5-Aminouracil as a Building Block in Heterocyclic Synthesis: Part I. One-pot Synthesis of Pyrimido[5,4-*b*]quinolin-2,4,9-triones under Microwave Irradiation without Catalyst

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A series of 6,7,8,10-tetrahydropyrimido[5,4-*b*]quinolin-2,4,9-(1*H*,3*H*,5*H*)-triones **6** were synthesized through one-pot condensation of 5-aminouracil, aldehydes and dimedone in DMF under microwave irradiation without catalyst. The products **6a**, **d** were oxidized to the 7,8-dihydro-pyrimido-[5,4-b]quinolin-2,4,9-(1*H*,3*H*,6*H*)-triones **11a**, **b**. Treatment of **6a**, **d** and/or **11a**, **b** with ethyl iodide in the presence of anhydrous potassium carbonate gave the ethylated derivatives **12a**, **b** and **13a**, **b**, respectively. The structures of the products were confirmed by elemental analyses, IR, MS, ^{1}H, and ^{13}C NMR spectra.

Key words: 5-Aminouracil, Dimedone, Pyrimido[5,4-*b*]quinolin-2,4,9-triones, One-pot Synthesis, Microwave Irradiation

Introduction

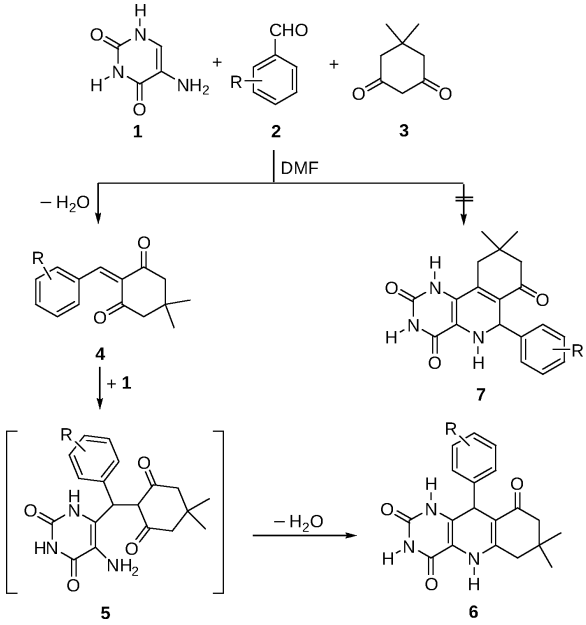
Multi-component reactions (MCRs) play an increasingly important role in organic and medicinal chemistry for their convergence, productivity, ease of execution, excellent yields, and broad applications in combinational chemistry [1 – 8]. Therefore, most of the scientific efforts have been focused on the development of multi-component procedures to prepare diverse heterocyclic compound libraries [8]. The microwave-assisted organic synthesis has been a topic of continued studies as it could lead to higher yields of pure products, easier operation and shorter reaction times as compared to the traditional heating methods [9 – 13]. Pyrimidoquinoline derivatives are important compounds because of their biological properties, which are known to depend mainly on the nature and position of substituents, and include antimalarial [14, 15], anticancer [16], antimicrobial [17] and antiinflammatory activities [18]. Recently, a number of reports have appeared in the literature revealing several methods for the preparation of pyrimido[4,5-*b*]quinolines [19 – 25]. In view of the above-mentioned findings, and following our recent work on the synthesis of polyheterocyclic systems [26 – 36], we report a convenient and efficient method for the synthesis of novel pyrimido-[5,4-*b*]quinolin-2,4,9-triones of the expected biological activity using 5-aminouracil as a building block under a variety of conditions.

Results and Discussion

A facile three-component one-pot cyclocondensation takes place between 5-amino-uracil (**1**), benzaldehyde derivatives **2** and dimedone (**3**) without catalyst in DMF affording 6,7,8,10-tetrahydropyrimido[5,4-*b*]quinoline-2,4,9-(1*H*,3*H*,5*H*)-triones **6a – f** (Scheme 1). Equimolar amounts of starting compounds **1**, **2** and **3** were irradiated in a domestic microwave oven to give compounds **6a – f** which were isolated in excellent yields (method A, 70 – 95 %, Table 1). In all cases the reactions gave a single product as indicated by TLC, which could be fully characterized by analytical and spectroscopic data. Regarding the heterocyclic unit, for example, compound **6a** exhibits an IR spectrum with strong absorption bands at 3295 and 3106 cm^{-1}, belonging to stretching vibrations of the NH group, and carbonyl absorption bands at 1709 and 1657 cm^{-1}. Its ^{1}H NMR spectrum revealed four characteristic, relatively sharp singlets at 9.74, 8.05, 7.39 and 5.53 ppm. The three former ones are assigned to the three NH groups, 3-NH, 1-NH and 5-NH, respectively, and the latter to H-10. Two couples of doublets appear around 2.35

Product	Time		Yield (%)	
	B (h)	A (MW, sec)	B	A (MW)
6a	3	100	83	90
6b	2	90	80	88
6c	3	90	78	89
6d	2	60	88	95
6e	4	120	73	90
6f	6	130	60	70

Table 1. Comparison between microwave (A) and conventional solution reactions (B).



Scheme 1. Synthesis of 6,7,8,10-tetrahydropyrimido[5,4-b]-quinolin-2,4,9-(1H,3H,5H)-triones **6**. **6a** R = H; **6b** R = 4-Cl; **6c** R = 4-F; **6d** R = 2,4-Cl_2; **6e** R = 4-H_3CO; **6f** R = 4-NMe_2.

and 2.65 ppm corresponding to the diastereotopic CH_2 groups at positions 6 and 8, respectively, in addition to the multiplet signals for phenyl protons and singlets for the two methyl groups. The ^{13}C NMR spectrum also agreed with the proposed structure **6a**. The mass spectrum of **6a** exhibited a molecular ion peak at *m/z* = 337.07 (79 %); loss of a phenyl group gave the base peak at *m/z* = 260.04 (100 %), and other significant peaks were as expected. Both the mass spectrum and elemental analysis established the molecular formula of **6a** as $C_{19}H_{19}N_3O_3$.

The formation of isomeric tricyclic systems **6** and **7** is possible in these reactions. The support for the linear structures of **6** was provided from ^1H NMR spectra in particular with respect to the chemical shift of the resonances for 5-NH and 10-H [37, 38]. The fact that 5-NH and 10-H are not coupled is an evidence for the linear structure **6** and allowed us to discard the angular structure **7**. In the latter one, coupling between the methine proton and NH is to be expected.

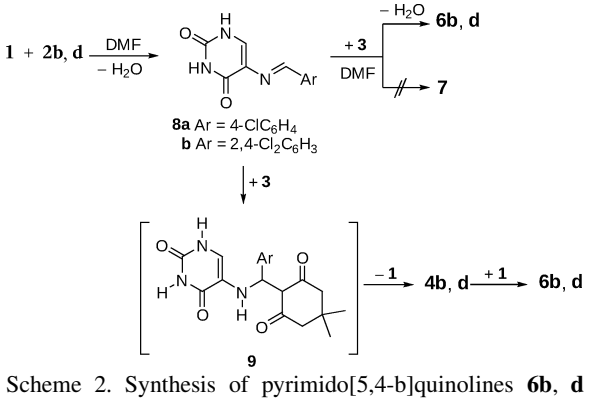
Conclusive evidence for the structure assigned for **6a** was obtained from a single crystal X-ray structure determination, which displays the linear tricyclic structure [39].

The molecular formula of compounds **6b** – **f** is supported by elemental analyses, and in the mass spectra all products **6** exhibit similar behavior in their fragmentation, showing the molecular peak along with a typical loss of the aryl group which gives the base peak. The IR, ^1H NMR as well as the ^{13}C NMR spectra agreed with the proposed structures **6b** – **f**.

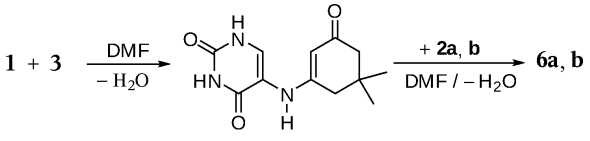
Additionally, to demonstrate the purely nonthermal microwave effects, we used the classical heating conditions in the conventional method (B), and compared it with the microwave irradiation method (A). The results listed in Table 1 showed the specific activation of this reaction by microwave heating. Simultaneously, the reaction time was strikingly shortened to minutes from hours required under traditional heating conditions, and the yields obviously were increased, too. The difference in yields (MW > classical heating) may be a consequence of both thermal effects and specific effects induced by the microwave field [11, 40].

In Scheme 1, we postulate a mechanism for the cyclocondensation between **1**, **2** and **3**, to provide pyrimido[5,4-*b*]quinolines **6**. This reaction may occur *via* a condensation, addition, cyclization, elimination mechanism. Firstly, we assume that the initial step is a Knoevenagel condensation between **2** and **3**, resulting in the adducts **4**, which undergo a Michael addition of the aminouracil (**1**) to the C=C bond of **4**. The Michael adducts **5** undergo a cyclocondensation reaction through the amino and carbonyl groups with elimination of a molecule of water to render compounds **6**. The structure of the pyrimidoquinolines **6** was further supported by an alternative synthesis. Thus, the two component condensation of **1** and arylidene derivatives [41, 42] **4a**, **b**, **e** in equimolar proportions in DMF under standard conditions also afforded **6a**, **b**, **e** (Scheme 1).

However, other reaction pathways cannot be ruled out. One of these includes initial formation of Schiff base **8** *via* reaction of **1** with **2** (Scheme 2), and the other involves possible formation of enaminoketone **10** by condensation of **1** with **3** (Scheme 3). To check this possibility we first synthesized the Schiff base **8a**, **b** by reaction of equimolar amounts of the corresponding aldehyde **2b**, **d** and **1** in DMF. The structure of



Scheme 2. Synthesis of pyrimido[5,4-b]quinolines **6b**, **d** from Schiff bases **8a**, **b**.

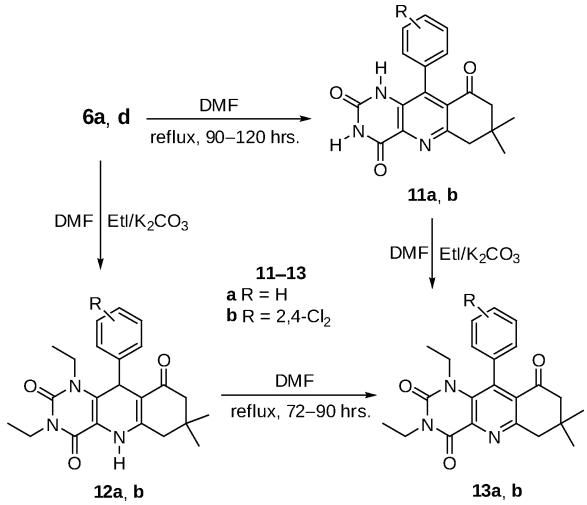


Scheme 3. Synthesis of pyrimido[5,4-b]quinolines **6a**, **b** from enaminoketone **10**.

8 was deduced on the basis of analytical and spectral data. Compounds **8a**, **b** were brought into reaction with dimedone (**3**) in DMF under standard conditions. As a result, we isolated only pyrimido[5,4-*b*]-quinoline **6b**, **d**. No alternative products like **7** were detected. The formation of **6** may have taken place through addition of dimedone to the C=N unit of the Schiff base **8** to form the adduct **9**. Subsequent elimination of the 5-aminouracil moiety, rather than cyclization to the pyrimido[5,4-*c*]isoquinoline-2,4,7-trione **7**, afforded the adduct **4**, which on reaction with **1** gave **6**. Therefore, Schiff bases **8** act in this reaction as synthetic equivalents of aldehydes (Scheme 2).

Enaminoketone **10** was obtained by reacting **3** with **1** in DMF (Scheme 3). Its structure was established on the basis of analytical and spectral data. Refluxing a mixture of equimolar amounts of **10** and **2a**, **b** in DMF for 45 – 50 h resulted in the formation of **6a**, **b** (Scheme 3). According to TLC data, under these conditions compound **10** very slowly decomposes to the initial amine **1** and dimedone **3**. Thus, the formation of compound **6** through the enaminoketone intermediate **10** seems to be improbable, and a mechanism as shown in Scheme 1 is more likely.

To test the reactivity of compound **6** towards oxidation, we heated **6a**, **d** in refluxing DMF without an oxidizing agent. The reaction proceeded after a long time of refluxing (90 – 120 h) to give 7,8-dihydro-pyrimido-



Scheme 4. Oxidation and ethylation of pyrimido[5,4-b]-quinolines.

[5,4-b]quinoline-2,4,9(1*H*,3*H*,6*H*)-triones **11a**, **b** in excellent yields as a result of air oxidation of **6** (Scheme 4). The structure of the products **11a**, **b** was confirmed by elemental analysis and spectral data. The disappearance of signals for 10-H and 5-NH in the ^{1}H NMR spectra indicated that only these protons were removed from **6a**, **d**.

We also studied the alkylation of **6a**, **d** and **11a**, **b** with ethyl iodide. The reactions were carried out at r. t. in DMF and in the presence of anhydrous potassium carbonate to afford the ethylated derivatives **12a**, **b** and **13a**, **b**, respectively (Scheme 4). The structure of the products was proved by elemental analysis and spectral data. These compounds are not the *O*-ethylation products. The IR spectra of the products contain bands around 1699 – 1701 cm^{-1}, characteristic of carbonyl absorptions, and the ^{1}H NMR spectra revealed that the alkylation occurs only at the N-1 and N-3 atoms. Thus, the ^{1}H NMR spectra of compounds **12a**, **b** and **13a**, **b** contained signals from the N^{1}CH$_2$ (δ = 3.48 – 3.80) and N^{3}CH$_2$ protons (δ = 4.06 – 4.17 ppm). Furthermore, the fragmentation patterns of the mass spectra of **12a** and **12b** showed the molecular ion peak at *m/z* = 393 (M$^+$, 21 %) and *m/z* = 461 (M$^+$, 13 %), respectively, along with peaks arising from the typical loss of the aryl group as the base peak at *m/z* = 316 (100 %) which is in good agreement with the assigned structure. Further confirmation of the structure of **13a**, **b** was obtained by comparison with an authentic sample prepared by refluxing **12a**, **b** in DMF for 72 – 90 h which

showed agreement in elemental analysis, m. p., and ^{1}H NMR data.

In conclusion, we have demonstrated very convenient procedures for the syntheses of pyrimido-[5,4-*b*]quinolin-2,4,9-triones. In the light of its operational simplicity, simple purification procedure, excellent yields, and reduced environmental impact as well as increased safety for small-scale high-speed synthesis, this protocol is superior to the existing methods.

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 F254) using $CHCl_3/CH_3OH$ (5 : 1) as eluent. Microwave irradiation was carried out using a commercial microwave oven (KOR-131G, 1350 W). The infrared spectra were recorded on a Jasco FT/IR-450 Plus spectrophotometer. The NMR spectra were obtained on a JHA-LAA 400 WB-FT instrument (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) and a Varian Mercury VX-300 NMR spectrometer (300 MHz for ^{1}H 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 / Finngan 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-7,7-dimethyl-6,7,8,10-tetrahydropyrimido[5,4-b]quinolin-2,4,9(1H,3H,5H)-triones **6a–f***

Method A: A mixture of 5-aminouracil (**1**) (1 mmol), the appropriate benzaldehyde derivative **2** (1 mmol) and dimedone (**3**) (1 mmol) was placed in an open Pyrex-glass vessel and irradiated in a domestic microwave oven with 600 W power for 60 – 130 seconds (TLC control) using DMF (1 mL) as energy transfer medium. The resulting solid was left to cool to r. t., and the solid product was then collected and crystallized from ethanol (Table 1).

Method B: Equimolar amounts of **1**, **2** and **3** in DMF (3 mL) were refluxed for 2 – 6 h (TLC control). The solvent was evaporated under vacuum, and the product obtained was recrystallized from ethanol (Table 1).

*7,7-Dimethyl-10-phenyl-6,7,8,10-tetrahydropyrimido[5,4-b]quinoline-2,4,9(1H,3H,5H)-trione (**6a**)*

Pale yellow crystals, m. p. 349 – 350 °C. – IR (film): ν = 3295, 3106, 3017, 2962, 2818, 1709, 1657 cm^{-1}. – ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C, TMS): δ = 0.89 (s, 3H, CH*Me*), 0.99 (s, 3H, CH*Me*), 2.25 and 2.40 (2H, dd, J = 16.0 Hz, CH_2), 2.62 and 2.68 (2H, dd, J = 16.0 Hz, CH_2), 5.53 (s, 1H, 10-H), 7.15 – 7.37 (m, 3H, ArH), 7.39 (s, 1H, 5-NH), 7.65 – 7.71 (m, 2H, ArH), 8.05 (s, 1H, 1-NH), 9.74 (s, 1H, 3-NH). – ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 27.05 and 29.31 (CMe_2), 33.38 (C-7), 35.71 (C-10), 41.01 (C-6), 50.86 (C-8), 106.25 (C-9a), 112.69 (C-4a), 127.37, 128.61, 128.78 (Ar-C), 134.34 (C-10a), 145.02 (Ar-C), 150.56 (C-6a), 151.78 (C-2), 163.40 (C-4), 195.40 (C-9). – MS (EI, 70 eV): *m/z* (%) = 339.11 (2), 338.14 (17), 337.07 (79) [M]$^+$, 336.03 (8), 260.04 (100) [M – C_6H_5]$^+$, 77.09 (5). – Anal. for $C_{19}H_{19}N_3O_3$: calcd. C 67.64, H 5.68, N 12.46; found C 67.71, H 5.61, N 12.50.

*10-(4-Chlorophenyl)-7,7-dimethyl-6,7,8,10-tetrahydropyrimido[5,4-b]quinoline-2,4,9(1H,3H,5H)-trione (**6b**)*

Yellow crystals, m. p. 291 – 293 °C. – IR (film): ν = 3225 (NH), 3177 (NH), 3012, 2959, 2803, 1711 (C=O), 1653 (C=O) cm^{-1}. – ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C, TMS): δ = 0.78 (s, 3H, CH*Me*), 0.93 (s, 3H, CH*Me*), 1.90 and 2.10 (2H, dd, J = 16.0 Hz, CH_2), 2.41 and 2.50 (2H, dd, J = 16.0 Hz, CH_2), 4.73 (s, 1H, 10-H), 7.20 – 7.37 (m, 5H, ArH + 5-NH), 9.00 (s, 1H, 1-NH), 10.28 (s, 1H, 3-NH). – ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 26.89 and 29.50 (CMe_2), 33.50 (C-7), 38.06 (C-6), 38.87 (C-10), 50.30 (C-8), 104.34 (C-9a), 111.69 (C-4a), 128.73, 130.08, 132.14, 134.07 (Ar-C), 143.63 (C-10a), 150.69 (C-6a), 152.46 (C-2), 159.17 (C-4), 194.37 (C-9). – MS (EI, 70 eV): *m/z* (%) = 374.23 (5), 373.10 (22), 372.15 (32.15), 370.88 (100) [M]$^+$, 259.92 (52) [M – 4-ClC_6H_4]$^+$. – Anal. for $C_{19}H_{18}ClN_3O_3$: calcd. C 61.38, H 4.88, N 11.30; found C 61.47, H 4.82, N 11.38.

*7,7-Dimethyl-10-(4-fluorophenyl)-6,7,8,10-tetrahydropyrimido[5,4-b]quinoline-2,4,9(1H,3H,5H)-trione (**6c**)*

Pale yellow crystals, m. p. 150 – 151 °C. – IR (film): ν = 3229, 3068, 2957, 2938, 1715, 1660 cm^{-1}. – ^{1}H NMR (400 MHz, [D_6]DMSO, 25 °C, TMS): δ = 0.91 (s, 3H, CH*Me*), 1.08 (s, 3H, CH*Me*), 1.95 and 2.17 (2H, dd, J = 16.0 Hz, CH_2), 2.45 and 2.50 (2H, dd, J = 16.0 Hz, CH_2), 4.71 (s, 1H, 10-H), 7.07 – 7.15 (m, 2H, ArH), 7.22 – 7.30 (m, 2H, ArH), 7.38 (s, 1H, 5-NH), 9.06 (s, 1H, 1-NH), 10.35 (s, 1H, 3-NH). – ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 26.94 and 28.30 (CMe_2), 29.54 (C-7), 33.51 (C-6), 37.85 (C-10), 50.35 (C-8), 105.06 (C-9a), 111.53 (C-4a), 115.43, 115.65, 130.02, 130.10 (Ar-C), 134.40 (C-10a), 140.96 (Ar-C), 150.37 (C-6a), 153.44 (C-2), 159.19 (C-4), 194.45 (C-9). – MS (EI, 70 eV): *m/z* (%) = 356.0 (24.9), 355.0 (61.3) [M]$^+$, 354.14 (14.2), 260.0 (100) [M – 4-FC_6H_4]$^+$. – Anal. for $C_{19}H_{18}FN_3O_3$: calcd. C 64.22, H 5.11, N 11.82; found C 64.29 H 5.18 N 11.88.

*10-(2,4-Dichlorophenyl)-7,7-dimethyl-6,7,8,10-tetrahydropyrimido[5,4-b]-quinoline-2,4,9(1H,3H,5H)-trione (**6d**)*

Yellow crystals, m. p. 289 – 291 °C. – IR (film): ν = 3254, 3167, 3012, 2932, 2835, 1733, 1668 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO, 25 °C, TMS): δ = 0.85 (s, 3H, CH*Me*), 0.99 (s, 3H, CH*Me*), 1.96 and 2.18 (2H, dd, J = 16.0 Hz, CH_2), 2.38 and 2.44 (2H, dd, J = 16.0 Hz, CH_2), 4.75 (s, 1H, 10-H), 7.16 – 7.50 (m, 3H, ArH), 9.15 (s, 1H, 5-NH), 10.78 (s, 1H, 1-NH), 11.36 (s, 1H, 3-NH). – ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 26.76 and 29.32 (CMe_2), 33.34 (C-7), 36.24 (C-6), 46.32 (C-10), 53.35 (C-8), 104.04 (C-9a), 111.43 (C-4a), 128.05 (C-10a), 129.71, 130.11, 130.73, 131.15, 132.75, 134.45 (Ar-C), 145.20 (C-6a), 151.93 (C-2), 162.75 (C-4), 193.42 (C-9). – MS (EI, 70 eV): *m/z* (%) = 410.0 (2.2), 409.0 (5.7), 408.0 (10.3), 407.0 (31.1), 406.0 (10.7), 405.0 (31.5) $[M]^+$, 260.0 (100) $[M - 2,4\text{-}Cl_2C_6H_3]^+$. – Anal. for $C_{19}H_{17}Cl_2N_3O_3$: calcd. C 56.17, H 4.22, N 10.34; found C 56.27, H 4.29, N 10.43.

*7,7-Dimethyl-10-(4-methoxyphenyl)-6,7,8,10-tetrahydropyrimido[5,4-b]-quinoline-2,4,9(1H,3H,5H)-trione (**6e**)*

Yellow crystals, m. p. 290 – 292 °C. – IR (film): ν = 3218, 3160, 3059, 2958, 2833, 1707, 1680 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO, 25 °C, TMS): δ = 0.81 (s, 3H, CH*Me*), 0.94 (s, 3H, CH*Me*), 1.90 and 2.10 (2H, dd, J = 16.0 Hz, CH_2), 2.77 and 3.08 (2H, dd, J = 16.0 Hz, CH_2), 3.70 (3H, s, OCH_3), 4.65 (s, 1H, 10-H), 6.76 – 7.13 (m, 4H, ArH), 7.70 (s, 1H, 5-NH), 9.80 (s, 1H, 1-NH), 10.40 (s, 1H, 3-NH). – MS (EI, 70 eV): *m/z* (%) = 368.0 (22.7), 367.0 (97.3) $[M]^+$, 366.0 (25.4), 365.0 (11), 260.0 (100) $[M - 4\text{-}CH_3OC_6H_4]^+$. – Anal. for $C_{20}H_{21}N_3O_4$: calcd. C 65.38, H 5.76, N 11.44; found C 65.47 H 5.87, N 11.48.

*7,7-Dimethyl-10-(4-(dimethylamino)phenyl)-6,7,8,10-tetrahydropyrimido[5,4-b]quinoline-2,4,9(1H,3H,5H)-trione (**6f**)*

Pale brown crystals, m. p. 280 – 282 °C. – IR (film): ν = 3245, 3127, 3081, 2954, 2929, 1732, 1666 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 0.88 (s, 3H, CH*Me*), 0.98 (s, 3H, CH*Me*), 1.90 and 2.15 (dd, 2H, J = 16.0 Hz, CH_2), 2.84 and 3.01 (dd, 2H, J = 16.0 Hz, CH_2), 3.32 (s, 6H, 2 CH_3), 4.63 (s, 1H, 10-H), 6.73 (d, 2H, J = 8.2 Hz, ArH), 7.38 (s, 1H, 5-NH), 7.60 (d, 2H, J = 8.2 Hz, ArH), 8.03 (s, 1H, 1-NH), 11.2 (s, 1H, 3-NH). – MS (EI, 70 eV): *m/z* (%) = 382.0 (20.1), 381.0 (23.3), 380.0 (100) $[M]^+$, 379.0 (1.1), 260.0 (37.8) $[M - 4\text{-}(CH_3)_2NC_6H_4)]^+$. – Anal. for $C_{21}H_{24}N_4O_3$: calcd. C 66.30, H 6.36, N 14.73; found C 66.38, H 6.43 N 14.79.

*An alternative synthesis of **6a, b, e***

A mixture of **1** (1 mmol) and **4a**, **b**, **e** (1 mmol) was placed in an open Pyrex-glass vessel and irradiated in a domestic microwave oven with 600 W power for 50 – 90 s 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 ethanol (yield **6a**: 92 %, **6b**: 94 %, **6e**: 91 %).

*Synthesis of Schiff base **8a, b***

Method A: A mixture of **1** (2 mmol) and **2b**, **d** (2 mmol) was placed in an open Pyrex-glass vessel and irradiated in a domestic microwave oven with 600 W power for 60 – 70 s 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 and crystallized from DMF.

Method B: A solution of **1** (2 mmol) and **2b**, **d** (2 mmol) in DMF (3 mL) was refluxed for 2 h. The mixture was cooled to r. t., the precipitate was filtered off and recrystallized from DMF.

*(E)-5-(4-Chlorobenzylideneamino)pyrimidine-2,4(1H,3H)-dione (**8a**)*

Pale yellow crystals [yield 85 % (method A), 78 % (method B)], m. p. 345 – 346 °C. – IR (film): ν = 3202, 3140, 3071, 2817, 1725, 1669 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 7.50 – 7.53 (m, 2H, Ar-H), 7.61 (s, 1H, CH), 7.80 – 7.83 (m, 2H, Ar-H), 9.37 (s, 1H, N=CH), 11.34 (brs, 2H, 2NH). – Anal. for $C_{11}H_8ClN_3O_2$: calcd. C 52.92, H 3.23, N 16.83; found C 52.84, H 3.27, N 16.75.

*(E)-5-(2,4-Dichlorobenzylideneamino)pyrimidine-2,4 (1H, 3H)-dione (**8b**)*

Pale brown crystals [yield 92 % (method A), 83 % (method B)], m. p. 312 – 315 °C. – IR (film): ν = 3208, 3130, 3062, 2960, 1710, 1671 cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 7.66 – 7.73 (m, 3H, Ar-H), 7.99 (s, 1H, CH), 9.40 (s, 1H, N=CH), 11.34 (brs, 2H, 2NH). – Anal. for $C_{11}H_7Cl_2N_3O_2$: calcd. C 46.50, H 2.48, N 14.79; found C 46.42, H 2.55, N 14.88.

*Alternative synthesis of **6b, d***

Method A: A mixture of **3** (1 mmol) and Schiff base **8a**, **b** (1 mmol) was placed in an open Pyrex-glass vessel and irradiated in a domestic microwave oven with 600 W power for 120 s 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 ethanol (yield **6b**: 85 %, **6d**: 91 %).

Method B: A mixture of **3** (1 mmol) and Schiff base **8a**, **b** (1 mmol) in 3 mL of DMF was refluxed for 3 h. Products **6b**, **d** were isolated as described above; yield 75 and 81 %, respectively.

*Synthesis of 5-(5,5-dimethyl-3-oxo-cyclohex-1-enylamino)-1H-pyrimidine-2,4-dione (**10**)*

Method A: A mixture of **1** (2 mmol) and **3** (2 mmol) was placed into a open Pyrex-glass vessel and irradiated in a domestic microwave oven with 600 W power for 240 s (TLC control) 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 and crystallized from DMF.

Method B: A mixture of **1** (1 mmol) and **3** (1 mmol) in 5 mL of DMF was refluxed for 50 – 60 h. Product **10** was isolated as described above. Pale-yellow crystals [yield 84 % (method A), 76 % (method B)], m. p. 344 – 345 °C. – IR (film): ν = 3217, 3127, 3063, 2953.93, 2932, 1712, 1679 cm^{-1}. – ^1H NMR (400 MHz, [D_6]DMSO, 25 °C, TMS): δ = 0.99 (s, 6H, 2*Me*), 1.98 (s, 2H, CH_2), 2.26 (s, 2H, CH_2), 4.82 (s, 1H, dimedone), 7.42 (s, 1H, CH uracil), 7.80 (s, 1H, NH), 10.84 (s, 1H, NH), 11.25 (s, 1H, NH). – ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 28.41, 33.02, 41.88, 50.37, 97.18, 112.43, 139.98, 151.42, 162.08, 163.74, 197.09. – MS (EI, 70 eV): *m/z* (%) = 249.15 (29) $[M]^+$, 248.07 (100). – Anal. for $C_{12}H_{15}N_3O_3$: calcd. C 57.82, H 6.07, N 16.86; found C 57.91, H 6.16, N 16.81.

*Alternative synthesis of **6a, b***

A mixture of 1 mmol of **10** and 1 mmol of **2a**, **b** in 5 mL of DMF was refluxed for 45 – 50 h. Products **6a**, **b** were isolated as described above; yield 68 and 71 %, respectively.

*Synthesis of 10-aryl-7,7-dimethyl-7,8-dihydro-pyrimido[5,4-b]quinoline-2,4,9(1H,3H,6H)-triones **11a, b***

A solution of 2 mmol of **6a**, **d** in 10 mL of DMF was refluxed for 90 – 120 h. The solvent was evaporated under vacuum, and the product obtained was recrystallized from acetone.

*7,7-Dimethyl-10-phenyl-7,8-dihydro-pyrimido[5,4-b]-quinoline-2,4,9(1H,3H,6H)-trione (**11a**)*

Brown crystals, (yield 84 %), m. p. 240 – 243 °C. – IR (film): ν = 3179, 3071, 2957, 2928, 1725, 1687 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.12 (s, 6H, 2 CH_3), 2.53 (s, 2H, CH_2), 3.25 (s, 2H, CH_2), 7.13 – 7.56 (m, 5H, ArH), 9.28 (brs, 2H, 2NH). – Anal. for $C_{19}H_{17}N_3O_3$: calcd. C 68.05, H 5.11, N 12.53; found C 68.14, H 5.21, N 12.44.

*10-(2,4-Dichlorophenyl)-7,7-dimethyl-7,8-dihydro-pyrimido[5,4-b]quinoline-2,4,9(1H,3H,6H)-trione (**11b**)*

Dark-brown crystals (yield 93 %), m. p. 286 – 288 °C. – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.12 (s, 6H, 2*Me*), 2.54 (s, 2H, CH_2), 3.36 (s, 2H, CH_2), 7.00 (d, 1H, *J* = 8.2 Hz, ArH), 7.54 (d, 1H, *J* = 8.2 Hz, ArH), 7.82 (s, 1H, ArH), 9.50 (brs, 2H, 2NH). – Anal. for $C_{19}H_{15}Cl_2N_3O_3$: calcd. C 56.45, H 3.74, N 10.39; found C 56.53, H 3.66, N 10.42.

*Synthesis of 10-aryl-1,3-diethyl-7,7-dimethyl-6,7,8,10-tetrahydropyrimido[5,4-b]-quinoline-2,4,9(1H,3H,5H)-triones **12a, b***

Ethyl iodide (3 mmol) was added to a mixture of **6a**, **d** (1 mmol) and anhydrous potassium carbonate (3 mmol) in DMF (5 mL). The reaction mixture was stirred for 30 – 36 h at r. t. and then poured into cold water. After stirring for 15 min, the precipitated product was collected by filtration, washed with water, dried and crystallized from acetone/*n*-hexane.

*1,3-Diethyl-7,7-dimethyl-10-phenyl-6,7,8,10-tetrahydro-pyrimido[5,4-b]quinoline-2,4,9(1H,3H,5H)-trione (**12a**)*

Pale-brown crystals (yield 85 %), m. p. 205 – 206 °C. – IR (film): ν = 3124, 3065, 3026, 2953, 2933, 1699, 1644 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 (s, 3H, CH*Me*), 1.04 (s, 3H, CH*Me*), 1.08 (t, 3H, *J* = 7 Hz, CH*Me*), 1.27 (t, 3H, *J* = 7 Hz, CH*Me*), 2.18 (m, 2H, CH_2), 2.39 (s, 2H, CH_2), 3.80 (q, 2H, *J* = 7 Hz, CH_2), 4.06 (q, 2H, *J* = 7 Hz, CH_2), 5.30 (s, 1H, 10-H), 7.17 – 7.34 (m, 6H, ArH + NH). – MS (EI, 70 eV): *m/z* (%) = 395.0 (5.7), 394.0 (23.4), 393.0 (21) $[M]^+$, 316.0 (100) $[M - C_6H_5]^+$. – Anal. for $C_{23}H_{27}N_3O_3$: calcd. C 70.21, H 6.92, N 10.68; found C 70.28, H 7.11, N 10.61.

*10-(2,4-Dichloropheny)l-1,3-diethyl-7,7-dimethyl-6,7,8,10-tetrahydro-pyrimido[5,4-b]quinoline-2,4,9(1H,3H,5H)-trione (**12b**)*

Brown crystals (yield 92 %), m. p. 215 – 218 °C. – IR (film): ν = 3104, 3036, 2960, 2930, 1701, 1656 cm^{-1}. – 1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (s, 3H, CH*Me*), 1.08 (s, 3H, CH*Me*), 1.12 (t, 3H, *J* = 7 Hz, CH*Me*), 1.28 (t, 3H, *J* = 7 Hz, CH_3), 2.20 (m, 2H, CH_2), 2.39 (s, 2H, CH_2), 3.56 (q, 2H, *J* = 7 Hz, CH_2), 4.08 (q, 2H, *J* = 7 Hz, CH_2), 5.28 (s, 1H, 10-H), 7.20 – 7.40 (m, 4H, ArH + NH). – MS (EI, 70 eV): *m/z* (%) = 465.0 (2), 464.0 (9.4), 463.0 (10.4), 462.0 (5.9), 461.0 (12.6) $[M]^+$, 316.0 (100) $[M - 2,4\text{-}Cl_2C_6H_3]^+$. – Anal. for $C_{23}H_{25}Cl_2N_3O_3$: calcd. C 59.75, H 5.45, N 9.09; found C 59.70 H 5.36 N 9.17.

*General procedure for the synthesis of 10-aryl-1,3-diethyl-7,7-dimethyl-7,8-dihydropyrimido[5,4-b] quinoline-2,4,9(1H,3H,6H)-triones **13a, b***

Method A: Ethyl iodide (3 mmol) was added to a mixture of **11a**, **b** (1 mmol) and anhydrous potassium carbonate (3 mmol) in DMF (5 mL). The reaction mixture was worked up analogously to the procedure for the synthesis of **12**, and the product **13** was isolated and recrystallized from acetone/*n*-hexane.

Method B: A solution of 2 mmol of **12a**, **b** in DMF (10 mL) was refluxed for 72 – 90 h. The reaction mixture was worked up analogously to the procedure for the synthesis of

11, and the product **13** was isolated and recrystallized from acetone/*n*-hexane.

*1,3-Diethyl-7,7-dimethyl-10-phenyl-7,8-dihydro-pyrimido-[5,4-b]quinoline-2,4,9(1H,3H,6H)-trione (**13a**)*

Brown crystals, [yield 82 % (method A), 88 % (method B)], m. p. 193 – 195 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (s, 6H, 2 *Me*), 1.41 – 1.60 (m, 6H, 2 *Me*), 2.50 (s, 2H, CH_2), 3.20 (s, 2H, CH_2), 3.48 (q, 2H, J = 7 Hz, CH_2), 4.17 (q, 2H, J = 7 Hz, CH_2), 7.20 – 7.50 (m, 5H, ArH). – Anal. for $C_{23}H_{25}N_3O_3$: calcd. C 70.57, H 6.44, N 10.73; found C 70.51, H 6.51, N 10.67.

*10-(2,4-Dichlorophenyl)-1,3-diethyl-7,7-dimethyl-7,8-dihydropyrimido[5,4-b]quinoline-2,4,9(1H,3H,6H)-trione (**13b**)*

Brown crystals, [yield 91 % (method A), 95 % (method B)], m. p. 202 – 204 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (s, 6H, 2*Me*), 1.42 – 1.59 (m, 6H, 2*Me*), 2.45 (m, 2H, CH_2), 3.15 (s, 2H, CH_2), 3.68 (q, 2H, J = 7 Hz, CH_2), 4.29 (q, 2H, J = 7 Hz, CH_2), 7.18 – 7.48 (m, 3H, ArH). – Anal. for $C_{23}H_{23}Cl_2N_3O_3$: calcd. C 60.01, H 5.04, N 9.13; found C 60.07, H 5.10 N 9.21.

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