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ORIGINAL ARTICLE

Synthesis of aminouracil-tethered tri-substituted methanes in water by iodine-catalyzed multicomponent reactions

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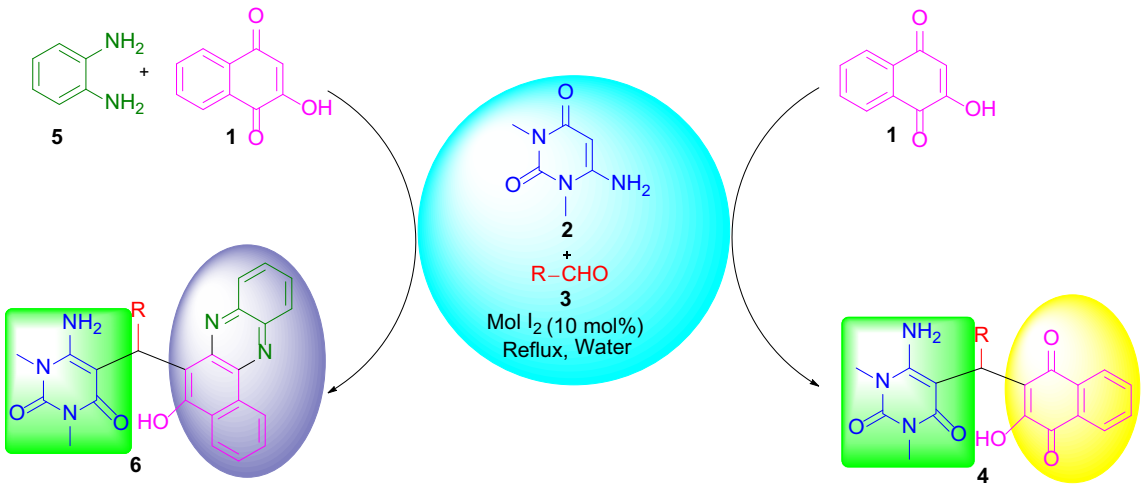
Abstract

An efficient, mild and environmentally benign protocol has been developed for the synthesis of aminouracil-tethered tri-substituted methane derivatives. The three-component reaction of 2-hydroxy-1,4-naphthaquinone, 6-amino-1,3-dimethyluracil and aldehydes in the presence of molecular iodine as catalyst under reflux conditions resulted in aminouracil-tethered tri-substituted methane derivatives **4** in aqueous medium. Similarly, the four-component reaction of 2-hydroxy-1,4-naphthaquinone, *o*-phenylenediamine, aldehydes and aminouracil derivatives resulted in aminouracil-tethered tri-substituted methane derivatives **6** under the same reaction conditions. The notable features of this protocol are simple experimental procedure, cheap catalyst, readily available starting materials, moderate-to-good yields of the products having biologically active important moieties such as aminouracil, hydroxy-naphthaquinone/benzophenazine.

Graphical Abstract



Keywords Aminouracil · Tri-substituted methanes · Multicomponent reactions · Benzophenazines · Water · Iodine

Introduction

Uracil, one of the nucleobases of pyrimidine family, is very well-known structural motif of several bioactive natural products [1, 2]. Uracil derivatives play important roles in our life cycle [3, 4] and exhibit wide range of biological properties [5, 6]. Amino uracils are useful starting material for the synthesis of xanthenes and theophylline-related

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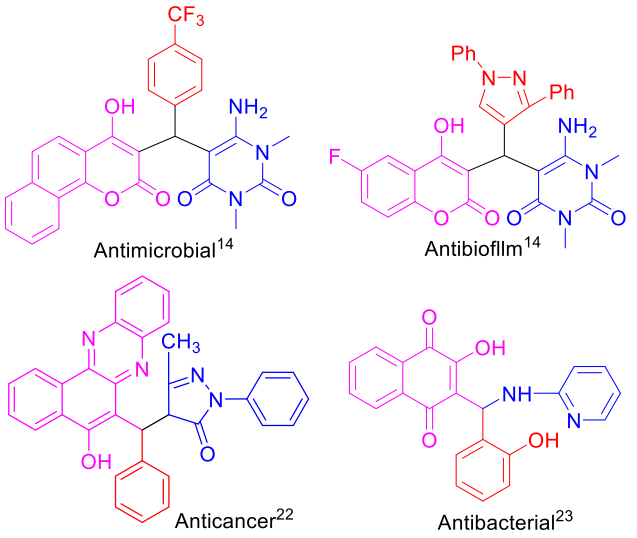


Fig. 1 Bioactive tri-substituted methanes tethered with hydroxynaphthaquinone/benzophenazine/pyrimidine moieties

compounds [7, 8] which are now routinely used as phosphodiesterase inhibitors for the treatment of asthma [9, 10]. Synthesis of aminouracil-tethered tri-substituted methanes [11–15] has gained more attention in multicomponent reactions due to their diverse biological and pharmaceutical activities. From the literature, it is well known that hydroxynaphthaquinone [16, 17], benzo[*a*]phenazine [18, 19] and aminouracil [20, 21] are pharmacologically active cores of diverse synthetic as well as natural bioactive compounds. Some representative examples of bioactive molecules having aminouracil/hydroxynaphthaquinone/benzophenazine moieties are shown in Fig. 1 [14, 22, 23].

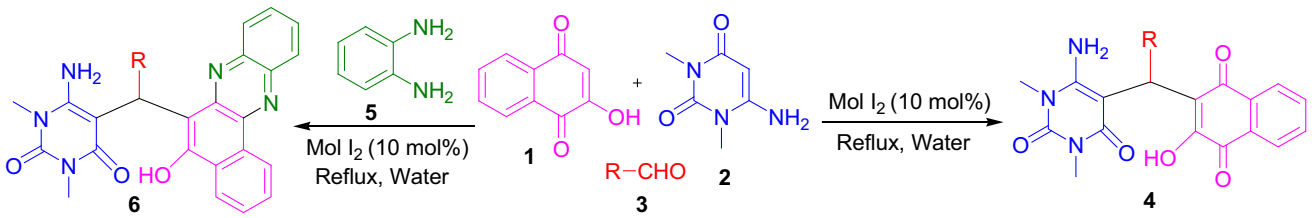
In view of the prominent pharmaceutical significance of tri-substituted methane derivatives, considerable attention has been paid in recent times by organic as well as medicinal chemists for the design and development of newer and greener methodologies for their efficient synthesis. In this regard, multicomponent reactions (MCRs) [24–31] have emerged as a powerful strategy in organic, combinatorial and medicinal chemistry due to their facileness, efficiency and also for atom economy. The development of novel synthetic routes for the synthesis of privileged heterocyclic scaffolds of medicinal relevance, which combine the benefits of multicomponent protocols with the environmental benefits of using nontoxic reagents and green solvents, remains a continuing challenge at the forefront of modern chemistry. In addition to this, replacement of hazardous solvents with environmentally benign solvents [32, 33] is one of the major focus areas of green chemistry.

Further, molecular iodine is an inexpensive, nontoxic, nonmetallic and commercially available catalyst which has attracted considerable interest in recent times. It has the ability to substitute hazardous, toxic, hygroscopic and expensive Lewis acid catalysts [34, 35]. One of the major advantages of iodine is its compatibility with a broad range of sensitive functional groups, which may not be compatible with the strongly acidic catalysts. Moreover, its high catalytic activity has enhanced its use in various organic transformations [36–38].

Very recently, we have published a review article on the recent advances of aminopyrimidines in multicomponent reactions [39] and also have been engaged in the development of novel green methodologies for the synthesis of diverse heterocyclic scaffolds using amino uracil as substrate [40, 41]. In continuation of our work in multicomponent reactions [42–46], we have demonstrated here an efficient green methodology for the synthesis of aminouracil-tethered tri-substituted methane derivatives in water under reflux conditions in the presence of molecular iodine catalyst (Scheme 1).

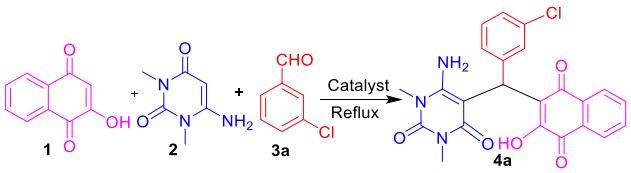
Results and discussion

Initially, the three-component reaction of 2-hydroxy-1,4-naphthaquinone **1**, 1,3-dimethyl-6-aminouracil **2** and 3-chlorobenzaldehyde **3a** in water was selected as the model reaction. When the reaction was done in the absence of any catalyst in reflux condition, we ended with aminouracil-tethered tri-substituted methane **4a** in 6 h (Table 1, entry 1). After confirming the structure of **4a** by spectroscopic analysis, we focused our attention to optimize the reaction condition by varying different parameters such as catalyst and solvent. The same model reaction was tested in the presence of various catalysts such as CAN, $CuCl_2$, $LaCl_3$, $CeCl_3$ and I_2 in water (Table 1, entries 2–6). Next, the same reaction was



Scheme 1 Molecular I_2-catalyzed MCRs for the synthesis of amino uracil-tethered tri-substituted methanes

Table 1 Optimization of reaction conditions[a]



Entry	Catalysts (10 mol%)	Solvent	Time (Hrs)	Yield[b] (%)
1	–	H_2O	6	34
2	CAN	H_2O	4.5	70
3	$CuCl_2$	H_2O	4	52
4	$LaCl_3$	H_2O	4.5	67
5	$CeCl_3$	H_2O	5.5	80
6	I_2	H_2O	1	60
7	I_2	H_2O	2	81
8	**I_2**	**H_2O**	**2.5**	**92**
9	I_2	H_2O	4	89
10	I_2	H_2O	6	86
11	I_2	CH_3CN	8	47
12	I_2	EtOH	6	72
13	I_2	Toluene	7	61
14	I_2	DMF	6	49
15	I_2	Et_2O	8	78
16	I_2	DMSO	5	73

[a]All the reactions were performed using 2-hydroxy-1,4-naphthaquinone (1.0 mmol), 1,3-dimethyl-6-aminouracil (1.0 mmol) and 3-chlorobenzaldehyde (1.0 mmol) under reflux conditions. [b]Isolated yield

performed under different time using 10 mol% I_2 in water (Table 1, entries 6–10). The best result was obtained in the presence of molecular I_2 in water in 2.5 h (Table 1, entry 8).

Then, the same model reaction was done in various solvents such as acetonitrile, ethanol, toluene, DMF, Et_2O, DMSO (Table 1, entries 7–12) using molecular I_2 as catalyst, but water was found to be the best solvent for the reaction (Table 1, entry 8).

In order to explore the generality of this multicomponent reaction, a wide variety of aldehydes were tested under the optimized reaction conditions and the results are demonstrated in Table 2. Aromatic aldehydes having both electron-donating and electron-withdrawing groups produced corresponding tri-substituted methanes in very good yields (Table 2, entries 1–8).

Aromatic aldehydes such as benzaldehyde and naphthaldehyde were also tested, and we observed good-to-moderate yields of products (Table 2, entry 9–10). Aliphatic aldehydes such as butyraldehyde and cyclohexanecarboxaldehyde were also tested, and the corresponding products were obtained in good yields (Table 2, entries 11–12).

Encouraged by this three-component reaction, and considering the biological activity of aminouracil-tethered tri-substituted methanes having benzophenazine moiety, we did the four-component reaction of 2-hydroxy-1,4-naphthaquinone **1**, *o*-phenylenediamine **5**, 1,3-dimethyl-6-aminouracil **2** and aldehydes **3** under the same reaction conditions which resulted in good-to-moderate yields of our expected tri-substituted methane derivatives **6**. A wide variety of aldehydes were tested, and we obtained good-to-moderate yields of corresponding products (Table 3 entries 1–12).

The proposed mechanism for the synthesis of aminouracil-tethered tri-substituted methane derivatives has been presented in Scheme 2. We believe that molecular iodine plays an important role in this reaction. Firstly, iodine activates the carbonyl group of aldehyde as it acts as a mild Lewis acid by forming aldehyde–iodine complex and increases the electrophilicity of carbonyl carbon. The aldol condensation of aldehyde and 2-hydroxy-1,4-naphthaquinone or 5-hydroxybenzophenazine (formed from the reaction of 2-hydroxy-1,4-naphthaquinone and *o*-phenylenediamine) followed by dehydration resulted in **A**. Then, molecular iodine also activates carbonyl group of **A** and facilitates the Michael addition with 1,3-dimethyl-6-aminouracil and provided **B**. Next, tautomerization of **B** resulted in the final product **4** or **6**.

Conclusions

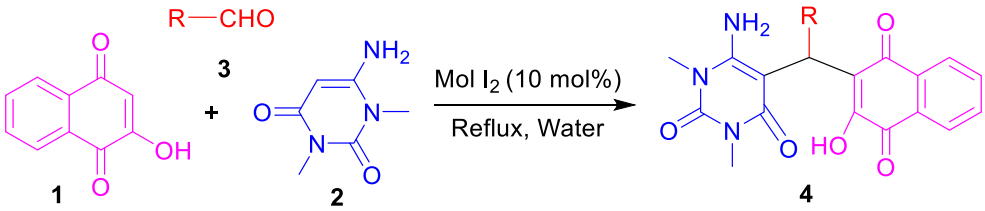
In conclusion, an efficient synthesis of aminouracil-tethered tri-substituted methane derivatives has been developed using molecular I_2 as catalyst in aqueous medium under reflux conditions. This protocol is environmentally benign and offers notable features such as operational simplicity, cheap catalyst, no need of column chromatographic separation, good-to-moderate yields of the products, water as reaction medium. These features make our methodology a useful and attractive strategy in organic synthesis. The presence of bioactive moieties like aminouracil, hydroxynaphthaquinone/benzophenazine in our synthesized products is expected to exhibit potent biological activities.

Experimental section

General

Commercially available reagents were used without additional purification. The progress of the reactions was monitored by TLC. The melting points were measured in a

Table 2 Synthesis of aminouracil-tethered tri-substituted methanes (**4a–l**)[a]



Entry	R	Product	Time (Hrs)	Yield[b]	M.P (°C)
1.	3-ClC_6H_4	**4a**	2.5	92	249–250
2.	4-$CH_3C_6H_4$	**4b**	4	77	218–220 [41]
3.	4-$OCH_3C_6H_4$	**4c**	6	85	245–247 [41]
4.	2-$OCH_3C_6H_4$	**4d**	3	72	257–258
5.	3-OHC_6H_4	**4e**	3	86	252–253
6.	4-BrC_6H_4	**4f**	6	72	251–253 [41]
7.	4-$NO_2C_6H_4$	**4g**	5	70	278–279 [41]
8.	2-FC_6H_4	**4h**	4	91	243–244
9.	C_6H_5	**4i**	3	80	248–250 [41]
10.	2-Naphthyl	**4j**	5	55	265–267
11.	n-C_4H_9	**4k**	10	60	245–246 [41]
12.	Cyclohexyl	**4l**	8	59	202–203 [41]

[a]Reaction conditions: 2-hydroxy-1,4-naphthaquinone (1.0 mmol), 1,3-dimethyl-6-aminouracil (1.0 mmol) and aldehyde (1.0 mmol) using molecular I_2 (10 mol%) as catalyst in water (3.0 ml). [b]Isolated yield

digital melting point apparatus. Shimadzu FTIR spectrophotometer was used to record IR spectra of products. Bruker 400 MHz spectrometer was used to record ^{1}H NMR and ^{13}C NMR spectra in DMSO-d_6 and $CDCl_3$ solvent using Me_4Si as an internal standard. HRMS analysis was recorded in Bruker Impact HD mass spectrometer. The data of known compounds were compared with the literature data, and the characterization data of unknown compounds are demonstrated below.

General procedure for the synthesis of compounds 4a–4l

2-Hydroxy-1,4-naphthaquinone (1.0 mmol) and aldehyde (1.0 mmol) were taken in water (3.0 ml) in a round-bottom flask. Then, molecular iodine (10 mol%) was added in the reaction mixture and refluxed for 15 min. After that, 1,3-dimethyl-6-aminouracil (1.0 mmol) was added to the mixture and refluxed till the completion of the reaction as indicated by TLC. After cooling the reaction mixture to room temperature, the solid precipitate was filtered off and washed with water to afford the crude product. Finally, the crude product was recrystallized in ethanol to afford the pure product.

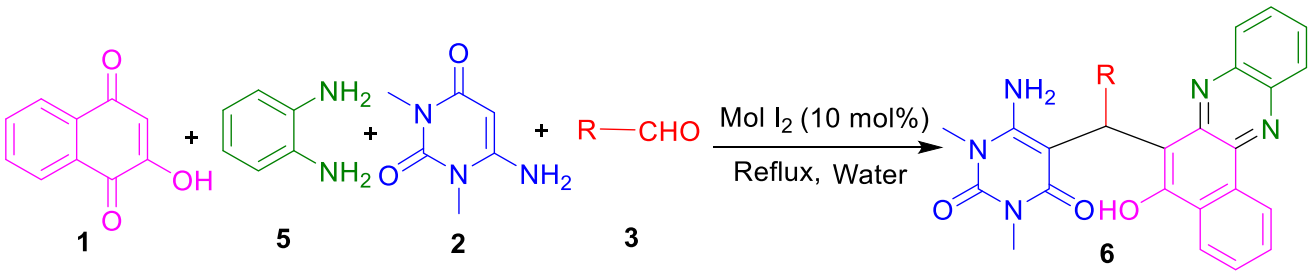
6-Amino-5-((3-chlorophenyl)(1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)1,3-dimethylpyrimidine-2,4(1H,3H)-dione (4a)

Maroon solid. mp 249–250 °C. IR (KBr): 3387, 3224, 3127, 2957, 1697, 1654, 1604, 1578, 1253, 1045, 852, 775 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.16 (s, 3H), 3.37 (s, 3H), 5.88 (s, 1H), 7.18 (s, 2H), 7.20 (s, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.30 (s, 1H), 7.80–7.87 (m, 2H), 8.01 (t, J = 8.0 Hz, 2H), 13.14 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.7, 29.7, 35.2, 89.2, 119.1, 121.5, 125.9, 126.0, 127.1, 129.5, 130.1, 130.2, 130.7, 131.6, 133.5, 134.9, 138.0, 143.6, 147.0, 150.4, 160.5, 178.7, 181.6 ppm; HRMS (ESI-TOF) calcd for $C_{23}H_{19}ClN_3O_5$ $[M+H]^+$ 452.1008, found 452.1004.

6-Amino-5-((1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)(2-methoxyphenyl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (4d)

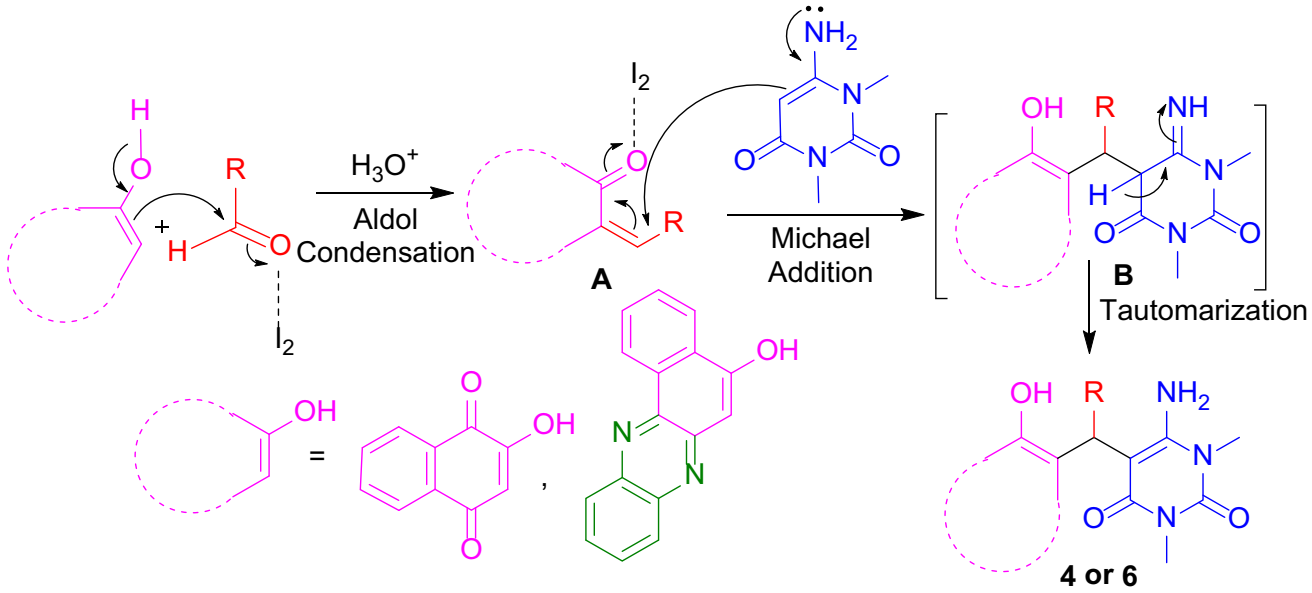
Maroon solid. mp 257–258 °C. IR (KBr): 3394, 3228, 3174, 2958, 1697, 1654, 1604, 1577, 1257, 1022, 856, 763 cm^1; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.20 (s, 3H), 3.37 (s, 3H), 3.59 (s, 3H), 5.94 (s, 1H), 6.76 (s, 2H), 6.86 (t, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.73–7.81 (m,

Table 3 Synthesis of tri-substituted methane derivatives **6** having aminouracil and benzophenazine moieties[a]



Entry	R	Product	Time (Hrs)	Yield[b]	M.P (°C)
1.	C_6H_5	**6a**	5	80	269–271 [15]
2.	4-$CHMe_2C_6H_4$	**6b**	3	90	262–263
3.	4-$OCH_3C_6H_4$	**6c**	6	83	274–277 [15]
4.	4-OHC_6H_4	**6d**	5.5	72	213–215 [15]
5.	3-$NO_2C_6H_4$	**6e**	5	66	325–327
6.	4-FC_6H_4	**6f**	6	75	242–243
7.	2-FC_6H_4	**6g**	4	79	256–258
8.	3-ClC_6H_4	**6h**	5	50	249–250
9.	4-BrC_6H_4	**6i**	6	68	265–267
10.	3-BrC_6H_4	**6j**	4.5	83	209–211
11.	4-CNC_6H_4	**6k**	8	80	295–298
12	2-Naphthyl	**6l**	4	90	302–304

[a]Reaction conditions: 2-hydroxy-1,4-naphthaquinone (1.0 mmol), *o*-phenylenediamine (1.0 mmol), 1,3-dimethyl-6-aminouracil (1.0 mmol) and aldehyde (1.0 mmol) using molecular I_2 (10 mol%) as catalyst in water (3.0 ml). [b]Isolated yield



Scheme 2 Proposed mechanism for the synthesis of amino uracil-tethered tri-substituted methane derivatives

2H), 7.99 (d, J = 8.0 Hz, 2H), 12.05 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 28.0, 30.0, 32.0, 55.3, 85.3, 110.6, 119.9, 125.0, 125.5, 126.0, 127.2, 127.3, 127.8, 130.1, 132.0, 133.1, 134.2, 150.4, 153.2, 156.0, 157.2, 162.7, 181.0, 185.0 ppm; HRMS (ESI-TOF) calcd for $C_{24}H_{22}N_3O_6$ $[M+H]^+$ 448.1503, found 448.1505.

6-Amino-5-((1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)(3-hydroxyphenyl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (4e)

Red solid. mp 252–253 °C. IR (KBr): 3379, 3251, 3134, 2958, 1697, 1658, 1635, 1608, 1585, 1296, 1014, 867, 748 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.18 (s, 3H), 3.40 (s, 3H), 5.77 (s, 1H), 6.56 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 8.0 Hz, 2H), 7.02 (t, J = 8.0 Hz, 1H), 7.18 (s, 2H), 7.78–7.86 (m, 2H), 8.01 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 9.07 (s, 1H), 13.30 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.2, 30.4, 34.7, 85.8, 112.7, 113.5, 117.4, 123.5, 125.7, 126.1, 129.0, 130.5, 131.7, 133.5, 134.4, 139.9, 150.2, 154.3, 157.3, 158.5, 163.6, 181.1, 185.8 ppm; HRMS (ESI-TOF) calcd for $C_{23}H_{20}N_3O_6$ $[M+H]^+$ 434.1347, found 434.1356.

6-Amino-5-((2-fluorophenyl)(1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (4h)

Orange solid. mp 243–244 °C. IR (KBr): 3406, 3360, 3236, 2962, 1697, 1654, 1608, 1597, 1489, 1253, 933, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.32 (s, 3H), 3.51 (s, 3H), 5.93 (s, 1H), 6.14 (s, 2H), 6.94–6.99 (m, 1H), 7.05–7.08 (m, 1H), 7.09–7.20 (m, 1H), 7.22–7.30 (m, 1H), 7.68–7.70 (m, 1H), 7.71–7.74 (m, 1H), 8.06–8.08 (m, 1H), 8.12–8.14 (m, 1H), 13.15 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 28.0, 30.1, 31.0, 84.4, 114.7, 123.6, 125.5, 126.1, 126.3, 127.7, 129.0, 130.1, 131.8, 133.1, 134.2, 150.2, 153.4, 156.9, 159.5, 161.9, 162.9, 180.9, 184.9 ppm; HRMS (ESI-TOF) calcd for $C_{23}H_{19}FN_3O_5$ $[M+H]^+$ 436.1303, found 436.1308.

6-Amino-5-((1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)(naphthalen-2-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (4j)

Orange solid, mp 265–267 °C. IR (KBr): 3383, 3240, 3142, 2920, 1728, 1701, 1655, 1604, 1577, 1257, 1045, 852, 729 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.17 (s, 3H), 3.40 (s, 3H), 6.06 (s, 1H), 7.19 (s, 2H), 7.40 (d, J = 8.0 Hz, 1H), 7.43–7.45 (m, 2H), 7.72 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.81–7.86 (m, 4H), 8.03 (t, J = 8.0 Hz, 2H), 13.10 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 28.1, 30.4, 35.0, 85.9, 123.3, 124.4, 125.2, 125.6, 125.8, 126.1, 127.1, 127.4, 127.5, 130.7, 131.5, 131.8, 133.1, 133.3, 134.1, 136.0, 150.2, 154.5, 158.8, 163.8, 170.1, 181.0, 186.0 ppm; HRMS (ESI-TOF) calcd for $C_{27}H_{22}N_3O_5$ $[M+H]^+$ 468.1554, found 468.1538.

General procedure for the synthesis of compounds 6a–6l

2-Hydroxy-1,4-naphthaquinone (1.0 mmol) and *o*-phenylenediamine (1.0 mmol) were taken in water (3.0 ml) in a round-bottom flask and refluxed for 10 min. Afterward, to this mixture, aldehyde (1.0 mmol) and 1,3-dimethyl-6-aminouracils (1.0 mmol) were added followed by 10 mol% molecular iodine. The reaction mixture was refluxed till the completion of the reaction as indicated by TLC. After cooling the reaction mixture to room temperature, the solid precipitate was filtered off and washed with water to afford the crude product. Finally, the crude product was recrystallized in ethanol to afford the pure product.

6-Amino-5-((5-hydroxybenzo[a]phenazin-6-yl)(4-isopropylphenyl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (6b)

Brown solid. mp 262–263 °C. IR (KBr): 3383, 3237, 3187, 2954, 2870, 1689, 1650, 1613, 1593, 1442, 1053, 810, 698 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.09 (d, J = 8.0 Hz, 6H), 2.73–2.76 (m, 1H), 3.18 (s, 3H), 3.35 (s, 3H), 6.83 (s, 1H), 6.95–7.00 (m, 2H), 7.04 (d, J = 8.0 Hz, 2H), 7.74–7.79 (m, 3H), 7.83 (t, J = 8.0 Hz, 1H), 8.11–8.13 (m, 1H), 8.15 (s, 2H), 8.24 (d, J = 8.0 Hz, 1H), 8.29–8.32 (m, 1H), 9.23–9.20 (m, 1H), 13.19 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.8, 23.9, 28.0, 30.3, 32.9, 35.2, 87.3, 114.0, 123.5, 124.5, 125.7, 126.4, 127.2, 128.2, 128.3, 129.1, 129.8, 129.9, 130.1, 130.2, 136.7, 139.2, 140.0, 140.5, 144.6, 145.2, 150.2, 155.4, 156.4, 164.0 ppm; HRMS (ESI-TOF) calcd for $C_{32}H_{30}N_5O_3$ $[M+H]^+$ 532.2343, found 532.2344.

6-Amino-5-((5-hydroxybenzo[a]phenazin-6-yl)(3-nitrophenyl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (6e)

Red solid. mp 325–327 °C. IR (KBr): 3441, 3076, 1705, 1660, 1620, 1597, 1558, 1506, 1471, 1340, 1199, 1028, 956, 804, 671 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.21 (s, 3H), 3.45 (s, 3H), 7.01 (s, 1H), 7.55 (t, J = 8.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.93–7.94 (m, 3H), 7.99 (s, 2H), 8.06 (d, J = 8.0 Hz, 1H), 8.25–8.28 (m, 3H), 8.38–8.39 (m, 2H), 9.30–9.32 (m, 1H), 13.29 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.7, 31.0, 36.2, 86.7, 114.1, 121.2, 121.9, 124.2, 125.1, 128.0, 129.4, 129.5, 129.6, 130.0, 130.1, 130.7, 131.0, 131.3, 134.4, 139.9, 140.4, 141.0, 143.0, 144.7, 148.5, 150.7, 156.1, 156.7, 164.6 ppm; HRMS (ESI-TOF) calcd for $C_{29}H_{23}N_6O_5$ $[M+H]^+$ 535.1724, found 535.1718.

6-Amino-5-((4-fluorophenyl)(5-hydroxybenzo[a]phenazin-6-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (6f)

Brown solid. mp 242–243 °C. IR (KBr): 3390, 3267, 3142, 2920, 1693, 1558, 1612, 1593, 1285, 1049, 817, 767 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.22 (s, 3H), 3.39 (s, 3H), 6.88 (s, 1H), 7.14–7.20 (m, 4H), 7.83–7.87 (m, 3H), 7.91 (t, J = 8.0 Hz, 1H), 8.18–8.21 (m, 1H), 8.25 (s, 2H), 8.33 (d, J = 8.0 Hz, 1H), 8.35–8.37 (m, 1H), 9.27–9.29 (m, 1H), 13.22 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.7, 29.6, 31.4, 89.9, 123.5, 125.7, 125.8, 125.9, 126.0, 126.2, 126.3, 128.3, 128.4, 129.3, 129.7, 129.9, 130.1, 131.6, 132.2, 133.4, 133.7, 134.6, 134.9, 135.8, 137.3, 143.0, 144.9, 150.3, 164.6 ppm; HRMS (ESI-TOF) calcd for $C_{29}H_{23}FN_5O_3$ $[M+H]^+$ 508.1779, found 508.1774.

6-Amino-5-((2-fluorophenyl)(5-hydroxybenzo[a]phenazin-6-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (6g)

Red solid. mp 256–258 °C. IR (KBr): 3064, 2918, 2850, 1708, 1672, 1595, 1560, 1498, 1448, 1419, 1363, 1278, 1220, 1139, 1055, 852, 748, 582 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.19 (s, 3H), 3.43 (s, 3H), 6.99 (s, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.88–7.92 (m, 2H), 7.95–7.98 (m, 2H), 8.04 (d, J = 8.0 Hz, 2H), 8.23 (d, J = 8.0 Hz, 1H), 8.29–8.35 (m, 2H), 8.37 (s, 2H), 9.25–9.27 (m, 1H), 13.29 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.2, 30.5, 35.7, 86.2, 113.6, 120.7, 121.4, 123.7, 124.6, 127.4, 128.9, 129.0, 129.1, 129.5, 129.6, 130.1, 130.4, 130.7, 133.9, 139.3, 139.9, 140.4, 142.5, 144.2, 147.9, 150.2, 155.6, 156.2, 164.1 ppm; HRMS (ESI-TOF) calcd for $C_{29}H_{23}FN_5O_3$ $[M+H]^+$ 508.1779, found 508.1776.

6-Amino-5-((3-chlorophenyl)(5-hydroxybenzo[a]phenazin-6-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (6h)

Maroon solid. mp 249–250 °C. IR (KBr): 3317, 3136, 2900, 1705, 1674, 1620, 1593, 1462, 1280, 1053, 862, 756 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.17 (s, 3H), 3.34 (s, 3H), 6.86 (s, 1H), 7.09 (s, 2H), 7.13 (t, J = 8.0 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.81–7.84 (m, 2H), 7.87–7.90 (m, 2H), 8.16–8.17 (m, 3H), 8.28 (d, J = 8.0 Hz, 1H), 8.31–8.33 (m, 1H), 9.22–9.25 (m, 1H), 13.19 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.7, 30.9, 36.1, 87.0, 114.4, 124.2, 125.1, 125.9, 126.0, 127.0, 127.9, 129.3, 129.4, 129.6, 130.2, 130.3, 130.6, 130.9, 131.1, 133.4, 139.8, 140.4, 141.0, 143.1, 144.8, 150.7, 156.0, 156.7, 164.5 ppm; HRMS (ESI-TOF) calcd for $C_{29}H_{23}ClN_5O_3$ $[M+H]^+$ 524.1484, found 524.1483.

6-Amino-5-((4-bromophenyl)(5-hydroxybenzo[a]phenazin-6-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (6i)

Maroon solid. mp 265–267 °C. IR (KBr): 3468, 3325, 3136, 2924, 1685, 1654, 1618, 1597, 1492, 1280, 1057, 848, 767 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.22 (s, 3H), 3.40 (s, 3H), 6.87 (s, 1H), 7.16 (d, J = 8.0 Hz, 2H), 7.38–7.39 (m, 2H), 7.88–7.89 (m, 1H), 7.92 (t, J = 8.0 Hz, 2H), 7.97 (d, J = 8.0 Hz, 1H), 8.24 (s, 1H), 8.25 (s, 2H), 8.35 (d, J = 8.0 Hz, 1H), 8.37–8.38 (m, 1H), 9.29–9.31 (m, 1H), 13.25 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.7, 31.0, 35.9, 87.1, 114.4, 118.9, 124.2, 125.1, 127.9, 129.1, 129.3, 129.5, 129.6, 129.8, 130.2, 130.6, 130.9, 131.2, 131.3, 132.5, 134.6, 139.7, 140.4, 141.0, 144.9, 150.7, 155.9, 156.7, 164.5 ppm; HRMS (ESI-TOF) calcd for $C_{29}H_{23}BrN_5O_3$ $[M+H]^+$ 568.0979, found 568.0959.

6-Amino-5-((3-bromophenyl)(5-hydroxybenzo[a]phenazin-6-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (6j)

White crystalline solid. mp 209–211 °C. IR (KBr): 3445, 3358, 3241, 3063, 2964, 1695, 1660, 1651, 1570, 1509, 1489, 1446, 1095, 1043, 856, 760 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.20 (s, 3H), 3.38 (s, 3H), 6.86 (s, 1H), 7.16 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.91–7.92 (m, 2H), 7.93–7.95 (m, 2H), 7.99 (t, J = 8.0 Hz, 1H), 8.23 (s, 2H), 8.36–8.38 (m, 2H), 9.27–9.30 (m, 1H), 13.32 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.1, 30.4, 35.5, 86.7, 113.6, 121.7, 123.6, 124.5, 124.7, 125.8, 127.3, 128.3, 128.5, 128.6, 129.1, 129.3, 129.7, 129.9, 130.1, 130.4, 139.3, 139.9, 140.4, 142.7, 144.3, 150.2, 155.5, 156.3, 164.0 ppm; HRMS (ESI-TOF) calcd for $C_{29}H_{23}BrN_5O_3$ $[M+H]^+$ 568.0979, found 568.0962.

4-((6-Amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)(5-hydroxybenzo[a]phenazin-6-yl)methyl)benzonitrile (6k)

Maroon solid. mp 295–298 °C. IR (KBr): 3385, 2922, 2850, 2364, 1653, 1647, 1593, 1558, 1498, 1070, 887, 781 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.19 (s, 3H), 3.38 (s, 3H), 6.93 (s, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.88–7.95 (m, 5H), 8.25 (s, 2H), 8.32 (d, J = 8.0 Hz, 2H), 9.23 (s, 1H), 13.29 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 29.0, 31.2, 36.6, 87.1, 108.7, 114.2, 119.6, 124.1, 125.0, 127.9, 128.4, 129.3, 129.4, 129.6, 130.1, 130.6, 130.8, 131.1, 132.4, 139.8, 140.4, 140.9, 144.7, 146.7, 150.7, 156.0, 156.7, 164.6 ppm; HRMS (ESI-TOF) calcd for $C_{30}H_{23}N_6O_3$ $[M+H]^+$ 515.1826, found 515.1821.

6-Amino-5-((5-hydroxybenzo[a]phenazin-6-yl)(naphthalen-2-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (6l)

Orange solid. mp 302–304 °C. IR (KBr): 3346, 3157, 1699, 1595, 1568, 1498, 1361, 1276, 1199, 1051, 819, 759 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.25 (s, 3H), 3.45 (s, 3H), 7.12 (s, 1H), 7.37–7.39 (m, 2H), 7.42 (d, J = 8.0 Hz, 1H), 7.64 (s, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.87–7.92 (m, 4H), 8.17 (s, 1H), 8.25 (s, 2H), 8.35 (d, J = 8.0 Hz, 1H), 8.39–8.41 (m, 1H), 9.34 (d, J = 8.0 Hz, 1H), 13.22 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 29.6, 30.4, 36.2, 88.8, 113.5, 116.9, 124.2, 124.8, 124.9, 125.1, 125.6, 125.7, 125.8, 127.2, 127.3, 127.4, 127.8, 128.2, 128.5, 129.7, 130.1, 131.9, 133.5, 137.1, 139.9, 140.9, 145.1, 150.9, 155.6, 157.3, 164.6 ppm; HRMS (ESI-TOF) calcd for $C_{33}H_{26}N_5O_3$ $[M+H]^+$ 540.2030, found 540.2021.

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