HETEROCYCLES, Vol. 104, No. 4, 2022, pp. 723 - 738. © 2022 The Japan Institute of Heterocyclic Chemistry
Received, 7th December, 2021, Accepted, 21st January, 2022, Published online, 28th January, 2022
DOI: 10.3987/COM-21-14608

MECHANO-BIOCATALYTIC RAPID SYNTHESIS OF 2-AMINO-3-CYANO-4*H*-PYRAN DERIVATIVES

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Abstract – A series of 2-amino-3-cyano-4*H*-pyrans **4a-4s** and **5a-5r** were synthesized in good to excellent yields *via* a simple one-pot reaction. The facile method depended on one-pot three-component reaction of aromatic aldehyde, malononitrile and dimedone or 3-(dimethylamino)phenol in the presence of bovine serum albumin (BSA) as the catalyst under ball-milling conditions. The reactions were completed in 40 min in 80-98% yields. The synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR and ESI-MS.

INTRODUCTION

Pyrans and their derivatives are an important class of heterocyclic compounds.[1] Among them, 2-amino-3-cyano-4*H*-pyran derivatives exhibit various pharmacological properties such as antibacterial,[2] anti-AChE,[3] antitumor,[4] and antituberculosis activities[5] (Figure 1).

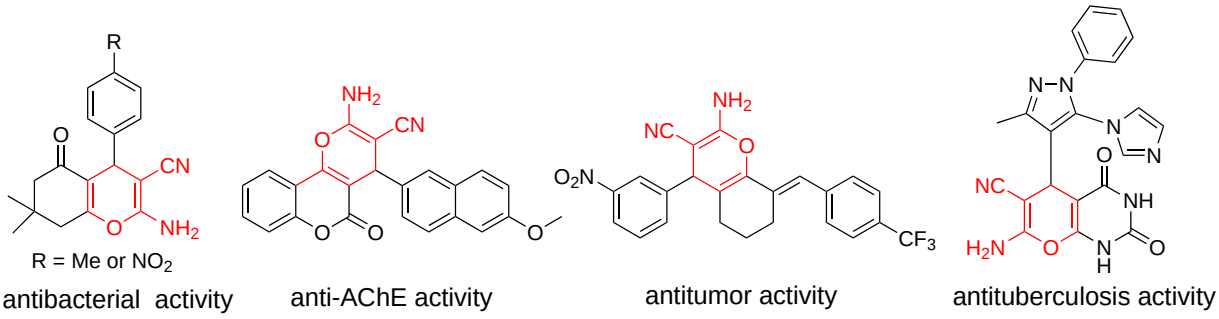


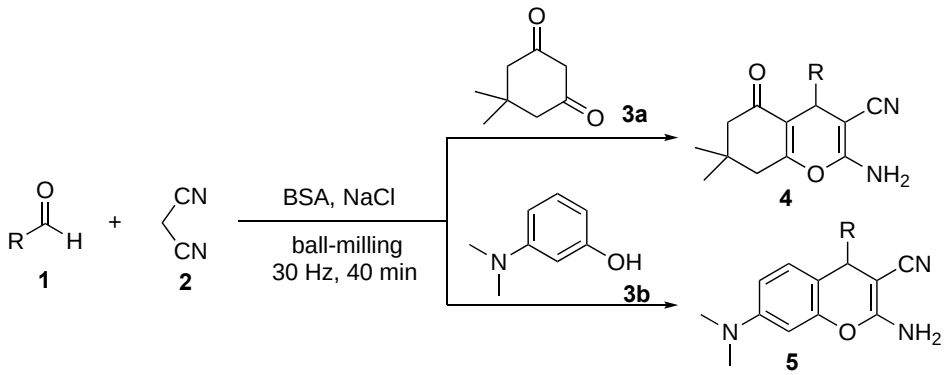
Figure 1. Examples of biologically important 2-amino-3-cyano-4*H*-pyran derivatives

The traditional synthesis method of 2-amino-3-cyano-4*H*-pyran derivatives involve the usage of ionic liquids,[6] mesoporous nanosheets Al-MCM-41-LDH@NH_2,[7] $ZnFe_2O_4$@alginic acid nanocomposite,[8] iodine under ultrasound irradiation,[9] etc. Although these protocols worked nicely, most of them suffer from one or more drawbacks such as the narrow substrate scope, long reaction time, tedious catalyst

preparation procedures and usage of volatile organic solvents. Therefore, a simple, rapid, versatile and eco-friendly approach for the synthesis of 2-amino-3-cyano-4*H*-pyran derivatives is highly desirable.

In recent years, mechano-biocatalytic reactions have attracted a great deal of interest in the field of organic synthesis as they possess some unique properties such as efficiency, operational simplicity, easy work-up and environmental friendliness.[10] For instance, Juaristi *et al.* reported a mechano-biocatalytic kinetic resolution method to obtain enantiopure (*R*)- and (*S*)-enantiomers of Ketorolac.[11] Auclair and co-workers developed a novel mechano-biocatalytic method to efficiently hydrolyze cellulose into glucose.[12] In 2020, the Liao group described a mechano-biocatalytic one-pot approach to release sugars from lignocellulosic materials.[13]

In continuation of our work on the mechano-biocatalytic reactions,[14] herein, we report a novel mechano-biocatalytic one-pot method for the rapid synthesis of 2-amino-3-cyano-4*H*-pyran derivatives using bovine serum albumin (BSA) as the catalyst under ball-milling conditions (Scheme 1).

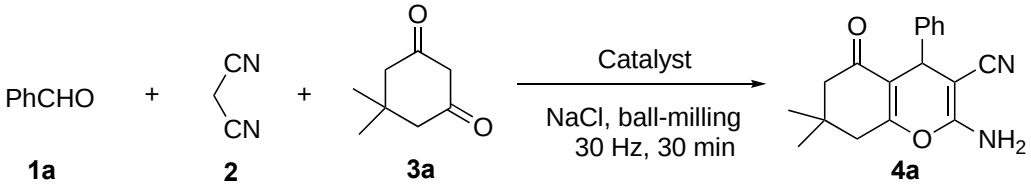


Scheme 1. Mechano-biocatalytic synthesis of 2-amino-3-cyano-4*H*-pyran derivatives

RESULTS AND DISCUSSION

Initially, the three-component reaction of benzaldehyde (**1a)**, malononitrile (**2**) and dimedone (**3a**) was used as a model reaction to optimize the reaction conditions including catalyst type, catalyst loading, grinding auxiliary, grinding frequency and reaction time. As shown in Table 1, the target molecule **4a** was obtained in 33% yield in the absence of catalyst (Table 1, entry 1). Lipozyme®RM IM, an immobilized lipase, displayed high activity and afforded the corresponding 2-amino-3-cyano-4*H*-pyran compound in 85% yield (Table 1, entry 2). L-Lysine and cyclohexylamine also showed the ability to catalyse the model reaction, the corresponding yields were 80% and 83%, respectively (Table 1, entries 3-4). To our surprise, the non-enzyme protein BSA (bovine serum albumin) afforded the corresponding product in 89% yield, which may be ascribed to the rich diversity of amino acids present on its surface (Table 1, entry 5). Moreover, the control experiment using denatured BSA as the catalyst afforded a yield of 34% (Table 1, entry 6). Based on the above experimental results, BSA was chosen as the catalyst for further investigation.

Table 1. Effect of catalysts on the model reaction[a]



1a **2** **3a** **4a**

Entry	Catalyst	Catalyst loading (mg)	Yield (%)[b]
1	-	-	33
2	Lipozyme®RM IM	50	85
3	L-Lysine	50	80
4	cyclohexylamine	50	83
5	BSA	50	89
6	denatured BSA[c]	50	34
7	BSA	30	57
8	BSA	40	60
9	BSA	60	89
10	BSA	80	92
11	BSA	100	93

[a] Reaction conditions: benzaldehyde **1a** (0.5 mmol), malononitrile **2** (0.5 mmol), dimedone **3a** (0.5 mmol), catalyst and NaCl (300 mg) were placed in a 50 mL stainless steel grinding jar along with three stainless steel grinding balls (diameter 10 mm) and milled for 30 min at 30 Hz. [b] Isolated yields. [c] Pre-treated at 150 ℃ for 4 h.

Catalyst loading plays an important role in the reaction. As shown in Table 1, the yields increased from 57% to 89% when the catalyst loading varied from 30 to 50 mg (Table 1, entry 5, entries 7-8). Further increasing the amount of BSA to 100 mg only slightly increased the yield (Table 1, entries 9-11). Considering the cost of BSA, 50 mg was chosen as the suitable catalyst loading for further investigation.

The effect of grinding auxiliary and grinding frequency were also investigated as both of them play an important role in the mechanochemical reaction.[15] As summarized in Table 2, when the reaction was conducted in the absence of grinding auxiliary, the desired product was obtained only in 43% yield (Table 2, entry 1). When the reaction was performed with Na_2SO_4, γ-Al_2O_3 (neutral) and silica gel as grinding auxiliary, the corresponding yields were 63%, 74%, and 87%, respectively (Table 2, entries 2-4). The best results were obtained when NaCl was employed, which afforded a yield of 89% (Table 2, entry 5). The possible reason might be that NaCl was favorable to mass transfer and prevent pasting of the reaction mixture, as observed by Browne *et al.*[16] The influence of grinding frequency on the model reaction was also investigated. When the grinding frequency increased from 15 Hz to 30 Hz, the yields increased from 52% to 89% (Table 2, entries 5-8). Therefore, NaCl was chosen as the optimum grinding auxiliary and 30 Hz was chosen as the optimum grinding frequency for the further reactions.

Table 2. Influence of grinding auxiliary and grinding frequency on the model reaction[a]

Entry	Grinding auxiliary	Grinding frequency (Hz)	Yield (%)[b]
1	-	30	43
2	Na_2SO_4	30	63
3	γ-Al_2O_3 (neutral)	30	74
4	Silica gel	30	87
5	NaCl	30	89
6	NaCl	15	52
7	NaCl	20	73
8	NaCl	25	84

[a] Reaction conditions: benzaldehyde **1a** (0.5 mmol), malononitrile **2** (0.5 mmol), dimedone **3a** (0.5 mmol), BSA (50 mg) and grinding auxiliary (300 mg) were placed in a 50 mL stainless steel grinding jar along with three stainless steel grinding balls (diameter 10 mm) and milled for 30 min at the specified grinding frequency. [b] Isolated yields.

In order to obtain more information about this mechano-biocatalytic reaction, the time course of the model reaction was investigated. As shown in Figure 2, the yield increased obviously in the first 20 min. After that, the reaction rate slowed down sharply. After 40 min of reaction, the yield reached a plateau. Thus, subsequent reactions were carried out for 40 min.

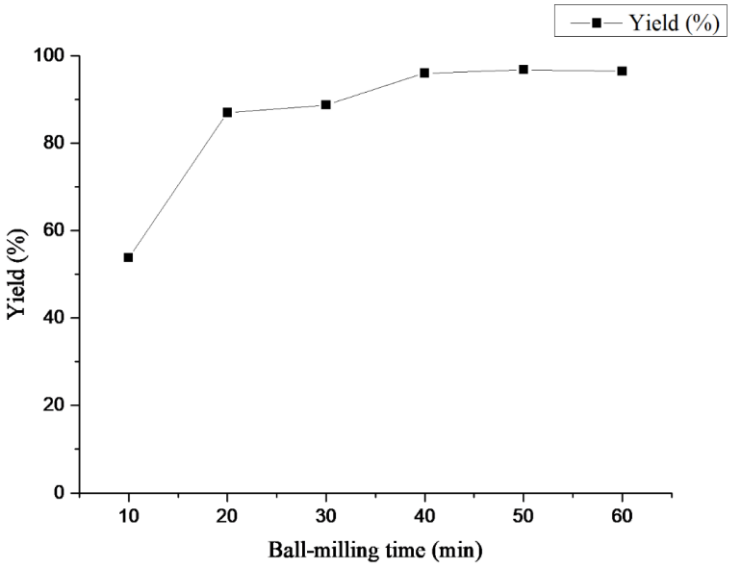
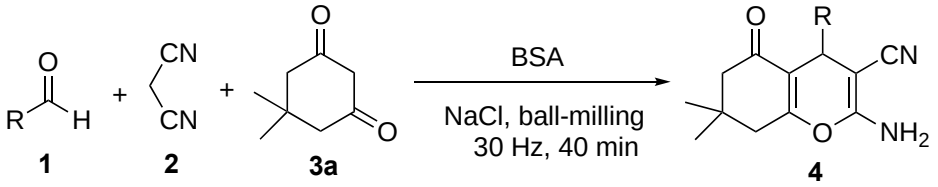


Figure 2. Time course of the mechano-biocatalytic synthesis of 2-amino-3-cyano-4*H*-pyrans. Reaction conditions: aldehyde (**1a**, 0.5 mmol), malononitrile (**2**, 0.5 mmol), dimedone (**3a**, 0.5 mmol), BSA (50 mg) and NaCl (300 mg) were placed in a 50 mL stainless steel grinding jar along with three stainless steel grinding balls (diameter 10 mm) and milled at 30 Hz. The yield was calculated based on the weight of purified product.

With the optimized conditions in hand, the reaction scope of substrates was investigated. As can be seen in Table 3, both electron-donating and electron-withdrawing substituents on the benzene ring gave the target 2-amino-3-cyano-4*H*-pyrans in high yields. Among them, product **4c** and **4i**, which have been reported with antibacterial activity, were efficiently synthesized in excellent yields (Table 3, entry 3, entry 9). In general, either electron-withdrawing or electron-donating substituents at the *para*-position gave slightly higher yields than those with *ortho*- and *meta*-substituents (Table 3, entry 3 *vs* entry 2, entry 6 *vs* entries 4-5, entry 12 *vs* entries 10-11). In addition, bis-substituted benzaldehyde also reacted well to give the corresponding products (Table 3, entries 17-19).

Table 3. Mechano-biocatalytic three-component reaction of aromatic aldehyde, malononitrile and dimedone[a]



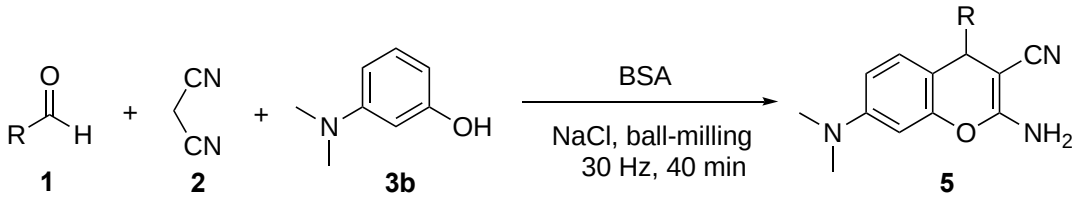
1 **2** **3a** **4**

Entry	R	Product	Yield (%)[b]
1	C_6H_5	**4a**	96
2	3-$NO_2C_6H_4$	**4b**	94
3	4-$NO_2C_6H_4$	**4c**	95
4	2-FC_6H_4	**4d**	92
5	3-FC_6H_4	**4e**	93
6	4-FC_6H_4	**4f**	98
7	2-MeC_6H_4	**4g**	92
8	3-MeC_6H_4	**4h**	92
9	4-MeC_6H_4	**4i**	92
10	2-$MeOC_6H_4$	**4j**	91
11	3-$MeOC_6H_4$	**4k**	91
12	4-$MeOC_6H_4$	**4l**	92
13	4-BrC_6H_4	**4m**	91
14	4-CNC_6H_4	**4n**	91
15	2-Furyl	**4o**	83
16	2-Thienyl	**4p**	80
17	2,3-$Cl_2C_6H_3$	**4q**	90
18	2-Br-5-$MeOC_6H_3$	**4r**	87
19	2,5-$(MeO)_2C_6H_3$	**4s**	87

[a] Reaction conditions: aldehyde (**1**, 0.5 mmol), malononitrile (**2**, 0.5 mmol), dimedone (**3a**, 0.5 mmol), BSA (50 mg) and NaCl (300 mg) were placed in a 50 mL stainless steel grinding jar along with three stainless steel grinding balls (diameter 10 mm) and milled at 30 Hz for 40 min. [b] Isolated yields.

Encouraged by the above results, the generality of the mechano-biocatalytic synthesis of 2-amino-3-cyano-4*H*-pyran derivatives was investigated by conducting three-component reaction between aromatic aldehydes, malononitrile and 3-(dimethylamino)phenol. After optimization of the reaction conditions (see Electronic Supplementary Information S3-5), it was found that all reactions proceeded smoothly to furnish the target compounds in good yields (Table 4, entries 1-18). The results demonstrated that substituted benzaldehydes carrying either electron-withdrawing or electron-donating substituents reacted successfully to give the corresponding 2-amino-3-cyano-4*H*-pyrans (Table 4, entries 2-14). The results also indicated that the substituent in the *para*-position led to a higher yield than the same substituent in the *ortho*- or *meta*-position (Table 4, entry 6 *vs* entries 4-5; entry 9 *vs* entries 7-8; entry 12 *vs* entries 10-11). To our surprise, successful reactions also occurred for poly-substituted benzaldehydes such as 2,3-dichlorobenzaldehyde and 2-bromo-5-methoxybenzaldehyde to give the target products, without any steric hindrances from the substituents of the benzene ring (Table 4, entries 17-18). These results indicated the wide applicability of this protocol in 2-amino-3-cyano-4*H*-pyran derivatives preparation.

Table 4. Mechano-biocatalytic three-component reaction of aromatic aldehyde, malononitrile and 3-(dimethylamino)phenol[a]



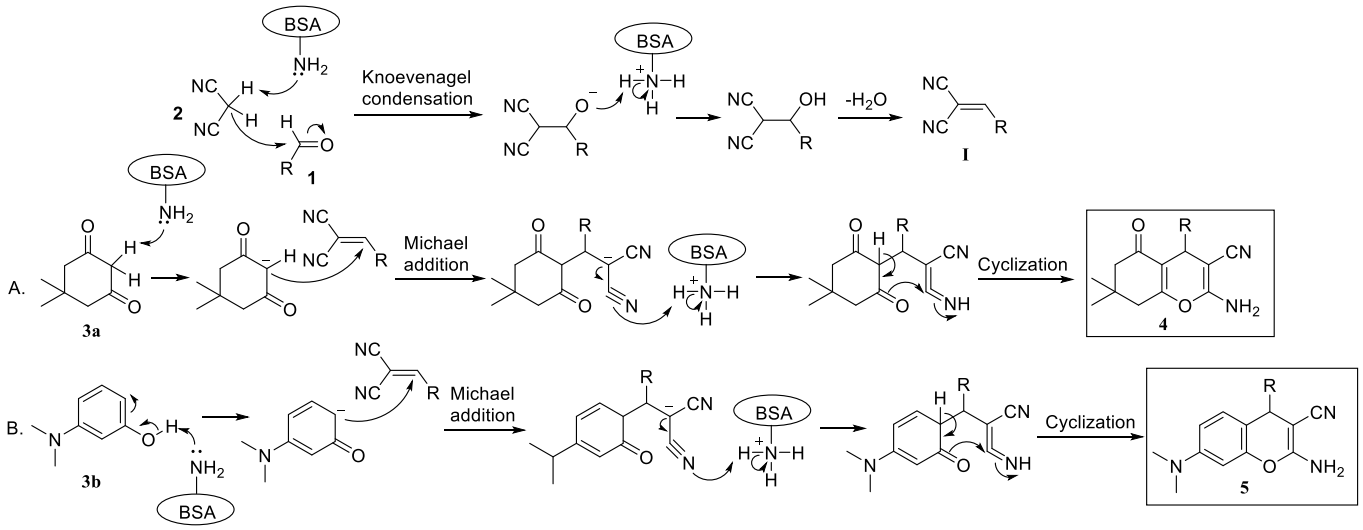
1 **2** **3b** **5**

Entry	R	Product	Yield (%)[b]
1	C_6H_5	**5a**	82
2	3-$NO_2C_6H_4$	**5b**	86
3	4-$NO_2C_6H_4$	**5c**	88
4	2-FC_6H_4	**4d**	83
5	3-FC_6H_4	**5e**	82
6	4-FC_6H_4	**5f**	86
7	2-MeC_6H_4	**5g**	80
8	3-MeC_6H_4	**5h**	89
9	4-MeC_6H_4	**5i**	90
10	2-$MeOC_6H_4$	**5j**	84
11	3-$MeOC_6H_4$	**5k**	87
12	4-$MeOC_6H_4$	**5l**	89
13	4-BrC_6H_4	**5m**	89
14	4-CNC_6H_4	**5n**	87
15	2-Furyl	**5o**	83
16	2-Thienyl	**5p**	81
17	2,3-$Cl_2C_6H_3$	**5q**	87

18	2-Br-5-MeOC$_6$H$_3$	**5r**	93

[a] Reaction conditions: aldehyde (**1**, 0.5 mmol), malononitrile (**2**, 0.5 mmol), 3-(dimethylamino)phenol (**3b**, 0.5 mmol), BSA (80 mg) and NaCl (300 mg) were placed in a 50 mL stainless steel grinding jar along with three stainless steel grinding balls (diameter 10 mm) and milled at 30 Hz for 40 min. [b] Isolated yields.

Based on the above-mentioned experimental results and the widely accepted viewpoint that the basic character of the amino group present in the side chain of some amino acid residues, especially the lysine residue, is responsible for its catalytic activity,[17] a plausible mechanism is proposed in Scheme 2. Firstly, an –NH_2 group on BSA promotes the Knoevenagel condensation of the aldehyde with malononitrile to produce the intermediate **I**. At the same time, dimedone **3a** or 3-(dimethylamino)phenol **3b** was activated by the –NH_2 on BSA to form a carbon anion. Then Michael addition and intramolecular cyclization occurred in turn to give the 2-amino-3-cyano-4*H*-pyran derivatives **4** or **5**.



Scheme 2. Plausible mechanism for the BSA-catalyzed synthesis of 2-amino-3-cyano-4*H*-pyran derivatives

In summary, we have developed a novel mechano-biocatalytic protocol for the rapid synthesis of 2-amino-3-cyano-4*H*-pyran derivatives *via* three-component reaction using bovine serum albumin (BSA) as the catalyst under solvent-free ball-milling conditions. The key factors influencing the reactions were studied, such as the kinds and amount of catalysts, grinding auxiliary, grinding frequency and reaction time. The advantages of this method are mild reaction conditions, easy and clean work-up, short reaction times, environmental friendliness and wide applicability. Further studies on improving its enantioselectivity by catalyst structural modification are still in progress in our lab.

EXPERIMENTAL

General. Melting points were determined with an Optimelt MPA100 melting point apparatus, and uncorrected. NMR spectra were recorded on a Bruker AVANCE III 400 spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) or Bruker AVANCE III 500 spectrometer (500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR) using DMSO-d_6 with tetramethylsilane (TMS) as the internal standard. Mass spectra were measured by a Bruker micrOTOF-Q II spectrometer with ESI.

Materials. Bovine serum albumin was purchased from Aladdin Chemicals. Lipozyme® RM IM (lipase from *Rhizomucor miehei* immobilized on macroporous anion exchange resin) was purchased from Novozyme. Unless otherwise noted, all the reagents were obtained from Shanghai Macklin Biochemical Co., Ltd. and used without further purification.

General procedure for the synthesis of 2-amino-3-cyano-4*H*-pyran derivatives. A mixture of aromatic aldehyde (0.5 mmol), malononitrile (0.5 mmol), dimedone (0.5 mmol) or 3-(dimethylamino)phenol (0.5 mmol), NaCl (300 mg) and BSA (50 mg for reactions with dimedone as substrate **3**, 80 mg for reactions with 3-(dimethylamino)phenol as substrate **3**) was milled for 40 min at 30 Hz in a Retsch MM 400 Mixer Mill (MM 400, Retsch, Germany) using a 50 mL stainless steel grinding jar with three stainless steel grinding balls (ø = 1 cm). After the milling was stopped, the reaction mixture was washed with EtOAc (10 mL), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with petroleum ether/EtOAc (2~4:1, v/v) as the eluent to afford the title compounds. All title compounds were characterized by ^{1}H NMR, ^{13}C NMR and ESI-MS.

2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4a**). White solid; mp 222-223 ℃. IR(KBr): 3398.0, 3317.5, 3214.5, 2966.5, 2203.4, 1668.9, 1604.5, 1372.6, 1214.8, 1140.8, 1031.3, 699.6 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29 (t, *J* = 7.4 Hz, 2H), 7.17 (dd, *J* = 20.2, 7.3 Hz, 3H), 7.01 (s, 2H), 4.18 (s, 1H), 2.49 (d, *J* = 12.1 Hz, 2H), 2.26 (d, *J* = 16.1 Hz, 1H), 2.11 (d, *J* = 16.1 Hz, 1H), 1.05 (s, 3H), 0.96 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 196.12, 162.96, 158.94, 145.21, 128.80, 127.61, 127.03, 120.20, 113.19, 58.75, 50.44, 36.04, 27.27. HRMS (ESI) *m/z* calcd for $C_{18}H_{18}N_2O_2Na$ $[M+Na]^+$: 317.126, found: 317.127.

2-Amino-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4b**). White solid; mp 213-215 ℃. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.09 (d, *J* = 8.1 Hz, 1H), 7.98 (s, 1H), 7.65 (dt, *J* = 15.7, 7.7 Hz, 2H), 7.19 (s, 2H), 4.43 (s, 1H), 2.56 (s, 2H), 2.28 (d, *J* = 16.1 Hz, 1H), 2.12 (d, *J* = 16.1 Hz, 1H), 1.05 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 196.21, 163.62, 159.09, 148.23, 147.47, 134.65, 130.49, 122.25, 119.82, 112.24, 57.66, 50.34, 35.88, 32.31, 28.80, 27.22. MS (ESI): $[2M+Na]^+$: 701.69.

2-Amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4c**). Faint yellow solid; mp 184-185 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.18 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.19 (s, 2H), 4.37 (s, 1H), 2.55 (d, *J* = 3.1 Hz, 2H), 2.27 (d, *J* = 16.1 Hz, 1H), 2.12 (d, *J* = 16.1 Hz, 1H), 1.05 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 196.14, 163.56, 159.04, 152.74, 146.73, 129.08, 124.13, 119.77, 112.20, 60.22, 57.45, 50.33, 36.12, 32.30, 28.73, 27.41, 21.23, 14.55. MS (ESI): $[2M+Na]^+$: 701.73.

2-Amino-4-(2-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4d**). Yellow solid; mp 237-239 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.28 – 7.09 (m, 4H), 7.06 (s, 2H), 4.45 (s, 1H), 2.60 – 2.50 (m, 2H), 2.27 (d, *J* = 16.1 Hz, 1H), 2.09 (d, *J* = 16.1 Hz, 1H), 1.05 (s, 3H), 0.97 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 196.05, 163.58, 161.62, 159.21, 131.72, 130.12, 129.08, 124.88, 119.98, 115.99, 115.77, 111.82, 57.14, 50.35, 32.27, 30.29, 28.96, 27.06. MS (ESI): $[2M+Na]^+$: 647.81.

2-Amino-4-(3-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4e**). Yellow solid; mp 211-212 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.18 (dd, *J* = 8.7, 5.6 Hz, 2H), 7.11 (t, *J* = 8.8 Hz, 2H), 7.05 (s, 2H), 4.20 (s, 1H), 2.51 (s, 2H), 2.25 (d, *J* = 16.1 Hz, 2H), 2.11 (d, *J* = 16.1 Hz, 2H), 1.04 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.16, 163.28, 161.39, 158.99, 148.18, 130.79, 123.71, 120.00, 114.44, 113.97, 112.62, 58.14, 50.40, 35.78, 32.29, 28.72, 27.39. MS (ESI): $[2M+Na]^+$: 647.72.

2-Amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4f**). White solid; mp 189-191 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.35 (dd, *J* = 14.1, 7.9 Hz, 1H), 7.09 (s, 2H), 7.06 – 6.98 (m, 2H), 6.96 – 6.92 (m, 1H), 4.23 (s, 1H), 2.53 (d, *J* = 2.8 Hz, 2H), 2.26 (d, *J* = 16.0 Hz, 1H), 2.14 (d, *J* = 16.0 Hz, 1H), 1.04 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.14, 162.94, 162.55, 160.14, 158.93, 141.39, 129.55, 129.46, 120.10, 115.59, 115.38, 113.05, 58.52, 50.42, 35.37, 32.27, 28.80, 27.31. MS (ESI): $[2M+Na]^+$: 647.75.

2-Amino-7,7-dimethyl-5-oxo-4-(*o*-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4g**). White solid; mp 208-210 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.12 (dd, *J* = 14.5, 7.1 Hz, 2H), 7.05 (td, *J* = 7.4, 1.3 Hz, 1H), 6.96 (s, 2H), 6.94 (s, 1H), 4.47 (s, 1H), 2.53 (d, *J* = 7.5 Hz, 2H), 2.47 (s, 3H), 2.25 (d, *J* = 16.1 Hz, 1H), 2.08 (d, *J* = 16.1 Hz, 1H), 1.05 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.25, 162.98, 158.74, 144.05, 135.22, 130.36, 127.74, 126.86, 126.66, 120.24, 113.92, 58.67, 50.40, 32.35, 31.37, 28.90, 27.25, 19.56. MS (ESI): $[2M+Na]^+$: 639.81.

2-Amino-7,7-dimethyl-5-oxo-4-(*m*-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4h**). White solid; mp 207-208 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.17 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 7.0 Hz, 3H), 6.95 – 6.89 (m, 2H), 4.12 (s, 1H), 2.52 (s, 2H), 2.27 (s, 3H), 2.24 (s, 1H), 2.11 (d, *J* = 16.1 Hz, 1H), 1.05

(s, 3H), 0.97 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.11, 162.90, 158.90, 145.19, 137.76, 128.71, 128.17, 127.72, 124.76, 120.22, 113.22, 58.84, 50.45, 35.95, 32.31, 28.89, 27.21, 21.56. MS (ESI): $[2M+Na]^+$: 639.79.

2-Amino-7,7-dimethyl-5-oxo-4-(*p*-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4i**). White solid; mp 218-220 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.09 (d, *J* = 7.9 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.98 (s, 2H), 4.12 (s, 1H), 2.51 (d, *J* = 1.4 Hz, 2H), 2.25 (s, 3H), 2.23 (s, 1H), 2.09 (d, *J* = 16.1 Hz, 1H), 1.04 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.09, 162.74, 158.88, 142.29, 136.07, 129.34, 127.54, 120.23, 113.32, 58.87, 50.45, 35.64, 32.27, 28.89, 27.22, 21.07. MS (ESI): $[2M+Na]^+$: 639.81.

2-Amino-4-(2-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4j**). Yellow solid; mp 200-202 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.12 (t, *J* = 7.0 Hz, 1H), 6.93 (dd, *J* = 16.7, 7.0 Hz, 2H), 6.82 (d, *J* = 7.4 Hz, 1H), 6.79 (s, 2H), 4.44 (s, 1H), 3.71 (s, 3H), 2.49 (s, 1H), 2.41 (d, *J* = 17.6 Hz, 1H), 2.21 (d, *J* = 16.1 Hz, 1H), 2.03 (d, *J* = 16.1 Hz, 1H), 1.01 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.04, 163.56, 159.45, 157.27, 132.61, 129.01, 128.26, 120.78, 120.32, 112.33, 111.91, 57.79, 56.06, 50.50, 32.25, 30.79, 29.09, 27.00. MS (ESI): $[2M+Na]^+$: 671.79.

2-Amino-4-(3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4k**). White solid; mp 193-195 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 (t, *J* = 7.9 Hz, 1H), 7.01 (s, 2H), 6.77 (dd, *J* = 8.1, 2.3 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 6.66 (d, *J* = 1.9 Hz, 1H), 4.15 (s, 1H), 3.72 (s, 3H), 2.52 (s, 2H), 2.26 (d, *J* = 15.9 Hz, 1H), 2.12 (d, *J* = 16.1 Hz, 1H), 1.04 (s, 3H), 0.98 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 196.10, 163.04, 159.66, 158.95, 146.78, 129.90, 120.16, 119.79, 113.70, 113.05, 111.91, 60.23, 58.67, 55.38, 50.44, 35.93, 32.27, 28.91, 27.23. MS (ESI): $[2M+Na]^+$: 671.75.

2-Amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4l**). White solid; mp 202-204 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.05 (d, *J* = 8.6 Hz, 2H), 6.97 (s, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.12 (s, 1H), 3.72 (s, 3H), 2.51 (s, 2H), 2.25 (d, *J* = 16.1 Hz, 1H), 2.09 (d, *J* = 16.1 Hz, 1H), 1.04 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.12, 162.59, 158.86, 158.36, 137.31, 128.68, 120.28, 114.13, 113.44, 58.99, 55.45, 50.47, 35.22, 32.26, 28.89, 27.23. MS (ESI): $[2M+Na]^+$: 671.76.

2-Amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4m**). Faint yellow solid; mp 201-203 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, *J* = 8.3 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.04 (s, 2H), 4.14 (s, 1H), 2.47 (s, 2H), 2.21 (d, *J* = 16.1 Hz, 1H), 2.07 (d, *J* = 16.0 Hz, 1H), 1.00 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.15, 163.09, 158.92, 144.65, 131.67, 129.98, 120.07, 120.03, 112.70, 58.11, 50.39, 35.65, 32.28, 28.78, 27.32. MS (ESI): $[2M+Na]^+$: 768.52.

2-Amino-4-(4-cyanophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4n**). White solid; mp 225-228 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.16 (s, 2H), 4.30 (s, 1H), 2.53 (s, 2H), 2.26 (d, *J* = 16.0 Hz, 1H), 2.12 (d, *J* = 16.0 Hz, 1H), 1.04 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.16, 163.55, 159.02, 150.71, 132.88, 128.81, 119.85, 119.25, 112.20, 109.90, 57.56, 50.33, 36.28, 32.30, 28.71, 27.42. MS (ESI): $[2M+Na]^+$: 661.83.

2-Amino-4-(furan-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4o**). Yellow solid; mp 226-228 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 (s, 1H), 7.15 (s, 2H), 6.39 (s, 1H), 6.12 (s, 1H), 4.39 (s, 1H), 2.57 (s, 2H), 2.35 (d, *J* = 16.1 Hz, 1H), 2.23 (d, *J* = 16.1 Hz, 1H), 1.11 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 195.89, 163.73, 159.76, 156.17, 142.22, 120.03, 110.91, 110.81, 105.52, 55.82, 50.35, 32.29, 29.45, 28.90, 27.02. MS (ESI): $[2M+Na]^+$: 591.77.

2-Amino-7,7-dimethyl-5-oxo-4-(thiophen-2-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4p**). White solid; mp 227-230 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.27 (d, *J* = 4.9 Hz, 1H), 7.09 (s, 2H), 6.86 (dd, *J* = 4.9, 3.6 Hz, 1H), 6.81 (d, *J* = 3.1 Hz, 1H), 4.48 (s, 1H), 2.50 (d, *J* = 17.7 Hz, 1H), 2.38 (d, *J* = 17.7 Hz, 1H), 2.26 (d, *J* = 16.2 Hz, 1H), 2.10 (d, *J* = 16.2 Hz, 1H), 1.00 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.00, 162.96, 159.35, 149.74, 127.27, 124.89, 124.46, 120.08, 113.36, 58.48, 50.32, 32.23, 30.87, 29.10, 26.92. MS (ESI): $[2M+Na]^+$: 623.73.

2-Amino-4-(2,3-dichlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4q**). Yellow solid; mp 231-233 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.21 – 7.15 (m, 1H), 7.13 (s, 2H), 4.78 (s, 1H), 2.53 (d, *J* = 4.0 Hz, 2H), 2.25 (d, *J* = 16.0 Hz, 1H), 2.09 (d, *J* = 16.0 Hz, 1H), 1.05 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.12, 163.79, 159.16, 132.25, 130.65, 129.25, 128.74, 119.58, 112.10, 56.79, 50.34, 32.27, 28.78, 27.44. MS (ESI): $[2M+Na]^+$: 748.73.

2-Amino-4-(2-bromo-5-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4r**). Faint yellow solid; mp 184-186 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, *J* = 8.8 Hz, 1H), 7.10 (s, 2H), 6.82 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.66 (d, *J* = 2.5 Hz, 1H), 4.70 (s, 1H), 3.76 (s, 3H), 2.59 (s, 2H), 2.31 (d, *J* = 16.0 Hz, 1H), 2.16 (d, *J* = 16.0 Hz, 1H), 1.11 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 195.96, 163.58, 159.38, 159.03, 133.79, 119.54, 114.25, 113.63, 112.42, 57.43, 55.74, 50.39, 32.25, 28.88, 27.34. MS (ESI): $[2M+Na]^+$: 828.75.

2-Amino-4-(2,5-dimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4s**). Faint yellow solid; mp 211-213 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.88 (d, *J* = 8.9 Hz, 1H), 6.86 (s, 2H), 6.73 (dd, *J* = 8.9, 3.1 Hz, 1H), 6.51 (d, *J* = 3.0 Hz, 1H), 4.44 (s, 1H), 3.70 (s, 3H), 3.65 (s, 3H), 2.55 (d, *J* = 17.7 Hz, 1H), 2.45 (d, *J* = 17.6 Hz, 1H), 2.26 (d, *J* = 16.1 Hz, 1H), 2.07 (d, *J* = 16.1 Hz, 1H),

1.04 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.03, 163.63, 159.40, 153.53, 151.48, 133.93, 120.25, 115.27, 113.08, 112.22, 111.97, 57.70, 56.72, 55.64, 50.46, 32.25, 30.74, 29.13, 26.93. MS (ESI): $[2M+Na]^+$: 731.11.

2-Amino-7-(dimethylamino)-4-phenyl-4*H*-chromene-3-carbonitrile (**5a**). Yellow solid; mp 201-203 ℃. IR(KBr): 3456.0, 3324.0, 3198.4, 2190.5, 1649.5, 1520.7, 1404.8, 1263.1, 1115.0, 1044.2, 818.8, 702.8 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30 (t, *J* = 7.5 Hz, 2H), 7.18 (dd, *J* = 16.3, 7.3 Hz, 3H), 6.83 (s, 2H), 6.79 (d, *J* = 8.6 Hz, 1H), 6.45 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.24 (d, *J* = 2.4 Hz, 1H), 4.60 (s, 1H), 2.86 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.85, 150.65, 149.42, 147.09, 129.91, 128.98, 127.82, 126.99, 121.31, 110.94, 109.85, 98.96, 56.79. HRMS (ESI) *m/z* calcd for $C_{18}H_{17}N_3ONa$ $[M+Na]^+$: 314.1264, found: 314.1257.

2-Amino-7-(dimethylamino)-4-(3-nitrophenyl)-4*H*-chromene-3-carbonitrile (**5b**). Orange solid; mp 196-198 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 – 8.07 (m, 1H), 8.02 (s, 1H), 7.65 (dt, *J* = 15.4, 7.7 Hz, 2H), 7.00 (s, 2H), 6.83 (d, *J* = 8.7 Hz, 1H), 6.47 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.26 (d, *J* = 2.5 Hz, 1H), 4.89 (s, 1H), 2.87 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.09, 150.90, 149.47, 149.37, 148.38, 134.76, 130.76, 129.93, 122.23, 122.17, 120.99, 109.99, 109.61, 98.98, 55.89. MS (ESI): $[2M+Na]^+$: 695.62.

2-Amino-7-(dimethylamino)-4-(4-nitrophenyl)-4*H*-chromene-3-carbonitrile (**5c**). Yellow solid; mp 186-188 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.01 (s, 2H), 6.79 (d, *J* = 8.7 Hz, 1H), 6.52 – 6.42 (m, 1H), 6.26 (d, *J* = 2.4 Hz, 1H), 4.84 (s, 1H), 2.87 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.03, 154.56, 150.93, 149.45, 146.68, 129.92, 129.12, 124.43, 120.97, 109.96, 109.38, 99.00, 55.65. MS (ESI): $[2M+Na]^+$: 695.66.

2-Amino-7-(dimethylamino)-4-(2-fluorophenyl)-4*H*-chromene-3-carbonitrile (**5d**). Purple solid; mp 207-209 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32 – 7.23 (m, 1H), 7.15 (dt, *J* = 12.5, 6.7 Hz, 3H), 6.88 (s, 2H), 6.78 (d, *J* = 8.6 Hz, 1H), 6.46 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.24 (d, *J* = 2.5 Hz, 1H), 4.88 (s, 1H), 2.86 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.47, 160.17, 158.04, 149.72, 148.59, 132.32, 129.17, 128.38, 128.11, 124.07, 120.00, 115.13, 108.77, 108.58, 97.90, 54.06, 33.53. MS (ESI): $[2M+Na]^+$: 641.72.

2-Amino-7-(dimethylamino)-4-(3-fluorophenyl)-4*H*-chromene-3-carbonitrile (**5e**). Orange solid; mp 144-146 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 (dd, *J* = 14.1, 7.9 Hz, 1H), 7.07 – 6.94 (m, 3H), 6.91 (s, 2H), 6.82 (d, *J* = 8.7 Hz, 1H), 6.46 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.24 (d, *J* = 2.5 Hz, 1H), 4.67 (s, 1H), 2.86 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.91, 161.48, 160.98, 150.77, 150.07, 149.40, 131.04, 129.85, 123.89, 121.16, 114.54, 113.94, 110.20, 109.88, 98.96, 56.20. MS (ESI): $[2M+Na]^+$: 641.74.

2-Amino-7-(dimethylamino)-4-(4-fluorophenyl)-4*H*-chromene-3-carbonitrile (**5f**). Yellow solid; mp 141-142 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24 – 7.16 (m, 2H), 7.12 (t, *J* = 8.8 Hz, 2H), 6.87 (s, 2H), 6.77 (d, *J* = 8.7 Hz, 1H), 6.46 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.24 (d, *J* = 2.4 Hz, 1H), 4.64 (s, 1H), 2.86 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.57, 160.80, 160.16, 150.69, 149.38, 143.30, 143.27, 129.90, 129.71, 129.63, 121.23, 115.79, 115.58, 110.69, 109.88, 98.95, 56.71. MS (ESI): $[2M+Na]^+$: 641.69.

2-Amino-7-(dimethylamino)-4-(*o*-tolyl)-4*H*-chromene-3-carbonitrile (**5g**). Yellow solid; mp 177-179 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19 – 7.04 (m, 3H), 6.97 (d, *J* = 7.2 Hz, 1H), 6.77 (s, 2H), 6.63 (d, *J* = 8.7 Hz, 1H), 6.43 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.24 (d, *J* = 2.4 Hz, 1H), 4.89 (s, 1H), 2.86 (s, 6H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.56, 150.62, 149.67, 144.70, 135.28, 131.09, 129.67, 126.87, 126.78, 121.21, 110.66, 109.84, 98.81, 56.56, 37.19, 19.51. MS (ESI): $[2M+Na]^+$: 633.73.

2-Amino-7-(dimethylamino)-4-(*m*-tolyl)-4*H*-chromene-3-carbonitrile (**5h**). Yellow solid; mp 174-176 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18 (t, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 1.6 Hz, 2H), 6.81 (s, 2H), 6.78 (d, *J* = 8.7 Hz, 1H), 6.45 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.23 (d, *J* = 2.5 Hz, 1H), 4.55 (s, 1H), 2.86 (s, 6H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.82, 150.61, 149.39, 147.07, 138.02, 129.91, 128.86, 128.31, 127.71, 125.05, 121.32, 111.00, 109.83, 98.97, 56.89, 21.57. MS (ESI): $[2M+Na]^+$: 633.71.

2-Amino-7-(dimethylamino)-4-(*p*-tolyl)-4*H*-chromene-3-carbonitrile (**5i**). Faint yellow solid; mp 164-166 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.10 (d, *J* = 7.9 Hz, 2H), 7.04 (d, *J* = 7.9 Hz, 2H), 6.79 (s, 2H), 6.76 (d, *J* = 8.7 Hz, 1H), 6.44 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.22 (d, *J* = 2.5 Hz, 1H), 4.55 (s, 1H), 2.86 (s, 6H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.66, 149.52, 148.30, 143.06, 134.95, 128.84, 128.44, 126.68, 120.24, 110.03, 108.74, 97.87, 55.88, 19.99. MS (ESI): $[2M+Na]^+$: 633.73.

2-Amino-7-(dimethylamino)-4-(2-methoxyphenyl)-4*H*-chromene-3-carbonitrile (**5j**). Yellow solid; mp 196-198 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.22 – 7.13 (m, 1H), 7.03 – 6.94 (m, 2H), 6.91 – 6.82 (m, 2H), 6.76 (s, 2H), 6.42 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.22 (d, *J* = 2.5 Hz, 1H), 4.99 (s, 1H), 3.80 (s, 3H), 2.84 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.55, 156.71, 150.55, 149.72, 134.78, 129.24, 128.95, 128.21, 121.18, 111.90, 111.33, 109.75, 99.00, 56.10, 55.83, 33.62. MS (ESI): $[2M+Na]^+$: 665.72.

2-Amino-7-(dimethylamino)-4-(3-methoxyphenyl)-4*H*-chromene-3-carbonitrile (**5k**). Yellow solid; mp 164-166 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 (t, *J* = 7.9 Hz, 1H), 6.83 (s, 2H), 6.81 (s, 1H), 6.77 (dd, *J* = 7.4, 2.0 Hz, 1H), 6.75 – 6.70 (m, 2H), 6.45 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.23 (d, *J* = 2.5 Hz, 1H), 4.57 (s, 1H), 3.72 (s, 3H), 2.86 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.91, 159.76, 150.66, 149.39, 148.69, 130.11, 129.85, 121.30, 120.05, 113.95, 111.81, 110.81, 109.82, 98.96, 56.65, 55.42. MS (ESI): $[2M+Na]^+$: 665.75.

2-Amino-7-(dimethylamino)-4-(4-methoxyphenyl)-4*H*-chromene-3-carbonitrile (**5l**). Yellow solid; mp 180-182 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.07 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.77 (s, 2H), 6.74 (s, 1H), 6.45 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.22 (d, *J* = 2.4 Hz, 1H), 4.54 (s, 1H), 3.71 (s, 3H), 2.85 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.57, 157.27, 149.50, 148.26, 138.12, 128.85, 127.78, 120.25, 113.24, 110.20, 108.76, 97.86, 56.06, 54.40. MS (ESI): $[2M+Na]^+$: 665.74.

2-Amino-4-(4-bromophenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (**5m**). Yellow solid; mp 211-213 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, *J* = 8.3 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.88 (s, 2H), 6.77 (d, *J* = 8.7 Hz, 1H), 6.46 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.23 (d, *J* = 2.5 Hz, 1H), 4.63 (s, 1H), 2.86 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.76, 149.67, 148.31, 145.40, 131.11, 130.80, 129.03, 128.81, 120.06, 119.00, 109.17, 108.82, 97.87, 55.25. MS (ESI): $[2M+Na]^+$: 762.59.

2-Amino-4-(4-cyanophenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (**5n**). Orange solid; mp 175-177 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 6.97 (s, 2H), 6.78 (d, *J* = 8.7 Hz, 1H), 6.46 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.25 (d, *J* = 2.5 Hz, 1H), 4.76 (s, 1H), 2.87 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.05, 152.52, 150.89, 149.48, 133.11, 129.87, 128.88, 121.00, 119.27, 109.94, 109.87, 109.57, 98.99, 55.77. MS (ESI): $[2M+Na]^+$: 655.73.

2-Amino-7-(dimethylamino)-4-(furan-2-yl)-4*H*-chromene-3-carbonitrile (**5o**). Red solid; mp 178-180 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, *J* = 0.8 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 1H), 6.90 (s, 2H), 6.50 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.34 (dd, *J* = 3.0, 1.9 Hz, 1H), 6.22 (d, *J* = 2.4 Hz, 1H), 6.13 (d, *J* = 3.1 Hz, 1H), 4.74 (s, 1H), 2.87 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.46, 156.61, 149.88, 148.63, 141.67, 128.47, 120.00, 109.64, 108.59, 107.10, 104.73, 98.03, 52.59, 33.00. MS (ESI): $[2M+Na]^+$: 585.73.

2-Amino-7-(dimethylamino)-4-(thiophen-2-yl)-4*H*-chromene-3-carbonitrile (**5p**). Purple solid; mp 176-178 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36 – 7.30 (m, 1H), 7.00 – 6.93 (m, 3H), 6.92 (s, 2H), 6.49 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.21 (d, *J* = 2.5 Hz, 1H), 4.96 (s, 1H), 2.86 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.82, 151.26, 149.76, 148.03, 128.77, 126.05, 124.29, 123.25, 120.07, 109.54, 108.69, 97.82, 55.94, 34.57. MS (ESI): $[2M+Na]^+$: 617.71.

2-Amino-4-(2,3-dichlorophenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (**5q**). White solid; mp 210-211 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 6.96 (s, 2H), 6.72 (d, *J* = 8.7 Hz, 1H), 6.45 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.24 (d, *J* = 2.5 Hz, 1H), 5.21 (s, 1H), 2.87 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.11, 149.86, 148.52, 145.09, 131.48, 129.31, 128.88, 128.40, 128.07, 127.96, 119.73, 108.82, 107.94, 97.82, 53.95. MS (ESI): $[2M+Na]^+$: 742.50.

2-Amino-4-(2-bromo-5-methoxyphenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile (**5r**). Yellow solid; mp 203-205 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, *J* = 8.8 Hz, 1H), 6.90 (s, 2H), 6.81 (dd, *J* = 8.8, 3.1 Hz, 1H), 6.75 (d, *J* = 8.7 Hz, 1H), 6.65 (s, 1H), 6.45 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.23 (d, *J* = 2.5 Hz, 1H), 5.06 (s, 1H), 3.69 (s, 3H), 2.86 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.08, 158.38, 149.76, 148.34, 133.03, 127.98, 119.76, 116.21, 113.36, 112.09, 108.77, 108.48, 97.84, 54.72, 54.42. MS (ESI): $[2M+Na]^+$: 822.65.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (No. 21706236) and China Postdoctoral Science Foundation funded project (No. 2016M592012).

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