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Organocatalytic approach toward the green one-pot synthesis of novel benzo[*f*]chromenes and 12*H*-benzo[5,6]chromeno[2,3-*b*]pyridines

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Abstract An efficient tandem reaction approach is described to prepare novel benzo[*f*]chromenes from 2,3-dihydroxynaphthalene, malononitrile and aldehydes using 10 mol% guanidine hydrochloride as the catalyst under solvent-free conditions. The method was also extended to the preparation of novel 12*H*-benzo[5,6]-chromeno[2,3-*b*]pyridines from 2-aminoprop-1-ene-1,1,3-tricarbonitrile instead of malononitrile under the same reaction conditions. The described one-pot three-component reaction is characterized by short reaction times, high-product yield, mild reaction conditions, simple workup procedure, and simple purification.

Keywords Benzo[*f*]chromene · Benzo[5,6]chromeno[2,3-*b*]pyridine · 2,3-Dihydroxynaphthalene · Malononitrile · 2-Aminoprop-1-ene-1,1,3-tricarbonitrile

Introduction

Benzochromenes are an important group of heterocyclic compounds being the main components of many naturally occurring products. These molecules are biologically active and find application in pharmacological properties such as anti-inflammatory [1], anti-microbial [2], anticancer [3], mutagenicitical, antiviral and central nervous system activities [4]. They can also be employed in industry as antioxidants [5], as cosmetics and pigments and as potential biodegradable agrochemicals [6]. Several conventional protocols have been well developed for the syntheses of these

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polyfunctionalized chromenes involving the three-component, one-pot condensation of malononitrile, aldehyde and phenol or naphthol with the use of various catalysts, such as methanesulfonic acid [7], $H_{14}[NaP_5W_{30}O_{110}]$ [8], poly(4-vinylpyridine) [9], ionic liquid [10], piperidine [11], $CaO–ZrO_2$ nanocomposite oxides [12], $Ni–Al_2O_3$ [13], potassium phthalimide-*N*-oxyl [14], diammonium hydrogen phosphate [15], thiourea dioxide [16], sodium malonate [17], nanozeolite clinoptilolite [18], and potassium hydrogen phthalate [19]. However, they are mostly suffer from one or more drawbacks including the use of expensive reagents, toxic metals, the use of volatile organic solvents, drastic reaction conditions, tedious work-up procedures, high cost and low product yields.

Chromenopyridines have biological properties such as antiproliferative [20], cancer chemopreventive [21], antibacterial [22, 23], antimyopic [24], hypotensive [25], hypotensive [26], antirheumatic [27], and antiasthmatic activities [28]. A few methods have been reported for the synthesis of chromeno[2,3-*b*]pyridine derivatives by a MCR of 2-amino-1,1,3-tricyanopropene or malononitrile and aldehydes with secondary cyclic amines [29], 3-phenylisoxazol-5(4*H*)-one [30], 4-hydroxycarbazole [31], thiols [32, 33], and naphthols [34, 35] in the presence of different catalysts under different reaction conditions.

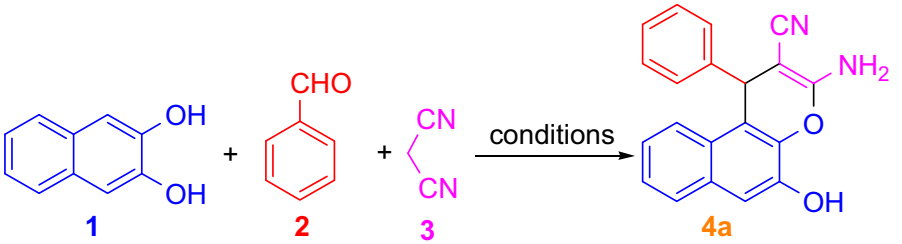
Organocatalysts have been used widely in many reactions as mono and bifunctional catalysts due to economic and environmental considerations. Among many organocatalysts, hydrogen bonding compounds such as guanidine derivatives are becoming powerful tools for activation of the carbonyl functionality in organic transformations. Recently, guanidinium salts have been successfully employed as novel chiral phase-transfer catalysts in the conjugate addition of nitroalkanes with enones [36, 37]. Moreover, these organocatalysts provide an environment for the process activating the nucleophile, the electrophile or both reagents through weak interactions, such as hydrogen bonding or ion pairing or much stronger interactions such as covalent bonding.

However, there are no reports available for the synthesis of benzo[*f*]chromenes and 12*H*-benzo[5,6]chromeno[2,3-*b*]pyridines from 2,3-dihydroxynaphthalene in the literature. Hence, our attention was devoted toward the reactions involving 2,3-dihydroxynaphthalene and aldehydes with malononitrile or 2-aminoprop-1-ene-1,1,3-tricarbonitrile using guanidine hydrochloride as the organocatalyst under solvent-free conditions.

Results and discussion

In continuation of our investigations on the synthesis of organic compounds in the presence of guanidine hydrochloride [38–42], initially we examined the three-component condensation reaction of 2,3-dihydroxynaphthalene (**1**, 1 mmol), benzaldehyde (**2**, 1 mmol), malononitrile (**3**, 1 mmol) and guanidine hydrochloride (10 mol%) in the different solvents such as EtOH, MeOH, CH_3CN, THF and toluene (Table 1, entries 1–6). However, no desired product was detected even after a long reaction time (5 h) under reflux conditions.

Table 1 Optimization of reaction conditions in the presence of guanidine hydrochloride (10 mol%) as catalyst



Entry	Solvent	Temp. (°C)	Time (h)	Yield[a] (%)
1	EtOH	78	5	NR[b]
2	MeOH	64	5	NR
3	CH_3CN	81	5	NR
4	THF	66	5	NR
5	Toluene	110	5	NR
6	H_2O	100	2	60
7	Neat	70	2	64
8	Neat	100	0.75	85
9	Neat	120	0.75	70

[a] Isolated yield

[b] No reaction

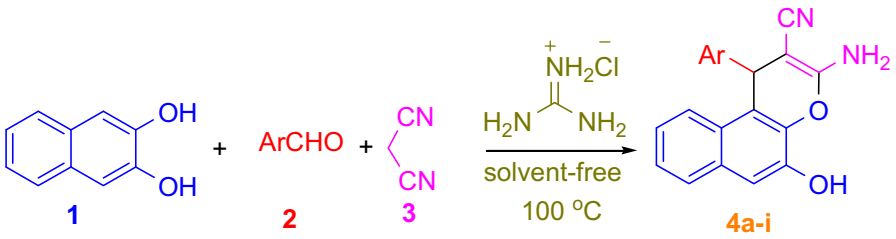
The above reaction was performed in water under reflux conditions. Interestingly, product **4a** was obtained in moderate yield (60%, entry 6) after 2 h. Also, the solvent-free condition was further used to optimize these reaction conditions (Table 1, entries 7–9). It was observed that as the temperature rises from 70 to 100 °C, both the reaction speed and the product yield increased. It is noteworthy that, increasing the temperature to 120 °C,the yield of the corresponding product was slightly decreased from 85 to 70% (entry 9) (Table 1).

Moreover, the optimal molar loading of guanidine hydrochloride as the catalyst was determined by performing the model reaction using 5, 10, 15 and 20 mol% of catalyst under solvent-free condition at 100 °C. The results show that in the absence of catalyst, the reaction did not proceed to completion even after 80 min and

Table 2 The optimization of catalyst loading for the synthesis of benzo[*f*]chromenes **4a**

Entry	Catalyst (mol%)	Temp. (°C)	Time (min)	Yield[a] (%)
1	None	100	80	20
2	5	100	80	72
3	10	100	40	85
4	15	100	40	86
5	20	100	40	85

[a]Isolated yield



Scheme 1 Three-component synthesis of benzo[*f*]chromenes **4**

Table 3 One-pot synthesis of benzo[*f*]chromene derivatives **4**

Entry	Aldehyde	Product	Time (min)	Yield (%)
1	Benzaldehyde	**4a**	40	85
2	2-Nitrobenzaldehyde	**4b**	45	81
3	3-Nitrobenzaldehyde	**4c**	55	78
4	2-Chlorobenzaldehyde	**4d**	30	83
5	4-Chlorobenzaldehyde	**4e**	60	81
6	3-Bromobenzaldehyde	**4f**	60	84
7	4-Bromobenzaldehyde	**4g**	70	79
8	4-Fluorobenzaldehyde	**4h**	45	80
9	3-Hydroxybenzaldehyde	**4i**	60	81

resulted in the isolation of product **4a** in 20% yield (Table 2, entry 1). However, increasing the amount of catalyst from 5 to 10 mol% led to an increase in the yield from 72 to 85% (Table 2, entries 2–3). The use of 15 and 20 mol% catalyst was identified as the most effective way of pushing this reaction toward completion and did not further improve the yield (Table 2, entry 5). The results of these screening experiments show that the optimum reaction conditions are 10 mol% guanidine hydrochloride at 100 °C under solvent-free conditions (Table 2).

With the optimum reaction conditions in hand, we evaluated the scope of the transformation using various substituted benzaldehyde **2**. A wide range of aldehydes **2**, which bear different substituent groups on the aryl ring, were utilized to react with 2,3-dihydroxynaphthalene and malononitrile under the optimal conditions (Scheme 1; Table 3).

The results show that all reactions of various substituted benzaldehydes proceeded smoothly to give the corresponding benzo[*f*]chromenes in high yields (Fig. 1). However, when some aliphatic aldehydes such as acetaldehyde, propionaldehyde and 3-phenylpropanaldehyde were used in this protocol under the above optimized conditions, unfortunately, the expected products could not be obtained.

Encouraged by the successful condensation of 2,3-dihydroxynaphthalene, aldehydes and malononitrile under solvent-free conditions to give benzo[*f*]chromene derivatives, we next attempted on the formation of novel bis-condensation products by executing the reaction of 2,3-dihydroxynaphthalene with double molar

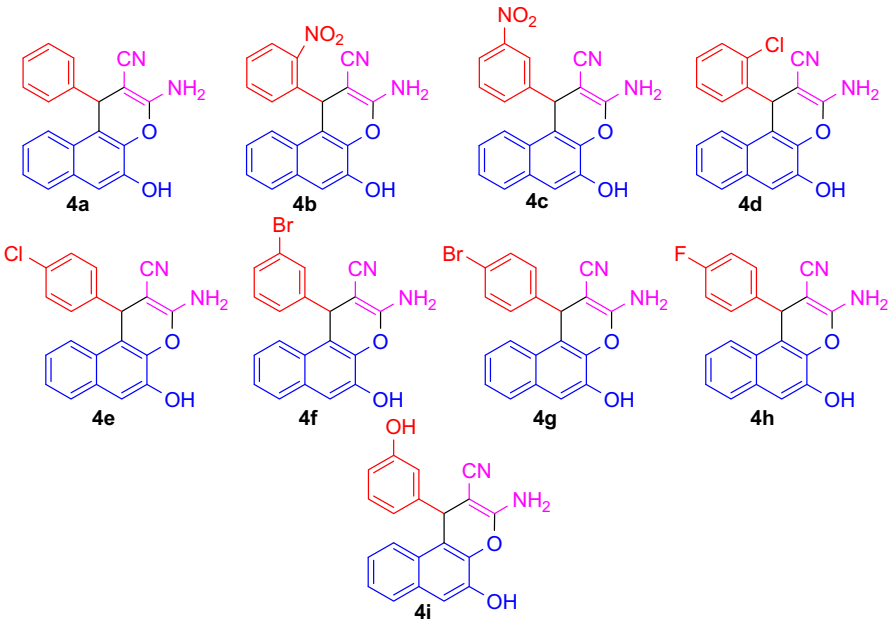
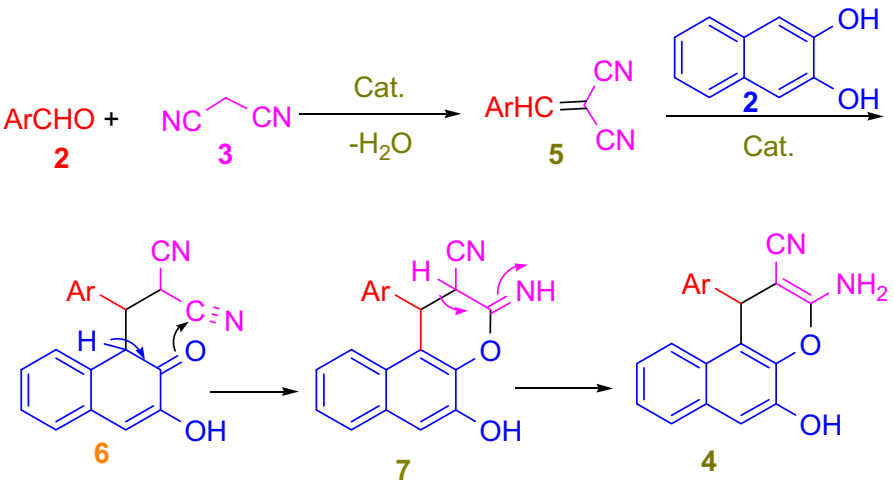


Fig. 1 Products **4a–i**



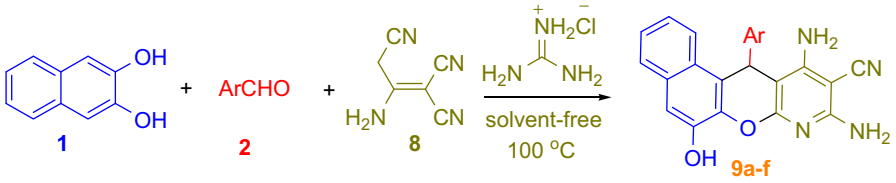
Scheme 2 Plausible mechanism for the organo catalyzed synthesis of benzo[*f*]chromenes **4**

ratios of benzaldehyde and malononitrile under similar reaction conditions. The result showed that the product **4a** was obtained as only product instead of the expected bis-condensed product (Table 3; Fig. 1). A plausible mechanism for the formation of the product **4** is proposed in Scheme 2. We assume that guanidine hydrochloride is an effective catalyst for the formation of olefin **5**, which is formed

in situ by Knoevenagel condensation of aryl aldehyde **2** and the active methylene compound **3**. Olefin **5** subsequently reacts with 2,3-dihydroxynaphthalene to give intermediate **6**. Further, the cyclization of **6** gives intermediate **7** which subsequently tautomerizes to yield the corresponding benzo[*f*]chromene **4** (Scheme 2).

Encouraged by the successful condensation of 2,3-dihydroxynaphthalene, aldehydes, and malononitrile under solvent-free conditions to give benzo[*f*]chromene derivatives, we next attempted the reaction with 2,3-dihydroxynaphthalene, aldehydes and 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**8**) under the same reaction conditions, which led to the formation of novel 12*H*-benzo[5,6]chromeno[2,3-*b*]pyridines **9a–f** in good yields (Scheme 3; Fig. 2). The results are shown in Table 4.

Inspired by the optimization of the reaction conditions, we continued to investigate the applicable scope of the methodology of this one-pot three-component heterocyclization using 2,3-dihydroxynaphthalene (1 mmol), 2-chlorobenzaldehyde (2 mmol) and 2-aminoprop-1-ene-1,1,3-tricarbonitrile (2 mmol). It is observed that the product **9a** was obtained as the only product



Scheme 3 Three-component synthesis of 12*H*-benzo[5,6]chromeno[2,3-*b*]pyridines **9**

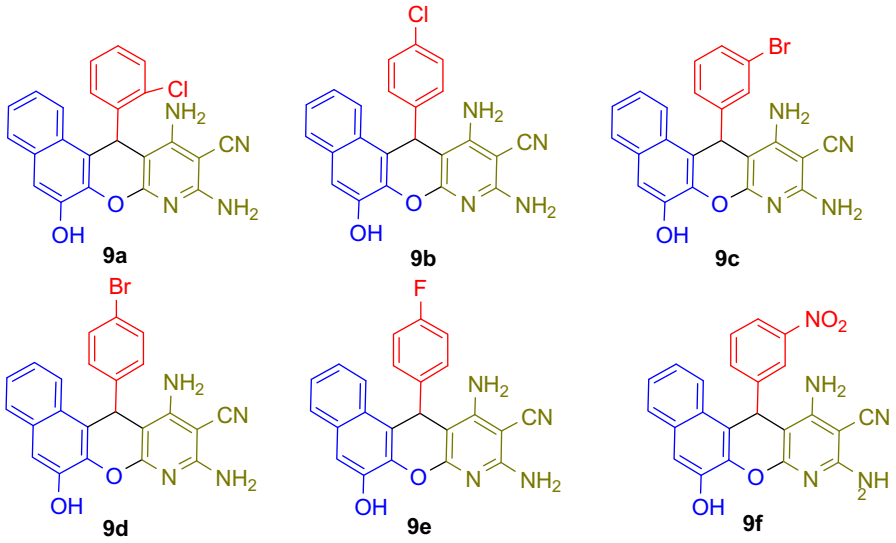
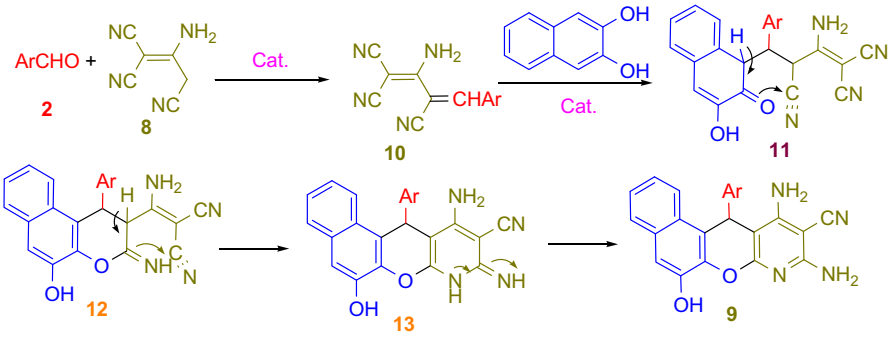


Fig. 2 Products **9a–f**

Table 4 One-pot synthesis of 12*H*-benzo[5,6]chromeno[2,3-*b*]pyridine derivatives **9**

Entry	Aldehyde	Product	Time (min)	Yield (%)
1	2-Chlorobenzaldehyde	**9a**	60	75
2	4-Chlorobenzaldehyde	**9b**	120	78
3	3-Bromobenzaldehyde	**9c**	100	81
4	4-Bromobenzaldehyde	**9d**	90	79
5	4-Fluorobenzaldehyde	**9e**	100	78
6	3-Nitrobenzaldehyde	**9f**	40	88



Scheme 4 Plausible mechanism for the synthesis of 12*H*-benzo[5,6]chromeno[2,3-*b*]pyridines **9**

instead of the expected bis-condensed product. Furthermore, we also carried out a one-pot pseudo four-component reaction of 2,3-dihydroxynaphthalene (1 mmol), 2-chlorobenzaldehyde (1 mmol) and malononitrile (2 mmol) under the same reaction conditions for the synthesis of compound **9a**. However, the reaction provided benzo[*f*]chromene **4d** as the only product instead of an expected 12*H*-benzo[5,6]chromeno[2,3-*b*]pyridine **9a** (Table 4; Fig. 2).

A mechanistic rationale portraying the probable sequence of events is given in Scheme 4. The first stage of this process is the Knoevenagel condensation promoted between 2-aminoprop-1-ene-1,1,3-tricarbonitrile **8** and aldehyde **2** in the presence of guanidine hydrochloride to give rise to intermediate **10**. Next, the Michael addition of 2,3-dihydroxynaphthalene to intermediate **10** provides the intermediate **11** which then undergoes tautomerization and subsequent intramolecular cyclization twice, to afford final the corresponding 12*H*-benzo[5,6]chromeno[2,3-*b*]pyridines **9** (Scheme 4).

Conclusion

In summary, we have introduced a one-pot three-component condensation reaction leading to a new class of benzo[*f*]chromene derivatives starting from 2,3-dihydroxynaphthalene, malononitrile and aldehydes using guanidine hydrochloride

as organo catalyst. Further investigation in our laboratory will focus on evaluating the process with 2-aminoprop-1-ene-1,1,3-tricarbonitrile instead of malononitrile for the synthesis of 12*H*-benzo[5,6]chromeno[2,3-*b*]pyridine derivatives. These reactions can be regarded as a new approach for the preparation of synthetically and pharmaceutically relevant heterocyclic systems. This approach includes some important aspects such as high atom economy, mild reaction conditions, high yields of the products, short reaction times, solvent-free nature of the reaction, ease of work-up and clean procedure, and involving no chromatography.

Experimental section

General information

All commercially available chemicals and reagents were used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on Bruker DRX-300 Avance spectrometers. Chemical shifts (δ) are reported in parts per million and are referenced to the NMR solvent. Mass spectra of the products were obtained with a HP (Agilent technologies) 5973 mass selective detector. Elemental analyses were carried out by a CHN–O–Rapid Heraeus elemental analyzer (Wellesley, MA).

*General procedure for the synthesis of benzo[f]chromens **4a–f** and 12H-benzo[5, 6]chromeno[2,3-b]pyridines **9a–f***

In a 25 mL round bottom flask, a mixture of 2,3-dihydroxynaphthalene (1 mmol), aldehyde (1 mmol), malononitrile (1 mmol) or 2-aminoprop-1-ene-1,1,3-tricarbonitrile (1 mmol) and guanidine hydrochloride (10 mol%) were taken, and the mixture was stirred at 100 °C in an oil bath for an appropriate amount of time as indicated in Tables 3 and 4. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion, the reaction mixture was cooled to room temperature and CH_3CN (5 mL) was added, and then a precipitate was allowed to form. The precipitate was filtered, washed with CH_3CN and dried. The crude product was stirred for 5 min in boiling EtOH,and the resulting precipitate was filtered. The product **4** and **9** thus obtained was found to be pure upon ^{1}H and ^{13}C NMR, mass spectra, elemental analyses, and TLC examination.

*3-Amino-5-hydroxy-1-phenyl-1H-benzo[f]chromene-2-carbonitrile (**4a**)*

Cream solid; mp 287–288 °C; IR (KBr, cm^{-1}): 3487, 3375, 3249, 3061, 2995, 2188, 1648, 1621, 1570, 1454, 1421, 1254, 1180; ^{1}H NMR (300 MHz, DMSO-d_6): 5.22 (s, 1H, methine-H), 6.93 (s, 2H, NH_2), 7.10–7.32 (m, 8H, Ar–H), 7.65–7.72 (t, 2H, $J = 9.0$ Hz, Ar–H), 10.32 (s, 1H, OH), ^{1}H NMR (300 MHz + D_2O, DMSO-d_6): 5.22 (s, 1H, methine-H), 7.10–7.31 (m, 8H, Ar–H), 7.63–7.68 (t, 2H, $J = 7.8$ Hz,

Ar–H), ^{13}C NMR (75 MHz, DMSO-d_6): 58.42, 110.32, 117.75, 120.93, 123.87, 124.15, 124.75, 125.56, 125.98, 126.89, 127.04, 127.35, 129.15, 131.73, 139.56, 145.47, 146.11, 160.18; MS *m/z* (%): 314 (M^+), 297, 247, 238, 237 (100), 208, 191, 164, 153, 127, 114, 77, 51; Anal. calcd. for $C_{20}H_{14}N_2O_2$: C, 76.43; H, 4.45; N, 8.91. Found: C, 76.50; H, 4.39; N, 8.94.

*3-Amino-5-hydroxy-1-(2-nitrophenyl)-1H-benzo[f]chromene-2-carbonitrile (**4b**)*

Pale green solid; mp 274–275 °C; IR (KBr, cm^{-1}): 3482, 3381, 3239, 3068, 2995, 2192, 1658, 1623, 1584, 1522, 1426, 1335, 1255, 1187; ^{1}H NMR (300 MHz, DMSO-d_6): 6.10 (s, 1H, methine-H), 6.99 (d, 1H, $J = 6.9$ Hz, Ar–H), 7.10 (s, 2H, NH_2), 7.20–7.46 (m, 4H, Ar–H), 7.51–7.56 (t, 1H, $J = 6.3$ Hz, Ar–H), 7.62 (d, 1H, $J = 8.4$ Hz, Ar–H), 7.72 (d, 1H, $J = 7.5$ Hz, Ar–H), 7.98 (d, 1H, $J = 6.9$ Hz, Ar–H), 10.46 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): 56.66, 111.07, 115.65, 120.07, 122.92, 124.66, 124.73, 125.21, 125.83, 127.17, 128.66, 130.37, 131.75, 134.80, 139.68, 140.40, 145.43, 147.78, 160.28; MS *m/z* (%): 359 (M^+), 342 (100), 311, 284, 255, 237, 227, 201, 191, 164, 127, 114, 105, 77, 57, 43; Anal. calcd. for $C_{20}H_{13}N_3O_4$: C, 66.85; H, 3.62; N, 11.70. Found: C, 66.81; H, 3.69; N, 11.76.

*3-Amino-5-hydroxy-1-(3-nitrophenyl)-1H-benzo[f]chromene-2-carbonitrile (**4c**)*

Yellow solid; mp 285–287 °C; IR (KBr, cm^{-1}): 3441, 3334, 3215, 3068, 2924, 2182, 1660, 1637, 1592, 1526, 1464, 1413, 1318, 1262, 1116; ^{1}H NMR (300 MHz, DMSO-d_6): 5.58 (s, 1H, methine-H), 7.10 (s, 2H, NH_2), 7.19–7.34 (m, 3H, Ar–H), 7.56–7.74 (m, 4H, Ar–H), 8.03–8.05 (m, 2H, Ar–H), 10.43 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): 57.39, 110.83, 116.67, 120.62, 121.66, 122.30, 123.74, 124.46, 125.79, 127.02, 130.92, 131.76, 134.11, 139.66, 139.71, 145.38, 145.66, 148.31, 148.45, 160.44; MS *m/z* (%): 359 (M^+), 342, 311, 237 (100), 208, 191, 164, 153, 126, 105, 77, 57, 43; Anal. calcd. for $C_{20}H_{13}N_3O_4$: C, 66.85; H, 3.62; N, 11.70. Found: C, 66.82; H, 3.67; N, 11.76.

*3-Amino-5-hydroxy-1-(2-chlorophenyl)-1H-benzo[f]chromene-2-carbonitrile (**4d**)*

Yellow solid; mp 286–287 °C; IR (KBr, cm^{-1}): 3490, 3381, 3258, 3079, 2916, 21.94, 1653, 1610, 1578, 1420, 1356, 1261, 1186, 1116; ^{1}H NMR (300 MHz, DMSO-d_6): 5.70 (s, 1H, methine-H), 7.02 (s, 2H, NH_2), 7.17–7.33 (m, 6H, Ar–H), 7.45–7.52 (m, 2H, Ar–H), 7.69 (d, 1H, $J = 7.8$ Hz, Ar–H), 10.40 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): 56.81, 110.67, 116.86, 120.29, 122.90, 124.51, 124.70, 125.68, 127.12, 128.68, 128.93, 129.97, 130.34, 131.38, 131.66, 139.98, 143.12, 145.45, 147.33, 160.34; MS *m/z* (%): 350 $(M + 2)^+$, 348 (M^+), 313, 238, 237 (100), 188, 164, 153, 126, 114, 100, 75, 57, 43; Anal. calcd. for $C_{20}H_{13}ClN_2O_2$: C, 68.86; H, 3.73; N, 8.03. Found: C, 68.90; H, 3.68; N, 8.00.

*3-Amino-5-hydroxy-1-(4-chlorophenyl)-1H-benzo[f]chromene-2-carbonitrile (**4e**)*

Cream solid; mp 275–276 °C; IR (KBr, cm^{-1}): 3408, 3357, 3223, 3034, 2936, 2186, 1655, 1621, 1578, 1488, 1351, 1247, 1149, 1115; ^{1}H NMR (300 MHz, DMSO-d_6): 5.32 (s, 1H, methine-H), 6.99 (s, 2H, NH_2), 7.19–7.35 (m, 7H, Ar–H), 7.68 (d, 2H, $J = 8.4$ Hz, Ar–H), 10.35 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): 57.94, 110.51, 117.23, 120.77, 123.80, 124.24, 124.62, 125.63, 126.94, 129.16, 129.21, 129.49, 131.62, 131.75, 139.56, 145.09, 145.46, 160.20; MS *m/z* (%): 350 $(M + 2)^+$, 348 (M^+), 311, 238, 237 (100), 208, 191, 164, 153, 127, 114, 81, 69, 55, 43; Anal. calcd. for $C_{20}H_{13}ClN_2O_2$: C, 68.86; H, 3.73; N, 8.03. Found: C, 68.90; H, 3.68; N, 8.09.

*3-Amino-5-hydroxy-1-(3-bromophenyl)-1H-benzo[f]chromene-2-carbonitrile (**4f**)*

Yellow solid; mp 262–264 °C; IR (KBr, cm^{-1}): 3490, 3382, 3171, 3072, 2977, 2189, 1655, 1621, 1574, 1427, 1362, 1151, 1114; ^{1}H NMR (300 MHz, DMSO-d_6): 5.35 (s, 1H, methine-H), 7.03 (s, 2H, NH_2), 7.16–7.38 (m, 7H, Ar–H), 7.67–7.72 (t, 2H, $J = 7.8$ Hz, Ar–H), 10.38 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): 57.85, 110.64, 117.05, 120.70, 122.37, 123.30, 123.77, 124.34, 124.58, 125.71, 126.48, 126.97, 129.88, 130.04, 131.49, 131.74, 139.61, 145.43, 148.81, 160.33; MS *m/z* (%): 394 $(M + 2)^+$, 392 (M^+), 348, 238, 237 (100), 208, 191, 164, 153, 127, 114, 97, 83, 69, 57, 43; Anal. calcd. for $C_{20}H_{13}BrN_2O_2$: C, 61.06; H, 3.30; N, 7.12. Found: C, 61.01; H, 3.25; N, 7.18.

*3-Amino-5-hydroxy-1-(4-bromophenyl)-1H-benzo[f]chromene-2-carbonitrile (**4g**)*

Cream solid; mp 276–278 °C; IR (KBr, cm^{-1}): 3497, 3387, 3225, 3076, 2938, 2183, 1660, 1622, 1584, 1506, 1424, 1351, 1248, 1220, 1181; ^{1}H NMR (300 MHz, DMSO-d_6): 5.31 (s, 1H, methine-H), 6.96 (s, 2H, NH_2), 7.06–7.33 (m, 7H, Ar–H), 7.66–7.71 (t, 2H, $J = 7.5$ Hz, Ar–H), 10.33 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): 58.17, 110.35, 115.77, 116.05, 117.58, 120.89, 123.85, 124.19, 124.61, 125.60, 126.92, 129.15, 129.26, 131.73, 139.48, 142.42, 145.47, 160.16; MS *m/z* (%): 394 $(M + 2)$, 392 (M^+), 348, 338, 332, 327 (100), 208, 191, 164, 153, 127, 114, 95, 83, 69, 57, 43; Anal. calcd. for $C_{20}H_{13}BrN_2O_2$: C, 61.06; H, 3.30; N, 7.12. Found: C, 61.09; H, 3.37; N, 7.13.

*3-Amino-5-hydroxy-1-(4-flourophenyl)-1H-benzo[f]chromene-2-carbonitrile (**4h**)*

Cream solid; mp 282–283 °C; IR (KBr, cm^{-1}): 3497, 3388, 3222, 3075, 2938, 2183, 1660, 1622, 1603, 1506, 1424, 1351, 1248, 1220, 1150; ^{1}H NMR (300 MHz, DMSO-d_6): 5.32 (s, 1H, methine-H), 6.96 (s, 2H, NH_2), 7.06–7.33 (m, 7H, Ar–H), 7.66–7.71 (t, 2H, $J = 7.5$ Hz, Ar–H), 10.34 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): 58.20, 110.39, 115.77, 116.09, 117.58, 120.91, 123.85, 124.21, 124.62, 125.62, 126.93, 129.16, 129.27, 131.75, 139.50, 142.39, 142.42, 145.49, 160.18; MS *m/z* (%): 332 (M^+), 303, 238, 237 (100), 208, 191, 164, 153, 127, 114, 95, 75,

57, 43; Anal. calcd. for $C_{20}H_{13}FN_2O_2$: C, 72.29; H, 3.91; N, 8.43. Found: C, 72.33; H, 3.86; N, 8.49.

*3-Amino-5-hydroxy-1-(3-hydroxyphenyl)-1H-benzo[f]chromene-2-carbonitrile (**4i**)*

Cream solid; mp 262–263 °C; IR (KBr, cm^{-1}): 3477, 3305, 3153, 3061, 2946, 2196, 1651, 1624, 1610, 1531, 1485, 1411, 1331, 1295, 1246, 1209, 1113; ^{1}H NMR (300 MHz, DMSO-d_6): 5.15 (s, 1H, methine-H), 6.50–6.55 (m, 2H, Ar–H), 6.68 (d, 1H, $J = 7.5$ Hz, Ar–H), 6.91 (s, 2H, NH_2), 7.03–7.33 (m, 4H, Ar–H), 7.66–7.71 (t, 2H, $J = 8.4$ Hz, Ar–H), 9.32 (s, 1H, OH), 10.32 (s, 1H, OH), ^{13}C NMR (75 MHz, DMSO-d_6): 58.35, 110.20, 114.12, 117.84, 117.87, 118.13, 121.04, 123.32, 123.89, 124.13, 124.82, 125.57, 126.86, 130.03, 131.70, 139.50, 145.48, 147.54, 158.05, 160.19; MS *m/z* (%): 332 (M + 2), 330 (M^+), 238, 237 (100), 208, 191, 164, 153, 127, 95, 83, 69, 57, 55, 43; Anal. calcd. for $C_{20}H_{14}N_2O_3$: C, 72.72; H, 4.24; N, 8.48. Found: C, 72.69; H, 4.20; N, 8.53.

*9,11-Diamino-6-hydroxy-12-(2-chlorophenyl)-12H-benzo[5,6]chromeno[2,3-b]pyridine-10-carbonitrile (**9a**)*

Cream solid; mp > 300 °C; IR (KBr, cm^{-1}): 3476, 3363, 3193, 3054, 2206, 1646, 1580, 1473, 1400, 1322, 1263, 1218; ^{1}H NMR (300 MHz, DMSO-d_6): 6.13 (s, 1H, methine-H), 6.38 (s, 2H, NH_2), 6.56 (s, 2H, NH_2), 7.13–7.35 (m, 6H, Ar–H), 7.55 (d, 1H, $J = 7.5$ Hz, Ar–H), 7.66 (d, 1H, $J = 5.1$ Hz, Ar–H), 8.07–8.09 (m, 1H, Ar–H), 10.23 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): 71.67, 90.61, 110.58, 116.77, 117.66, 123.28, 124.05, 125.29, 125.35, 125.99, 127.08, 128.36, 129.12, 130.42, 131.19, 131.33, 132.06, 141.19, 141.74, 145.98, 157.21, 159.06, 159.99; MS *m/z* (%): 416 $(M + 2)^+$, 414 (M^+), 342, 330, 303, 238, 237 (100), 208, 191, 164, 127, 114, 75, 57, 43; Anal. calcd. for $C_{23}H_{15}ClN_4O_2$: C, 66.58; H, 3.61; N, 13.51. Found: C, 66.52; H, 3.67; N, 13.48.

*9,11-Diamino-6-hydroxy-12-(4-chlorophenyl)-12H-benzo[5,6]chromeno[2,3-b]pyridine-10-carbonitrile (**9b**)*

Pale green solid; mp > 300 °C; IR (KBr, cm^{-1}): 3498, 3351, 3243, 3070, 2973, 2202, 1623, 1555, 1473, 1403, 1322, 1207, 1149; ^{1}H NMR (300 MHz, DMSO-d_6): 6.05 (s, 1H, methine-H), 6.50 (s, 2H, NH_2), 6.85 (s, 2H, NH_2), 7.19–7.46 (m, 7H, Ar–H), 7.65–7.68 (m, 1H, Ar–H), 8.11–8.14 (m, 1H, Ar–H), 10.22 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): 71.42, 91.76, 110.28, 117.01, 119.57, 123.44, 124.07, 125.07, 125.39, 127.02, 128.80, 129.56, 131.47, 131.54, 140.81, 144.19, 146.14, 147.31, 157.09, 159.37, 160.06; MS *m/z* (%): 416 $(M + 2)^+$, 414 (M^+), 342, 304, 303 (100), 238, 237, 189, 160, 127, 105, 77, 57, 43; Anal. calcd. for $C_{23}H_{15}ClN_4O_2$: C, 66.58; H, 3.61; N, 13.51. Found: C, 66.62; H, 3.57; N, 13.58.

*9,11-Diamino-6-hydroxy-12-(3-bromophenyl)-12H-benzo[5,6]chromeno[2,3-b]pyridine-10-carbonitrile (**9c**)*

Cream solid; mp > 300 °C; IR (KBr, cm^{-1}): 3494, 3355, 3239, 3062, 2900, 2202, 1623, 1605, 1469, 1400, 1322, 1253, 1079; ^{1}H NMR (300 MHz, DMSO-d_6): 6.04 (s, 1H, methine-H), 6.52 (s, 2H, NH_2), 6.88 (s, 2H, NH_2), 7.17–7.41 (m, 6H, Ar–H), 7.68 (s, 1H, Ar–H), 8.12 (d, 1H, J = 8.4 Hz, Ar–H), 10.25 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): 71.44, 91.56, 109.96, 116.46, 116.94, 119.36, 122.04, 123.31, 124.19, 125.02, 125.46, 126.82, 127.07, 129.83, 130.24, 131.18, 131.54, 140.88, 146.11, 147.83, 157.06, 159.39, 160.10; MS *m/z* (%): 460 (M + 2), 458 (M^+), 405, 391, 330, 303, 275, 237, 189, 164, 139 (100), 119, 111, 105, 91, 77; Anal. calcd. for $C_{23}H_{15}BrN_4O_2$: C, 60.13; H, 3.26; N, 12.20. Found: C, 60.11; H, 3.30; N, 12.27.

*9,11-Diamino-6-hydroxy-12-(4-bromophenyl)-12H-benzo[5,6]chromeno[2,3-b]pyridine-10-carbonitrile (**9d**)*

Yellow solid; mp > 300 °C; IR (KBr, cm^{-1}): 3498, 3351, 3239, 3077, 2969, 2202, 1623, 1565, 1473, 1400, 1322, 1257, 1149; ^{1}H NMR (300 MHz, DMSO-d_6): 6.04 (s, 1H, methine-H), 6.50 (s, 2H, NH_2), 6.86 (s, 2H, NH_2), 7.19–7.41 (m, 7H, Ar–H), 7.66–8.13 (m, 2H, Ar–H), 10.24 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): 71.42, 91.69, 110.28, 117.00, 119.49, 120.01, 123.42, 124.07, 125.07, 125.39, 125.98, 127.01, 129.94, 131.71, 140.80, 144.60, 146.13, 147.31, 157.09, 159.34, 160.05; MS *m/z* (%): 460 $(M + 2)^+$, 458 (M^+), 405, 391, 330, 303, 275, 237, 219, 191, 160, 139, 119, 111, 105 (100), 91, 77, 57, 43; Anal. calcd. for $C_{23}H_{15}BrN_4O_2$: C, 60.13; H, 3.26; N, 12.20. Found: C, 60.11; H, 3.25; N, 12.28.

*9,11-Diamino-6-hydroxy-12-(4-flourophenyl)-12H-benzo[5,6]chromeno[2,3-b]pyridine-10-carbonitrile (**9e**)*

Green solid; mp > 300 °C; IR (KBr, cm^{-1}): 3498, 3351, 3243, 3077, 2923, 2202, 1623, 1566, 1511, 1469, 1403, 1257; ^{1}H NMR (300 MHz, DMSO-d_6): 6.04 (s, 1H, methine-H), 6.48 (s, 2H, NH_2), 6.85 (s, 2H, NH_2), 6.99–7.67 (m, 7H, Ar–H), 7.98–8.16 (m, 2H, Ar–H), 10.21 (s, 1H, OH); ^{13}C NMR (75 MHz, DMSO-d_6): 71.41, 92.08, 110.16, 115.39, 115.66, 115.97, 116.26, 119.92, 123.50, 124.01, 125.08, 126.98, 129.49, 129.59, 131.54, 132.64, 140.77, 146.14, 157.04, 159.39; MS *m/z* (%): 398 (M^+), 391, 330, 303, 275, 237, 191, 164, 151, 141, 139 (100), 119, 111, 105, 91, 77, 57, 43; Anal. calcd. for $C_{23}H_{15}FN_4O_2$: C, 69.34; H, 3.76; N, 14.07. Found: C, 69.30; H, 3.71; N, 14.11.

*9,11-Diamino-6-hydroxy-12-(3-nitrophenyl)-12H-benzo[5,6]chromeno[2,3-b]pyridine-10-carbonitrile (**9f**)*

White solid; mp > 300 °C; IR (KBr, cm^{-1}): 3490, 3359, 3243, 3081, 2927, 2206, 1623, 1565, 1523, 1469, 1400, 1346, 1263, 1203; ^{1}H NMR (300 MHz, DMSO-d_6): 6.22 (s, 1H, methine-H), 6.56 (s, 2H, NH_2), 6.96 (s, 2H, NH_2), 7.22 (s, 7H, Ar–H), 7.32–8.15 (m, 7H, Ar–H), 8.43 (s, 1H, Ar–H), 10.31 (s, 1H, OH); ^{13}C NMR

(75 MHz, DMSO-d_6): 71.46, 91.24, 110.67, 116.89, 118.95, 122.07, 122.17, 122.28, 123.17, 124.33, 124.94, 125.53, 127.13, 130.59, 131.55, 134.33, 141.02, 146.15, 147.23, 148.10, 157.14, 159.41, 160.22; MS *m/z* (%): 444 (M^+), 398, 330, 303 (100), 274, 237, 191, 164, 151, 139, 127, 105, 77, 75, 43; Anal. calcd. for $C_{23}H_{15}FN_5O_4$: C, 64.94; H, 3.53; N, 16.47. Found: C, 64.98; H, 3.59; N, 16.42.

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