K^+/Cu^{2+} Co-Chelated Diastereoselective Friedel-Crafts Reaction with Chiral N-sulfinyl Ketimines for the Facile Synthesis of Chiral Bisindoles and Their Cytotoxicity

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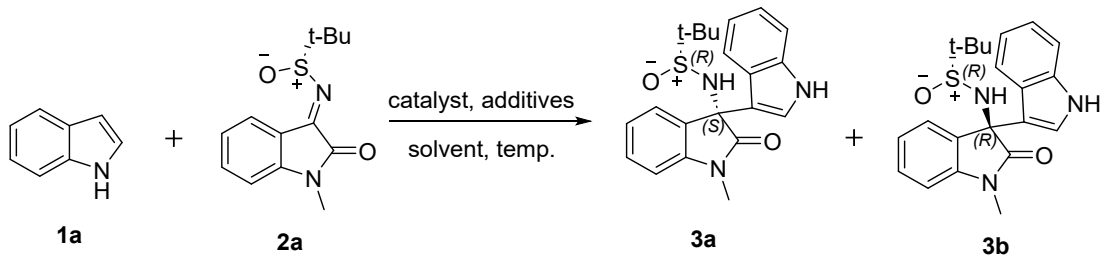
I General Information

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. The used solvents were purified and dried according to common procedures. Other chemicals and solvents were commercially available. High-resolution mass spectrometry (HRMS) analysis was performed on a Waters Xevo G2-XS Q-TOF mass spectrometer coupled to an ACQUITY UPLC system equipped with a BEH C18 column (1.7 μm, 2.1 × 50 mm). ^{1}H NMR spectra were obtained by using a Bruker AV 400 or AV 600. Chemical shifts are reported in parts per million (ppm) relative to either a tetramethylsilane internal standard or solvent signals. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants and integration. ^{13}C NMR spectra were recorded using a Bruker AV 400 spectrometer (100 MHz) using $CDCl_3$ or DMSO-d6 as the solvent. Chemical shifts (δ) are reported in parts per million measured relative to the solvent peak. Melting points (m.p.) were obtained on a Mel-Temp capillary melting point apparatus. Enantiomeric excess (*ee*) was determined using Essentia LC-16. IR spectra were recorded with a Bio-Rad FTS 6000 Fourier infrared spectrometer.

II Screening of the solvents.

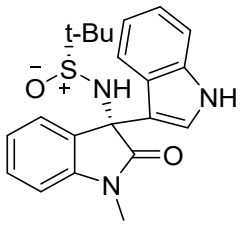
Table S1 Screening of the solvents.



Entries	Catalysts (10 mol %)	Additives (mol %)	Solvent	Temp.	Yield of **3a**[a] (%)	*dr* [b] (**3a**:**3b**)
1	$CuCl_2$	*t*-BuOK (100)	MeOH	r.t.	36	5:1

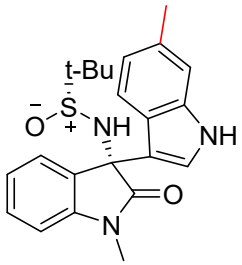
2	$CuCl_2$	*t*-BuOK (100)	DCM	r.t.	52	>25:1
3	$CuCl_2$	*t*-BuOK (100)	MeCN	r.t.	63	>25:1
4	$CuCl_2$	*t*-BuOK (100)	PhMe	r.t.	79	>25:1

III Characterization of bisindole compounds 3a-30



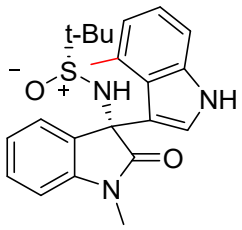
3a

(*R*)-*N*-((*S*)-3-(1H-indol-3-yl)-1-methyl-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**3a**). Under the protective of argon, *N*- (*tert*-butylsulfinyl) imide (100 mg, 0.38 mmol) was dissolved in toluene solution (1.9 mL) at -20 °C temperaterture, and then added *t*-BuOK (42.6 mg, 0.38 mmol) ,added $CuCl_2$ after the reaction ten minuters (5.1 mg, 0.038 mmol) , after five minuters indole (89 mg, 0.76 mmol) were added at -20 °C, until the TLC monitoring reaction was completed, slowly added Na_2CO_3 dropwise to quench and extracted with ethyl acetate (3×50 mL), and the organic phases were combined, anhydrous sodium sulfate was added for drying, concentrated and purified to obtain the target compound **3a** as a yellow solid (133 mg, 92% yield): $[\alpha]_D^{20}$= - 112.6 (c 0.2, DCM). m.p. 96.0 - 97.6 ℃. IR (KBr) Vmax: 3277, 3011, 1717, 1614, 1470, 1375, 1246, 1063, 754 cm^{-1}. ^1H NMR (400 MHz, Chloroform-d) δ 8.55 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.4 Hz, 1H), 7.42 (td, J = 7.8, 1.3 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.22–7.14 (m, 2H), 7.13–7.07 (m, 1H), 7.04 (d, J = 2.7 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 4.37 (s, 1H), 3.26 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 143.3, 137.2, 129.8, 129.6, 126.7, 124.9, 124.8, 122.9, 122.6, 121.2, 120.2, 114.3, 111.6, 108.5, 64.9, 56.8, 26.6, 22.5. HRMS (ESI) calculated for: $C_{21}H_{24}N_3O_2S^+[M+H]^+$: 382.1584, found: 382.1582.



4

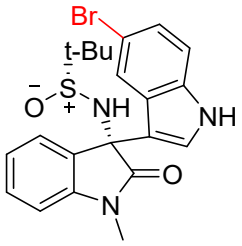
(R)-2-methyl-N-((S)-1-methyl-3-(6-methyl-1H-indol-3-yl)-2-oxoindolin-3-yl)propane-2-sulfinamide (**4**). The titled compound **4** was obtained following the procedure described for **3a** as a brown solid (134 mg, 90%): $[\alpha]_D^{20}$= - 91.3 (c 0.3, DCM). m.p. 150.3 - 152.9 °C. IR (KBr) Vmax: 1717, 1472, 1373, 1339, 1053, 922, 800, 752 cm^{-1}. ^1H NMR (400 MHz, Chloroform-d) δ 8.56 (s, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.33 (td, J = 7.7, 1.1 Hz, 1H), 7.11 (s, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.95 (dd, J = 8.4, 1.5 Hz, 1H), 6.92–6.86 (m, 2H), 4.59 (s, 1H), 3.27 (s, 3H), 2.41 (s, 3H), 1.25 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 143.4, 137.6, 132.3, 129.7, 128.7, 126.5, 123.5, 122.9, 121.8, 120.7, 113.3, 111.7, 108.8, 64.3, 56.1, 26.8, 22.9, 21.6. HRMS (ESI) calculated for:$C_{22}H_{26}N_3O_2S^+$ $[M+H]^+$: 396.1740, found: 396.1743.



5

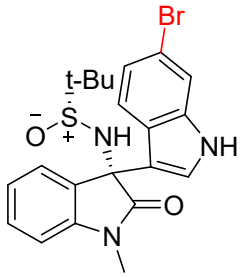
(R)-2-methyl-N-((S)-1-methyl-3-(4-methyl-1H-indol-3-yl)-2-oxoindolin-3-yl)propane-2-sulfinamide (**5**). The titled compound **5** was obtained following the procedure described for **3a** as a white solid (122 mg, 81% yield): $[\alpha]_D^{20}$= - 54.14 (c 0.2, DCM). m.p. 137.8 - 139.5 °C. IR (KBr) Vmax: 2929, 1717, 1614, 1472, 1369, 1339, 1051, 922, 752, 694 cm^{-1}. ^1H NMR (400 MHz, Chloroform-d) δ 8.64 (s, 1H), 7.54 (d, J = 2.7 Hz, 1H), 7.39 (td, J = 7.7, 1.5 Hz, 1H), 7.12 (d, J = 8.1 Hz, 1H), 7.08 (dd, J = 7.4, 1.4 Hz, 1H), 7.03 (dd, J = 7.5, 0.9 Hz, 1H), 7.01–6.97 (m, 1H), 6.96–6.92 (m, 1H),

6.72 (d, J = 7.1 Hz, 1H), 4.66 (s, 1H), 3.30 (s, 3H), 2.11 (s, 3H), 1.24 (s, 9H). ^{13}C NMR (100MHz, $CDCl_3$) δ 178.5, 144.5, 138.3, 130.5, 130.1, 129.4, 126.7, 125.2, 123.9, 123.1, 122.4, 122.2, 114.5, 109.5, 109.1, 64.2, 56.6, 26.9, 23.0, 20.6. HRMS (ESI) calculated for: $C_{22}H_{26}N_3O_2S^+[M+H]^+$: 396.1740, found: 396.1743.



6

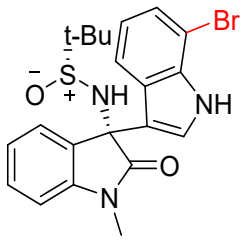
(R)-N-((S)-3-(5-bromo-1H-indol-3-yl)-1-methyl-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**6**). The titled compound **6** was obtained following the procedure described for **3a** as a yellow solid (118 mg, 68% yield): $[\alpha]_D^{20}$= - 60.5 (c 0.3, DCM). m.p. 102.1 - 104.4 °C. IR (KBr) Vmax: 2934, 1719, 1612, 1472, 1369, 1099, 1051, 885, 800, 752, 694 cm^{-1}. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.13 (s, 1H), 8.05 (d, J = 1.8 Hz, 1H), 7.62 (dd, J = 7.5, 1.2 Hz, 1H), 7.35 (td, J = 7.8, 1.2 Hz, 1H), 7.23 (dd, J = 8.7, 1.9 Hz, 1H), 7.17 (d, J = 8.7 Hz, 1H), 7.11–7.05 (m, 1H), 6.92–6.85 (m, 2H), 4.51 (s, 1H), 3.24 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 143.1, 135.8, 130.0, 128.6, 126.8, 126.4, 125.6, 125.3, 124.0, 123.2, 113.3, 113.3, 112.7, 109.0, 64.3, 56.4, 26.8, 22.9. HRMS (ESI) calculated for: $C_{21}H_{23}BrN_3O_2S^+[M+H]^+$: 460.0689, found: 460.0688.



7

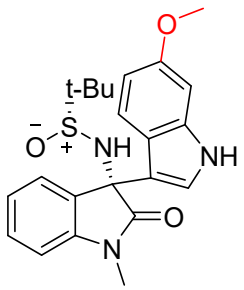
(R)-N-((S)-3-(6-bromo-1H-indol-3-yl)-1-methyl-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**7**). The titled compound **7** was obtained following the procedure described for **3a** as a yellow solid (112 mg, 64% yield): $[\alpha]_D^{20}$= - 49.76 (c

0.2, DCM). m.p. 120.9 - 122.2 °C. IR (KBr) Vmax: 1715, 1611, 1470, 1368, 1051, 897, 750, 692, 586 cm^{-1}. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.06 (s, 1H), 7.74 (d, J = 8.6 Hz, 1H), 7.60 (dd, J = 7.5, 1.2 Hz, 1H), 7.46 (d, J = 1.7 Hz, 1H), 7.35 (td, J = 7.7, 1.3 Hz, 1H), 7.20 (dd, J = 8.6, 1.8 Hz, 1H), 7.07 (td, J = 7.6, 1.0 Hz, 1H), 6.93–6.87 (m, 2H), 4.53 (s, 1H), 3.25 (s, 3H), 1.25 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 143.2, 138.0, 130.0, 128.5, 126.4, 125.1, 124.0, 123.3, 123.1, 122.5, 116.0, 114.8, 113.2, 109.0, 64.3, 56.2, 26.8, 22.9. HRMS (ESI) calculated for: $C_{21}H_{23}BrN_3O_2S^+[M+H]^+$: 460.0689, found: 460.0687.



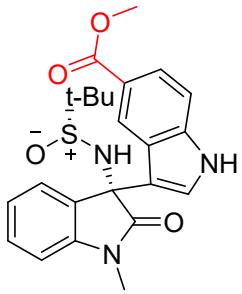
8

(R)-N-((S)-3-(7-bromo-1H-indol-3-yl)-1-methyl-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**8**). The titled compound **8** was obtained following the procedure described for **3a** as a brown solid (107 mg, 61% yield): $[\alpha]_D^{20}$= - 42.7 (c 0.4, DCM). m.p. 150.1 - 151.6 °C. IR (KBr) Vmax: 3165, 2959, 1728, 1612, 1493, 1470, 1368, 1341, 1308, 1260, 1204, 1096, 1051, 945, 818, 770, 750, 725, 696, 604, 527 cm^{-1}. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.58 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.60 (dd, J = 7.5, 1.2 Hz, 1H), 7.39–7.31 (m, 2H), 7.12–7.05 (m, 2H), 7.00 (t, J = 7.8 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 4.59 (s, 1H), 3.29 (s, 3H), 1.25 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 143.4, 135.7, 130.0, 128.3, 126.6, 126.3, 125.0, 124.8, 123.0, 121.3, 120.6, 115.0, 108.9, 105.1, 64.2, 56.2, 26.9, 22.9. HRMS (ESI) calculated for: $C_{21}H_{23}BrN_3O_2S^+[M+H]^+$: 460.0689, found: 460.0686.



9

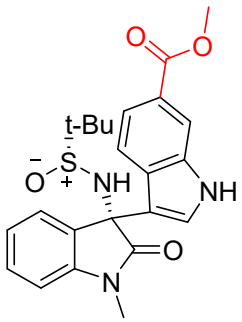
(R)-N-((S)-3-(6-methoxy-1H-indol-3-yl)-1-methyl-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**9**). The titled compound **9** was obtained following the procedure described for **3a** as a brown solid (129 mg, 82% yield): $[\alpha]_D^{20}$= -60.9 (c 0.3, DCM). m.p. 128.4 - 130.4 °C. IR (KBr) Vmax: 3389, 3283, 2931, 1721, 1614, 1539, 1493, 1470, 1369, 1304, 1260, 1202, 1200, 1165, 1022, 910, 814, 756, 696 cm^{-1}. ^1H NMR (400 MHz, Chloroform-d) δ 8.69 (s, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.60 (dd, J = 7.5, 1.2 Hz, 1H), 7.33 (td, J = 7.8, 1.3 Hz, 1H), 7.06 (td, J = 7.6, 1.0 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 6.82 (d, J = 2.6 Hz, 1H), 6.80–6.74 (m, 2H), 4.59 (s, 1H), 3.77 (s, 3H), 3.25 (s, 3H), 1.25 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 156.6, 143.3, 138.1, 129.7, 128.8, 126.4, 123.2, 122.9, 121.7, 119.3, 113.2, 110.1, 108.8, 95.0, 64.4, 56.2, 55.6, 26.8, 22.9. HRMS (ESI) calculated for: $C_{22}H_{26}N_3O_3S^+[M+H]^+$: 412.1689, found: 412.1689.



10

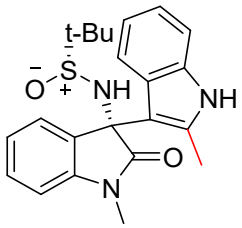
Methyl 3-((S)-3-(((R)-tert-butylsulfinyl)amino)-1-methyl-2-oxoindolin-3-yl)-1H-indole-5-carboxylate (**10**). The titled compound **10** was obtained following the procedure described for **3a** as a yellow solid (120 mg, 72% yield): $[\alpha]_D^{20}$= - 79.83 (c 0.2, DCM). m.p. 112.6 - 113.5 °C. IR (KBr) Vmax: 2955, 1709, 1612, 1472, 1437, 1312, 1258, 1113, 748 cm^{-1}. ^1H NMR (400 MHz, Chloroform-d) δ 9.29–9.18 (m, 1H), 8.71 (d, J = 1.5 Hz, 1H), 7.86 (dd, J = 8.7, 1.6 Hz, 1H),

7.62 (dd, J = 7.5, 1.2 Hz, 1H), 7.37–7.31 (m, 2H), 7.06 (td, J = 7.6, 1.0 Hz, 1H), 6.98 (d, J = 2.6 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 4.64 (s, 1H), 3.90 (s, 3H), 3.27 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 168.1, 143.2, 139.8, 129.9, 128.5, 126.4, 125.4, 124.8, 124.4, 123.7, 123.2, 122.0, 114.7 , 111.6, 109.0, 64.3, 56.4, 51.9, 26.8, 22.9. HRMS (ESI) calculated for: $C_{23}H_{26}N_3O_4S^+[M+H]^+$: 440.1639, found: 440.1642.



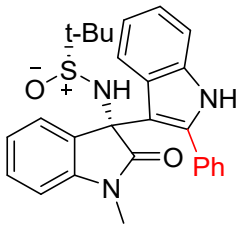
11

Methyl 3-((S)-3-(((R)-tert-butylsulfinyl)amino)-1-methyl-2-oxoindolin-3-yl)-1H-indole-6-carboxylate (**11**) The titled compound **11** was obtained following the procedure described for **3a** as a brown solid (117 mg, 70% yield): $[\alpha]_D^{20}$= - 72.0 (c 0.2, DCM). m.p. 119.9 - 122.8 °C. IR (KBr) Vmax: 2951, 1699, 1616, 1474, 1356, 1283, 1229, 1053, 918, 750 cm^{-1}. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.34 (s, 1H), 8.05 (d, J = 1.5 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.77 (dd, J = 8.5, 1.5 Hz, 1H), 7.62 (dd, J = 7.5, 1.2 Hz, 1H), 7.34 (td, J = 7.7, 1.3 Hz, 1H), 7.11 (d, J = 2.8 Hz, 1H), 7.07 (td, J = 7.6, 1.0 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 4.59 (s, 1H), 3.90 (s, 3H), 3.27 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 168.0, 143.3, 136.6, 130.0, 128.7, 128.6, 127.7, 126.4, 124.1, 123.1, 120.9, 120.8, 114.3, 113.5, 109.0, 64.3, 56.3, 52.0, 26.9, 22.9. HRMS (ESI) calculated for: $C_{23}H_{26}N_3O_4S^+[M+H]^+$: 440.1639, found: 440.1637.



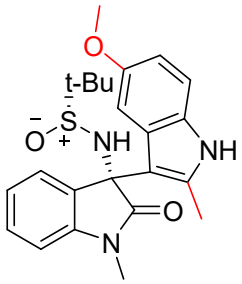
12

(R)-2-methyl-N-((R)-1-methyl-3-(2-methyl-1H-indol-3-yl)-2-oxoindolin-3-yl)propane-2-sulfinamide (**12**). The titled compound **12** was obtained following the procedure described for 3a as a yellow solid (125 mg, 83% yield): $[\alpha]_D^{20}$= - 225.63 (c 0.5, DCM). m.p. 132.8 - 135.6 ℃. IR (KBr) Vmax: 2934, 2367, 1717, 1611, 1472, 1373, 908, 748, 694 cm^{-1}. ^1H NMR (400 MHz, Chloroform-d) δ 8.48 (d, J = 3.5 Hz, 1H), 7.77–7.71 (m, 1H), 7.43 (dd, J = 7.4, 1.2 Hz, 1H), 7.32 (td, J = 7.7, 1.2 Hz, 1H), 7.21–7.18 (m, 1H), 7.07 (dd, J = 7.1, 1.3 Hz, 1H), 7.05–6.96 (m, 2H), 6.91 (d, J = 7.9 Hz, 1H), 4.85 (s, 1H), 3.31 (s, 3H), 2.20 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 143.4, 135.1, 132.1, 129.8, 128.8, 127.1, 126.2, 123.0, 121.2, 120.1, 119.5, 110.8, 109.0, 108.6, 64.7, 56.2, 26.9, 23.0, 13.8. HRMS (ESI) calculated for: $C_{22}H_{26}N_3O_2S^+[M+H]^+$: 396.1740, found: 396.1738.



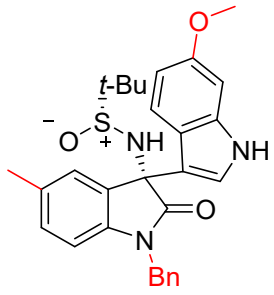
13

(R)-2-methyl-N-((R)-1-methyl-2-oxo-3-(2-phenyl-1H-indol-3-yl)indolin-3-yl)propane-2-sulfinamide (**13**). The titled compound **13** was obtained following the procedure described for **3a** as a white solid (146 mg, 84% yield): $[\alpha]_D^{20}$= - 73.00 (c 0.4, DCM). m.p. 156.6 - 158.8 ℃. IR (KBr) Vmax: 3281, 3049, 1724, 1611, 1491, 1472, 1466, 1367, 1051, 926, 849, 748, 704 cm^{-1}. ^1H NMR (400 MHz, Chloroform-d) δ 8.44 (d, J = 5.6 Hz, 1H), 7.44–7.26 (m, 9H), 7.13 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.05–6.96 (m, 2H), 6.91 (d, J = 7.8 Hz, 1H), 4.74 (s, 1H), 2.99 (s, 3H), 0.97 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 144.2, 136.3, 135.5, 133.7, 130.2, 130.0, 128.7, 128.6, 128.2, 126.9, 126.7, 122.8, 122.2, 120.7, 119.9, 111.2, 110.2, 108.8, 64.4, 55.8, 26.5, 22.6. HRMS (ESI) calculated for: $C_{27}H_{28}N_3O_2S^+[M+H]^+$: 458.1897, found: 458.1901.



14

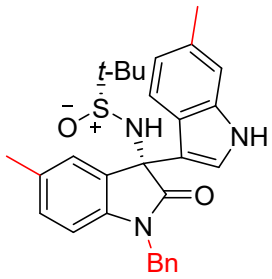
(R)-N-((R)-3-(5-methoxy-2-methyl-1H-indol-3-yl)-1-methyl-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**14**). The titled compound **14** was obtained following the procedure described for **3a** as a brown solid (119 mg, 74% yield): $[\alpha]_D^{20}$= - 210.98 (c 0.3, DCM). m.p. 118.3 - 120.1 ℃. IR (KBr) Vmax: 1717, 1490, 1368, 1217, 932, 752 cm^{-1}. ^1H NMR (400 MHz, Chloroform-d) δ 8.23 (s, 1H), 7.47 (dd, J = 7.5, 1.2 Hz, 1H), 7.33 (td, J = 7.7, 1.2 Hz, 1H), 7.23 (d, J = 2.5 Hz, 1H), 7.08 (d, J = 8.7 Hz, 1H), 7.00 (td, J = 7.6, 1.0 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 6.73 (dd, J = 8.7, 2.4 Hz, 1H), 4.84 (s, 1H), 3.78 (s, 3H), 3.31 (s, 3H), 2.19 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.45, 153.74, 143.39, 132.72, 130.19, 129.86, 128.84, 127.60, 126.12, 123.02, 111.24, 111.03, 108.91, 108.41, 102.79, 64.65, 56.12, 55.83, 26.88, 22.99, 13.92. HRMS (ESI) calculated for: $C_{23}H_{28}N_3O_3S^+[M+H]^+$: 426.1846, found: 426.1847.



15

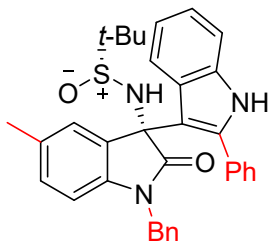
(R)-N-((S)-1-benzyl-3-(6-methoxy-1H-indol-3-yl)-5-methyl-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**15**). The titled compound **15** was obtained following the procedure described for **3a** as a brown solid (120 mg, 85% yield): $[\alpha]_D^{20}$= - 108.6 (c 0.1, DCM). m.p. 159.3 - 161.1 ℃. IR (KBr) Vmax: 2955, 2338, 1721, 1497, 1458, 1196, 1165, 1057, 810, 694 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.35 (s, 1H), 7.25 (d, *J* = 9.6 Hz, 4H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 2.3 Hz, 1H), 6.76 (d, *J* = 2.2 Hz, 1H), 6.72 – 6.67 (m, 2H), 4.97 (d, *J* = 15.8 Hz,

1H), 4.84 (d, J = 15.8 Hz, 1H), 4.41 (d, J = 1.8 Hz, 1H), 3.75 (d, J = 1.7 Hz, 3H), 2.26 (s, 3H), 1.25 – 1.22 (m, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.7, 156.7, 140.2, 138.2, 135.7, 132.6, 130.2, 129.6, 128.8, 127.7, 127.6, 127.4, 123.9, 121.8, 119.2, 114.3, 110.2, 109.4, 95.0, 65.1, 56.9, 55.6, 44.1, 22.6, 21.2. HRMS (ESI) calculated for: $C_{29}H_{32}N_3O_3S^+[M+H]^+$:502.2159, found: 502.2162.



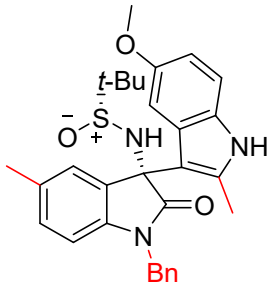
16

(R)-N-((S)-1-benzyl-5-methyl-3-(6-methyl-1H-indol-3-yl)-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**16**). The titled compound **16** was obtained following the procedure described for **3a** as a yellow solid (110 mg, 81% yield): $[\alpha]_D^{20}$= - 110.0 (c 0.1, DCM). m.p. 147.2 - 149.9 °C. IR (KBr) Vmax: 2916, 1721, 1497, 1458, 1358, 1188, 1049, 802, 748, 694 cm^{-1}. ^{1}H NMR (600 MHz, DMSO) δ 10.92 (d, J = 2.6 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.29 – 7.23 (m, 6H), 7.14 (s, 1H), 7.09 (d, J = 8.0 Hz, 1H), 6.88 (t, J = 2.2 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 6.26 (s, 1H), 4.94 (d, J = 15.9 Hz, 1H), 4.82 (d, J = 15.9 Hz, 1H), 2.34 (s, 3H), 2.25 (s, 3H), 1.17 (s, 9H). ^{13}C NMR (150 MHz, DMSO) δ 174.9, 139.6, 137.4, 136.3, 131.2, 131.1, 130.4, 129.3, 128.4, 127.3, 127.2, 126.7, 124.2, 122.8, 120.8, 120.4, 113.3, 111.4, 109.0, 79.2, 64.8, 56.1, 42.7, 22.6, 21.3, 20.8. HRMS (ESI) calculated for: $C_{29}H_{32}N_3O_2S^+[M+H]^+$: 486.2210, found: 486.2213.



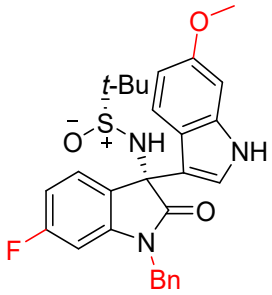
17

(R)-N-((R)-1-benzyl-5-methyl-2-oxo-3-(2-phenyl-1H-indol-3-yl)indolin-3-yl)-2-methylpropane-2-sulfinamide (**17**). The titled compound **17** was obtained following the procedure described for **3a** as a gold solid (103 mg, 77% yield): $[\alpha]_D^{20}$= - 44.0 (c 0.1, DCM). m.p. 150.6 - 152.4 °C. IR (KBr) Vmax: 3287, 2924, 2369, 1721, 1613, 1497, 1451, 1358, 1180, 1049, 818, 733, 702 cm^{-1}. ^1H NMR (400 MHz, Chloroform-d) δ 8.31 (s, 1H), 7.73–7.66 (m, 2H), 7.41–7.34 (m, 5H), 7.30–7.19 (m, 5H), 7.10 (ddd, J = 8.1, 7.0, 1.0 Hz, 1H), 7.07–7.02 (m, 2H), 6.86–6.80 (m, 1H), 6.66 (dd, J = 11.9, 8.3 Hz, 2H), 4.88 (d, J = 15.8 Hz, 1H), 4.70 (d, J = 15.7 Hz, 1H), 2.18 (s, 3H), 0.87 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 141.5, 136.8, 135.8, 135.4, 134.5, 132.4, 130.5, 130.3, 129.5, 128.9, 128.7, 128.6, 127.9, 127.6, 127.4, 126.2, 122.2, 120.6, 119.9, 110.9, 110.4, 109.7, 64.8, 55.8, 44.7, 22.5, 21.1. HRMS (ESI) calculated for: $C_{34}H_{34}N_3O_2S^+[M+H]^+$: 548.2366, found: 548.2367.



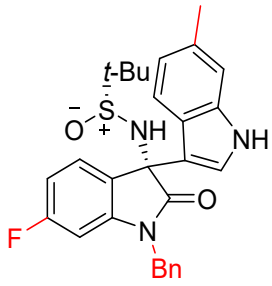
18

(R)-N-((R)-1-benzyl-3-(5-methoxy-2-methyl-1H-indol-3-yl)-5-methyl-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**18**). The titled compound **18** was obtained following the procedure described for **3a** as a gold solid (137 mg, 95% yield): $[\alpha]_D^{20}$= - 252.95 (c 0.5, DCM). m.p. 123.9 - 126.8 °C. IR (KBr) Vmax: 2901, 1721, 1620, 1489, 1454, 1339, 1217, 1031, 806, 702 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 7.52–7.47 (m, 2H), 7.33–7.24 (m, 4H), 7.11 (d, J = 8.7 Hz, 1H), 7.03 (dd, J = 8.0, 1.8 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 2.4 Hz, 1H), 6.61 (dd, J = 8.7, 2.4 Hz, 1H), 5.98 (s, 1H), 5.10 (d, J = 15.8 Hz, 1H), 4.80 (d, J = 15.8 Hz, 1H), 3.57 (s, 3H), 2.31 (s, 3H), 2.19 (s, 3H), 1.21 (s, 9H). ^{13}C NMR (100 MHz, DMSO) δ 176.7, 153.2, 140.4, 136.6, 134.7, 131.8, 130.9, 130.3, 129.8, 128.9, 128.0, 127.7, 127.3, 127.1, 111.5, 110.4, 109.8, 108.0, 102.5, 79.7, 65.3, 56.3, 55.5, 43.8, 23.3, 21.2, 14.7. HRMS (ESI) calculated for: $C_{30}H_{34}N_3O_3S^+[M+H]^+$: 516.2315, found: 516.2315.



19

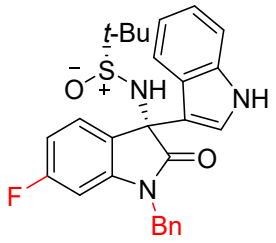
(R)-N-((S)-1-benzyl-6-fluoro-3-(6-methoxy-1H-indol-3-yl)-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**19**). The titled compound **19** was obtained following the procedure described for **3a** as a brown solid (112 mg, 79% yield): $[\alpha]_D^{20}$= - 96.0 (c 0.1, DCM). m.p. 127.1 - 129.1 °C. IR (KBr) Vmax: 3240, 2916, 1728, 1613, 1497, 1451, 1373, 1343, 1242, 1157, 1049, 934, 841, 802, 694 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.10 (d, J = 2.7 Hz, 1H), 6.77 (dd, J = 8.3, 5.7 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H), 6.51–6.47 (m, 2H), 6.46–6.38 (m, 4H), 6.29 (d, J = 3.9 Hz, 1H), 6.02–5.95 (m, 3H), 5.90 (dt, J = 8.4, 2.1 Hz, 1H), 4.09–3.97 (m, 2H), 1.49 (s, 3H), 0.30 (s, 9H). ^{13}C NMR (100 MHz, DMSO) δ 176.7, 141.1, 137.3, 136.3, 135.9, 134.6, 132.4, 130.6, 130.2, 129.2, 129.1, 128.9, 128.8, 127.9, 127.6, 126.0, 109.9, 109.4, 64.9, 56.0, 43.8, 22.5, 21.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.1. HRMS (ESI) calculated for: $C_{28}H_{29}FN_3O_3S^+[M+H]^+$: 506.1908, found: 506.1902.



20

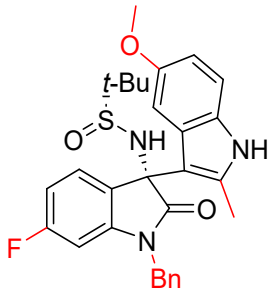
(R)-N-((S)-1-benzyl-6-fluoro-3-(6-methyl-1H-indol-3-yl)-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**20**). The titled compound **20** was obtained following the procedure described for **3a** as a brown solid (116 mg, 84% yield): $[\alpha]_D^{20}$= - 113.0 (c 0.1, DCM). m.p. 123.9 - 124.5 °C. IR (KBr) Vmax: 3256, 2955, 2916, 2862, 1712, 1613, 1497, 1458, 1373, 1351, 1250, 1165, 1057, 934, 841, 802, 733, 694, 594 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.94 (d, J = 2.6 Hz, 1H), 7.59 (dd, J = 8.2, 5.7 Hz,

1H), 7.54 (d, J = 8.2 Hz, 1H), 7.35–7.18 (m, 6H), 7.10 (s, 1H), 6.82 (qd, J = 10.2, 2.3 Hz, 3H), 6.71 (dd, J = 8.3, 1.5 Hz, 1H), 4.90–4.78 (m, 2H), 2.31 (s, 3H), 1.12 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.01, 166.61, 149.14, 149.02, 142.82, 141.13, 135.79, 133.72, 132.65, 132.51, 131.45, 130.21, 127.94, 126.64, 125.66, 116.72 (d, J = 5.0 Hz), 113.42, 113.21, 103.01, 102.74, 69.40, 60.77, 48.25, 28.26, 27.83, 26.4. ^{19}F NMR (564 MHz, $CDCl_3$) δ -109.6. HRMS (ESI) calculated for: $C_{28}H_{29}FN_3O_2S^+[M+H]^+$: 490.1959, found: 490.1960.



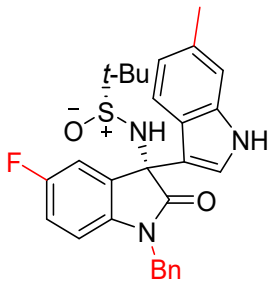
21

(R)-N-((S)-1-benzyl-6-fluoro-3-(1H-indol-3-yl)-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**21**). The titled compound **21** was obtained following the procedure described for **3a** as a brown solid (104 mg, 78% yield): $[\alpha]_D^{20}$= - 129.0 (c 0.1, DCM). m.p. 121.2 - 123.7 ℃. IR (KBr) Vmax: 3256, 2963, 1721, 1613, 1497, 1458, 1373, 1250, 1157, 1057, 941, 841, 741, 702 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.45 (dd, *J* = 8.4, 5.3 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 2H), 7.23 – 7.20 (m, 2H), 7.19 – 7.15 (m, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 2.6 Hz, 1H), 5.00 (d, *J* = 15.8 Hz, 1H), 4.74 – 4.69 (m, 1H), 4.60 (s, 1H), 1.19 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.2, 164.6, 163.0, 137.3, 135.2, 129.0, 128.0, 127.9, 127.6, 125.0, 124.0, 122.7, 121.0, 120.2, 113.8, 112.0, 109.5, 98.9, 64.0, 56.4, 44.8, 23.0. ^{19}F NMR (564 MHz, $CDCl_3$) δ -109.4. HRMS (ESI) calculated for: $C_{27}H_{27}FN_3O_2S^+[M+H]^+$: 476.1803, found: 476.1805.



22

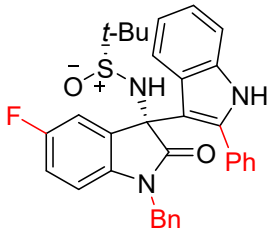
(R)-N-((R)-1-benzyl-6-fluoro-3-(5-methoxy-2-methyl-1H-indol-3-yl)-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**22**). The titled compound **22** was obtained following the procedure described for **3a** as a gold solid (87 mg, 60% yield): $[\alpha]_D^{20}$= - 227.0 (c 0.1, DCM). m.p. 113.6 - 115.5 °C. IR (KBr) Vmax: 3279, 2947, 1728, 1613, 1489, 1458, 1350, 1219, 1165, 1057, 949, 841, 702 cm^{-1}. ^1H NMR (600 MHz, DMSO) δ 10.90 (s, 1H), 7.53 (dd, *J* = 9.1, 5.3 Hz, 1H), 7.46 (d, *J* = 7.4 Hz, 2H), 7.28 (dt, *J* = 12.8, 7.1 Hz, 3H), 7.12 (d, *J* = 8.7 Hz, 1H), 6.82 (ddt, *J* = 9.9, 5.0, 2.5 Hz, 2H), 6.75 (d, *J* = 2.5 Hz, 1H), 6.62 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.14 (s, 1H), 5.06 (d, *J* = 15.7 Hz, 1H), 4.85 (d, *J* = 15.7 Hz, 1H), 3.58 (s, 3H), 2.24 (s, 3H), 1.19 (s, 9H). ^{13}C NMR (150 MHz, DMSO) δ 176.4, 161.9, 152.7, 144.0, 144.0, 135.8, 134.4, 129.9, 128.5, 127.9, 127.9, 127.6, 127.4, 126.8, 126.5, 126.5, 111.1, 110.0, 108.5, 108.3, 106.8, 102.3, 98.0, 97.8, 79.2, 64.5, 55.8, 55.0, 43.3, 22.8, 14.2. ^{19}F NMR (564 MHz, $CDCl_3$) δ -106.6. HRMS (ESI) calculated for: $C_{29}H_{31}FN_3O_3S^+[M+H]^+$: 520.2065, found: 520.2061.



23

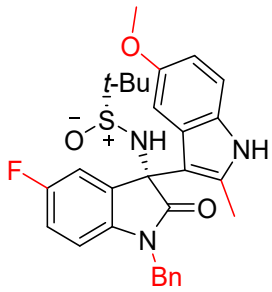
(R)-N-((S)-1-benzyl-5-fluoro-3-(6-methyl-1H-indol-3-yl)-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**23**). The titled compound **23** was obtained following the procedure described for **3a** as a brown solid (85 mg, 62% yield): $[\alpha]_D^{20}$= - 14.00 (c 0.1, DCM). m.p. 119.7 - 121.8 °C. IR (KBr) Vmax: 2916, 2855, 2353, 1713, 1620, 1489,

1451, 1343, 1258, 1165, 1026, 802, 694 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (d, J = 2.7 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.54 (dd, J = 8.4, 2.7 Hz, 1H), 7.33–7.23 (m, 5H), 7.17–7.09 (m, 2H), 6.89–6.83 (m, 2H), 6.78 (dd, J = 8.3, 1.5 Hz, 1H), 6.35 (s, 1H), 4.92–4.82 (m, 2H), 2.36 (s, 3H), 1.17 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.9, 160.2, 158.6, 156.4, 137.9, 135.8, 128.9, 127.9, 127.8, 123.2, 121.8, 120.2, 114.8, 114.3, 113.3, 109.9, 109.7, 94.9, 55.7, 53.4, 44.4, 29.8, 29.5, 27.3, 21.6. ^{19}F NMR (376 MHz, DMSO) δ -109.4. HRMS (ESI) calculated for: $C_{28}H_{29}FN_3O_2S^+[M+H]^+$: 490.1959, found: 490.1957.



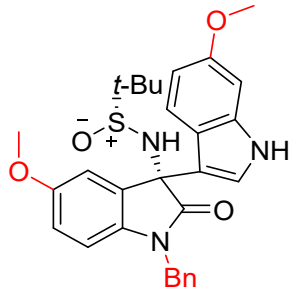
24

(R)-N-((R)-1-benzyl-5-fluoro-2-oxo-3-(2-phenyl-1H-indol-3-yl)indolin-3-yl)-2-methylpropane-2-sulfinamide (**24**). The titled compound **24** was obtained following the procedure described for **3a** as a gold solid (111 mg, 72% yield): $[\alpha]_D^{20}$= - 27.0(c 0.1, DCM). m.p. 120.9 - 122.2 °C. IR (KBr) Vmax: 3287, 2369, 1721, 1489, 1451, 1343, 1265, 1173, 1057, 910, 872, 733, 702 cm^{-1}. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.39 (s, 1H), 7.72 (dd, J = 6.5, 2.9 Hz, 2H), 7.44 (dd, J = 5.0, 1.9 Hz, 3H), 7.41–7.37 (m, 2H), 7.32–7.26 (m, 4H), 7.16 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 7.04–6.96 (m, 2H), 6.89 (ddd, J = 8.3, 7.1, 1.1 Hz, 1H), 6.71 (dd, J = 8.5, 3.7 Hz, 2H), 4.97–4.84 (m, 2H), 4.73 (d, J = 15.8 Hz, 1H), 0.91 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 160.5, 158.1, 139.8, 136.9, 135.5, 135.4, 134.2, 130.2, 129.1, 128.8, 128.7, 127.6, 125.9, 122.4, 120.1, 116.8, 116.5, 115.1, 114.8, 111.1, 110.6, 110.5, 109.5, 64.9, 55.9, 44.9, 22.4. ^{19}F NMR (564 MHz, $CDCl_3$) δ -108.7. HRMS (ESI) calculated for: $C_{33}H_{31}FN_3O_2S^+[M+H]^+$: 552.2116, found: 552.2113.



25

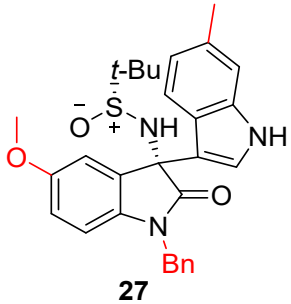
(R)-N-((R)-1-benzyl-5-fluoro-3-(5-methoxy-2-methyl-1H-indol-3-yl)-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**25**). The titled compound **25** was obtained following the procedure described for **3a** as a green solid (91 mg, 62% yield): $[\alpha]_D^{20}$= -15.0 (c 0.1, DCM). m.p. 92.6 - 93.1 °C. IR (KBr) Vmax: 3742, 3526, 3433, 3317, 3240, 2994, 2924, 2361, 1705, 1605, 1481, 1451, 1350, 1258, 1211, 1165, 1026, 772, 694 cm^{-1}. ^1H NMR (400 MHz, Chloroform-d) δ 8.26 (s, 1H), 7.46–7.39 (m, 2H), 7.33–7.25 (m, 3H), 7.21 (dd, J = 7.7, 2.6 Hz, 1H), 7.14–7.08 (m, 2H), 6.91 (td, J = 8.8, 2.6 Hz, 1H), 6.73 (td, J = 8.8, 3.2 Hz, 2H), 5.12 (d, J = 15.7 Hz, 1H), 4.85 (t, J = 7.9 Hz, 2H), 3.68 (s, 3H), 2.18 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 160.5, 158.1, 153.9, 139.0, 135.4, 133.0, 130.7, 130.2, 128.9, 127.8, 127.7, 127.3, 116.1, 114.0, 111.4, 111.3, 110.8, 110.7, 107.8, 102.6, 65.0, 65.0, 56.4, 55.8, 45.4, 23.0, 14.2. ^{19}F NMR (376 MHz, DMSO) δ -120.8. HRMS (ESI) calculated for: $C_{29}H_{31}FN_3O_3S^+[M+H]^+$: 520.2065, found: 520.2069.



26

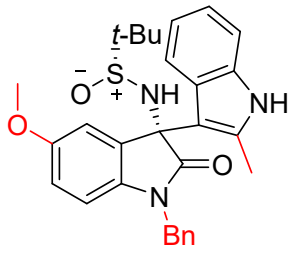
(R)-N-((S)-1-benzyl-5-methoxy-3-(6-methoxy-1H-indol-3-yl)-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**26**). The titled compound **26** was obtained following the procedure described for **3a** as a yellow solid (123 mg, 85% yield): $[\alpha]_D^{20}$= - 85.0 (c 0.1, DCM). m.p. 134.3 - 136.4 °C. IR (KBr) Vmax: 3294, 3233, 2947, 2338, 1713, 1628, 1497, 1451, 1343, 1258, 1165, 1049, 802, 694 cm^{-1}. ^1H NMR (400 MHz,

DMSO-d_6) δ 10.87 (d, J = 2.6 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.33–7.29 (m, 2H), 7.29–7.25 (m, 2H), 7.24 (d, J = 2.7 Hz, 2H), 6.83 (t, J = 1.8 Hz, 2H), 6.79 (d, J = 2.6 Hz, 1H), 6.74 (d, J = 8.5 Hz, 1H), 6.56 (dd, J = 8.8, 2.4 Hz, 1H), 6.15 (s, 1H), 4.85 (s, 1H), 4.82 (s, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 1.15 (s, 9H). ^{13}C NMR (100 MHz, DMSO) δ 175.8, 156.0, 138.3, 136.5, 135.7, 131.8, 129.0, 127.9, 127.7, 127.6, 124.7, 122.5, 119.4, 113.9, 113.7, 112.5, 110.2, 109.4, 65.3, 55.9, 55.6, 43.5, 23.4. HRMS (ESI) calculated for: $C_{29}H_{32}N_3O_4S^+$[M+H]$^+$: 518.2108, found: 518.2112.



27

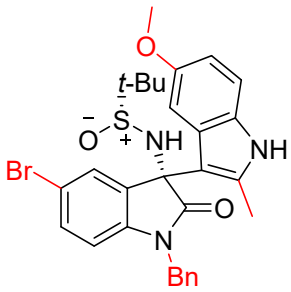
(R)-N-((S)-1-benzyl-5-methoxy-3-(6-methyl-1H-indol-3-yl)-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**27**). The titled compound **27** was obtained following the procedure described for **3a** as a grayish yellow solid (115 mg, 82% yield): $[\alpha]_D^{20}$= - 57 (c 0.1, DCM). m.p. 134.8 - 135.2 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 8.3 Hz, 1H), 7.09 – 7.05 (m, 2H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.74 – 6.72 (m, 2H), 5.16 (d, *J* = 15.7 Hz, 1H), 4.88 – 4.82 (m, 2H), 3.66 (d, *J* = 0.9 Hz, 3H), 2.24 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.4, 156.2, 136.7, 135.9, 135.2, 132.2, 130.3, 128.9, 128.0, 127.7, 127.4, 127.2, 121.4, 120.4, 119.7, 114.0, 113.8, 110.7, 110.6, 109.0, 65.2, 56.5, 55.8, 45.5, 29.8, 23.1, 14.3. HRMS (ESI) calculated for: $C_{29}H_{32}N_3O_3S^+$[M+H]$^+$: 502.2159, found: 502.2164.



28

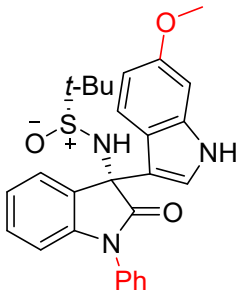
(R)-N-((R)-1-benzyl-5-methoxy-3-(2-methyl-1H-indol-3-yl)-2-oxoindolin-3-yl)-

2-methylpropane-2-sulfinamide (**28**). The titled compound **28** was obtained following the procedure described for **3a** as a brown solid (86 mg, 61% yield): $[\alpha]_D^{20}$= - 209.0 (c 0.1, DCM). m.p. 135.3 - 137.6 ℃. IR (KBr) Vmax: 3750, 2932, 2361, 1713, 1497, 1458, 1281, 1180, 748, 694 cm^{-1}. ^1H NMR (600 MHz, DMSO) δ 11.02 (s, 1H), 7.49 (d, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.29 – 7.24 (m, 2H), 7.20 (dd, *J* = 16.8, 8.1 Hz, 2H), 7.02 (t, *J* = 1.4 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 1.5 Hz, 2H), 6.76 (t, *J* = 7.6 Hz, 1H), 6.04 (s, 1H), 3.61 (s, 3H), 2.36 (s, 3H), 1.19 (s, 9H). ^{13}C NMR (150 MHz, DMSO) δ 175.9, 155.3, 136.2, 135.7, 134.8, 133.7, 131.8, 128.4, 128.3, 127.7, 127.3, 127.2, 126.3, 120.2, 119.6, 118.4, 113.3, 113.2, 110.5, 109.9, 107.6, 79.2, 65.0, 55.9, 55.4, 43.4, 22.8, 14.1. HRMS (ESI) calculated for: $C_{29}H_{32}N_3O_3S^+[M+H]^+$: 502.2159, found: 502.2157.



29

(R)-N-((R)-1-benzyl-5-bromo-3-(5-methoxy-2-methyl-1H-indol-3-yl)-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**29**). The titled compound **29** was obtained following the procedure described for **3a** as a brown solid (109 mg, 87% yield): $[\alpha]_D^{20}$= - 156.0 (c 0.1, DCM). m.p. 145.4 - 147.9 ℃. IR (KBr) Vmax: 3750, 3256, 2955, 2345, 1721, 1605, 1481, 1427, 1335, 1211, 1172, 1042, 802, 756, 702 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 7.76 (d, J = 2.1 Hz, 1H), 7.46 (dd, J = 8.4, 2.1 Hz, 1H), 7.39 (dd, J = 7.2, 2.4 Hz, 2H), 7.30–7.25 (m, 3H), 7.13 (d, J = 8.5 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 6.65–6.59 (m, 2H), 6.32 (s, 1H), 5.03 (d, J = 15.9 Hz, 1H), 4.84 (d, J = 15.9 Hz, 1H), 3.57 (s, 3H), 2.27 (s, 3H), 1.22 (s, 9H). ^{13}C NMR (100 MHz, DMSO) δ 176.1, 153.2, 142.0, 136.2, 135.6, 133.7, 132.2, 130.3, 129.8, 128.9, 127.9, 127.2, 114.6, 111.9, 111.6, 110.6, 106.2, 102.6, 79.7, 65.6, 56.4, 55.5, 43.6, 23.4, 14.8. HRMS (ESI) calculated for: $C_{29}H_{31}BrN_3O_3S^+[M+H]^+$: 580.1264, found: 580.1265.



30

(R)-N-((S)-3-(6-methoxy-1H-indol-3-yl)-2-oxo-1-phenylindolin-3-yl)-2-methylpropane-2-sulfinamide (**30**). The titled compound **30** was obtained following the procedure described for **3a** as a gold solid (108 mg, 74% yield): $[\alpha]_D^{20}$= - 123.0 (c 0.1, DCM). m.p. 135.3 - 136.7 ℃. IR (KBr) Vmax: 3232, 2955, 1728, 1613, 1497, 1466, 1366, 1250, 1173, 1049, 941, 810, 756, 702 cm^{-1}. ^1H NMR (400 MHz, Chloroform-d) δ 8.63–8.52 (m, 1H), 7.77–7.69 (m, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.49 (dt, J = 15.3, 7.6 Hz, 4H), 7.37 (t, J = 7.2 Hz, 1H), 7.25 (s, 1H), 7.07 (t, J = 7.5 Hz, 1H), 6.94 (d, J = 2.6 Hz, 1H), 6.86 (d, J = 7.9 Hz, 1H), 6.80–6.74 (m, 2H), 4.76 (s, 1H), 3.76 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 156.6, 143.7, 138.1, 134.4, 129.6, 128.3, 127.0, 126.7, 123.3, 122.8, 121.3, 119.3, 113.8, 110.2, 110.1, 95.1, 64.3, 56.2, 55.6, 23.0. HRMS (ESI) calculated for: $C_{27}H_{28}N_3O_3S^+[M+H]^+$: 474.1846, found:474.1847.

IV X-ray data of compound 3a

Single crystal growth: A solution of compound 3a (10 mg) in methanol (MeOH, 1 mL) was prepared in a 10 mL vial. After complete dissolution, n-hexane (3.0 mL) was carefully layered along the vial wall, forming a biphasic system (MeOH/n-hexane, v/v = 1:3). The vial was sealed and left undisturbed at room temperature for slow solvent evaporation. After 7-10 days, well-formed colorless crystals suitable for X-ray diffraction analysis were obtained.

X-ray Crystallography: Single-crystal X-ray diffraction data were collected on a Rigaku XtaLAB Pro II AFC12 diffractometer (Cu Kα radiation, λ = 1.54184 Å) equipped with a HyPix-3000 detector. The X-ray generator was operated at 50 kV and 1.0 mA. The crystal was maintained at 301 K during data collection. The ellipsoid

probability level was set at 50%. CCDC: 2423640 contains the supplementary crystallographic data for this work.

CDCC: 2423640

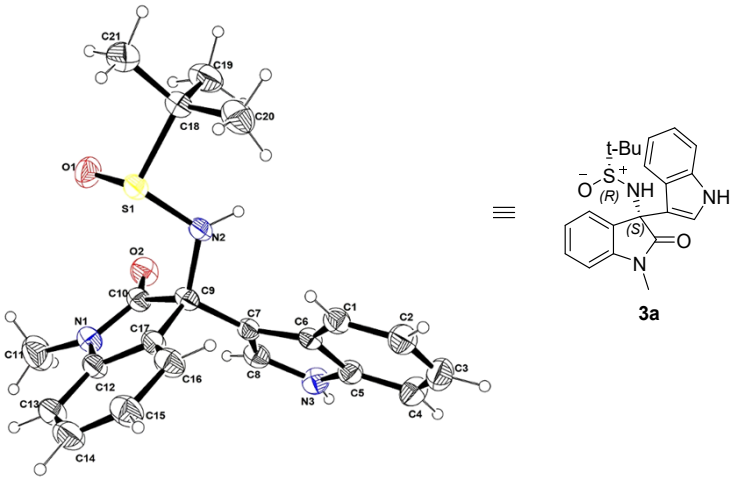


Figure S1 X-ray Structure of compound 3a.

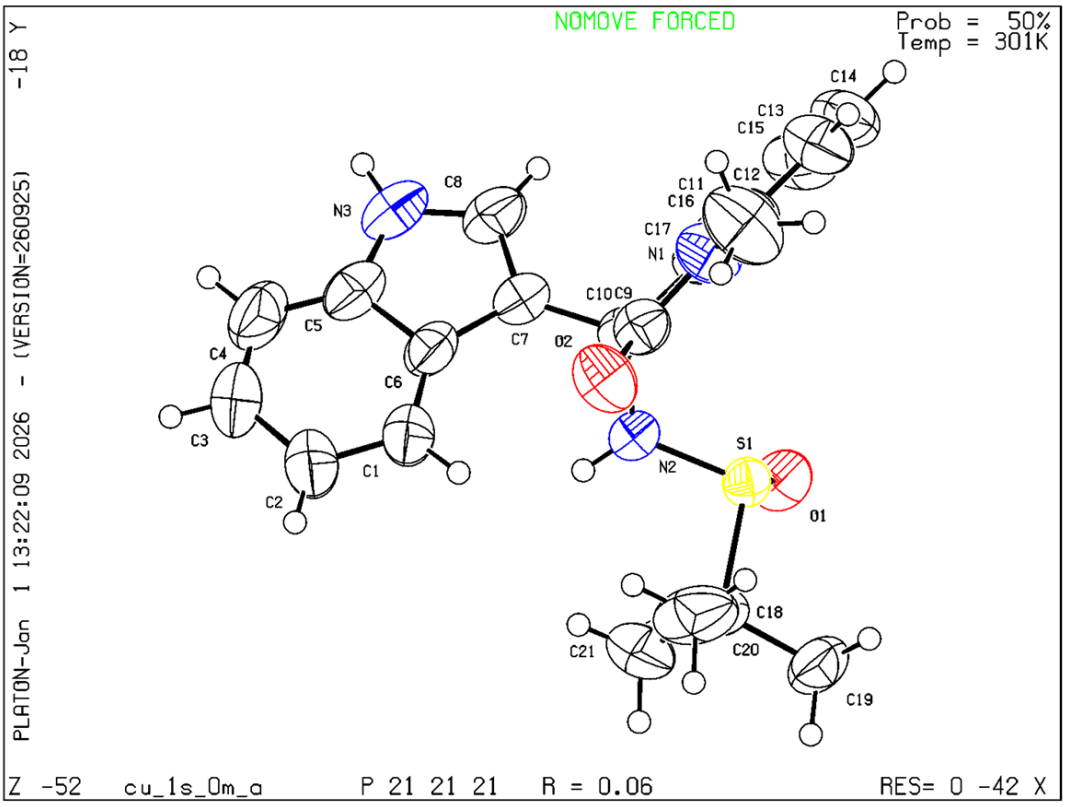


Table S2 Crystal data and structure refinement for **3a**.

Identification code	cu_1S_0m_a
Empirical formula	$C_{21}H_{23}N_3O_2S$
Formula weight	381.48

Temperature/K	301.00
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	10.4468(16)
b/Å	12.9783(11)
c/Å	19.993(3)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2710.7(7)
Z	4
ρ_{calc}g/cm^3	0.935
μ/mm^{-1}	1.181
F(000)	808.0
Crystal size/mm^3	0.54 × 0.48 × 0.25
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.122 to 144.368
Index ranges	$-12 \le h \le 12$, $-13 \le k \le 16$, $-24 \le l \le 24$
Reflections collected	26795
Independent reflections	5282 [R_{int} = 0.0592, R_{sigma} = 0.0443]
Data/restraints/parameters	5282/0/248
Goodness-of-fit on F^2	1.042
Final R indexes [I>=2σ (I)]	R_1 = 0.0575, wR_2 = 0.1651
Final R indexes [all data]	R_1 = 0.0698, wR_2 = 0.1788
Largest diff. peak/hole / e Å^{-3}	0.29/-0.31
Flack parameter	0.030(8)

Table S3 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **3a**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1	4283.1(7)	3666.4(6)	4379.0(3)	45.0(2)
O1	4987(3)	2824(2)	4034.3(15)	64.5(7)
O2	3331(3)	6464(3)	4631.5(18)	75.4(9)
N2	3852(3)	4569(2)	3841.0(16)	53.1(7)
N3	4419(5)	6894(3)	2197(2)	77.6(11)
N1	5524(4)	6471(3)	4694(2)	69.5(9)
C6	3004(5)	6370(3)	2972(2)	62.0(9)
C5	3147(6)	6866(3)	2350(2)	70.1(12)
C17	6084(4)	5370(3)	3861(2)	54.2(8)
C7	4276(4)	6094(3)	3188.6(19)	55.7(8)

C9	4651(4)	5510(3)	3805.9(19)	52.3(8)
C10	4370(4)	6207(3)	4421(2)	58.6(8)
C12	6547(4)	5966(3)	4401(3)	66.2(10)
C8	5090(5)	6439(4)	2699(2)	71.1(11)
C14	8648(5)	5421(5)	4185(4)	84.3(14)
C1	1775(5)	6268(4)	3257(2)	75.6(12)
C16	6933(5)	4776(3)	3494(3)	73.1(12)
C15	8224(5)	4836(4)	3664(4)	85.8(16)
C13	7816(5)	5995(5)	4550(4)	85.3(15)
C4	2141(8)	7228(5)	1995(3)	94.7(19)
C18	2703(4)	3142(3)	4603(2)	63.4(10)
C19	3008(5)	2182(4)	5019(3)	75.0(12)
C20	2038(6)	3963(5)	5018(5)	105(2)
C11	5648(7)	7147(6)	5288(3)	103(2)
C21	1985(6)	2843(6)	3980(4)	104(2)
C3	942(8)	7129(7)	2275(4)	108(2)
C2	722(7)	6618(6)	2909(4)	105(2)

Table S4 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for **3a**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	$\mathbf{U_{11}}$	$\mathbf{U_{22}}$	$\mathbf{U_{33}}$	$\mathbf{U_{23}}$	$\mathbf{U_{13}}$	$\mathbf{U_{12}}$
S1	44.5(4)	50.8(4)	39.8(3)	1.7(3)	3.6(3)	2.5(3)
O1	69.4(17)	59.5(14)	64.6(16)	0.5(12)	18.7(13)	13.9(13)
O2	61.8(16)	86(2)	78.5(18)	-18.7(17)	1.6(14)	13.0(16)
N2	55.3(16)	49.1(14)	55.0(15)	8.6(12)	-1.4(12)	-3.7(13)
N3	100(3)	65(2)	68(2)	18.4(16)	18(2)	-7(2)
N1	63(2)	75(2)	70(2)	-18.3(17)	1.4(16)	-4.0(17)
C6	77(2)	48.5(17)	60(2)	13.6(16)	-1.7(18)	-3.6(18)
C5	99(4)	48.7(19)	62(2)	6.6(16)	5(2)	-7(2)
C17	51.2(18)	53.7(17)	57.6(18)	1.7(14)	8.6(14)	-3.6(14)
C7	65(2)	47.0(16)	55.0(18)	3.1(13)	6.8(17)	-3.0(15)
C9	51.1(19)	52.0(17)	53.7(18)	0.5(14)	5.8(14)	-0.8(14)
C10	62(2)	52.9(17)	60.5(19)	0.0(15)	5.6(18)	3.2(16)
C12	60(2)	62(2)	77(3)	-2.8(19)	2(2)	-7.9(16)
C8	79(3)	66(2)	68(2)	14(2)	19(2)	-1(2)
C14	53(2)	85(3)	115(4)	0(3)	3(2)	-5(2)
C1	66(2)	90(3)	71(2)	24(2)	-7(2)	3(2)
C16	64(2)	57(2)	98(3)	-4(2)	22(2)	1.7(18)
C15	54(2)	73(3)	130(5)	-3(3)	28(3)	6(2)

C13	63(3)	89(3)	104(4)	-9(3)	-5(3)	-13(2)
C4	133(6)	90(3)	62(3)	25(2)	-28(3)	-25(4)
C18	51.1(19)	68(2)	71(2)	18.8(18)	5.4(17)	-8.0(17)
C19	80(3)	74(3)	71(3)	25(2)	13(2)	-2(2)
C20	74(3)	87(3)	155(6)	20(4)	56(4)	8(3)
C11	94(4)	126(5)	90(4)	-52(4)	-11(3)	-5(4)
C21	76(3)	120(5)	117(5)	20(4)	-28(3)	-41(3)
C3	103(5)	124(5)	97(4)	46(4)	-34(4)	-1(4)
C2	75(3)	140(6)	101(4)	50(4)	-21(3)	-3(4)

Table S5 Bond Lengths for **3a**.

Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**
S1	O1	1.487(3)	C17	C12	1.413(6)
S1	N2	1.653(3)	C17	C16	1.386(6)
S1	C18	1.841(4)	C7	C9	1.500(5)
O2	C10	1.212(6)	C7	C8	1.373(6)
N2	C9	1.482(5)	C9	C10	1.553(5)
N3	C5	1.364(8)	C12	C13	1.359(7)
N3	C8	1.358(7)	C14	C15	1.363(10)
N1	C10	1.367(6)	C14	C13	1.357(9)
N1	C12	1.384(6)	C1	C2	1.378(8)
N1	C11	1.483(6)	C16	C15	1.393(8)
C6	C5	1.408(6)	C4	C3	1.378(12)
C6	C7	1.442(7)	C18	C19	1.531(6)
C6	C1	1.411(7)	C18	C20	1.519(8)
C5	C4	1.352(9)	C18	C21	1.504(8)
C17	C9	1.512(6)	C3	C2	1.450(9)

Table S6 Bond Angles for **3a**.

Atom	**Atom**	**Atom**	**Angle/°**	**Atom**	**Atom**	**Atom**	**Angle/°**
O1	S1	N2	110.75(17)	C7	C9	C17	112.3(3)
O1	S1	C18	106.5(2)	C7	C9	C10	107.9(3)
N2	S1	C18	100.13(18)	O2	C10	N1	125.5(4)
C9	N2	S1	117.5(3)	O2	C10	C9	127.3(4)

C8	N3	C5	109.0(4)	N1	C10	C9	107.2(3)
C10	N1	C12	113.1(3)	N1	C12	C17	108.6(4)
C10	N1	C11	123.1(4)	C13	C12	N1	130.3(5)
C12	N1	C11	123.5(5)	C13	C12	C17	121.1(5)
C5	C6	C7	106.3(4)	N3	C8	C7	110.4(5)
C5	C6	C1	119.7(4)	C13	C14	C15	120.5(5)
C1	C6	C7	133.9(3)	C2	C1	C6	119.5(5)
N3	C5	C6	108.3(5)	C17	C16	C15	117.3(5)
C4	C5	N3	129.1(5)	C14	C15	C16	122.2(5)
C4	C5	C6	122.7(6)	C14	C13	C12	119.5(6)
C12	C17	C9	109.2(3)	C5	C4	C3	117.4(5)
C16	C17	C9	131.5(4)	C19	C18	S1	104.2(3)
C16	C17	C12	119.3(4)	C20	C18	S1	106.5(3)
C6	C7	C9	127.8(3)	C20	C18	C19	111.7(5)
C8	C7	C6	106.0(4)	C21	C18	S1	109.9(4)
C8	C7	C9	126.1(4)	C21	C18	C19	110.1(5)
N2	C9	C17	117.1(3)	C21	C18	C20	113.9(6)
N2	C9	C7	107.9(3)	C4	C3	C2	122.9(6)
N2	C9	C10	109.6(3)	C1	C2	C3	117.7(7)
C17	C9	C10	101.5(3)				

Table S7 Torsion Angles for **3a**.

A	**B**	**C**	**D**	**Angle/°**	**A**	**B**	**C**	**D**	**Angle/°**
S1	N2	C9	C17	39.1(4)	C9	C17	C12	N1	0.2(5)
S1	N2	C9	C7	167.0(3)	C9	C17	C12	C13	-178.5(5)
S1	N2	C9	C10	-75.7(4)	C9	C17	C16	C15	178.5(5)
O1	S1	N2	C9	-99.9(3)	C9	C7	C8	N3	177.1(4)
O1	S1	C18	C19	56.0(4)	C10	N1	C12	C17	4.2(5)
O1	S1	C18	C20	174.2(4)	C10	N1	C12	C13	-177.2(6)
O1	S1	C18	C21	-61.9(5)	C12	N1	C10	O2	172.5(5)
N2	S1	C18	C19	171.4(3)	C12	N1	C10	C9	-6.6(5)
N2	S1	C18	C20	-70.5(4)	C12	C17	C9	N2	-123.0(4)
N2	S1	C18	C21	53.4(5)	C12	C17	C9	C7	111.2(4)
N2	C9	C10	O2	-48.5(6)	C12	C17	C9	C10	-3.8(4)
N2	C9	C10	N1	130.6(4)	C12	C17	C16	C15	-2.6(7)
N3	C5	C4	C3	-178.1(6)	C8	N3	C5	C6	-0.2(5)
N1	C12	C13	C14	179.8(5)	C8	N3	C5	C4	-180.0(5)
C6	C5	C4	C3	2.2(9)	C8	C7	C9	N2	-127.8(4)
C6	C7	C9	N2	49.4(5)	C8	C7	C9	C17	2.8(6)

C6	C7	C9	C17	180.0(4)	C8	C7	C9	C10	113.8(5)
C6	C7	C9	C10	-69.0(5)	C1	C6	C5	N3	178.0(5)
C6	C7	C8	N3	-0.6(5)	C1	C6	C5	C4	-2.2(8)
C6	C1	C2	C3	-3.1(11)	C1	C6	C7	C9	5.0(8)
C5	N3	C8	C7	0.6(6)	C1	C6	C7	C8	-177.3(6)
C5	C6	C7	C9	-177.2(4)	C16	C17	C9	N2	55.9(6)
C5	C6	C7	C8	0.4(5)	C16	C17	C9	C7	-69.8(6)
C5	C6	C1	C2	2.7(9)	C16	C17	C9	C10	175.1(4)
C5	C4	C3	C2	-2.8(12)	C16	C17	C12	N1	-178.9(4)
C17	C9	C10	O2	-173.0(4)	C16	C17	C12	C13	2.4(7)
C17	C9	C10	N1	6.1(4)	C15	C14	C13	C12	1.4(10)
C17	C12	C13	C14	-1.7(9)	C13	C14	C15	C16	-1.8(10)
C17	C16	C15	C14	2.4(9)	C4	C3	C2	C1	3.3(13)
C7	C6	C5	N3	-0.1(5)	C18	S1	N2	C9	148.0(3)
C7	C6	C5	C4	179.6(5)	C11	N1	C10	O2	-1.8(8)
C7	C6	C1	C2	-179.8(6)	C11	N1	C10	C9	179.1(5)
C7	C9	C10	O2	68.8(5)	C11	N1	C12	C17	178.4(5)
C7	C9	C10	N1	-112.1(4)	C11	N1	C12	C13	-3.0(9)

Table S8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **3a**.

Atom	***x***	***y***	***z***	**U(eq)**
H2	3188.34	4494.6	3590.88	64
H3	4743.8	7157.08	1840.77	93
H8	5976.24	6370.74	2708.41	85
H14	9514.38	5426.27	4292.2	101
H1	1675.93	5966.88	3675.67	91
H16	6652.81	4354.39	3147.36	88
H15	8816.73	4464.85	3414.01	103
H13	8111.37	6404.34	4898.69	102
H4	2254.28	7532.46	1578.07	114
H19A	3506.71	1711.22	4755.45	112
H19B	2225.05	1854.83	5152.49	112
H19C	3485.08	2378.57	5408.93	112
H20A	2603.68	4194.22	5365.47	158
H20B	1277.34	3678.93	5215	158
H20C	1812.42	4533.76	4736.74	158
H11A	5997.67	7799.78	5154.82	155
H11B	6205.66	6829.32	5608.87	155

H11C	4819.62	7251.22	5485.15	155
H21A	1686.73	3452.23	3757.35	157
H21B	1267	2418.52	4098.6	157
H21C	2543.31	2466.31	3687.38	157
H3A	244.06	7400.86	2046.58	130
H2A	-102.08	6530.22	3076.24	126

Table S9 Solvent masks information for **3a**.

Number	X	Y	Z	Volume	Electron count	Content
1	-0.184	-0.884	-0.250	518.1	89.1	1.76 CH3CH2CH2CH2CH2CH3
2	-0.304	0.281	0.250	518.1	89.4	1.76 CH3CH2CH2CH2CH2CH3

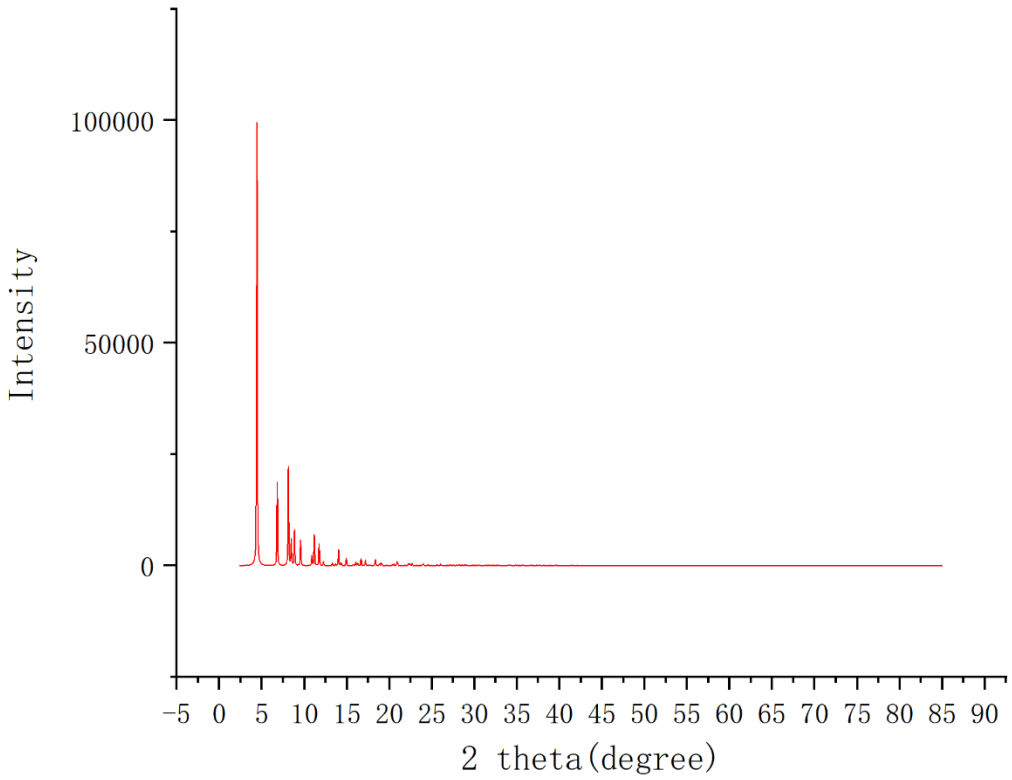


Figure S2 The X-ray analysis spectrum of compound **3a**.

V Gram-scale synthesis

Under the protective of argon, *N*- (*tert*-butylsulfinyl) imide (1 g, 2.37 mmol) was dissolved in toluene solution (12 mL) at -20 °C temperaterture, and then added *t*-BuOK

(0.31 g, 2.37 mmol) ,added $CuCl_2$ after the reaction ten minuters (26.59 mg, 0.237 mmol) , after five minuters 5-methoxy-2-methyl indole (0.76 g, 4.74 mmol) were added at -20 °C, until the TLC monitoring reaction was completed, slowly added Na_2CO_3 dropwise to quench and extracted with ethyl acetate (3×50 mL), and the organic phases were combined, anhydrous sodium sulfate was added for drying, concentrated and purified to obtain the target compound **29** as a brwon solid (1.18 g, 86% yield).

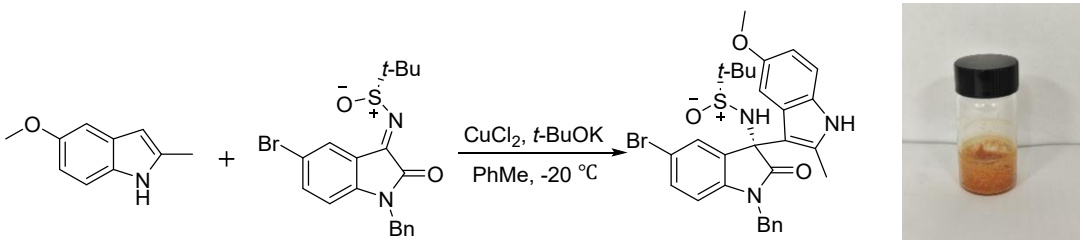
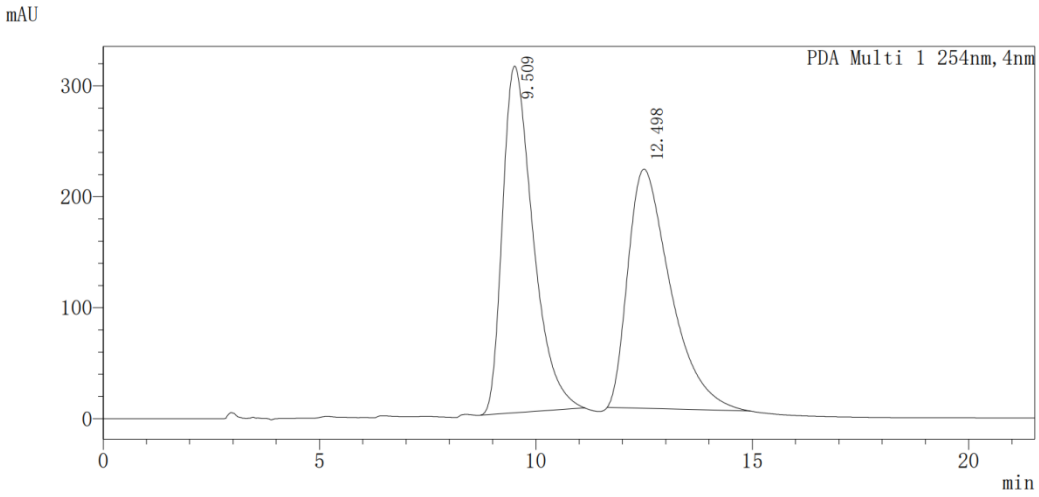


Figure S3 Gram-scale synthesis of compound **29**

VI HPLC analysis of compounds 29

The crude product **29** was analyzed directly by Chiral HPLC using OD-H column. Eluted by Hexane / i-PrOH (80:20 v:v), 1.0 mL/min.

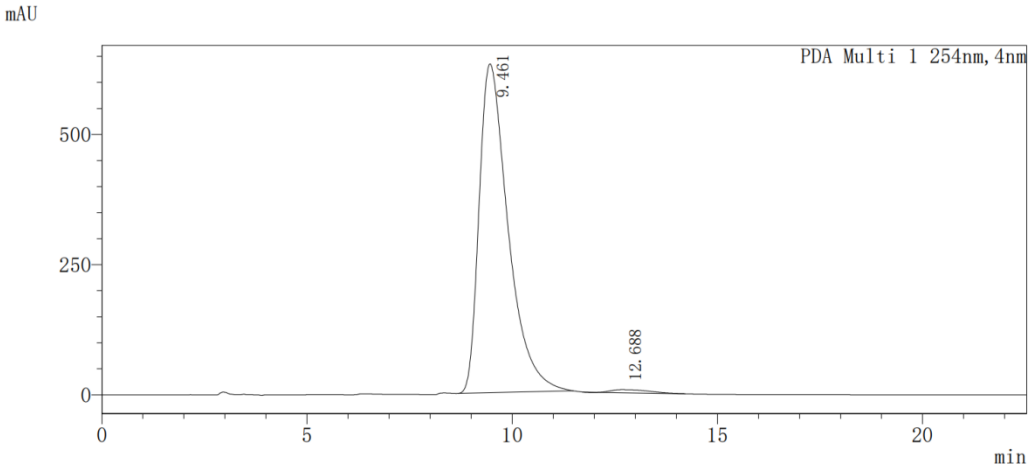
(1) Racemic **29**



Detector A Channel 1 254nm

Peak	Ret.Time	Area	Hight	Area %
1	9.509	15310040	312468	50.860
2	12.498	14792213	215587	49.140
Total		30102252	528055	100.00

(2) Compound **29**



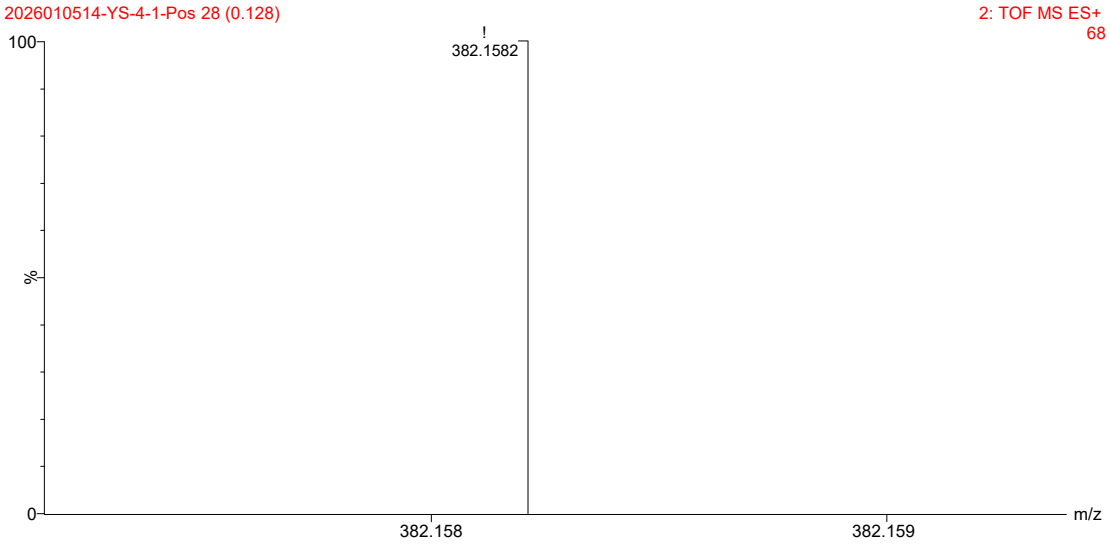
Detector A Channel 1 254nm

Peak	Ret.Time	Area	Hight	Area %
1	9.461	31058662	631482	98.802
2	12.688	376505	5931	1.198
Total		31435166	637413	100.00

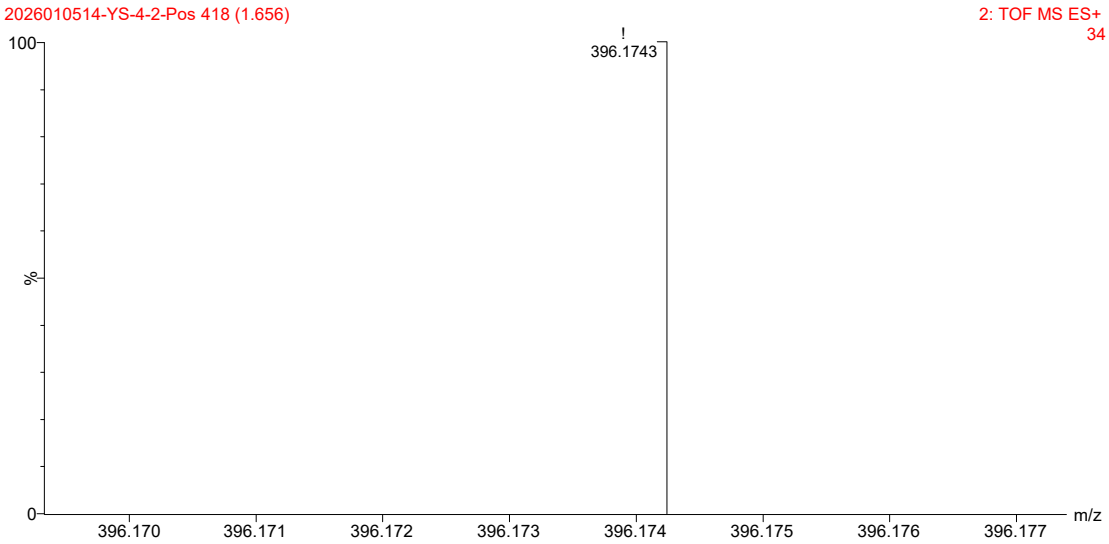
Figure S4 HPLC analysis of compounds **29**

VII Mass spectrum of compound 3a, 4-30

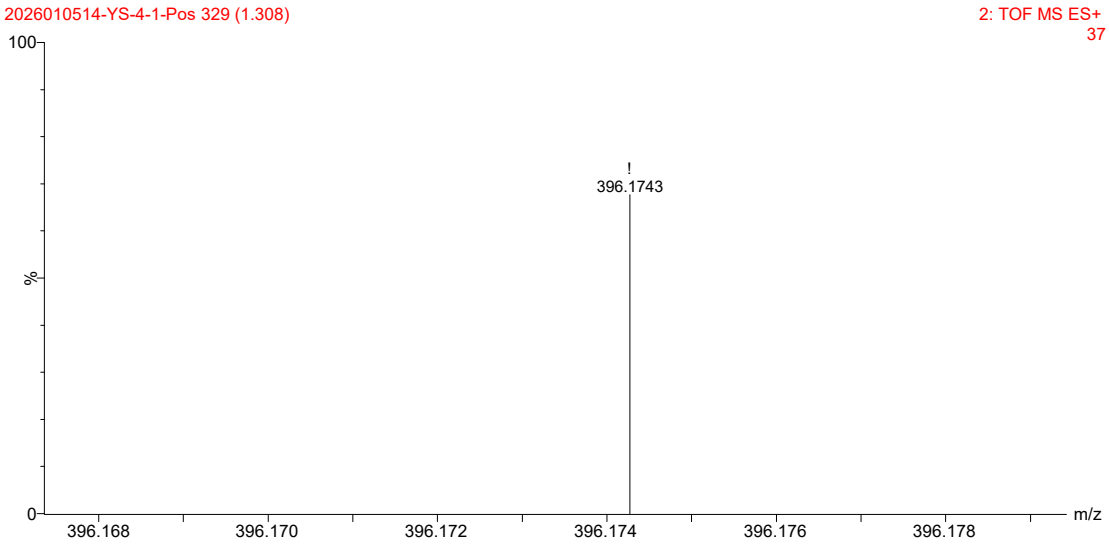
(1) Compound **3a**



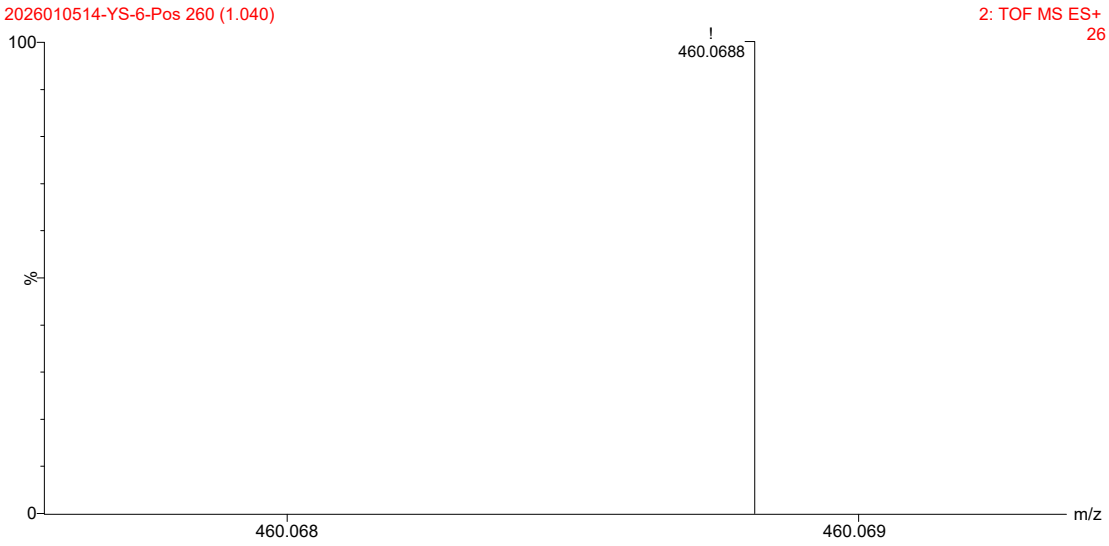
(2) Compound **4**



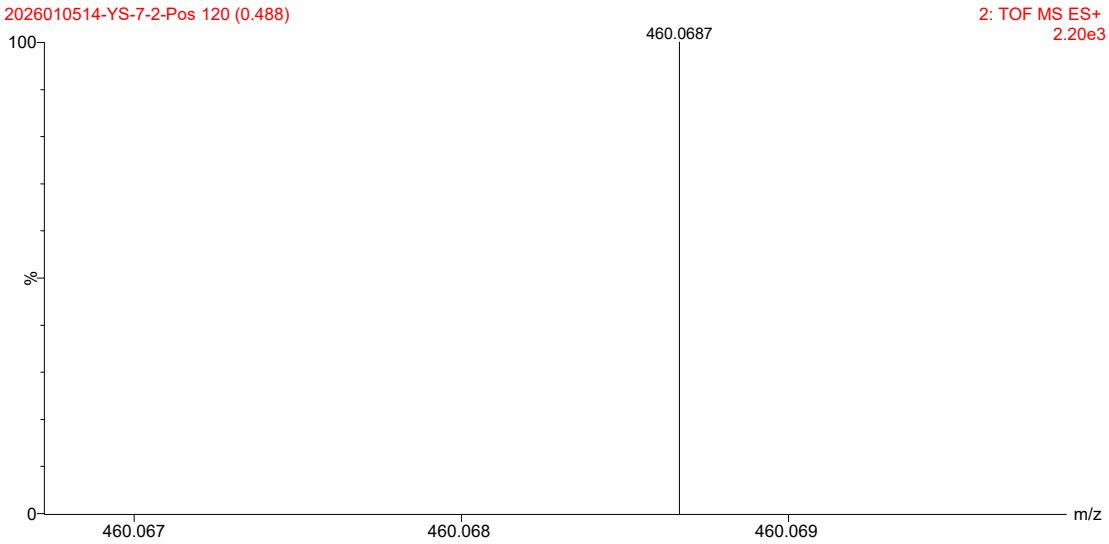
(3) Compound **5**



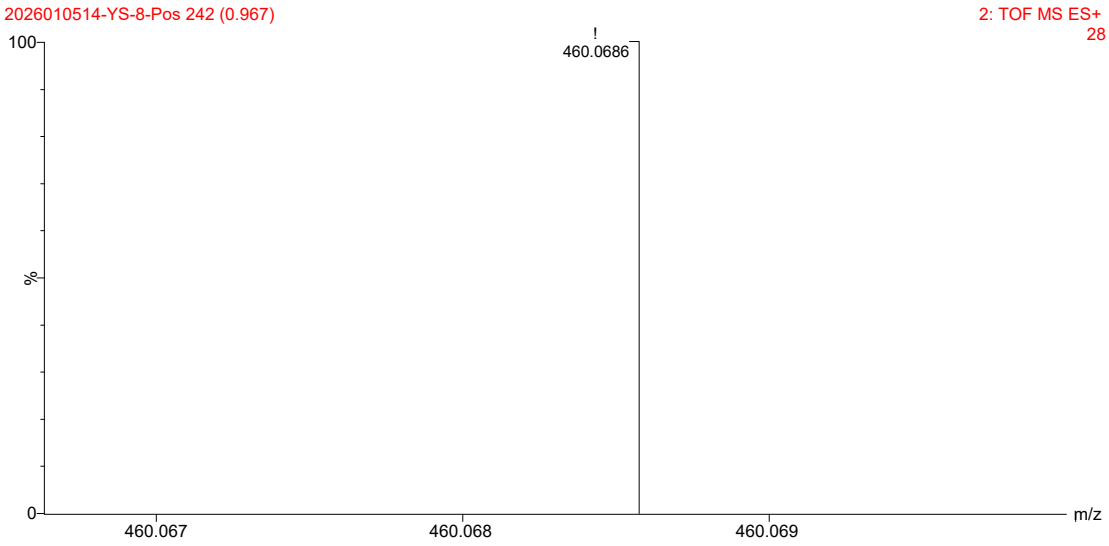
(4) Compound **6**



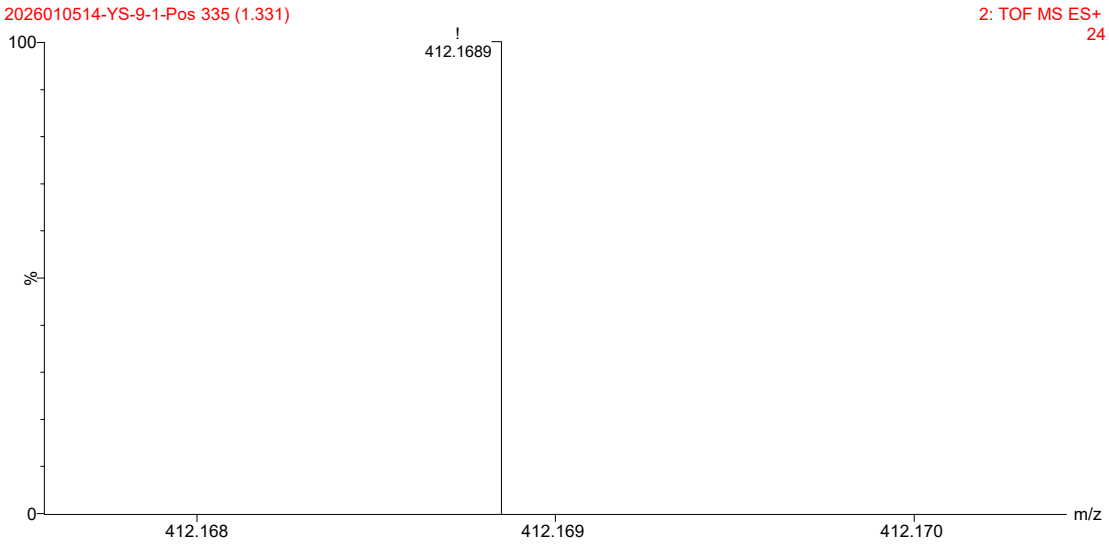
(5) Compound **7**



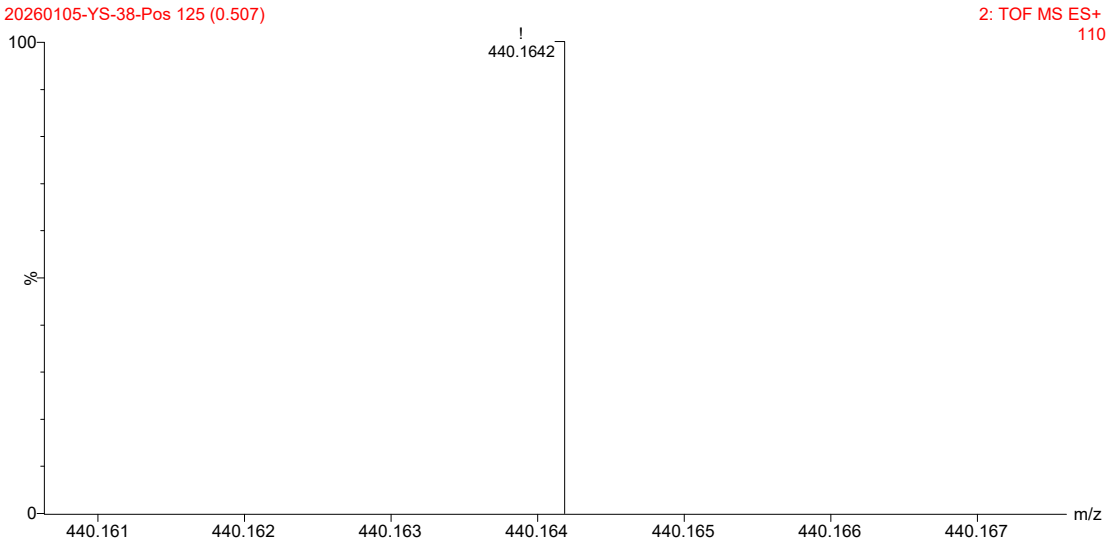
(6) Compound **8**



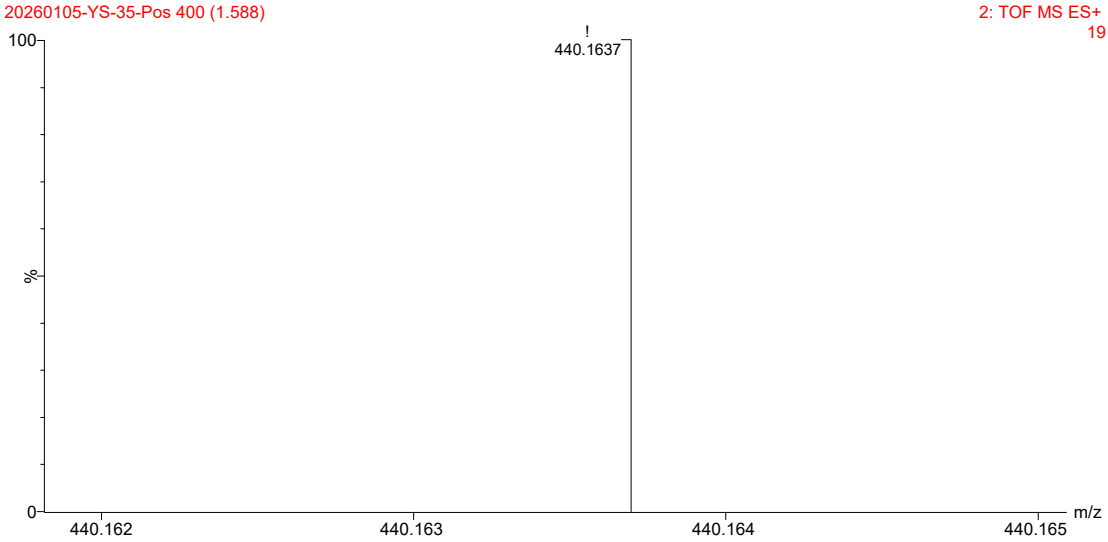
(7) Compound **9**



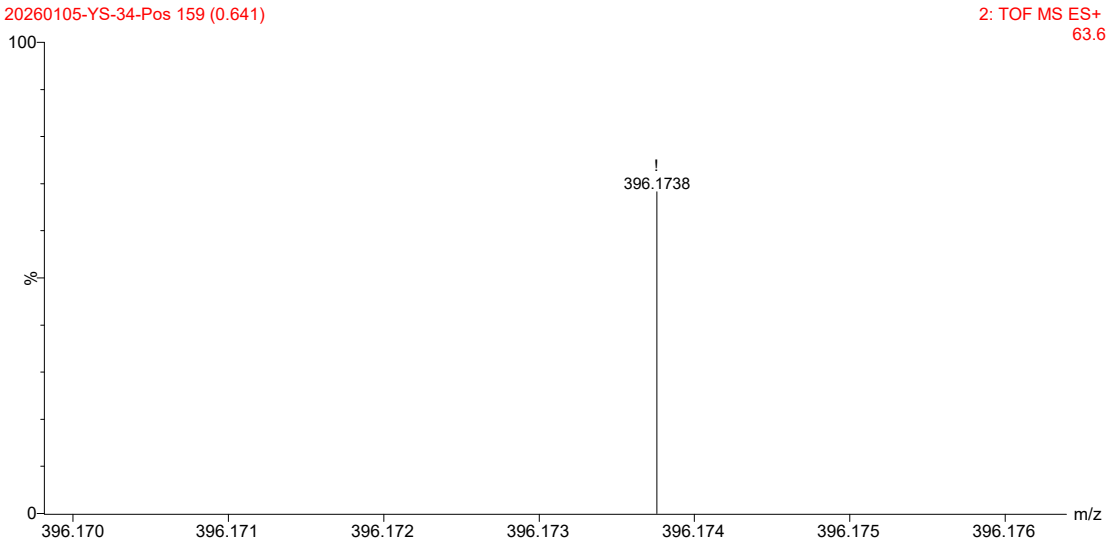
(8) Compound **10**



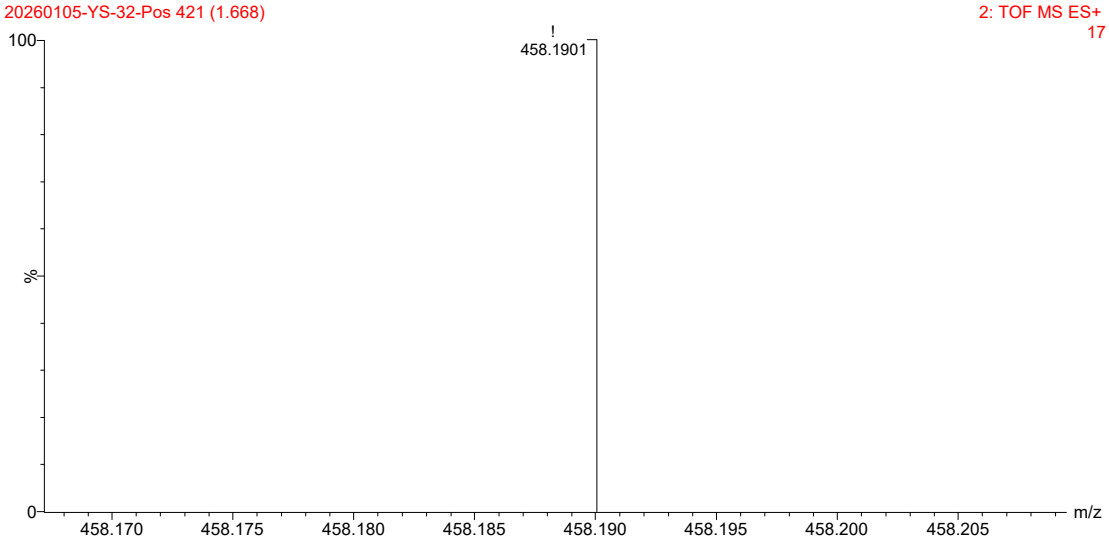
(9) Compound **11**



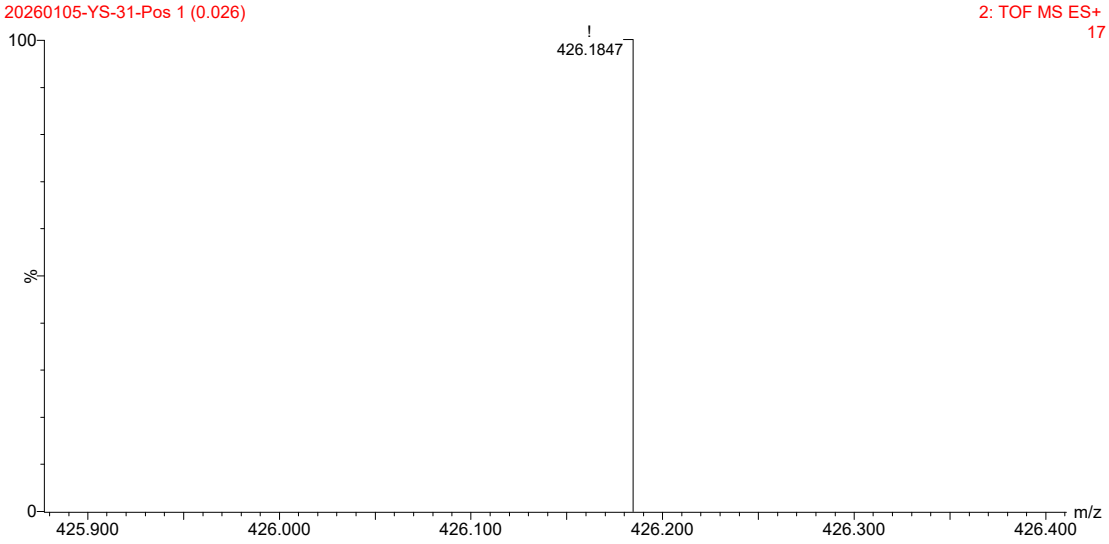
(10)Compound **12**



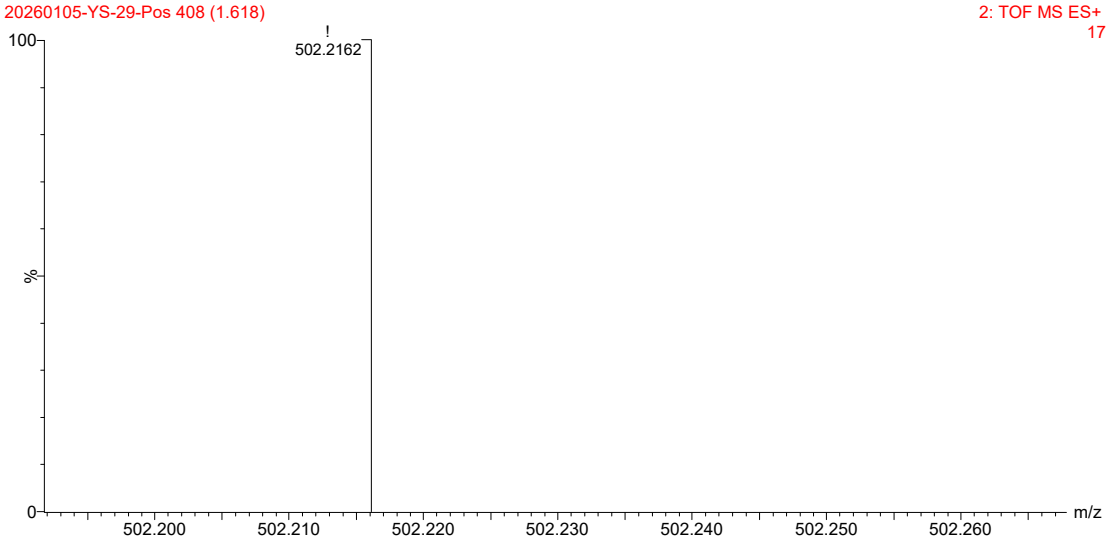
(11)Compound **13**



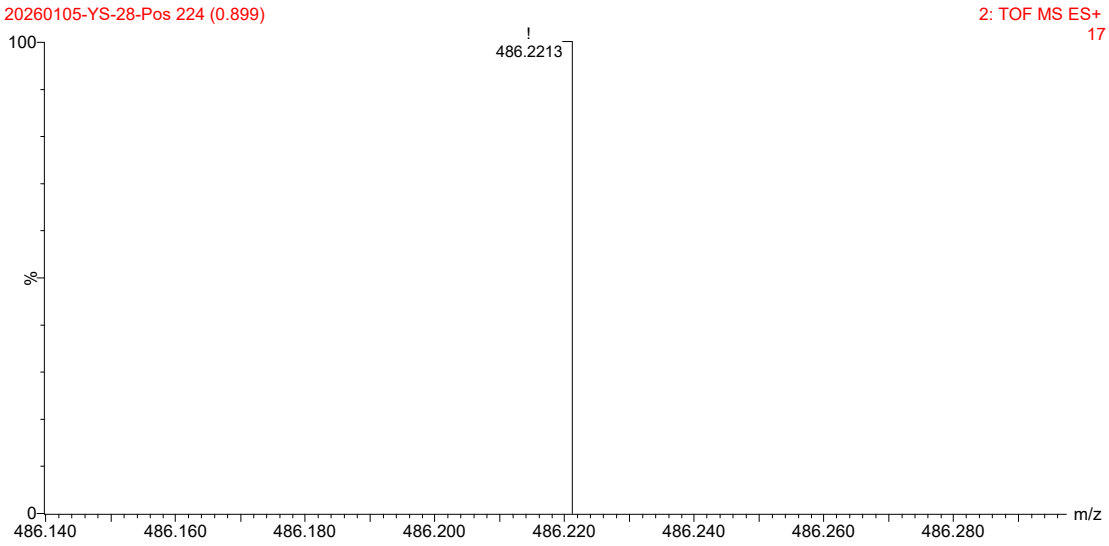
(12)Compound **14**



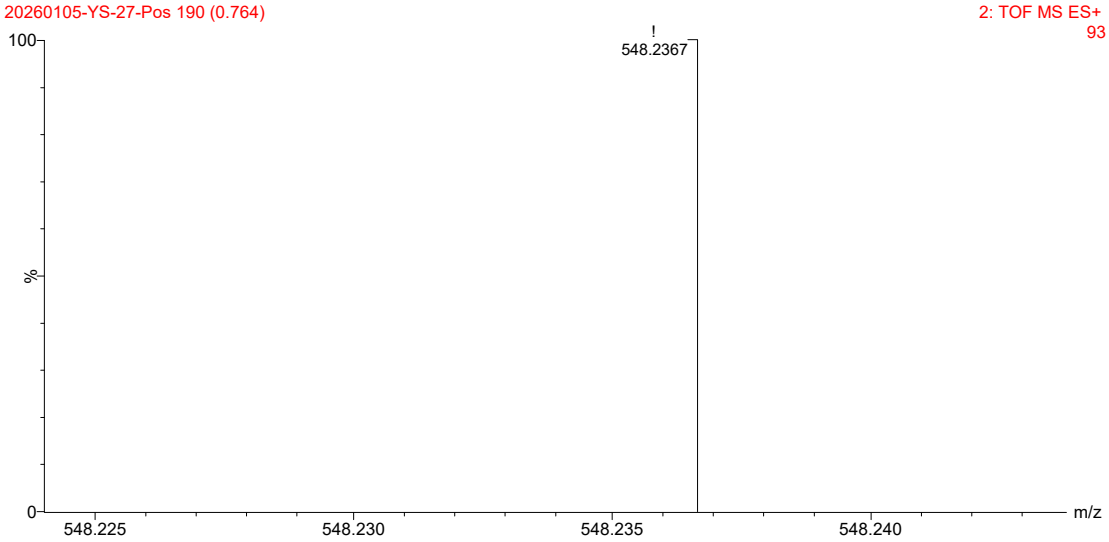
(13)Compound **15**



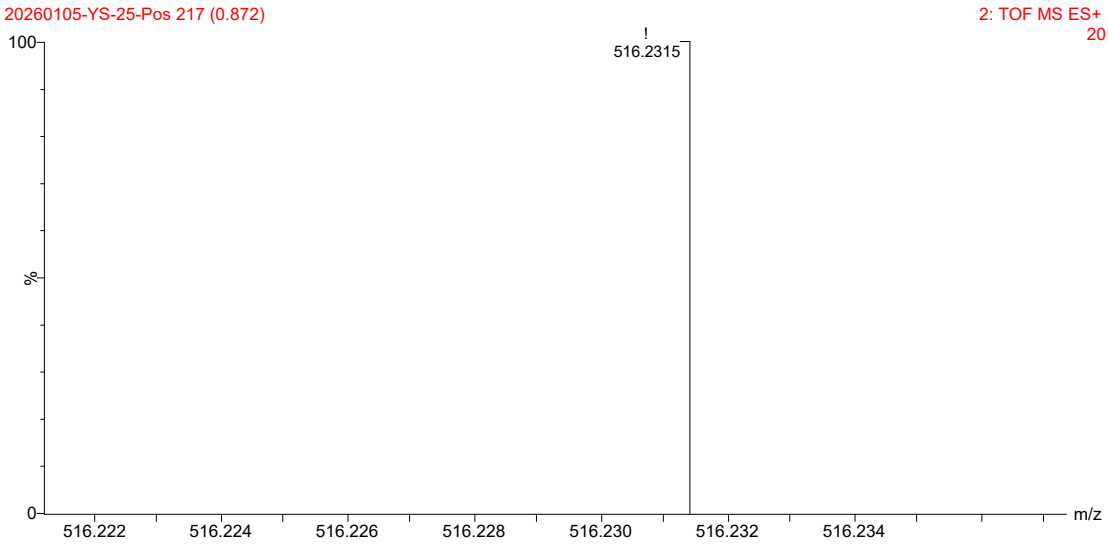
(14)Compound **16**



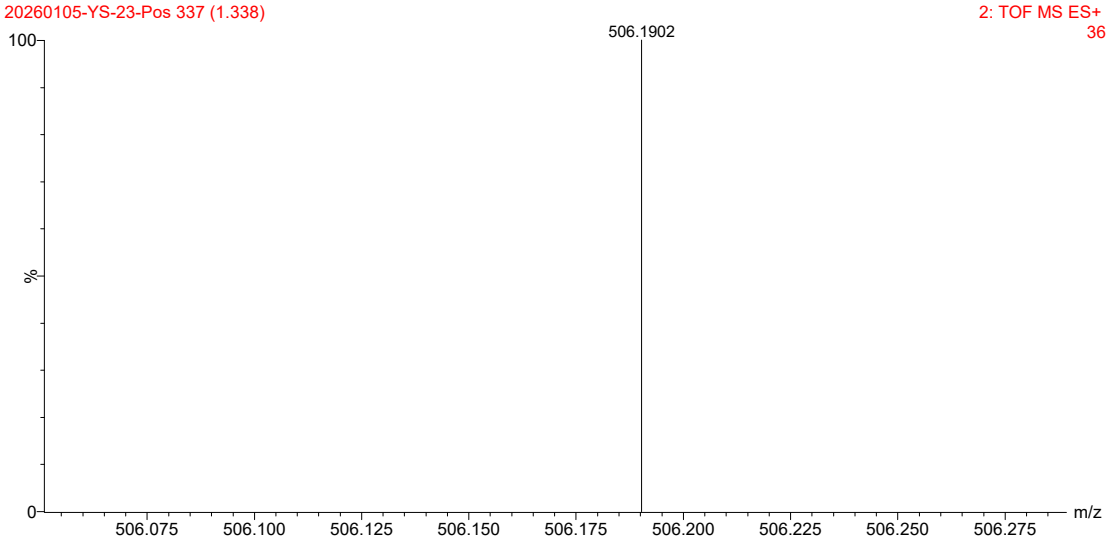
(15)Compound **17**



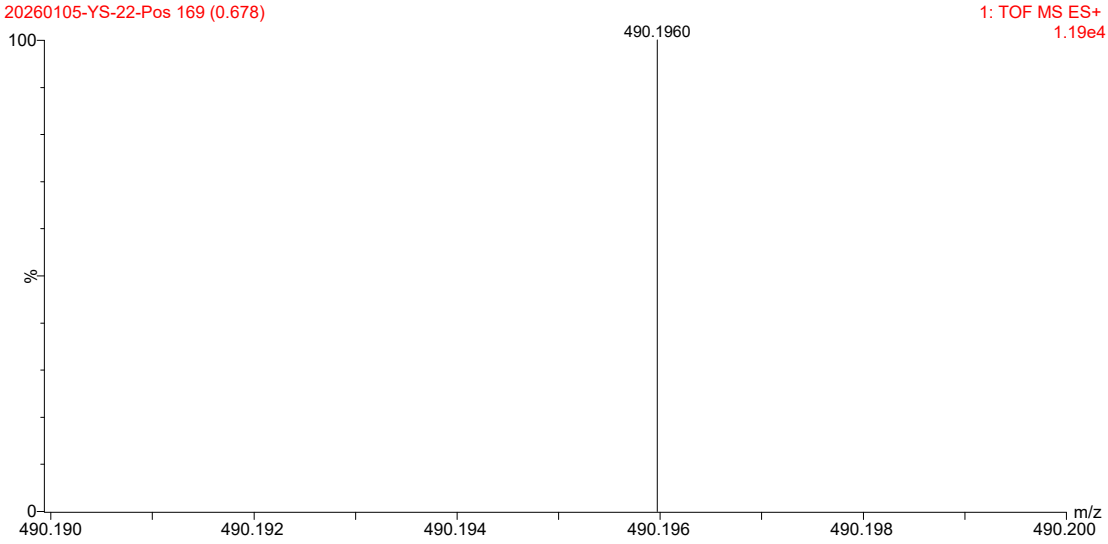
(16)Compound **18**



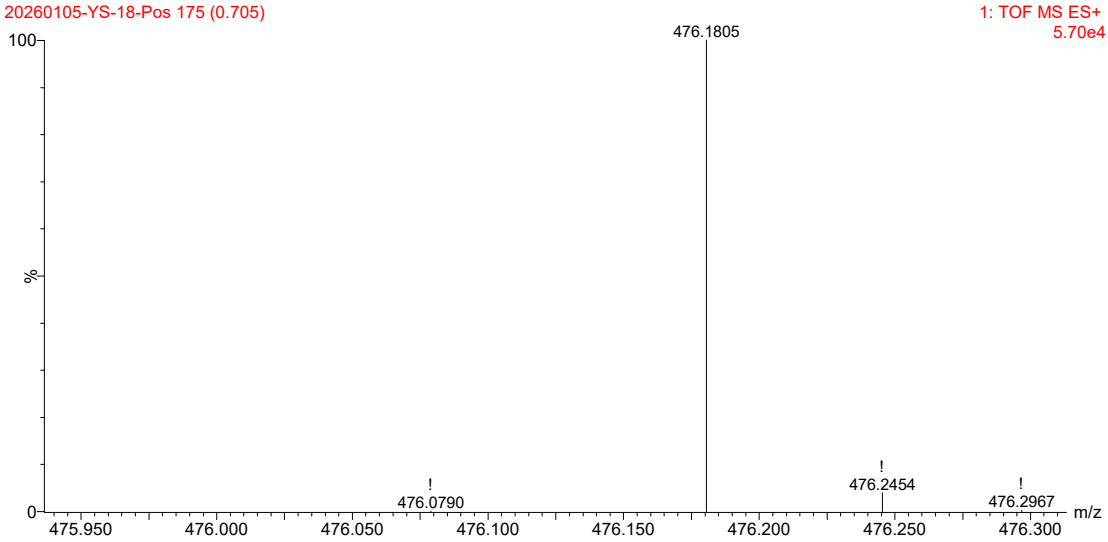
(17)Compound **19**



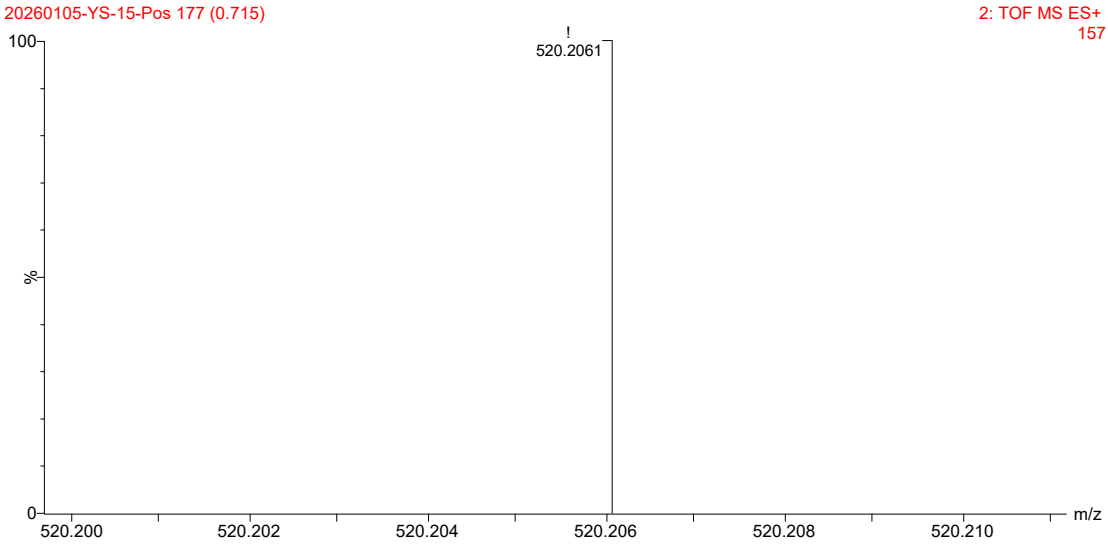
(18)Compound **20**



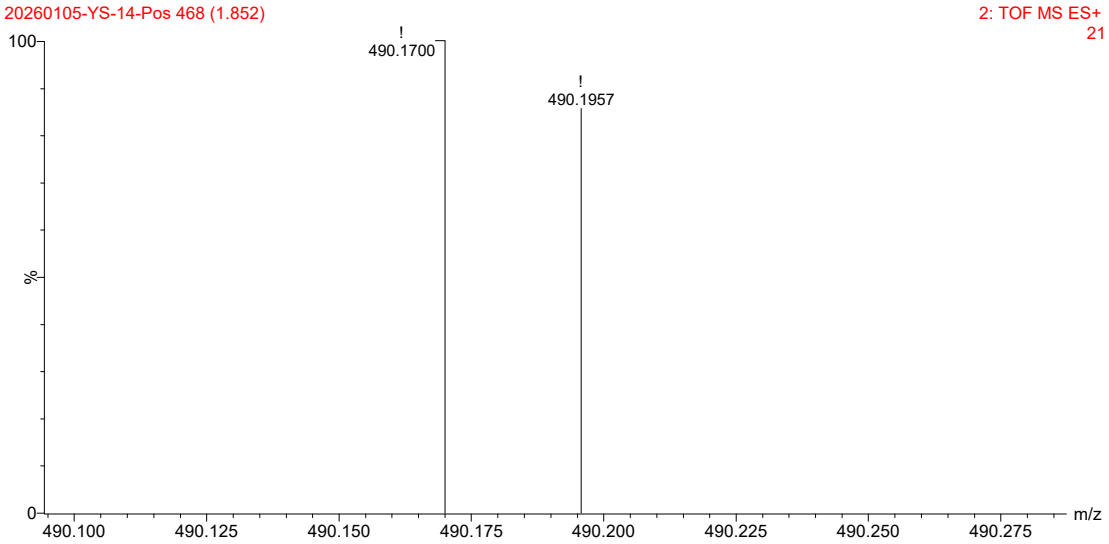
(19)Compound **21**



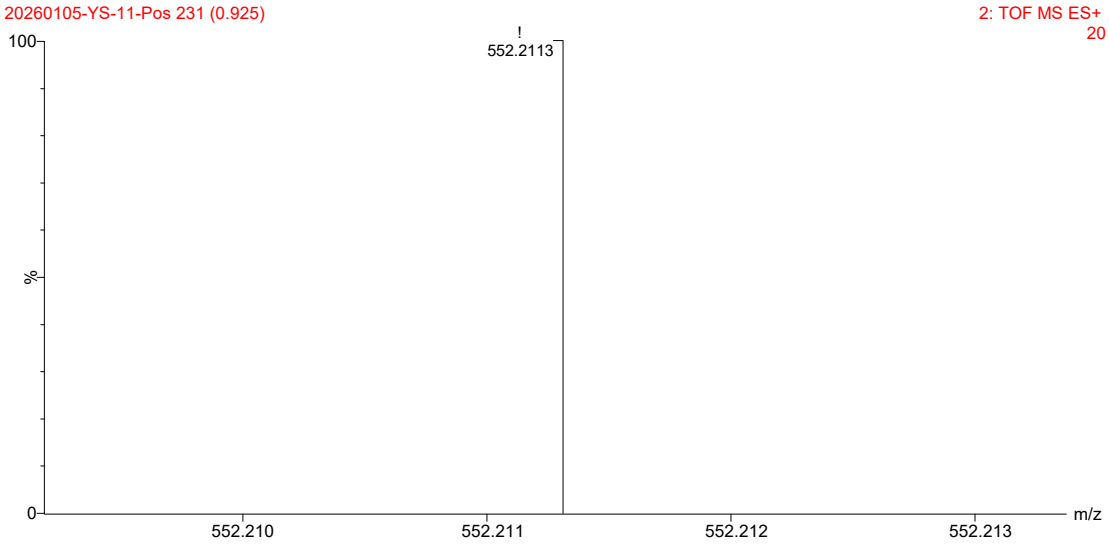
(20)Compound **22**



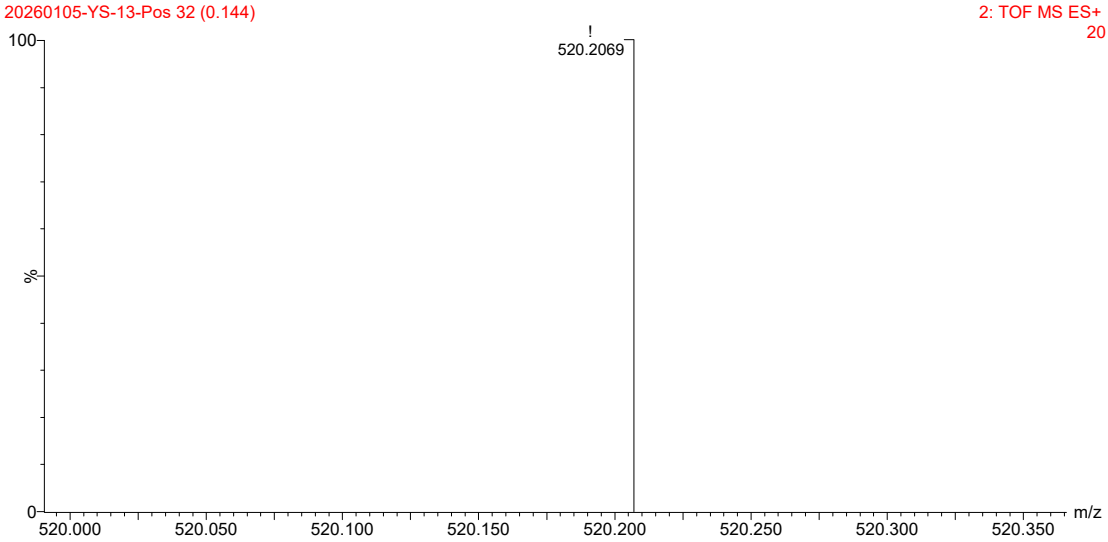
(21)Compound **23**



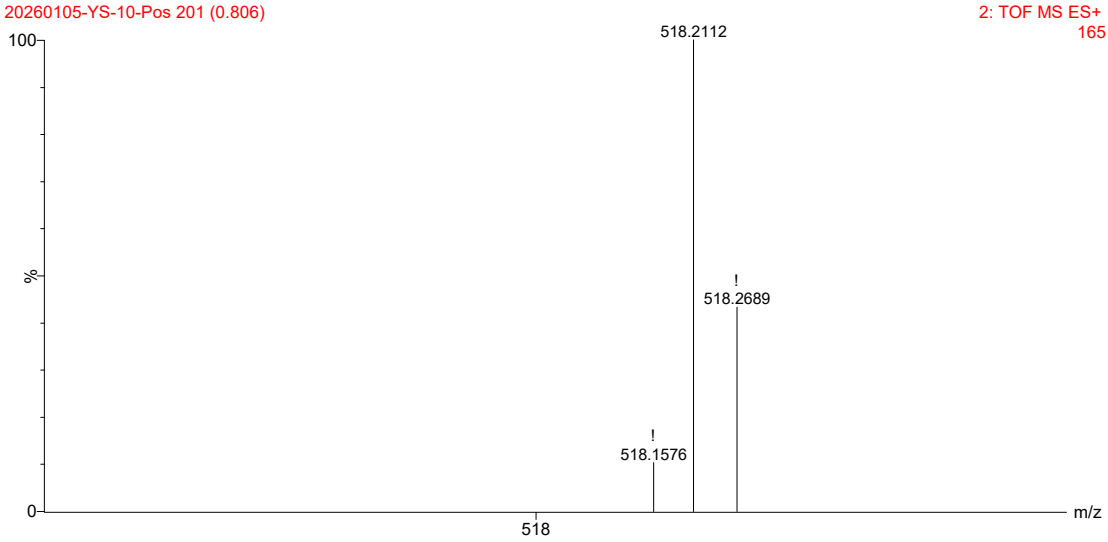
(22)Compound **24**



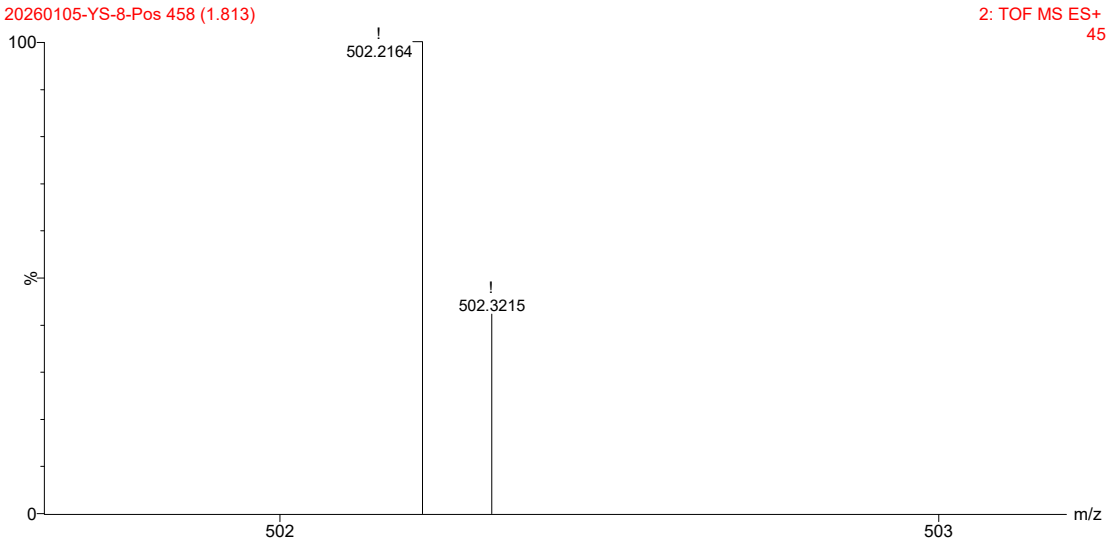
(23)Compound **25**



(24)Compound **26**



(25)Compound **27**



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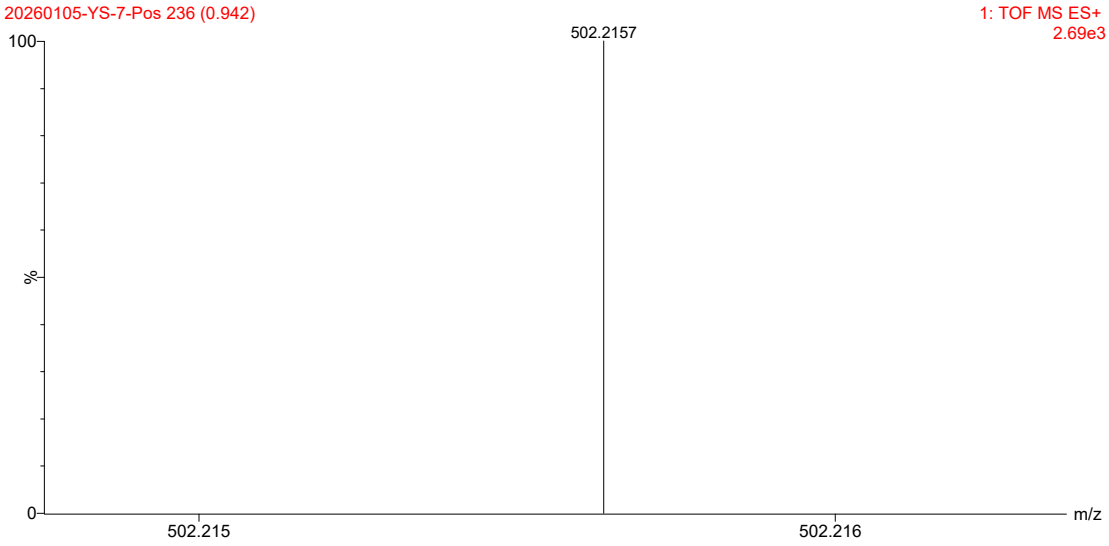
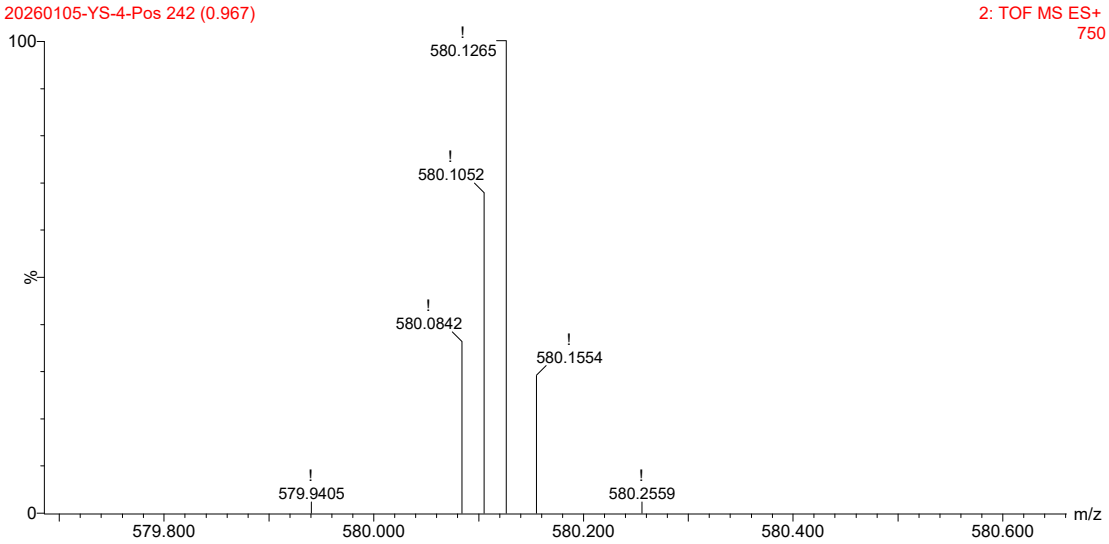
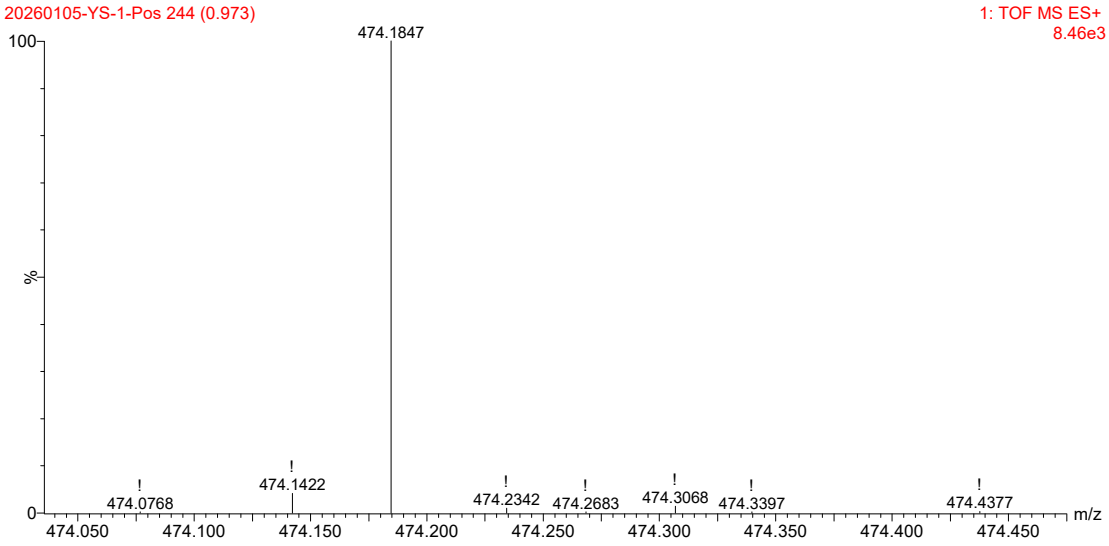


(27)Compound **29**



(28)Compound **30**



VIII Biological activity studies

General cell culture: The human cancer cell lines used in this study included breast adenocarcinoma (MCF-7), large-cell lung carcinoma (H460), lung adenocarcinoma (A549), ovarian carcinoma (SK-OV-3), glioblastoma (U251), hepatocellular carcinoma (HepG2), and osteosarcoma (MG63). All cell lines were obtained from the Tumor Research Institute at the Medical Transformation Center of the Tenth Affiliated Hospital of Southern Medical University. Cells were routinely cultured in 25 cm^2 tissue

culture flasks and subcultured once or twice weekly, depending on their growth rates. They were maintained at 37 °C in a humidified atmosphere of 95% air and 5% CO_2 using a LEEC incubator. To ensure optimal growth conditions, cells were passaged or used for experiments when reaching 70-80% confluency. The culture medium for all cell lines consisted of RPMI-1640 or DMEM (as appropriate for each cell type) supplemented with 10% (v/v) fetal bovine serum (FBS) and 1% penicillin-streptomycin. The medium was refreshed every 2-3 days to maintain cell viability. In all in vitro assays, all compounds were dissolved in DMSO, and the final concentration of DMSO was standardized at 0.1% in all culture conditions, including the control.

Cytotoxicity assay to evaluate the anticancer effect of compounds using MTT assay: After synthesizing several bisindole compounds under standard conditions, we thought of studying the preliminary biological activity of these new compounds.The anticancer potential of these compounds was tested on seven different cancer cell lines: human breast cancer cells MCF-7, human human lung cancer cells H460, human lung adenocarcinoma epithelial cells A549, human ovarian cancer cells SK-OV-3, human glioma cells U251, human hepatocellular carcinoma cells HepG2, uman osteosarcoma cells MG63 and Human mesenchymal stem cells (HMSCs).

Materials and methods:

MTT Assay:

Compounds are characterized by their cytotoxic properties on cells. Cytotoxicity is the percentage of cell survival or cell growth inhibition caused by chemical treatment. It can be determined by colorimetric assay in which the yellowish tetrazolium salt MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) is reduced to purple formazan crystals by the cellular enzyme succinate dehydrogenase. More purple indicates more viable cells. Briefly, regarding the procedure, 5000 individual breast cancer cells MCF-7, human large-cell lung carcinoma cells H460, human lung adenocarcinoma epithelial cells A549, human ovarian cancer cells SK-OV-3, human glioma cells U251, human hepatocellular carcinoma cells HepG2, human osteosarcoma cells MG63 and Human mesenchymal stem cells HMSC were seeded in 96-well plates and grown in DMEM at 37°C, 5% CO2 for one day. Different concentrations of

compounds were processed into cells at a specific degree of confluence, while control experiments were left untreated, and the entire plate was incubated for 48 h. Completely remove the medium from the wells and add MTT solution containing the medium (0.5 mg/ml working concentration). Incubate the plate in the dark for 4 h. Purple formazan crystals visible after DMSO dissolution treatment. Record the absorbance at 490 nm using a UV microplate reader. The data were exported, cell viability was calculated in an Excel spreadsheet, plotted using Graphpad Prism 8 software, and IC_{50} values were calculated.

Result Analysis:

Absorbance values are recorded in triplicate for each treated sample and exported to an Excel sheet. Average values are taken for each, and then the percentage of Survivability is calculated for each treated sample concerning the control sample using the following formula.

$$Survivability = \frac{Absorbance\ value\ of\ treated\ sample - Blank\ Absorbance}{Absorbance\ value\ of\ Control\ sample - Blank\ Absorbance} \times 100\ \%$$

The calculated survivability percentage vs. compound concentration was used to create the scatter plot. IC_{50} value (X) was calculated by generating the straight-line equation where Y=50. The standard division was calculated using Excel and is used for the error bar.

Table S10 Antiproliferative activity of the biindole compound library against cancer cells

	IC_{50}（μM）						
Compounds	MCF-7	H460	A549	SK-OV-3	U251	HepG2	MG63
3a	＞100	＞100	＞100	＞100	＞100	＞100	＞100
4	36.78	81.44	60.69	53.53	＞100	＞100	40.72
5	＞100	＞100	＞100	＞100	＞100	＞100	＞100
6	26.88	39.89	41.73	18.50	29.03	24.98	16.29
7	16.80	37.78	38.64	17.78	29.14	17.95	15.60
8	32.13	46.89	67.24	75.12	36.83	28.57	29.8

9	>100	>100	>100	>100	>100	>100	66.06
10	>100	>100	>100	>100	>100	>100	>100
11	>100	>100	>100	>100	>100	>100	>100
12	>100	>100	>100	>100	>100	>100	>100
13	32.17	30.39	35.37	55.12	75.23	42.34	45.08
14	>100	>100	>100	>100	>100	>100	>100
15	42.18	88.2	22.19	73.90	>100	>100	61.48
16	>100	>100	>100	>100	>100	>100	75.81
17	>100	>100	60.17	>100	>100	>100	>100
18	41.19	34.89	45.44	33.14	>100	>100	>100
19	18.84	35.67	34.54	23.13	20.70	26.00	15.95
20	37.09	39.85	60.51	43.89	31.28	36.76	25.11
21	81.78	83.28	36.34	83.93	>100	45.24	51.61
22	>100	>100	68.88	78.02	>100	>100	>100
23	>100	>100	>100	>100	>100	>100	>100
24	>100	74.22	23.64	63.89	>100	>100	83.72
25	57.64	19.80	35.23	40.26	32.10	56.98	62.84
26	>100	>100	>100	>100	>100	>100	>100
27	47.42	20.43	33.66	70.29	43.19	24.58	20.79
28	>100	>100	>100	>100	>100	>100	>100
29	39.1	25.22	16.87	28.67	83.36	17.4	3.29
30	>100	>100	>100	>100	>100	>100	>100
Doxorubicin	6.72	3.13	20.32	32.17	16.74	10.13	4.24

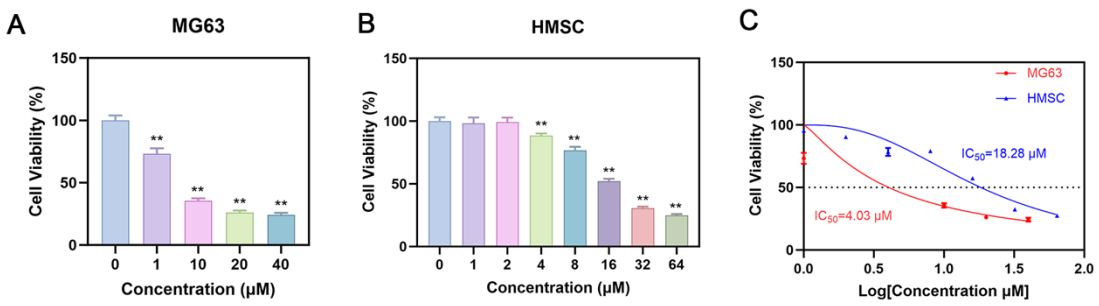


Figure S5 Effect of bisindole 29 on cell viability. (A) Quantification of MG63 osteosarcoma cell viability. (B) Quantification of HMSC osteosarcoma cell viability. (C) Comparative cytotoxicity of compound 29 in MG63 and HMSC cells. Data were processed with Graphpad Prism 8 software for statistical analysis. **P < 0.01 vs control group. Replicate the experiment three times independently.

EdU proliferation experiment: Cultures in 6-well plates allow the number of human osteosarcoma MG63 cells to reach 50% post-adherent overnight. The next day, compounds 29 with different concentration gradients were added for drug treatment, and the drug concentrations were marked on a six-well plate and transferred to an incubator for incubation for 48 h. Dilute EdU (10 mM) 1:500 with complete cell medium to obtain 2 × EdU working solution (20 μM), add this working solution to a six-well plate in a 1:1 ratio with the DMEM complete medium in which we cultured the cells (in order to avoid replacing all the medium and affecting the proliferation of the original cells, a semi-fed solution was used) and transferred to an incubator for 2 h. After a period of time has elapsed for the cells to be labeled with EdU, discard the original culture and add 1 mL of 4% paraformaldehyde fixative solution. Fix at room temperature for 15 min. Remove the in-plate fixative after the fixed cells, and make the 6-well plate wash the cells multiple times with 1 mL of wash solution per well, 3 times per well for 3-5 minutes each. Remove the above wash solution, add 1 mL of permeabilization solution per well to the 6-well plate, and incubate for 10-15 minutes at room temperature. Remove the permeabilization solution from the plate and make the 6-well plate wash multiple times with 1 mL wash solution per well for 2-3 times per well for 3-5 minutes each. Configure Click Reaction Solution (take 1 well as an example: Click Reaction Buffer: CuSO4: Azide 594: Click Additive Solution = 430:20:1:50, ready to use). Remove the wash solution from the previous step. Mix the reaction solution and add it to a 6-well plate so that 0.5 mL of Click reaction/well in the 6-well plate is gently shaken to evenly cover the sample. Incubate at room temperature in the dark for 30 minutes. Remove the reaction solution from the plate and repeat the wash with the wash solution for 3 times per well for 3-5 min each. Prepare 1 × Hoechst

33342 solution: dilute the stock solution with PBS at a ratio of 1:1000 to obtain 1 × Hoechst 33342 solution. After removing the previous in-well wash, add 1 × of 1 mL of diluted Hoechst 33342 solution per well and incubate for 10 minutes at room temperature in the dark. Remove 1 × Hoechst 33342 solution. Repeat multiple washes with 1 mL of wash solution per well, 3 times per well for 3–5 minutes each. After the above steps, the staining was completed, and the inverted fluorescence microscope was used to observe and photograph, each well was randomly observed, and multiple fields of view were selected to observe and photograph. Count with Image-J software and process the data with Graphpad Prism 8 software.

Result analysis: EdU staining is used to observe the number of cells in the S phase. Newly synthesized DNA can be fluorescently labeled and recognized by a high-content cell imaging analyzer to count the number of EdU-positive cells and compare cell proliferation capabilities. As shown in Figure S6, the proliferation level of osteosarcoma cells in the drug treatment group was significantly decreased compared with the control group after MG63 was treated with different concentrations of drugs for 48 h. These results indicate that compound 29 acts on osteosarcoma cells and can attenuate the proliferation of MG63 osteosarcoma cells, and there is a dose-dependent trend.

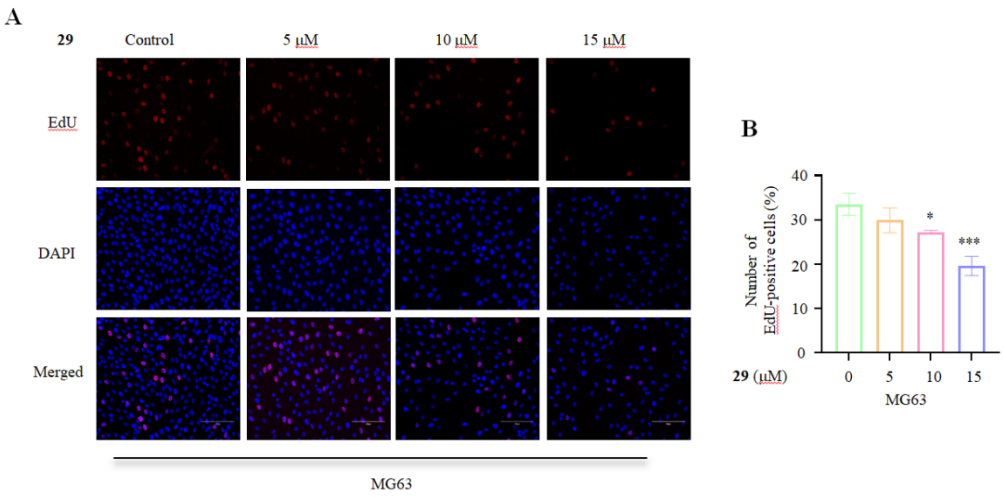


Figure S6 (A) The EdU proliferation assay assays determine the effect of bisindole compound 29 on MG63 osteosarcoma cells. (B) The number of EdU-positive cells was

counted using Image J software. Data were processed with Graphpad Prism 8 software for statistical analysis. *P < 0.05 vs control group，***P < 0.001 vs control group. Replicate the experiment three times independently.

Cloning experiments： Cells were observed to grow and when they were in good condition and at the appropriate density, digest and centrifuge human osteosarcoma cells MG63 seeded in six-well plates with 1000 cells per well, and then transferred to a CO_2 incubator. After the cells were attached, the medium of the control group and the medium of the experimental group were replaced, and compound 29 with different concentration gradients was configured with DMEM complete medium, labeled on the culture plate, and transferred to the CO_2 incubator for culture. Focus on the effect of intraplate cell cloning and stop cloning when a single cell is observed to grow into clumps of cells with approximately 50 cells per clump. Discard the original medium in the plate, add PBS and repeat the wash for 2-3 times, then add the pre-cooled 4% paraformaldehyde solution and fix it for 20 min. Discard the 4% paraformaldehyde in the culture plate, add PBS and repeat the washing for many times, after 2-3 times, add the pre-configured 0.1% crystal violet solution for staining for 20 min, recover the crystal violet solution, and wash it with distilled water for several times until there is no background color. Leave the six-well plate lid open, place in a ventilated place to dry, take photos, count the number of colonies, and perform statistical analysis.

Result analysis: We set up a control group and experiments with different concentrations of compound 29 to treat MG63 in human osteosarcoma cells, and the results showed that biindole compound 29 significantly inhibited the proliferation of human osteosarcoma cells MG63 in a concentration-gradient dependent manner. It can be seen that compound 29 can significantly affect the clonal formation ability of human osteosarcoma cells.

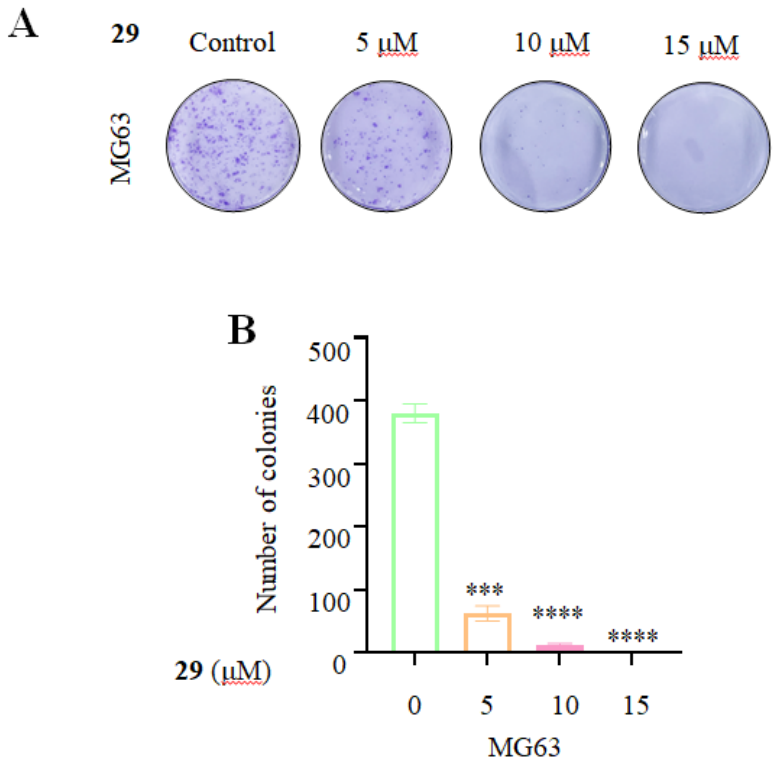


Figure S7 (A) Effect of bisindole compound 29 on MG63 clonal formation in human osteosarcoma cells. (B)The number of cloned colonies was counted by Image J software. Data were processed with Graphpad Prism 8 software for statistical analysis. ****P < 0.0001 vs control group. Replicate the experiment three times independently.

Cell cycle arresting effect on human osteosarcoma cells MG63: Cultures in 6-well plates allow the number of human osteosarcoma MG63 cells to reach 50% post-adherent overnight. The next day, different concentration gradients were added for drug treatment, the drug concentration was marked on a six-well plate, and the drug was transferred to an incubator for 48 h. After that, the complete medium in each well was collected, placed in a 15 mL centrifuge tube, PBS was added to the medium, the residues of adherent cell metabolism in the wells were washed, trypsin was added, and

after digestion for about 2 minutes, the complete medium corresponding to each well that had just been collected was added to abort the digestion process. Gently blow off the cells and collect them into a pre-prepared 15 mL centrifuge tube. The centrifugation speed was 1000 rpm and the centrifugation time was 5 min. After centrifugation, aspirate and supernatant, add 1 mL of pre-cooled PBS to each 15 mL tube, resuspend the cells in the tube, and centrifuge at 1000 rpm for 5 minutes. Once centrifugation is complete again, aspirate the supernatant and flick the bottom of the centrifuge tube to avoid clumping of cells. Add 1 mL of previously pre-chilled PBS and resuspend the cells. Take a new 5 mL tube, add 3 mL of pre-chilled absolute ethanol, slowly drop 1 mL of pre-chilled PBS containing resuspended cells into a 5 mL centrifuge tube, and mix gently to form 75% ethanol-fixed cells. Fix at 4 °C for 24 h. Cells were fixed for 24 h and then centrifuged at 1000 rpm for 5 min. Discard 75% ethanol, add 1 mL PBS to a 5 mL centrifuge tube, resuspend the fixed cells, place the tube into a centrifuge and centrifuge, and discard the supernatant. After the above steps are completed, you only need to follow the instructions of the kit, and the required reagents should be configured according to the ratio of staining buffer: propidium iodide staining solution (20 ×): RNase A (50 ×) = 500:25:10, and 500 μL of the configured working solution should be added to each group of samples to resuspend the cells. At 37°C, protect from light for 30 min. Flow cytometry detection was performed on the machine.

Result analysis: Flow cytometry was used to analyze and detect the cycle changes of MG63 cells treated with compound 29, and the control group was set up. The experimental results showed that with the increase of the administration concentration, the number of cells in the G1 phase of MG63 cells gradually increased, and the number of cells in the S phase and G2/M phase gradually decreased compared with the negative control group. This indicates that bisindole compound 29 mainly inhibits the proliferation of MG63 in human osteosarcoma cells by blocking the G1 phase of human osteosarcoma cells.

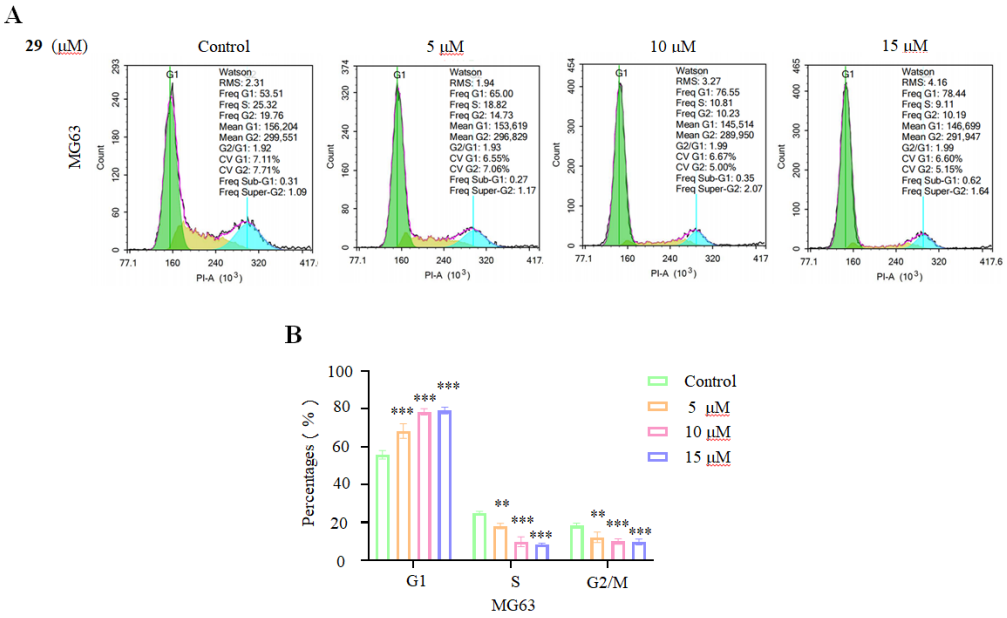


Figure S8 (A) Flow cytometry was used to detect the effect of bisindole compound 29 on the cell cycle of MG63 cells in human osteosarcoma cells. (B) Data were processed with Graphpad Prism 8 software for statistical analysis. **P < 0.01 vs control group，****P < 0.0001 vs control group. Replicate the experiment three times independently.

Wound healing experiments： When the cells are adherent and the growth confluence is high enough, use a 10 μL tip to make a "cross" at the bottom of the plate along the diameter of the 6-well plate. After all the scratches were successful, the supernatant was discarded, the cells that were detached by the scratches were washed with PBS, 2 mL of serum-free medium and serum-free medium containing different concentrations of drug 29 were added, and photos of each well were taken for 0 h and 24 h using an inverted microscope.

Result analysis: In human osteosarcoma MG63 cells, the migration rate after treatment with bisindole compound 29 was significantly lower than that of the control group, and showed a dose-dependent trend. This indicates that compound 29 has an inhibitory effect on human osteosarcoma cell migration.

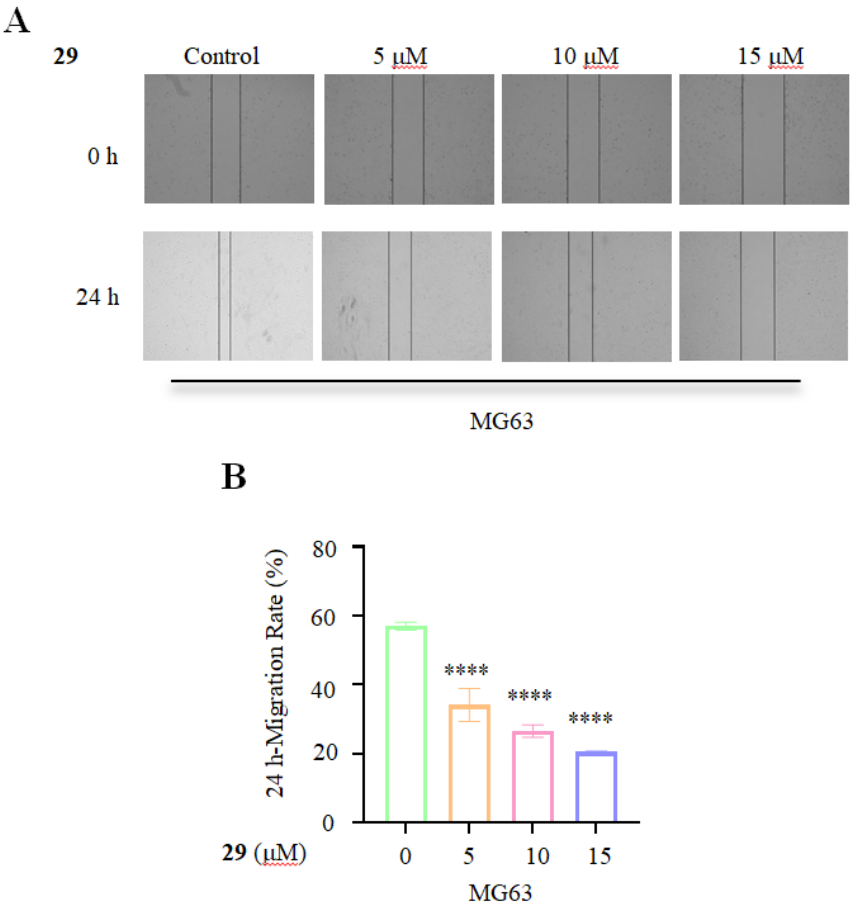


Figure S9 (A) Effect of bisindole compound 29 on MG63 cell migration in human osteosarcoma cells. (B)The migration rate was statistically performed with Image J software. Data were processed with Graphpad Prism 8 software for statistical analysis. ****P < 0.0001 vs control group. Replicate the experiment three times independently.

Inhibits the migration and invasion of human osteosarcoma cells MG63: Tumor cell migration assays are a commonly used method by seeding tumor cells in the upper chamber and adding complete medium with high fetal bovine serum content to the lower chamber. Under such conditions, tumor cells naturally migrate to the lower chamber with high serum concentration, that is, rich in nutrients, so the number of cells entering the lower chamber can be reflected by microscopic observation and statistics. Similarly, cell invasion assays are an important method, similar to cell migration assays, but with the exception that the upper chamber needs to be coated with a layer of Matrigel (Matrigel is diluted 1:8 with PBS), which mimics the extracellular matrix in

vivo. Therefore, in order for cells to enter the lower chamber, they must first secrete matrix metalloproteinases (MMPs) to degrade Matrigel, which is a prerequisite. Subsequently, the number of cells entering the lower chamber is counted under the microscope, which can be used to reflect the invasion ability of tumor cells.

Result analysis: As the concentration of drug 29 increases, the number of migrating and invading cells is greatly reduced and is dose-dependent. This indicates that drug 29 has an inhibitory effect on the migration and invasion of human osteosarcoma cells.

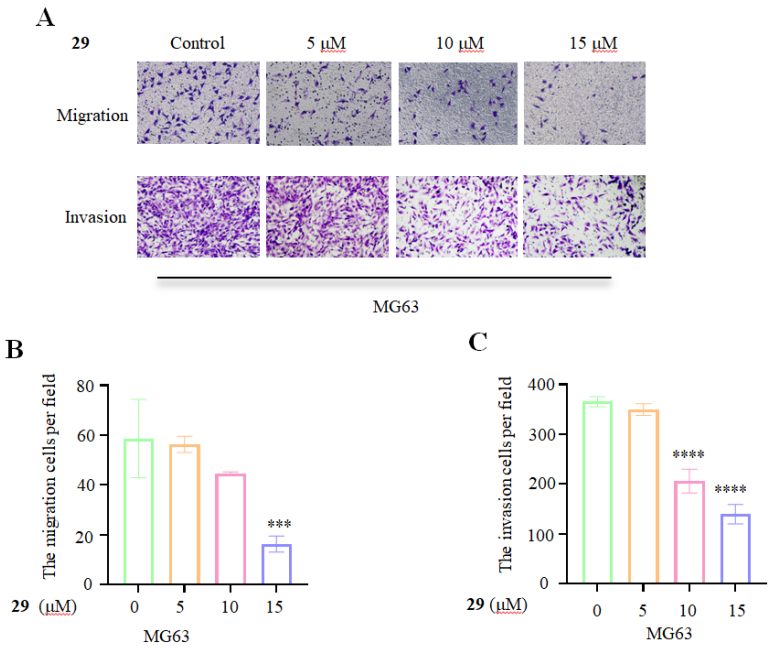
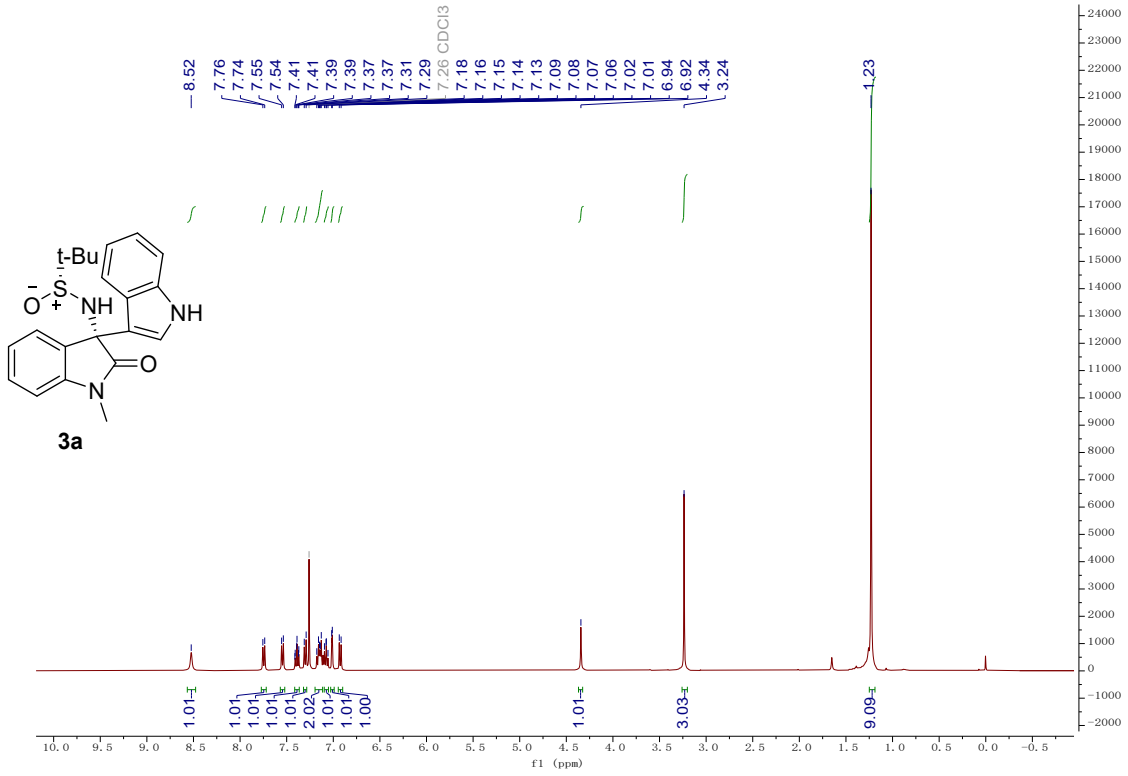


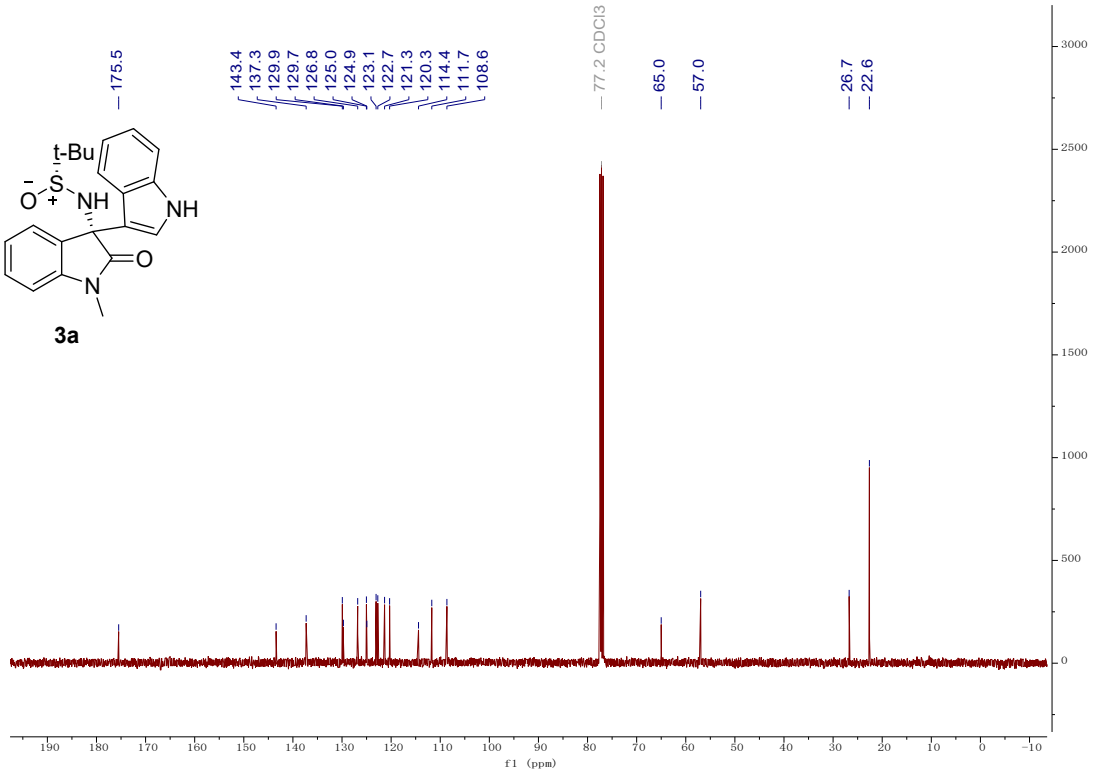
Figure S10 (A) Effect of bisindole compound 29 on the migration and invasion of human osteosarcoma cells MG63 cells. (B-C) Image J software was used to count the number of migrating and invading cells. Data were processed with Graphpad Prism 8 software for statistical analysis. **P < 0.01 vs control group，****P < 0.0001 vs control group. Replicate the experiment three times independently.

Statistical analysis: All experimental data were analyzed using GraphPad Prism 8 software and SPSS Statistics 26.0 software. Unpaired Student's t-tests were used for comparisons between two groups, and one-way ANOVA was employed for statistical evaluation among multiple groups. The results are presented as mean ± standard error of the mean (SEM). *P < 0.05, **P < 0.01, ***P < 0.001.

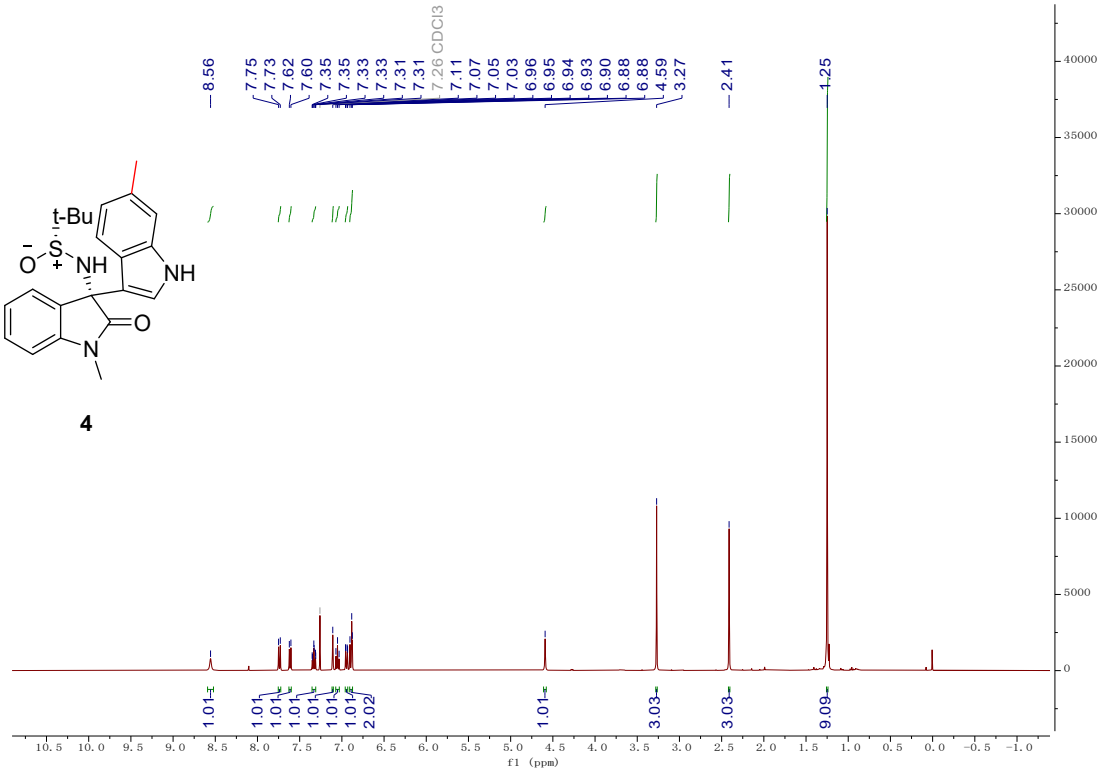
IX Copies of NMR spectra



^{1}H NMR spectrum of compound **3a**



^{13}C NMR spectrum of compound **3a**



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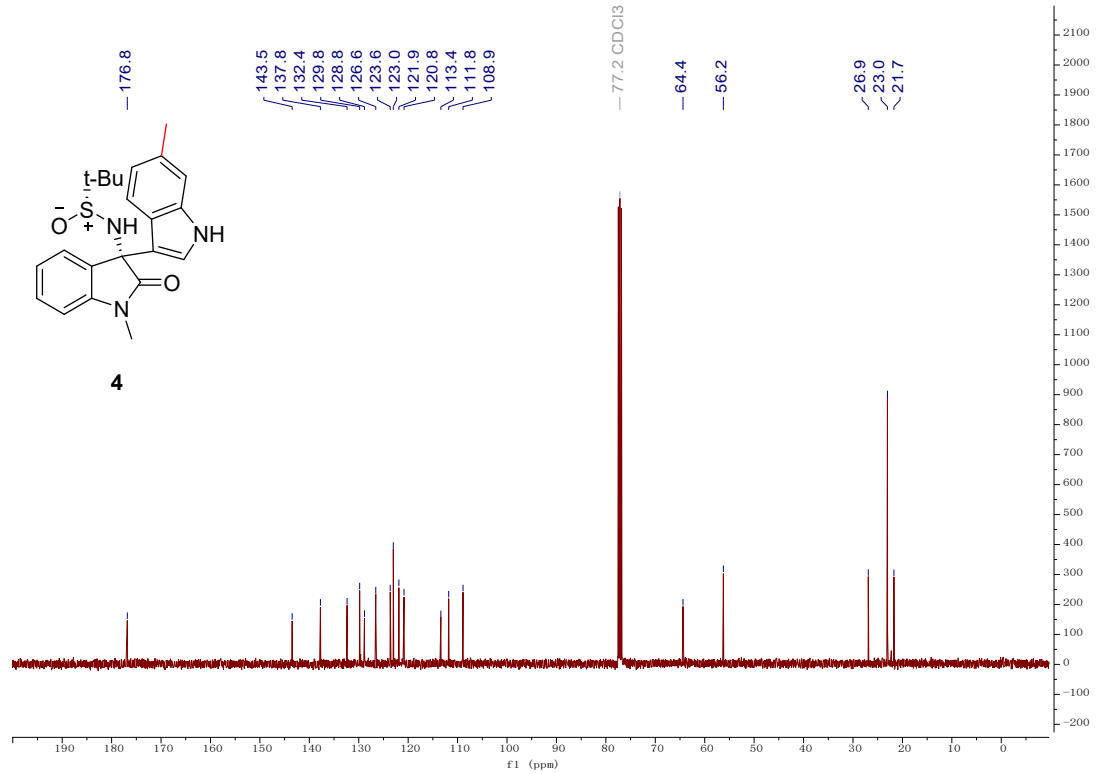

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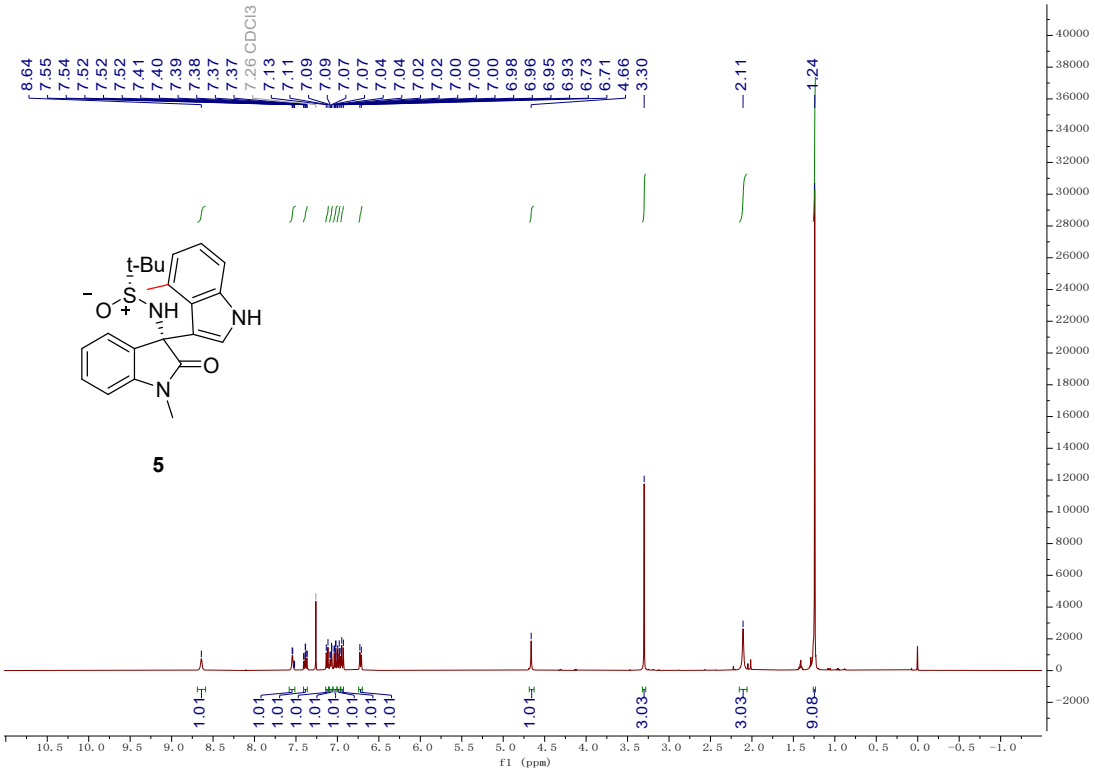

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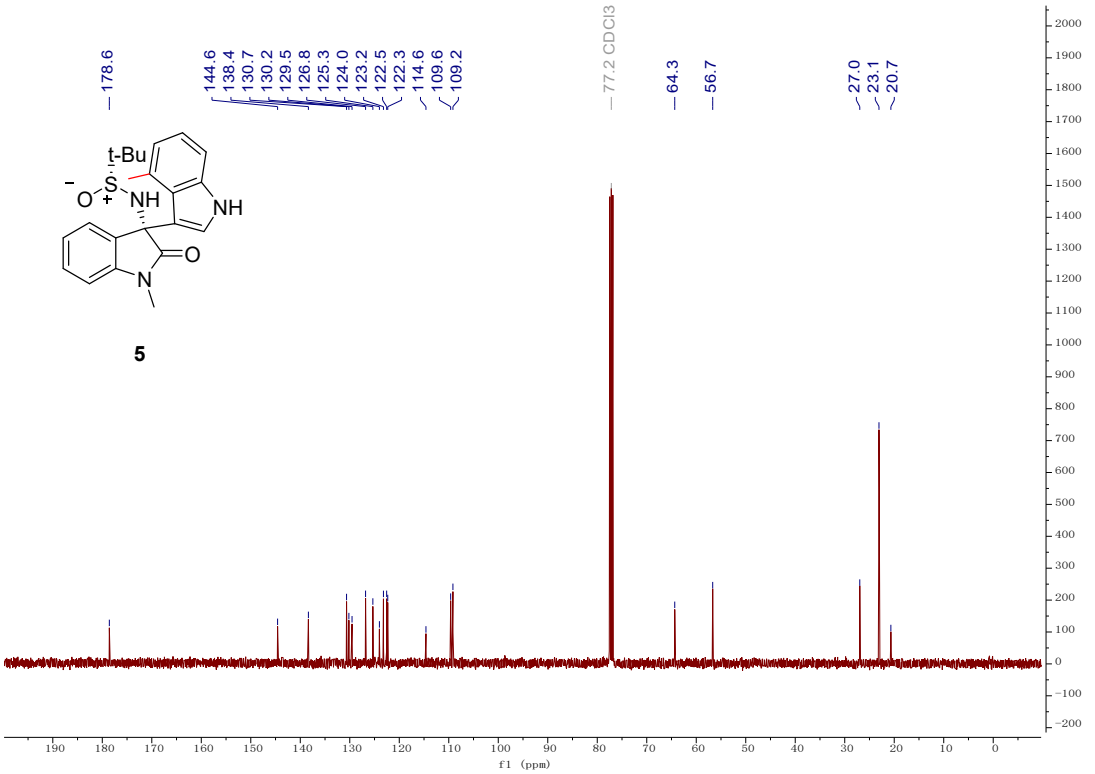
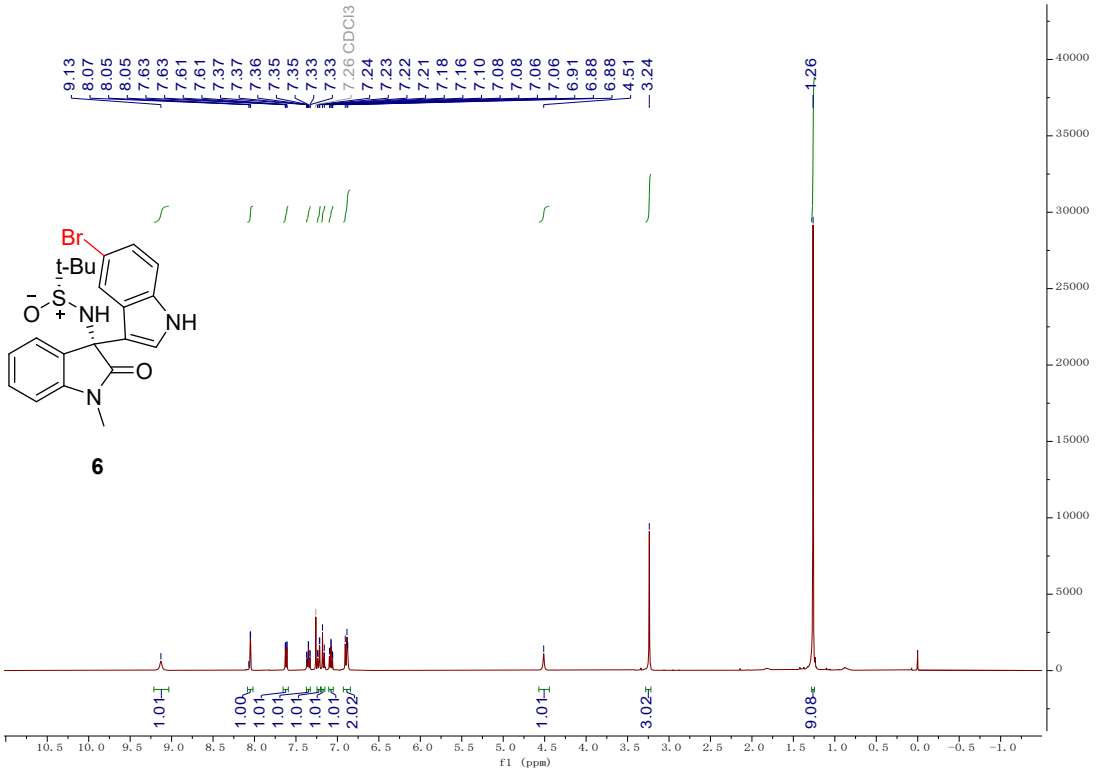


^{13}C NMR spectrum of compound 5



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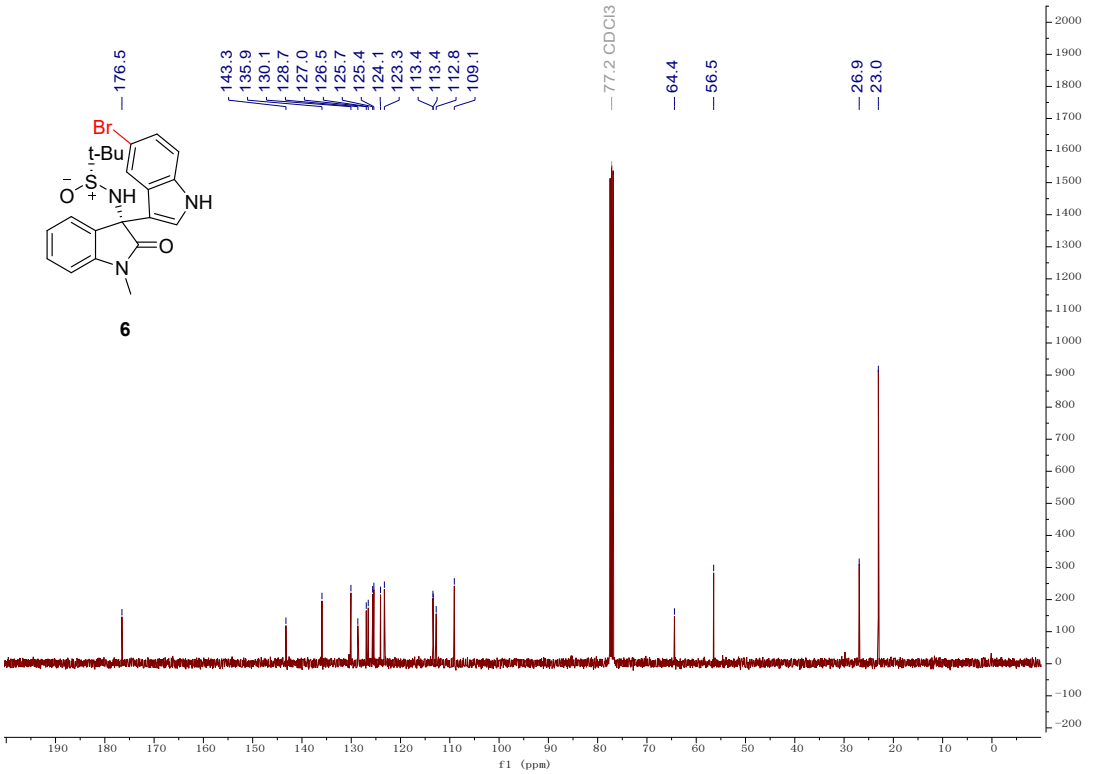

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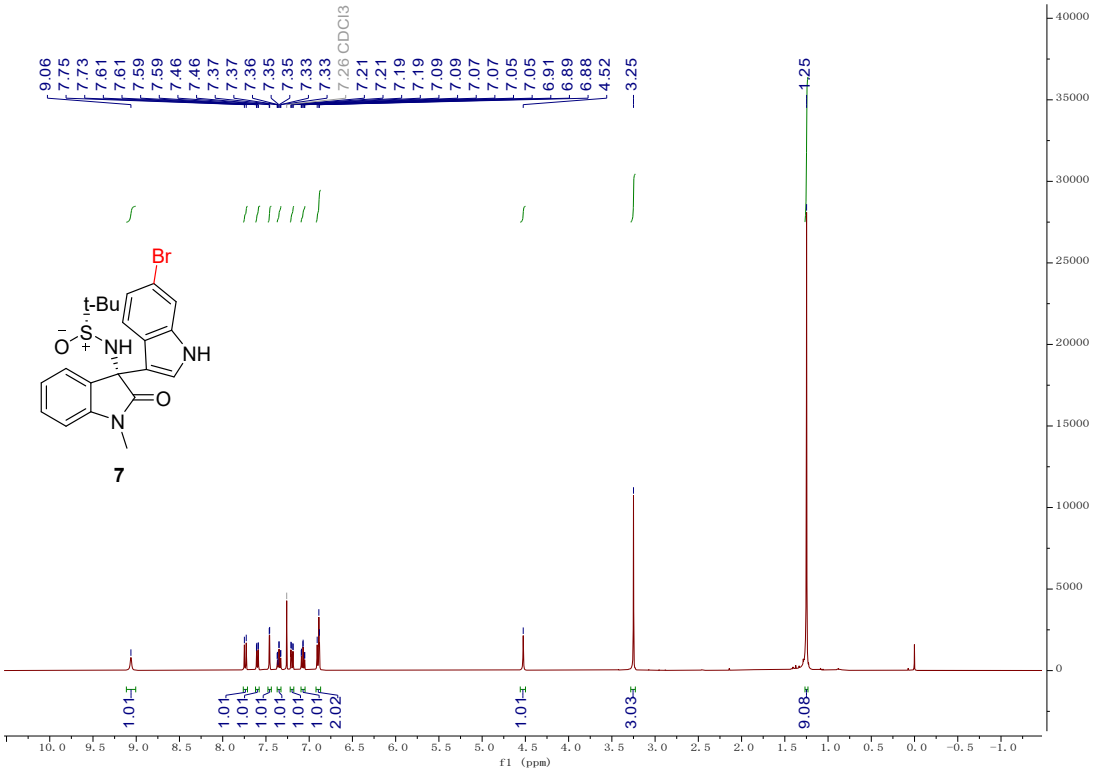

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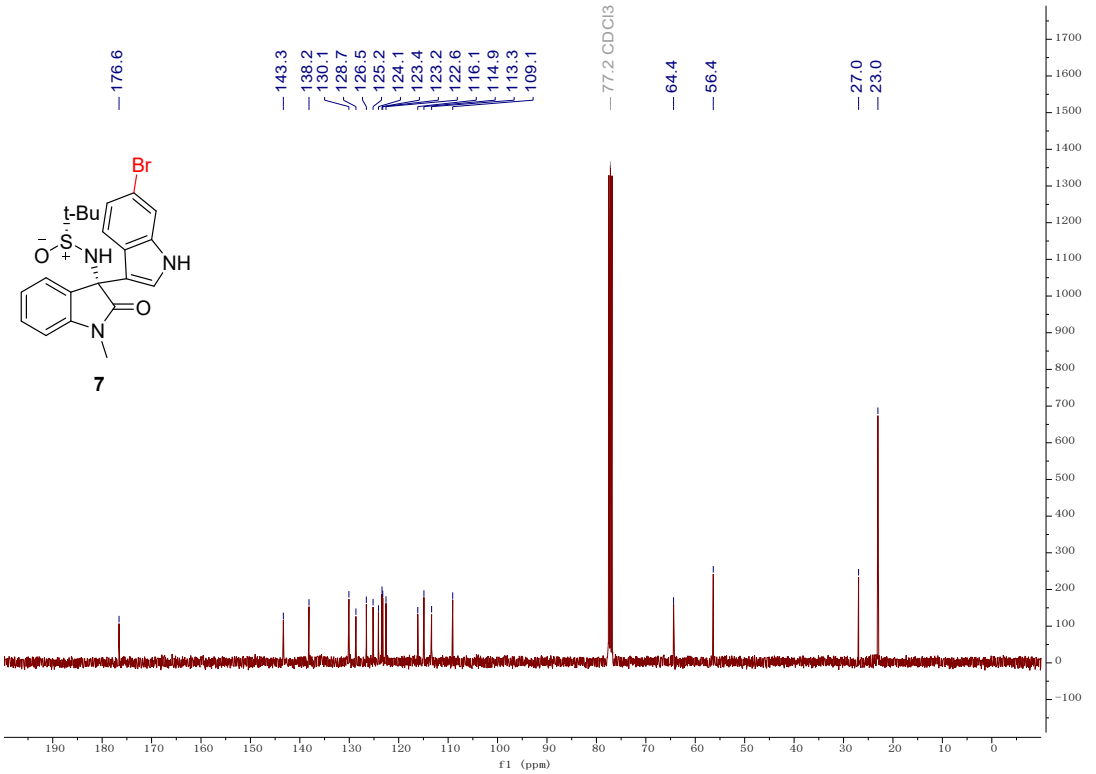

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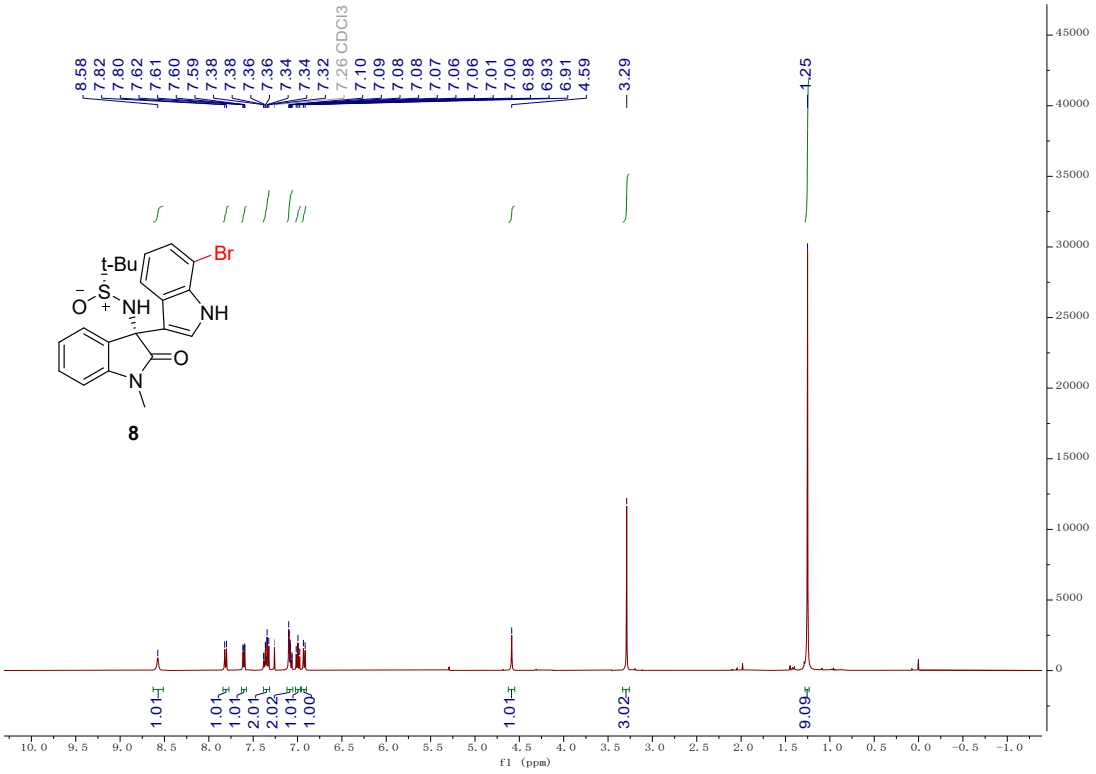

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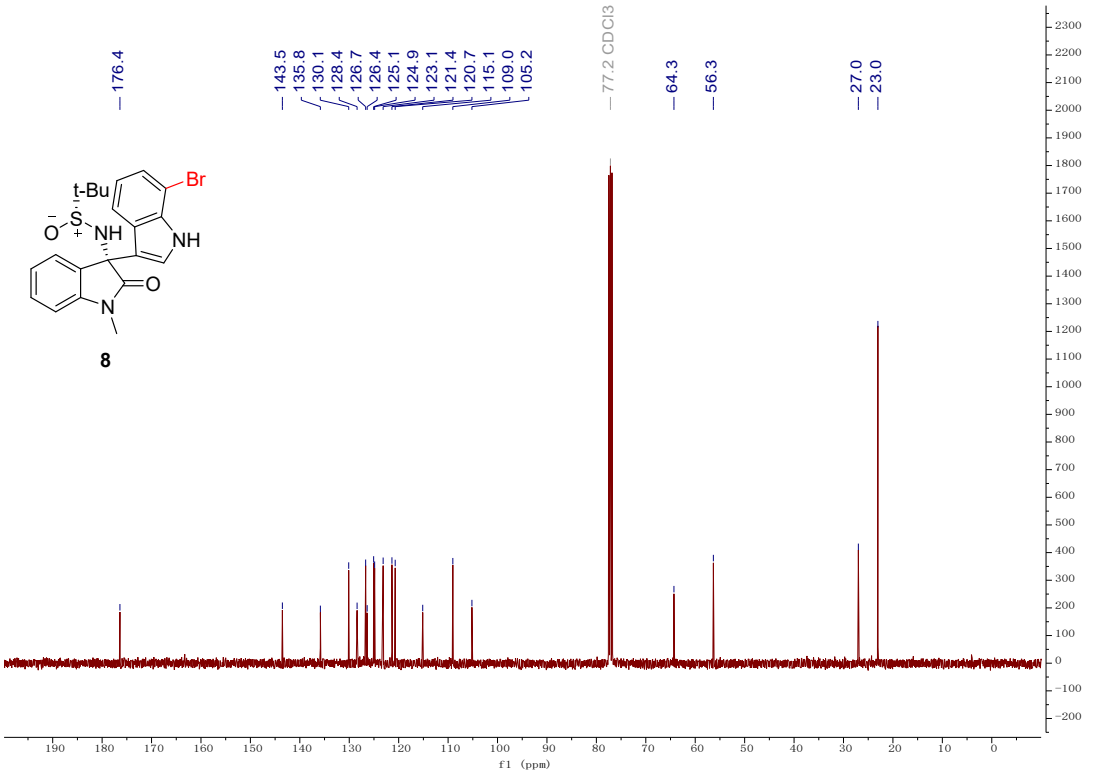

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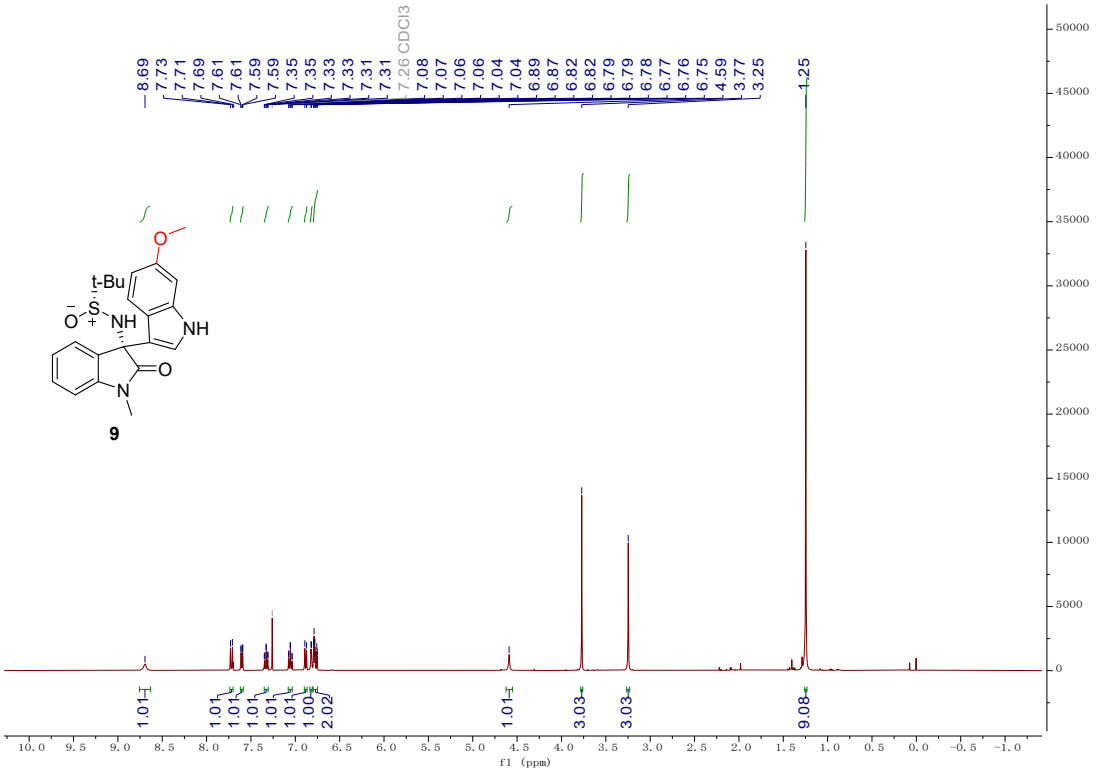

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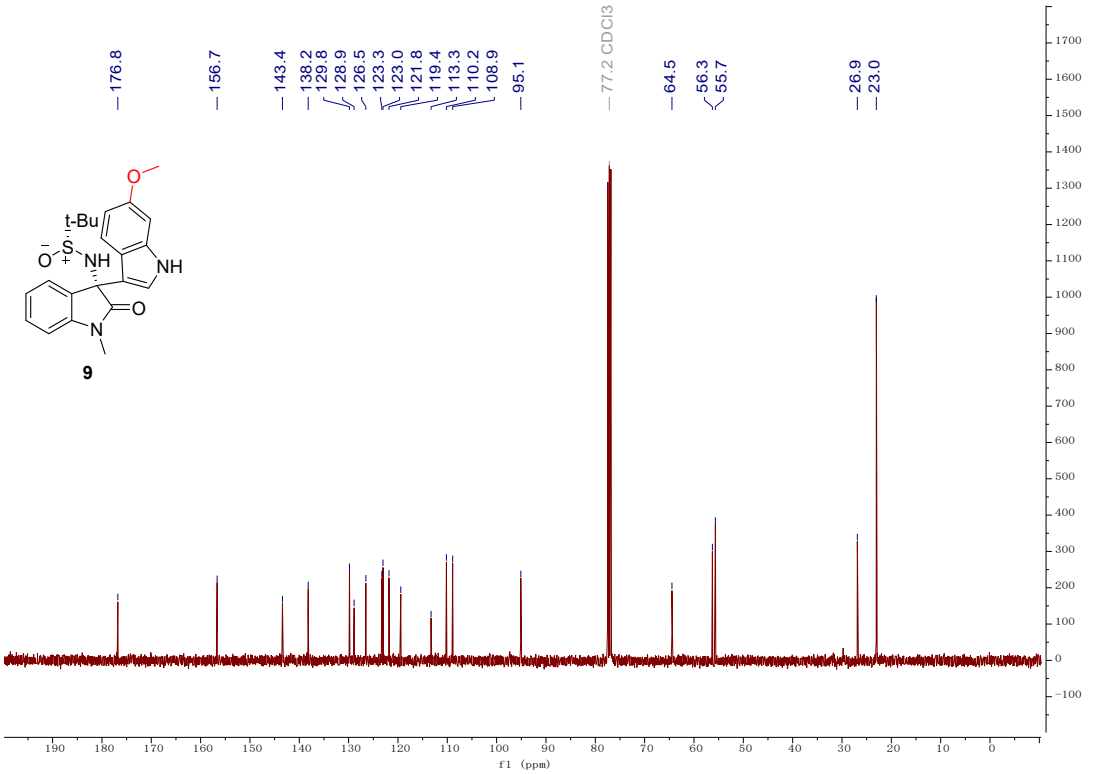

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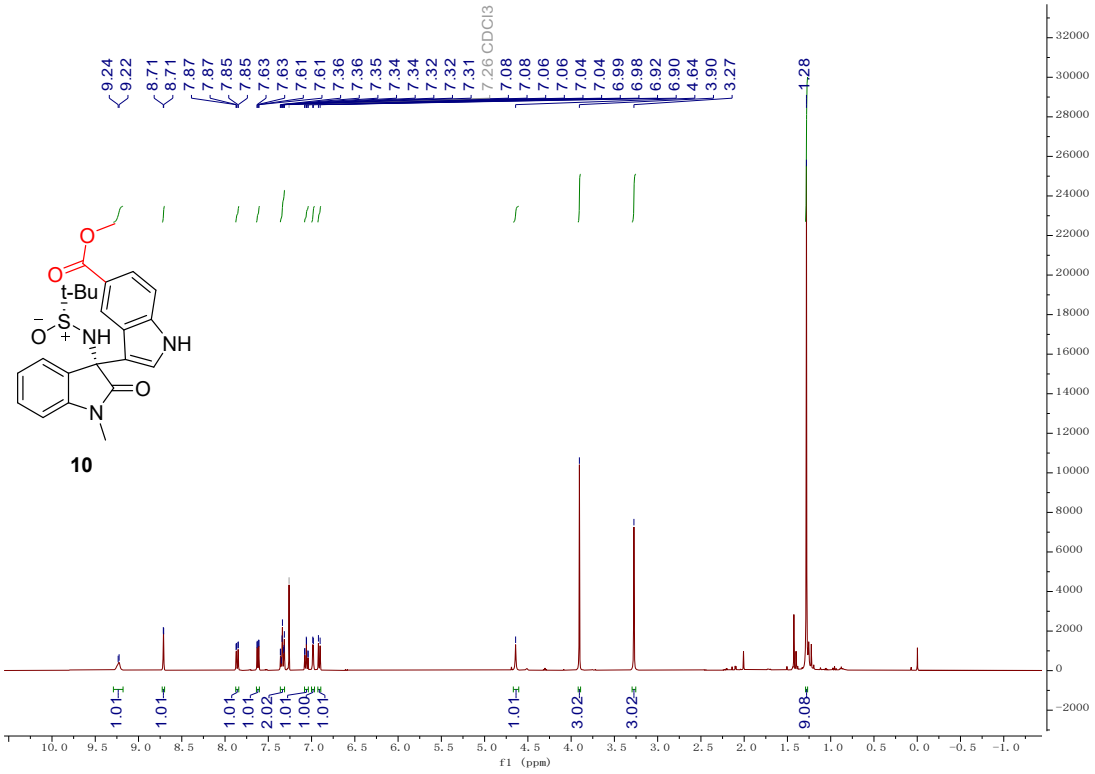

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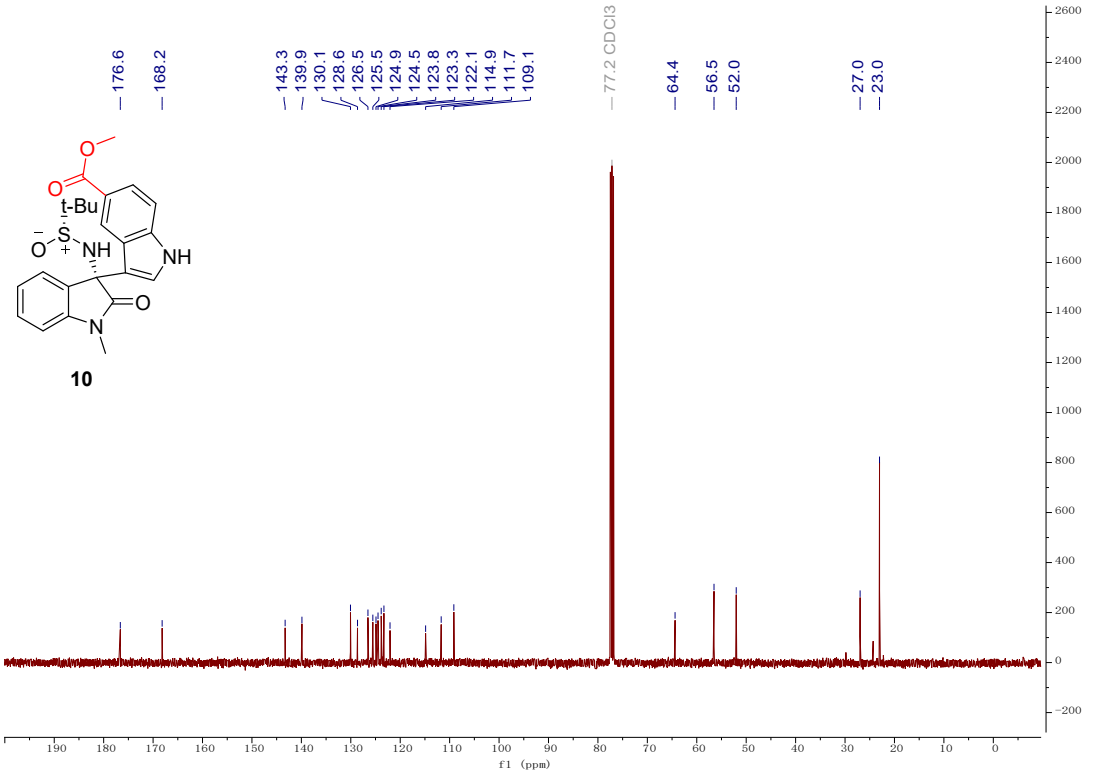

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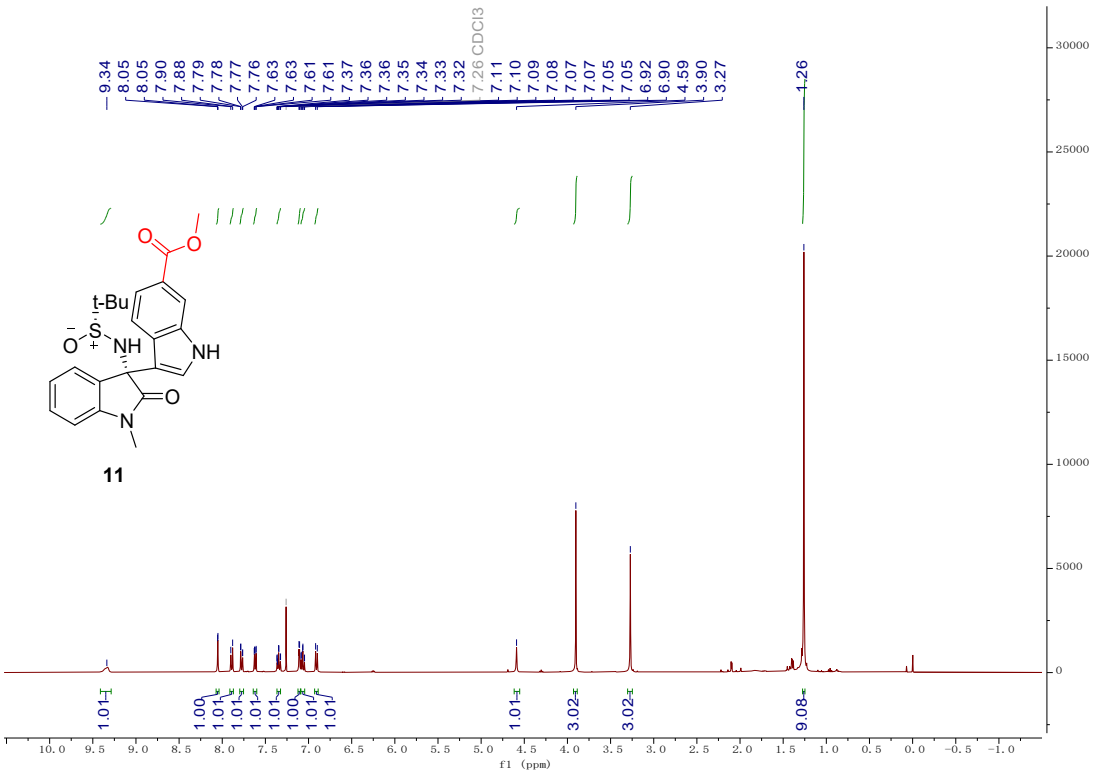

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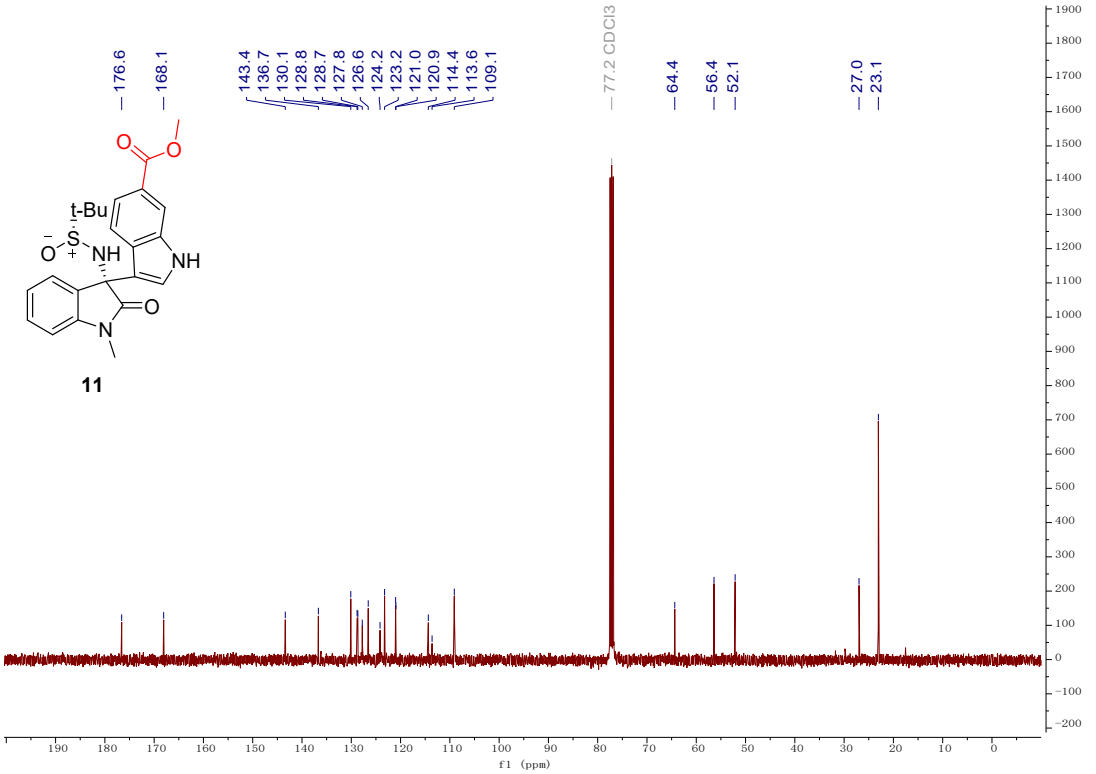

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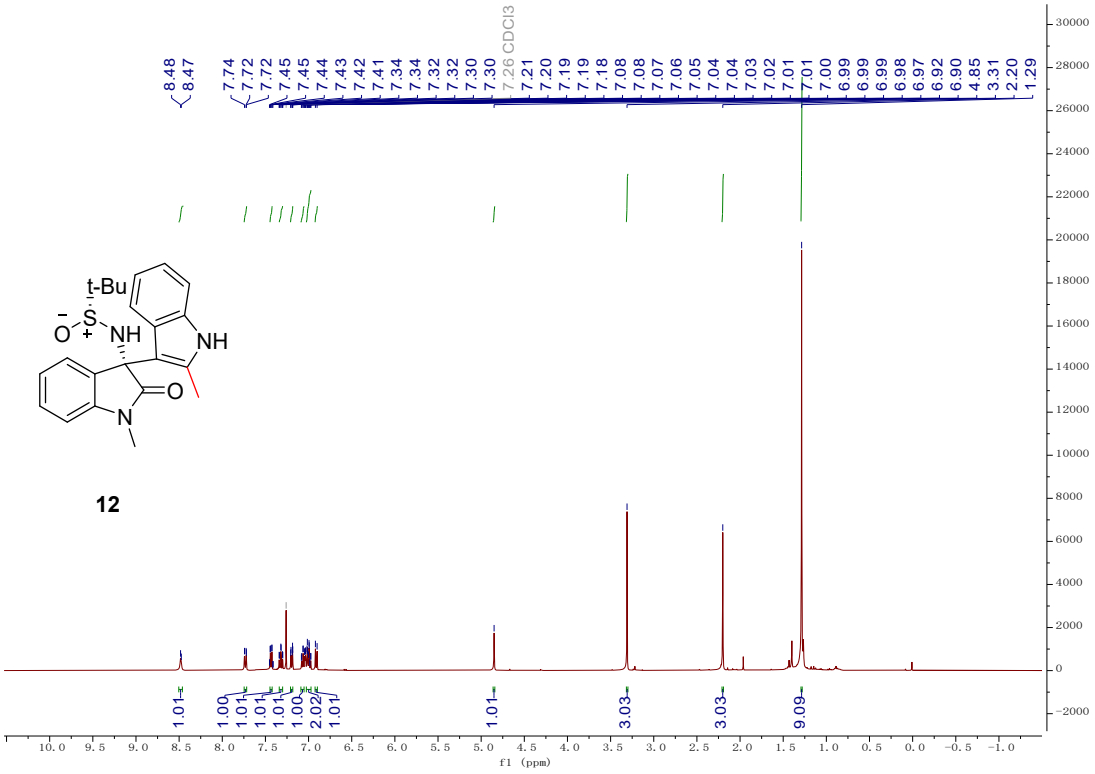

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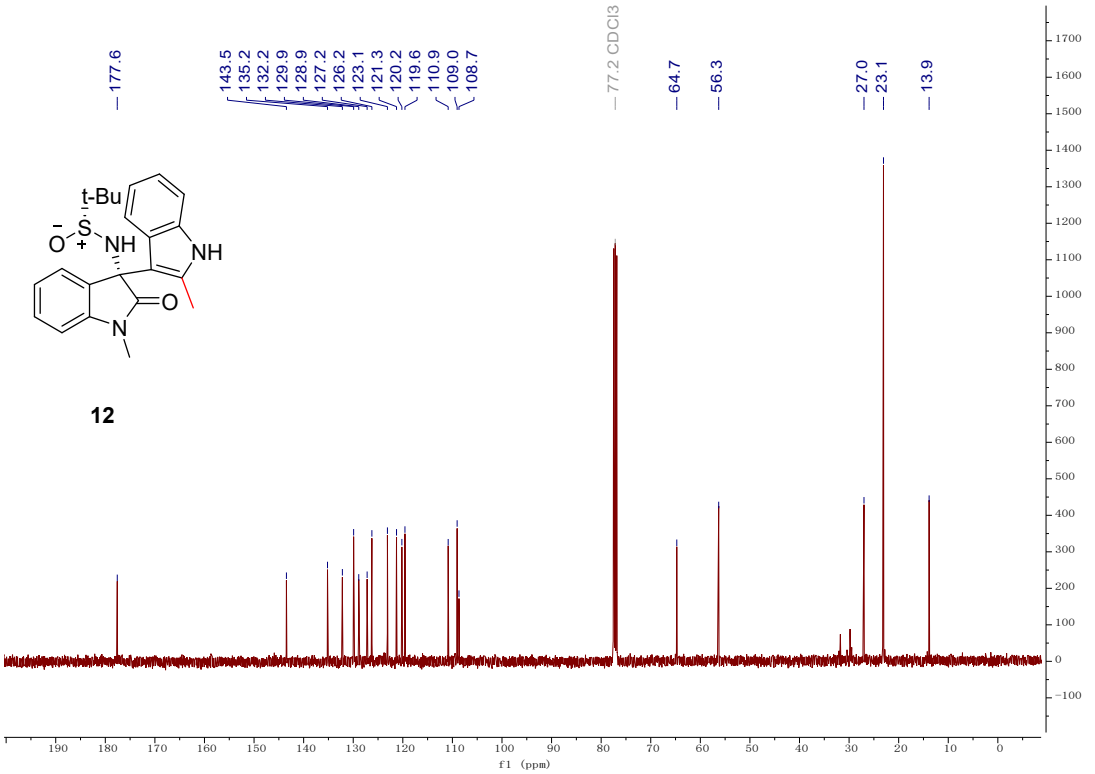

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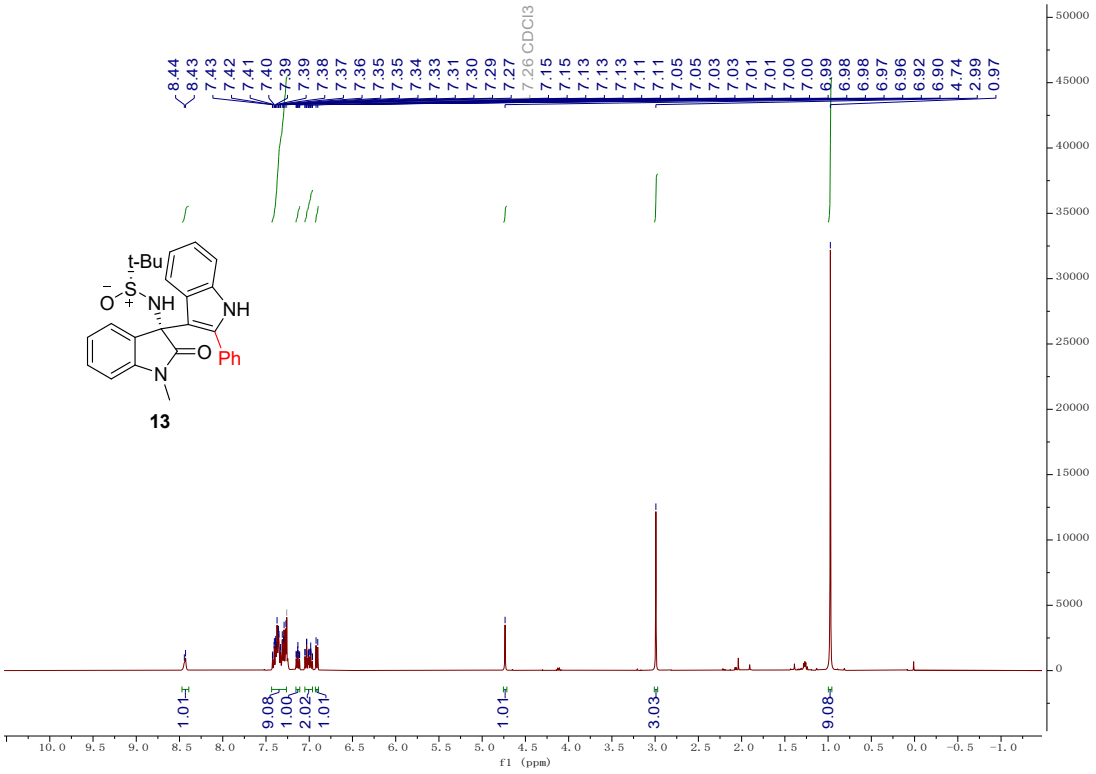

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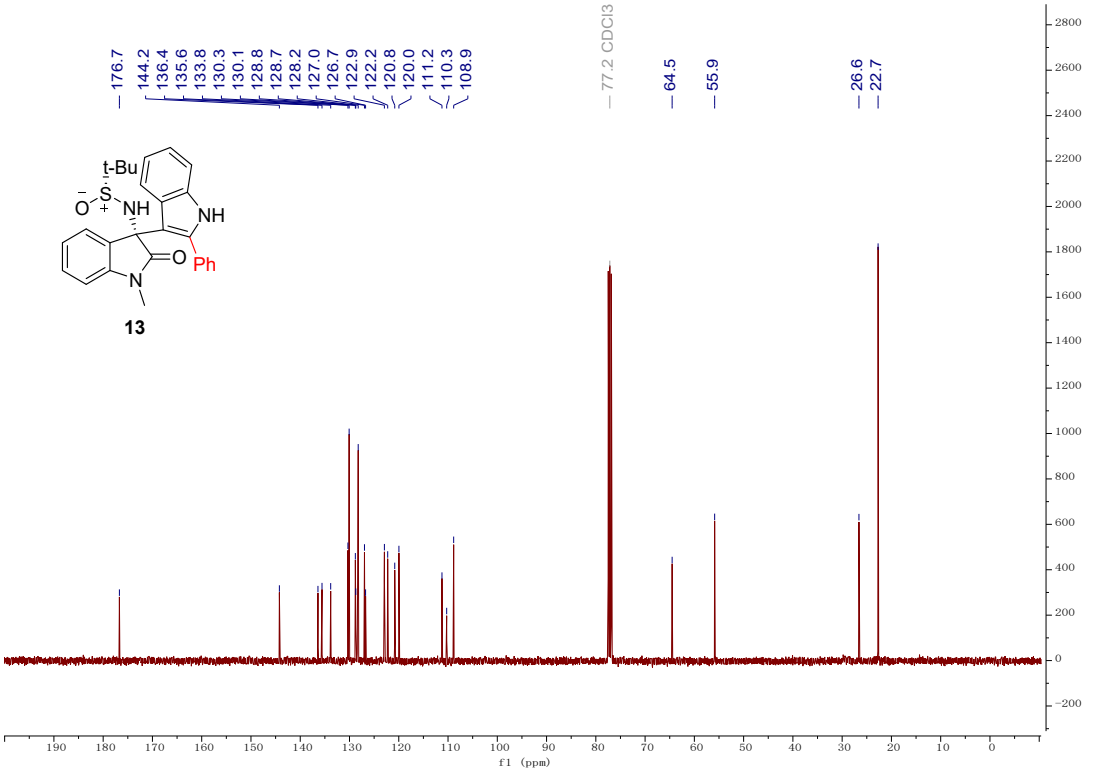

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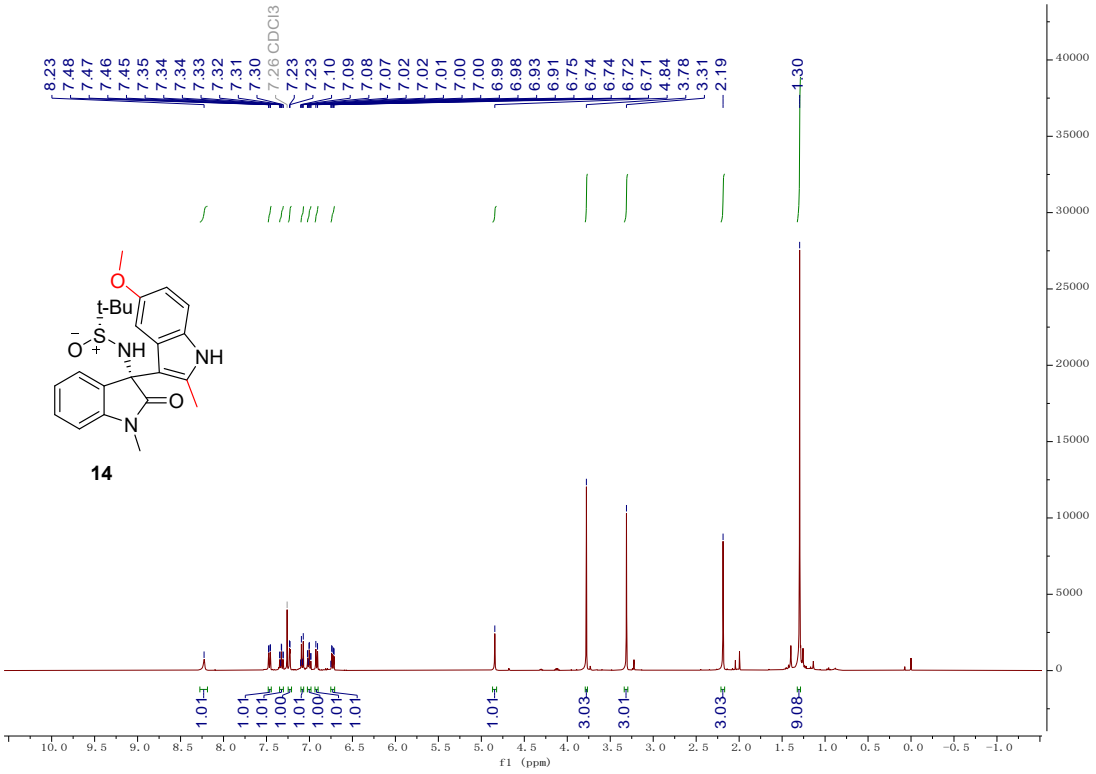

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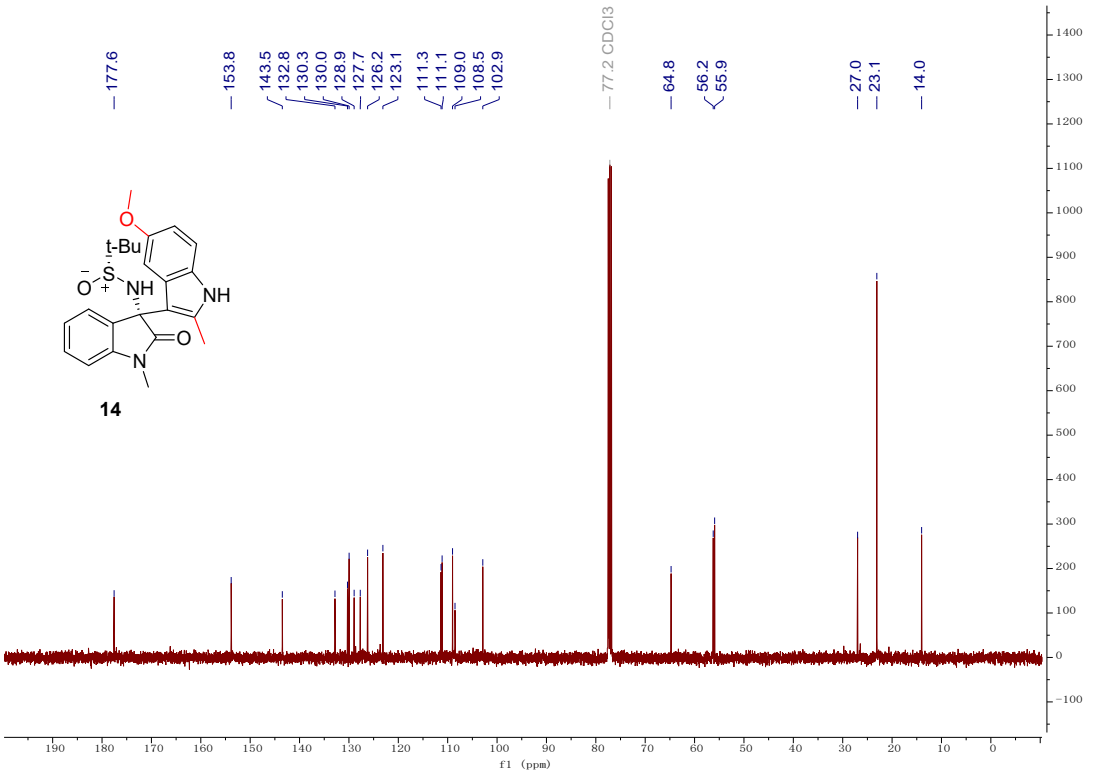

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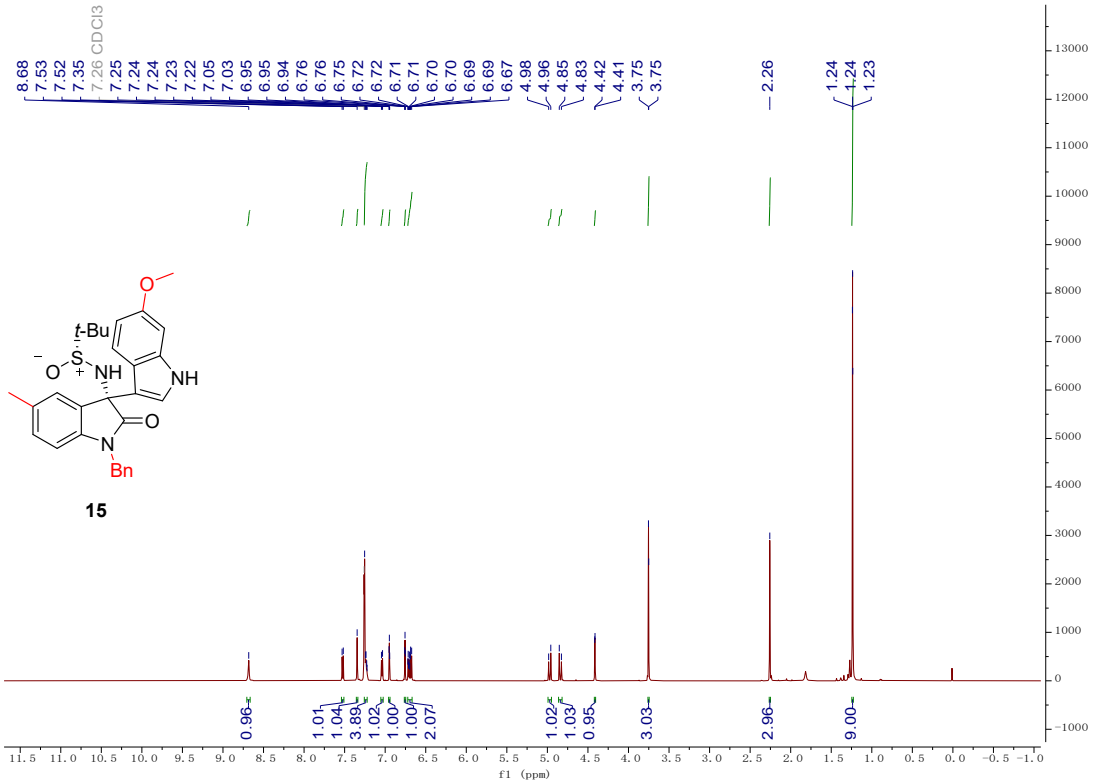

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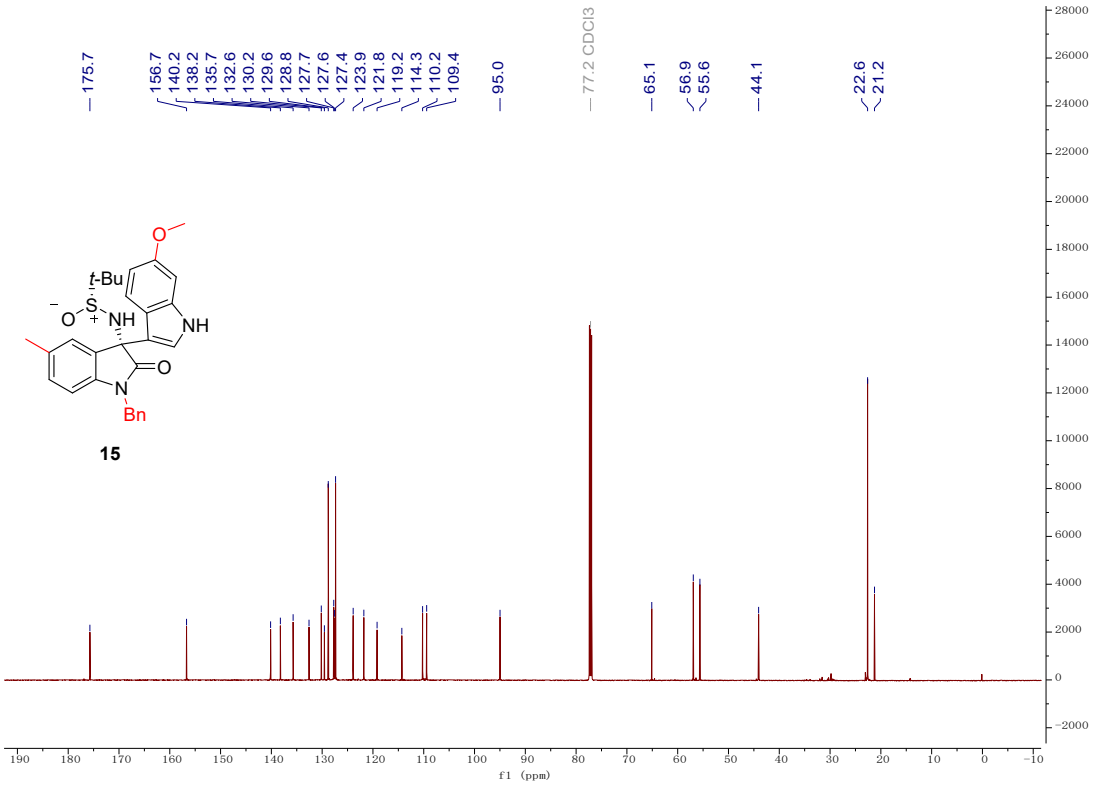
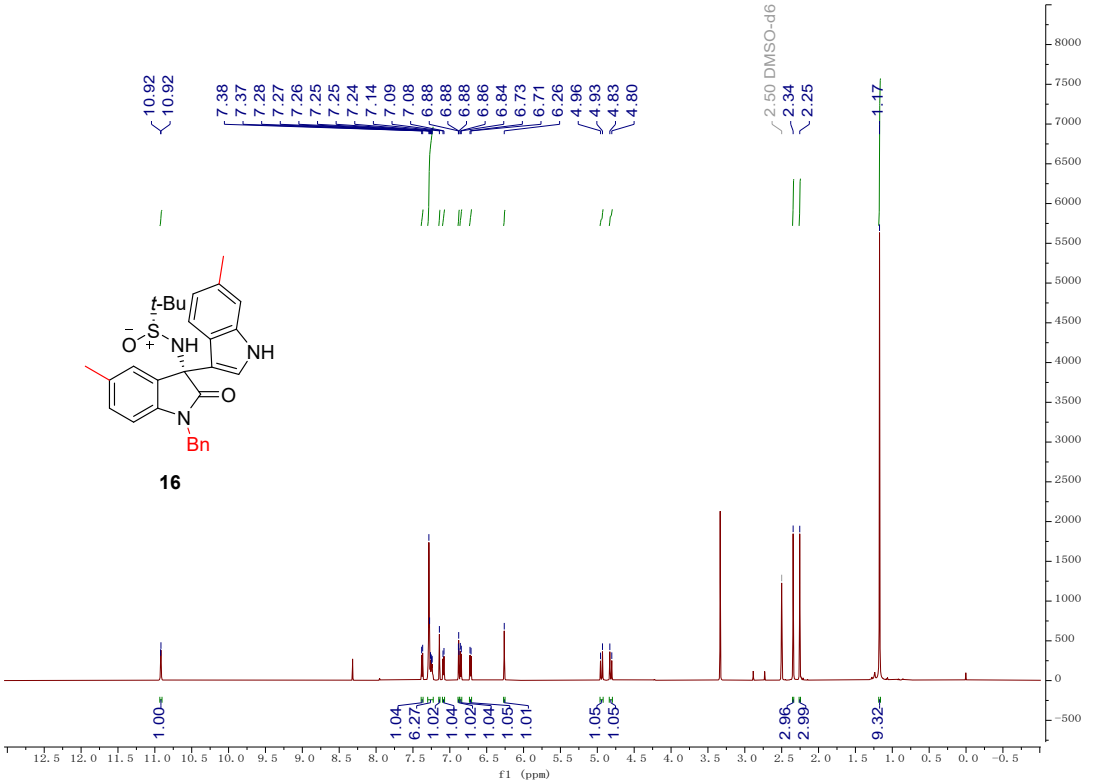
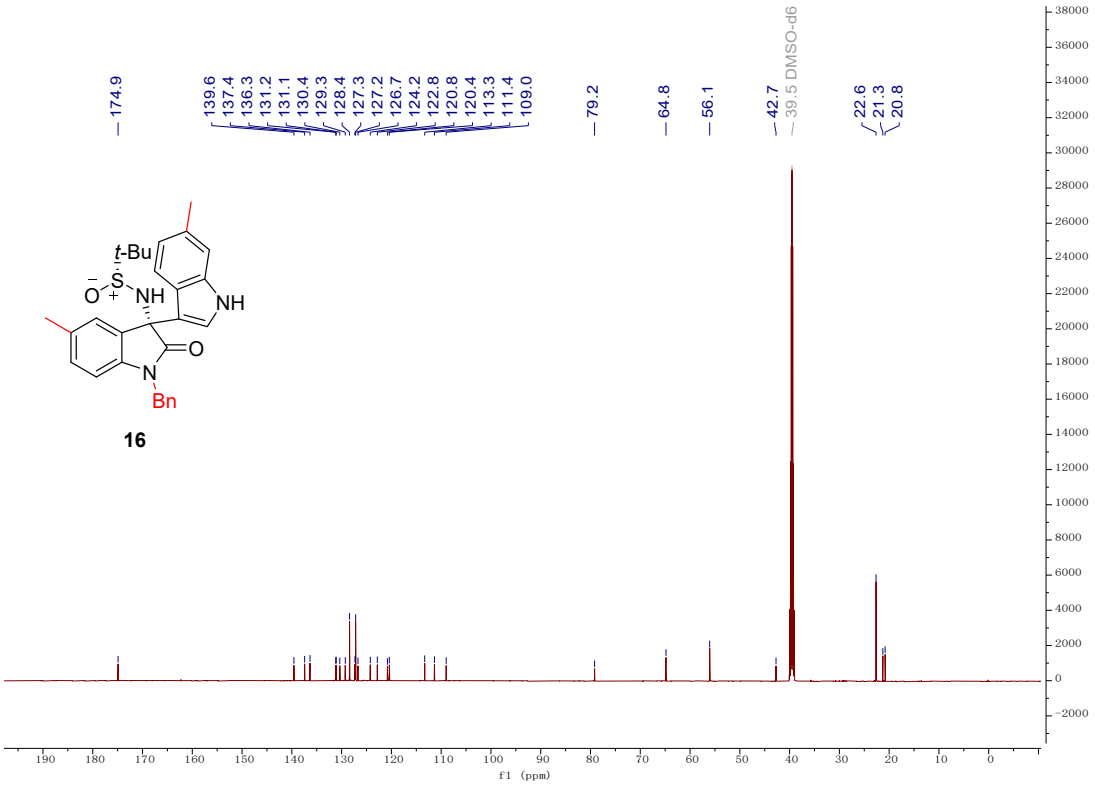


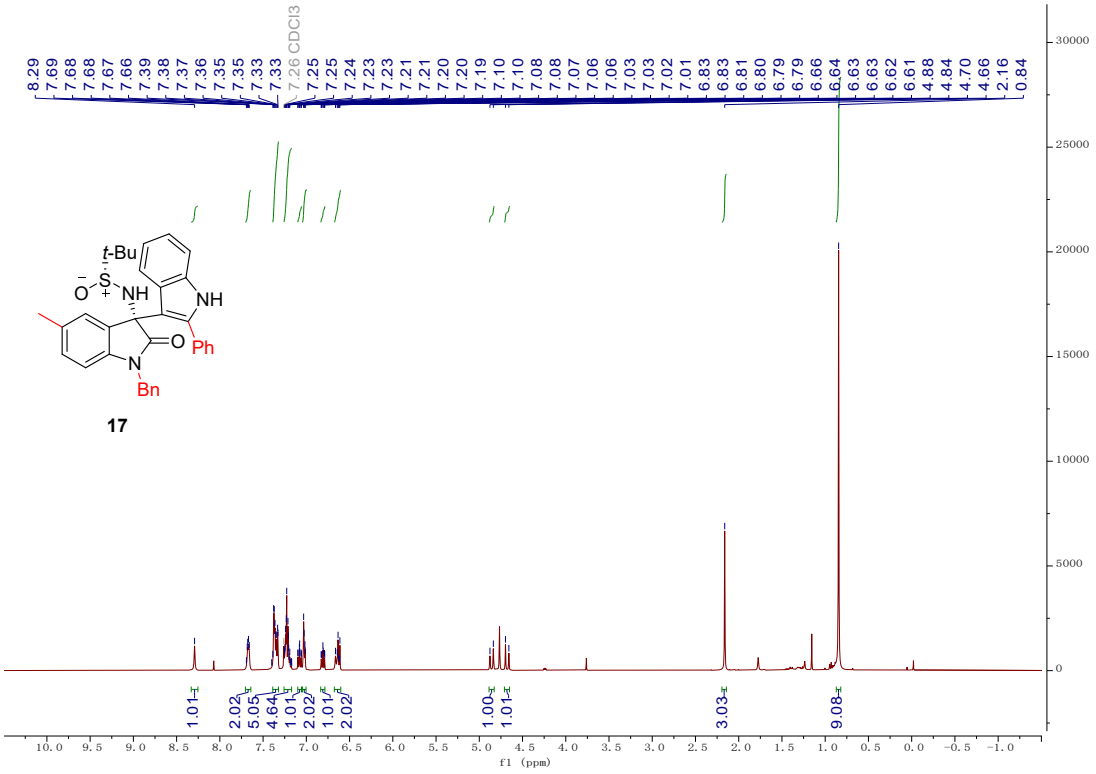
^{13}C NMR spectrum of compound **15**



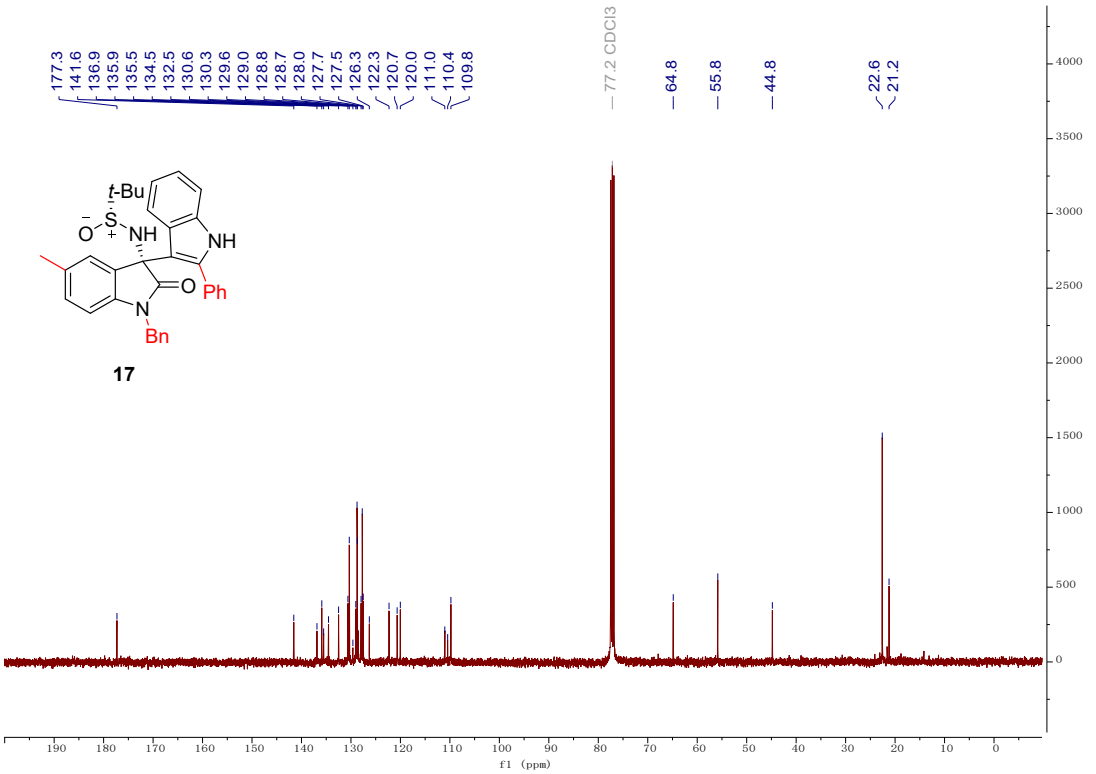
^{1}H NMR spectrum of compound **16**



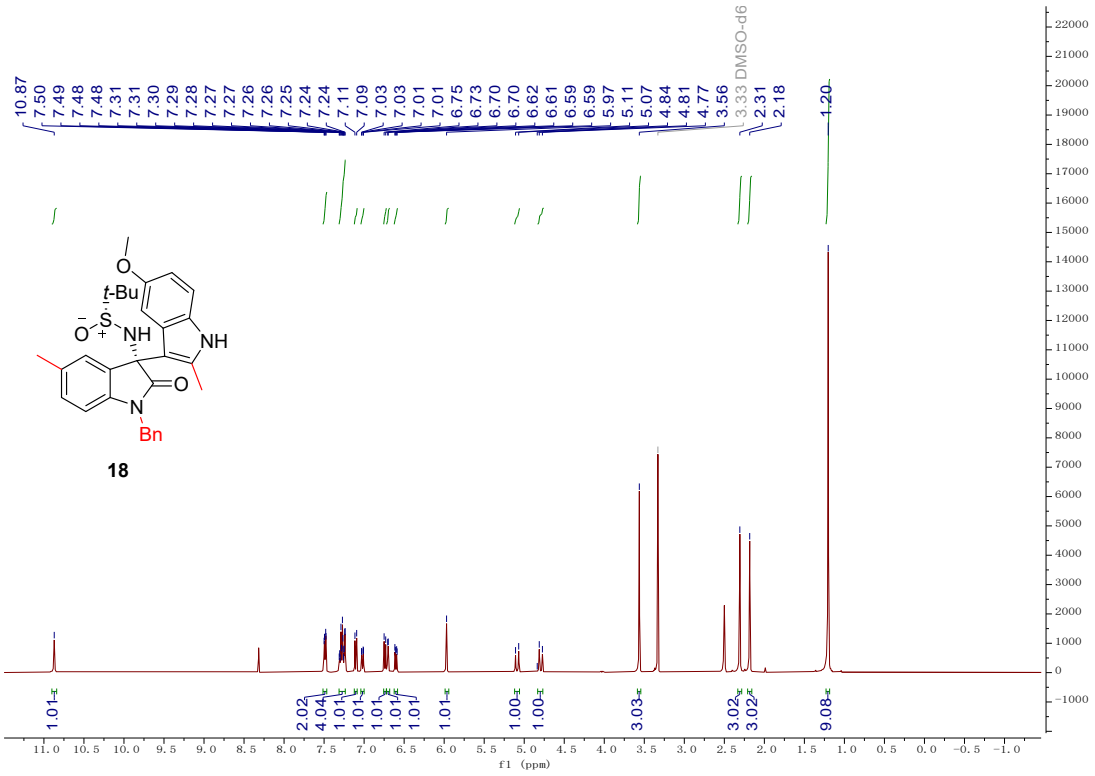
^{13}C NMR spectrum of compound **16**



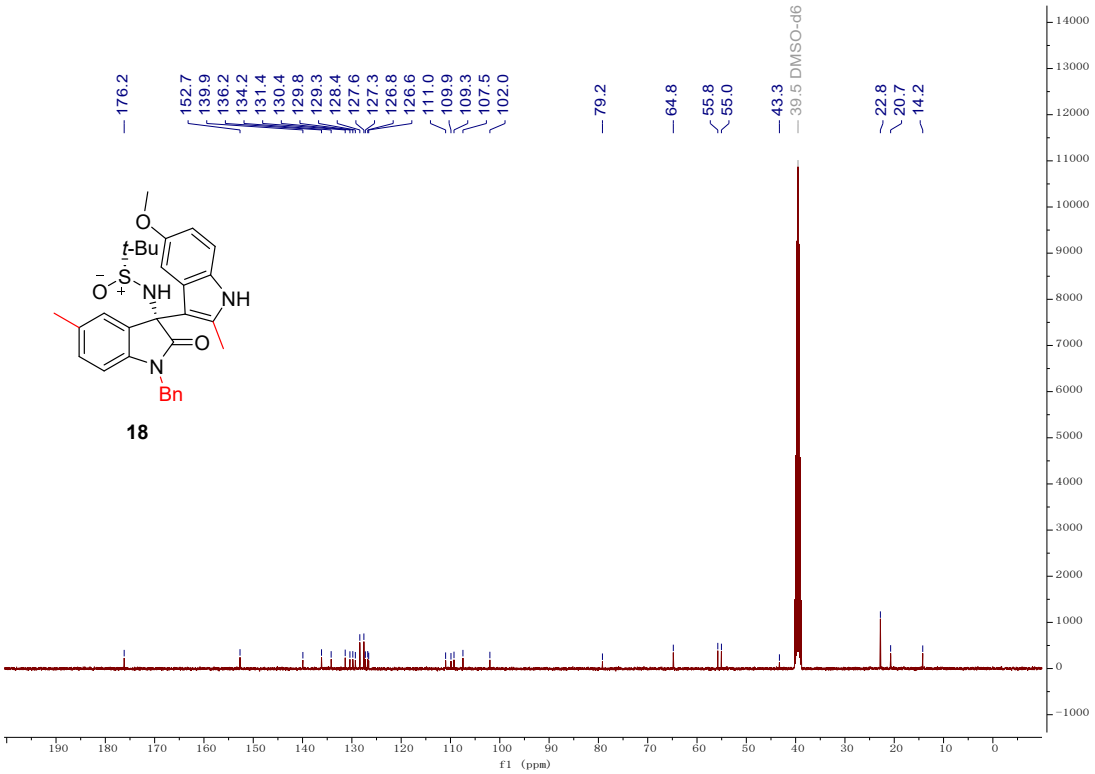
^{1}H NMR spectrum of compound **17**



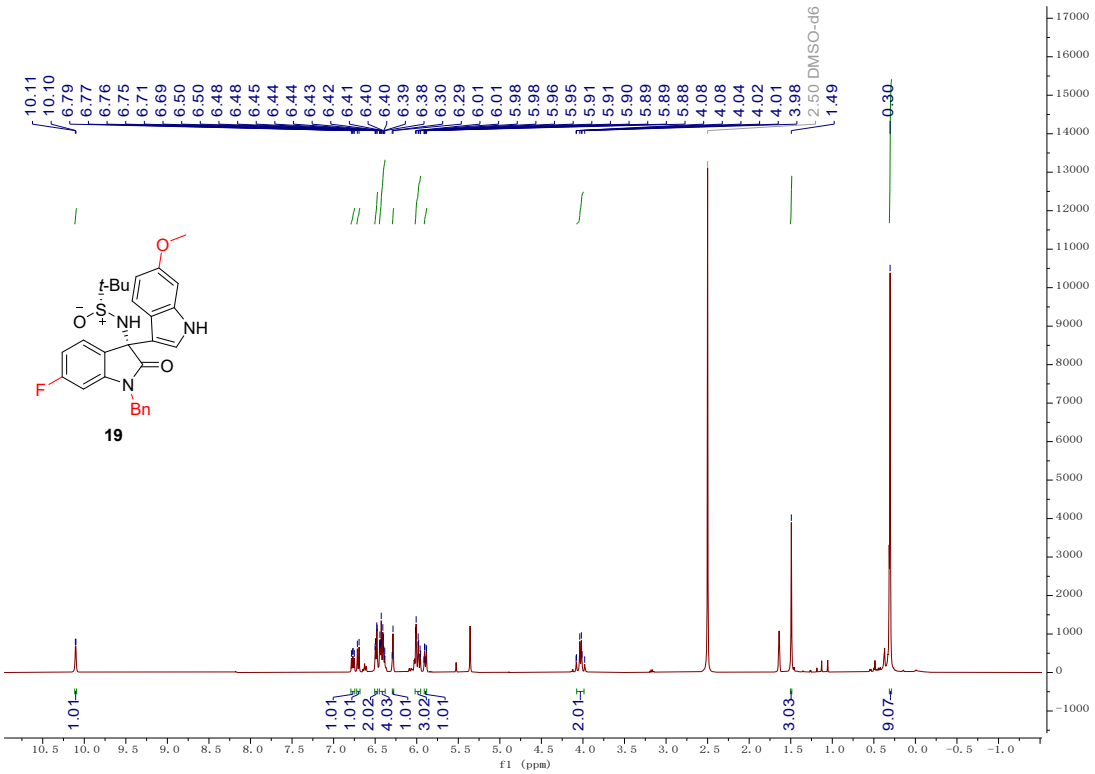
^{13}C NMR spectrum of compound **17**



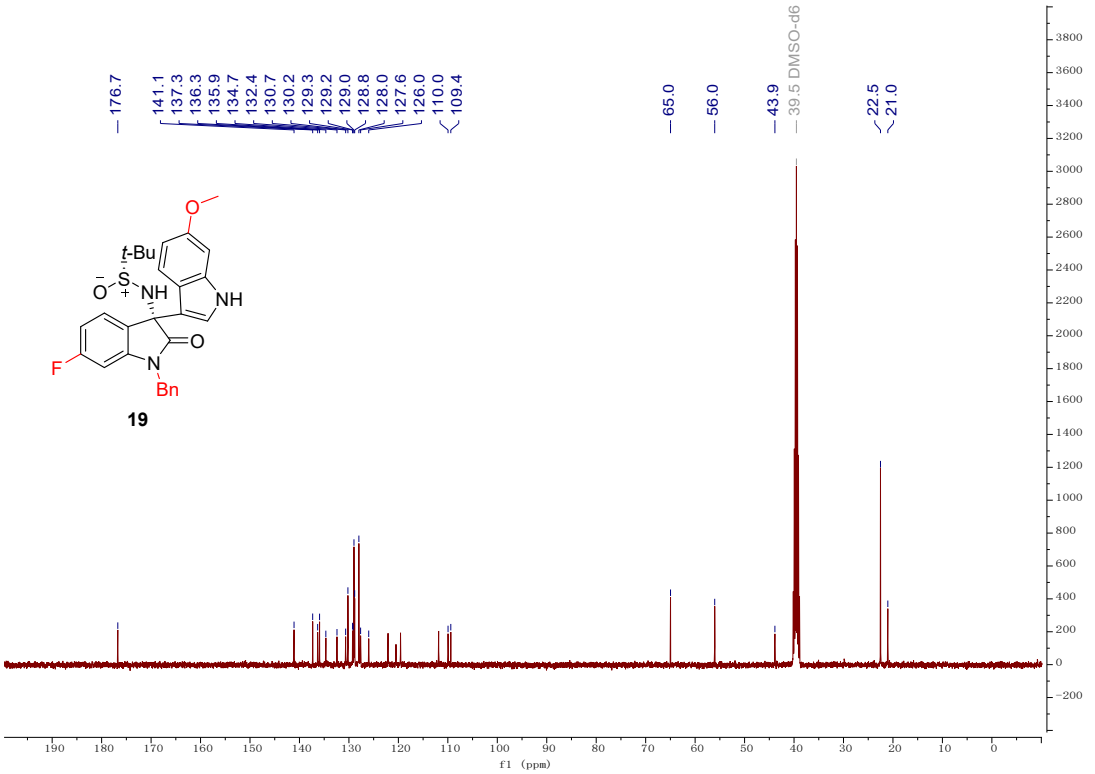
^{1}H NMR spectrum of compound **18**



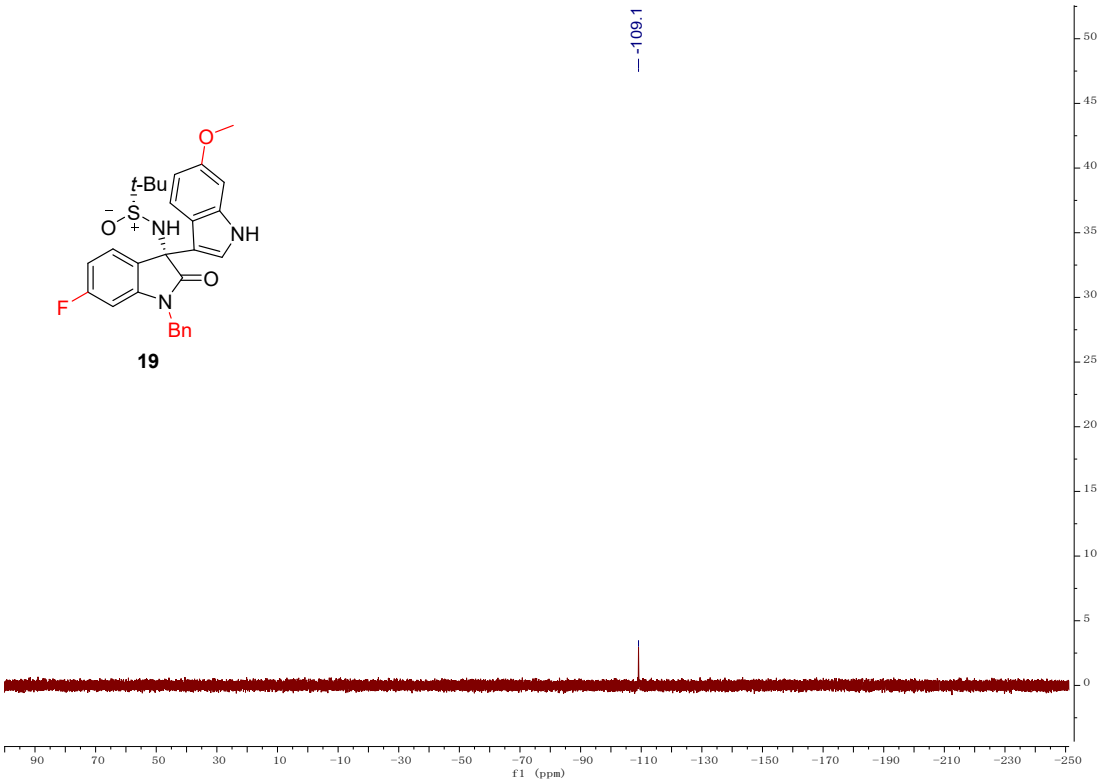
^{13}C NMR spectrum of compound 18



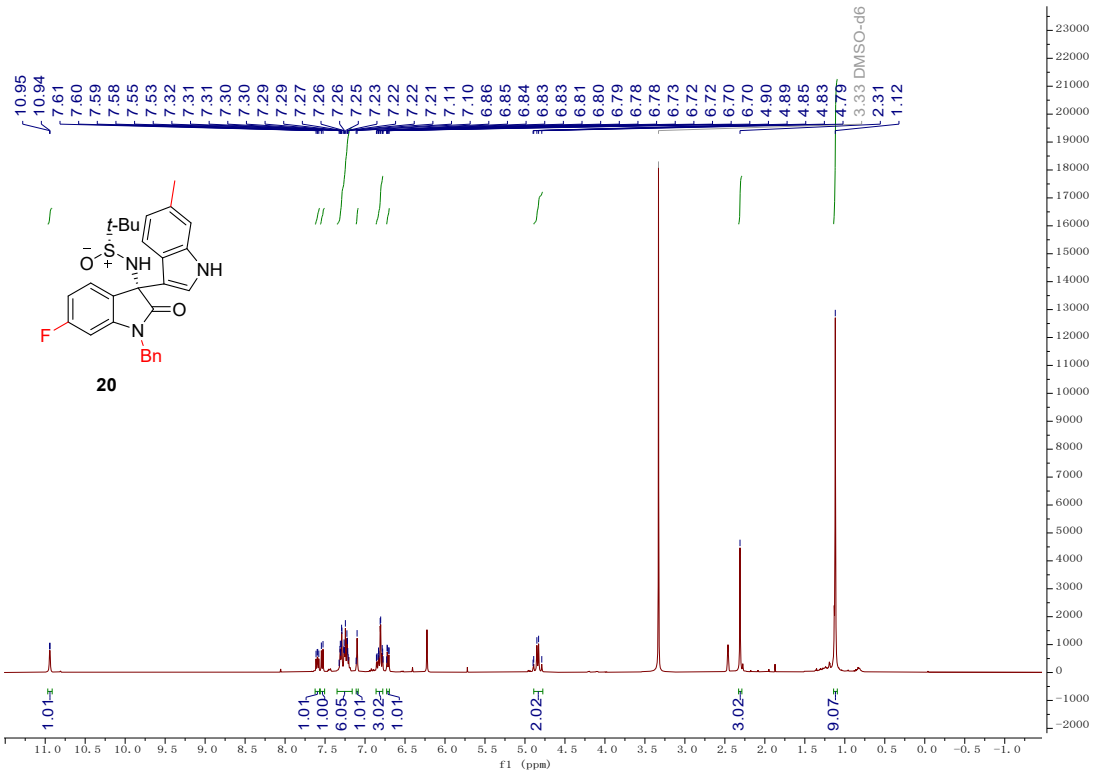
^{1}H NMR spectrum of compound **19**



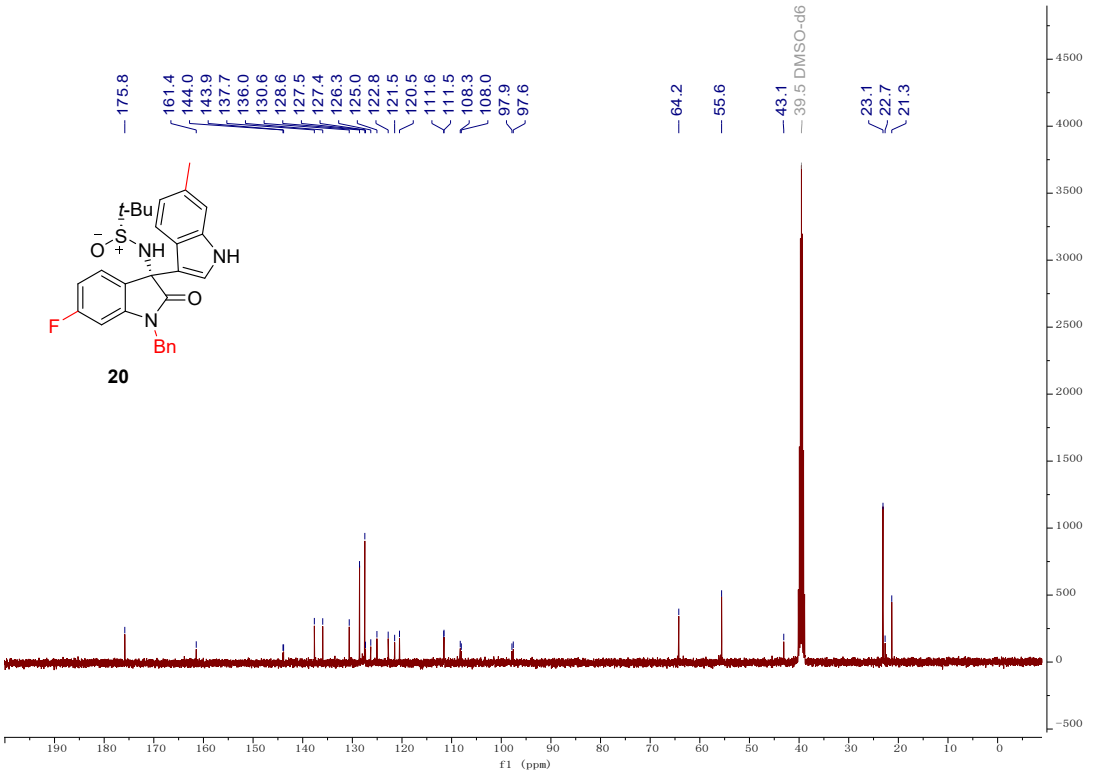
^{13}C NMR spectrum of compound **19**



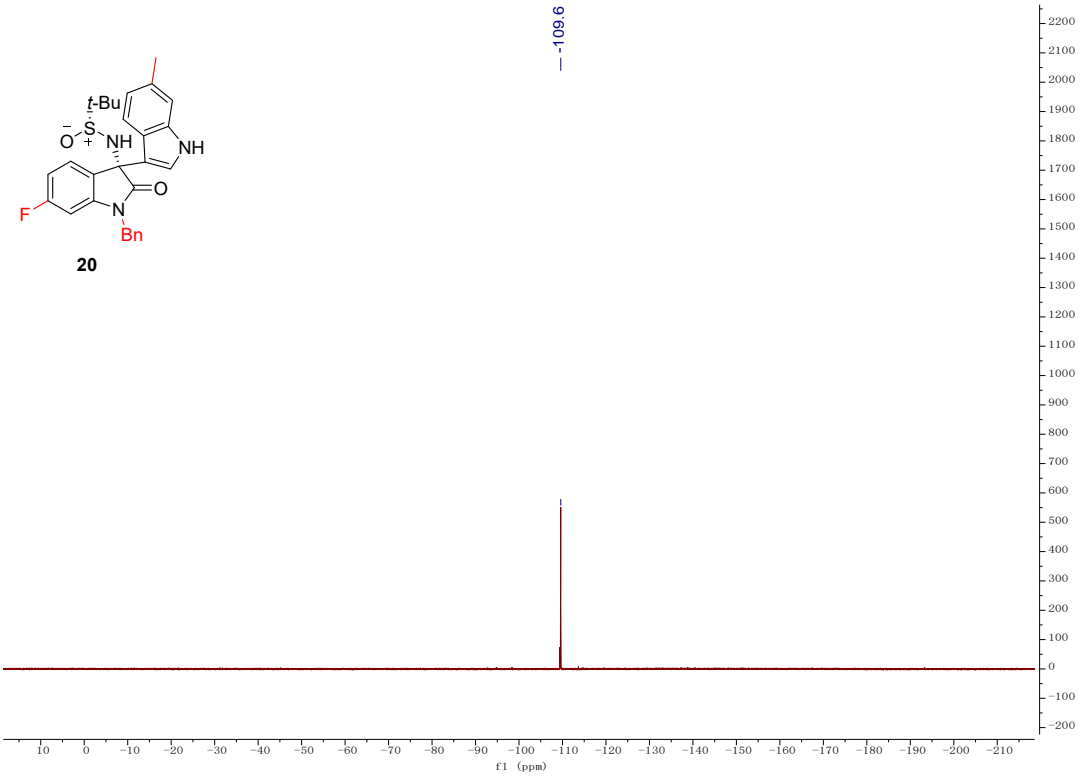
^{19}F NMR spectrum of compound **19**



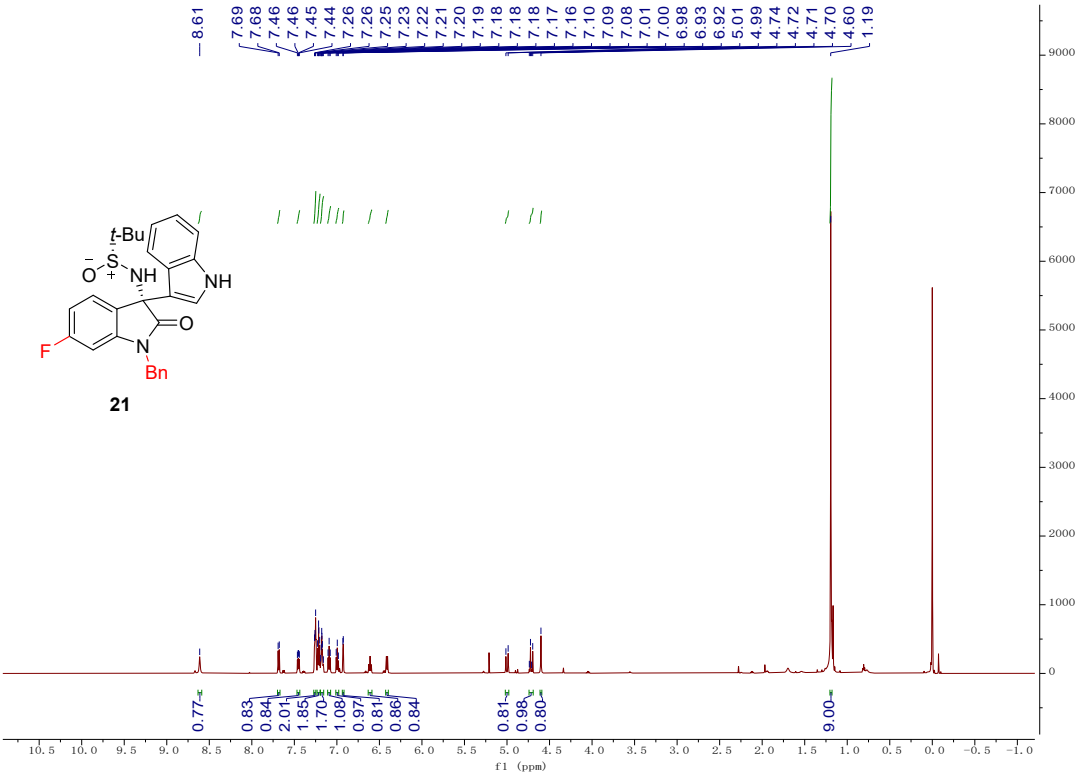
^{1}H NMR spectrum of compound **20**



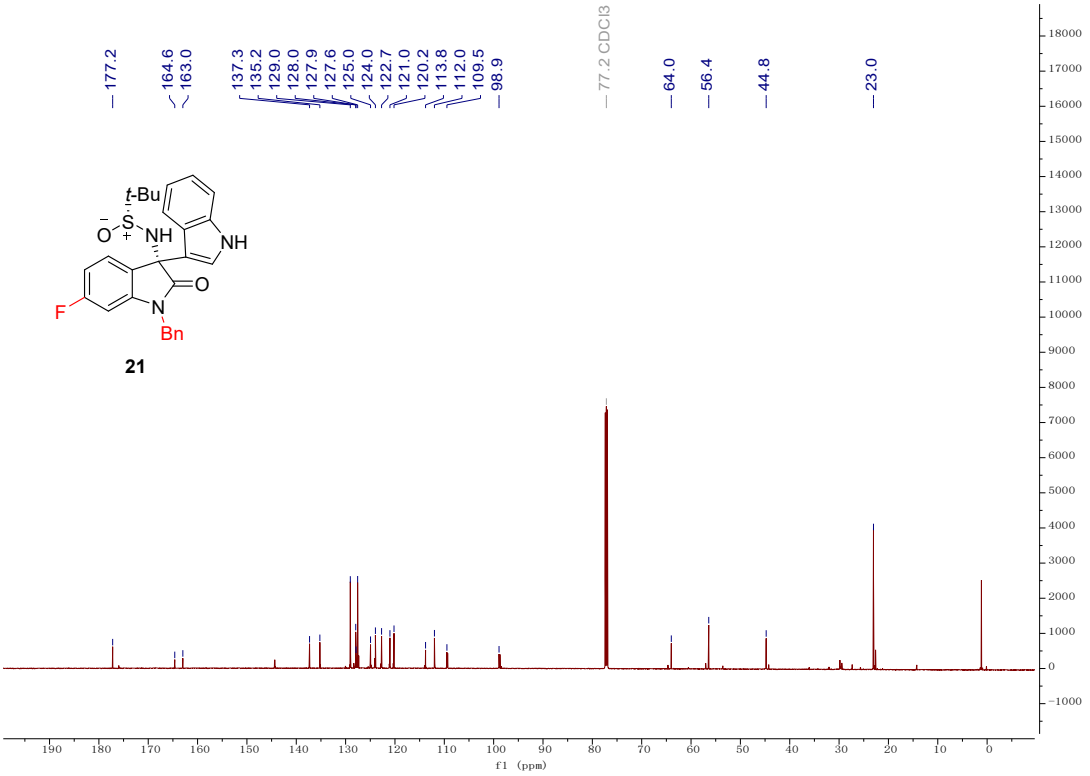
^{13}C NMR spectrum of compound **20**



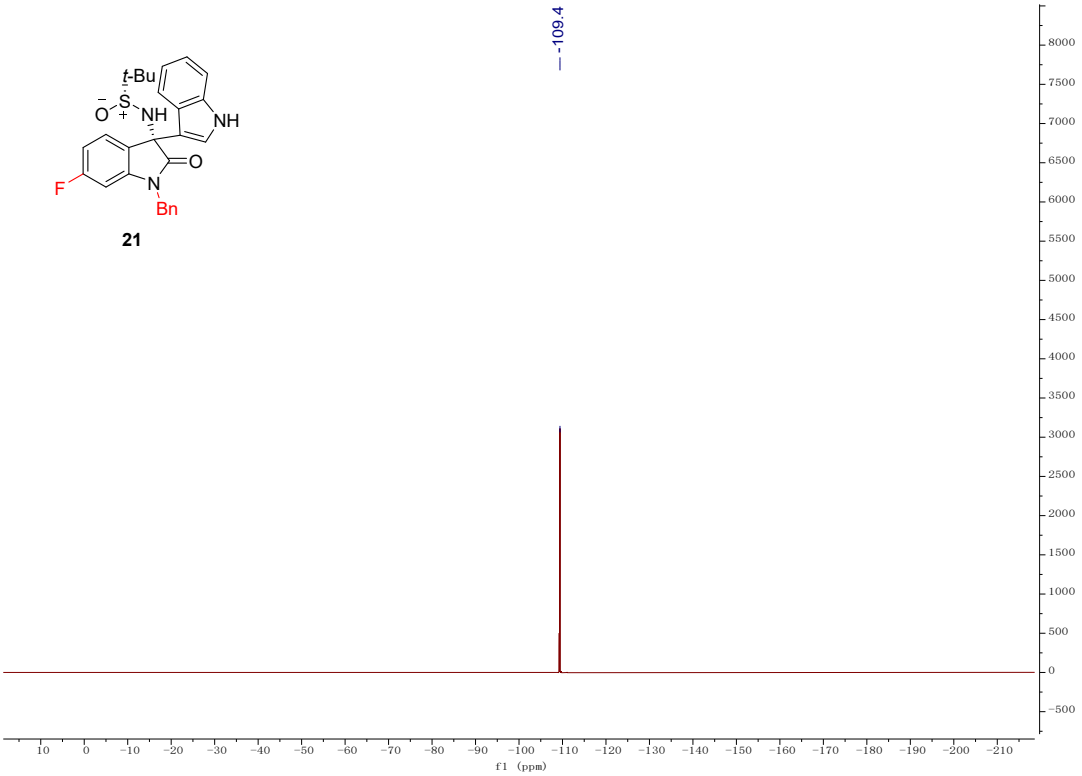
^{19}F NMR spectrum of compound **20**



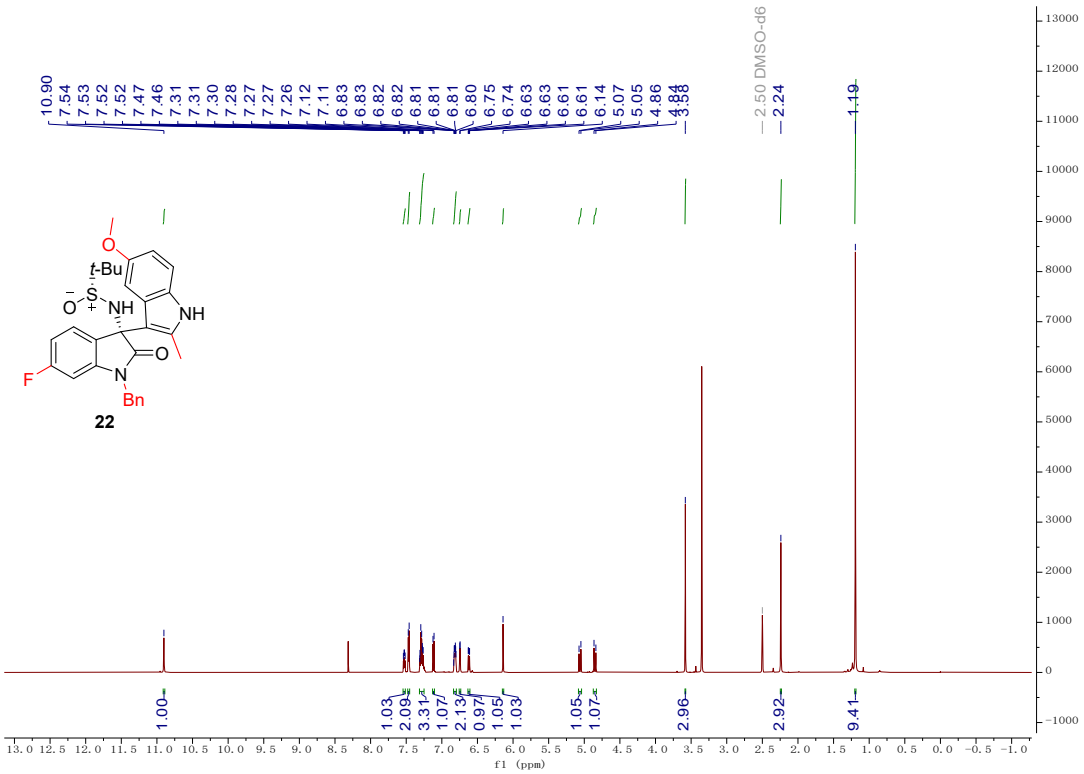
^{1}H NMR spectrum of compound **21**



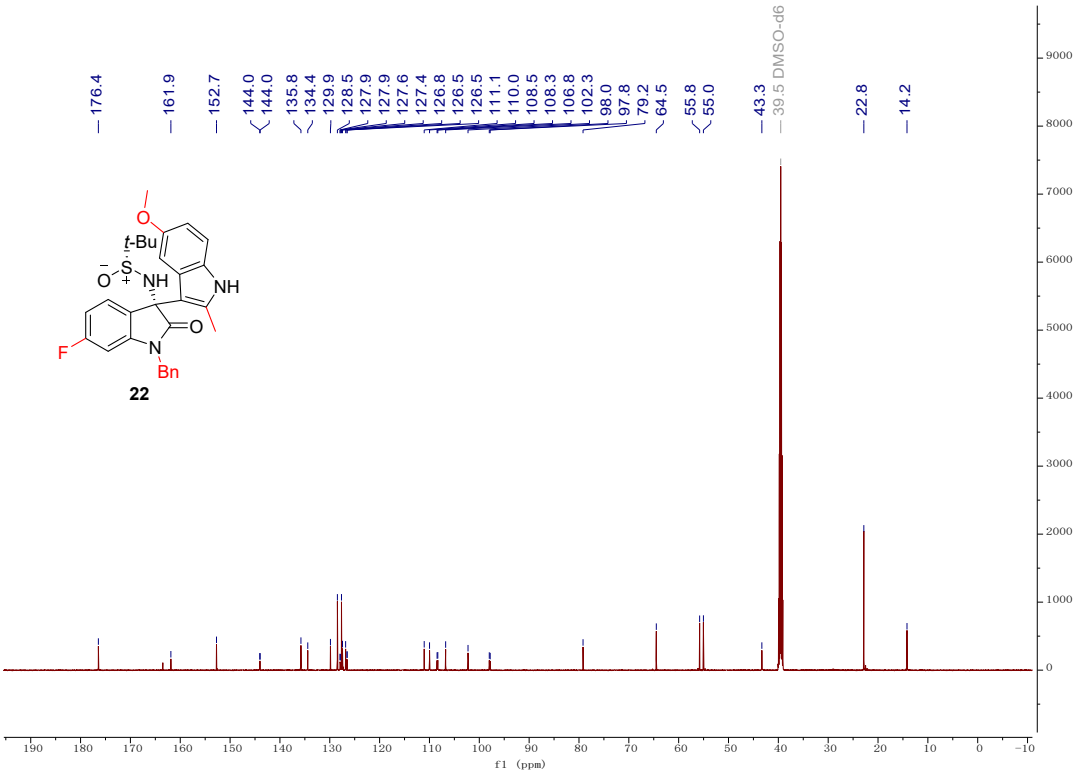
^{13}C NMR spectrum of compound **21**



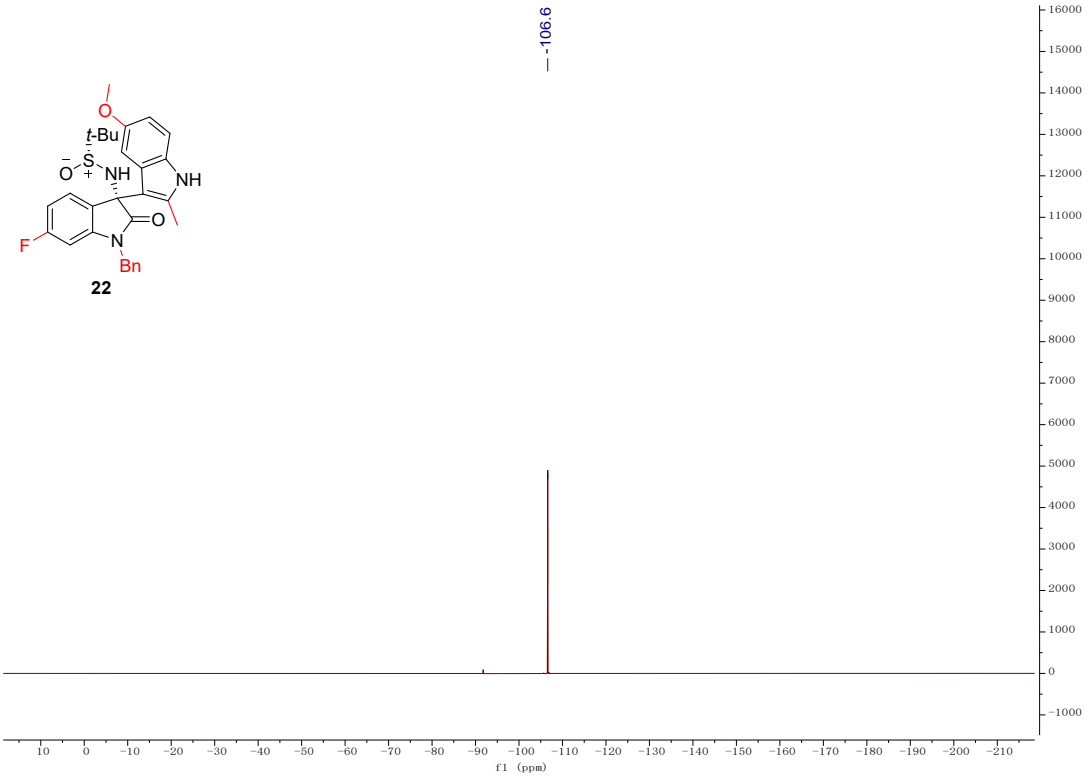
^{19}F NMR spectrum of compound **21**



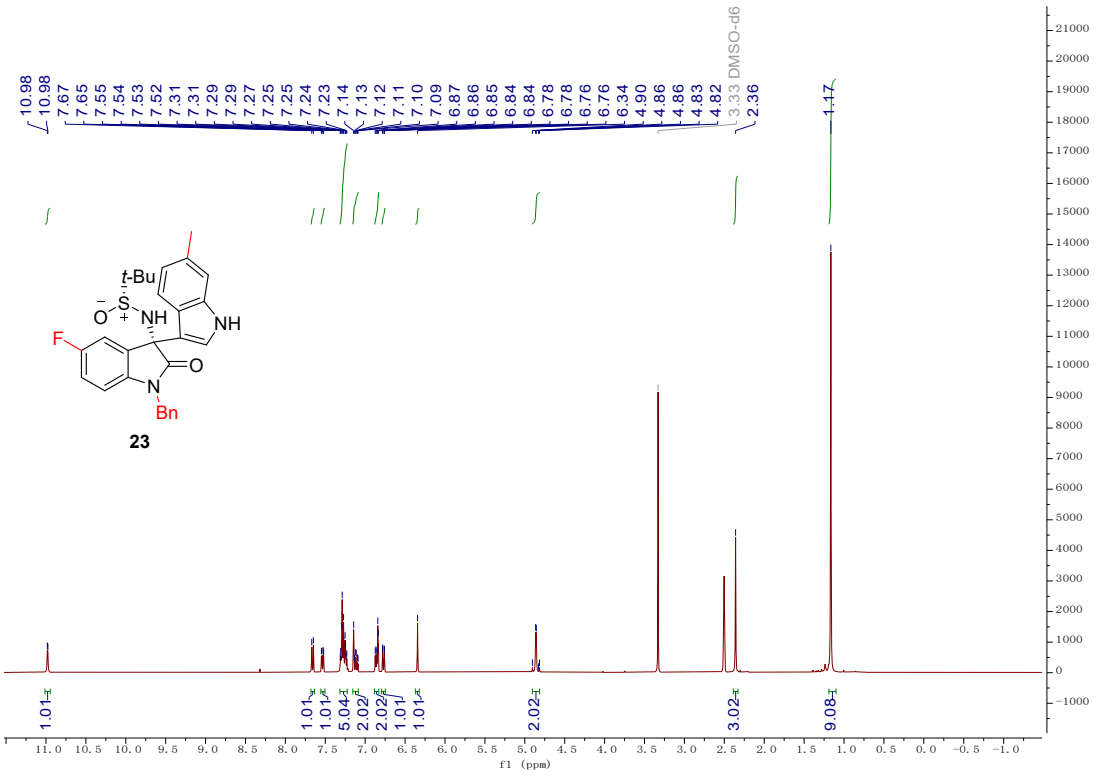
^{1}H NMR spectrum of compound **22**



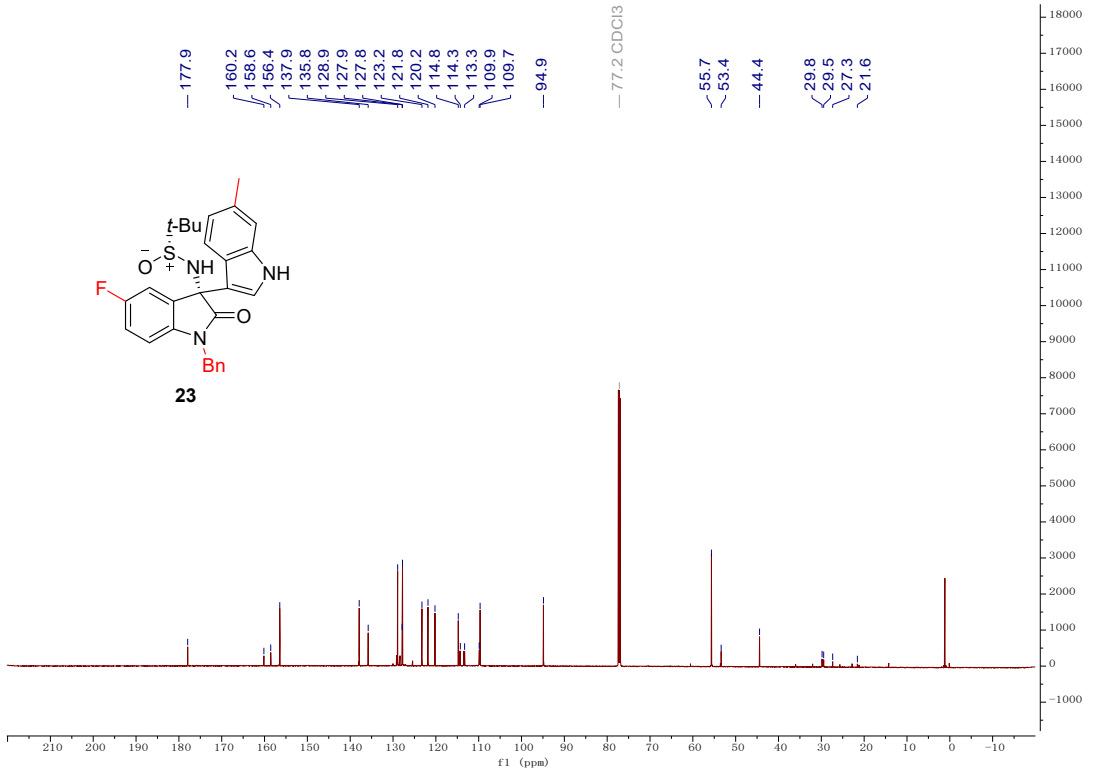
^{13}C NMR spectrum of compound **22**



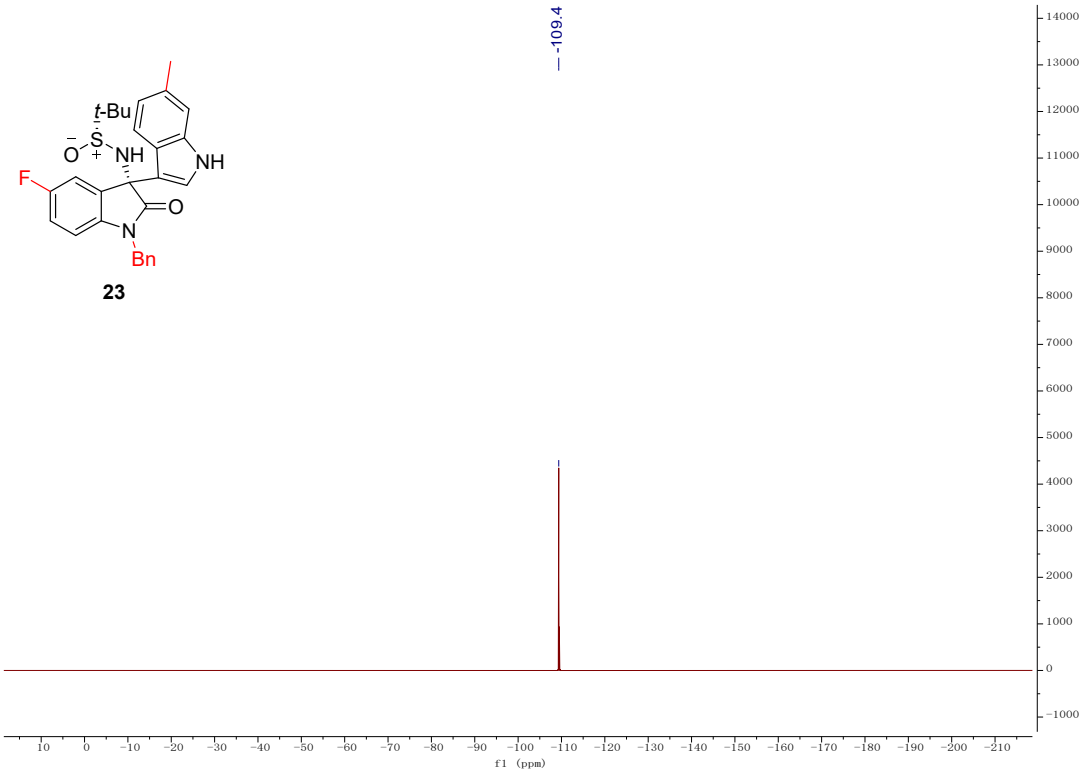
^{19}F NMR spectrum of compound **22**



^{1}H NMR spectrum of compound **23**

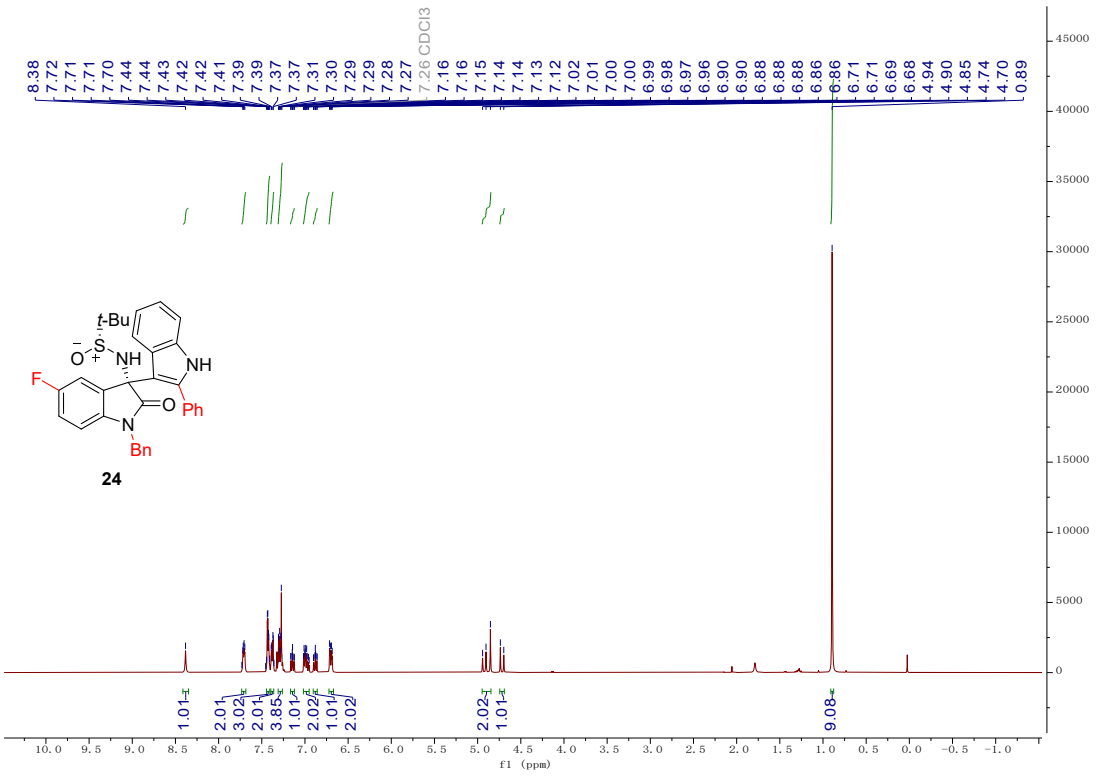


^{13}C NMR spectrum of compound **23**

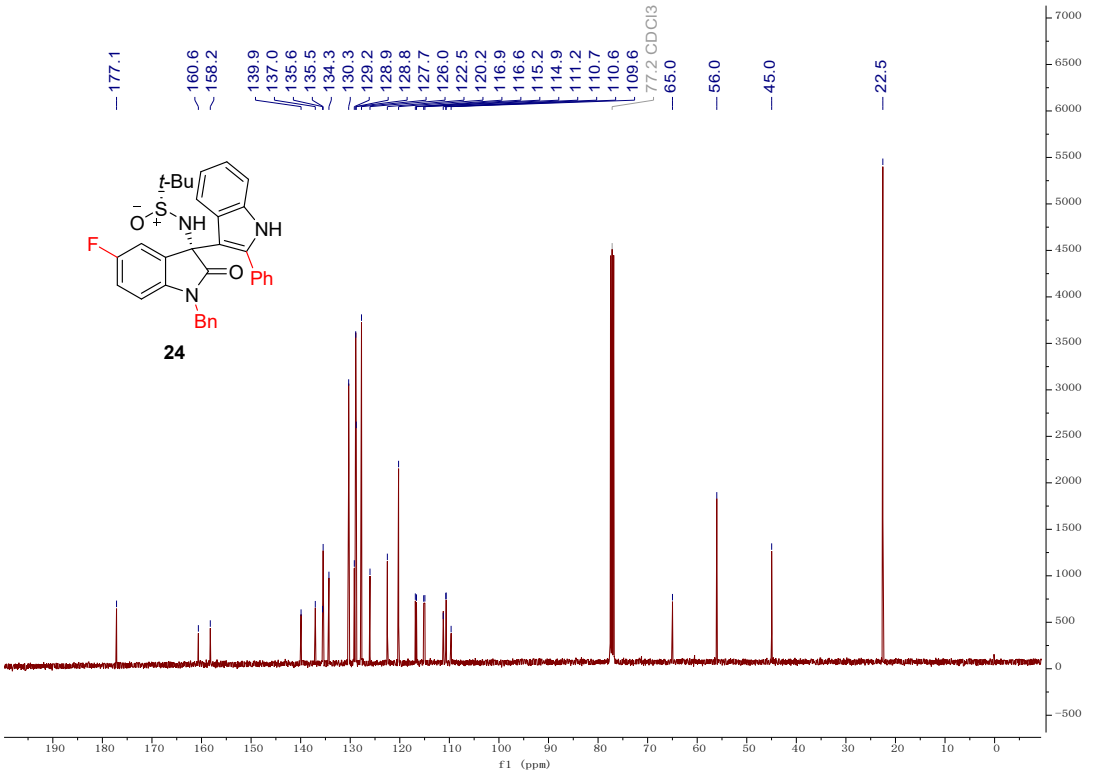


23

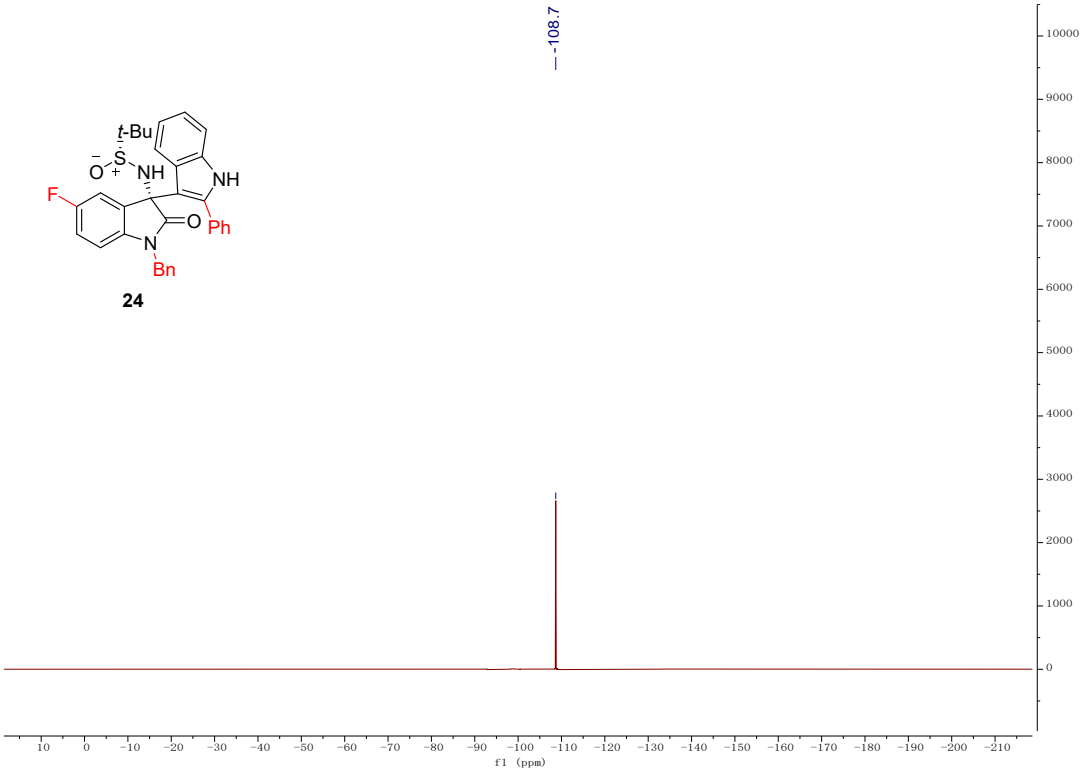
^{19}F NMR spectrum of compound **23**



^{1}H NMR spectrum of compound **24**

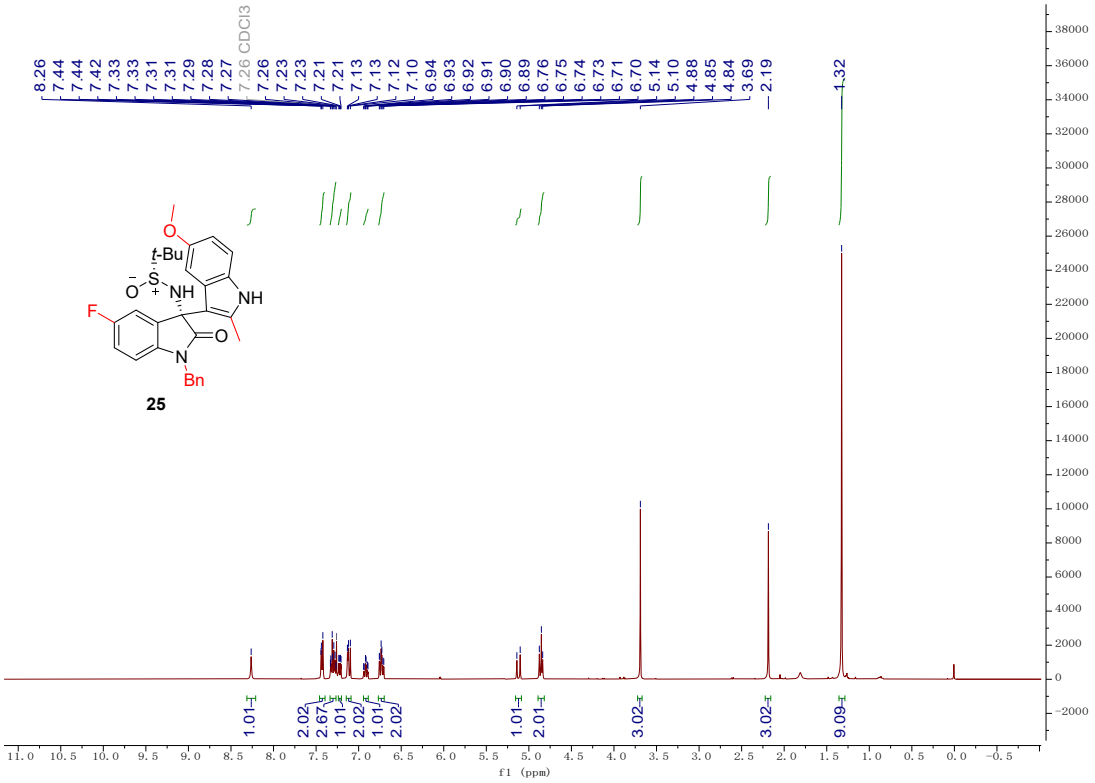


^{13}C NMR spectrum of compound **24**

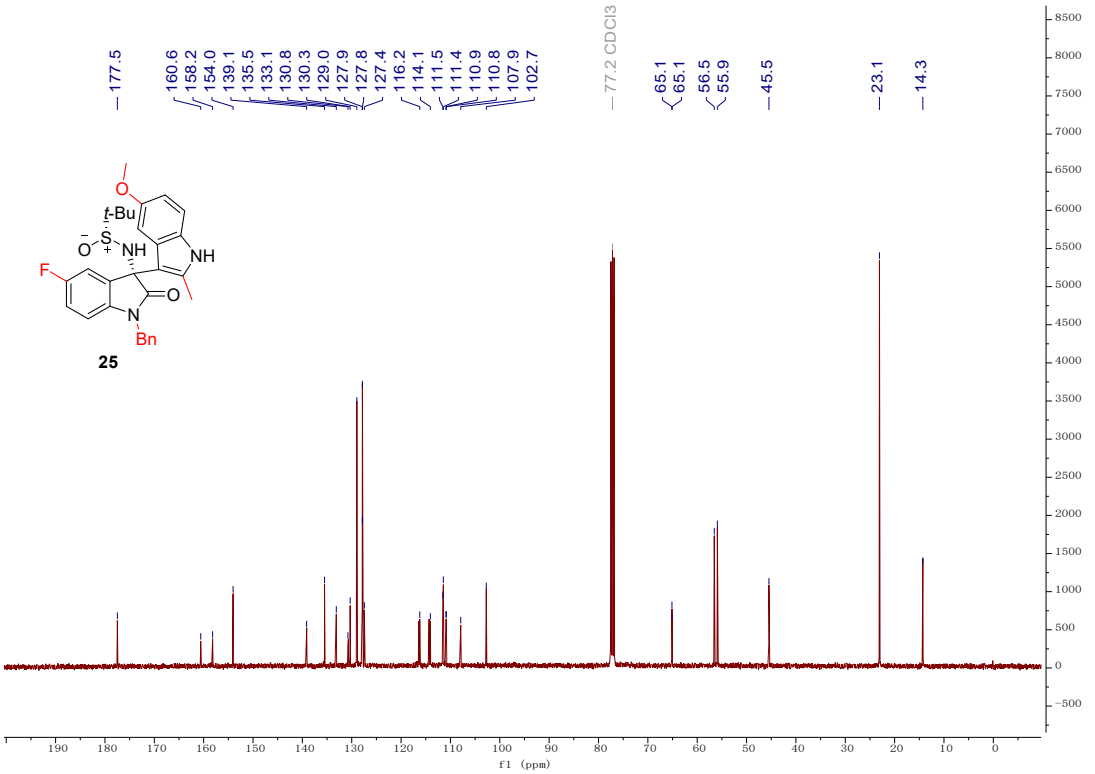


24

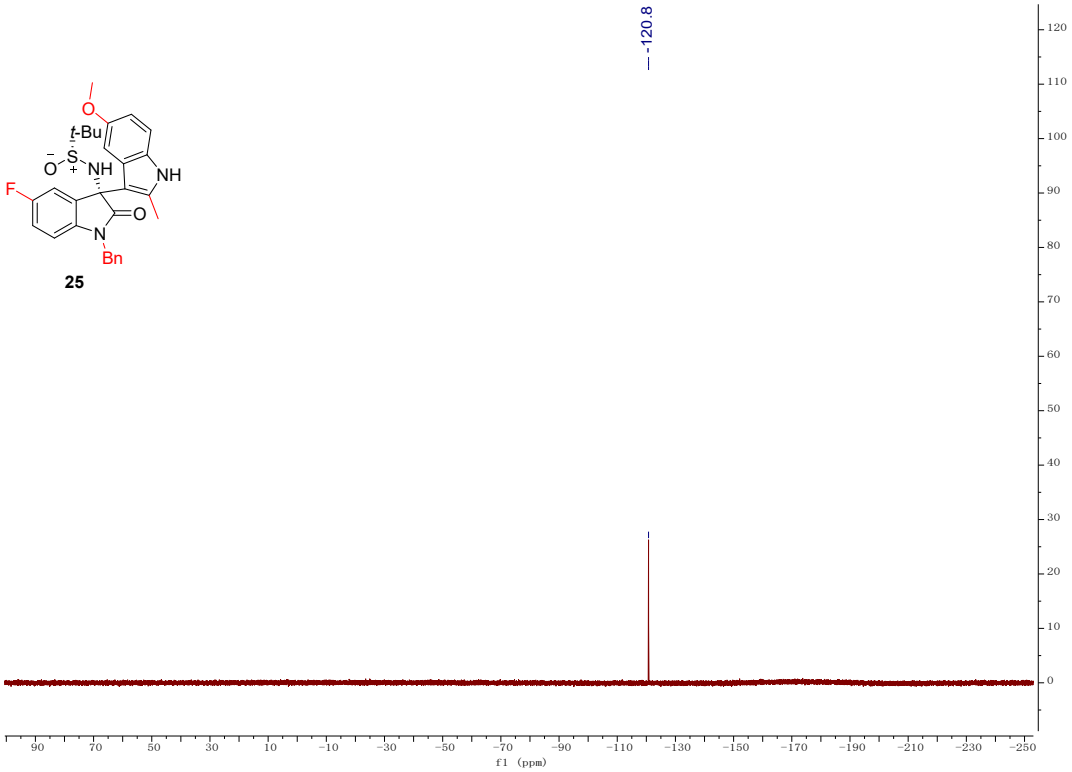
^{19}F NMR spectrum of compound **24**



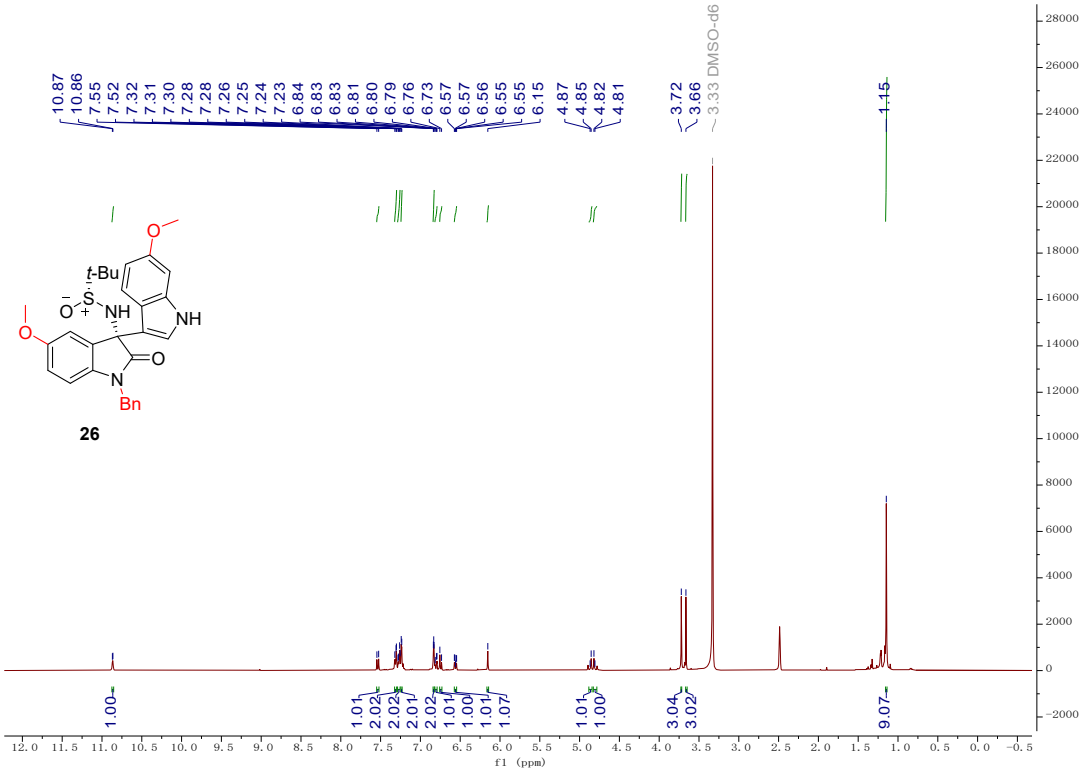
^{1}H NMR spectrum of compound **25**



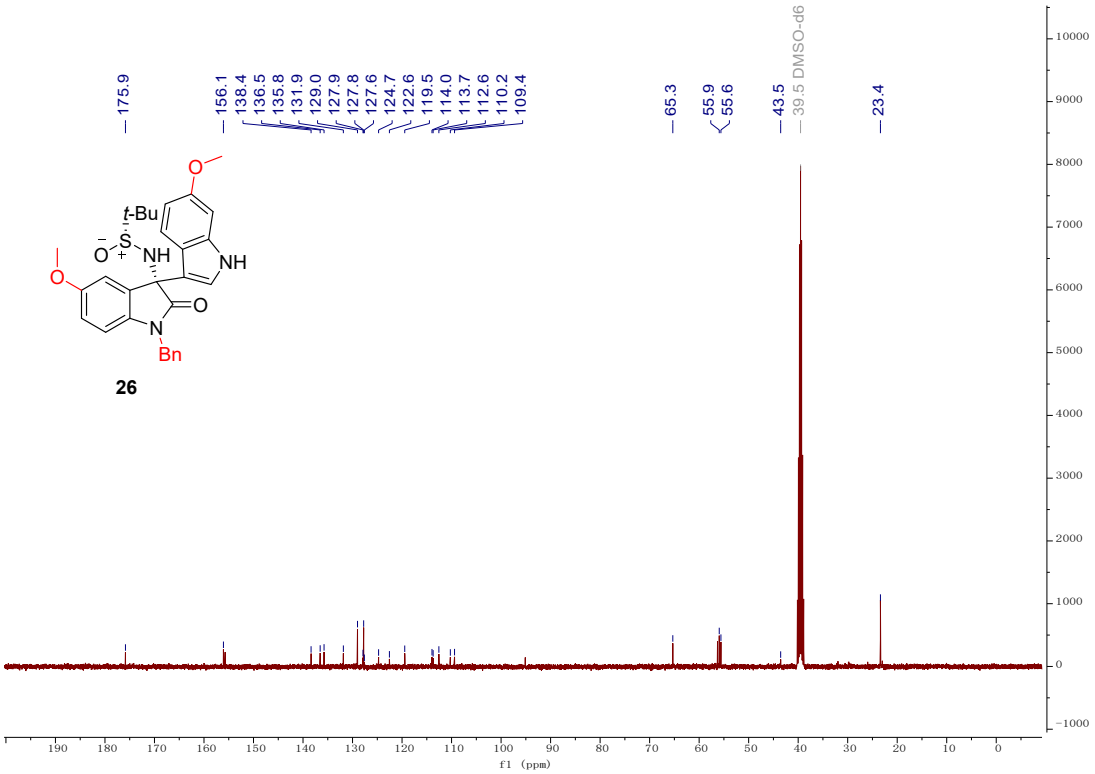
^{13}C NMR spectrum of compound **25**



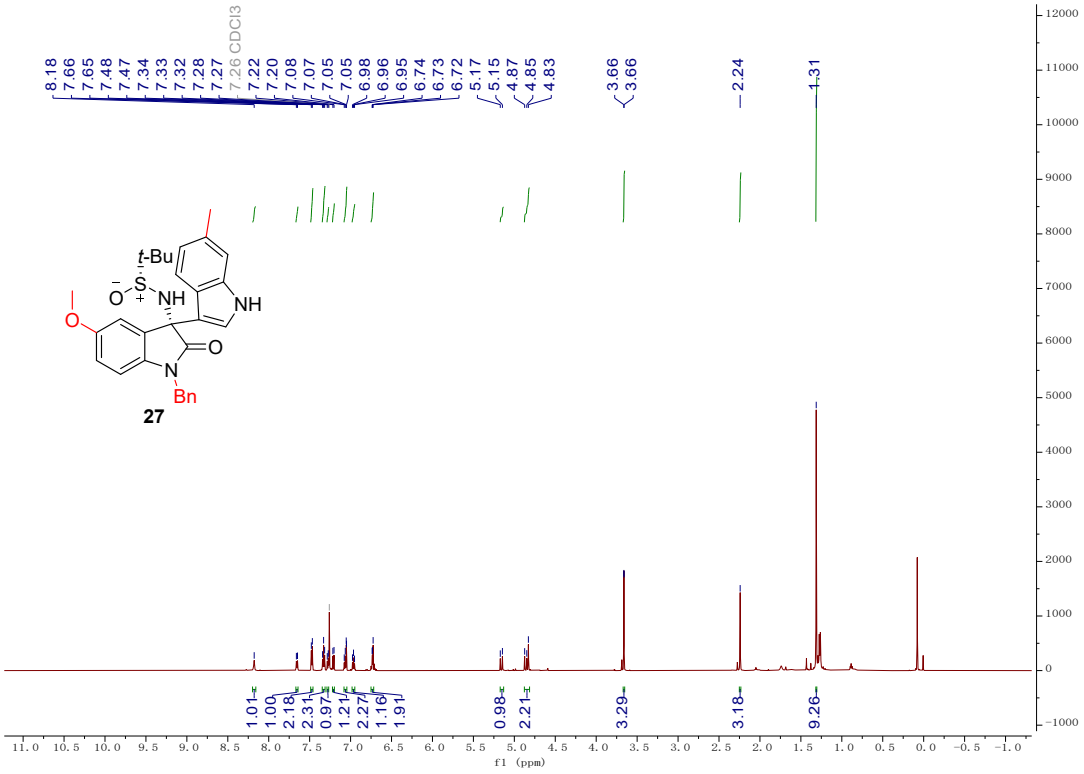
^{19}F NMR spectrum of compound **25**



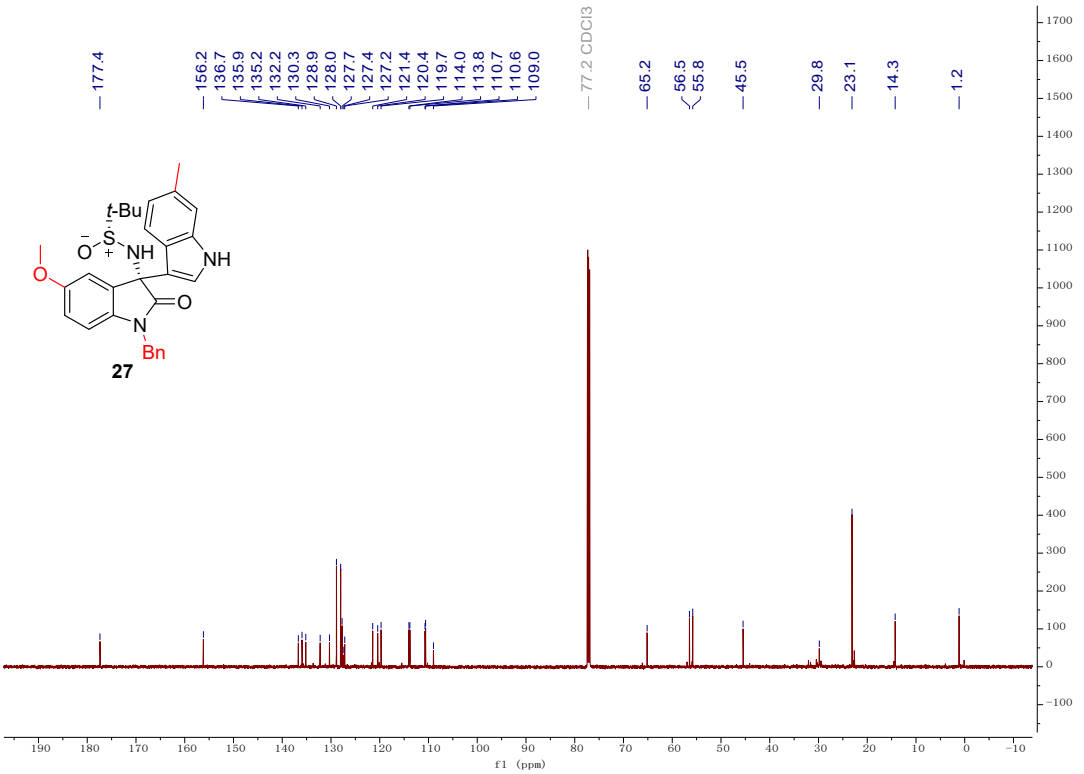
^{1}H NMR spectrum of compound **26**



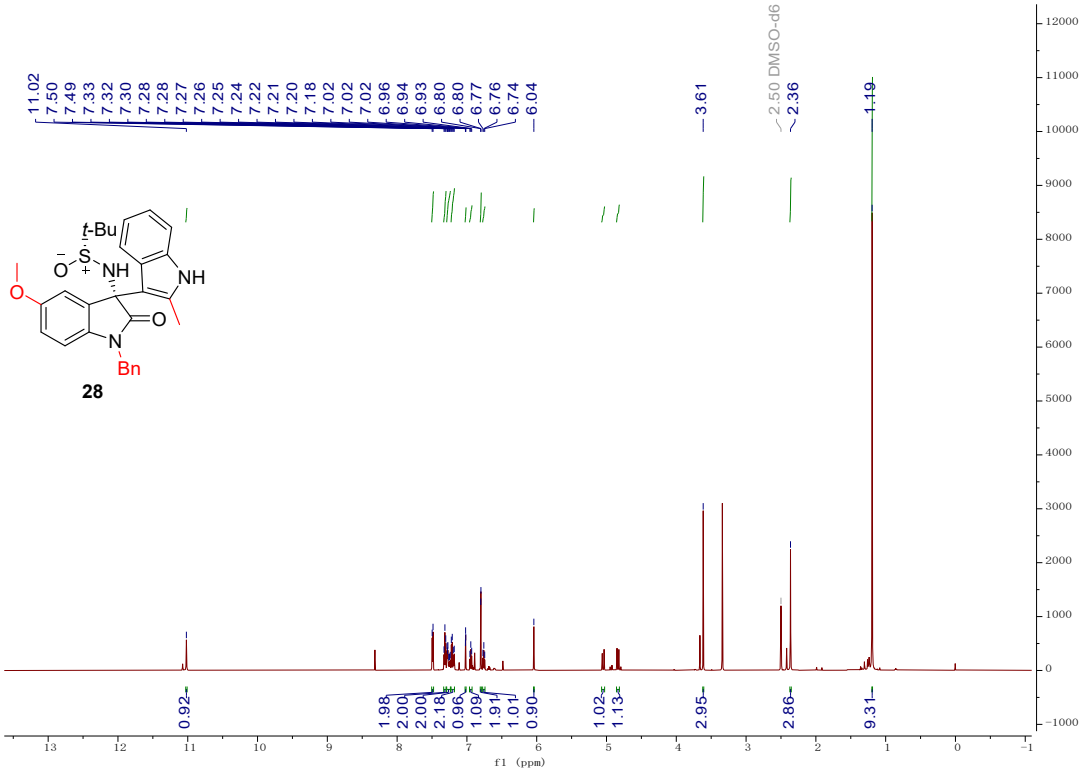
^{13}C NMR spectrum of compound **26**



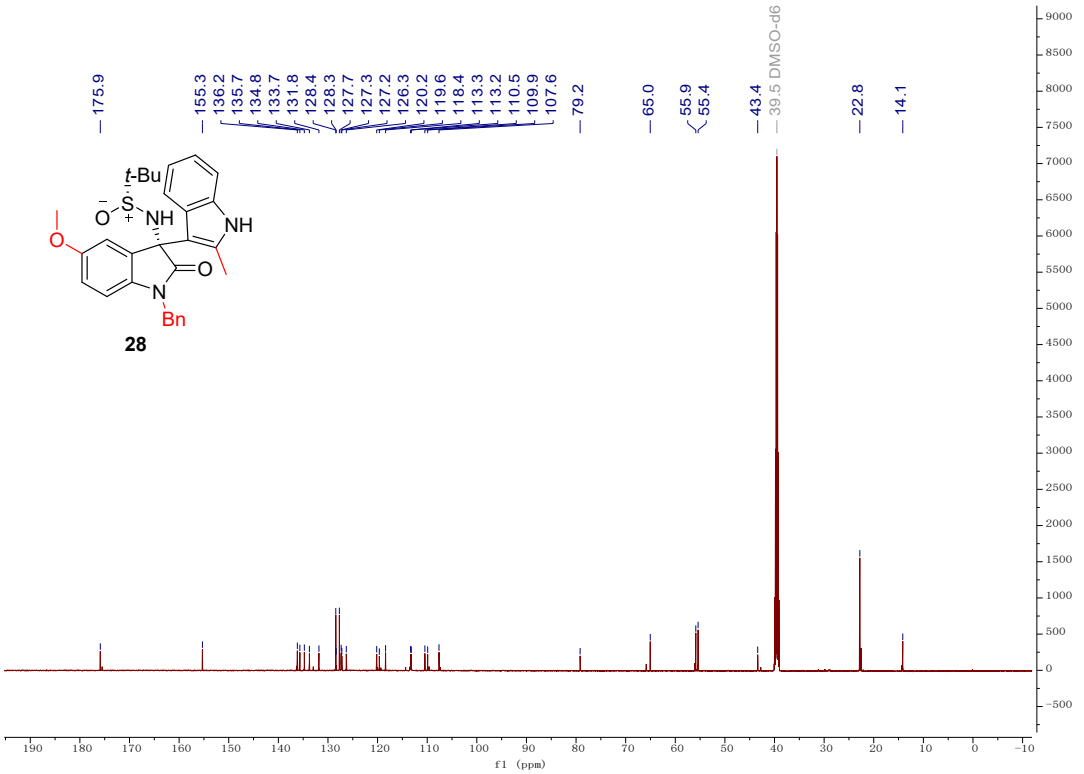
^{1}H NMR spectrum of compound **27**



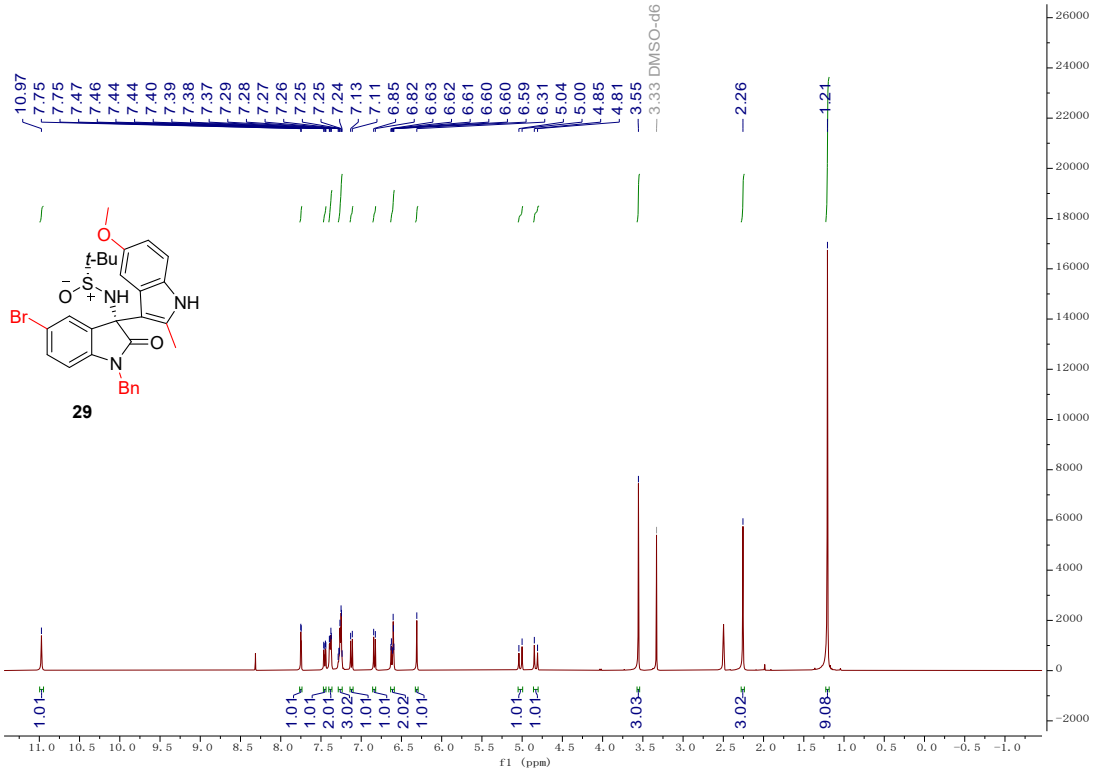
^{13}C NMR spectrum of compound **27**



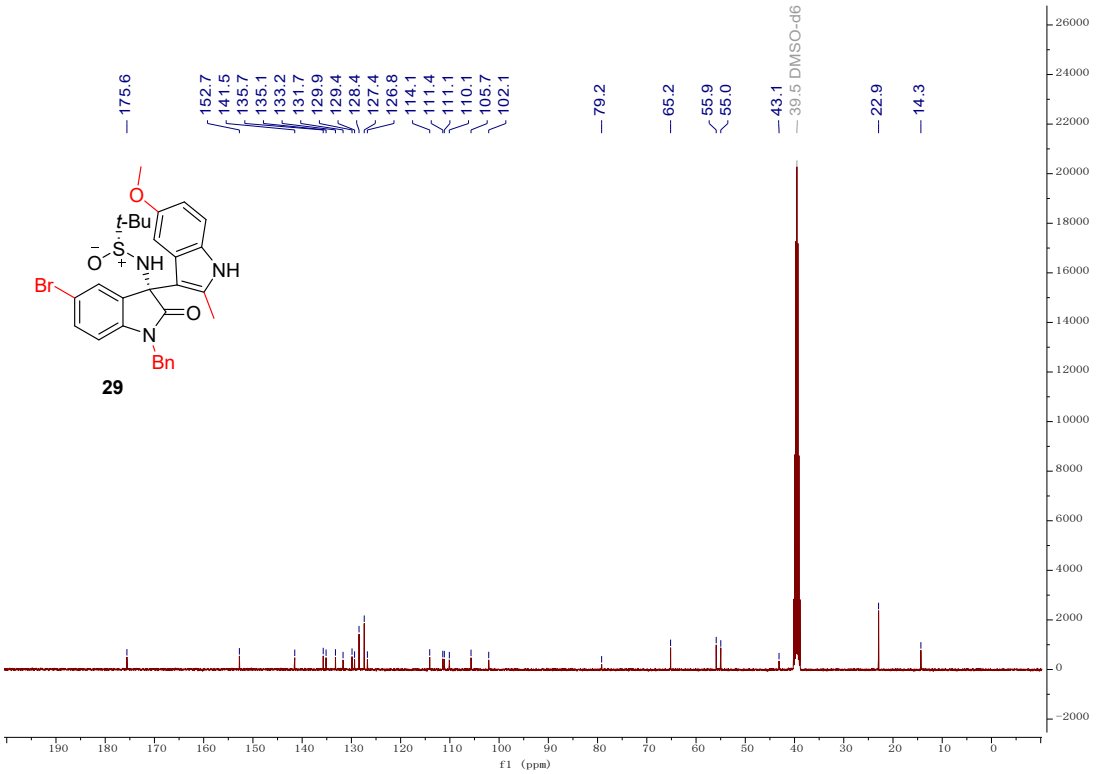
^{1}H NMR spectrum of compound **28**



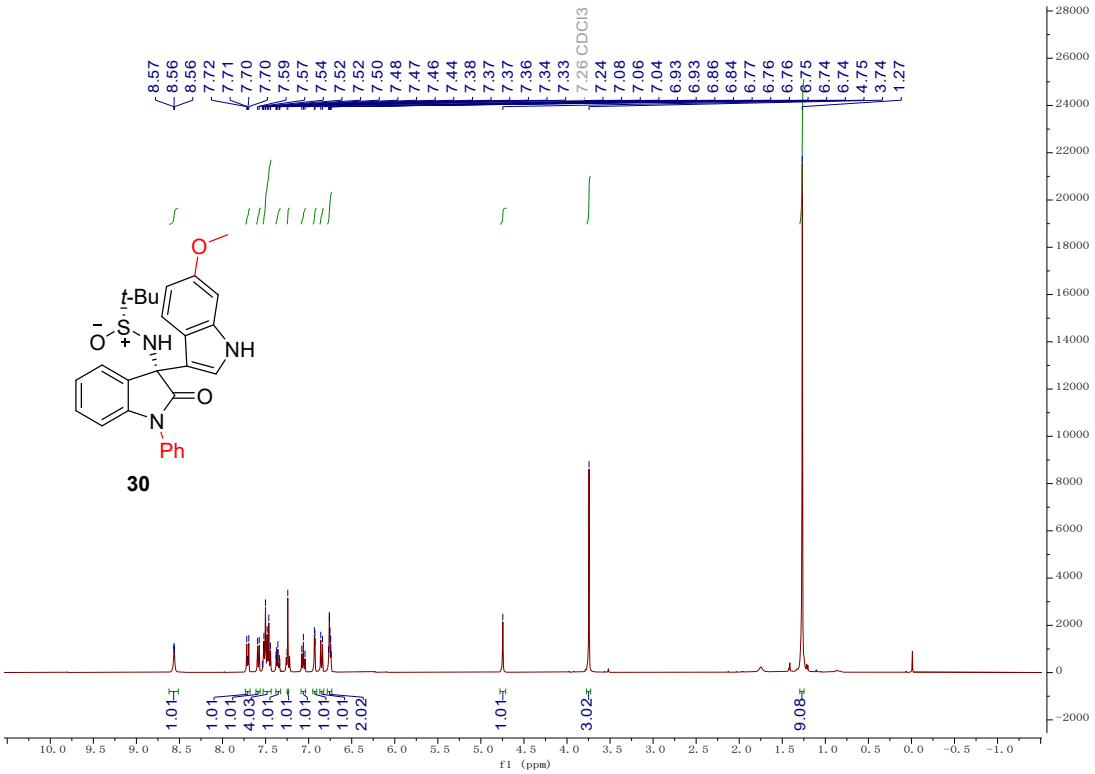
^{13}C NMR spectrum of compound **28**



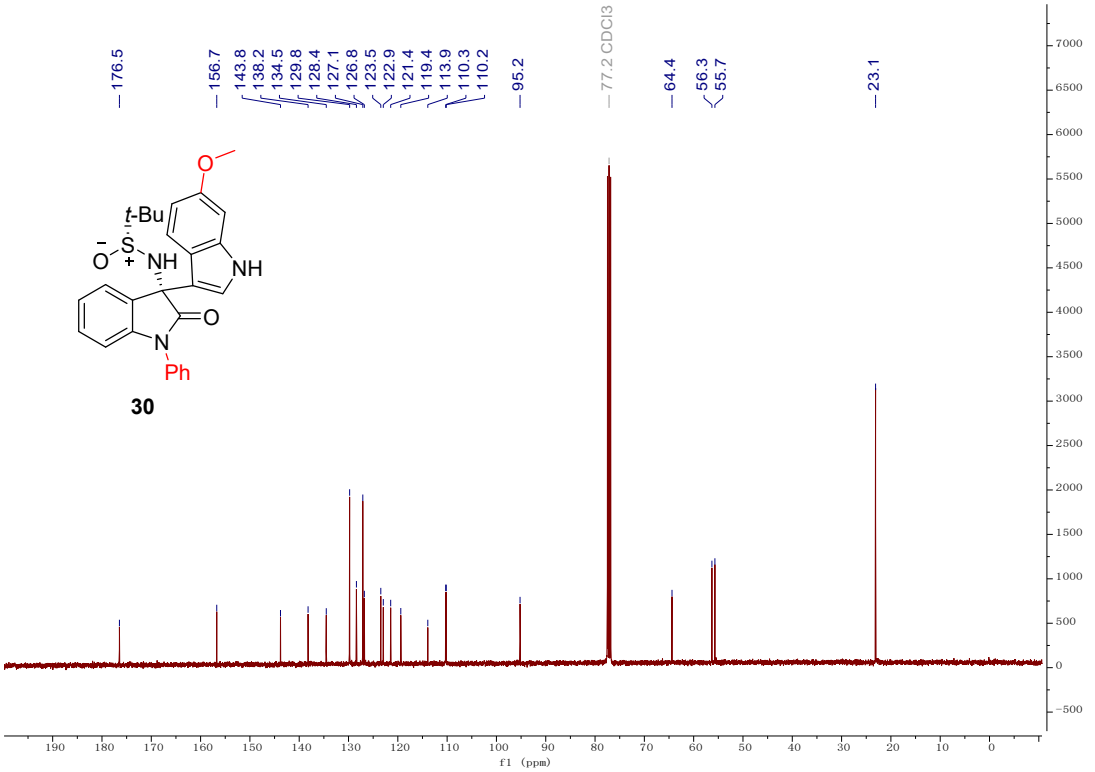
^{1}H NMR spectrum of compound **29**



^{13}C NMR spectrum of compound **29**



^{1}H NMR spectrum of compound **30**



^{13}C NMR spectrum of compound **30**