Supporting information

Cu-catalyzed synthesis of spiro imidazole derivatives via indolyl mediated cyclization-rearrangement reaction

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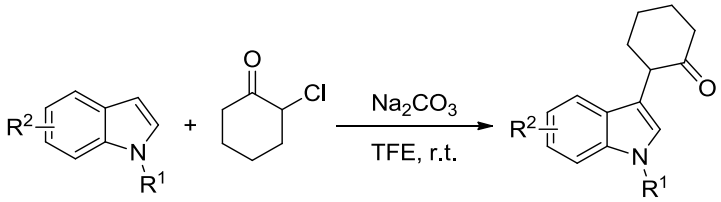
1. General information

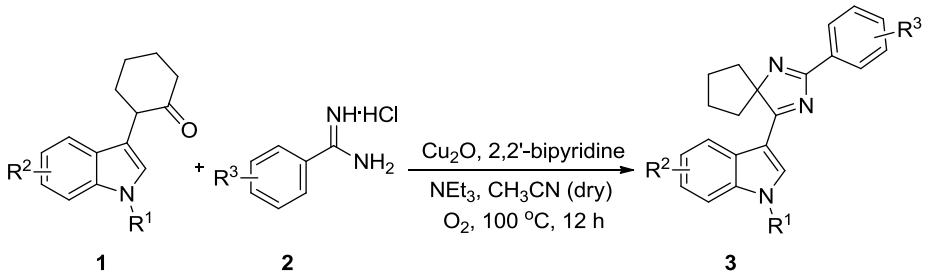
Unless otherwise noted, all commercially available reagents and solvents are reagent grade and were used without further purification. Column chromatography was performed using silica gel (200-300 mesh). ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on Bruker-AV (400, 100 and 376 MHz, respectively) instrument internally referenced solvent signals. Mass spectra were measured on Agilent 5977 GC-MS instrument (EI). High-resolution mass spectra (HRMS) were performed on FTMS ICR MS BRUKER 7T or Agilent 6230 TOF LC/MS. Melting points were measured on BÜCHI B-545 melting point instrument and were uncorrected. X-ray crystal structure data was using collected on a SuperNova, Dual, Cu at zero, AtlasS2 diffractometer. The structures were solved by direct methods using Olex2 software. The structures of known compounds were further corroborated by comparing their NMR and MS data with those of literature.

2. General procedure for synthesis of 2-(indol-3-yl)cyclohexan-1-ones



2-(indol-3-yl)cyclohexan-1-ones was prepared according to the previous literature.[1] Anhydrous Na_2CO_3 (2.4 mmol, 1.2 equiv), 2-chlorocyclohexan-1-ones (2.0 mmol, 1.0 equiv), indoles (2.0 mmol, 1.0 equiv) and 2,2,2-trifluoroethanol (TFE, 3.0 mL) was added to a 20 mL oven-dried reaction vessel and stirred at r.t for 48 h. The volatiles were removed under reduced pressure. The residue was purified by flash chromatography to give 2-(indol-3-yl)cyclohexan-1-ones.

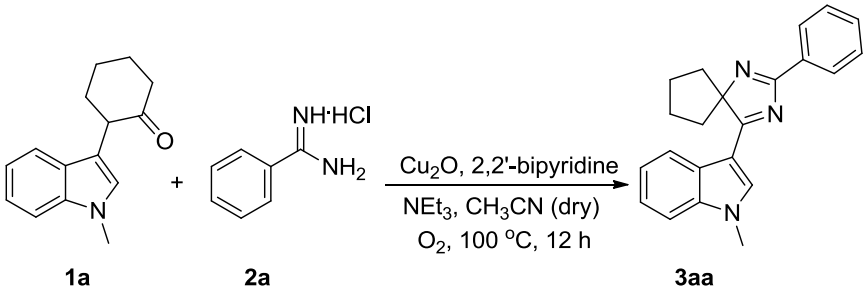
3. General procedure for the synthesis of products 3



1 **2** **3**

A 10 mL oven-dried reaction vessel was added with **1** (0.3 mmol, 1.5 equiv), benzamidine hydrochlorides **2** (0.2 mmo), Cu_2O (0.04 mmol, 20 mol%), 2,2'-bipyridine (0.04 mmol, 20 mol%), NEt_3 (0.2 mmol, 1 equiv) and dry CH_3CN (0.5 mL). The sealed reaction vessel was stirred in an oil bath at 100 ^oC for 12 h, under O_2 atmosphere. The reaction mixture was diluted with ethyl acetate and filtered. The volatiles were removed under reduced pressure and the residue was purified by column chromatography on silica gel to give products **3**.

4. Procedure for the gram-scale synthesis of 3aa

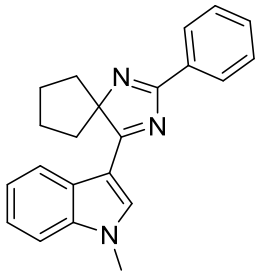


1a **2a** **3aa**

A 25 mL oven-dried reaction vessel was added with 2-(indol-3-yl)cyclohexan-1-one (**1a**, 1.702 g, 7.5 mmol), benzamidine hydrochloride (**2a**, 0.873 g, 5 mmol), Cu_2O (0.143 g, 1 mmol), 2,2'-bipyridine (0.156 g, 1 mmol), NEt_3 (0.693 mL, 5 mmol) and dry CH_3CN (8 mL). The sealed reaction vessel was stirred in an oil bath at 100 ^oC for 12 h, under O_2 atmosphere. The reaction mixture was diluted with ethyl acetate and filtered. The volatiles were removed under reduced pressure and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5 : 1) to give the product **3aa** (1.062 g, 65% yield).

5. Characterization data of products

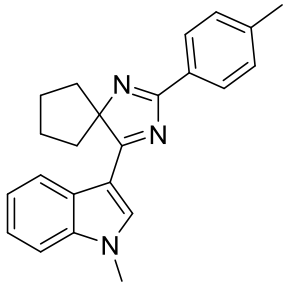
4-(1-Methyl-1*H*-indol-3-yl)-2-phenyl-1,3-diazaspiro[4.4]nona-1,3-diene (3aa)



The reaction was conducted with benzamidine hydrochloride (31.3 mg, 0.2 mmol) and 2-(1-methyl-1*H*-indol-3-yl)cyclohexan-1-one (68.1 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3aa** as pale-yellow solid (46.4 mg, 71% yield). mp: 173-175℃. R_f = 0.45 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87-8.84 (m, 1H), 8.48-8.46 (m, 2H), 7.61 (s, 1H), 7.52-7.50 (m, 3H), 7.44-7.39 (m, 3H), 3.93 (s, 3H), 2.35-2.30 (m, 2H), 2.19-2.10 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 171.0, 137.4, 133.3, 133.2, 130.7, 129.2, 128.5, 126.8, 124.0, 123.7, 122.6, 109.6, 108.6, 91.3, 40.2, 33.8, 27.6. HRMS calcd. for $C_{22}H_{21}N_3$ $[M+H]^+$ 328.1808; found 328.1813.

4-(1-Methyl-1*H*-indol-3-yl)-2-(*p*-tolyl)-1,3-diazaspiro[4.4]nona-1,3-diene (3ab)

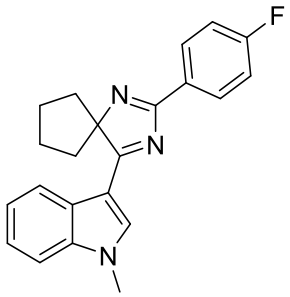


The reaction was conducted with 4-methylbenzamidine hydrochloride (34.1 mg, 0.2 mmol) and 2-(1-methyl-1*H*-indol-3-yl)cyclohexan-1-one (68.1 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3ab** as pale-yellow solid (46.4 mg, 68% yield). mp: 171-173℃. R_f = 0.47 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86-8.84 (m, 1H), 8.35 (d, J = 8.0 Hz, 2H), 7.59 (s, 1H), 7.43-7.39 (m, 3H), 7.31 (d, J = 8.0 Hz, 2H), 3.93 (s, 3H), 2.44 (s, 3H), 2.34-2.29 (m, 2H), 2.18-2.09 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 170.9, 140.8, 137.4, 133.2, 130.5, 129.2, 129.1, 126.8, 124.0, 123.7,

122.5, 109.5, 108.6, 91.3, 40.1, 33.8, 27.6, 21.8. HRMS calcd. for $C_{23}H_{23}N_3$ $[M+H]^+$ 342.1965; found 342.1971.

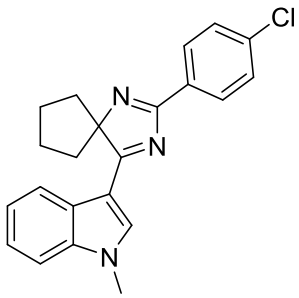
2-(4-Fluorophenyl)-4-(1-methyl-1*H*-indol-3-yl)-1,3-diazaspiro[4.4]nona-1,3-diene (3ac)



The reaction was conducted with 4-fluorobenzamidine hydrochloride (34.9 mg, 0.2 mmol) and 2-(1-methyl-1*H*-indol-3-yl)cyclohexan-1-one (68.1 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3ac** as pale-yellow solid (42.8mg, 62% yield). mp: 186-188℃. R_f = 0.48 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83-8.80 (m, 1H), 8.48-8.44 (m, 2H), 7.60 (s, 1H), 7.44-7.37 (m, 3H), 7.18 (t, J = 8.6 Hz, 2H), 3.93 (s, 3H), 2.33-2.31 (m, 2H), 2.18-2.06 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 170.0, 164.5 (d, J = 248.2 Hz), 137.4, 133.3, 131.2 (d, J = 8.4 Hz), 129.6 (d, J = 2.6 Hz), 126.7, 123.9, 123.8, 122.6, 115.5 (d, J = 21.5 Hz), 109.6, 108.5, 91.6, 40.2, 33.8, 27.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.2. HRMS calcd. for $C_{22}H_{20}FN_3$ $[M+H]^+$ 346.1714; found 346.1719.

2-(4-Chlorophenyl)-4-(1-methyl-1*H*-indol-3-yl)-1,3-diazaspiro[4.4]nona-1,3-diene (3ad)

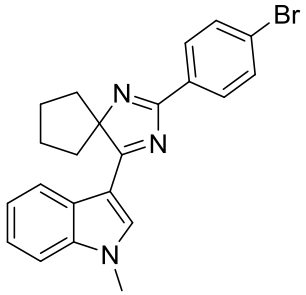


The reaction was conducted with 4-chlorobenzamidine hydrochloride (38.2 mg, 0.2 mmol) and 2-(1-methyl-1*H*-indol-3-yl)cyclohexan-1-one (68.1 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3ad** as pale-yellow solid (46.3 mg, 64% yield). mp: 215-217℃. R_f = 0.48 (petroleum ether/EtOAc

= 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83-8.80 (m, 1H), 8.40 (d, J = 8.4 Hz, 2H), 7.60 (s, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.44-7.40 (m, 3H), 3.93 (s, 3H), 2.33-2.31 (m, 2H), 2.17-2.05 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 170.0, 137.4, 136.5, 133.3, 131.9, 130.4, 128.7, 126.7, 123.9, 123.8, 122.6, 109.6, 108.5, 91.6, 40.2, 33.8, 27.5. HRMS calcd. for $C_{22}H_{20}ClN_3$ $[M+H]^+$ 362.1419; found 362.1424.

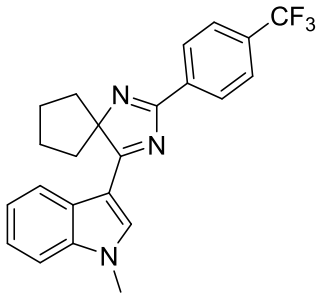
2-(4-Bromophenyl)-4-(1-methyl-1*H*-indol-3-yl)-1,3-diazaspiro[4.4]nona-1,3-diene (3ae)



The reaction was conducted with 4-bromobenzamidine hydrochloride (47.1 mg, 0.2 mmol) and 2-(1-methyl-1*H*-indol-3-yl)cyclohexan-1-one (68.1 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3ae** as pale-yellow solid (46.2 mg, 57% yield). mp: 223-225 ℃. R_f = 0.48 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82-8.80 (m, 1H), 8.33 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.60 (s, 1H), 7.44-7.40 (m, 3H), 3.93 (s, 3H), 2.33-2.28 (m, 2H), 2.19-2.05 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 170.2, 137.4, 133.4, 131.7, 130.7, 128.7, 126.7, 125.2, 123.9, 123.8, 122.7, 109.6, 108.6, 91.6, 40.3, 33.8, 27.5. HRMS calcd. for $C_{22}H_{20}BrN_3$ $[M+H]^+$ 406.0913; found 406.0923.

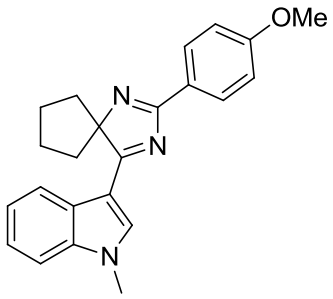
4-(1-Methyl-1*H*-indol-3-yl)-2-(4-(trifluoromethyl)phenyl)-1,3-diazaspiro[4.4]nona-1,3-diene (3af)



The reaction was conducted with 4-trifluoromethylbenzamidine hydrochloride (44.9 mg, 0.2 mmol) and 2-(1-methyl-1*H*-indol-3-yl)cyclohexan-1-one (68.1 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3af** as pale-yellow solid (57.7 mg, 73% yield). mp: 212-214℃. R_f = 0.51 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84-8.82 (m, 1H), 8.57 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.62 (s, 1H), 7.46-7.41 (m, 3H), 3.94 (s, 3H), 2.34-2.32 (m, 2H), 2.20-2.01 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 169.9, 137.4, 136.7, 133.4, 132.1 (q, J = 32.0 Hz), 129.4, 126.7, 125.7, 125.4 (q, J = 3.7 Hz), 123.9, 123.0, 122.7, 109.7, 108.6, 91.8, 40.3, 33.8, 27.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6. HRMS calcd. for $C_{23}H_{20}F_3N_3$ $[M+H]^+$ 396.1682; found 396.1695.

2-(4-Methoxyphenyl)-4-(1-methyl-1*H*-indol-3-yl)-1,3-diazaspiro[4.4]nona-1,3-diene (3ag)

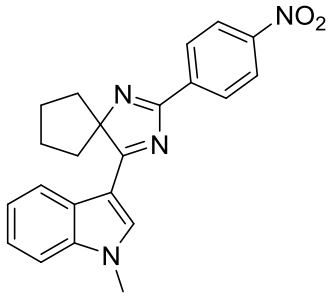


The reaction was conducted with 4-methoxyphenylformamidine hydrochloride (37.2 mg, 0.2 mmol) and 2-(1-methyl-1*H*-indol-3-yl)cyclohexan-1-one (68.1 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 2:1) to yield the desired product **3ag** as pale-yellow solid (54.3 mg, 76% yield). mp: 120-122℃. R_f = 0.39 (petroleum ether/EtOAc =1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, J = 8.8 Hz, 1H), 8.43 (d, J = 8.8 Hz, 2H), 7.59 (s, 1H), 7.42-7.39 (m, 3H), 7.02 (d, J = 8.8 Hz, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 2.34-2.28 (m, 2H), 2.16-2.09 (m, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 170.5, 161.7, 137.4, 133.2, 130.8, 126.8, 125.9, 124.0, 123.7, 122.5, 113.8, 109.6, 108.6, 91.2, 55.5, 40.2, 33.7, 27.5. HRMS calcd. for $C_{23}H_{23}N_3O$ $[M+H]^+$ 358.1914; found 358.1923.

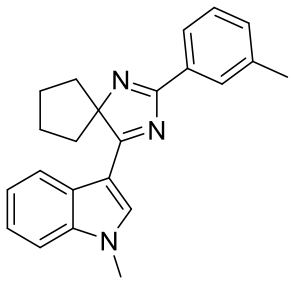
4-(1-Methyl-1*H*-indol-3-yl)-2-(4-nitrophenyl)-1,3-diazaspiro[4.4]nona-1,3-diene (3ah)



The reaction was conducted with 4-nitrobenzamidine hydrochloride (40.3 mg, 0.2 mmol) and 2-(1-methyl-1*H*-indol-3-yl)cyclohexan-1-one (68.1 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 2:1) to yield the desired product **3ah** as pale-yellow solid (46.1 mg, 62 % yield). mp: 281-283℃. R_f = 0.34 (petroleum ether/EtOAc = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82-8.79 (m, 1H), 8.61 (d, J = 8.8 Hz, 2H), 8.33 (d, J = 8.8 Hz, 2H), 7.63 (s, 1H), 7.46-7.41 (m, 3H), 3.95 (s, 3H), 2.40-2.32 (m, 2H), 2.19-2.10 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 169.3, 149.1, 139.3, 137.5, 133.7, 129.9, 124.0, 123.8, 123.7, 122.8, 109.7, 108.5, 92.2, 40.4, 33.9, 27.5. HRMS calcd. for $C_{22}H_{20}N_4O_2$ $[M+H]^+$ 373.1659; found 373.1670.

4-(1-Methyl-1*H*-indol-3-yl)-2-(*m*-tolyl)-1,3-diazaspiro[4.4]nona-1,3-diene (3ai)

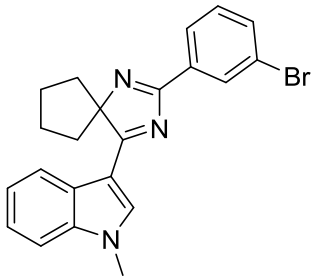


The reaction was conducted with 3-methylbenzamidine hydrochloride (34.1 mg, 0.2 mmol) and 2-(1-methyl-1*H*-indol-3-yl)cyclohexan-1-one (68.1 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3ai** as pale-yellow solid (44.3 mg, 65 % yield). mp: 203-205℃. R_f = 0.46 (petroleum ether/EtOAc

= 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, J = 7.2 Hz, 1H), 8.30 (d, J = 7.6 Hz, 1H), 8.26 (s, 1H), 7.59 (s, 1H), 7.45-7.40 (m, 4H), 7.31 (d, J = 7.6 Hz, 1H), 3.91 (s, 3H), 2.48 (s, 3H), 2.35-2.33 (m, 2H), 2.18-2.10 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 171.1, 138.1, 137.4, 133.2, 131.4, 129.3, 128.4, 126.8, 126.5, 124.0, 123.7, 122.5, 109.5, 108.6, 91.3, 40.1, 33.7, 27.6, 21.6. HRMS calcd. for $C_{23}H_{23}N_3$ $[M+H]^+$ 342.1965; found 342.1973.

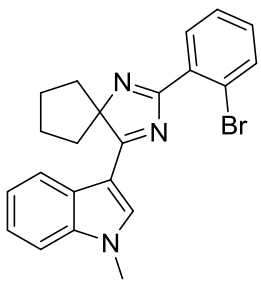
2-(3-Bromophenyl)-4-(1-methyl-1*H*-indol-3-yl)-1,3-diazaspiro[4.4]nona-1,3-diene (3aj)



The reaction was conducted with 3-bromobenzamidine hydrochloride (47.1 mg, 0.2 mmol) and 2-(1-methyl-1*H*-indol-3-yl)cyclohexan-1-one (68.1 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3aj** as pale-yellow solid (56.7 mg, 70 % yield). mp: 191-193℃. R_f = 0.47 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J = 7.2 Hz, 1H), 8.59 (s, 1H), 8.41 (d, J = 8.8 Hz, 1H), 7.63-7.60 (m, 2H), 7.45-7.36 (m, 4H), 3.92 (s, 3H), 2.33-2.31 (m, 2H), 2.16-2.01 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.1, 169.7, 137.4, 135.4, 133.5, 133.4, 131.8, 130.0, 127.8, 126.7, 123.9, 123.8, 122.7, 109.6, 108.5, 91.3, 40.3, 33.8, 27.5. HRMS calcd. for $C_{22}H_{20}BrN_3$ $[M+H]^+$ 406.0913; found 406.0926.

2-(2-Bromophenyl)-4-(1-methyl-1*H*-indol-3-yl)-1,3-diazaspiro[4.4]nona-1,3-diene (3ak)

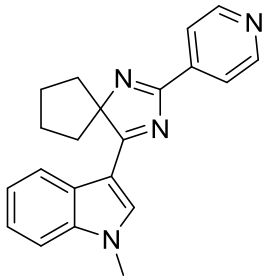


The reaction was conducted with 2-bromobenzamidine hydrochloride (47.1 mg, 0.2 mmol) and 2-

(1-methyl-1*H*-indol-3-yl)cyclohexan-1-one (68.1 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3ak** as pale-yellow solid (43.7 mg, 54 % yield). mp: 188-190℃. R_f = 0.47 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77-8.75 (m, 1H), 8.03-8.01 (m, 1H), 7.61 (s, 1H), 7.52-7.49 (m, 1H), 7.41-7.35 (m, 5H), 3.93 (s, 3H), 2.5-2.01 (m, 2H), 2.21-2.15 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 170.3, 137.4, 133.9, 133.3, 132.0, 130.7, 130.6, 126.7, 126.6, 124.0, 123.8, 122.6, 109.5, 108.6, 91.6, 40.1, 33.8, 27.5. HRMS calcd. for $C_{22}H_{20}BrN_3$ $[M+Na]^+$ 428.0733; found 428.0747.

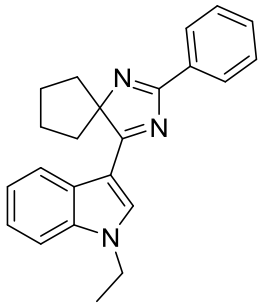
4-(1-Methyl-1*H*-indol-3-yl)-2-(pyridin-4-yl)-1,3-diazaspiro[4.4]nona-1,3-diene (3al)



The reaction was conducted with 4-carbamimidoylpyridine hydrochloride (31.5 mg, 0.2 mmol) and 2-(1-methyl-1*H*-indol-3-yl)cyclohexan-1-one (68.1 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 2:1) to yield the desired product **3al** as pale-yellow solid (40.0 mg, 61% yield). mp: 197-199℃. R_f = 0.48 (petroleum ether/EtOAc =1:1).

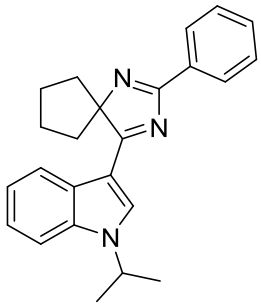
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81-8.78 (m, 3H), 8.28 (d, J = 6.0 Hz, 2H), 7.63 (s, 1H), 7.44-7.41 (m, 3H), 3.95 (s, 3H), 2.34-2.32 (m, 2H), 2.18-2.09 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 169.5, 150.4, 140.6, 137.5, 133.6, 126.7, 124.0, 123.9, 123.0, 122.8, 109.7, 108.6, 92.0, 40.4, 33.9, 27.5. HRMS calcd. for $C_{21}H_{20}N_4$ $[M+H]^+$ 329.1761; found 329.1780.

4-(1-Ethyl-1*H*-indol-3-yl)-2-phenyl-1,3-diazaspiro[4.4]nona-1,3-diene (3ba)



The reaction was conducted with benzamidine hydrochloride (31.3 mg, 0.2 mmol) and 2-(1-ethyl-1*H*-indol-3-yl)cyclohexan-1-one (72.0 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3ba** as pale-yellow solid (49.1 mg, 72 % yield). mp: 169-171℃. R_f = 0.52 (petroleum ether/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, J = 6.4 Hz, 1H), 8.48-8.46 (m, 2H), 7.65 (s, 1H), 7.54-7.50 (m, 3H), 7.44-7.36 (m, 3H), 4.30 (q, J = 7.3 Hz, 2H), 2.35-2.30 (m, 2H), 2.19-2.10 (m, 6H), 1.58 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 170.9, 136.5, 133.3, 131.5, 130.6, 129.1, 128.5, 127.0, 124.1, 123.6, 122.5, 109.7, 108.8, 91.4, 42.0, 40.2, 27.6, 15.5. HRMS calcd. for $C_{23}H_{23}N_3$ $[M+H]^+$ 342.1965; found 342.1980.

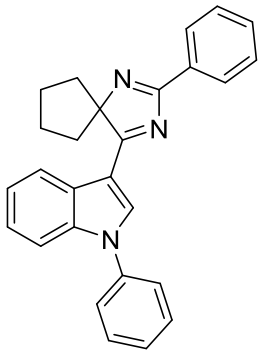
4-(1-Isopropyl-1*H*-indol-3-yl)-2-phenyl-1,3-diazaspiro[4.4]nona-1,3-diene (3ca)



The reaction was conducted with benzamidine hydrochloride (31.3 mg, 0.2 mmol) and 2-(1-isopropyl-1*H*-indol-3-yl)cyclohexan-1-one (76.6 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3ca** as pale-yellow solid (53.2 mg, 75 % yield). mp: 98-100℃. R_f = 0.55 (petroleum ether/EtOAc = 3:1).

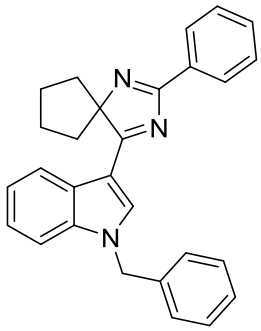
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 6.8 Hz, 1H), 8.49-8.46 (m, 2H), 7.74 (s, 1H), 7.54-7.51 (m, 3H), 7.46 (d, J = 7.6 Hz, 1H), 7.42-7.35 (m, 2H), 4.80-4.74 (m, 1H), 2.35-2.3 (m, 2H), 2.21-2.12 (m, 6H), 1.65 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 171.0, 136.4, 133.3, 130.6, 129.1, 128.5, 128.3, 127.0, 124.1, 123.4, 122.5, 109.9, 108.8, 91.3, 48.1, 40.2, 27.7, 22.8. HRMS calcd. for $C_{24}H_{25}N_3$ $[M+H]^+$ 356.2121; found 356.2133.

2-Phenyl-4-(1-phenyl-1*H*-indol-3-yl)-1,3-diazaspiro[4.4]nona-1,3-diene (3da)



The reaction was conducted with benzamidine hydrochloride (31.3 mg, 0.2 mmol) and 2-(1-phenyl-1*H*-indol-3-yl)cyclohexan-1-one (86.7 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3da** as pale-yellow solid (42.8 mg, 55 % yield). mp: 206-208℃. R_f = 0.59 (petroleum ether/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, J = 8.0 Hz, 1H), 8.50-8.48 (m, 2H), 7.84 (s, 1H), 7.64-7.44 (m, 10H), 7.38 (t, J = 7.6 Hz, 1H), 2.34-2.31 (m, 2H), 2.26-2.19 (m, 2H), 2.15-2.09 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 171.0, 138.7, 137.0, 132.1, 130.8, 130.1, 129.2, 129.2, 128.6, 128.1, 127.3, 125.1, 124.4, 124.3, 123.1, 110.8, 110.6, 91.7, 40.0, 27.6. HRMS calcd. for $C_{27}H_{23}N_3$ $[M+Na]^+$ 412.1784; found 412.1798.

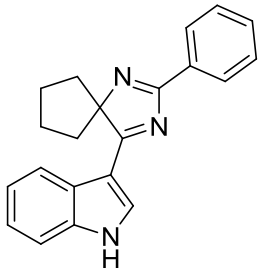
4-(1-Benzyl-1*H*-indol-3-yl)-2-phenyl-1,3-diazaspiro[4.4]nona-1,3-diene (3ea)



The reaction was conducted with benzamidine hydrochloride (31.3 mg, 0.2 mmol) and 2-(1-benzyl-1*H*-indol-3-yl)cyclohexan-1-one (90.9mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3ea** as pale-yellow solid (50.8 mg, 63 % yield). mp: 110-112℃. R_f = 0.58 (petroleum ether/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 8.0 Hz, 1H), 8.49-8.47 (m, 2H), 7.65 (s, 1H), 7.51 (d, J = 4.0 Hz, 3H), 7.43-7.39 (m, 1H), 7.36-7.34 (m, 5H), 7.16 (d, J = 6.8 Hz, 2H), 5.45 (s, 2H), 2.30-2.26 (m, 2H), 2.13-2.10 (m, 4H), 2.06-2.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 171.0, 137.1, 136.0, 133.2, 132.7, 130.7, 129.2, 129.2, 128.5, 128.3, 127.0, 126.9, 124.1, 123.9, 122.7, 110.2, 91.4, 50.9,

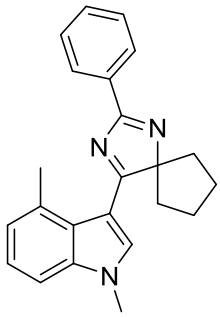
40.2, 27.5. HRMS calcd. for $C_{28}H_{25}N_3$ $[M+Na]^+$ 426.1941; found 426.1953.

4-(1*H*-indol-3-yl)-2-phenyl-1,3-diazaspiro[4.4]nona-1,3-diene (3fa)



The reaction was conducted with benzamidine hydrochloride (31.3 mg, 0.2 mmol) and 2-(1*H*-indol-3-yl)cyclohexan-1-one (63.9mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 2:1) to yield the desired product **3fa** as pale-yellow solid (40.1 mg, 64 % yield). mp: 268-270℃. R_f = 0.38 (petroleum ether/EtOAc =1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 8.85 (d, J = 7.6 Hz, 1H), 8.49-8.46 (m, 2H), 7.69 (s, 1H), 7.52-7.50 (m, 3H), 7.42-7.31 (m, 3H), 2.29-2.27 (m, 2H), 2.11-2.04 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 171.2, 136.4, 133.0, 131.0, 129.7, 129.2, 128.7, 126.0, 124.0, 123.6, 122.6, 111.6, 109.7, 91.5, 40.2, 27.5. HRMS calcd. for $C_{21}H_{19}N_3$ $[M+Na]^+$ 336.1471; found 336.1483.

4-(1,4-Dimethyl-1*H*-indol-3-yl)-2-phenyl-1,3-diazaspiro[4.4]nona-1,3-diene (3ga)

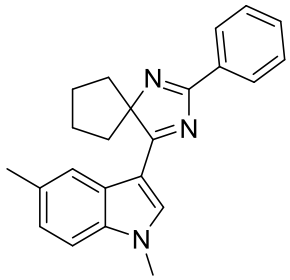


The reaction was conducted with benzamidine hydrochloride (31.3 mg, 0.2 mmol) and 2-(1,4-dimethyl-1*H*-indol-3-yl)cyclohexan-1-one (72.0 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3ga** as pale-yellow solid (38.9 mg, 57 % yield). mp: 91-93℃. R_f = 0.47 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39-8.37 (m, 2H), 7.55 (s, 1H), 7.49-7.47 (m, 3H), 7.29-7.21 (m, 2H), 7.09 (d, J = 6.8 Hz, 1H), 3.89 (s, 3H), 2.97 (s, 3H), 2.30-2.17 (m, 4H), 2.10-2.05 (m, 4H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 193.3, 170.3, 138.0, 133.8, 133.1, 132.8, 130.7, 129.1, 128.6, 125.6, 124.5, 123.7, 110.0, 107.3, 92.7, 38.8, 33.9, 27.6, 23.9. HRMS calcd. for $C_{23}H_{23}N_3$ $[M+H]^+$ 342.1965; found 342.1978.

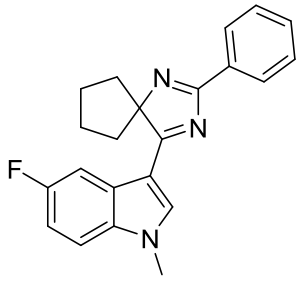
4-(1,5-Dimethyl-1*H*-indol-3-yl)-2-phenyl-1,3-diazaspiro[4.4]nona-1,3-diene (3ha)



The reaction was conducted with benzamidine hydrochloride (31.3 mg, 0.2 mmol) and 2-(1,5-dimethyl-1*H*-indol-3-yl)cyclohexan-1-one (72.0 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3ha** as pale-yellow solid (47.0 mg, 69 % yield). mp: 200-202℃. R_f = 0.48 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.48-8.46 (m, 2H), 7.56 (s, 1H), 7.54-7.50 (m, 3H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 3.89 (s, 3H), 2.60 (s, 3H), 2.35-2.32 (m, 2H), 2.18-2.07 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 170.9, 136.5, 133.4, 131.5, 130.6, 129.1, 128.5, 127.0, 124.2, 123.6, 122.5, 109.7, 108.8, 91.4, 42.0, 40.2, 27.6, 15.5. HRMS calcd. for $C_{23}H_{23}N_3$ $[M+H]^+$ 342.1965; found 342.1976.

4-(5-Fluoro-1-methyl-1*H*-indol-3-yl)-2-phenyl-1,3-diazaspiro[4.4]nona-1,3-diene (3ia)

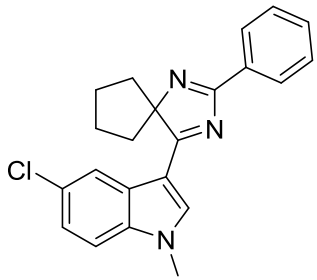


The reaction was conducted with benzamidine hydrochloride (31.3 mg, 0.2 mmol) and 2-(5-fluoro-1-methyl-1*H*-indol-3-yl)cyclohexan-1-one (73.5 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3ia** as pale-yellow solid (45.5 mg, 66 % yield). mp: 208-210℃. R_f = 0.48 (petroleum

ether/EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54-8.51 (m, 1H), 8.46-8.43 (m, 2H), 7.61 (s, 1H), 7.54-7.50 (m, 3H), 7.32-7.29 (m, 1H), 7.12 (t, *J* = 9.0 Hz, 1H), 3.91 (s, 3H), 2.34-2.28 (m, 2H), 2.11-2.05 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 170.8, 159.7 (d, *J* = 235.9 Hz), 134.2, 134.0, 133.2, 130.7, 129.1, 128.5, 127.5 (d, *J* = 11.4 Hz), 112.1 (d, *J* = 26.6 Hz), 110.4 (d, *J* = 9.5 Hz), 109.3 (d, *J* = 24.9 Hz), 108.6 (d, *J* = 4.1 Hz), 91.4, 40.0, 34.1, 27.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -121.1. HRMS calcd. for $C_{22}H_{20}FN_3$ $[M+H]^+$ 346.1714; found 346.1725.

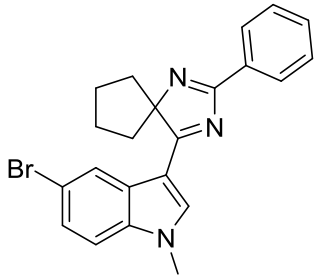
4-(5-Chloro-1-methyl-1*H*-indol-3-yl)-2-phenyl-1,3-diazaspiro[4.4]nona-1,3-diene (3ja)



The reaction was conducted with benzamidine hydrochloride (31.3 mg, 0.2 mmol) and 2-(5-chloro-1-methyl-1*H*-indol-3-yl)cyclohexan-1-one (78.3 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3ja** as pale-yellow solid (46.2 mg, 64 % yield). mp: 245-247℃. R_f = 0.48 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.46-8.40 (m, 2H), 7.59 (s, 1H), 7.53-7.51 (m, 3H), 7.32-7.29 (m, 2H), 3.91 (s, 3H), 2.34-2.32 (m, 2H), 2.11-2.08 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 170.9, 135.8, 134.0, 133.0, 130.8, 129.1, 128.6, 128.4, 127.6, 124.1, 123.6, 110.6, 108.3, 91.4, 40.0, 34.0, 27.5. HRMS calcd. for $C_{22}H_{20}ClN_3$ $[M+H]^+$ 362.1419; found 362.1434.

4-(5-Bromo-1-methyl-1*H*-indol-3-yl)-2-phenyl-1,3-diazaspiro[4.4]nona-1,3-diene (3ka)

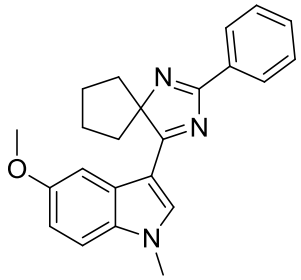


The reaction was conducted with benzamidine hydrochloride (31.3 mg, 0.2 mmol) and 2-(5-

bromo-1-methyl-1*H*-indol-3-yl)cyclohexan-1-one (91.5 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3ka** as pale-yellow solid (47.8 mg, 59 % yield). mp: 263-265℃. R_f = 0.48 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.48-8.46 (m, 2H), 7.59 (s, 1H), 7.55-7.54 (m, 3H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.28 (d, *J* = 2.0 Hz, 1H), 3.93 (s, 3H), 2.36-2.34 (m, 2H), 2.13-2.10 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 170.8, 136.1, 133.8, 133.1, 130.7, 129.1, 128.6, 128.3, 126.7, 126.6, 116.1, 111.03, 108.2, 91.4, 40.0, 34.0, 27.5. HRMS calcd. for $C_{22}H_{20}BrN_3$ $[M+H]^+$ 406.0913; found 406.0925.

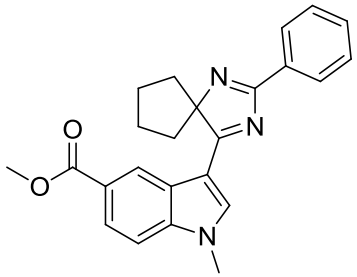
4-(5-Methoxy-1-methyl-1*H*-indol-3-yl)-2-phenyl-1,3-diazaspiro[4.4]nona-1,3-diene (3la)



The reaction was conducted with benzamidine hydrochloride (31.3 mg, 0.2 mmol) and 2-(5-methoxy-1-methyl-1*H*-indol-3-yl)cyclohexan-1-one (77.1 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 2:1) to yield the desired product **3la** as pale-yellow solid (54.3 mg, 76 % yield). mp: 150-152℃. R_f = 0.41 (petroleum ether/EtOAc = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46-8.43 (m, 2H), 8.40 (s, 1H), 7.56 (s, 1H), 7.52-7.49 (m, 3H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.04-7.01 (m, 1H), 4.01 (s, 3H), 3.90 (s, 3H), 2.34-2.29 (m, 2H), 2.17-2.07 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 170.9, 156.4, 133.3, 132.5, 130.6, 129.0, 128.5, 127.6, 113.8, 110.4, 108.2, 105.6, 91.3, 56.0, 40.2, 34.0, 27.5. HRMS calcd. for $C_{23}H_{23}N_3O$ $[M+H]^+$ 358.1914; found 358.1927.

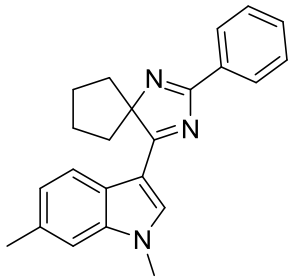
Methyl 1-methyl-3-(2-phenyl-1,3-diazaspiro[4.4]nona-1,3-dien-4-*yl*)-1*H*-indole-5-carboxylate (3ma)



The reaction was conducted with benzamidine hydrochloride (31.3 mg, 0.2 mmol) and methyl 1-methyl-3-(2-oxocyclohexyl)-1*H*-indole-5-carboxylate (85.5 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 1:1) to yield the desired product **3ma** as pale-yellow solid (47.7 mg, 62 % yield). mp: 199-201℃. R_f = 0.31 (petroleum ether/EtOAc =1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 8.48 (d, J = 7.6 Hz, 2H), 8.08 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 2.8 Hz, 1H), 7.54-7.50 (m, 3H), 7.41 (d, J = 8.8 Hz, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 2.35-2.33 (m, 2H), 2.16-2.06 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 170.9, 168.1, 139.8, 134.2, 133.0, 130.7, 129.1, 128.6, 126.8, 126.4, 125.0, 124.4, 109.8, 109.4, 91.6, 52.2, 39.8, 33.9, 27.5. HRMS calcd. for $C_{24}H_{23}N_3O_2$ $[M+H]^+$ 386.1863; found 386.1870.

4-(1,6-Dimethyl-1*H*-indol-3-yl)-2-phenyl-1,3-diazaspiro[4.4]nona-1,3-diene (3na)

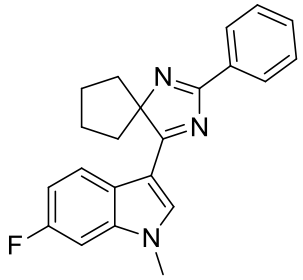


The reaction was conducted with benzamidine hydrochloride (31.3 mg, 0.2 mmol) and 2-(1,6-dimethyl-1*H*-indol-3-yl)cyclohexan-1-one (72.0 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3na** as pale-yellow solid (49.1 mg, 72 % yield). mp: 201-203℃. R_f = 0.47 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 8.0 Hz, 1H), 847-8.44 (m, 2H), 7.53 (s, 1H), 7.52-7.49 (m, 3H), 7.23 (d, J = 8.0 Hz, 1H), 7.19 (s, 1H), 3.89 (s, 3H), 2.55 (s, 3H), 2.34-2.29 (m, 2H), 2.17-2.09 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 171.0, 136.4, 133.3, 130.6, 129.1, 128.5, 128.3, 127.0, 124.1, 123.4, 122.5, 109.9, 108.8, 91.3, 48.1, 40.2, 27.7, 22.8. HRMS calcd. for $C_{23}H_{23}N_3$ $[M+H]^+$

342.1965; found 342.1977.

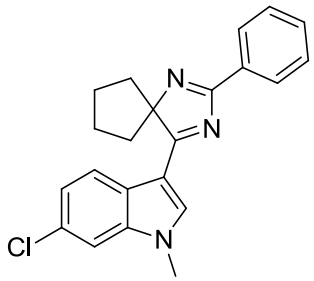
4-(6-Fluoro-1-methyl-1*H*-indol-3-yl)-2-phenyl-1,3-diazaspiro[4.4]nona-1,3-diene (3oa)



The reaction was conducted with benzamidine hydrochloride (31.3 mg, 0.2 mmol) and 2-(6-fluoro-1-methyl-1*H*-indol-3-yl)cyclohexan-1-one (73.5 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3oa** as pale-yellow solid (42.1 mg, 61 % yield). mp: 199-201℃. R_f = 0.49 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80-8.77 (m, 1H), 8.45-8.43 (m, 2H), 7.57 (s, 1H), 7.51-7.50 (m, 3H), 7.15 (t, J = 9.2 Hz, 1H), 7.07 (d, J = 9.2 Hz, 1H), 3.88 (s, 3H), 2.34-2.32 (m, 2H), 2.11-2.09 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 170.8, 137.6, 133.5, 133.1, 130.7, 129.1, 128.5, 125.3, 125.2, 123.2, 111.0 (d, J = 23.7 Hz), 108.8, 96.2 (d, J = 26.5 Hz), 91.5, 40.1, 33.9, 27.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -118.0. HRMS calcd. for $C_{22}H_{20}FN_3$ $[M+H]^+$ 346.1714; found 346.1731.

4-(6-Chloro-1-methyl-1*H*-indol-3-yl)-2-phenyl-1,3-diazaspiro[4.4]nona-1,3-diene (3pa)

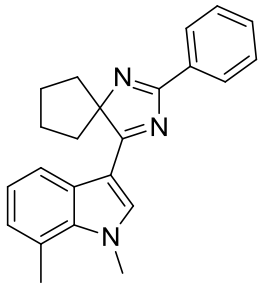


The reaction was conducted with benzamidine hydrochloride (31.3 mg, 0.2 mmol) and 2-(6-chloro-1-methyl-1*H*-indol-3-yl)cyclohexan-1-one (78.3 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3pa** as pale-yellow solid (46.9 mg, 65 % yield). mp: 227-229℃. R_f = 0.49 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 8.4 Hz, 1H), 8.45-8.42 (m, 2H), 7.57 (s, 1H), 7.52-7.50 (m,

3H), 7.38 (s, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 3.89 (s, 3H), 2.34-2.32 (m, 2H), 2.11-2.08 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 170.8, 137.8, 133.6, 133.1, 130.7, 129.7, 129.1, 128.5, 125.3, 125.1, 123.1, 109.7, 108.8, 91.5, 40.0, 33.9, 27.5. HRMS calcd. for $C_{22}H_{20}ClN_3$ $[M+H]^+$ 362.1419; found 362.1437.

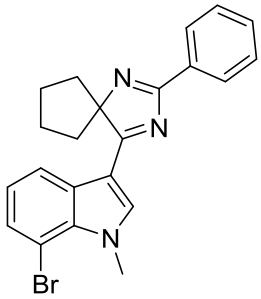
4-(1,7-Dimethyl-1*H*-indol-3-yl)-2-phenyl-1,3-diazaspiro[4.4]nona-1,3-diene (3qa)



The reaction was conducted with benzamidine hydrochloride (31.3 mg, 0.2 mmol) and 2-(1,7-dimethyl-1*H*-indol-3-yl)cyclohexan-1-one (72.0 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3qa** as pale-yellow solid (47.7 mg, 70 % yield). mp: 288-290℃. R_f = 0.46 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 8.0 Hz, 1H), 8.47-8.45 (m, 2H), 7.53-7.49 (m, 4H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 4.18 (s, 3H), 2.81 (s, 3H), 2.34-2.91 (m, 2H), 2.17-2.07 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 170.9, 136.1, 134.9, 133.3, 130.6, 129.1, 128.4, 127.9, 126.5, 122.7, 122.1, 121.4, 108.1, 91.5, 40.2, 38.0, 27.5, 19.8. HRMS calcd. for $C_{23}H_{23}N_3$ $[M+H]^+$ 342.1965; found 342.1981.

4-(7-Bromo-1-methyl-1*H*-indol-3-yl)-2-phenyl-1,3-diazaspiro[4.4]nona-1,3-diene (3ra)

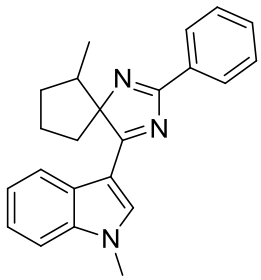


The reaction was conducted with benzamidine hydrochloride (31.3 mg, 0.2 mmol) and 2-(7-bromo-1-methyl-1*H*-indol-3-yl)cyclohexan-1-one (91.5 mg, 0.3 mmol). The residue was purified

by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3ra** as pale-yellow solid (47.9 mg, 59 % yield). mp: 266-268℃. R_f = 0.48 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, J = 8.0 Hz, 1H), 8.45-8.42 (m, 2H), 7.53 (s, 1H), 7.52-7.49 (m, 4H), 7.20 (t, J = 7.8 Hz, 1H), 4.30 (s, 3H), 2.34-2.29 (m, 2H), 2.11-2.08 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 170.8, 137.8, 133.6, 133.1, 130.7, 129.7, 129.1, 128.5, 125.3, 125.1, 123.1, 109.7, 108.8, 91.5, 40.0, 33.9, 27.5. HRMS calcd. for $C_{22}H_{20}BrN_3$ $[M+H]^+$ 406.0913; found 406.0929.

6-Methyl-4-(1-methyl-1*H*-indol-3-yl)-2-phenyl-1,3-diazaspiro[4.4]nona-1,3-diene (3sa)



The reaction was conducted with benzamidine hydrochloride (31.3 mg, 0.2 mmol) and 2 2-methyl-6-(1-methyl-1H-indol-3-yl)cyclohexan-1-one (72.0 mg, 0.3 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield the desired product **3sa** as pale-yellow solid (26.6 mg, 39 % yield). mp: 168-170℃. R_f = 0.45 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, J = 8.4 Hz, 1H), 8.47 (d, J = 7.6 Hz, 2H), 7.70 (s, 1H), 7.52-7.50 (m, 3H), 7.41-7.40 (m, 3H), 3.93 (s, 3H), 2.57-2.51 (m, 1H), 2.35-2.31 (m, 2H), 2.25-2.08 (m, 4H), 0.64 (d, J = 64 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 171.5, 137.3, 133.1, 130.6, 129.2, 128.5, 126.9, 126.6, 124.2, 123.7, 122.5, 109.5, 108.9, 50.6, 38.6, 34.9, 33.8, 29.8, 24.7, 12.8. HRMS calcd. for $C_{23}H_{23}N_3$ $[M+H]^+$ 342.1965; found 342.1972

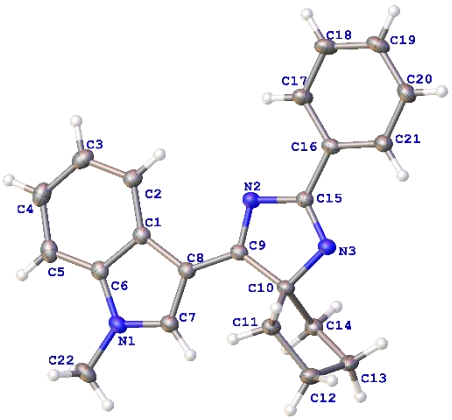
6. References

[1] Tang, Q.; Chen, X.; Tiwari, B.; Chi, Y. R.; Org. lett. 2012, 14 (7), 1922-1925.

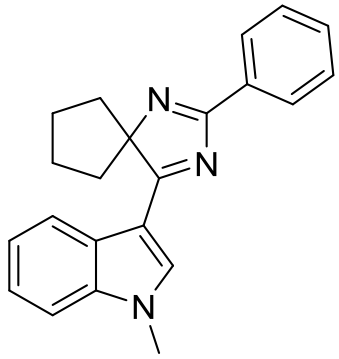
7. Crystal data and structure refinement for 3aa

The product **3aa** (20.0 mg) were complete dissolved in DCM (0.5 mL) in a test tube. Then *n*-hexane (2.0 mL) were added dropwise, slow volatilized at room temperature. A few days later, the crystal was grown at room temperature.

A suitable crystal was collected, on a SuperNova, Dual, Cu at zero, AtlasS2 diffractometer. The data were collected and processed using CrysAlisPro. The structures were solved by direct methods using Olex2 software. The crystal was kept at 150.0(10) K during data collection.



CCDC number: 2133077



3aa

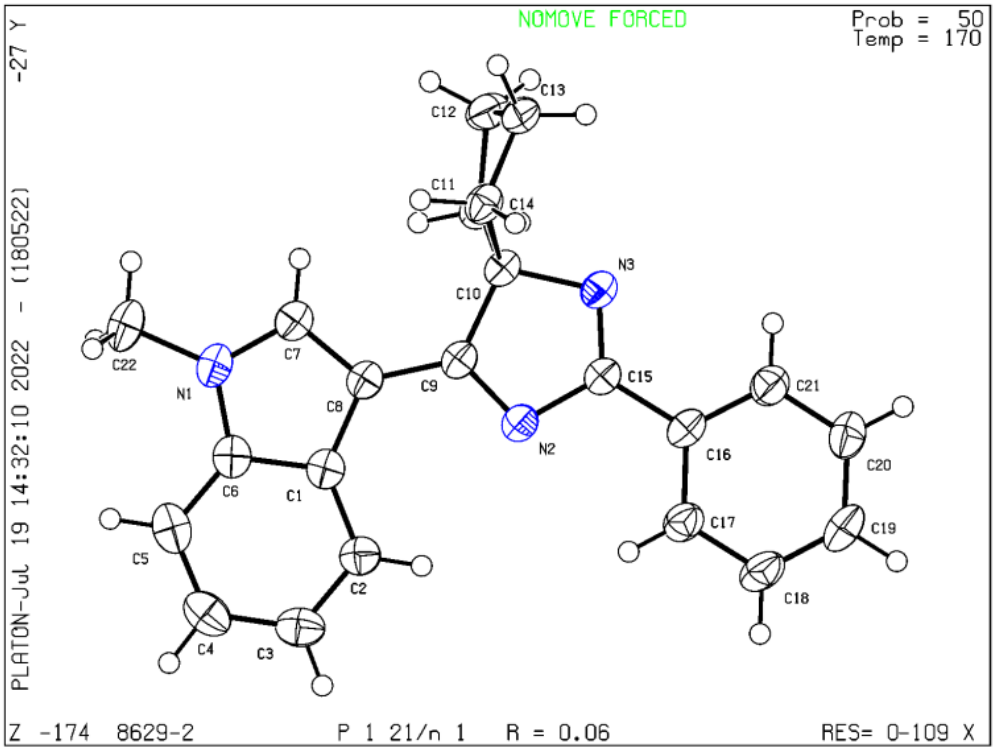


Figure S1. Ellipsoid plot of **3aa** (shown at 50% probability levels)

Table 1. Crystal data and structure refinement for **3aa**.

Identification code	**3aa**
Empirical formula	$C_{22}H_{21}N_3$
Formula weight	327.42
Temperature/K	169.99(10)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	8.0170(4)
b/Å	11.8451(7)
c/Å	18.3346(12)
α/°	90
β/°	99.131(5)
γ/°	90
Volume/Å^3	1719.03(18)
Z	4
ρ_{calc}g/cm^3	1.265
μ/mm^{-1}	0.584
F(000)	696.0
Crystal size/mm^3	0.12 × 0.1 × 0.08
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.922 to 147.43
Index ranges	$-6 \le h \le 9$, $-14 \le k \le 14$, $-21 \le l \le 22$
Reflections collected	6433
Independent reflections	3356 [R_{int} = 0.0524, R_{sigma} = 0.0630]
Data/restraints/parameters	3356/0/227
Goodness-of-fit on F^2	1.075
Final R indexes [I>=2σ (I)]	R_1 = 0.0647, wR_2 = 0.1722
Final R indexes [all data]	R_1 = 0.0768, wR_2 = 0.1881
Largest diff. peak/hole / e Å^{-3}	0.33/-0.27

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

Atom	***x***	***y***	***z***	**U(eq)**
N1	11940(2)	4350.9(15)	5870.1(10)	35.1(4)
N2	6858.6(19)	2597.5(14)	6057.5(9)	31.1(4)
N3	6280.9(19)	2765.0(14)	7247.2(9)	31.4(4)
C1	9758(2)	3280.2(16)	5321.5(11)	31.0(4)
C2	8856(3)	2664.9(17)	4740.9(11)	33.9(5)
C3	9481(3)	2617.8(18)	4077.0(12)	41.2(5)
C4	10976(3)	3172(2)	3982.4(12)	44.3(5)
C5	11901(3)	3773.0(19)	4551.1(13)	40.5(5)
C6	11271(2)	3817.2(16)	5218.1(11)	32.5(4)
C7	10896(2)	4167.5(17)	6373.1(11)	33.3(4)
C8	9525(2)	3521.9(16)	6072.8(10)	29.9(4)
C9	8127(2)	3160.1(16)	6419.4(10)	28.4(4)
C10	7898(2)	3337.3(17)	7213.4(10)	29.9(4)
C11	9313(2)	2843.1(17)	7804.0(11)	33.9(5)
C12	9338(3)	3584(2)	8497.0(11)	42.3(5)
C13	7893(3)	4429.8(19)	8308.1(11)	38.5(5)
C14	7741(2)	4570.2(17)	7474.4(11)	34.1(5)
C15	5796(2)	2379.0(16)	6588.8(10)	29.0(4)
C16	4238(2)	1725.6(16)	6366.0(10)	30.8(4)
C17	3861(3)	1295.8(18)	5647.6(11)	37.3(5)
C18	2435(3)	639(2)	5444.3(12)	43.6(5)
C19	1367(3)	413.4(19)	5947.8(13)	42.9(5)
C20	1721(3)	841(2)	6655.6(13)	43.1(5)
C21	3150(2)	1482.8(19)	6869.1(12)	37.8(5)
C22	13510(2)	4985(2)	5987.6(14)	45.4(6)

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

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
N1	27.5(8)	30.8(9)	46.6(10)	-0.1(7)	4.6(7)	-2.1(7)
N2	30.0(8)	30.2(9)	32.2(8)	1.0(7)	1.7(6)	-2.2(7)
N3	30.5(8)	27.8(9)	35.1(8)	-2.1(7)	2.9(6)	-2.7(7)
C1	32.1(9)	24.4(9)	36.2(10)	3.1(8)	4.4(7)	3.9(8)
C2	39.5(10)	26.8(10)	34.7(10)	1.2(8)	4.1(8)	1.2(8)
C3	55.8(12)	30.4(11)	36.3(10)	-1.6(9)	4.0(9)	6.3(9)
C4	56.7(13)	39.5(12)	39.6(11)	6.2(10)	16.4(10)	11.5(10)
C5	38.7(10)	34.1(11)	51.7(13)	10.3(9)	16.3(9)	8.5(9)
C6	32.2(9)	24.3(9)	41.1(10)	4.4(8)	6.4(8)	5.5(8)
C7	30.9(9)	30.4(10)	37.6(10)	0.3(8)	2.7(7)	0.8(8)
C8	29.3(8)	24.5(9)	35.3(10)	0.6(8)	3.4(7)	1.0(7)
C9	27.8(9)	22.5(9)	33.9(9)	1.4(7)	1.2(7)	0.5(7)
C10	27.2(9)	27.7(10)	33.4(9)	-1.8(8)	0.9(7)	-1.9(7)
C11	33.1(9)	32.0(10)	35.0(10)	0.1(8)	0.3(8)	-1.6(8)
C12	43.4(11)	45.8(13)	35.0(10)	-4.4(9)	-2.3(8)	-9.0(10)
C13	40.6(10)	35.8(11)	39.8(11)	-11.6(9)	8.4(8)	-11.9(9)
C14	32.0(9)	27.2(10)	42.4(11)	-4.2(8)	4.1(8)	-1.8(8)
C15	28.8(9)	24.8(9)	32.3(9)	1.0(7)	1.5(7)	0.9(7)
C16	28.0(9)	24.6(9)	37.2(10)	0.7(8)	-3.2(7)	1.0(7)
C17	35.5(10)	39.7(11)	33.9(10)	3.4(9)	-2.8(8)	-4.3(9)
C18	39.9(11)	46.7(13)	38.9(11)	0.9(10)	-9.9(9)	-7.2(10)
C19	29.9(10)	38.1(12)	56.0(13)	1.7(10)	-8.0(9)	-7.1(8)
C20	30.4(10)	44.5(13)	54.8(13)	-1.4(10)	8.0(9)	-4.8(9)
C21	33.3(10)	36.7(11)	43.3(11)	-6.7(9)	5.7(8)	-2.2(8)
C22	26.5(9)	43.1(13)	65.1(15)	2.6(11)	3.1(9)	-3.8(9)

Table 4. Bond Lengths for **3aa**

Atom	Atom	Length/Å	Atom	Atom	Length/Å
N1	C6	1.383(3)	C8	C9	1.438(3)
N1	C7	1.358(3)	C9	C10	1.511(3)
N1	C22	1.452(3)	C10	C11	1.553(3)
N2	C9	1.306(2)	C10	C14	1.548(3)
N2	C15	1.416(2)	C11	C12	1.542(3)
N3	C10	1.473(2)	C12	C13	1.529(3)
N3	C15	1.292(2)	C13	C14	1.523(3)
C1	C2	1.394(3)	C15	C16	1.471(3)
C1	C6	1.409(3)	C16	C17	1.400(3)
C1	C8	1.448(3)	C16	C21	1.396(3)
C2	C3	1.389(3)	C17	C18	1.384(3)
C3	C4	1.401(3)	C18	C19	1.381(3)
C4	C5	1.378(3)	C19	C20	1.380(3)
C5	C6	1.396(3)	C20	C21	1.379(3)
C7	C8	1.380(3)			

Table 5. Bond Angles for **3aa**

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C6	N1	C22	124.94(18)	N3	C10	C9	102.68(14)
C7	N1	C6	108.53(16)	N3	C10	C11	110.33(15)
C7	N1	C22	126.53(19)	N3	C10	C14	107.83(15)
C9	N2	C15	104.42(16)	C9	C10	C11	115.60(16)
C15	N3	C10	105.08(15)	C9	C10	C14	117.21(16)
C2	C1	C6	119.13(18)	C14	C10	C11	103.06(15)
C2	C1	C8	134.44(18)	C12	C11	C10	105.82(16)
C6	C1	C8	106.43(17)	C13	C12	C11	106.00(16)
C3	C2	C1	118.34(19)	C14	C13	C12	103.63(17)
C2	C3	C4	121.6(2)	C13	C14	C10	102.11(16)
C5	C4	C3	121.1(2)	N2	C15	C16	118.83(16)
C4	C5	C6	117.1(2)	N3	C15	N2	116.95(16)
N1	C6	C1	108.31(17)	N3	C15	C16	124.22(17)
N1	C6	C5	129.02(19)	C17	C16	C15	119.98(18)
C5	C6	C1	122.67(19)	C21	C16	C15	121.11(18)
N1	C7	C8	110.82(18)	C21	C16	C17	118.86(18)
C7	C8	C1	105.91(17)	C18	C17	C16	120.2(2)
C7	C8	C9	128.01(18)	C19	C18	C17	120.1(2)
C9	C8	C1	126.08(17)	C20	C19	C18	120.09(19)
N2	C9	C8	121.74(17)	C21	C20	C19	120.4(2)
N2	C9	C10	110.87(16)	C20	C21	C16	120.3(2)
C8	C9	C10	127.38(16)				

Table 6. Torsion Angles for **3aa**

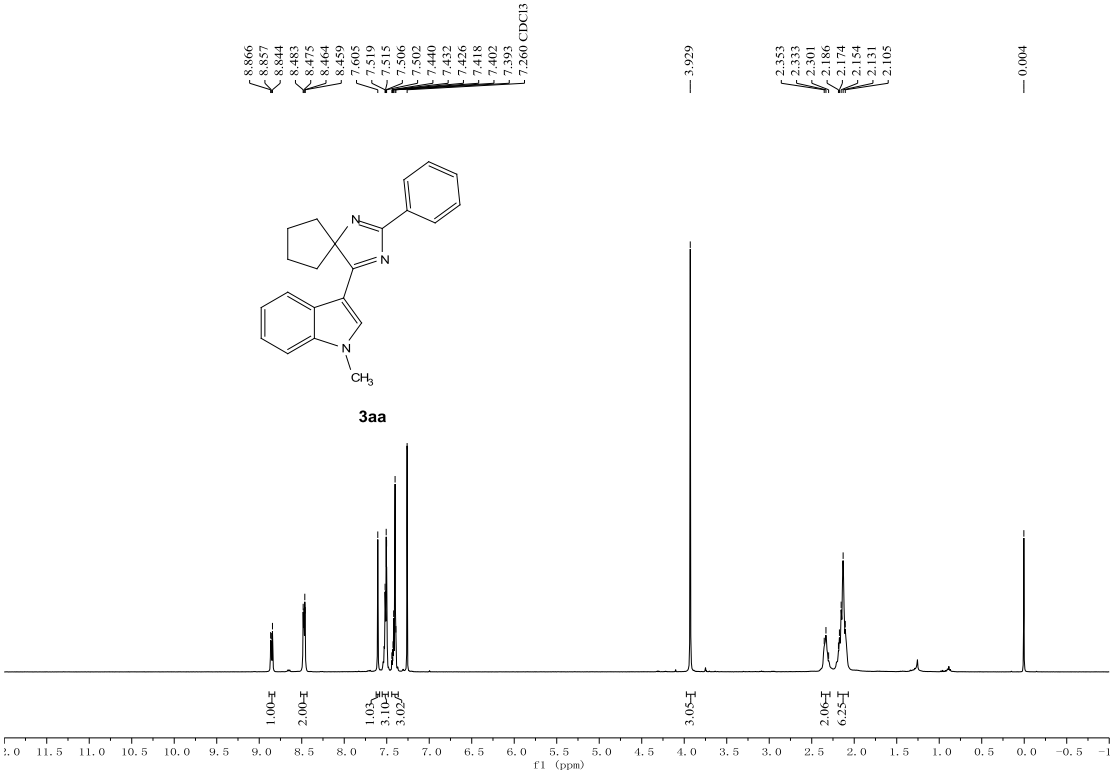
A	B	C	D	Angle/°	A	B	C	D	Angle/°
N1	C7	C8	C1	0.6(2)	C8	C1	C6	C5	-179.65(18)
N1	C7	C8	C9	-178.93(18)	C8	C9	C10	N3	-178.53(17)
N2	C9	C10	N3	0.7(2)	C8	C9	C10	C11	-58.4(3)
N2	C9	C10	C11	120.83(18)	C8	C9	C10	C14	63.5(2)
N2	C9	C10	C14	-117.28(18)	C9	N2	C15	N3	0.7(2)
N2	C15	C16	C17	2.4(3)	C9	N2	C15	C16	-178.66(16)
N2	C15	C16	C21	179.72(17)	C9	C10	C11	C12	152.22(17)
N3	C10	C11	C12	-91.87(18)	C9	C10	C14	C13	-168.95(16)
N3	C10	C14	C13	75.93(18)	C10	N3	C15	N2	-0.2(2)
N3	C15	C16	C17	-176.87(18)	C10	N3	C15	C16	179.04(17)
N3	C15	C16	C21	0.5(3)	C10	C11	C12	C13	3.2(2)
C1	C2	C3	C4	-0.2(3)	C11	C10	C14	C13	-40.77(18)
C1	C8	C9	N2	-3.1(3)	C11	C12	C13	C14	-28.8(2)
C1	C8	C9	C10	176.01(18)	C12	C13	C14	C10	43.19(19)
C2	C1	C6	N1	-178.96(17)	C14	C10	C11	C12	23.0(2)
C2	C1	C6	C5	0.9(3)	C15	N2	C9	C8	178.47(16)
C2	C1	C8	C7	178.7(2)	C15	N2	C9	C10	-0.8(2)
C2	C1	C8	C9	-1.8(4)	C15	N3	C10	C9	-0.23(19)
C2	C3	C4	C5	1.1(3)	C15	N3	C10	C11	-123.98(17)
C3	C4	C5	C6	-0.9(3)	C15	N3	C10	C14	124.15(17)
C4	C5	C6	N1	179.77(19)	C15	C16	C17	C18	177.17(19)
C4	C5	C6	C1	-0.1(3)	C15	C16	C21	C20	-178.09(19)
C6	N1	C7	C8	-0.3(2)	C16	C17	C18	C19	0.6(3)
C6	C1	C2	C3	-0.7(3)	C17	C16	C21	C20	-0.7(3)
C6	C1	C8	C7	-0.6(2)	C17	C18	C19	C20	-0.1(4)
C6	C1	C8	C9	178.87(18)	C18	C19	C20	C21	-0.8(4)
C7	N1	C6	C1	-0.2(2)	C19	C20	C21	C16	1.3(3)
C7	N1	C6	C5	180.0(2)	C21	C16	C17	C18	-0.2(3)
C7	C8	C9	N2	176.30(19)	C22	N1	C6	C1	179.12(18)
C7	C8	C9	C10	-4.6(3)	C22	N1	C6	C5	-0.7(3)
C8	C1	C2	C3	180.0(2)	C22	N1	C7	C8	-179.53(19)
C8	C1	C6	N1	0.5(2)					

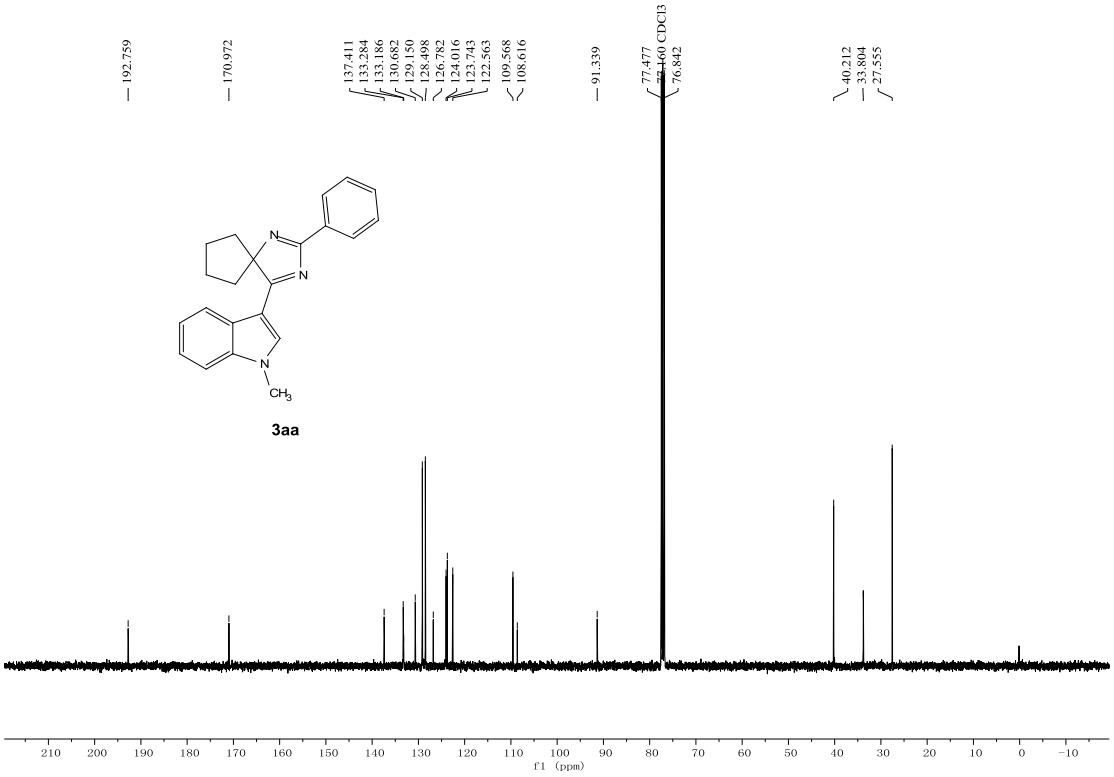
Table 7. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **3aa**

Atom	***x***	***y***	***z***	**U(eq)**
H2	7860.87	2295.26	4796.66	41
H3	8893.1	2208.26	3685.75	49
H4	11349.98	3133.89	3528.17	53
H5	12902.18	4133.57	4493.23	49
H7	11080.39	4440.04	6854.92	40
H11A	9068.42	2063.97	7911.23	41
H11B	10395.05	2873.38	7631.8	41
H12A	9170.17	3125.65	8917.56	51
H12B	10410.54	3975.25	8614.75	51
H13A	6852.99	4136.6	8442.35	46
H13B	8161.48	5142.57	8559.89	46
H14A	8642.65	5038.62	7345.05	41
H14B	6660.52	4895.82	7265.3	41
H17	4570.95	1452.17	5305.66	45
H18	2195.64	348.52	4967.88	52
H19	409.03	-27.05	5809.72	52
H20	990.27	695.01	6990.93	52
H21	3390.37	1755.14	7350.05	45
H22A	13671.76	5313.6	6472.36	68
H22B	13461.84	5572.65	5624.21	68
H22C	14435.31	4488.18	5943.93	68

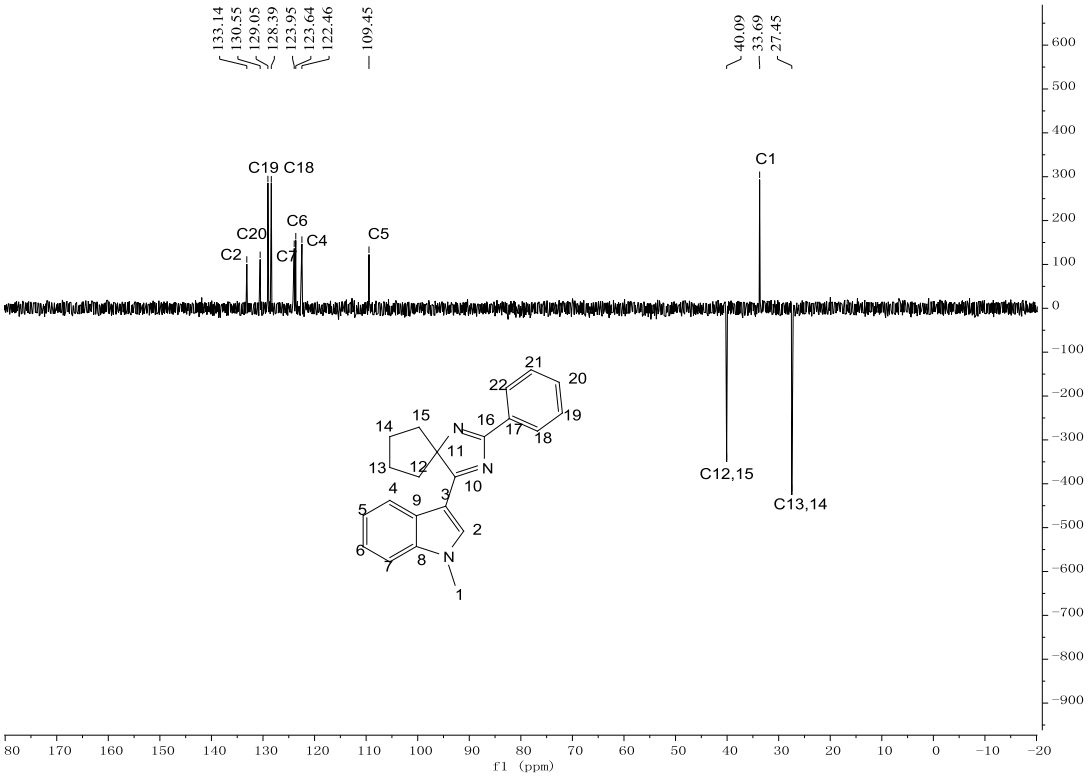
8. Copies of ^{1}H, ^{13}C and ^{19}F NMR spectra of all products

^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3aa** (**$CDCl_3$**)

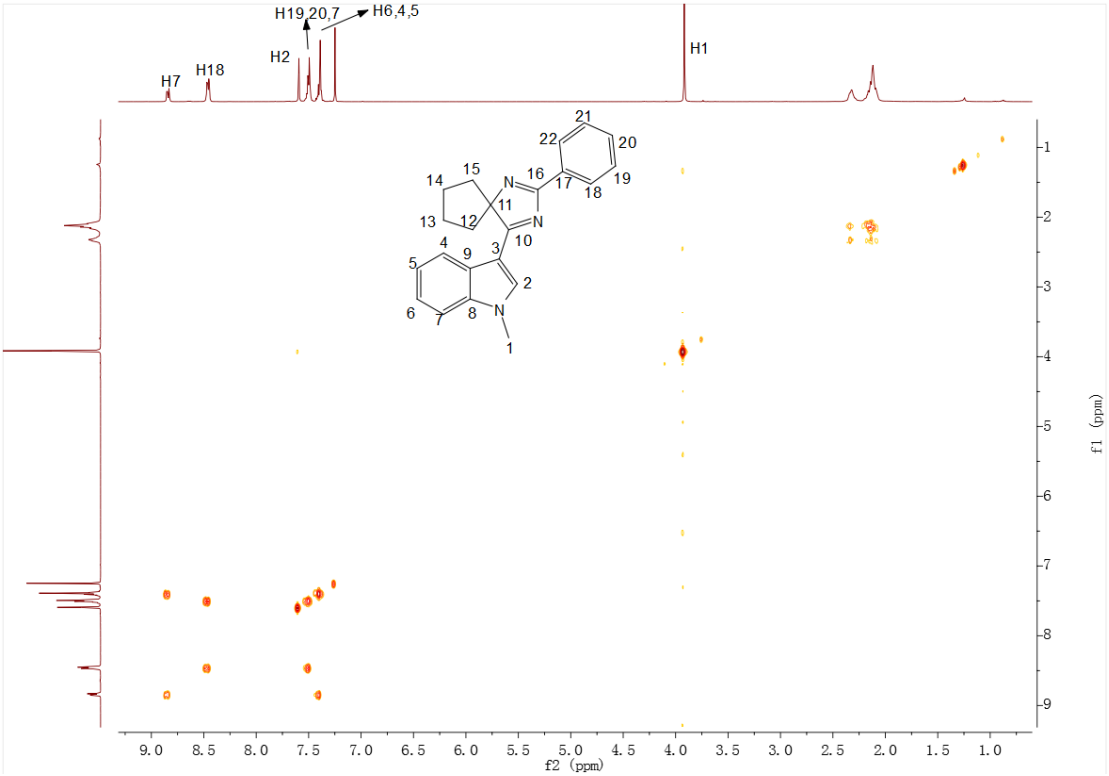




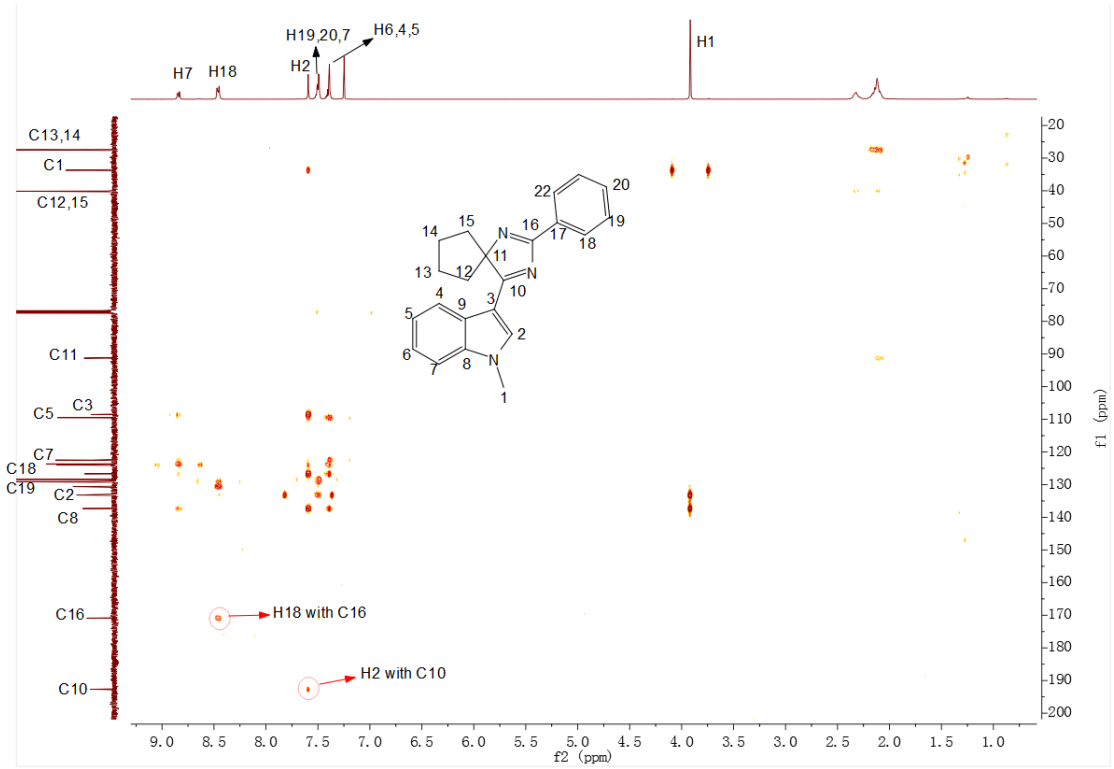
DPET spectra of **3aa** (**$CDCl_3$**)



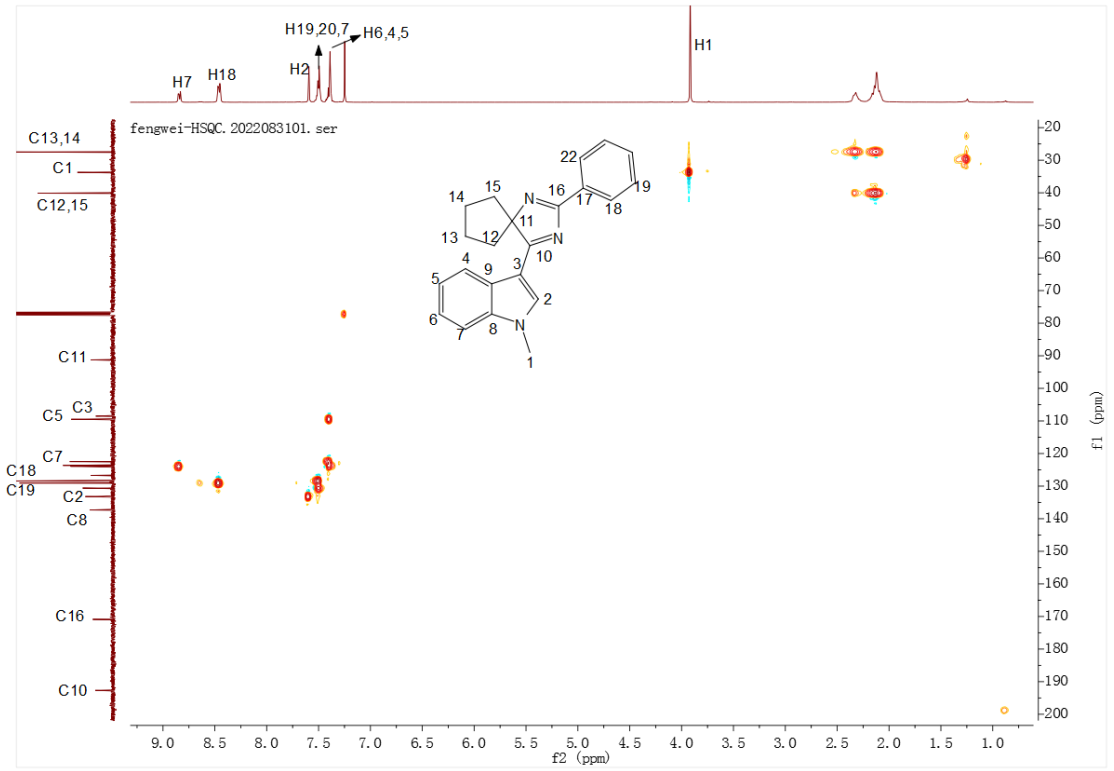
H-H COSY of **3aa** (**$CDCl_3$**)



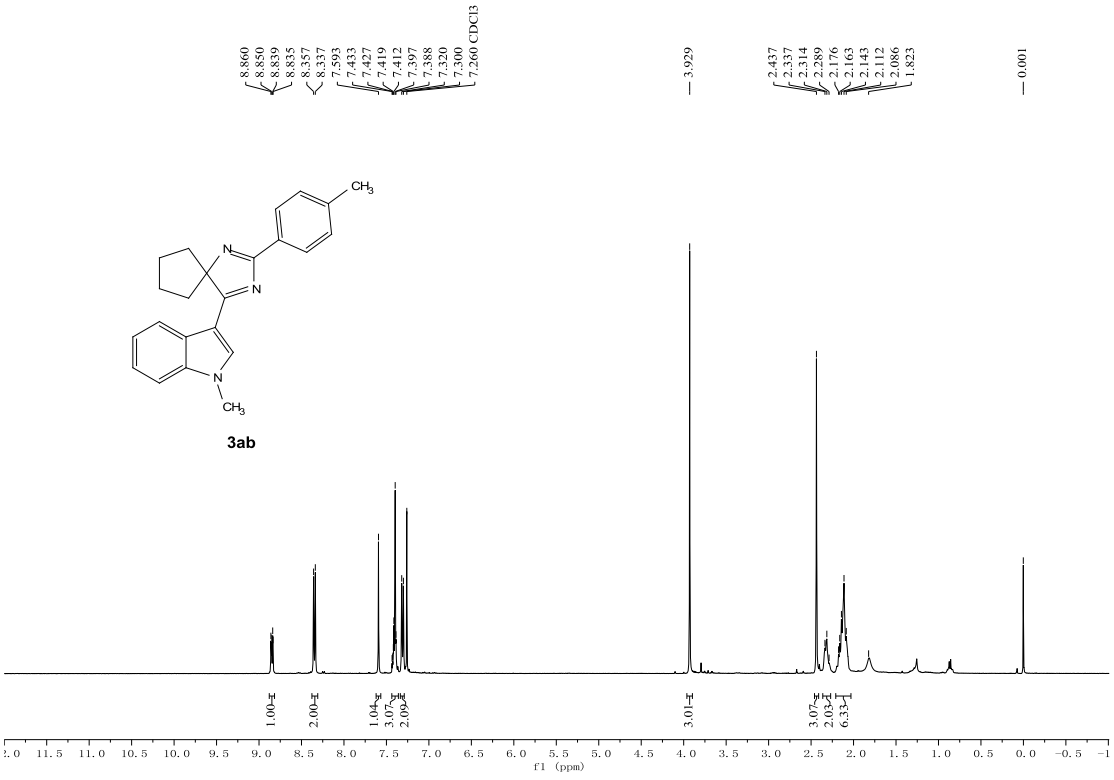
HMBC of **3aa** (**$CDCl_3$**)

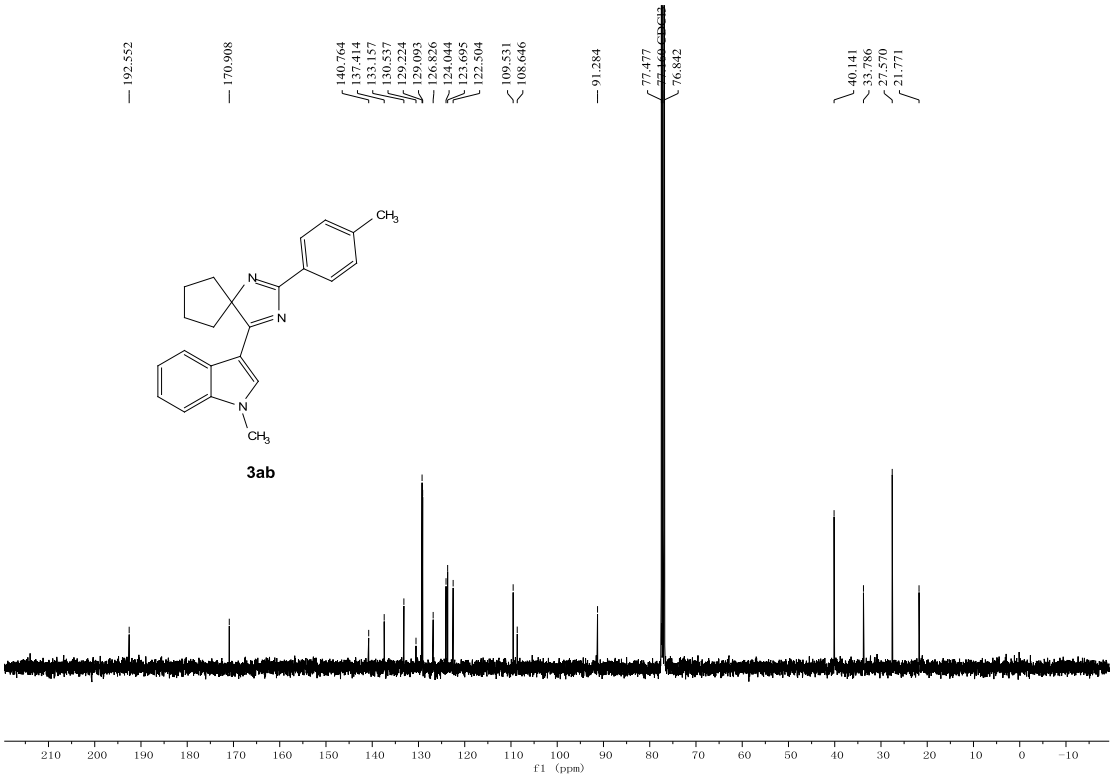


HSQC of **3aa** (**$CDCl_3$**)

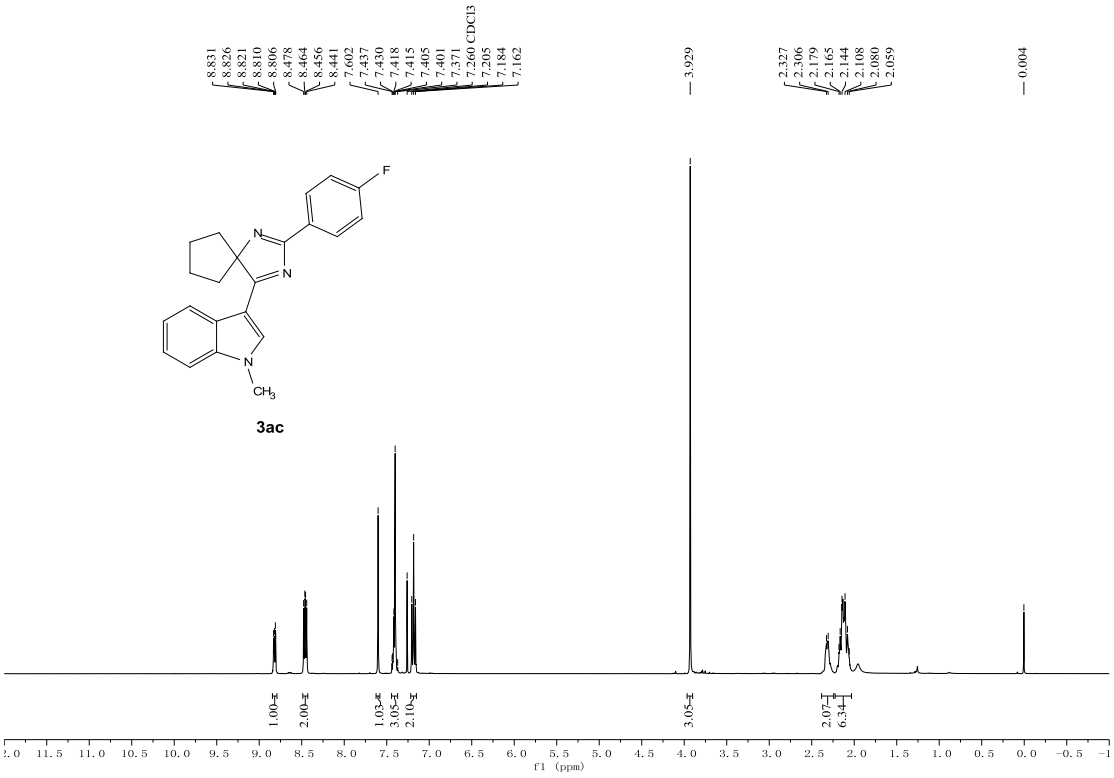


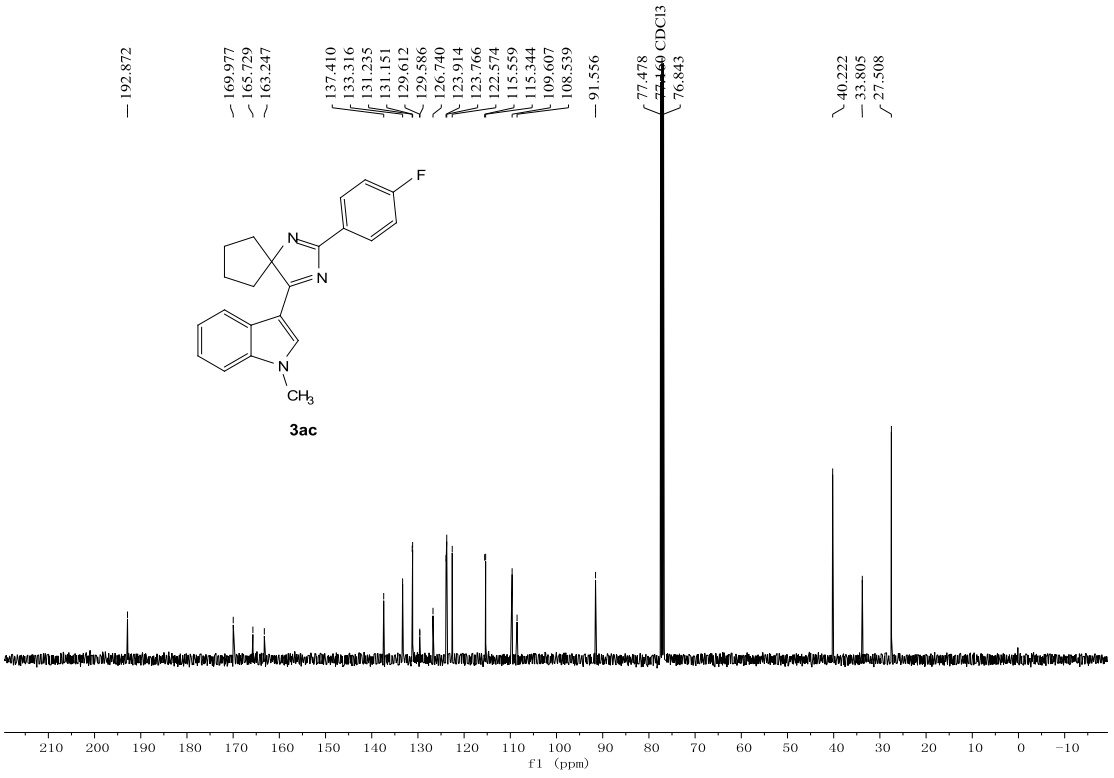
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3ab** (**$CDCl_3$**)

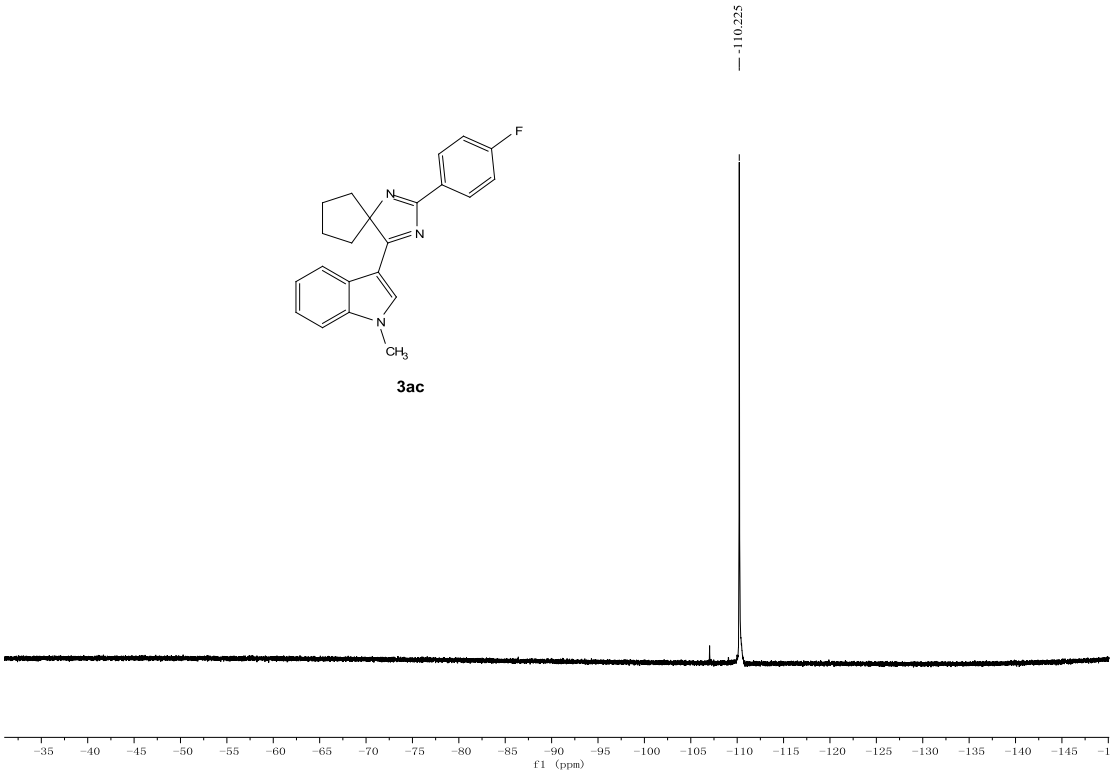




^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3ac** (**$CDCl_3$**)

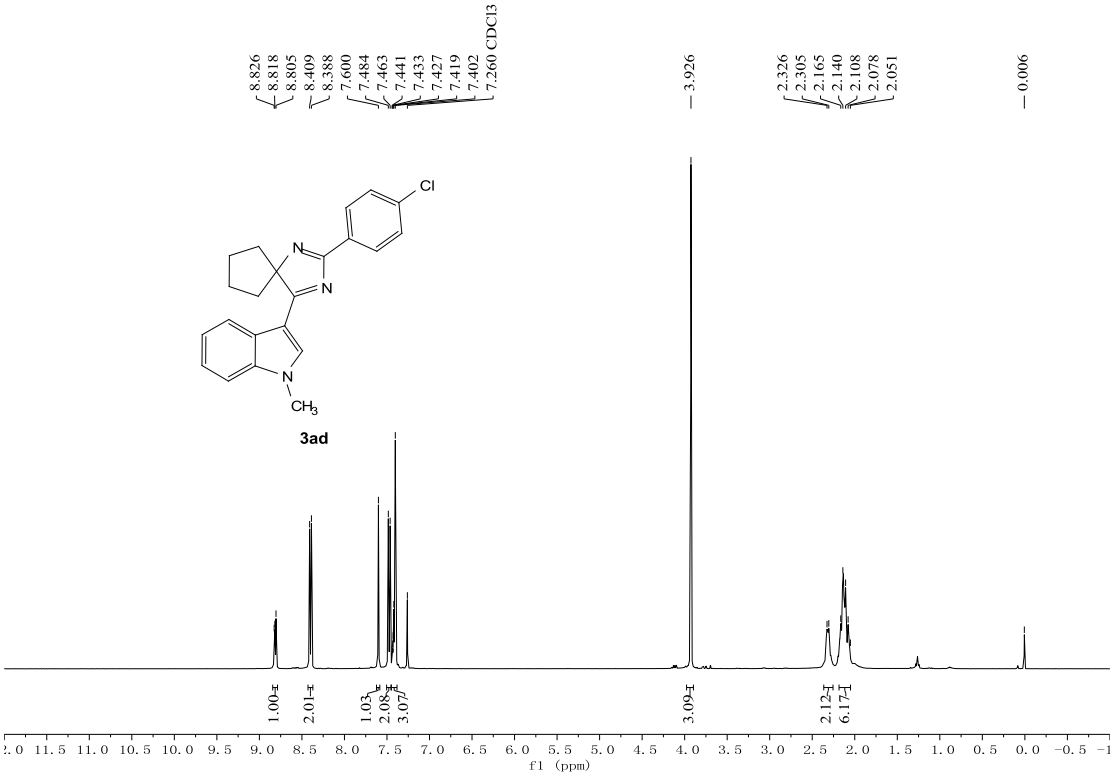


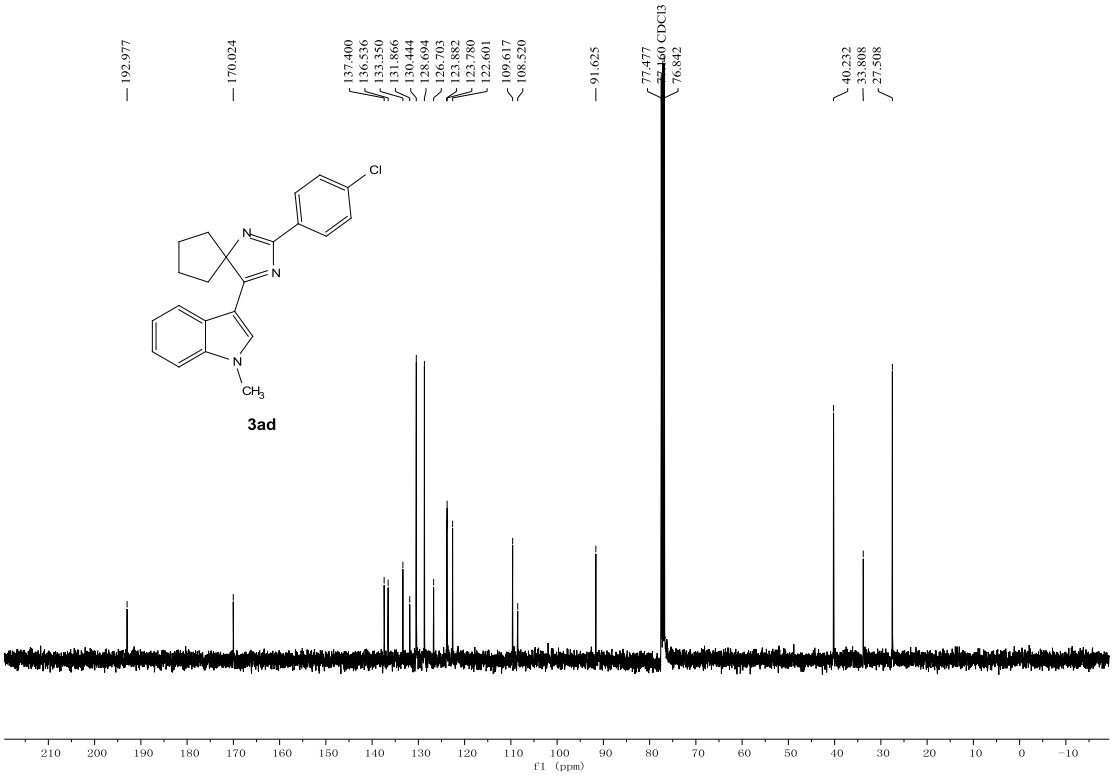



-110.225
F
N
N
N
CH3
−35 −40 −45 −50 −55 −60 −65 −70 −75 −80 −85 −90 −95 −100 −105 −110 −115 −120 −125 −130 −135 −140 −145
f1 (ppm)

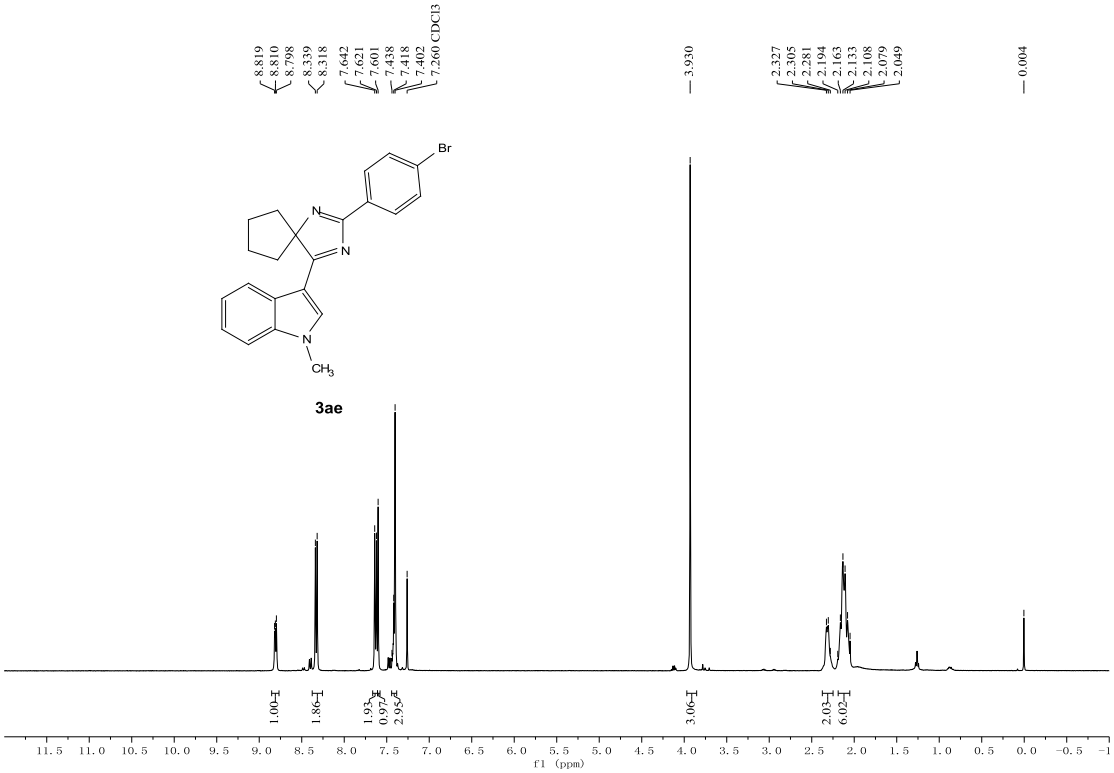
3ac

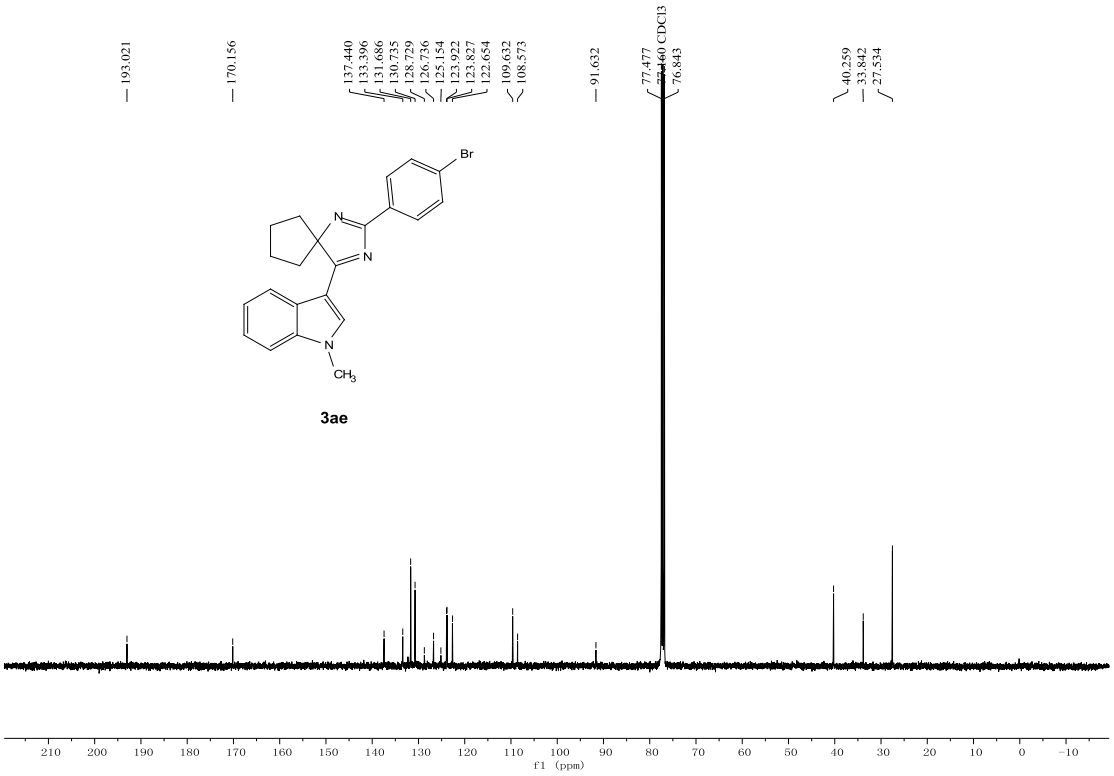
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3ad** (**$CDCl_3$**)



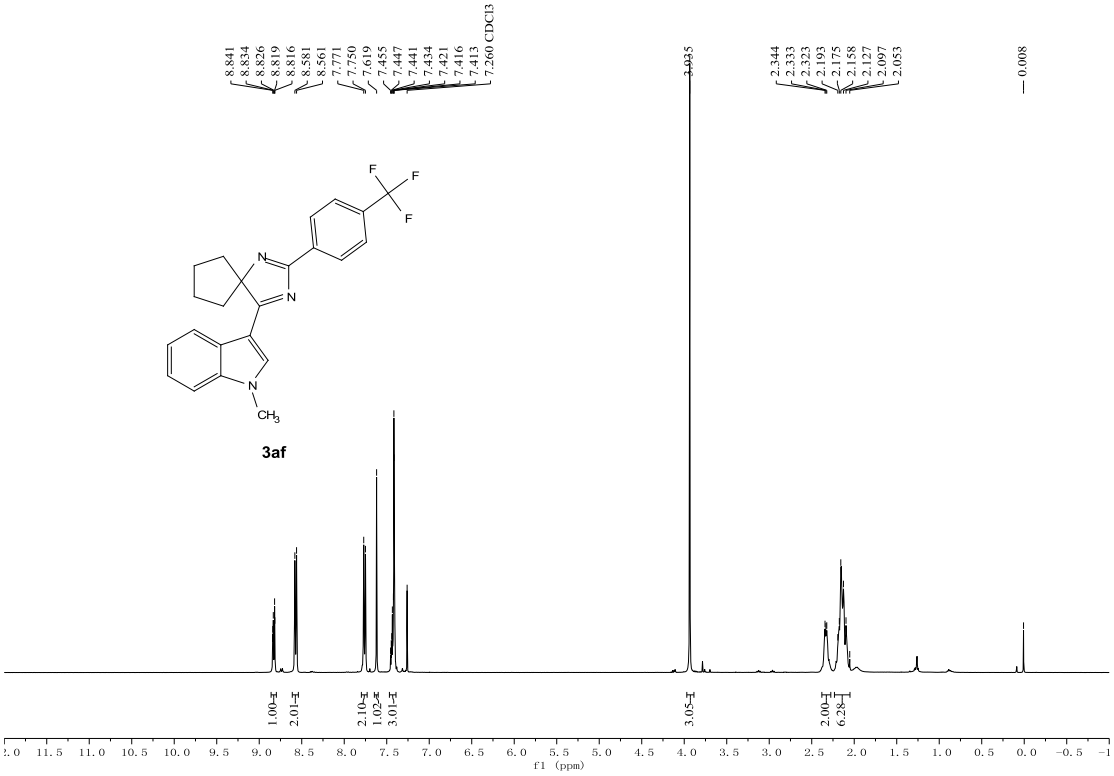


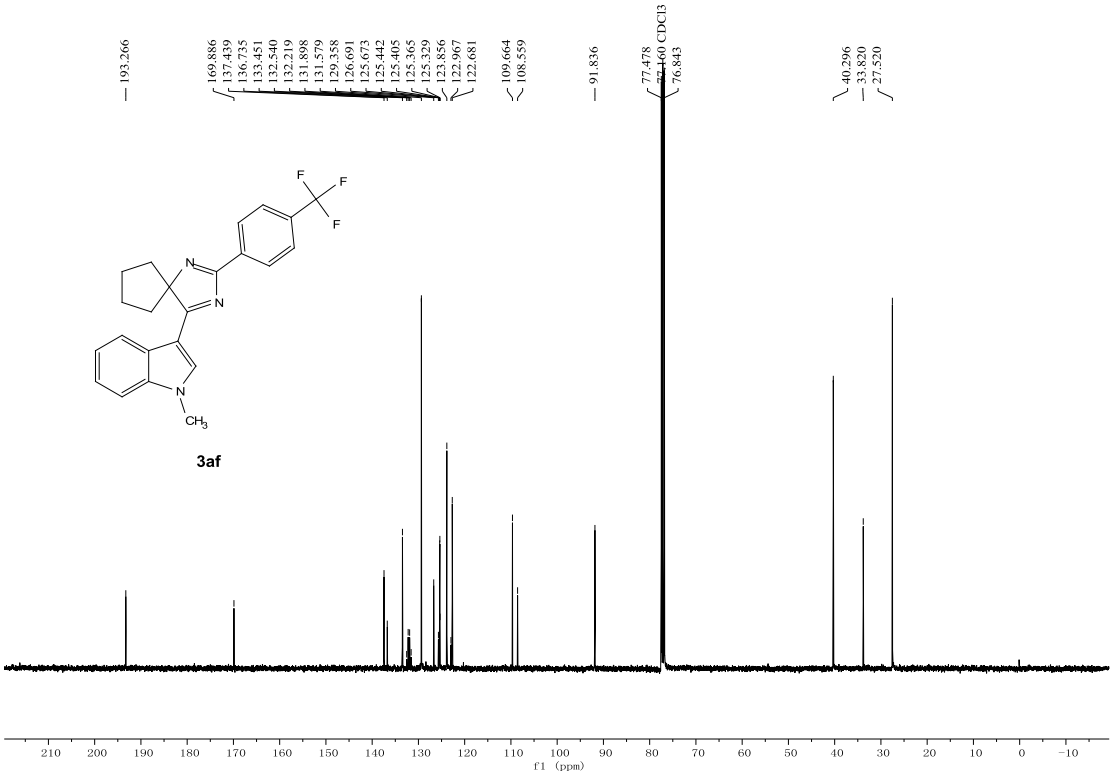
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3ae** (**$CDCl_3$**)

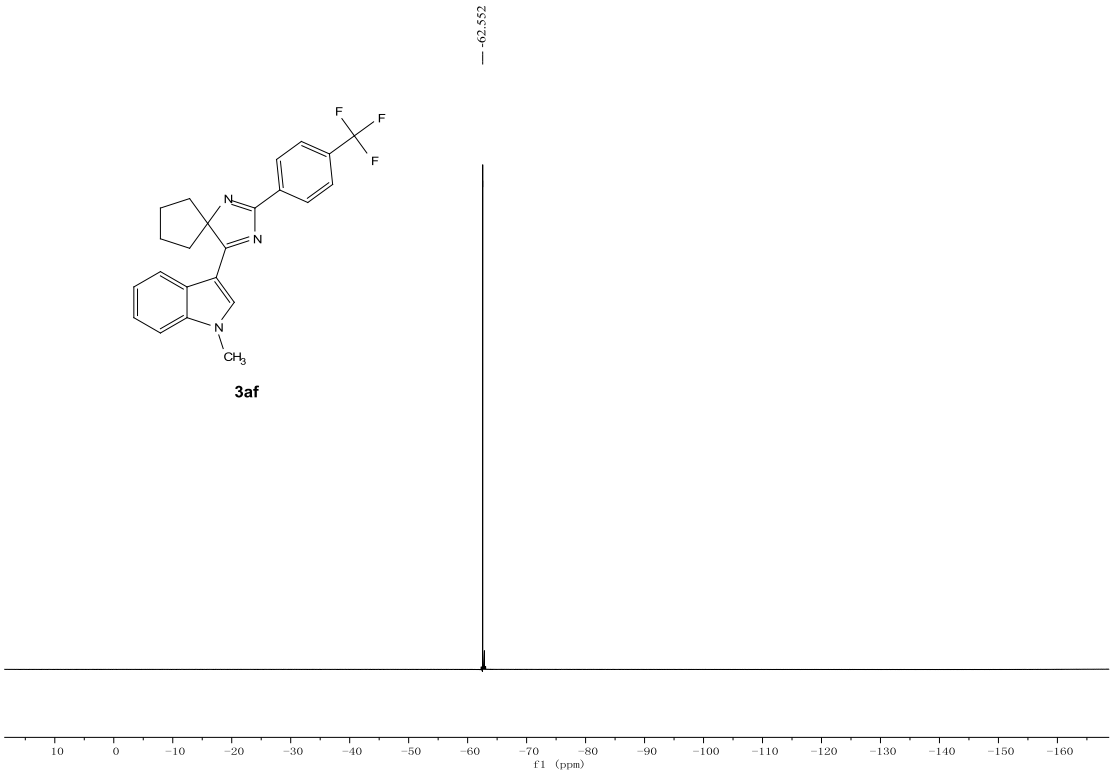




^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3af** (**$CDCl_3$**)

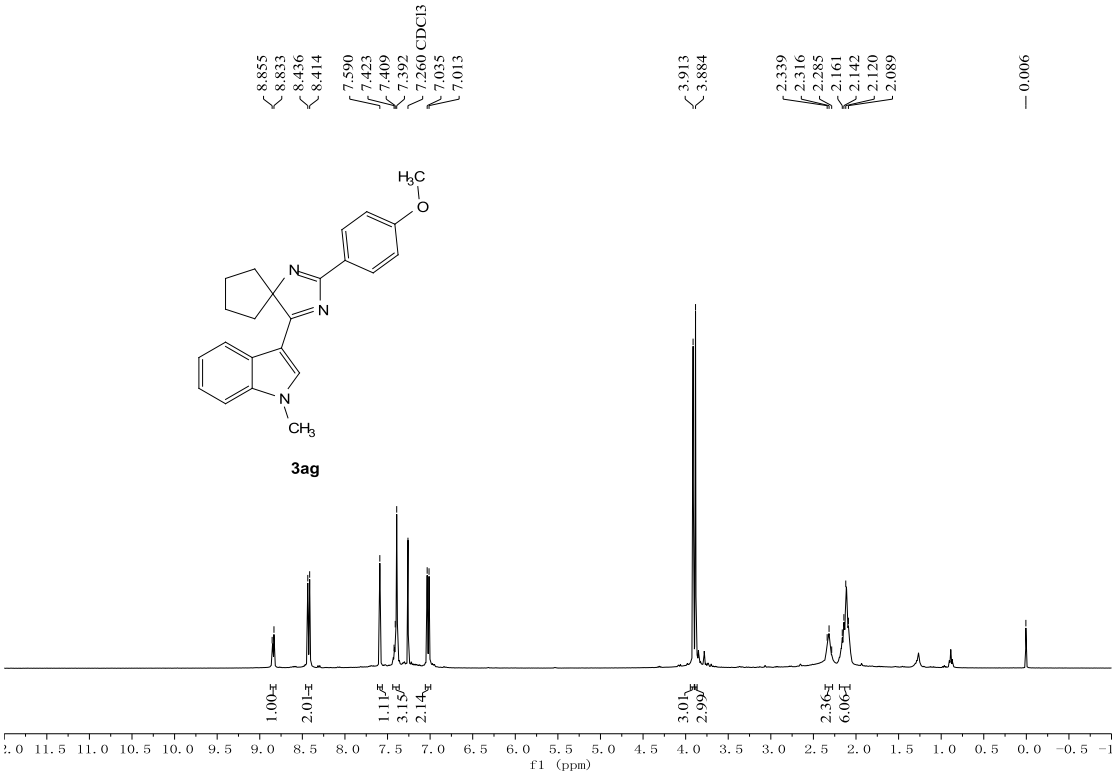


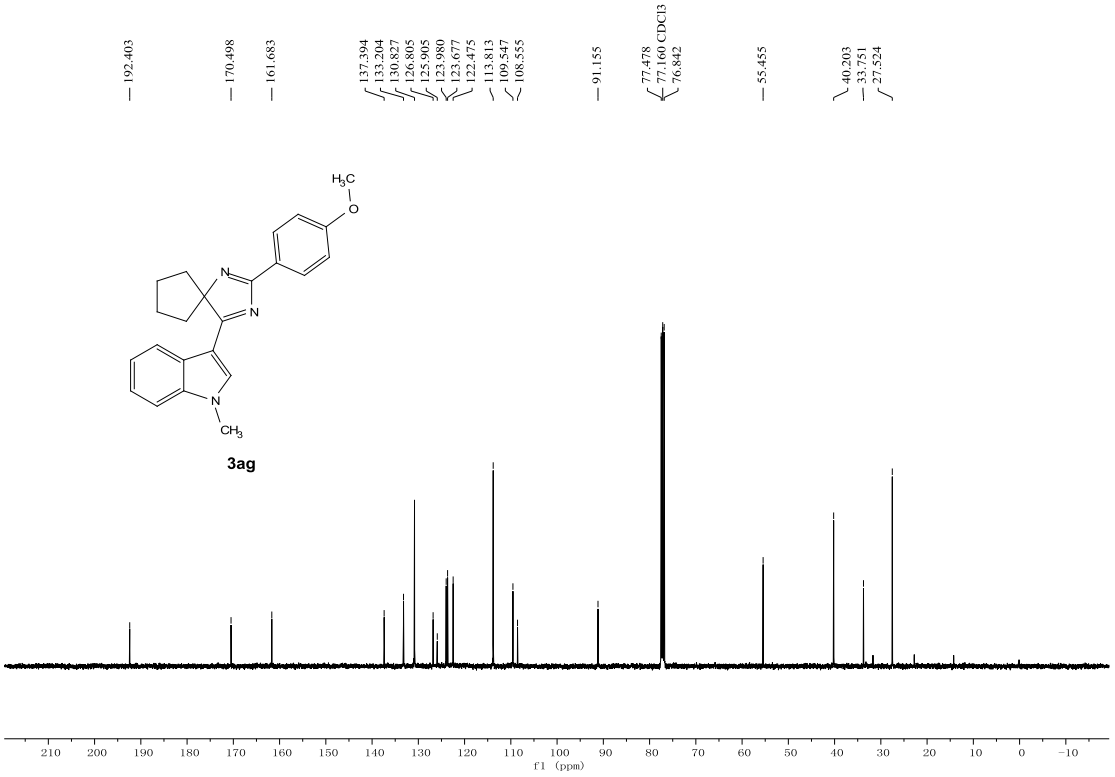



-62.552
F
F
F
N
N
N
CH3
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
f1 (ppm)

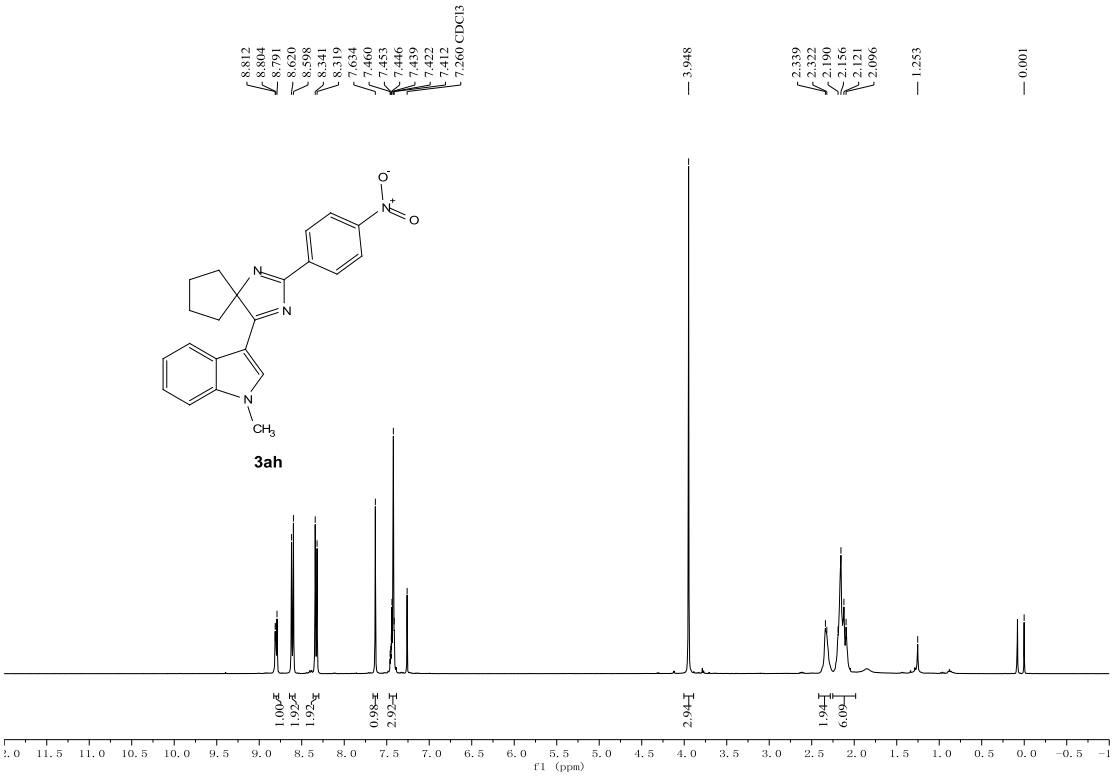
3af

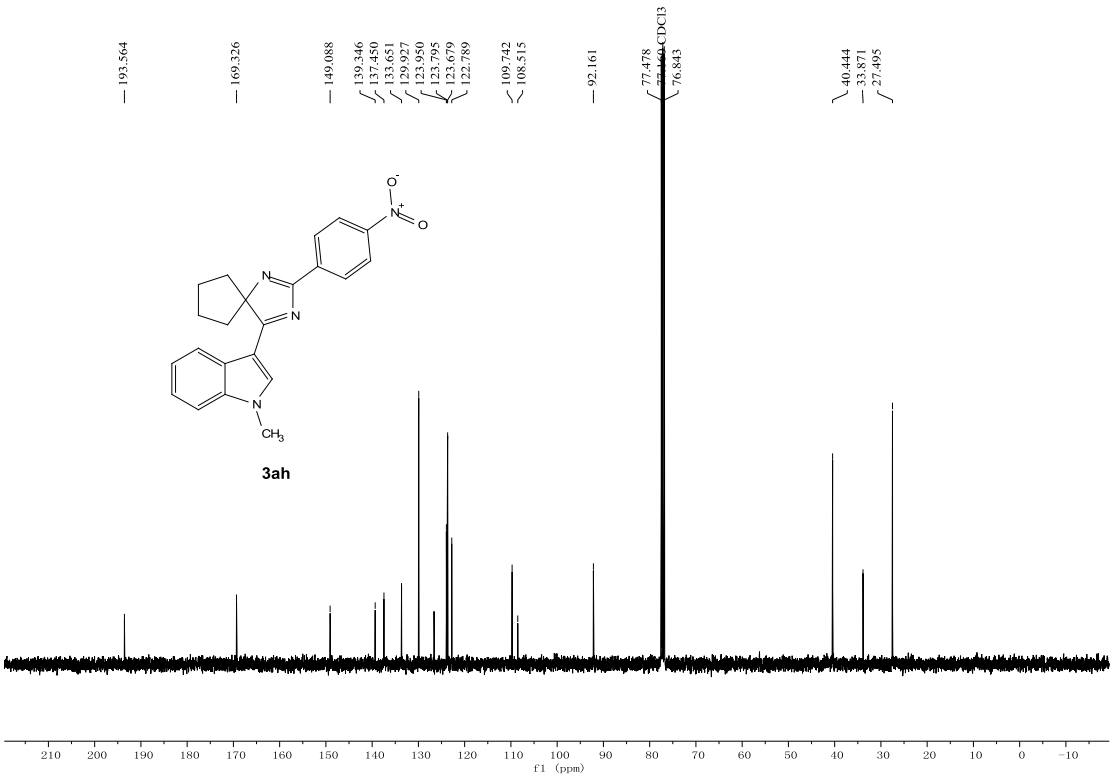
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3ag** (**$CDCl_3$**)



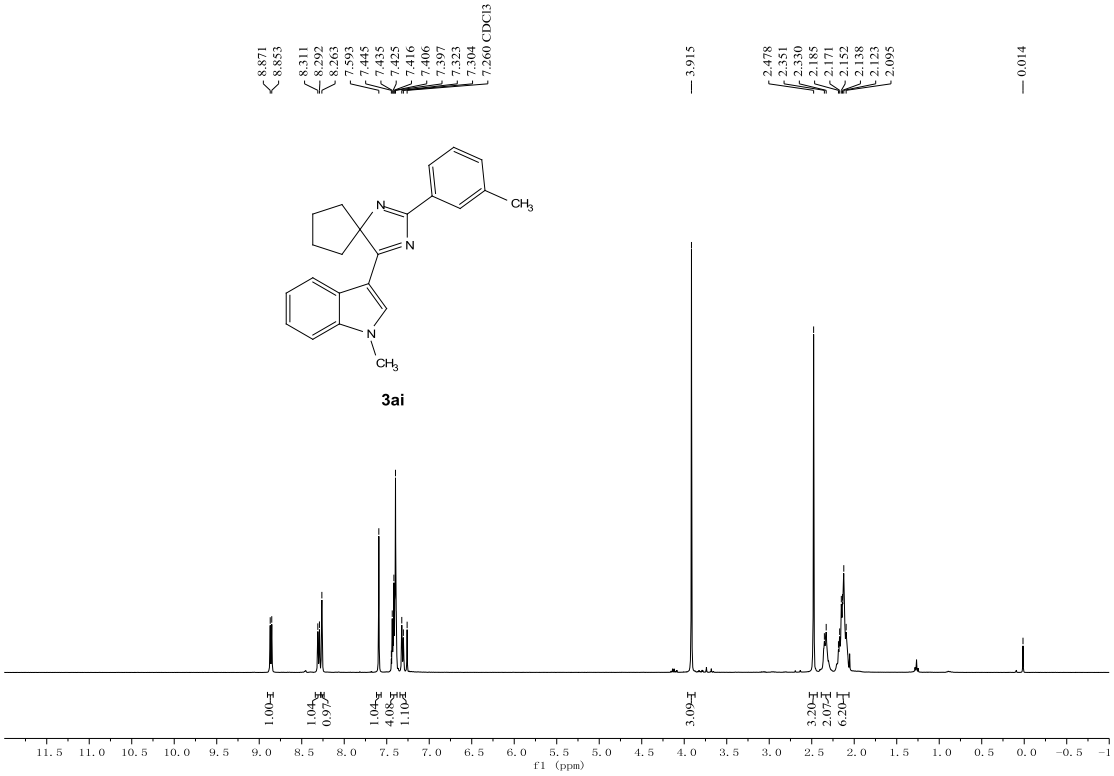


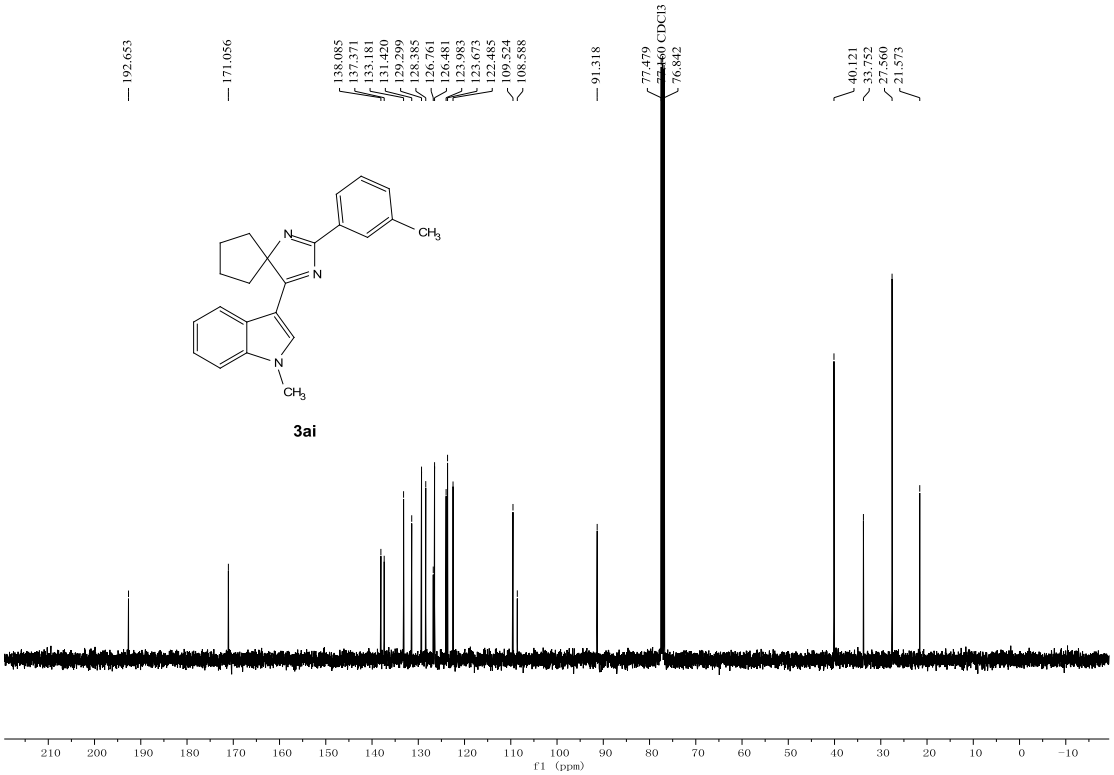
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3ah** (**$CDCl_3$**)



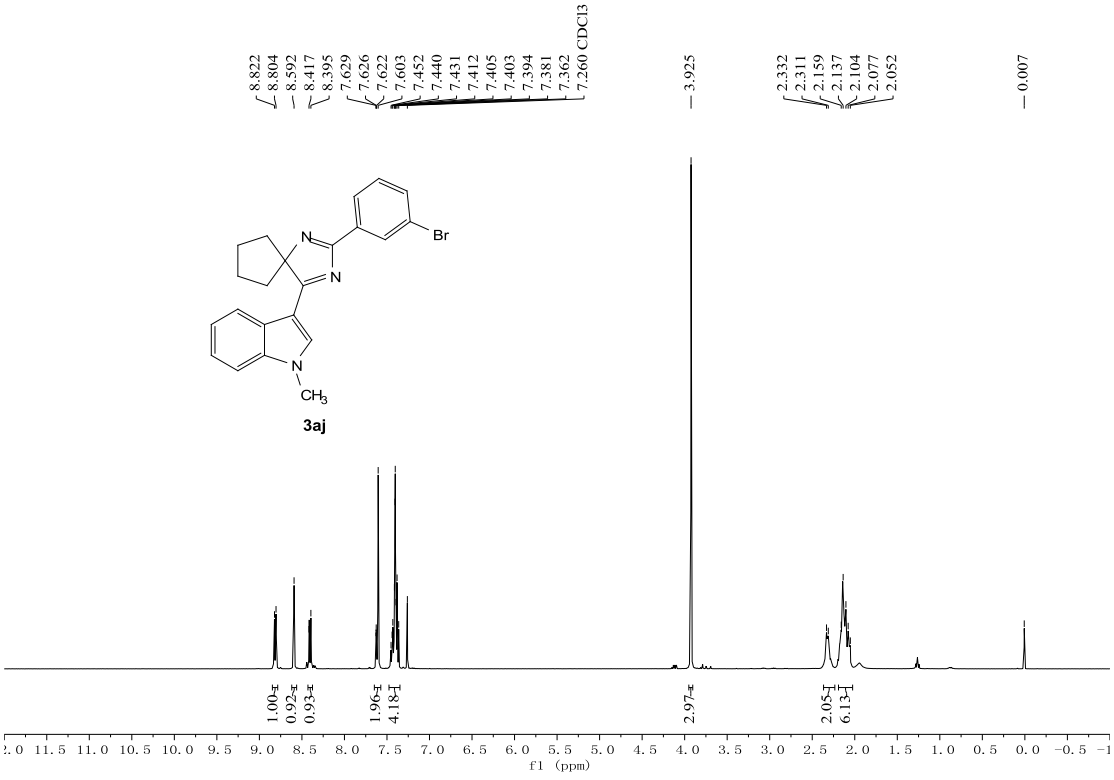


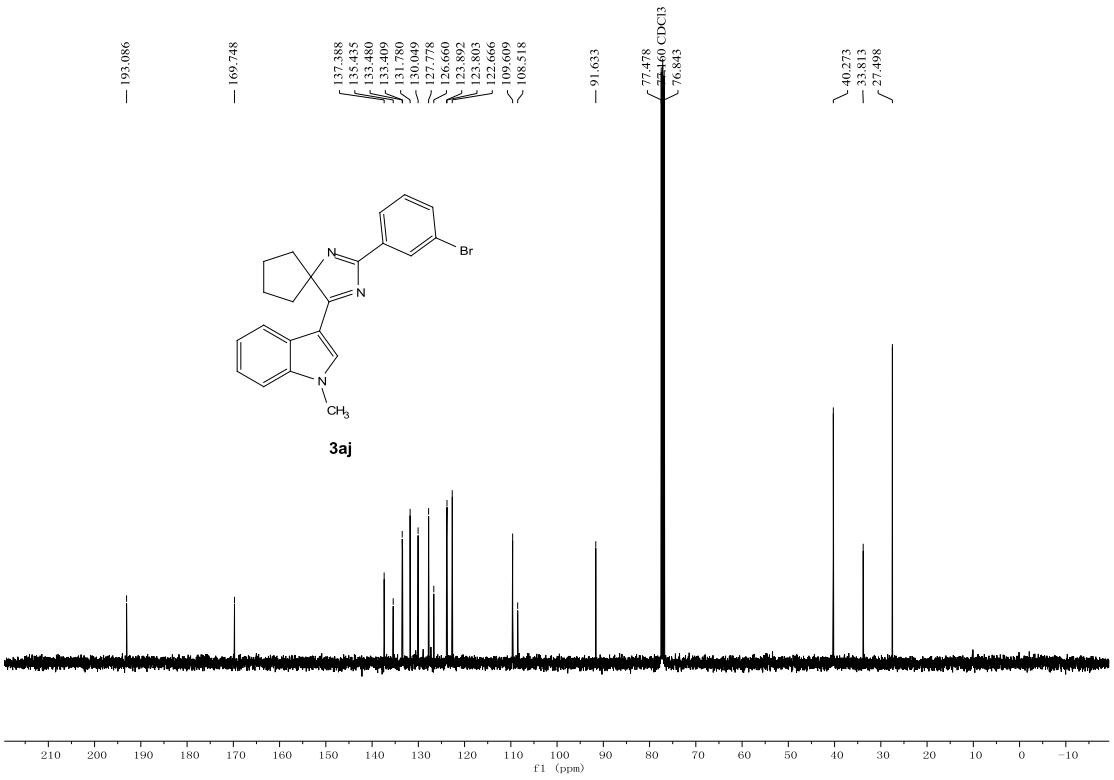
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3ai** (**$CDCl_3$**)



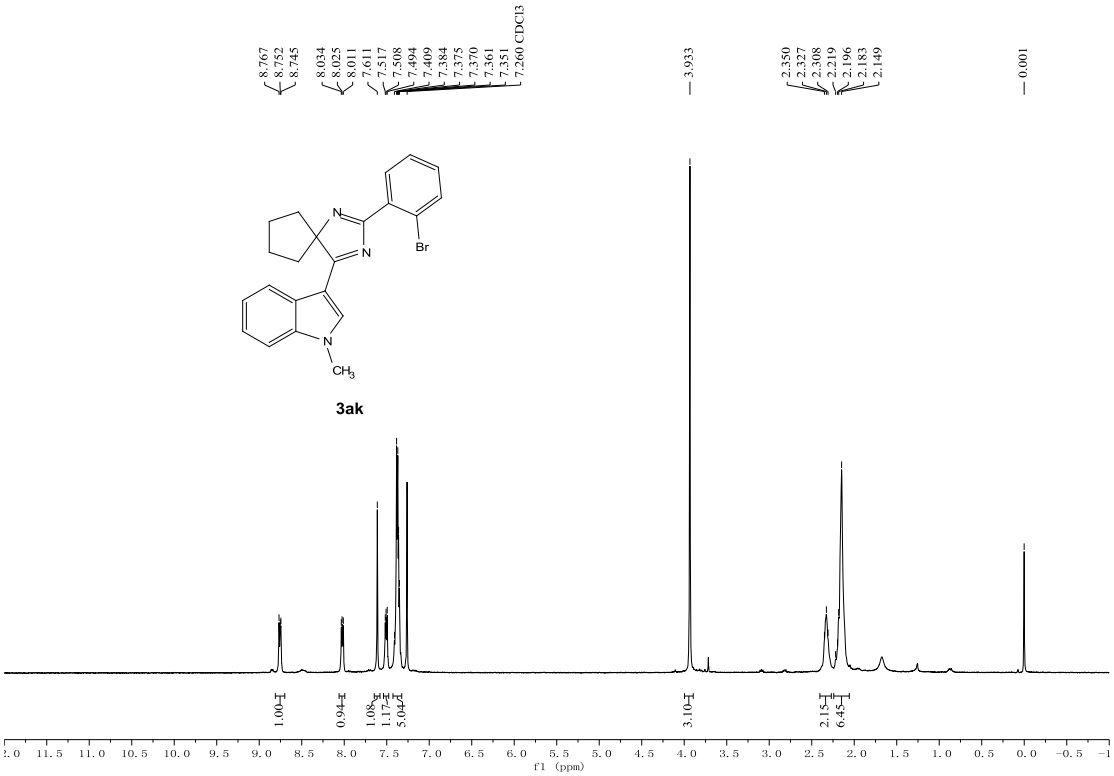


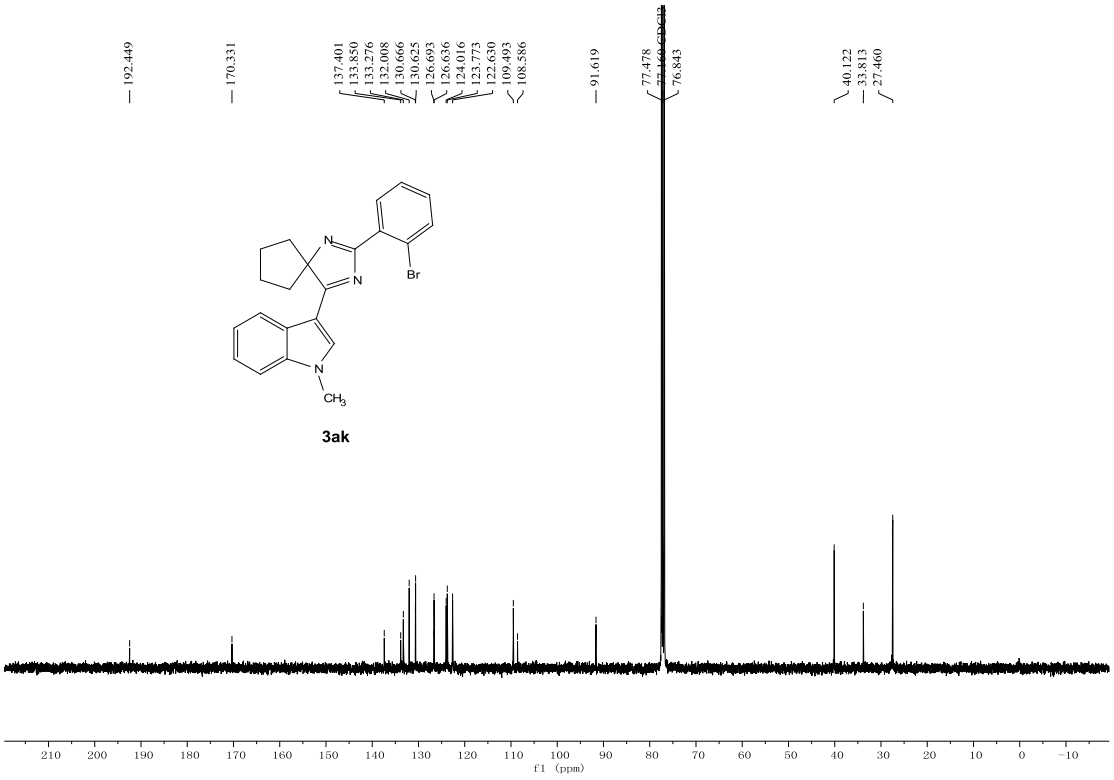
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3aj** (**$CDCl_3$**)



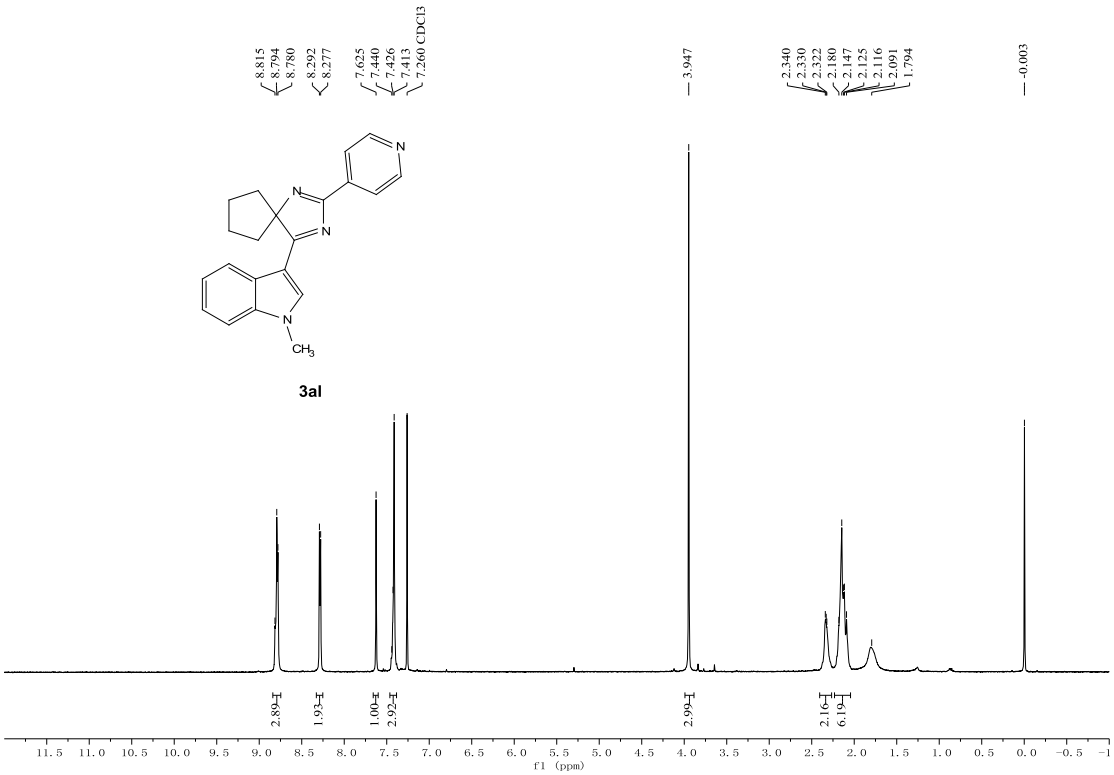


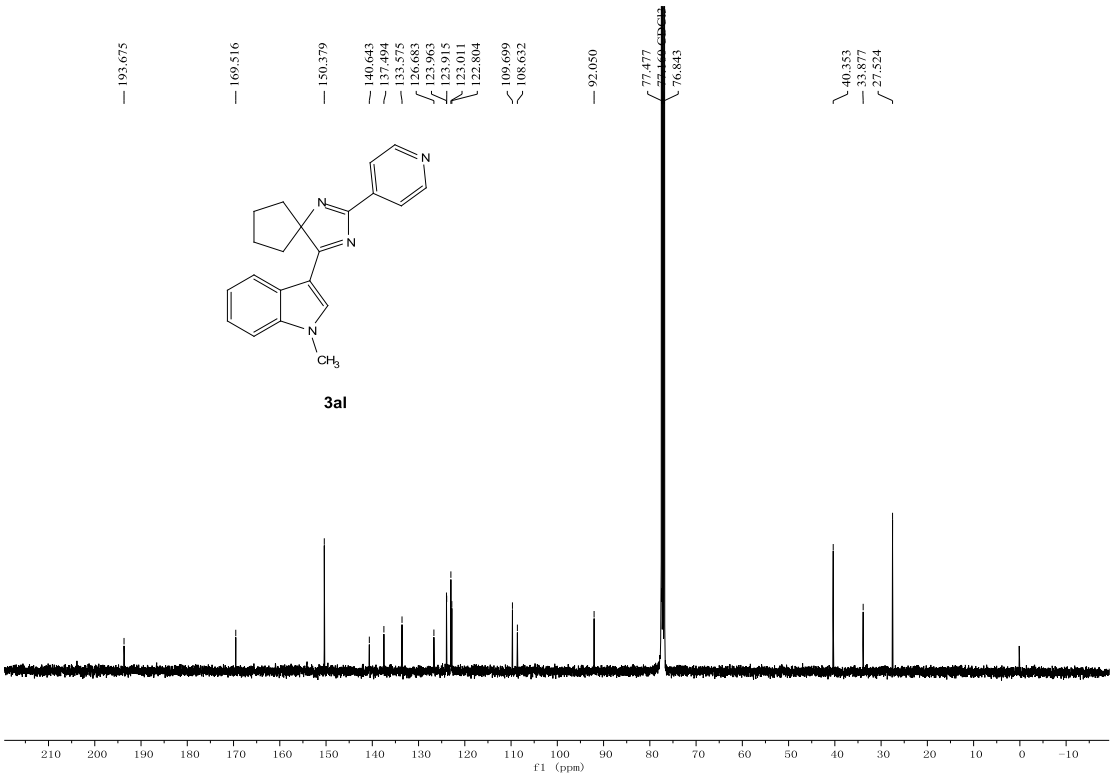
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3ak** (**$CDCl_3$**)



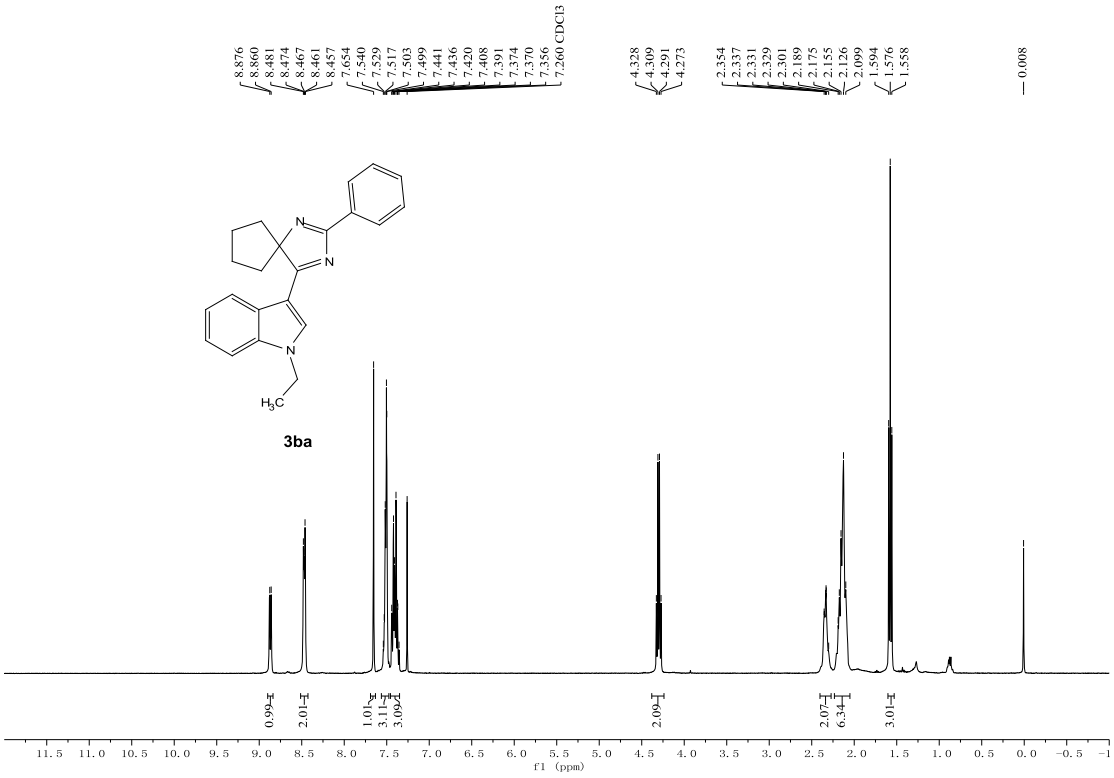


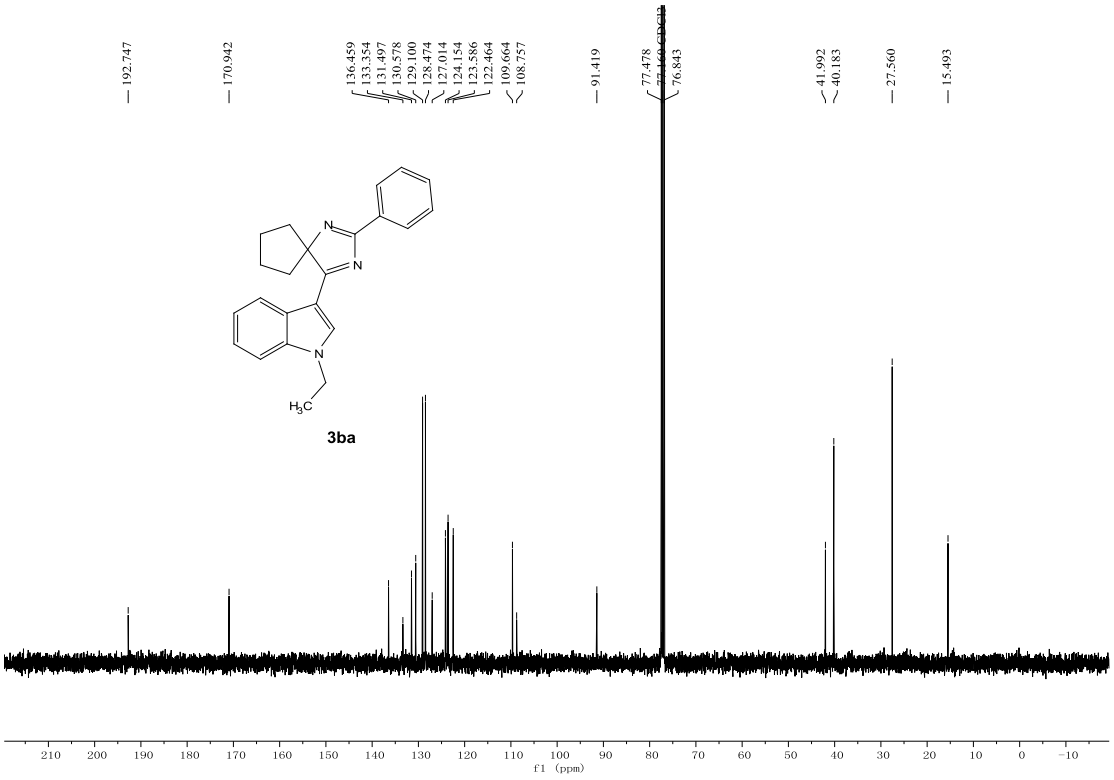
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3al** (**$CDCl_3$**)



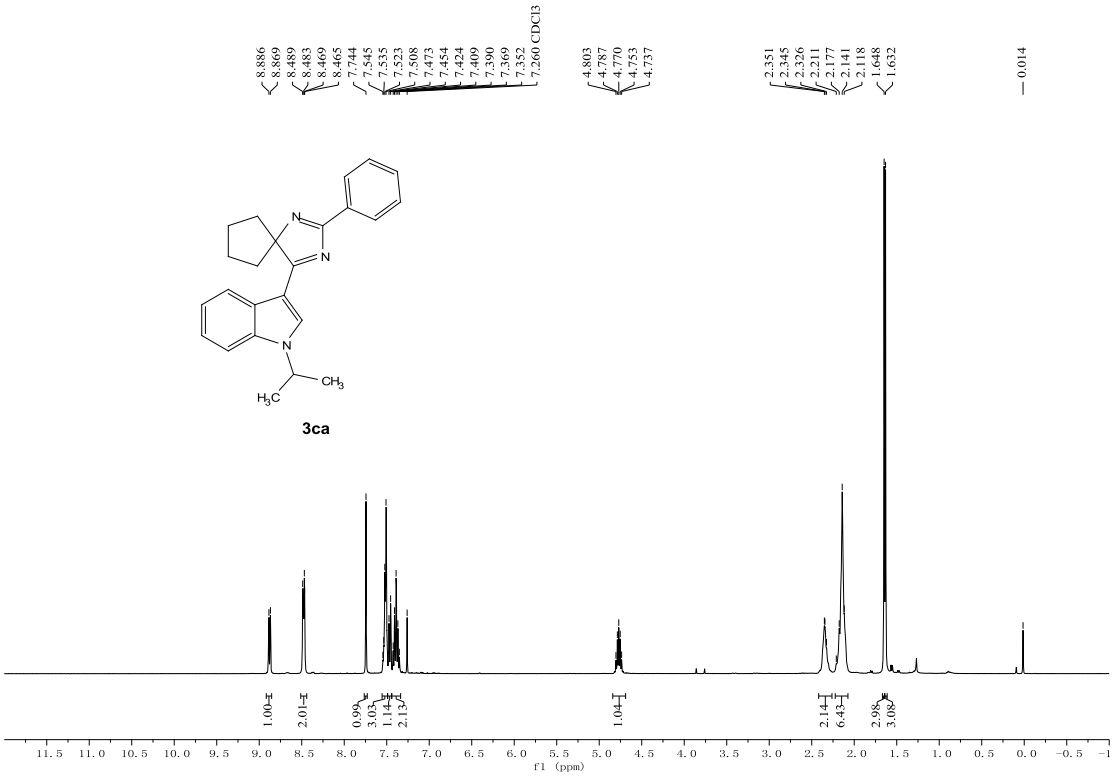


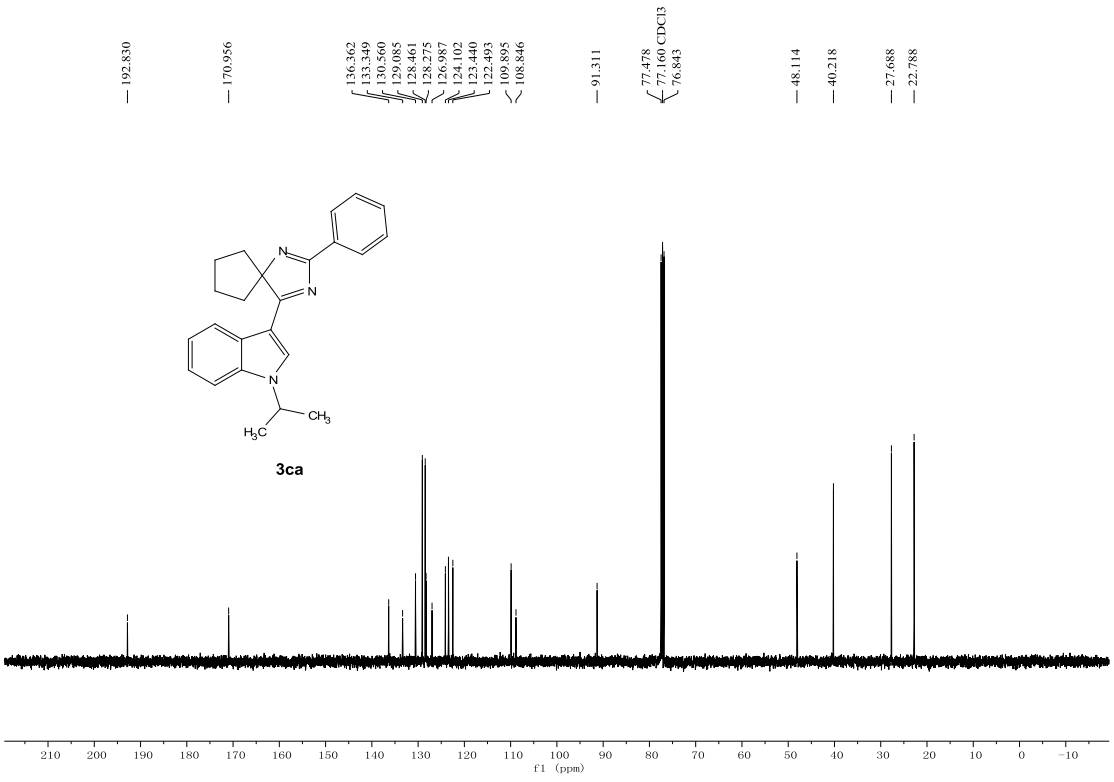
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3ba** (**$CDCl_3$**)



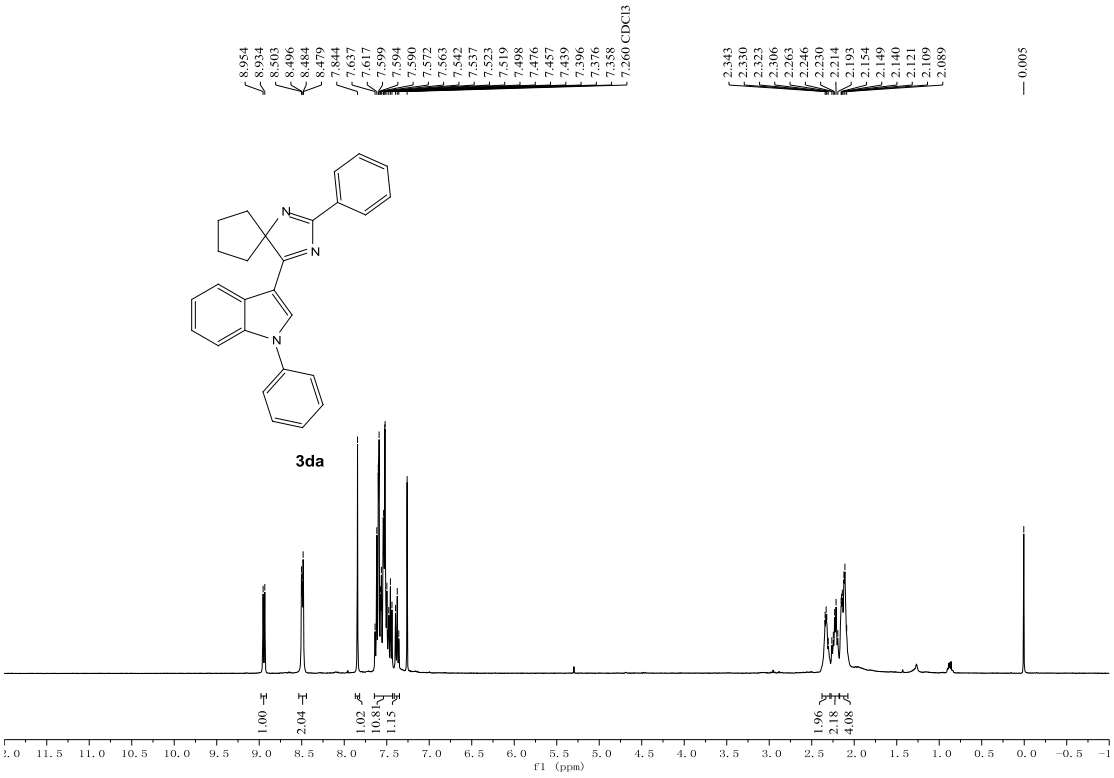


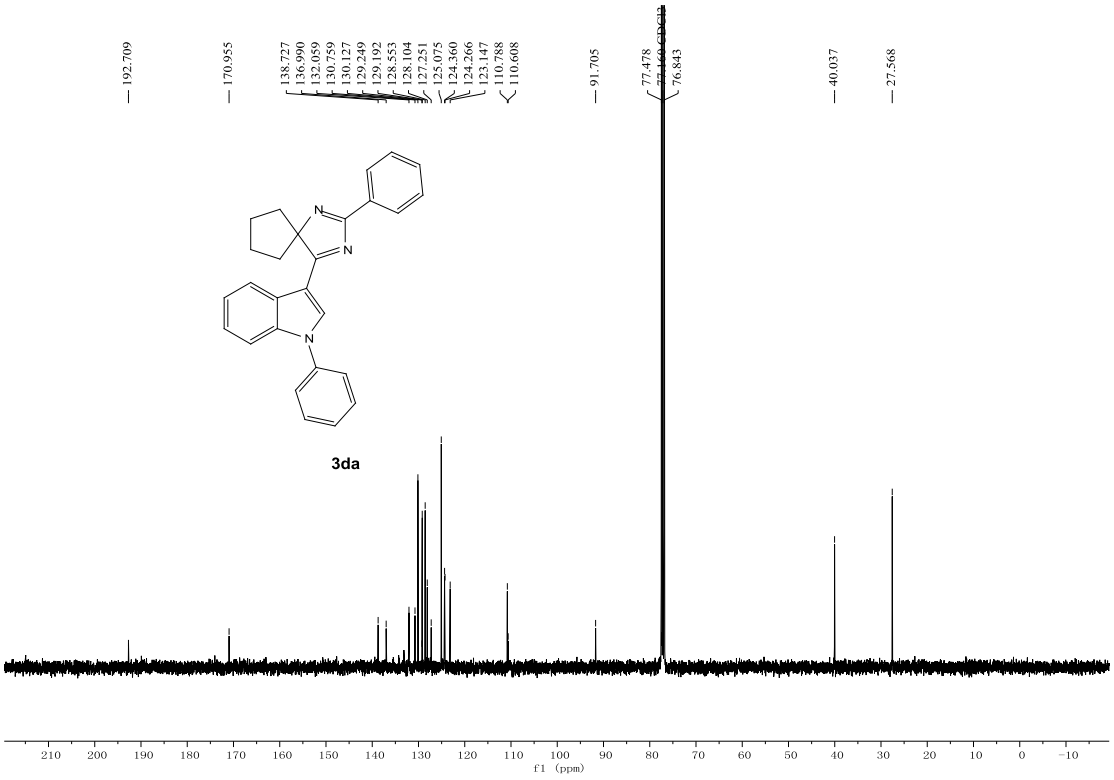
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3ca** (**$CDCl_3$**)



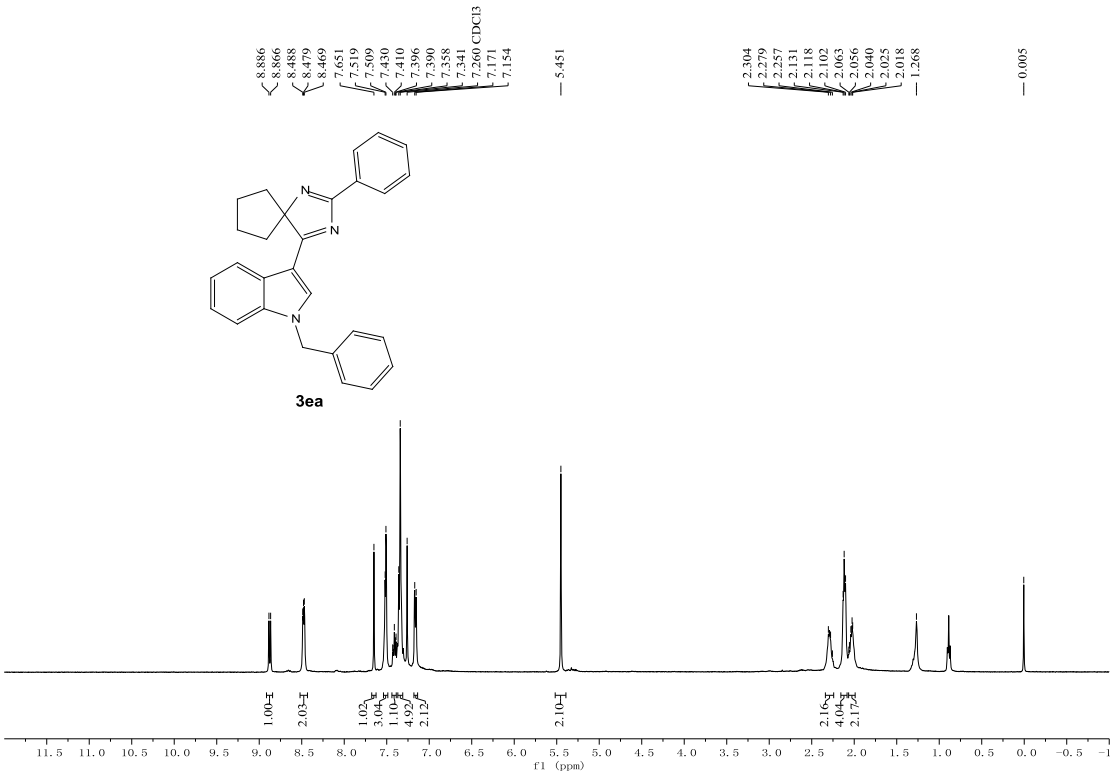


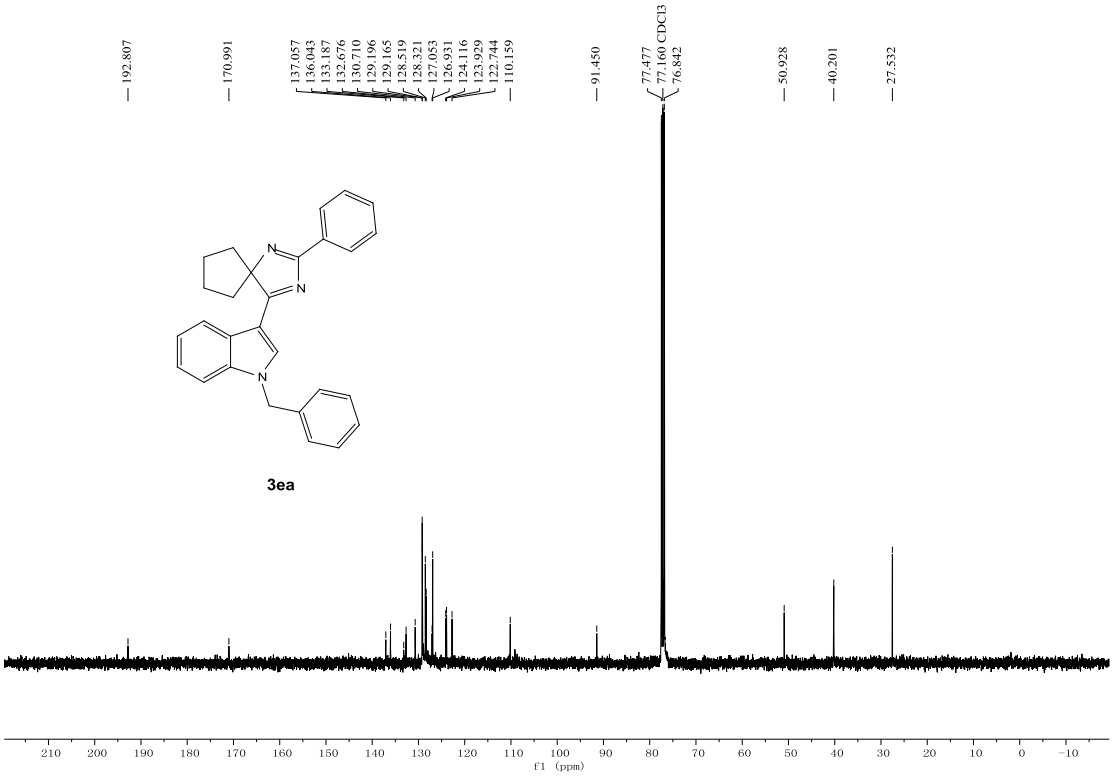
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3da** (**$CDCl_3$**)



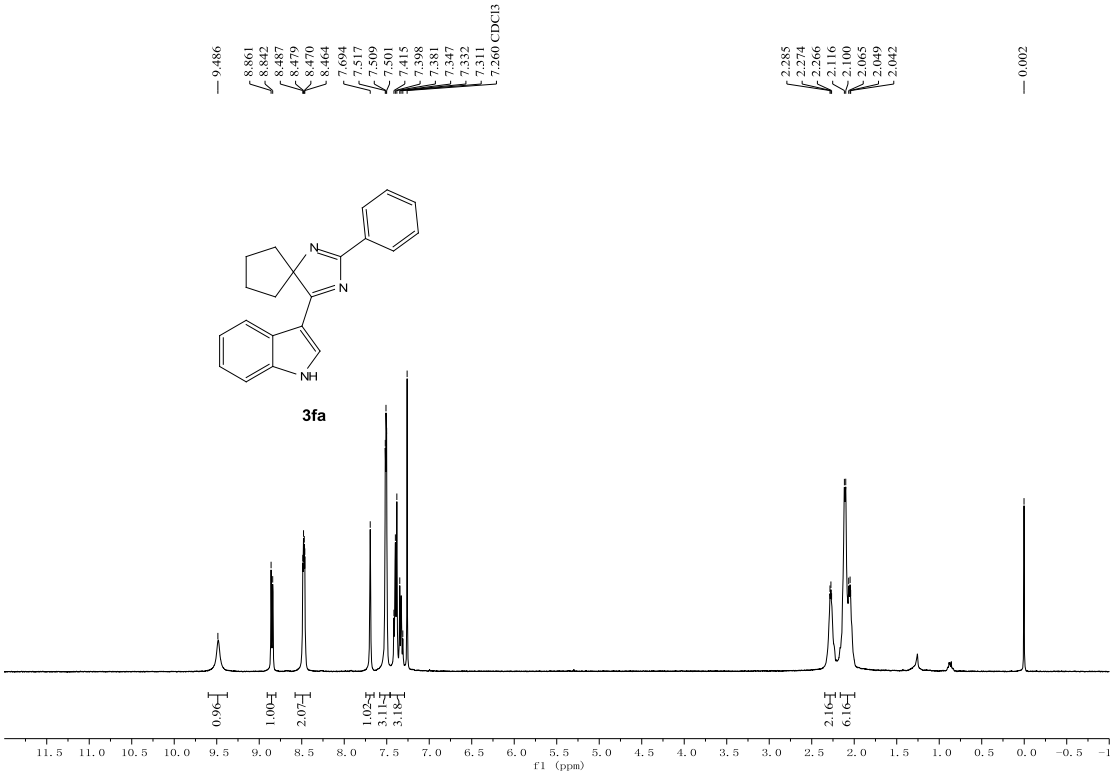


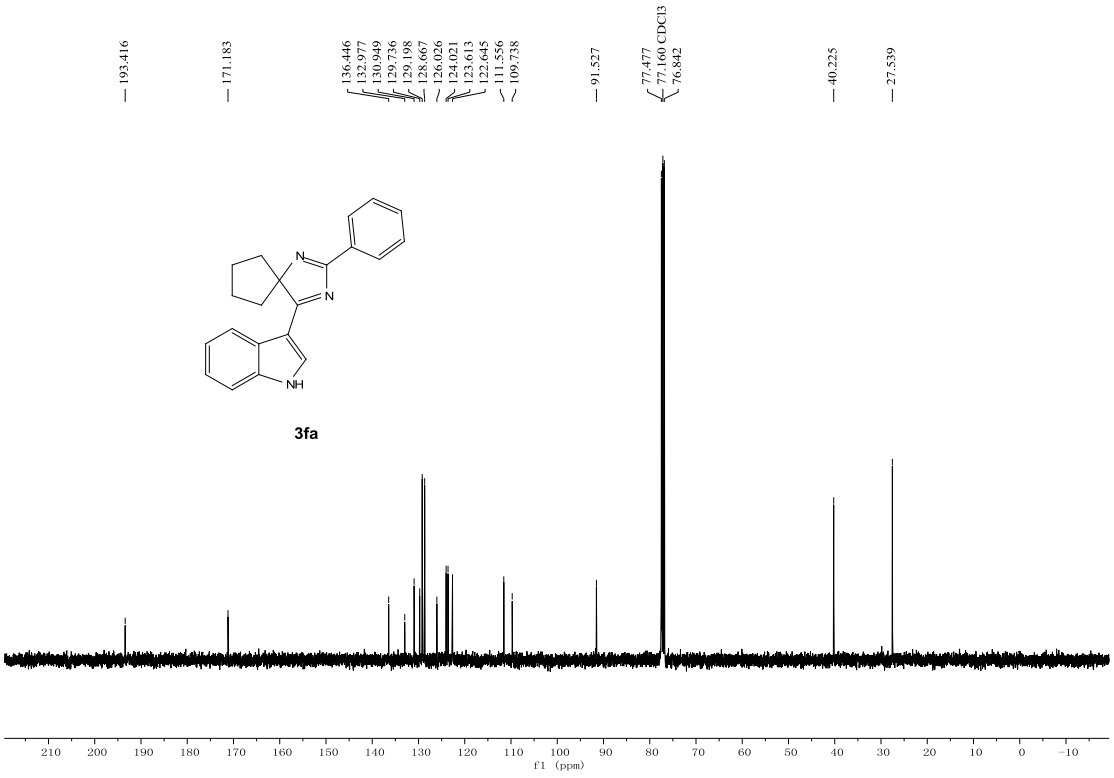
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3ea** (**$CDCl_3$**)



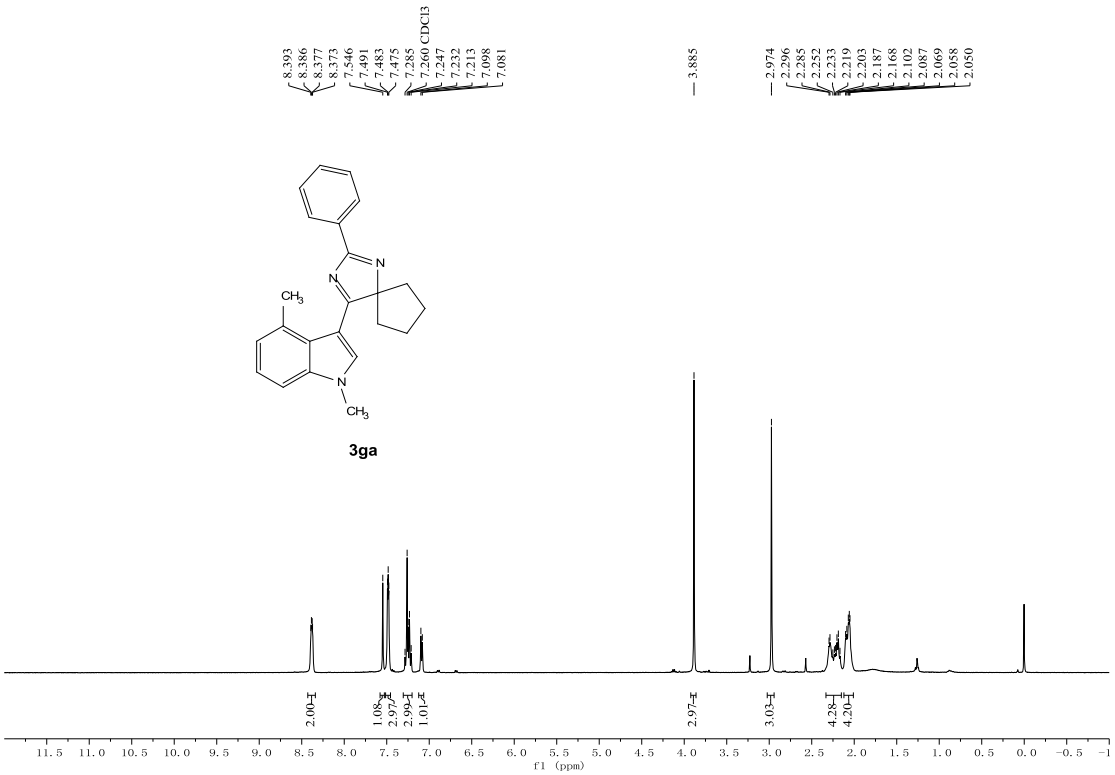


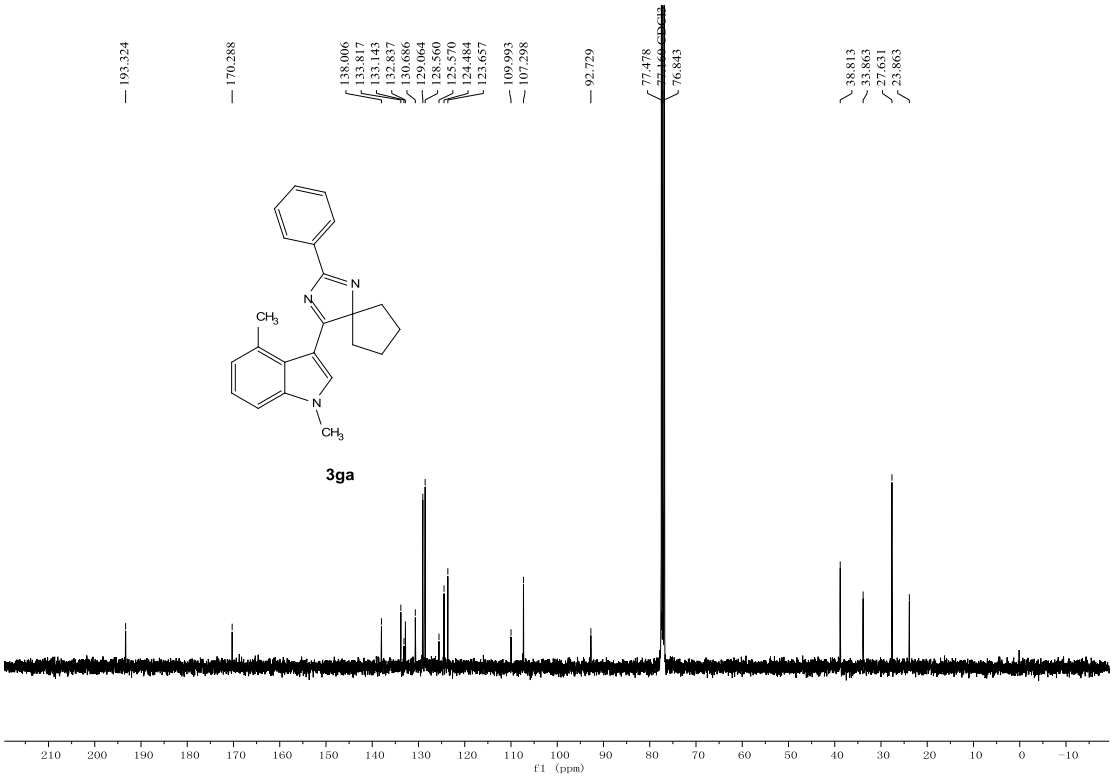
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3fa** (**$CDCl_3$**)



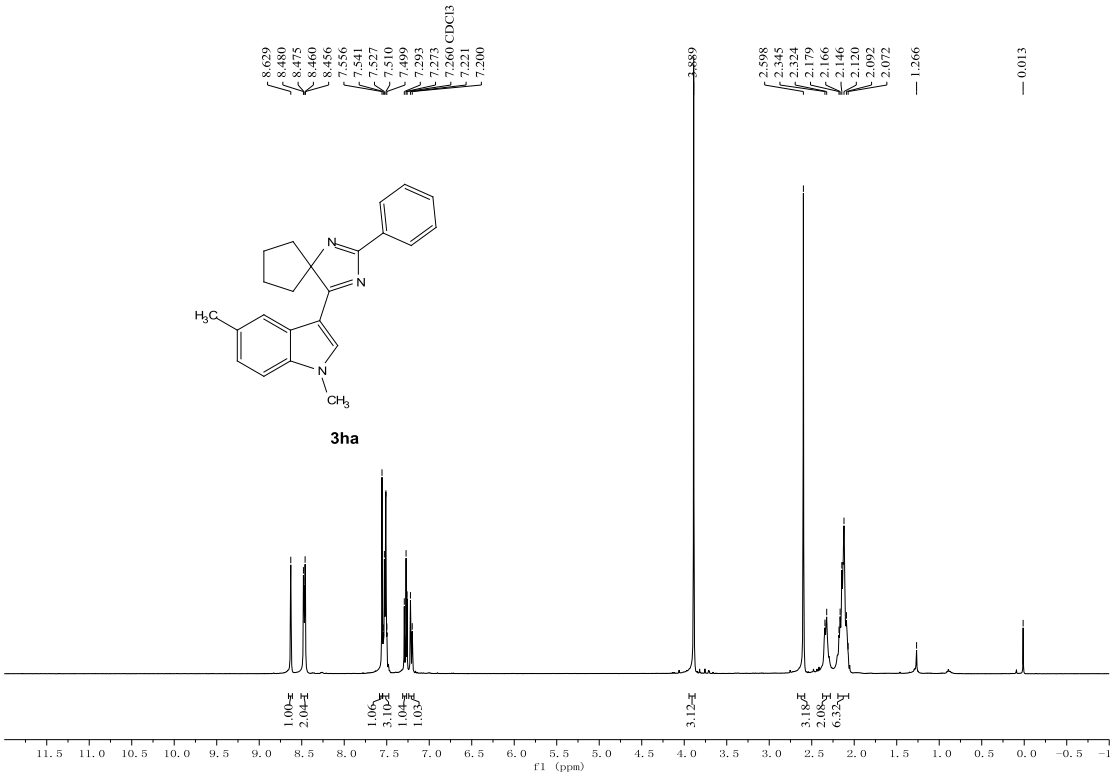


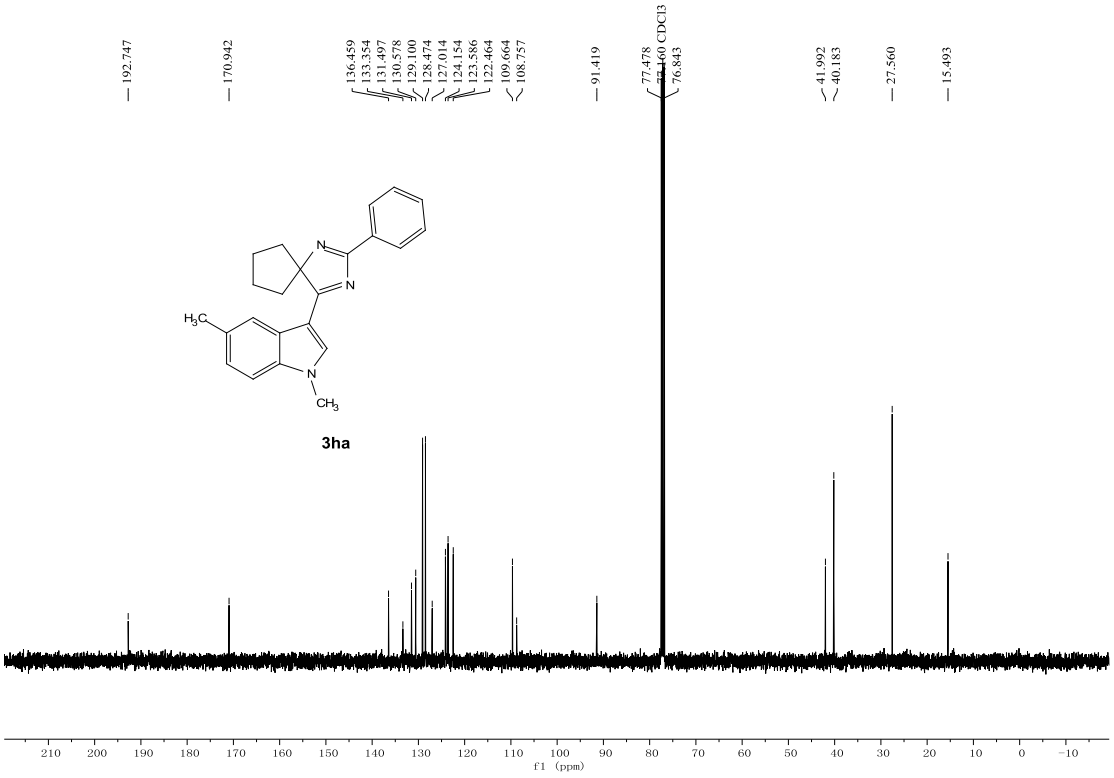
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3ga** (**$CDCl_3$**)



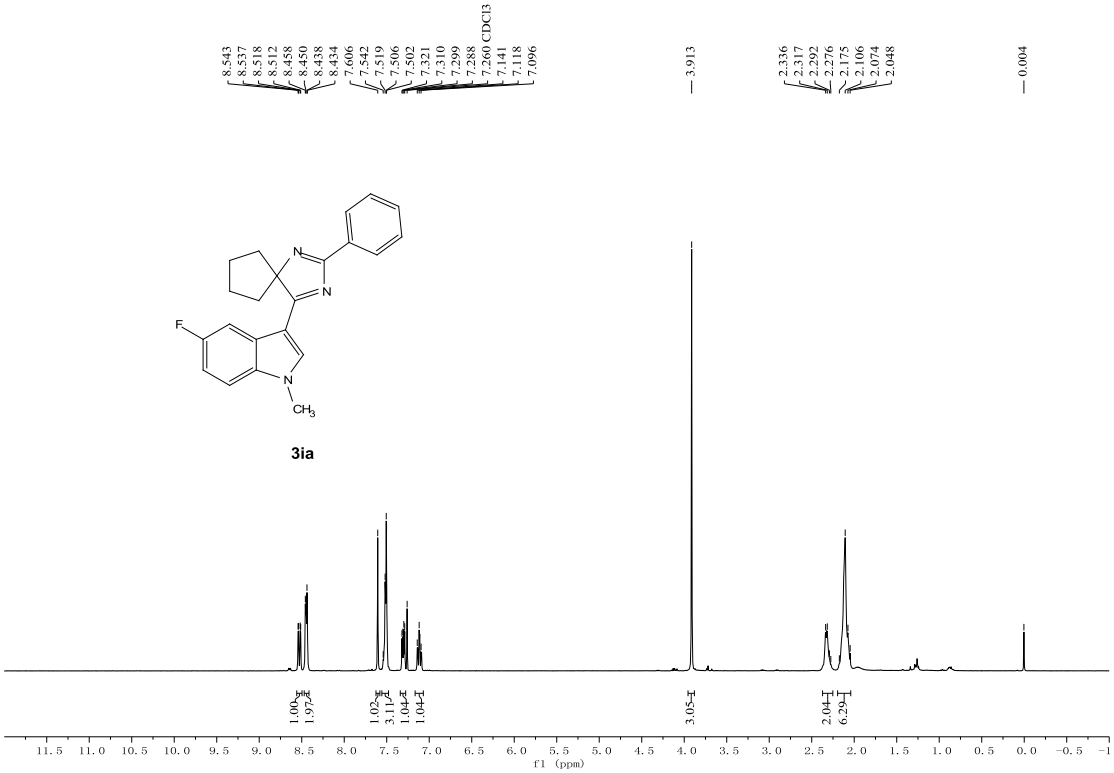


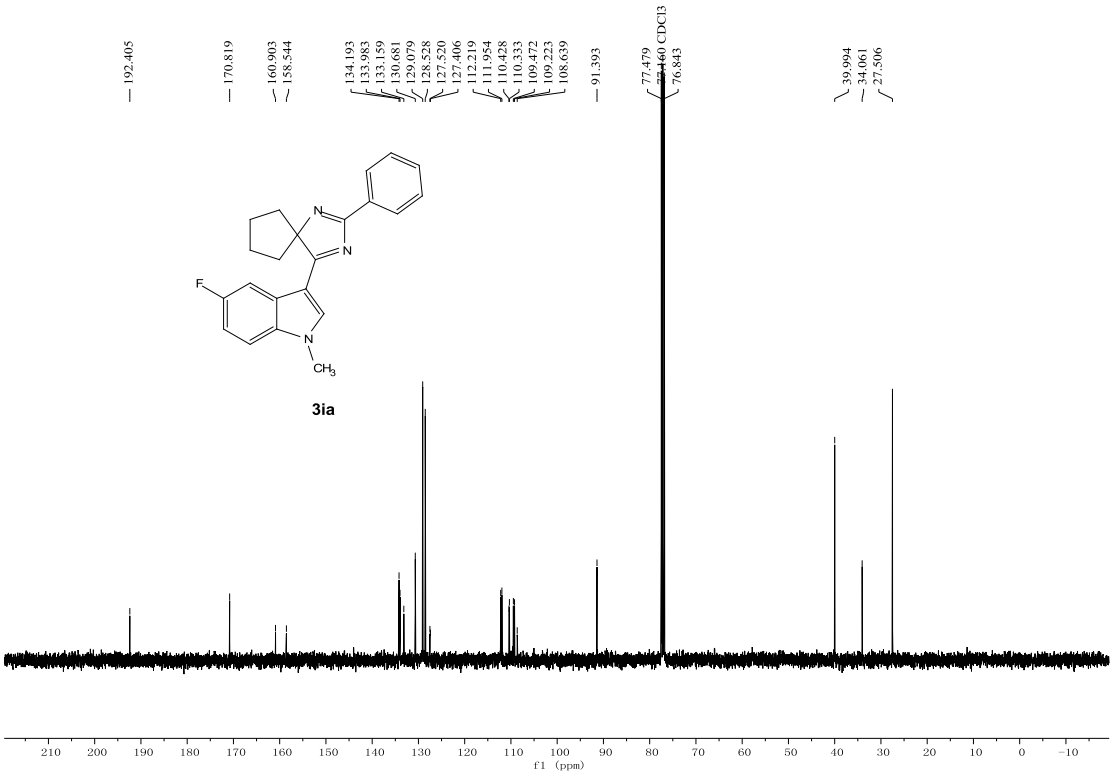
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3ha** (**$CDCl_3$**)





^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3ia** (**$CDCl_3$**)

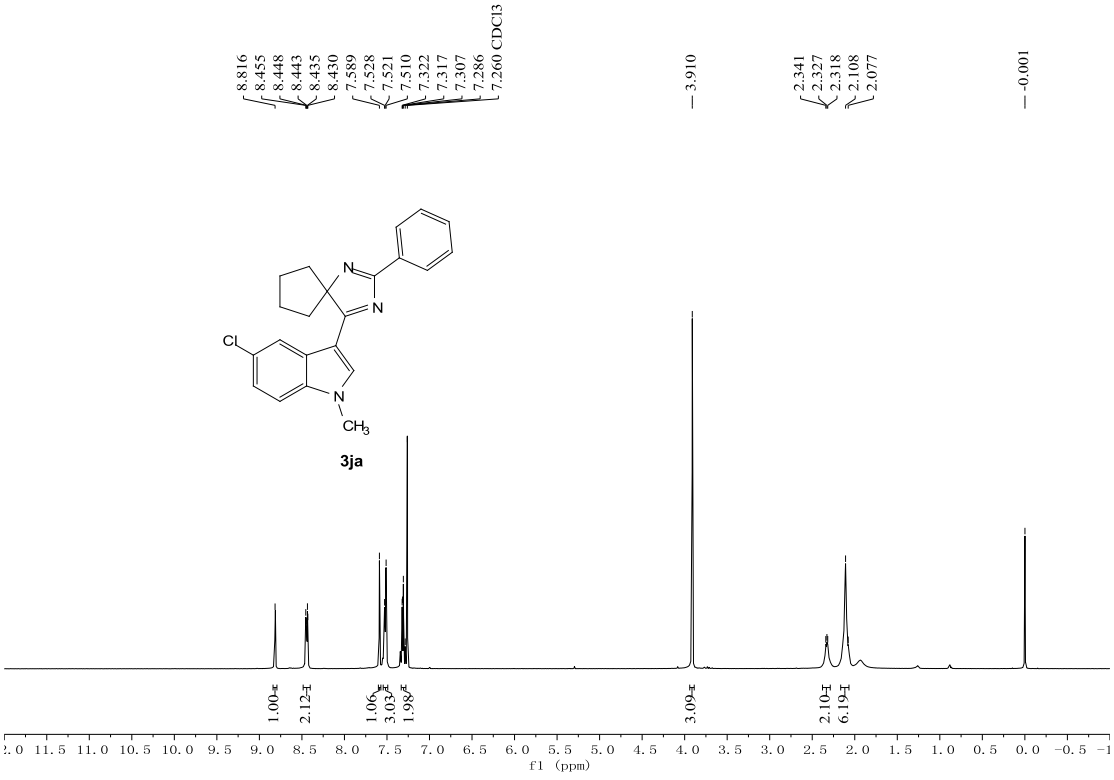


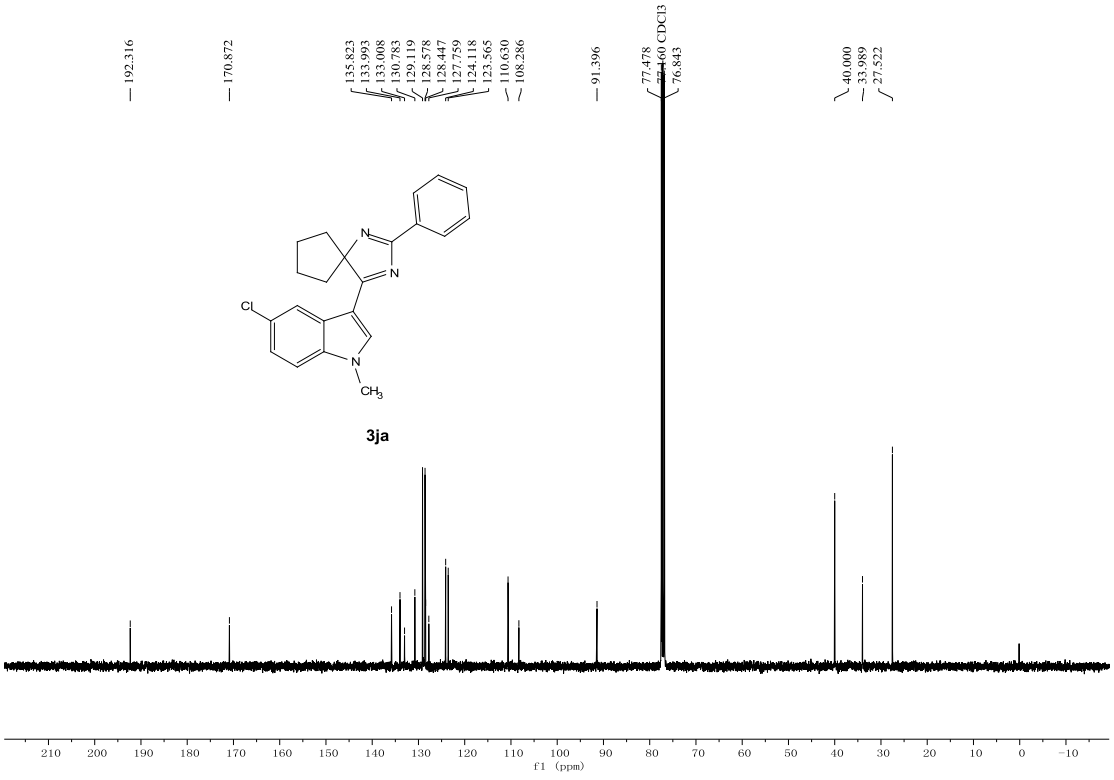



-121.055
F
N
N
N
CH3
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
−210
f1 (ppm)

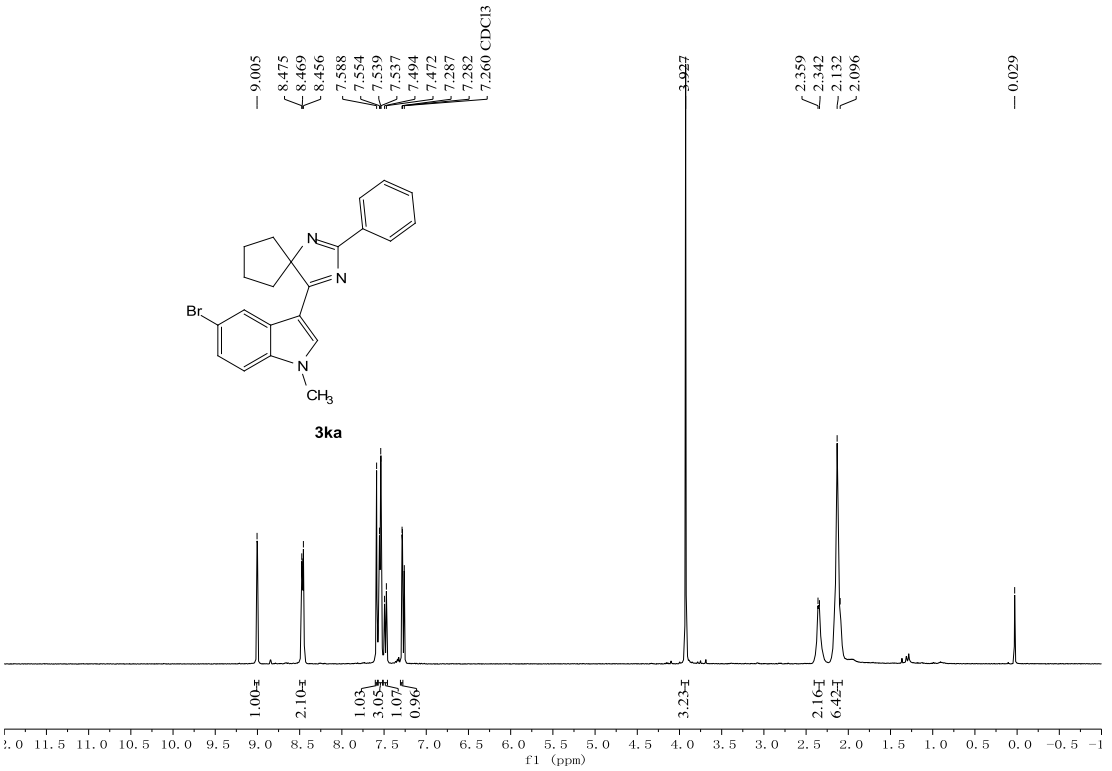
3ia

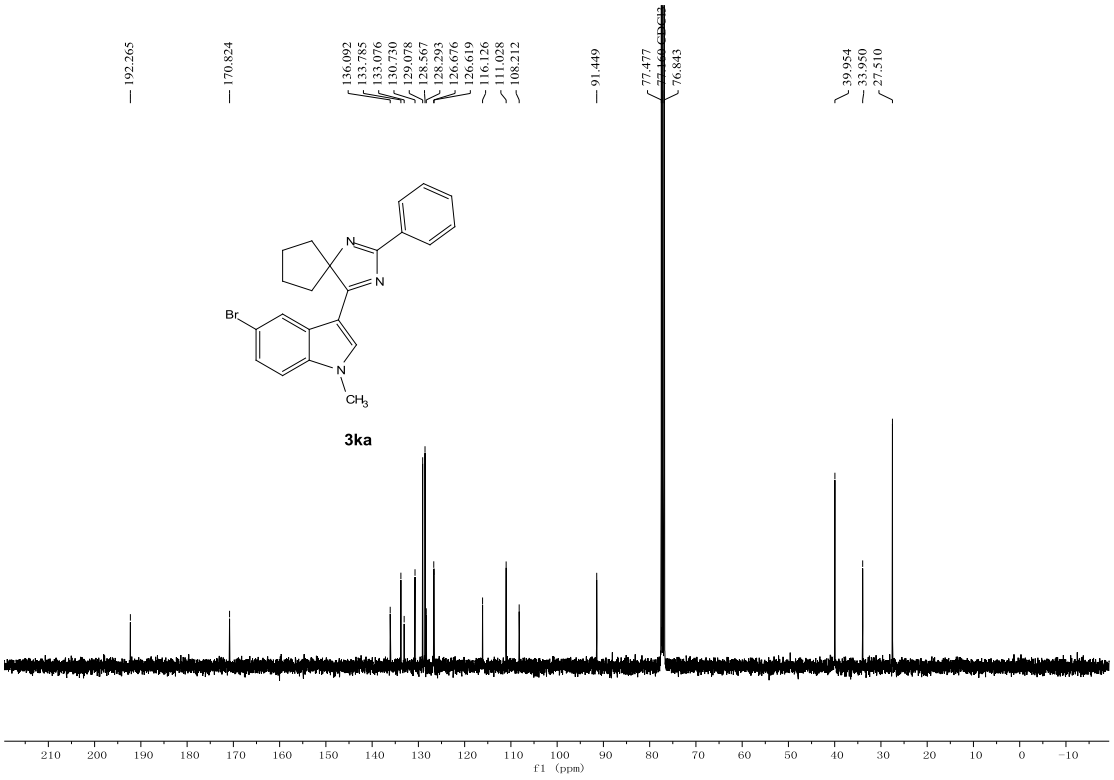
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3ja** (**$CDCl_3$**)



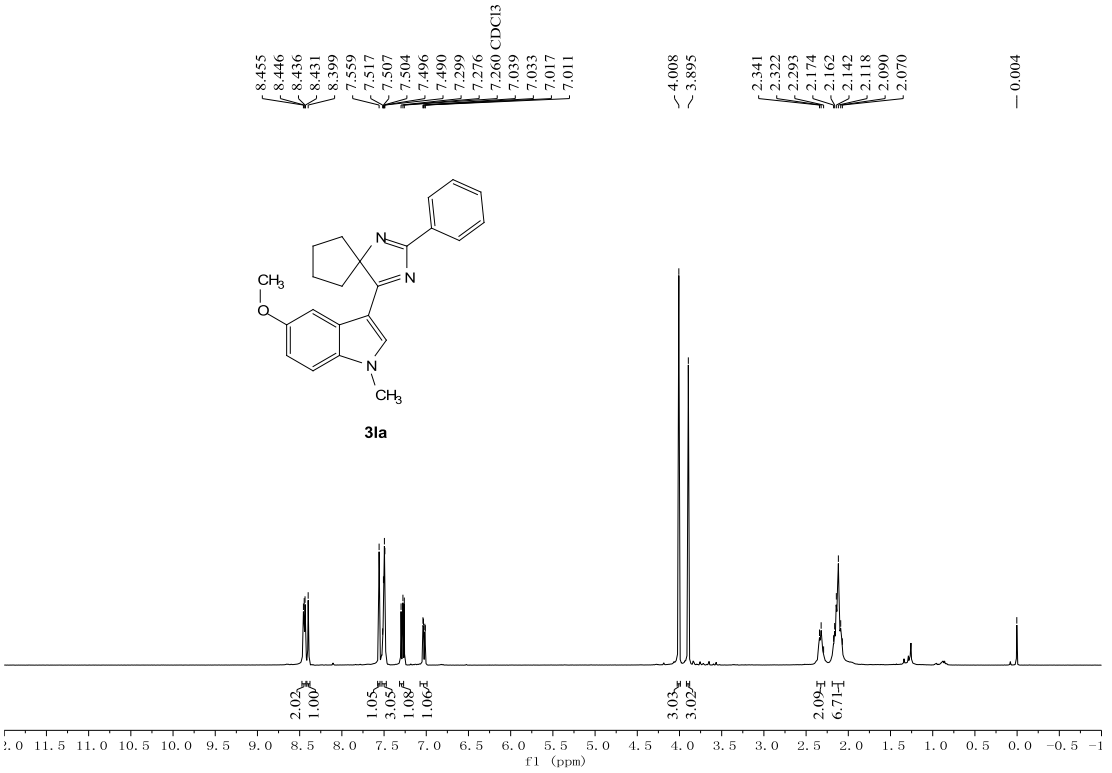


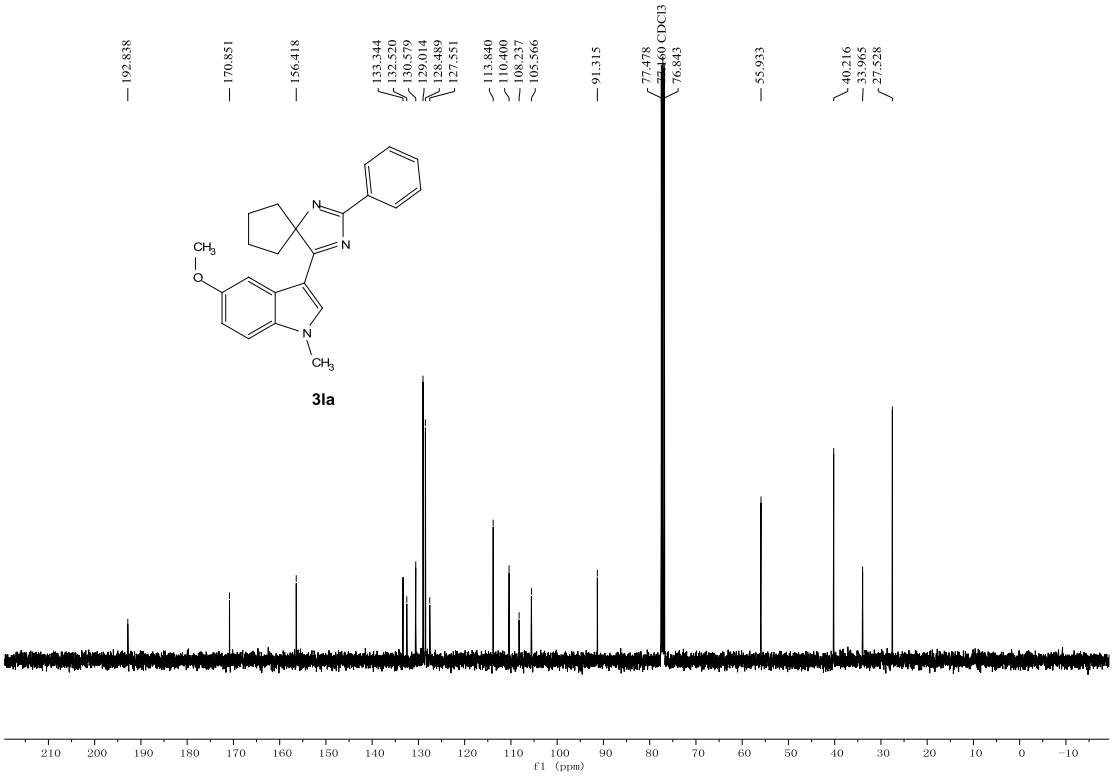
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3ka** (**$CDCl_3$**)



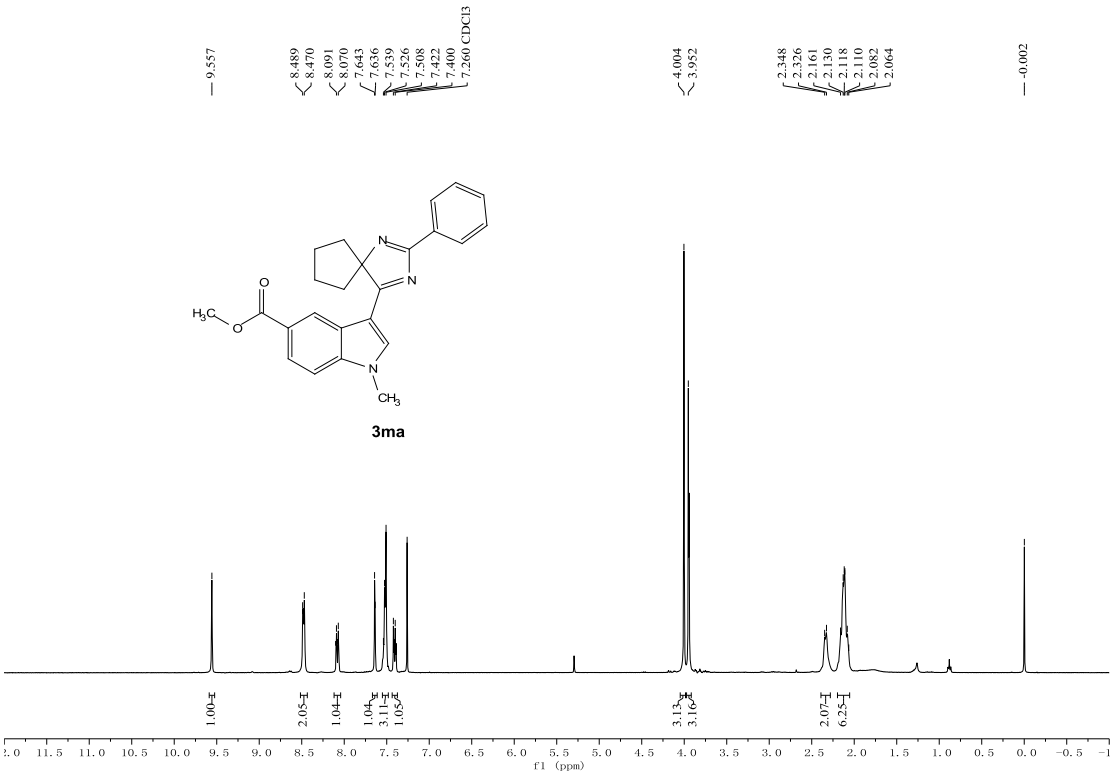


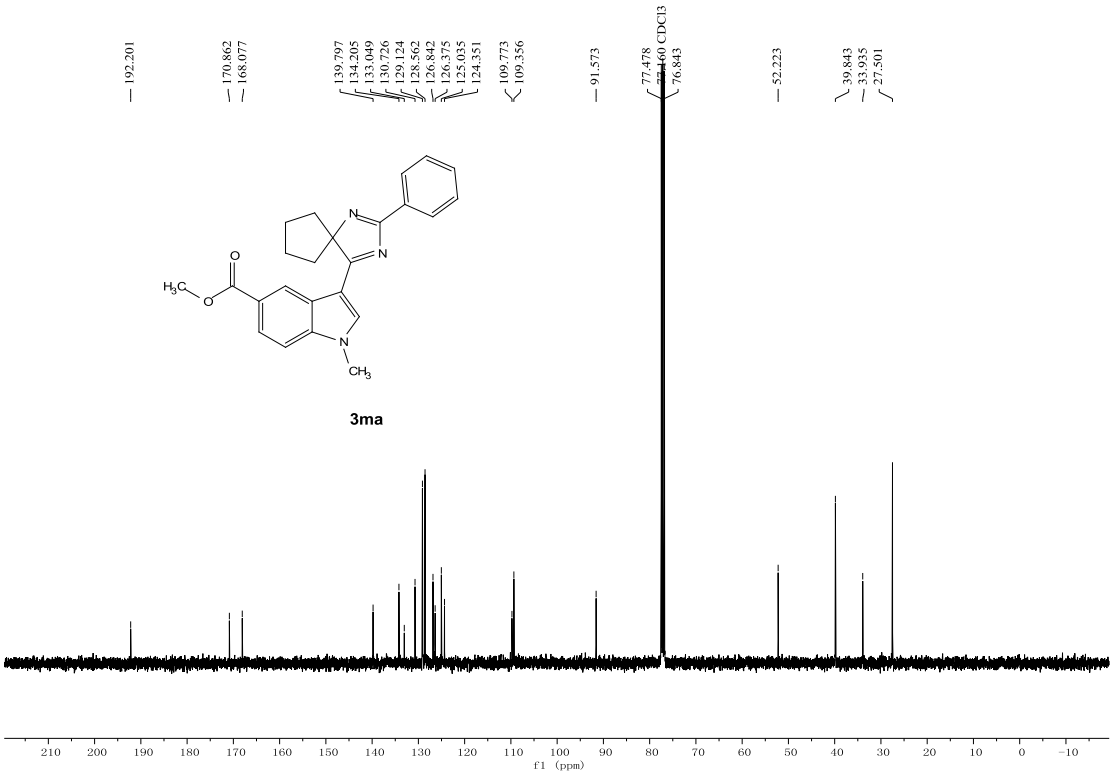
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3la** (**$CDCl_3$**)



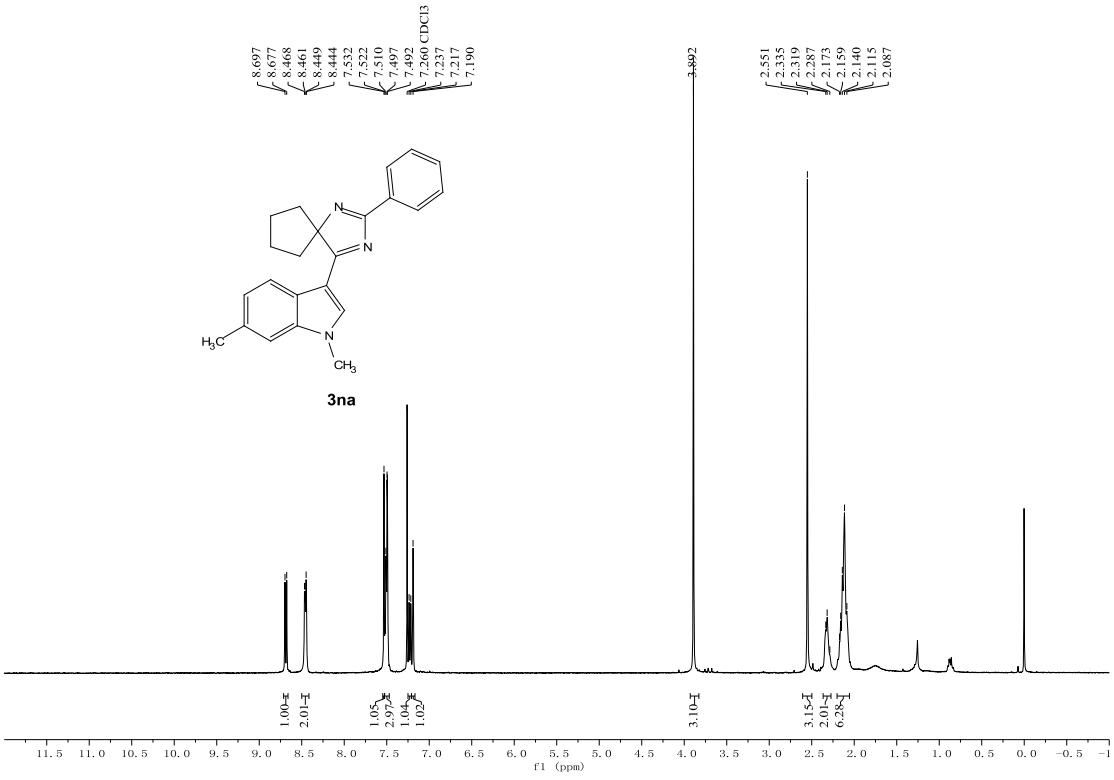


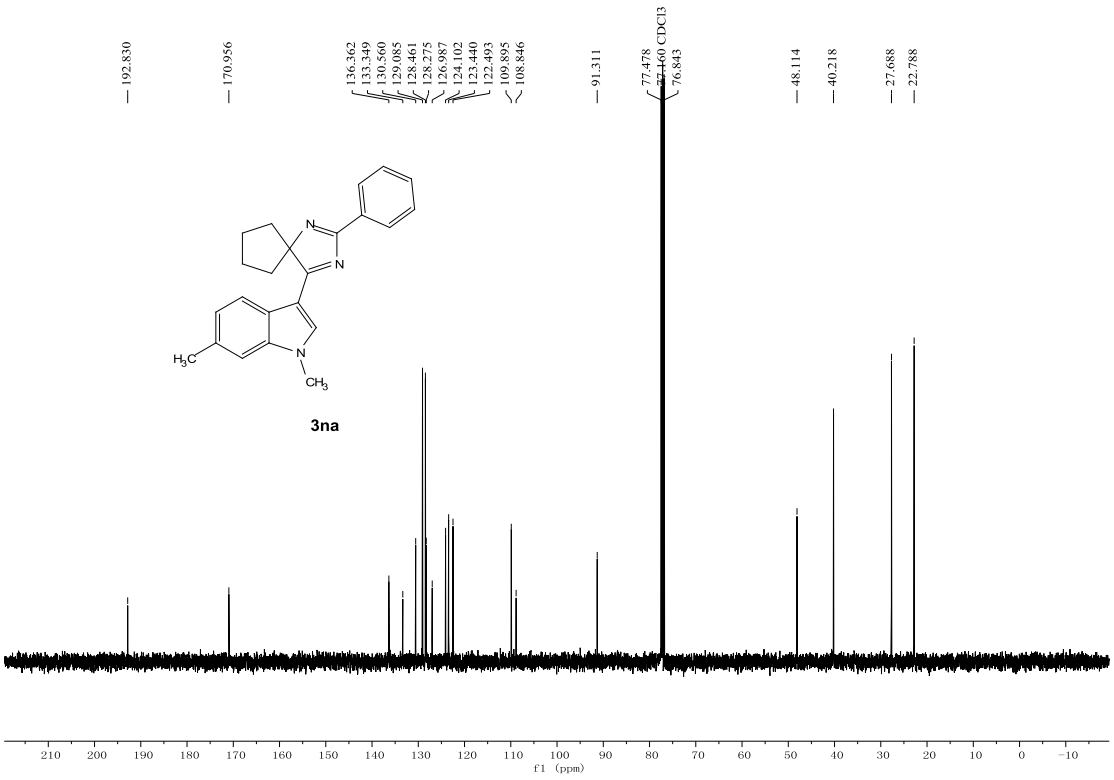
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3ma** (**$CDCl_3$**)



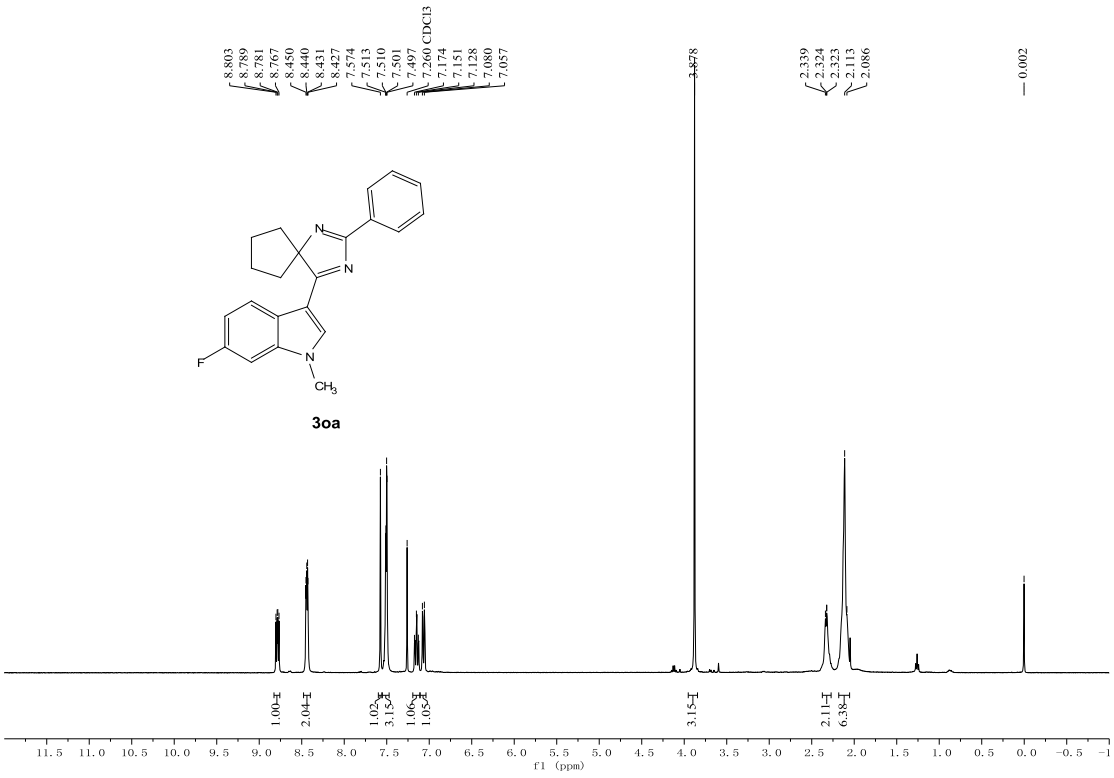


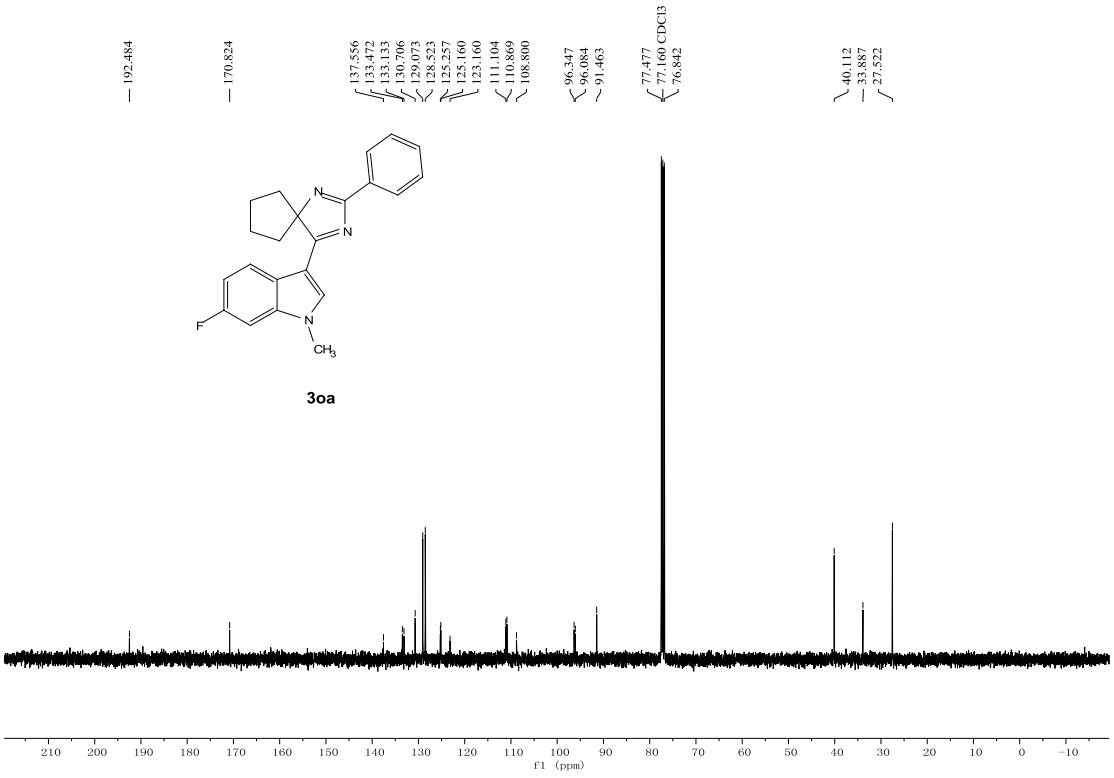
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3na** (**$CDCl_3$**)

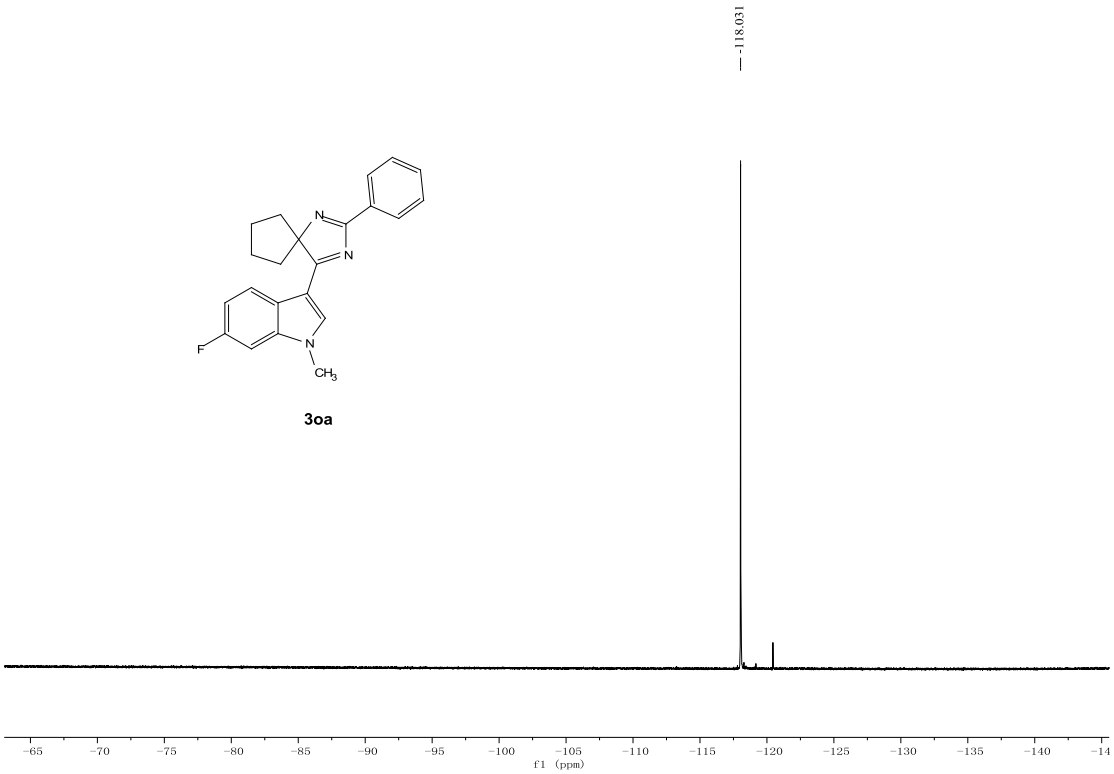




^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3oa** (**$CDCl_3$**)

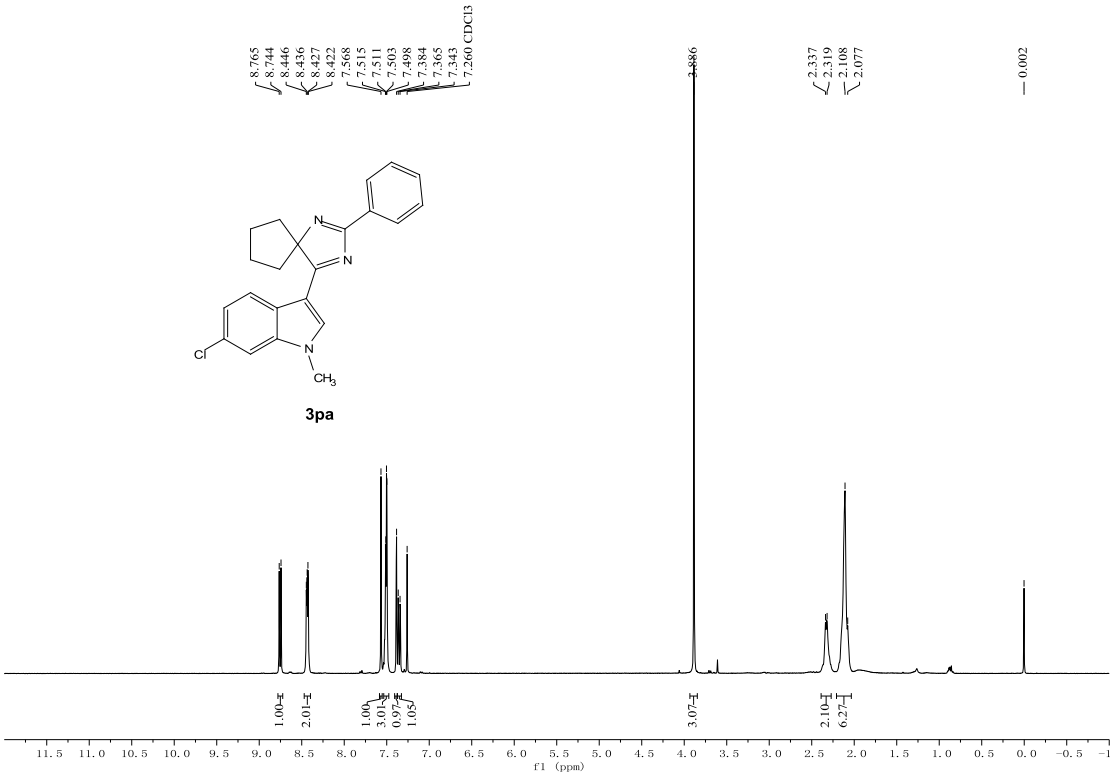


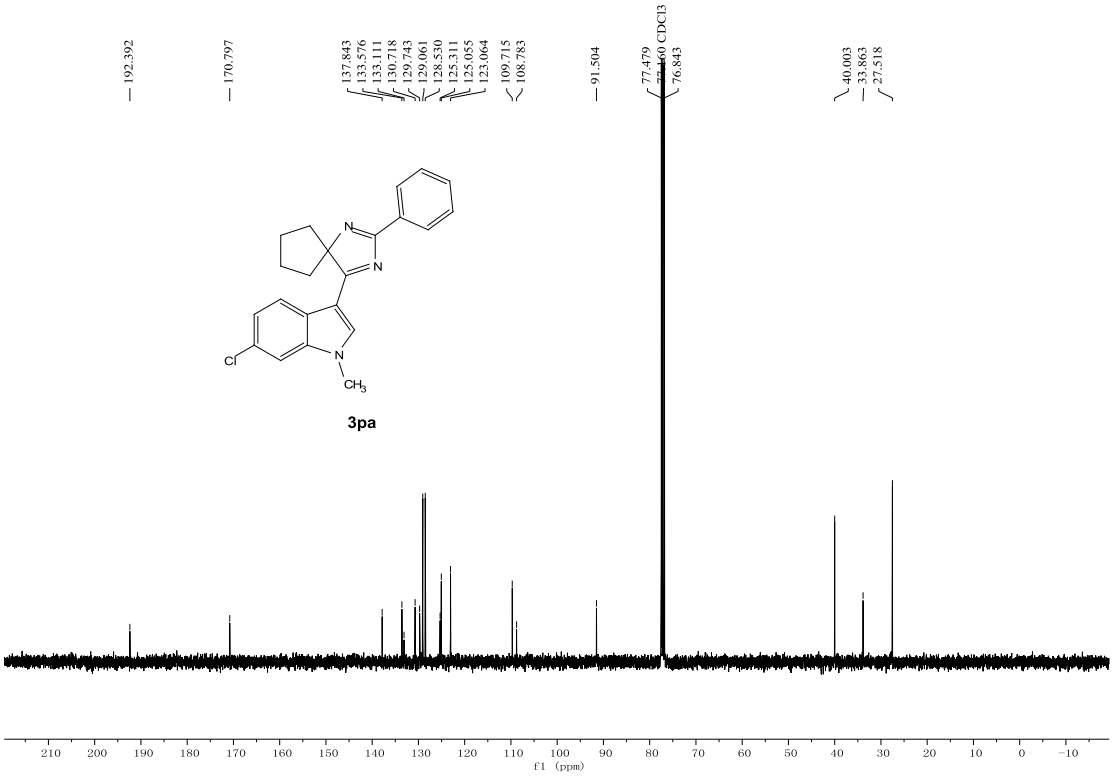



-118.031
N
N
F
N
CH3
−65
−70
−75
−80
−85
−90
−95
−100
−105
−110
−115
−120
−125
−130
−135
−140
−14
f1 (ppm)

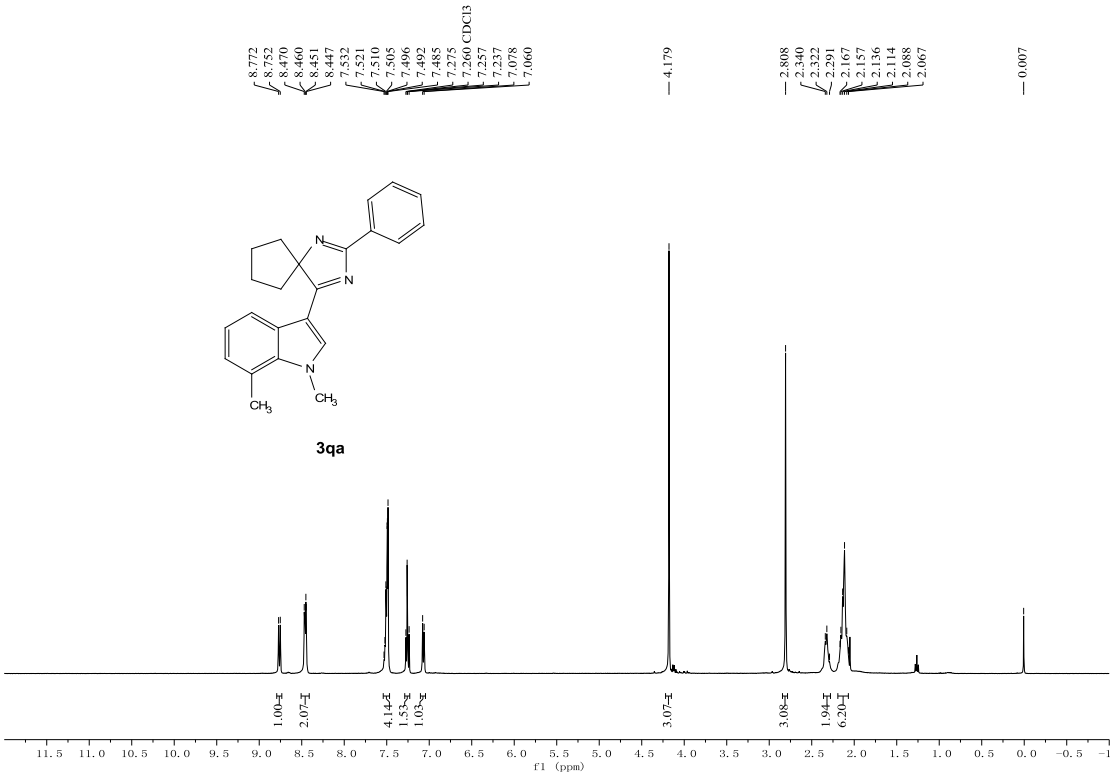
3oa

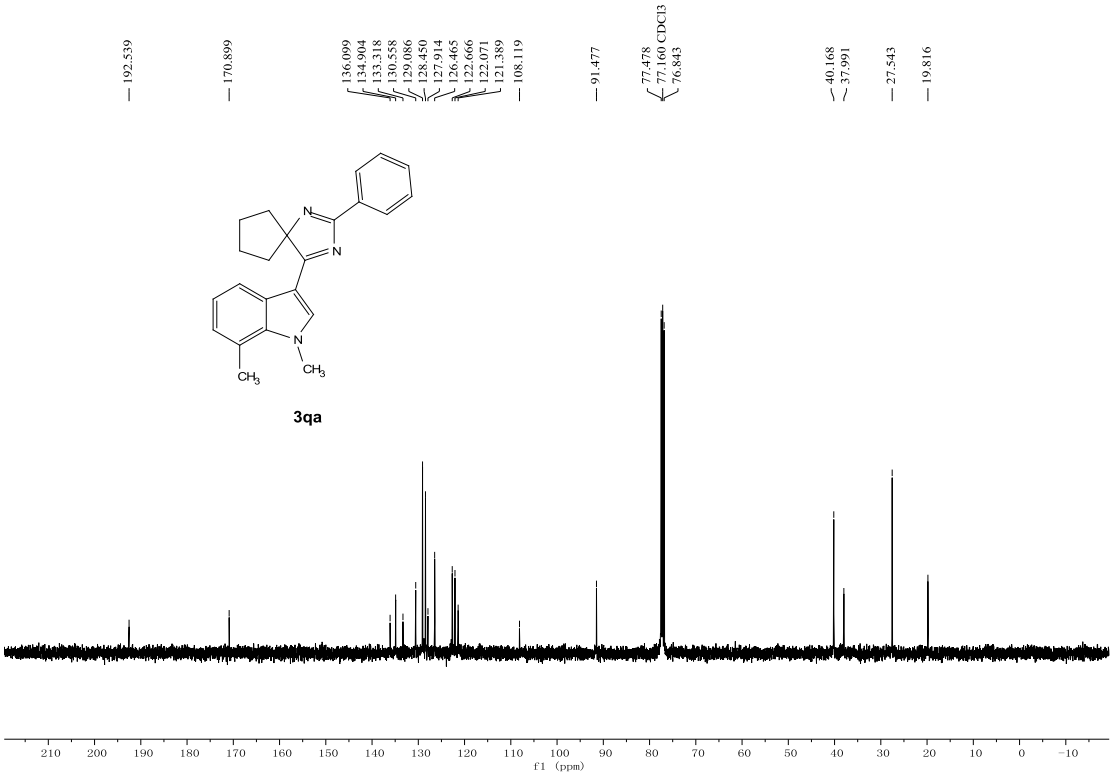
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3pa** (**$CDCl_3$**)



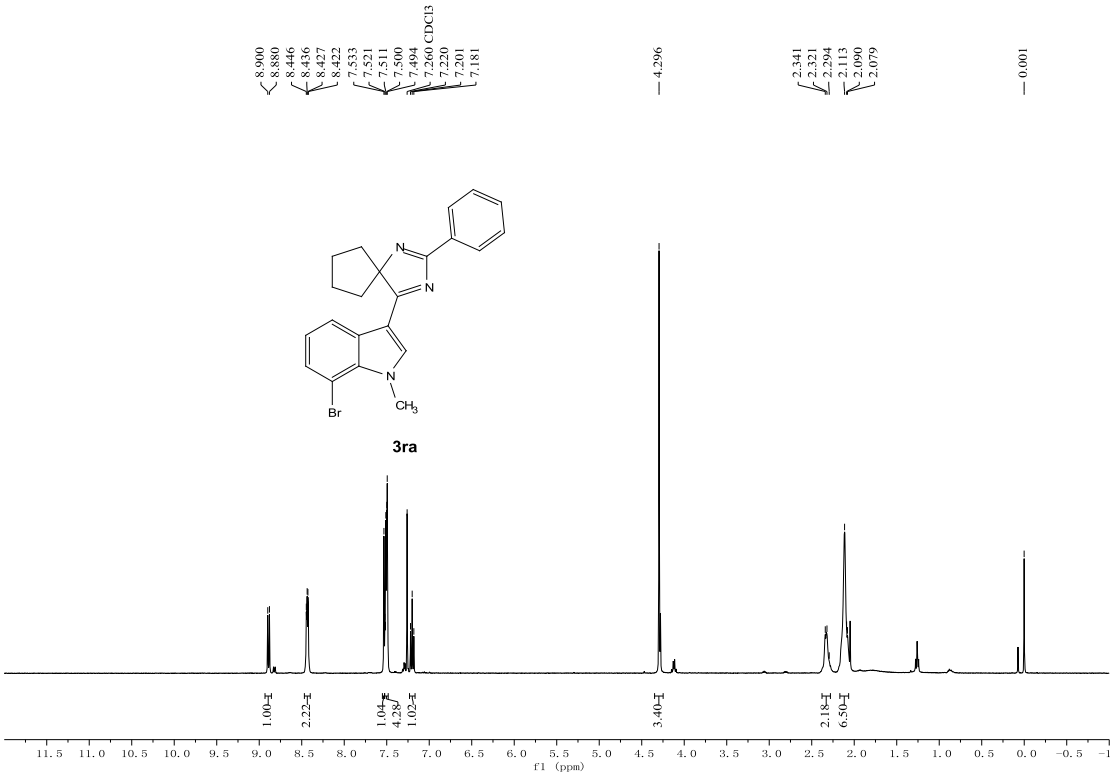


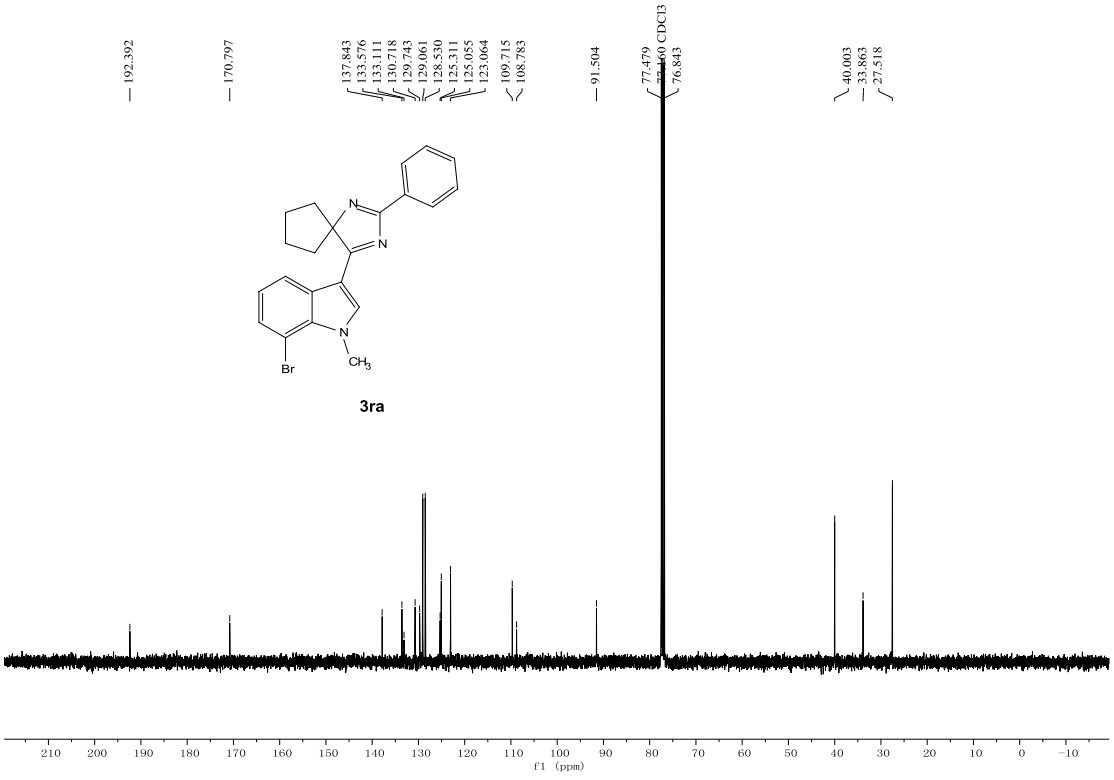
^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3qa** (**$CDCl_3$**)





^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3ra** (**$CDCl_3$**)





^{1}H NMR (400 MHz) and **^{13}C NMR** (100 MHz) spectra of **3sa** (**$CDCl_3$**)