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DIRECT CONSTRUCTION OF 9-AMINO-7-ARYL-6*H*-BENZO[*c*]CHROMENE-8,10-DICARBONITRILES BY MEANS OF A CASCADE MICHAEL/CYCLIZATION REACTION

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Abstract – An easy and practical synthesis method was developed for the preparation of potentially biologically active 9-amino-7-aryl-6*H*-benzo[*c*]chromene-8,10-dicarbonitriles. Starting from chroman-4-one derivatives, aldehydes and malononitrile, the one-pot three-component reaction went on smoothly in the presence of DBU at 60 °C for 32 hours using tetrahydrofuran as solvent. More diverse 9-amino-7-aryl-6*H*-benzo[*c*]chromene-8,10-dicarbonitriles were synthesized and separated in good yields. The outstanding advantages of this demonstrated method mainly reflects in the easy access to starting materials, high atom economical manner, simple operation steps and wide applicability.

Benzo[*c*]chromenes are important structural skeletons comprising two benzene rings joined by an oxygenated heterocycle, served as a basic structural unit in many bioactive natural products[1-5] and synthetic compounds. Scientific and industrial interest have been promoted by medicinal potential of numerous diverse benzo[*c*]chromenes, including anticancer activity,[6-8] N-myristoyltransferases inhibitory activity,[9] the treatment of allergic rhinitis,[10] antifungal activity,[11] HIV inhibitor,[12] the drug candidates of Alzheimer's disease,[13] cytoprotective effect,[14] the treatment of periodontal diseases,[15] α-glucosidase inhibitory activity,[16,17] anxiolytic and antidepressant.[18] Due to its structural diversity and significant biological activity, more and more attention has been given to benzo[*c*]chromenes. As a class of valuable compounds, the development of simple and feasible synthesized method for benzo[*c*]chromenes can be considered of extremely critical and important.

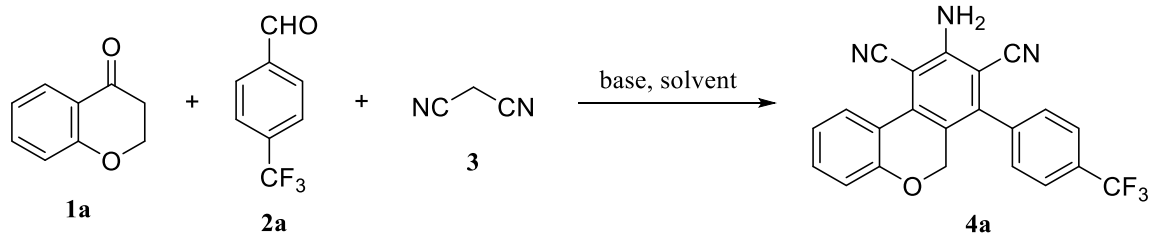
Most recently, chroman-4-one derivatives have been selected as a starting material for the construction of new type of compounds, including the gain of (*E*)-3-arylidenechroman-4-ones through the reaction of

chroman-4-one derivatives and aromatic aldehydes,[19-21] the obtainment of 2-(chroman-4-ylidene)malononitrile derivatives by the reaction between chroman-4-one derivatives and malononitrile,[22,23] the further conversion of (*E*)-3-arylidenechroman-4-ones or 2-(chroman-4-ylidene)malononitrile derivatives to other heterocyclic compounds.[24-26] Through these reactions mentioned above, a rich variety of tricyclic and tetracyclic heterocyclic compounds have been synthesized, especially Zhang et al. reported the synthesis of benzo[*c*]chromenes through the three-component reaction of 2-(2,3-dihydrochromen-4-ylidene)malononitrile, malononitrile and aromatic aldehyde.[26] However, 2-(2,3-dihydrochromen-4-ylidene)malononitrile is not an easily available starting material. To further simplify the reaction process, we have made some new useful explorations using chroman-4-one as starting material by one-pot synthesis method. It is worth noting that the so-called "multicomponent reactions (MCRs)" has many unique advantages, such as higher atom economy, reduced by-products, more inherent molecular diversities, simpler operation process and experimental equipment, diminished costs, and so on.[27-29] As a classical methodology, the Michael addition has become one of the most basic and powerful carbon–carbon bond-constructing means, playing an increasing important role in multicomponent reactions especially in the construction of novel ring.[30] As a result, we try hard to supplement a fresh and candidate reaction pathway for the preparation of diverse benzo[*c*]chromenes by a tandem Michael addition−cyclization procedure. The present study is focused on the preparation of biologically important 9-amino-7-aryl-6*H*-benzo[*c*]chromene-8,10-dicarbonitriles with satisfactory results.

Initially, chroman-4-one **1a**, 4-(trifluoromethyl)benzaldehyde **2a** and malononitrile **3** were selected as reactants in the optimization of the reaction conditions. The reaction was conducted in [BMIm]BF_4 at room temperature or 50 °C for 16 hours, no reaction product was detected by thin layer chromatography (TLC). After the replacement of [BMIm]BF_4 by [BMIm]Br, there was still no reaction product was detected. Considering the inconvenience caused by the viscosity of ionic liquids, we made some new explorations for the reaction conditions. The reaction was then conducted in toluene at 100 °C for 16 hours with the addition of 2 equiv. of DBU to speed up the reaction rate. It was discovered that the desired benzo[*c*]chromene **4a** was synthesized with the yield of 29% (Table 1, entry 1). In addition to DBU, some other organic bases, such as pyrrolidine, piperidine, morpholine, triethylamine, N,N-diisopropylethylamine (DIEA), triethylenediamine (DABCO), sodium methanolate and sodium ethoxide were used under similar conditions to explore the performance of different organic bases. To our disappointment, the product yield of the three-component reaction with replaced organic bases showed inferior results (Table 1, entries 2-9). Considering that sodium methanolate and sodium ethoxide were insoluble in toluene, the reaction solvent was replaced by ethanol with higher but not ideal yields (Table 1,

entries 10,11). Obviously, DBU was the most excellent organic base in terms of the performance in this reaction.

Table 1. Optimization of reaction process conditions



Entry	Solvent	Base	Equiv. of malononitrile	Equiv. of base	Temp (°C)	Time (h)	Yield of **4a**[a] (%)
1	toluene	DBU	2	2	100	16	29
2	toluene	pyrrolidine	2	2	100	16	28
3	toluene	piperidine	2	2	100	16	20
4	toluene	morpholine	2	2	100	16	15
5	toluene	triethylamine	2	2	100	16	27
6	toluene	DIEA	2	2	100	16	8
7	toluene	DABCO	2	2	100	16	22
8	toluene	MeONa	2	2	100	16	trace
9	toluene	EtONa	2	2	100	16	trace
10	EtOH	MeONa	2	2	60	16	7
11	EtOH	EtONa	2	2	60	16	5
12	toluene	DBU	3	2	100	16	32
13	toluene	DBU	4	2	100	16	38
14	toluene	DBU	5	2	100	16	38
15	MeOH	DBU	4	2	60	16	32
16	EtOH	DBU	4	2	70	16	29
17	THF	DBU	4	2	60	16	50
18	ethylene glycol	DBU	4	2	100	16	10
19	THF	DBU	4	2	60	32	61
20	THF	DBU	4	3	60	32	61

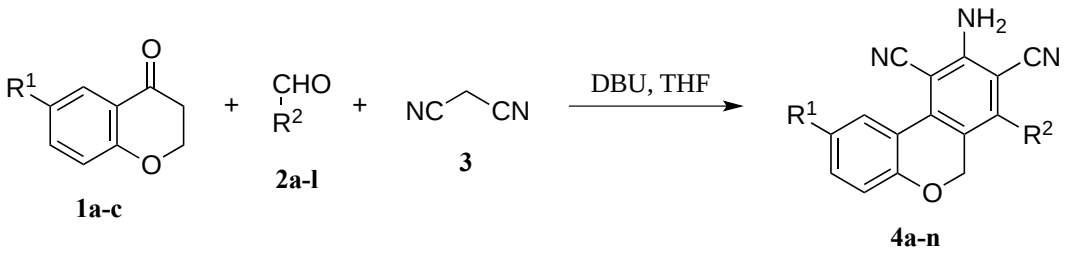
[a] The isolated yield after purification by silica gel column chromatography.

Meanwhile, it was found that chroman-4-one **1a** has many surpluses in the reaction solution in monitoring the progress of the reaction by TLC. Therefore, more malononitrile **3** was added into the reaction mixture to better promote the consumption of chroman-4-one **1a** and the formation of more product. The experimental results revealed that the product yield will increase significantly with the increase of the amount of malononitrile **3** and the most suitable amount of malononitrile **3** was a double dose of initial dosage (Table 1, entry 1 and entries 12-14). Then, many other common organic solvents, including methanol, ethanol, tetrahydrofuran and ethylene glycol, were used for the reaction at a temperature close to the boiling point of the solvent. The solvent screening result shown that tetrahydrofuran was the most suitable solvent for this reaction (Table 1, entry 13 and entries 15-18).

In order to further increase the product yield, the reaction time has been extended to 32 hours and the target product was isolated in a barely satisfying yield (Table 1, entry 19). In addition, the amount of DBU was increased to 3 equiv. for the increase of yield, but the experimental result was not as expected (Table 1, entry 20). In summarizing the above process optimization results, we can conclude that the model reaction proceeded most smoothly with a double dose of malononitrile **3** in the presence of 2 equiv. of DBU in tetrahydrofuran at 60 °C for 32 hours, and the corresponding product **4a** was isolated in acceptable yield (61%) (Table 1, entry 19).

Having optimized a set of suitable process conditions in hand, we directed our attention to explore the substrate scope of the model reaction (Table 2). Firstly, a series of different aromatic aldehydes were used for the three-component reaction (Table 2, entries 1-11). Among them, it was discovered that if the substitution position of trifluoromethyl group on benzene ring was different, the yield was also changed obviously (Table 2, entries 1-3). When 2-(trifluoromethyl)benzaldehyde was used in the reaction, only a lower yield was gained due to the larger steric hindrance, which was not conducive to the reaction. Other aromatic aldehydes containing an electron-withdrawing group on the phenyl ring were also selected as reaction substrates in this reaction, and the desired target products were separated in medium yield (Table 2, entries 4-6). Simultaneously, some aromatic aldehydes containing an electron-donating group were adopted for this model reaction, and it was pleased to observe that the reaction processing conditions were also suitable for these reaction substrates (Table 2, entries 8,9). Then, 2-naphthaldehyde was involved in this reaction as a representative of polycyclic aromatic hydrocarbons, and high product yield was obtained (Table 2, entry 10). Afterward, heterocyclic analogue **2k** was employed in this reaction with acceptable yield (Table 2, entry 11). Furthermore, pivalaldehyde took part in the reaction as one of the non-aromatic aldehydes, and it was successfully transformed into the corresponding product (Table 2, entry 12). Finally, the possibility of using other chroman-4-one derivatives as the Michael donor was explored, and the domino reaction went on smoothly as expected (Table 2, entries 13,14). In brief, the one-pot reaction is applicable to a wide range of substrates under optimized reaction conditions.

Table 2. Synthesis of 9-amino-7-aryl-6*H*-benzo[*c*]chromene-8,10-dicarbonitrile derivatives



Entry	R^1 (**1**)	R^2 (**2**)	Compound	Yield (%)[a]
1	H (**1a**)	4-$CF_3C_6H_4$ (**2a**)	**4a**	61
2	H (**1a**)	3-$CF_3C_6H_4$ (**2b**)	**4b**	70
3	H (**1a**)	2-$CF_3C_6H_4$ (**2c**)	**4c**	35
4	H (**1a**)	4-CNC_6H_4 (**2d**)	**4d**	60
5	H (**1a**)	4-FC_6H_4 (**2e**)	**4e**	68
6	H (**1a**)	4-BrC_6H_4 (**2f**)	**4f**	41
7	H (**1a**)	C_6H_5 (**2g**)	**4g**	45
8	H (**1a**)	4-*i*PrC_6H_4 (**2h**)	**4h**	55
9	H (**1a**)	4-$MeOC_6H_4$ (**2i**)	**4i**	75
10	H (**1a**)	2-naphthyl (**2j**)	**4j**	81
11	H (**1a**)	2-thienyl (**2k**)	**4k**	37
12	H (**1a**)	*tert*-butyl (**2l**)	**4l**	20
13	Br (**1b**)	4-$CF_3C_6H_4$ (**2a**)	**4m**	38
14	F (**1c**)	4-$CF_3C_6H_4$ (**2a**)	**4n**	40

[a] The isolated yield after purification by silica gel column chromatography.

In summary, we have provided a novel and efficient strategy for the preparation of potentially biologically active 9-amino-7-aryl-6*H*-benzo[*c*]chromene-8,10-dicarbonitriles via one-pot Michael/cyclization reaction of chroman-4-one derivatives, aldehydes and malononitrile. This transformation involved a cascade Knoevenagel condensation, Michael addition and intramolecular nucleophilic addition reaction. The reaction has great application potential in many aspects due to its significant advantages, such as high atom utilization efficiency, broad substrate applicability as well as easy and fast operation process.

EXPERIMENTAL

Unless otherwise noted, chemical reagents used in the experiment were purchased from different reagent companies without further purification procedures. All reaction processes were well-monitored with the

help of thin layer chromatography (TLC) using 60 F254 silica gel plates. After the completion of the reaction, the separation of all products was performed with the aid of silica gel column chromatography (200–300 mesh silica gel). The ^{1}H NMR and ^{13}C NMR spectra with the reported chemical shifts in ppm were used for the structure identification of all synthetic compound, measured by a Bruker AM400 NMR spectrometer using tetramethylsilane (TMS) as an internal reference. High-resolution mass spectrometry (HRMS) data were recorded using an Agilent time-of-flight mass spectrometer.

General experimental procedure for the one-pot synthesis of 9-amino-7-aryl-6*H*-benzo[*c*]chromene-8,10-dicarbonitrile derivatives 4: Chroman-4-one derivatives **1** (0.3 mmol), aldehydes **2** (0.3 mmol), malononitrile **3** (1.2 mmol) and DBU (0.6 mmol) were added into the dry reaction tube, and then 3 mL THF was added to the reaction mixture as reaction solvent. The reaction tube was placed in a magnetic stirring constant-temperature oil bath at 60 °C and heated for 32 h. After the accomplish of the three-component reaction (confirmed by TLC), the reaction solvent was evaporated with a rotary evaporator, and the crude product was separated by silica gel column chromatography using petroleum ether/EtOAc (6:1, v/v) as eluent. The target product **4a-n** were dried in a vacuum drying oven at 60 °C for 6 h. The spectral data of synthetic compound are enumerated as follows.

9-Amino-7-(4-(trifluoromethyl)phenyl)-6*H*-benzo[*c*]chromene-8,10-dicarbonitrile (4a): Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.64 (s, 2H; CH_2), 5.40 (s, 2H; NH_2), 7.04-7.06 (m, 1H; Ar-H), 7.19-7.23 (m, 1H; Ar-H), 7.41-7.46 (m, 3H; Ar-H), 7.80-7.82 (m, 2H; Ar-H), 8.42-8.45 (m, 1H; Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 65.54, 91.67, 95.97, 115.23, 116.51, 119.04 (q, J = 224 Hz), 121.73, 122.78, 126.16 (q, J = 3.7 Hz), 126.53, 128.84, 129.12, 131.89 (q, J = 32.8 Hz), 133.08, 138.28, 144.91, 148.23, 152.61, 152.85, 156.78. HRMS (ESI) *m/z* calcd for $C_{22}H_{11}F_3N_3O$ $[M-H]^-$ 390.0860, found 390.0869.

9-Amino-7-(3-(trifluoromethyl)phenyl)-6*H*-benzo[*c*]chromene-8,10-dicarbonitrile (4b): Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.61-4.69 (m, 2H; CH_2), 5.41 (s, 2H; NH_2), 7.04-7.06 (m, 1H; Ar-H), 7.18-7.23 (m, 1H; Ar-H), 7.41-7.46 (m, 1H; Ar-H), 7.53-7.55 (m, 2H; Ar-H), 7.68-7.72 (m, 1H; Ar-H), 7.79-7.81 (m, 1H; Ar-H), 8.42-8.44 (m, 1H; Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 65.74, 91.12, 96.29, 115.99, 117.15, 118.15, 120.79, 121.04, 122.83, 126.07, 126.95, 129.84, 130.48, 133.28, 133.45, 136.54, 137.81, 145.50, 154.21, 156.83 (Coupling with F atom was eliminated). HRMS (ESI) *m/z* calcd for $C_{22}H_{11}F_3N_3O$ $[M-H]^-$ 390.0860, found 390.0862.

9-Amino-7-(2-(trifluoromethyl)phenyl)-6*H*-benzo[*c*]chromene-8,10-dicarbonitrile (4c): Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.35-4.43 (m, 2H; CH_2), 5.29 (s, 2H; NH_2), 6.94-6.96 (m, 1H; Ar-H), 7.10-7.14 (m, 1H; Ar-H), 7.24-7.26 (m, 1H; Ar-H), 7.32-7.37 (m, 1H; Ar-H), 7.57-7.61 (m, 1H; Ar-H), 7.64-7.67 (m, 1H; Ar-H), 7.79-7.81 (m, 1H; Ar-H), 8.38-8.40 (m, 1H; Ar-H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ (ppm) 65.59, 91.83, 97.14, 113.61, 114.71, 116.50, 117.94, 121.45 (q, *J* = 224 Hz), 122.67, 126.58, 126.91 (q, *J* = 5.1 Hz), 128.71 (q, *J* = 30.6 Hz), 129.97, 130.11, 132.68, 132.98, 133.60, 137.67, 143.38, 152.19, 156.87. HRMS (ESI) *m/z* calcd for $C_{22}H_{11}F_3N_3O$ $[M-H]^-$ 390.0860, found 390.0866.

9-Amino-7-(4-cyanophenyl)-6*H*-benzo[*c*]chromene-8,10-dicarbonitrile (4d): Pale yellow solid; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.62 (s, 2H; CH_2), 5.41 (s, 2H; NH_2), 7.04-7.06 (m, 1H; Ar-H), 7.19-7.23 (m, 1H; Ar-H), 7.42-7.46 (m, 3H; Ar-H), 7.84-7.86 (m, 2H; Ar-H), 8.42-8.44 (m, 1H; Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 65.44, 92.00, 95.73, 113.97, 115.03, 117.88, 117.97, 120.25, 121.56, 122.87, 123.52, 126.55, 129.51, 132.88, 133.22, 139.56, 144.22, 152.74, 154.27, 156.75. HRMS (ESI) *m/z* calcd for $C_{22}H_{11}N_4O$ $[M-H]^-$ 347.0938, found 347.0944.

9-Amino-7-(4-fluorophenyl)-6*H*-benzo[*c*]chromene-8,10-dicarbonitrile (4e): Pale yellow solid; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.67 (s, 2H; CH_2), 5.37 (s, 2H; NH_2), 7.03-7.05 (m, 1H; Ar-H), 7.18-7.25 (m, 3H; Ar-H), 7.28-7.31 (m, 2H; Ar-H), 7.40-7.45 (m, 1H; Ar-H), 8.41-8.43 (m, 1H; Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 65.66, 91.27, 96.46, 115.48, 116.32 (d, *J* = 21.8 Hz), 116.64, 117.89, 120.52, 122.05, 122.70, 126.52, 130.55 (d, *J* = 8.7 Hz), 130.92 (d, *J* = 2.9 Hz), 132.91, 138.06, 145.61, 152.75, 156.75, 158.57, 163.41 (d, *J* = 249.4 Hz). HRMS (ESI) *m/z* calcd for $C_{21}H_{11}FN_3O$ $[M-H]^-$ 340.0892, found 340.0902.

9-Amino-7-(4-bromophenyl)-6*H*-benzo[*c*]chromene-8,10-dicarbonitrile (4f): Pale yellow solid; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.59 (s, 2H; CH_2), 5.31 (s, 2H; NH_2), 6.96-6.98 (m, 1H; Ar-H), 7.10-7.14 (m, 3H; Ar-H), 7.33-7.38 (m, 1H; Ar-H), 7.59-7.61 (m, 2H; Ar-H), 8.34-8.36 (m, 1H; Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 65.61, 91.42, 96.16, 115.36, 116.57, 117.91, 120.47, 121.86, 122.72, 124.32, 126.52, 130.14, 132.39, 132.96, 133.82, 138.15, 145.33, 152.72, 156.78. HRMS (ESI) *m/z* calcd for $C_{21}H_{11}BrN_3O$ $[M-H]^-$ 400.0091, found 400.0096.

9-Amino-7-phenyl-6*H*-benzo[*c*]chromene-8,10-dicarbonitrile (4g): Yellow solid; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.60 (s, 2H; CH_2), 5.30 (s, 2H; NH_2), 6.94-6.97 (m, 1H; Ar-H), 7.07-7.13 (m, 1H; Ar-H), 7.20-7.23 (m, 2H; Ar-H), 7.31-7.35 (m, 2H; Ar-H), 7.44-7.45 (m, 2H; Ar-H), 8.33-8.36 (m, 1H; Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 65.76, 91.06, 96.48, 115.55, 116.75, 117.86, 120.63, 122.00, 122.62, 126.52, 128.49, 129.04, 129.73, 132.79, 135.00, 137.92, 146.76, 152.75, 156.81. HRMS (ESI) *m/z* calcd for $C_{21}H_{12}N_3O$ $[M-H]^-$ 322.0986, found 322.0991.

9-Amino-7-(4-isopropylphenyl)-6*H*-benzo[*c*]chromene-8,10-dicarbonitrile (4h): Pale yellow solid; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (d, *J* = 8 Hz, 6H; $2CH_3$), 2.96-3.03 (m, 1H; CH), 4.71 (s, 2H; CH_2), 5.35 (s, 2H; NH_2), 7.02-7.04 (m, 1H; Ar-H), 7.16-7.22 (m, 3H; Ar-H), 7.36-7.43 (m, 3H; Ar-H), 8.40-8.43 (m, 1H; Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 23.84, 34.01, 65.85, 90.88, 96.53, 116.21, 116.81, 117.83, 120.71, 122.20, 122.57, 124.83, 126.50, 127.06, 128.53, 132.69, 137.84, 150.61, 152.74, 156.83. HRMS (ESI) *m/z* calcd for $C_{24}H_{18}N_3O$ $[M-H]^-$ 364.1455, found 364.1446.

9-Amino-7-(4-methoxyphenyl)-6*H*-benzo[*c*]chromene-8,10-dicarbonitrile (4i): Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (s, 3H; OCH_3), 4.72 (s, 2H; CH_2), 5.34 (s, 2H; NH_2), 7.02-7.05 (m, 3H; Ar-H), 7.16-7.21 (m, 1H; Ar-H), 7.22-7.24 (m, 2H; Ar-H), 7.39-7.43 (m, 1H; Ar-H), 8.40-8.42 (m, 1H; Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 55.38, 65.83, 90.78, 96.62, 114.43, 115.84, 116.83, 117.82, 120.73, 122.21, 122.59, 126.50, 127.04, 129.77, 130.02, 132.69, 137.84, 146.69, 152.79, 156.78, 160.63. HRMS (ESI) *m/z* calcd for $C_{22}H_{14}N_3O_2$ $[M-H]^-$ 352.1092, found 352.1102.

9-Amino-7-(naphthalen-2-yl)-6*H*-benzo[*c*]chromene-8,10-dicarbonitrile (4j): Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.65-4.66 (m, 2H; CH_2), 5.33 (s, 2H; NH_2), 6.95-6.97 (m, 1H; Ar-H), 7.11-7.14 (m, 1H; Ar-H), 7.29-7.37 (m, 2H; Ar-H), 7.50-7.53 (m, 2H; Ar-H), 7.72 (s, 1H; Ar-H), 7.82-7.87 (m, 2H; Ar-H), 7.92-7.94 (m, 1H; Ar-H), 8.36-8.39 (m, 1H; Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 65.82, 96.63, 115.62, 116.78, 117.88, 120.64, 122.24, 122.64, 125.53, 126.53, 127.12, 127.40, 127.98, 128.30, 128.39, 129.03, 132.82, 132.96, 137.96, 146.73, 152.77, 156.83. HRMS (ESI) *m/z* calcd for $C_{25}H_{14}N_3O$ $[M-H]^-$ 372.1142, found 372.1148.

9-Amino-7-(thiophen-2-yl)-6*H*-benzo[*c*]chromene-8,10-dicarbonitrile (4k): Tawny fawn solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.82 (s, 2H; CH_2), 5.38 (s, 2H; NH_2), 7.04-7.06 (m, 1H; Ar-H), 7.16-7.21 (m, 3H; Ar-H), 7.40-7.44 (m, 1H; Ar-H), 7.56-7.57 (m, 1H; Ar-H), 8.38-8.40 (m, 1H; Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 65.79, 97.24, 115.41, 116.58, 117.88, 120.50, 122.67, 123.37, 126.52, 127.82, 128.62, 129.53, 132.89, 134.37, 137.95, 139.20, 152.66, 156.78. HRMS (ESI) *m/z* calcd for $C_{19}H_{10}N_3OS$ $[M-H]^-$ 328.0550, found 328.0559.

9-Amino-7-(*tert*-butyl)-6*H*-benzo[*c*]chromene-8,10-dicarbonitrile (4l): Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (s, 9H; $3CH_3$), 4.82 (s, 2H; CH_2), 5.21 (s, 2H; NH_2), 6.99-7.02 (m, 1H; Ar-H), 7.09-7.12 (m, 1H; Ar-H), 7.33-7.37 (m, 1H; Ar-H), 8.35-8.36 (m, 1H; Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 31.95, 34.60, 67.47, 94.90, 116.49, 116.75, 122.63, 122.72, 122.93, 126.23, 128.49, 129.05, 129.75, 132.36, 132.80, 138.99, 159.41. HRMS (ESI) *m/z* calcd for $C_{19}H_{18}N_3O$ $[M+H]^+$ 304.1444, found 304.1441.

9-Amino-2-bromo-7-(4-(trifluoromethyl)phenyl)-6*H*-benzo[*c*]chromene-8,10-dicarbonitrile (4m): Bright yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.57 (s, 2H; CH_2), 5.38 (s, 2H; NH_2), 6.86-6.88 (m, 1H; Ar-H), 7.36-7.38 (m, 2H; Ar-H), 7.44-7.46 (m, 1H; Ar-H), 7.73-7.75 (m, 2H; Ar-H), 8.47-8.48 (m, 1H; Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 65.66, 93.78, 97.41, 115.08, 115.62, 116.01, 120.22, 120.25, 120.91 (q, J = 224 Hz), 125.18, 125.88 (q, J = 3.6 Hz), 128.84, 129.08, 131.57 (q, J = 33.8 Hz), 135.65, 140.92, 148.22, 148.26, 152.60, 155.77. HRMS (ESI) *m/z* calcd for $C_{22}H_{10}BrF_3N_3O$ $[M-H]^-$ 467.9965, found 467.9966.

9-Amino-2-fluoro-7-(4-(trifluoromethyl)phenyl)-6*H*-benzo[*c*]chromene-8,10-dicarbonitrile (4n): Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.63 (s, 2H; CH_2), 5.43 (s, 2H; NH_2), 7.00-7.04 (m, 1H;

Ar-H), 7.12-7.17 (m, 1H; Ar-H), 7.44-7.46 (m, 2H; Ar-H), 7.80-7.83 (m, 2H; Ar-H), 8.14-8.17 (m, 1H; Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 65.72, 93.77, 97.40, 112.81 (d, *J* = 25.5 Hz), 115.08, 115.62, 119.22 (d, *J* = 8 Hz), 120.22 (d, *J* = 2.9 Hz), 121.15 (d, *J* = 8.8 Hz), 121.35 (q, *J* = 224 Hz), 121.75, 125.88 (q, *J* = 3.6 Hz), 128.84, 129.08, 131.57 (q, *J* = 32.8 Hz), 137.21, 140.93, 145.12, 148.24 (d, *J* = 3.7 Hz), 152.62, 157.67 (d, *J* = 239.9 Hz). HRMS (ESI) *m/z* calcd for $C_{22}H_{10}F_4N_3O$ $[M-H]^-$ 408.0765, found 408.0766.

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