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

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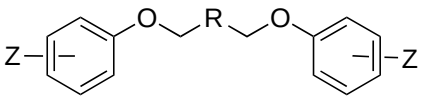
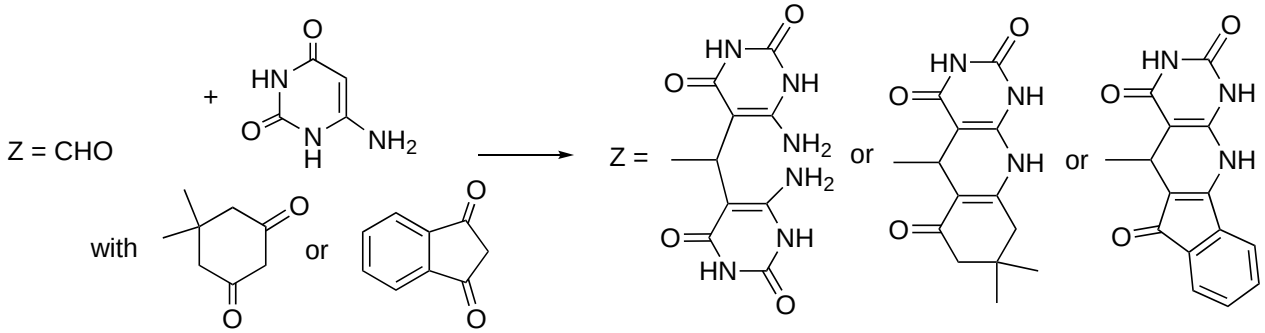
## Abstract

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.




R = $(CH_2)_n$, n = 0, 1 or 2
or R = *o*-, *m*- or *p*-phenylene



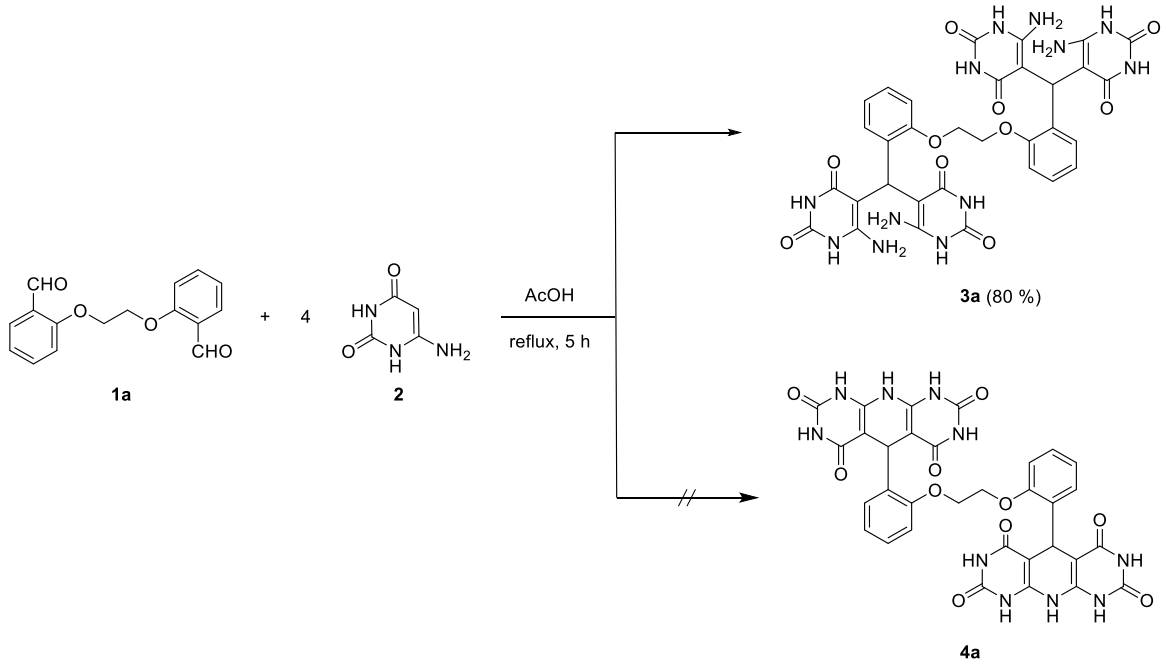

**Keywords:** Bis(aldehydes), Michael addition, uracils, fused pyrimidines, quinolinones, indenones

## Introduction

Uracil is a common and naturally occurring pyrimidine derivative and is one of the four nucleobases in the biopolymer RNA.[1–5] The uracil scaffold and its derivatives exhibit a wide range of biological activities, including treatment of cancer and viral diseases.[6–8] The annelated derivatives have also several applications as bronchodilators,[9,10] antiviral agents,[11] antiallergic compounds,[9,10] adenosine receptor antagonists[12,13] and antihypertensive agents.[14] Uracil derivatives have also been used as versatile building blocks for the synthesis of a variety of heterocycles, including pyrimido[4,5-*d*]pyrimidines,[15] pyrido[2,3-*d*]pyrimidines,[15,16] pyrimido-[4,5-*b*]quinolines,[16–21] and indeno[2′,1′:5,6]pyrido[2,3-*d*]pyrimidines.[16,19,20] 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[22,23] and as radioprotective[22] 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.[24–28] Keeping in mind the importance of the uracil moiety and in continuation of our work on multicomponent reactions,[29–31] Michael addition,[32–35] Hantzsch reactions[31,36,37] as well as on the synthesis of bis-heterocycles,[29–31,36,37] 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



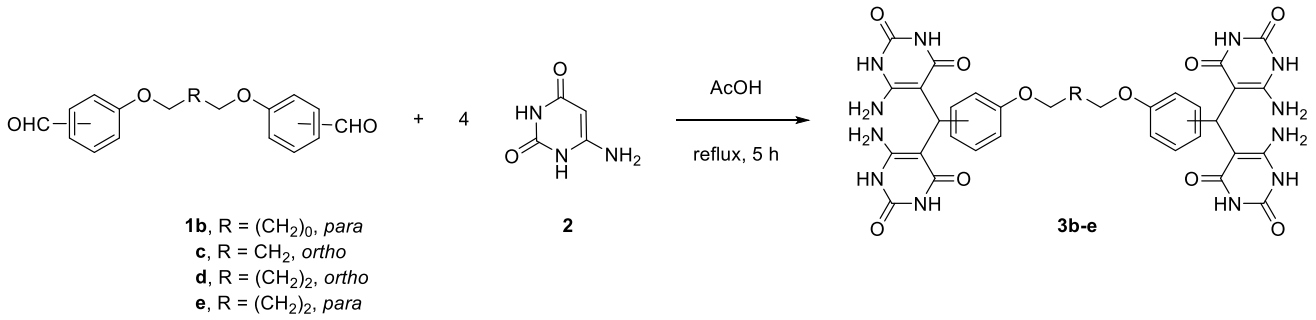

**Scheme 1.** The reaction of bis(aldehyde) **1a** with 6-aminouracil **2** in acetic acid at reflux.

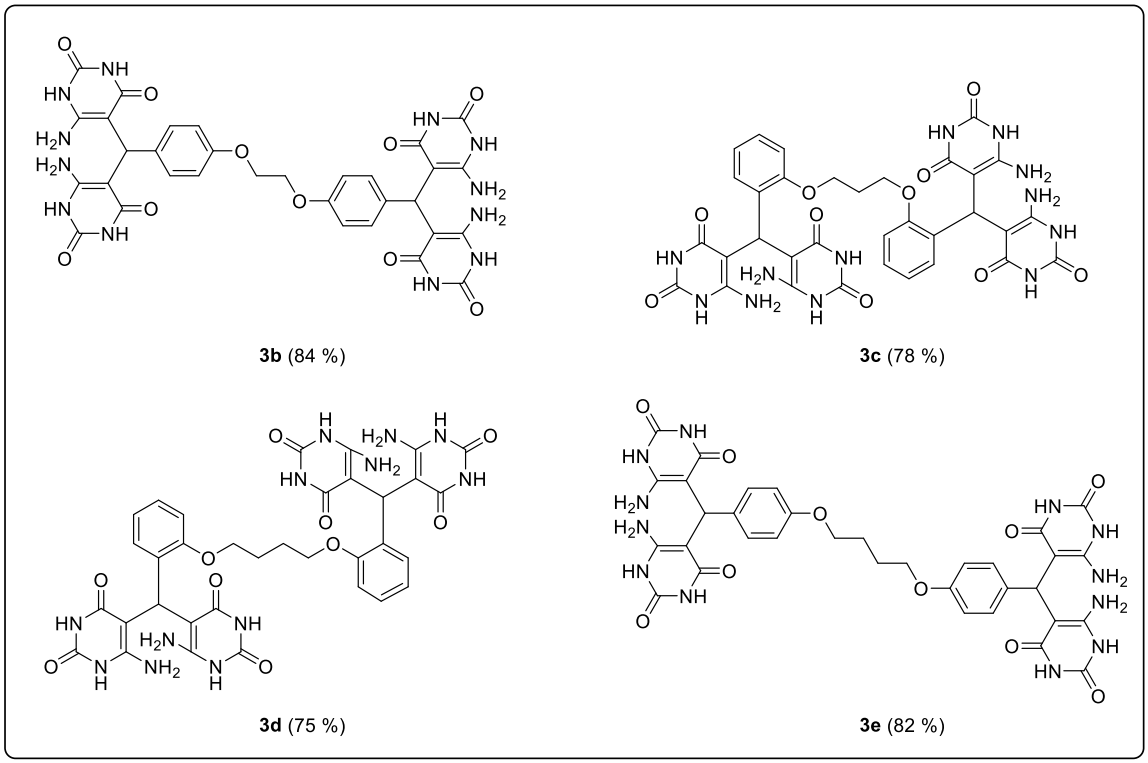
Firstly, we investigated the reaction of bis(aldehyde) **1a** with 6-aminouracil **2** in acetic acid at reflux aiming at the synthesis of bis(9,10-dihydropyrido[2,3-*d*:6,5-*d*']dipyrimidinetetraone) **4a**. Contrary to our expectation, the reaction did not yield compound **4a** and instead gave the tetrakis(6-aminopyrimidine-2,4(1*H*,3*H*)-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(uracils) **3b-e**, in which the tetra-uracil 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 *v* 3407, 3181 $cm^{-1}$. In addition, it revealed two different carbonyl groups at $\tilde{\nu}$ 1711 and 1624 $cm^{-1}$. The $^1H$ 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 $OCH_2CH$, 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 losses 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.



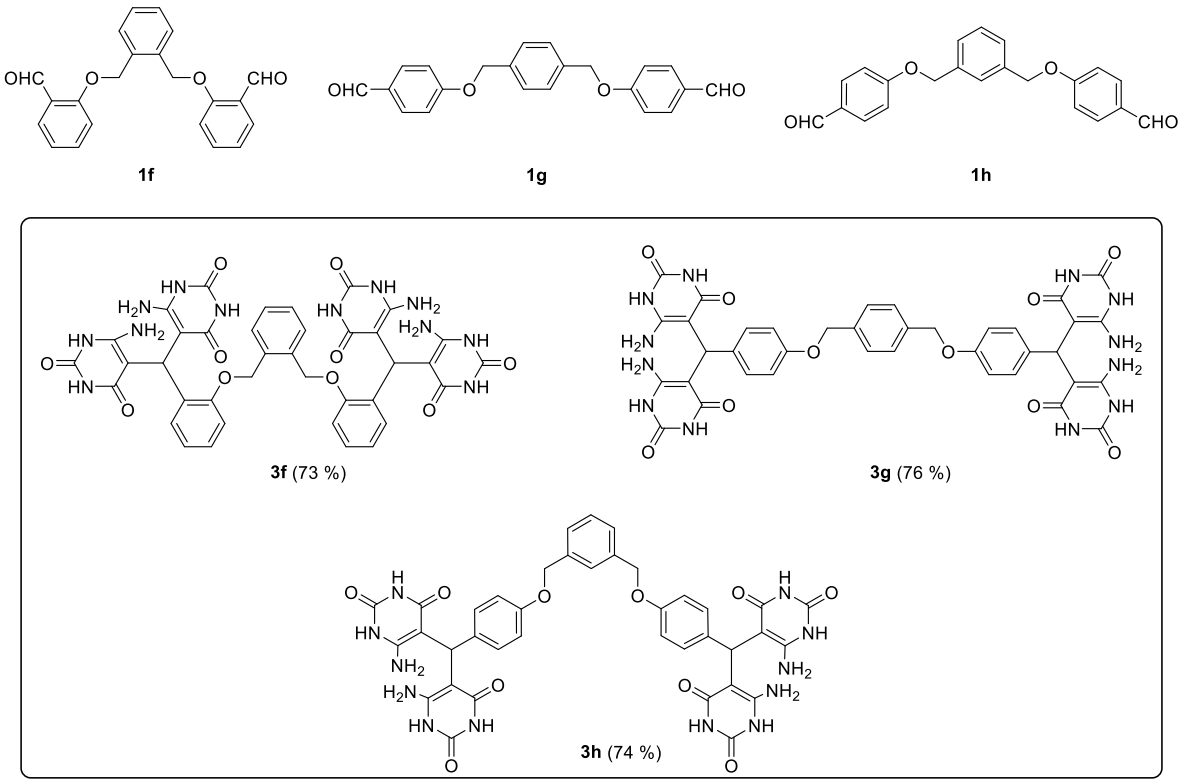




**Scheme 2.** Synthesis of tetrakis(uracils) **3b-e** linked to alkyl spacer *via* a phenoxy group.

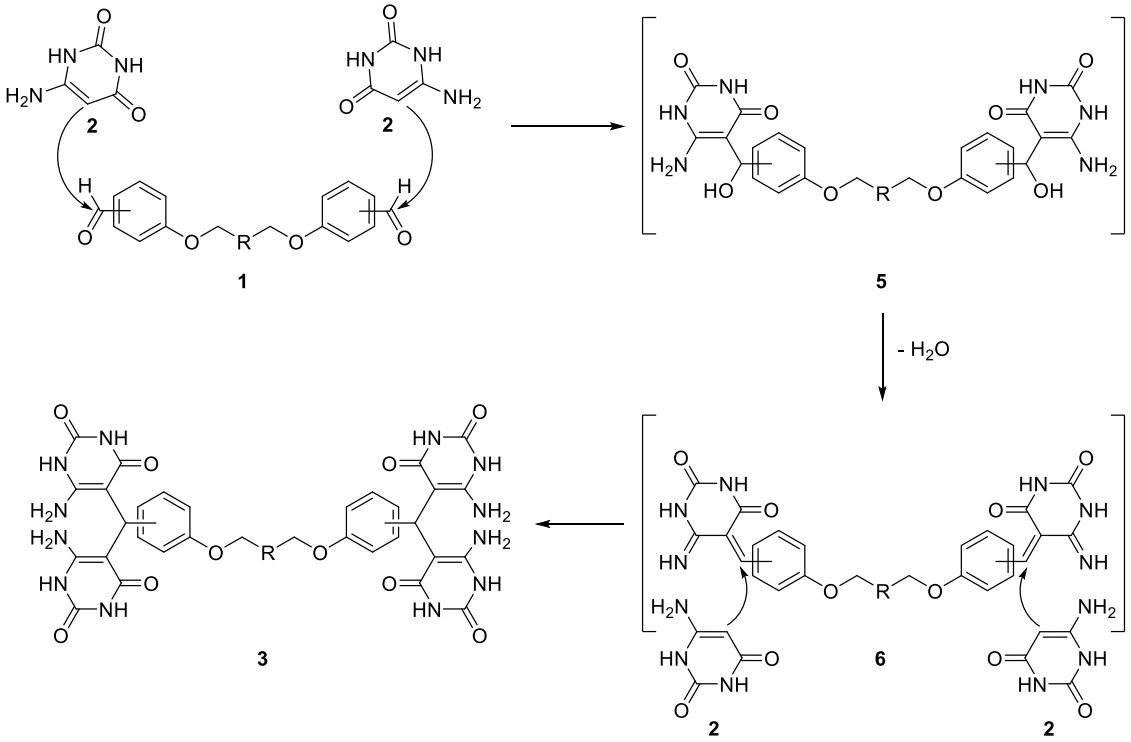
Encouraged by the above results, and in a trial to ascertain the scope and generality of the protocol, a series of bis(aldehydes) containing aromatic linkages **1f-1h**, was used. Thus, the reaction of bis(aldehydes) **1f-1h** with four equivalents of 6-aminouracil **2** afforded the tetrakis(uracil) 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).



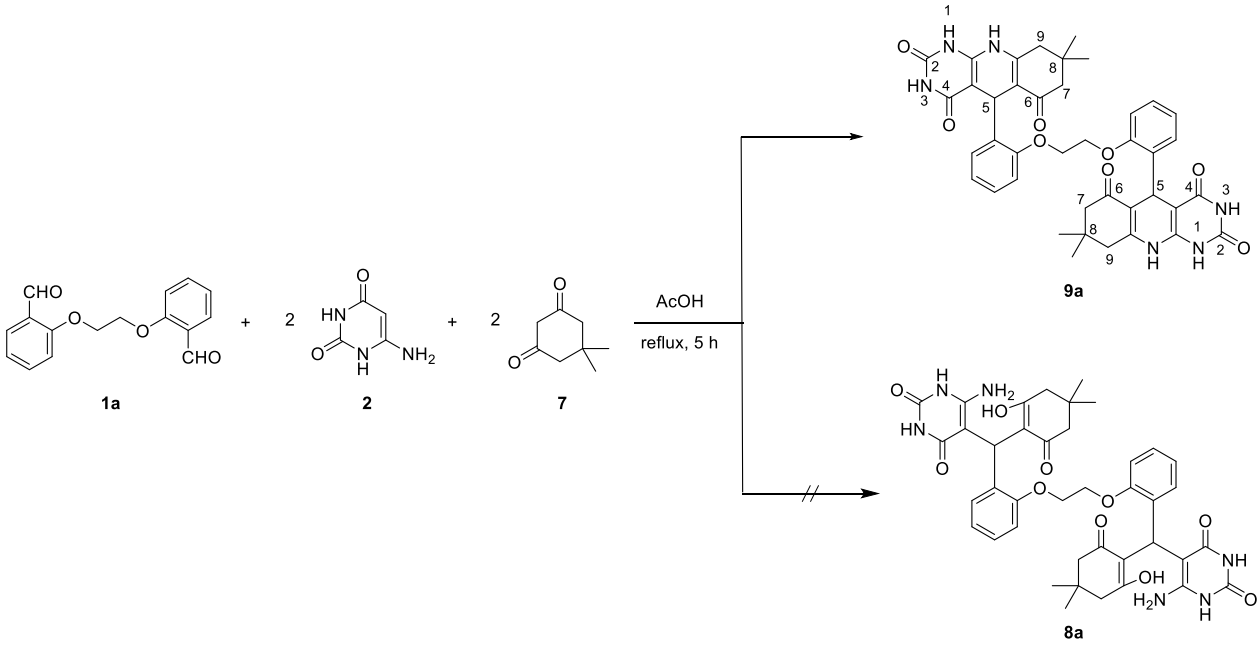

**Scheme 3. T**etrakis(uracil) derivatives containing benzene core and phenoxymethyl linkages **3f-3h.**



**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).

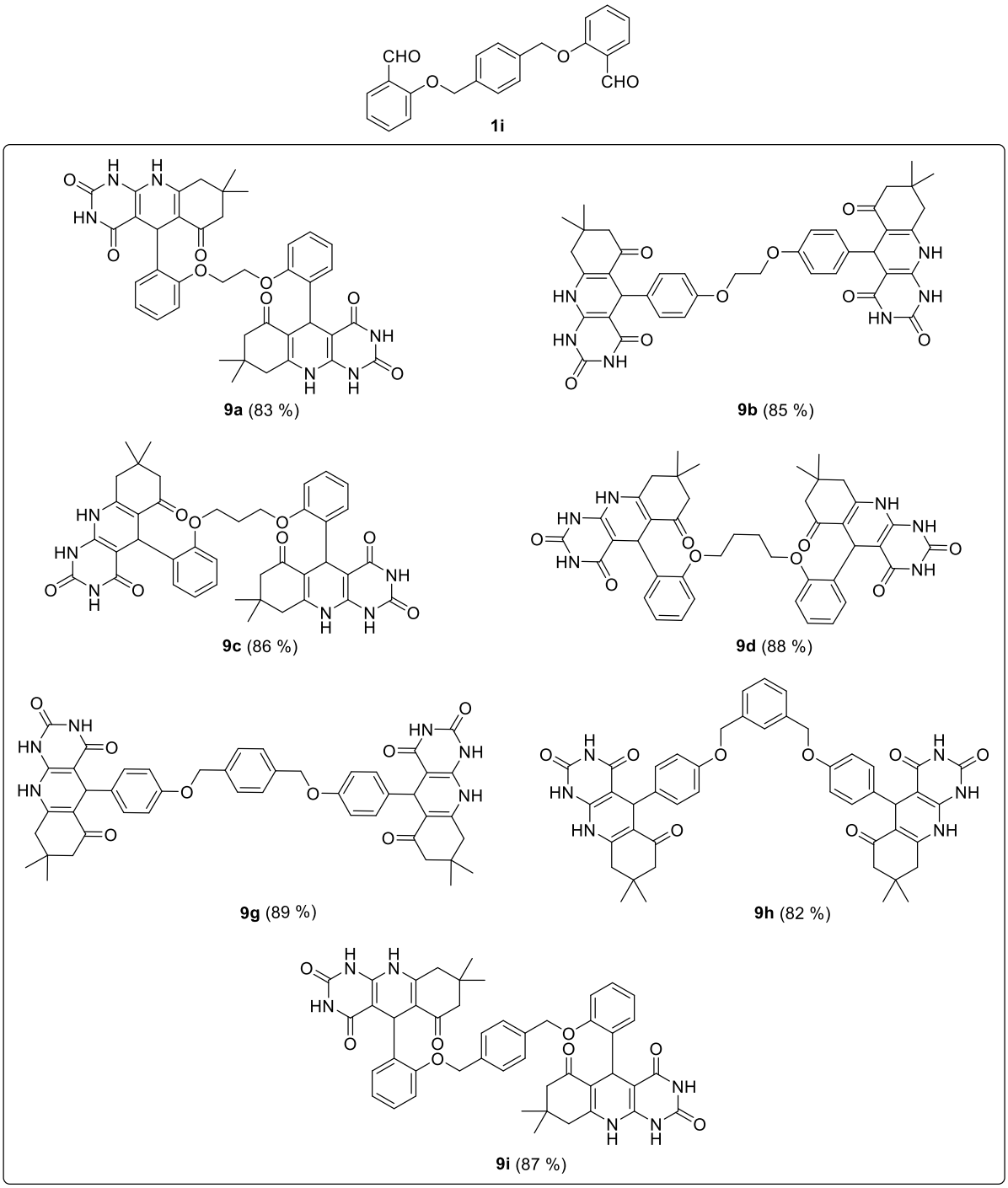


**Scheme 5.** A three-component reaction of bisaldehyde **1a**, 6-aminouracil **2** and dimedone **7.**

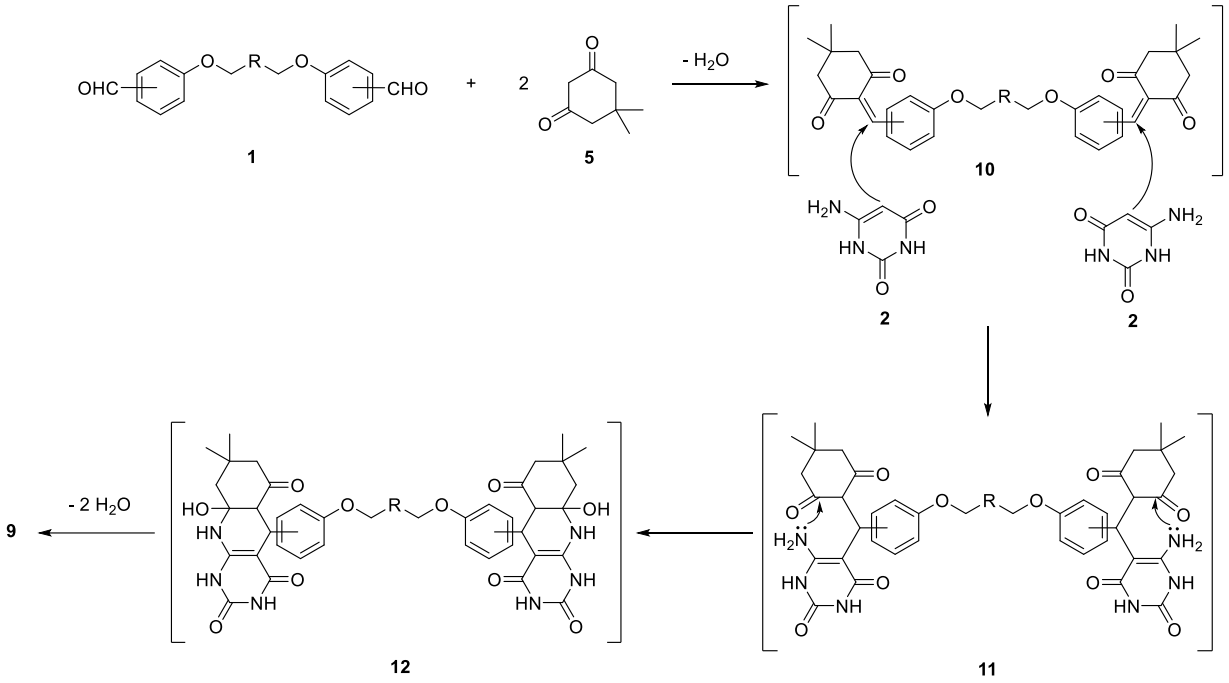
The structure of compound **9a** was established based on the elemental analyses and spectral data. The IR spectra indicated the presence of NH groups with absorption bands at *v* 3424, 3294 and 3227 $cm^{-1}$. In addition, it revealed a sharp band at *v* 1721 $cm^{-1}$ corresponding to the ketonic C=O and a broad band at *v* 1632 $cm^{-1}$ for both amidic carbonyl groups (C=O -2,4). The $^{1}H$ 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 $OCH_2$ 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 $^{1}H$ and $^{13}C$ 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**.

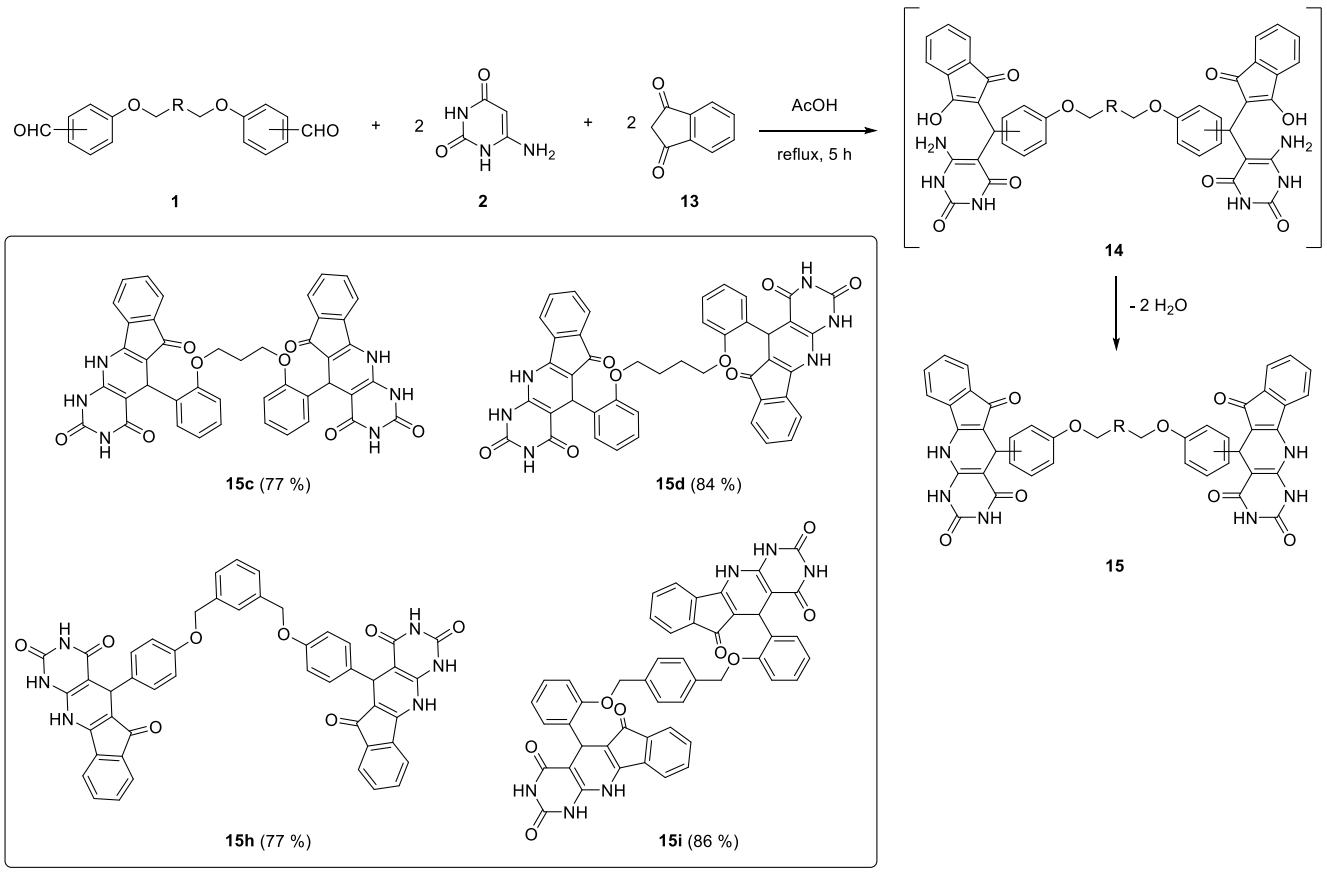
 




**Scheme 6.** Bis(pyrimido[4,5-*b*]quinolines) **9b-d** and **9g-i** with aliphatic or aromatic spacers.



**Scheme 7.** A proposed mechanism for the synthesis of compounds **9**.



**Scheme 8.** Synthesis of bis(indeno[2′,1′:5,6]-pyrido[2,3-*d*]pyrimidines) **15**.

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(uracil), 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 $^{1}$H and $^{13}$C NMR spectra were recorded in DMSO-$d_6$ as solvent at 400 MHz and 100 MHz, respectively, on Bruker Ultrashield or Ascend NMR spectrometers. Chemical shifts are reported as $\delta$ 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 EI (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. $NaHCO_3$ solution (0.5 N, 20 mL), washed thoroughly with distilled $H_2O$ (20 mL) and left to dry in air. The crude product was purified by crystallization from EtOH/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(1*H*,3*H*)-dione) (3a).** Yellowish white crystals (594 mg, 80%), m. p. >300 °C. IR (KBr): $\nu_{max}$ 3357, 3181 (br, $NH_2$ and NH), 1712 (CO), 1630 (CO) cm$^{-1}$. $^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 4.26 (m, 4 H, 2 OC$H_2$C$H_2$), 5.32 (s, 2 H, 2 C*H*-5), 6.61 (br s, 8 H, 4 N$H_2$), 6.77-6.91 (m, 8 H, Ar-*H*), 10.27 (br s, 2 H, 2 N*H*-1), 10.36 (br s, 2 H, 4 N*H*-3) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 31.9 (*C*H), 66.6 (O*C*H$_2$), 68.1 (*C*5), 114.0 (Ar-*C*H), 121.4 (Ar-*C*H), 124.5 (Ar-*C*), 126.9 (Ar-*C*H), 128.2 (Ar-*C*H), 150.2 (Ar-*C*), 155.6 and 164.8 (CO-2 and CO-4) ppm. MS (EI, 70 eV): *m/z* 742 [M]$^{+}$. Anal. calcd for $C_{32}H_{30}N_{12}O_{10}$: C, 51.75; H, 4.07; N, 22.63. Found: C, 51.44; H, 3.71; N, 22.34%.

**5,5′,5″,5‴-(((Ethane-1,2-diylbis(oxy))bis-(4,1-phenylene))bis(methanetriyl))tetrakis-(6-aminopyrimidine-2,4(1*H*,3*H*)-dione) (3b)**. Yellowish white crystals (623 mg, 84%), m. p. >300 °C. IR (KBr): $\nu_{max}$ 3377, 3144 (br, $NH_2$ and NH), 1711 (CO), 1624 (CO) cm$^{-1}$. $^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 4.23 (s, 4H, 2 OC$H_2$), 5.26 (s, 2 H, 2 C*H*-5), 6.70 (br s, 8 H, 4 N$H_2$), 6.81-6.98 (m, 8 H, Ar-*H*), 10.28 (br s, 2 H, 2 N*H*-1), 10.48 (br s, 2 H, 4 N*H*-3) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 32.3 (*C*H), 66.7 (O*C*H$_2$), 67.4 (*C*5), 114.2 (Ar-*C*H), 128.1 (Ar-*C*H), 131.1 (Ar-*C*), 150.2 (Ar-*C*), 156.3 and 163.8 (CO-2 and CO-4) ppm. MS (EI, 70 eV): *m/z* 742 [M]$^{+}$. Anal. calcd for $C_{32}H_{30}N_{12}O_{10}$: 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(1*H*,3*H*)-dione) (3c)**. Yellowish white crystals (590 mg, 78%), m. p. 288-290 °C. IR (KBr): $\nu_{max}$ 3377, 3185 (br, $NH_2$ and NH), 1712 (CO), 1631 (CO) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.12 (m, 2 H, $OCH_2CH_2$), 3.86 (m, 4 H, 2 $OCH_2CH_2$), 5.30 (s, 2 H, 2 C*H*-5), 6.64 (br s, 8 H, 4 $NH_2$), 6.77-7.09 (m, 8 H, Ar-*H*), 10.11 (br s, 2 H, 2 N*H*-1), 10.30 (br s, 2 H, 4 N*H*-3) ppm. $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 29.7 ($OCH_2CH_2$), 32.3 (*C*H), 63.9 ($OCH_2CH_2$), 65.2 (*C*5), 113.7 (Ar-*C*H), 120.0 (Ar-*C*H), 125.1 (Ar-*C*), 127.3 (Ar-*C*H), 130.3 (Ar-*C*H), 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 $C_{33}H_{32}N_{12}O_{10}$: 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(1*H*,3*H*)-dione) (3d).** Yellow crystals (578 mg, 75%), m. p. >300 °C. IR (KBr): $\nu_{max}$ 3358, 3180 (br, $NH_2$ and NH), 1708, 1631 (CO-2,4) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.91 (m, 4 H, $2OCH_2CH_2$), 3.90 (m, 4 H, 2 $OCH_2CH_2$), 5.29 (s, 2 H, 2 C*H*-5), 6.19 (br s, 8 H, 4 $NH_2$), 6.80-7.25 (m, 8 H, Ar-*H*), 10.30 (br s, 2 H, 2 N*H*-1), 10.43 (br s, 2 H, 4 N*H*-3) ppm. $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 29.7 ($OCH_2CH_2$), 32.5 (*C*H), 66.8 ($OCH_2CH_2$), 68.6 (*C*5), 113.8 (Ar-*C*H), 121.0 (Ar-*C*H), 125.8 (Ar-*C*H), 128.9 (Ar-*C*), 129.4 (Ar-*C*H), 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 $C_{34}H_{34}N_{12}O_{10}$: 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(1*H*,3*H*)-dione) (3e)**. Yellowish white crystals (631 mg, 82%), m. p. 294-296 °C. IR (KBr): $\nu_{max}$ 3407, 3181 (br, NH and $NH_2$), 1711 (CO), 1624 (CO) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.84 (m, 4 H, 2 $OCH_2CH_2$), 3.97 (m, 4 H, 2 $OCH_2CH_2$), 5.26 (s, 2 H, 2 C*H*-5), 6.64 (br s, 8 H, 4 $NH_2$), 6.71-6.97 (m, 8 H, Ar-*H*), 10.29 (br s, 2 H, 2 N*H*-1), 10.48 (br s, 2 H, 4 N*H*-3) ppm. $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 26.1 ($OCH_2CH_2$), 32.0 (*C*H), 67.5 ($OCH_2CH_2$), 68.2 (*C*5), 114.1 (Ar-*C*H), 127.4 (Ar-*C*H), 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 $C_{34}H_{34}N_{12}O_{10}$: 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(1*H*,3*H*)-dione) (3f)**. Yellowish white crystals (597 mg, 73%), m. p. 298-300 °C. IR (KBr): $\nu_{max}$ 3368, 3191 (br, $NH_2$ and NH), 1706 (CO), 1631 (CO) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 5.02 (s, 2 H, $OCH_2$), 5.29 (s, 2 H, 2 C*H*-5), 6.62 (br s, 8 H, 4N$H_2$), 6.83-7.35 (m, 8 H, Ar-*H*), 10.20 (br s, 2 H, 2N*H*-1), 10.42 (br s, 2 H, 4 N*H*-3) ppm. MS (EI, 70 eV): *m/z* 818 $[M]^+$. Anal. calcd for $C_{38}H_{34}N_{12}O_{10}$: 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(1*H*,3*H*)-dione) (3g)**. Yellowish white crystals (622 mg, 76%), m. p. >300 °C. IR (KBr): $\nu_{max}$ 3410, 3189 (br, $NH_2$ and NH), 1711 (CO), 1626 (CO) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 5.05 (m, 2 H, $OCH_2$), 5.26 (s, 2 H, 2 C*H*-5), 6.61 (br s, 8 H, 4 $NH_2$), 6.83-7.00 (m, 8 H, Ar-*H*), 10.28 (br s, 2H, 2N*H*-1), 10.48 (br s, 2 H, 4 N*H*-3) ppm, $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 32.2 (*C*H), 69.3 (O*C*H), 69.9 (*C*5), 114.4 (Ar-*C*H), 128.2 (Ar-*C*H), 132.3 (Ar-*C*H), 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 $C_{38}H_{34}N_{12}O_{10}$: 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(1*H*,3*H*)-dione) (3h)**. Yellowish white crystals (605 mg, 74%), m. p. 292-294 °C. IR (KBr): $\nu_{max}$ 3381, 3164 (br, $NH_2$ and NH), 1712 (CO-6), 1627 (CO) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 5.06 (s, 2 H, $OCH_2$), 5.26 (s, 2 H, 2C*H*-5), 6.61 (br s, 8 H, 4 $NH_2$), 6.85-7.02 (m, 8 H, Ar-*H*), 10.20 (br s, 2 H, 2 N*H*-1), 10.42 (br s, 2 H, 4 N*H*-3) ppm. $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 32.2 (*C*H), 69.5 ($OCH_2$), 70.0 (*C*5), 114.4 (Ar-*C*H), 127.5 (Ar-*C*H), 128.0 (Ar-*C*H), 129.1 (Ar-*C*H), 132.3 (Ar-*C*H), 136.2 (Ar-*C*), 138.0 (Ar-*C*), 150.2 (Ar-*C*), 155.6 and 164.7

(CO-2 and CO-4) ppm. MS (EI, 70 eV): *m/z* 818 $[M]^+$. Anal. calcd for $C_{38}H_{34}N_{12}O_{10}$: C, 55.74; H, 4.19; N, 20.53. Found: C, 55.56; H, 4.43; N, 20.18%.

**Synthesis of compounds 9a-d and 9g-l. General procedure**

A mixture of bisaldehyde **1a-i** (1 mmol), 6-aminouracil **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. $NaHCO_3$ solution (0.5 N, 20 mL), washed thoroughly with distilled $H_2O$ (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(oxy))bis-(2,1-phenylene))bis-(8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-*b*]-quinoline-2,4,6(1*H*,3*H*,7*H*)-trione) (9a).** Yellowish white crystals (608 mg, 83%), m. p. 292-294 °C. IR (KBr): $\nu_{max}$ 3424 (NH), 3294 (NH), 3227 (NH), 1721 (CO-6), 1632 (br, CO-2,4) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): single stereoisomer, $\delta$ 0.80 (s, 6 H, 2 C$H_3$), 0.99 (s, 6 H, 2 C$H_3$), 1.90-2.29 (m, 8 H, 2 C$H_2$-9 and 2 C$H_2$-7), 4.10-4.25 (m, 4 H, 2 OC$H_2$), 4.86 (s, 2 H, 2 C*H*-5), 6.81 -7.27 (m, 8 H, Ar-*H*), 8.98 (br s, 2 H, 2 N*H*-10), 10.11 (br s, 2 H, 2 N*H*-1), 10.56 (br s, 2 H, 2 N*H*-3) ppm. $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 26.5 (*C*$H_3$), 29.7 (*C*$H_3$), 32.5 (*C*-8), 33.0 (*C*H), 40.6 (*C*$H_2$-9), 50.7 (*C*$H_2$-7), 66.2 (O*C*$H_2$), 88.6 (*C*-4a), 110.1 (*C*-5a), 112.7 (Ar-*C*H), 120.3 (Ar-*C*H), 127.7 (Ar-*C*H), 132.7 (Ar-*C*H), 133.2 (Ar-*C*), 149.7 (*C*-9a), 150.4 (Ar-*C*), 157.2 and 163.1 (*C*O-2, *C*O-4), 194.6 (*C*O-6) ppm. MS (EI, 70 eV): *m/z* 732 $[M]^+$. Anal. calcd for $C_{40}H_{40}N_6O_8$: 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(oxy))bis-(4,1-phenylene))bis-(8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-*b*]-quinoline-2,4,6(1*H*,3*H*,7*H*)-trione) (9b)**. Yellow crystals (622 mg, 85%), m. p. 294-296 °C. IR (KBr):$\nu_{max}$ 3424 (NH), 3286 (NH), 3222 (NH), 1719 (CO-6), 1664 (br, CO-2,4) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 0.89 (s, 6 H, 2 C$H_3$), 1.02 (s, 6 H, 2 C$H_3$), 1.92-2.22 (m, 4 H, 2 C$H_2$-9), 2.39-2.45 (m, 4 H, 2 C$H_2$-7), 4.18 (s, 4 H, 2 OC$H_2$), 4.69 (s, 2 H, 2 C*H*-5), 6.77 -7.10 (m, 8 H, Ar-*H*), 8.79 (br s, 2 H, 2 N*H*-10), 10.12 (br s, 2 H, 2 N*H*-1), 10.70 (br s, 2 H, 2 N*H*-3) ppm. $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 27.0 (*C*$H_3$), 29.4 (*C*$H_3$), 32.6 (*C*-8), 32.7 (*C*H), 40.6 (*C*$H_2$-9), 50.6 (*C*$H_2$-7), 66.7 (O*C*$H_2$), 90.3 (*C*-4a), 111.9 (*C*-5a), 114.3 (Ar-*C*H), 129.0 (Ar-*C*H), 139.5 (Ar-*C*), 149.3 (*C*-9a), 156.9 and 163.2 (*C*O-2 and *C*O-4), 194.8 (*C*O-6) ppm. MS (EI, 70 eV): *m/z* 732 $[M]^+$. Anal. calcd for $C_{40}H_{40}N_6O_8$: 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(oxy))bis-(2,1-phenylene))bis-(8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-*b*]-quinoline-2,4,6(1*H*,3*H*,7*H*)-trione) (9c).** Yellow crystals (642 mg, 86%), m. p. 266-268 °C. IR (KBr): $\nu_{max}$ 3411 (NH), 3265 (NH), 3159 (NH), 1708 (CO-6), 1638 (br, CO-2,4) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): major diastereomer, $\delta$ 0.80 (s, 6 H, 2 C$H_3$), 0.98 (s, 6 H, 2 C$H_3$), 1.91 (m, 2 H, OCH$_2$C$H_2$), 2.12-2.47 (m, 8 H, 2 C$H_2$-9 and 2 C$H_2$-7), 4.01 (m, 4 H, 2 OC$H_2$CH$_2$), 4.90 (s, 2 H, 2 C*H*-5), 6.72 -7.24 (m, 8 H, Ar-*H*), 8.75 (br s, 2 H, 2 N*H*-10), 10.12 (br s, 2 H, 2 N*H*-1), 10.60 (br s, 2 H, 2 N*H*-3) ppm. $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 26.4 (*C*$H_3$), 29.6 (OCH$_2$*C*H$_2$), 29.9 (*C*$H_3$), 32.5 (*C*-8), 32.8 (*C*H), 40.6 (*C*$H_2$-9), 50.8 (*C*$H_2$-7), 65.1 (O*C*H$_2$CH$_2$), 89.1 (*C*-4a), 110.5 (*C*-5a), 111.9 (Ar-*C*H), 119.8 (Ar-*C*H), 127.6 (Ar-*C*H), 132.3 (Ar-*C*H), 133.4 (Ar-*C*), 149.4 (*C*-9a), 152.5 (Ar-*C*), 157.4 and 163.1 (*C*O-2), 163.2 (*C*O-4), 194.5 (*C*O-6) ppm. MS (EI, 70 eV): *m/z* 746 $[M]^+$. Anal. calcd for $C_{41}H_{42}N_6O_8$: 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(oxy))bis-(2,1-phenylene))bis-(8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-*b*]-quinoline-2,4,6(1*H*,3*H*,7*H*)-trione) (9d)**. Yellowish white crystals (669 mg, 88%), m. p. >300 °C. IR (KBr): $\nu_{max}$ 3431, 3291 (br, 3 NH), 1714 (CO-6), 1647 (CO-2 and CO-4) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): a pair of diastereomers (1:1), $\delta$ 0.83 (0.84) (s, 6 H, 2 C$H_3$), 0.97 (0.99) (s, 6 H, 2 C$H_3$), 1.85 (m, 4 H, 2 OCH$_2$C$H_2$), 2.12-2.48 (m, 8 H, 2 C$H_2$-9 and 2 C$H_2$-7), 3.89 (4.00) (m, 4 H, 2 OC$H_2$CH$_2$), 4.89 (4.96) (s, 2 H, 2 C*H*-5), 6.72-7.24 (m, 8 H, Ar-*H*), 8.68 (8.73) (br s, 2 H, 2 N*H*-10), 10.06 (10.10) (br s, 2 H, 2 N*H*-1), 10.59 (10.67) (br s, 2 H, 2 N*H*-3) ppm. $^{13}C$ NMR (100 MHz, DMSO-$d_6$): a pair of diastereomers (1 : 1), $\delta$ 26.2 (26.4) (*C*$H_3$), 26.6 (26.7) (OCH$_2$*C*H$_2$), 29.6 (29.7) (*C*$H_3$), 32.4 (32.5) (*C*-8), 32.6 (32.7) (*C*H), 40.6 (40.7) (*C*$H_2$-9), 50.7 (50.8) (*C*$H_2$-7), 68.0 (68.1) (O*C*H$_2$CH$_2$),

89.0 (89.4) (*C*-4a), 110.4 (110.8) (*C*-5a), 112.0 (112.4) (Ar-*C*H), 119.6 (119.8) (Ar-*C*H), 127.5 (127.6) (Ar-*C*H), 132.0 (132.5) (Ar-*C*H), 133.3 (133.7) (Ar-*C*), 149.5 (149.7) (*C*-9a), 150.3 (150.4) (*C*-10a), 157.3 (157.6) and 163.1 (163.4) (*C*O-2 and *C*O-4), 194.5 (194.7) (*C*O-6) ppm. MS (EI, 70 eV): *m/z* 760 $[M]^+$. Anal. calcd for $C_{42}H_{44}N_6O_8$: C, 66.30; H, 5.83; N, 11.05. Found: C, 66.09; H, 5.44; N, 10.78%.

**5,5'-(((1,4-Phenylenebis(methylene))bis(oxy))bis-(4,1-phenylene))bis-(8,8-dimethyl-5,8,9,10-tetrahydro-pyrimido[4,5-*b*]quinoline-2,4,6(1*H*,3*H*,7*H*)-trione) (9g)**. Pale yellow crystals (719 mg, 89%), m. p. >300 °C. IR (KBr): $\nu_{max}$ 3428, 3198 (br, NH), 1720 (CO-6), 1664 (br, CO-2 and CO-4) $cm^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$): single stereoisomer, $\delta$ 0.90 (s, 6 H, 2 C$H_3$), 1.02 (s, 6 H, 2 C$H_3$), 2.00-2.21 (m, 4 H, 2 C$H_2$-9), 2.43 (m, 4 H, 2 C$H_2$-7), 4.70 (s, 2 H, 2 C*H*-5), 5.01 (s, 4 H, 2 OC$H_2$), 6.81-7.10 (m, 8 H, Ar-*H*-4,1-phenylene), 7.41 (s, 4H, Ar-*H*-1,4-phenylene), 8.79 (br s, 2H, 2N*H*-10), 10.27 (br s, 2H, 2N*H*-1), 10.70 (br s, 2H, 2N*H*-3) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 27.0 (*C*H$_3$), 29.4 (*C*H$_3$), 32.4 (*C*-8), 32.6 (*C*H), 40.6 (*C*H$_2$-9), 50.6 (*C*H$_2$-7), 69.3 (O*C*H$_2$), 90.3 (*C*-4a), 111.9 (*C*-5a), 114.5 (Ar-*C*H), 128.1 (Ar-*C*H), 129.0 (Ar-*C*H), 137.3 (Ar-*C*), 139.5 (Ar-*C*), 149.4 (*C*-9a), 150.2 (*C*-10a), 156.7 and 163.2 (*C*O-2 and *C*O-4), 194.6 (*C*O-6) ppm. MS (EI, 70 eV): *m/z* 808 $[M]^+$. Anal. calcd for $C_{46}H_{44}N_6O_8$: C, 68.30; H, 5.48; N, 10.39. Found: C, 68.13; H, 5.12; N, 10.13%.

**5,5'-(((1,3-Phenylenebis(methylene))bis(oxy))bis-(4,1-phenylene))bis-(8,8-dimethyl-5,8,9,10-tetrahydro-pyrimido[4,5-*b*]quinoline-2,4,6(1*H*,3*H*,7*H*)-trione) (9h)**. Yellow crystals (663 mg, 82%), m. p. >300 °C. IR (KBr): $\nu_{max}$ 3205 (br, NH), 1717 (CO-6), 1664 (CO-2 and CO-4) $cm^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 0.90 (s, 6 H, 2 C$H_3$), 1.02 (s, 6 H, 2 C$H_3$), 2.00-2.22 (m, 4 H, 2 C$H_2$-9), 2.44 (m, 4 H, 2 C$H_2$-7), 4.70 (s, 2 H, 2 C*H*-5), 5.02 (s, 4 H, 2 OC$H_2$), 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-*H*2-1,3-phenylene), 8.80 (br s, 2 H, 2 N*H*-10), 10.27 (br s, 2 H, 2 N*H*-1), 10.70 (br s, 2 H, 2 N*H*-3) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 27.0 (*C*H$_3$), 29.4 (*C*H$_3$), 32.5 (*C*-8), 32.6 (*C*H), 40.6 (*C*H$_2$-9), 50.6 (*C*H$_2$-7), 69.5 (O*C*H$_2$), 90.3 (*C*-4a), 111.9 (*C*-5a), 114.4 (Ar-*C*H), 127.5 (Ar-*C*H), 127.5 (Ar-*C*H), 128.9 (Ar-*C*H), 137.9 (Ar-*C*), 139.5 (Ar-*C*), 149.4 (*C*-9a), 150.3 (*C*-10a), 157.0 and 163.2 (*C*O-2 and *C*O-4), 194.8 (*C*O-6) ppm. MS (EI, 70 eV): *m/z* 808 $[M]^+$. Anal. calcd for $C_{46}H_{44}N_6O_8$: C, 68.30; H, 5.48; N, 10.39. Found: C, 68.03; H, 5.19; N, 10.17%.

**5,5'-(((1,4-Phenylenebis(methylene))bis(oxy))bis-(2,1-phenylene))bis-(8,8-dimethyl-5,8,9,10-tetrahydro-pyrimido[4,5-*b*]quinoline-2,4,6(1*H*,3*H*,7*H*)-trione) (9i)**. Yellowish white crystals (703 mg, 87%), m. p. >300 °C. IR (KBr): $\nu_{max}$ 3416, 3234 (br, NH), 1712 (CO-6), 1650 (CO-2 and CO-4) $cm^{-1}$, $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 0.85 (s, 6 H, 2 C$H_3$), 0.97 (s, 6 H, 2 C$H_3$), 1.91-2.37 (m, 8 H, 2 C$H_2$-9 and 2 C$H_2$-7), 5.00 (s, 2 H, 2 C*H*-5), 5.08 (s, 4 H, 2 OC$H_2$), 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, 2 H, 2 N*H*-10), 10.06 (br s, 2 H, 2 N*H*-1), 10.58 (br s, 2 H, 2 N*H*-3) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 26.9 (*C*H$_3$), 29.4 (*C*H$_3$), 32.4 (*C*-8), 32.7 (*C*H), 40.6 (*C*H$_2$-9), 50.8 (*C*H$_2$-7), 69.6 (O*C*H$_2$), 89.5 (*C*-4a), 110.8 (*C*-5a), 112.6 (Ar-*C*H), 120.1 (Ar-*C*H), 127.4 (Ar-*C*H), 127.8 (Ar-*C*H), 131.6 (Ar-*C*H), 137.6 (Ar-*C*), 144.4 (Ar-*C*), 149.5 (*C*-9a), 150.3 (*C*-10a), 156.7 and 163.0 (*C*O-2 and *C*O-4), 194.5 (*C*O-6) ppm. MS (EI, 70 eV): *m/z* 808 $[M]^+$. Anal. calcd for $C_{46}H_{44}N_6O_8$: C, 68.30; H, 5.48; N, 10.39. Found: C, 68.08; H, 5.16; N, 10.21%.

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

A mixture of bisaldehyde **1c**, **1d**, **1h** or **1i** (1 mmol), 6-aminouracil **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. $NaHCO_3$ solution (0.5 N, 20 mL), washed thoroughly with distilled $H_2O$ (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-diylbis(oxy))bis-(2,1-phenylene))bis-(5,11-dihydro-1*H*-indeno[2′,1′:5,6]pyrido[2,3-*d*]-pyrimidine-2,4,6(3*H*)-trione) (15c).** Orange crystals (584 mg, 77%), m. p. >300 °C. IR (KBr): $\nu_{max}$ 3430, 3276 (br, NH), 1725 (CO-6), 1648, 1612 (CO-2,4) $cm^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$): two diastereomers (1 : 1) $\delta$ 2.08 (br m, 2 H, 2 OCH$_2$C$H_2$), 3.74 (3.87) (m, 4 H, 2 OC$H_2$CH$_2$), 4.76 (4.83) (s, 2 H, 2 C*H*-5), 6.10-7.52 (m, 16 H, Ar-*H*),

10.07 (br s, 2 H, 2 N*H*-11), 10.18 (10.25) (br s, 2 H, 2 N*H*-1), 10.78 (10.82) (br s, 2 H, 2 N*H*-3) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): two diastereomers, $\delta$ 29.8 (29.9) ($OCH_2CH_2$), 31.7 (32.3) (*C*H), 64.6 (64.8) ($OCH_2$), 91.0 (91.2) (*C*-4a), 109.2 (109.4) (*C*-5a), 111.5 (111.8) (Ar-*C*H), 119.0 (119.1) (Ar-*C*H), 119.9 (120.1) (Ar-*C*H), 121.1 (121.2) (Ar-*C*H), 127.9 (128.0) (Ar-*C*H), 130.6 (130.7) (Ar-*C*H), 131.5 (131.7) (Ar-*C*H), 131.8 (132.2) (Ar-*C*), 132.4 (132.5) (Ar-*C*H), 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) (*C*O-2 and *C*O-4), 191.1 (191.2) (*C*O-6) ppm. MS (EI, 70 eV): *m/z* 758 $[M]^+$. Anal. calcd for $C_{43}H_{30}N_6O_8$: C, 68.07; H, 3.99; N, 11.08. Found: C, 67.81; H, 3.73; N, 10.77%.

**5,5′-((Butane-1,4-diylbis(oxy))bis-(2,1-phenylene))bis-(5,11-dihydro-1*H*-indeno[2′,1′:5,6]pyrido[2,3-*d*]-pyrimidine-2,4,6(3*H*)-trione) (15d)**. Orange crystals (648 mg, 84%), m. p. 290-292 °C. IR (KBr): $\nu_{max}$ 3427 (br, NH), 1713 (CO-6), 1655 (CO-2 and CO-4) cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$): major diastereomer, $\delta$ 1.72 (m, 4 H, 2 $OCH_2CH_2$), 3.89 (m, 4 H, $OCH_2CH_2$), 4.87 (s, 2 H, 2 C*H*-5), 6.79-7.43 (m, 16 H, Ar-*H*), 10.08 (br s, 2 H, 2 N*H*-11), 10.18 (br s, 2 H, 2 N*H*-1), 10.76 (br s, 2 H, 2 N*H*-3) ppm. MS (EI, 70 eV): *m/z* 772 $[M]^+$. Anal. calcd for $C_{44}H_{32}N_6O_8$: C, 68.39; H, 4.17; N, 10.88. Found: C, 68.13; H, 4.04; N, 10.69.

**5,5'-(((1,3-Phenylenebis(methylene))bis(oxy))bis-(4,1-phenylene))bis-(5,11-dihydro-1*H*-indeno[2′,1′:5,6]-pyrido[2,3-*d*]pyrimidine-2,4,6(3*H*)-trione) (15h)**. Brick red crystals (631 mg, 77%), m. p. 296-298 °C. IR (KBr): $\nu_{max}$ 3420, 3244 (br, $NH_2$ and NH), 1712 (CO-6), 1608 (CO-2 and CO-4) cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 4.62 (s, 2 H, 2 C*H*-5), 5.02 (s, 4 H, 2 $CH_2$), 6.85-7.42 (m, 20 H, Ar-*H*), 10.14 (br s, 2 H, 2 N*H*-11), 10.31 (br s, 2 H, 2 N*H*-1), 10.90 (br s, 2 H, 2 N*H*-3) ppm. $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 33.1 (*C*H), 69.5 ($OCH_2CH_2$), 91.7 (*C*-4a), 110.3 (*C*-5a), 114.7 (Ar-*C*H), 119.4 (Ar-*C*H), 121.3 (Ar-*C*H), 127.4 (Ar-*C*H), 127.5 (Ar-*C*H), 129.1 (Ar-*C*H), 130.8 (Ar-*C*H), 132.6 (Ar-*C*H), 133.1 (Ar-*C*), 136.4 (Ar-*C*), 137.5 (Ar-*C*H), 137.9 (Ar-*C*), 138.2 (Ar-*C*), 144.9 (*C*-10b), 153.7 (*C*-11a), 157.3 and 163.3 (*C*O-2 and *C*O-4), 191.4 (*C*O-6) ppm. MS (EI, 70 eV): *m/z* 820 $[M]^+$. Anal. calcd for $C_{48}H_{32}N_6O_8$: C, 70.24; H, 3.93; N, 10.24. Found: C, 70.01; H, 3.66; N, 10.06%.

**5,5′-(((1,4-Phenylenebis(methylene))bis(oxy))bis-(4,1-phenylene))bis-(5,11-dihydro-1*H*-indeno[2′,1′:5,6]-pyrido[2,3-*d*]pyrimidine-2,4,6(3*H*)-trione) (15i)**. Pale brown crystals (705 mg,86%), m. p. >300 °C. IR (KBr): $\nu_{max}$ 3427, 3168 (br, $NH_2$ and NH), 1714 (CO-6), 1659, 1608 (CO-2 and CO-4) cm$^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 4.97-5.14 (m, 6 H, 2 C*H*-5 and 2 $CH_2$), 6.81-7.83 (m, 20 H, Ar-*H*), 9.81 (br s, 2 H, 2 N*H*-11), 10.15 (br s, 2 H, 2 N*H*-1), 10.81 (br s, 2 H, 2 N*H*-3) ppm. MS (EI, 70 eV): *m/z* 820 $[M]^+$. Anal. calcd for $C_{48}H_{32}N_6O_8$: C, 70.24; H, 3.93; N, 10.24. Found: C, 70.11; H, 3.78; N, 10.08%.

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## References

1. Fathalla, M.; Lawrence, C. M.; Zhang, N.; Sessler, J. L.; Jayawickramarajah, J. *Chem. Soc. Rev.* **2009**, *38*, 1608. https://doi.org/10.1039/b806484a
2. Sivakova, S.; Rowan, S. J. *Chem. Soc. Rev.* **2005**, *34*, 9. https://doi.org/10.1039/b304608g
3. Parker, J. B.; Bianchet, M. A.; Krosky, D. J.; Friedman, J. I.; Amzel, L. M.; Stivers, J. T. *Nature* **2007**, *449* 433.

 

https://doi.org/10.1038/nature06131
4. Okamoto, A. *Org. Biomol. Chem.* **2009**, *7*, 21. https://doi.org/10.1039/B813595A
5. McCarthy, O.; Musso-Buendia, A.; Kaiser, M.; Brun, R.; Ruiz-Perez, L. M.; Johansson, N. G.; Pacanowska, D. G.; Gilbert, I. H. *Eur. J. Med. Chem.* **2009**, *44*, 678. https://doi.org/10.1016/j.ejmech.2008.05.018
6. Nair, V.; Chi, G.; Shu, Q.; Julander, J.; Smee, D. F. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1425. https://doi.org/10.1016/j.bmcl.2009.01.031
7. Samanta, A.; Leonidas, D. D.; Dasgupta, S.; Pathak, T.; Zographos, S. E.; Oikonomakos, N. G. *J. Med. Chem.* **2009**, *52*, 932. https://doi.org/10.1021/jm800724t
8. Rico-Gómez, R.; López-Romero, J. M.; Hierrezuelo, J.; Brea, J.; Loza, M. I.; Pérez-González, M. *Carbohydr. Res.* **2008**, *343*, 855. https://doi.org/10.1016/j.carres.2008.01.011
9. Tucci, F. C.; Zhu, Y.-F.; Guo, Z.; Gross, T. D.; Connors, P. J.; Gao, Y.; Rowbottom, M. W.; Struthers, R. S.; Reinhart, G. J.; Xie, Q.; Chen, T. K.; Bozigian, H.; Bonneville, A. L. K.; Fisher, A.; Jin, L.; Saunders, J.; Chen, C. *J. Med. Chem.* **2004**, *47*, 3483. https://doi.org/10.1021/jm049791w
10. Sutherlin, D. P.; Sampath, D.; Berry, M.; Castanedo, G.; Chang, Z.; Chuckowree, I.; Dotson, J.; Folkes, A.; Friedman, L.; Goldsmith, R.; Heffron, T.; Lee, L.; Lesnick, J.; Lewis, C.; Mathieu, S.; Nonomiya, J.; Zhu, B.-Y. *J. Med. Chem.* **2010**, *53*, 1086. https://doi.org/10.1021/jm901284w
11. Strobel, S.; Dervan, P.; Berg, R.; Buchardt, O. *Science* **1990**, *249*, 73. https://doi.org/10.1126/science.2195655
12. Bansal, R.; Kumar, G.; Gandhi, D.; Young, L. C.; Harvey, A. L. *Eur. J. Med. Chem.* **2009**, *44*, 2122. https://doi.org/10.1016/j.ejmech.2008.10.017
13. Drabczyńska, A.; Müller, C. E.; Schiedel, A.; Schumacher, B.; Karolak-Wojciechowska, J.; Fruziński, A.; Zobnina, W.; Yuzlenko, O.; Kieć-Kononowicz, K. *Bioorg. Med. Chem.* **2007**, *15*, 6956. https://doi.org/10.1016/j.bmc.2007.07.051
14. Thureau, P.; Ancian, B.; Viel, S.; Thévand, A. *Chem. Commun.* **2006**, *2006*, 200. https://doi.org/10.1039/B513580J
15. Thakur, A. J.; Saikia, P.; Prajapati, D.; Sandhu, J. S. *Synlett* **2001**, 1299. https://doi.org/10.1055/s-2001-16036
16. Agarwal, A.; Chauhan, P. M. S. *Tetrahedron Lett.* **2005**, *46*, 1345. https://doi.org/10.1016/j.tetlet.2004.12.109
17. Shi, D.-Q.; Niu, L.-H.; Yao, H.; Jiang, H. *J. Heterocycl. Chem.* **2009**, *46*, 237. https://doi.org/10.1002/jhet.57
18. Edjlali, L.; Khanamiri, R. H.; Abolhasani, J. *Monatsh. Chem.* **2015**, *146*, 1339. https://doi.org/10.1007/s00706-014-1368-5
19. Shi, D.-Q.; Ni, S.-N.; Yang, F.; Shi, J.-W.; Dou, G.-L.; Li, X.-Y.; Wang, X.-S.; Ji, S.-J. *J. Heterocycl. Chem.* **2008**, *45*, 693. https://doi.org/10.1002/jhet.5570450310
20. Tanifum, E. A.; Kots, A. Y.; Choi, B.-K.; Murad, F.; Gilbertson, S. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3067. https://doi.org/10.1016/j.bmcl.2009.04.024

 

21. Tu, S.; Fang, F.; Li, T.; Zhu, S.; Zhang, X. *J. Heterocycl. Chem.* **2005**, *42*, 707. https://doi.org/10.1002/jhet.5570420436
22. Ghorab, M.; Ragab, F.; Noaman, E.; Heiba, H.; El-Hossary, E. *Arzneimittelforschung* **2011**, *57*, 795. https://doi.org/10.1055/s-0031-1296682
23. Ghorab, M. M.; Ragab, F. a; Heiba, H. I.; Arafa, R. K.; El-Hossary, E. M. *Eur. J. Med. Chem.* **2010**, *45*, 3677. https://doi.org/10.1016/j.ejmech.2010.05.014
24. Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169. https://doi.org/10.1021/cr100108k
25. Isambert, N.; Duque, M. del M. S.; Plaquevent, J.-C.; Génisson, Y.; Rodriguez, J.; Constantieux, T. *Chem. Soc. Rev.* **2011**, *40*, 1347. https://doi.org/10.1039/C0CS00013B
26. Shiri, M. *Chem. Rev.* **2012**, *112*, 3508. https://doi.org/10.1021/cr2003954
27. Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083. https://doi.org/10.1021/cr100233r
28. Brauch, S.; van Berkel, S. S.; Westermann, B. *Chem. Soc. Rev.* **2013**, *42*, 4948. https://doi.org/10.1039/c3cs35505e
29. Abdella, A. M.; Elwahy, A. H. M.; Abdelhamid, I. A. *Curr. Org. Synth.* **2016**, *13* (4), 601. https://doi.org/10.2174/1570179413999151211115100
30. Diab, H. M.; Abdelhamid, I. A.; Elwahy, A. H. M. *Synlett* **2018**, 1627. https://doi.org/10.1055/s-0037-1609967
31. Sanad, S. M. H.; Kassab, R. M.; Abdelhamid, I. A.; Elwahy, A. H. M. *Heterocycles* **2016**, *92*, 910. https://doi.org/10.3987/COM-16-13441
32. Abdella, A. M.; Mohamed, M. F.; Mohamed, A. F.; Elwahy, A. H. M.; Abdelhamid, I. A. *J. Heterocycl. Chem.* **2018**, *55* (2), 498. https://doi.org/10.1002/jhet.3072
33. Abdelmoniem, A. M.; Ghozlan, S. A. S.; Abdelmoniem, D. M.; Elwahy, A. H. M.; Abdelhamid, I. A. *J. Heterocycl. Chem.* **2017**, *54*, 2844. https://doi.org/10.1002/jhet.2890
34. Salama, S. K.; Mohamed, M. F.; Darweesh, A. F.; Elwahy, A. H. M.; Abdelhamid, I. A. *Bioorg. Chem.* **2017**, *71*, 19. https://doi.org/10.1016/j.bioorg.2017.01.009
35. Hebishy, A. M. S.; Abdelhamid, I. A.; Elwahy, A. H. M. *Arkivoc* **2018**, (5) 97. https://doi.org/10.24820/ark.5550190.p010.367
36. Mohamed, M. F.; Darweesh, A. F.; Elwahy, A. H. M.; Abdelhamid, I. A. *RSC Adv.* **2016**, *6*, 40900. https://doi.org/10.1039/C6RA04974E
37. Abdelhamid, I. A.; Darweesh, A. F.; Elwahy, A. H. M. *Tetrahedron Lett.* **2015**, *56*, 7085 https://doi.org/10.1016/j.tetlet.2015.11.015


 