Supporting Information

DBU-Promoted [3+2] Cycloaddition for the Synthesis of Trispiro Heterocycles from Acetylpyrazolyl-Substituted Oxindoles and Substituted Isatins

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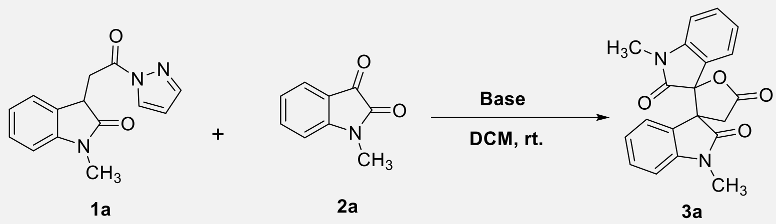
General Information

Reagents were purchased from commercial sources and were used as received unless mentioned otherwise. Reactions were monitored by TLC. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6. ^{1}H NMR chemical shifts are reported in ppm relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$ at 77.20 ppm, DMSO-d_6 at 39.51 ppm). The enantiomeric excesses were determined by chiral HPLC analysis. HRMS was recorded on Bruker Q TOF. Optical rotations were measured with a Perkin-Elmer-341 polarimeter. Melting points were recorded on a Büchi Melting Point B-545.

2. Optimization of reaction conditions

Table 1: Optimization of the Base

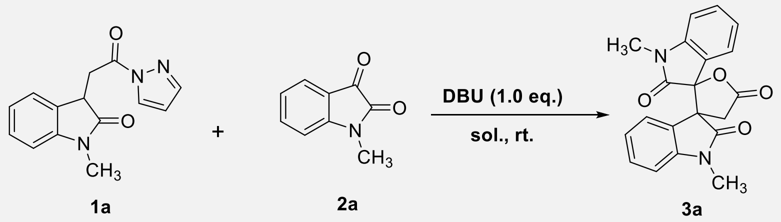


1a + 2a → 3a

entry	base	time/h	yield/%[b]	dr[c]
1	CS_2CO_3	16	messy	-
2	Na_2CO_3	16	n.d.	-
3	K_2CO_3	4	82.5	1.4:1
4	DABCO	5	40.2	17:1
5	DMAP	5	47.3	19.1:1
6	Et_3N	5	45	5.5:1
7	DIPEA	5	54	1.5:1
8	TMG	2	35	2.1:1
9	DBU	3	81	1.1:1
10	N,N-Dimethylaniline	24	n.d.	-
11	Quinoline	4	79	1.4:1

[a]Unless noted, the reactions were carried out with 1a (0.1 mmol), 2a (0.11 mmol) and 1.0 eq. base in 1.0 mL of solvent at room temperature. [b]Isolated yields. [c]The diastereomeric ratio (dr) was determined from the isolated yields of the diastereomers.

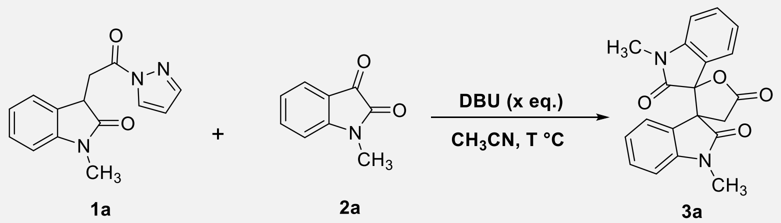
Table 2: Optimization of the Base



entry	base	time/h	yield/%[b]	dr[c]
1	THF	5	54	1.3:1
2	DCE	5	76	2.5:1
3	CH_3CN	3	94	1.2:1
4	CH_3OH	27	19	1.3:1
5	$CHCl_3$	4	65	2.2:1
6	$PhCH_3$	6	49	1.9:1

[a]Unless noted, the reactions were carried out with 1a (0.1 mmol), 2a (0.11 mmol) and 1.0 eq. DBU in 1.0 mL of solvent at room temperature. [b]Isolated yields. [c]The diastereomeric ratio (dr) was determined from the isolated yields of the diastereomers.

Table 3: Optimization of other useful conditions

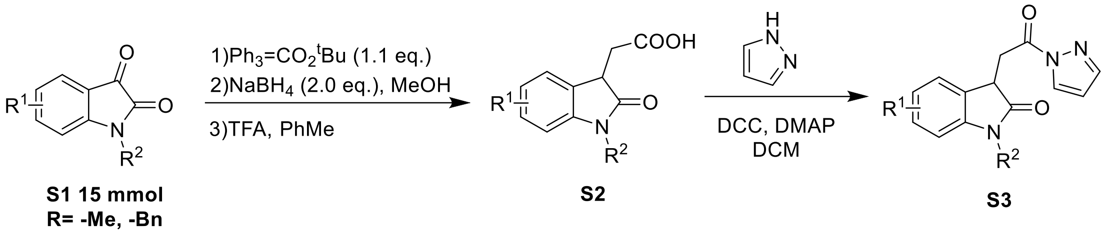


entry	x /eq.	T/°C	yield/%[b]	dr[c]
1	0.2	25	79	1.7:1
2	0.5	25	82	1.35:1
3	1.5	25	96	2.7:1
4	2.0	25	74	1.2:1
5	1.5	0	90	1.4:1
6	1.5	6	92	1.1:1
7[d]	1.5	25	95	2.7:1
8[e]	1.5	25	96	1.5:1

[a]Unless noted, the reactions were carried out with 1a (0.1 mmol), 2a (0.11 mmol) and 1.0 eq. DBU in 1.0 mL of CH_3CN at room temperature. [b]Isolated yields. [c]The diastereomeric ratio (dr) was determined from the isolated yields of the diastereomers. [d]1a:2a=1:1.2. [e]1a:2a=1.1:1

3. General procedure for the synthesis of 1 and 3

3.1 Synthesis of Substrate 1



To a solution of N-substituted isatin (S1, 15 mmol) in toluene (30 mL) was added tert-butyl (triphenylphosphoranylidene)acetate (16.5 mmol, 5.5 mL). The resulting mixture was heated to reflux and monitored by thin-layer chromatography (TLC). Upon completion of the reaction, the mixture was cooled to room temperature, filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure.

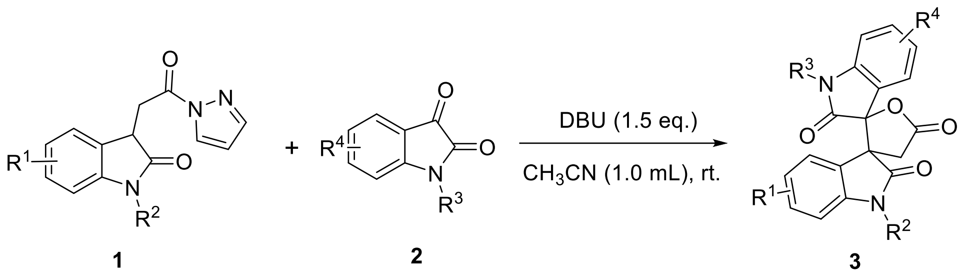
The crude residue was dissolved in methanol (35 mL) and cooled to 0 °C. Sodium borohydride ($NaBH_4$, 30 mmol, 1.1 g) was added portionwise, and the reaction mixture was stirred at 0 °C. After the reaction was complete, it was quenched with 50 mL of water and extracted with dichloromethane (DCM). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure.

The resulting concentrate was dissolved in toluene (50 mL), heated to 50 °C, and then treated with trifluoroacetic acid (TFA, 21 mL) for 2 h. After the reaction was finished, the mixture was allowed to warm to room temperature and then carefully poured into a saturated aqueous $NaHCO_3$ solution. The layers were separated, and the organic layer was discarded. The aqueous layer was acidified to pH ≈ 1 with 1 M HCl and extracted with DCM. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography to afford S2. (85 % yield).

To a solution of S2 (10 mmol) obtained from the previous step and pyrazole (15 mmol, 1.02 g) in dichloromethane (DCM, 15 mL) were added N,N'-dicyclohexylcarbodiimide (DCC, 3.1 g, 15 mmol) and 4-dimethylaminopyridine (DMAP, 0.18 g, 1.5 mmol) under an ice bath. The mixture was stirred at 0 °C for 30 min, then allowed to warm to room temperature and stirred for an additional 24 h.

Upon completion of the reaction, the mixture was filtered to remove solid impurities, and the filtrate was concentrated under reduced pressure. The resulting crude product was purified by column chromatography and then recrystallized from petroleum ether to afford 3-acetylpyrazole oxindole S3 as a pure solid (75% yield).

3.2 Synthesis of Substrate 3

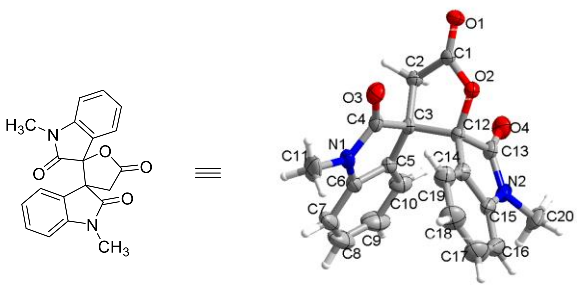


In an ordinary vial equipped with a magnetic stirring bar, the *substituted isatin* **2** (0.11mmol, 1.1 equiv) were added to a solution of the *acetylpyrazolyl-substituted Oxindole* **1** (0.10mmol, 1.0 equiv), the base 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.15mmol, 1.5 equiv) in 1,2-Dichloroethane (1.0 mL) at room temperature. And then, the mixture was stirred at the same temperature for the specified time. After completion of the reaction, as indicated by TLC. the products **3** were isolated by flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/1～2/1).

4. Scale-up experiment

In an ordinary vial equipped with a magnetic stirring bar, *1-methylindoline-2,3-dione* **2a** (8.8 mmol, 1.417 g) were added to a solution of the *acetylpyrazolyl-substituted Oxindole* **1a** (8.0 mmol, 2.040 g), the base 1,8-Diazabicyclo[5.4.0]undec-7-ene (12 mmol, 1.838 g) in 1,2-Dichloroethane (8.0 mL) at room temperature. And then, the whole was stirred for 10 hours until the completion of the reaction, as indicated by TLC. Finally the reaction mixture was directly purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 8/1) and obtained the products **3a** (2.562 g, 92% yield, 2.5:1 dr).

5. X-ray crystal data for compound 3a



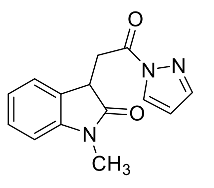
3a CCDC 2496634

Table 4 Crystal data and structure refinement for 20250498a_auto.	
Identification code	20250498a_auto
Empirical formula	$C_{20}H_{16}N_2O_4$
Formula weight	348.35
Temperature/K	293(2)

Crystal system	monoclinic
Space group	Cc
a/Å	13.1194(4)
b/Å	12.8734(4)
c/Å	10.0344(5)
α/°	90
β/°	100.177(4)
γ/°	90
Volume/Å^3	1668.06(11)
Z	4
ρ_{calc}g/cm^3	1.387
μ/mm^{-1}	0.808
F(000)	728.0
Crystal size/mm^3	0.15 × 0.12 × 0.1
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.702 to 141.892
Index ranges	-10 ≤ h ≤ 15, -15 ≤ k ≤ 15, -12 ≤ l ≤ 12
Reflections collected	6201
Independent reflections	2199 [R_{int} = 0.0295, R_{sigma} = 0.0276]
Data/restraints/parameters	2199/2/237
Goodness-of-fit on F^2	1.057
Final R indexes [I>=2σ (I)]	R_1 = 0.0457, wR_2 = 0.1298
Final R indexes [all data]	R_1 = 0.0484, wR_2 = 0.1343
Largest diff. peak/hole / e Å^{-3}	0.17/-0.14
Flack parameter	0.3(2)

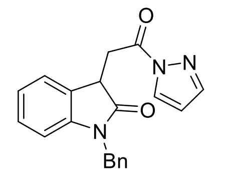
6. The copies of ^{1}H NMR, ^{13}C NMR spectra for compounds 1 and 3

Representative results for Substrate 1 are shown below.



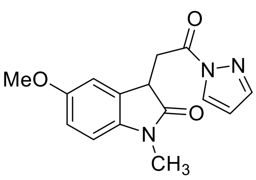
1a

It was purified by flash chromatography (petroleum ether / EtOAc, 8:1) to afford yellow solid (2.17 g, 86% yield); m.p. 102.3-102.6 ºC. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.23 (dd, *J* = 2.9, 0.7 Hz, 1H), 7.72 – 7.66 (m, 1H), 7.36 – 7.18 (m, 2H), 7.01 (td, *J* = 7.5, 1.0 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.44 (dd, *J* = 2.9, 1.5 Hz, 1H), 3.99 (t, *J* = 5.2 Hz, 1H), 3.97 (dd, *J* = 19.6, 4.2 Hz, 1H), 3.66 (dd, *J* = 19.6, 9.1 Hz, 1H), 3.27 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 176.8, 169.8, 144.6, 144.4, 128.5, 128.2, 124.0, 122.6, 110.0, 108.3, 41.3, 35.3, 26.5. **HRMS (ESI)** m/z calcd for $C_{14}H_{13}N_3O_2Na^+$ $[M+Na]^+$278.0900, found 278.0902.



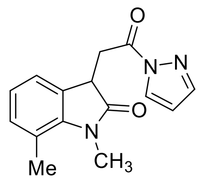
1b

It was purified by flash chromatography (petroleum ether / EtOAc, 8:1) to afford brown solid (2.58 g, 78% yield); m.p. 102.3-102.6 ºC. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.58 (d, *J* = 2.1 Hz, 4H), 7.16 (t, *J* = 7.8 Hz, 2H), 6.98 (dt, *J* = 11.2, 7.5 Hz, 2H), 6.73 (t, *J* = 7.0 Hz, 2H), 6.34 (t, *J* = 2.1 Hz, 2H), 4.98 (d, *J* = 15.7 Hz, 1H), 4.90 (d, *J* = 15.7 Hz, 1H), 3.92 (d, *J* = 5.8 Hz, 1H), 3.19 (dd, *J* = 17.0, 4.5 Hz, 1H), 2.93 (dd, *J* = 17.0, 7.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.4, 177.1, 174.9, 144.5, 135.9, 133.4, 128.8, 127.5, 127.4, 124.0, 122.7, 110.0, 109.3, 109.2, 105.4, 42.1, 35.2, 25.6. **HRMS (ESI)** m/z calcd for $C_{20}H_{17}N_3O_2Na^+$ $[M+Na]^+$354.1213, found 354.1216.



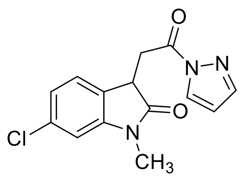
1d

It was purified by flash chromatography (petroleum ether / EtOAc, 7:1) to afford yellow solid (2.37 g, 83% yield); m.p. 113.2-113.6 ºC. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.60 (d, *J* = 2.1 Hz, 2H), 6.83 – 6.79 (m, 1H), 6.76 – 6.72 (m, 1H), 6.35 (t, *J* = 2.1 Hz, 2H), 3.83 (dd, *J* = 4.1, 0.0 Hz, 1H), 3.75 (s, 3H), 3.21 (s, 3H), 3.13 (dd, *J* = 17.0, 4.5 Hz, 1H), 2.81 (dd, *J* = 17.0, 8.4 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 174.9, 156.1, 144.4, 133.5, 129.9, 129.5, 128.5, 112.5, 111.8, 110.0, 105.3, 55.9, 42.5, 35.3, 26.6. **HRMS (ESI)** m/z calcd for $C_{15}H_{15}N_3O_3Na^+$ $[M+Na]^+$308.1006, found 308.1004.



1e

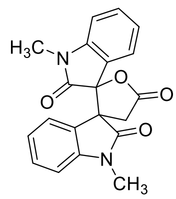
It was purified by flash chromatography (petroleum ether / EtOAc, 10:1) to afford white solid (2.07 g, 77% yield); m.p. 118.4-118.7 ºC. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.22 (dd, *J* = 2.9, 0.8 Hz, 1H), 7.69 (d, *J* = 0.8 Hz, 1H), 7.07 (dd, *J* = 7.0, 2.2 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.88 (t, *J* = 7.5 Hz, 1H), 6.43 (dd, *J* = 2.9, 1.5 Hz, 1H), 3.94 (dt, *J* = 12.9, 4.4 Hz, 2H), 3.66 (dd, *J* = 19.0, 8.3 Hz, 1H), 3.54 (s, 3H), 2.59 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 177.6, 169.8, 144.4, 142.3, 132.2, 128.7, 128.5, 122.5, 121.7, 119.9, 110.0, 40.9, 35.5, 29.9, 19.1. **HRMS (ESI)** m/z calcd for $C_{15}H_{15}N_3O_2Na^+$ $[M+Na]^+$ 292.1056, found 292.1053.



1f

It was purified by flash chromatography (petroleum ether / EtOAc, 11:1) to afford brown solid (2.17 g, 75% yield); m.p. 103.5-103.7 ºC. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.21 (dd, *J* = 2.9, 0.5 Hz, 1H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.27 (s, 1H), 7.17 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.98 (dd, *J* = 7.9, 1.9 Hz, 1H), 6.86 (d, *J* = 1.9 Hz, 1H), 3.97 (dd, *J* = 17.7, 4.3 Hz, 1H), 3.94 (t, *J* = 4.9 Hz, 1H), 3.65 (dd, *J* = 17.8, 7.4 Hz, 1H), 3.25 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 176.8, 169.6, 145.9, 144.6, 134.4, 128.5, 126.5, 124.9, 122.4, 110.2, 109.1, 41.0, 35.2, 26.7. **HRMS (ESI)** m/z calcd for $C_{14}H_{12}ClN_3O_2Na^+$ $[M+Na]^+$312.0510, found 312.0513.

1,1''-dimethyldispiro[indoline-3,2'-furan-3',3''-indoline]-2,2'',5'(4'H)-trione (3a)

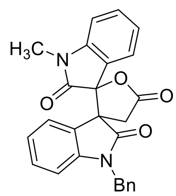


It was purified by flash chromatography (petroleum ether / EtOAc, 5:1) to afford white solid (33.4 mg, 96% yield, separation yield of diastereoisomers, *dr* 2.7:1;); m.p. 138.5-138.8 ºC.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.22 (dt, *J* = 15.5, 7.7 Hz, 2H), 6.74 (t, *J* = 7.2 Hz, 2H), 6.65 (t, 1H), 6.49 (d, *J* = 7.6 Hz, 1H), 4.27 (d, *J* = 16.6 Hz, 1H), 3.20 (s, 3H), 3.01 (s, 3H), 2.73 (d, *J* = 16.6 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 174.3, 172.5, 171.2, 145.1, 143.0, 131.7, 130.3, 128.5, 126.3, 123.9, 123.2, 122.3, 120.5, 109.0, 108.7, 85.5, 58.1, 37.6, 26.7, 26.7.

HRMS (ESI) m/z calcd for $C_{20}H_{16}N_2O_4Na^+$ $[M+Na]^+$371.1002, found 371.1000.

(3R,3'S)-1''-benzyl-1-methyldispiro[indoline-3,2'-furan-3',3''-indoline]-2,2'',5'(4'H)-trione (3b)

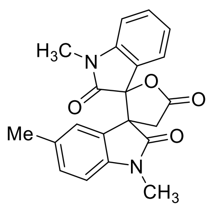


It was purified by flash chromatography (petroleum ether / EtOAc, 5:1) to afford white solid (40.3 mg, 95% yield, separation yield of diastereoisomers, *dr* 1.5:1;); m.p. 145.3-145.6 ºC.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.64 – 7.59 (m, 1H), 7.56 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.46 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.30 (td, *J* = 7.8, 1.3 Hz, 1H), 7.20 – 7.15 (m, 2H), 7.15 – 7.10 (m, 2H), 6.99 (td, *J* = 7.7, 1.1 Hz, 1H), 6.91 – 6.87 (m, 2H), 6.65 (d, *J* = 7.8 Hz, 1H), 6.49 (d, *J* = 7.7 Hz, 1H), 5.03 (d, *J* = 15.9 Hz, 1H), 4.57 (d, *J* = 15.8 Hz, 1H), 3.86 (d, *J* = 16.9 Hz, 1H), 3.05 (s, 3H), 2.95 (d, *J* = 16.9 Hz, 1H).**^{13}C NMR (151 MHz, $CDCl_3$)** δ 175.7, 173.4, 173.2, 144.4, 143.8, 138.5, 131.6, 130.2, 128.9, 127.8, 127.1, 125.5, 124.8, 124.0, 123.3, 110.1, 109.9, 108.9, 85.1, 56.2, 49.5, 43.9, 36.7, 33.9.

HRMS (ESI) m/z calcd for $C_{26}H_{20}N_2O_4Na^+$ $(M+Na)^+$447.1315, found 447.1318.

1,1'',5''-trimethyldispiro[indoline-3,2'-furan-3',3''-indoline]-2,2'',5'(4'H)-trione (3c)

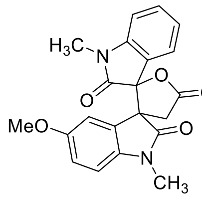


It was purified by flash chromatography (petroleum ether / EtOAc, 4:1) to afford white solid (34.8 mg, 96% yield, separation yield of diastereoisomers, *dr* 2.5:1;); m.p. 145.3-145.6 ºC.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.6 Hz, 1H), 7.28 – 7.23 (m, 2H), 7.06 – 6.98 (m, 2H), 6.61 (d, J = 7.8 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 3.82 (d, J = 16.9 Hz, 1H), 3.04 (s, 3H), 3.03 (s, 3H), 2.86 (d, J = 16.8 Hz, 1H), 2.29 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 175.4, 173.7, 173.0, 144.4, 142.0, 132.9, 131.7, 130.5, 126.3, 125.3, 123.4, 122.2, 121.3, 108.7, 108.3, 85.2, 56.3, 35.8, 34.0, 26.1, 21.2.

HRMS (ESI) m/z calcd for $C_{21}H_{18}N_2O_4Na^+$ $[M+Na]^+$385.1158, found 385.1157.

5''-methoxy-1,1''-dimethyldispiro[indoline-3,2'-furan-3',3''-indoline]-2,2'',5'(4'H)-trione (3d)

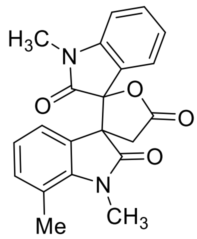


It was purified by flash chromatography (petroleum ether / EtOAc, 4:1) to afford white solid (34.8 mg, 92% yield, separation yield of diastereoisomers, *dr* 2.1:1;); m.p. 143.3-143.8 ºC.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.56 (ddd, J = 7.6, 1.3, 0.6 Hz, 1H), 7.28 (dd, J = 7.8, 1.3 Hz, 1H), 7.07 (d, J = 2.6 Hz, 1H), 7.01 (td, J = 7.6, 1.0 Hz, 1H), 6.77 (dd, J = 8.5, 2.6 Hz, 1H), 6.62 (dt, J = 7.8, 0.8 Hz, 1H), 6.54 (d, J = 8.5 Hz, 1H), 3.83 (d, J = 16.8 Hz, 1H), 3.75 (s, 3H), 3.07 (s, 3H), 3.04 (s, 3H), 2.88 (d, J = 16.8 Hz, 1H).**^{13}C NMR (151 MHz, $CDCl_3$)** δ 175.2, 173.5, 173.0, 156.4, 144.4, 137.8, 131.7, 126.5, 123.5, 123.4, 121.3, 115.3, 111.4, 109.1, 108.7, 85.1, 56.4, 56.1, 36.0, 26.2, 26.2.

HRMS (ESI) m/z calcd for $C_{21}H_{18}N_2O_5Na^+$ $[M+Na]^+$401.1108, found 401.1107.

1,1'',7''-trimethyldispiro[indoline-3,2'-furan-3',3''-indoline]-2,2'',5'(4'H)-trione (3e)

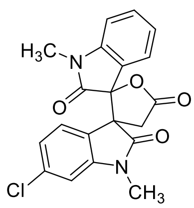


It was purified by flash chromatography (petroleum ether / EtOAc, 2:1) to afford white solid (30.8 mg, 85% yield, separation yield of diastereoisomers, *dr* 1.9:1;); m.p. 143.2-143.7 ºC.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (dd, J = 7.6, 1.5 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.05 – 6.99 (m, 1H), 6.96 (d, J = 7.7 Hz, 1H), 6.88 (t, J = 7.7 Hz, 1H), 6.62 (d, J = 7.9 Hz, 1H), 3.80 (d, J = 16.8 Hz, 1H), 3.33 (s, 3H), 3.02 (s, 3H), 2.85 (d, J = 16.7 Hz, 1H), 2.38 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 176.3, 173.7, 173.0, 144.5, 142.2, 134.0, 131.7, 126.3, 123.4, 123.0, 122.7, 122.5, 121.3, 120.2, 108.8, 85.3, 55.7, 36.1, 29.5, 26.1, 19.0.

HRMS (ESI) m/z calcd for $C_{21}H_{18}N_2O_4Na^+$ $[M+Na]^+$385.1158, found 385.1158.

6''-chloro-1,1''-dimethyldispiro[indoline-3,2'-furan-3',3''-indoline]-2,2'',5'(4'H)-trione (3f)

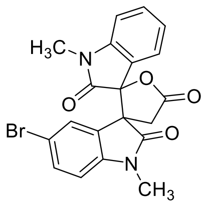


It was purified by flash chromatography (petroleum ether / EtOAc, 2:1) to afford white solid (34.4 mg, 90% yield, separation yield of diastereoisomers, *dr* 1.7:1); m.p. 150.7-151.1 ºC.

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.51 (ddd, *J* = 7.6, 1.3, 0.5 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.30 (td, *J* = 7.7, 1.3 Hz, 1H), 7.02 (td, *J* = 7.6, 1.0 Hz, 1H), 6.98 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.67 – 6.62 (m, 2H), 3.82 (d, *J* = 16.9 Hz, 1H), 3.05 (s, 3H), 3.05 (s, 3H), 2.87 (d, *J* = 16.8 Hz, 1H). **^{13}C NMR (151 MHz, CDCl$_3$)** δ 175.5, 173.1, 172.8, 145.6, 144.4, 136.3, 132.0, 126.2, 125.7, 123.6, 123.1, 121.0, 120.7, 109.5, 109.0, 84.9, 55.9, 35.8, 26.3, 26.2.

HRMS (ESI) m/z calcd for $C_{20}H_{15}ClN_2O_4Na^+$ $[M+Na]^+$405.0612, found 405.0612.

5''-bromo-1,1''-dimethyldispiro[indoline-3,2'-furan-3',3''-indoline]-2,2'',5'(4'H)-trione (3g)

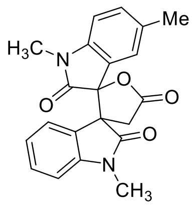


It was purified by flash chromatography (petroleum ether / EtOAc, 4:1) to afford white solid (38.8 mg, 91% yield, separation yield of diastereoisomers, *dr* 3.7:1); m.p. 153.1-153.5 ºC.

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.70 (d, *J* = 2.0 Hz, 1H), 7.46 – 7.32 (m, 2H), 7.26 (dd, *J* = 15.5, 1.3 Hz, 1H), 7.07 – 6.92 (m, 1H), 6.68 (d, *J* = 7.7 Hz, 1H), 6.49 (d, *J* = 8.3 Hz, 1H), 3.82 (d, *J* = 16.9 Hz, 1H), 3.11 (s, 3H), 3.02 (s, 3H), 2.88 (d, *J* = 16.8 Hz, 1H). **^{13}C NMR (151 MHz, CDCl$_3$)** δ 175.3, 173.1, 172.5, 144.4, 143.4, 134.6, 130.5, 129.4, 124.6, 123.3, 123.1, 121.9, 116.2, 110.2, 108.8, 84.6, 56.2, 35.5, 33.9, 31.6.

HRMS (ESI) m/z calcd for $C_{20}H_{15}BrN_2O_4Na^+$ $[M+Na]^+$449.0107, found 449.0108.

1,1'',5-trimethyldispiro[indoline-3,2'-furan-3',3''-indoline]-2,2'',5'(4'H)-trione (3h)



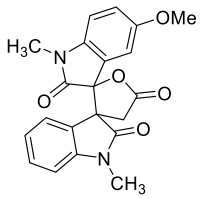
It was purified by flash chromatography (petroleum ether / EtOAc, 4:1) to afford white solid (34.0 mg, 94% yield, separation yield of diastereoisomers, *dr* 3.1:1); m.p. 144.4-144.8 ºC.

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.54 (d, *J* = 7.5 Hz, 1H), 7.41 – 7.35 (m, 1H), 7.21 – 7.15 (m, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 7.9 Hz, 1H), 6.57 – 6.49 (m, 1H), 6.41 (d, *J* = 7.6 Hz, 1H), 4.26 (d, *J* = 16.6 Hz, 1H), 3.47 (s, 3H), 3.03 (s, 3H), 2.71 (d, *J* = 16.6 Hz, 1H), 2.48 (s, 3H). **^{13}C**

NMR (151 MHz, CDCl3)** δ 174.5, 173.4, 171.4, 143.0, 142.7, 135.5, 130.2, 128.4, 124.2, 124.0, 123.1, 122.1, 121.1, 120.2, 109.0, 85.0, 58.3, 37.8, 30.2, 26.8, 19.2.

HRMS (ESI) m/z calcd for $C_{21}H_{18}N_2O_4Na^+$ $[M+Na]^+$385.1158, found 385.1158.

5-methoxy-1,1''-dimethyldispiro[indoline-3,2'-furan-3',3''-indoline]-2,2'',5'(4'H)-trione (3i)

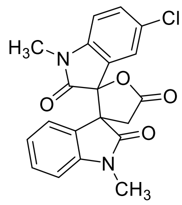


It was purified by flash chromatography (petroleum ether / EtOAc, 4:1) to afford white solid (34.4 mg, 92% yield, separation yield of diastereoisomers, *dr* 2.8:1); m.p. 147.2-147.7 ºC.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.36 (d, J = 9.3 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.22 – 7.14 (m, 1H), 6.96 – 6.90 (m, 1H), 6.59 (d, J = 9.3 Hz, 1H), 6.39 (dd, J = 8.6, 2.4 Hz, 1H), 6.09 (d, J = 1.5 Hz, 1H), 3.75 (d, J = 16.9 Hz, 1H), 3.69 (s, 3H), 3.01 (s, 3H), 2.93 (s, 3H), 2.78 (d, J = 16.9 Hz, 1H). **^{13}C NMR (101 MHz, CDCl3)** δ 175.6, 173.6, 173.3, 162.6, 145.9, 144.3, 130.1, 127.2, 124.5, 123.0, 122.3, 112.5, 108.6, 107.0, 96.7, 85.0, 55.5, 35.9, 31.5, 30.1, 29.7.

HRMS (ESI) m/z calcd for $C_{21}H_{18}N_2O_5Na^+$ $[M+Na]^+$ 401.1108, found 401.1108.

5-chloro-1,1''-dimethyldispiro[indoline-3,2'-furan-3',3''-indoline]-2,2'',5'(4'H)-trione (3j)

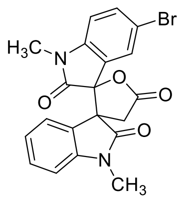


It was purified by flash chromatography (petroleum ether / EtOAc, 4:1) to afford white solid (33.6 mg, 88% yield, separation yield of diastereoisomers, *dr* 3.3:1); m.p. 151.5-151.8 ºC.

^{1}H NMR (600 MHz, CDCl3) δ 7.56 (d, J = 2.1 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 7.7 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.04 – 6.99 (m, 1H), 6.68 (d, J = 7.8 Hz, 1H), 6.54 (d, J = 8.3 Hz, 1H), 3.83 (d, J = 16.8 Hz, 1H), 3.11 (s, 3H), 3.02 (s, 3H), 2.88 (d, J = 16.8 Hz, 1H). **^{13}C NMR (101 MHz, CDCl3)** δ 175.3, 173.1, 172.6, 144.4, 142.9, 131.7, 130.5, 129.1, 126.7, 124.6, 123.3, 122.8, 121.9, 109.7, 108.8, 84.6, 56.1, 48.8, 35.5, 33.9.

HRMS (ESI) m/z calcd for $C_{20}H_{15}ClN_2O_4Na^+$ $[M+Na]^+$405.0612, found 405.0612.

5-bromo-1,1''-dimethyldispiro[indoline-3,2'-furan-3',3''-indoline]-2,2'',5'(4'H)-trione (3k)

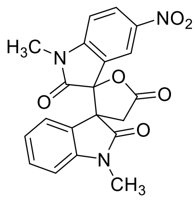


It was purified by flash chromatography (petroleum ether / EtOAc, 5:1) to afford white solid (35.8 mg, 84% yield, separation yield of diastereoisomers, *dr* 2.1:1); m.p. 150.2-150.6 ºC.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.54 (d, *J* = 7.5 Hz, 1H), 7.44 – 7.35 (m, 1H), 7.23 – 7.14 (m, 1H), 7.03 – 6.89 (m, 1H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.64 – 6.51 (m, 1H), 6.32 (d, *J* = 7.4 Hz, 1H), 4.24 (d, *J* = 16.7 Hz, 1H), 3.41 (s, 3H), 3.05 (s, 3H), 2.73 (d, *J* = 18.0 Hz, 1H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 174.0, 172.2, 171.0, 148.7, 146.3, 143.0, 130.5, 128.1, 123.8, 123.2, 122.9, 122.2, 119.8, 119.6, 109.1, 85.1, 58.1, 37.4, 29.3, 26.8.

HRMS (ESI) m/z calcd for $C_{20}H_{15}BrN_2O_4Na^+$ $[M+Na]^+$449.0107, found 449.0109.

1,1''-dimethyl-5-nitrodispiro[indoline-3,2'-furan-3',3''-indoline]-2,2'',5'(4'H)-trione (3l)

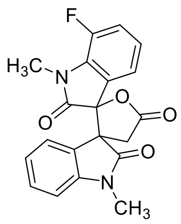


It was purified by flash chromatography (petroleum ether / EtOAc, 5:1) to afford white solid (35.4 mg, 90% yield, separation yield of diastereoisomers, *dr* 3.2:1); m.p. 147.5-147.8 ºC.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.45 (d, *J* = 2.3 Hz, 1H), 8.26 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.37 (d, *J* = 1.4 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.04 (td, *J* = 7.7, 1.0 Hz, 1H), 6.74 (d, *J* = 8.7 Hz, 1H), 6.68 (dd, *J* = 7.8, 0.9 Hz, 1H), 3.83 (d, *J* = 16.9 Hz, 1H), 3.13 (s, 3H), 3.09 (s, 3H), 2.94 (d, *J* = 16.9 Hz, 1H). **^{13}C NMR (151 MHz, CDCl$_3$)** δ 175.0, 173.2, 172.5, 149.9, 144.4, 144.2, 130.8, 128.5, 124.5, 123.5, 122.4, 122.3, 121.5, 109.1, 108.7, 83.8, 56.0, 35.4, 26.7, 26.3.

HRMS (ESI) m/z calcd for $C_{20}H_{15}N_3O_6Na^+$ $[M+Na]^+$416.0853, found 416.0852.

7-fluoro-1,1''-dimethyldispiro[indoline-3,2'-furan-3',3''-indoline]-2,2'',5'(4'H)-trione (3m)

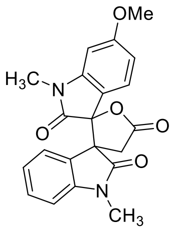


It was purified by flash chromatography (petroleum ether / EtOAc, 2:1) to afford white solid (30.4 mg, 83% yield, separation yield of diastereoisomers, *dr* 2.8:1); m.p. 152.3-152.6 ºC.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.40 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.37 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.29 (td, *J* = 7.7, 1.3 Hz, 1H), 7.07 – 6.98 (m, 2H), 6.98 – 6.92 (m, 1H), 6.68 (d, *J* = 7.8 Hz,

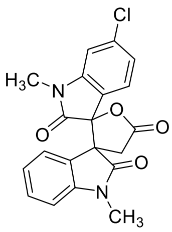
1H), 3.83 (d, J = 16.9 Hz, 1H), 3.24 (d, J = 2.8 Hz, 3H), 3.06 (s, 3H), 2.88 (d, J = 16.9 Hz, 1H).
^{13}C NMR (101 MHz, CDCl$_3$) δ 174.0, 172.2, 171.0, 147.5 (d, J = 244.4 Hz), 143.0, 131.8 (d, J = 8.9 Hz), 130.5, 128.1, 123.8, 123.2, 122.9, 122.8, 122.2 (d, J = 3.5 Hz), 119.7 (d, J = 19.1 Hz), 109.7, 85.1, 58.1, 37.4, 29.3, 26.8.
HRMS (ESI) m/z calcd for $C_{20}H_{15}FN_2O_4Na^+$ $[M+Na]^+$389.0908, found 389.0908.

6-methoxy-1,1''-dimethyldispiro[indoline-3,2'-furan-3',3''-indoline]-2,2'',5'(4'H)-trione (3n)



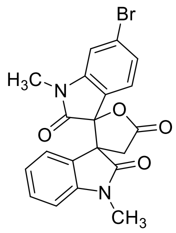
It was purified by flash chromatography (petroleum ether / EtOAc, 4:1) to afford white solid (34.0 mg, 94% yield, separation yield of diastereoisomers, *dr* 3.1:1); m.p. 144.4-144.8 ºC.
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.43 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.03 – 6.96 (m, 1H), 6.67 (d, J = 7.8 Hz, 1H), 6.46 (dd, J = 8.5, 2.2 Hz, 1H), 6.16 (d, J = 2.2 Hz, 1H), 3.82 (d, J = 16.9 Hz, 1H), 3.76 (s, 3H), 3.08 (s, 3H), 3.01 (s, 3H), 2.86 (d, J = 16.9 Hz, 1H).
^{13}C NMR (101 MHz, CDCl$_3$) δ 175.7, 173.7, 173.4, 162.7, 146.0, 144.4, 130.2, 127.3, 124.6, 123.1, 122.4, 112.6, 108.7, 107.1, 96.7, 85.1, 56.1, 55.6, 36.0, 26.1, 26.1.
HRMS (ESI) m/z calcd for $C_{21}H_{18}N_2O_5Na^+$ $[M+Na]^+$401.1107, found 401.1106.

6-chloro-1,1''-dimethyldispiro[indoline-3,2'-furan-3',3''-indoline]-2,2'',5'(4'H)-trione (3o)



It was purified by flash chromatography (petroleum ether / EtOAc, 4:1) to afford white solid (33.2 mg, 87% yield, separation yield of diastereoisomers, *dr* 2.7:1); m.p. 141.2-141.7 ºC.
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.47 (d, J = 8.2 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.05 – 7.01 (m, 1H), 6.99 (dd, J = 8.1, 1.0 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 6.62 (d, J = 1.8 Hz, 1H), 3.81 (d, J = 16.9 Hz, 1H), 3.08 (s, 3H), 3.02 (s, 3H), 2.88 (d, J = 16.9 Hz, 1H).
^{13}C NMR (101 MHz, CDCl$_3$) δ 175.4, 173.2, 173.0, 145.7, 144.4, 137.8, 130.5, 127.3, 124.5, 123.4, 123.3, 122.0, 119.6, 109.7, 108.9, 86.0, 56.1, 35.7, 26.3, 26.2.
HRMS (ESI) m/z calcd for $C_{20}H_{15}ClN_2O_4Na^+$ $[M+Na]^+$405.0612, found 405.0613.

6-bromo-1,1''-dimethyldispiro[indoline-3,2'-furan-3',3''-indoline]-2,2'',5'(4'H)-trione (3p)



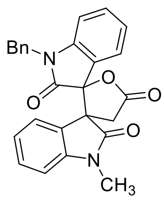
It was purified by flash chromatography (petroleum ether / EtOAc, 4:1) to afford white solid (38.3 mg, 90% yield, separation yield of diastereoisomers, *dr* 3.2:1); m.p. 145.2-145.7 ºC.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.45 – 7.35 (m, 2H), 7.29 – 7.24 (m, 1H), 7.15 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.05 – 6.99 (m, 1H), 6.77 (d, *J* = 1.7 Hz, 1H), 6.69 (d, *J* = 9.3 Hz, 1H), 3.81 (d, *J* = 16.9 Hz, 1H), 3.08 (s, 3H), 3.02 (s, 3H), 2.87 (d, *J* = 16.9 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 175.3, 173.2, 172.9, 145.7, 144.4, 130.5, 127.6, 126.4, 125.8, 124.6, 123.3, 122.0, 120.2, 112.5, 108.9, 84.6, 56.0, 35.8, 26.3, 26.2.

HRMS (ESI) m/z calcd for $C_{20}H_{15}BrN_2O_4Na^+$ $[M+Na]^+$449.0107, found 449.0109.

1-benzyl-1''-methyldispiro[indoline-3,2'-furan-3',3''-indoline]-2,2'',5'(4'H)-trione (3q)

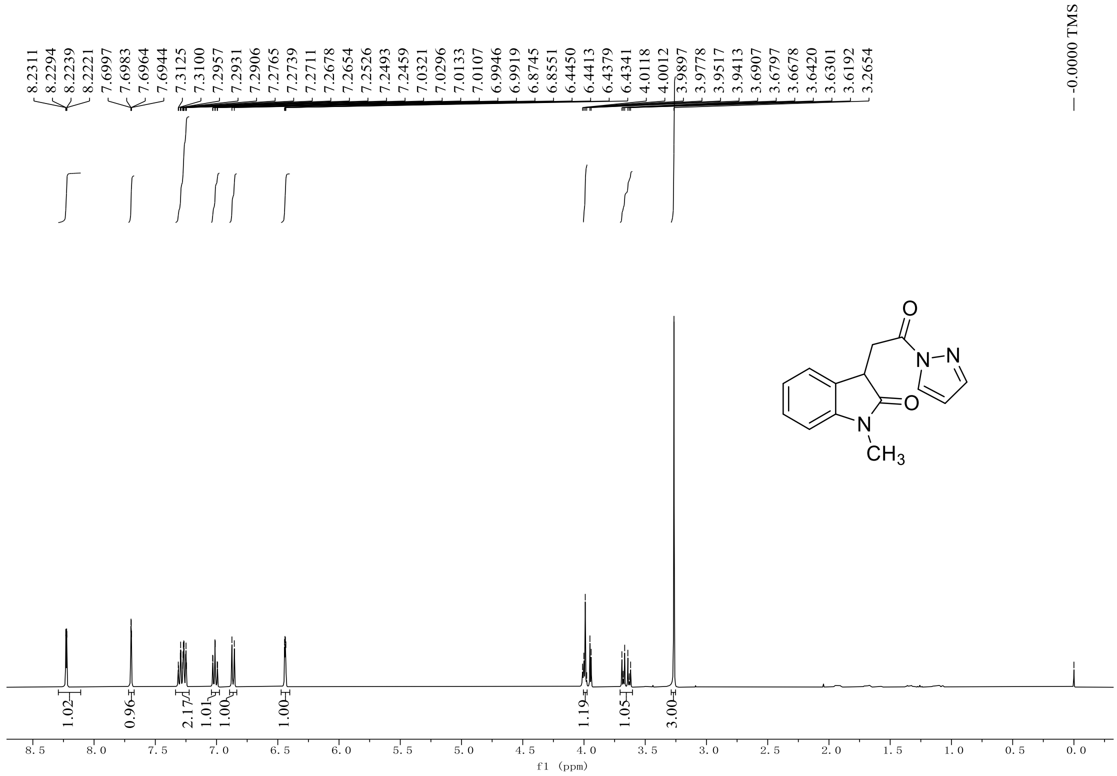


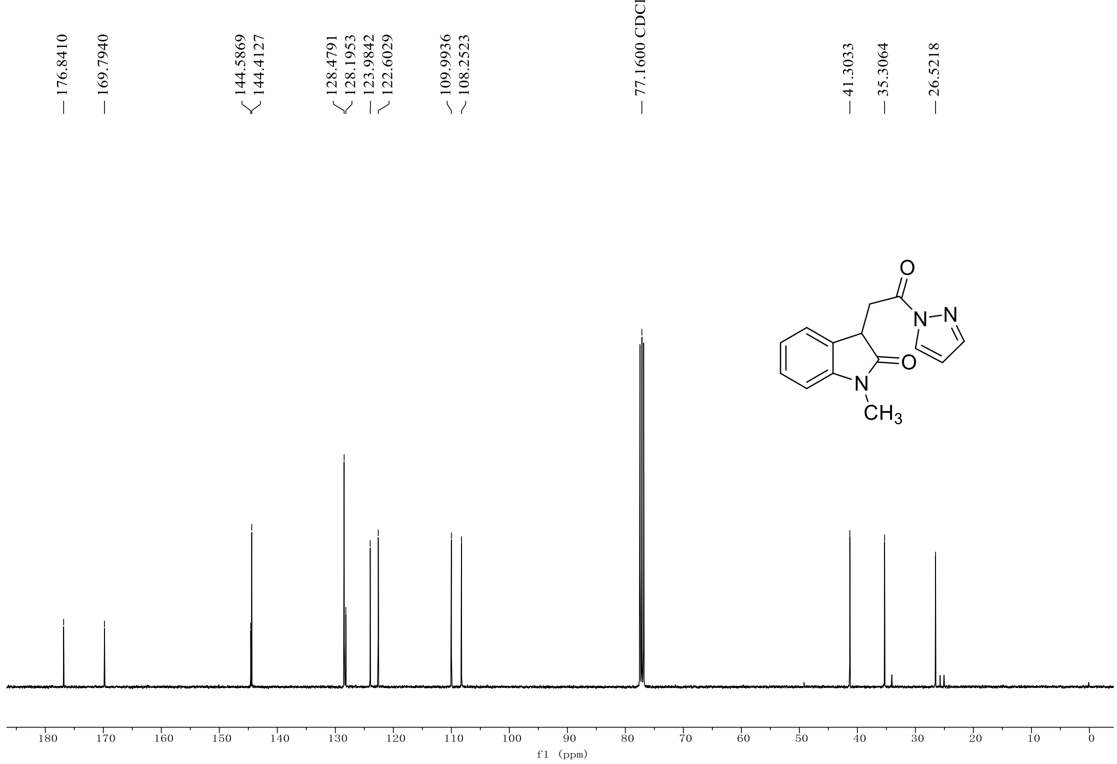
It was purified by flash chromatography (petroleum ether / EtOAc, 3:1) to afford white solid (35.6 mg, 84% yield, separation yield of diastereoisomers, *dr* 4.7:1); m.p. 147.3-147.8 ºC.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.54 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.38 (td, *J* = 7.8, 1.2 Hz, 1H), 7.36 – 7.31 (m, 4H), 7.26 (s, 1H), 7.20 (td, *J* = 7.6, 1.9 Hz, 1H), 7.08 (td, *J* = 7.8, 1.3 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.61 (td, *J* = 7.7, 1.0 Hz, 1H), 6.54 (d, *J* = 7.9 Hz, 1H), 6.51 (dd, *J* = 7.7, 1.2 Hz, 1H), 5.11 (d, *J* = 15.7 Hz, 1H), 4.65 (d, *J* = 15.7 Hz, 1H), 4.29 (d, *J* = 16.7 Hz, 1H), 3.03 (s, 3H), 2.79 (d, *J* = 16.7 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 175.7, 173.4, 173.2, 158.4, 151.6, 144.4, 138.5, 131.6, 130.2, 128.9, 127.8, 127.1, 127.0, 125.5, 124.8, 110.1, 109.9, 108.9, 85.1, 56.2, 49.4, 43.9, 36.7, 34.0.

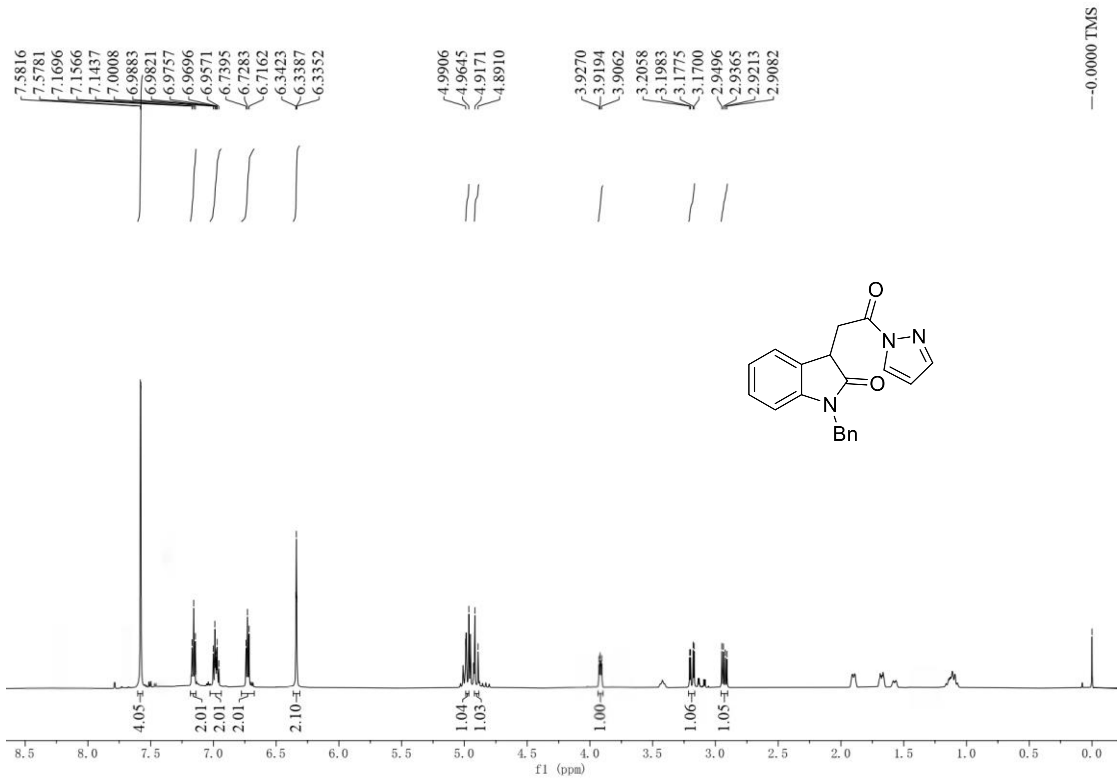
HRMS (ESI) m/z calcd for $C_{26}H_{20}N_2O_4Na^+$ $[M+Na]^+$447.1315, found 447.

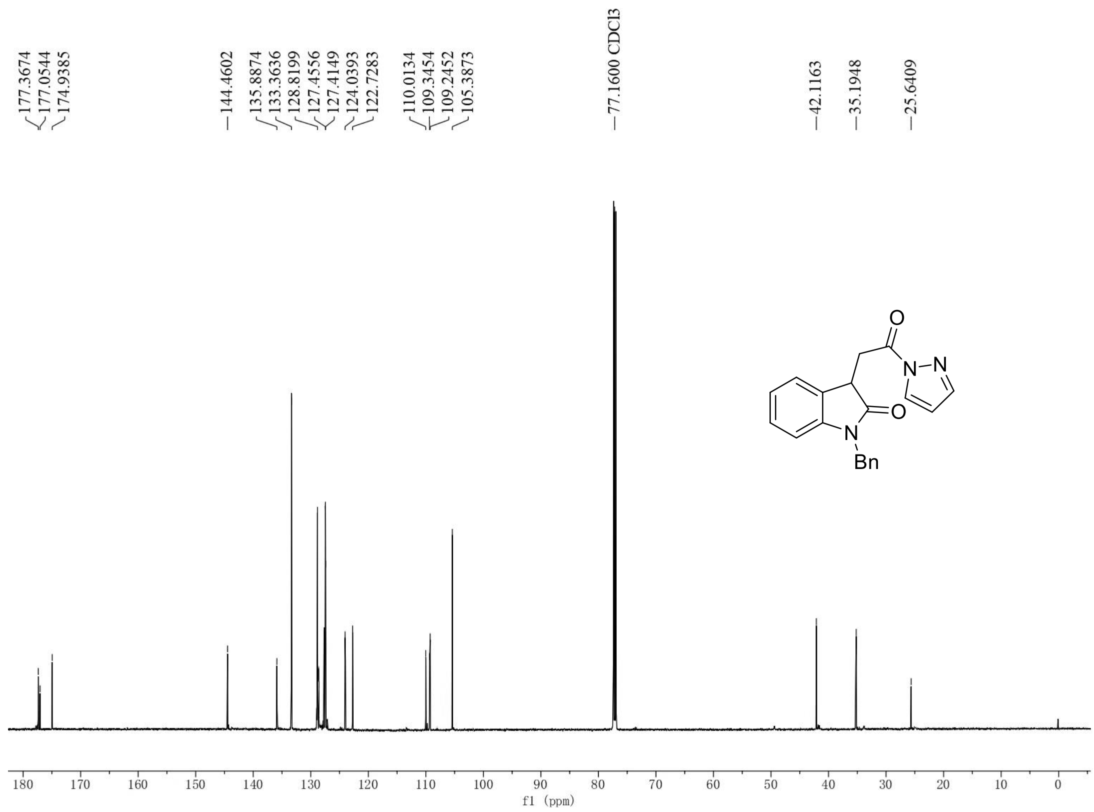
^{1}H NMR, ^{13}C NMR spectra of 1a



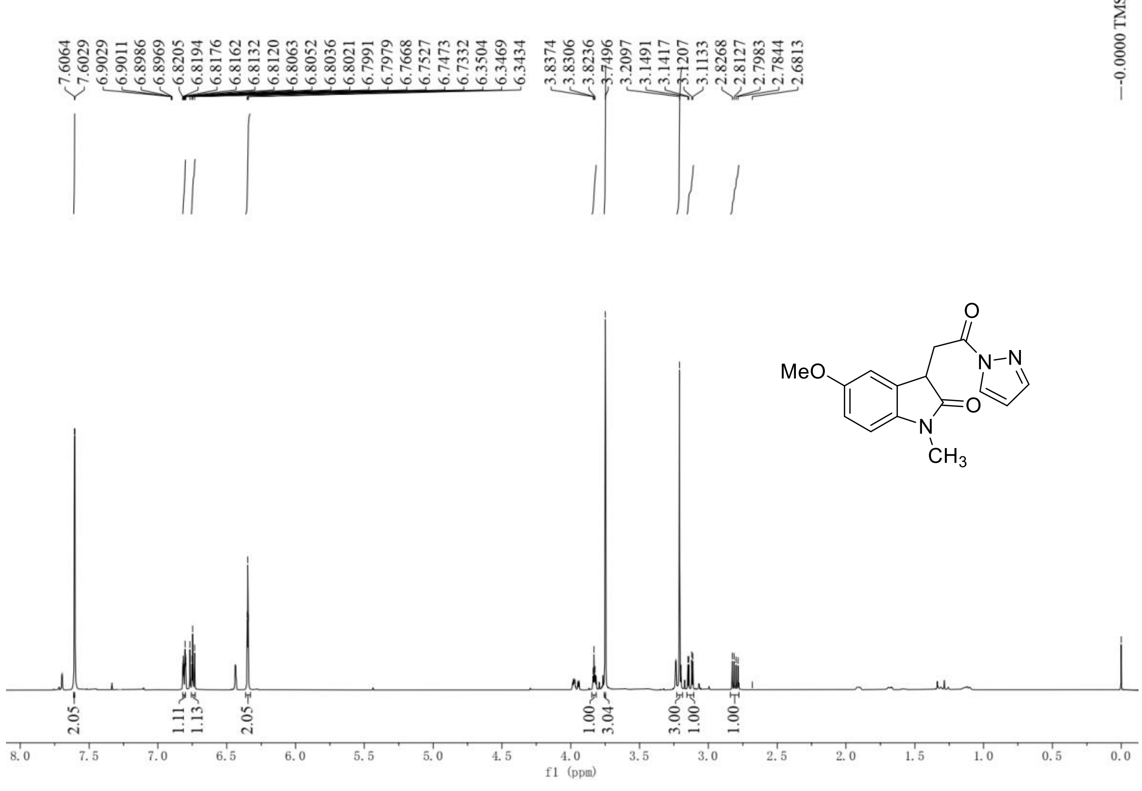


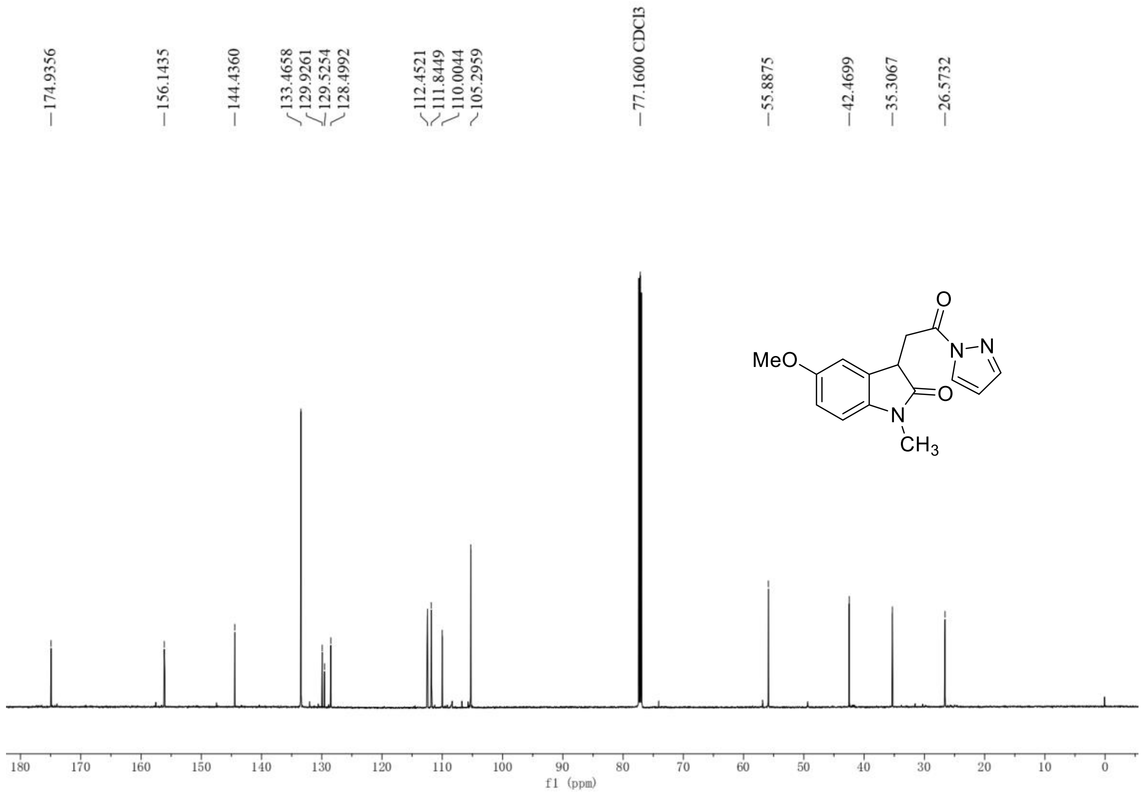
^{1}H NMR, ^{13}C NMR spectra of 1b



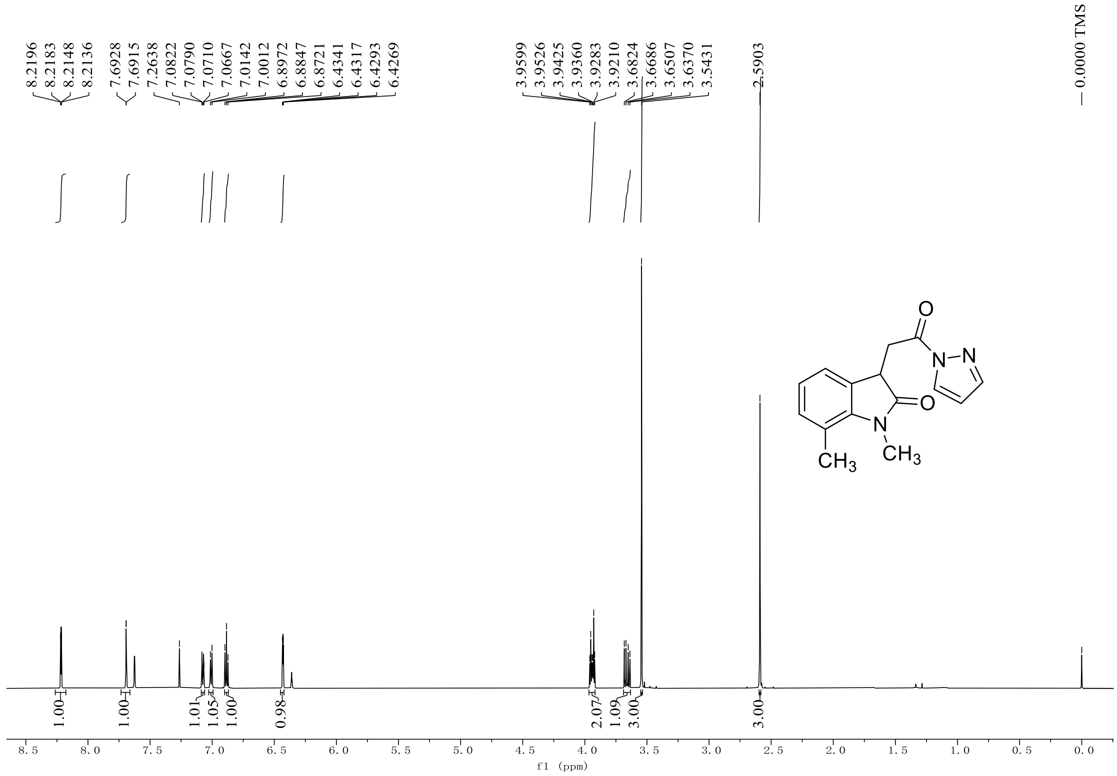


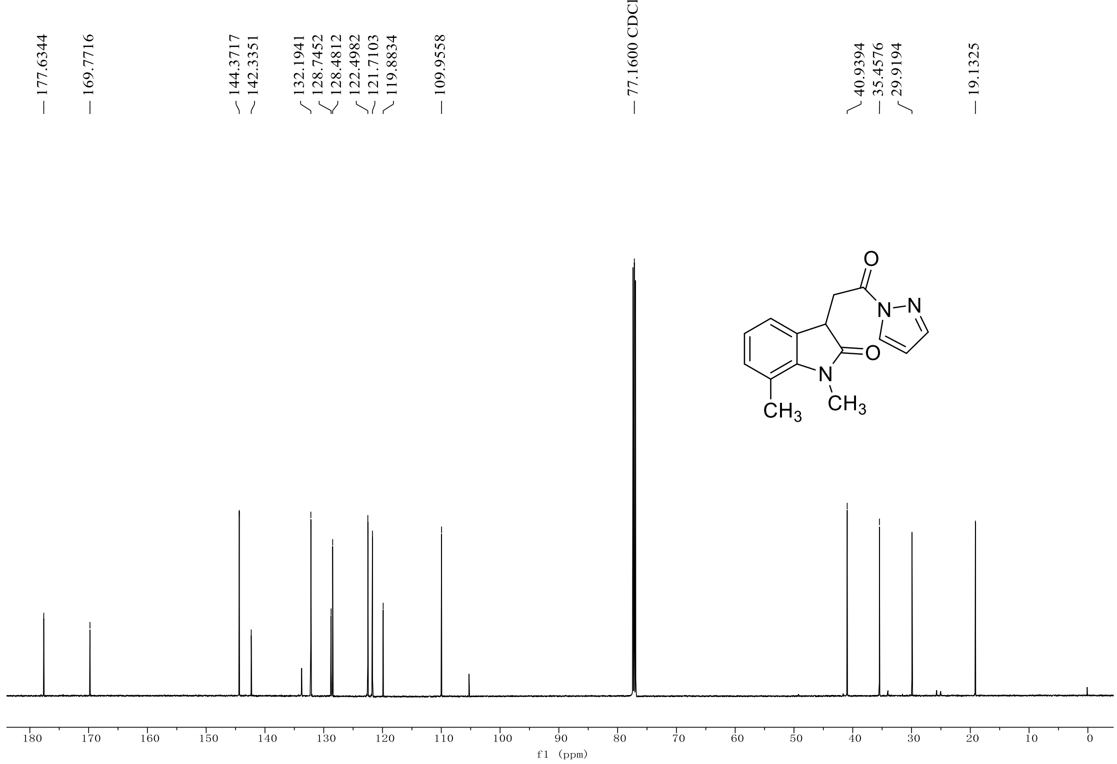
^{1}H NMR, ^{13}C NMR spectra of 1d



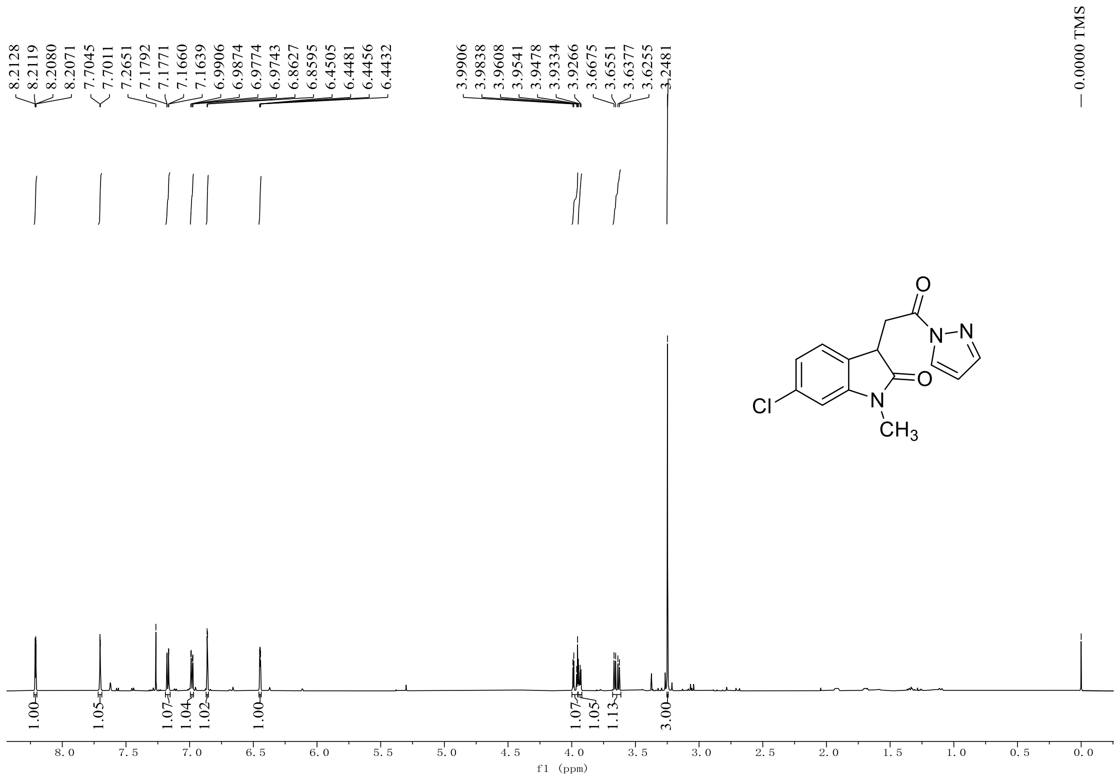


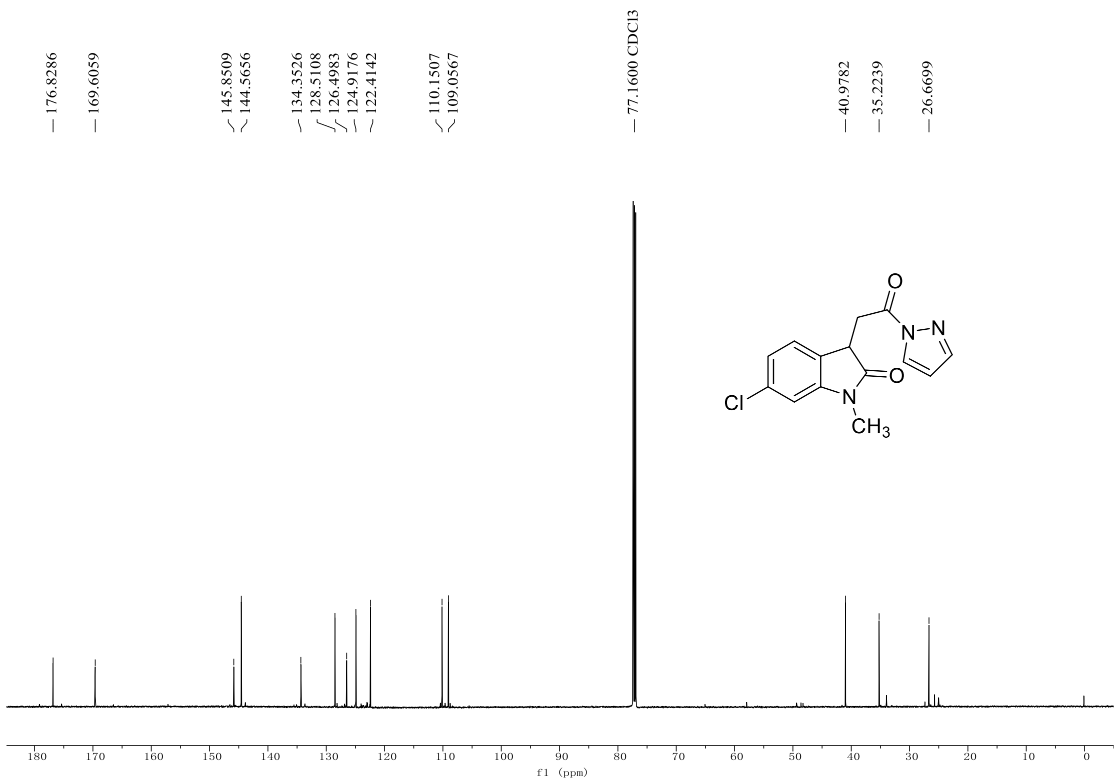
^{1}H NMR, ^{13}C NMR spectra of 1e



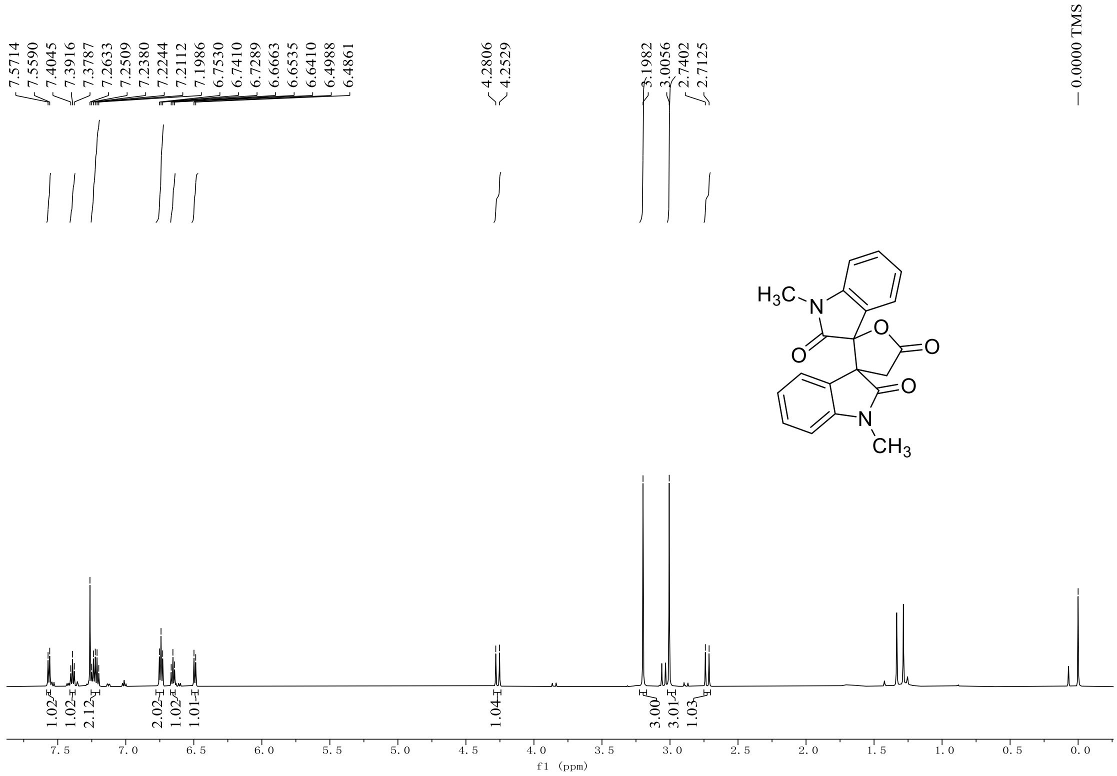


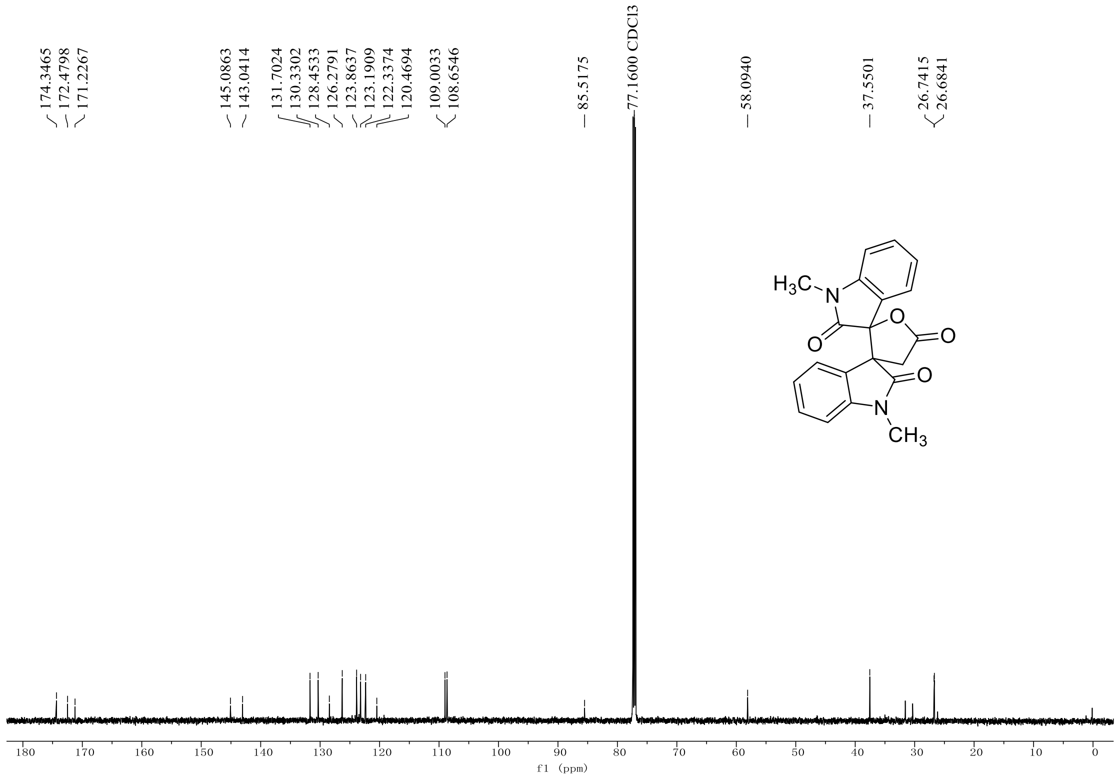
^{1}H NMR, ^{13}C NMR spectra of 1f



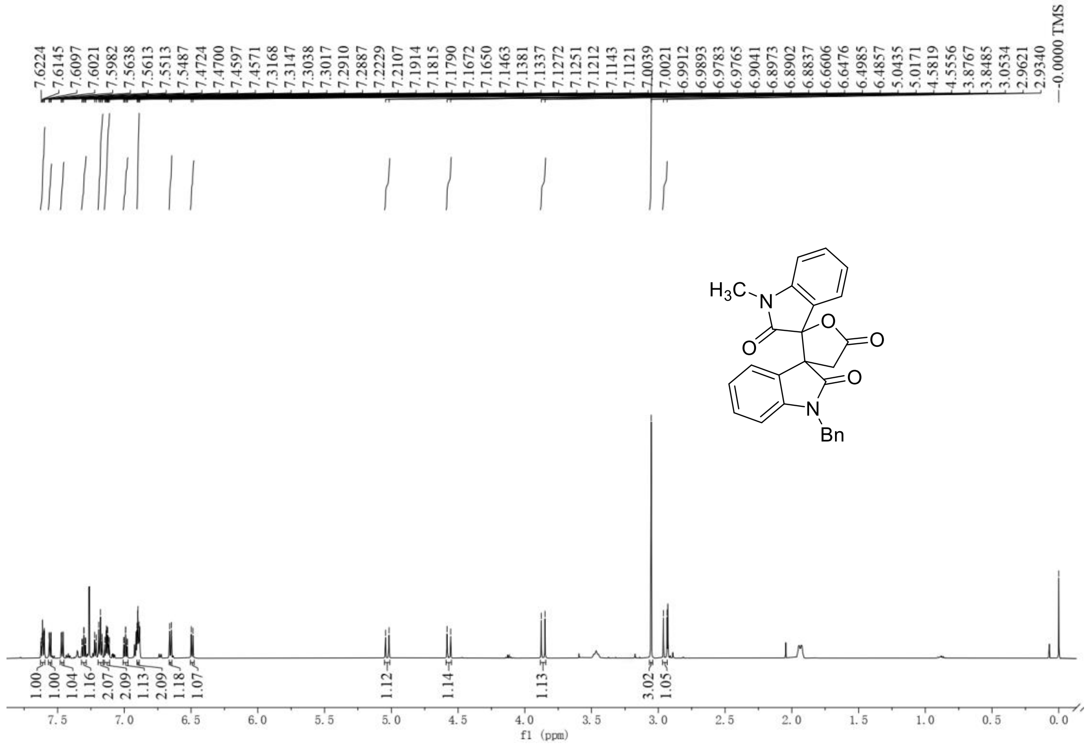


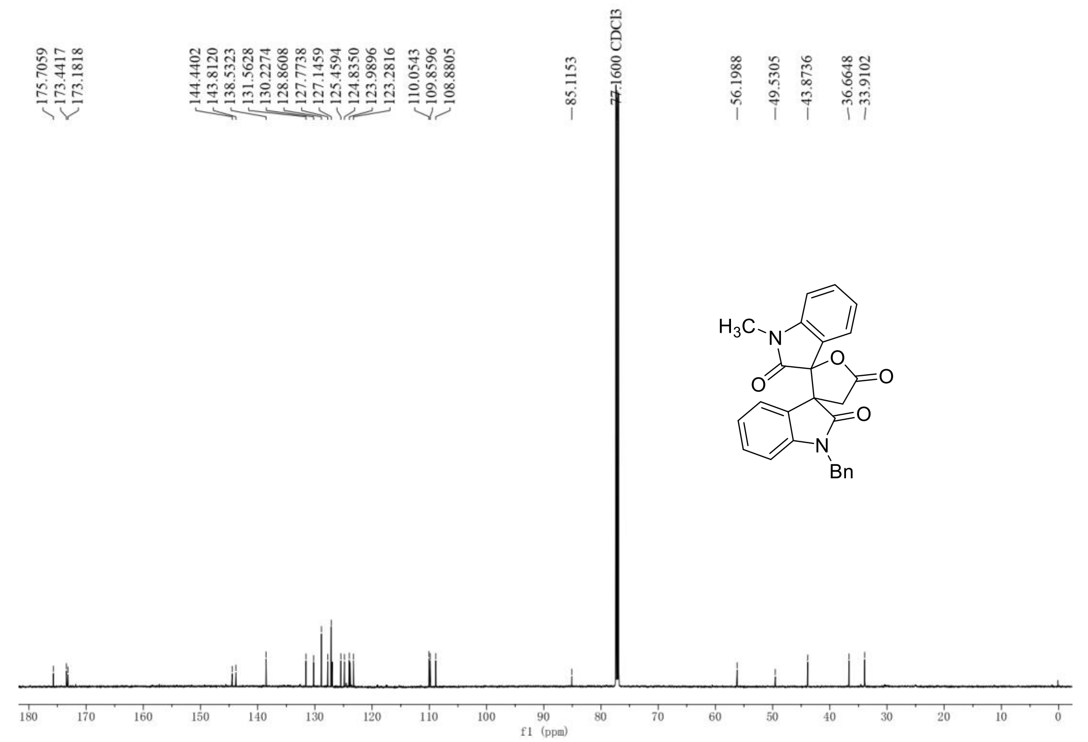
^{1}H NMR, ^{13}C NMR spectra of 3a



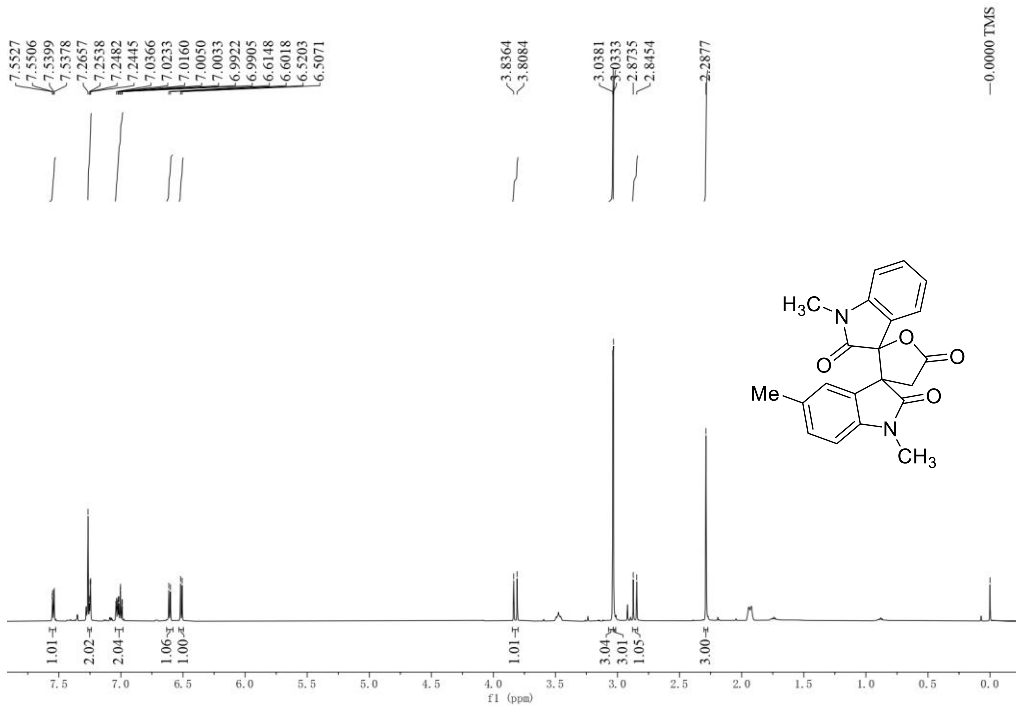


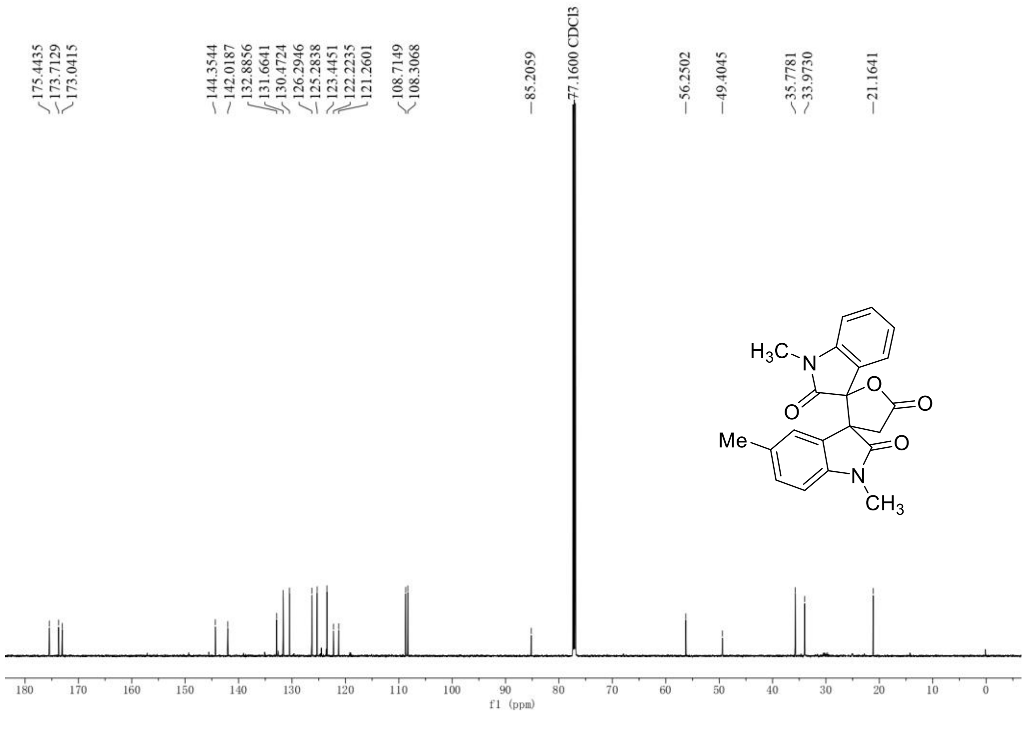
^{1}H NMR, ^{13}C NMR spectra of 3b



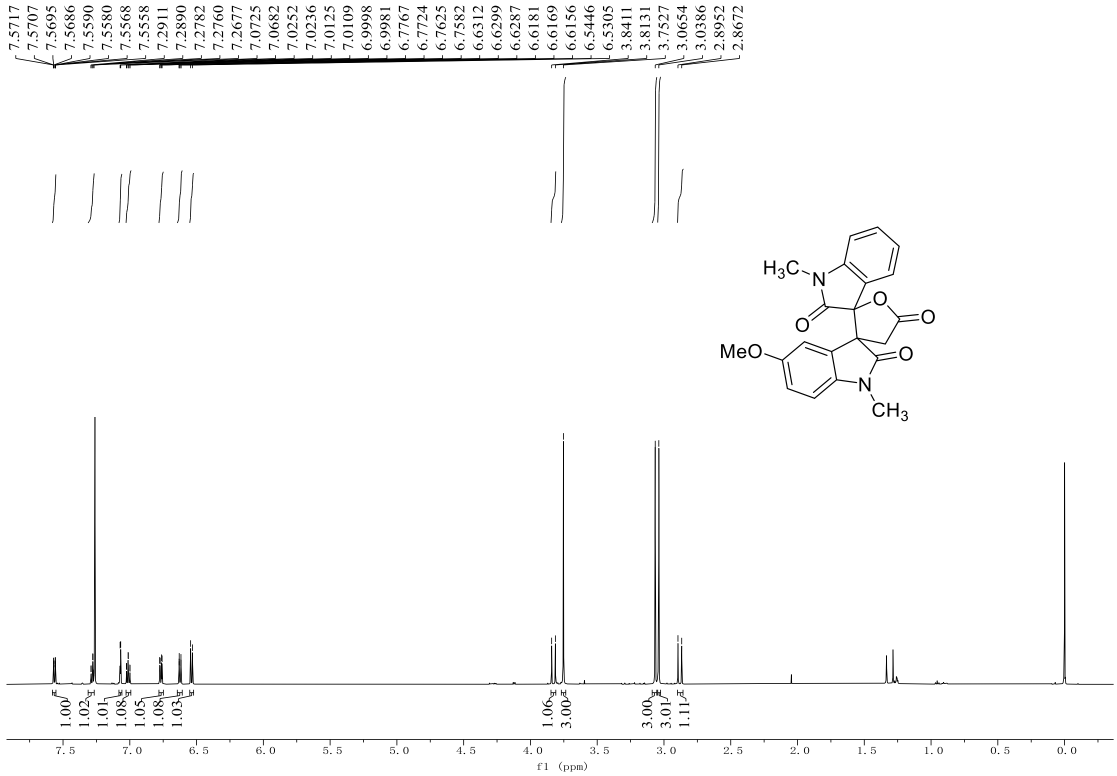


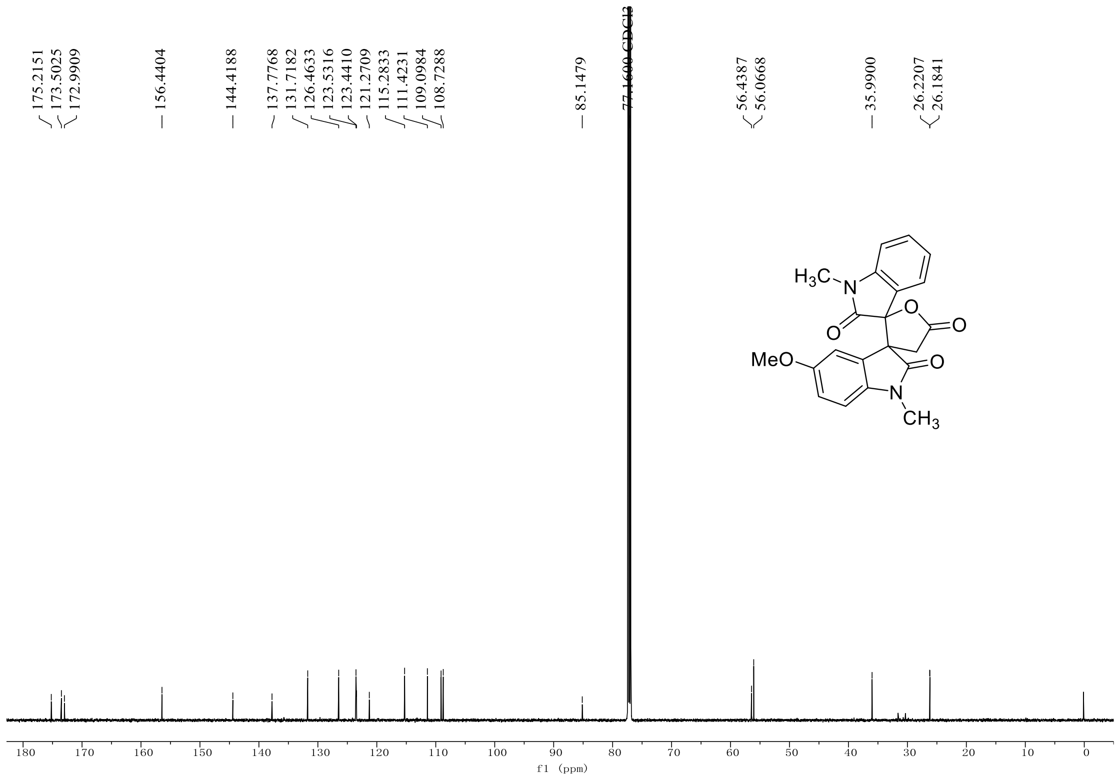
[1]H NMR, [13]C NMR spectra of 3c



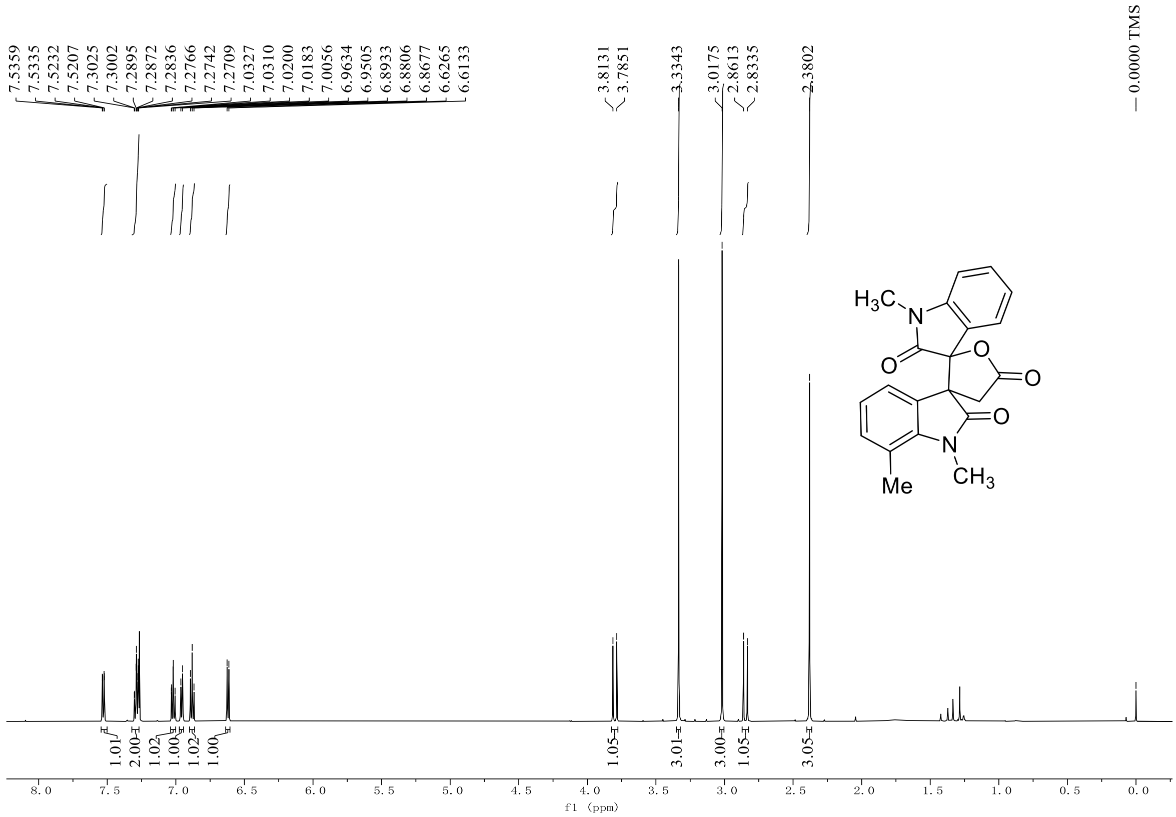


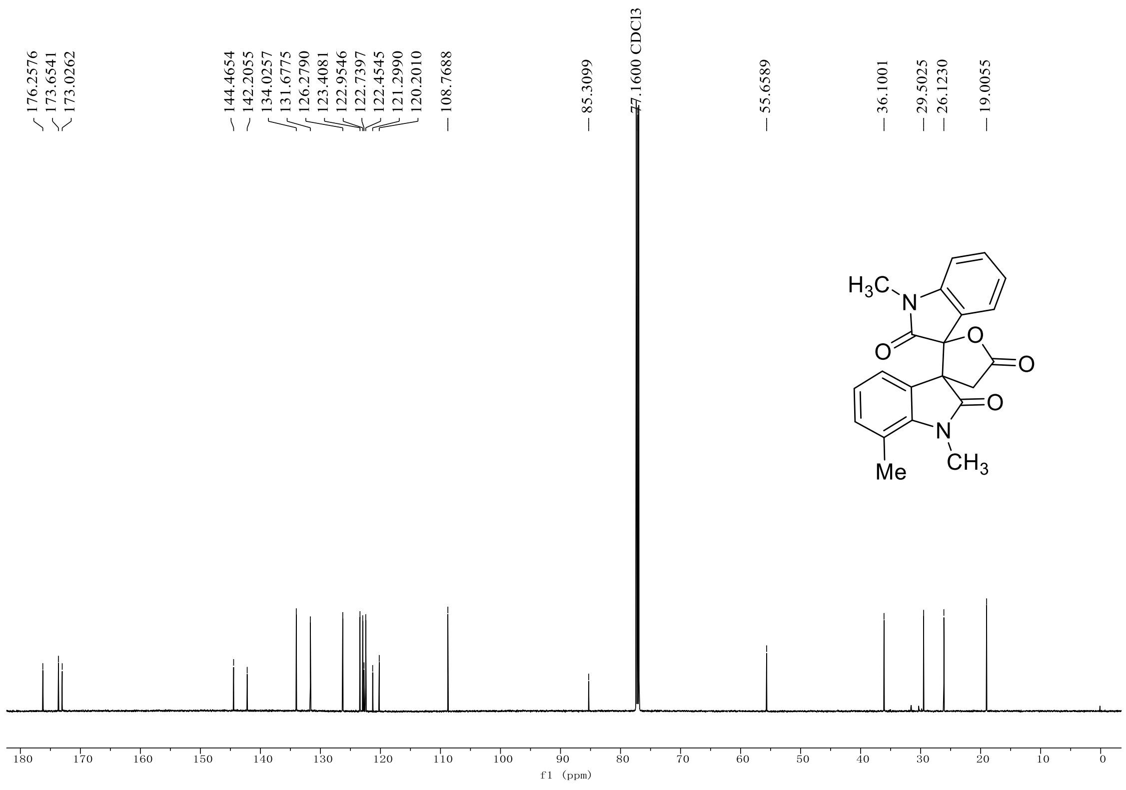
^{1}H NMR, ^{13}C NMR spectra of 3d



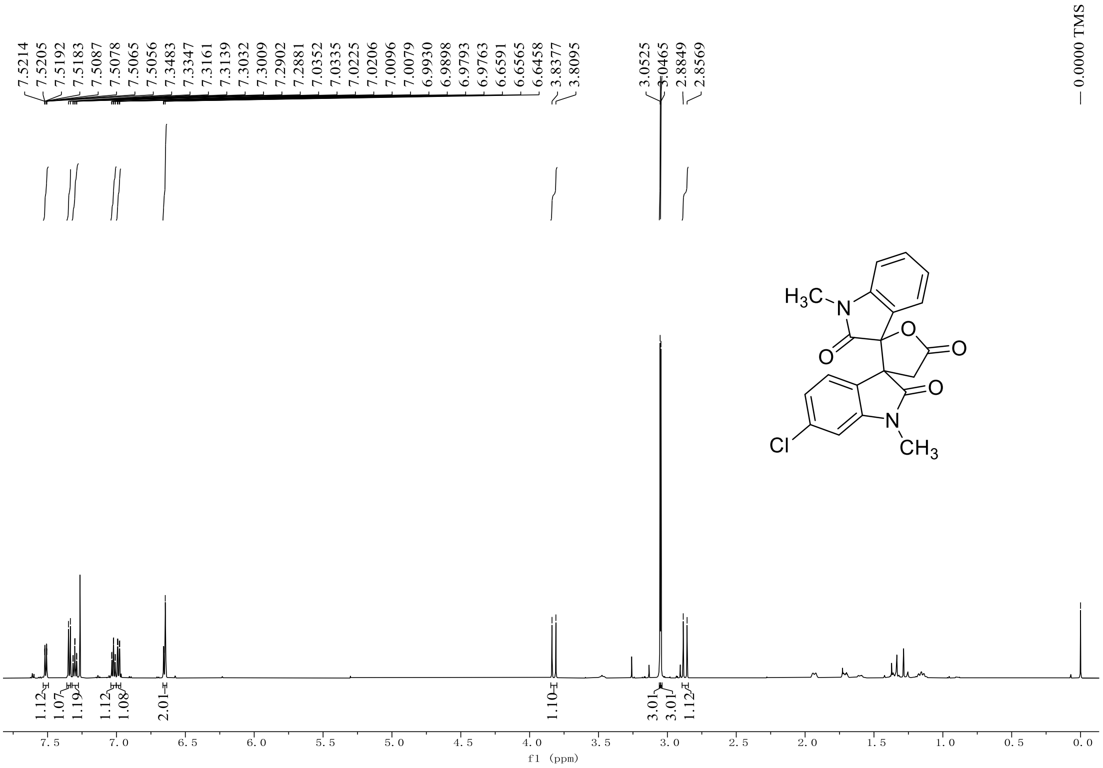


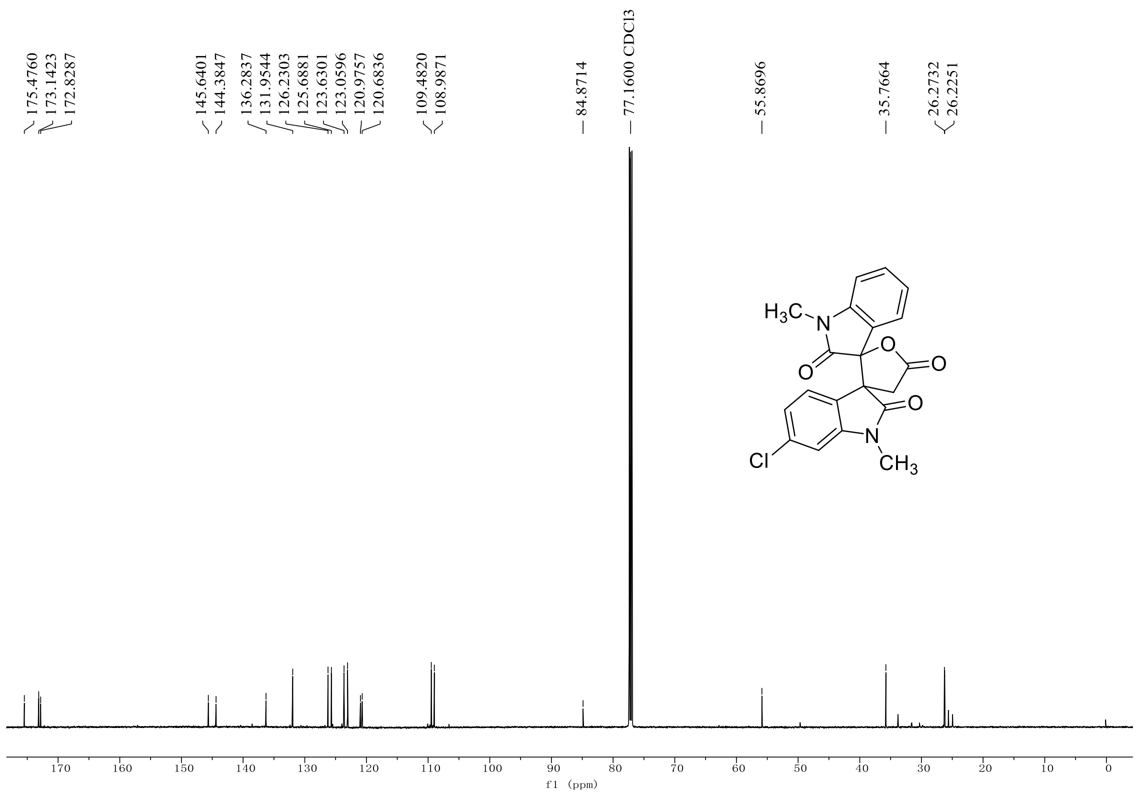
^{1}H NMR, ^{13}C NMR spectra of 3e



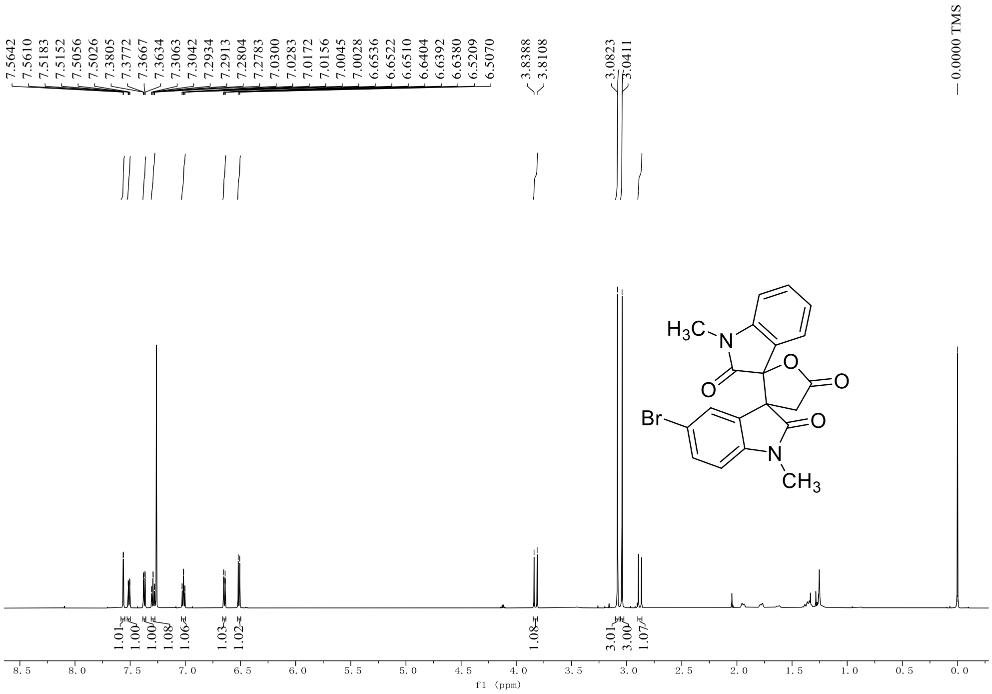


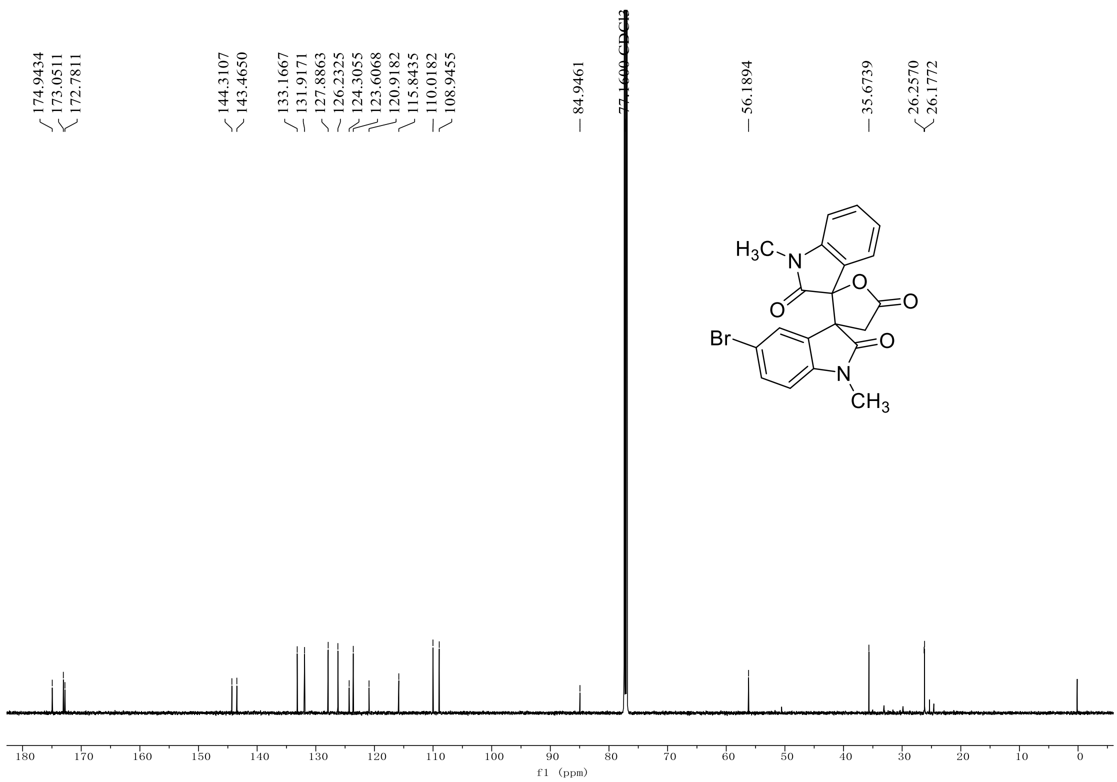
^{1}H NMR, ^{13}C NMR spectra of 3f



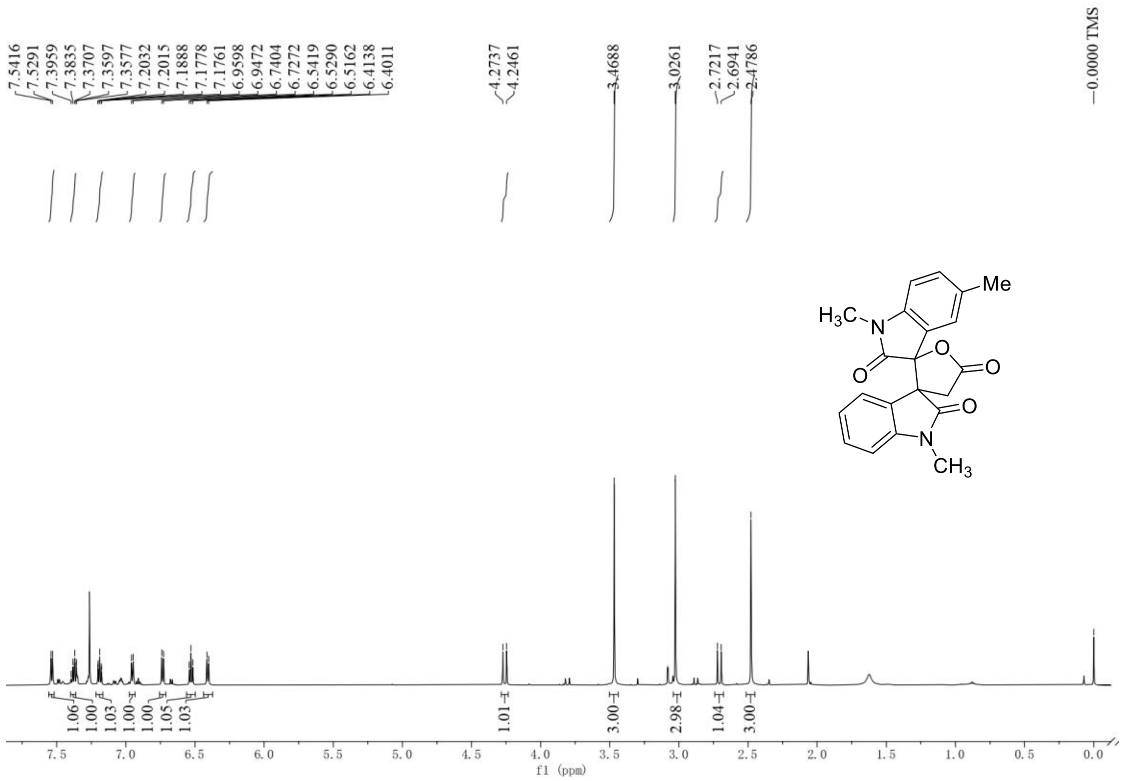


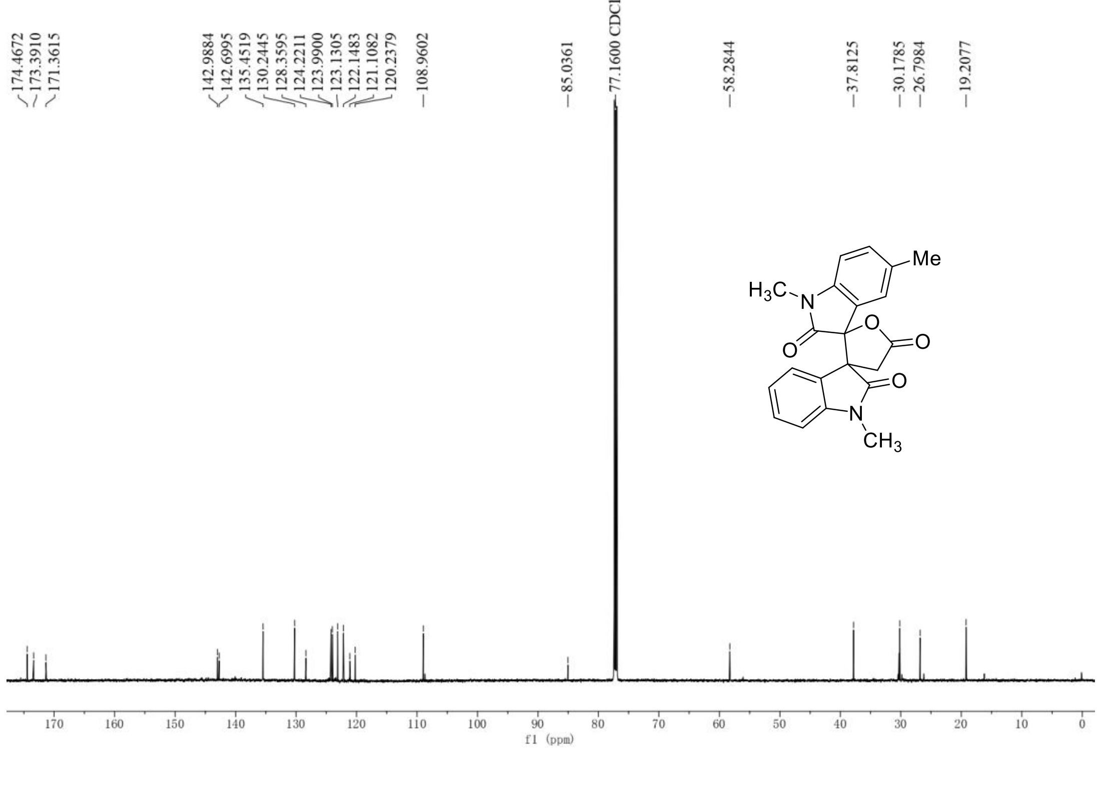
^{1}H NMR, ^{13}C NMR spectra of 3g



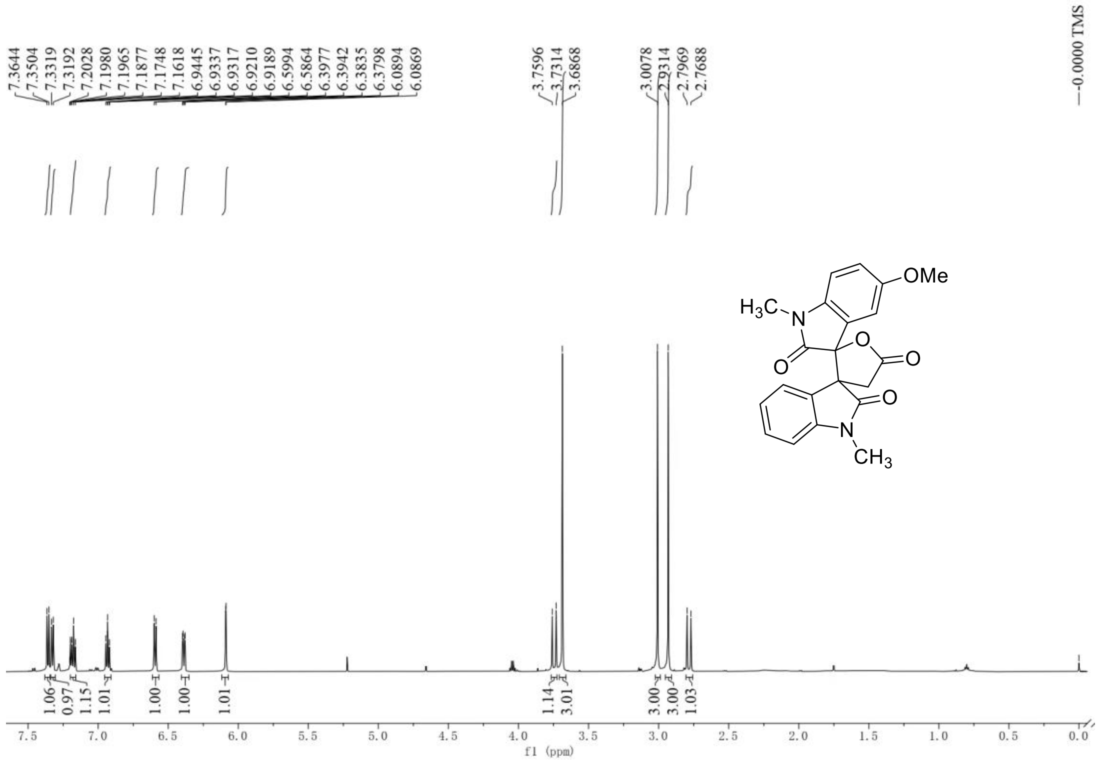


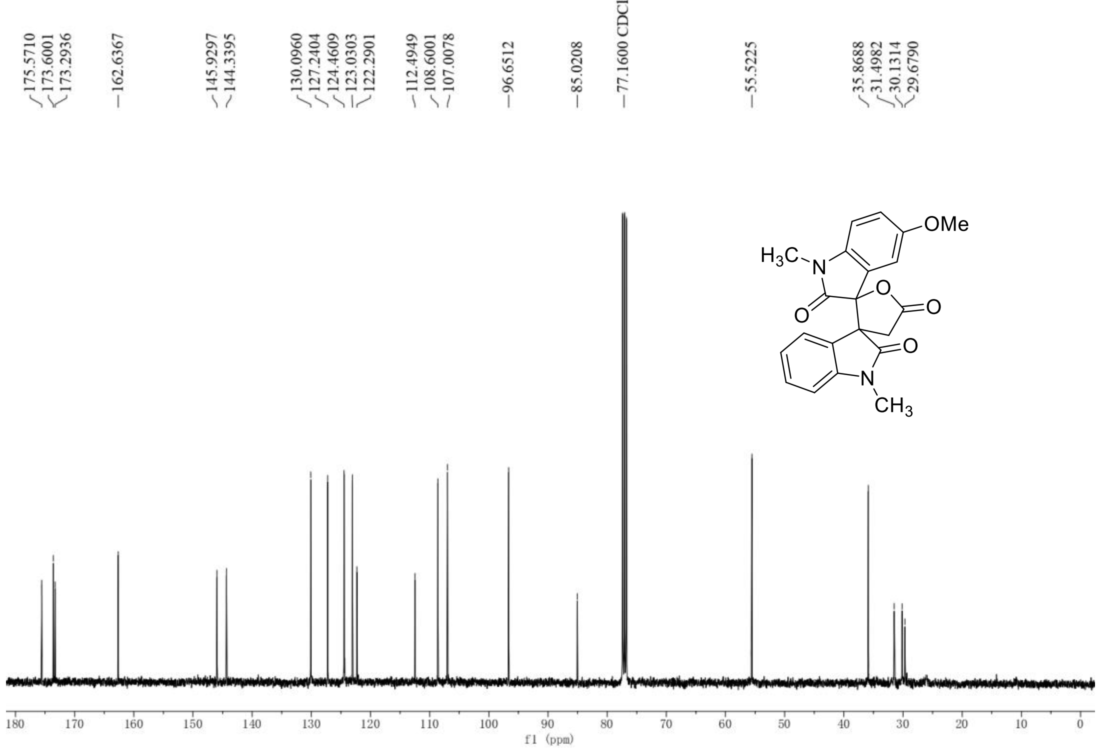
^{1}H NMR, ^{13}C NMR spectra of 3h



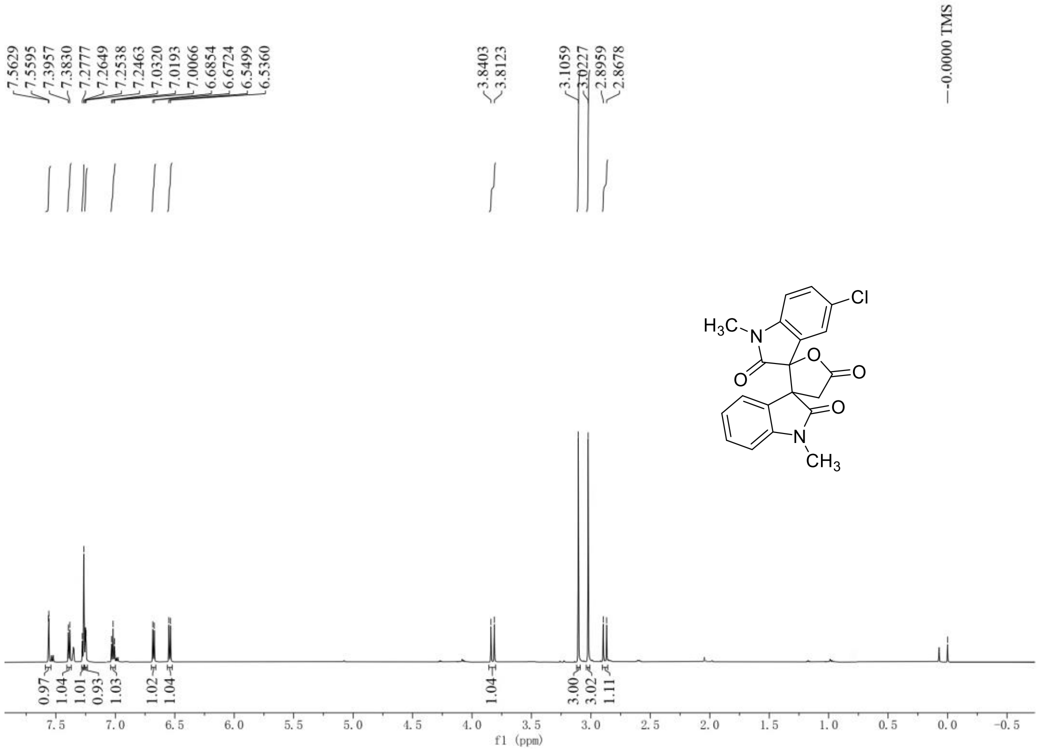


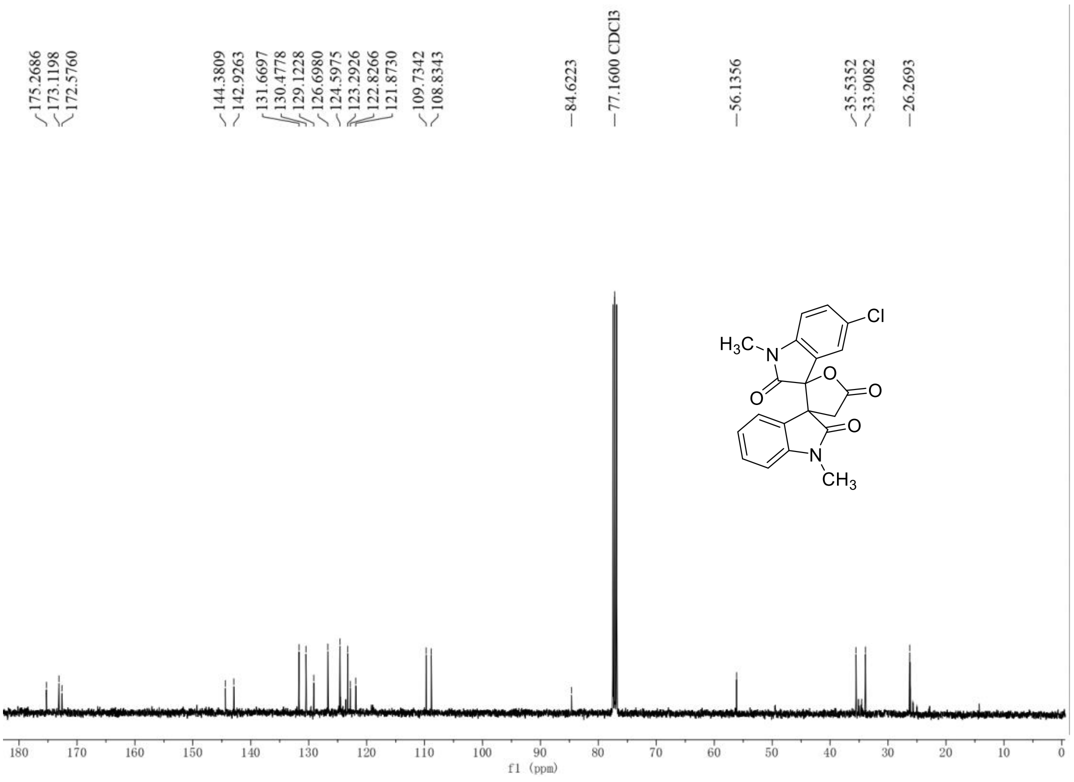
^1H NMR, ^{13}C NMR spectra of 3i



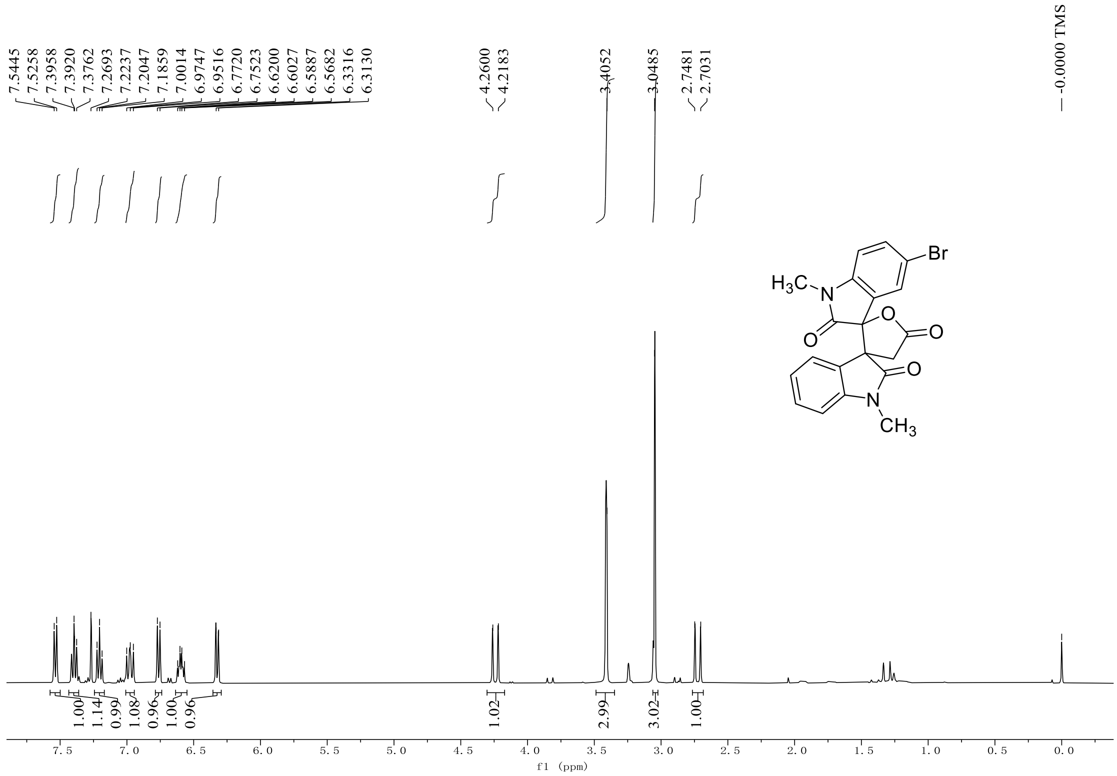


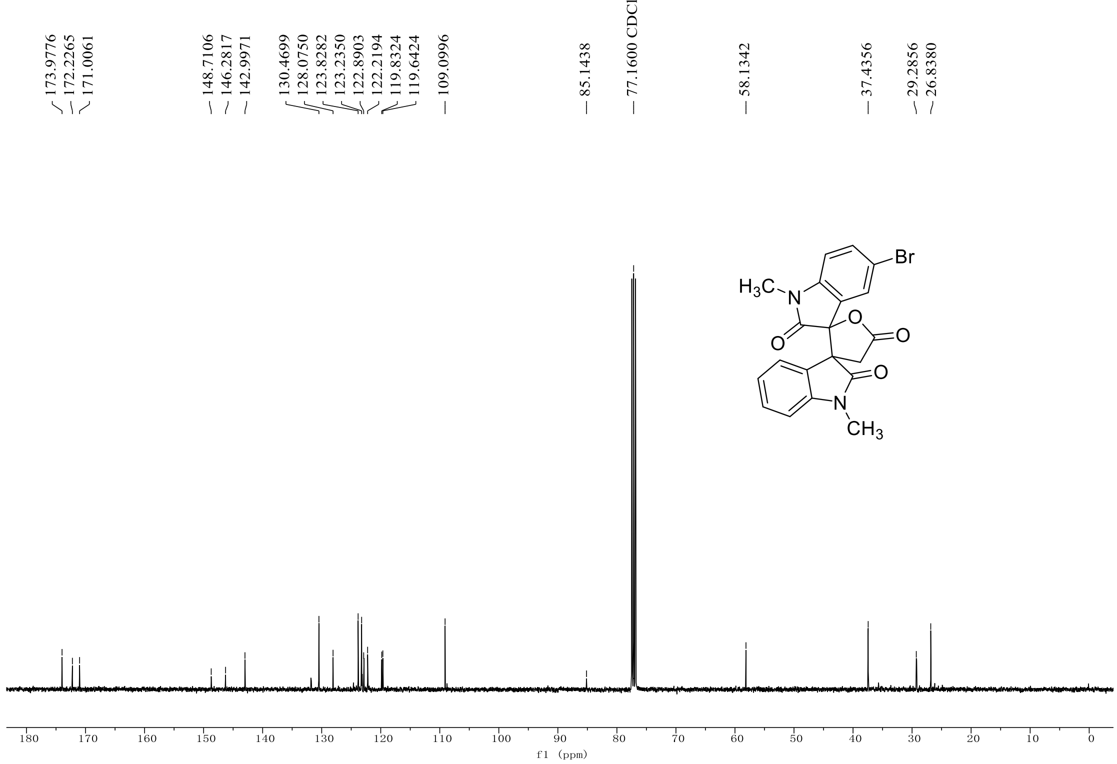
^{1}H NMR, ^{13}C NMR spectra of 3j



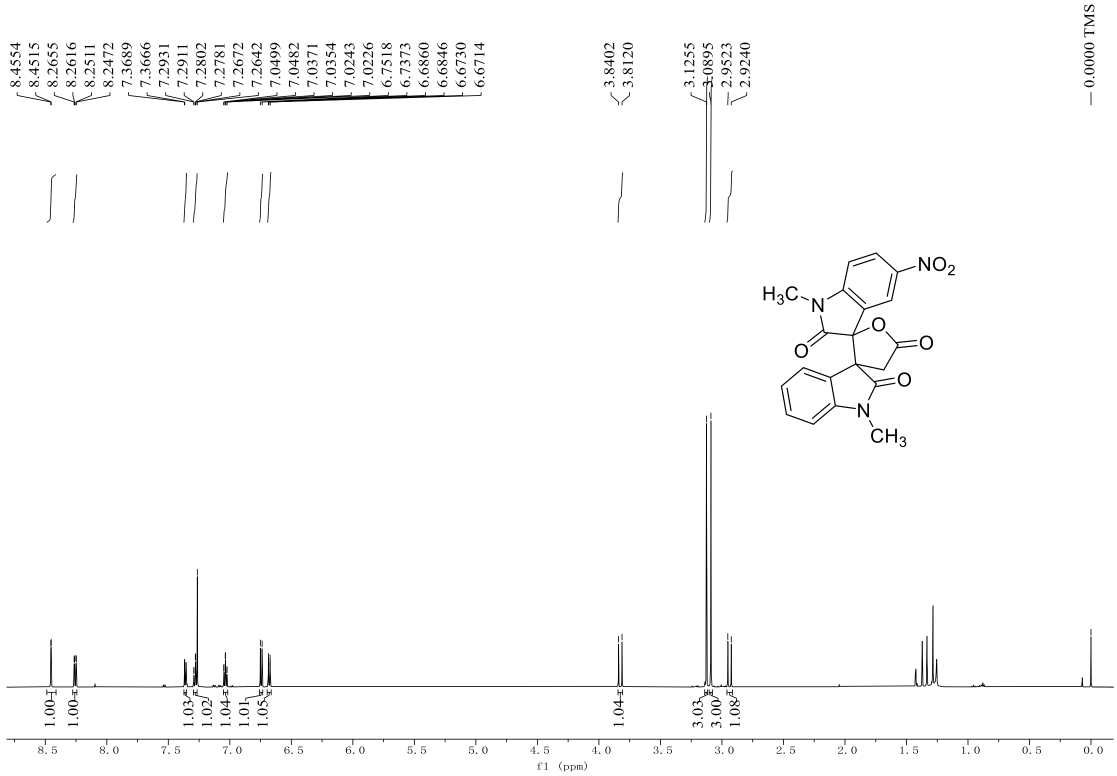


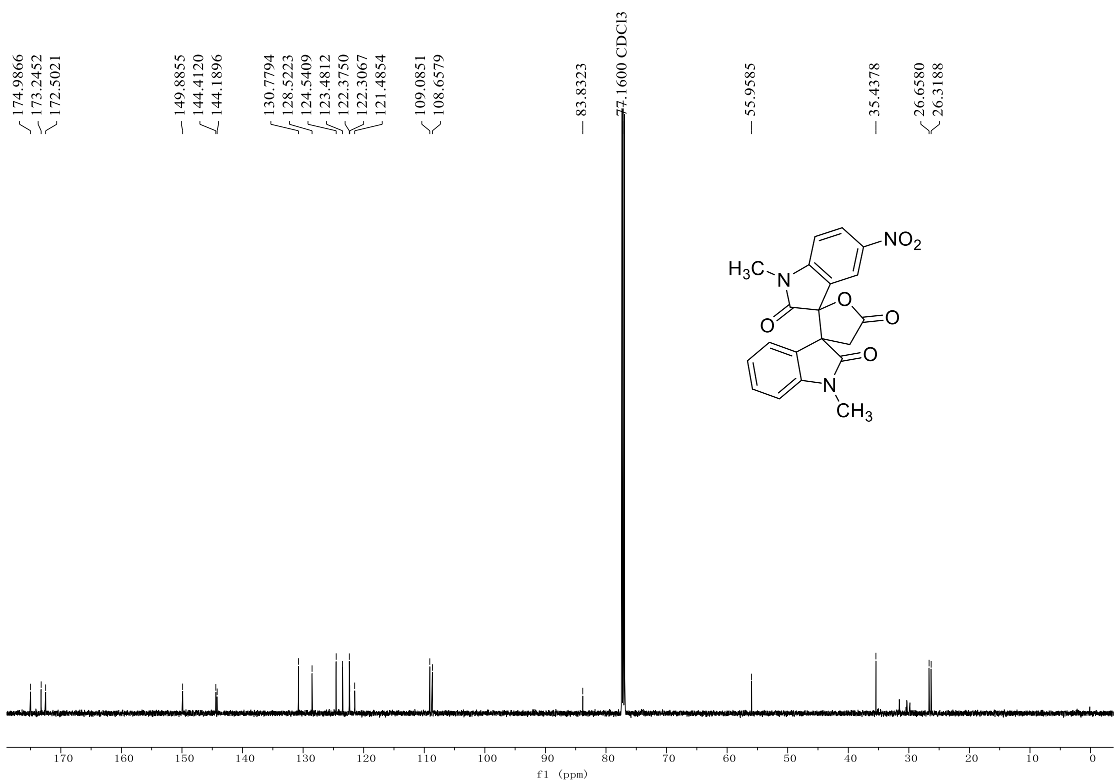
^{1}H NMR, ^{13}C NMR spectra of 3k



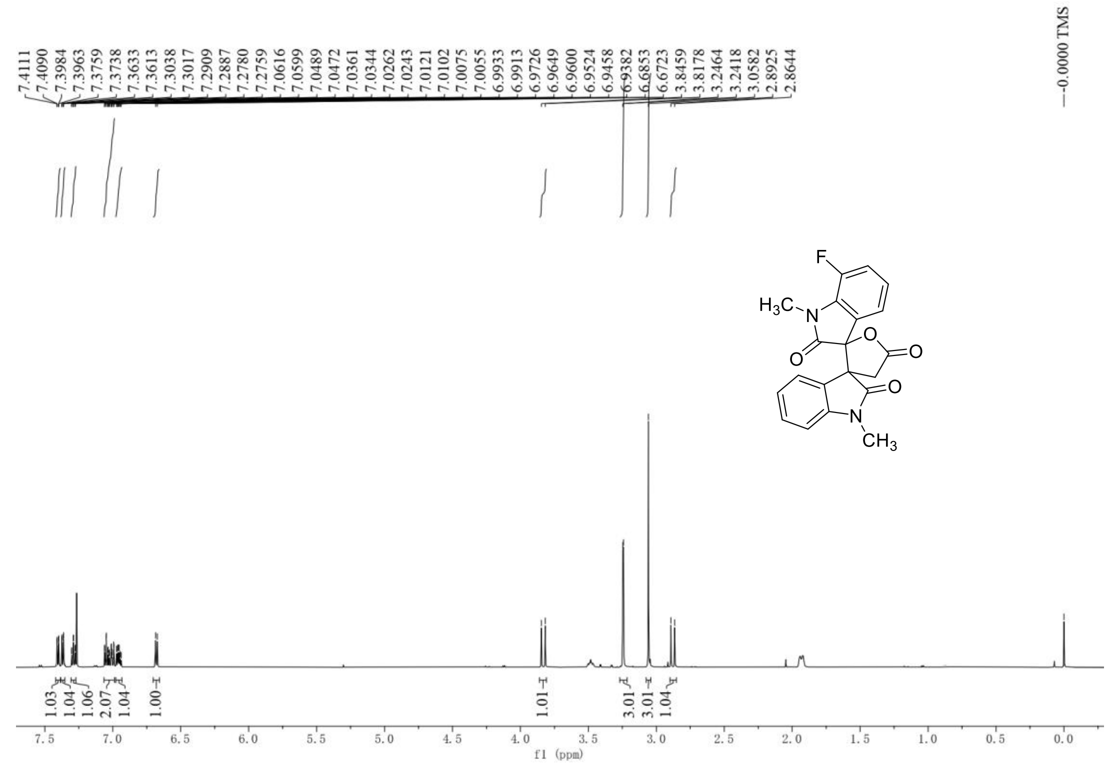


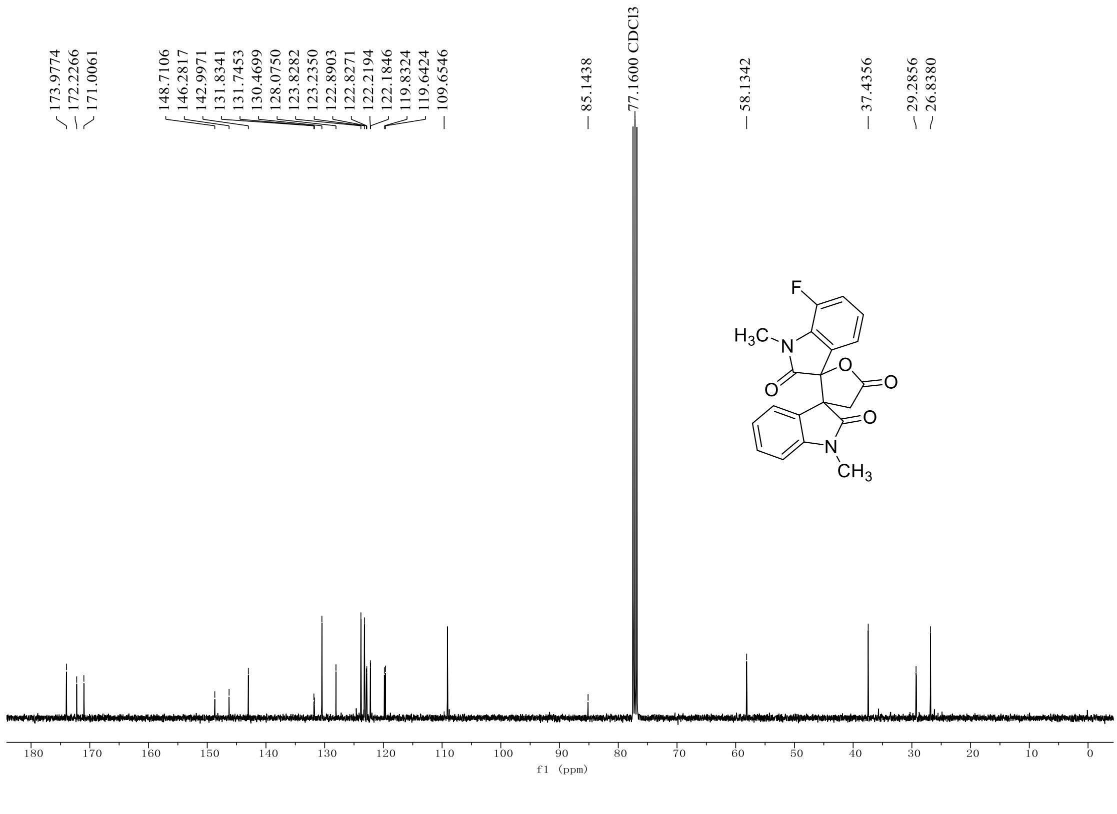
^{1}H NMR, ^{13}C NMR spectra of 3l



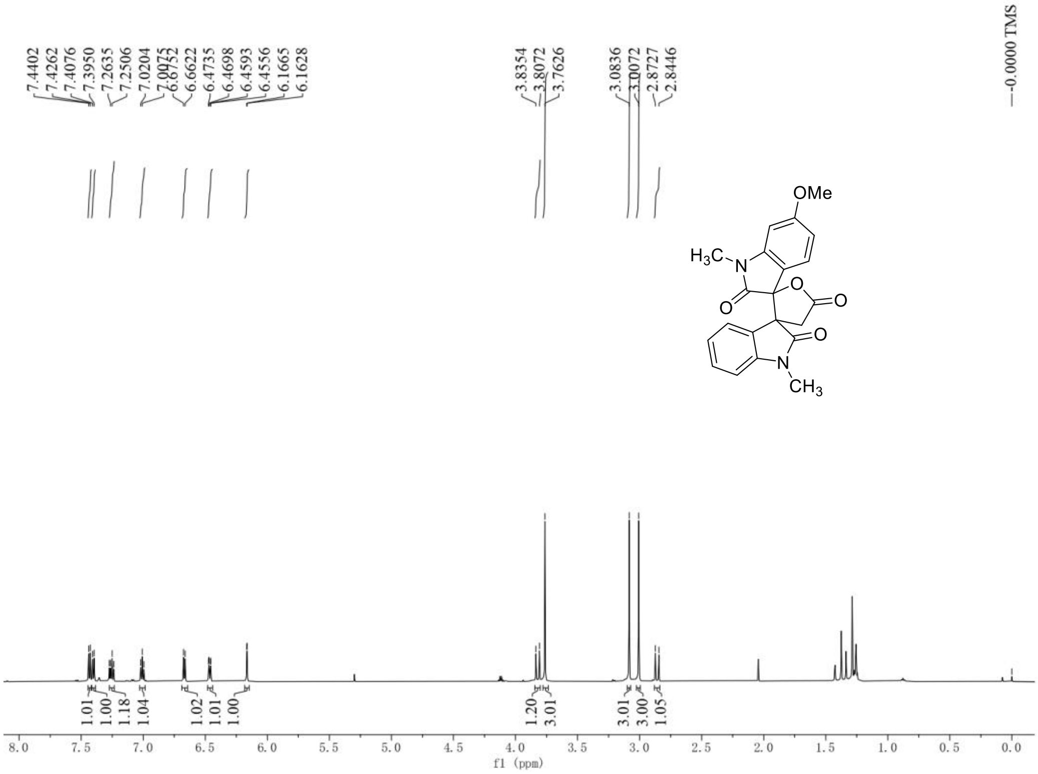


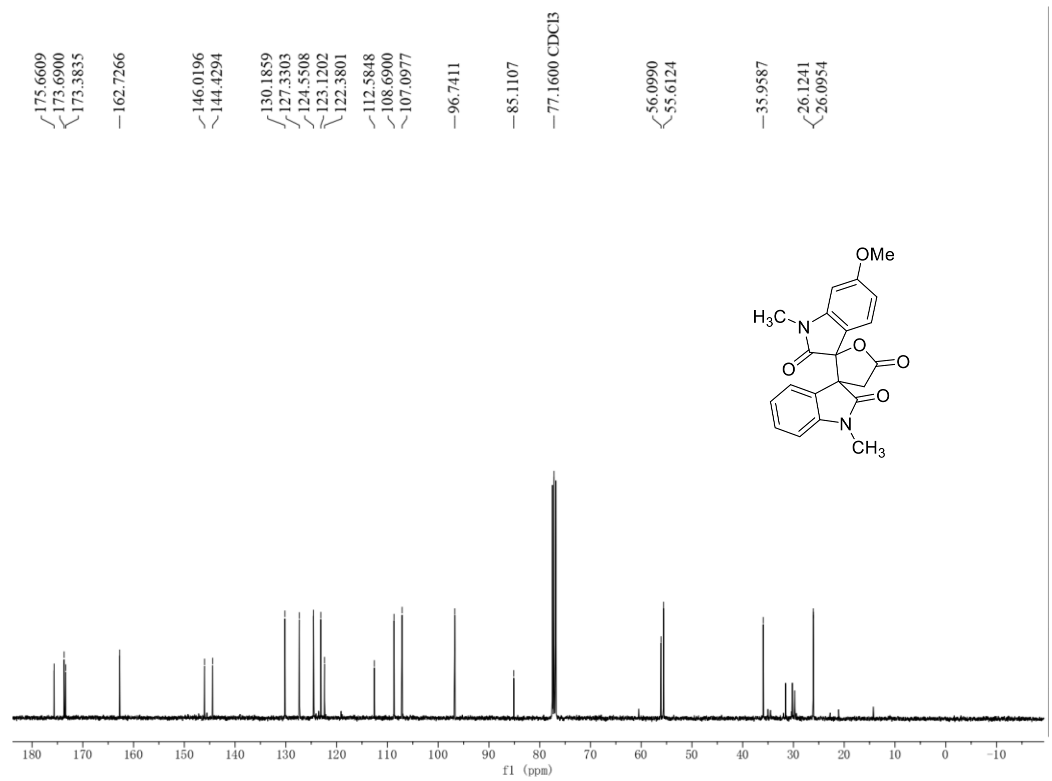
^{1}H NMR, ^{13}C NMR spectra of 3m



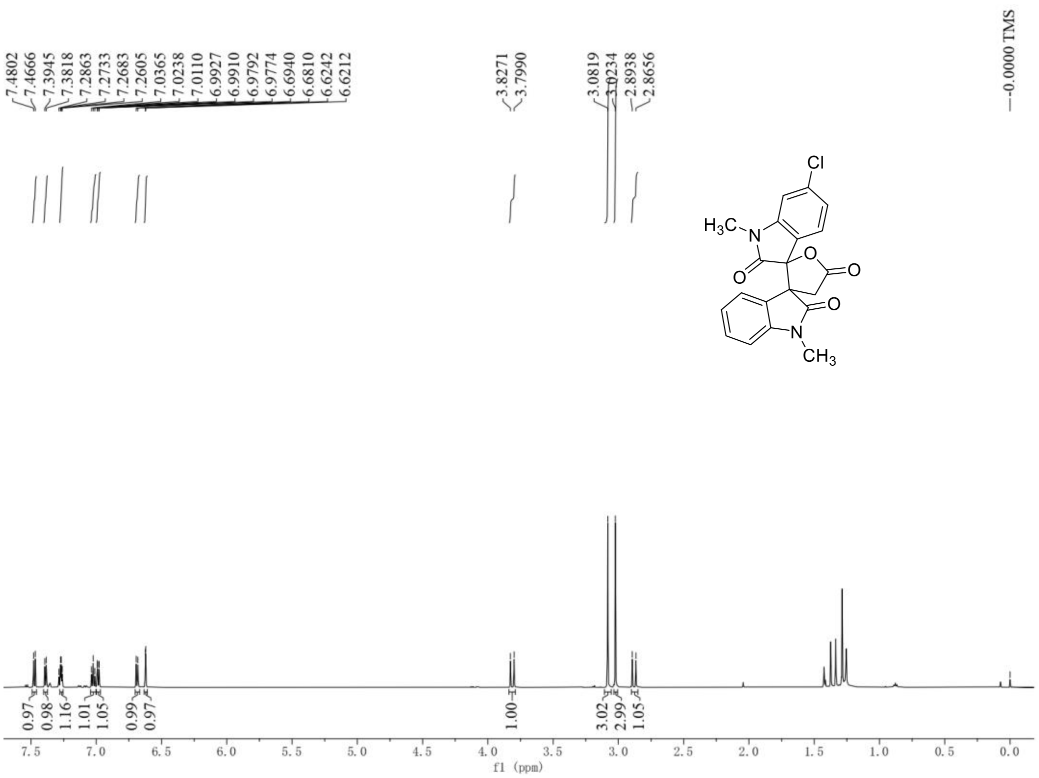


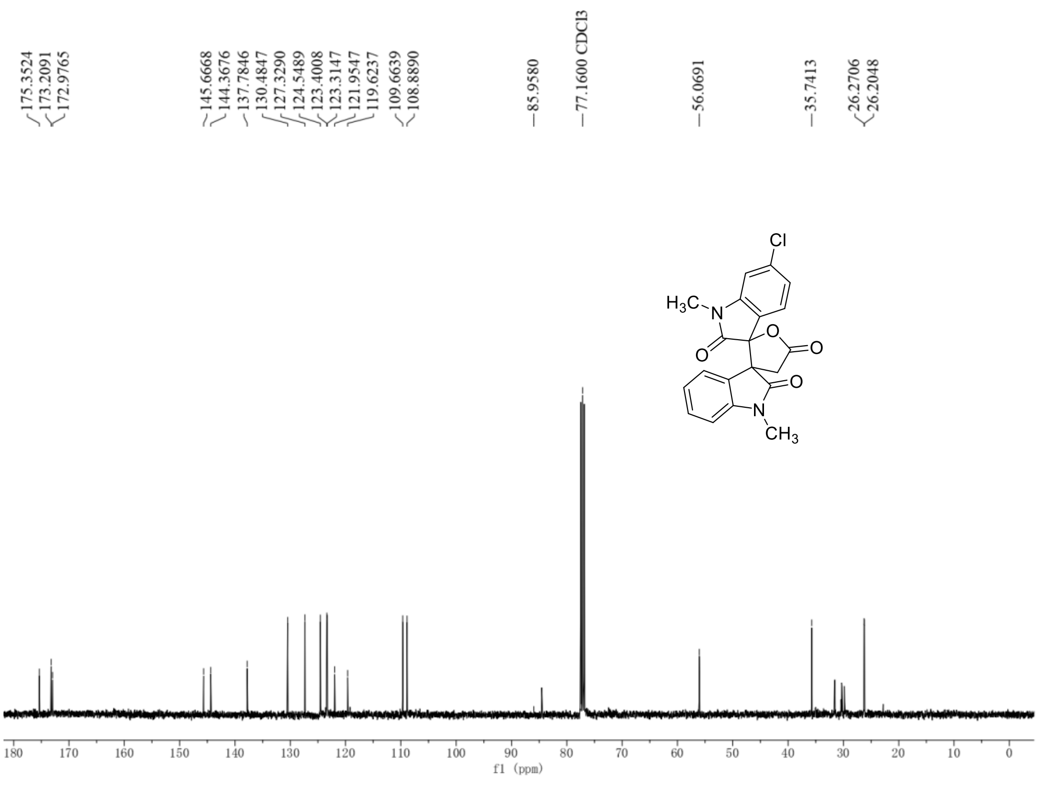
^{1}H NMR, ^{13}C NMR spectra of 3n



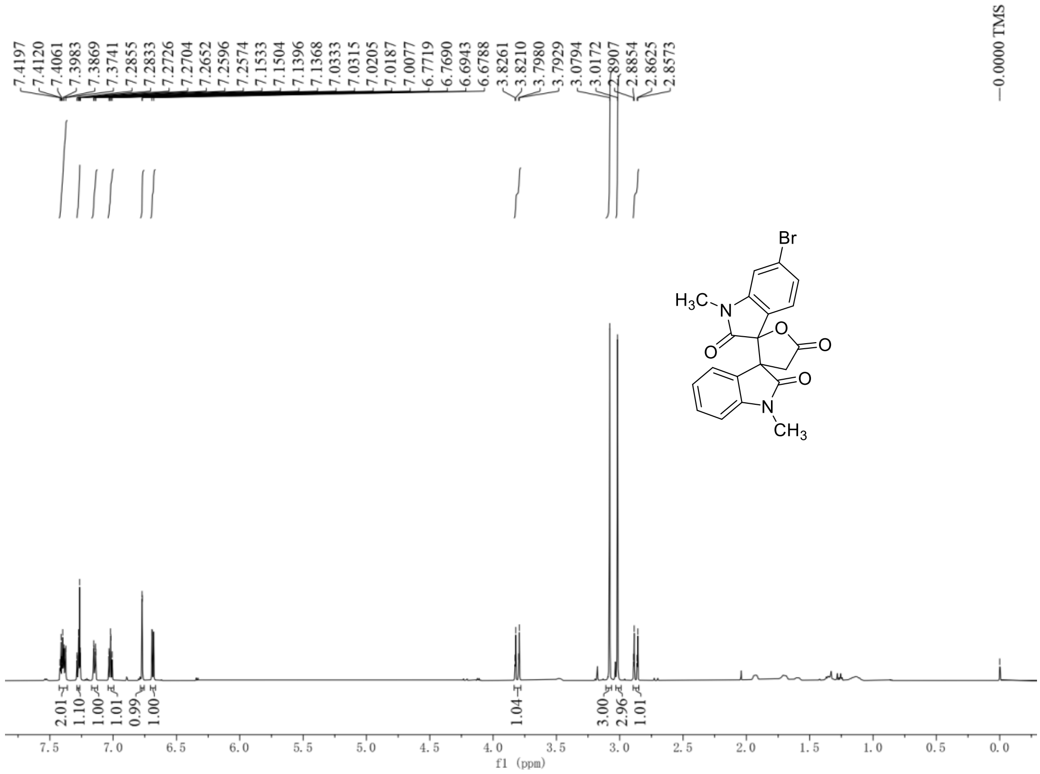


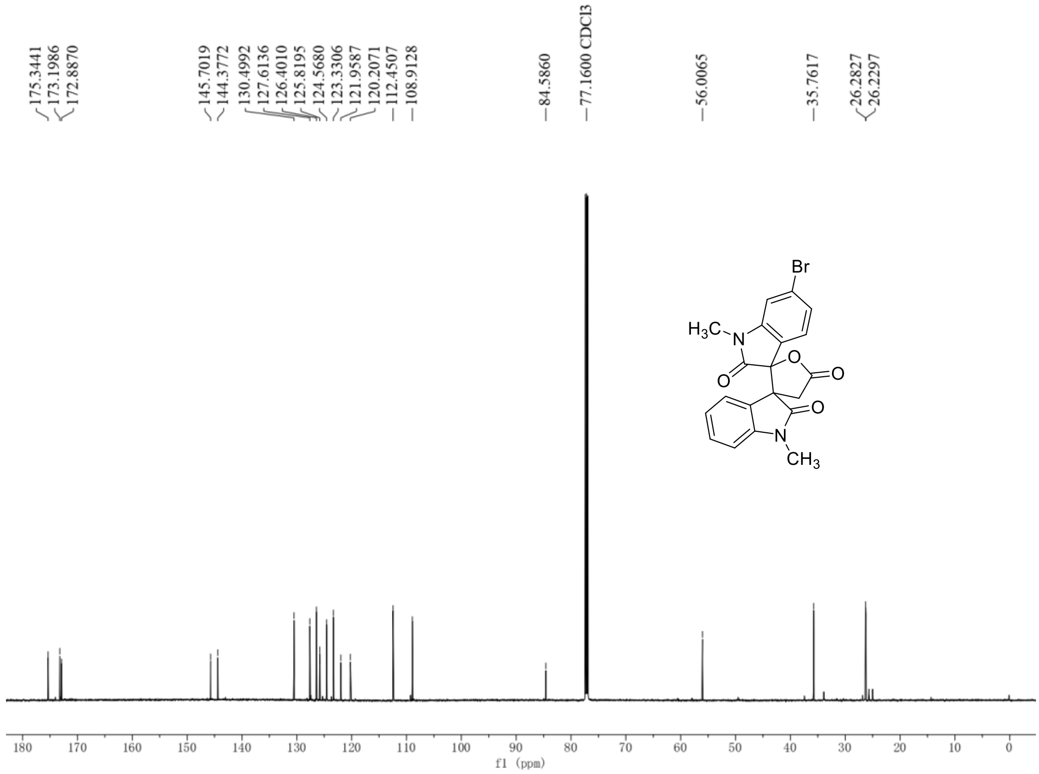
^{1}H NMR, ^{13}C NMR spectra of 3o





^{1}H NMR, ^{13}C NMR spectra of 3p





^{1}H NMR, ^{13}C NMR spectra of 3q