Synthesis N. Etivand Paper

Fast and Efficient Green Procedure for the Synthesis of Benzo[5,6]chromene Derivatives and Their Sulfur Analogues in Water by Organocatalyst Potassium Phthalimide-*N*-oxyl

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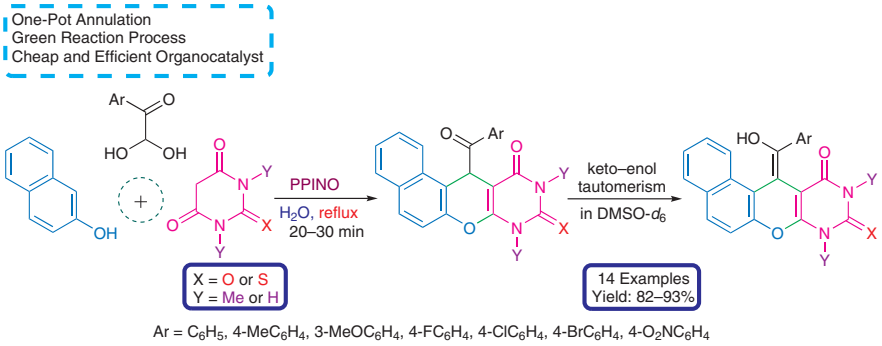

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Abstract A simple, clean, straightforward, and environmentally benign one-pot, three-component reaction of various arylglyoxal monohydrates, β-naphthol, and barbituric acid [pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione] or thiobarbituric acid in the presence of catalytic amounts potassium phthalimide-*N*-oxyl (PPINO), as a mild and efficient organocatalyst in aqueous media under reflux conditions is reported. This transformation produced the novel diverse-substituted 12-benzoyl-8,12-dihydro-9*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidine-9,11(10*H*)-diones and their sulfur analogues in 82–93% yield via filtration and without utilization of any chromatography. The high yields of products, very simple operation, easy workup, availability of starting materials, green process, and high atom-economy are the main benefits of this synthetic strategy.

Keywords potassium phthalimide-*N*-oxyl, arylglyoxal monohydrate, benzo[5,6]chromenes, one-pot, three-component reaction, green process

In the past years, due to the emergence of drug compounds, the demand for efficient, environmentally friendly, and economical methods for the synthesis of biological molecules, especially heterocyclic scaffolds, has increased. According to global environmental concern and green chemistry roles, the important issue is to use waste-free, hazard-free, less toxic, and energy-effective syntheses as a final goal in the syntheses of organic and medicinal compounds. One of the powerful, valuable and green protocol that provides an efficient way and high degree of atom economy for the preparation of organic molecules is the multi-component reactions (MCRs). The importance of this class of reactions is that they can reduce workups, extraction, and purification steps, reduce waste production and save both solvents and reagents. During MCRs three or more dissimilar reactants combine and generate several new bonds in a one-pot process for the synthesis of highly functionalized heterocyclic compounds.[1]

The presence of organocatalyst and water as a green solvent with MCRs has developed as the best technique for suitable access to a wide range of biologically heterocyclic scaffolds. Hence, the sketch of a new MCR strategy has attracted abundant attention from academic and industrial research groups as a pivotal theme for the synthesis of many important heterocyclic compounds such as benzopyran (chromene) derivatives.[2]

More than fifty percent of the organic compounds, identified so far, consist of heterocyclic structures.[3] These spectacular category of compounds are important because of their significant biological activity. Very particularly, functionalized nitrogen and oxygen heterocycles are privileged structures due to their biological and pharmaceutical virtues. In this direction, chromene and their fused analogues containing heterocyclic rings are important and essential targets in the synthesis of organic compounds.[4] Chromene-annulated frameworks belong to a major class of natural compounds, which are broadly found in alkaloids, flavonoids,[5] and edible fruits and vegetables.[6] Chromene structure moiety have occupied a significant place in drug research in recent years for their various pharmacological properties such as antioxidant,[7] anticoagulant,[8] anticancer,[9] antimicrobial,[10] antiviral,[11] antifungal,[12] antidiabetic,[13] antiallergenic,[14] antimalarial,[15] antirheumatic,[16] spasmolytic, and anti-anaphylactic[17] activities. Moreover, this moiety as chemically useful synthon is widely used in pigments,[18] laser dyes[19] and cosmetics.[20] Some diverse chromenes with strong biological properties are shown in Figure 1.

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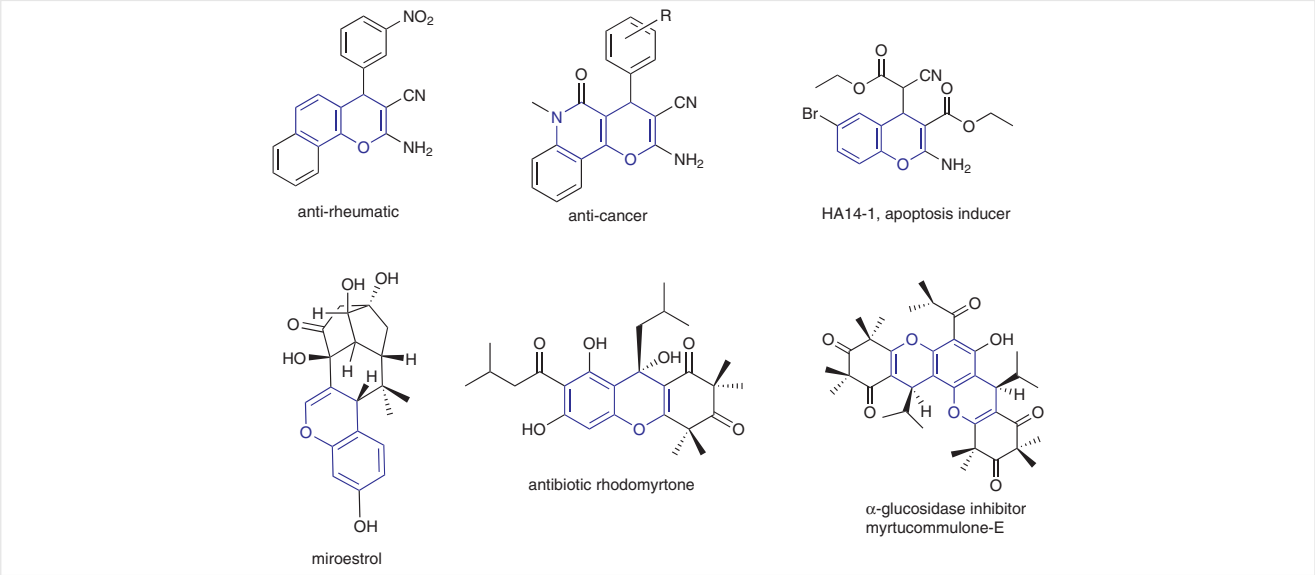


Figure 1 Bioactive agents and natural compounds containing the benzopyran (chromene) core

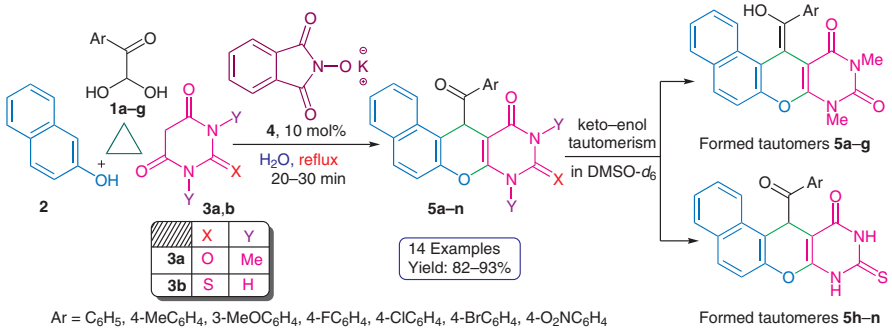
Due to aforementioned important biological activity of these compounds, research by chemists has been focused on the development of various one-pot, green strategies for their preparation.

Several modified methods for the synthesis of a large number of chromene derivatives have been proposed in recent years. Benzopyran (chromene) scaffolds are typically synthesized from aldehydes, various enolizable C–H activated acidic compounds and varying nucleophiles such as malononitrile,[21] ethyl cyanoacetate,[22] phenols,[23] thiols,[24] naphthols,[25] 4-hydroxycoumarins,[26] Lawsone (2-hydroxy-1,4-naphthoquinone),[27] and many more under different reaction conditions, involving the use of organic solvents, under grinding, heating/refluxing, microwaves, ultrasonic irradiation, electrolysis, etc.[28] A large number of homogeneous or heterogeneous catalysts have been used for this reaction, such as tetrabutylammonium bromide (TBAB),[29] chitosan,[30] DABCO,[31] DBU,[32] KSF,[33] piperidine,[34] K_2CO_3,[35] Na_2CO_3,[36] K_3PO_4,[37] nano-sized MgO,[38] Mg/Al hydrotalcite,[39] $TiCl_4$,[40] $FeCl_3$,[41] $[RuCl_2(p\text{-cymene})]_2$,[42] TMG-[bmim][x],[43] [2-amim][PF_6],[44] and so forth.

Although excessive progress has been attained, these methods for the synthesis chromene scaffolds are limited by disadvantages including time-consuming multi-step conditions, the use of expensive reagents, toxic organic catalysts or solvents, difficult workup procedure, extended reaction times, harmful by-product formation, and low yields.[45] Hence, obviation of these limitations and development of a simple, practical, economic, and green strategy for one-pot multicomponent synthesis of this series of compounds in high yield is still desired.

The phthalimide-*N*-oxyl (PINO) anion is an readily accessible Lewis base and impressive organocatalyst used in the protection of hydroxy group in various phenol and alcohol compounds with trimethylsilyl group,[46a] cyanosilylations of carbonyl scaffolds,[46b] and cyclotrimerization of isocyanate derivatives.[46c] Based on these applications, we decided to investigate a transition-metal-free three-component reaction (TCR) in a single-step operation for the synthesis of chromene compounds with diverse substituents in the presence of catalytic amounts potassium phthalimide-*N*-oxyl (PPINO) in water. Moreover, the use of water as a green, inexpensive, nontoxic, nonflammable, easily available, and inherent eco-friendly solvent strongly improves the rate of reaction process due to its excellent polarity properties and strong hydrogen bonding ability.[47] The structure of synthesized compounds were characterized by their spectral data and microanalysis.

In continuation of our investigation to progress the catalytic amplitude based on arylglyoxal in the synthesis of various and novel heterocyclic compounds,[48] we envisaged that the existence of two or more heterocyclic portion in a single molecule often improves remarkably the biological properties of this scaffold. We report herein a facial TCR strategy for the synthesis of 12-benzoyl-8,12-dihydro-9*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidine-9,11(10*H*)-diones and their sulfur analogues in a single step using arylglyoxal monohydrates **1a–g**, β-naphthol (**2**), and barbituric acid **3a** or thiobarbituric acid (**3b**) in the presence of PPINO (**4**) in water under reflux conditions (Scheme 1). This synthetic route is promising for the synthesis of new alkaloid compounds, which may exhibit biological and pharmaceutical properties.

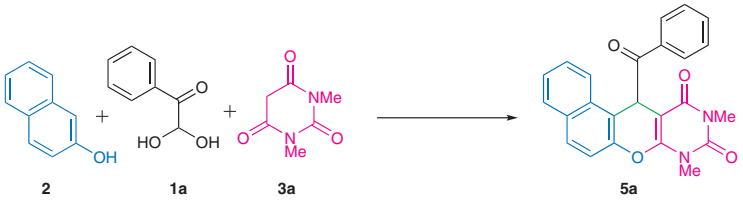


Scheme 1 One-pot three-component reaction of arylglyoxal monohydrates, β-naphthol, and barbituric acid or thiobarbituric acid catalyzed by PPINO in water

Arylglyoxal monohydrates are important precursors in the synthesis of heterocyclic compound with biological and pharmaceutical activities.[49] The arylglyoxal monohydrates with electron-withdrawing and electron-donating substituents as starting materials in this context were prepared via oxidation of the corresponding acetophenones with SeO_2 in 1,4-dioxane/H_2O under reflux conditions and subsequently recrystallized from boiling water according to standard literature method.[50]

To find the optimum reaction conditions, we started our investigation with the synthesis of benzo[5,6]chromene **5a** by a systematic study on the model reaction of phenylglyoxal monohydrate (**1a**), β-naphthol (**2**) and *N*,*N*-dimethylbarbituric acid (**3a**) (molar ratio: 1:1:1) using various solvents, catalysts, times, and temperatures for evaluating the rate and the yield of reaction (all conditions) (Table 1).

Table 1 Optimization of Reaction Conditions for the Preparation of **5a**[a]



Entry	Catalyst	Solvent (v/v %)	Temp (°C)	Time (h)	Yield (%)[b]
1	–	H_2O	RT	24	–[c]
2	–	EtOH	reflux	24	–
3	–	CH_2Cl_2	reflux	8	–
4	–	THF	reflux	8	–
5	TPAB	H_2O	reflux	12	28
6	TPAB	EtOH	reflux	12	25
7	$FeCl_3$	H_2O	reflux	8	33
8	$ZnCl_2$	H_2O	reflux	8	45
9	L-proline	H_2O	reflux	12	27
10	L-alanine	H_2O	reflux	12	27
11	AcOH	H_2O	reflux	12	29
12	sulfamic acid	H_2O	reflux	12	34
13	Et_3N	H_2O	RT	24	43
14	Et_3N	EtOH	reflux	24	26
15	K_2CO_3	H_2O	reflux	24	31
16	DABCO	H_2O	reflux	24	42

Table 1 (continued)

Entry	Catalyst	Solvent (v/v %)	Temp (°C)	Time (h)	Yield (%)[b]
17	DBU	H_2O	reflux	24	40
18	NAPINO[d]	H_2O	reflux	2	56
19	LIPINO[e]	H_2O	reflux	2	61
20	**PPINO**	**H_2O**	**reflux**	**1**	**75**

[a] Reaction conditions: phenylglyoxal monohydrate (**1a**; 1 mmol), β-naphthol (**2**; 1 mmol), and *N*,*N*-dimethylbarbituric acid (**3a**; 1 mmol), and catalyst (20 mol%).
[b] Isolated yield of **5a**.
[c] Reaction failed to occur.
[d] Sodium phthalimide-*N*-oxyl.
[e] Lithium phthalimide-*N*-oxyl.

To preserve green chemistry features, safe and nonhazardous solvents such as water and ethanol were favored as the ideal solvents in the optimization tests. Initially, we examined this model condensation reaction without any catalyst in various solvents, but did not obtain the desired product **5a** under stirring at room temperature to reflux conditions even after a long reaction time (24 h) (Table 1, entries 1–4). Next, the model reaction was tested in the presence of tetrapropylammonium bromide (TPAB) in H_2O and EtOH under reflux conditions for 12 hours, which produced the desired product **5a** in 28 and 25% yield, respectively (entries 5 and 6). Afterwards, to find the optimum catalyst in H_2O, the model reaction was carried out in the presence of a series of Lewis and Brønsted acidic catalysts including $FeCl_3$, $ZnCl_2$, L-proline, L-alanine, sulfamic acid, and AcOH under reflux conditions forming the desired product in 33–45% yield (entries 7–12).

In another study, the same model reaction was designed in the presence of common basic catalysts such as Et_3N, K_2CO_3, DABCO (1,4-diazabicyclo[2.2.2]octane), or DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in water or ethanol under stirring at room temperature to reflux conditions to produce the desired product in 26–43% yield (Table 1, entries 13–17). As can be seen, the use of water as a solvent, enhanced the yield of the desired reaction. Interestingly, when we shifted our attention to PINO anion as an organocatalyst salt soluble in H_2O under reflux condition, the reaction proceeded well and afforded the desired product **5a** within 1–2 hours in 58–77% yield. PPINO produced a higher yield in lower time related to other salts including Li^+, Na^+ (entries 18–20). The optimum reaction conditions are shown in bold text (entry 20).

As indicated in Table 2, using 20–30 mol% of PPINO as a catalyst gave the product **5a** within 60–120 minutes in 38–67% yield under stirring at room temperature to reflux conditions (Table 2, entries 1–5). In the following, using 15 mol% amount of PPINO in water under reflux conditions compared to room temperature improved the yield of the desired product **5a** within 60 minutes from 41% to 77 % yield (entries 6 and 7). Changing the molar ratio of catalysts to 10 mol% had a good effect on the efficiency of the reaction. The best result in terms of yield (88%) was obtained with a reaction time of 30 minutes (entry 8). Decreasing the molar ratio of catalysts to 5 mol% with stirring under reflux for 60 minutes reduces the product yield to 75% (entry 9).

Table 2 Effect of the Diverse Molar Ratio of Catalyst PPINO for the Synthesis of Compound **5a**

Entry	Catalyst (mol%)	Solvent (v/v %)	Temp (°C)	Time (min)	Yield (%)
1	PPINO (30)	H_2O	RT	120	43
2	PPINO (25)	EtOH	RT	120	40
3	PPINO (25)	H_2O	reflux	120	67
4	PPINO (25)	EtOH	reflux	120	55
5	PPINO (20)	H_2O	RT	120	38
6	PPINO (15)	H_2O	RT	60	41
7	PPINO (15)	H_2O	reflux	60	77
8	**PPINO (10)**	**H_2O**	**reflux**	**30**	**88**
9	PPINO (5)	H_2O	reflux	60	75

By generalizing the optimum conditions for the one-pot three-component reaction of a mixture of arylglyoxal derivatives **1a–g** (monohydrate form), β-naphthol (**2**), and *N*,*N*-dimethylbarbituric acid (**3a**) or thiobarbituric acid (**3b**) in the presence of a catalytic amount of PPINO (**4**) (10 mol %) in H_2O under reflux conditions, the desired products **5a–n** were obtained. The results including the product, melting point, color, reaction time, and yield are summarized in Table 3. The reaction performed efficiently with functionally substituted arylglyoxal monohydrates and barbiturates to give the chromene derivatives in high yields. Diversity of the electron-donating and electron-withdrawing substituents, the location of these functional groups on the aromatic ring of the arylglyoxal monohydrates, and also the existence of various functional groups on the barbituric compounds did show a partial effect on the yield of the reactions. However, a few substituents (4-Cl, 4-Br, and 4-NO_2) needed longer reaction times.

Table 3 Synthesis of Chromenes **5a–n** via the One-Pot, Three-Component Reaction[a]

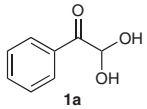
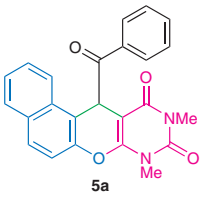
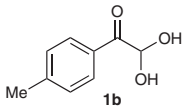
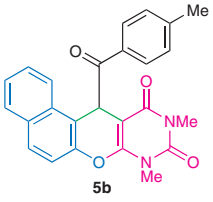
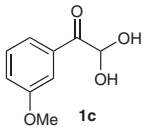
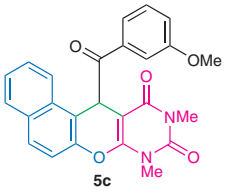
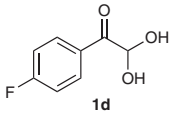
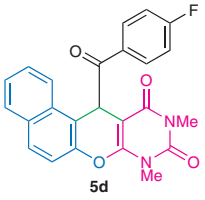
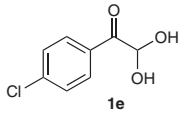
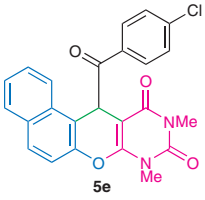
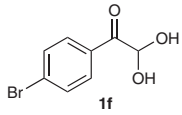
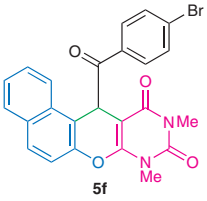
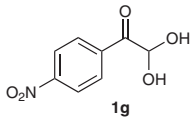
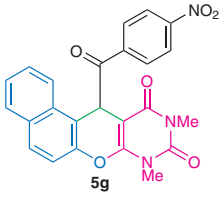
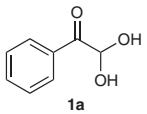
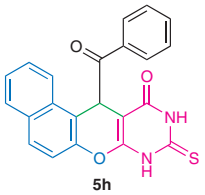
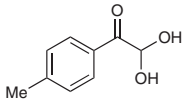
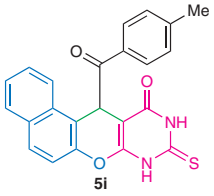
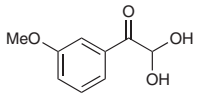
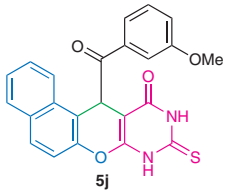
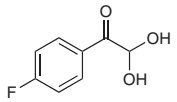
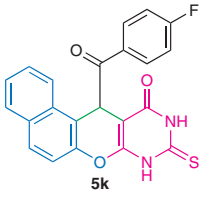
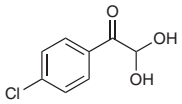
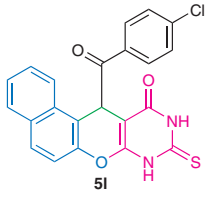
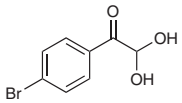
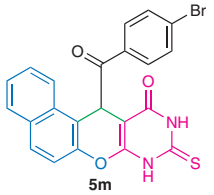
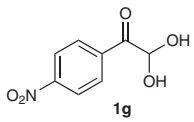
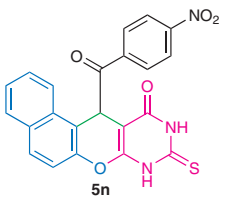
Entry	Arylglyoxal monohydrate	Barbituric acid	Product	Time (min)	Mp (°C)	Yield (%)[b]	Color
1	 **1a**	**3a**	 **5a**	25	180–181	88	colorless
2	 **1b**	**3a**	 **5b**	20	254–255	93	colorless
3	 **1c**	**3a**	 **5c**	25	218–219	91	colorless
4	 **1d**	**3a**	 **5d**	20	211–212	87	colorless
5	 **1e**	**3a**	 **5e**	30	281–282	85	colorless
6	 **1f**	**3a**	 **5f**	30	295–296	82	colorless
7	 **1g**	**3a**	 **5g**	30	316 (dec.)	82	yellow

Table 3 (continued)

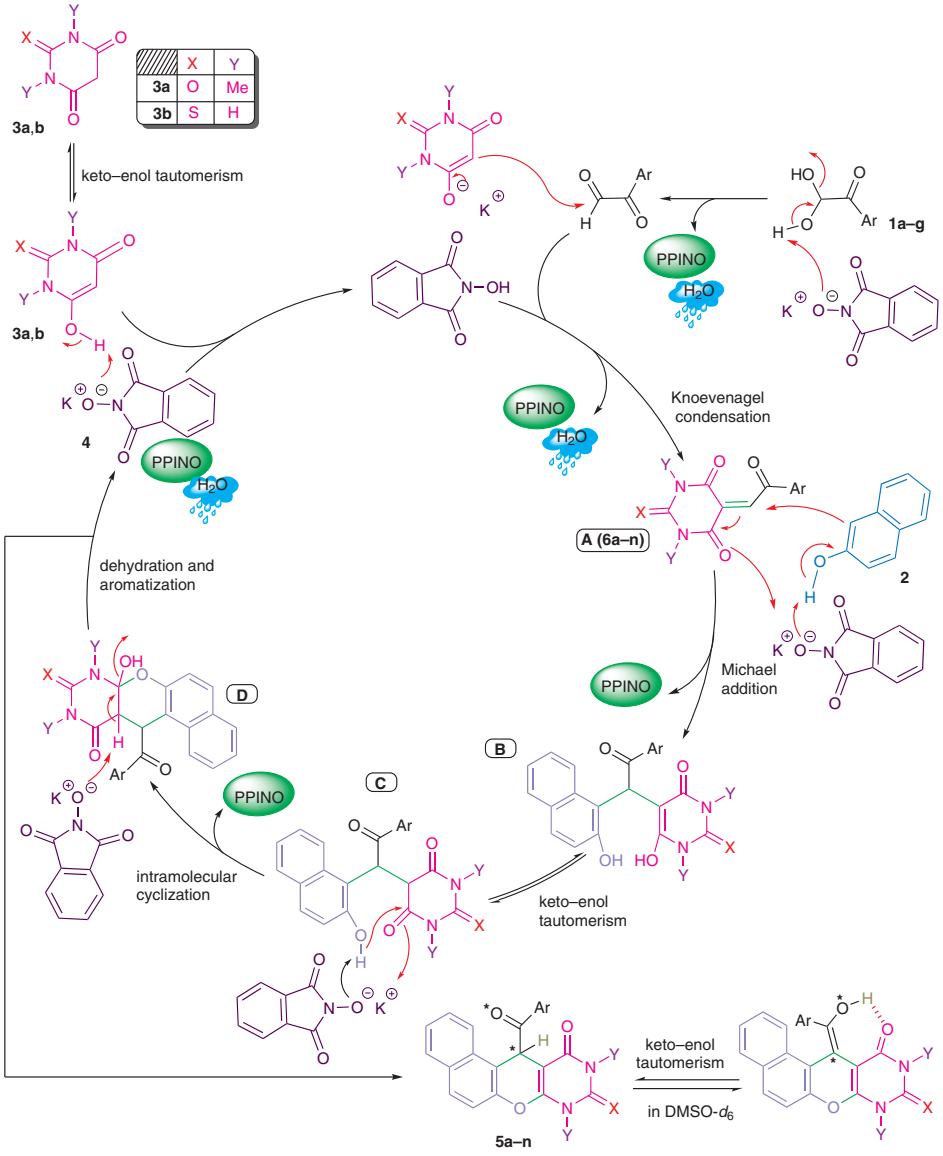
Entry	Arylglyoxal monohydrate	Barbituric acid	Product	Time (min)	Mp (°C)	Yield (%)[b]	Color
8	 1a	**3b**	 5h	25	223–224	86	colorless
9	 1b	**3b**	 5i	20	263–264	89	colorless
10	 1c	**3b**	 5j	25	202–203	89	colorless
11	 1d	**3b**	 5k	20	255–256	84	colorless
12	 1e	**3b**	 5l	30	249–250	85	colorless
13	 1f	**3b**	 5m	30	266–267	83	colorless
14	 1g	**3b**	 5n	30	254–255	82	yellow

[a] Reaction conditions for synthesis of **5a–n**: **1a–g** (1 mmol), **2** (1 mmol), **3a**,**b** (1 mmol), and PPINO (**4**; 10 mol%) in H_2O (5 mL) under reflux for 20–30 min.
[b] Isolated yield.

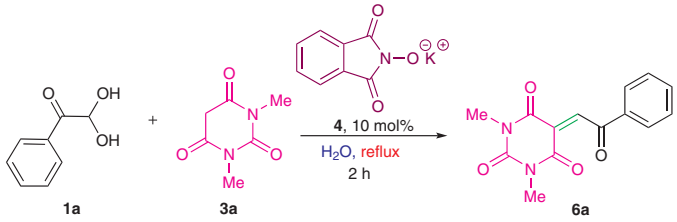
A possible reaction mechanism for the synthesis of benzo[5,6]chromeno[2,3-*d*]pyrimidine derivatives **5a–n** by the one-pot three-component technique catalyzed by PPINO (**4**) in water is suggested in Scheme 2.

In the first step, PPINO reacts with barbituric acid **3a** or thiobarbituric acid (**3b**) to form its enolate ion, which would be stabilized by keto-enol tautomerization. Simultaneous dehydration of arylglyoxal monohydrates **1a–g** in the presence of PPINO, converts them into the arylglyoxals. In the second step, regioselective Knoevenagel condensation between the previously formed two reactants by loss of one molecule of water leads to the formation of the intermediate **A**. PPINO plays an important role in the formation of intermediate **B** via the regioselective Michael addition of β-naphthol (**2**) to the intermediate **A** resulting in the formation of intermediate **B**, which would be converted into intermediate **C** by keto-enol tautomerization. Then, intermediate **C** undergoes intramolecular condensation to give intermediate **D**, which finally gets converted into the final products **5a–n** in the presence of PPINO by dehydration and aromatization (Scheme 2).

In order to understand the accuracy of the proposed mechanism, intermediate **A** (Scheme 2) must be isolated and the structure of the compounds confirmed by FT-IR (KBr), ^{1}H NMR, and ^{13}C NMR spectra and elemental analysis data. We experimented with the isolated **6a** as an example and then reacted it separately with β-naphthol to finally form the foretold product **5a**. Compound **6a** was



Scheme 2 Plausible mechanism for the synthesis of benzo[5,6]chromeno[2,3-*d*]pyrimidine derivatives catalyzed by PPINO



Scheme 3 The reaction of phenylglyoxal monohydrate (**1a**) and *N*,*N*-dimethylbarbituric acid (**3a**) for the synthesis of compound **6a** as a Knoevenagel condensation intermediate

synthesized by the Knoevenagel reaction of phenylglyoxal monohydrate (**1a**) and *N*,*N*-dimethylbarbituric acid (**3a**) (Scheme 3).

The structures of all the benzo[5,6]chromene compounds **5a–n** were characterized using ^{1}H and ^{13}C NMR spectroscopy, FT-IR spectral data, and microanalyses.

The FT-IR (KBr) spectra of **5a–n** showed absorption bonds due to vibrations of C–H group at 3057–2947 cm^{-1} and absorption bonds due to vibrations of C=O at 1707–1693 cm^{-1}. The FT-IR (KBr) spectra of **5h–n** showed absorption bonds due to vibrations of NH group at 3410–3350 and 3264–3289 cm^{-1}.

In the FT-IR (KBr) spectra of intermediate **6a**, sharp bands were observed due to the stretching vibration of all carbonyl groups (at 1662–1690 cm^{-1}) and bands of C=C group (at 1630 cm^{-1}).

As indicated in Scheme 2, the reasonable elucidation for the incident of the proposed keto-enol tautomerization in the ^{13}C NMR spectra is on the basis of the appearance of the signal for C=O* of aryloyl at higher than 170 ppm and also in the ^{1}H NMR spectra, the presence or absence of C*–H or O*–H proton as a singlet. Due to tautomeric interchanges, which are ordinarily very fast processes, this signal appeared as a broad singlet. In the enol form, OH protons can be stabilized via formation of intramolecular hydrogen bonding with the adjacent carbonyl group.

In the ^{1}H NMR spectra of the products **5a–n**, the protons of aromatic rings were located at around δ = 8.37–7.26 and a very broad singlet showed at δ = 6.48–4.55 related to C*–H or O*–H proton, which disappeared on addition of D_2O. The N–H groups of **5h–n** appeared as a singlet at δ = 12.04–11.85, which disappeared on addition of D_2O. The methyl hydrogens of the products **5a–g** appeared as a singlet at δ = 3.34–3.32.

In the ^{1}H NMR spectra of the intermediate **6a**, a singlet was located at 8.15 ppm related to the vinyl proton.

In the ^{13}C NMR spectra of **5a–n**, δ =160.3–159.0 was ascribed to amide carbonyl group and C=S group, respectively. In the ^{13}C NMR spectra of the sulfur analogues **5h–n**, δ = 174.8–174.5 was ascribed to C=O* of aryloyl, but this signal was not observed in compounds **5a–g** due to prevailing enol form. The signals located at around δ = 148.9–90.7 were assigned to other carbons of aromatic rings and O–C–N of alkene group. A signal located at around δ = 87.4–83.3 was ascribed to another carbon of alkene group. The microanalyses data of the synthesized compounds are all in agreement with their proposed structures.

In summary, we have reported a green, simple, and highly efficient procedure for the preparation of a new series of benzo[5,6]chromeno[2,3-*d*]pyrimidine derivatives **5a–n** by a one-pot three-component reaction between arylglyoxal derivatives (monohydrate form), β-naphthol, and *N*,*N*-dimethylbarbituric acid or thiobarbituric acid in the presence of a catalytic amount of PPINO (10 mol%) in H_2O under reflux conditions. It is expected that these compounds will show promising pharmacological properties. The present procedure required a low catalyst loading of PPINO as a mild Lewis base organocatalyst in aqueous conditions. The main advantages of this technique are the use of an inexpensive and efficient organocatalyst, easily available materials, facile and clean workup route, avoidance of dangerous by-products, and excellent yields.

The chemicals used in this work were obtained from Arcos and Merck and used without purification. Melting points were measured on a Philip Harris C4954718 apparatus and are uncorrected. Reaction progress was monitored by TLC on Merck silica plates. IR spectra were recorded on a Thermo Nicolet Nexus 670 FT-IR instrument using KBr discs. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance AQS 300 MHz spectrometer at 300 and 75.5 MHz, respectively. Chemical shifts were measured in DMSO-d_6 as solvent relative to TMS as an internal standard. Elemental analyses were performed using a Leco Analyzer 932.

PPINO (4)

PPINO (**4**) was simply produced in excellent yield by the reaction of *N*-hydroxyphthalimide (1.63 g, 10 mmol) with an equivalent amount of the KOH (560 mg, 10 mmol) in EtOH (20 mL) at RT for 5 min. After reaction completion, the red salt was filtered, and washed with cold absolute EtOH (10 mL) to obtain the pure desired product **4**.[51]

1,3-Dimethyl-5-(2-oxo-2-phenylethylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (6a)

To a suspension of *N*,*N*-dimethylbarbituric acid (**3a**; 128 mg, 1 mmol) in H_2O (5 mL) was added PPINO (**4**; 20 mg, 10 mol%). The reaction mixture was stirred under reflux condition for 5 min to dissolve the reactant. Then phenylglyoxal monohydrate (**1a**; 152 mg, 1 mmol) was added to the mixture, which was stirred under reflux for 2 h. The progress of the reaction was monitored by TLC (eluent: $CHCl_3$/MeOH

10:2). After reaction completion, the mixture was cooled to r.t., the solid product was filtered, washed with H_2O (2 ×) and dried to give pure products **6a**; colorless solid; yield: 193 mg (71%); mp 198–199 °C.

FT-IR (KBr): 1690, 1675, 1662, 1630 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.15 (s, 1 H, CH), 7.87 (d, *J* = 8.0 Hz, 2 H, Ar), 7.63 (d, *J* = 8.0 Hz, 2 H, Ar), 7.48 (m, 1 H, Ar), 3.37 (s, 6 H, 2 × CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 194.8, 161.1, 160.6, 152.1, 151.9, 135.4, 134.7, 129.6, 129.1, 29.0, 28.5, 125.3.

Anal. Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.68; H, 4.40; N, 10.37

12-Benzoyl-8,12-dihydro-9*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidine-9,11(10*H*)-diones and Their Sulfur Analogues 5a–n; General Procedure

To a suspension of barbituric acid **3a**,**b** (1 mmol) in H_2O (5 mL) was added PPINO (**4**; 20 mg, 10 mol%). The reaction mixture was stirred under reflux condition for 5 min to dissolve the reactant. Then arylglyoxal monohydrate **1a–g** (1 mmol) and β-naphthol (**2**; 144 mg, 1 mmol) were added to the mixture, which was stirred under reflux for appropriate times as mentioned in Table 3. The progress of the reaction was monitored by TLC (eluent: $CHCl_3$/MeOH 10:2). After reaction completion, the mixture was cooled to r.t. and the pH was adjusted to 7. The solid product was filtered, washed with H_2O and cold aq EtOH to obtain the respective pure product **5a–n**.

12-Benzoyl-8,10-dimethyl-8,12-dihydro-9*H*-benzo[5,6]chromeno-[2,3-*d*]pyrimidine-9,11(10*H*)-dione (5a)

Colorless solid; yield: 350 mg (88%); mp 180–181 °C.

FT-IR (KBr): 3210, 3063, 2957, 1695, 1626, 1498, 1387, 1184, 1100, 801 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.09 (d, *J* = 8.4 Hz, 1 H, Ar), 8.03 (d, *J* = 7.2 Hz, 1 H, Ar), 7.87 (s, 2 H, Ar), 7.80 (d, *J* = 7.2 Hz, 2 H, Ar), 7.54–7.47 (m, 4 H, Ar), 5.48 (br s, 1 H, CH or OH, D_2O exch.), 3.34 (s, 6 H, 2 × CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 160.4, 152.7, 151.7, 131.1, 130.8, 130.4, 129.7, 128.6, 128.3, 127.8, 127.1, 125.9, 124.9, 124.6, 123.9, 113.9, 111.6, 109.3, 84.1, 30.1, 28.0.

Anal. Calcd for $C_{24}H_{18}N_2O_4$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.76; H, 4.50; N, 7.62.

8,10-Dimethyl-12-(4-methylbenzoyl)-8,12-dihydro-9*H*-benzo-[5,6]chromeno[2,3-*d*]pyrimidine-9,11(10*H*)-dione (5b)

Colorless solid; yield: 383 mg (93%); mp 254–255 °C.

FT-IR (KBr): 3398, 2922, 1706, 1560, 1507, 1151, 1096, 787 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.07 (d, *J* = 7.2 Hz, 1 H, Ar), 8.02 (d, *J* = 6.6 Hz, 1 H, Ar), 7.85 (br s, 2 H, Ar), 7.67 (d, *J* = 8.1 Hz, 2 H, Ar), 7.50–7.43 (m, 2 H, Ar), 6.27 (br s, 1 H, CH or OH, D_2O exch.), 3.32 (s, 6 H, 2 × CH_3), 2.33 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 160.4, 153.0, 151.7, 151.6, 138.3, 130.8, 130.4, 128.9, 128.3, 128.0, 127.3, 126.8, 125.8, 125.0, 124.6, 123.9, 113.8, 111.6, 108.5, 84.2, 30.1, 28.0, 21.4.

Anal. Calcd for $C_{25}H_{20}N_2O_4$: C, 72.80; H, 4.89; N, 6.79. Found: C, 73.06; H, 4.81; N, 6.92.

12-(3-Methoxybenzoyl)-8,10-dimethyl-8,12-dihydro-9*H*-benzo-[5,6]chromeno[2,3-*d*]pyrimidine-9,11(10*H*)-dione (5c)

Colorless solid; yield: 389 mg (91%); mp 218–219 °C.

FT-IR (KBr): 3429, 3064, 2952, 1693, 1632, 1493, 1390, 1249, 1184, 1037, 789 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.10 (d, *J* = 8.1 Hz, 1 H, Ar), 8.03 (d, *J* = 7.2 Hz, 1 H, Ar), 7.87 (s, 2 H, Ar), 7.54–7.48 (m, 2 H, Ar), 7.39–7.31 (m, 4 H, Ar), 5.54 (br s, 1 H, CH or OH, D_2O exch.), 3.76 (s, 3 H, OCH_3), 3.33 (s, 6 H, 2 × CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 160.4, 152.4, 151.7, 151.4, 132.3, 130.8, 129.5, 128.7, 127.2, 126.0, 125.0, 124.6, 124.0, 121.5, 119.5, 117.5, 115.5, 113.9, 112.1, 111.6, 109.7, 84.1, 56.1, 30.1, 28.0.

Anal. Calcd for $C_{25}H_{20}N_2O_5$: C, 70.09; H, 4.71; N, 6.54. Found: C, 70.26; H, 4.69; N, 6.62.

12-(4-Fluorobenzoyl)-8,10-dimethyl-8,12-dihydro-9*H*-benzo-[5,6]chromeno[2,3-*d*]pyrimidine-9,11(10*H*)-dione (5d)

Colorless solid; yield: 361 mg (87%); mp 211–212 °C.

FT-IR (KBr): 3399, 2944, 1707, 1562, 1503, 1392, 1157, 1097, 1052, 782 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.07 (d, *J* = 8.1 Hz, 1 H, Ar), 8.02 (d, *J* = 7.2 Hz, 1 H, Ar), 7.86–7.75 (m, 4 H, Ar), 7.52–7.47 (m, 2 H, Ar), 7.31 (t, *J* = 8.4 Hz, 2 H, Ar), 5.90 (br s, 1 H, CH or OH, D_2O exch.), 3.32 (s, 6 H, 2 × CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 160.5, 151.9, 151.7, 151.6, 130.8, 129.4, 128.6, 127.7, 127.1, 125.9, 124.9, 124.5, 124.0, 123.7, 117.5, 115.2, 113.8, 111.6, 109.2, 83.8, 30.1, 28.0.

Anal. Calcd for $C_{24}H_{17}FN_2O_4$: C, 69.23; H, 4.12; N, 6.73. Found: C, 69.54; H, 4.09; N, 6.98.

12-(4-Chlorobenzoyl)-8,10-dimethyl-8,12-dihydro-9*H*-benzo-[5,6]chromeno[2,3-*d*]pyrimidine-9,11(10*H*)-dione (5e)

Colorless solid; yield: 367 mg (85%); mp 281–282 °C.

FT-IR (KBr): 3399, 2947, 1706, 1558, 1499, 1392, 1158, 1097, 1052, 777 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.09 (d, *J* = 8.1 Hz, 1 H, Ar), 8.03 (d, *J* = 7.8 Hz, 1 H, Ar), 7.88 (s, 2 H, Ar), 7.81 (d, *J* = 8.7 Hz, 2 H, Ar), 7.55–7.42 (m, 4 H, Ar), 6.48 (br s, 1 H, CH or OH, D_2O exch.), 3.33 (s, 6 H, 2 × CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 160.4, 151.8, 151.7, 151.5, 133.2, 130.8, 130.6, 130.0, 128.9, 128.6, 128.4, 127.5, 126.6, 125.2, 124.5, 124.0, 113.9, 111.6, 110.1, 83.8, 30.1, 28.0.

Anal. Calcd for $C_{24}H_{17}ClN_2O_4$: C, 66.60; H, 3.96; N, 6.47. Found: C, 66.63; H, 3.91; N, 6.76.

12-(4-Bromobenzoyl)-8,10-dimethyl-8,12-dihydro-9*H*-benzo-[5,6]chromeno[2,3-*d*]pyrimidine-9,11(10*H*)-dione (5f)

Colorless solid; yield: 391 mg (82%); mp 295–296 °C.

FT-IR (KBr): 3396, 3056, 2948, 1705, 1558, 1498, 1391, 1273, 1158, 1096, 1007, 812 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.07 (d, *J* = 8.1 Hz, 1 H, Ar), 8.03 (d, *J* = 7.2 Hz, 1 H, Ar), 7.87 (s, 2 H, Ar), 7.72 (t, *J* = 7.8 Hz, 2 H, Ar), 7.67 (t, *J* = 7.2 Hz, 2 H, Ar), 7.50–7.43 (m, 2 H, Ar), 5.35 (br s, 1 H, CH or OH, D_2O exch.), 3.32 (s, 6 H, 2 × CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 160.4, 151.8, 151.7, 151.5, 133.4, 131.3, 130.8, 130.3, 129.1, 128.6, 127.5, 126.9, 126.0, 125.2, 124.5, 121.9, 113.9, 111.6, 110.2, 83.7, 30.1, 28.0.

Anal. Calcd for $C_{24}H_{17}BrN_2O_4$: C, 60.39; H, 3.59; N, 5.87. Found: C, 60.47; H, 3.53; N, 6.77.

8,10-Dimethyl-12-(4-nitrobenzoyl)-8,12-dihydro-9*H*-benzo-[5,6]chromeno[2,3-*d*]pyrimidine-9,11(10*H*)-dione (5g)

Yellow solid; yield: 363 mg (82%); mp 316 °C (dec.).

FT-IR (KBr): 3405, 2929, 1710, 1588, 1511, 1338, 1285, 1167, 1102, 1051 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.31 (d, *J* = 8.7 Hz, 2 H, Ar), 8.12–8.01 (m, 4 H, Ar), 7.97–7.88 (m, 2 H, Ar), 7.57–7.50 (m, 2 H, Ar), 6.29 (br s, 1 H, CH or OH, D_2O exch.), 3.32 (s, 6 H, 2 × CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 160.4, 152.5, 151.8, 150.2, 146.7, 137.1, 130.8, 128.7, 128.5, 127.7, 126.3, 125.8, 125.5, 124.5, 124.1, 123.6, 114.0, 113.7, 111.6, 83.3, 30.1, 28.0.

Anal. Calcd for $C_{24}H_{17}N_3O_6$: C, 65.01; H, 3.86; N, 9.48. Found: C, 65.17; H, 3.80; N, 9.72.

12-Benzoyl-9-thioxo-8,9,10,12-tetrahydro-11*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidin-11-one (5h)

Colorless solid; yield: 332 mg (86%); mp 223–224 °C.

FT-IR (KBr): 3355, 3052, 1540, 1454, 1392, 1346, 1263, 1169, 1133, 802, 709 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.85 (s, 2 H, 2 × NH, D_2O exch.), 8.17 (d, *J* = 8.4 Hz, 1 H, Ar), 8.02 (d, *J* = 7.8 Hz, 1 H, Ar), 7.84–7.80 (m, 4 H, Ar), 7.55 (t, *J* = 7.2 Hz, 1 H, Ar), 7.49–7.45 (m, 2 H, Ar), 7.35 (t, *J* = 7.5 Hz, 1 H, Ar), 4.66 (br s, 1 H, CH or OH, D_2O exch.).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 174.6, 161.5, 152.0, 151.6, 131.4, 130.7, 130.1, 129.5, 129.0, 128.1, 127.1, 127.0, 125.6, 125.0, 124.6, 123.9, 113.8, 111.6, 110.5, 87.1.

Anal. Calcd for $C_{22}H_{14}N_2O_3S$: C, 68.38; H, 3.65; N, 7.25. Found: C, 68.18; H, 3.69; N, 7.73.

12-(4-Methylbenzoyl)-9-thioxo-8,9,10,12-tetrahydro-11*H*-benzo-[5,6]chromeno[2,3-*d*]pyrimidin-11-one (5i)

Colorless solid; yield: 356 mg (89%); mp 263–264 °C.

FT-IR (KBr): 3409, 3290, 3022, 1630, 1538, 1428, 1443, 1272, 1170, 1142, 810 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.93 (s, 2 H, 2 × NH, D_2O exch.), 8.14 (d, *J* = 8.1 Hz, 1 H, Ar), 8.01 (d, *J* = 7.5 Hz, 1 H, Ar), 7.82 (s, 2 H, Ar), 7.67 (d, *J* = 7.5 Hz, 2 H, Ar), 7.59–7.44 (m, 2 H, Ar), 7.29 (d, *J* = 7.8 Hz, 2 H, Ar), 4.87 (br s, 1 H, CH or OH, D_2O exch.), 2.33 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 174.5, 161.4, 152.4, 151.5, 138.1, 130.7, 130.3, 128.8, 128.6, 127.7, 127.0, 126.7, 125.6, 125.0, 124.6, 123.9, 113.8, 111.6, 109.3, 87.4, 21.4.

Anal. Calcd for $C_{23}H_{16}N_2O_3S$: C, 68.99; H, 4.03; N, 7.00. Found: C, 68.79; H, 4.07; N, 7.53.

12-(3-Methoxybenzoyl)-9-thioxo-8,9,10,12-tetrahydro-11*H*-benzo-[5,6]chromeno[2,3-*d*]pyrimidin-11-one (5j)

Colorless solid; yield: 370 mg (89%); mp 202–203 °C.

FT-IR (KBr): 3383, 3176–3054, 3008, 2936, 1590, 1536, 1469, 1394, 1242, 1170, 1132, 1040, 797 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.87 (s, 2 H, 2 × NH, D_2O exch.), 8.17 (d, *J* = 8.7 Hz, 1 H, Ar), 8.01 (d, *J* = 8.7 Hz, 1 H, Ar), 7.84 (s, 2 H, Ar), 7.53 (t, *J* = 8.1 Hz, 1 H, Ar), 7.47 (t, *J* = 7.8 Hz, 1 H, Ar), 7.41–7.35 (m, 4 H, Ar), 4.55 (br s, 1 H, CH or OH, D_2O exch.), 3.79 (s, 3 H, OCH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 174.6, 161.5, 159.7, 151.7, 151.6, 132.6, 130.2, 129.3, 128.9, 127.8, 127.0, 125.7, 125.5, 124.6, 124.0, 123.7, 117.5, 113.9, 112.5, 111.6, 110.7, 87.1, 56.2.

Anal. Calcd for $C_{23}H_{16}N_2O_4S$: C, 66.34; H, 3.87; N, 6.73. Found: C, 65.98; H, 3.90; N, 6.92.

12-(4-Fluorobenzoyl)-9-thioxo-8,9,10,12-tetrahydro-11*H*-benzo-[5,6]chromeno[2,3-*d*]pyrimidin-11-one (5k)

Colorless solid; yield: 340 mg (84%); mp 255–256 °C.

FT-IR (KBr): 3391, 3288, 3027, 1538, 1430, 1339, 1253, 1148, 809, 730, 558 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 12.00 (s, 2 H, 2 × NH, D_2O exch.), 8.14 (d, *J* = 8.4 Hz, 1 H, Ar), 8.02 (d, *J* = 8.1 Hz, 1 H, Ar), 7.85–7.79 (m, 4 H, Ar), 7.54 (t, *J* = 8.1 Hz, 1 H, Ar), 7.48 (t, *J* = 7.5 Hz, 1 H, Ar), 7.35 (t, *J* = 8.7 Hz, 1 H, Ar), 5.54 (br s, 1 H, CH or OH, D_2O exch.).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 174.7, 161.4, 151.6, 151.3, 130.8, 129.4, 128.8, 128.0, 127.0, 125.7, 124.8, 124.4, 123.7, 117.4, 117.2, 115.4, 113.8, 111.6, 109.8, 87.2.

Anal. Calcd for $C_{22}H_{13}FN_2O_3S$: C, 65.34; H, 3.24; N, 6.93. Found: C, 65.38; H, 3.27; N, 7.03.

12-(4-Chlorobenzoyl)-9-thioxo-8,9,10,12-tetrahydro-11*H*-benzo-[5,6]chromeno[2,3-*d*]pyrimidin-11-one (5l)

Colorless solid; yield: 357 mg (85%); mp 249–250 °C.

FT-IR (KBr): 3351, 3264, 3034, 2881, 1540, 1394, 1347, 1264, 1170, 1135, 1009, 805, 729, 552 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.98 (s, 2 H, 2 × NH, D_2O exch.), 8.13 (d, *J* = 7.5 Hz, 1 H, Ar), 8.02 (d, *J* = 8.7 Hz, 1 H, Ar), 7.88–7.78 (m, 4 H, Ar), 7.65–7.41 (m, 4 H, Ar), 5.00 (br s, 1 H, CH or OH, D_2O exch.).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 174.7, 161.3, 151.7, 151.0, 133.1, 130.8, 130.4, 130.2, 128.8, 128.3, 127.9, 127.4, 126.6, 125.1, 124.4, 123.8, 113.8, 111.6, 110.7, 87.1.

Anal. Calcd for $C_{22}H_{13}ClN_2O_3S$: C, 62.79; H, 3.11; N, 6.66. Found: C, 62.85; H, 3.15; N, 6.78.

12-(4-Bromobenzoyl)-9-thioxo-8,9,10,12-tetrahydro-11*H*-benzo-[5,6]chromeno[2,3-*d*]pyrimidin-11-one (5m)

Colorless solid; yield: 386 mg (83%); mp 266–267 °C.

FT-IR (KBr): 3265, 3042, 2884, 1541, 1346, 1264, 1171, 1138, 1007, 807, 730, 553 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 11.99 (s, 2 H, 2 × NH, D_2O exch.), 8.13 (d, *J* = 8.1 Hz, 1 H, Ar), 8.02 (d, *J* = 8.1 Hz, 1 H, Ar), 7.89–7.82 (m, 2 H, Ar), 7.76–7.68 (m, 4 H, Ar), 7.57 (t, *J* = 7.2 Hz, 1 H, Ar), 7.48 (t, *J* = 8.1 Hz, 1 H, Ar), 5.15 (br s, 1 H, CH, D_2O exch.).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 174.7, 161.3, 151.8, 151.0, 133.4, 131.1, 130.5, 129.0, 128.8, 127.4, 126.8, 125.8, 125.2, 124.4, 123.8, 121.8, 113.9, 111.6, 110.8, 87.1.

Anal. Calcd for $C_{22}H_{13}BrN_2O_3S$: C, 56.79; H, 2.82; N, 6.02. Found: C, 56.88; H, 2.83; N, 6.47.

12-(4-Nitrobenzoyl)-9-thioxo-8,9,10,12-tetrahydro-11*H*-benzo-[5,6]chromeno[2,3-*d*]pyrimidin-11-one (5n)

Yellow solid; yield: 353 mg (82%); mp 254–255 °C.

FT-IR (KBr): 3406, 3333, 2980, 1590, 1525, 1336, 1167, 1115, 849, 804 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.04 (s, 2 H, 2 × NH, D_2O exch.), 8.35 (d, *J* = 8.7 Hz, 2 H, Ar), 8.14 (d, *J* = 8.1 Hz, 1 H, Ar), 8.06–7.96 (m, 3 H, Ar), 7.92–7.86 (m, 2 H, Ar), 7.59 (t, *J* = 7.2 Hz, 1 H, Ar), 7.51 (t, *J* = 7.8 Hz, 1 H, Ar), 5.08 (br s, 1 H, CH or OH, D_2O exch.).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 174.8, 161.3, 160.9, 152.5, 149.7, 146.6, 137.3, 130.8, 128.8, 127.7, 126.2, 125.8, 125.3, 124.3, 124.0, 123.7, 114.2, 114.0, 111.6, 86.7.

Anal. Calcd for $C_{22}H_{13}N_3O_5S$: C, 61.25; H, 3.04; N, 9.74. Found: C, 61.95; H, 3.10; N, 9.92.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610755.

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