Synthesis of New Dihydropyrimido[4,5-*b*]quinolinetrione Derivatives Using a Four-Component Coupling Reaction

A. Khalafi-Nezhad,* F. Panahi*

Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran
Fax +98(711)2280926; E-mail: khalafi@chem.susc.ac.ir

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Abstract: A convenient and one-pot method for the efficient synthesis of the novel 8,9-dihydro-8,8-dimethyl-5,10-diphenylpyrimido[4,5-*b*]quinoline-2,4,6(1*H*,3*H*,5*H*,7*H*,10*H*)-trione derivatives via a four-component condensation reaction of aldehydes, amines, dimedone, and barbituric acid in the presence of tungestophosphoric acid ($H_3PW_{12}O_{40}$) as catalyst is described. This new approach proceeded smoothly in good to excellent yields and the pure products are separated from the reaction mixture by simple filtration.

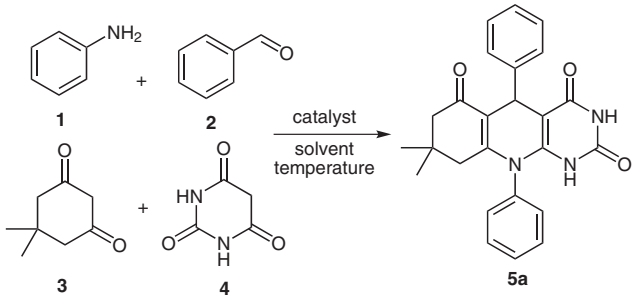
Key words: multicomponent reaction, pyrimidine, dihydropyridine, barbituric acid, dimedone

Multicomponent reactions (MCRs) are an attractive synthetic strategy, because complex products are formed in a single step and diversity can be simply achieved by varying the reaction components.[1] Furthermore, multiple molecular scaffolds in both biologically active and natural compounds can be generated using combinatorial approaches.[2] In the field of medicinal chemistry, functionally substituted starting materials have been used in multicomponent approaches to obtain desired biologically active compounds.

Pyrimidine derivatives and their analogues have attracted great interest for their biological activity and applications in medicine and therapeutics such as chemotherapy of cancer, and against human immunodeficiency virus (HIV) infection, and other viral diseases.[3] A large number of barbituric acid derivatives have been widely used as drugs for treatment of cancer and osteoporosis. Also, there is widespread interest on barbituric acid derivatives due to their previous medical utilization.[4] On the other hand, dihydropyridine derivatives are particularly well known in pharmacology as L-type calcium channel blockers.[5]

In this paper, condensation reactions of amines, aldehydes, and dimedone (5,5-dimethylcyclohexane-1,3-dione) with barbituric acid [pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione] allow a broad access to new derivatives of dihydropyrimido[4,5-*b*]quinolinetrione. As a result, we set out to obtain appropriate condition for this reaction using aniline (**1**), benzaldehyde (**2**), dimedone (**3**) and barbituric acid (**4**) as a simple model substrate (Table 1).

Table 1 Optimization of Four-Component Reaction between Barbituric Acid, Benzaldehyde, Dimedone, and Aniline[a]



Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	none	EtOH	80	24	15
2	$H_3PMo_{12}O_{40}$	EtOH	80	5	82
3	$H_3PW_{12}O_{40}$	EtOH	80	5	95
4	$H_3PW_{12}O_{40}$	EtOH	80	5	91[c]
5	$H_3PW_{12}O_{40}$	EtOH	80	24	63[d]
6	$H_3PW_{12}O_{40}$	MeCN	80	5	55
7	$H_3PW_{12}O_{40}$	DMSO	100	5	75
8	$H_3PW_{12}O_{40}$	none	80	5	70
9	$H_3PW_{12}O_{40}$	toluene	100	5	32
10	$H_3PW_{12}O_{40}$	H_2O	100	12	57
11	PTSA	EtOH	80	5	81
12	PTSA	H_2O	100	12	trace
13	$AlCl_3$	EtOH	80	12	35

[a] Amount of materials in all reactions: barbituric acid (1 mmol), benzaldehyde (1 mmol), dimedone (1 mmol), aniline (1 mmol), and catalyst: heteropoly acid (HPA) (2 mol%), or *p*-toluenesulfonic acid (PTSA, 0.1 g, 58 mol%), or $AlCl_3$ (0.04 g, 30 mol%).
[b] Isolated yield.
[c] Amount of catalyst used: 0.05 g (2.5 mol%).
[d] Amount of catalyst used: 0.03 g (1.5 mol%).

In our initial selection, the reaction was accomplished without any catalyst in ethanol, where the product was obtained in 15% isolated yield (Table 1, entry 1). The yield of the product was improved to 82% when 0.04 g (2 mol%) of molybdatophosphoric acid ($H_3PMo_{12}O_{40}$)[6] was added to the reaction media (Table 1, entry 2). It was seen that the yield of desired product increased to 95%, when

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$H_3PW_{12}O_{40}$[7] (0.04 g, 2 mol%) was used as catalyst (Table 1, entry 3). Similar results were obtained by increasing the amount of catalyst (2.5 mol%) (Table 1, entry 4). As a result of decreasing the amount of catalyst (1.5 mol%), both reaction time and yield of product were changed (Table 1, entry 5). The reaction was then examined in different types of solvent, and the results show that in polar solvents such as ethanol an excellent yield of product was obtained (Table 1, entries 2, 3, 4, and 11). As shown in Table 1, in solvent-free condition a remarkable amount of product was produced (Table 1, entry 8). During optimization studies, for the purpose of comparison, *p*-toluenesulfonic acid[8] and aluminum trichloride ($AlCl_3$)[9] were applied under the same reaction conditions. The *p*-toluenesulfonic acid showed a significant reactivity for this reaction in ethanol (Table 1, entry 11). A low isolated yield of 35% for the corresponding product was obtained when $AlCl_3$ was used as catalyst.

Thus, $H_3PW_{12}O_{40}$ was selected as the catalyst for condensation coupling reaction between amines, aldehydes, dimedone, and barbituric acid (or 2-thiobarbituric acid). All reactions were carried out under aerobic conditions at 80 °C in ethanol (Table 2). To determine the scope of the designed protocol, a number of commercially available aldehydes and amines were condensed with dimedone and barbituric acid under optimized reaction conditions, and the results are summarized in Table 2. As shown in Table 2, both electron-deficient and electron-rich aromatic aldehydes were applicable to the reaction, affording the products in excellent yields. In addition, the existence of electron-donating groups on aromatic amines decreased the reaction times and also increased the yield of products.

Table 2 Products of Four-Component Coupling Reaction[a]

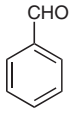
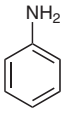
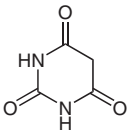
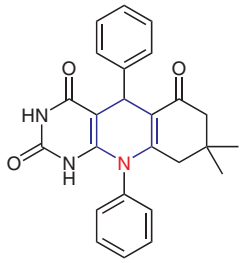
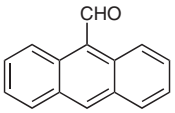
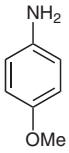
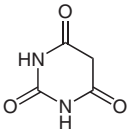
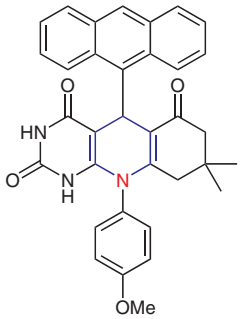
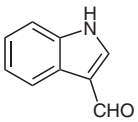
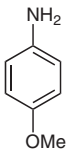
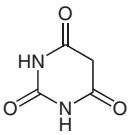
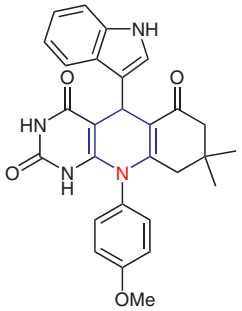
Entry	Aldehyde	Amine	Barbituric acid	Product	Time (h)	Yield (%)[b]
1				 **5a**	5	91
2				 **5b**	5	92
3				 **5c**	6	95

Table 2 Products of Four-Component Coupling Reaction[a] (continued)

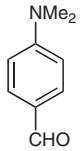
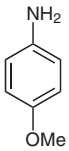
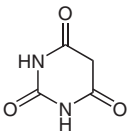
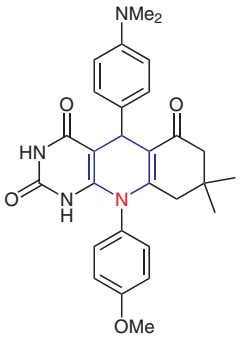
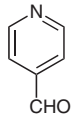
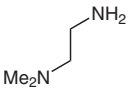
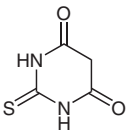
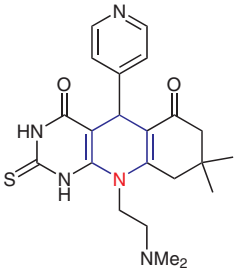
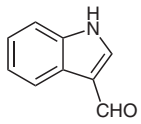
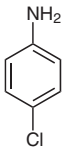
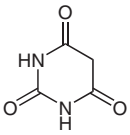
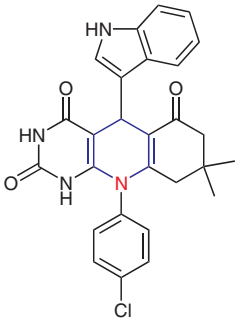
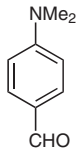
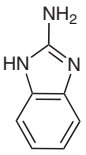
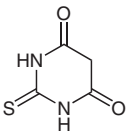
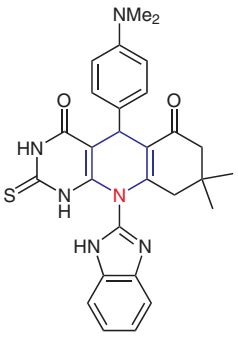
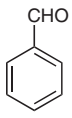
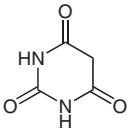
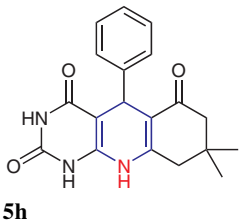
Entry	Aldehyde	Amine	Barbituric acid	Product	Time (h)	Yield (%)[b]
4				 **5d**	5	90
5				 **5e**	7	87
6				 **5f**	8	92
7				 **5g**	8	85
8		NH_4OAc		 **5h**	3	85[c]

Table 2 Products of Four-Component Coupling Reaction[a] (continued)

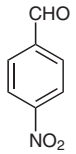
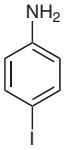
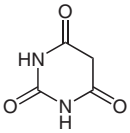
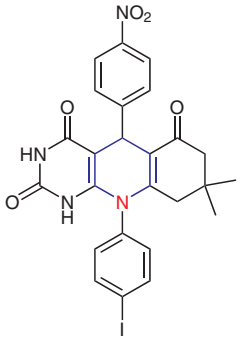
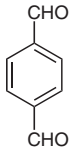
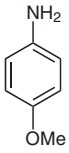
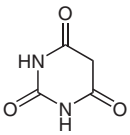
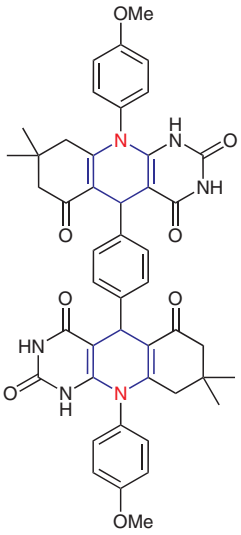
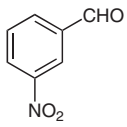
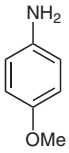
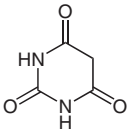
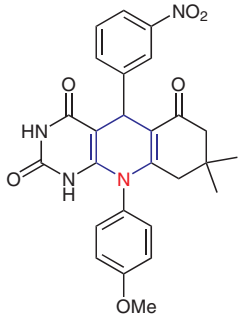
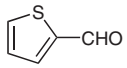
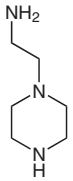
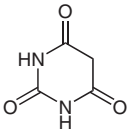
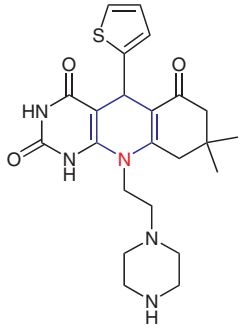
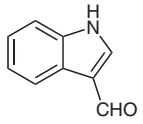
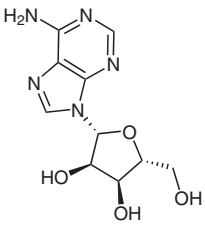
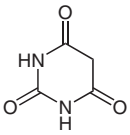
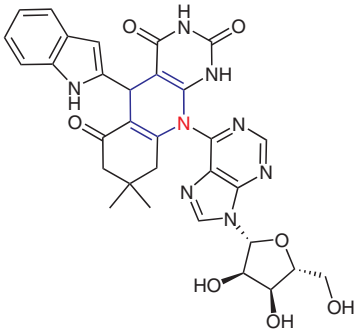
Entry	Aldehyde	Amine	Barbituric acid	Product	Time (h)	Yield (%)[b]
9				 **5i**	6	89
10				 **5j**	10	85
11				 **5k**	5	93
12				 **5l**	6	95

Table 2 Products of Four-Component Coupling Reaction[a] (continued)

Entry	Aldehyde	Amine	Barbituric acid	Product	Time (h)	Yield (%)[b]
13				 **5m**	24	73[d]

[a] The four-component coupling reaction was carried out between barbituric acid (or 2-thiobarbituric acid), aldehydes, dimedone, and amines in the presence of $H_3PW_{12}O_{40}$ as catalyst in refluxing EtOH.
[b] Isolated yield.
[c] Amount of NH_4OAc used: 3 equiv.
[d] At 50 °C.

The different heterocyclic aldehydes and amines were successfully employed to produce the different heterocyclic substituted dihydropyrimido[4,5-*b*]quinolinetrione products (Table 2, entries 3, 5, 6, 7, 12, and 13). The functional group compatibility of this reaction was highlighted using amines attached to desired functional groups by spacer (Table 2, entries 5 and 12). A further extension of this new multicomponent coupling sequence is the preparation of 2-thioxotetrahydropyrimido[4,5-*b*]quinoline-4,6-dione derivatives (Table 2, entries 5 and 7). Also, the practical synthetic efficiency of this reaction was highlighted by the reaction of terephthaldehyde with dimedone, 4-methoxyaniline, and barbituric acid to give structurally complex dihydropyrimido[4,5-*b*]quinolinetrione derivative (Table 2, entry10).

Interestingly, the structural diversity of this process was further increased using adenosine[10] as the amine component, leading to the formation of new nucleobase derivatives (Table 2, entry 13). Since these compounds may possess biological activity, our convenient procedure for synthesize of this new class of nucleobase compounds may have clinical significance. Another important feature

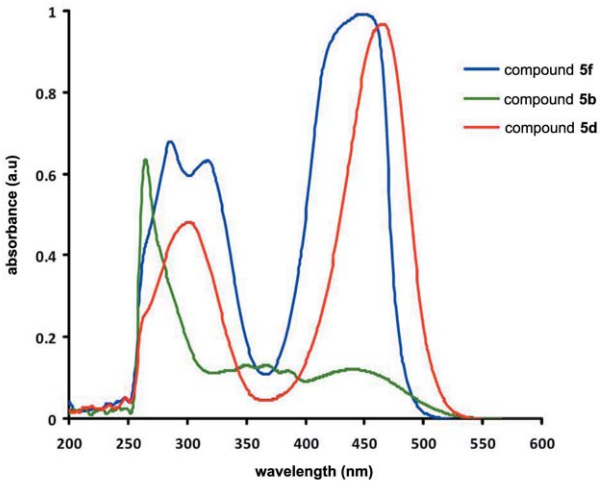
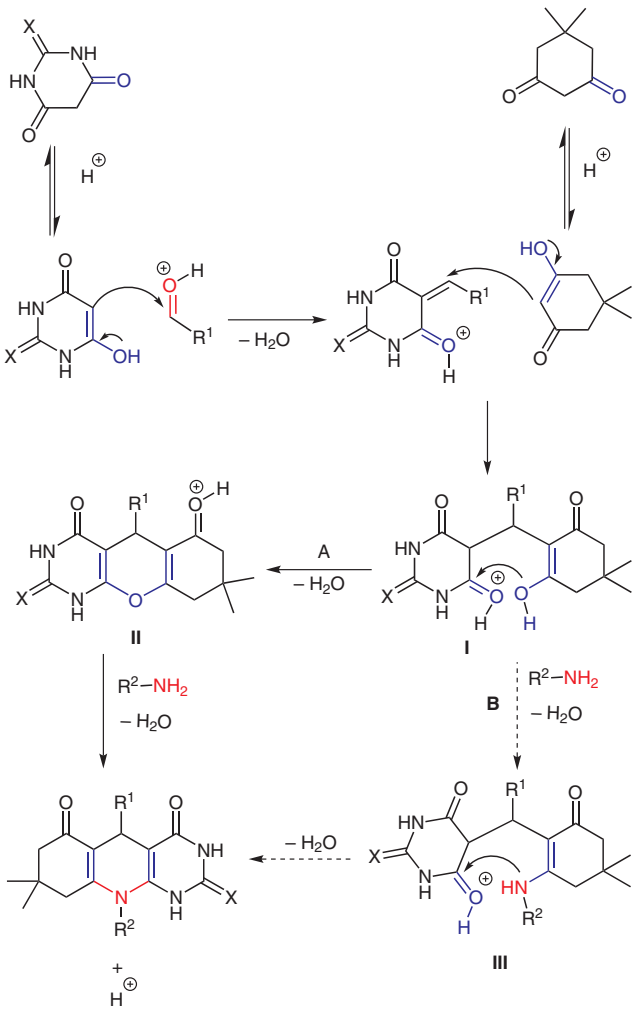


Figure 1 Normalized UV-Vis absorption of compounds **5f**, **5b**, and **5d** in DMSO



Scheme 1

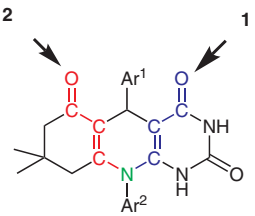


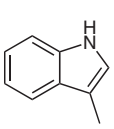
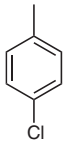
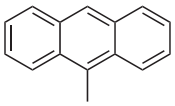
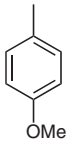
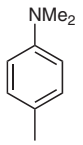
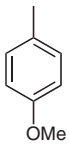
Figure 2 Allowed π–π* transitions with charge-transfer characters in the products (cf. Table 3)

of this method is the use of ammonia (ammonium acetate) as an amine component, to generate the new dihydropyridine derivative (Table 2, entry 8).

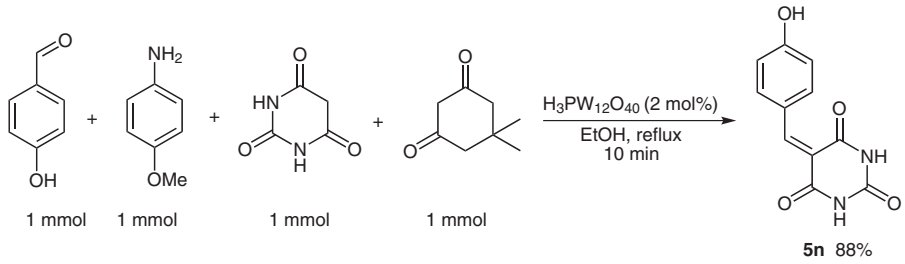
Since, barbituric acid derivatives can be used as a potentially useful fragment in the design of dyes,[11] we investigated the UV-Vis absorption spectroscopic behaviors of compounds **5f**, **5b**, and **5d** in DMSO solvent (Figure 1). The normalized absorption spectra of these materials show that in each compound there are two chromophore centers (Figure 1). Also, Figure 2 and Table 3 indicate two strongly allowed π–π* transitions with charge-transfer characters in these molecules.[11]

It seems that the intramolecular charge-transfer (ICT) of these compounds arises from the interaction between aryl rings and the chromophore fragments.[11] Thus, the bathochromic shift of the absorption in these compounds by changing the aryl ring can be explained.

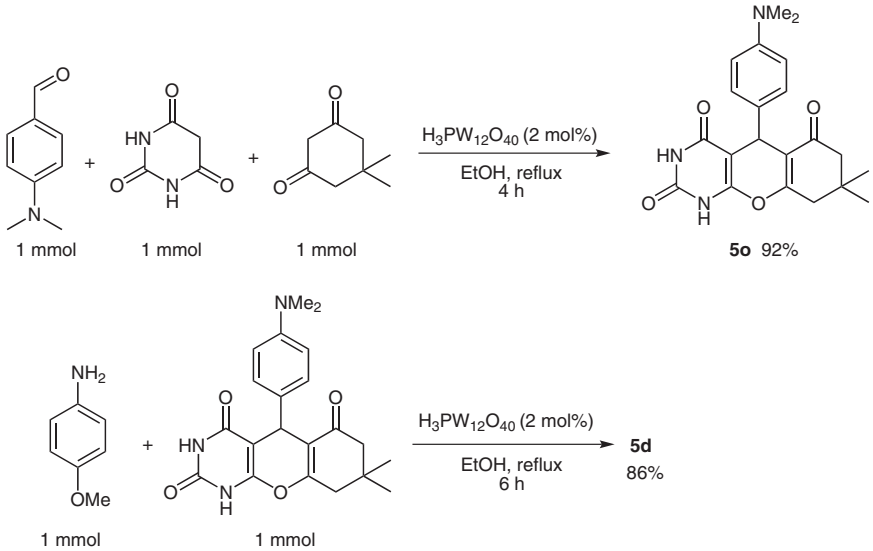
Table 3 λ_{max} Values of Compounds **5f**, **5b**, and **5d**

Product	Ar^1	Ar^2	$\lambda_{max\text{-}1}$ (nm)	$\lambda_{max\text{-}2}$ (nm)
5f			270	440
5b			305	460
5d			260	450

The reaction pathway was investigated next and the results prompted us to propose a plausible reaction pathway as shown in Scheme 1. Stopping the reaction about 10 minutes after the start leads to the formation of only Knoevenagel condensation product between barbituric acid and aldehyde[12] (compound **5n**, Scheme 2). According to this observation, it can be assumed that initially, barbituric acid reacts with aldehyde to form a Knoevenagel



Scheme 2



Scheme 3

product and then dimedone (in the enol form) adds to this adduct in a conjugate manner to produce the intermediate **I**. This intermediate can pass through two paths (**A** and **B**). It is noteworthy that both **A** and **B** routes gives the same product. As shown in Scheme 1, in the direction of **A**, the intermediate **II** is formed, which undergoes reaction with the amine present to generate the desired product.

To confirm the suggested route **A**, we examined the following reaction (Scheme 3). Thus, the chromeno[2,3-*d*]pyrimidinetrione (compound **5o**),[13] which was obtained from the three-component coupling reaction between aldehyde, dimedone, and barbituric acid, was exposed to an amine component under the reaction condition to give the dihydropyrimido[4,5-*b*]quinolinetrione (compound **5d**) in good yield (Scheme 3).

In the route **B** (dashed line, Scheme 1), initially the amine component reacts with one of the carbonyl group in the intermediate **I** to form an enamine species. This enamine participates in subsequent reaction to produce the desired product.

In conclusion, we have developed an efficient method for the synthesis of dihydropyrimido[4,5-*b*]quinolinetrione derivatives in high yields using heteropoly acid ($H_3PW_{12}O_{40}$) as catalyst in refluxing ethanol. This strategy offers a powerful tool for the preparation of a new scaffold, which has high potential for application in medicinal chemistry. Further study on this structure may lead to exploration of new drugs or biologically active compounds in future.

Chemicals were purchased from Fluka, Merck, and Aldrich Chemical Companies and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 250 MHz spectrometer in DMSO solution with TMS as an internal standard. FT-IR spectroscopy (Shimadzu FT-IR 8300 spectrophotometer) was employed for the characterization of the compounds. Melting points were determined in open capillary tubes in a Barnstead Electrothermal 9100 BZ circulating oil melting point apparatus. The reaction monitoring was accomplished by TLC on silica gel PolyGram SILG/UV254 plates.

Dihydropyrimido[4,5-*b*]quinolinetrione Derivatives; General Procedure

A mixture of 5,5-dimethylcyclohexane-1,3-dione (0.14 g, 1 mmol), barbituric acid (0.13 g, 1 mmol), aldehyde (1 mmol), amine (1 mmol), and $H_3PW_{12}O_{40}$ (0.04 g, 2 mol%) in refluxing EtOH (5 mL) was stirred for the time indicated in Table 2. After completion of the reaction as confirmed by TLC (eluent: EtOAc–*n*-hexane), the reaction mixture was cooled to r.t. The precipitate was collected by filtration and washed with H_2O (2 × 10 mL) and EtOH (5 mL) to afford the pure product (Table 2).

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

Yield: 91%; pale yellow solid; mp 230–232 °C.

IR (KBr): 3200, 1730, 1670, 1560 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ = 0.94 (s, 3 H), 1.0 (s, 3 H), 2.48–2.75 (m, 4 H), 4.34 (s, 1 H), 7.08–7.13 (m, 2 H), 7.26 (q, *J* = 2.3, 2.05 Hz, 4 H), 7.60 (t, *J* = 3.0 Hz, 2 H), 7.74 (d, *J* = 6.1 Hz, 2 H), 11.08 (s, 1 H), 11.16 (s, 1 H).

^{13}C NMR (250 MHz, DMSO-d_6/TMS): δ = 25.7, 30.2, 42.4, 49.7, 82.8, 111.9, 119.6, 122.5, 126.0, 134.0, 139.3, 151.1, 152.4, 153.8, 161.8, 184.6.

Anal. Calcd for $C_{25}H_{23}N_3O_3$ (413.47): C, 72.62; H, 5.61; N, 10.16. Found: C, 72.58; H, 5.59; N, 10.13.

5-(Anthracen-10-yl)-10-(4-methoxyphenyl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-*b*]quinoline-2,4,6(1*H*,3*H*,5*H*,7*H*,10*H*)-trione (5b)

Yield: 92%; deep red solid; mp 241–243 °C.

IR (KBr): 3210, 1735, 1670, 1570 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ = 1.00 (s, 3 H), 1.04 (s, 3 H), 2.34–2.63 (m, 4 H), 3.72 (s, 3 H), 4.86 (s, 1 H), 7.09–7.17 (m, 2 H), 7.45–7.55 (m, 5 H), 7.91 (d, *J* = 7.6 Hz, 2 H), 8.12 (t, *J* = 2.0 Hz, 2 H), 8.63 (s, 1 H), 8.79 (s, 1 H), 11.79 (s, 1 H), 11.53 (s, 1 H).

^{13}C NMR (250 MHz, DMSO-d_6/TMS): δ = 27.4, 33.3, 52.5, 84.5, 112.4, 118.4, 120.1, 125.3, 125.5, 126.2, 127.6, 127.7, 128.6, 129.4, 130.5, 150.5, 151.2, 160.5, 162.3.

Anal. Calcd for $C_{33}H_{27}N_3O_3$ (513.59): C, 77.17; H, 5.30; N, 8.18. Found: C, 77.14; H, 5.28; N, 8.15.

5-(1*H*-Indol-3-yl)-10-(4-methoxyphenyl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-*b*]quinoline-2,4,6(1*H*,3*H*,5*H*,7*H*,10*H*)-trione (5c)

Yield: 95%; yellow solid; mp 254–256 °C.

IR (KBr): 3290, 3215, 1740, 1665, 1564 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ = 1.00 (s, 3 H), 1.03 (s, 3 H), 2.31–2.48 (m, 4 H), 3.73 (s, 3 H), 5.08 (s, 1 H), 6.90–6.94 (m, 2 H), 7.06 (t, *J* = 6.5 Hz, 2 H), 7.28–7.33 (m, 2 H), 7.57 (t, *J* = 2.7 Hz, 2 H), 7.86 (t, *J* = 3.0 Hz, 1 H), 11.02 (s, 1 H), 11.10 (s, 1 H), 12.72 (s, 1 H).

^{13}C NMR (250 MHz, DMSO-d_6/TMS): δ = 27.9, 33.2, 50.1, 55.2, 95.6, 108.6, 111.3, 113.1, 114.3, 117.6, 122.6, 123.6, 125.2, 129.1, 131.6, 136.3, 139.7, 143.6, 150.3, 161.2, 163.2, 164.5, 194.8.

Anal. Calcd for $C_{28}H_{26}N_4O_4$ (482.53): C, 69.70; H, 5.43; N, 11.61. Found: C, 69.68; H, 5.39; N, 11.60.

5-[4-(Dimethylamino)phenyl]-10-(4-methoxyphenyl)-8,8-dimethyl-8,9-dihydropyrimido [4,5-*b*]quinoline-2,4,6(1*H*,3*H*,5*H*,7*H*,10*H*)-trione (5d)

Yield: 90%; orange solid; mp 265–267 °C.

IR (KBr): 3208, 1743, 1660, 1567 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ = 1.00 (s, 6 H), 2.25–2.48 (m, 4 H), 3.10 (s, 6 H), 3.68 (s, 3 H), 5.07 (s, 1 H), 6.62 (d, *J* = 5.7 Hz, 2 H), 6.77 (d, *J* = 7.9 Hz, 2 H), 6.86–6.93 (m, 2 H), 7.28 (d, *J* = 9.5 Hz, 2 H), 10.91 (s, 1 H), 11.04 (s, 1 H).

^{13}C NMR (250 MHz, DMSO-d_6/TMS): δ = 27.3, 32.2, 37.5, 52.2, 54.6, 80.2, 112.1, 114.3, 117.3, 118.3, 131.0, 132.2, 133.3, 145.1, 149.0, 150.2, 151.1, 162.1, 185.9.

Anal. Calcd for $C_{28}H_{30}N_4O_4$ (486.56): C, 69.12; H, 6.21; N, 11.51. Found: C, 69.08; H, 6.19; N, 11.49.

10-[2-(Dimethylamino)ethyl]-8,8-dimethyl-5-(pyridin-4-yl)-2-thioxo-2,3,8,9-tetrahydropyrimido[4,5-*b*]quinoline-4,6(1*H*,5*H*,7*H*,10*H*)-dione (5e)

Yield: 87%; pale yellow solid; mp 225–227 °C.

IR (KBr): 3212, 1740, 1665, 1570 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ = 1.03 (s, 6 H), 2.26 (s, 6 H), 2.40–2.60 (m, 4 H), 2.81 (t, *J* = 14.2 Hz, 2 H), 3.75 (d, *J* = 4.7 Hz, 2 H), 4.48 (s, 1 H), 7.47 (d, *J* = 5.5 Hz, 2 H), 8.69 (d, *J* = 6.0 Hz, 2 H), 9.79 (s, 1 H), 10.30 (s, 1 H).

^{13}C NMR (250 MHz, DMSO-d_6/TMS): δ = 27.3, 32.0, 40.0, 42.1, 48.1 52.9, 57.6, 80.2, 109.9, 126.8, 145.1, 150.2, 152.1, 161.1, 163.2, 168.9, 169.9, 194.3.

Anal. Calcd for $C_{22}H_{27}N_5O_2S$ (425.55): C, 62.09; H, 6.40; N, 16.46. Found: C, 62.06; H, 6.38; N, 16.45.

10-(4-Chlorophenyl)-5-(1*H*-indol-3-yl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-*b*]quinoline-2,4,6(1*H*,3*H*,5*H*,7*H*,10*H*)-trione (5f)
Yield: 92%; yellow color; mp 275–277 °C.

IR (KBr): 3290, 3220, 1742, 1660, 1560 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ = 1.00 (s, 6 H), 2.35–2.50 (m, 4 H), 5.30 (s, 1 H), 7.17 (d, *J* = 8.8 Hz, 2 H), 7.31–7.41 (m, 3 H), 7.57–7.61 (m, 2 H), 7.87–7.90 (m, 2 H), 12.18 (s, 1 H), 12.22 (s, 1 H), 12.92 (s, 1 H).

^{13}C NMR (250 MHz, DMSO-d_6/TMS): δ = 27.8, 32.2, 50.0, 97.1, 108.7, 112.3, 113.3, 117.8, 123.1, 124.0, 124.2, 129.1, 136.6, 141.0, 144.5, 160.9, 162.7, 177.6.

Anal. Calcd for $C_{27}H_{23}ClN_4O_3$ (486.95): C, 66.60; H, 4.76; N, 11.51. Found: C, 66.57; H, 4.71; N, 11.47.

10-(1*H*-Benzo[*d*]imidazol-2-yl)-5-[4-(dimethylamino)phenyl]-8,8-dimethyl-2-thioxo-2,3,8,9-tetrahydropyrimido[4,5-*b*]quinoline-4,6(1*H*,5*H*,7*H*,10*H*)-dione (5g)
Yield: 85%; violet solid; mp 233–235 °C.

IR (KBr): 3300, 3217, 1751, 1655, 1557 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ = 0.93 (s, 3 H), 1.00 (s, 3 H), 2.77–2.85 (m, 4 H), 3.13 (s, 6 H), 5.87 (s, 1 H), 6.54 (t, *J* = 4.4 Hz, 2 H), 6.77 (t, *J* = 9.2 Hz, 2 H), 7.10–7.20 (m, 2 H), 7.32–7.37 (m, 2 H), 12.02 (s, 1 H), 12.12 (s, 1 H), 13.13 (s, 1 H).

^{13}C NMR (250 MHz, DMSO-d_6/TMS): δ = 27.2, 32.3, 51.1, 80.0, 104.2, 110.1, 115.0, 117.9, 121.9, 126.2, 136.1, 139.1, 141.1, 144.4, 149.9, 151.7, 162.8, 192.6.

Anal. Calcd for $C_{28}H_{28}N_6O_2S$ (512.63): C, 65.60; H, 5.51; N, 16.39. Found: C, 65.56; H, 5.48; N, 16.36.

8,8-Dimethyl-5-phenyl-8,9-dihydropyrimido[4,5-*b*]quinoline-2,4,6(1*H*,3*H*,5*H*,7*H*,10*H*)-trione (5h)
Yield: 85%; white solid; mp 210–212 °C.

IR (KBr): 3320, 3280, 1754, 1649, 1552 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ = 1.00 (s, 6 H), 2.40–2.61 (m, 4 H), 4.67 (s, 1 H), 7.26–7.33 (m, 3 H), 7.57–7.60 (m, 2 H), 10.21 (s, 1 H), 10.40 (s, 1 H), 12.01 (s, 1 H).

^{13}C NMR (250 MHz, DMSO-d_6/TMS): δ = 27.2, 31.2, 51.9, 81.2, 110.3, 126.0, 129.2, 141.8, 150.5, 180.3.

Anal. Calcd for $C_{19}H_{19}N_3O_3$ (337.37): C, 67.64; H, 5.68; N, 12.46. Found: C, 67.61; H, 5.65; N, 12.42.

10-(4-Iodophenyl)-8,8-dimethyl-5-(4-nitrophenyl)-8,9-dihydropyrimido[4,5-*b*]quinoline-2,4,6(1*H*,3*H*,5*H*,7*H*,10*H*)-trione (5i)
Yield: 89%; yellow solid; mp 281–283 °C.

IR (KBr): 3212, 3090, 1730, 1677 1565, 1522, 1335, 853 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ = 0.69 (s, 3 H), 0.87 (s, 3 H), 2.48 (m, 4 H), 5.10 (s, 1 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 7.55 (d, *J* = 8.5 Hz, 2 H), 7.76 (d, *J* = 8.2 Hz, 2 H), 8.00 (d, *J* = 7.0 Hz, 2 H), 10.21 (s, 1 H), 10.51 (s, 1 H).

^{13}C NMR (250 MHz, DMSO-d_6/TMS): δ = 30.0, 33.1, 80.1, 85.1, 109.7, 120.9, 123.4, 121.4, 138.9, 141.2, 145.2, 147.2, 150.1, 153.5, 163.1, 185.5.

Anal. Calcd for $C_{25}H_{21}IN_4O_5$ (584.36): C, 51.38; H, 3.62; N, 9.59. Found: C, 51.35; H, 3.59; N, 9.57.

1,4-Bis[10-(4-methoxyphenyl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-*b*]quinoline-2,4,6(1*H*,3*H*,5*H*,7*H*,10*H*)-trione]benzene (5j)
Yield: 85%; yellow solid; >300 °C (dec.).

IR (KBr): 3210, 1732, 1674, 1565 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ = 0.97 (s, 3 H), 1.10 (s, 3 H), 2.48 (m, 4 H), 3.77 (s, 3 H), 5.06 (s, 1 H), 7.02 (d, *J* = 3.2 Hz, 2 H), 7.36 (d, *J* = 3.2 Hz, 2 H), 7.72 (d, *J* = 10.8 Hz, 2 H), 9.50 (s, 1 H), 10.35 (s, 1 H).

^{13}C NMR (250 MHz, DMSO-d_6/TMS): δ = 27.2, 33.2, 52.5, 56.5, 81.2, 110.0, 115.3, 117.2, 126.1, 132.4, 133.6, 143.1, 150.1, 152.1, 153.7, 162.9, 192.5.

Anal. Calcd for $C_{46}H_{44}N_6O_8$ (808.88): C, 68.30; H, 5.48; N, 10.39. Found: C, 68.25; H, 5.44; N, 10.36.

10-(4-Methoxyphenyl)-8,8-dimethyl-5-(3-nitrophenyl)-8,9-dihydropyrimido[4,5-*b*]quinoline-2,4,6(1*H*,3*H*,5*H*,7*H*,10*H*)-trione (5k)
Yield: 93%; yellow color; mp 257–259 °C.

IR (KBr): 3215, 3095, 1732, 1674, 1565, 1520, 1330, 850 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ = 0.87 (s, 3 H), 1.01 (s, 3 H), 2.24–2.49 (m, 4 H), 3.71 (s, 3 H), 6.04 (s, 1 H), 6.96–7.00 (m, 2 H), 7.21–7.25 (m, 2 H), 7.49 (t, *J* = 3.9 Hz, 1 H), 7.80 (s, 1 H), 7.92 (m, 2 H), 10.19 (s, 1 H), 11.11 (s, 1 H).

^{13}C NMR (250 MHz, DMSO-d_6/TMS): δ = 27.5, 30.6, 50.1, 55.4, 90.2, 114.8, 119.8, 121.0, 123.9, 124.7, 129.0, 129.6, 133.7, 147.5, 147.7, 150.6, 158.4, 178.3, 200.9.

Anal. Calcd for $C_{26}H_{24}N_4O_6$ (488.49): C, 63.93; H, 4.95; N, 11.47. Found: C, 63.90; H, 4.91; N, 11.43.

8,8-Dimethyl-10-[2-(piperazin-1-yl)ethyl]-5-(thiophen-2-yl)-8,9-dihydropyrimido[4,5-*b*]quinoline-2,4,6(1*H*,3*H*,5*H*,7*H*,10*H*)-trione (5l)
Yield: 95%; yellow color; mp 218–220 °C.

IR (KBr): 3332, 3204, 1731, 1676, 1568, 1235 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ = 0.94 (s, 3 H), 1.08 (s, 3 H), 1.85 (s, 1 H), 2.40–2.55 (m, 4 H), 2.85–2.89 (m, 4 H), 3.15–3.23 (m, 6 H), 3.52–3.71 (m, 2 H), 4.65 (s, 1 H), 7.27 (q, *J* = 12.2, 2.9 Hz, 1 H), 7.32 (d, *J* = 1.6 Hz, 1 H) 7.55 (d, *J* = 2.1 Hz, 1 H), 9.98 (s, 1 H), 10.61 (s, 1 H).

^{13}C NMR (250 MHz, DMSO-d_6/TMS): δ = 27.1, 31.0, 33.4, 47.4, 52.1, 55.1, 84.9, 111.2, 121.4, 126.2, 140.2, 150.2, 152.6, 158.3, 162.6, 175.1.

Anal. Calcd for $C_{23}H_{29}N_5O_3S$ (455.57): C, 60.64; H, 6.42; N, 15.37. Found: C, 60.61; H, 6.38; N, 15.32.

10-{9-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-9*H*-purin-6-yl}-5-(1*H*-indol-2-yl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-*b*]quinoline-2,4,6(1*H*,3*H*,5*H*,7*H*,10*H*)-trione (5m)
Yield: 73%; yellow solid; mp 260–262 °C.

IR (KBr): 3540, 3330, 3212, 1728, 1672, 1565 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ = 0.99 (s, 3 H), 1.02 (s, 3 H), 2.45–2.49 (m, 4 H), 2.57–2.59 (m, 3 H), 4.20 (d, *J* = 1.7 Hz, 1 H), 4.41 (d, *J* = 2.3 Hz, 1 H), 4.81 (d, *J* = 2.0 Hz, 1 H), 5.62 (d, *J* = 1.9 Hz, 1 H), 6.30 (br s, 4 H), 7.31 (d, *J* = 3.2 Hz, 2 H), 7.56 (q, *J* = 3.8, 3.0 Hz, 2 H), 7.85 (t, *J* = 1.5 Hz, 1 H), 7.86 (s, 1 H), 7.88 (s, 1 H), 11.02 (s, 1 H), 11.27 (s, 1 H), 12.70 (s, 1 H).

^{13}C NMR (250 MHz, DMSO-d_6/TMS): δ = 27.7, 31.2, 53.1, 62.9, 74.0, 75.1, 82.9, 113.8, 116.6, 118.4, 122.9, 128.9, 134.3, 141.6, 145.0, 148.9, 155.6, 168.4, 169.8, 194.2.

Anal. Calcd for $C_{31}H_{30}N_8O_7$ (626.62): C, 59.42; H, 4.83; N, 17.88. Found: C, 59.40; H, 4.80; N, 17.85.

5-(4-Hydroxybenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (5n)

Yield: 88%; yellow solid; mp 188–190 °C.

IR (KBr): 3530, 3212, 1741, 1672, 1573 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6/TMS): δ = 6.86 (d, *J* = 8.8 Hz, 1 H), 8.16 (s, 2 H), 8.31 (d, *J* = 8.8 Hz, 2 H), 10.77 (s, 1 H), 11.10 (s, 1 H), 11.23 (s, 1 H).

Anal. Calcd for $C_{11}H_8N_2O_4$ (232.19): C, 56.90; H, 3.47; N, 12.06. Found: C, 56.87; H, 3.44; N, 12.04.

5-[4-(Dimethylamino)phenyl]-8,8-dimethyl-8,9-dihydro-1*H*-chromeno[2,3-*d*]pyrimidine-2,4,6(3*H*,5*H*,7*H*)-trione (5o)

Yield: 92%; orange solid; mp 192–194 °C.

IR (KBr): 3234, 1745, 1675, 1580 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6/TMS): δ = 0.87 (s, 3 H), 1.01 (s, 3 H), 2.02–2.09 (m, 4 H), 2.48 (s, 6 H), 4.47 (s, 1 H), 7.51 (d, *J* = 8.5 Hz, 2 H), 8.06 (d, *J* = 8.6 Hz, 2 H), 11.25 (s, 1 H), 11.39 (s, 1 H).

Anal. Calcd for $C_{21}H_{23}N_3O_4$ (381.43): C, 66.13; H, 6.08; N, 11.02. Found: C, 66.15; H, 6.12; N, 11.05.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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