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Rhodium-Catalyzed [3+2] Annulation of Cyclic *N*-Acyl Ketimines with Activated Olefins: Anticancer Activity of Spiroisoindolinones

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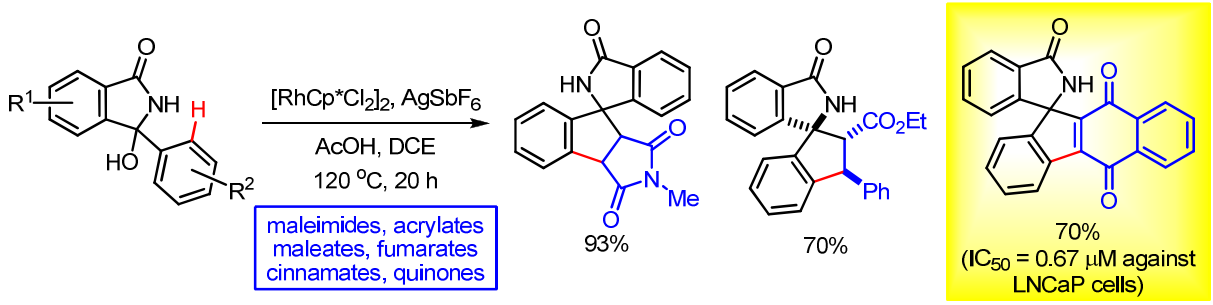
Keywords: Annulation; C–H Functionalization; Ketimines; Rhodium; Spiroisoindolinones.



Abstract

The rhodium(III)-catalyzed redox-neutral coupling reaction of *N*-acyl ketimines generated in situ from 3-hydroxyisoindolinones with various activated olefins is described. This approach leads to the synthesis of bioactive spiroisoindolinone derivatives in moderate to high yields. In case of internal olefins such as maleimides, maleates, fumarates and cinnamates, spiroindanes were obtained by the [3+2] annulations reaction. In sharp contrast, acrylates and quinones displayed the β-H elimination followed by Prins-type cyclization furnishing spiroindenes. The synthetic compounds were evaluated for in vitro anticancer activity against androgen-sensitive human prostate adenocarcinoma cells (LNCaP), human prostate adenocarcinoma cells (DU145), human endometrial adenocarcinoma cells (Ishikawa), human breast cancer cell (MCF-7), and triple negative human breast cancer cells (MDA-MB-231). Notably,

quinone-containing spiroindenes displayed potent anticancer activity about two to three folds stronger than that of anticancer agent doxorubicin.

Introduction

Isoindolinones are among the most interesting class of nitrogen-containing heterocycles, as they are found in various natural products and biologically active compounds.[1] Among those, spiroisoindolinones also have their own importance as they exhibit various properties such as aldose reductase inhibition or can act as chemical sensors (Figure 1).[2] However, limited methodologies for the construction of spiroisoindolinones have been reported so far.[3] Therefore, the synthesis of spiroisoindolinones has been an attractive area for synthetic chemists.

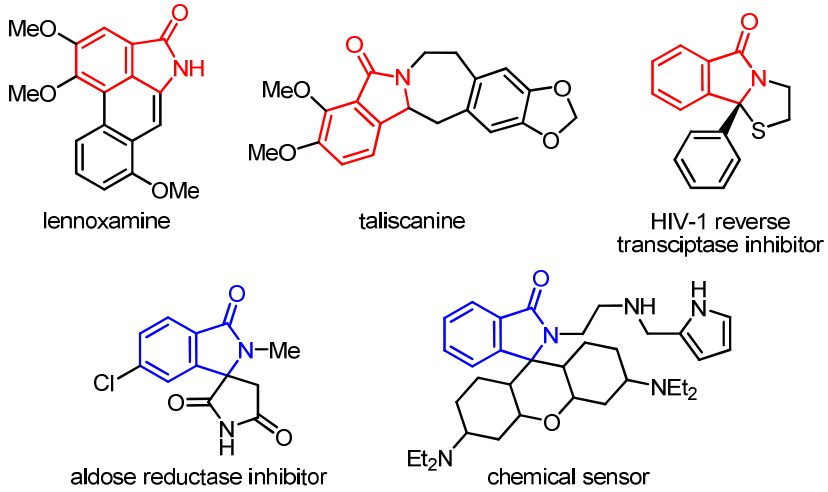
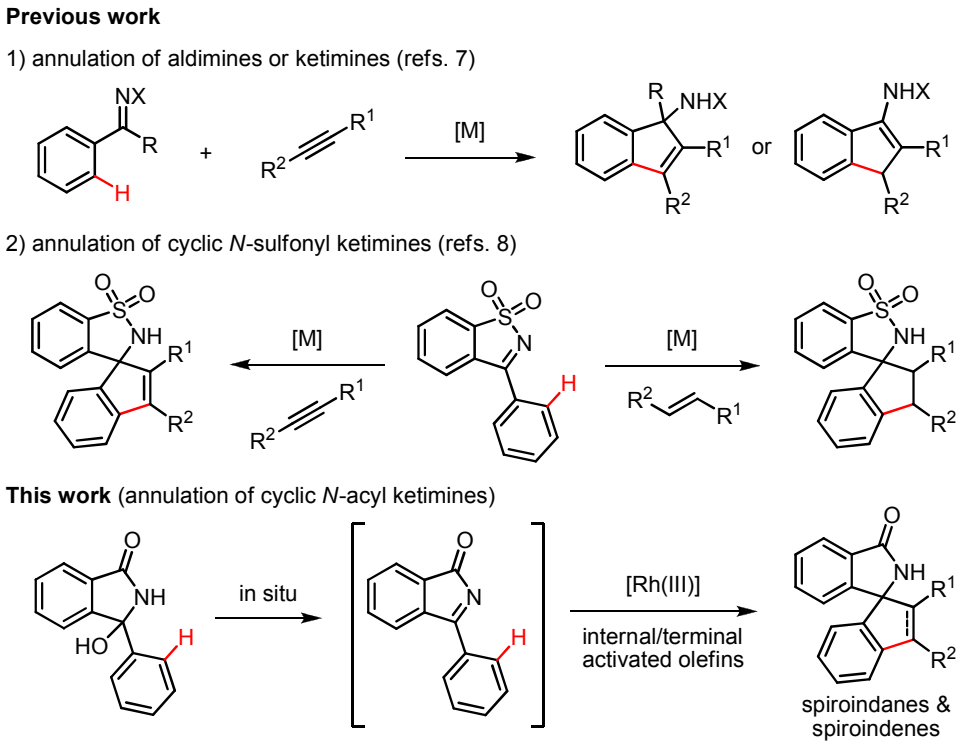


Figure 1. Typical examples of isoindolinone and spiroisoindolinone scaffolds.

The [3+2] annulation reactions have been a versatile strategy to synthesize various complex molecules, especially for the construction of spirocompounds.[4] With the rapid advancement in C–H functionalization for the synthesis of various complex organic scaffolds,[5] the [3+2] annulation reaction based on the transition-metal-catalyzed C–H bond activation has been widely investigated in the past.[6] To this end, imines have been utilized for the [3+2] cyclization reaction to provide aminoindanes or

aminoindenes under transition-metal catalysis.[7] In 2005, Takai reported a pioneering work for the annulation of aromatic imines with unsaturated carbon-carbon bonds to give indene and indane derivatives under rhenium catalysis.[7a] Since then, various research groups showed that metal-alkenyl intermediates generated from alkyne insertion underwent the Grignard-type [3+2] annulation to imine functionality (Scheme 1).[7b–g]

Scheme 1. Transition-Metal-Catalyzed [3+2] Annulations Reactions using Ketimines.



In this context, cyclic imines are of prime importance as they could lead to the formation of spirocompounds via [3+2] annulation reaction. Particularly, a number of reactions have been carried out on cyclic *N*-sulfonylketimines under various transition-metal catalysts.[8] For example, Nishimura reported Ir-catalyzed annulations of *N*-sulfonyl ketimines with 1,3-dienes to give aminoindane derivatives.[8a,b] In addition, alkynes were used as coupling partner for the Grignard-type annulations with *N*-sulfonyl ketimines under Rh catalyst by Dong.[8c,d] Moreover, Co catalyst has also been used for the synthesis of

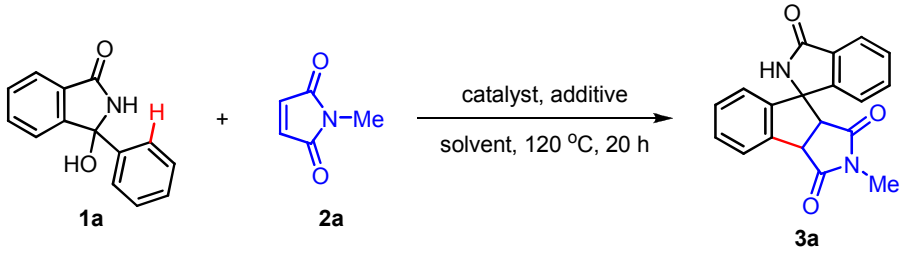
spirosultams by Wang.[8e] In addition, Cramer's group disclosed the asymmetric version by use of a chiral rhodium catalyst.[9] In general, *N*-sulfonyl imines are sufficiently stable to be isolated and they are often used in the addition of organometallic reagents. However, *N*-acyl ketimines are less stable to be used directly, thus their precursors are often used. The use of 3-aryl-3-hydroxyisoindolin-1-ones as stable precursors for the generation of cyclic *N*-acyl ketimines has been reported earlier.[10] To the best of our knowledge, the [3+2] annulation reactions of cyclic *N*-acyl ketimines have been limited to only Ir catalysis, which has been reported by Nishimura.[11] Herein, we report the [3+2] annulation reaction between cyclic *N*-acyl ketimines generated in situ by the dehydration of 3-aryl-3-hydroxyisoindolin-1-ones and activated olefins, i.e. maleimides, acrylates, maleates, fumarates, cinnamates and quinones, for the formation of various spiroisoindolinone frameworks. Furthermore, the synthesized spiroisoindolinones have been evaluated for the cytotoxic effect against androgen-sensitive human prostate adenocarcinoma cells (LNCaP), human prostate adenocarcinoma cells (DU145), human endometrial adenocarcinoma cells (Ishikawa), human breast cancer cell (MCF-7), and triple negative human breast cancer cells (MDA-MB-231).

Results and Discussion

Our study was initiated by treatment of 3-hydroxy-3-phenylisoindolin-1-one (**1a**) having a hemiaminal moiety with *N*-methylmaleimide (**2a**) as an activated internal olefin.[12] The coupling of **1a** with **2a** in the presence of 2.5 mol % of $[RhCp^*Cl_2]_2$, 10 mol % of $AgSbF_6$, 50 mol % of $Cu(OAc)_2$ and 2 equiv. of AcOH in DCE at 120 °C for 20 h afforded the [3+2] annulation spiroisoindolinone **3a** in 77% yield (Table 1, entry 1). To our surprise, the formation of product is in sharp contrast with the Rh(III)-catalyzed annulations reaction between *N*-sulfinyl ketoimines and maleimides to give tricyclic pyrrolidone-fused isoquinolines as reported by Li.[12e] Moreover, the exclusion of $Cu(OAc)_2$ increased the catalytic reactivity to afford our desired product **3a** in 93% yield (Table 1, entry 2). Control experiments revealed that both cationic rhodium catalyst and acid additive are highly crucial for this annulation

reaction (Table 1, entries 2–7). Other catalysts such as Co(III) and Ru(II) were found to be less effective in this transformation (Table 1, entries 8 and 9). Further screening of solvents showed that DCE was found to be an optimal solvent for the formation of **3a** (Table 1, entries 10–12). Lowering the amount of Rh(III) catalyst to 1 mol % or AcOH to 100 mol % provided a slightly decreased formation of spiroisoindolinone **3a** in 74% and 82% yields, respectively (Table 1, entries 13 and 14). Finally, this process was compatible under argon atmosphere to furnish spiro adduct **3a** in high yield, suggesting that this transformation proceeds via a redox-neutral catalytic cycle (Table 1, entry 15).

Table 1. Selected Optimization of Reaction Conditions.[a]

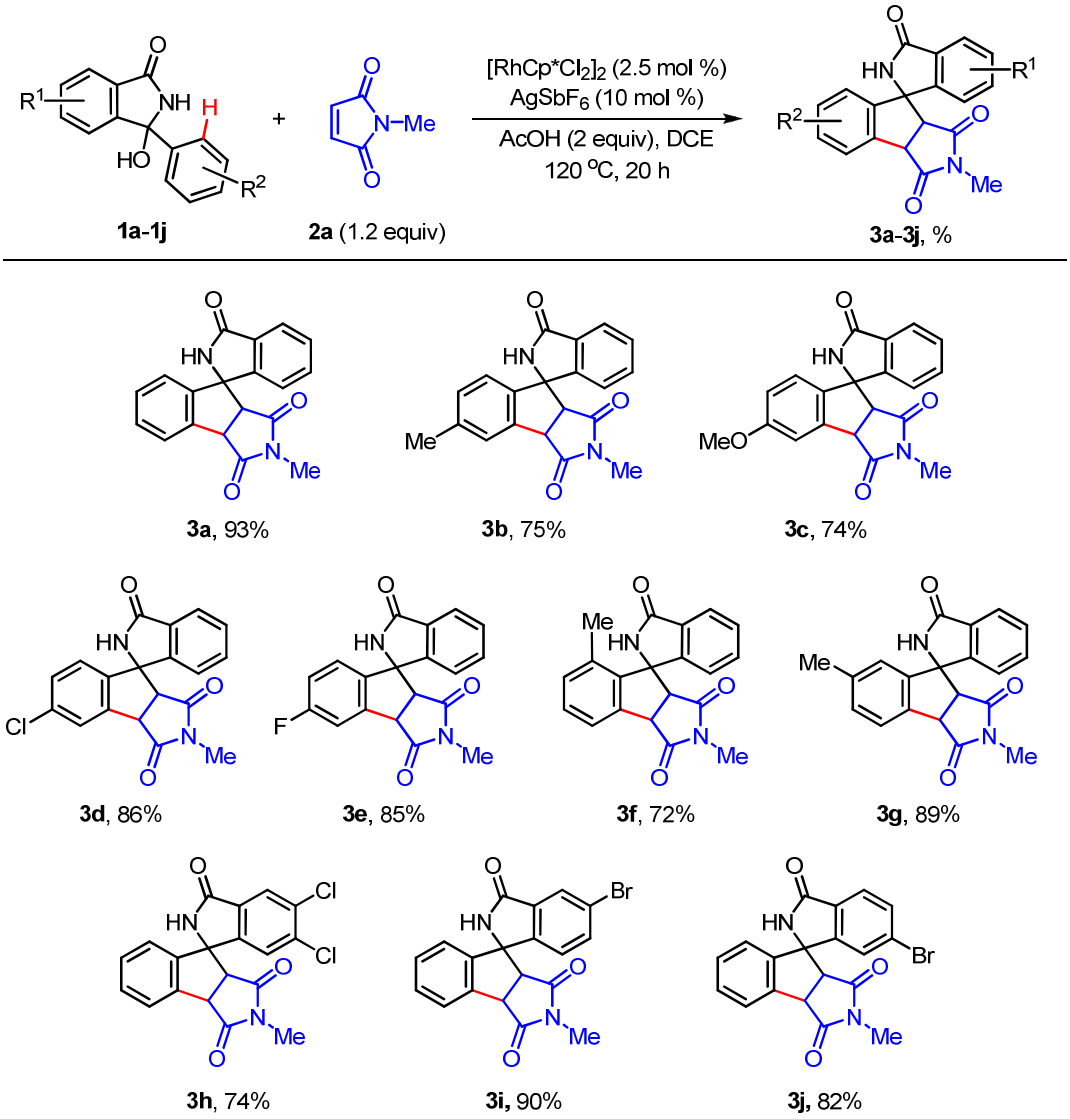


entry	catalyst (mol %)	additive (mol %)	solvent	yield (%)[b]
1	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), AcOH (200), $Cu(OAc)_2$ (50)	DCE	77
2	**$[RhCp^*Cl_2]_2$**	**$AgSbF_6$ (10), AcOH (200)**	**DCE**	**93**
3	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), PivOH (200)	DCE	92
4	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), NaOAc (200)	DCE	50
5	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10)	DCE	trace
6	$[RhCp^*Cl_2]_2$	AcOH (200)	DCE	N.R.
7		$AgSbF_6$ (10), AcOH (200)	DCE	N.R.
8[c]	$[CoCp^*(CO)I_2]$	$AgSbF_6$ (10), AcOH (200)	DCE	25
9	$[Ru(p\text{-cymene})Cl_2]_2$	$AgSbF_6$ (10), AcOH (200)	DCE	45
10	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), AcOH (200)	THF	60
11	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), AcOH (200)	MeCN	12
12	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), AcOH (200)	toluene	10
13[d]	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (4), AcOH (200)	DCE	74
14	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), AcOH (100)	DCE	82

15[e]	$[RhCp^*Cl_2]_2$	$AgSbF_6$ (10), AcOH (200)	DCE	84

[a] *Reaction conditions:* **1a** (0.2 mmol), **2a** (0.24 mmol), catalyst (2.5 mol %), additive (quantity noted), solvent (1 mL) under air at 120 °C for 20 h in pressure tubes. [b] Yield by flash column chromatography. [c] 5 mol % of Co(III) catalyst was used. [d] 1 mol % of Rh(III) catalyst was used. [e] The reaction was carried out under argon atmosphere.

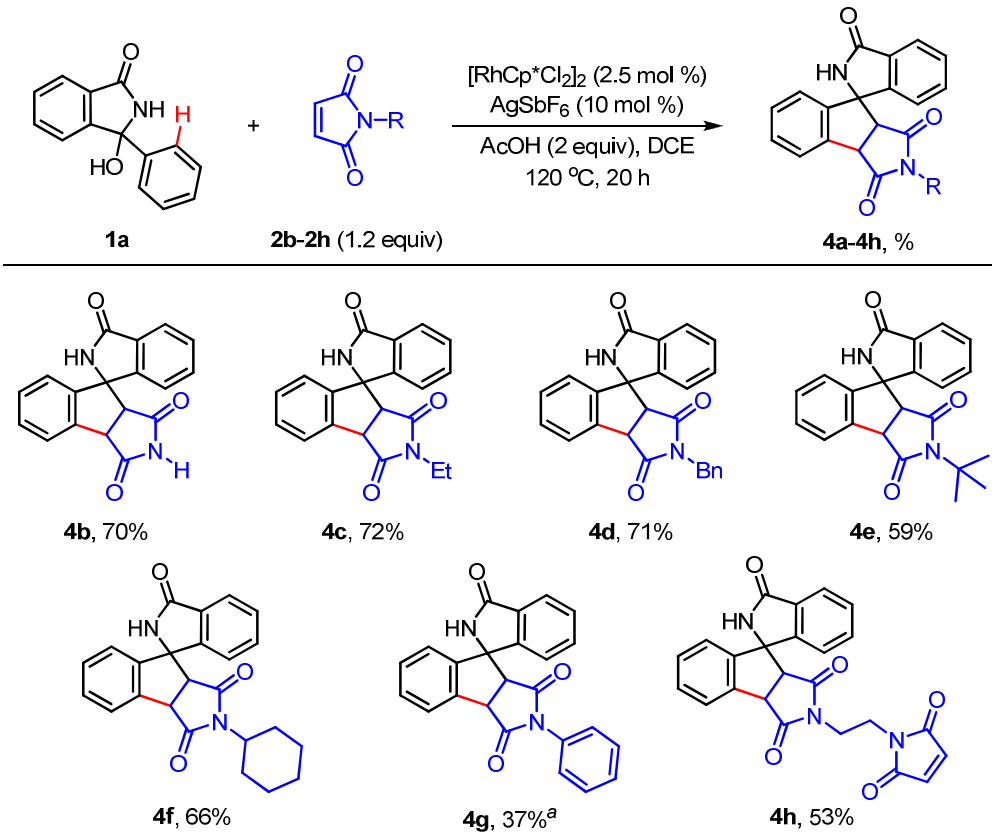
Scheme 2. Scope of 3-Aryl-3-hydroxyisoindolin-1-ones.



With the optimal reaction conditions in hand, we explored the scope and limitations of this [3+2] annulation reaction. Various 3-aryl-3-hydroxyisoindolin-1-ones **1b**–**1j** were examined with *N*-

methylmaleimide (**2a**) (Scheme 2). The reactions of hemiaminals containing C3-*para*-substituted phenyl rings of isoindolinones **1b–1e** were found to smoothly undergo the annulations reaction. Both electron donating and electron withdrawing groups on the C3-phenyl ring provided the corresponding compounds **3b–3e** in good yields. The structures of products were supported by x-ray crystal analysis of compound **3c** (see the Supporting Information). The annulations of sterically congested *ortho*-substituted substrate **1f** also underwent the reaction to afford the desired spiro compound **3f** in 72 % yield. In addition, *meta*-substituted substrate **1g** showed good regioselectivity at less sterically hindered C–H bond to furnish **3g** in 89% yield. Moreover, C5- and C6-substituted 3-aryl-3-hydroxyisoindolin-1-ones **1h–1j** also displayed good reactivity towards the [3+2] annulations providing the desired products **3h–3j** in good to high yields.

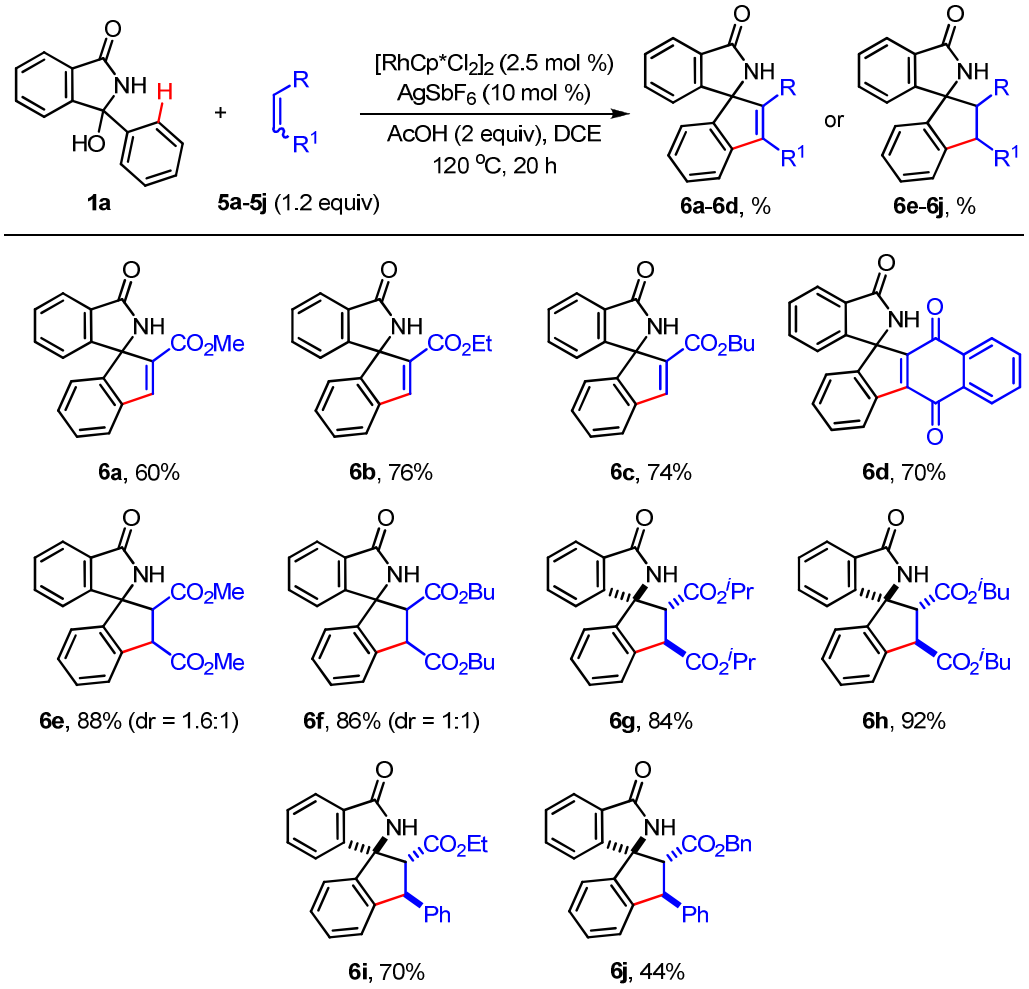
Scheme 3. Scope of Maleimides.



[a] Reaction conditions: $AdCO_2H$ (2 equiv) was used instead of AcOH under otherwise identical conditions.

To further evaluate the scope of this process, the coupling of various maleimides **2b**–**2h** with 3-hydroxy-3-phenylisoindolin-1-one (**1a**) was carried out under the optimal reaction conditions (Scheme 3). Gratifyingly, unprotected maleimide **2b** was found to be coupled with **1a** to afford **4b** in 70% yield. Other *N*-alkyl substituted maleimides **2c**–**2f**, such as *N*-ethyl, *N*-benzyl, *N*-*tert*-butyl, and *N*-cyclohexyl, were favoured in the coupling reaction to furnish the desired products **4c**–**4f** in good yields. Notably, *N*-phenylmaleimide **2g** displayed very low reactivity under the standard reaction conditions. However, the use of admantyl carboxylic acid ($AdCO_2H$) instead of AcOH delivered the corresponding product **4g** in 37% yield. In addition, this reaction showed good mono-selectivity for the coupling of **2h** with **1a** under the optimized reaction conditions to afford **4h** in 53% yield.

Scheme 4. Scope of Activated Olefins.



Next, we explored the scope of other activated terminal and internal olefins under the optimal reaction conditions, as shown in Scheme 4. To our surprise, acrylates **5a**–**5c** were found to undergo the [3+2] annulation reaction to furnish spiroindenes **6a**–**6c** instead of spiroindanes, suggesting that the reaction might proceed via β-H elimination followed by subsequent cyclization.[11b] Interestingly, 1,4-naphthoquinone (**5d**) showed the similar reactivity to give spiroindene **6d** in 70% yield. In addition, maleates **5e** and **5f** as internal *cis*-olefins displayed the [3+2] annulation reaction without β-H elimination process to afford spiroindanes **6e** and **6f** in high yields, but a diastereomeric mixture was formed in these cases. Notably, *trans*-olefins **5g**–**5j** such as fumarates and cinnamates provided the corresponding products **6g**–**6j** as single diastereomers. These results might be explained by the steric repulsion between C3-substituents and isoindolinone moiety. The structures of **6i** and **6j** were confirmed unambiguously based on the x-ray crystal analysis (see the Supporting Information). However, non-activated alkenes such as styrene and cyclohexene did not provide the desired spiro products under the standard reaction conditions.

A plausible mechanistic pathway is depicted in Scheme 5. Coordination of a cationic Rh(III) catalyst with intermediate **A** and subsequent C–H activation delivers rhodacycle intermediate **B**, which on coordination with **2a** followed by migratory insertion affords rhodacycle species **C**. Nucleophilic addition of C–Rh bond into ketimine provides intermediate **D**, which on protonation by AcOH releases spiroindane **3a** and an active Rh(III) catalyst can recycle in the catalytic pathway. In case of acrylates and quinones, the alternative pathway through β-H elimination followed by Prins-type cyclization[11b,13] affording the corresponding spiroindenes is suggested.

Scheme 5. Plausible Reaction Pathway.

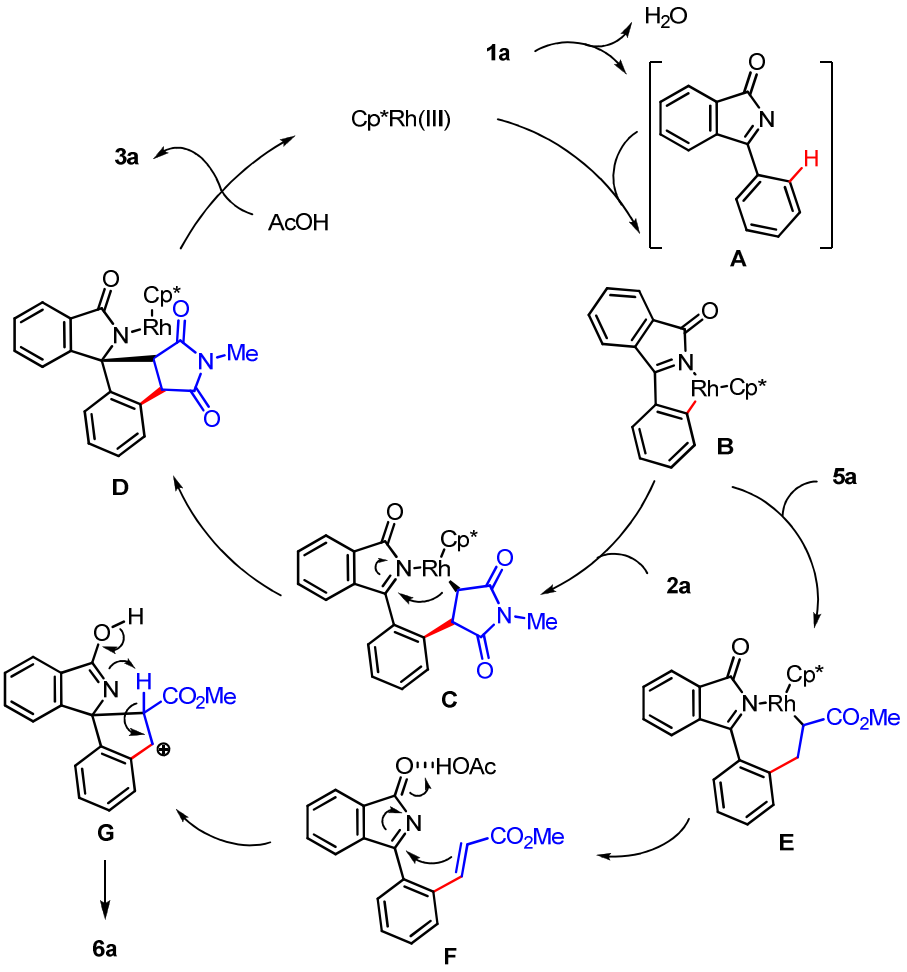
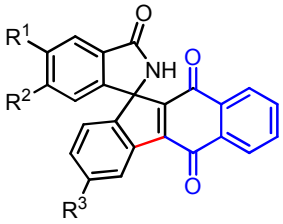


Table 2. Anticancer Activity of Synthetic Compounds.[a]



6d ($R^1 = R^2 = R^3 = H$)
6k ($R^1 = R^2 = Cl$, $R^3 = H$)
6l ($R^1 = R^2 = H$, $R^3 = OMe$)
6m ($R^1 = R^2 = H$, $R^3 = Cl$)
6n ($R^1 = R^2 = H$, $R^3 = F$)

	LNCap	DU145	Ishikawa	MCF-7	MDA-MB-231
6d	0.67	2.18	1.90	0.82	6.88
6k	1.10	2.13	0.75	1.02	3.01
6l	1.03	5.49	3.91	3.01	7.34
6m	5.34	1.68	1.39	5.11	17.6
6n	1.97	2.64	4.10	2.23	10.9
doxorubicin	3.02	2.56	3.67	5.50	8.62

[a] IC_{50} value: substance concentration for 50% inhibition of cell viability.

Meanwhile the synthesized spiroindanes (**3a**–**3j**, **4b**–**4h** and **6e**–**6j**) and spiroindenes (**6a**–**6d**) were first screened for growth inhibitory activity against human breast cancer cell (MCF-7) by using the MTT (3-

(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay[14] (see Supporting Information for cytotoxicity data of all synthetic compounds). To our delight, quinone-containing spiroindene **6d** displayed the most potent activity (IC_{50} = 0.82 μM against MCF-7 cells), After finding promising activity of **6d** in MCF-7 cell lines, we prepared other quinone-containing spiroindenes **6k**–**6n** according to above synthetic protocol. These compounds were evaluated against LNCaP, DU145, Ishikawa, MCF-7, and MDA-MB-231 cell lines. In all cases, powerful anti-proliferative activities were observed. In particular, compounds **6d** (IC_{50} = 0.67 μM against LNCaP cells) and **6k** (IC_{50} = 0.75 μM against Ishikawa cells) showed most potent anticancer activity, which are stronger than that of well-known anticancer agent doxorubicin as a positive control (Table 2).[15] These results reveal that quinone-containing spiroindene derivatives represent a new class of strong inhibitors against human prostate and endometrial cancer cells.

Conclusion

In conclusion, we described the rhodium(III)-catalyzed [3+2] annulations reaction of a range of *N*-acyl ketimines generated in situ from 3-hydroxyisoindolinones with various activated olefins to afford biologically important spiroisoindolinone derivatives. These transformations have been applied to a wide range of substrates, and typically proceed with excellent levels of chemoselectivity as well as with high functional group tolerance. In addition, all synthesized compounds were evaluated for in vitro anticancer activity against various human cancer cell lines. Compounds **6d** and **6k** were found to exhibit potent cytotoxicity stronger than anticancer agent doxorubicin. Further studies to determine the biological action of quinone-containing spiroindenes are underway.

Experimental Section

Typical procedure for the preparation of 3-hydroxy-3-phenylisoindolin-1-one (1a): To a solution of phthalimide (1.47 g, 10.0 mmol) in CH_2Cl_2 (25 mL) in a round bottom flask was slowly added PhMgBr (30 mL, 30 mmol, 1.0 M in THF) at 0 °C. The reaction mixture was stirred at room temperature

for 5 h. The reaction mixture was quenched with saturated NH_4Cl solution (30 mL) and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The solid residue was recrystallized from hot CH_2Cl_2 and hexane to give **1a** (2.0 g) in 89% yield.

Typical procedure for the preparation of spiro compounds (3a–3j, 4b–4h and 6a–6n): To an oven-dried sealed tube charged with 3-hydroxy-3-phenylisoindolin-1-one (**1a**) (45.0 mg, 0.2 mmol, 100 mol %), $[RhCp^*Cl_2]_2$ (3.1 mg, 0.005 mmol, 2.5 mol %), $AgSbF_6$ (6.8 mg, 0.02 mmol, 10 mol %) and AcOH (24.0 mg, 0.4 mmol, 200 mol %) were added 1-methyl-(1*H*)-pyrrole-2,5-dione (**2a**) (26.6 mg, 0.24 mmol, 120 mol %) and DCE (1 mL). The reaction mixture was allowed to stir for 20 h at 120 °C. The reaction mixture was diluted with EtOAc (3 mL) and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc = 3:1 to 1:2) to afford **3a** (59.2 mg) in 93% yield.

2-Methyl-1*H*-spiro[indeno[1,2-*c*]pyrrole-8,1'-isoindoline]-1,3,3'(2*H*,3a*H*,8a*H*)-trione (3a): 59.2 mg (93%); white solid; mp = 287.3–288.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.57 (br s, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.45–7.40 (m, 2H), 7.27 (t, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.59 (d, *J* = 7.6 Hz, 1H), 4.63 (d, *J* = 7.6 Hz, 1H), 4.05 (d, *J* = 8.0 Hz, 1H), 2.93 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 175.7, 173.9, 169.8, 147.9, 142.2, 136.8, 132.3, 130.6, 130.3, 129.9, 129.2, 125.8, 124.5, 123.8, 122.7, 55.5, 50.4, 29.7, 25.0; IR (KBr) υ 3344, 2922, 1703, 1431, 1378, 1302, 1281, 1133, 1085, 1059, 968, 782, 774, 753 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{19}H_{15}N_2O_3$ $[M+H]^+$ 319.1083, found 319.1069.

2,5-Dimethyl-3a,8a-dihydro-1*H*-spiro[indeno[1,2-*c*]pyrrole-8,1'-isoindoline]-1,3,3'(2*H*)-trione (3b): 49.8 mg (75%); white solid; mp = 253.7–254.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.2 Hz, 1H), 7.55 (br s, 1H), 7.52 (s, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 8.0

Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.59 (d, *J* = 7.2 Hz, 1H), 4.58 (d, *J* = 7.6 Hz, 1H), 4.02 (d, *J* = 8.0 Hz, 1H), 2.92 (s, 3H), 2.39 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 175.8, 174.0, 169.8, 148.0, 140.7, 139.3, 137.0, 132.2, 130.9, 130.7, 129.1, 126.1, 124.1, 123.8, 122.8, 72.5, 55.8, 50.3, 25.0, 21.3; IR (KBr) υ 3168, 3073, 1697, 1429, 1379, 1343, 1279, 1128, 1062, 964, 816, 765, 756 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{20}H_{17}N_2O_3$ $[M+H]^+$ 333.1239, found 333.1225.

5-Methoxy-2-methyl-3a,8a-dihydro-1*H*-spiro[indeno[1,2-*c*]pyrrole-8,1'-isoindoline]-1,3,3'(2*H*)-trione (3c): 51.5 mg (74%); white solid; mp = >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (br s, 1H), 7.70 (d, *J* = 6.4 Hz, 1H), 7.49–7.41 (m, 2H), 7.10 (d, *J* = 2.2 Hz, 1H), 6.84 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.60 (d, *J* = 7.0 Hz, 1H), 6.56 (d, *J* = 8.5 Hz, 1H), 4.63 (d, *J* = 8.2 Hz, 1H), 4.01 (d, *J* = 8.2 Hz, 1H), 3.78 (s, 3H), 2.76 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 175.9, 174.5, 168.2, 160.4, 148.6, 138.8, 135.1, 132.0, 131.0, 128.6, 124.9, 122.8, 122.6, 116.2, 109.5, 71.5, 55.7, 55.4, 50.3, 24.5; IR (KBr) υ 3254, 2920, 2852, 1691, 1603, 1462, 1431, 1312, 1274, 1128, 1081, 1024, 965, 831, 754 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{20}H_{17}N_2O_4$ $[M+H]^+$ 349.1188, found 349.1174.

5-Chloro-2-methyl-3a,8a-dihydro-1*H*-spiro[indeno[1,2-*c*]pyrrole-8,1'-isoindoline]-1,3,3'(2*H*)-trione (3d): 60.6 mg (86%); white solid; mp = 252.8–253.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.32 (br s, 1H), 7.72 (d, *J* = 6.4 Hz, 1H), 7.64 (s, 1H), 7.51–7.44 (m, 2H), 7.32 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.61 (d, *J* = 7.2 Hz, 1H), 4.71 (d, *J* = 8.4 Hz, 1H), 4.05 (d, *J* = 8.0 Hz, 1H), 2.72 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 175.5, 174.2, 168.2, 147.9, 142.6, 139.3, 133.9, 132.2, 131.0, 129.5, 128.9, 125.8, 125.3, 122.9, 122.8, 71.3, 55.3, 50.2, 24.6; IR (KBr) υ 3252, 2946, 1701, 1430, 1365, 1272, 1294, 1134, 1076, 966, 830, 755 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{19}H_{14}ClN_2O_3$ $[M+H]^+$ 353.0693, found 353.0680.

5-Fluoro-2-methyl-3a,8a-dihydro-1*H*-spiro[indeno[1,2-*c*]pyrrole-8,1'-isoindoline]-1,3,3'(2*H*)-

trione (3e): 57.1 mg (85%); white solid; mp = >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (br s, 1H), 7.71 (d, *J* = 6.4 Hz, 1H), 7.51–7.38 (m, 3H), 7.11 (t, *J* = 8.8 Hz, 1H), 6.72–6.69 (m, 1H), 6.62 (d, *J* = 7.2 Hz, 1H), 4.70 (d, *J* = 8.4 Hz, 1H), 4.06 (d, *J* = 8.4 Hz, 1H), 2.77 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 175.5, 174.3, 168.2, 162.8 (d, $J_{C\text{-}F}$ = 244.1 Hz), 148.2, 139.6 (d, $J_{C\text{-}F}$ = 2.2 Hz), 139.5 (d, $J_{C\text{-}F}$ = 9.4 Hz), 132.1, 131.0, 128.8, 126.0 (d, $J_{C\text{-}F}$ = 9.4 Hz), 122.8, 122.7, 116.8 (d, $J_{C\text{-}F}$ = 23.1 Hz), 112.1 (d, $J_{C\text{-}F}$ = 22.9 Hz), 71.2, 55.6, 50.2 (d, $J_{C\text{-}F}$ = 1.3 Hz), 24.6; IR (KBr) υ 3320, 2872, 1698, 1464, 1432, 1381, 1276, 1228, 1124, 1084, 1044, 966, 884, 750 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{19}H_{14}FN_2O_3$ $[M+H]^+$ 337.0988, found 337.0974.

2,7-Dimethyl-3a,8a-dihydro-1*H*-spiro[indeno[1,2-*c*]pyrrole-8,1'-isoindoline]-1,3,3'(2*H*)-trione (3f): 47.8 mg (72%); white solid; mp = 255.7–256.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (br s, 1H), 7.72 (d, *J* = 6.4 Hz, 1H), 7.49–7.44 (m, 3H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.56 (d, *J* = 7.2 Hz, 1H), 4.63 (d, *J* = 8.4 Hz, 1H), 3.98 (d, *J* = 8.4 Hz, 1H), 2.72 (s, 3H), 1.46 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 176.2, 174.5, 168.4, 147.1, 139.8, 137.8, 135.1, 132.1, 132.0, 131.3, 129.7, 128.8, 123.4, 122.6, 122.4, 72.6, 55.7, 50.0, 24.4, 15.9; IR (KBr) υ 3381, 2866, 1690, 1588, 1431, 1379, 1273, 1131, 1110, 1046, 963, 954, 772, 754, 710 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{20}H_{17}N_2O_3$ $[M+H]^+$ 333.1239, found 333.1226.

2,6-Dimethyl-3a,8a-dihydro-1*H*-spiro[indeno[1,2-*c*]pyrrole-8,1'-isoindoline]-1,3,3'(2*H*)-trione (3g): 59.1 mg (89%); white solid; mp = 268.5–269.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29 (br s, 1H), 7.71 (d, *J* = 6.8 Hz, 1H), 7.50–7.42 (m, 3H), 7.22 (d, *J* = 7.6 Hz, 1H), 6.58 (d, *J* = 7.2 Hz, 1H), 6.46 (s, 1H), 4.62 (d, *J* = 8.0 Hz, 1H), 4.01 (d, *J* = 8.4 Hz, 1H), 2.76 (s, 3H), 2.16 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 176.2, 174.5, 168.2, 148.4, 143.6, 138.9, 134.4, 132.0, 131.0, 130.4, 128.7, 125.2, 123.9, 122.8, 122.7, 71.8, 55.4, 50.1, 24.5, 20.6; IR (KBr) υ 3284, 2918, 1687, 1562, 1429, 1375, 1284, 1128, 1114, 1032, 986, 833, 758, 701 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{20}H_{17}N_2O_3$ $[M+H]^+$

333.1239, found 333.1226.

5',6'-Dichloro-2-methyl-3a,8a-dihydro-1*H*-spiro[indeno[1,2-*c*]pyrrole-8,1'-isoindoline]-1,3,3'(2*H*)-trione (3h): 57.3 mg (74%); white solid; mp = >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (br s, 1H), 7.95 (s, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.11 (s, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 4.66 (d, *J* = 8.4 Hz, 1H), 4.00 (d, *J* = 8.0 Hz, 1H), 2.79 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 175.7, 174.4, 165.6, 147.8, 142.3, 137.8, 134.7, 132.2, 132.0, 129.9, 129.4, 126.0, 125.4, 124.5, 124.2, 71.3, 55.3, 50.4, 24.8; IR (KBr) υ 3344, 2874, 1698, 1428, 1401, 1310, 1279, 1057, 984, 913, 782, 767 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{19}H_{13}Cl_2N_2O_3$ $[M+H]^+$ 387.0303, found 387.0292.

5'-Bromo-2-methyl-3a,8a-dihydro-1*H*-spiro[indeno[1,2-*c*]pyrrole-8,1'-isoindoline]-1,3,3'(2*H*)-trione (3i): 71.4 mg (90%); white solid; mp = 264.5–265.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (br s, 1H), 7.86 (s, 1H), 7.63–7.60 (m, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 4.69 (d, *J* = 8.4 Hz, 1H), 4.03 (d, *J* = 8.4 Hz, 1H), 2.78 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 176.0, 174.5, 166.7, 147.4, 142.8, 137.4, 134.9, 133.5, 129.8, 129.4, 125.6, 125.5, 125.4, 124.1, 122.1, 71.8, 55.1, 50.5, 24.7; IR (KBr) υ 3341, 2915, 1694, 1460, 1421, 1375, 1298, 1279, 1132, 1058, 1030, 1058, 964, 808, 783, 769 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{19}H_{14}BrN_2O_3$ $[M+H]^+$ 397.0188, found 397.0177.

6'-Bromo-2-methyl-3a,8a-dihydro-1*H*-spiro[indeno[1,2-*c*]pyrrole-8,1'-isoindoline]-1,3,3'(2*H*)-trione (3j): 65.1 mg (82%); white solid; mp = >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.44 (br s, 1H), 7.72–7.66 (m, 2H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 6.81 (s, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 4.69 (d, *J* = 8.0 Hz, 1H), 4.02 (d, *J* = 8.4 Hz, 1H), 2.78 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 175.9, 174.5, 167.2, 150.2, 142.7, 137.5, 132.1, 130.5, 129.8, 129.5, 126.1, 125.6,

125.5, 124.8, 124.1, 71.6, 55.3, 50.4, 24.6; IR (KBr) υ 3359, 2923, 1698, 1604, 1587, 1428, 1452, 1267, 1110, 1132, 1057, 964, 837, 794, 780, 767 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{19}H_{14}BrN_2O_3$ $[M+H]^+$ 397.0188, found 397.0177.

3a,8a-Dihydro-1*H*-spiro[indeno[1,2-*c*]pyrrole-8,1'-isoindoline]-1,3,3'(2*H*)-trione (4b): 42.6 mg (70%); white solid; mp = >300 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.34 (br s, 1H), 9.29 (br s, 1H), 7.72–7.70 (m, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.49–7.47 (m, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 6.70–6.68 (m, 1H), 6.65 (d, *J* = 7.6 Hz, 1H), 4.66 (d, *J* = 8.4 Hz, 1H), 3.97 (d, *J* = 8.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 177.5, 175.8, 168.2, 148.4, 143.7, 137.4, 131.9, 131.1, 129.4, 129.1, 128.6, 125.4, 123.9, 122.9, 122.7, 71.8, 56.3, 51.7; IR (KBr) υ 3285, 2922, 2854, 1694, 1427, 1366, 1267, 1217, 740 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{18}H_{13}N_2O_3$ $[M+H]^+$ 305.0926, found 305.0915.

2-Ethyl-3a,8a-dihydro-1*H*-spiro[indeno[1,2-*c*]pyrrole-8,1'-isoindoline]-1,3,3'(2*H*)-trione (4c): 47.8 mg (72%); white solid; mp = 263.8–265.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.32 (br s, 1H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.50–7.40 (m, 3H), 7.27 (t, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 6.55 (d, *J* = 7.6 Hz, 1H), 4.69 (d, *J* = 8.8 Hz, 1H), 4.02 (d, *J* = 7.6 Hz, 1H), 3.83–3.26 (m, 2H), 1.00 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 175.9, 174.2, 168.3, 148.4, 143.6, 137.1, 131.9, 131.0, 129.5, 129.3, 128.8, 125.5, 123.9, 123.0, 122.7, 71.9, 54.9, 50.4, 12.5; IR (KBr) υ 3372, 2932, 1686, 1397, 1341, 1315, 1246, 1221, 1126, 1077, 776, 752 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{20}H_{17}N_2O_3$ $[M+H]^+$ 333.1239, found 333.1226.

2-Benzyl-3a,8a-dihydro-1*H*-spiro[indeno[1,2-*c*]pyrrole-8,1'-isoindoline]-1,3,3'(2*H*)-trione (4d): 56.0 mg (71%); white solid; mp = 208.7–209.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.58 (br s, 1H), 7.43–7.36 (m, 2H), 7.33–7.22 (m, 6H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 6.08 (d, *J* = 7.6 Hz, 1H), 4.64–4.61 (m, 2H), 4.52 (d, *J* = 13.6 Hz, 1H), 4.01

(d, *J* = 8.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 175.4, 173.5, 169.8, 147.8, 142.4, 136.6, 135.2, 132.3, 130.3 (one carbon overlap), 129.8, 129.6, 128.9, 128.7, 128.2, 125.8, 124.5, 123.6, 123.0, 72.7, 55.1, 50.5, 42.9; IR (KBr) υ 3395, 2928, 1702, 1391, 1365, 1313, 1167, 1084, 783, 751, 702 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{25}H_{19}N_2O_3$ $[M+H]^+$ 395.1396, found 395.1377.

2-(*tert*-Butyl)-3a,8a-dihydro-1*H*-spiro[indeno[1,2-*c*]pyrrole-8,1'-isoindoline]-1,3,3'(2*H*)-trione (4e): 42.5 mg (59%); light yellow solid; mp = 282.9–283.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29 (br s, 1H), 7.72–7.70 (m, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.49–7.46 (m, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 6.63–6.61 (m, 1H), 4.57 (d, *J* = 8.8 Hz, 1H), 3.90 (d, *J* = 8.8 Hz, 1H), 1.40 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 177.1, 175.3, 168.3, 148.5, 143.6, 137.6, 131.8, 130.9, 129.4, 129.2, 128.7, 125.7, 123.8, 123.1, 122.7, 77.3, 57.8, 54.6, 50.08, 27.8; IR (KBr) υ 3284, 2970, 1693, 1359, 1335, 1220, 1170, 1071, 776, 754 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{22}H_{21}N_2O_3$ $[M+H]^+$ 361.1552, found 361.1537.

2-Cyclohexyl-3a,8a-dihydro-1*H*-spiro[indeno[1,2-*c*]pyrrole-8,1'-isoindoline]-1,3,3'(2*H*)-trione (4f): 50.9 mg (66%); light orange solid; mp = 265.6–266.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (br s, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.50–7.39 (m, 3H), 7.26 (t, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.55 (d, *J* = 7.6 Hz, 1H), 4.66 (d, *J* = 8.4 Hz, 1H), 3.99 (d, *J* = 8.4 Hz, 1H), 3.76–3.70 (m, 1H), 1.97–1.82 (m, 2H), 1.78–1.69 (m, 2H), 1.57–1.50 (m, 3H), 1.24–1.14 (m, 2H), 1.08–1.01 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 176.0, 174.3, 168.3, 148.4, 143.6, 137.2, 131.9, 130.9, 129.5, 129.2, 128.8, 125.5, 123.9, 123.0, 122.7, 71.9, 51.0, 50.0, 28.4, 27.9, 25.3, 25.2, 24.7; IR (KBr) υ 3354, 2911, 1693, 1417, 1368, 1227, 748 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{24}H_{23}N_2O_3$ $[M+H]^+$ 387.1709, found 387.1688.

2-Phenyl-3a,8a-dihydro-1*H*-spiro[indeno[1,2-*c*]pyrrole-8,1'-isoindoline]-1,3,3'(2*H*)-trione (4g):

28.1 mg (37%); white solid; mp = >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (br s, 1H), 7.74–7.72 (m, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.50–7.44 (m, 5H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 6.81–6.79 (m, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 4.90 (d, *J* = 8.4 Hz, 1H), 4.21 (d, *J* = 8.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 175.2, 173.5, 168.4, 148.4, 143.7, 136.9, 132.2, 132.0, 129.6, 129.4, 129.0, 128.9, 128.4, 126.8, 125.8, 123.9, 123.0, 122.9, 72.2, 55.1, 50.6; IR (KBr) υ 3160, 2920, 2852, 1693, 1608, 1499, 1456, 1375, 1345, 1314, 1238, 1174, 1151, 1084, 1029, 794, 782, 762, 750 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{24}H_{16}N_2O_3$ $[M]^+$ 380.1161, found 380.1158.

2-(2-(2,5-Dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl)-3a,8a-dihydro-1*H*-spiro[indeno[1,2-*c*]pyrrole-8,1'-isoindoline]-1,3,3'(2*H*)-trione (4h): 43.5 mg (51%); white solid; mp = 150.7–152.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 6.8 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.60 (br s, 1H), 7.52–7.43 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.60 (s, 2H), 4.62 (d, *J* = 8.4 Hz, 1H), 3.95 (d, *J* = 8.0 Hz, 1H), 3.79–3.69 (m, 2H), 3.67–3.62 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 175.7, 173.8, 170.5, 169.7, 147.4, 142.3, 136.9, 134.1, 132.3, 131.0, 130.9, 130.2, 129.9, 129.2, 125.5, 124.6, 123.7, 123.6, 72.5, 55.4, 50.2, 38.0, 35.7; IR (KBr) υ 3177, 2937, 1699, 1433, 1412, 1332, 1264, 1151, 1106, 1075, 916, 832, 782, 752, 727 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{24}H_{18}N_3O_5$ $[M+H]^+$ 428.1246, found 428.1230.

Methyl 3''-oxospiro[indene-1,1'-isoindoline]-2-carboxylate (6a): 34.9 mg (60%); light yellow solid; mp = 172.5–173.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.6 Hz, 1H), 7.85 (s, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.41–7.35 (m, 2H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.36 (br s, 1H), 3.56 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.5, 162.6, 146.8, 145.2, 144.0, 139.4, 138.1, 132.3, 132.0, 129.7, 129.4, 128.6, 124.3, 124.1, 123.1, 120.8, 72.1, 51.6; IR (KBr) υ 3367, 2933, 1692, 1570, 1460, 1432, 1321, 1243, 1187, 1154, 1188, 1016, 991, 755, 739 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{18}H_{13}NO_3$ $[M]^+$ 291.0895, found 291.0894.

Ethyl 3'-oxospiro[indene-1,1'-isoindoline]-2-carboxylate (6b): 46.3 mg (76%); white sticky solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.87 (s, 1H), 7.51–7.43 (m, 2H), 7.41–7.35 (m, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.28 (br s, 1H), 3.39–3.95 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.5, 162.3, 146.7, 145.4, 143.9, 139.5, 138.8, 132.3, 132.2, 129.7, 129.4, 128.5, 124.1, 124.0, 123.2, 120.8, 72.1, 60.4, 13.7; IR (KBr) υ 3365, 2935, 1697, 1570, 1461, 1432, 1323, 1243, 1180, 1153, 1180, 1018, 990, 755 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{19}H_{16}NO_3$ $[M+H]^+$ 306.1130, found 306.1120.

Butyl 3'-oxospiro[indene-1,1'-isoindoline]-2-carboxylate (6c): 49.3 mg (74%); light yellow sticky solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.6 Hz, 1H), 7.88 (s, 1H), 7.51–7.44 (m, 2H), 7.41–7.34 (m, 2H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.08 (br s, 1H), 4.02–3.87 (m, 2H), 1.33–1.28 (m, 2H), 1.07–0.96 (m, 2H), 0.77 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.4, 162.5, 146.8, 145.4, 144.2, 139.4, 138.8, 132.3, 132.2, 129.7, 129.4, 128.5, 124.2, 124.0, 123.1, 120.9; IR (KBr) υ 3364, 2929, 1696, 1571, 1461, 1434, 1321, 1243, 1188, 1145, 1189, 1010, 992, 755 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{21}H_{20}NO_3$ $[M+H]^+$ 334.1443, found 334.1434.

Spiro[benzo[*b*]fluorene-11,1'-isoindoline]-3',5,10-trione (6d): 50.8 mg (70%); yellow solid; mp = >300 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 7.6 Hz, 1H), 8.17 (dd, *J* = 7.6, 1.6 Hz, 1H), 8.00 (d, *J* = 7.6 Hz, 1H), 7.93 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.76–7.68 (m, 2H), 7.52–7.47 (m, 2H), 7.41–7.36 (m, 2H), 7.16 (d, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.48 (br s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 183.4, 180.3, 171.2, 146.9, 146.4, 145.7, 144.6, 136.2, 134.2, 133.7, 133.1, 132.8, 132.6, 131.1, 130.1, 129.2, 126.6, 126.5, 126.4, 124.7, 123.5, 121.0, 71.4; IR (KBr) υ 3391, 2963, 1702, 1656, 1570, 1460, 1297, 1270, 1284, 1124, 996, 1017, 759, 746, 710 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{24}H_{14}NO_3$ $[M+H]^+$ 364.0974, found 364.0960.

Dimethyl 3'-oxo-2,3-dihydrospiro[indene-1,1'-isoindoline]-2,3-dicarboxylate (6e): 61.8 mg (88%); white solid; mp = 183.5–184.1 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.2 Hz, 1H), 7.81 (d, *J* = 6.4 Hz, 1H, diasteromeric), 7.59 (td, *J* = 7.6, 1.2 Hz, 1H), 7.58–7.50 (m, 2H), 7.58–7.50 (m, 2H, diasteromeric), 7.42–7.30 (m, 2H), 7.42–7.30 (m, 3H, diasteromeric), 7.22–7.17 (m, 1H), 7.22–7.17 (m, 1H, diasteromeric), 7.12 (br s, 1H), 6.94 (d, *J* = 7.6 Hz, 1H, diasteromeric), 6.86 (d, *J* = 6.4 Hz, 1H, diasteromeric), 6.67 (d, *J* = 7.6 Hz, 1H), 4.89 (d, *J* = 7.6 Hz, 1H), 4.87 (d, *J* = 7.6 Hz, 1H, diasteromeric), 4.32 (d, *J* = 8.8 Hz, 1H), 4.26 (d, *J* = 9.2 Hz, 1H, diasteromeric), 3.85 (s, 3H), 3.83 (s, 3H, diastereomeric), 3.49 (s, 3H), 3.17 (s, 3H, diastereomeric); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.8, 171.6, 170.4, 170.0, 169.9, 169.5, 149.6, 147.5, 141.4, 141.2, 139.0, 137.1, 132.8, 132.1, 131.4, 130.4, 129.8, 129.5, 129.1, 129.0, 128.9, 128.8, 124.9, 124.6, 124.2, 123.6, 123.5, 123.4, 122.4, 122.3, 72.0, 71.4, 56.5, 56.4, 52.7, 52.6, 52.2, 51.8, 50.0, 49.1; IR (KBr) υ 3340, 2920, 1696, 1470, 1430, 1322, 1225, 1170, 1013, 955, 757, 729 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{20}H_{18}NO_5$ $[M+H]^+$ 352.1185, found 352.1174.

Dibutyl 3'-oxo-2,3-dihydrospiro[indene-1,1'-isoindoline]-2,3-dicarboxylate (6f): 74.9 mg (86%); white sticky solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 6.8 Hz, 1H, diasteromeric), 7.62 (td, *J* = 7.6, 1.2 Hz, 1H), 7.57–7.51 (m, 1H), 7.57–7.51 (m, 2H, diasteromeric), 7.44–7.32 (m, 2H), 7.42–7.32 (m, 3H, diasteromeric), 7.24–7.19 (m, 1H), 7.24–7.19 (m, 1H, diasteromeric), 6.95 (d, *J* = 7.6 Hz, 1H), 6.92–6.89 (m, 2H, diasteromeric), 6.69 (d, *J* = 7.6 Hz, 1H), 6.53 (br s, 1H), 6.87 (d, *J* = 9.2 Hz, 1H), 4.83 (d, *J* = 8.8 Hz, 1H, diasteromeric), 4.32 (d, *J* = 8.8 Hz, 1H), 4.29–4.23 (m, 2H), 4.29–4.23 (m, 2H, diasteromeric), 4.21 (d, *J* = 9.2Hz, 1H, diasteromeric), 4.04–3.98 (m, 1H), 3.88–3.82 (m, 1H, diasteromeric), 3.70–3.66 (m, 1H), 3.58–3.55 (m, 1H, diasteromeric), 1.76–1.69 (m, 2H), 1.76–1.69 (m, 2H, diasteromeric), 1.48–1.41 (m, 2H), 1.48–1.41 (m, 2H, diasteromeric), 1.31–1.22 (m, 2H), 1.31–1.22 (m, 2H, diasteromeric), 1.11–1.04 (m, 2H), 1.11–1.04 (m, 2H, diasteromeric), 0.97 (t, *J* = 7.6 Hz, 3H), 0.97 (t, *J* = 7.6 Hz, 3H, diasteromeric), 0.76–0.71 (m, 3H), 0.76–0.71 (m, 2H, diasteromeric);

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 171.4, 171.3, 170.1, 169.6, 169.5, 169.3, 149.6, 147.6, 141.6, 141.3, 139.1, 137.4, 132.9, 132.2, 131.6, 130.6, 129.9, 129.5, 129.1, 129.0, 128.8, 124.8, 124.6, 124.2, 123.6, 123.5, 123.4, 122.6, 122.5, 71.8, 71.3, 65.7, 65.6, 65.1, 64.9, 56.6, 56.5, 50.0, 49.4, 30.6, 30.2, 20.0, 19.1, 18.8, 18.7, 13.7, 13.5, 13.4; IR (KBr) υ 3340, 2920, 1696, 1471, 1430, 1322, 1225, 1165, 1013, 954, 757, 730 cm^{-1}; HRMS (orbitrap, ESI) calcd for $C_{26}H_{30}NO_5$ $[M+H]^+$ 436.2124, found 436.2104.

Diisopropyl 3'-oxo-2,3-dihydrospiro[indene-1,1'-isoindoline]-2,3-dicarboxylate (6g): 68.4 mg (84%); white solid; mp = 148.9–150.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 6.4 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.44–7.33 (m, 3H), 7.24 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 6.8 Hz, 1H), 6.64 (br s, 1H), 5.21–5.14 (m, 1H), 4.82 (d, *J* = 9.2 Hz, 1H), 4.61–4.55 (m, 1H), 4.17 (d, *J* = 9.6 Hz, 1H), 1.37 (d, *J* = 6.4 Hz, 6H), 1.05 (d, *J* = 6.0 Hz, 3H), 0.48 (d, *J* = 6.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 170.7, 170.1, 168.9, 147.7, 141.8, 137.6, 132.3, 130.8, 129.5, 129.0, 128.9, 124.7, 123.7, 123.4, 122.6, 71.7, 69.5, 68.8, 56.5, 49.5, 22.0, 21.8, 21.5, 20.5; IR (KBr) υ 3073, 2977, 1701, 1465, 1375, 1310, 1269, 1213, 1174, 1145, 1105, 990, 885, 767, 755, 729 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{24}H_{25}NO_5$ $[M]^+$ 407.1733, found 407.1736.

Diisobutyl 3'-oxo-2,3-dihydrospiro[indene-1,1'-isoindoline]-2,3-dicarboxylate (6h): 80.1 mg (92%); white solid; mp = 163.9–164.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 6.4 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.42–7.31 (m, 4H), 7.22 (t, *J* = 7.6 Hz, 1H), 6.94–6.90 (m, 2H), 4.91 (d, *J* = 9.2 Hz, 1H), 4.25 (d, *J* = 9.2 Hz, 1H), 4.01 (d, *J* = 6.4 Hz, 3H), 3.55–3.51 (m, 1H), 3.24–3.20 (m, 1H), 2.08–2.01 (m, 1H), 1.49–1.43 (m, 1H), 1.00 (d, *J* = 6.8 Hz, 6H), 0.69 (d, *J* = 6.8 Hz, 3H), 0.65 (d, *J* = 6.8 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 171.2, 170.3, 169.7, 147.6, 141.7, 137.4, 132.2, 130.6, 129.5, 128.9, 128.8, 124.9, 123.6, 123.5, 122.5, 71.9, 71.8, 71.3, 56.5, 49.5, 27.7, 27.3, 19.1, 18.9, 18.7; IR (KBr) υ 3372, 2957, 1692, 1472, 1364, 1318, 1263, 1152, 994, 887, 753, 731 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{26}H_{29}NO_5$ $[M]^+$ 435.2046, found 435.2047.

Ethyl 3'-oxo-3-phenyl-2,3-dihydrospiro[indene-1,1'-isoindoline]-2-carboxylate (6i): 53.6 mg (70%); white solid; mp = 249.4–250.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.85 (m, 1H), 7.48–7.45 (m, 2H), 7.39–7.35 (m, 4H), 7.33–7.28 (m, 3H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.15–7.13 (m, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 5.22 (d, *J* = 10.0 Hz, 1H), 3.80 (d, *J* = 10.0 Hz, 1H), 3.68–3.58 (m, 2H), 0.70 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.6, 169.4, 147.8, 143.7, 142.1, 141.6, 132.2, 130.6, 129.4, 128.9, 128.8, 128.2, 127.3, 125.9, 123.5, 123.0, 72.6, 64.3, 60.7, 50.2, 13.4; IR (KBr) υ 3331, 2973, 1702, 1592, 1465, 1440, 1334, 1223, 1143, 1095, 1010, 964, 803, 790, 775, 755, 727 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{25}H_{21}NO_3$ $[M]^+$ 383.1521, found 383.1524.

Benzyl 3'-oxo-3-phenyl-2,3-dihydrospiro[indene-1,1'-isoindoline]-2-carboxylate (6j): 39.2 mg (44%); white solid; mp = 269.6–271.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.2 Hz, 1H), 7.38–7.27 (m, 9H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.15–7.13 (m, 3H), 7.10–7.05 (m, 2H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.93–6.91 (m, 2H), 5.23 (d, *J* = 10.0 Hz, 1H), 4.52 (q, *J* = 12.0 Hz, 2H), 3.80 (d, *J* = 10.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.4, 169.4, 147.5, 143.5, 141.9, 141.7, 134.6, 132.1, 130.2, 129.4, 128.9, 128.8, 128.5, 128.4, 128.3, 128.1, 127.4, 125.9, 123.6, 123.0, 122.8, 72.6, 66.8, 64.3, 50.4; IR (KBr) υ 3073, 2891, 1698, 1596, 1452, 1330, 1322, 1223, 1171, 952, 772, 749 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{30}H_{23}NO_3$ $[M]^+$ 445.1678, found 445.1680.

5',6'-Dichlorospiro[benzo[*b*]fluorene-11,1'-isoindoline]-3',5,10-trione (6k): 24.1 mg (28%); yellow solid; mp = >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (br s, 1H), 8.33 (d, *J* = 7.6 Hz, 1H), 8.16 (dt, *J* = 6.8, 1.2 Hz, 1H), 8.06 (s, 1H), 7.94–7.87 (m, 3H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.50–7.46 (m, 2H), 7.22 (d, *J* = 7.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 182.9, 180.4, 167.8, 146.2, 145.9, 145.3, 144.9, 136.3, 134.9, 134.5, 134.2, 133.1, 132.8, 132.6, 132.2, 131.0, 130.1, 126.1, 125.9, 125.7, 125.3, 124.4, 123.4, 70.3; IR (KBr) υ 3363, 2920, 1705, 1659, 1588, 1464, 1396, 1349, 1294, 1269, 1179,

1116, 957, 889, 752, 715 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{24}H_{11}Cl_2NO_3$ $[M]^+$ 431.0116, found 431.0119.

3-Methoxyspiro[benzo[*b*]fluorene-11,1'-isoindoline]-3',5,10-trione (6l): 22.8 mg (29%); red solid; mp = >300 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.76 (br s, 1H), 8.14 (d, *J* = 6.8 Hz, 1H), 7.91–7.85 (m, 4H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.02–7.00 (m, 3H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 183.1, 180.1, 170.1, 160.4, 147.8, 145.0, 144.8, 139.0, 137.5, 134.5, 134.1, 132.7, 132.6, 132.5, 132.1, 128.7, 126.0, 125.7, 124.1, 123.5, 121.7, 116.6, 110.7, 70.5, 55.6; IR (KBr) υ 3384, 2918, 1702, 1654, 1591, 1461, 1365, 1294, 1216, 1089, 1025, 783, 742, 710 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{25}H_{15}NO_4$ $[M]^+$ 393.1001, found 393.1003.

3-Chlorospiro[benzo[*b*]fluorene-11,1'-isoindoline]-3',5,10-trione (6m): 26.2 mg (33%); orange solid; mp = >300 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.82 (br s, 1H), 8.28 (d, *J* = 2.0 Hz, 1H), 8.15 (d, *J* = 7.2 Hz, 1H), 7.93–7.83 (m, 4H), 7.55–7.50 (m, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 182.7, 180.1, 170.1, 147.7, 146.0, 144.1, 144.0, 138.1, 134.6, 134.3, 134.1, 132.6, 132.5, 132.4, 132.3, 130.4, 129.1, 126.1, 125.8, 125.1, 124.9, 123.6, 121.8, 70.7; IR (KBr) υ 3371, 2947, 1655, 1365, 1287, 1225, 1132, 1110, 1078, 982, 887, 748, 712 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{24}H_{12}ClNO_3$ $[M]^+$ 397.0506, found 397.0504.

3-Fluorospiro[benzo[*b*]fluorene-11,1'-isoindoline]-3',5,10-trione (6n): 22.8 mg (30%); yellow solid; mp = >300 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.2 Hz, 1H), 8.15 (d, *J* = 7.6 Hz, 1H), 8.02 (d, *J* = 7.2 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.79–7.71 (m, 2H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.13–7.10 (m, 2H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.25 (br s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$ + 2 drop of DMSO-d_6) δ 182.9, 180.1, 171.1, 163.6 (d, $J_{C\text{-}F}$ = 246.7 Hz), 148.4, 144.1, 142.0, 138.0 (d, $J_{C\text{-}F}$ = 9.8 Hz), 134.2, 133.7, 132.9, 132.6, 132.4, 132.1, 129.1, 126.3 (d, $J_{C\text{-}F}$ = 9.0 Hz), 124.6 (d,

$J_{C\text{-}F}$ = 9.1 Hz), 124.5, 120.9, 117.6 (d, $J_{C\text{-}F}$ = 23.5 Hz), 113.5 (d, $J_{C\text{-}F}$ = 24.8 Hz), 70.9; IR (KBr) υ 3370, 2923, 1701, 1655, 1585, 1462, 1386, 1293, 1269, 1242, 1173, 1074, 996, 832, 819, 791, 743, 708 cm^{-1}; HRMS (quadrupole, EI) calcd for $C_{24}H_{12}FNO_3$ $[M]^+$ 381.0801, found 381.0802.

Cancer cell growth inhibition assay (MTT assay): Human prostate adenocarcinoma cells (LNCaP), human prostate adenocarcinoma cells (DU145), human endometrial adenocarcinoma cells (Ishikawa), human breast cancer cell (MCF-7), and triple negative human breast cancer cells (MDA-MB-231) were grown in DMEM medium supplemented with 1% of penicillin/streptomycin, and 10% fetal bovine serum (all from Life Technologies, Grand Island, NY). Cells were seeded in 96-well plates (3 × 103 cells/well) containing 100 μL of growth medium for 24 h. After medium removal, 100 μL of fresh medium containing individual analogue compounds (dissolved in DMSO less than 0.025% in each preparation) at different concentrations were added to each well and incubated at 37 °C for 48 h. After 48 h of incubation, 100 μL of the MTT reagent were added to each well. After 4 h of incubation at 37 °C, the supernatant was aspirated, and the formazan crystals were dissolved in 100 μL of DMSO at 37 °C for 10 min with gentle agitation. The absorbance per well was measured at 540 nm using a VERSA max Microplate Reader (Molecular Devices Corp., USA). The IC50 was defined as the compound concentration requiredinhibiting cell proliferation by 50% in comparison with cells treated with the maximum amount of DMSO (0.025%) and considered as 100% viability.

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Supporting Information Available: X-ray crystallographic data of compounds (**3c**, **6i** and **6j**),

cytotoxicity data of all synthetic compounds, and ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the internet at http://pubs.acs.org.

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