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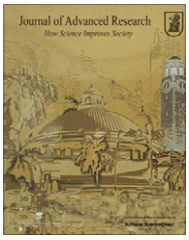

ORIGINAL ARTICLE

Facile construction of substituted pyrimido[4,5-*d*]pyrimidones by transformation of enaminouracil

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KEYWORDS

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Abstract The reaction of 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**1**) as a binucleophile with primary aromatic or heterocyclic amines and formaldehyde or aromatic (heterocyclic) aldehydes in a molar ratio (1:1:2) gave the pyrimido[4,5-*d*]pyrimidin-2,4-dione ring systems **2**–**5**. Treatment of **1** with diamines and formalin in molar ratio (2:1:4) gave the *bis*-pyrimido[4,5-*d*]pyrimidin-2,4-diones **6**–**8**. Furthermore, substituted pyrimido[4,5-*d*]pyrimidin-2,4-diones with uracil derivative **11** or spiro indole **16** were synthesized. Synthesis of pyrimido[4,5-*d*]pyrimidin-2,4-diones with different substitution at C-5 and C-7 was achieved to give **13** and **18**, respectively.

Introduction

A large number of pyrimidine derivatives were reported to exhibit interesting pharmacological activity [1–8]. A class of compounds of biological relevance was used in the plant protection area as plant growth regulators [9]. In continuation of our studies, the development of expedient methods for the synthesis of pyrimido[4,5-*d*]pyrimidine-2,4-dione, were implemented [10]. Pyrimidopyrimidines are annulated uracils that have attracted considerable interest in recent years. Derivatives of pyrimidopyrimidine are known to display a wide range of pharmacological activities, and their potent inhibitory properties regarding the tyrosine kinase domain of epidermal growth factor receptor [11], 5-phosphoribosyl-1-pyrophosphate synthetase [12] and dihydrofolate-reductase [13], have been fully demonstrated. Numerous reports delineate the antitumour [14], antiviral [15], antioxidant [16], antifungal [17] and hepatoprotective [18] activities. The multicomponent reactions (MCR's) [19,20], are masterpieces of synthetic efficiency and reaction design.

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Experimental

All melting points were measured on a Gallenkamp electric melting point apparatus. Infrared spectra measured using KBr discs on a Mattson 5000 FTIR spectrometer at the Microanalytical Center (Cairo University, Egypt). The ^{1}H

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NMR and ^{13}C NMR spectra were carried out on Varian Gemini 200 MHz spectrophotometer, Microanalytical center (Cairo University, Egypt), using TMS as an internal standard and chemical shifts were recorded in ppm on δ scale and coupling constants (J) are given in Hz. The mass spectra recorded on a GC–MS (Shimadzu QP-1000 EX). Reactions were monitored by thin layer chromatography (TLC) using silica gel (EM science) coated plates. The starting 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**1**) was purchased from Aldrich Company. Elemental analyses were measured with a ECS 4010 Elemental combustion system instrument at the Microanalytical Unit, Faculty of Science, Cairo University; their results were found to be in good agreement with the calculated values.

Synthesis of pyrimido[4,5-d]pyrimidone ring systems ***2–5***

General procedure: A solution of 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**1**) (1.01 g, 6.5 mmol) in ethanol (30 mL) was added to a mixture of amines [*p*-anisidine (0.8 g, 6.5 mmol), *m*-nitroaniline (0.898 g, 6.5 mmol), *p*-anisidine (0.8 g, 6.5 mmol), or 2-aminothiazole (0.65 g, 6.5 mmol)] and aldehydes [formaldehyde (0.39 g, 13 mmol), piperonal (1.95 g, 13 mmol), *p*-anisaldehde (1.77 g, 13 mmol), or furfural (1.25 g, 13 mmol)] in ethanol (20 mL). The reaction mixture was stirred at 35 °C for 2 h, then left to stand at room temperature for 3 days. The resulting precipitate was collected by filtration, dried and purified by crystallization from ethanol to give the corresponding products **2–5**, respectively.

*6-(4-Methoxyphenyl)-1,3-dimethyl-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione (**2**)*

Recrystallization from ethanol to give (25%) **2**; white crystals. M.p.: 160 °C; R_f = 0.7 [pet. ether 40–60 °C/ethyl acetate, (1:2)]; IR (KBr): $\bar{V}$ = 3257 (NH), 2971 (CH, str.), 1677, 1621 (CO), 1511 cm^{-1} (C=C); ^1H NMR (200 MHz, DMSO): δ = 3.32 (s, 3H, NCH_3), 3.73 (s, 3H, OCH_3), 4.59 (s, 2H, CH_2), 5.04 (s, 1H, NH–$\underline{CH_2}$–N), 6.3 (br, 1H, NH), 6.65–7.12 (m, 12H, Ar–H); MS (*m*/*z*) (I%) = 302 (M^+, 24), 303 ($M^+ + 1$, 5), 288 (13), 285 (3), 242 (1), 214 (1), 155 (5), 137 (2) 135 (100), 121 (10), 120 (54), 107 (3), 91 (2); Calc for ($C_{15}H_{18}N_4O_3$) C, 59.59; H, 6.00; N, 18.53; Found C 59.63, H, 5.97, N 18. 47.

*5,7-Di(benzo[d][1,3]dioxol-5-yl)-1,3-dimethyl-6-(3-nitrophenyl)-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione (**3**)*

Recrystallization from ethanol to give to give (35%) **3**; yellow crystals. M.p.: 212 °C; R_f = 0.57 [pet. ether 40–60 °C/ethyl acetate, (1:2)]; IR (KBr): $\bar{V}$ = 3424 (NH), 1700, 1618 (CO), 1530 cm^{-1} (C=C); ^1H NMR (200 MHz, DMSO): δ = 3.32 (s, 3H, CH_3), 3.37 (s, 3H, CH_3), 4.6 (s, 4H, $2CH_2$), 5.4 (s, 1H, CH), 5.8 (s, 1H, CH), 6.9 (br., 1H, NH), 7.1–7.5 (m, 10 H, Ar–H); MS (*m*/*z*) (*I*%) = 555 ($M^+ - 2$, 2), 380 (1), 313 (1), 288 (1), 196 (2), 138 (2), 137 (100), 65 (3); Calc for ($C_{28}H_{23}N_5O_8$) C, 60.32; H, 4.16; N, 12.56; Found C, 60.39; H, 4.23; N, 12.48.

*5,6,7-Tris(4-methoxyphenyl)-1,3-dimethyl-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione (**4**)*

Recrystallization from ethanol to give (93%) **4**; white crystal. M.p.: 130 °C; R_f = 0.56 [pet. ether 40–60 °C/ethyl acetate, (1:1)]; IR (KBr): $\bar{V}$ = 3402 (NH), 3129, 2948 (CH, str.), 1625 cm^{-1} (CO); ^1H NMR (200 MHz, DMSO): δ = 3.32 (s, 6H, $2NCH_3$), 3.73 (s, 9H, $3OCH_3$), 4.59 (s, 1H, CH), 5.04 (s, 1H, NH–$\underline{CH}$), 6.3 (br., 1H, NH), 6.65-7.1 (m, 12H, Ar–H); MS (*m*/*z*) (*I*%) = 514 (M^+, 14), 330 (30), 253 (20), 193 (44), 175 (43), 122 (100); Calc for ($C_{29}H_{30}N_4O_5$) C, 67.69; H, 5.88; N, 10.89; Found C, 67.74; H, 5.93; N, 10.78.

*5,7-Di(furan-2-yl)-1,3-dimethyl-6-(thiazol-2-yl)-5,6,7,8-tetrahydro-pyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione (**5**)*

Recrystallization from ethanol to give (31%) **5**; green crystals. M.p.: 325 °C; R_f = 0.46 [pet. ether 40–60 °C/ ethyl acetate (1:2)]; IR (KBr): $\bar{V}$ = 3418, 3357 (NH), 3144, 2955 (CH, str.), 1675, 1615 (CO), 1554 cm^{-1} (C=C); ^1H NMR (200 MHz, DMSO): δ = 3.35 (s, 3H, NCH_3), 3.77 (s, 3H, OCH_3), 4.59 (s, 1H, CH), 5.04 (s, 1H, N–CH–N), 6.45 (br, 1H, NH), 6.65–7.16 (m, 12H, Ar–H); MS (*m*/*z*) (*I*%) = 411 (M^+, 17), 383 (21), 354 (8), 271 (20), 225 (18), 178 (2), 55 (100); Calc for ($C_{19}H_{17}N_5O_4S$) C, 55.47; H, 4.16; N, 17.02; Found C, 55.38; H, 4.23; N, 17.00.

General procedure for the synthesis of bis-pyrimido[4,5-d]pyrimidones ring system ***6****,* ***7*** *and* ***8***

A solution of **1** (1.01 g, 6.5 mmol) in ethanol (30 mL) was added to a solution of formaldehyde (13 mmol, 40% solution) with diamine namely; *p*-phenylenediamine (0.35 g, 3.25 mmol), ethane-1,2-diamine (0.195 g, 3.25 mmol) and hydrazine hydrate (0.16 g, 3.25 mmol) in ethanol (20 mL), the reaction mixture was stirred for 2 h then left to stand at room temperature for 3 days. The resulting precipitate was collected by filtration, then purified by recrystallization from ethanol to gave *bis*-pyrimido[4,5-*d*]pyrimidines **6-8**, respectively.

*6-(4-(6,8-Dimethyl-5,7-dioxooctahydropyrimido[4,5-d]pyrimidin-3(4H)-yl)phenyl)-1,3-dimethyl-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione (**6**)*

Recrystallization from ethanol to give (39%) **6**; green crystals. M.p.: 224 °C; R_f = 0.5 [pet. ether 40–60 °C/ethyl acetate (1:2)]; IR (KBr): $\bar{V}$ = 3399, 3358 (NH), 3225 (CH, str.) 1687, 1658 (CO), 1607 cm^{-1} (C=C); ^1H NMR (200 MHz, DMSO): δ = 3.12 (s, 3H, CH_3), 3.16 (s, 3H, CH_3), 3.17 (s, 3H, CH_3), 3.2 (s, 3H, CH_3), 3.94 (s, 4H, $2CH_2$), 4.51 (s, 4H, $2CH_2$), 6.5–6.9 (m, 4H, Ar–H), 7.3 (br., 2H, 2NH); MS (*m*/*z*) (*I*%) = 465 ($M^+ - 1$, 2), 461 (2), 311 (10), 272 (2), 196 (4), 181 (3), 168 (6), 154 (10), 120 (100); Calc for ($C_{22}H_{28}N_8O_4$) C, 56.40; H, 6.02; N, 23.92; Found C, 56.57; H, 6.08; N, 24.01.

*6-(2-(6,8-Dimethyl-5,7-dioxooctahydropyrimido[4,5-d]pyrimidin-3(4H)-yl)ethyl)-1,3-dimethyl-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione (**7**)*

Recrystallization from ethanol to give (40%) **7**; white crystals. M.p.: 255 °C; R_f = 0.76 [pet. ether 40–60 °C/ethyl acetate,

(1:1)]; IR (KBr): $\bar{V}$ = 3402 (NH), 3129 (CH, str.), 1692, 1670, 1620 cm^{-1} (CO); ^1H NMR (200 MHz, DMSO): δ = 3.12 (s, 6H, $2CH_3$), 3.21 (s, 6H, $2CH_3$), 3.29 (t, J = 6.4 Hz, 4H, $2CH_2$), 3.42 (s, 4H, $2CH_2$), 4.02 (s, 4H, $2CH_2$), 7.1 (br., 2H, 2NH); MS (*m*/*z*) (*I*%) = 209 (M^+-2, 5), 222 (4), 196 (2), 140 (7), 56 (35), 55 (100); Calc for ($C_{18}H_{28}N_8O_4$) C, 51.42; H, 6.71; N, 26.65; Found C, 51.47; H, 6.74; N, 26.72.

*6,6′,8,8′-Tetramethyl-4′,4′a-dihydro-1H,1′H-3,3′-bipyrimido-[4,5-d]pyrimidine-5,5′,7,7′(2H,2′H,4H,6H,6′H,8H,8′H,8′aH)-tetraone (**8**)*

Recrystallization from ethanol to give (40%) **8**; white crystals. M.p.: 230–233 °C; R_f = 0.58 [pet. ether 40–60 °C/ethyl acetate (1:2)]; IR (KBr): $\bar{V}$ = 3402 (NH), 3135, 2948 (CH, str.), 1693, 1680 (CO), 1584 cm^{-1} (C═C); MS (*m*/*z*) (*I*%) = 390 (M^+-2, 2), 371 (2), 357 (3), 322 (35), 304 (5), 233 (6), 190 (4), 168 (100), 111 (2), 57 (76); Calc for ($C_{16}H_{24}N_8O_4$) C, 48.97; H, 6.16; N, 28.56; Found C, 48.93; H, 6.19; N, 28.62.

*Synthesis of 6-((6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)methyl)-1,3-dimethyl-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione (**11**)*

A mixture of **10** (1.05 g, 3 mmol) and formaldehyde (2 mL, 40% solution) was heated at 60 °C in ethanol (10 mL). The reaction mixture was cooled, product filtered, dried and crystallized from ethanol to give (55%) **11**; white crystals. M.p.: 150 °C; IR (KBr): $\bar{V}$ = 3350, 3283 (NH_2), 3209 (NH), 1695, 1677 cm^{-1} (CO); ^1H NMR (200 MHz, DMSO): δ = 3.32 (s, 6H, $2CH_3$), 3.37 (s, 6H, $2CH_3$), 3.6 (s, 2H, NH_2), 4.2 (s, 4H, $2CH_2$, pyrimidine), 4.3 (s, 2H, CH_2), 6.3 (br., 1H, NH); ^{13}C NMR (200 MHz, DMSO): δ = 162.8 (CO–N), 162.5 (CO–N), 154.8, 152.6, 151.5, 83.3, 62.3, 45.9, 43.5, 31.0, 30.7, 29.7, 29.5; MS (*m*/*z*) (*I*%) = 363 (M^+, 8), 303 (41), 304 (100), 209 (3), 208 (14), 192 (11), 154 (5); Calc for ($C_{15}H_{21}N_7O_4$) C, 49.58; H, 5.83; N, 26.98; Found C, 49.62; H, 5.72; N, 26.86.

*Synthesis of secondary Mannich bases **12** and **15***

General procedure: A mixture of **1** (1.01 g, 6.5 mmol), aldimines namely; *N*-(4-chlorobenzylidene)-3-nitroaniline (1.69 g, 6.5 mmol) or **14** (1.44 g, 6.5 mmol) in ethanol (30 mL) containing three drops of acetic acid was heated under reflux for 9 h. The reaction mixture was kept in refrigerator overnight whereby the formed precipitate was filtered off, dried and recrystallized from appropriate to furnish compounds **12** and **15**, respectively.

*6-Amino-5-((4-chlorophenyl)(3-nitrophenylamino)methyl)-1,3-dimethyl-pyrimidine-2,4(1H,3H)-dione (**12**)*

Recrystallized from acetic acid to give (45%) **12**; yellow crystals. M.p.: 260 °C; R_f = 0.64 [pet. ether 40–60 °C/ethyl acetate (1:2)]; IR (KBr): $\bar{V}$ = 3350, 3225 (NH_2), 3209 (NH), 3138 (CH, str.) 1693, 1668 (CO), 1592 cm^{-1} (C═C); ^1H NMR (200 MHz, DMSO): δ = 3.1 (s, 3H, CH_3) 3.3 (s, 3H, CH_3), 5.57 (s, 1H, CH), 7.6 (br., 2H, NH_2), 7.7–8.0 (m, 8H, Ar–H), 8.78 (s, 1H, NH); MS (*m*/*z*) (*I*%) = 415 (M^+, 27), 413 (79), 278 (72), 276 (100), 242 (8), 166 (10), 155 (27), 137 (8); Calc for ($C_{19}H_{18}ClN_5O_4$) C, 54.88; H, 4.36; N, 16.84; Found C, 54.69; H, 4.43; N, 16.79.

*6-Amino-1,3-dimethyl-5-(2-oxo-3-(phenylamino)indolin-3-yl)pyrimidine-2,4(1H,3H)-dione (**15**)*

Recrystallized from acetic acid to give (54%) **15**; yellow crystals. M.p.: 330–332 °C; R_f = 0.67 [chloroform/methanol (1:4)]; IR (KBr): $\bar{V}$ = 3465, 3409 (NH_2), 3282, 3198 (NH), 1754 (CO, isatin), 1696, 1689 (CO, amidic), 1600 cm^{-1} (C═C); ^1H NMR (200 MHz, DMSO): δ = 3.02 (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 6.95 (br., 2H, NH_2), 6.98–7.32 (m, 9H, Ar–H), 9.36 (s, 1H, NH), 11.55 (br., 1H, NH); MS (*m*/*z*) (*I*%) = 378 (M^+ + 1, 17), 313 (25), 285 (11), 153 (7), 152 (23), 133 (13), 91 (27), 57 (100), 56 (43); Calc for ($C_{20}H_{19}N_5O_3$) C, 63.65; H, 5.07; N, 18.56; Found C, 63.59; H, 5.16; N, 18.46.

*Annulations of secondary Mannich bases: Synthesis of **13** and **16***

A mixture of **12** (1.25 g, 3 mmol) or **15** (1.13 g, 3 mmol) and formaldehyde (2 mL, 40% solution) was heated at 60 °C in ethanol (10 mL) for 3 h. The reaction mixture was cooled, product filtered, dried and recrystallized from ethanol to give **13** and **16**, respectively.

*5-(4-Chlorophenyl)-1,3-dimethyl-6-(3-nitrophenyl)-5,6,7,8-tetrahydropyrimido[4,5-d] pyrimidine-2,4(1H,3H)-dione (**13**)*

Recrystallized from ethanol to give (75%) **13**; white crystals. M.p.: 120 °C; IR (KBr): $\bar{V}$ = 3314, 3181 (NH), 2922 (CH, str.), 1651 (CO), 1600 cm^{-1} (C═C); MS (*m*/*z*) (*I*%) = 429 (M^+ + 1, 15), 372 (41), 310 (16), 256 (29), 222 (36), 165 (56), 52 (100); Calc for ($C_{20}H_{18}ClN_5O_4$) C, 56.15; H, 4.24; N, 16.37; Found C, 56.21; H, 4.32; N, 16.35.

*6′,8′-Dimethyl-3′-phenyl-2′,3′-dihydro-1′H-spiro[indoline-3,4′-pyrimido[4,5-d]pyrimidine]-2,5′,7′(6′H,8′H)-trione (**16**)*

Recrystallized from ethanol to give (45%) **16**; white crystals. M.p.: 190 °C; IR (KBr): $\bar{V}$ = 3308, 3185 (2NH), 2983, 2921 (CH, str.), 1752, 1697, 1648 cm^{-1} (CO); ^1H NMR (200 MHz, DMSO): δ = 3.32 (s, 3H, CH_3), 3.37 (s, 3H, CH_3), 4.6 (s, 2H, CH_2), 6.2 (br., s, 1H, CH_2–<u>NH</u>), 7.1–7.52 (m, 9H, Ar–H), 8.6 (s, 1H, CO–<u>NH</u>); ^{13}C NMR (200 MHz, DMSO): δ = 168.7, 163.4, 155.1, 154.1, 149.6, 141.2, 129.9, 129.7, 127.8, 126.9, 122.0, 118.3, 114.3, 95.6, 63.6, 47.2, 30.9, 29.7; MS (*m*/*z*) (*I*%) = 390 (M^+ + 1, 15), 368 (29), 358 (24), 264 (100), 227 (22); Calc for ($C_{21}H_{19}N_5O_3$) C, 64.77; H, 4.92; N, 17.98; Found C, 64.73; H, 4.83; N, 17.82.

*Synthesis of 6-amino-1,3-dimethyl-2,4-dioxo-N-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carbo-thioamide (**17**)*

A mixture of **1** (1.01 g, 6.5 mmol) and phenyl isothiocyanate (0.88 g, 6.5 mmol) in toluene (20 mL), was refluxed for 9 h until the disappearance of the starting materials as evidenced by the TLC. The formed precipitate was collected by filtration, dried and crystallized from ethanol to give (55%) **17**, yellow crystals. M.p.: 300 °C; R_f = 0.67 [chloroform: methanol (5:1)]; IR (KBr): $\bar{V}$ = 3400, 3356 (NH_2) 3227 (NH), 2948

(CH, str.), 1660, 1613 (CO), 1236, 1213 (C=S); MS (*m*/*z*) (*I*%) = 290 (M^+, 0.13), 257 (0.31), 222 (0.09), 154 (100), 136 (6.77), 127 (13.67), 82 (76.88), 77 (0.35); Calc for ($C_{13}H_{14}N_4O_2S$) C, 53.78; H, 4.86; N, 19.30; Found C, 53.65; H, 4.93; N, 19.26.

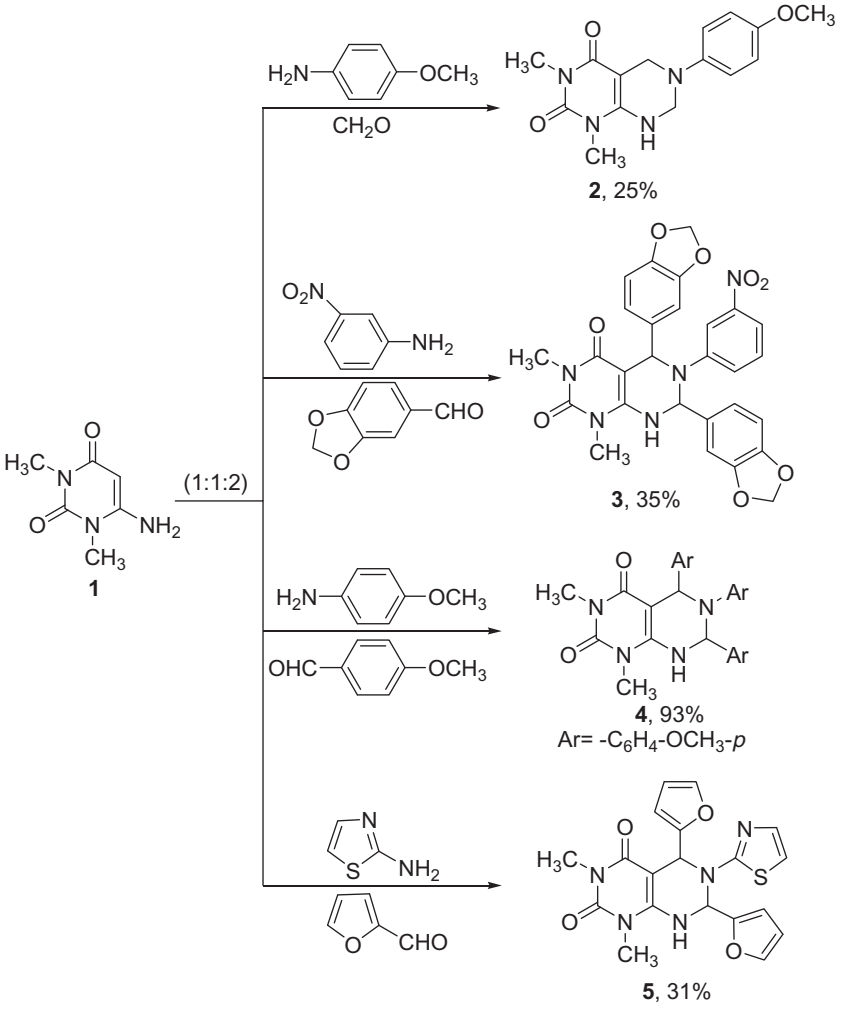
*Synthesis of 1,3-dimethyl-6,7-diphenyl-5-thioxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione (**18**)*

A mixture of **17** (0.87 g, 3 mmol) and benzyldehyde (0.32 g, 3 mmol) was refluxed in ethanol (10 mL) for 3 h. The reaction mixture was cooled, product filtered, dried and crystallized from ethanol to give (61%) **18**, yellow crystal. M.p.: 125 °C; IR (KBr): $\bar{V}$ = 3068, 3005 (NH), 2880, 2834 (CH, str.), 1789, 1686 (CO), 1326, 1292 cm^{-1} (C=S); ^1H NMR (200 MHz, DMSO): δ = 3.32 (s, 3H, CH_3), 3.37 (s, 3H, CH_3), 5.06 (s, 1H, CH), 6.3 (s, 1H, NH), 6.5–7.3 (m, 10H, Ar–H); MS (*m*/*z*) (*I*%) = 379 ($M^+ + 1$, 2), 378 (M^+, 6), 331 (3), 269 (2), 256 (5), 213 (4), 105 (36), 55 (100); Calc for ($C_{20}H_{18}N_4O_2S$) C, 63.47; H, 4.79; Found C, 63.53; H, 4.83.

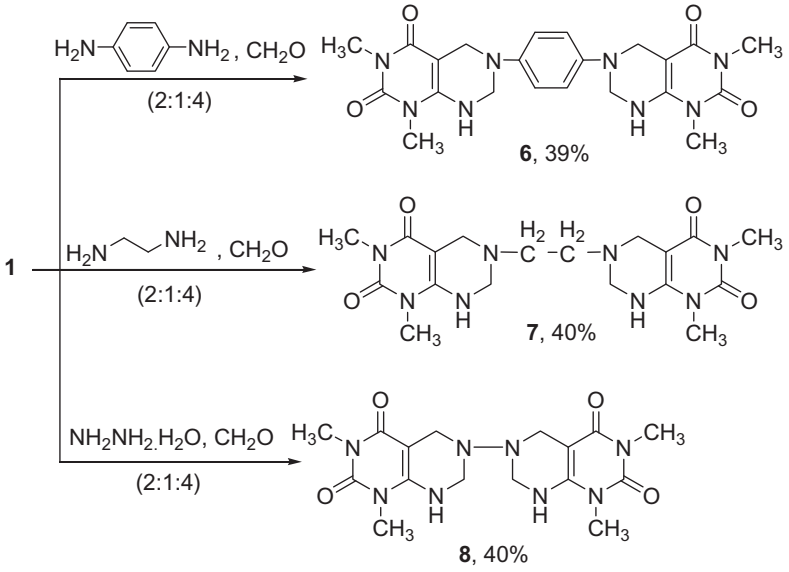
Results and discussion

The objective of the present work was to investigate the behavior of Mannich reaction towards 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**1**) as a bifunctional nucleophile with primary amines. Mannich reaction of **1** with primary aromatic or heterocyclic amines, namely, *p*-anisidine and *m*-nitroaniline, 2-aminothiazole, aromatic and heterocyclic aldehydes, namely; formaldehyde, piperonal, *p*-anisaldehyde as well as furfural in a molar ratio (1:1:2) gave pyrimido[4,5-*d*]pyrimidine ring systems **2**–**5** *via* a double Mannich reaction (Scheme 1), similar methods to obtain pyrimido[4,5-*d*]pyrimidines have been reported [21–25]. Furthermore, involvement of both C-5 and 6-amino group in this reaction is in line with our reported work [10,26,27] and to Roth & Hagen work [28]. The ^1H NMR spectrum of **3** showed singlet signals at δ 3.32 and 3.37 ppm for two N–CH_3 groups, singlet signals at δ 4.6, 5.4 and 5.8 ppm due to two (–O–CH_2–O–), (CH–N) and (N–CH–N) groups, respectively, broad signal at δ 6.9 ppm for NH and multiplet signals at δ 7.1–7.5 ppm for ten aromatic protons. The mass spectra of compounds **2**–**5** showed the molecular ion peaks at *m*/*z* 302 (M^+, 24%), 555 ($M^+ - 2$, 2%), 514 (M^+, 14%) and 411 (M^+, 17%), respectively.

On the other hand, treatment of **1** with primary aliphatic or aromatic diamines and formalin in a molar ratio (2:1:4) gave *bis*-pyrimido[4,5-*d*]pyrimidine ring systems **6**–**8** (Scheme 2). The ^1H NMR of **6** showed singlet signals at δ 3.12, 3.16, 3.17 and 3.2 ppm for four (N–CH_3) groups, singlet signals at 3.94 and 4.51 ppm for two (N–CH_2) and two (N–CH_2–N)



Scheme 1 Reaction of **1** with primary amines and different aldehyde in a molar ratio (1:1:2).



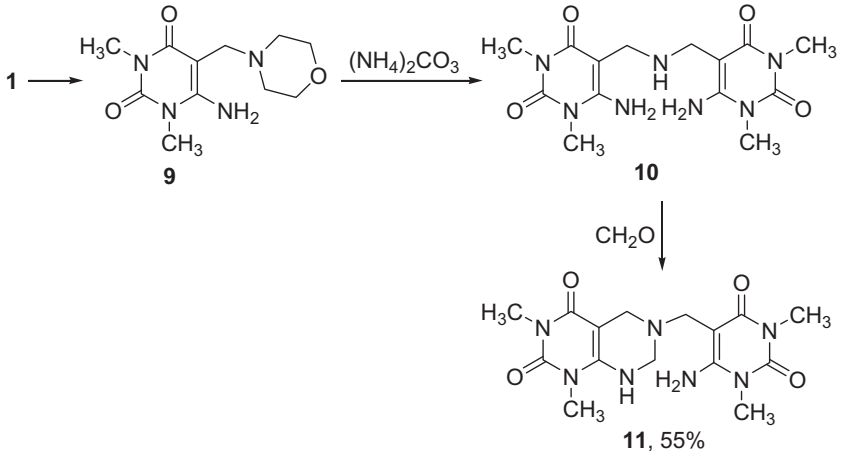
Scheme 2 Synthesis of bis-pyrimido[4,5-*d*]pyrimidine ring systems **6-8**.

groups, respectively, multiplet signals at δ 6.5–6.9 for four aromatic protons and broad signal at δ 7.3 ppm for two NH protons. Additionally, the mass spectra of compounds **6**, **7** and **8** showed the molecular ion peaks at *m*/*z* 463 (M^+-2), 209 (M^+-2) and 390 (M^+), respectively.

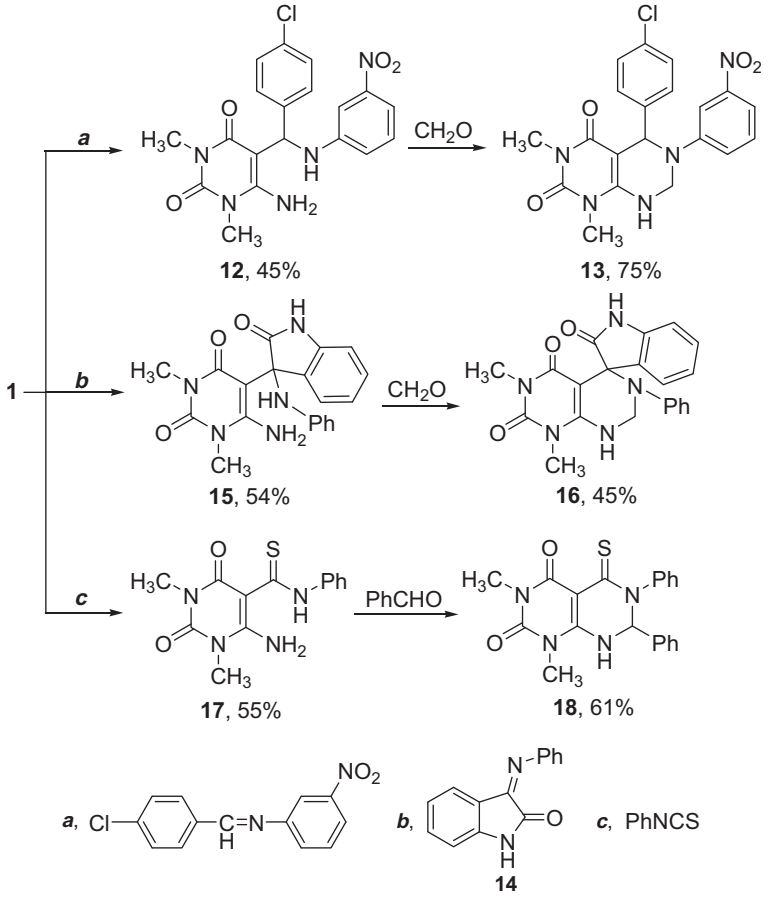
Therefore, 6-amino-1,3-dimethyl-5-(morpholinomethyl) pyrimidine-2,4(1*H*,3*H*)-dione (**9**) [10], was trans-aminated with ammonium carbonate to the symmetrical *bis*-Mannich base **10**, which annulated by formalin to give 6-((6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl)-1,3-dimethyl-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**11**) (Scheme 3). The mass spectrum of **11** showed the molecular ion peak at *m*/*z* 363 (M^+, 7.5%).

Another route was also accomplished to obtain the pyrimido[4,5-*d*]pyrimidine derivative with different substitution at C-5 and C-7 [since in Mannich reaction the new constructed pyrimidine moieties have symmetrical substitutions at C-5 and C-7 according to the aldehyde used]. Therefore, the present work has focused on the reaction of **1** with aldimine or ketimine as a route to the corresponding secondary Mannich bases [27,28]. Treatment of **1** with *N*-(4-chlorobenzylidene)-3-nitroaniline afforded **12**. Additionally, compound **12** was annulated with formalin to afford the target compounds **13**. The assigned structure **12** was established on the basis of analytical and spectral data. Its mass spectrum showed the molecular ion peak at *m*/*z* 415 (M^+, 26.5) and 413 (M^+-2, 78.7) by relative intensity (1:3). In addition, treatment of **1** with 3-(phenylimino)indolin-2-one (**14**) afforded **15** which annulated with formalin to give the corresponding spiro[indoline-3,4′-pyrimido[4,5-*d*]pyrimidine]-2,5′,7′(6′*H*,8′*H*)-trione (**16**). The mass spectrum of compound **15** showed the molecular ion peak at *m*/*z* 378 ($M^+ + 1$, 17). Once more, the synthesis of pyrimido[4,5-*d*]pyrimidine-5-thione derivative **18** was conducted. Hence, reaction of **1** with phenyl isothiocyanate afforded compound **17**. Annulation of **17** with benzaldehyde gave the target product **18** (Scheme 4) which was established on the basis of its analytical and spectral data. The mass spectrum of **17** showed the molecular ion peak at *m*/*z* 290 (M^+, 0.13%).

In conclusion, 6-amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**1**) contain enamino system including bis-nucleophilic



Scheme 3 Synthesis of pyrimido[4,5-*d*]pyrimidine **11**.



Scheme 4 Synthesis of pyrimido[4,5-*d*]pyrimidine derivatives **13**, **16** and **18**.

centers as amino group and beta position of amino group which reacted with two moles of different aldehydes to give dimethylol followed by its reaction with one mole of primary amine *via* double Mannich reaction. Eleven pyrimido[4,5-*d*]pyrimidine derivatives and their related analogs were synthesized and elucidated on the basis of elemental analyses and spectral data (*C.f.* Experimental section). Newly prepared compounds were obtained through reaction of **1** with primary amines and formaldehyde or aldehydes in a molar ratio (1:1:2). *Bis*-pyrimido[4,5-*d*]pyrimidine ring systems **6**–**8** were obtained through reaction of **1** with primary amines and formaldehyde in molar ration (2:1:4). Furthermore, transamination of **9** with ammonium carbonate gave symmetrical *bis*-Mannich base **10** which upon reaction with formalin gave the target pyrimido[4,5-*d*]pyrimidine **11**. In other routes, compound **1** reacted with Schiff bases followed by reaction with formaldehyde or reacted with phenyl isothiocyanate followed by reaction with benzaldehyde. Yields are low (around 30%) for most of the substrates except for compound **4** (93%). because aldehyde and amine contains electron donating group "OCH_3" which activate the two substrates then activate the reaction and therefore gave high yield.

References

[1] Aly AA. Synthesis and pharmacological activity of annelated pyrimidine derivatives. Phosphorus Sulfur Silicon Relat Elem 2006;181(6):1285–98.

[2] Pinna C, Glass R, Knight GE, Bolego C, Puglisi L, Burnstock G. Purine- and pyrimidine-induced responses and P2Y receptor characterization in the hamster proximal urethra. Br J Pharmacol 2005;144(4):510–8.

[3] Reznik VS, Pashkurov NG, Mikhailov AS, Akamsin VD, Galyametdinova IV, Zobov VV, et al. Synthesis and pharmacological activity of ω-(4-phenylpiperazin-1-yl)alkylthiopyrimidines. Pharm Chem J 2004;38(12):654–8.

[4] Sondhi SM, Singh N, Johar M, Kumar A. Synthesis, anti-inflammatory and analgesic activities evaluation of some mono, bi and tricyclic pyrimidine derivatives. Bioorg Med Chem 2005;13(22):6158–66.

[5] Bruno O, Brullo C, Ranise A, Schenone S, Bondavalli F, Barocelli E, et al. Synthesis and pharmacological evaluation of 2,5-cycloamino-5*H*-[1]benzopyrano[4,3-*d*]pyrimidines endowed with*in vitro* antiplatelet activity. Bioorg Med Chem Lett 2001;11(11):1397–400.

[6] Gangjee A, Vidwans A, Elzein E, Mc Cuire JJ, Queener SF, Kisliuk RL. Synthesis, antifolate, and antitumor activities of classical and nonclassical 2-amino-4-oxo-5-substituted-pyrrolo[2,3-*d*]pyrimidines. J Med Chem 2001;44(12):1993–2003.

[7] Banjanac M, Tatic I, Ivezic Z, Tomic S, Dumic J. Pyrimidopyrimidines: a novel class of dihydrofolate reductase inhibitors. Food Technol Biotechnol 2009;47(3):236–45.

[8] Mangalagiu G, Ungureanu M, Grosu G, Mangalagiu I, Petrovanu M. New pyrrolopyrimidine derivatives with antifungal or antibacterial properties. Ann Pharm Fr 2001;59(2):139–40.

[9] Wamhoff H, Dzenis J, Hirota K. In: Katritzky AR, editor. Advances in heterocyclic chemistry, vol. 55, 2nd ed. New York: Academic Press Inc.; 1992. p. 163–5.

[10] Hamama WS. Enaminouracils as precursors for the synthesis of pyrimido[4,5-*d*]pyrimidine-2,4-diones. Z Naturforsch 2000;55b: 443–7.

[11] Rewcastle GW, Bridges AJ, Fry DW, Rubin JR, Denny WA. Tyrosine kinase inhibitors. 12. Synthesis and structure−activity relationships for 6-substituted 4-(phenylamino)pyrimido[5,4-*d*]pyrimidines designed as inhibitors of the epidermal growth factor receptor. J Med Chem 1997;40(12):1820–6.

[12] Fry DW, Becker MA, Switzer RL. Inhibition of human 5-phosphoribosyl-1-pyrophosphate synthetase by 4-amino-8-[β-D-ribofuranosylamino]pyrimido[5,4-*d*]pyrimidine-5′-monophosphate: evidence for interaction at the adenosine-5′-diphosphate allosteric site. Mol Pharmacol 1995;47(4):810–5.

[13] Gready JE, McKinlay C, Gebauer MG. Synthesis of quaternised 2-aminopyrimido[4,5-*d*]pyrimidin-4(3*H*)-ones and their biological activity with dihydrofolate reductase. Eur J Med Chem 2003;38(7):719–28.

[14] Sanghhvi YS, Larson SB, Matsumoto SS, Nord LD, Smee DF, Willis RC, et al. Antitumor and antiviral activity of synthetic alpha- and beta-ribonucleosides of certain substituted pyrimido[5,4-*d*]pyrimidines: a new synthetic strategy for exocyclic aminonucleosides. J Med Chem 1989;32(3):629–37.

[15] Tenser RB, Gaydos A, Hay KA. Inhibition of herpes simplex virus reactivation by dipyridamole. Antimicrob Agent Chemother 2001;45(12):3657–9.

[16] De la Cruz JP, Carrasco T, Ortega G, Sanchez De la Cuesta F. Inhibition of ferrous-induced lipid peroxidation by pyrimidopyrimidine derivatives in human liver membranes. Lipids 1992;27(3):192–4.

[17] Furuya S, Ohtaki T. Pyrido[2,3-*d*]pyrimidines and their uses as anatagonists. Eur Pat Appl Ep. 608565, 1994; Chem Abstr.; 1994, 121:205395w.

[18] Singh G, Singh G, Yadav AK, Mishraa K. Synthesis and antimicrobial evaluation of some new pyrido[2,3-*d*]pyrimidines and their riboufuranosides. Ind J Chem 2002;41(2):430–2.

[19] Domling A. Recent developments in isocyanide based multicomponent reactions in applied chemistry. Chem Rev 2006;106(1):17–89.

[20] Ram VJ, Goel A, Sarkhel S, Maulik PR. A convenient synthesis and hepatoprotective activity of imidazo[1,2-*c*]pyrimido[5,4-*e*]pyrimidine, tetraazaacenaphthene and tetraazaphenalene from cyclic ketene aminals through tandem addition-cyclization reactions. Bioorg Med Chem 2002;10(5):1275–80.

[21] Bernier JL, Henichart JP, Warin V, Baert F. Synthesis and structure–activity relationship of a pyrimido[4,5-*d*]pyrimidine derivative with antidepressant activity. J Pharm Sci 1980;69(11):1343–5.

[22] Abonia R, Albornoz A, Larrahondo H, Quiroga J, Insuasty B, Insuasty H, et al. Synthesis of pyrazole and pyrimidine Tröger's-base analogues. J Chem Soc Perkin Trans 2002;1:1588–91.

[23] Youssif S. 6-Aminouracil as precursors for the synthesis of fused di- and tricyclic pyrimidines. J Chem Res 2004;2004(5):341–3.

[24] Aksinenko AYu, Sokolov VB, Goreva TV, Epishina TA, Pushin AN. Synthesis of 6-substituted 5,6,7,8-tetrahydropyrimido [4,5-*d*]pyrimidine-2,4-diones and 2-thioxo-5,6,7,8-tetrahydro-pyrimido[4,5-*d*]pyrimidin-4-ones. Russ Chem Bull 2008;57(7): 1543–6.

[25] Youssif S, Agili F. One-Pot Synthesis of fused 2-thiouracils: pyrimido-pyrimidines, pyridopyrimidines and imidazolo-pyrimidines. Z Naturforsch B 2008;63b:860–4.

[26] Hammouda M, Hamama WS, Afsah EM. A study on the Mannich reaction with 1-phenylam-ino-3-indenone. Z Naturforsch 1987;42b:94–6.

[27] Hamama WS, Hammouda M, Afsah EM. Mannich reaction with 5,5-dimethyl-3-phenylamino-2-cyclohexen-1-one. Z Naturforsch 1988;43b:483–6.

[28] Roth HJ, Hagen H-E. Aminomethylation of enamines of cyclic β-dicarbonyl compounds. Arch Pharm 1971;304(5):331–41.