Efficient One-Pot Synthesis of Spirooxindole Derivatives Bearing Hexahydroquinolines Using Multicomponent Reactions Catalyzed by Ethylenediamine Diacetate

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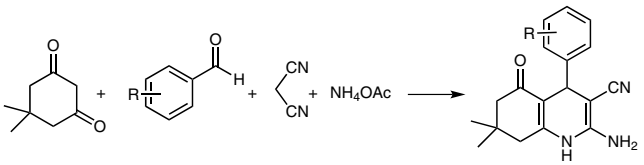
Abstract: A simple and efficient one-pot synthesis of biologically interesting spirooxindole derivatives bearing hexahydroquinoline skeleton was accomplished by EDDA-catalyzed, three-component reactions between isatins, malononitrile, and enaminones in good yields. The value of this methodology lies in its inexpensive and nontoxic organocatalyst, mild reaction conditions, and ease of handling.

Key words: multicomponent reaction, spirooxindoles, enaminone, hexahydroquinolines, ethylenediamine diacetate

Quinolines and their derivatives have received considerable attention as leading pharmaceutical compounds because of their pivotal roles in various biological activities such as anti-inflammatory, antiasthmatic, antituberculosis, antibacterial, antihypertensive, antitumor, and antimalarial properties.[1] Of these, hexahydroquinolines with a 1,4-dihydropyridine nucleus are particularly important and have been shown to possess potent antibacterial, anticancer, cytotoxic, myorelaxant, and neuroprotective, and calcium channel modulatory activities.[2] 1,4-Dihydropyridine moieties are well-known, significant compounds that selectively block L-type calcium channels, and are one of the most important classes of drugs for the treatment of cardiovascular diseases including hypertension.[3] Furthermore, they have been shown to possess a variety of biological activities, such as vasodilatory, bronchodilatory, anti-atherosclerotic, antitumor, geroprotective, hepatoprotective, antidiabetic, antioxidant, antiviral, anticancer activities.[4] They also exhibit several medicinal properties, which include neuroprotectant and platelet anti-aggregatory activities, chemosensitization activities in tumor therapy, and anti-ischemic activities during the treatment of Alzheimer's disease.[5]

In view of the biological importance of hexahydroquinolines bearing a 1,4-dihydropyridine nucleus, several synthetic methods have been reported based on four-component reactions between dimedone, aromatic aldehydes, malononitrile, and ammonium acetate (Scheme 1).[6–19] Microwaves,[6] ionic liquids,[7] ZnO nanoparticles,[8] Bu_4NHSO_4,[9] L-proline,[10] HY-zeolite,[11] silica-supported acids,[12] boronic acids,[7a,13] TMSCl/NaI,[14] ceric ammonium nitrate,[15] metal triflates,[16] polymers,[17] baker's yeast,[18] and *p*-TSA[19] have been used in these reactions as catalytic and stoichiometric reagents. Nevertheless, these known methods still suffer from several limitations, such as high reaction temperatures, long reaction times, the need for expensive catalysts, and unsatisfactory yields. Therefore, the search is still on for a better method of synthesizing hexahydroquinolines with a 1,4-dihydropyridine nucleus.



Scheme 1 Formation of 1,4-dihydropyridne products via the three-component reaction

Molecules bearing the spirooxindole moiety are found widely in nature[20] and have been shown to possess a variety of important biological activities.[21] Their unique structural array and prominent pharmacological activities have stimulated interest in the synthesis of spirooxindole derivatives. Thus, the development of new simpler synthetic methods for the preparation of spirooxindole derivatives has become an interesting challenge. Many synthetic methodologies have been developed for constructing spirooxindole derivatives, and the majority of these methods were based on cycloaddition or condensation reactions.[22] In particular, multicomponent reactions have emerged as an efficient and powerful means of synthesizing complex molecules using one-pot procedures.[23] Several means of synthesizing spirooxindoles based on multicomponent reactions have been developed using TBAF[24] or triethylbenzylammonium chloride (TEBA)[25] as phase-transfer catalysts, $InCl_3$[26] as a Lewis acid catalyst, or electrocatalysis.[27]

In related work on the synthesis of spirooxindole derivatives bearing a hexahydroquinoline moiety, one microwave-assisted synthesis has been reported.[28] However, there is still demand for more concise and efficient synthetic routes to biologically interesting spirooxindole derivatives bearing a hexahydroquinoline moiety.

Recently, the potential of organocatalysts to serve as active catalysts for a variety of synthetically useful reactions was demonstrated.[29] In particular, we developed a new

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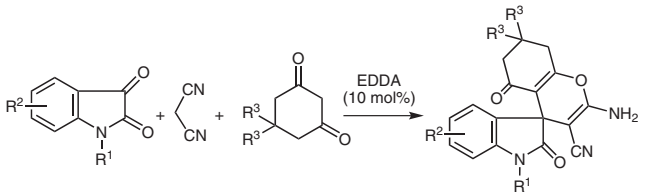
and useful method for synthesizing a variety of benzopyrans using ethylenediamine diacetate (EDDA) as an organocatalyst.[30] Pursuant to this, we reported a method for synthesizing a variety of spirooxindole derivatives with a 2-aminotetrahydrochromene nucleus using EDDA-catalyzed three-component reactions between isatins, malononitrile, and cyclohexane-1,3-diones (Scheme 2).[31]



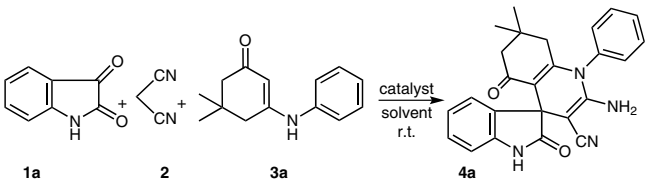
Scheme 2 Formation of spirooxoindoles via EDDA-catalyzed three-component reaction

As part of our ongoing studies on the syntheses of novel types of spirooxindoles, we examined three-component reactions between substituted isatins, malononitrile, and enaminones in the presence of different catalysts and reagents. Here, we report the one-pot synthesis of biologically interesting spirooxindoles bearing hexahydroquinoline nucleus using EDDA-catalyzed three-component reactions.

To produce spirooxindole derivatives bearing the hexahydroquinoline moiety, we first examined the reaction between isatin (**1a**), malononitrile (**2**), and 3-anilino-5,5-dimethylcyclohex-2-en-1-one (**3a**) under several catalysts and solvents. The results are summarized in Table 1. With 20 mol% of $Yb(OTf)_3$ and $InCl_3$ as a Lewis acid catalyst in THF at room temperature for 24 hours, no desired products were produced. The use of AcOH (10 mol%) as a Brønsted acid gave product **4a** in low yield (10%), whereas the use of ethylenediamine (10 mol%) as a Brønsted base afforded **4a** in 58% yield. Using $Ca(OH)_2$ (20 mol%), K_2CO_3 (10 mol%), or Cs_2CO_3 (10 mol%), the desired product **4a** was produced in 34, 52, and 35% yields, respectively. With 10 mol% of ethylenediamine diacetate, the best yield (72%) was obtained in THF at room temperature for 7 hours. This result is probably due to the driving force of precipitation of product **4a**, which is hardly soluble in THF. When other solvents such as water, methanol, dimethylformamide, or dichloromethane were used, yields decreased. The structure of compound **4a** was determined by ^{1}H NMR analysis and by comparison with reported data.[28] ^{1}H NMR spectrum of **4a** showed an amide proton at δ = 10.23 as a singlet and two amine protons at δ = 5.38 as a broad singlet. In its ^{13}C NMR spectrum, two carbonyl peaks at δ = 193.8 and 179.4 were attributed to an enone and an amide, and one characteristic quaternary carbon peak on the spirooxindole ring was shown at δ = 49.3.

To explore the generality and scope of this methodology, additional reactions between isatins **1a**–**g**, malononitrile, and several cyclic enaminones **3a**–**f** under the optimized conditions were conducted to synthesize spirooxindole

Table 1 Effects of Catalyst and Solvents for the Synthesis of Spirooxindole **4a** Bearing Hexahydroquinoline Moiety



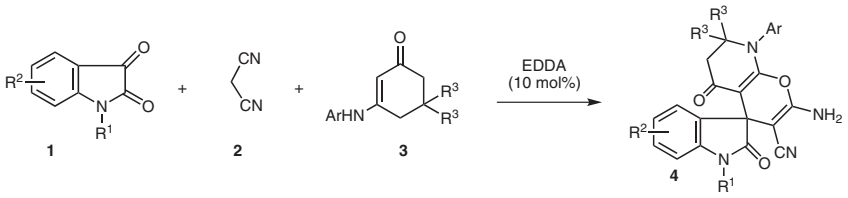
1a **2** **3a** **4a**

Catalyst	Solvent	Time	Yield (%)
$Yb(OTf)_3$ (20 mol%)	THF	24 h	0
$InCl_3$ (20 mol%)	THF	24 h	0
AcOH (10 mol%)	THF	12 h	10
$NH_2CH_2CH_2NH_2$ (10 mol%)	THF	10 h	58
$Ca(OH)_2$ (20 mol%)	THF	12 h	34
K_2CO_3 (10 mol%)	THF	12 h	52
Cs_2CO_3 (10 mol%)	THF	12 h	35
EDDA (10 mol%)	H_2O	24 h	21
EDDA (10 mol%)	DMF	24 h	36
EDDA (10 mol%)	MeOH	24 h	30
EDDA (10 mol%)	THF	7 h	72
EDDA (10 mol%)	CH_2Cl_2	24 h	41

derivatives bearing the hexahydroquinoline moiety. Results are summarized in Table 2. Reactions between isatin (**1a**), malononitrile, and cyclic enaminones **3b**–**e** with electron-donating or -withdrawing groups on the benzene ring in the presence of 10 mol% of EDDA in THF at room temperature for seven to eight hours afforded products **4b**–**e** in 66–72% yields (Table 2, entries 1–4). Using 3-anilinocyclohex-2-ene-1-one (**3f**), which does not have a substituent on the cyclohexenone ring, the desired product **4f** was produced in 69% yield (entry 5). Reactions using isatins with electron-donating and -withdrawing groups on the benzene ring were also successful. For example, reactions using 5-methylisatin (**1b**) with an electron-donating group on the benzene ring provided products **4g** and **4h** in 70 and 68% yield, respectively (entries 6, 7). Similarly, reactions using 5-bromoisatin, 5-chloroisatin, and 5-nitroisatin, which all possess an electron-withdrawing group on the benzene ring, gave products **4i**–**n** in 60–84% yields (entries 8–13). When 1-methylisatin (**1f**) or 1-phenylisatin (**1g**) was used, the desired products **4o**–**r** were produced in 65–76% yields (entries 14–17). Accordingly, these reactions provided rapid routes to the synthesis of a variety spirooxindole derivatives bearing the hexahydroquinoline moiety.

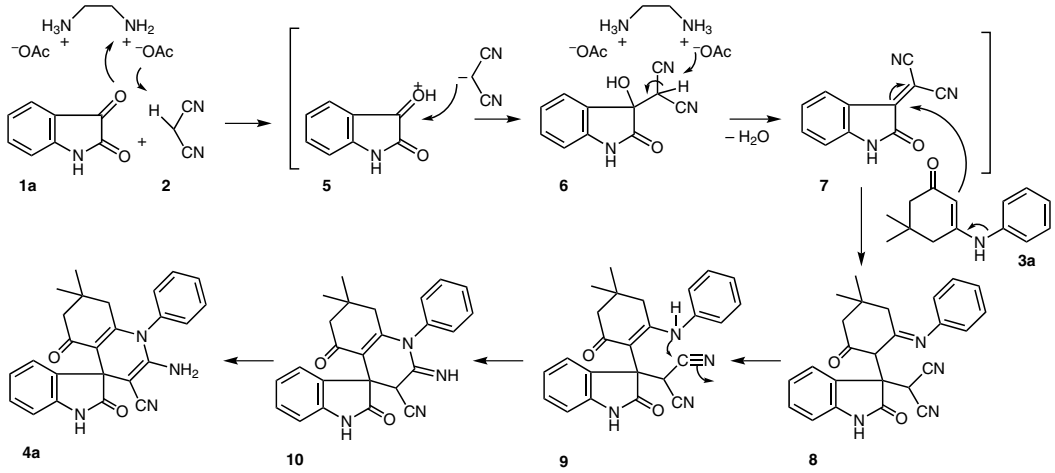
The formation of spirooxindole **4a** could be explained by domino Knoevenagel condensation and Michael addition followed by cyclization, as shown in Scheme 3. We suppose that isatin (**1a**) is first protonated by EDDA to give the intermediate **5**, which is then attacked by the carban-

Table 2 Additional Reactions for the Synthesis of a Variety of Spirooxindole Derivatives Bearing Hexahydroquinoline Moieties



Entry	Isatin	R^1	R^2	Enaminone	R^3	Ar	Time (h)	Product	Yield (%)
1	**1a**	H	H	**3b**	Me	4-MeC_6H_4	8	**4b**	72
2	**1a**	H	H	**3c**	Me	4-$MeOC_6H_4$	8	**4c**	70
3	**1a**	H	H	**3d**	Me	4-BrC_6H_4	7	**4d**	66
4	**1a**	H	H	**3e**	Me	4-ClC_6H_4	8	**4e**	70
5	**1a**	H	H	**3f**	H	Ph	8	**4f**	69
6	**1b**	H	Me	**3a**	Me	Ph	9	**4g**	70
7	**1b**	H	Me	**3f**	H	Ph	8	**4h**	68
8	**1c**	H	Br	**3a**	Me	Ph	9	**4i**	68
9	**1c**	H	Br	**3f**	H	Ph	9	**4j**	70
10	**1d**	H	Cl	**3a**	Me	Ph	9	**4k**	84
11	**1d**	H	Cl	**3f**	H	Ph	9	**4l**	76
12	**1e**	H	NO_2	**3a**	Me	Ph	12	**4m**	62
13	**1e**	H	NO_2	**3f**	H	Ph	12	**4n**	60
14	**1f**	Me	H	**3a**	Me	Ph	9	**4o**	65
15	**1f**	Me	H	**3f**	H	Ph	9	**4p**	67
16	**1g**	Ph	H	**3a**	Me	Ph	12	**4q**	76
17	**1g**	Ph	H	**3f**	H	Ph	12	**4r**	74

ion produced by malononitrile in the presence of EDDA to yield the intermediate **6**. Dehydration of **6** in the presence of EDDA then gives isatylidene malononitrile **7** as a Knoevenagel condensation product, and the intermediate **7** is attacked by the enaminone **3a** to give **8**, which then undergoes isomerization to furnish **9**. Intramolecular attack of a nitrogen of **9** toward its cyano moiety affords the imine **10**, which finally undergoes further reaction to give the desired product **4a**.



Scheme 3 Plausible mechanism for the synthesis of spirooxindole **4a**

In conclusion, we have described an efficient, one-pot, EDDA-catalyzed syntheses of a variety of spirooxindole derivatives bearing hexahydroquinolines starting from readily available isatins, malononitrile, and enaminones. These reactions provide a rapid synthetic route for the preparation of biologically interesting spirooxindole derivatives bearing hexahydroquinoline skeleton.

All experiments were carried out under open air without using any inert gases protection. Merck precoated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). Melting points were determined with micro-cover glasses on a Fisher-Johns apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker-DPX (300 MHz) and Varian-VNS (600 MHz) spectrometer in DMSO-d_6 using 2.50 ppm as the solvent chemical shift. ^{13}C NMR spectra were recorded on a Bruker-DPX (75 MHz) and Varian-VNS (150 MHz) spectrometer in DMSO-d_6 using 39.51 ppm as the solvent chemical shift. IR spectra were recorded on a FT IR (BIO-RAD) spectrophotometer. HRMS was carried out at Korean Basic Science Institute (Daegu) on a JEOL JMS 700 spectrometer.

Compounds 4a–r; General Procedure

To a solution of isatin **1** (1.0 mmol) and malononitrile (**2**; 66 mg, 1.0 mmol) and enaminone **3** (1.0 mmol) in THF (4 mL) was added EDDA (18 mg, 10 mol%). The reaction mixture was stirred for 7 to 12 h until the completion of the reaction as indicated by TLC (eluent: *n*-hexane–EtOAc, 1:1). The solvent was evaporated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel with *n*-hexane–EtOAc (2:1) (Table 2).

2′-Amino-7′,7′-dimethyl-2,5′-dioxo-1′-phenyl-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (4a)

Reaction of **1a** (147 mg, 1.0 mmol) with **2** (66 mg, 1.0 mmol) and **3a** (215 mg, 1.0 mmol) in THF (4 mL) for 7 h afforded **4a**; yield: 295 mg (72%); white solid; mp >300 °C.

IR (KBr): 3462, 3338, 2182, 1722, 1641, 1498, 1365, 1223, 1086, 1016, 756 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.23 (s, 1 H), 7.60–7.48 (m, 5 H), 7.18–7.10 (m, 2 H), 6.91 (t, *J* = 7.0 Hz, 1 H), 6.76 (d, *J* = 7.8 Hz, 1 H), 5.38 (s, 2 H), 2.15–1.99 (m, 2 H), 1.98–1.77 (m, 2 H), 0.87 (s, 3 H), 0.80 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 193.8, 179.4, 151.8, 151.1, 141.4, 136.6, 136.0, 130.2, 129.9, 127.6, 123.1, 121.3, 118.8, 110.4, 108.8, 61.0, 49.3, 48.5, 41.3, 32.0, 28.2, 26.6.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{25}H_{22}N_4O_2$: 410.1745; found: 410.1743.

2′-Amino-7′,7′-dimethyl-2,5′-dioxo-1′-(*p*-tolyl)-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (4b)

Reaction of **1a** (147 mg, 1.0 mmol) with **2** (66 mg, 1.0 mmol) and **3b** (229 mg, 1.0 mmol) in THF (4 mL) for 8 h afforded **4b**; yield: 305 mg (72%); white solid; mp >300 °C.

IR (KBr): 3321, 3244, 2185, 1715, 1615, 1366 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.12 (s, 1 H), 7.31 (d, *J* = 7.2 Hz, 2 H), 7.19–7.08 (m, 3 H), 6.90 (t, *J* = 7.2 Hz, 2 H), 6.78 (d, *J* = 7.2 Hz, 1 H), 5.48 (s, 2 H), 2.34 (s, 3 H), 2.14–2.03 (m, 2 H), 1.94–1.73 (m, 2 H), 0.90 (s, 3 H), 0.84 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 193.9, 179.8, 151.0, 150.0, 141.8, 136.9, 134.8, 130.9, 129.8, 127.9, 123.2, 121.3, 119.1, 117.2, 110.1, 108.9, 60.72, 50.28, 48.18, 42.02, 32.12, 28.22, 27.99, 21.11.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{26}H_{24}N_4O_2$: 424.1899; found: 424.1902.

2′-Amino-1′-(4-methoxyphenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (4c)

Reaction of **1a** (147 mg, 1.0 mmol) with **2** (66 mg, 1.0 mmol) and **3c** (245 mg, 1.0 mmol) in THF (4 mL) for 8 h afforded **4c**; yield: 308 mg (70%); white solid; mp >300 °C.

IR (KBr): 3453, 3327, 3207, 2178, 1712, 1615, 1533, 1366, 1243 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.14 (s, 1 H), 7.48–7.32 (m, 2 H) 7.16–7.09 (m, 3 H), 6.90 (t, *J* = 7.5 Hz, 2 H), 6.77 (d, *J* = 7.8 Hz, 1 H), 5.27 (s, 2 H), 3.86 (s, 3 H), 2.16–2.06 (m, 2 H), 1.98–1.84 (m, 2 H), 0.89 (s, 3 H), 0.83 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 195.0, 178.3, 151.9, 150.9, 141.4, 136.2, 134.1, 131.9, 131.0, 127.8, 125.0, 122.0, 121.0, 118.8, 110.7, 108.9, 60.2, 58.9, 55.1, 50.6, 42.1, 31.9, 27.8, 26.1.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{26}H_{24}N_4O_3$: 440.1848; found: 440.1845.

2′-Amino-1′-(4-bromophenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (4d)

Reaction of **1a** (147 mg, 1.0 mmol) with **2** (66 mg, 1.0 mmol) and **3d** (293 mg, 1.0 mmol) in THF (4 mL) for 7 h afforded **4d**; yield: 322 mg (66%); light yellow solid; mp >300 °C.

IR (KBr): 3464, 3339, 3213, 2193, 1734, 1643, 1362 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.15 (s, 1 H), 7.71–7.60 (m, 3 H), 7.53 (t, *J* = 7.4 Hz, 1 H), 7.19–7.09 (m, 2 H), 6.90 (t, *J* = 7.2 Hz, 1 H), 6.76 (d, *J* = 7.2 Hz, 1 H), 5.42 (s, 2 H), 2.04–1.76 (m, 4 H), 0.92 (s, 3 H), 0.85 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 193.7, 179.0, 151.1, 150.3, 141.5, 136.7, 134.8, 132.1, 132.0, 129.7, 127.5, 123.1, 121.2, 118.8, 110.5, 108.6, 60.6, 49.4, 48.5, 41.9, 32.0, 27.6, 27.3.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{25}H_{21}BrN_4O_2$: 488.0848; found: 488.0850.

2′-Amino-1′-(4-chlorophenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (4e)

Reaction of **1a** (147 mg, 1.0 mmol) with **2** (66 mg, 1.0 mmol) and **3e** (249 mg, 1.0 mmol) in THF (4 mL) for 8 h afforded **4e**; yield: 311 mg (70%); light yellow solid; mp >300 °C.

IR (KBr): 3438, 3323, 3253, 2188, 1743, 1645, 1365 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.15 (s, 1 H), 7.65 (d, *J* = 8.1 Hz, 2 H), 7.52 (d, *J* = 7.8 Hz, 2 H), 7.17–7.08 (m, 2 H), 6.90 (t, *J* = 7.34 Hz, 1 H), 6.76 (d, *J* = 7.8 Hz, 1 H), 5.46 (s, 2 H), 2.16–2.07 (m, 2 H), 1.98–1.81 (m, 2 H), 0.90 (s, 3 H), 0.83 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 193.7, 179.3, 151.5, 151.0, 141.4, 136.5, 134.9, 134.5, 131.9, 130.2, 127.6, 123.1, 121.3, 118.7, 110.5, 108.7, 61.0, 49.3, 48.4, 41.3, 32.0, 28.1, 26.6.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{25}H_{21}N_4O_2$: 444.1353; found: 444.1350.

2′-Amino-2,5′-dioxo-1′-phenyl-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (4f)

Reaction of **1a** (147 mg, 1.0 mmol) with **2** (66 mg, 1.0 mmol) and **3f** (187 mg, 1.0 mmol) in THF (4 mL) for 8 h afforded **4f**; yield: 264 mg (69%); white solid; mp >300 °C.

IR (KBr): 3469, 3390, 3313, 3208, 2190, 1734, 1643, 1358 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.19 (s, 1 H), 7.63–7.59 (m, 3 H) 7.50–7.48 (m, 2 H), 7.19–7.09 (m, 2 H), 6.91 (t, *J* = 7.5 Hz, 1 H), 6.76 (d, *J* = 7.5 Hz, 1 H), 5.31 (s, 2 H), 2.20–2.07 (m, 3 H), 2.02–1.99 (m, 1 H), 1.79–1.66 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 193.9, 179.5, 153.9, 150.8, 141.4, 136.8, 135.9, 130.1, 129.8, 127.6, 123.2, 121.3, 118.8, 111.6, 108.7, 61.0, 48.6, 36.0, 28.1, 20.8.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{23}H_{18}N_4O_2$: 382.1430; found: 382.1427.

2′-Amino-5,7′,7′-trimethyl-2,5′-dioxo-1′-phenyl-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (4g)
Reaction of **1b** (161 mg, 1.0 mmol) with **2** (66 mg, 1.0 mmol) and **3a** (187 mg, 1.0 mmol) in THF (4 mL) for 9 h afforded **4g**; yield: 296 mg (70%); white solid; mp >300 °C.

IR (KBr): 3457, 3339, 2191, 1707, 1642, 1362 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.08 (s, 1 H), 7.65–7.60 (m, 3 H), 7.48–7.46 (m, 2 H), 6.94 (m, 2 H), 6.65 (d, *J* = 7.8 Hz, 1 H), 5.29 (s, 2 H), 2.25 (s, 3 H), 2.11–1.98 (m, 2 H), 1.92–1.82 (m, 2 H), 0.88 (s, 3 H), 0.83 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 193.9, 179.4, 151.8, 151.0, 139.1, 136.8, 136.0, 130.3, 130.1, 129.9, 127.9, 123.7, 118.9, 110.4, 108.6, 61.2, 49.3, 48.6, 41.4, 32.1, 28.0, 26.9, 20.7.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{26}H_{24}N_4O_2$: 424.1899; found: 424.1903.

2′-Amino-5-methyl-2,5′-dioxo-1′-phenyl-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (4h)
Reaction of **1b** (161 mg, 1.0 mmol) with **2** (66 mg, 1.0 mmol) and **3f** (187 mg, 1.0 mmol) in THF (4 mL) for 8 h afforded **4h**; yield: 269 mg (68%); white solid; mp >300 °C.

IR (KBr): 3437, 3329, 3194, 2185, 1720, 1644, 1357 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.06 (s, 1 H), 7.62–7.59 (m, 3 H), 7.50–7.48 (m, 2 H), 6.97–6.90 (m, 2 H), 6.65 (d, *J* = 7.5 Hz, 1 H), 5.25 (s, 2 H), 2.14 (s, 3 H), 2.11–2.09 (m, 3 H), 2.03–1.96 (m, 1 H), 1.77–1.74 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 193.7, 179.2, 153.5, 150.6, 138.9, 136.7, 135.9, 129.9, 129.6, 129.6, 127.7, 123.4, 118.4, 111.7, 108.4, 61.9, 48.7, 35.9, 27.9, 20.5, 20.4.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{24}H_{20}N_4O_2$: 396.1586; found: 396.1586.

2′-Amino-5-bromo-7′,7′-dimethyl-2,5′-dioxo-1′-phenyl-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (4i)
Reaction of **1c** (226 mg, 1.0 mmol) with **2** (66 mg, 1.0 mmol) and **3a** (215 mg, 1.0 mmol) in THF (4 mL) for 9 h afforded **4i**; yield: 332 mg (68%); light yellow solid; mp >300 °C.

IR (KBr): 3456, 3341, 2190, 1714, 1643, 1365 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.35 (s, 1 H), 7.62–7.56 (m, 5 H), 7.35–7.28 (m, 2 H), 6.73 (d, *J* = 8.1 Hz, 1 H), 5.40 (s, 2 H), 2.09–1.96 (m, 2 H), 1.91–1.86 (m, 2 H), 0.88 (s, 3 H), 0.84 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 194.1, 179.1, 152.4, 151.2, 141.0, 139.1, 135.7, 130.1, 130.0, 125.9, 118.7, 115.0, 113.1, 110.8, 109.6, 60.1, 49.2, 49.1, 41.4, 32.1, 27.7, 27.1.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{25}H_{21}BrN_4O_2$: 488.0848; found: 488.0851.

2′-Amino-5-bromo-2,5′-dioxo-1′-phenyl-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (4j)
Reaction of **1c** (226 mg, 1.0 mmol) with **2** (66 mg, 1.0 mmol) and **3f** (187 mg, 1.0 mmol) in THF (4 mL) for 9 h afforded **4j**; yield: 322 mg (70%); light yellow solid; mp >300 °C.

IR (KBr): 3350, 3262, 2183, 1722, 1642, 1570, 1359, 1248, 1186, 699 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.3 (s, 1 H), 7.61–7.59 (m, 3 H), 7.39–7.31 (m, 2 H), 7.18–7.13 (m, 2 H), 6.72 (d, *J* = 8.4 Hz, 1 H), 5.30 (s, 2 H), 2.17–2.08 (m, 4 H), 1.92–1.86 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 195.3, 178.8, 161.8, 150.7, 140.8, 139.0, 135.6, 130.0, 129.8, 129.5, 125.6, 124.0, 122.8, 112.8, 110.4, 98.2, 60.2, 48.9, 36.1, 28.2, 21.2.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{23}H_{17}BrN_4O_2$: 460.0535; found: 460.0537.

2′-Amino-5-chloro-7′,7′-dimethyl-2,5′-dioxo-1′-phenyl-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (4k)
Reaction of **1d** (181 mg, 1.0 mmol) with **2** (66 mg, 1.0 mmol) and **3a** (215 mg, 1.0 mmol) in THF (4 mL) for 9 h afforded **4k**; yield: 373 mg (84%); light yellow solid; mp >300 °C.

IR (KBr): 3456, 3338, 2190, 1711, 1641, 1477, 1363 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.32 (s, 1 H), 7.62–7.52 (m, 5 H), 7.24 (d, *J* = 2.1 Hz, 1 H), 7.16 (dd, *J* = 8.1, 2.1 Hz, 1 H), 6.78 (d, *J* = 8.1 Hz, 1 H), 5.38 (s, 2 H), 2.10–2.01 (m, 3 H), 1.92–1.86 (m, 1 H), 0.88 (s, 3 H), 0.84 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 193.9, 179.1, 152.3, 151.1, 140.5, 138.6, 135.7, 130.2, 130.0, 127.4, 125.3, 123.2, 118.6, 115.0, 110.1, 109.6, 60.2, 49.2, 49.0, 41.3, 32.0, 27.7, 27.1.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{25}H_{21}ClN_4O_2$: 444.1353; found: 444.1355.

2′-Amino-5-chloro-2,5′-dioxo-1′-phenyl-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (4l)
Reaction of **1d** (226 mg, 1.0 mmol) with **2** (66 mg, 1.0 mmol) and **3f** (187 mg, 1.0 mmol) in THF (4 mL) for 9 h afforded **4l**; yield: 316 mg (76%); light yellow solid; mp >300 °C.

IR (KBr): 3499, 3348, 3206, 2184, 1724, 1643, 1358 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.36 (s, 1 H), 7.59–7.37 (m, 5 H), 7.29 (s, 1 H), 7.16 (d, *J* = 8.1 Hz, 1 H), 6.7 (d, *J* = 8.1 Hz, 1 H), 5.45 (s, 2 H), 2.11–2.01 (m, 4 H), 1.99–1.74 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 194.1, 179.2, 154.5, 150.9, 140.4, 138.8, 135.7, 130.1, 130.0, 129.89, 127.4, 125.4, 123.4, 118.7, 110.8, 110.1, 60.2, 49.1, 35.9, 28.1, 20.7.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{23}H_{17}ClN_4O_2$: 416.1040; found: 416.1037.

2′-Amino-7′,7′-dimethyl-5-nitro-2,5′-dioxo-1′-phenyl-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (4m)
Reaction of **1e** (192 mg, 1.0 mmol) with **2** (66 mg, 1.0 mmol) and **3a** (215 mg, 1.0 mmol) in THF (4 mL) for 12 h afforded **4m**; yield: 282 mg (62%); light yellow solid; mp >300 °C.

IR (KBr): 3238, 2189, 1749, 1571, 1366, 1336, 1266, 707 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.95 (s, 1 H), 8.14 (d, *J* = 8.7 Hz, 1 H), 8.02 (s, 1 H), 7.63–7.52 (m, 5 H), 7.00 (d, *J* = 8.4 Hz, 1 H), 5.48 (s, 2 H), 2.04–2.00 (m, 4 H), 0.89 (s, 3 H), 0.85 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 195.2, 180.9, 153.9, 152.4, 149.2, 143.2, 138.5, 136.4, 131.2, 131.0, 130.8, 126.2, 119.4, 119.4, 110.1, 109.9, 60.2, 50.0, 49.8, 42.3, 33.0, 28.4, 28.2.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{25}H_{21}N_5O_4$: 455.1594; found: 455.1596.

2′-Amino-5-nitro-2,5′-dioxo-1′-phenyl-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (4n)
Reaction of **1e** (192 mg, 1.0 mmol) with **2** (66 mg, 1.0 mmol) and **3f** (187 mg, 1.0 mmol) in THF (4 mL) for 12 h afforded **4n**; yield: 256 mg (60%); light yellow solid; mp >300 °C.

IR (KBr): 3453, 3331, 3250, 2185, 1744, 1634, 1525, 1336 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.99 (s, 1 H), 8.15–8.04 (m, 2 H), 7.70–7.51 (m, 3 H), 7.38 (t, *J* = 7.8 Hz, 1 H), 7.15 (t, *J* = 7.9 Hz, 1 H), 6.98 (d, *J* = 8.4 Hz, 1 H), 5.57 (s, 2 H), 2.17–2.06 (m, 4 H), 1.90–1.86 (m, 1 H), 1.79–1.70 (m, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 194.4, 180.0, 161.8, 155.2, 151.2, 148.2, 142.4, 137.7, 135.5, 130.1, 130.0 125.2, 118.8, 118.4, 110.3, 108.8, 59.3, 49.0, 35.7, 28.1, 20.7.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{23}H_{17}N_5O_4$: 427.1281; found: 427.1279.

2′-Amino-1,7′,7′-trimethyl-2,5′-dioxo-1′-phenyl-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (4o)
Reaction of **1f** (161 mg, 1.0 mmol) with **2** (66 mg, 1.0 mmol) and **3a** (215 mg, 1.0 mmol) in THF (4 mL) for 9 h afforded **4o**; yield: 275 mg (65%); white solid; mp >300 °C.

IR (KBr): 3457, 3373, 3317, 2186, 1716, 1650, 1363 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.64–7.61 (m, 3 H), 7.52–7.50 (m, 2 H), 7.25 (t, *J* = 7.5 Hz, 2 H), 7.04–6.96 (m, 2 H), 5.40 (s, 2 H), 3.16 (s, 3 H), 2.19–2.07 (m, 2 H), 2.00–1.81 (m, 2 H), 0.89 (s, 3 H), 0.82 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 193.8, 177.9, 151.9, 151.2, 142.9, 135.9, 135.7, 130.3, 129.9, 127.9, 122.9, 122.1, 118.7, 110.3, 107.6, 60.5, 49.2, 48.2, 41.3, 32.1, 28.1, 26.6, 26.2.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{26}H_{24}N_4O_2$: 424.1899; found: 424.1902.

2′-Amino-1-methyl-2,5′-dioxo-1′-phenyl-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (4p)
Reaction of **1f** (161 mg, 1.0 mmol) with **2** (66 mg, 1.0 mmol) and **3f** (187 mg, 1.0 mmol) in THF (4 mL) for 9 h afforded **4p**; yield: 265 mg (67%); white solid; mp >300 °C.

IR (KBr): 3466, 3329, 2180, 1721, 1629, 1356 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.59–7.51 (m, 5 H), 7.27–7.19 (m, 2 H), 7.02–6.93 (m, 2 H), 5.38 (s, 2 H), 3.14 (s, 3 H), 2.17–1.89 (m, 4 H), 1.76–1.67 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 193.8, 177.9, 154.0, 150.9, 142.8, 135.9, 130.1, 129.9, 129.1, 127.8, 122.9, 122.0, 118.7, 111.4, 107.5, 60.5, 48.3, 35.9, 28.0, 26.2, 20.7.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{24}H_{20}N_4O_2$: 396.1586; found: 396.1588.

2′-Amino-7′,7′-dimethyl-2,5′-dioxo-1,1′-diphenyl-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (4q)
Reaction of **1g** (223 mg, 1.0 mmol) with **2** (66 mg, 1.0 mmol) and **3a** (215 mg, 1.0 mmol) in THF (4 mL) for 12 h afforded **4q**; yield: 370 mg (76%); white solid; mp >300 °C.

IR (KBr): 3418, 3296, 2951, 2188, 1713, 1654, 1366 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.65–7.59 (m, 5 H), 7.58–7.51 (m, 2 H), 7.47 (t, *J* = 3.8 Hz, 1 H), 7.43 (d, *J* = 3.9 Hz, 2 H), 7.35 (d, *J* = 3.6 Hz, 1 H), 7.18 (t, *J* = 3.8 Hz, 1 H), 7.06 (t, *J* = 3.8 Hz, 1 H), 6.64 (d, *J* = 3.9 Hz, 1 H), 5.50 (s, 2 H), 2.09–2.14 (m, 2 H), 2.00–1.85 (m, 2 H), 0.90 (s, 3 H), 0.84 (s, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 194.5, 177.7, 152.5, 151.4, 142.8, 136.1, 135.7, 135.5, 130.6, 130.3, 129.9, 129.8, 128.2, 128.1, 126.8, 123.8, 123.1, 119.0, 110.6, 108.4, 60.8, 49.4, 48.6, 41.6, 32.5, 28.5, 26.9.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{31}H_{26}N_4O_2$: 486.2056; found: 486.2058.

2′-Amino-2,5′-dioxo-1,1′-diphenyl-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (4r)
Reaction of **1g** (223 mg, 1.0 mmol) with **2** (66 mg, 1.0 mmol) and **3f** (187 mg, 1.0 mmol) in THF (4 mL) for 12 h afforded **4r**; yield: 339 mg (74%); white solid; mp >300 °C.

IR (KBr): 3466, 3334, 2184, 1727, 1640, 1497, 1364, 1296 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.62–7.55 (m, 6 H), 7.49–7.42 (m, 4 H), 7.36 (d, *J* = 6.9 Hz, 1 H), 7.18 (t, *J* = 7.5 Hz, 1 H), 7.06 (t, *J* = 7.2 Hz, 1 H), 6.63 (d, *J* = 7.5 Hz, 1 H), 5.46 (s, 2 H), 2.26–2.09 (m, 3 H), 2.03–1.97 (m, 1 H), 1.81–1.70 (m, 2 H).

^{13}C NMR (150 MHz, C_6D_6 + CD_3OD): δ = 196.7, 180.5, 156.0, 152.1, 144.2, 136.4, 136.0, 131.0, 130.9, 130.2, 129.0, 128.9, 128.7, 128.5, 128.1, 124.1, 124.0, 119.4, 112.5, 109.9, 61.0, 50.2, 36.6, 29.1, 21.5.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{29}H_{22}N_4O_2$: 458.1743; found: 458.1740.

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