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ORIGINAL ARTICLE

Regioselective synthesis of pyrimidine-fused tetrahydropyridines and pyridines by microwave-assisted one-pot reaction

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Abstract

A regioselective three-component reaction of α,β-unsaturated aldehydes, cyclic 1,3-dicarbonyls and 6-aminouracils in the presence of $FeCl_3{\cdot}6H_2O$ as catalyst under microwave irradiation has been demonstrated. Three-component reaction of α,β-unsaturated aldehydes like cinnamaldehyde/crotonaldehyde, cyclic 1,3-diketones such as 2-hydroxy-1,4-naphthaquinone/dimedone and 6-aminouracils provides regioselective pyrimidine-fused tetrahydropyridines tethered with cyclic 1,3-diketones. On the other hand, replacing cyclic 1,3-diketones by 4-hydroxycoumarin and keeping all other conditions the same provided a two-component pyrimidine-fused pyridines. The salient features of this methodology are operational simplicity, short reaction time, good-to-moderate yields of the products, easy purification method and regioselective products having medicinally important heterocyclic rings such as pyrimidine, tetrahydropyridine or pyridine.

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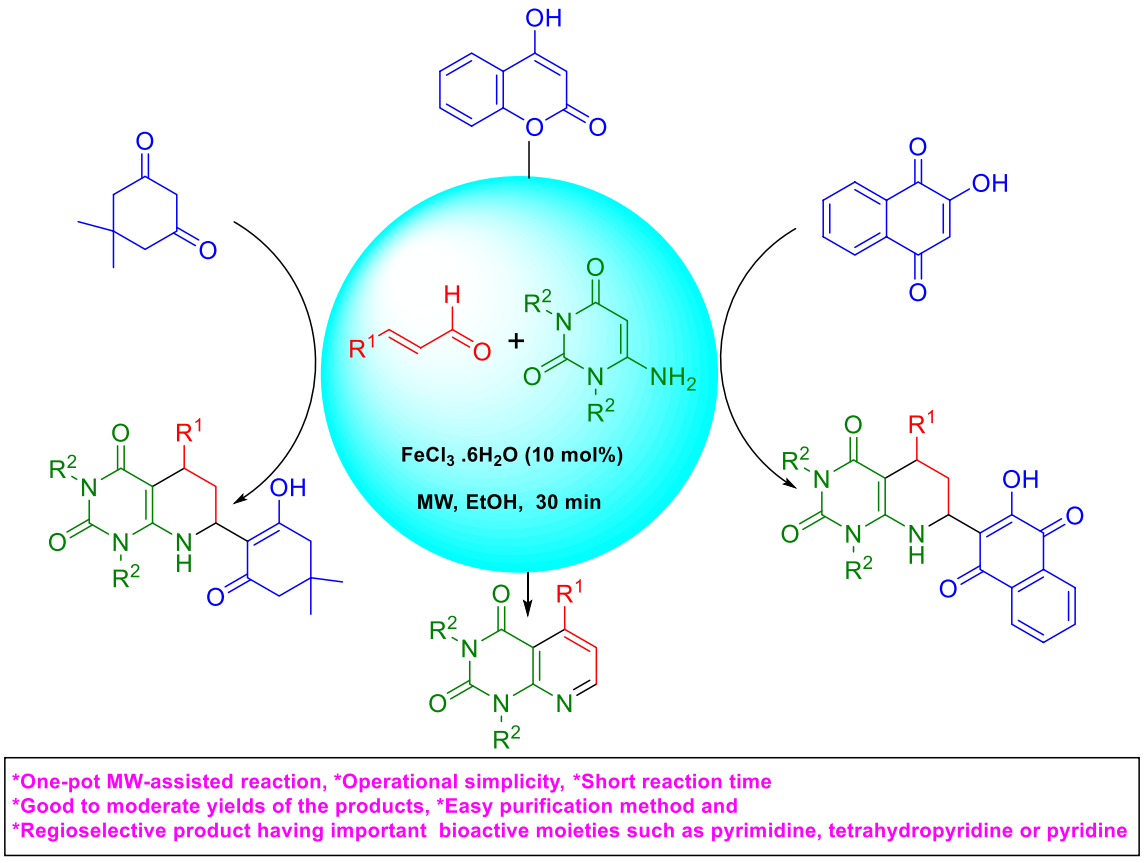
Graphical abstract



Keywords Multicomponent reactions · Microwave-assisted reactions · Pyrimidine-fused tetrahydropyridines · Pyridines · $FeCl_3{\cdot}6H_2O$

Introduction

Multicomponent reactions (MCRs) are one of the popular synthetic strategies in organic chemistry for the synthesis of large libraries of diverse heterocycles using minimum pot and steps [1–5]. Considering their easy execution, environment-friendly nature, better atom economy and green characteristics, MCRs have gained significant interest in organic synthesis. Microwave (MW) heating reduces reaction time drastically and many a time provides cleaner products compared to conventional heating [6–9]. Thus, the combination of MW in MCRs has many advantages in organic chemistry, especially for the synthesis of diverse biologically active heterocycles [10–12].

Fused heterocyclic compounds, especially pyrimidine-fused pyridine derivatives, are important molecules found in several natural and synthetic compounds with wide pharmacological applications. They exhibit anti-microbial [13–15], anti-inflammatory [16], anti-bacterial, [17] anti-tumour [18] and antifungal [19] activities. Pyrimidine-fused pyridine derivatives also find applications as versatile biological redox co-enzyme [20]. In addition, they have been identified as potential acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzyme

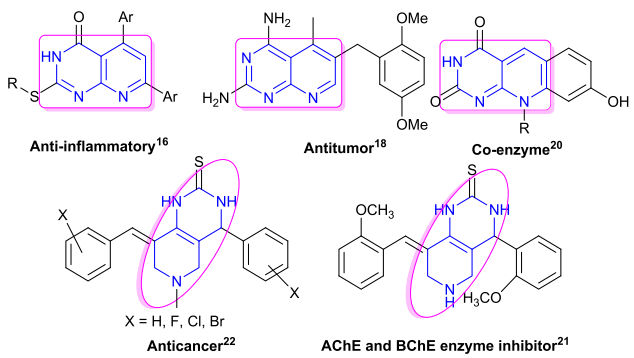


Fig. 1 Some bioactive pyridopyrimidine derivatives

inhibitors [21] as well as anticancer agents [22]. Some of the bioactive pyrimidine-fused pyridine derivatives along with their medicinal properties are shown in Fig. 1.

Considering the wide applications of these heterocyclic motifs, synthesis of pyrimidine-fused pyridine derivatives has found significant attention in recent years using multicomponent reactions. Recently, Zhang et al. [23] reported synthesis of a series of pyrido[2,3-*d*]pyrimidine derivatives using carbonaceous material as a catalyst from the reaction of 2,6-diaminopyrimidin-4(3*H*)-one, nitroolefin and aldehydes in water. Similarly, the multicomponent reaction of 2,4-thiazolidinedione, aromatic aldehydes and *N*,*N*-dimethyl-6-aminouracil was reported for the synthesis of pyrido[2,3-*d*]pyrimidine derivatives in the presence of heterogeneous ionic liquid catalyst [24]. Likewise, pyrido[2,3-*d*] pyrimidines were synthesized electrochemically using NaBr as supporting electrolyte and ethanol as solvent via multicomponent reaction of aromatic aldehydes, dimedone/malononitrile and 6-aminouracil [25]. Recently, we have reported the synthesis of pyrimidine-fused quinolines via the domino reaction of 6-aminouracils and 2-bromobenzaldehydes or 2-bromobenzyl bromide in the presence of Cu(II) catalyst [26]. We have also reported the synthesis of 1,4-dihydropyridines fused with naphthaquinone and pyrimidines from the three-component reaction of 2-hydroxy-1,4-naphthaquinone, aldehydes and 6-aminouracils in acetic acid/water (1:1; v/v) under microwave heating conditions [27]. $FeCl_3{\cdot}6H_2O$ is an inexpensive, environment-friendly, versatile catalyst used in various organic reactions [28–31]. In continuation of our research work [32–37] for the synthesis of diverse heterocycles, herein we report an efficient methodology for the synthesis of fused heterocycles from the reaction of *α,β*-unsaturated aldehydes, cyclic 1,3-dicarbonyls and 6-aminouracils in ethanol medium in the presence of $FeCl_3{\cdot}6H_2O$ as catalyst under microwave irradiation (Scheme 1).

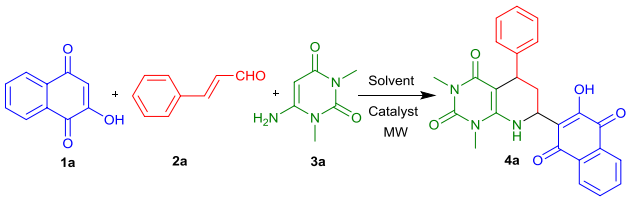
Results and discussion

Initially, we have chosen the three-component reaction of 2-hydroxy-1,4-naphthaquinone (**1a**), cinnamaldehyde (**2a**) and 1,3-dimethyl-6-aminouracil (**3a**) as the model reaction.

In the absence of any catalyst, when we did the reaction under MW heating for 30 min in ethanol medium, we observed a three-component product with 50% yield (Table 1, entry 1).

MCRs can generate multiple products; thus, first, we tried to characterize the obtained product. In ^{1}H NMR spectrum, two singlets of N-CH_3 were observed at 3.13 and 3.29 ppm, respectively. In the aliphatic region, another four peaks were found with one hydrogen for each peak. Similarly, in ^{13}C NMR, we observed two peaks for the N-CH_3 at 27.8 and 29.7 ppm along with other three aliphatic peaks in 31.8, 35.8 and 43.6 ppm, respectively. Initially, we were not sure

Table 1 Optimization of reaction conditions



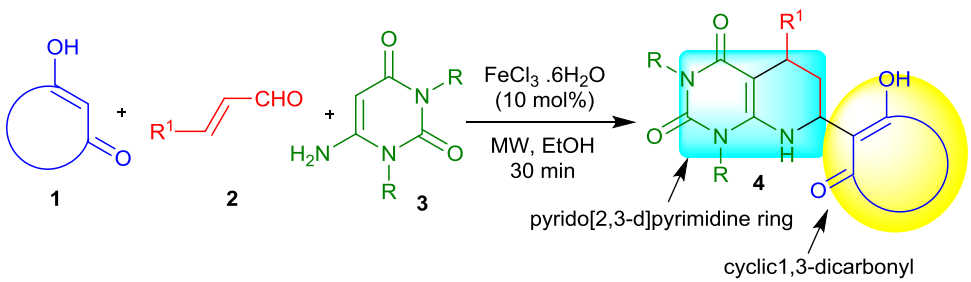
Entry	Catalyst (10 mol%)	Solvent	Reaction conditions	Yield%[a]
1	–	EtOH	MW	50
2	**$FeCl_3{\cdot}6H_2O$**	**EtOH**	MW	**85**
3	$FeCl_3{\cdot}6H_2O$	EtOH	reflux	74
4	$CeCl_3{\cdot}7H_2O$	EtOH	MW	69
5	I_2	EtOH	MW	60
6	$Bi(NO_3)_3{\cdot}5H_2O$	EtOH	MW	70
7	$FeCl_3{\cdot}6H_2O$	H_2O	MW	46
8	$FeCl_3{\cdot}6H_2O$	CH_3CN	MW	72
9	$FeCl_3{\cdot}6H_2O$	DMF	MW	20
10	$FeCl_3{\cdot}6H_2O$	DMSO	MW	25
11	$FeCl_3{\cdot}6H_2O$	DCM	MW	65
12	$FeCl_3{\cdot}6H_2O$	Toluene	MW	62

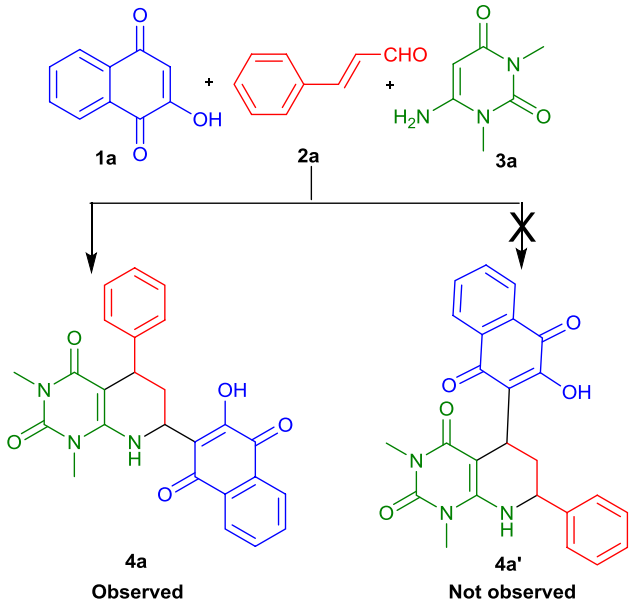
Bold values highlight the optimized reaction condition

Reaction conditions: 2-hydroxy-1,4-naphthaquinone (1.0 mmol), cinnamaldehyde (1.0 mmol) and 1,3-dimethyl-6-aminouracil (1.0 mmol), microwave irradiation under sealed condition for 30 min

[a]Isolated yields

Scheme 1 One-pot reaction of cyclic 1,3-dicarbonyls, *α,β*-unsaturated aldehydes and 6-aminouracils



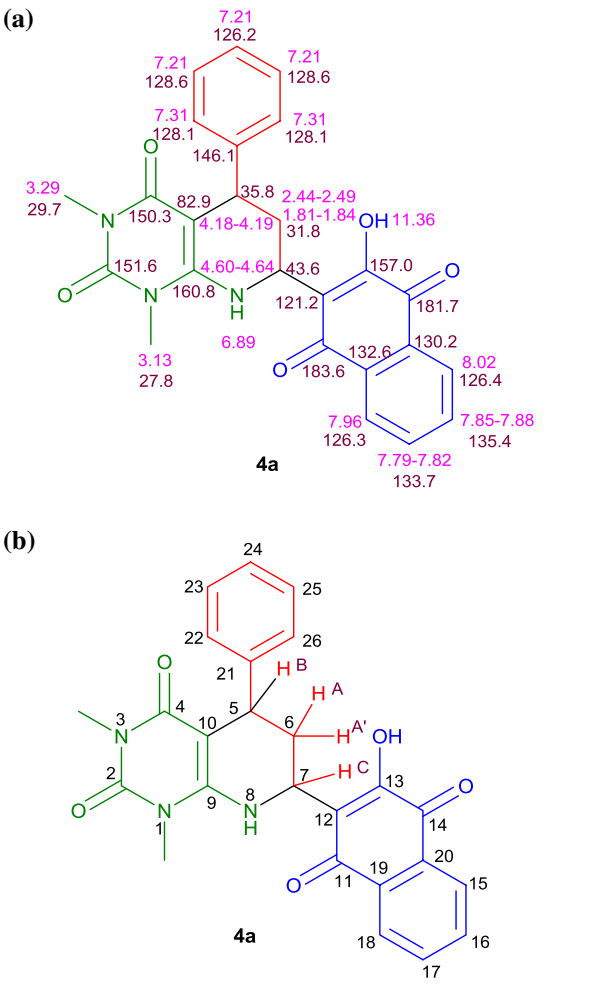


Scheme 2 Probable regioisomers from the three-component reaction of 2-hydroxy-1,4-naphthaquinone, cinnamaldehyde and 1,3-dimethyl-6-aminouracil

about the structure of our three-component product. From this three-component reaction, two regioisomers **4a** or **4a′** (Scheme 2) are possible.

The structure of our product was unambiguously confirmed as **4a** with the help of ^{1}H, ^{13}C and DEPT as well as 2D NMR experiments such as ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC NMR. Based on these experiments, the assignment of proton and carbons of **4a** was done and is shown in Fig. 2a. Similarly, the structure of **4a** with atom numbering, and HMBC correlation table are shown in Fig. 2b. In ^{1}H–^{13}C HMBC NMR spectra, the proton **B** is correlated with carbon nos. 6, 7, 10, 22, 26, 21, 4 and 9. On the other hand, the proton **C** is correlated with carbon nos. 6, 12, 13 and 11. This clearly proves that the phenyl ring is attached to carbon no. 5, and the 2-hydroxynaphthaquinone is attached to carbon no. 7. Therefore, the structure of our obtained product is **4a** not **4a′**. This interesting regioselectivity prompted us to fully study this reaction methodology by optimization of yield and checking substrate scope of the reaction.

Next, the same model reaction was tried in the presence of 10 mol% $FeCl_3{\cdot}6H_2O$ as catalyst without changing the solvent and microwave heating. Interestingly, in this case within 30 min, we ended with very good yield (85%) of **4a** (Table 1, entry 2). We also tried our model reaction in the presence of 10 mol% $FeCl_3{\cdot}6H_2O$ in ethanol medium under reflux conditions by conventional heating. In this case, even after 8-h reflux, we observed only 74% yield (Table 1, entry 3). After having these results, the three-component reaction was screened under microwave irradiation in the presence



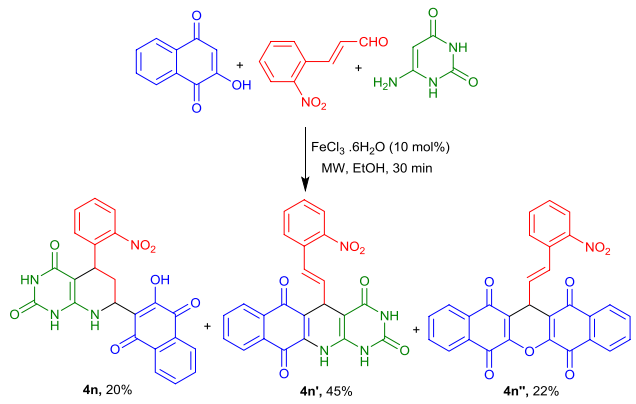
Proton	HMBC (^{1}H-^{13}C)
A'	10, 5, 21
A	5, 7, 12, 21
B	6, 7, 10, 22, 26, 21, 4, 9
C	6, 12, 13, 11

Fig. 2 **a** Structure of **4a** based on ^{1}H NMR, ^{13}C NMR, DEPT, ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC NMR spectra. Pink colour: ^{1}H NMR data in ppm; brown colour: ^{13}C NMR data in ppm. **b** Structure of **4a** with atom numbering and HMBC (^{1}H–^{13}C) correlation table

of various other Lewis acid catalysts such as $CeCl_3{\cdot}7H_2O$, I_2 and $Bi(NO_3)_3{\cdot}5H_2O$ (Table 1, entries 4–6). Among all these, the best result was observed in the presence of $FeCl_3{\cdot}6H_2O$ (Table 1, entry 2). We also screened the same reaction in various other solvents such as H_2O, CH_3CN, DMF, DMSO, DCM and toluene under microwave irradiation for 30 min (Table 1, entries 7–12). Among all the screened solvents, EtOH was found to be the best solvent for this reaction in terms of yield obtained.

After optimizing the reaction conditions, the generality and scope of this three-component reaction was studied by

varying α,β-unsaturated aldehydes, cyclic 1,3-dicarbonyls and 6-aminouracils. The results are summarized in Fig. 3. Various α,β-unsaturated aldehydes such as 4-methoxycinnamaldehyde, 4-bromocinnamaldehyde, 4-fluorocinnamaldehyde, 4-nitrocinnamaldehyde and crotonaldehyde were tested with 2-hydroxy-1,4-naphthaquinone and 6-amino uracil derivatives, and the corresponding products **4a**–**4j** were observed in good-to-moderate yields (Fig. 3). Both 6-aminouracil and 1,3-dimethyl-6-aminouracil are suitable for this reaction. Cyclic 1,3-diketone such as dimedone was also found suitable for this MCR and provided the corresponding products **4k**–**4m** in good yields. Interestingly, when ortho-substituted cinnamaldehyde such as 2-nitro cinnamaldehyde was reacted with 6-amino uracil and 2-hydroxy-1,4-naphthaquinone under the similar reaction conditions, we ended



Scheme 3 One-pot reaction of 2-hydroxy-1,4-naphthaquinone, 2-nitrocinnamaldehyde and 6-aminouracil

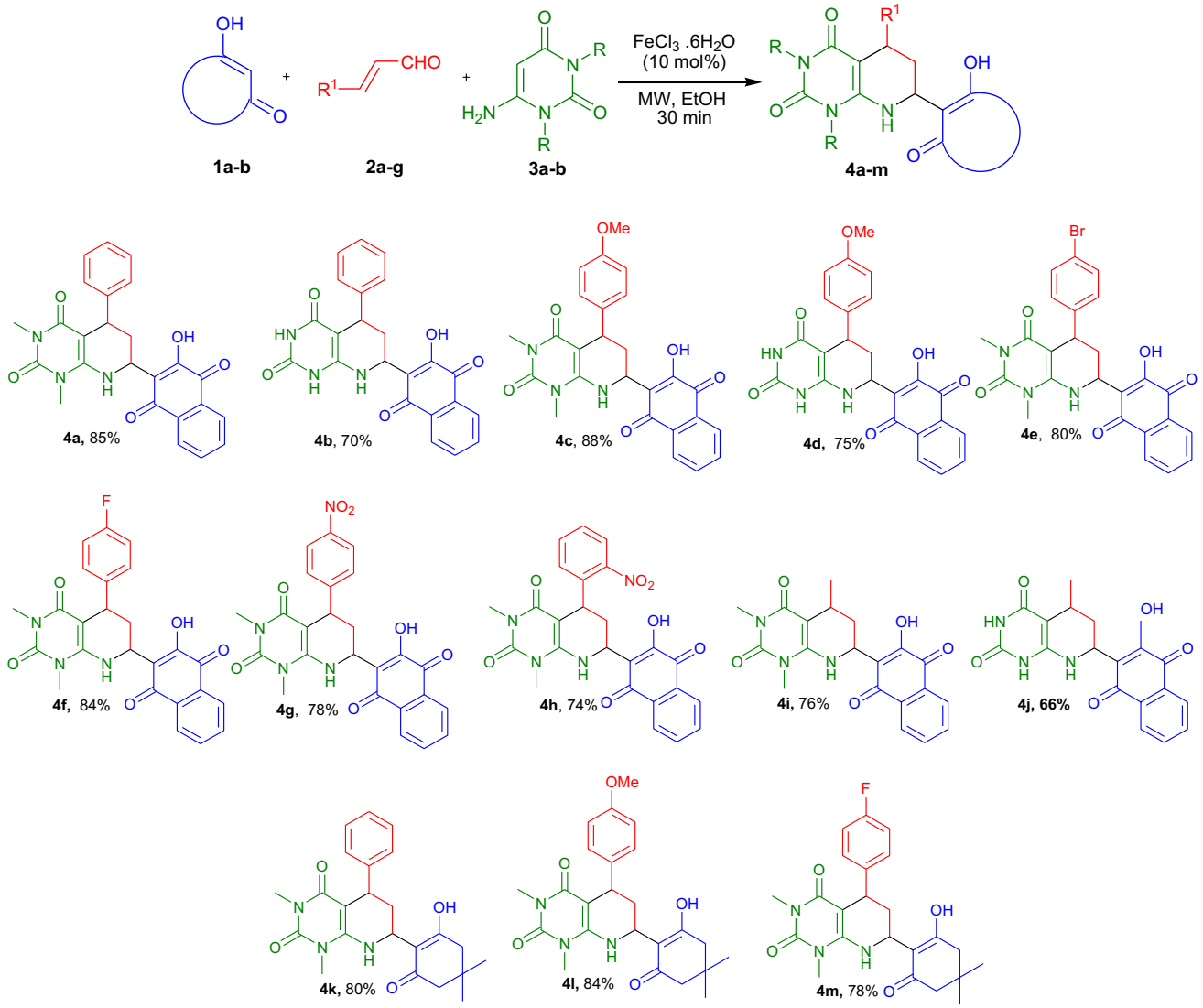
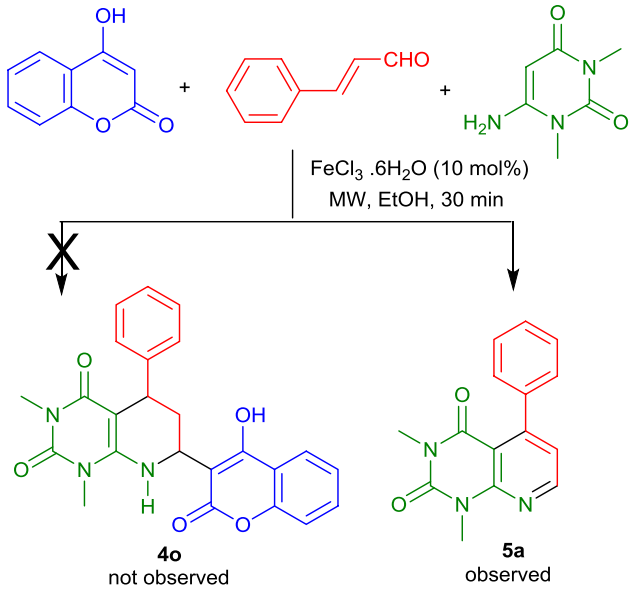


Fig. 3 Three-component reaction of cyclic 1,3-diketones, α,β-unsaturated aldehydes and 6-aminouracils. Reaction conditions: cyclic 1,3-dicarbonyls (1.0 mmol), α,β-unsaturated aldehydes (1.0 mmol) and 6-aminouracils (1.0 mmol) in 2.0 ml EtOH in the presence of 10 mol% $FeCl_3{\cdot}6H_2O$ in MW irradiation under sealed condition for 30 min



Scheme 4 One-pot reaction of 4-hydroxycoumarin, α,β-unsaturated aldehydes and 6-aminouracils

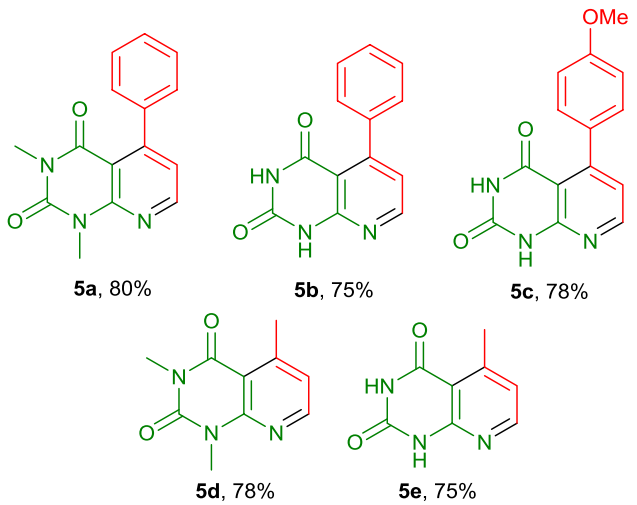


Fig. 4 Synthesis of two-component products **5** from the reaction of 4-hydroxycoumarin, α,β-unsaturated aldehydes and 6-aminouracils. Reaction conditions: 4-hydroxycoumarin (1.0 mmol), α,β-unsaturated aldehydes (1.0 mmol) and 6-aminouracils (1.0 mmol) in 2.0 ml EtOH in the presence of 10 mol% $FeCl_3{\cdot}6H_2O$ in MW irradiation under sealed condition for 30 min

up with a mixture of compounds (Scheme 3). Along with our expected product **4n**, we have also isolated other two products **4n′** and **4n″**.

Encouraged by these results, next, we wanted to explore 4-hydroxycoumarin as cyclic 1,3-dicarbonyl derivative. When we performed the reaction of 4-hydroxycoumarin, cinnamaldehyde and 1,3-dimethyl-6-aminouracil under the optimized reaction conditions, surprisingly, we observed only a two-component product **5a** rather than our expected three-component product **4o**. 4-Hydroxycoumarin may be involved in the reaction, but got detached from the expected product as it is a very good leaving group and leads to the formation of two-component product **5a** (Scheme 4).

Based on this observation, our next endeavour was to check the feasibility of this reaction with other α,β-unsaturated aldehydes such as 4-methoxycinnamaldehyde and crotonaldehyde with 6-aminouracils and the results are summarized in Fig. 4. All the reactions went smoothly and provided corresponding two-component products in moderate-to-good yields (Fig. 4).

The plausible reaction pathway for the formation of pyrimidine-fused tetrahydropyridines **4** from the three-component reaction of cyclic 1,3-dicarbonyls, α,β-unsaturated aldehydes and 6-aminouracils in the presence of $FeCl_3{\cdot}6H_2O$ as Lewis acid catalyst under microwave irradiation is illustrated in Scheme 5. It is believed that in the initial step, the cyclic 1,3-dicarbonyl **1** undergoes Knoevenagel-type reaction with the α,β-unsaturated aldehyde **2** to generate the intermediate **A**. Next, 6-aminouracil **3** attacks **A** by 1,6-addition to give the intermediate **B** which on tautomerization followed by 1,4-addition provides our desired three-component product **4**.

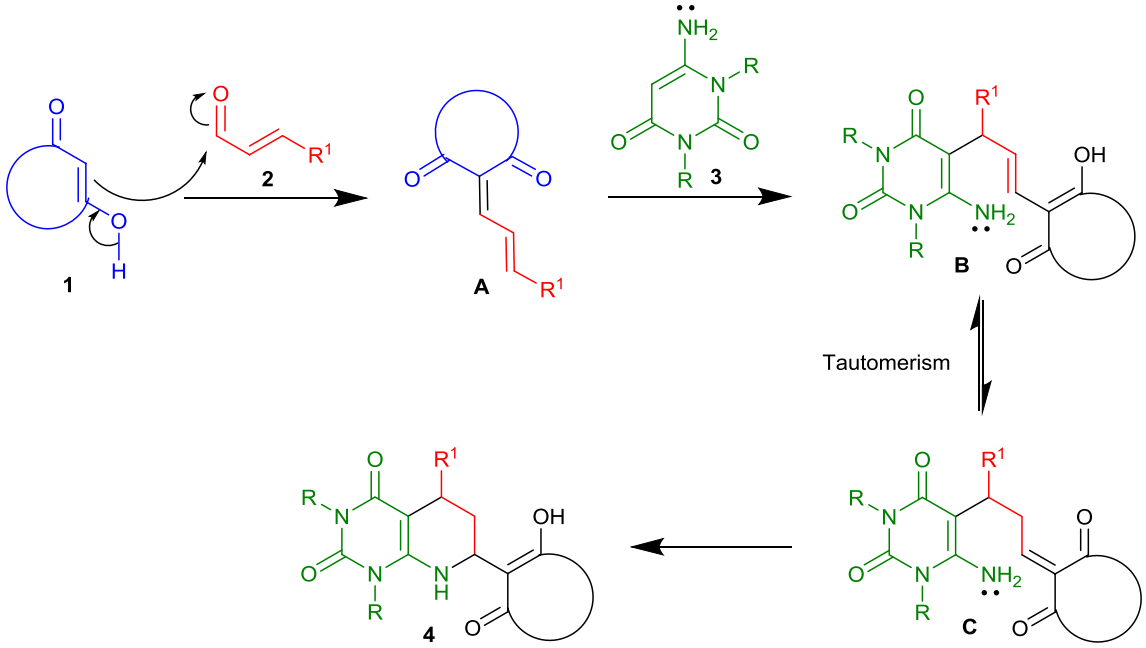
Conclusions

In conclusion, we have developed an efficient microwave-assisted methodology for the synthesis of pyrimidine-fused tetrahydropyridines and pyridines by the three-component reaction of cyclic 1,3-dicarbonyls, α,β-unsaturated aldehydes and 6-aminouracils in ethanol in the presence of $FeCl_3{\cdot}6H_2O$ as catalyst. The key advantages of the present methodology include short reaction time, moderate-to-good yields of the products, operational simplicity, inexpensive starting materials and easy purification process. Considering the presence of bioactive pyrimidine-fused pyridine moiety in the products, it is expected that these molecules will show potent biological activity and will be useful in medicinal chemistry.

Experimental section

General

All the starting materials used in these reactions are commercially available. The capillary tube method was used for the determination of melting point of synthesized products. Shimadzu FTIR spectrophotometer was used to record IR. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on Bruker Avance II 400 MHz spectrophotometer. The chemical shifts of NMR are reported on the δ scale



Scheme 5 Plausible reaction pathway

(ppm) downfield from tetramethyl silane ($\delta = 0.0$ ppm). Data are reported as follows: chemical shift and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet and brs = broad singlet). HRMS analysis data were recorded in Bruker Impact HD mass spectrometer. Initiator 2.5 Microwave Synthesizers from Biotage, Uppsala, Sweden, were used for performing the reactions.

General procedure for the synthesis of pyrimidine-fused tetrahydropyridines 4

To a mixture of cyclic 1,3-dicarbonyl (1.0 mmol) and α,β-unsaturated aldehyde (1.0 mmol) in a 5.0-ml reaction vial, 2.0 ml ethanol and $FeCl_3 \cdot 6H_2O$ (10 mol%) were added and the mixture was stirred for 10 min at room temperature. Then, 6-aminouracil (1.0 mmol) was added and the reaction mixture was irradiated in MW (74–75 W) under sealed and stirring condition for 30 min keeping the temperature at 100 °C. After completion of the reaction, the reaction mixture was cooled in an ice bath for 20 min, and solid precipitate was observed. The crude solid was separated by simple filtration and recrystallized in ethanol or ethyl acetate to obtain the pure product **4.**

5,6,7,8-Tetrahydro-7-(1,4-dihydro-2-hydroxy-1,4-dioxo naphthalen-3-yl)-1,3-dimethyl-5-phenylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (4a) Yield: 85%; Red solid; mp: 302–303 °C; IR (ATR, cm^{-1}): 3366, 3159, 1683, 1621, 1520, 1355, 1219, 999, 727; ^{1}H NMR (400 MHz, DMSO): δ ppm; 1.81–1.84 (m, 1H), 2.44–2.49 (m, 1H), 3.13 (s, 3H), 3.29 (s, 3H), 4.18–4.19 (m, 1H), 4.60–4.64 (m, 1H), 6.89 (s, 1H), 7.21 (t, $J = 8.0$ Hz, 3H), 7.31 (t, $J = 8.0$ Hz, 2H), 7.79–7.82 (m, 1H), 7.85–7.88 (m, 1H), 7.96 (d, $J = 8.0$ Hz, 1H), 8.02 (d, $J = 8.0$ Hz, 1H), 11.36 (brs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.8, 29.7, 31.8, 35.8, 43.6, 82.9, 121.2, 126.2, 126.3, 126.4, 128.1, 128.6, 130.2, 132.6, 133.7, 135.4, 146.1, 150.3, 151.6, 157.0, 160.8, 181.7, 183.6 ppm; HRMS (ESI-TOF) calcd for $C_{25}H_{22}N_3O_5$ $[M+H]^+$ 444.1554, found 444.1560.

5,6,7,8-Tetrahydro-7-(1,4-dihydro-2-hydroxy-1,4-dioxo naphthalen-3-yl)-5-phenylpyrido[2,3-d]pyrimidine-2,4 (1H,3H)-dione (4b) Yield: 70%; Yellow solid; mp: 238–240 °C; IR (ATR, cm^{-1}): 3379, 3230, 3199, 1695, 1546, 1536, 1432, 1328, 1254, 1093, 965, 876, 787; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.04–2.07 (m,1H), 2.34–2.41 (m, 1H), 3.81–3.84 (m, 1H), 4.81–4.83 (m, 1H), 6.25 (s, 1H), 6.88 (t, $J = 8.0$ Hz, 1H), 7.00–7.03 (m, 2H), 7.07–7.08 (m, 2H), 7.73–7.76 (m, 1H), 7.80–7.83 (m, 1H), 7.91 (t, $J = 8.0$ Hz, 2H), 10.09 (s, 1H), 10.12 (s, 1H), 11.22 (brs, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 36.2, 36.3, 47.0, 83.5, 120.8, 125.5, 125.9, 126.2, 127.0, 127.9, 130.0, 130.1, 132.6, 133.5, 135.1, 145.9, 150.9, 152.1, 163.0, 181.4, 183.9 ppm; HRMS (ESI-TOF) calcd for $C_{23}H_{18}N_3O_5$ $[M+H]^+$ 416.1241, found 416.1236.

5,6,7,8-Tetrahydro-7-(1,4-dihydro-2-hydroxy-1,4-dioxo naphthalen-3-yl)-5-(4-methoxyphenyl)-1,3-dimethyl pyrido[2,3-d] pyrimidine-2,4(1H,3H)-dione (4c) Yield: 88%; Orange solid; mp: 209–210 °C; IR (ATR, cm^{-1}): 3367, 3019, 1674, 1620,

1573, 1512, 1473, 1354, 1273, 1211, 1126, 999, 873, 736; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76–1.80 (m, 1H), 2.40–2.45 (m, 1H), 3.12 (s, 3H), 3.28 (s, 3H), 3.74 (s, 3H), 4.11–4.12 (m, 1H), 4.60–4.64 (m, 1H), 6.84 (brs, 1H), 6.86 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 7.80 (t, J = 8.0 Hz, 1H), 7.86 (t, J = 8.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 11.35 (brs, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.3, 29.2, 31.4, 34.4, 43.1, 55.0, 82.8, 113.4, 120.8, 125.7, 125.9, 128.5, 129.7, 132.1, 133.2, 134.9, 137.5, 149.7, 151.1, 156.3, 157.5, 160.3, 181.1, 183.2 ppm; HRMS (ESI-TOF) calcd for $C_{26}H_{24}N_3O_6$ $[M+H]^+$ 474.1660, found 474.1663.

***5,6,7,8-Tetrahydro-7-(1,4-dihydro-2-hydroxy-1,4-dioxo naphthalen-3-yl)-5-(4-methoxyphenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione* (4d)** Yield: 75%; Brown solid; mp: 219–220 °C; IR (ATR, cm^{-1}): 3367, 3275, 3212, 2945, 1693, 1593, 1539, 1473, 1338, 1273, 1215, 1056, 964, 852, 729; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.72–1.75 (m, 1H), 2.36–2.44 (m, 1H), 3.74 (s, 3H), 3.98–3.99 (m, 1H), 4.51–4.55 (m, 1H), 6.20 (s, 1H), 6.87 (d, J = 8.0 Hz, 2H), 7.06–7.09 (m, 2H), 7.79 (t, J = 8.0 Hz, 1H), 7.85 (t, J = 8.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 9.99 (s, 1H), 10.22 (s, 1H), 11.46 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 32.0, 33.4, 42.3, 55.0, 82.0, 113.5, 120.3, 125.7, 125.9, 128.4, 129.7, 132.0, 133.2, 134.9, 137.5, 150.1, 150.5, 156.7, 157.4, 162.6, 181.0, 183.1 ppm; HRMS (ESI-TOF) calcd for $C_{24}H_{20}N_3O_6$ $[M+H]^+$ 446.1347, found 446.1351.

***5-(4-Bromophenyl)-5,6,7,8-tetrahydro-7-(1,4-dihydro-2-hydroxy-1,4-dioxo naphthalen-3-yl)-1,3-dimethylpyrido [2,3-d] pyrimidine-2,4(1H,3H)-dione* (4e)** Yield: 80%; Orange solid; mp: 264–265 °C; IR (ATR, cm^{-1}): 3369, 3257, 1674, 1616, 1521, 1473, 1355, 1273, 1161, 1037, 999, 837, 734; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.79–1.82 (m, 1H), 2.45–2.49 (m, 1H), 3.13 (s, 3H), 3.28 (s, 3H), 4.15–4.16 (m, 1H), 4.56–4.60 (m, 1H), 6.92 (s, 1H), 7.16–7.19 (m, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.81 (t, J = 8.0 Hz, 1H), 7.87 (t, J = 8.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 11.39 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.8, 29.7, 31.6, 35.4, 43.5, 82.6, 119.4, 121.0, 126.2, 126.4, 130.2, 130.4, 131.4, 132.6, 133.8, 135.4, 145.7, 150.4, 151.6, 156.9, 160.9, 181.6, 183.6 ppm; HRMS (ESI-TOF) calcd for $C_{25}H_{21}$ BrN_3O_5 $[M+H]^+$ 522.0659, found 522.0661.

***5-(4-Fluorophenyl)-5,6,7,8-tetrahydro-7-(1,4-dihydro-2-hydroxy-1,4-dioxo naphthalen-3-yl)-1,3-dimethylpyrido [2,3-d] pyrimidine-2,4(1H,3H)-dione* (4f)** Yield: 84%; Yellow solid; mp: 248–250 °C; IR (ATR, cm^{-1}): 3381, 3182, 1680, 1618, 1527, 1475, 1355, 1274, 1170, 1037, 999, 835, 731; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.79–1.82 (m, 1H), 2.44–2.48 (m, 1H), 3.13 (s, 3H), 3.28 (s, 3H), 4.18 (m, 1H), 4.57–4.61 (m, 1H), 6.90 (s, 1H), 7.10–7.15 (m, 2H), 7.23 (t, J = 8.0 Hz, 2H), 7.81 (t, J = 8.0 Hz, 1H), 7.87 (t, J = 8.0 Hz, 1H), 7.96–7.97 (m, 1H), 8.02 (d, J = 8.0 Hz, 1H), 11.38 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.8, 29.7, 31.9, 35.1, 43.5, 83.0, 115.1, 115.3, 121.2, 126.2, 126.4, 129.7, 129.8, 130.2, 132.6, 135.4, 142.2, 150.3, 151.6, 156.8, 159.9, 160.9, 162.3, 181.6, 183.7 ppm; HRMS (ESI-TOF) calcd for $C_{25}H_{21}$ FN_3O_5 $[M+H]^+$ 462.1460, found 462.1469.

***5,6,7,8-Tetrahydro-7-(1,4-dihydro-2-hydroxy-1,4-dioxo naphthalen-3-yl)-1,3-dimethyl-5-(4-nitrophenyl)pyrido [2,3-d] pyrimidine-2,4(1H,3H)-dione* (4g)** Yield: 78%; Orange solid; mp: 259–261 °C; IR (ATR, cm^{-1}): 3233, 1673, 1592, 1504, 1437, 1378, 1302, 1237, 1056, 946, 849, 762; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.84–1.87 (m, 1H), 2.57–2.59 (m, 1H), 3.09 (s, 3H), 3.31 (s, 3H), 4.52–4.53 (m, 1H), 4.76–4.79 (m, 1H), 7.06 (s, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.50–7.53 (m, 1H), 7.68 (t, J = 8.0 Hz, 1H), 7.80–7.83 (m, 1H), 7.86–7.89 (m, 1H), 7.96 (t, J = 8.0 Hz, 2H), 8.03 (d, J = 8.0 Hz, 1H), 11.45 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.7, 29.8, 30.4, 32.3, 43.5, 82.6, 120.5, 124.9, 126.2, 126.4, 128.1, 130.7, 133.3, 133.7, 135.4, 140.3, 149.4, 151.0, 151.5, 157.3, 160.8, 181.6, 183.6 ppm; HRMS (ESI-TOF) calcd for $C_{25}H_{21}N_4O_7$ $[M+H]^+$ 489.1405, found 489.1416.

***5,6,7,8-Tetrahydro-7-(1,4-dihydro-2-hydroxy-1,4-dioxo naphthalen-3-yl)-1,3-dimethyl-5-(2-nitrophenyl)pyrido [2,3-d] pyrimidine-2,4(1H,3H)-dione* (4h)** Yield: 74%; Orange solid; mp: 218–220 °C; IR (ATR, cm^{-1}): 3356; 3284, 2941, 1686, 1601, 1524, 1336, 1268, 1206, 1041, 727; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87–1.91 (m, 1H), 2.58–2.65 (m, 1H), 3.10 (s, 3H), 3.31 (s, 3H), 4.56–4.57 (m, 1H), 4.79–4.83 (m, 1H), 7.01 (s, 1H), 7.42–7.45 (m, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.63–7.66 (m, 1H), 7.77 (t, J = 8.0 Hz, 1H), 7.83 (t, J = 8.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 8.00 (t, J = 8.0 Hz, 2H), 11.35 (brs, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 27.1, 29.1, 29.9, 31.8, 43.0 82.3, 120.1, 124.3, 125.5, 125.9, 127.3, 129.6, 130.1, 132.0, 132.5, 132.9, 134.6, 139.9, 148.9, 150.4, 150.9, 156.5, 160.3, 181.0, 183.0 ppm; HRMS (ESI-TOF) calcd for $C_{25}H_{21}N_4O_7$ $[M+H]^+$ 489.1405, found 489.1408.

***5,6,7,8-Tetrahydro-7-(1,4-dihydro-2-hydroxy-1,4-dioxo naphthalen-3-yl)-1,3,5-trimethyl pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione* (4i)** Yield: 76%; Red solid; mp: 247–249 °C; IR (ATR, cm^{-1}): 3421, 2958, 1674, 1577, 1554, 1504, 1373, 1273, 1165, 941, 767; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11 (d, J = 8.0 Hz, 3H), 1.55–1.58 (m, 1H), 2.15–2.20 (m, 1H), 2.92–2.98 (m, 1H), 3.14 (s, 3H), 3.21 (s, 3H), 4.93–4.97 (m, 1H), 6.77 (s, 1H), 7.83 (t, J = 8.0 Hz, 1H), 7.89 (t, J = 8.0 Hz, 1H), 8.02–8.07 (m, 2H), 11.41 (s, 1H) ppm;

^{13}C NMR (100 MHz, DMSO-d_6): δ 21.2, 24.8, 27.7, 29.5, 30.6, 43.5, 86.3, 121.6, 126.2, 126.5, 130.2, 132.6, 133.8, 135.4, 149.1, 151.4, 156.9, 160.9, 181.7, 183.8 ppm; HRMS (ESI-TOF) calcd for $C_{20}H_{20}N_3O_5$ $[M+H]^+$ 382.1397, found 382.1400.

***5,6,7,8-Tetrahydro-7-(1,4-dihydro-2-hydroxy-1,4-dioxo naphthalen-3-yl)-5-methylpyrido[2,3-d]pyrimidine-2,4 (1H,3H)-dione* (4j)** Yield: 66%; Orange solid; mp: 224–226 °C; IR (ATR, cm^{-1}): 3298, 2954, 2924, 1712, 1674, 1643, 1589, 1458, 1396, 1296, 1138, 1083, 983, 856, 775; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.08–1.09 (m, 3H), 1.50–1.53 (m, 1H), 2.11–2.16 (m, 1H), 2.79–2.83 (m, 1H), 4.84–4.88 (m, 1H), 6.09 (s, 1H), 7.82 (t, J = 8.0 Hz, 1H), 7.89 (t, J = 8.0 Hz, 1H), 8.01–8.04 (m, 2H), 9.83 (s, 1H), 10.14 (s, 1H), 11.56 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.9, 23.4, 30.6, 42.3, 85.2, 120.6, 125.7, 125.9, 129.8, 132.0, 133.3, 134.8, 149.1, 150.3, 156.6, 162.8, 181.0, 183.3 ppm; HRMS (ESI-TOF) calcd for $C_{18}H_{16}N_3O_5$ $[M+H]^+$ 354.1084, found 354.1077.

***5,6,7,8-Tetrahydro-7-(2-hydroxy-4,4-dimethyl-6-oxocyclo hex-1-enyl)-1,3-dimethyl-5-phenylpyrido[2,3d]pyrimidine-2,4(1H, 3H)-dione* (4k)** Yield: 80%; Colourless solid; mp: 242–244 °C; IR (ATR, cm^{-1}): 3264, 2955, 2870, 1692,1689, 1589, 1533, 1469, 1350, 1254, 1172, 1003, 887, 756; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.98 (s, 6H), 1.56–1.60 (m, 1H), 2.19 (s, 4H), 2.33–2.38 (m, 1H), 3.10 (s, 3H), 3.30 (s, 3H), 4.06–4.07 (m, 1H), 4.37–4.41 (m, 1H), 6.53 (s, 1H), 7.13–7.17 (m, 3H), 7.26 (t, J = 8.0 Hz, 2H), 10.72 (brs, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.2, 27.9, 29.1, 31.3, 31.9, 35.5, 42.4, 82.7, 111.9, 125.6, 127.5, 127.9, 146.0, 150.2, 151.2, 160.4 ppm; HRMS (ESI-TOF) calcd for $C_{23}H_{28}N_3O_4$ $[M+H]^+$ 410.2074, found 410.2094.

***5,6,7,8-Tetrahydro-7-(2-hydroxy-4,4-dimethyl-6-oxocyclo hex-1-enyl)-5-(4-methoxyphenyl)-1,3-dimethylpyrido [2,3-d] pyrimidine-2,4(1H,3H)-dione* (4l)** Yield: 84%; Colourless solid; mp: 312–315 °C; IR (ATR, cm^{-1}): 3250, 2965, 2858, 1635, 1596, 1520, 1438, 1382, 1254, 1013, 956, 867, 735; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.98 (s, 6H), 1.53–1.56 (m, 1H), 2.19 (s, 4H), 2.27–2.34 (m, 1H), 3.10 (s, 3H), 3.29 (s, 3H), 3.72 (s, 3H), 3.99–4.00 (m, 1H), 4.36–4.40 (m, 1H), 6.51 (s, 1H), 6.82 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 10.75 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.2, 27.9, 29.1, 31.3, 32.1, 34.6, 42.4, 54.9, 83.0, 112.0, 113.3, 128.4, 137.9, 150.1, 151.2, 157.3, 160.3 ppm; HRMS (ESI-TOF) calcd for $C_{24}H_{30}N_3O_5$ $[M+H]^+$ 440.2180, found 440.2172.

***5-(4-Fluorophenyl)-5,6,7,8-tetrahydro-7-(2-hydroxy-4,4-dimethyl-6-oxocyclo hex-1-enyl)-1,3-dimethyl pyrido[2,3-d] pyrimidine-2,4(1H,3H)-dione* (4m)** Yield: 78%; Yellow solid; mp: 248–250 °C; IR (ATR, cm^{-1}): 3280, 2952, 2931, 1687, 1586, 1537, 1471, 1380. 1310, 1209, 1006, 859,775; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.99 (s, 6H), 1.55–1.58 (m, 1H), 2.20 (brs, 4H), 2.30–2.37 (m, 1H), 3.11 (s, 3H), 3.29 (s, 3H), 4.06 (s, 1H), 4.33–4.37 (m, 1H), 6.56 (s, 1H), 7.05–7.10 (m, 2H), 7.15–7.18 (m, 2H), 10.74 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.7, 28.4, 29.6, 31.8, 32.5, 35.3, 42.9, 83.1, 112.4, 114.9, 115.1, 129.7, 129.8, 142.6, 150.7, 151.7, 159.8, 160.8, 162.2 ppm; HRMS (ESI-TOF) calcd for $C_{23}H_{27}FN_3O_4$ $[M+H]^+$ 428.1980, found 428.1984.

***5,6,7,8-Tetrahydro-7-(1,4-dihydro-2-hydroxy-1,4-dioxo naphthalen-3-yl)-5-(2-nitrophenyl)pyrido[2,3-d]pyrimidine-2,4 (1H,3H)-dione* (4n)** Yield: 22%; Orange solid; mp: 221–223 °C; IR (ATR, cm^{-1}): 3387, 3296, 3145, 1683, 1560, 1468, 1398, 1273, 1098, 947, 843, 749; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.81–1.85 (m, 1H), 2.56–2.58 (m, 1H), 4.47–4.48 (m, 1H), 4.67–4.70 (m, 1H), 6.38 (s, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.68 (t, J = 8.0 Hz, 1H), 7.77 (t, J = 8.0 Hz, 1H), 7.82 (t, J = 8.0 Hz, 1H), 7.92–7.95 (m, 2H), 8.01 (d, J = 8.0 Hz, 1H), 10.10 (s, 1H), 10.26 (s, 1H), 11.57 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 31.0, 31.2, 42.8, 81.7, 120.0, 125.0, 126.2, 126.4, 128.1, 130.3, 130.6, 132.6, 133.4, 133.7, 135.3, 140.1, 149.3, 150.9, 151.4, 157.5, 163.0, 181.5, 183.6 ppm; HRMS (ESI-TOF) calcd for $C_{23}H_{17}N_4O_7$ $[M+H]^+$ 461.1092, found 461.1096.

***(E)-5-(2-nitrostyryl)benzo[g]pyrimido[4,5-b]quinoline-2,4,6, 11(1H,3H,5H,12H)-tetraone* (4n')** Yield: 45%; Red Solid; mp: 312–315 °C; IR (ATR, cm^{-1}): 3382, 3259, 3133, 2802, 1702, 1579, 1378, 1268, 1015, 857, 721; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.78 (d, J = 8.0 Hz, 1H), 6.37–6.42 (m, 1H), 6.65 (d, J = 16 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.84 (t, J = 8.0 Hz, 1H), 7.87–7.92 (m, 2H), 8.03—–8.07 (m, 2H), 9.32 (s, 1H), 10.16 (s, 1H), 11.03 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 31.7, 86.4, 117.3, 124.7, 125.3, 126.4, 126.5, 128.6, 128.9, 130.6, 131.8, 132.4, 133.7, 133.9, 135.5, 136.1, 138.9, 144.6, 148.0, 149.9, 163.1, 179.4, 182.2 ppm; HRMS (ESI-TOF) calcd for $C_{23}H_{15}N_4O_6$ $[M+H]^+$ 443.0986, found 443.0992.

(E)-13-(2-nitrostyryl)-5H-dibenzo[b,i]xanthene-5,7,12,14 (13 H)-tetraone (4n") Yield: 22%; Yellow Solid; mp: 198–202 °C; IR (ATR, cm^{-1}): 2982, 1702, 1579, 1378, 1268, 1015, 857, 721; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.43 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 16 Hz, 1H), 7.06 (dd, J = 16 Hz, J = 8.0 Hz, 1H), 7.46–7.49 (m, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.78 (t, J = 8.0 Hz, 2H), 7.86 (t, J = 8.0 Hz, 3H), 7.91 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.7, 121.9, 123.5, 124.7, 126.1,

126.5, 128.5, 128.8, 130.2, 132.5, 132.7, 133.6, 133.8, 135.2, 135.8, 147.8, 156.0, 181.6, 183.7 ppm; Anal. Calcd. For $C_{29}H_{15}NO_7$ (489.43): C, 71.17; H, 3.09; N, 2.86%; Found: C, 71.22; H, 3.12; N, 2.98%. HRMS (ESI-TOF) calcd for $C_{29}H_{16}NO_7$ $[M+H]^+$ 490.0927, found 490.0930.

General procedure for the synthesis of pyrimidine-fused pyridines 5

To a mixture of 4-hydroxycoumarin (1.0 mmol) and α,β-unsaturated aldehyde (1.0 mmol) in a 5.0-ml reaction vial, 2.0 ml ethanol and $FeCl_3{\cdot}6H_2O$ (10 mol%) were added and the mixture was stirred for 10 min at room temperature. Then, 6-aminouracil (1.0 mmol) was added to the reaction mixture and it was irradiated in MW (74–75 W) under sealed and stirring condition for 30 min keeping temperature at 100 °C. After completion of the reaction, the reaction mixture was cooled in an ice bath for 20 min, and solid precipitate was observed. The crude solid was washed with ethanol to get the pure product 5.

1,3-Dimethyl-5-phenylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (5a) Yield: 80%; Pale Yellow Solid; mp: 224–226 °C; IR (ATR, cm^{-1}): 2954, 1711, 1651, 1547, 1458, 1332, 1279, 1174, 999, 841; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.19 (s, 3H), 3.63 (s, 3H), 7.09–7.10 (m, 1H), 7.31–7.33 (m, 2H), 7.41–7.42 (m, 2H), 8.68–8.69 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.6, 30.3, 108.1, 122.2, 128.0, 128.3, 128.6, 139.7, 151.3, 152.1, 152.7, 153.6, 160.4 ppm; HRMS (ESI-TOF) calcd for $C_{15}H_{14}N_3O_2$ $[M+H]^+$ 268.1081, found 268.1091.

5-Phenylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (5b) Yield: 75%; Colourless Solid; mp: 330–333 °C; IR (ATR, cm^{-1}): 3283, 3170, 2810, 1737, 1707, 1574, 1399, 1251, 843, 754 693; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.99 (d, J = 8.0 Hz, 1H), 7.33–7.35 (m, 2H), 7.38–7.41 (m, 3H), 8.54–8.55 (m, 1H), 11.21 (s, 1H), 11.67 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 107.5, 122.1, 127.9, 128.4, 128.8, 139.2, 150.6, 153.2, 153.4, 154.0, 162.0 ppm; HRMS (ESI-TOF) calcd for $C_{13}H_{10}N_3O_2$ $[M+H]^+$ 240.0768, found 240.0766.

5-(4-Methoxyphenyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (5c) Yield: 78%; Colourless Solid; mp: 358–360 °C; IR (ATR, cm^{-1}): 3383, 3165, 2963, 1693, 1595, 1392, 1291, 1016, 811; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.81 (s, 3H), 6.95 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.0 Hz, 1H), 7.30–7.33 (m, 2H), 8.50–8.51 (m, 1H), 11.19 (s, 1H), 11.61 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.6, 107.4, 113.4, 122.1, 130.6, 131.1, 150.6, 153.0, 153.3, 154.1, 159.8, 162.1 ppm; HRMS (ESI-TOF) calcd for $C_{14}H_{12}N_3O_3$ $[M+H]^+$ 270.0873, found 270.0877.

1,3,5-Trimethyl pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (5d) Yield: 78%; Colourless Solid; mp: 330–333 °C; IR (ATR, cm^{-1}): 2948, 1696, 1645, 1422, 1335, 1273, 1028, 855; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.70 (s, 3H), 3.25 (s, 3H), 3.52 (s, 3H), 7.12 (d, J = 8.0 Hz, 1H), 8.47–8.48 (m, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.2, 28.4, 30.1, 109.2, 122.5, 151.1, 151.8, 152.5, 152.7, 161.8 ppm; HRMS (ESI-TOF) calcd for $C_{10}H_{12}N_3O_2$ $[M+H]^+$ 206.0924, found 206.0938.

5-Methylpyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (5e) Yield: 75%; Colourless Solid; mp: 289–291 °C; IR (ATR, cm^{-1}): 3389, 3159, 2989, 1666, 1580, 1398, 1267, 1025, 841; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.68 (s, 3H), 7.03–7.04 (m, 1H), 8.36–8.37 (m, 1H), 11.27 (s, 1H), 11.50 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.6, 108.7, 122.2, 150.5, 152.3, 153.3, 153.8, 163.7 ppm; HRMS (ESI-TOF) calcd for $C_8H_8N_3O_2$ $[M+H]^+$ 178.0611, found 178.0604.

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