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Microwave-assisted, mild, facile, and rapid one-pot three-component synthesis of some novel pyrano[2,3-*d*]pyrimidine-2,4,7-triones

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ABSTRACT

Novel pyrano[2,3-*d*]pyrimidine-2,4,7-triones were synthesized in 90–97% yield via a three-component reaction of an aromatic aldehyde, Meldrums acid, and barbituric acid in the presence of 10 mol % K_2CO_3 under microwave irradiation. This is the first protocol to be reported for the synthesis of title compounds and the significant features of the present protocol are simplicity, high yields, short reaction time, involvement of aqueous work-up procedure, environmentally benign nature, and no chromatographic purification.

The diversity and interesting biological activities[1,2] of dihydropyrimidinones (DHPMs) have been explored through the generation of libraries of compounds via microwave, solid-phase, and fluorous-phase technologies.[2] Pyrimidinone derivatives exhibit various biological[3] and pharmaceutical[4] activities such as anti-tumor action; in the treatment of B16 melanoma and P388 leukemia[5] or antagonize cell proliferation and induce cell differentiation by inhibiting (a nontelomeric) endogenous reverse transcriptase.[6] Pyrimidine derivatives are very interesting due to their wide range of biological activities.[7] The synthesis of naturally occurring molecules containing a uracil ring show significant synthetic challenges.[8] The development of clinically useful anticancer (5-fluorouracil)[9] and antiviral drugs (AZT, DDI, BVDU)[10–12] has renewed the interest in the synthetic manipulation of uracils.[13] All the compounds which have a uracil moiety in the skeleton of an organic molecule show antitumor, antibacterial, bronchodilator, vasodilator, antihypertensive, cardiotonic, hepatoprotective, and antiallergic activities; some of them also exhibit antimalarial, analgesic, antifungal, and herbicidal properties.[14–21]

Multicomponent reactions (MCRs) being highly flexible, selective, and convergent in nature constitute a significant group of methods in organic synthesis.[22] These type of reactions have led to interesting heterocyclic scaffolds, and are very useful in the construction of diverse chemical libraries of 'drug-like' molecules. [23,24]

In the last decade microwave irradiation technique has been utilized as a powerful tool for the various organic transformations.[25] The main benefits of the use of microwave irradiation include significant enhancement of the rate of the reactions, improvement in the yields, and selectivity.[26]

As a part of our ongoing research program on the development of new protocols in the heterocyclic synthesis of biological interest using readily available, inexpensive, and environment friendly catalysts,[27–33] herein, we report a new, facile, and rapid one-pot three-component route to the synthesis[34] of some novel 5-aryl-5,6-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine-2,4,7-triones by the reaction of aromatic aldehydes, Meldrums acid, and barbituric acid in the presence of readily available, inexpensive, mild, green, and common laboratory chemical K_2CO_3 as the basic catalyst under neat microwave condition as shown in Scheme 1.

Initially, in order to optimize the reaction conditions, we carried out the reaction between an aryl aldehyde, Meldrums acid, and barbituric acid in the presence of 10 mol % K_2CO_3 at different reaction conditions such as stirring in water at 26 °C, at reflux, under ultrasonic irradiation in water; and under solvent-free microwave irradiation, and found that, no product is formed at room temperature even after 12 h (Table 1, entry 1). However, at reflux only 10% product formed (entry 2), and the major product was Knoevenagel condensation product. Under sonication the yield was 20% (entry 3), on heating under neat condition in an oil bath for 1 min there was no product formation (entry 4), and under the influence of microwaves the product was obtained in a very high yield within 1 min (entry 5) and the results of this study are presented in Table 1.

In order to optimize the amount of K_2CO_3 for the synthesis of the target compounds, we started the study by treating a mixture of 4-nitrobenzaldehyde, Meldrums acid, and barbituric acid in the

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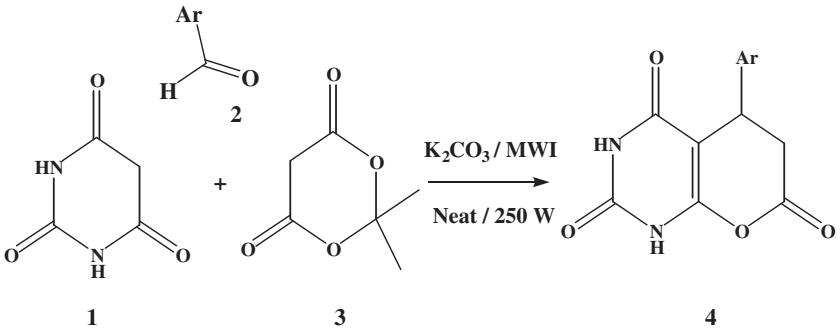


Scheme 1. Synthesis of 5-aryl-5,6-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine-2,4,7-triones.

Table 1
Optimization of the reaction conditions using 10 mol % of K_2CO_3[a] as catalyst

Entry	Condition	Catalyst (mol %)	Time (h)	Yield[b] (%)
1	Silent, water/RT	10	12	ND
2	Water/Reflux	10	8	10
3	Water/)))))	10	2	20
4	Heat/neat in oil bath	10	1 min	ND
5	MWI	10	1 min	97

[a] Reactions are performed on a1 mmol scale of all the reactants.
[b] Isolated yield; ND - not detected.

Table 2
Optimization of the amount of K_2CO_3[a]

Entry	Catalyst (mol %)	Time (min)	Yield[b] (%)
1	00	6	35
2	5	3	65
3	10	1	97
4	15	2	95

[a] Reactions are performed on a1 mmol scale of all the reactants.
[b] Isolated yield.

presence of different amounts of K_2CO_3 in a microwave reactor under solvent-free condition to get the 5-(4′-nitrophenyl)-5,6-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine-2,4,7-trione (**4a**). The results of this study are summarized in Table 2.

It is noted that, 10 mol % of K_2CO_3 gave the best result in terms of time of completion and the product was obtained in 97% yield (entry 3).

To generalize this methodology, we subjected a series of other aldehydes having electron-donating as well as electron-withdrawing substituents to obtain the corresponding 5-aryl-5,6-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine-2,4,7-triones, we also examined the use of aliphatic aldehydes to get the corresponding products (Table 3 entries 10, 11, and 12) but there was no product formation even after 4 min of irradiation under the optimized reaction conditions and the results are presented in Table 3. It can be seen from this table that, variation in the yields is very little for both electron-rich and electron-deficient aldehydes. The reactions proceeded to completion in short durations, and the pure products were obtained simply by recrystallization from ethanol:acetone (3:2) without involving any chromatographic purification. All the synthesized compounds are new and were characterized by IR, ^{1}H NMR, ^{13}C NMR spectral, and elemental analyses.

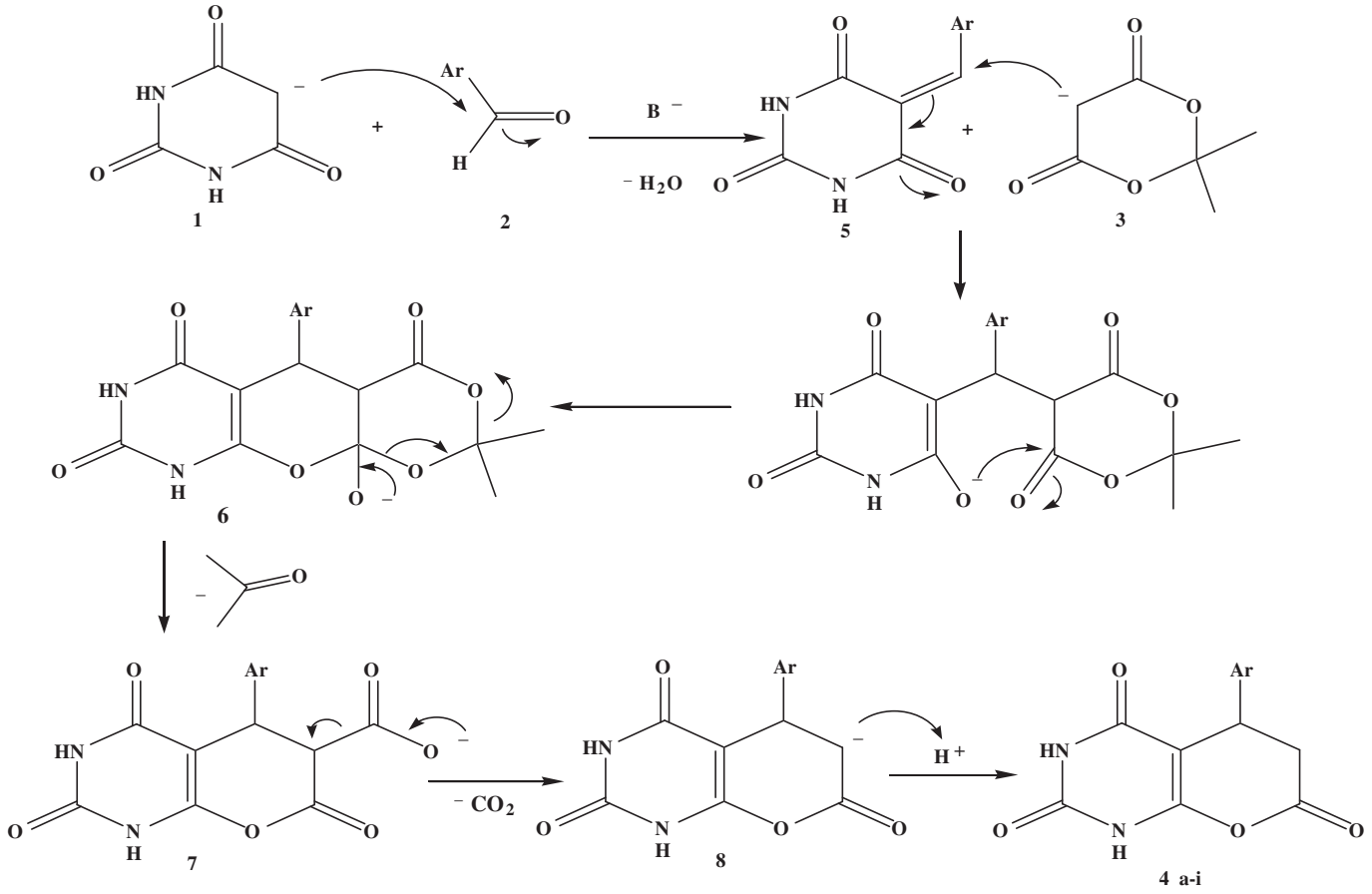
The formation of the product is expected to involve the formation of a Knoevenagel adduct **5** by the condensation between **1** and **2**; followed by the Michael addition between **3** and **5** to give the tricyclic intermediate **6**. Compound **6** may lose a molecule of acetone to give **7**; and **7** may lose a molecule of CO_2 to give **8**, which may pick up a proton in the last step to give 5-aryl-5,6-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine-2,4,7-triones (**4a–i**) as shown in Scheme 2.

In summary, we have devised a new, simple, and efficient one-pot three-component protocol for the synthesis of 5-aryl-5,6-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine-2,4,7-trione derivatives using K_2CO_3 as a mild, readily available, inexpensive, and efficient catalyst under neat condition in a microwave reactor at 250 W. The advantages offered by this method are: simple reaction condition, short reaction time, ease of product isolation, and excellent yields. We wish to state that this method involves an environment friendly procedure, and is the first procedure for the synthesis of novel H-pyrano[2,3-*d*]pyrimidine-2,4,7-triones.

Table 3
Synthesis of 5-aryl-5,6-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine-2,4,7-trione catalyzed by K_2CO_3 under microwave irradiation

Entry	Aldehyde (3)	Product[a]	Time (Sec)	Yield[b] (%)	Melting point (°C)
1	4-$NO_2C_6H_4CHO$	**4a**	55	97	248–250
2	2-HOC_6H_4CHO	**4b**	50	95	292
3	2-$NO_2C_6H_4CHO$	**4c**	60	97	218–220
4	2-ClC_6H_4CHO	**4d**	50	95	240
5	2,4-$(MeO)_2C_6H_3CHO$	**4e**	45	96	235–237
6	4-FC_6H_4CHO	**4f**	40	95	266
7	3-$NO_2C_6H_4CHO$	**4g**	60	96	273
8	4-ClC_6H_4CHO	**4h**	45	95	282
9	3,4-$(MeO)_2C_6H_3CHO$	**4i**	50	95	277
10	HCHO	**4j**	180	ND	—
11	CH_3CHO	**4k**	180	ND	—
12	CH_3CH_2CHO	**4l**	180	ND	—

[a] All the products are new and were characterized by IR (KBr); ^{1}HNMR; ^{13}CNMR spectral, and CHN analyses.
[b] Isolated yields; ND–not detected.



Scheme 2. A plausible mechanism for the formation of 5-aryl-5,6-dihydro-1*H*-pyrano[2,3-*d*]pyrimidine-2,4,7-triones.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.056.

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34. *General Procedure*: in a pyrex cylindrical tube equipped with a magnetic stir bar, a mixture of aromatic aldehyde (2 mmol), Meldrums acid (2 mmol), barbituric acid (2 mmol), and K_2CO_3 (10 mol %) were taken and mixed well; then irradiated in a MILESTONE microwave reactor for (1 min) at 100 °C/250 W (Table 3). After the completion of the reaction, the mixture was cooled to room temperature and EtOH (5 mL) was added to the crude product and left aside for 5 min; the product thus separated was filtered, washed with water, the solid was dried, and recrystallized from ethanol: acetone (3:2) to get the pure product. The structures of all the products were confirmed by ^{1}HNMR, ^{13}CNMR spectral, and CHN analyses.*Spectral and elemental analysis data: 5-(4′-nitrophenyl)-5,6-dihydro-1H-pyrano[2,3-d]pyrimidine-2,4,7-trione (**4a**)*: Mp 248–250 °C; IR (KBr): *ν* 3415 (s), 3293 (w), 2931 (s), 1733 (s), 1694 (vs), 1589 (vs), 1504 (s), 1447 (s), 1347 (vs), 1247 (s), 1173 (s), 1034 (s) cm^{-1}; ^{1}HNMR (400 MHz, DMSO-d_6): *δ* 3.38 (d, *J* = 6.8 Hz, 2H, CH2), 4.49 (t, *J* = 6.8 Hz, 1H, CH), 7.27 (d, *J* = 8.8 Hz,2H, Ph), 7.57 (d, *J* = 8.8 Hz,1H, Ph), 8.05 (d, *J* = 8.8 Hz,1H, Ph), 11.32 (s, 1H, NH), 11.57 (s, 1H, NH); ^{13}CNMR (100 MHz, DMSO-d_6): *δ* 168.8 (O–*C*=O), 163.8 (NH–*C*O–C=C pyrimidine), 151.5 (NH–***C***O–NH pyrimidine), 155.0 (NH–*C*=C–C pyrimidine), 145.8, 142.8, 128.7, 127.9, 124.2, 123.7 (all ArCs), 91.4 (C–*C*=C–NH pyrimidine), 32.2 (*C*H$_2$), 22.8 (*C*H). Anal. Calcd for $C_{13}H_9N_3O_6$: C, 51.49; H, 2.99; N, 13.86%. Found: C, 51.48; H, 2.98; N,13.85%.*5-(2′-hydroxyphenyl)-5,6-dihydro-1H-pyrano[2,3-d]pyrimidine-2,4,7-trione (**4b**)*: Mp 292 °C; IR (KBr): *ν* 3597 (br), 3405 (s), 3290 (w), 2931 (s), 1726 (vs), 1629 (s), 1583 (vs), 1452 (s), 1386 (vs), 1249 (vs), 1173 (s), 1034 (s) cm^{-1}; ^{1}HNMR (400 MHz, DMSO-d_6): *δ* 3.30 (d, *J* = 8.4 Hz, 2H, CH2), 3.75 (s, 1H, OH), 4.35 (t, *J* = 8.0 Hz, 1H, CH), 7.40 (d, *J* = 8.4 Hz,1H, Ph), 7.60 (t, *J* = 8.4 Hz,1H, Ph), 7.72 (t, *J* = 8.4 Hz,1H, Ph), 8.07 (d, *J* = 9.6 Hz,1H, Ph), 10.09 (s, 1H, NH), 11.74 (s, 1H, NH); ^{13}CNMR (100 MHz, DMSO-d$_6$): *δ* 169.9 (O–*C*=O), 164.5 (NH–*C*O–C=C pyrimidine), 150.9 (NH–*C*O–NH pyrimidine), 153.5 (NH–*C*=C–C pyrimidine), 156.5, 130.5, 127.6, 126.5, 122.5, 116.6 (all ArCs), 90.7 (C–*C*=C–NH pyrimidine), 34.7 (*C*H2), 24.0 (*C*H). Anal. Calcd for $C_{13}H_{10}N_2O_5$: C, 56.94; H, 3.68; N, 10.22%. Found: C, 56.95; H, 3.67; N, 10.22%.*5-(2′-nitrophenyl)-5,6-dihydro-1H-pyrano[2,3-d]pyrimidine-2,4,7-trione (**4c**)*: Mp 218–220 °C; IR (KBr): *ν* 3413 (s), 3293(w), 2983 (s), 1727 (s), 1687 (vs), 1589 (vs), 1524 (s), 1447 (s), 1361 (vs), 1289 (s), 1173 (s), 1040 (s) cm^{-1}; ^{1}HNMR (400 MHz, DMSO-d_6): *δ* 3.35 (d, *J* = 6.8 Hz, 2H, CH$_2$), 4.47 (t, *J* = 7.2 Hz, 1H, CH), 7.22–7.29 (m, 2H, Ph), 7.41–7.46 (m, 2H, Ph), 11.24 (s, 1H, NH), 11.41 (s, 1H, NH); ^{13}CNMR (100 MHz, DMSO-d$_6$): *δ* 165.1 (O–*C*=O), 161.9 (NH–*C*O–C=C pyrimidine), 150.8 (NH–*C*O–NH pyrimidine), 151.6 (NH–*C*=C–C pyrimidine), 147.2, 138.5, 131.5, 130.4, 126.9, 124.1 (all ArCs), 91.0 (C–*C*=C–NH pyrimidine), 30.0 (*C*H2), 24.0 (*C*H). Anal. Calcd for $C_{13}H_9N_3O_6$: C, 51.49; H, 2.99; N, 13.86%. Found: C, 51.48; H, 2.98; N, 13.85%.*5-(2′-chlorophenyl)-5,6-dihydro-1H-pyrano[2,3-d]pyrimidine-2,4,7-trione (**4d**)*: Mp 240 °C; IR (KBr): *ν* 3408 (s), 3298 (w), 2978 (s), 1738 (s), 1694 (vs), 1589 (vs), 1516 (s), 1465 (s), 1347 (vs), 1276 (s), 1173 (s), 1033 (s), 746 (s) cm^{-1}; ^{1}HNMR (400 MHz, DMSO-d_6): *δ* 3.35 (d, *J* = 7.2 Hz, 2H, CH$_2$), 4.39 (t, *J* = 7.2 Hz, 1H, CH), 7.06–7.15 (m, 2H, Ph), 7.19–7.27 (m, 2H, Ph), 11.23 (s, 1H, NH), 11.43 (s, 1H, NH); ^{13}CNMR (100 MHz, DMSO-d_6): *δ* 165.3 (O–*C*=O), 161.7 (NH–*C*O–C=C pyrimidine), 151.6 (NH–*C*O–NH pyrimidine), 154.9 (NH–*C*=C–C pyrimidine), 143.2, 133.6, 131.1, 130.0, 127.3, 126.4 (all ArCs), 91.0 (C–*C*=C–NH pyrimidine), 31.6 (*C*H$_2$), 24.8 (*C*H). Anal. Calcd for $C_{13}H_9ClN_2O_4$: C, 53.35; H, 3.10; N, 9.57%. Found: C, 53.34; H, 3.10; N, 9.55%.*5-(2′,4′-dimethoxyphenyl)-5,6-dihydro-1H-pyrano[2,3-d]pyrimidine-2,4,7-trione (**4e**)*: Mp 235–237 °C; IR (KBr): *ν* 3404 (s), 3298 (w), 2989 (s), 1720 (vs), 1694 (s), 1583 (vs), 1498 (s), 1447 (s), 1367 (s), 1269 (vs), 1173 (s), 1030 (s) cm^{-1}; ^{1}HNMR (400 MHz, DMSO-d_6): *δ* 3.33 (d, *J* = 10.8 Hz, 2H, CH$_2$), 3.89 (s, 3H, OCH$_3$), 3.92 (s, 3H,OCH$_3$), 4.57 (t, *J* = 7.2 Hz, 1H, CH), 6.65–6.68 (d, *J* = 11.2 Hz,1H, Ph), 7.21–7.23 (d, *J* = 8.4 Hz, 1H, Ph), 7.58 (s, 1H, Ph) 11.04 (s, 1H, NH), 11.18 (s, 1H, NH); ^{13}CNMR (100 MHz, DMSO-d_6): *δ* 164.9 (O–*C*=O), 163.5 (NH–*C*O–C=C pyrimidine), 151.3 (NH–*C*O–NH pyrimidine), 152.3 (NH–C=C–C pyrimidine), 144.6, 135.6, 129.1, 114.6, 107.5, 104.9 (all Ar*C*s), 91.6 (C–*C*=C–NH pyrimidine), 57.2(O*C*H$_3$), 56.8 (O*C*H$_3$), 27.7 (*C*H$_2$), 20.5 (*C*H). Anal. Calcd for $C_{15}H_{14}N_2O_6$: C, 56.60; H, 4.43; N, 8.80%. Found: C, 56.58; H, 4.421; N, 8.80%.*5-(4′-florophenyl)-5,6-dihydro-1H-pyrano[2,3-d]pyrimidine-2,4,7-trione (**4f**)*: Mp 266 °C; IR (KBr): *ν* 3417 (w), 3295 (w), 2959 (s), 1734 (s), 1694 (vs), 1583 (vs), 1504 (s), 1447 (s), 1347 (vs), 1249 (s), 1034 (s) cm^{-1}; ^{1}HNMR (400 MHz, DMSO-d_6): *δ* 3.33 (d, *J* = 7.6 Hz, 2H, CH$_2$), 4.39 (t, *J* = 7.2 Hz, 1H, CH), 7.42–7.48 (dd, J_1 = 8.8 Hz, J_1 = 7.2 Hz, 2H, Ph), 7.98–8.02 (dd, J_1 = 5.6 Hz, J_1 = 6.0, 2H, Ph), 11.19 (s, 1H, NH), 11.41 (s, 1H, NH); ^{13}CNMR (100 MHz, DMSO-d_6): *δ* 170.0 (O–*C*=O), 163.5 (NH–*C*O–C=C pyrimidine), 151.5 (NH–*C*O–NH pyrimidine), 154.6 (NH–*C*=C–C pyrimidine), 159.6, 133.2, 129.2, 129.1, 117.4, 117.2 (all Ar*C*s), 91.9 (C–*C*=C–NH pyrimidine), 30.9 (*C*H2), 26.4 (*C*H); Anal. Calcd for $C_{13}H_9FN_2O_4$: C, 56.53; H, 3.28; N, 10.14%. Found: C, 56.53; H, 3.27; N, 10.15%.*5-(3′-nitrophenyl)-5,6-dihydro-1H-pyrano[2,3-d]pyrimidine-2,4,7-trione (**4g**)*: Mp 273 °C; IR (KBr): *ν* 3391 (s), 3291(w), 2959 (w), 1724 (s), 1699 (vs), 1589 (vs), 1527 (s), 1447 (s), 1339 (vs), 1200 (s), 1173 (w), 1020 (s) cm^{-1}; ^{1}HNMR (400 MHz, DMSO-d_6): *δ* 3.34 (d, *J* = 8.0 Hz, 2H, CH$_2$), 4.47 (t, *J* = 7.2 Hz, 1H, CH), 6.95 (s, 1H, Ph), 7.47 (d, *J* = 5.2 Hz,1H, Ph), 7.81 (d, *J* = 4.8 Hz,1H, Ph), 7.94–7.97(t, *J* = 5.6 Hz, 1H, Ph), 10.15 (s, 1H, NH), 11.14 (s, 1H, NH); ^{13}CNMR (100 MHz, DMSO-d_6): *δ* 168.7 (O–*C*=O), 164.6 (NH–*C*O–C=C pyrimidine), 153.5 (NH–*C*O–NH pyrimidine), 156.7 (NH–*C*O–*C*=O C–C pyrimidine), 147.6, 140.4, 131.6, 128.8, 122.7, 118.6 (all Ar*C*s), 91.6 (C–*C*=C–NH pyrimidine), 34.7 (*C*H$_2$), 23.0 (*C*H); Anal. Calcd for $C_{13}H_9N_3O_6$: C, 51.49; H, 2.99; N, 13.86%. Found: C, 51.48; H, 2.99; N, 13.85%.*5-(4′-chlorophenyl)-5,6-dihydro-1H-pyrano[2,3-d]pyrimidine-2,4,7-trione (**4h**)*: Mp 282 °C; IR (KBr): *ν* 3394 (s), 3291(w), 2959 (s), 1738 (s), 1681 (s), 1589 (w), 1524 (s), 1447 (w), 1354 (vs), 1216 (s), 1173 (w), 1010 (s), 746 (s) cm^{-1}; ^{1}HNMR (400 MHz, DMSO-d_6): *δ* 3.46 (d, *J* = 7.2 Hz, 2H, CH$_2$), 4.39 (t, *J* = 7.2 Hz, 1H, CH), 7.00–7.02 (d, *J* = 8.8 Hz, 2H, Ph), 7.87–7.89 (d, *J* = 8.4 Hz, 2H, Ph), 11.23 (s, 1H, NH), 11.43 (s, 1H, NH); ^{13}CNMR (100 MHz, DMSO-d_6): *δ* 168.6 (O–*C*=O), 162.5 (NH–*C*O–C=C pyrimidine), 152.5 (NH–*C*O–NH pyrimidine), 157.6 (NH–*C*=C–C pyrimidine), 148.7, 135.5, 127.8, 126.6, 119.9, 118.0 (all Ar*C*s), 92.7 (C–*C*=C–NH pyrimidine), 32.2 (*C*H$_2$), 22.4 (*C*H). Anal. Calcd for $C_{13}H_9ClN_2O_4$: C, 53.35; H, 3.10; N, 9.57%. Found: C, 53.34; H, 3.11; N, 9.55%.*5-(3′,4′-dimethoxyphenyl)-5,6-dihydro-1H-pyrano[2,3-d]pyrimidine-2,4,7-trione (**4i**)*: Mp 277 °C; IR (KBr): *ν* 3404 (s), 3288 (w), 2969 (s), 1730 (s), 1694 (s), 1589 (s), 1504 (s), 1447 (w), 1340 (s), 1276 (vs), 1173 (s), 1040 (s) cm^{-1}; ^{1}HNMR (400 MHz, DMSO-d_6), *δ* 3.34 (d, *J* = 8.0 Hz, 2H, CH$_2$), 3.80 (s, 3H, OCH$_3$), 3.88 (s, 3H, OCH$_3$), 4.39 (t, *J* = 7.2 Hz, 1H, CH), 7.09 (d, *J* = 8.8 Hz, 1H, Ph), 7.88–7.90 (d, *J* = 8.4 Hz, 1H, Ph), 8.24 (s, 1H, Ph), 11.19 (s, 1H, NH), 11.31 (s, 1H, NH); ^{13}CNMR (100 MHz, DMSO-d_6): *δ* 164.9 (O–*C*=O), 163.2 (NH–*C*O–C=C pyrimidine), 154.5 (NH–**C**O–NH pyrimidine), 156.3 (NH–C=C–C pyrimidine), 151.1, 148.6, 132.6, 126.1, 117.6, 116.1 (all Ar*C*s), 91.4 (C–*C*=C–NH pyrimidine), 56.7(O*C*H$_3$), 56.3 (O*C*H$_3$), 31.9 (*C*H$_2$), 24.8 (*C*H). Anal. Calcd for $C_{15}H_{14}N_2O_6$: C, 56.60; H, 4.43; N, 8.80%. Found: C, 56.60; H, 4.43; N, 8.79%.