An efficient one-pot three-component synthesis of tetrakis(uracil) and their corresponding bis-fused derivatives

Amr M. Abdelmoniem, a Said A. S. Ghozlan, a Holger Butenschön, b Doaa M. Abdelmoniem, a Ahmed H. M. Elwahy, *a and Ismail A. Abdelhamid**a

a Department of Chemistry, Faculty of Science, Cairo University, 12613 Giza, A. R. Egypt
b Institut für Organische Chemie, Leibniz Universität Hannover, Schneiderberg 1B, 30167 Hannover, Germany
Email:aelwahy@hotmail.com, ismail_shafy@yahoo.com

Received 01-07-2019 Accepted 03-03-2019 Published on line 03-17-2019

Abstract

A concise and efficient approach to tetrakis(uracil) derivatives by the reaction of bis(aldehydes) with four equivalents of 6-aminouracil is reported. Also, the synthesis of bis(pyrimido[4,5-b]quinolones) and bis(indeno-[2′,1′:5,6]pyrido[2,3-d]pyrimidine) derivatives has been accomplished by a three-component reaction involving bis(aldehydes), 6-aminouracil and the appropriate cyclic 1,3-diketone. The method involves domino Knoevenagel condensation / Michael addition reaction sequences.

Keywords: Bis(aldehydes), Michael addition, uracils, fused pyrimidines, quinolinones, indenones

DOI: https://doi.org/10.24820/ark.5550190.p010.875
Introduction

Uracil is a common and naturally occurring pyrimidine derivative and is one of the four nucleobases in the biopolymer RNA. The uracil scaffold and its derivatives exhibit a wide range of biological activities, including treatment of cancer and viral diseases. The annelated derivatives have also several applications as bronchodilators, antiviral agents, antiallergic compounds, adenine receptor antagonists and antihypertensive agents. Uracil derivatives have also been used as versatile building blocks for the synthesis of a variety of heterocycles, including pyrimido[4,5-d]pyrimidines, pyrido[2,3-d]pyrimidines, pyrimido[4,5-b]quinolines, and indeno[2',1':5,6]pyrido[2,3-d]pyrimidines. Pyrimido[4,5-b]quinolines have received much attention over the past years due to their wide range of applications including their use as anticancer and as radioprotective agents. Furthermore, multicomponent reactions (MCRs) represent an important attractive synthetic strategy as they provide a rapid access to organic compounds of high structural complexity. MCRs offer the advantage of selectivity, simplicity, atom-economy and an overall efficiency much more than conventional chemical reactions. Keeping in mind the importance of the uracil moiety and in continuation of our work on multicomponent reactions, Michael addition, Hantzsch reactions as well as on the synthesis of bis-heterocycles, we report herein a highly efficient one-pot synthesis of tetrakis(uracil), bis(pyrimido[4,5-b]quinolones) and bis(indeno[2',1':5,6]pyrido[2,3-d]pyrimidine) derivatives.

Results and Discussion

Scheme 1. The reaction of bis(aldehyde) 1a with 6-aminouracil 2 in acetic acid at reflux.

Firstly, we investigated the reaction of bis(aldehyde) 1a with 6-aminouracil 2 in acetic acid at reflux aiming at the synthesis of bis(9,10-dihydropyrido[2,3-d:6,5-d']dipyrimidinetetraone) 4a. Contrary to our expectation, the reaction did not yield compound 4a and instead gave the tetrakis(6-aminopyrimidine-2,4(1H,3H)-dione) 3a in 80% yield (Scheme 1).
Using a similar approach, reaction of aminouracil 2 with the appropriate bis(aldehyde)s 1b-e afforded the corresponding tetrakis(urate)n 3b-e, in which the tetra-urate units are linked to alkyl spacer via phenoxy groups, in 75-84% yields (Scheme 2).

Evidence for these structures came, for example for compound 3e, from the IR spectrum that indicated the presence of NH$_2$ and NH groups at $\nu$ 3407, 3181 cm$^{-1}$. In addition, it revealed two different carbonyl groups at $\tilde{\nu}$ 1711 and 1624 cm$^{-1}$. The $^1$H NMR spectrum of 3e indicated the presence of a multiplet signal integrating for four protons at $\delta$ 3.97 ppm assigned to the two OCH$_2$ groups, in addition to a singlet signal at $\delta$ 5.26 characteristic for the two methine protons. Moreover, signals assigned to the two amino groups appear as broad signals at $\delta$ 6.64 ppm. The signals of the NH groups appear as broad singlets at $\delta$ 10.29 and 10.48 ppm.

The $^{13}$C NMR spectrum of 3e is in agreement with the proposed structure. The particularly distinct signals at $\delta$ 26.1, $\delta$ 32.0, $\delta$ 67.5 and $\delta$ 68.2 are readily related to OCH$_2$CH, methine CH, OCH$_2$ and C-5 of pyrimidinone moiety, respectively. The mass spectrum of compound 3e exhibits the correct molecular ion peak at m/z 770 (3.5%). The compound readily loses a CN moiety to give an ion at m/z 744 (2.6%). The formation of peaks at m/z 646 (3.3%) and 508 (2.9%) are characteristic for loss of uracil [M-uracil +1] and 2 uracil-CH [M-2 uracil-CH] fragments, respectively.

**Scheme 2.** Synthesis of tetrakis(urate)n 3b-e linked to alkyl spacer via a phenoxy group.
Encouraged by the above results, and in a trial to ascertain the scope and generality of the protocol, a series of bis(aldehydes) containing aromatic linkages 1f-1h, was used. Thus, the reaction of bis(aldehydes) 1f-1h with four equivalents of 6-aminouracil 2 afforded the tetrakis(uracil) derivatives 3f-3h, which are linked to the benzene core via phenoxymethyl linkages in 73-76% yields (Scheme 3).

A proposed mechanism for the reaction is shown in Scheme 4. Nucleophilic addition of the enamine β-carbon of 6-aminouracil 2 to the two carbonyl centers of the bis(aldehydes) 1 affords the corresponding adducts 5. Subsequent elimination of water leads to the formation of the corresponding ene-imine intermediate 6. Michael addition of two molecules of 2 then react with 6 to afford the products 3 (Scheme 4).

Scheme 3. Tetrakis(uracil) derivatives containing benzene core and phenoxymethyl linkages 3f-3h.
Scheme 4. A proposed mechanism for the synthesis of compounds 3.

Similarly, the three-component reaction of bis(aldehyde) 1a with two moles of either 6-aminouracil 2 or 5,5-dimethyl-1,3-cyclohexanedione 7 afforded the corresponding bis(pyrimido[4,5-b]quinolines) 9a in 83% yield. In this case, uncyclized adduct 8a was not obtained (Scheme 5).

Scheme 5. A three-component reaction of bisaldehyde 1a, 6-aminouracil 2 and dimedone 7.
The structure of compound 9a was established based on the elemental analyses and spectral data. The IR spectra indicated the presence of NH groups with absorption bands at ν 3424, 3294 and 3227 cm⁻¹. In addition, it revealed a sharp band at ν 1721 cm⁻¹ corresponding to the ketonic C=O and a broad band at ν 1632 cm⁻¹ for both amidic carbonyl groups (C=O -2,4). The ¹H NMR spectrum of 9a indicated the presence of two singlets at δ 0.8 and 0.99 ppm assigned to the four methyl groups. In addition, a multiplet at δ 1.90-2.29 ppm was assigned to H7 and H9. It also featured the diastereotopic methylene ether linkage OCH₂ as a multiplet at δ 4.10-4.25 ppm. The singlet signal at 4.86 ppm is assigned to H5. The spectrum also featured the aromatic protons as multiplets at δ 6.81-7.27 ppm. The NH groups appeared as three broad signals integrating for six protons at δ 8.98, 10.11 and 10.56 ppm. Similarly, bis(pyrimido[4,5-b]quinolines) 9b-d and 9g-i, in which the pyrimido[4,5-b]quinoline moieties are linked to aliphatic or aromatic spacers, were successfully prepared in 82-89% yield by reaction of the appropriate bis-aldehyde 1b-d and 1g-i with two mole equivalents of both 6-aminouracil 2 and 5,5-dimethyl-1,3-cyclohexanedione 7 (Scheme 6). Compounds 9 should exist as a mixture of meso and R,S diastereomers because there is no obvious reason for a diastereoselective reaction. Inspection of the ¹H and ¹³C NMR spectra indicated that in most cases only one diastereomeric isomer (compounds 9a, 9b, 9g, 9h and 9i) was formed. However, in some cases, a mixture of meso and R, S diastereomers (9c and 9d) was apparently produced (cf. experimental data).

A reasonable mechanistic pathway is shown in Scheme 7. The first step involves the Knoevenagel condensation of the bis(aldehydes) 1 and cyclic 1,3-diketone 5 to generate diadduct 10. Intermediate 10 acts as a Michael acceptor, while 6-aminouracil can be considered a Michael donor. The reaction of one mole of compound 10 with two moles of 2 affords the Michael diadduct 11. The intermediate 11 undergoes an intramolecular cyclization involving the nucleophilic addition of the amino to the carbonyl group, followed by dehydration to afford the final isolated products 9 via the intermediacy of 12.
Scheme 6. Bis(pyrimido[4,5-b]quinolines) $9_b$-$d$ and $9_g$-$i$ with aliphatic or aromatic spacers.
Scheme 7. A proposed mechanism for the synthesis of compounds 9.


In order to extend the scope of this reaction, the replacement of dimedone 7 with 1,3-indanedione 13 was investigated. Thus, under comparable reaction conditions, the condensation of bis(aldehydes) with two moles
of both 6-aminouracil 2 and indanedione 13 proceeded smoothly and a new series of bis[indeno[2',1':5,6]-pyrido[2,3-d]pyrimidines] 15 was obtained (Scheme 8). Similarly, as in the case of compounds 9, NMR spectra of compounds 15 indicated the formation of one compound in all cases except 15c, which gave a mixture of meso and R, S diastereomers. One might assume that the stereogenic centers in 15c are more close to one another, so that the diastereomers may be distinguished, whereas in the other compounds, they are so far away from one another to show similar NMR signals (cf. experimental data).

Conclusions

In conclusion, we have demonstrated a simple and efficient route for the formation of tetrakis(urate), bis(pyrimido[4,5-b]quinolones) and bis(indeno[2',1':5,6]pyrido[2,3-d]pyrimidine) derivatives by a three-component reaction involving bis(aldehydes), 6-aminouracil and the appropriate cyclic-1,3-dione.

Experimental Section

General. Melting points were measured with a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded using a FTIR Bruker–vector 22 spectrophotometer as KBr pellets. The 1H and 13C NMR spectra were recorded in DMSO-d6 as solvent at 400 MHz and 100 MHz, respectively, on Bruker Ultrashield or Ascend NMR spectrometers. Chemical shifts are reported as δ values in ppm and referenced to the residual solvent signals as internal standards. Mass spectra were recorded with a Shimadzu GCMS–QP–1000 EX mass spectrometer in El (70 eV) mode. The elemental analyses were performed at the Microanalytical center, Cairo University.

Synthesis of compounds 3a-h. General procedure

A mixture of bisaldehyde 1a-h (1 mmol) and 6-aminouracil 2 (254 mg, 4 mmol) was heated at reflux in glacial AcOH (20 mL) for 5 h. The solvent was evaporated under reduced pressure. The residue was treated with aq. NaHCO3 solution (0.5 N, 20 mL), washed thoroughly with distilled H2O (20 mL) and left to dry in air. The crude product was purified by crystallization from EtO/1,4-dioxane (1:1, v/v, 10 mL).

5,5′,5″,5‴-(((Ethane-1,2-diylbis(oxy))bis(2,1-phenylene))bis(methanetriyl))tetrakis(6-aminopyrimidine-2,4(1H,3H)-dione) (3a). Yellowish white crystals (594 mg, 80%), m. p. >300 °C. IR (KBr): νmax 3357, 3181 (br, NH2 and NH), 1712 (C=O), 1630 (C=O) cm−1. 1H NMR (400 MHz, DMSO-d6): δ 4.26 (m, 4 H, 2 OCH2CH2), 5.32 (s, 2 H, 2 CH-5), 6.61 (br s, 8 H, 4 NH2), 6.77-6.91 (m, 8 H, Ar-H), 10.27 (br s, 2 H, 2 NH-1), 10.36 (br s, 2 H, 4 NH-3) ppm. 13C NMR (100 MHz, DMSO-d6): δ 31.9 (CH), 66.6 (OCH2), 68.1 (CS), 114.0 (Ar-CH), 121.4 (Ar-CH), 124.5 (Ar-C), 126.9 (Ar-CH), 128.2 (Ar-CH), 150.2 (Ar-C), 155.6 and 164.8 (CO-2 and CO-4) ppm. MS (El, 70 eV): m/z 742 [M]+. Anal. calcd for C32H30N12O10: C, 51.75; H, 4.07; N, 22.63. Found: C, 51.38; H, 3.87; N, 22.19%.

5,5′,5″,5‴-(((Ethane-1,2-diylbis(oxy))bis(4,1-phenylene))bis(methanetriyl))tetrakis(6-aminopyrimidine-2,4(1H,3H)-dione) (3b). Yellowish white crystals (623 mg, 84%), m. p. >300 °C. IR (KBr): νmax 3377, 3144 (br, NH2 and NH), 1711 (CO), 1624 (CO) cm−1. 1H NMR (400 MHz, DMSO-d6): δ 4.23 (s, 4H, 2 OCH2), 5.26 (s, 2 H, 2 CH-5), 6.70 (br s, 8 H, 4 NH2), 6.81-6.98 (m, 8 H, Ar-H), 10.28 (br s, 2 H, 2 NH-1), 10.48 (br s, 2 H, 4 NH-3) ppm. 13C NMR (100 MHz, DMSO-d6): δ 32.3 (CH), 66.7 (OCH2), 67.4 (CS), 114.2 (Ar-CH), 128.1 (Ar-CH), 131.1 (Ar-C), 150.2 (Ar-C), 156.3 and 163.8 (CO-2 and CO-4) ppm. MS (El, 70 eV): m/z 742 [M]+. Anal. calcd for C32H30N12O10: C, 51.75; H, 4.07; N, 22.63. Found: C, 51.38; H, 3.87; N, 22.19%.
5,5',5'',5''''-(((Propane-1,3-diylbis(oxy))bis(2,1-phenylene))bis(methanetriyl))tetrakis-(6-aminopyrimidine-2,4(1H,3H)-dione) (3c). Yellowish white crystals (590 mg, 78%), m. p. 288-290 °C. IR (KBr): ν\text{max} 3377, 3185 (br, NH₂ and NH), 1712 (CO), 1631 (CO) cm⁻¹. ¹H NMR (400 MHz, DMSO-δ₆): δ 2.12 (m, 2 H, OCH₂CH₂), 3.86 (m, 4 H, 2 OCH₂CH₂), 5.30 (s, 2 H, 2 CH-5), 6.64 (br s, 8 H, 4 NH₂), 6.77-7.09 (m, 8 H, Ar-H), 10.11 (br s, 2 H, 2 NH-1), 10.30 (br s, 2 H, 4 NH-3) ppm. ¹³C NMR (100 MHz, DMSO-δ₆): δ 29.7 (OCH₂CH₂), 32.3 (CH), 63.9 (OCH₂CH₂), 65.2 (C₅), 113.7 (Ar-CH), 120.0 (Ar-CH), 125.1 (Ar-C), 127.3 (Ar-CH), 130.3 (Ar-CH), 150.6 (Ar-C), 155.6 and 164.8 (CO-2 and CO-4) ppm. MS (EI, 70 eV): m/z 756 [M⁺]. Anal. calcd for C₃₃H₃₂N₁₂O₁₀: C, 52.38; H, 4.26; N, 22.21. Found: C, 52.09; H, 4.13; N, 22.05%.

5,5',5'',5''''-(((Butane-1,4-diylbis(oxy))bis(2,1-phenylene))bis(methanetriyl))tetrakis-(6-aminopyrimidine-2,4(1H,3H)-dione) (3d). Yellowish crystals (578 mg, 75%), m. p. >300 °C. IR (KBr): ν\text{max} 3358, 3180 (br, NH₂ and NH), 1708, 1631 (CO-2,4) cm⁻¹. ¹H NMR (400 MHz, DMSO-δ₆): δ 1.91 (m, 4 H, 2 OCH₂CH₂), 3.90 (m, 4 H, 2 OCH₂CH₂), 5.29 (s, 2 H, 2 CH-5), 6.19 (br s, 8 H, 4 NH₂), 6.80-7.25 (m, 8 H, Ar-H), 10.30 (br s, 2 H, 2 NH-1), 10.43 (br s, 2 H, 4 NH-3) ppm. ¹³C NMR (100 MHz, DMSO-δ₆): δ 29.7 (OCH₂CH₂), 32.5 (CH), 66.8 (OCH₂CH₂), 68.6 (C₅), 113.8 (Ar-CH), 121.0 (Ar-CH), 125.8 (Ar-CH), 128.9 (Ar-C), 129.4 (Ar-CH), 150.2 (Ar-C), 155.6 and 164.6 (CO-2 and CO-4) ppm. MS (EI, 70 eV): m/z 770 [M⁺]. Anal. calcd for C₃₄H₃₄N₁₂O₁₀: C, 52.99; H, 4.45; N, 21.81. Found: C, 52.74; H, 4.21; N, 21.67%.

5,5',5'',5''''-(((Butane-1,4-diylbis(oxy))bis(4,1-phenylene))bis(methanetriyl))tetrakis-(6-aminopyrimidine-2,4(1H,3H)-dione) (3e). Yellowish white crystals (631 mg, 82%), m. p. 294-296 °C. IR (KBr): ν\text{max} 3407, 3181 (br, NH and NH₂), 1711 (CO), 1624 (CO) cm⁻¹. ¹H NMR (400 MHz, DMSO-δ₆): δ 1.84 (m, 4 H, 2 OCH₂CH₂), 3.97 (m, 4 H, 2 OCH₂CH₂), 5.26 (s, 2 H, 2 CH-5), 6.64 (br s, 8 H, 4 NH₂), 6.71-6.97 (m, 8 H, Ar-H), 10.29 (br s, 2 H, 2 NH-1), 10.48 (br s, 2 H, 4 NH-3) ppm. ¹³C NMR (100 MHz, DMSO-δ₆): δ 26.1 (OCH₂CH₂), 32.0 (CH), 67.5 (OCH₂CH₂), 68.2 (C₅), 114.1 (Ar-CH), 127.4 (Ar-CH), 130.0 (Ar-C), 150.3 (Ar-C), 156.7 and 164.1 (CO-2 and CO-4) ppm. MS (EI, 70 eV): m/z 770 [M⁺]. Anal. calcd for C₃₄H₃₄N₁₂O₁₀: C, 52.99; H, 4.45; N, 21.81. Found: C, 52.62; H, 4.19; N, 21.66%.

5,5',5'',5''''-(((1,2-Phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))bis(methanetriyl))tetrakis-(6-aminopyrimidine-2,4(1H,3H)-dione) (3f). Yellowish white crystals (597 mg, 73%), m. p. 298-300 °C. IR (KBr): ν\text{max} 3368, 3191 (br, NH₂ and NH), 1706 (CO), 1631 (CO) cm⁻¹. ¹H NMR (400 MHz, DMSO-δ₆): δ 5.02 (s, 2 H, OCH₂), 5.29 (s, 2 H, 2 CH-5), 6.62 (br s, 8 H, 4 NH₂), 6.83-7.35 (m, 8 H, Ar-H), 10.20 (br s, 2 H, 2NH-1), 10.42 (br s, 2 H, 4 NH-3) ppm. MS (EI, 70 eV): m/z 818 [M⁺]. Anal. calcd for C₃₈H₃₄N₁₂O₁₀: C, 55.74; H, 4.19; N, 20.53. Found: C, 55.42; H, 4.01; N, 20.36%.

5,5',5'',5''''-(((1,4-Phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis(methanetriyl))tetrakis-(6-aminopyrimidine-2,4(1H,3H)-dione) (3g). Yellowish white crystals (622 mg, 76%), m. p. >300 °C. IR (KBr): ν\text{max} 3410, 3189 (br, NH₂ and NH), 1711 (CO), 1626 (CO) cm⁻¹. ¹H NMR (400 MHz, DMSO-δ₆): δ 5.05 (m, 2 H, OCH₂), 5.26 (s, 2 H, 2 CH-5), 6.61 (br s, 8 H, 4 NH₂), 6.83-7.00 (m, 8 H, Ar-H), 10.28 (br s, 2H, 2NH-1), 10.48 (br s, 2 H, 4 NH-3) ppm. ¹³C NMR (100 MHz, DMSO-δ₆): δ 32.2 (CH), 69.3 (OCH₂), 69.9 (C₅), 114.4 (Ar-CH), 128.2 (Ar-CH), 132.3 (Ar-CH), 136.2 (Ar-C), 137.4 (Ar-C), 150.2 (Ar-C), 155.6 and 164.8 (CO-2 and CO-4) ppm. MS (EI, 70 eV): m/z 818 [M⁺]. Anal. calcd for C₃₈H₃₄N₁₂O₁₀: C, 55.74; H, 4.19; N, 20.53. Found: C, 55.38; H, 3.98; N, 20.42%.

5,5',5'',5''''-(((1,3-Phenylenebis(methylene))bis(oxy))bis(4,1-phenylene))bis(methanetriyl))tetrakis-(6-aminopyrimidine-2,4(1H,3H)-dione) (3h). Yellowish white crystals (605 mg, 74%), m. p. 292-294 °C. IR (KBr): ν\text{max} 3381, 3164 (br, NH₂ and NH), 1712 (CO-6), 1627 (CO) cm⁻¹. ¹H NMR (400 MHz, DMSO-δ₆): δ 5.06 (s, 2 H, OCH₂), 5.26 (s, 2 H, 2CH-5), 6.61 (br s, 8 H, 4 NH₂), 6.85-7.02 (m, 8 H, Ar-H), 10.20 (br s, 2 H, 2 NH-1), 10.42 (br s, 2 H, 4 NH-3) ppm. ¹³C NMR (100 MHz, DMSO-δ₆): δ 32.2 (CH), 69.5 (OCH₂), 70.0 (C₅), 114.4 (Ar-CH), 127.5 (Ar-CH), 128.0 (Ar-CH), 129.1 (Ar-CH), 132.3 (Ar-CH), 136.2 (Ar-C), 138.0 (Ar-C), 150.2 (Ar-C), 155.6 and 164.7
Synthesis of compounds 9a-d and 9g-l. General procedure
A mixture of bisaldehyde 1a-i (1 mmol), 6-aminoaracil 2 (254 mg, 2 mmol) and dimedone 7 (280 mg, 2 mmol) was heated at reflux in glacial AcOH (20 mL) for 5 h. The solvent was evaporated under reduced pressure. The residue was treated with aq. NaHCO₃ solution (0.5 N, 20 mL), washed thoroughly with distilled H₂O (20 mL) and left to dry. The crude product was purified by crystallization from EtOH/1,4-dioxane (1:1, v/v, 10 mL).

5,5′-((Ethane-1,2-diylbis(oxyl))bis-(2,1-phenylene))bis-(8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]-quinoline-2,4,6(1H,3H,7H)-trione) (9a). Yellowish white crystals (608 mg, 83%), m. p. 292-294 °C. IR (KBr): νmax 3424 (NH), 3294 (NH), 3227 (NH), 1721 (CO-6), 1632 (br, CO-2,4) cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): δ 0.80 (s, 6 H, 2 CH₃), 0.99 (s, 6 H, 2 CH₃), 1.90-2.29 (m, 8 H, 2 CH₂-9 and 2 CH₂-7), 4.10-4.25 (m, 4 H, 2 OCH₂), 4.86 (s, 2 H, 2 CH-5), 6.81-7.27 (m, 8 H, Ar-H), 8.98 (br s, 2 H, 2 NH-10), 10.11 (br s, 2 H, 2 NH-1), 10.56 (br s, 2 H, 2 NH-3) ppm. ¹³C NMR (100 MHz, DMSO-d₆): δ 26.5 (CH₃), 29.7 (CH₃), 32.5 (C-8), 33.0 (CH), 40.6 (CH₂-9), 50.7 (CH₂-7), 66.2 (OCH₂), 88.6 (C-4a), 110.1 (C-5a), 112.7 (Ar-CH), 120.3 (Ar-CH), 127.7 (Ar-CH), 132.7 (Ar-CH), 133.2 (Ar-C), 149.7 (C-9a), 150.4 (Ar-C), 157.2 and 163.1 (CO-2, CO-4), 194.6 (CO-6) ppm. MS (EI, 70 eV): m/z 732 [M⁺]. Anal. calcd for C₄₀H₄₀N₆O₈: C, 65.56; H, 5.50; N, 11.47. Found: C, 65.29; H, 5.31; N, 11.17%.

5,5′-((Ethane-1,2-diylbis(oxyl))bis-(4,1-phenylene))bis-(8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]-quinoline-2,4,6(1H,3H,7H)-trione) (9b). Yellow crystals (622 mg, 85%), m. p. 294-296 °C. IR (KBr): νmax 3424 (NH), 3286 (NH), 3222 (NH), 1719 (CO-6), 1664 (br, CO-2,4) cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): δ 0.89 (s, 6 H, 2 CH₃), 1.02 (s, 6 H, 2 CH₂), 1.92-2.22 (m, 4 H, 2 CH₂-9), 2.39-2.45 (m, 4 H, 2 CH₂-7), 4.18 (s, 4 H, 2 OCH₂), 4.69 (s, 2 H, 2 CH-5), 6.77-7.10 (m, 8 H, Ar-H), 8.79 (br s, 2 H, 2 NH-10), 10.12 (br s, 2 H, 2 NH-1), 10.70 (br s, 2 H, 2 NH-3) ppm. ¹³C NMR (100 MHz, DMSO-d₆): δ 27.0 (CH₃), 29.4 (CH₃), 32.6 (C-8), 32.7 (CH), 40.6 (CH₂-9), 50.6 (CH₂-7), 66.7 (OCH₂), 90.3 (C-4a), 111.9 (C-5a), 114.3 (Ar-CH), 129.0 (Ar-CH), 139.5 (Ar-C), 149.3 (C-9a), 156.9 and 163.2 (CO-2 and CO-4), 194.8 (CO-6) ppm. MS (EI, 70 eV): m/z 732 [M⁺]. Anal. calcd for C₄₀H₄₀N₆O₈: C, 65.56; H, 5.50; N, 11.47. Found: C, 65.34; H, 5.27; N, 11.21%

5,5′-((Propane-1,3-diylbis(oxyl))bis-(2,1-phenylene))bis-(8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]-quinoline-2,4,6(1H,3H,7H)-trione) (9c). Yellow crystals (642 mg, 86%), m. p. 266-268 °C. IR (KBr): νmax 3411 (NH), 3265 (NH), 3159 (NH), 1708 (CO-6), 1638 (br, CO-2,4) cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): δ 0.80 (s, 6 H, 2 CH₃), 0.98 (s, 6 H, 2 CH₂), 1.91 (m, 2 H, OCH₂CH₂), 2.12-2.47 (m, 8 H, 2 CH₂-9 and 2 CH₂-7), 4.01 (m, 4 H, 2 OCH₂CH₂), 4.90 (s, 2 H, 2 CH-5), 6.72-7.24 (m, 8 H, Ar-H), 8.75 (br s, 2 H, 2 NH-10), 10.12 (br s, 2 H, 2 NH-1), 10.60 (br s, 2 H, 2 NH-3) ppm. ¹³C NMR (100 MHz, DMSO-d₆): δ 26.4 (CH₃), 29.6 (OCH₂CH₂), 29.9 (CH₃), 32.5 (C-8), 32.8 (CH), 40.6 (CH₂-9), 50.8 (CH₂-7), 65.1 (OCH₂CH₂), 89.1 (C-4a), 110.5 (C-5a), 111.9 (Ar-CH), 119.8 (Ar-CH), 127.6 (Ar-CH), 132.3 (Ar-CH), 133.4 (Ar-C), 149.4 (C-9a), 152.5 (Ar-C), 157.4 and 163.1 (CO-2), 163.2 (CO-4), 194.5 (CO-6) ppm. MS (EI, 70 eV): m/z 746 [M⁺]. Anal. calcd for C₄₁H₄₂N₆O₈: C, 65.94; H, 5.67; N, 11.25. Found: C, 65.63; H, 5.41; N, 11.09%

5,5′-((Butane-1,4-diylbis(oxyl))bis-(2,1-phenylene))bis-(8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]-quinoline-2,4,6(1H,3H,7H)-trione) (9d). Yellowish white crystals (669 mg, 88%), m. p. >300 °C. IR (KBr): νmax 3431, 3291 (br, 3 NH), 1714 (CO-6), 1647 (CO-2 and CO-4) cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): a pair of diastereomers (1:1), δ 0.83 (0.84) (s, 6 H, 2 CH₃), 0.97 (0.99) (s, 6 H, 2 CH₃), 1.85 (m, 4 H, 2 OCH₂CH₂), 2.12-2.48 (m, 8 H, 2 CH₂-9 and 2 CH₂-7), 3.89 (4.00) (m, 4 H, 2 OCH₂CH₂), 4.89 (4.96) (s, 2 H, 2 CH-5), 6.72-7.24 (m, 8 H, Ar-H), 8.68 (8.73) (br s, 2 H, 2 NH-10), 10.06 (10.10) (br s, 2 H, 2 NH-1), 10.59 (10.67) (br s, 2 H, 2 NH-3) ppm. ¹³C NMR (100 MHz, DMSO-d₆): a pair of diastereomers (1:1), δ 26.2 (26.4) (CH₃), 26.6 (26.7) (OCH₂CH₂), 29.6 (29.7) (CH₃), 32.4 (32.5) (C-8), 32.6 (32.7) (CH), 40.6 (40.7) (CH₂-9), 50.7 (50.8) (CH₂-7), 68.0 (68.1) (OCH₂CH₂),
5,5′-((1,4-Phenylenebis(methylene))bis(oxo))bis-(4,1-phenylene)bis-(8,8-dimethyl-5,8,9,10-tetrahydro-pyrimidino[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione) (9g). Pale yellow crystals (719 mg, 89%), m. p. >300 °C. IR (KBr): νmax 3428, 3198 (br, NH), 1720 (CO-6), 1664 (br, CO-2 and CO-4) cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): single stereoisomer, δ 0.90 (s, 6 H, 2 CH₃), 1.02 (s, 6 H, 2 CH₃), 2.00-2.21 (m, 4 H, 2 CH₂-9), 2.43 (m, 4 H, 2 CH₂-7), 4.70 (s, 2 H, 2 CH₅), 5.01 (s, 4 H, 2 OCH₂), 6.81-7.10 (m, 8 H, Ar-H-4,1-phenylene), 7.41 (s, 4 H, Ar-H-1,4-phenylene), 8.79 (br s, 2H, 2NH-10), 10.27 (br s, 2H, 2NH-1), 10.70 (br s, 2H, 2NH-3) ppm. ¹³C NMR (100 MHz, DMSO-d₆): δ 27.0 (CH₃), 29.4 (CH₃), 32.4 (C-8), 32.6 (CH), 40.6 (CH-2), 50.6 (CH₂-7), 69.3 (OCH₂), 90.3 (C-4a), 111.9 (C-5a), 114.5 (Ar-CH), 128.1 (Ar-CH), 129.0 (Ar-CH), 137.3 (Ar-C), 139.5 (Ar-C), 149.4 (C-9a), 150.2 (C-10a), 156.7 and 163.2 (CO-2 and CO-4), 194.6 (CO-6) ppm. MS (EI, 70 eV): m/z 760 [M⁺]. Anal. calcd for C₄₂H₄₄N₆O₆: C, 66.30; H, 5.83; N, 11.05. Found: C, 66.09; H, 5.44; N, 10.78%.

5,5′-((1,3-Phenylenebis(methylene))bis(oxo))bis-(4,1-phenylene)bis-(8,8-dimethyl-5,8,9,10-tetrahydro-pyrimidino[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione) (9h). Yellow crystals (663 mg, 82%), m. p. >300 °C. IR (KBr): νmax 3205 (br, NH), 1717 (CO-6), 1664 (CO-2 and CO-4) cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): δ 0.90 (s, 6 H, 2 CH₃), 1.02 (s, 6 H, 2 CH₃), 2.00-2.22 (m, 4 H, 2 CH₂-9), 2.44 (m, 4 H, 2 CH₂-7), 4.70 (s, 2 H, 2 CH₅), 5.02 (s, 4 H, 2 OCH₂), 6.82-7.10 (m, 8 H, Ar-H-4,1-phenylene), 7.37 (s, 3 H, Ar-H), 4,5,6,1-3-phenylene), 7.47 (s, 1 H, Ar-H2,1-phenylene), 8.80 (br s, 2 H, 2 NH-10), 10.27 (br s, 2 H, 2 NH-1), 10.70 (br s, 2 H, 2 NH-3) ppm. ¹³C NMR (100 MHz, DMSO-d₆): δ 27.0 (CH₃), 29.4 (CH₃), 32.5 (C-8), 32.6 (CH), 40.6 (CH-2), 50.6 (CH₂-7), 69.5 (OCH₂), 90.3 (C-4a), 111.9 (C-5a), 114.4 (Ar-CH), 127.5 (Ar-CH), 127.5 (Ar-CH), 128.9 (Ar-CH), 137.9 (Ar-C), 139.5 (Ar-C), 149.4 (C-9a), 150.3 (C-10a), 157.0 and 163.2 (CO-2 and CO-4), 194.8 (CO-6) ppm. MS (EI, 70 eV): m/z 808 [M⁺]. Anal. calcd for C₄₆H₄₄N₆O₆: C, 68.30; H, 5.48; N, 10.39. Found: C, 68.13; H, 5.12; N, 10.13%.

5,5′-((1,4-Phenylenebis(methylene))bis(oxo))bis-(2,1-phenylene)bis-(8,8-dimethyl-5,8,9,10-tetrahydro-pyrimidino[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione) (9i). Yellowish white crystals (703 mg, 87%), m. p. >300 °C. IR (KBr): νmax 3416, 3234 (br, NH), 1712 (CO-6), 1650 (CO-2 and CO-4) cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): δ 0.85 (s, 6 H, 2 CH₃), 0.97 (s, 6 H, 2 CH₃), 1.91-2.37 (m, 8 H, 2 CH₂-9 and 2 CH₂-7), 5.00 (s, 2 H, 2 CH₅), 5.08 (s, 4 H, 2 OCH₂), 6.75-7.19 (m, 8 H, Ar-H-2,1-phenylene), 7.44 (s, 4H, Ar-H-1,4-phenylene), 8.33 (br s, 2H, 2 NH-10), 10.06 (br s, 2H, 2 NH-1), 10.58 (br s, 2H, 2 NH-3) ppm. ¹³C NMR (100 MHz, DMSO-d₆): δ 26.9 (CH₃), 29.4 (CH₃), 32.4 (C-8), 32.7 (CH), 40.6 (CH₂-9), 50.8 (CH₂-7), 69.6 (OCH₂), 89.5 (C-4a), 110.8 (C-5a), 112.6 (Ar-CH), 120.1 (Ar-CH), 127.4 (Ar-CH), 127.8 (Ar-CH), 131.6 (Ar-CH), 137.6 (Ar-C), 144.4 (Ar-C), 149.5 (C-9a), 150.3 (C-10a), 156.7 and 163.0 (CO-2 and CO-4), 194.5 (CO-6) ppm. MS (EI, 70 eV): m/z 808 [M⁺]. Anal. calcd for C₄₆H₄₄N₆O₆: C, 68.30; H, 5.48; N, 10.39. Found: C, 68.08; H, 5.16; N, 10.21%.

**Synthesis of compounds 15c, 15d, 15i and 15j. General procedure**

A mixture of bisaldehyde 1c, 1d, 1h or 1i (1 mmol), 6-amionauracil 2 (254 mg, 2 mmol) and 1,3-indanedione 13 (292 mg, 2 mmol) was heated at reflux in glacial AcOH (20 mL) for 5 h. The solvent was evaporated under reduced pressure. The residue was treated with aq. NaHCO₃ solution (0.5 N, 20 mL), washed thoroughly with distilled H₂O (20 mL) and left to dry. The crude product was purified by crystallization from EtOH/1,4-dioxane (1:1, v/v, 10 mL).

5,5′-((Propane-1,3-diylibis(oxo))bis-(2,1-phenylene)bis-(5,11-dihydro-1H-indeno[2',1':5,6]pyrido[2,3-d]pyrimidino-2,4,6(3H)-trione) (15c). Orange crystals (584 mg, 77%), m. p. >300 °C. IR (KBr): νmax 3430, 3276 (br, NH), 1725 (CO-6), 1648, 1612 (CO-2,4) cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): two diastereomers (1:1) δ 2.08 (br m, 2 H, 2 OCH₂CH₂), 3.74 (3.87) (m, 4 H, 2 OCH₂CH₂), 4.76 (4.83) (s, 2 H, 2 CH-5), 6.10-7.52 (m, 16 H, Ar-H),
10.07 (br s, 2 H, 2 NH-11), 10.18 (10.25) (br s, 2 H, 2 NH-1), 10.78 (10.82) (br s, 2 H, 2 NH-3) ppm. 13C NMR (100 MHz, DMSO-d6): two diastereomers, ν 29.8 (29.9) (OCH2CH2), 131.7 (32.3) (CH), 64.6 (64.8) (OCH2), 91.0 (91.2) (C-4a), 109.2 (109.4) (C-5a), 111.5 (111.8) (Ar-CH), 119.0 (119.1) (Ar-CH), 119.9 (120.1) (Ar-CH), 121.1 (121.2) (Ar-CH), 127.9 (128.0) (Ar-CH), 130.6 (130.7) (Ar-CH), 131.5 (131.7) (Ar-CH), 131.8 (132.2) (Ar-C), 132.4 (132.5) (Ar-CH), 133.2 (133.3) (Ar-C), 136.3 (136.4) (Ar-C), 145.3 (150.3) (C-10b), 154.3 (154.4) (C-11a), 157.3 (157.4) and 163.1 (163.2) (CO-2 and CO-4), 191.1 (191.2) (CO-6) ppm. MS (EI, 70 eV): m/z 758 [M]+. Anal. calcd for C48H32N6O8: C, 68.07; H, 3.99; N, 11.08. Found: C, 68.71; H, 3.73; N, 10.77%.

5,5′-((Butane-1,4-diylbis(oxy)))bis-(2,1-phenylene)bis-(5,11-dihydro-1H-indeno[2′,1′:5,6]pyrido[2,3-d]pyrimidine-2,4,6(3H)-trione) (15d). Orange crystals (648 mg, 84%), m. p. 290-292 °C. IR (KBr): νmax 3427 (br, NH), 1713 (CO-6), 1655 (CO-2 and CO-4) cm-1. 1H NMR (400 MHz, DMSO-d6): major diastereomer, ν 1.72 (m, 4 H, 2 OCH2CH2), 3.89 (m, 4 H, OCH2CH2), 4.87 (s, 2 H, 2 CH-5), 6.79-7.43 (m, 16 H, Ar-H), 10.08 (br s, 2 H, 2 NH-11), 10.18 (br s, 2 H, 2 NH-1), 10.76 (br s, 2 H, 2 NH-3) ppm. MS (EI, 70 eV): m/z 772 [M]+. Anal. calcd for C46H32N6O8: C, 68.39; H, 4.17; N, 10.88. Found: C, 68.13; H, 4.04; N, 10.69.

Acknowledgements

Prof. Ismail A. Abdelhamid, Prof. Ahmed H. M. Elwyah and Dr. Amr M. Abdelmoniem acknowledge the Alexander von Humboldt Foundation for scientific fellowships.

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