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Hantzsch reaction with 6-aminouracil: Synthesis of novel tetrakis(6-aminouracil-5-yl)methanes and bis(decahydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-tetraones) linked to aliphatic or aromatic cores *via* ether-amide or ester-amide linkages

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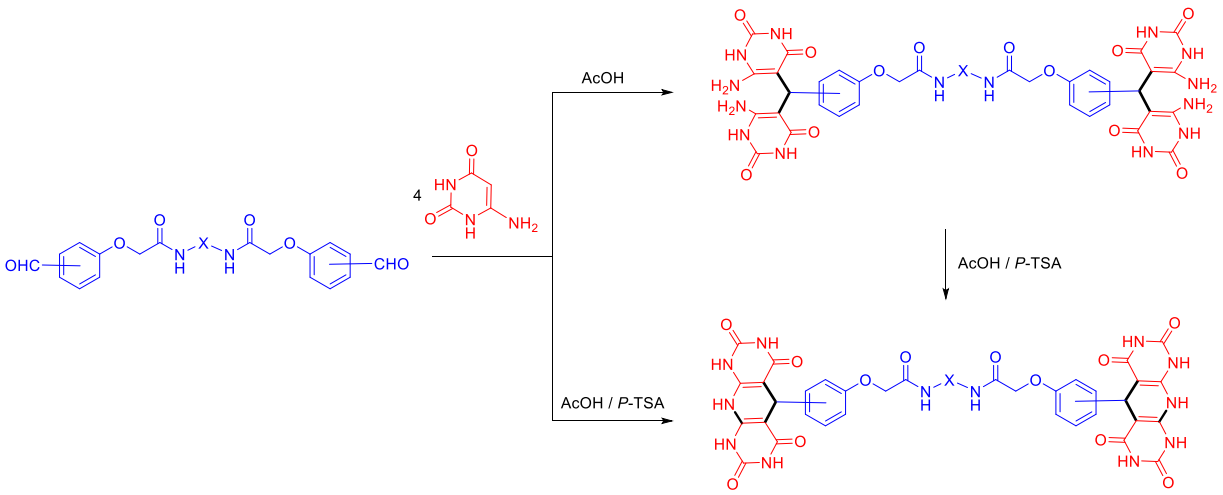
Abstract

One-pot three-component cyclo-condensation reaction of bis(aldehydes) containing ether-amide or ester-amide linkages with 6-aminouracil in boiling acetic acid afforded tetrakis(6-aminopyrimidine-2,4-diones) or bis(tetraoxodecahydropyrido[2,3-*d*:6,5-*d*']dipyrimidines) depending on the reaction conditions.



Keywords: Hantzsch reaction, bis(aldehydes), amide linkages, tetrakis(6-aminopyrimidine-2,4-diones), bis(tetraoxodecahydropyrido[2,3-*d*:6,5-*d*']dipyrimidines)

Introduction

Hantzsch reaction is one of the most common routes for the synthesis of 1,4-dihydropyridines (1,4-DHPs) having therapeutic and pharmacological properties.[1–19] In addition, Uracil is considered to be one of the major motifs present in the biopolymer RNA[20,21] and it plays several roles in our life.[22,23] The uracil scaffold and its derivatives exhibit a wide range of biological activities, including anticancer agents,[24–26] antihypertensive agents,[27] antiallergic compounds[28] and antiviral agents.[29–31] Structures of some FDA-approved uracil drugs are depicted in figure 1. Moreover, dipyrimidines exhibit a broad range of pharmacological properties, such as antimicrobial,[32,33] antitumor,[34] and antiviral.[35,36] Furthermore, the multicomponent reactions (MCRs) provide an easy and rapid access to diversity of heterocycles as they have the advantages of atom-economy and selectivity.[18,37-51]

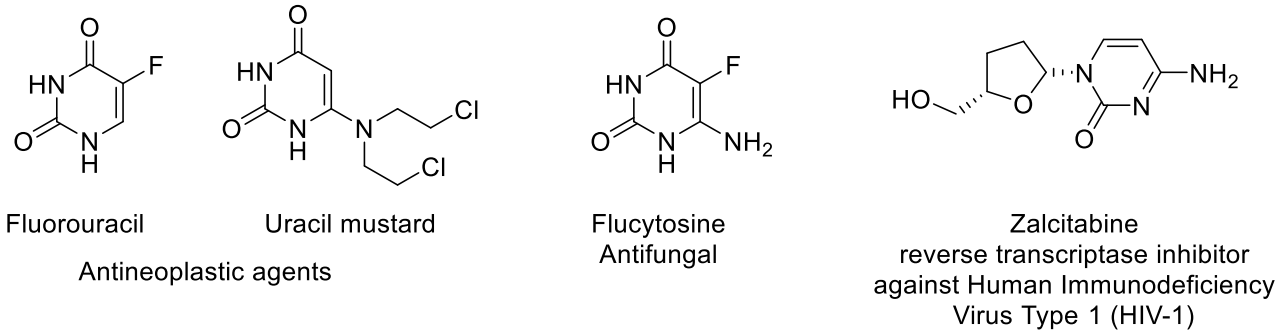
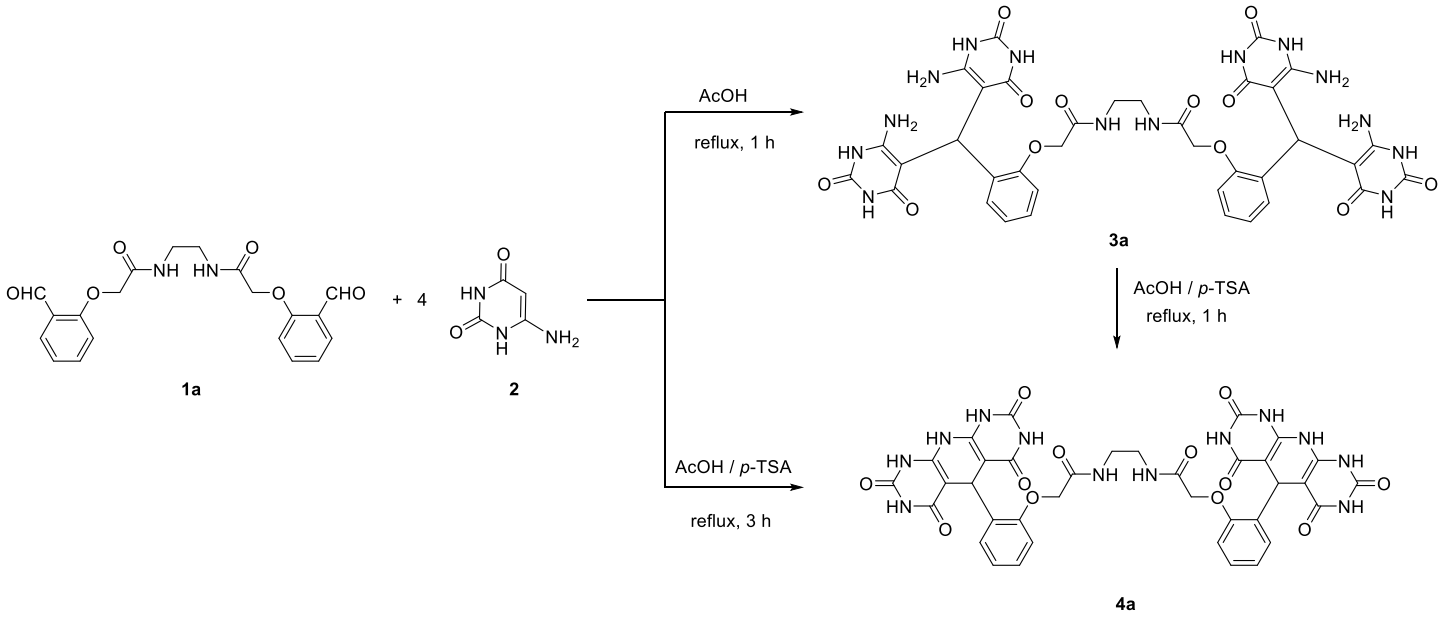


Figure 1. Some selected FDA-approved uracil drugs.

In connection with the importance of both 1,4-dihydropyridine and the dipyrimidine moiety and in continuation to our interest in enamine chemistry,[52–56] the synthesis of bis(heterocycles)[17,47–60] as well as the *C*-*C* bond formation reactions,[52,71–73] we report herein a highly efficient method for the synthesis of bis(pyrido[2,3-*d*:6,5-*d'*]dipyrimidinetetraones) linked to aliphatic or aromatic core *via* ether-amide or ester-amide linkages through the reaction of bis(aldehydes) with 6-aminouracil.

Results and Discussion

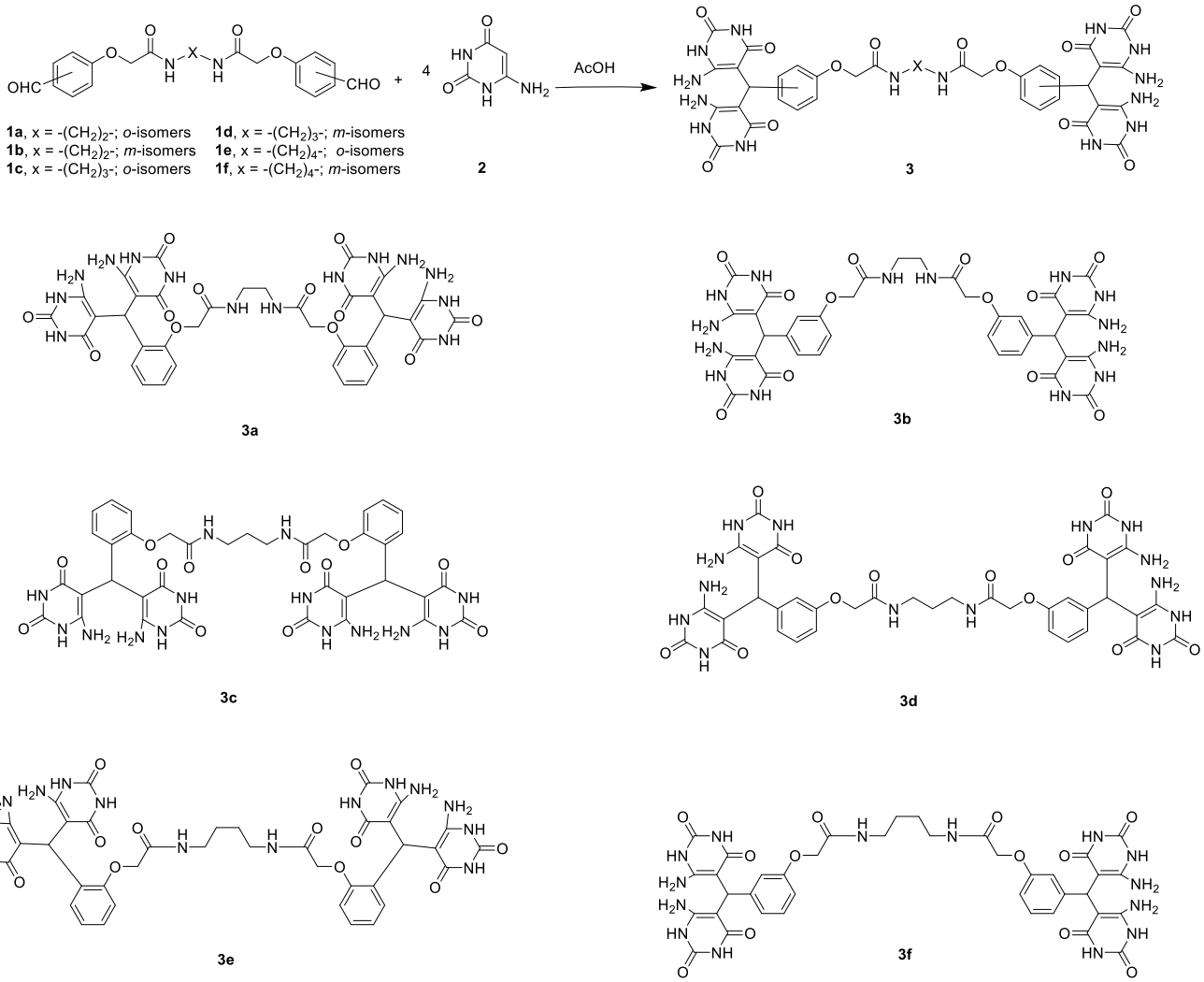
Firstly, the bis(2-(2-formylphenoxy)acetamide) **1a** was prepared following our reported procedure *via* the reaction of the potassium salt of salicylaldehyde with *N*,*N*'-(ethane-1,2-diyl)bis(2-chloroacetamide) in DMF.[74] The reactivity of the bis(aldehyde) **1a** towards 6-aminouracil **2** was then investigated aiming at the synthesis of bis(decahydropyrido[2,3-*d*:6,5-*d*']dipyrimidin-5-yl)phenoxy)acetamide) **4a**. Contrary to our expectation, the reaction did not yield compound **4a**, instead it gave the uncyclized tetrakis(6-aminopyrimidine-2,4-dione) **3a** in 88% yield (Scheme 1). It worth mentioning that trials to cyclize similar systems in acetic acid at reflux were unsuccessful.[75] On the other hand, heating a mixture of the bis(aldehyde) **1a** with the aminouracil **2** in acetic acid in the presence of *p*-TSA for 3 h afforded the target **4a** as the sole product. Moreover, we have found that heating of compound **3a** in acetic acid /*p*-TSA for 1 h afforded **4a** directly in one step.



Scheme 1. Synthesis of tetrakis(6-aminopyrimidine-2,4-dione) **3a** and bis(decahydropyrido[2,3-*d*:6,5-*d*']dipyrimidin-5-yl)phenoxy)acetamide) **4a**.

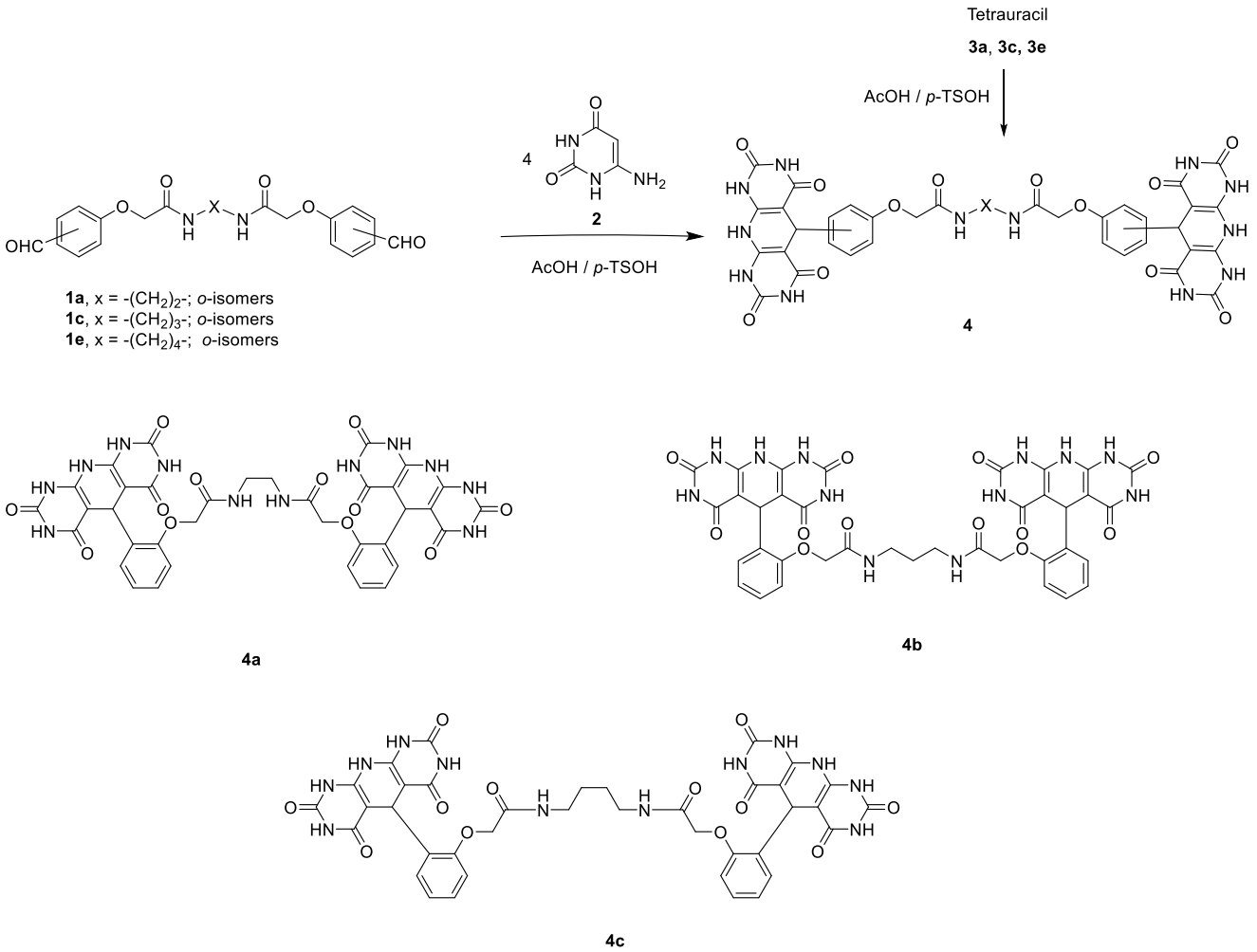
The structures of compounds **3a** and **4a** were supported based on the different spectral tools. Thus, the ^{1}H NMR spectrum of compound **3a** revealed a characteristic broad integrated by 4H at *δ* 3.30 ppm for the two methylene linkage. It also showed two characteristic singlets at *δ* 4.31 and 5.38 ppm for the -O$\underline{CH_2}$CO- and the bridging CH protons, respectively. In addition, it exhibited four broad singlet signals characteristic for the NH_2 and three NH groups at *δ* 6.74 and *δ* 7.48, 10.30 and 10.42, respectively. It also featured aromatic protons at *δ* 6.83-7.15. On the other hand, the ^{1}H NMR spectrum of compound **4a**, indicated the disappearance of the characteristic broad signals at the range of 6-7 ppm for the amino groups. It also featured in addition to the signals of methylene groups, singlet signal at *δ* 5.13 ppm for the pyridine-H5. It also indicated three different broad singlets at *δ* 8.41, 10.64 and 11.18 ppm corresponding to three different NH groups.

Stimulated by these noteworthy results, a series of bis(aldehydes) **1b-f** were prepared[74] and used to ascertain the generality and the scope of the protocol. The reaction of 6-aminouracil **2** with the appropriate bis(aldehydes) **1b-f** in acetic acid afforded the corresponding tetrakis(uracil) **3b-f** (Scheme 2) .



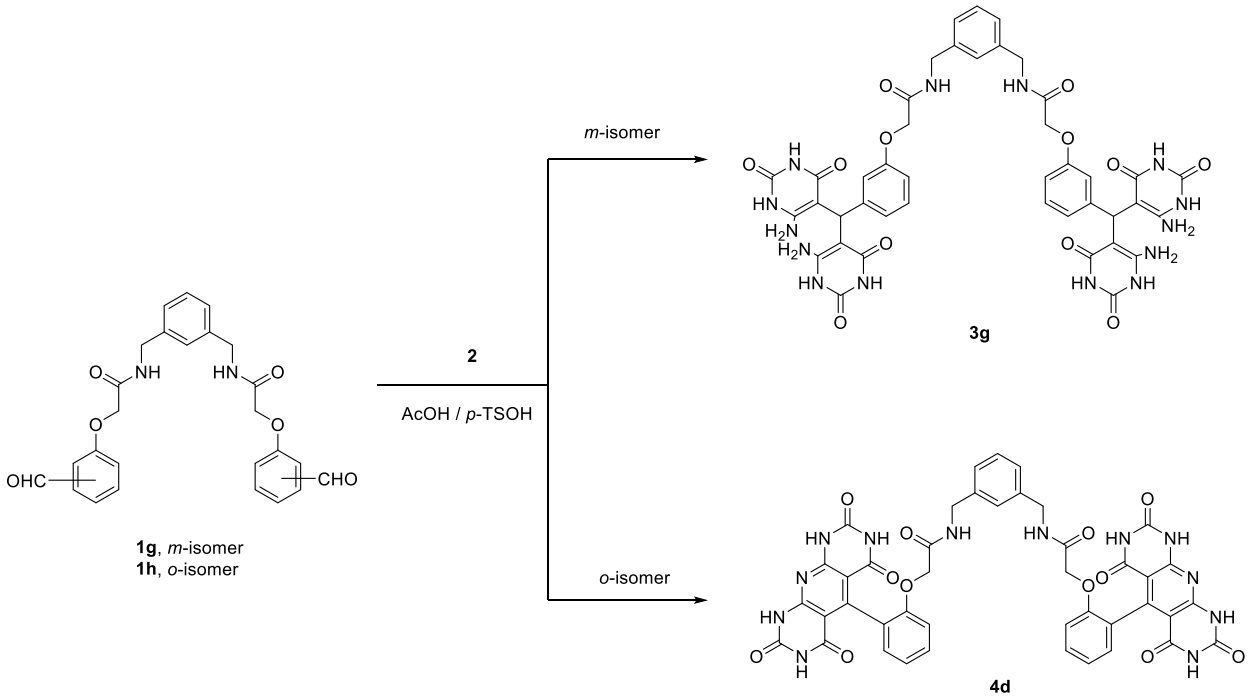
Scheme 2. Multicomponent synthesis of tetrakis(6-aminopyrimidine-2,4-dione) derivatives **3a-f**.

However, the reaction of 6-aminouracil **2** with the bis(aldehydes) **1a, 1c, 1e** in acetic acid / *p*-TSA resulted in the formation of bis(decahydropyrido[2,3-*d*:6,5-*d'*]dipyrimidin-5-yl)phenoxy)acetamides) **4a-c**, respectively, in good yields (Scheme 3). The latter compounds were alternatively obtained in good yields, by heating the corresponding tetra-uracil **3a**, **3c** and **3e** in acetic acid containing *p*-TSA at reflux.



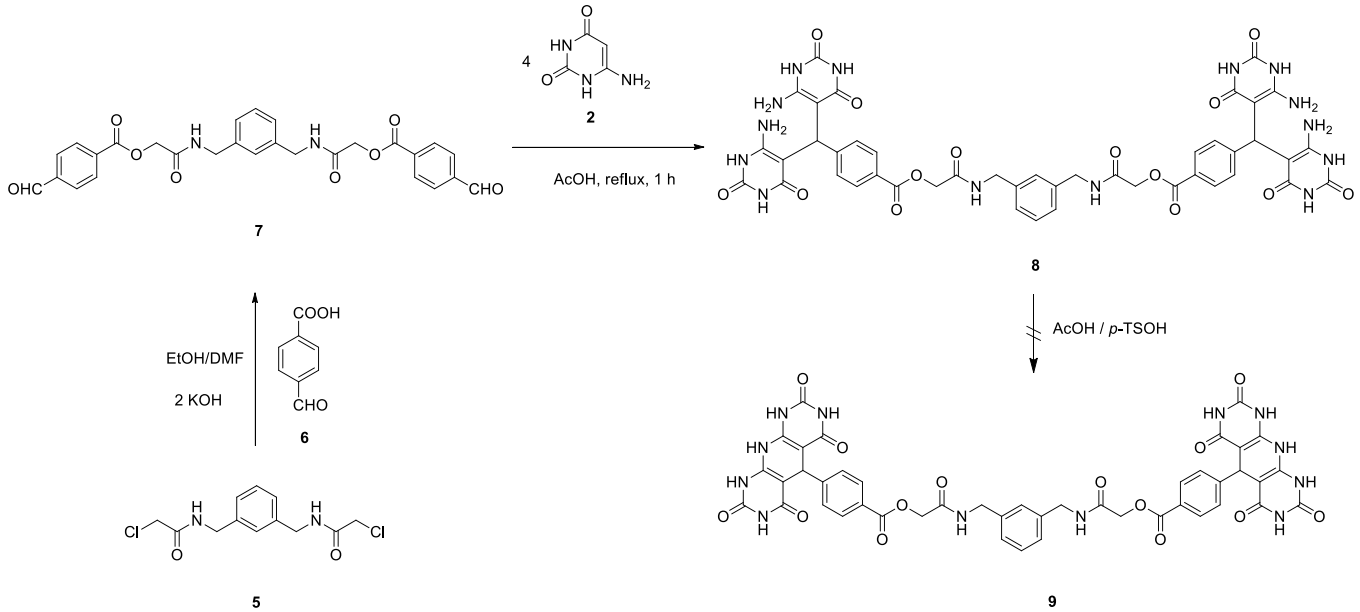
Scheme 3. Multicomponent synthesis of bis(decahydropyrido[2,3-*d*:6,5-*d*']dipyrimidin-5-yl)phenoxy)-acetamide) derivatives **4a-c**.

The scope of the reaction was further extended towards aldehydes which are linked to the benzene core *via* ether-amide linkage. It has been found that the reaction of bis(aldehyde) **1g** (aldehydic groups in *meta* position) with 6-aminouracil in acetic acid failed to give the target cyclized product pyridodipyrimidine even after prolonged heating in the presence of *p*-TSA (Scheme 4). The reaction gave instead the tetrakis(6-aminopyrimidine-2,4-dione) **3g**. On the other hand, the reaction of the bis(aldehyde) **1h** (aldehydic groups in *ortho* position) with 6-aminouracil **2** in acetic acid/*p*-TSA affords directly, the cyclic aromatized pyridodipyrimidine product **4d** (Scheme 4).



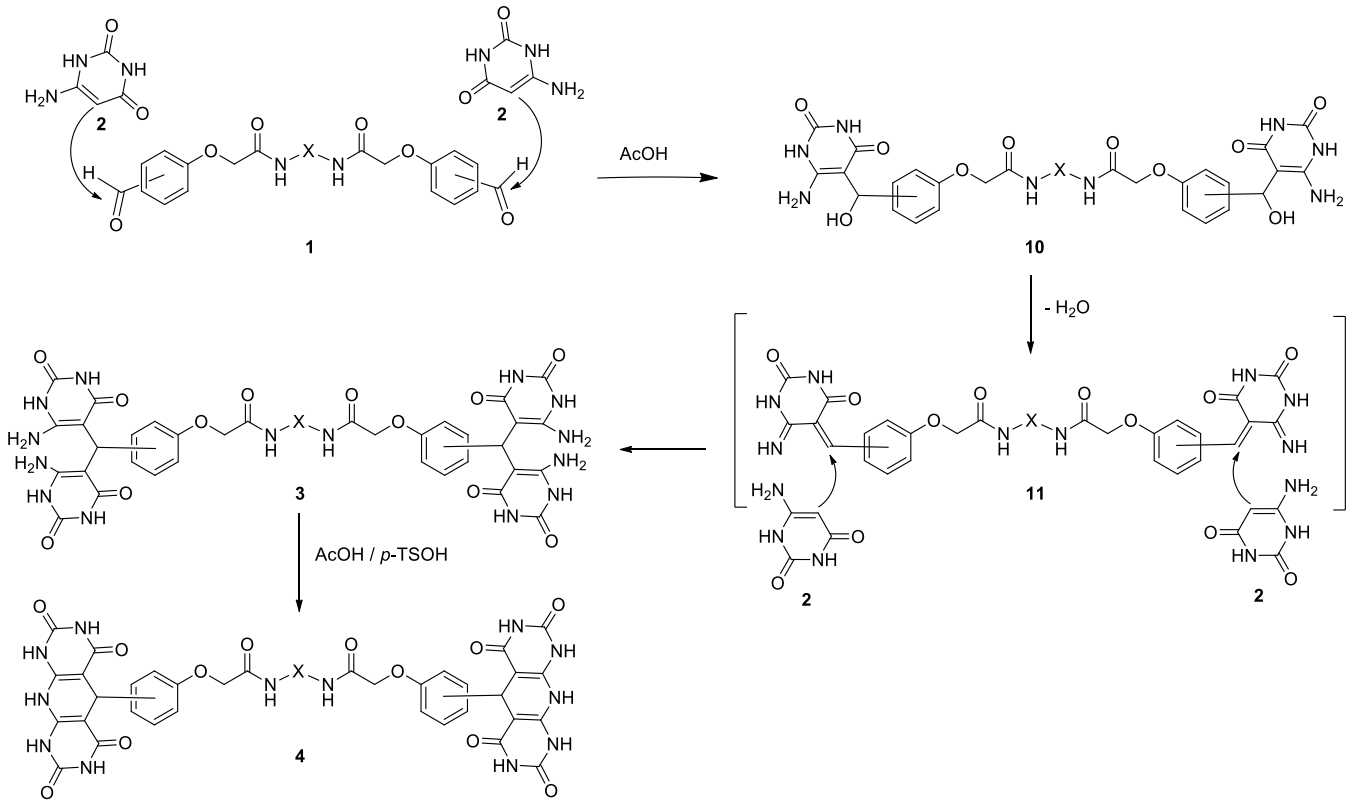
Scheme 4. Synthesis of tetrakis(6-aminopyrimidine-2,4-dione) **3g** and bis(tetraoxo-octahydropyrido[2,3-*d*:6,5-*d'*]dipyrimidine) **4d** which are linked to the benzene core *via* amide linkage.

Interestingly, the same methodology was also applied for the synthesis of the corresponding tetrakis(uracil) linked to ester-amide core linkage **8** *via* the direct reaction of the bis(aldehyde) **7** with four equivalents of 6-aminouracil **2** in acetic acid. Unfortunately, trials to cyclize **8** into bis(decahydropyrido[2,3-*d*:6,5-*d*']dipyrimidin-5-yl)phenoxy)acetamide) **9** upon heating **8** in acetic acid / *p*-TSA were unsuccessful (Scheme 5). The aldehyde containing ester-amide linkage **7** was prepared *via* the reaction of the potassium salt of the *p*-formylbenzoic acid **6** with the corresponding bis(2-chloroacetamide) **5** in boiling DMF.[74]



Scheme 5. Unsuccessful trial to obtain bis(decahydropyrido[2,3-*d*:6,5-*d*']dipyrimidin-5-yl)phenoxy)-acetamide) **9**.

A proposed synthetic pathway for the reaction of bisaldehydes with 6-aminouracil is shown in scheme 5. 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 **10**. Subsequent elimination of water leads to the formation of the corresponding ene-imine intermediate **11**. The Michael addition of another two moles of 6-aminouracil **2** to the intermediate **11** affords the products **3**. Subsequent removal of ammonia using *p*-TSA led to the formation of **4** (Scheme 6).



Scheme 6. A proposed pathway for the synthesis of compounds **3** and **4.**

Conclusions

We developed a synthetic approach for the synthesis of novel tetrakis(6-aminopyrimidine-2,4-diones) or bis(tetraoxodecahydropyrido[2,3-*d*:6,5-*d'*]dipyrimidines) *via* one-pot three-component cyclo-condensation reaction of bis(aldehydes) containing ether-amide or ester-amide linkages with 6-aminouracil. The reaction products was found to be dependent on the reaction conditions. It is expected that the novel structures prepared in this paper would be useful in the field of medicinal and synthetic organic chemistry.

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 on Varian Gemini NMR spectrometer at 400 MHz and 100 MHz, respectively, using TMS as internal standard. Chemical shifts are reported as δ values in ppm. Mass spectra

were recorded with a Shimadzu GCMS–QP–1000 EX mass spectrometer in EI (70 eV) model. Elemental analyses were performed on a Perkin-Elmer 240 micoanalyser at the Micro analytical Center of Cairo University.

General procedure for the synthesis of 3a-3g and 8. A solution of each of bisaldehydes **1a-1g** and **7** (1 mmol) and 6-aminouracil (4 mmol) in acetic acid (3 ml) was heated at reflux for 1 h. The solid obtained was collected and crystallized from DMF/EtOH to give compounds **3a-g** and **8**.

***N,N'*-(Ethane-1,2-diyl)bis(2-(2-(bis(6-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)phenoxy)-acetamide) (3a).** Pale yellow powder (88%). mp 270-272 °C. IR (KBr): ν 3344, 3155 (NH and NH_2), 1708 (CO). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.30 (br, 4H, CH_2N), 4.31 (s, 4H, CH_2O), 5.38 (s, 2H, CH), 6.47 (br, 8H, NH_2), 6.83-7.15 (m, 8H, Ar-H), 7.48 (br, 2H, NH), 10.30 (br, 4H, NH), 10.42 (br, 4H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 29.7, 36.3, 68.1, 112.8, 121.3, 127.2, 128.4, 129.2, 150.2, 153.9, 156.0, 162.8, 165.6, 168.4. MS (EI, 70 eV): *m/z* (%) 856 [M^+]. Anal. Calcd for $C_{36}H_{36}N_{14}O_{12}$: C, 50.47; H, 4.24; N, 22.89 found C, 50.73; H, 4.43; N, 23.13.

***N,N'*-(Ethane-1,2-diyl)bis(2-(3-(bis(6-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)phenoxy)-acetamide) (3b).** Pale yellow powder (85%). mp 288-290 °C. IR (KBr): ν 3325, 3147 (NH and NH_2), 1712 (CO). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.24 (br, 4H, CH_2N), 4.36 (s, 4H, CH_2O), 5.30 (s, 2H, CH), 6.70-7.15 (m, 16H, NH2+Ar-H), 8.19 (br, 2H, NH), 10.32 (br, 4H, NH), 10.51 (br, 4H, NH). MS (EI, 70 eV): *m/z* (%) 856 [M^+]. Anal. Calcd for $C_{36}H_{36}N_{14}O_{12}$: C, 50.47; H, 4.24; N, 22.89 found C, 50.69; H, 4.07; N, 23.14.

***N,N'*-(Propane-1,3-diyl)bis(2-(2-(bis(6-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)phenoxy)-acetamide) (3c).** Pale yellow powder (90%). mp 242-244 °C. IR (KBr): ν 3348, 3171 (NH and NH_2), 2978 (NH), 2850 (NH_2), 1712 (CO). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.60-1.62 (m,2H, CH2), 3.14-3.17 (m, 4H, CH_2N), 4.34 (s, 4H, CH_2O), 5.34 (s, 2H, CH), 6.50 (br, 8H, NH_2), 6.81-7.11 (m, 8H, Ar-H), 7.14 (br, 2H, NH), 10.45 (br, 8H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.9, 29.2, 36.1, 67.2, 86.5, 111.8, 120.6, 120.7, 126.6, 128.6, 149.6, 153.4, 155.3, 165.0, 167.5. MS (EI, 70 eV): *m/z* (%) 870 [M^+]. Anal. Calcd for $C_{37}H_{38}N_{14}O_{12}$: C, 51.03; H, 4.40; N, 22.52 found C, 51.31; H, 4.66; N, 22.25.

***N,N'*-(Propane-1,3-diyl)bis(2-(3-(bis(6-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)phenoxy)-acetamide) (3d).** Pale yellow powder (87%). mp > 300 °C. IR (KBr): ν 3325, 3178 (NH and NH_2), 1724 (CO). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.57-1.64 (m, 2H, CH2), 3.11-3.13 (m, 4H, CH_2N), 4.37 (s, 4H, CH_2O), 5.30 (s, 2H, CH), 6.69 (br, 8H, NH_2), 6.72-7.13 (m, 8H, Ar-H), 8.08 (br, 2H, NH), 10.28 (br, 4H, NH), 10.47 (br, 4H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 29.7, 32.9, 36.2, 67.5, 110.8, 114.6, 120.4, 129.1, 138.0, 142.0, 150.2, 158.0, 167.8, 168.2, 172.7. MS (EI, 70 eV): *m/z* (%) 870 [M^+]. Anal. Calcd for $C_{37}H_{38}N_{14}O_{12}$: .C, 51.03; H, 4.40; N, 22.52 found C, 51.32; H, 4.60; N, 22.20.

***N,N'*-(Butane-1,4-diyl)bis(2-(2-(bis(6-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)phenoxy)-acetamide) (3e).** Pale yellow powder (91%). mp 242-244 °C. IR (KBr): ν 3429, 3367, 3179 (NH and NH_2), 1724 (CO). ^{1}H NMR (300 MHz, DMSO-d_6):): δ 1.42 (br, 4H, CH_2),), 3.16 (br, 4H, CH_2N), 4.34 (s, 4H, CH_2O),), 5.34 (s, 2H, CH), 6.46 (br, 8H, NH_2), 6.83-7.11 (m, 8H, Ar-H), 7.12 (br, 2H, NH), 10.33 (br, 4H, NH), 10.42 (br, 4H, NH)). MS (EI, 70 eV): *m/z* (%) 884 [M^+]. Anal. Calcd for $C_{38}H_{40}N_{14}O_{12}$: C, 51.58; H, 4.56; N, 22.16 found C, 51.84; H, 4.75; N, 22.45.

***N,N'*-(Butane-1,4-diyl)bis(2-(3-(bis(6-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)phenoxy)-acetamide)(3f).** Pale yellow powder (88%). mp 284-286 °C. IR (KBr): ν 3379, 3125 (NH and NH_2), 1708 (CO). ^{1}H NMR (300 MHz, DMSO-d_6):): δ 1.41 (br, 4H, CH_2), 3.12 (br, 4H, CH_2N), 4.35 (s, 4H, CH_2O), 5.29 (s, 2H, CH), 6.68 (br, 8H, NH_2), 6.70-7.13 (m, 8H, Ar-H), 8.03 (br, 2H, NH), 10.28 (br, 4H, NH), 10.47 (br, 4H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.1, 32.8, 38.5, 67.4, 110.7, 114.5, 120.3, 129.0, 142.0, 150.2, 158.0, 158.9, 165.1, 168.0,

172.8. MS (EI, 70 eV): *m/z* (%) 884[M^+]. Anal. Calcd for $C_{38}H_{40}N_{14}O_{12}$: C, 51.58; H, 4.56; N, 22.16 found C, 51.35; H, 4.35; N, 22.42.

***N,N'*-(1,3-Phenylenebis(methylene))bis(2-(3-(bis(6-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-methyl)phenoxy)acetamide) (3g).** Pale yellow powder (89%). mp 296-298 °C. IR (KBr): ν 3356, 3152 (NH and NH_2), 1716 (CO). ^{1}H NMR (300 MHz, DMSO-d_6): 4.30-4.32 (d, *J* = 5.7 Hz, 4H, CH_2N), 4.44 (s, 4H, CH_2O), 5.30 (s, 2H, CH), 6.70 (br, 8H, NH_2), 6.73-7.15 (m, 12H, Ar-H), 8.59-8.62 (t, *J* = 6.6 Hz, 2H, NH), 10.29 (br, 4H, NH), 10.47 (br, 4H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 33.1, 42.2, 67.4, 110.7, 114.6, 120.3, 126.2, 126.8, 128.7, 129.0, 139.8, 139.9, 142.0, 150.2, 158.0, 167.9, 168.2, 172.8. MS (EI, 70 eV): *m/z* (%) 932[M^+]. Anal. Calcd for $C_{42}H_{40}N_{14}O_{12}$: C, 54.08; H, 4.32; N, 21.02 found C, 53.89; H, 4.12; N, 21.22.

((1,3-Phenylenebis(methylene))bis(azanediyl))bis(2-oxoethane-2,1-diyl)bis(4-(bis(6-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)benzoate) (8). Pale yellow powder (86%). mp 294-296 °C. IR (KBr): ν 3368, 3151 (NH and NH_2), 1713 (CO), 1624 (CO). ^{1}H NMR (300 MHz, DMSO-d_6): 4.30-4.32 (d, *J* = 5.4 Hz, 4H, CH_2N), 4.75 (s, 4H, CH_2O), 5.36 (s, 2H, CH), 6.71 (br, 8H, NH_2), 7.14-7.16 (m, 4H, Ar-H),7.23-7.26 (d, *J* = 8.7 Hz, 4H, Ar-H), 7.87-7.90 (d, *J* = 8.7Hz, 4H, Ar-H), 8.60-8.62 (t, *J* = 6 Hz, 2H, NH), 10.33 (br, 4H, NH), 10.52 (br, 4H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 33.3, 42.3, 63.3, 126.1, 126.6, 127.4, 128.8, 129.6, 130.0, 130.7, 139.7, 146.7, 150.2, 164.7, 165.9, 167.3, 172.5. MS (EI, 70 eV): *m/z* (%) 988[M^+]. Anal. Calcd for $C_{44}H_{40}N_{14}O_{14}$: C, 53.44; H, 4.08; N, 19.83 found C, 53.70; H, 3.86; N, 19.64.

General procedure for the synthesis of 4a-d. A solution of each of bisaldehydes (**1a, 1c**, **1e** and **1h**) (1 mmol) and 6-aminouracil (4 mmol) in acetic acid (3 ml) in the presence of *p*-TSA was heated at reflux for 1 h. The solid obtained was collected and crystallized from DMF/EtOH to give compounds **4a-d**.

***N,N'*-(Ethane-1,2-diyl)bis(2-(2-(2,4,6,8-tetraoxo-1,2,3,4,5,6,7,8,9,10-decahydropyrido[2,3-*d*:6,5-*d*']-dipyrimidin-5-yl)phenoxy)acetamide) (4a).** Pale yellow powder (93%). mp >300 °C. IR (KBr): ν 3070 (NH), 1690 (CO). ^{1}H NMR (300 MHz, DMSO-d_6): 3.24 (br, 4H, CH_2N), 4.46 (s, 4H, CH_2O), 5.13 (s, 2H, Pyridine-H), 6.72-7.10 (m,10H, Ar-H+NH), 8.41 (br, 2H, NHCO), 10.64 (br, 4H, NH), 11.18 (br, 4H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.3, 38.3, 67.5, 90.2, 111.5, 121.5, 127.6, 130.0, 136.1, 144.1, 150.2, 154.7, 163.1, 170.0. MS (EI, 70 eV): *m/z* (%) 822[M^+]. Anal. Calcd for $C_{36}H_{30}N_{12}O_{12}$: C, 52.56; H, 3.68; N, 20.43 found C, 52.77; H, 3.44; N, 20.61.

***N,N'*-(Propane-1,3-diyl)bis(2-(2-(2,4,6,8-tetraoxo-1,2,3,4,5,6,7,8,9,10-decahydropyrido[2,3-d:6,5-d']-dipyrimidin-5-yl)phenoxy)acetamide) (4b).** Pale yellow powder (91%). mp >300 °C. IR (KBr): ν 3035 (br, NH), 1690 (CO). ^{1}H NMR (300 MHz, DMSO-d_6): 1.50-1.60 (m, 2H, CH2), 3.04-3.10 (m, 4H, CH_2N), 4.49 (s, 4H, CH_2O), 5.14 (s, 2H, Pyridine-H), 6.72-7.12 (m, 10H, Ar-H+NH), 8.34 (br, 4H, NHCO), 10.65 (br, 4H, NH), 11.18 (br, 4H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 29.2, 36.6, 38.3, 67.6, 90.2, 111.5, 121.6, 127.7, 130.2, 135.8, 144.3, 150.3, 154.6, 163.2, 168.7. MS (EI, 70 eV): *m/z* (%) 836 [M^+]. Anal. Calcd for $C_{37}H_{32}N_{12}O_{12}$: C, 53.11; H, 3.85; N, 20.09 found C, 52.89; H, 4.10; N, 20.30.

***N,N'*-(Butane-1,4-diyl)bis(2-(2-(2,4,6,8-tetraoxo-1,2,3,4,5,6,7,8,9,10-decahydropyrido[2,3-*d*:6,5-*d*']-dipyrimidin-5-yl)phenoxy)acetamide) (4c).** Pale yellow powder (94%). mp 294-296 °C. IR (KBr): ν 3032 (br, NH), 1690 (CO). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.26 (br, 4H, CH2), 3.05 (br, 4H, CH_2N), 4.50 (s, 4H, CH_2O), 5.15 (s, 2H, Pyridine -H), 6.70-7.10 (m, 10H, Ar-H+NH), 8.35 (br, 2H, NH), 10.72 (br, 4H, NH), 11.15 (br, 4H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 26.6, 37.8, 38.6, 67.0, 89.6, 110.9, 120.2, 121.0, 127.0, 129.4, 135.4, 143.8, 153.9, 162.5, 168.0. MS (EI, 70 eV): *m/z* (%) 850 [M^+]. Anal. Calcd for $C_{38}H_34N_{12}O_{12}$: C, 53.65; H, 4.03; N, 19.76 found C, 53.84; H, 3.79; N, 20.02.

***N,N'*-(1,3-Phenylenebis(methylene))bis(2-(2-(2,4,6,8-tetraoxo-1,2,3,4,6,7,8,9-octahydropyrido[2,3-*d*:6,5-*d*']dipyrimidin-5-yl)phenoxy)acetamide) (4d).** Pale yellow powder (89%). mp >300 °C. IR (KBr): ν 3201 (NH), 3070 (br, NH), 1705 (CO). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.19-4.21(d, *J* = 6.3 Hz, 4H, CH_2N), 4.78 (s, 4H, CH_2O),

6.90-7.31 (m, 14H, Ar-H+NH), 7.76-7.78 (t, *J* = 6.3 Hz, 2H, NHCO), 11.15 (br, 4H, NH), 11.84 (br, 4H, NH). MS (EI, 70 eV): *m/z* (%) 894 [M^+]. Anal. Calcd for $C_{42}H_{30}N_{12}O_{12}$: C, 56.38; H, 3.38; N, 18.78 found C, 56.17; H, 3.56; N, 19.04.

Supplementary Material

Supplementary material related to this article, including Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR) figures for all new compounds **3a**, **3c**, **8**, **4a** and **4d** are available in the online version of the text.

References

1. Shamim, T.; Gupta, M.; Paul, S. *J. Mol. Catal. A Chem.* **2009**, *302*, 15–19. https://doi.org/10.1016/j.molcata.2008.11.024
2. Gómez-Pliego, R.; Gómez-Zamudio, J.; Velasco-Bejarano, B.; Ibarra-Barajas, M.; Villalobos-Molina, R. *J. Pharmacol. Sci.* **2013**, *122*, 184–192. https://doi.org/10.1254/jphs.12248FP
3. Ibrahim, N.S.; Mohamed, M.F.; Elwahy, A.H.M.; Abdelhamid, I.A. *Lett. Drug Des. Discov.* **2018**, *15*, 1036–1045. https://doi.org/10.2174/1570180815666180105162323
4. Sridhar, R.; Perumal, P.T. *Tetrahedron* **2005**, *61*, 2465–2470. https://doi.org/10.1016/j.tet.2005.01.008
5. Paul, S.; Sharma, S.; Gupta, M.; Choudhary, D.; Gupta, R. *Bull. Korean Chem. Soc.* **2007**, *28*, 336–338. https://doi.org/10.5012/bkcs.2007.28.2.336
6. Saikh, F.; De, R.; Ghosh, S. *Tetrahedron Lett.* **2014**, *55*, 6171–6174. https://doi.org/10.1016/j.tetlet.2014.09.025
7. Sridharan, V.; Perumal, P.T.; Avendaño, C.; Menéndez, J.C. *Tetrahedron* **2007**, *63*, 4407–4413. https://doi.org/10.1016/j.tet.2007.03.092
8. Navidpour, L.; Shafaroodi, H.; Miri, R.; Dehpour, A.R.; Shafiee, A. *Farmaco* **2004**, *59*, 261–269. https://doi.org/10.1016/j.farmac.2003.11.013
9. Debache, A.; Ghalem, W.; Boulcina, R.; Belfaitah, A.; Rhouati, S.; Carboni, B. *Tetrahedron Lett.* **2009**, *50*, 5248–5250. https://doi.org/10.1016/j.tetlet.2009.07.018
10. Miri, R.; Javidnia, K.; Hemmateenejad, B.; Tabarzad, M.; Jafarpour, M. *Chem. Biol. Drug Des.* **2009**, *73*, 225–235. https://doi.org/10.1111/j.1747-0285.2008.00770.x
11. Abbas, H.A.S.; El Sayed, W.A.; Fathy, N.M. *Eur. J. Med. Chem.* **2010**, *45*, 973–982. https://doi.org/10.1016/j.ejmech.2009.11.039
12. Safak, C.; Simsek, R. *Mini-Reviews Med. Chem.* **2006**, *6*, 747–755. https://doi.org/10.2174/138955706777698606
13. Murthy, Y.L.N.; Rajack, A.; Taraka Ramji, M.; Jeson Babu, J.; Praveen, C.; Aruna Lakshmi, K. *Bioorganic Med. Chem. Lett.* **2012**, *22*, 6016–6023. https://doi.org/10.1016/j.bmcl.2012.05.003

14. Samzadeh-Kermani, A.; Shafaroodi, H.; Miri, R.; Mirkhani, H.; Vosooghi, M.; Shafiee, A. *Med. Chem. Res.* **2009**, *18*, 112–126. c https://doi.org/10.1007/s00044-008-9112-5
15. Huber, I.; Wappl, E.; Herzog, A. *Biochem. J.* **2000**, *836*, 829–836. https://doi.org/10.1042/bj3470829
16. Ghozlan, S.A.S.; Ramadan, M.A.; Abdelmoniem, A.M.; Elwahy, A.H.M.; Abdelhamid, I.A. *Turkish J. Chem.* **2017**, *41*, 410 – 419. https://doi.org/10.3906/kim-1609-42
17. Kassab, R.M.; Elwahy, A.H.M.; Abdelhamid, I.A. *Monat. Chem.* **2016**, *147*, 1227–1232. https://doi.org/10.1007/s00706-015-1644-z
18. Mohamed, M.F.; Darweesh, A.F.; Elwahy, A.H.M.; Abdelhamid, I.A. *RSC Adv.* **2016**, *6*, 40900–40910. https://doi.org/10.1039/c6ra04974e
19. Abdelhamid, I.A.; Darweesh, A.F.; Elwahy, A.H.M. *Tetrahedron Lett.* **2015**, *56*, 7085–7088. https://doi.org/10.1016/j.tetlet.2015.11.015
20. Fathalla, M.; Lawrence, C.M.; Zhang, N.; Sessler, J.L.; Jayawickramarajah, J. *Chem. Soc. Rev.* **2009**, *38*, 1608–1620. https://doi.org/10.1039/b806484a
21. Sivakova, S.; Rowan, S.J. *Chem. Soc. Rev.* **2005**, *34*, 9–21. https://doi.org/10.1039/b304608g
22. Dinner, A.R.; Blackburn, G.M.; Karplus, M. *Nature* **2001**, *413*, 752–755. https://doi.org/10.1038/35099587
23. Di Noia, J.; Neuberger, M.S. *Nature* **2002**, *419*, 43–48. https://doi.org/10.1038/nature00981
24. Tucci, F.C.; Zhu, Y.F.; Guo, Z.; Gross, T.D.; Connors Jr., P.J.; Gao, Y.; Rowbottom, M.W.; Struthers, R.S.; Reinhart, G.J.; Xie, Q.; et al. *J Med Chem* **2004**, *47*, 3483–3486. https://doi.org/10.1021/jm049791w
25. 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.; Olivero, A.; Pang, J.; Prior, W. W.; Salphati, L.; Sideris, S.; Tian, Q.; Tsui, V.; Wan, N. C.; Wang, S.; Wiesmann, C.; Wong, S.; Zhu, B. Y. *J. Med. Chem.* **2010**, *53*, 1086–1097. https://doi.org/10.1021/jm901284w
26. Brognara, E.; Lampronti, I.; Breveglieri, G.; Accetta, A.; Corradini, R.; Manicardi, A.; Borgatti, M.; Canella, A.; Multineddu, C.; Marchelli, R.; et al. *Eur. J. Pharmacol.* **2011**, *672*, 30–37. https://doi.org/10.1016/j.ejphar.2011.09.024
27. Liu, Y.Y.; Zeng, S.Y.; Leu, Y.L.; Tsai, T.Y. *J. Agric. Food Chem.* **2015**, *63*, 7333–7342. https://doi.org/10.1021/acs.jafc.5b01649
28. Tobe, M.; Isobe, Y.; Goto, Y.; Obara, F.; Tsuchiya, M.; Matsui, J.; Hirota, K.; Hayashi, H. *Bioorganic Med. Chem.* **2000**, *8*, 2037–2047. https://doi.org/10.1016/S0968-0896(00)00126-7
29. Sapozhnikova, K.A.; Slesarchuk, N.A.; Orlov, A.A.; Khvatov, E. V.; Radchenko, E. V.; Chistov, A.A.; Ustinov, A. V.; Palyulin, V.A.; Kozlovskaya, L.I.; Osolodkin, D.I.; et al. *RSC Adv.* **2019**, *9*, 26014–26023. https://doi.org/10.1039/c9ra06313g
30. Geant, P.Y.; Uttaro, J.P.; Périgaud, C.; Mathé, C. *Molecules* **2020**, *25*, 3708. https://doi.org/10.3390/molecules25163708

31. Maslova, A.A.; Matyugina, E.S.; Snoeck, R.; Andrei, G.; Kochetkov, S.N.; Khandazhinskaya, A.L.; Novikov, M.S. *Molecules* **2020**, *25*. https://doi.org/10.3390/molecules25153350
32. Fatma, S.; Bishnoi, A.; Singh, V.; Al-Omary, F.A.M.; El-Emam, A.A.; Pathak, S.; Srivastava, R.; Prasad, O.; Sinha, L. *J. Mol. Struct.* **2016**, *1110*, 128–137. https://doi.org/10.1016/j.molstruc.2016.01.054
33. Suresh, T.; Nandha Kumar, R.; Mohan, P.S. *Heterocycl. Commun.* **2003**, *9*, 203–208. https://doi.org/10.1515/HC.2003.9.2.203
34. Maddila, S.; Naicker, K.; Gorle, S.; Rana, S.; Yalagala, K.; N. Maddila, S.; Singh, M.; Singh, P.; B. Jonnalagadda, S. *Anticancer. Agents Med. Chem.* **2016**, *16*, 1031–1037. https://doi.org/10.2174/1871520616666151123095932
35. Neamati, N. *Expert Opin. Investig. Drugs* **2003**, *12*, 289–292. https://doi.org/10.1517/13543784.12.2.289
36. Pannecouque, C.; Pluymers, W.; Van Maele, B.; Tetz, V.; Cherepanov, P.; De Clercq, E.; Witvrouw, M.; Debyser, Z. *Curr. Biol.* **2002**, *12*, 1169–1177. https://doi.org/10.1016/S0960-9822(02)00952-1
37. Elwahy, A.H.M.; Shaaban, M.R. *Curr. Org. Synth.* **2015**, *11*, 835–873. https://doi.org/10.2174/1570179411061410231140 39
38. Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005; ISBN 3527308067.
39. Elwahy, A.; Shaaban, M. *Curr. Org. Synth.* **2010**, *7*, 433–454. https://doi.org/10.2174/157017910792246117
40. Elwahy, A.H.M.; Shaaban, M.R. *Curr. Org. Synth.* **2015**, *10*, 425–466. https://doi.org/10.2174/1570179411310030007
41. Shaaban, M.R.; Elwahy, A.H.M. *Curr. Org. Synth.* **2015**, *11*, 471–525. https://doi.org/10.2174/1570179411310666007 6
42. Khoobi, M.; Ramazani, A.; Foroumadi, A.; Souldozi, A.; Ślepokura, K.; Lis, T.; Mahyari, A.; Shafiee, A.; Joo, S.W. *Helv. Chim. Acta* **2013**, *96*, 906–918. https://doi.org/10.1002/hlca.201200187
43. Zareai, Z.; Khoobi, M.; Ramazani, A.; Foroumadi, A.; Souldozi, A.; Ślepokura, K.; Lis, T.; Shafiee, A. *Tetrahedron* **2012**, *68*, 6721–6726. https://doi.org/10.1016/j.tet.2012.05.112
44. Khoobi, M.; Ramazani, A.; Mahdavi, M.; Foroumadi, A.; Emami, S.; Joo, S.W.; Ślepokura, K.; Lis, T.; Shafiee, A. *Helv. Chim. Acta* **2014**, *97*, 847–853. https://doi.org/10.1002/hlca.201300310
45. Ramazani, A.; Khoobi, M.; Torkaman, A.; Zeinali Nasrabadi, F.; Forootanfar, H.; Shakibaie, M.; Jafari, M.; Ameri, A.; Emami, S.; Faramarzi, M.A.; et al. *Eur. J. Med. Chem.* **2014**, *78*, 151–156. https://doi.org/10.1016/j.ejmech.2014.03.049
46. Sanad, S.M.H.; Kassab, R.M.; Abdelhamid, I.A.; Elwahy, A.H.M. *Heterocycles* **2016**, *92*, 910–924. https://doi.org/10.3987/COM-16-13441
47. Sharma, M.G.; Rajani, D.P.; Patel, H.M. *R. Soc. Open Sci.* 2017, *4*, 170006. https://doi.org/10.1098/rsos.170006
48. Patel, D.M.; Patel, H.J.; Padrón, J.M.; Patel, H.M. *RSC Adv.* **2020**, *10*, 19600–19609. https://doi.org/10.1039/D0RA02990D

49. Patel, D.M.; Sharma, M.G.; Vala, R.M.; Lagunes, I.; Puerta, A.; Padrón, J.M.; Rajani, D.P.; Patel, H.M. *Bioorg. Chem.* **2019**, *86*, 137–150. https://doi.org/10.1016/j.bioorg.2019.01.029
50. Patel, D.M.; Patel, H.M. *ACS Sustain. Chem. Eng.* **2019**, *7*, 18667–18676. https://doi.org/10.1021/acssuschemeng.9b05184
51. Santosh, R.; Paul, P.; Selvam, M.K.; Raril, C.; Krishna, P.M.; Manjunatha, J.G.; Nagaraja, G.K. *ChemistrySelect* **2019**, *4*, 990–996. https://doi.org/https://doi.org/10.1002/slct.201803416
52. Darwish, E.S.; Abdelhamid, I.A.; Nasra, M.A.; Abdel-Gallil, F.M.; Fleita, D.H. *Helv. Chim. Acta* **2010**, *93*, 1204–1208. https://doi.org/10.1002/hlca.200900355
53. Abdelhamid, I.A.; Ghozlan, S.A.S.; Kolshorn, H.; Meier, H.; Elnagdi, M.H. *Heterocycles* **2007**, *71*, 2627–2637. https://doi.org/10.3987/com-07-11141
54. Ghozlan, S.A.S.; Abdelhamid, I.A.; Gaber, H.M.; Elnagdi, M.H. *J. Heterocycl. Chem.* **2005**, *42*, 1185–1189. https://doi.org/10.1002/jhet.5570420623
55. Ghozlan, S.A.S.; Ahmed, A.G.; Abdelhamid, I.A. *J. Heterocycl. Chem.* **2016**, *53*, 817–823. https://doi.org/10.1002/jhet.2341
56. Abdelhamid, I.A.; Darwish, E.S.; Nasra, M.A.; Abdel-Gallil, F.M.; Fleita, D.H. *Synthesis (Stuttg).* **2010**, 1107–1112. https://doi.org/10.1055/s-0029-1219235
57. Abdella, A.M.; Moatasim, Y.; Ali, M.A.; Elwahy, A.H.M.; Abdelhamid, I.A. *J. Heterocycl. Chem.* **2017**, *54*, 1854–1862. https://doi.org/10.1002/jhet.2776
58. Abdelmoniem, A.M.; Ghozlan, S.A.S.; Abdelmoniem, D.M.; Elwahy, A.H.M.; Abdelhamid, I.A. *J. Heterocycl. Chem.* **2017**, *54*, 2844–2849. https://doi.org/10.1002/jhet.2890
59. Abdelmoniem, A.M.; Salaheldin, T.A.; Abdelhamid, I.A.; Elwahy, A.H.M. *J. Heterocycl. Chem.* **2017**, *54*, 2670–2677. https://doi.org/10.1002/jhet.2867
60. Darweesh, A.F.; Abd El-Fatah, N.A.; Abdelhamid, I.A.; Elwahy, A.H.M.; Salem, M.E. *Synth. Commun.* **2020**, *50*, 2531–2544. https://doi.org/10.1080/00397911.2020.1784436
61. Eid, E.M.; Hassaneen, H.M.E.; Abdelhamid, I.A.; Elwahy, A.H.M. *J. Heterocycl. Chem.* **2020**, *57*, 2243–2255. https://doi.org/10.1002/jhet.3945
62. Abdella, A.M.; Abdelmoniem, A.M.; Abdelhamid, I.A.; Elwahy, A.H.M. *J. Heterocycl. Chem.* **2020**, *57*, 1476–1523. https://doi.org/10.1002/jhet.3883
63. Abdella, A.M.; Mohamed, M.F.; Mohamed, A.F.; Elwahy, A.H.M.; Abdelhamid, I.A. *J. Heterocycl. Chem.* **2018**, *55*, 498–507. https://doi.org/10.1002/jhet.3072
64. Salama, S.K.; Mohamed, M.F.; Darweesh, A.F.; Elwahy, A.H.M.; Abdelhamid, I.A. *Bioorg. Chem.* **2017**, *71*, 19–29. https://doi.org/10.1016/j.bioorg.2017.01.009

65. Salama, S.K.; Darweesh, A.F.; Abdelhamid, I.A.; Elwahy, A.H.M. *J. Heterocycl. Chem.* **2017**, *54*, 305–312. https://doi.org/10.1002/jhet.2584
66. Salem, M.E.; Darweesh, A.F.; Mekky, A.E.M.; Ahmad M. Farag, A.; Elwahy, and A.H.M. *J. Heterocycl. Chem.* **2017**, *54*, 226–234. https://doi.org/10.1002/jhet.2571
67. El-Fatah, N.A.A.; Darweesh, A.F.; Mohamed, A.A.; Abdelhamid, I.A.; Elwahy, A.H.M. *Monatshefte fur Chemie* **2017**, *148*, 2107–2122. https://doi.org/10.1007/s00706-017-2040-7
68. Abd El-Fatah, N.A.; Darweesh, A.F.; Mohamed, A.A.; Abdelhamid, I.A.; Elwahy, A.H.M. *Tetrahedron* **2017**, *73*, 1436–1450. https://doi.org/10.1016/j.tet.2017.01.047
69. Diab, H.M.; Abdelhamid, I.A.; Elwahy, A.H.M. *Synlett* **2018**, *29*, 1627–1633. https://doi.org/10.1055/s-0037-1609967
70. M. Abdella, A.; H. M. Elwahy, A.; A. Abdelhamid, I. *Curr. Org. Synth.* **2016**, *13*, 601–610. https://doi.org/10.2174/1570179413999151211115100
71. Al-Awadi, N.A.; Abdelhamid, I.A.; Al-Etaibi, A.M.; Elnagdi, M.H. *Synlett* **2007**, 2205–2208. https://doi.org/10.1055/s-2007-985573
72. Abdelhamid, I.A.; Darwish, E.S.; Nasra, M.A.; Abdel-Gallil, F.M.; Fleita, D.H. *Arkivoc* **2008**, *2008*, 117–121. https://doi.org/10.3998/ark.5550190.0009.h11
73. Al-Awadi, N.A.; Ibrahim, M.R.; Abdelhamid, I.A.; Elnagdi, M.H. *Tetrahedron* **2008**, *64*, 8202–8205. https://doi.org/10.1016/j.tet.2008.06.026
74. Abdella, A.M.; Abdelmoniem, A.M.; Ibrahim, N.S.; El-Hallouty, S.M.; Abdelhamid, I.A.; Elwahy, A.H.M. *Mini-Reviews Med. Chem.* **2019**, *20*, 801–816. https://doi.org/10.2174/1389557519666190919160019
75. Abdelmoniem, A.M.; Ghozlan, S.A.S.; Butenschön, H.; Abdelmoniem, D.M.; Elwahy, A.H.M.; Abdelhamid, I.A. *Arkivoc* **2019**, *2019*, 163–177. https://doi.org/10.24820/ark.5550190.p010.875