Convenient Synthesis of 2-Amino-4*H*-chromenes from Photochemically Generated *o*-Quinone Methides and Malononitrile

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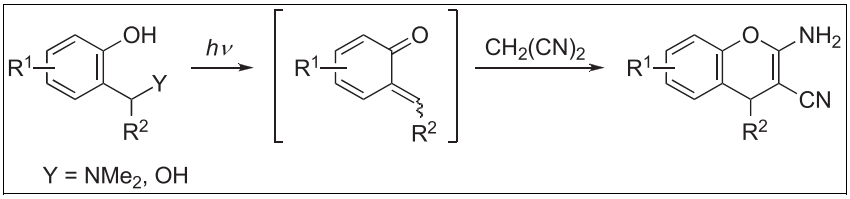

2-Amino-4*H*-chromenes were synthesized in moderate to good yields by the reaction of *o*-quinone methides photochemically generated from *o*-(dimethylaminomethyl)phenols with malononitrile. This method was applicable to the synthesis of fluorinated chromenes that were difficult to obtain by other methods. In addition, *o*-(hydroxymethyl)phenols could be used for the reaction in the presence of tertiary amine bases.

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INTRODUCTION

2-Amino-4*H*-chromene constituents are widely found in natural products, and their biological activities have attracted much attention in medicinal chemistry [1–3]. Of their synthetic methods, the reaction of phenols (naphthols) with benzylidenemalononitriles or three-component reaction of the phenols, aldehydes, and malononitrile via intermediate **A** has been used most frequently using various catalysts and promoters (Scheme 1, path A) [1,3–8]. This reaction is, however, hardly applicable to the phenols having electron-withdrawing substituents. Chromenes (**3**) with nitrogen-functional groups at 4-position ($R^2 = CH_2NO_2$, NHBoc) could be synthesized by amine-thiourea organocatalysts (path B) [2,9]. On the synthesis of nonsubstituted chromenes (**3**) ($R^2 = H$) from salicylaldehyde by use of $InCl_3$, expensive Hantzsch dihydropyridine ester was necessary as a reductant [10]. For discovery of new biologically active 2-amino-4*H*-chromenes (**3**), exploitation of their simple and convenient synthetic methods is desired further.

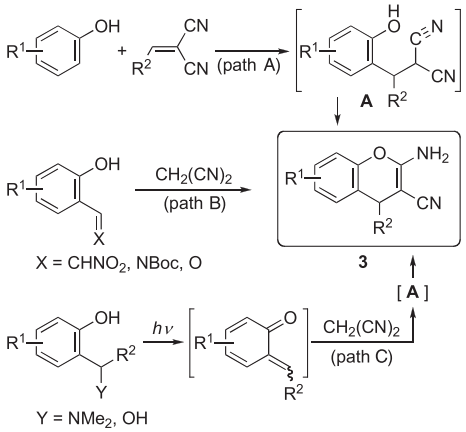
ortho-Quinone methides (*o*-QMs) have been used as reactive intermediates for the synthesis of a variety of heterocyclic compounds through [4 + 2] cycloaddition with alkenes [11,12] and conjugate addition of various nucleophiles [13]. If addition of malononitrile to *o*-QMs would take place similarly as diethyl malonate [14] and phenacyl phenyl sulfone [15], then the intermediate **A** would be generated as well as path A to yield the 2-aminochromenes (**3**) (path C). Although this process has remained unexplored [16], electron-withdrawing substituent (R^1) could be expected to facilitate the reaction in contrast to path A. Of the various procedures to generate *o*-QMs such as thermal, base, and acid initiation [13], photochemical method would be preferable in many respects, because it can be cleanly carried out at ambient temperature without any additives. Herein, we would like to disclose the reaction of photochemically generated *o*-QMs with malononitrile leading to 2-amino-4*H*-chromenes (**3**).

RESULTS AND DISCUSSION

The reaction of *o*-(dimethylaminomethyl)phenol (**1a**) with malononitrile (**2**) was carried out under various conditions as a model reaction (Table 1). When a mixture of **1a** and **2** in MeCN/H_2O (1:1) was irradiated by Hg lamp with Pyrex filter, the expected chromene (**3a**) was formed in 59% yield (entry 1). Irradiation without the filter decreased the yield, and, of course, no reaction took place in the dark (entries 2 and 3). Water is necessary for the reaction (entry 4). The ratio of **2** to **1a** affected the reaction efficiency; that is, the optimum yield was attained with 1.5 equiv of **2**, but higher ratio decreased the yield (entries 1 and 5–8). Moreover, as the concentration of **1a** increased from 0.01 to 0.1 *M*, the product yield decreased drastically (entries 6 and 9–11).

Under the optimal conditions, the reaction of variously substituted *o*-(dimethylaminomethyl)phenols (**1**) was investigated (Table 2). 2-Aminochromenes (**3b–3d**) having methyl group at 6–8 position were obtained in good yields, wherein the substituent at 6- and 8-position seemed to facilitate the reaction better than 7-methyl group (entries 2–4). Similarly, phenols (**1e–1g**) with electron-donating substituents gave the corresponding 2-aminochromenes (**3e–3g**) in high yields (entries 5–7). Although the product **3h** with Et_2N substituent was formed in 72% yield, the reaction of **1i** with NH_2 group gave trace amounts of the expected product **3i** (entries 8 and 9). These results suggested a depressing effect of NH_2 substituent on the reaction, *vide infra*. The products **3** with electron-withdrawing groups were formed in somewhat lower yields than those with electron-donating

Scheme 1



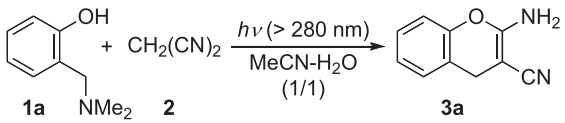
ones unexpectedly. Nevertheless, the product **3k** having 6-fluoride substituent was obtained in quantitative yield (entry 11). Halogenated phenols (**1l–1p**) could be tolerated under irradiation, although their product yields were moderate (entries 12–16). Both 2- and 1-naphthol derivatives **1s** and **1t** could participate in the reaction, wherein the former showed better reactivity than the latter (entries 19 and 20). Utility of the present method has been also demonstrated by the synthesis of 2-aminochoromene (**3u**), which was reported to exhibit high potent activity against human breast tumor cells and human lung cancer cells [1]. Thus, simple irradiation of the phenol (**1u**) ($R^1 = 5\text{-}NEt_2$, $R^2 = C_6H_4Cl\text{-}p$) gave **3u** in 93% yield (entry 21).

Other than malononitrile (**2**), ethyl cyanoacetate (**4**) reacted with *o*-(dimethylaminomethyl)phenol (**1b**) under standard conditions to give the 2-aminochromene (**5**) in 30% yield (Scheme 2, method A). Preliminary investigation revealed that the yield of **5** was improved to 96% by use of DMSO/H_2O solvent and a large amount of **4** (method B).

Next, we investigated the reaction using *o*-(hydroxymethyl)phenols (**6**) instead of **1** to compare their efficiency for the 2-aminochromene synthesis (Table 3) [17]. The expected product **3a** was not formed from **6a** in the absence of base (entry 1). *N*,*N*-Diisopropylethylamine (DIPEA) showed the best results, of the bases tested, which were comparable with the reaction of *o*-(dimethylaminomethyl) phenol (**1a**), although longer reaction period was necessary than that of **1a** (entry 2). Because the yield of **3a** decreased drastically in the dark reaction even in the presence of DIPEA (entry 3), the bases should be necessary for deprotonation of **2**, not for generation of *o*-QM. Although Me_2NH liberated together with *o*-QM would act as a base in the reaction of **1**, secondary amines such as dimethylamine and piperidine gave no or little product **3a** in this reaction (entries 7 and 8). Chromenes (**3v–3x**) having aromatic and aliphatic substituents at 4-position were obtained in moderate to good yields starting from **6b–6d** (entries 9–11).

Table 1

Optimization of the reaction of **1a** with **2**.

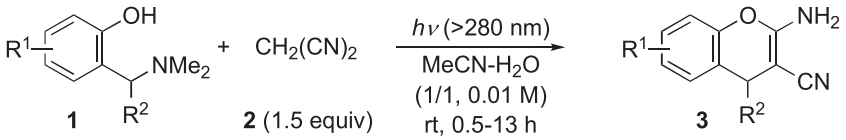


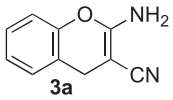
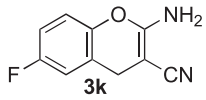
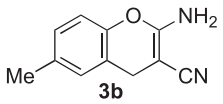
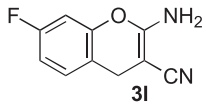
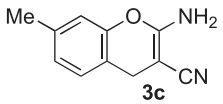
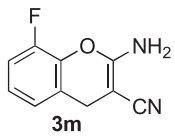
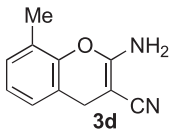
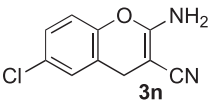
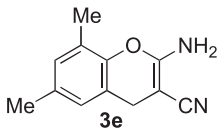
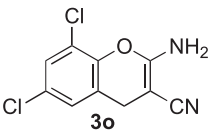
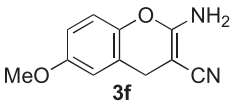
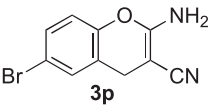
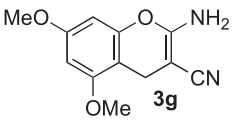
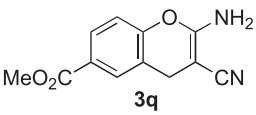
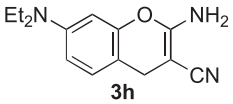
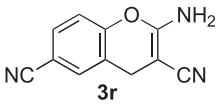
Entry	Equiv of **2**	Conc (*M*)	Time (h)	Yield[a] (%)
1	5	0.01	20	59
2[b]	5	0.01	20	10
3[c]	5	0.01	20	0
4[d]	5	0.01	20	0
5	1	0.01	0.5	74
6	1.5	0.01	0.5	88 (70)
7	2	0.01	1	59
8	10	0.01	20	50
9	1.5	0.03	0.5	35
10	1.5	0.05	2	22
11	1.5	0.10	2	6

[a]NMR yield (isolated yield).
[b]Without Pyrex filter.
[c]Dark reaction.
[d]Anhydrous MeCN solvent.

Table 2

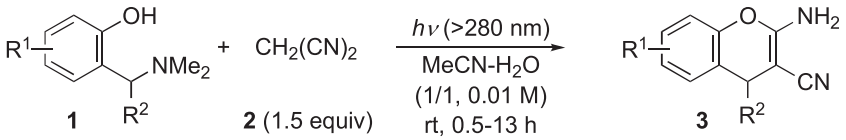
Synthesis of 2-amino-4*H*-chromene derivatives (**3**) from **1**.

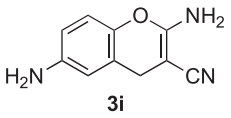
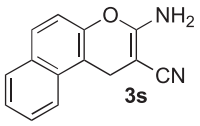
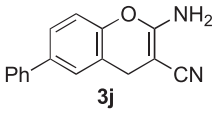
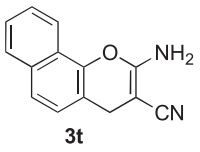
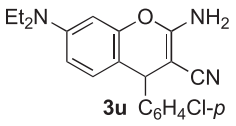


Entry	Product **3**	Time (h)	Yield[a] (%)	Entry	Product **3**	Time (h)	Yield[a] (%)
1	 **3a**	0.5	88	11	 **3k**	0.5	Quant
2	 **3b**	0.5	Quant	12	 **3l**	0.5	40
3	 **3c**	0.5	70	13	 **3m**	0.5	43
4	 **3d**	0.5	90	14	 **3n**	2	67[b]
5	 **3e**	1	89	15	 **3o**	5	51
6	 **3f**	0.5	98	16	 **3p**	2	37
7	 **3g**	5	70[b]	17	 **3q**	5	55
8	 **3h**	2	72[b]	18	 **3r**	1	30[b]

(*Continued*)

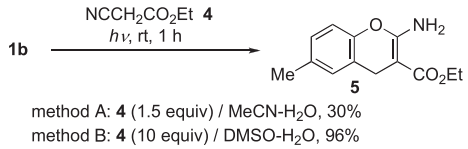
Table 2
(Continued)



Entry	Product **3**	Time (h)	Yield[a] (%)	Entry	Product **3**	Time (h)	Yield[a] (%)
9	 **3i**	1	Trace[c]	19	 **3s**	1	81[b]
10[d]	 **3j**	0.5	59	20	 **3t**	13	47
				21	 **3u** C_6H_4Cl-*p*	0.5	93

[a]NMR yield.
[b]Isolated yield.
[c]Detected by MS.
[d]2 equiv of **2** were used.

Scheme 2

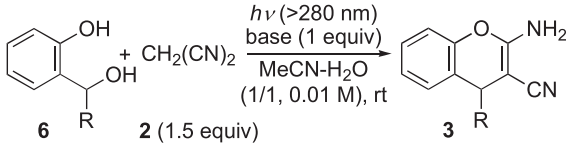


When resorcinol derivative (**7a**) was irradiated for 0.5 h in the presence of malononitrile (**2**) (3 equiv), monocyclization product **8a** was formed in 87% yield, wherein one *o*-(dimethylaminomethyl)phenol moiety was remained unchanged (Scheme 3). Irradiation was continued for longer period (5 h) to promote biscyclization, but the yield of **8a** diminished to 71% without a formation of the expected product. Similar results were observed for the reaction of catechol (**7b**) and 1,5-dihydroxynaphthalene (**7c**). Thus, monocyclization took place readily to give **8b** and **8c** in 75% (2 h) and 86% (0.5 h) yield, respectively, which were decomposed faster than the second cyclization by further irradiation. These results may be caused by the NH_2 group of 2-aminochromenes (**8**) formed in the first cyclization, in analogy with the reaction of **1i** (Table 2, entry 9).

Although the failure in biscyclization showed a limitation of the present method, compared with the procedure using methylenemalononitrile [18], it is worthwhile to comment on this subject. *o*-QM photochemically generated from **1a** and **6a** should essentially exist in an equilibrium state (Scheme 4). When the irradiation of **1a** in the absence of malononitrile was monitored by ^{1}H-NMR under standard conditions (CD_3CN/D_2O solvent), signals of **1a** disappeared after 5 h, but those of **6a** were not observed throughout the reaction, suggesting that hydration of *o*-QM to **6a** could be ignored. On the other hand, similar treatment of **6a** in the presence of equimolecular amounts of Me_2NH exhibited signals of **6a** and **1a** (22% and 24% yield after 30 min, 0% and 20% yield after 1.5 h). Thus, in the reaction of **1a** with malononitrile, the equilibrium would shift to *o*-QM, because liberated Me_2NH was consumed for deprotonation of malononitrile, giving rise to the product **3a** efficiently within 30 min. On the irradiation of the substrates having NH_2 group such as **1i** and **8**, the equilibrium would exclusively shift to *o*-aminomethylphenols (**1**) by facile amination of *o*-QM with another molecule of the substrates, which were present in large excess relatively to *o*-QM.

Table 3

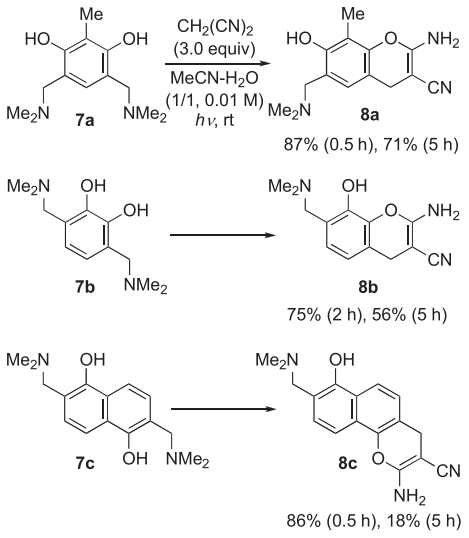
Synthesis of 2-amino-4*H*-chromenes (**3**) from **6**.



Entry	Phenol 6	R	Base	Time (h)	Product **3**	Yield[a] (%)
1	**6a**	H	None	4	**3a**	No reaction
2			DIPEA	3		88
3[b]			DIPEA	3		13
4			DMAP	3		28
5			DBU	1.5		57
6			NaOH	3		53
7			Me_2NH	4		No reaction
8			Piperidine	4		7
9	**6b**	Ph	DIPEA	1.5	**3v**	Quant
10	**6c**	*n*-Bu	DIPEA	2	**3w**	51
11	**6d**	Ph	DIPEA	4	**3x**	49[c]

DIPEA, *N*,*N*-diisopropylethylamine; DMAP, 4-(dimethylamino)pyridine; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene.
[a]NMR yield.
[b]Dark reaction.
[c]Isolated yield.

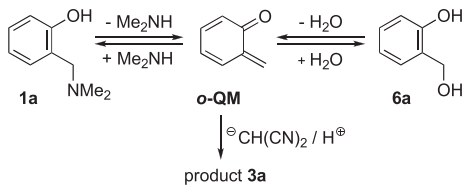
Scheme 3



Hence, 2-aminochromene synthesis from **1i** and biscyclization of **7a** would be difficult.

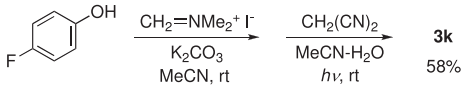
Base effect in the reaction of **6a** with malononitrile could be explained similarly. That is, use of secondary amines such as Me_2NH and piperidine gave no or little **3a**, because these amines quickly converted *o*-QM to *o*-aminomethylphenols (**1**). In contrast, quenching of *o*-QM with tertiary amines was very slow or did not take place, and, thus, **3a** was formed in fairly good yields.

Scheme 4



Because fluoride substituent often have a profound effect on the biological properties of the target molecule [19], the procedure applicable to the synthesis of fluorinated 2-aminochromenes (**3**) is strongly desired. However, few examples have been found in the literature via path B in Scheme 1 [2,9]. The process via path A is less likely to meet this requirement. In fact, piperidine-mediated reaction of 4-fluorophenol with benzylidenemalononitrile was tested under various conditions, but the expected product **3k** was not formed at all. In contrast, the *o*-QM process gave **3k** quantitatively as described earlier (Table 2, entry 11). Moreover, the reaction could be conveniently carried out in one-pot, starting from the fluorophenol, although the yield decreased (Scheme 5).

Scheme 5



CONCLUSIONS

Synthesis of 2-amino-4*H*-chromens (**3**) has been achieved by the reaction of *o*-QMs photochemically generated from *o*-(dimethylaminomethyl)phenols (**1**) with malononitrile (**2**). The reaction of phenols having NH_2 substituent was exceptionally failed, probably because of quenching of the active species. Ethyl cyanoacetate (**4**) reacted also with *o*-QM to give the chromenes (**5**) in high yield, depending on the reaction conditions. *o*-(Hydroxymethyl)phenols (**6**) could be used for the synthesis of **3** in the presence of tertiary amines. Moreover, some biologically active compounds and fluorinated chromenes were readily obtained by the present method.

EXPERIMENTAL

^{1}H and ^{13}C-NMR spectra were recorded with a Varian 500-MR and a 400-MR spectrometers. Mass spectra were obtained at 70 eV on a Shimadzu GCMS-QP5050 apparatus. High resolution mass spectra were recorded by ESI or APCI (Atmospheric Pressure Chemical Ionization) mode on a Thermo Fisher Scientific LTC Orbitrap XL. Melting points were uncorrected. All reactions were carried out under nitrogen. Acetonitrile and distilled water for the solvent were degassed with nitrogen. Other commercially available materials were utilized as provided without further purification. Irradiation was conducted using high-pressure Hg lamp (100 W, Riko UVL-100HA) attached with a Pyrex-cooling jacket.

Materials. *o*-(Dimethylaminomethyl)phenols and naphthols (**1**) were prepared by the conventional method as follows. Formalin (35 wt.% in H_2O, 1.3 equiv) was added slowly to a solution of the corresponding phenol and dimethylamine (40 wt. % in H_2O, 1.3 equiv) at RT, and stirring was continued for 12 h. The reaction mixture was extracted with $CHCl_3$, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using hexane/AcOEt eluent. The substrates **7** were prepared similarly from the corresponding dihydroxybenzenes and naphthalenes, dimethylamine (2.6 equiv), and formalin (2.6 equiv). *o*-(Hydroxymethyl)phenols (**6**) were prepared from salicylaldehyde and the corresponding Grignard or lithium reagents (2.2 equiv).

General procedure for synthesis of 2-amino-4*H*-chromenes 3, 5, and 8. *o*-(Dimethylaminomethyl)phenol (**1a**) (15 mg, 0.10 mmol) and malononitrile (**2**) (10 mg, 0.15 mmol) were charged in a 20 mL Pyrex test tube. The tube was purged with N_2, closed with a rubber septum, and attached with N_2 balloon. The solution was diluted with MeCN (5 mL) and H_2O (5 mL). Then, the mixture was irradiated at RT by high-pressure Hg lamp with monitoring by GC. The phenol (**1a**) was consumed within 30 min. After addition of diphenylmethane as an internal standard and water, the reaction mixture was extracted with Et_2O, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. ^{1}H-NMR spectra of the crude mixture showed 88% yield of 2-amino-3-cyano-4*H*-chromene (**3a**). The product **3a** was isolated in 70% yield (12 mg) by column chromatography on silica gel with a hexane/AcOEt eluent (10:1–5:1). The reactions of *o*-(hydroxymethyl) phenols (**6**) and dihydroxybenzenes (**7**) were carried out similarly, except for addition of *N*,*N*-diisopropylethylamine (1 equiv) in the former and use of 3 equiv of malononitrile (**2**) in the latter.

One-pot synthesis of 3k. 4-Fluorophenol (11 mg, 0.1 mmol), *N*,*N*-dimethylmethyleneiminium iodide (20 mg, 0.11 mmol), K_2CO_3 (15 mg, 0.11 mmol), and MeCN (1 mL) were charged in a 20 mL Pyrex test tube. After purging with nitrogen, the mixture was stirred at RT for 12 h. Then, malononitrile (10 mg, 0.15 mmol) was added to the test tube, and the mixture was diluted with MeCN (4 mL) and water (5 mL). The resulting solution was irradiated by high-pressure Hg lamp for 1 h. Usual workup and purification by column chromatography on silica gel gave **3k** (11 mg, 58%).

Monitoring of 1a and 6a under irradiation by ^{1}H-NMR. A solution of *o*-(hydroxymethyl)phenols (**6a**) (0.6 mg, 4.8 μmol), dimethylamine (40 wt.% in H_2O, 0.2 mg, 4.4 μmol), and Ph_2CH_2 (an internal standard) in CD_3CN-D_2O (0.25 mL each) was charged in a Pyrex NMR tube. The mixture was irradiated by high-pressure Hg lamp. Concentrations of **6a** and **1a** were measured at adequate intervals by ^{1}H-NMR on the basis of the integration of their methylene units (**1a**: δ 4.09 ; **6a**: δ 5.04 Ph_2CH_2: δ 4.30). Irradiation of **1a** was carried out similarly.

2-Amino-3-cyano-4H-chromene (3a) [10]. Isolated yield 70%; white solid, mp 120–121°C (lit. mp 125°C); R_f (Hexane/AcOEt = 5:1) 0.12; ^{1}H-NMR ($CDCl_3$, 399.82 MHz) δ 3.54 (2H, s), 4.54 (2H, br s), 6.93 (1H, d, J = 8.0 Hz), 7.06–7.11 (2H, m), 7.19 (1H, td, J = 8.0, 2.4 Hz); ^{13}C-NMR ($CDCl_3$, 125.68 MHz) δ 23.8, 53.8, 116.3, 118.9, 120.3, 124.8, 127.9, 128.7, 149.3, 159.9; MS *m*/*z* (%) 172 (M^+, 62), 171 (100), 146 (11), 128 (10), 116 (9).

2-Amino-3-cyano-6-methyl-4H-chromene (3b) [10]. Isolated yield 90%; yellow solid, mp 186–187°C; R_f (Hexane/AcOEt = 3:1) 0.32; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 2.29 (3H, s), 3.48 (2H, s), 4.54 (2H, br s), 6.81 (1H, d, J = 8.0 Hz), 6.90 (1H, s), 6.97 (1H, d, J = 8.0 Hz); ^{13}C-NMR ($CDCl_3$, 125.68 MHz) δ 20.6, 23.8, 53.6, 116.0, 118.5, 120.6, 128.5, 128.9, 134.3, 147.2, 160.2; MS *m*/*z* (%) 186 (M^+, 52), 185 (100), 160 (9), 140 (6).

2-Amino-3-cyano-7-methyl-4H-chromene (3c). Isolated yield 59%; white solid, mp 163–165°C; R_f (Hexane/AcOEt = 3:1) 0.35; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 2.31 (3H, s), 3.48 (2H, s), 4.53 (2H, br s), 6.74 (1H, s), 6.89 (1H, d, J = 7.5 Hz), 6.97 (1H, d, J = 7.5 Hz); ^{13}C-NMR ($CDCl_3$, 125.68 MHz) δ 21.0, 23.5, 53.8, 115.7, 116.7, 120.5, 125.6, 128.4, 138.1, 149.1, 160.1; MS *m*/*z* (%) 186 (M^+, 52), 185 (100), 160 (9), 140 (7), 115 (8); HRMS Calcd for $C_{11}H_{10}N_2NaO$ [$(M + Na)^+$] 209.0685, found 209.0686.

2-Amino-3-cyano-8-methyl-4H-chromene (3d). Isolated yield 77%; white solid, mp 94–95°C; R_f (Hexane/AcOEt = 5:1) 0.21; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 2.24 (3H, s), 3.52 (2H, s), 4.58 (2H, br s), 6.92 (1H, d, J = 7.5 Hz), 6.97 (1H, t, J = 7.5 Hz), 7.02 (1H, d, J = 7.5 Hz); ^{13}C-NMR ($CDCl_3$, 125.68 MHz) δ 15.7, 24.0, 53.8, 118.6, 120.5, 124.2, 125.6, 126.2, 129.4, 147.7, 160.0; MS *m*/*z* (%) 186 (M^+, 50), 185 (100), 160 (12), 140 (10), 115 (15); HRMS Calcd for $C_{11}H_{10}N_2NaO$ [$(M + Na)^+$] 209.0685, found 209.0685.

2-Amino-3-cyano-6,8-dimethyl-4H-chromene (3e). Isolated yield 78%; white solid, mp 201–202°C; R_f (Hexane/AcOEt = 3:1) 0.24; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 2.20

(3H, s), 2.24 (3H, s), 3.47 (2H, s), 4.54 (2H, br s), 6.73 (1H, s), 6.83 (1H, s); ^{13}C-NMR ($CDCl_3$, 125.68 MHz) δ 15.6, 20.5, 24.0, 53.7, 118.2, 120.6, 125.2, 126.4, 130.0, 133.7, 145.6, 160.1; MS *m/z* (%) 200 (M^+, 52), 199 (100), 185 (9), 156 (12), 135 (11); HRMS Calcd for $C_{12}H_{12}N_2NaO$ [$(M+Na)^+$] 223.0842, found 223.0841.

2-Amino-3-cyano-6-methoxy-4H-chromene (3f) [16]. Isolated yield 83%; yellow solid, mp 195–196°C (lit. mp 193–194°C); R_f (Hexane/AcOEt = 3:1) 0.23; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 3.51 (2H, s), 3.77 (3H, s), 4.51 (2H, br s), 6.59 (1H, d, *J* = 3.0 Hz), 6.72 (1H, dd, *J* = 9.0, 3.0 Hz), 6.86 (1H, d, *J* = 9.0 Hz); ^{13}C-NMR ($CDCl_3$, 125.68 MHz) δ 24.2, 53.2, 55.6, 112.7, 113.8, 117.2, 119.7, 120.5, 143.3, 156.3, 160.2; MS *m/z* (%) 202 (M^+, 58), 201 (100), 186 (14), 158 (122), 137 (15).

2-Amino-3-cyano-5,7-dimethoxy-4H-chromene (3g). Isolated yield 70%; yellow solid, mp 223–224°C; R_f (Hexane/AcOEt = 1:1) 0.44; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 3.29 (2H, s), 3.77 (3H, s), 3.78 (3H, s), 4.45 (2H, br s), 6.08 (1H, d, *J* = 2.0 Hz), 6.19 (1H, d, *J* = 2.0 Hz); ^{13}C-NMR ($CDCl_3$, 125.68 MHz) δ 19.1, 54.5, 55.5, 55.7, 92.9, 94.5, 100.7, 120.6, 150.2, 157.8, 159.6, 159.8; MS *m/z* (%) 232 (M^+, 29), 231 (48), 230 (88), 207 (100), 203 (60); HRMS Calcd for $C_{12}H_{12}N_2NaO_3$ [$(M+Na)^+$] 255.0740, found 255.0741.

2-Amino-3-cyano-7-diethylamino-4H-chromene (3h). Isolated yield 72%; white solid, mp 218–220°C; R_f (Hexane/AcOEt = 5:1) 0.25; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 1.14 (6H, t, *J* = 6.0 Hz), 3.30 (4H, q, *J* = 6.0 Hz), 3.40 (2H, s), 4.45 (2H, br s), 6.19 (1H, s), 6.42 (1H, d, *J* = 7.5 Hz), 6.90 (1H, d, *J* = 7.5 Hz); ^{13}C-NMR ($CDCl_3$, 100.53 MHz) δ 12.4, 23.0, 44.4, 54.4, 98.9, 104.9, 108.8, 120.8, 129.1, 147.7, 150.2, 160.0; HRMS Calcd for $C_{14}H_{17}N_3NaO$ [$(M+Na)^+$] 266.1265, found 266.1264.

2-Amino-3-cyano-6-phenyl-4H-chromene (3j). Isolated yield 48%; white solid, mp 211–212°C; R_f (Hexane/AcOEt = 5:1) 0.13; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 3.60 (2H, s), 4.59 (2H, br s), 7.00 (1H, d, *J* = 8.0 Hz), 7.32 (1H, d, *J* = 2.0 Hz), 7.35 (1H, dd, *J* = 7.5, 1.5 Hz), 7.40–7.45 (3H, m), 7.53 (2H, dd, *J* = 8.0, 1.5 Hz); ^{13}C-NMR ($CDCl_3$, 125.68 MHz) δ 24.0, 53.7, 116.7, 119.2, 120.4, 126.7, 126.8, 127.3, 127.4, 128.8, 138.0, 139.9, 148.7, 160.0; HRMS Calcd for $C_{16}H_{12}N_2NaO$ [$(M+Na)^+$] 271.0844, found 271.0842.

2-Amino-3-cyano-6-fluoro-4H-chromene (3k). Isolated yield 86%; white solid, mp166–167°C; R_f (Hexane/AcOEt = 3:1) 0.32; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 3.52 (2H, s), 4.54 (2H, br s), 6.81 (1H, d, *J* = 8.0 Hz), 6.89–6.90 (2H, m); ^{13}C-NMR ($CDCl_3$, 100.53 MHz) δ 24.1, 53.1, 114.8 (d, *J* = 3.8 Hz), 115.0 (d, *J* = 3.6 Hz), 117.7 (d, *J* = 8.4 Hz), 120.1, 120.6 (d, *J* = 8.3 Hz), 145.3 (d, *J* = 2.4 Hz), 159.2 (d, *J* = 243.8 Hz), 160.0; HRMS Calcd for $C_{10}H_7FN_2NaO$ [$(M+Na)^+$] 213.0435, found 213.0436.

2-Amino-3-cyano-7-fluoro-4H-chromene (3l). Isolated yield 31%; white solid, mp 200–202°C; R_f (Hexane/AcOEt = 3:1) 0.24; ^{1}H-NMR ($CDCl_3$, 99.82 MHz) δ 3.49 (2H, s), 4.54 (2H, br s), 6.67 (1H, dd, *J* = 8.5, 2.5 Hz), 6.81 (1H, td, *J* = 8.5, 2.5 Hz), 7.06 (1H, dd, *J* = 8.5, 6.0 Hz); ^{13}C-NMR ($CDCl_3$, 100.53 MHz) δ 23.3, 54.1, 104.1(d, *J* = 26.0 Hz), 112.1 (d, *J* = 21.3 Hz), 114.7, 120.0, 129.7 (d, *J* = 9.3 Hz), 149.7, 159.5, 161.7 (d, *J* = 246.6 Hz); HRMS Calcd for $C_{10}H_8FN_2O$ [$(M+H)^+$] 191.0615, found 191.0615.

2-Amino-3-cyano-8-fluoro-4H-chromene (3m). Isolated yield 36%; white solid, mp 164–165°C; R_f (Hexane/AcOEt = 3:1) 0.33; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 3.55 (2H, s), 4.67 (2H, br s), 6.88 (1H, d, *J* = 7.0 Hz), 6.96–7.04 (2H, m); ^{13}C-NMR ($CDCl_3$, 100.53 MHz) δ 23.7, 53.9, 114.8 (d, *J* = 17.2 Hz), 121.5, 123.5 (d, *J* = 3.7 Hz), 124.5 (d, *J* = 7.5 Hz), 137.7 (d, *J* = 11.1 Hz), 150.4 (d, *J* = 249.3 Hz), 159.4 (one carbon was obscured); HRMS Calcd for $C_{10}H_7FN_2NaO$ [$(M+Na)^+$] 213.0435, found 213.0435.

2-Amino-6-chrolo-3-cyano-4H-chromene (3n) [16]. Isolated yield 67%; white solid, mp 210–212°C (lit. mp 213–215°C); R_f (Hexane/AcOEt = 3:1) 0.28; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 3.51 (2H, s), 4.55 (2H, br s), 6.87 (1H, d, *J* = 8.5 Hz), 7.10 (1H, d, *J* = 2.0 Hz), 7.16 (1H, dd, *J* = 8.5, 2.0 Hz); ^{13}C-NMR ($CDCl_3$, 100.53 MHz) δ 23.7, 53.5, 117.7, 119.9, 120.6, 128.0, 128.4, 129.7, 147.8, 159.7; HRMS Calcd for $C_{10}H_8ClN_2O$ [$(M+H)^+$] 207.0312, found 207.0312.

2-Amino-3-cyano-6,8-dichloro-4H-chromene (3o). Isolated yield 40%; white solid, mp 243–244°C; R_f (Hexane/AcOEt = 3:1) 0.18; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 3.54 (2H, s), 4.68 (2H, br s), 7.02 (1H, d, *J* = 2.5 Hz), 7.27 (1H, d, *J* = 2.5 Hz); ^{13}C-NMR ($CDCl_3$, 125.68 MHz) δ 24.2, 53.8, 119.3, 122.1, 122.6, 126.9, 128.6, 129.6, 144.1, 159.4; MS *m/z* (%) 241 (M^+, 26), 207 (100), 191 (23), 177 (34), 114 (25); HRMS Calcd for $C_{10}H_7Cl_2N_2O$ [$(M+H)^+$] 240.9930, found 240.9930.

2-Amino-6-bromo-3-cyano-4H-chromene (3p) [10]. Isolated yield 32%; white solid, mp 192–193°C; R_f (Hexane/AcOEt = 3:1) 0.24; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 3.51 (2H, s), 4.57 (2H, br s), 6.82 (1H, d, *J* = 9.0 Hz), 7.25 (1H, d, *J* = 2.0 Hz), 7.29 (1H, dd, *J* = 9.0, 2.0 Hz); ^{13}C-NMR ($CDCl_3$, 125.68 MHz) δ 23.7, 53.5, 117.2, 118.1, 119.9, 121.1, 131.0, 131.4, 148.4, 159.7; MS *m/z* (%) 251 (M^+, 95), 250 (80), 249 (100), 143 (41), 114 (64).

2-Amino-3-cyano-6-methoxycarbonyl-4H-chromene (3q). Isolated yield 41%; white solid, mp 203–205°C; R_f (Hexane/AcOEt = 3:1) 0.11; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 3.58 (2H, s), 3.91 (3H, s), 4.58 (2H, br s), 6.98 (1H, d, *J* = 8.5 Hz), 7.83 (1H, s), 7.88 (1H, d, *J* = 8.5 Hz); ^{13}C-NMR ($CDCl_3$, 125.68 MHz) δ 23.7, 52.3, 54.0, 116.5, 119.1, 119.8, 126.7, 129.7, 130.7, 152.5, 159.5, 166.0; HRMS Calcd for $C_{12}H_{10}N_2NaO_3$ [$(M+Na)^+$] 253.0584, found 253.0584.

2-Amino-3,6-dicyano-4H-chromene (3r). Isolated yield 30%; white solid, mp 253–254°C; R_f (Hexane/AcOEt = 1:1) 0.12; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 3.58 (2H, s), 4.63 (2H, br s), 7.03 (1H, d, *J* = 8.5 Hz), 7.45 (1H, s), 7.50 (1H, d, *J* = 8.5 Hz); ^{13}C-NMR (DMSO-d_6, 125.68 MHz) δ 23.7, 49.4, 107.4, 117.8, 118.8, 120.9, 122.0, 132.8, 133.8, 152.9, 160.9; HRMS Calcd for $C_{11}H_7N_3NaO$ [$(M+Na)^+$] 220.0481, found 220.0482.

2-Amino-3-cyano-4H-benzo[f]chromene (3s) [16]. Isolated yield 81%; Yellow solid, mp 205–207°C (lit. mp 209–211°C); R_f (Hexane/AcOEt = 3:1) 0.30; ^{1}H-NMR ($CDCl_3$, 399.82 MHz) δ 3.85 (2H, s), 4.59 (2H, br s), 7.12 (1H, d, *J* = 8.0 Hz), 7.49 (1H, td, *J* = 8.0, 1.2 Hz), 7.59 (1H, td, *J* = 8.0, 1.2 Hz), 7.74 (2H, d, *J* = 8.0 Hz), 7.83 (1H, d, *J* = 8.0 Hz); ^{13}C-NMR ($CDCl_3$, 125.68 MHz) δ 21.9, 54.3, 115.1, 116.7, 120.5, 122.7, 125.2, 127.3, 128.4, 128.8, 130.7, 131.2, 146.4, 159.5.

2-Amino-3-cyano-4H-benzo[h]chromene (3t) [20]. Isolated yield 40%; orange solid, mp 200–201°C; R_f (Hexane/AcOEt = 3:1) 0.28; ^{1}H-NMR ($CDCl_3$, 399.82 MHz) δ 3.69 (2H, s), 4.69 (2H, br s), 7.17 (1H, d, *J* = 8.0 Hz), 7.52 (2H, td, *J* = 7.6, 1.6 Hz), 7.58 (1H, d, *J* = 8.0 Hz), 7.80 (1H, dd, *J* = 7.6, 1.6 Hz), 8.08 (1H, dd, *J* = 8.0, 1.6 Hz); ^{13}C-NMR ($CDCl_3$, 125.68 MHz) δ 24.4, 54.3, 113.6, 120.4, 124.4, 125.7, 126.4, 126.5, 127.3, 127.7, 133.3, 143.9, 153.6, 159.9.

2-Amino-4-(4-chlorophenyl)-3-cyano-7-diethylamino-4H-chromene (3u) [1]. Isolated yield 85%; yellow solid, mp 155–156°C (lit. mp 152–153°C); R_f (Hexane/AcOEt = 3:1)

0.38; ^{1}H-NMR ($CDCl_3$, 399.82 MHz) δ 1.15 (6H, t, J = 6.8 Hz), 3.31 (4H, q, J = 6.8 Hz), 4.54 (2H, br s), 4.61 (1H, s), 6.23 (1H, s), 6.36 (1H, d, J = 7.2 Hz), 6.70 (1H, d, J = 7.2 Hz), 7.14 (2H, d, J = 8.0 Hz), 7.27 (2H, d, J = 8.0 Hz); ^{13}C-NMR ($CDCl_3$, 125.68 MHz) δ 12.4, 30.9, 39.7, 44.4, 98.1, 109.1, 120.0, 128.8, 129.3, 129.9, 132.7, 143.8, 147.9, 149.5, 159.3, 165.7.

2-Amino-3-cyano-4-phenyl-4H-chromene (3v) [21]. Isolated yield 87%; white solid, mp 210–211°C (lit. mp 210°C); R_f (Hexane/AcOEt = 3:1) 0.24; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 4.59 (2H, br s), 4.75 (1H, s), 6.98–7.05 (3H, m), 7.20 (3H, d, J = 7.5 Hz), 7.24 (1H, t, J = 7.5 Hz), 7.32 (2H, t, J = 7.5 Hz); ^{13}C-NMR ($CDCl_3$, 125.68 MHz) δ 40.9, 60.9, 116.3, 119.7, 122.8, 125.1, 127.3, 127.9, 128.2, 128.8, 129.7, 144.5, 148.5, 159.1; MS m/z (%) 248 (M^+, 23), 201 (10), 172 (17), 171 (100).

2-Amino-4-butyl-3-cyano-4H-chromene (3w). Isolated yield 44%; yellow solid, mp 79–80°C; R_f (Hexane/AcOEt = 3:1) 0.38; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 0.85 (3H, t, J = 7.5 Hz), 1.06–1.33 (4H, m), 1.70–1.75 (2H, m), 3.64 (1H, t, J = 5.0 Hz), 4.55 (2H, br s), 6.94 (1H, dd, J = 8.0, 1.0 Hz), 7.10–7.16 (2H, m), 7.19 (1H, td, J = 8.0, 1.0 Hz); ^{13}C-NMR ($CDCl_3$, 125.68 MHz) δ 14.0, 22.6, 26.8, 34.5, 37.8, 58.9, 116.1, 120.3, 123.7, 124.8, 127.7, 128.1, 149.5, 160.4; MS *m/z* (%) 228 (M^+, 2), 207 (1), 171 (100), 142 (3), 128 (6); HRMS Calcd for $C_{14}H_{16}N_2NaO$ [$(M + Na)^+$] 251.1156, found 251.1155.

2-Amino-3-cyano-4-phenylethynyl-4H-chromene (3x). Isolated yield 49%; orange solid, mp 235–236°C; R_f (Hexane/AcOEt = 5:1) 0.12; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 4.67 (2H, br s), 4.90 (1H, s), 6.98 (1H, dd, J = 8.0, 1.0 Hz), 7.19 (1H, td, J = 8.0, 1.0 Hz), 7.27–7.29 (4H, m), 7.43–7.45 (2H, m), 7.50 (1H, d, J = 7.5 Hz); ^{13}C-NMR ($CDCl_3$, 125.68 MHz) δ 27.6, 57.4, 82.4, 88.8, 116.5, 119.3, 119.5, 122.7, 125.3, 128.2, 128.3, 128.9, 129.2, 131.8, 148.0, 159.5; MS *m/z* (%) 272 (M^+, 100), 243 (7), 214 (15), 195 (31); HRMS Calcd for $C_{18}H_{12}N_2NaO$ [$(M + Na)^+$] 295.0842, found 295.0843.

2-Amino-3-ethoxycarbonyl-6-methyl-4H-chromene (5). Isolated yield 80%; colorless viscous oil; R_f (Hexane/AcOEt = 10:1) 0.35; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 1.31 (3H, t, J = 7.5 Hz), 2.28 (3H, s), 3.53 (2H, s), 4.20 (2H, q, J = 7.5 Hz), 6.19 (2H, br s), 6.79 (1H, d, J = 8.0 Hz), 6.93 (1H, d, J = 8.0 Hz), 6.94 (1H, s); ^{13}C-NMR ($CDCl_3$, 125.68 MHz) δ 14.7, 20.7, 23.2, 59.4, 115.5, 121.5, 128.3, 129.1, 129.4, 133.5, 147.6, 160.2, 169.9; MS *m/z* (%) 233 (M^+, 36), 204 (98), 160 (100), 121 (30); HRMS Calcd for $C_{13}H_{16}NO_3$ [$(M + H)^+$] 234.1127, found 234.1125.

2-Amino-3-cyano-6-dimethylaminomethyl-7-hydroxy-8-methyl-4H-chromene (8a). Isolated yield 72%; yellow solid, mp 246–247°C; R_f (AcOEt/MeOH = 10:1) 0.64; ^{1}H-NMR ($CDCl_3$, 399.82 MHz) δ 2.11 (3H, s,), 2.31 (6H, s), 3.41 (2H, s), 3.56 (2H, s), 4.54 (2H, br s), 6.53 (1H, s); ^{13}C-NMR ($CDCl_3$, 125.68 MHz) δ 8.06, 23.5, 44.3, 54.0, 62.3, 108.4, 118.0, 120.8, 124.6, 128.0, 147.6, 155.5, 160.0; HRMS Calcd for $C_{14}H_{18}N_3O_2$ [$(M + H)^+$] 260.1394, found 260.1397.

2-Amino-3-cyano-7-dimethylaminomethyl-8-hydroxy-4H-chromene (8b). Isolated yield 65%; yellow solid, mp 154–155°C; R_f (DCM/MeOH = 10:1) 0.25; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 2.37 (6H, s), 3.49 (2H, s), 3.69 (2H, s), 4.50 (1H, br s), 4.67 (2H, s), 6.51(1H, d, J = 6.8 Hz), 6.69 (1H, d, J = 6.8 Hz); ^{13}C-NMR ($CDCl_3$, 100.53 MHz) δ 25.4, 46.6, 59.2, 119.8, 120.5, 122.0, 124.3, 130.6, 131.1, 143.5, 148.0, 178.2; HRMS Calcd for $C_{13}H_{16}N_3O_2$ [$(M + H)^+$] 246.1238, found 246.1237.

2-Amino-3-cyano-8-dimethylaminomethyl-7-hydroxy-4H-benzo[h]chromene (8c). Isolated yield 75%; yellow solid, mp183–184°C; R_f (DCM/MeOH = 10:1) 0.65; ^{1}H-NMR ($CDCl_3$, 499.82 MHz) δ 2.39 (6H, s), 3.49 (1H, br s), 3.66 (2H, s), 3.81 (2H, s), 4.65 (2H, s), 7.11 (2H, dd, J = 8.6, 2.0 Hz), 7.48 (1H, d, J = 8.6 Hz), 7.97 (1H, d, J = 8.6 Hz); ^{13}C-NMR ($CDCl_3$, 100.53 MHz) δ 24.4, 44.4, 54.5, 62.7, 90.2, 110.5, 113.8, 115.0, 118.7, 120.4, 121.9, 124.5, 127.0, 169.4 (two carbons were obscured); HRMS Calcd for $C_{17}H_{18}N_3O_2$ [$(M + H)^+$] 296.1399, found 296.1394.

REFERENCES AND NOTES

[1] Sabry, N. M.; Mohamed, H. M.; Khattab, E. S.A.E.H.; Motlaq, S. S.; El-Agrody, A. M. Eur J Med Chem 2011, 46, 765.

[2] Ren, Q.; Siau, W.-Y.; Du, Z.; Zhang, K.; Wang, J. Chem Eur J 2011, 17, 7781.

[3] Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Wang, Y.; Zhao, J.; Jia, S.; Herich, J.; Labreque, D.; Storer, R.; Meerovitch, K.; Bouffard, D.; Rej, R.; Denis, R.; Blais, C.; Lamothe, S.; Attardo, G.; Gourdeau, H.; Tseng, B.; Kasibhatla, S.; Cai, S. X. J Med Chem 2004, 47, 6299.

[4] Mahmoud, A. F.; Abd El-Latif, F. F.; Ahmed, A. M. Chin J Chem 2010, 28, 91.

[5] Surpur, M. P.; Kshirsagar, S., Samant, S. D. Tetrahedron Lett 2009, 50, 719.

[6] Wang, X.; Shi, D.; Yu, H.; Wang, G.; Tu, S. Synth Commun 2004, 34, 509.

[7] Maggi, R.; Ballini, R.; Sartori, G.; Sartorio, R. Tetrahedron Lett 2004, 45, 2297.

[8] Ballini, R.; Bosica, G.; Conforti, M. L.; Maggi, R.; Mazzacani, A.; Righi, P.; Sartori, G. Tetrahedron 2001, 57, 1395.

[9] Du, Z.; Siau, W.-Y.; Wang, J. Tetrahedron Lett 2011, 52, 6137.

[10] Shanthi, G.; Perumal, P. T. Tetrahedron Lett 2007, 48, 6785.

[11] Radomkit, S.; Sarnpitak, P.; Tummatorn, J.; Batsomboon, P.; Ruchirawat, S.; Ploypradith, P. Tetrahedron 2011, 67, 3904.

[12] Arumugam, S.; Popik, V. V. J Am Chem Soc 2011, 133, 5573.

[13] For a review, see: Van De Water, R. W.; Pettus, T. R. R. Tetrahedron 2002, 58, 5367.

[14] Gardner, P. D.; Rafsanjani, H. S.; Rand, L. J Am Chem Soc 1959, 81, 3364.

[15] Balasubramanian, K. K.; Selvaraj, S. Synthesis 1980, 138.

[16] During the course of our study, it has been reported that base mediated reaction of *o*-hydroxybenzylammonium salts with malononitrile under reflux gave 2-aminochromenes: Osyanin, V. A.; Osipov, D. V.; Klimochkin, Y. N. Tetrahedron 2012, 68, 5612.

[17] It has been reported that **1** was superior to **6** in the reaction of *o*-QM with ethyl vinyl ether, see: Nakatani, K.; Higashida, N.; Saito, I. Tetrahedron Lett 1997, 38, 5005.

[18] Elagamey, A. G. A.; El-Taweel, F. M. A.-A.; Khodeir, M. N. M.; Elnagdi, M. H. Bull Chem Soc Jpn 1993, 66, 464.

[19] For a review, see: Hagmann, W. K. J Med Chem 2008, 51, 4359.

[20] Mekheimer, R. A.; Sadek, K. U. Chin Chem Lett 2009, 20, 271.

[21] Kamdar, N. R.; Heveliwala, D. D.; Mistry, P. T.; Patel, S. K. Med Chem Res 2011, 20, 854.