Biomimetic synthesis of dispiro sesquiterpene lactone type of alkaloids and discovery of potential anticancer scaffolds

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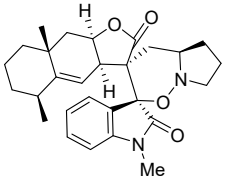
1. General information

Reactions were monitored by thin layer chromatography using UV light to visualize the course of reaction. Purification of reaction products was carried out by flash chromatography on silica gel or just by simple filtration and washing. ^{1}H and ^{13}CNMR spectra were obtained using a Bruker DPX-400 spectrometer. ^{1}H NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR chemical shifts are reported in ppm (δ) from tetramethylsilane (TMS) with the solvent resonance as the internal standard. Melting points were measured on an electrothermal digital melting point apparatus.

All cell lines were purchased from the Chinese Academy of Sciences, Kunming Cell Bank. All of which were cultured in RPMI-1640 or DMEM medium (Gibco, USA) supplemented with 10% foetal bovine serum, 1% glutamine, 100 U/mL penicillin and 100 μg/mL streptomycin in a humidified atmosphere with 5% CO_2 at 37℃. The synthetic compounds were placed at -20℃ after dissolved in DMSO. Cisplatin purchased from Aladdin Company.

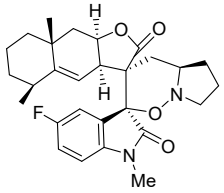
2. Synthesis of dispiro sesquiterpene lactone type of alkaloids 3 and 5

In a sealed tube equipped with a magnetic stirring bar, a mixture of 0.3 mmol of compound **1** (1.5 eq), 0.2 mmol of compound **2**, 0.5 mmol of proline (2.5 eq) in 2.0 mL of CH_3CN was stirred at 80 ^{o}C for 3 h, and then was purified by flash chromatography to give the desired intermediate **B**. Then, a mixture of intermediate **B**, *m*-CPBA (2.2 eq) in 2.0 mL of $CHCl_3$ was stirred at rt for 30 min, and then was directly loaded onto a silica gel and purified by flash chromatography to give the desired product **3** or **5**, using MeOH/EtOAc (1/20, v/v) as the eluent.

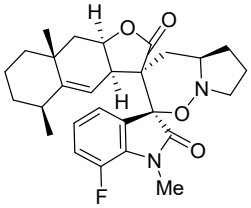


(3S,3'R,3a''R,4a'R,5''S,8a''R,9a''R)-1,5'',8a''-trimethyl-3a'',4a',5',5'',6',6'',7',7'',8'',8a'',9'',9a''-dodecahydro-2''H,4'H-dispiro[indoline-3,2'-pyrrolo[1,2-b][1,2]oxazine-3',3''-naphtho[2,3-b]furan]-2,2''-dione (3a): Light yellow solid,

m.p. 127.5-128.8 °C, overall yield 42% (38.8 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.02-1.05 (m, 6H), 1.16-1.20 (m, 1H), 1.31-1.38 (m, 2H), 1.44-1.49 (m, 3H), 1.68-1.91 (m, 6H), 2.23-2.31 (m, 2H), 2.43-2.47 (m, 1H), 2.71-2.73 (m, 1H), 2.87-2.91 (m, 1H), 3.08 (s, 3H), 3.14-3.18 (m, 1H), 4.01-4.07 (m, 1H), 4.43 (s, 1H), 5.21 (d, J = 3.6 Hz, 1H), 6.69 (d, J = 7.6 Hz, 1H), 6.97-7.01 (m, 1H), 7.21-7.26 (m, 1H), 7.80 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.7, 18.2, 22.2, 25.5, 27.4, 29.6, 31.2, 31.7, 37.2, 37.8, 40.8, 42.3, 52.4, 60.3, 72.5, 80.7, 107.2, 116.0, 121.6, 126.1, 127.9, 129.1, 141.8, 149.8, 171.9, 174.6; HRMS (ESI-TOF) m/z: Calcd. for $C_{28}H_{34}N_2NaO_4$ $[M+Na]^+$: 485.2411; Found: 485.2415.

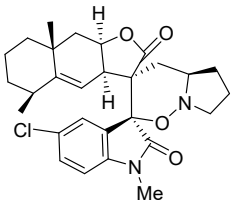


(3S,3'R,3a''R,4a'R,5''S,8a''R,9a''R)-5-fluoro-1,5'',8a''-trimethyl-3a'',4a',5',5'',6',6'',7',7'',8'',8a'',9'',9a''-dodecahydro-2''H,4'H-dispiro[indoline-3,2'-pyrrolo[1,2-b][1,2]oxazine-3',3''-naphtho[2,3-b]furan]-2,2''-dione (3b): Light yellow solid, m.p. 130.5-131.4 °C, overall yield 40% (38.4 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.01-1.05 (m, 6H), 1.16-1.23 (m, 1H), 1.33-1.38 (m, 2H), 1.45-1.49 (m, 3H), 1.65-1.97 (m, 6H), 2.18-2.24 (m, 1H), 2.28-2.34 (m, 1H), 2.44-2.47 (m, 1H), 2.65-2.72 (m, 1H), 2.78 (s, 1H), 3.07 (s, 3H), 3.14-3.18 (m, 1H), 4.15-4.19 (m, 1H), 4.54 (s, 1H), 5.19 (d, J = 4.0 Hz, 1H), 6.60-6.63 (m, 1H), 6.92-6.97 (m, 1H), 7.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.7, 17.5, 22.2, 25.1, 25.7, 27.4, 30.0, 31.2, 31.7, 37.2, 40.8, 42.3, 51.8, 53.0, 60.0, 80.9, 107.5 (d, J_{CF} = 6.3 Hz), 115.1 (d, J_{CF} = 24.2 Hz), 116.1, 116.9 (d, J_{CF} = 20.3 Hz), 127.9 (d, J_{CF} = 9.1 Hz), 137.7, 150.0, 157.8 (d, J_{CF} = 239.4 Hz), 171.6, 174.3; ^{19}F NMR ($CDCl_3$, 470 MHz) δ: -119.71; HRMS (ESI-TOF) m/z: Calcd. for $C_{28}H_{33}FN_2NaO_4$ $[M+Na]^+$: 503.2317; Found: 503.2325.

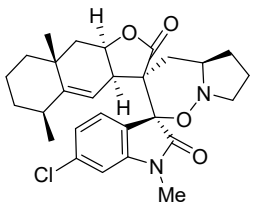


(3S,3'R,3a''R,4a'R,5''S,8a''R,9a''R)-7-fluoro-1,5'',8a''-trimethyl-

3a'',4a',5',5'',6',6'',7',7'',8'',8a'',9'',9a''-dodecahydro-2''H,4'H-dispiro[indoline-3,2'-pyrrolo[1,2-b][1,2]oxazine-3',3''-naphtho[2,3-b]furan]-2,2''-dione (3c): Light yellow solid, m.p. 129.8-131.0 °C, overall yield 39% (37.4 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.02-1.05 (m, 6H), 1.16-1.20 (m, 1H), 1.32-1.41 (m, 2H), 1.45-1.49 (m, 3H), 1.69-1.92 (m, 6H), 2.23-2.29 (m, 2H), 2.43-2.47 (m, 1H), 2.70-2.73 (m, 1H), 2.81-2.88 (m, 1H), 3.14-3.18 (m, 1H), 3.30 (d, J = 2.8 Hz, 3H), 3.95-4.07 (m, 1H), 4.43 (s, 1H), 5.19 (d, J = 3.6 Hz, 1H), 6.90-7.01 (m, 2H), 7.63-7.64 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.7, 17.9, 22.2, 25.4, 27.3, 28.0, 28.1, 31.2, 31.7, 37.3, 37.7, 40.8, 42.2, 52.7, 60.2, 75.1, 75.6, 80.6, 115.9, 117.0 (d, J_{CF} = 19.6 Hz), 122.0 (d, J_{CF} = 2.4 Hz), 124.2 (d, J_{CF} = 8.3 Hz), 128.6 (d, J_{CF} = 22.1 Hz), 145.3, 147.8, 150.0, 171.5, 174.4; ^{19}F NMR ($CDCl_3$, 470 MHz) δ: -132.91; HRMS (ESI-TOF) m/z: Calcd. for $C_{28}H_{33}FN_2NaO_4$ $[M+Na]^+$: 503.2317; Found: 503.2314.

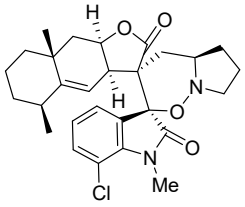


(3S,3'R,3a''R,4a'R,5''S,8a''R,9a''R)-5-chloro-1,5'',8a''-trimethyl-3a'',4a',5',5'',6',6'',7',7'',8'',8a'',9'',9a''-dodecahydro-2''H,4'H-dispiro[indoline-3,2'-pyrrolo[1,2-b][1,2]oxazine-3',3''-naphtho[2,3-b]furan]-2,2''-dione (3d): Light yellow solid, m.p. 145.0-146.6 °C, overall yield 43% (42.7 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.01-1.05 (m, 6H), 1.16-1.20 (m, 1H), 1.33-1.51 (m, 5H), 1.69-1.94 (m, 6H), 2.19-2.34 (m, 2H), 2.44-2.47 (m, 1H), 2.65-2.72 (m, 1H), 2.77-2.82 (m, 1H), 3.07 (s, 3H), 3.14-3.19 (m, 1H), 4.02-4.12 (m, 1H), 4.51 (s, 1H), 5.19 (d, J = 3.6 Hz, 1H), 7.21-7.23 (m, 1H), 7.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.7, 17.5, 22.2, 25.2, 25.7, 27.3, 29.9, 31.2, 31.7, 37.2, 40.8, 42.3, 52.1, 60.1, 75.8, 80.8, 108.1, 116.0, 126.9, 127.8, 128.8, 140.3, 150.1, 171.5, 174.3; HRMS (ESI-TOF) m/z: Calcd. for $C_{28}H_{33}ClN_2NaO_4$ $[M+Na]^+$: 519.2021; Found: 519.2026.

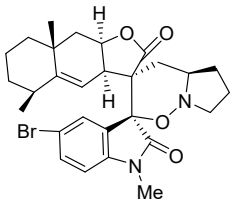


(3S,3'R,3a''R,4a'R,5''S,8a''R,9a''R)-6-chloro-1,5'',8a''-trimethyl-

3a'',4a',5',5'',6',6'',7',7'',8'',8a'',9'',9a''-dodecahydro-2''H,4'H-dispiro[indoline-3,2'-pyrrolo[1,2-b][1,2]oxazine-3',3''-naphtho[2,3-b]furan]-2,2''-dione (3e): Light yellow solid, m.p. 151.5-152.3 °C, overall yield 41% (40.7 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.02-1.06 (m, 6H), 1.17-1.18 (m, 1H), 1.33-1.37 (m, 2H), 1.45-1.49 (m, 3H), 1.65-1.92 (m, 6H), 2.23-2.28 (m, 2H), 2.43-2.47 (m, 1H), 2.69-2.71 (m, 1H), 2.82-2.89 (m, 1H), 3.08 (s, 3H), 3.12-3.17 (m, 1H), 3.92-4.05 (m, 1H), 4.47 (s, 1H), 5.19 (d, J = 4.0 Hz, 1H), 6.71 (d, J = 2.0 Hz, 1H), 6.95-6.98 (m, 1H), 7.74 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.7, 18.1, 22.2, 25.3, 25.6, 27.4, 30.1, 31.2, 31.7, 37.2, 37.7, 40.8, 42.2, 52.6, 61.2, 73.6, 80.5, 108.0, 115.9, 121.5, 124.7, 129.1, 135.0, 142.9, 150.0, 171.8, 174.4; HRMS (ESI-TOF) m/z: Calcd. for $C_{28}H_{33}ClN_2NaO_4$ $[M+Na]^+$: 519.2021; Found: 519.2015.

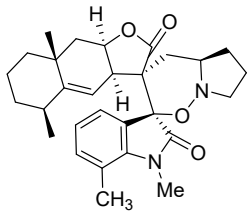


(3S,3'R,3a''R,4a'R,5''S,8a''R,9a''R)-7-chloro-1,5'',8a''-trimethyl-3a'',4a',5',5'',6',6'',7',7'',8'',8a'',9'',9a''-dodecahydro-2''H,4'H-dispiro[indoline-3,2'-pyrrolo[1,2-b][1,2]oxazine-3',3''-naphtho[2,3-b]furan]-2,2''-dione (3f): Light yellow solid, m.p. 131.1-131.8 °C, overall yield 42% (41.7 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.02-1.05 (m, 6H), 1.16-1.21 (m, 1H), 1.31-1.39 (m, 2H), 1.45-1.49 (m, 3H), 1.67-1.91 (m, 6H), 2.22-2.26 (m, 2H), 2.42-2.46 (m, 1H), 2.72-2.74 (m, 1H), 2.87 (s, 1H), 3.13-3.17 (m, 1H), 3.47 (s, 3H), 3.95-4.06 (m, 1H), 4.36 (s, 1H), 5.18 (d, J = 4.0 Hz, 1H), 6.88-6.92 (m, 1H), 7.16-7.18 (m, 1H), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.7, 18.3, 22.2, 25.5, 27.3, 29.0, 31.2, 31.7, 37.2, 38.1, 40.8, 42.2, 52.5, 60.2, 75.5, 79.9, 114.5, 115.8, 122.3, 126.7, 128.8, 131.4, 137.7, 149.9, 172.1, 174.3; HRMS (ESI-TOF) m/z: Calcd. for $C_{28}H_{33}ClN_2NaO_4$ $[M+Na]^+$: 519.2021; Found: 519.2023.

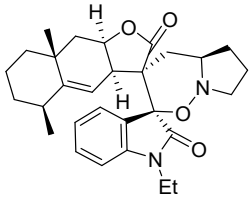


(3S,3'R,3a''R,4a'R,5''S,8a''R,9a''R)-5-bromo-1,5'',8a''-trimethyl-3a'',4a',5',5'',6',6'',7',7'',8'',8a'',9'',9a''-dodecahydro-2''H,4'H-dispiro[indoline-3,2'-

pyrrolo[1,2-b][1,2]oxazine-3',3''-naphtho[2,3-b]furan]-2,2''-dione (3g): Light yellow solid, m.p. 147.5-148.3 °C, overall yield 40% (43.2 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.01-1.05 (m, 6H), 1.17-1.20 (m, 1H), 1.32-1.41 (m, 2H), 1.45-1.49 (m, 3H), 1.66-1.94 (m, 6H), 2.19-2.33 (m, 2H), 2.43-2.47 (m, 1H), 2.66-2.72 (m, 1H), 2.79 (s, 1H), 3.06 (s, 3H), 3.15-3.20 (m, 1H), 4.04-4.10 (m, 1H), 4.50 (s, 1H), 5.18 (d, J = 3.6 Hz, 1H), 6.57 (d, J = 8.4 Hz, 1H), 7.36-7.38 (m, 1H), 7.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.7, 17.8, 22.2, 25.2, 25.6, 27.3, 30.1, 31.2, 31.7, 37.2, 37.4, 40.8, 42.3, 52.1, 52.8, 60.1, 75.7, 80.8, 108.6, 114.4, 116.0, 128.2, 131.4, 131.8, 140.7, 150.1, 171.4, 174.2; HRMS (ESI-TOF) m/z: Calcd. for $C_{28}H_{33}BrN_2NaO_4$ $[M+Na]^+$: 563.1516; Found: 563.1512.

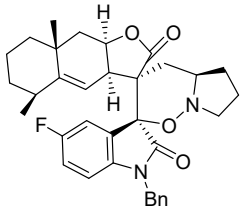


(3S,3'R,3a''R,4a'R,5''S,8a''R,9a''R)-1,5'',7,8a''-tetramethyl-3a'',4a',5',5'',6',6'',7',7'',8'',8a'',9'',9a''-dodecahydro-2''H,4'H-dispiro[indoline-3,2'-pyrrolo[1,2-b][1,2]oxazine-3',3''-naphtho[2,3-b]furan]-2,2''-dione (3h): Light yellow solid, m.p. 131.2-131.9 °C, overall yield 43% (40.9 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.03-1.05 (m, 3H), 1.16-1.20 (m, 1H), 1.32-1.37 (m, 2H), 1.44-1.48 (m, 3H), 1.65-1.86 (m, 6H), 2.23-2.27 (m, 2H), 2.44 (s, 3H), 2.73-2.75 (m, 1H), 2.87-2.90 (m, 1H), 3.14-3.18 (m, 1H), 3.29-3.37 (m, 4H), 3.91-4.07 (m, 1H), 4.31 (s, 1H), 5.20 (d, J = 3.6 Hz, 1H), 6.85-6.89 (m, 1H), 6.97 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.7, 18.3, 18.9, 22.2, 25.7, 27.3, 28.9, 31.2, 31.7, 37.3, 38.4, 40.9, 42.2, 52.3, 60.3, 75.4, 79.9, 116.0, 118.5, 121.5, 125.7, 126.7, 133.0, 139.6, 149.7, 172.7, 174.7; HRMS (ESI-TOF) m/z: Calcd. for $C_{29}H_{36}N_2NaO_4$ $[M+Na]^+$: 499.2567; Found: 499.2573.

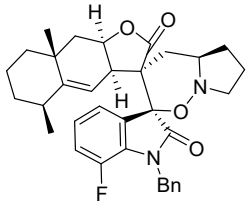


(3S,3'R,3a''R,4a'R,5''S,8a''R,9a''R)-1-ethyl-5'',8a''-dimethyl-

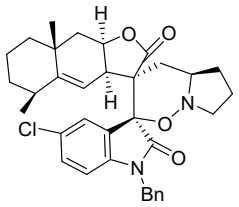
3a'',4a',5',5'',6',6'',7',7'',8'',8a'',9'',9a''-dodecahydro-2''H,4'H-dispiro[indoline-3,2'-pyrrolo[1,2-b][1,2]oxazine-3',3''-naphtho[2,3-b]furan]-2,2''-dione (3i): Light yellow solid, m.p. 127.6-128.3 °C, overall yield 41% (39.0 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.02-1.05 (m, 7H), 1.15-1.19 (m, 3H), 1.32-1.40 (m, 2H), 1.44-1.51 (m, 3H), 1.69-1.92 (m, 6H), 2.23-2.33 (m, 2H), 2.43-2.47 (m, 1H), 2.70-2.72 (m, 1H), 2.81-2.88 (m, 1H), 3.15-3.19 (m, 1H), 3.51-3.56 (m, 1H), 3.73-3.78 (m, 1H), 4.00-4.06 (m, 1H), 4.48 (s, 1H), 5.21 (d, J = 4.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.97-7.01 (m, 1H), 7.22-7.26 (m, 1H), 7.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 11.4, 15.7, 18.1, 22.2, 25.4, 27.3, 29.6, 31.2, 31.7, 33.9, 37.2, 37.7, 40.8, 42.3, 52.7, 60.2, 75.6, 80.7, 107.2, 116.2, 121.4, 126.5, 129.0, 140.7, 149.8, 171.5, 174.6; HRMS (ESI-TOF) m/z: Calcd. for $C_{29}H_{36}N_2NaO_4$ $[M+Na]^+$: 499.2567; Found: 499.2563.



(3S,3'R,3a''R,4a'R,5''S,8a''R,9a''R)-1-benzyl-5-fluoro-5'',8a''-dimethyl-3a'',4a',5',5'',6',6'',7',7'',8'',8a'',9'',9a''-dodecahydro-2''H,4'H-dispiro[indoline-3,2'-pyrrolo[1,2-b][1,2]oxazine-3',3''-naphtho[2,3-b]furan]-2,2''-dione (3j): Light yellow solid, m.p. 128.3-129.8 °C, overall yield 36% (40.0 mg), 16:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.02-1.05 (m, 6H), 1.16-1.21 (m, 1H), 1.33-1.36 (m, 2H), 1.44-1.49 (m, 3H), 1.65-1.83 (m, 5H), 1.92-1.99 (m, 1H), 2.18-2.23 (m, 1H), 2.32-2.38 (m, 1H), 2.44-2.47 (m, 1H), 2.66-2.73 (m, 1H), 2.79 (s, 1H), 3.16-3.20 (m, 1H), 4.19 (s, 1H), 4.48 (s, 1H), 4.57 (d, J = 16.0 Hz, 1H), 4.96 (d, J = 16.0 Hz, 1H), 5.20 (d, J = 4.0 Hz, 1H), 6.46-6.49 (m, 1H), 6.80-6.85 (m, 1H), 7.15-7.27 (m, 5H), 7.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.7, 17.7, 22.3, 25.2, 27.4, 30.2, 31.2, 31.7, 37.2, 40.8, 42.2, 43.3, 51.9, 60.1, 75.7, 80.9, 108.6 (d, J_{CF} = 8.2 Hz), 115.1 (d, J_{CF} = 24.1 Hz), 116.1, 117.1, 125.8, 126.7, 127.8, 127.9, 133.7, 136.9, 150.0, 157.8 (d, J_{CF} = 239.4 Hz), 171.8, 174.3; ^{19}F NMR ($CDCl_3$, 470 MHz) δ: -119.30; HRMS (ESI-TOF) m/z: Calcd. for $C_{34}H_{37}FN_2NaO_4$ $[M+Na]^+$: 579.2630; Found: 579.2636.

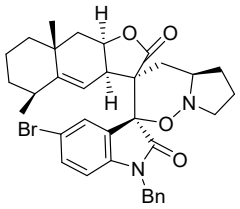


(3S,3'R,3a''R,4a'R,5''S,8a''R,9a''R)-1-benzyl-7-fluoro-5'',8a''-dimethyl-3a'',4a',5',5'',6',6'',7',7'',8'',8a'',9'',9a''-dodecahydro-2''H,4'H-dispiro[indoline-3,2'-pyrrolo[1,2-b][1,2]oxazine-3',3''-naphtho[2,3-b]furan]-2,2''-dione (3k): Light yellow solid, m.p. 130.7-131.2 °C, overall yield 39% (43.4 mg), 14:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.01-1.05 (m, 6H), 1.16-1.18 (m, 1H), 1.29-1.35 (m, 2H), 1.42-1.49 (m, 3H), 1.68-1.92 (m, 6H), 2.23-2.30 (m, 2H), 2.42-2.46 (m, 1H), 2.72-2.75 (m, 1H), 2.86 (s, 1H), 3.16-3.20 (m, 1H), 3.95-4.00 (m, 1H), 4.16-4.23 (m, 1H), 4.91-5.00 (m, 2H), 5.18 (d, J = 3.2 Hz, 1H), 6.91-6.95 (m, 2H), 7.17-7.24 (m, 5H), 7.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.7, 18.7, 22.2, 25.4, 27.3, 29.5, 31.2, 31.7, 37.3, 37.8, 40.8, 42.1, 44.7, 44.8, 52.7, 60.2, 75.4, 80.5, 115.9, 117.1 (d, J_{CF} = 20.2 Hz), 122.2 (d, J_{CF} = 6.3 Hz), 126.3, 126.6, 126.8, 127.6, 127.7, 127.8 (d, J_{CF} = 10.1 Hz), 135.2, 146.5 (d, J_{CF} = 242.4 Hz), 150.0, 171.6, 174.5; ^{19}F NMR ($CDCl_3$, 470 MHz) δ: -135.77; HRMS (ESI-TOF) m/z: Calcd. for $C_{34}H_{37}FN_2NaO_4$ $[M+Na]^+$: 579.2630; Found: 579.2635.

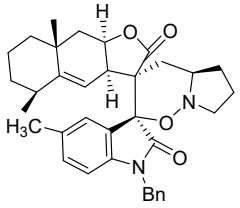


(3S,3'R,3a''R,4a'R,5''S,8a''R,9a''R)-1-benzyl-5-chloro-5'',8a''-dimethyl-3a'',4a',5',5'',6',6'',7',7'',8'',8a'',9'',9a''-dodecahydro-2''H,4'H-dispiro[indoline-3,2'-pyrrolo[1,2-b][1,2]oxazine-3',3''-naphtho[2,3-b]furan]-2,2''-dione (3l): Light yellow solid, m.p. 133.9-135.0 °C, overall yield 43% (49.2 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.02-1.05 (m, 6H), 1.17-1.21 (m, 1H), 1.32-1.35 (m, 2H), 1.43-1.49 (m, 3H), 1.65-1.82 (m, 5H), 1.90-1.96 (m, 1H), 2.18-2.23 (m, 1H), 2.32-2.38 (m, 1H), 2.43-2.47 (m, 1H), 2.66-2.73 (m, 1H), 2.81 (s, 1H), 3.16-3.21 (m, 1H), 4.13-4.19 (m, 1H), 4.44 (s, 1H), 4.60 (d, J = 15.6 Hz, 1H), 4.91 (d, J = 16.0 Hz, 1H), 5.19 (d, J = 3.6 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 7.08-7.26 (m, 6H), 7.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.7, 17.7, 22.2, 25.1, 25.9, 27.4, 30.1, 31.2, 31.7, 37.2, 40.8, 42.2, 43.2, 52.9, 60.1, 75.7, 80.8, 109.1, 116.1, 125.8, 126.8, 126.9, 127.9, 128.8, 133.6, 139.5, 150.1, 171.6,

174.3; HRMS (ESI-TOF) m/z: Calcd. for $C_{34}H_{37}ClN_2NaO_4$ $[M+Na]^+$: 595.2334; Found: 595.2325.

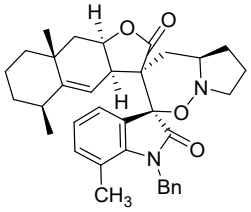


(3S,3'R,3a''R,4a'R,5''S,8a''R,9a''R)-1-benzyl-5-bromo-5'',8a''-dimethyl-3a'',4a',5',5'',6',6'',7',7'',8'',8a'',9'',9a''-dodecahydro-2''H,4'H-dispiro[indoline-3,2'-pyrrolo[1,2-b][1,2]oxazine-3',3''-naphtho[2,3-b]furan]-2,2''-dione (3m): Light yellow solid, m.p. 129.3-130.4 °C, overall yield 44% (54.2 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.02-1.05 (m, 6H), 1.16-1.19 (m, 1H), 1.32-1.35 (m, 2H), 1.43-1.49 (m, 3H), 1.65-1.82 (m, 5H), 1.90-1.96 (m, 1H), 2.18-2.23 (m, 1H), 2.31-2.37 (m, 1H), 2.43-2.47 (m, 1H), 2.67-2.73 (m, 1H), 2.81 (s, 1H), 3.17-3.21 (m, 1H), 4.13-4.20 (m, 1H), 4.44 (s, 1H), 4.59 (d, J = 16.0 Hz, 1H), 4.92 (d, J = 16.0 Hz, 1H), 5.20 (d, J = 4.0 Hz, 1H), 6.44 (d, J = 8.4 Hz, 1H), 7.14-7.26 (m, 6H), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.7, 17.7, 22.2, 25.1, 25.9, 27.3, 30.1, 31.2, 31.7, 37.2, 40.8, 42.2, 43.2, 53.0, 60.2, 75.7, 80.7, 109.6, 114.4, 116.0, 125.8, 126.8, 127.9, 128.2, 131.7, 133.6, 140.0, 150.1, 171.5, 174.3; HRMS (ESI-TOF) m/z: Calcd. for $C_{34}H_{37}BrN_2NaO_4$ $[M+Na]^+$: 639.1829; Found: 639.1835.

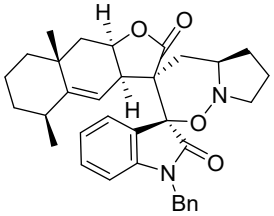


(3S,3'R,3a''R,4a'R,5''S,8a''R,9a''R)-1-benzyl-5,5'',8a''-trimethyl-3a'',4a',5',5'',6',6'',7',7'',8'',8a'',9'',9a''-dodecahydro-2''H,4'H-dispiro[indoline-3,2'-pyrrolo[1,2-b][1,2]oxazine-3',3''-naphtho[2,3-b]furan]-2,2''-dione (3n): Light yellow solid, m.p. 136.7-137.3 °C, overall yield 42% (46.4 mg), 20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.03-1.08 (m, 6H), 1.15-1.20 (m, 1H), 1.25-1.34 (m, 2H), 1.42-1.48 (m, 3H), 1.67-1.90 (m, 6H), 1.98-2.00 (m, 1H), 2.21-2.24 (m, 3H), 2.33 (s, 1H), 2.42-2.46 (m, 1H), 2.75-2.76 (m, 1H), 2.92 (s, 1H), 3.17-3.21 (m, 1H), 3.91-4.03 (m, 1H), 4.31 (s, 1H), 4.61 (d, J = 15.6 Hz, 1H), 4.91 (d, J = 16.0 Hz, 1H), 5.21 (d, J = 3.6 Hz, 1H), 6.46 (d, J = 8.0 Hz, 1H), 6.90-6.92 (m, 1H), 7.16-7.24 (m, 5H), 7.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.7, 19.1, 20.4, 22.2, 25.9, 27.3, 29.5, 31.2, 31.7, 37.3,

38.1, 40.9, 42.2, 43.0, 52.6, 60.4, 75.3, 80.7, 107.9, 116.0, 125.9, 126.5, 127.8, 127.9, 129.4, 131.0, 134.3, 138.7, 149.7, 171.9, 174.7; HRMS (ESI-TOF) m/z: Calcd. for $C_{35}H_{40}N_2NaO_4$ $[M+Na]^+$: 575.2880; Found: 575.2877.

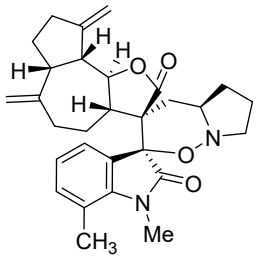


(3S,3'R,3a''R,4a'R,5''S,8a''R,9a''R)-1-benzyl-5'',7,8a''-trimethyl-3a'',4a',5',5'',6',6'',7',7'',8'',8a'',9'',9a''-dodecahydro-2''H,4'H-dispiro[indoline-3,2'-pyrrolo[1,2-b][1,2]oxazine-3',3''-naphtho[2,3-b]furan]-2,2''-dione (3o): Light yellow solid, m.p. 144.2-145.8 °C, overall yield 40% (44.2 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.04-1.05 (m, 6H), 1.16-1.21 (m, 1H), 1.29-1.35 (m, 2H), 1.42-1.48 (m, 3H), 1.70-1.77 (m, 3H), 1.84-1.92 (m, 1H), 2.15 (s, 3H), 2.31-2.44 (m, 3H), 2.75-2.77 (m, 1H), 2.89 (s, 1H), 3.18-3.22 (m, 1H), 3.95-4.00 (m, 1H), 4.29 (s, 1H), 5.00 (d, J = 17.2 Hz, 1H), 5.12-5.20 (m, 2H), 6.88-6.94 (m, 2H), 7.10 (d, J = 7.2 Hz, 2H), 7.14-7.18 (m, 1H), 7.22-7.26 (m, 2H), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.7, 117.9, 18.6, 22.2, 25.7, 27.4, 29.0, 31.2, 31.7, 37.3, 38.7, 40.9, 42.2, 44.4, 52.8, 61.2, 75.3, 79.8, 116.1, 118.6, 121.6, 124.5, 124.8, 126.2, 127.8, 133.2, 136.0, 139.2, 149.7, 173.0, 174.7; HRMS (ESI-TOF) m/z: Calcd. for $C_{35}H_{40}N_2NaO_4$ $[M+Na]^+$: 575.2880; Found: 575.2884.

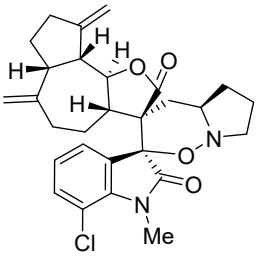


(3S,3'R,3a''R,4a'R,5''S,8a''R,9a''R)-1-benzyl-5'',8a''-dimethyl-3a'',4a',5',5'',6',6'',7',7'',8'',8a'',9'',9a''-dodecahydro-2''H,4'H-dispiro[indoline-3,2'-pyrrolo[1,2-b][1,2]oxazine-3',3''-naphtho[2,3-b]furan]-2,2''-dione (3p): Light yellow solid, m.p. 139.0-140.3 °C, overall yield 40% (43.0 mg), 16:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.02-1.05 (m, 6H), 1.15-1.18 (m, 1H), 1.28-1.34 (m, 2H), 1.42-1.48 (m, 3H), 1.68-1.92 (m, 6H), 2.22-2.35 (m, 2H), 2.43-2.46 (m, 1H), 2.71-2.74 (m, 1H), 2.87 (s, 1H), 3.15-3.20 (m, 1H), 3.94-4.07 (m,

1H), 4.36 (s, 1H), 4.61 (d, J = 16.0 Hz, 1H), 4.95 (d, J = 16.0 Hz, 1H), 5.21 (d, J = 4.0 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 6.94-6.97 (m, 1H), 7.10-7.25 (m, 6H), 7.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.7, 18.4, 22.2, 25.5, 27.4, 29.8, 31.2, 31.7, 37.2, 37.9, 40.8, 42.2, 43.0, 52.6, 60.3, 75.4, 80.7, 108.2, 116.1, 121.6, 125.9, 126.6, 127.8, 128.0, 129.0, 134.1, 141.0, 149.8, 169.7, 172.0, 174.6; HRMS (ESI-TOF) m/z: Calcd. for $C_{34}H_{38}N_2NaO_4$ $[M+Na]^+$: 561.2724; Found: 561.2717.

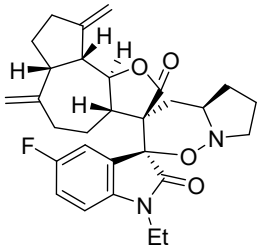


(2'S,3R,3aS,4a'R,6aR,9aR,9bS)-1'',7''-dimethyl-6,9-dimethylene-3a,4,4a',5,5',6,6a,6',7,7',8,9,9a,9b-tetradecahydro-2H,4'H-dispiro[azuleno[4,5-b]furan-3,3'-pyrrolo[1,2-b][1,2]oxazine-2',3''-indoline]-2,2''-dione (5a): Light yellow solid, m.p. 171.5-172.8 ^{o}C; overall yield 47% (44.6 mg), 15:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.23-1.30 (m, 1H), 1.60-1.84 (m, 7H), 1.97-2.01 (m, 2H), 2.19-2.37 (m, 4H), 2.44-2.51 (m, 5H), 2.90-2.92 (m, 1H), 3.15-3.17 (m, 1H), 3.23-3.28 (m, 1H), 3.38-3.45 (m, 4H), 3.75-3.80 (m, 1H), 4.62 (s, 1H), 4.72 (s, 1H), 4.90 (s, 1H), 5.00 (s, 1H), 6.83-6.87 (m, 1H), 7.00 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 18.3, 22.0, 23.4, 25.9, 26.2, 27.4, 28.4, 28.8, 31.2, 35.0, 44.7, 46.3, 51.7, 57.3, 60.9, 78.4, 81.5, 108.6, 110.8, 118.1, 122.2, 124.1, 125.0, 133.4, 141.0, 148.6, 150.2, 171.2, 174.9; HRMS (ESI-TOF) m/z: Calcd. for $C_{29}H_{35}N_2O_4$ $[M+H]^+$: 475.2591; Found: 475.2585.

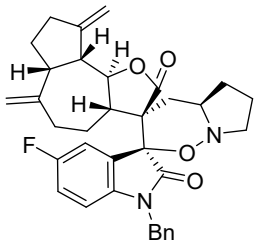


(2'S,3R,3aS,4a'R,6aR,9aR,9bS)-7''-chloro-1''-methyl-6,9-dimethylene-3a,4,4a',5,5',6,6a,6',7,7',8,9,9a,9b-tetradecahydro-2H,4'H-dispiro[azuleno[4,5-b]furan-3,3'-

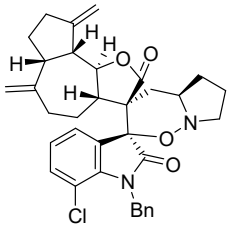
pyrrolo[1,2-b][1,2]oxazine-2',3''-indoline]-2,2''-dione (5b): Light yellow solid, m.p. 187.2-187.7 °C; overall yield 40% (39.5 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.24-1.31 (m, 1H), 1.62-1.86 (m, 7H), 1.97-2.05 (m, 2H), 2.19-2.24 (m, 1H), 2.29-2.38 (m, 3H), 2.55-2.57 (m, 2H), 2.93 (s, 1H), 3.05-3.14 (m, 1H), 3.22-3.27 (m, 1H), 3.46-3.52 (m, 4H), 3.77-3.82 (m, 1H), 4.64 (s, 1H), 4.73 (s, 1H), 4.92 (d, J = 1.2 Hz, 1H), 5.01 (d, J = 1.2 Hz, 1H), 6.87-6.91 (m, 1H), 7.20-7.22 (m, 1H), 7.45 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 22.2, 23.5, 25.9, 26.0, 27.5, 28.5, 28.7, 31.2, 35.1, 44.7, 46.1, 51.7, 57.1, 60.8, 78.5, 81.7, 108.6, 110.9, 114.1, 123.0, 125.0, 131.9, 139.2, 148.4, 150.2, 170.7, 174.6; HRMS (ESI-TOF) m/z: Calcd. for $C_{28}H_{32}ClN_2O_4$ $[M+H]^+$: 495.2045; Found: 495.2049.



(2'S,3R,3aS,4a'R,6aR,9aR,9bS)-1''-ethyl-5''-fluoro-6,9-dimethylene-3a,4,4a',5,5',6,6a,6',7,7',8,9,9a,9b-tetradecahydro-2H,4'H-dispiro[azuleno[4,5-b]furan-3,3'-pyrrolo[1,2-b][1,2]oxazine-2',3''-indoline]-2,2''-dione (5c): Light yellow solid, m.p. 177.8-178.4 °C; overall yield 39% (38.4 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.16-1.20 (m, 3H), 1.26-1.29 (m, 1H), 1.55-1.74 (m, 7H), 1.85 (d, J = 14.4 Hz, 1H), 2.02-2.24 (m, 3H), 2.31-2.39 (m, 3H), 2.50 (s, 1H), 2.92 (s, 1H), 3.14 (s, 1H), 3.23-3.28 (m, 1H), 3.46-3.51 (m, 2H), 3.80-3.84 (m, 1H), 4.61 (s, 1H), 4.73 (s, 1H), 4.94 (s, 1H), 5.03 (s, 1H), 6.66-6.69 (m, 1H), 6.96-7.01 (m, 1H), 7.34 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 11.6, 19.7, 21.6, 25.9, 26.0, 27.6, 28.8, 31.2, 33.6, 35.8, 45.1, 45.9, 51.7, 57.4, 61.1, 79.2, 81.6, 107.3 (d, J_{CF} = 8.0 Hz), 108.7, 110.8, 114.9 (d, J_{CF} = 30.0 Hz), 115.8 (d, J_{CF} = 23.3 Hz), 125.2, 138.2, 148.5, 150.1, 160.2 (d, J_{CF} = 233.4 Hz), 169.9, 174.5; ^{19}F NMR ($CDCl_3$, 470 MHz) δ: -119.41; HRMS (ESI-TOF) m/z: Calcd. for $C_{29}H_{34}FN_2O_4$ $[M+H]^+$: 493.2497; Found: 493.2504.

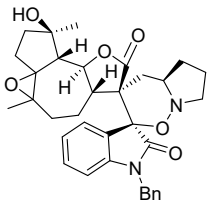


(2'S,3R,3aS,4a'R,6aR,9aR,9bS)-1''-benzyl-5''-fluoro-6,9-dimethylene-3a,4,4a',5,5',6,6a,6',7,7',8,9,9a,9b-tetradecahydro-2H,4'H-dispiro[azuleno[4,5-b]furan-3,3'-pyrrolo[1,2-b][1,2]oxazine-2',3''-indoline]-2,2''-dione (5d): Light yellow solid, m.p. 197.7-198.5 °C; overall yield 45% (49.9 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.24-1.30 (m, 1H), 1.51-1.71 (m, 6H), 1.74-1.80 (m, 1H), 1.87 (d, J = 14.0 Hz, 1H), 2.18-2.41 (m, 6H), 2.48 (s, 1H), 2.88-2.94 (m, 1H), 3.20-3.30 (m, 2H), 3.45 (s, 1H), 3.79-3.84 (m, 1H), 4.57-4.61 (m, 2H), 4.72 (s, 1H), 4.94 (d, J = 1.6 Hz, 1H), 4.99-5.04 (m, 2H), 6.58-6.61 (m, 1H), 6.86-6.91 (m, 1H), 7.19-7.27 (m, 5H), 7.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 22.2, 23.1, 25.9, 28.1, 28.7, 31.3, 36.1, 42.9, 45.6, 51.4, 59.5, 61.2, 79.1, 82.0, 108.3 (d, J_{CF} = 8.2 Hz), 108.6 (d, J_{CF} = 30.0 Hz), 110.5, 115.6, 115.9, 124.7, 125.0, 126.4, 126.9, 127.9, 134.4, 138.7, 148.7, 150.1, 157.9 (d, J_{CF} = 257.3 Hz), 170.4, 174.5; ^{19}F NMR ($CDCl_3$, 470 MHz) δ: -118.63; HRMS (ESI-TOF) m/z: Calcd. for $C_{34}H_{36}FN_2O_4$ $[M+H]^+$: 555.2654; Found: 555.2657.

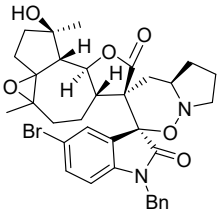


(2'S,3R,3aS,4a'R,6aR,9aR,9bS)-1''-benzyl-7''-chloro-6,9-dimethylene-3a,4,4a',5,5',6,6a,6',7,7',8,9,9a,9b-tetradecahydro-2H,4'H-dispiro[azuleno[4,5-b]furan-3,3'-pyrrolo[1,2-b][1,2]oxazine-2',3''-indoline]-2,2''-dione (5e): Light yellow solid, m.p. 194.6-195.5 °C; overall yield 36% (41.0 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.17-1.20 (m, 1H), 1.35-1.40 (m, 1H), 1.64-1.71 (m, 4H), 1.75-1.86 (m, 3H), 2.15-2.24 (m, 3H), 2.31-2.39 (m, 2H), 2.50-2.53 (m, 2H), 2.88-2.93 (m, 1H), 3.16 (s, 1H), 3.25-3.30 (m, 1H), 3.44 (s, 1H), 3.76-3.81 (m, 1H), 4.59 (s, 1H), 4.69 (s, 1H), 4.93 (d, J = 1.6 Hz, 1H), 5.03 (d, J = 1.2 Hz, 1H), 5.20 (d, J = 16.0 Hz, 1H), 5.37 (d, J = 16.0 Hz, 1H), 6.88-6.92 (m, 1H), 7.17-7.23 (m, 6H), 7.52 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 22.2, 23.4, 26.0, 28.1, 28.6, 31.3, 35.9, 43.9, 44.7, 45.6, 51.4, 57.0,

61.0, 78.2, 81.9, 108.6, 110.5, 114.0, 123.1, 125.3, 125.8, 126.3, 127.6, 132.3, 136.3, 148.7, 150.2, 170.9, 174.8; HRMS (ESI-TOF) m/z: Calcd. for $C_{34}H_{36}ClN_2O_4$ $[M+H]^+$: 571.2358; Found: 571.2352.

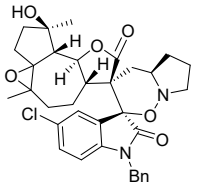


(3S,3'R,3a''S,4a'R,6a''S,6b''S,7''R)-1-benzyl-7''-hydroxy-1a'',7''-dimethyl-1a'',2'',3a'',4a',5',6',6a'',6b'',7',7'',8'',9''-dodecahydro-3''H,4'H,5''H-dispiro[indoline-3,2'-pyrrolo[1,2-b][1,2]oxazine-3',4''-oxireno[2',3':8,8a]azuleno[4,5-b]furan]-2,5''-dione (6a): Light yellow solid, m.p. 281.0-281.5 °C; overall yield 46% (52.4 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.76-0.83 (m, 1H), 1.07 (s, 3H), 1.19-1.22 (m, 1H), 1.35-1.36 (m, 4H), 1.47-1.53 (m, 1H), 1.60-1.80 (m, 7H), 1.92-2.03 (m, 2H), 2.16-2.24 (m, 2H), 2.74 (s, 1H), 2.90 (s, 1H), 3.06 (s, 1H), 3.24-3.28 (m, 1H), 3.41-3.44 (m, 1H), 4.04-4.09 (m, 1H), 4.61 (d, J = 14.8 Hz, 1H), 4.92 (d, J = 15.2 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.92-6.96 (m, 1H), 7.17-7.26 (m, 6H), 7.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.8, 22.3, 25.9, 26.0, 28.0, 32.4, 36.4, 42.8, 49.0, 54.7, 60.9, 61.2, 68.5, 77.9, 78.7, 107.7, 122.5, 125.0, 126.8, 127.9, 129.4, 134.7, 170.6, 174.0; HRMS (ESI-TOF) m/z: Calcd. for $C_{34}H_{39}N_2O_6$ $[M+H]^+$: 571.2803; Found: 571.2801.

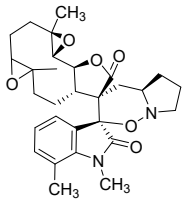


(3S,3'R,3a''S,4a'R,6a''S,6b''S,7''R)-1-benzyl-5-bromo-7''-hydroxy-1a'',7''-dimethyl-1a'',2'',3a'',4a',5',6',6a'',6b'',7',7'',8'',9''-dodecahydro-3''H,4'H,5''H-dispiro[indoline-3,2'-pyrrolo[1,2-b][1,2]oxazine-3',4''-oxireno[2',3':8,8a]azuleno[4,5-b]furan]-2,5''-dione (6b): Light yellow solid, m.p. 290.5-291.7 °C; overall yield 45% (58.3 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.76-0.82 (m, 1H), 1.12 (s, 3H), 1.19 (s, 1H), 1.35-1.37 (m, 4H), 1.50-1.56 (m, 1H), 1.65-1.82 (m, 6H), 1.94-2.07 (m, 5H), 2.74-2.83 (m, 3H), 3.24-3.35 (m, 2H), 4.08-4.13 (m, 1H), 4.60-4.68 (m, 1H), 4.86-4.90 (m, 1H), 6.56 (d, J = 8.0 Hz, 1H), 7.20-7.32 (m, 6H), 7.71 (s, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.9, 22.3, 25.8, 25.9, 27.9, 32.3, 36.5, 42.9, 49.7, 54.5, 60.9, 61.2, 68.5, 77.8, 78.7, 109.2, 114.9, 126.5, 126.9, 128.0, 132.1, 134.1, 170.1, 173.6; HRMS (ESI-TOF) m/z: Calcd. for $C_{34}H_{38}BrN_2O_6$ $[M+H]^+$: 649.1908; Found: 649.1913.

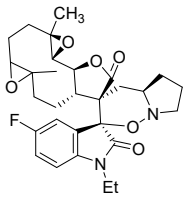


(3S,3'R,3a''S,4a'R,6a''S,6b''S,7''R)-1-benzyl-5-chloro-7''-hydroxy-1a'',7''-dimethyl-1a'',2'',3a'',4a',5',6',6a'',6b'',7',7'',8'',9''-dodecahydro-3''H,4'H,5''H-dispiro[indoline-3,2'-pyrrolo[1,2-b][1,2]oxazine-3',4''-oxireno[2',3':8,8a]azuleno[4,5-b]furan]-2,5''-dione (6c): Light yellow solid, m.p. 287.5-287.9 °C; overall yield 41% (49.5 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.76-0.82 (m, 1H), 1.12 (s, 3H), 1.17-1.20 (m, 1H), 1.35-1.36 (m, 4H), 1.50-1.56 (m, 1H), 1.64-1.82 (m, 6H), 1.90-2.07 (m, 5H), 2.74-2.83 (m, 3H), 3.24-3.35 (m, 2H), 4.08-4.13 (m, 1H), 4.63-4.66 (m, 1H), 4.87-4.90 (m, 1H), 6.60 (d, J = 8.0 Hz, 1H), 7.14-7.27 (m, 6H), 7.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.9, 22.3, 25.8, 25.9, 27.9, 32.3, 36.5, 42.9, 54.5, 60.9, 61.2, 68.5, 77.8, 78.7, 108.7, 122.3, 124.8, 126.3, 126.5, 126.9, 128.0, 129.1, 134.1, 170.2, 173.6; HRMS (ESI-TOF) m/z: Calcd. for $C_{34}H_{38}ClN_2O_6$ $[M+H]^+$: 605.2413; Found: 605.2416.

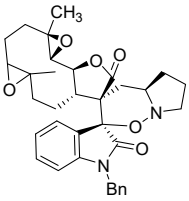


(1aR,1bS,2'S,4R,4aS,4a'R,9aR)-1'',6a,7'',9a-tetramethyl-1a,1b,4a,4a',5,5',6,6a,6',7a,7',8,9,9a-tetradecahydro-3H,4'H-dispiro[bis(oxireno)[2',3':5,6;2'',3'':9,10]cyclodeca[1,2-b]furan-4,3'-pyrrolo[1,2-b][1,2]oxazine-2',3''-indoline]-2'',3-dione (7a): Light yellow solid, m.p. 267.0-267.9 °C; overall yield 47% (47.8 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.42-0.48 (m, 1H), 0.89-0.96 (m, 1H), 1.10-1.17 (m, 1H), 1.20 (s, 3H), 1.26 (s, 3H), 1.34-1.37 (m, 1H), 1.41-1.45 (m, 1H), 1.63-1.67 (m, 1H), 1.81 (d, J = 14.4 Hz, 1H), 1.94-2.02 (m, 2H), 2.09-2.13 (m, 1H), 2.24-2.36 (m, 4H), 2.43-2.51 (m, 5H), 2.89-2.97 (m, 1H), 3.22-3.32 (m, 2H), 3.36 (s, 3H), 3.51-3.57 (m, 1H), 3.71-3.76 (m, 1H), 6.83-6.87 (m, 1H), 7.01 (d, J = 7.6 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H); ^{13}C NMR

($CDCl_3$, 100 MHz) δ: 15.9, 16.3, 18.3, 18.5, 19.8, 21.3, 22.0, 23.2, 26.3, 28.4, 34.4, 39.6, 45.4, 47.7, 57.4, 59.2, 59.9, 60.8, 61.2, 61.9, 64.2, 78.5, 118.3, 122.6, 124.5, 133.8, 140.8, 170.9, 173.4; HRMS (ESI-TOF) m/z: Calcd. for $C_{29}H_{37}N_2O_6$ $[M+H]^+$: 509.2646; Found: 509.2651.

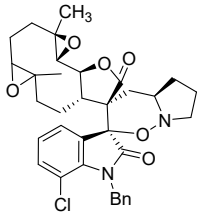


(1aR,1bS,2'S,4R,4aS,4a'R,9aR)-1''-ethyl-5''-fluoro-6a,9a-dimethyl-1a,1b,4a,4a',5,5',6,6a,6',7a,7',8,9,9a-tetradecahydro-3H,4'H-dispiro[bis(oxireno)[2',3':5,6;2'',3'':9,10]cyclodeca[1,2-b]furan-4,3'-pyrrolo[1,2-b][1,2]oxazine-2',3''-indoline]-2'',3-dione (7b): Light yellow solid, m.p. 267.3-268.7 °C; overall yield 42% (44.2 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.47-0.50 (m, 1H), 0.99-1.04 (m, 1H), 1.17-1.20 (m, 7H), 1.28 (s, 3H), 1.35-1.41 (m, 1H), 1.45-1.54 (m, 1H), 1.63-1.68 (m, 2H), 1.85 (d, J = 14.0 Hz, 1H), 1.96-2.02 (m, 1H), 2.11-2.32 (m, 4H), 2.39-2.51 (m, 3H), 2.92 (s, 1H), 3.19 (s, 1H), 3.26-3.31 (m, 1H), 3.47-3.53 (m, 2H), 3.72-3.82 (m, 2H), 6.65-6.69 (m, 1H), 6.96-7.01 (m, 1H), 7.35 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 11.3, 15.9, 16.4, 18.6, 21.3, 22.1, 23.1, 26.1, 33.9, 34.4, 39.5, 45.5, 47.9, 57.3, 59.4, 59.7, 60.6, 62.3, 64.0, 78.5, 107.6 (d, J_{CF} = 8.0 Hz), 115.3 (d, J_{CF} = 28.1 Hz), 116.0 (d, J_{CF} = 34.5 Hz), 125.6 (d, J_{CF} = 15.1 Hz), 138.3, 157.8 (d, J_{CF} = 243.2 Hz), 169.7, 173.2; HRMS (ESI-TOF) m/z: Calcd. for $C_{29}H_{36}FN_2O_6$ $[M+H]^+$: 527.2557; Found: 527.2556.

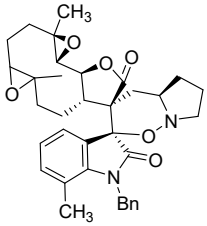


(1aR,1bS,2'S,4R,4aS,4a'R,9aR)-1''-benzyl-6a,9a-dimethyl-1a,1b,4a,4a',5,5',6,6a,6',7a,7',8,9,9a-tetradecahydro-3H,4'H-dispiro[bis(oxireno)[2',3':5,6;2'',3'':9,10]cyclodeca[1,2-b]furan-4,3'-pyrrolo[1,2-b][1,2]oxazine-2',3''-indoline]-2'',3-dione (7c): Light yellow solid, m.p. 269.0-270.8 °C; overall yield 49% (55.9 mg), 12:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.42 (s, 1H), 0.94-0.98 (m, 1H), 1.08-1.15 (m, 1H), 1.18 (s, 3H), 1.26 (s, 3H), 1.32-1.35 (m, 1H), 1.48-1.53 (m, 1H), 1.64-1.68 (m,

2H), 1.86 (d, J = 17.0 Hz, 1H), 1.93-1.96 (m, 1H), 2.08-2.21 (m, 3H), 2.32 (d, J = 8.8 Hz, 2H), 2.44 (d, J = 10.6 Hz, 2H), 2.94-2.98 (m, 1H), 3.24-3.35 (m, 2H), 3.54-3.59 (m, 1H), 3.76-3.81 (m, 1H), 4.39 (d, J = 15.2 Hz, 1H), 5.12 (d, J = 15.6 Hz, 1H), 6.63 (d, J = 7.6 Hz, 1H), 6.91-6.94 (m, 1H), 7.14-7.25 (m, 6H), 7.53 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.9, 16.4, 18.8, 22.1, 22.9, 26.2, 34.4, 39.3, 42.6, 45.4, 47.8, 57.2, 59.3, 59.8, 60.9, 62.1, 64.1, 78.4, 108.1, 122.7, 126.5, 126.8, 127.9, 128.0, 129.8, 134.0, 142.4, 170.4, 173.5; HRMS (ESI-TOF) m/z: Calcd. for $C_{34}H_{39}N_2O_6$ $[M+H]^+$: 571.2803; Found: 571.2809.

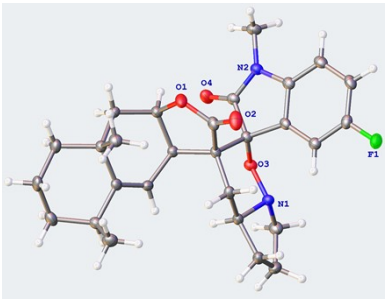


(1aR,1bS,2'S,4R,4aS,4a'R,9aR)-1''-benzyl-7''-chloro-6a,9a-dimethyl-1a,1b,4a,4a',5,5',6,6a,6',7a,7',8,9,9a-tetradecahydro-3H,4'H-dispiro[bis(oxireno)[2',3':5,6;2'',3'':9,10]cyclodeca[1,2-b]furan-4,3'-pyrrolo[1,2-b][1,2]oxazine-2',3''-indoline]-2'',3-dione (7d): Light yellow solid, m.p. 272.1-272.7 ^{o}C; overall yield 50% (60.4 mg), >20:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.53 (s, 1H), 0.99-1.03 (m, 1H), 1.17-1.19 (m, 4H), 1.27 (s, 3H), 1.33-1.38 (m, 1H), 1.53-1.57 (m, 1H), 1.68-1.74 (m, 2H), 1.87 (d, J = 14.2 Hz, 1H), 1.97-2.01 (m, 1H), 2.10-2.24 (m, 4H), 2.37-2.40 (m, 2H), 2.52 (d, J = 10.8 Hz, 1H), 2.90-2.97 (m, 1H), 3.20 (s, 1H), 3.30-3.35 (m, 1H), 3.52 (s, 1H), 3.76-3.81 (m, 1H), 5.10 (d, J = 16.0 Hz, 1H), 5.38 (d, J = 16.0 Hz, 1H), 6.88-6.92 (m, 1H), 7.15-7.24 (m, 6H), 7.55 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.9, 16.4, 19.0, 22.2, 23.1, 26.1, 34.4, 39.2, 43.8, 45.6, 48.0, 57.3, 59.5, 59.7, 60.6, 62.3, 63.9, 78.5, 114.2, 123.5, 125.6, 126.3, 127.6, 132.5, 135.5, 138.4, 170.9, 173.3; HRMS (ESI-TOF) m/z: Calcd. for $C_{34}H_{38}ClN_2O_6$ $[M+H]^+$: 605.2413; Found: 605.2413.



(1aR,1bS,2'S,4R,4aS,4a'R,9aR)-1''-benzyl-6a,7'',9a-trimethyl-1a,1b,4a,4a',5,5',6,6a,6',7a,7',8,9,9a-tetradecahydro-3H,4'H-dispiro[bis(oxireno)[2',3':5,6;2'',3'':9,10]cyclodeca[1,2-b]furan-4,3'-pyrrolo[1,2-b][1,2]oxazine-2',3''-indoline]-2'',3-dione (7e): Light yellow solid, m.p. 265.0-266.3 °C; overall yield 48% (56.1 mg), 15:1 dr; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.54-0.59 (m, 1H), 0.93-1.00 (m, 1H), 1.15-1.18 (m, 1H), 1.21 (s, 3H), 1.28 (s, 3H), 1.35-1.39 (m, 1H), 1.63-1.70 (m, 4H), 1.85 (d, J = 14.4 Hz, 1H), 1.96-2.01 (m, 1H), 2.10-2.14 (m, 1H), 2.17 (s, 3H), 2.27-2.38 (m, 3H), 2.43-2.54 (m, 2H), 2.92-2.98 (m, 1H), 3.24-3.27 (m, 1H), 3.33-3.38 (m, 1H), 3.52-3.55 (m, 1H), 3.76-3.81 (m, 1H), 4.71 (d, J = 16.6 Hz, 1H), 5.38 (d, J = 16.8 Hz, 1H), 6.84-6.94 (m, 2H), 7.06 (d, J = 7.2 Hz, 2H), 7.13-7.17 (m, 1H), 7.20-7.23 (m, 2H), 7.47 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.9, 16.4, 18.0, 18.5, 21.9, 22.1, 22.2, 26.3, 34.4, 39.6, 43.7, 45.5, 47.8, 57.1, 59.3, 59.9, 60.8, 62.1, 64.1, 78.5, 118.5, 122.7, 124.6, 125.5, 126.3, 127.8, 127.9, 133.9, 135.7, 140.3, 171.3, 173.5; HRMS (ESI-TOF) m/z: Calcd. for $C_{35}H_{41}N_2O_6$ $[M+H]^+$: 585.2959; Found: 585.2965.

3. X-ray crystal data for compound 3b



CCDC 2496422

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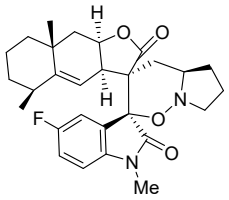


3b

Table S1 Crystal data and structure refinement for 3b

Identification code	**3b**
Empirical formula	$C_{28}H_{33}FN_2O_4$
Formula weight	480.56
Temperature/K	100.00(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å, b/Å, c/Å	11.07456(8), 19.22227(13), 23.30686(16)
α/°, β/°, γ/°	90, 90, 90
Volume/Å^3	4961.52(6)
Z	8

ρ_{calc}g/cm^3	1.287
μ/mm^{-1}	0.742
F(000)	2048.0
Radiation	Cu Kα (λ = 1.54184)
Crystal size/mm^3	0.15 × 0.12 × 0.1
2Θ range for data collection/°	5.96 to 146.748
Index ranges	-10 ≤ h ≤ 13, -23 ≤ k ≤ 17, -28 ≤ l ≤ 28
Reflections collected	33378
Independent reflections	9661 [R_{int} = 0.0343, R_{sigma} = 0.0296]
Data/restraints/parameters	9661/0/637
Goodness-of-fit on F^2	1.043
Final R indexes [I>=2σ (I)]	R_1 = 0.0296, wR_2 = 0.0709
Final R indexes [all data]	R_1 = 0.0311, wR_2 = 0.0718
Largest diff. peak/hole / e Å^{-3}	0.14/-0.22
Flack parameter	-0.08(4)/-0.06(4)

Crystal Data for $C_{28}H_{33}FN_2O_4$ (*M* =480.56 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 11.07456(8) Å, *b* = 19.22227(13) Å, *c* = 23.30686(16) Å, *V* = 4961.52(6) Å^3, *Z* = 8, *T* = 100.00(10) K, μ(Cu Kα) = 0.742 mm^{-1}, *Dcalc* = 1.287 g/cm^3, 33378 reflections measured (5.96° ≤ 2Θ ≤ 146.748°), 9661 unique (R_{int} = 0.0343, R_{sigma} = 0.0296) which were used in all calculations. The final R_1 was 0.0296 (I > 2σ(I)) and wR_2 was 0.0718 (all data).

4. MTT assay

A total of 5×10^3 cells in the logarithmic growth phase were inoculated into a 96-well platein RPMI-1640 medium and cultured for 24 h to allow cell adherence. Subsequently,compounds at various concentrations were added to the medium, and the cells were incubated for an additional 48 h. Next, 10 μL of MTT solution with a concentration of 5 mg/mL was added for 4 h, the supernatant culture medium was discarded, shaken with 150 μL of DMSO for 10 min, and the absorbance (OD value) value was detected at 490 nm on a microplate reader[9]. IBM SPSS Statistics 23 software was used to to calculate the concentration of the compound that causes half cell death (IC_{50}). Among them, inhibition rate (%)=(1-(treatment group OD_{490}-blank group OD_{490})/(control group OD_{490}-blank group OD_{490})) × 100%.

5. Cytomorphologic analysis

A549 cells in logarithmic growth phase were digested with trypsin and diluted cells were seeded in 6-well plates at 3×10^5 cells. Cultivate for 24 h, and treat with different concentrations of compound **3j** (0, 12.5, 25.0 and 50.0 μM) for 48 h. At the end of culture, A549 cells were

photographed under an inverted microscope (Leica Inc., Germany) to record morphological changes.

6. AO/EB staining analysis

A549 cells were seeded into 6-well plates at 3×10^5 cells/well and cultured for 24 h at 37°C, 5% CO_2. After 48 h of drug treatment with control and drug groups. At the end of the culture, PBS was washed twice, and 100 μL of AO/EB staining solution prepared 1:1 immediately before use was added for incubation for 5 min, observed under an inverted fluorescence microscope, photographed and analyzed.

7. Apoptosis analysis

A549 cells in logarithmic growth phase were inoculated into 6-well plates at a density of 3×10^5 cells/well and cultured at 37°C in 5% CO_2 for 24 h. After treating the cells with 0, 12.5, 25.0 and 50.0 μM compound **3j** for 48 h, they were washed twice with precooled PBS. Then, 1 mL Hoechst 33258 staining solution was added to each well to fully cover the samples. The cells were incubated for 20 minutes. the staining solution was discarded, and the cells were washed 2-3 times with PBS. Fluorescence detection was performed by observation under an inverted fluorescence microscope, followed by photography and analysis.

8. Mitochondrial membrane potential analysis

A549 cells were seeded into 6-well plates at 3×10^5 cells/well and cultured for 24 h at 37°C with 5% CO_2. Cultivate cells with different concentrations of compound **3j** (0, 12.5, 25.0 and 50.0 μM) for 48 h. Following treatment, the culture medium was removed by aspiration and the cells were washed once with PBS. Then, 1 mL cell culture medium and 1 mL JC-1 staining working solution were added to each well and mixed thoroughly. The cells were incubated at 37°C for 20 minutes in a cell incubator. After incubation, the supernatant was aspirated and the cells were washed twice with JC-1 staining buffer (1×). Subsequently, 2 mL cell culture medium was added to each well, and the cells were observed under fluorescence microscope.

9. DCFH-DA reactive oxygen species assessment

A549 cells were plated in 6-well plates at a cell count of 3×10^5 cells/well and grown for 24 h at 37°C, 5% CO_2. Control and drug groups (12.5, 25.0 and 50.0 μM) were set up for 48 h of drug

treatment. The culture medium was aspirated, the cells were washed once with PBS, and 1 mL of diluted DCFH-DA was added to fully cover the cells, and the cells were incubated in a cell culture incubator at 37°C for 20 minutes. Cells were washed three times with serum-free cell culture medium to adequately remove DCFH-DA that did not enter the cells. An inverted fluorescence microscope was used to excite at 488 nm, photograph at 525 nm emission and record intracellular reactive oxygen species production.

10. Apoptosis detection by flow cytometry

After treating A549 cells with different concentrations of compound **3j** for 48 h, the cells were digested, centrifuged, and collected. The cells were then resuspended in pre-chilled PBS and centrifuged again. The supernatant was discarded after centrifugation, and the cell pellet containing 1 × 10^6 cells was collected. The 5× Binding Buffer was diluted with double-distilled water to 1× working solution, and the cells were resuspended in 500 μL of this solution. Next, 5 μL Annexin V-PE and 10 μL 7-AAD were added to each tube. The tubes were gently vortexed to mix and incubated at room temperature in the dark for 5 minutes. Finally, the stained cells were immediately analyzed by flow cytometry.

11. Cycles detected by flow cytometry

After A549 cells were subjected to drug treatment for 48 h, 1×10^6 cells were collected by centrifugation, and the supernatant was discarded. The cell pellet was washed once with PBS, followed by centrifugation and supernatant removal. The cells were resuspended in 1 mL of DNA Staining solution and 10 μL of permeabilization solution. then vortexed for 10 s. The mixture was incubated for 30 minutes at room temperature in the dark. Furthermore, the stained cells were analyzed immediately using a flow cytometer at the lowest flow rate.

12. Western blot analysis

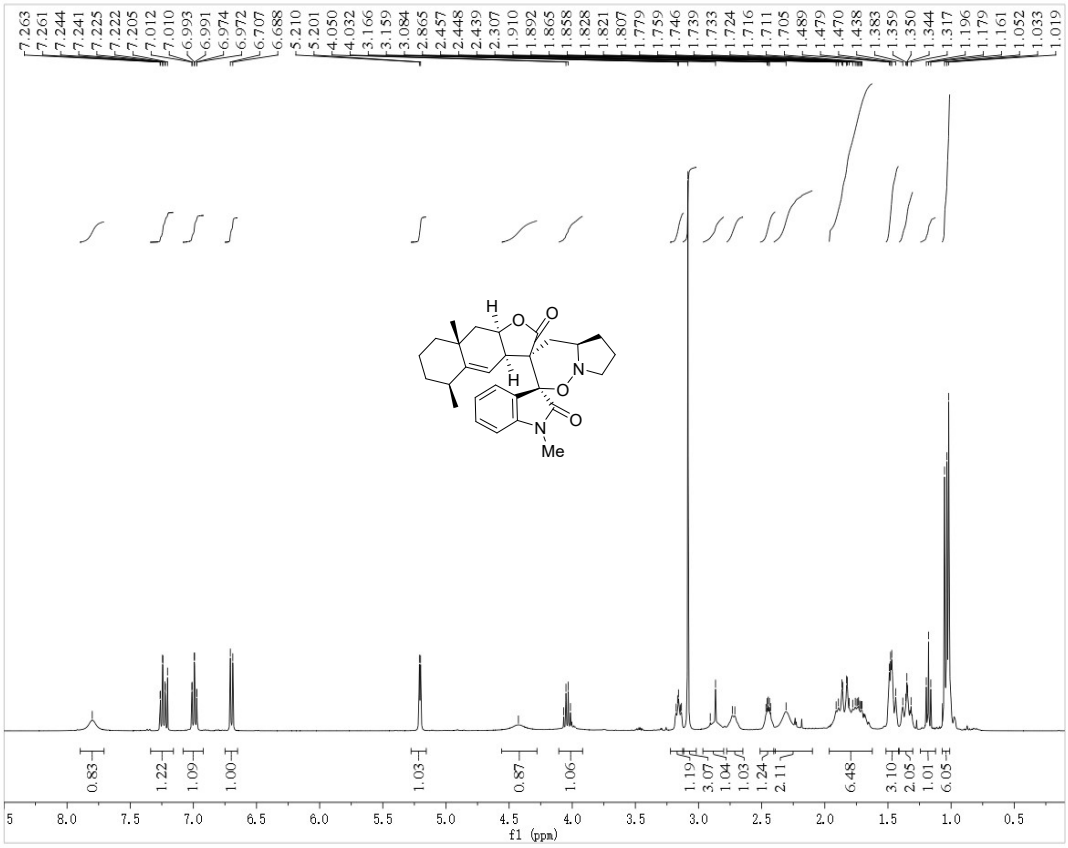
A549 cells were trypsinized and seeded into 6-well plates at a density of 3×10^5 cells/well and cultured at 37°C in 5% CO_2 for 24 h. Control and drug groups (12.5, 25.0, 50.0, and 100 μM) were set up for 48 h of drug treatment. Cells were detached using with a cell scraper, and the cell pellet was collected by centrifugation. After washing twice with PBS, the pellet was resuspended in 200 μL of lysis buffer and lysed on ice for 30 minutes. The lysate was collected by centrifugation at 12,000 rpm/min for 5 minutes, at 4°C to collect the supernatant containing the

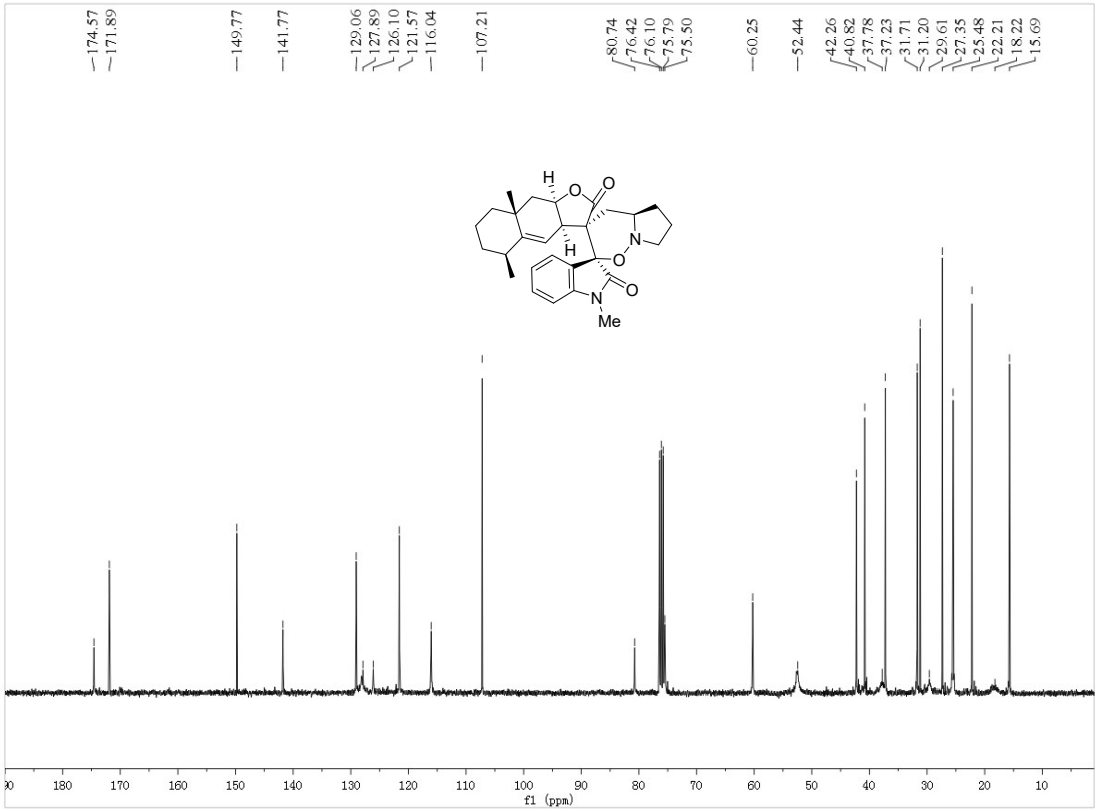
extracted proteins. Five microliters of the supernatant was used for BCA protein concentration determination, while the remaining supernatant was mixed with 1/5 volume of 1×SDS loading buffer, denatured at 100°C for 5 minutes, and stored at -80°C.

Protein sample loading amount 20-40 μg. Electrophoresis condition: 80 V for about 30 minutes, then adjust the voltage to 120 V to continue electrophoresis, and stop electrophoresis when bromophenol blue reaches the bottom of the gel. Next, use the classic "sandwich" method to transfer the film. After the membrane transfer was completed, the PVDF membrane was washed three times with TBST and then sealed at room temperature with 5% skim milk powder for 1 h. Subsequently, the washed membrane was incubated overnight at 4 ℃ in the corresponding antibody dilution solution; Finally, after washing with TBST, the membrane was incubated with the secondary antibody at room temperature for 1 h. ECL chemiluminescence solution was added, and the PVDF membrane was developed and exposed in the Bio-Rad imaging system.

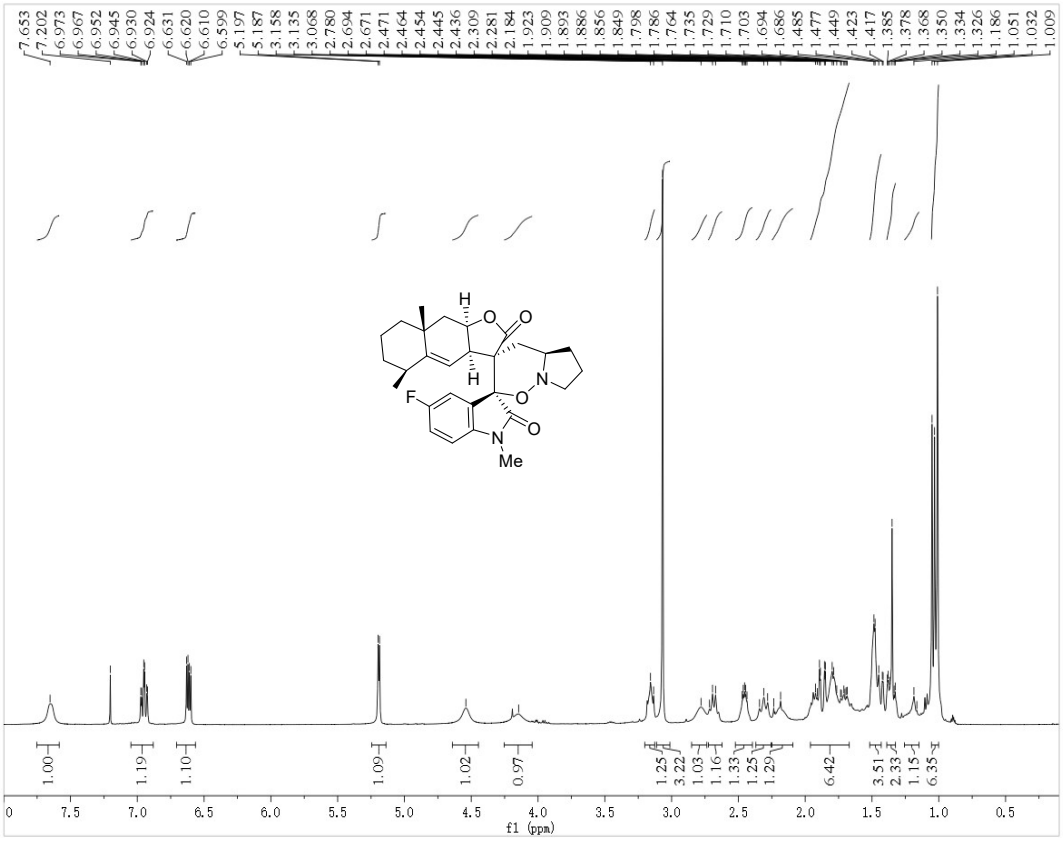
13. The copies of ^{1}H NMR and ^{13}C NMR spectra for compounds 3 and 5

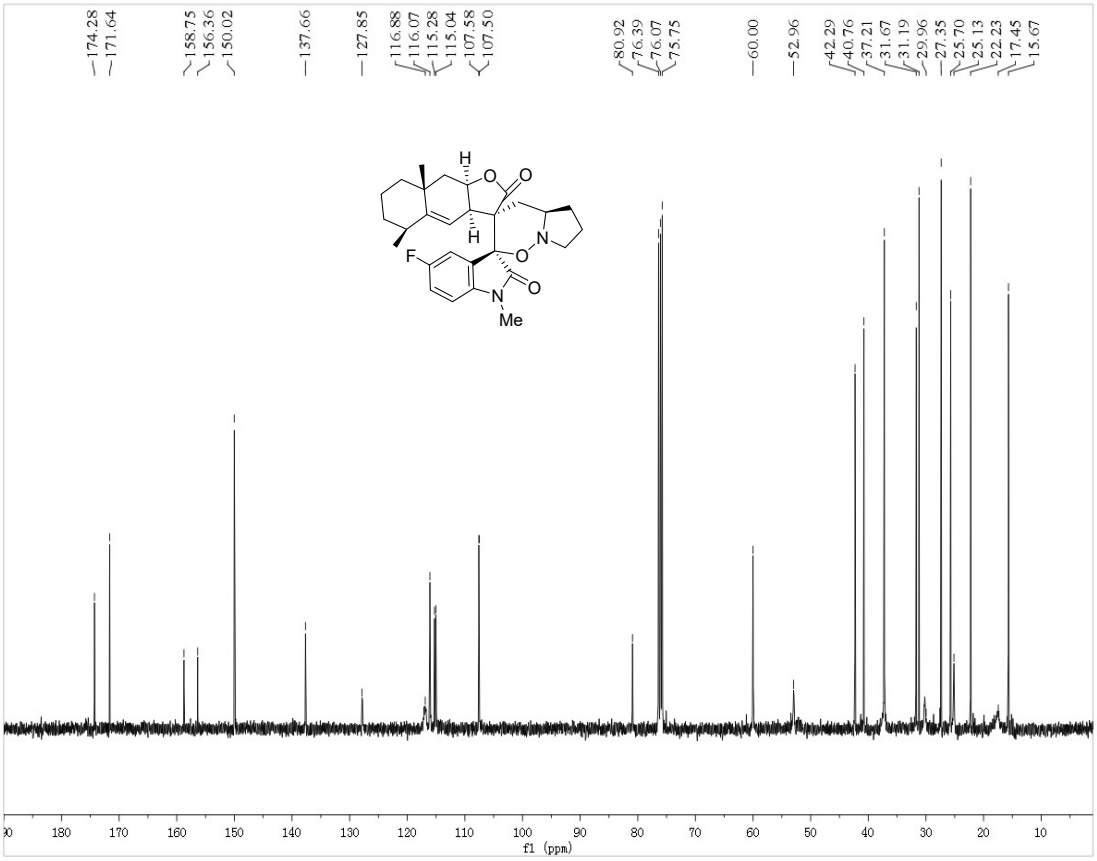
^{1}H and ^{13}C NMR of 3a





^{1}H and ^{13}C NMR of 3b

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156.36
150.02
137.66
127.85
116.88
116.07
115.28
115.04
107.58
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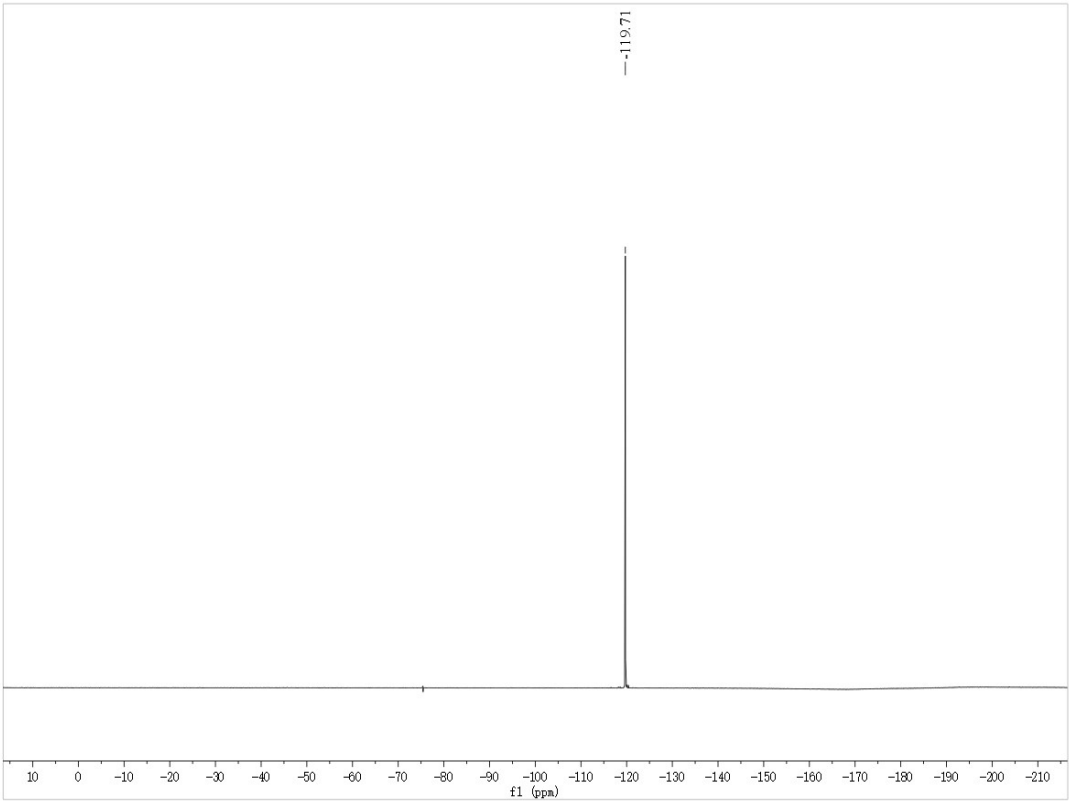
80.92
76.39
76.07
75.75
60.00
52.96
42.29
40.76
37.21
31.67
31.19
29.96
27.35
25.70
25.13
22.23
17.45
15.67
H
O
O
H
N
F
O
O
N
Me
f1 (ppm)

^{19}F NMR of 3b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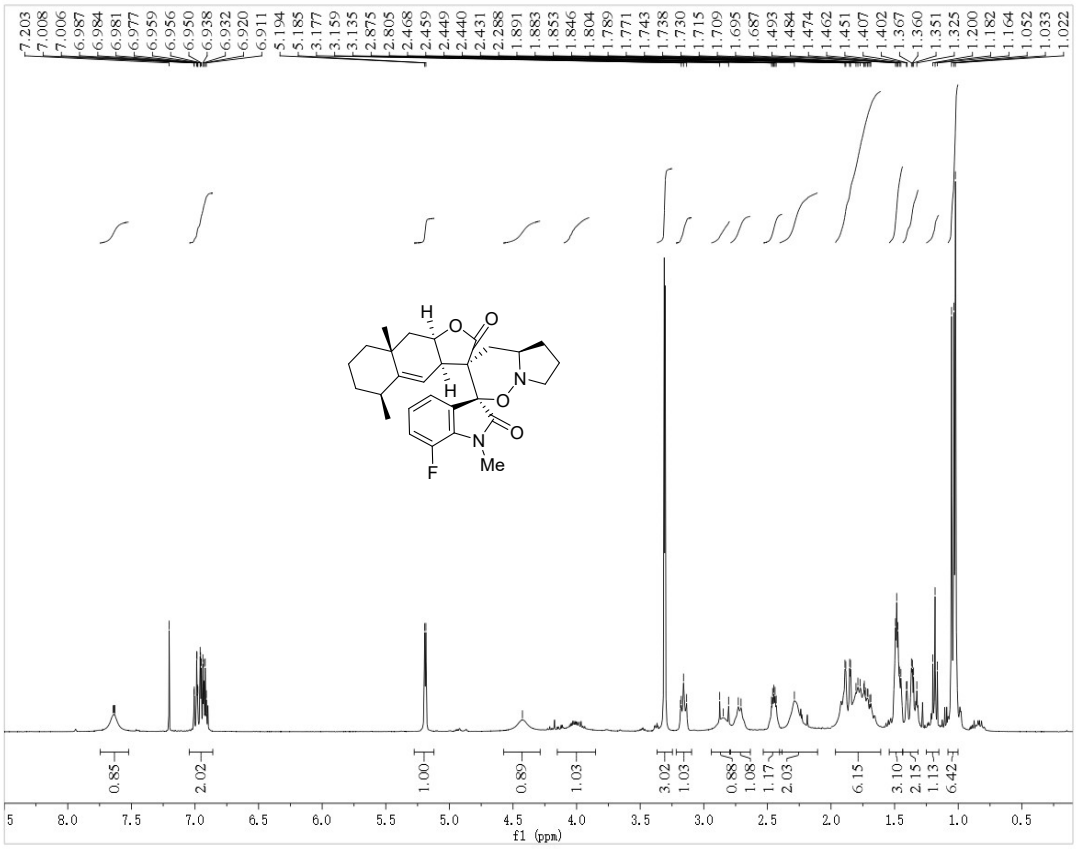
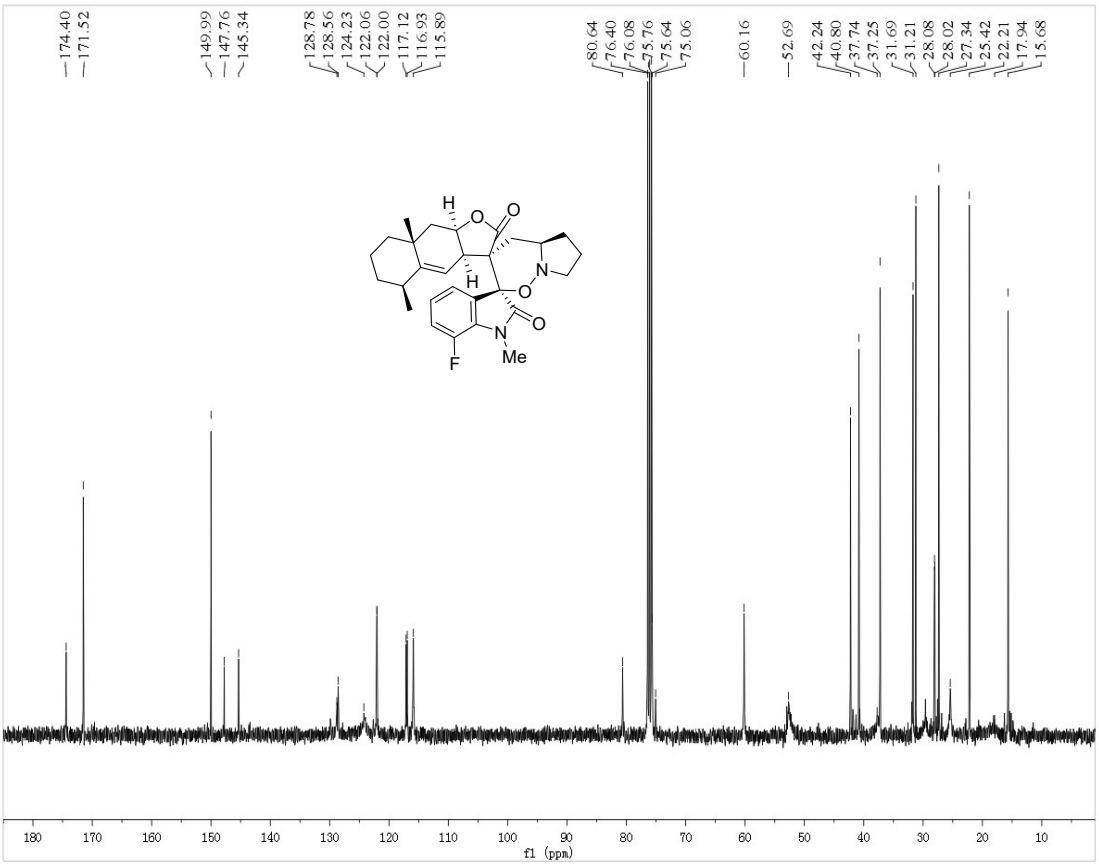
^{1}H and ^{13}C NMR of 3c

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122.00
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116.93
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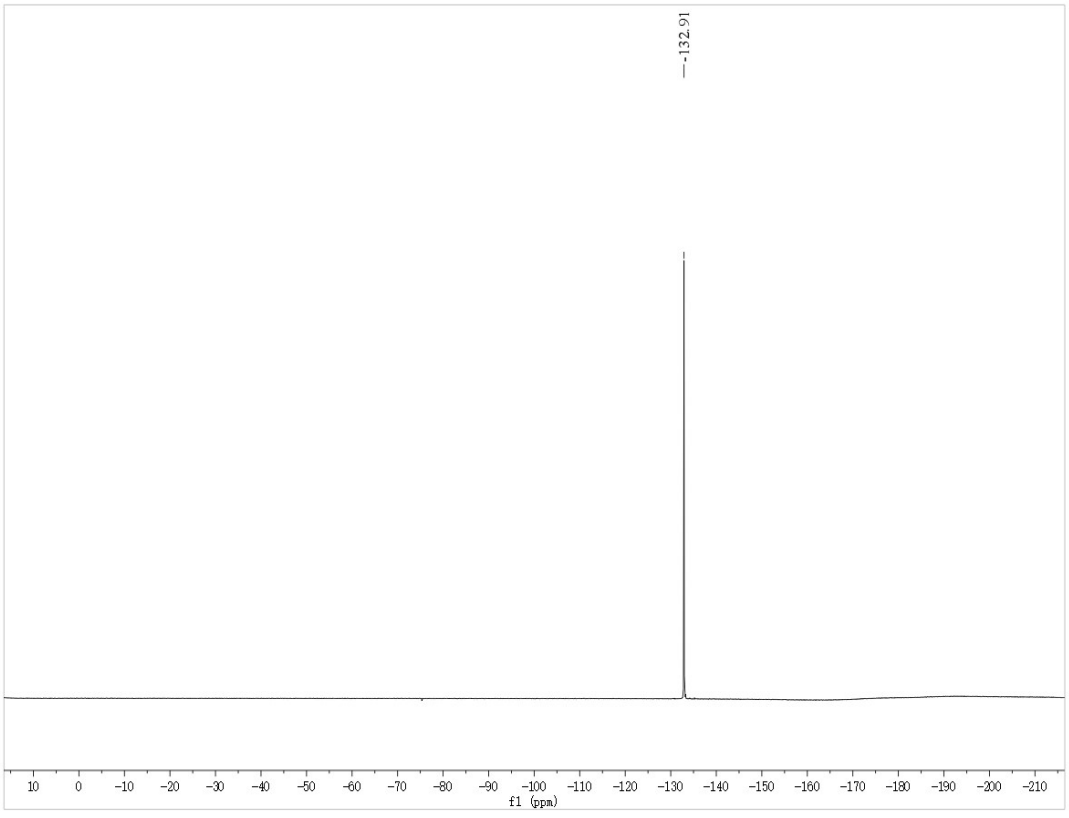
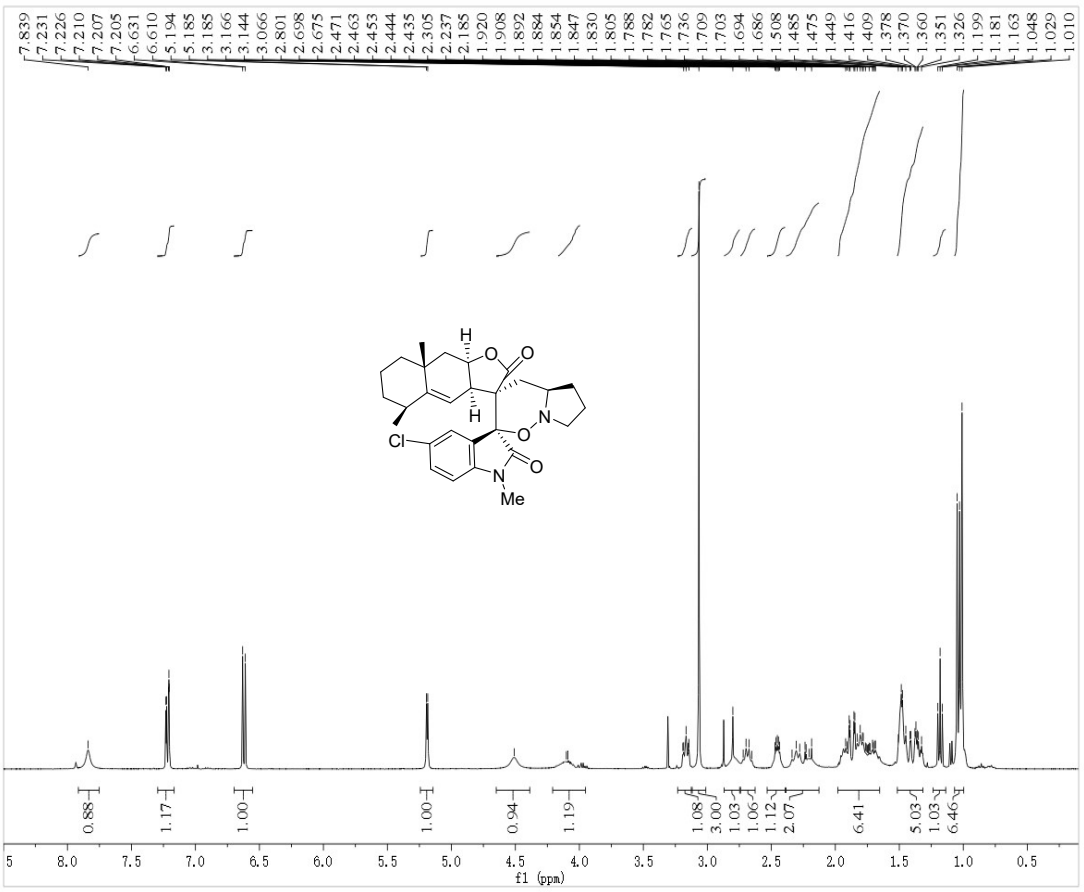
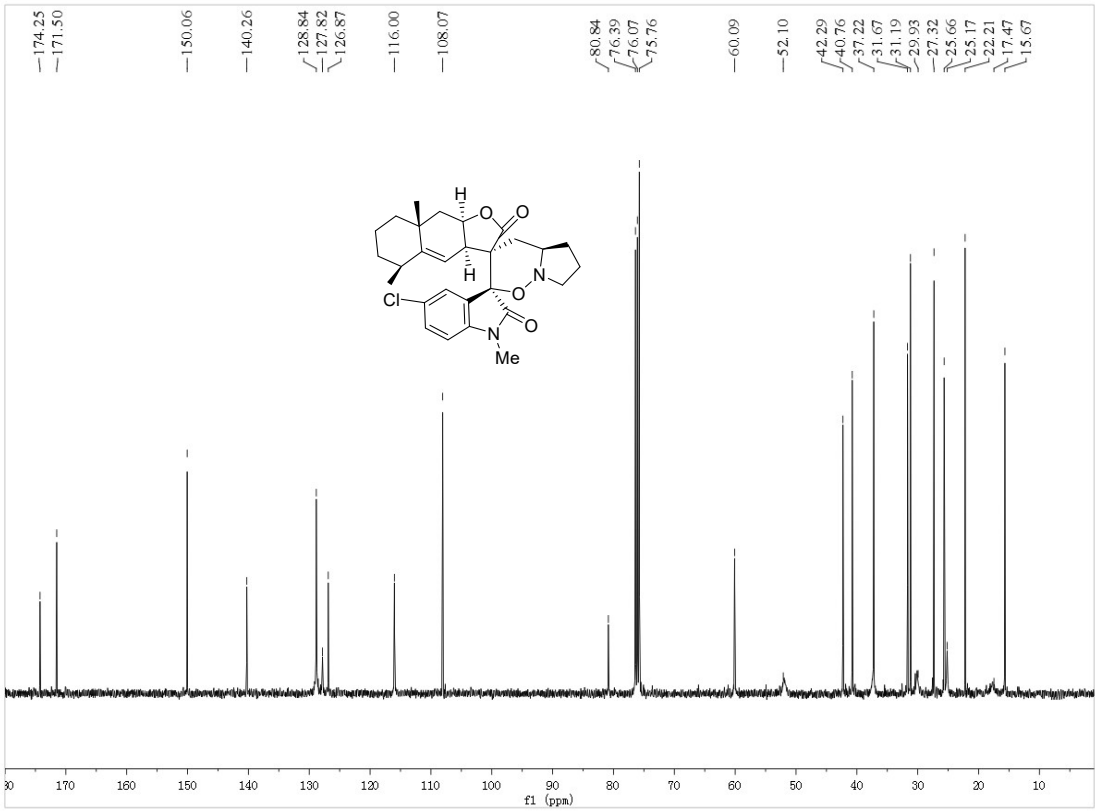
76.40
76.08
75.76
75.64
75.06
60.16
52.69
42.24
40.80
37.74
37.25
31.69
31.21
28.08
28.02
27.34
25.42
22.21
17.94
15.68
H
O
O
N
H
O
O
N
Me
F
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

^{19}F NMR of 3c

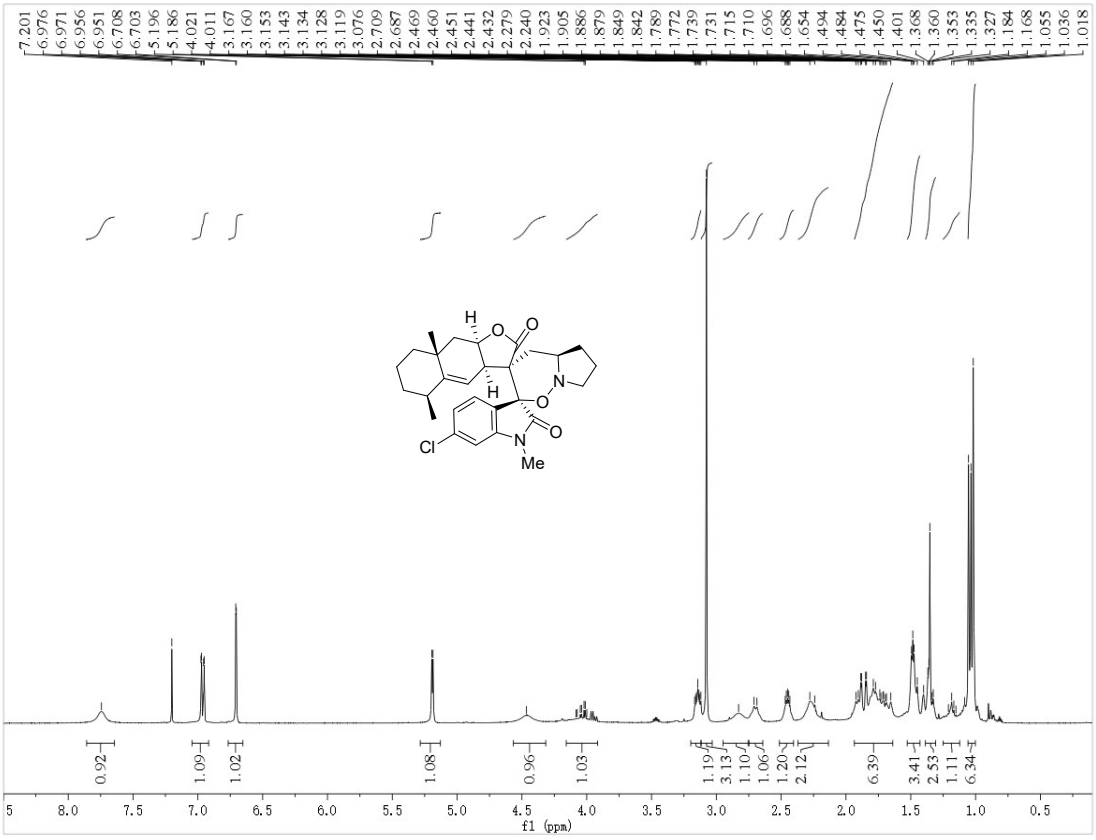

-132.91
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

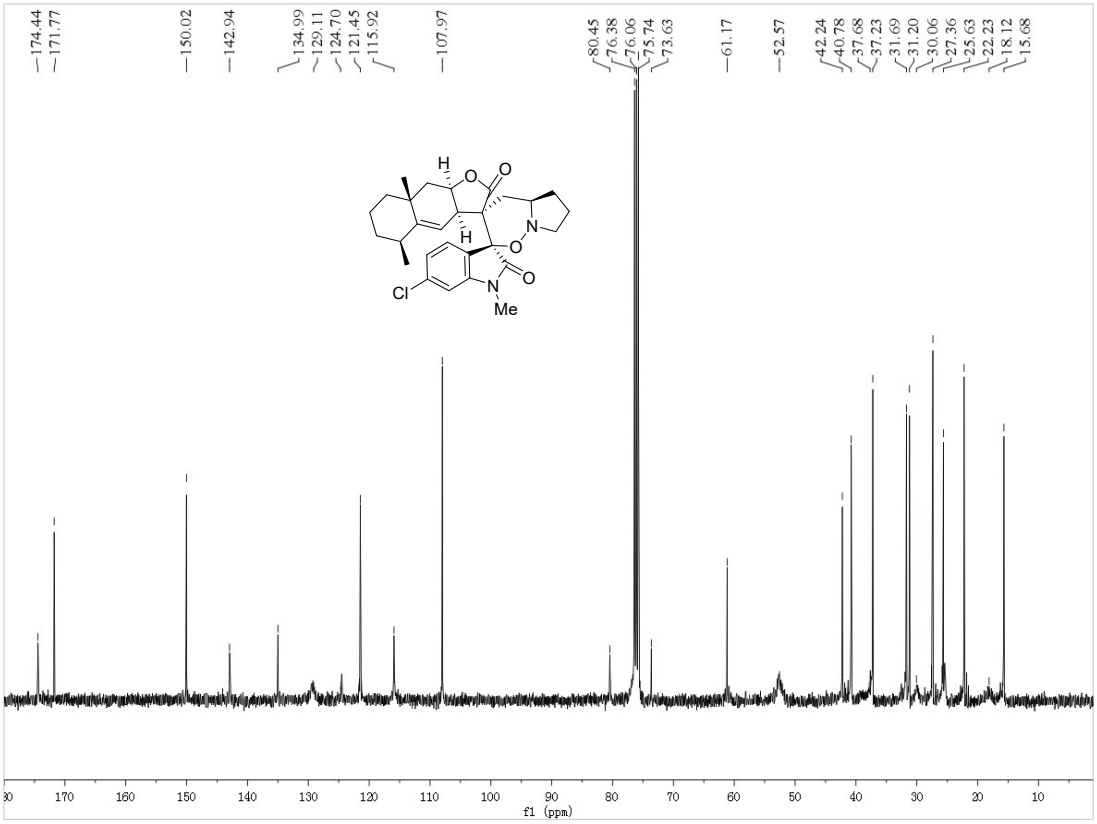
^{1}H and ^{13}C NMR of 3d



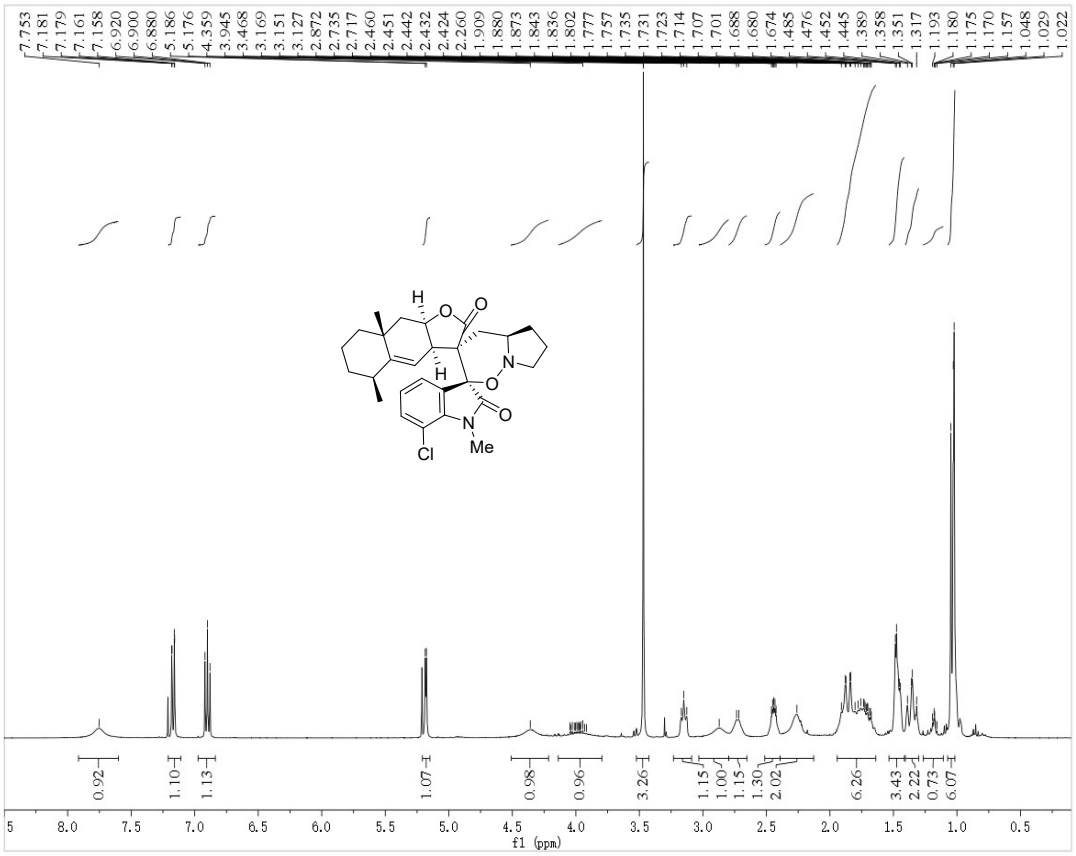


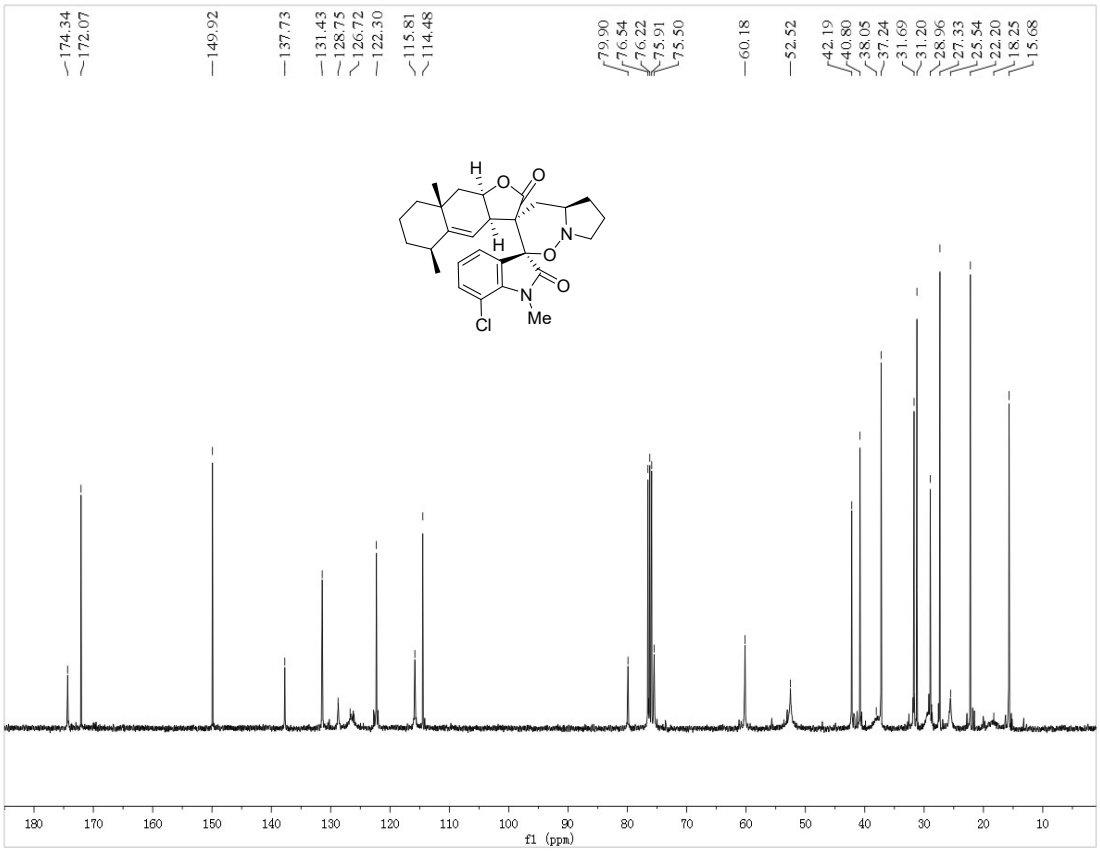
^{1}H and ^{13}C NMR of 3e



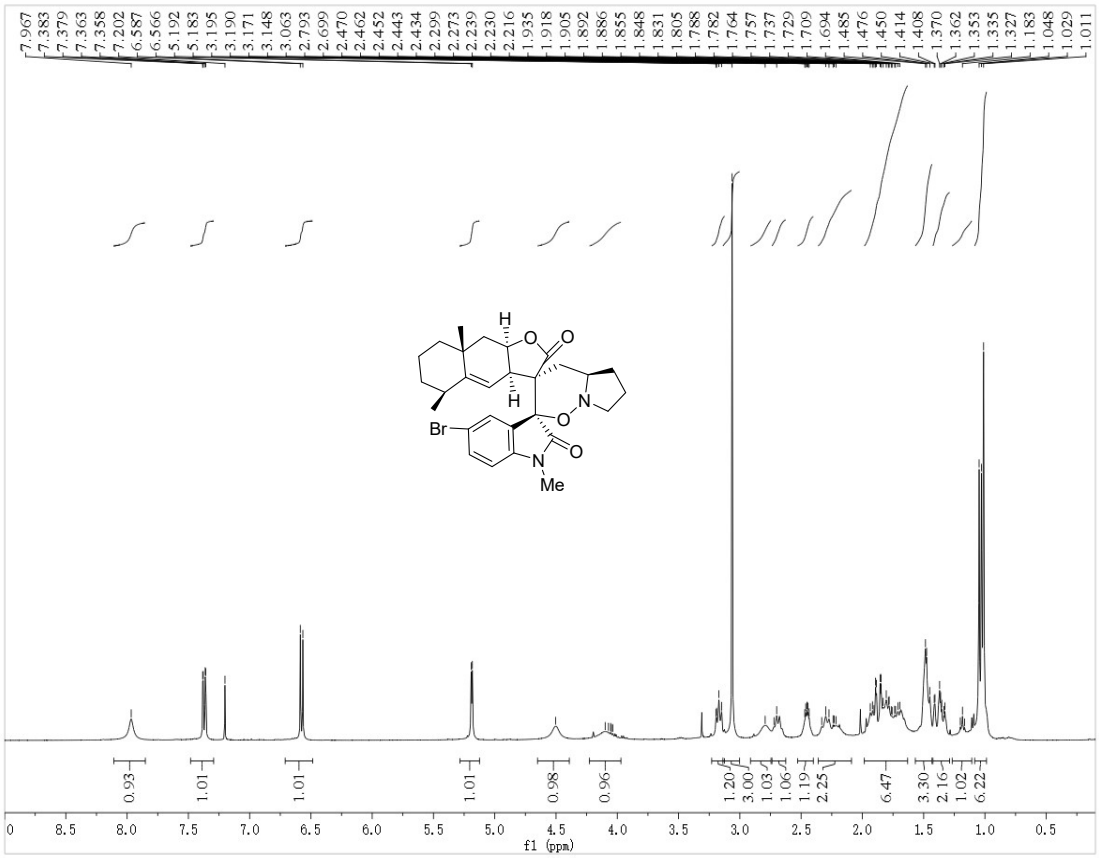


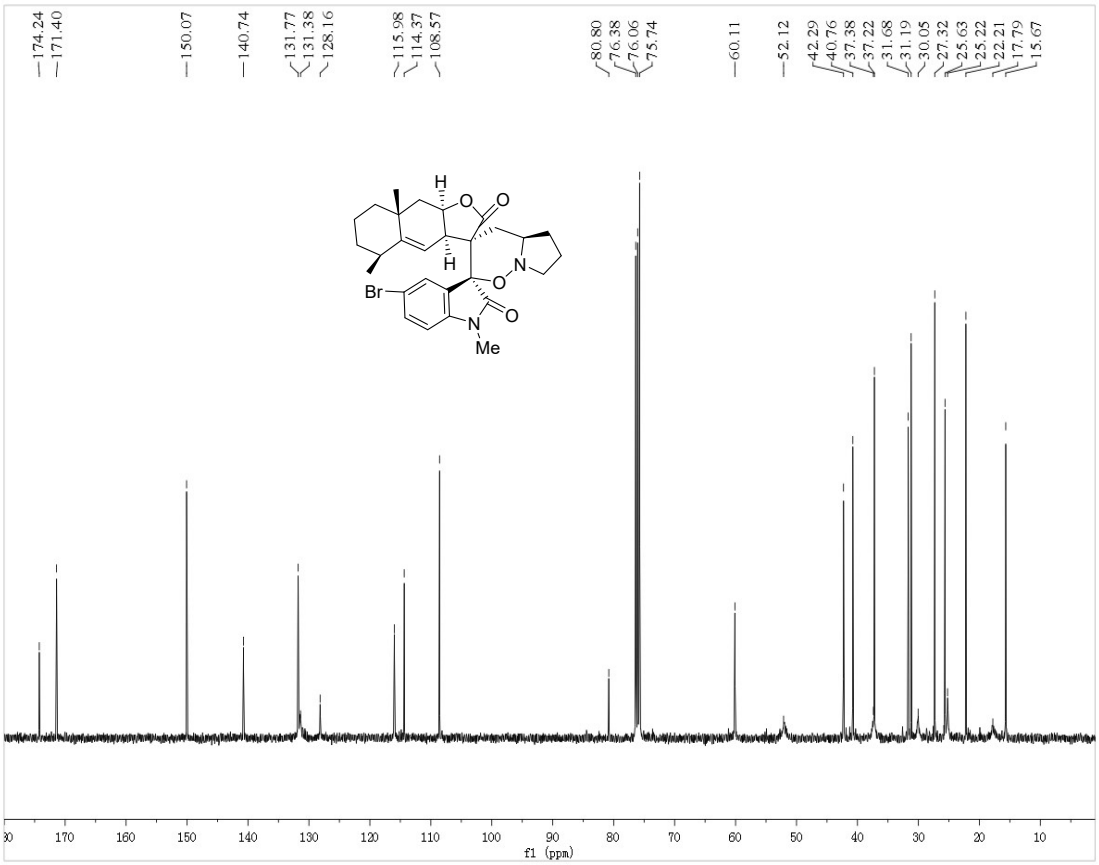
^{1}H and ^{13}C NMR of 3f



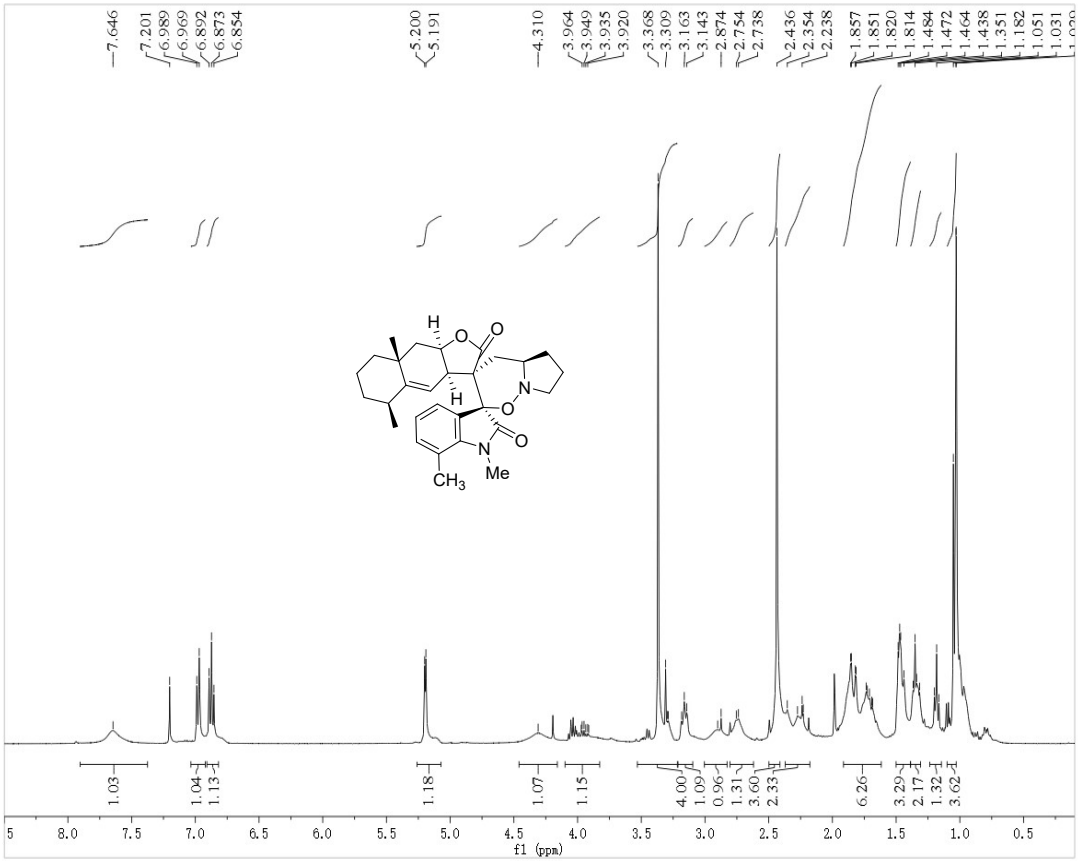


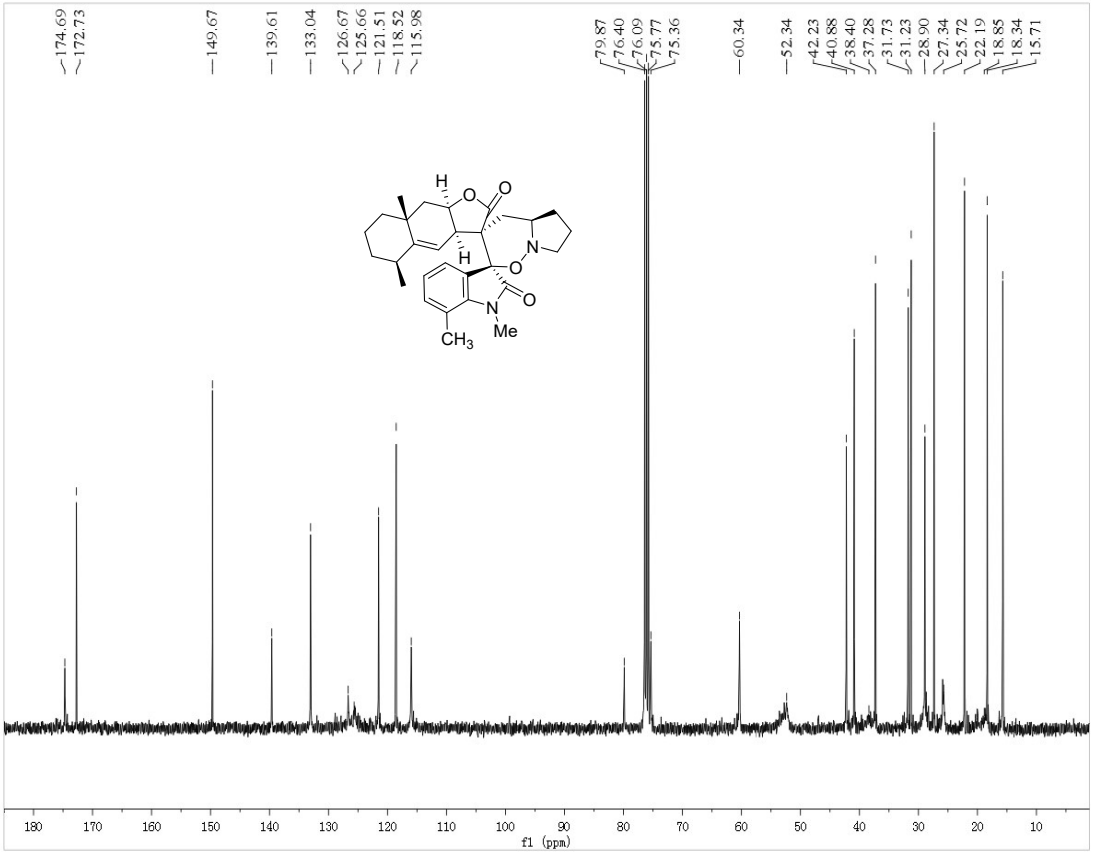
^{1}H and ^{13}C NMR of 3g



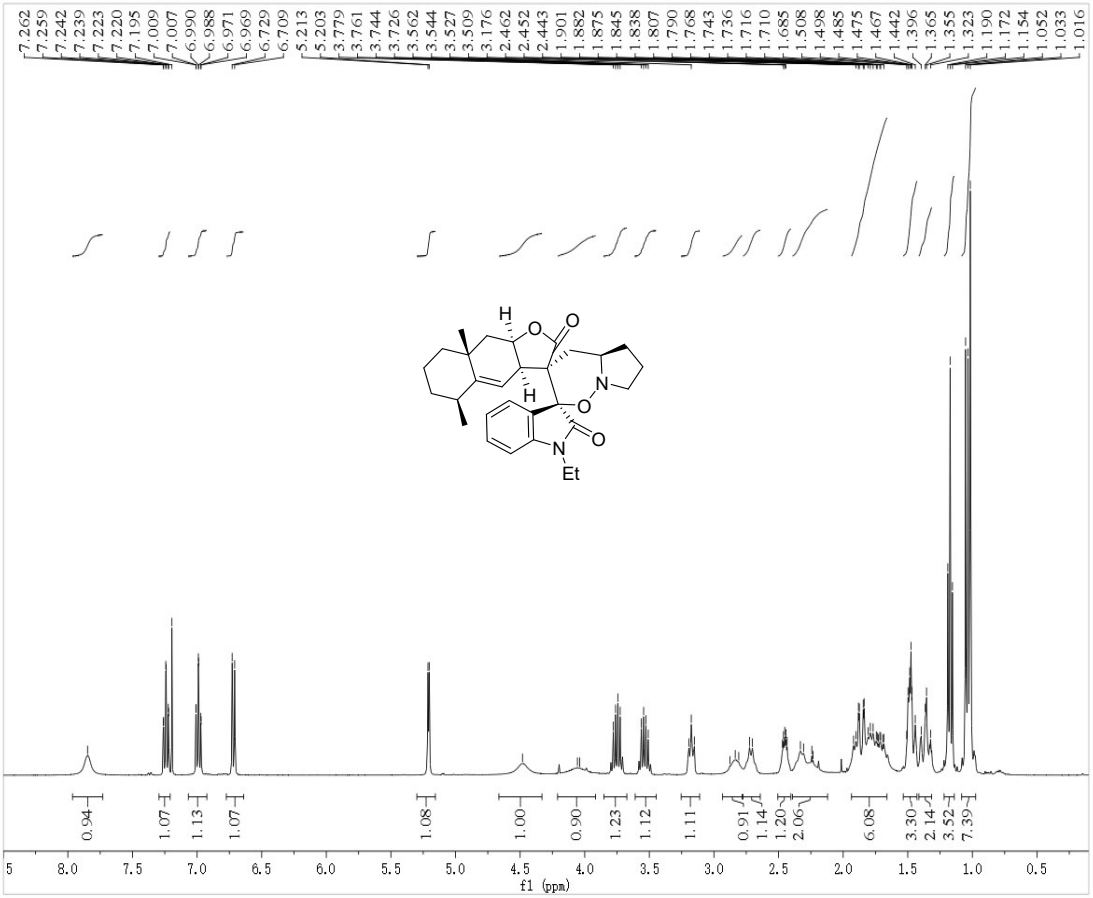


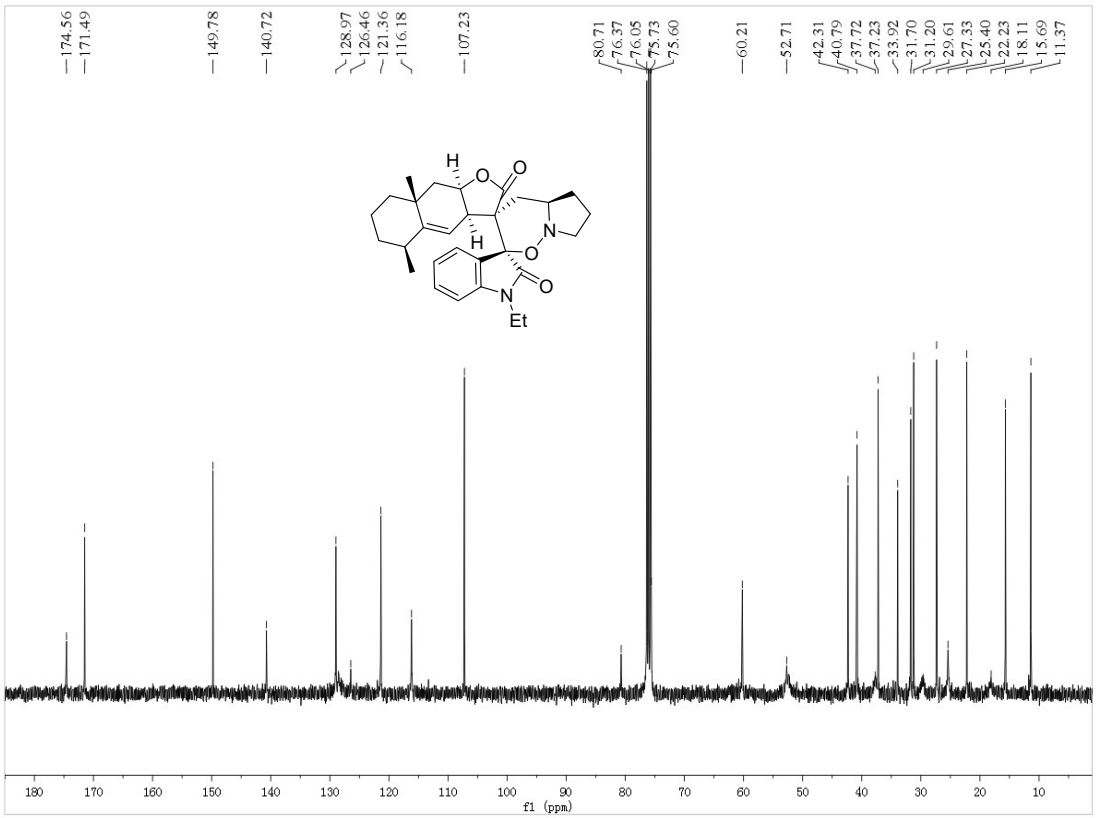
^{1}H and ^{13}C NMR of 3h



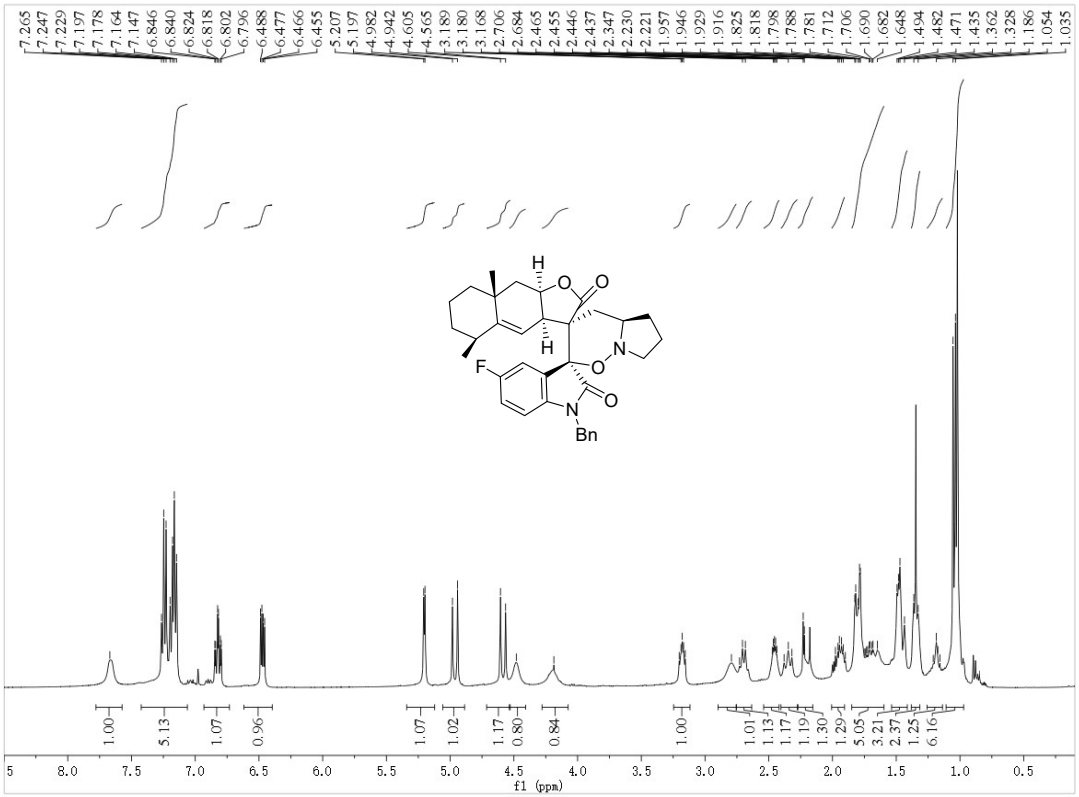


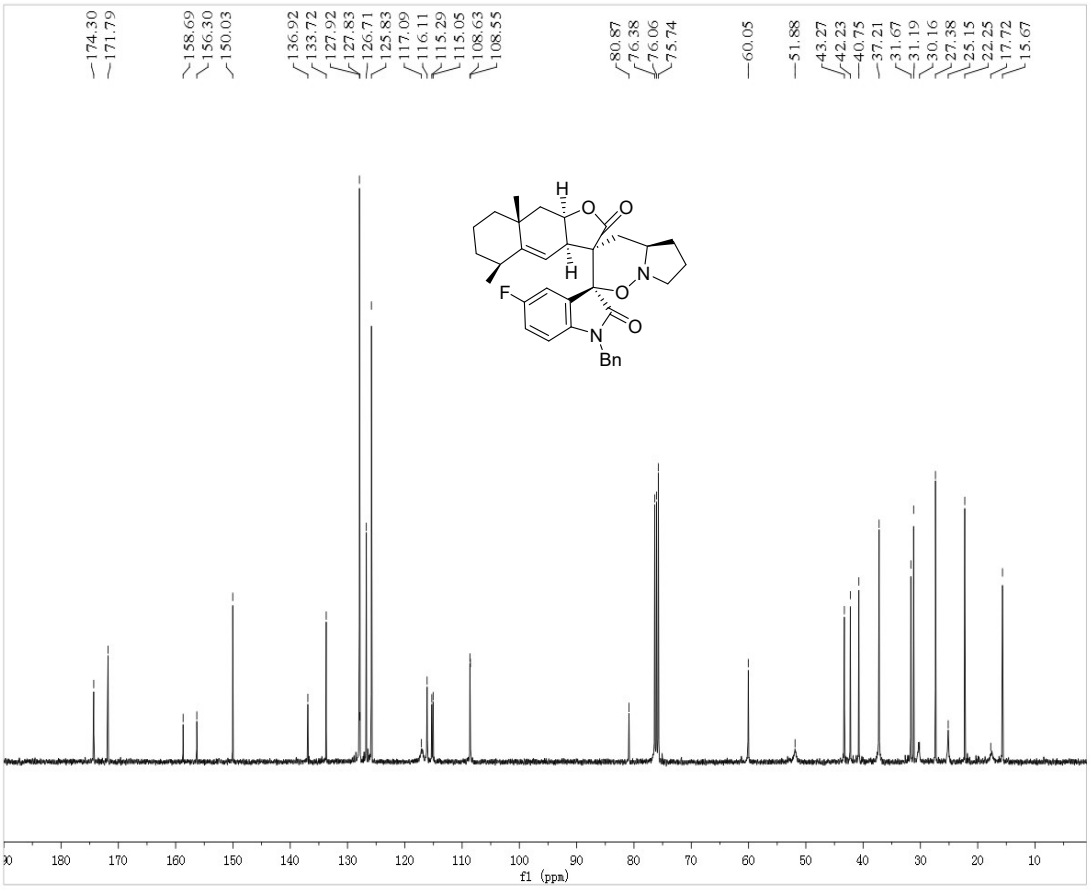
^{1}H and ^{13}C NMR of 3i



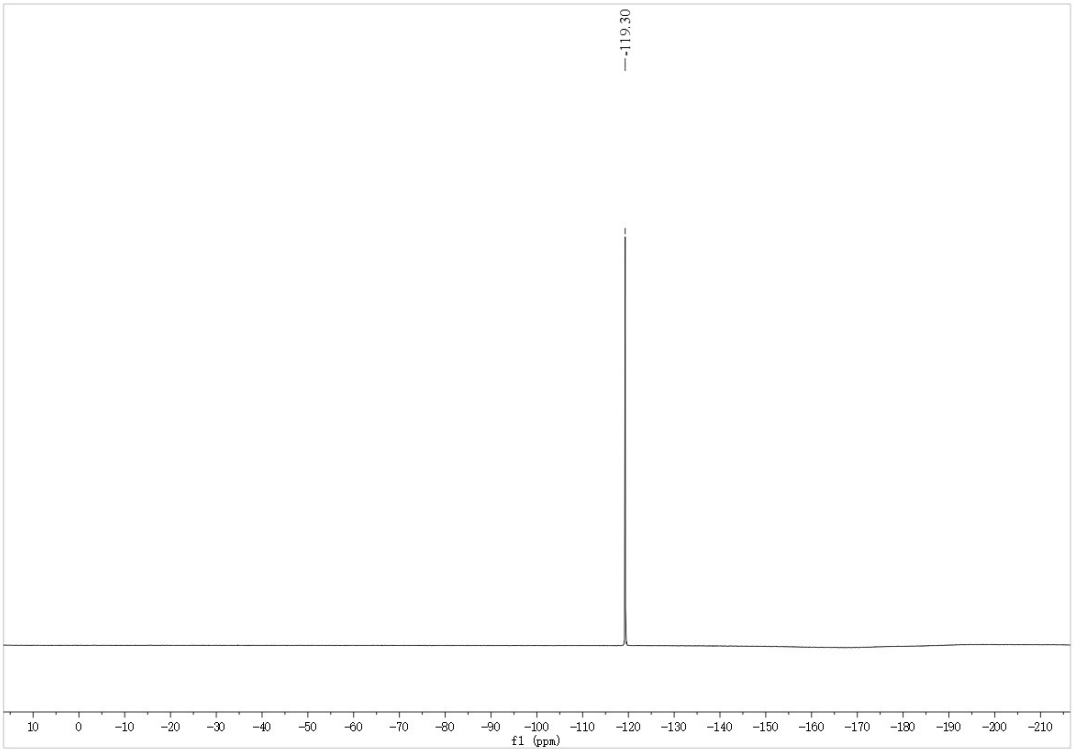


^{1}H and ^{13}C NMR of 3j

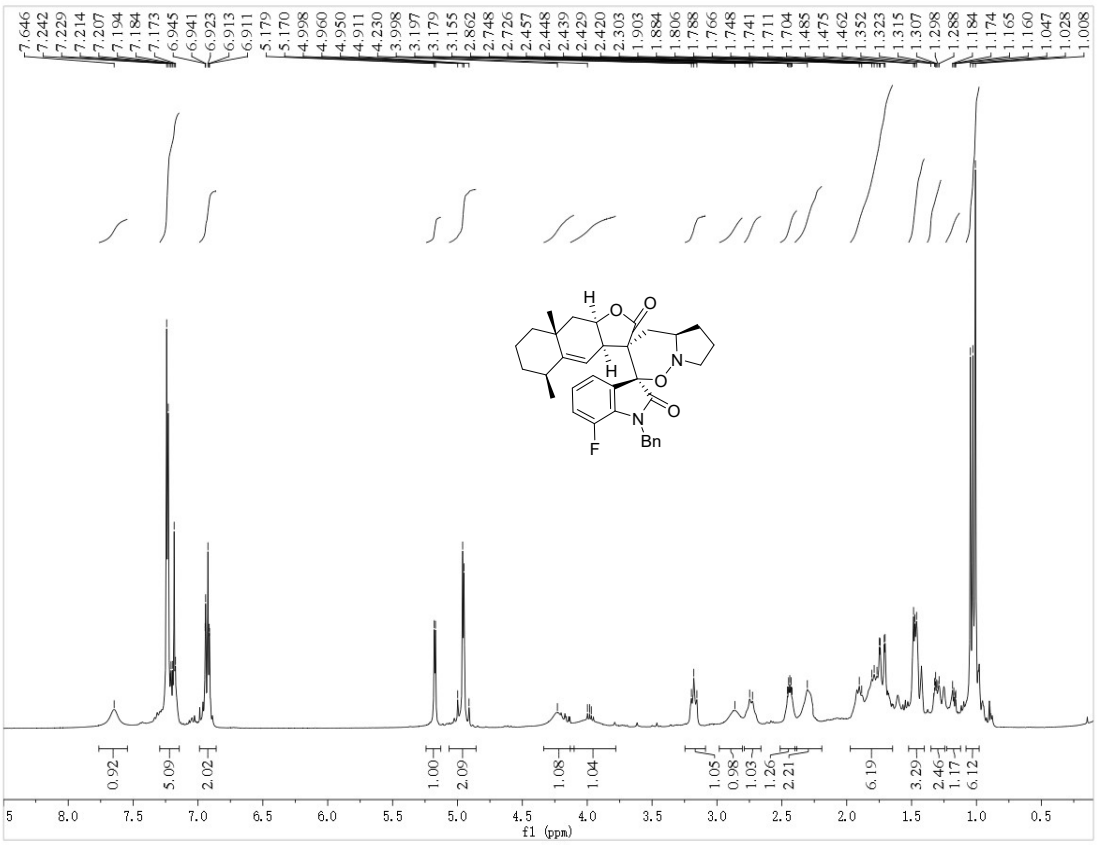


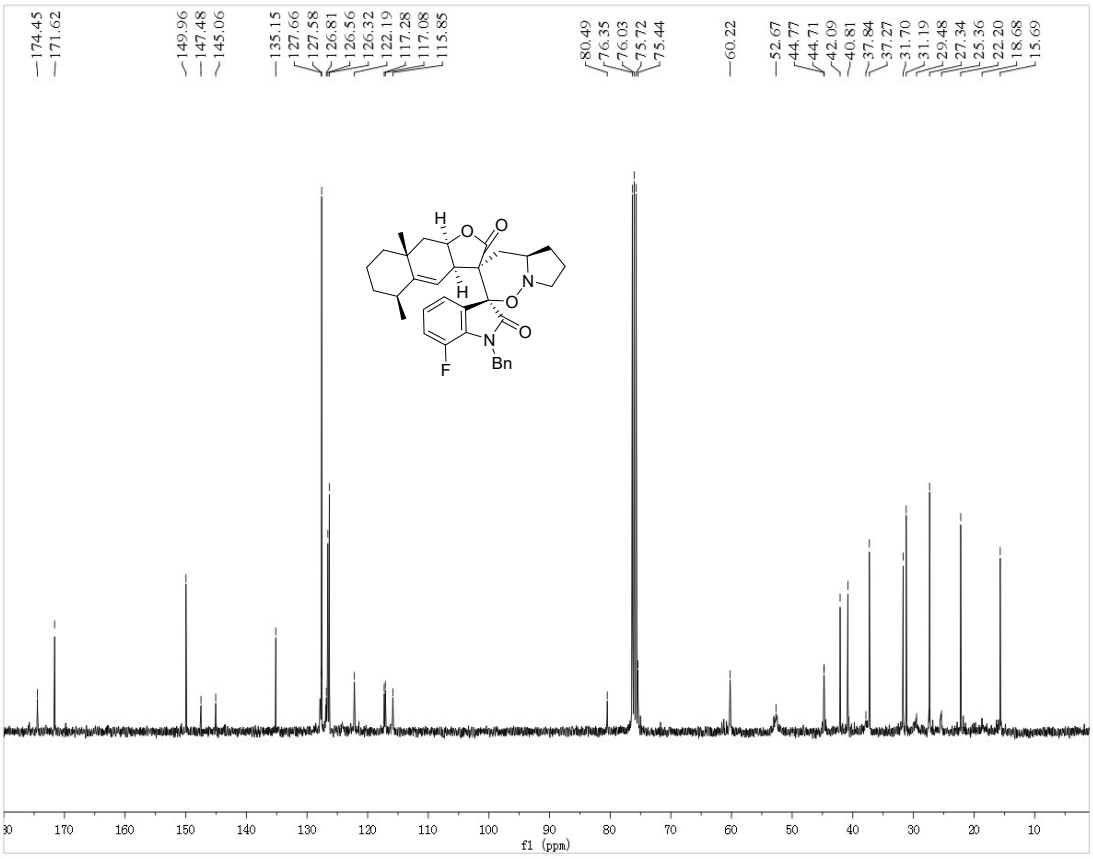

174.30
171.79
158.69
156.30
150.03
136.92
133.72
127.92
127.83
126.71
125.83
117.09
116.11
115.29
115.05
108.63
108.55
80.87
76.38
76.06
75.74
60.05
51.88
43.27
42.23
40.75
37.21
31.67
31.19
30.16
27.38
25.15
22.25
17.72
15.67
H
O
O
H
N
O
F
O
N
Bn
f1 (ppm)

^{19}F NMR of 3j

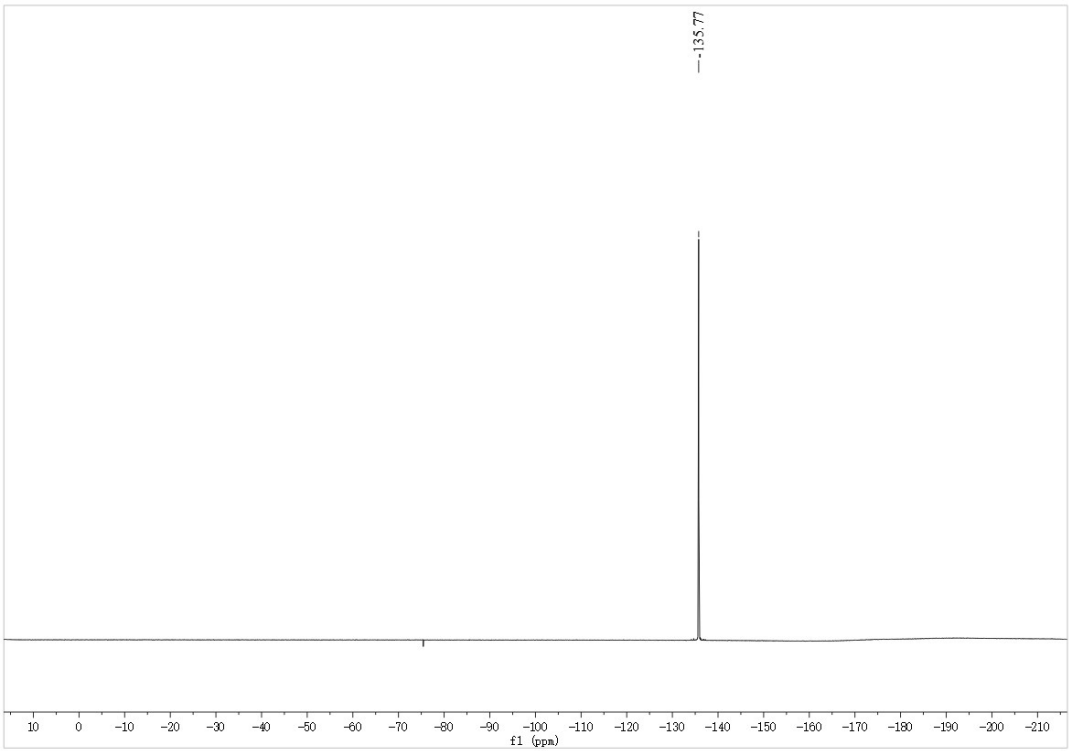

-119.30
f1 (ppm)

^{1}H and ^{13}C NMR of 3k

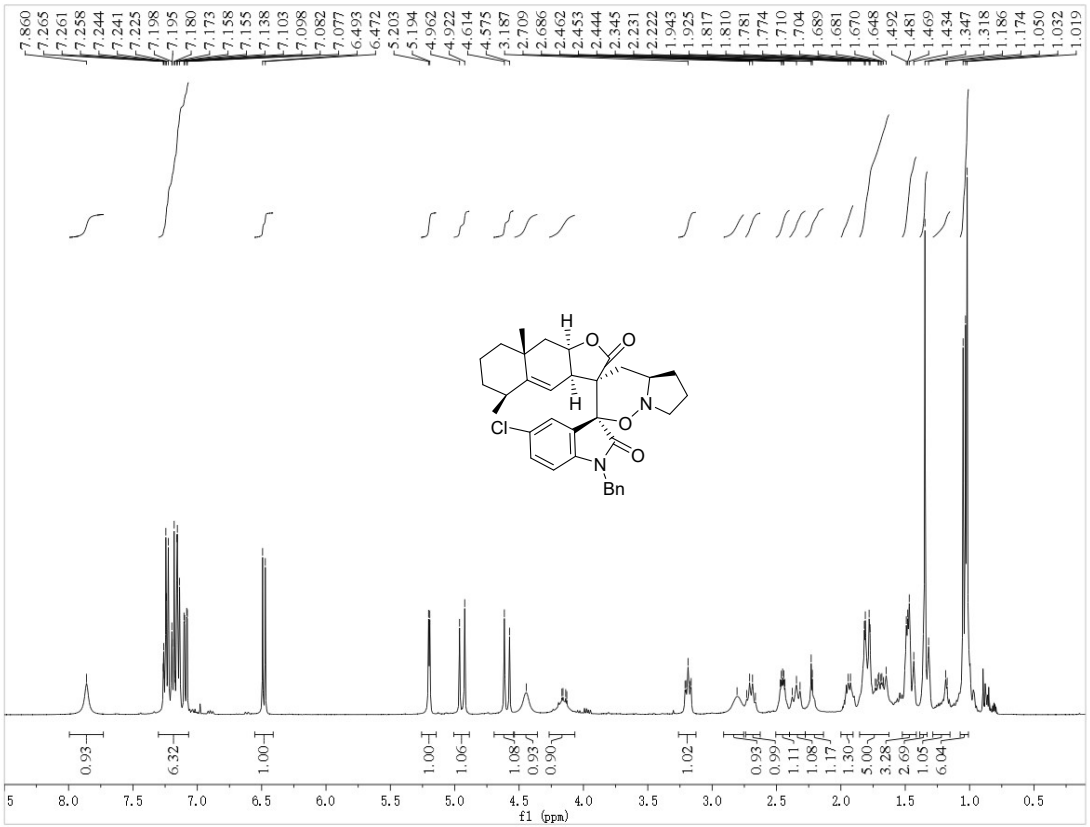


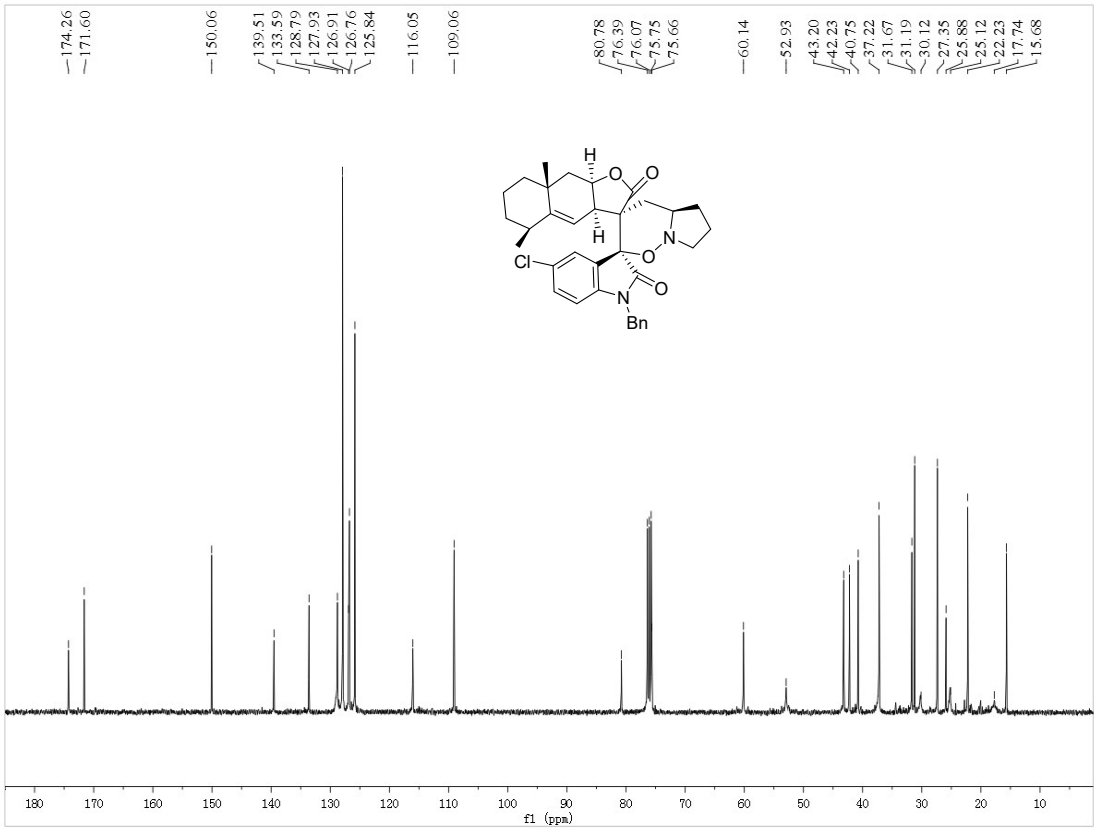

174.45
171.62
149.96
147.48
145.06
135.15
127.66
127.58
126.81
126.56
126.32
122.19
117.28
117.08
115.85
80.49
76.35
76.03
75.72
75.44
60.22
52.67
44.77
44.71
42.09
40.81
37.84
37.27
31.70
31.19
29.48
27.34
25.36
22.20
18.68
15.69
H
O
O
N
O
H
O
N
Bn
F
f1 (ppm)

^{19}F NMR of 3k

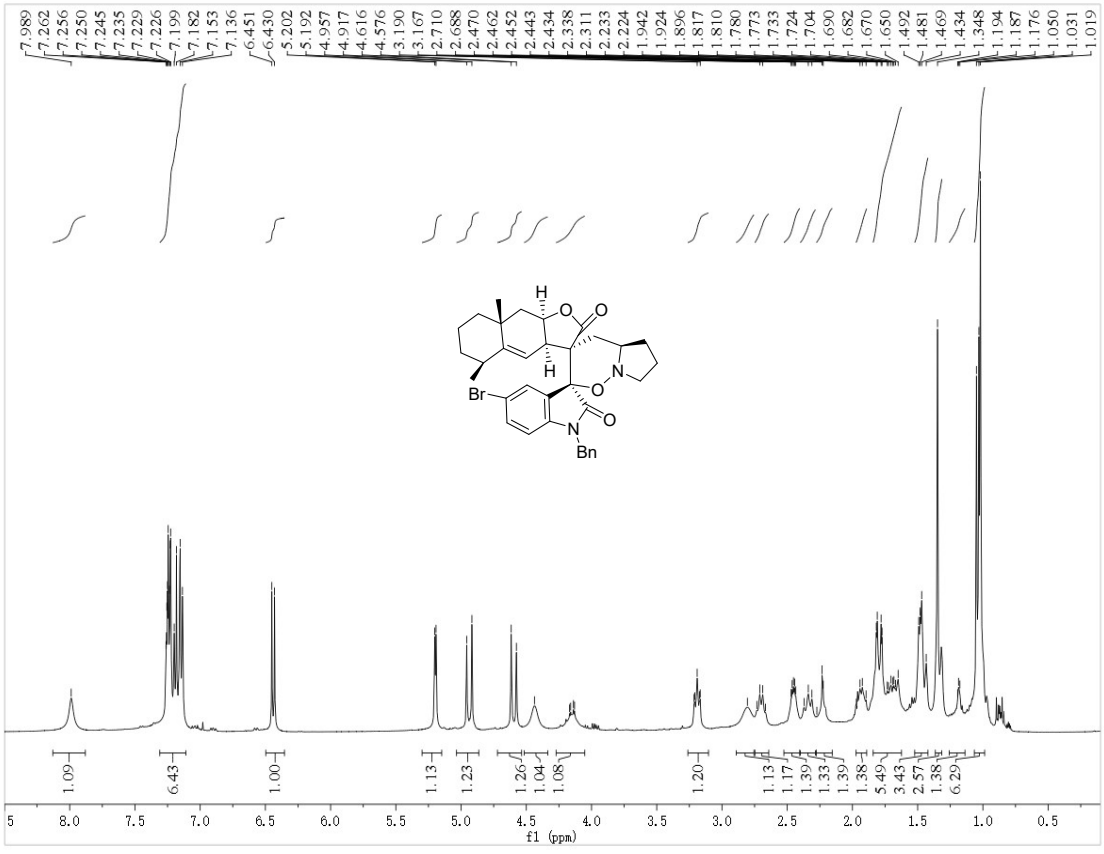

-135.77
f1 (ppm)

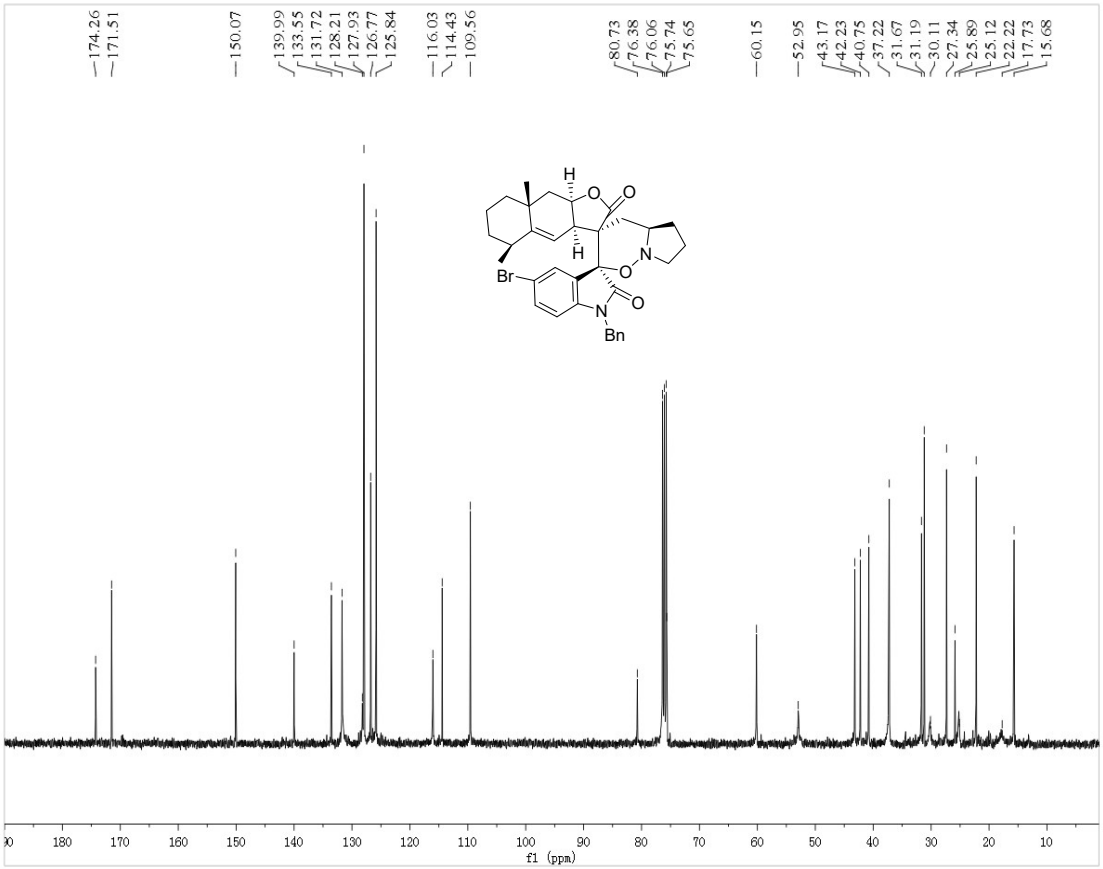
^{1}H and ^{13}C NMR of 3l



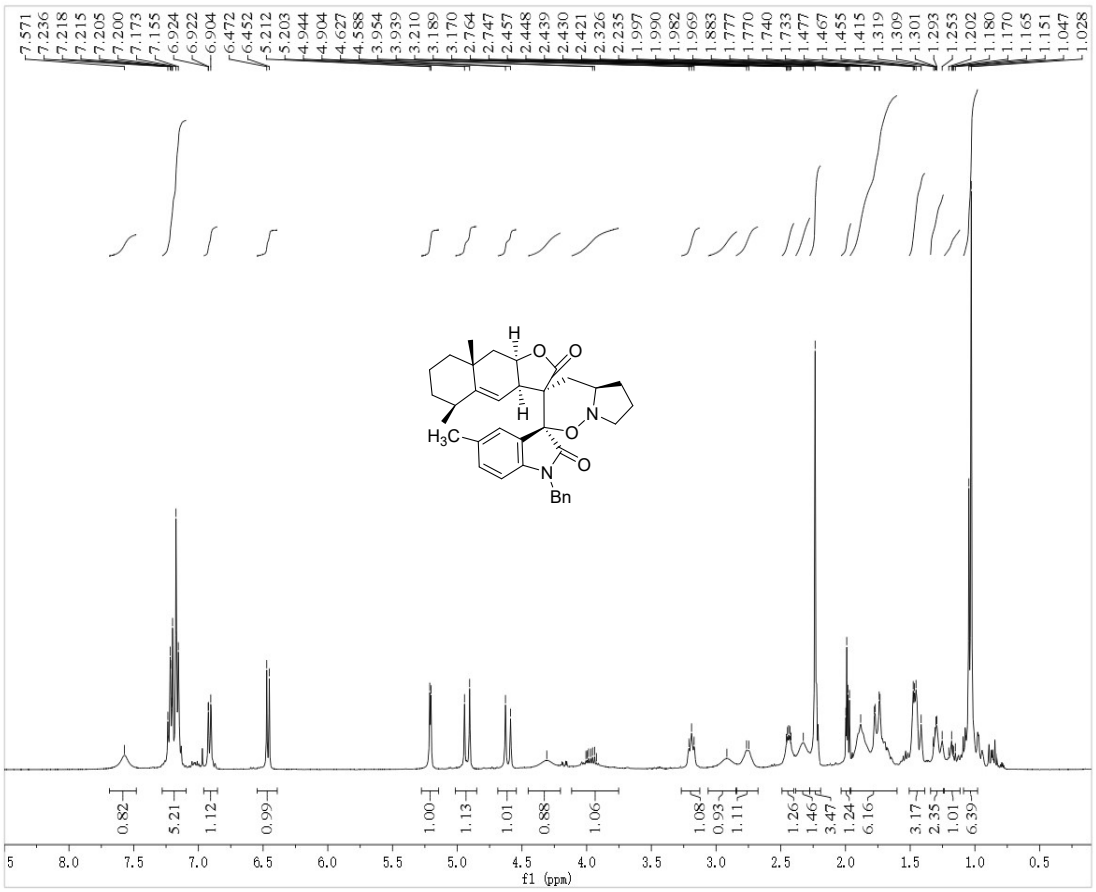


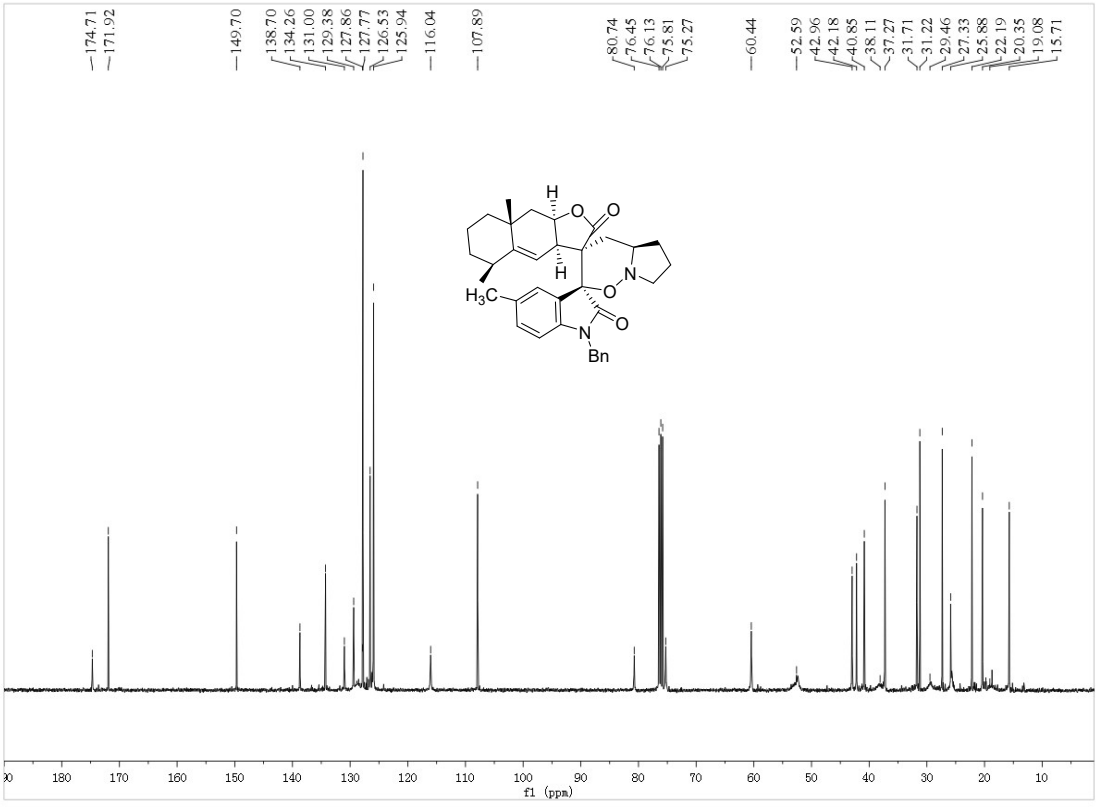
^{1}H and ^{13}C NMR of 3m



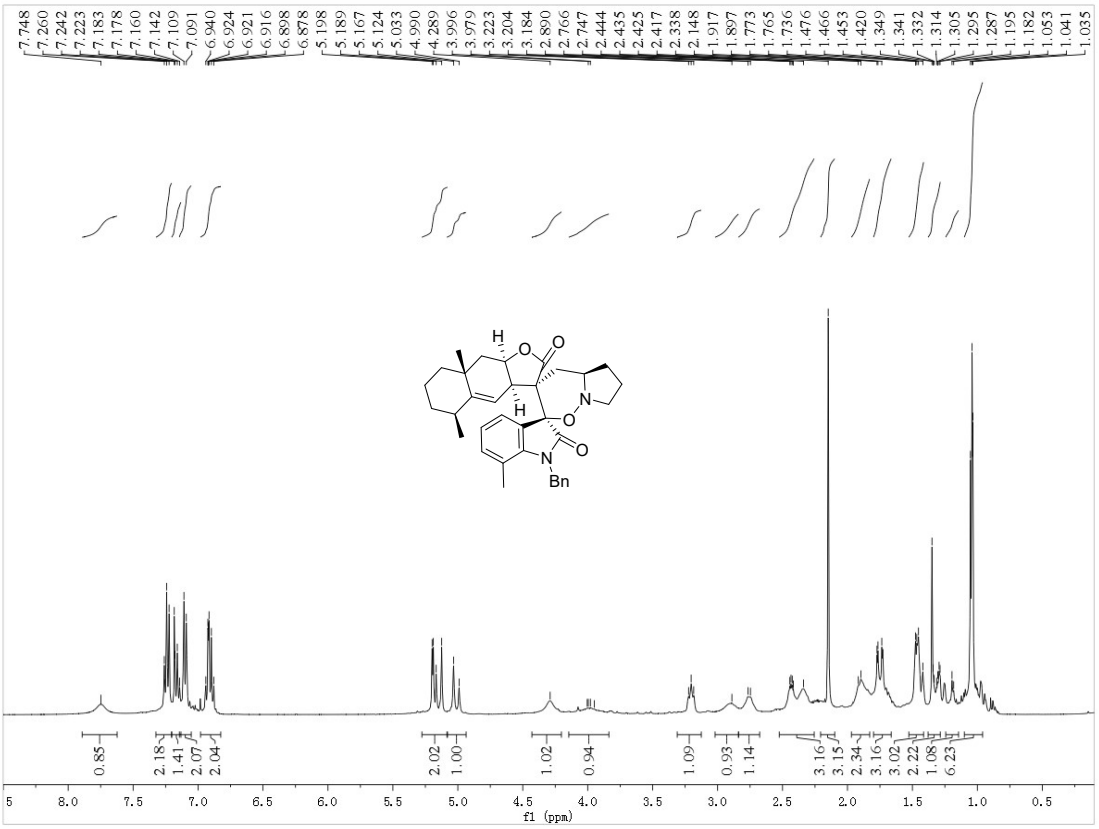


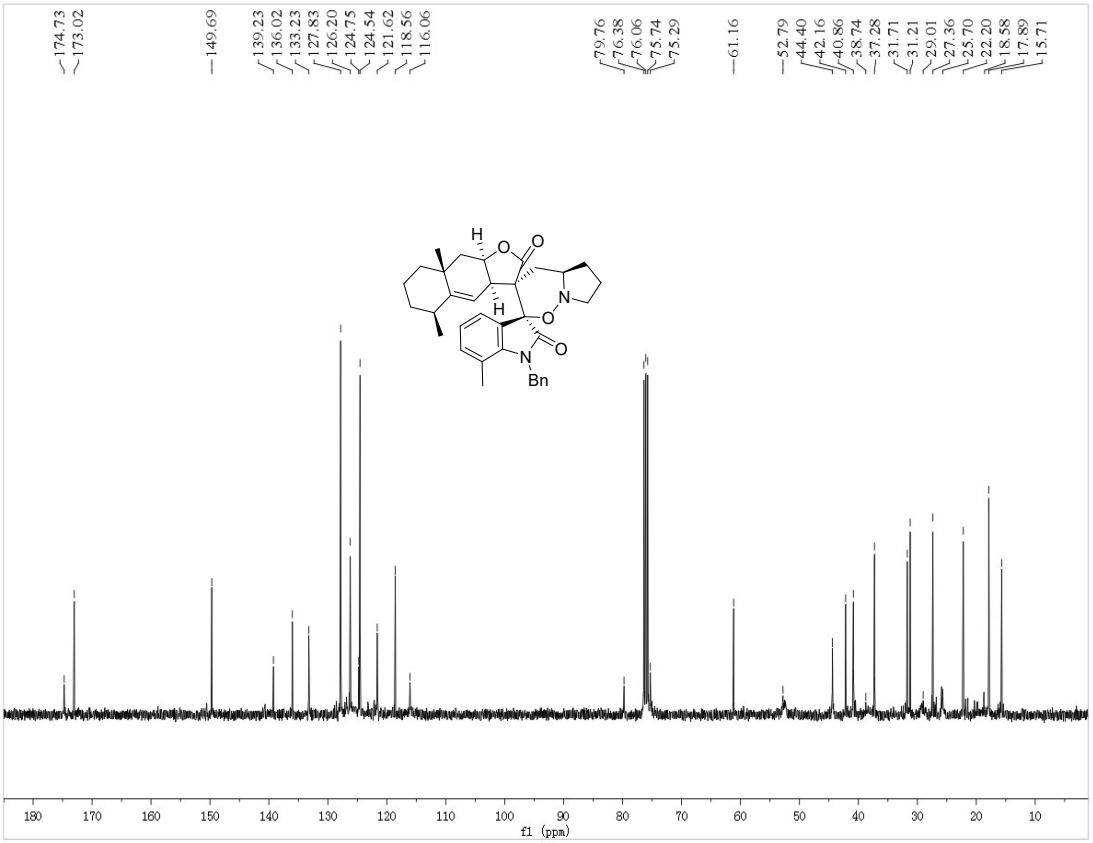
^{1}H and ^{13}C NMR of 3n



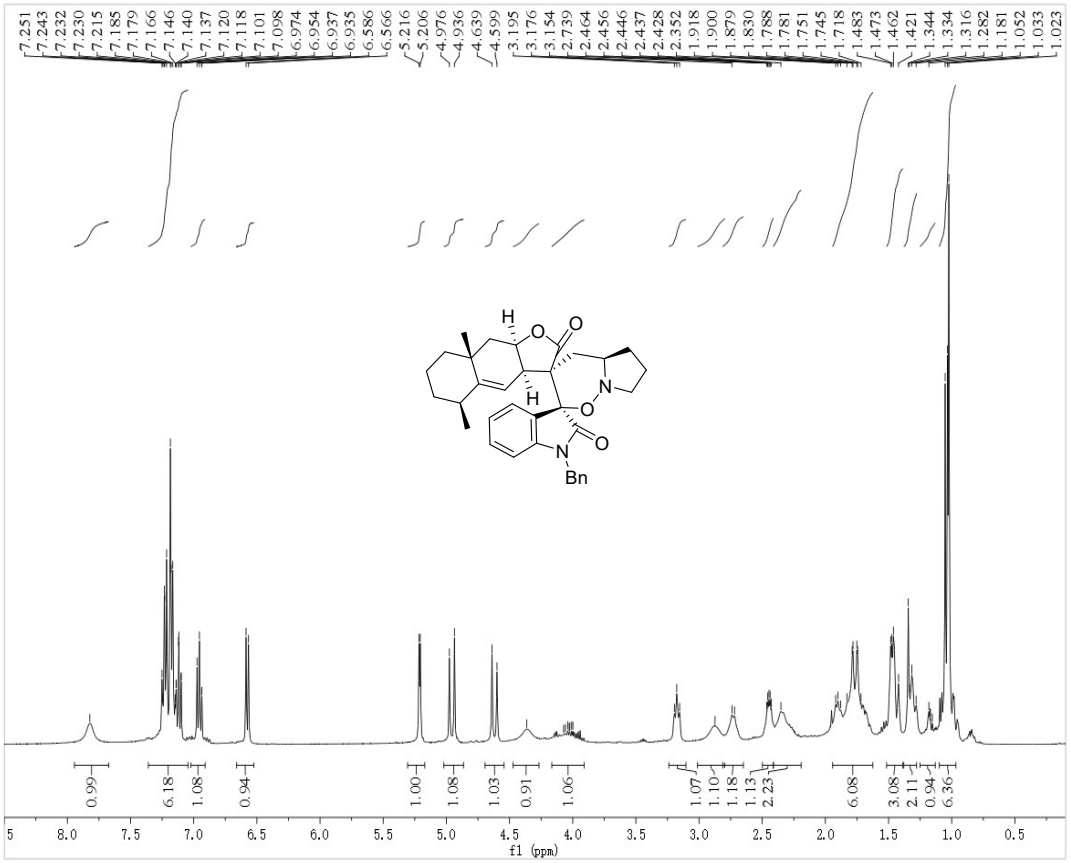


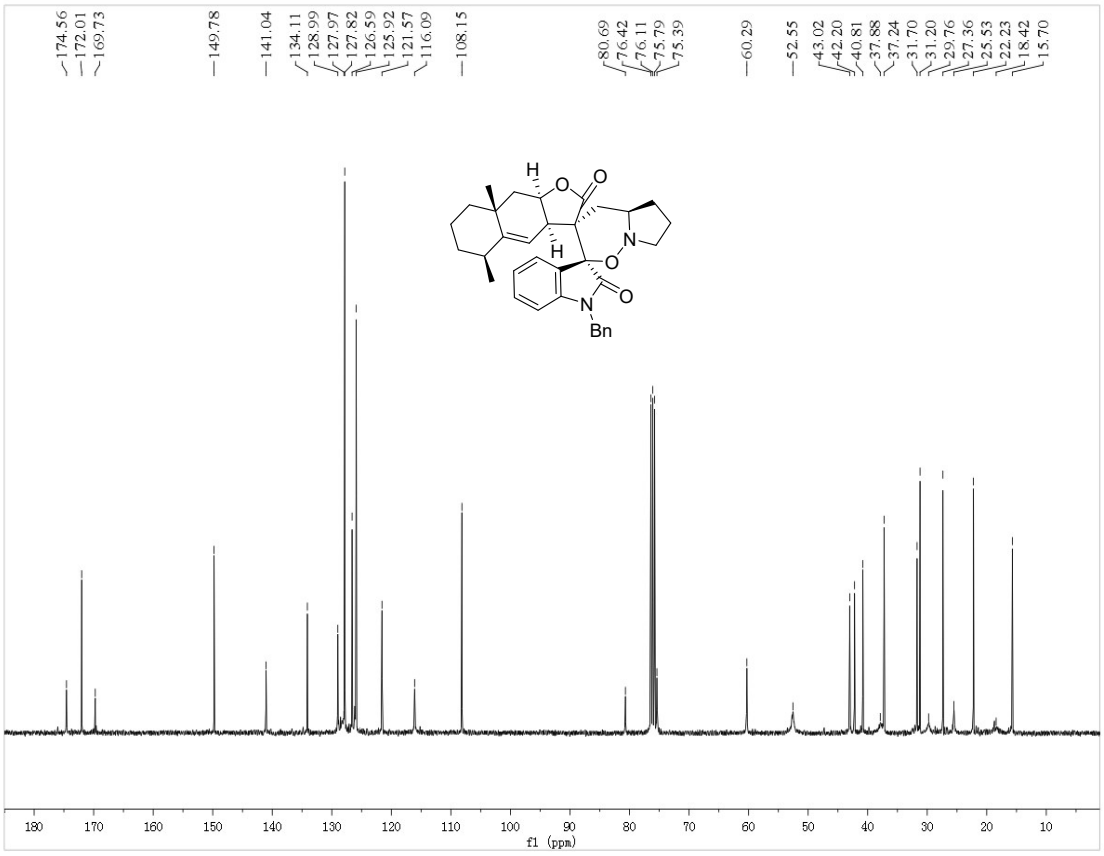
^{1}H and ^{13}C NMR of 3o



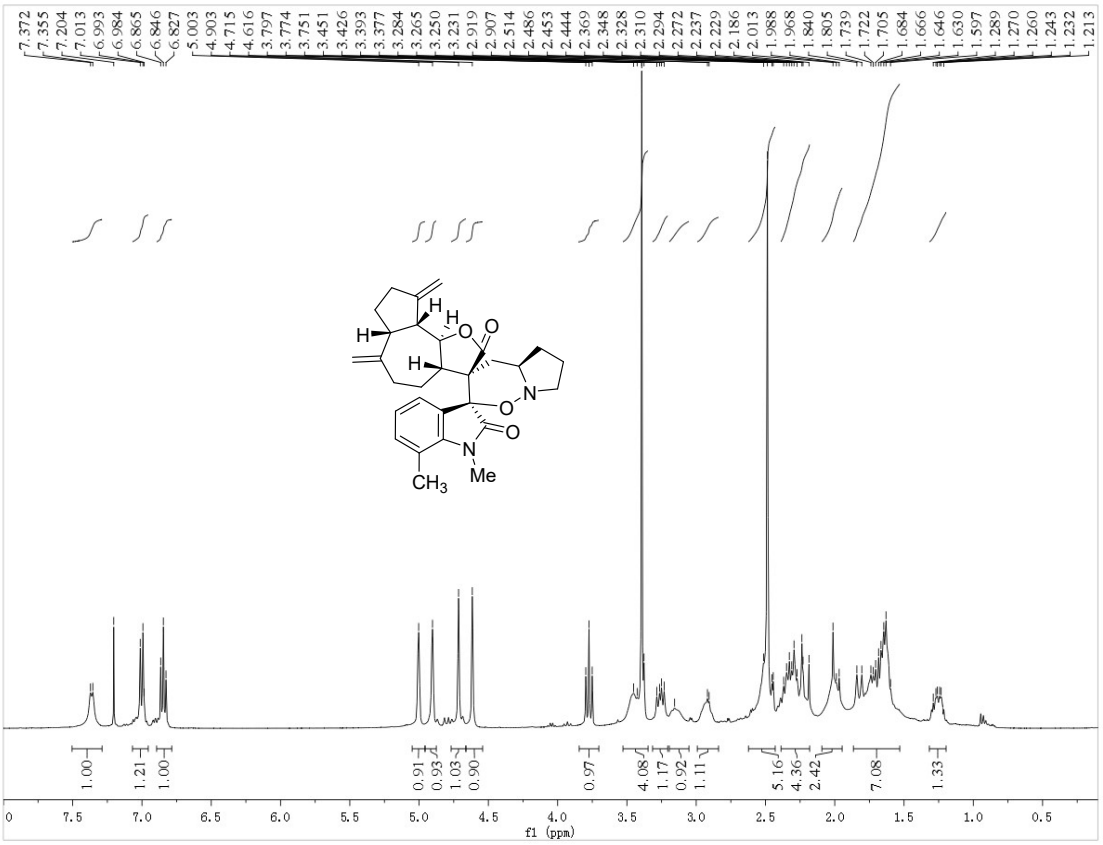


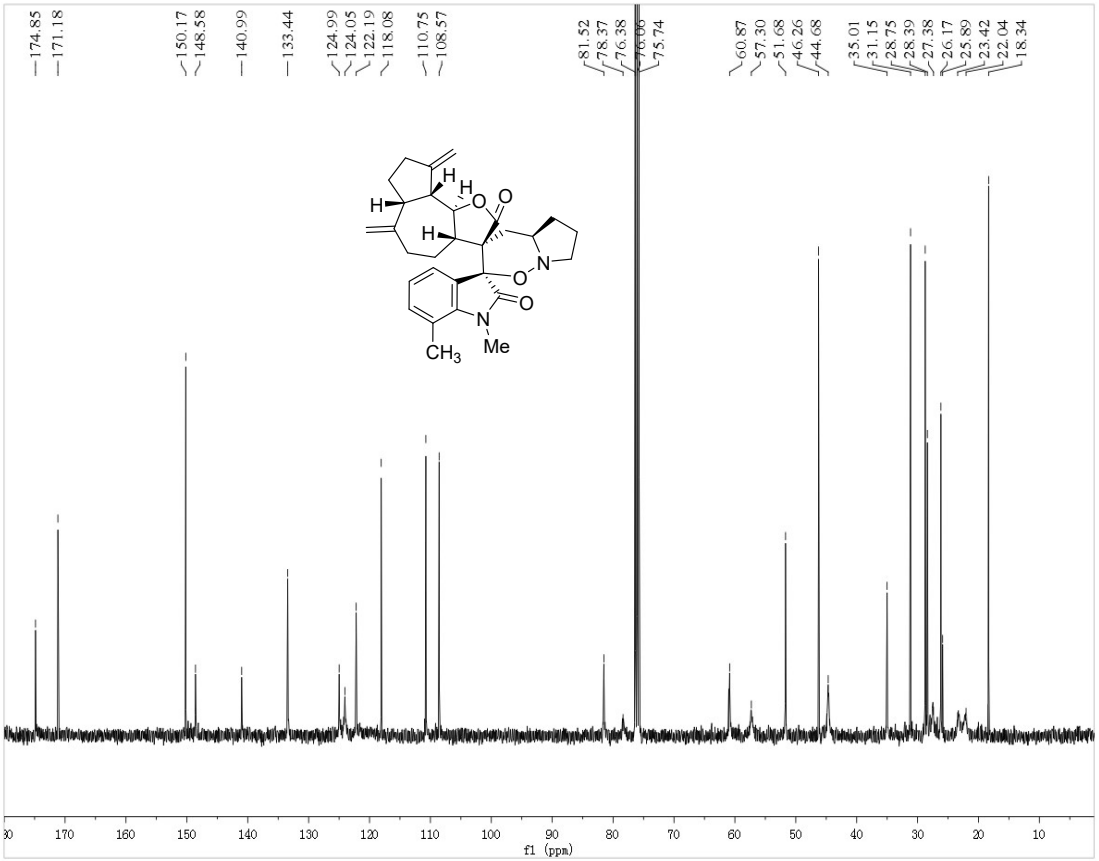
^{1}H and ^{13}C NMR of 3p



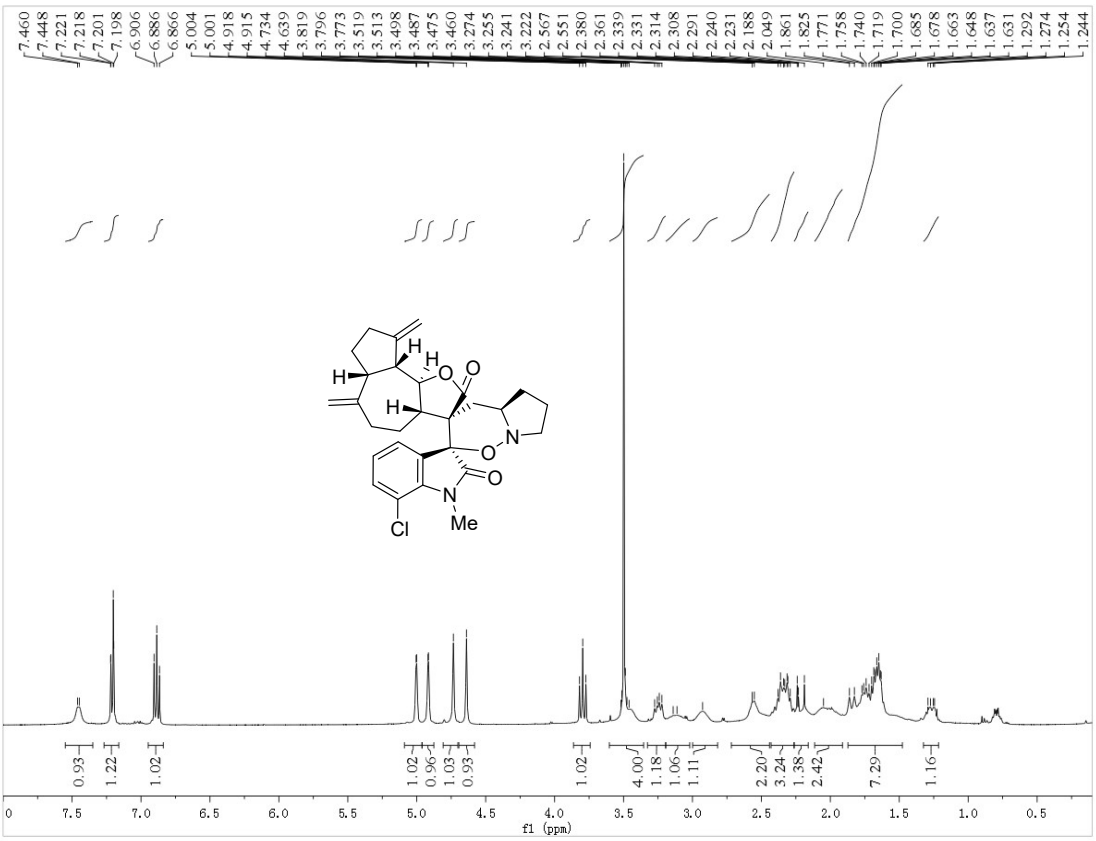


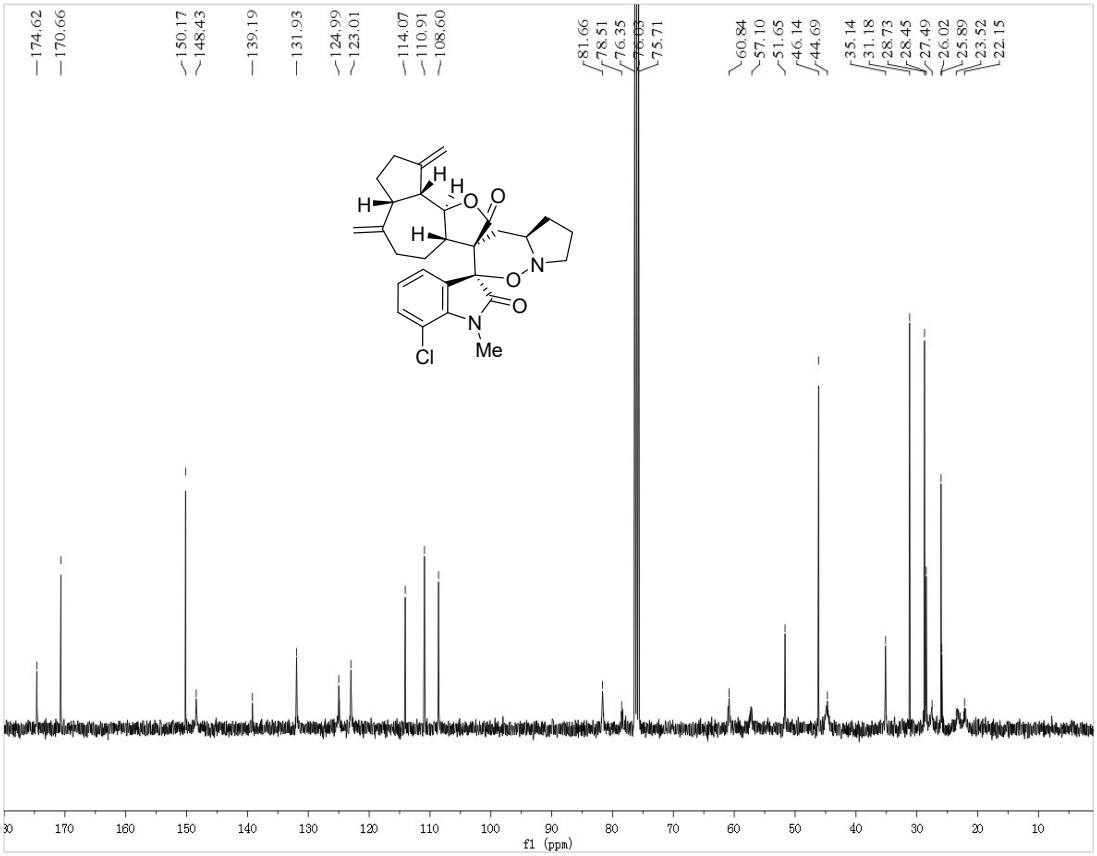
^{1}H and ^{13}C NMR of 5a



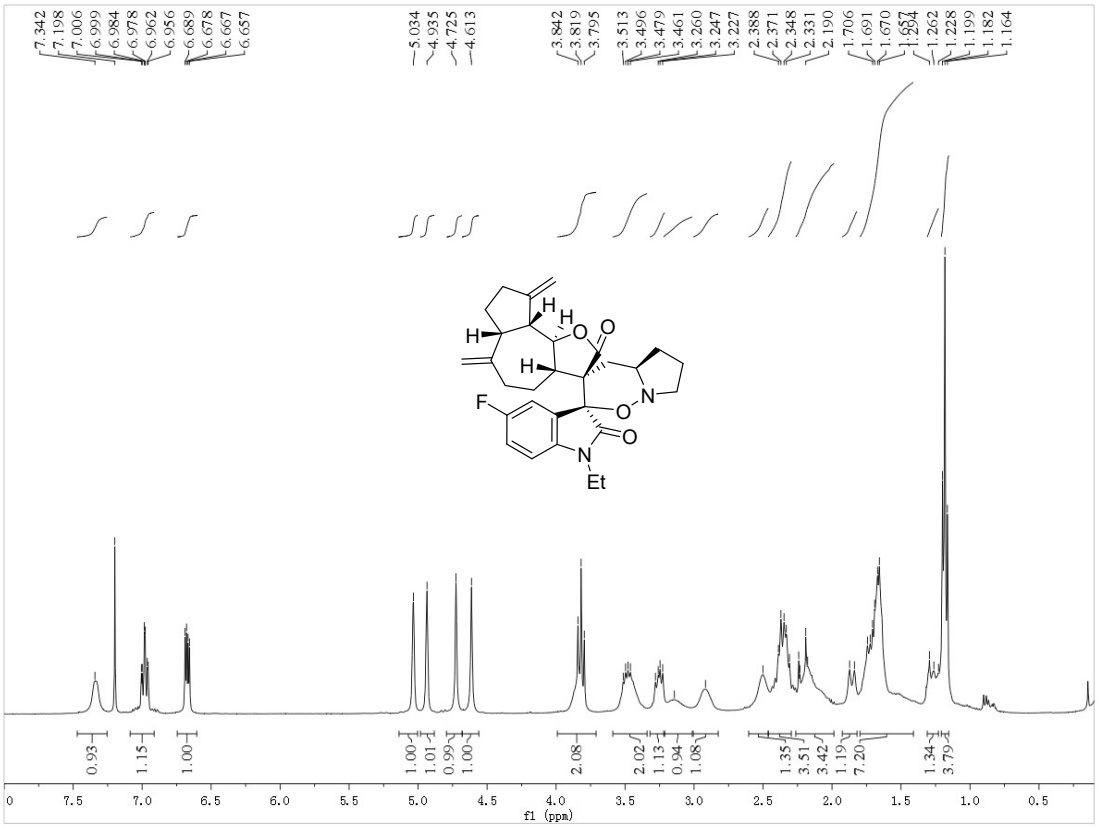


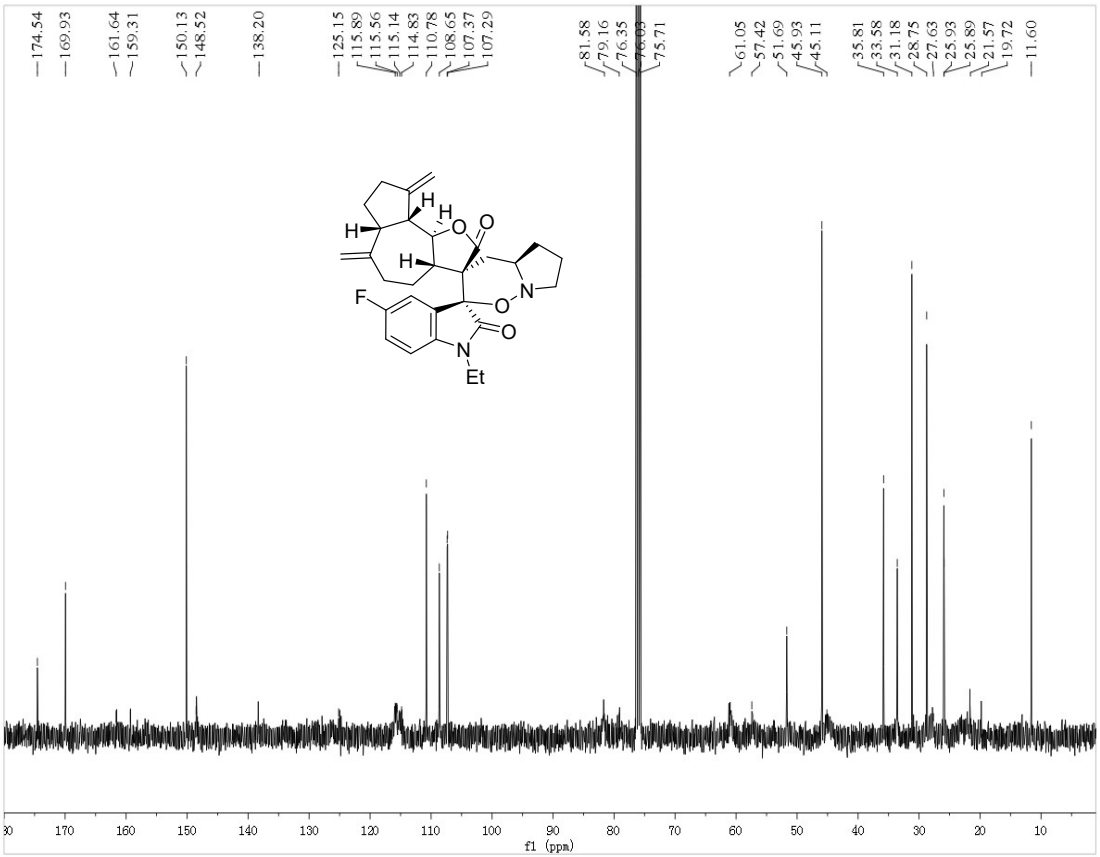
^{1}H and ^{13}C NMR of 5b



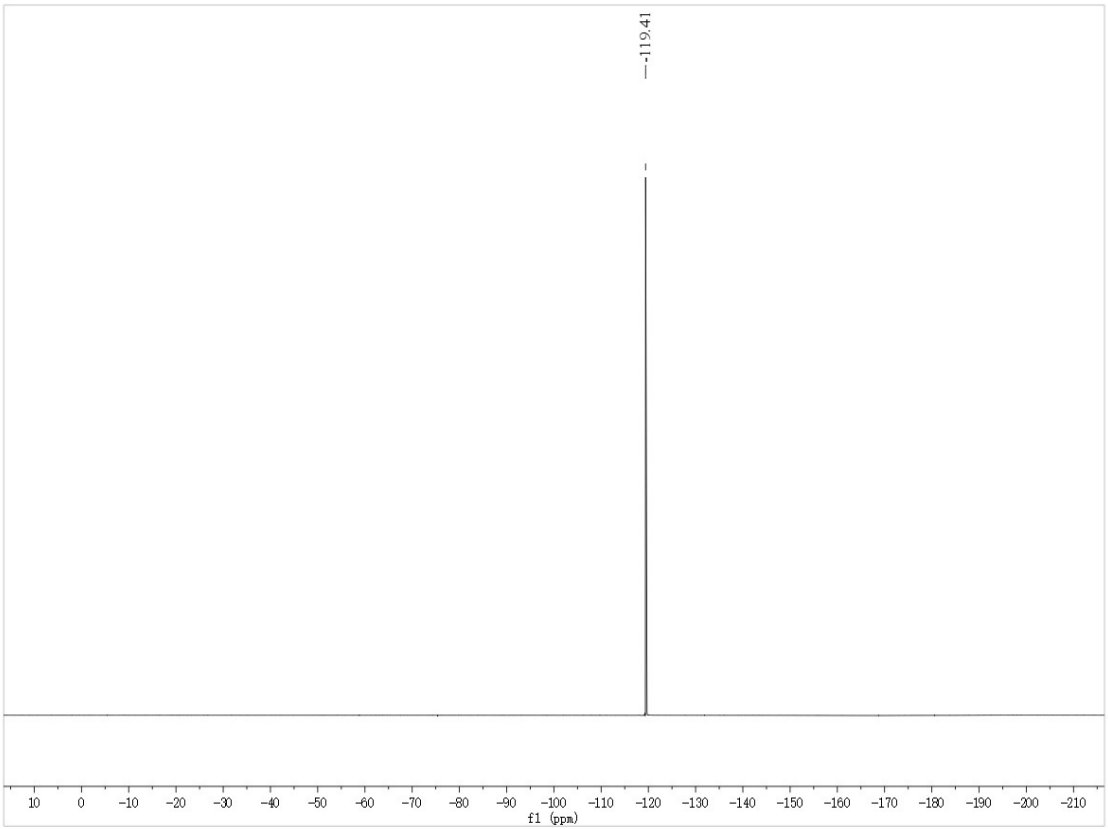


^{1}H and ^{13}C NMR of 5c

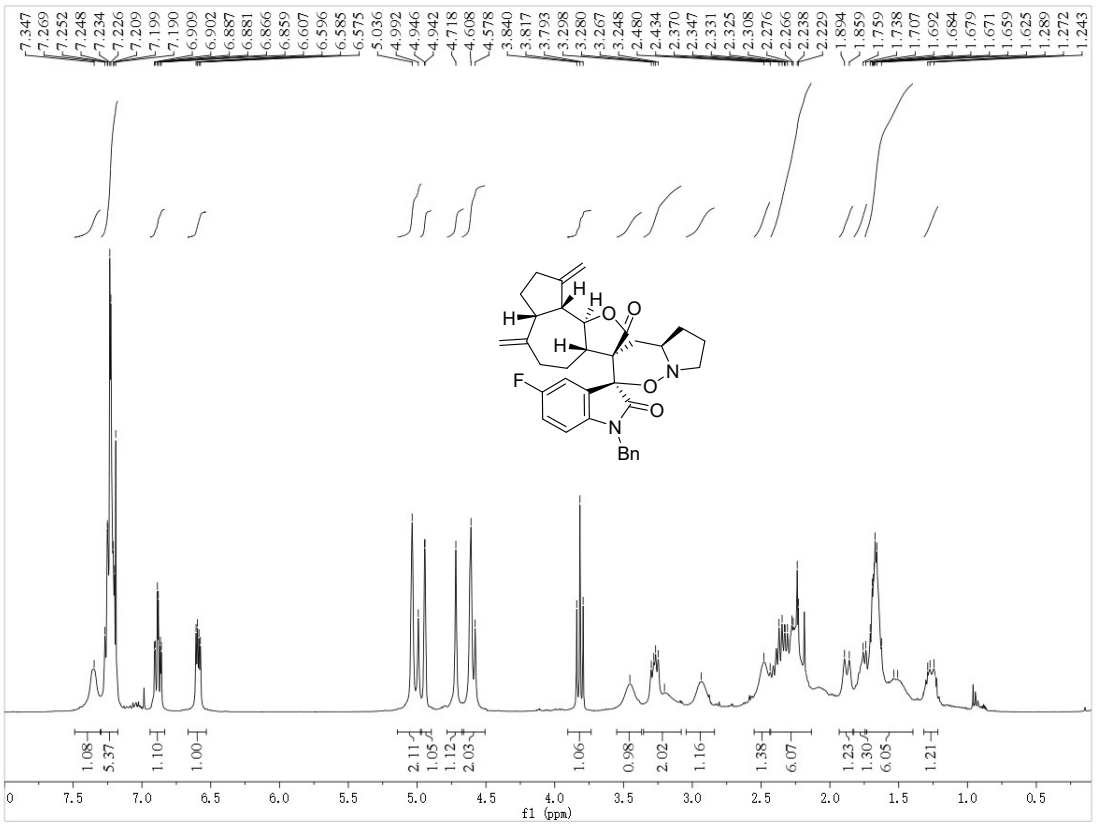

7.342
7.198
7.006
6.999
6.984
6.978
6.962
6.956
6.689
6.678
6.667
6.657
5.034
4.935
4.725
4.613
3.842
3.819
3.795
3.513
3.496
3.479
3.461
3.260
3.247
3.227
2.388
2.371
2.348
2.331
2.190
1.706
1.691
1.670
1.262
1.228
1.199
1.182
1.164
0.93
1.15
1.00
1.00
1.01
0.99
1.00
2.08
2.02
1.13
0.94
1.08
1.35
3.51
3.42
1.19
7.20
1.34
3.79
f1 (ppm)

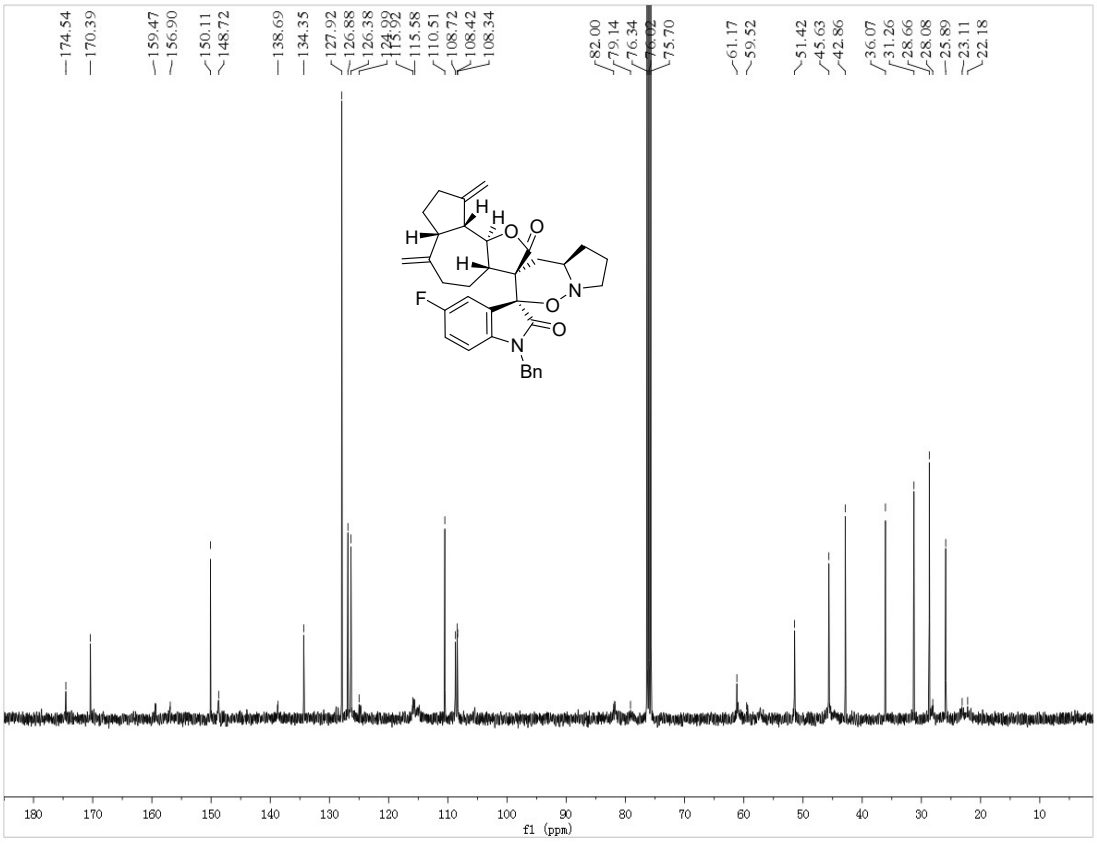

174.54
169.93
161.64
159.31
150.13
148.52
138.20
125.15
115.89
115.56
115.14
114.83
110.78
108.65
107.37
107.29
81.58
79.16
76.35
75.71
61.05
57.42
51.69
45.93
45.11
35.81
33.58
31.18
28.75
27.63
25.93
25.89
21.57
19.72
11.60
f1 (ppm)

^{19}F NMR of 5c

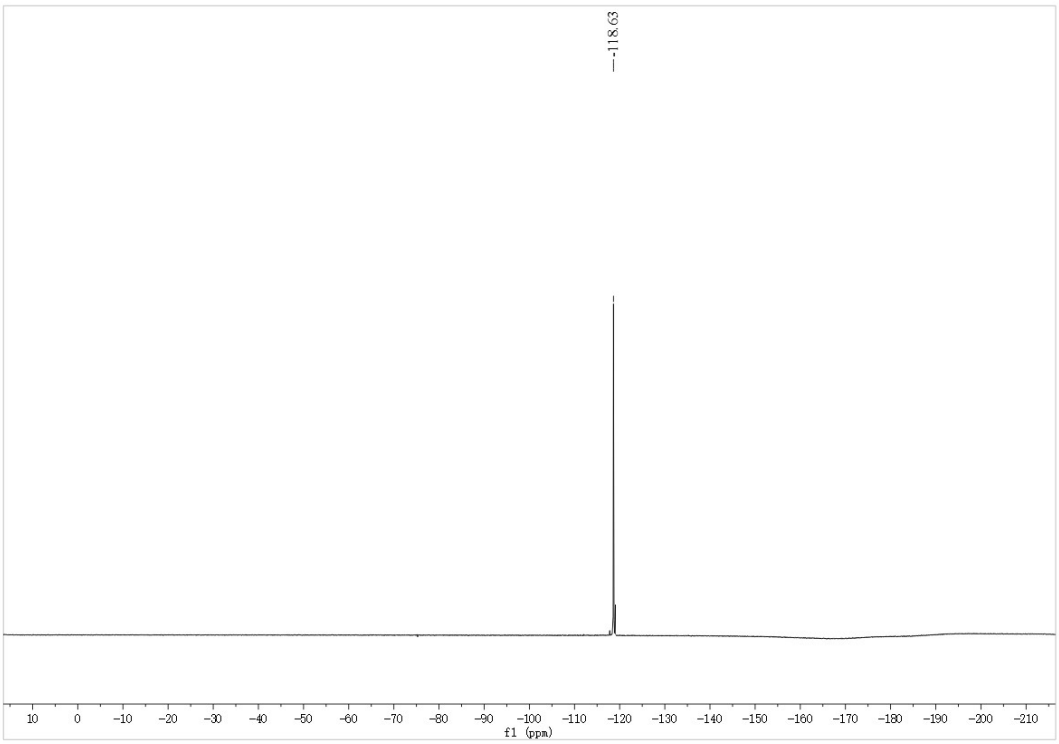


^{1}H and ^{13}C NMR of 5d

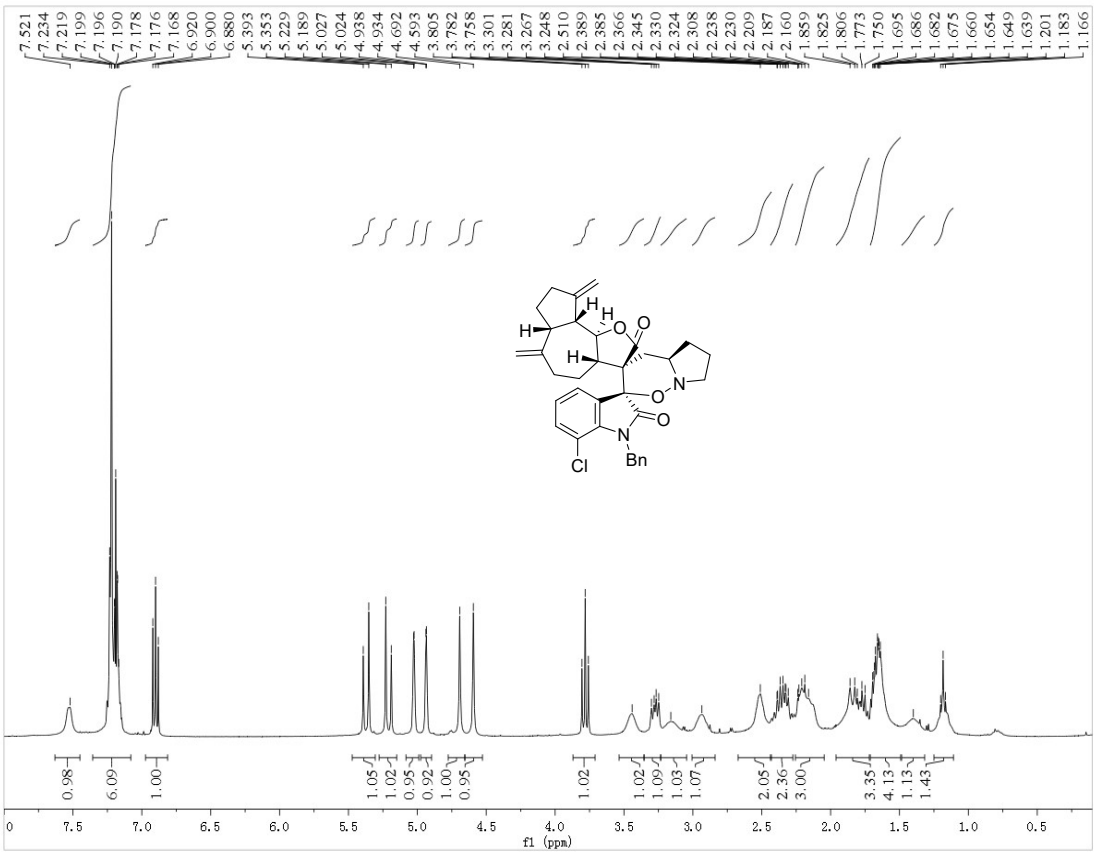

7.347
7.269
7.252
7.248
7.234
7.226
7.209
7.199
7.190
6.909
6.902
6.887
6.881
6.866
6.859
6.607
6.596
6.585
6.575
5.036
4.992
4.946
4.942
4.718
4.608
4.578
3.840
3.817
3.793
3.298
3.280
3.267
3.248
2.480
2.434
2.370
2.347
2.331
2.325
2.308
2.276
2.266
2.238
2.229
1.894
1.859
1.759
1.738
1.707
1.692
1.684
1.679
1.671
1.659
1.625
1.289
1.272
1.243
H
H
H
O
O
O
N
F
O
O
N
Bn
1.08
5.37
1.10
1.00
2.11
1.05
1.12
2.03
1.06
0.98
2.02
1.16
1.38
6.07
1.23
1.30
6.05
1.21
f1 (ppm)

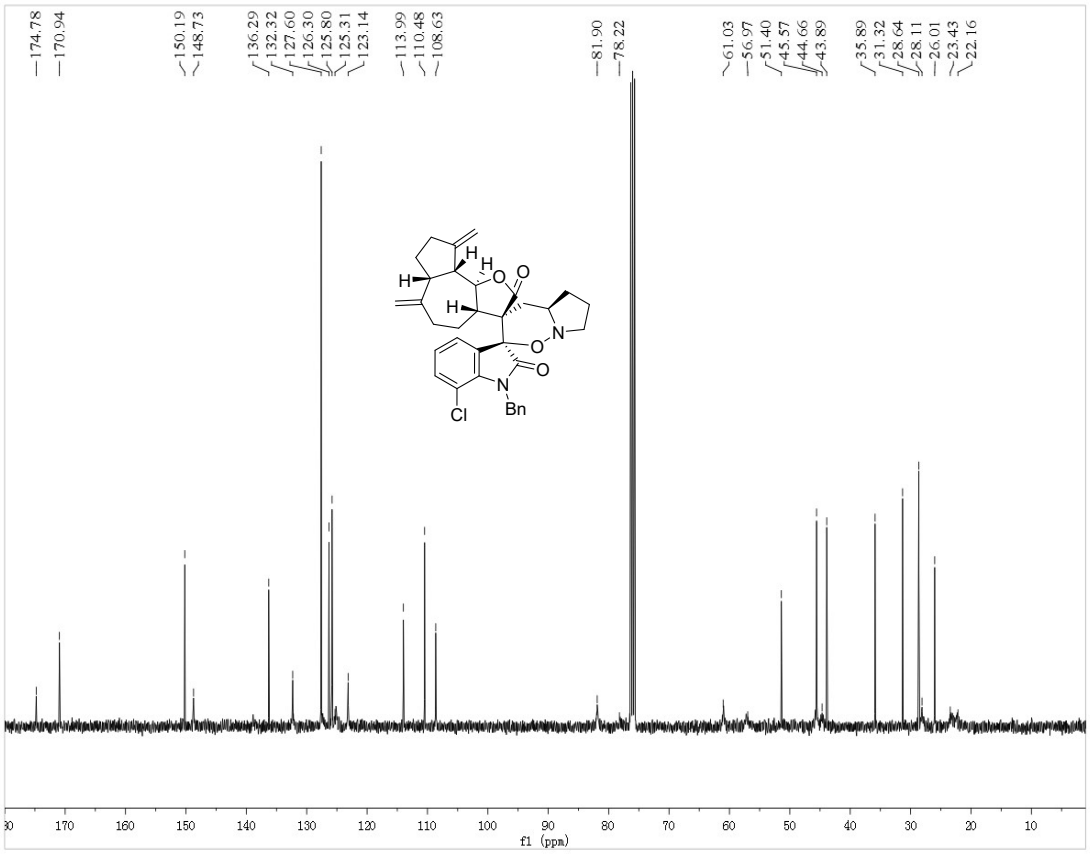

174.54
170.39
159.47
156.90
150.11
148.72
138.69
134.35
127.92
126.88
126.38
115.58
110.51
108.72
108.42
108.34
82.00
79.14
76.34
75.70
61.17
59.52
51.42
45.63
42.86
36.07
31.26
28.66
28.08
25.89
23.11
22.18
H
H
H
O
O
O
N
F
O
O
N
Bn
f1 (ppm)

^{19}F NMR of 5d

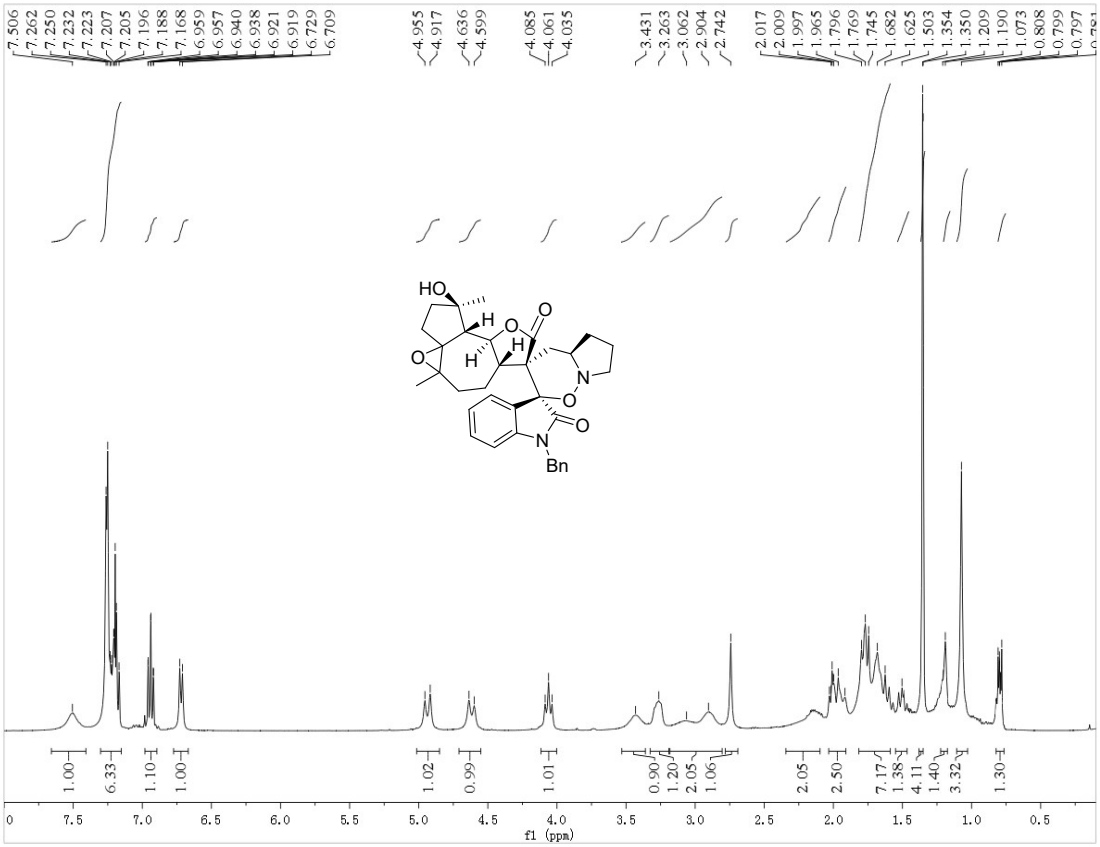


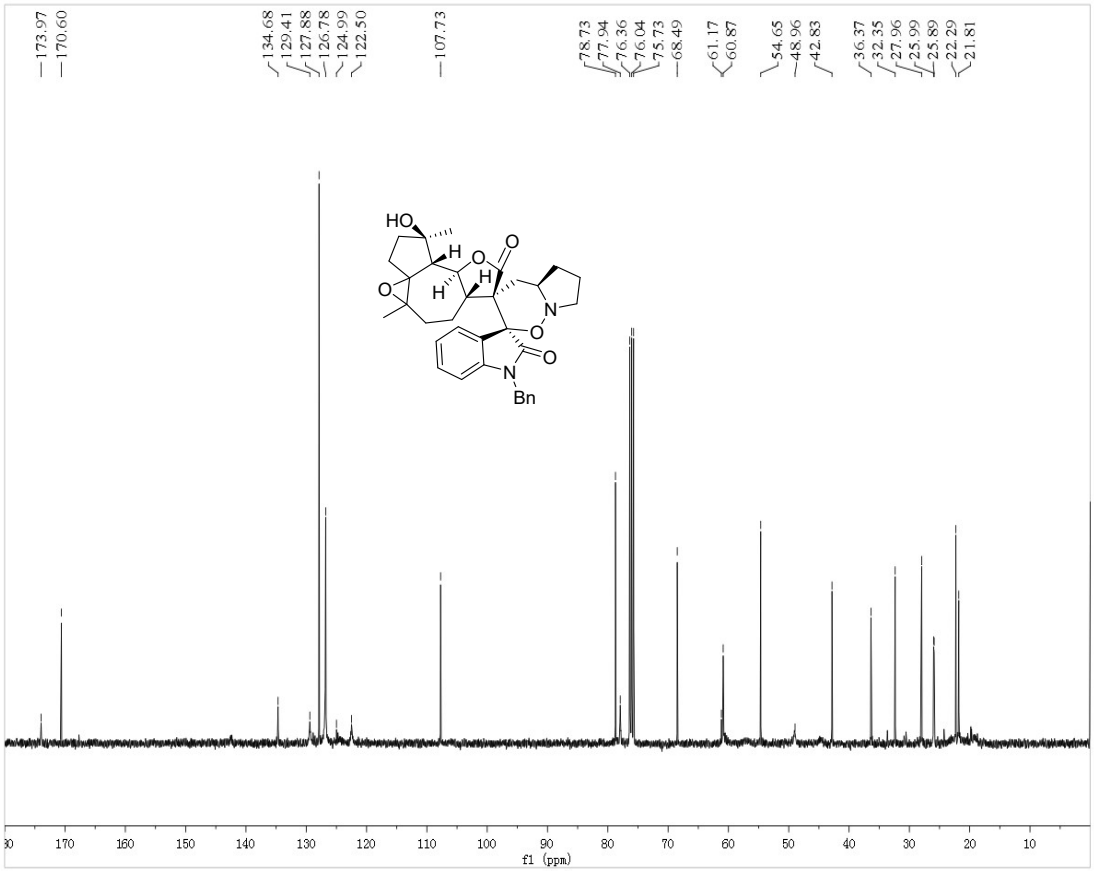
^{1}H and ^{13}C NMR of 5e



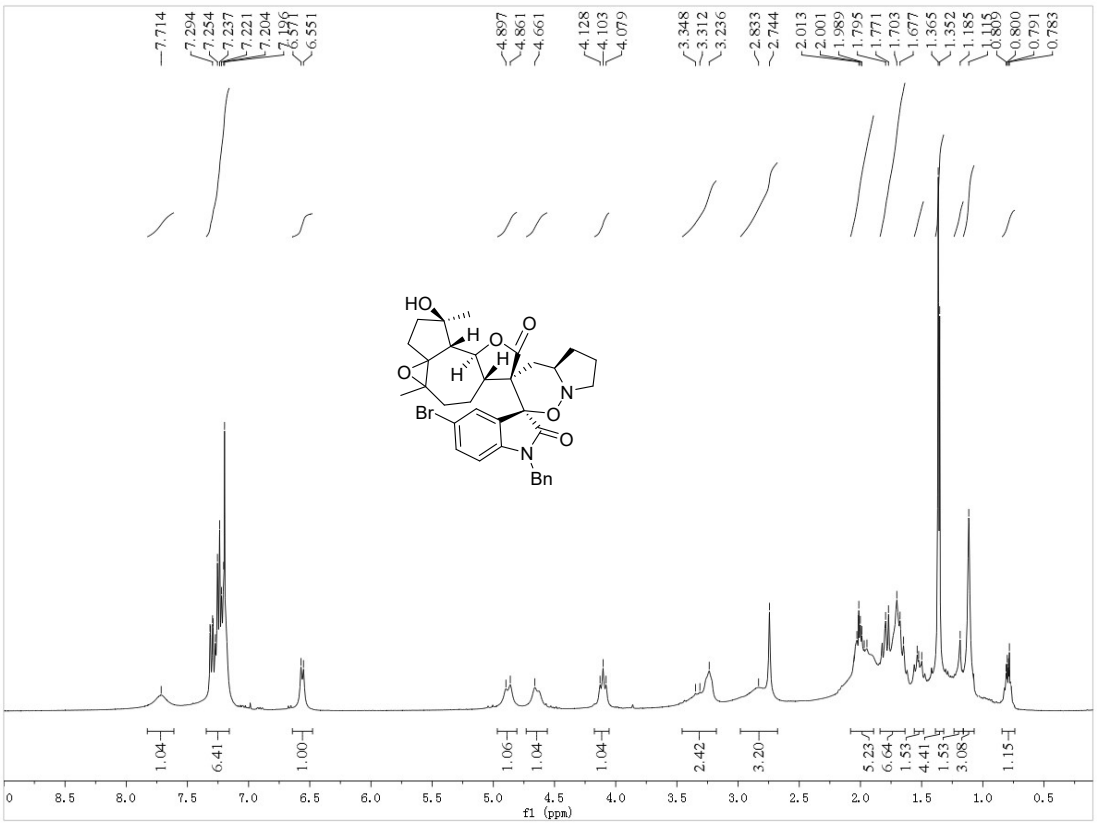


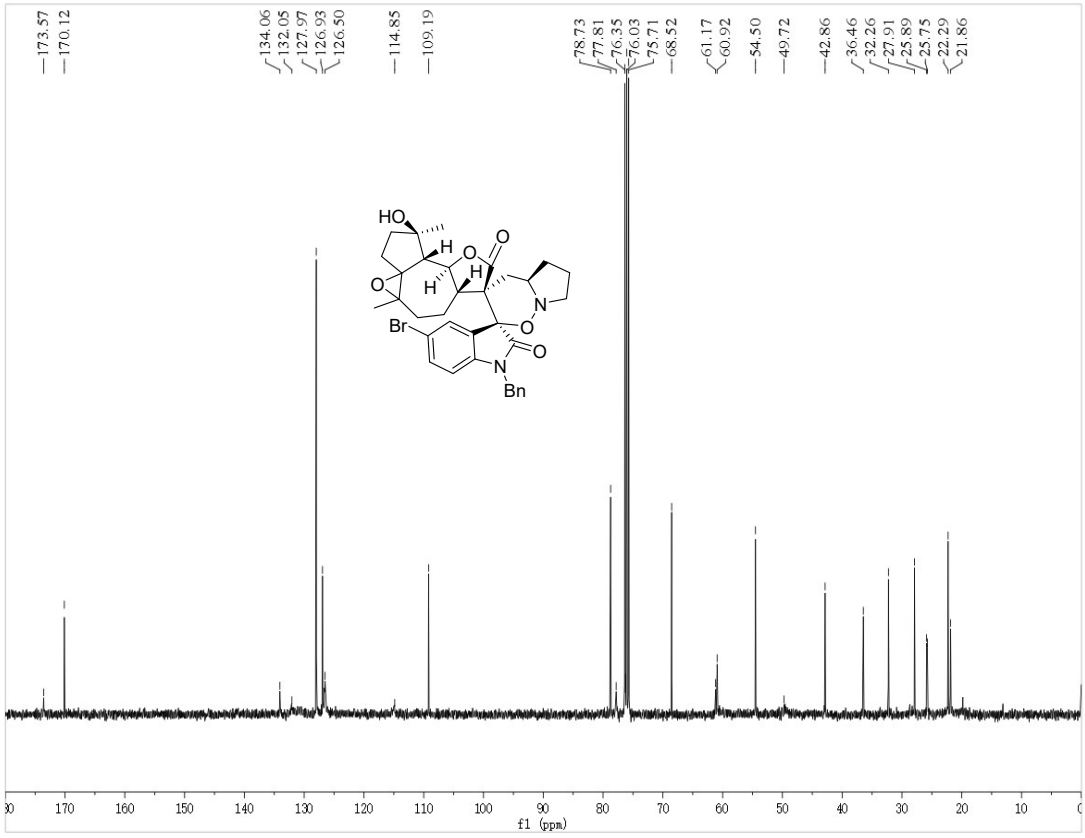
^{1}H and ^{13}C NMR of 6a


7.506
7.262
7.250
7.232
7.223
7.207
7.205
7.196
7.188
7.168
6.959
6.957
6.940
6.938
6.921
6.919
6.729
6.709
4.955
4.917
4.636
4.599
4.085
4.061
4.035
3.431
3.263
3.062
2.904
2.742
2.017
2.009
1.997
1.965
1.796
1.769
1.745
1.682
1.625
1.503
1.354
1.350
1.209
1.190
1.073
0.808
0.799
0.797
HO
H
O
O
H
O
N
O
O
N
Bn
1.00
6.33
1.10
1.00
1.02
0.99
1.01
0.90
1.20
2.05
1.06
2.05
2.50
7.17
1.38
4.11
1.40
3.32
1.30
f1 (ppm)

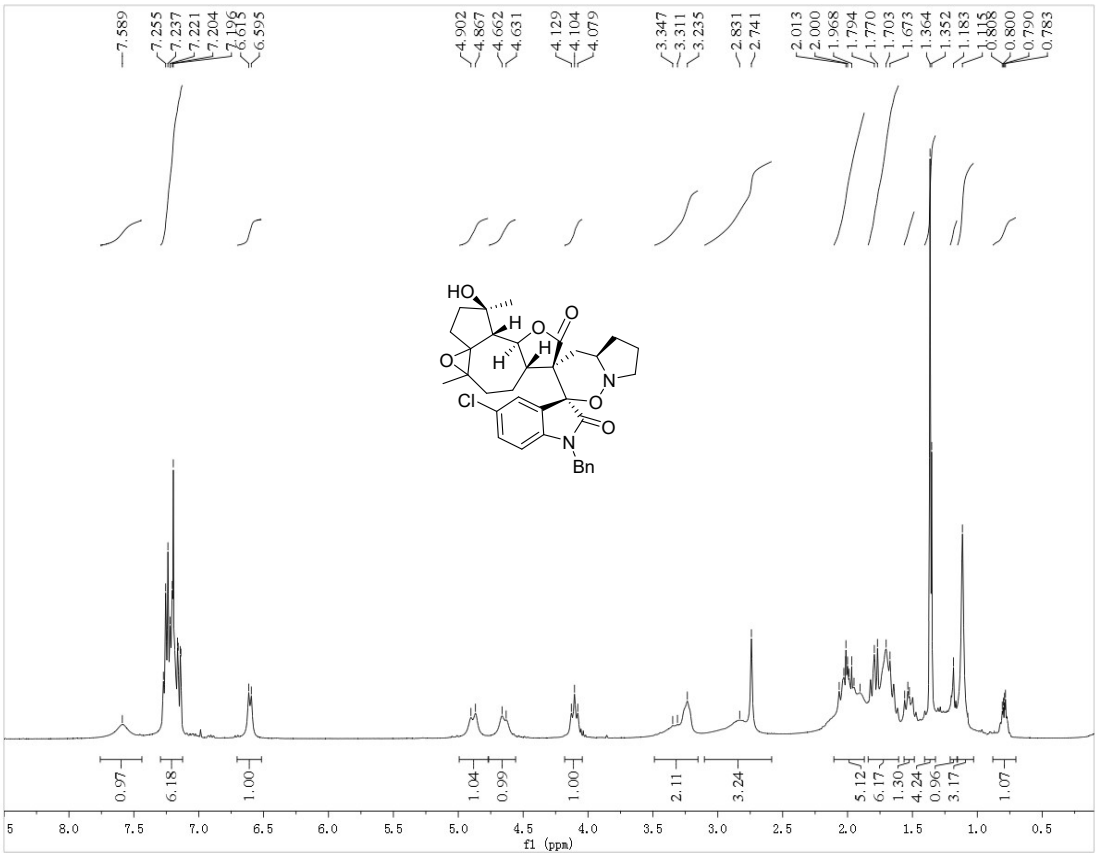

173.97
170.60
134.68
129.41
127.88
126.78
124.99
122.50
107.73
78.73
77.94
76.36
76.04
75.73
68.49
61.17
60.87
54.65
48.96
42.83
36.37
32.35
27.96
25.99
25.89
22.29
21.81
HO
H
O
O
H
O
N
O
O
N
Bn
f1 (ppm)

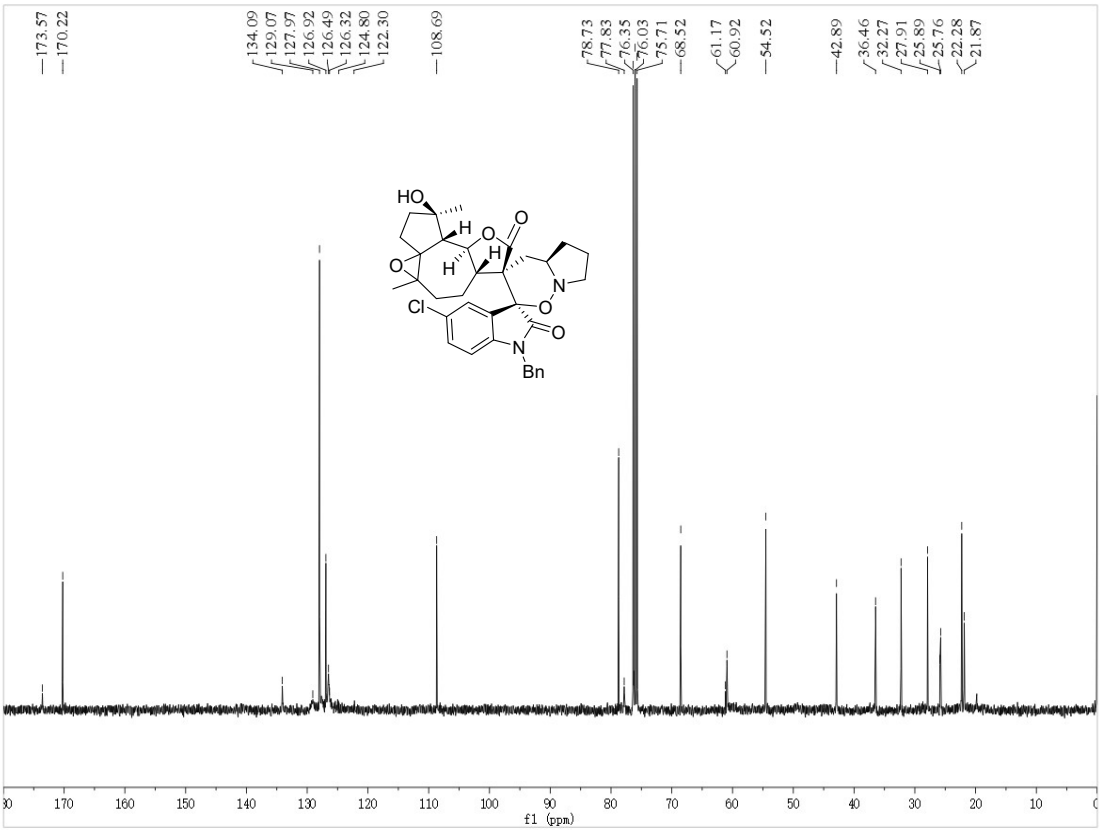
^{1}H and ^{13}C NMR of 6b



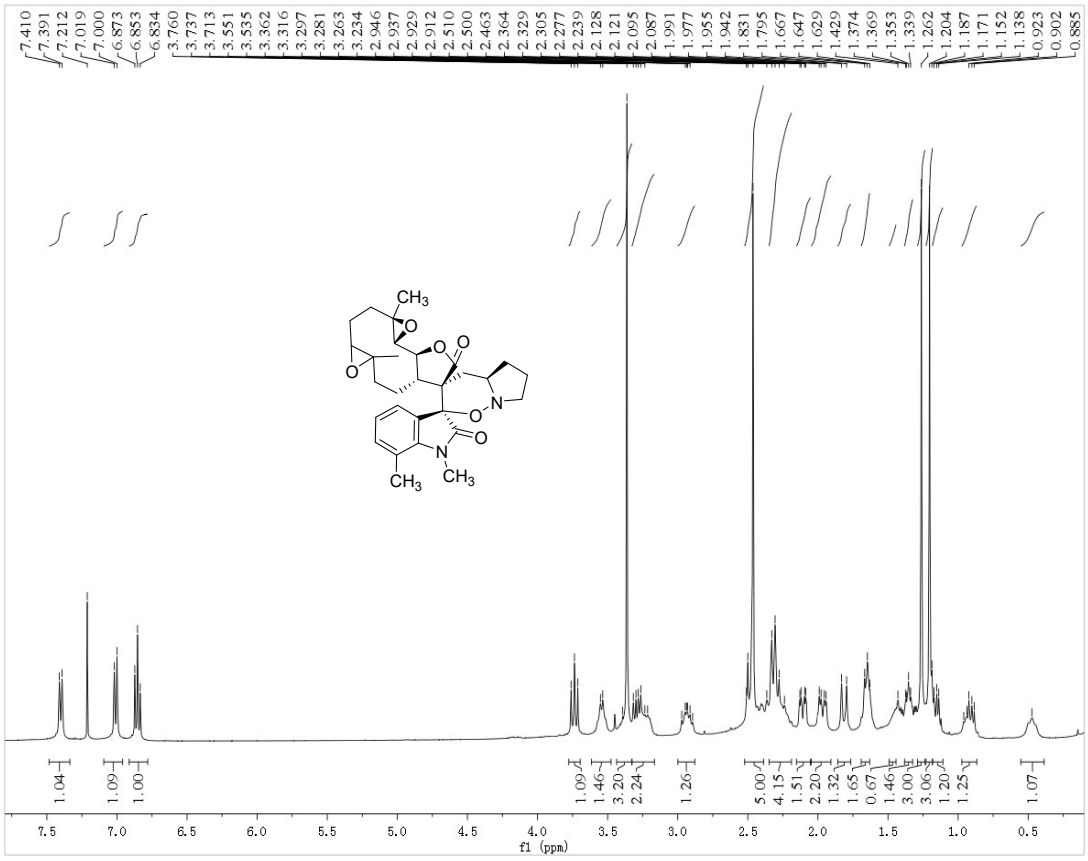


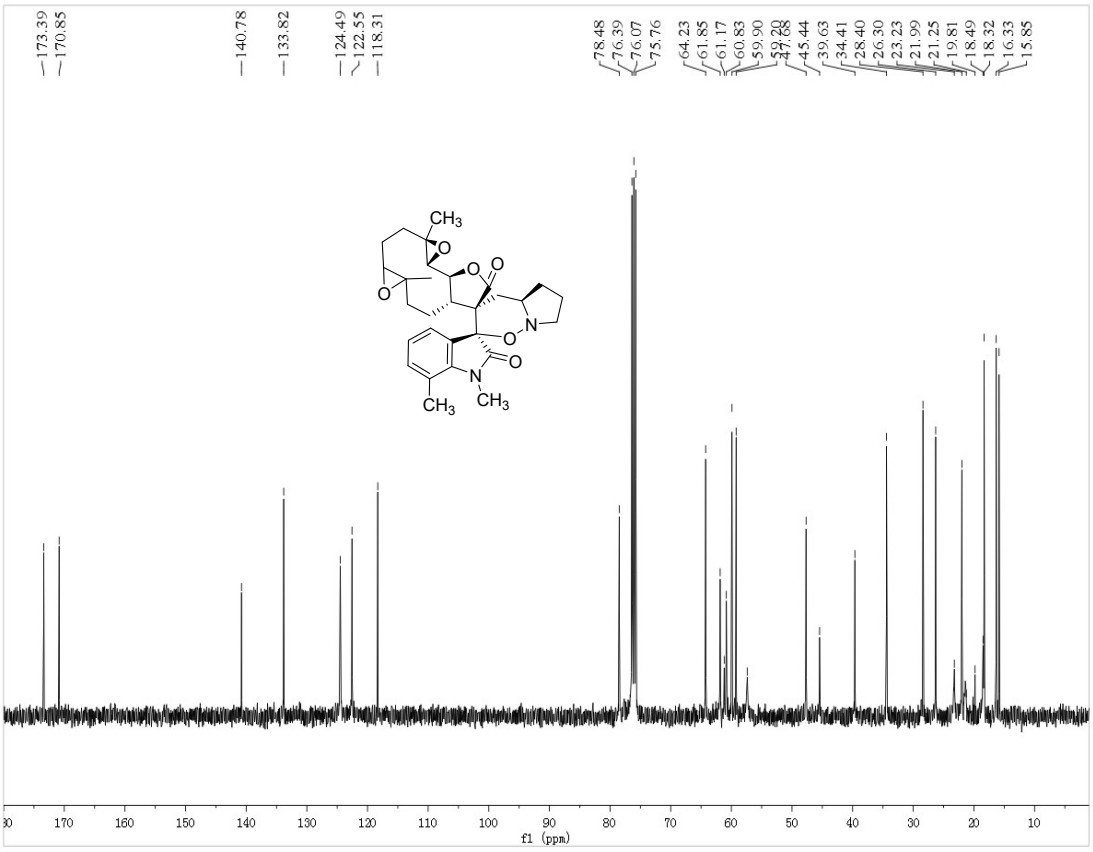
^{1}H and ^{13}C NMR of 6c



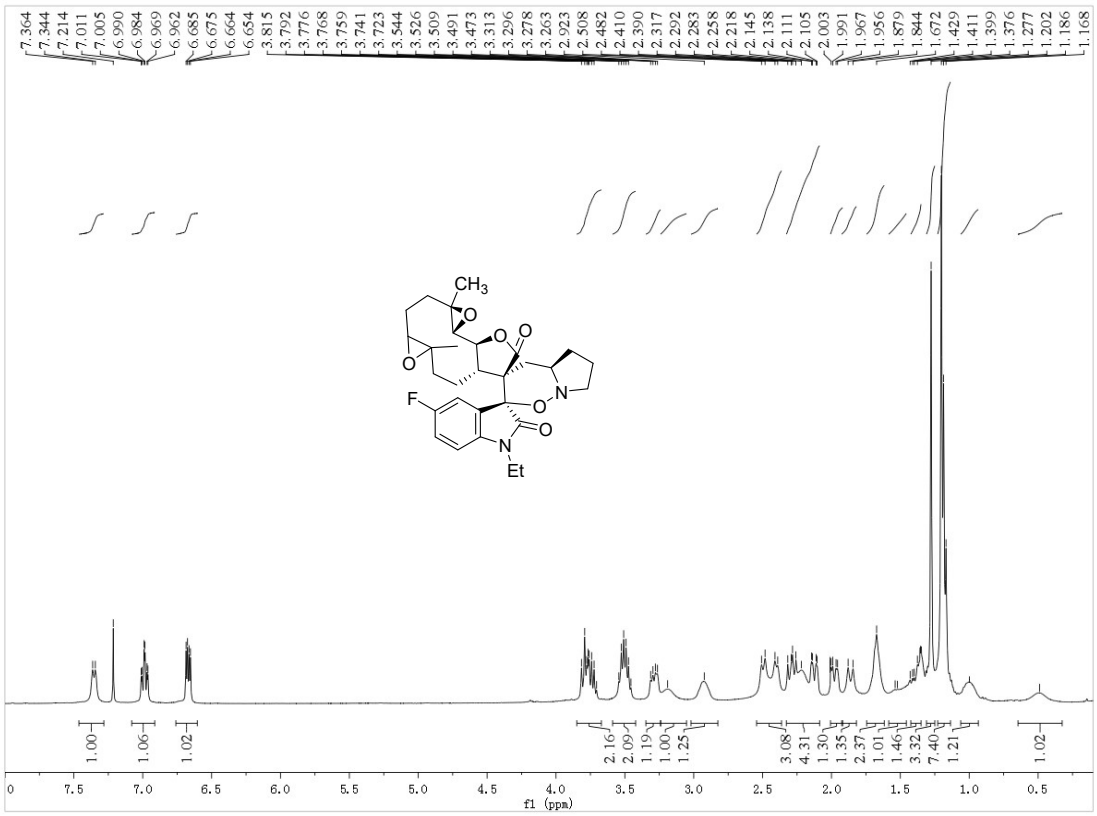


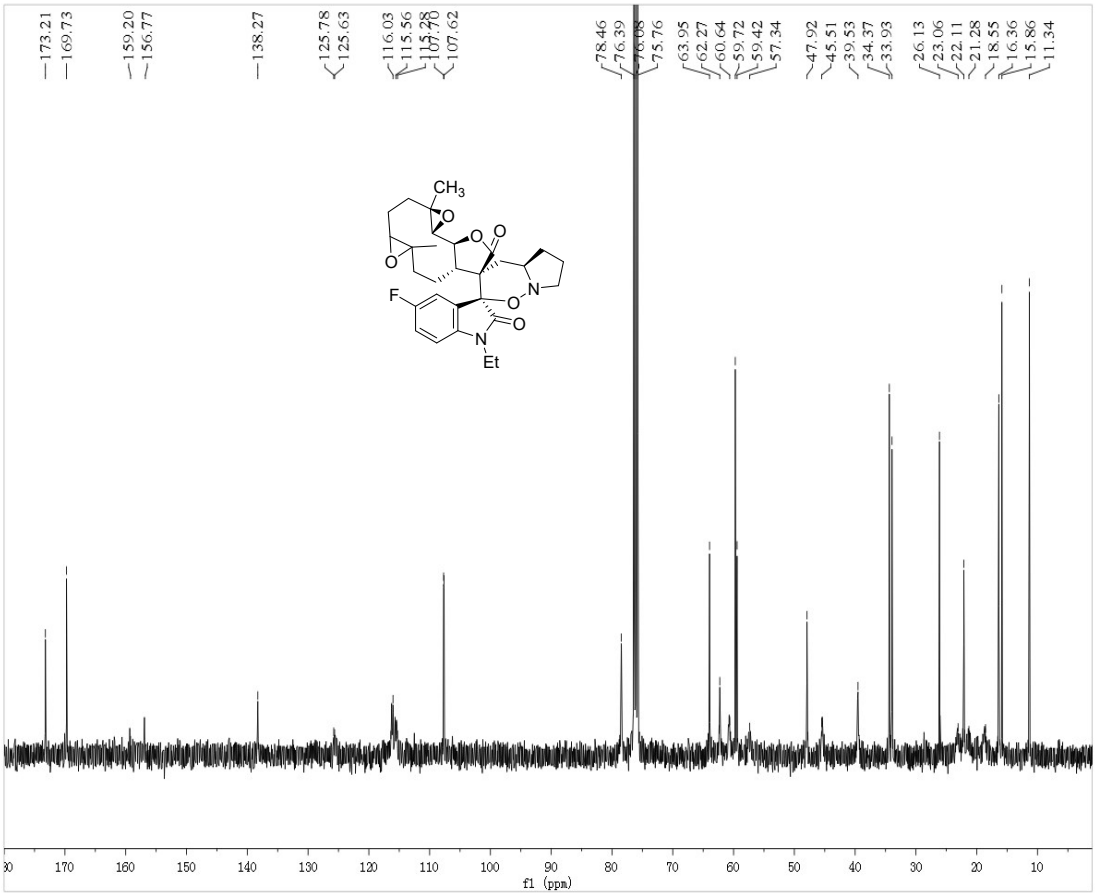
^{1}H and ^{13}C NMR of 7a



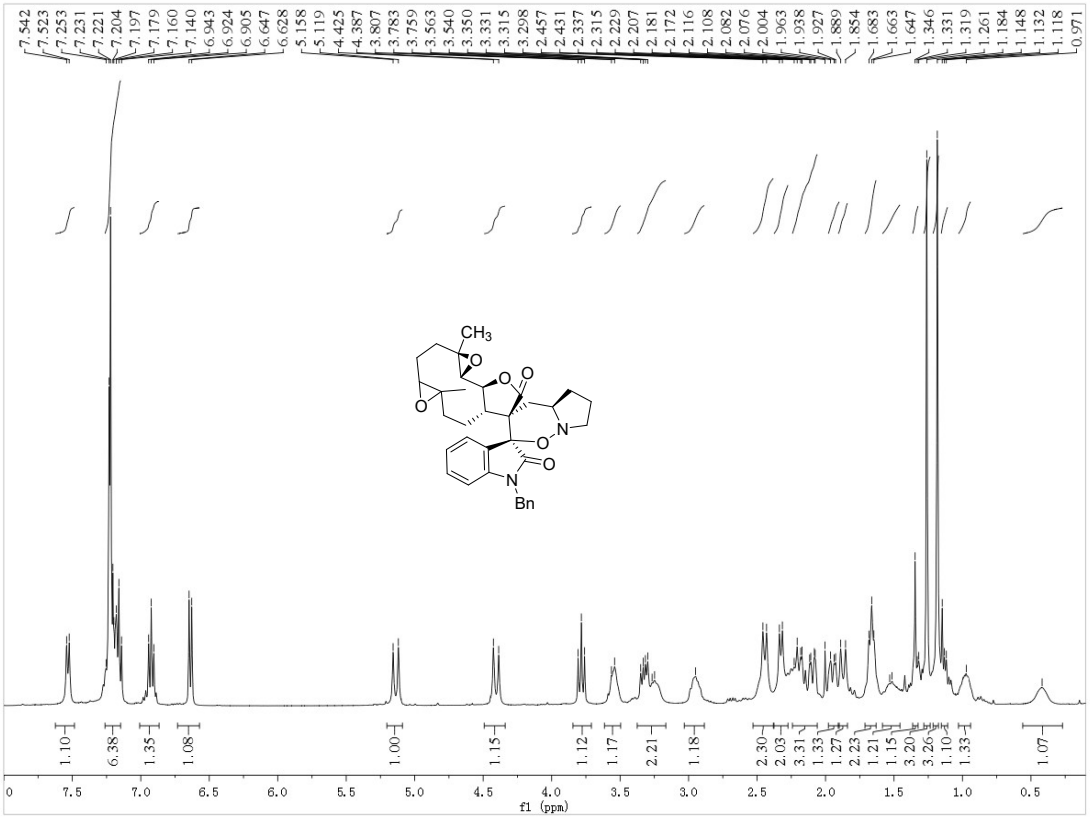


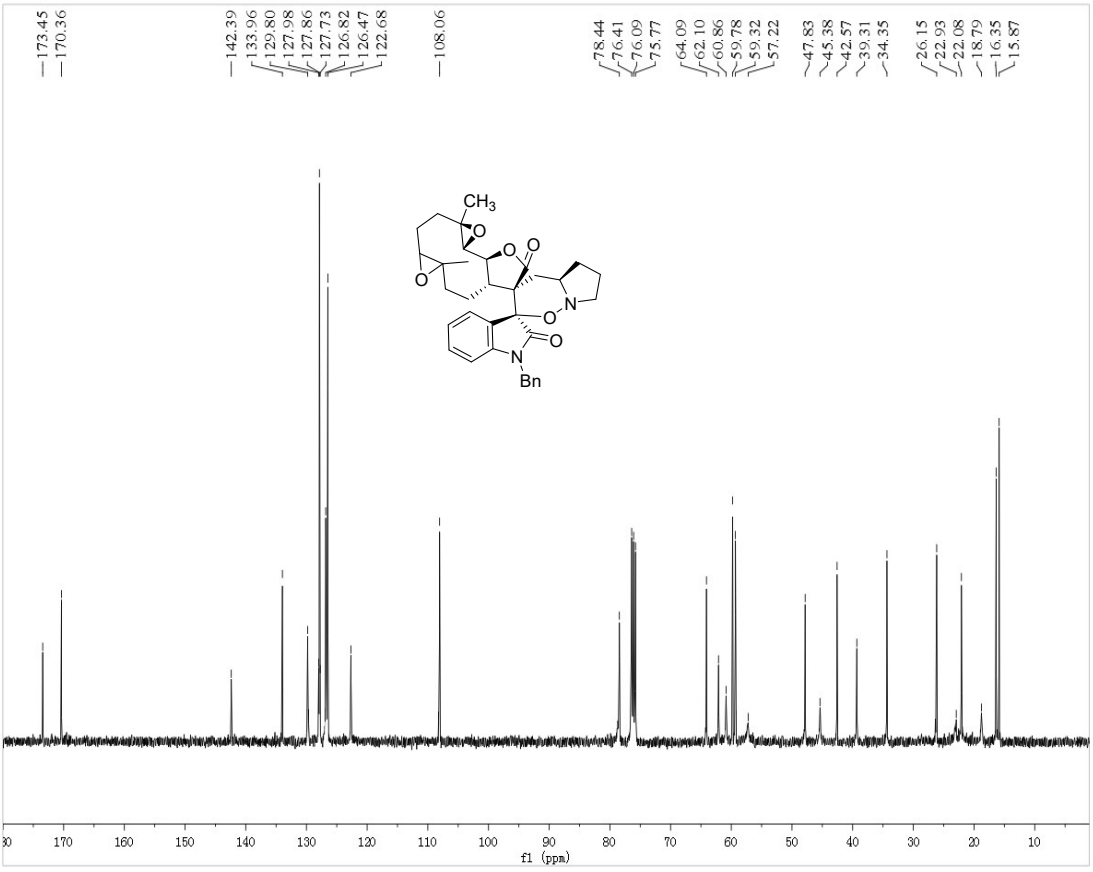
^{1}H and ^{13}C NMR of 7b



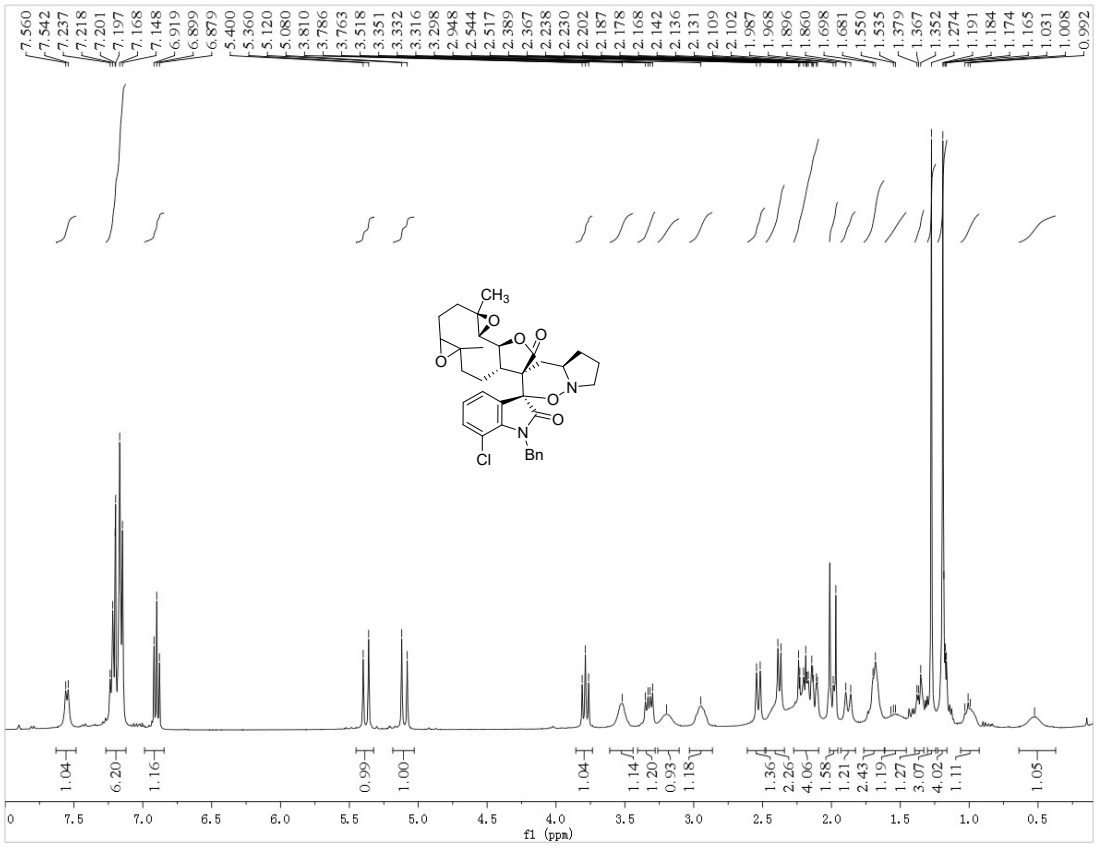


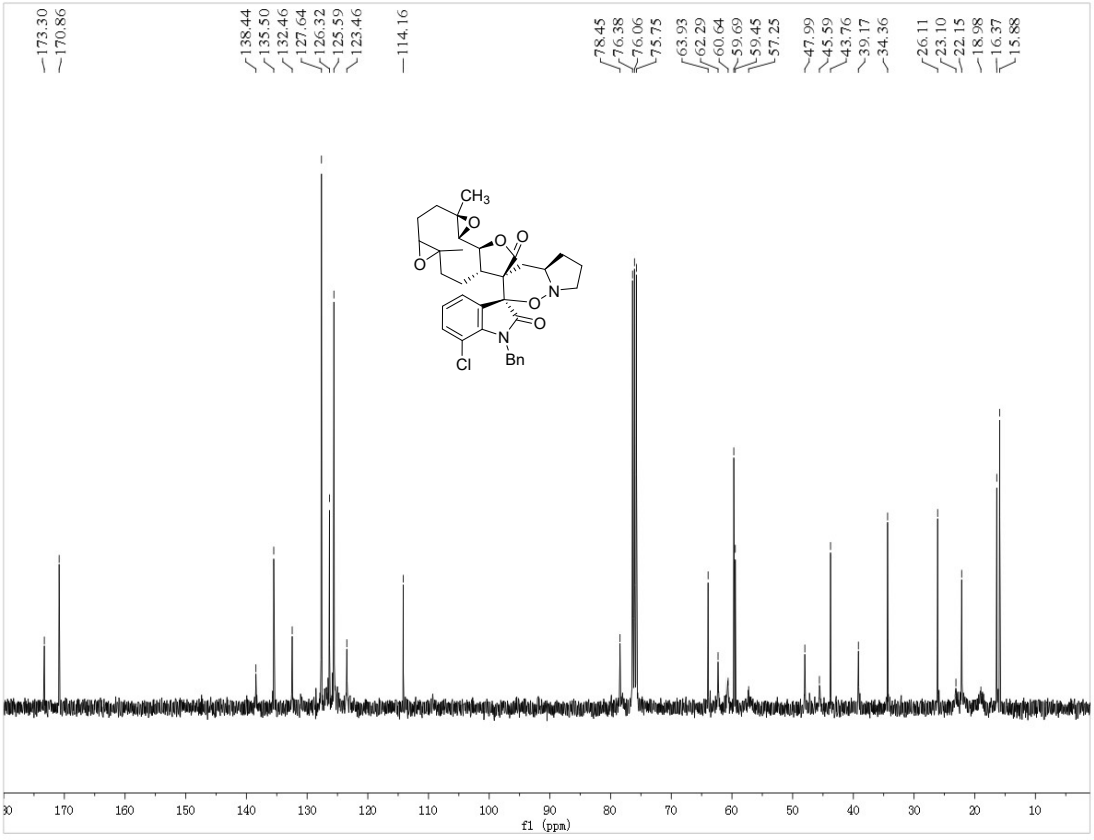
^{1}H and ^{13}C NMR of 7c



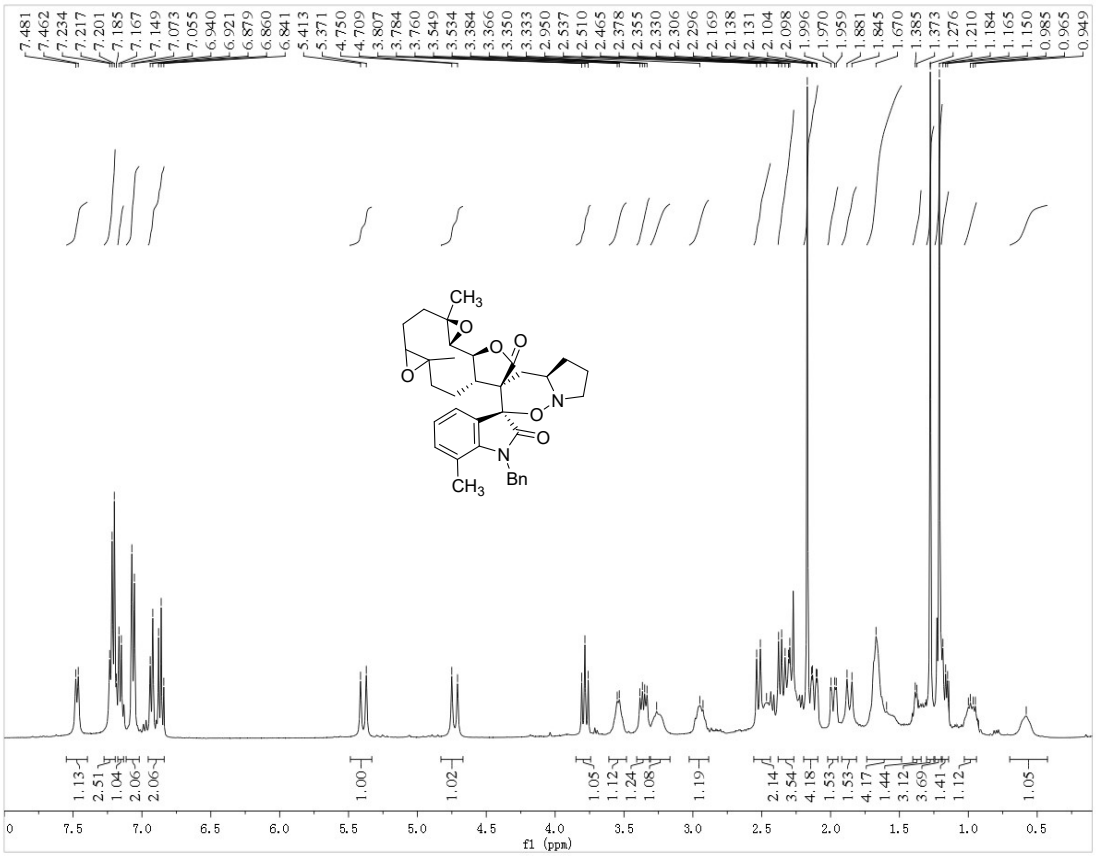


^{1}H and ^{13}C NMR of 7d





^{1}H and ^{13}C NMR of 7e


7.481
7.462
7.234
7.217
7.201
7.185
7.167
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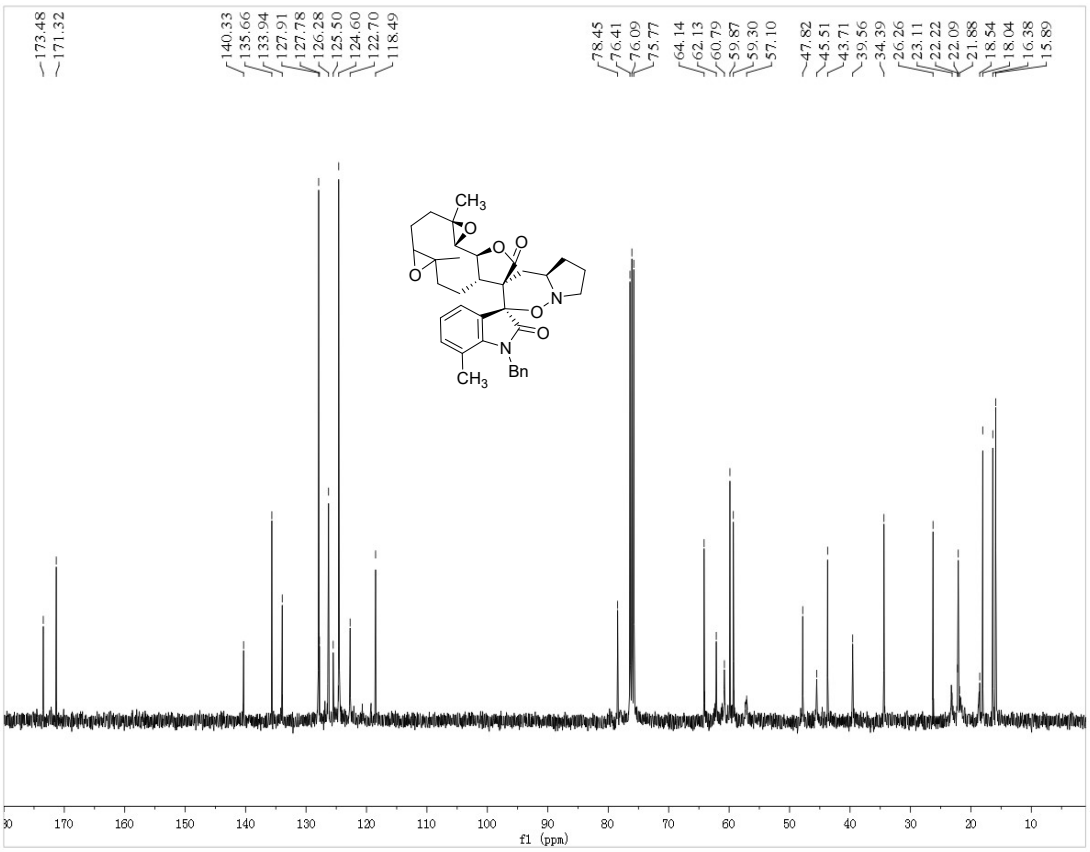
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