5-Aminouracil as a Building Block in Heterocyclic Synthesis, Part II. One-pot Synthesis of Pyrido[3,2-*d*:6,5-*d*′]dipyrimidines under Microwave Irradiation without Catalyst

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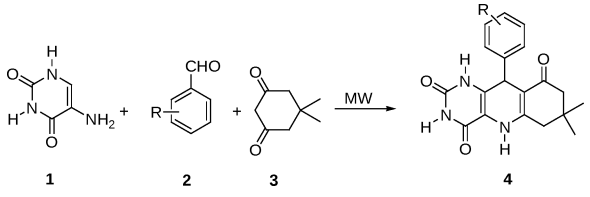
An efficient and direct procedure for the synthesis of pyrido[3,2-*d*:6,5-*d*′]dipyrimidine derivatives under microwave-assisted conditions is been described. The structures of the products were characterized by elemental analyses, and their IR, ^{1}H NMR, ^{13}C NMR, and MS spectra.

Key words: 5-Aminouracil, Barbituric Acid, Thiobarbituric Acid, Microwave Irradiation, Pyrido[3,2-*d*:6,5-*d*′]dipyrimidine

Introduction

The derivatives of fused pyrimidines are valued not only for their rich and varied chemistry, but also for many important biological properties [1 – 3]. Among them, the pyridodipyrimidines (PDP) have been shown to exhibit antibacterial and antiviral properties [4, 5] as well as NAD-type redox catalytic activity [6 – 10]. A few methods are reported in the literature for the preparation of pyrido[2,3-*d*:6,5-*d*′]dipyrimidine-2,4,6,8-tetrones [4 – 18], but to the best of our knowledge, there are no reports in the literature for the formation of pyrido[3,2-*d*:6,5-*d*′]dipyrimidine-2,4,6,8-tetrones.

Recently, we described a new, simple and efficient synthesis of 6,7,8,10-tetrahydropyrimido[5,4-*b*]quinoline-2,4,9-(1*H*,3*H*,5*H*)-triones (**4**) [19], by the reaction of 5-aminouracil (**1**), benzaldehyde derivatives **2** and dimedone (**3**) under microwave irradiation without catalyst, which could have interesting effects on biological targets (Scheme 1).



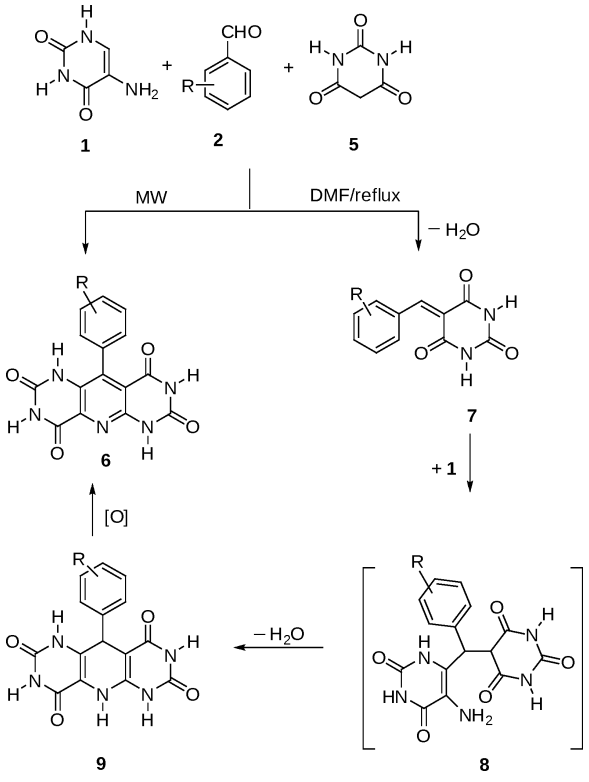
1 2 3 4

Scheme 1. Synthesis of 6,7,8,10-tetrahydropyrimido[5,4-*b*]-quinolinetriones **4**.

Considering the above reports in conjunction with our recent work on the synthesis of polyheterocyclic systems [19 – 30], we wish to report a novel, efficient, one-pot and three-component method for the preparation of pyrido[3,2-*d*:6,5-*d*′]dipyrimidines under microwave-assisted conditions.

Results and Discussion

The synthesis of 10-aryl-pyrido[3,2-*d*:6,5-*d*′]dipyrimidin-2,4,7,9-tetrones **6a** – **e** through a one-pot reaction of 5-aminouracil (**1**), benzaldehydes **2** and barbituric acid (**5**) was accomplished under microwave irradiation (method A), as shown in Scheme 2. The molecular structures of the pyridodipyrimidines **6a** – **e** were supported on the basis of elemental and spectral analyses, which were found to be in good agreement with the assigned structures. For example, compound **6e** exhibits an IR spectrum with strong absorption bands at 3402 and 3189 cm^{-1}, belonging to stretching vibrations of the NH groups, and a carbonyl absorption band at 1706 cm^{-1}. Its ^{1}H NMR spectrum revealed four characteristic, relatively sharp singlets at 11.79, 11.67, 11.21 and 8.96 ppm due to NH groups, in addition to the methoxy and phenyl protons at 3.83 and 7.00 – 7.16 ppm, respectively. The ^{13}C NMR spectrum also agreed with the proposed structure **6e**. Moreover, the mass spectrum of **6e** exhibited a molecular ion peak at *m/z* = 353 (100 %), and other significant peaks were as expected. Structural

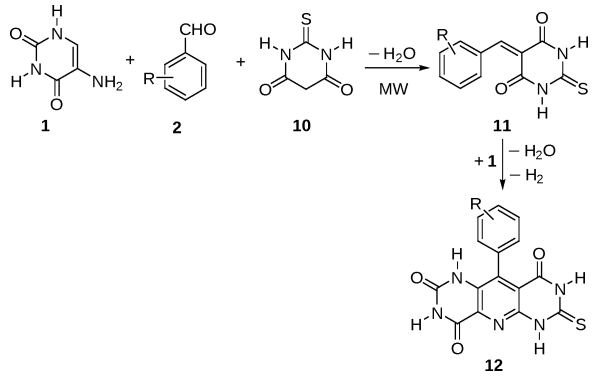


a, R = H; **b**, R = 4-Cl; **c**, R = 4-F; **d** R = 2,4-Cl_2; **e**, R = 4 -OCH_3

Scheme 2. Synthesis of pyrido[3,2-*d*:6,5-*d*′]dipyrimidines **6** and **9**.

proof was obtained through a two-component condensation of **1** with 5-arylidenebarbiturates **7a**, **b** [31, 32] in equimolar proportions under the previous conditions (method B).

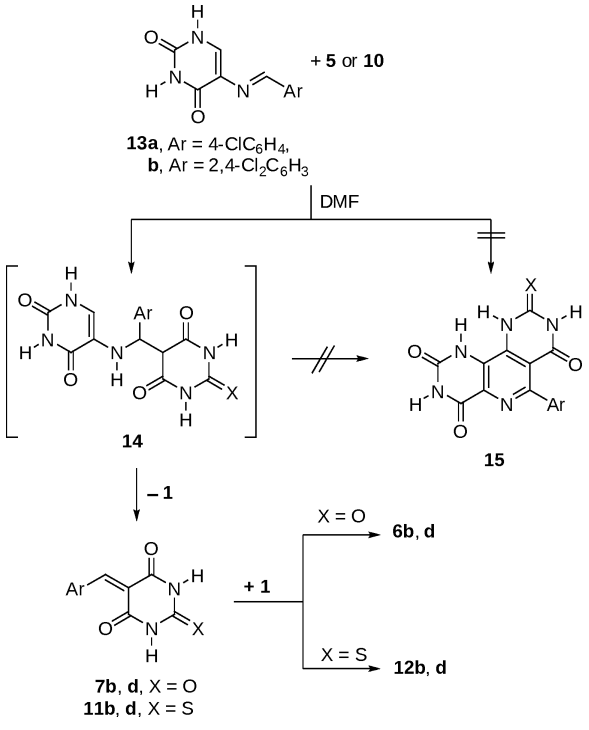
For the investigation of the reaction mechanism, it is notable that, when 5-aminouracil, benzaldehydes and barbituric acid were refluxed in DMF for 2 – 5 h, the intermediate **9** was formed, which was isolated and characterized by spectroscopic methods. The structure of compound **9d** was confirmed by its elemental and spectral analyses, which showed the molecular ion peak at *m/z* = 394.41 (6.5 %). Its ^{1}H NMR spectrum showed characteristic singlets at δ = 8.40, 9.88 and 11.52 for three NH groups, a broad singlet at δ = 10.64 for two NH groups, a singlet at δ = 4.74 due to 10-H, in addition to the multiplet signals for the phenyl protons at δ = 7.23 – 7.58 ppm. Moreover, the ^{13}C NMR spectrum of **9d** showed signals at δ_C = 36.26 (C-10), 83.86 (C-9a), 110.95 (C-4a), 128.52 (C-10a), 131.10 (C-Ar, C-5′), 136.49 (C-Ar, C-3′), 144.42 (C-Ar, C-6′), 145.38 (C-Ar, C-4′), 149.92 (C-Ar, C-2′), 150.15 (C-Ar, C1′), 150.37 (C-5a), 159.00 (C-2 and C-7), and 162.82 (C-4 and C-9). The structure proof of **9** was further supported by an alternative synthesis. Thus, the two-component condensation of **1** and arylidenebarbiturates **7a**, **b** in equimolar proportions in DMF under reflux also afforded **9a**, **b** (Scheme 2). Refluxing **9** in DMF for 2 – 6 h gave the pyrido[3,2-*d*:6,5-*d*′]dipyrimidines **6** in excellent yields (Scheme 2). According to this results, the reaction can mechanistically be considered to proceed *via* the initial formation of arylidenebarbiturates **7**, which suffer a Michael addition of the aminouracil **1** to the C=C bond of **7**. The Michael adducts **8** undergo intramolecular cyclization through elimination of a molecule of water to afford the final products **9** which by air oxidation afford **6** (Scheme 2). The disappearance of 10-H and 5-NH in the ^{1}H NMR spectra indicated that only these protons were removed from **9**.



a, R = H; **b**, R = 4-Cl; **c**, R = 4-F; **d** R = 2,4-Cl_2; **e**, R = 4 -OCH_3.

Scheme 3. Synthesis of pyrido[3,2-*d*:6,5-*d*′]dipyrimidines **12**.

As an extension of our synthetic methodology, 5-aminouracil (**1**), benzaldehydes **2** and thiobarbituric acid (**10**) were also exposed to MW irradiation. The reactions proceeded similarly to give **12a** – **e** (Scheme 3). The molecular formula of compounds **12a** – **e** is supported by elemental analyses and mass spectra that gave the expected molecular ion peaks at *m/z* = 407.44 (90 %), and other significant peaks were as expected. The IR, ^{1}H NMR as well as the ^{13}C NMR spectra agreed with the proposed structures **12a** – **e**. For example, the IR spectrum of **12d** showed absorption bands at 3360, 3220 (NH) and 1730, 1652 cm^{-1} (CO groups). Its ^{1}H NMR spectrum characteristically revealed four relatively sharp singlets at δ =



Scheme 4. Synthesis of pyrido[3,2-*d*:6,5-*d*′]dipyrimidines **6b**, **d** or **12b**, **d** from Schiff base **13a**, **b**.

8.20, 10.90, 11.58 and at 12.11 ppm assigned to the four NH groups, in addition to the signals for the phenyl protons. Structural proof of **12** was obtained through another route of synthesis by refluxing 5-arylidene-thiobarbiturates **11a**, **b** [33] with **1** in DMF (Scheme 3).

However, other reaction pathways cannot be ruled out. One of these includes the initial formation of Schiff base **13** [19]. Hence, the structures of **6** and **12** were confirmed further by the reaction of Schiff base **13** with **5** or **10** under the previous conditions (Scheme 4). No alternative products like **15** were detected. The formation of **6** or **12** may have taken place through addition of the barbituric acid to the C=N function of the Schiff base **13** to form the adduct **14**. Subsequent elimination of the 5-aminouracil moiety, rather than cyclization to the dipyrimidines **15**, afforded the adduct **7** and/or **11**, which by reaction with **1** gave **6b**, **d** and **12b**, **d**, respectively. These products were identical in all aspects with the corresponding compounds obtained by three-component reactions. According to the TLC data, under these conditions compound **13** decomposes to the initial amine **1** and aldehyde **2**.

Experimental Section

General procedures

Melting points were measured with a Gallenkamp apparatus and are uncorrected. The reactions and purity were monitored by thin layer chromatography (TLC) on aluminum plates coated with silica gel with fluorescent indicator (Merck, 60 F_{254}) using $CHCl_3/CH_3OH$ (5:2) as eluent. Microwave irradiation was carried out using a commercial microwave oven (KOR-131G, 1350 W). The infrared spectra were recorded in potassium bromide disks on a Jasco FT/IR-450 Plus infrared spectrophotometer. The NMR spectra were obtained on a JHA-LAA 400 WB-FT spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR), with deuterated chloroform ($CDCl_3$) or dimethylsulfoxide ([D_6]DMSO) as solvent. Chemical shifts are quoted in δ and are referenced to TMS or the solvent signal. The mass spectra were recorded on a Trace GC 2000 / Finnigan Mat SSQ 7000 and a Shimadzu GCMS-QP-1000EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

*Synthesis of 10-aryl-pyrido[3,2-d:6,5-d′]dipyrimidin-2,4,7,9-tetrones **6a – e***

Method A: These compounds were prepared by reaction of **1** with the appropriate benzaldehyde derivatives **2** and barbituric acid (**5**), which were placed in an open Pyrex-glass vessel and irradiated in a microwave oven with a power of 1000 Watt for 7 – 11 min using DMF (1 mL) as energy transfer medium. The resulting product was left to cool to r. t., collected by filtration, dried and crystallized from DMF/EtOH.

Method B: A mixture of 1 mmol of **1** and 1 mmol of **7a**, **b** was placed in an open Pyrex-glass vessel and irradiated in a microwave oven with 1000 Watt power for 6 – 10 min using DMF (1 mL) as energy transfer medium. The resulting mixture was left to cool to r. t., and the solid product was then collected by filtration and crystallized from DMF/EtOH.

*10-Phenyl-1,3,6,8-tetrahydropyrido[3,2-d:6,5-d′]dipyrimidine-2,4,7,9-tetrone (**6a**)*

Yellow crystals, (yield: method A: 88 %; method B: 80 %), m. p. 339 – 341 °C. – IR (film): ν = 3338, 3275, 3177, 1708, 1617 cm^{-1}. – ^{1}H NMR (400 MHz, [D_6]DMSO, TMS): δ = 7.12 – 7.25 (m, 5H, ArH), 9.60 (s, 1H, NH), 10.3 (s, 1H, NH), 10.71 (s, 1H, NH), 11.52 (s, 1H, NH). – MS (EI, 70 eV): *m/z* (%) = 323.3 (75) $[M]^+$, 246.12 (90) $[M–C_6H_5]^+$ 77.09 (7). – Anal. for $C_{15}H_9N_5O_4$: calcd. C 55.73, H 2.81, N 21.66; found C 55.62, H 2.71, N 21.54.

*10-(4-Chlorophenyl)-1,3,6,8-tetrahydropyrido[3,2-d:6,5-d′]dipyrimidine-2,4,7,9-tetrone (**6b**)*

Pale-brown crystals (yield: method A: 85 %; method B: 88 %), m. p. 350 – 354 °C. – IR (film): ν = 3360, 3190,

3073, 1712, 1612 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO, TMS): δ = 7.15 – 7.44 (m, 4H, ArH), 9.63 (s, 1H, 1NH), 10.21 (s, 1H, 1NH), 11.11 (brs, 2H, 2NH). – MS (EI, 70 eV): *m/z* (%) = 359.31 (21), 357.13 (79) $[M]^+$. – Anal. for $C_{15}H_8ClN_5O_4$: calcd. C 50.37, H 2.25, N 19.58; found C 50.28, H 2.17, N 19.67.

*10-(4-Fluorophenyl)-1,3,6,8-tetrahydro-pyrido[3,2-d:6,5-d′]dipyrimidine-2,4,7,9-tetrone (**6c**)*

Pale-brown crystals (yield: method A: 91 %; method B: 85 %), m. p. 340 – 341 °C. – IR (film): ν = 3343, 3378, 3179, 3014, 1703, 1663 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO, TMS): δ = 7.19 – 7.35 (m, 5H, ArH), 8.64 (s, 1H, 2NH), 10.59 (s, 1H, 1NH), 11.43 (brs, 2H, 2NH). – MS (EI, 70 eV): *m/z* (%) = 341.21 (90) $[M]^+$. – Anal. for $C_{15}H_8FN_5O_4$: calcd. C 52.48, H 2.94, N 20.40; found C 52.41, H 2.87, N 20.31.

*10-(2,4-Dichlorophenyl)-1,3,6,8-tetrahydropyrido[3,2-d:6,5-d′]dipyrimidine-2,4,7,9-tetrone (**6d**)*

Brown crystals (yield: method A: 96 %; method B: 91 %), m. p. 285 °C (decomp.). – IR (film): ν = 3387, 3317, 3130, 3010, 1725, 1670, 1629 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO, TMS): δ = 7.20 – 7.25 (m, 1H, ArH), 7.49 – 7.55 (m, 2H, ArH), 9.66 (s, 1H, NH), 10.98 (brs, 2H, NH), 11.31 (brs, 1H, NH). – MS (EI, 70 eV): *m/z* (%) = 393.13 (25), 391.01 (80) $[M]^+$, 246.0263 (92) [M–2,4-$Cl_2C_6H_3$]$^+$. – Anal. for $C_{15}H_7Cl_2N_5O_5$: calcd. C 45.94, H 1.80, N 17.86; found C 45.83, H 1.89, N 17.75.

*10-(4-Methoxyphenyl)-1,3,6,8-tetrahydropyrido[3,2-d:6,5-d′]dipyrimidine-2,4,7,9-tetrone (**6e**)*

Pale-brown crystals (yield: method A: 74 %, method B: 67 %), m. p. 340 – 342 °C. – IR (film): ν = 3402, 3189, 3053, 1706, 1610 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO, TMS): δ = 3.83 (s, 3H, OCH_3), 7.00 – 7.04 (d, 2H, *J* = 8.70 Hz, ArH), 7.13 – 7.16 (d, 2H, ArH), 8.96 (brs, 1H, NH), 11.21 (s, 1H, NH), 11.67 (s, 1H, NH), 11.79 (s, 1H, NH). – ^{13}CNMR (100 MHz, [D_6]DMSO): δ = 56.70 (C-OCH_3), 110.02 (C-Ar, C-3′), 114.39 (C-9a), 129.17 (C-Ar, C-2′), 131.30 (C-Ar, C1′), 133.37 (C-10a), 137.99 (C-4a), 143.40 (C-10), 150.43 (C-Ar, C-4′), 150.88 (C-5a), 158.22 (C-2), 159.99 (C-7), 163.25 (C-4), 163.45 (C-9). – MS (EI, 70 eV): *m/z* (%) = 352 (35.7), 353 (100) $[M]^+$, 354 (21), 322 (32) [M–OCH_3]$^+$. – Anal. for $C_{16}H_{11}N_5O_5$: calcd. C 54.39, H 3.14, N 19.82; found C 54.28, H 3.06, N 19.89.

*Synthesis of 10-aryl-1,3,5,6,7,10-hexahydropyrido[3,2-d:6,5-d′]dipyrimidines **9a – e***

Method A: A Solution of 5-aminouracil (**1**), the appropriate benzaldehyde derivative **2** and barbituric acid (**5**) in DMF (2 mL) was refluxed for 2 – 5 h (TLC control). The solvent was concentrated, and the product obtained was recrystallized from DMF.

Method B: A Solution of equimolar amounts of **1** and **7a**, **b** in DMF (3 mL) was refluxed for 2 – 6 h (TLC control). Products **9a**, **b** were isolated as described above.

*10-Phenyl-1,3,5,6,8,10-hexahydropyrido[3,2-d:6,5-d′]dipyrimidine-2,4,7,9-tetrone (**9a**)*

Pale-yellow crystals (yield: method A: 80 %; method B: 76 %), m. p. > 360 °C. – IR (film): ν = 3345, 3273, 3186, 1704, 1617 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO, TMS): δ = 4.73 (s, 1H, 10-H), 7.23 – 7.35 (m, 5H, ArH), 8.33 (s, 1H, NH), 9.85 (s, 1H, NH), 10.59 (s, 1H, NH), 10.88 (s, 1H, NH), 11.47 (s, 1H, NH). – MS (EI, 70 eV): *m/z* (%) = 325.3 (60) $[M]^+$, 323.1 (20.0) $[M–2]^+$, 248.4 (95.0) [M–C_6H_5]$^+$. – Anal. for $C_{15}H_{11}N_5O_4$: calcd. C 55.39, H 3.41, N 21.53; found C 55.27, H 3.34 N 21.45.

*10-(4-Chlorophenyl)-1,3,5,6,8,10-hexahydropyrido[3,2-d:6,5-d′]dipyrimidine-2,4,7,9-tetrone (**9b**)*

Yellow crystals (yield: method A: 76 %; method B: 71 %), m. p. > 360 °C. – IR (film): ν = 3354, 3175, 3062, 1712, 1614 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO, TMS): δ = 4.73 (s, 1H, 10-H), 7.19 – 7.23 (m, 2H, ArH), 7.33 (s, 1H, NH), 7.46 – 7.50 (m, 2H, ArH), 9.85 (s, 1H, 1NH), 10.66 (s, 1H, 1NH), 11.47 (brs, 2H, 2NH). – MS (EI, 70 eV): *m/z* (%) = 359.32 (60) $[M]^+$. – Anal. for $C_{15}H_{10}ClN_5O_4$: calcd. C 50.08, H 2.80, N 19.47; found C 50.21, H 2.72, N 19.41.

*10-(4-Fluorophenyl)-1,3,5,6,8,10-hexahydropyrido[3,2-d:6,5-d′]dipyrimidine-2,4,7,9-tetrone (**9c**)*

Yellow crystals (yield: 85 %), m. p. > 360 °C. – IR (film): ν = 3347, 3398, 3156, 2992, 1708, 1660 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO, TMS): δ = 4.73 (s, 1H, 10-H) 7.07 – 7.13 (m, 2H, ArH), 7.20 (s, 1H, NH), 7.25 – 7.35 (m, 2H, ArH), 10.59 (brs, 2H, 2NH), 11.56 (brs, 2H, 2NH). – MS (EI, 70 eV): *m/z* (%) = 343.18 (83) $[M]^+$. – Anal. for $C_{15}H_{10}FN_5O_4$: calcd. C 52.48, H 2.94, N 20.40; found C 52.41, H 2.87, N 20.31.

*10-(2,4-Dichlorophenyl)-1,3,5,6,8,10-hexahydropyrido[3,2-d:6,5-d′]dipyrimidine-2,4,7,9-tetrone (**9d**)*

Yellow crystals (yield: 90 %), m. p. 352 – 354 °C (decomp.). – IR (film): ν = 3382, 3306, 3156, 3021, 1711, 1676, 1629 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO, TMS): δ = 4.74 (s, 1H, 10-H), 7.23 – 7.27 (m, 1H, ArH), 7.53 – 7.58 (m, 2H, ArH), 8.40 (s, 1H, NH), 9.88 (s, 1H, NH), 10.64 (brs, 2H, NH), 11.52 (s, 1H, NH). – ^{13}C NMR: (100 MHz, [D_6]DMSO): δ = 36.26 (C-10), 83.86 (C-9a), 110.95 (C-4a), 128.52 (C-10a), 131.10 (C-Ar, C-5′), 136.49 (C-Ar, C-3′), 144.42 (C-Ar, C-6′), 145.38 (C-Ar, C-4′), 149.92 (C-Ar, C-2′), 150.15 (C-Ar, C1′), 150.37 (C-5a), 159.00 (C-2 and

C-7), 162.82 (C-4 and C-9). – MS (EI, 70 eV): *m/z* (%) = 394.41 (6.5) $[M]^+$, 393.40 (30), 322.20 (93). – Anal. for $C_{15}H_9Cl_2N_5O_4$: calcd. C 45.71, H 2.30, N 17.77; found C 45.79, H 2.39, N 17.61.

*10-(4-Methoxyphenyl)-1,3,5,6,8,10-hexahydropyrido[3,2-d:6,5-d′]dipyrimidine-2,4,7,9-tetrone (**9e**)*

Yellow crystals (yield: 73 %), m. p. > 360 °C. – IR (film): ν = 3210, 3079, 1712, 1614 cm^{-1}. – ^1H NMR (400 MHz, [D$_6$]DMSO, TMS): δ = 3.80 (s, 3H, O-CH$_3$), 4.67 (s, 1H, 10-H) 7.00 – 7.03 (d, 2H, ArH), 10-H), 6.8 – 6.9 (m, 2H, ArH), 7.13 – 7.20 (m, 2H, ArH), 7.95 (s, 1H, 5-NH), 8.96 (brs, 1H, NH), 9.07 (s, 1H, 6-NH), 10.96 (s, 1H, 1-NH), 11.65 (s, 1H, NH). – ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 37.13 (C-10), 55.51 (C-OCH$_3$), 83.3 (C-9a), 114.14 (C-4a), 127.93 (C-Ar, C-3′), 128.67 (C-10a), 129.17 (C-Ar, C-2′), 136.00 (C-Ar, C1′), 150.00 (C-Ar, C-4′), 150.45 (C-5a), 159.10 (C-2 and C-7), 162.82 (C-4 and C-9). – MS (EI, 70 eV): *m/z* (%) = 355.02 (100) $[M]^+$. – Anal. for $C_{16}H_{13}N_5O_5$: calcd. C 54.09, H 3.69, N 19.71; found C 54.17, H 3.57 N 19.61.

*Alternative synthesis of **6***

A solution of 1 mmol of **9a – c** in DMF (3 mL) was refluxed for 3 – 5 h. The solvent was concentrated, and the product obtained was recrystallized from DMF/EtOH (yield of **6a**: 82 %; **6b**: 85 %; **6c**: 89 %).

*Synthesis of 10-aryl-1,3,6,8-tetrahydro-7-thioxopyrido[3,2-d:6,5-d′]dipyrimidine-2,4,9-triones **12a – e***

Method A: Using the procedure described for the synthesis of compound **6** (method A), compounds **12a – e** were prepared by reaction of equmolar amounts of **1** with the appropriate benzaldehyde derivatives **2** and thiobarbituric acid (**10**) with microwave heating at 800 Watt for 4 – 7 min. The products were recrystallized from DMF/MeOH.

Method B: A mixture of **1** (1 mmol), **11a**, **b** (1 mmol) and DMF (1 mL) was placed in open Pyrex-glass vessels and irradiated in a microwave oven with 800 Watt power for 4 – 6 min. The resulting mixture was left to cool to r. t., and the solid product was then collected by filtration and crystallized from DMF/MeOH (yield of **12a**: 83 %; **12b**: 90 %).

*10-Phenyl-1,3,6,8-tetrahydro-7-thioxo-pyrido[3,2-d:6,5-d′]dipyrimidine-2,4,9-trione (**12a**)*

Pale-brown crystals (yield: method A: 83 %), m. p. 338 – 340 °C. – IR (film): ν = 3154, 3030, 2922, 2830, 1713, 1639 cm^{-1}. – ^1H NMR (400 MHz, [D$_6$]DMSO, TMS): δ = 7.22 – 7.36 (m, 5H, ArH), 9.10 (s, 1H, 6-NH), 10.98 (s, 1H, 1-NH), 11.51 (s, 1H, 8-NH), 12.03 (s, 1H, 3-NH). – ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 112.43 (C-9a), 128.86 (C-Ar, C-4′), 129.45 (C-Ar, C-2′), 131.33 (C-10a), 132.37 (C-Ar, C-3′), 133.43 (C-4a), 135.33 (C-Ar, C1′), 136.26 (C-10), 139.57 (C-5a), 150.23 (C-2), 158.84 (C-4), 162.83 (C-9), 167 (C-7). – MS (EI, 70 eV): *m/z* (%) = 339.04 (60) $[M]^+$, 265.07 (100) $[M–CH_2N_2S]^+$. – Anal. for $C_{15}H_9N_5O_3S$: calcd. C 53.09, H 2.67, N 20.64, S 9.45; found C 53.14, H 2.62, N 20.59, S 9.41.

*10-(4-Chlorophenyl)-1,3,6,8-tetrahydro-7-thioxopyrido[3,2-d:6,5-d′]dipyrimidine-2,4,9-trione (**12b**)*

Brown crystals (yield: method A: 94 %), m. p. > 360 °C. – IR (film): ν = 3325, 3140, 2965, 2927, 2883, 1722, 1662, 1617 cm^{-1}. – ^1H NMR (400 MHz, [D$_6$]DMSO, TMS): δ = 7.31 – 7.37 (m, 4H, ArH), 8.39 (s, 1H, 6-NH), 10.91 (s, 1H, 1-NH), 11.53 (s, 1H, 8-NH), 12.06 (s, 1H, 3-NH). – MS (EI, 70 eV): *m/z* (%) = 373.2 (55) $[M]^+$. – Anal. for $C_{15}H_8ClN_5O_3S$: calcd. C 48.20, H 2.16, N 18.74, S 8.58; found C 48.25, H 2.22, N 18.69, S 8.52.

*10-(4-Fluorophenyl)-1,3,6,8-tetrahydro-7-thioxopyrido[3,2-d:6,5-d′]dipyrimidine-2,4,9-trione (**12c**)*

Brown crystals (yield: method A: 98 %), m. p. > 340 – 338 °C. – IR (film): ν = 3390, 3335, 3114, 3046, 2929, 1726, 1669, 1614 cm^{-1}. – ^1H NMR (400 MHz, [D$_6$]DMSO, TMS): δ = 7.08 – 7.14 (m, 2H, ArH), 7.32 – 7.36 (m, 2H, ArH), 8.38 (s, 1H, 6-NH), 10.91 (s, 1H, 1-NH), 11.47 (s, 1H, 8-NH), 12.04 (s, 1H, 3-NH). – ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 110.26 (C-9a), 115.65 (C-Ar, C-3′), 130.24 (C-10a), 130.33 (C-Ar, C-2′), 132.08 (C-Ar, C1′), 134.29 (C-4a), 136.26 (C-10), 144.64 (C-5a), 159.97 (C-Ar, C-4′), 150.39 (C-2), 160.30 (C-4), 162.83 (C-9), 173.81 (C-7). – MS (EI, 70 eV): *m/z* (%) = 357.19 (65.0) $[M]^+$, 359.44 (40.0) $[M+2]^+$. – Anal. for $C_{15}H_8FN_5O_3S$: calcd. C 50.42, H 2.26, N 19.60, S 8.97; found C 50.49, H 2.31, N 19.53, S 8.92.

*10-(2,4-Dichlorophenyl)-1,3,6,8-tetrahydro-7-thioxopyrido[3,2-d:6,5-d′]dipyrimidine-2,4,9-trione (**12d**)*

Dark-brown crystals (yield: method A: 95 %), m. p. 350 – 353 °C. – IR (film): ν = 3360, 3220, 2980, 2892, 1730, 1652, 1612 cm^{-1}. – ^1H NMR (400 MHz, [D$_6$]DMSO, TMS): δ = 7.17 – 7.19 (dd, 1H, ArH), 7.49 – 7.50 (s, 1H, ArH), 7.68 – 7.70 (dd, 1H, ArH), 8.2 (s, 1H, 6-NH), 10.90 (s, 1H, 1-NH), 11.58 (s, 1H, 8-NH), 12.11 (s, 1H, 3-NH). – H, H COSY spectrum indicated the correlation between a double doublet at δ_H = 7.2 (J = 1.8, 8.2 Hz, 5′-H) with a doublet at δ_H = 7.7 (J = 8.2 Hz, 6′-H) and a long-range correlation with δ_H = 7.5 (J = 1.8 Hz, 3′-H). – ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 113.6 (C-9a), 127.12 and 134.10 (Ar-C and C-10a, C-4a), 137.43 (C-10), 146.97 (C-5a), 149.28 (C-2), 158.1 (C-4), 159.91 (C-9), 174.70 (C-7). – MS (EI, 70 eV): *m/z* (%) = 407.44 (90) $[M]^+$, 262.08 (73) $[M–2,4\text{-}Cl_2C_6H_3]^+$. – Anal. for $C_{15}H_7Cl_2N_5O_3S$: calcd. C 44.13, H 1.73, N 17.16, S 7.85; found C 44.09, H 1.81, N 17.23, S 7.79.

*10-(4-Methoxyphenyl)-1,3,6,8-tetrahydro-7-thioxopyrido-[3,2-d:6,5-d′]dipyrimidine-2,4,9-trione (**12e**)*

Brown crystals (yield: method A: 74 %), m. p. > 360 °C. – IR (film): ν = 3323, 3289, 3144, 2962, 2813, 1718, 1667, 1618 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO, TMS): δ = 3.70 (s, 3H, OCH_3), 6.83 – 6.92 (m, 2H, ArH), 7.13 – 7.20 (m, 2H, ArH), 9.07 (s, 1H, 6-NH), 10.88 (s, 1H, 1-NH), 11.49 (s, 1H, 8-NH), 12.01 (s, 1H, 3-NH). – MS (EI, 70 eV): *m/z* (%) = 369.0 (53) $[M]^+$, 371.2 (60) $[M]^+$, 264.1 (100) $[M–CH_3OC_6H_4]^+$, 263.0 (25). – Anal. for $C_{16}H_{11}N_5O_4S$: calcd. C 52.03, H 3.00, N 18.96, S 8.68; found C 52.11, H 2.94, N 18.91, S 8.61.

*Alternative synthesis of **6** and **12***

A mixture of **5** and/or **10** (1 mmol) and Schiff base **13a**, **b** (1 mmol) in 1 mL of DMF was irradiated in a microwave oven with 1000 Watt power for 4 – 10 min. Products **6b**, **d** and/or **12b**, **d** were isolated as described above; yield of **6b**: 85 %; **6d**: 96 %; **12b**: 92 %; **12d**: 95 %.

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