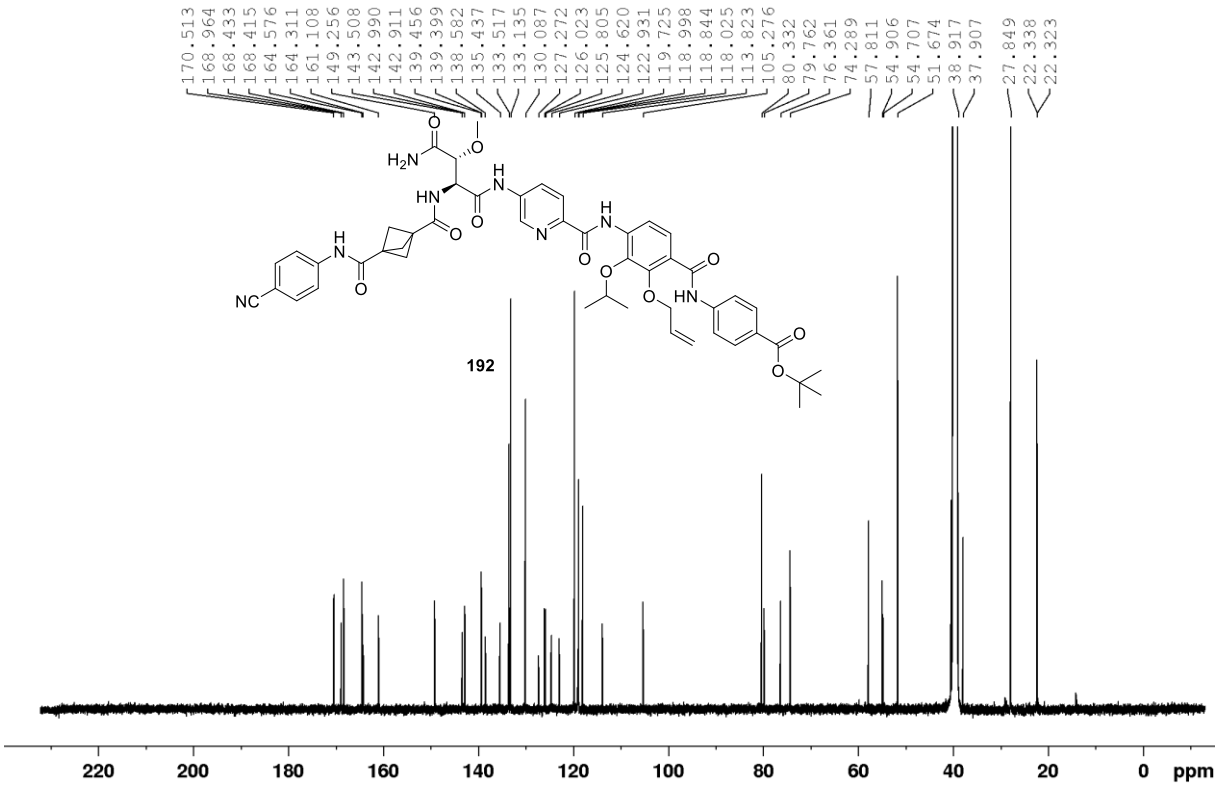

12.895
10.710
10.513
9.307
9.279
8.443
8.430
8.130
8.127
8.119
8.116
8.052
8.049
8.041
8.038
7.905
7.900
7.890
7.885
7.882
7.871
7.867
7.785
7.771
7.760
7.757
7.528
7.463
7.281
7.267
7.233
7.219
6.869
6.855
4.911
4.898
4.884
4.079
4.074
4.066
4.054
4.043
3.376
3.297
1.020
1.009
TSD08
1.00
1.00
1.00
0.96
0.97
0.92
1.82
1.89
5.90
3.96
1.93
1.86
0.84
0.86
0.98
2.03
3.09
2.93
5.63
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

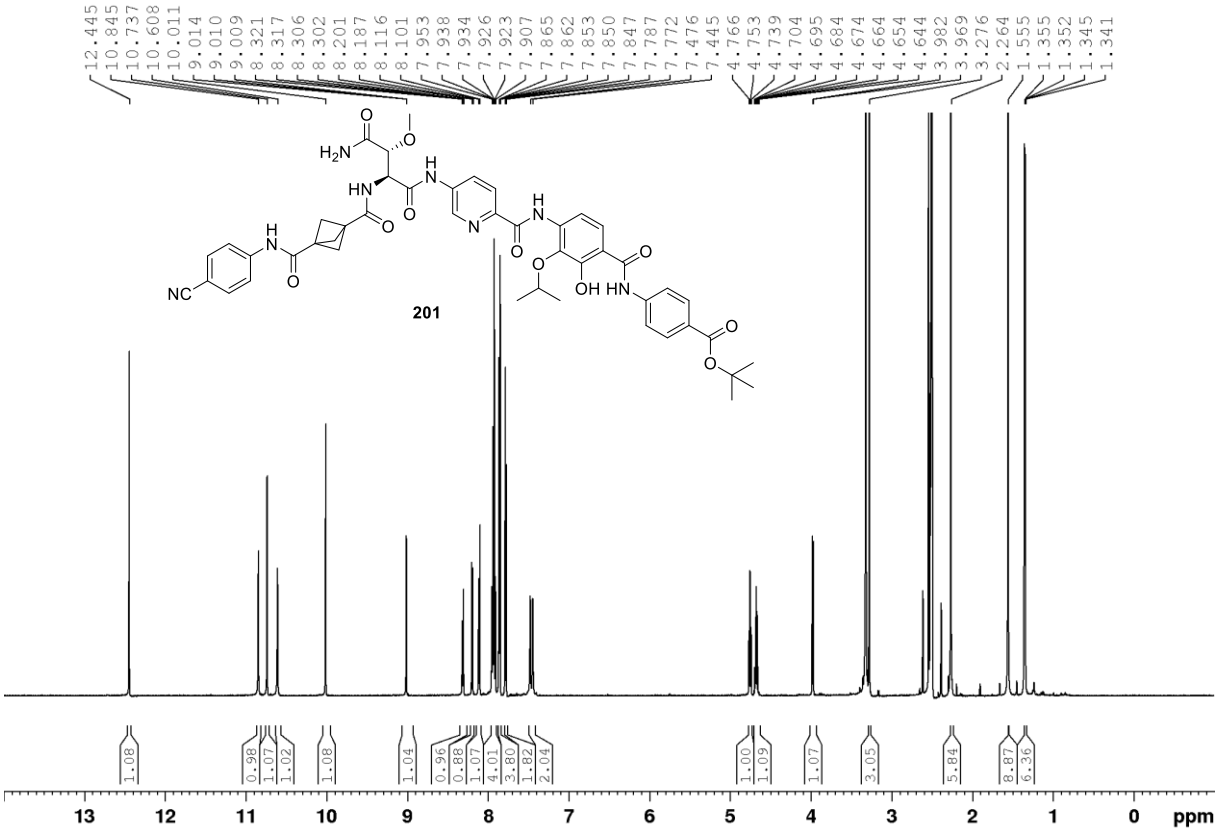

170.884
168.625
168.040
166.656
165.419
164.472
164.030
147.783
147.296
141.927
141.754
138.664
137.540
133.381
132.506
129.533
128.883
128.775
128.628
128.253
128.129
126.257
122.916
121.737
119.585
118.809
118.280
114.589
114.040
79.953
74.642
57.721
55.720
36.741
21.703
TSD08
220
200
180
160
140
120
100
80
60
40
20
0
ppm

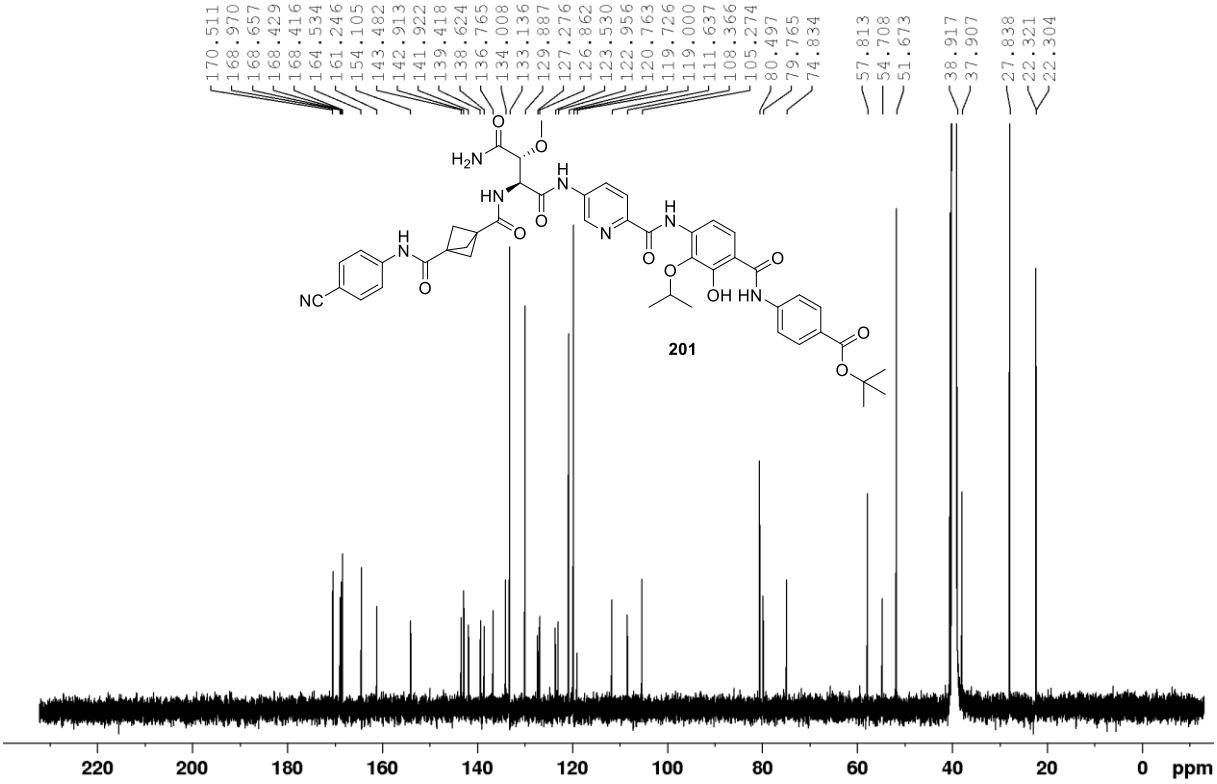

10.678
10.666
10.483
9.014
9.011
8.352
8.338
8.305
8.302
8.291
8.288
8.197
8.182
7.899
7.887
7.884
7.833
7.818
7.489
7.475
7.435
6.866
6.852
6.043
6.035
6.026
6.014
6.006
6.005
5.997
5.406
5.403
5.401
5.398
5.378
5.375
5.372
5.224
5.222
5.219
5.217
5.206
5.204
5.201
5.199
4.661
4.651
4.641
4.621
4.611
4.435
3.892
3.880
3.268
1.547
1.389
1.370
1.360
121
1.09
0.88
1.00
1.05
0.93
0.97
0.95
2.10
2.04
3.15
0.87
1.03
1.12
1.11
1.22
2.12
0.91
0.93
3.23
8.91
8.41
6.21
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

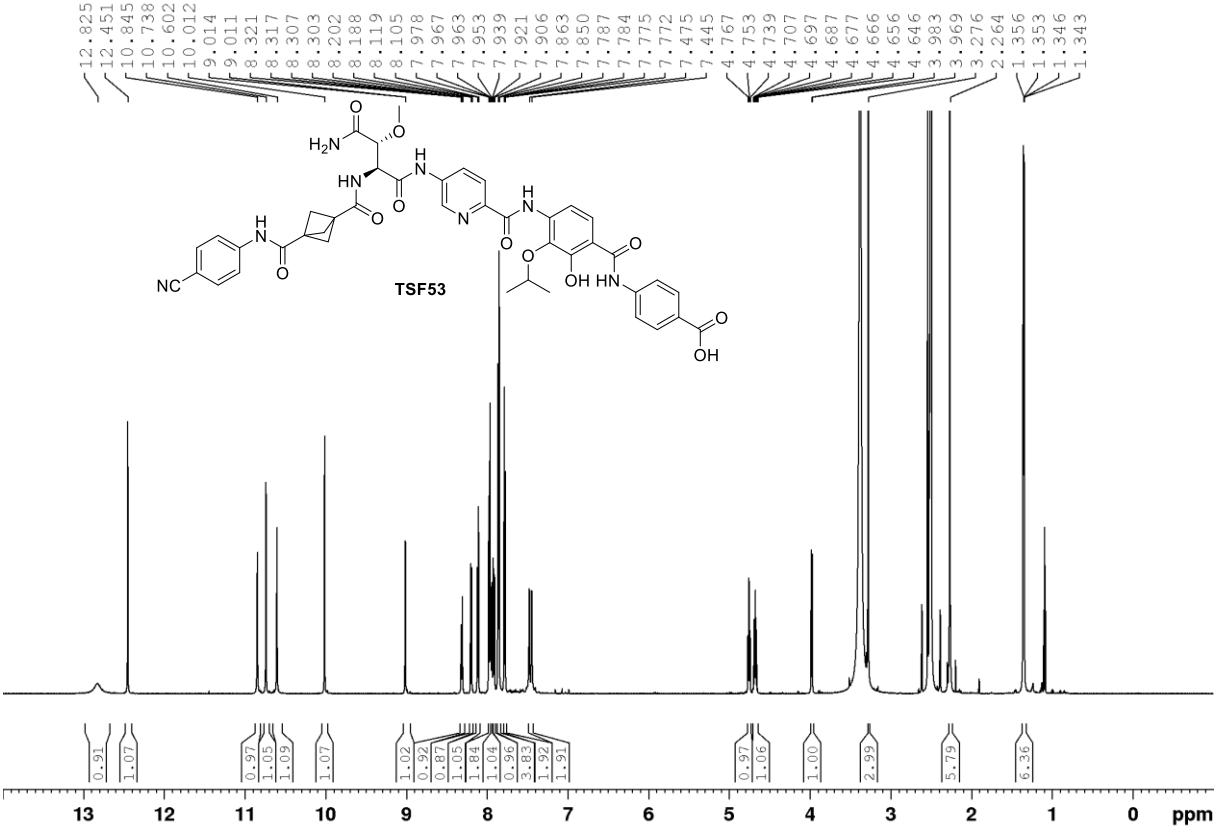

170.498
169.483
164.578
164.313
161.123
154.908
149.257
143.389
142.991
139.438
138.669
135.459
133.518
130.087
127.253
126.020
125.774
124.617
122.895
118.844
118.026
113.802
80.332
80.027
78.821
76.343
74.288
57.686
56.565
28.095
27.850
22.324
121
220
200
180
160
140
120
100
80
60
40
20
0
ppm

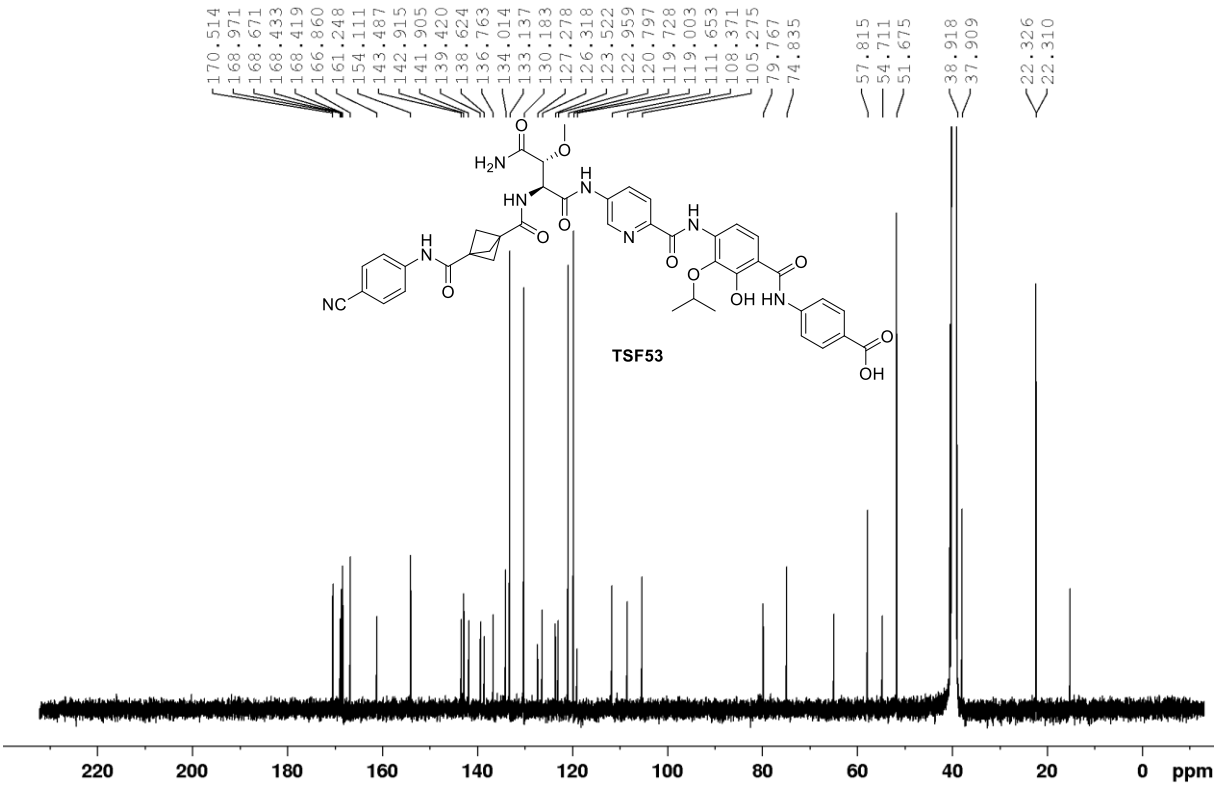

10.843
10.674
10.485
10.012
9.016
9.012
8.353
8.339
8.320
8.316
8.305
8.301
8.205
8.191
7.953
7.939
7.899
7.885
7.865
7.850
7.834
7.819
7.787
7.773
7.491
7.477
7.446
6.044
6.026
6.015
5.998
5.404
5.401
5.375
5.372
5.225
5.222
5.220
5.207
5.205
5.202
4.767
4.753
4.739
4.662
4.652
4.642
4.621
4.612
3.984
3.971
3.277
2.265
1.547
1.373
1.370
1.363
1.360
192
1.00
1.08
1.08
1.07
1.05
0.91
0.93
0.93
0.99
2.00
2.14
1.91
1.97
2.84
1.01
1.08
1.07
1.01
1.22
2.04
1.01
3.02
6.00
9.26
6.22
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

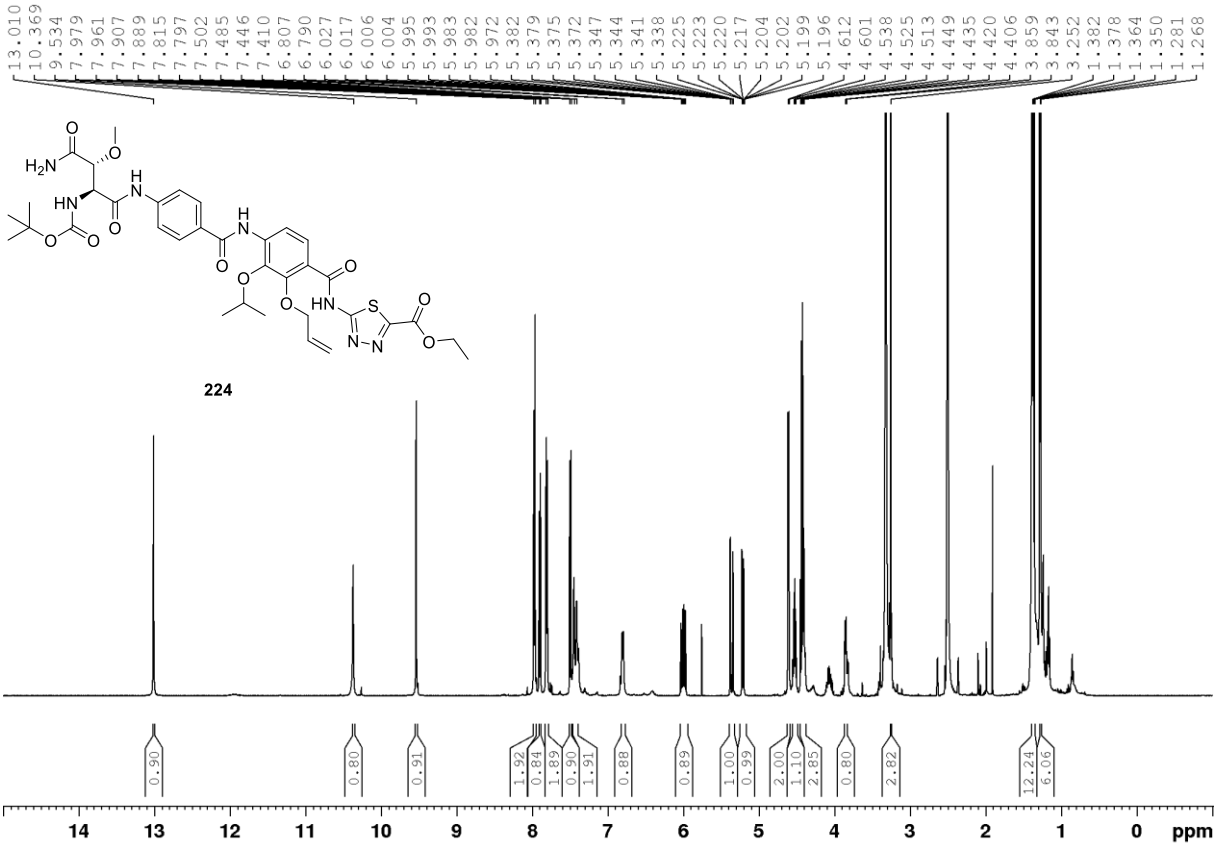

170.513
168.964
168.433
168.415
164.576
164.311
161.108
149.256
143.508
142.990
142.911
139.456
139.399
138.582
135.437
133.517
133.135
130.087
127.272
126.023
125.805
124.620
122.931
119.725
118.998
118.844
118.025
113.823
105.276
80.332
79.762
76.361
74.289
57.811
54.906
54.707
51.674
38.917
37.907
27.849
22.338
22.323
192
220
200
180
160
140
120
100
80
60
40
20
0
ppm

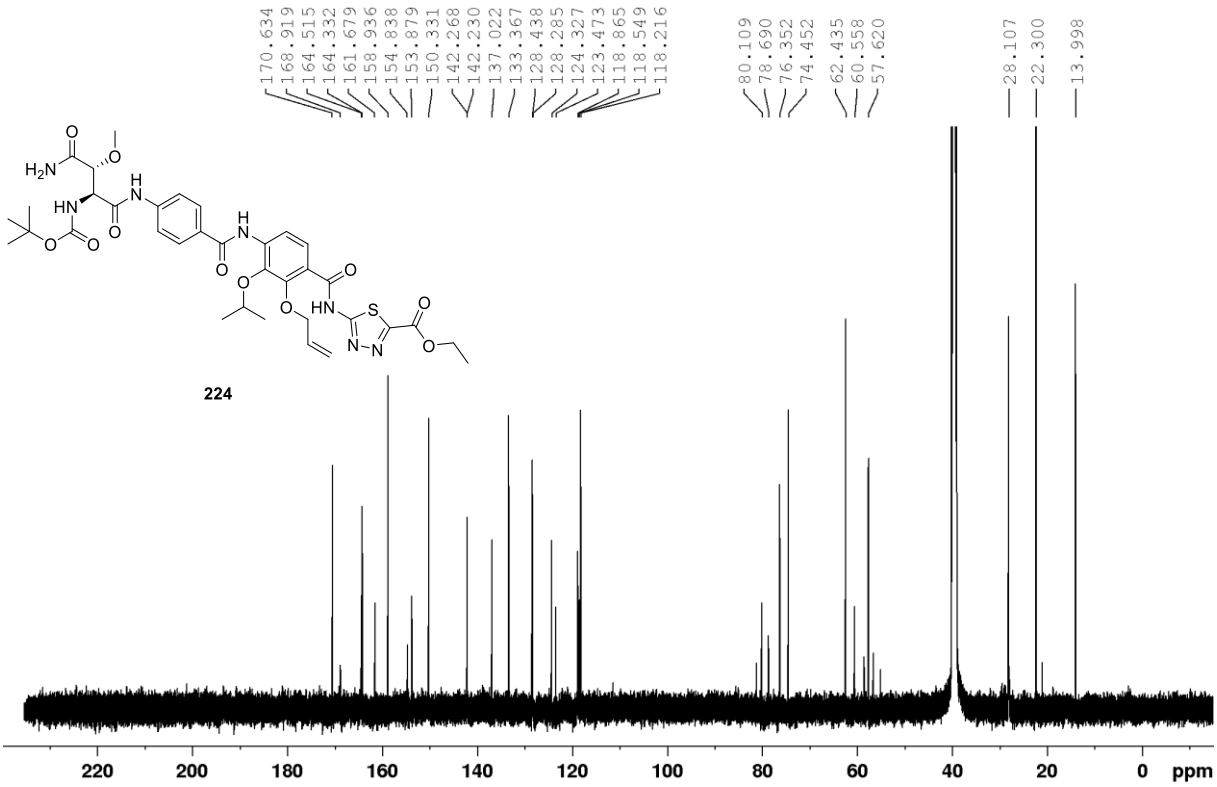

12.445
10.845
10.737
10.608
10.011
9.014
9.010
9.009
8.321
8.317
8.306
8.302
8.201
8.187
8.116
8.101
7.953
7.938
7.934
7.926
7.923
7.907
7.865
7.862
7.853
7.850
7.847
7.787
7.772
7.476
7.445
4.766
4.753
4.739
4.704
4.695
4.684
4.674
4.664
4.654
4.644
3.982
3.969
3.276
2.264
1.555
1.355
1.352
1.345
1.341
201
1.08
0.98
1.07
1.02
1.08
1.04
0.96
0.88
1.07
4.01
3.80
1.82
2.04
1.00
1.09
1.07
3.05
5.84
8.87
6.36
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

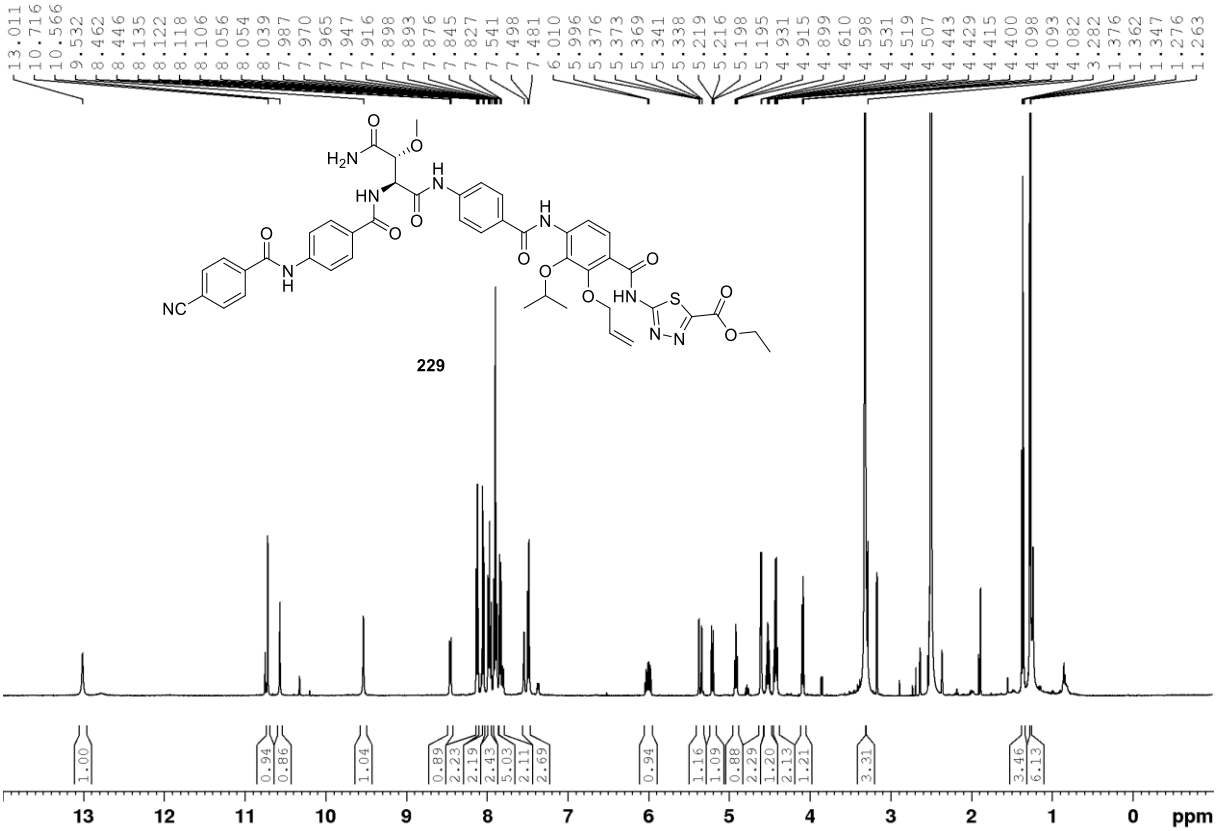

170.511
168.970
168.657
168.429
168.416
164.534
161.246
154.105
143.482
142.913
141.922
139.418
138.624
136.765
134.008
133.136
129.887
127.276
126.862
123.530
122.956
120.763
119.726
119.000
111.637
108.366
105.274
80.497
79.765
74.834
57.813
54.708
51.673
38.917
37.907
27.838
22.321
22.304
201
220
200
180
160
140
120
100
80
60
40
20
0
ppm

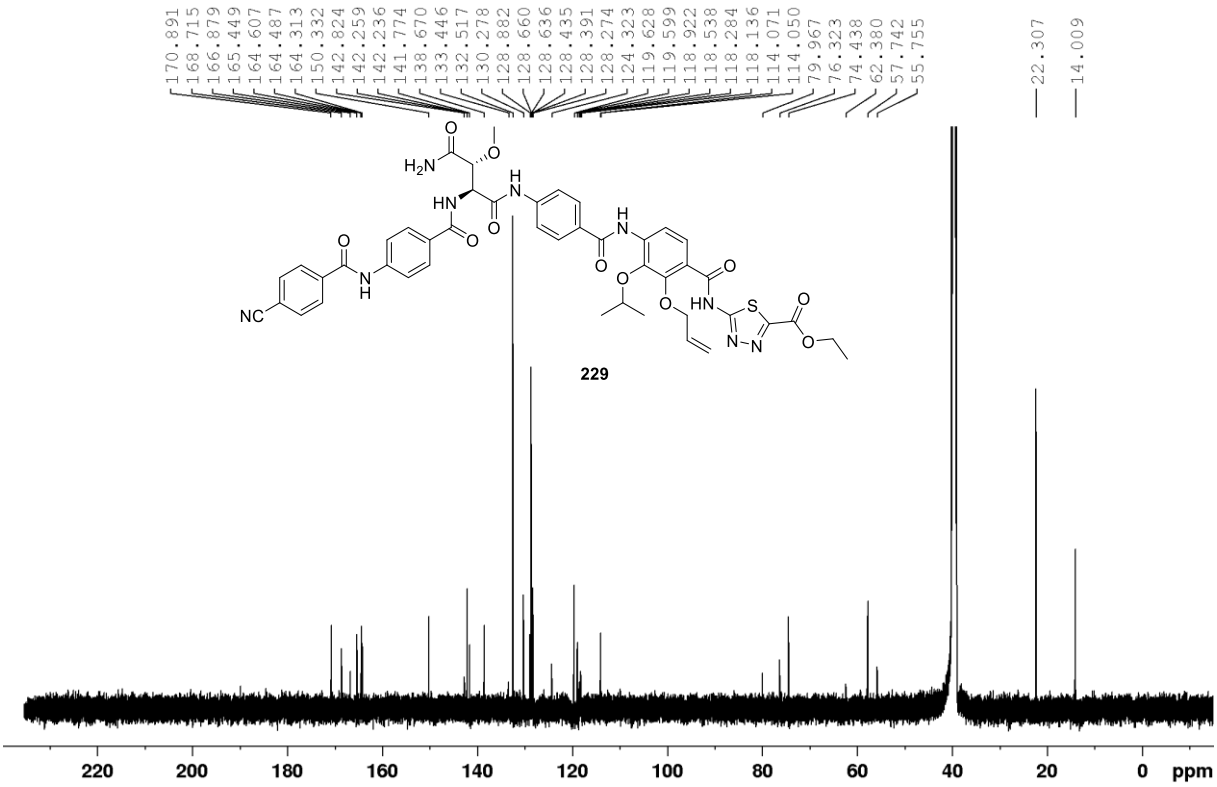

12.825
12.451
10.845
10.738
10.602
10.012
9.014
9.011
8.321
8.317
8.307
8.303
8.202
8.188
8.119
8.105
7.978
7.967
7.963
7.953
7.939
7.921
7.906
7.863
7.850
7.787
7.784
7.775
7.772
7.475
7.445
4.767
4.753
4.739
4.707
4.697
4.687
4.677
4.666
4.656
4.646
3.983
3.969
3.276
2.264
1.356
1.353
1.346
1.343
TSF53
0.91
1.07
0.97
1.05
1.09
1.07
1.02
0.92
0.87
1.05
1.84
1.04
0.96
3.83
1.92
1.91
0.97
1.06
1.00
2.99
5.79
6.36
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

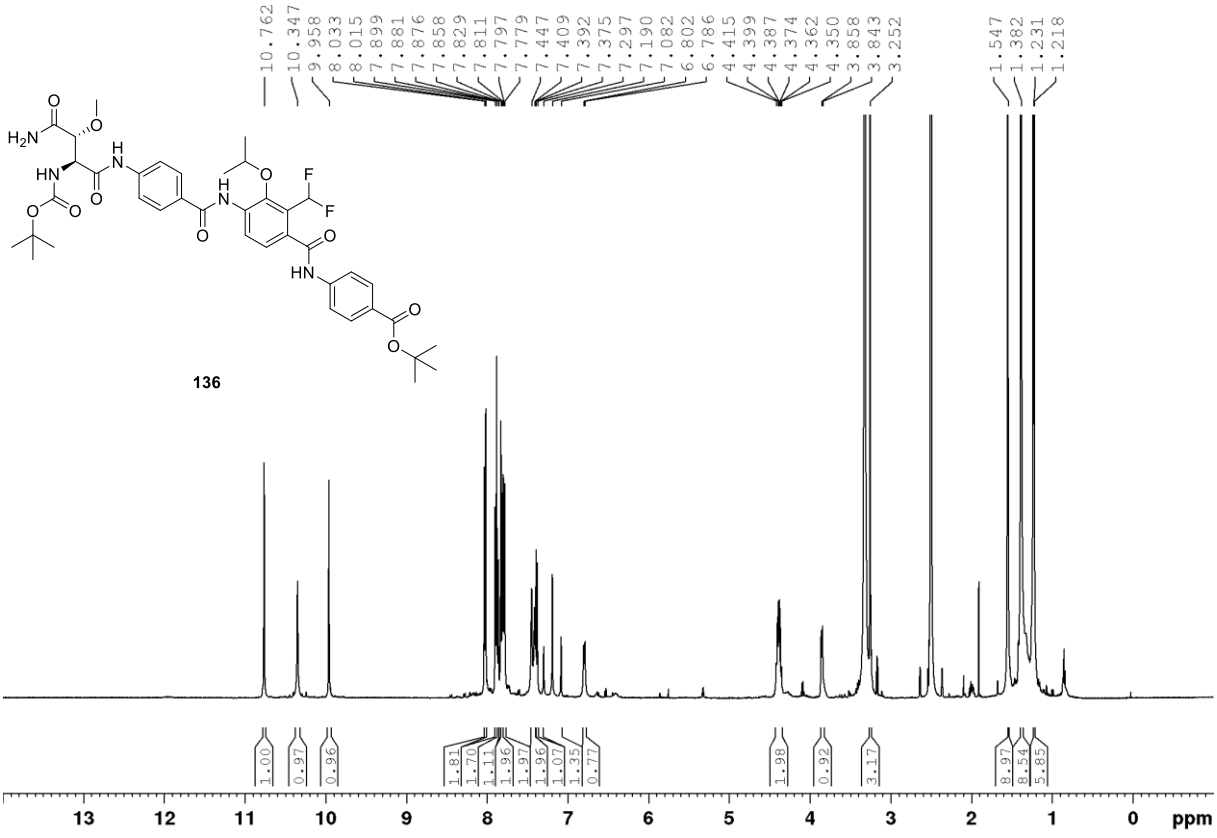

170.514
168.971
168.671
168.433
168.419
166.860
161.248
154.111
143.487
142.915
141.905
139.420
138.624
136.763
134.014
133.137
130.183
127.278
126.318
123.522
122.959
120.797
119.728
119.003
111.653
108.371
105.275
79.767
74.835
57.815
54.711
51.675
38.918
37.909
22.326
22.310
TSF53
220
200
180
160
140
120
100
80
60
40
20
0
ppm

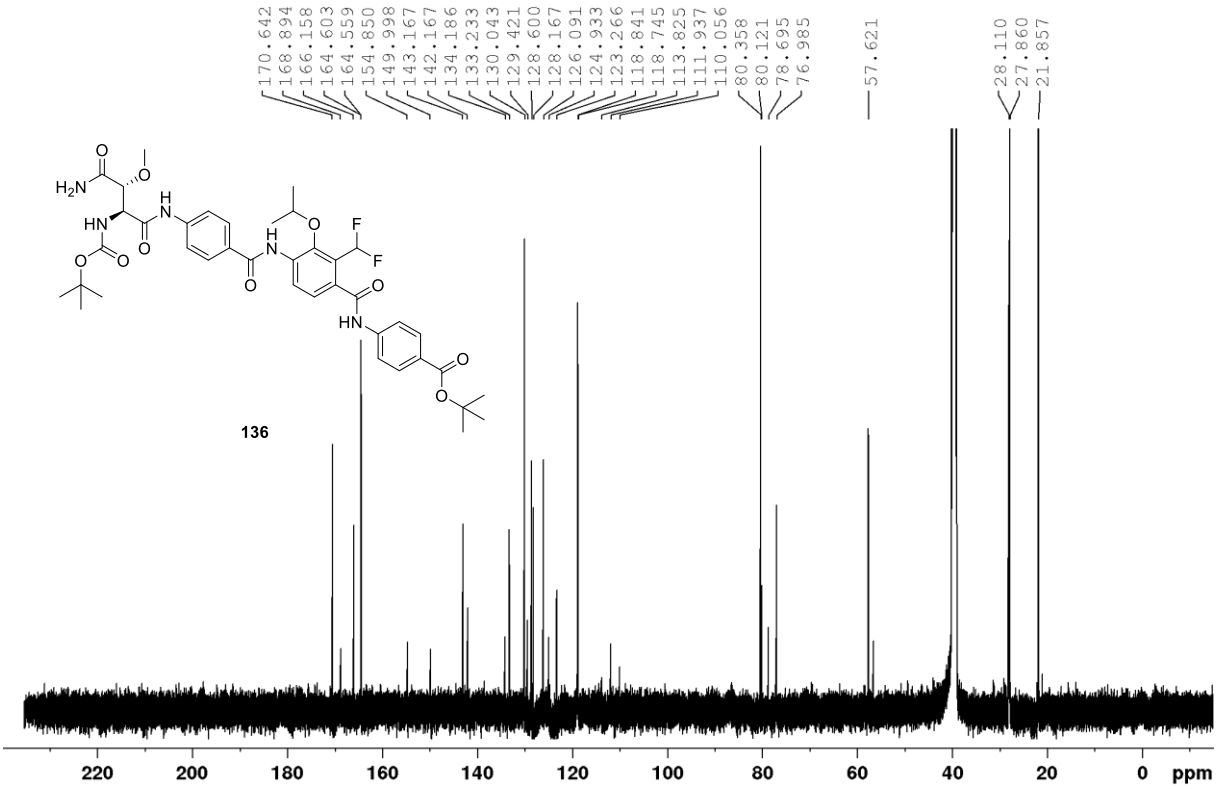

13.010
10.369
9.534
7.979
7.961
7.907
7.889
7.815
7.797
7.502
7.485
7.446
7.410
6.807
6.790
6.027
6.017
6.006
6.004
5.995
5.993
5.983
5.982
5.972
5.382
5.379
5.375
5.372
5.347
5.344
5.341
5.338
5.225
5.223
5.220
5.217
5.204
5.202
5.199
5.196
4.612
4.601
4.538
4.525
4.513
4.449
4.435
4.420
4.406
3.859
3.843
3.252
1.382
1.378
1.364
1.350
1.281
1.268
224
0.90
0.80
0.91
1.92
0.84
1.89
0.90
1.91
0.88
0.89
1.00
0.99
2.00
1.10
2.85
0.80
2.82
12.24
6.06
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

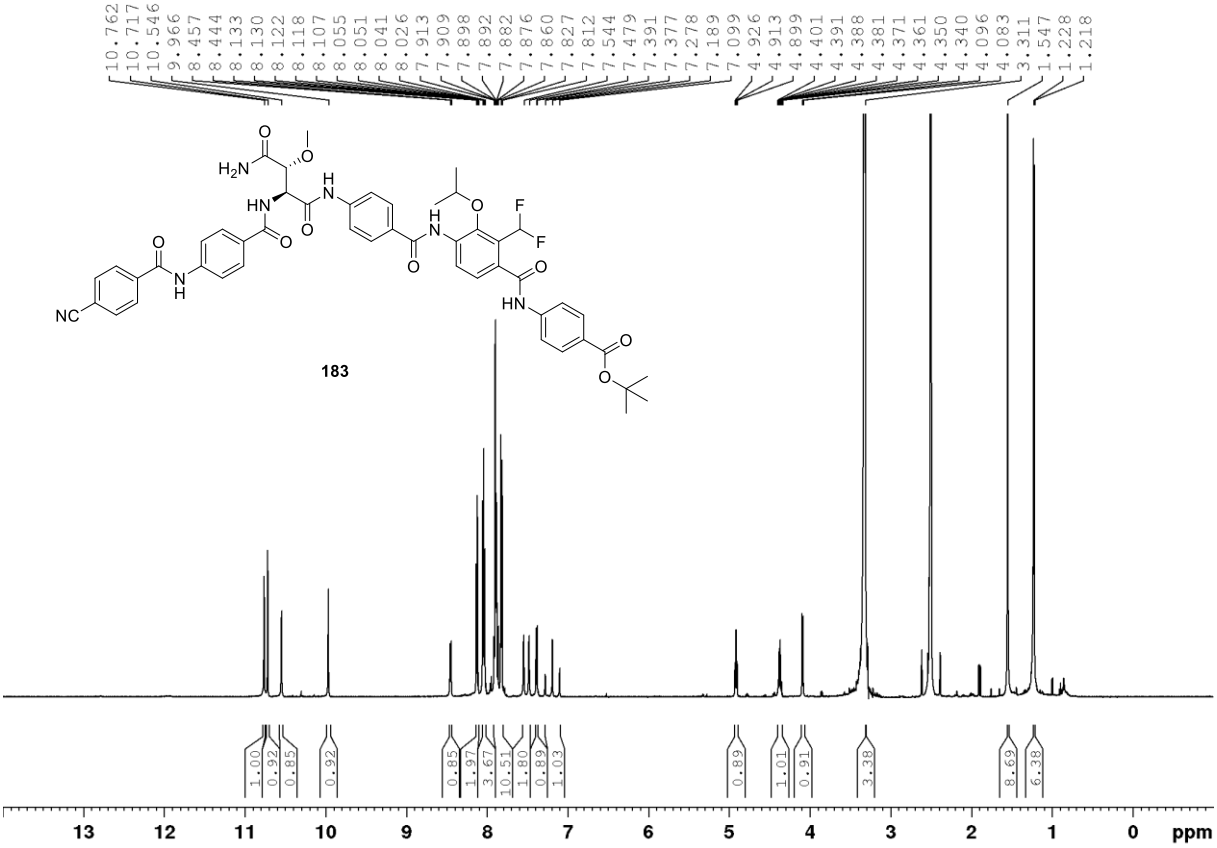

170.634
168.919
164.515
164.332
161.679
158.936
154.838
153.879
150.331
142.268
142.230
137.022
133.367
128.438
128.285
124.327
123.473
118.865
118.549
118.216
80.109
78.690
76.352
74.452
62.435
60.558
57.620
28.107
22.300
13.998
224
220
200
180
160
140
120
100
80
60
40
20
0
ppm

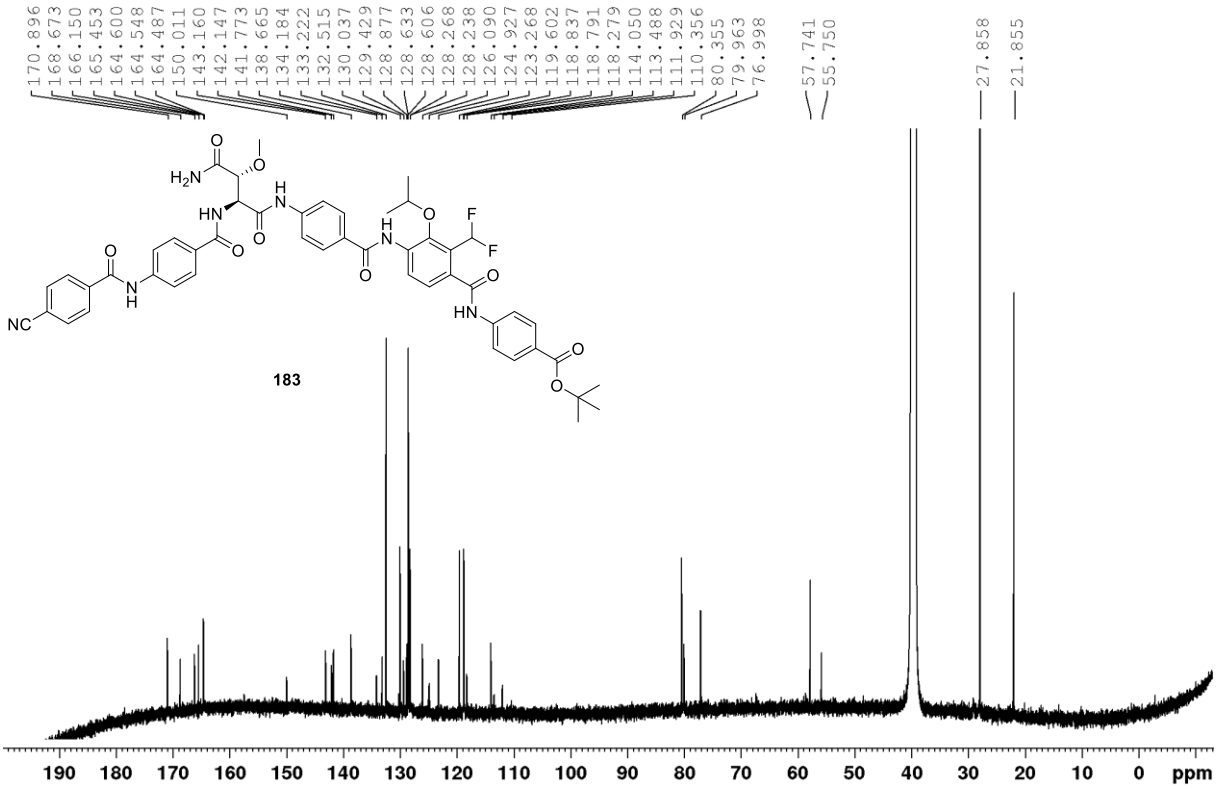

13.011
10.716
10.566
9.532
8.462
8.446
8.135
8.122
8.118
8.106
8.056
8.054
8.039
7.987
7.970
7.965
7.947
7.916
7.898
7.893
7.876
7.845
7.827
7.541
7.498
7.481
6.010
5.996
5.376
5.373
5.369
5.341
5.338
5.219
5.216
5.198
5.195
4.931
4.915
4.899
4.610
4.598
4.531
4.519
4.507
4.443
4.429
4.415
4.400
4.098
4.093
4.082
3.282
1.376
1.362
1.347
1.276
1.263
229
1.00
0.94
0.86
1.04
0.89
2.23
2.19
2.43
5.03
2.11
2.69
0.94
1.16
1.09
0.88
2.29
1.20
2.13
1.21
3.31
3.46
6.13
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

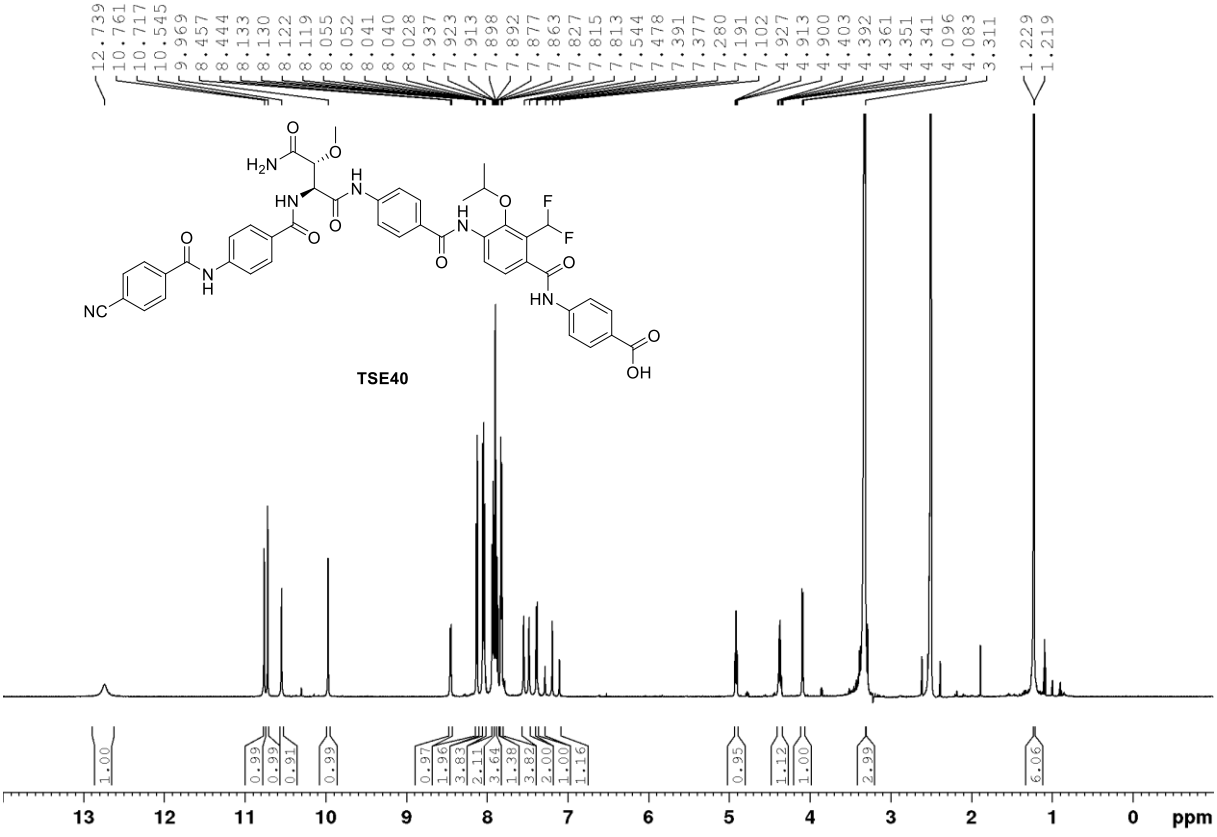

170.891
168.715
166.879
165.449
164.607
164.487
164.313
150.332
142.824
142.259
142.236
141.774
138.670
133.446
132.517
130.278
128.882
128.660
128.636
128.435
128.391
128.274
124.323
119.628
119.599
118.922
118.538
118.284
118.136
114.071
114.050
79.967
76.323
74.438
62.380
57.742
55.755
22.307
14.009
229
220
200
180
160
140
120
100
80
60
40
20
0
ppm

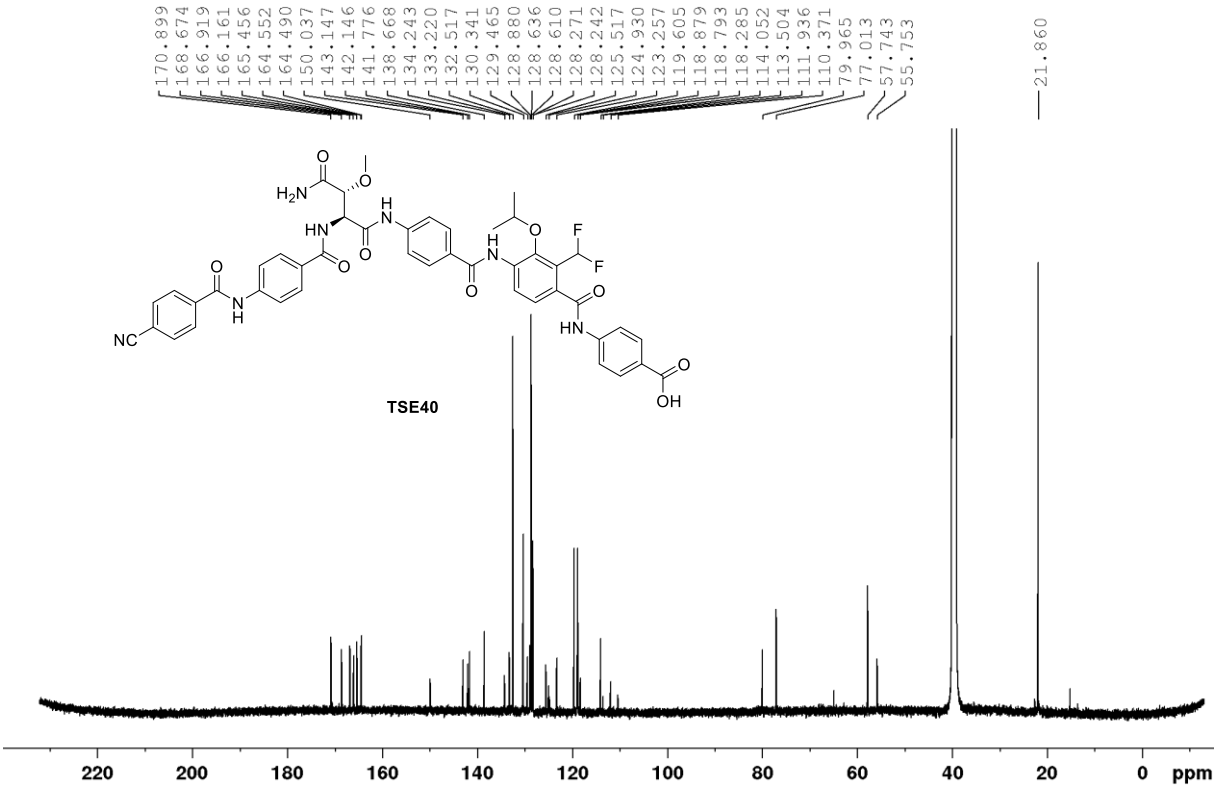

10.762
10.347
9.958
8.033
8.015
7.899
7.881
7.876
7.858
7.829
7.811
7.797
7.779
7.447
7.409
7.392
7.375
7.297
7.190
7.082
6.802
6.786
4.415
4.399
4.387
4.374
4.362
4.350
3.858
3.843
3.252
1.547
1.382
1.231
1.218
136
1.00
0.97
0.96
1.81
1.70
1.11
1.96
1.97
1.96
1.07
1.35
0.77
1.98
0.92
3.17
8.97
8.54
5.85
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

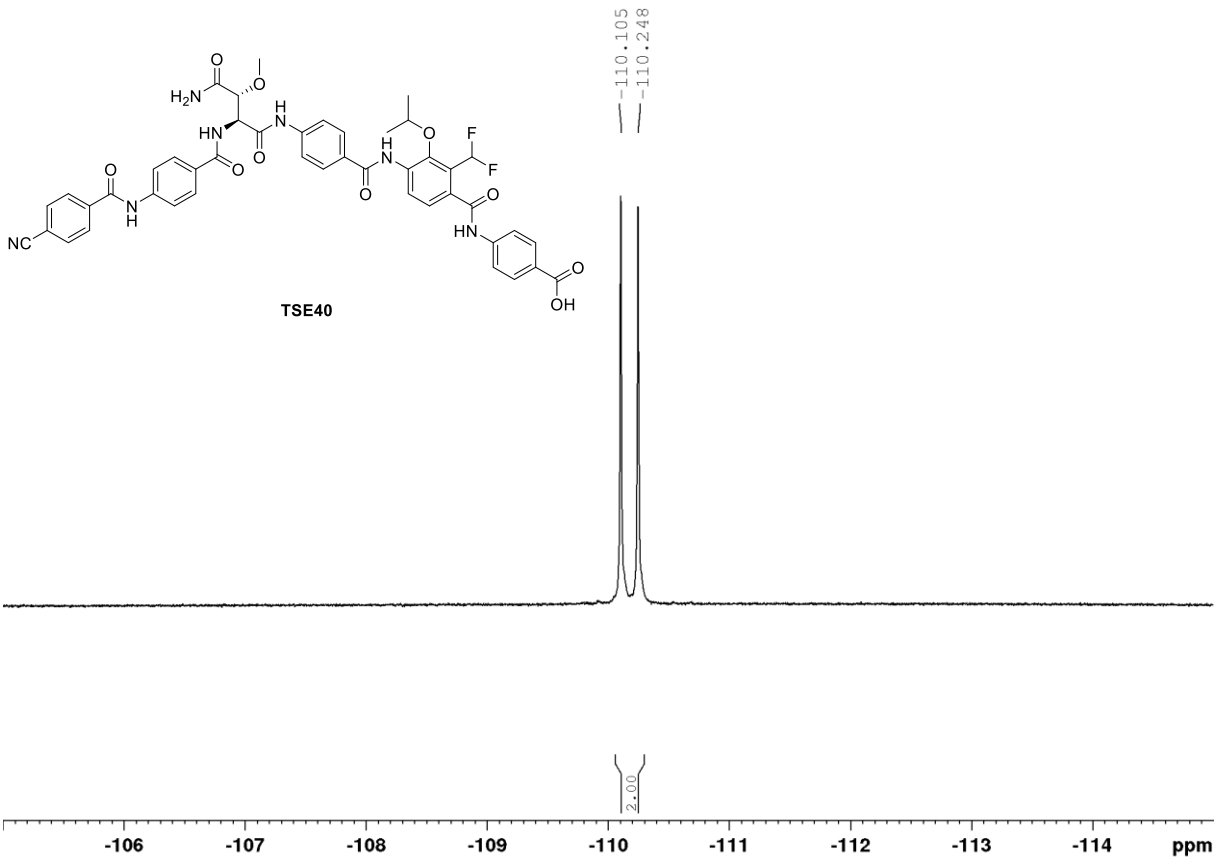

170.642
168.894
166.158
164.603
164.559
154.850
149.998
143.167
142.167
134.186
133.233
130.043
129.421
128.600
128.167
126.091
124.933
123.266
118.841
118.745
113.825
111.937
110.056
80.358
80.121
78.695
76.985
57.621
28.110
27.860
21.857
136
220
200
180
160
140
120
100
80
60
40
20
0
ppm

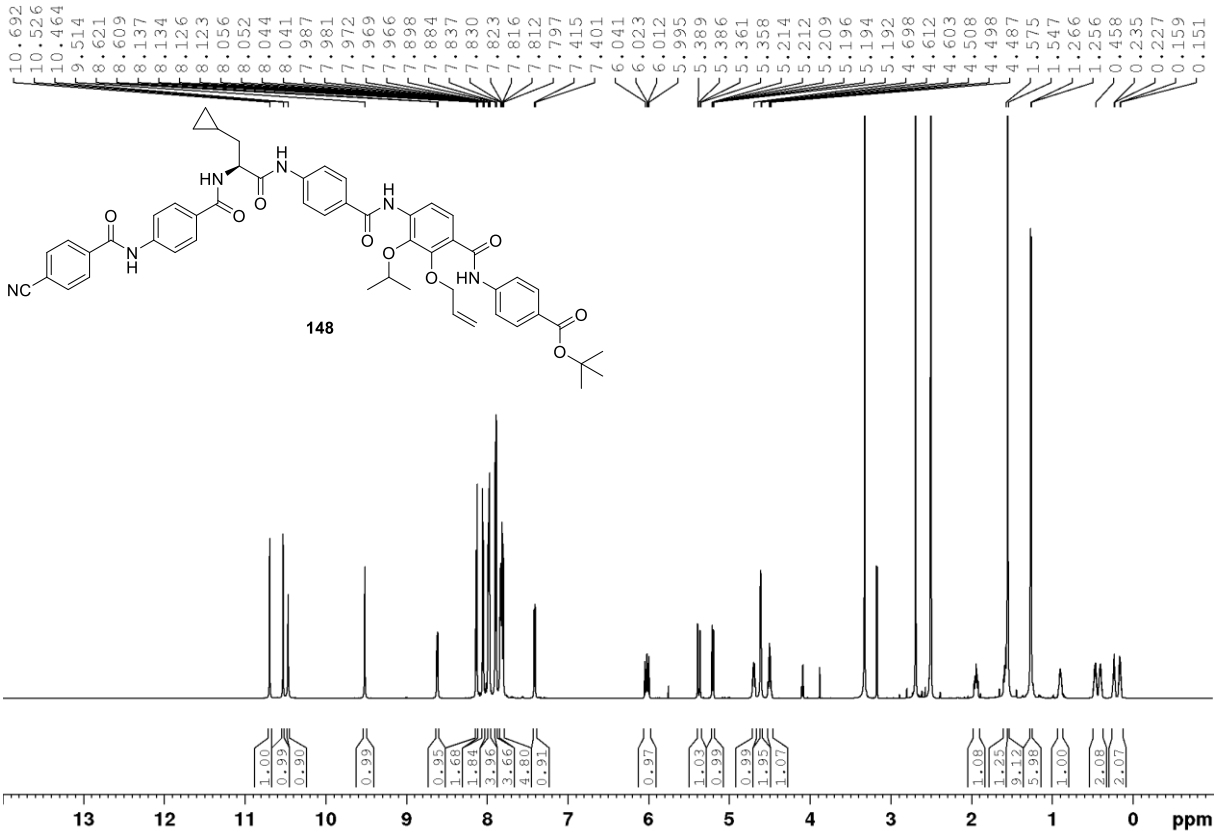

10.762
10.717
10.546
9.966
8.457
8.444
8.133
8.130
8.122
8.118
8.107
8.055
8.051
8.041
8.026
7.913
7.909
7.898
7.892
7.882
7.876
7.860
7.827
7.812
7.544
7.479
7.391
7.377
7.278
7.189
7.099
4.926
4.913
4.899
4.401
4.391
4.388
4.381
4.371
4.361
4.350
4.340
4.096
4.083
3.311
1.547
1.228
1.218
183
1.00
0.92
0.85
0.92
0.85
1.97
3.67
10.51
1.80
0.89
1.03
0.89
1.01
0.91
3.38
8.69
6.38
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

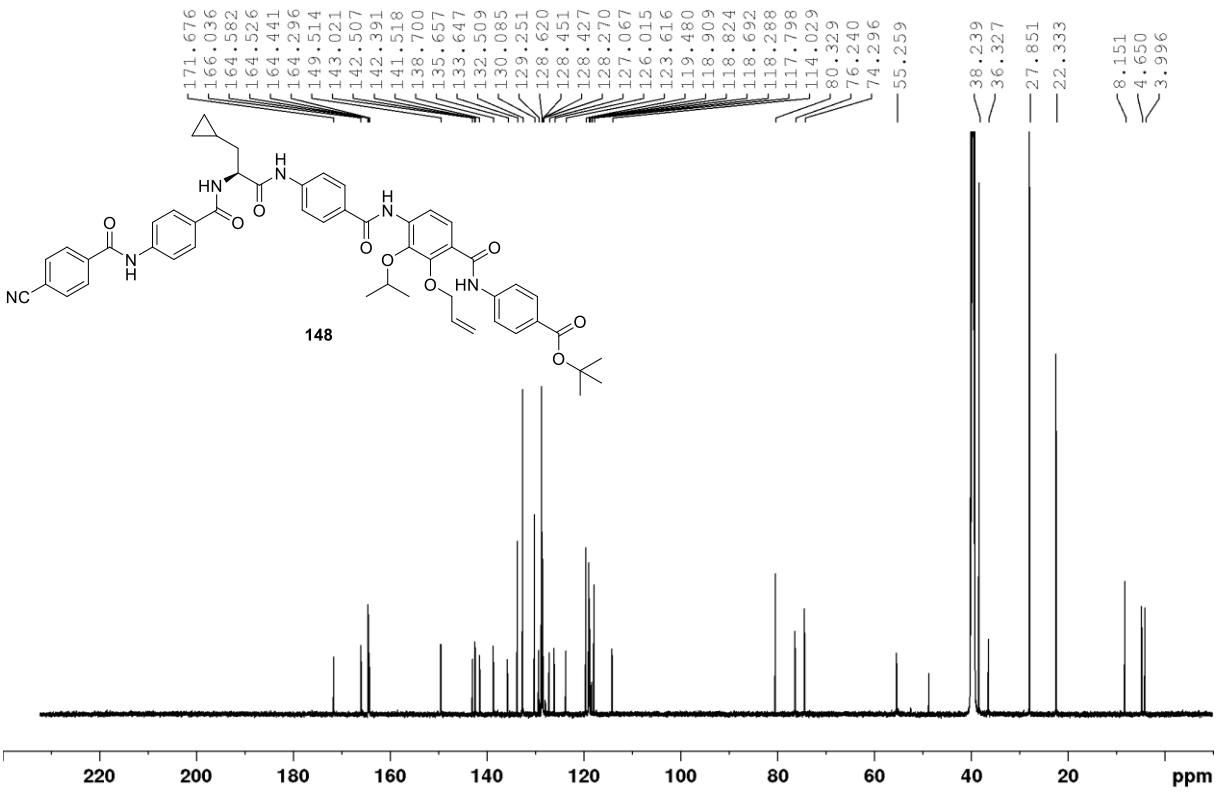

170.896
168.673
166.150
165.453
164.600
164.548
164.487
150.011
143.160
142.147
141.773
138.665
134.184
133.222
132.515
130.037
129.429
128.877
128.633
128.606
128.268
128.238
126.090
124.927
123.268
119.602
118.837
118.791
118.279
114.050
113.488
111.929
110.356
80.355
79.963
76.998
57.741
55.750
27.858
21.855
183
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

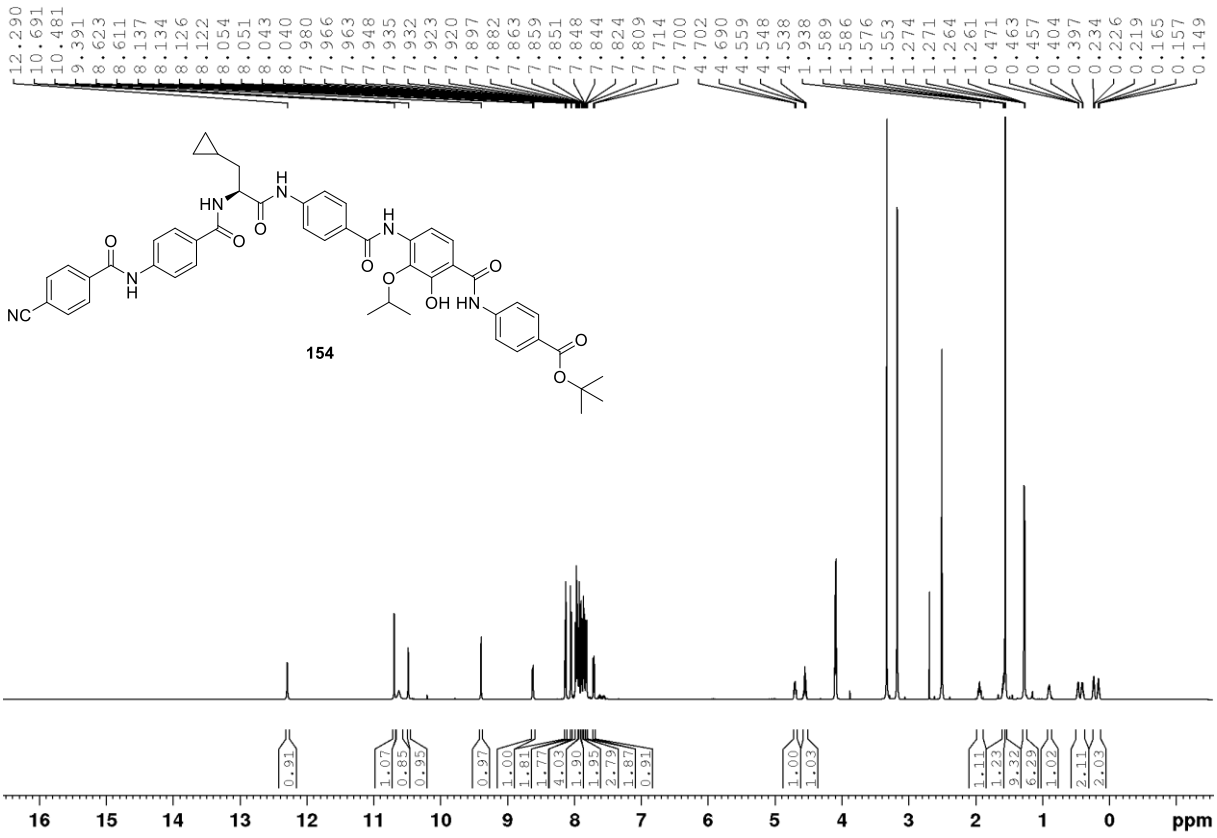

12.739
10.761
10.717
10.545
9.969
8.457
8.444
8.133
8.130
8.122
8.119
8.055
8.052
8.041
8.040
8.028
7.937
7.923
7.913
7.898
7.892
7.877
7.863
7.827
7.815
7.813
7.544
7.478
7.391
7.377
7.280
7.191
7.102
4.927
4.913
4.900
4.403
4.392
4.361
4.351
4.341
4.096
4.083
3.311
1.229
1.219
TSE40
1.00
0.99
0.99
0.91
0.99
0.97
1.96
3.83
2.11
3.64
1.38
3.82
2.00
1.00
1.16
0.95
1.12
1.00
2.99
6.06
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

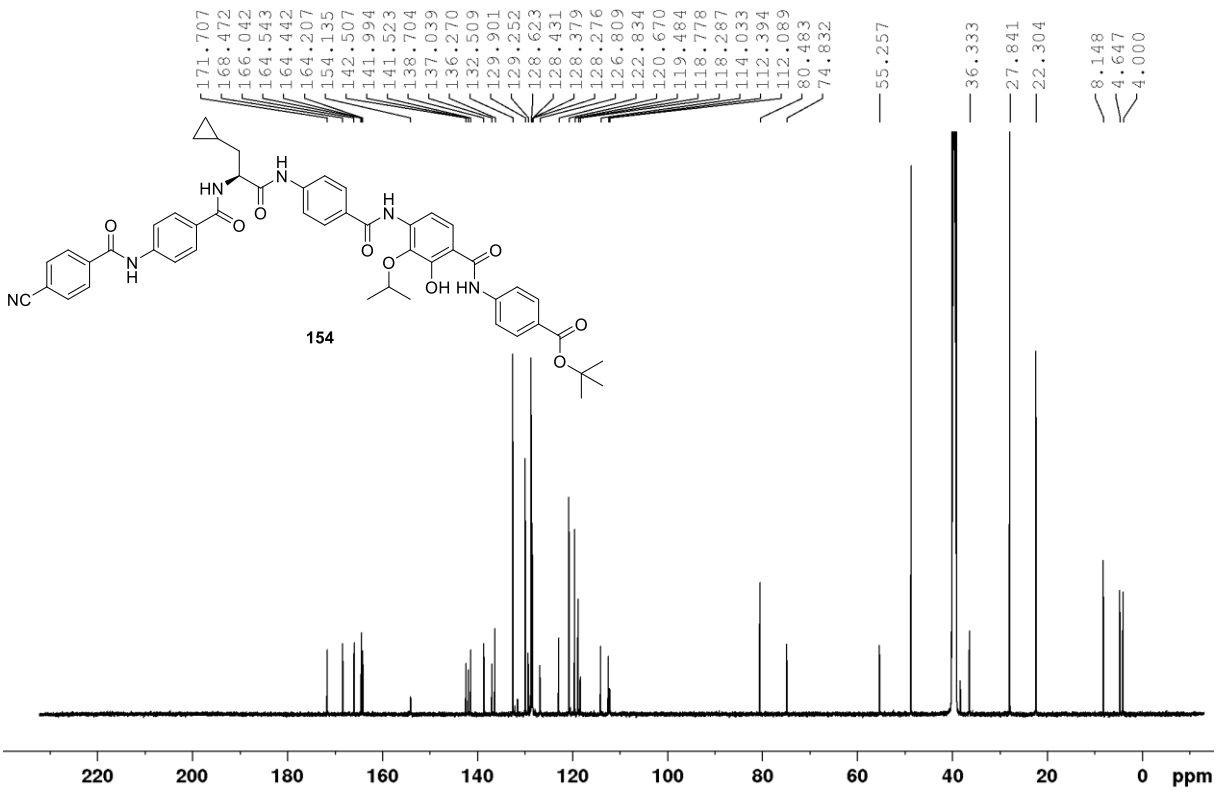

170.899
168.674
166.919
166.161
165.456
164.552
164.490
150.037
143.147
142.146
141.776
138.668
134.243
133.220
132.517
130.341
129.465
128.880
128.636
128.610
128.271
128.242
125.517
124.930
123.257
119.605
118.879
118.793
118.285
114.052
113.504
111.936
110.371
79.965
77.013
57.743
55.753
21.860
TSE40
220
200
180
160
140
120
100
80
60
40
20
0
ppm

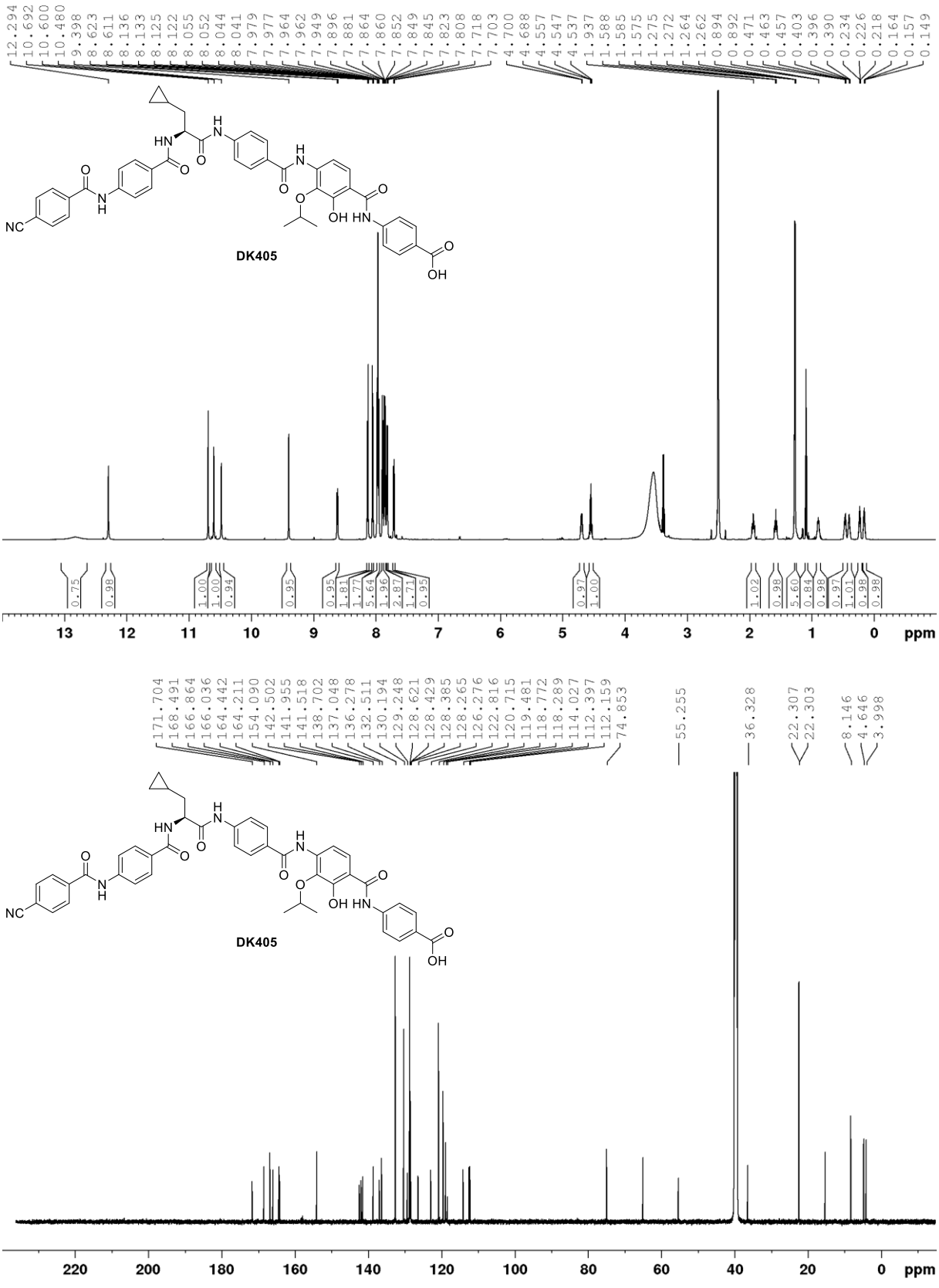

-110.105
-110.248
TSE40
2.00
-106
-107
-108
-109
-110
-111
-112
-113
-114
ppm


10.692
10.526
10.464
9.514
8.621
8.609
8.137
8.134
8.126
8.123
8.056
8.052
8.044
8.041
7.987
7.981
7.972
7.969
7.966
7.898
7.884
7.837
7.830
7.823
7.816
7.812
7.797
7.415
7.401
6.041
6.023
6.012
5.995
5.389
5.386
5.361
5.358
5.214
5.212
5.209
5.196
5.194
5.192
4.698
4.612
4.603
4.508
4.498
4.487
1.575
1.547
1.266
1.256
0.458
0.235
0.227
0.159
0.151
148
1.00
0.99
0.90
0.99
0.95
1.68
1.84
3.96
3.66
4.80
0.91
0.97
1.03
0.99
0.99
1.95
1.07
1.08
1.25
9.12
5.98
1.00
2.08
2.07
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

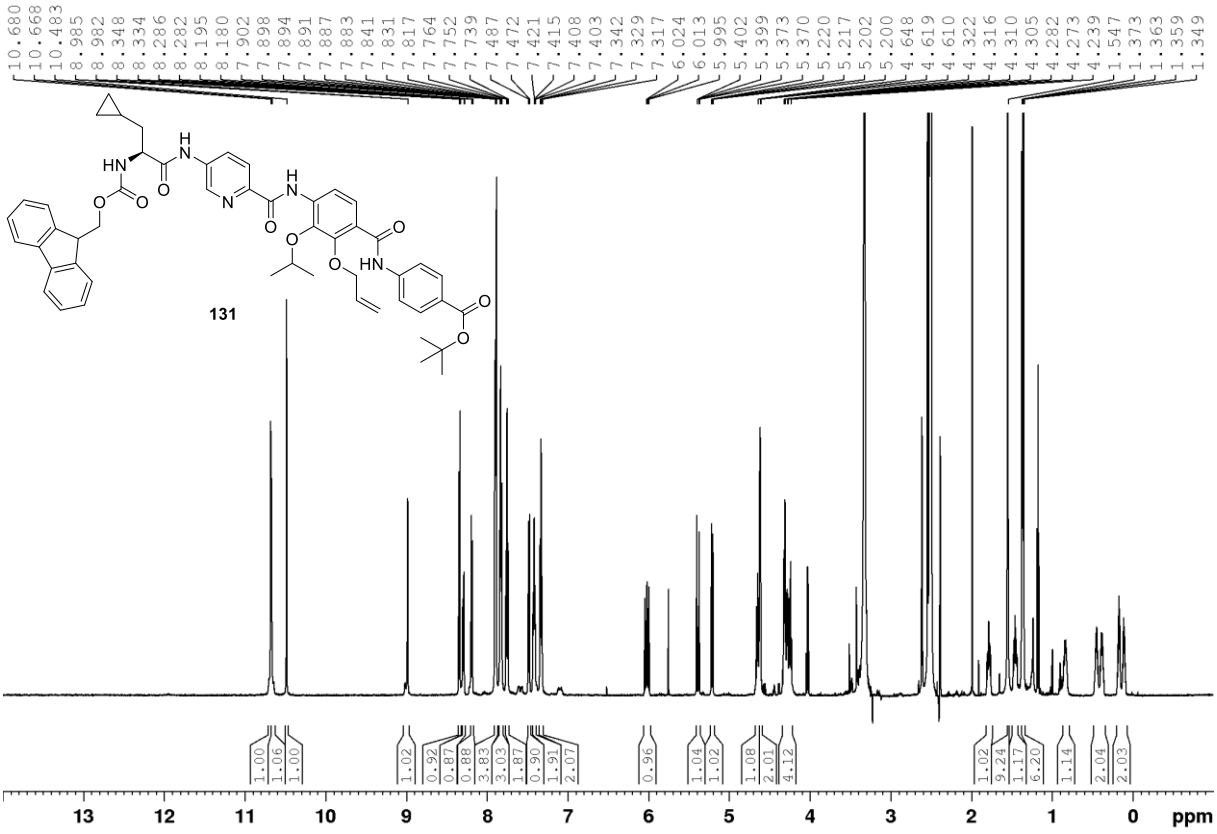

171.676
166.036
164.582
164.526
164.441
164.296
149.514
143.021
142.507
142.391
141.518
138.700
135.657
133.647
132.509
130.085
129.251
128.620
128.451
128.427
128.270
127.067
126.015
123.616
119.480
118.909
118.824
118.692
118.288
117.798
114.029
80.329
76.240
74.296
55.259
38.239
36.327
27.851
22.333
8.151
4.650
3.996
148
220
200
180
160
140
120
100
80
60
40
20
ppm

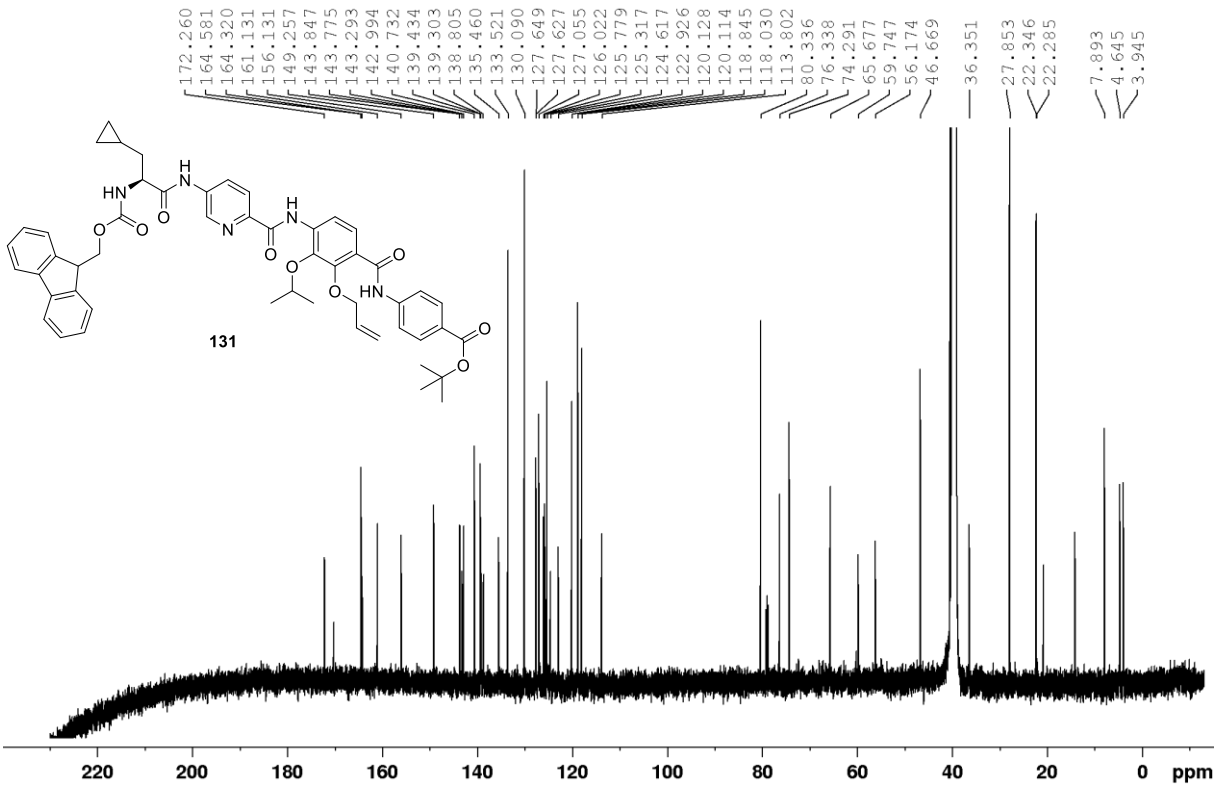

12.290
10.691
10.481
9.391
8.623
8.611
8.137
8.134
8.126
8.122
8.054
8.051
8.043
8.040
7.980
7.966
7.963
7.948
7.935
7.932
7.923
7.920
7.897
7.882
7.863
7.859
7.851
7.848
7.844
7.824
7.809
7.714
7.700
4.702
4.690
4.559
4.548
4.538
1.938
1.589
1.586
1.576
1.553
1.274
1.271
1.264
1.261
0.471
0.463
0.457
0.404
0.397
0.234
0.226
0.219
0.165
0.157
0.149
154
0.91
1.07
0.85
0.95
0.97
1.00
1.81
1.77
4.03
1.90
1.95
2.79
1.87
0.91
1.00
1.03
1.11
1.23
9.32
6.29
1.02
2.11
2.03
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

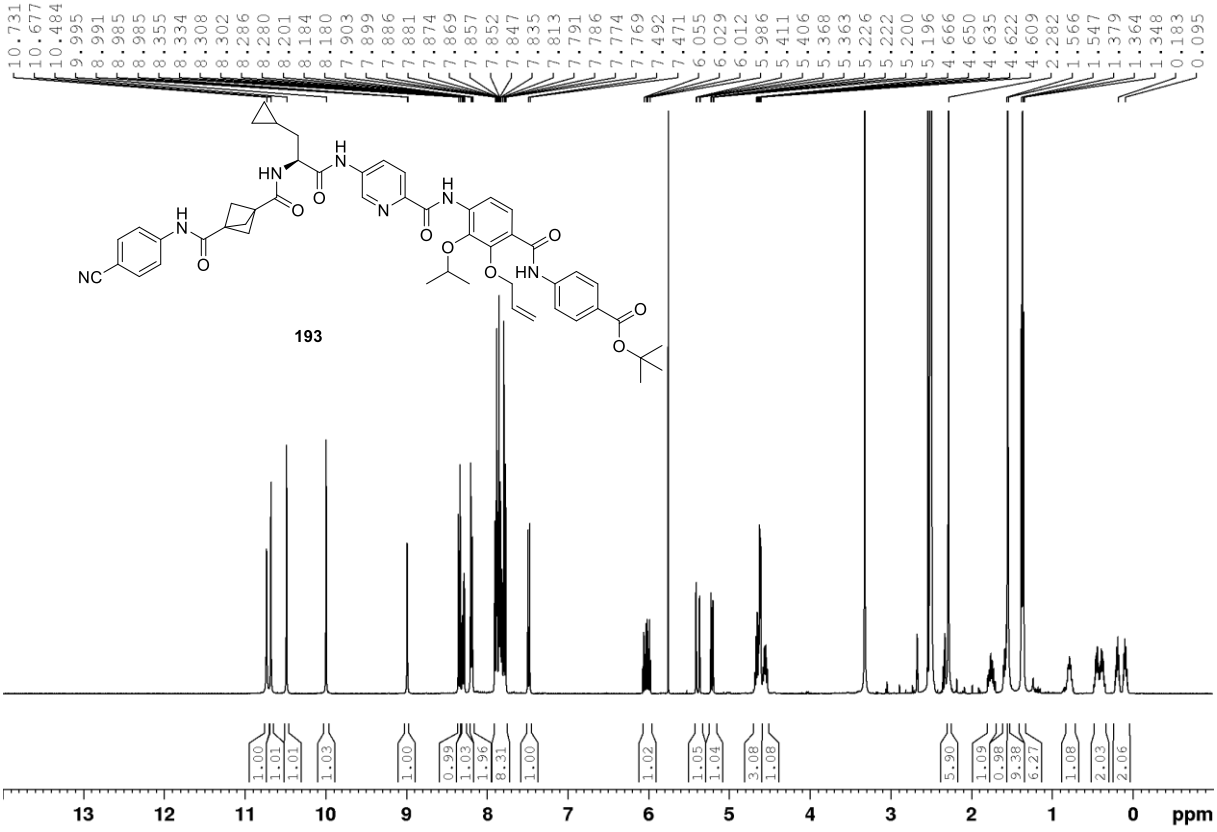

171.707
168.472
166.042
164.543
164.442
164.207
154.135
142.507
141.994
141.523
138.704
137.039
136.270
132.509
129.901
129.252
128.623
128.431
128.379
128.276
126.809
122.834
120.670
119.484
118.778
118.287
114.033
112.394
112.089
80.483
74.832
55.257
36.333
27.841
22.304
8.148
4.647
4.000
154
220
200
180
160
140
120
100
80
60
40
20
0
ppm

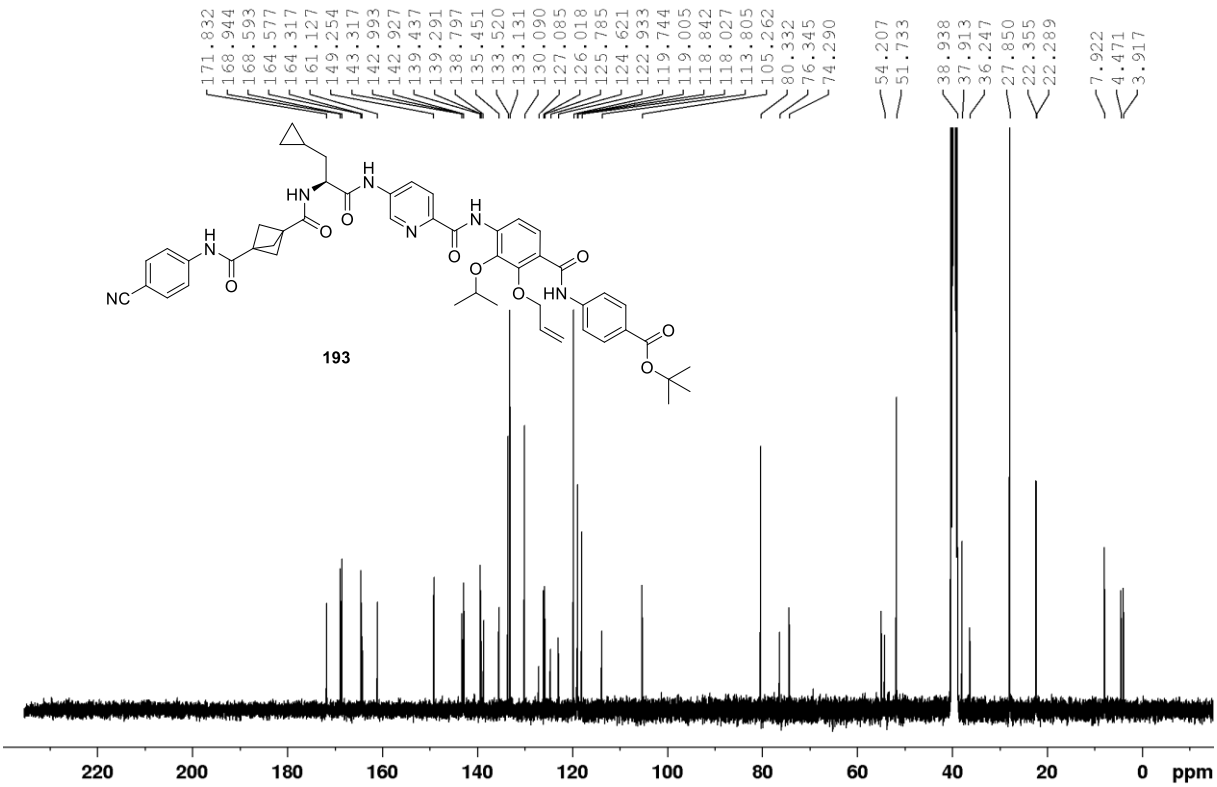

12.294
10.692
10.600
10.480
9.398
8.623
8.611
8.136
8.133
8.125
8.122
8.055
8.052
8.044
8.041
7.979
7.977
7.964
7.962
7.949
7.896
7.881
7.864
7.860
7.852
7.849
7.845
7.823
7.808
7.718
7.703
4.700
4.688
4.557
4.547
4.537
1.937
1.588
1.585
1.575
1.275
1.272
1.264
1.262
0.894
0.892
0.471
0.463
0.457
0.403
0.396
0.390
0.234
0.226
0.218
0.164
0.157
0.149
DK405
0.75
0.98
1.00
1.00
0.94
0.95
0.95
1.81
1.77
5.64
1.96
2.87
1.71
0.95
0.97
1.00
1.02
0.98
5.60
0.84
0.98
0.97
1.01
0.98
0.98
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

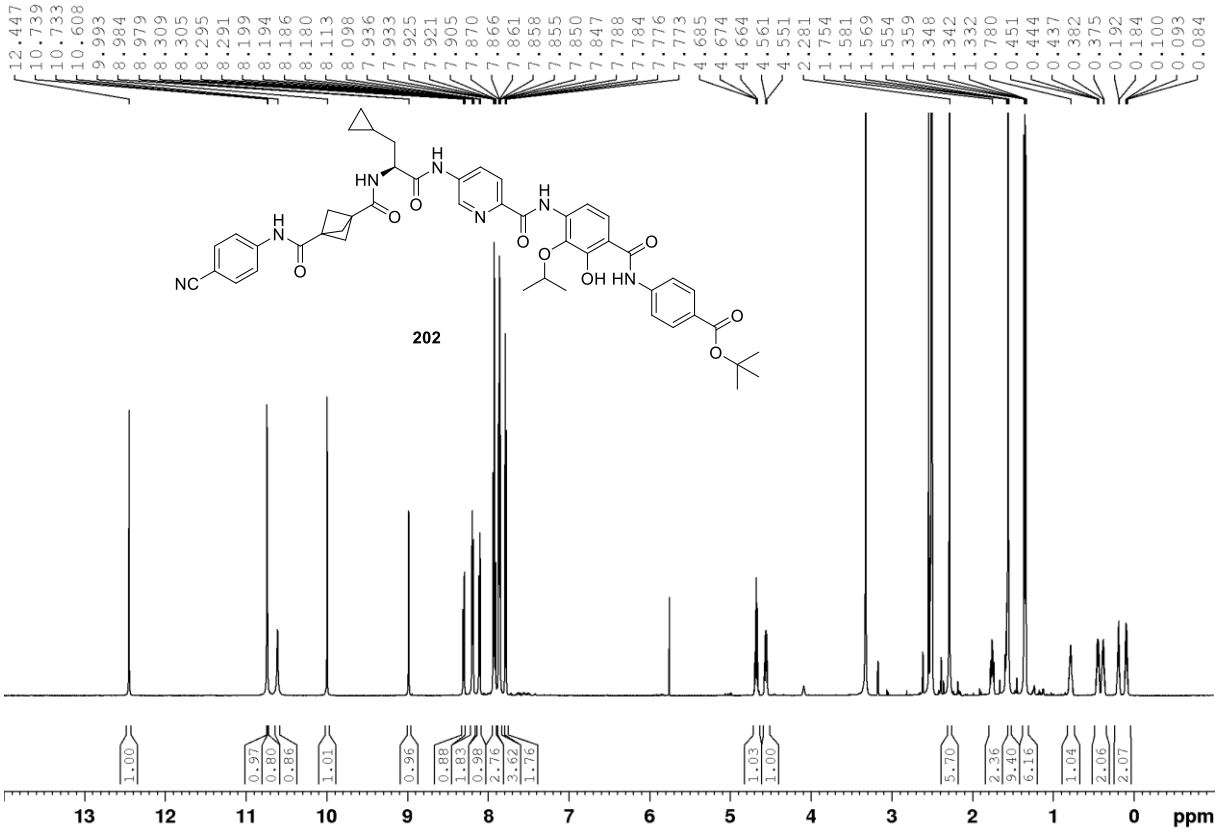
171.704
168.491
166.864
166.036
164.442
164.211
154.090
142.502
141.955
141.518
138.702
137.048
136.278
132.511
130.194
129.248
128.621
128.429
128.385
128.265
126.276
122.816
120.715
119.481
118.772
118.289
114.027
112.397
112.159
74.853
55.255
36.328
22.307
22.303
8.146
4.646
3.998
DK405
220
200
180
160
140
120
100
80
60
40
20
0
ppm

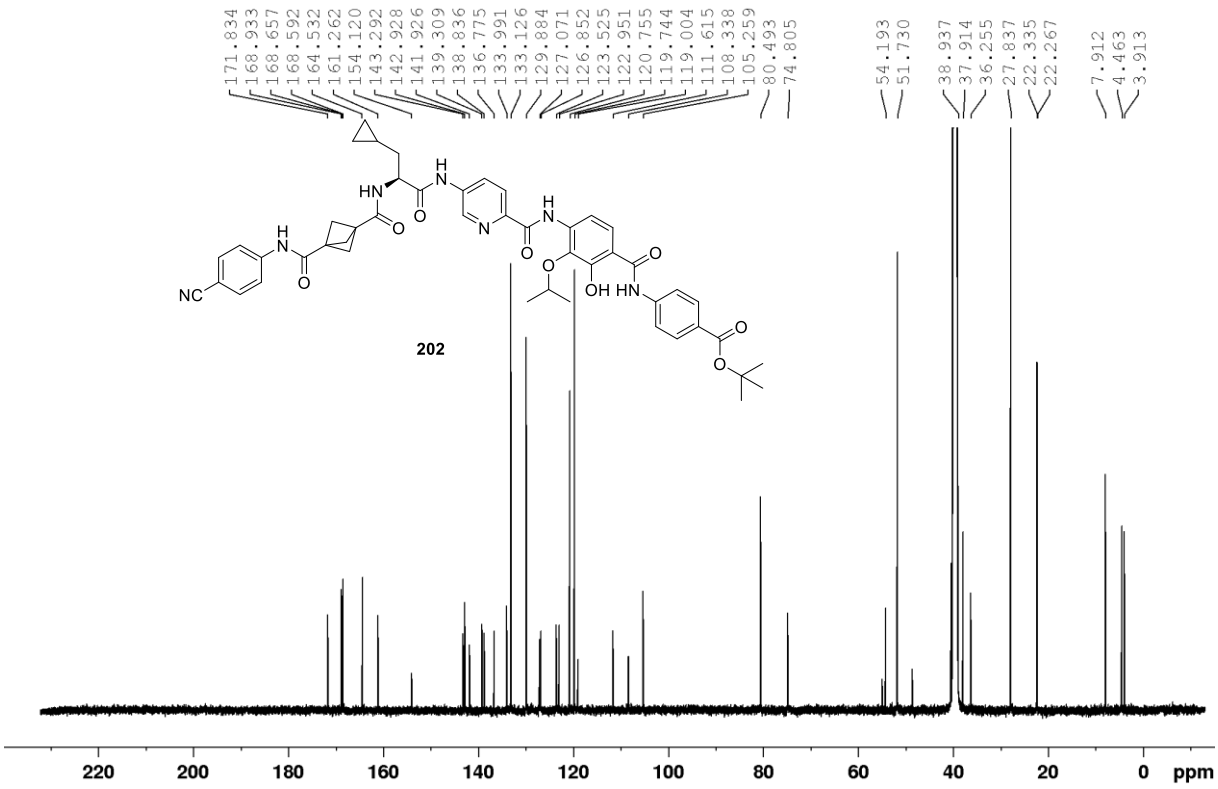

10.680
10.668
10.483
8.985
8.982
8.348
8.334
8.286
8.282
8.195
8.180
7.902
7.898
7.894
7.891
7.887
7.883
7.841
7.831
7.817
7.764
7.752
7.739
7.487
7.472
7.421
7.415
7.408
7.403
7.342
7.329
7.317
6.024
6.013
5.995
5.402
5.399
5.373
5.370
5.220
5.217
5.202
5.200
4.648
4.619
4.610
4.322
4.316
4.310
4.305
4.282
4.273
4.239
1.547
1.373
1.363
1.359
1.349
131
1.00
1.06
1.00
1.02
0.92
0.87
0.88
3.83
3.03
1.87
0.90
1.91
2.07
0.96
1.04
1.02
1.08
2.01
4.12
1.02
9.24
1.17
6.20
1.14
2.04
2.03
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

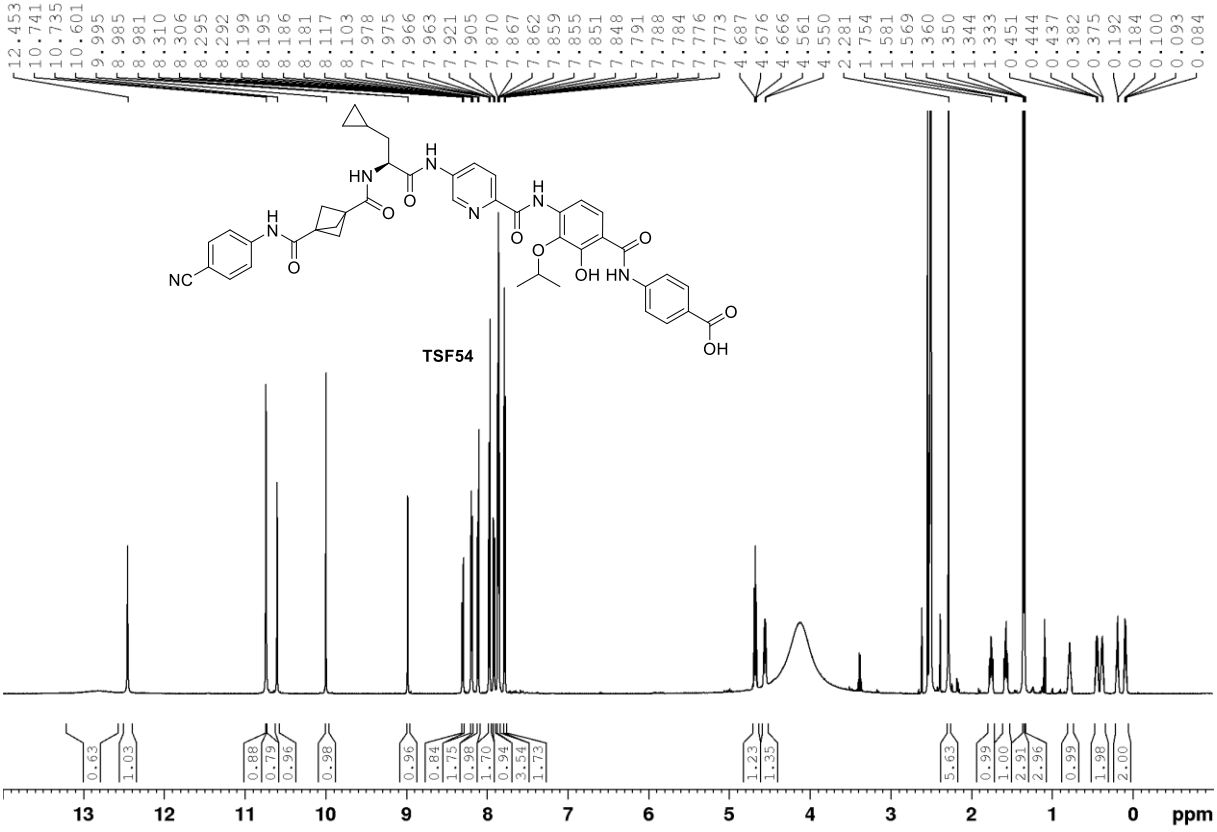

172.260
164.581
164.320
161.131
156.131
149.257
143.847
143.775
143.293
142.994
140.732
139.434
139.303
138.805
135.460
133.521
130.090
127.649
127.627
127.055
126.022
125.779
125.317
124.617
122.926
120.128
120.114
118.845
118.030
113.802
80.336
76.338
74.291
65.677
59.747
56.174
46.669
36.351
27.853
22.346
22.285
7.893
4.645
3.945
131
220
200
180
160
140
120
100
80
60
40
20
0
ppm

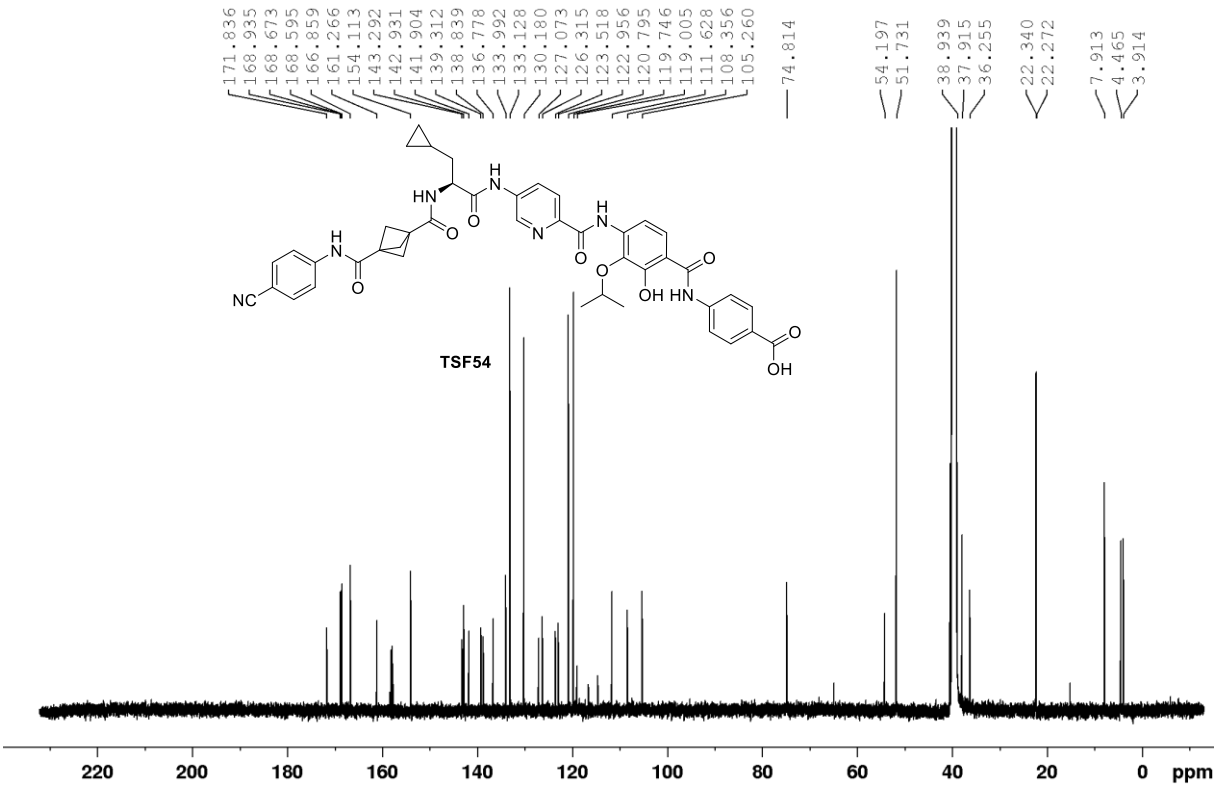

10.731
10.677
10.484
9.995
8.991
8.985
8.985
8.355
8.334
8.308
8.302
8.286
8.280
8.201
8.184
8.180
7.903
7.899
7.886
7.881
7.874
7.869
7.857
7.852
7.847
7.835
7.813
7.791
7.786
7.774
7.769
7.492
7.471
6.055
6.029
6.012
5.986
5.411
5.406
5.368
5.363
5.226
5.222
5.200
5.196
4.666
4.650
4.635
4.622
4.609
2.282
1.566
1.547
1.379
1.364
1.348
0.183
0.095
193
1.00
1.01
1.01
1.03
1.00
0.99
1.03
1.96
8.31
1.00
1.02
1.05
1.04
3.08
1.08
5.90
1.09
0.98
9.38
6.27
1.08
2.03
2.06
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

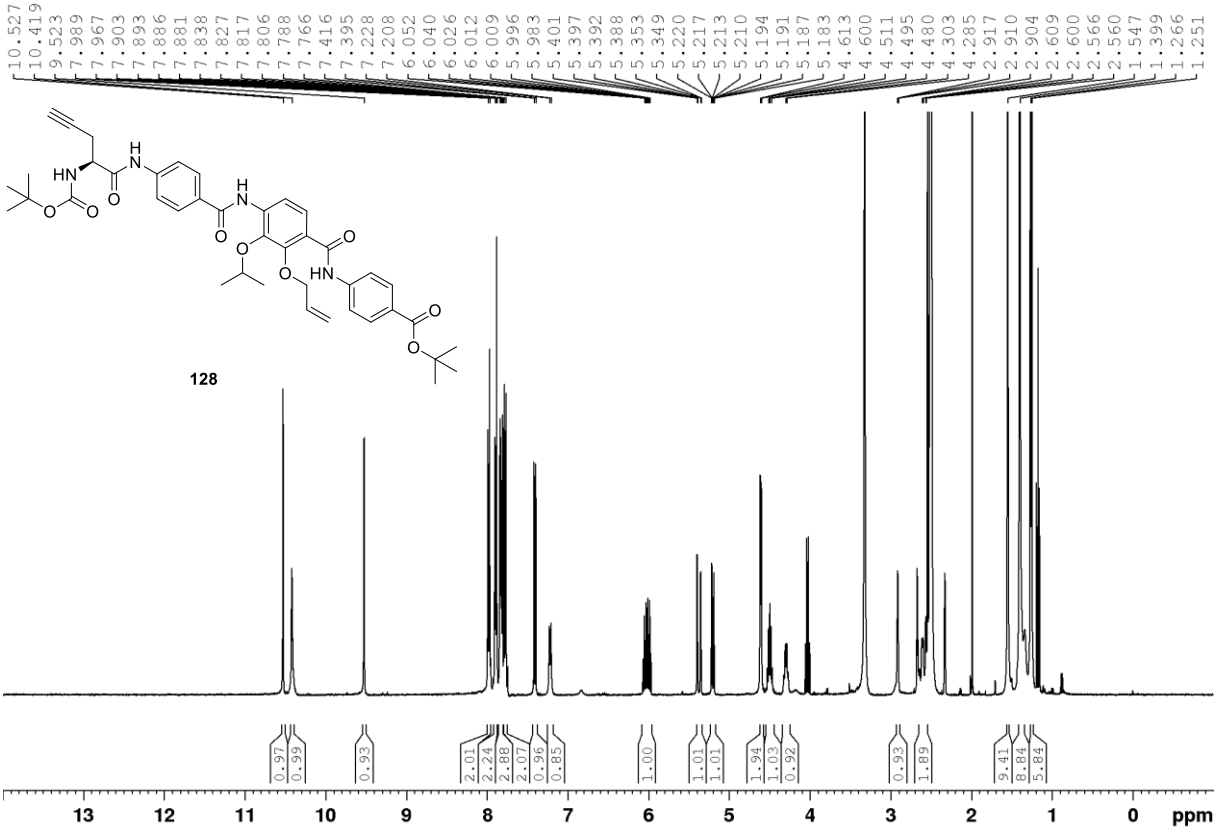

171.832
168.944
168.593
164.577
164.317
161.127
149.254
143.317
142.993
142.927
139.437
139.291
138.797
135.451
133.520
133.131
130.090
127.085
126.018
125.785
124.621
122.933
119.744
119.005
118.842
118.027
113.805
105.262
80.332
76.345
74.290
54.207
51.733
38.938
37.913
36.247
27.850
22.355
22.289
7.922
4.471
3.917
193
220
200
180
160
140
120
100
80
60
40
20
0
ppm

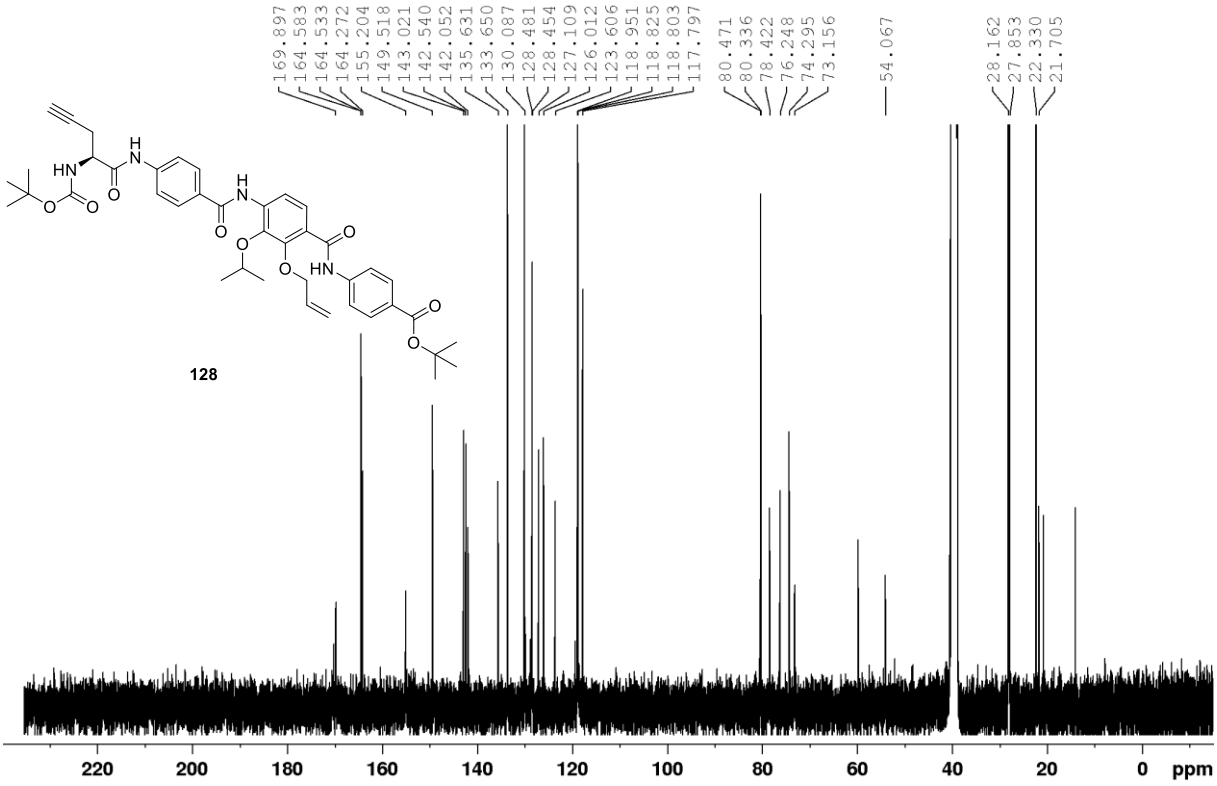

12.447
10.739
10.733
10.608
9.993
8.984
8.979
8.309
8.305
8.295
8.291
8.199
8.194
8.186
8.180
8.113
8.098
7.936
7.933
7.925
7.921
7.905
7.870
7.866
7.861
7.858
7.855
7.850
7.847
7.788
7.784
7.776
7.773
4.685
4.674
4.664
4.561
4.551
2.281
1.754
1.581
1.569
1.554
1.359
1.348
1.342
1.332
0.780
0.451
0.444
0.437
0.382
0.375
0.192
0.184
0.100
0.093
0.084
202
1.00
0.97
0.80
0.86
1.01
0.96
0.88
1.83
0.98
2.76
3.62
1.76
1.03
1.00
5.70
2.36
9.40
6.16
1.04
2.06
2.07
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

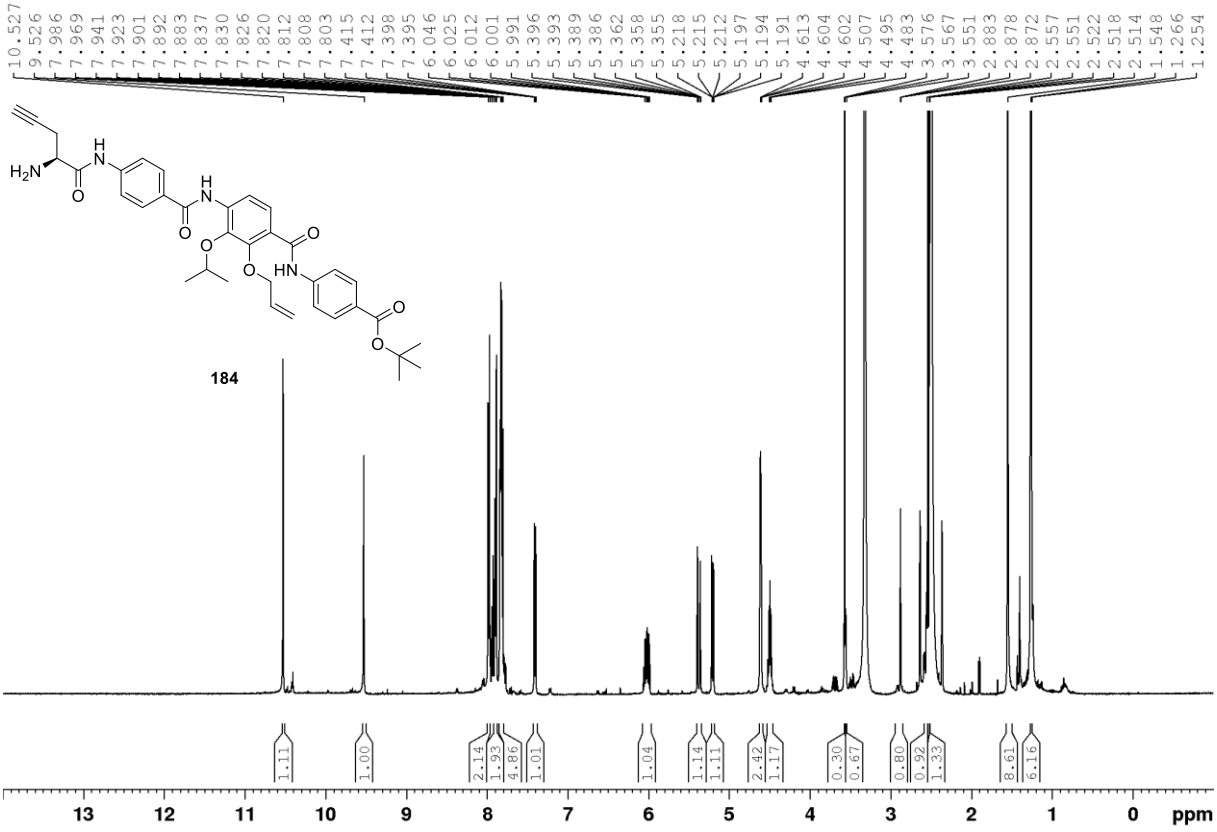

171.834
168.933
168.657
168.592
164.532
161.262
154.120
143.292
142.928
141.926
139.309
138.836
136.775
133.991
133.126
129.884
127.071
126.852
123.525
122.951
120.755
119.744
119.004
111.615
108.338
105.259
80.493
74.805
54.193
51.730
38.937
37.914
36.255
27.837
22.335
22.267
7.912
4.463
3.913
202
220
200
180
160
140
120
100
80
60
40
20
0
ppm

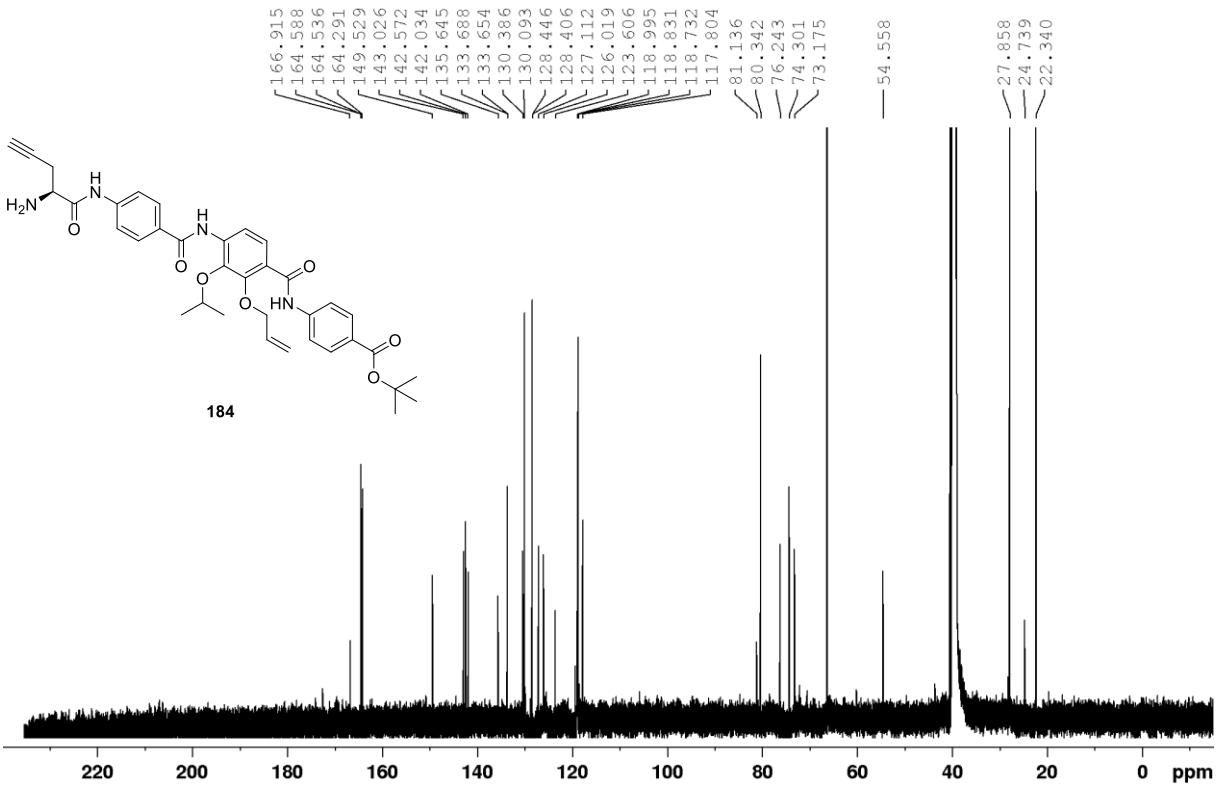

12.453
10.741
10.735
10.601
9.995
8.985
8.981
8.310
8.306
8.295
8.292
8.199
8.195
8.186
8.181
8.117
8.103
7.978
7.975
7.966
7.963
7.921
7.905
7.870
7.867
7.862
7.859
7.855
7.851
7.848
7.791
7.788
7.784
7.776
7.773
4.687
4.676
4.666
4.561
4.550
2.281
1.754
1.581
1.569
1.360
1.350
1.344
1.333
0.451
0.444
0.437
0.382
0.375
0.192
0.184
0.100
0.093
0.084
TSF54
0.63
1.03
0.88
0.79
0.96
0.98
0.96
0.84
1.75
0.98
1.70
0.94
3.54
1.73
1.23
1.35
5.63
0.99
1.00
2.91
2.96
0.99
1.98
2.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

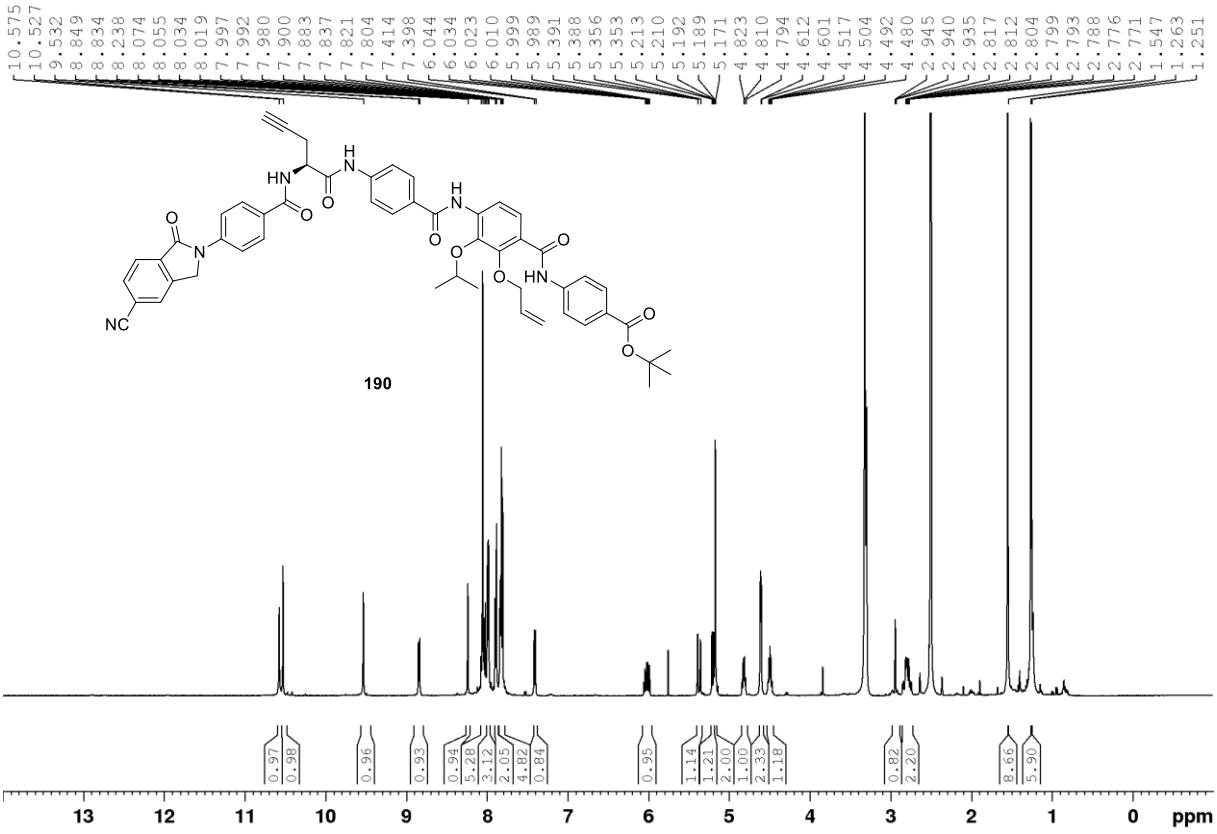

171.836
168.935
168.673
168.595
166.859
161.266
154.113
143.292
142.931
141.904
139.312
138.839
136.778
133.992
133.128
130.180
127.073
126.315
123.518
122.956
120.795
119.746
119.005
111.628
108.356
105.260
74.814
54.197
51.731
38.939
37.915
36.255
22.340
22.272
7.913
4.465
3.914
TSF54
220
200
180
160
140
120
100
80
60
40
20
0
ppm

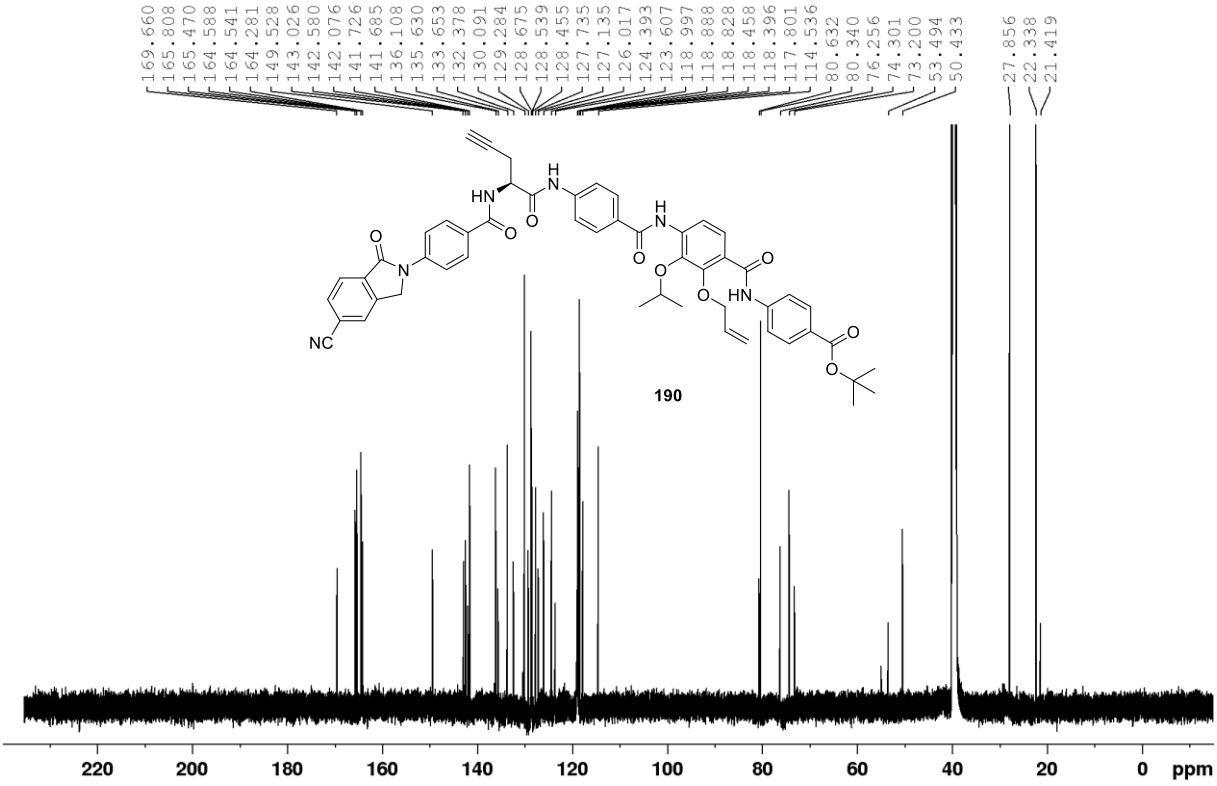

10.527
10.419
9.523
7.989
7.967
7.903
7.893
7.886
7.881
7.838
7.827
7.817
7.806
7.788
7.766
7.416
7.395
7.228
7.208
6.052
6.040
6.026
6.012
6.009
5.996
5.983
5.401
5.397
5.392
5.388
5.353
5.349
5.220
5.217
5.213
5.210
5.194
5.191
5.187
5.183
4.613
4.600
4.511
4.495
4.480
4.303
4.285
2.917
2.910
2.904
2.609
2.600
2.566
2.560
1.547
1.399
1.266
1.251
128
0.97
0.99
0.93
2.01
2.24
2.88
2.07
0.96
0.85
1.00
1.01
1.01
1.94
1.03
0.92
0.93
1.89
9.41
8.84
5.84
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

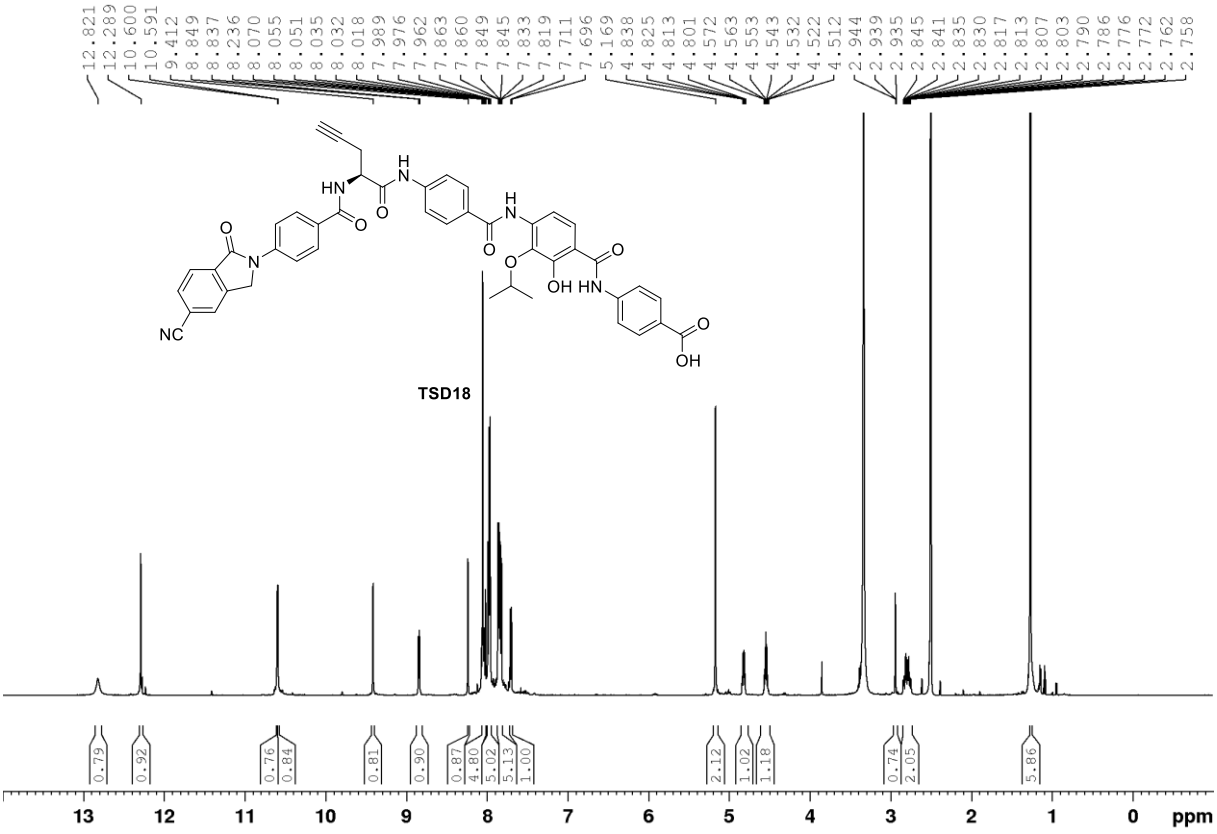

169.897
164.583
164.533
164.272
155.204
149.518
143.021
142.540
142.052
135.631
133.650
130.087
128.481
128.454
127.109
126.012
123.606
118.951
118.825
118.803
117.797
80.471
80.336
78.422
76.248
74.295
73.156
54.067
28.162
27.853
22.330
21.705
128
220
200
180
160
140
120
100
80
60
40
20
0
ppm

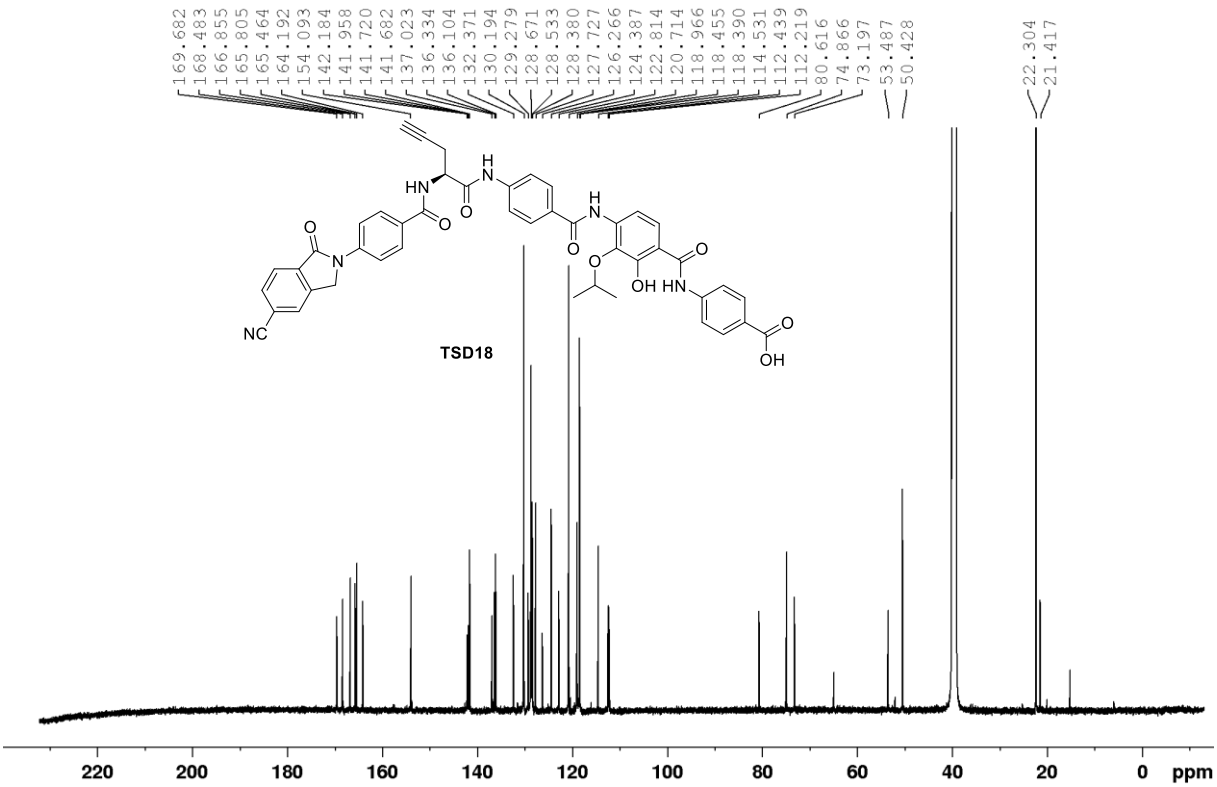

10.527
9.526
7.986
7.969
7.941
7.923
7.901
7.892
7.883
7.837
7.830
7.826
7.820
7.812
7.808
7.803
7.415
7.412
7.398
7.395
6.046
6.025
6.012
6.001
5.991
5.396
5.393
5.389
5.386
5.362
5.358
5.355
5.218
5.215
5.212
5.197
5.194
5.191
4.613
4.604
4.602
4.507
4.495
4.483
3.576
3.567
3.551
2.883
2.878
2.872
2.557
2.551
2.522
2.518
2.514
1.548
1.266
1.254
184
1.11
1.00
2.14
1.93
4.86
1.01
1.04
1.14
1.11
2.42
1.17
0.30
0.67
0.80
0.92
1.33
8.61
6.16
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

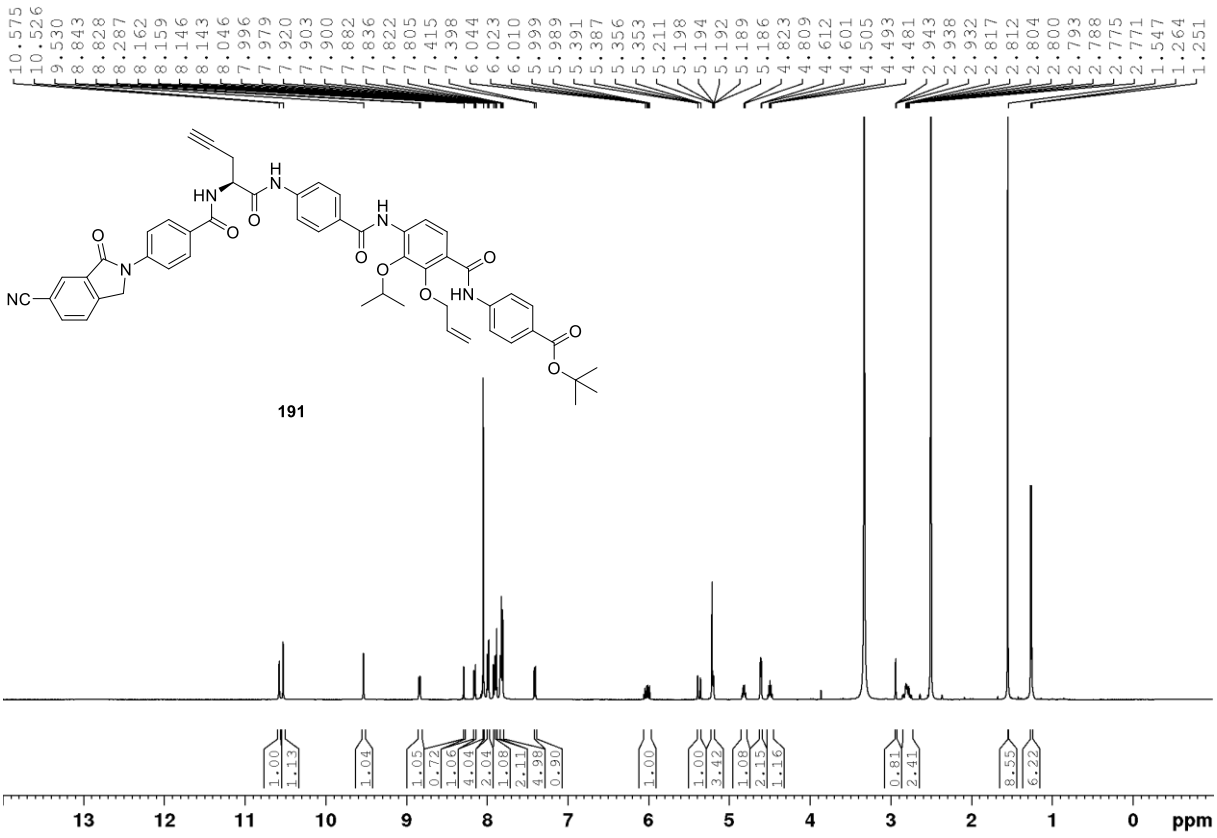

166.915
164.588
164.536
164.291
149.529
143.026
142.572
142.034
135.645
133.688
133.654
130.386
130.093
128.446
128.406
127.112
126.019
123.606
118.995
118.831
118.732
117.804
81.136
80.342
76.243
74.301
73.175
54.558
27.858
24.739
22.340
184
220
200
180
160
140
120
100
80
60
40
20
0
ppm

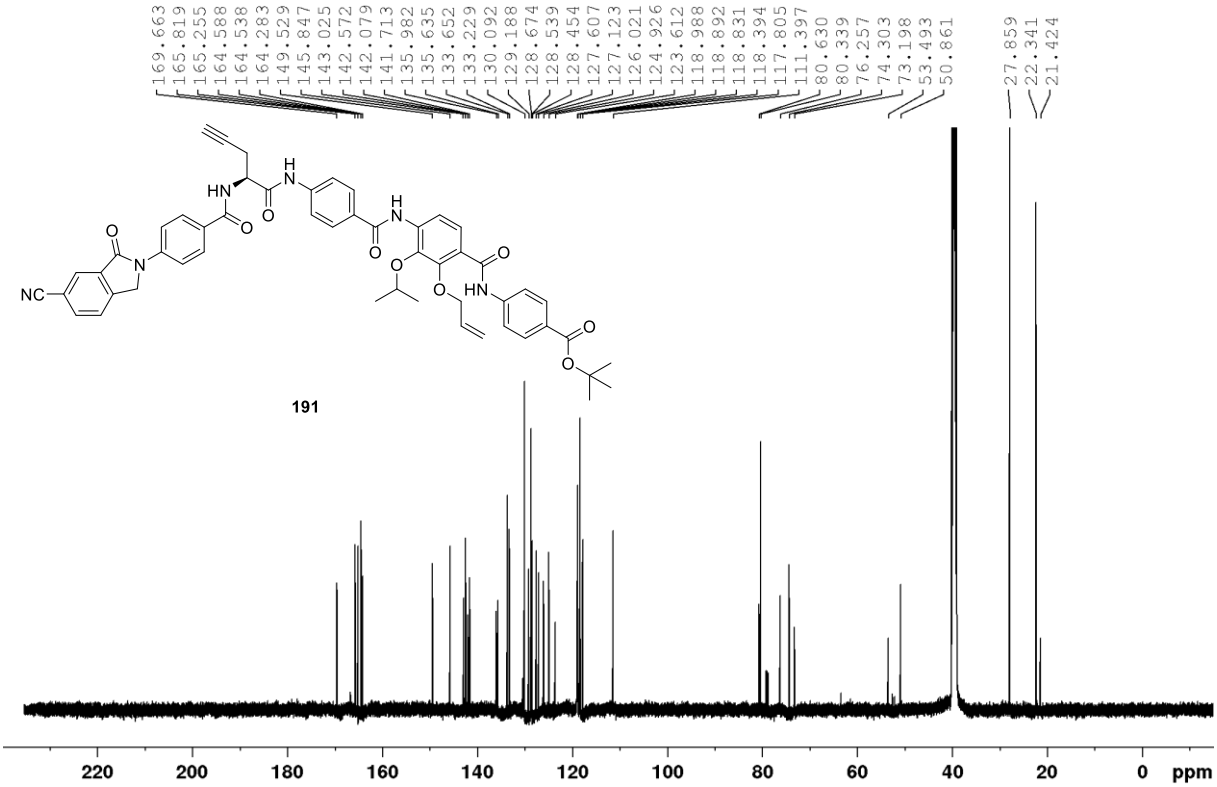

10.575
10.527
9.532
8.849
8.834
8.238
8.074
8.055
8.034
8.019
7.997
7.992
7.980
7.900
7.883
7.837
7.821
7.804
7.414
7.398
6.044
6.034
6.023
6.010
5.999
5.989
5.391
5.388
5.356
5.353
5.213
5.210
5.192
5.189
5.171
4.823
4.810
4.794
4.612
4.601
4.517
4.504
4.492
4.480
2.945
2.940
2.935
2.817
2.812
2.804
2.799
2.793
2.788
2.776
2.771
1.547
1.263
1.251
190
0.97
0.98
0.96
0.93
0.94
5.28
3.12
2.05
4.82
0.84
0.95
1.14
1.21
2.00
1.00
2.33
1.18
0.82
2.20
8.66
5.90
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

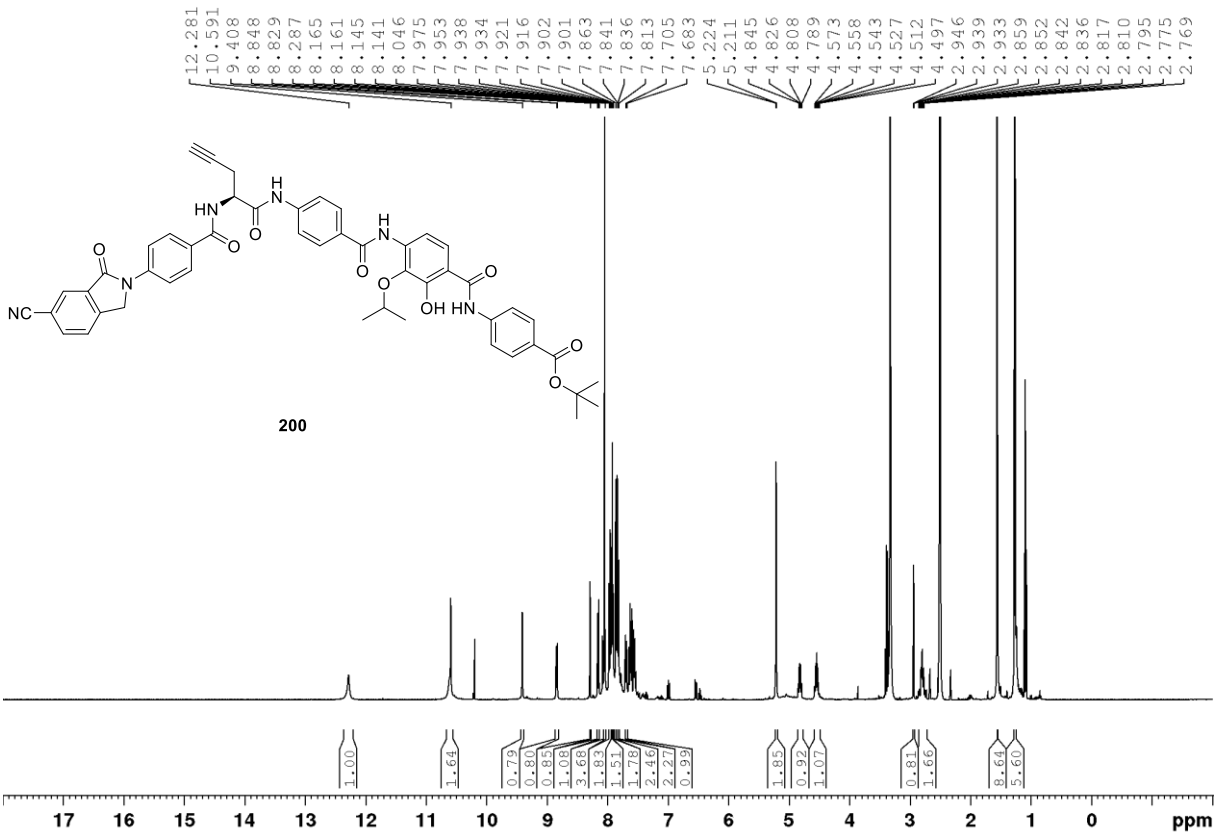

169.660
165.808
165.470
164.588
164.541
164.281
149.528
143.026
142.580
142.076
141.726
141.685
136.108
135.630
133.653
132.378
130.091
129.284
128.675
128.539
128.455
127.735
127.135
126.017
124.393
123.607
118.997
118.888
118.828
118.458
118.396
117.801
114.536
80.632
80.340
76.256
74.301
73.200
53.494
50.433
27.856
22.338
21.419
190
220
200
180
160
140
120
100
80
60
40
20
0
ppm

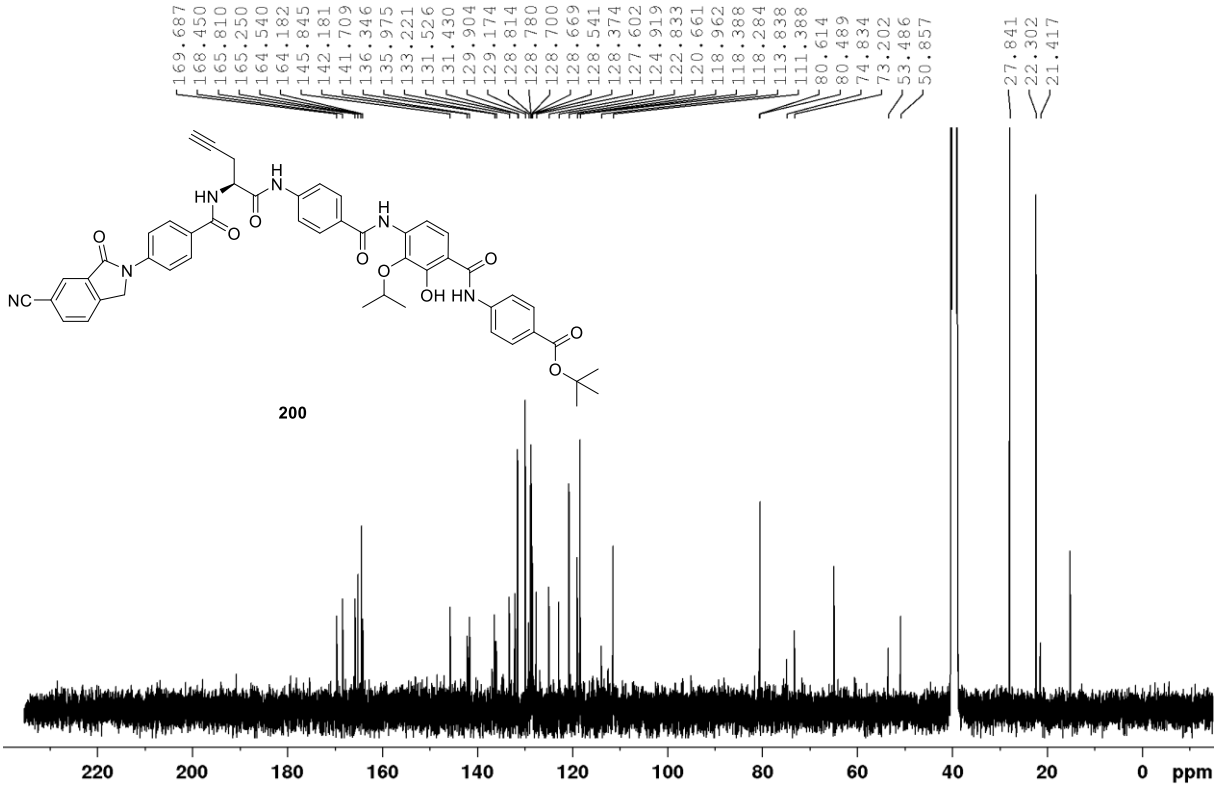

12.821
12.289
10.600
10.591
9.412
8.849
8.837
8.236
8.070
8.055
8.051
8.035
8.032
8.018
7.989
7.976
7.962
7.863
7.860
7.849
7.845
7.833
7.819
7.711
7.696
5.169
4.838
4.825
4.813
4.801
4.572
4.563
4.553
4.543
4.532
4.522
4.512
2.944
2.939
2.935
2.845
2.841
2.835
2.830
2.817
2.813
2.807
2.803
2.790
2.786
2.776
2.772
2.762
2.758
TSD18
0.79
0.92
0.76
0.84
0.81
0.90
0.87
4.80
5.02
5.13
1.00
2.12
1.02
1.18
0.74
2.05
5.86
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

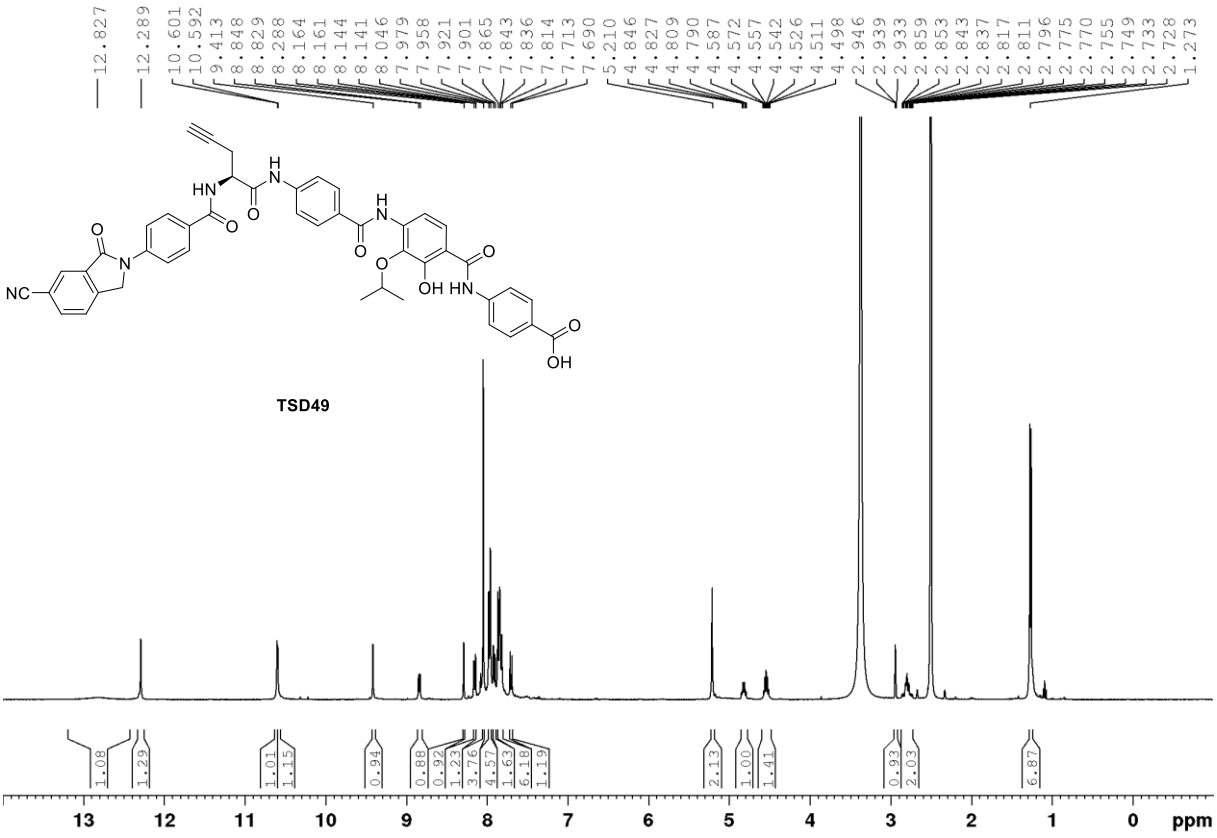

169.682
168.483
166.855
165.805
165.464
164.192
154.093
142.184
141.958
141.720
141.682
137.023
136.334
136.104
132.371
130.194
129.279
128.671
128.533
128.380
127.727
126.266
124.387
122.814
120.714
118.966
118.455
118.390
114.531
112.439
112.219
80.616
74.866
73.197
53.487
50.428
22.304
21.417
TSD18
220
200
180
160
140
120
100
80
60
40
20
0
ppm

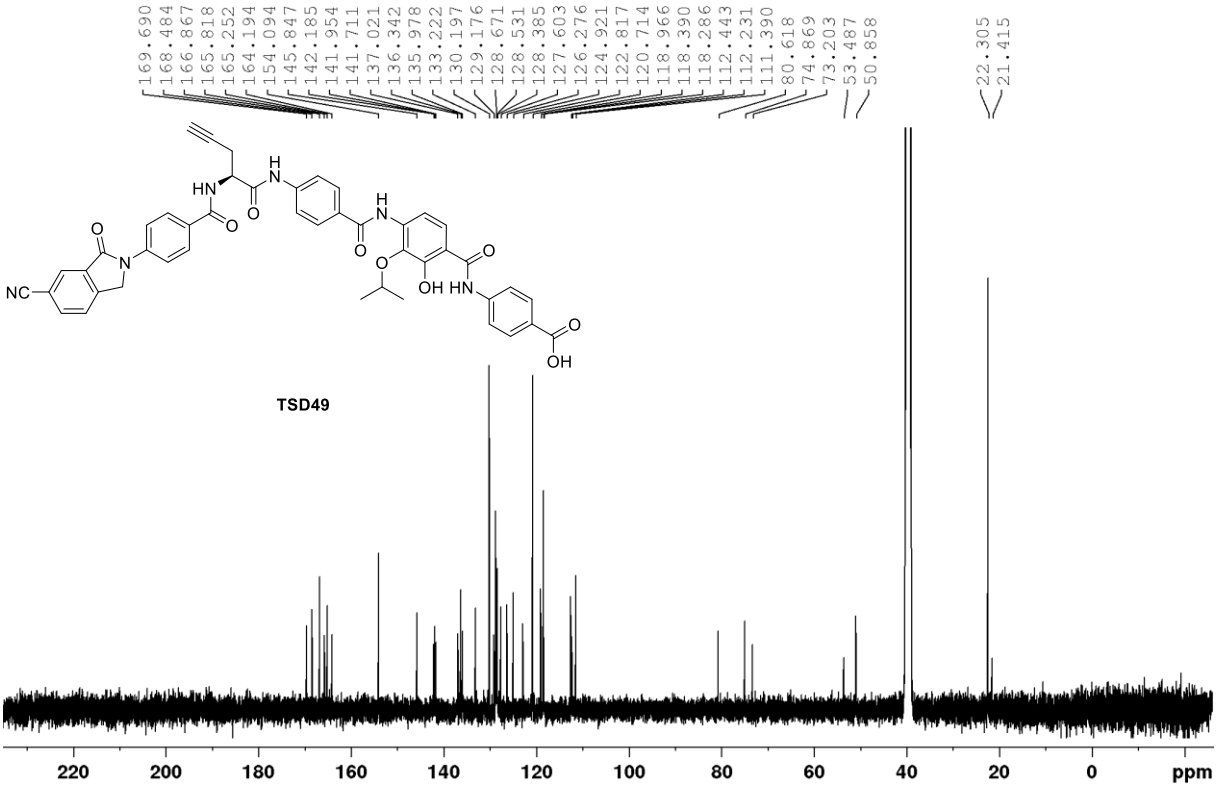

10.575
10.526
9.530
8.843
8.828
8.287
8.162
8.159
8.146
8.143
8.046
7.996
7.979
7.920
7.903
7.900
7.882
7.836
7.822
7.805
7.415
7.398
6.044
6.023
6.010
5.999
5.989
5.391
5.387
5.356
5.353
5.211
5.198
5.194
5.192
5.189
5.186
4.823
4.809
4.612
4.601
4.505
4.493
4.481
2.943
2.938
2.932
2.817
2.812
2.804
2.800
2.793
2.788
2.775
2.771
1.547
1.264
1.251
191
1.00
1.13
1.04
1.05
0.72
1.06
4.04
2.04
1.08
2.11
4.98
0.90
1.00
1.00
3.42
1.08
2.15
1.16
0.81
2.41
8.55
6.22
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

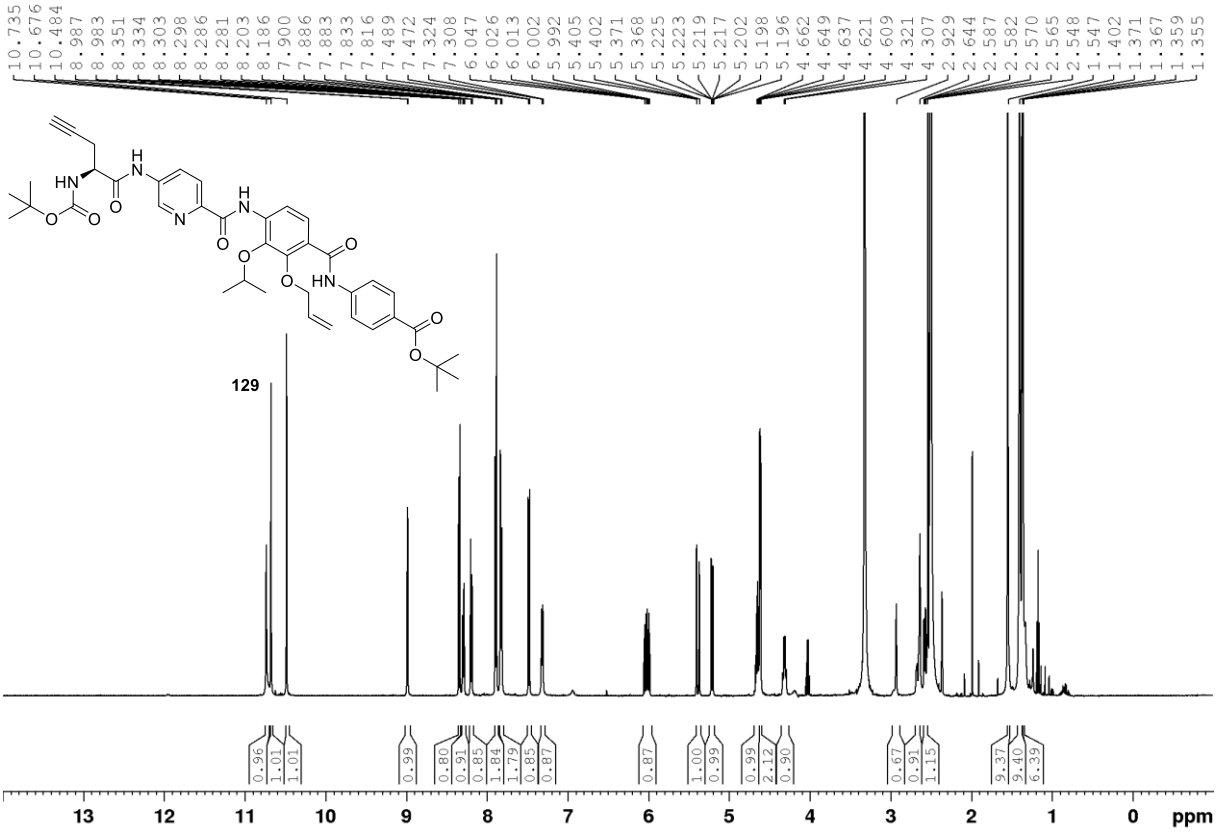

169.663
165.819
165.255
164.588
164.538
164.283
149.529
145.847
143.025
142.572
142.079
141.713
135.982
135.635
133.652
133.229
130.092
129.188
128.674
128.539
128.454
127.607
127.123
126.021
124.926
123.612
118.988
118.892
118.831
118.394
117.805
111.397
80.630
80.339
76.257
74.303
73.198
53.493
50.861
27.859
22.341
21.424
191
220
200
180
160
140
120
100
80
60
40
20
0
ppm

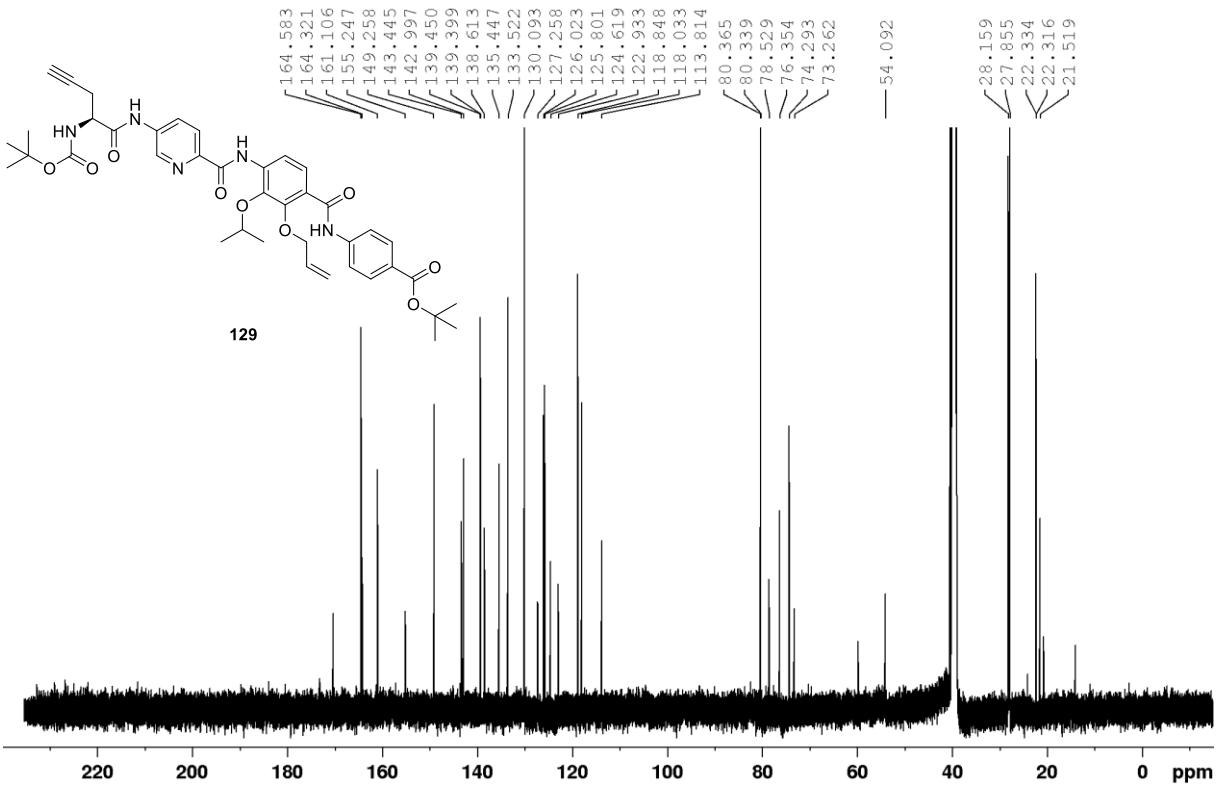

12.281
10.591
9.408
8.848
8.829
8.287
8.165
8.161
8.145
8.141
8.046
7.975
7.953
7.938
7.934
7.921
7.916
7.902
7.901
7.863
7.841
7.836
7.813
7.705
7.683
5.224
5.211
4.845
4.826
4.808
4.789
4.573
4.558
4.543
4.527
4.512
4.497
2.946
2.939
2.933
2.859
2.852
2.842
2.836
2.817
2.810
2.795
2.775
2.769
NC
OH HN
200
1.00
1.64
0.79
0.80
0.85
1.08
3.68
1.82
1.51
1.78
2.46
2.27
0.93
1.85
0.92
1.07
0.81
1.66
8.64
5.60
17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

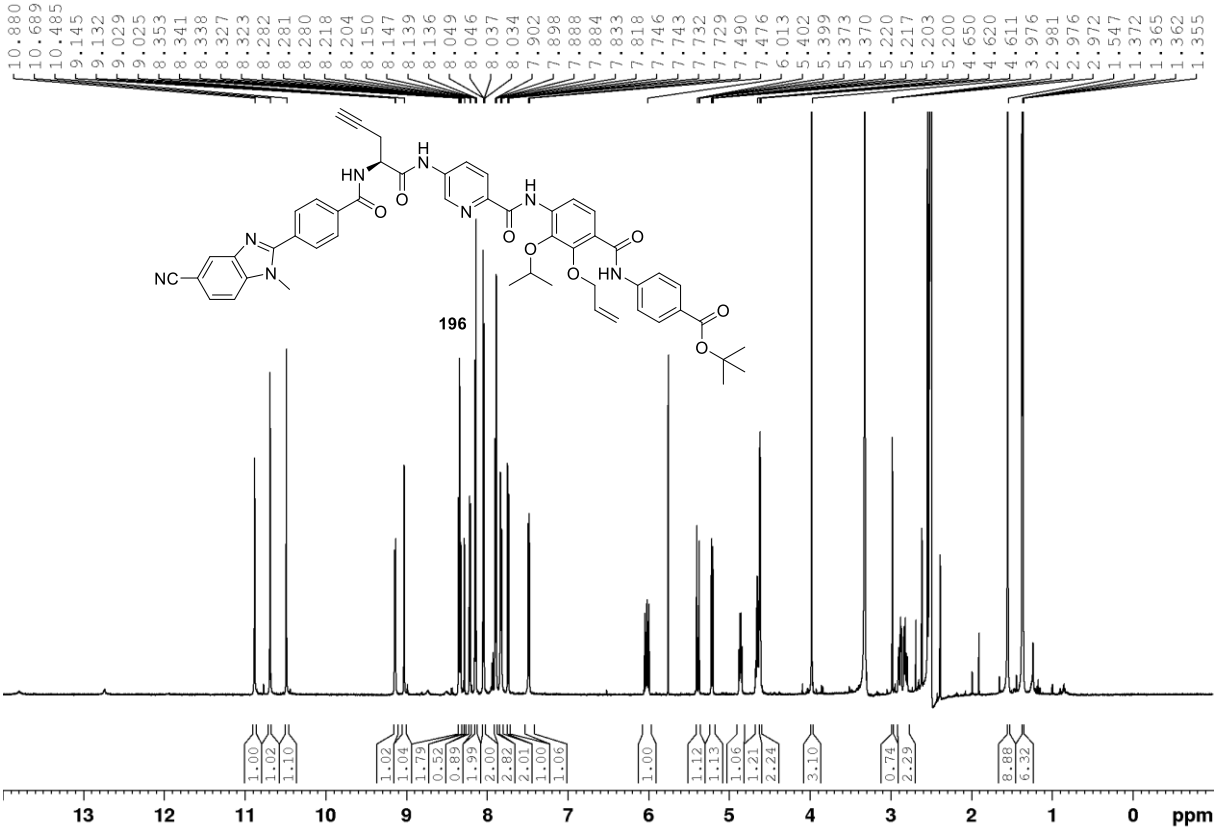

169.687
168.450
165.810
165.250
164.540
164.182
145.845
142.181
141.709
136.346
135.975
133.221
131.526
131.430
129.904
129.174
128.814
128.780
128.700
128.669
128.541
128.374
127.602
124.919
122.833
120.661
118.962
118.388
118.284
113.838
111.388
80.614
80.489
74.834
73.202
53.486
50.857
27.841
22.302
21.417
NC
OH HN
200
220 200 180 160 140 120 100 80 60 40 20 0 ppm

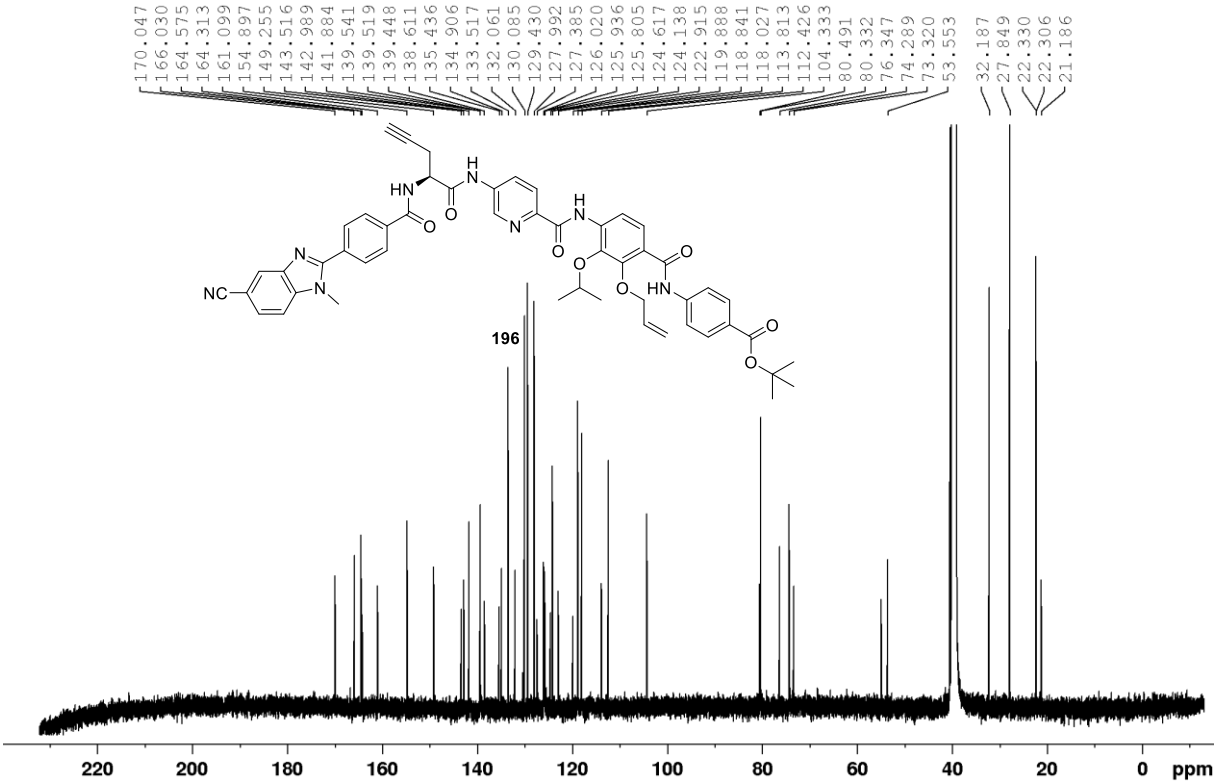

12.827
12.289
10.601
10.592
9.413
8.848
8.829
8.288
8.164
8.161
8.144
8.141
8.046
7.979
7.958
7.921
7.901
7.865
7.843
7.836
7.814
7.713
7.690
5.210
4.846
4.827
4.809
4.790
4.587
4.572
4.557
4.542
4.526
4.511
4.498
2.946
2.939
2.933
2.859
2.853
2.843
2.837
2.817
2.811
2.796
2.775
2.770
2.755
2.749
2.733
2.728
1.273
TSD49
1.08
1.29
1.01
1.15
0.94
0.88
0.92
1.23
3.76
4.57
1.62
6.18
1.19
2.13
1.00
1.41
0.93
2.03
6.87
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

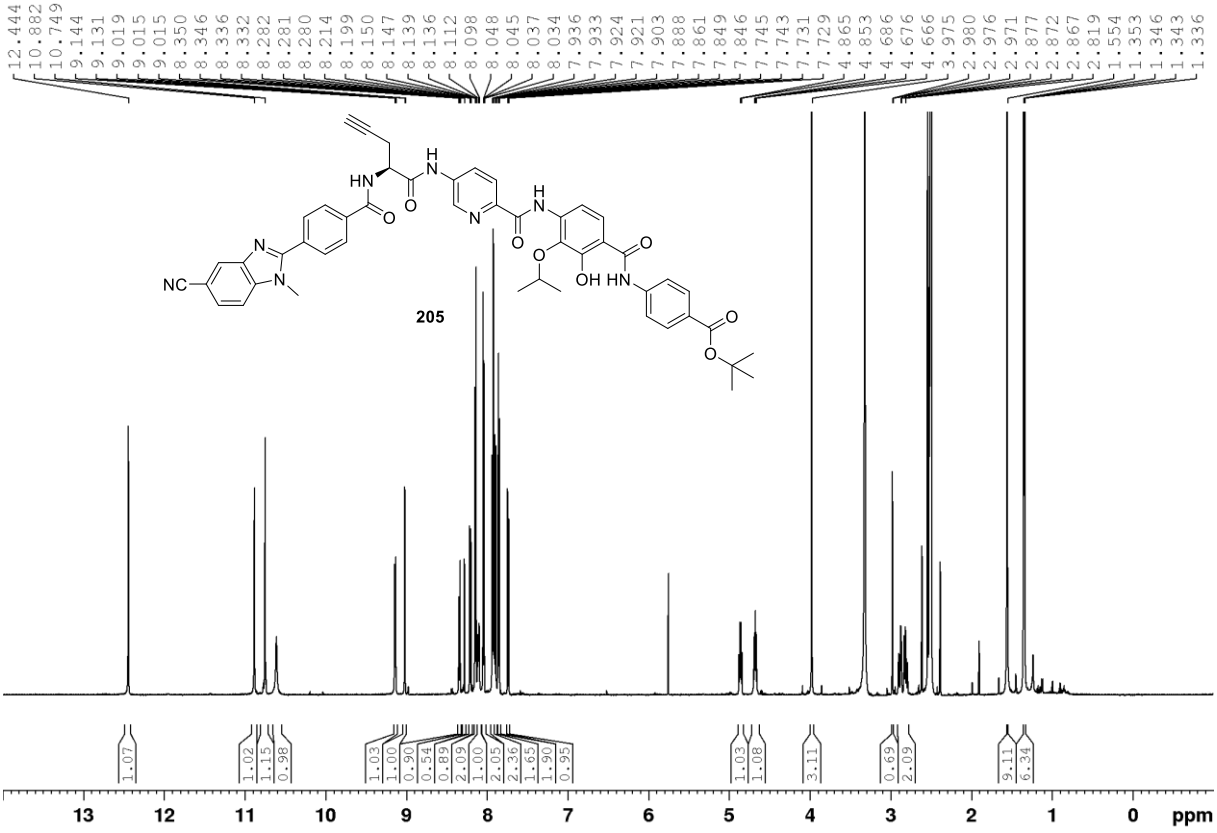

169.690
168.484
166.867
165.818
165.252
164.194
154.094
145.847
142.185
141.954
141.711
137.021
136.342
135.978
133.222
130.197
129.176
128.671
128.531
128.385
127.603
126.276
124.921
122.817
120.714
118.966
118.390
118.286
112.443
112.231
111.390
80.618
74.869
73.203
53.487
50.858
22.305
21.415
TSD49
220
200
180
160
140
120
100
80
60
40
20
0
ppm

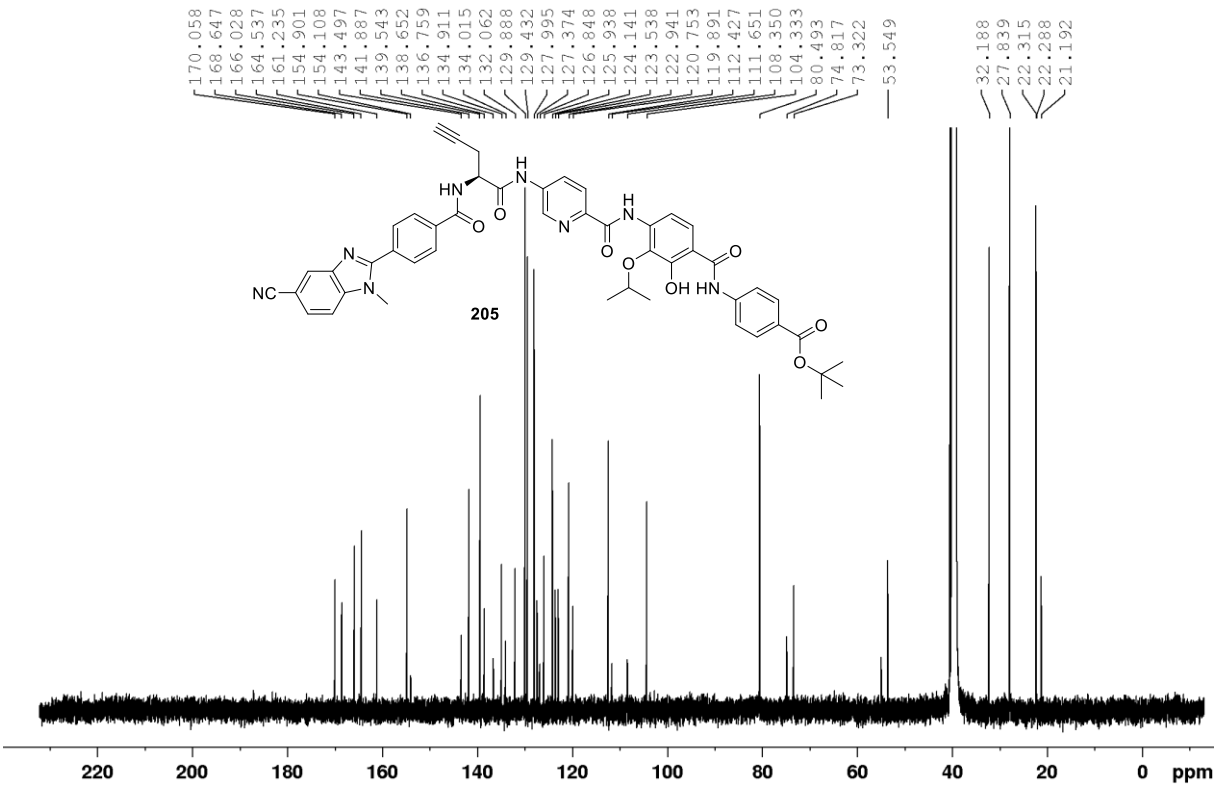

10.735
10.676
10.484
8.987
8.983
8.351
8.334
8.303
8.298
8.286
8.281
8.203
8.186
7.900
7.886
7.883
7.833
7.816
7.489
7.472
7.324
7.308
6.047
6.026
6.013
6.002
5.992
5.405
5.402
5.371
5.368
5.225
5.223
5.219
5.217
5.202
5.198
5.196
4.662
4.649
4.637
4.621
4.609
4.321
4.307
2.929
2.644
2.587
2.582
2.570
2.565
2.548
1.547
1.402
1.371
1.367
1.359
1.355
129
0.96
1.01
1.01
0.99
0.80
0.91
0.85
1.84
1.79
0.85
0.87
0.87
1.00
0.99
0.99
2.12
0.90
0.67
0.91
1.15
9.37
9.40
6.39
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

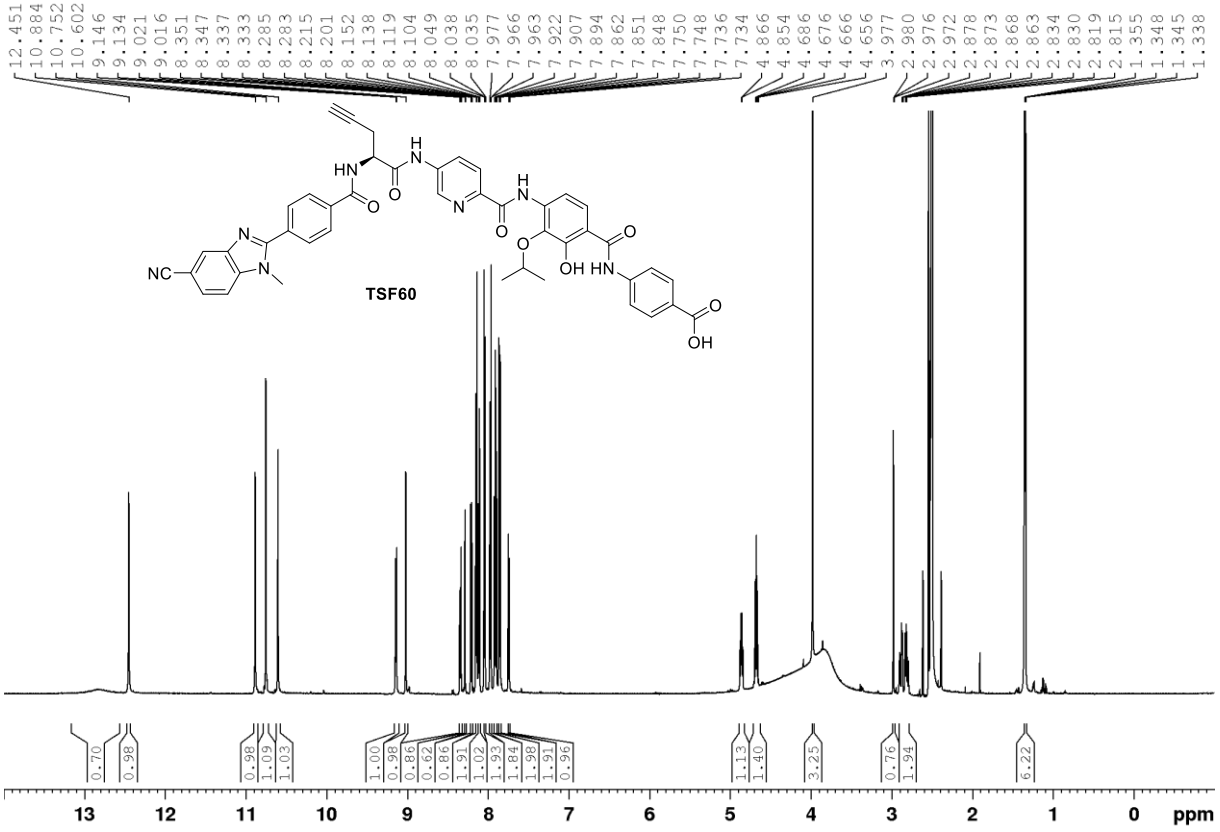

164.583
164.321
161.106
155.247
149.258
143.445
142.997
139.450
139.399
138.613
135.447
133.522
130.093
127.258
126.023
125.801
124.619
122.933
118.848
118.033
113.814
80.365
80.339
78.529
76.354
74.293
73.262
54.092
28.159
27.855
22.334
22.316
21.519
129
220
200
180
160
140
120
100
80
60
40
20
0
ppm

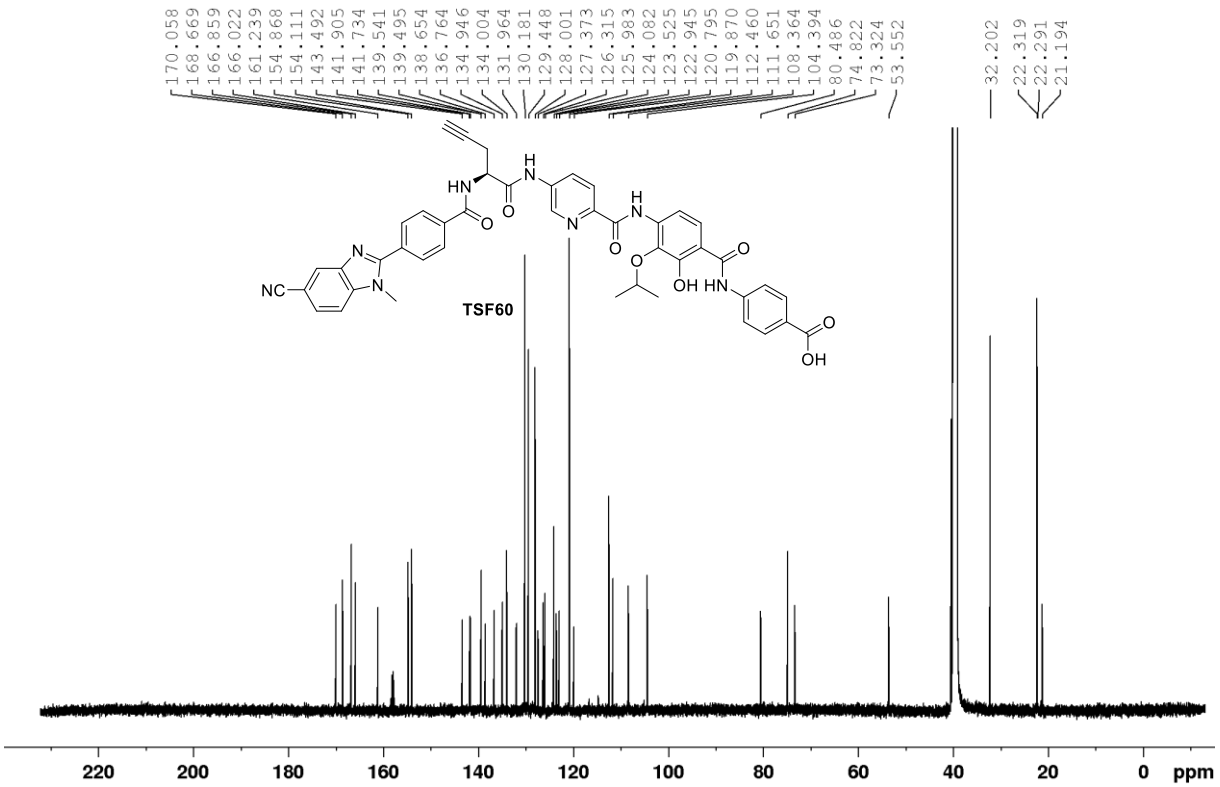

10.880
10.689
10.485
9.145
9.132
9.029
9.025
8.353
8.341
8.338
8.327
8.323
8.282
8.281
8.280
8.218
8.204
8.150
8.147
8.139
8.136
8.049
8.046
8.037
8.034
7.902
7.898
7.888
7.884
7.833
7.818
7.746
7.743
7.732
7.729
7.490
7.476
6.013
5.402
5.399
5.373
5.370
5.220
5.217
5.203
5.200
4.650
4.620
4.611
3.976
2.981
2.976
2.972
1.547
1.372
1.365
1.362
1.355
196
1.00
1.02
1.10
1.02
1.04
1.79
0.52
0.89
1.99
2.00
2.82
2.01
1.00
1.06
1.00
1.12
1.13
1.06
1.21
2.24
3.10
0.74
2.29
8.88
6.32
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

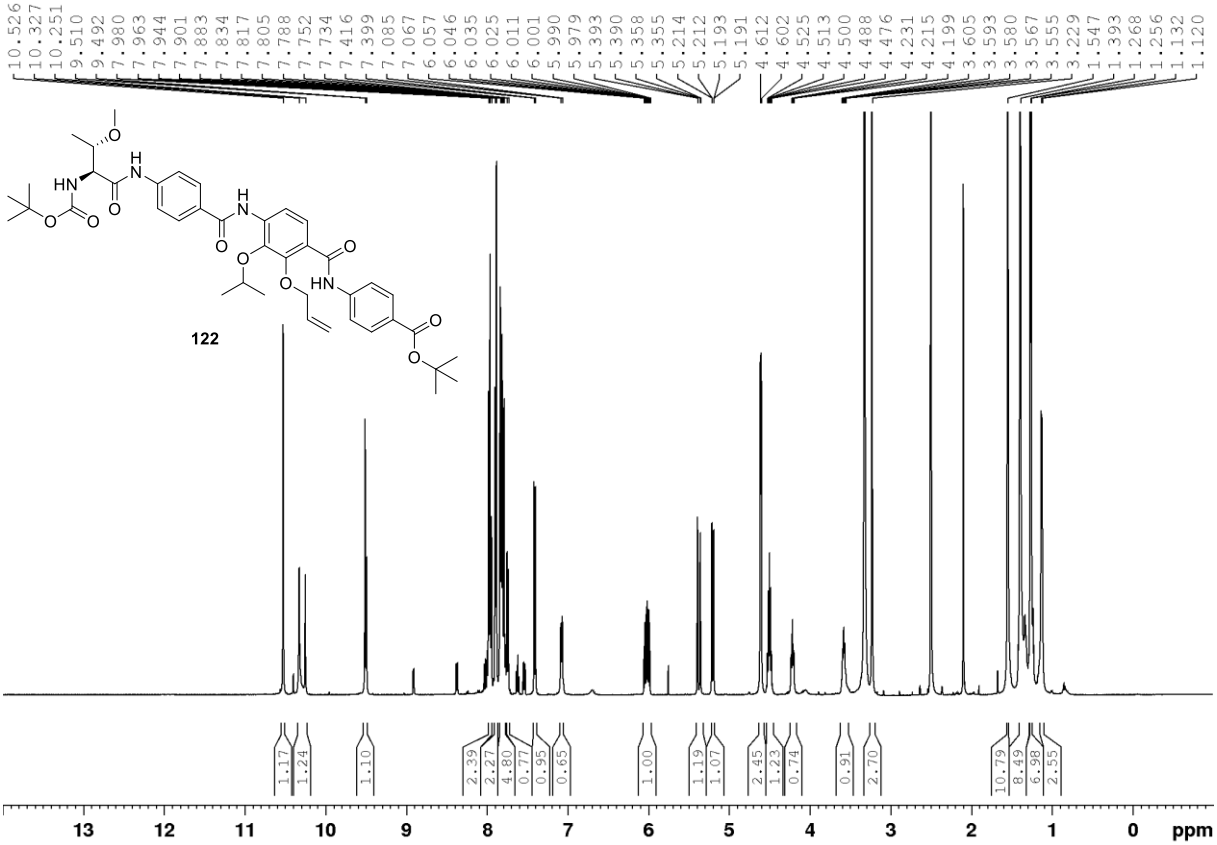

170.047
166.030
164.575
164.313
161.099
154.897
149.255
143.516
142.989
141.884
139.541
139.519
139.448
138.611
135.436
134.906
133.517
132.061
130.085
129.430
127.992
127.385
126.020
125.936
125.805
124.617
124.138
122.915
119.888
118.841
118.027
113.813
112.426
104.333
80.491
80.332
76.347
74.289
73.320
53.553
32.187
27.849
22.330
22.306
21.186
196
220
200
180
160
140
120
100
80
60
40
20
0
ppm

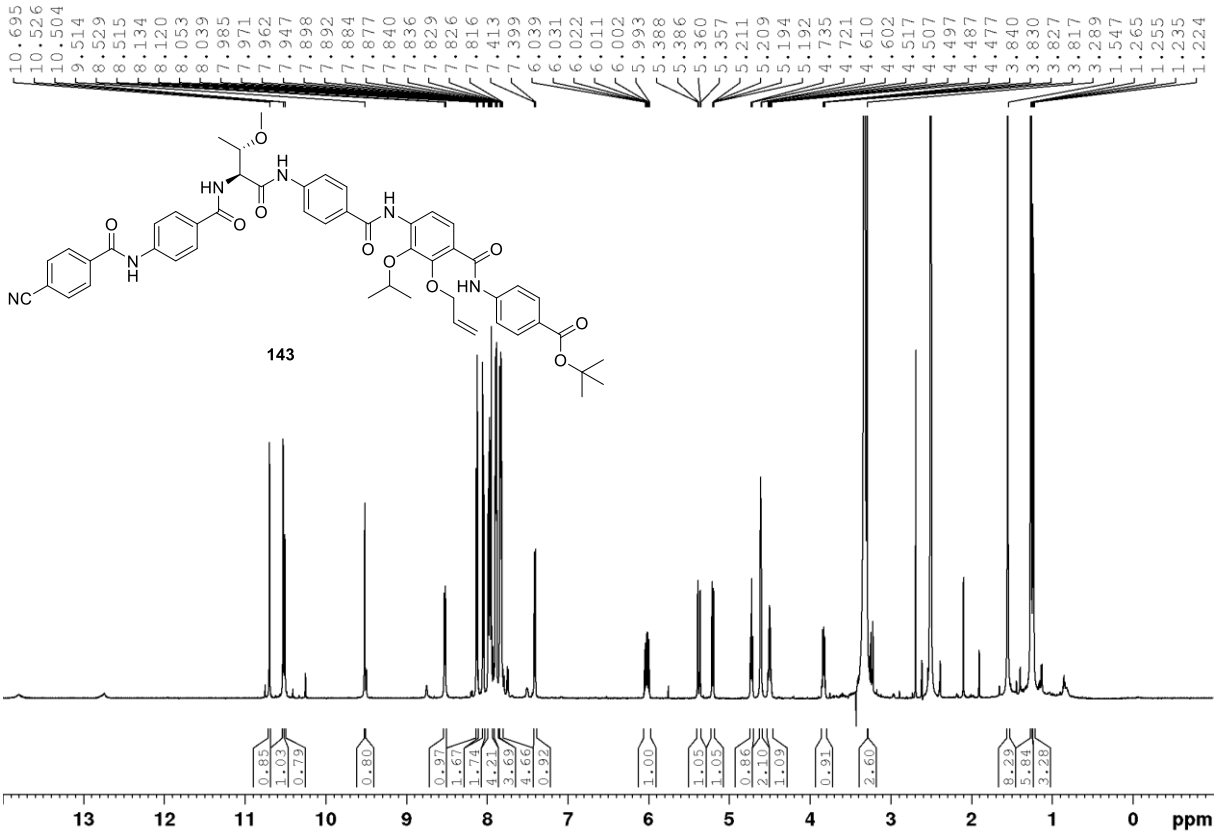

12.444
10.882
10.749
9.144
9.131
9.019
9.015
9.015
8.350
8.346
8.336
8.332
8.282
8.281
8.280
8.214
8.199
8.150
8.147
8.139
8.136
8.112
8.098
8.048
8.045
8.037
8.034
7.936
7.933
7.924
7.921
7.903
7.888
7.861
7.849
7.846
7.745
7.743
7.731
7.729
4.865
4.853
4.686
4.676
4.666
3.975
2.980
2.976
2.971
2.877
2.872
2.867
2.819
1.554
1.353
1.346
1.343
1.336
205
1.07
1.02
1.15
0.98
1.03
1.00
0.90
0.54
0.89
2.09
1.00
2.05
2.36
1.65
1.90
0.95
1.03
1.08
3.11
0.69
2.09
9.11
6.34
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

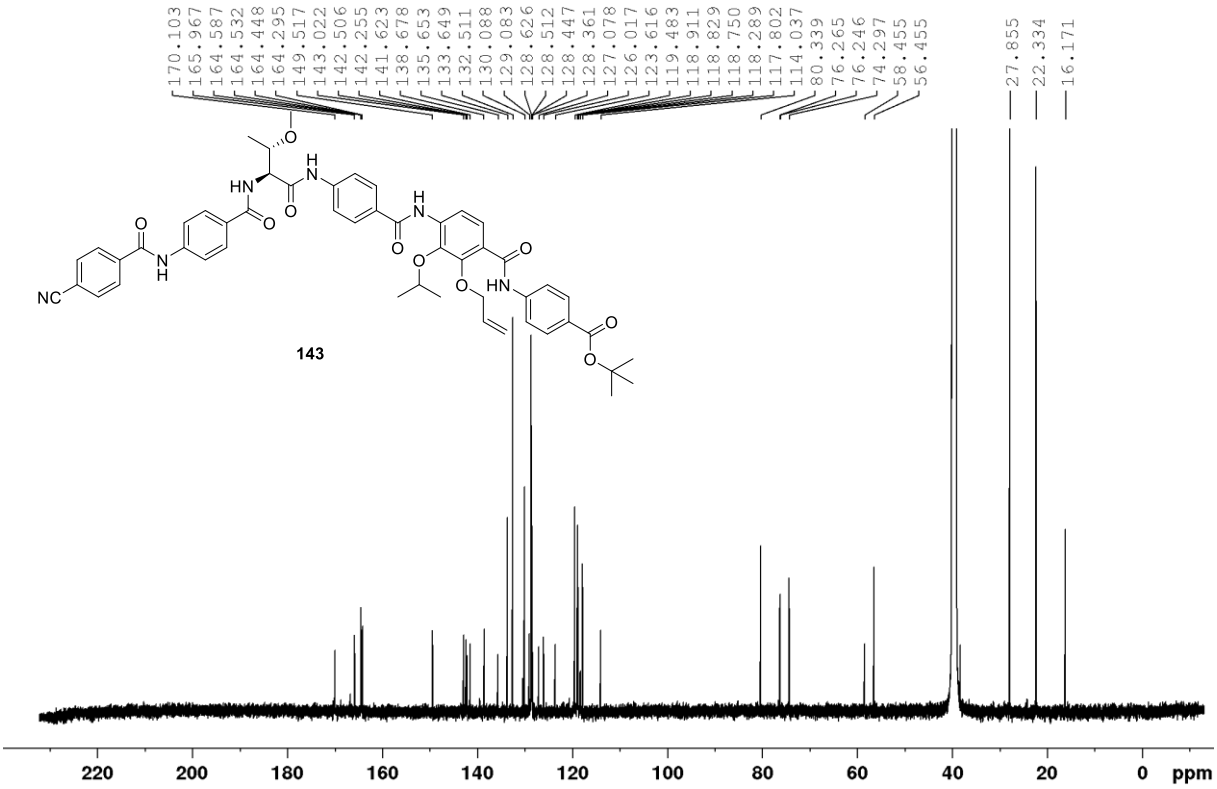

170.058
168.647
166.028
164.537
161.235
154.901
154.108
143.497
141.887
139.543
138.652
136.759
134.911
134.015
132.062
129.888
129.432
127.995
127.374
126.848
125.938
124.141
123.538
122.941
120.753
119.891
112.427
111.651
108.350
104.333
80.493
74.817
73.322
53.549
32.188
27.839
22.315
22.288
21.192
205
220
200
180
160
140
120
100
80
60
40
20
0
ppm

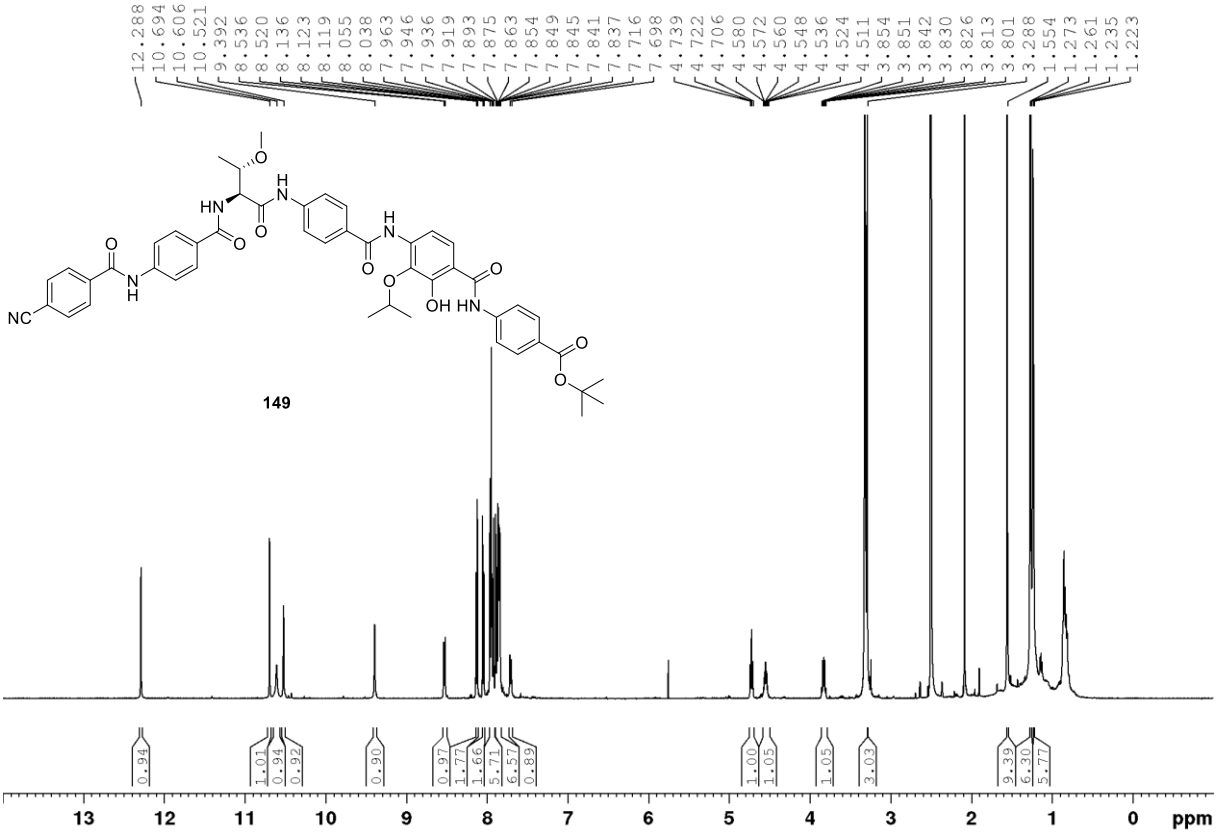

12.451
10.884
10.752
10.602
9.146
9.134
9.021
9.016
8.351
8.347
8.337
8.333
8.285
8.283
8.215
8.201
8.152
8.138
8.119
8.104
8.049
8.038
8.035
7.977
7.966
7.963
7.922
7.907
7.894
7.862
7.851
7.848
7.750
7.748
7.736
7.734
4.866
4.854
4.686
4.676
4.666
4.656
3.977
2.980
2.976
2.972
2.878
2.873
2.868
2.863
2.834
2.830
2.819
2.815
1.355
1.348
1.345
1.338
TSF60
0.70
0.98
0.98
1.09
1.03
1.00
0.98
0.86
0.62
0.86
1.91
1.02
1.93
1.84
1.98
1.91
0.96
1.13
1.40
3.25
0.76
1.94
6.22
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

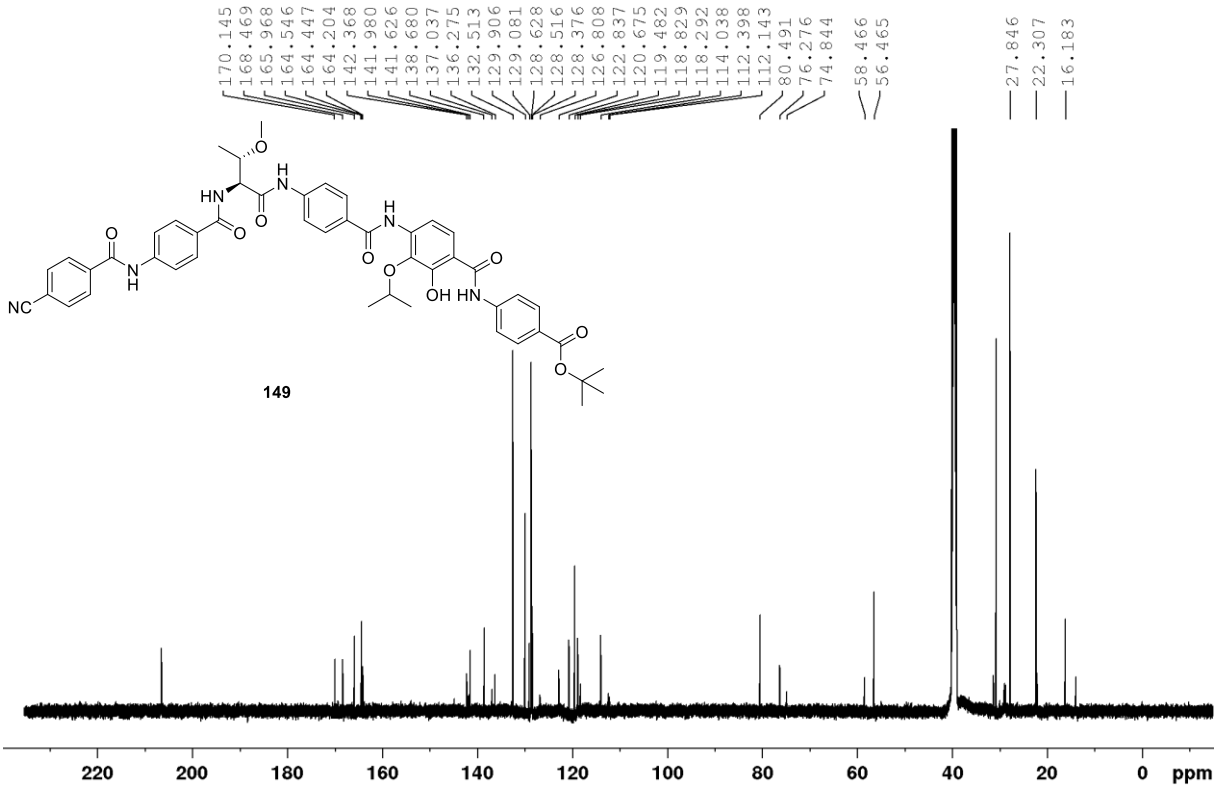

170.058
168.669
166.859
166.022
161.239
154.868
154.111
143.492
141.905
141.734
139.541
139.495
138.654
136.764
134.946
134.004
131.964
130.181
129.448
128.001
127.373
126.315
125.983
124.082
123.525
122.945
120.795
119.870
112.460
111.651
108.364
104.394
80.486
74.822
73.324
53.552
32.202
22.319
22.291
21.194
TSF60
220
200
180
160
140
120
100
80
60
40
20
0
ppm

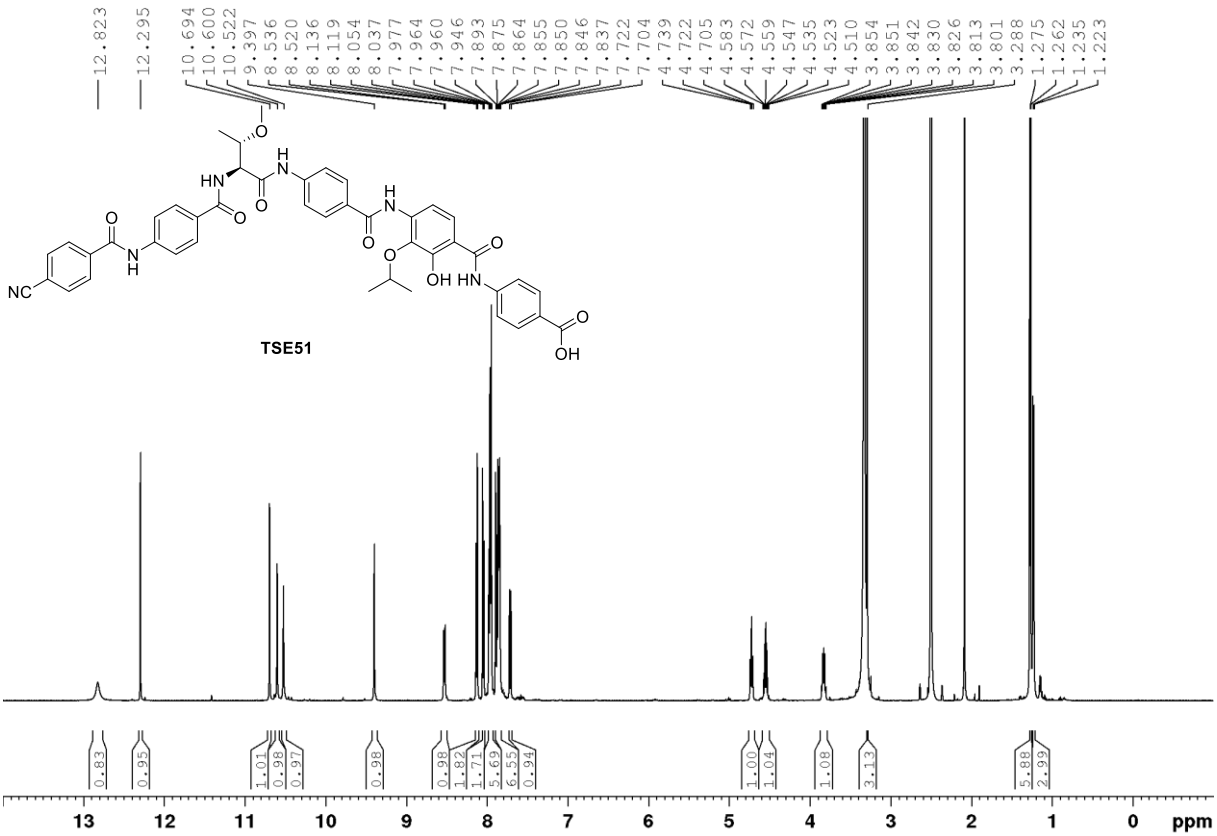

10.526
10.327
10.251
9.510
9.492
7.980
7.963
7.944
7.901
7.883
7.834
7.817
7.805
7.788
7.752
7.734
7.416
7.399
7.085
7.067
7.057
6.046
6.035
6.025
6.011
6.001
5.990
5.979
5.393
5.390
5.358
5.355
5.214
5.212
5.193
5.191
4.612
4.602
4.525
4.513
4.500
4.488
4.476
4.231
4.215
4.199
3.605
3.593
3.580
3.567
3.555
3.229
1.547
1.393
1.268
1.256
1.132
1.120
122
1.17
1.24
1.10
2.39
2.27
4.80
0.77
0.95
0.65
1.00
1.19
1.07
2.45
1.23
0.74
0.91
2.70
10.79
8.49
6.98
2.55
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

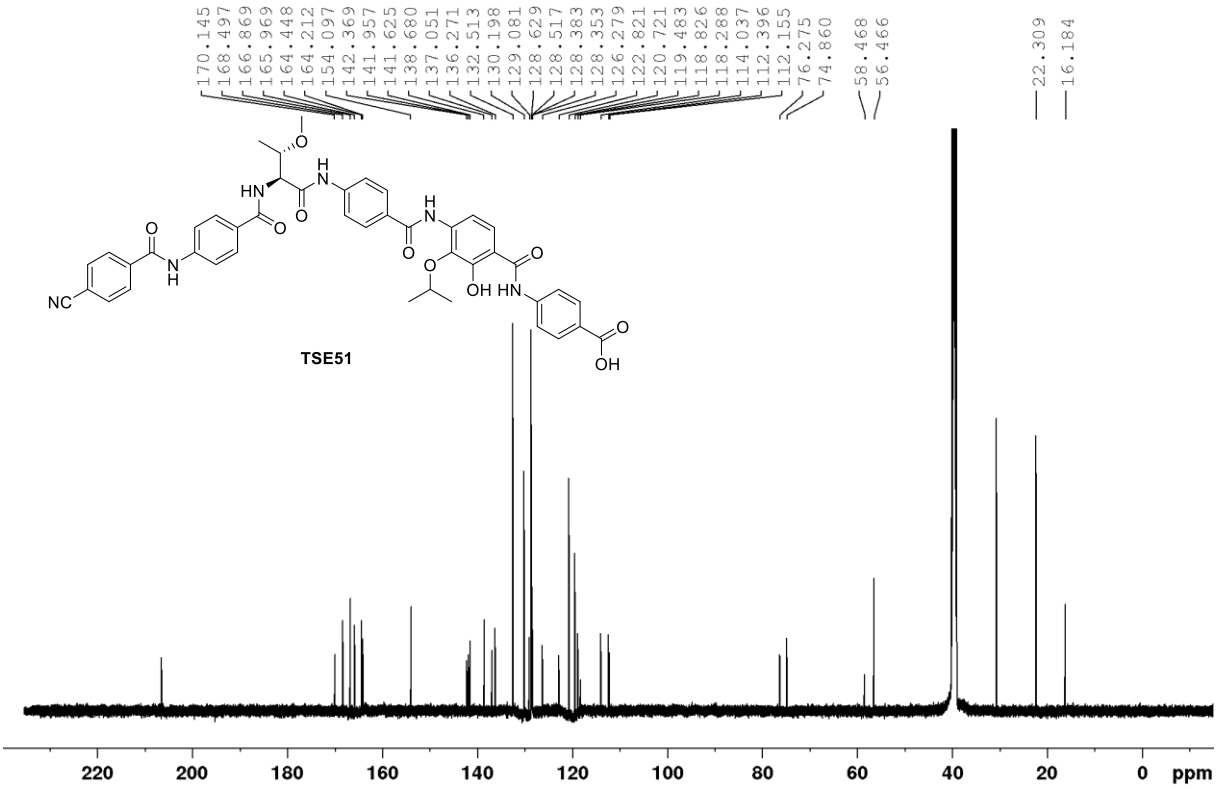

10.695
10.526
10.504
9.514
8.529
8.515
8.134
8.120
8.053
8.039
7.985
7.971
7.962
7.947
7.898
7.892
7.884
7.877
7.840
7.836
7.829
7.826
7.816
7.413
7.399
6.039
6.031
6.022
6.011
6.002
5.993
5.388
5.386
5.360
5.357
5.211
5.209
5.194
5.192
4.735
4.721
4.610
4.602
4.517
4.507
4.497
4.487
4.477
3.840
3.830
3.827
3.817
3.289
1.547
1.265
1.255
1.235
1.224
143
0.85
1.03
0.79
0.80
0.97
1.67
1.74
4.21
3.69
4.66
0.92
1.00
1.05
1.05
0.86
2.10
1.09
0.91
2.60
8.29
5.84
3.28
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

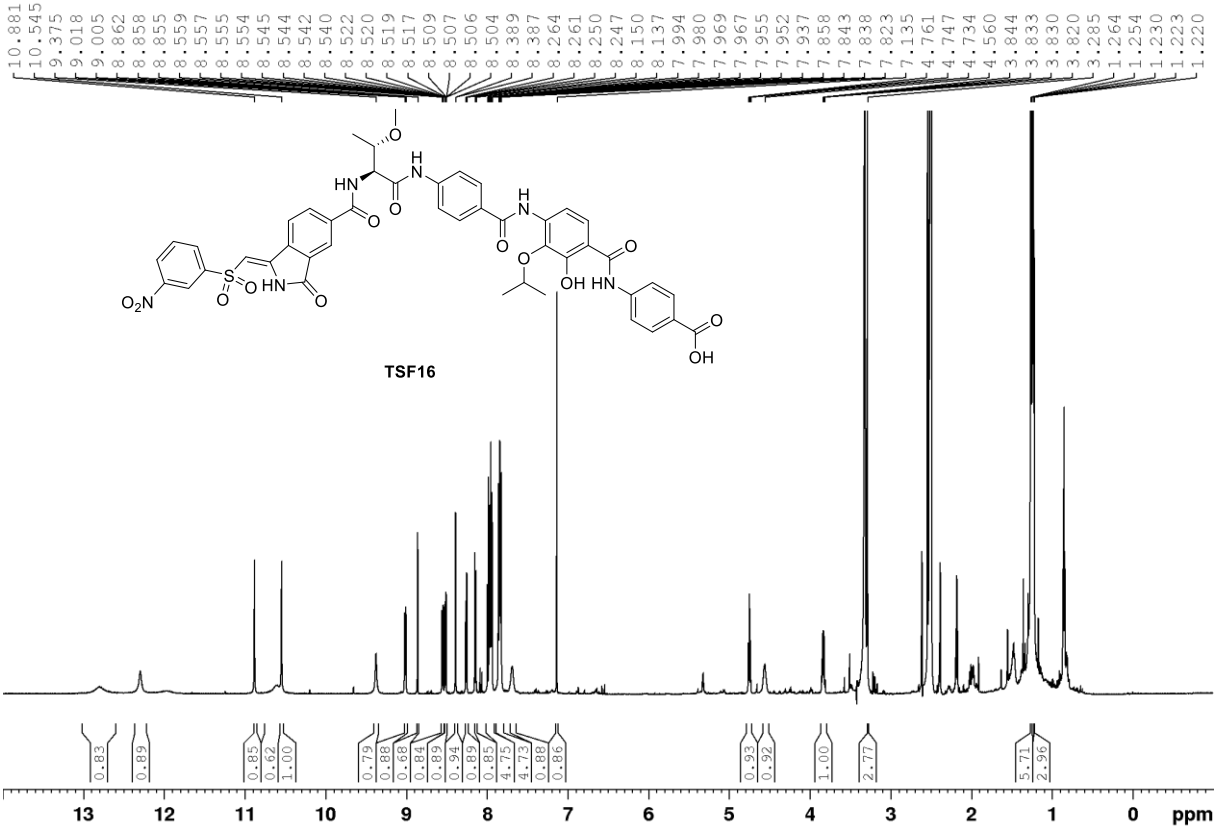

170.103
165.967
164.587
164.532
164.448
164.295
149.517
143.022
142.506
142.255
141.623
138.678
135.653
133.649
132.511
130.088
129.083
128.626
128.512
128.447
128.361
127.078
126.017
123.616
119.483
118.911
118.829
118.750
118.289
117.802
114.037
80.339
76.265
76.246
74.297
58.455
56.455
27.855
22.334
16.171
143
220
200
180
160
140
120
100
80
60
40
20
0
ppm

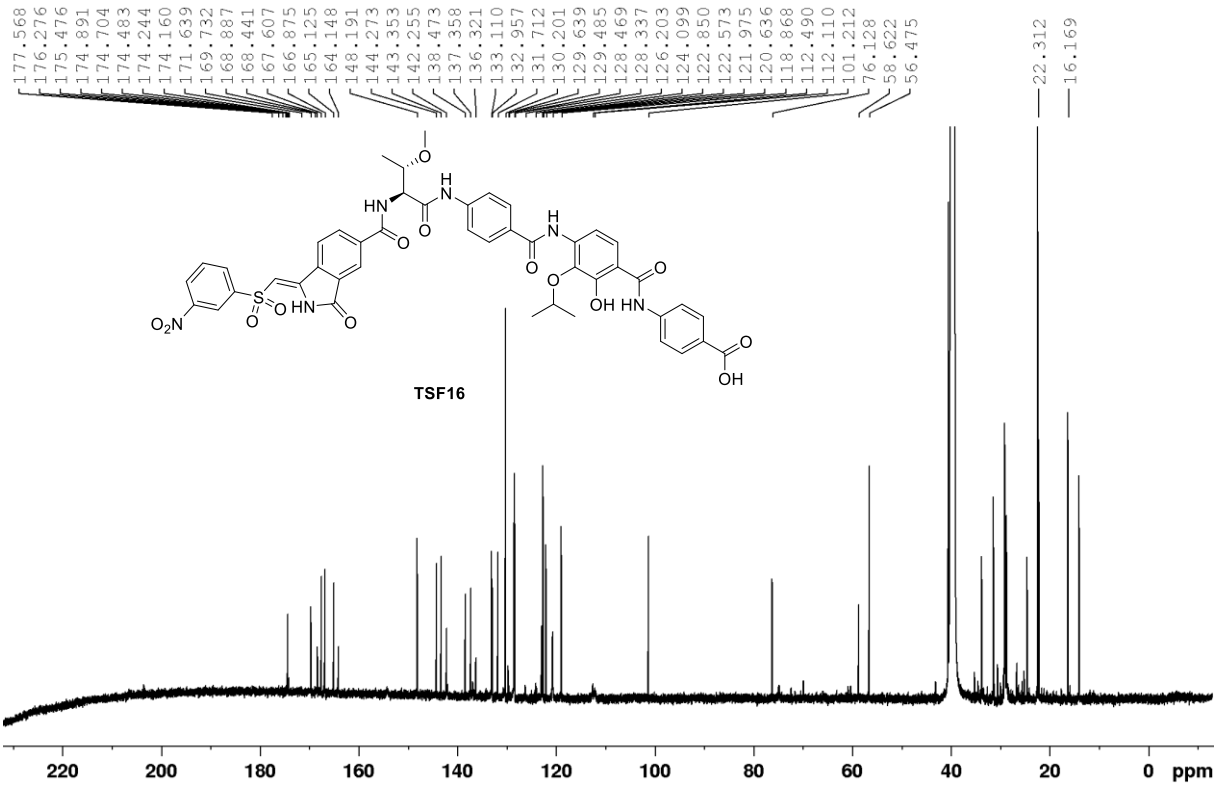

12.288
10.694
10.606
10.521
9.392
8.536
8.520
8.136
8.123
8.119
8.055
8.038
7.963
7.946
7.936
7.919
7.893
7.875
7.863
7.854
7.849
7.845
7.841
7.837
7.716
7.698
4.739
4.722
4.706
4.580
4.572
4.560
4.548
4.536
4.524
4.511
3.854
3.851
3.842
3.830
3.826
3.813
3.801
3.288
1.554
1.273
1.261
1.235
1.223
149
0.94
1.01
0.94
0.92
0.90
0.97
1.77
1.66
5.71
6.57
0.89
1.00
1.05
1.05
3.03
9.39
6.30
5.77
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

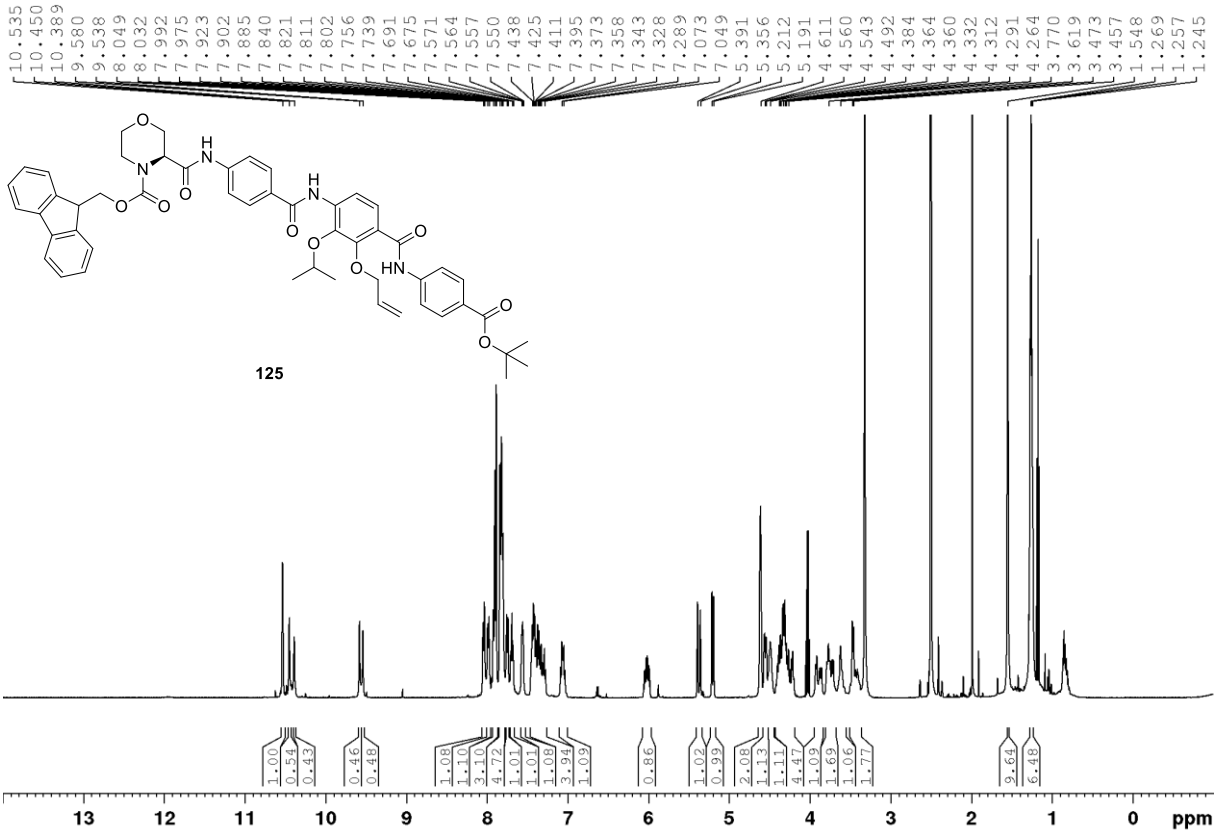

170.145
168.469
165.968
164.546
164.447
164.204
142.368
141.980
141.626
138.680
137.037
136.275
132.513
129.906
129.081
128.628
128.516
128.376
126.808
122.837
120.675
119.482
118.829
118.292
114.038
112.398
112.143
80.491
76.276
74.844
58.466
56.465
27.846
22.307
16.183
149
220
200
180
160
140
120
100
80
60
40
20
0
ppm

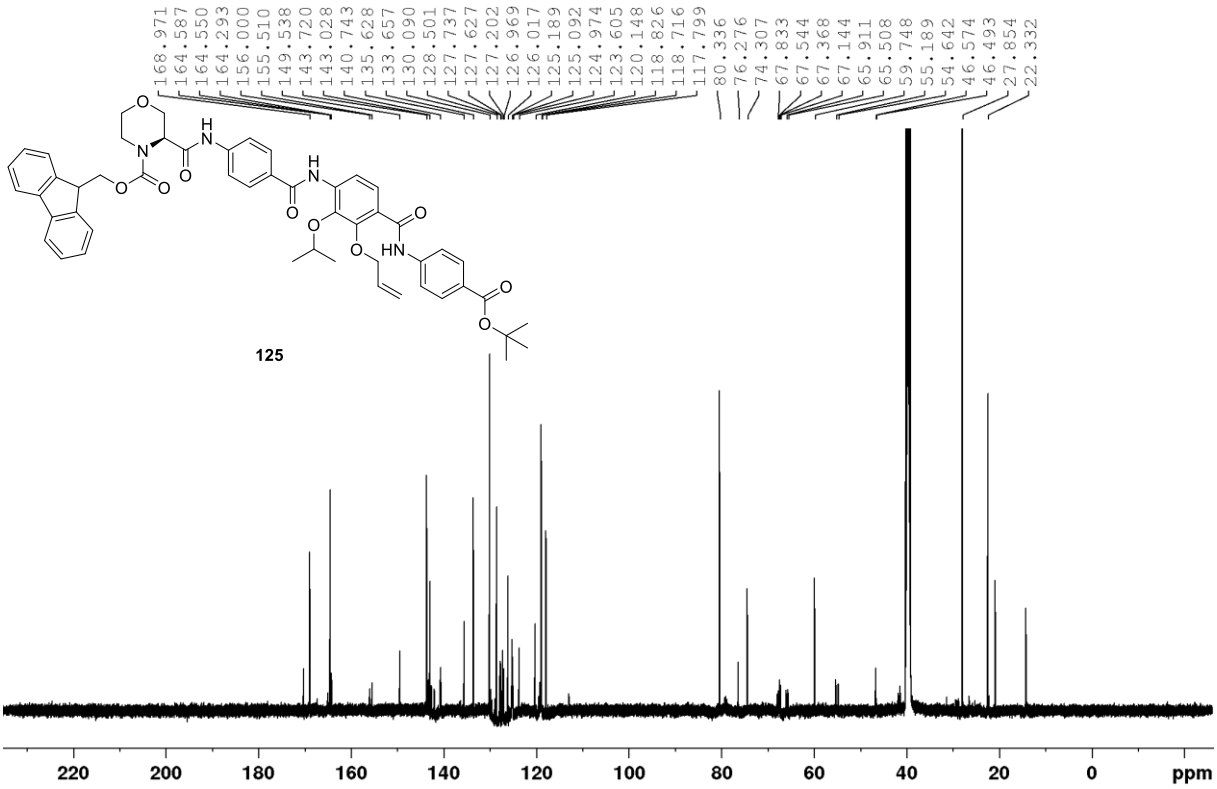

12.823
12.295
10.694
10.600
10.522
9.397
8.536
8.520
8.136
8.119
8.054
8.037
7.977
7.964
7.960
7.946
7.893
7.875
7.864
7.855
7.850
7.846
7.837
7.722
7.704
4.739
4.722
4.705
4.583
4.572
4.559
4.547
4.535
4.523
4.510
3.854
3.851
3.842
3.830
3.826
3.813
3.801
3.288
1.275
1.262
1.235
1.223
TSE51
0.83
0.95
1.01
0.98
0.97
0.98
0.98
1.82
1.71
5.69
6.55
0.94
1.00
1.04
1.08
3.13
5.88
2.99
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

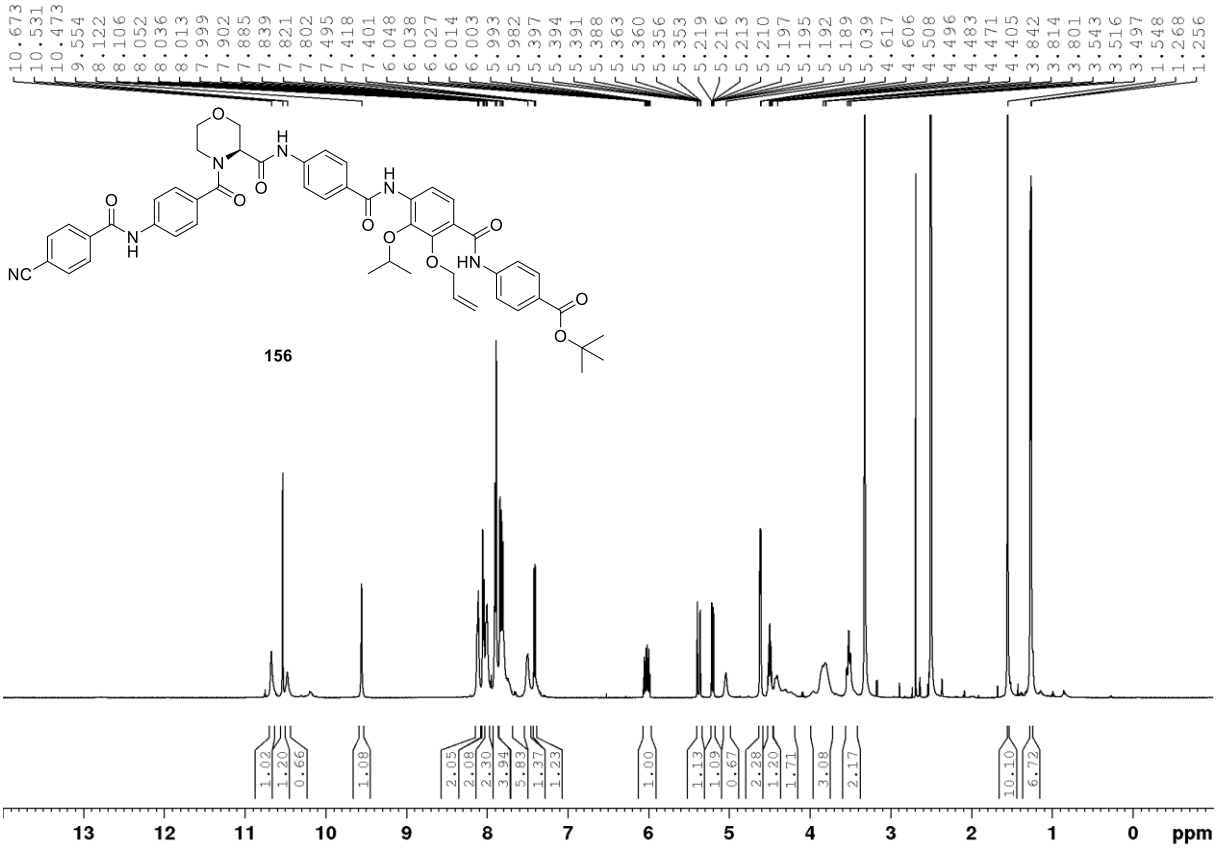

170.145
168.497
166.869
165.969
164.448
164.212
154.097
142.369
141.957
141.625
138.680
137.051
136.271
132.513
130.198
129.081
128.629
128.517
128.383
128.353
126.279
122.821
120.721
119.483
118.826
118.288
114.037
112.396
112.155
76.275
74.860
58.468
56.466
22.309
16.184
TSE51
220
200
180
160
140
120
100
80
60
40
20
0
ppm

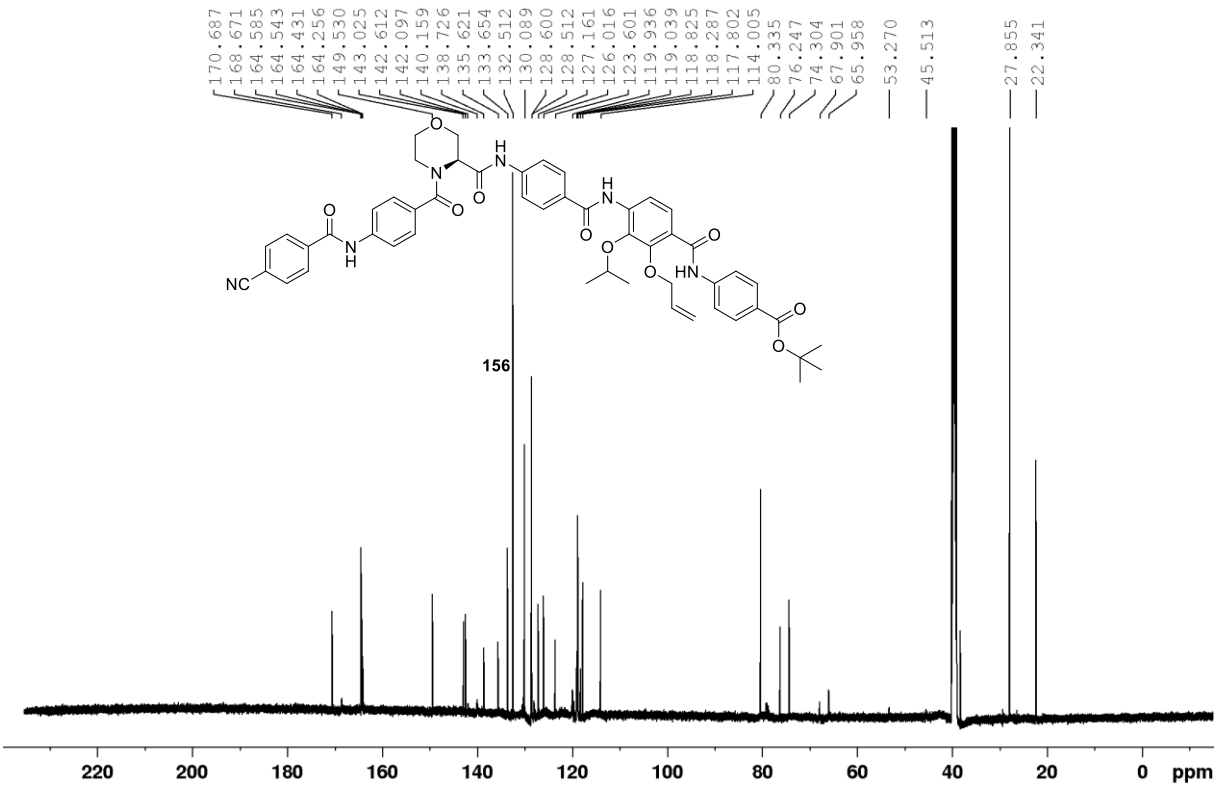

10.881
10.545
9.375
9.018
9.005
8.862
8.858
8.855
8.559
8.557
8.555
8.554
8.545
8.544
8.542
8.540
8.522
8.520
8.519
8.517
8.509
8.507
8.506
8.504
8.389
8.387
8.264
8.261
8.250
8.247
8.150
8.137
7.994
7.980
7.969
7.967
7.955
7.952
7.937
7.858
7.843
7.838
7.823
7.135
4.761
4.747
4.734
4.560
3.844
3.833
3.830
3.820
3.285
1.264
1.254
1.230
1.223
1.220
TSF16
0.83
0.89
0.85
0.62
1.00
0.79
0.88
0.68
0.84
0.89
0.94
0.89
0.85
4.75
4.73
0.88
0.86
0.93
0.92
1.00
2.77
5.71
2.96
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

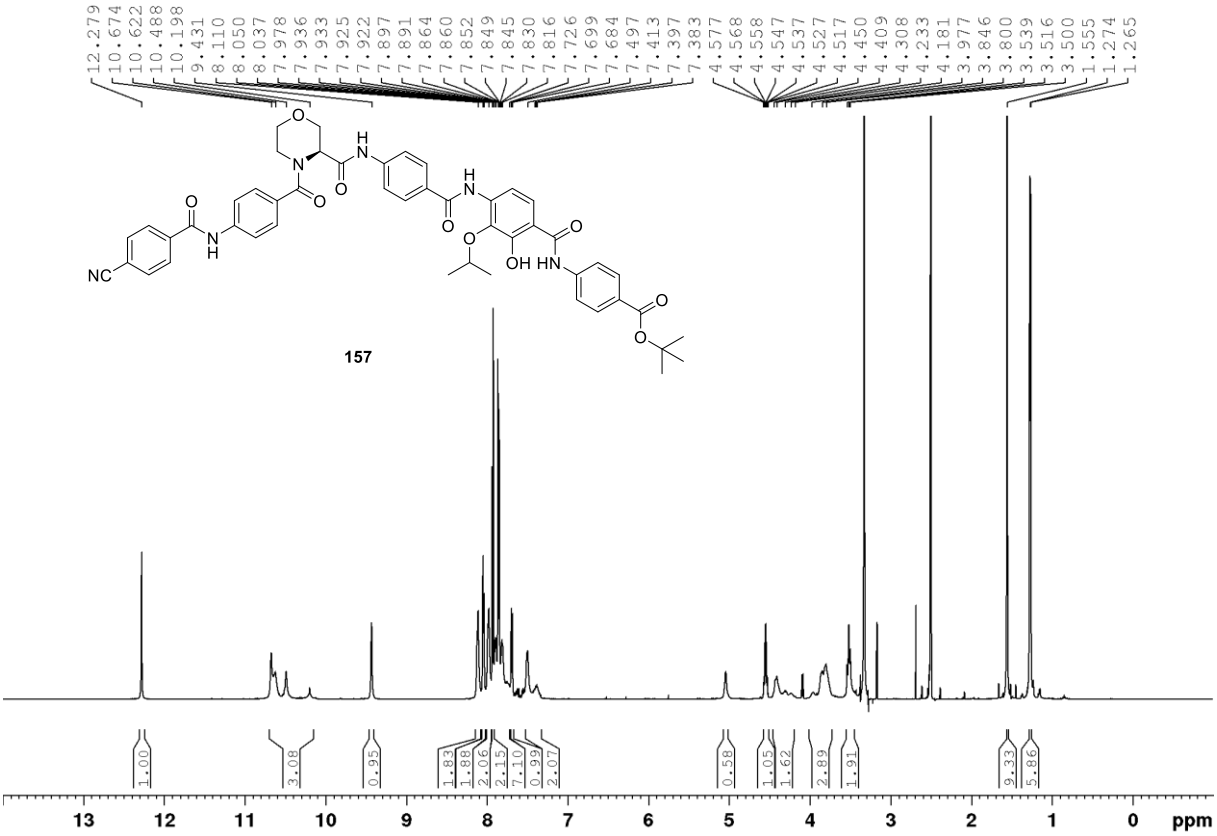

TSF16

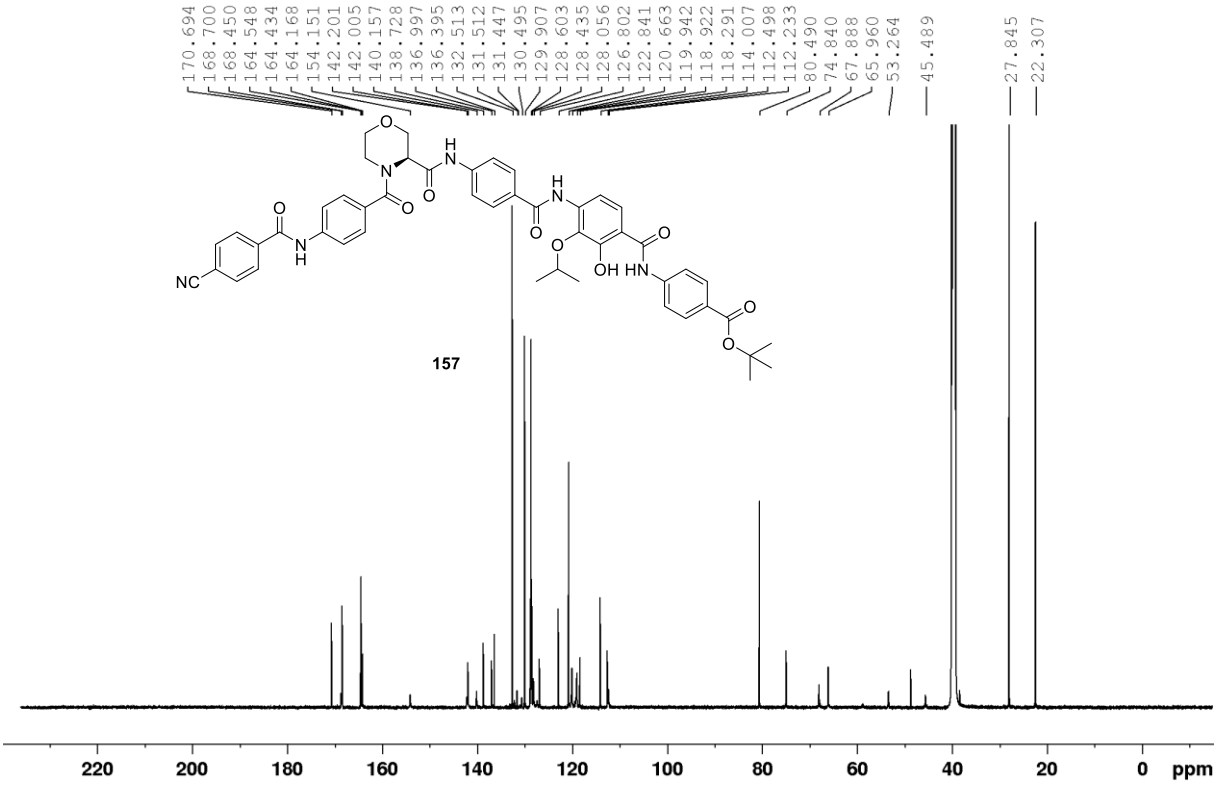

125

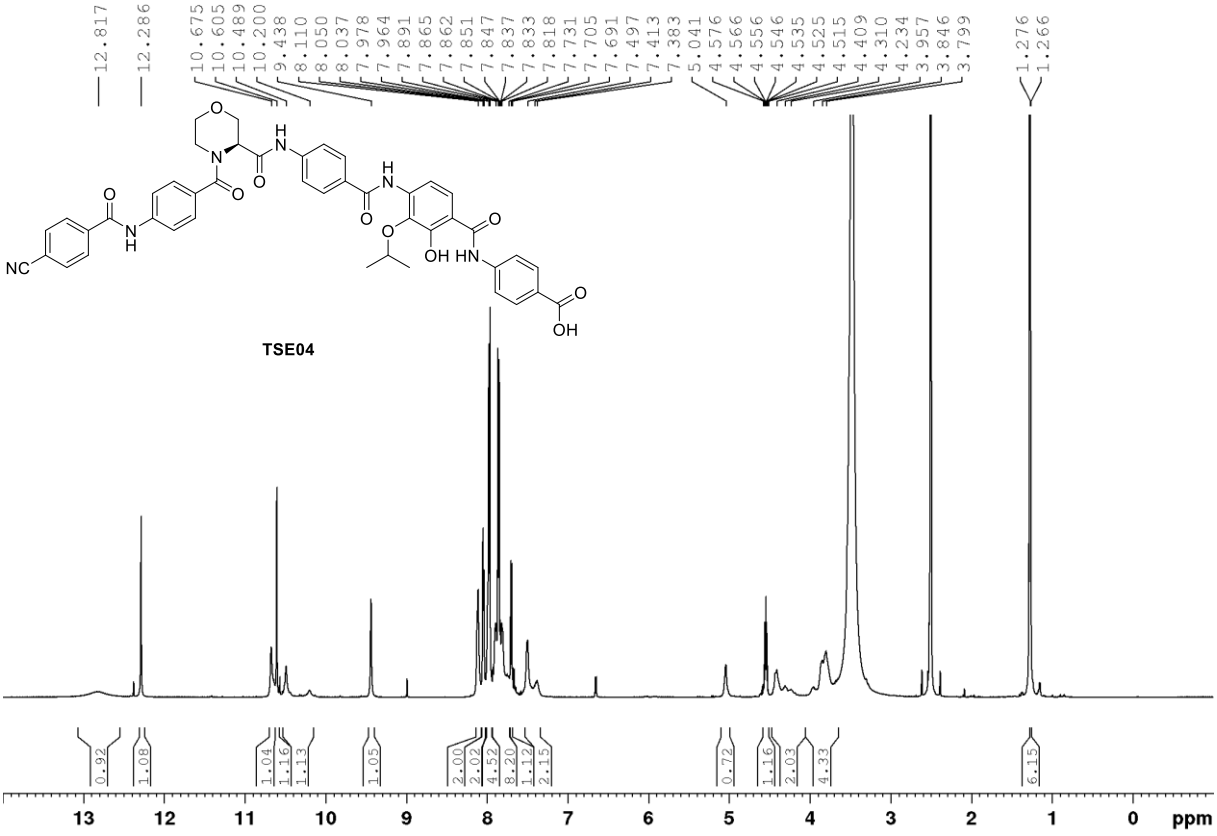

168.971
164.587
164.550
164.293
156.000
155.510
149.538
143.720
143.028
140.743
135.628
133.657
130.090
128.501
127.737
127.627
127.202
126.969
126.017
125.189
125.092
124.974
123.605
120.148
118.826
118.716
117.799
80.336
76.276
74.307
67.833
67.544
67.368
67.144
65.911
65.508
59.748
55.189
54.642
46.574
46.493
27.854
22.332
125
220
200
180
160
140
120
100
80
60
40
20
0
ppm

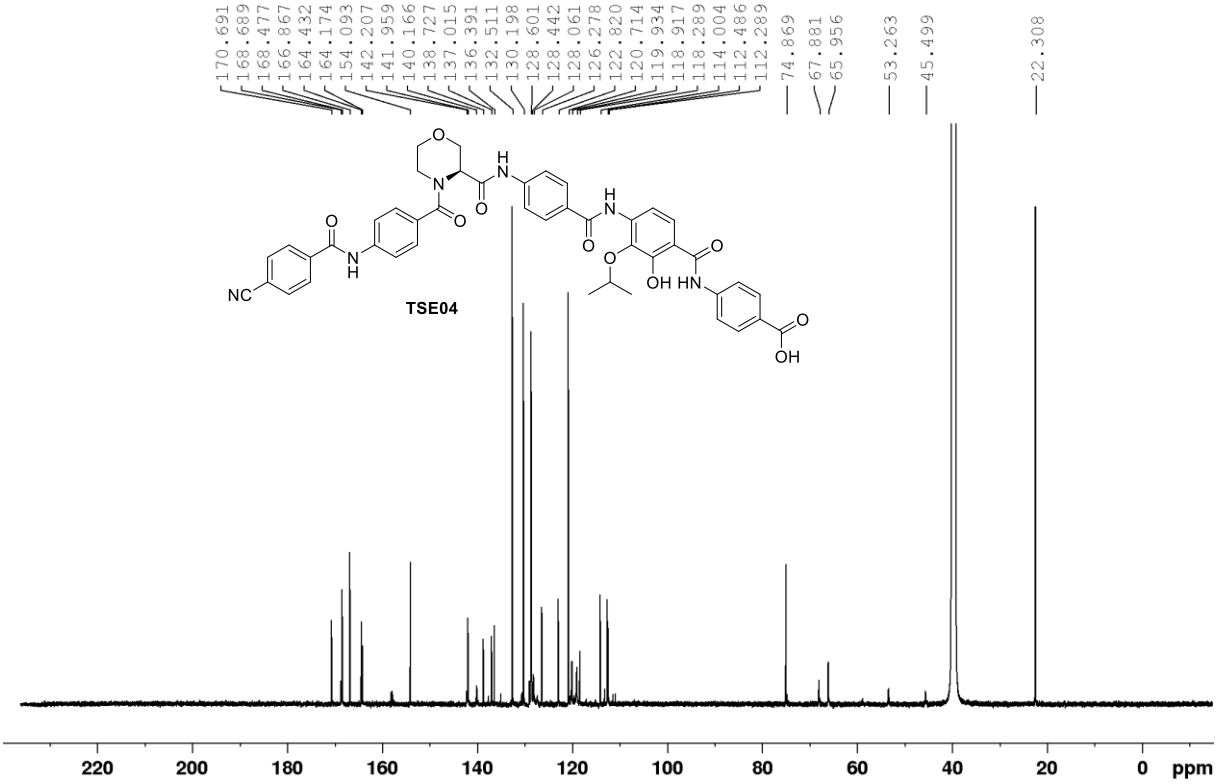

10.673
10.531
10.473
9.554
8.122
8.106
8.052
8.036
8.013
7.999
7.902
7.885
7.839
7.821
7.802
7.495
7.418
7.401
6.048
6.038
6.027
6.014
6.003
5.993
5.982
5.397
5.394
5.391
5.388
5.363
5.360
5.356
5.353
5.219
5.216
5.213
5.210
5.197
5.195
5.192
5.189
5.039
4.617
4.606
4.508
4.496
4.483
4.471
4.405
3.842
3.814
3.801
3.543
3.516
3.497
1.548
1.268
1.256
NC
156
1.02
1.20
0.66
1.08
2.05
2.08
2.30
3.94
5.83
1.37
1.23
1.00
1.13
1.09
0.67
2.28
1.20
1.71
3.08
2.17
10.10
6.72
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

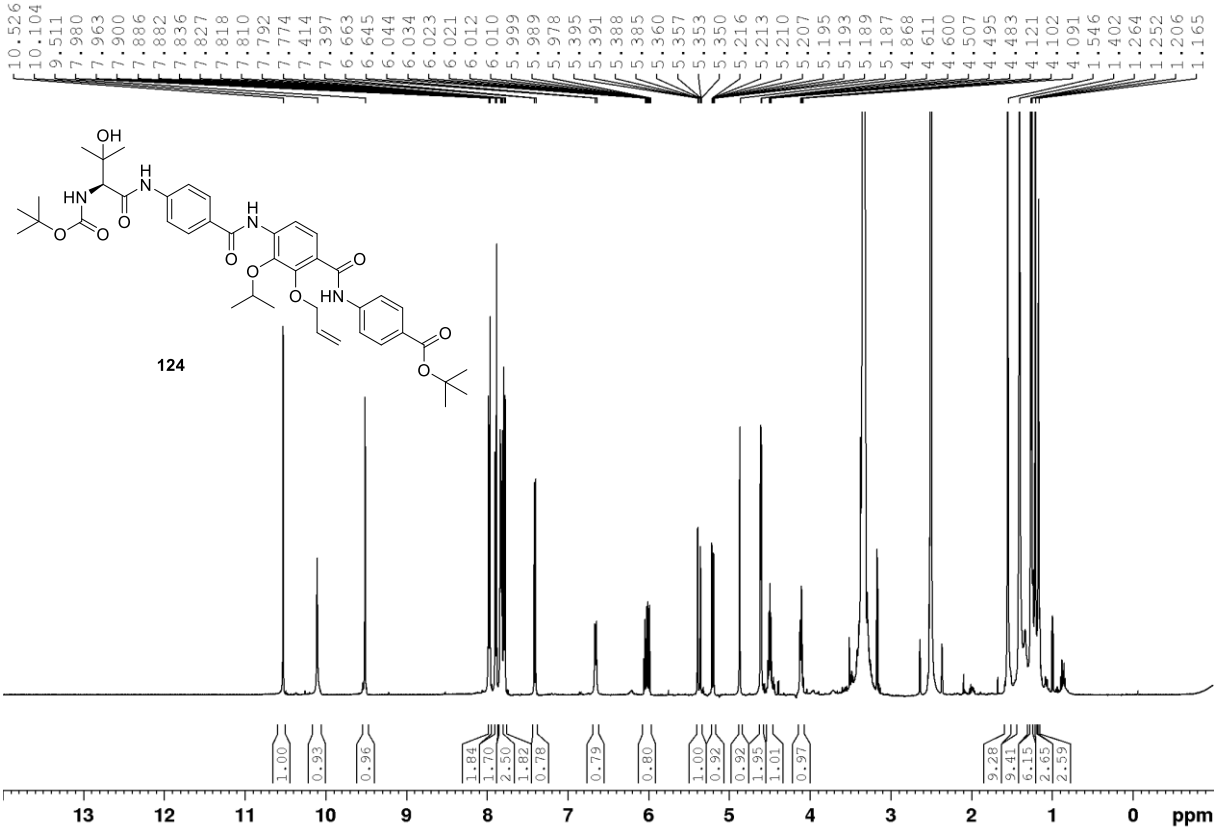

170.687
168.671
164.585
164.543
164.431
164.256
149.530
143.025
142.612
142.097
140.159
138.726
135.621
133.654
132.512
130.089
128.600
128.512
127.161
126.016
123.601
119.936
119.039
118.825
118.287
117.802
114.005
80.335
76.247
74.304
67.901
65.958
53.270
45.513
27.855
22.341
156
220
200
180
160
140
120
100
80
60
40
20
0
ppm

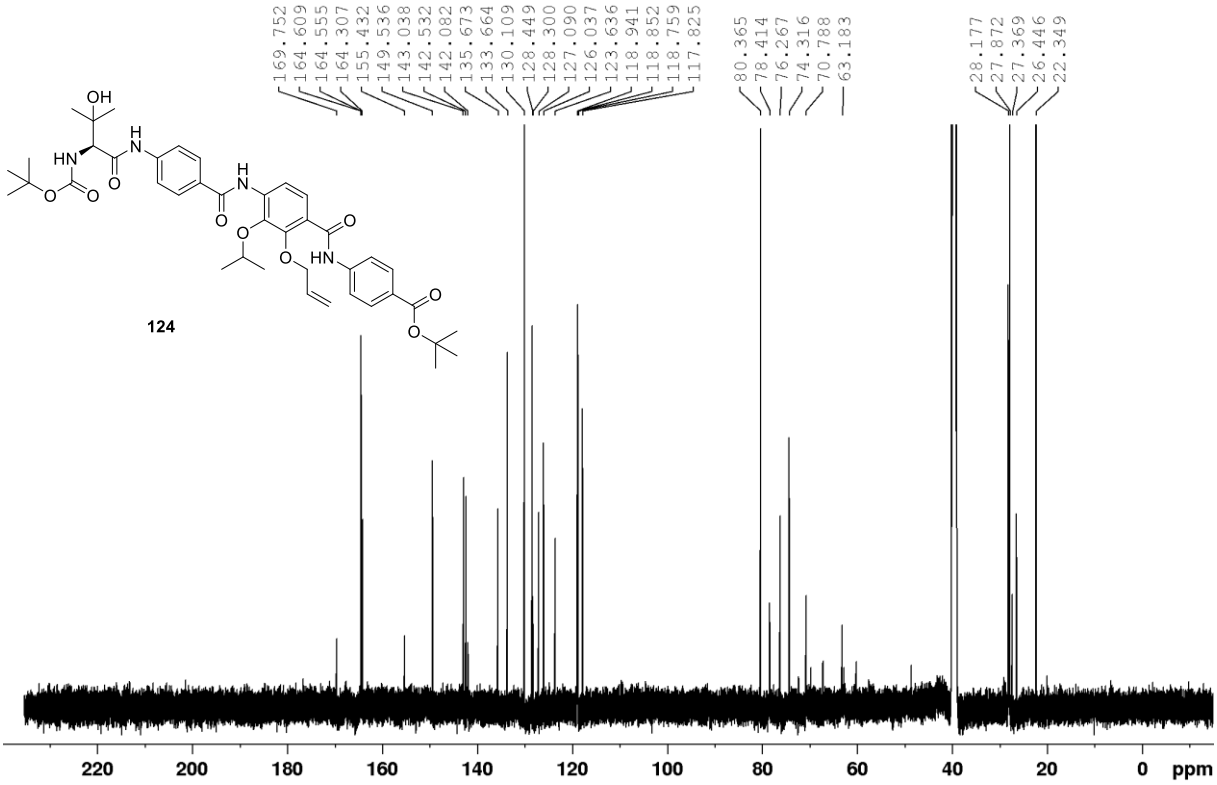

12.279
10.674
10.622
10.488
10.198
9.431
8.110
8.050
8.037
7.978
7.936
7.933
7.925
7.922
7.897
7.891
7.864
7.860
7.852
7.849
7.845
7.830
7.816
7.726
7.699
7.684
7.497
7.413
7.397
7.383
4.577
4.568
4.558
4.547
4.537
4.527
4.517
4.450
4.409
4.308
4.233
4.181
3.977
3.846
3.800
3.539
3.516
3.500
1.555
1.274
1.265
157
1.00
3.08
0.95
1.83
1.88
2.06
2.15
7.10
0.99
2.07
0.58
1.05
1.62
2.89
1.91
9.33
5.86
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

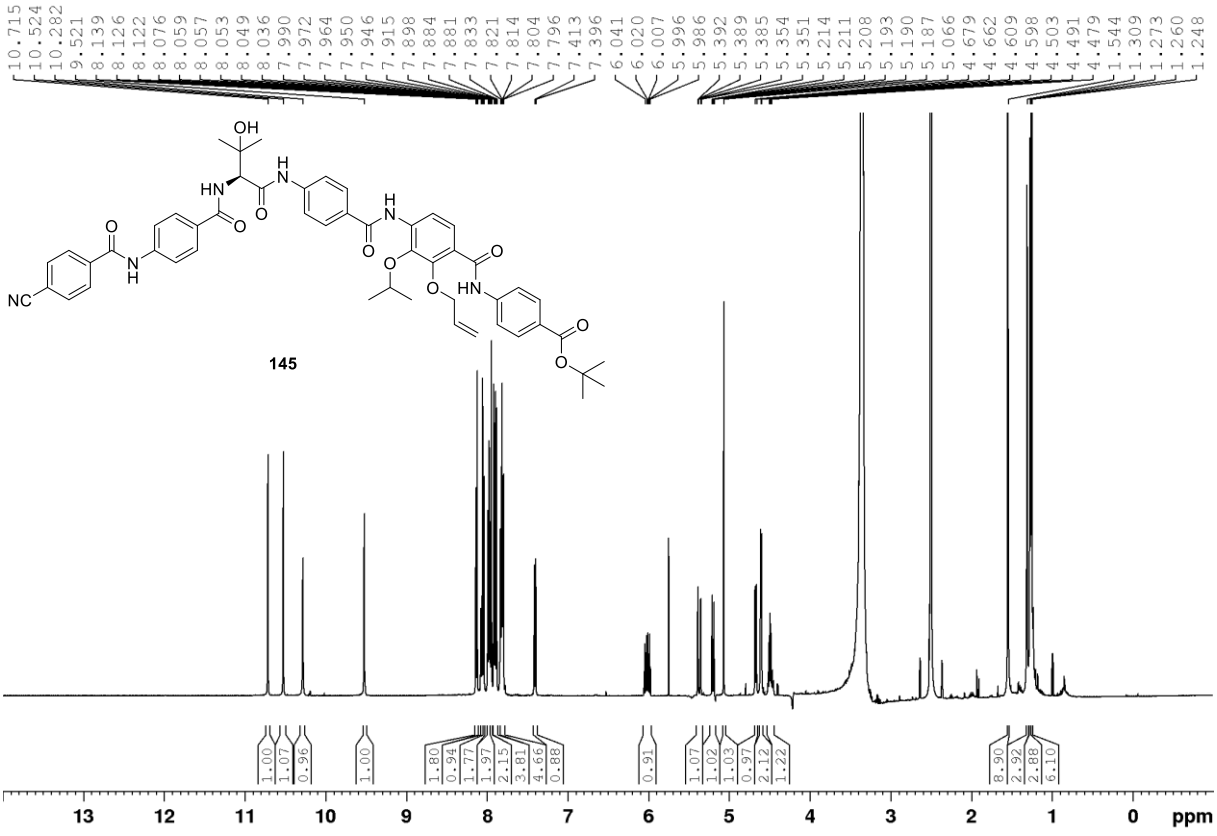

170.694
168.700
168.450
164.548
164.434
164.168
154.151
142.201
142.005
140.157
138.728
136.997
136.395
132.513
131.512
131.447
130.495
129.907
128.603
128.435
128.056
126.802
122.841
120.663
119.942
118.922
118.291
114.007
112.498
112.233
80.490
74.840
67.888
65.960
53.264
45.489
27.845
22.307
157
220
200
180
160
140
120
100
80
60
40
20
0
ppm

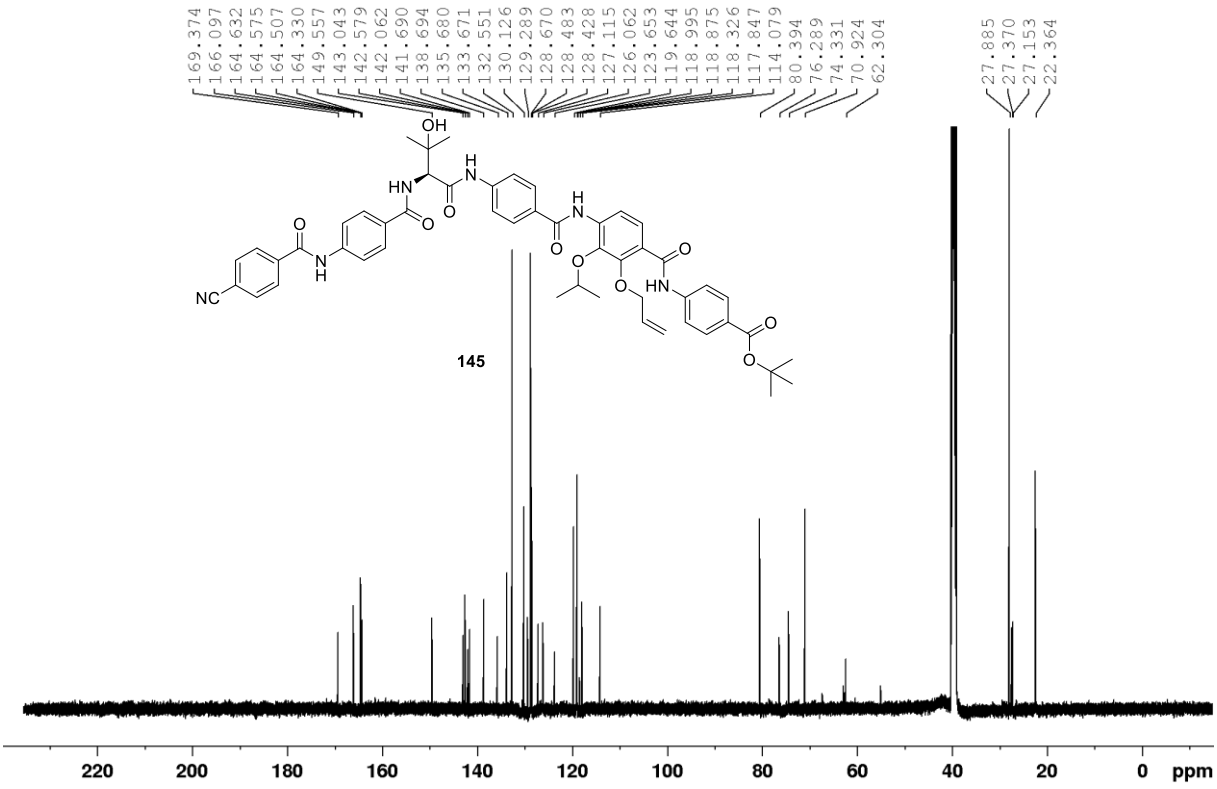

12.817
12.286
10.675
10.605
10.489
10.200
9.438
8.110
8.050
8.037
7.978
7.964
7.891
7.865
7.862
7.851
7.847
7.837
7.833
7.818
7.731
7.705
7.691
7.497
7.413
7.383
5.041
4.576
4.566
4.556
4.546
4.535
4.525
4.515
4.409
4.310
4.234
3.957
3.846
3.799
1.276
1.266
TSE04
0.92
1.08
1.04
1.16
1.13
1.05
2.00
2.02
4.52
8.20
1.12
2.15
0.72
1.16
2.03
4.33
6.15
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

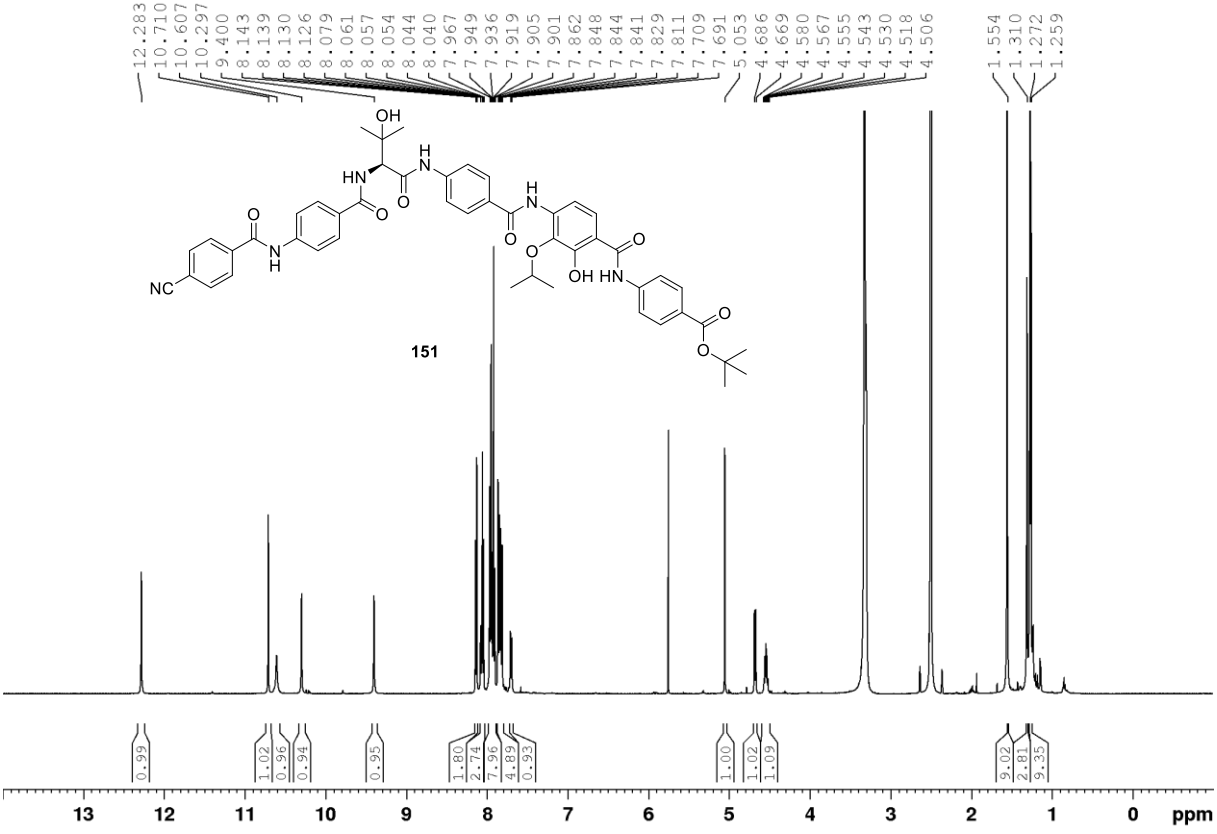

170.691
168.689
168.477
166.867
164.432
164.174
154.093
142.207
141.959
140.166
138.727
137.015
136.391
132.511
130.198
128.601
128.442
128.061
126.278
122.820
120.714
119.934
118.917
118.289
114.004
112.486
112.289
74.869
67.881
65.956
53.263
45.499
22.308
TSE04
220
200
180
160
140
120
100
80
60
40
20
0
ppm

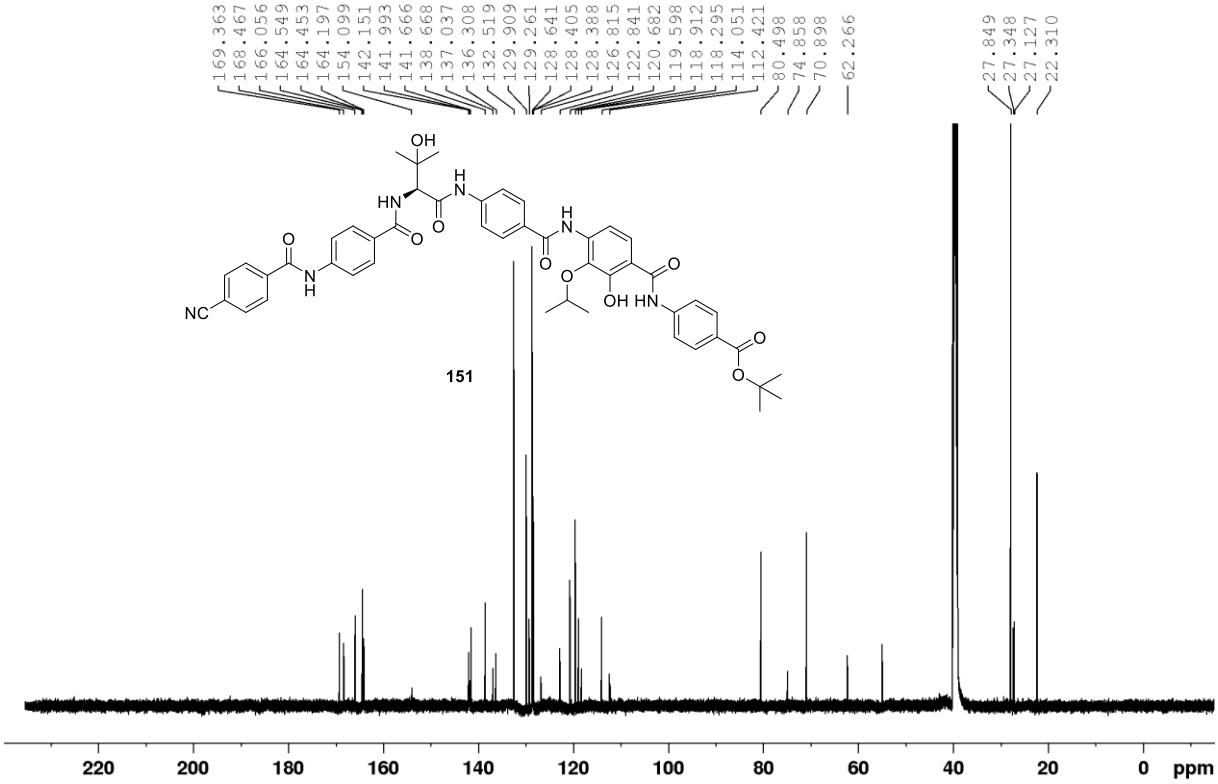

10.526
10.104
9.511
7.980
7.963
7.900
7.886
7.882
7.836
7.827
7.818
7.810
7.792
7.774
7.414
7.397
6.663
6.645
6.044
6.034
6.023
6.021
6.012
6.010
5.999
5.989
5.978
5.395
5.391
5.388
5.385
5.360
5.357
5.353
5.350
5.216
5.213
5.210
5.207
5.195
5.193
5.189
5.187
4.868
4.611
4.600
4.507
4.495
4.483
4.121
4.102
4.091
1.546
1.402
1.264
1.252
1.206
1.165
124
1.00
0.93
0.96
1.84
1.70
2.50
1.82
0.78
0.79
0.80
1.00
0.92
0.92
1.95
1.01
0.97
9.28
9.41
6.15
2.65
2.59
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

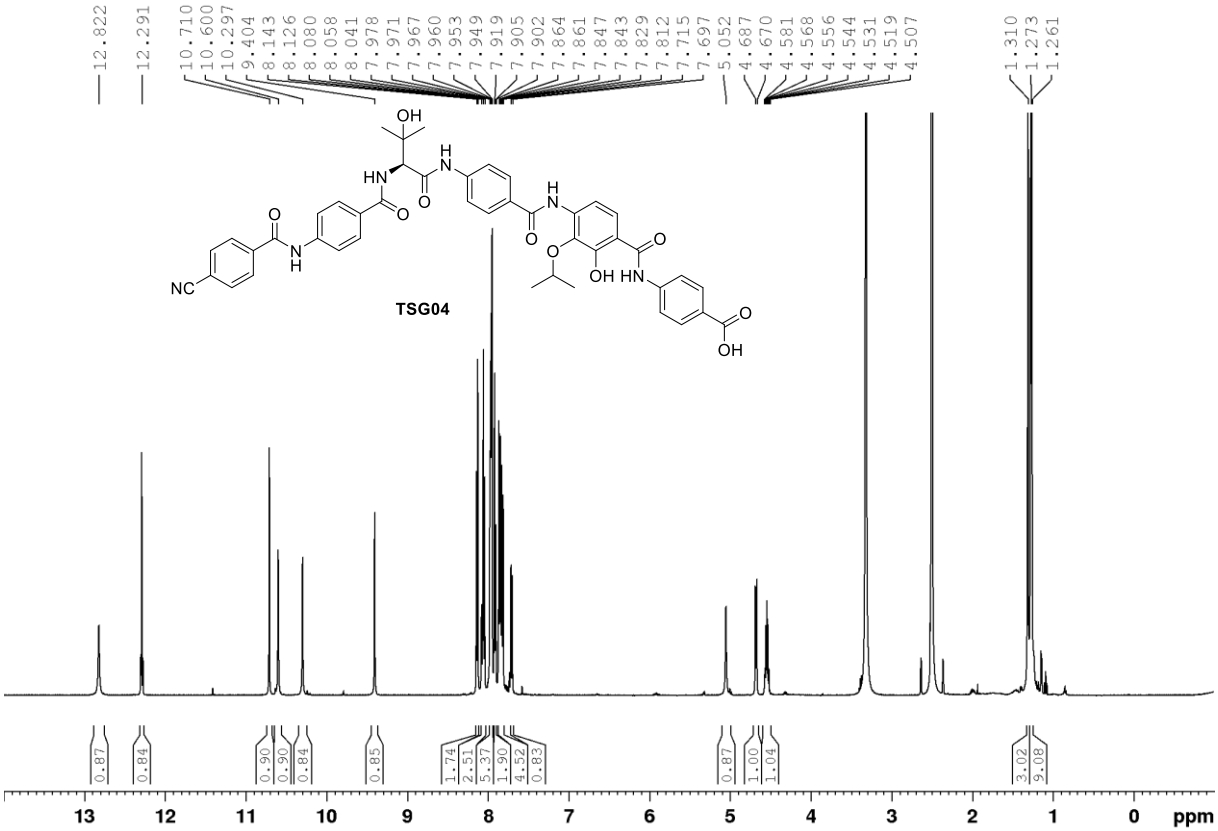

169.752
164.609
164.555
164.307
155.432
149.536
143.038
142.532
142.082
135.673
133.664
130.109
128.449
128.300
127.090
126.037
123.636
118.941
118.852
118.759
117.825
80.365
78.414
76.267
74.316
70.788
63.183
28.177
27.872
27.369
26.446
22.349
124
220
200
180
160
140
120
100
80
60
40
20
0
ppm

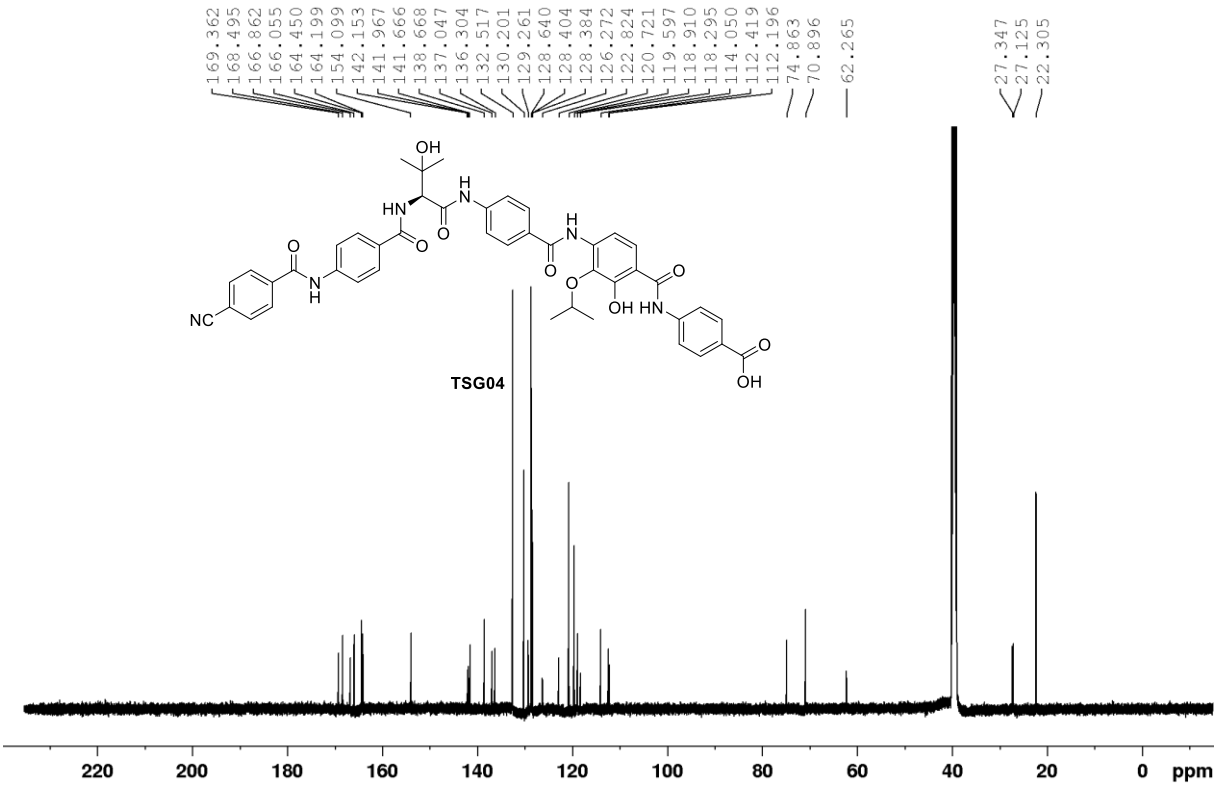

10.715
10.524
10.282
9.521
8.139
8.126
8.122
8.076
8.059
8.057
8.053
8.049
8.036
7.990
7.972
7.964
7.950
7.946
7.915
7.898
7.884
7.881
7.833
7.821
7.814
7.804
7.796
7.413
7.396
6.041
6.020
6.007
5.996
5.986
5.392
5.389
5.385
5.354
5.351
5.214
5.211
5.208
5.193
5.190
5.187
5.066
4.679
4.662
4.609
4.598
4.503
4.491
4.479
1.544
1.309
1.273
1.260
1.248
145
1.00
1.07
0.96
1.00
1.80
0.94
1.77
1.97
2.15
3.81
4.66
0.88
0.91
1.07
1.02
1.03
0.97
2.12
1.22
8.90
2.92
2.88
6.10
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

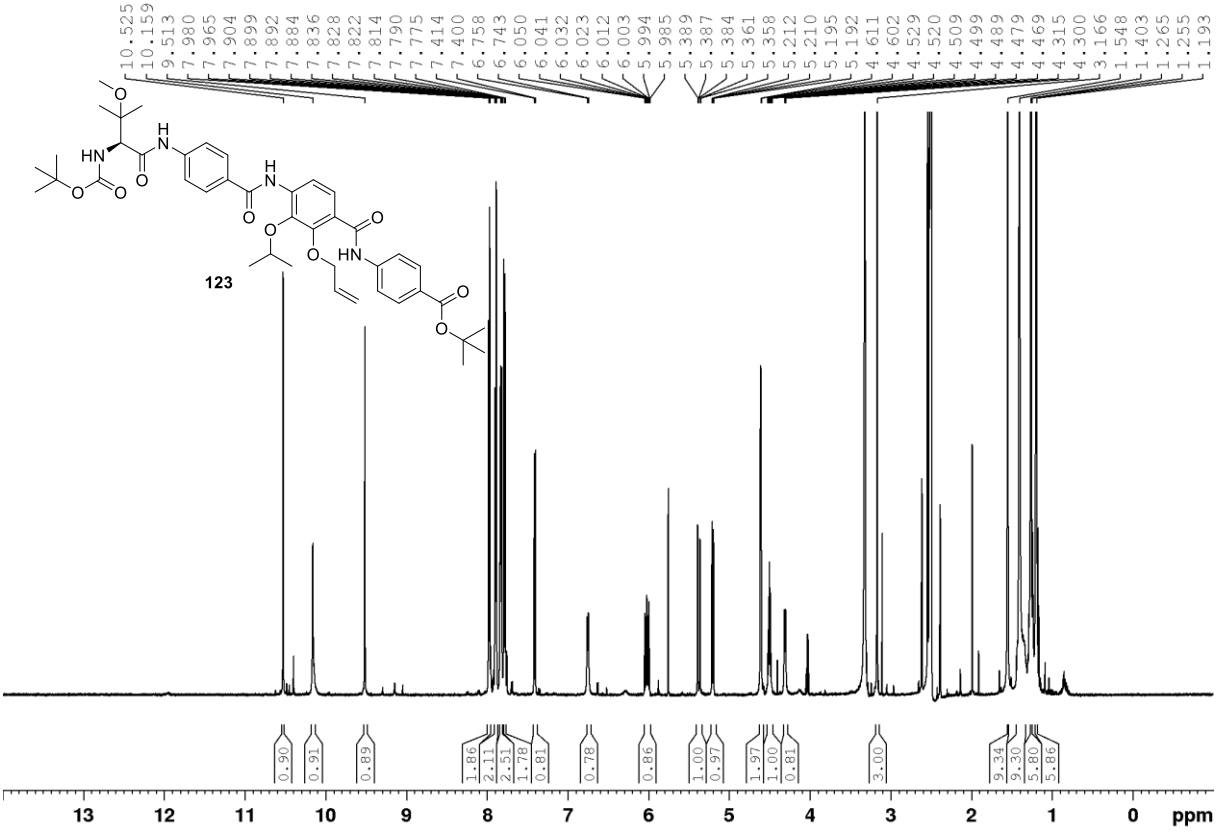

169.374
166.097
164.632
164.575
164.507
164.330
149.557
143.043
142.579
142.062
141.690
138.694
135.680
133.671
132.551
130.126
129.289
128.670
128.483
128.428
127.115
126.062
123.653
119.644
118.995
118.875
118.326
117.847
114.079
80.394
76.289
74.331
70.924
62.304
27.885
27.370
27.153
22.364
145
220
200
180
160
140
120
100
80
60
40
20
0
ppm

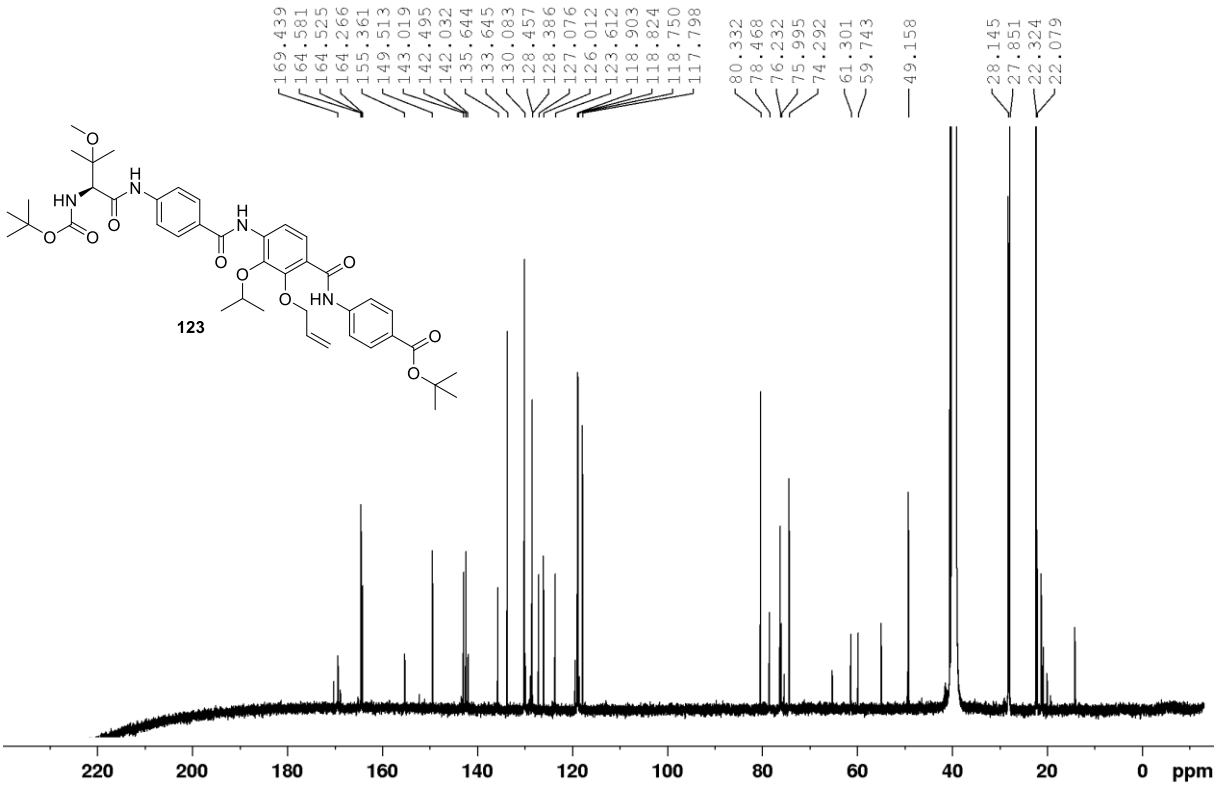

12.283
10.710
10.607
10.297
9.400
8.143
8.139
8.130
8.126
8.079
8.061
8.057
8.054
8.044
8.040
7.967
7.949
7.936
7.919
7.905
7.901
7.862
7.848
7.844
7.841
7.829
7.811
7.709
7.691
5.053
4.686
4.669
4.580
4.567
4.555
4.543
4.530
4.518
4.506
1.554
1.310
1.272
1.259
151
0.99
1.02
0.96
0.94
0.95
1.80
2.74
7.96
4.89
0.93
1.00
1.02
1.09
9.02
2.81
9.35
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

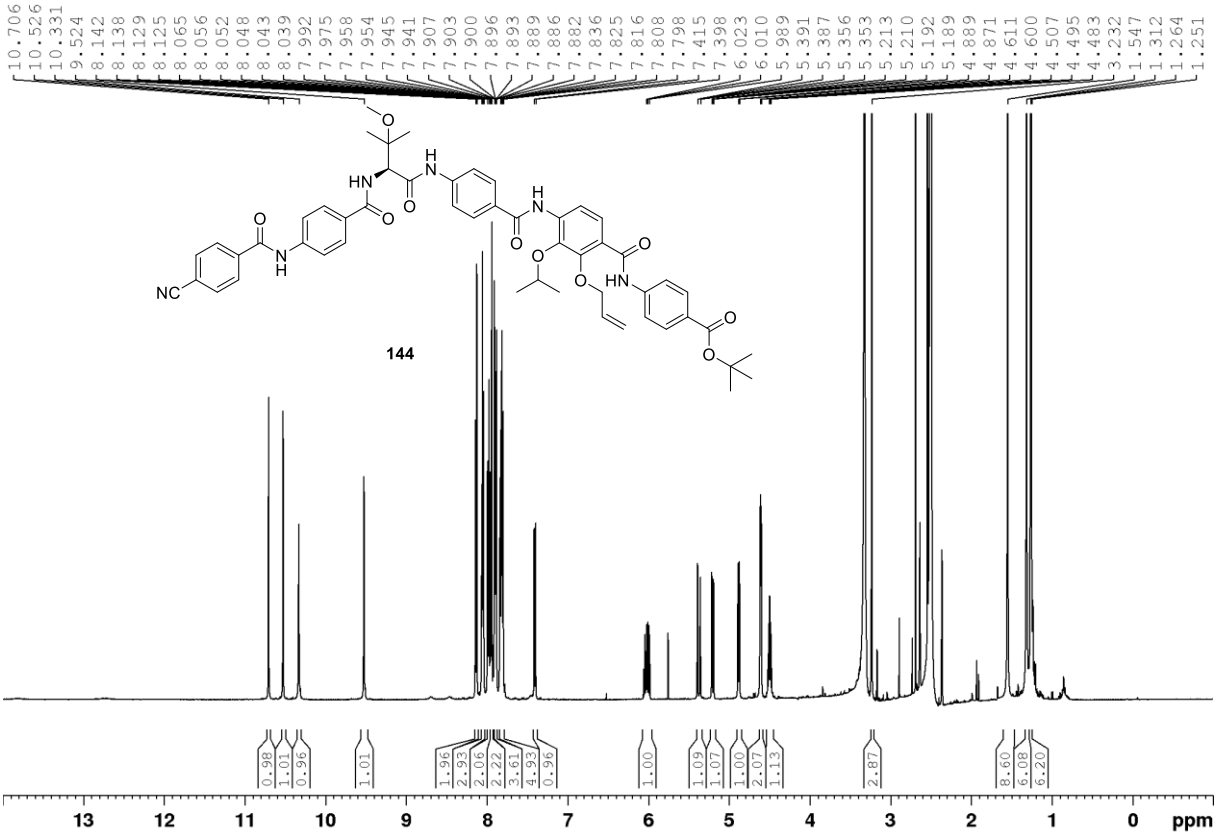

169.363
168.467
166.056
164.549
164.453
164.197
154.099
142.151
141.993
141.666
138.668
137.037
136.308
132.519
129.909
129.261
128.641
128.405
128.388
126.815
122.841
120.682
119.598
118.912
118.295
114.051
112.421
80.498
74.858
70.898
62.266
27.849
27.348
27.127
22.310
151
220
200
180
160
140
120
100
80
60
40
20
0
ppm

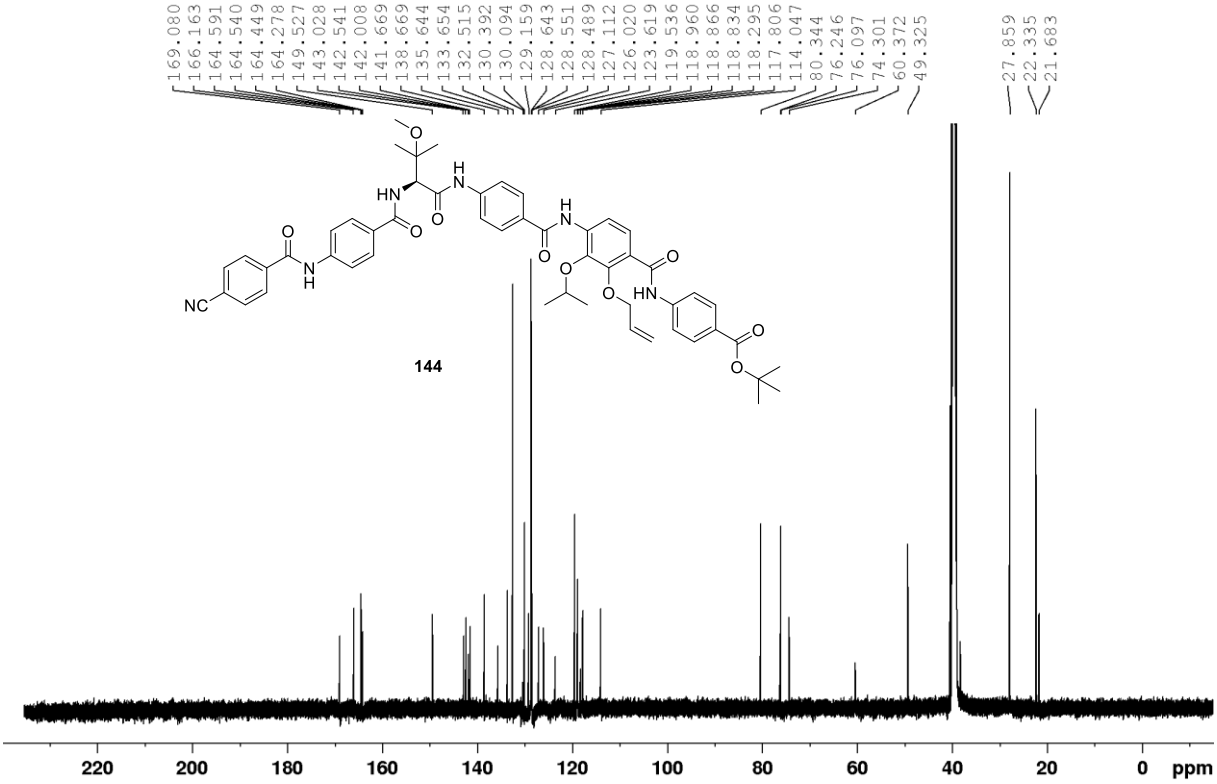

12.822
12.291
10.710
10.600
10.297
9.404
8.143
8.126
8.080
8.058
8.041
7.978
7.971
7.967
7.960
7.953
7.949
7.919
7.905
7.902
7.864
7.861
7.847
7.843
7.829
7.812
7.715
7.697
5.052
4.687
4.670
4.581
4.568
4.556
4.544
4.531
4.519
4.507
1.310
1.273
1.261
TSG04
0.87
0.84
0.90
0.90
0.84
0.85
1.74
2.51
5.37
1.90
4.52
0.83
0.87
1.00
1.04
3.02
9.08
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

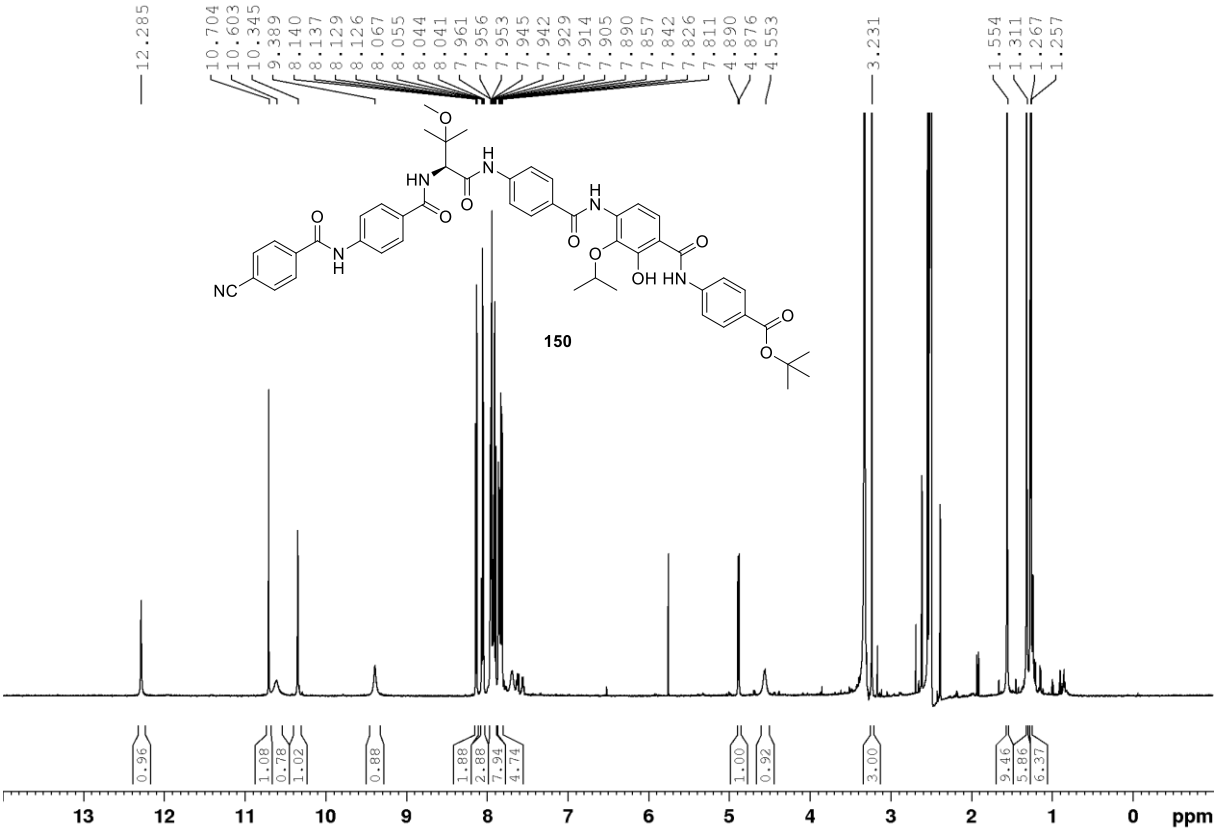

169.362
168.495
166.862
166.055
164.450
164.199
154.099
142.153
141.967
141.666
138.668
137.047
136.304
132.517
130.201
129.261
128.640
128.404
128.384
126.272
122.824
120.721
119.597
118.910
118.295
114.050
112.419
112.196
74.863
70.896
62.265
27.347
27.125
22.305
TSG04
220
200
180
160
140
120
100
80
60
40
20
0
ppm

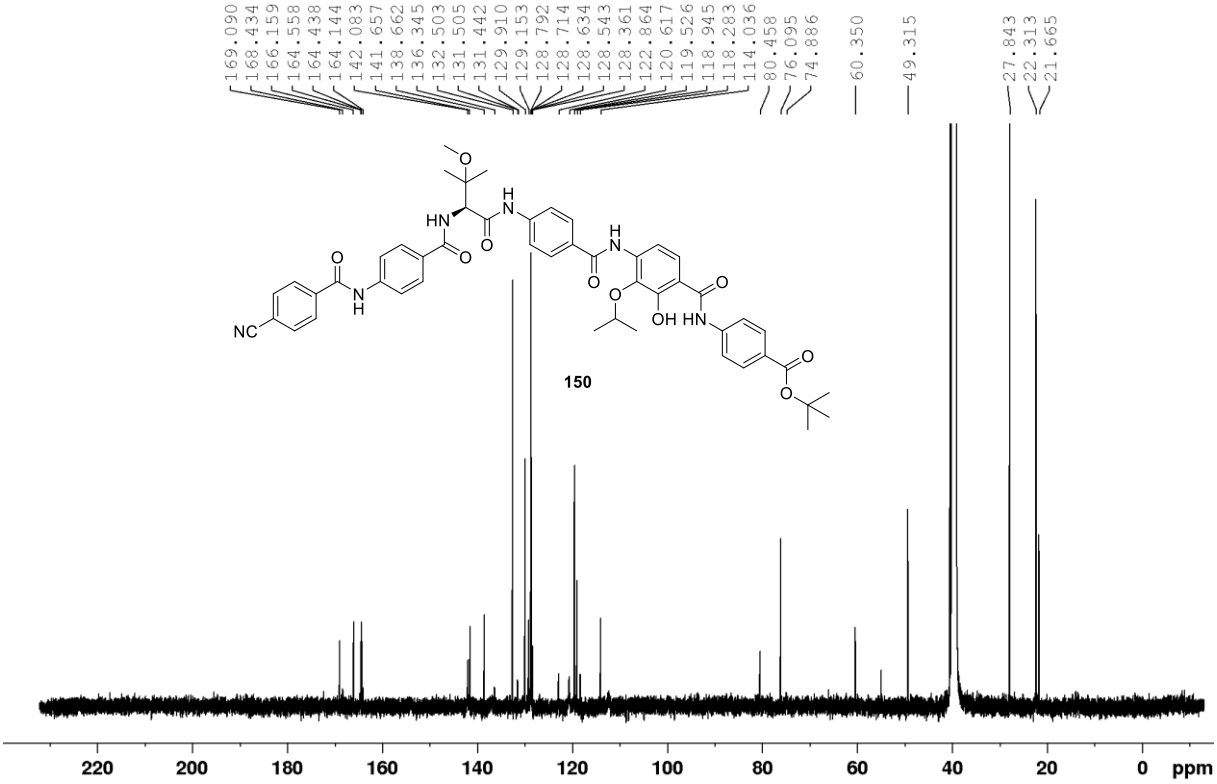

10.525
10.159
9.513
7.980
7.965
7.904
7.899
7.892
7.884
7.836
7.828
7.822
7.814
7.790
7.775
7.414
7.400
6.758
6.743
6.050
6.041
6.032
6.023
6.012
6.003
5.994
5.985
5.389
5.387
5.384
5.361
5.358
5.212
5.210
5.195
5.192
4.611
4.602
4.529
4.520
4.509
4.499
4.489
4.479
4.469
4.315
4.300
3.166
1.548
1.403
1.265
1.255
1.193
123
0.90
0.91
0.89
1.86
2.11
2.51
1.78
0.81
0.78
0.86
1.00
0.97
1.97
1.00
0.81
3.00
9.34
9.30
5.80
5.86
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

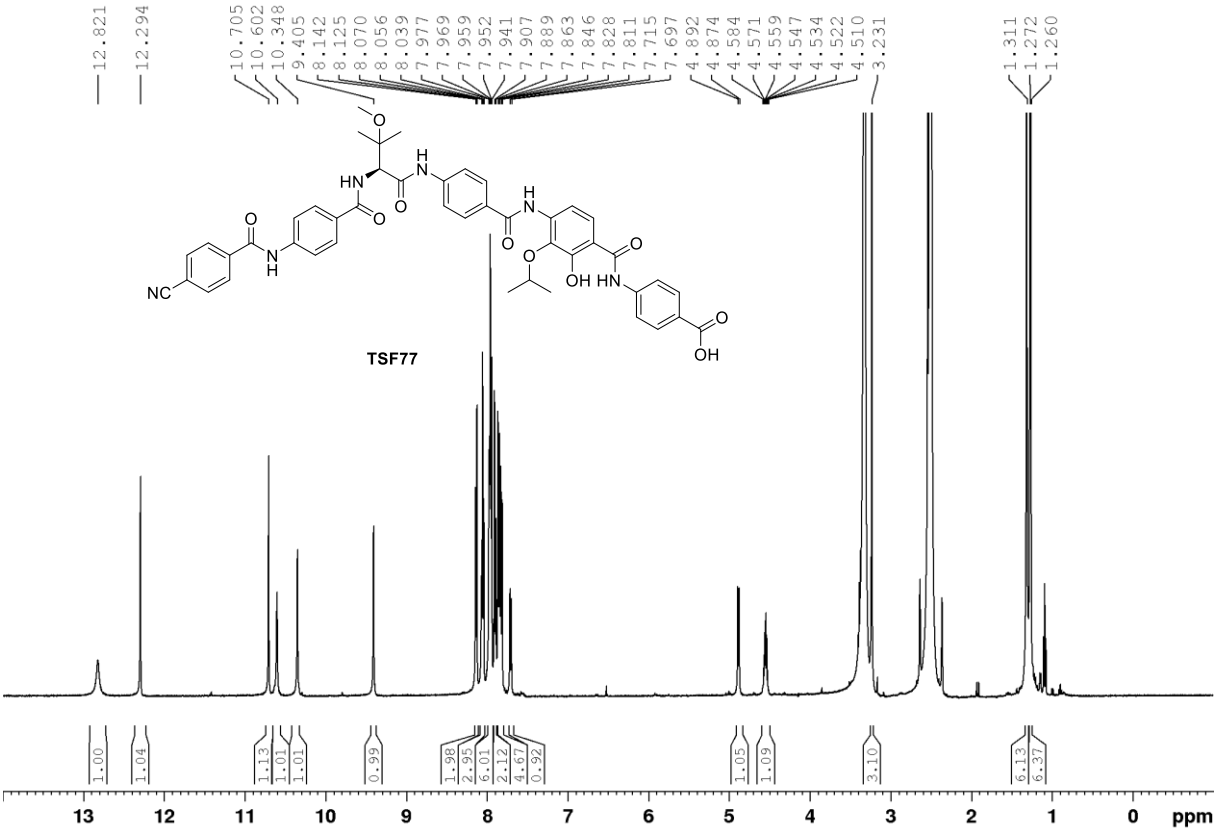

169.439
164.581
164.525
164.266
155.361
149.513
143.019
142.495
142.032
135.644
133.645
130.083
128.457
128.386
127.076
126.012
123.612
118.903
118.824
118.750
117.798
80.332
78.468
76.232
75.995
74.292
61.301
59.743
49.158
28.145
27.851
22.324
22.079
123
220
200
180
160
140
120
100
80
60
40
20
0
ppm

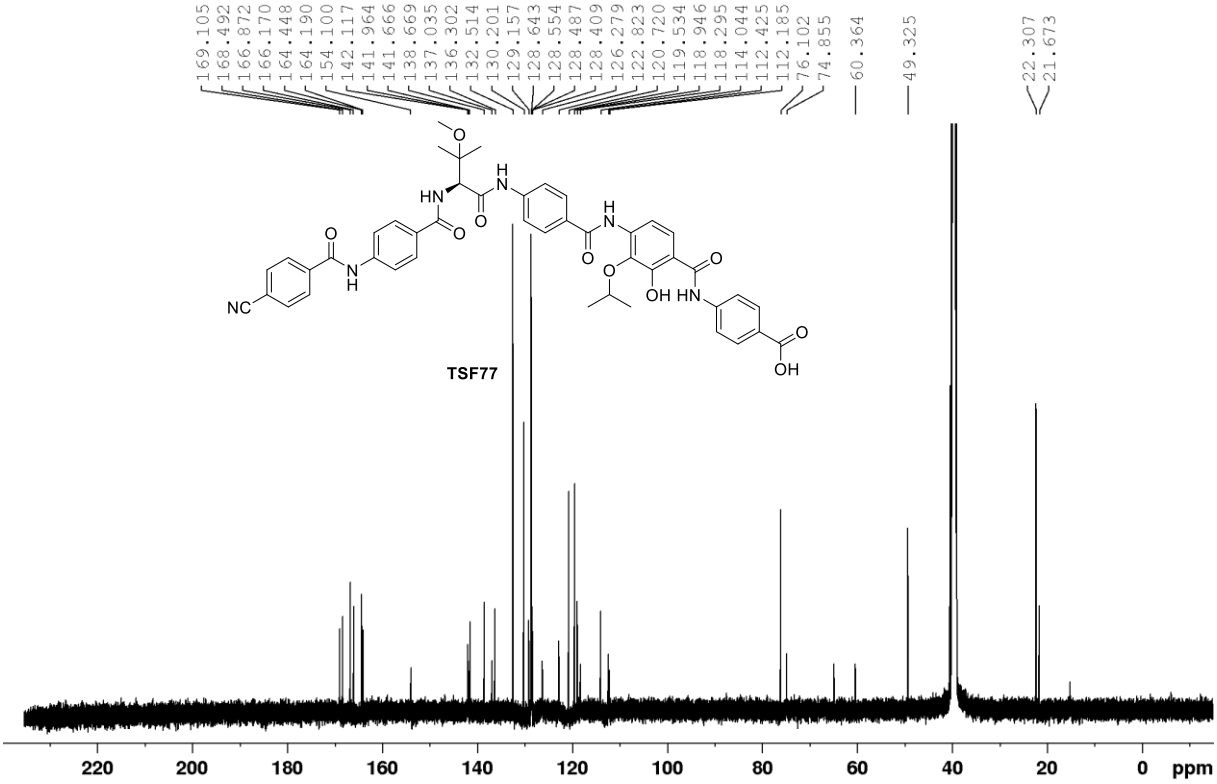

10.706
10.526
10.331
9.524
8.142
8.138
8.129
8.125
8.065
8.056
8.052
8.048
8.043
8.039
7.992
7.975
7.958
7.954
7.945
7.941
7.907
7.903
7.900
7.896
7.893
7.889
7.886
7.882
7.836
7.825
7.816
7.808
7.798
7.415
7.398
6.023
6.010
5.989
5.391
5.387
5.356
5.353
5.213
5.210
5.192
5.189
4.889
4.871
4.611
4.600
4.507
4.495
4.483
3.232
1.547
1.312
1.264
1.251
144
0.98
1.01
0.96
1.01
1.96
2.93
2.06
2.22
3.61
4.93
0.96
1.00
1.09
1.07
1.00
2.07
1.13
2.87
8.60
6.08
6.20
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

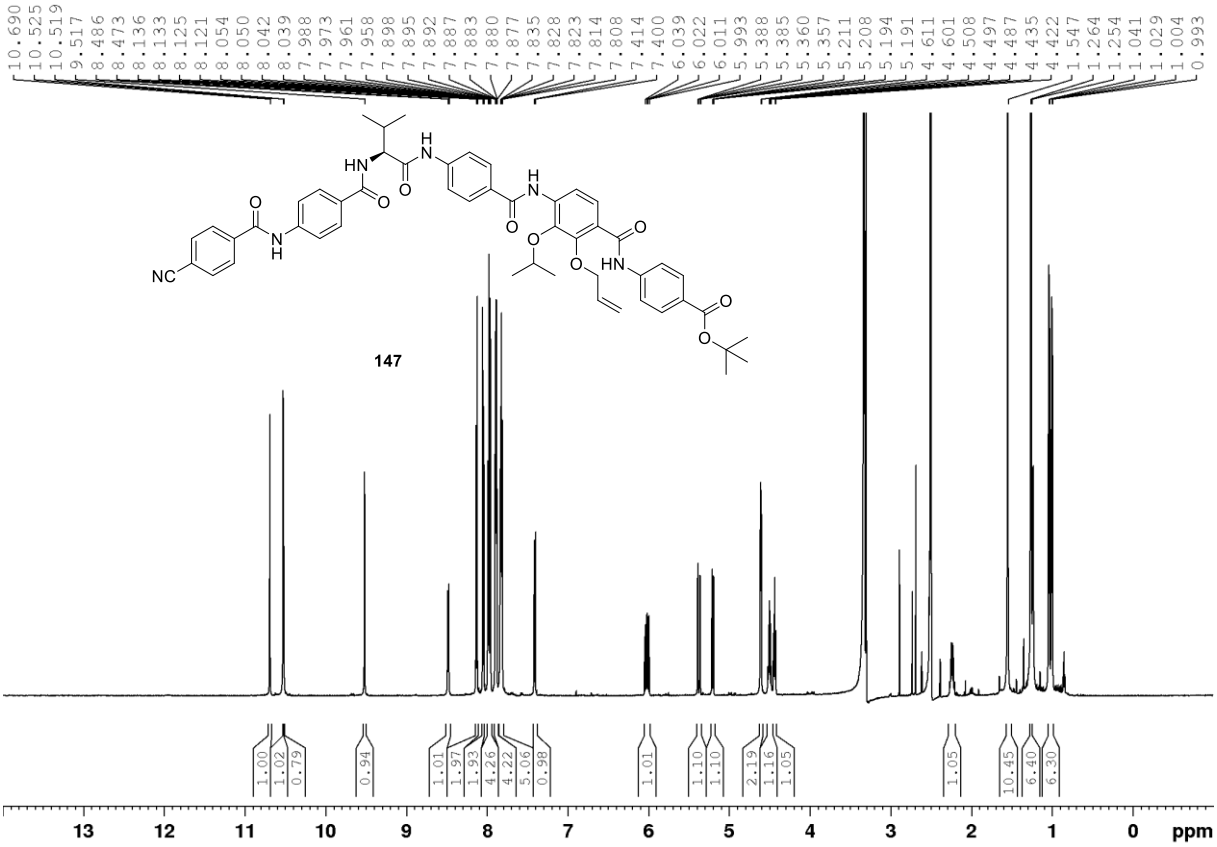

169.080
166.163
164.591
164.540
164.449
164.278
149.527
143.028
142.541
142.008
141.669
138.669
135.644
133.654
132.515
130.392
130.094
129.159
128.643
128.551
128.489
127.112
126.020
123.619
119.536
118.960
118.866
118.834
118.295
117.806
114.047
80.344
76.246
76.097
74.301
60.372
49.325
27.859
22.335
21.683
144
220
200
180
160
140
120
100
80
60
40
20
0
ppm

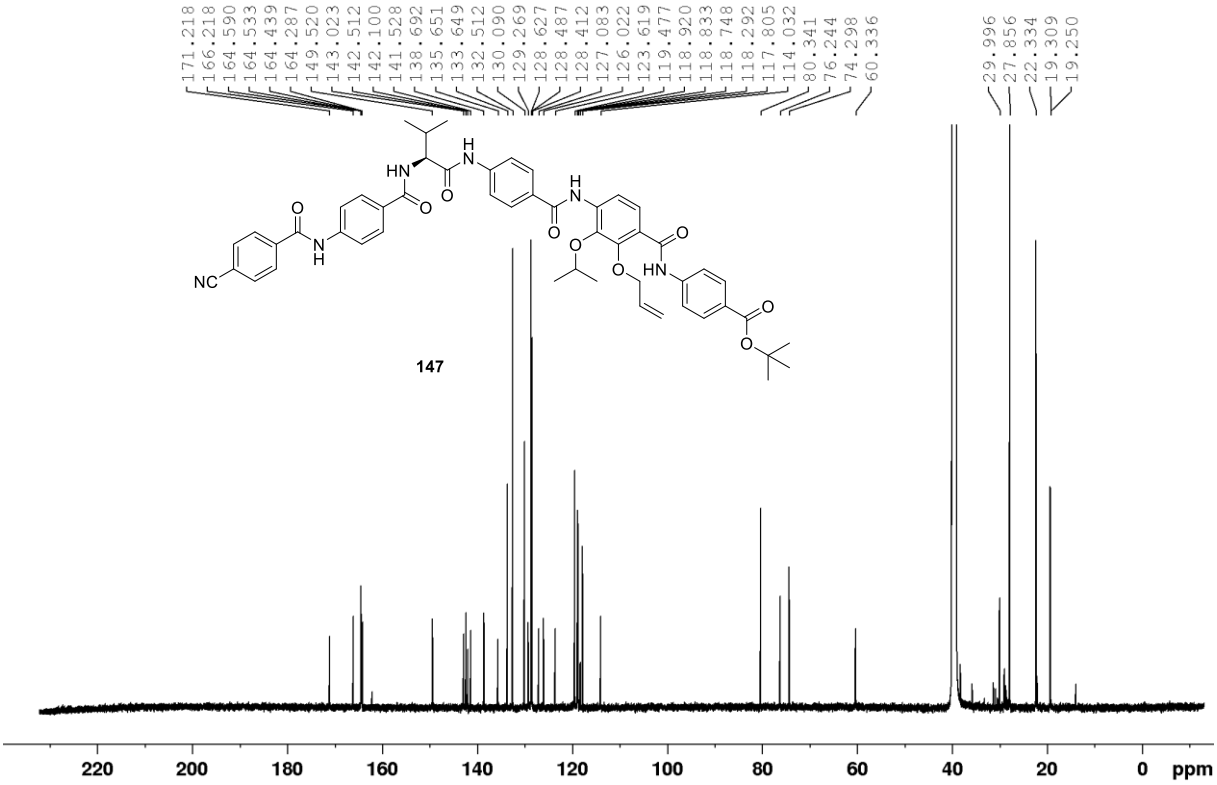

12.285
10.704
10.603
10.345
9.389
8.140
8.137
8.129
8.126
8.067
8.055
8.044
8.041
7.961
7.956
7.953
7.945
7.942
7.929
7.914
7.905
7.890
7.857
7.842
7.826
7.811
4.890
4.876
4.553
3.231
1.554
1.311
1.267
1.257
150
0.96
1.08
0.78
1.02
0.88
1.88
2.88
7.94
4.74
1.00
0.92
3.00
9.46
5.86
6.37
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

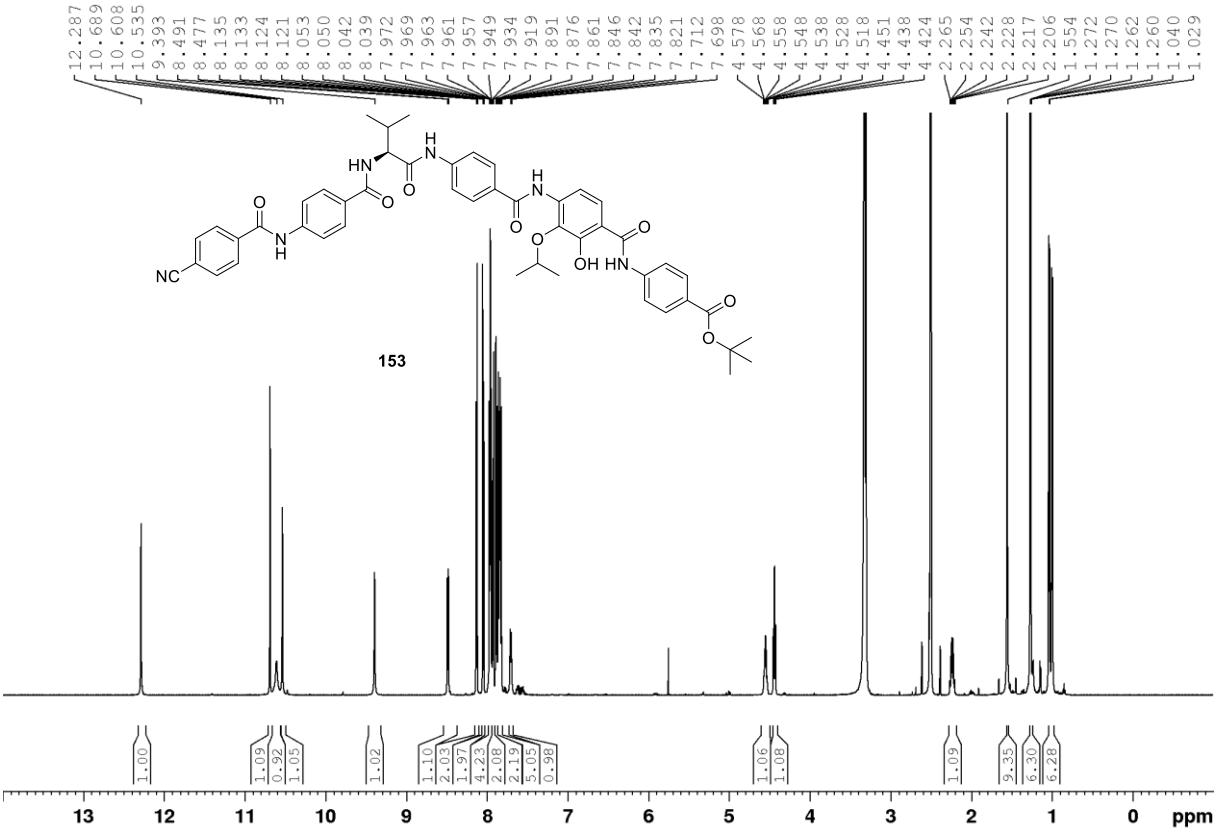

169.090
168.434
166.159
164.558
164.438
164.144
142.083
141.657
138.662
136.345
132.503
131.505
131.442
129.910
129.153
128.792
128.714
128.634
128.543
128.361
122.864
120.617
119.526
118.945
118.283
114.036
80.458
76.095
74.886
60.350
49.315
27.843
22.313
21.665
150
220
200
180
160
140
120
100
80
60
40
20
0
ppm

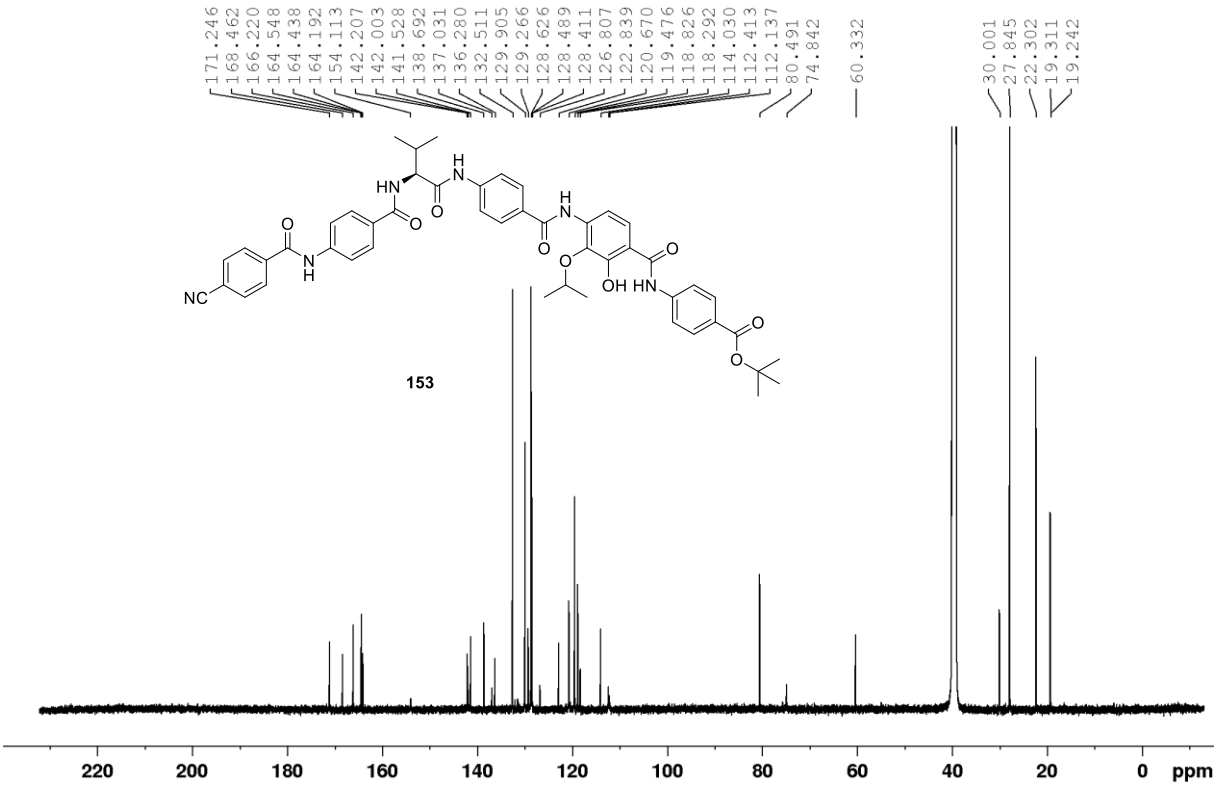

12.821
12.294
10.705
10.602
10.348
9.405
8.142
8.125
8.070
8.056
8.039
7.977
7.969
7.959
7.952
7.941
7.907
7.889
7.863
7.846
7.828
7.811
7.715
7.697
4.892
4.874
4.584
4.571
4.559
4.547
4.534
4.522
4.510
3.231
1.311
1.272
1.260
TSF77
1.00
1.04
1.13
1.01
1.01
0.99
1.98
2.95
6.01
2.12
4.67
0.92
1.05
1.09
3.10
6.13
6.37
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

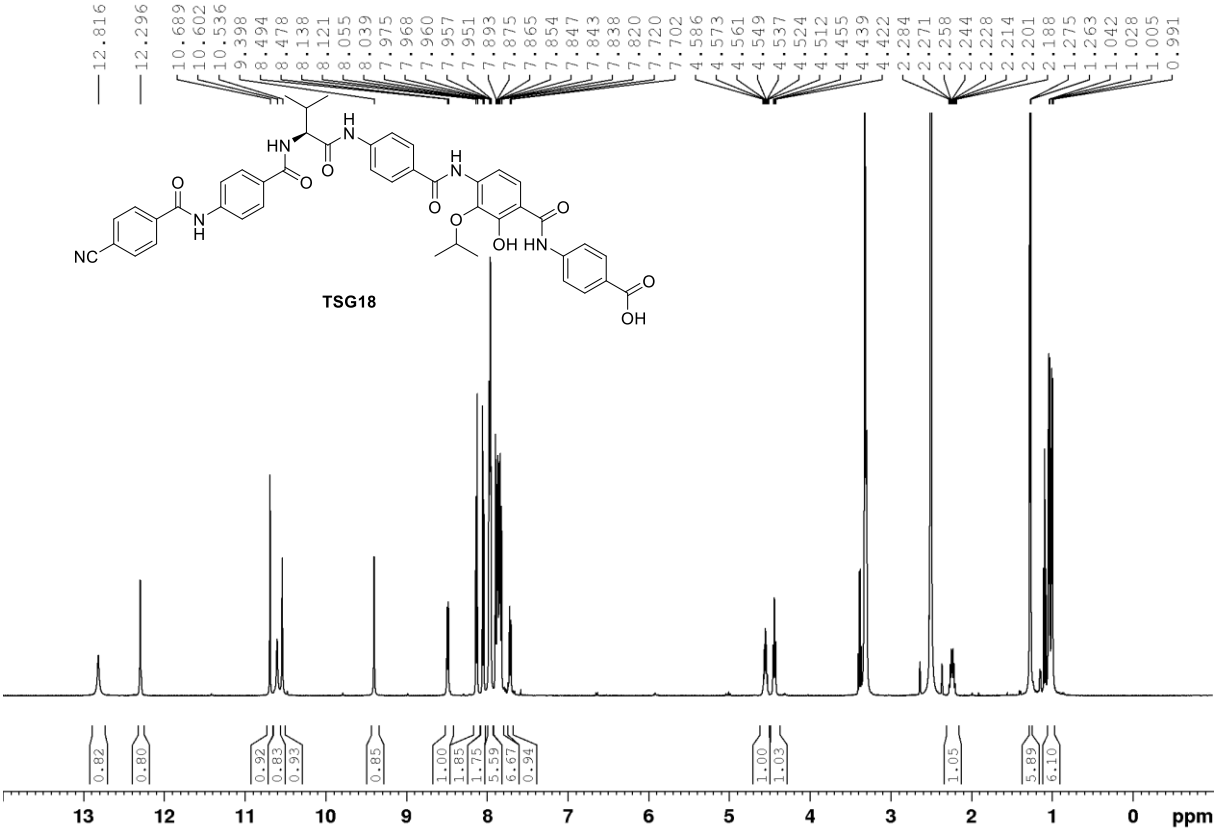

169.105
168.492
166.872
166.170
164.448
164.190
154.100
142.117
141.964
141.666
138.669
137.035
136.302
132.514
130.201
129.157
128.643
128.554
128.487
128.409
126.279
122.823
120.720
119.534
118.946
118.295
114.044
112.425
112.185
76.102
74.855
60.364
49.325
22.307
21.673
TSF77
220
200
180
160
140
120
100
80
60
40
20
0
ppm

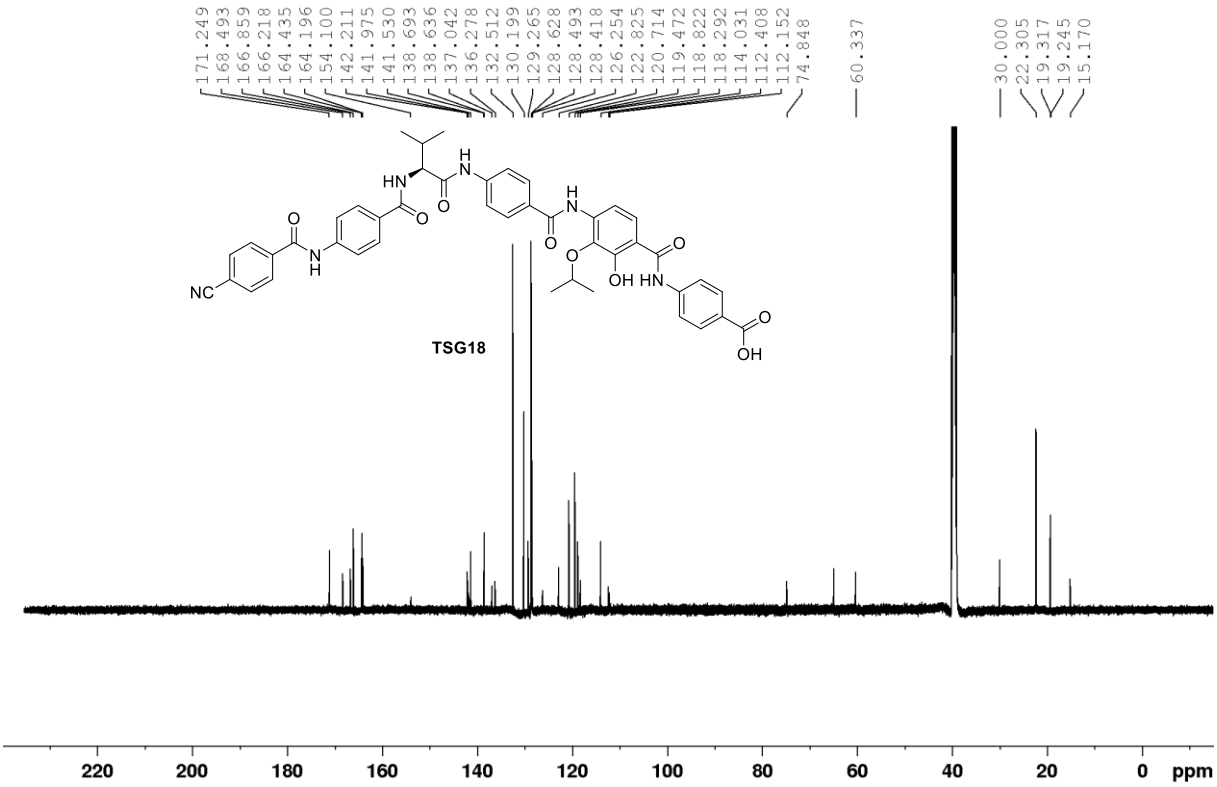

10.690
10.525
10.519
9.517
8.486
8.473
8.136
8.133
8.125
8.121
8.054
8.050
8.042
8.039
7.988
7.973
7.961
7.958
7.898
7.895
7.892
7.887
7.883
7.880
7.877
7.835
7.828
7.823
7.814
7.808
7.414
7.400
6.039
6.022
6.011
5.993
5.388
5.385
5.360
5.357
5.211
5.208
5.194
5.191
4.611
4.601
4.508
4.497
4.487
4.435
4.422
1.547
1.264
1.254
1.041
1.029
1.004
0.993
147
1.00
1.02
0.79
0.94
1.01
1.97
1.93
4.26
5.06
0.98
1.01
1.10
1.10
2.19
1.16
1.05
1.05
10.45
6.40
6.30
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

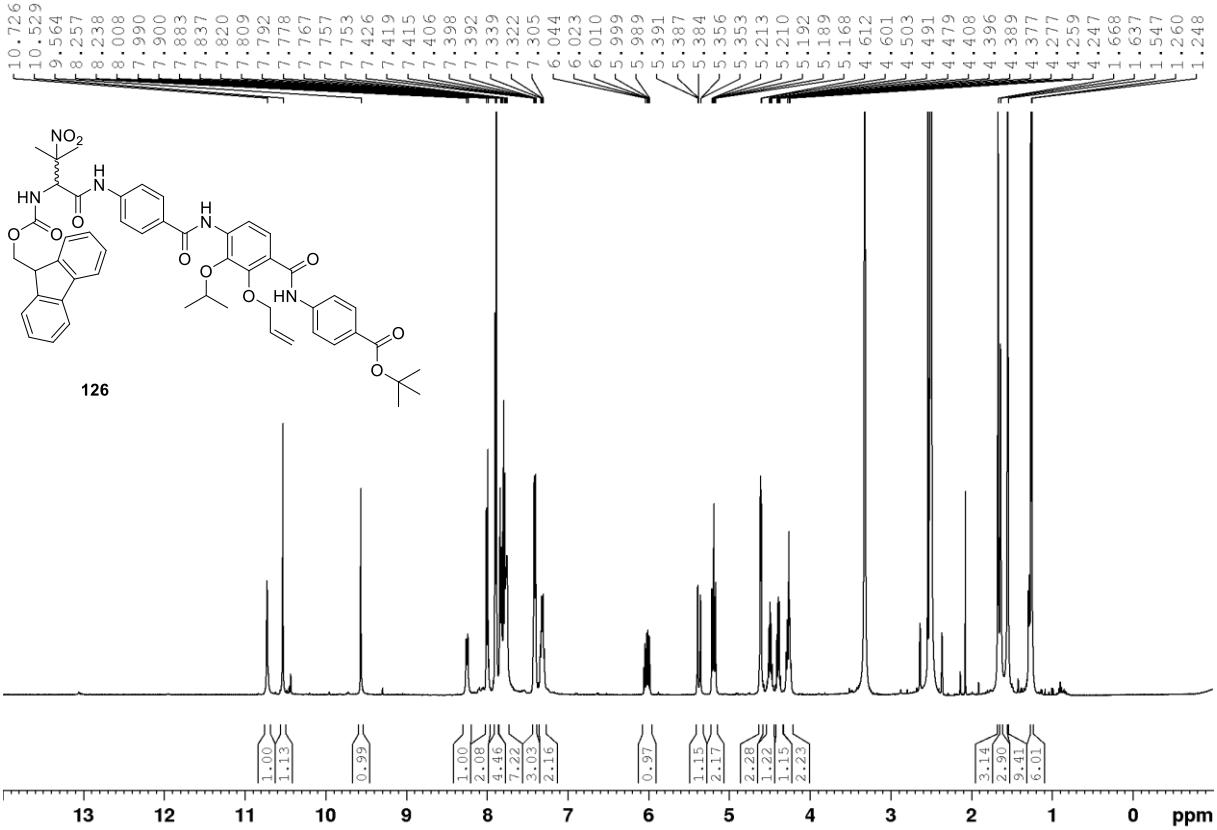

171.218
166.218
164.590
164.533
164.439
164.287
149.520
143.023
142.512
142.100
141.528
138.692
135.651
133.649
132.512
130.090
129.269
128.627
128.487
128.412
127.083
126.022
123.619
119.477
118.920
118.833
118.748
118.292
117.805
114.032
80.341
76.244
74.298
60.336
29.996
27.856
22.334
19.309
19.250
147
220
200
180
160
140
120
100
80
60
40
20
0
ppm

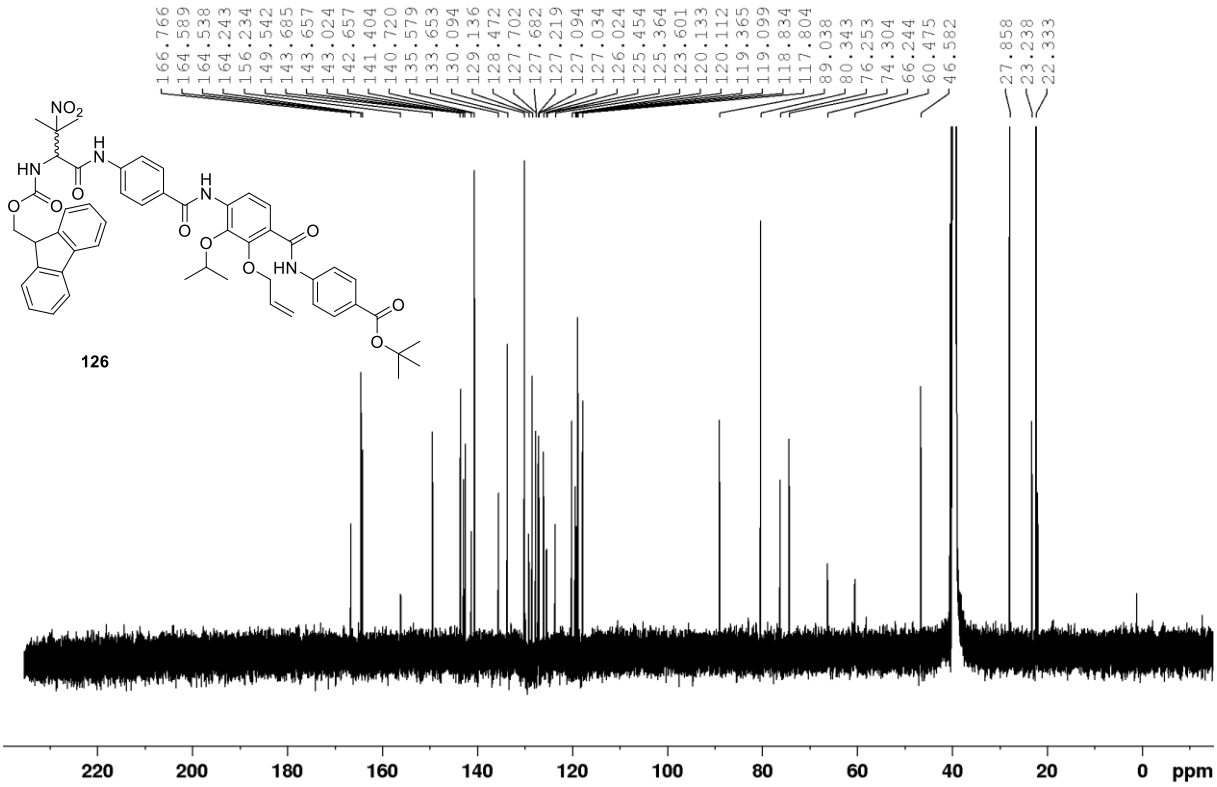

12.287
10.689
10.608
10.535
9.393
8.491
8.477
8.135
8.133
8.124
8.121
8.053
8.050
8.042
8.039
7.972
7.969
7.963
7.961
7.957
7.949
7.934
7.919
7.891
7.876
7.861
7.846
7.842
7.835
7.821
7.712
7.698
4.578
4.568
4.558
4.548
4.538
4.528
4.518
4.451
4.438
4.424
2.265
2.254
2.242
2.228
2.217
2.206
1.554
1.272
1.270
1.262
1.260
1.040
1.029
153
1.00
1.09
0.92
1.05
1.02
1.10
2.03
1.97
4.23
2.08
2.19
5.05
0.98
1.06
1.08
1.09
9.35
6.30
6.28
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

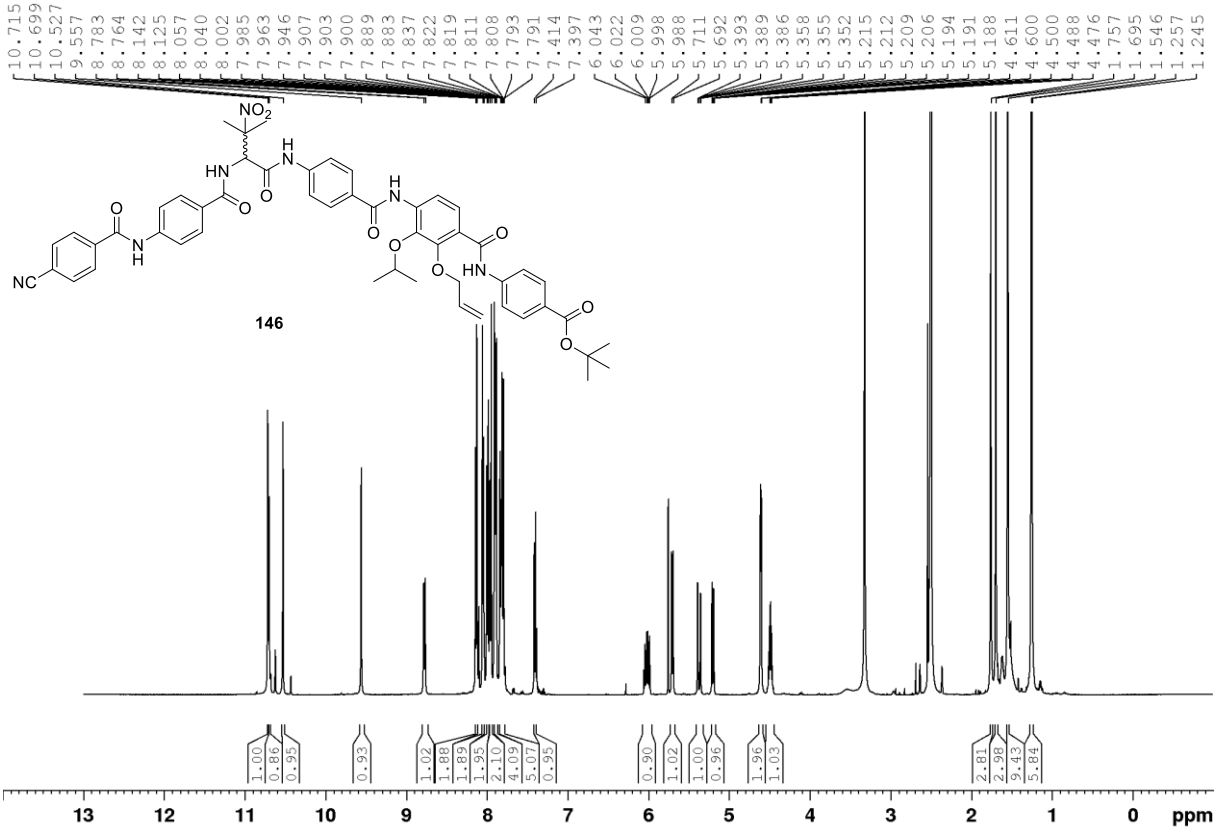

171.246
168.462
166.220
164.548
164.438
164.192
154.113
142.207
142.003
141.528
138.692
137.031
136.280
132.511
129.905
129.266
128.626
128.489
128.411
126.807
122.839
120.670
119.476
118.826
118.292
114.030
112.413
112.137
80.491
74.842
60.332
30.001
27.845
22.302
19.311
19.242
153
220
200
180
160
140
120
100
80
60
40
20
0
ppm

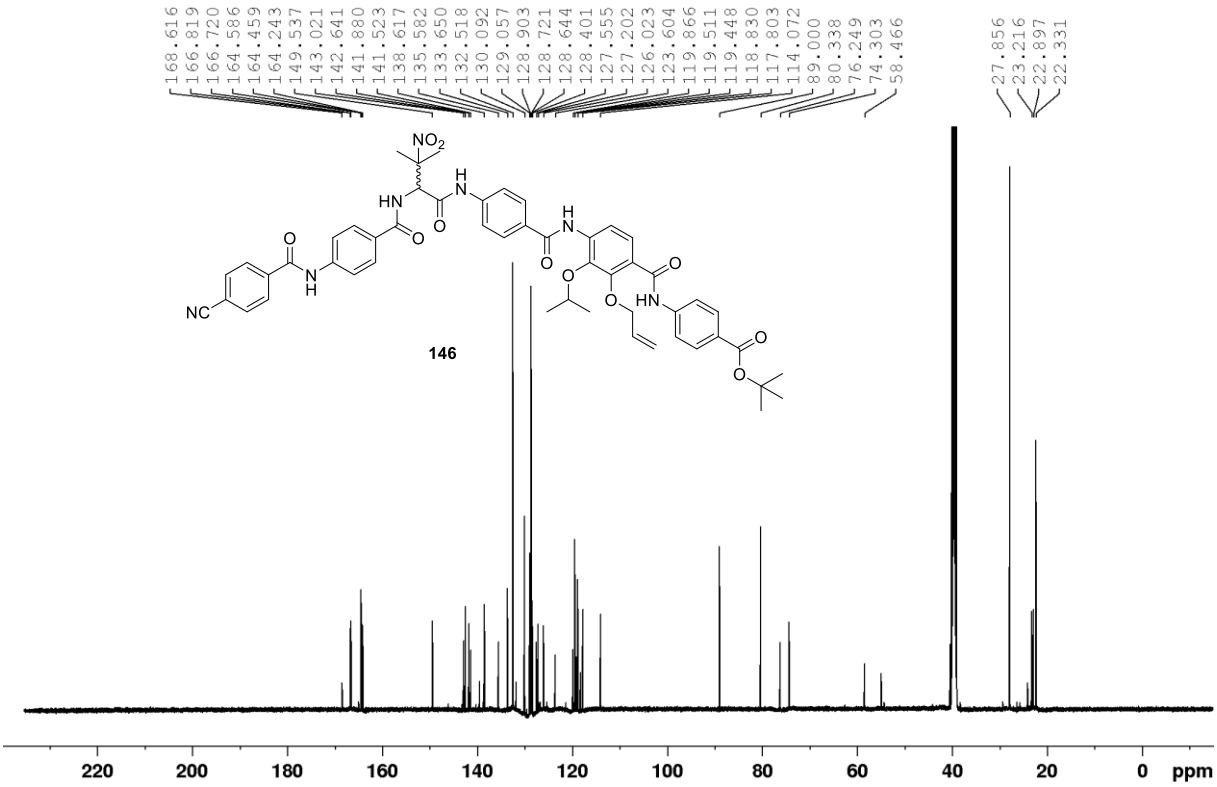

12.816
12.296
10.689
10.602
10.536
9.398
8.494
8.478
8.138
8.121
8.055
8.039
7.975
7.968
7.960
7.957
7.951
7.893
7.875
7.865
7.854
7.847
7.843
7.838
7.820
7.720
7.702
4.586
4.573
4.561
4.549
4.537
4.524
4.512
4.455
4.439
4.422
2.284
2.271
2.258
2.244
2.228
2.214
2.201
2.188
1.275
1.263
1.042
1.028
1.005
0.991
TSG18
0.82
0.80
0.92
0.83
0.93
0.85
1.00
1.85
1.75
5.59
6.67
0.94
1.00
1.03
1.05
5.89
6.10
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

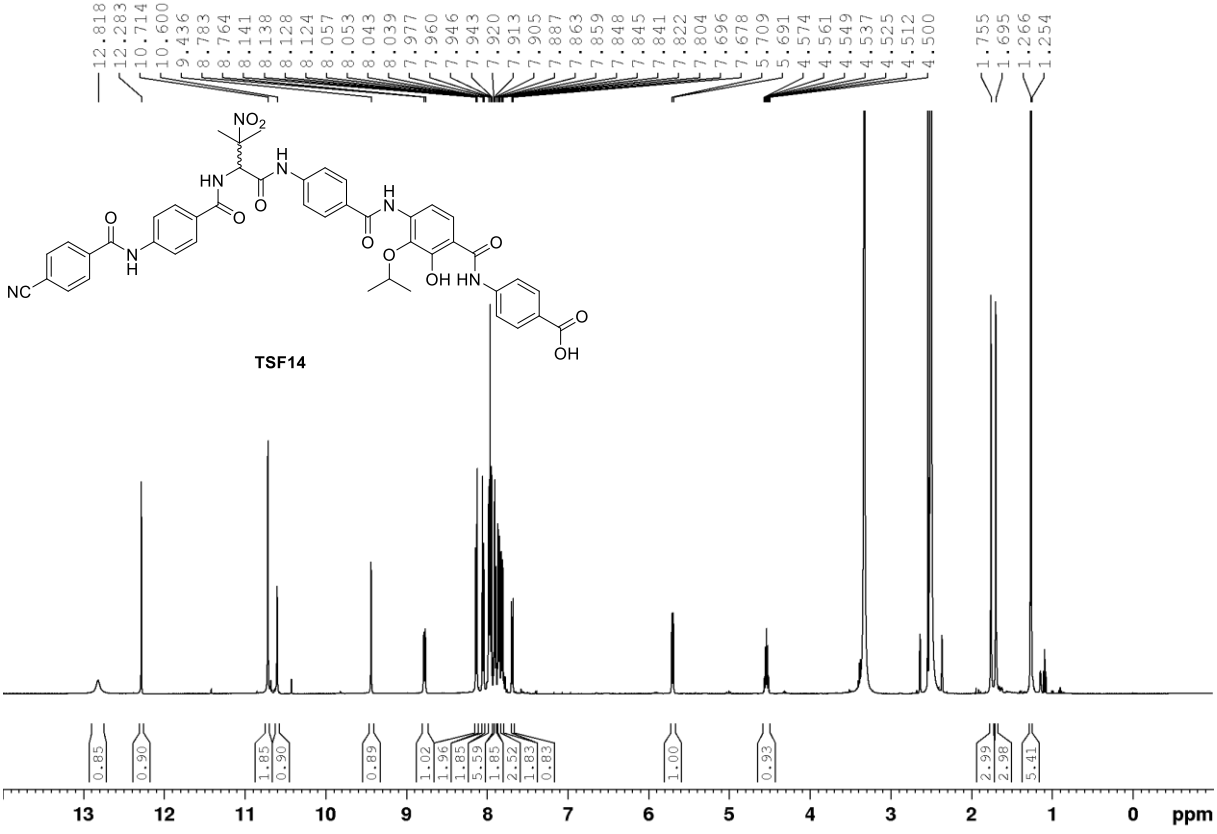

171.249
168.493
166.859
166.218
164.435
164.196
154.100
142.211
141.975
141.530
138.693
138.636
137.042
136.278
132.512
130.199
129.265
128.628
128.493
128.418
126.254
122.825
120.714
119.472
118.822
118.292
114.031
112.408
112.152
74.848
60.337
30.000
22.305
19.317
19.245
15.170
TSG18
220
200
180
160
140
120
100
80
60
40
20
0
ppm

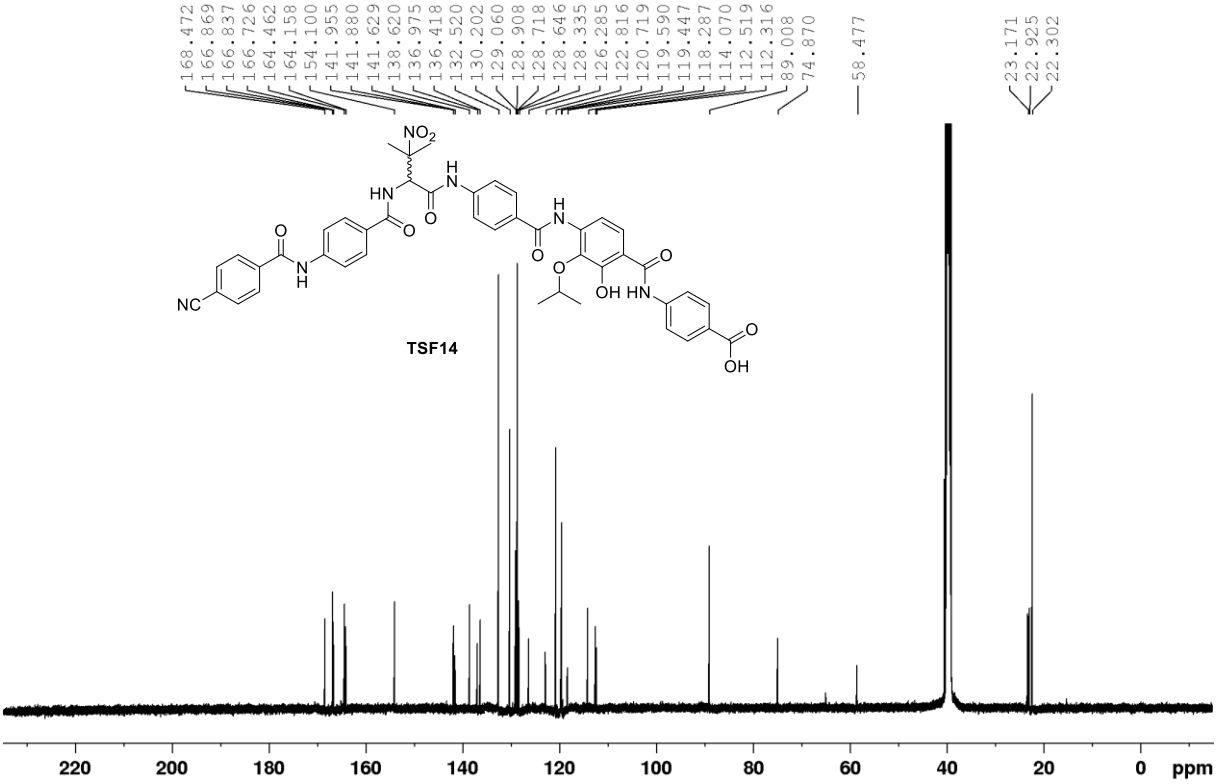

10.726
10.529
9.564
8.257
8.238
8.008
7.990
7.900
7.883
7.837
7.820
7.809
7.792
7.778
7.767
7.757
7.753
7.426
7.419
7.415
7.406
7.398
7.392
7.339
7.322
7.305
6.044
6.023
6.010
5.999
5.989
5.391
5.387
5.384
5.356
5.353
5.213
5.210
5.192
5.189
5.168
4.612
4.601
4.503
4.491
4.479
4.408
4.396
4.389
4.377
4.277
4.259
4.247
1.668
1.637
1.547
1.260
1.248
126
1.00
1.13
0.99
1.00
2.08
4.46
7.22
3.03
2.16
0.97
1.15
2.17
2.28
1.22
1.15
2.23
3.14
2.90
9.41
6.01
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

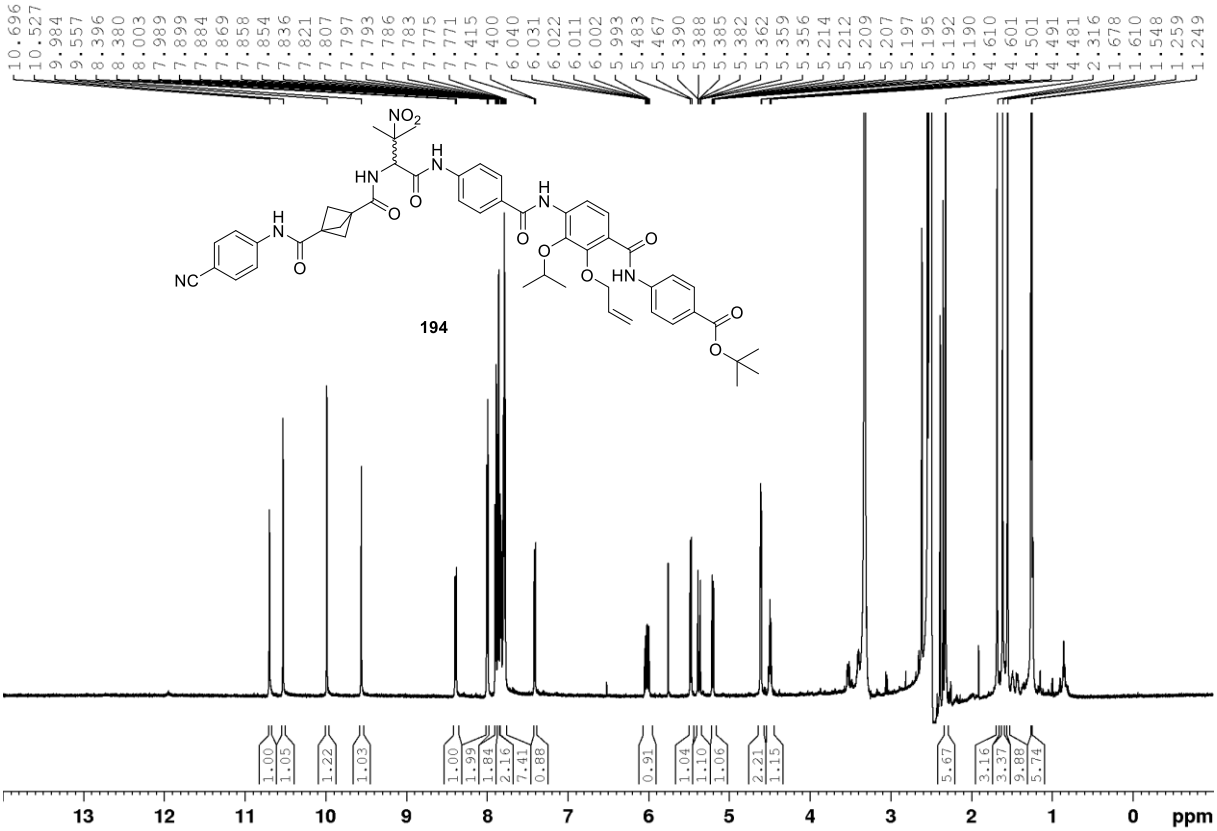

166.766
164.589
164.538
164.243
156.234
149.542
143.685
143.657
143.024
142.657
141.404
140.720
135.579
133.653
130.094
129.136
128.472
127.702
127.682
127.219
127.094
127.034
126.024
125.454
125.364
123.601
120.133
120.112
119.365
119.099
118.834
117.804
89.038
80.343
76.253
74.304
66.244
60.475
46.582
27.858
23.238
22.333
126
220
200
180
160
140
120
100
80
60
40
20
0
ppm

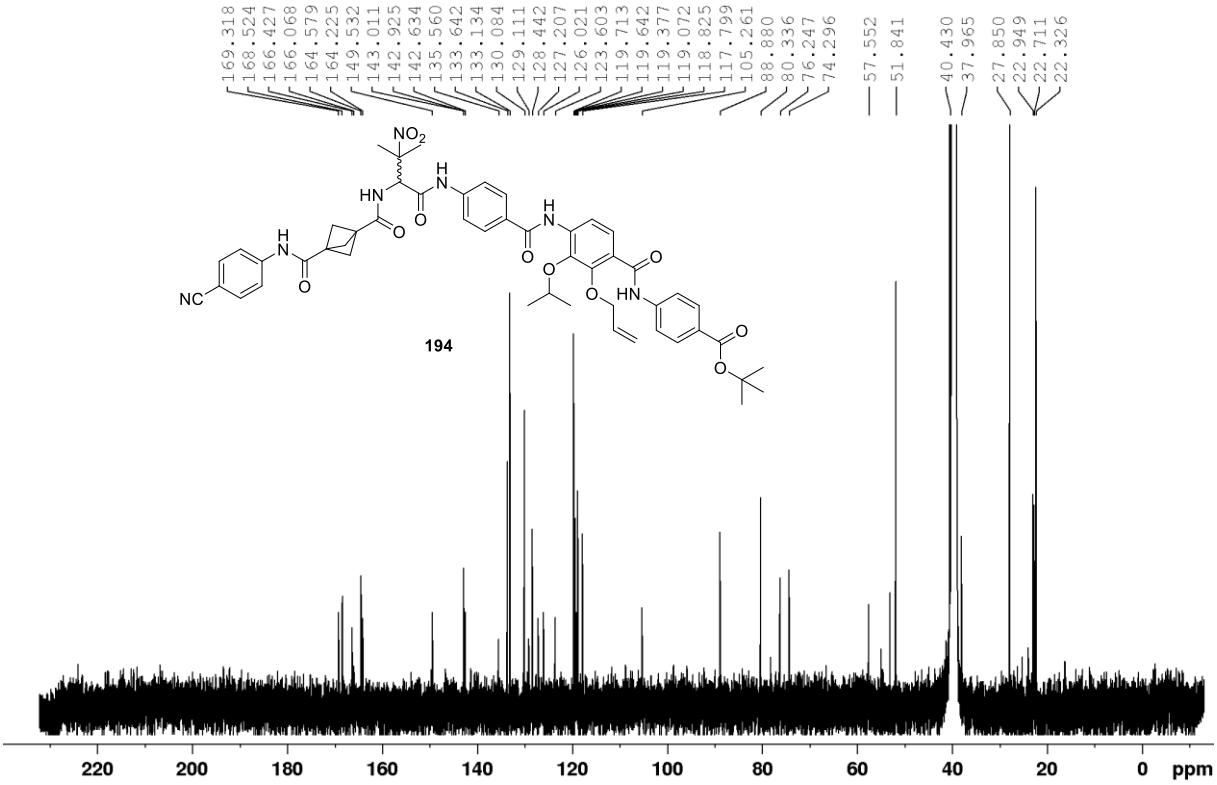

10.715
10.699
10.527
9.557
8.783
8.764
8.142
8.125
8.057
8.040
8.002
7.985
7.963
7.946
7.907
7.903
7.900
7.889
7.883
7.837
7.822
7.819
7.811
7.808
7.793
7.791
7.414
7.397
6.043
6.022
6.009
5.998
5.988
5.711
5.692
5.393
5.389
5.386
5.358
5.355
5.352
5.215
5.212
5.209
5.206
5.194
5.191
5.188
4.611
4.600
4.500
4.488
4.476
1.757
1.695
1.546
1.257
1.245
146
1.00
0.86
0.95
0.93
1.02
1.88
1.89
1.95
2.10
4.09
5.07
0.95
0.90
1.02
1.00
0.96
1.96
1.03
2.81
2.98
9.43
5.84
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

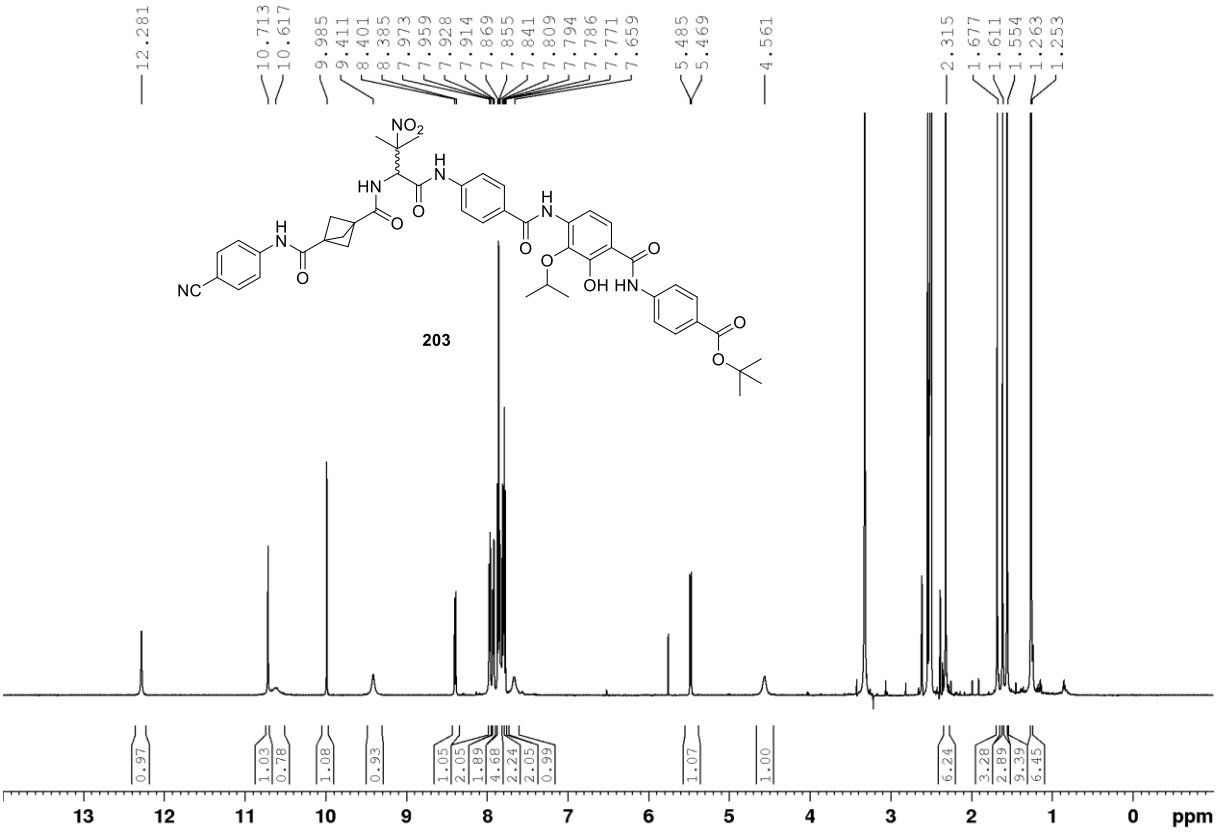

168.616
166.819
166.720
164.586
164.459
164.243
149.537
143.021
142.641
141.880
141.523
138.617
135.582
133.650
132.518
130.092
129.057
128.903
128.721
128.644
128.401
127.555
127.202
126.023
123.604
119.866
119.511
119.448
118.830
117.803
114.072
89.000
80.338
76.249
74.303
58.466
27.856
23.216
22.897
22.331
146
220
200
180
160
140
120
100
80
60
40
20
0
ppm

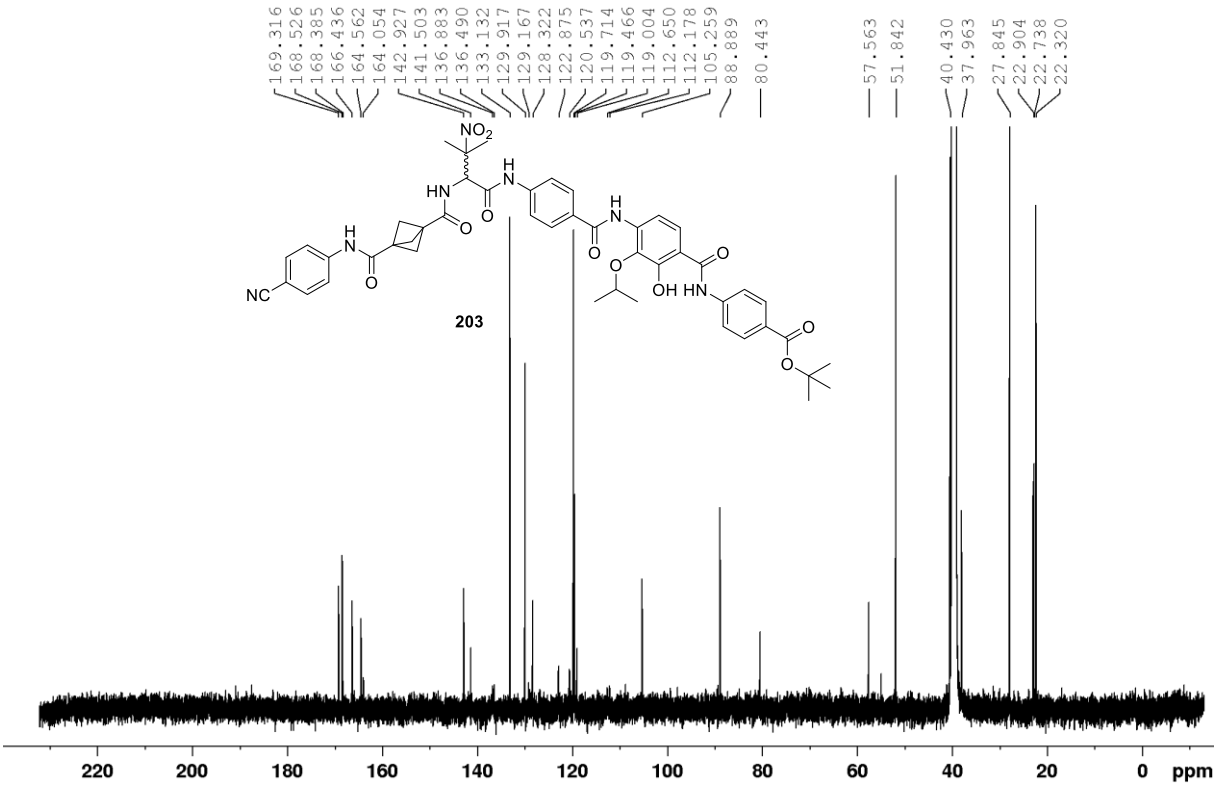

12.818
12.283
10.714
10.600
9.436
8.783
8.764
8.141
8.138
8.128
8.124
8.057
8.053
8.043
8.039
7.977
7.960
7.946
7.943
7.920
7.913
7.905
7.887
7.863
7.859
7.848
7.845
7.841
7.822
7.804
7.696
7.678
5.709
5.691
4.574
4.561
4.549
4.537
4.525
4.512
4.500
1.755
1.695
1.266
1.254
TSF14
0.85
0.90
1.85
0.90
0.89
1.02
1.96
1.85
5.59
1.85
2.52
1.83
0.83
1.00
0.93
2.99
2.98
5.41
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

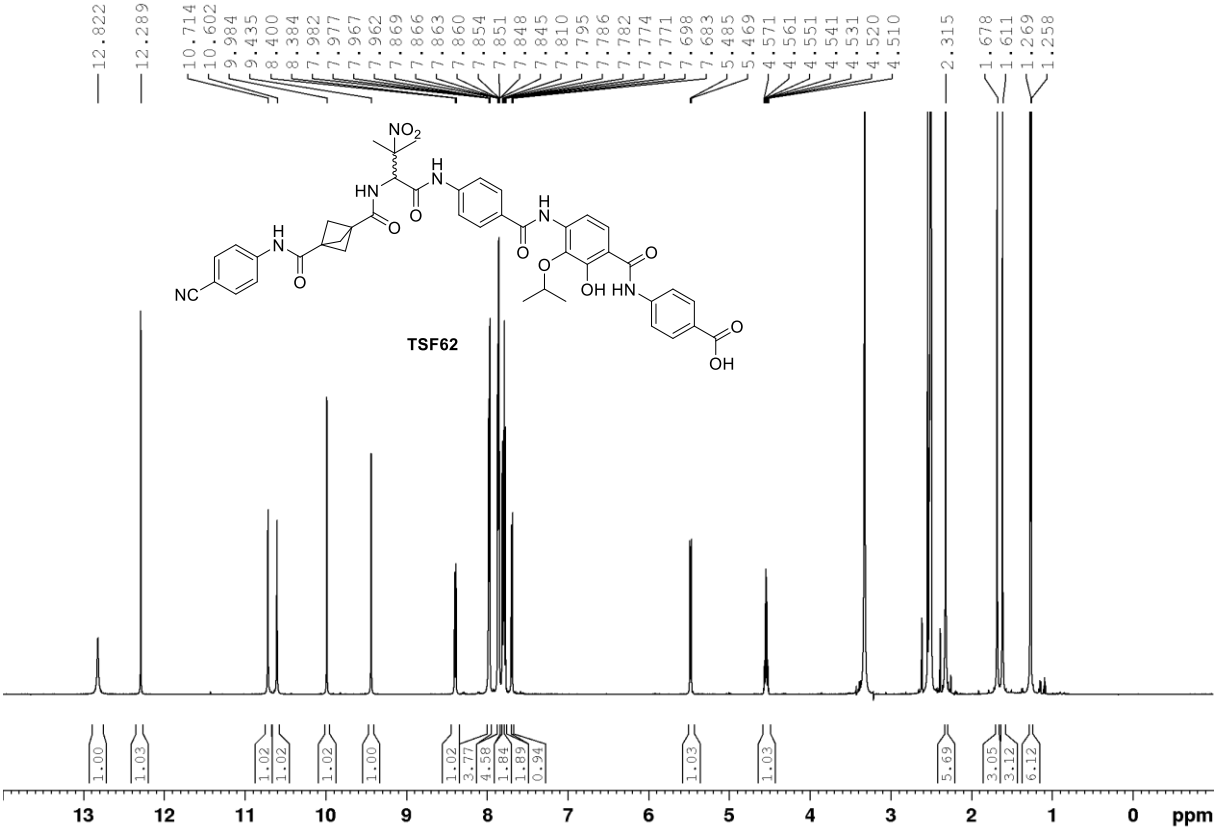

168.472
166.869
166.837
166.726
164.462
164.158
154.100
141.955
141.880
141.629
138.620
136.975
136.418
132.520
130.202
129.060
128.908
128.718
128.646
128.335
126.285
122.816
120.719
119.590
119.447
118.287
114.070
112.519
112.316
89.008
74.870
58.477
23.171
22.925
22.302
TSF14
220
200
180
160
140
120
100
80
60
40
20
0
ppm

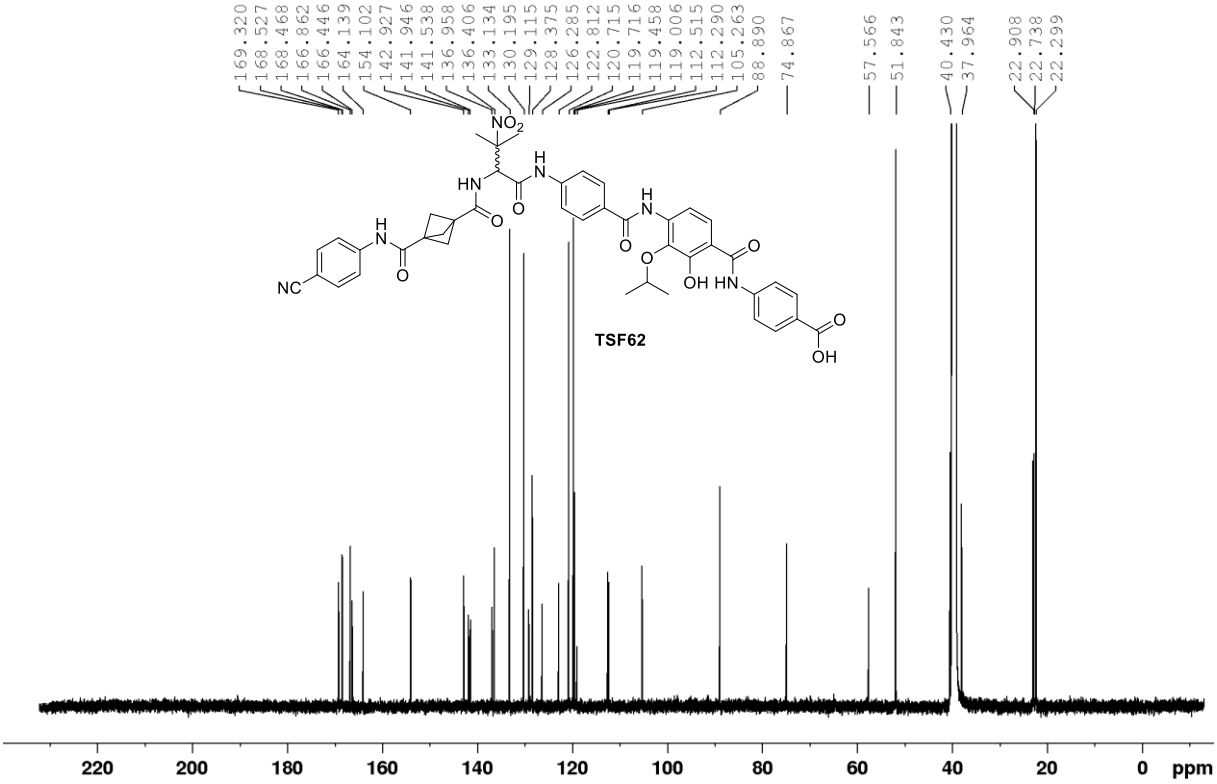

10.696
10.527
9.984
9.557
8.396
8.380
8.003
7.989
7.899
7.884
7.869
7.858
7.854
7.836
7.821
7.807
7.797
7.793
7.786
7.783
7.775
7.771
7.415
7.400
6.040
6.031
6.022
6.011
6.002
5.993
5.483
5.467
5.390
5.388
5.385
5.382
5.362
5.359
5.356
5.214
5.212
5.209
5.207
5.197
5.195
5.192
5.190
4.610
4.601
4.501
4.491
4.481
2.316
1.678
1.610
1.548
1.259
1.249
194
1.00
1.05
1.22
1.03
1.00
1.99
1.84
2.16
7.41
0.88
0.91
1.04
1.10
1.06
2.21
1.15
5.67
3.16
3.37
9.88
5.74
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

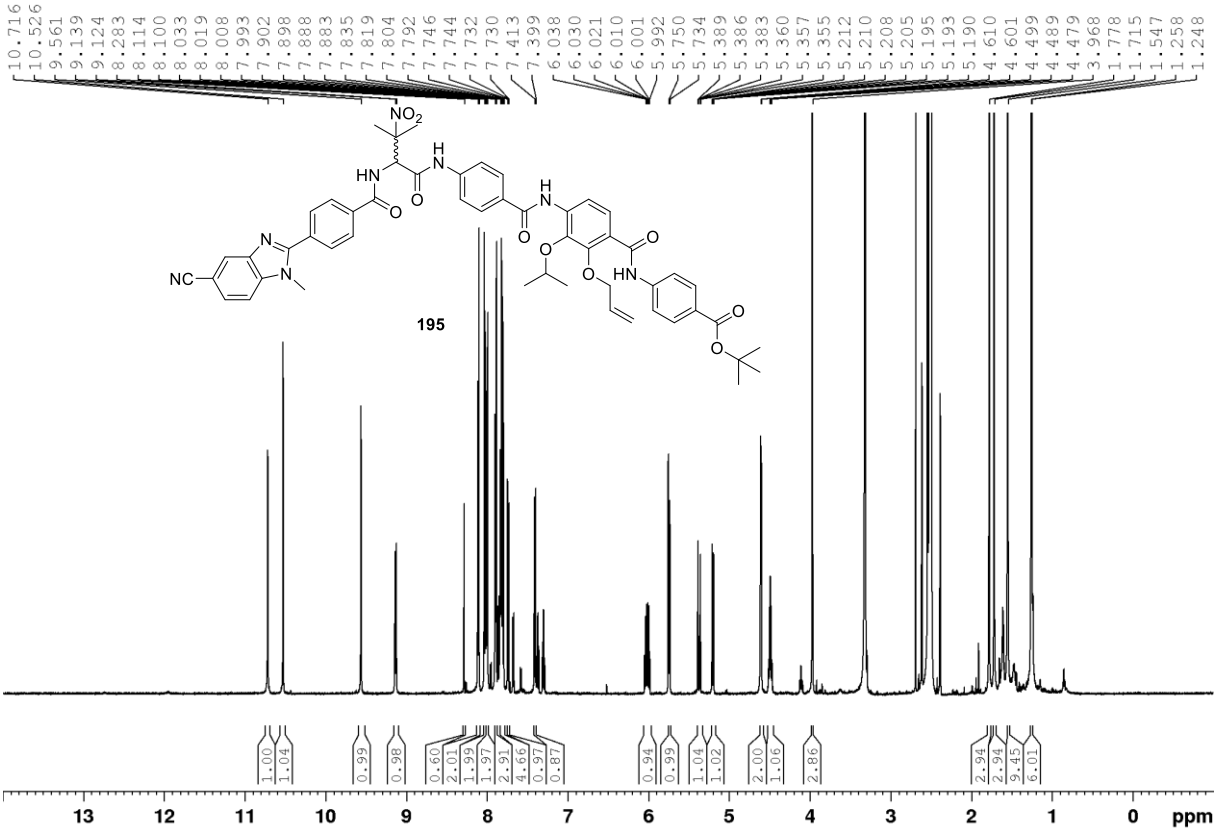

169.318
168.524
166.427
166.068
164.579
164.225
149.532
143.011
142.925
142.634
135.560
133.642
133.134
130.084
129.111
128.442
127.207
126.021
123.603
119.713
119.642
119.377
119.072
118.825
117.799
105.261
88.880
80.336
76.247
74.296
57.552
51.841
40.430
37.965
27.850
22.949
22.711
22.326
194
220
200
180
160
140
120
100
80
60
40
20
0
ppm

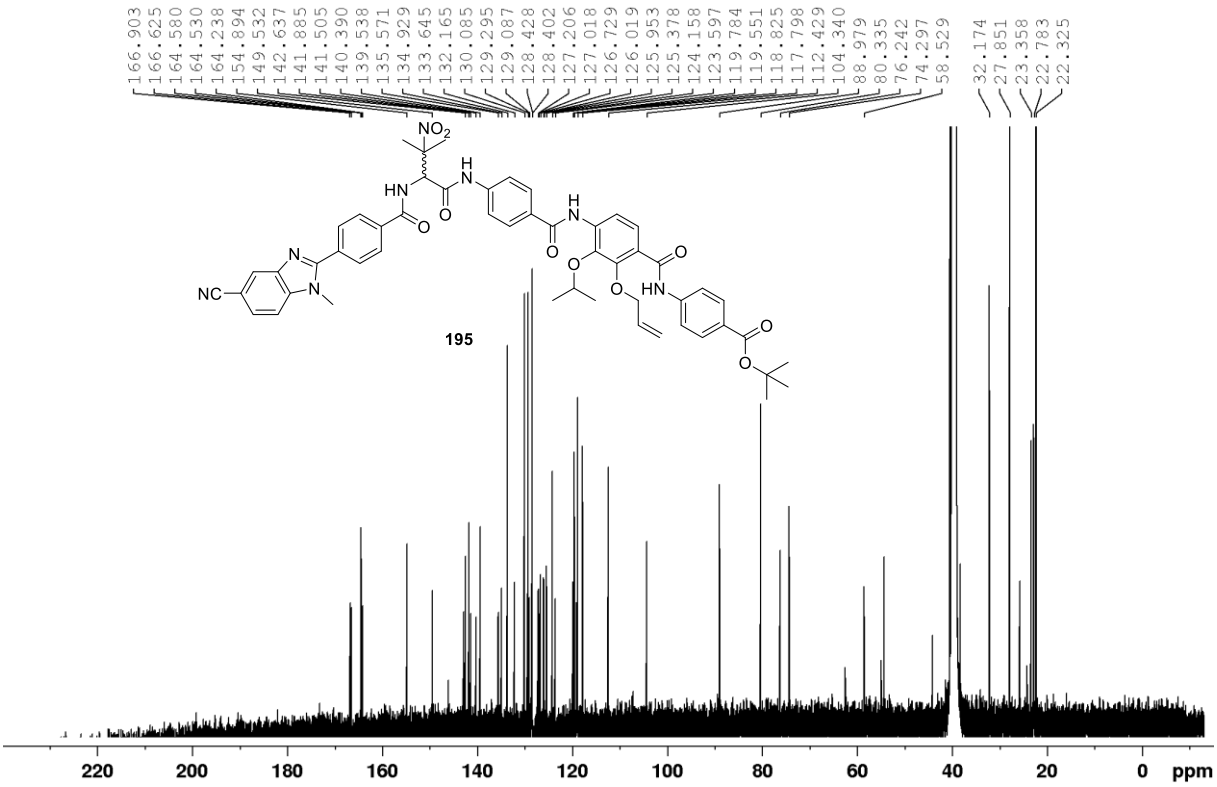

12.281
10.713
10.617
9.985
9.411
8.401
8.385
7.973
7.959
7.928
7.914
7.869
7.855
7.841
7.809
7.794
7.786
7.771
7.659
5.485
5.469
4.561
2.315
1.677
1.611
1.554
1.263
1.253
203
0.97
1.03
0.78
1.08
0.93
1.05
2.05
1.89
4.68
2.24
2.05
0.99
1.07
1.00
6.24
3.28
2.89
9.39
6.45
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

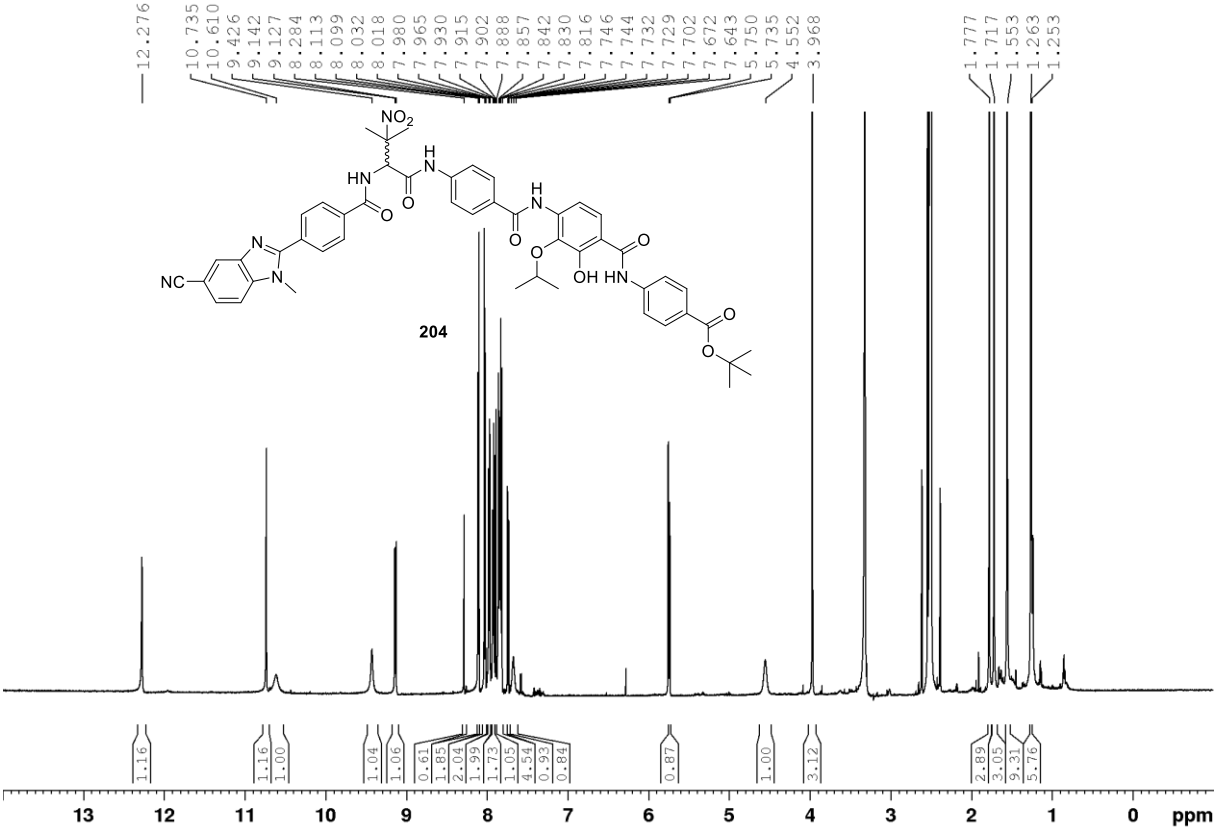

169.316
168.526
168.385
166.436
164.562
164.054
142.927
141.503
136.883
136.490
133.132
129.917
129.167
128.322
122.875
120.537
119.714
119.466
119.004
112.650
112.178
105.259
88.889
80.443
57.563
51.842
40.430
37.963
27.845
22.904
22.738
22.320
203
220
200
180
160
140
120
100
80
60
40
20
0
ppm

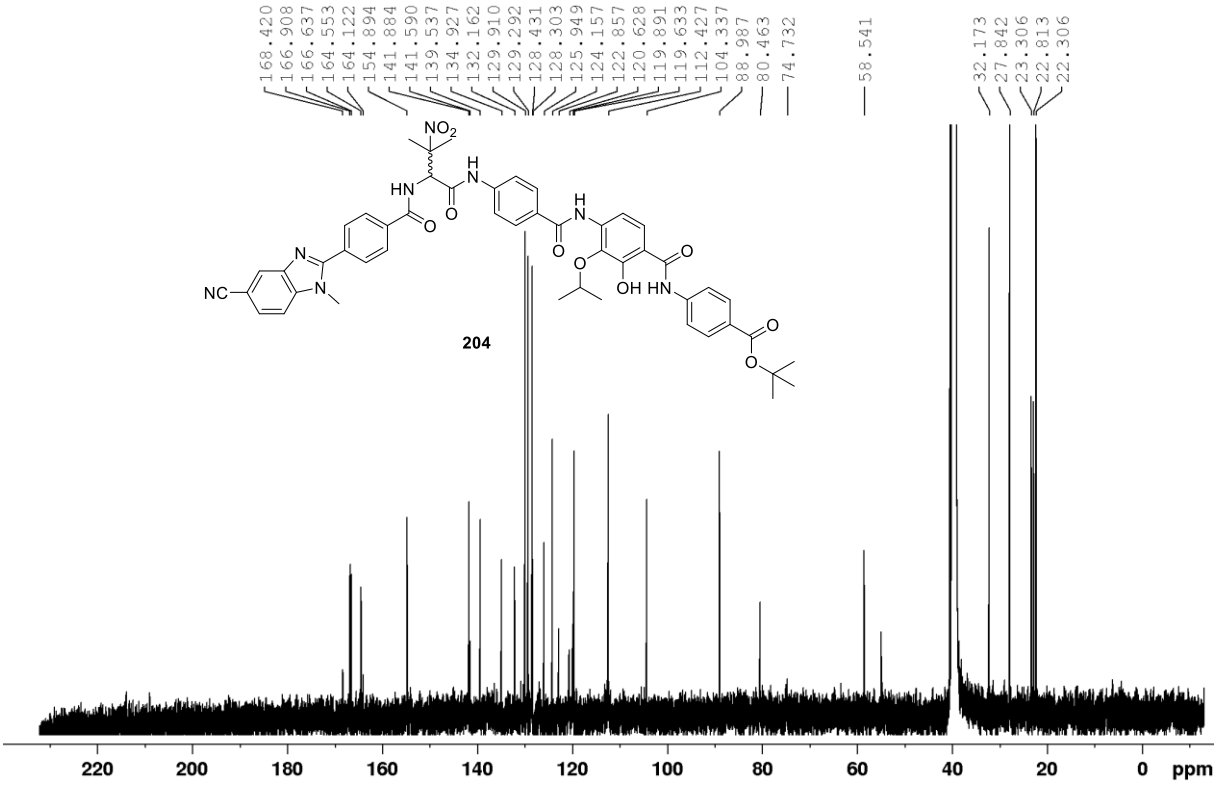

12.822
12.289
10.714
10.602
9.984
9.435
8.400
8.384
7.982
7.977
7.967
7.962
7.869
7.866
7.863
7.860
7.854
7.851
7.848
7.845
7.810
7.795
7.786
7.782
7.774
7.771
7.698
7.683
5.485
5.469
4.571
4.561
4.551
4.541
4.531
4.520
4.510
2.315
1.678
1.611
1.269
1.258
TSF62
1.00
1.03
1.02
1.02
1.02
1.00
1.02
3.77
4.58
1.84
1.89
0.94
1.03
1.03
5.69
3.05
3.12
6.12
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

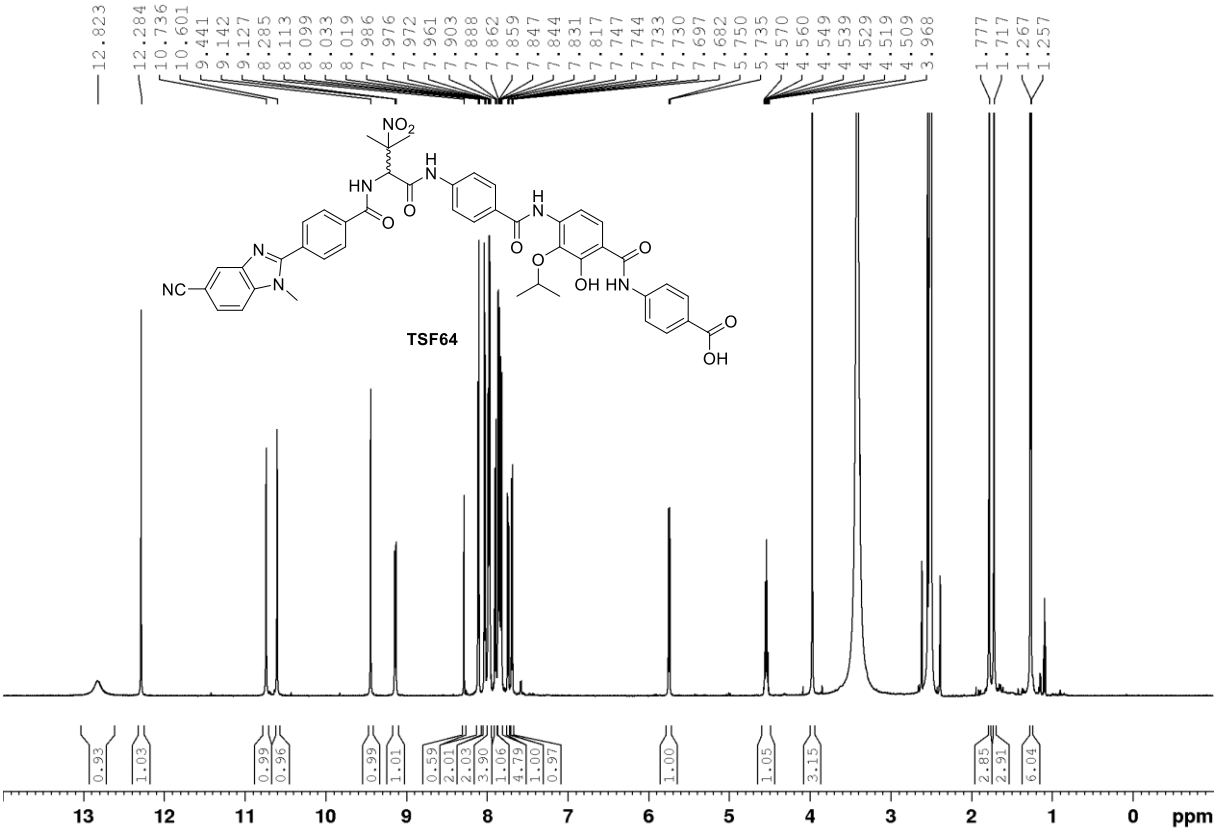

169.320
168.527
168.468
166.862
166.446
164.139
154.102
142.927
141.946
141.538
136.958
136.406
133.134
130.195
129.115
128.375
126.285
122.812
120.715
119.716
119.458
119.006
112.515
112.290
105.263
88.890
74.867
57.566
51.843
40.430
37.964
22.908
22.738
22.299
TSF62
220
200
180
160
140
120
100
80
60
40
20
0
ppm

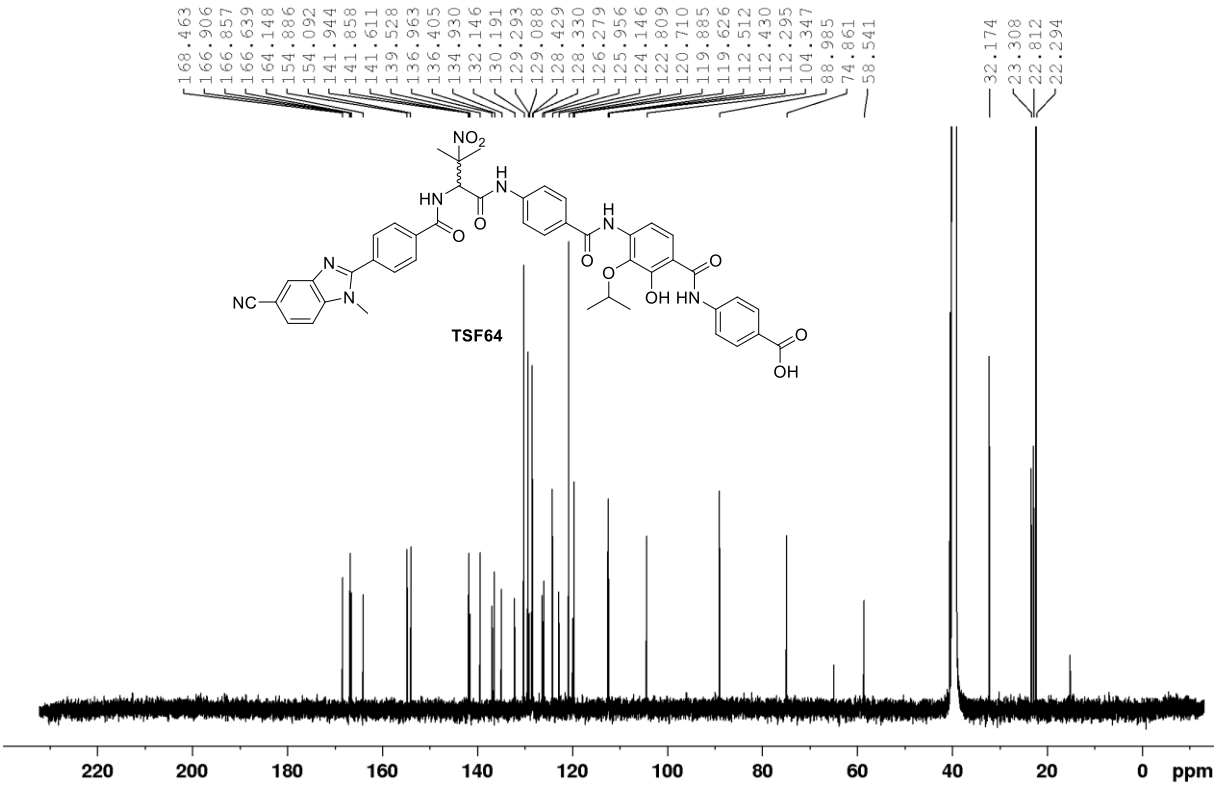

10.716
10.526
9.561
9.139
9.124
8.283
8.114
8.100
8.033
8.019
8.008
7.993
7.902
7.898
7.888
7.883
7.835
7.819
7.804
7.792
7.746
7.744
7.732
7.730
7.413
7.399
6.038
6.030
6.021
6.010
6.001
5.992
5.750
5.734
5.389
5.386
5.383
5.360
5.357
5.355
5.212
5.210
5.208
5.205
5.195
5.193
5.190
4.610
4.601
4.499
4.489
4.479
3.968
1.778
1.715
1.547
1.258
1.248
195
1.00
1.04
0.99
0.98
0.60
2.01
1.99
1.97
2.91
4.66
0.97
0.87
0.94
0.99
1.04
1.02
2.00
1.06
2.86
2.94
2.94
9.45
6.01
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

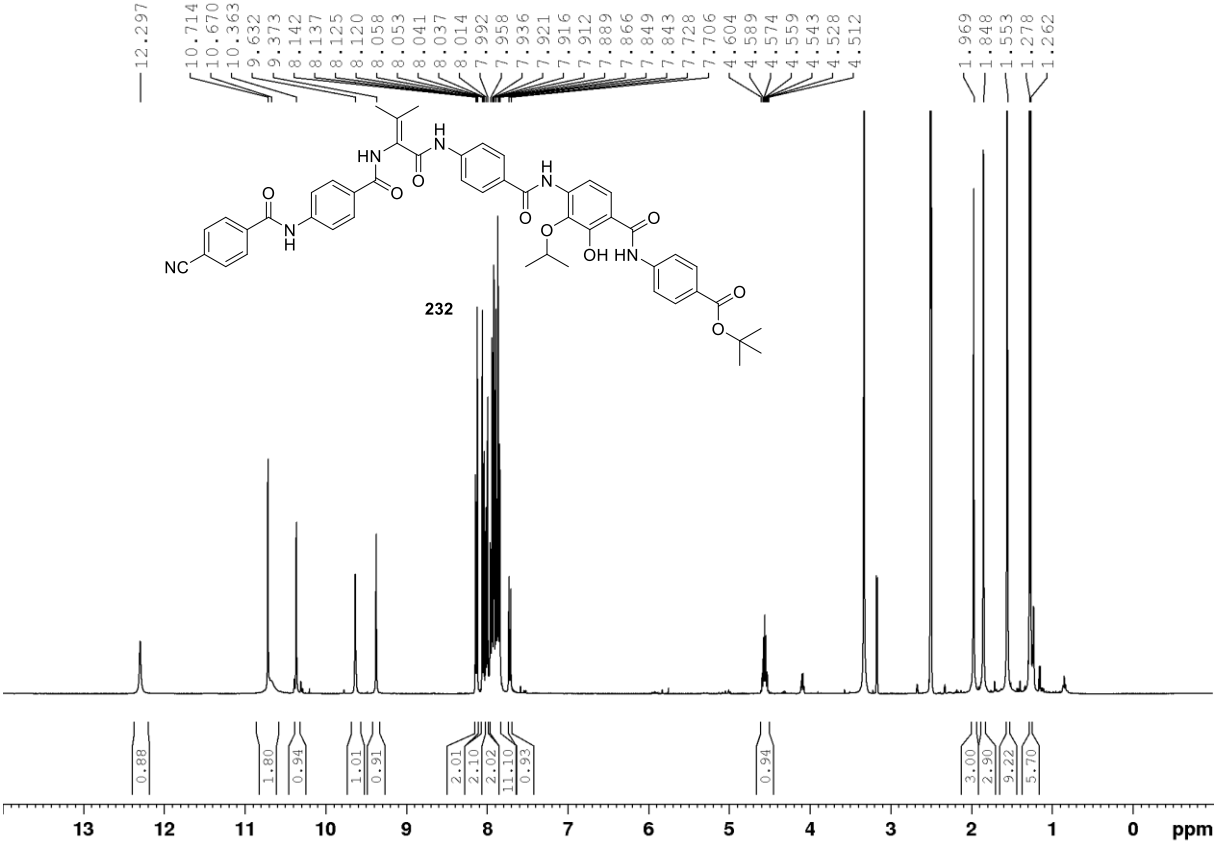

166.903
166.625
164.580
164.530
164.238
154.894
149.532
142.637
141.885
141.505
140.390
139.538
135.571
134.929
133.645
132.165
130.085
129.295
129.087
128.428
128.402
127.206
127.018
126.729
126.019
125.953
125.378
124.158
123.597
119.784
119.551
118.825
117.798
112.429
104.340
88.979
80.335
76.242
74.297
58.529
32.174
27.851
23.358
22.783
22.325
195
220
200
180
160
140
120
100
80
60
40
20
0
ppm

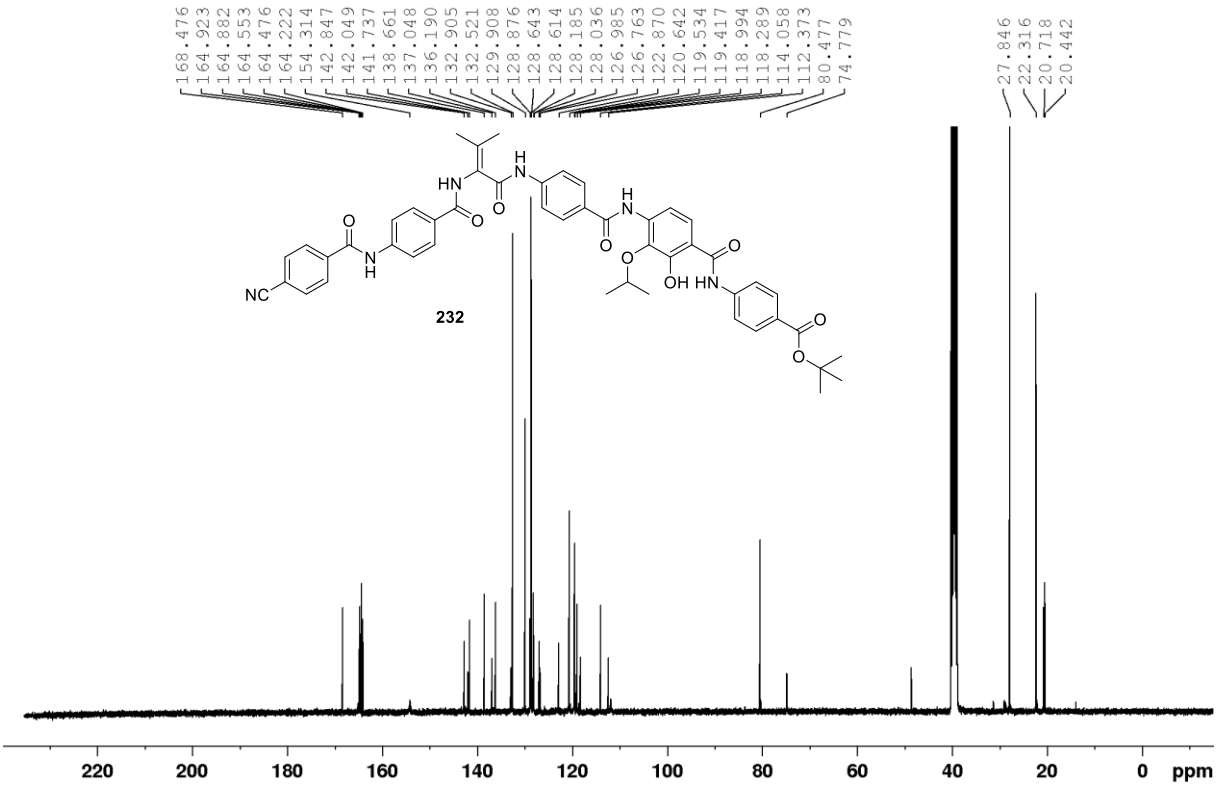

12.276
10.735
10.610
9.426
9.142
9.127
8.284
8.113
8.099
8.032
8.018
7.980
7.965
7.930
7.915
7.902
7.888
7.857
7.842
7.830
7.816
7.746
7.744
7.732
7.729
7.702
7.672
7.643
5.750
5.735
4.552
3.968
1.777
1.717
1.553
1.263
1.253
204
1.16
1.16
1.00
1.04
1.06
0.61
1.85
2.04
1.99
1.73
1.05
4.54
0.93
0.84
0.87
1.00
3.12
2.89
3.05
9.31
5.76
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

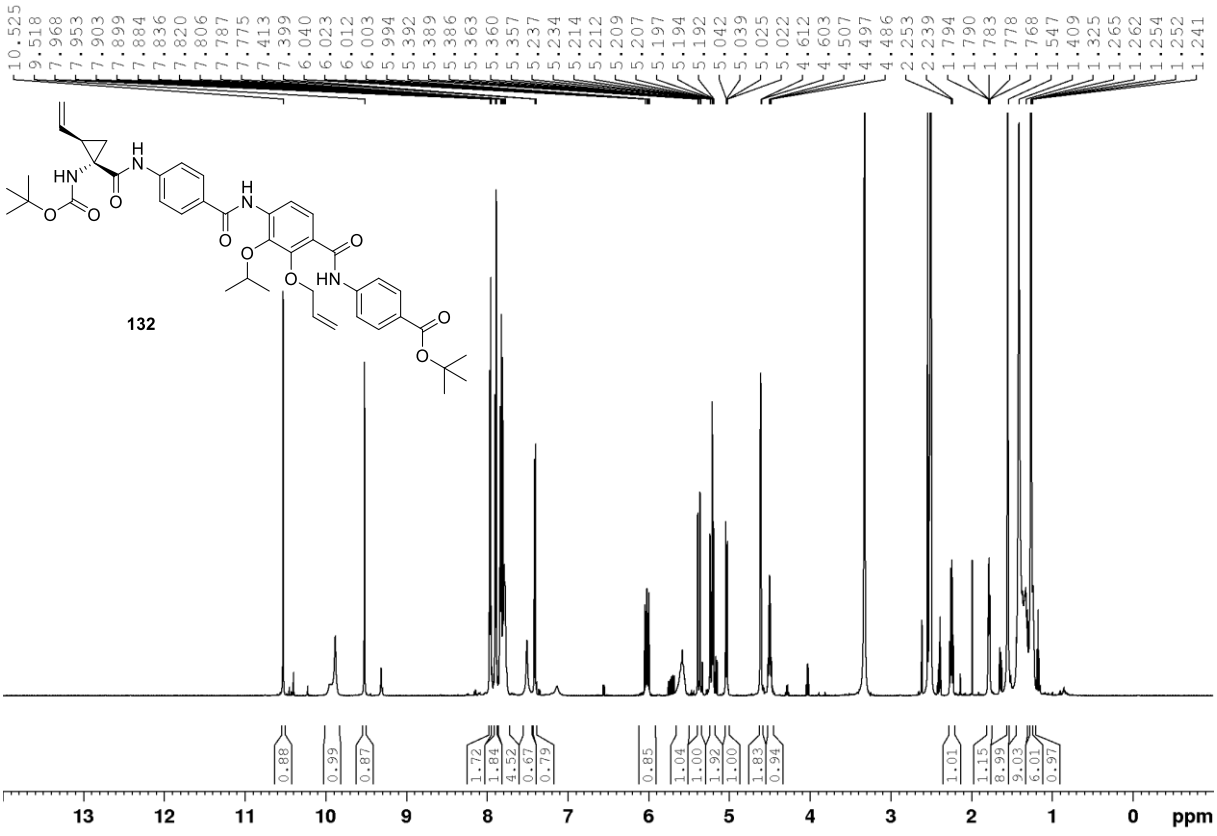

168.420
166.908
166.637
164.553
164.122
154.894
141.884
141.590
139.537
134.927
132.162
129.910
129.292
128.431
128.303
125.949
124.157
122.857
120.628
119.891
119.633
112.427
104.337
88.987
80.463
74.732
58.541
32.173
27.842
23.306
22.813
22.306
204
220
200
180
160
140
120
100
80
60
40
20
0
ppm

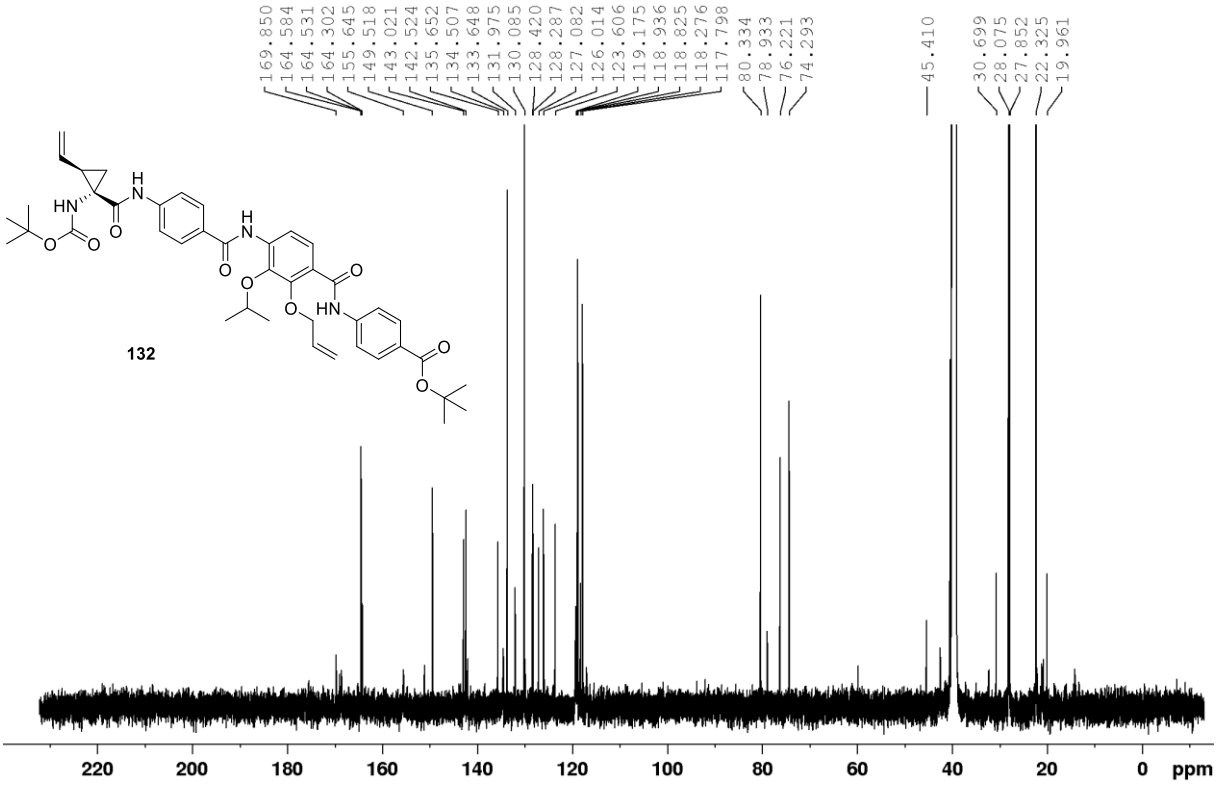

12.823
12.284
10.736
10.601
9.441
9.142
9.127
8.285
8.113
8.099
8.033
8.019
7.986
7.976
7.972
7.961
7.903
7.888
7.862
7.859
7.847
7.844
7.831
7.817
7.747
7.744
7.733
7.730
7.697
7.682
5.750
5.735
4.570
4.560
4.549
4.539
4.529
4.519
4.509
3.968
1.777
1.717
1.267
1.257
TSF64
0.93
1.03
0.99
0.96
0.99
1.01
0.59
2.01
2.03
3.90
1.06
4.79
1.00
0.97
1.00
1.05
3.15
2.85
2.91
6.04
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

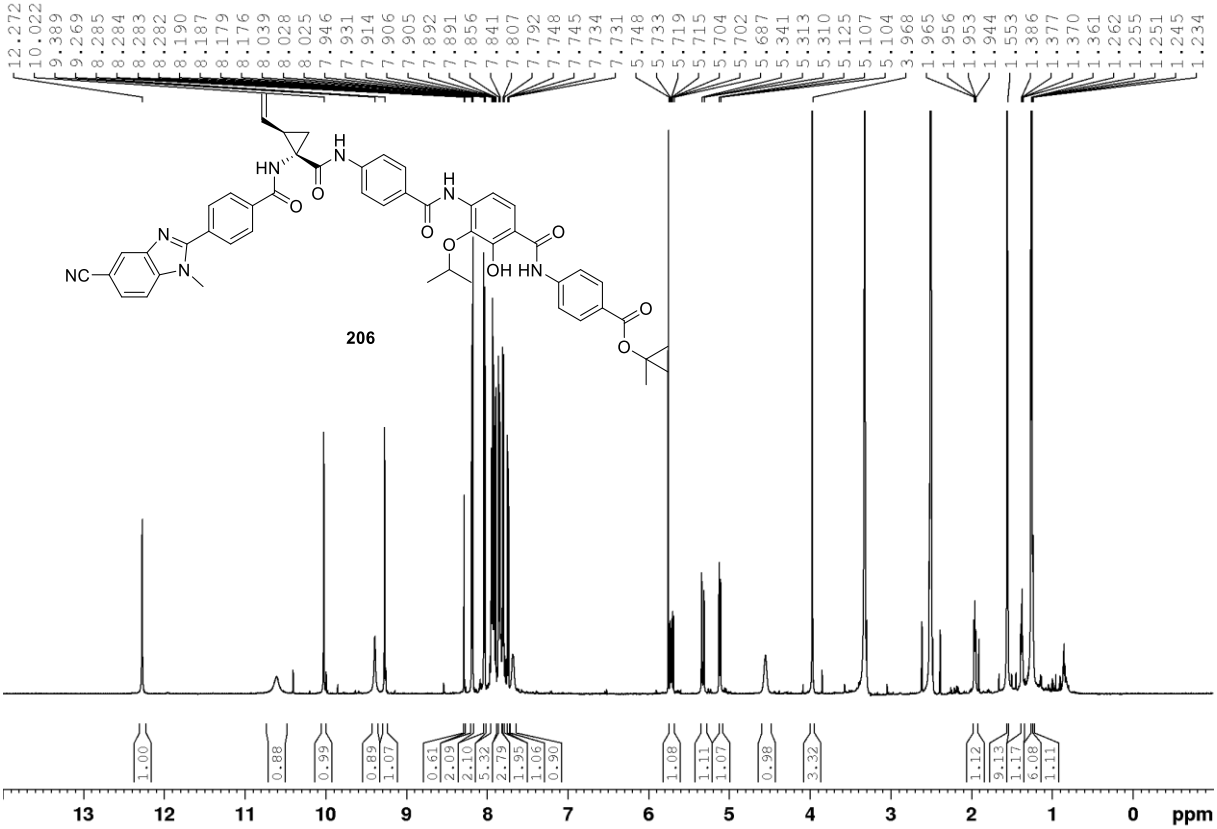

168.463
166.906
166.857
166.639
164.148
154.886
154.092
141.944
141.858
141.611
139.528
136.963
136.405
134.930
132.146
130.191
129.293
129.088
128.429
128.330
126.279
125.956
124.146
122.809
120.710
119.885
119.626
112.512
112.430
112.295
104.347
88.985
74.861
58.541
32.174
23.308
22.812
22.294
TSF64
220
200
180
160
140
120
100
80
60
40
20
0
ppm

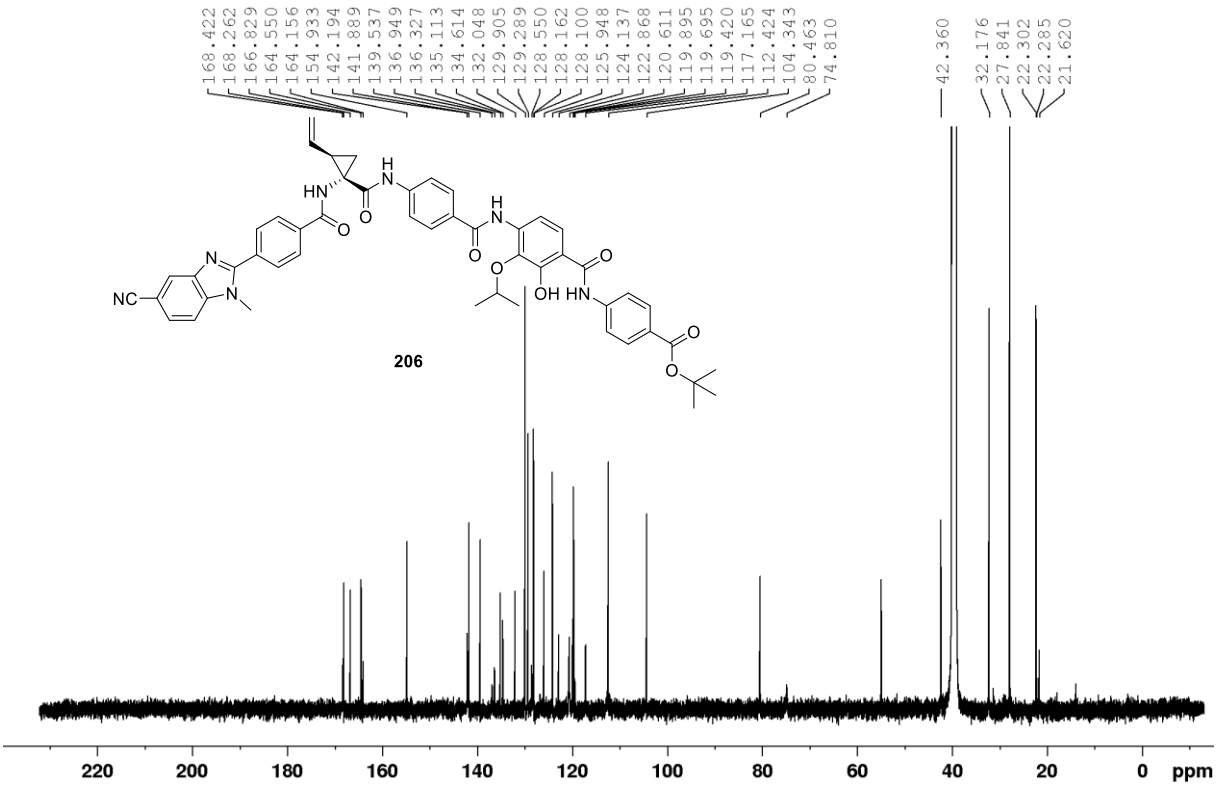

12.297
10.714
10.670
10.363
9.632
9.373
8.142
8.137
8.125
8.120
8.058
8.053
8.041
8.037
8.014
7.992
7.958
7.936
7.921
7.916
7.912
7.889
7.866
7.849
7.843
7.728
7.706
4.604
4.589
4.574
4.559
4.543
4.528
4.512
1.969
1.848
1.553
1.278
1.262
232
0.88
1.80
0.94
1.01
0.91
2.01
2.10
2.02
11.10
0.93
0.94
3.00
2.90
9.22
5.70
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

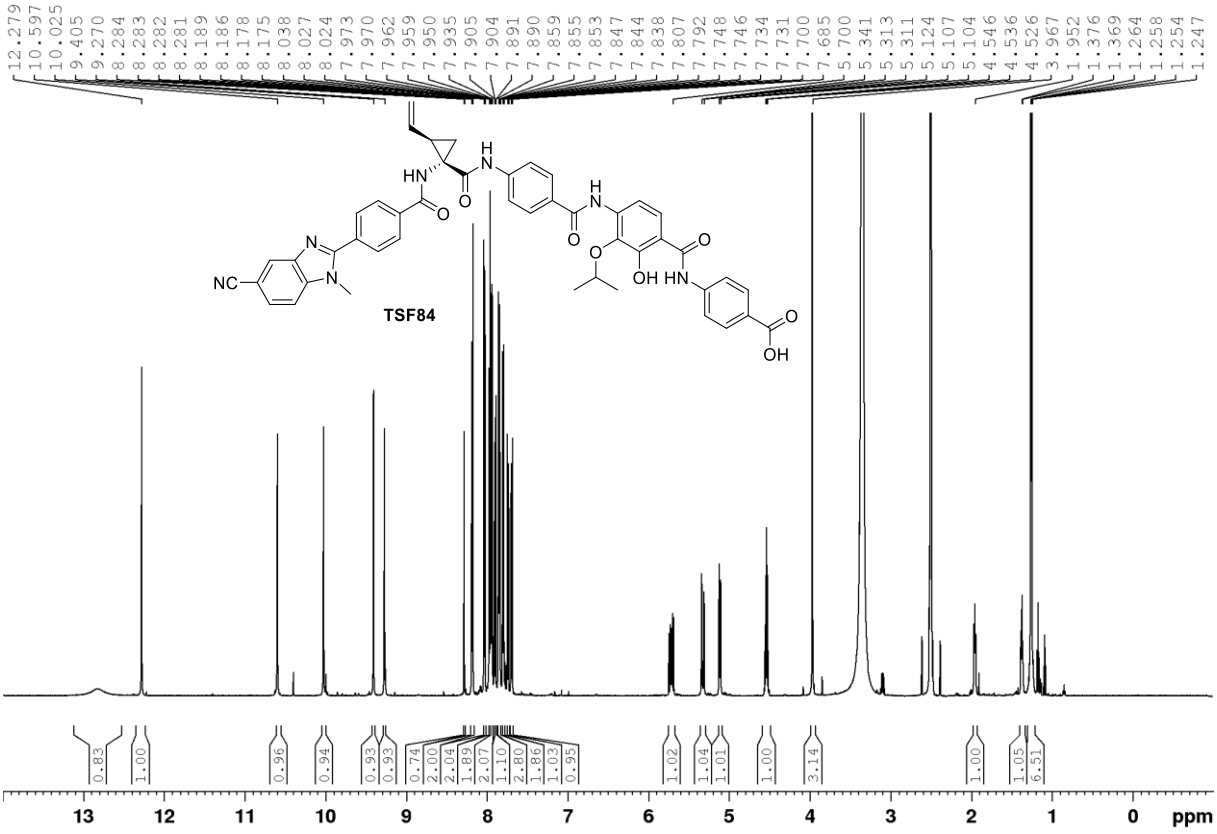

168.476
164.923
164.882
164.553
164.476
164.222
154.314
142.847
142.049
141.737
138.661
137.048
136.190
132.905
132.521
129.908
128.876
128.643
128.614
128.185
128.036
126.985
126.763
122.870
120.642
119.534
119.417
118.994
118.289
114.058
112.373
80.477
74.779
27.846
22.316
20.718
20.442
232
220
200
180
160
140
120
100
80
60
40
20
0
ppm

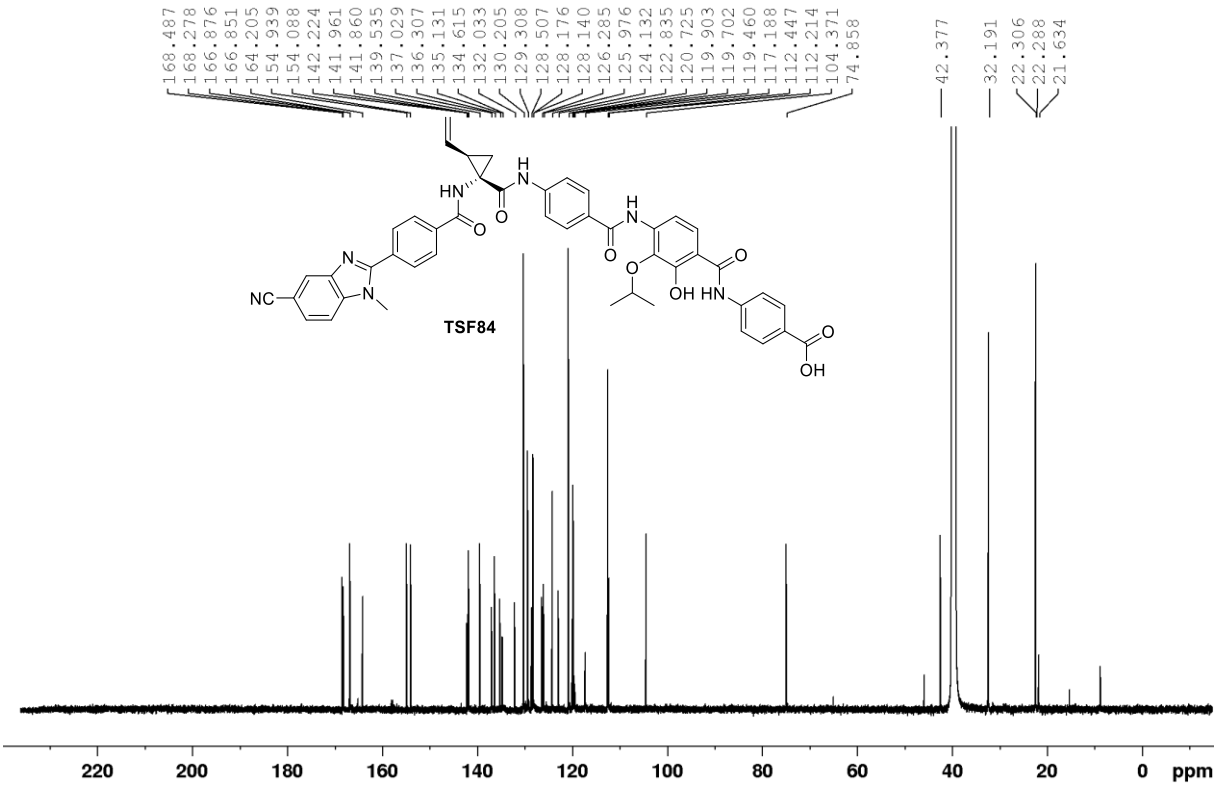

10.525
9.518
7.968
7.953
7.903
7.899
7.884
7.836
7.820
7.806
7.787
7.775
7.413
7.399
6.040
6.023
6.012
6.003
5.994
5.392
5.389
5.386
5.363
5.360
5.357
5.237
5.234
5.214
5.212
5.209
5.207
5.197
5.194
5.192
5.042
5.039
5.025
5.022
4.612
4.603
4.507
4.497
4.486
2.253
2.239
1.794
1.790
1.783
1.778
1.768
1.547
1.409
1.325
1.265
1.262
1.254
1.252
1.241
132
0.88
0.99
0.87
1.72
1.84
4.52
0.67
0.79
0.85
1.04
1.00
1.92
1.00
1.83
0.94
1.01
1.15
8.99
2.03
6.01
0.97
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

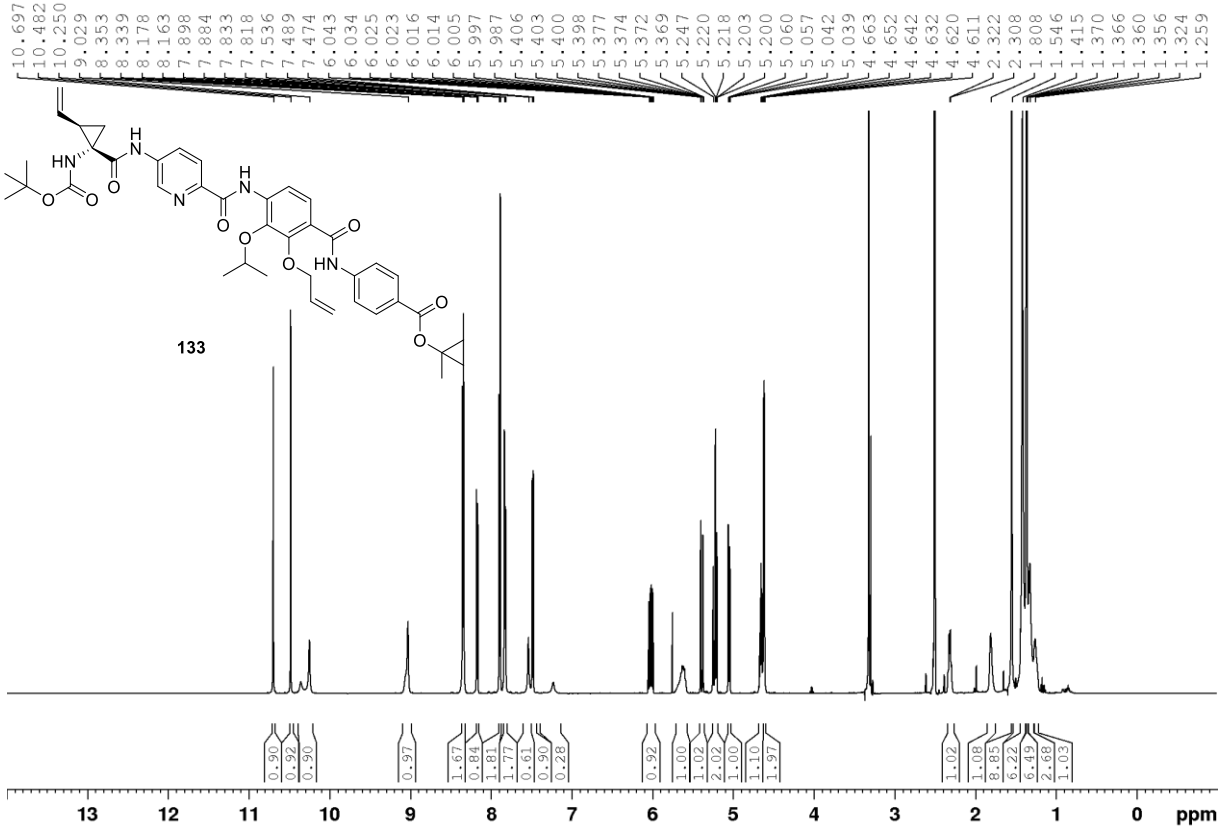

169.850
164.584
164.531
164.302
155.645
149.518
143.021
142.524
135.652
134.507
133.648
131.975
130.085
128.420
128.287
127.082
126.014
123.606
119.175
118.936
118.825
118.276
117.798
80.334
78.933
76.221
74.293
45.410
30.699
28.075
27.852
22.325
19.961
132
220
200
180
160
140
120
100
80
60
40
20
0
ppm

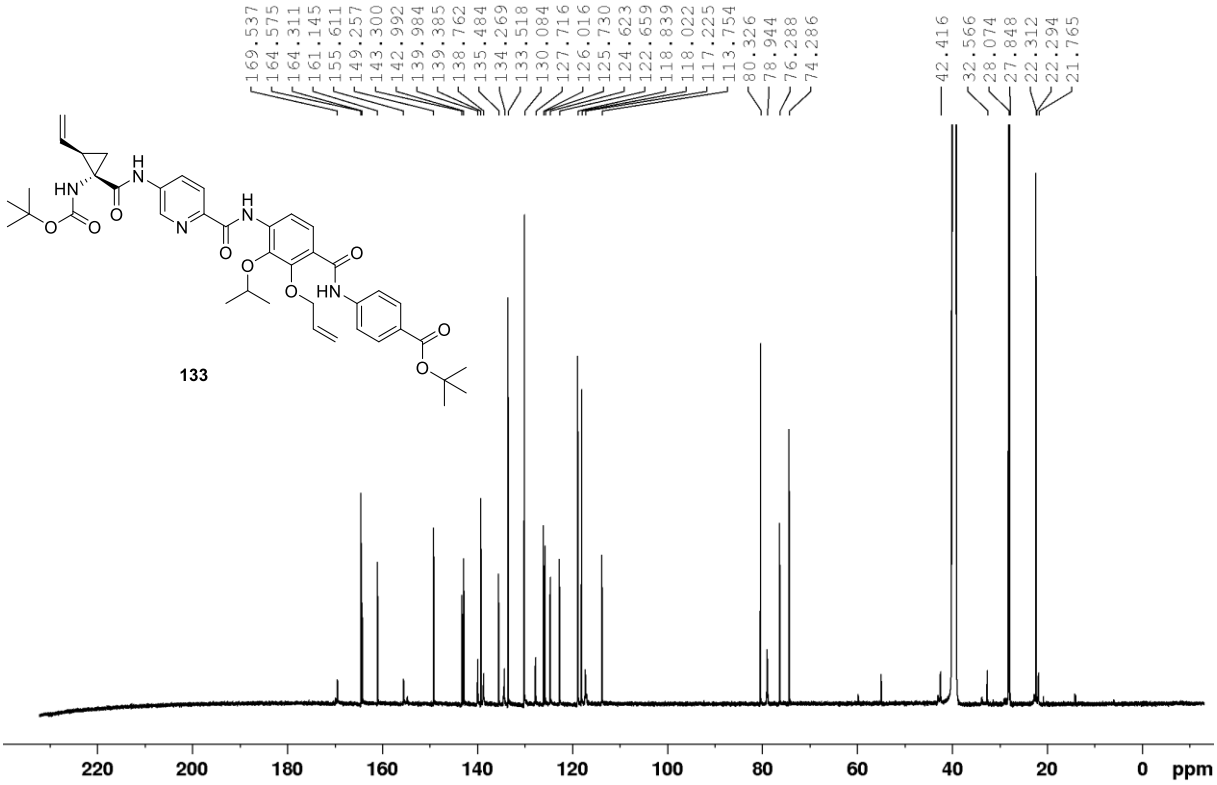

12.272
10.022
9.389
9.269
8.285
8.284
8.283
8.282
8.190
8.187
8.179
8.176
8.039
8.028
8.025
7.946
7.931
7.914
7.906
7.905
7.892
7.891
7.856
7.841
7.807
7.792
7.748
7.745
7.734
7.731
5.748
5.733
5.719
5.715
5.704
5.702
5.687
5.341
5.313
5.310
5.125
5.107
5.104
3.968
1.965
1.956
1.953
1.944
1.553
1.386
1.377
1.370
1.361
1.262
1.255
1.251
1.245
1.234
206
1.00
0.88
0.99
0.89
1.07
0.61
2.09
2.10
5.32
2.79
1.95
1.06
0.90
1.08
1.11
1.07
0.98
3.32
1.12
9.13
1.17
6.08
1.11
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

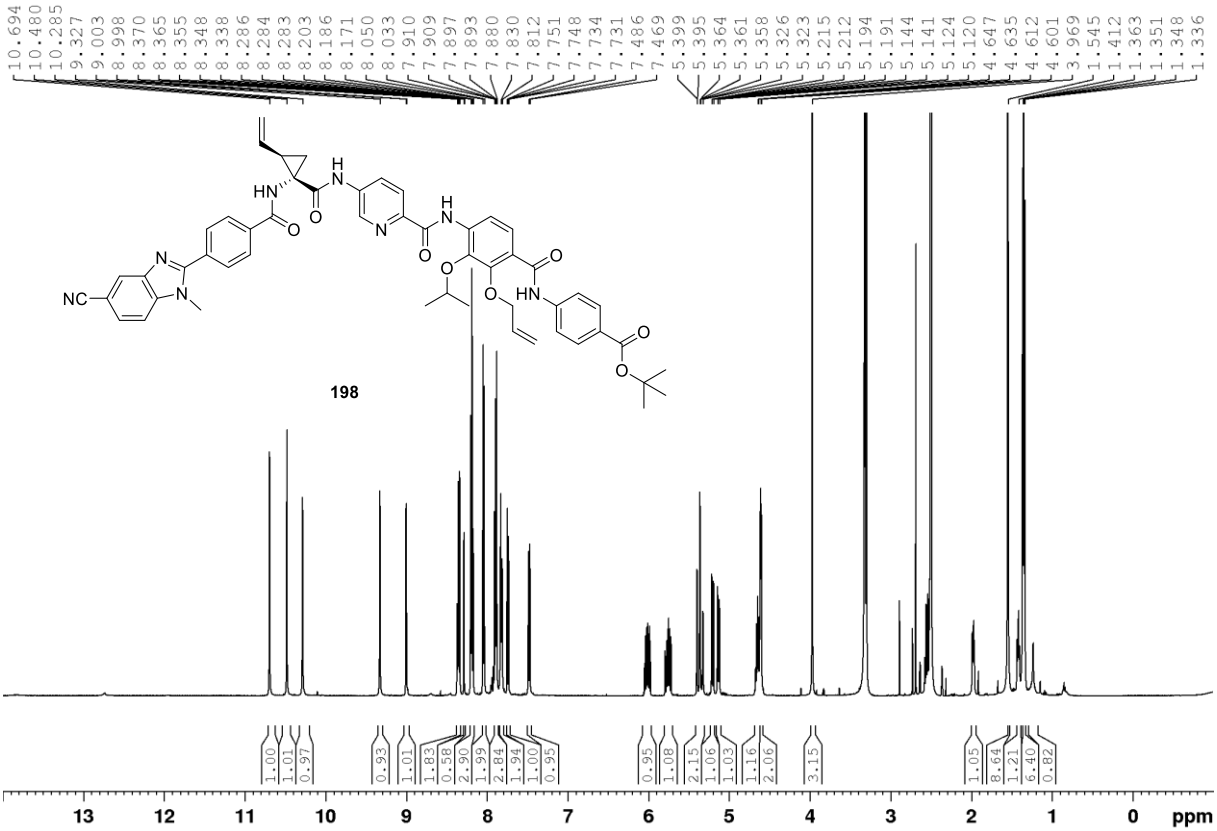

168.422
168.262
166.829
164.550
164.156
154.933
142.194
141.889
139.537
136.949
136.327
135.113
134.614
132.048
129.905
129.289
128.550
128.162
128.100
125.948
124.137
122.868
120.611
119.895
119.695
119.420
117.165
112.424
104.343
80.463
74.810
42.360
32.176
27.841
22.302
22.285
21.620
206
220
200
180
160
140
120
100
80
60
40
20
0
ppm

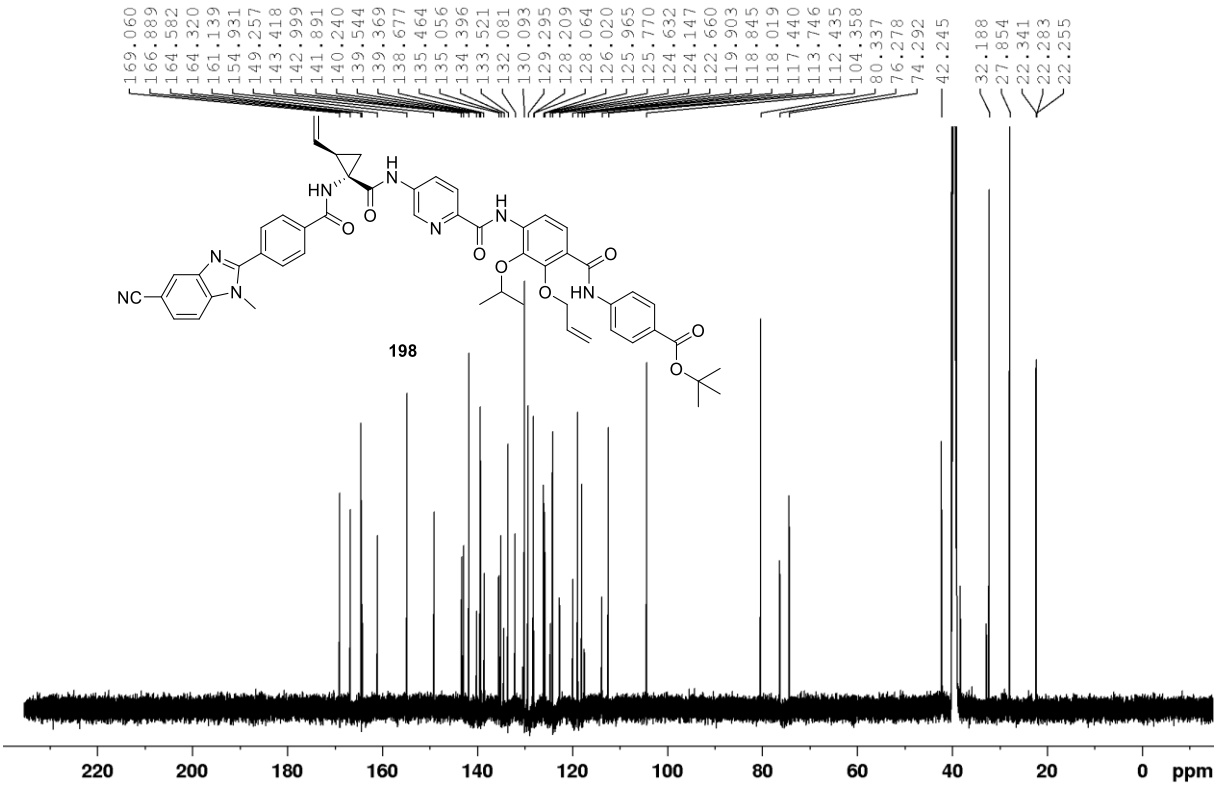

12.279
10.597
10.025
9.405
9.270
8.284
8.283
8.282
8.281
8.189
8.186
8.178
8.175
8.038
8.027
8.024
7.973
7.970
7.962
7.959
7.950
7.935
7.905
7.904
7.891
7.890
7.859
7.855
7.853
7.847
7.844
7.838
7.807
7.792
7.748
7.746
7.734
7.731
7.700
7.685
5.700
5.341
5.313
5.311
5.124
5.107
5.104
4.546
4.536
4.526
3.967
1.952
1.376
1.369
1.264
1.258
1.254
1.247
TSF84
0.83
1.00
0.96
0.94
0.93
0.93
0.74
2.00
2.04
1.89
2.07
1.10
2.80
1.86
1.03
0.95
1.02
1.04
1.01
1.00
3.14
1.00
1.05
6.51
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

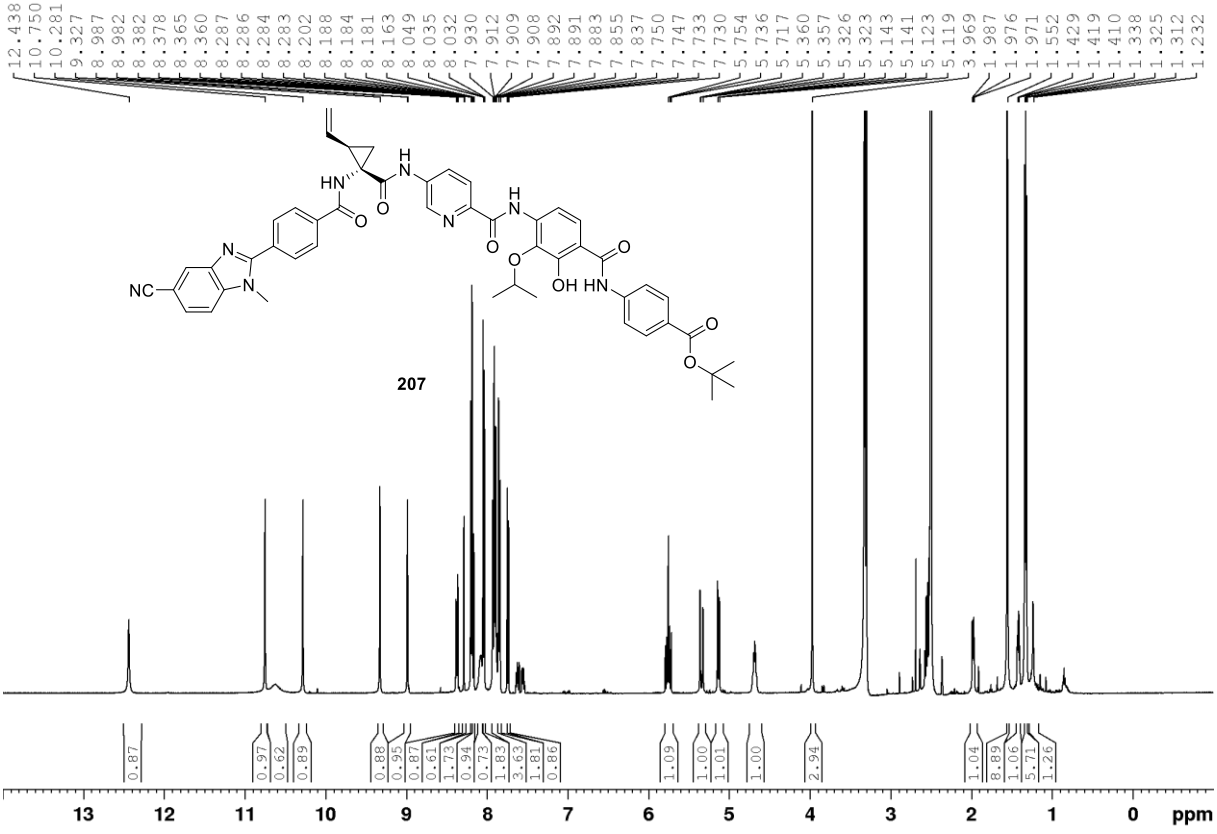

168.487
168.278
166.876
166.851
164.205
154.939
154.088
142.224
141.961
141.860
139.535
137.029
136.307
135.131
134.615
132.033
130.205
129.308
128.507
128.176
128.140
126.285
125.976
124.132
122.835
120.725
119.903
119.702
119.460
117.188
112.447
112.214
104.371
74.858
42.377
32.191
22.306
22.288
21.634
TSF84
220
200
180
160
140
120
100
80
60
40
20
0
ppm

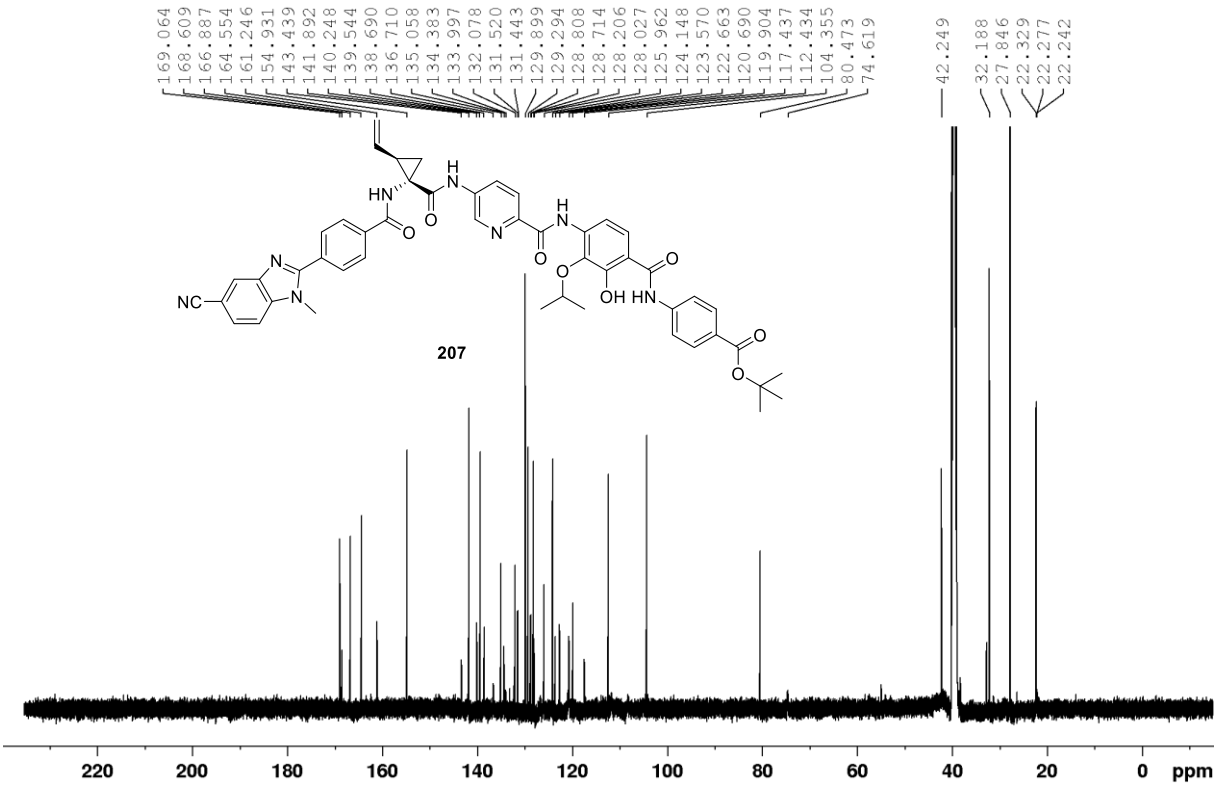

10.697
10.482
10.250
9.029
8.353
8.339
8.178
8.163
7.898
7.884
7.833
7.818
7.536
7.489
7.474
6.043
6.034
6.025
6.023
6.016
6.014
6.005
5.997
5.987
5.406
5.403
5.400
5.398
5.377
5.374
5.372
5.369
5.247
5.220
5.218
5.203
5.200
5.060
5.057
5.042
5.039
4.663
4.652
4.642
4.632
4.620
4.611
2.322
2.308
1.808
1.546
1.415
1.370
1.366
1.360
1.356
1.324
1.259
133
0.90
0.92
0.90
0.97
1.67
0.84
1.81
1.77
0.61
0.90
0.28
0.92
1.00
1.02
2.02
1.00
1.10
1.97
1.02
1.08
8.85
6.22
6.49
2.68
1.03
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

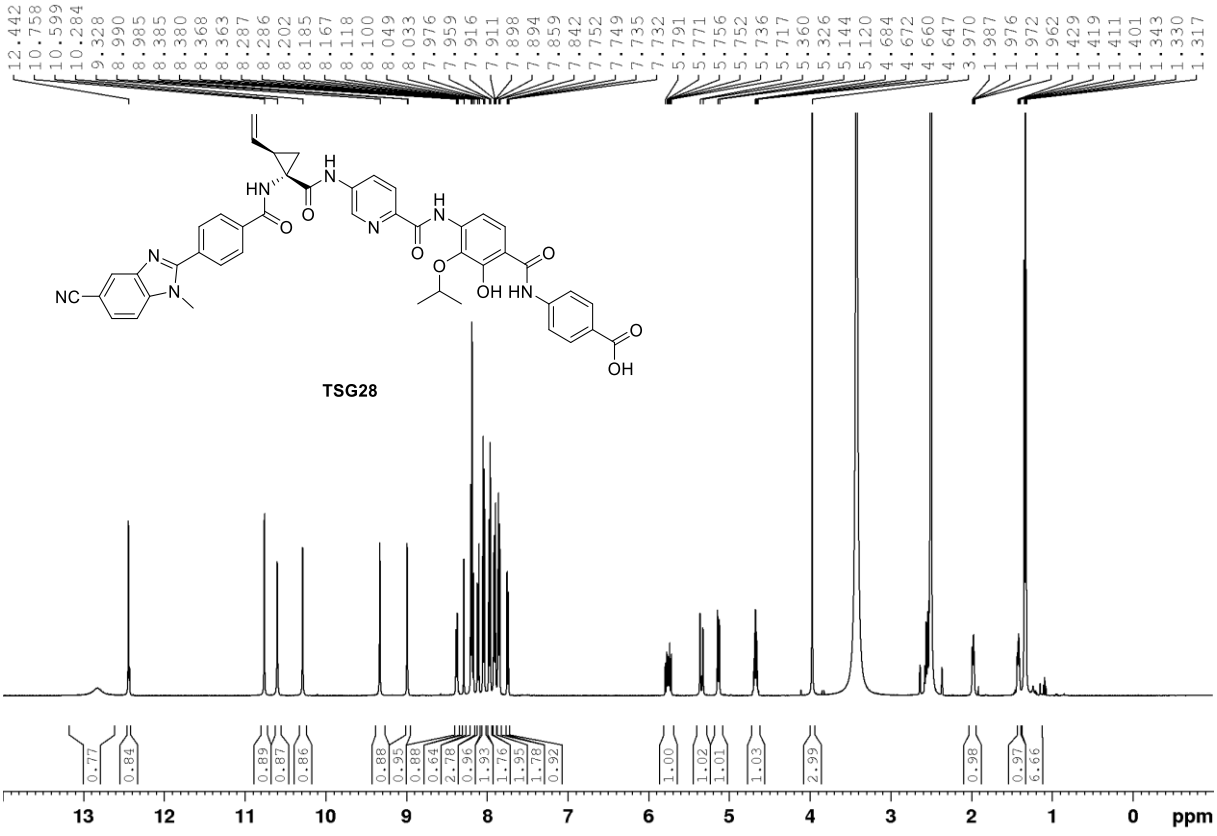

169.537
164.575
164.311
161.145
155.611
149.257
143.300
142.992
139.984
139.385
138.762
135.484
134.269
133.518
130.084
127.716
126.016
125.730
124.623
122.659
118.839
118.022
117.225
113.754
80.326
78.944
76.288
74.286
42.416
32.566
28.074
27.848
22.312
22.294
21.765
133
220
200
180
160
140
120
100
80
60
40
20
0
ppm

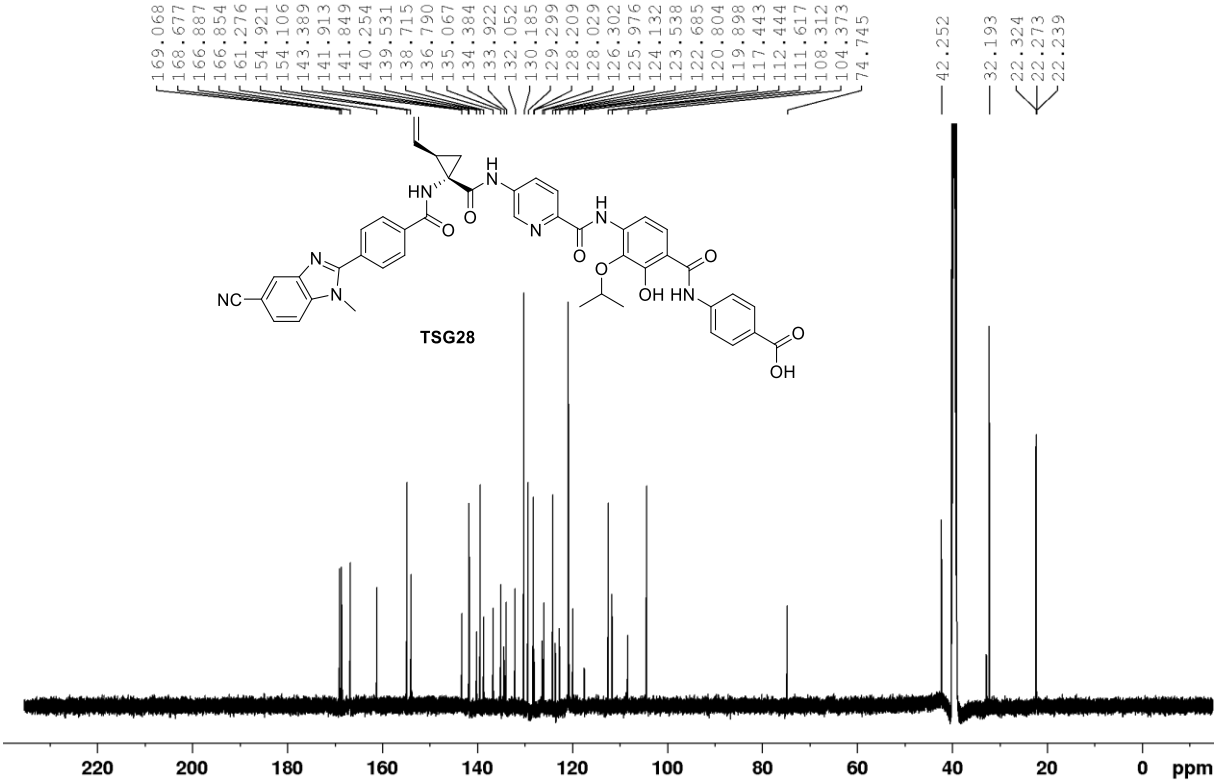

10.694
10.480
10.285
9.327
9.003
8.998
8.370
8.365
8.355
8.348
8.338
8.286
8.284
8.283
8.203
8.186
8.171
8.050
8.033
7.910
7.909
7.897
7.893
7.880
7.830
7.812
7.751
7.748
7.734
7.731
7.486
7.469
5.399
5.395
5.364
5.361
5.358
5.326
5.323
5.215
5.212
5.194
5.191
5.144
5.141
5.124
5.120
4.647
4.635
4.612
4.601
3.969
1.545
1.412
1.363
1.351
1.348
1.336
198
1.00
1.01
0.97
0.93
1.01
1.83
0.58
2.90
1.99
2.84
1.94
1.00
0.95
0.95
1.08
2.15
1.06
1.03
1.16
2.06
3.15
1.05
8.64
1.21
6.40
0.82
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

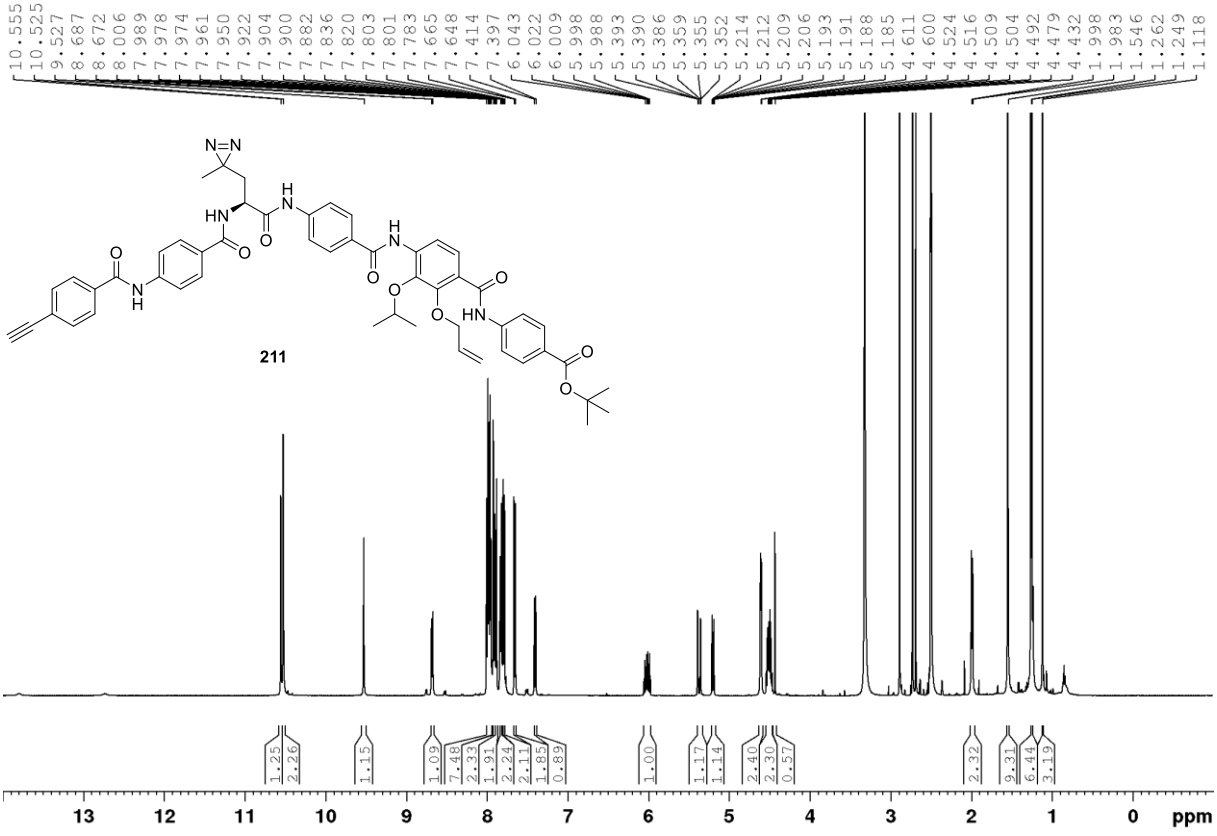

169.060
166.889
164.582
164.320
161.139
154.931
149.257
143.418
142.999
141.891
140.240
139.544
139.369
138.677
135.464
135.056
134.396
133.521
132.081
130.093
129.295
128.209
128.064
126.020
125.965
125.770
124.632
124.147
122.660
119.903
118.845
118.019
117.440
113.746
112.435
104.358
80.337
76.278
74.292
42.245
32.188
27.854
22.341
22.283
22.255
198
220
200
180
160
140
120
100
80
60
40
20
0
ppm

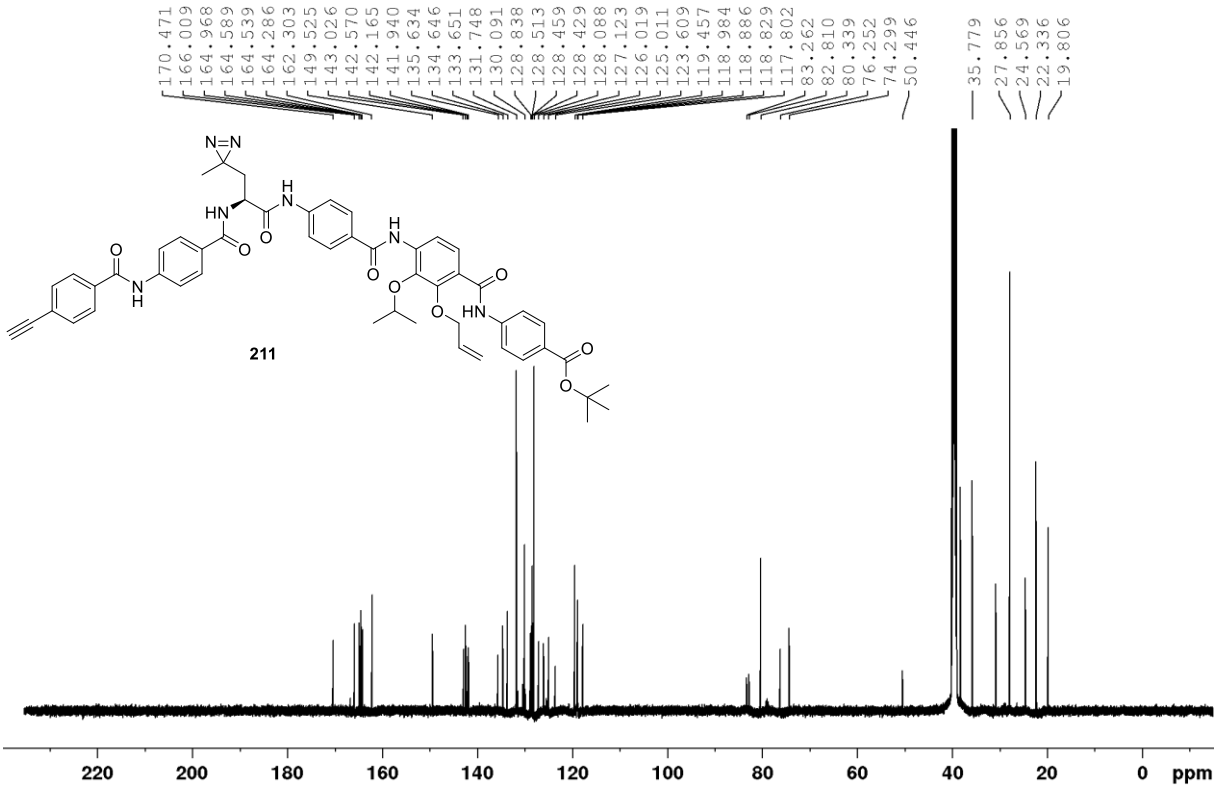

12.438
10.750
10.281
9.327
8.987
8.982
8.382
8.378
8.365
8.360
8.287
8.286
8.284
8.283
8.202
8.188
8.184
8.181
8.163
8.049
8.035
8.032
7.930
7.912
7.909
7.908
7.892
7.891
7.883
7.855
7.837
7.750
7.747
7.733
7.730
5.754
5.736
5.717
5.360
5.357
5.326
5.323
5.143
5.141
5.123
5.119
3.969
1.987
1.976
1.971
1.552
1.429
1.419
1.410
1.338
1.325
1.312
1.232
207
0.87
0.97
0.62
0.89
0.88
0.95
0.87
0.61
1.73
0.94
0.73
1.83
3.63
1.81
0.86
1.09
1.00
1.01
1.00
2.94
1.04
8.89
1.06
5.71
1.26
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

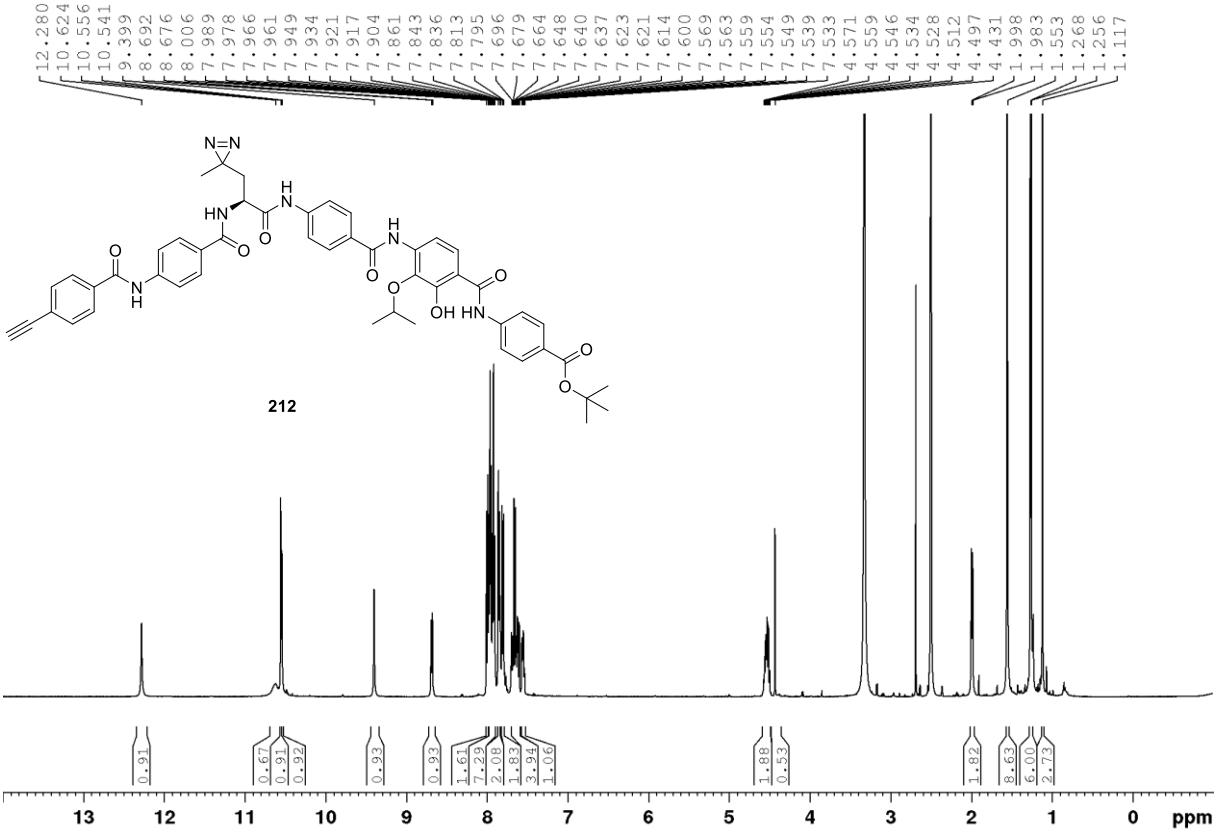

169.064
168.609
166.887
164.554
161.246
154.931
143.439
141.892
140.248
139.544
138.690
136.710
135.058
134.383
133.997
132.078
131.520
131.443
129.899
129.294
128.808
128.714
128.206
128.027
125.962
124.148
123.570
122.663
120.690
119.904
117.437
112.434
104.355
80.473
74.619
42.249
32.188
27.846
22.329
22.277
22.242
207
220
200
180
160
140
120
100
80
60
40
20
0
ppm

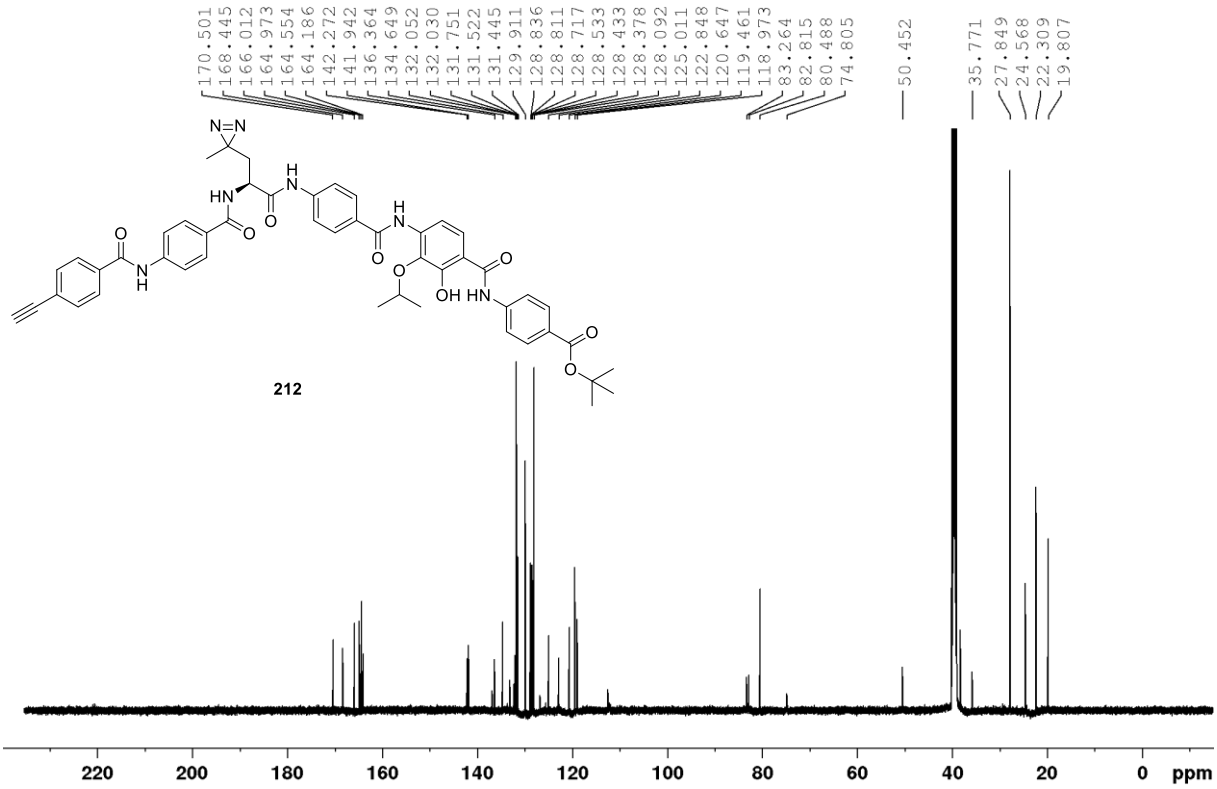

12.442
10.758
10.599
10.284
9.328
8.990
8.985
8.385
8.380
8.368
8.363
8.287
8.286
8.202
8.185
8.167
8.118
8.100
8.049
8.033
7.976
7.959
7.916
7.911
7.898
7.894
7.859
7.842
7.752
7.749
7.735
7.732
5.791
5.771
5.756
5.752
5.736
5.717
5.360
5.326
5.144
5.120
4.684
4.672
4.660
4.647
3.970
1.987
1.976
1.972
1.962
1.429
1.419
1.411
1.401
1.343
1.330
1.317
TSG28
0.77
0.84
0.89
0.87
0.86
0.88
0.95
0.88
0.64
2.78
0.96
1.93
1.76
1.95
1.78
0.92
1.00
1.02
1.01
1.03
2.99
0.98
0.97
6.66
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

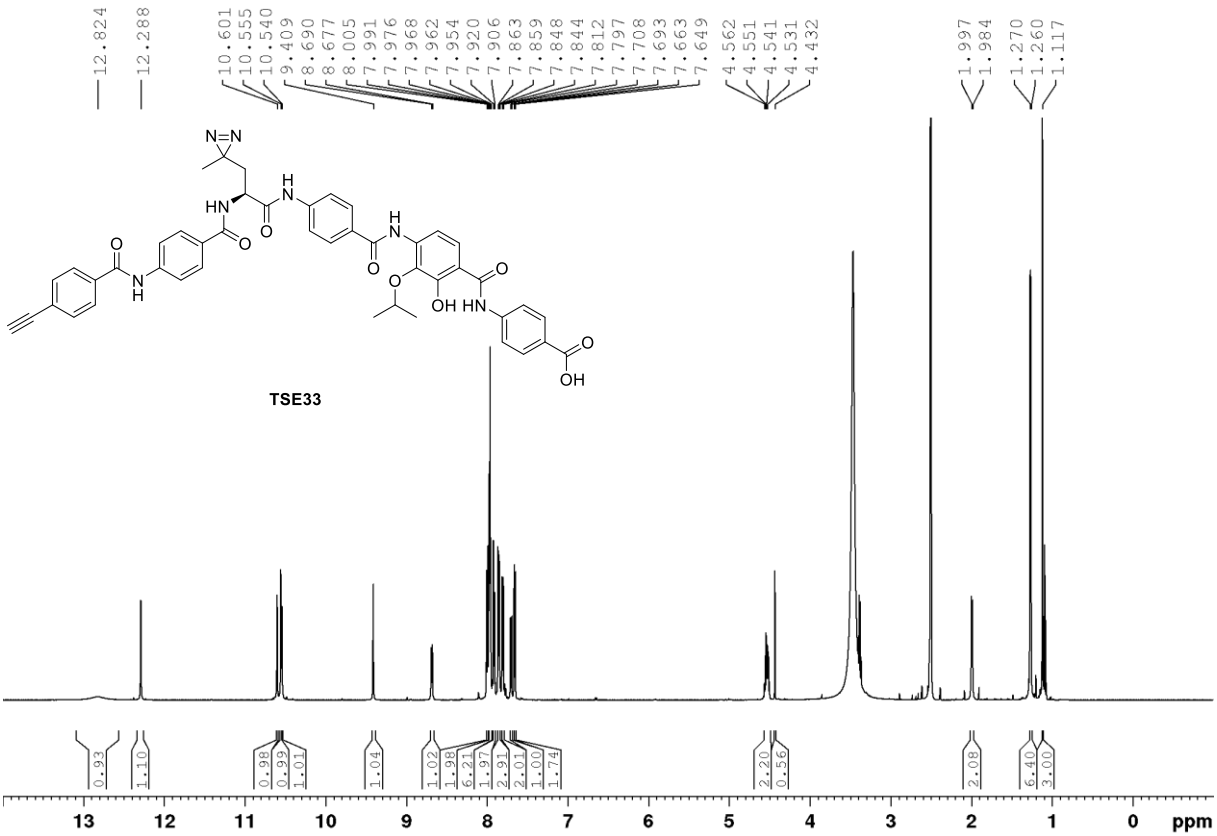

169.068
168.677
166.887
166.854
161.276
154.921
154.106
143.389
141.913
141.849
140.254
139.531
138.715
136.790
135.067
134.384
133.922
132.052
130.185
129.299
128.209
128.029
126.302
125.976
124.132
123.538
122.685
120.804
119.898
117.443
112.444
111.617
108.312
104.373
74.745
42.252
32.193
22.324
22.273
22.239
TSG28
220
200
180
160
140
120
100
80
60
40
20
0
ppm

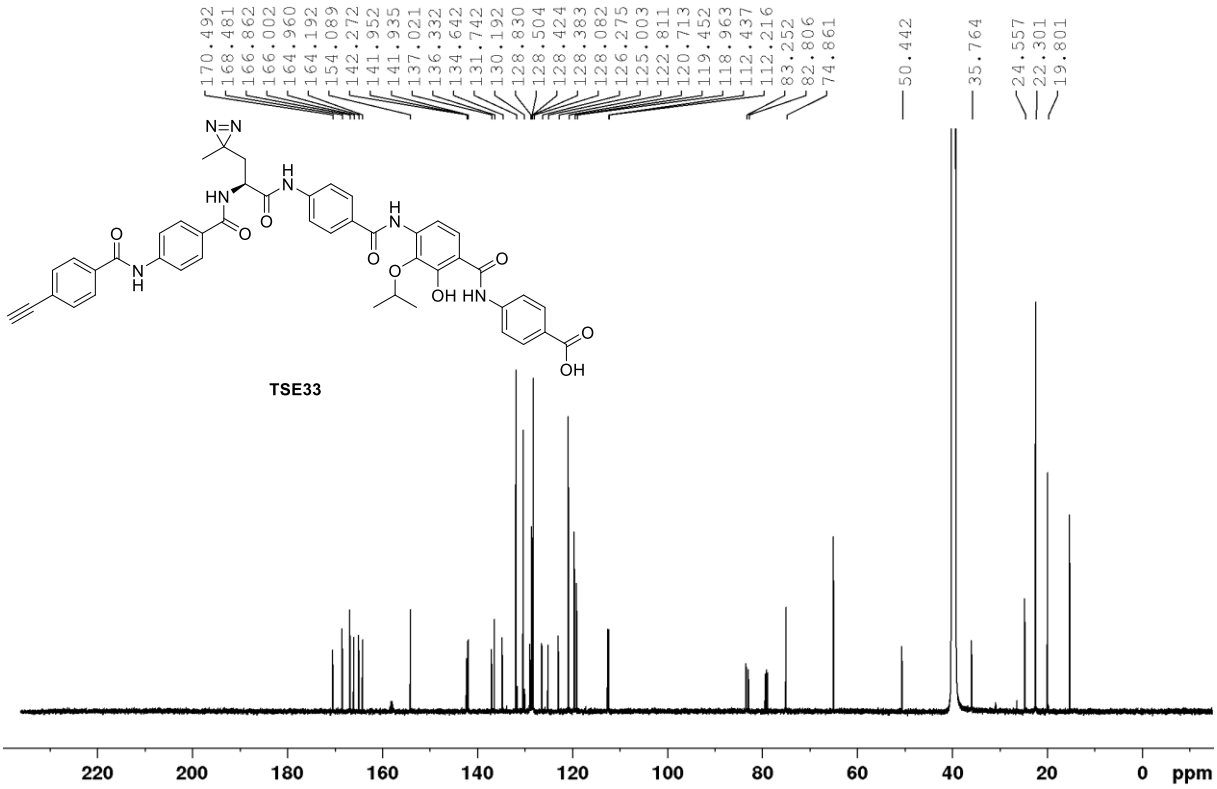

10.555
10.525
9.527
8.687
8.672
8.006
7.989
7.978
7.974
7.961
7.950
7.922
7.904
7.900
7.882
7.836
7.820
7.803
7.801
7.783
7.665
7.648
7.414
7.397
6.043
6.022
6.009
5.998
5.988
5.393
5.390
5.386
5.359
5.355
5.352
5.214
5.212
5.209
5.206
5.193
5.191
5.188
5.185
4.611
4.600
4.524
4.516
4.509
4.504
4.492
4.479
4.432
1.998
1.983
1.546
1.262
1.249
1.118
211
1.25
2.26
1.15
1.09
7.48
2.33
1.91
2.24
2.11
1.85
0.89
1.00
1.17
1.14
2.40
2.30
0.57
2.32
9.31
6.44
3.19
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

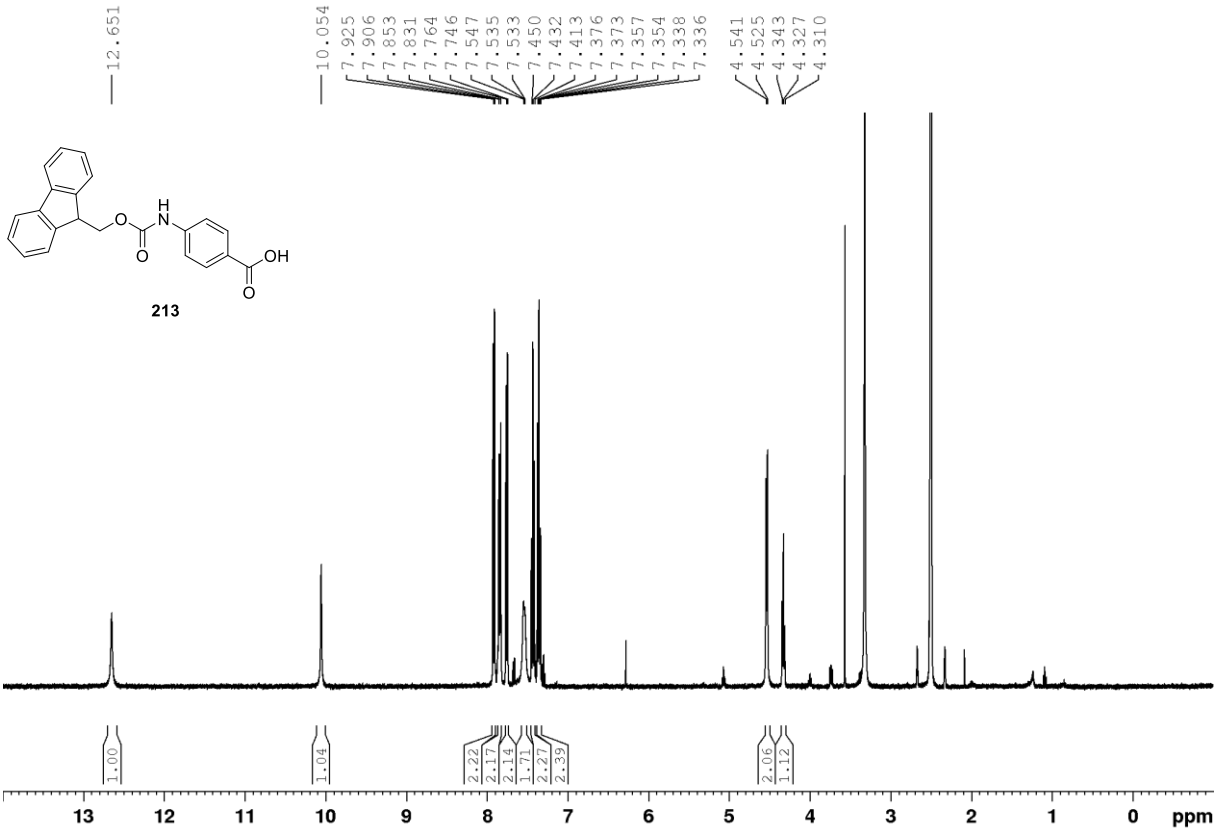

170.471
166.009
164.968
164.589
164.539
164.286
162.303
149.525
143.026
142.570
142.165
141.940
135.634
134.646
133.651
131.748
130.091
128.838
128.513
128.459
128.429
128.088
127.123
126.019
125.011
123.609
119.457
118.984
118.886
118.829
117.802
83.262
82.810
80.339
76.252
74.299
50.446
35.779
27.856
24.569
22.336
19.806
211
220
200
180
160
140
120
100
80
60
40
20
0
ppm

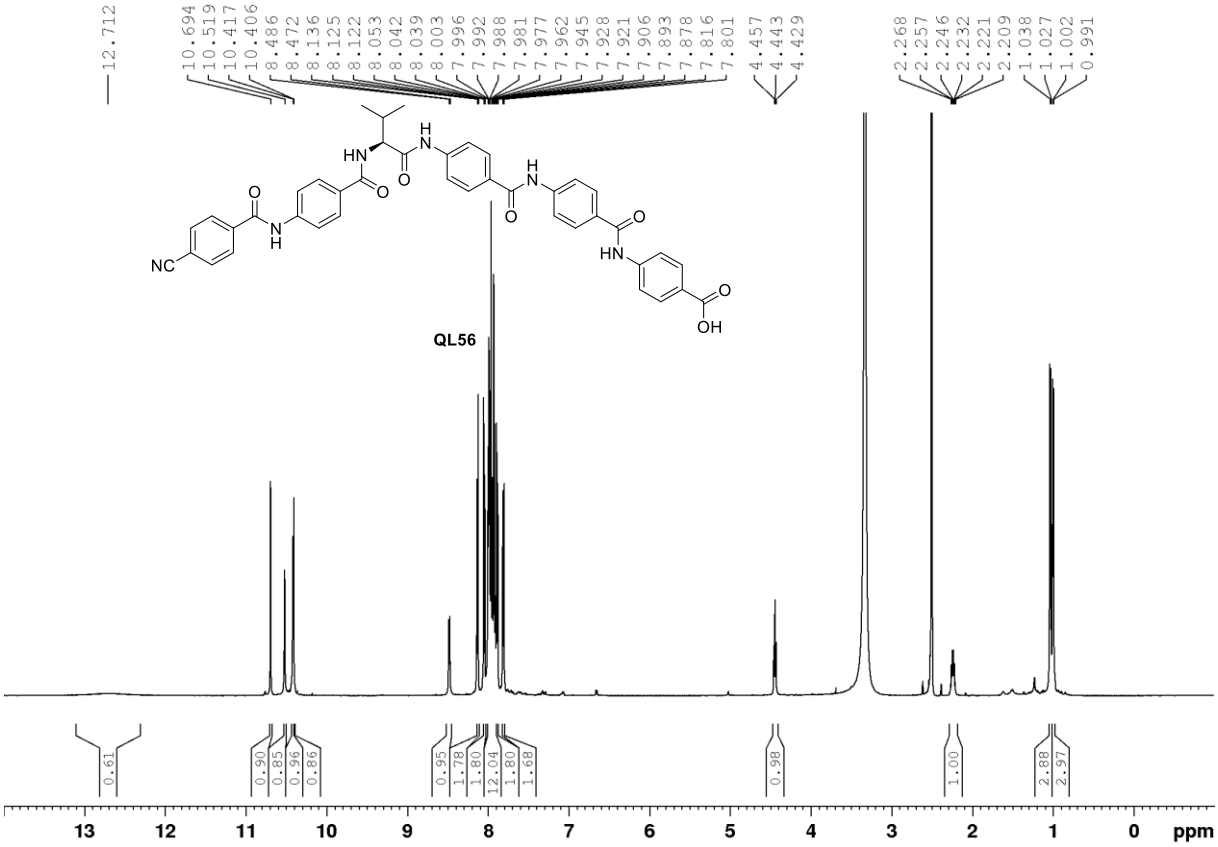

12.280
10.624
10.556
10.541
9.399
8.692
8.676
8.006
7.989
7.978
7.966
7.961
7.949
7.934
7.921
7.917
7.904
7.861
7.843
7.836
7.813
7.795
7.696
7.679
7.664
7.648
7.640
7.637
7.623
7.621
7.614
7.600
7.569
7.563
7.559
7.554
7.549
7.539
7.533
4.571
4.559
4.546
4.534
4.528
4.512
4.497
4.431
1.998
1.983
1.553
1.268
1.256
1.117
212
0.91
0.67
0.91
0.92
0.93
0.93
1.61
7.29
2.08
1.83
3.94
1.06
1.88
0.53
1.82
8.63
6.00
2.73
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

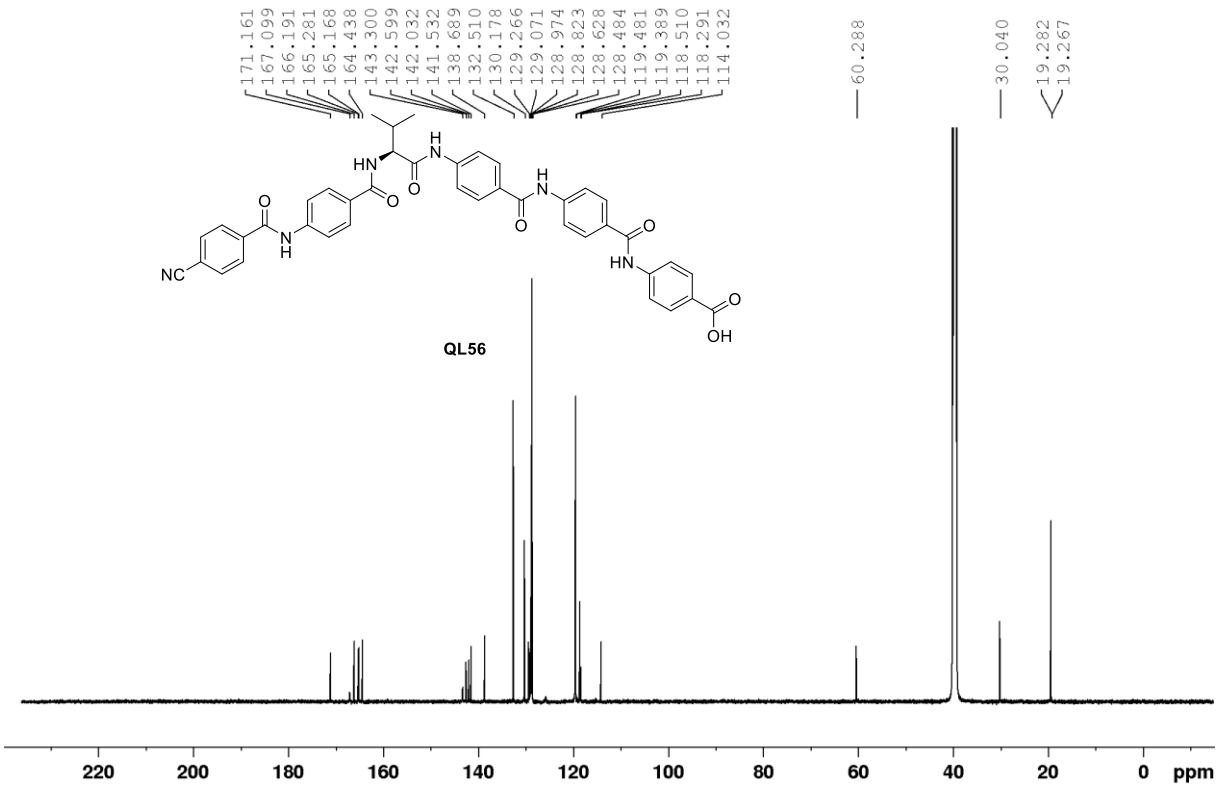

170.501
168.445
166.012
164.973
164.554
164.186
142.272
141.942
136.364
134.649
132.052
132.030
131.751
131.522
131.445
129.911
128.836
128.811
128.717
128.533
128.433
128.378
128.092
125.011
122.848
120.647
119.461
118.973
83.264
82.815
80.488
74.805
50.452
35.771
27.849
24.568
22.309
19.807
212
220
200
180
160
140
120
100
80
60
40
20
0
ppm

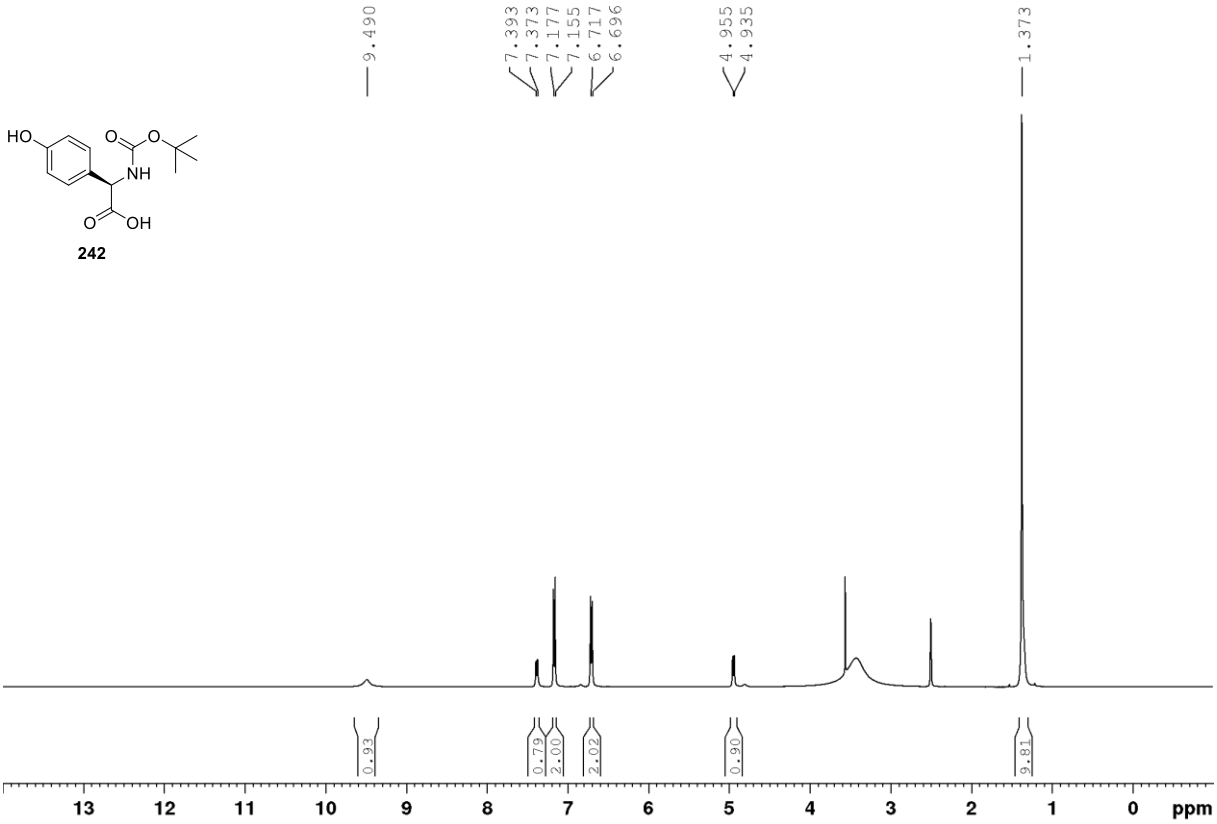

12.824
12.288
10.601
10.555
10.540
9.409
8.690
8.677
8.005
7.991
7.976
7.968
7.962
7.954
7.920
7.906
7.863
7.859
7.848
7.844
7.812
7.797
7.708
7.693
7.663
7.649
4.562
4.551
4.541
4.531
4.432
1.997
1.984
1.270
1.260
1.117
TSE33
0.93
1.10
0.98
0.99
1.01
1.04
1.02
1.98
6.21
1.97
2.91
2.01
1.00
1.74
2.20
0.56
2.08
6.40
3.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

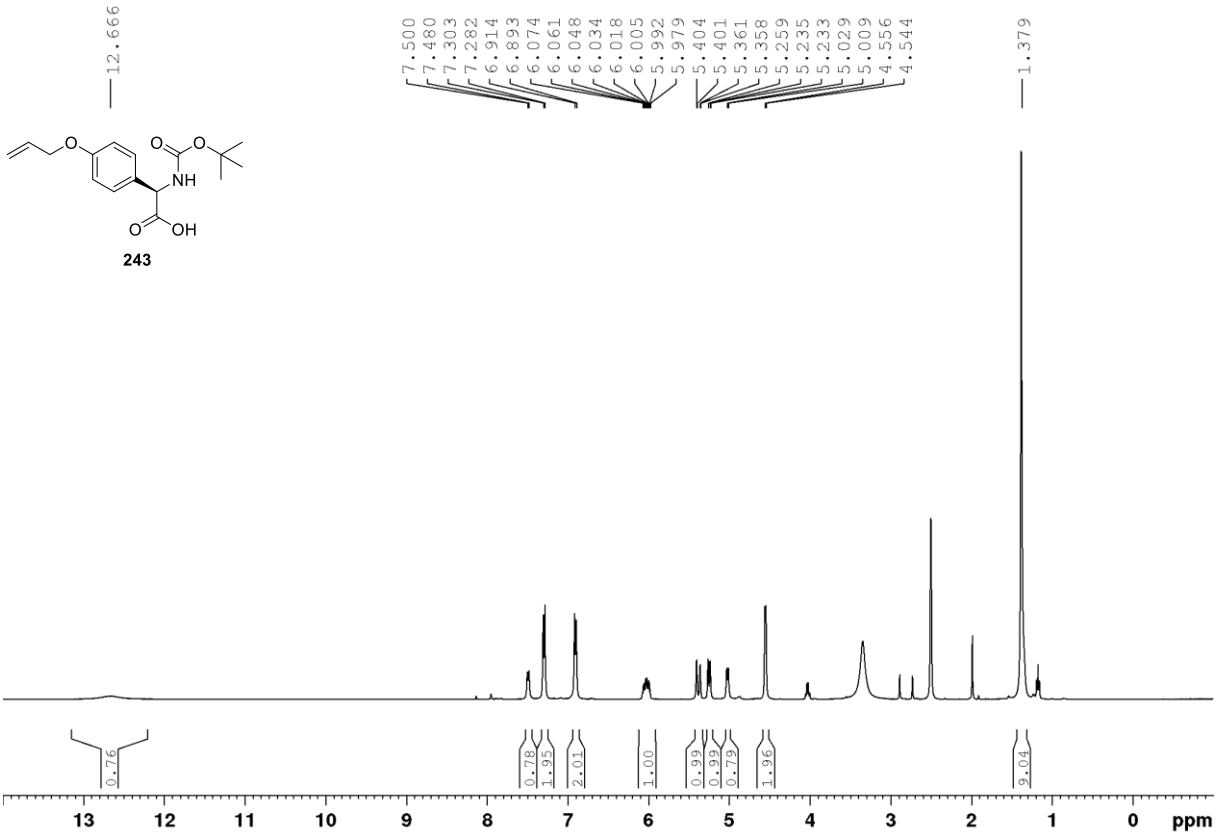

170.492
168.481
166.862
166.002
164.960
164.192
154.089
142.272
141.952
141.935
137.021
136.332
134.642
131.742
130.192
128.830
128.504
128.424
128.383
128.082
126.275
125.003
122.811
120.713
119.452
118.963
112.437
112.216
83.252
82.806
74.861
50.442
35.764
24.557
22.301
19.801
TSE33
220
200
180
160
140
120
100
80
60
40
20
0
ppm

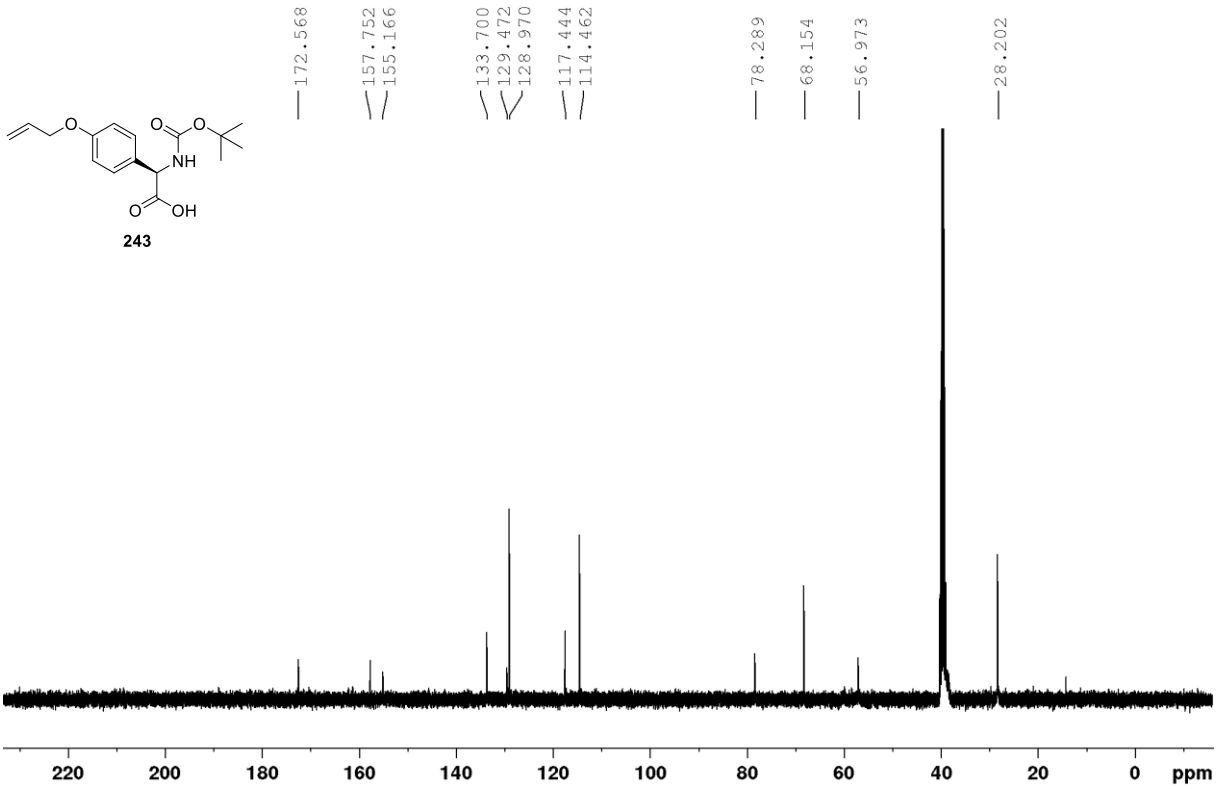

12.651
10.054
7.925
7.906
7.853
7.831
7.764
7.746
7.547
7.535
7.533
7.450
7.432
7.413
7.376
7.373
7.357
7.354
7.338
7.336
4.541
4.525
4.343
4.327
4.310
213
1.00
1.04
2.22
2.17
2.14
1.71
2.27
2.39
2.06
1.12
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


12.712
10.694
10.519
10.417
10.406
8.486
8.472
8.136
8.125
8.122
8.053
8.042
8.039
8.003
7.996
7.992
7.988
7.981
7.977
7.962
7.945
7.928
7.921
7.906
7.893
7.878
7.816
7.801
4.457
4.443
4.429
2.268
2.257
2.246
2.232
2.221
2.209
1.038
1.027
1.002
0.991
QL56
0.61
0.90
0.85
0.96
0.86
0.95
1.78
1.80
12.04
1.80
1.68
0.98
1.00
2.88
2.97
ppm

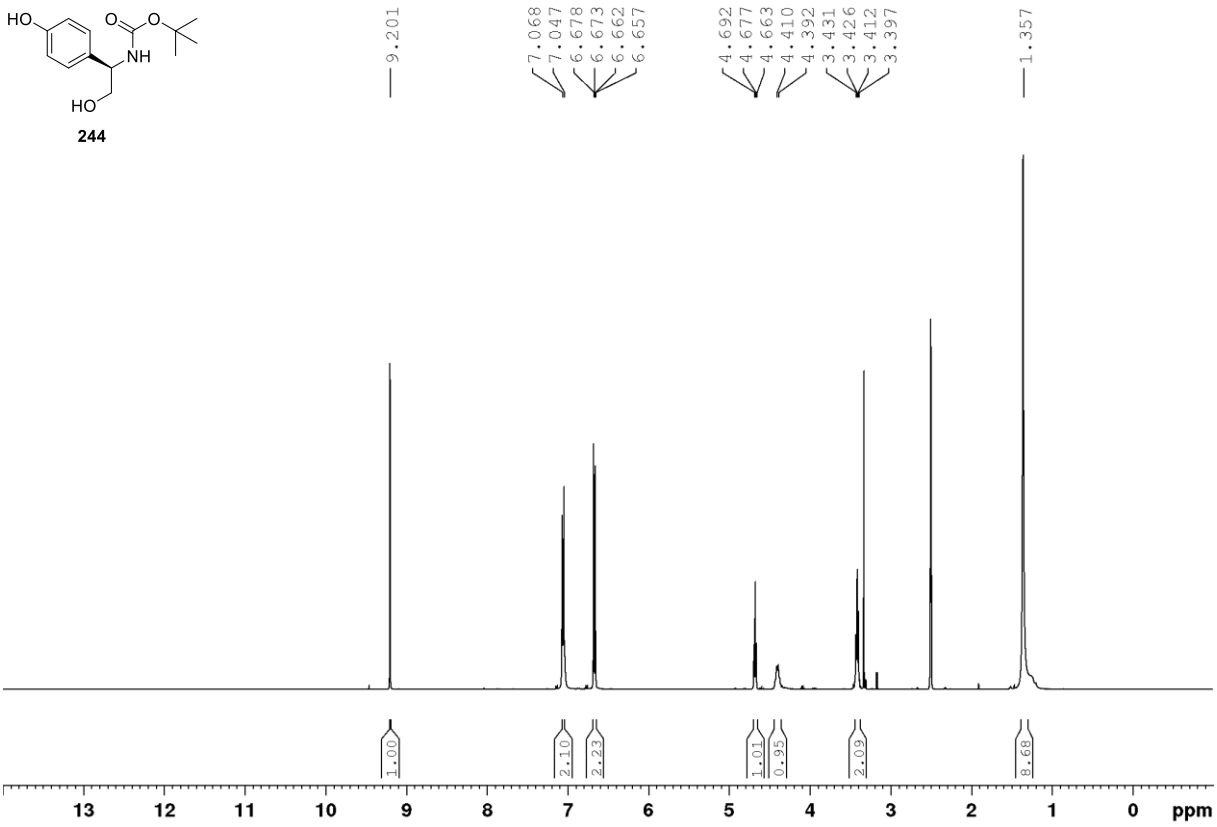

171.161
167.099
166.191
165.281
165.168
164.438
143.300
142.599
142.032
141.532
138.689
132.510
130.178
129.266
129.071
128.974
128.823
128.628
128.484
119.481
119.389
118.510
118.291
114.032
60.288
30.040
19.282
19.267
QL56
ppm


9.490
7.393
7.373
7.177
7.155
6.717
6.696
4.955
4.935
1.373
HO
O
O
NH
O
OH
242
0.93
0.79
2.00
2.02
0.90
9.81
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

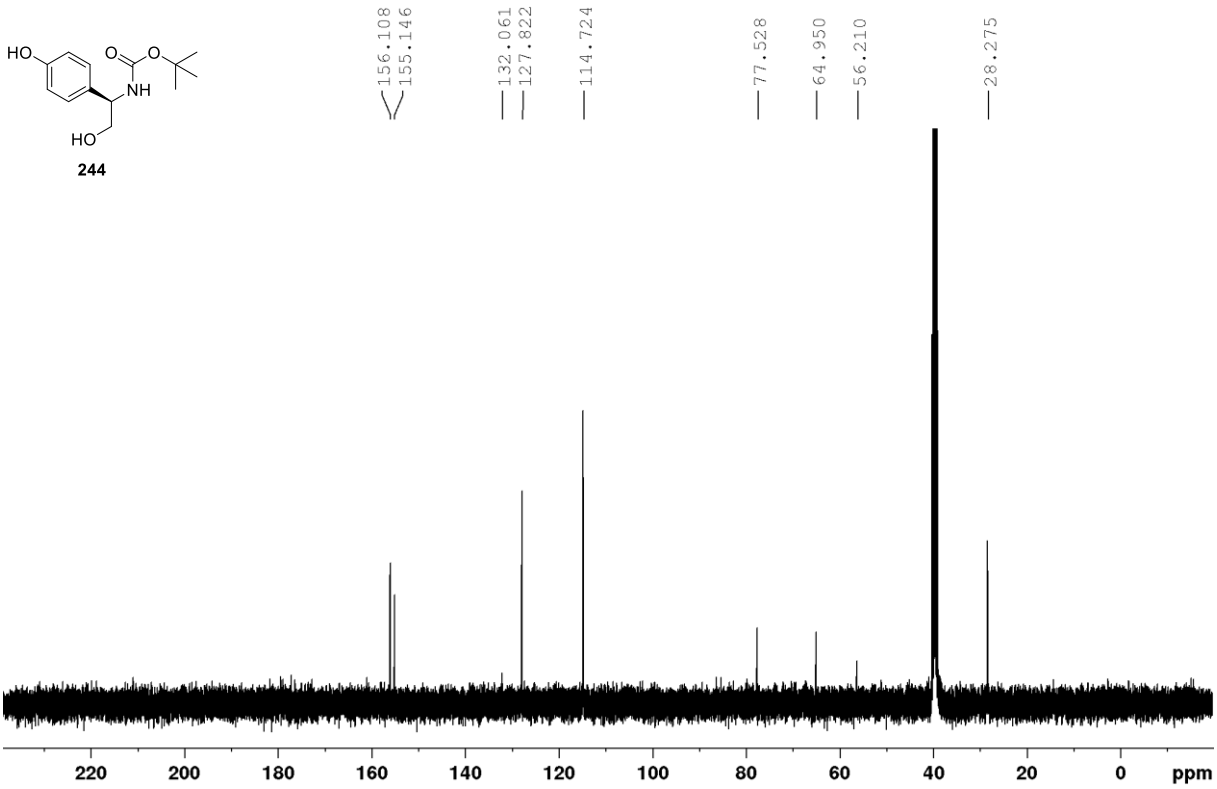

12.666
7.500
7.480
7.303
7.282
6.914
6.893
6.074
6.061
6.048
6.034
6.018
6.005
5.992
5.979
5.404
5.401
5.361
5.358
5.259
5.235
5.233
5.029
5.009
4.556
4.544
1.379
O
O
O
NH
O
OH
243
0.76
0.78
1.95
2.01
1.00
0.99
0.93
0.79
1.96
9.04
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

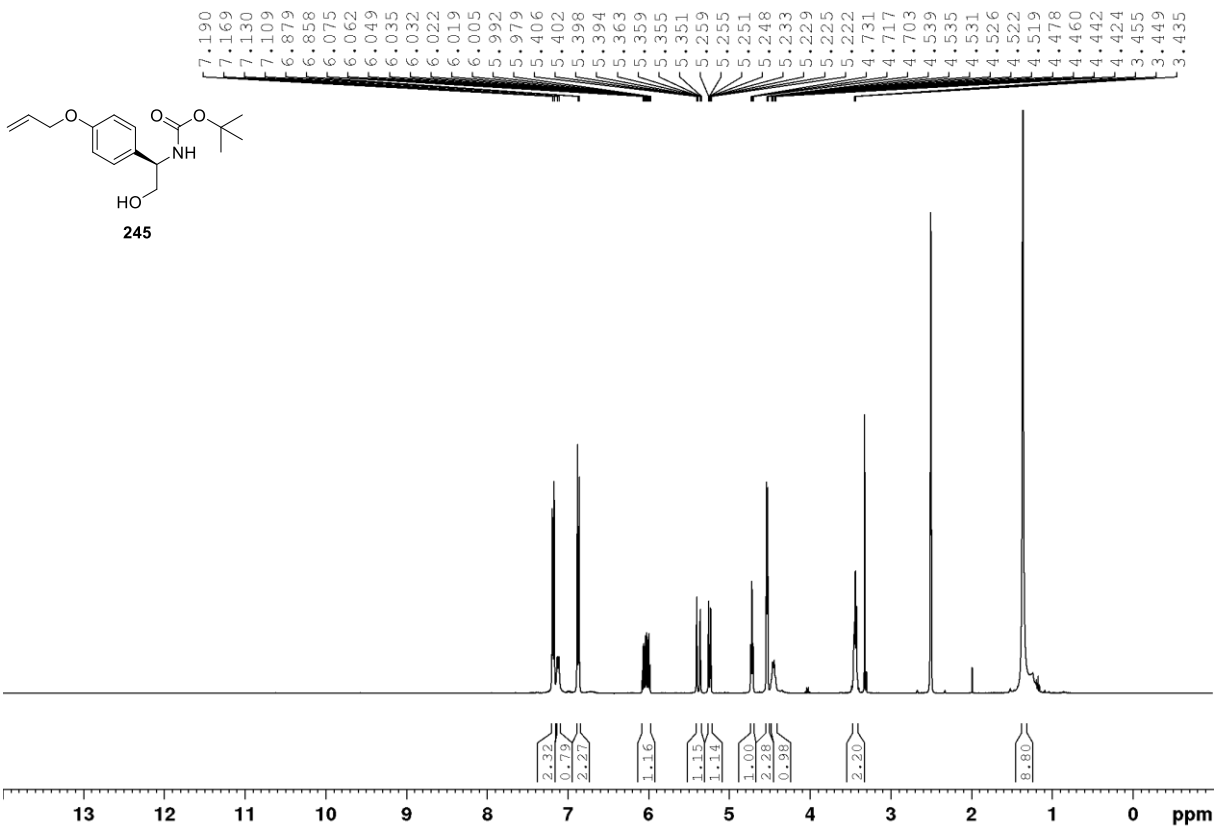

172.568
157.752
155.166
133.700
129.472
128.970
117.444
114.462
78.289
68.154
56.973
28.202
O
O
O
NH
O
OH
220
200
180
160
140
120
100
80
60
40
20
0
ppm

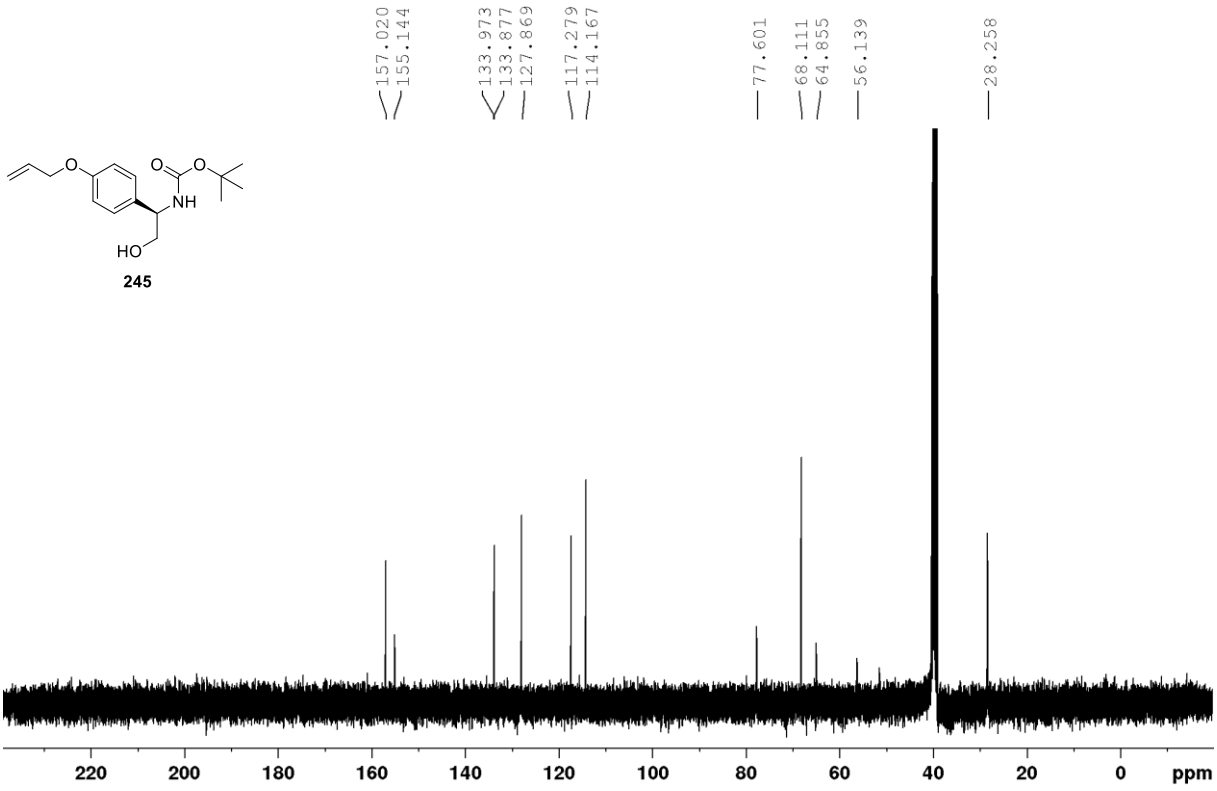
243

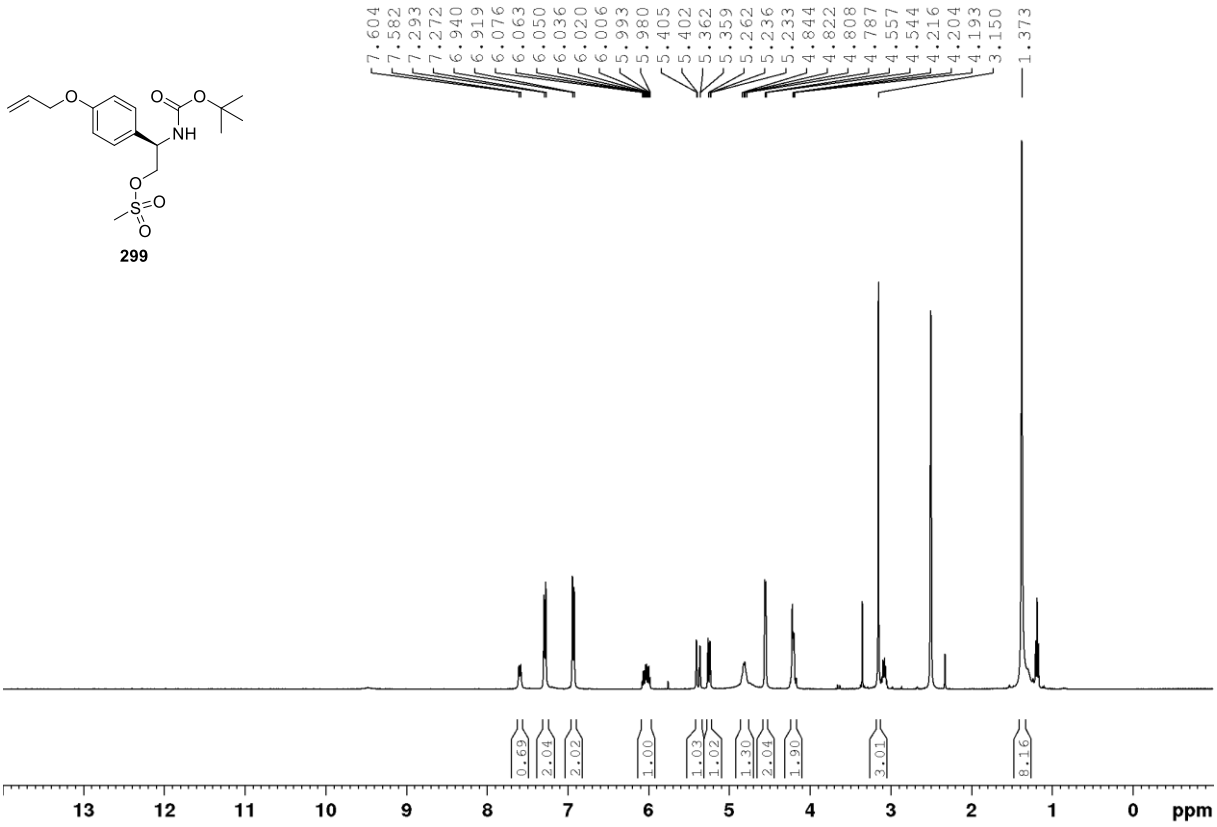

9.201
7.068
7.047
6.678
6.673
6.662
6.657
4.692
4.677
4.663
4.410
4.392
3.431
3.426
3.412
3.397
1.357
HO
O
O
NH
HO
1.00
2.10
2.23
1.01
0.95
2.09
8.68
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

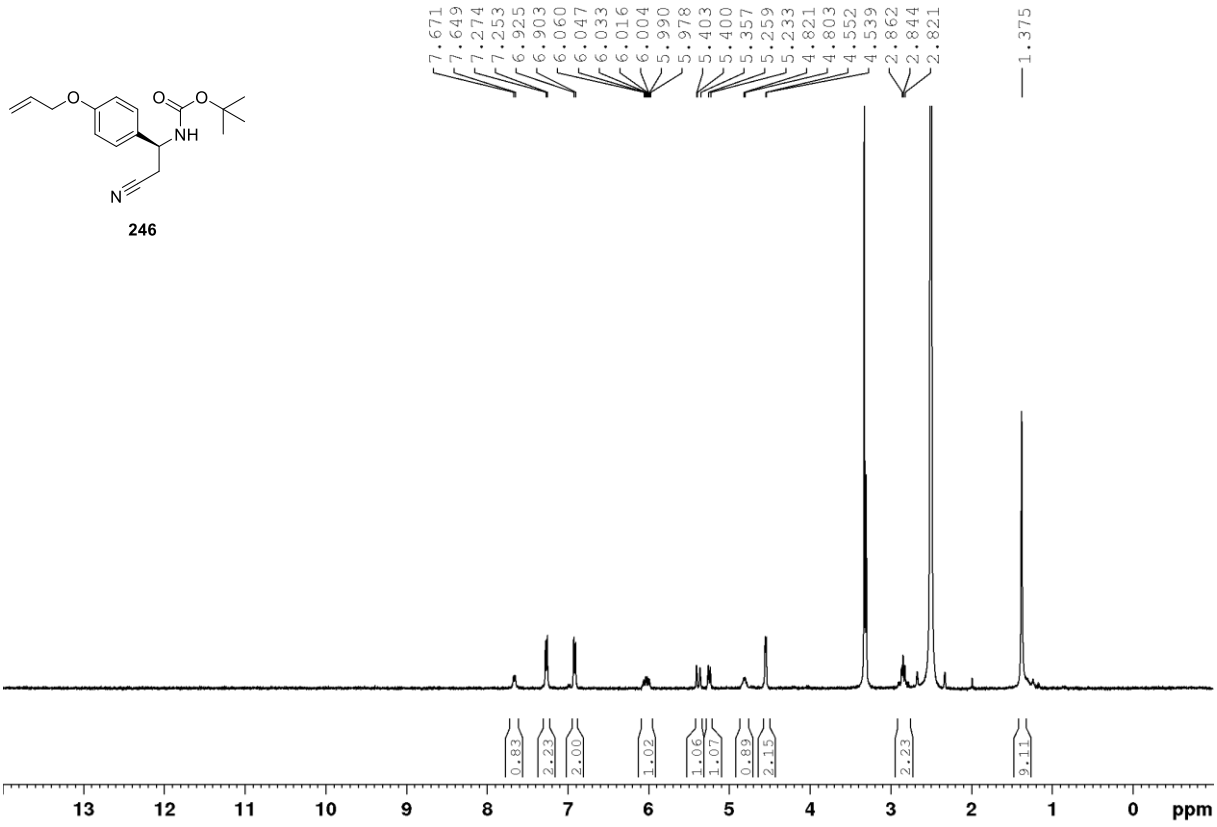
244

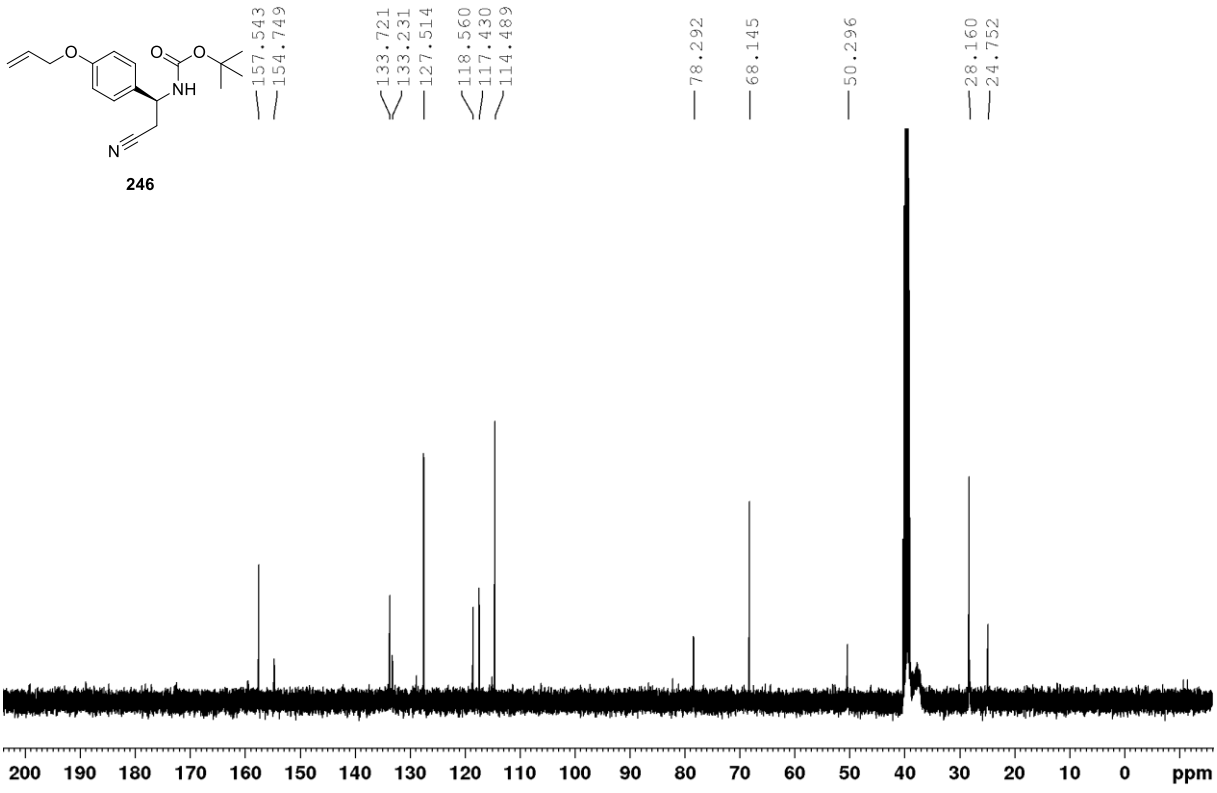

HO
O
O
NH
HO
244
156.108
155.146
132.061
127.822
114.724
77.528
64.950
56.210
28.275
220
200
180
160
140
120
100
80
60
40
20
0
ppm

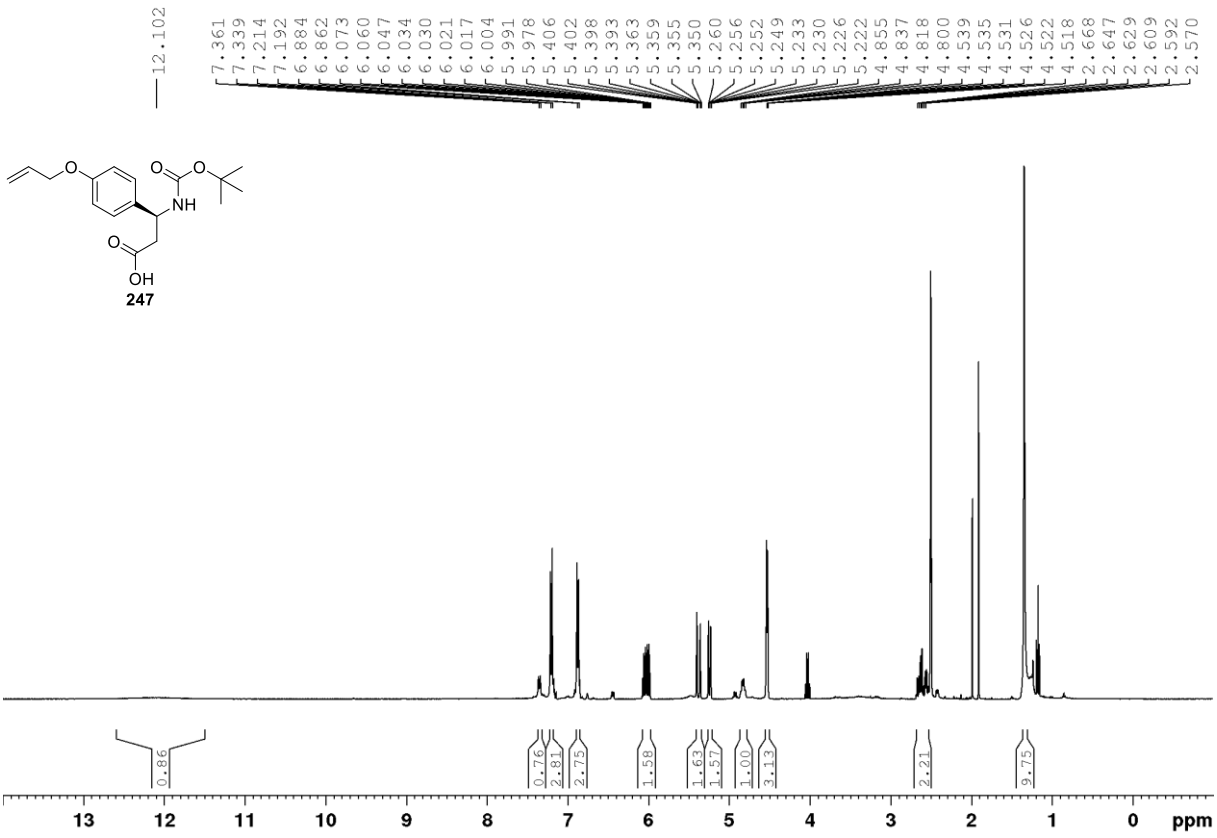

7.190
7.169
7.130
7.109
6.879
6.858
6.075
6.062
6.049
6.035
6.032
6.022
6.019
6.005
5.992
5.979
5.406
5.402
5.398
5.394
5.363
5.359
5.355
5.351
5.259
5.255
5.251
5.248
5.233
5.229
5.225
5.222
4.731
4.717
4.703
4.539
4.535
4.531
4.526
4.522
4.519
4.478
4.460
4.442
4.424
3.455
3.449
3.435
O
O
O
NH
HO
245
2.32
0.79
2.27
1.16
1.15
1.14
1.00
2.28
0.98
2.20
8.80
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

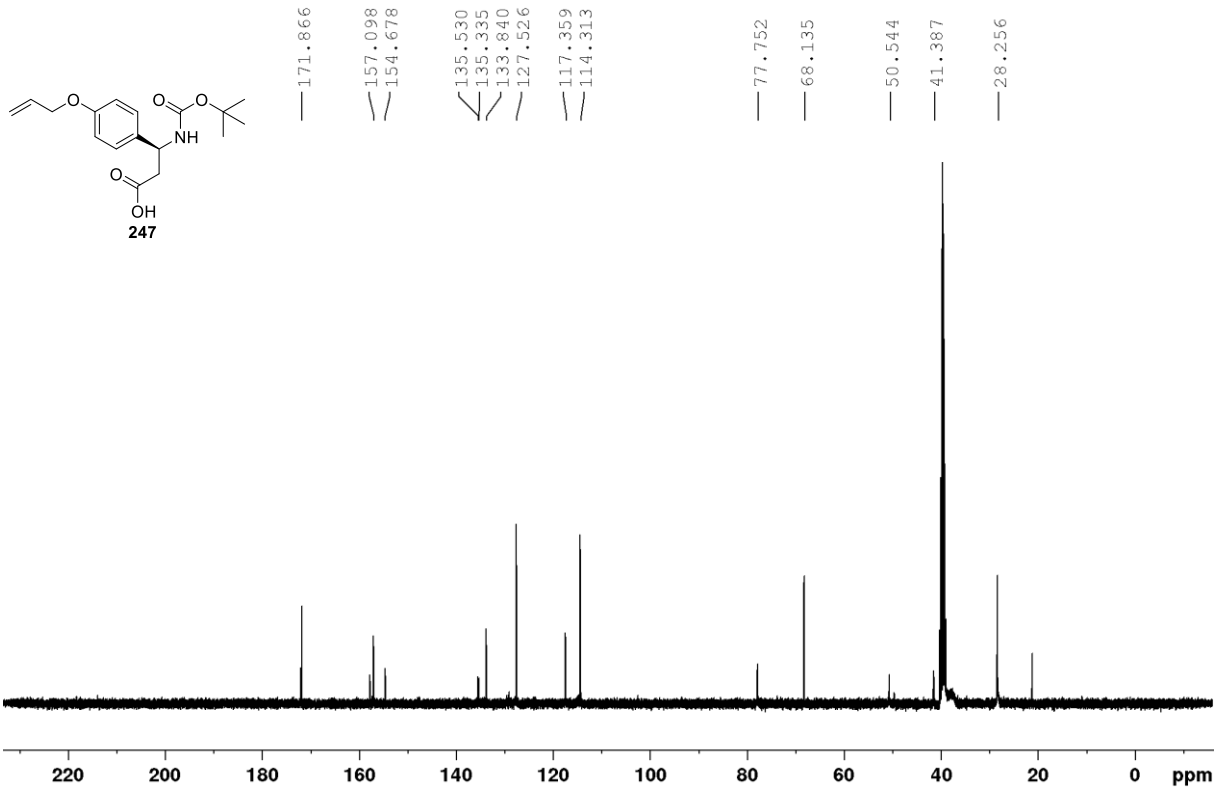

157.020
155.144
133.973
133.877
127.869
117.279
114.167
77.601
68.111
64.855
56.139
28.258
245
220
200
180
160
140
120
100
80
60
40
20
0
ppm

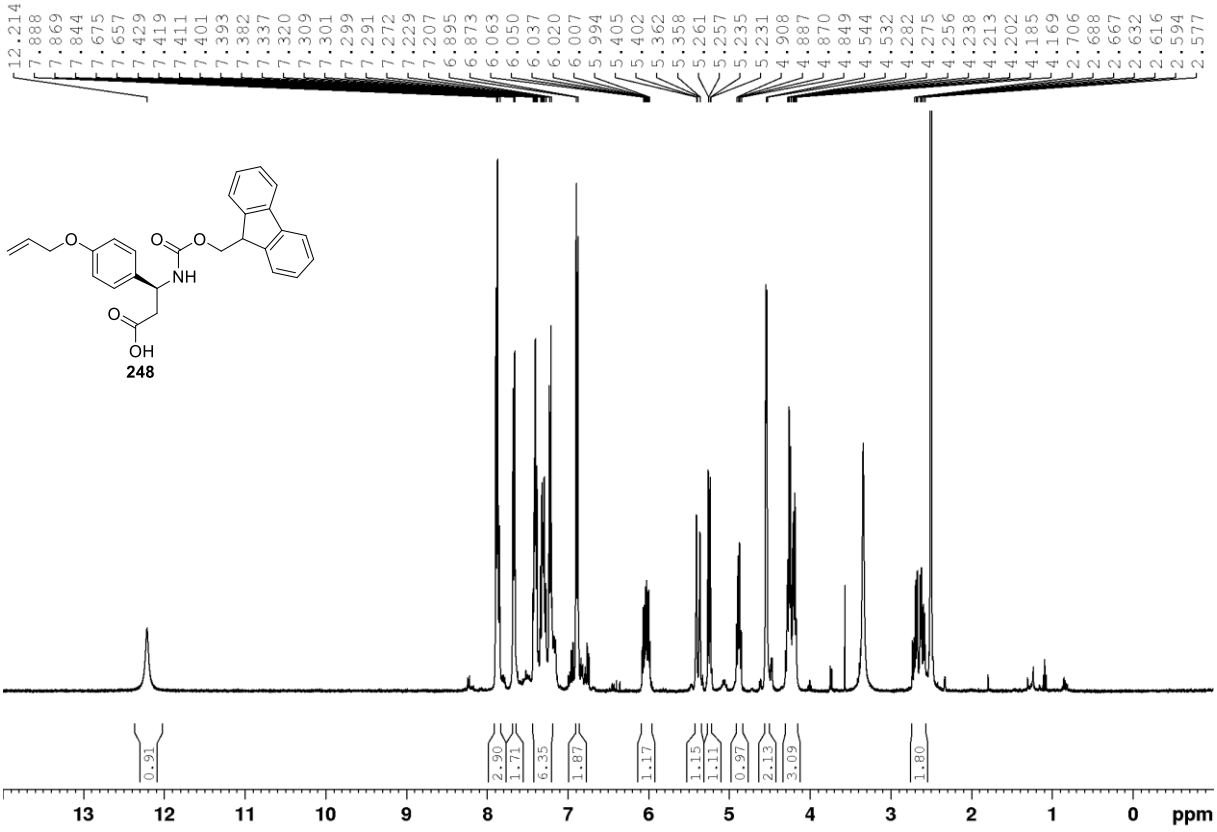

7.604
7.582
7.293
7.272
6.940
6.919
6.076
6.063
6.050
6.036
6.020
6.006
5.993
5.980
5.405
5.402
5.362
5.359
5.262
5.236
5.233
4.844
4.822
4.808
4.787
4.557
4.544
4.216
4.204
4.193
3.150
1.373
299
0.69
2.04
2.02
1.00
1.03
1.02
1.30
2.04
1.90
3.01
8.16
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

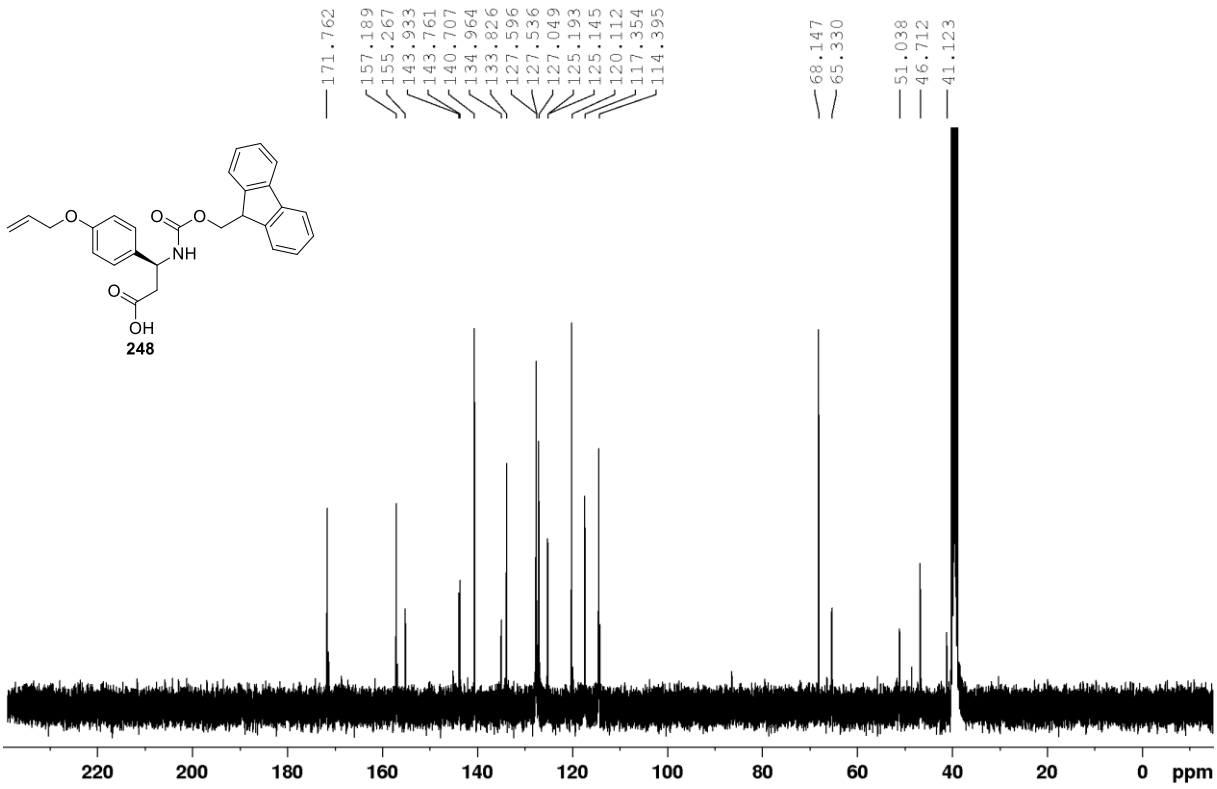

7.671
7.649
7.274
7.253
6.925
6.903
6.060
6.047
6.033
6.016
6.004
5.990
5.978
5.403
5.400
5.357
5.259
5.233
4.821
4.803
4.552
4.539
2.862
2.844
2.821
1.375
0.83
2.23
2.00
1.02
1.06
1.07
0.89
2.15
2.23
9.11
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
246

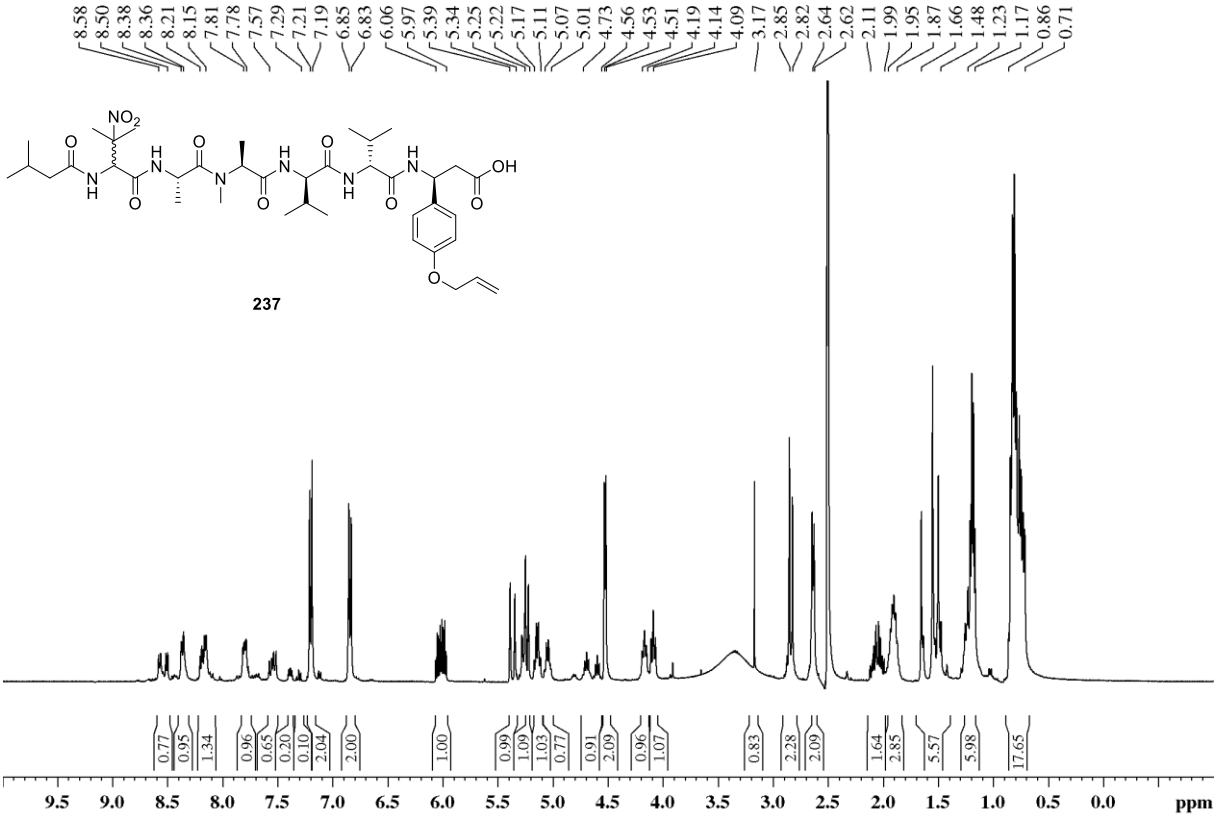

157.543
154.749
133.721
133.231
127.514
118.560
117.430
114.489
78.292
68.145
50.296
28.160
24.752
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
246

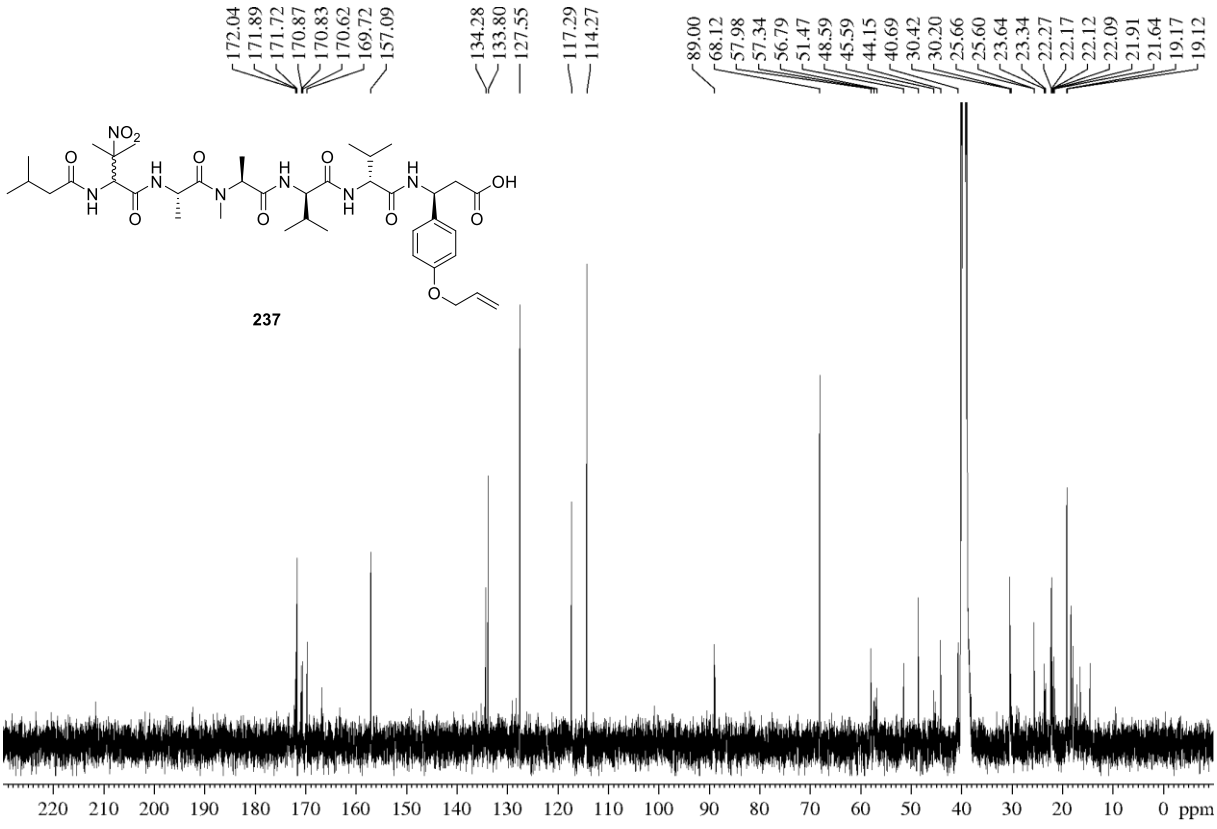

12.102
7.361
7.339
7.214
7.192
6.884
6.862
6.073
6.060
6.047
6.034
6.030
6.021
6.017
6.004
5.991
5.978
5.406
5.402
5.398
5.393
5.363
5.359
5.355
5.350
5.260
5.256
5.252
5.249
5.233
5.230
5.226
5.222
4.855
4.837
4.818
4.800
4.539
4.535
4.531
4.526
4.522
4.518
2.668
2.647
2.629
2.609
2.592
2.570
O
O
O
NH
O
OH
247
0.86
0.76
2.81
2.75
1.58
1.63
1.57
1.00
3.13
2.21
9.75
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

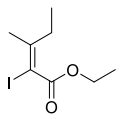

171.866
157.098
154.678
135.530
135.335
133.840
127.526
117.359
114.313
77.752
68.135
50.544
41.387
28.256
O
O
O
NH
O
OH
247
220
200
180
160
140
120
100
80
60
40
20
0
ppm


12.214
7.888
7.869
7.844
7.675
7.657
7.429
7.419
7.411
7.401
7.393
7.382
7.337
7.320
7.309
7.301
7.299
7.291
7.272
7.229
7.207
6.895
6.873
6.063
6.050
6.037
6.020
6.007
5.994
5.405
5.402
5.362
5.358
5.261
5.257
5.235
5.231
4.908
4.887
4.870
4.849
4.544
4.532
4.282
4.275
4.256
4.238
4.213
4.202
4.185
4.169
2.706
2.688
2.667
2.632
2.616
2.594
2.577
O
O
O
NH
O
OH
248
0.91
2.90
1.71
6.35
1.87
1.17
1.15
1.11
0.97
2.13
3.09
1.80
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


171.762
157.189
155.267
143.933
143.761
140.707
134.964
133.826
127.596
127.536
127.049
125.193
125.145
120.112
117.354
114.395
68.147
65.330
51.038
46.712
41.123
O
O
O
NH
O
OH
248
220
200
180
160
140
120
100
80
60
40
20
0
ppm

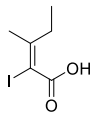

8.58
8.50
8.38
8.36
8.21
8.15
7.81
7.78
7.57
7.29
7.21
7.19
6.85
6.83
6.06
5.97
5.39
5.34
5.25
5.22
5.17
5.11
5.07
5.01
4.73
4.56
4.53
4.51
4.19
4.14
4.09
3.17
2.85
2.82
2.64
2.62
2.11
1.99
1.95
1.87
1.66
1.48
1.23
1.17
0.86
0.71
NO2
OH
O
N
H
237
0.77
0.95
1.34
0.96
0.65
0.20
0.10
2.04
2.00
1.00
0.99
1.09
1.03
0.77
0.91
2.09
0.96
1.07
0.83
2.28
2.09
1.64
2.85
5.57
5.98
17.65
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm


172.04
171.89
171.72
170.87
170.83
170.62
169.72
157.09
134.28
133.80
127.55
117.29
114.27
89.00
68.12
57.98
57.34
56.79
51.47
48.59
45.59
44.15
40.69
30.42
30.20
25.66
25.60
23.64
23.34
22.27
22.17
22.12
22.09
21.91
21.64
19.17
19.12
NO2
OH
O
N
H
237
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



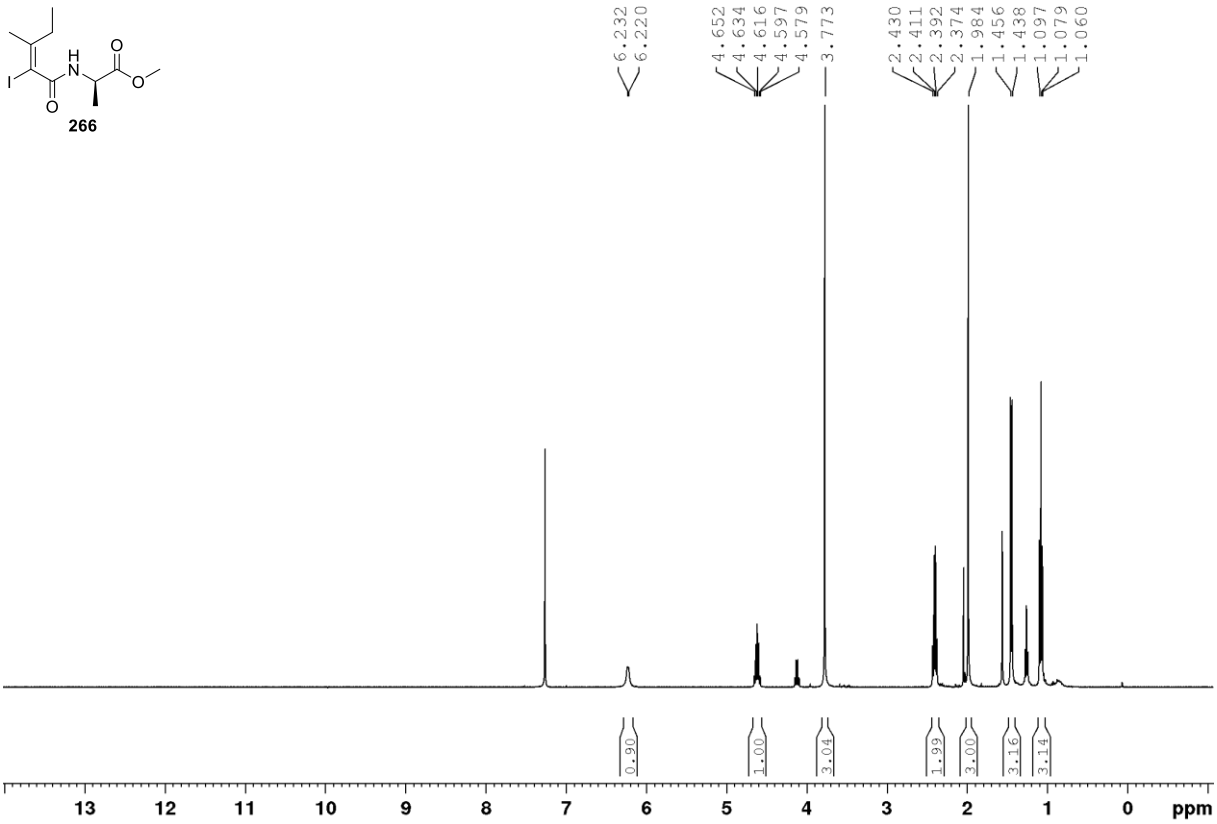
264

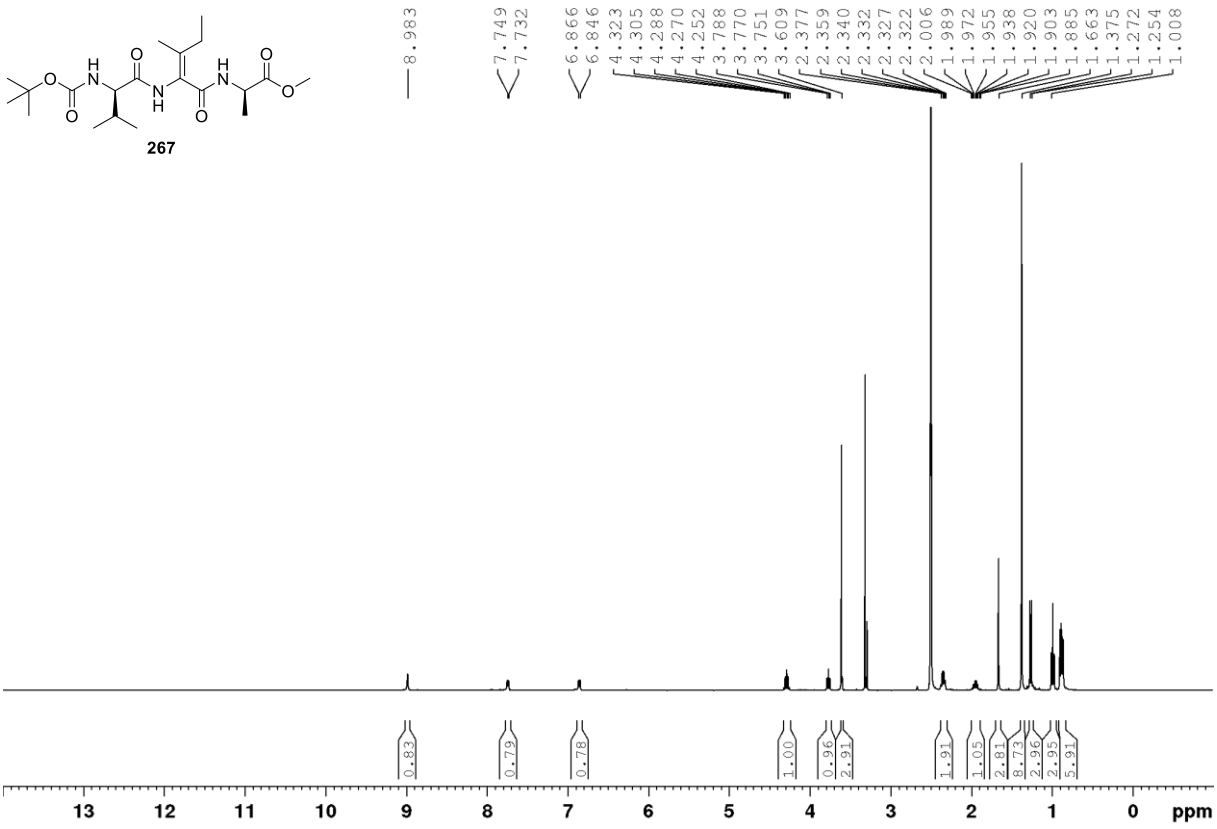
4.271
4.253
4.235
4.218
2.477
2.459
2.440
2.421
2.051
1.337
1.319
1.301
1.104
1.086
1.067
2.00
2.27
2.92
3.44
3.40
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

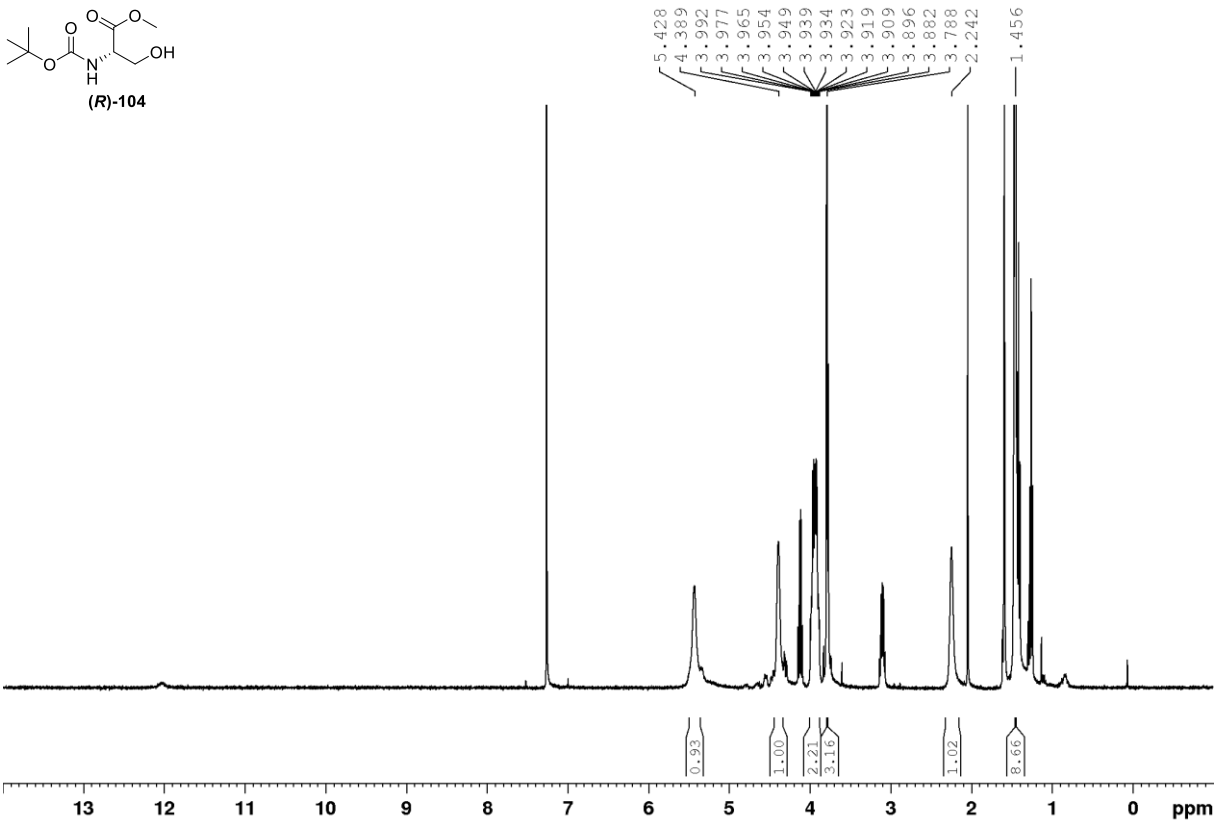


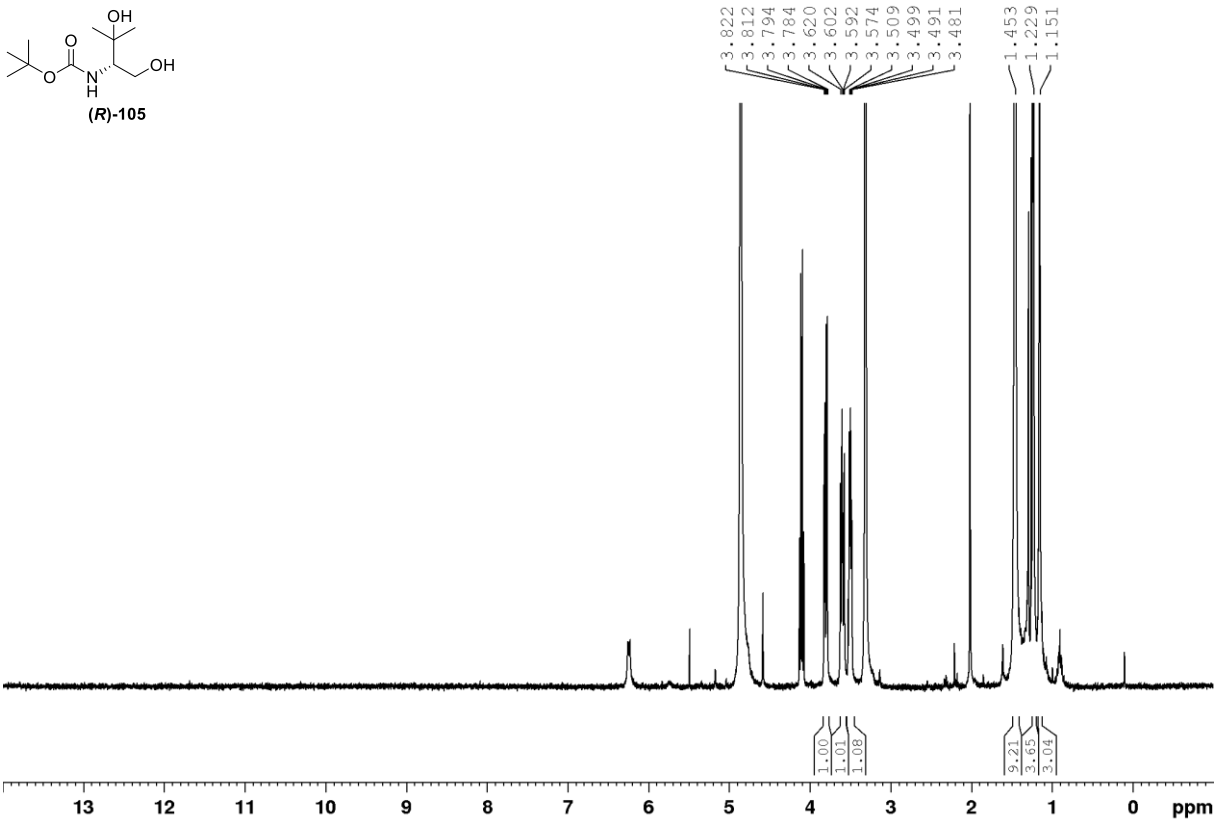
265

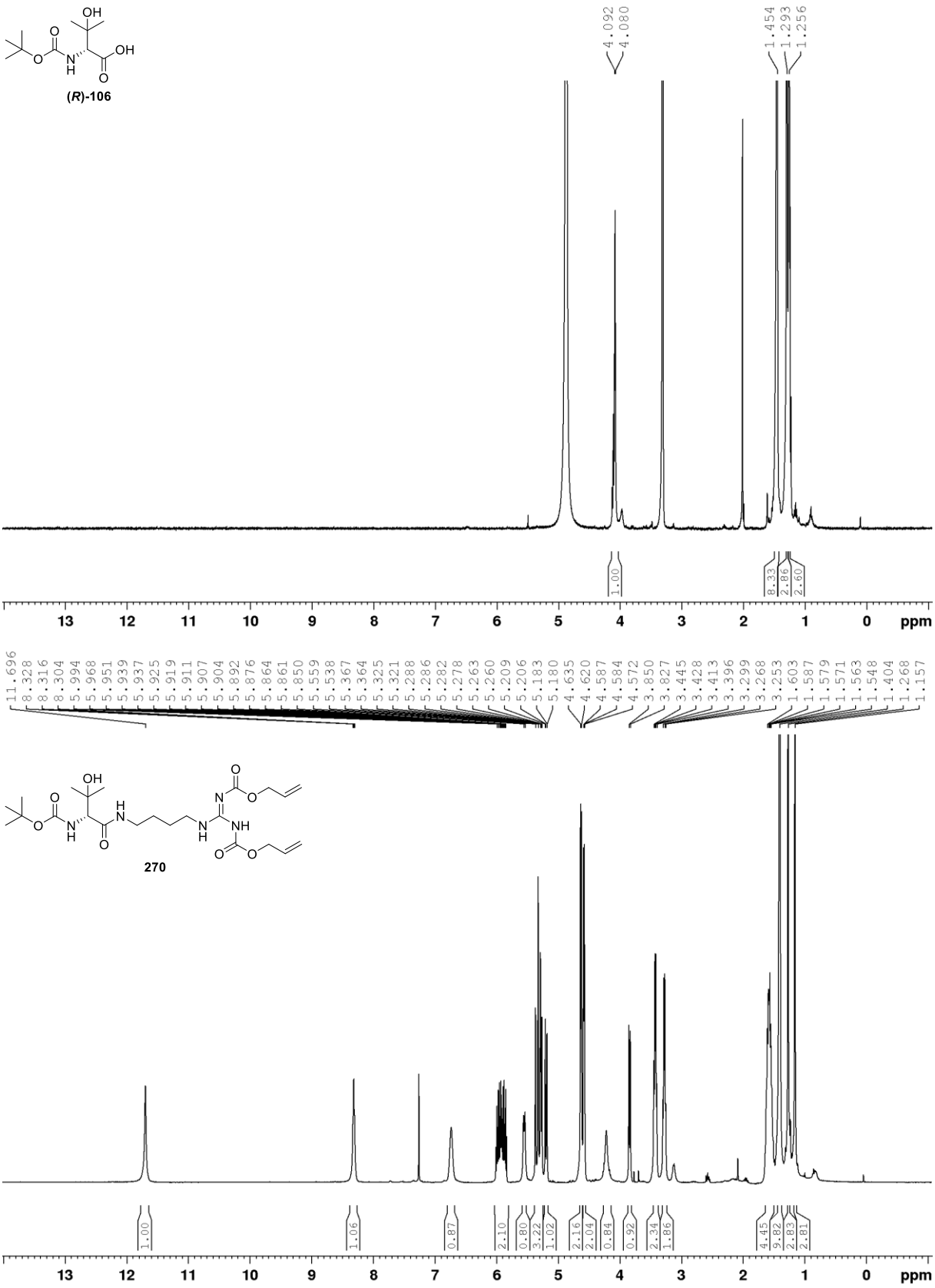
2.631
2.612
2.593
2.575
2.130
1.126
1.108
1.089
2.09
3.00
3.47
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

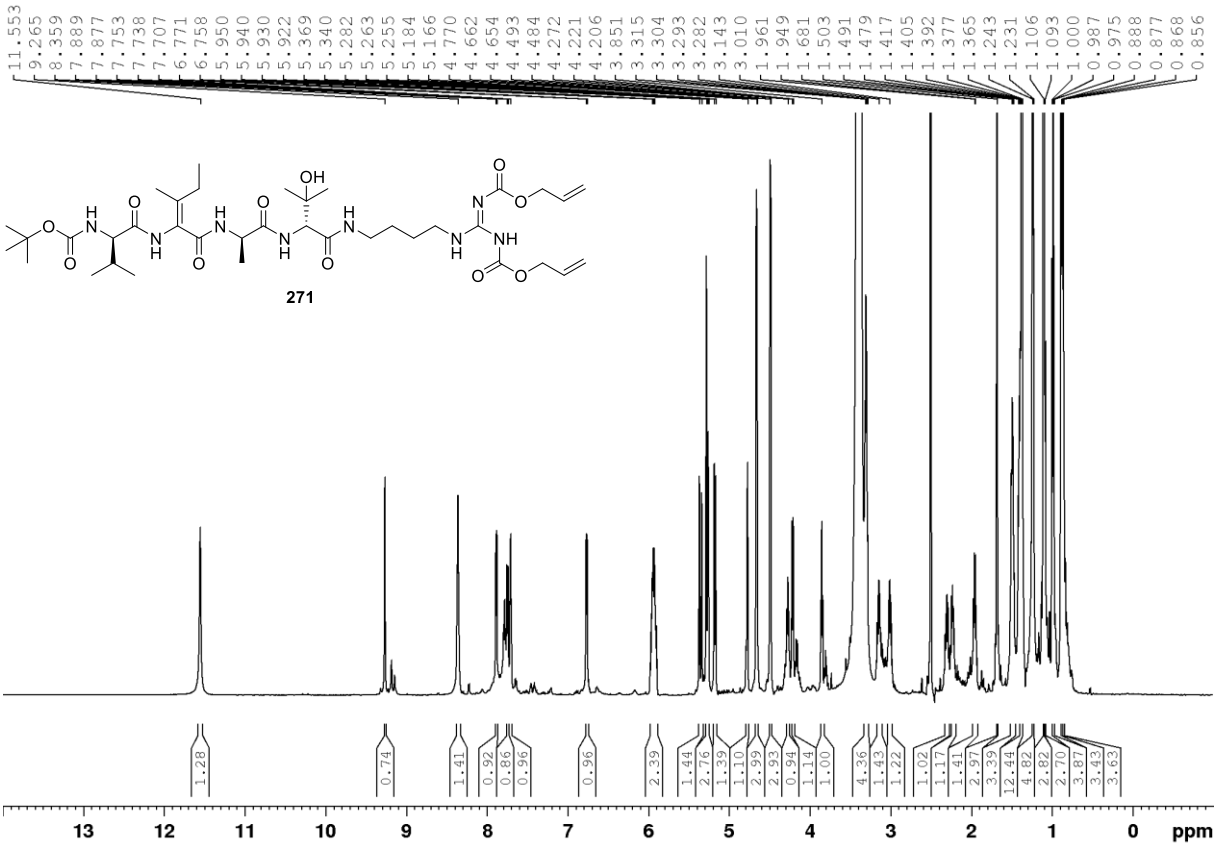

266
6.232
6.220
4.652
4.634
4.616
4.597
4.579
3.773
2.430
2.411
2.392
2.374
1.984
1.456
1.438
1.097
1.079
1.060
0.90
1.00
3.04
1.99
3.00
3.16
3.14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

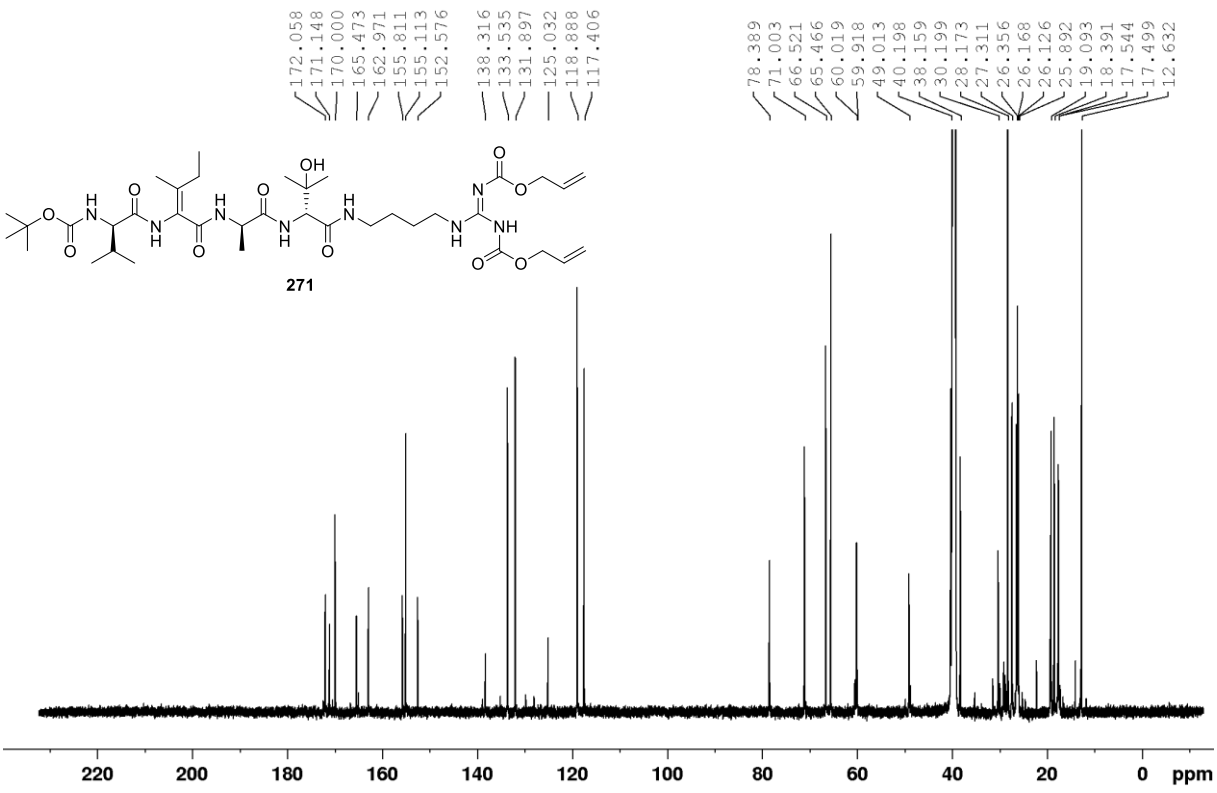

267
8.983
7.749
7.732
6.866
6.846
4.323
4.305
4.288
4.270
4.252
3.788
3.770
3.751
3.609
2.377
2.359
2.340
2.332
2.327
2.322
2.006
1.989
1.972
1.955
1.938
1.920
1.903
1.885
1.663
1.375
1.272
1.254
1.008
0.83
0.79
0.78
1.00
0.96
2.91
1.91
1.05
2.81
8.73
2.96
2.95
5.91
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


(R)-104
5.428
4.389
3.992
3.977
3.965
3.954
3.949
3.939
3.934
3.923
3.919
3.909
3.896
3.882
3.788
2.242
1.456
0.93
1.00
2.21
3.16
1.02
8.66
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


(R)-105
3.822
3.812
3.794
3.784
3.620
3.602
3.592
3.574
3.509
3.499
3.491
3.481
1.453
1.229
1.151
1.00
1.01
1.08
9.21
3.65
3.04
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


(R)-106
4.092
4.080
1.454
1.293
1.256
1.00
8.33
2.86
2.60
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
11.696
8.328
8.316
8.304
5.994
5.968
5.951
5.939
5.937
5.925
5.919
5.911
5.907
5.904
5.892
5.876
5.864
5.861
5.850
5.559
5.538
5.367
5.364
5.325
5.321
5.288
5.286
5.282
5.278
5.263
5.260
5.209
5.206
5.183
5.180
4.635
4.620
4.587
4.584
4.572
3.850
3.827
3.445
3.428
3.413
3.396
3.299
3.268
3.253
1.603
1.587
1.579
1.571
1.563
1.548
1.404
1.268
1.157
270
1.00
1.06
0.87
2.10
0.80
3.22
1.02
2.16
2.04
0.84
0.92
2.34
1.86
4.45
9.82
2.83
2.81
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm


271
ppm


271
ppm

7 Acknowledgement

Ganz besonders möchte ich mich bei Herrn Prof. Dr. Andreas Kirschning bedanken, der mir die Promotion zugetraut und die Themen dieser Arbeit anvertraut hat. Die Zusammenarbeit, aber auch alle Gespräche abseits der Chemie, haben mir stets Freude bereitet und ich habe mich immer wertgeschätzt gefühlt. Das lässt einen gerne zur Arbeit kommen.

Herrn Prof. Dr. Mark Brönstrup danke ich zunächst herzlich für die Übernahme des Korreferats, weiterhin aber auch für die enge Zusammenarbeit im OpCyBac-Projekt. Der regelmäßige, fachliche Austausch hat einen großen Beitrag zu dieser Arbeit geleistet.

Während meiner Forschnung habe ich mit vielen Personen an verschiedenen Projekten zusammengearbeitet. Diesen Personen gilt ein großer Dank für die konstruktive Kooperation.

Ich bedanke mich herzlich bei allen Personen der Analytikabteilungen, deren Hilfe ich oft und gerne in Anspruch genommen habe. Ein großer Dank gilt den Mitarbeiterinnen des Sekretariats, die ich immer um Hilfe in organisatorischen und bürokratischen Angelegenheiten bemühen durfte.

Während meiner Zeit als Promotionsstudent durfte ich mein Wissen mit zahlenreichen Studierenden teilen. Im Rahmen von Abschlussarbeiten und Praktika wurde ich im Gegenzug tatkräftig von Louis, Jonathan, Kevin, Norman, Tim, Laurent und Quynh unterstützt.

Vielen Dank an alle Personen, die meine Arbeit Korrektur gelesen haben.

Weiterhin bin ich sehr dankbar für die universelle Unterstützung von Gerald während meiner Promotion.

Nicht selten überkommt einen das Gefühl, dass man sein Leben im Labor verbringt. Das macht die Personen im eigenem Labor zu besonderen Weggefährten und Weggefährtinnen. Ich erinnere mich gerne daran, dass Christian, Janina und Ruben diesen Weg mit mir bestritten haben. Wenn auch nicht im selben Labor zuhause, ist Göran für mich ein mindestens genauso wertvoller Begleiter meiner Promotion und darüber hinaus. Immer bemerkenswert war für mich die freundschaftliche Arbeitsatmosphäre. Dafür verantwortlich sind all die lieben Kollegen und Kolleginnen, Freunde und Freundinnen, mit denen ich zusammen arbeiten und Pause machen durfte. Dafür bin ich sehr dankbar.

Ferner bin ich dankbar, dass ich priviligiert durch unbedingte Unterstützung meiner Familie und Freunde den Weg des Studiums bis zur Promotion beschreiten durfte.

8 *Curriculum Vitae* and list of publications

Personal data

Name: Tim Seedorf

Date and place of birth: 13.07.1993 in Hannover, Germany

Nationality: German

Academic background

06/2019-06/2023	**Doctoral studies in Organic Chemistry**, Leibniz Universität Hannover, Germany Insitute of Organic Chemistry, research group of Prof. Dr. Andreas Kirschning Doctoral thesis topic: „Synthesis of an antibacterial oligopeptide library“
10/2022 – 11/2022	**DAAD PhD exchange**, Indian Institute of Technology, Indore, India DAAD exhange mobility program „A New Passage to India“ Department of Chemistry Research group of Assoc. Prof. Dr. Chelvam Venkatesh „Synthesis of an antibacterial oligopeptide library“
08/2017 – 01/2018	**ERASMUS+ Internship**, Stockholms universitet, Sweden Department of Organic Chemistry Reseach group of. Prof. Dr. Berit Olofsson „metal-free thiocyanation of arenes using diaryliodonium salts“
10/2016 – 04/2019	**M. Sc. In Medicinal and Natural Product Chemistry**, Leibniz Universität Hannover, Germany Master thesis: „Synthetic studies towards Carolacton derivatives“ at Institute of Organic Chemistry, research group of Prof. Dr. Kirschning
09/2012 – 06/2016	**B. Sc. Biochemistry**, Leibniz Universität Hannover and Medizinische Hochschule Hannover, Germany Bachelor thesis: „Synthesis of a flunarizine library“ at Institute of Organic Chemistry, research group of Prof. Dr. Kirschning
08/2012	**Abitur**, Gymnasium Burgdorf, Burgdorf, Germany

Poster presentation

22nd Tetrahedron Symposium, **2022**, Lisbon, Portugal
„Synthesis of a cystobactamid library – highly potent antibiotic aromatic oligoamides through structure-activity relation studies“

Publications

[1] Natural and Synthetic Oligoarylamides: Privileged Structures for Medical Applications, T. Seedorf, A. Kirschning, D. Solga, *Chem. Eur. J.* **2021**, 27, 7321-7339.

[2] The Myxobacterial Antibiotic Myxovalargin: Biosynthesis, Structural Revision, Total Synthesis, and Molecular Characterization of Ribosomal Inhibition, T. O. Koller, U. Scheid, T. Kösel, J. Herrmann, D. Krug, H. I. M. Boshoff, B. Beckert, J. C. Evans, J. Schlemmer, B. Sloan, D. M. Weiner, L. E. Via, A. Moosa, T. R. Ioerger, M. Graf, B. Zinshteyn, M. Abdelshahid, F. Nguyen, S. Arenz, F. Gille, M. Siebke, T. Seedorf, O. Plettenburg, R. Green, A.-L. Warnke, J. Ullrich, R. Warrass, C. E. Barry 3rd, D. F. Warner, V. Mizrahi, A. Kirschning, D. N. Wilson, R. Müller, *J. Am. Chem. Soc.* **2023**, *145*, 2, 851-863.