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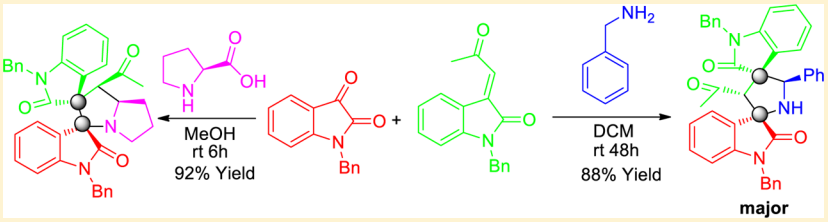
Synthesis of Pyrrolo(spiro-[2.3′]-oxindole)-spiro-[4.3″]-oxindole via 1,3-Dipolar Cycloaddition of Azomethine Ylides with 3-Acetonylideneoxindole

Jun-An Xiao, Hong-Gang Zhang, Shan Liang, Ji-Wei Ren, Hua Yang,* and Xiao-Qing Chen*

School of Chemistry and Chemical Engineering, Central South University, Changsha, 410083, PR China

Supporting Information



ABSTRACT: A series of novel dispirooxindole derivatives, 3-acetyl-5-phenyl-pyrrolo(spiro-[2.3′]-1′-benzyl-oxindole)-spiro-[4.3″]-1″-benzyl-oxindoles, were synthesized via 1,3-dipolar cycloaddition of the azomethine ylide with 3-acetonylideneoxindole in high regioselectivities and yields. An unusual regioselectivity was observed in this 1,3-dipolar cycloaddition, leading to the construction of novel dispirooxindole skeleton. The substituent effects on the regioselectivity were also investigated.

Spirooxindole and their derivatives have recently attracted significant attention due to its unique core structure and great biological activities (Figure 1).[1] For instance, compound

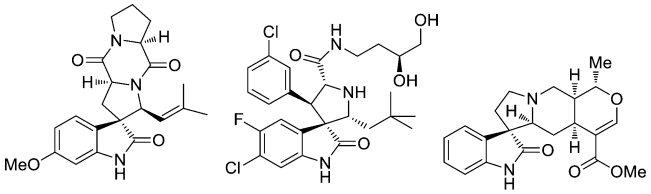


Figure 1. Examples of biologically active spirooxindole derivatives.

MI-219 is an MDM2 inhibitor, and it can effectively block the MDM2-p53 protein−protein interaction in cells.[2] Until now, several synthetic methods have been developed to prepare spirooxindole, including 1,3-dipolar cycloaddition reaction,[3] M−B−H reactions,[4] Pictet−Spengler reactions,[5] and cascade reactions[6] and so on. Recently, a 1,3-dipolar cycloaddition reaction was reported by Wang et al.[7] to synthesize the spirooxindole-containing MDM2 inhibitor, and this compound exhibits significant biological activities.

As one of the most efficient approaches for the synthesis of five-membered heterocycles in a highly regio- and stereoselective manner, 1,3-dipolar cycloaddition reaction has attracted much interest in recent years.[8] In particular, the chemistry of azomethine ylides generated from α-amino acids with isatin serves as an expedient route for the construction of nitrogen-containing five-membered spirooxindoles, which constitute the central skeleton for numerous alkaloids and pharmacologically important compounds.[9] Consequently, various 1,3-dipolar cycloaddition reactions of azomethine ylides with indolone-derived olefins have been widely studied for the construction of the dispirooxindole. Raghunathan et al.[10] reported a 1,3-dipolar addition of 3-aroylmethyleneindol-2-one with azomethine ylides to synthesize 4-aryl-5-phenyl-pyrrolo(spiro-[2.3″]-oxindole)-spiro-[3.2′]6′-arylmethylidene cyclohexanone derivatives exclusively. Generally, it has been found that the dispirooxindole derivatives, pyrrolo(spiro-[2.3′]-oxindole)-spiro-[3.3″]-oxindoles, were selectively formed in this type of 1,3-diploar cycloadditions and the other regioisomers, pyrrolo(spiro-[2.3′]-oxindole)-spiro-[4.3″]-oxindoles, have never been observed.[10,11] Therefore, it is highly desirable to develop an efficient and convenient strategy to synthesize pyrrolo-(spiro-[2.3′]-oxindole)-spiro-[4.3″]-oxindoles to facilitate the investigation of their biological activities. On the other hand, the employment of 3-acetonylideneoxindoles as dipolarophiles in the 1,3-dipolar cycloaddition has scarcely been studied although they have various synthetic potential applications.[12] Yan et al.[13] successfully developed a 1,3-dipolar cycloaddition of 3-phenacylideneoxindole with *N*-phenacylquinoliniumylides. Herein, we disclose the 1,3-dipolar cycloaddition of 3-acetonylideneoxindole with azomethine ylides, which are generated from benzylamine with isatins. More importantly, novel dispirooxindole derivatives, pyrrolo-(spiro-[2.3′]-oxindole)-spiro-[4.3″]-oxindoles, were obtained in good regioselectivities and excellent diastereoselectivities. As far as we know, it is the first time that this unexpected regioselectivity in 1,3-dipolar cycloaddition of azomethine

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Scheme 1. Different Regioselectivities in the 1,3-Dipolar Cycloaddition of Azomethine Ylide

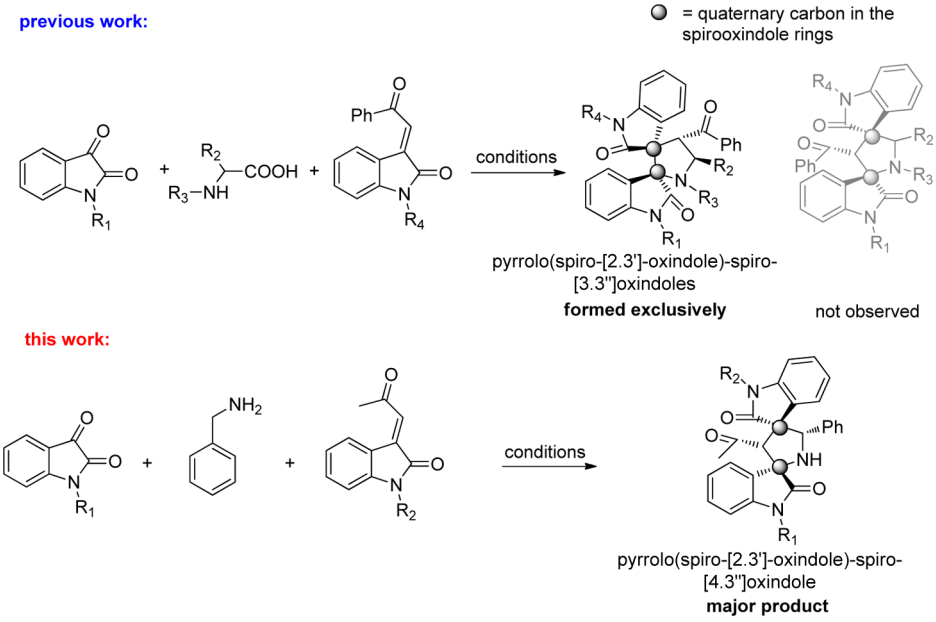
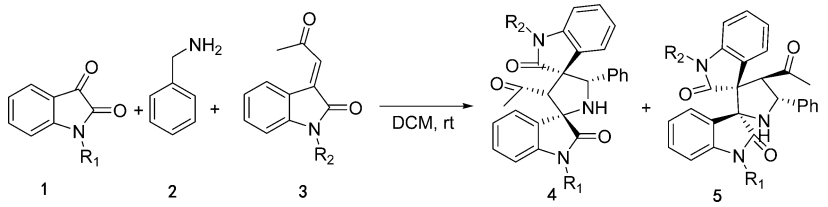


Table 1. 1,3-Dipolar Cycloaddition Reaction of Isatin Derivatives 1 and Benzylamine 2 with 3-Acetonylideneoxindole Derivatives 3[a]



entry	1	3	products	time (h)	yield[b] (%)	regioisomeric ratio[c] (4:5)
1	**1a** R_1 = H	**3a** R_2 = H	**4a+5a**	24	87	61:39
2	**1b** R_1 = H	**3b** R_2 = Bn	**4b+5b**	36	76	60:40[d]
3	**1c** R_1 = Bn	**3c** R_2 = H	**4c+5c**	36	82	76:24
4	**1d** R_1 = Bn	**3d** R_2 = Bn	**4d+5d**	48	88	89:11
5[e]	**1d** R_1 = Bn	**3d** R_2 = Bn	**4d+5d**	60	68	86:14

[a]Unless otherwise noted, the reaction was carried out in 0.2 mmol scale in DCM (2 mL) at rt, and the ratio of **1**/**2**/**3** is 1:1.5:1. [b]Combined yield of isolated **4** and **5**. [c]Unless otherwise noted, the regioisomeric ratio was determined by the isolated yields of **4** and **5**. [d]Determined by ^{1}H NMR. [e]1.0 equiv of benzylamine was used in this reaction.

ylides to construct dispirooxindoles (as shown in Scheme 1) is observed.[14]

Initially, a three-component reaction of isatin derivatives **1**, benzylamine **2** and 3-acetonylideneoxindoles **3** was conducted in dichloromethane at room temperature. This reaction went smoothly to completion, and two dispirooxindole cycloadducts were obtained. Surprisingly, 3-acetyl-5-phenyl-pyrrolo-spiro-[2.3′]-oxindole-spiro-[4.3″]-oxindole **4a** was formed as the major product, and the other regioisomer **5a** was also observed, which is contrary to the commonly observed regioselectivity outcome in this type of 1,3-dipolar cycloaddition reaction. However, the regioselectivity was quite poor (**4a**:**5a** = 61:39, Table 1, entry 1). Unfortunately, either unprotected isatins or unprotected 3-acetonylideneoxindoles afforded the corresponding cyclization products in moderate yields and poor regioselectivities (Table 1, entries 2 and 3). Satisfyingly, the regioselectivity was significantly improved to 89:11 when using the 1-benzyl-isatin and 1-benzyl-3-acetonylideneoxindole (entry 4). Presumably, this might be attributed to the electronic and steric effects induced by the benzyl protecting group. We also investigated the effect of amount of benzylamine on this reaction. When 1.0 equiv of benzylamine was used, the relatively lower yield (68%) and regioisomer ratio (86:14) were obtained respectively (entry 5). Therefore, 1.5 equiv of benzylamine was applied in the following tests.

Encouraged by the above results, we extended the scope of this reaction to various substituted 1-benzyl-isatin derivatives and 1-benzyl-3-acetonylideneoxindole derivatives. As can be seen from Table 2, moderate to high yields (up to 95%, entry 6) and good regioisomeric ratio (up to 91:9, entry 5) were achieved. It seems that the steric effects induced by the substituents were deleterious to the regioselectivities and led to the decreased regioselectivity (entry 7).

The cycloadducts **8a**−**g** and **9a**−**g** were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. For example, signals at δ 5.02, 4.80, 4.65, 4.39 ppm in the ^{1}H NMR spectrum of compound **8e** were assigned to the protons of PhC$\underline{H}_2$−; methyl group on benzene ring resonated at δ 2.12 and δ 1.41

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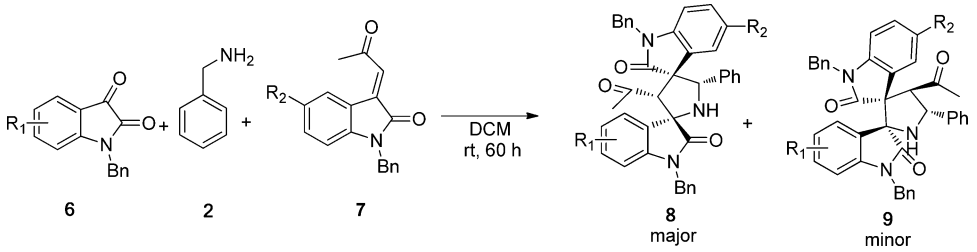
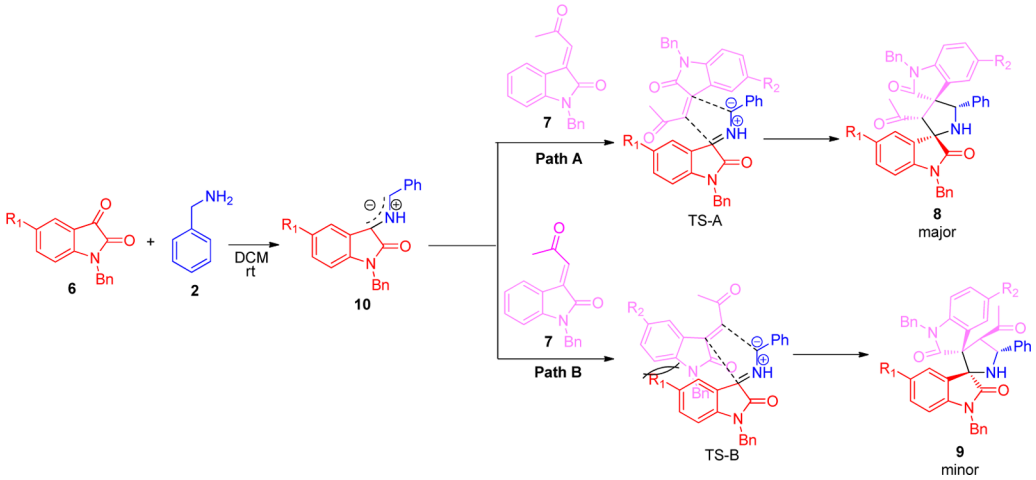
Table 2. 1,3-Dipolar Cycloaddition Reaction of Isatin Derivatives 6 and Benzylamine 2 with 3-Acetonylideneoxindole Derivatives 7[a]



entry	6	7	products	yield[b] (%)	regioisomeric ratio[c] (8:9)
1	**6a** R_1 = 5-Cl	**7a** R_2 = H	**8a+9a**	71	85:15
2	**6b** R_1 = H	**7b** R_2 = Cl	**8b+9b**	76	79:21
3	**6c** R_1 = 5-F	**7c** R_2 = H	**8c+9c**	88	88:12
4	**6d** R_1 = 6-Br	**7d** R_2 = H	**8d+9d**	77	87:13
5	**6e** R_1 = 5-Me	**7e** R_2 = H	**8e+9e**	74	91:9
6	**6f** R_1 = 5-F	**7f** R_2 = Me	**8f+9f**	95	80:20
7	**6g** R_1 = 6-Br	**7g** R_2 = Cl	**8g+9g**	90	74:26

[a]Unless otherwise noted, the reaction was carried out in 0.2 mmol scale in DCM (2 mL) at rt, and the ratio of **6**/**2**/**7** is 1:1.5:1. [b]Combined yield of isolated **8** and **9**. [c]Unless otherwise noted, the regioisomeric ratio was determined by the isolated yields of **8** and **9**.

Scheme 2. Proposed Mechanism for 1,3-Dipolar Cycloaddition of Azomethine Ylides with 3-Acetonylideneoxindole Derivatives

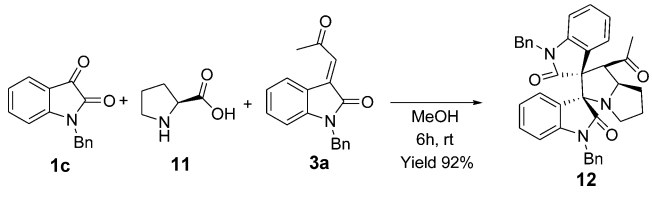


and was assigned to $C\underline{H}_3CO-$. Three carbonyl groups in compound **8e** show peaks at δ 204.26, 178.26, and 176.95 ppm in ^{13}C NMR spectrum, which proves the incorporation of two oxindole moieties in the cycloadduct. Finally, the regio- and stereochemical outcome of this reaction were unambiguously established by single crystal X-ray analysis of cycloadducts **8e** and **9e**.

Although the detailed mechanism of this reaction has not been fully clarified, the formation of regioisomers **8** and **9** could be explained as follows: the condensation of isatin derivatives **6** with benzylamine **2** gives the azomethine ylide (dipole **10**), which subsequently undergoes 1,3-dipolar cycloaddition reaction with the dipolarophile, 3-acetonylideneoxindole **7**, to afford the corresponding cyclization products as shown in Scheme 2. Path **A** leads to the formation of the cycloadduct **8**, while path **B** affords the product **9**. The observed regioselectivity in the product formation might be explained as the severe steric repulsion exists between the two indolone moieties in path **B**. However, this steric effect and dipolar repulsion could be significantly relieved by the approach mode in path **A**. Accordingly, path **A** is more favorable, and the regioisomer **8** was therefore obtained as the major product.

This unusual regioselectivity of 1,3-cycloaddition prompted us to extend this reaction to employ the widely used proline to generate the azomethine ylide. The three-component reaction of 1-benzyl-isatin derivatives **1c**, proline **11** with 1-benzyl-3-acetonylideneoxindole **3a** went smoothly and afforded only one cycloadduct in 92% yield (as shown in Scheme 3). Interestingly, pyrrolo(spiro-[2.3′]-oxindole)-spiro-[3.3″]-oxindole ring system was obtained as a single regioisomer, which was confirmed

Scheme 3. Regioselective Synthesis of Dispirooxindole Derivative Using 1-Benzyl-isatin, L-Proline and 1-Benzyl-3-acetonylideneoxindole



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by single crystal X-ray analysis (see Supporting Information). As a result, it can be concluded that benzylamine played a critical role in the regioselectivity of this 1,3-cycloaddition to construct the pyrrolo(spiro-[2.3′]-oxindole)-spiro-[4.3″]-oxindole ring system.

In conclusion, a three-component 1,3-dipolar cycloaddition reaction has been developed for the synthesis of novel dispirooxindoles, 3-acetyl-5-phenyl-pyrrolo(spiro-[2.3′]-1′-benzyl-oxindole)-spiro-[4.3″]-1″-benzyl-oxindoles, in good regioselectivities and chemical yields for the first time. This protocol could serve as an efficient and regioselective pathway to construct this novel dispirooxindole ring systems, which would facilitate the biological evaluation of these dispirooxindole compounds. The structural assignments of the corresponding cycloadducts were confirmed by NMR spectroscopy, IR, HRMS, and X-ray crystallographic analysis.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all the reagents were purchased from commercial suppliers and used without further purification. ^{1}H NMR spectra were recorded at 400 MHz. The chemical shifts were recorded in ppm relative to tetramethylsilane and with the solvent resonance as the internal standard. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration. ^{13}C NMR data were collected at 100 MHz with complete proton decoupling. Chemical shifts were reported in ppm from the tetramethylsilane with the solvent resonance as internal standard. Infrared spectra (IR) were measured by FT-IR apparatus. High resolution mass spectroscopy (HRMS) was recorded on TOF MS ES+ mass spectrometer, and acetonitrile was used to dissolve the sample. Column chromatography was carried out on silica gel (200−300 mesh).

General Experimental Procedure for 1,3-Dipolar Cycloaddition of Isatin Derivatives, Benzylamine with 3-Acetonylideneoxindole. A mixture of isatin (29.4 mg, 0.2 mmol), benzylamine **2** (32.1 mg, 0.3 mmol, 1.5 equiv), 3-acetonylideneoxindole (37.4 mg, 0.2 mmol) in DCM (2 mL) was stirred at rt for the given time. After completion of the reaction monitored by TLC, the solvent was removed *in vacuo*. The crude mixture was purified via flash silica gel chromatography using petroleum ether/ethyl acetate as the eluent to give the corresponding cycloadducts.

3-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-oxindole)-spiro-[4.3″]-oxindole (4a). White powder (45.6 mg, yield 54%): mp 252−254 °C; IR (KBr) ν 3390, 3253, 2362, 1711, 1620, 1473, 754 cm^{-1}; ^{1}H NMR (DMSO-d_6, TMS, 400 MHz) δ 10.85 (s, 1H), 10.15 (s, 1H), 7.99 (d, J = 7.2 Hz, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.06−7.17 (m, 6H), 6.95 (d, J = 7.2 Hz, 1H), 6.81 (d, J = 7.2 Hz, 2H), 6.65 (d, J = 7.6 Hz, 1H), 4.89 (d, J = 12.0 Hz, 1H), 4.50 (s, 1H), 4.18 (d, J = 11.6 Hz, 1H), 1.34 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 201.9, 181.2, 178.0, 143.1, 143.1, 135.0, 130.4, 129.8, 129.0, 128.6, 128.1, 127.0, 126.6, 122.8, 122.5, 121.7, 110.3, 109.6, 71.8, 67.5, 66.9, 60.7, 28.6; HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{26}H_{21}N_3O_3Na$ 446.1481, found 446.1487.

3-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-oxindole)-spiro-[4.3″]-1″-benzyl-oxindole (4b) and 4-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-oxindole)-spiro-[3.3″]-1″-benzyl-oxindole (5b) (Inseparable Regioisomers). White powder (77.9 mg, yield 76%): ^{1}H NMR (DMSO-d_6, TMS, 400 MHz) δ 10.40 (s, 1.5H), 10.11 (s, 1.0H), 7.99 (d, J = 7.2 Hz, 1.6H), 7.67 (d, J = 7.2 Hz, 2.1H), 7.52 (d, J = 7.6 Hz, 1.2H), 7.46 (d, J = 7.2 Hz, 1.9H), 7.39 (t, J = 7.4 Hz, 3.2H), 7.31 (t, J = 6.0 Hz, 4.1H), 7.01−7.27 (m, 30H), 6.79−6.94 (m, 8H), 6.71 (d, J = 8.0 Hz, 2H), 6.59 (d, J = 7.6 Hz, 6.0H), 5.99 (t, J = 8.0 Hz, 1H), 5.76 (s, 0.9H), 5.64 (d, J = 6.0 Hz, 1.5H), 4.98 (d, J = 16.0 Hz, 1.5H), 4.86 (d, J = 15.6 Hz, 2H), 4.64 (d, J = 16.0 Hz, 1H), 4.44 (d, J = 16.0 Hz, 2H), 4.35 (s, 1H), 1.37 (s, 3H), 1.23 (s, 3H); HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{33}H_{27}N_3O_3Na$ 536.1950, found 536.1943. Compound **4b** and **5b** cannot be separated by column chromatography. And the regioisomeric ratio was determined by ^{1}H NMR spectroscopy of the mixture of **4b** and **5b**.

3-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-1′-benzyl-oxindole)-spiro-[4.3″]-oxindole (4c). White powder (64.6 mg, yield 63%): mp 227−229 °C; IR (KBr) ν 3401, 3060, 2362, 1715, 1613, 1468, 754 cm^{-1}; ^{1}H NMR (DMSO-d_6, TMS, 400 MHz) δ 10.57 (s, 1H), 7.66 (d, J = 7.2 Hz, 2H), 7.62 (d, J = 7.2 Hz, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 6.6 Hz, 2H), 7.21−7.28 (m, 2H), 7.11−7.19 (m, 4H), 6.98 (t, J = 7.2 Hz, 2H), 6.84 (d, J = 7.6 Hz, 1H), 6.71 (d, J = 6.0 Hz, 1H), 6.43 (d, J = 7.6 Hz, 2H), 5.96 (t, J = 8.0 Hz, 1H), 4.86 (d, J = 16.0 Hz, 1H), 4.36 (d, J = 16.4 Hz, 1H), 3.92 (d, J = 7.2 Hz, 1H), 1.45 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 204.4, 179.8, 176.7, 143.6, 143.1, 142.7, 136.0, 129.2, 128.9, 128.8, 128.8, 128.2, 128.0, 127.9, 127.5, 127.2, 126.59, 126.56, 125.49, 122.5, 122.0, 74.9, 67.6, 62.1, 61.2, 42.7, 31.1; HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{33}H_{27}N_3O_3Na$ 536.1950, found 536.1930.

3-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-1′-benzyl-oxindole)-spiro-[4.3″]-1″-benzyl-oxindole (4d). White solid (94.0 mg, yield 78%): mp 208−209 °C; IR (KBr) ν 3414, 3274, 2362, 1710, 1612, 1419, 743 cm^{-1}; ^{1}H NMR (DMSO-d_6, TMS, 400 MHz) δ 8.05 (d, J = 6.8 Hz, 1H), 7.58 (t, J = 9.8 Hz, 3H), 7.06−7.35 (m, 16H), 6.74 (d, J = 7.2 Hz, 2H), 6.62 (d, J = 6.0 Hz, 2H), 5.71(d, J = 4.8 Hz, 1H), 5.10 (d, J = 16.0 Hz, 1H), 4.90 (t, J = 16.0 Hz, 2H), 4.47 (d, J = 13.2 Hz, 2H), 4.22 (d, J = 4.8 Hz, 1H), 1.27 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 203.0, 178.8, 177.8, 144.0, 143.1, 137.4, 137.0, 136.2, 130.0, 129.7, 129.6, 129.3, 128.9, 128.5, 128.3, 127.8, 127.7, 127.64, 127.55, 127.2, 125.7, 124.3, 123.5, 122.6, 109.5, 109.4, 71.4, 67.2, 60.0, 43.5, 43.3, 28.8; HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{40}H_{33}N_3O_3Na$ 626.2420, found 626.2390.

4-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-oxindole)-spiro-[3.3″]-oxindole (5a). White powder (27.9 mg, yield 33%): mp 208−209 °C; IR (KBr) ν 3419, 3245, 2362, 1707, 1619, 1471, 750 cm^{-1}; ^{1}H NMR (DMSO-d_6, TMS, 400 MHz) δ 10.45 (s, 1H), 10.17 (s, 1H), 7.72 (d, J = 7.2 Hz, 3H), 7.31 (t, J = 7.4 Hz, 2H), 7.19−7.26 (m, 2H), 7.01−7.12 (m, 2H), 6.69 (d, J = 7.6 Hz, 1H), 6.65 (d, J = 7.6 Hz, 1H), 6.30−6.47 (m, 1H), 6.31 (d, J = 7.2 Hz, 1H), 5.49 (t, J = 6.8 Hz, 1H), 4.74 (d, J = 9.6 Hz, 1H), 4.28 (d, J = 8.0 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 204.4, 178.2, 174.8, 144.5, 143.3, 142.0, 129.9, 129.5, 128.5, 128.1, 127.3, 126.8, 126.7, 125.7, 125.5, 121.6, 120.5, 110.0, 109.3, 74.1, 64.4, 64.3, 61.2, 29.9; HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{26}H_{21}N_3O_3Na$ 446.1481, found 446.1492.

4-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-1′-benzyl-oxindole)-spiro-[3.3″]-oxindole (5c). White powder (19.5 mg, yield 19%): mp 214−216 °C; IR (KBr) ν 3417, 2924, 1727, 1613, 1468, 751 cm^{-1}; ^{1}H NMR (DMSO-d_6, TMS, 400 MHz) δ 10.54 (s, 1H), 7.76 (d, J = 6.8 Hz, 3H), 7.43 (d, J = 7.2 Hz, 2H), 7.21−7.33 (m, 6H), 7.13 (t, J = 7.4 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 6.70 (d, J = 7.6 Hz, 1H), 6.50−6.59 (m, 2H), 6.39 (d, J = 7.6 Hz, 1H), 5.54 (t, J = 8.6 Hz, 1H), 5.02 (d, J = 15.6 Hz, 1H), 4.85 (d, J = 9.6 Hz, 1H), 4.60 (d, J = 16.0 Hz, 1H), 4.43 (d, J = 8.0 Hz, 1H), 1.25 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 204.2, 176.8, 174.8, 144.4, 143.8, 142.1, 136.8, 130.0, 129.7, 128.9, 128.4, 128.2, 128.0, 127.7, 127.4, 126.9, 126.5, 125.5, 125.1, 121.7, 121.3, 110.1, 109.0, 73.9, 64.5, 64.4, 61.2, 43.4, 29.9; HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{33}H_{27}N_3O_3Na$ 536.1950, found 536.1938.

4-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-1′-benzyl-oxindole)-spiro-[3.3″]-1″-benzyl-oxindole (5d). White solid (12.0 mg, yield 10%): mp 206−207 °C; IR (KBr) ν 3414, 3350, 3051, 1955, 1735, 1607, 1355, 738, 697 cm^{-1}; ^{1}H NMR (DMSO-d_6, TMS, 400 MHz) δ 7.86 (d, J = 7.2 Hz, 1H), 7.79 (d, J = 7.2 Hz, 2H), 7.32−7.37 (m, 4H), 7.21−7.25 (m, 3H), 7.04−7.13 (m, 5H), 6.96 (t, J = 7.6 Hz, 2H), 6.61−6.66 (m, 2H), 6.50−6.53 (m, 3H), 6.35 (d, J = 7.6 Hz, 1H), 5.59 (t, J = 8.8 Hz, 1H), 5.09 (d, J = 16.4 Hz, 1H), 5.00 (d, J = 16.0 Hz, 1H), 4.95 (d, J = 9.6 Hz, 1H), 4.54−4.63 (m, 3H), 1.65 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 204.2, 176.6, 173.1, 144.2, 143.8, 142.7, 136.4, 135.6, 130.2, 129.7, 128.8, 128.7, 128.5, 128.2, 127.8, 127.5, 127.3, 127.2, 127.0, 126.5, 125.9, 125.5, 124.7, 122.5, 121.5, 109.9, 109.3, 74.1, 64.3, 64.0, 61.4, 43.4, 43.0, 30.0; HRMS

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(TOF-ES+) m/z $[M + Na]^+$ calcd for $C_{40}H_{33}N_3O_3Na$ 626.2420, found 626.2401.

3-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-1′-benzyl-5′-chloro-oxindole)-spiro-[4.3″]-1″-benzyl-oxindole (8a). White solid (77.7 mg, yield 61%): mp 224−226 °C; IR (KBr) ν 3425, 3279, 2918, 2361, 1711, 1610, 1488, 1359, 810, 755 cm^{-1}; ^1H NMR(DMSO-d_6, TMS, 400 MHz) δ 8.00 (d, J = 6.8 Hz, 1H), 7.57 (d, J = 7.2 Hz, 2H), 7.53 (d, J = 2.0 Hz, 1H), 7.25−7.37 (m, 2H), 7.12−7.22 (m, 6H), 7.07 (d, J = 7.2 Hz, 2H), 6.73−6.76 (m, 2H), 6.63 (d, J = 6.4 Hz, 2H), 5.66 (d, J = 5.6 Hz, 1H), 5.11 (d, J = 16.0 Hz, 1H), 4.83−4.92 (m, 2H), 4.46−4.53 (m, 2H), 4.38 (d, J = 6.0 Hz, 1H), 1.28 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 203.2, 178.5, 177.6, 143.1, 142.8, 137.2, 136.6, 136.2, 131.6, 129.9, 129.4, 129.0, 128.9, 128.6, 128.3, 127.8, 127.6, 127.2, 126.5, 125.5, 124.8, 123.6, 110.8, 109.6, 71.6, 71.1, 67.2, 59.9, 43.4, 43.3, 28.8; HRMS (TOF-ES+) m/z $[M + Na]^+$ calcd for $C_{40}H_{32}ClN_3O_3Na$ 660.2030, found 660.2015.

3-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-1′-benzyl-oxindole)-spiro-[4.3″]-1″-benzyl-5″-chloro-oxindole (8b). White solid (77.7 mg, yield 61%): mp 268−269 °C; IR (KBr) ν 3425, 3062, 2917, 2368, 1701, 1610, 1357, 819, 755 cm^{-1}; ^1H NMR (DMSO-d_6, TMS, 400 MHz) δ 8.12 (d, J = 7.2 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.49 (d, J = 7.6 Hz, 2H), 7.29−7.38 (m, 5H), 7.22−7.24 (m, 1H), 7.10−7.19 (m, 6H), 7.05 (d, J = 7.6 Hz, 1H), 6.96 (d, J = 8.0 Hz, 2H), 6.64 (d, J = 7.2 Hz, 2H), 6.49 (d, J = 8.4 Hz, 1H), 5.09−5.14 (m, 2H), 5.01 (d, J = 15.6 Hz, 1H), 4.83 (s, 1H), 4.78 (d, J = 16.0 Hz, 1H), 4.53 (d, J = 16.0 Hz, 1H), 4.45 (d, J = 10.4 Hz, 1H), 1.29 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 202.2, 179.6, 175.8, 143.5, 142.5, 136.7, 136.0, 134.4, 130.5, 130.2, 129.3, 129.2, 128.8, 128.6, 128.4, 128.1, 128.0, 127.3, 127.0, 126.9, 126.5, 123.7, 123.3, 110.5, 110.0, 71.8, 70.0, 66.5, 60.8, 43.5, 43.0, 28.5; HRMS (TOF-ES+) m/z $[M + H]^+$ calcd for $C_{40}H_{33}ClN_3O_3$ 638.2210, found 638.2194.

3-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-1′-benzyl-5′-fluoro-oxindole)-spiro-[4.3″]-1″-benzyl-oxindole (8c). White solid (98.1 mg, yield 79%): mp 200−202 °C; IR (KBr) ν 3415, 3275, 2919, 1709, 1612, 1492, 1350, 814, 738 cm^{-1}; ^1H NMR (DMSO-d_6, TMS, 400 MHz) δ 8.03 (d, J = 7.2 Hz, 1H), 7.58 (d, J = 7.2 Hz, 2H), 7.26−7.37 (m, 6H), 7.13−7.25 (m, 7H), 7.06−7.10 (m, 3H), 6.70−6.74 (m, 2H), 6.62 (d, J = 6.4 Hz, 2H), 5.69 (d, J = 5.6 Hz, 1H), 5.10 (d, J = 16.4 Hz, 1H), 4.88 (t, J = 16.0 Hz, 2H), 4.46−4.50 (m, 2H), 4.35 (d, J = 5.6 Hz, 1H), 1.28 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 203.1, 178.7, 177.7, 160.1, 157.5, 143.1, 140.1, 137.3, 136.8, 136.2, 131.5, 131.4, 129.9, 129.4, 128.94, 128.90, 128.5, 128.3, 127.8, 127.7, 127.6, 127.2, 125.6, 123.5, 115.9, 115.7, 112.6, 112.3, 110.2, 110.1, 109.5, 71.4, 71.2, 67.4, 59.9, 43.44, 43.36, 28.8; HRMS (TOF-ES+) m/z $[M + Na]^+$ calcd for $C_{40}H_{32}FN_3O_3Na$ 644.2325, found 644.2311.

3-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-1′-benzyl-6′-bromo-oxindole)-spiro-[4.3″]-1″-benzyl-oxindole (8d). White solid (91.2 mg, yield 67%): mp 207−209 °C; IR (KBr) ν 3419, 3277, 3060, 2921, 1727, 1601, 1373, 816, 755 cm^{-1}; ^1H NMR (DMSO-d_6, TMS, 400 MHz) δ 7.69 (d, J = 7.2 Hz, 2H), 7.52 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 7.2 Hz, 2H), 7.29−7.33 (m, 1H), 7.01−7.17 (m, 10H), 6.88 (t, J = 7.6 Hz, 1H), 6.68−6.75 (m, 4H), 6.61 (d, J = 7.2 Hz, 1H), 5.95−5.98 (m, 1H), 5.02 (d, J = 16.0 Hz, 1H), 4.84 (d, J = 16.0 Hz, 1H), 4.63 (d, J = 16.0 Hz, 1H), 4.39 (d, J = 16.0 Hz, 1H), 4.21 (d, J = 5.6 Hz, 2H), 3.90 (d, J = 9.2 Hz, 1H), 1.37 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 204.1, 177.8, 177.1, 145.2, 142.5, 135.9, 135.4, 129.8, 128.9, 128.82, 128.79, 128.2, 127.8, 127.6, 127.5, 127.1, 127.0, 125.3, 124.8, 123.2, 74.4, 61.5, 61.1, 59.9, 43.4, 42.6, 31.0; HRMS (TOF-ES+) m/z $[M + Na]^+$ calcd for $C_{40}H_{32}BrN_3O_3Na$ 704.1525, found 704.1490.

3-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-1′-benzyl-5′-methyl-oxindole)-spiro-[4.3″]-1″-benzyl-oxindole (8e). White solid (82.6 mg, yield 67%): mp 211−212 °C; IR (KBr) ν 3443, 3058, 2917, 2364, 1722, 1612, 1359, 732 cm^{-1}; ^1H NMR (DMSO-d_6, TMS, 400 MHz) δ 7.85 (d, J = 7.2 Hz, 1H), 7.78 (d, J = 7.6 Hz, 2H), 7.20−7.37 (m, 7H), 7.06−7.13 (m, 4H), 6.94−7.01 (m, 3H), 6.65 (d, J = 7.6 Hz, 1H), 6.52 (d, J = 7.2 Hz, 2H), 6.48 (d, J = 8.0 Hz, 1H), 6.12 (s, 1H), 5.59 (t, J = 8.8 Hz, 1H), 5.08 (d, J = 16.0 Hz, 1H), 4.97 (d, J = 6.0 Hz, 1H), 4.94 (s, 1H), 4.55−4.62 (m, 2H), 4.50 (d, J = 8.0 Hz, 1H), 1.80 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 204.3, 176.5, 173.1, 144.3, 142.8, 141.4, 136.5, 135.6, 130.2, 130.1, 129.5, 128.8, 128.7, 128.5, 128.2, 127.7, 127.5, 127.3, 127.0, 126.5, 126.0, 124.6, 122.3, 109.9, 108.9, 74.3, 64.1, 64.0, 61.4, 43.3, 43.0, 30.1, 20.9; HRMS (TOF-ES+) m/z $[M + Na]^+$ calcd for $C_{41}H_{35}N_3O_3Na$ 640.2576, found 640.2586.

3-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-1′-benzyl-5′-fluoro-oxindole)-spiro-[4.3″]-1″-benzyl-5″-methyl-oxindole (8f). White solid (96.5 mg, yield 76%): mp 290−291 °C; IR (KBr) ν 3421, 3064, 2918, 1718, 1618, 1363, 816, 751 cm^{-1}; ^1H NMR (DMSO-d_6, TMS, 400 MHz) δ 8.10 (d, J = 6.4 Hz, 1H), 7.49 (d, J = 7.2 Hz, 2H), 7.37−7.39 (m, 3H), 7.27−7.31 (m, 2H), 7.10−7.15 (m, 7H), 6.96 (d, J = 7.6 Hz, 3H), 6.62 (d, J = 7.2 Hz, 2H), 6.36 (d, J = 8.0 Hz, 1H), 5.04−5.12 (m, 3H), 4.78 (d, J = 16.4 Hz, 1H), 4.70 (s, 1H), 4.46−4.51 (m, 2H), 2.37 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 204.3, 176.6, 173.0, 144.3, 143.8, 140.3, 136.4, 135.7, 131.5, 130.1, 129.8, 128.8, 128.7, 128.4, 128.2, 127.9, 127.8, 127.2, 124.6, 121.5, 109.5, 109.3, 74.2, 64.3, 64.1, 61.3, 43.4, 43.0, 30.0, 21.4; HRMS (TOF-ES+) m/z $[M + Na]^+$ calcd for $C_{41}H_{34}FN_3O_3Na$ 658.2482, found 658.2455.

3-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-1′-benzyl-6′-bromo-oxindole)-spiro-[4.3″]-1″-benzyl-5″-chloro-oxindole (8g). White solid (95.8 mg, yield 67%): mp 259−261 °C; IR (KBr) ν 3426, 3061, 2920, 1701, 1606, 1349, 820, 735 cm^{-1}; ^1H NMR (DMSO-d_6, TMS, 400 MHz) δ 8.10 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.50 (d, J = 7.2 Hz, 2H), 7.38 (t, J = 7.0 Hz, 3H), 7.29−7.31 (m, 3H), 7.09−7.19 (m, 6H), 6.98 (d, J = 7.6 Hz, 2H), 6.63 (d, J = 7.2 Hz, 2H), 6.48 (d, J = 8.4 Hz, 1H), 5.05−5.15 (m, 3H), 4.75−4.82 (m, 2H), 4.49−4.54 (m, 2H), 1.35 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 202.0, 179.7, 175.7, 145.1, 142.4, 136.4, 136.0, 134.5, 130.0, 129.2, 129.1, 129.0, 128.8, 128.7, 128.4, 128.2, 128.0, 127.3, 127.1, 126.96, 126.87, 126.5, 126.4, 123.33, 123.27, 113.0, 110.5, 71.3, 70.0, 66.1, 60.6, 43.5, 43.0, 28.7; HRMS (TOF-ES+) m/z $[M + Na]^+$ calcd for $C_{40}H_{31}BrClN_3O_3Na$ 738.1135, found 738.1166.

4-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-1′-benzyl-5′-chloro-oxindole)-spiro-[3.3″]-1″-benzyl-oxindole (9a). White solid (12.7 mg, yield 10%): mp 200−201 °C; IR (KBr) ν 3423, 3349, 3279, 3057, 3026, 2920, 2846, 1710, 1609, 1488, 1359, 1175, 806, 747; ^1H NMR (DMSO-d_6, TMS, 400 MHz) δ 7.78−7.85 (m, 3H), 7.07−7.38 (m, 13H), 7.00 (t, J = 7.6 Hz, 2H), 6.73 (d, J = 7.6 Hz, 1H), 6.60 (t, J = 8.8 Hz, 2H), 6.30 (d, J = 2.4 Hz, 1H), 5.57 (t, J = 9.2 Hz, 1H), 5.08 (d, J = 16.0 Hz, 1H), 5.00 (d, J = 16.0 Hz, 1H), 4.92 (d, J = 10.0 Hz, 1H), 4.56−4.64 (m, 3H), 1.67 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 204.1, 176.4, 172.9, 143.9, 142.7, 142.6, 136.1, 135.6, 129.9, 128.79, 128.77, 128.5, 128.3, 127.8, 127.6, 127.4, 127.2, 126.7, 126.6, 125.9, 125.7, 125.6, 122.5, 110.6, 110.1, 74.1, 63.9, 63.8, 61.5, 43.5, 43.1, 30.1; HRMS (TOF-ES+) m/z $[M + H]^+$ calcd for $C_{40}H_{33}ClN_3O_3$ 638.2210, found 638.2198.

4-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-1′-benzyl-oxindole)-spiro-[3.3″]-1″-benzyl-5″-chloro-oxindole (9b). White solid (19.1 mg, yield 15%): mp 205−207 °C; IR (KBr) ν 3354, 3064, 2891, 1951, 1724, 1607, 1355, 756 cm^{-1}; ^1H NMR (DMSO-d_6, TMS, 400 MHz) δ 7.92 (d, J = 2.0 Hz, 1H), 7.81 (d, J = 7.2 Hz, 2H), 7.31−7.38 (m, 5H), 7.26 (t, J = 7.4 Hz, 1H), 7.12−7.18 (m, 4H), 7.07 (t, J = 7.2 Hz, 1H), 6.97 (t, J = 7.6 Hz, 2H), 6.59−6.68 (m,3H), 6.51 (d, J = 7.2 Hz, 2H), 6.43 (d, J = 7.2 Hz, 1H), 5.53 (t, J = 8.8 Hz, 1H), 5.08 (d, J = 16.4 Hz, 1H), 4.70 (d, J = 8.0 Hz, 1H), 4.55−4.64 (m, 2H), 1.69 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 204.3, 176.4, 172.7, 144.0, 143.8, 141.6, 136.4, 135.3, 130.4, 129.5, 128.8, 128.7, 128.5, 128.3, 127.9, 127.8, 127.6, 127.4, 127.1, 126.9, 126.5, 125.3, 124.3, 121.6, 111.2, 109.5, 74.0, 64.3, 64.2, 61.4, 43.4, 43.1, 30.2; HRMS (TOF-ES +) m/z $[M + H]^+$ calcd for $C_{40}H_{33}ClN_3O_3$ 638.2210, found 638.2227.

4-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-1′-benzyl-5′-fluoro-oxindole)-spiro-[3.3″]-1″-benzyl-oxindole (9c). White solid (11.1 mg, yield 9%): mp 204−205 °C; IR (KBr) ν 3431, 2920, 2379, 1730, 1612, 1490, 1360, 807, 738 cm^{-1}; ^1H NMR (DMSO-d_6, TMS, 400 MHz) δ 7.80−7.84 (m, 3H), 7.21−7.38 (m, 8H), 7.13−7.15 (m, 3H), 7.07−7.10 (m, 1H), 6.99−7.01 (m, 3H), 6.72 (d, J = 8.0 Hz, 1H), 6.58−6.62 (m, 3H), 6.08 (dd, J = 9.2, 1.4 Hz, 1H), 5.54−5.58 (m, 1H), 5.09 (d, J = 16.0 Hz, 1H), 5.01 (d, J = 15.6 Hz, 1H), 4.94 (d, J = 9.6 Hz, 1H), 4.55−4.62 (m, 3H), 1.67 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 204.2, 176.6, 172.9, 158.8, 156.4, 144.0, 142.7,

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140.1, 136.3, 135.7, 129.9, 128.78, 128.75, 128.6, 128.4, 127.9, 127.7, 127.5, 127.2, 126.6, 125.6, 122.6, 116.5, 116.2, 113.7, 113.4, 110.1, 74.1, 64.1, 63.9, 61.6, 43.5, 43.1, 30.0; HRMS (TOF-ES+) m/z $[M + Na]^+$ calcd for $C_{40}H_{32}FN_3O_3Na$ 644.2325, found 644.2331.

4-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-1′-benzyl-6′-bromo-oxindole)-spiro-[3.3″]-1″-benzyl-oxindole (9d). White solid (13.6 mg, yield 10%): mp 187−188 °C; IR (KBr) ν 3442, 3060, 2901, 2362, 1732, 1604, 1360, 811, 740 cm^{-1}; ^1H NMR (DMSO-d_6, TMS, 400 MHz) δ 7.78−7.84 (m, 3H), 7.33−7.38 (m, 4H), 7.18−7.26 (m, 3H), 7.13−7.15 (m, 3H), 7.09 (d, J = 7.2 Hz, 1H), 7.01 (t, J = 7.6 Hz, 2H), 6.83 (d, J = 1.6 Hz, 1H), 6.69−7.74 (m, 2H), 6.54 (d, J = 7.6 Hz, 2H), 6.21 (d, J = 8.0 Hz, 1H), 5.57 (t, J = 8.0 Hz, 1H), 5.13 (d, J = 16.4 Hz, 1H), 5.03 (d, J = 16.0 Hz, 1H), 4.90 (d, J = 9.6 Hz, 1H), 4.53−4.65 (m, 3H), 1.66 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 204.2, 176.8, 172.9, 145.4, 144.1, 142.9, 136.3, 135.7, 128.8, 128.6, 128.5, 128.3, 127.8, 127.2, 126.5, 125.5, 124.3, 123.6, 122.8, 112.6, 110.2, 73.6, 64.2, 63.8, 61.8, 43.4, 43.0, 29.9; HRMS (TOF-ES+) m/z $[M + Na]^+$ calcd for $C_{40}H_{32}BrN_3O_3Na$ 704.1525, found 704.1511.

4-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-1′-benzyl-5′-methyl-oxindole)-spiro-[3.3″]-1″-benzyl-oxindole (9e). White solid (8.6 mg, yield 7%): mp 193−194 °C; IR (KBr) ν 3410, 3320, 3060, 2917, 1714, 1605, 1358, 810, 734 cm^{-1}; ^1H NMR (DMSO-d_6, TMS, 400 MHz) δ 7.71 (d, J = 7.2 Hz, 2H), 7.31−7.44 (m, 5H), 6.98−7.21 (m, 9H), 6.65−6.90 (m, 6H), 6.37 (d, J = 7.6 Hz, 1H), 6.03 (t, J = 7.6 Hz, 1H), 5.02 (d, J = 16.0 Hz, 1H), 4.80 (d, J = 16.0 Hz, 1H), 4.65 (d, J = 16.0 Hz, 1H), 4.39 (d, J = 16.0 Hz, 1H), 4.04 (d, J = 6.4 Hz, 1H), 3.90 (d, J = 8.8 Hz, 1H), 2.12 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 204.3, 178.3, 177.0, 143.6, 142.7, 141.3, 136.0, 135.9, 131.7, 130.3, 129.6, 128.9, 128.82, 128.75, 128.2, 127.9, 127.54, 127.47, 127.4, 127.3, 127.1, 127.0, 126.4, 124.9, 122.7, 109.7, 109.0, 75.0, 68.1, 61.8, 61.2, 43.4, 42.7, 31.1, 21.2; HRMS (TOF-ES+) m/z $[M + Na]^+$ calcd for $C_{41}H_{35}N_3O_3Na$ 640.2576, found 640.2570.

4-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-1′-benzyl-5′-fluoro-oxindole)-spiro-[3.3″]-1″-benzyl-5″-methyl-oxindole (9f). White solid (24.1 mg, yield 19%): mp 202−204 °C; IR (KBr) ν 3393, 3064, 2920, 2375, 1708, 1618, 1352, 811, 759 cm^{-1}; ^1H NMR (DMSO-d_6, TMS, 400 MHz) δ 7.79 (d, J = 7.6 Hz, 2H), 7.67 (s, 1H), 7.34−7.38 (m, 4H), 7.24−7.27 (m, 1H), 7.06−7.14 (m, 5H), 6.96−7.02 (m, 3H), 6.57−6.61 (m, 4H), 6.09−6.12 (m, 1H), 5.57 (t, J = 8.8 Hz, 1H), 4.99−5.08 (m, 2H), 4.92 (d, J = 9.6 Hz, 1H), 4.52−4.64 (m, 3H), 2.42 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 204.3, 176.8, 172.8, 144.0, 140.3, 136.2, 135.8, 131.6, 128.8, 128.5, 128.3, 127.9, 127.8, 127.6, 127.1, 126.6, 125.5, 109.8, 74.1, 64.2, 61.5, 43.6, 42.8, 30.1, 21.0; HRMS (TOF-ES+) m/z $[M + Na]^+$ calcd for $C_{41}H_{34}FN_3O_3Na$ 658.2482, found 658.2466.

4-Acetyl-5-phenylpyrrolo(spiro-[2.3′]-1′-benzyl-6′-bromo-oxindole)-spiro-[3.3″]-1″-benzyl-5″-chloro-oxindole (9g). White solid (32.8 mg, yield 23%): mp 221−222 °C; IR (KBr) ν 3409, 3308, 3062, 2954, 2362, 1716, 1606, 1351, 810, 761 cm^{-1}; ^1H NMR (DMSO-d_6, TMS, 400 MHz) δ 7.88 (d, J = 1.6 Hz, 1H), 7.81 (d, J = 7.6 Hz, 2H), 7.27−7.39 (m, 6H), 7.10−7.16 (m, 4H), 7.02 (d, J = 7.6 Hz, 2H), 6.87 (s, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 7.6 Hz, 2H), 6.29 (d, J = 8.0 Hz, 1H), 5.50 (t, J = 9.2 Hz, 1H), 5.12 (d, J = 16.4 Hz, 1H), 5.01 (d, J = 15.6 Hz, 1H), 4.94 (d, J = 9.6 Hz, 1H), 4.73 (d, J = 7.6 Hz, 1H), 4.64 (d, J = 16.0 Hz, 1H), 4.56 (d, J = 16.4 Hz, 1H), 1.70 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 204.1, 176.3, 172.5, 145.4, 143.6, 141.6, 136.0, 135.4, 129.7, 128.8, 128.7, 128.5, 128.4, 127.8, 127.7, 127.5, 127.3, 127.0, 126.9, 126.6, 124.2, 123.8, 123.5, 112.5, 111.4, 73.7, 64.0, 63.9, 61.4, 43.4, 43.1, 30.2; HRMS (TOF-ES+) m/z $[M + Na]^+$ calcd for $C_{40}H_{31}BrClN_3O_3Na$ 738.1135, found 738.1133.

Synthesis of Spiro-[2.3′]-1′-benzyl-oxindole-spiro-[3.3″]-1″-benzyl-oxindole-4-acetyl-pyrro-lizidine (12). A mixture of 1-benzyl-isatin **1c** (47.4 mg, 0.2 mmol), L-proline **11** (23.0 mg, 0.2 mmol) and 1-benzyl-3-acetonylideneoxindole **3a** (54.4 mg, 0.2 mmol) in methanol (2 mL) was stirred at rt for 6 h. Then the solvent was removed *in vacuo*. And the resulting mixture was purified via silica gel column using petroleum ether/ethyl acetate (9:1) as the eluent to give the cycloadduct **12** as a white solid (104.3 mg, yield 92%): mp 222−223 °C; IR (KBr) ν 3426, 3033, 2962, 2362, 1701, 1607, 1380, 754 cm^{-1}; ^1H NMR (DMSO-d_6, TMS, 400 MHz) δ 7.64 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.04−7.18 (m, 7H), 6.97 (t, J = 7.6 Hz, 1H), 6.88 (t, J = 7.6 Hz, 1H), 6.80 (d, J = 7.2 Hz, 1H), 6.65 (t, J = 7.2 Hz, 3H), 6.60 (d, J = 8.0 Hz, 1H), 5.04−5.06 (m, 1H), 4.87 (d, J = 16.0 Hz, 1H), 4.79 (d, J = 16.0 Hz, 1H), 4.59 (d, J = 15.6 Hz, 1H), 4.39 (d, J = 16.0 Hz, 1H), 3.92 (d, J = 10.0 Hz, 1H), 3.33−3.45 (m, 1H), 2.68 (t, J = 6.8 Hz, 1H), 1.81−2.22 (m, 4H), 1.51 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 204.8, 177.1, 174.4, 143.5, 142.9, 136.0, 136.0, 130.2, 129.2, 128.9, 128.7, 128.2, 127.5, 127.4, 127.2, 126.9, 125.8, 124.6, 122.33, 122.30, 109.5, 109.4, 78.0, 66.3, 65.8, 65.2, 47.8, 43.4, 42.7, 30.5, 29.7, 26.3; HRMS (TOF-ES+) m/z $[M + Na]^+$ calcd for $C_{37}H_{33}N_3O_3Na$ 590.2420, found 590.2436.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H NMR and ^{13}C NMR spectra for compounds **4a**, **4b+5b**, **4c**, **4d**, **5a**, **5c**, **5d**, **8a**, **8b**, **8c**, **8d**, **8e**, **8f**, **8g**, **9a**, **9b**, **9c**, **9d**, **9e**, **9f**, **9g**, and **12**, X-ray structure of compound **12**, and CIFs of **8e**, **9e**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*Tel.: +86-731-88830833. E-mail: hyangchem@csu.edu.cn.

*E-mail: xqchen@mail.csu.edu.cn.

Notes

The authors declare no competing financial interest.

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