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$Ca(OH)_2$-mediated efficient synthesis of 2-amino-5-hydroxy-4*H*-chromene derivatives with various substituents

Srinivasa Rao Kolla, Yong Rok Lee *

School of Chemical Engineering and Technology, Yeungnam University, Gyeongsan 712-749, Republic of Korea

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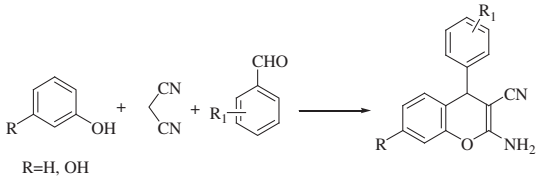
ABSTRACT

A variety of novel 2-amino-5-hydroxy-4*H*-chromene derivatives with various substituents on the 4*H*-chromene ring were efficiently synthesized by one-pot reactions of substituted resorcinols and various 2-benzylidenemalononitriles in the presence of calcium hydroxide in methanol at room temperature. This simple method provided 2-amino-5-hydroxy-4*H*-chromenes with high yields under mild reaction conditions.

1. Introduction

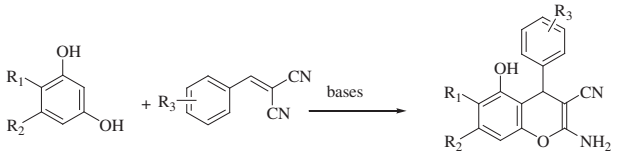
2-Amino-4*H*-chromenes are important heterocyclic compounds[1] with a number of biological and pharmacological properties including anti-microbial,[2] anti-viral,[3,4] anti-proliferative,[5] anti-tumor,[6] and anti-cancer[7] activities. They have also been widely employed as cosmetics, pigments,[8] and potent biodegradable agrochemicals.[9] In particular, derivatives, such as HA 14-1 and MX58151, with proapoptotic activity, are being developed as anti-cancer agents.[10,11]

2-Amino-4*H*-chromenes are generally synthesized by reactions of phenol or resorcinol with malononitrile and arylaldehydes (Scheme 1). Basic alumina,[12] piperidine,[13] morpholine,[14] cetyltrimethylammonium chloride,[15] [bmim]OH,[16] K_2CO_3/microwave,[17] DBU/microwave,[18] and chitosan[19] have been used for these reactions as catalytic and stoichiometric reagents. Interestingly, reactions of resorcinol with malononitrile and arylaldehydes afforded 2-amino-7-hydroxy-4*H*-chromene derivatives as sole products without requiring isolation of expected 2-amino-5-hydroxy-4*H*-chromene derivatives. In these cases, resorcinol reacted with malononitrile and arylaldehydes at the position 6 rather than at the position 2 under above described conditions and further cyclized to give 2-amino-7-hydroxy-4*H*-chromenes regioselectively, probably due to steric hindrance between two hydroxyl groups in a *meta*-disubstituted compound.



Scheme 1.

Although several syntheses of 2-amino-4*H*-chromenes from phenol or resorcinol have been described, reactions employing substituted resorcinols have not previously been reported. This work reports reactions between resorcinols with various substituents and 2-benzylidenemalononitriles in the presence of several bases (Scheme 2). A variety of 2-amino-5-hydroxy-4*H*-chromene derivatives with various substituents on the 4*H*-chromene ring were easily and efficiently synthesized.



Scheme 2.

2. Results and discussion

To give a variety of 2-amino-5-hydroxy-4*H*-chromene derivatives, reactions of readily available resorcinols with substituents of

* Corresponding author. Tel.: +82 53 810 2529; fax: +82 53 810 4631; e-mail address: yrlee@yu.ac.kr (Y.R. Lee).

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electron-withdrawing groups were investigated. The reaction of 2,4-dihydroxy acetophenone (**1a**) with 2-benzylidenemalononitrile **2a** under several bases was first attempted based on reported reactions of resorcinol with malononitrile and benzaldehyde in the presence of several bases (Table 1). 1 equiv of triethylamine, piperidine, morpholine, ethylenediamine, or DBU as organic bases for 12 h in methanol at room temperature did not result in the desired products (entries 1–5). Using KOH as an inorganic base resulted in no products (entry 6). $Ca(OH)_2$ in several solvents resulted in the desired product **3a**. Reaction using 20 mo% of $Ca(OH)_2$ in methanol at room temperature for 20 h produced **3a** in 55% yield (entry 7). Interestingly, despite low solubility of $Ca(OH)_2$ in alcohol, 1 equiv of $Ca(OH)_2$ in methanol at room temperature for 3 h increased the yield of **3a** to 80% (entry 8). It has been reported by other group that $Ca(OH)_2$ is an important metal reagent and a useful promoter in the aldol-type reaction of phenolic enolates of resorcinols with benzaldehyde in methanol.[20] Other polar solvents, EtOH and H_2O, produced **3a** in 61 and 51% yield, respectively (entries 9 and 10). Importantly, in these reactions, only **3a** was formed and the expected 2-amino-7-hydroxy-4*H*-chromene as a regioisomer was not produced. The structure of compound **3a** was determined by ^1H NMR analysis. The spectrum of **3a** showed a characteristic peak of methine on the chromene ring at δ 4.65 as a singlet and a methyl peak of an acetyl group appeared at δ 2.58 as a singlet. The compound was further identified by AB coupling constants of aromatic protons on the 4H-chromene ring at δ 7.90 (J=8.7 Hz) and δ 6.72 (J=8.7 Hz). The ^{13}C NMR spectrum showed a characteristic tertiary carbon peak with a methine proton at δ 36.1 and a carbonyl carbon peak at δ 204.4.

reaction quickly produced 2-amino-5-hydroxy-4*H*-chromene derivatives **3b**–**k** with various substituents on the benzene ring. Unsubstituted resorcinol **1f** produced **3l** in 90% yield (entry 11).

The formation of product **3a** can be explained by comparing with previously described mechanism as shown in Scheme 3.[21] The regioselectivity of **3a** may be determined by the deactivation of the *o*-hydroxy group of **1a** by intramolecular hydrogen bonding to neighboring carbonyl group. The more reactive proton of the 4-hydroxy group of **1a** was extracted by calcium hydroxide to form an intermediate **4**, which reacted with 2-benzylidenemalononitrile (**2a**) to give **5**. Tautomerism of the intermediate **5** gave intermediate **6**, which was deprotonated by $Ca(OH)_2$ to produce **7**. Intramolecular nucleophilic addition of phenoxide to the cyano group of **7**, followed by protonation and isomerization produced **3a**.

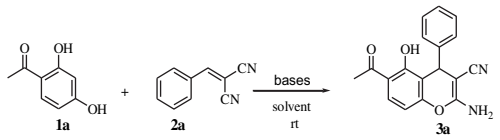
In summary, a one-pot, two-component condensation reaction of various resorcinols and substituted 2-benzylidenemalononitriles was successfully accomplished to give 2-amino-5-hydroxy-4*H*-chromene derivatives. This methodology has advantages of mild reaction conditions, simple experimentation, and high yields.

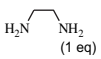
3. Experimental

3.1. General

All experiments were carried out in the methanol. Pre-coated silica gel plates (Merck, Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). ^1H and ^{13}C NMR spectra were recorded on a Varian Model VNS spectrometer in DMSO-d_6 and CD_3OD. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. HRMS spectra were recorded at the Korea Basic Science Institute on a Jeol JMS-700 spectrometer.

Table 1
Reaction of 2,4-dihydroxy acetophenone with 2-benzylidenemalononitrile under several bases



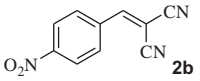
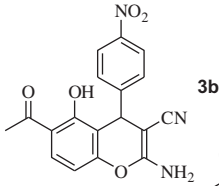
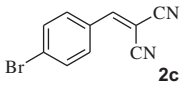
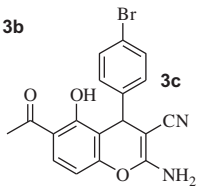
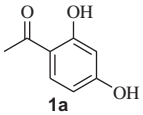
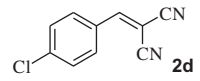
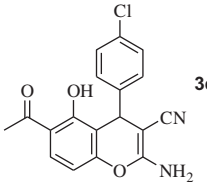
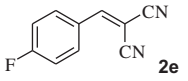
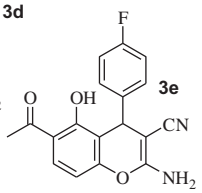
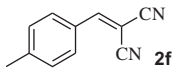
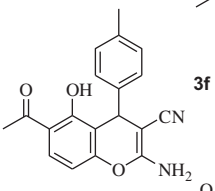
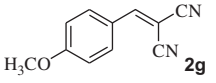
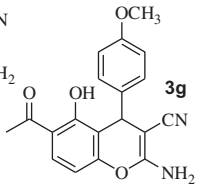
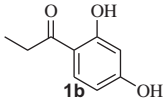
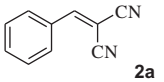
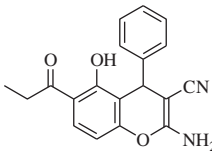
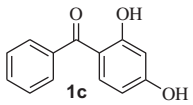
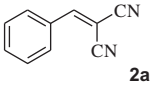
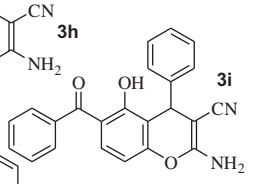
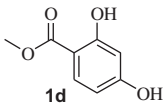
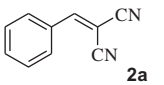
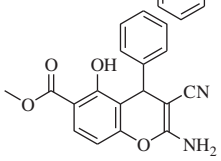
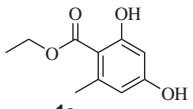
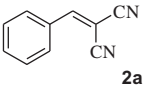
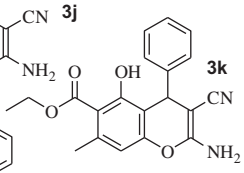
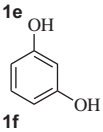
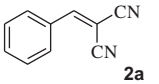
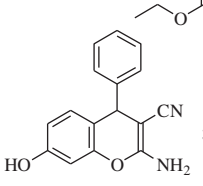
Entry	Base	Solvent	Time (h)	Yield (%)	Entry	Base	Solvent	Time (h)	Yield (%)
1	 (1 eq)	MeOH	12	0	6	KOH (1 equiv)	MeOH	12	0
2	 (1 eq)	MeOH	12	0	7	$Ca(OH)_2$ (0.2 equiv)	MeOH	20	55
3	 (1 eq)	MeOH	12	0	8	$Ca(OH)_2$ (1 equiv)	MeOH	3	80
4	 (1 eq)	MeOH	12	0	9	$Ca(OH)_2$ (1 equiv)	EtOH	4	61
5	DBU (1 equiv)	MeOH	12	0	10	$Ca(OH)_2$ (1 equiv)	H_2O	6	51

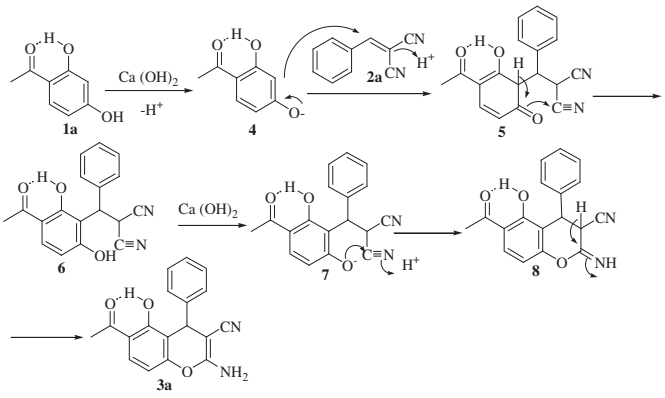
To explore the generality and scope of this methodology, additional reactions of various substituted resorcinols and 2-benzylidenemalononitriles were attempted under the optimized conditions (Table 2). Reactions of 2,4-dihydroxy acetophenone (**1a**) and 2-benzylidenemalononitriles **2b**–**e**, with electron-withdrawing groups on the benzene ring, at room temperature for 2–4 h produced **3b**–**e** in 81–87% yield (entries 1–4). Electron-donating group on the 2-benzylidenemalononitriles resulted in **3f** and **3g** in 74 and 73% yield, respectively, after reaction for 10–12 h at room temperature (entries 5 and 6). Other resorcinols, **1b** and **1c** produced **3h** and **3i** in 82 and 79%, respectively (entries 7 and 8). Resorcinols with ester groups on the benzene ring produced the expected cycloadducts **3j** and **3k** in 84 and 81% yield, respectively (entries 9 and 10). Each

3.2. General procedure for the preparation of 2-amino-3-cyano-6-acetoxy-5-hydroxy-4*H*-chromene derivatives 3a–l

A mixture of various resorcinols (1.0 mmol), substituted 2-benzylidenemalononitrile (1.5 mmol), and calcium hydroxide (1.0 mmol) in MeOH (5 mL) was stirred at room temperature until the completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane). The reaction mixture was filtered through sintered funnel

Table 2
Additional reactions for the synthesis of 2-amino-5-hydroxy-4*H*-chromene derivatives in the presence of $Ca(OH)_2$

Entry	resorcinol	malononitrile	Time (h)	Product	Yield (%)
1		 **2b**	2	 **3b**	82
2		 **2c**	4	 **3c**	87
3	 **1a**	 **2d**	2	 **3d**	81
4		 **2e**	3	 **3e**	85
5		 **2f**	10	 **3f**	74
6		 **2g**	12	 **3g**	73
7	 **1b**	 **2a**	5	 **3h**	82
8	 **1c**	 **2a**	5	 **3i**	79
9	 **1d**	 **2a**	5	 **3j**	84
10	 **1e**	 **2a**	3	 **3k**	81
11	 **1f**	 **2a**	5	 **3l**	90



Scheme 3.

and the solid was washed with ethyl acetate (10 mL) to remove excess 2-benzylidenemalononitrile. The solid containing product was dissolved in THF (30 mL) and filtered to remove remaining $Ca(OH)_2$. The THF layer was evaporated under reduced pressure and finally recrystallization with ethanol give pure white solid.

*3.2.1. 6-Acetyl-2-amino-5-hydroxy-4-phenyl-4H-chromene-3-carbonitrile (**3a**).* A mixture of 2,4-dihydroxy acetophenone **1a** (152 mg, 1.0 mmol), 2-benzylidenemalononitrile **2a** (231 mg, 1.5 mmol), and $Ca(OH)_2$ (74 mg, 1.0 mmol) in 5 mL of methanol was stirred at room temperature for 3 h. After completion of the reaction, recrystallization with ethanol gave product **3a** (245 mg, 80%) as a white solid: charred at 290 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.95 (1H, s), 7.90 (1H, d, J=8.7 Hz), 7.30–7.25 (2H, m), 7.20–7.11 (3H, m), 7.08 (2H, s,), 6.72 (1H, d, J=8.7 Hz), 4.65 (1H, s), 2.58 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 204.4, 160.1, 159.4, 153.8, 144.7, 131.8, 128.4, 127.1, 126.6, 120.0, 115.9, 111.7, 107.3, 57.2, 36.1, 26.6; IR (KBr)

3438, 3317, 3200, 2881, 2195, 1660, 1414, 1251, 1076, 824 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{18}H_{14}N_2O_3$: 306.1004. Found: 306.1008.

*3.2.2. 6-Acetyl-2-amino-5-hydroxy-4-(4-nitrophenyl)-4H-chromene-3-carbonitrile (**3b**).* A mixture of 2,4-dihydroxy acetophenone **1a** (152 mg, 1.0 mmol), 2-(4-nitrobenzylidene) malononitrile **2b** (300 mg, 1.5 mmol), and $Ca(OH)_2$ (74 mg, 1.0 mmol) in 5 mL of methanol was stirred at room temperature for 2 h. After completion of the reaction, recrystallization with ethanol gave product **3b** (288 mg, 82%) as a solid: mp 246–248 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 12.96 (1H, s), 8.16 (2H, d, *J*=8.7 Hz), 7.94 (1H, d, *J*=9.0 Hz), 7.41 (2H, d, *J*=8.7 Hz), 7.21 (2H, s), 6.75 (1H, d, *J*=9.0 Hz), 4.86 (1H, s), 2.58 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 204.6, 160.1, 159.5, 153.7, 152.1, 146.3, 132.4, 128.6, 123.8, 119.7, 116.0, 110.3, 107.5, 55.9, 36.1, 26.6; IR (KBr) 3439, 3337, 3209, 2935, 2193, 1654, 1520, 1409, 1348, 1253, 820 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{18}H_{13}N_3O_5$: 351.0855. Found: 351.0856.

*3.2.3. 6-Acetyl-2-amino-4-(4-bromophenyl)-5-hydroxy-4H-chromene-3-carbonitrile (**3c**).* A mixture of 2,4-dihydroxy acetophenone **1a** (152 mg, 1.0 mmol), 2-(4-bromobenzylidene) malononitrile **2c** (350 mg, 1.5 mmol), and $Ca(OH)_2$ (74 mg, 1.0 mmol) in 5 mL of methanol was stirred at room temperature for 4 h. After completion of the reaction, recrystallization with ethanol gave product **3c** (335 mg, 87%) as a solid: mp 283–285 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 12.94 (1H, s), 7.87 (1H, d, *J*=8.7 Hz), 7.45 (2H, d, *J*=8.1 Hz), 7.08 (2H, s), 7.07 (2H, d, *J*=8.1 Hz), 6.66 (1H, d, *J*=8.7 Hz), 4.64 (1H, s), 2.55 (3H, s); ^{13}C NMR (150 MHz, DMSO-d_6) δ 204.6, 160.5, 159.7, 153.9, 144.4, 132.3, 131.5, 129.6, 120.0, 119.9, 116.3, 111.4, 107.5, 56.9, 35.9, 26.9; IR (KBr) 3442, 3327, 3205, 2967, 2197, 1661, 1485, 1410, 1253, 1075, 820 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{18}H_{13}BrN_2O_3$: 384.0110. Found: 384.0113.

*3.2.4. 6-Acetyl-2-amino-4-(4-chlorophenyl)-5-hydroxy-4H-chromene-3-carbonitrile (**3d**).* A mixture of 2,4-dihydroxy acetophenone **1a** (152 mg, 1.0 mmol), 2-(4-chlorobenzylidene) malononitrile **2d** (282 mg, 1.5 mmol), and $Ca(OH)_2$ (74 mg, 1.0 mmol) in 5 mL of methanol was stirred at room temperature for 2 h. After completion of the reaction, recrystallization with ethanol gave product **3d** (276 mg, 81%) as a solid: mp 288–290 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 12.95 (1H, s), 7.89 (H, d, *J*=8.7 Hz), 7.32 (2H, d, *J*=8.1 Hz), 7.13 (2H, d, *J*=8.1 Hz), 7.12 (2H, s), 6.69 (1H, d, *J*=8.7 Hz), 4.66 (1H, s), 2.56 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 204.4, 160.1, 159.4, 153.7, 143.7, 132.0, 131.2, 129.0, 128.4, 119.8, 115.9, 111.1, 107.4, 56.7, 35.6, 26.5; IR (KBr) 3440, 3328, 3210, 2928, 2200, 1662, 1487, 1412, 1251, 1080, 821 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{18}H_{13}ClN_2O_3$: 340.0615. Found: 340.0616.

*3.2.5. 6-Acetyl-2-amino-4-(4-fluorophenyl)-5-hydroxy-4H-chromene-3-carbonitrile (**3e**).* A mixture of 2,4-dihydroxy acetophenone **1a** (152 mg, 1.0 mmol), 2-(4-fluorobenzylidene) malononitrile **2e** (260 mg, 1.5 mmol), and $Ca(OH)_2$ (74 mg, 1.0 mmol) in 5 mL of methanol was stirred at room temperature for 3 h. After completion of the reaction, recrystallization with ethanol gave product **3e** (275 mg, 85%) as a solid: mp 275–277 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 12.97 (1H, s), 7.91 (1H, d, *J*=8.7 Hz), 7.19–7.07 (6H, m), 6.71 (1H, d, *J*=8.7 Hz), 4.68 (1H, s), 2.58 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 204.4, 162.5, 160.2, 159.4, 153.7, 141.0, 131.9, 129.0 (d, J_{CF}=8.3 Hz), 119.9, 116.0, 115.1 (d, J_{CF}=21.4 Hz), 111.5, 107.3, 57.1, 35.4, 26.6; IR (KBr) 3431, 3331, 3214, 2878, 2198, 1663, 1505, 1414, 1247, 1078, 818 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{18}H_{13}FN_2O_3$: 324.0910. Found: 324.0908.

*3.2.6. 6-Acetyl-2-amino-5-hydroxy-4-p-tolyl-4H-chromene-3-carbonitrile (**3f**).* A mixture of 2,4-dihydroxy acetophenone **1a** (152 mg, 1.0 mmol), 2-(4-methylbenzylidene) malononitrile **2f** (252 mg, 1.5 mmol), and $Ca(OH)_2$ (74 mg, 1.0 mmol) in 5 mL of methanol was stirred at room temperature for 10 h. After completion of the reaction, recrystallization with ethanol gave product **3f** (237 mg, 74%) as a solid: mp 280–282 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 12.89 (1H, s), 7.80 (1H, d, *J*=8.7 Hz), 7.02–6.94 (6H, m), 6.63 (1H, d, *J*=8.7 Hz), 4.54 (1H, s), 2.50 (3H, s), 2.16 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 204.4, 160.1, 159.4, 153.8, 141.8, 135.8, 131.7, 128.9, 127.0, 120.0, 115.9, 111.9, 107.3, 57.4, 35.7, 26.5, 20.5; IR (KBr) 3627, 3427, 3330, 3213, 2955, 2194, 1653, 1415, 1251, 1129, 1069, 814 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{19}H_{16}N_2O_3$: 320.1161. Found: 320.1164.

*3.2.7. 6-Acetyl-2-amino-5-hydroxy-4-(4-methoxyphenyl)-4H-chromene-3-carbonitrile (**3g**).* A mixture of 2,4-dihydroxy acetophenone **1a** (152 mg, 1.0 mmol), 2-(4-methoxybenzylidene) malononitrile **2g** (276 mg, 1.5 mmol), and $Ca(OH)_2$ (74 mg, 1.0 mmol) in 5 mL of methanol was stirred at room temperature for 12 h. After completion of the reaction, recrystallization with ethanol gave product **3g** (245 mg, 73%) as a solid: mp 248–250 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 12.96 (1H, s), 7.88 (1H, d, *J*=8.7 Hz), 7.06–7.03 (4H, m), 6.83 (2H, d, *J*=8.4 Hz), 6.70 (1H, d, *J*=8.7 Hz), 4.60 (1H, s), 3.70 (3H, s), 2.57 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 204.4, 160.1, 159.4, 158.0, 153.7, 136.8, 131.7, 128.2, 120.1, 115.9, 113.7, 112.1, 107.3, 57.5, 55.0, 30.4, 26.5; IR (KBr) 3433, 3324, 3203, 2950, 2194, 1655, 1509, 1410, 1252, 1068, 823 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{19}H_{16}N_2O_4$: 336.1110. Found: 336.1111.

*3.2.8. 2-Amino-5-hydroxy-4-phenyl-6-propionyl-4H-chromene-3-carbonitrile (**3h**).* A mixture of 1-(2,4-dihydroxyphenyl)propan-1-one **1b** (166 mg, 1.0 mmol), 2-benzylidenemalononitrile **2a** (231 mg, 1.5 mmol), and $Ca(OH)_2$ (74 mg, 1.0 mmol) in 5 mL of methanol was stirred at room temperature for 5 h. After completion of the reaction, recrystallization with ethanol gave product **3h** (263 mg, 82%) as a solid: mp 268–270 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 12.99 (1H, s), 7.92 (1H, d, *J*=9.0 Hz), 7.30–7.25 (2H, m), 7.20–7.11 (3H, m), 7.07 (2H, s), 6.71 (1H, d, *J*=9.0 Hz), 4.65 (1H, s), 3.05 (2H, q, *J*=7.2 Hz), 1.05 (3H, t, *J*=7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 206.7, 160.0, 159.5, 153.7, 144.7, 130.8, 128.4, 127.1, 126.6, 120.0, 115.4, 111.8, 107.3, 57.2, 36.1, 30.9, 7.9; IR (KBr) 3430, 3331, 3217, 2980, 2194, 1651, 1409, 1260, 1081, 835 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{19}H_{16}N_2O_3$: 320.1161. Found: 320.1161.

*3.2.9. 2-Amino-6-benzoyl-5-hydroxy-4-phenyl-4H-chromene-3-carbonitrile (**3i**).* A mixture of 2,4-dihydroxybenzophenone **1c** (214 mg, 1.0 mmol), 2-benzylidenemalononitrile **2a** (231 mg, 1.5 mmol), and $Ca(OH)_2$ (74 mg, 1.0 mmol) in 5 mL of methanol was stirred at room temperature for 5 h. After completion of the reaction, recrystallization with ethanol gave product **3i** (291 mg, 79%) as a solid: mp 280–282 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 12.40 (1H, s), 7.65–7.62 (3H, m), 7.56–7.54 (2H, m), 7.50 (1H, d, *J*=8.4 Hz), 7.31–7.28 (2H, m), 7.23–7.17 (3H, m), 7.11 (2H, s), 6.73 (1H, d, *J*=8.4 Hz), 4.73 (1H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 199.6, 178.5, 160.4, 159.5, 153.8, 144.7, 137.1, 133.4, 132.1, 128.8, 128.4, 127.2, 126.7, 120.0, 115.9, 112.4, 107.6, 57.2, 36.2; IR (KBr) 3431, 3323, 2187, 1650, 1599, 1404, 1342, 1254, 1081, 832, 705 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{23}H_{16}N_2O_3$: 368.1161. Found: 368.1157.

*3.2.10. Methyl 2-amino-3-cyano-5-hydroxy-4-phenyl-4H-chromene-6-carboxylate (**3j**).* A mixture of methyl 2,4-dihydroxybenzoate **1d** (168 mg, 1.0 mmol), 2-benzylidenemalononitrile **2a** (231 mg, 1.5 mmol), and $Ca(OH)_2$ (74 mg, 1.0 mmol) in 5 mL of methanol was stirred at room temperature for 5 h. After completion of the reaction, recrystallization with ethanol gave product **3j** (271 mg, 84%) as a solid: mp 275–277 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.99 (1H, s), 7.73 (1H, d, *J*=9.0 Hz), 7.28–7.23 (2H, m), 7.19–7.08 (3H, m), 7.04 (2H, s), 6.69 (1H, d, *J*=9.0 Hz), 4.64 (1H, s), 3.82 (3H, s); ^{13}C NMR (75 MHz. DMSO-d_6) δ 169.2, 159.6, 158.7, 153.6, 144.8, 129.7, 128.4, 127.1, 126.6, 120.1, 111.9, 108.4, 107.7, 57.2, 52.6, 36.3; IR (KBr) 3428, 3332, 3216, 3071, 2957, 2875, 2197, 1664, 1408, 1338, 1262, 1075, 782 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{18}H_{14}N_2O_4$: 322.0954. Found: 322.0958.

*3.2.11. Ethyl 2-amino-3-cyano-5-hydroxy-7-methyl-4-phenyl-4H-chromene-6-carboxylate (**3k**).* A mixture of ethyl 2,4-dihydroxy-6-

methylbenzoate **1e** (196 mg, 1.0 mmol), 2-benzylidenemalononitrile **2a** (231 mg, 1.5 mmol), and $Ca(OH)_2$ (74 mg, 1.0 mmol) in 5 mL of methanol was stirred at room temperature for 3 h. After completion of the reaction, recrystallization with ethanol gave product **3k** (284 mg, 81%) as a solid: mp 268–270 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.09 (1H, s), 7.29–7.24 (2H, m), 7.20–7.09 (3H, m), 6.98 (2H, s), 6.55 (1H, s), 4.62 (1H, s), 4.28 (2H, q, J=7.2 Hz), 2.40 (3H, s), 1.28 (3H, t, J=7.2 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.7, 159.9, 157.9, 151.8, 145.3, 140.3, 128.6, 127.3, 126.7, 120.4, 111.7, 110.2, 110.1, 61.7, 57.6, 36.6, 22.4, 14.1; IR (KBr) 3427, 3325, 3213, 2978, 2198, 1661, 1404, 1273, 1172, 1022, 818 cm^{-1}; HRMS m/z (M^+) calcd for $C_{20}H_{18}N_2O_4$: 350.1267. Found: 350.1267.

*3.2.12. 2-Amino-7-hydroxy-4-phenyl-4H-chromene-3-carbonitrile (**3l**).* A mixture of resorcinol **1f** (110 mg, 1.0 mmol), 2-benzylidenemalononitrile **2a** (231 mg, 1.5 mmol), and $Ca(OH)_2$ (74 mg, 1.0 mmol) in 5 mL of methanol was stirred at room temperature for 5 h. After completion of the reaction, recrystallization with ethanol gave product **3l** (238 mg, 90%) as a solid: mp 233–235 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.68 (1H, s), 7.32–7.27 (2H, m), 7.22–7.15 (3H, m), 6.85 (2H, s), 6.80 (1H, d, J=8.4 Hz), 6.47 (1H, d, J=8.4 Hz), 6.41 (s, 1H), 4.61 (1H, s); ^{13}C NMR (75 MHz, CD_3OD) δ 162.4, 158.6, 150.8, 147.5, 131.3, 129.7, 128.9, 128.0, 122.1, 115.5, 113.6, 103.7, 58.6, 42.1; IR (KBr) 3494, 3426, 3336, 2189, 1645, 1506, 1406, 1155, 1050, 853 cm^{-1}; HRMS m/z (M^+) calcd for $C_{16}H_{12}N_2O_2$: 264.0899. Found: 264.0898.

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