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Ruthenium/Iridium-Catalyzed C-2 Activation of Indoles with Bicyclic Olefins: An Easy Access to Functionalized Heterocyclic Motifs

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General Methods

All chemicals were of the best grade commercially available and are used without further purification. All solvents were purified according to standard procedure; dry solvents were obtained according to the literature methods and stored over molecular sieves. Thin layer chromatography was performed on TLC Silica gel 60 F_{254} aluminium sheets purchased from Merck Pvt Ltd. Gravity column chromatography was performed using silica gel and alumina, and mixtures of hexane-ethyl acetate were used for elution. Melting points were determined on a Buchi melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker AMX 500 spectrophotometer [acetone-d_6, CD_3CN, $CDCl_3$ or $CDCl_3/CCl_4$ (7:3 mixture) as solvents]. Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signals of chloroform-d (δ 7.25, singlet), acetone –d_6 (δ 2.05, quintet), and acetonitrile-d_3 (δ 1.93, quintet) respectively. Multiplicities were given as: s (singlet); brs (broad singlet); d (doublet); t (triplet); m (multiplet). Coupling constants are reported as *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signals of chloroform-d (δ 77.03, triplet), acetone –d_6 (δ 29.97, septet; 206.68, singlet), and acetonitrile-d_3 (δ 1.39, septet; 118.69, singlet) respectively. Mass spectra were recorded under ESI/HRMS at 60,000 resolution using Thermo Scientific Exactive mass spectrometer. IR spectra were recorded on Bruker FT-IR spectrometer.

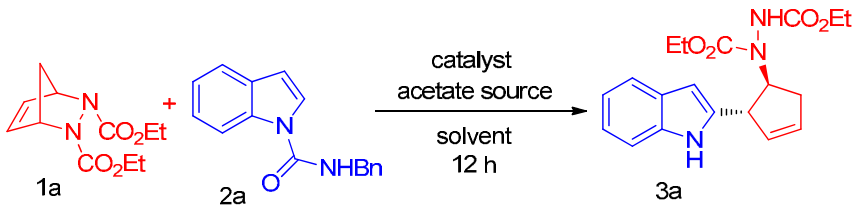
General Procedure for the Ruthenium catalyzed regiospecific cyclopentenylation of suitably protected indoles with bicyclic hydrazines:-

A mixture of diazabicyclic olefin (60 mg, 0.2497 mmol, 1.5 equiv.), indole (42 mg, 0.1665 mmol, 1.0 equiv.), $[RuCl_2(p\text{- cymene})]_2$ (3 mg, 0.0050 mmol, 3 mol%) and $Cu(OAc)_2.H_2O$ (7 mg, 0.0333 mmol, 20 mol%) were weighed in a schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 110 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography using ethyl acetate/hexane mixture yielded cyclopentene substituted indoles.

General Procedure for the Iridium catalyzed hydroheteroarylation of bicyclic olefins:-

A mixture of bicyclic alkene (80 mg, 0.3329 mmoles, 1.0 equiv.), indole (35 mg, 0.2996 mmoles, 0.9 equiv.), $[Ir(1,5\text{-cod})Cl]_2$ (11 mg, 0.0166 mmoles, 5 mol%) and dppe (13 mg, 0.0333 mmoles, 10 mol%) were weighed in a schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 110 ^{o}C for 16 hours. The crude reaction mixture on alumina column chromatography using ethyl acetate/hexane mixture yielded hydroheteroarylated bicyclic olefins.

Table 3. Optimization studies for desymmetrization of diazabicyclic olefins



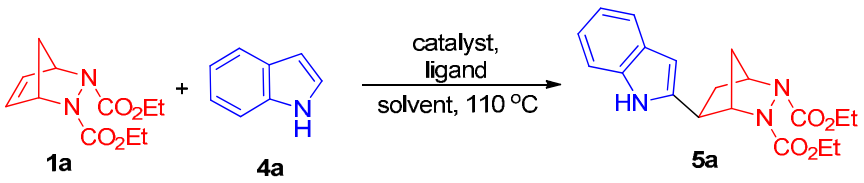
entry	catalyst	acetate source	solvent	temp (°C)	yield (%)
1	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2.H_2O$	toluene	80	56
2	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2.H_2O$	toluene	110	80
3	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2.H_2O$	xylene	110	40
4	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2.H_2O$	dioxane	110	NR
5	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2.H_2O$	DMF	110	NR
6	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2.H_2O$	t-amyl alcohol	110	NR
7	$[RuCl_2(p\text{-cymene})]_2$	AgOAc	toluene	110	20
8	$[RuCl_2(p\text{-cymene})]_2$	CsOAc	toluene	110	22
9	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	toluene	110	48
10	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2.H_2O$	toluene	110	51
11[a]	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2.H_2O$	toluene	110	0

Reaction Conditions : 1a (1.5 equiv.), 2a (1 equiv.), catalyst (3 mol%), acetate source (20 mol%), solvent (2 mL), 12 h.[a] with 4a

The yield of the reaction was found to increase dramatically when the reaction temperature was changed to 110 ºC. Changing the catalyst system to $[RhCp^*Cl_2]_2$ furnished the product in 51% yield only. Toluene was chosen as the optimal solvent for the transformation, and the reaction was futile with other solvents like xylene, dioxane, DMF and *t*-amyl alcohol. Among

the different acetate sources tested, NaOAc provided a moderate yield of 48% (Table 4, entry 9). The reaction was futile with *N*-free indoles.

Table 4. Optimization studies for hydroheteroarylation of bicyclic olefins



1a **4a** **5a**

entry	catalyst	ligand	solvent	yield (%)
1	$[Ir(1,5\text{-cod})Cl]_2$	dppp	toluene	54
2	$[Ir(OMe)(1,5\text{-cod})]_2$	dppp	toluene	trace
3	$[IrCl(CO)(PPh_3)_2]$	dppp	toluene	nr
4	**$[Ir(1,5\text{-cod})Cl]_2$**	**dppe**	**toluene**	**64**
5	$[Ir(1,5\text{-cod})Cl]_2$	dppf	toluene	trace
6	$[Ir(1,5\text{-cod})Cl]_2$	(*rac*)-binap	toluene	20
7	$[Ir(1,5\text{-cod})Cl]_2$	PPh_3	toluene	nr
8	$[Ir(1,5\text{-cod})Cl]_2$	dppe	DMF	nr
9	$[Ir(1,5\text{-cod})Cl]_2$	dppe	CH_3CN	nr
10	$[Ir(1,5\text{-cod})Cl]_2$	dppe	DMSO	nr
11[a]	$[Ir(1,5\text{-cod})Cl]_2$	dppe	toluene	nr

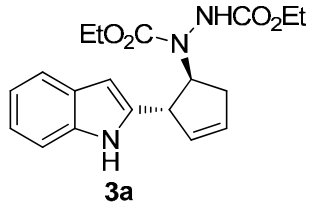
Reaction conditions :- adduct (1 equiv.), indole (0.9 equiv.), $[Ir(1,5\text{-cod})Cl]_2$ (5 mol%), dppe (10 mol%), toluene (2 mL), 110 °C, 16 h. [a] with 2a

Detailed optimization studies revealed that the reaction did not proceed well with other catalysts like $[Ir(OMe)(1,5\text{-cod})]_2$ and $[IrCl(CO)(PPh_3)_2]$. Among the ligands screened, dppe gave a better yield of 64%. Best solvent for this transformation was found to be toluene, and the reaction was futile with other solvents like DMF, DMSO and CH_3CN. The reaction with **2a** didn't give any satisfactory results.

Characterization of the Products

The synthesized products were characterized based on various spectroscopic techniques like IR, ^{1}H NMR, ^{13}C NMR and HRMS analysis. The synthesized diazabicyclic olefin derivatives bear hydrazine moiety, and the proton NMR signals of these compounds are broadened due to rotational isomerism exhibited by the hydrazine group.[1]

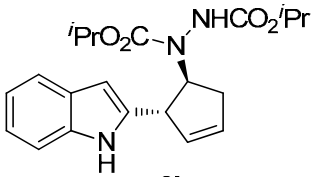
diethyl-1-(2-(1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3a)



3a

Yield: 48 mg, 80% as colourless viscous liquid. $\mathbf{R_f}$ **:** 0.85 (7:3 hexane/ethyl acetate). **IR (neat)** $\mathbf{\nu_{max}}$**:** 3289, 2919, 1716, 1606, 1532, 1419, 1262, 1172, 1096, 1061, 758 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 9.99 (brs, 1 H), 7.49 (d, *J* = 8 Hz, 1 H), 7.34 (d, *J* = 8 Hz, 1 H), 7.08 (t, *J* = 7 Hz, 1 H), 7.01 (t, *J* = 7.5 Hz, 1 H), 6.57 (brs, 1 H), 6.19 (s, 1 H), 5.94 (s, 1 H), 5.88 (s, 1 H), 4.76 (brs, 1 H), 4.33-3.99 (m, 5 H), 2.57 (brs, 2 H), 1.37-1.25 (m, 4 H), 0.89-0.85 (m, 2 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 155.7, 138.8, 130.8, 128.1, 127.5, 120.9, 119.7, 118.8, 110.5, 99.7, 62.5, 34.7, 29.5, 14.4. **HRMS (ESI):** *m/z* calcd for $C_{19}H_{23}N_3O_4Na$: 380.15863; Found: 380.15851.

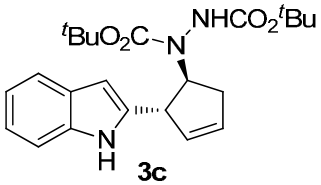
diisopropyl-1-(2-(1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3b)



3b

Yield: 37 mg, 65% as yellow viscous liquid. $\mathbf{R_f}$ **:** 0.67 (7:3 hexane/ethyl acetate). **IR (neat)** $\mathbf{\nu_{max}}$**:** 3308, 2982, 2935, 1696, 1518, 1459, 1381, 1255, 1106, 953, 746 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d_6):** δ 10.29 (brs, 1 H), 8.63-8.34 (m, 1 H), 7.46 (d, *J* = 12 Hz, 1 H) 7.31 (d, *J* = 12 Hz, 1 H), 7.02 (t, *J* = 7.5 Hz, 1 H), 6.95 (t, *J* = 7.5 Hz, 1 H), 6.21 (brs, 1 H), 5.90 (brs, 2 H), 5.03-4.79 (m, 3 H), 4.16 (brs, 1 H), 2. 60 (brs, 2 H), 1.29-1.22 (m, 12 H). **^{13}C NMR (125 MHz, Acetone-d_6):** δ 158.7, 156.3, 129.1, 121.32, 119.9, 119.4, 111.3, 101.1, 96.9, 70.2, 69.9, 58.7, 48.0, 35.7, 21.7. **HRMS (ESI):** *m/z* calcd for $C_{21}H_{27}N_3O_4Na$: 408.18993; Found: 408.18799.

di-tert-butyl-1-(2-(1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3c)

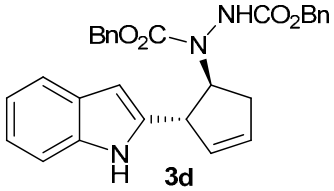


3c

Yield: 35 mg, 58% as colourless liquid. $\mathbf{R_f}$ **:** 0.78 (7:3 hexane/ethyl acetate). **IR (neat)** $\mathbf{\nu_{max}}$**:** 3386, 2984, 1701, 1586, 1212, 1113, 1109, 1016 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d_6):** δ 10.26-9.88 (m, 1 H), 8.36-8.12 (m, 1 H), 7.32 (d, *J* = 8 Hz, 1 H), 7.16 (brs, 1 H), 6.89 (t, *J* = 7 Hz, 1 H), 6.81 (t, *J* = 7 Hz, 1 H), 6.06 (brs, 1 H), 5.81-5.77 (m, 2 H), 4.76-4.63 (m,

1 H), 4.11-3.97 (m, 1 H), 2.49-2.42 (m, 2 H), 1.39-1.16 (m, 18 H). **^{13}C NMR (125 MHz, Acetone-d$_6$):** δ 158.1, 155.2, 143.2, 137.2, 131.6, 129.8, 128.9, 120.2, 119.4, 114.4, 100.9, 97.3, 81.4, 65.2, 46.1, 35.4, 28.3. **HRMS (ESI):** *m/z* calcd for $C_{23}H_{31}N_3O_4Na$: 436.22123; Found: 436.21901.

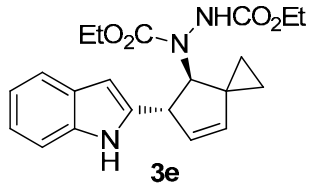
dibenzyl-1-(2-(1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3d)



3d

Yield: 12 mg, 22% as yellow viscous liquid. **R$_f$:** 0.50 (7:3 hexane/ethyl acetate). **IR (neat) ν$_{max}$:** 3298, 3034, 2950, 1709, 1499, 1454, 1386, 1217, 1171, 1108, 1022, 916, 740, 698 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d$_6$):** δ 10.22-9.99 (m, 1 H), 8.98-8.81 (m, 1 H), 7.47-7.31 (m, 12 H), 7.05-6.98 (m, 2 H), 6.24 (s, 1 H), 5.89 (s, 2 H), 5.30-4.97 (m, 5 H), 4.24 (s, 1 H), 2.66 (brs, 2 H). **^{13}C NMR (125 MHz, Acetone-d$_6$):** δ 156.1, 136.9, 129.3, 128.5, 121.3, 120.2, 119.4, 115.5, 100.9, 97.6, 68.2, 68.1, 48.9, 35.4. **HRMS (ESI):** *m/z* calcd for $C_{29}H_{27}N_3O_4Na$: 504.18993; Found: 504.18736.

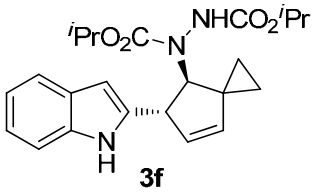
diisopropyl-1-(5-isopropyl-9-oxo-2,3,3a,9-tetrahydrocyclopenta[b]chromen-2-yl)hydrazine-1,2-dicarboxylate (3e)



3e

Yield: 29 mg, 34% as colourless viscous liquid. **R$_f$:** 0.55 (7:3 hexane/ethyl acetate). **IR (neat) ν$_{max}$:** 3317, 2981, 2923, 1700, 1612, 1414, 1297, 1244, 1061, 967 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d$_6$):** δ 10.04-9.96 (m, 1 H), 8.43-8.29 (m,1 H), 7.33 (d, *J* = 7 Hz, 1 H), 7.21 (d, *J* = 8 Hz, 1 H), 6.89 (t, *J* = 7 Hz, 1 H), 6.83-6.81 (m, 1 H), 6.10 (brs, 1 H), 5.71 (d, *J* = 5 Hz, 1 H), 5.37 (d, *J* = 8 Hz, 1 H), 4.74 (brs, 1 H), 4.32 (brs, 1 H), 4.09-3.94 (m,4 H), 1.15-.94 (m, 6 H), .74-.55 (m,4 H). **^{13}C NMR (125 MHz, Acetone–d$_6$):** δ 158.1, 156.0, 138.7, 137.7, 129.9, 121.5, 120.7, 119.9, 100.9, 62.4, 60.6, 44.9, 14.9, 10.5. **HRMS (ESI):** *m/z* calcd for $C_{21}H_{25}N_3O_4Na$: 406.17428; Found: 406.17515.

diethyl-1-(2-(1-(benzylcarbamoyl)-1H-indol-3-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3f)

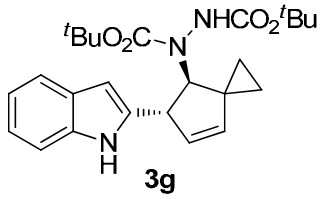


3f

Yield: 22 mg, 40% as colourless viscous liquid. **R$_f$:** 0.75 (7:3 hexane/ethyl acetate). **IR (neat) ν$_{max}$:** 3302, 3056, 2958, 2919, 1699, 1615, 1494, 1381, 1296, 1251, 1106 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d$_6$):** δ10.06-10.01 (m, 1 H), 8.32-8.19 (m, 1 H), 7.33(d, *J* = 8 Hz, 1 H), 7.19 (d, *J* = 8 Hz, 1 H), 6.89 (t, *J* = 7 Hz, 1 H), 6.82 (t, *J* = 7.5 Hz, 1 H), 6.09 (s,1 H), 5.72 (d, *J* = 6 Hz, 1 H), 5.37-5.35 (m, 2 H), 4.86-4.65 (m, 2 H), 1.15-.88 (m, 12 H), 0.74-0.53 (m, 4 H). **^{13}C NMR (125 MHz,**

Acetone-d_6): δ 156.5, 155.9, 138.4, 138.3, 137.2, 135.2, 129.7, 121.5, 120.5, 119.8, 111.5, 100.9, 98.3, 70.4, 47.6, 31.9, 21.9, 12.8, 10.7. **HRMS (ESI):** *m/z* calcd for $C_{23}H_{29}N_3O_4Na$: 434.20558; Found: 434.20396.

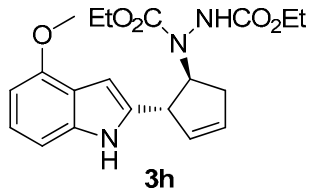
diisopropyl-1-(2-(1-(benzylcarbamoyl)-1H-indol-3-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3g)



3g

Yield: 13 mg, 34% as colourless viscous liquid. **R_f :** 0.85 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3315, 3057, 2997, 1698, 1523, 1393, 1250, 1155, 1059 cm^{-1}. **^{1}H NMR (500 MHz, CD_3CN):** 9.90 (brs, 1 H), 7.64-7.61 (m, 1 H), 7.50 (d, *J* = 8 Hz, 1 H), 7.44 (d, *J* = 7 Hz, 1 H), 7.09 (t, *J* = 7 Hz, 1 H),7.02 (t, *J* = 7.5 Hz, 1 H), 6.23 (s, 1 H), 5.86 (s, 1 H), 5.49(s, 1 H), 4.76-4.59 (m, 1 H), 4.58-4.32 (m, 1 H), 1.53-1.29 (m,18 H), .91-.64 (m, 4 H). **^{13}C NMR (125 MHz, CD_3CN):** δ 157.9, 156.2, 129.8, 128.4, 124.9, 123.11, 121.6, 120.5, 120.2, 116.2, 111.8, 110.8, 106.4, 81.6, 45.1, 44.9, 28.6, 12.7, 10.6. **HRMS (ESI):** *m/z* calcd for $C_{25}H_{33}N_3O_4Na$: 462.23688; Found: 462.23740.

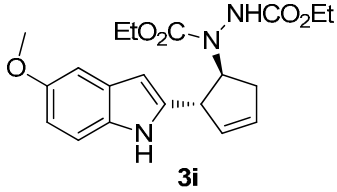
diethyl-1-(2-(4-methoxy-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3h)



3h

Yield: 43 mg, 66% as yellow viscous liquid. **R_f :** 0.65 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3301, 2981, 2935, 1707, 1615, 1511, 1465, 1414, 1375, 1249, 1174, 1102, 1058, 866, 766 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d_6):** δ 10.29-9.99 (m, 1 H), 8.78-8.40 (m, 1 H), 6.97-6.93 (m, 2 H), 6.47 (d, *J* = 8Hz, 1 H), 6.28 (s, 1 H), 5.89 (s, 2 H), 4.93 (brs, 1 H), 4.23-3.94 (m, 5 H), 3.88 (s, 3 H), 2.62 (brs, 2 H), 1.28-1.04 (m, 6 H). **^{13}C NMR (125 MHz, Acetone-d_6):** δ 156.3, 153.9, 138.7, 131.3, 130.6, 128.7, 127.2, 122.4, 119.8, 104.8, 99.5, 62.6, 54.8, 48.5, 35.6, 14.8. **HRMS (ESI):** *m/z* calcd for $C_{20}H_{25}N_3O_5Na$: 410.16919; Found: 410.16772.

diethyl-1-(2-(5-methoxy-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3i)

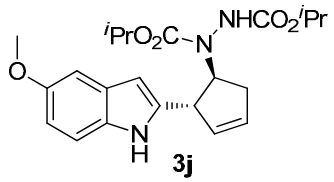


3i

Yield: 41 mg, 63% as yellow viscous liquid. **R_f :** 0.20 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3302, 2983, 2937, 1712, 1625, 1588, 1486, 1450, 1413, 1376, 1254, 1217, 1171, 1124, 1058, 1030, 950, 842, 767 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d_6):** δ 9.95 (brs, 1 H), 8.52-8.26 (m, 1 H), 7.07 (d, *J* = 9 Hz, 1 H), 6.84 (d, *J* = 2 Hz, 1 H), 6.55 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1 H), 6.01 (s, 1 H), 5.75 (s, 2 H), 4.11-3.98 (m, 6 H), 3.63 (s, 3 H), 2.48 (brs, 2 H), 1.14-1,08 (m, 6 H). **^{13}C NMR (125 MHz, Acetone-d_6):** δ 157.1, 155.1, 131.7, 129.9, 121.2, 112.2, 111..6, 102.6, 62.6, 55.9, 48.7, 35.7, 14.8. **HRMS (ESI):** *m/z* calcd for $C_{20}H_{25}N_3O_5Na$: 410.16919;

Found: 410.16773.

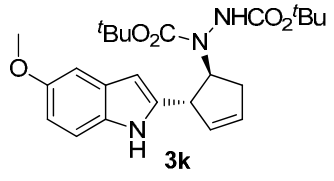
diisopropyl-1-(2-(5-methoxy-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3j)



3j

Yield: 38 mg, 61% as colourless viscous liquid. $\mathbf{R_f}$ **:** 0.25 (7:3 hexane/ethyl acetate). **IR (neat)** $\mathbf{\nu_{max}}$**:** 3325, 2918, 1716, 1589, 1466, 1157, 1061, 966 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d_6):** δ 10.14 (brs, 1 H), 8.58-8.42 (m, 1 H), 7.19 (d, J = 8.5 Hz, 1 H), 6.98 (d, J = 5 Hz, 1 H), 6.68 (dd, J_1= 9 Hz, J_2=2.5 Hz,1 H), 6.14 (s, 1 H), 5.89 (s, 2 H), 5.17-4.94 (m, 1 H), 4.93-4.87 (m, 2 H), 4.13 (brs, 3 H), 3.77 (s, 3 H) 2.61 (brs, 2 H), 1.35-1,09 (m, 12 H). **^{13}C NMR (125 MHz, Acetone-d_6):** δ 155.1, 131.7, 130.5, 129.7, 128.5, 126.7, 112.3, 110.8, 100.9, 70.8, 55.7, 48.4, 22.4. **HRMS (ESI):** *m/z* calcd for $C_{22}H_{29}N_3O_5Na$: 438.20049; Found: 438.19815.

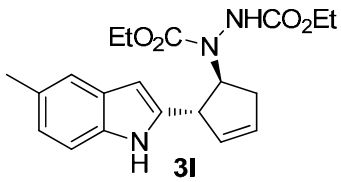
di-tert-butyl-1-(2-(5-methoxy-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3k)



3k

Yield: 36 mg, 60% as yellow viscous liquid. $\mathbf{R_f}$ **:** 0.70 (7:3 hexane/ethyl acetate). **IR (neat)** $\mathbf{\nu_{max}}$**:** 3381, 2977, 2933, 1712, 1588, 1454, 1252, 1112, 965 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 9.91 (brs, 1 H), 7.25-7.22 (m, 1 H), 7.01 (s, 1 H), 6.76 (d, J = 9 Hz, 1 H), 6.38 (s, 1 H), 6.13 (s, 1 H), 5.92-5.85 (m, 2 H), 4.62 (s, 1 H), 4.05 (s, 1 H), 3.83 (s, 3 H), 2.53 (brs, 2 H), 1.54-1.43 (m, 18 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 155.6, 153.7, 128.9, 124.3, 114.8, 113.5, 107.1, 103.0, 81.7, 55.8, 47.6, 31.0. **HRMS (ESI):** *m/z* calcd for $C_{24}H_{33}N_3O_5Na$: 466.23179; Found: 466.23260.

diethyl-1-(2-(5-methyl-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3l)

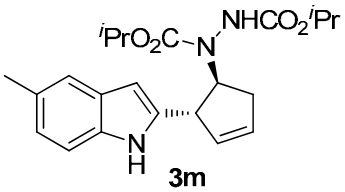


3l

Yield: 44 mg, 71% as yellow viscous liquid. $\mathbf{R_f}$ **:** 0.53 (7:3 hexane/ethyl acetate). **IR (neat)** $\mathbf{\nu_{max}}$**:** 3299, 2983, 2934, 2864, 1699, 1589, 1489, 1452, 1416, 1325, 1270, 1127, 1066, 952 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d_6):** δ 10.15-9.84 (m, 1 H), 8.76-8.40 (m, 1 H), 7.21 (d, J = 8 Hz, 1 H), 6.87 (d, J = 8.5 Hz, 1 H), 6.14 (s, 1 H), 5.89 (s, 2 H), 4.93 (brs, 1 H), 4.24-3.96 (m, 5 H), 2.63 (brs, 2 H), 2.37 (s, 3 H), 1.29-.82 (m, 6 H). **^{13}C NMR (125 MHz, Acetone-d_6):** δ 156.5, 131.6, 130.7, 128.1, 122.9, 120.0, 111.1, 62.8, 46.7, 35.6, 21.4, 14.7. **HRMS (ESI):** *m/z* calcd for $C_{20}H_{25}N_3O_5Na$: 394.17428; Found: 394.17253.

diisopropyl-1-(2-(5-methyl-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3m)

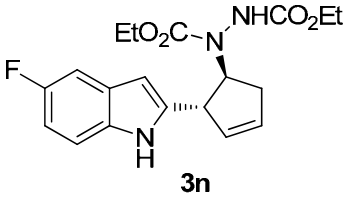
Yield: 43 mg, 73% as yellow viscous liquid. $\mathbf{R_f}$ **:** 0.53 (7:3 hexane/ethyl



3m

acetate). **IR (neat) ν_{max}:** 3301, 2982, 1713, 1592, 1496, 1409, 1179, 1143, 1108, 1042 cm^{-1}. **^{1}H NMR (500 MHz, CD_3CN):** δ 9.97-9.95 (m, 1 H), 7.52 (brs, 1 H), 7.29 (s, 1 H), 7.26-7.7.15 (m, 1 H), 6.89 (d, *J* = 8 Hz, 1 H), 6.11 (s, 1 H), 5.88 (s, 1 H), 5.24-4.76 (m, 5 H), 4.06 (brs, 1 H), 2.63-2.53 (m, 2 H), 2.37 (s, 3 H), 1.28-1.21 (m, 6 H). **^{13}C NMR (125 MHz, CD_3CN):** δ 156.3, 154.7, 130.0, 128.6, 127.9, 126.7, 128.8, 121.8, 117.0, 109.9, 99.5, 69.6, 43.5, 34.3, 20.9. **HRMS (ESI):** *m/z* calcd for $C_{22}H_{29}N_3O_4Na$: 422.20558; Found: 422.20508.

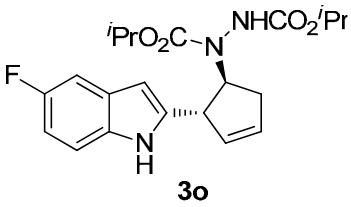
diethyl-1-(2-(5-fluoro-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3n)



3n

Yield: 46 mg, 74% as yellow viscous liquid. **R_f:** 0.48 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3289, 2983, 1714, 1533, 1254, 1062, 1016, 966 cm^{-1}. **^{1}H NMR (500 MHz, CD_3CN):** δ 10.35 (brs, 1 H), 8.77 (brs, 1 H), 7.34-7.29 (m, 1 H), 7.18-7.15 (m, 1 H),6.83 (dt, J_1 = 9.5 Hz, J_2 = 2.5 Hz, 1 H), 6.24 (s, 1 H), 5.91 (s, 2 H), 4.93 (brs, 1 H), 4.24-4.04 (m, 5 H), 2.63 (brs, 2 H), 1.29-1,19 (m, 6 H). **^{13}C NMR (125 MHz, CD_3CN):** δ 159.2, 157.5, 133.7, 131.1, 129.9, 128.8, 125.9, 112.3, 109.1, 105.0, 62.7, 46.7, 35.7, 14.8. **HRMS (ESI):** *m/z* calcd for $C_{19}H_{22}FN_3O_4Na$: 398.14920; Found: 398.14769.

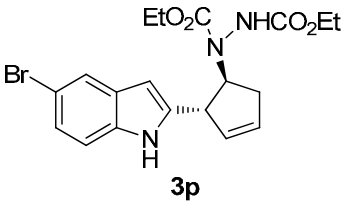
diisopropyl-1-(2-(5-fluoro-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3o)



3o

Yield: 42 mg, 60% as yellow viscous liquid. **R_f:** 0.70 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3314, 2981, 2922, 2851, 1716, 1485, 1381, 1287, 1230, 1164, 1132, 1059, 1032, 870, 761 cm^{-1}. **^{1}H NMR (500 MHz, CD_3CN):** δ 10.16 (brs, 1 H), 7.51 (brs, 1 H), 7.38-7.26 (m, 2 H), 6.86-6.79 (m, 1 H), 6.20 (brs, 1 H), 5.89 (brs, 2 H), 5.23-4.83 (m, 5 H), 4.08 (brs, 1 H), 2.53 (brs, 2 H), 1.29-1.17 (m, 6 H). **^{13}C NMR (125 MHz, CD_3CN):** δ 156.2, 131.2, 130.1, 129.7, 129.2, 128.4, 118.3, 112.3, 109.2, 105.1, 70.9, 46.4, 35.3, 21.9. **HRMS (ESI):** *m/z* calcd for $C_{21}H_{26}FN_3O_4Na$: 426.18050; Found: 426.18013.

diethyl-1-(2-(5-bromo-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3p)

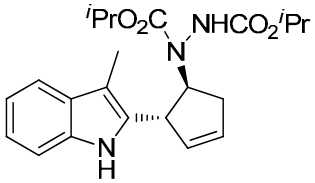


3p

Yield: 54 mg, 60% as yellow viscous liquid. **R_f:** 0.73 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3229, 2983, 1711, 1576, 1469, 1404, 1376, 1115, 1057, 1018 cm^{-1}. **^{1}H NMR (500 MHz, CD_3CN):** δ 10.18 (brs, 1 H), 7.64 (s, 1 H), 7.27 (d, *J* = 8.5 Hz, 1 H),7.16 (d, *J* = 10.8 Hz, 1 H), 6.51 (brs, 1 H), 6.21 (s, 1 H), 5.90-5.87 (m, 2 H), 4.85-4.77 (m,1 H), 4.21-4.08 (m, 5 H), 2.55 (brs, 2 H), 1.28-1,21 (m, 6 H). **^{13}C NMR (125 MHz, CD_3CN):** δ

160.2, 156.5, 135.5, 131.5, 130.9, 124.6, 122.8, 122.4, 118.3, 113.5, 101.0, 63.1, 48.8, 48.5, 35.6, 14.8. **HRMS (ESI):** *m/z* calcd for $C_{19}H_{22}BrN_3O_5Na$: 458.06914; Found: 458.06876.

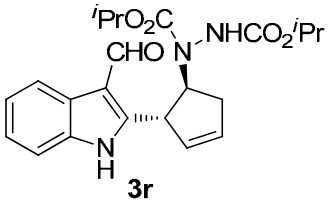
diisopropyl-1-(2-(3-methyl-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3q)



3q

Yield: 36 mg, 60% as yellow viscous liquid. **R_f :** 0.55 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3296, 2977, 2929, 1706, 1584, 1521, 1455, 1392, 1368, 1253, 1156, 1052, 854, 755 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d_6):** δ 9.80 (brs, 1 H), 8.17 (brs, 1 H), 7.44 (d, *J* = 7.5 Hz, 1 H), 7.23-7.22 (m, 1 H), 6.57 (s, 1 H), 5.88-5.79 (m, 2 H), 5.10-4.86 (m, 2 H), 4.29 (s, 1 H), 2.6 (brs, 2 H), 2.28 (s, 3 H), 1.49-1.29 (m, 12 H). **^{13}C NMR (125 MHz, Acetone-d_6):** δ 155.2, 129.7, 129.1, 126.2, 121.3, 118.9, 118.0, 111.1, 100.4, 70.5, 65.6, 48.2, 35.7, 21.9, 9.0. **HRMS (ESI):** *m/z* calcd for $C_{22}H_{29}N_3O_4Na$: 422.20558; Found: 422.20510.

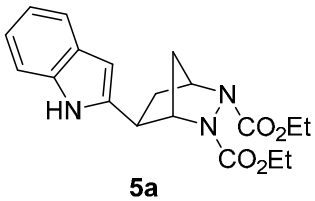
diisopropyl-1-(2-(3-formyl-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (3r)



3r

Yield: 41 mg, 67% as yellow viscous liquid. **R_f :** 0.30 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3299, 2983, 2934, 2864, 1699, 1589, 1489, 1452, 1416, 1325, 1270, 1127, 1066, 952 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 11.06, 10.04 (s, 1 H), 9.29 (s, 1 H), 8.31-8.29 (m, 1 H), 7.44-7.42 (m, 1 H), 7.31-7.29 (m, 2 H), 6.69 (s, 1 H), 6.09 (t, *J* = 3 Hz, 1 H), 5.87-5.86 (m, 1 H), 5.49 (d, *J* =7.5 Hz, 1 H), 5.00-4.45 (m, 2 H), 4.55 (brs, 1 H), 2.69-2.56 (m, 2 H), 1.29-1.25 (m, 12 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 184.9, 155.2, 135.2, 127.9, 124.5, 124.1, 122.7, 121.7, 119.5, 111.5, 99.8, 57.9, 30.6, 29.8, 21.9. **HRMS (ESI):** *m/z* calcd for $C_{22}H_{27}N_3O_5Na$: 436.18484; Found: 436.18499.

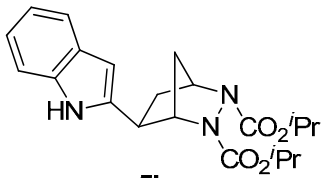
diethyl-5-(1H-indol-2-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (5a)



5a

Yield: 76 mg, 64% as reddish brown viscous liquid; **R_f:** 0.28 (hexane/ethyl acetate = 7:3). **IR (neat) ν_{max}:** 3333, 3054, 2982, 2911, 1713, 1618, 1459, 1402, 1374, 1323, 1171 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.88-8.41 (m, 1 H), 7.53 (d, *J* = 8.0 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.15 (t, *J* = 7.0 Hz, 1 H), 7.07 (t, *J* = 7.0 Hz, 1 H), 6.21 (s, 1 H), 4.73-4.61 (m, 2 H), 4.27 (m, 4 H), 3.40 (brs, 1 H), 2.36-2.26 (m, 1 H), 2.11 (brs, 1 H), 1.92-1.90 (m, 1 H), 1.72 (brs, 1 H), 1.33-1.24 (m, 6 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 157.7, 139.3, 136.4, 128.1, 121.8, 120.0, 119.8, 110.8, 99.2, 64.4, 62.8, 60.2, 39.5, 35.6, 14.5. **HRMS (ESI):** *m/z* calcd for $C_{19}H_{23}N_3O_4Na$: 380.15863; Found: 380.16012.

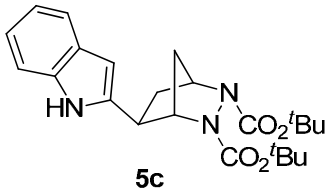
diisopropyl-5-(1H-indol-2-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (5b)



5b

Yield: 67 mg, 58% as pale brown viscous liquid; **R_f:** 0.42 (hexane/ethyl acetate = 7:3). **IR (neat) ν_{max}:** 3329, 3056, 2982, 1710, 1619, 1458, 1315, 1098 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 9.30-8.75 (m, 1 H), 7.48 (d, *J* = 8.0 Hz, 1 H), 7.30 (s, 1 H), 7.10 (t, *J* = 7.5 Hz, 1 H), 7.03 (t, *J* = 7.5 Hz, 1 H), 6.15 (s, 1 H), 5.03 (brs, 2 H), 4.72 (brs, 1 H), 4.56 (brs, 1 H), 3.52-3.39 (m, 1 H), 2.34-2.14 (m, 2 H), 1.90-1.88 (m, 1 H), 1.67-1.60 (m, 1 H), 1.31-1.17 (m, 12 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 157.3, 139.6, 136.5, 128.1, 121.6, 119.9, 119.7, 111.0, 98.7, 70.5, 64.9, 64.3, 59.9, 39.1, 35.6, 22.1, 21.9. **HRMS (ESI):** *m/z* calcd for $C_{21}H_{27}N_3O_4Na$: 408.18993; Found: 408.18894.

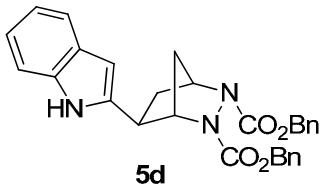
di-tert-butyl-5-(1H-indol-2-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (5c)



5c

Yield: 57 mg, 51% as pale brown viscous liquid; **R_f:** 0.50 (hexane/ethyl acetate = 7:3). **IR (neat) ν_{max}:** 3317, 2978, 2932, 1713, 1457, 1367, 1345, 1290, 1256, 1144, 1107, 1050 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 9.37-8.27 (m, 1 H), 7.49 (d, *J* = 7.5 Hz, 1 H), 7.34-7.28 (m, 1 H), 7.11 (t, *J* = 7.5 Hz, 1 H), 7.03 (t, *J* = 7.5 Hz, 1 H), 6.16 (s, 1 H), 4.72-4.66 (m, 1 H), 4.51 (brs, 1 H), 3.53-3.44 (m, 1 H), 2.39-2.16 (m, 2 H), 1.85 (brs, 1 H), 1.64 (brs, 1 H), 1.55-1.47 (m, 15 H), 1.29-1.26 (m, 3 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 156.8, 139.7, 136.5, 129.0, 128.2, 125.3, 121.7, 120.0, 119.7, 110.7, 99.7, 81.6, 64.8, 64.1, 60.0, 39.2, 35.4, 28.4, 28.2. **HRMS (ESI):** *m/z* calcd for $C_{23}H_{31}N_3O_4Na$: 436.22123; Found: 436.22126.

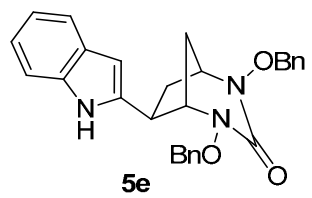
dibenzyl-5-(1H-indol-2-yl)-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (5d)



5d

Yield: 52 mg, 49% as pale yellow viscous liquid; **R_f:** 0.39 (hexane/ethyl acetate = 7:3). **IR (neat) ν_{max}:** 3340, 3033, 2956, 1714, 1456, 1391, 1322, 1294, 1264, 1165, 1106 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.81-8.36 (m, 1 H), 7.47 (d, *J* = 7.5 Hz, 1 H), 7.30 (m, 11 H), 7.09 (t, *J* = 7.0 Hz, 1 H), 7.03 (t, *J* = 7.0 Hz, 1 H), 6.11 (s, 1 H), 5.18-5.07 (m, 4 H), 4.69-4.59 (m, 2 H), 3.47-3.29 (m, 1 H), 2.26-2.21 (m, 1 H), 2.03 (brs, 1 H), 1.86-1.84 (m, 1 H), 1.66 (brs, 1 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 157.5, 138.9, 135.8, 128.6, 128.3, 128.1, 121.8, 120.0, 119.8, 110.8, 99.1, 68.2, 65.1, 60.3, 39.4, 35.6. **HRMS (ESI):** *m/z* calcd for $C_{29}H_{27}N_3O_4Na$: 504.18993; Found: 504.18909.

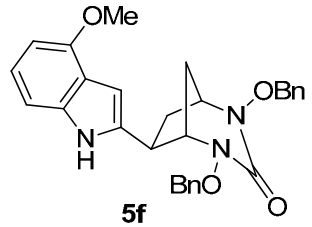
2,4-bis(benzyloxy)-6-(1H-indol-2-yl)-2,4-diazabicyclo[3.2.1]octan-3-one (5e)



5e

Yield: 86 mg, 80% as colourless viscous liquid; **R_f:** 0.42 (hexane/ethyl acetate = 3:2). **IR (neat) ν_{max}:** 3296, 3032, 2979, 2945, 1699, 1545, 1495, 1456, 1371, 1274, 1214, 1170, 1078, 1029, 990, 911, 786, 749 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.70-8.65 (m, 1 H), 7.44-7.38 (m, 5 H), 7.33-7.30 (m, 7 H), 7.11-7.08 (m, 1 H), 7.02 (t, *J* = 7.5 Hz, 1 H), 5.95 (s, 1 H), 5.02-5.00 (m, 2 H), 4.89-4.84 (m, 2 H), 3.77 (s, 1 H), 3.70 (t, *J* = 4.0 Hz, 1 H), 3.57 (d, *J* = 4.0 Hz, 1 H), 2.72-2.67 (m, 1 H), 2.06-2.03 (m, 1 H), 1.89-1.86 (m, 1 H), 1.84-1.79 (m, 1 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 160.8, 140.8, 136.2, 136.1, 136.0, 129.7, 129.6, 128.4, 121.5, 119.8, 119.6, 110.8, 97.6, 77.9, 77.8, 67.9, 62.6, 40.9, 36.4, 32.0. **HRMS (ESI):** *m/z* calcd for $C_{28}H_{27}N_3O_3Na$: 476.19501; Found: 476.19604.

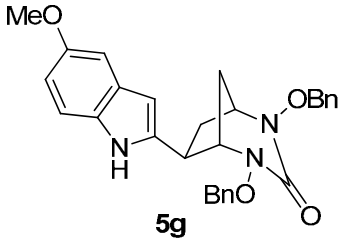
2,4-bis(benzyloxy)-6-(4-methoxy-1H-indol-2-yl)-2,4-diazabicyclo[3.2.1]octan-3-one (5f)



5f

Yield: 66 mg, 57% as colourless solid (m.p. = 192-194 °C); **R_f:** 0.36 (hexane/ethyl acetate = 3:2). **IR (neat) ν_{max}:** 3389, 1649, 1453, 1428, 1391, 1360, 1268, 1241, 1168, 1093, 997, 910, 738, 697 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.42 (s, 1 H), 7.44-7.40 (m, 4 H), 7.34-7.32 (m, 6 H), 7.02 (t, *J* = 8.0 Hz, 1 H), 6.93 (d, *J* = 8.5 Hz, 1 H), 6.45 (d, *J* = 8.0 Hz, 1 H), 6.08 (d, *J* = 2.0 Hz, 1 H), 5.03-5.01 (m, 2 H), 4.89-4.84 (m, 2 H), 3.90 (s, 3 H), 3.73-3.69 (m, 2 H), 3.55 (d, *J* = 4.5 Hz, 1 H), 2.71-2.66 (m, 1 H), 2.04-2.01 (m, 1 H), 1.92-1.82 (m, 2 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 160.7, 152.7, 139.2, 137.4, 136.3, 136.0, 129.7, 129.6, 128.6, 128.5, 128.4, 122.3, 118.6, 104.3, 99.4, 95.0, 77.9, 77.8, 68.0, 62.6, 55.1, 40.9, 36.3, 31.9. **HRMS (ESI):** *m/z* calcd for $C_{29}H_{30}N_3O_4$: 484.22363; Found: 484.22456.

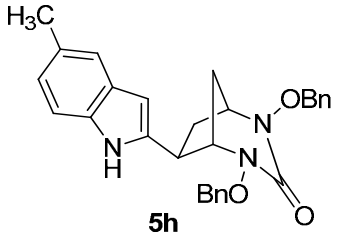
2,4-bis(benzyloxy)-6-(5-methoxy-1H-indol-2-yl)-2,4-diazabicyclo[3.2.1]octan-3-one (5g)



5g

Yield: 76 mg, 66% as yellow viscous liquid; **R_f:** 0.37 (hexane/ethyl acetate = 3:2). **IR (neat) ν_{max}:** 3303, 3063, 3033, 2944, 1697, 1589, 1488, 1455, 1372, 1326, 1268, 1209, 1169, 1030, 912, 739, 700 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.36 (brs, 1 H), 7.36-7.32 (m, 4 H), 7.27-7.24 (m, 6 H), 7.12 (d, *J* = 9.0 Hz, 1 H), 6.86 (d, *J* = 2.5 Hz, 1 H), 6.70 (dd, J_1 = 8.5 Hz, J_2 = 7.5 Hz, 1 H), 5.84 (t, *J* = 1.0 Hz, 1 H), 4.95-4.93 (m, 2 H), 4.82-4.77 (m, 2 H), 3.72 (s, 3 H), 3.66-3.63 (m, 2 H), 3.49 (d, *J* = 4.0 Hz, 1 H), 2.63-2.58 (m, 1 H), 1.98-1.96 (m, 1 H), 1.82-1.72 (m, 2 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 159.7, 153.1, 140.5, 135.2, 134.9, 130.2, 128.6, 128.5, 127.5, 127.5, 127.4, 110.5, 100.9, 96.5, 76.9, 76.8, 66.9, 61.5, 54.9, 40.0, 35.3, 31.0. **HRMS (ESI):** *m/z* calcd for $C_{29}H_{30}N_3O_4$: 484.22363; Found: 484.22291.

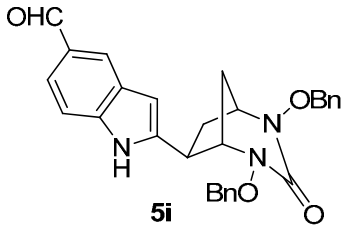
2,4-bis(benzyloxy)-6-(5-methyl-1H-indol-2-yl)-2,4-diazabicyclo[3.2.1]octan-3-one (5h)



5h

Yield: 79 mg, 71% as brownish viscous liquid; **R_f:** 0.45 (hexane/ethyl acetate = 3:2). **IR (neat) ν_{max}:** 3391, 2929, 2864, 1691, 1455, 1372, 1319, 1267, 1213, 1170, 1028, 992, 911, 784, 740, 700 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.48 (brs, 1 H), 7.34-7.30 (m, 4 H), 7.25-7.22 (m, 6 H), 7.14-7.11 (m, 2 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 5.79-5.78 (m, 1 H), 4.93-4.91 (m, 2 H), 4.80-4.75 (m, 2 H), 3.68-3.65 (m, 1 H), 3.60 (t, *J* = 4.0 Hz, 1 H), 3.47 (d, *J* = 4.0 Hz, 1 H), 2.62-2.57 (m, 1 H), 2.32 (s, 3 H), 1.96-1.94 (m, 1 H), 1.81-1.76 (m, 1 H), 1.74-1.69 (m, 1 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 160.9, 141.0, 136.3, 136.0, 134.5, 129.7, 129.6, 128.6, 128.5, 128.5, 128.5, 128.4, 123.0, 119.5, 110.5, 97.1, 77.9, 77.8, 67.9, 62.7, 41.0, 36.5, 32.1, 21.5. **HRMS (ESI):** *m/z* calcd for $C_{29}H_{30}N_3O_3$: 468.22872; Found: 468.22867.

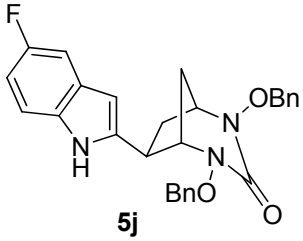
2,4-bis(benzyloxy)-3-oxo-2,4-diazabicyclo[3.2.1]octan-6-yl)-1H-indole-5-carbaldehyde (5i)



5i

Yield: 78 mg, 68% as reddish brown viscous liquid; **R_f:** 0.34 (hexane/ethyl acetate = 1:1). **IR (neat) ν_{max}:** 3409, 1677, 1615, 1549, 1488, 1455, 1428, 1374, 1331, 1306, 1267, 1221, 1163, 1114, 1078, 1029, 998, 909, 786, 741, 701 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 10.30 (s, 1 H), 9.97 (s, 1 H), 7.97 (s, 1 H), 6.80 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1 H), 7.47 (d, *J* = 8.5 Hz, 1 H), 7.37-7.35 (m, 2 H), 7.31-7.29 (m, 3 H), 7.28-7.26 (m, 2 H), 7.23-7.17 (m, 3 H), 6.04-6.03 (m, 1 H), 4.98-4.96 (m, 1 H), 4.92-4.87 (m, 2 H), 4.82-4.80 (m, 1 H), 3.90 (dd, J_1 = 9.0 Hz, J_2 = 6.0 Hz, 1 H), 3.73 (t, *J* = 4.0 Hz, 1 H), 3.62 (d, *J* = 4.5 Hz, 1 H), 2.74-2.69 (m, 1 H), 2.15-2.12 (m, 1 H), 1.97-1.93 (m, 1 H), 1.77-1.72 (m, 1 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 192.5, 161.4, 143.5, 140.0, 135.7, 129.5, 129.5, 129.4, 128.6, 128.5, 128.4, 128.4, 128.2, 124.8, 122.2, 111.7, 98.5, 77.8, 77.8, 67.4, 62.8, 40.8, 37.2, 32.4. **HRMS (ESI):** *m/z* calcd for $C_{29}H_{27}N_3NaO_4$: 504.18993; Found: 504.19184.

2,4-bis(benzyloxy)-6-(5-fluoro-1H-indol-2-yl)-2,4-diazabicyclo[3.2.1]octan-3-one (5j)

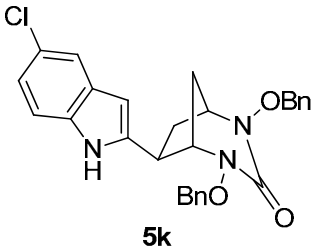


5j

Yield: 78 mg, 70% as reddish brown viscous liquid; **R_f:** 0.39 (hexane/ethyl acetate = 3:2). **IR (neat) ν_{max}:** 3433, 1650, 1490, 1454, 1375, 1326, 1269, 1211, 1176, 1113, 1029, 995, 959, 911, 852, 747, 699 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 9.24 (brs, 1 H), 7.39-7.37 (m, 2 H), 7.33-7.31 (m, 5 H), 7.26-7.23 (m, 4 H), 7.08-7.06 (m, 1 H), 6.84 (td, J_1 = 9.0 Hz, J_2 = 2.5 Hz, 1 H), 5.88 (t, *J* = 1.0 Hz, 1 H), 4.99-4.93 (m, 2 H), 4.88-4.80 (m, 2 H), 3.79 (s, 1 H), 3.70 (t, *J* = 4.0 Hz, 1 H), 5.80 (d, *J* = 4.0 Hz, 1 H), 2.70-2.65 (m, 1 H), 2.09-2.06 (m, 1 H), 1.92-1.88 (m, 1 H),

1.78-1.73 (m, 1 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 161.2, 158.8, 156.9, 142.9, 135.9, 135.8, 132.7, 129.6, 129.5, 128.6, 128.5, 128.4, 128.4, 111.6, 111.5, 109.6, 109.4, 104.6, 104.5, 97.3, 77.8, 67.7, 62.7, 40.9, 36.9, 32.3. **HRMS (ESI):** *m/z* calcd for $C_{28}H_{26}FN_3NaO_3$: 494.18559; Found: 494.18571.

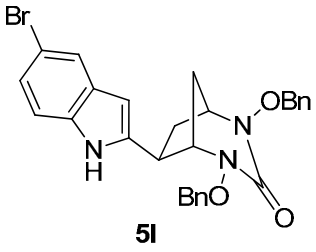
2,4-bis(benzyloxy)-6-(5-chloro-1H-indol-2-yl)-2,4-diazabicyclo[3.2.1]octan-3-one (5k)



5k

Yield: 86 mg, 74% as brownish viscous liquid; **R_f:** 0.45 (hexane/ethyl acetate = 3:2). **IR (neat) ν_{max}:** 3301, 1696, 1580, 1542, 1496, 1453, 1368, 1315, 1267, 1218, 1169, 1062, 1029, 992, 915, 867, 779, 740, 699 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 9.30 (s, 1 H), 7.41-7.38 (m, 3 H), 7.33-7.31 (m, 5 H), 7.28-7.23 (m, 4 H), 7.06 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1 H), 5.88-5.87 (m, 1 H), 4.99-4.93 (m, 2 H), 4.89-4.80 (m, 2 H), 3.80 (dd, J_1 = 8.5 Hz, J_2 = 6.0 Hz, 1H), 3.72 (t, J = 4.0 Hz, 1 H), 3.57 (d, J = 4.5 Hz, 1 H), 2.70-2.65 (m, 1 H), 2.10-2.07 (m, 1H), 1.91-1.87 (m, 1 H), 1.78-1.73 (m, 1 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 161.1, 142.7, 135.9, 134.5, 129.6, 129.5, 129.3, 128.6, 128.6, 128.5, 128.5, 112.0, 97.0, 77.9, 77.8, 67.7, 62.7, 40.9, 36.9, 32.2. **HRMS (ESI):** *m/z* calcd for $C_{28}H_{27}ClN_3O_3$: 488.17409; Found: 488.17340.

2,4-bis(benzyloxy)-6-(5-bromo-1H-indol-2-yl)-2,4-diazabicyclo[3.2.1]octan-3-one (5l)

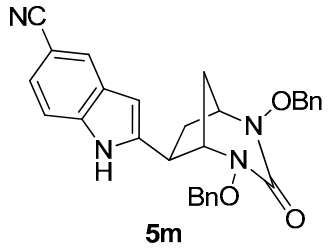


5l

Yield: 99 mg, 78% as brownish viscous liquid; **R_f:** 0.37 (hexane/ethyl acetate = 3:2). **IR (neat) ν_{max}:** 3279, 3032, 2979, 2944, 1696, 1577, 1540, 1495, 1456, 1373, 1313, 1268, 1214, 1169, 1111, 1078, 1029, 991, 905, 827, 780, 738, 699 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 9.35 (s, 1 H), 7.49 (d, J = 2.0 Hz, 1 H), 7.31-7.29 (m, 2 H), 7.27-7.22 (m, 5 H), 7.19-7.15 (m, 4 H), 7.11-7.09 (m, 1 H), 5.79 (t, J = 1.0 Hz, 1 H), 4.91-4.84 (m, 2 H), 4.80-4.72 (m, 2 H), 3.72 (dd, J_1 = 9.0 Hz, J_2 = 6.0 Hz, 1 H), 3.63 (t, J = 4.0 Hz, 1 H), 3.49 (d, J = 4.0 Hz, 1 H), 2.62-2.57 (m, 1 H), 2.02-1.99 (m, 1 H), 1.83-1.77 (m, 1 H), 1.68-1.64 (m, 1 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 161.1, 142.6, 135.9, 134.8, 130.0, 129.6, 129.5, 128.6, 128.6, 128.5, 128.5, 122.2, 112.6, 112.5, 96.8, 77.9, 77.8, 67.6, 62.7, 40.9, 36.9, 32.3. **HRMS (ESI):** *m/z* calcd for $C_{28}H_{26}BrN_3O_3Na$: 554.10552; Found: 554.10531.

2-(-2,4-bis(benzyloxy)-3-oxo-2,4-diazabicyclo[3.2.1]octan-6-yl)-1H-indole-5-carbonitrile (5m)

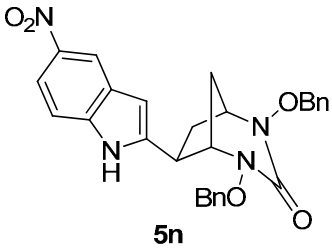
Yield: 77 mg, 68% as pale yellow viscous liquid; **R_f:** 0.39 (hexane/ethyl acetate = 1:1). **IR (neat) ν_{max}:** 3303, 1645, 1455, 1372, 1321, 1268, 1214,



5m

1025, 754 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 10.04 (brs, 1 H), 7.71 (s, 1 H), 7.36-7.34 (m, 1 H), 7.30-7.22 (m, 6 H), 7.21-7.19 (m, 2 H), 7.17-7.12 (m, 3 H), 5.90 (s, 1 H), 4.91-4.89 (m, 1 H), 4.85-4.80 (m, 2 H), 4.75-4.72 (m, 1 H), 3.80 (dd, J_1 = 8.5 Hz, J_2 = 6.0 Hz, 1 H), 3.67 (t, J = 4.0 Hz, 1 H), 3.52 (d, J = 4.5 Hz, 1 H), 2.67-2.61 (m, 1 H), 2.08-2.06 (m, 1 H), 1.88-1.84 (m, 1 H), 1.69-1.64 (m, 1 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 160.3, 142.7, 137.0, 134.5, 128.4, 128.3, 127.6, 127.5, 127.4, 127.0, 124.1, 123.3, 119.8, 110.9, 101.4, 96.5, 76.8, 66.3, 61.6, 39.7, 36.2, 31.3. **HRMS (ESI):** *m/z* calcd for $C_{29}H_{26}N_4NaO_3$: 501.19026; Found: 501.19153.

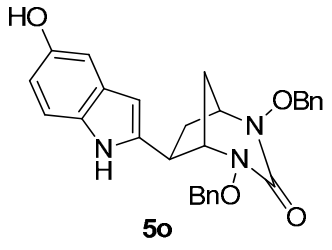
2,4-bis(benzyloxy)-6-(5-nitro-1H-indol-2-yl)-2,4-diazabicyclo[3.2.1]octan-3-one (5n)



5n

Yield: 89 mg, 75% as pale yellow solid (m.p. = 185-187 °C); **R_f:** 0.43 (hexane/ethyl acetate = 1:1). **IR (neat) ν_{max}:** 3409, 1687, 1556, 1518, 1470, 1374, 1331, 1270, 1215, 1172, 1070, 1029, 994, 892, 815, 783, 740, 700 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 10.70 (s, 1 H), 8.39 (d, J = 2.0 Hz, 1 H), 8.02 (dd, J_1 = 9.0 Hz, J_2 = 2.5 Hz, 1 H), 7.41 (d, J = 9.0 Hz, 1 H), 7.35-7.33 (m, 2 H), 7.32-7.29 (m, 3 H), 7.23-7.19 (m, 3 H), 7.17-7.14 (m, 2 H), 6.04 (t, J = 0.5 Hz, 1 H), 4.97-4.95 (m, 1 H), 4.89-4.87 (m, 2 H), 4.81-4.79 (m, 1 H), 3.92 (dd, J_1 = 8.5 Hz, J_2 = 6.0 Hz, 1 H), 3.76 (t, J = 4.0 Hz, 1 H), 3.63 (d, J = 4.5 Hz, 1 H), 2.74-2.69 (m, 1 H), 2.19-2.17 (m, 1 H), 2.00-1.95 (m, 1 H), 1.74-1.69 (m, 1 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 161.4, 144.7, 141.6, 139.4, 135.5, 135.5, 129.5, 129.4, 128.7, 128.6, 128.4, 127.6, 117.1, 116.9, 110.9, 99.0, 77.9, 77.8, 67.3, 62.7, 40.8, 37.3, 32.4. **HRMS (ESI):** *m/z* calcd for $C_{28}H_{26}N_4O_5Na$: 521.18009; Found: 521.18112.

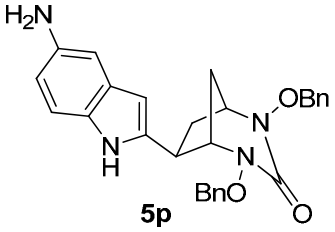
2,4-bis(benzyloxy)-6-(5-hydroxy-1H-indol-2-yl)-2,4-diazabicyclo[3.2.1]octan-3-one (5o)



5o

Yield: 45 mg, 40% as light brown viscous liquid; **R_f:** 0.29 (hexane/ethyl acetate = 1:1). **IR (neat) ν_{max}:** 3396, 3367, 3034, 2955, 2876, 1668, 1543, 1493, 1456, 1370, 1268, 1211, 1181, 1126, 1029, 924, 844, 750, 700 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.97 (brs, 1 H), 7.44-7.43 (m, 4 H), 7.37-7.34 (m, 6 H), 7.08 (d, J = 8.5 Hz, 1 H), 6.85 (d, J = 2.5 Hz, 1 H), 6.67 (dd, J_1 = 9.0 Hz, J_2 = 2.5 Hz, 1 H), 5.85 (s, 1 H), 5.07-5.01 (m, 2 H), 4.89-4.86 (m, 2 H), 3.69 (t, J = 4.0 Hz, 1 H), 3.65 (dd, J_1 = 9.0 Hz, J_2 = 6.0 Hz, 1 H), 3.54 (d, J = 4.5 Hz, 1 H), 2.70-2.64 (m, 1 H), 2.04-2.01 (m, 1 H), 1.86-1.80 (m, 2 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 160.6, 149.7, 141.4, 136.3, 136.0, 131.2, 129.7, 129.6, 128.6, 128.5, 128.4, 111.3, 111.1, 104.5, 97.6, 77.9, 77.8, 68.0, 62.5, 41.1, 36.0, 31.9. **HRMS (ESI):** *m/z* calcd for $C_{28}H_{27}N_3O_4Na$: 492.18993; Found: 492.19013.

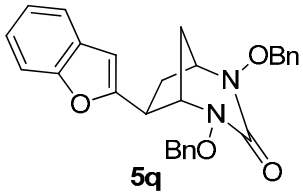
6-(5-amino-1H-indol-2-yl)-2,4-bis(benzyloxy)-2,4-diazabicyclo[3.2.1]octan-3-one (5p)



5p

Yield: 61 mg, 55% as brownish viscous liquid; **R_f:** 0.29 (hexane/ethyl acetate = 3:7). **IR (neat) ν_{max}:** 3617, 3248, 1651, 1425, 1266, 1027, 781, 732 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.10 (s, 1 H), 7.45-7.43 (m, 4 H), 7.36-7.34 (m, 6 H), 7.06 (d, *J* = 8.5 Hz, 1 H), 6.79 (d, *J* = 2.0 Hz, 1 H), 5.80 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1 H), 5.82 (t, *J* = 1.0 Hz, 1 H), 5.06-5.01 (m, 2 H), 4.89-4.86 (m, 2 H), 3.71 (t, *J* = 4.0 Hz, 1 H), 3.66 (dd, J_1 = 8.5 Hz, J_2 = 5.5 Hz, 1 H), 3.55 (d, *J* = 9.0 Hz, 1 H), 3.25 (brs, 2 H), 2.69-2.63 (m, 1 H), 2.04-2.02 (m, 1 H), 1.87-1.80 (m, 2 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 160.6, 150.4, 141.2, 138.7, 136.3, 136.0, 131.0, 129.7, 129.6, 129.0, 128.6, 128.6, 128.4, 112.6, 111.2, 105.5, 97.2, 78.0, 77.9, 68.0, 62.5, 41.1, 36.1, 32.0. **HRMS (ESI):** *m/z* calcd for $C_{28}H_{29}N_4O_3$: 469.22397; Found: 469.22344.

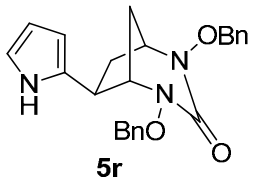
6-(benzofuran-2-yl)-2,4-bis(benzyloxy)-2,4-diazabicyclo[3.2.1]octan-3-one (5q)



5q

Yield: 52 mg, 48% as pale yellow viscous liquid; **R_f:** 0.50 (hexane/ethyl acetate = 3:2). **IR (neat) ν_{max}:** 2923, 2851, 1643, 1457, 1364, 1266, 1210, 1166, 1026, 914, 749, 702 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.47-7.42 (m, 5 H), 7.38-7.31 (m, 7 H), 7.21-7.13 (m, 2 H), 6.31 (s, 1 H), 5.08-5.03 (m, 2 H), 4.90-4.86 (m, 2 H), 3.87 (dd, J_1 = 9.0 Hz, J_2 = 5.5 Hz, 1 H), 3.72-3.70 (m, 2 H), 2.71-2.66 (m, 1 H), 2.12-2.09 (m, 1 H), 2.04-1.99 (m, 1 H), 1.94-1.89 (m, 1 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 160.6, 158.6, 154.7, 136.2, 136.1, 129.6, 129.4, 128.4, 128.4, 123.8, 122.7, 120.5, 110.9, 102.2, 77.8, 77.8, 67.0, 62.7, 40.9, 34.9, 32.6. **HRMS (ESI):** *m/z* calcd for $C_{28}H_{26}N_2NaO_4$: 477.17903; Found: 477.17776.

2,4-bis(benzyloxy)-6-(1H-pyrrol-2-yl)-2,4-diazabicyclo[3.2.1]octan-3-one (5r)

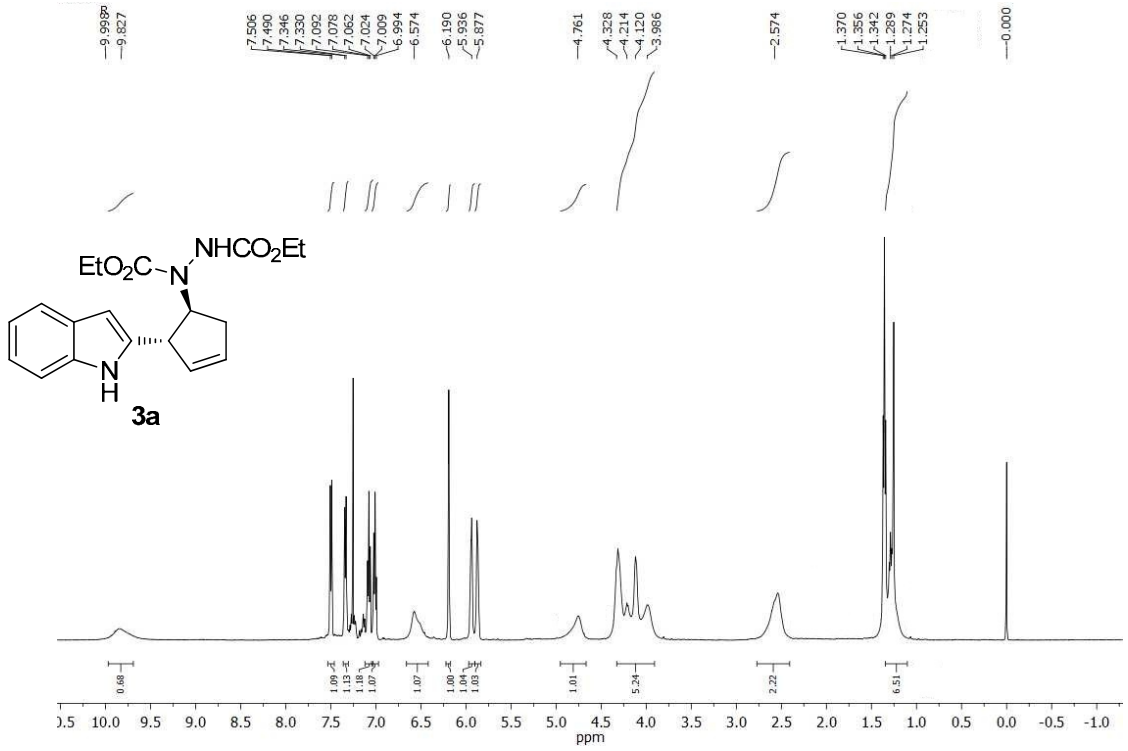


5r

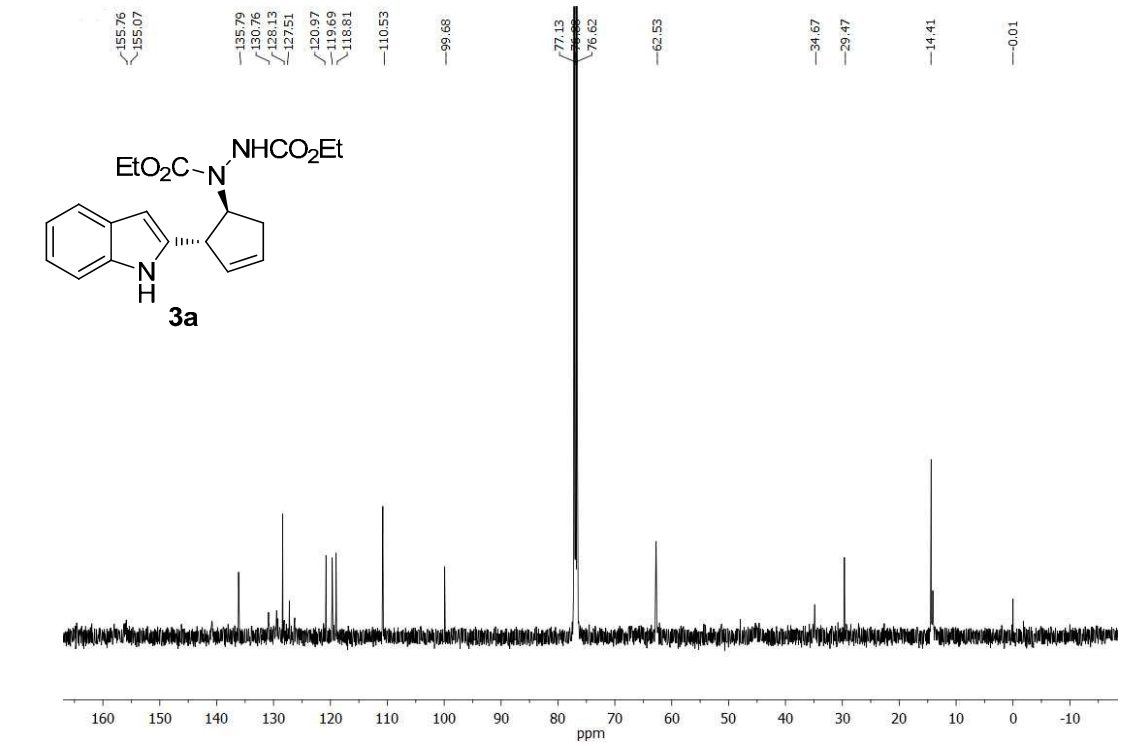
Yield: 51 mg, 53% as light brown viscous liquid; **R_f:** 0.39 (hexane/ethyl acetate = 3:2). **IR (neat) ν_{max}:** 3272, 1653, 1498, 1454, 1374, 1264, 1214, 1166, 1028, 784, 728 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.25 (brs, 1 H), 7.35-7.34 (m, 4 H), 7.29-7.23 (m, 6 H), 6.53-6.52 (m, 1 H), 5.93 (q, *J* = 3.0 Hz, 1 H), 5.59 (s, 1 H), 4.95-4.91 (m, 2 H), 4.79-4.75 (m, 2 H), 3.59 (t, *J* = 4.0 Hz, 1 H), 3.55-3.52 (m, 1 H), 3.39 (d, *J* = 4.5 Hz, 1 H), 2.59-2.54 (m, 1 H), 1.93-1.91 (m, 1 H), 1.78-1.74 (m, 1 H), 1.69-1.64 (m, 1 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 160.7, 136.3, 136.1, 133.7, 129.6, 129.5, 128.5, 128.4, 117.1, 108.0, 103.6, 77.8, 77.8, 68.2, 62.5, 40.5, 36.4, 31.8. **HRMS (ESI):** *m/z* calcd for $C_{24}H_{25}N_3NaO_3$: 426.17936; Found: 426.17895.

References

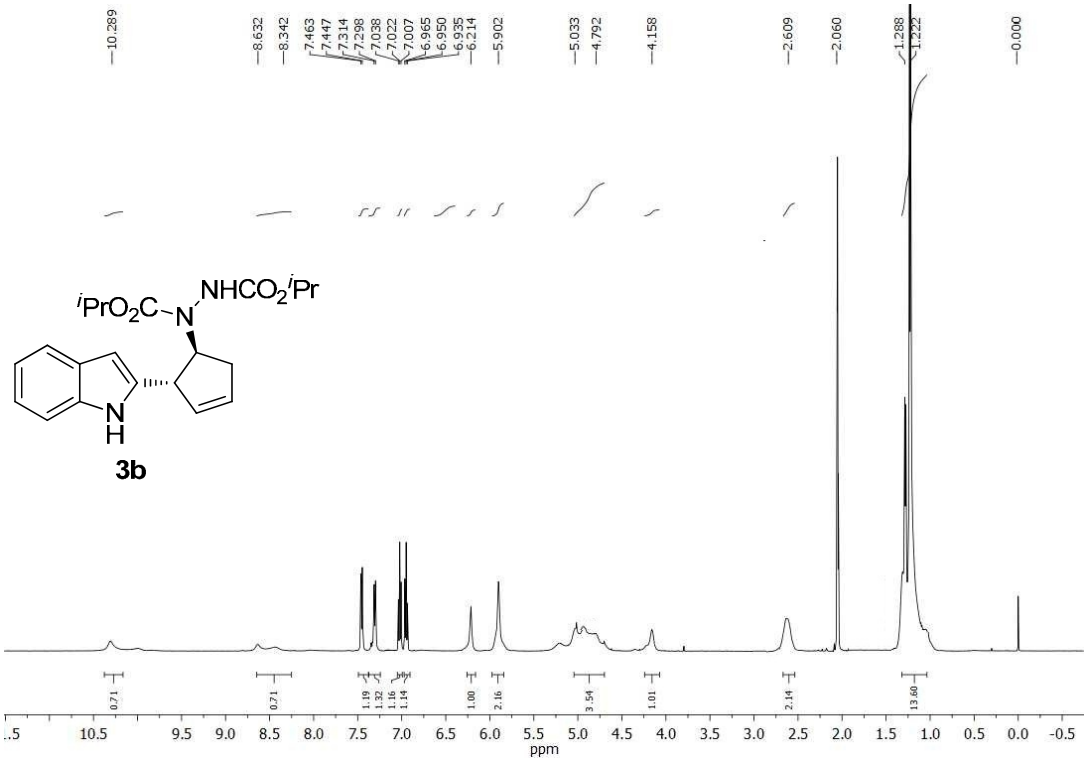
1. Hu, D. X.; Grice, P.; Ley, S. V. *J. Org. Chem.* **2012**, *77*, 5198.



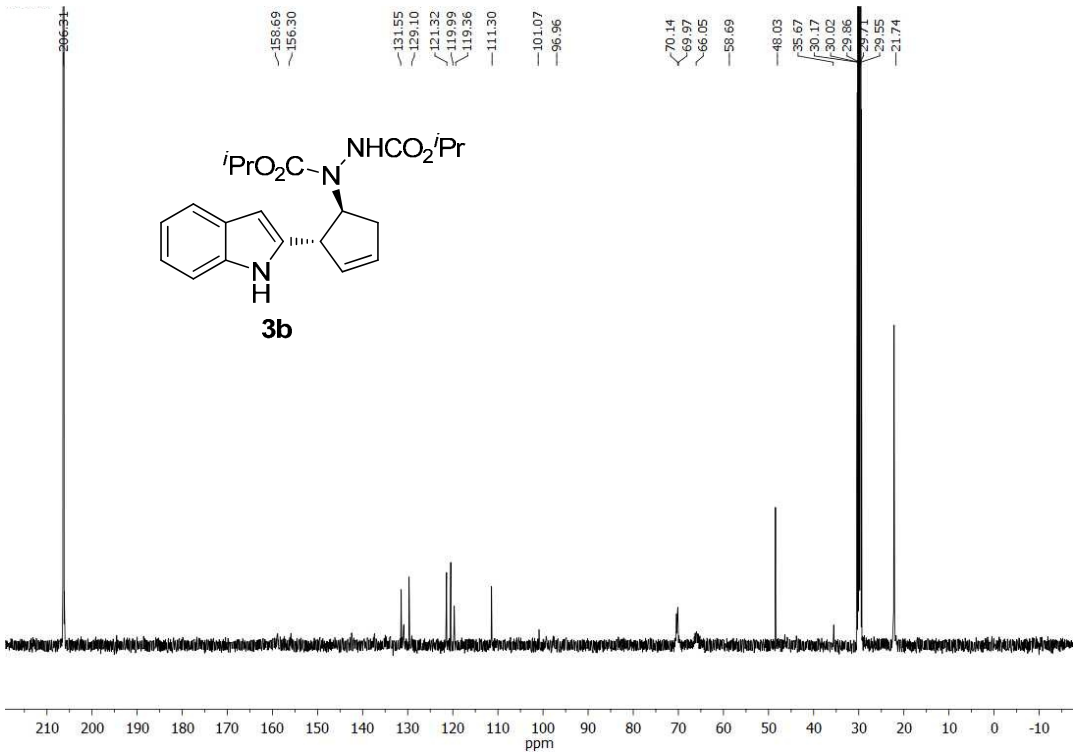
^{1}H NMR of 3a



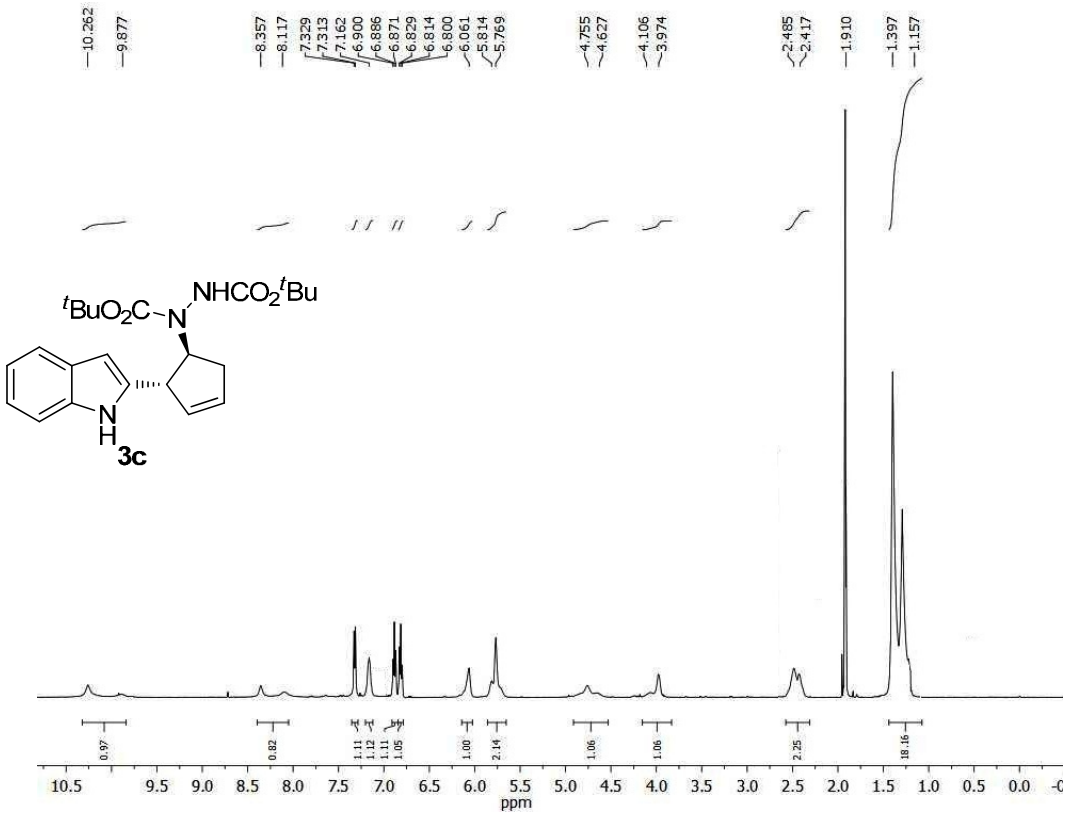
^{13}C NMR of 3a



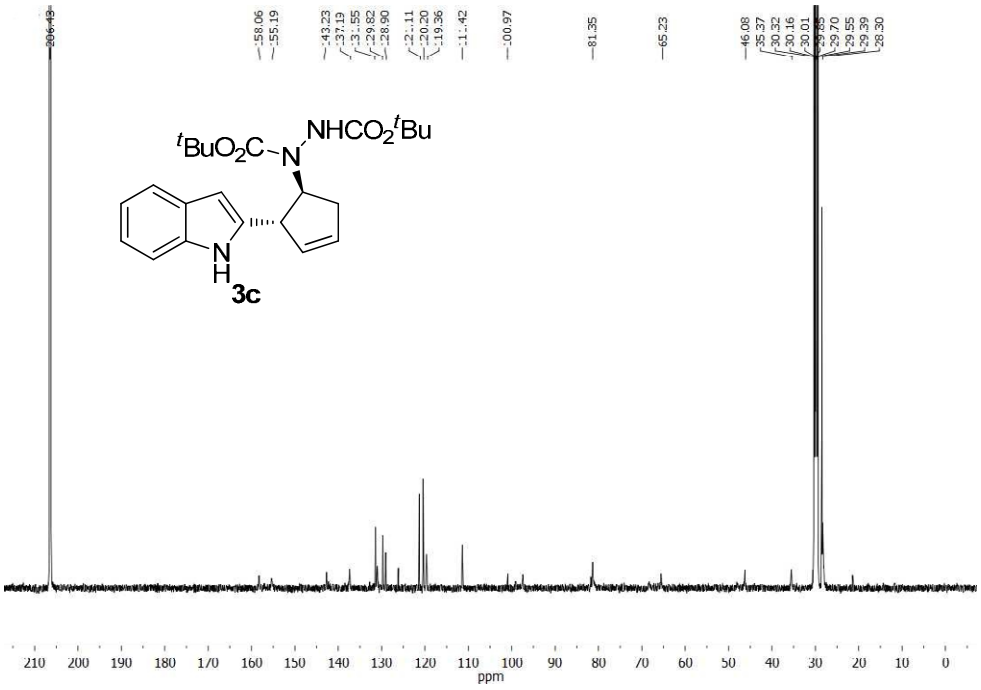
^{1}H NMR of 3b



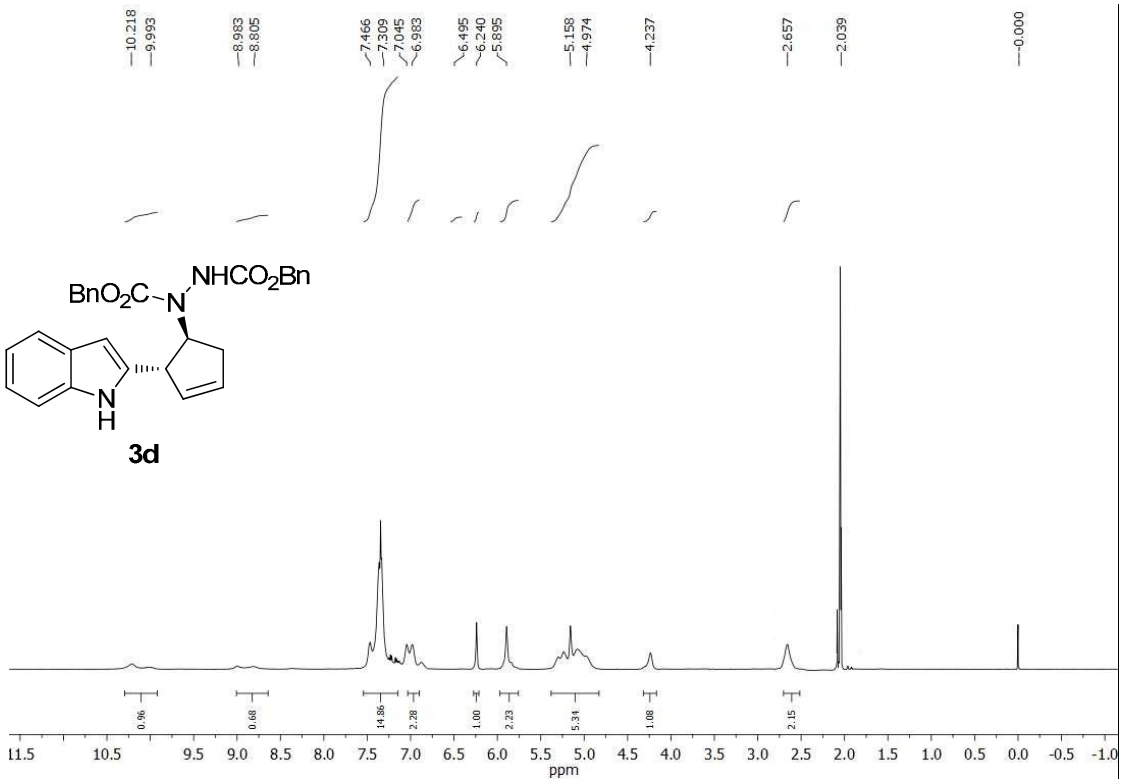
^{13}C NMR of 3b



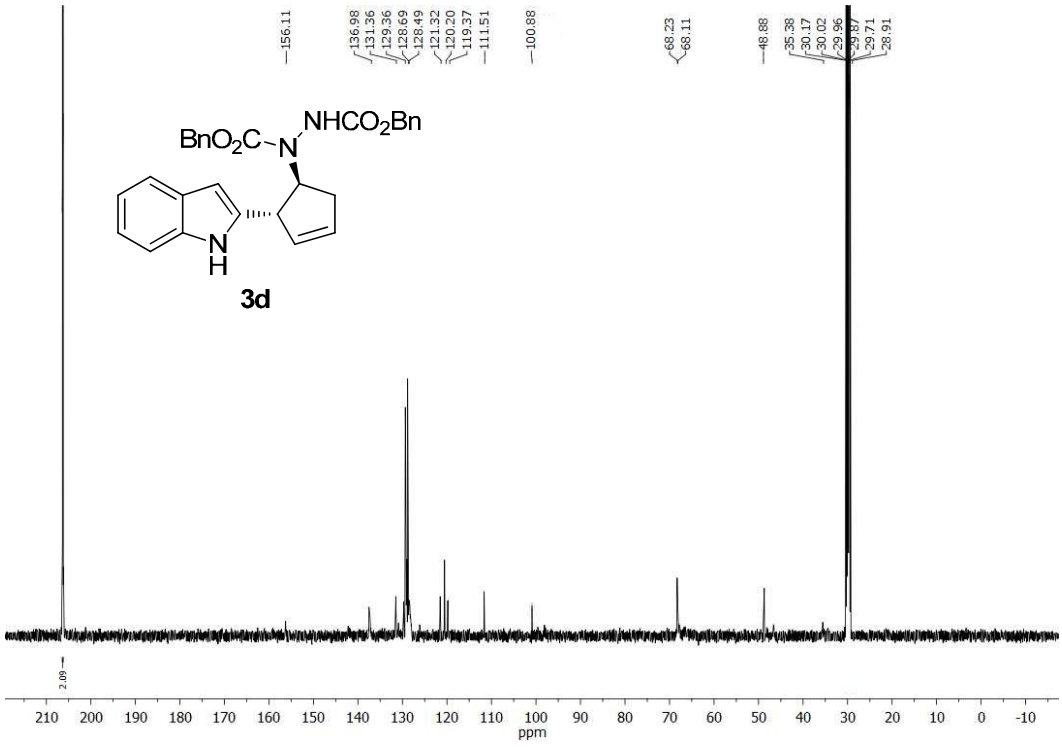
^{1}H NMR of 3c



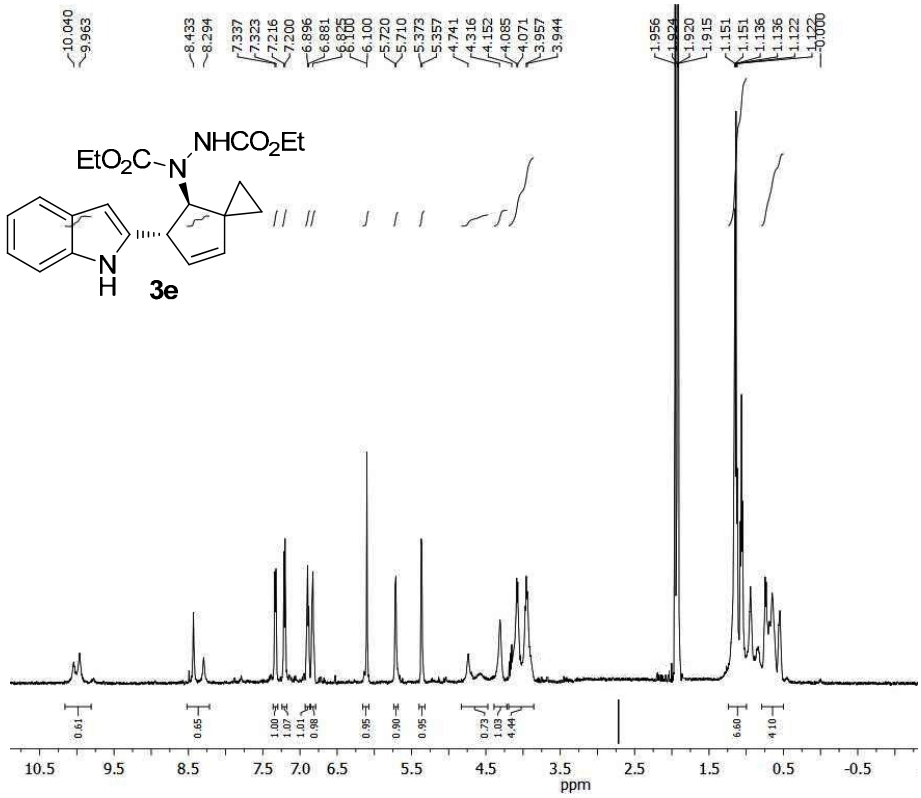
^{13}C NMR of 3c



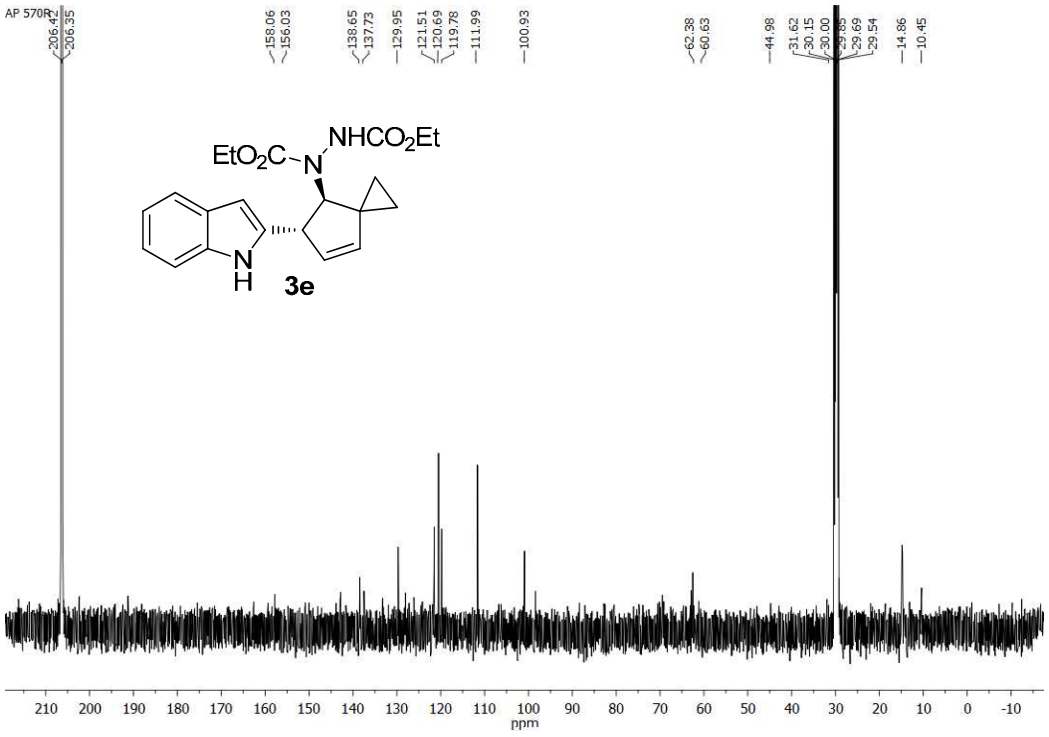
^{1}H NMR of 3d



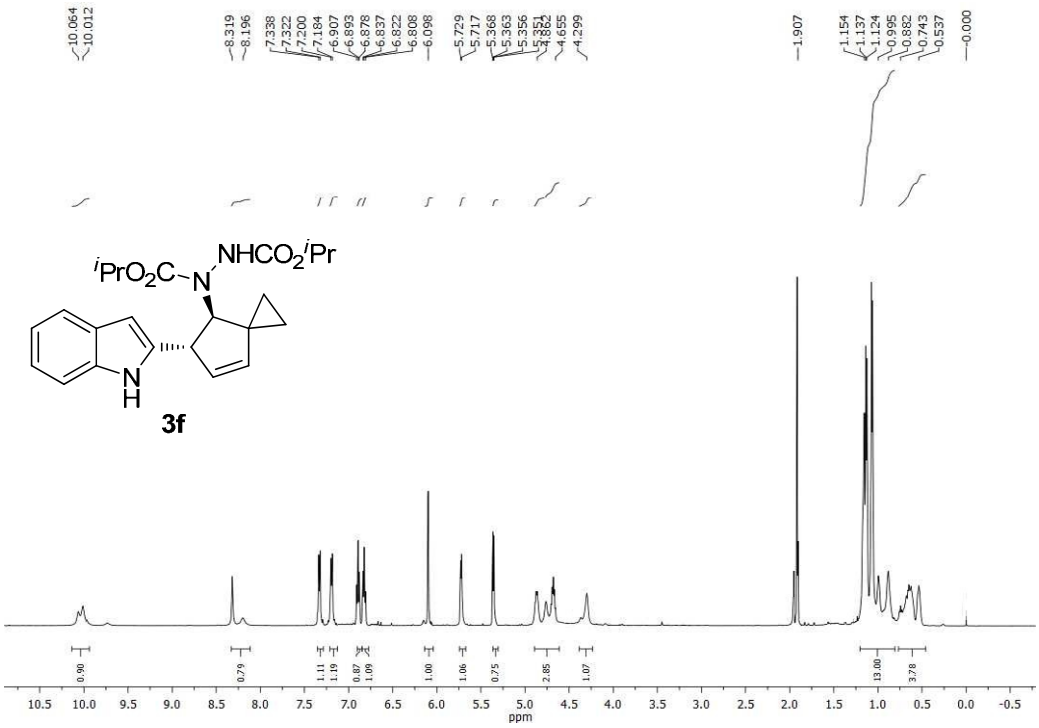
^{13}C NMR of 3d



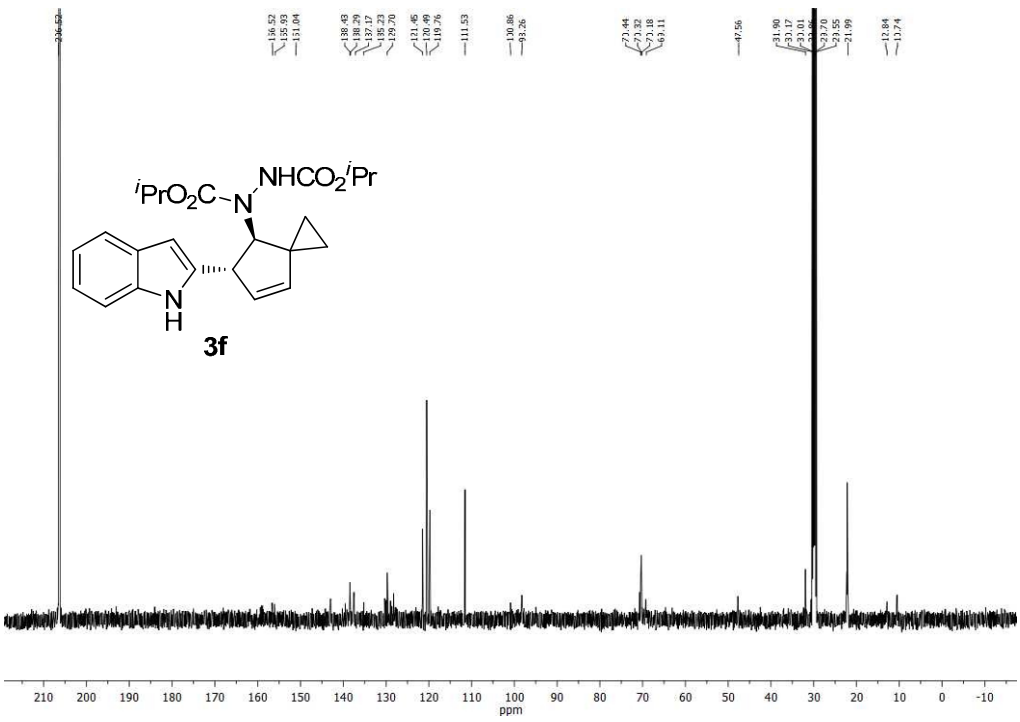
^{1}H NMR of 3e



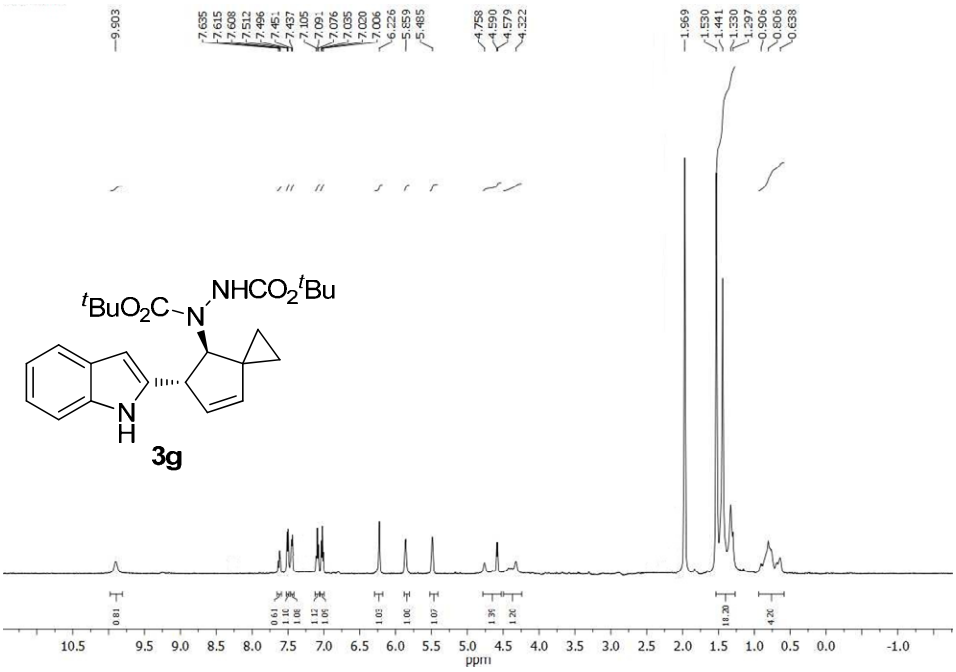
^{13}C NMR of 3e



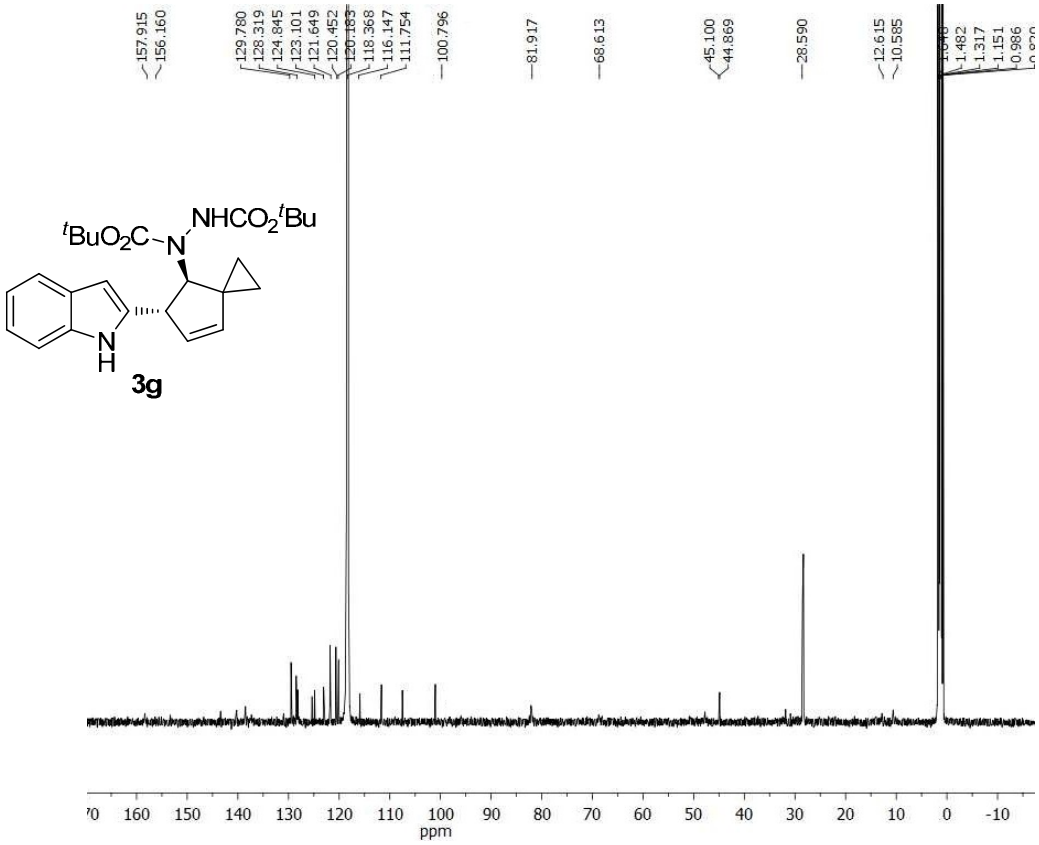
^{1}H NMR of 3f



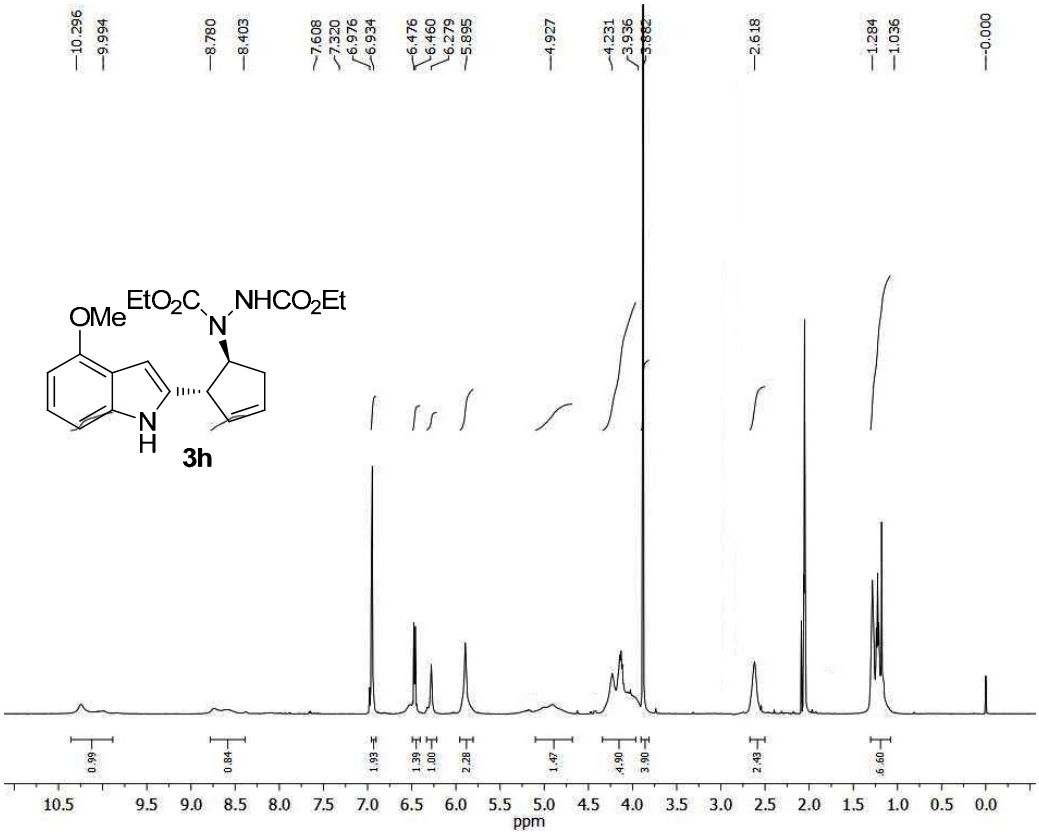
^{13}C NMR of 3f



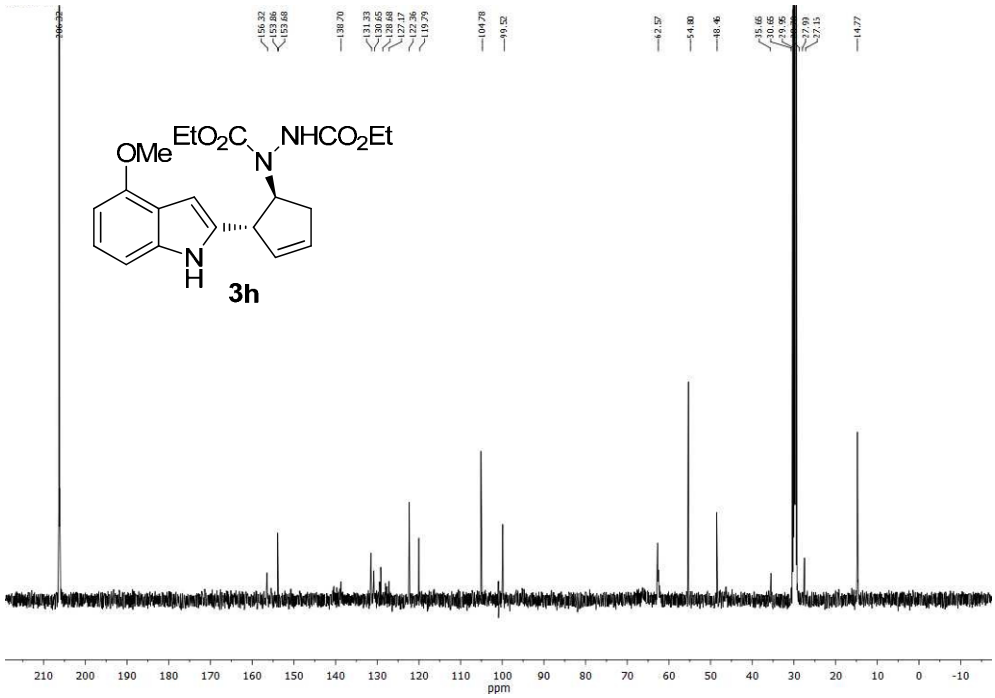
^{1}H NMR of 3g



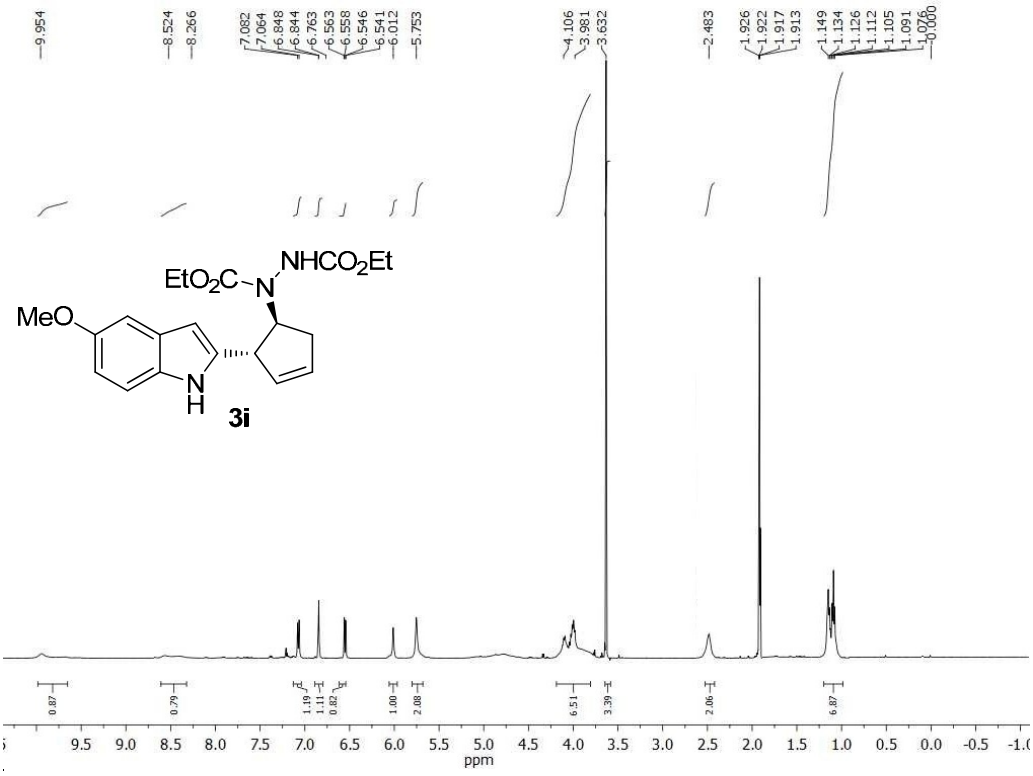
^{13}C NMR of 3g



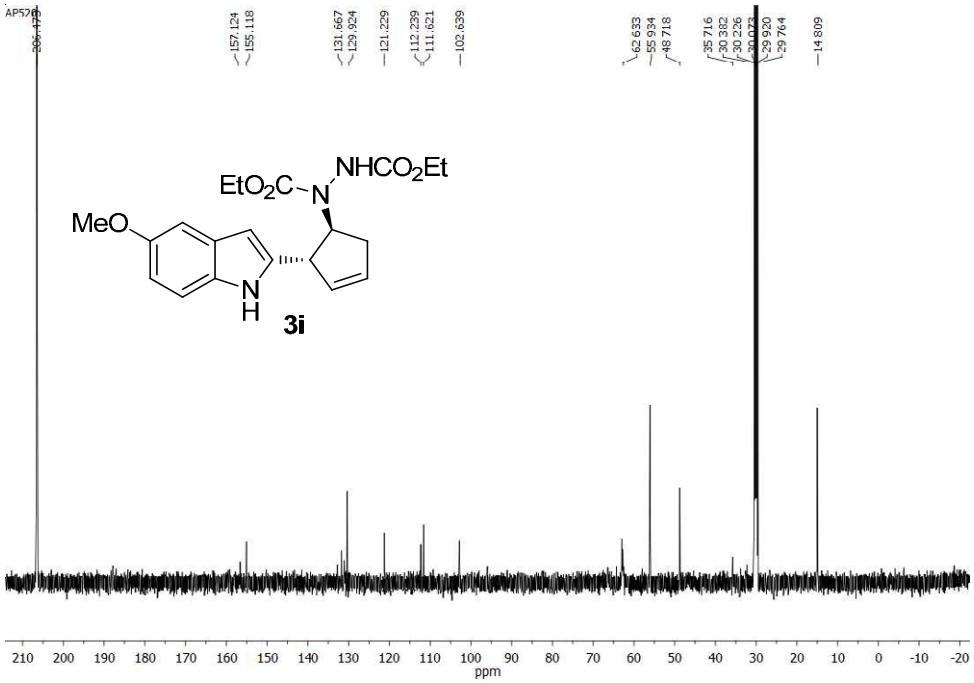
^{1}H NMR of 3h



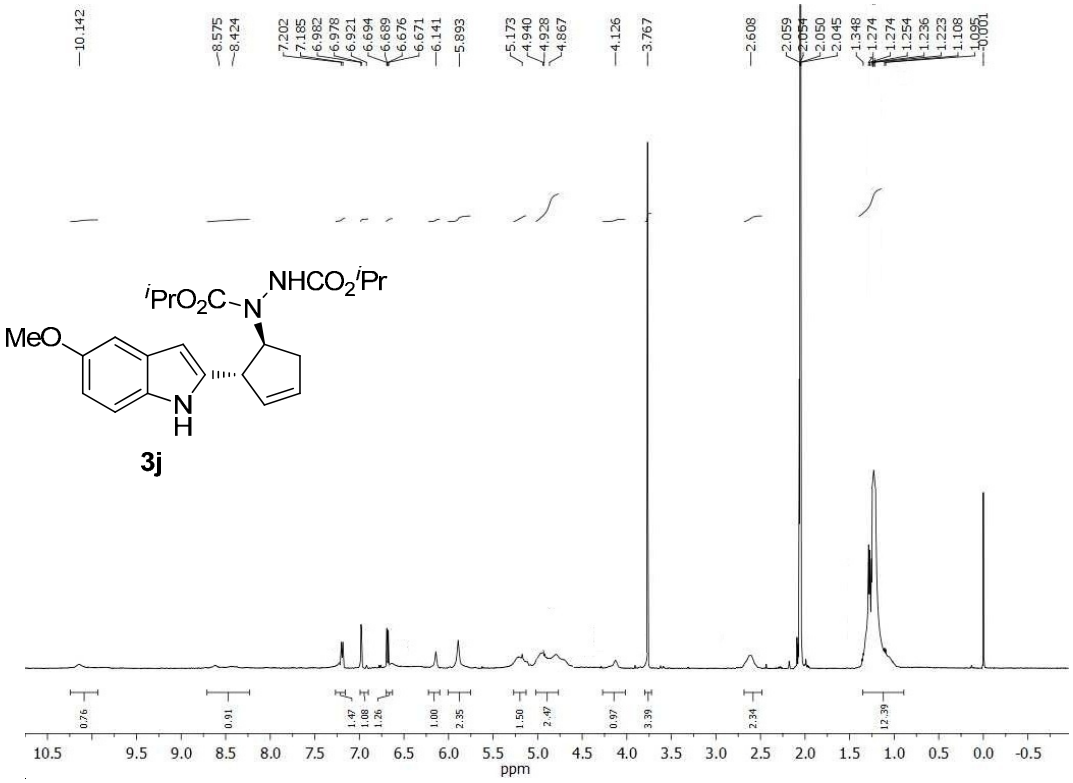
^{13}C NMR of 3h



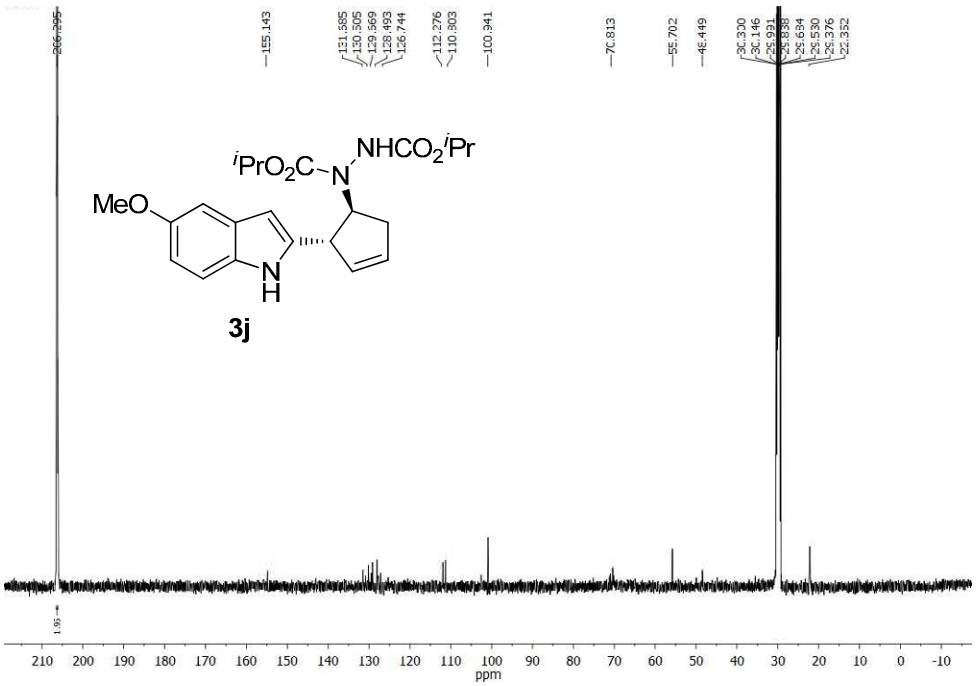
^{1}H NMR of 3i



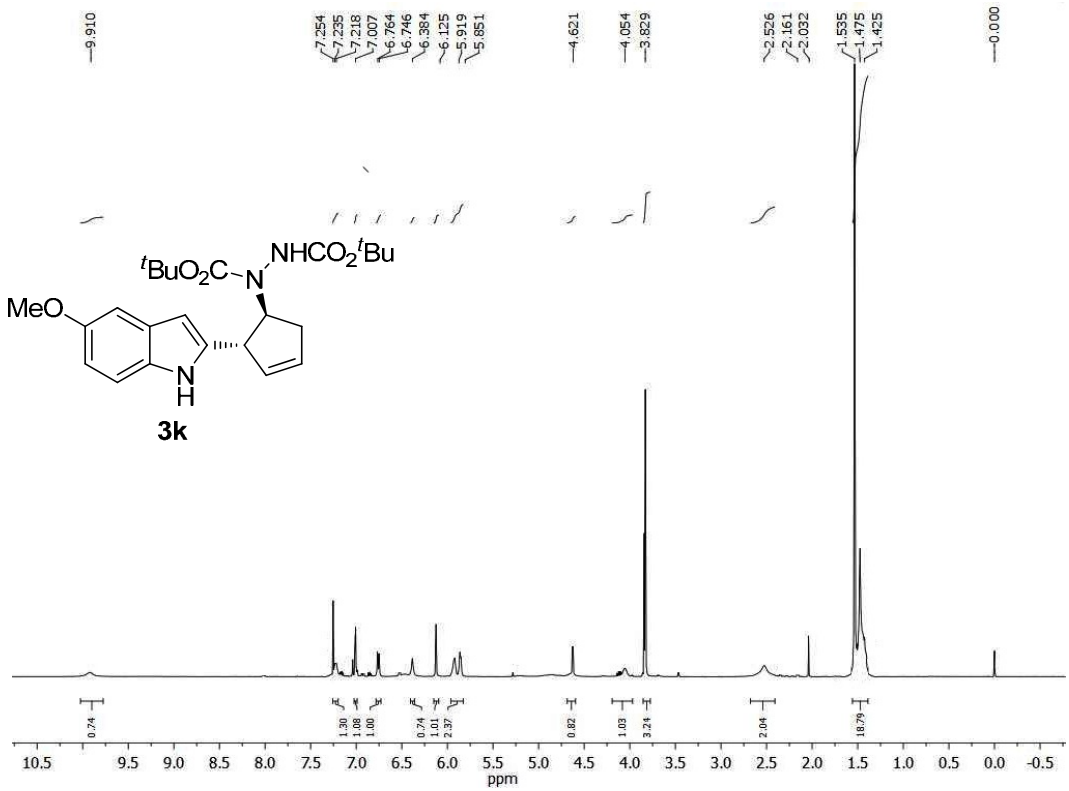
^{13}C NMR of 3i



^{1}H NMR of 3j



^{13}C NMR of 3j



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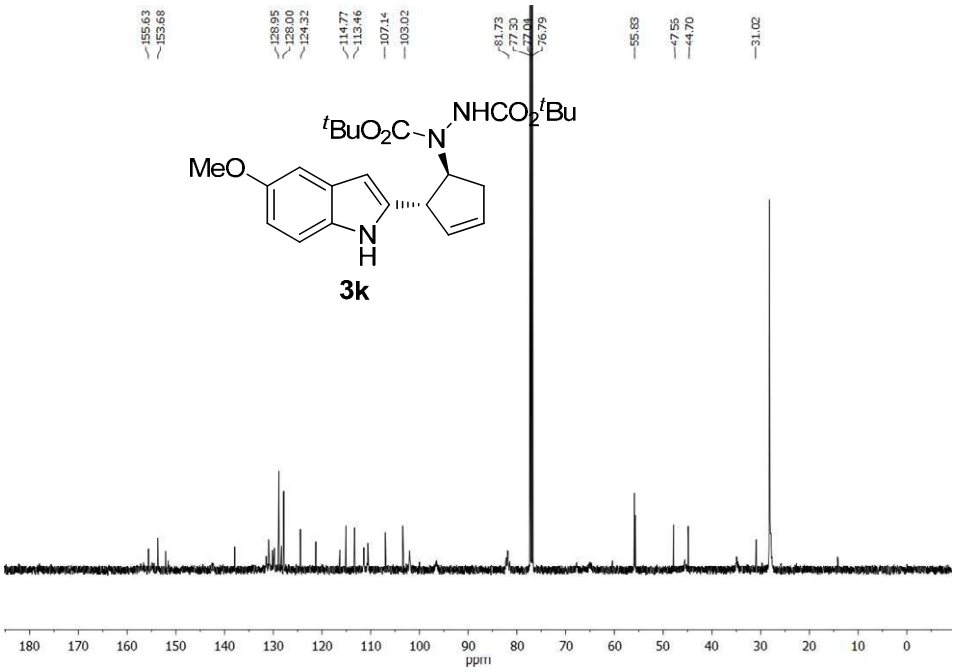

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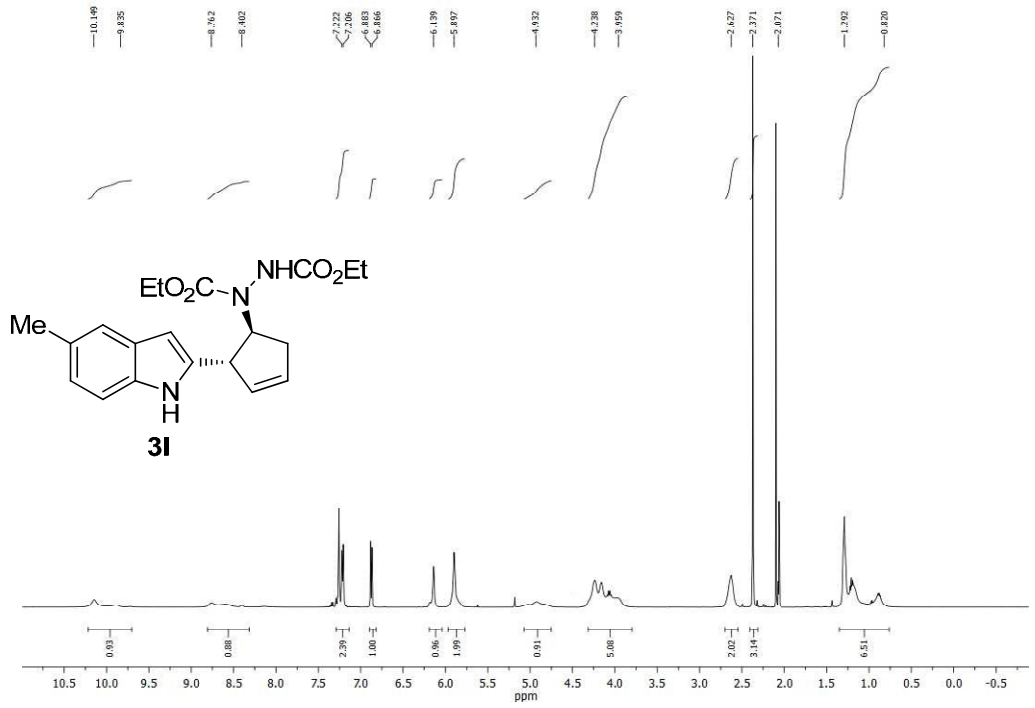
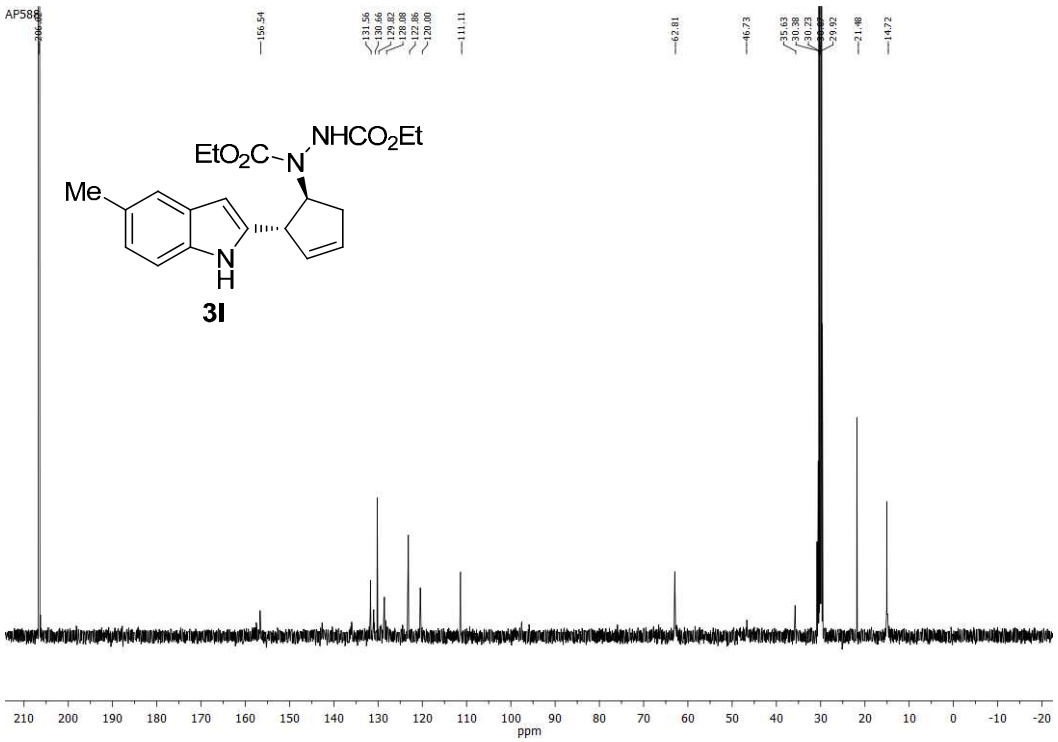


^{1}H NMR of 3l



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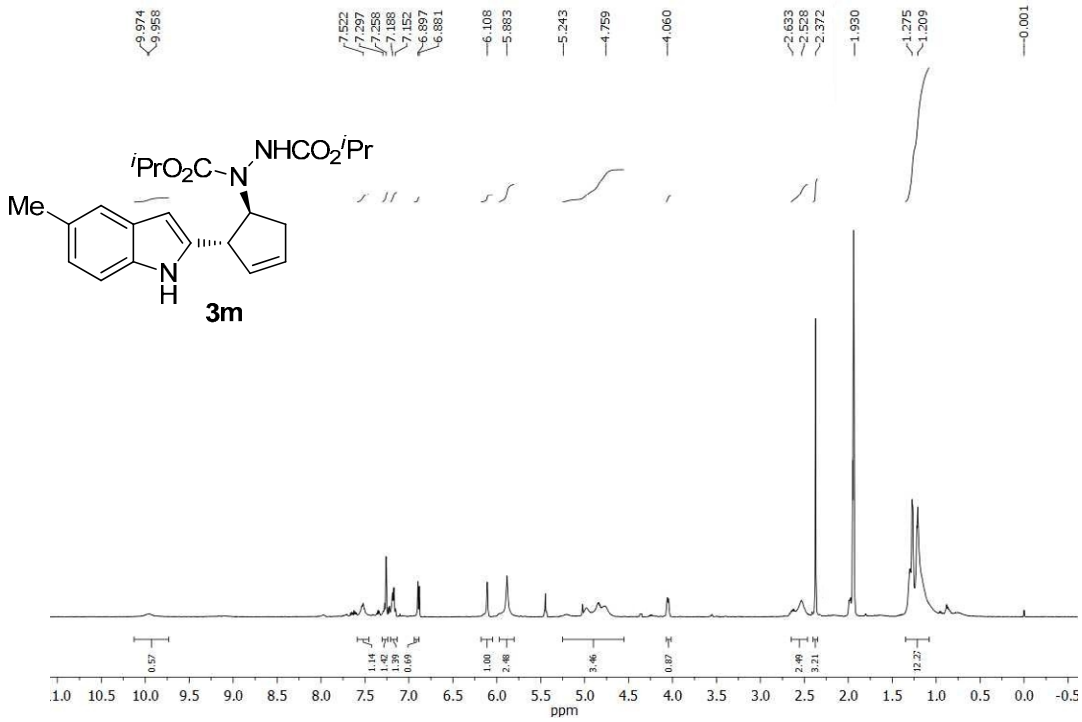
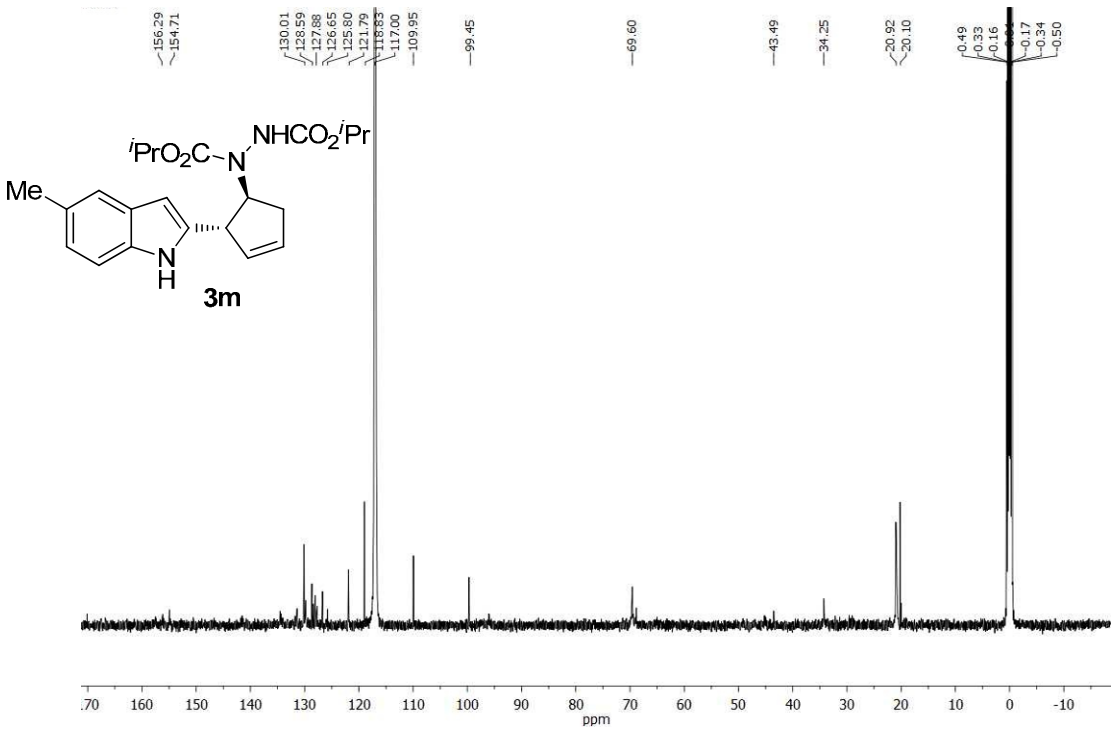
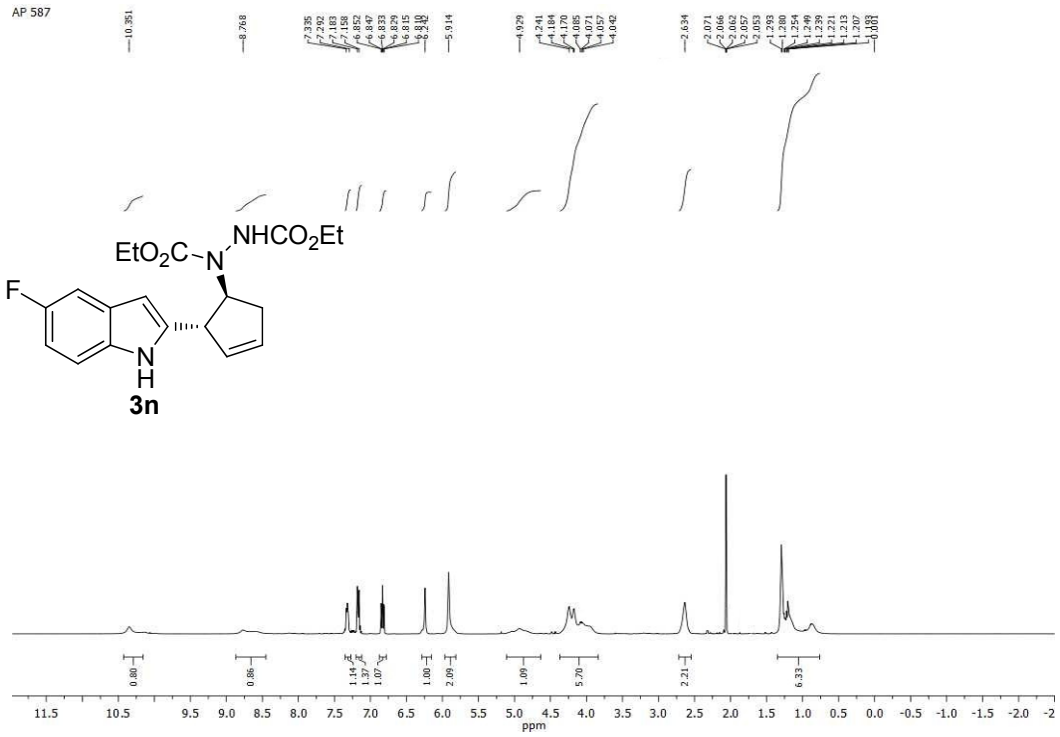


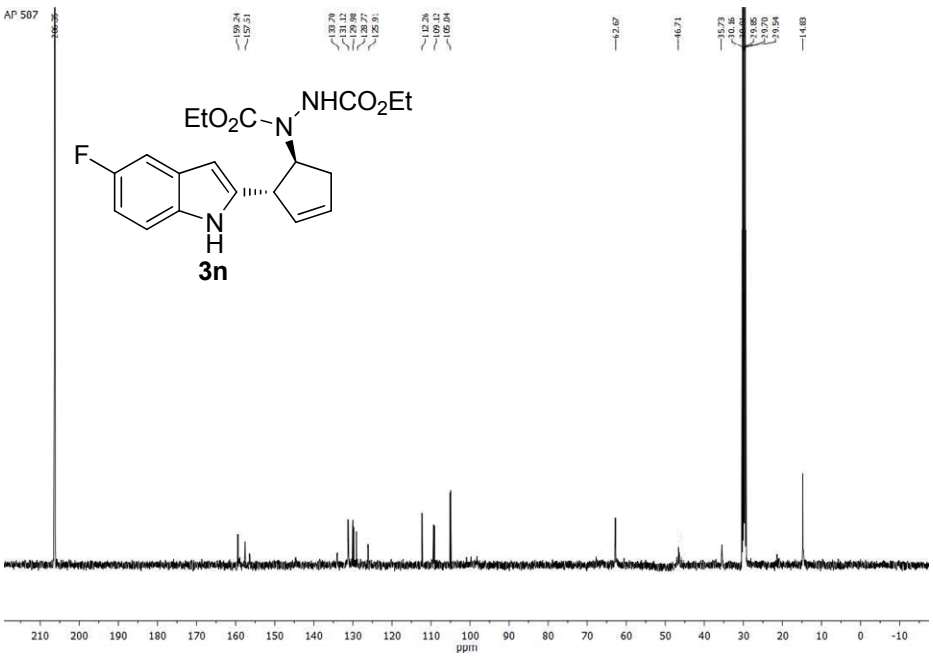
^{1}H NMR of 3m



^{13}C NMR of 3m



^{1}H NMR of 3n



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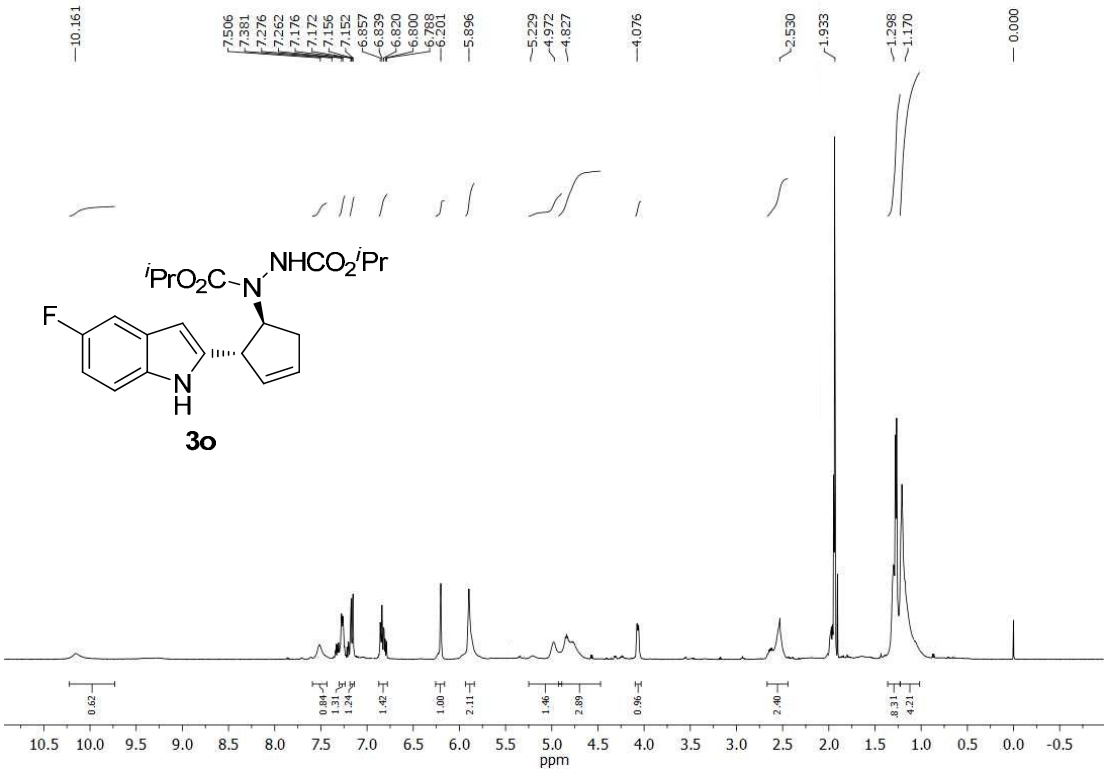

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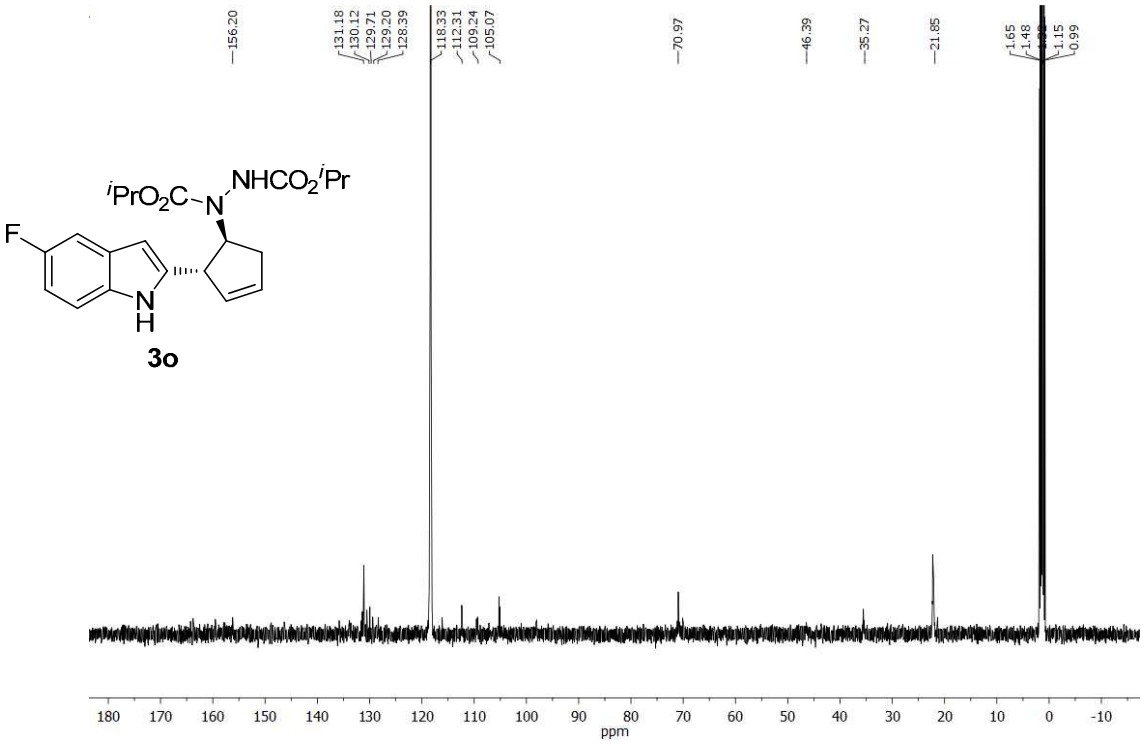

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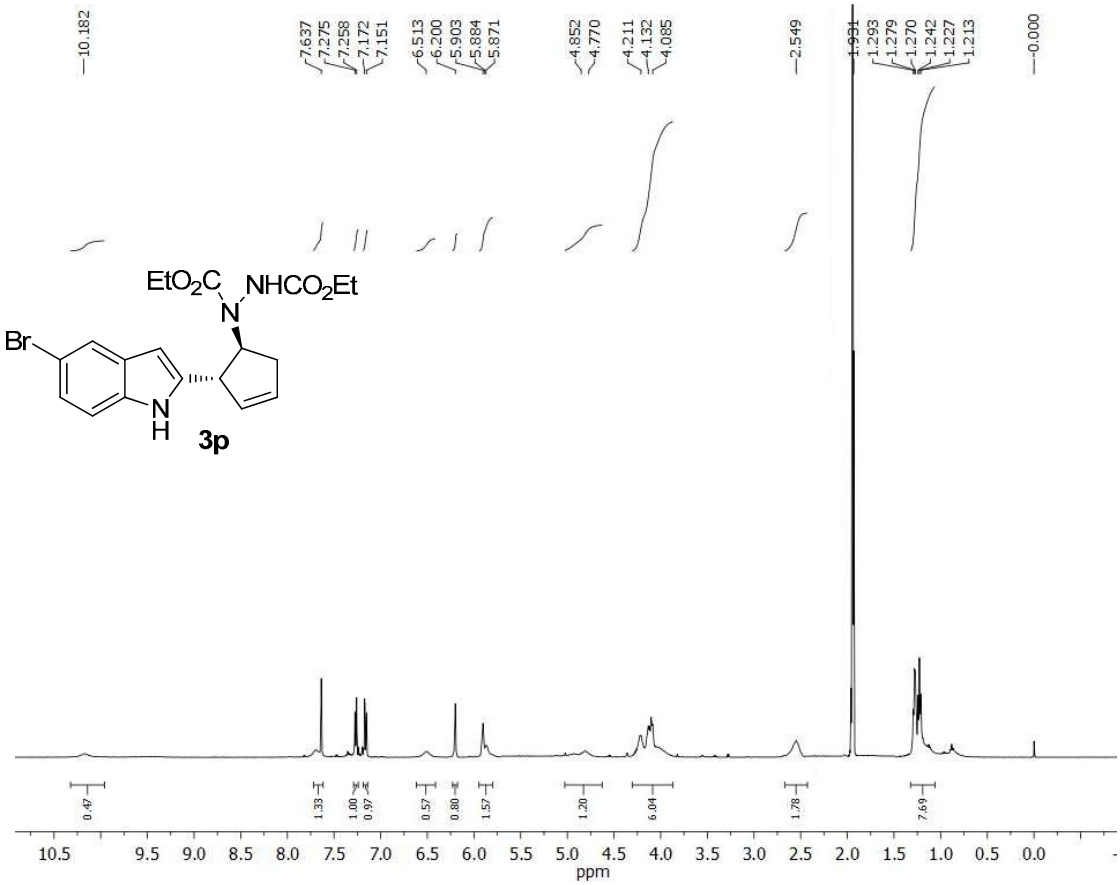
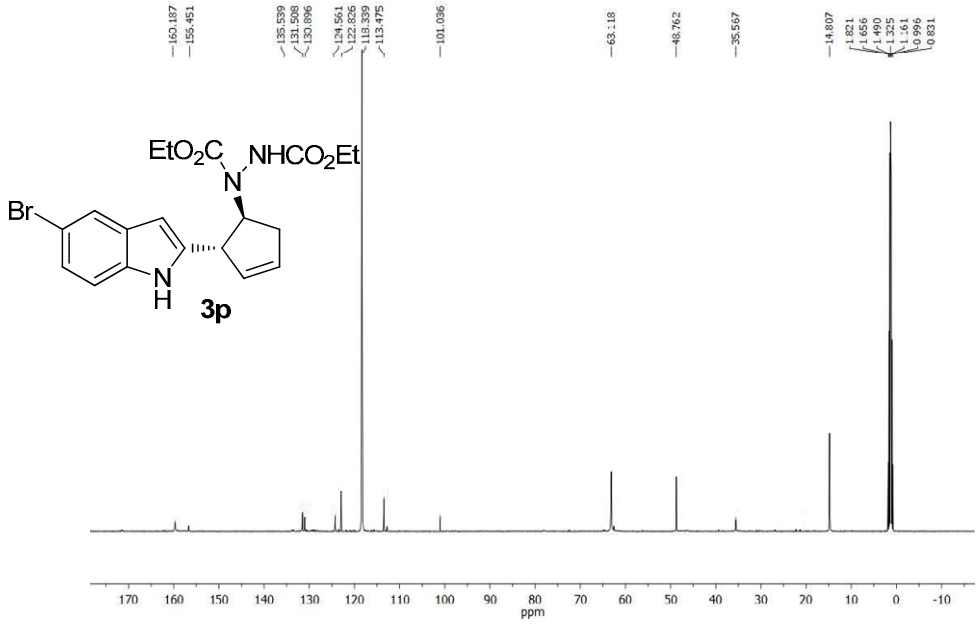
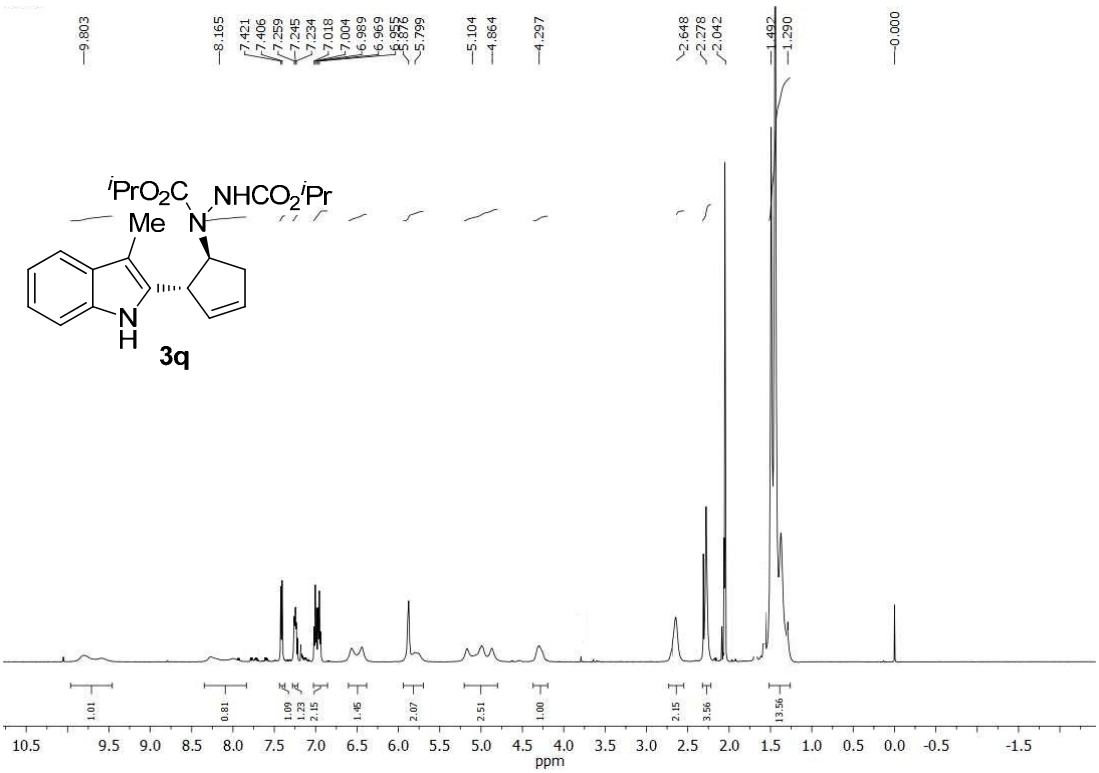


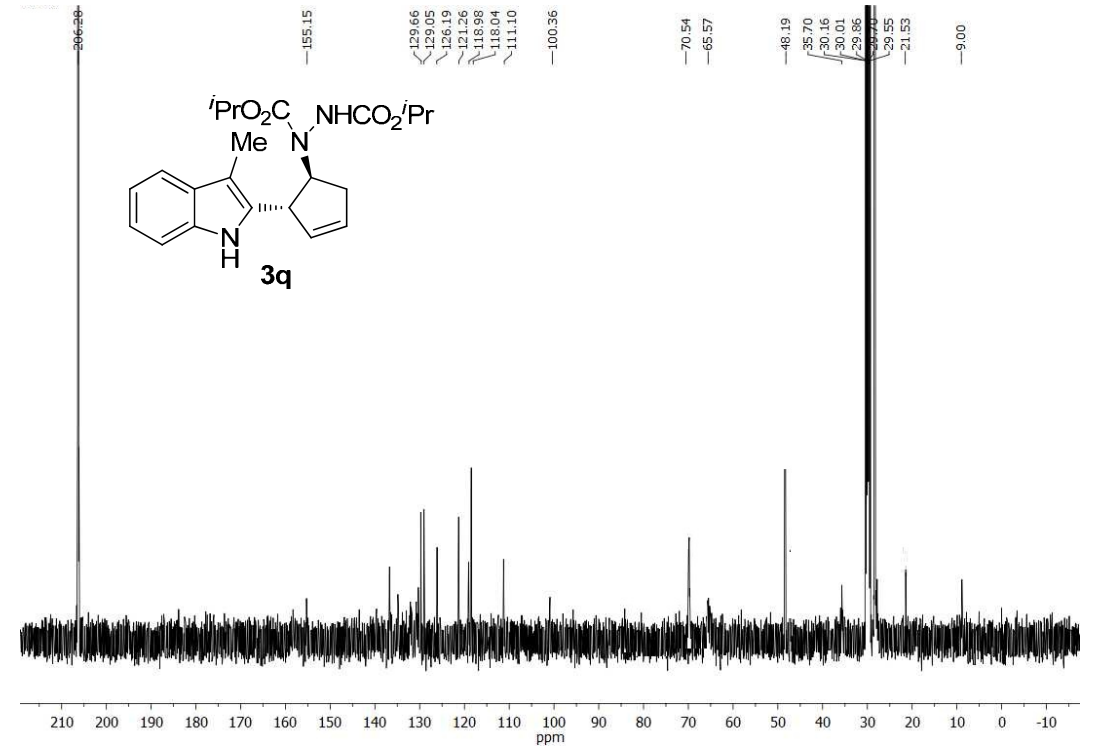
^{1}H NMR of 3p



^{13}C NMR of 3p



^{1}H NMR of 3q



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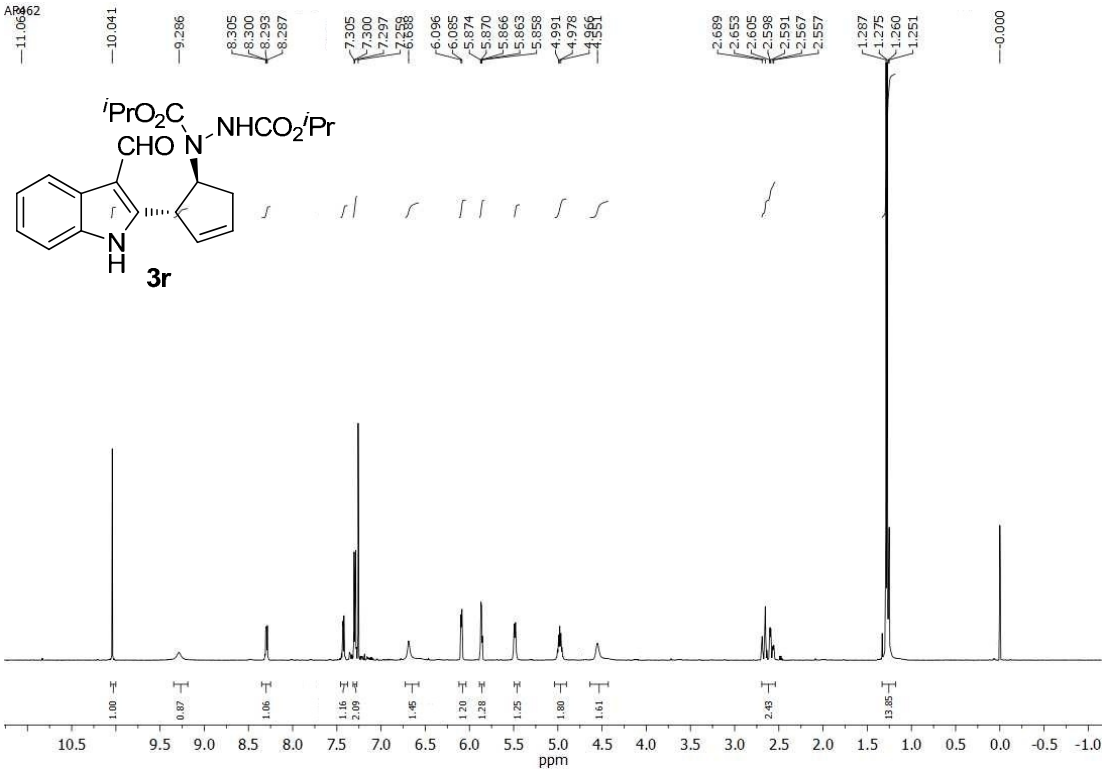

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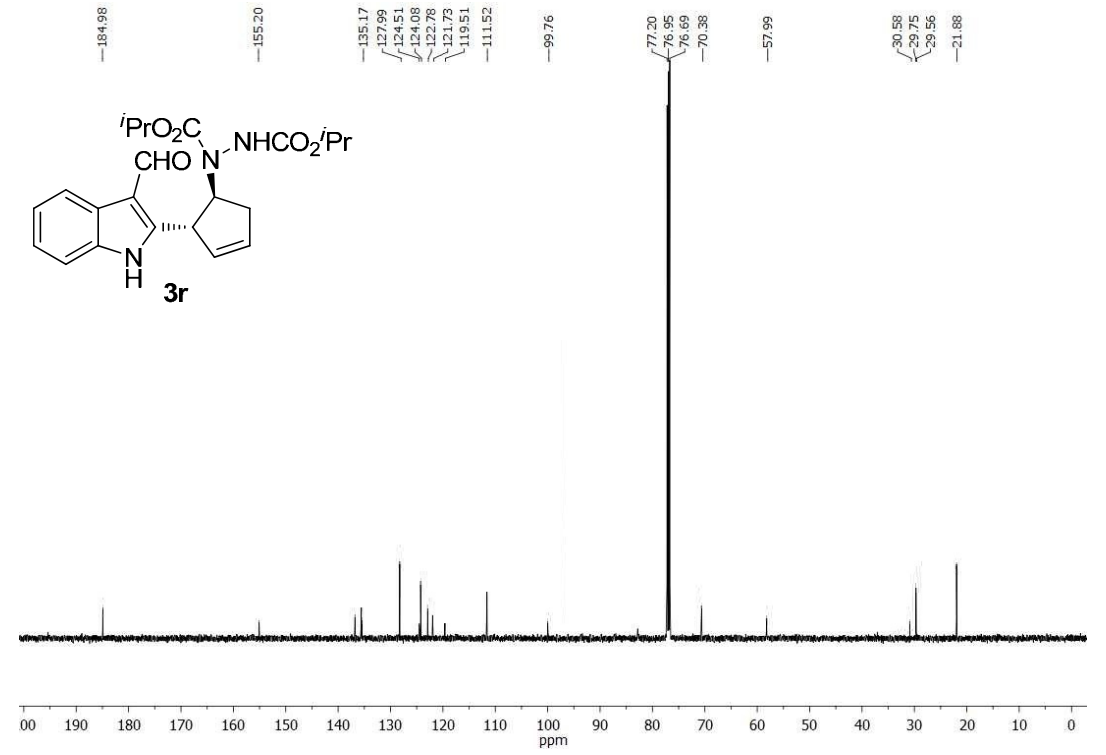
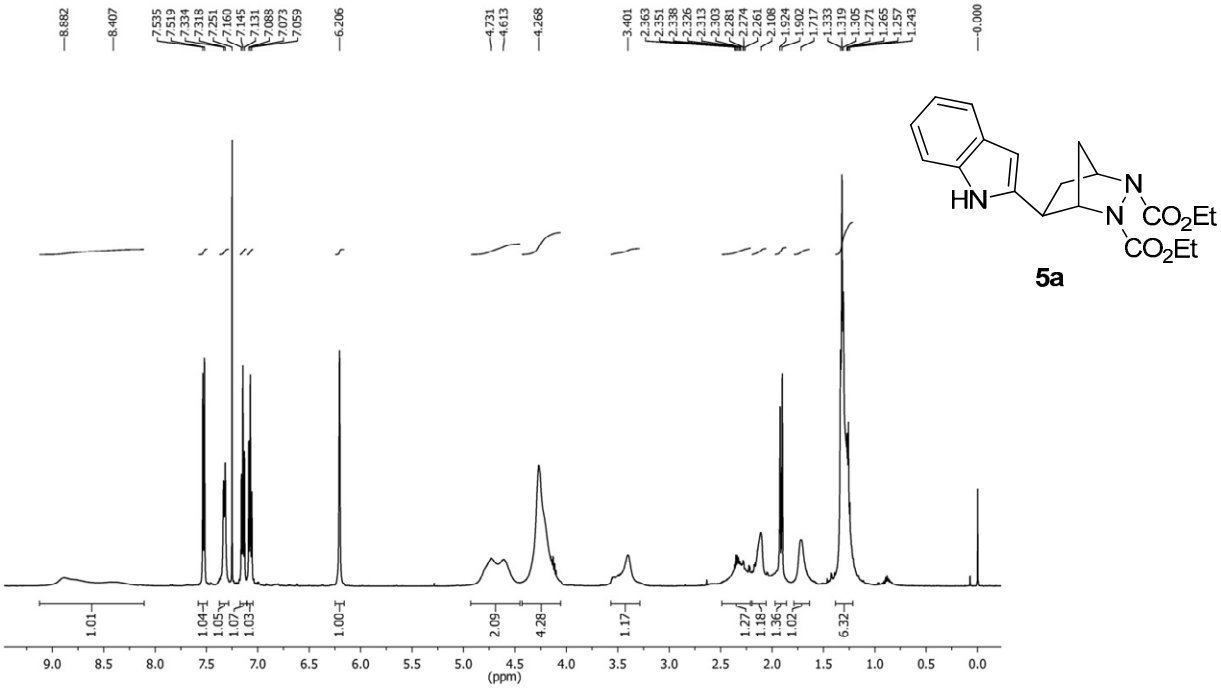
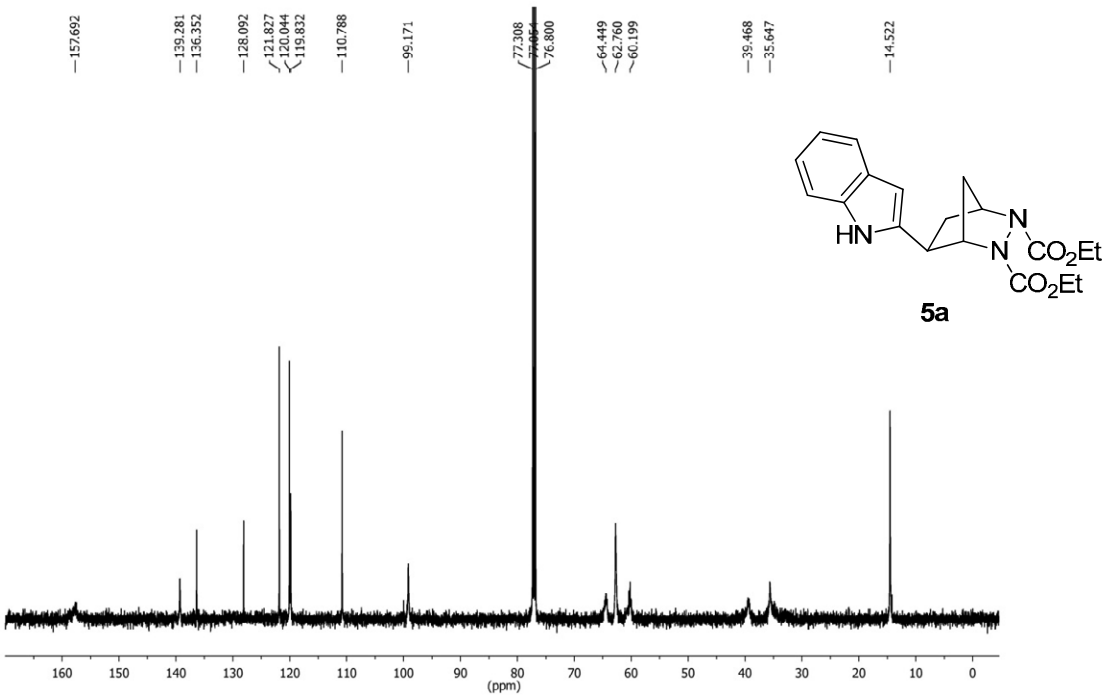


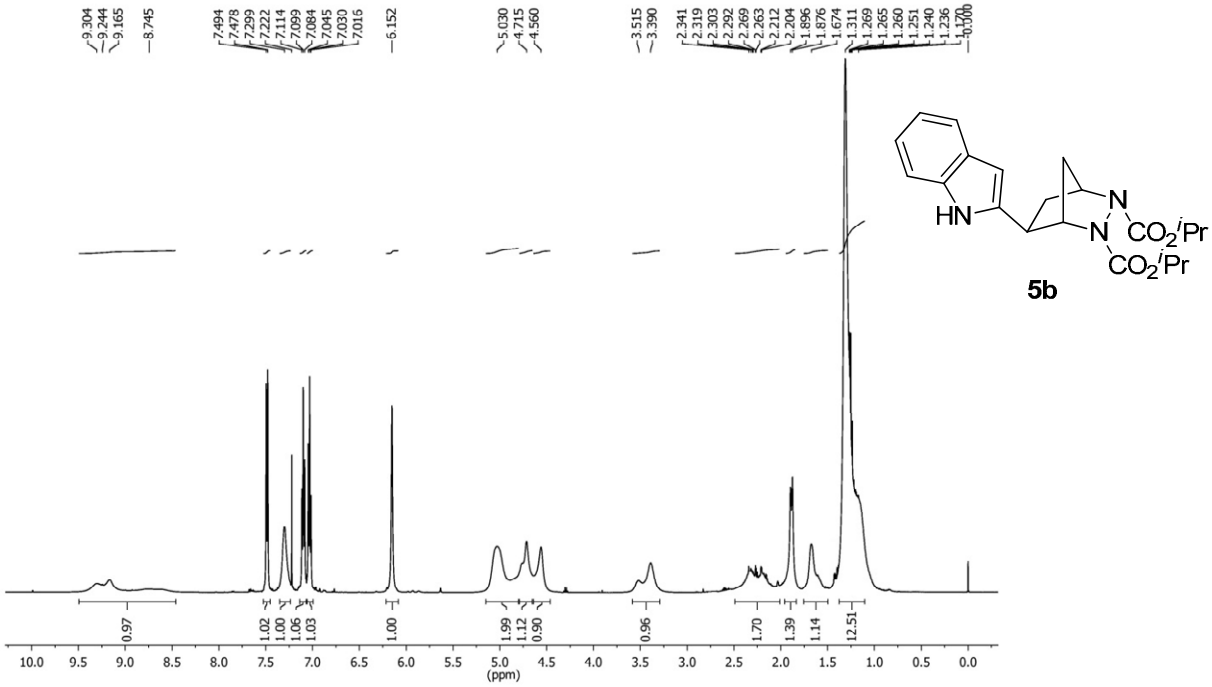
^{13}C NMR of 3r



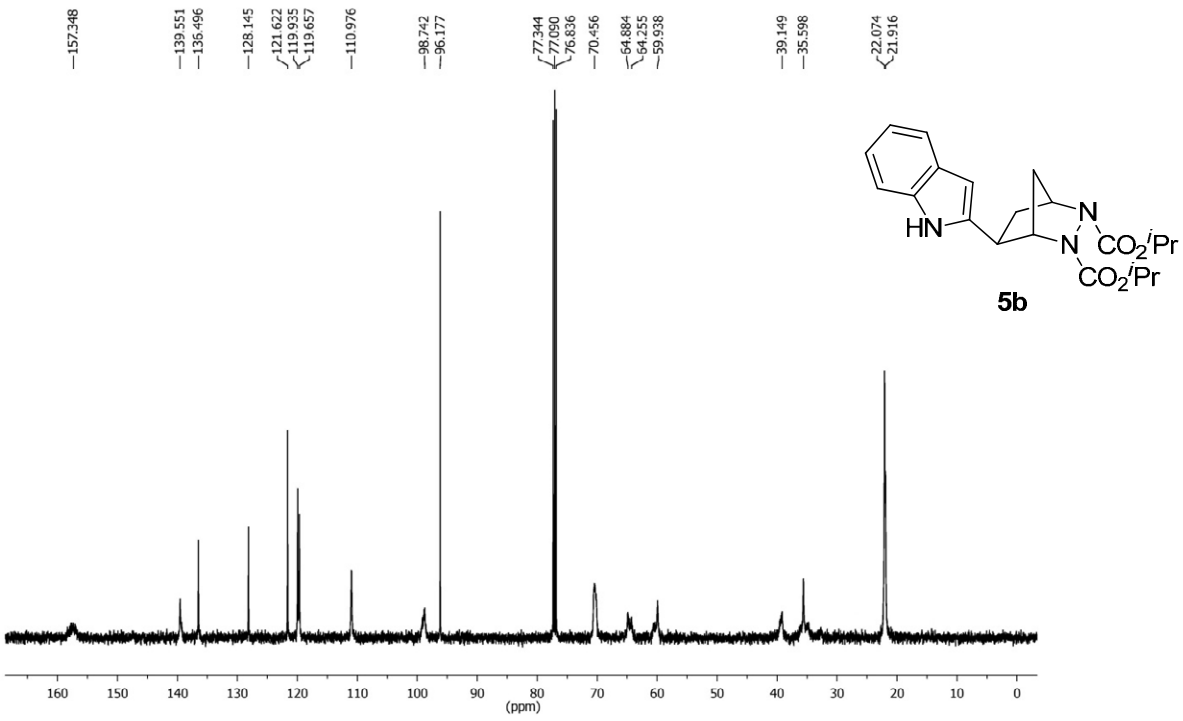
^{1}H NMR of compound 5a



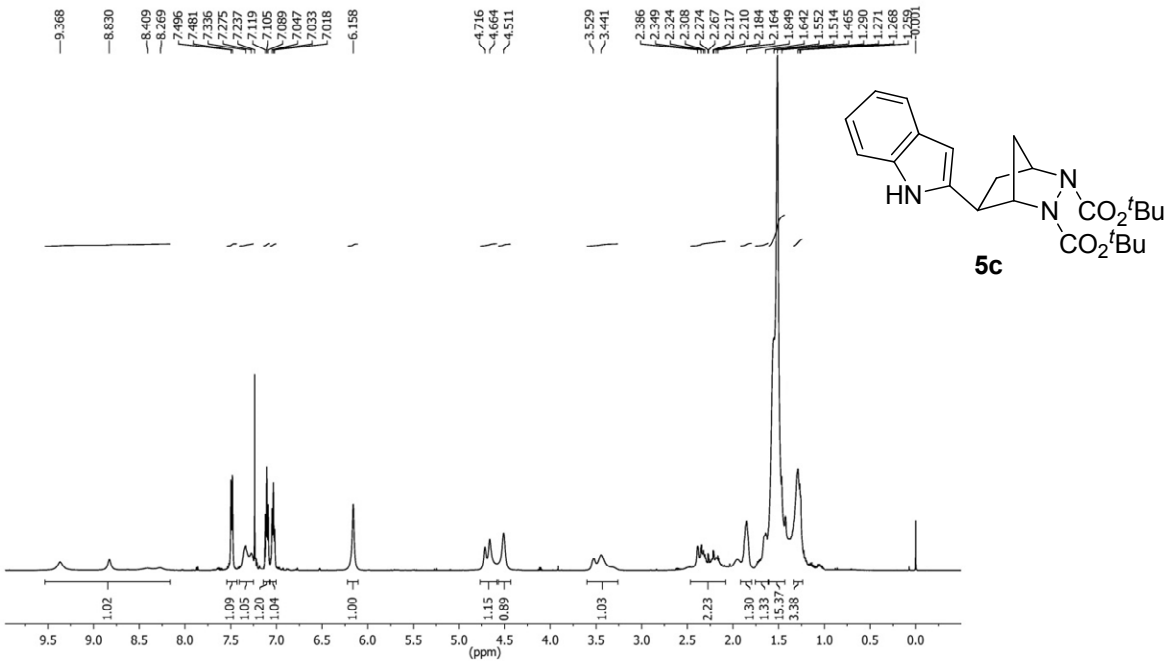
^{13}C NMR of compound 5a



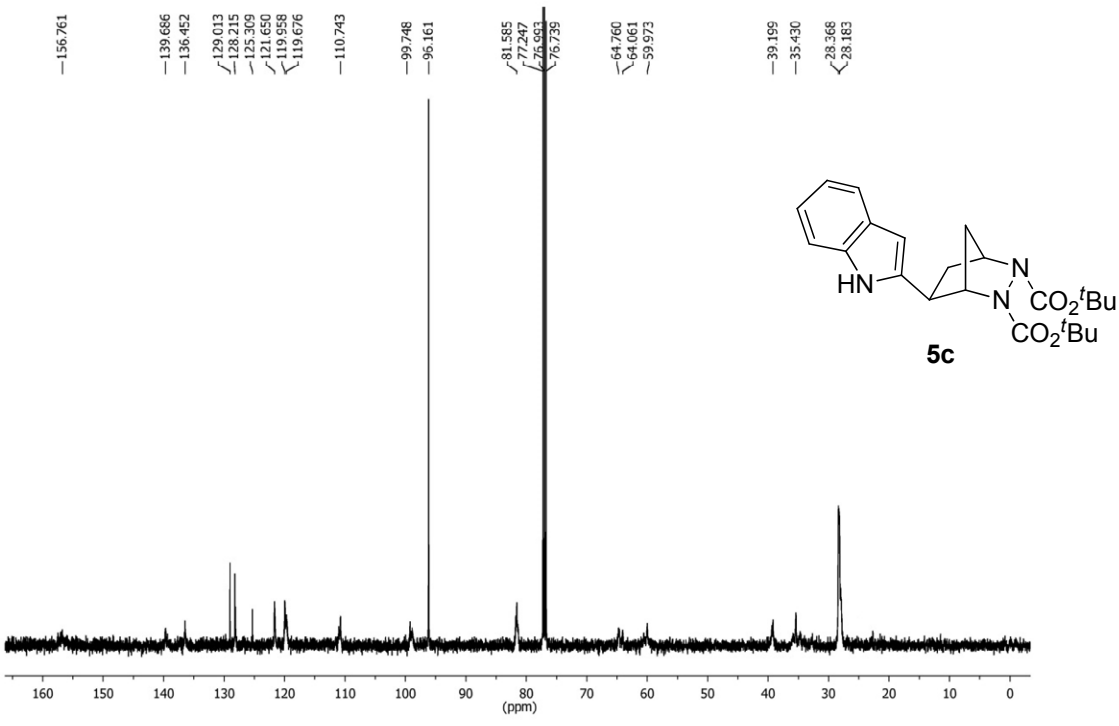
^{1}H NMR of compound 5b



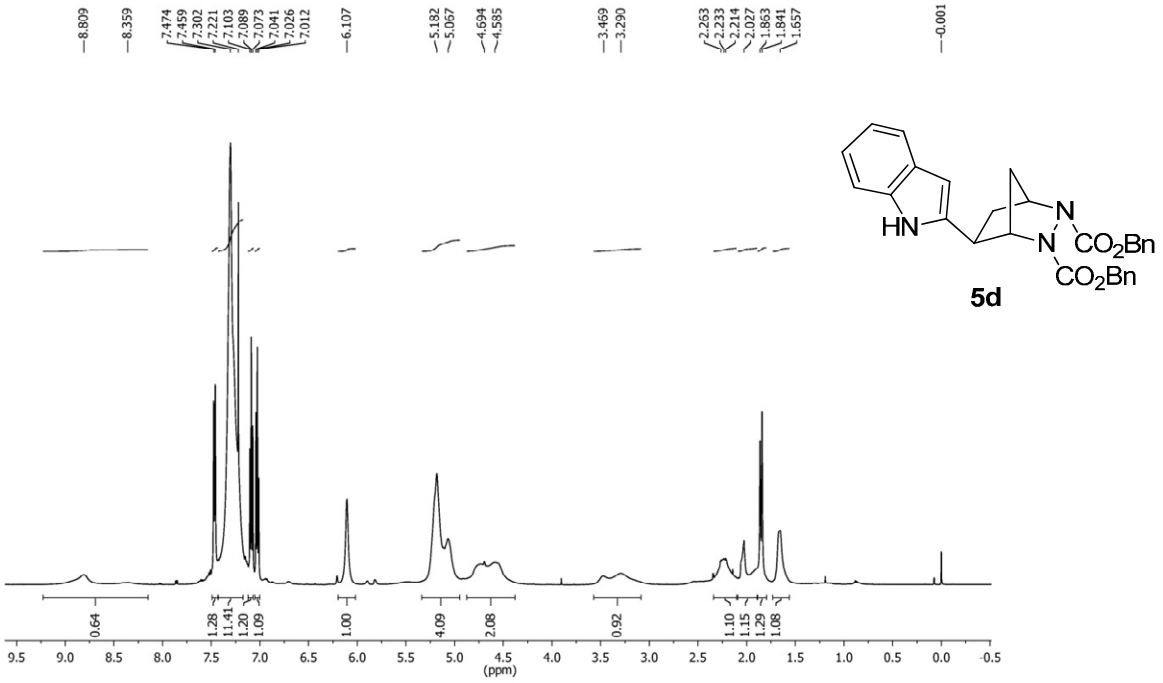
^{13}C NMR of compound 5b



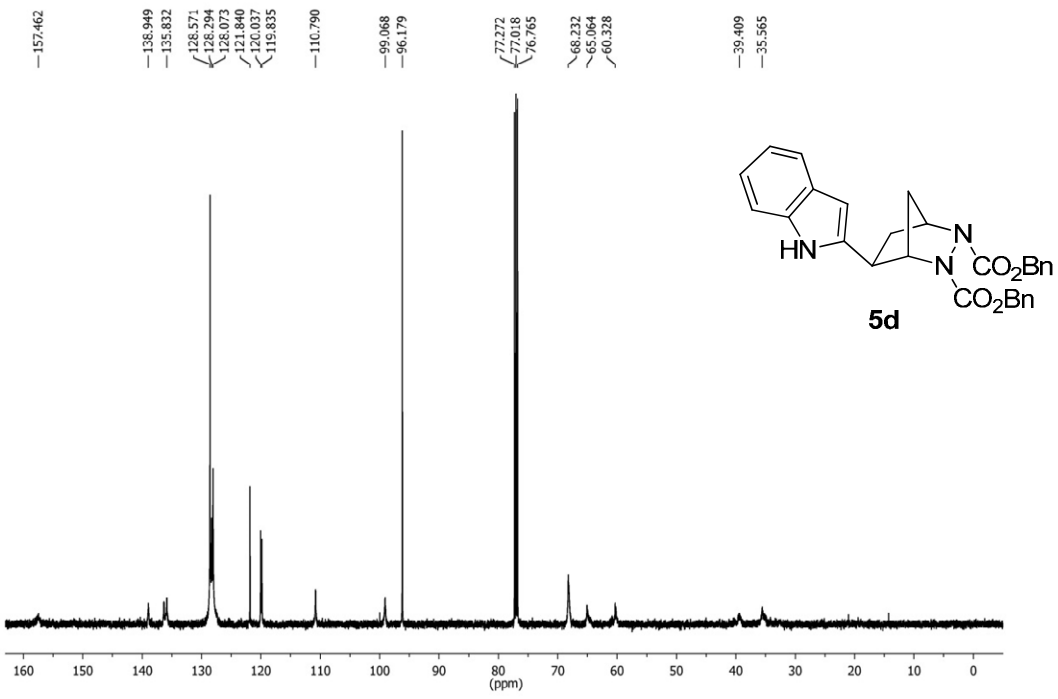
^{1}H NMR of compound 5c



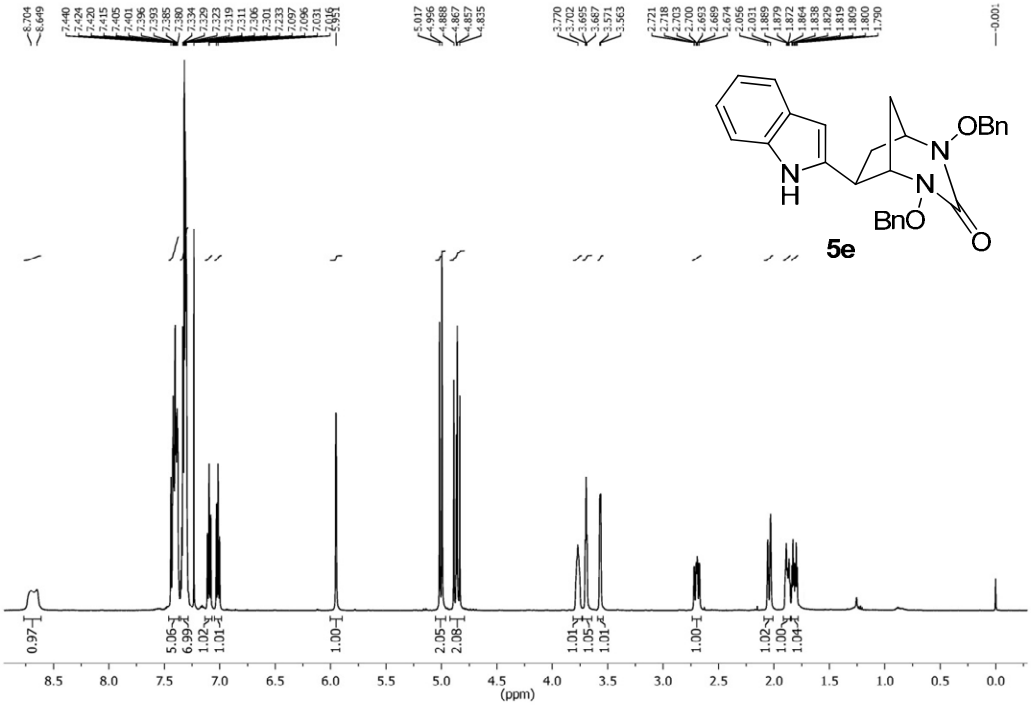
^{13}C NMR of compound 5c



^{1}H NMR of compound 5d



^{13}C NMR of compound 5d



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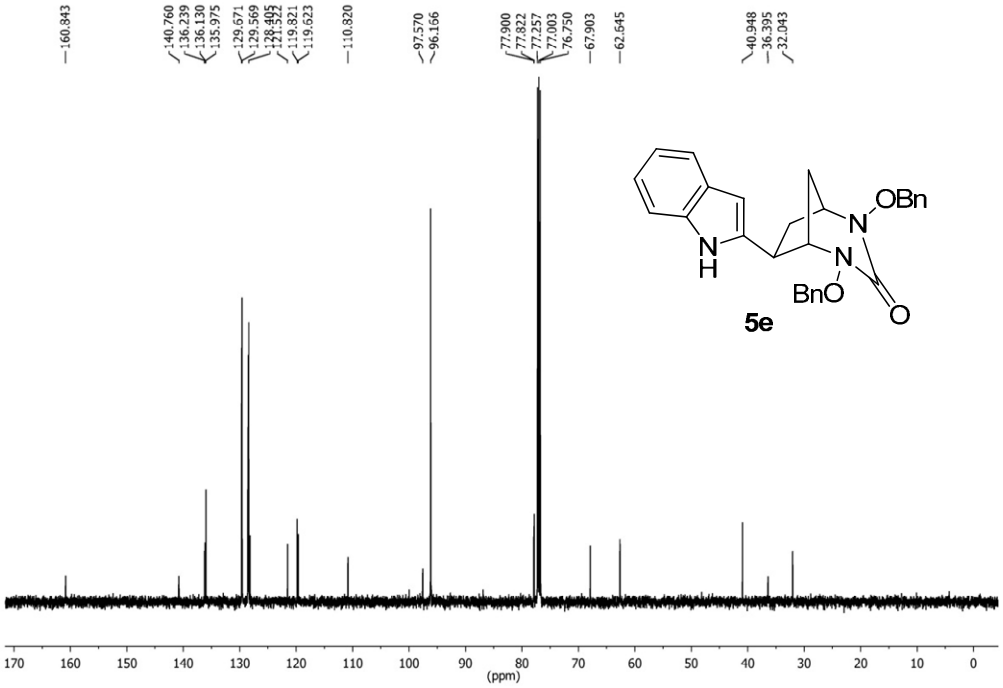
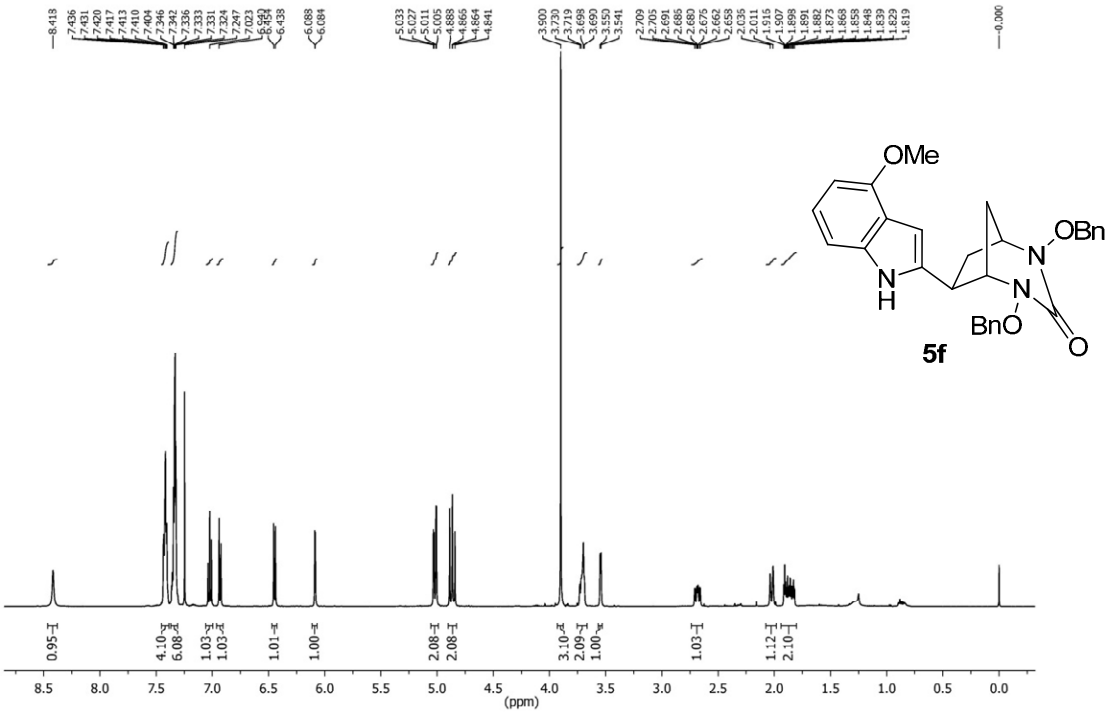
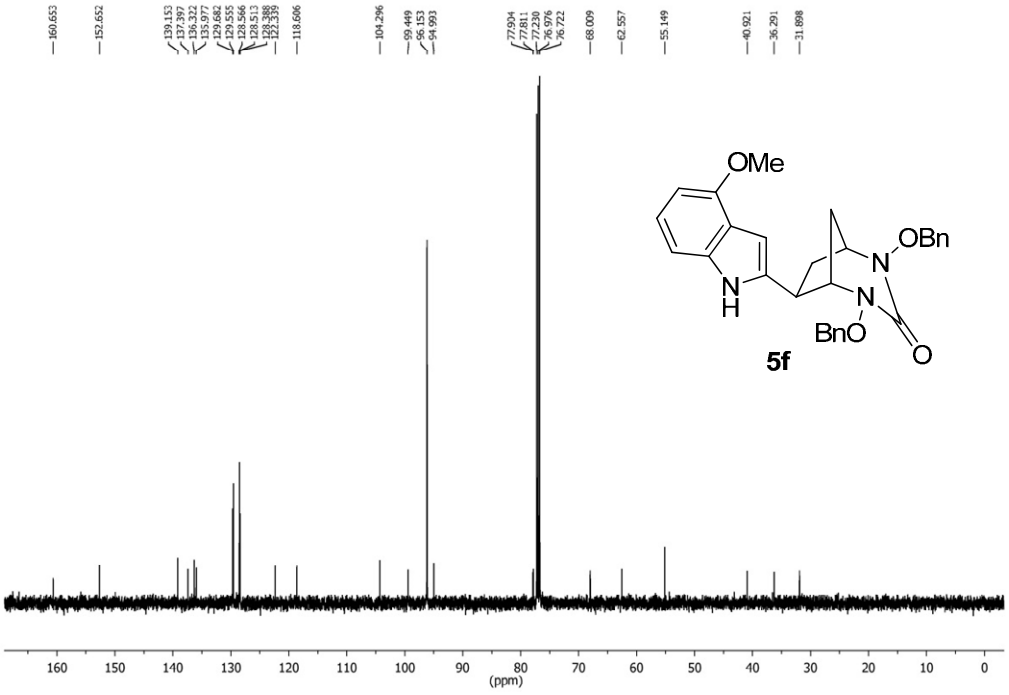


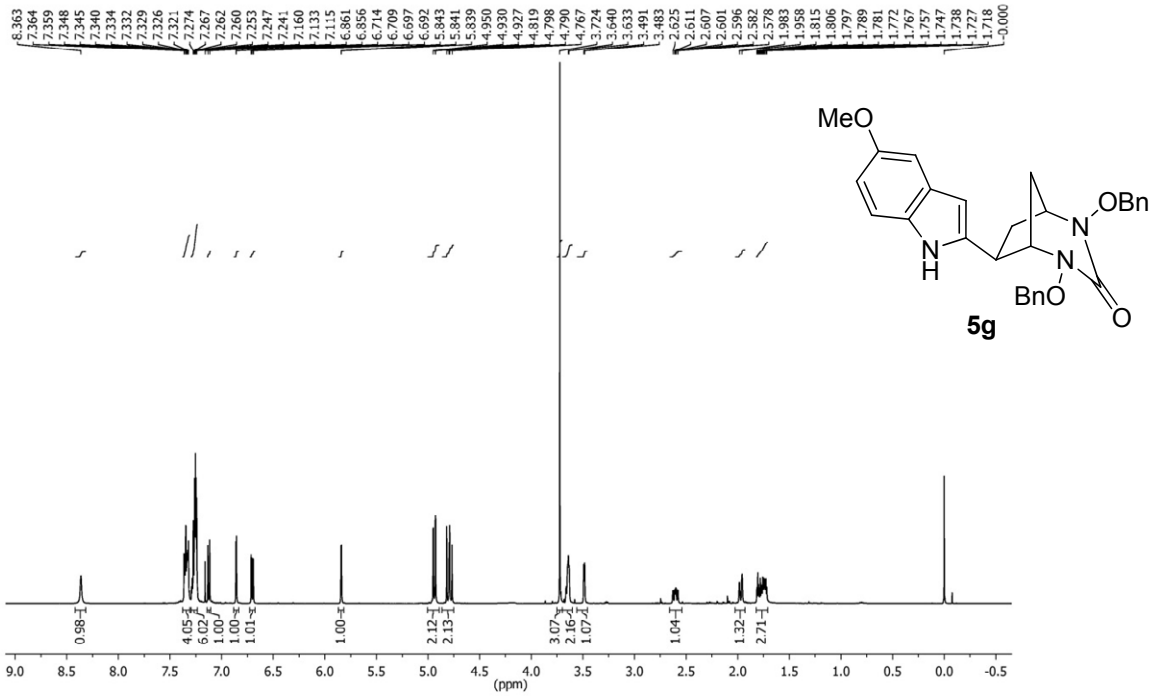
^{13}C NMR of compound 5e



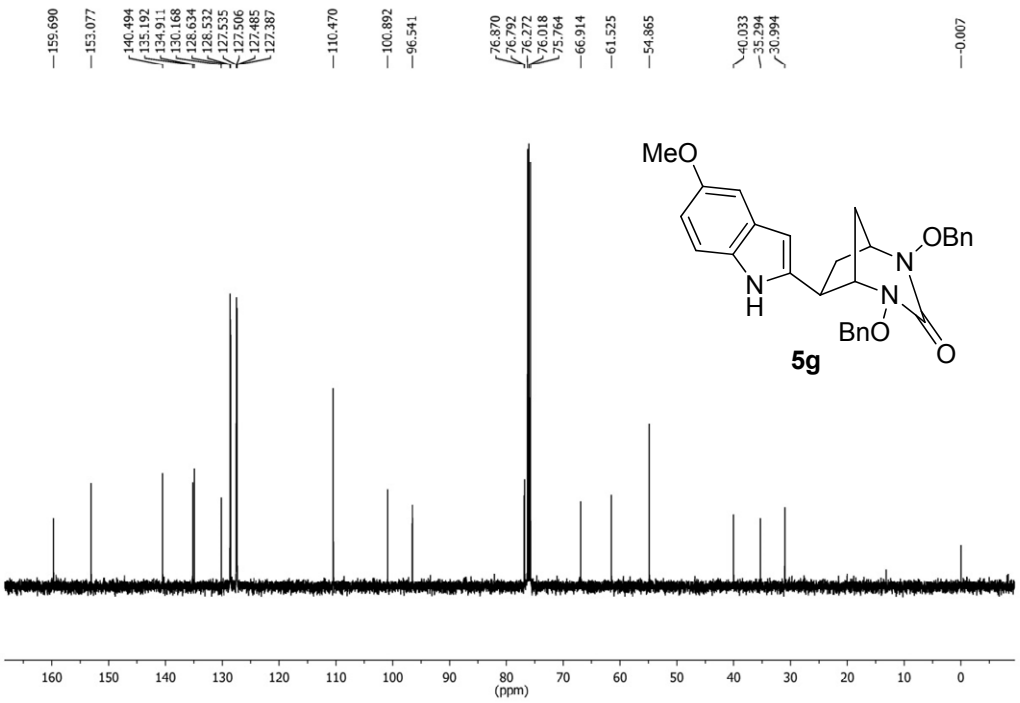
^{1}H NMR of compound 5f



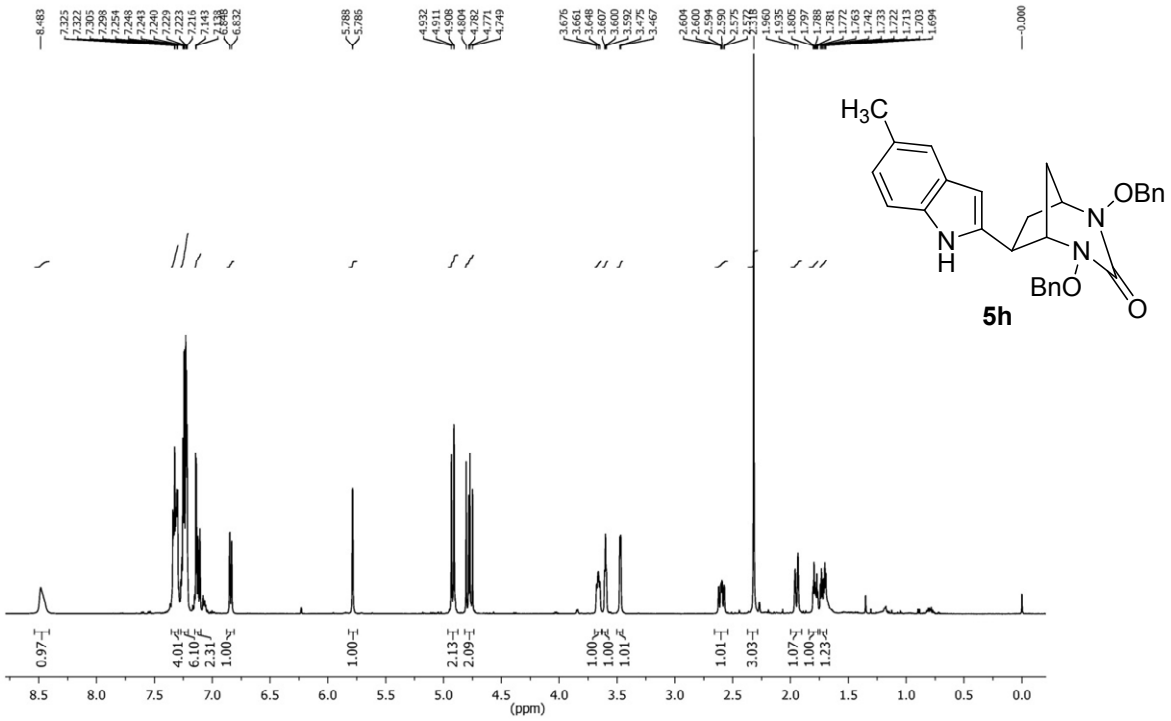
^{13}C NMR of compound 5f



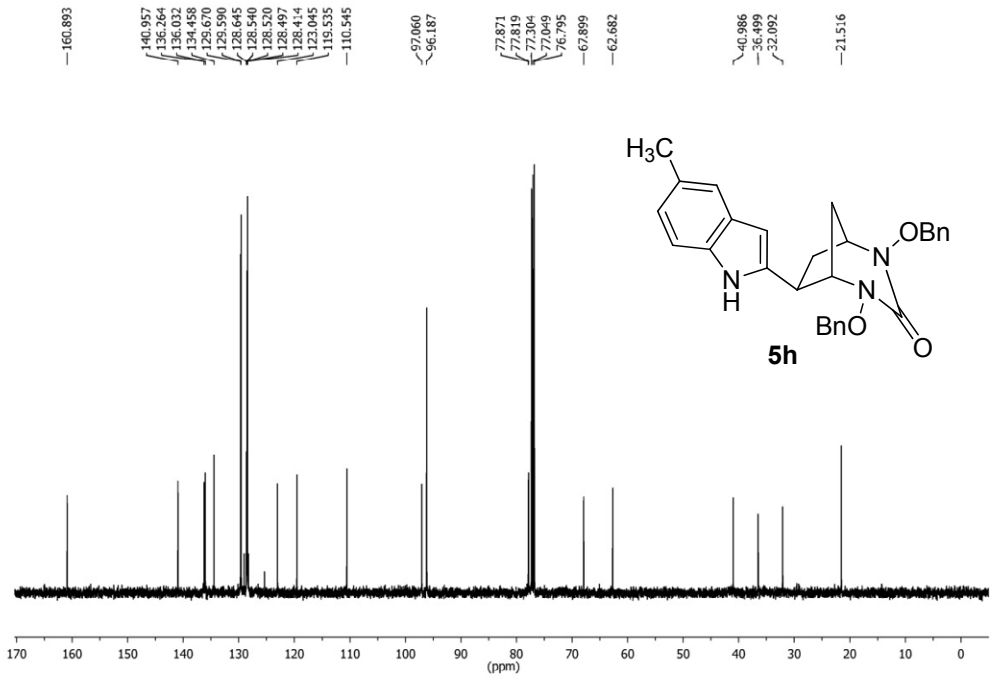
^{1}H NMR of compound 5g



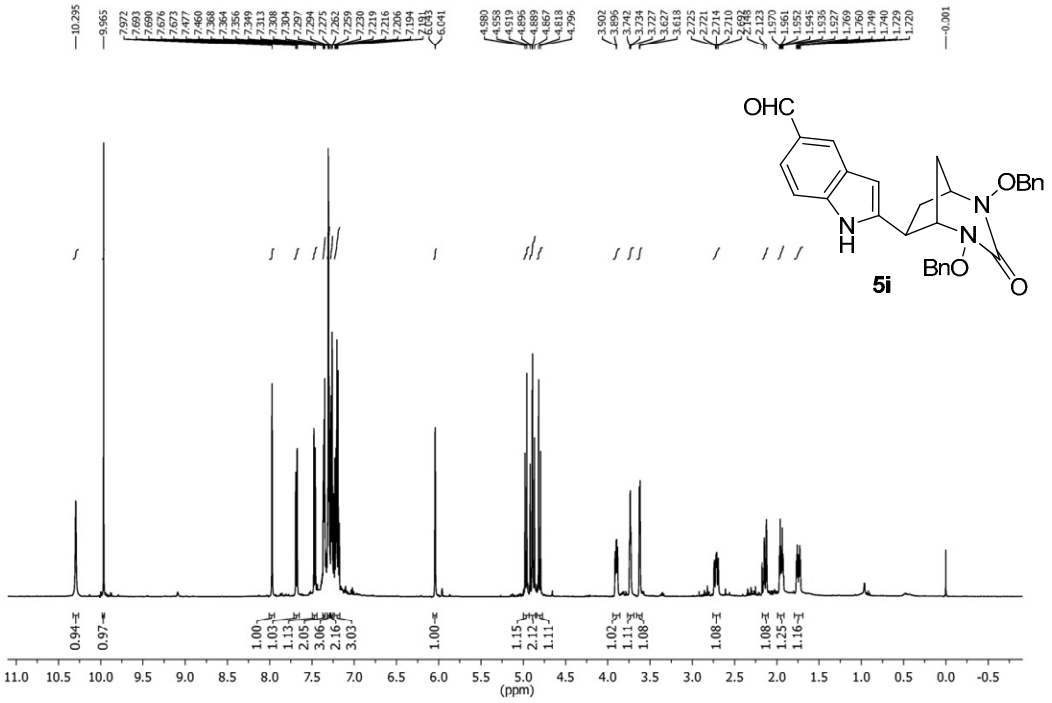
^{13}C NMR of compound 5g



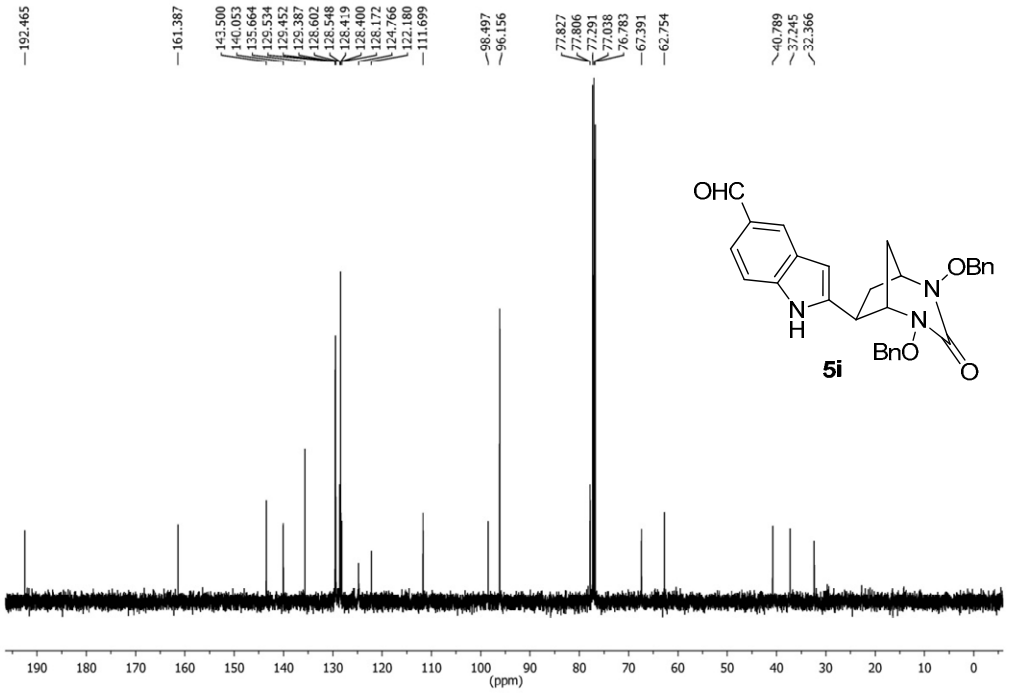
^{1}H NMR of compound 5h



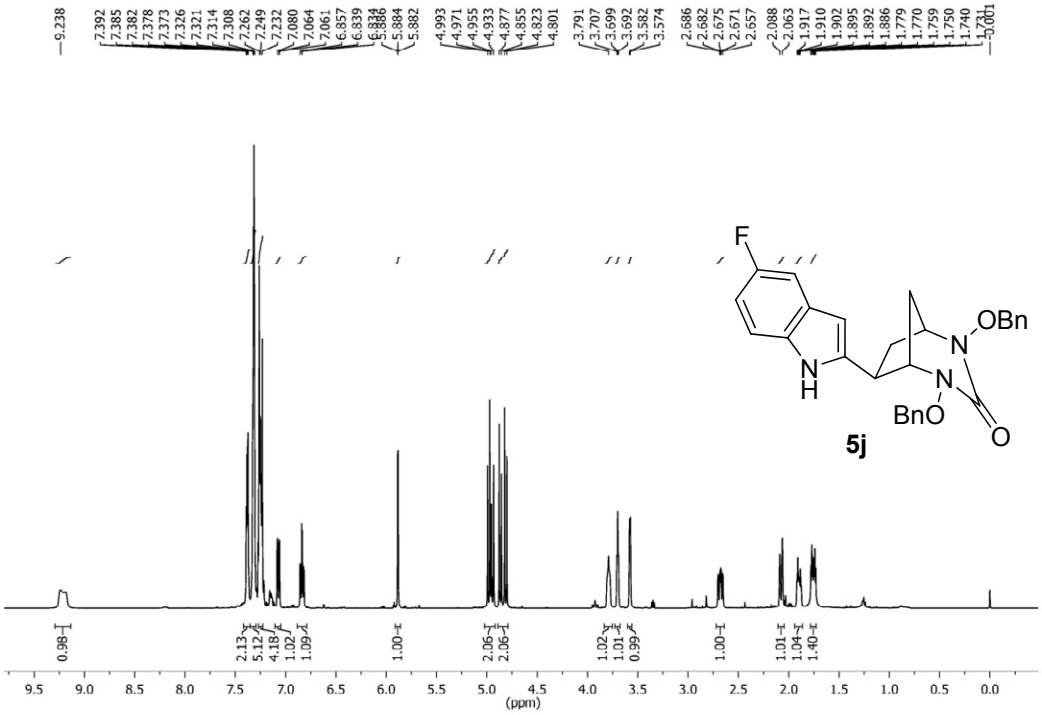
^{13}C NMR of compound 5h



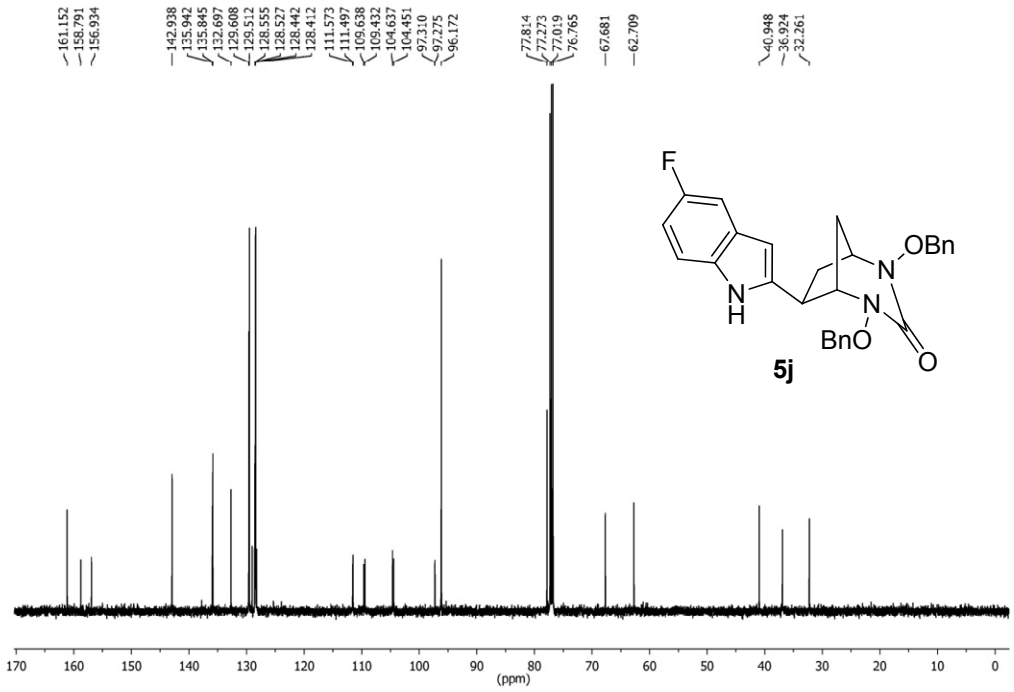
^{1}H NMR of compound 5i



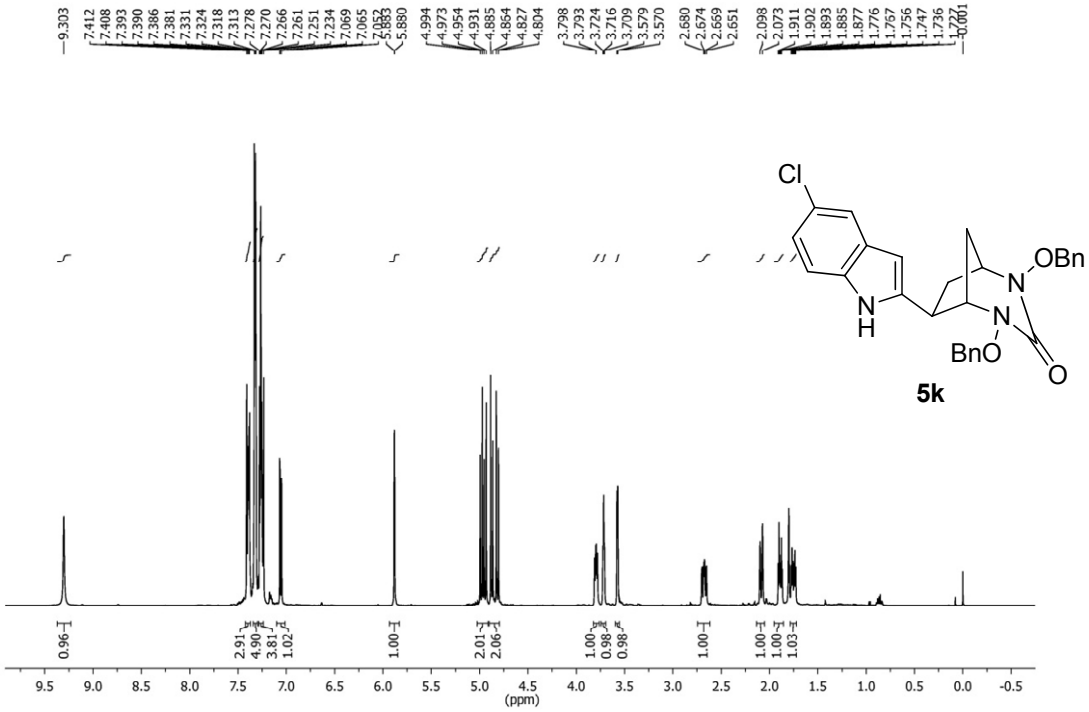
^{13}C NMR of compound 5i



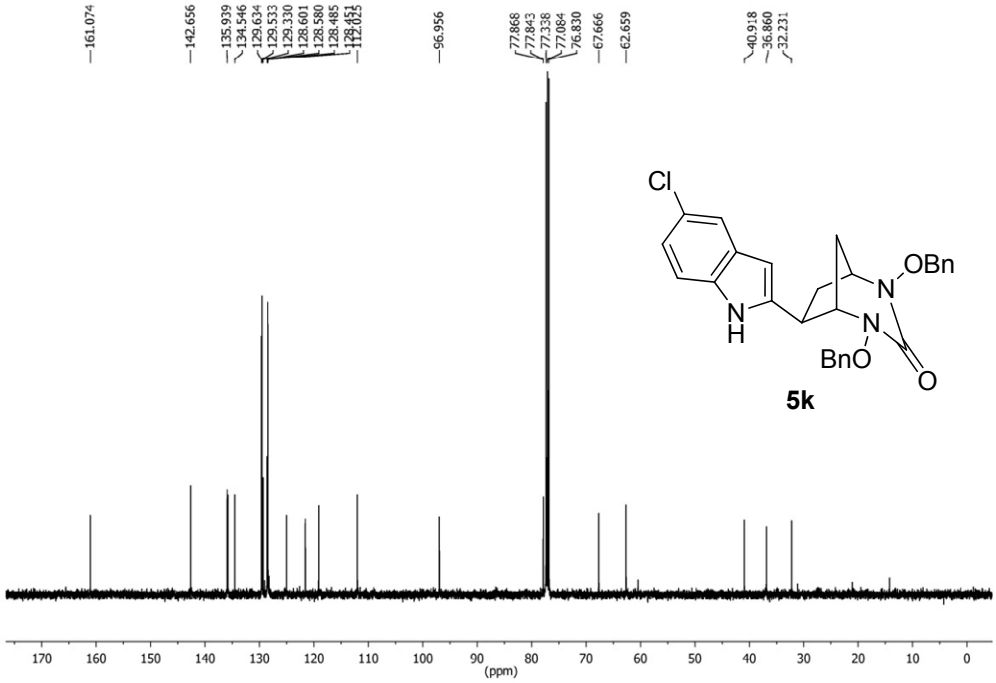
^{1}H NMR of compound 5j



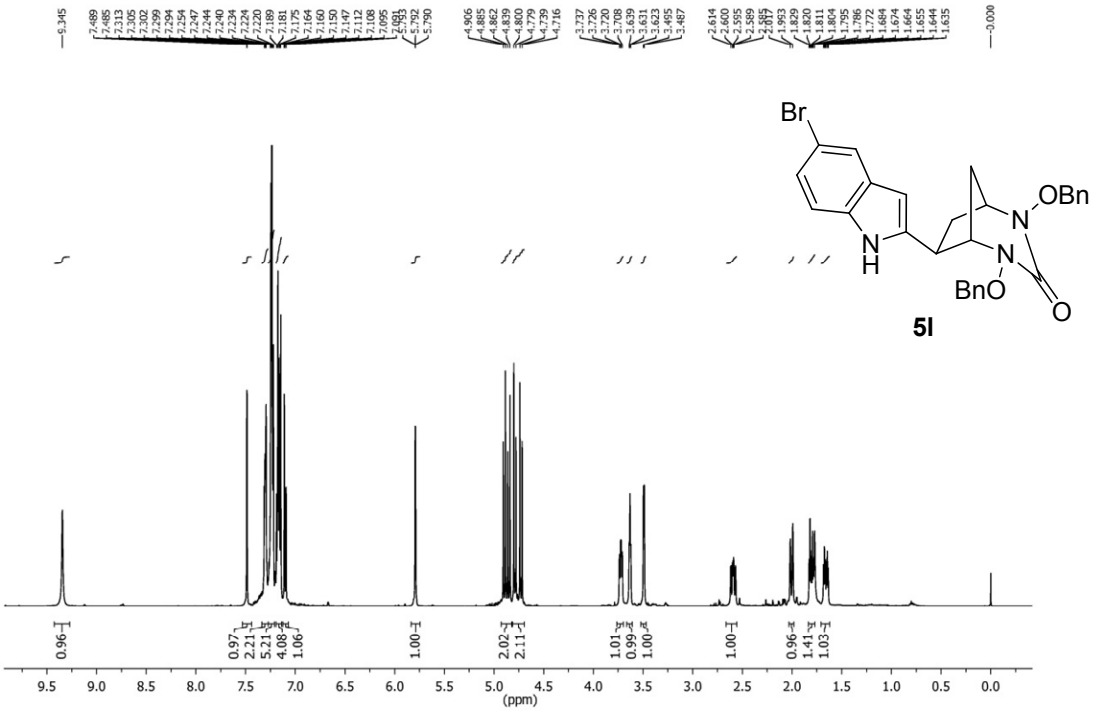
^{13}C NMR of compound 5j



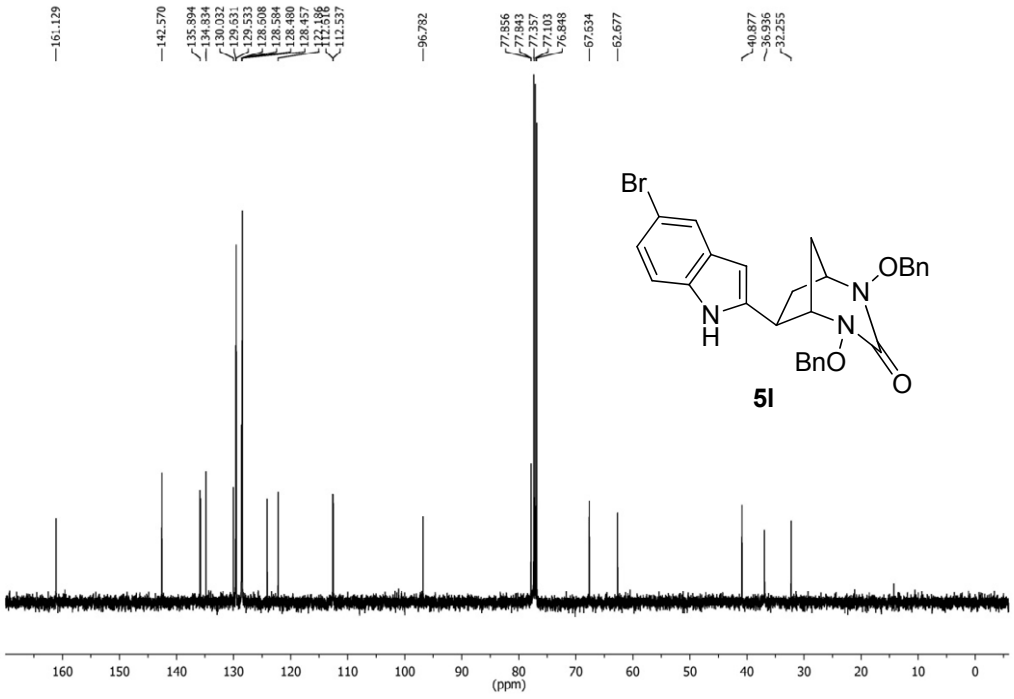
^{1}H NMR of compound 5k



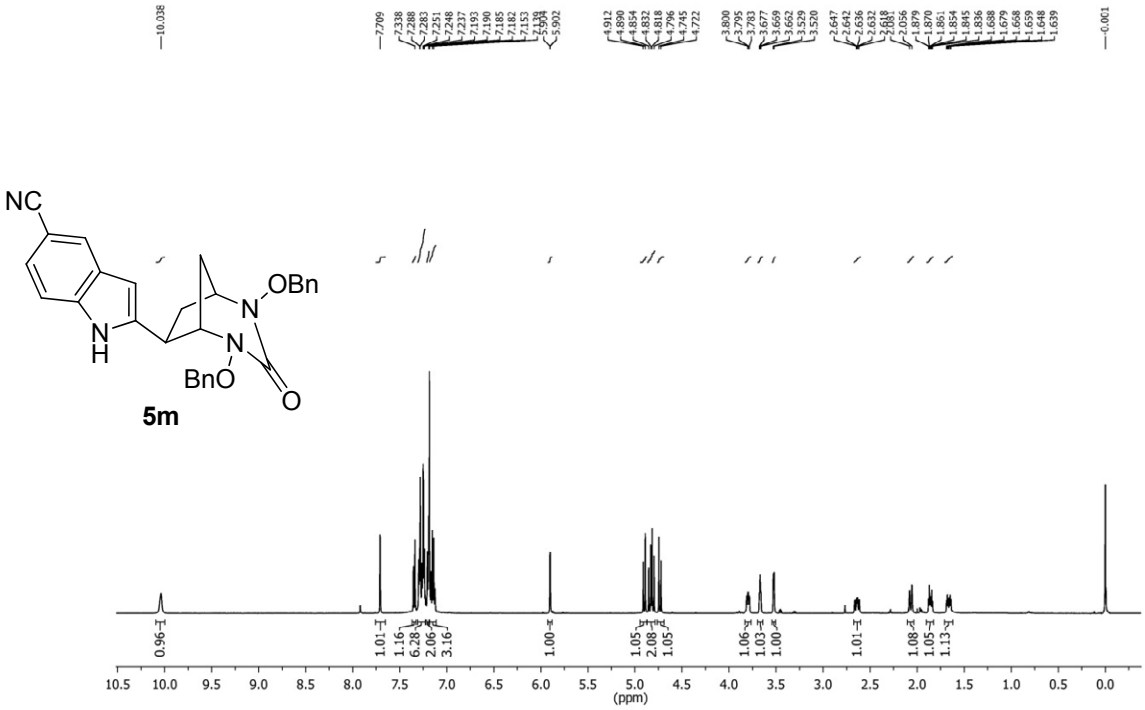
^{13}C NMR of compound 5k



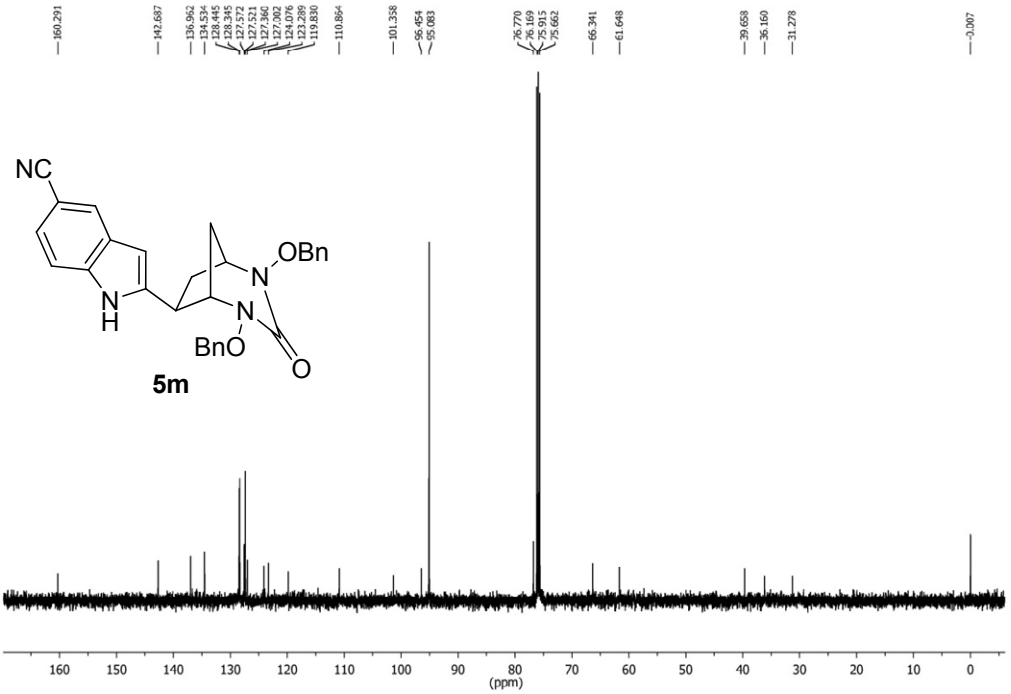
^{1}H NMR of compound 5l



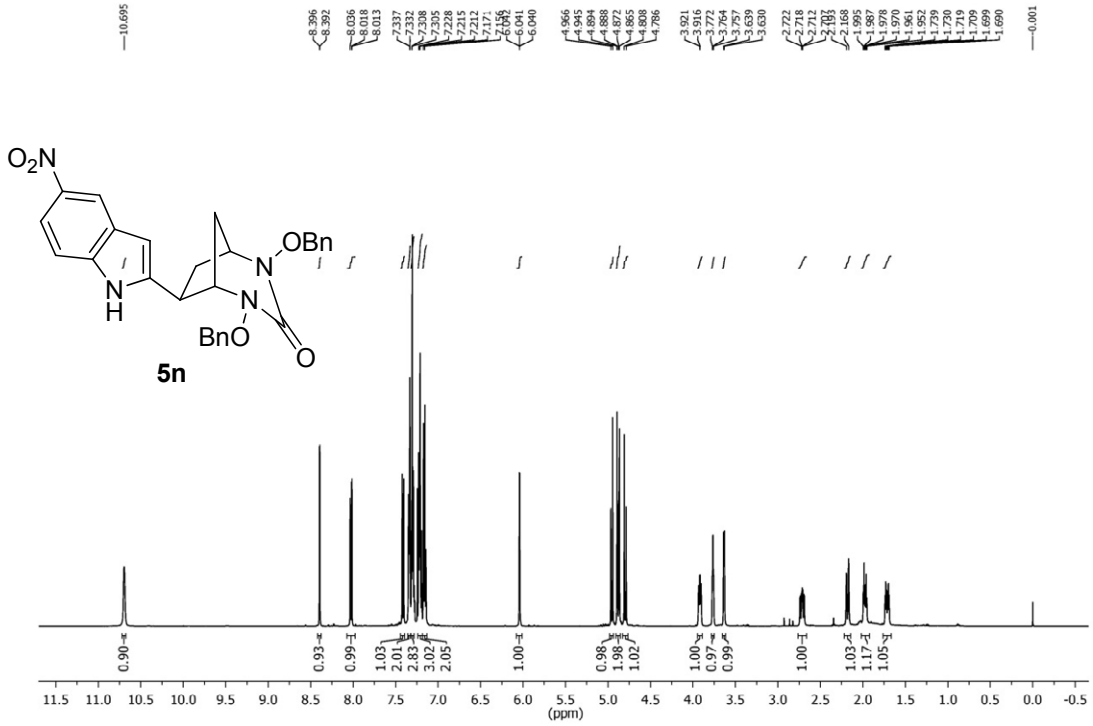
^{13}C NMR of compound 5l



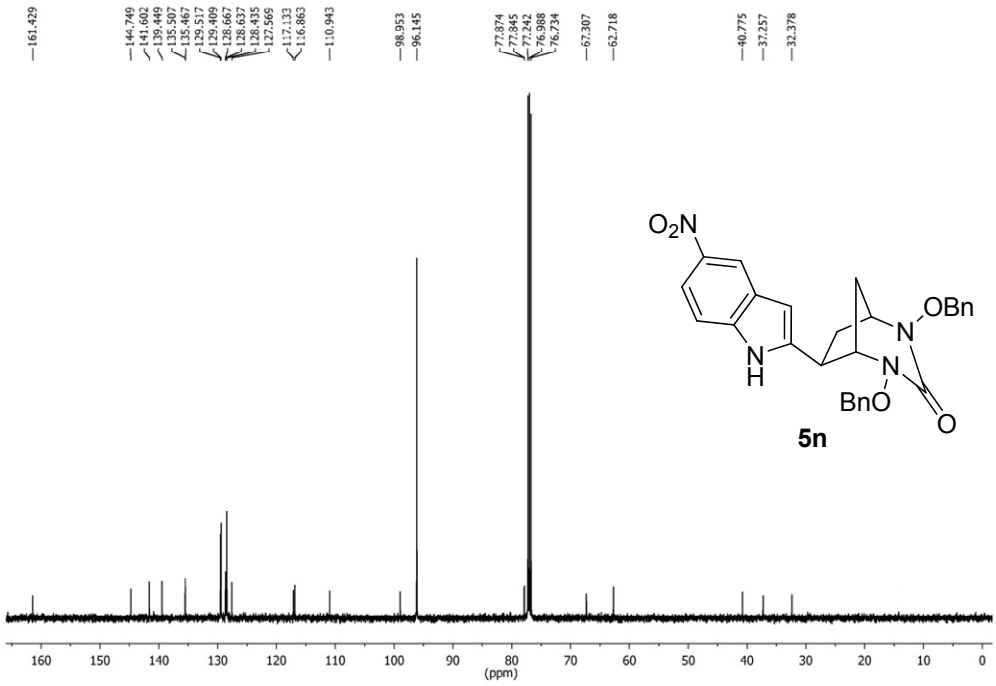
^{1}H NMR of compound 5m



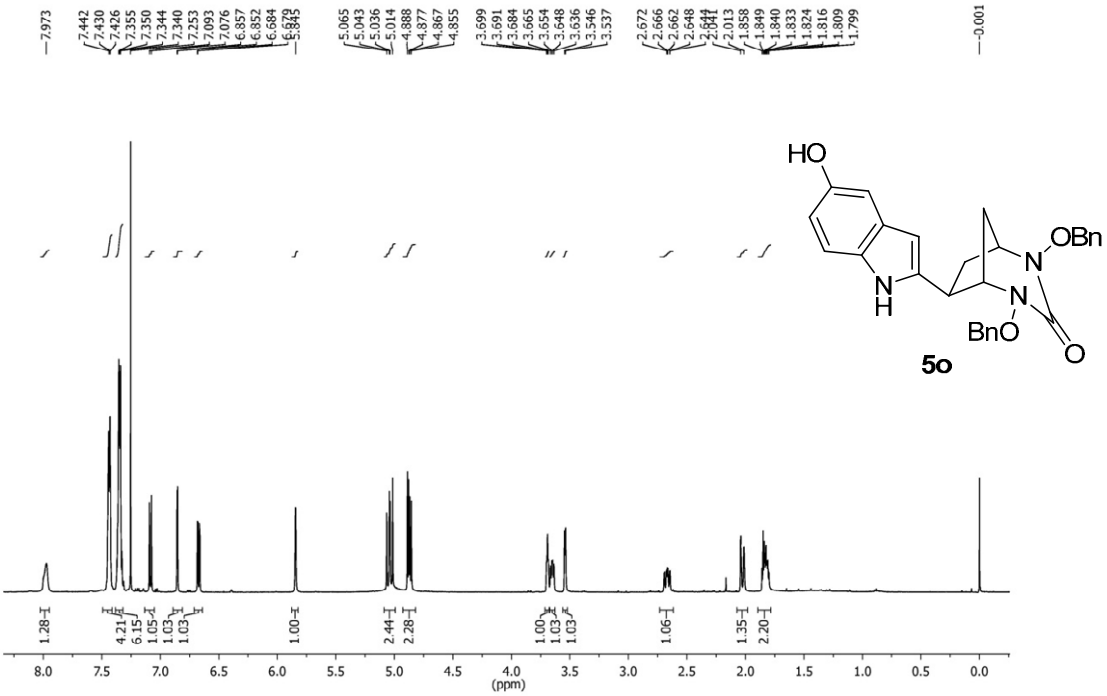
^{13}C NMR of compound 5m



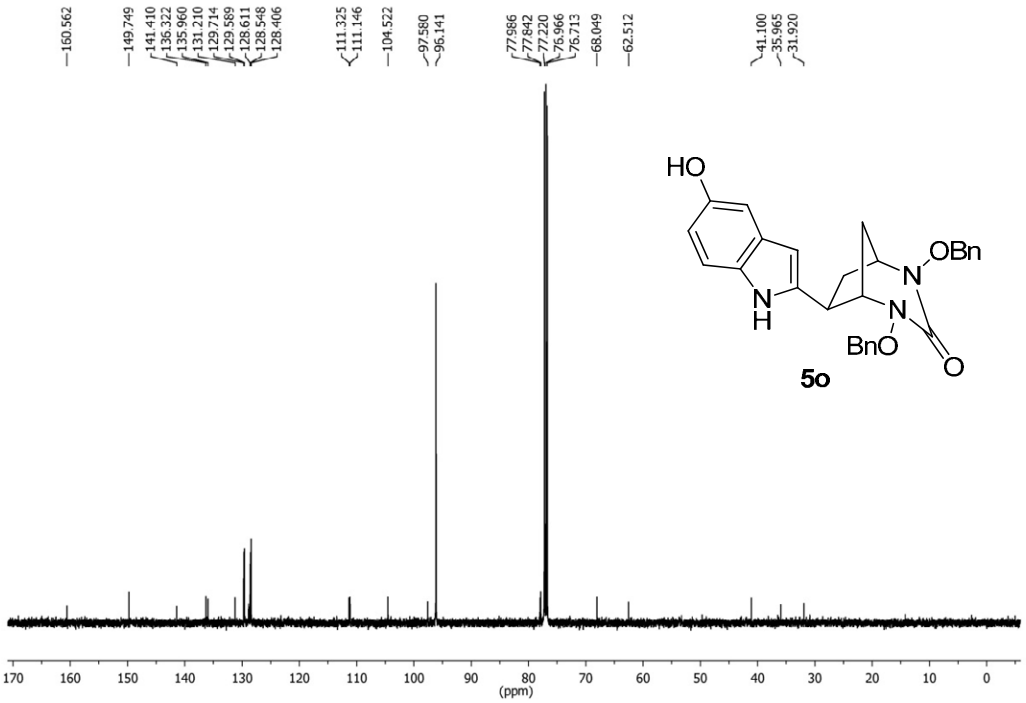
^{1}H NMR of compound 5n



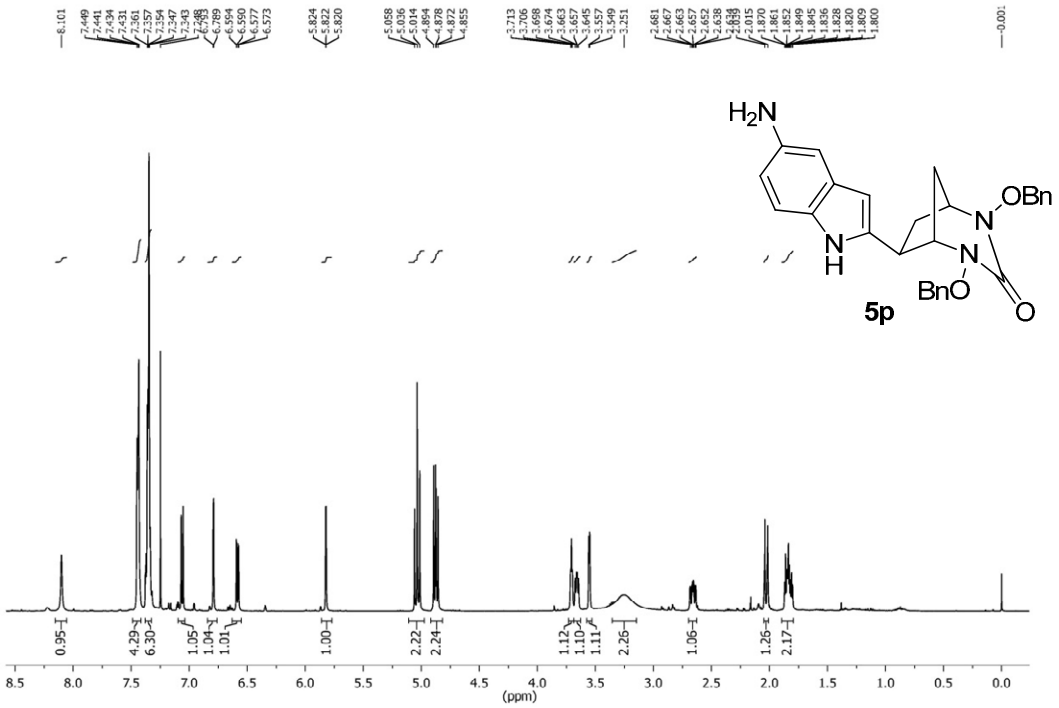
^{13}C NMR of compound 5n



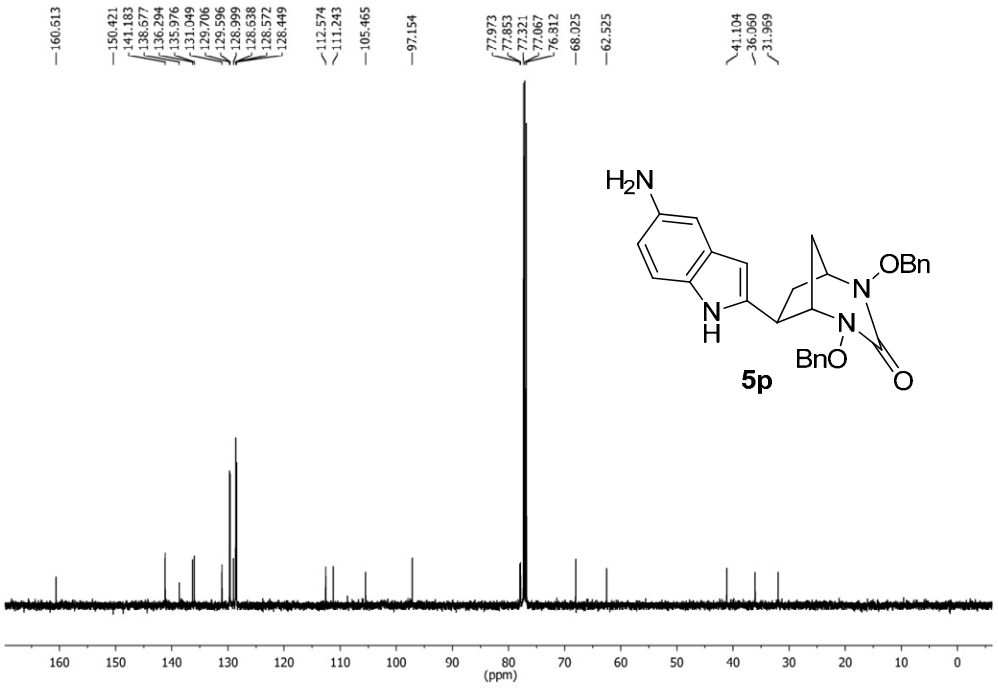
^{1}H NMR of compound 5o



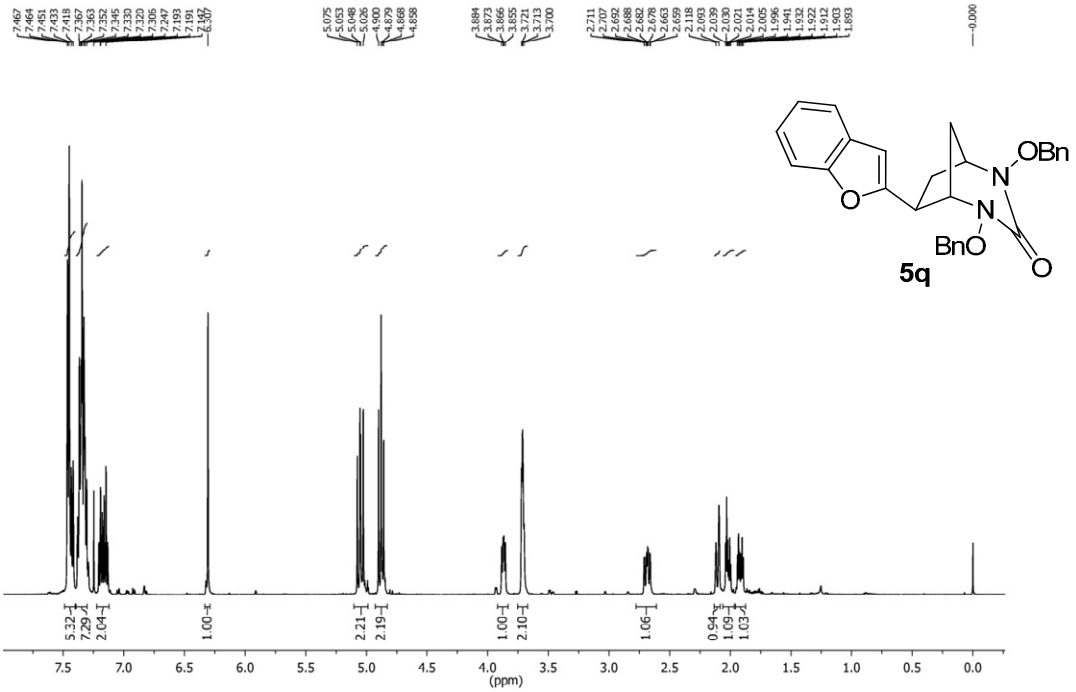
^{13}C NMR of compound 5o



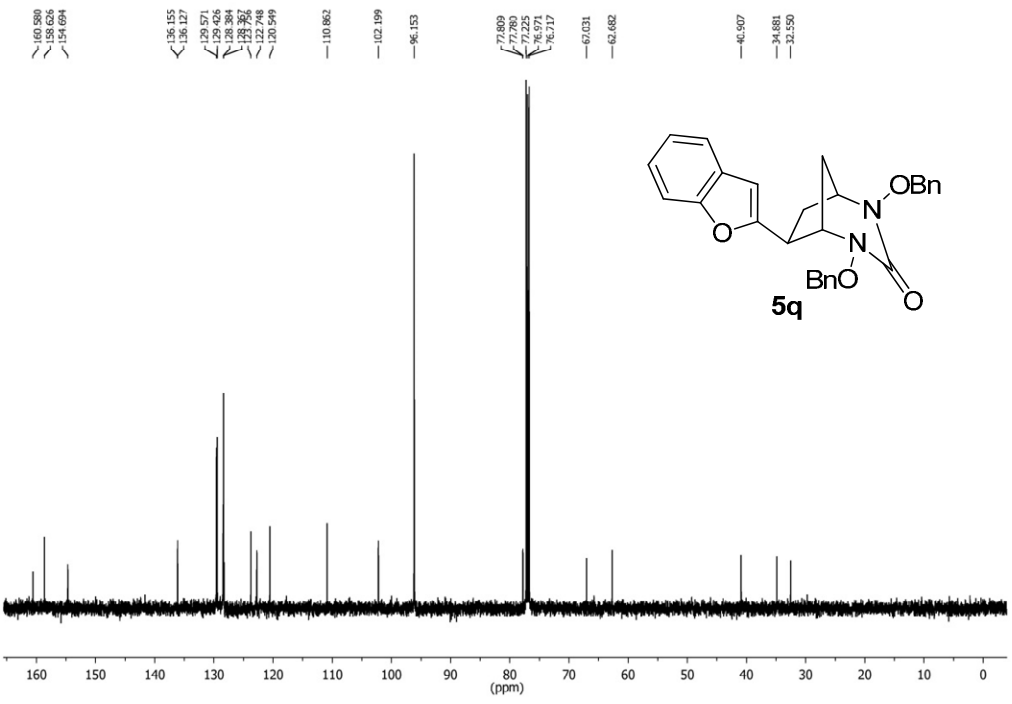
^{1}H NMR of compound 5p



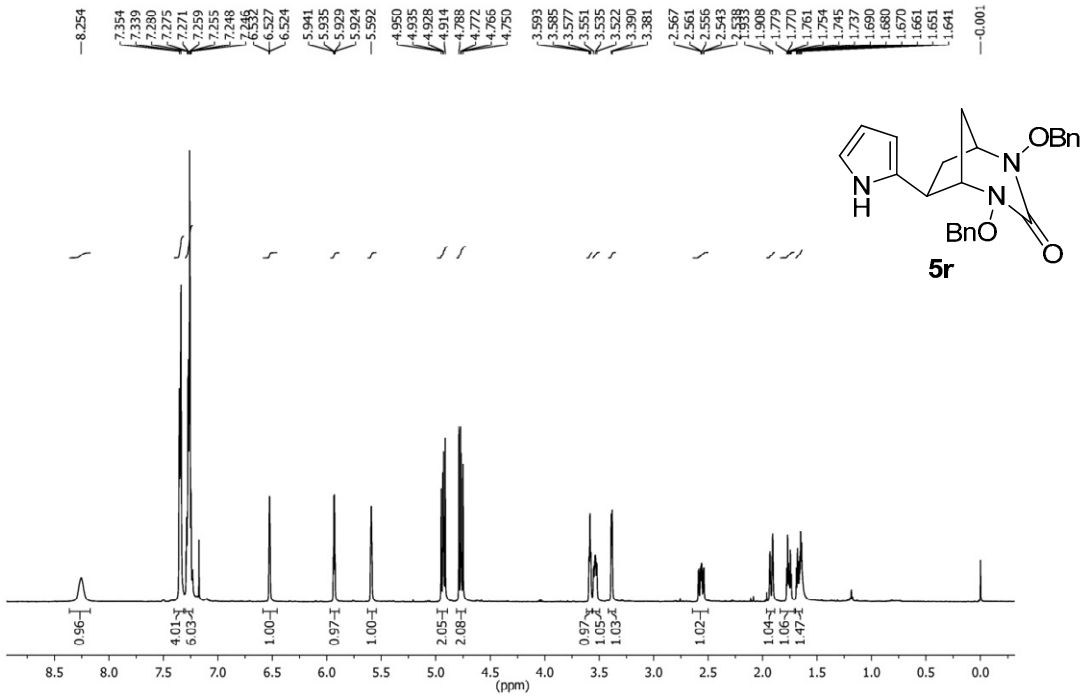
^{13}C NMR of compound 5p



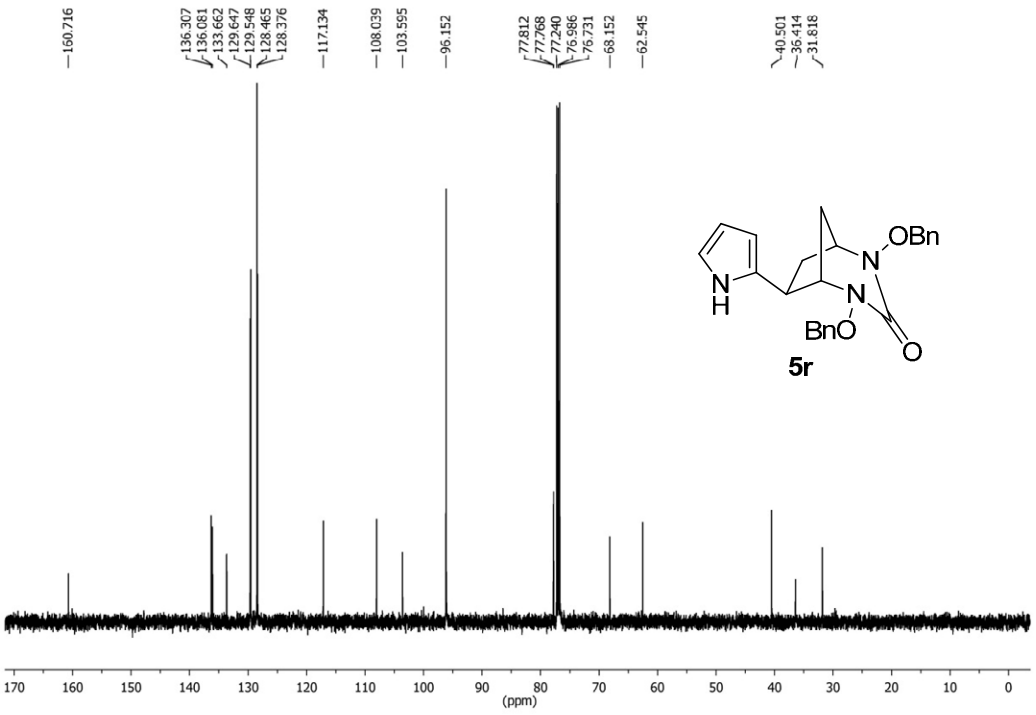
^{1}H NMR of compound 5q



^{13}C NMR of compound 5q



^{1}H NMR of compound 5r



^{13}C NMR of compound 5r

Single Crystal X-ray Structure of 5n