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Synthesis and Antitumor Activity of Novel Coumarin Derivatives via a Three-component Reaction in Water

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An efficient synthesis of novel coumarin derivatives via a three-component condensation of 4-hydroxycoumarin, aldehydes and aromatic amines catalyzed by sulfonic acid functionalized ionic liquid *L*-2-(hydroxymethyl)-1-(4-sulfobutyl)pyrrolidinium hydrogen sulfate ([HYSBPI]•HSO_4) is reported. The condensed product was obtained with excellent yields in water under microwave irradiation condition. The antitumor activities of all the synthesized compounds were assessed on two different human cancer cell lines (A-549 and MCF-7), and the results showed that these compounds had weak-to-good antitumor activities and their IC_{50} ranged from 0.05 to more than 100 μmol•L^{-1}.

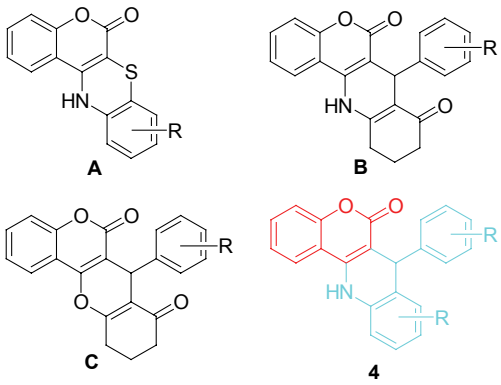
Keywords coumarins, multicomponent reactions, antitumor activity, sulfonic acid functionalized ionic liquids

Introduction

Multicomponent reactions (MCRs) have proven to be a valuable asset in medicinal chemistry, drug design, and drug discovery because of their simplicity, efficiency and high selectivity.[1] Besides typical multi-step syntheses, an increasing number of bioactive small molecules were synthesized by multicomponent reactions (MCRs). Such processes in which three or more reactants are combined together in a single reaction flask to provide a product incorporating most of the atoms contained in the starting materials have the advantages of the intrinsic atom economy, simpler procedures and equipment, time and energy savings, as well as wide environmental friendliness.[2]

The coumarin derivatives have interesting biological properties, such as antiallergic, antitumor, anticoagulant, antibacterial, and calcium channel blocking activity.[3] In particular, 1-benzopyrano[3,4-*b*][1,4]benzothiazin-6-ones **A**[4] have been synthesized and displayed interesting antioxidant and estrogenic-like effects in HepG2 and MCF-7 cells. Chromeno[4,3-*b*]quinoline derivatives **B**[5] were synthesized from 4-amino-coumarin, aldehydes and 1,3-cyclohexadione, and showed moderate cytotoxic capacity and very low calcium channel antagonist activity. Also, coumarin derivatives have been synthesized by three-component condensation of 4-hydroxycoumarin, aldehydes and *β*-naphthylamine[6] or 2-aminoanthracene[7] or cyclic 1,3-dicarbonyl compounds **C**.[8] Benzopyrano[3,2-*c*]-chromene-6,8-dione derivatives **C** showed weak-to-moderate anticancer activity against four cell lines (Raji, HeLa, LS180, and MCF-7) (Scheme 1).

Scheme 1



To the best of our knowledge, the preparation of 7,12-dihydro-6*H*-chromeno[4,3-*b*]quinoline derivatives **4** via a three-component condensation of 4-hydroxycoumarin, aldehydes and aniline has not been reported (Scheme 1). In continuing with our ongoing work on the development of multicomponent reaction for the rapid access to biologically active coumarin derivatives,[9] herein we report the first construction of 7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolines via three-component reaction catalyzed by a novel sulfonic acidic ionic liquid (Scheme 2) in water. Most importantly, these previously unreported novel series of coumarin derivatives displayed good antitumor activity.

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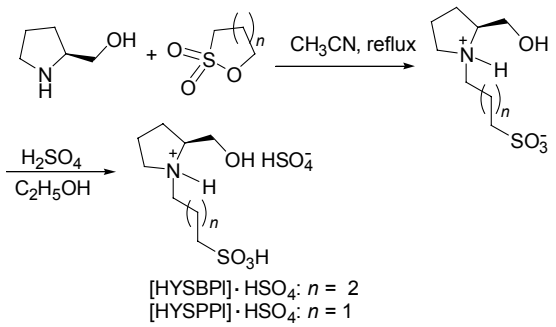
Scheme 2

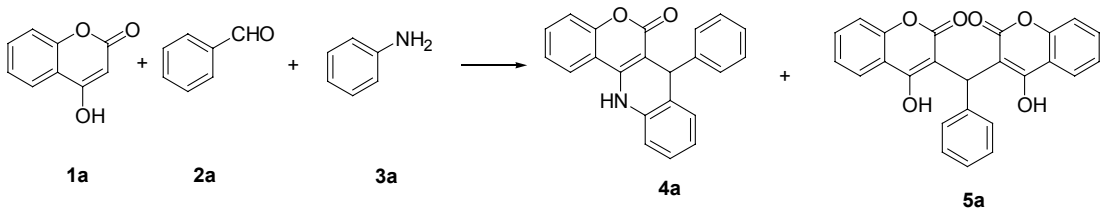


Results and Discussion

Previously, manolov[10] has reported a two-step reaction for the preparation of 3-benzylidene-4-phenyliminocoumarin used 4-hydroxycoumarin, aniline and benzaldehyde as starting materials. During our work, the unexpected condensation product **4a** was obtained in good yields via one-pot three-component condensation of 4-hydroxycoumarin, benzaldehyde and aniline.

In our initial study, 4-hydroxycoumarin (**1a**), benzaldehyde (**2a**) and aniline (**3a**) were chosen as model reagents to optimize the reaction conditions, and the results are summarized in Table1. Firstly, several catalysts such as *p*-TSA, $Yb(OTf)_3$, $Zn(OTf)_2$, NH_4OAc, $ZnCl_2$ and $FeCl_3$ were examined to establish standard reaction conditions. It was found that 54% of the target compound **4a** was obtained in refluxing CH_3COOH for 8 h in the presence of catalyst *p*-TSA (Table1, Entry 3). When ionic liquid [DMDBSI]•$2HSO_4$ was used, we were delighted to find that 83% yield of **4a** was got in CH_3COOH reflux condition, compared to 15% in refluxing EtOH and 56% of **4a** in water reflux condition (Table 1, Entries 7—9). Finally, the best result was achieved when [HYSBPI]•HSO_4 was used as the catalyst in H_2O (Table1, Entry 10). It is possible that the novel SO_3H-functionalized ionic liquid [HYSBPI]•HSO_4 has a structure of hydroxyl group in the cation, which enhanced the solubility of reactant in water.

Table 1 Optimization of reaction conditions for the synthesis of **4a**[a]



Entry	Catalyst (Loading/mol%)	Reaction condition	Yield[c]/%	
			4a	**5a**
1	None	EtOH, reflux, 8 h	Trace	56
2	*L*-Proline (10)	EtOH, reflux, 8 h	15	62
3	*p*-TSA (10)	CH_3COOH, reflux, 8 h	54	23
4	$Yb(OTf)_3$ (10)	EtOH, reflux, 8 h	13	65
5	NH_4OAc (10)	CH_3COOH, reflux, 8 h	25	49
6	$ZnCl_2$ (10)	EtOH, reflux, 8 h	20	46
7	[DMDBSI]•$2HSO_4$ (10)	EtOH, reflux, 8 h	15	43
8	[DMDBSI]•$2HSO_4$ (10)	CH_3COOH, reflux, 6 h	83	Trace
9	[DMDBSI]•$2HSO_4$ (10)	H_2O, reflux, 8 h	56	16
10	[HYSBPI]•HSO_4 (10)	H_2O, reflux, 8 h	84	Trace
11[b]	[HYSBPI]•HSO_4 (10)	H_2O, 150 ℃, 15 min	93	Trace
12[b]	[HYSBPI]•HSO_4 (20)	H_2O, 150 ℃, 13 min	94	Trace
13[b]	[HYSBPI]•HSO_4 (15)	H_2O, 150 ℃, 13 min	93	Trace
14[b]	[HYSBPI]•HSO_4 (10)	H_2O, 140 ℃, 20 min	86	Trace
15[b]	[HYSBPI]•CF_3SO_3 (10)	H_2O, 150 ℃, 15 min	90	Trace
16[b]	[HYSBPI]•CF_3CO_3 (10)	H_2O, 150 ℃, 15 min	92	Trace
17[b]	[HYSBPI]•CH_3COO (10)	H_2O, 150 ℃, 15 min	87	Trace
18[b]	[HYSPPI]•HSO_4 (10)	H_2O, 150 ℃, 15 min	92	Trace

[a] 1 mmol 4-hydroxycoumarin, 1 mmol benzaldehyde, 1 mmol aniline. [b] Experiments were carried out in a Discover-CEM monomode microwave apparatus. [c] Isolated yields based on **1a**.

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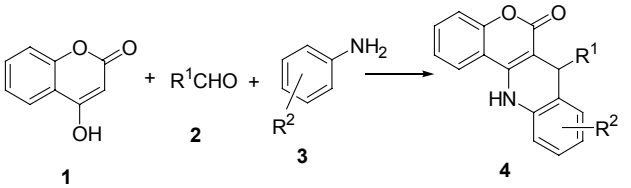
Recently, organic reactions accelerated by microwave irradiation have drawn attention and exhibited several advantages over conventional heating.[11] In order to improve yield and shorten the reaction time, the microwave irradiation was exploited. The desired product **4a** was obtained with 93% isolated yield at 150 ℃ for 15 min as shown in Table 1 (Entry 11). To further optimize the reaction conditions, the amount of [HYSBPI]•HSO_4 required for this reaction was tested, and the results from Table 1 (Entries 11—13) showed that 10 mol% of [HYSBPI]•HSO_4 was enough to promote the reaction efficiently. Some other TSILs with different anions such as $CF_3SO_3^-$, CH_3COO^-, CF_3COO^- were undertaken and proved to be very active, leading to 87%—92% yields of **4a** (Table 1, Entries 15—17). In addition, the change of the length of alkyl sulfonic acid (n=1) of the TSILs also resulted in excellent yields (Table 1, Entry 18).

The experimental procedure was remarkably simple in view of the fact that the insoluble crude products were isolated by simple filtration after the completion of the reaction and recrystallized to obtain pure products, while the catalyst [HYPPSI]•HSO_4 dissolved in water could directly be recovered and recycled. When the recovered catalyst was applied for six cycles of reactions, there was almost no effect in the yields (yield: 93%, 92%, 92%, 91%, 90%, 91%).

The subsequent study was performed under the optimized conditions: with 10 mol% [HYSBPI]•HSO_4 in water under microwave irradiation for 15 min at 150 ℃. As shown in Table 2, this protocol could be applied not only to the aromatic aldehydes with either electron-withdrawing groups (such as halide groups) or electron-donating groups (such as alkoxyl and hydroxyl groups) but also to the aliphatic aldehydes under the same conditions. When aliphatic aldehyde such as isobutyraldehyde was used, the yield was slightly decreased due to the incomplete consume of raw materials. Furthermore, a wide range of aromatic amines including *p*-toluidine, *m*-toluidine, *p*-ethoxyaniline, *p*-methoxyaniline, *p*-chloroaniline and *p*-bromoaniline were employed successfully in this reaction with excellent results, and the anilines with electron-donating groups generally showed slightly higher yields than those with electron-withdrawing groups. However, the reaction failed with *p*-nitroaniline due to the strong electron withdrawing effect.

Based on the literature,[12] the proposed mechanism for the synthesis of **4a** is described in Scheme 3. First, the condensation of aldehyde **2** and aromatic amine **3** gave Schiff base **7**. 4-Hydroxycoumarin **I** with the addition of Schiff base **7** furnished the intermediate product **IV**, which then formed **4** via the intermolecular cyclization and the subsequent dehydration. To test the mechanism described above, the reaction of intermediate product *N*-benzylideneaniline and 4-hydroxycoumarin was carried out in water at 150 ℃ in the presence of catalyst [HYSBPI]•HSO_4 under microwave irradiation

Table 2 Synthesis of 7,12-dihydro-6*H*-chromeno[4,3-*b*]quinoline derivatives[a]



1 2 3 4

Entry	R^1	R^2	Product	Yield[b]/%
1	Ph	H	**4a**	93
2	Ph	4-Me	**4b**	94
3	4-Cl-C_6H_4	4-Me	**4c**	91
4	4-Me-C_6H_4	4-Me	**4d**	90
5	4-F-C_6H_4	4-Me	**4e**	91
6	4-MeO-C_6H_4	4-Me	**4f**	90
7	2,4-$(Cl)_2$-C_6H_3	4-Me	**4g**	89
8	3-MeO-C_6H_4	4-Me	**4h**	92
9	2-MeO-C_6H_4	4-Me	**4i**	90
10	3-MeO-4-OH-C_6H_3	4-Me	**4j**	90
11	2-Cl-C_6H_4	4-Me	**4k**	91
12	1-Naphthyl	4-Me	**4l**	92
13	*t*-Bu	4-Me	**4m**	81
14	Ph	4-Cl	**4n**	83
15	4-Me-C_6H_4	4-Cl	**4o**	84
16	4-Cl-C_6H_4	4-Cl	**4p**	80
17	Ph	4-Br	**4q**	81
18	Ph	4-MeO	**4r**	93
19	Ph	4-EtO	**4s**	94
20	Ph	3-Me	**4t**	92

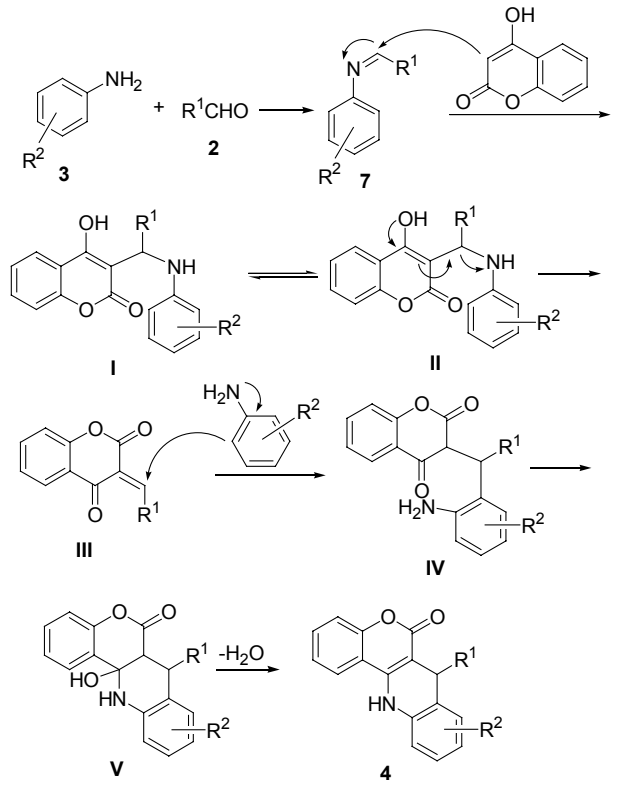
[a] All reactions were carried out with 1 mmol 4-hydroxycoumarin, 1 mmol aldehydes, and 1 mmol aniline compounds in the presence of 0.1 mmol [HYSBPI]•HSO_4 in H_2O (2 mL). [b] Isolated yields based on **1a**.

condition. The target compound **4a** was obtained in similar yield.

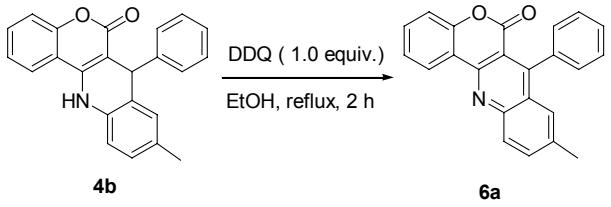
Considering that pyridine is also a core skeleton in bioactive molecules, the aromatization of the products **4b** or **4d** was attempted by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidant (Scheme 4). It was fortunately found that products **6a** and **6b** could be attained in high yields (96%, 95%) under the reflux condition.

All the synthesized compounds were subjected to *in vitro* anticancer evaluation using the MTT assay in two human cancer cell lines representative of major cancer sub-types-MCF-7 (breast) and A-549 (non-small cell lung) and IC_{50} (μmol•L^{-1}) are presented in Table 3. Among the tested compounds, the products **4b**, **4d**, **4e**, **4h**, **4m**, **4j**, **4n**, **4q**, **4r** had stronger inhibitory effects than Cisplatin both in MCF-7 cells and in A-549 cells.

Scheme 3



Scheme 4



But the compounds **4l**, **6a** and **6b** were found to be fairly inactive for IC_{50} values of higher than 100 μmol•L^{-1} in all cell lines. Compounds **4b**, **4e**, **4h**, **4n**, **4r** could be used as the most potent anticancer drugs for IC_{50} values of lower than 1 μmol•L^{-1}. Furthermore, IC_{50} (>100 μmol•L^{-1}) values of the oxidation products **6a** and **6b** were higher than those of **4b** and **4d**, and the results show that the cytotoxic activity of 7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolines was higher than that of the oxidation products 6*H*-chromeno[4,3-*b*]quinolines.

Experimental

All microwave irradiation experiments were carried out in a Discover-CEM monomode microwave apparatus. Melting points were determined on a Büchi B-540 capillary melting point apparatus and uncorrected. IR spectra were recorded on an AVATAR-370, samples were prepared as KBr plates. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian 400-MHz spectrometer. Mass spectra were measured with a Thermo Finnigan LCQ-Advantage. High resolution mass spectra (HRMS) were measured on an Agilent 6210 TOF LC/MS using ESI or EI (electrospray ionization) techniques.

Table 3 Cytotoxic activity of synthetic compounds assessed by the MTT reduction assay

Entry	Compound	IC_{50}/(μmol•L^{-1})	
		MCF-7	A-549
1	**4a**	30.10	9.21
2	**4b**	0.52	0.14
3	**4c**	68.86	1.02
4	**4d**	4.41	0.42
5	**4e**	0.63	0.16
6	**4f**	30.80	3.95
7	**4g**	51.96	>100
8	**4h**	0.65	0.05
9	**4i**	29.82	14.00
10	**4j**	1.53	1.19
11	**4k**	48.13	77.01
12	**4l**	>100	>100
13	**4m**	1.11	1.04
14	**4n**	0.82	0.74
15	**4o**	10.01	2.15
16	**4p**	7.86	7.46
17	**4q**	1.69	0.91
18	**4r**	0.82	0.41
19	**4s**	41.41	25.66
20	**4t**	12.53	0.32
21	**6a**	>100	>100
22	**6b**	>100	>100
23	Cisplatin	6.38	10.32

General procedure for the synthesis of [HYSBPI]•HSO_4

To a solution of *L*-prolinol (20 mmol) in CH_3CN (10 mL) was added 1,4-butanesultone (20 mmol) in portion within 30 min, and then the mixture was stirred at reflux for 5 h and then filtered, and washed with ether. Then H_2SO_4 (20 mmol) was added dropwise in ethanol (3 mL) in 30 min. The final solution was stirred at 50 ℃ for another 1 h and evaporated under reduced pressure to give [HYSBPI]•HSO_4 as a viscous light liquid.

[HYSBPI]•HSO_4: n=2, viscous light brown liquid. ^{1}H NMR (400 MHz, D_2O) δ: 4.25－4.21 (m, 1H), 4.09－4.04 (m, 1H), 3.76－3.70 (m, 1H), 3.61－3.46 (m, 2H), 3.34－3.22 (m, 1H), 3.09－2.93 (m, 2H), 2.81－2.77 (m, 2H), 2.18－1.63 (m, 7H); ^{13}C NMR (100 MHz, D_2O) δ: 69.5, 67.4, 65.9, 59.93, 50.6, 26.3, 24.3, 22.5, 21.9; MS (ESI) m/z: 238.1 $[M–HSO_4]^+$.

[HYSPPI]•HSO_4: n=1, viscous light brown liquid. ^{1}H NMR (400 MHz, D_2O) δ: 4.14－4.10 (m, 1H), 3.98－3.93 (m, 1H), 3.66－3.62 (m, 1H), 3.50－3.24 (m, 3H), 3.08－2.90 (m, 2H), 2.79－2.67 (m, 2H),

2.07－1.55 (m, 5H); ^{13}C NMR (100 MHz, D_2O) δ: 69.7, 67.5, 65.8, 55.2, 55.0, 26.2, 22.4, 21.3; MS (ESI) *m*/*z*: 224.1 $[M–HSO_4]^+$.

General procedure for the synthesis of 7,12-dihydro-6*H*-chromeno[4,3-*b*]quinoline derivatives 4a－4t

In a 10 mL pressurized vial snap-on cap, 4-hydroxycoumarin **1** (1 mmol), aldehyde **2** (1 mmol), aniline **3** (1 mmol) and [HYSBPI]•HSO_4 (0.1 mmol) in water (2 mL) were added. The reaction mixture was irradiated for 15 min at 150 ℃. After the completion of the reaction, the reaction mixture was cooled to room temperature, filtered, and washed with water, and recrystallized from acetic acid/ethylenedichloride chloride (12 mL, V∶V=1∶3) to give the corresponding compounds **4a－4t**.

7-Phenyl-7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolin-6-one (**4a**): White solid, m.p.＞300 ℃; ^{1}H NMR (400 MHz, DMSO) δ: 9.88 (s, 1H, NH), 8.33 (d, J_1= 0.8 Hz, J_2=8.0 Hz, 1H), 7.61－7.65 (m, 1H), 7.44 (t, J=8.0 Hz, 1H), 7.35 (t, J=8.0 Hz, 2H), 7.17－7.24 (m, 6H), 7.07－7.11 (m, 1H), 6.97 (t, J=8.0 Hz, 1H), 5.24 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ: 151.9, 147.1, 143.5, 135.2, 131.5, 129.2, 128.1, 127.2, 126.8, 126.0, 124.1, 123.6, 123.5, 122.5, 116.7, 116.1, 113.2, 96.1, 40.9; IR (KBr) *v*: 3312, 1659, 1618, 1528, 1482, 1445, 1254, 1089 cm^{-1}; MS (ESI) *m*/*z*: 326.2 $[M+H]^+$; HRMS (ESI) calcd for $C_{22}H_{16}NO_2$ $[M+H]^+$ 326.1181, found 326.1186.

9-Methyl-7-phenyl-7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolin-6-one (**4b**): White solid, m.p.＞300 ℃; ^{1}H NMR (400 MHz, DMSO) δ: 9.83 (s, 1H, NH), 8.31 (dd, J_1=1.2 Hz, J_2=8.0 Hz, 1H), 7.59－7.63 (m, 1H), 7.40 －7.44 (m, 1H), 7.34 (d, J=8.0 Hz, 1H), 7.16－7.24 (m, 5H), 7.06－7.10 (m, 1H), 6.98－7.00 (m, 2H), 5.17 (s, 1H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ: 160.1, 151.9, 147.3, 143.4, 132.8, 132.6, 131.5, 129.4, 128.1, 127.8, 126.9, 126.0, 124.0, 123.5, 122.5, 116.7, 116.0, 113.3, 95.8, 41.1, 20.5; IR (KBr) *v*: 3323, 1658, 1612, 1527, 1504, 1481, 1384, 1203, 1054 cm^{-1}; MS (ESI) *m*/*z*: 340.0 $[M+H]^+$.

7-(4-Chlorophenyl)-9-methyl-7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolin-6-one (**4c**): White solid, m.p. 297.4－298.6 ℃; ^{1}H NMR (400 MHz, DMSO) δ: 9.87 (s, 1H, NH), 8.31 (d, J=7.6 Hz, 1H), 7.61 (t, J=7.6 Hz, 1H), 7.43 (d, J=8.0 Hz, 1H), 7.35 (d, J=8.4 Hz, 1H), 7.25 (s, 5H), 6.99－7.02 (m, 2H), 5.21 (s, 1H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ: 160.1, 151.9, 146.2, 143.4, 132.7, 132.7, 131.5, 130.6, 129.3, 128.8, 128.0, 128.0, 123.5, 123.4, 122.6, 116.6, 116.1, 113.2, 95.4, 40.5, 20.4; IR (KBr) *v*: 3322, 1658, 1611, 1529, 1503, 1480, 1386, 1257, 1052, 1013 cm^{-1}; MS (ESI) *m*/*z*: 374.1 $[M+H]^+$; HRMS (ESI) calcd for $C_{23}H_{17}ClNO_2$ $[M+H]^+$ 374.0948, found 374.0945.

9-Methyl-7-*p*-tolyl-7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolin-6-one (**4d**): White solid, m.p. 291.3－292.6 ℃; ^{1}H NMR (400 MHz, DMSO) δ: 9.80 (s, 1H , NH), 8.30 (d, J=8.0 Hz, 1H), 7.61 (t, J=8.0 Hz, 1H), 7.42 (t, J=7.6 Hz, 1H), 7.34 (d, J=8.0 Hz, 1H), 7.22 (d, J= 8.0 Hz, 1H), 7.08 (d, J=7.2 Hz, 2H), 6.98 (d, J=7.6 Hz, 4H), 5.12 (s, 1H), 2.17 (s, 6H); ^{13}C NMR (100 MHz, DMSO) δ: 160.2, 152.0, 144.5, 143.3, 135.0, 132.8, 132.5, 131.5, 129.4, 128.7, 127.8, 126.8, 124.2, 123.5, 122.57, 116.7, 116.0, 113.3, 96.0, 40.7, 20.6, 20.5; IR (KBr) *v*: 3326, 1664, 1612, 1529, 1503, 1480, 1413, 1197, 1050 cm^{-1}; MS (ESI) *m*/*z*: 353.9 $[M+H]^+$.

7-(4-Fluorophenyl)-9-methyl-7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolin-6-one (**4e**): White solid, m.p. 293.4－294.5 ℃; ^{1}H NMR (400 MHz, DMSO) δ: 9.85 (s, 1H, NH), 8.13 (dd, J_1=1.2 Hz, J_2=8.0 Hz, 1H), 7.63－7.59 (m, 1H), 7.45－7.41 (m, 1H), 7.36－7.33 (m, 1H), 7.25－7.22 (m, 3H), 7.03－6.99 (m, 3H), 5.20 (s, 1H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ: 161.3, 159.7, 158.9, 151.7, 143.0, 132.6, 132.3, 130.9, 128.9, 128.3, 128.3, 127.5, 123.4, 122.9, 122.1, 116.2, 115.7, 114.5, 114.4, 114.21, 113.0, 95.6, 19.9; IR (KBr) *v*: 3311, 1660, 1613, 1526, 1506, 1480, 1384, 1229, 1199, 1052 cm^{-1}; MS (ESI) *m*/*z*: 358.1 $[M+H]^+$.

7-(4-Methoxyphenyl)-9-methyl-7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolin-6-one (**4f**): White solid, m.p. ＞300 ℃; ^{1}H NMR (400 MHz, DMSO) δ: 9.80 (s, 1H, NH), 8.30 (dd, J_1=1.2 Hz, J_2=8.0 Hz, 1H), 7.63－7.58 (m, 1H), 7.44－7.40 (m, 1H), 7.35－7.33 (m, 1H), 7.23 －7.21 (d, J=8.8 Hz, 1H), 7.12－7.10 (m, 2H), 6.99－6.95 (m, 2H), 6.76－6.72 (m, 2H), 5.11 (s, 1H), 3.64 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ: 159.7, 157.1, 151.7, 142.7, 139.3, 137.1, 132.7, 132.1, 130.8, 128.9, 127.5, 127.2, 123.9, 122.9, 122.0, 116.1, 115.6, 113.3, 113.1, 96.0, 54.6, 20.0; IR (KBr) *v*: 3317, 1663, 1609, 1527, 1504, 1215, 1049, 1024 cm^{-1}; MS (ESI) *m*/*z*: 369.9 $[M+H]^+$.

7-(2,4-Dichlorophenyl)-9-methyl-7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolin-6-one (**4g**): White solid, m.p. ＞300 ℃; ^{1}H NMR (400 MHz, DMSO) δ: 9.87 (s, 1H, NH), 8.32 (dd, J_1=1.2 Hz, J_2=8.0 Hz, 1H), 7.65－7.61 (m, 1H), 7.52 (dd, J_1=0.4 Hz, J_2=2.0 Hz, 1H), 7.46－7.42 (m, 1H), 7.36－7.34 (m, 1H), 7.27－7.20 (m, 3H), 6.99 (dd, J_1=1.6 Hz, J_2=8.0 Hz, 1H), 6.91 (s, 1H), 5.69 (s, 1H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ: 159.8, 152.0, 144.2, 144.0, 132.7, 132.5, 131.7, 131.6, 131.2, 128.5, 128.3, 127.7, 123.5, 122.8, 122.7, 116.7, 116.4, 113.0, 94.8, 37.6, 20.5; IR (KBr) *v*: 3271, 1669, 1611, 1533, 1503, 1385, 1254, 1049, 1022 cm^{-1}; MS (ESI) *m*/*z*: 407.9 $[M+H]^+$.

7-(3-Methoxyphenyl)-9-methyl-7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolin-6-one (**4h**): White solid, m.p. 280.1－281.4 ℃; ^{1}H NMR (400 MHz, DMSO) δ: 9.83 (s, 1H, NH), 8.31－8.29 (m, 1H), 7.63－7.59 (m, 1H), 7.45－7.40 (m, 1H), 7.36－7.33 (m, 1H), 7.23 (d, J= 8.0 Hz, 1H), 7.10 (t, J=8.0 Hz, 1H), 7.02－6.98 (m, 2H), 6.79－6.74 (m, 2H), 6.69－6.66 (m, 1H), 5.14 (s, 1H), 3.65 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ: 160.2, 158.9, 152.0, 148.8, 143.5, 132.9, 132.6, 131.5, 129.4, 129.3, 127.9, 123.9, 123.5, 122.6, 119.3, 116.7, 116.1, 113.5, 113.4, 110.7, 95.8, 54.9, 41.1, 20.5; IR (KBr) *v*: 3320, 1670, 1612, 1505, 1481,

1263, 1193, 1047 cm^{-1}; MS (ESI) *m/z*: 370.0 $[M+H]^+$.

7-(2-Methoxyphenyl)-9-methyl-7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolin-6-one (**4i**): White solid, m.p. 292.1−293.9 ℃; ^1H NMR (400 MHz, DMSO) δ: 9.75 (s, 1H, NH), 8.32 (dd, J_1=1.2 Hz, J_2=8.0 Hz, 1H), 7.63−7.59 (m, 1H), 7.45−7.41 (m, 1H), 7.36−7.33 (m, 1H), 7.16 (d, J=8.0 Hz, 1H), 7.10−7.00 (m, 3H), 6.94−6.92 (m, 2H), 6.76−6.73 (m, 1H), 5.59 (m, 1H), 3.83 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ: 159.5, 155.3, 151.8, 143.7, 135.8, 132.6, 131.7, 130.8, 128.4, 127.8, 127.0, 126.7, 124.2, 122.8, 122.0, 120.1, 116.1, 115.5, 113.1, 111.6, 95.2, 55.5, 34.6, 20.1; IR (KBr) *v*: 3334, 1664, 1610, 1529, 1458, 1385, 1251, 1191, 1025 cm^{-1}; MS (ESI) *m/z*: 369.9 $[M+H]^+$.

7-(4-Hydroxy-3-methoxyphenyl)-9-methyl-7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolin-6-one (**4j**): White solid, m.p.>300 ℃; ^1H NMR (400 MHz, DMSO) δ: 9.78 (s, 1H, NH), 8.73 (s, 1H), 8.29 (d, J=8.0 Hz, 1H), 7.62−7.58 (m, 1H), 7.43−7.33 (m, 2H), 7.21 (d, J=8.0 Hz, 1H), 7.02−6.97 (m, 2H), 6.87 (d, J=1.6 Hz, 1H), 6.56 (d, J=8.0 Hz, 1H), 6.48−6.45 (m, 1H), 5.06 (s, 1H), 3.68 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ: 159.7, 151.7, 146.7, 144.6, 142.7, 138.3, 132.7, 132.0, 130.8, 128.9, 127.2, 124.0, 122.9, 122.0, 119.1, 116.1, 115.5, 115.0, 113.1, 112.0, 96.2, 55.6, 20.0; IR (KBr) *v*: 3552, 3317, 1665, 1614, 1527, 1509, 1272, 1199, 1050, 1029 cm^{-1}; MS (ESI) *m/z*: 385.7 $[M+H]^+$.

7-(2-Chlorophenyl)-9-methyl-7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolin-6-one (**4k**): White solid, m.p. 270.1−271.9 ℃; ^1H NMR (400 MHz, DMSO) δ: 9.85 (s, 1H, NH), 8.32 (dd, J_1=1.2 Hz, J_2=8.0 Hz, 1H), 7.65−7.61 (m, 1H), 7.46−7.42 (m, 1H), 7.37−7.34 (m, 2H), 7.25−7.20 (m, 2H), 7.17−7.10 (m, 2H), 6.99−6.97 (m, 2H), 5.72 (s, 1H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ: 159.8, 152.0, 145.1, 143.9, 132.5, 131.5, 130.5, 130.0, 129.0, 128.4, 128.1, 127.6, 127.4, 123.4, 123.3, 122.6, 116.6, 116.3, 113.1, 95.2, 20.5; IR (KBr) *v*: 3316, 1706, 1667, 1610, 1529, 1501, 1419, 1254, 1049 cm^{-1}; MS (ESI) *m/z*: 374.0 $[M+H]^+$.

9-Methyl-7-(naphthalen-1-yl)-7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolin-6-one (**4l**): White solid, m.p.>300 ℃; ^1H NMR (400 MHz, DMSO) δ: 9.89 (s, 1H, NH), 8.67 (s, 1H), 8.37 (s, 1H), 7.87−7.26 (m, 10), 6.93−6.84 (m, 2H), 6.06 (s, 1H), 2.03 (s, 3H); IR (KBr) *v*: 3276, 1653, 1609, 1527, 1501, 1392, 1199, 1055 cm^{-1}; MS (ESI) *m/z*: 389.9 $[M+H]^+$; HRMS (ESI) calcd for $C_{27}H_{20}NO_2$ $[M+H]^+$ 390.1494, found 390.1482.

7-Isopropyl-9-methyl-7,12-dihydro-6*H*-chromeno-[4,3-*b*]quinolin-6-one (**4m**): White solid, m.p. 276.4−278.0 ℃; ^1H NMR (400 MHz, DMSO) δ: 9.66 (s, 1H, NH), 8.23 (dd, J_1=1.2 Hz, J_2=8.0 Hz, 1H), 7.63−7.58 (m, 1H), 7.42−7.35 (m, 2H), 7.17 (d, J=8.0 Hz, 1H), 7.05−7.02 (m, 1H), 6.96 (s, 1H), 3.89 (d, J=3.6 Hz, 1H), 2.28 (s, 3H), 0.84 (d, J=6.8 Hz, 3H), 0.60 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO) δ: 160.6, 151.8, 144.5, 134.8, 131.7, 131.2, 129.5, 127.5, 123.3, 122.1, 121.0, 116.6, 115.2, 113.3, 94.6, 40.8, 35.2, 20.5, 19.7, 17.6; IR (KBr) *v*: 3340, 1660, 1612, 1529, 1503, 1481, 1196, 1041 cm^{-1}; MS (ESI) *m/z*: 306.1 $[M+H]^+$; HRMS (ESI) calcd for $C_{20}H_{20}NO_2$ $[M+H]^+$ 306.1494, found 306.1481.

9-Chloro-7-phenyl-7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolin-6-one (**4n**): White solid, m.p.>300 ℃; ^1H NMR (400 MHz, DMSO) δ: 9.99 (s, 1H, NH), 8.29 (d, J=8.0 Hz, 1H), 7.65−7.61 (m, 1H), 7.46−7.10 (m, 10H), 5.25 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ: 160.02, 152.02, 146.80, 143.44, 134.29, 131.75, 128.71, 128.37, 127.24, 126.95, 126.36, 126.24, 123.68, 122.61, 117.88, 116.78, 113.13, 96.12, 40.75; IR (KBr) *v*: 3316, 1658, 1607, 1525, 1479, 1276, 1185, 1053 cm^{-1}; MS (ESI) *m/z*: 360.0 $[M+H]^+$.

9-Chloro-7-*p*-tolyl-7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolin-6-one (**4o**): White solid, m.p.>300 ℃; ^1H NMR (400 MHz, DMSO) δ: 9.96 (s, 1H, NH), 8.29 (d, J=8.0 Hz, 1H), 765−7.61 (m, 1H), 7.44 (t, J=7.6 Hz, 1H), 7.37−7.32 (m, 2H), 7.27 (s, 1H), 7.24−7.21 (m, 1H), 7.12 (d, J=8.0 Hz, 2H), 7.01 (d, J=8.0 Hz, 2H), 5.20 (s, 1H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ: 159.5, 151.7, 143.4, 142.8, 134.9, 134.0, 131.1, 128.4, 128.2, 126.6, 126.5, 126.4, 126.0, 123.1, 122.1, 117.4, 116.2, 112.8, 96.1, 20.1; IR (KBr) *v*: 3313, 1660, 1627, 1524, 1488, 1478, 1376, 1054 cm^{-1}; MS (ESI) *m/z*: 374.0 $[M+H]^+$; HRMS (ESI) calcd for $C_{23}H_{17}ClNO_2$ $[M+H]^+$ 374.0948, found 374.0939.

9-Chloro-7-(4-chlorophenyl)-7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolin-6-one (**4p**): White solid, m.p.> 300 ℃; ^1H NMR (400 MHz, DMSO) δ: 10. 01 (s, 1H, NH), 8.29 (s, 1H), 7.63−7.27 (m, 10H), 5.29 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ: 159.3, 151.6, 144.9, 142.9, 133.9, 131.1, 130.5, 128.3, 128.1, 127.6, 126.8, 126.6, 125.1, 122.9, 122.0, 117.4, 116.1, 112.6, 95.4; IR (KBr) *v*: 3311, 1661, 1615, 1523, 1488, 1407, 1257, 1090, 1052 cm^{-1}; MS (ESI) *m/z*: 394.0 $[M+H]^+$.

9-Bromo-7-phenyl-7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolin-6-one (**4q**): White solid, m.p. 281.3−283.0 ℃; ^1H NMR (400 MHz, DMSO) δ: 10.00 (s, 1H, NH), 8.30 (d, J=8.0 Hz, 1H), 7.66−7.62 (m, 1H), 7.47−7.10 (m, 9H), 6.80 (d, J=8.4 Hz, 1H), 5.26 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ: 159.9, 152.0, 146.8, 143.4, 134.7, 131.7, 131.5, 130.0, 128.3, 126.9, 126.6, 126.3, 123.6, 122.6, 120.09, 118.2, 116.7, 114.8, 113.1, 96.2; IR (KBr) *v*: 3324, 1659, 1624, 1524, 1478, 1404, 1053 cm^{-1}; MS (ESI) *m/z*: 404.0 $[M+H]^+$.

9-Methoxy-7-phenyl-7,12-dihydro-6*H*-chromeno-[4,3-*b*]quinolin-6-one (**4r**): Yellow solid, m.p. 289.2−290.8 ℃; ^1H NMR (400 MHz, DMSO) δ: 9.83 (s, 1H, NH), 8.29 (d, J=8.0 Hz, 1H), 7.61 (t, J=7.6 Hz, 1H), 7.42 (t, J=7.6 Hz, 1H), 7.35−7.17 (m, 6H), 7.11−7.07 (m, 1H), 6.82−6.80 (m, 2H), 5.22 (s, 1H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ: 160.2, 155.6, 151.9, 147.0, 143.3, 131.4, 128.8, 128.1, 126.8, 126.0, 125.3, 123.4, 122.5, 117.2, 116.7, 113.9, 113.3, 113.0, 94.2, 55.1, 41.2; IR (KBr) *v*: 3325, 1655, 1612, 1533, 1503, 1391, 1250, 1208, 1053 cm^{-1}; MS (ESI) *m/z*: 356.0 $[M+H]^+$.

9-Ethoxy-7-phenyl-7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolin-6-one (**4s**): Yellow solid, m.p. 249.1—252.0 ℃; ^{1}H NMR (400 MHz, DMSO) δ: 9.81 (s, 1H, NH), 8.29 (d, J=7.6 Hz, 1H), 7.61 (t, J=7.6 Hz, 1H), 7.44—7.40 (m, 1H), 7.34 (d, J=8.0 Hz, 1H), 7.27—7.17 (m, 5H), 7.10—7.07 (m, 1H), 6.80—6.77 (m, 2H), 5.20 (s, 1H), 3.91 (q, J=6.8 Hz, 2H), 1.25 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO) δ: 159.7, 154.6, 151.7, 146.6, 142.9, 130.9, 128.6, 127.6, 126.4, 125.5, 125.0, 122.9, 122.0, 116.8, 116.2, 114.5, 113.5, 113.1, 94.6, 63.0, 41.0, 14.2; IR (KBr) v: 3315, 1657, 1611, 1529, 1502, 1481, 1388, 1237, 1204, 1184, 1049 cm^{-1}; MS (ESI) m/z: 370.1 $[M+H]^+$.

10-Methyl-7-phenyl-7,12-dihydro-6*H*-chromeno-[4,3-*b*]quinolin-6-one (**4t**): White solid, m.p. 284.6—286.2 ℃; ^{1}H NMR (400 MHz, DMSO) δ: 9.80 (s, 1H, NH), 8.32 (d, J=8.0 Hz, 1H), 7.64—7.60 (m, 1H), 7.46—7.42 (m, 1H), 7.35 (d, J=8.4 Hz, 1H), 7.21—7.15 (m, 5H), 7.09—7.06 (m, 2H), 6.79 (d, J=7.6 Hz, 1H), 5.18 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ: 160.1, 151.9, 147.3, 143.4, 136.3, 135.0, 131.5, 129.0, 128.1, 126.8, 125.9, 124.4, 123.5, 122.5, 121.3, 116.6, 116.3, 113.2, 96.2, 40.6, 20.8; IR (KBr) v: 3322, 1667, 1617, 1533, 1502, 1413, 1211, 1049 cm^{-1}; MS (ESI) m/z: 340.0 $[M+H]^+$; HRMS (ESI) calcd for $C_{23}H_{18}NO_2$ $[M+H]^+$ 340.1338, found 340.1330.

General procedure for the synthesis of 9-methyl-7-phenyl-6*H*-chromeno[4,3-*b*]quinolin-6-ones 6a, 6b

The mixture of 9-methyl-7-phenyl-7,12-dihydro-6*H*-chromeno[4,3-*b*]quinolin (**4b**) (1 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1 mmol) in EtOH (2 mL) was stirred under reflux for 3 h. After the completion of the oxidation reaction (monitored by TLC), the reaction mixture was cooled to room temperature and then water (50 mL) was added. The aqueous phase was extracted with dichloromethane (10 mL ×3), and the combined organic extracts were washed with brine (10 mL), then dried over Na_2SO_4 and filtered off. The residue was then purified by column chromatography on silica to give the corresponding compound **6a**. Product **6b** was prepared according to the same method of **6a**.

9-Methyl-7-phenyl-6*H*-chromeno[4,3-*b*]quinolin-6-one (**6a**): White solid, m.p. 270.8—272.6 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.85 (dd, J_1=1.6 Hz, J_2=7.6 Hz, 1H), 8.16 (d, J=8.8 Hz, 1H), 7.71—7.69 (m, 1H), 7.60—7.52 (m, 5H), 7.43—7.39 (m, 1H), 7.33—7.27 (m, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.3, 154.6, 152.7, 149.3, 149.1, 137.2, 135.1, 131.9, 129.3, 128.2, 128.1, 128.0, 126.7, 125.6, 124.4, 120.1, 116.9, 113.3, 22.0; IR (KBr) v: 1743, 1719, 1597, 1551, 1492, 1461, 1171, 1095 cm^{-1}; MS (ESI) m/z: 338.2 $[M+H]^+$; HRMS (ESI) calcd for $C_{23}H_{16}NO_2$ $[M+H]^+$ 338.1181, found 338.1173.

9-Methyl-7-*p*-tolyl-6*H*-chromeno[4,3-*b*]quinolin-6-one (**6b**): White solid, m.p. 211.9—214.0 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.84—8.81 (m, 1H), 8.15—8.12 (m, 1H), 7.71—7.67 (m, 1H), 7.57—7.52 (m, 1H), 7.42—7.36 (m, 3H), 7.33—7.30 (m, 2H), 7.18—7.16 (m, 2H), 2.53 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.3, 154.7, 152.3, 148.9, 148.7, 137.6, 137.0, 135.0, 134.0, 131.8, 130.8, 129.0, 128.9, 127.8, 126.6, 125.4, 124.3, 119.8, 116.7, 113.15, 22.0, 21.7; IR (KBr) v: 1750, 1735, 1594, 1549, 1460, 1264, 1182, 1100 cm^{-1}; MS (ESI) m/z: 352.2 $[M+H]^+$.

Biology cell viability assay

The cytotoxicity of compounds was assessed with a MTT viability assay against MCF-7 cells and A-549 cells. Cells were seeded in 96-well plates at 10000 cells per well in 100 μL of complete DMEM medium supplemented with 10% FBS. After incubated at 37 ℃ in a 5% CO_2 atmosphere for 24 h, cells were treated with the compounds at different concentration and further incubated for 72 h. MTT stock solution was then added to each well to achieve a final concentration of 0.5 mg/mL. Following 4 h incubation at 37 ℃, the MTT-containing medium was carefully aspirated to avoid disturbing any formazan crystals formed and 150 μL DMSO was added to each well. Plates were incubated at room temperature for 30 min and optical densities were recorded at 570 nm using a Microplate reader (Sunrise, Tecan Trading, Switzerland). Cell viability was expressed as a percentage of the untreated control cells. IC_{50} values were calculated with the software Curve Expert version 1.34 for windows.

Conclusions

In summary, we have developed an efficient, clean, and environmentally friendly procedure to generate 7,12-dihydro-6*H*-chromeno[4,3-*b*]quinoline derivatives via the microwave-assisted three-component condensation of 4-hydroxycoumarin, aldehydes and aromatic amines. Moreover, the cytotoxic activities of these compounds were evaluated *in vitro* on two different cancer cell lines, and the results show that some compounds exhibited excellent antitumor activities against MCF-7 and A-549.

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