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

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Synthesis of a series of tri-substituted methane derivatives has been reported *via* a one-pot multicomponent reaction of aldehyde, 1,3-dimethyl-6-aminouracil and 2-hydroxy-1,4-naphthoquinone/4-hydroxycoumarin using a bifunctional thiourea-based organocatalyst in aqueous medium. Use of the organocatalyst, and water as a solvent, without the need for column chromatographic purification, are the notable features of this methodology.

Introduction

Tri-substituted methanes (TRSMs)[1] are an important class of molecules, with 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 with substituents such as aminouracil, hydroxynaphthoquinone/hydroxycoumarin are considered as important bioactive molecules. Some representative examples of tri-substituted methanes with anticoagulant,[7] antioxidant,[8] antibacterial,[9] antimicrobial[10] and antibiofilm[10] activities are shown in Fig. 1.

Considering the importance of tri-substituted methanes, Karami *et al.* have recently reported a three component reaction of aryl aldehydes, 4-hydroxycoumarin and 3-methyl-1-phenyl-2-pyrazolin-5-one using ZnO nanoparticles for the green synthesis of tri-substituted methane derivatives.[11] Panda *et al.* have also reported the synthesis of tri-substituted methanes with 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 is present in the literature for the synthesis of tri-substituted methane derivatives.[13] From the green chemistry point of view, the design of methodology with a pot, atom and step economic approach has remained one of the prime goals 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 times. Similarly organocatalysis[16] imparts environmental 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 with some bioactive moieties such as aminouracil and hydroxynaphthoquinone/hydroxycoumarin as substituents. Among the organocatalysts, bifunctional thiourea-based organocatalysts[19] are popular in organic synthesis due to their activation of electrophiles by double-hydrogen-bonding interactions with a thiourea moiety, as well as the activation of nucleophiles by the other part (basic moiety). In this paper we have reported a three component

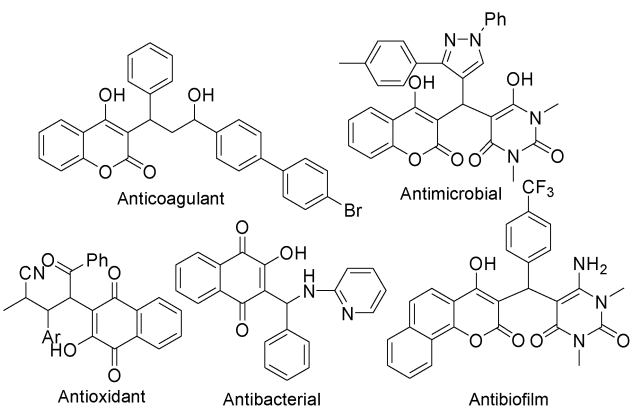

Fig. 1 Biologically active tri-substituted methane derivatives containing aminouracil and the hydroxynaphthoquinone/hydroxycoumarin moiety.

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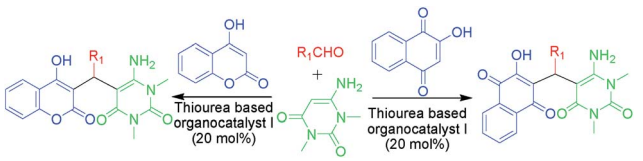
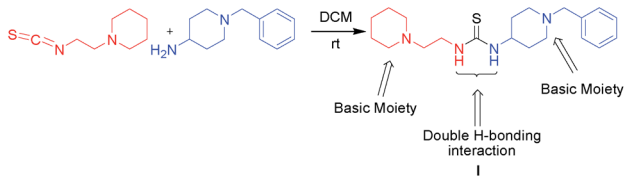
† Electronic supplementary information (ESI) available: ^{1}H NMR and ^{13}C NMR spectra for all reactions products are available. See DOI: 10.1039/c5ra13093j

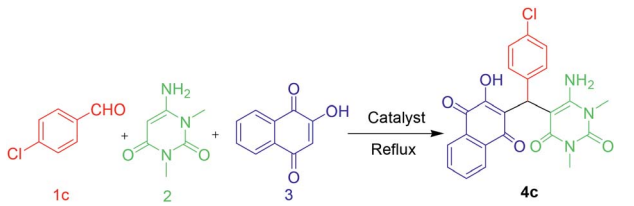


Scheme 1 Synthesis of tri-substituted methane derivatives.



Scheme 2 Synthesis of bifunctional thiourea-based organocatalyst I.

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.

reaction of aldehyde, 1,3-dimethyl-6-aminouracil and 2-hydroxy-1,4-naphthoquinone/4-hydroxycoumarin in aqueous medium in the presence of a bifunctional thiourea-based organocatalyst for the synthesis of tri-substituted methane derivatives (Scheme 1).

Result and discussion

Considering the popularity, as well as the virtues of bifunctional thiourea-based organocatalysts in organic synthesis, we initially synthesized organocatalyst **I** with 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 Scheme 2.

Recently we have reported a L-proline catalyzed three component reaction of 2-hydroxy-1,4-naphthoquinone, aldehydes, and aminopyrazoles, which gives a 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 work when we carried out a reaction of 4-chlorobenzaldehyde **1c**, 1,3-dimethyl-6-aminouracil **2** and 2-hydroxy-1,4-naphthoquinone **3** in H_2O without any catalyst under reflux conditions, we ended with an acyclic product *i.e.*, tri-substituted methane derivatives instead of the cyclic product. The yield of the reaction was only 33% after 6 h (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 noteworthy 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).

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.

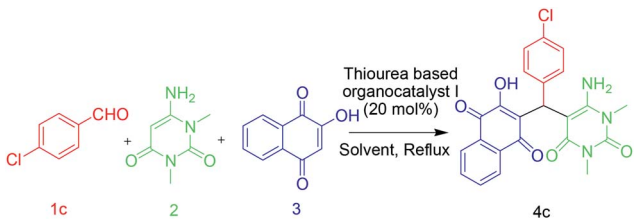
With the optimized reaction conditions, we then explored the generality of the method by using various aldehydes (both aromatic and aliphatic) with 2-hydroxy-1,4-naphthoquinone and 1,3-dimethyl-6-aminouracil. The results are summed up in Table 3. Aromatic aldehydes containing various substituents like 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 underwent smooth reactions to provide the corresponding tri-substituted methane derivatives (**4a–4l**) in good to moderate yields. Next we tried a reaction with phenylacetaldehyde. However, in this case the reaction provided an inseparable mixture of products. It is quite clear from Table 3 that neither the nature nor the positions of the substituents on the aromatic ring in the 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 reduced stability as well as the tendency of those aldehydes to exist in enol form.

After the successful synthesis of tri-substituted methane derivatives containing hydroxynaphthoquinone, aminouracil and aromatic/aliphatic rings, we carried out a three component reaction of 4-hydroxycoumarin, aldehyde and 1,3-dimethyl-6-aminouracil under similar reaction conditions and we obtained the corresponding tri-substituted methane derivatives (Scheme 3).

Looking at the molecular skeleton with pyrimidine and coumarin fragments in the 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 Table 4 (**6a–f**).

All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis. To remove the ambiguity in structure further, a D_2O exchange experiment was performed with compound **4c**. The labile protons of –NH_2 and –OH vanished in the D_2O exchanged ^{1}H NMR spectra of **4c** (Fig. 2). From

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.

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.

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

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-hydroxy-1,4-naphthoquinone/4-hydroxycoumarin in aqueous medium, for the synthesis of diverse tri-substituted methane derivatives with biologically active moieties such as pyrimidine and naphthoquinone/coumarin as substituents. In addition there are free –OH, $-NH_2$ and CO groups in our product molecules, which can be explored as ligands 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 were 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 vapour as the detecting agent. Melting points were determined by the melting point apparatus using a capillary tube method. IR spectra were recorded on a Shimadzu FTIR spectrophotometer in KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded either in $CDCl_3$ or in DMSO-d_6, and were expressed in parts per million (δ, ppm) downfield using Me_4Si as the internal standard on a Bruker Avance II 400 MHz spectrophotometer. Elemental analyses were carried out on 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 2 ml dichloromethane and allowed to cool at 0 °C. Then 2-piperidinoethyl isothiocyanate (0.5 mmol) was added into the reaction mixture and stirred at room temperature until completion of the reaction, as checked by TLC. The reaction mixture was cooled, and the solid was filtered off and washed with ethanol to afford the desired product.

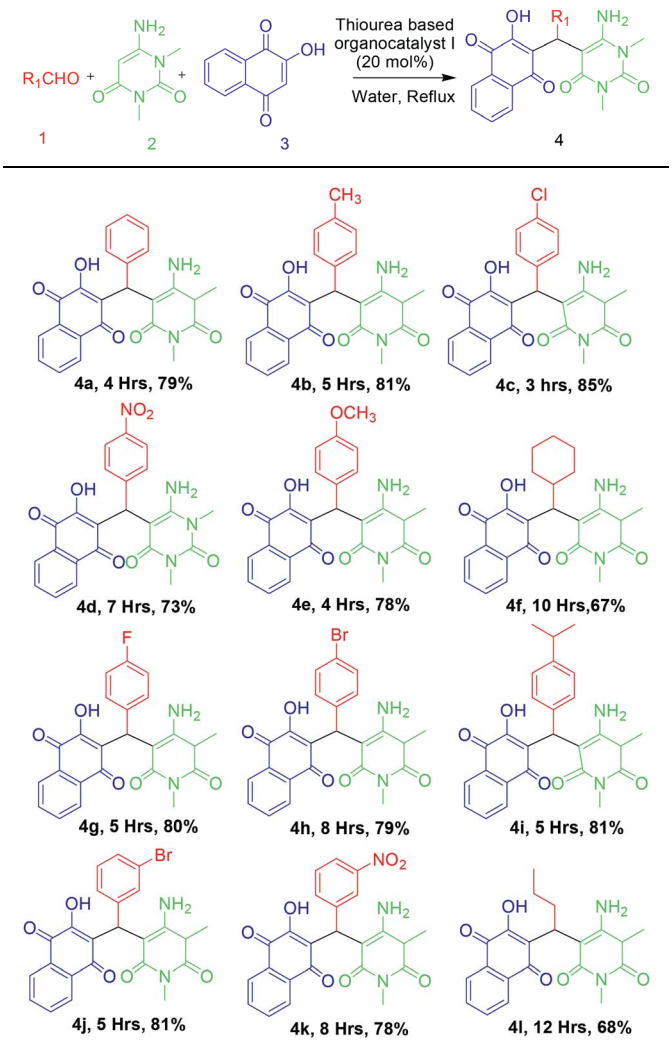
1-(1-Benzylpiperidin-4-yl)-3-(2-(piperidin-1-yl)ethyl)thiourea (I). White powdery solid; mp = 240–242 °C; IR (KBr): 3273, 3151, 3054, 2929, 1574, 1495, 1240, 961, 860, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 7.33–7.22 (m, 5H), 6.72 (brs, 1H), 4.02 (brs, 1H), 3.51 (s, 2H), 3.45–3.38 (m, 2H), 2.88–2.85 (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 (100 MHz, $CDCl_3$): 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

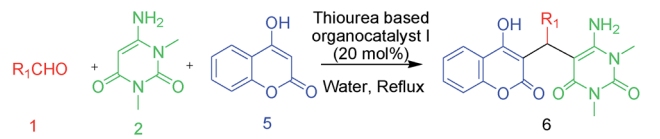
To a solution of 0.174 g (1 mmol) 2-hydroxy-1,4-naphthoquinone and 0.14 g (1 mmol) 4-chlorobenzaldehydes in 1 ml water, 20 mol% thiourea-based organocatalyst **I** was added and stirred under reflux conditions for 15 minutes. Afterwards, 0.155 g (1 mmol) 1,3-dimethyl-6-aminouracil was introduced and stirring was continued until completion of the reaction, as checked by TLC. The resulting mixture was cooled at room temperature, and the solid was filtered off and 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(1*H*,3*H*)-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.

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



[a] Isolated yield.



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

6-Amino-5-((1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-(*p*-tolyl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-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}; ^1H 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-dioxonaphthalen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-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}; ^1H 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.

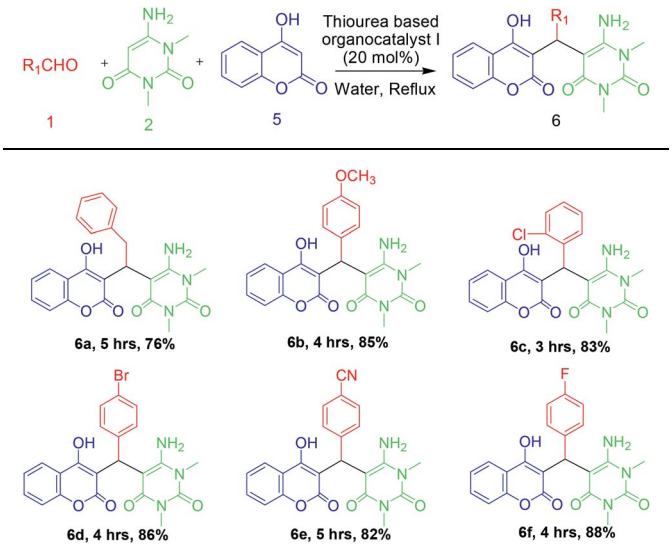
6-Amino-5-((1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-(4-nitrophenyl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione 4d. Yield 73%; yellow crystalline solid; mp = 278–279 °C; IR (KBr): 3397, 3241, 2929, 1697, 1665, 1603, 1556, 1473, 1351, 963, 810, 756 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 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(1*H*,3*H*)-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}; ^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), 7.85 (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-dioxonaphthalen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-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-dioxonaphthalen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione 4g. Yield 80%; red crystalline solid; mp = 241–242 °C; IR

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



[a] Isolated yield.

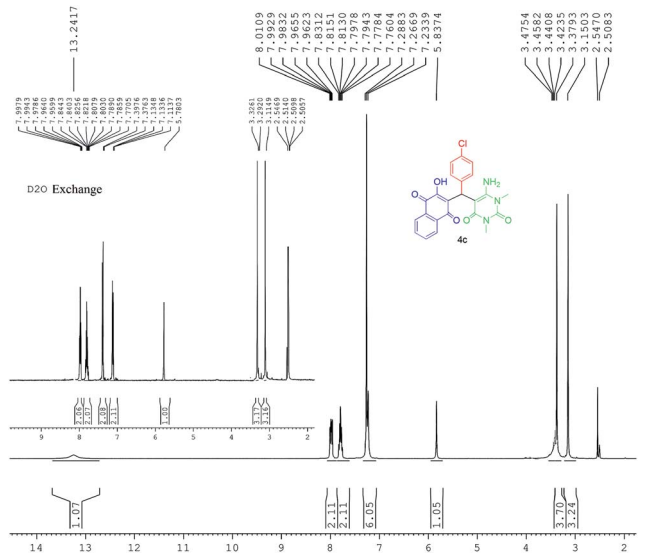


Fig. 2 ^{1}H NMR and D_2O exchanged ^{1}H NMR spectra of **4c**.

(KBr): 3396, 3246, 2922, 1738, 1687, 1665, 1659, 1608, 1578, 1371, 969, 893, 753 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), 7.84 (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.

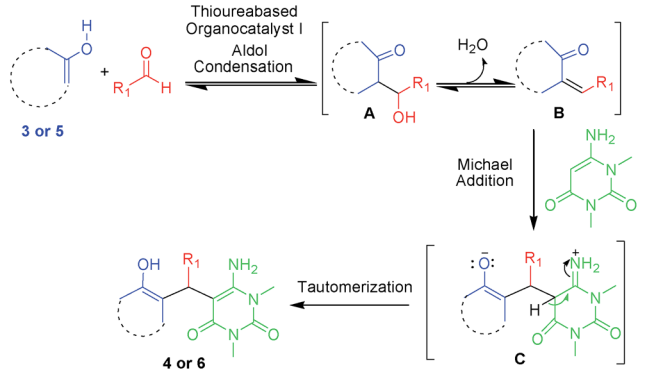
6-Amino-5-((4-bromophenyl)(1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione 4h. Yield 79%; orange solid; mp = 251–252 °C; IR (KBr): 3393, 3210, 2921, 1680, 1650, 1603, 1573, 1488, 1343, 905, 835, 756 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 13.15 (s, 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(1*H*,3*H*)-dione 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}; ^{1}H 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-dioxonaphthalen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-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}; ^{1}H 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(1*H*,3*H*)-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}; ^{1}H 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(1*H*,3*H*)-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}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 14.01 (s, 1H), 8.01 (d, J = 8.0 Hz, 1H),



Scheme 4 Proposed reaction mechanism.

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

6-Amino-5-((1-4-hydroxy-2-oxo-2*H*-chromen-3-yl)(2-phenyl ethyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-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}; ^{1}H 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-2*H*-chromen-3-yl)(4-methoxyphenyl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-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}; ^{1}H 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-2*H*-chromen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-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}; ^{1}H 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-2*H*-chromen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-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}; ^{1}H 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-2*H*-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}; ^{1}H 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-2*H*-chromen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-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}; ^{1}H 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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