Supplementary Information (SI) for Organic & Biomolecular Chemistry.
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Synthesis of Spirooxindoles by Catalytic Tandem Reaction of 2-Arylidene-1,3-indanediones with 2-(2-Oxoindolin-3-yl)malononitriles

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Supporting Information

Contents

1. General information and starting materials

Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Column chromatography was performed with silica gel (200-300 mesh). Melting points were determined with an WRX-4 melting-point apparatus and are uncorrected. ^{1}H NMR spectra were measured with Bruker Ascend 400 MHz spectrometer in DMSO-d_6, chemical shifts were reported in δ (ppm) units relative to tetramethylsilane (TMS) as the internal standard. ^{13}C NMR spectra were measured at 100 MHz (Bruker Ascend 400 MHz spectrometer), chemical shifts were reported in ppm relative to TMS with the solvent resonance as internal standard (DMSO-d_6 at 39.43 ppm). ^{19}F NMR spectra were measured at 376 MHz (Bruker Ascend 400 MHz spectrometer). Proton coupling patterns are described as broad (br), singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). High resolution mass spectra were measured with an Agilent 6520 Accurate-Mass-Q-TOF MS system equipped with an electrospray ionization (ESI) source.

2-Arylidene-1,3-indanediones **1** were prepared according to the reported literature procedures.[1] 2-(2-oxoindolin-3-yl)malononitrile **2** was prepared following the method reported in the literature.[2]

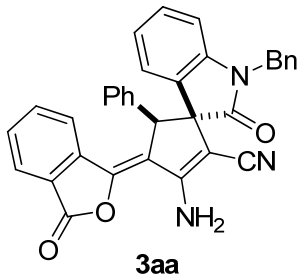
References

[1] H.-Y. Liu, D.-M. Du, *Molecules*, **2024**, *29*, 4856.

[2] Y. Lin, B. L. Zhao, D.-M. Du, *J. Org. Chem.* **2019**, *84*, 10209-10220.

2. General procedure for the synthesis and characterization of compounds 3

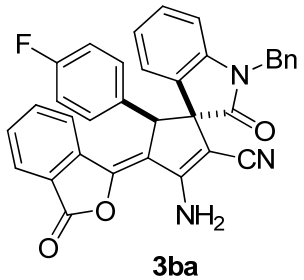
2-Arylidene-1,3-indanedione **1** (0.10 mmol, 1.0 equiv.) and 2-(2-oxoindolin-3-yl)malononitrile **2** (0.12 mmol, 1.2 equiv.) were placed in a small flask, dissolved in CH_3CN (1.0 mL). K_2CO_3 (1.4 mg, 0.01 mmol, 10 mol%) was added, and the mixture was stirred at room temperature for 24 h. After completion of the reaction, the solvent was evaporated, and the product was rapidly purified by column chromatography (petroleum ether/ethyl acetate, v:v = 5:1) to afford **3** as a yellow solids.



3aa

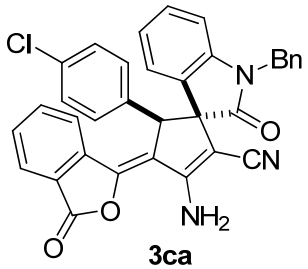
rel-(1*R*,5*R*)-3-Amino-1'-benzyl-2'-oxo-4-(3-oxoisobenzofuran-1(3*H*)-ylidene)-5-phenylspiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile (3aa). The synthesis of **3aa** was conducted using a standardized protocol, followed by purification through column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (5:1 *v*/*v*) as

the eluent to give 49.6 mg, 95% yield, yellow solid; m.p. 205–207 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (d, *J* = 7.6 Hz, 1H, ArH), 7.67 (t, *J* = 7.6 Hz, 1H, ArH), 7.62 (t, *J* = 7.6 Hz, 1H, ArH), 7.51 (d, *J* = 7.6 Hz, 1H, ArH), 7.36–7.06 (m, 13H, ArH + NH_2), 6.84 (d, *J* = 7.6 Hz, 1H, ArH), 6.57 (t, *J* = 7.6 Hz, 1H, ArH), 5.80 (d, *J* = 7.2 Hz, 1H, NH), 5.10 (d, *J* = 16.0 Hz, 1H, CH_2), 4.99 (s, 1H, CH), 4.92 (d, *J* = 16.0 Hz, 1H, CH_2) ppm; 13C NMR(101 MHz, DMSO-d_6): δ 177.7, 164.7, 159.6, 142.7, 142.0, 139.0, 136.4, 135.9, 135.2, 131.0, 128.7, 128.6, 128.4, 127.6, 127.4, 126.9, 126.5, 125.8, 125.5, 124.3, 123.5, 122.3, 121.8, 116.9, 109.2, 81.9, 61.9, 52.0, 43.0 ppm; HRMS (ESI): *m/z* calcd. for $C_{34}H_{24}N_3O_3$ $[M+H]^+$522.1817, found 522.1813.



3ba

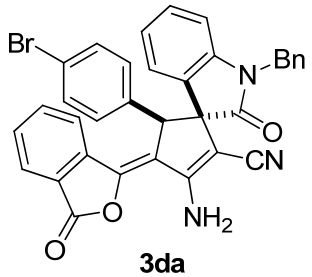
rel-(1*R*,5*R*)-3-Amino-1'-benzyl-5-(4-fluorophenyl)-2'-oxo-4-(3-oxoisobenzofuran-1(3*H*)-ylidene)spiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile (3ba).The synthesis of **3ba** was conducted using a standardized protocol, followed by purification through column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (5:1 *v*/*v*) as the eluent to give 40.5 mg, 75% yield, yellow solid; m.p. 202–204 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (d, *J* = 7.2 Hz, 1H, ArH), 7.71–7.62 (m, 2H, ArH), 7.50 (d, *J* = 8.0 Hz, 1H, ArH), 7.35–7.26 (m, 5H, ArH), 7.20–6.93 (m, 7H, ArH + NH_2), 6.84 (d, *J* = 8.0 Hz, 1H, ArH), 6.64 (t, *J* = 7.6 Hz, 1H, ArH), 5.84 (d, *J* = 7.6 Hz, 1H, ArH), 5.08 (d, *J* = 16.0 Hz, 1H, CH_2), 5.04 (s, 1H, CH), 4.89 (d, *J* = 15.6 Hz, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ 177.6, 164.6, 161.2 (d, $^1J_{C-F}$ = 245.4 Hz), 159.4, 142.7, 142.1, 136.3, 135.9, 135.2 (d, $^4J_{C-F}$ = 3.0 Hz), 135.1, 131.1, 128.8, 128.6, 127.3, 126.8, 126.3, 125.8, 125.5, 124.3, 123.6, 122.1, 121.8, 116.8, 109.2, 81.7, 61.8, 51.0, 43.0 ppm; ^{19}F NMR (376 MHz, DMSO-d_6): δ −114.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{34}H_{23}N_3O_3F$ $[M+H]^+$540.1718, found 540.1718.



3ca

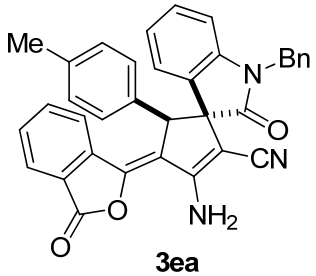
rel-(1*R*,5*R*)-3-Amino-1'-benzyl-5-(4-chlorophenyl)-2'-oxo-4-(-3-oxoisobenzofuran-1(3*H*)-ylidene)spiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile (3ca). The synthesis of **3ca** was conducted using a standardized protocol, followed by purification through column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (5:1 *v*/*v*) as

the eluent to give 44.5mg, 80% yield, yellow solid; m.p. 197–200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00 (d, *J* = 7.2 Hz, 1H, ArH), 7.72–7.62 (m, 2H, ArH), 7.51 (d, *J* = 7.6 Hz, 1H, ArH), 7.36–7.24 (m, 7H, ArH), 7.18–7.03 (m, 5H, ArH + NH_2), 6.85 (d, *J* = 8.0 Hz, 1H, ArH), 6.65 (t, *J* = 7.6 Hz, 1H, ArH), 5.89 (d, *J* = 7.2 Hz, 1H, ArH), 5.10 (d, *J* = 16.0 Hz, 1H, CH_2), 5.06 (s, 1H, CH), 4.90 (d, *J* = 16.0 Hz, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ 177.5, 164.5, 159.4, 142.7, 142.1, 138.0, 136.3, 135.9, 135.1, 132.0, 131.1, 128.9, 128.6, 127.3, 126.8, 126.2, 125.8, 125.5, 124.2, 123.6, 121.85, 121.76, 116.7, 109.3, 81.7, 61.6, 51.0, 43.1 ppm; HRMS (ESI): *m/z* calcd. for $C_{34}H_{23}N_3O_3Cl$ $[M+H]^+$ 556.1423, found 556.1431.



3da

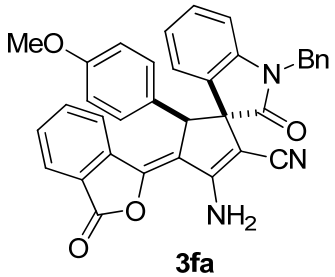
rel-(1*R*,5*R*)-3-Amino-1'-benzyl-5-(4-bromophenyl)-2'-oxo-4-(3-oxoisobenzofuran-1(3*H*)-ylidene)spiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile (3da). The synthesis of **3da** was conducted using a standardized protocol, followed by purification through column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (5:1 *v*/*v*) as the eluent to give 50.4 mg, 84% yield, yellow solid; m.p. 209–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00 (d, *J* = 7.6 Hz, 1H, ArH), 7.72–7.62 (m, 2H, ArH), 7.50 (d, *J* = 7.6 Hz, 2H, ArH), 7.36–7.26 (m, 6H, ArH), 7.14–6.94 (m, 5H, ArH + NH_2), 6.85 (d, *J* = 7.6 Hz, 1H, ArH), 6.65 (t, *J* = 7.6 Hz, 1H, ArH), 5.89 (d, *J* = 7.6 Hz, 1H, ArH), 5.09 (d, *J* = 16.0 Hz, 1H, CH_2), 5.05 (s, 1H, CH), 4.90 (d, *J* = 16.0 Hz, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ 177.5, 164.5, 159.4, 142.7, 142.1, 136.3, 135.8, 135.1, 131.1, 128.9, 128.6, 127.3, 126.8, 126.2, 125.8, 125.5, 124.2, 123.6, 121.9, 121.7, 120.6, 116.7, 109.3, 81.7, 61.6, 51.1, 43.1 ppm; HRMS (ESI): *m/z* calcd. for $C_{34}H_{23}N_3O_3{}^{79}Br$ $[M+H]^+$ 600.0918, found 600.0927; *m/z* calcd. for $C_{34}H_{23}N_3O_3{}^{81}Br$ $[M+H]^+$ 602.0897, found 602.0909.



3ea

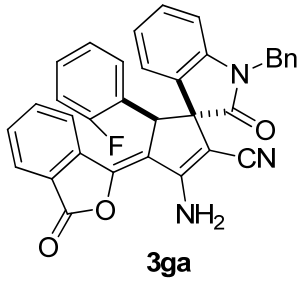
rel-(1*R*,5*R*)-3-Amino-1'-benzyl-2'-oxo-4-(3-oxoisobenzofuran-1(3*H*)-ylidene)-5-(p-tolyl)spiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile (3ea). The synthesis of **3ea** was conducted using a standardized protocol, followed by purification through column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (5:1 *v*/*v*) as

the eluent to give 49.3 mg, 92% yield, yellow solid; m.p. 195–197 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 7.99 (d, *J* = 7.6 Hz, 1H, ArH), 7.70–7.61 (m, 2H, ArH), 7.50 (d, *J* = 8.0 Hz, 2H, ArH), 7.35–7.26 (m, 5H, ArH), 7.10–6.82 (m, 8H, ArH + NH$_2$), 6.59 (t, *J* = 7.6 Hz, 1H, ArH), 5.83 (d, *J* = 7.6 Hz, 1H, ArH), 5.06 (d, *J* = 16.0 Hz, 1H, CH$_2$), 4.91 (s, 1H, CH), 4.89 (d, *J* = 16.4 Hz, 1H, CH$_2$), 2.19 (s, 3H, CH$_3$) ppm; ^{13}C NMR (101 MHz, DMSO-d$_6$): δ 177.7, 164.6, 159.5, 142.6, 141.8, 136.6, 136.4, 135.9, 135.1, 130.9, 128.7, 128.6, 128.2, 127.3, 127.0, 126.8, 126.5, 125.8, 125.6, 124.3, 123.5, 122.6, 121.8, 116.9, 109.1, 82.0, 61.9, 51.8, 43.0, 20.6 ppm; HRMS (ESI): *m/z* calcd. for C$_{35}$H$_{26}$N$_3$O$_3$ [M+H]$^+$ 536.1969, found 536.1971.



3fa

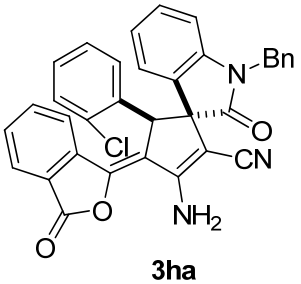
rel-(1*R*,5*R*)-3-Amino-1'-benzyl-5-(4-methoxyphenyl)-2'-oxo-4-(3-oxoisobenzofuran-1(3*H*)-ylidene)spiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile (3fa). The synthesis of **3fa** was conducted using a standardized protocol, followed by purification through column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (5:1 *v*/*v*) as the eluent to give 49.7 mg, 90% yield, yellow solid; m.p. 191–193 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 8.00 (d, *J* = 7.6 Hz, 1H, ArH), 7.71–7.62 (m, 2H, ArH), 7.52 (d, *J* = 7.6 Hz, 1H, ArH), 7.35–7.26 (m, 5H, ArH), 7.22–7.08 (m, 5H, ArH + NH$_2$), 6.96–6.82 (m, 3H, ArH), 6.63 (t, *J* = 7.6 Hz, 1H, ArH), 5.86 (d, *J* = 7.6 Hz, 1H, ArH), 5.06 (d, *J* = 16.4 Hz, 1H, CH$_2$), 4.91 (s, 1H, CH), 4.89 (d, *J* = 16.8 Hz, 1H, CH$_2$), 3.65 (s, 3H, OCH$_3$) ppm; ^{13}C NMR (101 MHz, DMSO-d$_6$): δ 177.7, 164.6, 159.5, 158.4, 142.6, 141.8, 136.5, 135.9, 135.1, 130.9, 128.7, 128.6, 127.3, 126.8, 126.5, 125.8, 125.7, 124.3, 123.5, 122.7, 121.8, 116.9, 113.6, 109.1, 81.9, 62.0, 54.9, 51.4, 43.0 ppm; HRMS (ESI): *m/z* calcd. for C$_{35}$H$_{26}$N$_3$O$_4$ [M+H]$^+$ 552.1918, found 552.1918.



3ga

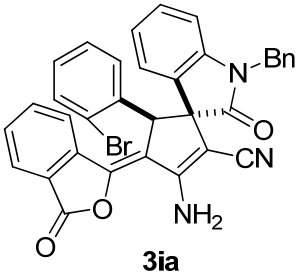
rel-(1*R*,5*R*)-3-Amino-1'-benzyl-5-(2-fluorophenyl)-2'-oxo-4-(3-oxoisobenzofuran-1(3*H*)-ylidene)spiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile (3ga). The synthesis of **3ga** was conducted using a standardized protocol, followed by purification through column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (5:1 *v*/*v*) as

the eluent to give 37.8 mg, 70% yield, yellow solid; m.p. 202–204 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 8.02 (d, *J* = 7.6 Hz, 1H, ArH), 7.71 (t, *J* = 7.4 Hz, 1H, ArH), 7.65 (t, *J* = 7.4 Hz, 1H, ArH), 7.36 (d, *J* = 4.4 Hz, 4H, ArH), 7.30–7.25 (m, 3H, ArH), 7.18–7.12 (m, 4H, ArH + NH$_2$), 7.08 (d, *J* = 8.0 Hz, 1H, ArH), 6.98–6.89 (m, 2H, ArH), 6.63 (t, *J* = 7.6 Hz, 1H, NH), 5.90 (d, *J* = 7.2 Hz, 1H, ArH), 5.03 (d, *J* = 16.4 Hz, 1H, CH$_2$), 4.98 (d, *J* = 16.0 Hz, 1H, CH$_2$), 4.95 (s, 1H, CH) ppm; ^{113}C NMR (101 MHz, DMSO-d$_6$): δ 177.5, 164.5, 160.1 (d, $^{1}J_{C–F}$ = 245.1 Hz), 159.0, 142.8, 142.2, 136.2, 135.9, 135.4, 131.2, 130.1 (d, $^{3}J_{C–F}$ = 8.4 Hz), 129.0, 128.5, 127.9 (d, $^{4}J_{C–F}$ = 2.4 Hz), 127.3, 126.7, 126.2, 126.1, 125.5, 125.3, 124.9, 124.8, 123.7, 122.8, 121.9, 120.0, 116.6, 115.0 (d, $^{2}J_{C–F}$ = 21.1 Hz), 109.2, 81.6, 61.2, 45.7, 42.9 ppm; ^{19}F NMR (376 MHz, DMSO-d$_6$): δ −116.21 ppm. HRMS (ESI): *m/z* calcd. for $C_{34}H_{23}N_3O_3F$ $[M+H]^+$ 540.1718, found 540.1726.



3ha

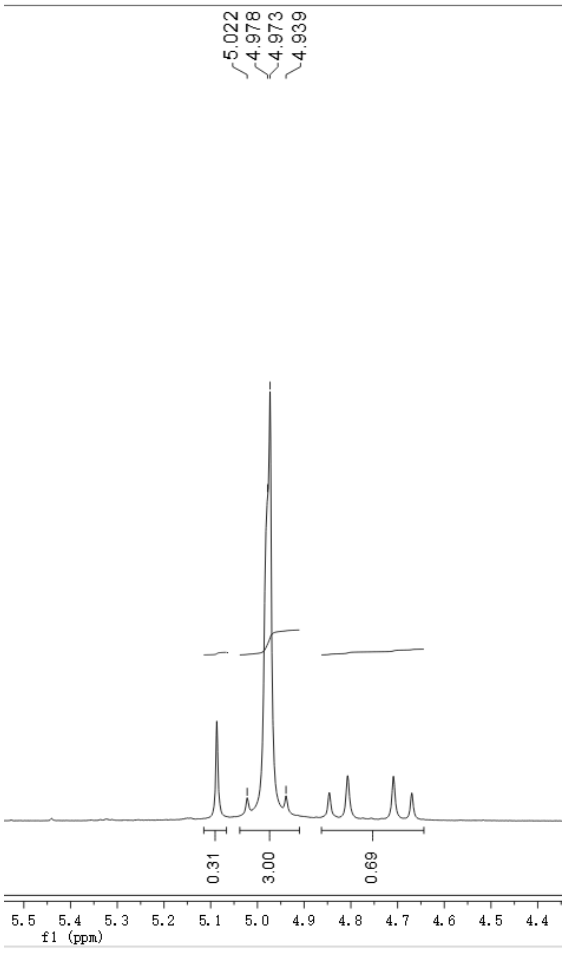
rel-(1*R*,5*R*)-3-Amino-1'-benzyl-5-(2-chlorophenyl)-2'-oxo-4-(3-oxoisobenzofuran-1(3*H*)-ylidene)spiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile (3ha). The synthesis of **3ha** was conducted using a standardized protocol, followed by purification through column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (5:1 *v*/*v*) as the eluent to give 42.8 mg, 77% yield, yellow solid; m.p. 193-195 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 8.03 (d, *J* = 7.2 Hz, 1H, ArH), 7.72–7.62 (m, 2H, ArH), 7.40 (d, *J* = 8.0 Hz, 2H, ArH), 7.36–7.12 (m, 11H, ArH + NH$_2$), 6.97 (d, *J* = 8.0 Hz, 1H, ArH), 6.60 (t, *J* = 7.2 Hz, 1H, ArH), 5.83 (d, *J* = 6.8 Hz, 1H, ArH), 5.03–4.94 (m, 3H, CH$_2$ + CH) ppm; ^{13}C NMR (101 MHz, DMSO-d$_6$): δ 177.4, 164.4, 158.8, 143.2, 142.2, 136.2, 135.9, 135.8, 135.4, 134.2, 131.2, 129.7, 129.0, 128.9, 128.6, 128.4, 127.7, 127.5, 127.4, 126.2, 126.1, 124.7, 123.7, 122.4, 121.8, 120.7, 116.5, 109.1, 82.0, 61.0, 49.3, 43.1 ppm; HRMS (ESI): *m/z* calcd. for $C_{34}H_{23}N_3O_3Cl$ $[M+H]^+$ 556.1423, found 556.1435.



3ia

rel-(1*R*,5*R*)-3-Amino-1'-benzyl-5-(2-bromophenyl)-2'-oxo-4-(-3-oxoisobenzofuran-1(3*H*)-ylidene)spiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile (3ia).The synthesis of **3ia**

was conducted using a standardized protocol, followed by purification through column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (5:1 *v*/*v*) as the eluent to give 48.0 mg, 80% yield (3:1 dr), yellow solid; m.p. 204–206 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 (d, *J* = 7.6 Hz, 1H, ArH), 7.72–7.63 (m, 2H, ArH), 7.43–7.25 (m, 9H, ArH), 7.17–7.13 (m, 3H, ArH + NH_2), 7.01–6.98 (m, 2H, ArH), 6.60 (t, *J* = 7.4 Hz, 1H, ArH), 5.81 (d, *J* = 7.2 Hz, 1H, ArH), 5.02–4.94 (m, 3H, CH_2 + CH) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ 177.3, 164.4, 158.7, 143.4, 142.2, 137.3, 136.3, 135.8, 135.3, 132.2, 131.3, 129.9, 129.0, 128.4, 128.3, 127.6, 127.5, 127.2, 126.2, 126.0, 125.9, 124.8, 123.7, 122.4, 121.8, 121.0, 116.5, 109.2, 82.2, 60.9, 51.7, 43.2 ppm; HRMS (ESI): *m/z* calcd. for $C_{34}H_{23}N_3O_3{}^{79}Br$ $[M+H]^+$ 600.0918, found 600.0942; *m/z* calcd. for $C_{34}H_{23}N_3O_3{}^{81}Br$ $[M+H]^+$ 602.0897, found 602.0925.



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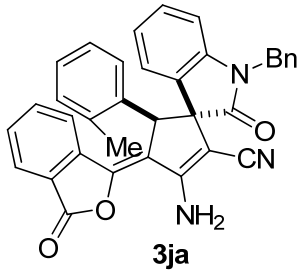
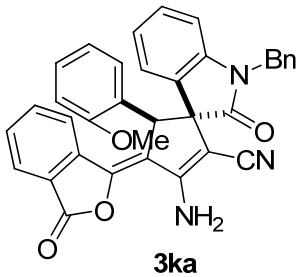


3ja

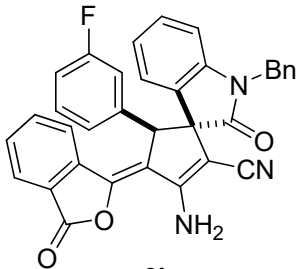
rel-(1*R*,5*R*)-3-Amino-1'-benzyl-2'-oxo-4-(3-oxoisobenzofuran-1(3*H*)-ylidene)-5-(*o*-

tolyl)spiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile (3ja). The synthesis of **3ja** was conducted using a standardized protocol, followed by purification through column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (5:1 *v*/*v*) as the eluent to give 46.1 mg, 86% yield, yellow solid; m.p. 195–197 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (d, *J* = 7.2 Hz, 1H, ArH), 7.70–7.61 (m, 2H, ArH), 7.41–7.26 (m, 5H, ArH), 7.19–7.10 (m, 6H, ArH + NH_2), 7.01–6.93 (m, 3H, ArH) 6.58 (t, *J* = 7.6 Hz, 1H, ArH), 5.72 (d, *J* = 7.2 Hz, 1H, ArH), 5.03 (d, *J* = 16.4 Hz, 1H, CH_2), 4.96 (d, *J* = 15.6 Hz, 1H, CH_2), 4.85 (s, 1H, CH), 1.63 (s, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ 177.5, 164.5, 159.2, 142.8, 141.9, 137.0, 136.8, 136.3, 135.9, 135.3, 131.0, 130.0, 128.9, 128.5, 127.8, 127.5, 127.3, 126.7, 126.3, 126.2, 126.0, 125.3, 123.5, 123.1, 122.4, 121.9, 116.7, 109.1, 82.2, 61.3, 48.9, 43.1, 18.5 ppm; HRMS (ESI): *m/z* calcd. for $C_{35}H_{26}N_3O_3$ $[M+H]^+$ 536.1969, found 536.1969.



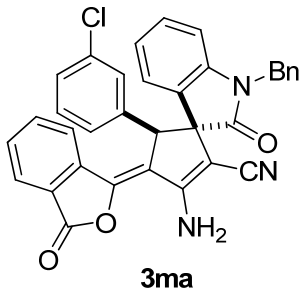
3ka

rel-(1*R*,5*R*)-3-Amino-1'-benzyl-5-(2-methoxyphenyl)-2'-oxo-4-(3-oxoisobenzofuran-1(3*H*)-ylidene)spiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile (3ka). The synthesis of **3ka** was conducted using a standardized protocol, followed by purification through column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (5:1 *v*/*v*) as the eluent to give 46.4 mg, 84% yield, yellow solid; m.p. 187–189 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (d, *J* = 6.8 Hz, 1H, ArH), 7.69–7.61 (m, 2H, ArH), 7.43–7.36 (m, 4H, ArH), 7.30 (t, *J* = 7.0 Hz, 1H, ArH), 7.21–7.17 (m, 1H, ArH), 7.12–7.07 (m, 4H, ArH + NH_2), 6.98–6.93 (m, 2H, ArH), 6.87 (t, *J* = 7.6 Hz, 1H, ArH), 6.69 (d, *J* = 8.0 Hz, 1H, ArH), 6.56 (t, *J* = 7.4 Hz, 1H, ArH), 5.77 (d, *J* = 7.6 Hz, 1H, ArH), 5.03 (d, *J* = 15.6 Hz, 1H, CH_2), 4.97 (d, *J* = 16.0 Hz, 1H, CH_2), 4.91 (s, 1H, CH), 2.96 (s, 3H, OCH_3) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ 177.8, 164.6, 158.9, 156.6, 142.8, 141.6, 136.5, 136.2, 135.3, 131.0, 129.2, 128.6, 127.4, 127.1, 126.6, 126.3, 126.0, 124.3, 123.6, 122.9, 121.4, 121.2, 120.5, 116.8, 110.7, 108.6, 82.1, 61.3, 54.8, 46.8, 42.9 ppm; HRMS (ESI): *m/z* calcd. for $C_{35}H_{26}N_3O_4$ $[M+H]^+$ 552.1918, found 552.1929.



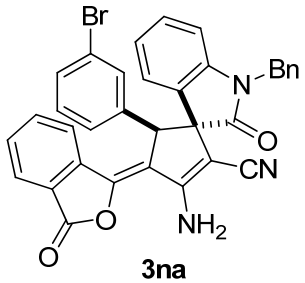
3la

rel-(1*R*,5*R*)-3-Amino-1'-benzyl-5-(3-fluorophenyl)-2'-oxo-4-(3-oxoisobenzofuran-1(3*H*)-ylidene)spiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile (3la). The synthesis of **3la** was conducted using a standardized protocol, followed by purification through column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (5:1 *v*/*v*) as the eluent to give 39.4 mg, 73% yield, yellow solid; m.p. 202–204 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 8.00 (d, *J* = 7.6 Hz, 1H, ArH), 7.75–7.50 (m, 3H, ArH), 7.37–7.26 (m, 6H, ArH), 7.14–7.09 (m, 3H, ArH + NH$_2$), 7.05–7.00 (m, 2H, ArH), 6.86 (d, *J* = 8.0 Hz, 2H, ArH), 6.63 (t, *J* = 7.6 Hz, 1H, ArH), 5.91–5.81 (m, 1H, ArH), 5.10 (d, *J* = 16.4 Hz, 1H, CH$_2$), 5.08 (s, 1H, CH), 4.90 (d, *J* = 16.0 Hz, 1H, CH$_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d$_6$): δ 177.5, 164.6, 159.4, 142.7, 142.0 (d, $^{1}J_{C–F}$= 48.2 Hz), 136.3, 135.9, 135.1, 131.1, 128.9, 128.6, 127.3, 126.8, 126.3, 125.8, 125.3, 124.2, 123.6 (d, $^{4}J_{C–F}$ = 2.5 Hz), 121.8, 116.7, 114.4 (d, $^{2}J_{C–F}$ = 19.5 Hz), 109.3, 81.7, 61.6, 51.2, 43.1 ppm; ^{19}F NMR (376 MHz, DMSO-d$_6$): δ −113.12, −112.20 ppm (two ^{19}F NMR signals for a monofluoro product may be owing to steric impulsion). HRMS (ESI): *m/z* calcd. for C$_{34}$H$_{23}$N$_3$O$_3$F [M+H]$^+$540.1718, found 540.1741.



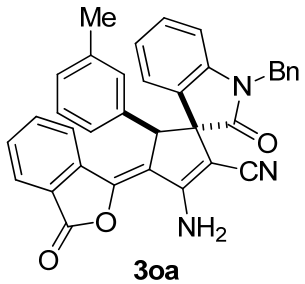
3ma

rel-(1*R*,5*R*)-3-Amino-1'-benzyl-5-(3-chlorophenyl)-2'-oxo-4-(3-oxoisobenzofuran-1(3*H*)-ylidene)spiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile (3ma).The synthesis of **3ma** was conducted using a standardized protocol, followed by purification through column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (5:1 *v*/*v*) as the eluent to give 43.3 mg, 78% yield, yellow solid; m.p. 202–204 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 8.01 (d, *J* = 7.2 Hz, 1H, ArH), 7.75–7.54 (m, 3H, ArH), 7.37–6.86 (m, 13H, ArH + NH$_2$), 6.64 (t, *J* = 7.6 Hz, 1H, ArH), 5.86–5.78 (m, 1H, ArH), 5.11 (d, *J* = 16.4 Hz, 1H, CH$_2$), 5.09 (s, 1H, CH), 4.90 (d, *J* = 16.0 Hz, 1H, CH$_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d$_6$): δ 177.4, 164.5, 159.5, 142.7, 142.2, 141.3, 136.3, 135.9, 135.1, 132.6, 131.1, 130.6, 130.2, 128.9, 128.6, 127.6, 127.3, 126.8, 126.1, 125.8, 125.4, 124.9, 124.1, 123.6, 121.7, 121.4, 116.8, 109.3, 81.5, 61.7, 51.1, 43.1 ppm; HRMS (ESI): *m/z* calcd. for C$_{34}$H$_{23}$N$_3$O$_3$Cl [M+H]$^+$ 556.1423, found 556.1453.



3na

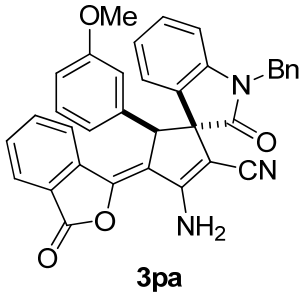
rel-(1*R*,5*R*)-3-Amino-1'-benzyl-5-(3-bromophenyl)-2'-oxo-4-(3-oxoisobenzofuran-1(3*H*)-ylidene)spiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile (3na).The synthesis of **3na** was conducted using a standardized protocol, followed by purification through column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (5:1 *v*/*v*) as the eluent to give 48.0 mg, 80% yield, yellow solid; m.p. 207-209. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (d, *J* = 7.6 Hz, 1H, ArH), 7.74–7.63 (m, 2H, ArH), 7.54 (d, *J* = 3.2 Hz, 1H, ArH), 7.41–7.05 (m, 12H, ArH + NH_2), 6.87 (br s, 1H, ArH), 6.65 (t, *J* = 7.6 Hz, 1H, ArH), 5.83–5.75 (m, 1H, ArH), 5.11 (d, *J* = 15.6 Hz, 1H, CH_2), 5.08 (s, 1H, CH), 4.89 (d, *J* = 16.0 Hz, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ 177.4, 164.5, 159.5, 142.7, 142.2, 141.5, 136.3, 135.9, 135.1, 133.5, 131.1, 130.5, 128.9, 128.6, 127.3, 126.8, 126.1, 125.8, 125.4, 124.1, 123.6, 121.7, 121.2, 116.8, 109.3, 81.5, 61.7, 51.0, 43.1 ppm. HRMS (ESI): *m/z* calcd. for $C_{34}H_{23}N_3O_3{}^{79}Br$ $[M+H]^+$ 600.0918, found 600.0953; calcd. for $C_{34}H_{23}N_3O_3{}^{81}Br$ $[M+H]^+$ 602.0897, found 602.0938.



3oa

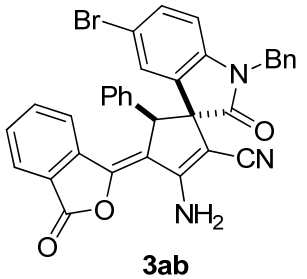
rel-(1*R*,5*R*)-3-Amino-1'-benzyl-2'-oxo-4-(3-oxoisobenzofuran-1(3*H*)-ylidene)-5-(*m*-tolyl)spiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile (3oa). The synthesis of **3oa** was conducted using a standardized protocol, followed by purification through column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (5:1 *v*/*v*) as the eluent to give 47.1 mg, 88% yield, yellow solid; m.p. 201–203 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (d, *J* = 7.2 Hz, 1H, ArH), 7.70–7.49 (m, 3H, ArH), 7.35–7.26 (m, 5H, ArH), 7.16–6.68 (m, 8H, ArH + NH_2), 6.58 (t, *J* = 7.6 Hz, 1H, ArH), 5.82 (br s, 1H, ArH), 5.07 (d, *J* = 16.0 Hz, 1H, CH_2), 4.92 (s, 1H, CH), 4.90 (d, *J* = 15.6 Hz, 1H, CH_2), 2.24, 2.01 (s, 3H, CH_3) ppm (the presence of two singlets for a single methyl may be owing to steric impulsion, the rotation is not freedom); ^{13}C NMR (101 MHz, DMSO-d_6): δ 177.7, 164.6, 159.5, 142.6, 141.9, 138.8, 136.5, 135.9, 135.1, 130.9, 128.64, 128.55, 128.2, 127.3, 126.8, 126.5, 125.8, 125.6,

124.2, 123.5, 122.3, 121.7, 116.9, 109.1, 81.8, 61.9, 52.1, 43.0, 21.1 ppm; HRMS (ESI): *m/z* calcd. for $C_{35}H_{26}N_3O_3$ $[M+H]^+$ 536.1969, found 536.1988.



3pa

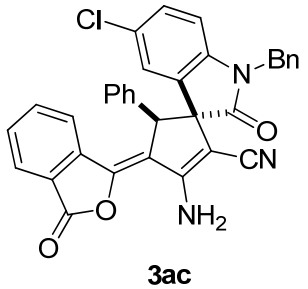
rel-(1*R*,5*R*)-3-Amino-1'-benzyl-5-(3-methoxyphenyl)-2'-oxo-4-(3-oxoisobenzofuran-1(3*H*)-ylidene)spiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile (3pa).The synthesis of **3pa** was conducted using a standardized protocol, followed by purification through column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (5:1 *v*/*v*) as the eluent to give 48.6 mg, 88% yield, yellow solid; m.p. 195–197 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 7.99 (d, *J* = 7.2 Hz, 1H, ArH), 7.71–7.52 (m, 3H, ArH), 7.38–7.26 (m, 5H, ArH), 7.18–6.69 (m, 7H, ArH + NH$_2$), 6.62–6.51 (m, 2H, ArH), 5.88 (br s, 1H, ArH), 5.07 (d, *J* = 16.0 Hz, 1H, CH$_2$), 4.95 (s, 1H, CH), 4.92 (d, *J* = 16.0 Hz, 1H, CH$_2$), 3.67, 3.41 (s, 3H, CH$_3$) ppm (the presence of two singlets for a single methyoxy may be owing to steric impulsion, the rotation is not freedom); ^{13}C NMR (101 MHz, DMSO-d$_6$): δ 177.7, 164.6, 159.5, 142.5, 142.0, 140.3, 136.5, 135.9, 135.1, 130.9, 129.3, 128.7, 128.6, 127.3, 126.8, 126.6, 125.8, 125.4, 124.3, 123.5, 121.9, 121.8, 118.4, 116.8, 116.2, 113.5, 109.1, 81.8, 61.8, 54.8, 52.1, 43.0 ppm; HRMS (ESI): *m/z* calcd. for $C_{35}H_{26}N_3O_4$ $[M+H]^+$ 552.1918, found 552.1938.



3ab

rel-(1*R*,5*R*)-3-Amino-1'-benzyl-5'-bromo-2'-oxo-4-(3-oxoisobenzofuran-1(3*H*)-ylidene)-5-phenylspiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile (3ab). The synthesis of **3ab** was conducted using a standardized protocol, followed by purification through column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (5:1 *v*/*v*) as the eluent to give 46.8 mg, 78% yield, yellow solid; m.p. 193–195 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 8.00 (d, *J* = 7.2 Hz, 1H, ArH), 7.71–7.61 (m, 2H, ArH), 7.54 (d, *J* = 8.0 Hz, 1H, ArH), 7.37–7.03 (m, 13H, ArH + NH$_2$), 6.81 (d, *J* = 8.4 Hz, 1H, ArH), 5.78 (d, *J* = 2.0 Hz, 1H, ArH), 5.09 (d, *J* = 16.4 Hz, 1H, CH$_2$), 5.05 (s, 1H, CH), 4.90 (d, *J* = 16.0 Hz, 1H, CH$_2$) ppm; ^{13}C NMR (101 MHz, DMSO-d$_6$): δ 177.2, 164.5, 159.7, 142.2, 141.9, 138.7, 136.3, 135.5, 135.1, 131.3, 131.1, 128.8, 128.6, 128.4, 127.8, 127.4, 126.8, 125.8, 124.3, 123.6, 121.6, 116.7, 113.8,

111.0, 80.8, 62.0, 51.7, 43.1 ppm; HRMS (ESI): *m/z* calcd. for $C_{34}H_{23}{}^{79}BrN_3O_3$ $[M+H]^+$ 600.0918, found 600.0932; calcd. for $C_{34}H_{23}{}^{81}BrN_3O_3$ $[M+H]^+$ 602.0897, found 602.0919.



3ac

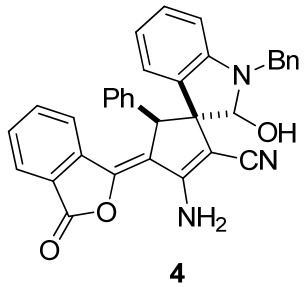
rel-(1*R*,5*R*)-3-Amino-1'-benzyl-5'-chloro-2'-oxo-4-(-3-oxoisobenzofuran-1(3*H*)-ylidene)-5-phenylspiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile (3ac). The synthesis of **3ac** was conducted using a standardized protocol, followed by purification through column chromatography on silica gel (200–300 mesh) with petroleum ether/ethyl acetate (5:1 *v*/*v*) as the eluent to give 44.5 mg, 80% yield, yellow solid; m.p. 193–195 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00 (d, *J* = 7.2 Hz, 1H, ArH), 7.71–7.61 (m, 2H, ArH), 7.54 (d, *J* = 8.0 Hz, 1H, ArH), 7.37–7.04 (m, 13H, ArH + NH_2), 6.86 (d, *J* = 8.4 Hz, 1H, ArH), 5.67 (d, *J* = 2.4 Hz, 1H, ArH), 5.09 (d, *J* = 16.0 Hz, 1H, CH_2), 5.06 (s, 1H, CH), 4.91 (d, *J* = 16.0 Hz, 1H, CH_2) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ 177.3, 164.5, 159.7, 142.1, 141.5, 138.7, 136.3, 135.5, 135.1, 131.1, 128.6, 128.5, 127.8, 127.4, 126.8, 126.0, 125.8, 125.5, 124.2, 123.6, 121.6, 116.7, 110.5, 80.8, 61.9, 51.7, 43.1 ppm; HRMS (ESI): *m/z* calcd. for $C_{34}H_{23}ClN_3O_3$ $[M+H]^+$ 556.1423, found 556.1447.

3. Scale-up preparation of product 3aa

2-benzylidene-1*H*-indene-1,3(2*H*)-dione **1a** (1.0 g, 4.4 mmol) and 2-(1-benzyl-2-oxoindolin-3-yl)malononitrile **2a** (1.5 g, 5.3 mmol) were placed in a flask, dissolved in CH_3CN (50 mL). K_2CO_3 (68 mg, 0.49 mmol) was added, and the mixture was stirred at room temperature for 24 h. After completion of the reaction, the solvent was evaporated, and the product was rapidly purified by column chromatography (petroleum ether/ethyl acetate, 5:1) to afford **3aa** 1.95 g, 85% yield.

4. Derivatization reaction of compound 3aa

rel-(1*R*,5*R*)-3-Amino-1'-benzyl-2'-oxo-4-(3-oxoisobenzofuran-1(3*H*)-ylidene)-5-phenylspiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile **(3aa)** (0.54 g, 1.0 mmol) was placed in a flask, dissolved in DCM and EtOH (30 mL, DCM:EtOH/1:1), and the mixture was stirred at 0 °C for 0.5 h. $NaBH_4$ (46 mg, 1.2 mmol) was added, and the mixture was stirred at room temperature for 8 h. After completion of the reaction, the reaction was quenched with water until gas evolution ceased. The resulting mixture was extracted with DCM, and the combined organic layers were evaporated, and the product was rapidly purified by column chromatography (petroleum ether/ethyl acetate, 3:1) to afford **4** as a white solid, 0.29 g, 55% yield.



4

rel-(1*R*,5*R*)-3-amino-1'-benzyl-2'-hydroxy-4-(3-oxoisobenzofuran-1(3*H*)-ylidene)-5-phenylspiro[cyclopentane-1,3'-indolin]-2-ene-2-carbonitrile (4). m.p. 233–235 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.56 (d, *J* = 6.8 Hz, 1H, ArH), 7.48–7.41 (m, 3H, NH_2 + ArH), 7.27 (d, *J* = 7.2 Hz, 1H, ArH), 7.20–7.12 (m, 5H, ArH), 6.99–6.93 (m, 4H, ArH), 6.70 (t, *J* = 7.2 Hz, 1H, ArH), 6.64–6.46 (m, 6H, ArH + OH), 4.83 (d, *J* = 16.4 Hz, 1H, CH_2), 4.78 (dd, *J* = 11.2, 2.4, 1H, CH), 4.67 (d, *J* = 16.0 Hz, 1H, CH_2), 3.53 (d, *J* = 11.2 Hz, 1H, CH) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ 177.0, 169.8, 163.3, 146.6, 141.3, 135.5, 135.2, 133.1, 129.6, 128.8, 128.4, 128.2, 127.0, 126.8, 126.3, 125.5, 124.8, 124.2, 123.5, 121.7, 117.2, 108.7, 77.3, 73.3, 62.0, 51.2, 49.2, 42.6 ppm; HRMS (ESI): *m/z* calcd. for $C_{34}H_{26}N_3O_3$ $[M+H]^+$ 524.1969, found 524.1995.

5. Copies of ^{1}H and ^{13}C NMR spectra of new compounds 3

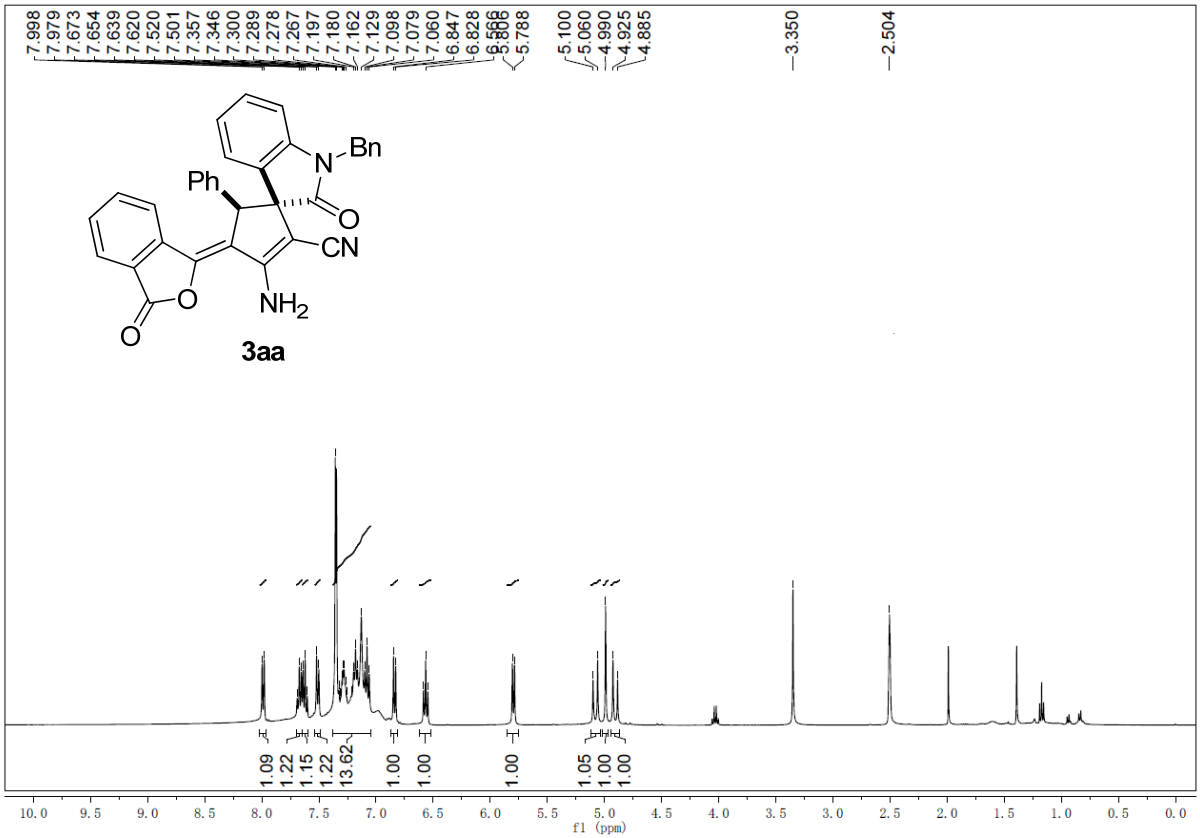


Figure S1. ^{1}H NMR of **3aa** (400 MHz, DMSO-d_6)

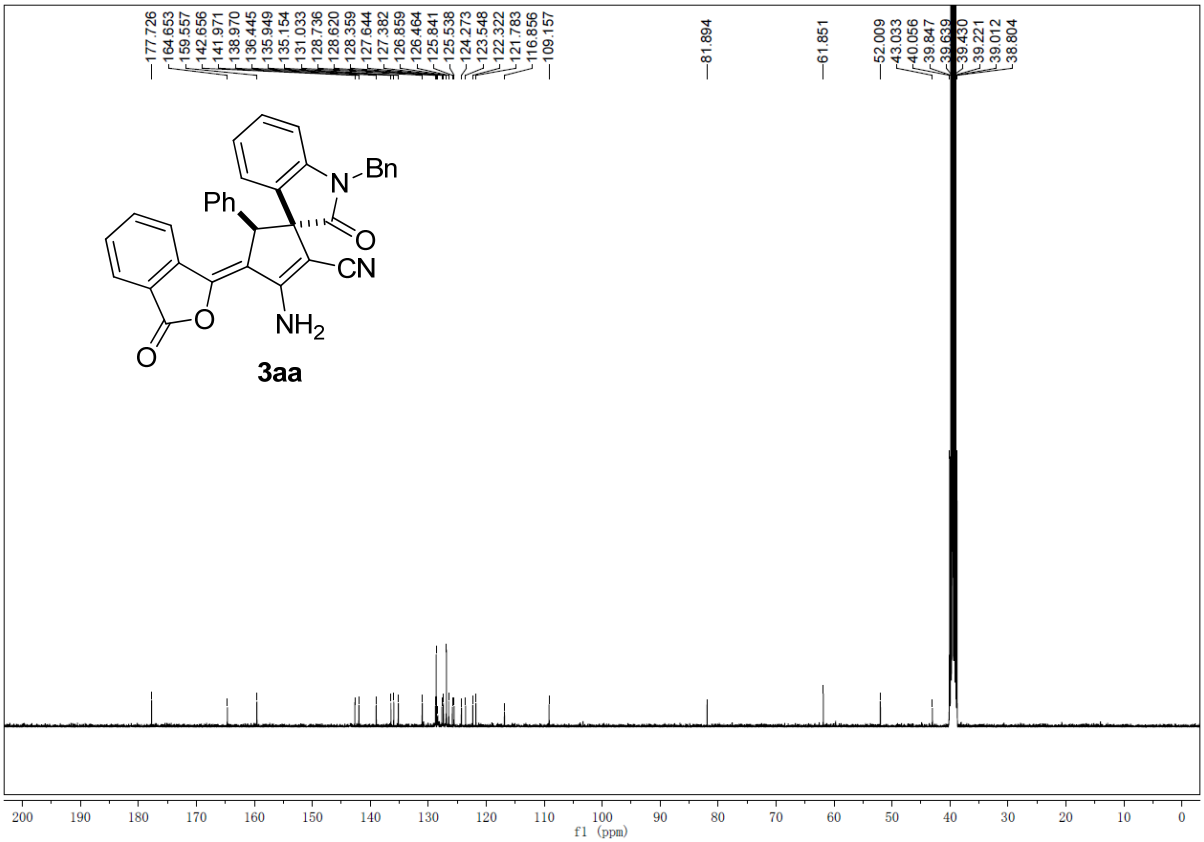


Figure S2. ^{13}C NMR of **3aa** (101 MHz, DMSO-d_6)

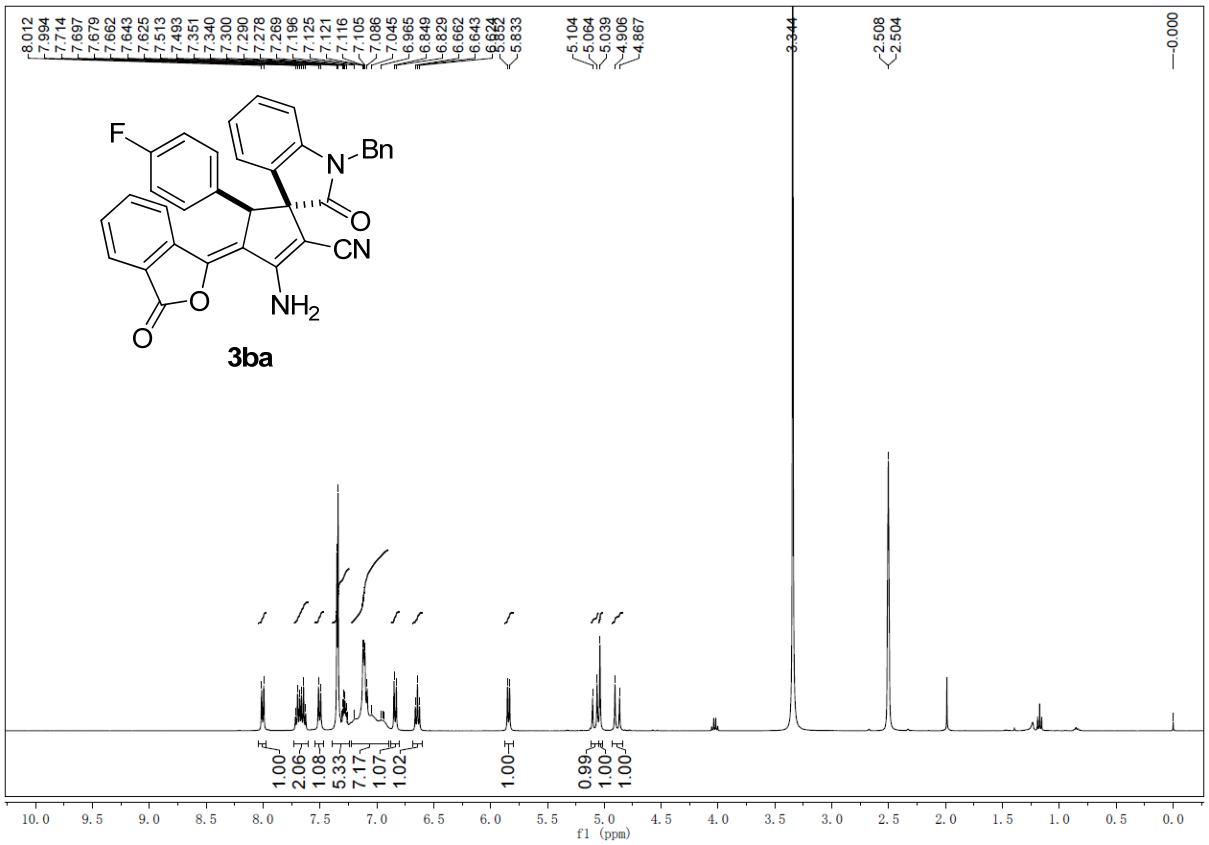


Figure S3. ^{1}H NMR of **3ba** (400 MHz, DMSO-d$_6$)

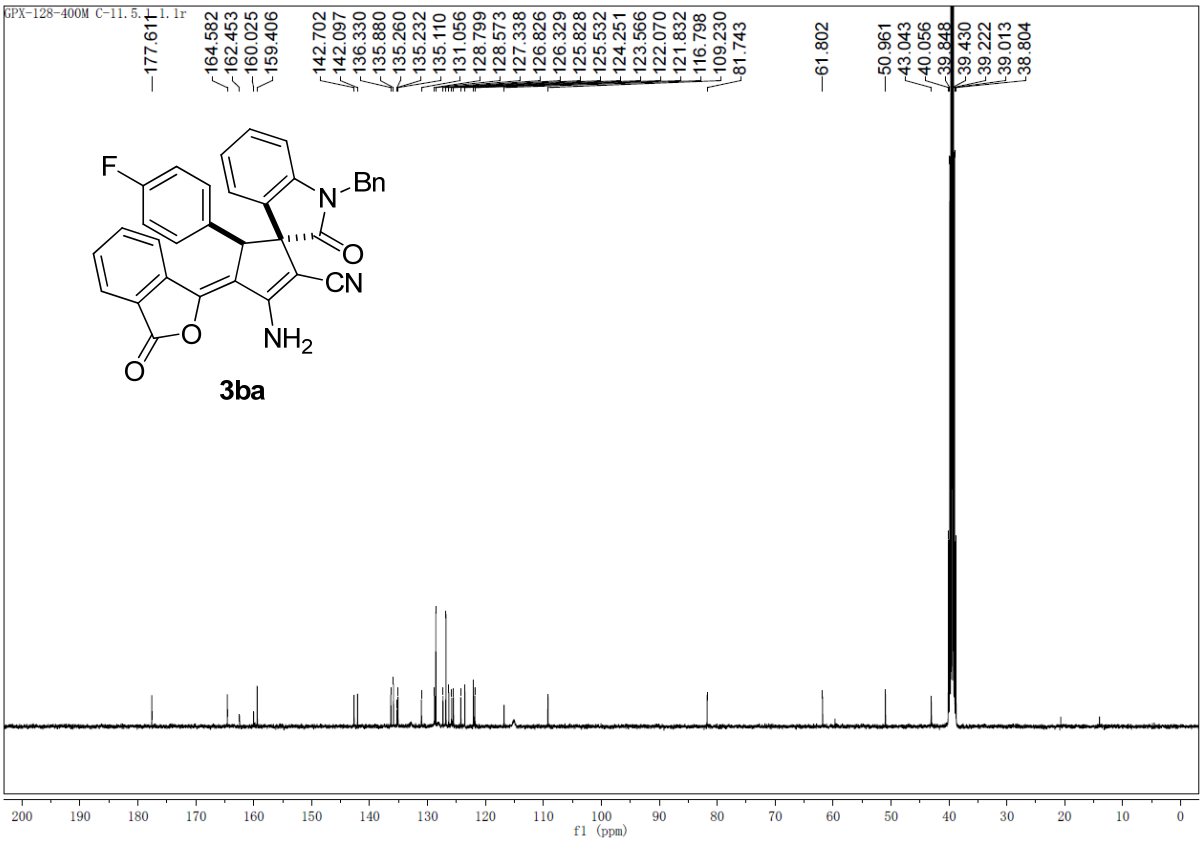


Figure S4. ^{13}C NMR of **3ba** (101 MHz, DMSO-d$_6$)

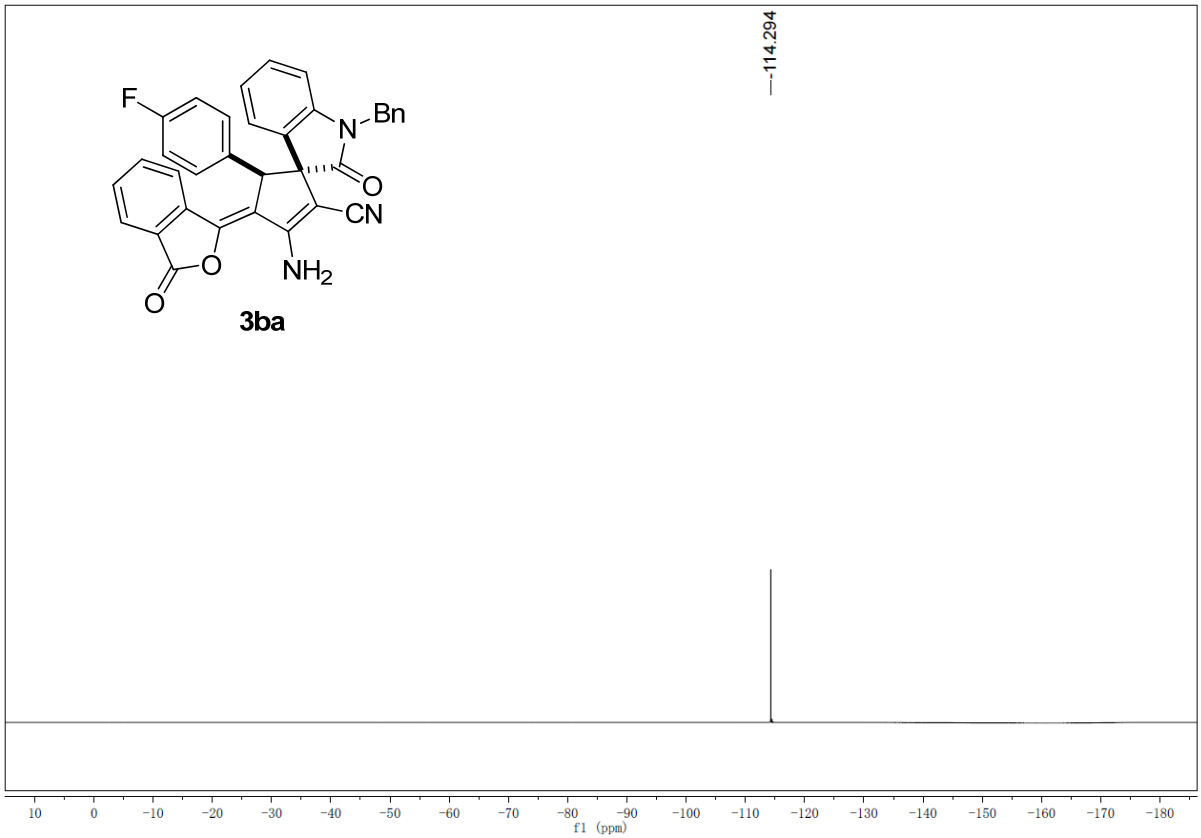


Figure S5. ^{19}F NMR of **3ba** (376 MHz, DMSO-d$_6$)

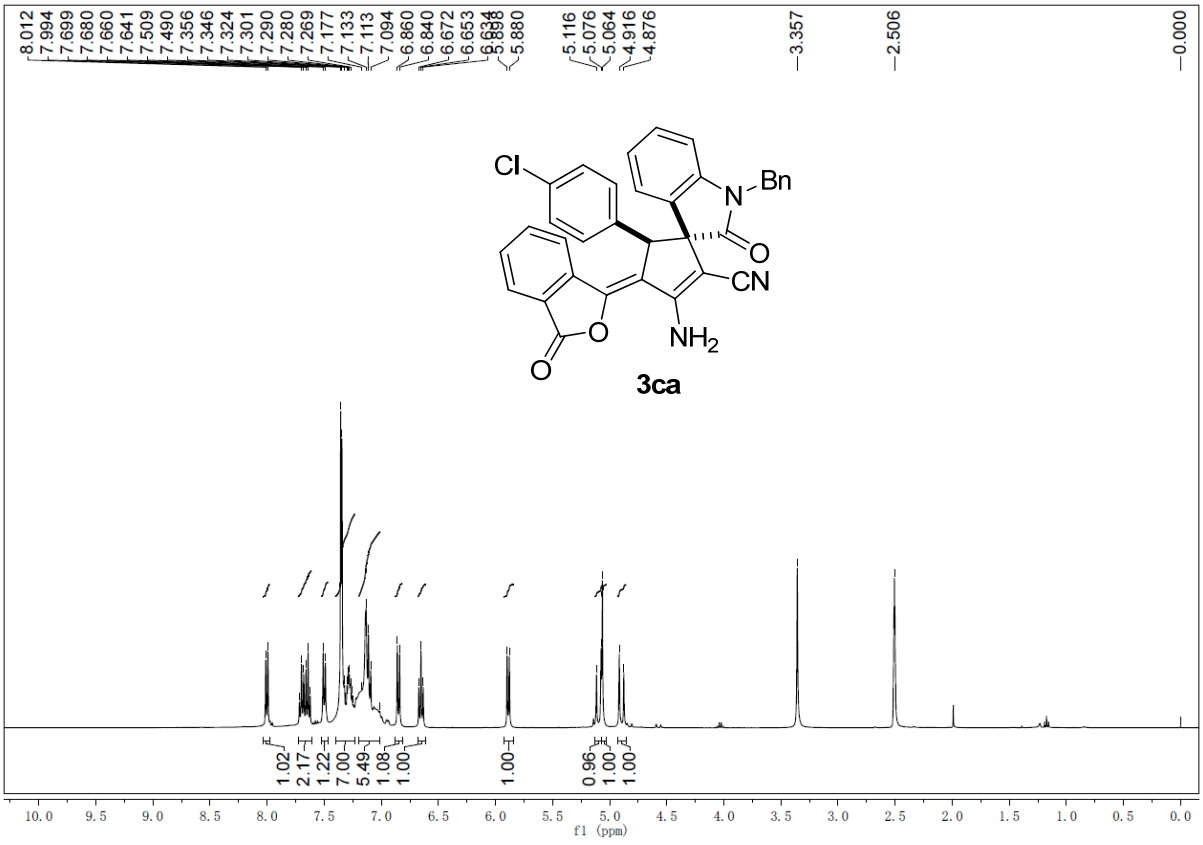


Figure S6. ^{1}H NMR of 3**ca** (400 MHz, DMSO-d$_6$)

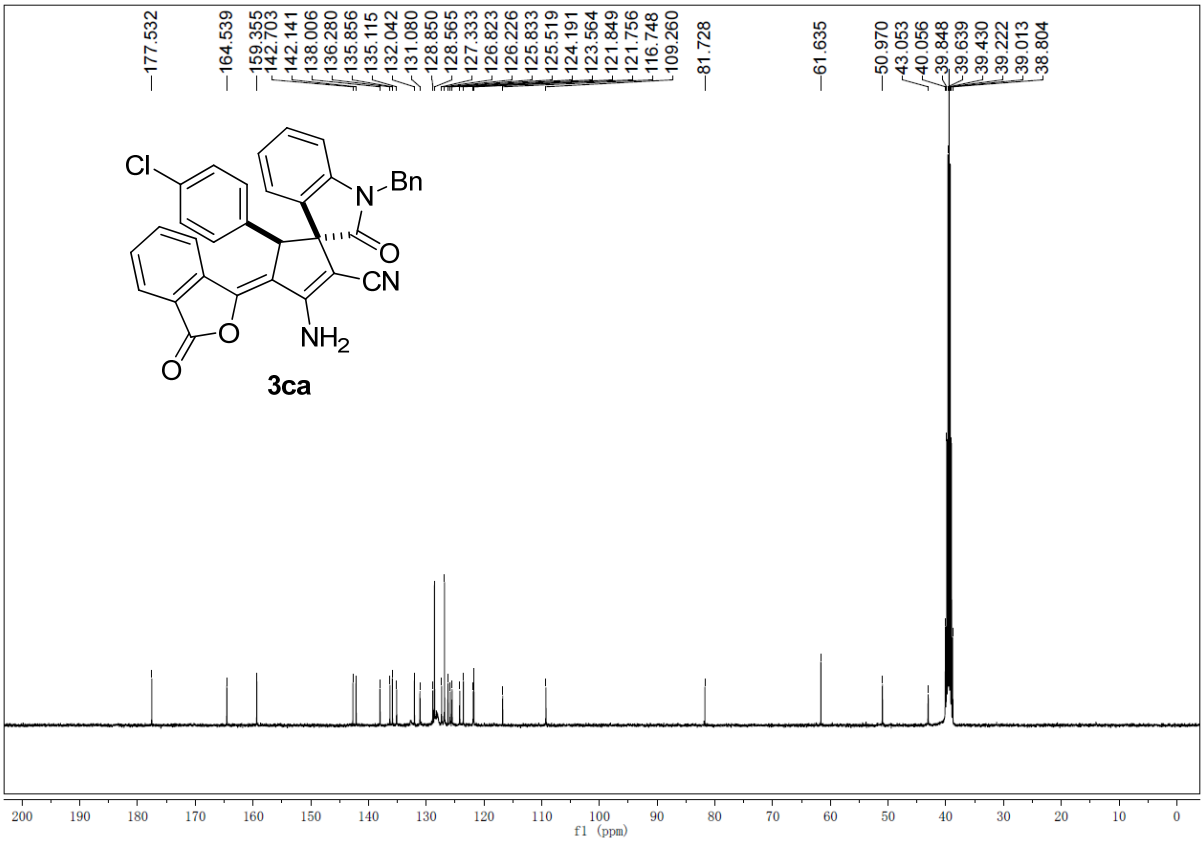


Figure S7. ^{13}C NMR of **3ca** (101 MHz, DMSO-d$_6$)

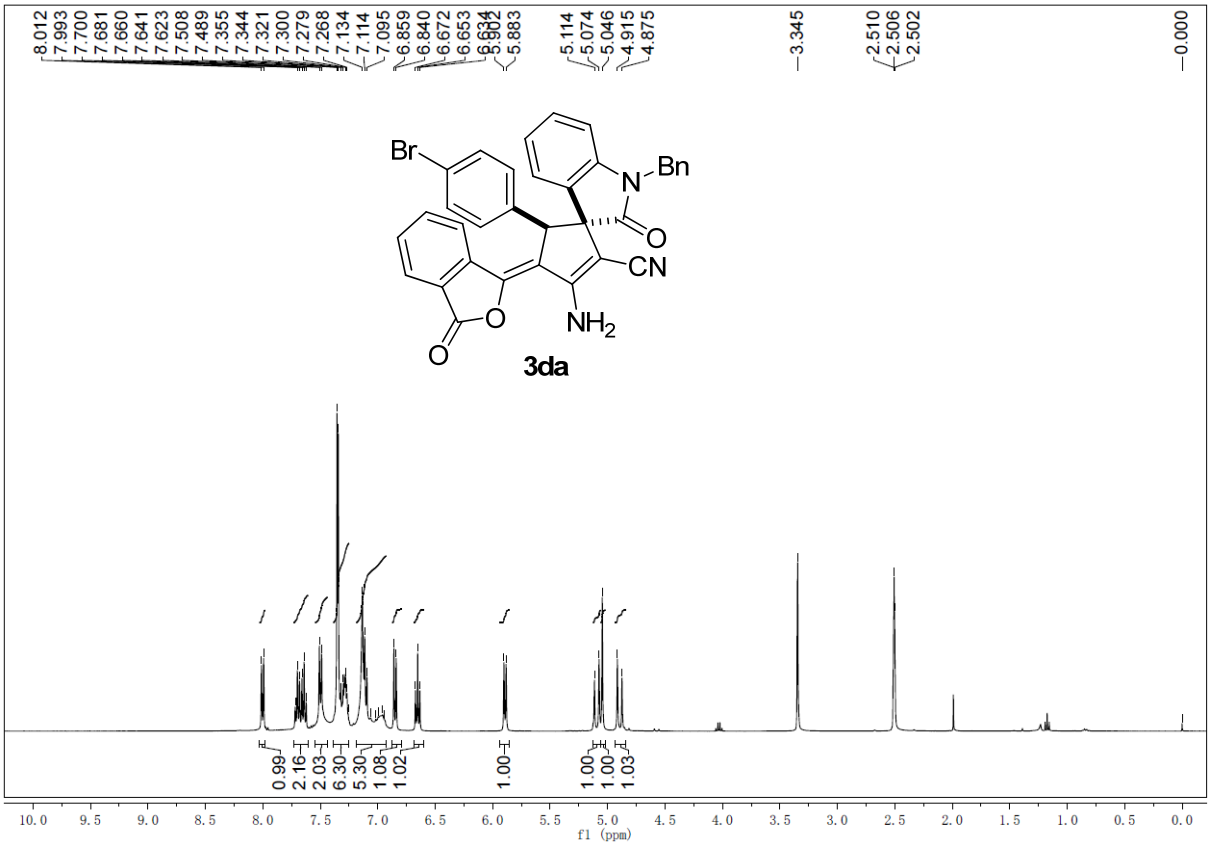


Figure S8. ^{1}H NMR of **3da** (400 MHz, DMSO-d$_6$)

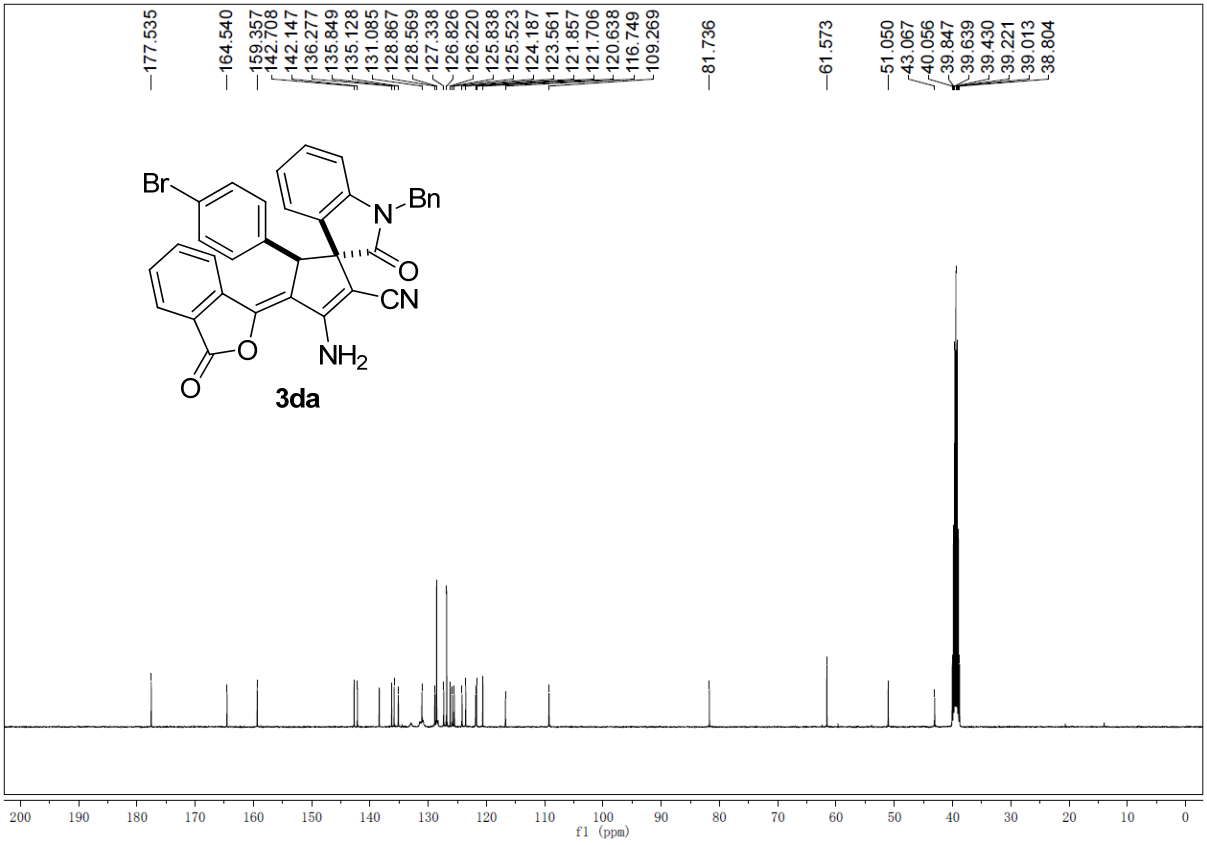


Figure S9. ^{13}C NMR of **3da** (101 MHz, DMSO-d$_6$)

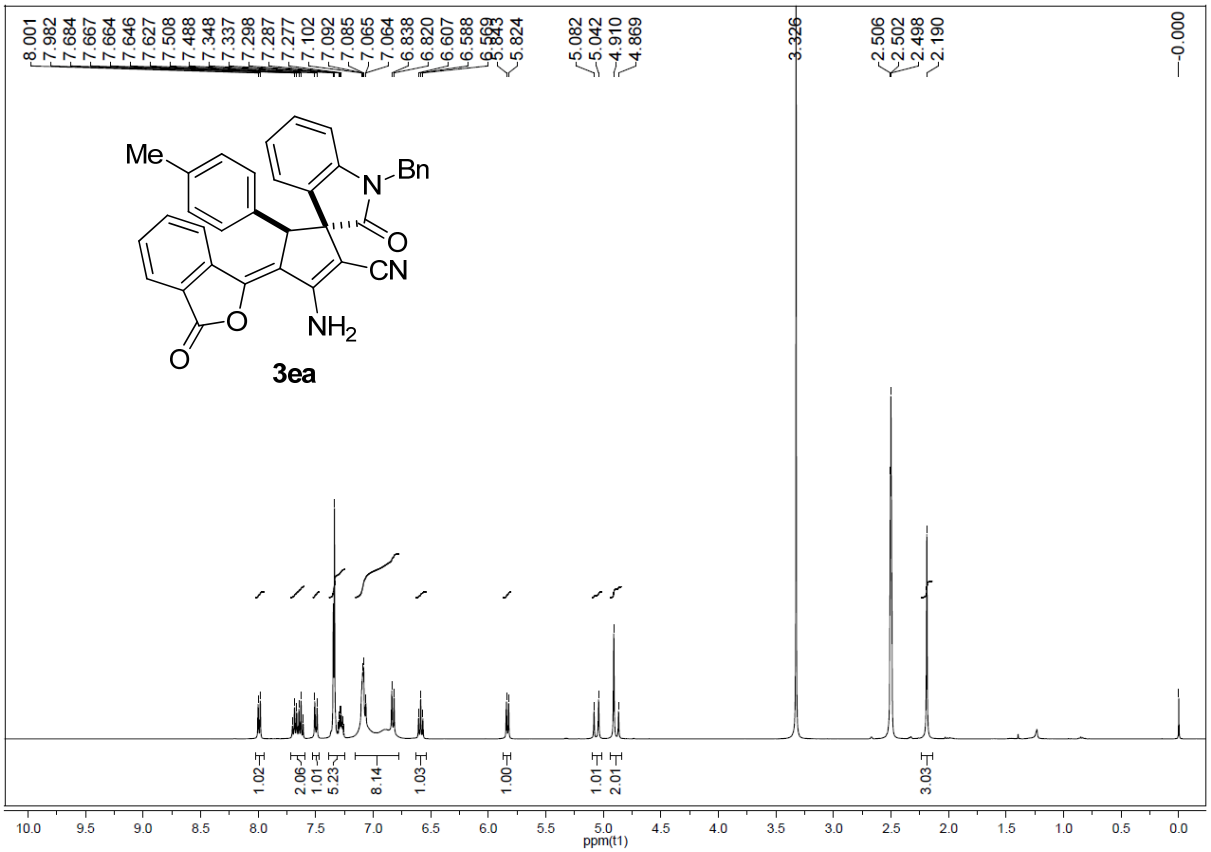


Figure S10. ^{1}H NMR of **3ea** (400 MHz, DMSO-d$_6$)

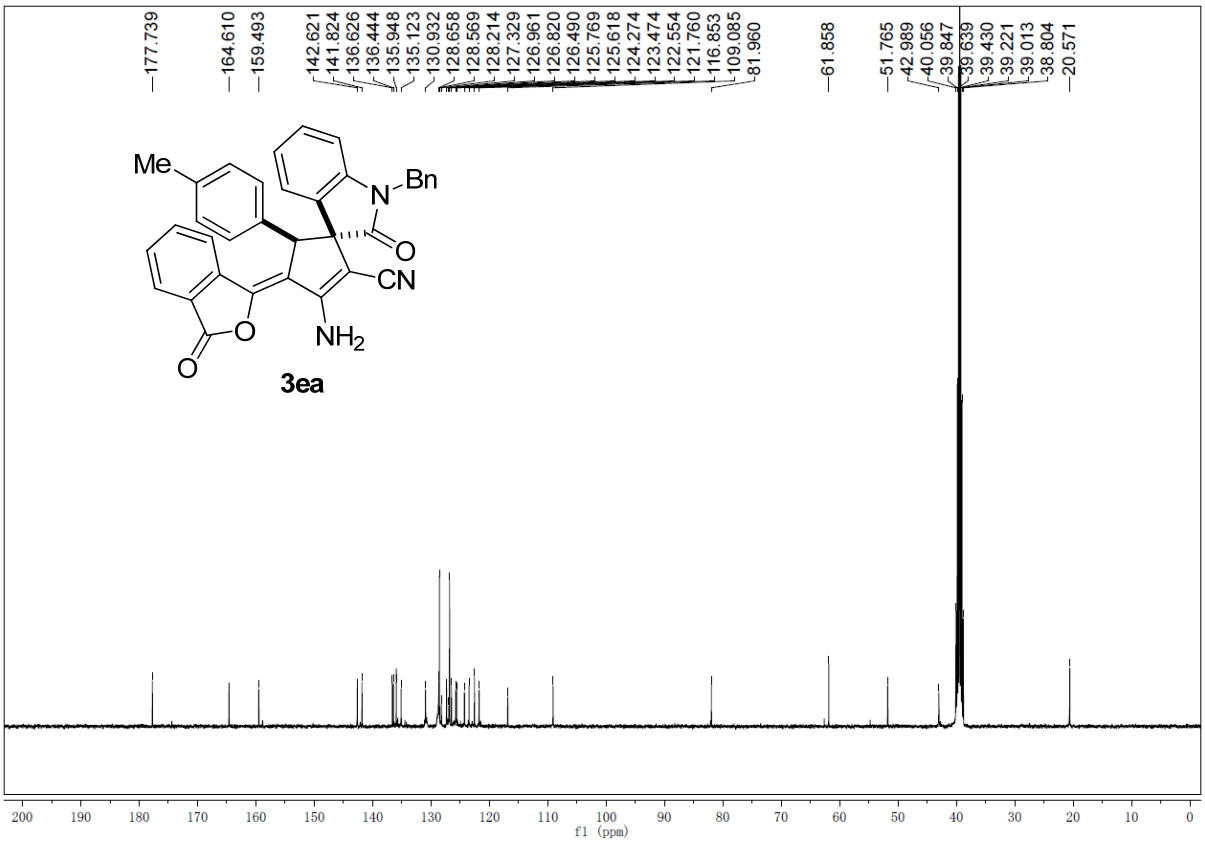


Figure S11. ^{13}C NMR of **3ea** (101 MHz, DMSO-d_6)

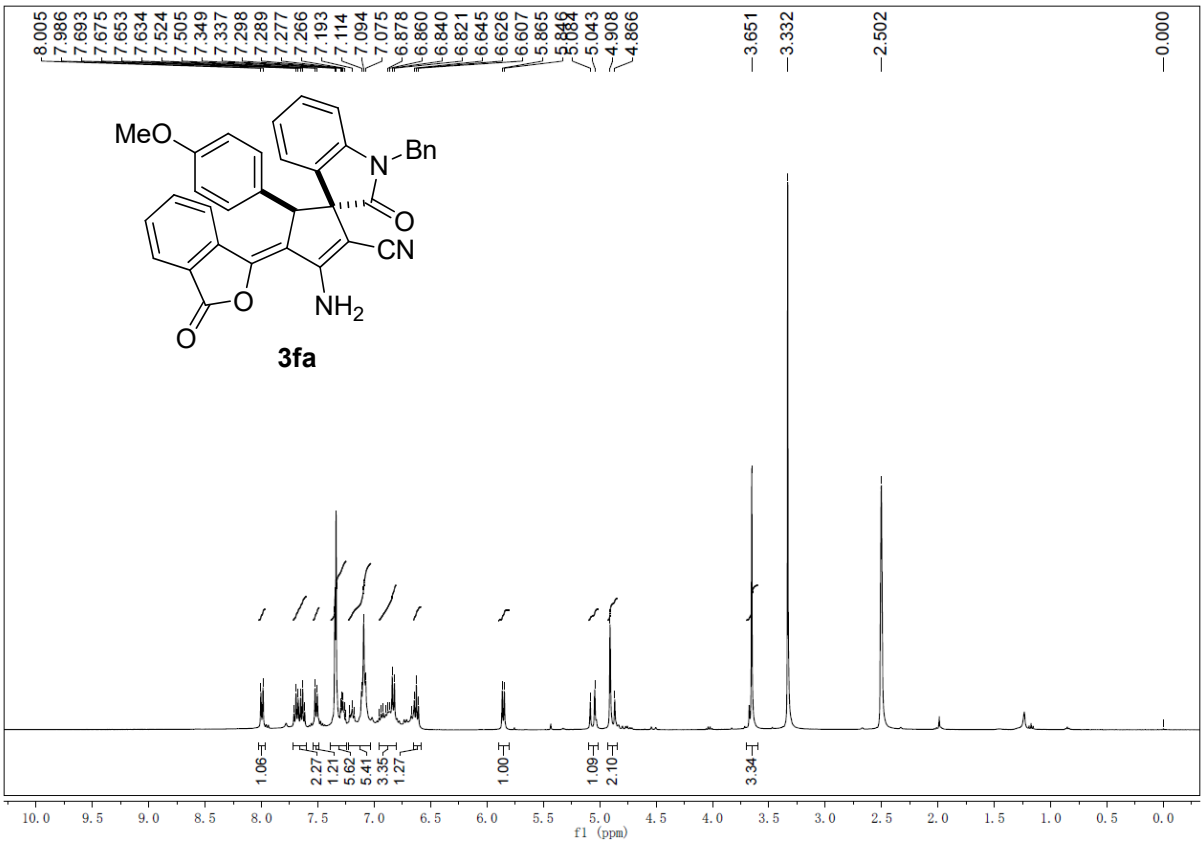


Figure S12. ^{1}H NMR of **3fa** (400 MHz, DMSO-d_6)

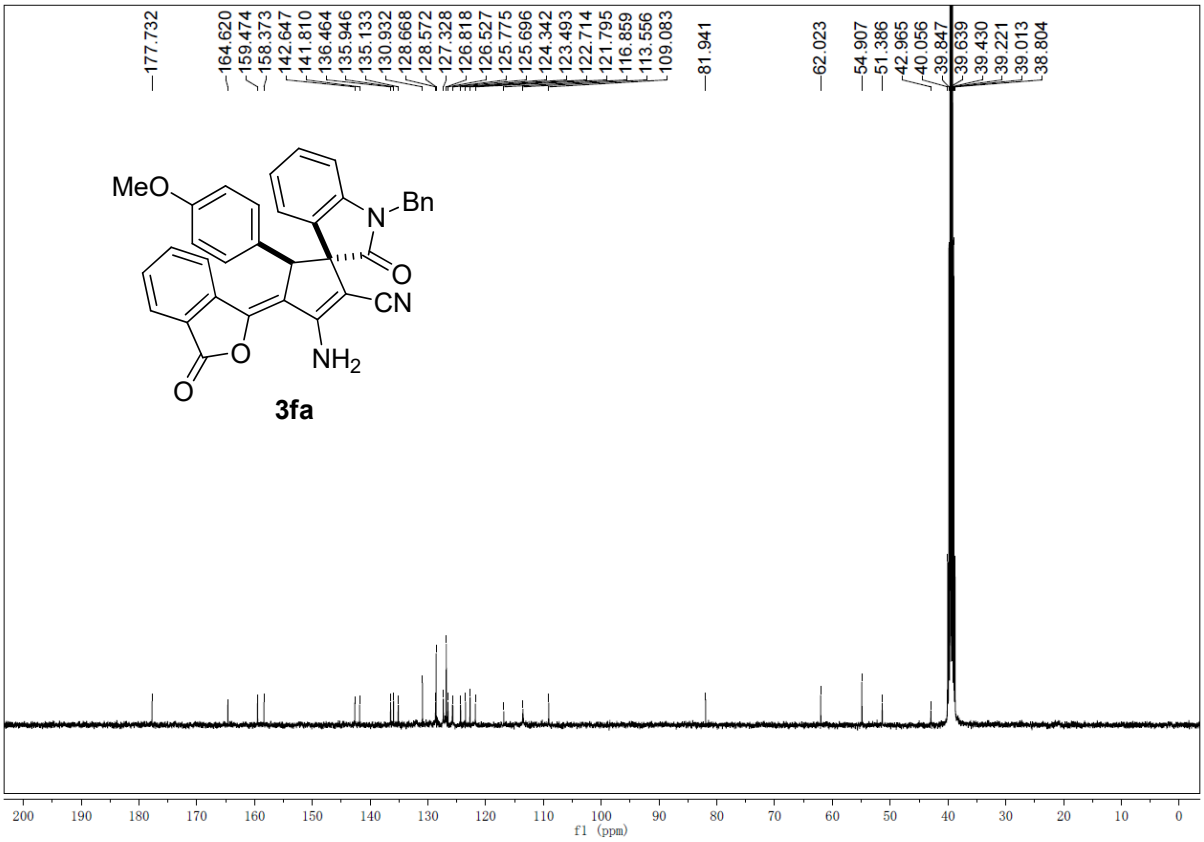


Figure S13. ^{13}C NMR of **3fa** (101 MHz, DMSO-d$_6$)

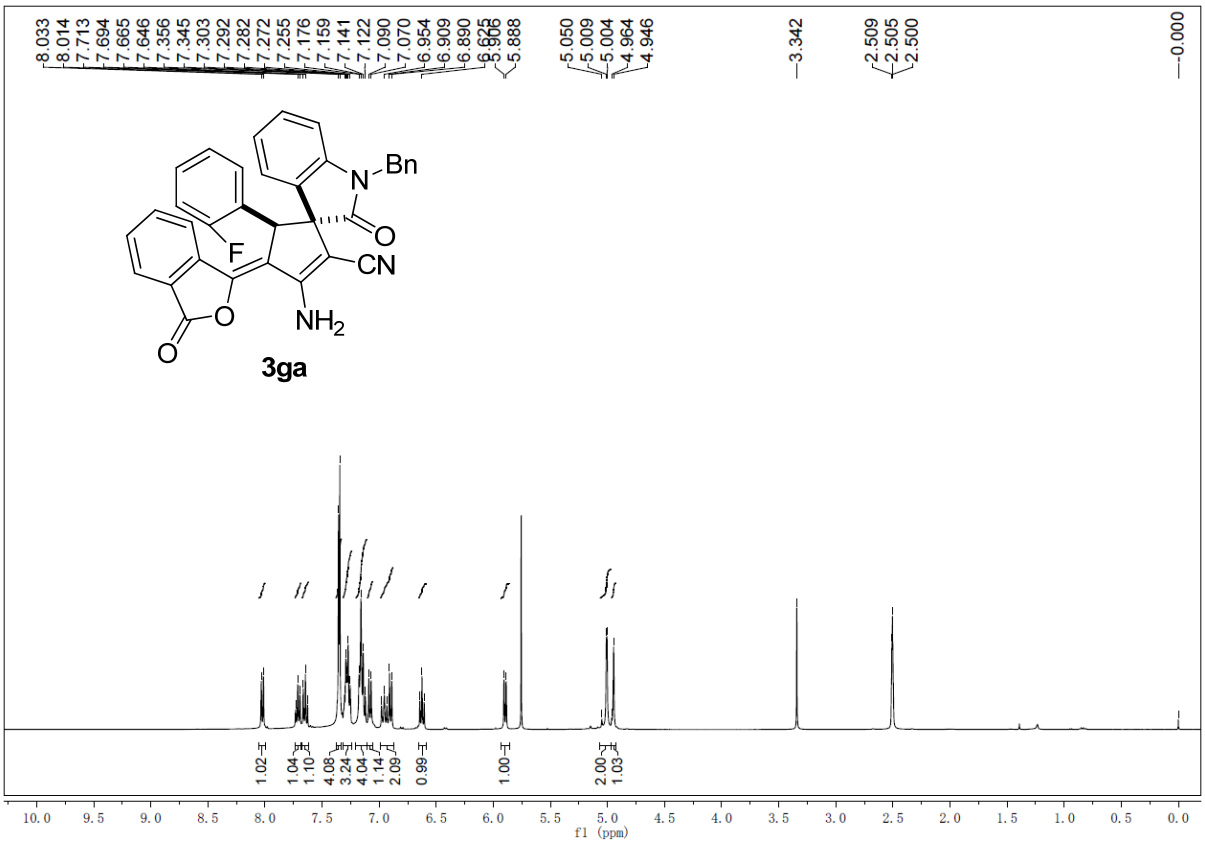


Figure S14. ^{1}H NMR of **3ga** (400 MHz, DMSO-d$_6$)

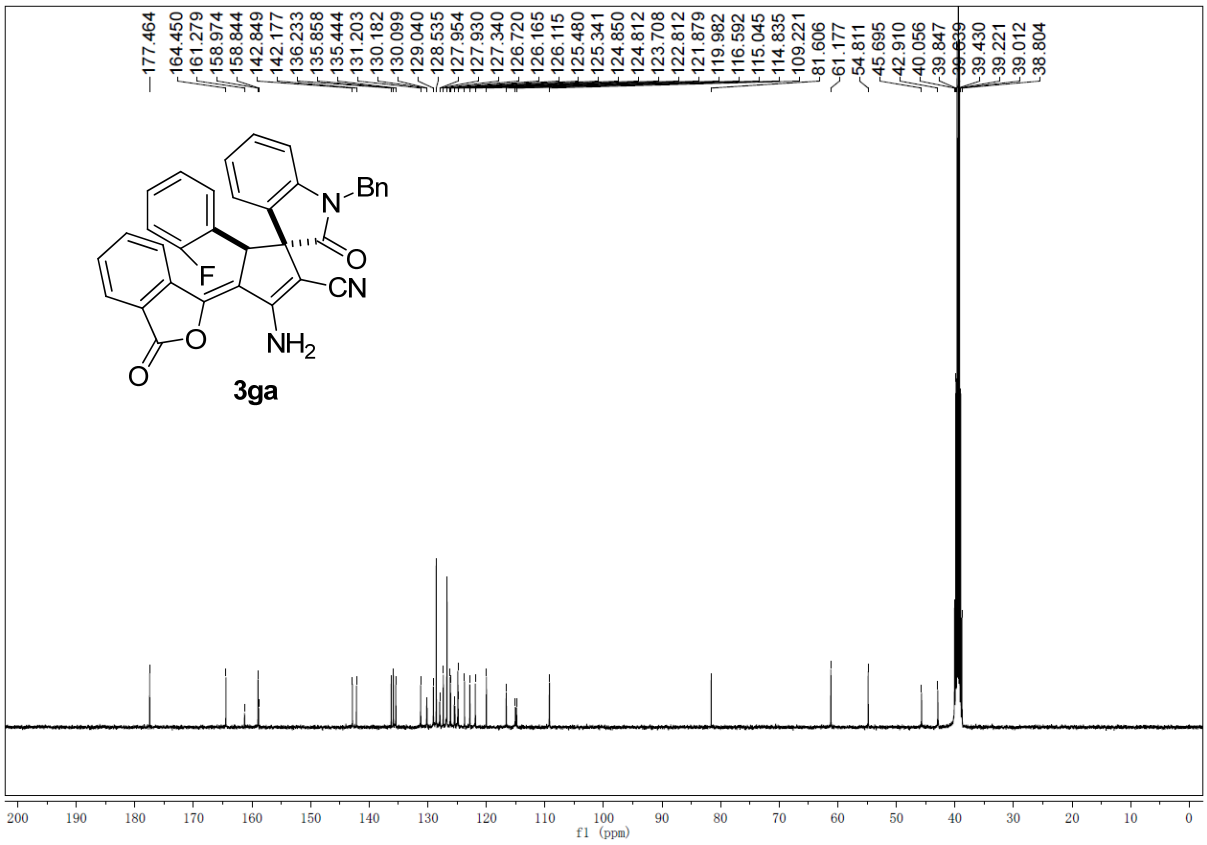


Figure S15. ^{13}C NMR of **3ga** (101 MHz, DMSO-d_6)

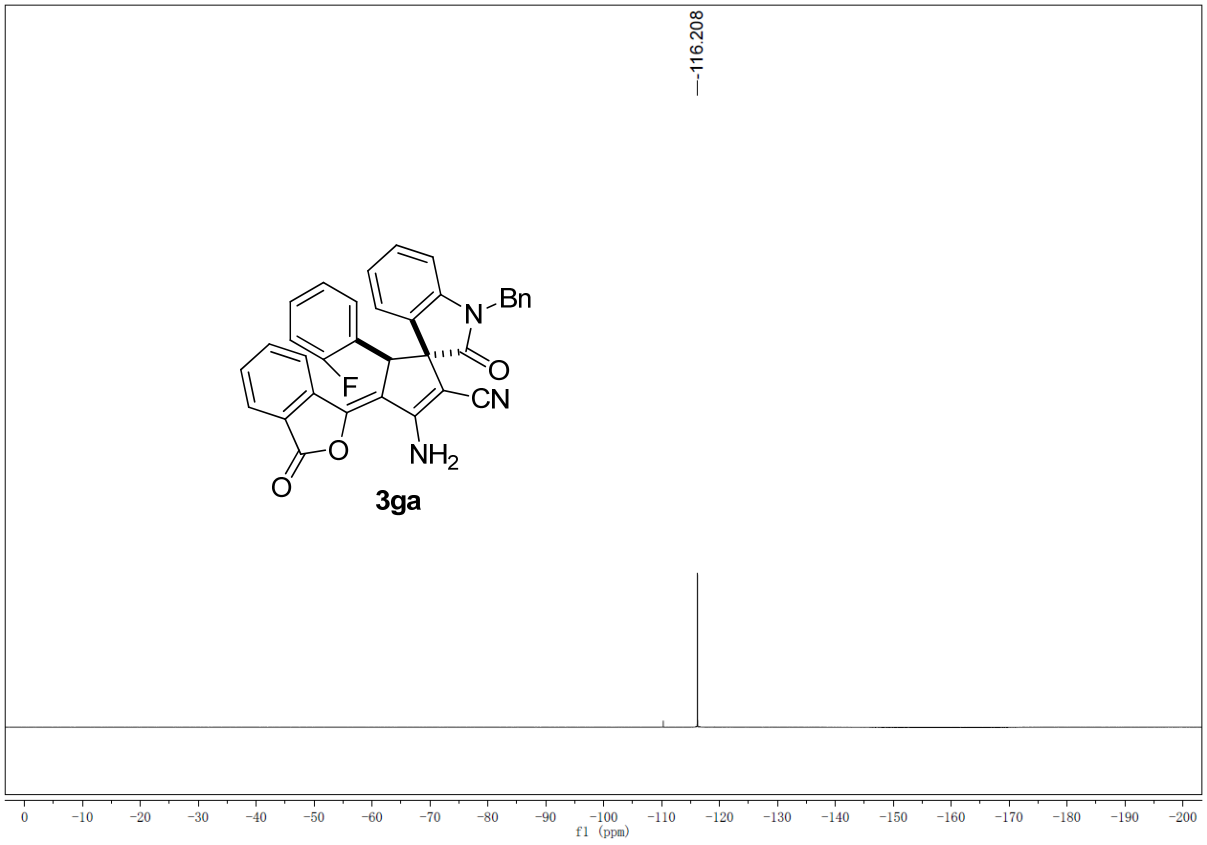


Figure S16. ^{19}F NMR of **3ga** (376 MHz, DMSO-d_6)

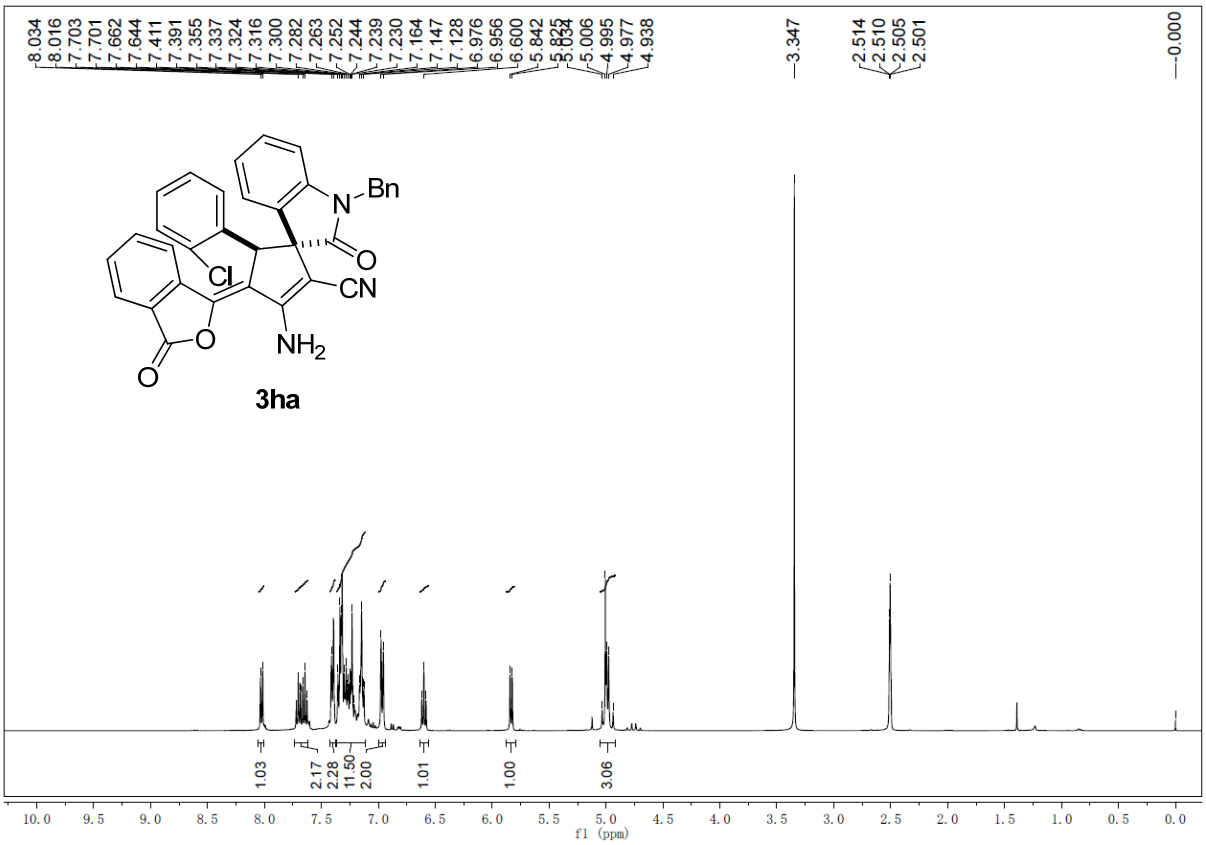


Figure S17. ^{1}H NMR of **3ha** (400 MHz, DMSO-d$_6$)

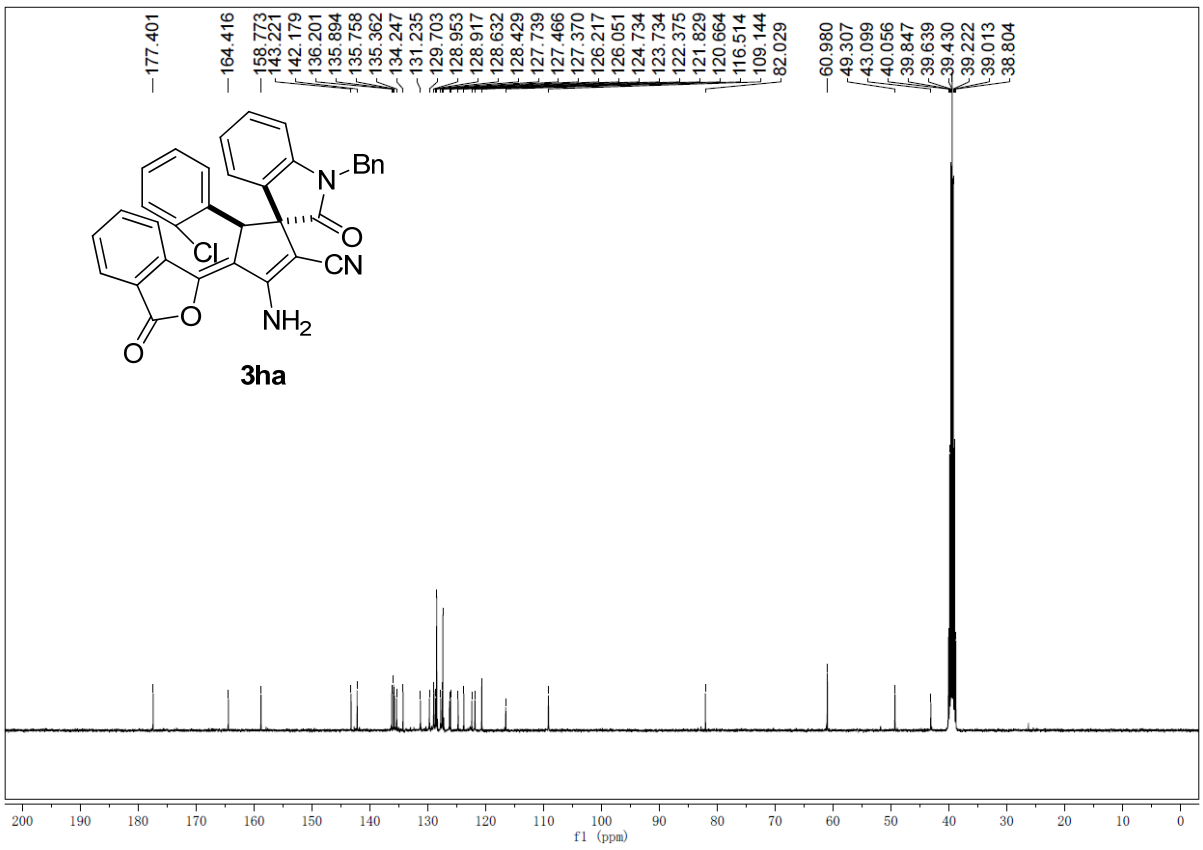


Figure S18. ^{13}C NMR of **3ha** (101 MHz, DMSO-d$_6$)

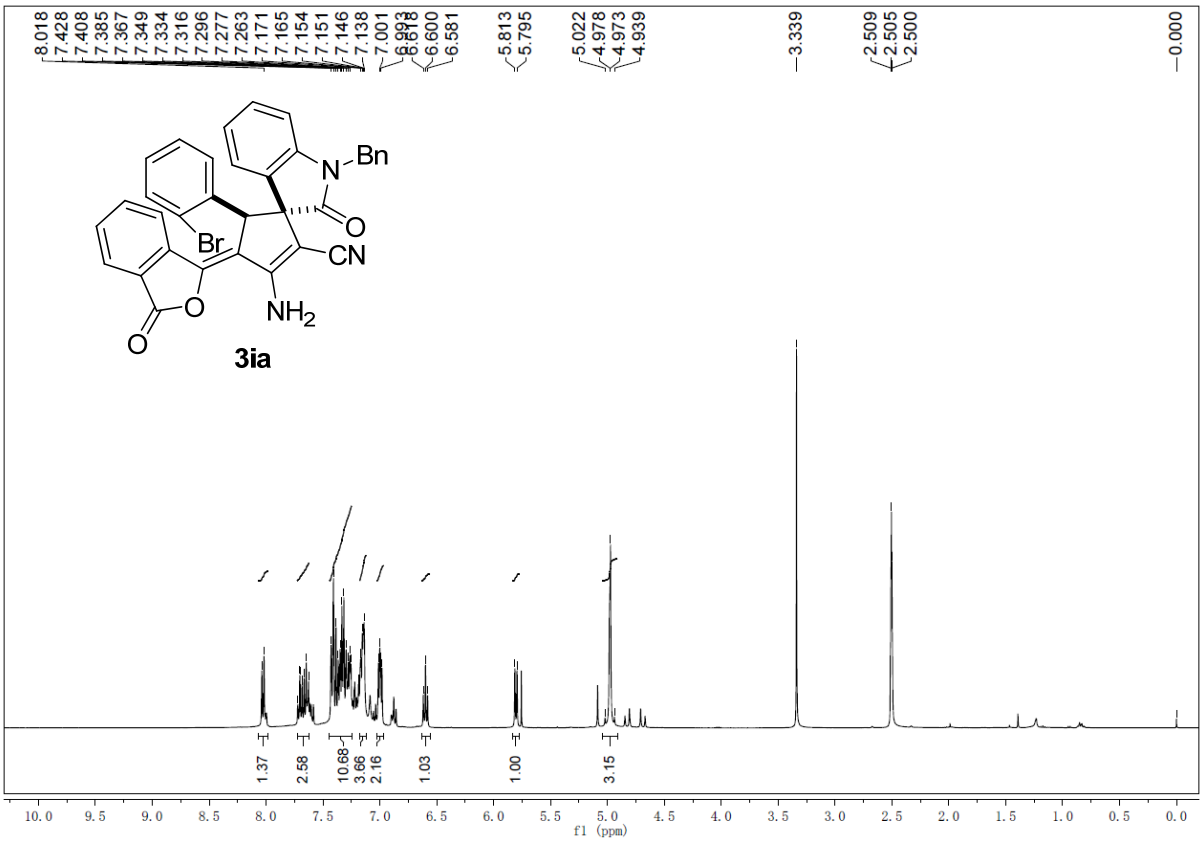


Figure S19. ^{1}H NMR of **3ia** (400 MHz, DMSO-d$_6$)

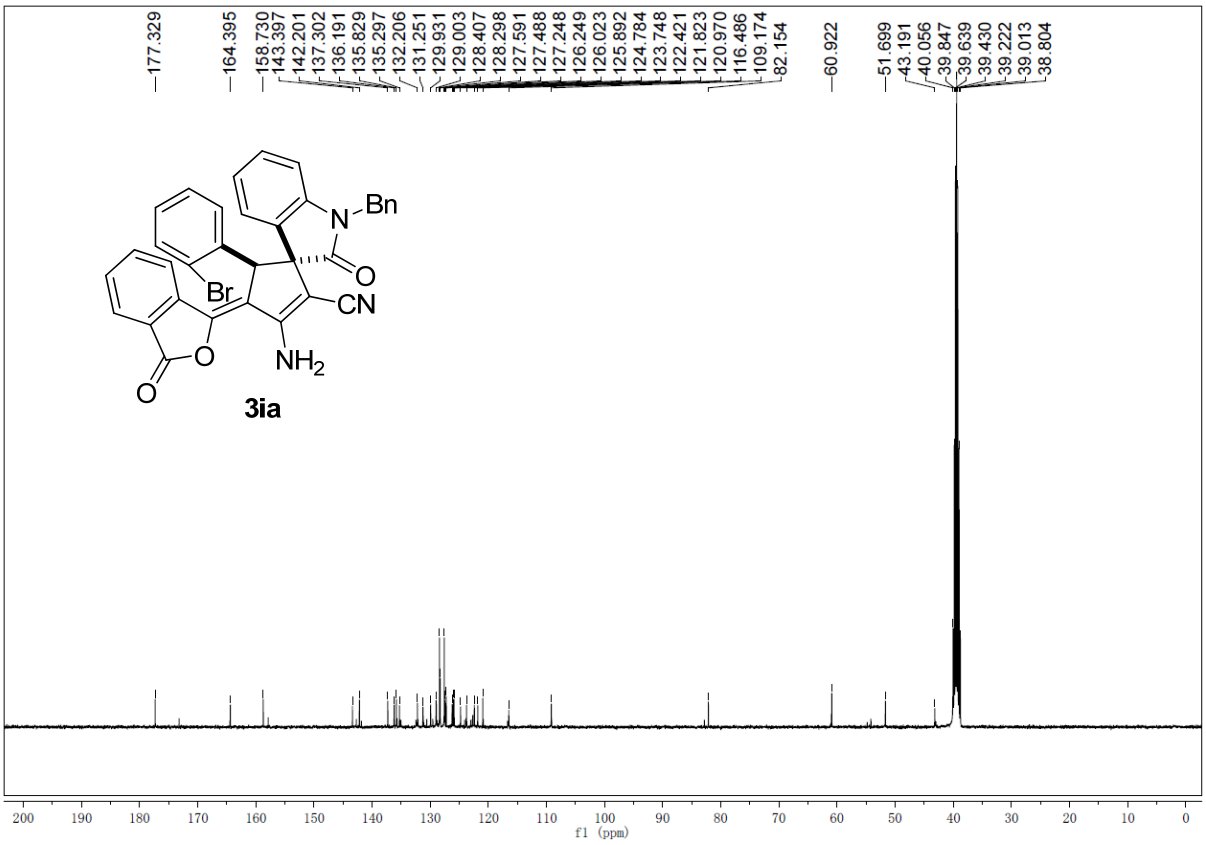


Figure S20. ^{13}C NMR of **3ia** (101 MHz, DMSO-d$_6$)

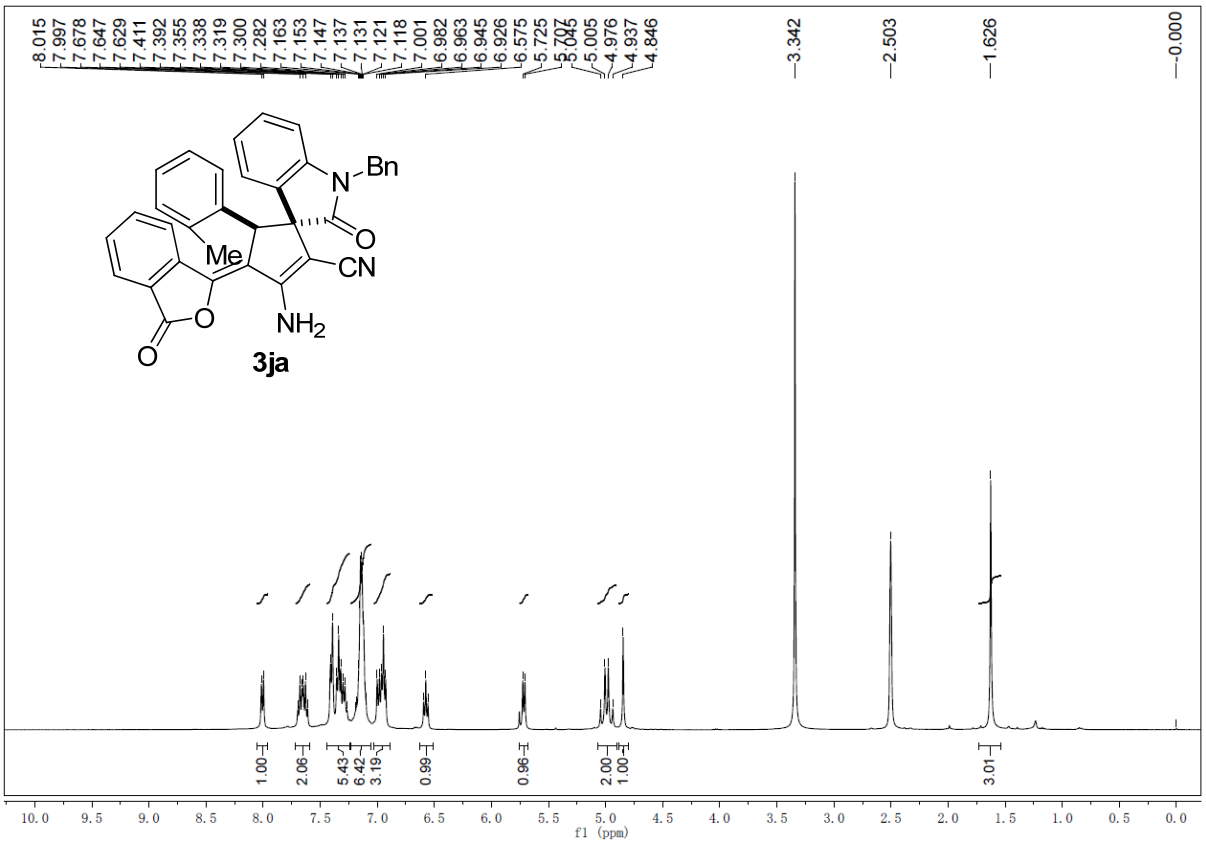


Figure S21. ^{1}H NMR of **3ja** (400 MHz, DMSO-d$_6$)

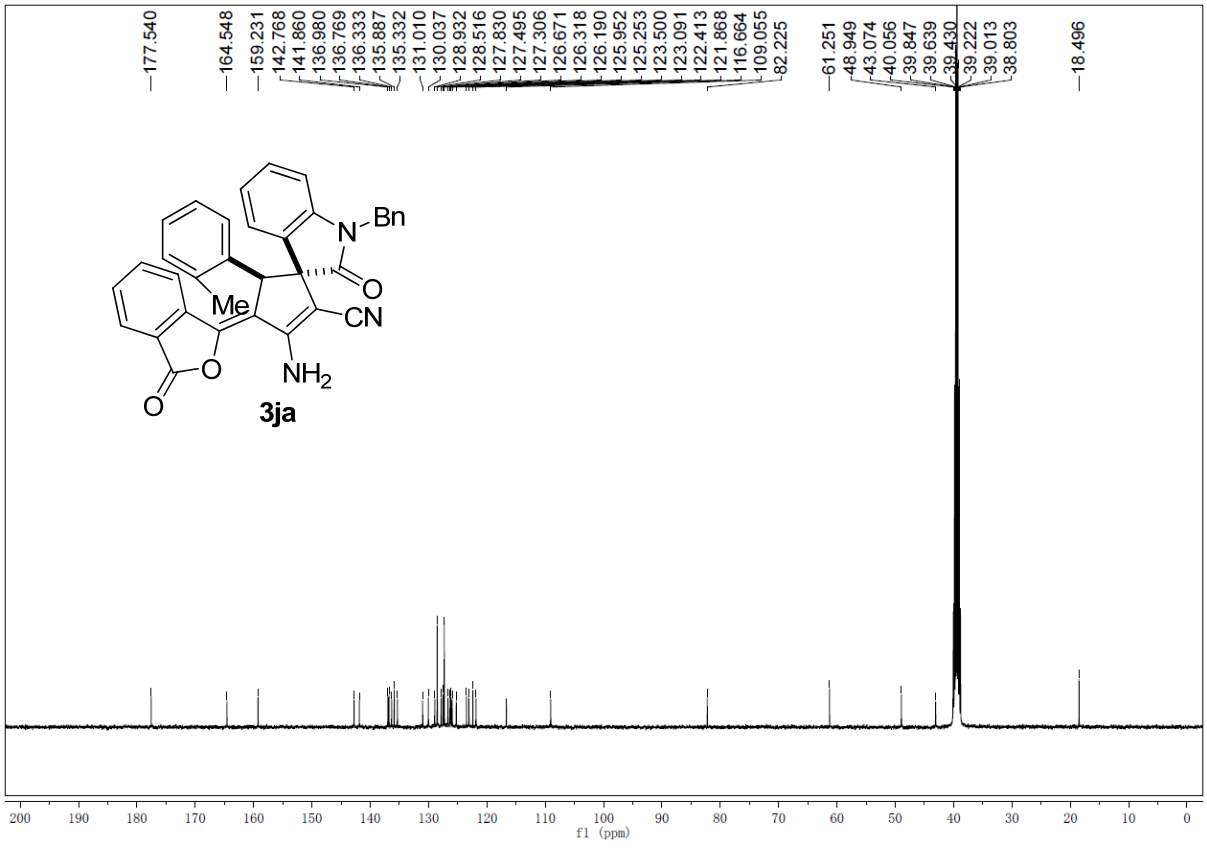


Figure S22. ^{13}C NMR of **3ja** (101 MHz, DMSO-d$_6$)

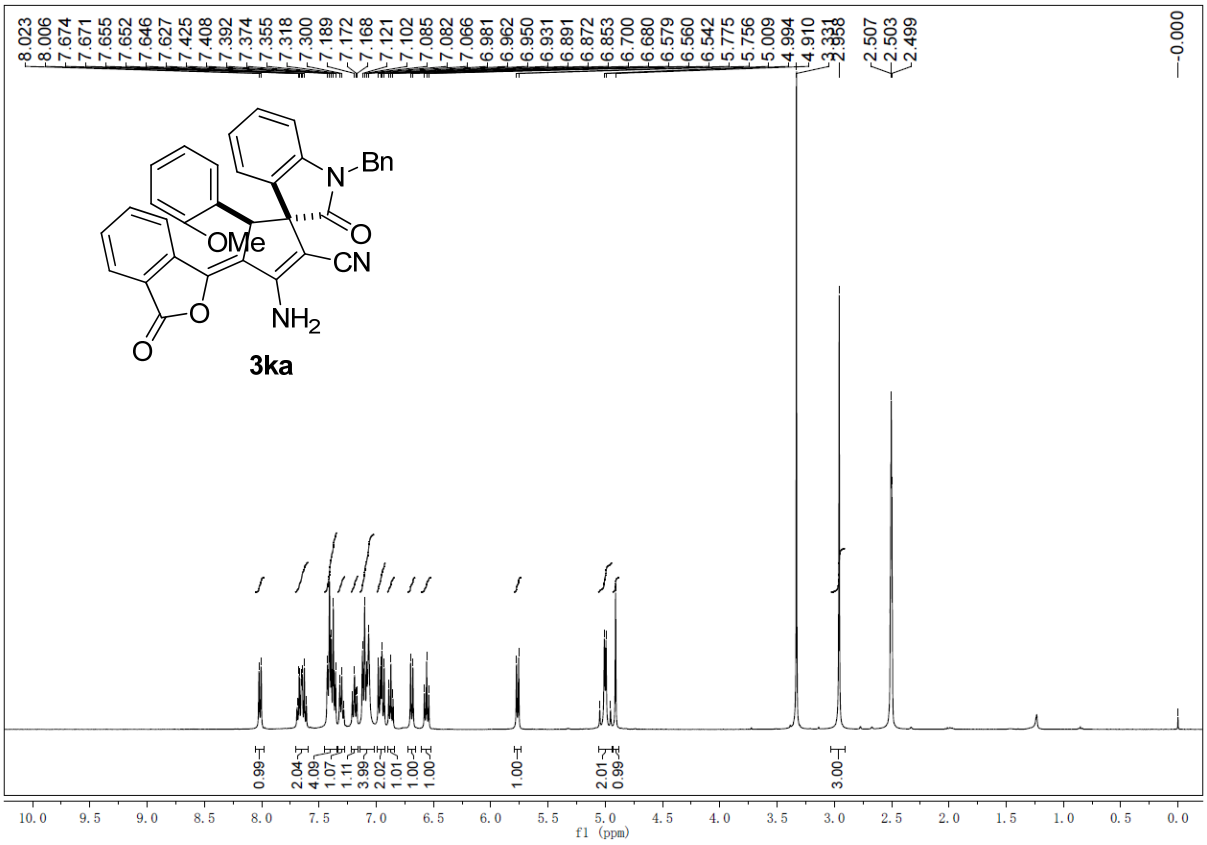


Figure S23. ^{1}H NMR of **3ka** (400 MHz, DMSO-d$_6$)

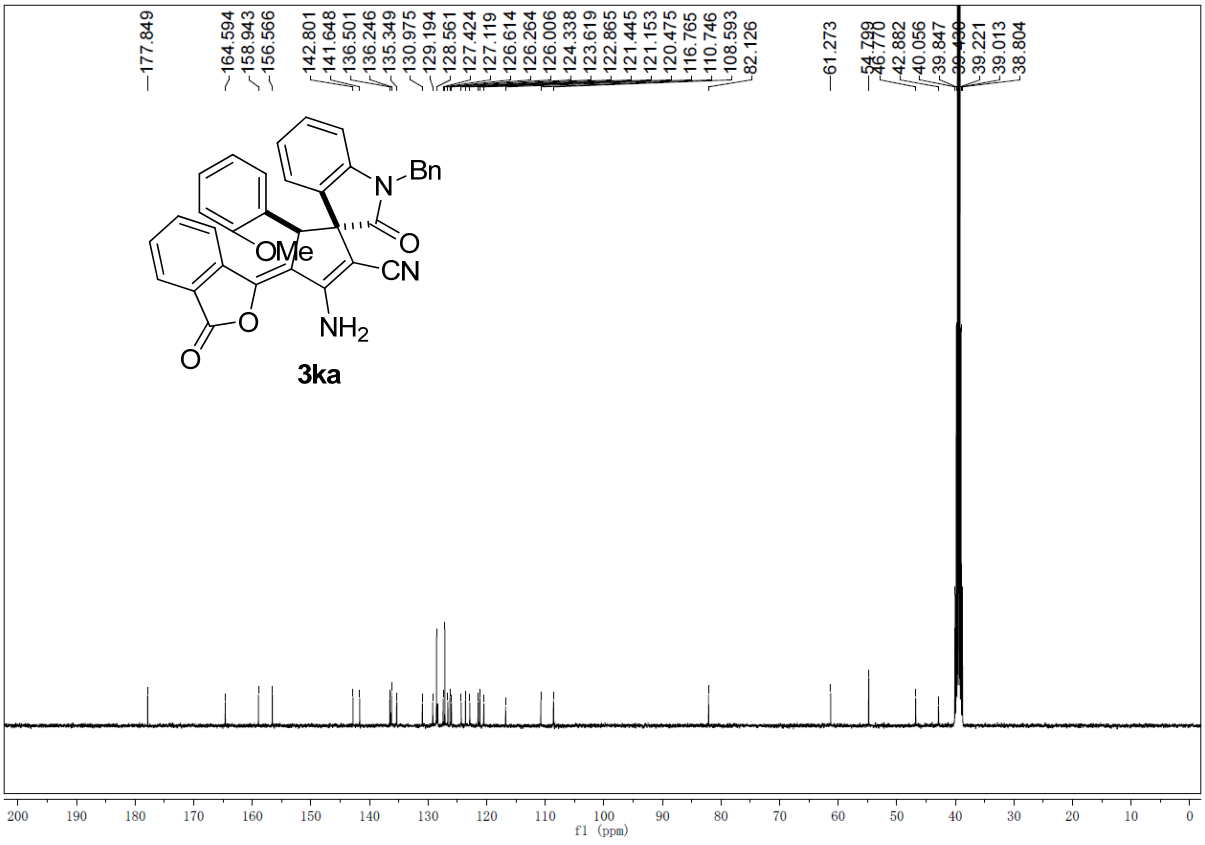


Figure S24. ^{13}C NMR of **3ka** (101 MHz, DMSO-d$_6$)

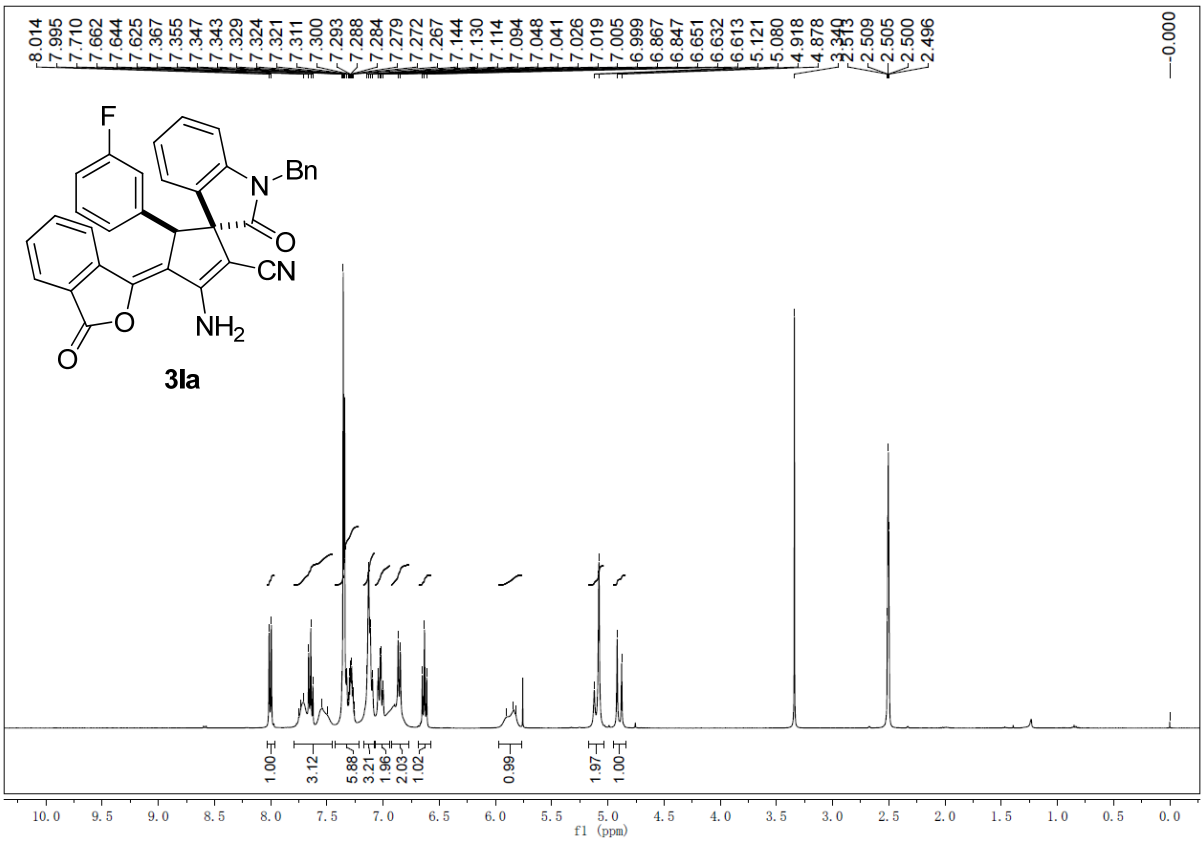


Figure S25. ^{1}H NMR of **3la** (400 MHz, DMSO-d$_6$)

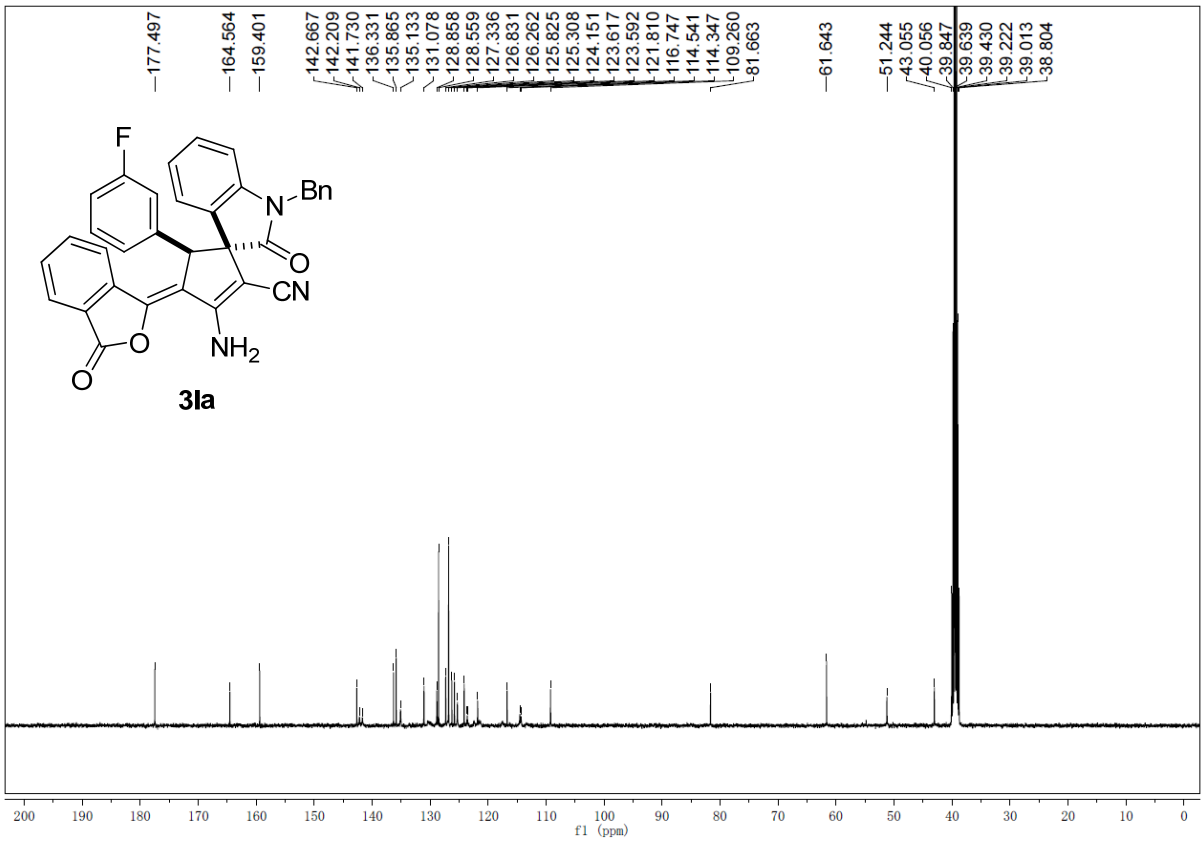


Figure S26. ^{13}C NMR of **3la** (101 MHz, DMSO-d$_6$)

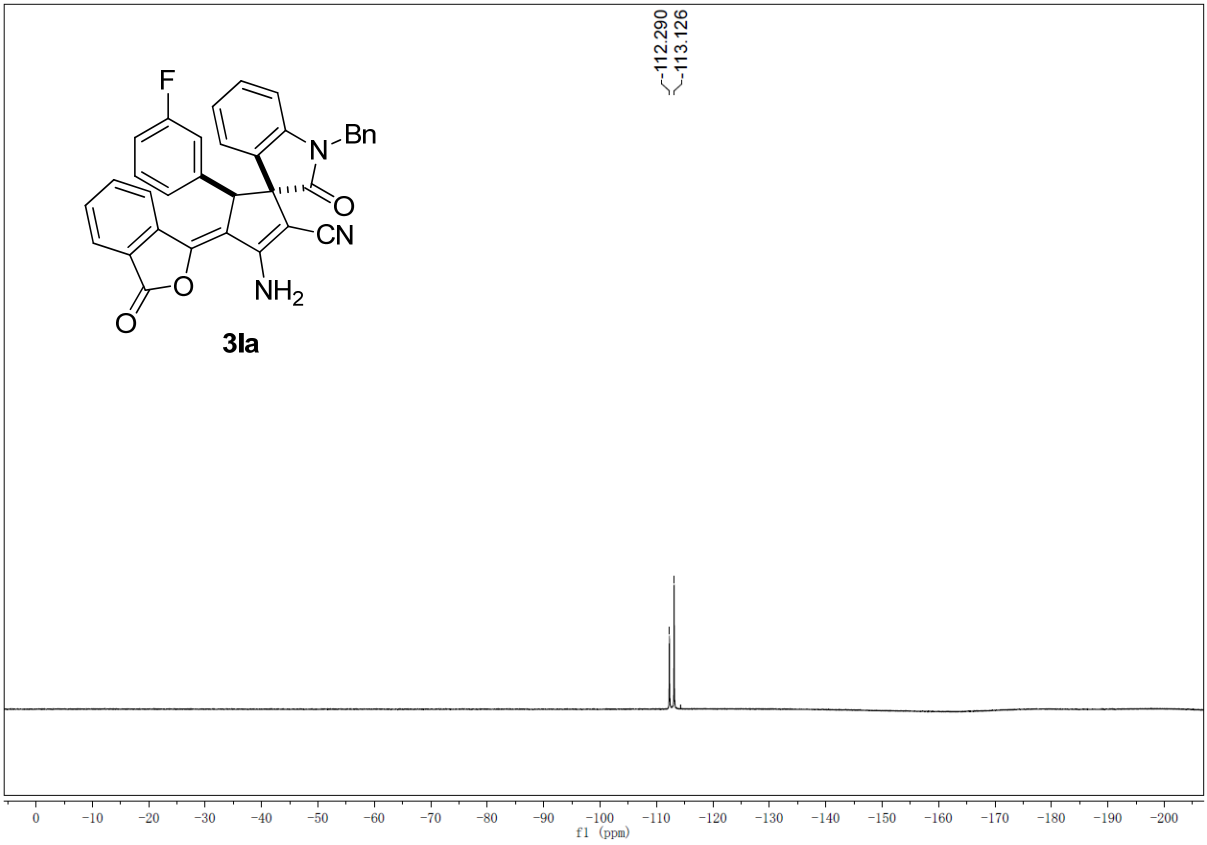


Figure S27. ^{19}F NMR of **3la** (376 MHz, DMSO-d$_6$)

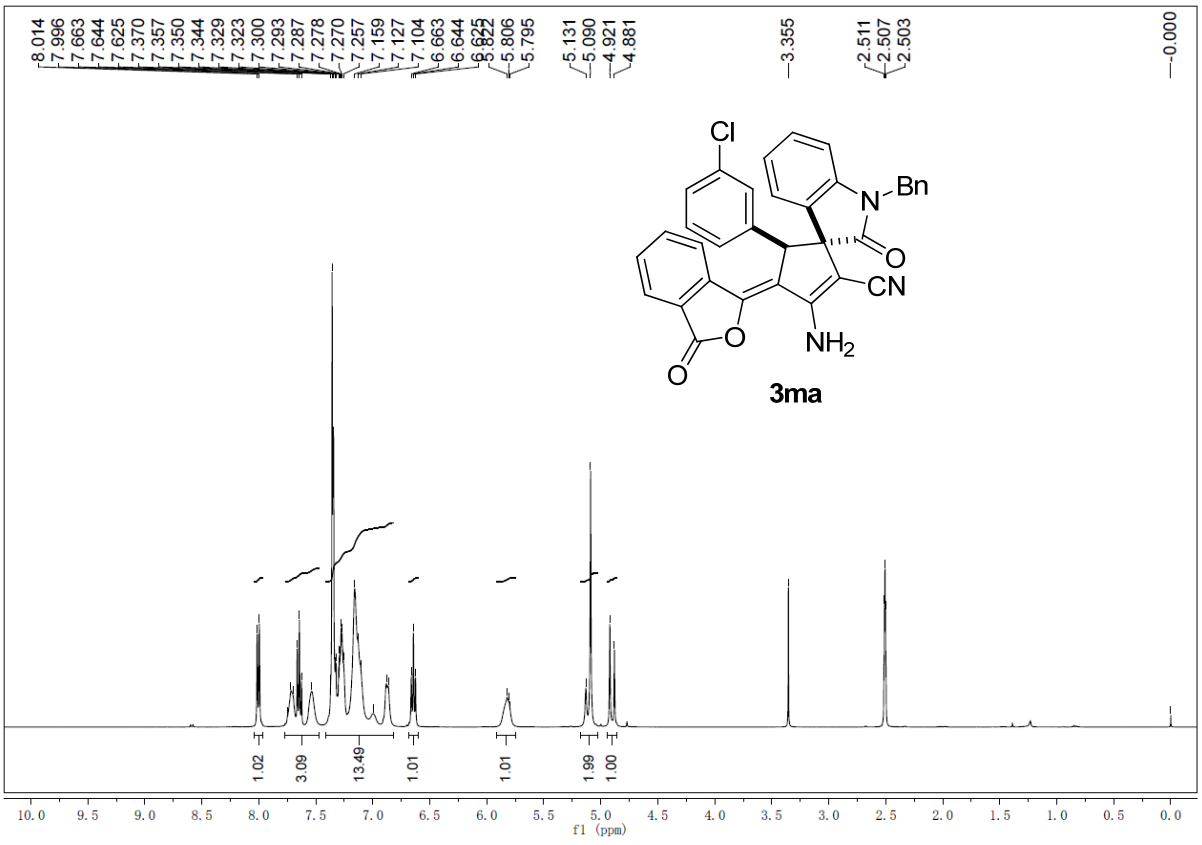


Figure S28. ^{1}H NMR of **3ma** (400 MHz, DMSO-d$_6$)

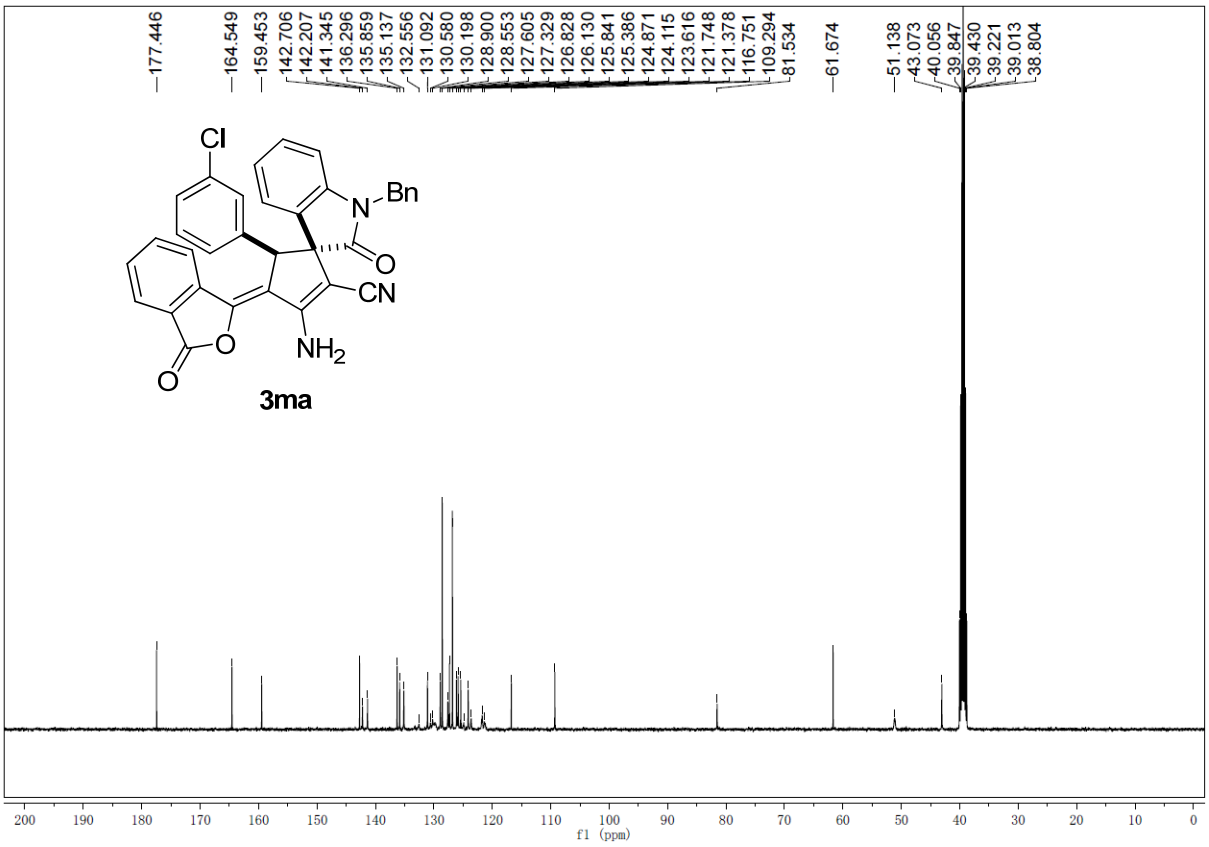


Figure S29. ^{13}C NMR of **3ma** (101 MHz, DMSO-d$_6$)

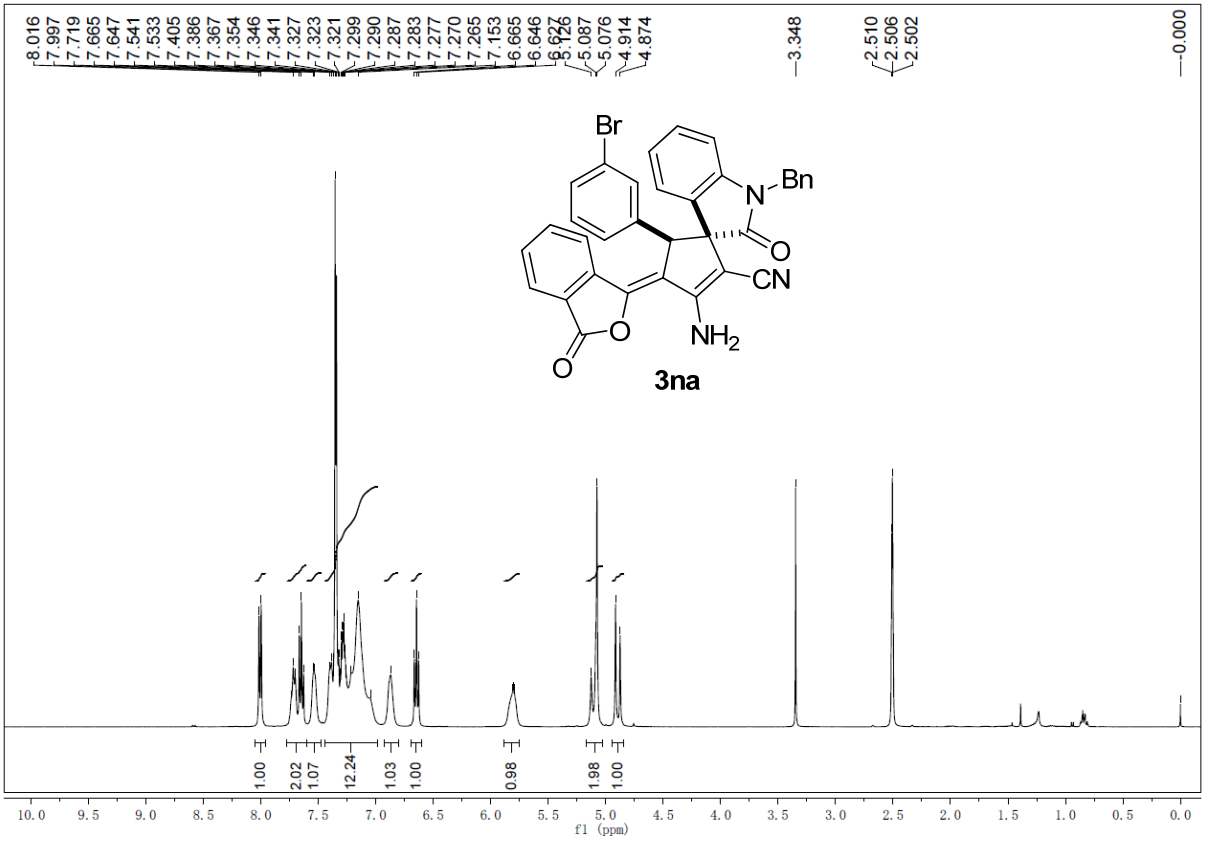


Figure S30. ^{1}H NMR of **3na** (400 MHz, DMSO-d$_6$)

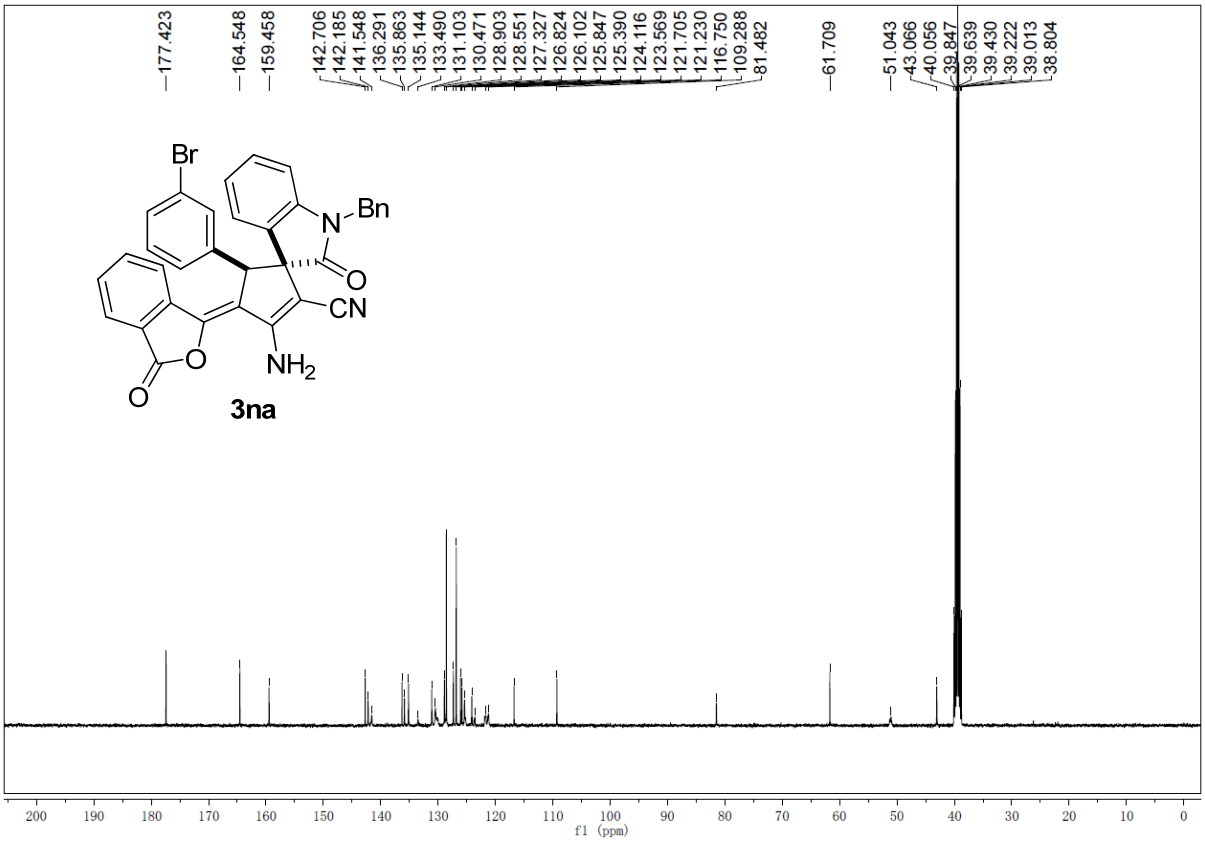


Figure S31. ^{13}C NMR of **3na** (101 MHz, DMSO-d_6)

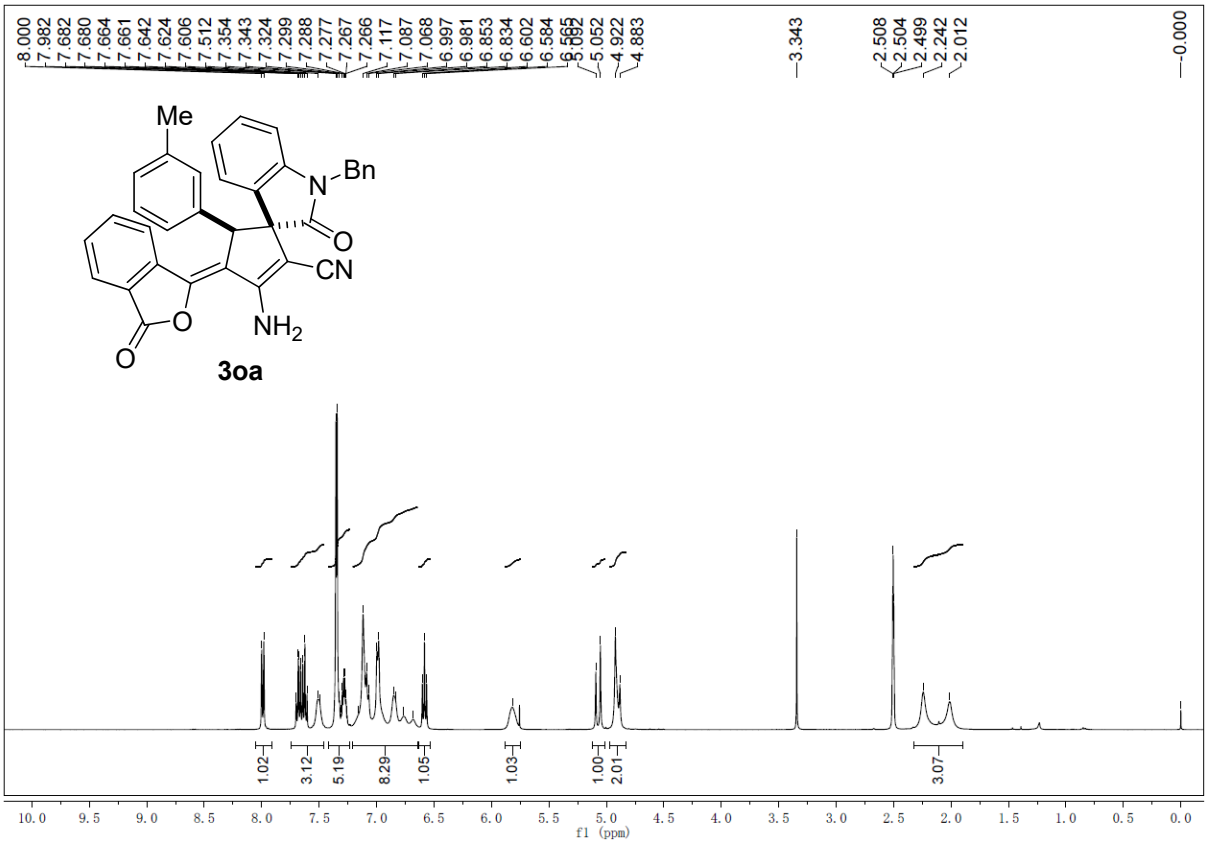


Figure S32. ^{1}H NMR of **3oa** (400 MHz, DMSO-d_6)

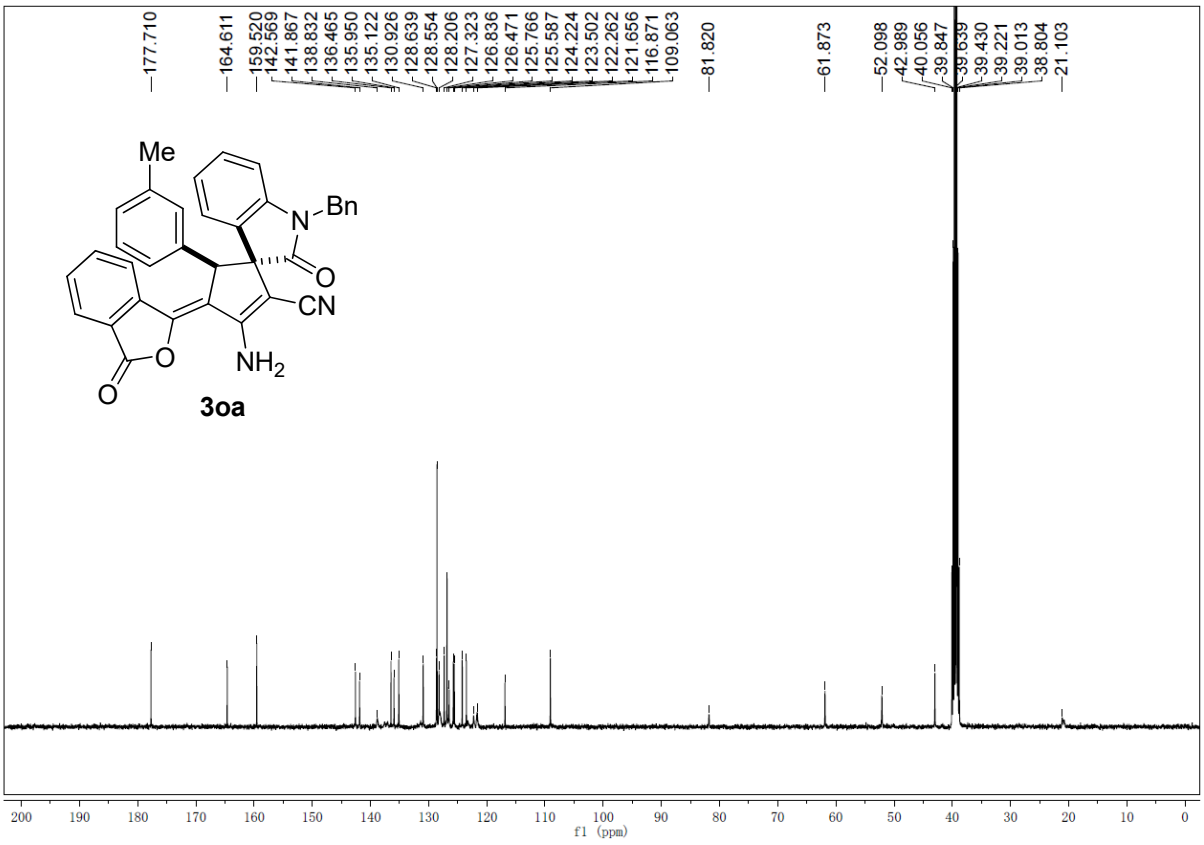


Figure S33. ^{13}C NMR of **3oa** (101 MHz, DMSO-d_6)

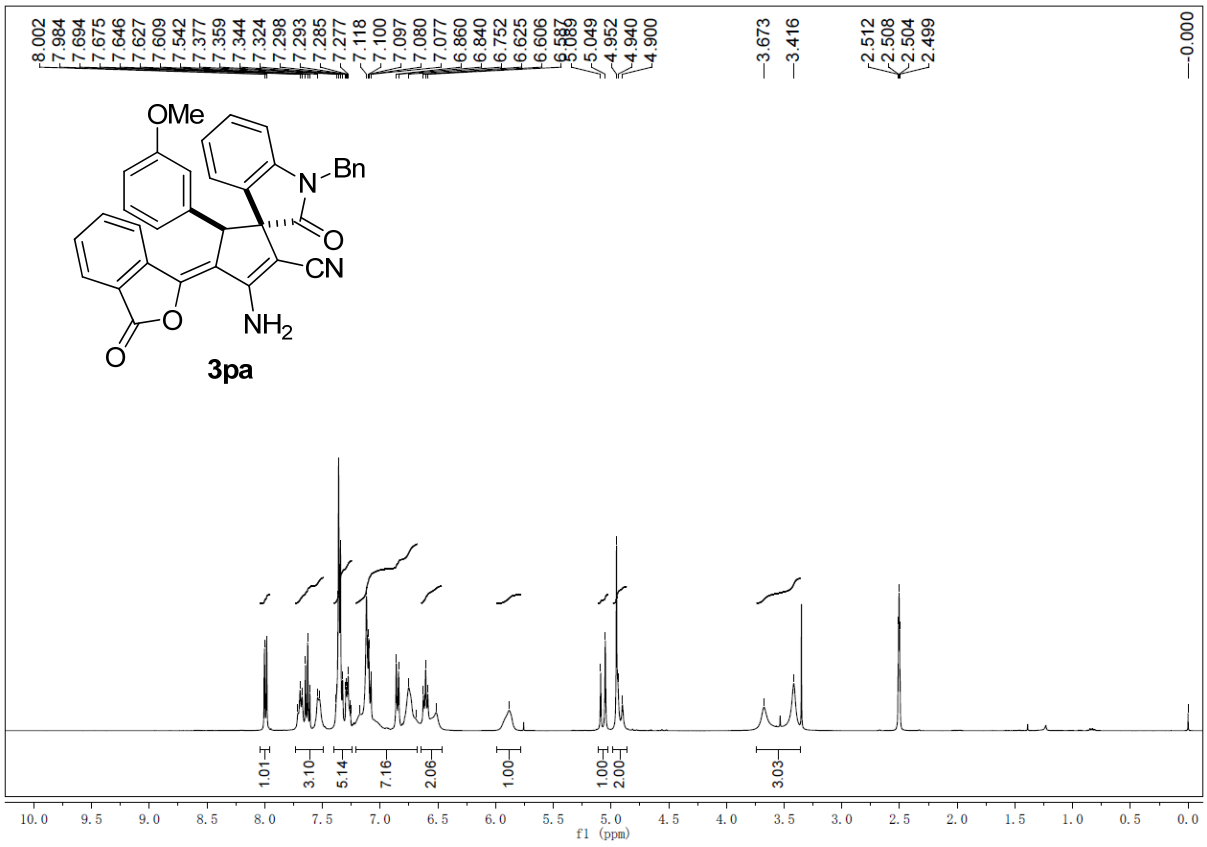


Figure S34. ^{1}H NMR of **3pa** (400 MHz, DMSO-d_6)

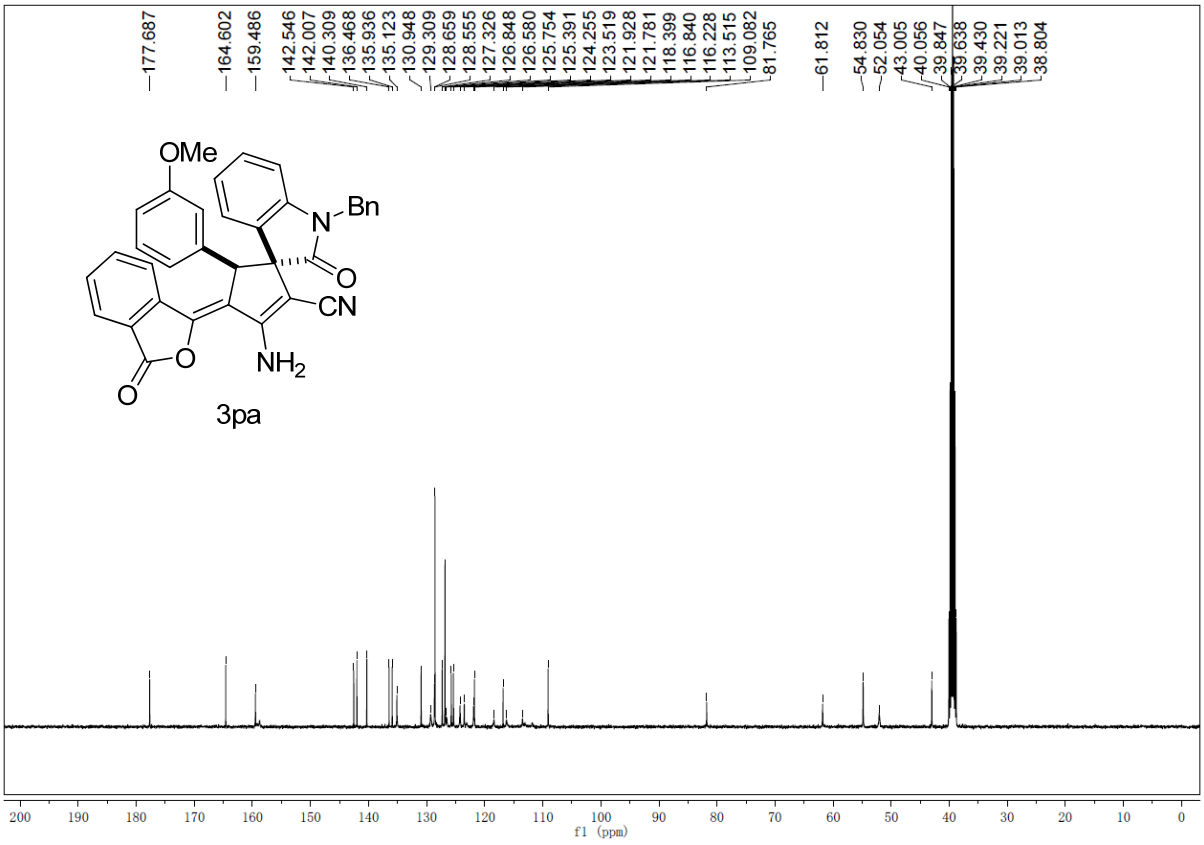


Figure S35. ^{13}C NMR of **3pa** (101 MHz, DMSO-d$_6$)

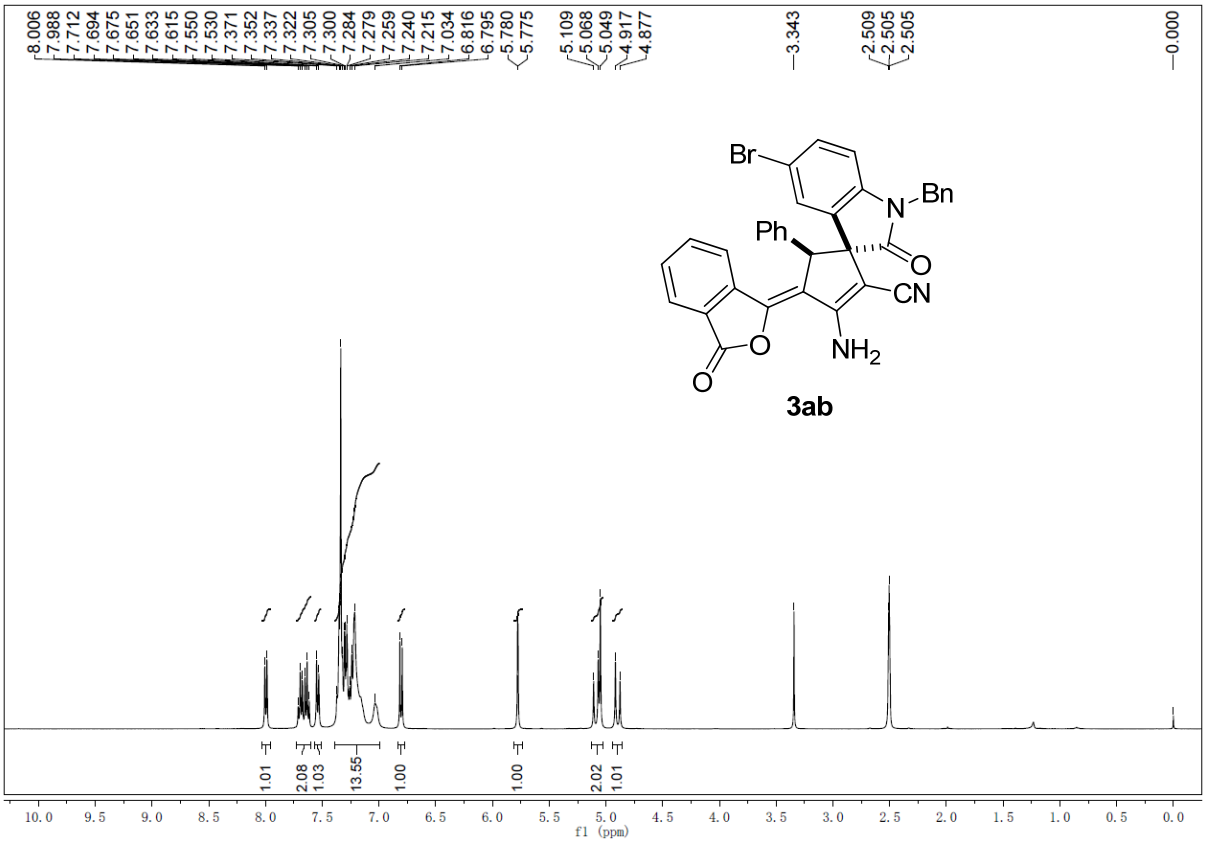


Figure S36. ^{13}H NMR of **3ab** (400 MHz, DMSO-d$_6$)

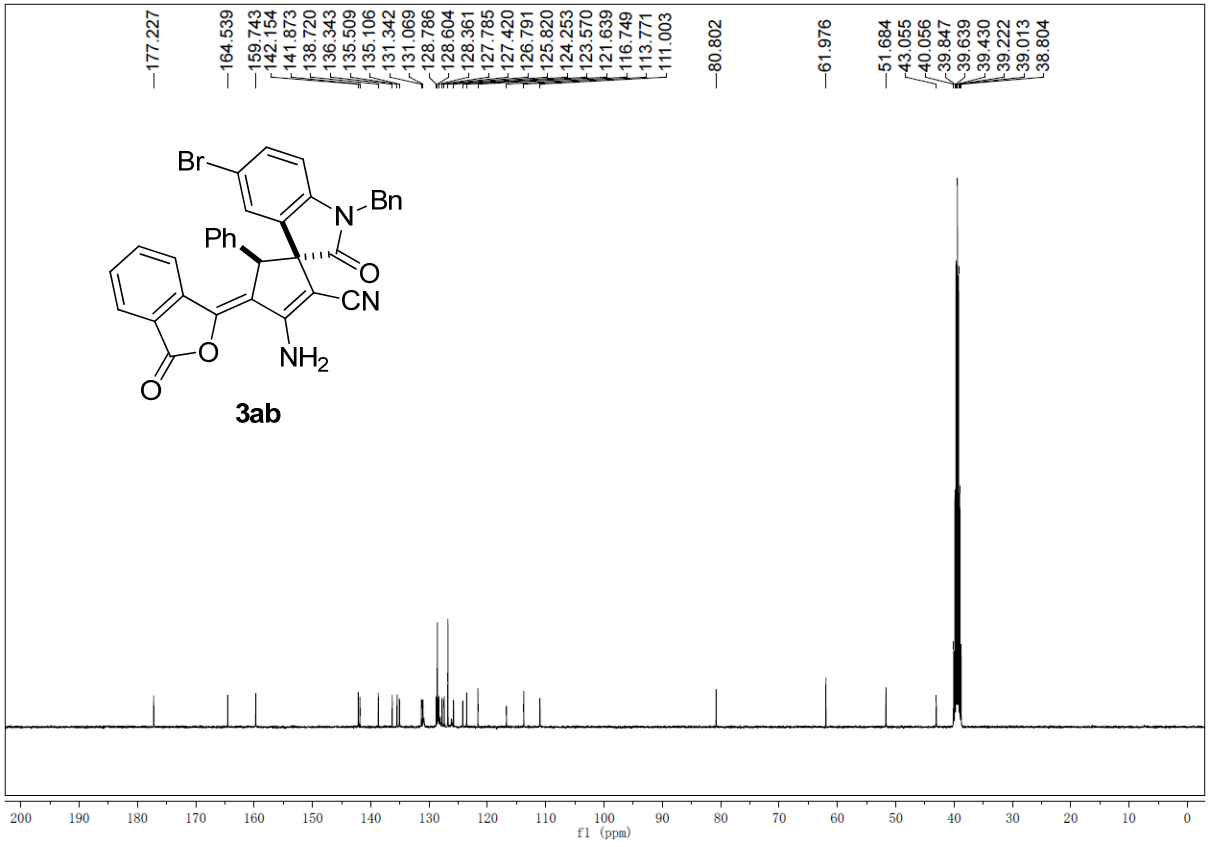


Figure S37. ^{13}C NMR of **3ab** (101 MHz, DMSO-d$_6$)

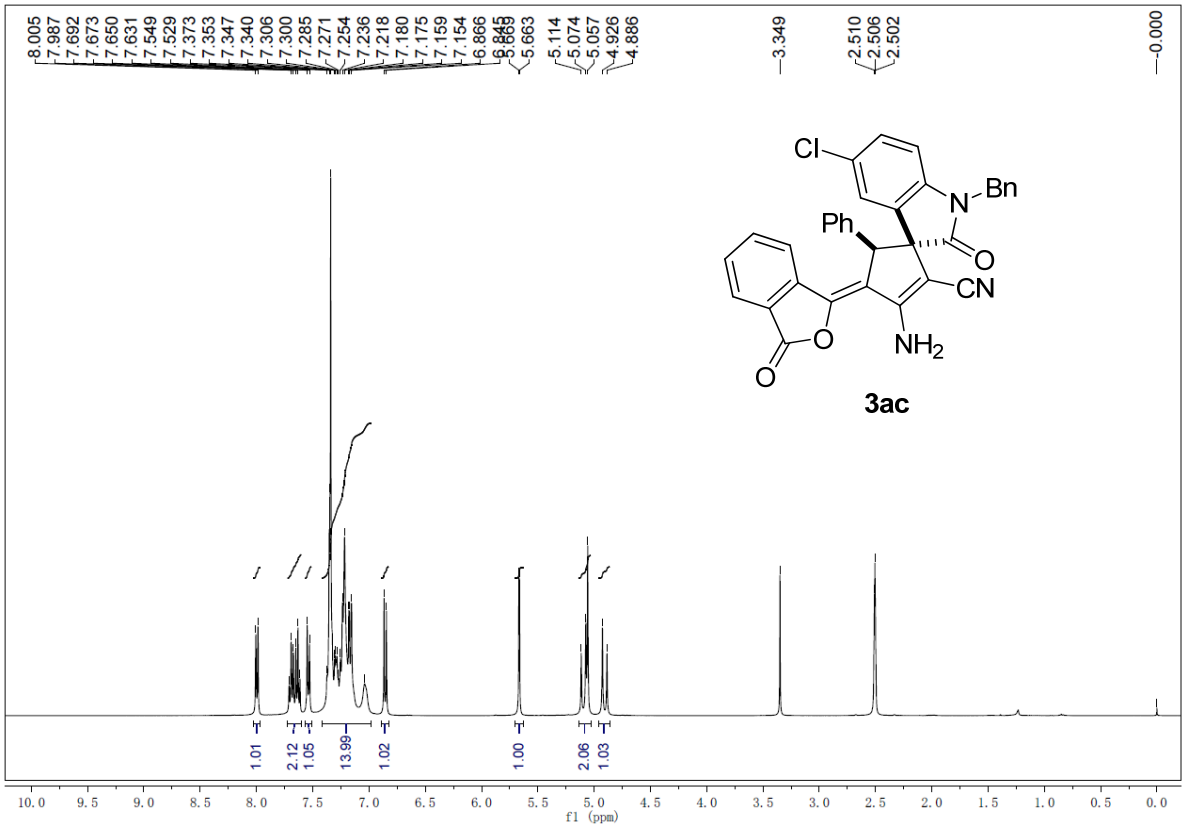


Figure S38. ^{13}H NMR of **3ac** (400 MHz, DMSO-d$_6$)

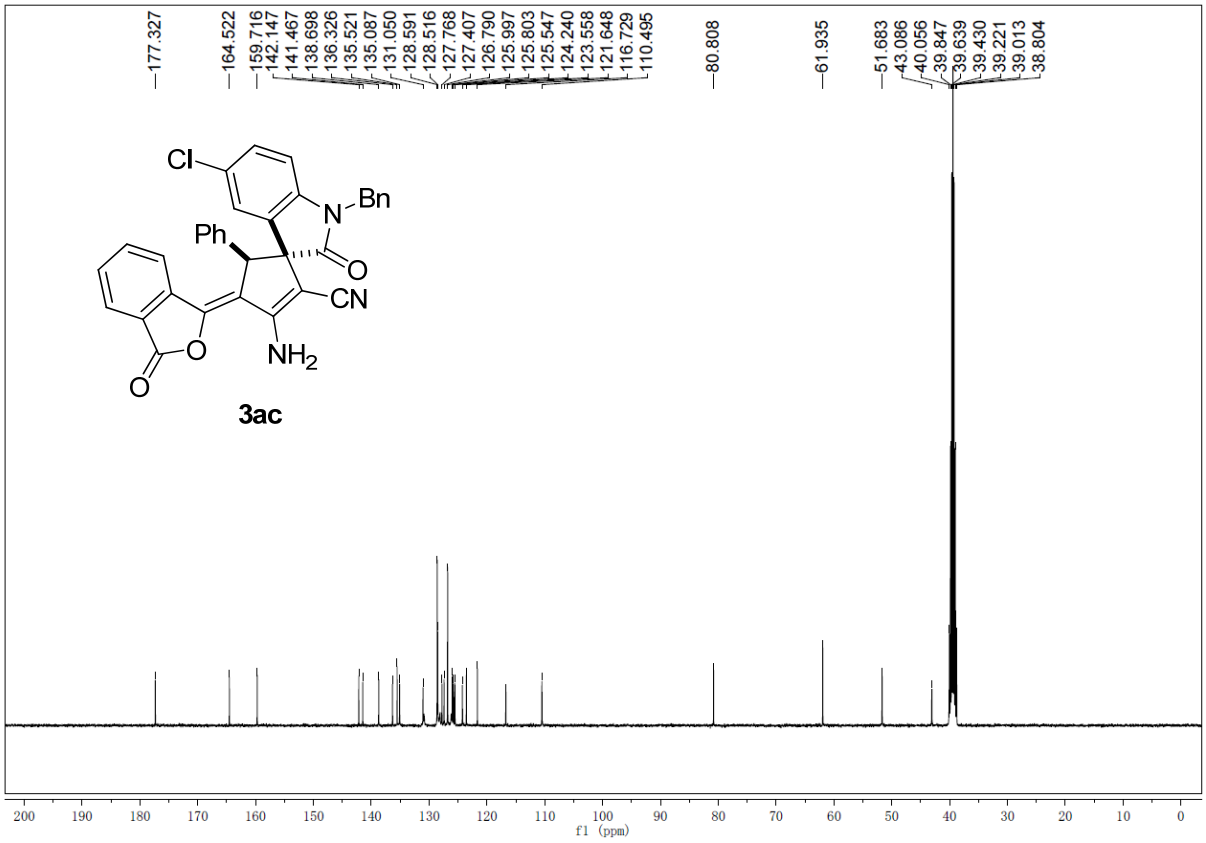


Figure S39. ^{13}C NMR of **3ac** (101 MHz, DMSO-d$_6$)

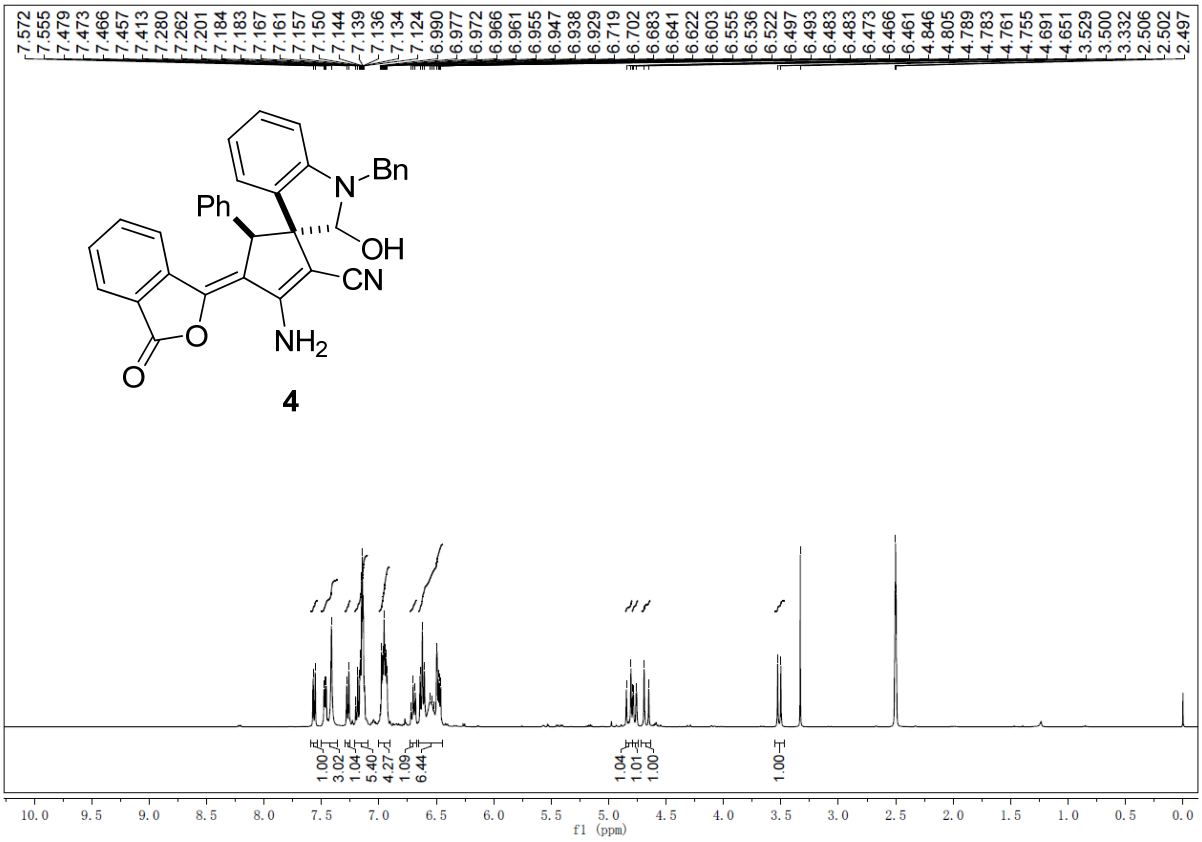


Figure S40. ^{13}H NMR of **4** (400 MHz, DMSO-d$_6$)

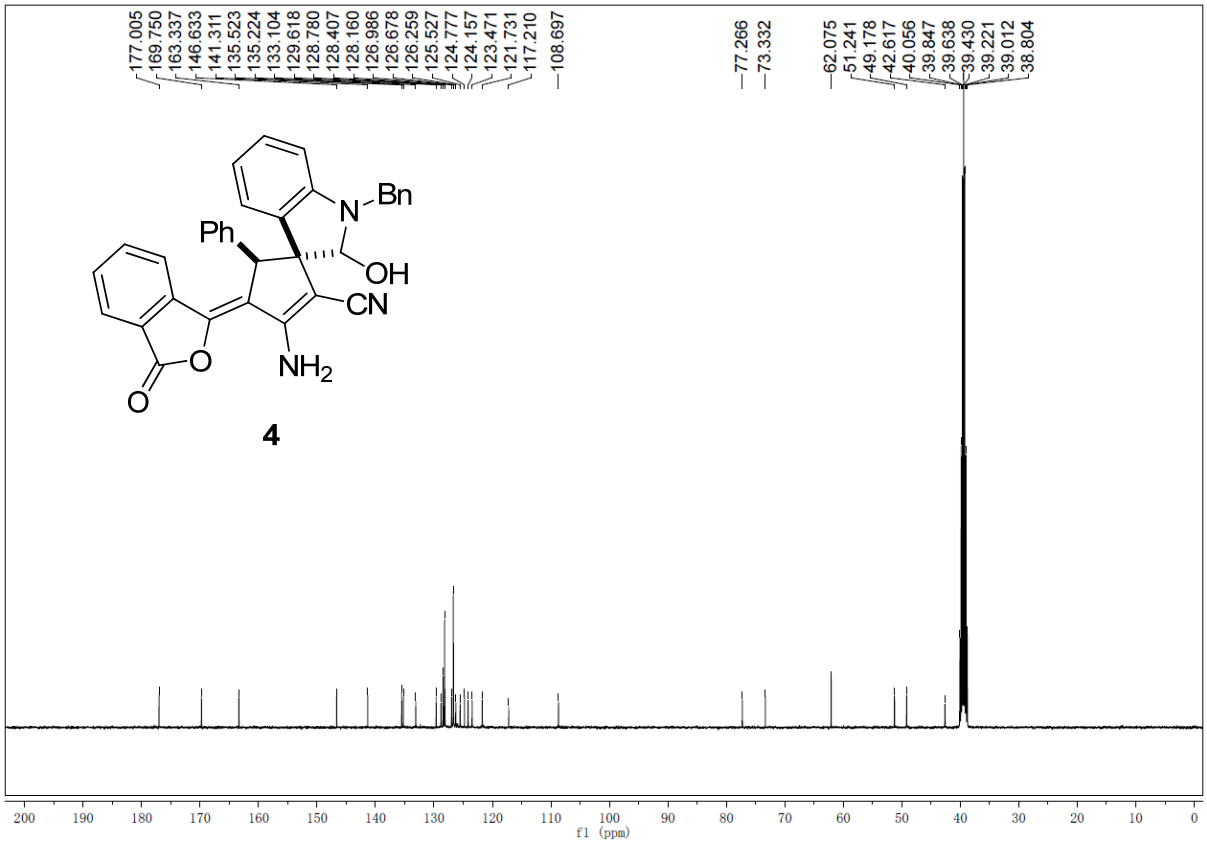


Figure S41. ^{13}C NMR of **4** (101 MHz, DMSO-d_6)