Tetrahedron xxx (2013) 1–8

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A novel synthesis of diverse 2-amino-5-hydroxy-4*H*-chromene derivatives with a spirooxindole nucleus by $Ca(OH)_2$-mediated three-component reactions of substituted resorcinols with isatins and malononitrile

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ARTICLE INFO

Article history:
Received 31 May 2013
Received in revised form 6 September 2013
Accepted 7 September 2013
Available online xxx

Keywords:
Multi-component reaction
One-pot synthesis
Resorcinols
Isatin
Malononitrile
Calcium hydroxide

ABSTRACT

An efficient and facile one-pot synthesis is described for the preparation of novel 2-amino-5-hydroxy-4*H*-chromene derivatives with a spirooxindole nucleus using $Ca(OH)_2$-mediated three-component reactions of substituted resorcinols with isatins and malononitrile. This simple method provided a variety of biologically interesting diverse 2-amino-5-hydroxy-4*H*-chromene derivatives in moderate yields under mild reaction conditions.

1. Introduction

2-Aminochromenes are important heterocyclic compounds with a number of biological and pharmacological properties.[1] For example, they are known to possess potent antimicrobial,[2] antiviral,[3] anticonvulsant,[4] antiproliferative,[5] antitumor,[6] anti-cancer,[7] and central nervous system activities,[8a] and are widely employed as cosmetics, pigments,[9] and potent biodegradable agrochemicals.[10] Furthermore, their derivatives, such as, HA 14-1 and MX58151, which have proapoptotic effects, are being developed as anti-cancer agents.[11] 2-Amino-4*H*-chromenes are generally synthesized by reactions of phenol or resorcinol, arylaldehydes, and malononitrile (Scheme 1). Basic alumina,[12] piperidine,[13] morpholine,[14] cetyltrimethylammonium chloride,[8b] [bmim]OH,[15] K_2CO_3/microwave,[16] DBU/microwave,[17] and chitosan[18] have been used in these reactions as catalytic and stoichiometric reagents. Interestingly, all known reactions of resorcinol, arylaldehydes, and malononitrile afford 2-amino-7-hydroxy-4*H*-chromene derivatives as sole products, and thus, isolation of the expected 2-amino-5-hydroxy-4*H*-chromene derivatives is not required.[19] In addition, reactions of naphthols with arylaldehydes and malononitrile in the presence of $Na_2CaP_2O_7$[20] or ceric ammonium nitrate[21] have been described to afford 2-aminochromene derivatives. Interestingly, resorcinol reacts with arylaldehydes and malononitrile at position 6 rather than at position 2 under the above-described conditions to give 2-amino-7-hydroxy-4*H*-chromenes regioselectively, probably due to steric hindrance between two hydroxyl groups in the meta-disubstituted compound.[19]

Spirooxindole derivatives also represent an important class of naturally occurring substances with pronounced biological activities and properties.[22] The spirooxindole unit is a core structure of many pharmacological agents and alkaloids.[23] Furthermore, molecules bearing a spirooxindole moiety have been shown to possess a number of important and interesting biological activities.[24]

In view of these important characteristics, our current research focus has been targeted toward the facile synthesis of 2-amino-5-hydroxy-chromenes and spirooxindoles. The unique structural array and highly prominent pharmacological activities of these entities stimulated interest in their syntheses, and in particular, the development of new, simple one-pot synthetic methods for the preparation of both 2-amino-5-hydroxy-chromenes and spirooxindole derivatives has become an interesting challenge.

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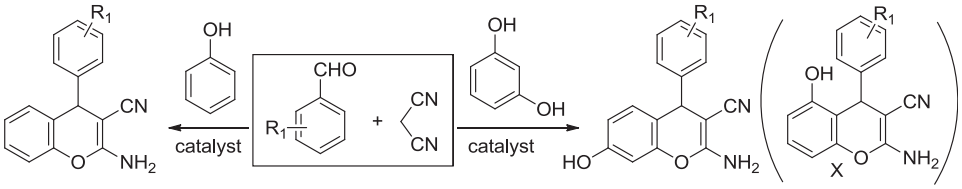
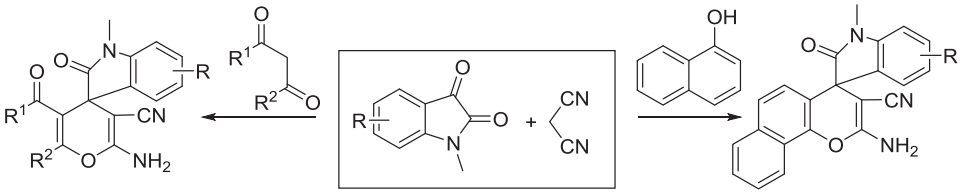
0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.09.021



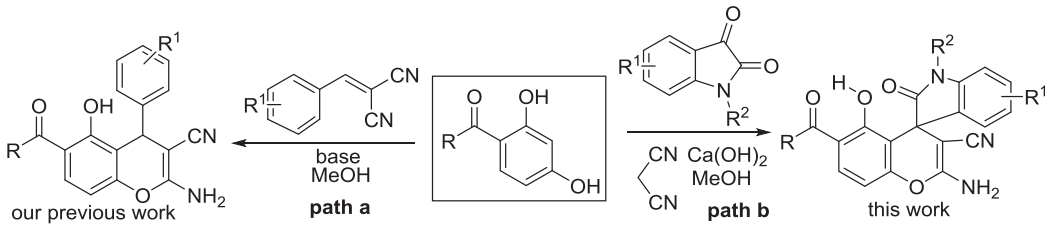
Scheme 1.

Recently, several synthetic methods have been reported for the synthesis of 4*H*-pyrans and 4*H*-benzo[*h*]chromenes bearing the spirooxindole moiety based on multi-component reactions of 1,3-dicarbonyl compound or 1-naphthol with isatins and malononitrile (Scheme 2). A variety of catalysts and reagents, such as, Al_2O_3,[25] MgO,[26] $InCl_3$,[27] $NiCl_2$,[28] $KAl(SO_4)_2{\cdot}12H_2O$,[29] *p*-$MeC_6H_4SO_3H$,[30] ammonium salt,[31] $Bu_4N^+{\cdot}Br^-$,[32] $Me(CH_2)16CO_2^-{\cdot}Na^+$ (disodium carbonate),[33] $[BMIm]BF_4$,[34] $HOCH_2CH_2OH$ polymer,[35] beta-cyclodextrin,[36] and lipase[37] have been studied in the contexts of these reactions, which provide rapid synthetic methods to the production of 2-amino-4*H*-pyrans and 2-amino-4*H*-benzo[*h*]chromene derivatives bearing the spirooxindole moiety. Furthermore, reactions of substituted resorcinols with isatins and malononitrile to afford a variety of 6-acyl-2-amino-5-hydroxy-4*H*-chromenes bearing various spirooxindoles have not been reported.



Scheme 2.

Recently, we developed a method for synthesizing 2-amino-5-hydroxy-4*H*-chromene derivatives based on two-component reactions between 2,4-dihydroxyacetophenone and 2-benzylidenemalononitriles in methanol in the presence of base (path a, Scheme 3).[38] As part of our ongoing studies on the syntheses of novel types of 2-aminochromene derivatives, we examined three-component reactions of substituted resorcinols with various isatins and malononitrile in the presence of different catalysts and other reagents. Here, we describe a one-pot synthesis of biologically interesting diverse 2-amino-5-hydroxy-4*H*-chromene derivatives using $Ca(OH)_2$-mediated three-component reactions of substituted resorcinols with isatins and malononitrile (path b, Scheme 3).



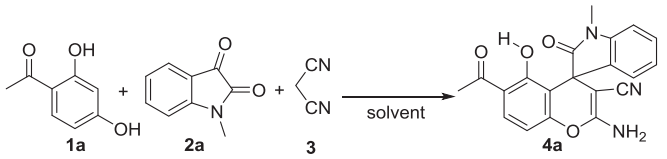
Scheme 3.

2. Results and discussion

To afford 2-amino-5-hydroxy-4*H*-chromenes bearing the spirooxindole moiety, three-component reactions of 2,4-dihydroxyacetophenone (**1a**) with 1-methylisatin (**2a**) and malononitrile (**3**) were first examined in the presence of several catalysts and bases (Table 1). Using 20 mol % of $InCl_3$ and $Yb(OTf)_3$ as Lewis acids, no products were produced (entries 1 and 2). When 20 mol % of ethylenediamine diacetate (EDDA) was used as an organocatalyst, no products were isolated (entry 3). In addition, the use of 1 equiv of DBU and K_2CO_3 as bases in refluxing methanol for 12 h did not produce the desired products (entries 4 and 5). Interestingly, reactions using 1.0 equiv of $Ca(OH)_2$ in refluxing toluene or acetonitrile for 12 h gave no products (entries 6 and 7), but reactions in refluxing ethanol or methanol provided the desired product **4a** at yields of 40 and 60%, respectively (entries 8 and 9). Two equivalent of $Ca(OH)_2$ in refluxing methanol for 5 h increased the yield of **4a** to 75% (entry 10). The use of H_2O as a solvent resulted in the production of **4a** in only 5% yield (entry 11). Importantly, in these reactions, only **4a** was formed and other possible regioisomers were not produced. The structure of **4a** was determined by ^1H NMR, which showed AB aromatic protons on the 4*H*-chromene ring at δ 6.71 (J=8.6 Hz) and δ 7.90 (J=8.6 Hz) ppm and two methyl peaks at δ 3.15 and 2.50 ppm attributed to a *N*-methyl and an acyl group. The ^{13}C NMR spectrum of **4a** contained a characteristic quaternary carbon peak at δ 47.3 ppm due to a spirooxindole moiety.

To explore the generality and scope of this method, additional reactions of substituted resorcinols containing electron-donating or -withdrawing groups on the benzene ring with malononitrile and isatins were attempted under optimized conditions. The results are summarized in Table 2. Reaction of 2,4-dihydroxyacetophenone (**1a**), with isatin (**2b**) and malononitrile (**3**) in the presence of 2 equiv of $Ca(OH)_2$ in refluxing methanol for 4 h provided compound **4b** in 60% yield (entry 1). When 5-methylisatin with an electron-donating group on the benzene ring was used, product **4c** was produced in 68% yield (entry 2). When 5-bromoisatin, 5-chloroisatin, 7-chloroisatin, and 5-nitroisatin with electron-withdrawing groups

Table 1
Three-component reactions of 2,4-dihydroxyacetophenone (**1a**) with isatin (**2a**) and malononitrile (**3**) under several conditions



Entry	Catalyst/reagent	Solvent	Condition	Yield (%)
1	$InCl_3$ (0.2 equiv)	MeOH	Reflux, 12 h	0
2	Yb $(OTf)_3$ (0.2 equiv)	CH_3CN	Reflux, 12 h	0
3	EDDA (0.2 equiv)	MeOH	Reflux, 12 h	0
4	DBU (1.0 equiv)	MeOH	Reflux, 12 h	0
5	K_2CO_3 (1.0 equiv)	MeOH	Reflux, 12 h	0
6	$Ca(OH)_2$ (1.0 equiv)	Toluene	Reflux, 12 h	0
7	$Ca(OH)_2$ (1.0 equiv)	CH_3CN	Reflux, 12 h	0
8	$Ca(OH)_2$ (1.0 equiv)	EtOH	Reflux, 8 h	40
9	$Ca(OH)_2$ (1.0 equiv)	MeOH	Reflux, 5 h	60
10	$Ca(OH)_2$ (2.0 equiv)	MeOH	Reflux, 5 h	75
11	$Ca(OH)_2$ (2.0 equiv)	H_2O	Reflux, 12 h	5

on the benzene ring were used, the desired products **4d**–**g** were obtained in 57–70% yield (entries 3–6). When 1-phenylisatin was used, **4h** was produced in 69% yield (entry 7). For other resorcinols, reactions of 2,4-dihydroxypropiophenone (**1b**) and 2′,4′-dihydroxy-2-phenylacetophenone (**1c**) afforded the desired products **4i**–**s** in 45–75% yield (entries 8–18). Similarly, reactions of 2,4-dihydroxybenzophenone (**1d**) were also successful. Reaction of **1d** with isatin and malononitrile in refluxing methanol for 6 h provided **4t** in 55% yield, whereas that of 5-chloroisatin afforded **4u** in 40% yield. These reactions provided a rapid means of synthesizing a variety of 2-amino-5-hydroxy-4*H*-chromene derivatives **4b**–**u** containing various spirooxindole moieties. To confirm the structures of **4a**–**u**, the structure of **4i** was determined by X-ray crystallography (Fig. 1).[39]

The formation of **4a** can be explained by the mechanism shown in Scheme 4. 2,4-Dihydroxyacetophenone (**1a**) first gives the phenoxide intermediate **5** in the presence of base, which attacks the 2-(1-methyl-2-oxoindolin-3-ylidene)malononitrile (**6**) formed by Knoevenagel condensation between 1-methylisatin (**2a**) and malononitrile (**3**), to give intermediate **7**. As an evidence of this reaction pathway, intermediate 6 was isolated and identified by comparison with spectral data of the reported compound.[40] The attack of **5** to **6** at more crowded 3-position on the benzene ring in comparison with 5-position may due to higher electron density at the 3-position.[41] Tautomerism of **7** followed by intramolecular nucleophilic addition of oxygen to the cyano group and protonation provides **8**, which undergoes isomerization to give **4a**. The regioselective ring closure of **7** to **8** may be determined by the deactivation of the *O*-hydroxy group by intramolecular hydrogen bonding to the neighboring carbonyl.

In summary, we describe the efficient and general one-pot synthesis of biologically interesting 2-amino-5-hydroxy-4*H*-chromene derivatives bearing spirooxindole skeletons via a $Ca(OH)_2$-mediated three-component reaction of substituted resorcinols with isatins and malononitrile. This method has advantages of requiring mild reaction conditions, ease of handling, and the use of an effective reagent.

3. Experimental section

All experiments were carried out in a nitrogen atmosphere. Merck pre-coated silica gel plates (Art. 5554) and 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 Bruker Model ARX (300 and 75 MHz, respectively) spectrometer in DMSO-d_6. IR spectra were recorded on a JASCO FTIR 5300 spectrophotometer. HRMS was carried out at the Korea Basic Science Institute (Daegu) on a Jeol JMS 700 spectrometer.

3.1. General procedure for the synthesis of spirooxindoles (4a–u)

To a solution of substituted isatin (1.0 mmol) in methanol (5 mL) was added various resorcinols (1.0 mmol), malononitrile (1.0 mmol), and $Ca(OH)_2$ (2.0 mmol). The mixture was stirred at reflux until the completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane). Then the reaction mixture was quenched with NH_4Cl solution (50 mL) and extracted with ethyl acetate (50 mL×3). The organic layer was washed with water (50 mL), dried (MgSO4), and evaporated under reduced pressure to give the residue. Chromatography on silica gel using ethyl acetate/*n*-hexane (1:1) afforded the desired products.

*3.1.1. 6-Acetyl-2-amino-5-hydroxy-1′-methyl-2′-oxospiro[chromene-4,3′-indoline]-3-carbonitrile (**4a**).* Yield: 270 mg (75%) as a solid; mp 274–276 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 12.84 (1H, s), 7.90 (1H, d, J=8.6 Hz), 7.32–7.03 (3H, m), 7.01–6.80 (3H, m), 6.71 (1H, d, J=8.6 Hz), 3.15 (3H, s), 2.50 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 204.7, 176.2, 160.3, 159.4, 154.1, 143.5, 133.5, 132.7, 128.6, 123.2, 122.6, 117.4, 115.8, 108.2, 107.6, 56.2, 54.8, 47.3, 26.4; IR (KBr) 3421, 3324, 3178, 2196, 1710, 1655, 1611, 1489, 1472, 1398, 1368, 1327, 1256, 1127, 1081, 1026, 808, 753 cm^{-1}; HRMS m/z (M^+) calcd for $C_{20}H_{15}N_3O_4$: 361.1063; found: 361.1067.

*3.1.2. 6-Acetyl-2-amino-5-hydroxy-2′-oxospiro[chromene-4,3′-indoline]-3-carbonitrile (**4b**).* Yield: 208 mg (60%) as a solid; mp 290 °C (decomp.); ^1H NMR (300 MHz, DMSO-d_6) δ 13.05 (1H, s), 10.59 (1H, s), 7.94 (1H, d, J=8.9 Hz), 7.31–7.10 (3H, m), 6.99–6.80 (3H, m), 6.74 (1H, d, J=8.9 Hz), 2.56 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 204.9, 177.9, 160.7, 159.4, 154.3, 142.0, 134.5, 132.8, 128.5, 123.6, 122.0, 117.7, 115.8, 109.4, 108.4, 107.6, 56.5, 47.7, 26.6; IR (KBr) 3316, 3176, 2194, 1711, 1651, 1475, 1401, 1326, 1255, 1129, 1079, 808, 752 cm^{-1}; HRMS m/z (M^+) calcd for $C_{19}H_{13}N_3O_4$: 347.0906; found: 347.0903.

*3.1.3. 6-Acetyl-2-amino-5-hydroxy-5′-methyl-2′-oxospiro[chromene-4,3′-indoline]-3-carbonitrile (**4c**).* Yield: 245 mg (68%) as a solid; mp 205–207 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 13.04 (1H, s), 10.45 (1H, s), 7.94 (1H, d, J=8.7 Hz), 7.17 (2H, br s), 6.97 (1H, d, J=7.5 Hz), 6.80–6.63 (3H, m), 2.56 (3H, s), 2.16 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 204.6, 177.6, 160.6, 159.2, 154.2, 139.5, 134.4, 132.4, 130.7, 128.6, 123.9, 117.4, 115.7, 109.0, 108.5, 107.4, 56.9, 47.6, 26.3, 20.4; IR (KBr) 3331, 3198, 2197, 1719, 1655, 1492, 1398, 1324, 1255, 1132, 1079, 810 cm^{-1}; HRMS m/z (M^+) calcd for $C_{20}H_{15}N_3O_4$: 361.1063; found: 361.1059.

*3.1.4. 6-Acetyl-2-amino-5′-bromo-5-hydroxy-2′-oxospiro[chromene-4,3′-indoline]-3-carbonitrile (**4d**).* Yield: 243 mg (57%) as a solid; mp 279 °C (decomp.); ^1H NMR (300 MHz, DMSO-d_6) δ 13.07 (1H, s), 10.71 (1H, s), 7.96 (1H, d, J=9.0 Hz), 7.36 (1H, d, J=8.3 Hz), 7.28 (2H, br s), 7.16 (1H, br s), 6.84 (1H, d, J=8.3 Hz), 6.75 (1H, d, J=9.0 Hz), 2.56 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 204.9, 177.6, 160.5, 159.5, 154.3, 141.4, 136.7, 132.9, 131.3, 126.5, 117.6, 115.8, 113.7, 111.4, 107.7, 107.7, 55.7, 47.9, 26.6; IR (KBr) 3318, 3180, 2197, 1718, 1653, 1475, 1401, 1325, 1254, 1127, 1079, 807, 632 cm^{-1}; HRMS m/z (M^+) calcd for $C_{19}H_{12}BrN_3O_4$: 425.0011; found: 425.0009.

*3.1.5. 6-Acetyl-2-amino-5′-chloro-5-hydroxy-2′-oxospiro[chromene-4,3′-indoline]-3-carbonitrile(**4e**).* Yield: 218 mg (57%) as a solid; mp 280 °C (decomp.); ^1H NMR (300 MHz, DMSO-d_6) δ 12.38 (1H, s), 10.05 (1H, s), 7.26 (1H, d, J=8.7 Hz), 6.64 (2H, s), 6.53 (1H, d, J=8.0 Hz), 6.37 (1H, s), 6.17 (1H, d, J=8.0 Hz), 6.05 (1H, d, J=8.7 Hz), 1.86 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 205.1, 177.9, 160.8, 159.8, 154.6, 141.3, 136.6, 133.2, 128.7, 126.2, 124.1, 117.8, 116.1, 111.1, 108.0, 56.1, 48.2, 26.8; IR (KBr) 3389, 3323, 3178, 2197, 1707, 1654, 1477,

Table 2
Additional reactions for the synthesis of a variety of 2-amino-5-hydroxy-4*H*-chromenes bearing spirooxindole moieties in the presence of $Ca(OH)_2$

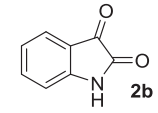
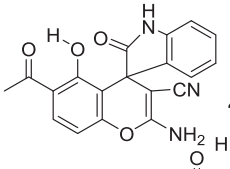
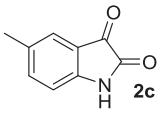
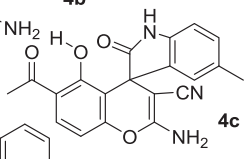
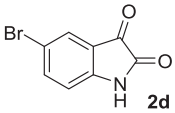
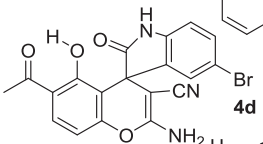
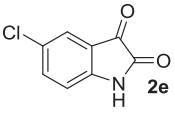
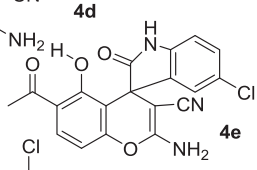
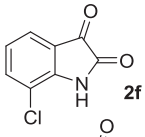
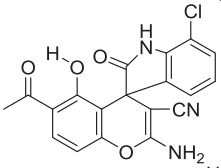
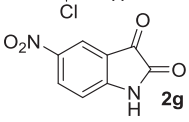
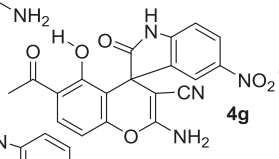
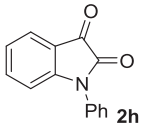
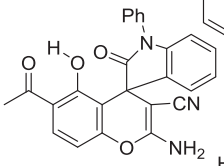
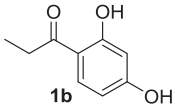
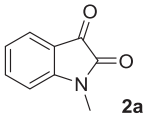
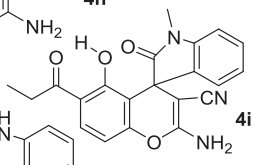
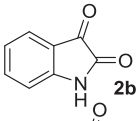
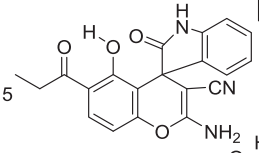
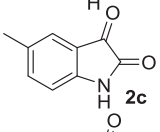
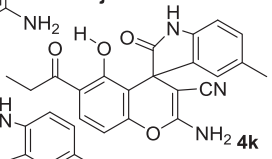
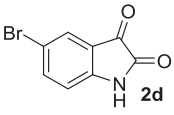
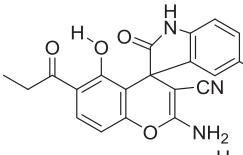
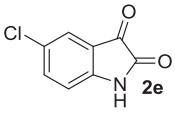
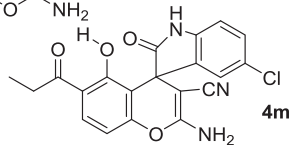
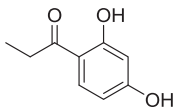
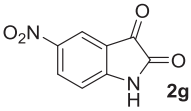
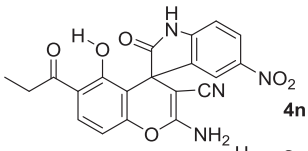
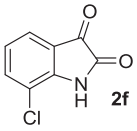
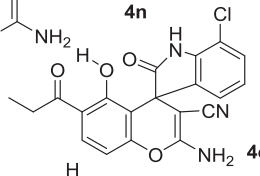
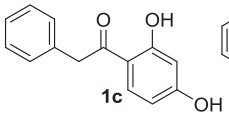
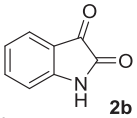
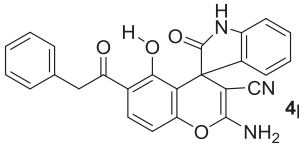
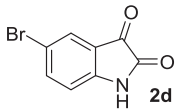
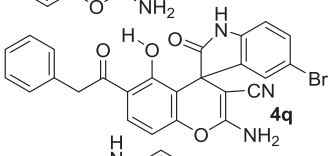
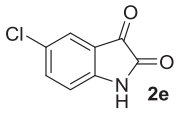
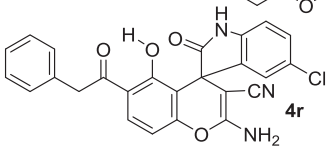
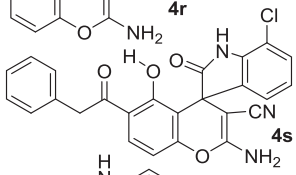
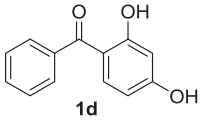
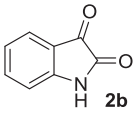
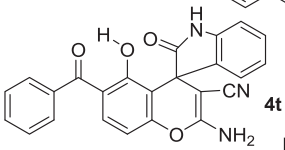
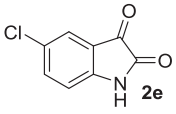
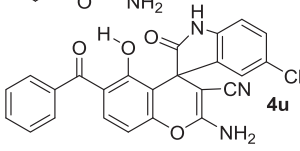
entry	resorcinols	isatins	malononitrile	time (h)	product	yield (%)
1	**1a**	 **2b**	 **3**	4	 **4b**	60
2		 **2c**		4	 **4c**	68
3		 **2d**		4	 **4d**	57
4		 **2e**		4	 **4e**	57
5		 **2f**		4	 **4f**	70
6		 **2g**		4	 **4g**	61
7		 **2h**		5	 **4h**	69
8	 **1b**	 **2a**		5	 **4i**	52
9		 **2b**		5	 **4j**	53
10		 **2c**		5	 **4k**	45
11		 **2d**		6	 **4l**	61
12		 **2e**		4	 **4m**	50

Table 2. *(continued)*

entry	resorcinols	isatins	malononitrile	time (h)	product	yield (%)
13	 **1b**	 **2g**		5	 **4n**	46
14		 **2f**		5	 **4o**	59
15	 **1c**	 **2b**		4	 **4p**	75
16		 **2d**		6	 **4q**	49
17		 **2e**	 **3**	5	 **4r**	55
18		 **2f**		5	 **4s**	50
19	 **1d**	 **2b**		6	 **4t**	55
20		 **2e**		6	 **4u**	40

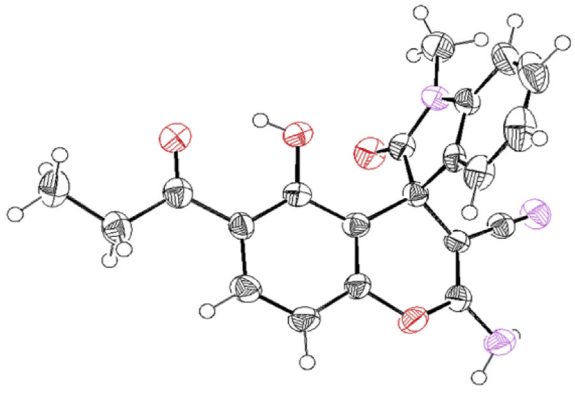


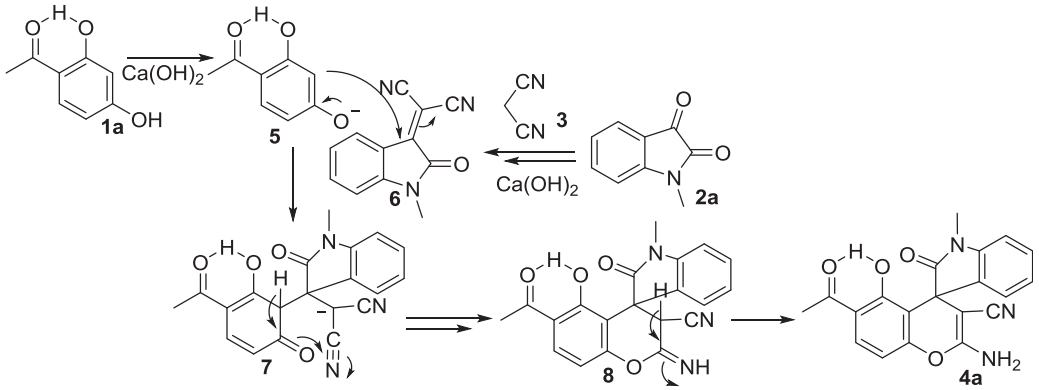
Fig. 1. The X-ray structure of compound **4i**.

1404, 1325, 1255, 1126, 1079, 809, 633 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{19}H_{12}ClN_3O_4$: 381.0516; found: 381.0518.

*3.1.6. 6-Acetyl-2-amino-7′-chloro-5-hydroxy-2′-oxospiro[chromene-4,3′-indoline]-3-carbonitrile (**4f**).* Yield: 267 mg (70%) as a solid; mp 269 °C (decomp.); ^1H NMR (300 MHz, DMSO-d_6) δ 12.97 (1H, s), 10.60 (1H, s), 7.90 (1H, d, *J*=8.9 Hz), 7.23–7.03 (3H, m), 6.98 (1H, s), 6.82 (1H, d, *J*=8.4 Hz), 6.68 (1H, d, *J*=8.9 Hz), 2.50 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 204.6, 177.4, 160.4, 159.4, 154.2, 140.9, 136.2, 132.7, 128.2, 125.8, 123.6, 117.3, 115.8, 110.7, 107.6, 107.5, 55.9, 47.9, 26.4; IR (KBr) 3390, 3319, 3175, 2197, 1707, 1653, 1478, 1405, 1325, 1254, 1127, 1079, 809, 633 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{19}H_{12}ClN_3O_4$: 381.0516; found: 381.0514.

*3.1.7. 6-Acetyl-2-amino-5-hydroxy-5′-nitro-2′-oxospiro[chromene-4,3′-indoline]-3-carbonitrile (**4g**).* Yield: 239 mg (61%) as a solid; mp 260 °C (decomp.); ^1H NMR (300 MHz, DMSO-d_6) δ 13.08 (1H, s), 11.37 (1H, s), 8.17 (1H, d, *J*=8.3 Hz), 7.97 (1H, d, *J*=9.0 Hz), 7.92 (1H, s), 7.45 (2H, s), 7.08 (1H, d, *J*=8.3 Hz), 6.77 (1H, d, *J*=9.0 Hz), 2.54 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 205.1, 178.7, 160.6, 160.0, 154.6, 148.8, 143.0, 135.6, 133.5, 126.3, 119.7, 117.7, 116.2, 110.0, 108.2, 107.3, 55.2, 48.1, 26.8; IR (KBr) 3442, 3364, 3276, 2197, 1731, 1652, 1484, 1404, 1333, 1254, 1079, 809, 632 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{19}H_{12}N_4O_6$: 392.0757; found: 392.0759.

*3.1.8. 6-Acetyl-2-amino-5-hydroxy-2′-oxo-1′-phenylspiro[chromene-4,3′-indoline]-3-carbonitrile (**4h**).* Yield: 292 mg (69%) as a solid; mp 254–256 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 13.08 (1H, s), 8.00 (1H, d, *J*=9.0 Hz), 7.78–7.56 (2H, m), 7.55–7.40 (3H, m), 7.36 (2H, s), 7.22 (1H, t, *J*=7.5 Hz), 7.13–6.96 (2H, m), 6.80 (1H, d, *J*=9.0 Hz), 6.71 (1H, d, *J*=7.8 Hz), 2.58 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 204.5, 175.7, 160.2, 159.2, 154.1, 143.1, 134.5, 133.2, 132.7, 129.6, 128.5, 128.1, 126.6, 123.7, 123.1, 117.3, 115.9, 108.5, 108.1, 107.5, 56.4, 47.4, 26.4; IR



Scheme 4. Plausible mechanism for the formation of **4a**.

(KBr) 3463, 3318, 3192, 2196, 1722, 1657, 1609, 1498, 1369, 1327, 1254, 1077, 810, 749, 700, 625 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{25}H_{17}N_3O_4$: 423.1219; found: 423.1217.

*3.1.9. 2-Amino-5-hydroxy-1′-methyl-2′-oxo-6-propionylspiro[chromene-4,3′-indoline]-3-carbonitrile (**4i**).* Yield: 195 mg (52%) as a solid; mp 270–272 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 13.00 (1H, s), 7.97 (1H, d, *J*=9.0 Hz), 7.32–7.19 (3H, m), 7.09–6.91 (3H, m), 6.76 (1H, d, *J*=9.0 Hz), 3.21 (3H, s), 3.02 (2H, q, *J*=7.5 Hz), 1.03 (3H, t, *J*=7.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 207.3, 176.5, 160.6, 159.7, 154.2, 143.8, 133.8, 132.1, 128.8, 123.5, 122.9, 117.7, 115.5, 108.6, 108.5, 107.8, 56.4, 47.6, 31.2, 26.7, 8.2; IR (KBr) 3385, 3309, 3198, 2194, 1718, 1655, 1468, 1367, 1236, 1120, 1080, 1023, 803, 748 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{21}H_{17}N_3O_4$: 375.1219; found: 375.1217.

*3.1.10. 2-Amino-5-hydroxy-2′-oxo-6-propionylspiro[chromene-4,3′-indoline]-3-carbonitrile (**4j**).* Yield: 191 mg (53%) as a solid; mp 289 °C (decomp.); ^1H NMR (300 MHz, DMSO-d_6) δ 13.08 (1H, s), 10.57 (1H, s), 7.96 (1H, d, *J*=8.9 Hz), 7.25–7.12 (3H, m), 6.94–6.81 (3H, m), 6.74 (1H, d, *J*=8.9 Hz), 3.02 (2H, q, *J*=6.9 Hz), 1.04 (3H, t, *J*=6.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 207.1, 177.8, 160.5, 159.3, 154.1, 142.0, 134.4, 131.7, 128.4, 123.5, 121.9, 117.6, 115.3, 109.3, 108.5, 107.5, 56.6, 47.7, 31.0, 8.0; IR (KBr) 3472, 3332, 3193, 2197, 1721, 1655, 1469, 1393, 1299, 1236, 1119, 1076, 808, 747 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{20}H_{15}N_3O_4$: 361.1063; found: 361.1060.

*3.1.11. 2-Amino-5-hydroxy-5′-methyl-2′-oxo-6-propionylspiro[chromene-4,3′-indoline]-3-carbonitrile (**4k**).* Yield: 169 mg (45%) as a solid; mp >300 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 13.06 (1H, s), 10.42 (1H, s), 7.98 (1H, d, *J*=9.0 Hz), 7.14 (2H, br s), 6.98 (1H, d, *J*=7.8 Hz), 6.78–6.67 (3H, m), 3.04 (2H, q, *J*=7.1 Hz), 2.18 (3H, s), 1.07 (3H, t, *J*=7.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 207.2, 177.9, 160.6, 159.3, 154.1, 139.6, 134.6, 131.8, 130.9, 128.8, 124.1, 117.8, 115.3, 109.2, 108.6, 107.6, 56.7, 47.7, 31.1, 20.6, 8.0; IR (KBr) 3472, 3322, 3185, 2197, 1719, 1655, 1491, 1393, 1305, 1239, 1131, 1110, 809 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{21}H_{17}N_3O_4$: 375.1219; found: 375.1219.

*3.1.12. 2-Amino-5′-bromo-5-hydroxy-2′-oxo-6-propionylspiro[chromene-4,3′-indoline]-3-carbonitrile (**4l**).* Yield: 268 mg (61%) as a solid; mp 188–190 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 13.10 (1H, s), 10.70 (1H, s), 7.98 (1H, d, *J*=8.6 Hz), 7.36 (1H, d, *J*=8.1 Hz), 7.26 (2H, s), 7.15 (1H, s), 6.83 (1H, d, *J*=8.1 Hz), 6.74 (1H, d, *J*=8.6 Hz), 3.03 (2H, q, *J*=6.6 Hz), 1.05 (3H, t, *J*=6.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 207.0, 177.3, 160.3, 159.4, 154.0, 141.4, 136.7, 131.9, 131.1, 126.3, 117.4, 115.3, 113.5, 111.2, 107.7, 107.5, 55.8, 47.8, 30.9, 7.9; IR (KBr) 3476, 3309, 3182, 2197, 1722, 1655, 1472, 1396, 1303, 1239, 1119, 1080, 807 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{20}H_{14}BrN_3O_4$: 439.0168; found: 439.0171.

*3.1.13. 2-Amino-5′-chloro-5-hydroxy-2′-oxo-6-propionylspiro[chromene-4,3′-indoline]-3-carbonitrile (**4m**).* Yield: 198 mg (50%) as a solid; mp >300 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 13.08 (1H, s), 10.68 (1H, s), 7.98 (1H, d, *J*=8.7 Hz), 7.29–7.17 (3H, m), 7.03 (1H, s), 6.88 (1H, d, *J*=8.1 Hz), 6.74 (1H, d, *J*=8.7 Hz), 3.03 (2H, q, *J*=6.6 Hz), 1.04 (3H, t, *J*=6.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 207.0, 177.5, 160.4, 159.4, 154.0, 141.0, 136.3, 131.9, 128.3, 125.8, 123.6, 117.4, 115.3, 110.7, 107.7, 107.5, 55.9, 47.9, 30.9, 7.9; IR (KBr) 3475, 3305, 3180, 2196, 1724, 1654, 1473, 1395, 1302, 1238, 1119, 807 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{20}H_{14}ClN_3O_4$: 395.0673; found: 395.0677.

*3.1.14. 2-Amino-5-hydroxy-5′-nitro-2′-oxo-6-propionylspiro[chromene-4,3′-indoline]-3-carbonitrile (**4n**).* Yield: 187 mg (46%) as a solid; mp >300 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 13.10 (1H, s), 11.32 (1H, s), 8.18 (1H, d, *J*=8.7 Hz), 8.00 (1H, d, *J*=9.0 Hz), 7.89 (1H, s), 7.37 (2H, s), 7.09 (1H, d, *J*=8.7 Hz), 6.77 (1H, d, *J*=9.0 Hz), 3.02 (2H, q, *J*=7.2 Hz), 1.02 (3H, t, *J*=7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 207.0, 178.3, 160.2, 159.6, 154.1, 148.5, 142.6, 135.3, 132.2, 125.9, 119.2, 117.3, 115.4, 109.6, 107.7, 107.1, 55.0, 47.8, 30.9, 7.8; IR (KBr) 3421, 3306, 3182, 2195, 1725, 1653, 1524, 1479, 1406, 1340, 1232, 1118, 1077, 833, 690 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{20}H_{14}N_4O_6$: 406.0913; found: 406.0910.

*3.1.15. 2-Amino-7′-chloro-5-hydroxy-2′-oxo-6-propionylspiro[chromene-4,3′-indoline]-3-carbonitrile (**4o**).* Yield: 234 mg (59%) as a solid; mp >300 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 13.11 (1H, s), 10.97 (1H, s), 7.98 (1H, d, *J*=8.7 Hz), 7.31–7.18 (3H, m), 6.95–6.86 (2H, m), 6.74 (1H, d, *J*=8.7 Hz), 3.02 (2H, q, *J*=7.1 Hz), 1.04 (3H, t, *J*=7.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 207.0, 177.7, 160.3, 159.3, 153.8, 139.7, 136.0, 131.9, 128.3, 123.1, 122.1, 117.3, 115.3, 113.5, 107.9, 107.5, 56.0, 48.5, 30.9, 7.8; IR (KBr) 3413, 3326, 3199, 2197, 1729, 1649, 1466, 1400, 1239, 1124, 1088, 800, 751 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{20}H_{14}ClN_3O_4$: 395.0673; found: 395.0676.

*3.1.16. 2-Amino-5-hydroxy-1′-methyl-2′-oxo-6-(2-phenylacetyl) spiro[chromene-4,3′-indoline]-3-carbonitrile (**4p**).* Yield: 317 mg (75%) as a solid; mp >300 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 12.91 (1H, s), 10.53 (1H, s), 8.14 (1H, d, *J*=8.7 Hz), 7.35–7.09 (8H, m), 6.95–6.70 (4H, m), 4.36 (2H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 203.9, 177.6, 160.9, 159.2, 154.2, 141.9, 134.3, 134.2, 132.3, 129.5, 128.3, 128.2, 126.7, 123.4, 121.8, 117.4, 115.1, 109.2, 108.6, 107.5, 56.6, 47.6, 44.1; IR (KBr) 3432, 3289, 3181, 2198, 1716, 1650, 1478, 1404, 1345, 1255, 1109, 1040, 804, 746 cm^{-1}; HRMS *m*/*z* (M^+) calcd for $C_{25}H_{17}N_3O_4$: 423.1219; found: 423.1216.

*3.1.17. 2-Amino-5′-bromo-5-hydroxy-2′-oxo-6-(2-phenylacetyl)spiro [chromene-4,3′-indoline]-3-carbonitrile (**4q**).* Yield: 246 mg (49%) as a solid; mp >300 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 12.94 (1H, s), 10.69 (1H, s), 8.15 (1H, d, *J*=8.7 Hz), 7.40–7.12 (9H, m), 6.89–6.71 (2H, m), 4.36 (2H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 203.9, 177.3, 160.8, 159.3, 154.3, 141.3, 136.6, 134.2, 132.5, 131.1, 129.6, 128.3, 126.7, 126.3, 117.4, 115.2, 113.5, 111.2, 107.9, 107.6, 55.9, 47.8, 44.2; IR

(KBr) 3359, 3170, 2195, 1724, 1649, 1475, 1401, 1349, 1258, 1111, 1036, 806, 696 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{25}H_{16}BrN_3O_4$: 501.0324; found: 501.0325.

*3.1.18. 2-Amino-5′-chloro-5-hydroxy-2′-oxo-6-(2-phenylacetyl)spiro[chromene-4,3′-indoline]-3-carbonitrile (**4r**).* Yield: 252 mg, (55%) as a solid; mp >300 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 12.96 (1H, s), 10.71 (1H, s), 8.17 (1H, d, *J*=8.7 Hz), 7.36–7.16 (8H, m), 7.07 (1H, s), 6.87 (1H, d, *J*=8.1 Hz), 6.78 (1H, d, *J*=8.7 Hz), 4.38 (2H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 203.9, 177.4, 160.8, 159.3, 154.3, 140.9, 136.2, 134.2, 132.5, 129.6, 128.3, 128.2, 126.7, 125.8, 123.6, 117.3, 115.1, 110.7, 107.8, 107.7, 55.9, 47.9, 44.2; IR (KBr) 3357, 3169, 2196, 1724, 1648, 1478, 1401, 1349, 1257, 1111, 1037, 806, 698 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{25}H_{16}ClN_3O_4$: 457.0829; found: 457.0831.

*3.1.19. 2-Amino-7′-chloro-5-hydroxy-2′-oxo-6-(2-phenylacetyl)spiro[chromene-4,3′-indoline]-3-carbonitrile (**4s**).* Yield: 229 mg (50%) as a solid; mp 177–179 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 12.95 (1H, s), 10.98 (1H, s), 8.17 (1H, d, *J*=8.9 Hz), 7.40–7.16 (8H, m), 6.93 (2H, br s), 6.78 (1H, d, *J*=8.9 Hz), 4.38 (2H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 203.9, 177.6, 161.3, 160.8, 159.3, 154.1, 139.7, 136.0, 134.2, 132.5, 129.6, 128.3, 126.7, 123.1, 122.1, 117.3, 115.2, 113.5, 108.0, 107.6, 56.0, 48.4, 44.1; IR (KBr) 3338, 3200, 2197, 1730, 1650, 1469, 1402, 1360, 1255, 1114, 1041, 800, 741, 717 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{25}H_{16}ClN_3O_4$: 457.0829; found: 457.0829.

*3.1.20. 2-Amino-6-benzoyl-5-hydroxy-2′-oxospiro[chromene-4,3′-indoline]-3-carbonitrile (**4t**).* Yield: 225 mg (55%) as a solid; mp >300 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 12.54 (1H, s), 10.61 (1H, s), 7.67–7.45 (6H, m), 7.29–7.12 (3H, m), 7.02–6.82 (3H, m), 6.75 (1H, d, *J*=8.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 199.7, 177.8, 161.0, 159.3, 154.2, 142.0, 136.9, 134.4, 134.2, 132.2, 128.8, 128.5, 128.4, 123.6, 122.0, 117.6, 115.7, 109.3, 109.0, 107.6, 56.6, 47.8; IR (KBr) 3421, 3319, 3187, 2193, 1713, 1648, 1478, 1397, 1343, 1256, 1093, 1019, 802, 754, 704 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{24}H_{15}N_3O_4$: 409.1063; found: 409.1065.

*3.1.21. 2-Amino-6-benzoyl-5′-chloro-5-hydroxy-2′-oxospiro[chromene-4,3′-indoline]-3-carbonitrile (**4u**).* Yield: 178 mg (40%) as a solid; mp >300 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 12.54 (1H, s), 10.74 (1H, s), 7.70–7.68 (3H, m), 7.68–7.46 (3H, m), 7.31 (2H, s), 7.24 (1H, d, *J*=8.3 Hz), 7.12 (1H, s), 6.88 (1H, d, *J*=8.3 Hz), 6.75 (1H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 199.5, 177.5, 160.7, 159.4, 154.1, 141.0, 136.9, 136.3, 134.2, 132.1, 128.7, 128.4, 128.2, 125.8, 123.7, 117.4, 115.8, 110.7, 108.2, 107.6, 55.9, 48.0; IR (KBr) 3352, 3309, 3183, 2195, 1714, 1648, 1628, 1478, 1401, 1342, 1254, 1092, 803, 698 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{24}H_{14}ClN_3O_4$: 443.0673; found: 443.0670.

Acknowledgements

This research was supported by the Nano Material Technology Development Program of the Korean National Research Foundation (NRF) funded by the Korean Ministry of Education, Science, and Technology (2012M3A7B4049675).

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.09.021.

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Please cite this article in press as: Park, J. H.; et al., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.09.021