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PAPER

Diversity oriented synthesis of tri-substituted methanes containing aminouracil and hydroxynaphthaquinone/ hydroxycoumarin moiety using organocatalysed multicomponent reactions in aqueous medium

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Synthesis of a series of tri-substituted methane derivatives have been reported via one-pot multicomponent reaction of aldehyde, 1,3-dimethyl-6-aminouracil and 2-hydroxy-1,4-naphthaquinone/ 4-hydroxycoumarin using bifunctional thiourea based organocatalyst in aqueous medium. Use of organocatalyst, water as solvent and no need of column chromatographic purification are the notable features of this methodology.

Introduction

Tri-substituted methanes (TRSMs)[1] are important class of molecules having a wide range of pharmacological and biological activities such as anti-cancer,[2] antiproliferative,[3] antitubercular[4] etc. They are also used as molecular chemosensors[5] and for the generation of dendrimers.[6] Substituted methane derivatives having substituents such as aminouracil, hydroxynaphthaquinone/ hydroxycoumarin are considered as important bioactive molecules. Some representative examples of trisubstituted methanes having anticoagulant,[7] antioxidant,[8] antibacterial,[9] antimicrobial[10] and antibiofilm[10] activities are shown in Figure 1.

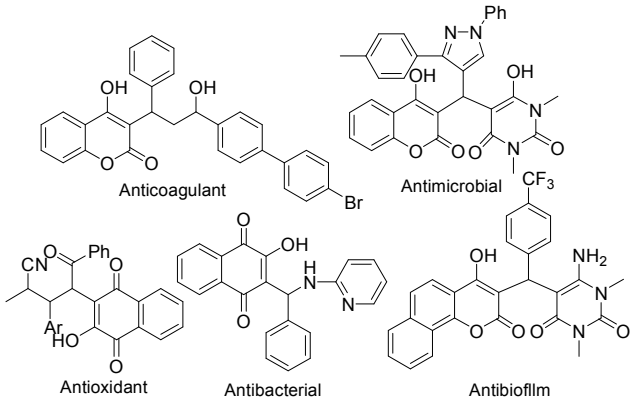
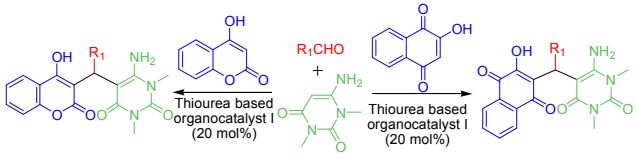


Figure 1 Biologically active tri-substituted methane derivatives containing aminouracil, hydroxynaphthaquinone/ hydroxycoumarin moiety

Considering the importance of tri-substituted methanes recently Karami et al have reported a three component reaction of aryl aldehydes, 4-hydroxycoumarin and 3-methyl-1-phenyl-2-pyrazolin-5-one using ZnO nanoparticle for the green synthesis of trisubstituted methane derivatives.[11] Panda et al have also reported the synthesis of tri-substituted methanes having aryl and heteroaryl rings.[12] Similarly,Atmakur et al.[10] reported the regioselective synthesis of highly functionalized 3-benzylpyrimidino chromen-2-ones in a one pot three component reaction in acetic acid and determined their anti-microbial and anti-biofilm activities. Thus a plethora of methods are known in literature for the synthesis of tri-substituted methane derivatives.[13] From the green chemistry point of view design of methodology with pot, atom and step economic approach has remained one of the prime goal in organic synthesis.[14] In this direction multicomponent reactions (MCRs)[15] where more than two components react in one pot have gained considerable attention in recent time. Similarly organocatalysis[16] imparts environment friendliness in organic synthesis due to its inherent low toxicity, metal free and simple reaction conditions. Thus employing organocatalysis in MCRs[17] makes the process greener. In continuation of our work[18] on MCRs we wanted to design an organocatalyzed MCR for the synthesis of some structurally divergent tri-substituted methanes having some bioactive moieties such as aminouracil, hydroxynaphthaquinone/ hydroxycoumarin as substituents. Among the organocatalysts bifunctional thiourea based organocatalysts[19] are popular in organic synthesis due to their activation of electrophile by double-hydrogen-bonding interactions with thiourea moiety as well as the activation of nucleophile by the other part (basic moiety). In this paper we have reported a three component reaction of aldehyde, 1,3-dimethyl-6-aminouracil and 2-hydroxy-1,4-naphthaquinone/4-hydroxycoumarin in aqueous medium in presence of bifunctional thiourea based organocatalyst for the synthesis of trisubstituted methane derivatives (Scheme1).



Scheme 1 Synthesis of tri-substituted methane derivatives.

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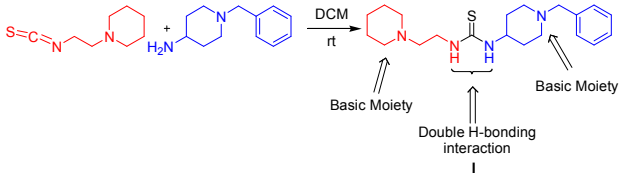
† Electronic Supplementary Information (ESI) available:: ^{1}H NMR and ^{13}C NMR spectra for all reactions products are available. See DOI: 10.1039/b000000x/

Result and discussion

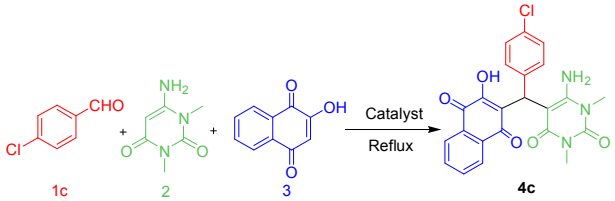
Considering the popularity as well as virtues of bifunctional thiourea based organocatalysts in organic synthesis, we initially synthesized organocatalyst **I** having a thiourea moiety and two basic sites using a two component reaction of 2-piperidinoethyl isothiocyanate and 4-amino-1-benzyl piperidine as shown in Scheme2.



Scheme 2 Synthesis of bifunctional thiourea based organocatalyst I

Recently we have reported a L-proline catalyzed three component reaction of 2-hydroxy-1,4-naphthaquinone, aldehydes, and aminopyrazoles which gives cyclised product 2*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10(4*H*,11*H*)-diones in ethanol under reflux conditions.[20] In continuation of our that work when we have carried out the reaction of 4-chlorobenzaldehyde **1c**, 1,3-dimethyl-6-aminouracil **2** and 2-hydroxy-1,4-naphthaquinone **3** in H_2O without any catalyst under reflux conditions, we ended with acyclic product i.e, tri-substituted methane derivatives instead of the cyclic product. The yield of the reaction was only 33% after 6 hrs (Table 1, entry 1). Our next endeavour was to enhance the yield of the reaction by employing various catalysts. For this purpose, various catalysts were tested. We achieved a slight improvement in the yield of the product, but the results were still not very satisfactory (Table 1, entries 2-6). Interestingly, when we performed the same reaction in the presence of our newly synthesized thiourea-based organocatalyst I (Table 1, entry 7), the maximum yield was obtained. It is note worthy to mention that a mixture of Et_3N and thiourea (20+ 20) mol% provided lower yields as compared to organocatalyst I (Table 1, entry 8).

Table 1 Screening of catalysts

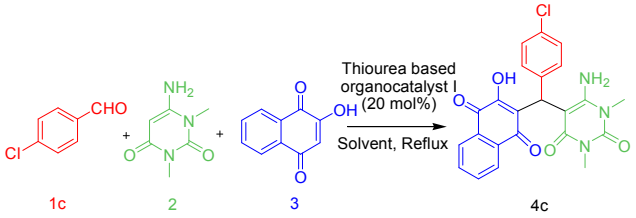


Entries	Catalyst	Solvent	Time (h)	Yield[a] (%)
1.	----	H_2O	6	33
2.	----	AcOH	4	60
3.	L-proline	H_2O	7	40
4.	Thiourea	H_2O	6	58
5.	Et_3N	H_2O	8	38
6.	DABCO	H_2O	5	65
7.	I	H_2O	3	85
8.	Et_3N+ Thiourea	H_2O	6	68

[a]Isolated yield.

Next, we performed a screening of various solvents such as H_2O, EtOH, MeCN, THF, DMSO and Toluene (Table 2, entries 1–6) to see the effect of solvents on the reaction. The results of Table 2 revealed that water was the best solvent for the reaction in terms of yield and reaction time.

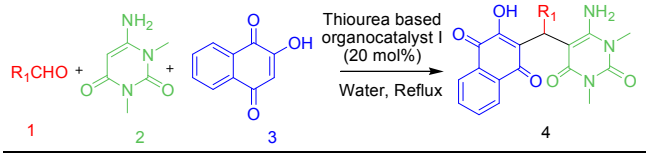
Table 2 Effects of solvents

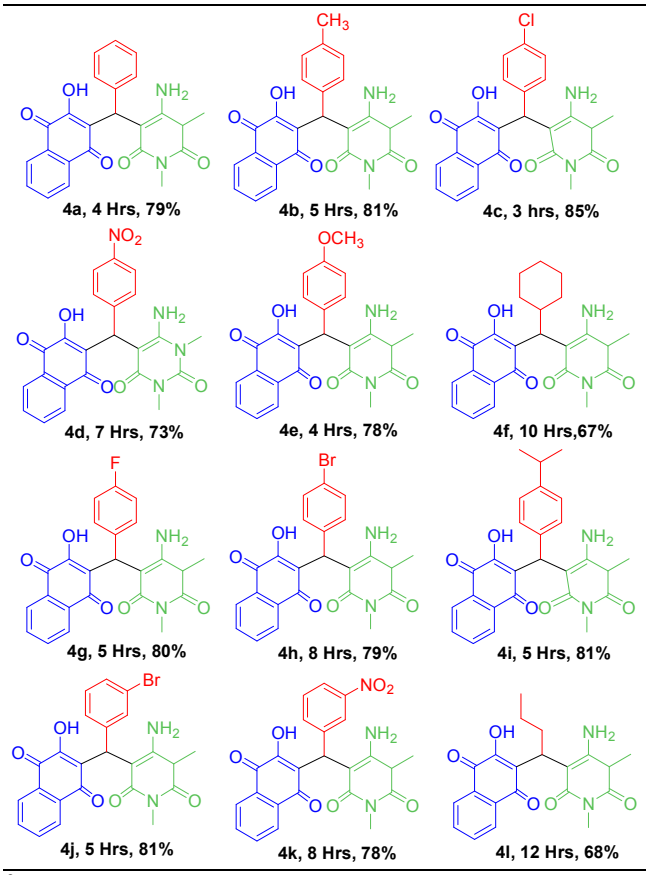


Entries	Catalyst	Solvent	Time (h)	Yield[a] (%)
1.	I	H_2O	3	85
2.	I	EtOH	5	75
3.	I	MeCN	7	72
4.	I	THF	12	34
5.	I	DMSO	8	<30
6.	I	Toluene	6	58

[a]Isolated yield

Table 3 Synthesis of tri-substituted methane derivatives[a] containing aminouracil and hydroxynaphthaquinone moiety



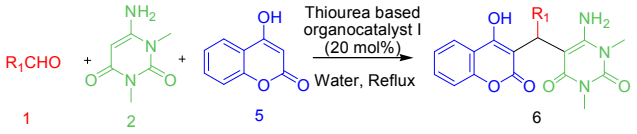


[a]Isolated yield.

With the optimized reaction conditions, we then explored the generality of the method by using various aldehydes (both aromatic and aliphatic) with 2-hydroxy-1,4-naphthaquinone and 1,3-dimethyl-6-aminouracil. The results are summed up in Table

3. Aromatic aldehydes containing various substituents like 4-Me, 4-Cl, 4-NO_2, 4-OMe, 4-F, 4-Br, 4-$CH(Me)_2$, 3-Br, 3-NO_2 and aliphatic aldehydes like cyclohexyl aldehyde, butyraldehyde were underwent smoothly to provide the corresponding tri-substituted methane derivatives (**4a-4l**) in good to moderate yields. Next we tried the reaction with phenylacetaldehyde, however, in this case the reaction provided a inseparable mixture of products. It is quite clear from Table 3 that neither the nature nor the positions of substituents on aromatic ring in aromatic aldehydes alter the yield of reaction to any significant extent. However, aliphatic aldehydes provide lower yields as compared to aromatic one, which may be due to the less stability as well as tendency of those aldehydes to exist in enol form.

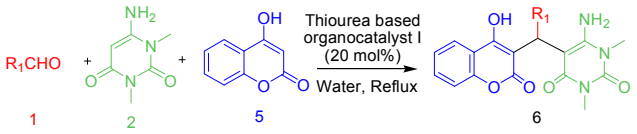
After the successful synthesis of tri-substituted methane derivatives containing hydroxynaphthaquinone, aminouracil and aromatic/aliphatic ring, we did the three component reaction of 4-hydroxycoumarin, aldehyde and 1,3-dimethyl-6-aminouracil under the similar reaction condition and we obtained the corresponding tri-substituted methane derivatives (Scheme 3).

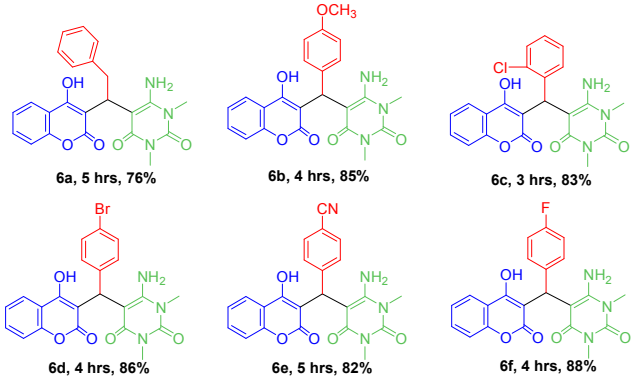


Scheme 3 The three component reaction of 4-hydroxycoumarin, aldehyde and 1,3-dimethyl-6-aminouracil.

Looking at the molecular skeleton having pyrimidine and coumarin fragments in tri-substituted methane derivatives as well as their biological activity, the scope of the reaction was tested with different substituted aldehydes and the results are presented in the Table 4 **(6a-f)**.

Table 4 Synthesis of tri-substituted methane derivatives[a] containing aminouracil and hydroxycoumarin moiety





[a]Isolated yield.

All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis. To remove the ambiguity in structure further D_2O exchange experiment was performed with compound **4c**. The labile protons of -NH_2 and -OH were vanished in the D_2O exchanged ^{1}H NMR spectra of **4c** (Figure 2). From this it was confirmed that the product was not cyclised and free -NH_2 and -OH groups were present in the tri-substituted methane derivatives.

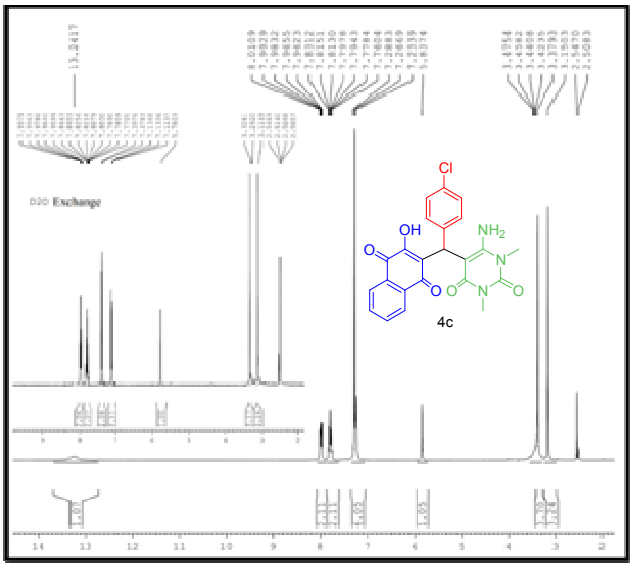
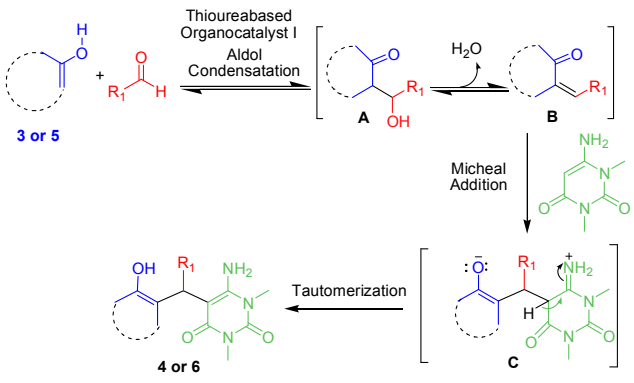


Figure 2 ^{1}H NMR and D_2O exchanged ^{1}H NMR spectra of 4c

A plausible mechanism for the formation of trisubstituted methane derivatives has been proposed in Scheme 4. Similar to literature reports[21] we believe initially aldehyde reacts with **3** or **5** via Aldol condensation followed by dehydration to give intermediate **B**. Then third component undergoes Micheal addition followed by tautomerization to provide the corresponding trisubstituted methane derivatives **4** or **6**. We believe our synthesized thiourea based organocatalyst **I** plays dual role in this reaction. The basic functionalities present in this organocatalyst activates nucleophile and the thiourea moiety activates the C=O group by the double hydrogen bonding interaction.



Scheme 4 Proposed reaction mechanism

Conclusions

We have synthesized a bifunctional thiourea-based organocatalyst and explored its application in the one-pot three component reaction of aldehyde, 1,3-dimethyl-6-aminouracil and 2-hyroxy-1,4-naphthaquinone/4-hydroxycoumarin in aqueous medium for the synthesis of diverse tri-substituted methane derivatives having biologically active moieties such as pyrimidine and naphthaquinone/coumarin as substituents. In addition there are free -OH, -NH_2 and CO groups in our product molecules which can be explored as ligand in coordination chemistry as well as in heterocyclic chemistry for further functionalization or for the synthesis of fused heterocycles. Studies towards the application of this methodology are under way.

Experimental

Starting materials and solvents are commercially available and used without further purification. The purity of the synthesized compounds were ascertained by thin layer chromatography on silica gel GF 254 in ethyl acetate using iodine vapours as detecting agent. Melting points were determined by the melting point apparatus using capillary tube method. IR spectra were recorded on a Shimadzu FTIR spectrophotometer in KBr pellet. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 and were expressed in parts per million (δ, ppm) downfield using Me_4Si as internal standard on Bruker Avance II 400 MHz spectrophotometer. Elemental analyses were carried out in a Perkin Elmer 2400 automatic carbon, hydrogen, nitrogen analyzer.

Typical experimental procedure for the synthesis of bifunctional thiourea based organocatalyst I :
First, 4-amino-1-benzyl piperidine (0.5 mmol) was dissolved in DCM and allowed to cool at 0°C. Then 2-piperidinoethyl isothiocyanate (0.5 mmol) was added in the reaction mixture and allowed to stir at room temperature till the completion of the reaction as checked by TLC. The reaction mixture was cooled, the solid was filtered off and washed with ethanol to afford the desired product.

1-(1-benzylpiperidin-4-yl)-3-(2-(piperidin-1-yl)ethyl)thiourea (I): White powdery solid; mp = 240-242 °C; IR (KBr): 3273, 3151, 3054, 2929, 1574, 1495, 1240, 961, 860, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 7.33-7.22 (m, 5H), 6.72 (brs, 1H), 4.02 (brs, 1H), 3.51 (s, 2H), 3.45-3.38 (m, 2H), 2.88-2.85 (m, 2H), 2.48-2.42 (m, 7H), 2.15-2.09 (m, 2H), 2.05-2.02 (m, 2H), 1.59-1.51 (m, 6H), 1.48-1.47 (m, 2H) ppm; ^{13}C (100MHz, $CDCl_3$): 181.1, 138.3, 129.3, 128.4, 127.9, 62.9, 54.5, 52.4, 41.8, 32.2, 30.9, 25.8, 24.1 ppm; Anal. Calcd for $C_{20}H_{32}N_4S$ (360.56): C, 66.62; H, 8.95; N, 15.54; Found: C, 66.71; H, 8.98; N, 15.68.

Typical experimental procedure for the synthesis of 4c: To a solution of 2-hydroxy-1,4-naphthaquinone 0.174 g (1 mmol) and 4-chlorobenzaldehydes 0.14 g (1 mmol) in 1 ml water, 20 mol% thiourea-based organocatalyst I was added and stirred under reflux condition for 15 minutes. Afterwards, 1,3-dimethyl-6-aminouracil 0.155g (1 mmol) was introduced and stirring was continued till the completion of the reaction as checked by TLC. The resulting mixture was cooled at room temperature, the solid was filtered off, washed with water first, then with 5 ml ethanol to afford the pure product.

6-amino-5-((1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)(phenyl)methyl)-1,3-dimethylpyrimidine-2,4 (1H,3H)-dione 4a: Yield 79%; Red powdered solid; mp = 250-251 °C; IR (KBr): 3405, 3254, 2923, 1694, 1653, 1603, 1578, 1498, 1345, 967, 878, 755 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.20 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.85 (t, J = 8.0 Hz, 1H), 7.82 (t, J = 8.0 Hz, 1H), 7.27-7.17 (m, 5H), 7.15 (s, 2H), 5.86 (s, 1H), 3.38 (s, 3H), 3.15 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 185.9, 181.0, 163.6, 158.5, 154.4, 150.1, 138.3, 134.3, 133.4, 131.7, 130.5, 128.0, 126.6, 126.0, 125.6, 123.4, 100.4, 85.6, 34.7, 30.4, 28.1 ppm; Anal. Calcd. for $C_{23}H_{19}N_3O_5$ (417.41): C, 66.18; H, 4.59; N, 10.07; Found: C, 66.26; H, 4.62; N, 10.20.

6-amino-5-((1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)(p-tolyl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione 4b: Yield 81%; Orange solid; mp = 217-218 °C; IR (KBr): 3421, 3247, 2921, 1698, 1661, 1607, 1567, 1475, 1356, 915, 878, 752 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.28 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.83 (t, J = 8.0 Hz, 1H), 7.79 (t, J = 8.0 Hz, 1H), 7.19 (s, 2H), 7.09 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 5.79 (s, 1H), 3.40 (s, 3H), 3.17 (s, 3H), 2.27 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 186.0, 181.0, 163.7, 158.7, 154.4, 150.1, 134.9, 134.5, 134.1, 133.3, 131.7, 130.6, 128.6, 126.5, 126.0, 125.6, 123.5, 85.9, 34.3, 30.3, 28.0, 20.5 ppm; Anal. Calcd. for $C_{24}H_{21}N_3O_5$ (431.44): C, 66.81; H, 4.91; N, 9.74; Found: C, 66.88; H, 4.94; N, 9.86.

6-amino-5-((4-chlorophenyl)(1,4-dihydro-2-hydroxy-1,4-dioxo naphthalen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione 4c: Yield 85%; Red solid; mp = 254-255 °C; IR (KBr): 3385, 3261, 2987, 1702, 1663, 1605, 1580, 1489, 1342, 928, 836, 776 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.24 (s, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.81 (t, J = 8.0 Hz, 1H), 7.78 (t, J = 8.0 Hz, 1H), 7.29-7.27 (m, 4H), 7.23 (s, 2H), 5.84 (s, 1H), 3.38 (s, 3H), 3.15 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 185.8, 180.9, 163.6, 158.5, 154.4, 150.1, 137.7, 134.2, 133.4, 131.7, 130.6, 130.2, 128.7, 127.8, 126.0, 125.6, 123.2, 85.4, 34.4, 30.4, 28.2 ppm; Anal. Calcd. For $C_{23}H_{18}ClN_3O_5$ (451.86): C, 61.14; H, 4.02; N, 9.30; Found: C, 61.22; H, 4.05; N, 9.44.

6-amino-5-((1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)(4-nitrophenyl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione 4d: Yield 73%; Yellow crystalline solid; mp = 278-279 °C; IR (KBr): 3397, 3241, 2929, 1697, 1665, 1603, 1556, 1473, 1351, 963, 810, 756 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.14 (s, 1H), 8.08 (d, J = 8.0 Hz, 2H), 8.00 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.85-7.75 (m, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.25 (s, 2H), 5.83 (s, 1H), 3.38 (s, 3H), 3.15 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 185.8, 181.2, 163.6, 158.5, 154.4, 150.1, 147.7, 145.7, 134.4, 133.5, 131.7, 130.6, 128.2, 126.1, 125.7, 123.8, 110.9, 85.9, 35.3, 30.4, 28.2 ppm; Anal. Calcd. For $C_{23}H_{18}N_4O_7$ (462.41): C, 59.74; H, 3.92; N, 12.12; Found: C, 59.82; H, 3.88; N, 12.25.

6-amino-5-((1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)(4-methoxyphenyl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione 4e: Yield 78%; Orange solid; mp = 247-248 °C; IR (KBr): 3394, 3230, 2920, 1695, 1656, 1608, 1565, 1472, 1343, 965, 814, 773 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.18 (s, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.85 (t, J = 8.0 Hz, 1H), 7.81 (t, J = 8.0 Hz, 1H), 7.16 (s, 2H), 7.11 (d, J = 8.0 Hz, 2H), 6.80 (d, J = 8.0 Hz, 2H), 5.78 (s, 1H), 3.72 (s, 3H), 3.37 (s, 3H), 3.15 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 185.0, 181.2, 162.4, 158.0, 153.9, 150.4, 142.9, 134.4, 133.2, 131.8, 130.5, 129.7, 129.2, 127.9, 125.9, 125.4, 121.4, 86.5, 58.8, 35.1,

29.9, 27.9 ppm; Anal. Calcd. For $C_{24}H_{21}N_3O_6$ (447.44): C, 64.42; H, 4.73; N, 9.39; Found: C, 64.49; H, 4.77; N, 9.53.

6-amino-5-(cyclohexyl(1,4-dihydro-2-hydroxy-1,4-dioxonaphtha len-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione 4f: Yield 67%; Orange red solid; mp = 201-202 °C; IR (KBr): 3372, 3239, 2920, 1697, 1670, 1608, 1579, 1371, 975, 861, 752 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 14.08 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.78 (t, J = 8.0 Hz, 1H), 7.75 (t, J = 8.0 Hz, 1H), 7.23 (s, 2H), 3.82 (d, J = 8.0 Hz, 1H), 3.34 (s, 3H), 3.19 (s, 3H), 1.59-1.52 (m, 5H), 1.12-1.01 (m, 4H), 0.76-0.73 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 186.8, 180.9, 164.2, 158.2, 154.8, 152.7, 149.8, 134.1, 133.4, 131.2, 130.5, 125.9, 124.0, 85.2, 33.7, 31.5, 30.9, 29.9, 28.1, 27.6, 26.1 ppm; Anal. Calcd. For $C_{23}H_{25}N_3O_5$ (423.46): C, 65.24; H, 5.95; N, 9.92; Found: C, 65.32; H, 5.92; N, 10.04.

6-amino-5-((4-fluorophenyl)(1,4-dihydro-2-hydroxy-1,4-dioxo naphthalen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H) dione 4g: Yield 80%; Red crystalline solid; mp = 241-242 °C; IR (KBr): 3396, 3246, 2922, 1738, 1687, 1665, 1659, 1608, 1578, 1371, 969, 893, 753 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 13.18 (s, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.84 (t, J = 8.0 Hz, 2H), 7.80 (t, J = 8.0 Hz, 2H), 7.30-7.24 (m, 4H), 7.21 (s, 2H), 5.84 (s, 1H), 3.37 (s, 3H), 3.15 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 185.8, 181.0, 163.5, 158.5, 154.4, 150.1, 137.7, 134.3, 133.4, 131.7, 130.6, 130.2, 128.7, 127.9, 126.0, 125.7, 123.2, 85.4, 34.4, 30.4, 28.2 ppm; Anal. Calcd. For $C_{23}H_{18}FN_3O_5$ (435.4): C, 63.45; H, 4.17; N, 9.65; Found: C, 63.53; H, 4.20; N, 9.78.

6-amino-5-((4-bromophenyl)(1,4-dihydro-2-hydroxy-1,4-dioxo naphthalen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione 4h: Yield 79%; Orange solid; mp = 251-252 °C; IR (KBr): 3393, 3210, 2921, 1680, 1650, 1603, 1573, 1488, 1343, 905, 835, 756 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 13.15 (s, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.85 (t, J = 8.0 Hz, 1H), 7.81 (t, J = 8.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.21-7.19 (m, 4H), 5.82 (s, 1H), 3.37 (s, 3H), 3.15 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 185.7, 180.9, 163.5, 158.5, 154.4, 150.1, 138.2, 134.3, 133.5, 131.7, 130.8, 130.6, 129.2, 126.0, 125.7, 123.2, 118.7, 85.3, 34.5, 30.4, 28.2 ppm; Anal. Calcd. For $C_{23}H_{18}BrN_3O_5$ (496.31): C, 55.66; H, 3.66; N, 8.47; Found: C, 55.75; H, 3.62; N, 8.60.

6-amino-5-((1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)(4-isopropylphenyl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-di one 4i: Yield 81%; Orange red crystalline solid; mp = 259-260 °C; IR (KBr): 3389, 3237, 2950, 1705, 1655, 1607, 1578, 1462, 1341, 951, 841, 761 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 13.27 (s, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.83 (t, J = 8.0 Hz, 1H), 7.79 (t, J = 8.0 Hz, 1H), 7.21 (s, 2H), 7.15-7.08 (m, 4H), 5.80 (s, 1H), 3.38 (s, 3H), 3.16 (s, 3H), 2.86-2.79 (m, 1H), 1.16 (d, J = 8.0 Hz, 6H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 185.9, 181.1, 163.6, 158.6, 154.4, 150.1, 145.5, 135.5, 134.3, 133.4, 131.7, 130.5, 126.6, 126.0, 125.9, 125.7, 123.7, 85.6, 34.4, 32.8, 30.4, 28.2, 23.9 ppm; Anal. Calcd. For $C_{26}H_{25}N_3O_5$ (459.49): C, 67.96; H, 5.48; N, 9.14; Found: C, 68.05; H, 5.44; N, 9.28.

6-amino-5-((3-bromophenyl)(1,4-dihydro-2-hydroxy-1,4-dioxo naphthalen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione 4j: Yield 81%; Yellow solid; mp = 234-235 °C; IR (KBr): 3420, 3366, 2920, 1763, 1715, 1665, 1648, 1575, 1492, 1378, 968, 812, 754 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 13.26 (s, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.38 (s, 1H), 7.18 (s, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.19-7.17 (m, 4H), 5.87 (s, 1H), 3.40 (s, 3H), 3.18 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 185.7, 180.9, 163.6, 158.5, 154.4, 150.0, 141.3, 134.0, 133.2, 131.7, 130.6, 129.8, 129.2, 128.5, 126.0, 122.8, 121.7, 85.3, 34.5, 30.3, 28.0 ppm; Anal. Calcd. For $C_{23}H_{18}BrN_3O_5$ (496.31): C, 55.66; H, 3.66; N, 8.47; Found: C, 55.75; H, 3.70; N, 8.60.

6-amino-5-((1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)(3-nitrophenyl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione 4k: Yield 78%; Red crystalline solid; mp = 224-225 °C; IR (KBr): 3371, 3230, 2941, 1685, 1670, 1605, 1552, 1465, 1350, 965, 879, 765 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 13.18 (s, 1H), 8.03 (t, J = 8.0 Hz, 2H), 7.95 (d, J = 8.0 Hz, 2H), 7.83-7.72 (m, 3H), 7.54 (t, J = 8.0 Hz, 1H), 7.27 (s, 2H), 5.98 (s, 1H), 3.41 (s, 3H), 3.17 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 185.6, 181.2, 163.5, 158.4, 154.5, 150.1, 148.0, 141.4, 134.2, 133.0, 131.7, 130.5, 129.2, 126.0, 125.3, 121.4, 110.9, 84.8, 34.8, 30.4, 28.1 ppm; Anal. Calcd. For $C_{23}H_{18}N_4O_7$ (462.41): C, 59.74; H, 3.92; N, 12.12; Found: C, 59.82; H, 3.89; N, 12.26.

6-amino-5-(1-(1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl) butyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione 4l: Yield 68%; Red solid; mp = 246-247 °C; IR (KBr): 3375, 3215, 2958, 1681, 1673, 1608, 1581, 1458, 1346, 968, 879, 794 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 14.01 (s, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.78 (t, J = 8.0 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.27 (s, 2H), 4.22 (t, J = 8.0 Hz, 1H), 3.37 (s, 3H), 3.12 (s, 3H), 2.19-2.07 (m, 2H), 1.26-1.21 (m, 2H), 0.88-0.85 (m, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 185.6, 180.9, 164.3, 158.5, 154.2, 149.8, 133.8, 133.1, 131.4, 130.4, 125.8, 125.5, 124.8, 86.4, 30.7, 30.4, 30.2, 27.9, 21.1, 13.6 ppm; Anal. Calcd. For $C_{20}H_{21}N_3O_5$ (383.4): C, 62.65; H, 5.52; N, 10.96; Found: C, 62.73; H, 5.55; N, 11.10.

Typical experimental procedure for the synthesis of 6b: To a solution of 4-hydroxycoumarin 0.162 g (1 mmol) and 4-methoxybenzaldehydes 0.136 g (1 mmol) in 1 ml water, 20 mol% thiourea-based organocatalyst I was added and stirred under reflux condition for 15 minutes. Afterwards, 1,3-dimethyl-6-aminouracil 0.155g (1 mmol) was introduced and stirring was continued till the completion of the reaction as checked by TLC. The resulting mixture was cooled at room temperature, the solid was filtered off, washed with water first, then with 5 ml ethanol to afford the pure product.

6-amino-5-(1-(4-hydroxy-2-oxo-2H-chromen-3-yl)(2-phenyleth yl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione 6a: Yield, 76%; White crystalline solid; mp = 247-249 °C; IR (KBr): 3529, 3428, 3155, 3017, 1708, 1671, 1623, 1490, 1378, 1049, 1013, 860, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 14.05 (s, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.26-7.22 (m, 2H), 7.18 (d, J = 8.0 Hz, 3H), 7.15-7.12 (m, 1H), 6.21 (s, 2H), 4.51 (t, J = 8.0 Hz, 1H), 3.53-3.48 (m, 2H), 3.41 (s, 3H), 3.39 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 163.5, 161.5, 151.8, 151.6, 149.8, 140.1, 131.9, 128.2, 128.0, 126.1, 125.9, 124.1, 123.5, 115.9, 105.5, 88.5, 34.5, 30.3, 28.1, 26.9 ppm; Anal. Calcd. for $C_{23}H_{21}N_3O_5$ (419.43): C, 65.86; H, 5.05; N, 10.02; Found C, 65.93; H, 5.09; N, 10.15.

6-amino-5-((4-hydroxy-2-oxo-2H-chromen-3-yl)(4-methoxyphen yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione 6b: Yield 85%; White needle like solid; mp = 191-194 °C; IR (KBr): 3555, 3346, 3184, 2972, 1691, 1655, 1608, 1573, 1443, 1071, 1032,

859, 763 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 13.88 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.36-7.30 (m, 4H), 7.06 (d, J = 8.0 Hz, 2H), 6.77 (d, J = 8.0 Hz, 2H), 5.63 (s, 1H), 3.74 (s, 3H), 3.46 (s, 3H), 3.23 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.2, 164.0, 163.4, 157.2, 154.9, 151.9, 149.9, 131.9, 129.5, 127.1, 123.8, 123.6, 116.9, 115.8, 113.2, 104.4, 87.5, 54.7, 35.2, 30.2, 28.0 ppm. Anal. Calcd. for $C_{23}H_{21}N_3O_6$ (435.43): C, 63.44; H, 4.86; N, 9.65; Found C, 63.51; H, 4.90; N, 9.76.

6-amino-5-((2-chlorophenyl)(4-hydroxy-2-oxo-2H-chromen-3-yl) methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione 6c: Yield 83%; White crystalline solid; mp = 227- 228 °C; IR (KBr): 3534, 3402, 3199, 2970, 1703, 1695, 1621, 1574, 1472, 1060, 1040, 862, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 13.68 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.36–7.31 (m, 3H), 7.26–7.16 (m, 2H), 6.48 (s, 2H), 5.75 (s, 1H), 3.57 (s, 3H), 3.30 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 165.8, 164.7, 154.3, 152.3, 150.6, 135.9, 133.3, 132.5, 130.4, 129.2, 128.1, 126.5, 124.5, 124.4, 117.3, 116.2, 103.6, 89.4, 35.9, 30.1, 28.7 ppm; Anal. Calcd. for $C_{22}H_{18}N_3O_5$ (439.85): C, 60.07; H, 4.12; N, 9.55; Found C, 60.13; H, 4.15; N, 9.66.

6-amino-5-((4-bromophenyl)(4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4 (1H,3H)-dione 6d: Yield 86%; White crystalline solid; mp = 237- 238 °C; IR (KBr): 3367, 3196, 2979, 1734, 1704, 1660, 1573, 1487, 1444, 1065, 1045, 854, 758 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 13.95 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.42-7.41 (m, 3H), 7.38 (s, 2H), 7.34 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 2H), 5.65 (s, 1H), 3.45 (s, 3H), 3.21 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.1, 165.9, 164.0, 155.1, 151.9, 149.9, 137.8, 132.2, 130.7, 128.6, 124.0, 123.7, 118.8, 116.9, 115.9, 104.1, 86.7, 35.7, 30.4, 28.1 ppm; Anal. Calcd. for $C_{22}H_{18}BrN_3O_5$ (484.3): C, 54.56; H, 3.75; N, 8.68; Found C, 54.63; H, 3.78; N, 8.80.

4-((6-amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)(4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)benzonitrile 6e: Yield 82%; White crystalline solid; mp 221-223 °C; IR (KBr): 3382, 3186, 2989, 1734, 1715, 1663, 1571, 1452, 1069, 1042, 860, 766 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 13.97 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.66 (t, J = 8.0 Hz, 1H), 7.46-7.35 (m, 6H), 5.72 (s, 1H), 3.39 (s, 3H), 3.16 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.6, 164.1, 163.8, 155.3, 151.9, 149.9, 144.9, 132.5, 131.9, 127.7, 124.3, 123.7, 118.9, 116.9, 116.1, 108.6, 104.2, 86.1, 36.5, 30.6, 28.2 ppm; Anal. Calcd. for $C_{23}H_{18}N_4O_5$ (430.41): C, 64.18; H, 4.22; N, 13.02; Found C, 64.24; H, 4.26; N, 13.14.

6-amino-5-((4-fluorophenyl)(4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione 6f: Yield 88%; White solid; mp = 248-250 °C; IR (KBr): 3389, 3194, 3077, 2952, 1735, 1705, 1675, 1565, 1493, 1060, 858, 755 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 13.88 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.38-7.32 (m, 4H), 7.20-7.17 (m, 2H), 6.99 (t, J = 8.0 Hz, 2H), 5.65 (s, 1H), 3.47 (s, 3H), 3.21 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.9, 164.0, 161.7, 159.3, 155.1, 151.9, 149.9, 133.9, 132.0, 128.0, 123.9, 123.7, 116.9, 115.8, 114.6, 104.3, 87.1, 35.4, 30.3, 28.1 ppm; Anal. Calcd. for $C_{22}H_{18}FN_3O_5$ (423.39): C, 62.41; H, 4.29; N, 9.92; Found C, 62.48; H, 4.32; N, 10.03.

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