A simple and convenient approach to the synthesis of aminofuropyrimidindiones

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The one-pot three-component reactions of 1,3-dimethylbarbituric acid, aromatic aldehydes and alkyl or aryl isocyanides proceed smoothly at room temperature to give the corresponding 5-aryl-6-alkyl or arylamino-1,3-dimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives in good to excellent yields within 30 minutes in DMF. This three-component reaction represents a facile and efficient route to the described biologically interesting molecules.

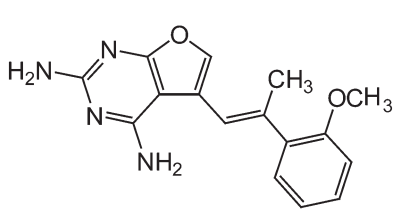
Keywords: *N,N*-dimethylformamide, fused furans, isocyanide, multicomponent reaction

Compounds containing a fused pyrimidine ring represent a broad class of compounds, which have received considerable attention due to their wide range of biological activities.[1] Hetero-fused pyrimidines are known to exhibit promising antiviral,[2] antibacterial,[3] anti-AIDS,[4] and antinociceptive[5] activities. Among them, the furo[2,3-*d*]pyrimidines are an important class of annulated uracils with biological significance because of their connection with purine systems.[6–10] They have numerous pharmacological and agrochemical applications such as Akt1 kinase inhibitors,[6] antifolates,[7] and antivirus,[8] as well as potential radiation protection agents.[9] For example, Gangjee and co-workers reported the synthesis of a series of 2,4-diaminofuro[2,3-*d*]pyrimidines as multireceptor tyrosine kinase and dihydrofolate reductase inhibitors (Scheme 1).[7,10] To optimise dual receptor tyrosine kinase (RTK) and dihydrofolate reductase (DHFR) inhibition, the *E* and *Z*-isomers of 5-[2-(2-methoxyphenyl)prop-1-en-1-yl] furo[2,3-*d*]pyrimidine-2,4-diamines (**A** and **B**) were separated by HPLC and the X-ray crystal structures with mouse DHFR and NADPH as well as **1b** with human DHFR were determined.[10] Also, some furopyrimidines were shown to be potent VEGFR2 (vascular endothelial growth factor receptor **2**) and EGFR (epidermal growth factor receptor) inhibitors.[11] A survey of the literature revealed that furopyrimidines have been the object of intense investigations in organic synthesis and medicinal chemistry and several approaches have been reported for the synthesis of these heterocyclic compounds.[11–16] However, many of the synthetic protocols reported so far suffer from several limitations, such as relying on multistep reactions,[11] needing anhydrous conditions,[12] prolonged reaction times,[12,13] harsh reaction conditions,[13] low yields,[14] use of metal-containing reagents[15] and special instruments.[16] Due to the biological significance of furopyrimidine derivatives, the development of new, facile and efficient alternative methods for the preparation of them is still strongly desirable.

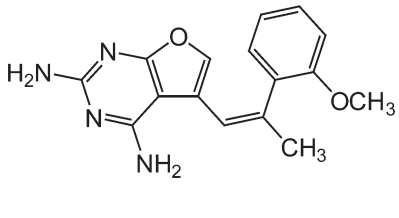
In our earlier publications,[17–19] we described three routes to fused furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones. These compounds were obtained by treatment of 1,3-dimethylbarbituric acid with substituted benzaldehydes and isocyanides in hot water[17] or in the presence of montmorillonite K10 using microwave irradiation under solvent-free conditions[18] or in 1-butyl-3-methylimidazolium bromide as an ionic liquid.[19] Based on the above-mentioned three-component reaction, more efforts were made to investigate the reactions of unsubstituted barbituric acid. In 2007, some unexpected results were obtained when barbituric acid was used.[20] The condensation reactions between alkyl isocyanide, substituted benzaldehydes and barbituric acid were performed in water/acetonitrile (1:1) under reflux conditions to give *N*-alkyl-*N*-[aryl-(2,4,6-trioxohexahydropyrimidin-5-yl)methyl]formamides in 3 h.

To the best of our knowledge, there has been only one report on the synthesis of 1,4-bis(furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione-5-yl)benzene derivatives via the reaction of isocyanides, 1,3-dimethylbarbituric acid, and terephthaldialdehyde in DMF.[21] We now report the synthesis of a library based on the scaffold of aminofuropyrimidindione.[21] The reaction of aromatic aldehydes **1** with 1,3-dimethylbarbituric acid **2** in the presence of alkyl or aryl isocyanides **3** proceeds with a smooth reaction in a small amount of *N,N*-dimethylformamide at ambient temperature, to produce 5-aryl-6-alkyl or arylamino-1,3-dimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **4** in high yields (71–95%) within 30 min (Scheme 2). ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of these aminofuropyrimidindione **4**. All the products were characterised by FT-IR, ^{1}H and ^{13}C NMR spectra, and elemental analysis. The results are summarised in Table 1.

The ^{1}H NMR spectrum of **4a** exhibited six single sharp line readily recognised as arising from *tert*-butyl (δ_H 1.01 ppm), geminal methyl groups (δ_H 1.19 ppm), methylene protons (δ_H 1.54 ppm), two NCH_3 groups (δ_H 3.38 and 3.57 ppm) and



A (*E*-isomer)



B (*Z*-isomer)

Scheme 1

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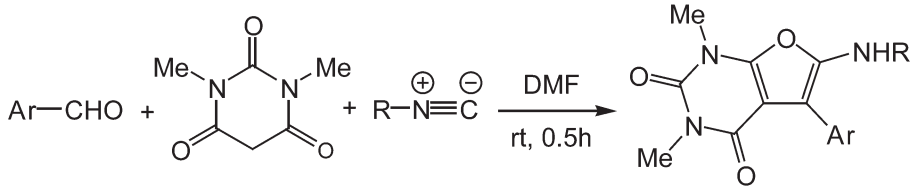

Scheme 2

Table 1 Synthesis of aminofuropyrimidindione derivatives **4a–q** in DMF

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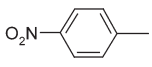
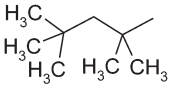
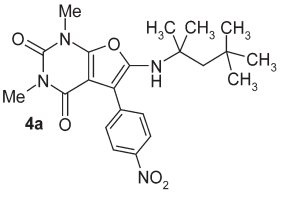
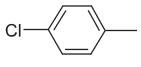
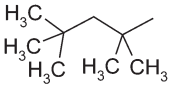
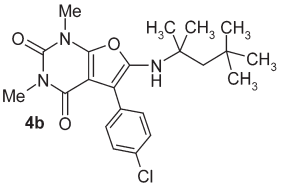
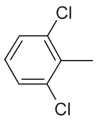
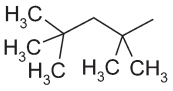
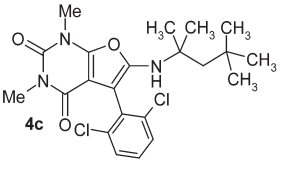
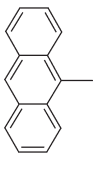
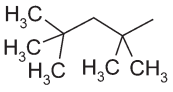
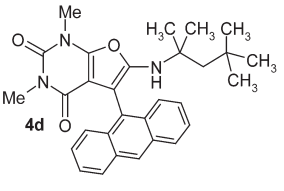
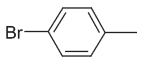
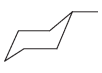
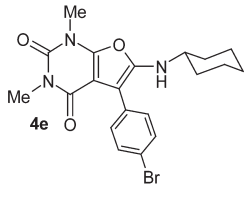
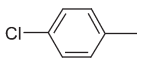
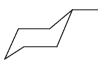
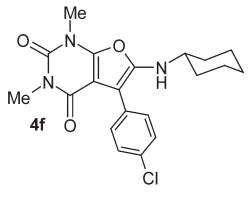
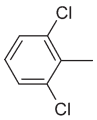
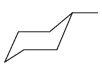
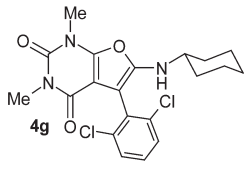
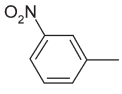
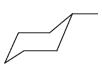
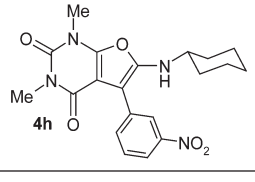
1				91
2				76
3				80
4				71
5				82
6				83
7				74
8				87

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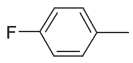
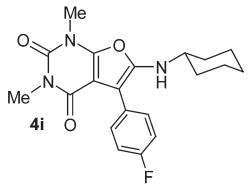
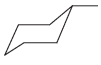
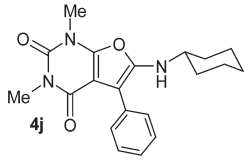
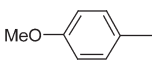
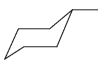
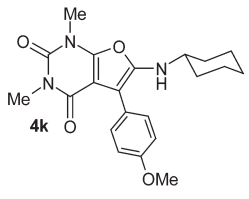
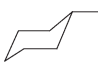
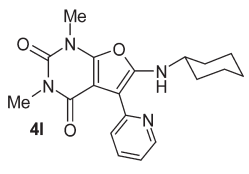
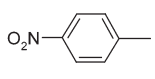
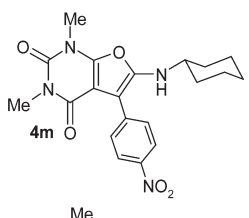
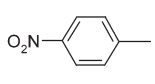
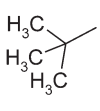
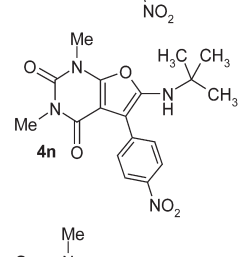
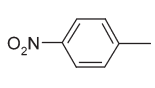
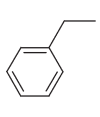
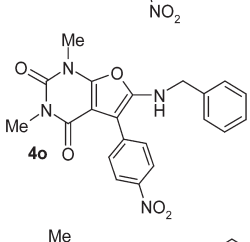
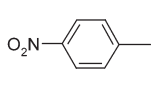
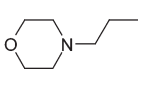
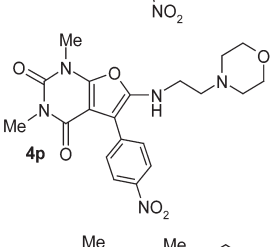
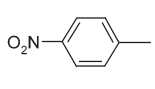
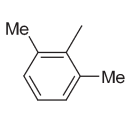
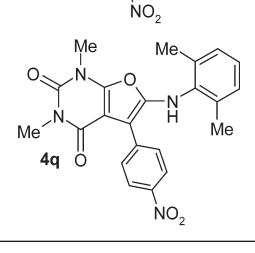
9			 **4i**	90
10			 **4j**	86
11			 **4k**	82
12			 **4l**	90
13			 **4m**	95
14			 **4n**	92
15			 **4o**	89
16			 **4p**	90
17			 **4q**	86

[a] Refers to purified yield, which is >95% as determined by ^{1}H NMR.

NH group (δ_H 3.62 ppm). The 4-nitrophenylamino moiety gave rise to characteristic signals in the aromatic region of the spectrum (δ_H 7.79 and 8.23 ppm, 2 d, $^3J_{HH}$ = 8.6 Hz). The ^{1}H decoupled ^{13}C NMR spectra of **4a** showed 17 distinct resonances, which confirmed the proposed structure. Partial assignment of these resonances is given in the Experimental section.

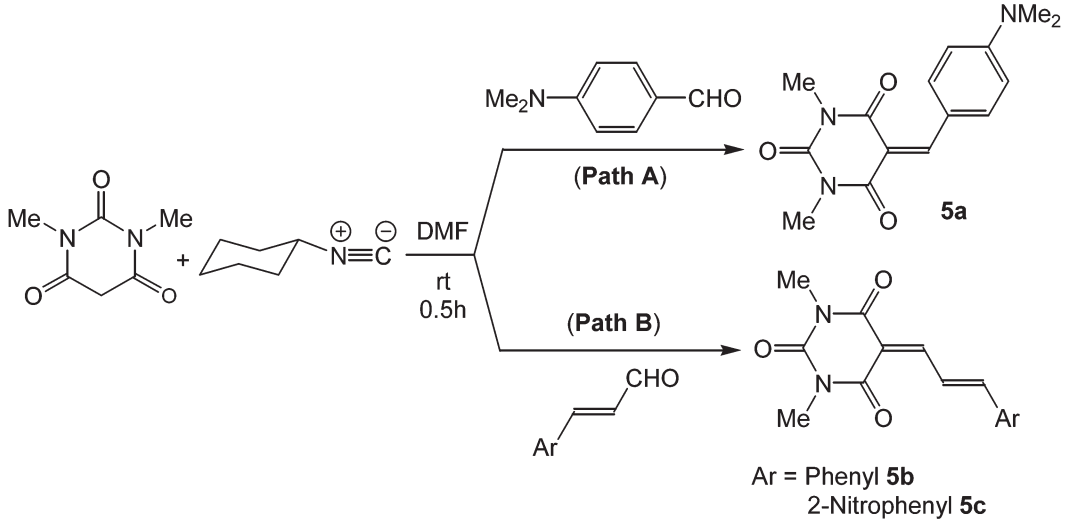
The structural assignments made on the basis of the ^{1}H and ^{13}C NMR spectra of compounds **4a** were supported by measurement of their IR spectra. The IR spectrum of **4a** showed strong absorptions at 1706 and 1663 cm^{-1} due to the carbonyls and the amino group at 3435 cm^{-1} as a weak broad band.

The scope and limitations of this three-component reaction were explored by using ten aromatic aldehydes and six alkyl or aryl isocyanides. The results show that substituted aromatic aldehydes containing electron-withdrawing groups (–NO_2, –F, –Cl, Br) and electron-donating groups (phenyl, anthryl, –OCH_3) all tolerate the reaction conditions with excellent yields. But, when the reaction was performed using equivalent ratios of 4-(dimethylamino)benzaldehyde [Ar=4-(NMe_2)C_6H_4], 1,3-dimethylbarbituric acid and cyclohexyl isocyanide under similar reaction conditions, ^{1}H NMR and ^{13}C NMR analyses of the isolated product indicated the formation of 5-[4-(dimethylamino)benzylidene]-1,3-dimethylbarbituric acid **5a**[22] in nearly 95% yield (Scheme 3, Path **A**). Under similar reaction conditions, starting with cyclohexyl isocyanide, 1,3-dimethylbarbituric acid, and α,β-unsaturated aldehydes such as cinnamaldehye or 2′-nitrocinnamaldehye, the corresponding *Knoevenagel* adducts **5b**[23] and **5c** were isolated in 88 and 91% yield, respectively without the participation of cyclohexyl isocyanide, which did not enter into these reactions (Scheme 3, Path **B**).

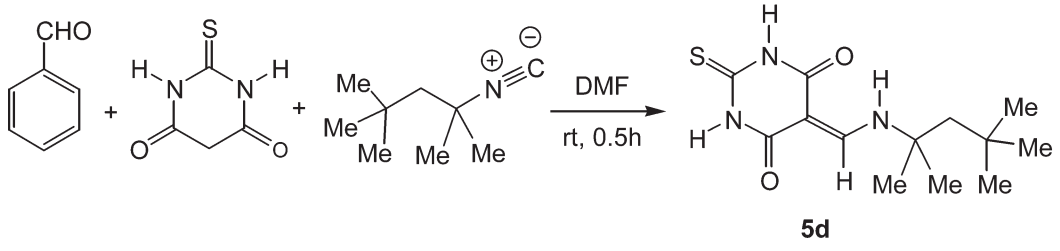
To explore the scope of this reaction with respect to isocyanides, we have examined six alkyl or aryl isocyanides. We have found that the reaction proceeds very efficiently even with hindered alkyl or aryl isocyanides. Our attempts to carry out this reaction under the same reaction conditions with another substituted barbituric acid compound such as 1,3-diethyl-2-thiobarbituric acid were not successful up to now and unfortunately the reactions led to intractable mixtures. But under similar reaction conditions, starting with benzaldehyde, 2-thiobarbituric acid as an unsubstituted barbituric acid and *tert*-octyl isocyanide, 5-[(*tert*-octylamino)methylene]-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-dione **5d**[24] was isolated in 91% yield without the participation of benzaldehyde, which did not enter into the reaction (Scheme 4).

We next examined the effect of solvents on the present three-component condensation reaction and found that among CH_2Cl_2, EtOH, MeCN, toluene, H_2O and DMF, the last one was the best solvent in terms of the yield as well as the reaction time (Scheme 5, Table 2). It was noted that a higher reaction temperature, for example, in a refluxing solvent instead of at room temperature, led to increased yield.

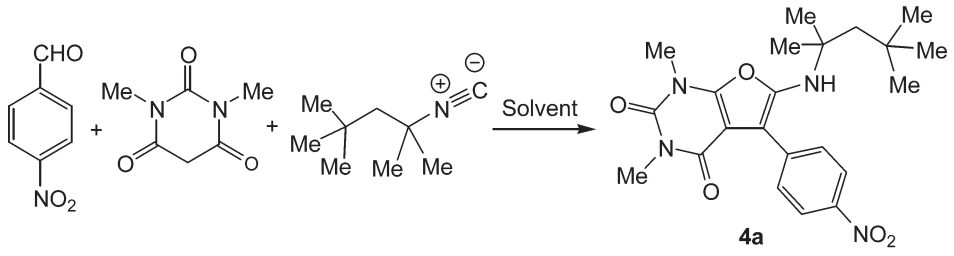
The synthesis of these aminofuropyrimidindiones can be rationalised by initial formation of a conjugated electron-deficient heterodiene by a Knoevenagel condensation of the 1,3-dimethylbarbituric acid and the aldehyde followed by a [1+4] cycloaddition reaction with isocyanide to afford an iminolactone intermediate, which then isomerises to yield the furopyrimidindione derivatives. High rates of reactions at room temperature have led us to establish a significant catalytic role for DMF in the Knoevenagel condensation reaction of 1,3-dimethylbarbituric acid with an aromatic aldehyde.[21]



Scheme 3



Scheme 4



Scheme 5

Table 2 Effect of solvents and temperature on the formation of furopyrimidindione **4a**

Entry	Solvent	Temperature/°C	Time/h	Yield[a]/%
1	CH_2Cl_2	Rt	24	56
2	CH_2Cl_2	Reflux	3	73
3	EtOH	Rt	24	39
4	EtOH	Reflux	3	76
5	MeCN	Rt	24	44
6	MeCN	Reflux	3	80
7	Toluene	Rt	24	25
8	Toluene	Reflux	3	82
9	H_2O	Rt	24	–
10	H_2O	Reflux	0.5	70
11	DMF	Rt	0.5	91

[a] Isolated yield. Reactions were carried out using 4-nitrobenzaldehyde (1 mmol), 1,3-dimethylbarbituric acid (1 mmol) and *tert*-octyl isocyanide (1 mmol) in 20 mL of solvents (except for entry 11 which was in 0.5 mL of DMF).

In order to confirm the mechanism of the reaction, the 5-benzylidene-1,3-dimethylbarbituric acid as a representative Knoevenagel condensation adduct was synthesised separately by the condensation of benzaldehyde and 1,3-dimethylbarbituric acid in water at room temperature.[25] Then we examined the reaction of the isolated 5-benzylidene-1,3-dimethylbarbituric acid with one equivalent amount of cyclohexyl isocyanide in DMF at room temperature, and we obtained the product **4j** in 92%. Also, we found that reaction of benzaldehyde for 20 min with only 1,3-dimethylbarbituric acid and in the absence of any isocyanide component in DMF at room temperature predominantly led to formation of 5-benzylidene-1,3-dimethylbarbituric acid, which was subjected to the cyclocondensation with cyclohexyl isocyanide, providing the desired furopyrimidindione **4j** in 89% yield.

In conclusion, we have demonstrated that the one-pot three-component reactions of various aromatic aldehydes with 1,3-dimethylbarbituric acid in the presence of alkyl or aryl isocyanides in a small amount of DMF at room temperature by shaking provides a facile and efficient method for the preparation of 5-(aryl)-6-(alkyl or arylamino)-1,3-dimethylfuro [2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives of potential synthetic and biological interest. The main advantages of this method with respect to the other methods are: (i) the reaction is very simple to perform, (ii) starts from readily accessible inexpensive commercial reagents and solvents, (iii) the reaction occurs at room temperature, (iv) the yields are good to high, (v) no need for any other catalyst and special instruments, (vi) reaction is complete within a short period of time, (vii) purification of the products is not necessary, and (viii) it provides biologically interesting aminofuropyrimidindione derivatives in good yields without any other additive to promote the reaction.

Experimental

Melting points were measured on a Büchi 535 apparatus and are uncorrected. Elemental analyses were performed using an Elementar Vario EL III instrument. FT-IR spectra were recorded on a Bruker Equinox-55 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 Avance spectrometer at 500.1 and 125.8 MHz, respectively, with $CDCl_3$ as solvents and calibrated using residual undeuterated solvent as an internal reference. Chemical shifts are reported in ppm relative to TMS as internal reference. Analytical TLC was carried out on pre-coated plates (Merck silica gel 60, F254) and visualised with UV light. All chemical reagents were obtained from Aldrich, Merck or Acros and were used without further purification. The products **4h**,[19] **4j–k**,[18] **4m–q**,[17] **5a**[22] and **5b**[23] are known compounds, which were identified by IR and ^{1}H NMR spectral data and comparing their melting points with literature reports.

Preparation of **4a***; typical procedure*

To a solution of 4-nitrobenzaldialdehyde (0.151 g, 1.0 mmol) and 1,1,3,3-tetramethylbutyl isocyanide (0.140 g, 1.0 mmol) in DMF (0.5 mL) in a screw-capped vial was added 1,3-dimethylbarbituric acid (0.156 g, 1.0 mmol) and was shaken for 1 min. The reaction mixture was then kept for about 30 min at room temperature (25 °C) and the completion of reaction was confirmed by TLC (EtOAc-hexane 1:3). Then, the resulting solid was filtered and washed with diethyl ether (20 mL) to yield **4a** as red powder (0.390 g, 91%). The dried product thus obtained showed a single spot on TLC and was pure enough for all analytical purposes.

*1,3-Dimethyl-5-(4-nitrophenyl)-6-[(1,1,3,3-tetramethylbutyl)amino] furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione* (**4a**): M.p. 143–145 °C; IR (KBr) (ν_{max}, cm^{-1}): 3435 (N–H), 1706 and 1663 (C=O); ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 1.01 (9 H, s, $C(CH_3)_3$), 1.19 (6 H, s, $C(CH_3)_2$), 1.54 (2 H, s, CH_2), 3.38 and 3.57 (6 H, 2 s, 2 NCH_3), 3.62 (1 H, s, NH), 7.79 and 8.23 (4 H, 2 d, $^3J_{HH}$ = 8.6 Hz, $C_6H_4NO_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_c 28.3, 29.5, 29.9, 30.1, 31.7, 55.5, 58.7, 95.1, 108.7, 123.3, 130.2, 137.9, 146.5, 148.9, 150.3, 151.8, 158.1; Anal. Calcd for $C_{22}H_{28}N_4O_5$ (428.48): C, 61.67; H, 6.59; N, 13.08. Found: C, 61.89; H, 6.62; N, 13.03%.

*5-(4-Chlorophenyl)-1,3-dimethyl-6-[(1,1,3,3-tetramethylbutyl)amino] furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione* (**4b**): White powder (0.318 g, 76%); m.p. 128–130 °C; IR (KBr) (ν_{max}, cm^{-1}): 3442 (N–H), 1704 and 1660 (C=O); ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 1.00 (9 H, s, $C(CH_3)_3$), 1.15 (6 H, s, $C(CH_3)_2$), 1.50 (2 H, s, CH_2), 3.38 and 3.56 (6 H, 2 s, 2 NCH_3), 3.43 (1 H, s, NH), 7.36 and 7.52 (4 H, 2 d, $^3J_{HH}$ = 9.4 Hz, C_6H_4Cl); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_c 28.2, 29.4, 29.7, 29.8, 31.7, 55.5, 58.4, 95.6, 110.3, 128.3, 129.1, 131.0, 133.2, 148.0, 150.5, 151.5, 158.2; Anal. Calcd for $C_{22}H_{28}ClN_3O_3$ (417.92): C, 63.22; H, 6.75; N, 10.05. Found: C, 62.98; H, 6.78; N, 10.00%.

*5-(2,6-Dichlorophenyl)-1,3-dimethyl-6-[(1,1,3,3-tetramethylbutyl) amino]furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione* (**4c**): White powder (0.362 g, 80%); m.p. 164–165 °C; IR (KBr) (ν_{max}, cm^{-1}): 3313 (N–H), 1709 and 1648 (C=O); ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 0.93 (9 H, s, $C(CH_3)_3$), 1.20 (6 H, s, $C(CH_3)_2$), 1.44 (2 H, s, CH_2), 3.00 (1 H, br s, NH), 3.37 and 3.59 (6 H, 2 s, 2 NCH_3), 7.27–7.30 and 7.41–7.42 (3 H, m, $C_6H_3Cl_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_c 28.5, 29.8, 30.1, 31.9, 31.9, 55.6, 58.2, 96.9, 107.1, 128.4, 129.6, 130.4, 136.7, 148.8, 151.0, 151.8, 158.1; Anal. Calcd for $C_{22}H_{27}Cl_2N_3O_3$ (452.37): C, 58.41; H, 6.02; N, 9.29. Found: C, 58.25; H, 5.99; N, 9.32%.

*5-(9-Anthryl)-1,3-dimethyl-6-[(1,1,3,3-tetramethylbutyl)amino]furo [2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione* (**4d**): Yellow powder (0.344 g, 71%); m.p. 160–161 °C; IR (KBr) (ν_{max}, cm^{-1}): 3420 (N–H), 1713 and 1657 (C=O); ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 0.59 (9 H, s, $C(CH_3)_3$), 1.04 (6 H, s, $C(CH_3)_2$), 1.18 (2 H, s, CH_2), 3.10 (1 H, br s, NH), 3.31 and 3.72 (6 H, 2 s, 2 NCH_3), 7.45–7.50 (4 H, m, arom.), 7.85–7.87 and 8.07–8.08 (4 H, 2 m, arom.), 8.55 (1 H, s, arom.); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_c 28.6, 29.9, 30.1, 31.5, 31.6, 55.3, 58.3, 98.8,

117.2, 125.0, 125.6, 126.1, 126.7, 128.3, 129.3, 131.5, 131.9, 145.7, 151.3, 152.1, 158.1; Anal. Calcd for $C_{30}H_{33}N_3O_3$ (483.60): C, 74.51; H, 6.88; N, 8.69. Found: C, 74.39; H, 6.90; N, 8.71%.

*5-(4-Bromophenyl)-6-(cyclohexylamino)-1,3-dimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione* (**4e**): White powder (0.355 g, 82%); m.p. 156–157 °C; IR (KBr) (ν_{max}, cm^{-1}): 3259 (N–H), 1703 and 1662 (C=O); ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 1.18–1.95 (10 H, m, 5 CH_2), 3.16–3.20 (1 H, m, N-CH), 3.37 (1 H, s, NH), 3.40 and 3.58 (6 H, 2 s, 2 NCH_3), 7.49 and 7.53 (4 H, 2 d, $^3J_{HH}$ = 8.5 Hz, C_6H_4Br); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_c 25.1, 25.9, 28.7, 29.9, 34.3, 55.9, 96.2, 104.5, 121.4, 129.9, 131.3, 131.8, 149.1, 150.8, 151.3, 158.6; Anal. Calcd for $C_{20}H_{22}BrN_3O_3$ (432.31): C, 55.57; H, 5.13; N, 9.72. Found: C, 55.29; H, 5.10; N, 9.68%.

*5-(4-Chlorophenyl)-6-(cyclohexylamino)-1,3-dimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione* (**4f**): White powder (0.322 g, 83%); m.p. 150–152 °C; IR (KBr) (ν_{max}, cm^{-1}): 3433 (N–H), 1703 and 1663 (C=O); ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 1.18–1.96 (10 H, m, 5 CH_2), 3.16–3.20 (1 H, m, N–CH), 3.36 (1 H, s, NH), 3.41 and 3.59 (6 H, 2s, 2 NCH_3)), 7.39 and 7.56 (4 H, 2 d, $^3J_{HH}$ = 8.5 Hz, C_6H_4Cl); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_c 25.1, 25.9, 28.7, 29.9, 34.3, 56.0, 96.2, 117.6, 128.8, 129.3, 129.5, 131.0, 133.3, 151.3, 152.8, 158.6; Anal. Calcd for $C_{20}H_{22}ClN_3O_3$ (387.86): C, 61.93; H, 5.72; N, 10.38. Found: C, 62.17; H, 5.69; N, 10.44%.

*6-(Cyclohexylamino)-5-(2,6-dichlorophenyl)-1,3-dimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione* (**4g**): White powder (0.313 g, 74%); m.p. 162–163 °C; IR (KBr) (ν_{max}, cm^{-1}): 3303 (N–H), 1709 and 1670 (C=O); ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 1.13–1.95 (10 H, m, 5 CH_2), 3.12–3.16 (1 H, m, N–CH), 3.29 (1 H, s, NH), 3.37 and 3.60 (6 H, 2 s, 2 NCH_3)), 7.29–7.44 (3 H, m, $C_6H_3Cl_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_c 25.1, 25.9, 28.5, 29.9, 34.3, 55.5, 97.5, 99.1, 128.4, 129.2, 130.3, 137.1, 149.4, 150.7, 150.9, 158.1; Anal. Calcd for $C_{20}H_{21}Cl_2N_3O_3$ (422.30): C, 56.88; H, 5.01; N, 9.95. Found: C, 57.02; H, 4.97; N, 10.02%.

*5-(4–Fluorophenyl)-6-(cyclohexylamino)-1,3-dimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione* (**4i**): Pink powder (0.335 g, 90%); m.p. 147–149 °C; IR (KBr) (ν_{max}, cm^{-1}): 3255 (N–H), 1708 and 1661 (C=O); ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 1.08–1.92 (10 H, m, 5 CH_2), 3.13 (1 H, m, N–CH), 3.37 and 3.55 (6 H, 2 s, 2 NCH_3), 3.44 (1 H, d, $^3J_{HH}$ = 6.0 Hz, NH), 7.07–7.56 (4 H, m, arom.); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_c 24.7, 25.5, 33.9, 28.3, 29.4, 55.6, 95.9, 104.8, 115.2 (d, $^2J_{CF}$ = 21.7 Hz, C_{ortho}–F), 126.4 (d, $^4J_{CF}$ = 3.5 Hz, C_{para}–F), 131.0 (d, $^3J_{CF}$ = 7.9 Hz, C_{meta}–F), 148.6, 150.4, 150.9, 158.2, 161.9 (d, $^1J_{CF}$ = 246.6 Hz, C–F); Anal. Calcd for $C_{20}H_{22}FN_3O_3$ (371.40): C, 64.68; H, 5.97; N, 11.31. Found: C, 64.81; H, 5.93; N, 11.26%.

*6-(Cyclohexylamino)-1,3-dimethyl-5-pyridin-2-ylfuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione* (**4l**): Cream powder (0.319 g, 90%); m.p. 136–138 °C; IR (KBr) (ν_{max}, cm^{-1}): 3475 (N–H), 1701 and 1662 (C=O); ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 1.38–2.00 (10 H, m, 5 CH_2), 3.43 and 3.55 (6 H, 2 s, 2 NCH_3), 3.56–3.61 (1 H, m, N–CH), 6.92–6.94 (1 H, m, arom.), 7.62–7.65 (1 H, m, arom.), 8.38 (1 H, br s, NH), 8.40–8.42 (1 H, m, arom.), 8.80 (1 H, d, $^3J_{HH}$ = 8.2 Hz, arom.); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_c 24.5, 25.6, 28.7, 29.5, 33.9, 52.3, 91.4, 95.8, 118.4, 122.4, 136.2, 147.3, 149.4, 149.9, 153.4, 154.5, 158.6; Anal. Calcd for $C_{19}H_{22}N_4O_3$ (354.40): C, 64.39; H, 6.26; N, 15.81. Found: C, 64.21; H, 6.30; N, 15.77%.

*1,3-Dimethyl-5-[(2E)-3-(2-nitrophenyl)prop-2-en-1-ylidene]pyrimidine-2,4,6(1*H*,3*H*,5H)-trione* (**5c**): Yellow powder (0.300 g, 95%); m.p. 200–202 °C; IR (KBr) (ν_{max}, cm^{-1}): 1709 and 1642 (C=O), 1522 and 1340 (NO_2); ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 3.38 (6 H, br s, 2 NCH_3), 7.23–8.52 (7 H, m, CH=CH-CH= and arom.); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_c 28.4, 29.0, 116.9, 125.3, 129.2, 129.5, 131.0, 131.1, 133.7, 147.1, 148.7, 151.4, 155.9, 161.6, 161.9; Anal. Calcd for $C_{15}H_{13}N_3O_5$ (315.28): C, 57.14; H, 4.16; N, 13.33. Found: C, 57.26; H, 4.15; N, 13.28%.

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