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.\textsuperscript{1–19} In addition, Uracil is considered to be one of the major motifs present in the biopolymer RNA\textsuperscript{20,21} and it plays several roles in our life.\textsuperscript{22,23} The uracil scaffold and its derivatives exhibit a wide range of biological activities, including anticancer agents,\textsuperscript{24–26} antihypertensive agents,\textsuperscript{27} antiallergic compounds\textsuperscript{28} and antiviral agents.\textsuperscript{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,\textsuperscript{32,33} antitumor,\textsuperscript{34} and antiviral.\textsuperscript{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.\textsuperscript{18,37–51}

![Chemical structures of Fluorouracil, Uracil mustard, Flucytosine, and Zalcitabine](image)

**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,\textsuperscript{52–56} the synthesis of bis(heterocycles)\textsuperscript{17,47–60} as well as the C-C bond formation reactions,\textsuperscript{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) \textbf{1a} was prepared following our reported procedure via the reaction of the potassium salt of salicylaldehyde with \textit{N,N}'-(ethane-1,2-diyl)bis(2-chloroacetamide) in DMF.\textsuperscript{74} The reactivity of the bis(aldehyde) \textbf{1a} towards 6-aminouracil \textbf{2} was then investigated aiming at the synthesis of bis(decahydropyrido[2,3-d:6,5-d']dipyrimidin-5-yl)phenoxy)acetamide) \textbf{4a}. Contrary to our expectation, the reaction did not yield compound \textbf{4a}, instead it gave the uncyclized tetrakis(6-aminopyrimidine-2,4-dione) \textbf{3a} in 88% yield (Scheme 1). It worth mentioning that trials to cyclize similar systems in acetic acid at reflux were unsuccessful.\textsuperscript{75} On the other hand, heating a mixture of the bis(aldehyde) \textbf{1a} with the aminouracil \textbf{2} in acetic acid in the presence of \textit{p-TSA} for 3 h afforded the target \textbf{4a} as the sole product. Moreover, we have found that heating of compound \textbf{3a} in acetic acid /\textit{p-TSA} for 1 h afforded \textbf{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 $\delta$ 3.30 ppm for the two methylene linkage. It also showed two characteristic singlets at $\delta$ 4.31 and 5.38 ppm for the $\text{-OCH}_2\text{CO-}$ and the bridging CH protons, respectively. In addition, it exhibited four broad singlet signals characteristic for the NH$_2$ and three NH groups at $\delta$ 6.74 and $\delta$ 7.48, 10.30 and 10.42, respectively. It also featured aromatic protons at $\delta$ 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 $\delta$ 5.13 ppm for the pyridine-H$_5$. It also indicated three different broad singlets at $\delta$ 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(urate) 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)phenoxyacetamides) 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).
Interestingly, the same methodology was also applied for the synthesis of the corresponding tetrakis(urate) 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.  

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.

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 El (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-{(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 NH2), 1708 (CO). ¹H NMR (300 MHz, DMSO-d6): δ 3.30 (br, 4H, CH₂N), 4.31 (s, 4H, CH₂O), 5.38 (s, 2H, CH), 6.47 (br, 8H, NH₂), 6.83-7.15 (m, 8H, Ar-H), 7.48 (br, 2H, NH), 10.30 (br, 4H, NH), 10.42 (br, 4H, NH). ¹³C NMR (100 MHz, DMSO-d6): 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 (El, 70 eV): m/z (%) 856 [M⁺]. Anal. Calcd for C₃₆H₃₆N₁₂O₁₂: 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-{(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 NH₂), 1712 (CO). ¹H NMR (400 MHz, DMSO-d6): δ 3.24 (br, 4H, CH₂N), 4.36 (s, 4H, CH₂O), 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 (El, 70 eV): m/z (%) 856 [M⁺]. Anal. Calcd for C₃₆H₃₆N₁₂O₁₂: 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-{(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 NH₂), 2978 (NH), 2850 (NH₂), 1712 (CO). ¹H NMR (300 MHz, DMSO-d6): δ 1.60-1.62 (m, 2H, CH₂), 3.14-3.17 (m, 4H, CH₂N), 4.34 (s, 4H, CH₂O), 5.34 (s, 2H, CH), 6.60 (br, 8H, NH₂), 6.81-7.11 (m, 8H, Ar-H), 7.14 (br, 2H, NH), 10.45 (br, 8H, NH). ¹³C NMR (75 MHz, DMSO-d6): δ 20.9, 29.2, 36.1, 67.2, 86.5, 111.8, 120.6, 120.7, 126.6, 126.8, 149.6, 153.4, 155.3, 165.0, 167.5. MS (El, 70 eV): m/z (%) 870 [M⁺]. Anal. Calcd for C₃₇H₃₈N₁₄O₁₂: 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-{(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 NH₂), 1724 (CO). ¹H NMR (300 MHz, DMSO-d6): δ 1.57-1.64 (m, 2H, CH₂), 3.11-3.13 (m, 4H, CH₂N), 4.37 (s, 4H, CH₂O), 5.30 (s, 2H, CH), 6.69 (br, 8H, NH₂), 6.72-7.13 (m, 8H, Ar-H), 8.08 (br, 2H, NH), 10.28 (br, 4H, NH), 10.47 (br, 4H, NH). ¹³C NMR (100 MHz, DMSO-d6): 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 (El, 70 eV): m/z (%) 870 [M⁺]. Anal. Calcd for C₃₇H₃₈N₁₄O₁₂: 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-{(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 NH₂), 1724 (CO). ¹H NMR (300 MHz, DMSO-d6): δ 1.42 (br, 4H, CH₂), 3.16 (br, 4H, CH₂N), 4.34 (s, 4H, CH₂O), 6.64 (br, 8H, NH₂), 6.50 (br, 2H, NH), 8.08 (br, 2H, NH), 10.28 (br, 4H, NH), 10.47 (br, 4H, NH). MS (El, 70 eV): m/z (%) 884 [M⁺]. Anal. Calcd for C₃₈H₄₀N₁₄O₁₂: 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-{(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 NH₂), 1708 (CO). ¹H NMR (300 MHz, DMSO-d6): δ 1.41 (br, 4H, CH₂), 3.12 (br, 4H, CH₂N), 4.35 (s, 4H, CH₂O), 5.29 (s, 2H, CH), 6.68 (br, 8H, NH₂), 6.70-7.13 (m, 8H, Ar-H), 8.03 (br, 2H, NH), 10.28 (br, 4H, NH), 10.47 (br, 4H, NH). ¹³C NMR (100 MHz, DMSO-d6): 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 (El, 70 eV): m/z (%) 884[M⁺]. Anal. Calcd for C₃₈H₄₀N₁₄O₁₂: 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-(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): v 3356, 3152 (NH and NH₂), 1716 (CO). ¹H NMR (300 MHz, DMSO-d₆): 4.30-4.32 (d, J = 5.7 Hz, 4H, CH₂N), 4.44 (s, 4H, CH₂O), 5.30 (s, 2H, CH), 6.70 (br, 8H, NH₂), 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). ¹³C NMR (100 MHz, DMSO-d₆): 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 (El, 70 eV): m/z (%) 932[M⁺]. Anal. Calcd for C₄₂H₄₀N₁₄O₁₂: 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-diyld)bis(4-(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): v 3368, 3151 (NH and NH₂), 1713 (CO), 1624 (CO). ¹H NMR (300 MHz, DMSO-d₆): 4.30-4.32 (d, J = 5.4 Hz, 4H, CH₂N), 4.75 (s, 4H, CH₂O), 5.36 (s, 2H, CH), 6.71 (br, 8H, NH₂), 7.14-7.16 (m, 4H, Ar-H), 7.33-7.26 (d, J = 8.7 Hz, 4H, Ar-H), 7.87-7.90 (d, J = 8.7Hz, 4H, Ar-H). ¹³C NMR (100 MHz, DMSO-d₆): δ 33.1, 42.2, 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 (El, 70 eV): m/z (%) 988[M⁺]. Anal. Calcd for C₄₄H₄₄N₁₄O₁₄: 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): v 3070 (NH), 1690 (CO). ¹H NMR (300 MHz, DMSO-d₆): 3.24 (br, 4H, CH₂O), 4.46 (s, 4H, CH₂O), 5.13 (s, 2H, CH₂N), 6.72-7.10 (m, 10H, Ar-H+NH), 8.41 (br, 2H, NHCO), 10.64 (br, 4H, NH). ¹³C NMR (100 MHz, DMSO-d₆): 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 C₃₆H₃₈O₄₁N₁₂: 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): v 3035 (br, NH), 1690 (CO). ¹H NMR (300 MHz, DMSO-d₆): 1.50-1.60 (m, 2H, CH₂), 3.04-3.10 (m, 4H, CH₂N), 4.49 (s, 4H, CH₂O), 5.14 (s, 2H, CH₂N), 6.72-7.12 (m, 10H, Ar-H+NH), 8.34 (br, 4H, NHCO), 10.65 (br, 4H, NH). ¹³C NMR (100 MHz, DMSO-d₆): 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 C₃₇H₃₂N₁₂O₁₂: 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): v 3032 (br, NH), 1690 (CO). ¹H NMR (300 MHz, DMSO-d₆): δ 1.26 (br, 4H, CH₂), 3.05 (br, 4H, CH₂N), 4.50 (s, 4H, CH₂O), 5.15 (s, 2H, Pyridine -H), 6.70-7.10 (m, 10H, Ar-H+NH), 8.27 (br, 2H, NH), 10.72 (br, 4H, NH), 11.15 (br, 4H, NH). ¹³C NMR (75 MHz, DMSO-d₆): 26.8, 38.3, 51.7, 89.6, 110.3, 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 C₃₈H₃₄N₁₂O₁₂: 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-1,2,3,4,5,6,7,8,9-octahydropyrido[2,3-d:6,5-d’]dipyrimidin-5-yl)phenoxy)acetamide** (4d). Pale yellow powder (89%). mp >300 °C. IR (KBr): v 3201 (NH), 3070 (br, NH), 1705 (CO). ¹H NMR (300 MHz, DMSO-d₆): δ 4.19-4.21(d, J = 6.3 Hz, 4H, CH₂N), 4.78 (s, 4H, CH₂O),
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 C₄₂H₃₀N₁₂O₁₂: 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 (¹H and ¹³C 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](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](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](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](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](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](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](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.j.farmac.2003.11.013](https://doi.org/10.1016/j.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](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](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](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](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](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**, *386*, 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. Cassab, 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. 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

20. Mohamed, M.F.; Darweesh, A.F.; Elwahy, A.H.M.; Abdelhamid, I.A. *J. Med Chem.* **2015**, *56*, 7085–7088. https://doi.org/10.1021/jm501284w

21. 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

22. Di Noia, J.; Neuberger, M.S. *Nature* **2002**, *419*, 43–48. https://doi.org/10.1038/nature00981

23. Sivakova, S.; Rowan, S.J. *Chem. Soc. Rev.* **2005**, *34*, 9–21. https://doi.org/10.1039/b304608g

24. Tobe, M.; Isobe, Y.; Goto, Y.; Obara, F.; Tsuchiya, M.; Matsui, J.; Hirota, K.; Hayashi, H. *Bioorganic Med. Chem.* **2010**, *53*, 1086–1097. https://doi.org/10.1021/jm901284w

25. 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

26. 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

27. 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

28. Sapozhnikova, K.A.; Slesarchuk, N.A.; Orlov, A.A.; Khvotov, E. V.; Radchenko, E. V.; Chistov, A.A.; Ustinov, A. V.; Palyulin, V.A.; Kozlovskaya, L.I.; Osoledkin, D.I.; et al. *RSC Adv.* **2019**, *9*, 26014–26023. https://doi.org/10.1039/c9ra06313g

29. Geant, P.Y.; Uttaaro, 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/10.2174/1570179411310030007

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/10.2174/15701794113106660076

42. Khoobi, M.; Ramazani, A.; Foroumadi, A.; Soulodozi, 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.; Soulodozi, 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/hc.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

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