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Shaken not stirred: A facile synthesis of 1,4-bis(furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione-5-yl)benzenes by one-pot reaction of isocyanides, *N*,*N*′-dimethylbarbituric acid, and terephthaldialdehyde

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Abstract—A simple and efficient synthesis of 1,4-bis(furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione-5-yl)benzene derivatives was achieved via a one-pot three-component reaction of isocyanides, *N*,*N*′-dimethylbarbituric acid, and terephthaldialdehyde in DMF at room temperature for 30 min. These improved reaction conditions allow the preparation of highly substituted furopyrimidinones in high yields and purity under mild reaction conditions.

Fused pyrimidine compounds are valued not only for their rich and varied chemistry, but also for many important biological properties.[1] Among them, the furopyrimidine ring system, because of a formal isoelectronic relationship with purine, is of special biological interest.[2] It has numerous pharmacological and agrochemical applications viz. antimalarials,[2a] antifolates,[2b–f] and antivirus,[2g] as well as potential radiation protection agents.[2h] Recently, some furopyrimidines were shown to be potent VEGFR2 (vascular endothelial growth factor receptor 2) and EGFR (epidermal growth factor receptor) inhibitors.[2i] Because of the importance of furo[2,3-*d*]pyrimidine derivatives, several methodologies for synthesizing them have already been developed.[3–14] However, many of the synthetic protocols reported so far suffer from disadvantages, such as relying on multistep reactions,[3] needing anhydrous conditions,[4] prolonged reaction times,[4–6] harsh reaction conditions,[6] low yields,[7–9] use of metal-containing reagents,[10,11] and special instruments[12] or starting materials.[13,14] Therefore, the development of new, efficient methods for the preparation of furo[2,3-*d*]pyrimidine derivatives is still strongly desirable.

In recent years, multicomponent reactions (MCRs) have become important tools in modern preparative synthetic chemistry because these reactions increase the efficiency by combining several operational steps without any isolation of intermediates or changes of the conditions.[15,16] This principle, therefore, is highly efficient in terms of time as well as resources.[17] Meanwhile, isocyanide-based multicomponent condensation reactions (IMCRs) by virtue of their synthetic potential, their inherent atom efficiency, convergent nature, ease of implementation, and the generation of molecular diversity, have attracted much attention because of the advantages that they offer to the field of combinatorial chemistry.[18]

In connection with our recent interest aimed at the development of efficient protocols for the preparation of biologically active heterocycles[19] and continuing our general interest in chemistry of isocyanides,[20] we herein report an efficient one-pot condensation reaction of alkyl or aryl isocyanides, *N*,*N*′-dimethylbarbituric acid, and terephthaldialdehyde in *N*,*N*-dimethylformamide (DMF) at room temperature which afforded 1,4-bis(furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione-5-yl)benzene derivatives in good isolated yields (see Scheme 1).

The one-pot three-component condensation reactions of alkyl or aryl isocyanides **1** with *N*,*N*′-dimethylbarbituric acid **2** in the presence of terephthaldialdehyde **3** proceeded spontaneously at room temperature in small amount

Keywords: Furopyrimidine; Isocyanide; Multicomponent reaction, *N*,*N*′-Dimethylbarbituric acid; Terephthaldialdehyde.
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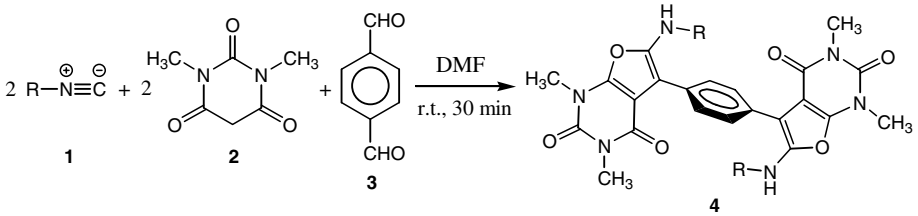


1 2 3 4

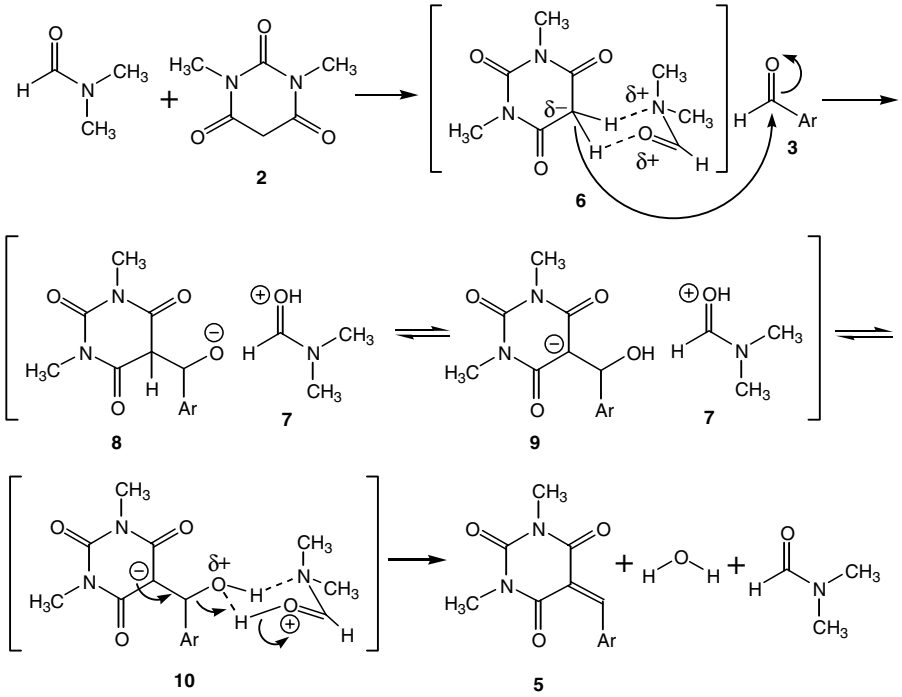
4	R	Yield (%)
a	1,1,3,3-Tetramethylbutyl	82
b	*tert*-Butyl	90
c	Cyclohexyl	74
d	Benzyl	71
e	Tosylmethyl	67
f	2,6-Dimethylphenyl	91
g	2-Chlorophenyl	76

Scheme 1.

of DMF and were complete after 30 min to afford corresponding 1,4-bis(6-alkyl or arylamino-1,3-dimethyl furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione-5-yl)benzenes **4**, in good yields (67–91%).[21] ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of 1,4-bis(furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione-5-yl)benzene derivatives **4**. Any product other than **4** could not be detected by NMR spectroscopy. The structures of the products **4a**–**g** were deduced from their elemental analyses and IR, ^{1}H NMR, and ^{13}C NMR spectra. The nature of these compounds as 2:2:1 adducts was apparent from the mass spectra which displayed molecular ion peaks at the appropriate *m*/*z* values.

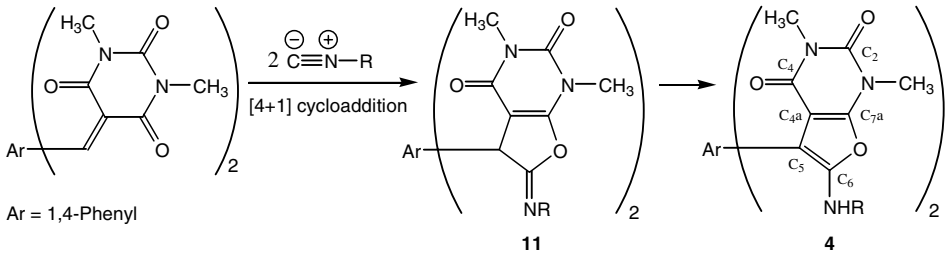
The ^{1}H NMR spectrum of **4a** exhibited five single sharp lines readily recognized as arising from two *tert*-butyl (δ 1.08 ppm), two geminal methyl groups (δ 1.13 ppm), two methylene protons (δ 1.46 ppm), and two sets of *N*-methyl (δ 2.99 and 3.45 ppm). A singlet (δ 3.30 ppm) was observed for the two NH groups. The presence of amine protons was confirmed by exchange with D_2O. The *para*-substituted phenyl moieties gave rise to a singlet in the aromatic region of the spectrum (δ 8.14 ppm). The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 15 distinct resonances in agreement with the suggested structure. Partial assignment of these resonances is given in Ref. 21.

The structural assignments made on the basis of the ^{1}H and ^{13}C NMR spectra of compounds **4a** were supported by measurement of its IR spectra. The IR spectrum of **4a** showed strong absorptions at 1710 and 1660 cm^{-1} due to the carbonyls and the amino group at 3310 cm^{-1}.



2 6 3 8 7 9 7 10 5

Scheme 2.



Scheme 3.

The ^{1}H and ^{13}C NMR spectra of **4b–g** are similar to those of **4a** except for the alkyl or arylamino groups, which exhibit characteristic signals with appropriate chemical shifts and the results are summarized in Ref. 21.

The synthesis of 1,4-bis(furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione-5-yl)benzenes can be rationalized by initial formation of a conjugated electron-deficient heterodiene **5** by a Knoevenagel condensation of the cyclic *N*,*N*′-dimethylbarbituric acid **2** and the terephthaldialdehyde **3**. High rates of reactions at room temperature have made us to establish a significant catalytic role for DMF as well as urea[22] in Knoevenagel condensation reaction of *N*,*N*′-dimethylbarbituric acid with aromatic aldehyde. A reasonable possibility for DMF-catalyzed Knoevenagel reaction has been suggested in Scheme 2. The first step may involve formation of a six-membered cyclic chair-like intermediate **6**. The nucleophilic addition of *N*,*N*′-dimethylbarbituric acid **2** to aromatic aldehyde **3** is facilitated by strong attraction of active hydrogens with highly electronegative oxygen and nitrogen atoms of DMF moiety (double non-conventional hydrogen bonds)[23,24] in intermediate **6**. Upon leaving of the protonated-DMF **7**, two anionic intermediates **8** and **9** can be produced in equilibrium with each other. Finally, the reaction of intermediate **9** on its OH site with protonated-DMF **7** via another six-membered cyclic transition state **10** can catalyze the deleting of water as a good leaving group, regeneration of DMF, and production of heterodiene molecule **5**.

The next step of this mechanism could involve the [4 + 1] cycloaddition reaction[25] of the electron-deficient heterodiene moiety of 5-arylidene-*N*,*N*′-dimethylbarbituric acid with the isocyanide to afford an iminolactone intermediate **11**. The subsequent isomerization of iminolactone **11** leads to formation of product **4** (Scheme 3).

In order to confirm the mechanism of the reaction in Schemes 2 and 3, we examined the reaction of the isolated Knoevenagel condensation adduct **5** with two equivalent amount of *tert*-butyl isocyanide, and we obtained the product **4b**.

The crystalline products **4a–g** have colors from white through yellow and green to brown. The UV–vis spectra of these products demonstrate that the compounds have significantly different absorption spectra and the differences in colors cannot be due to surface impurities (Fig. 1).

In summary, we have demonstrated that the one-pot three-component reactions of alkyl or aryl isocyanides with *N*,*N*′-dimethylbarbituric acid in the presence of terephthaldialdehyde in small amount of DMF at room temperature by shaking provide a facile and efficient method for the preparation of 1,4-bis(6-alkyl or arylamino-1,3-dimethyl furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione-5-yl)benzene derivatives. The present method may find some values in organic synthesis because of its reasonably high yields, fast reaction times, the ready availability of the starting materials, mild reaction conditions, and the ease of operation. Detailed mechanistic studies of the high rates of these reactions in DMF are now in progress.

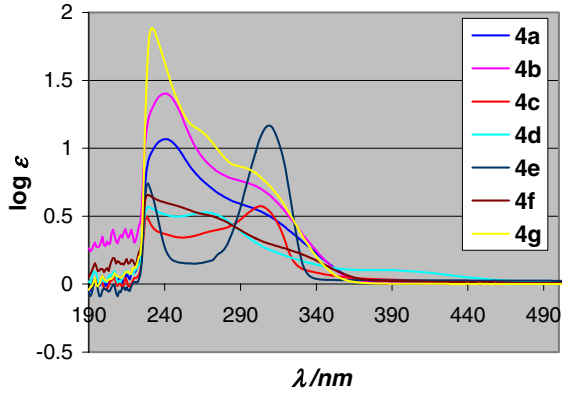


Figure 1. UV–vis spectra of compounds **4a–g** in dichloromethane.

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21. Typical procedure for preparation of 6-[(1,1,3,3-tetramethylbutyl)amino]-5-{4-[6-[(1,1,3,3-tetramethylbutyl)amino]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrofuro[2, 3-*d*]pyrimidin-5-yl]phenyl}-1,3-dimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione (**4a**): To a solution of *N*,*N*′-dimethylbarbituric acid (0.156 g, 1.0 mmol) and terephthaldialdehyde (0.067 g, 0.5 mmol) in DMF (1 mL) in a screw-capped vial was added 1,1,3,3-tetramethylbutyl isocyanide (0.140 g, 1.0 mmol) via a syringe 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 1:2). Then, the resulting crystals were filtered and washed with diethyl ether (20 mL) to yield **4a** as pale yellow crystals (0.283 g, 82%). The dried product thus obtained showed a single spot on TLC and was pure enough for all analytical purposes. Mp. 174–176 °C; IR (KBr) (ν_{max}, cm^{-1}): 3310 (N–H), 1710 and 1660 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.08 (18 H, s, 2 $C(CH_3)_3$), 1.13 (12 H, s, 2 $C(CH_3)_2$), 1.45 (4 H, s, 2 CH_2), 2.99 and 3.45 (12 H, 2 s, 2 × 2 NCH_3), 3.30 (2 H, s, 2 NH), 8.14 (4 H, s, C_6H_4). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 28.25 and 29.38 (4 NCH_3), 29.90 (2 C*Me*$_2$), 31.41 (2 *C*Me$_3$), 31.72 (2 C*Me*$_3$), 55.35 (2 CH_2) 58.14 (2 N*C*Me$_2$), 95.79 (2 C_4a), 109.18 (2 C_5), 129.24 (4 C_{ortho}), 129.47 (2 C_{ipso}), 148.36 (2 C_6), 150.51 (2 C_7a), 151.22 (2 C_2), 158.11 (2 C_4). MS (EI, 70 eV) (*m*/*z*, %): 688 (M^+, <1), 603 (2), 512 (3), 410 (26), 283 (47), 156 (49), 57 (100). Anal. Calcd. for $C_{38}H_{52}N_6O_6$ (688.85): C, 66.26; H, 7.61; N, 12.20%. Found: C, 66.35; H, 7.58; N, 12.26%. 6-(*tert*-Butylamino)-5-{4-[6-(*tert*-butylamino)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrofuro[2,3-*d*]pyrimidin-5-yl]phenyl}-1,3-dimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione (**4b**): lemon yellow crystals (0.260 g, 90%). Mp 207–208 °C; IR (KBr) (ν_{max}, cm^{-1}): 3360 (N–H), 1707 and 1655 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.20 (18 H, s, 2 $C(CH_3)_3$), 3.39 and 3.56 (12 H, 2 s, 4 NCH_3), 3.55 (2 H, s, 2 NH), 7.63 (4 H, s, C_6H_4). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 28.27 and 29.38 (4 NCH_3), 30.29 (2 C*Me*$_3$), 54.37 (2 *C*Me$_3$), 95.76 (2 C_4a), 109.61 (2 C_5), 129.20 (4 C_{ortho}), 129.46 (2 C_{ipso}), 148.44 (2 C_6), 150.52 (2 C_7a), 151.39 (2 C_2), 158.19 (2 C_4). MS (EI, 70 eV) (*m*/*z*, %): 577 (MH^+, <1), 520 (1), 495 (3), 465 (5), 68 (51), 57 (100), 39 (98). Anal. Calcd. for $C_{30}H_{36}N_6O_6$ (576.69): C, 62.48; H, 6.25; N, 14.57%. Found: C, 62.54; H, 6.30; N, 14.55%. 6-(Cyclohexylamino)-5-{4-[6-(cyclohexylamino)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrofuro[2,3-*d*]pyrimidin-5-yl]phenyl}-1,3-dimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione (**4c**): Dark brown crystals (0.233 g, 74%). Mp 194–196 °C; IR (KBr) (ν_{max}, cm^{-1}): 3415 (N–H), 1708 and 1653 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.16-1.99 (20 H, m, 10 CH_2), 3.30 (2 H, m, 2 N–CH), 3.36 (2 H, d, $^3J_{HH}$ = 6.9 Hz, 2 NH), 3.39 and 3.57 (12 H, 2 s, 4 NCH_3), 7.61 (4 H, s, C_6H_4). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 24.97, 25.55, and 34.06 (10 CH_2), 28.31 and 29.45 (4 NCH_3), 55.45 (2 N–CH), 96.15 (2 C_4a), 102.92 (2 C_5), 129.04 (4 C_{ortho}), 129.11 (2 C_{ipso}), 149.12 (2 C_6), 150.37 (2 C_7a), 150.64 (2 C_2), 158.29 (2 C_4). MS (EI, 70 eV) (*m*/*z*, %): 628 (M^+, <1), 553 (2), 465 (2), 369 (5), 314 (6), 285 (3), 265 (71), 222 (55), 169 (24), 110 (39), 97 (100), 83 (50), 69 (54), 55 (72), 41 (51). Anal. Calcd for $C_{34}H_{40}N_6O_6$ (628.71): C, 64.95; H, 6.41; N, 13.37%. Found: C, 65.01; H, 6.38; N, 13.43%. 6-(Benzylamino)-5-{4-[6-(benzylamino)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrofuro[2,3-*d*]pyrimidin-5-yl]phenyl}-1,3-dimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione (**4d**): henna green crystals (0.229 g, 71%). Mp 209–211 °C; IR (KBr) (ν_{max}, cm^{-1}): 3200 (N–H), 1704 and 1653 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.34 and 3.37 (12 H, 2 s, 4 NCH_3), 4.34 (6 H, br s, 2 NH and 2 CH_2), 7.26–7.34 (10 H, m, 2 C_6H_5), 7.51 (4 H, s, C_6H_4). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 28.30 and 29.91 (4 NCH_3), 50.56 (2 N–CH_2), 97.46 (2 C_4a), 102.03 (2 C_5), 127.72, 127.80, 128.71, 128.93, 129.02, 139.00 (C_6H_4 and 2 C_6H_5), 149.25 (2 C_6), 150.41 (2 C_7a), 150.51 (2 C_2), 158.31 (2 C_4). MS (EI, 70 eV) (*m*/*z*, %): 644 (M^+, <1), 515 (2), 410 (5), 306 (3), 299 (4), 285 (4), 243 (100), 194 (10), 156 (52), 106 (75), 91 (83), 42 (67). Anal. Calcd for $C_{36}H_{32}N_6O_6$ (644.67): C, 67.07; H, 5.00; N, 13.04%. Found: C, 66.98; H, 5.05; N, 12.98%. 6-({[(4-Methylphenyl)sulfonyl]methyl}amino)-5-{4-[6-({[(4-methylphenyl)sulfonyl]methyl}amino)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrofuro[2,3-*d*]pyrimidin-5-yl]phen-

yl}-1,3-dimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**4e**): white crystals (0.269 g, 67%). Mp 232–234 °C; IR (KBr) (ν_{max}, cm^{-1}): 3255 (N–H), 1750, 1716 and 1631 (C=O). ^1H NMR (400 MHz, CD_3COCD_3 + DMSO-d_6): δ_H 2.44 (6 H, s, 2 CH_3), 3.18 (12 H, s, 4 NCH_3), 5.12 (4 H, d, $^3J_{HH}$ = 6.8 Hz, 2 NCH_2SO_2), 7.11 and 7.45 (8 H, 2 d, $^3J_{HH}$ = 8.0 Hz, 2 $C_6H_4SO_2$), 7.64 and 7.74 (4 H, 2 d, C_6H_4). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 21.24 (2 CH_3), 21.60 (2 NCH_2SO_2), 27.36 and 27.99 (4 NCH_3), 67.82 (2 C_4a), 93.19 (2 C_5), 125.94, 128.58, 129.12, 130.57, 133.92, 138.26, 145.91 (C_6H_4 and 2 $C_6H_4SO_2$), 151.89 (2 C_6), 160.33 (2 C_7a), 162.32 (2 C_2), 164.09 (2 C_4). MS (EI, 70 eV) (*m*/*z*, %): 800 (M^+, <1), 645 (3), 265 (100), 156 (50), 69 (54), 57 (46). Anal. Calcd. for $C_{38}H_{36}N_6O_{10}S_2$ (800.85): C, 56.99; H, 4.53; N, 10.49%. Found: C, 57.08; H, 4.50; N, 10.53%. 6-(2,6-Dimethylphenylamino)-5-{4-[6-(2,6-dimethylphenylamino)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrofuro[2,3-*d*]pyrimidin-5-yl]phenyl}-1,3-dimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**4f**): Deep green crystals (0.306 g, 91%). Mp 266–268 °C; IR (KBr) (ν_{max}, cm^{-1}): 3269 (N–H), 1713 and 1656 (C=O). ^1H NMR (400 MHz, $CDCl_3$): δ_H 2.18 (12 H, s, 4 CH_3), 3.39 and 3.41 (12 H, 2 s, 4 NCH_3), 5.56 (2 H, br s, 2 NH), 6.92–7.01 (6 H, m, 2 $C_6H_3Me_2$), 7.75 (4 H, s, C_6H_4). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 18.81 (4 CH_3), 28.43 and 29.71 (4 NCH_3), 94.88 (2 C_4a), 108.60 (2 C_5), 123.11, 129.97, 130.75, 131.46, 135.65, 139.72 (C_6H_4 and 2 $C_6H_3Me_2$), 145.51 (2 C_6), 150.31 (2 C_7a), 151.90 (2 C_2), 158.07 (2 C_4). MS (EI, 70 eV) (*m*/*z*, %): 672 (M^+, <1), 541 (23), 410 (98), 352 (10), 268 (10), 242 (63), 185 (5), 130 (100), 106 (71), 103 (41), 77 (31), 39 (48). Anal. Calcd for $C_{38}H_{36}N_6O_6$ (672.72): C, 67.84; H, 5.39; N, 12.49%. Found: C, 67.92; H, 5.44; N, 12.45%. 6-(2-Chlorophenylamino)-5-{4-[6-(2-chlorophenylamino)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrofuro[2,3-*d*]pyrimidin-5-yl]phenyl}-1,3-dimethylfuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**4g**): yellow crystals (0.261 g, 76%). Mp. 196–198 °C; IR (KBr) (ν_{max}, cm^{-1}): 3240 (N–H), 1703 and 1658 (C=O). ^1H NMR (400 MHz, $CDCl_3$): δ_H 3.36 and 3.54 (12 H, 2 s, 4 NCH_3), 5.77 (2 H, br s, 2 NH), 7.38–7.76 (12 H, m, C_6H_4 and 2 C_6H_4Cl). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 28.27 and 29.44 (4 NCH_3), 95.81 (2 C_4a), 109.17 (2 C_5), 128.38, 129.01, 130.57, 132.77, 136.12, 139.63 (C_6H_4 and 2 C_6H_4Cl), 148.90 (2 C_6), 150.35 (2 C_7a), 150.89 (2 C_2), 158.17 (2 C_4). MS (EI, 70 eV) (*m*/*z*, %): 685 (M^+, <1), 657 (3), 601 (5), 531 (18), 387 (25), 306 (10), 280 (68), 259 (42), 165 (53), 125 (100), 101 (26), 55 (53). Anal. Calcd for $C_{34}H_{26}Cl_2N_6O_6$ (685.52): C, 59.57; H, 3.82; N, 12.26%. Found: C, 59.49; H, 3.80; N, 12.31%.

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