Electronic Supplementary Material (ESI) for ChemComm.

Facile Regiospecific Synthesis of 2,3-Disubstituted Indoles from Isatins

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Supporting Information

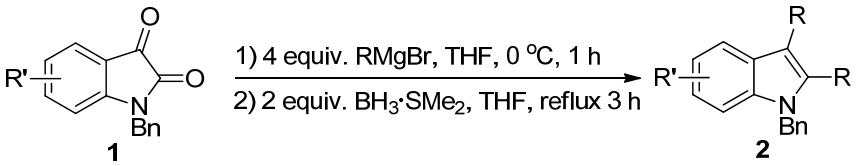
A. General Information

All the starting materials were obtained from commercial sources and used without further purification unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF300 or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with iodine, or ceric ammonium molybdate followed by heating on a hot plate. Flash chromatographic separations were performed on Merck 60 (0.040- 0.063 mm) mesh silica gel.

Benzyl protected isatins and 3-substituted-3-hydroxy oxindole were prepared according to the literature precedure.[1] Alkyl Grignard reagents, such as MeMgBr (3.0 M solution in Et_2O), EtMgBr (3.0 M solution in Et_2O), *n*-HexMgBr (2.0 M solution in Et_2O) and *i*-PrMgBr (2.0 M solution in Et_2O) were purchased from Sigma-Aldrich and used directly, other aryl Grignard reagents were prepared and stored as 1.0 M solution in THF.

B. Representative Procedure for the Synthesis of Indoles.

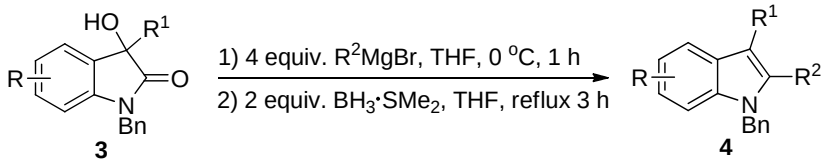
One-pot synthesis of 2-3-disubstituted indoles bearing the same substituent.



1 **2**

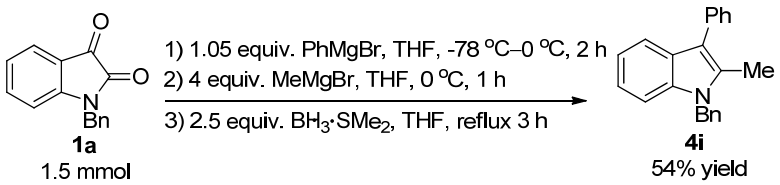
N-Benzylisatin **1** (0.2 mmol) was stirred in THF (1.0 mL) at 0 °C under an atmosphere of argon. RMgBr (0.8 mmol) was added and the reaction mixture was stirred at 0 °C for 1 h, and borane dimethyl sulfide complex (0.2 mL, 2M in THF, 0.4 mmol) was then added, and the resulting mixture was brought to reflux for 3 h. At the end of the reaction, the mixture was cooled to 0 °C and quenched by addition of MeOH (0.5 mL) and 1 M HCl (2.5 mL). The resulting mixture was extracted with EtOAc 3 times (5 mL×3). The organic layers were combined and concentrated, and the residue was purified by flash chromatography (hexane/CH_2Cl_2 10:1) to afford indole products **2**.

One-pot synthesis of 2-3-disubstituted indoles bearing different substituents.



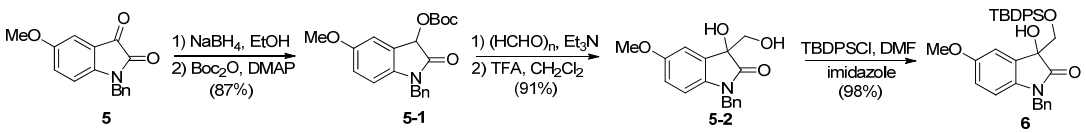
N-Benzyloxindole **3** (0.2 mmol) was stirred in THF (1.0 mL) at 0 °C under an atmosphere of argon. R^2MgBr (0.8 mmol) was added and the reaction mixture was stirred at 0 °C for 1 h, and borane dimethyl sulfide complex (0.2 mL, 2M in THF, 0.4 mmol) was then added, and the resulting mixture was brought to reflux for 3 h. At the end of the reaction, the reaction solution was cooled to 0 °C and quenched by addition of MeOH (0.5 mL) and 1M HCl (2.5 mL). The resulting mixture was extracted with EtOAc 3 times (5 mL×3). The organic layers were combined and concentrated, and the residue was purified by flash chromatography (hexane/CH_2Cl_2 10:1) to afford indole products **4**.

<u>One-pot synthesis of 2-Me-3-Ph-indole from isatin.</u>



N-Benzylisatin **1a** (1.5 mmol) was stirred in THF (7.5 mL) at -78 °C under an atmosphere of argon. PhMgBr (1.6 mmol) was added and the reaction mixture was stirred at -78 °C for 1 h, and then was allowed to slowly warm up to 0 °C over 1 h. MeMgBr (6.0 mmol) was added and the reaction mixture was stirred at 0 °C for another 1 h, and borane dimethyl sulfide complex (1.9 mL, 2M in THF, 3.8 mmol) was added, and the resulting mixture was brought to reflux for 3 h. At the end of the reaction, the reaction solution was cooled to 0 °C and quenched by addition of MeOH (2.0 mL) and 1M HCl (15 mL). The resulting mixture was extracted with EtOAc 3 times (20 mL×3). The organic layers were combined and concentrated, and the residue was purified by flash chromatography (hexane/CH_2Cl_2 10:1) to afford indole **4i** as a white solid (241.2 mg, 54% yield).

<u>C. Application to the Synthesis of LY311727.</u>



<u>Preparation of **5-1**</u>: $NaBH_4$ (45.6 mg, 1.2 mmol) in EtOH (2 mL) was cooled to 0 °C before isatin **5** (267 mg, 1.0 mmol) was added. The reaction mixture was then allowed to warm up to room temperature and stirred for 10 minutes. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (15 mL×3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude 3-hydroxy oxindole

intermediate as an yellow solid, which was then dissolved CH_2Cl_2 (10 mL) and cooled to 0 ^oC. Boc_2O (218.0 mg, 1.0 mmol) was added, followed by DMAP (12.2 mg, 0.1 mmol), and the reaction mixture was stirred at 0 ^oC for 0.5 h. The resulting reaction solution was concentrated and subject to flash chromatography (hexane/EtOAc 4:1) to provid oxindole **5-1** as a colorless oil (321.2 mg, 87% yield for two steps).

5-1: A colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 1.53 (s, 9H), 3.74 (s, 3H), 4.85 (d, *J* = 15.6 Hz, 1H), 4.88 (d, *J* = 15.6 Hz, 1H), 5.85 (s, 1H), 6.58 (d, *J* = 8.2 Hz, 1H), 6.74 (dd, *J* = 2.5 Hz, 8.2 Hz, 1H), 7.05 (d, *J* = 2.5 Hz, 1H), 7.25-7.33 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.64, 43.97, 55.74, 71.96, 83.74, 109.99, 112.68, 114.73, 125.27, 127.29, 127.68, 128.77, 135.20, 136.77, 152.78, 156.14, 171.63; HRMS (ESI) m/z calcd for $C_{21}H_{23}NNaO_5$ $[M+Na]^+$ = 392.1468, found =392.1477.

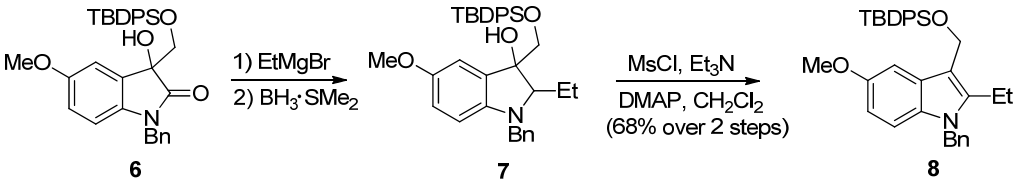
Preparation of **5-2**: To a solution of **5-1** (220 mg, 0.6 mmol) in CH_2Cl_2 (6.0 mL) were added paraformaldehyde (180.0 mg, 6.0 mmol) and Et_3N (101.0 mg, 1.0 mmol), and the resulting mixture was stirred at room temperature for 4 h. The mixture was directly subject to a pad of silica gel to remove excess paraformaldehyde with EtOAc as eluent, and the eluent was then concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (8.0 mL). TFA (1.0 mL) was added and the resulting reaction solution was stirred at room temperature for 3 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 (20 mL×3), and combined organic extracts were concentrated and the residue was purified by flash chromatography (hexane/EtOAc 1:1 to 1:2) to yield **5-2** as a white solid (163.5 mg, 91% yield for two steps)

5-2: A white solid; ^1H NMR (500 MHz, d_6-Acetone:$CDCl_3$ v/v = 1:1) δ 3.71 (s, 3H), 3.89 (d, *J* = 15.7 Hz, 1H), 3.93 (d, *J* = 15.7 Hz, 1H), 4.75 (d, *J* = 15.8 Hz, 1H), 4.93 (d, *J* = 15.8 Hz, 1H), 6.59 (d, *J* = 8.9 Hz, 1H), 6.68 (dd, *J* = 2.5 Hz, 8.2 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, d_6-Acetone:$CDCl_3$ v/v = 1:1) δ 43.17, 55.29, 66.52, 76.68, 109.47, 111.65, 113.58, 127.21, 127.30, 128.55, 131.13, 136.26, 136.58, 156.10, 176.92; HRMS (ESI) m/z calcd for $C_{17}H_{17}NNaO_4$ $[M+Na]^+$ = 322.1050, found =322.1062.

Preparation of **6**: To a solution of **5-2** (90.0 mg, 0.3 mmol) in DMF (0.5 mL) under Ar were added imidazole (61.2 mg, 0.9 mmol) and TBDPSCl (106.9 mg, 0.4 mmol), and the resulting mixture was stirred at r.t. for 20 h. The reaction was quenched by addition of water and the resulting mixture was extracted with EtOAc (10 mL×3). The organic extracts were combined and concentrated, and purified by flash chromatography (hexane/EtOAc 3:1) to afford **6** as a white solid (158.0 mg, 98% yield).

6: A white solid; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (s, 9H), 3.74 (s, 3H), 3.96 (d, *J* = 9.5 Hz, 1H), 4.14 (d, *J* = 9.5 Hz, 1H), 4.84 (d, *J* = 15.8 Hz, 1H), 4.91 (d, *J* = 15.8 Hz, 1H), 6.62 (d, *J* = 8.9 Hz, 1H), 6.77 (dd, *J* = 2.5 Hz, 8.2 Hz, 1H), 6.99 (d, *J* = 2.5 Hz, 1H), 7.22 (d, *J* = 6.3 Hz, 3H), 7.28-7.43 (m, 8H), 7.49 (d, *J* = 6.3 Hz, 2H), 7.59 (dd, *J* = 1.3 Hz, 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.08, 26.54, 43.95, 55.70, 67.69, 109.86, 111.08, 114.68, 127.18, 127.45,

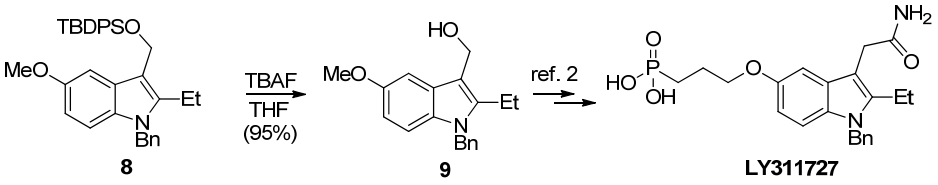
127.61, 127.68, 128.67, 129.69, 129.72, 129.94, 132.46, 132.72, 135.36, 135.46, 135.59, 135.75, 156.20, 177.18; HRMS (ESI) m/z calcd for $C_{33}H_{35}NNaO_4Si$ $[M+Na]^+$ = 560.2233, found =560.2244.



6 **7** **8**

Preparation of **8**: To a stirred solution of *N*-Benzyloxindole **6** (0.2 mmol) in THF (1.0 mL) at 0 °C under an atmosphere of argon was added EtMgBr (1.2 mmol, 3.0 M solution in Et_2O), and the reaction mixture was stirred at 0 °C for 1 h. Borane dimethyl sulfide complex (0.5 mmol, 2M in THF) was added to the reaction mixture, and the resulting mixture was brought to reflux for 3 h. The reaction mixture was then cooled to 0 °C and quenched by addition of MeOH (0.5 mL) and saturated aqueous $NaHCO_3$ (2.5 mL). The resulting mixture was extracted with EtOAc (5 mL×3). The organic layers were combined and concentrated to afford crude **7**, which was directly dissolved in CH_2Cl_2 (2.0 mL) at 0 °C, followed by addition of Et_3N (2.0 mmol), MsCl (1.0 mmol) and DMAP (0.02 mmol). The resulting mixture was stirred at 0 °C for 5 minutes. The reaction mixture was concentrated and purified by flash chromatography (hexane/EtOAc 12:1) to afford indole **8** as a colorless oil (72.5 mg, 68% yield for two steps).

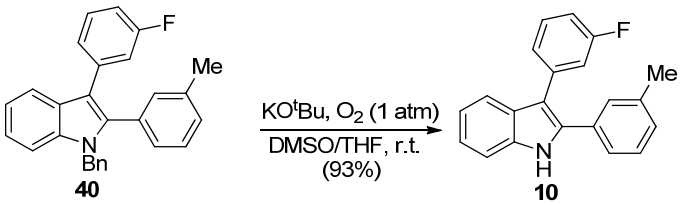
8: A colorless oil; ^{1}H NMR (300 MHz, d_6-Acetone) δ 1.05-1.08 (m, 12H), 2.68 (q, *J* = 7.6 Hz, 2H), 3.77 (s, 3H), 4.99 (s, 2H), 5.42 (s, 2H), 6.71 (dd, *J* = 2.2 Hz, 8.8 Hz, 1H), 7.00 (d, *J* = 7.6 Hz, 2H), 7.11 (d, *J* = 2.5 Hz, 1H), 7.15 (d, *J* = 8.7 Hz, 1H), 7.23-7.31 (m, 3H), 7.39-7.51 (m, 6H), 7.80 (d, *J* = 7.3 Hz, 4H); ^{13}C NMR (125 MHz, d_6-Acetone) δ 14.61, 17.60, 18.99, 26.37, 46.08, 54.94, 57.48, 100.74, 110.22, 110.46, 110.79, 125.95, 127.00, 127.71, 128.50, 129.69, 131.75, 133.87, 134.74, 135.60, 138.86, 140.91, 154.26; HRMS (ESI) m/z calcd for $C_{35}H_{39}NNaO_2Si$ $[M+Na]^+$ = 556.2648, found =556.2671.



8 **9** **LY311727**

Preparation of **9**: TBAF (0.25 mmol, 1.0 M solution in THF) was added to a THF solution of indole **8** (0.05 mmol in 0.5 mL THF), and the resulting mixture was stirred at room temperature for 24 h. The reaction mixtue was then concentrated and the residue was purified by flash chromatography (CH_2Cl_2 to hexane/EtOAc 1:1) to afford indole **9** (14.1 mg, 95% yield). The analytical data obtained were in agreement with the data reported in literature.[2]

D. Debenzylation of Product 4o.



N-Benzylindole **4o** (39.1 mg, 0.1 mmol) was dissolved in a mixed solvent of THF (0.5 mL) and DMSO (2.0 mL), and ^{t}BuOK (112.0 mg, 1.0 mmol) was then added to the solution. The reaction system was then charged with an oxygen balloon and stirred at room temperature for 0.5 h. The reaction was quenched by addition of water and the resulting mixture was extracted with EtOAc (10 mL×3). The organic layers were combined, concentrated and purified by flash chromatography (hexane/CH_2Cl_2 3:1) to afford indole **10** as a white solid (28.1 mg, 93% yield).

10: A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3H), 7.01 (t, *J* = 8.5 Hz, 1H), 7.15-7.30 (m, 8H), 7.36 (dd, *J* = 7.6 Hz, 14.5 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 8.23 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.48, 111.00, 112.97, 113.13, 113.74, 116.70, 116.86, 119.45, 120.67, 122.83, 125.61, 125.89, 125.91, 128.47, 128.71, 128.76, 128.83, 129.86, 129.92, 132.28, 134.78, 135.83, 137.50, 137.57, 138.51, 162.08, 164.03; HRMS (ESI) m/z calcd for $C_{21}H_{15}FN$ $[M-H]^-$ = 300.1189, found =300.1196.

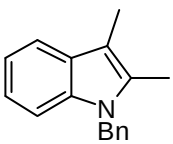
Reference

[1] B. M. Trost, J. Xie, J. D. Sieber, *J. Am. Chem. Soc.* **2011**, *133*, 20611.

[2] J. M. Paolak, V. V. Khau, D. R. Hutchison, M. J. Martinelli, *J. Org. Chem.* **1996**, *61*, 9055

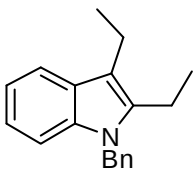
E. Analytical Data of the Products.

1-Benzyl-2,3-dimethyl-1*H*-indole **2a**



A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.36 (s, 3H), 5.34 (s, 2H), 7.03 (d, *J* = 6.9 Hz, 2H), 7.15-7.18 (m, 2H), 7.25-7.33 (m, 4H), 7.60 (dd, *J* = 2.5 Hz, 4.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.85, 10.11, 46.45, 106.96, 108.76, 117.96, 118.80, 120.74, 125.97, 127.10, 128.63, 128.66, 132.38, 136.36, 138.25; HRMS (ESI) m/z calcd for $C_{17}H_{18}N$ $[M+H]^+$ = 236.1434, found = 236.1429.

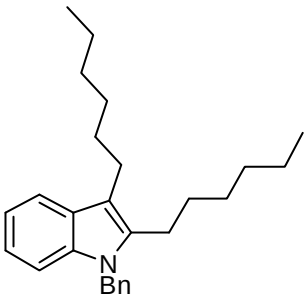
1-Benzyl-2,3-diethyl-1*H*-indole **2b**



A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, *J* = 7.6 Hz, 3H), 1.31 (t, *J* = 7.6 Hz, 3H), 2.75 (q, *J* = 7.6 Hz, 2H), 2.81 (q, *J* = 7.6 Hz, 2H), 5.35 (s, 2H), 6.98 (d, *J* = 7.0 Hz, 2H), 7.10-7.13 (m,

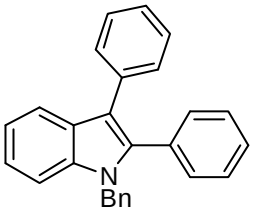
2H), 7.16-7.19 (m, 1H), 7.22-7.29 (m, 3H), 7.60-7.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.16, 16.12, 17.71, 17.75, 46.41, 109.26, 113.46, 118.22, 118.82, 120.74, 125.86, 127.07, 127.81, 128.63, 136.48, 137.84, 138.38; HRMS (ESI) m/z calcd for $C_{19}H_{22}N$ $[M+H]^+$ = 264.1747, found = 264.1748.

1-Benzyl-2,3-dihexyl-1*H*-indole **3c**



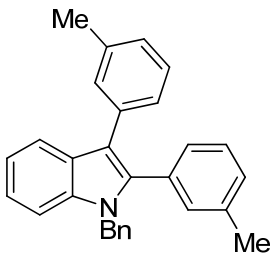
A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89-0.94 (m, 6H), 1.28-1.54 (m, 14H), 1.67-1.74 (m, 2H), 2.69-2.73 (m, 2H), 2.75-2.79 (m, 2H), 5.34 (s, 2H), 6.97 (d, *J* = 7.0 Hz, 2H), 7.11-7.17 (m, 3H), 7.22-7.27 (m, 3H), 7.61-7.63 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.04, 14.11, 22.54, 22.70, 24.68, 24.72, 29.24, 29.54, 30.39, 31.22, 31.54, 31.84, 46.55, 109.24, 112.53, 118.38, 118.75, 120.65, 125.84, 127.05, 128.17, 128.62, 136.53, 136.91, 138.45; HRMS (ESI) m/z calcd for $C_{27}H_{38}N$ $[M+H]^+$ = 376.2999, found = 376.3004.

1-Benzyl-2,3-diphenyl-1*H*-indole **2d**



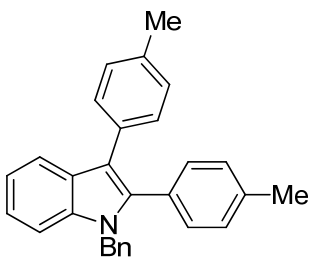
A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.32 (s, 2H), 7.04 (d, *J* = 7.0 Hz, 2H), 7.19-7.33 (m, 14H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.86 (dd, *J* = 2.2 Hz, 6.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.58, 110.50, 115.65, 119.69, 120.40, 122.35, 125.57, 126.09, 127.13, 127.36, 128.12, 128.15, 128.36, 128.64, 129.89, 131.05, 131.77, 135.09, 136.96, 137.85, 138.08; HRMS (ESI) m/z calcd for $C_{27}H_{22}N$ $[M+H]^+$ = 360.1747, found = 360.1741.

1-Benzyl-2,3-di-m-tolyl-1*H*-indole **2e**



A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.34 (s, 3H), 5.31 (s, 2H), 7.03-7.10 (m, 5H), 7.13-7.30 (m, 11H), 7.87 (dd, *J* = 2.2 Hz, 6.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.41, 21.58, 47.68, 110.48, 115.54, 119.84, 120.32, 122.26, 126.24, 126.36, 127.04, 127.15, 127.47, 128.05, 128.22, 128.31, 128.65, 128.93, 130.59, 131.72, 131.78, 135.11, 137.01, 137.53, 137.85, 138.11, 138.35; HRMS (ESI) m/z calcd for $C_{29}H_{26}N$ $[M+H]^+$ = 388.2060, found = 388.2074.

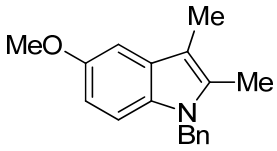
1-Benzyl-2,3-di-p-tolyl-1*H*-indole **2f**



A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 6H), 5.30 (s, 2H), 7.05 (d, *J* = 7.6 Hz, 2H), 7.11-7.13 (m, 4H), 7.16-7.30 (m, 10H), 7.82-7.84 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.16, 21.30, 47.50, 110.41, 115.26, 119.66, 120.20, 122.11, 126.07, 127.05, 127.47, 128.61, 128.82, 128.90, 129.09, 129.69, 130.86, 132.19, 134.92, 136.87, 137.77, 137.84, 138.22; HRMS (ESI) m/z calcd for $C_{29}H_{26}N$ $[M+H]^+$ = 388.2060, found

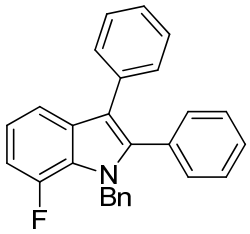
= 388.2074.

1-Benzyl-5-methoxy-2,3-dimethyl-1*H*-indole **2g**



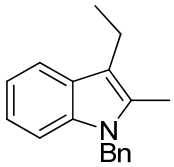
A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 6H), 3.91 (s, 3H), 5.28 (s, 2H), 6.81 (dd, *J* = 2.5 Hz, 8.8 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 2H), 7.04 (d, *J* = 1.9 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 1H), 7.25-7.30 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.92, 10.19, 46.56, 55.91, 100.42, 106.58, 109.45, 110.30, 125.92, 127.08, 128.65, 128.88, 131.61, 133.15, 138.33, 153.77; HRMS (ESI) m/z calcd for $C_{18}H_{20}NO$ $[M+H]^+$ = 266.1539, found = 266.1548.

1-Benzyl-7-fluoro-2,3-diphenyl-1*H*-indole **2h**



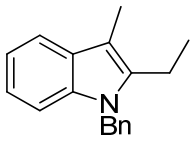
A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46 (s, 2H), 6.89-6.93 (m, 3H), 7.05-7.09 (m, 1H), 7.18-7.36 (m, 13H), 7.56 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 49.35, 49.39, 108.12, 108.26, 115.50, 115.52, 116.80, 120.44, 120.49, 124.81, 124.89, 125.90, 126.03, 127.07, 128.20, 128.44, 128.48, 129.92, 131.19, 131.27, 134.64, 139.02, 139.26, 149.15, 151.10; HRMS (ESI) m/z calcd for $C_{27}H_{21}NF$ $[M+H]^+$ = 378.1653, found = 378.1651.

1-Benzyl-3-ethyl-2-methyl-1*H*-indole **4a**



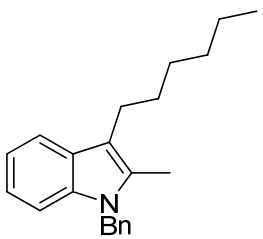
A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31-1.34 (m, 3H), 2.35 (s, 3H), 2.84 (dd, *J* = 6.9 Hz, 13.9 Hz, 2H), 5.34 (s, 2H), 7.02 (d, *J* = 7.6 Hz, 2H), 7.15-7.17 (m, 2H), 7.25-7.33 (m, 5H), 7.65 (dd, *J* = 2.5 Hz, 4.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.02, 15.70, 17.71, 46.43, 108.92, 113.94, 118.07, 118.78, 120.64, 125.97, 127.10, 127.70, 128.67, 131.85, 136.46, 138.24; HRMS (ESI) m/z calcd for $C_{18}H_{20}N$ $[M+H]^+$ = 250.1590, found = 250.1592.

1-Benzyl-2-ethyl-3-methyl-1*H*-indole **4b**



A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, *J* = 7.6 Hz, 3H), 2.36 (d, *J* = 1.3 Hz, 3H), 2.77 (dd, *J* = 7.6 Hz, 15.2 Hz, 2H), 5.36 (s, 2H), 7.00 (d, *J* = 7.6 Hz, 2H), 7.13-7.15 (m, 2H), 7.18-7.21 (m, 1H), 7.23-7.30 (m, 3H), 7.59-7.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.68, 14.49, 17.83, 46.43, 106.43, 109.11, 118.03, 118.86, 120.81, 125.87, 127.09, 128.63, 128.72, 136.33, 138.30, 138.42; HRMS (ESI) m/z calcd for $C_{18}H_{20}N$ $[M+H]^+$ = 250.1590, found = 250.1592.

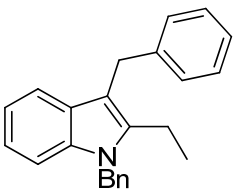
1-Benzyl-3-hexyl-2-methyl-1*H*-indole **4c**



A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, *J* = 6.9 Hz, 3H), 1.28-1.39 (m, 6H), 1.62-1.68 (m, 2H), 2.29 (s, 3H), 2.75 (t, *J* = 7.6 Hz, 2H), 5.30 (s, 2H), 6.96 (d, *J* = 6.9 Hz, 2H),

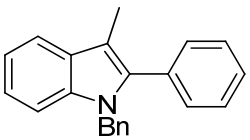
7.08-7.13 (m, 2H), 7.19-7.28 (m, 4H), 7.56-7.59 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.22, 14.11, 22.71, 24.48, 29.27, 31.00, 31.82, 46.43, 108.86, 112.49, 118.19, 118.75, 120.60, 125.92, 127.10, 128.07, 128.67, 132.32, 136.45, 138.28; HRMS (ESI) m/z calcd for $C_{22}H_{28}N$ $[M+H]^+$ = 306.2216, found = 306.2229.

1,3-Dibenzyl-2-ethyl-1*H*-indole **4d**



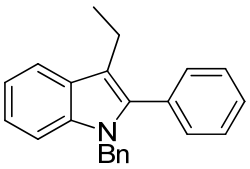
A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (t, *J* = 7.6 Hz, 3H), 2.78 (dd, *J* = 7.6 Hz, 15.1 Hz, 2H), 4.20 (s, 2H), 5.39 (s, 2H), 7.01 (d, *J* = 7.6 Hz, 2H), 7.06-7.14 (m, 2H), 7.18-7.22 (m, 2H), 7.24-7.32 (m, 7H), 7.48 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.68, 17.95, 30.29, 46.52, 109.29, 109.84, 118.61, 119.18, 120.96, 125.63, 125.84, 127.16, 128.22, 128.24, 128.34, 128.69, 136.57, 138.22, 139.33, 141.86; HRMS (ESI) m/z calcd for $C_{24}H_{24}N$ $[M+H]^+$ = 326.1903, found = 326.1916.

1-Benzyl-3-methyl-2-phenyl-1*H*-indole **4e**



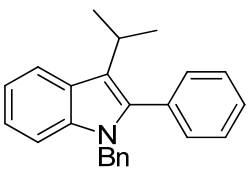
A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 3H), 5.25 (s, 2H), 6.97 (d, *J* = 7.0 Hz, 2H), 7.16-7.26 (m, 6H), 7.34-7.35 (m, 2H), 7.38-7.43 (m, 3H), 7.64-7.67 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.42, 47.57, 109.14, 110.16, 118.85, 119.37, 121.91, 126.05, 126.97, 127.87, 128.33, 128.54, 128.84, 130.54, 132.02, 136.82, 137.77, 138.49; HRMS (ESI) m/z calcd for $C_{22}H_{20}N$ $[M+H]^+$ = 298.1590, found = 298.1596.

1-Benzyl-3-ethyl-2-phenyl-1*H*-indole **4f**



A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30-1.33 (m, 3H), 2.78-2.83 (m, 2H), 5.25 (s, 2H), 6.98 (d, *J* = 6.9 Hz, 2H), 7.20-7.28 (m, 5H), 7.36-7.44 (m, 5H), 7.74 (d, *J* = 3.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.98, 17.98, 47.47, 110.28, 115.90, 119.09, 119.28, 121.76, 126.06, 126.94, 127.83, 127.99, 128.29, 128.51, 130.53, 132.08, 136.84, 137.37, 138.47; HRMS (ESI) m/z calcd for $C_{23}H_{22}N$ $[M+H]^+$ = 312.1747, found = 312.1754.

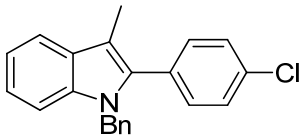
1-Benzyl-3-isopropyl-2-phenyl-1*H*-indole **4g**



A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 3H), 1.47 (s, 3H), 3.10-3.18 (m, 1H), 5.19 (s, 2H), 6.96 (d, *J* = 7.0 Hz, 2H), 7.16-7.20 (m, 2H), 7.23-7.27 (m, 4H), 7.33-7.35 (m, 2H), 7.41-7.43 (m, 3H), 7.89 (dd, *J* = 1.9 Hz, 6.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.44, 26.39, 47.38, 110.40, 118.94, 119.88, 120.51, 121.45, 126.07, 126.49, 126.93, 128.09,

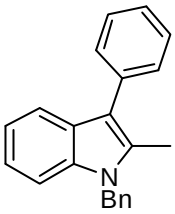
128.18, 128.49, 130.83, 132.42, 136.63, 137.04, 138.45; HRMS (ESI) m/z calcd for $C_{24}H_{24}N$ $[M+H]^+$ = 326.1903, found = 326.1916.

1-Benzyl-2-(4-chlorophenyl)-3-methyl-1*H*-indole **4h**



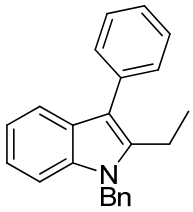
A white foam; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 3H), 5.23 (s, 2H), 6.95 (d, *J* = 8.2 Hz, 2H), 7.17-7.26 (m, 8H), 7.37-7.39 (m, 2H), 7.65 (dd, *J* = 2.6 Hz, 6.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.42, 47.58, 109.68, 110.17, 119.00, 119.58, 122.27, 125.99, 127.15, 128.67, 128.74, 130.51, 131.80, 134.04, 136.45, 137.02, 138.33; HRMS (ESI) m/z calcd for $C_{22}H_{19}NCl$ $[M+H]^+$ = 332.1201, found = 332.1204.

1-Benzyl-2-methyl-3-phenyl-1*H*-indole **4i**



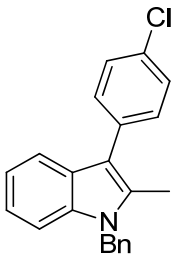
A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (s, 3H), 5.41 (s, 2H), 7.07 (d, *J* = 7.6 Hz, 2H), 7.15-7.22 (m, 2H), 7.27-7.36 (m, 5H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 2H), 7.75 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.05, 46.66, 109.16, 114.68, 118.82, 119.87, 121.39, 125.76, 126.03, 127.25, 127.30, 128.44, 128.79, 129.75, 133.18, 135.62, 136.53, 137.70; HRMS (ESI) m/z calcd for $C_{22}H_{20}N$ $[M+H]^+$ = 298.1590, found = 298.1596.

1-Benzyl-2-ethyl-3-phenyl-1*H*-indole **4j**



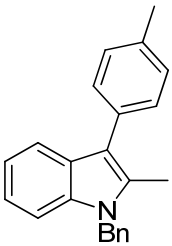
A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.6 Hz, 3H), 2.87 (q, *J* = 7.6 Hz, 2H), 5.45 (s, 2H), 7.06 (d, *J* = 7.0 Hz, 2H), 7.14-7.20 (m, 2H), 7.23-7.38 (m, 5H), 7.51 (t, *J* = 7.9 Hz, 2H), 7.57 (t, *J* = 4.1 Hz, 2H), 7.71 (dd, *J* = 1.6 Hz, 6.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.24, 18.14, 46.65, 109.53, 114.40, 119.01, 119.88, 121.47, 125.88, 125.92, 127.24, 127.55, 128.45, 128.74, 129.73, 135.71, 136.53, 137.88, 138.95; HRMS (ESI) m/z calcd for $C_{23}H_{22}N$ $[M+H]^+$ = 312.1747, found = 312.1754.

1-benzyl-3-(4-chlorophenyl)-2-methyl-1*H*-indole **4k**



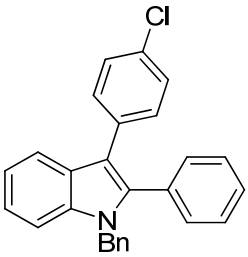
A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (s, 3H), 5.40 (s, 2H), 7.06 (d, *J* = 7.0 Hz, 2H), 7.15-7.22 (m, 2H), 7.27-7.33 (m, 4H), 7.45-7.49 (m, 4H), 7.68 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.01, 46.70, 109.28, 113.56, 118.54, 120.07, 121.60, 126.02, 127.02, 127.38, 128.63, 128.82, 130.94, 131.51, 133.34, 134.11, 136.54, 137.53; HRMS (ESI) m/z calcd for $C_{22}H_{19}NCl$ $[M+H]^+$ = 332.1201, found = 332.1204.

1-Benzyl-2-methyl-3-(p-tolyl)-1*H*-indole **4l**



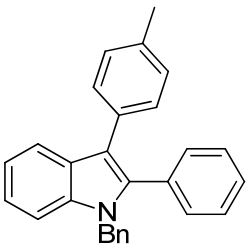
A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49 (s, 3H), 2.50 (s, 3H), 5.45 (s, 2H), 7.11 (d, *J* = 11.8 Hz, 2H), 7.17-7.24 (m, 2H), 7.26-7.38 (m, 6H), 7.50 (d, *J* = 13.5 Hz, 2H), 7.76-7.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.02, 21.19, 46.64, 109.11, 114.54, 118.86, 119.77, 121.30, 126.03, 127.27, 127.35, 128.77, 129.17, 129.62, 132.57, 132.99, 135.30, 136.51, 137.77; HRMS (ESI) m/z calcd for $C_{23}H_{22}N$ $[M+H]^+$ = 312.1747, found = 312.1753.

1-Benzyl-3-(4-chlorophenyl)-2-phenyl-1*H*-indole **4m**



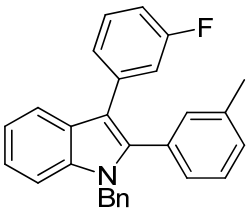
A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.31 (s, 2H), 7.02 (d, *J* = 7.0 Hz, 2H), 7.20-7.35 (m, 15H), 7.79 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.62, 110.62, 114.48, 119.40, 120.61, 122.54, 126.10, 127.11, 127.22, 128.37, 128.39, 128.51, 128.68, 131.00, 131.04, 131.31, 131.48, 133.67, 136.96, 137.93, 138.07; HRMS (ESI) m/z calcd for $C_{27}H_{20}NClNa$ $[M+Na]^+$ = 416.1176, found = 416.1195.

1-Benzyl-2-phenyl-3-(p-tolyl)-1*H*-indole **4n**



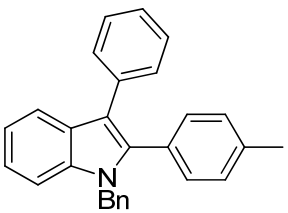
A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H), 5.32 (s, 2H), 7.05 (d, *J* = 7.6 Hz, 2H), 7.13 (d, *J* = 7.6 Hz, 2H), 7.20-7.35 (m, 13H), 7.86 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.15, 47.57, 110.44, 115.56, 119.77, 120.28, 122.27, 126.11, 127.10, 127.45, 128.05, 128.34, 128.63, 128.92, 129.72, 131.06, 131.91, 132.05, 135.04, 136.95, 137.63, 138.14; HRMS (ESI) m/z calcd for $C_{28}H_{24}N$ $[M+H]^+$ = 374.1903, found = 374.1912.

1-Benzyl-3-(3-fluorophenyl)-2-(m-tolyl)-1*H*-indole **4o**



A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.27 (s, 3H), 5.30 (s, 2H), 6.87-6.91 (m, 1H), 7.02-7.10 (m, 5H), 7.13 (d, *J* = 8.2 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.20-7.31 (m, 8H), 7.84-7.86 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.33, 47.61, 110.55, 112.21, 112.38, 114.26, 116.25, 116.43, 119.42, 120.58, 122.43, 125.44, 125.46, 126.14, 127.02, 127.18, 128.09, 128.34, 128.63, 129.20, 129.39, 129.47, 131.26, 131.56, 136.88, 137.51, 137.58, 138.05, 138.47, 161.79, 163.73; HRMS (ESI) m/z calcd for $C_{28}H_{23}NF$ $[M+H]^+$ = 392.1809, found = 392.1815.

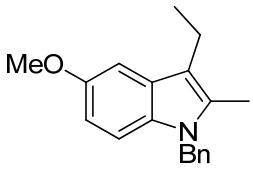
1-Benzyl-3-phenyl-2-(p-tolyl)-1*H*-indole **4p**



A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3H), 5.31 (s, 2H), 7.05 (d, *J* = 7.6 Hz, 2H), 7.11 (d, *J* = 7.6 Hz, 2H), 7.16-7.32 (m, 11H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.84 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.40, 47.62, 110.57, 115.46, 119.69, 120.42, 122.29, 125.57, 126.16, 127.18, 127.48, 128.22, 128.72, 128.77, 129.22, 129.97, 130.96, 135.34, 136.99, 138.03, 138.10, 138.27; HRMS (ESI) m/z calcd for $C_{28}H_{24}N$

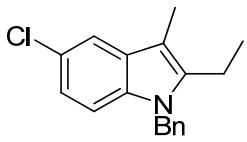
$[M+H]^+$ = 374.1903, found = 374.1912.

1-Benzyl-3-ethyl-5-methoxy-2-methyl-1*H*-indole **4q**



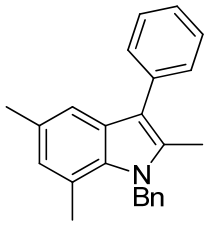
A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.6 Hz, 3H), 2.29 (s, 3H), 2.76 (q, *J* = 7.6 Hz, 2H), 3.89 (s, 3H), 5.27 (s, 2H), 6.77 (dd, *J* = 1.9 Hz, 8.9 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 2H), 7.06-7.10 (m, 2H), 7.21-7.28 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.11, 15.57, 17.71, 46.55, 55.96, 100.63, 109.57, 110.10, 113.59, 125.92, 127.09, 127.97, 128.67, 131.75, 132.68, 138.33, 153.71; HRMS (ESI) m/z calcd for $C_{19}H_{22}NO$ $[M+H]^+$ = 280.1696, found = 280.1705.

1-Benzyl-5-chloro-2-ethyl-3-methyl-1*H*-indole **4r**



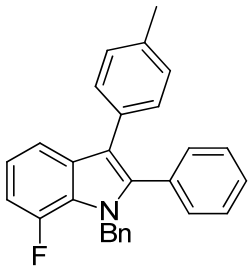
A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (t, *J* = 7.6 Hz, 3H), 2.28 (s, 3H), 2.73 (q, *J* = 7.6 Hz, 2H), 5.31 (s, 2H), 6.94 (d, *J* = 7.0 Hz, 2H), 7.05 (s, 2H), 7.22-7.29 (m, 3H), 7.52 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.60, 14.34, 17.91, 46.59, 106.28, 110.12, 117.62, 120.90, 124.63, 125.77, 127.27, 128.72, 129.82, 134.71, 137.93, 139.88; HRMS (ESI) m/z calcd for $C_{18}H_{19}NCl$ $[M+H]^+$ = 284.1201, found = 284.1210.

1-Benzyl-2,5,7-trimethyl-3-phenyl-1*H*-indole **4s**



A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.42 (s, 3H), 2.56 (s, 3H), 5.63 (s, 2H), 6.77 (s, 1H), 6.96 (d, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.31-7.37 (m, 4H), 7.49-7.55 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.94, 19.62, 21.12, 48.22, 114.80, 116.54, 120.01, 125.15, 125.76, 126.32, 127.05, 128.35, 128.41, 128.86, 129.04, 130.06, 133.46, 133.82, 135.89, 139.49; HRMS (ESI) m/z calcd for $C_{24}H_{24}N$ $[M+H]^+$ = 326.1903, found = 326.1911.

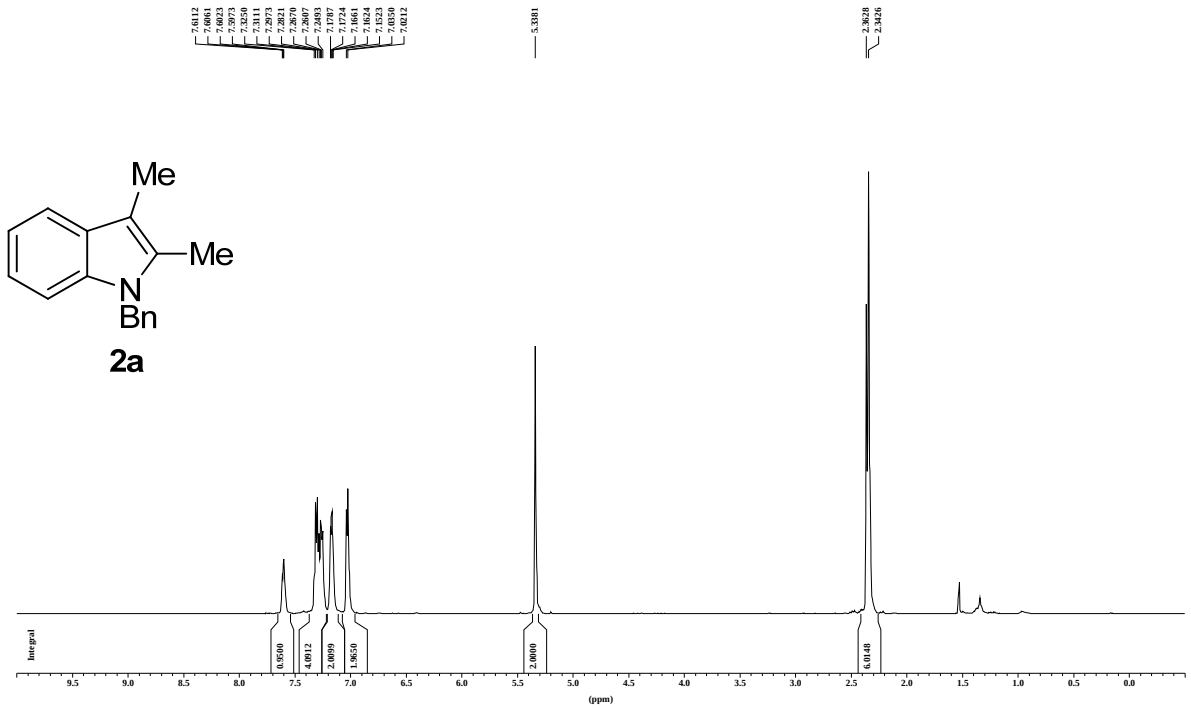
1-Benzyl-7-fluoro-2-phenyl-3-(p-tolyl)-1*H*-indole **4t**



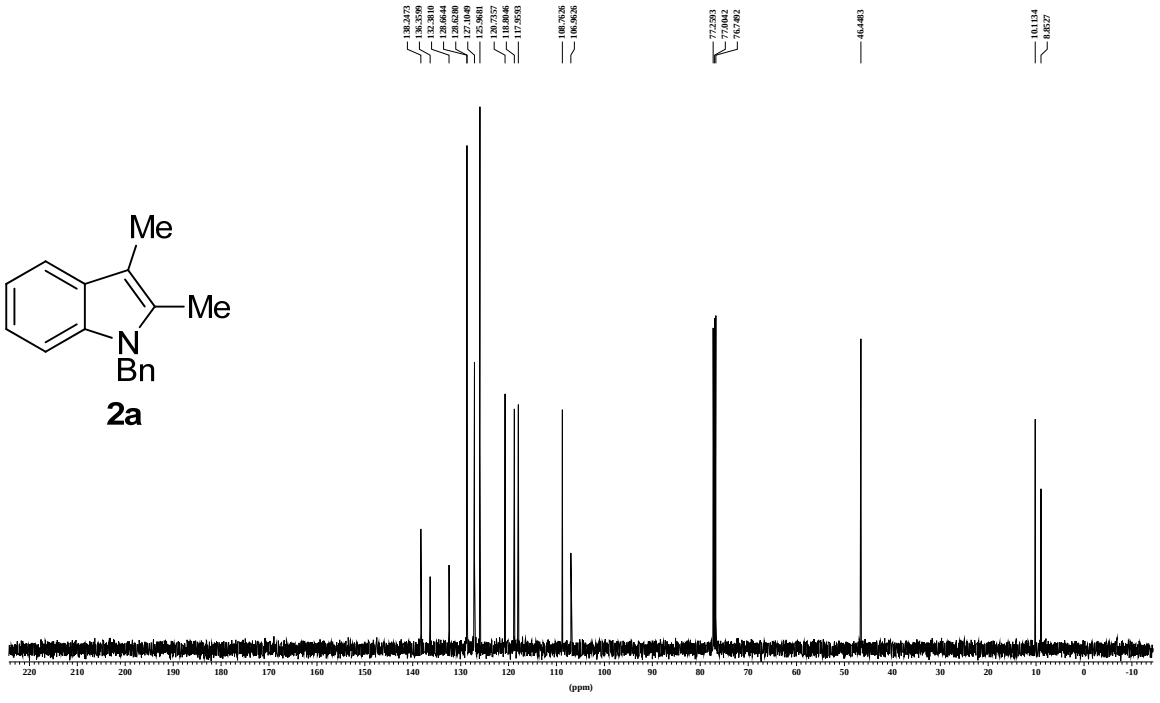
A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 3H), 5.46 (s, 2H), 6.89-6.93 (m, 3H), 7.04-7.11 (m, 3H), 7.20-7.35 (m, 10H), 7.56 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.17, 49.28, 49.33, 108.01, 108.16, 115.54, 115.56, 116.65, 120.30, 120.35, 124.74, 124.81, 126.00, 127.02, 128.32, 128.39, 128.45, 128.96, 129.72, 131.24, 131.28, 131.56, 135.40, 139.00, 139.05, 149.10, 151.05; HRMS (ESI) m/z calcd for $C_{28}H_{23}NF$ $[M+H]^+$ = 392.1809, found = 392.1815.

F. NMR Spectra of the Substrates and Products.

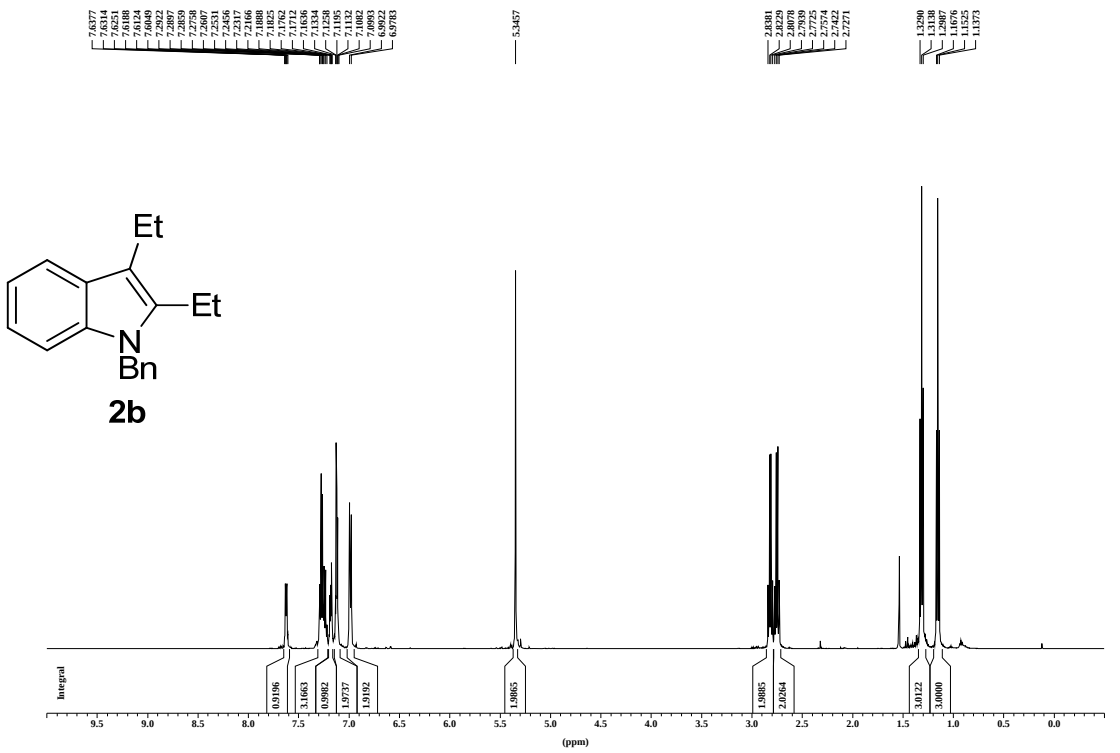
1H AMX500 dxw1023-1 1935-1H



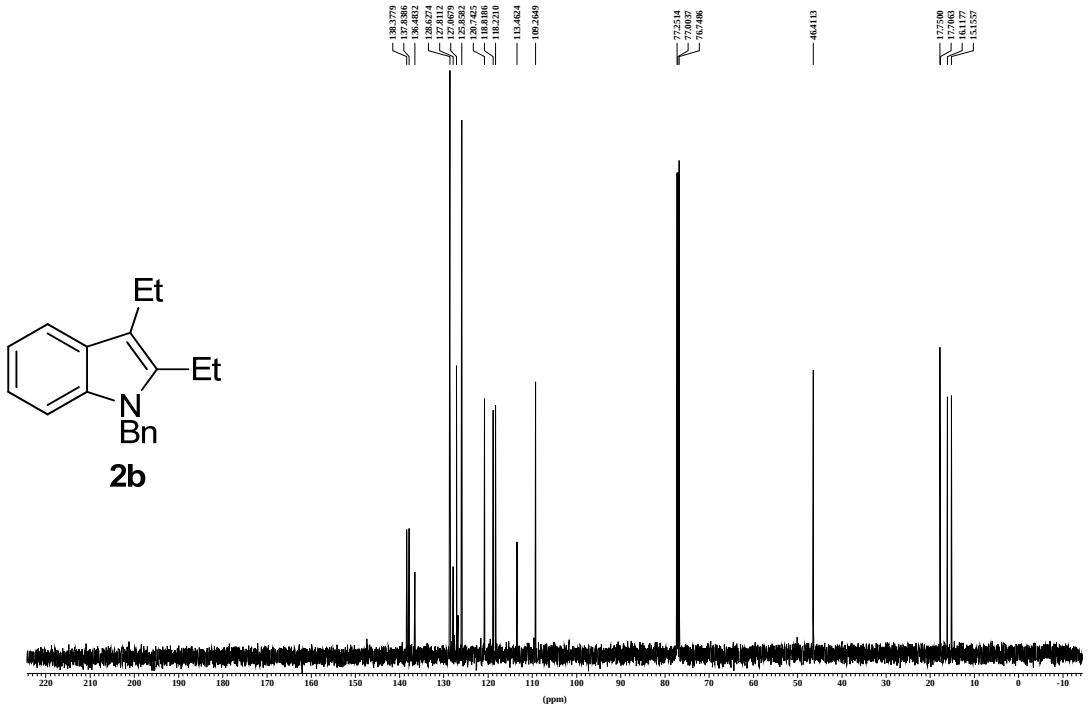
13C AMX500 dxw1023-2 1935-1C



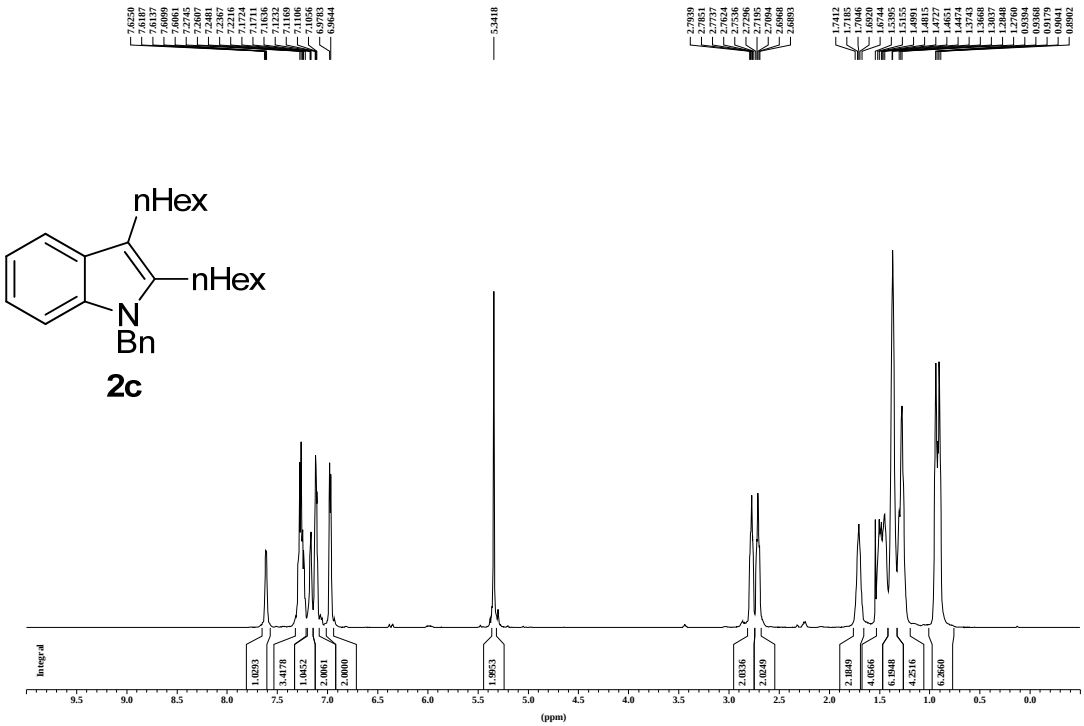
1H AMX500 dxw1031-3 1937H



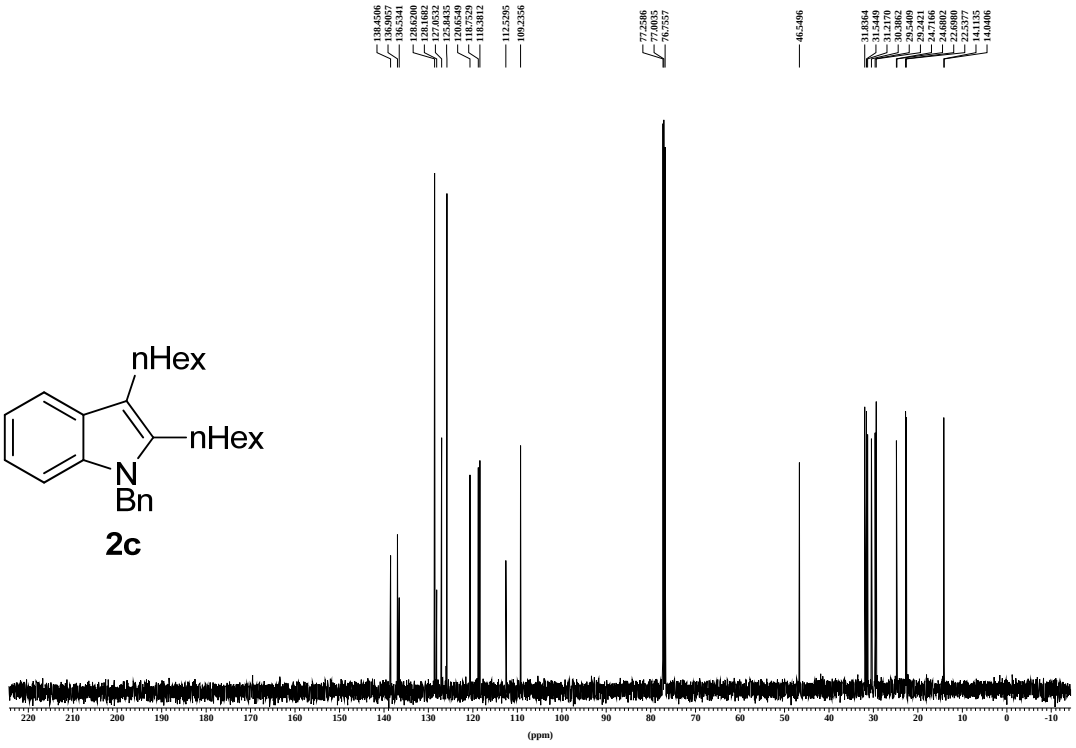
13C AMX500 dxw1029-2 1937C



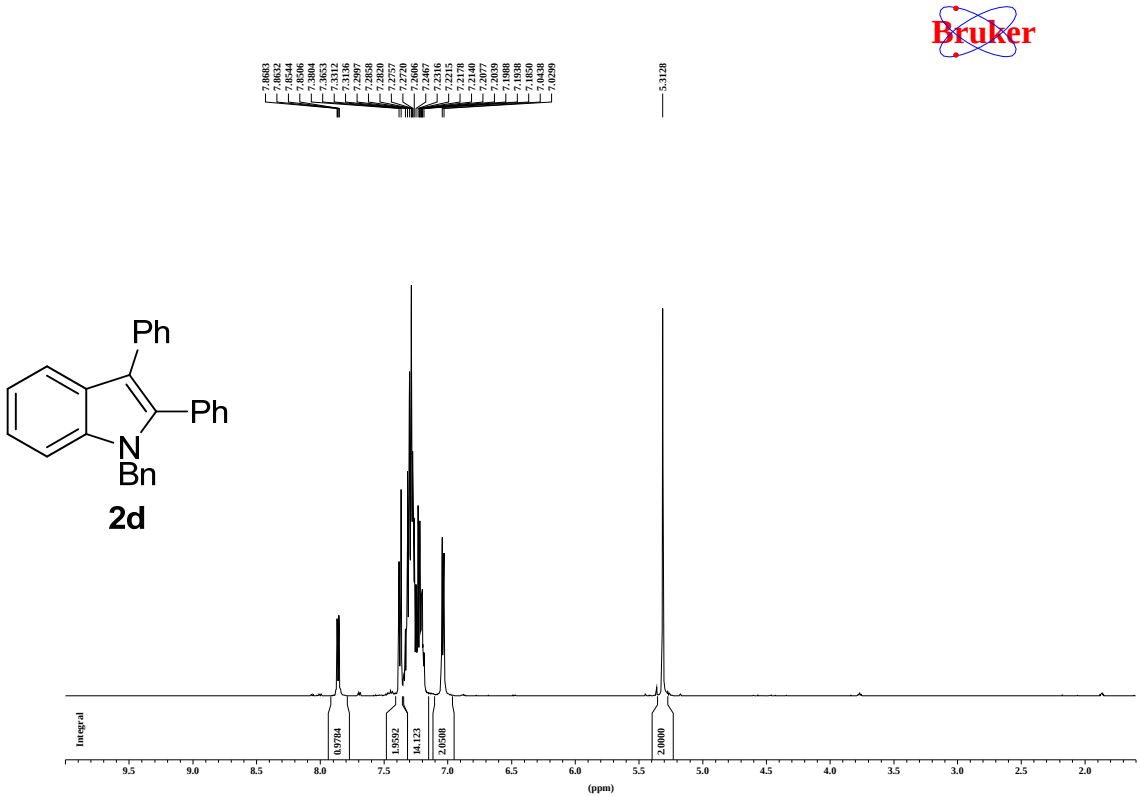
1H AMX500 dxw1030-1 1939H



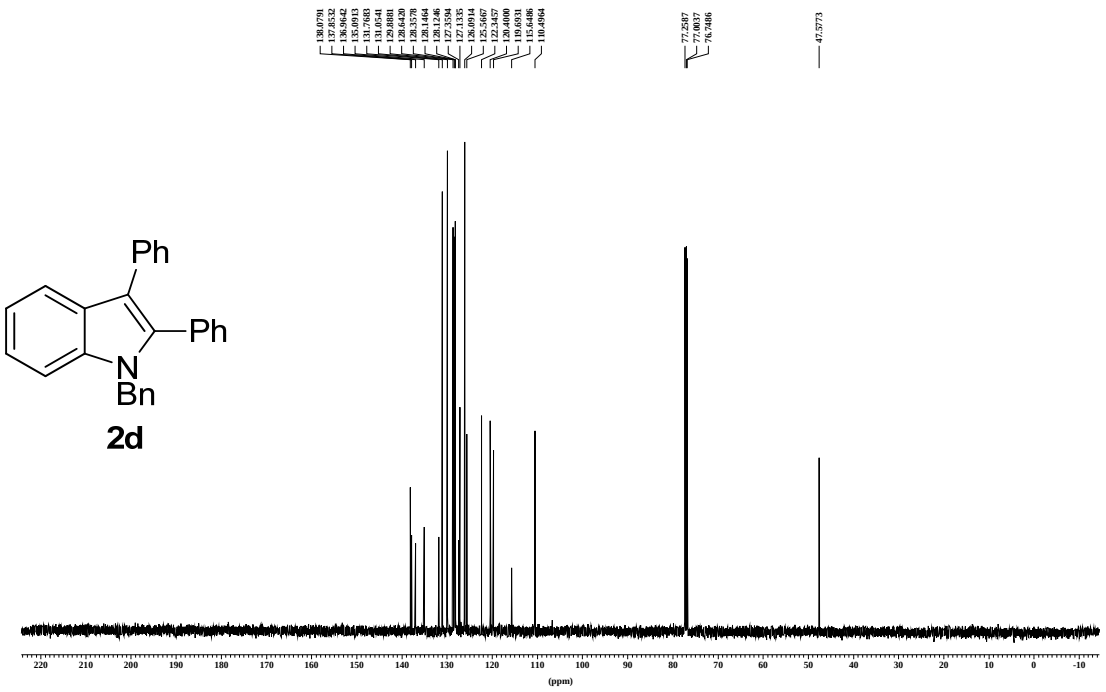
13C AMX500 dxw1030-2 1939C



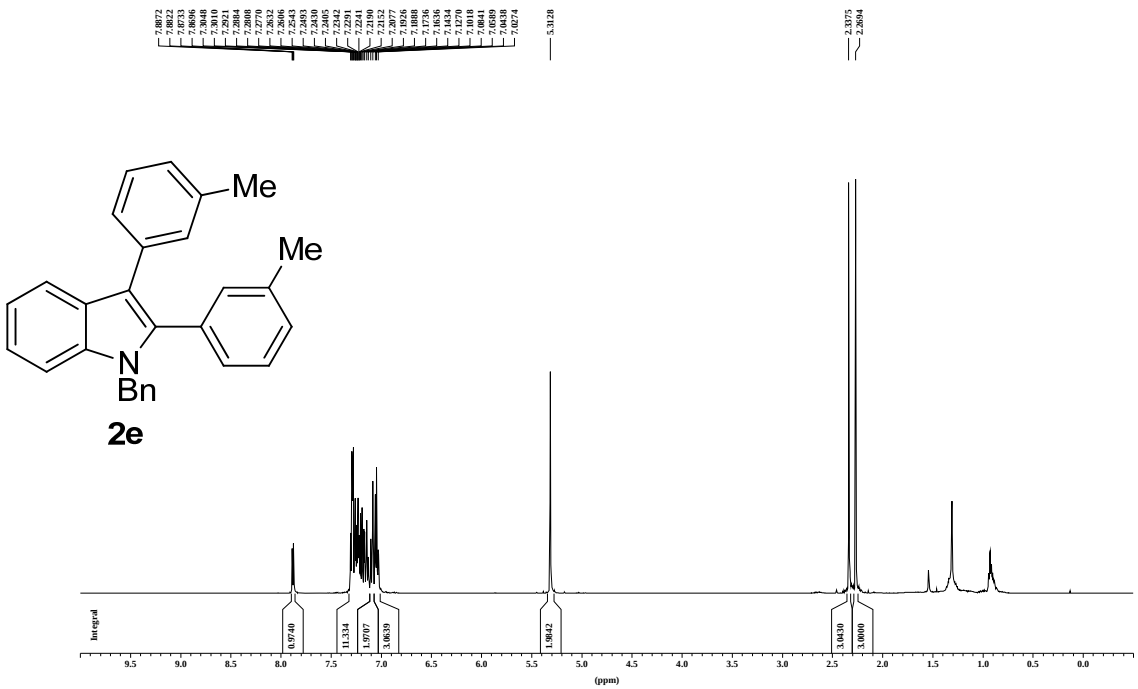
1H AMX500 dxw1101-3 1942H



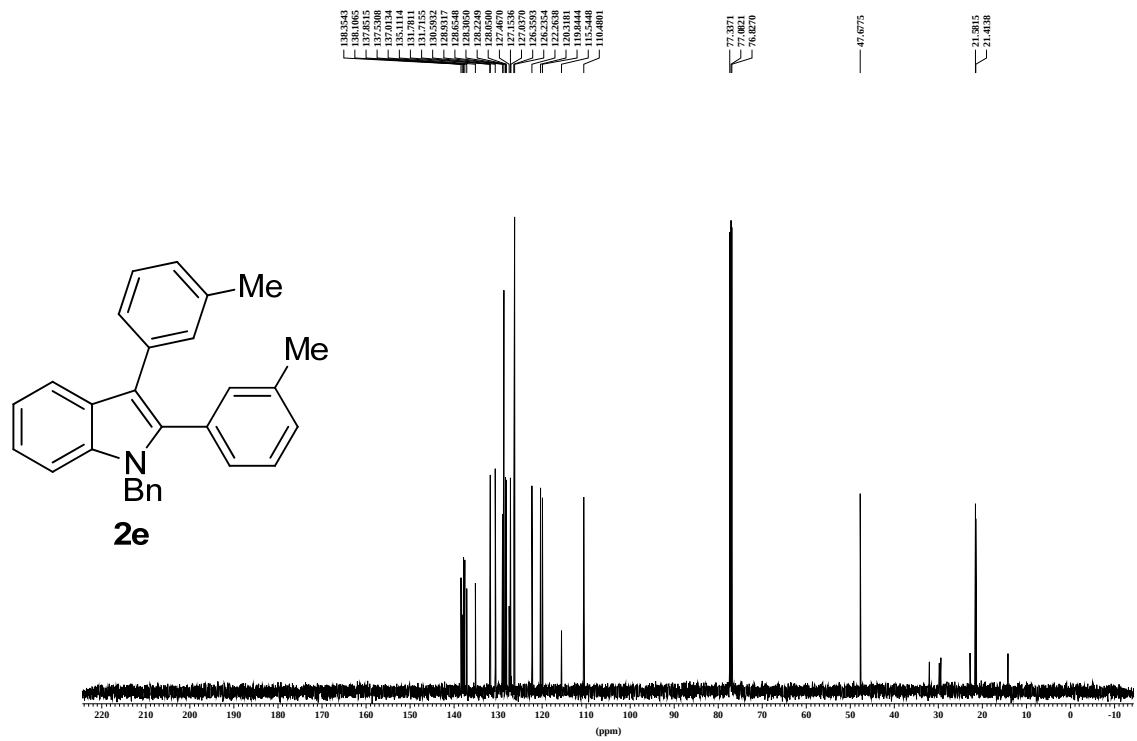
13C AMX500 dxw1101-4 1942C



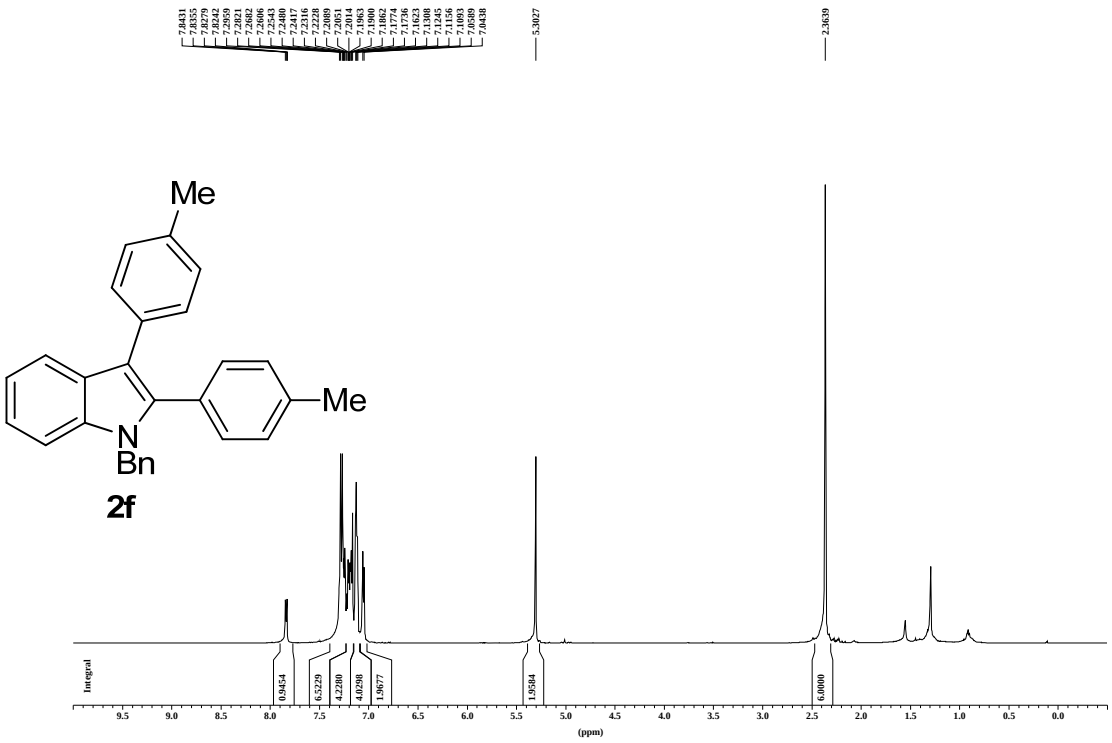
1H AMX500 dxw1227-3 1991H



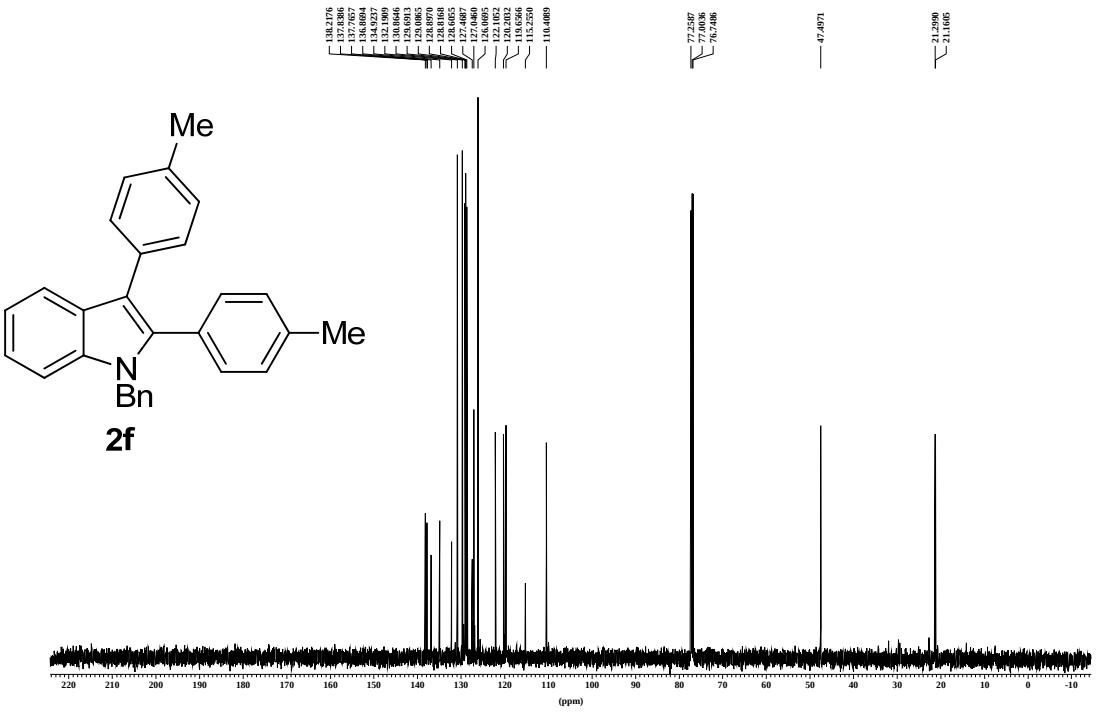
13C AMX500 dxw1227-5 1991C



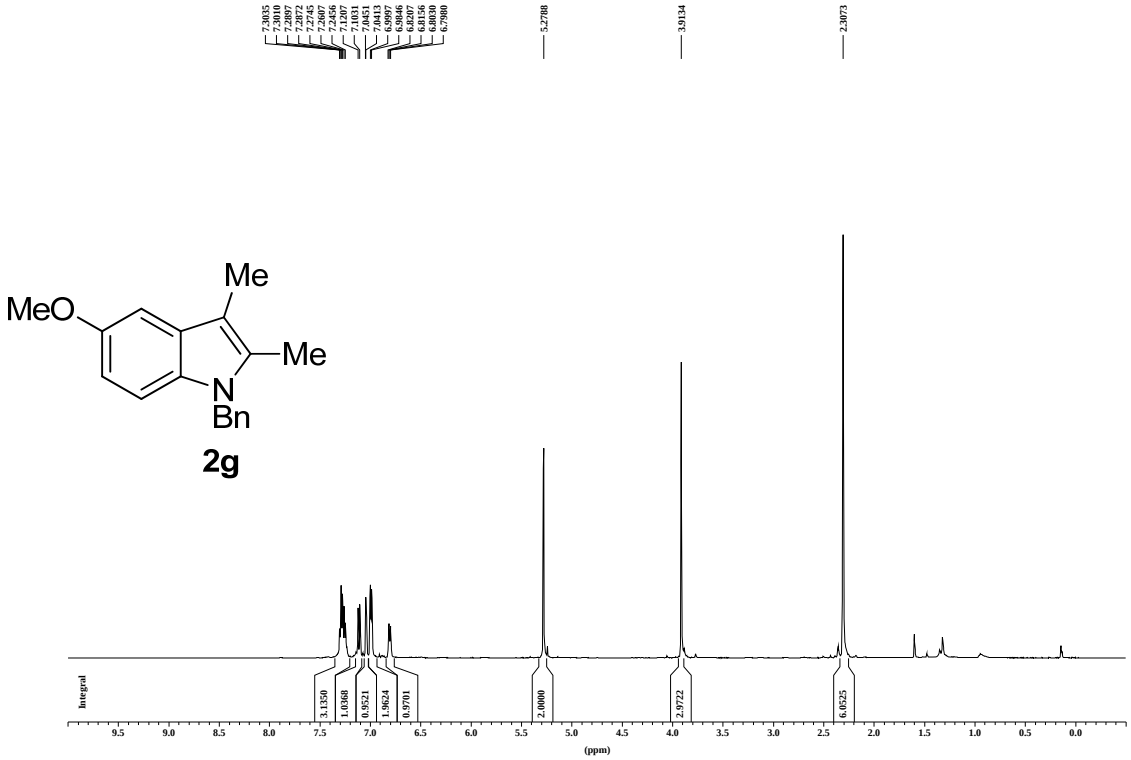
1H AMX500 dxw1220-3 1983H



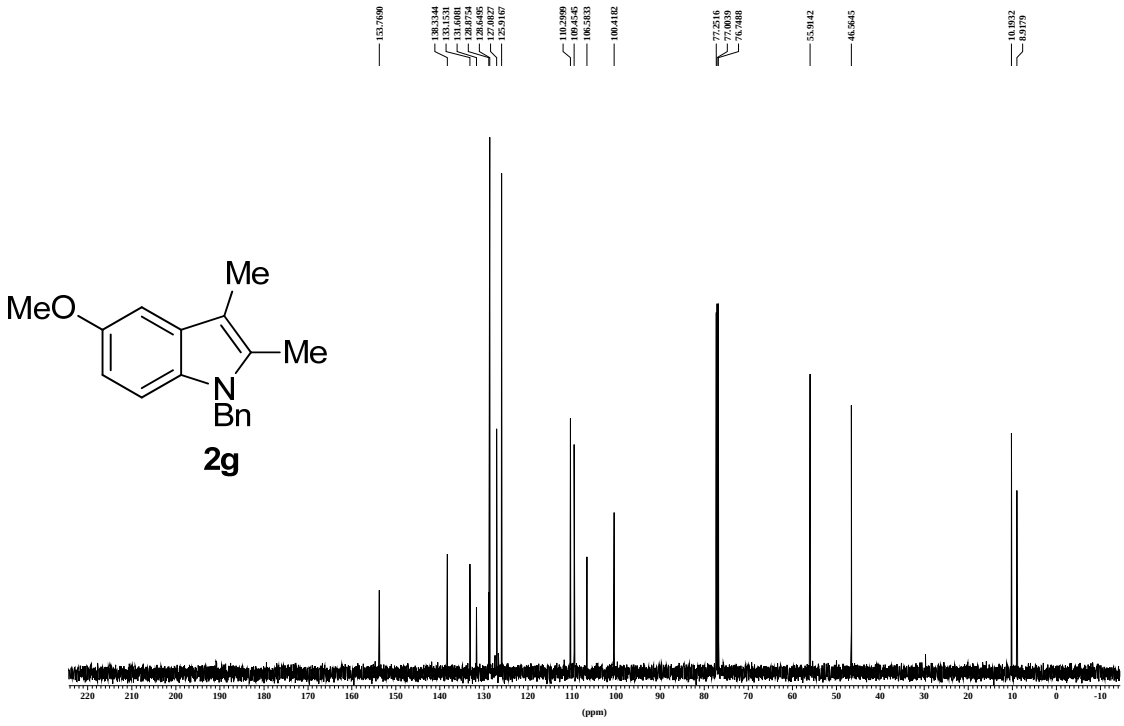
13C AMX500 dxw1226-4 1983C



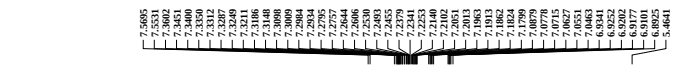
1H AMX500 dxw1105-1 1947H

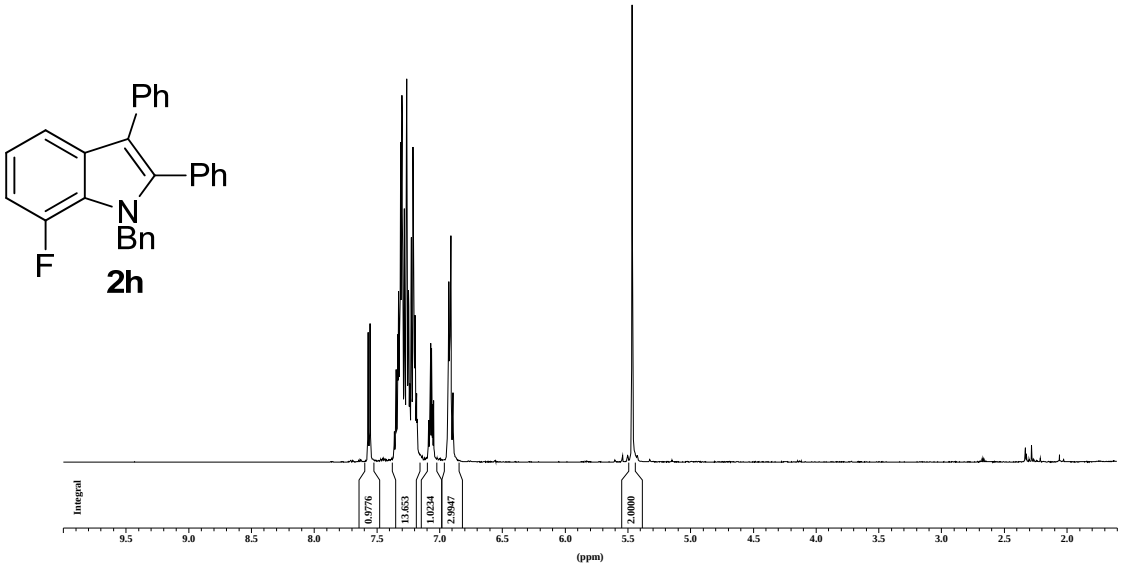


13C AMX500 dxw1105-2 1947C

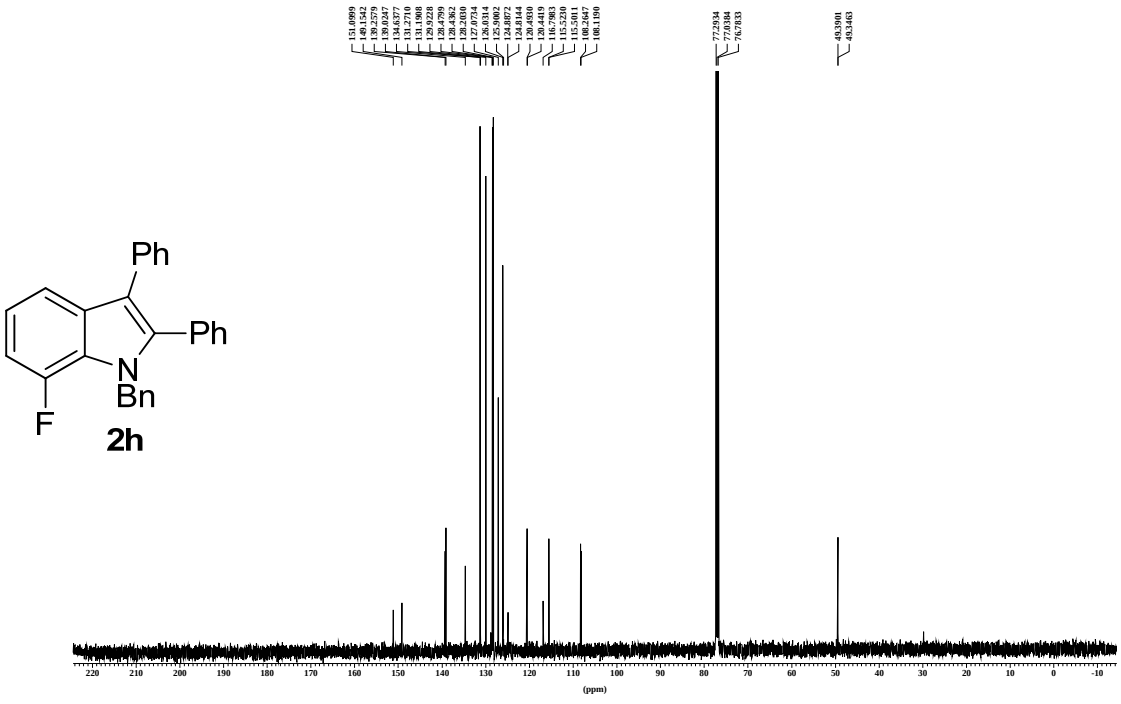


1H AMX500 dxw1204-3 1962H

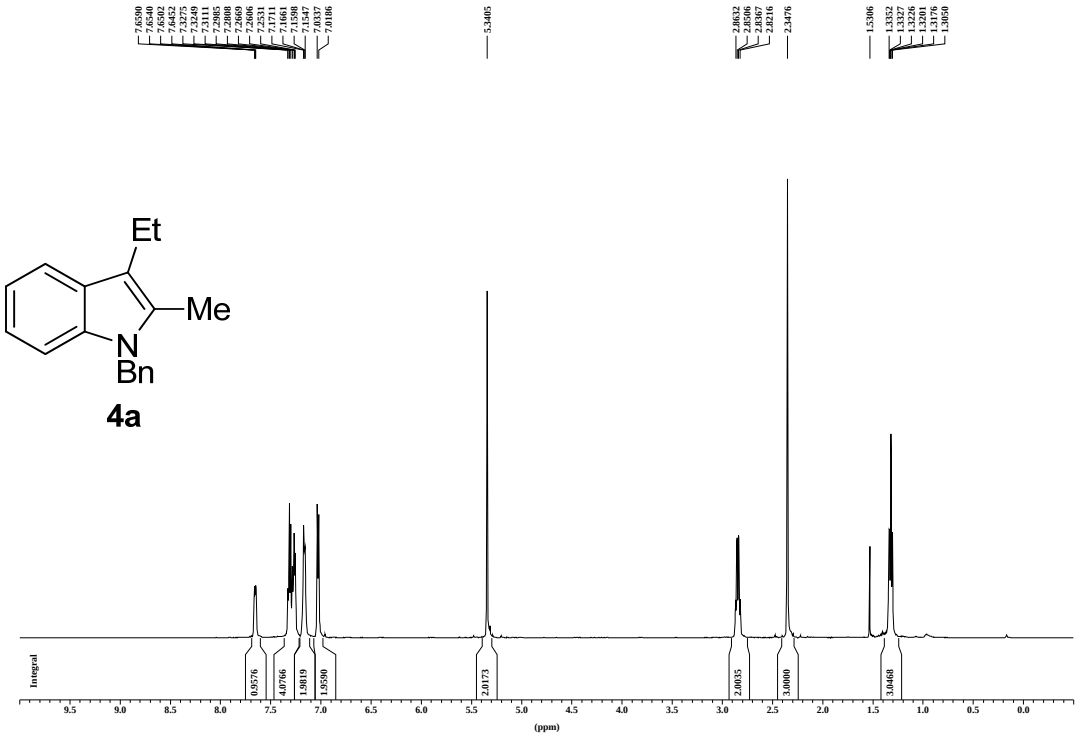




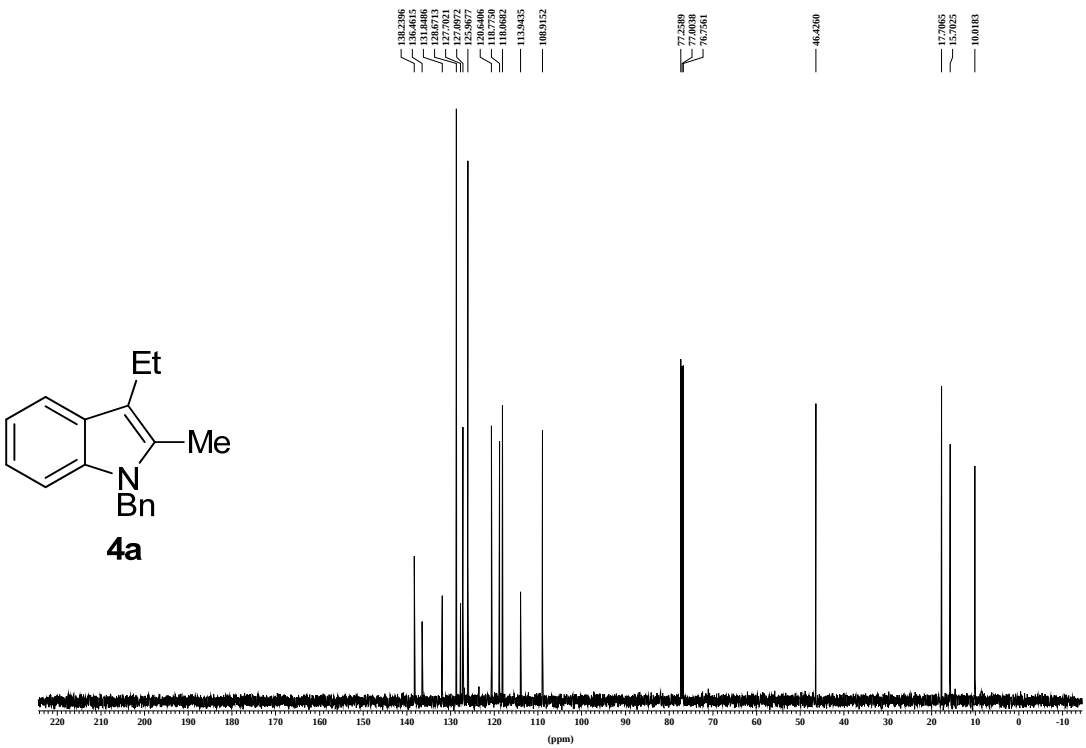
13C AMX500 dxw1204-4 1962C



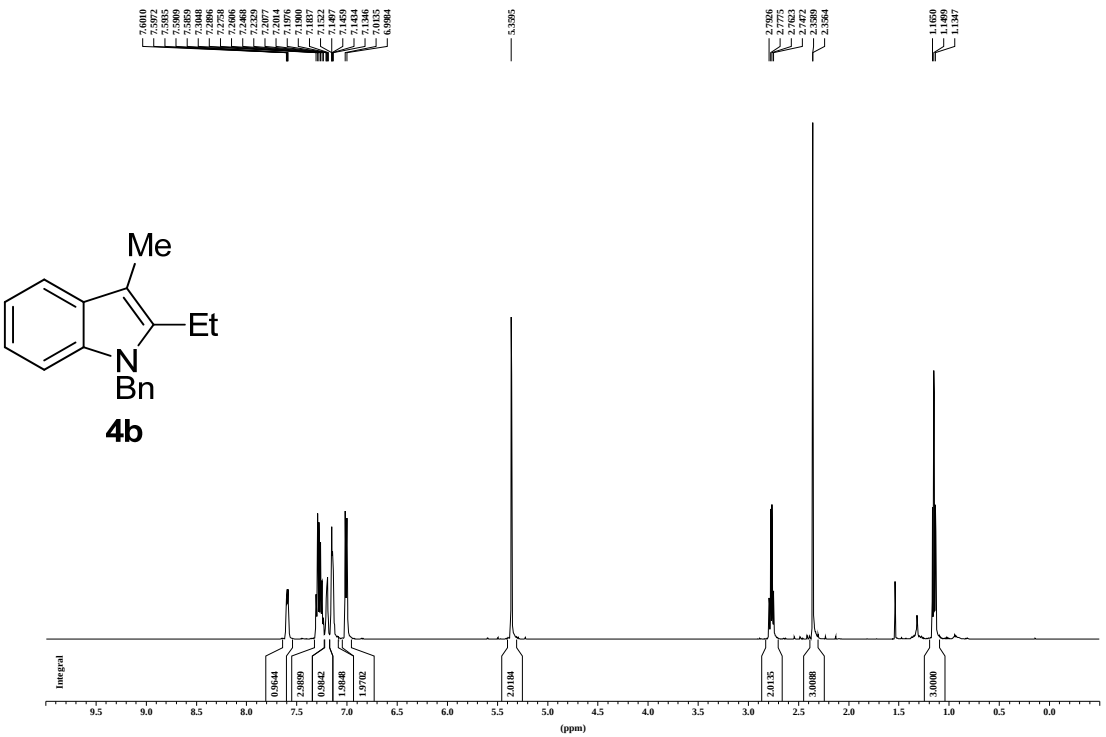
1H AMX500 dxw1104-1 1945H



13C AMX500 dxw1104-2 1945C



1H AMX500 dxw1115-1 1950H



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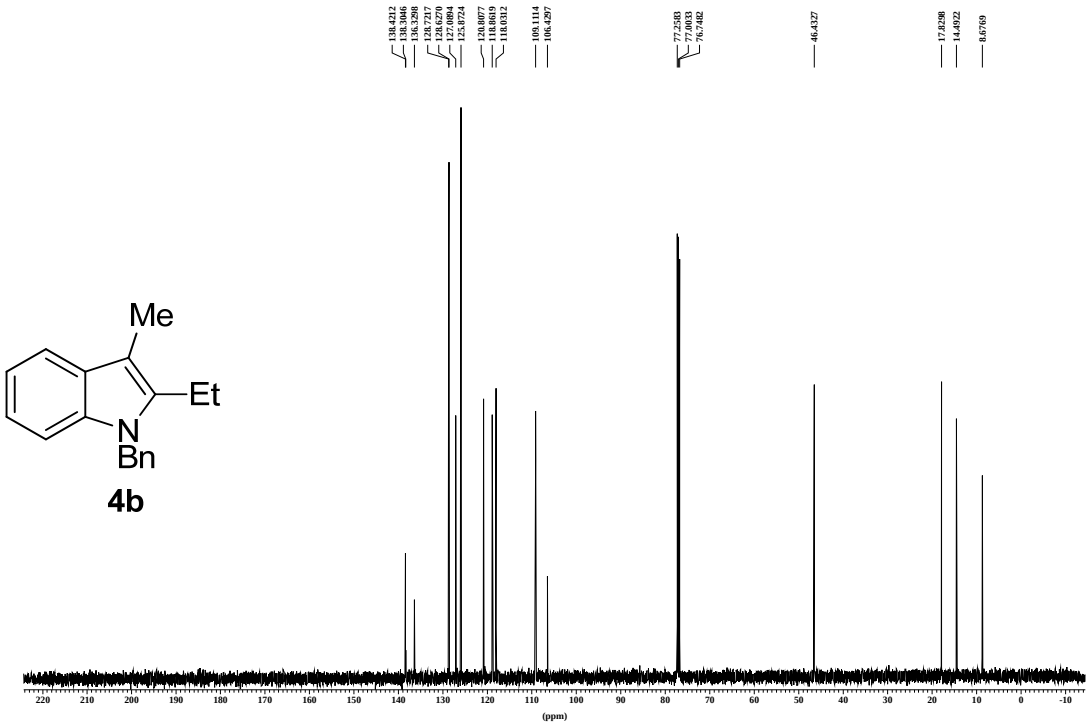

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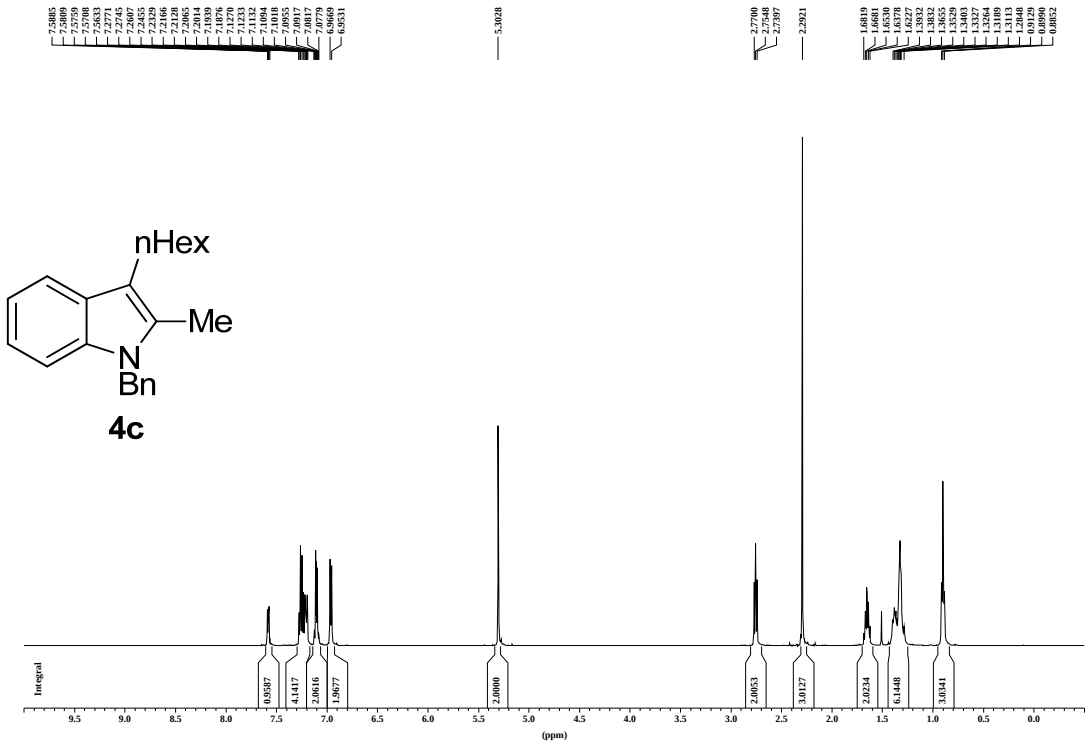
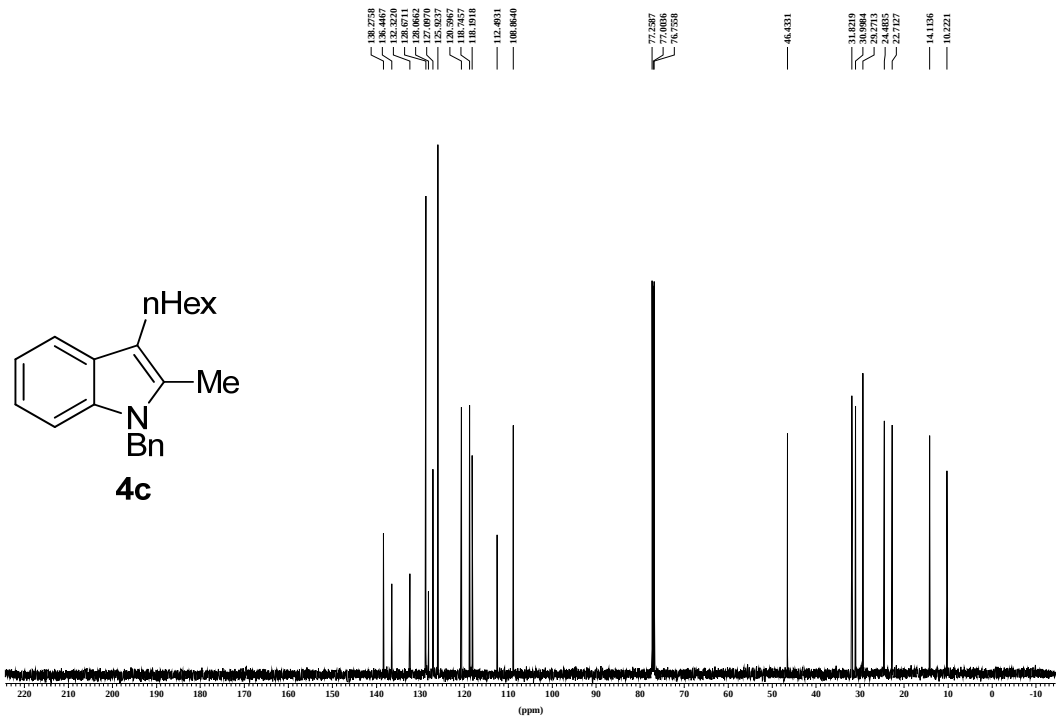
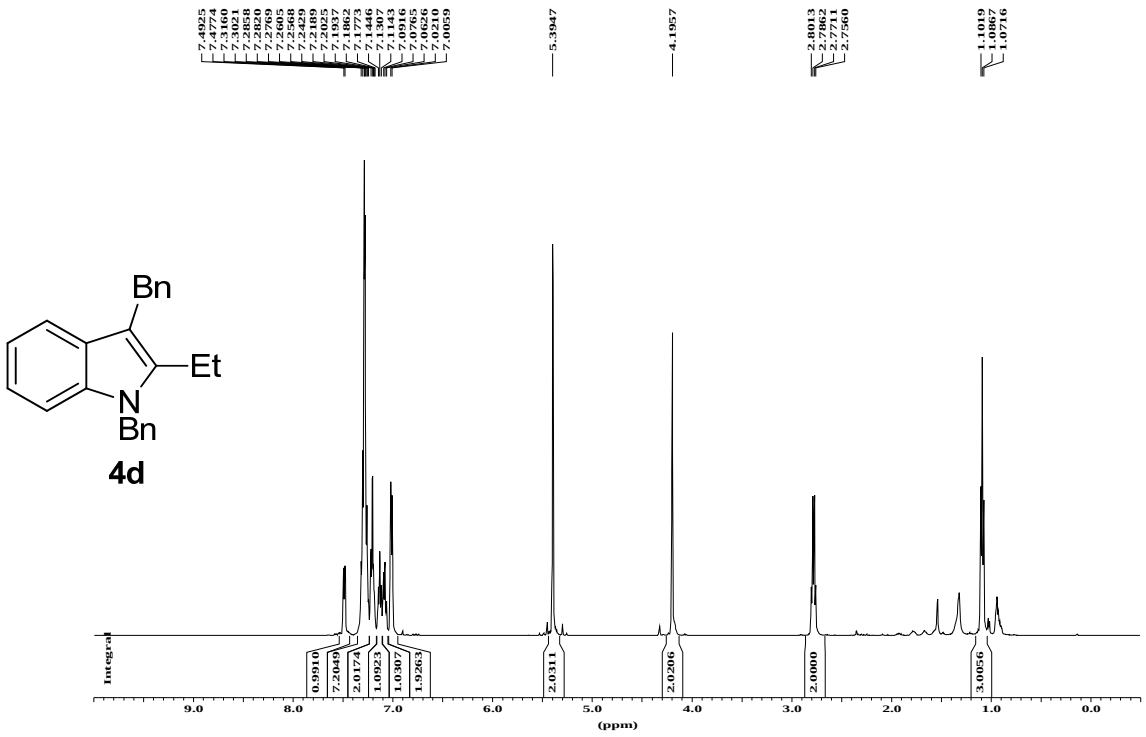


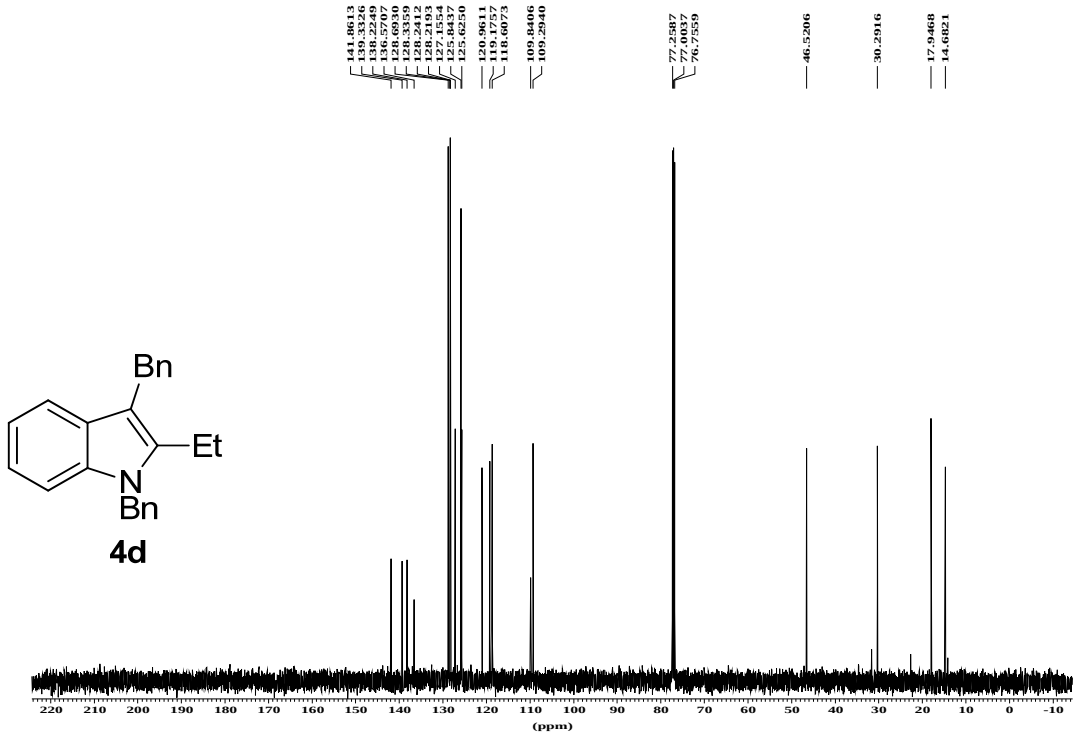
13C AMX500 dxw1114-6 1953C



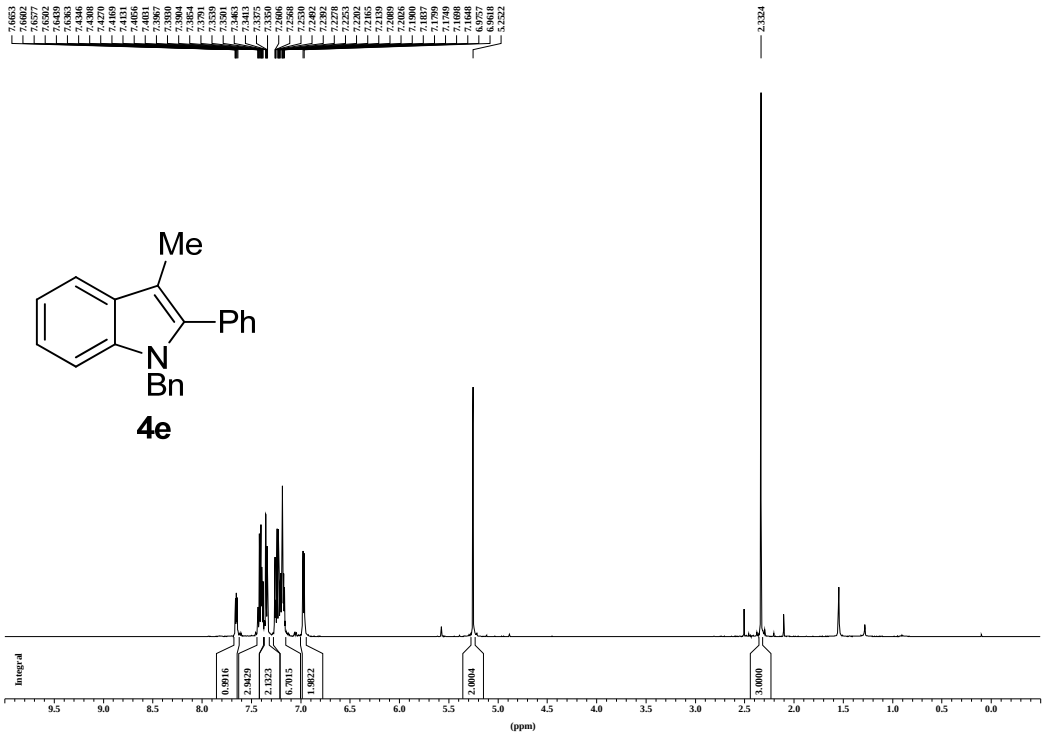
1H AMX500 dxw1216-3 1977H



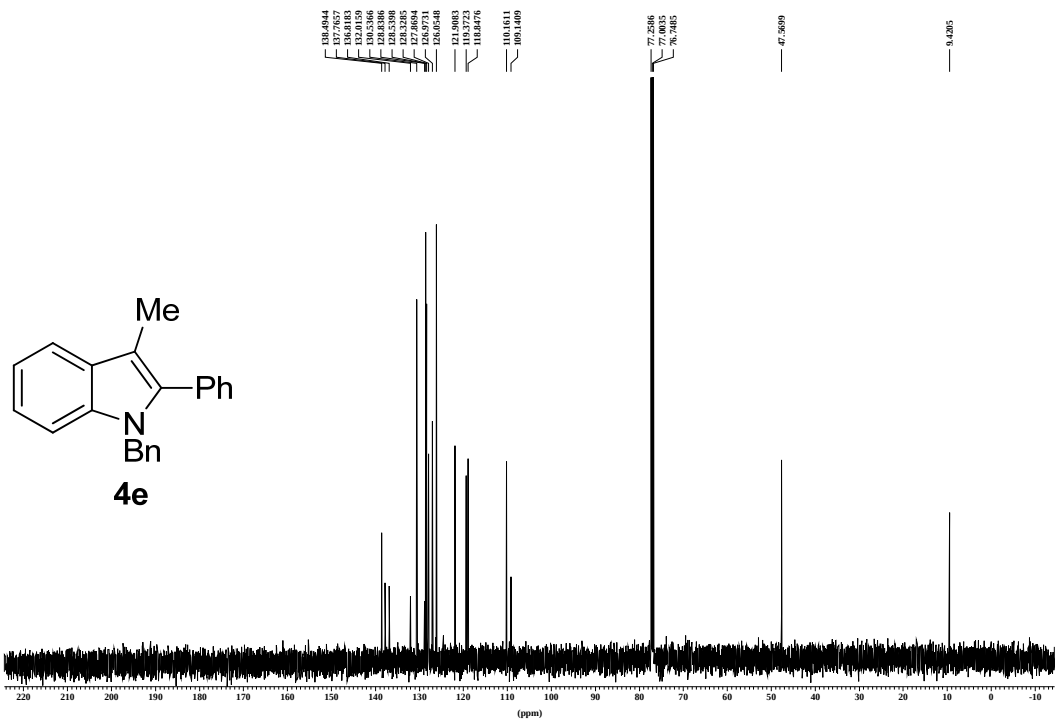
13C AMX500 dxw1216-4 1977C



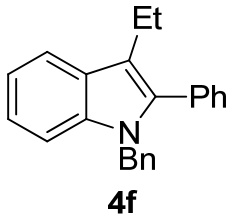
1H AMX500 dxw1213-1 1962H



13C AMX500 dxw1213-2 1962C



1H AMX500 dxw0108-1 1963H



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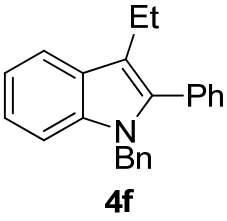
13C AMX500 dxw0108-2 1963C



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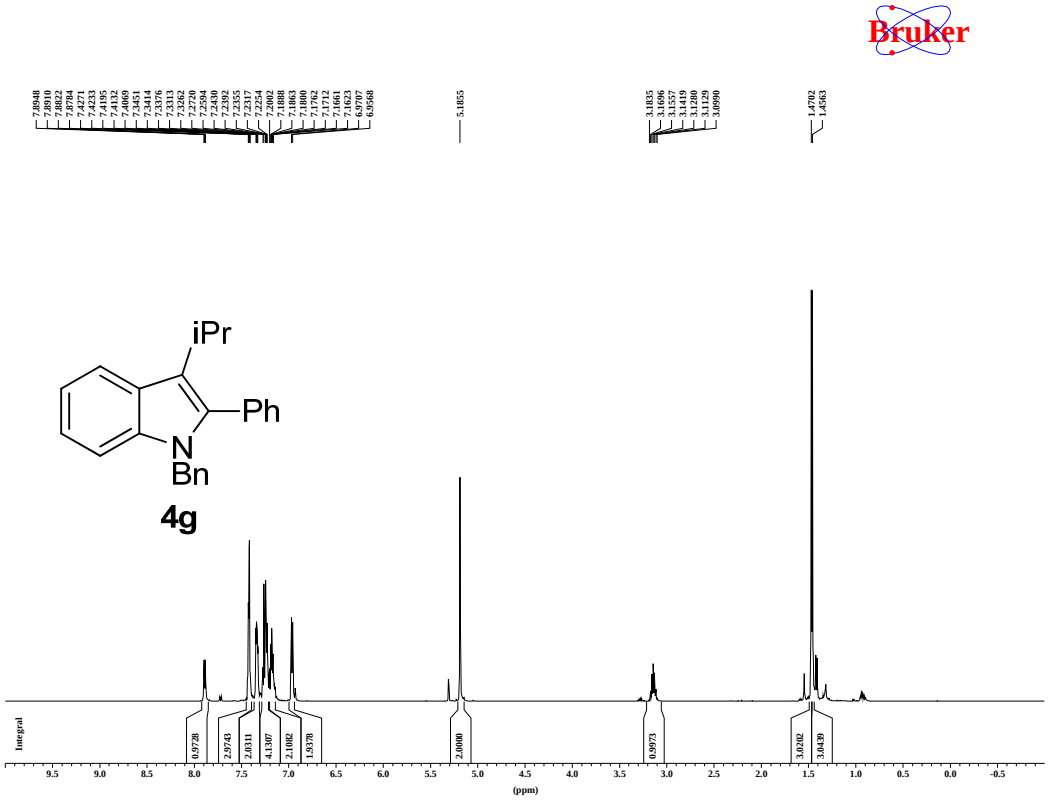
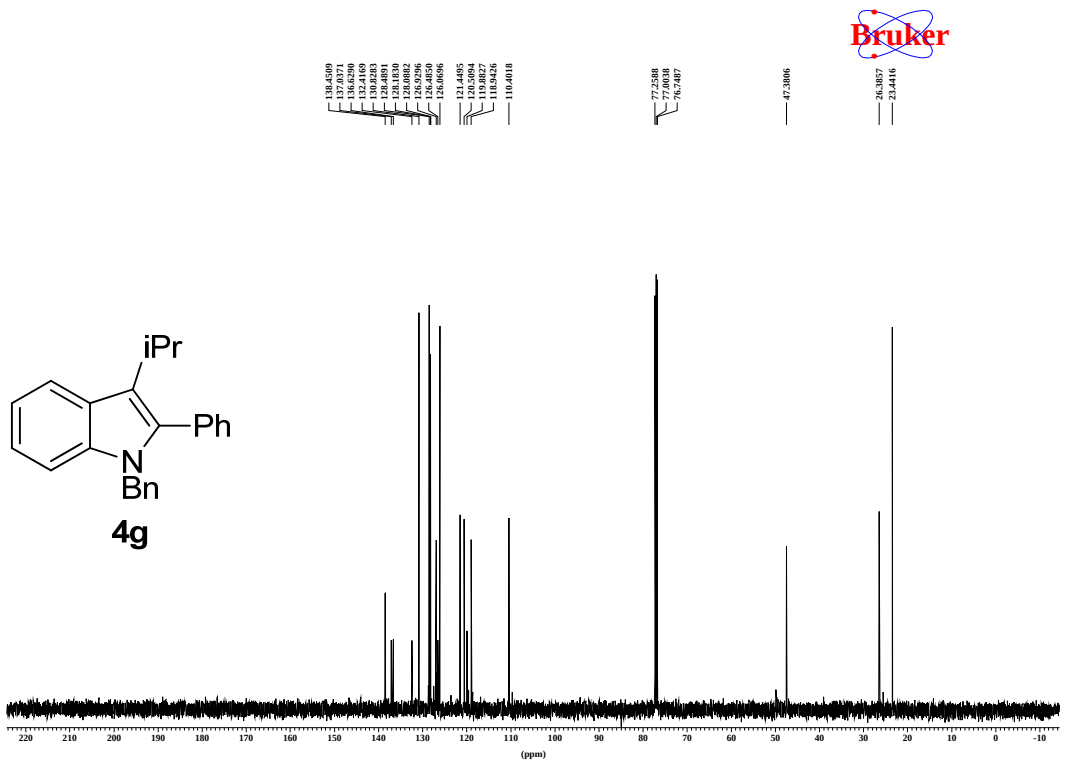
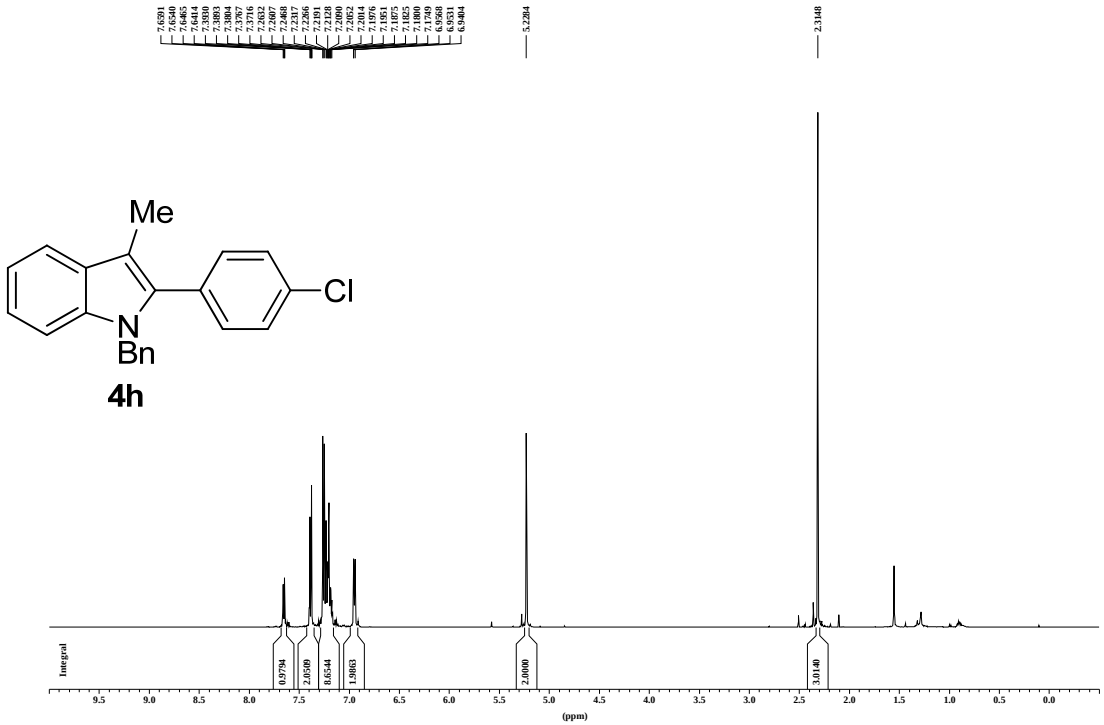
1H AMX500 dxw0108-3 1996H



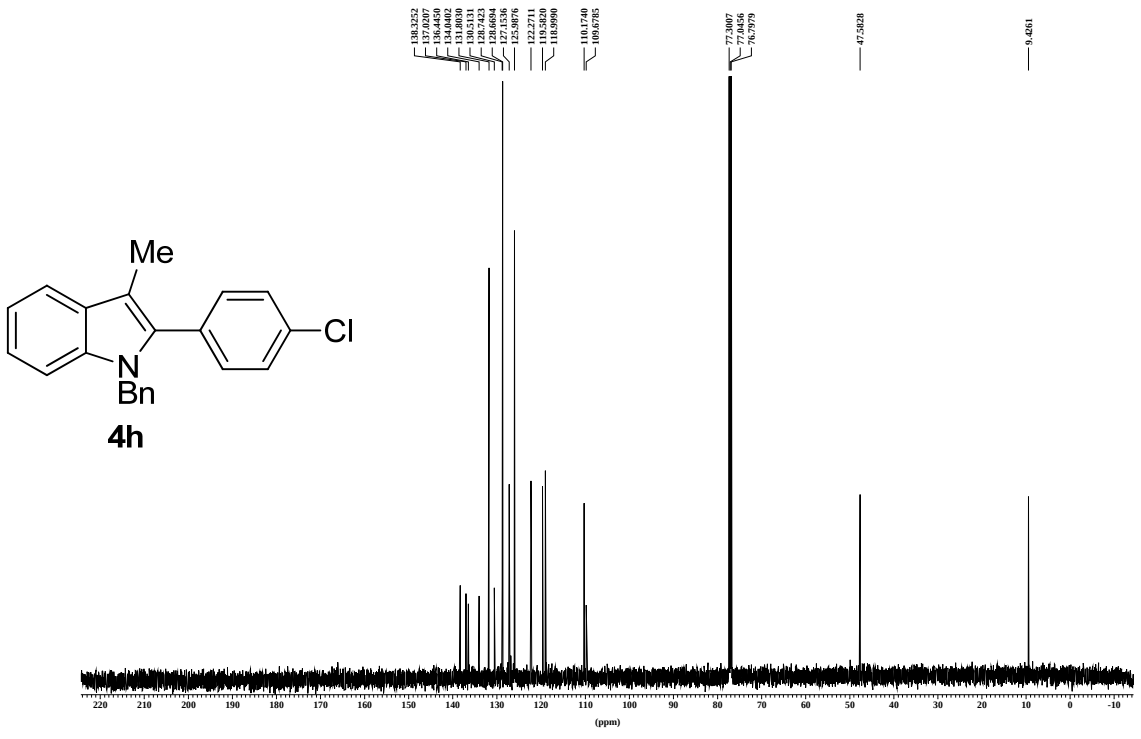
13C AMX500 dxw0108-4 1996C



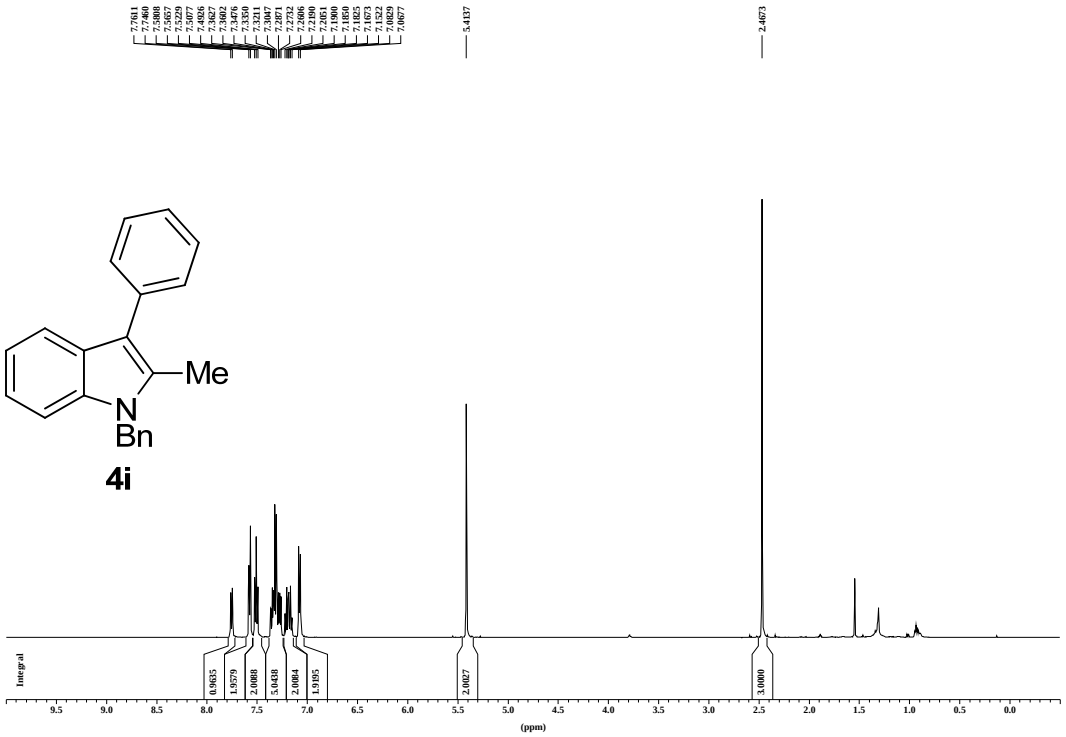
1H AMX500 dxw0103-3 1974H



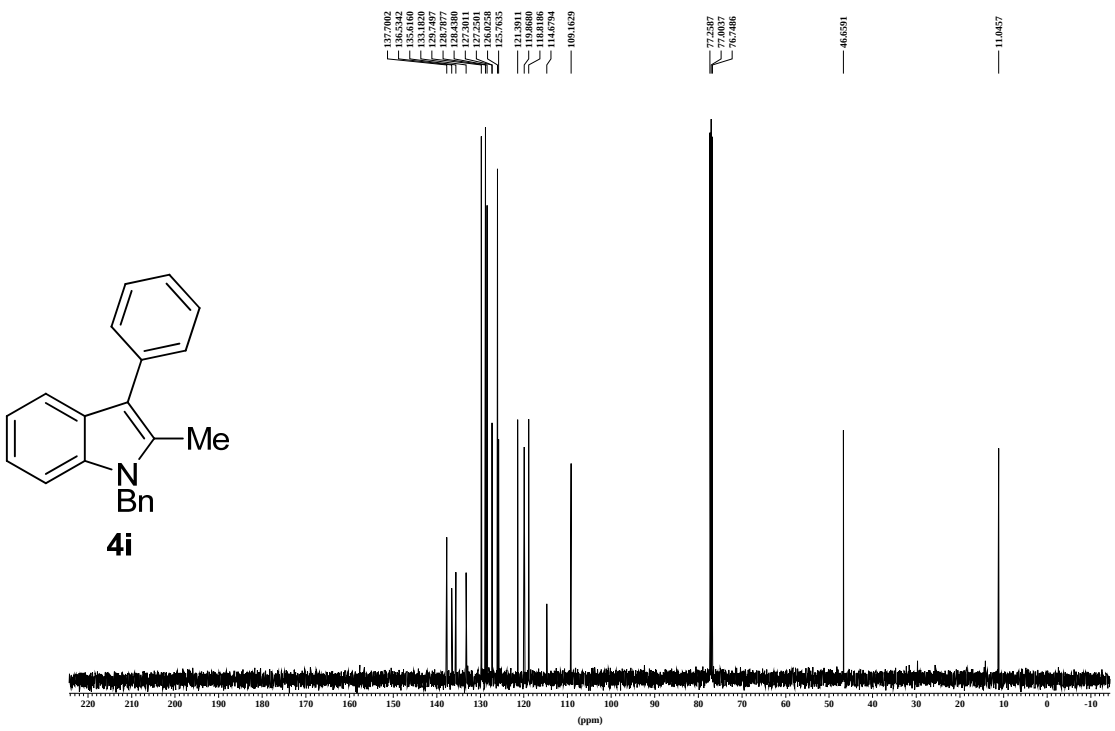
13C AMX500 dxw0103-2 1974C



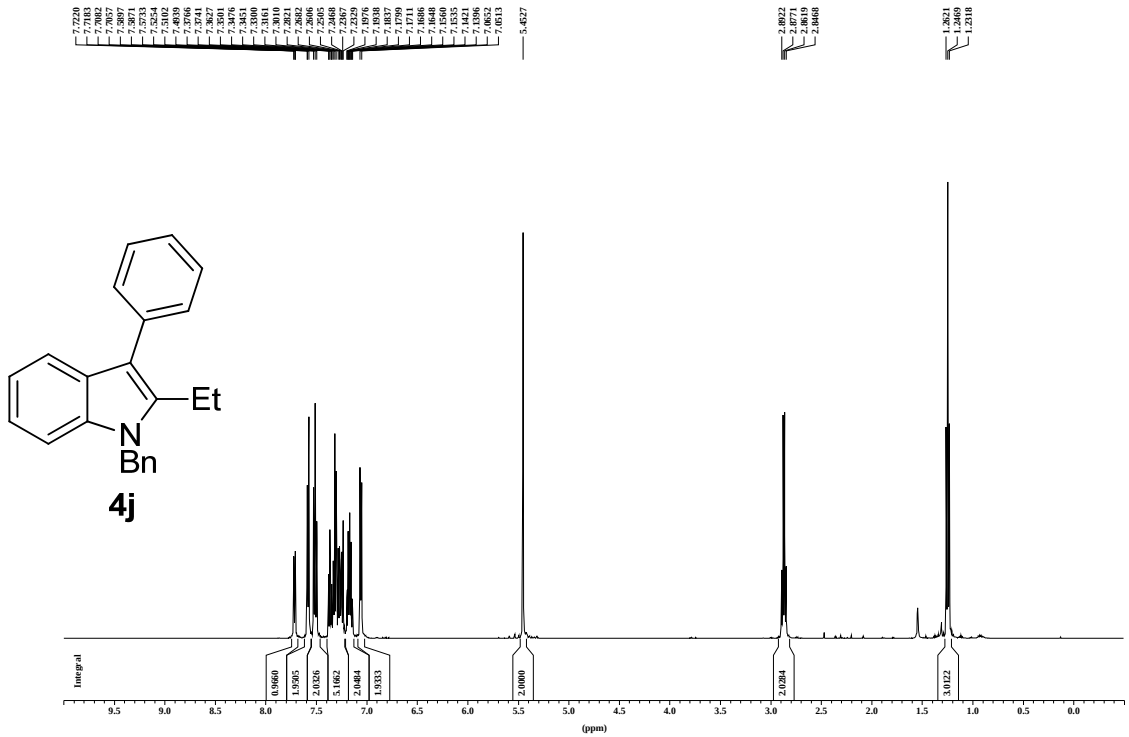
1H AMX500 dxw1101-1 1940H



13C AMX500 dxw1101-2 1940C



1H AMX500 dxw1202-1 1959H



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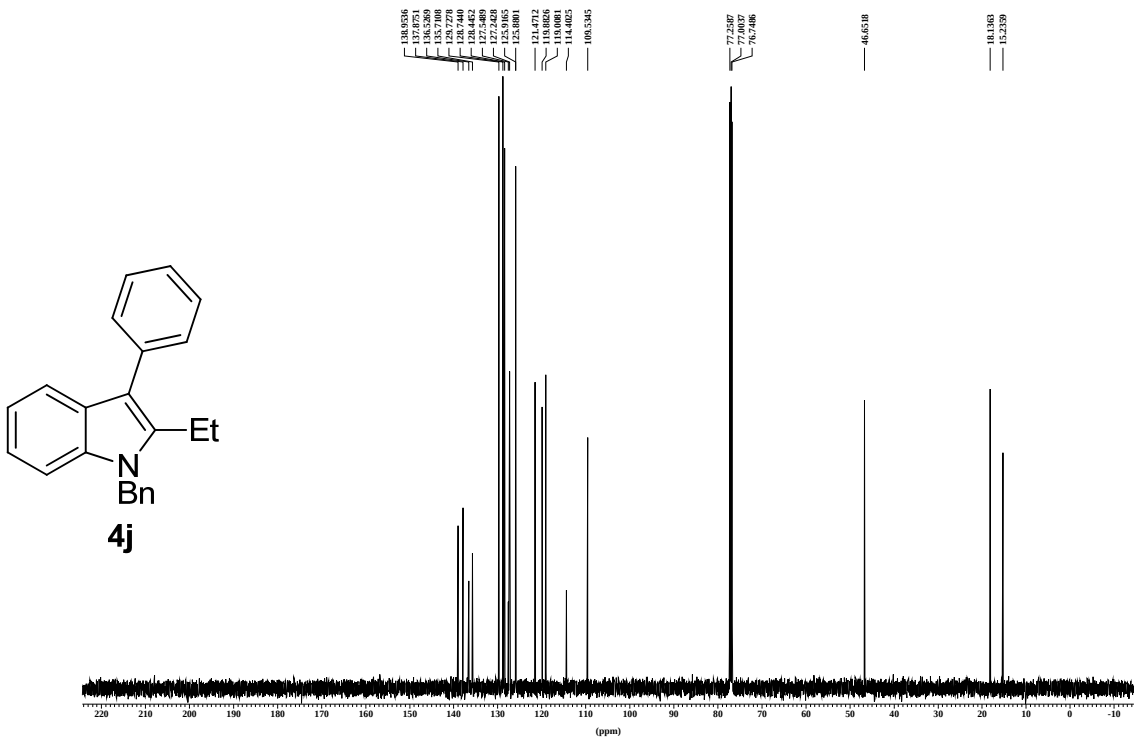
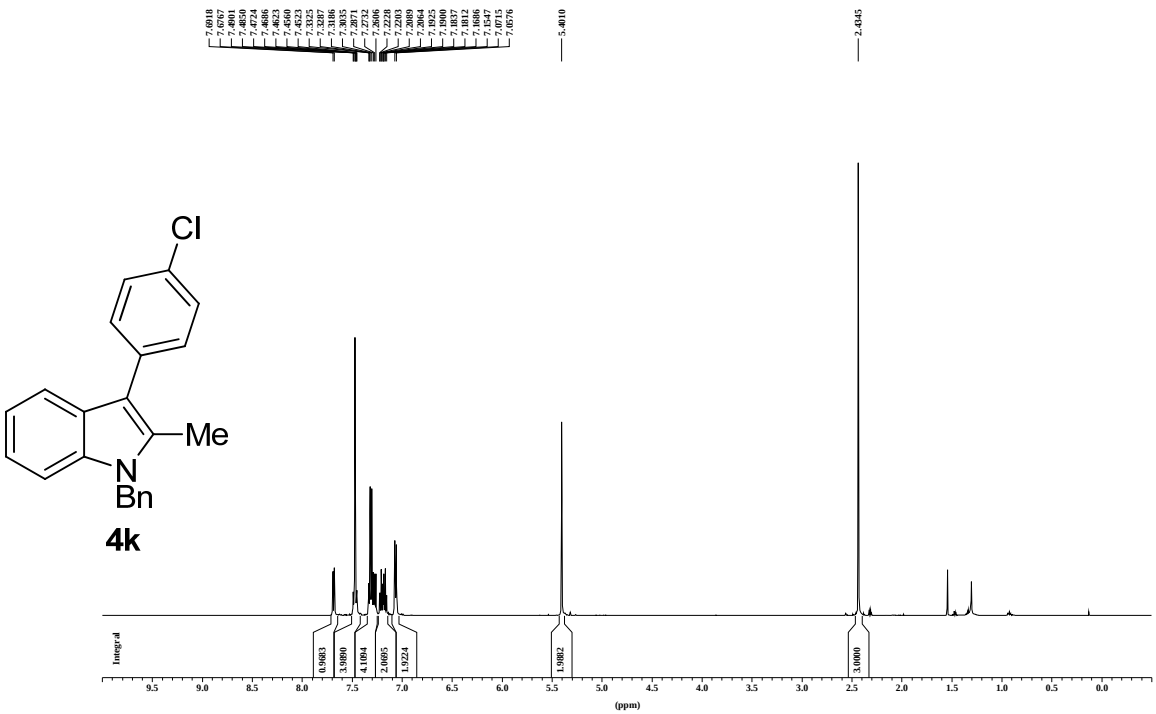
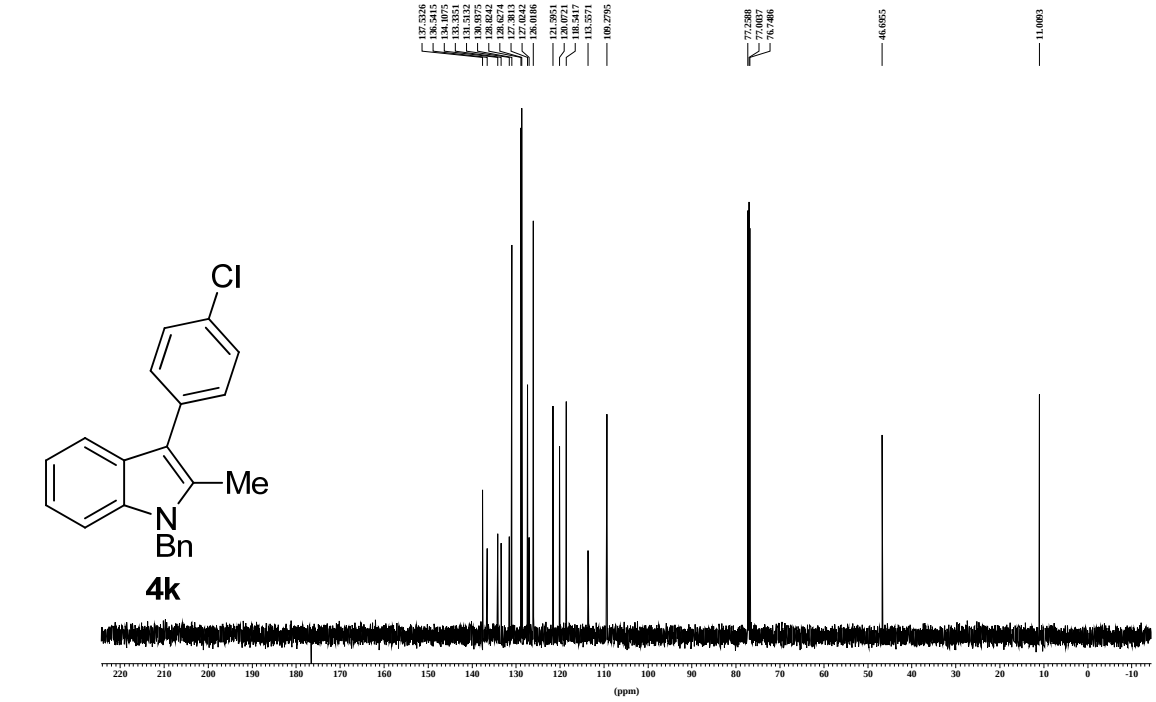


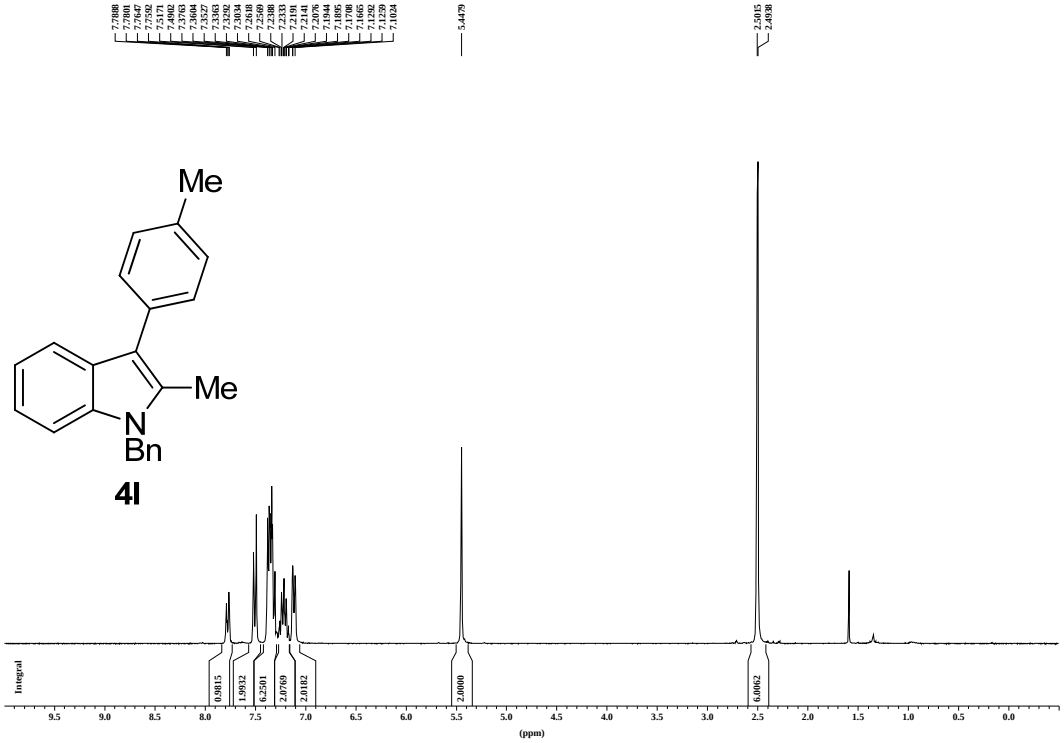
1H AMX500 dxw1119-3 1956H



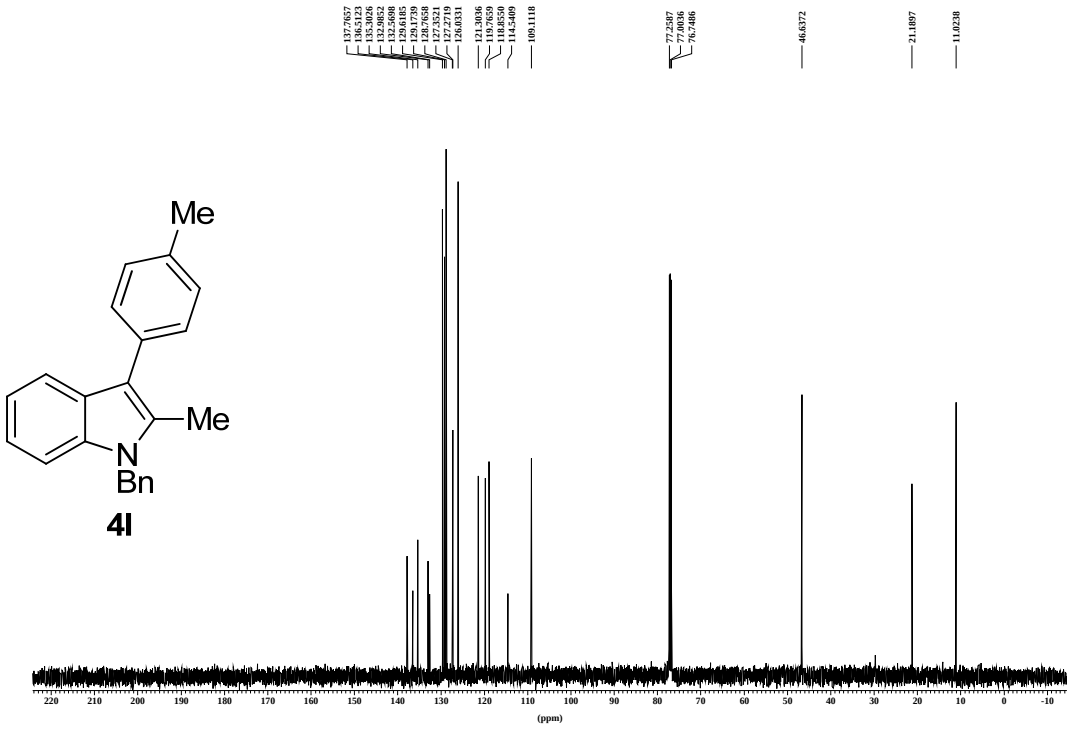
13C AMX500 dxw1119-6 1956C



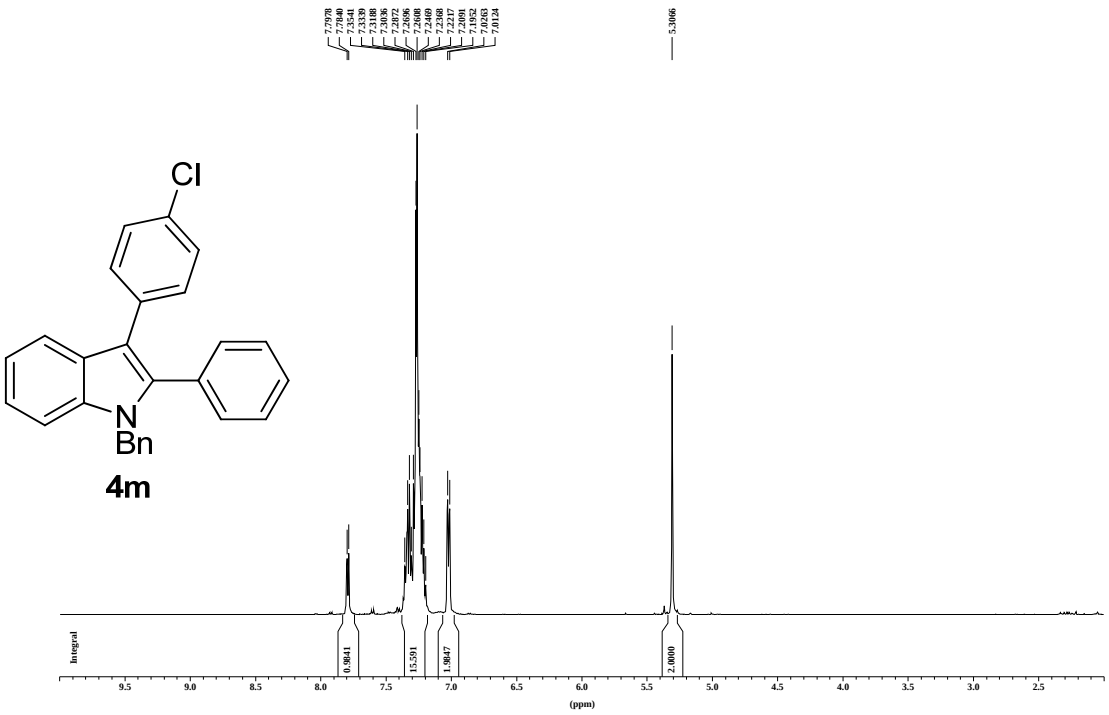
1H normal range AC300 nv29dxw-7 1955H



13C AMX500 dxw1119-2 1955C



1H AMX500 dxw1211-3 1971H



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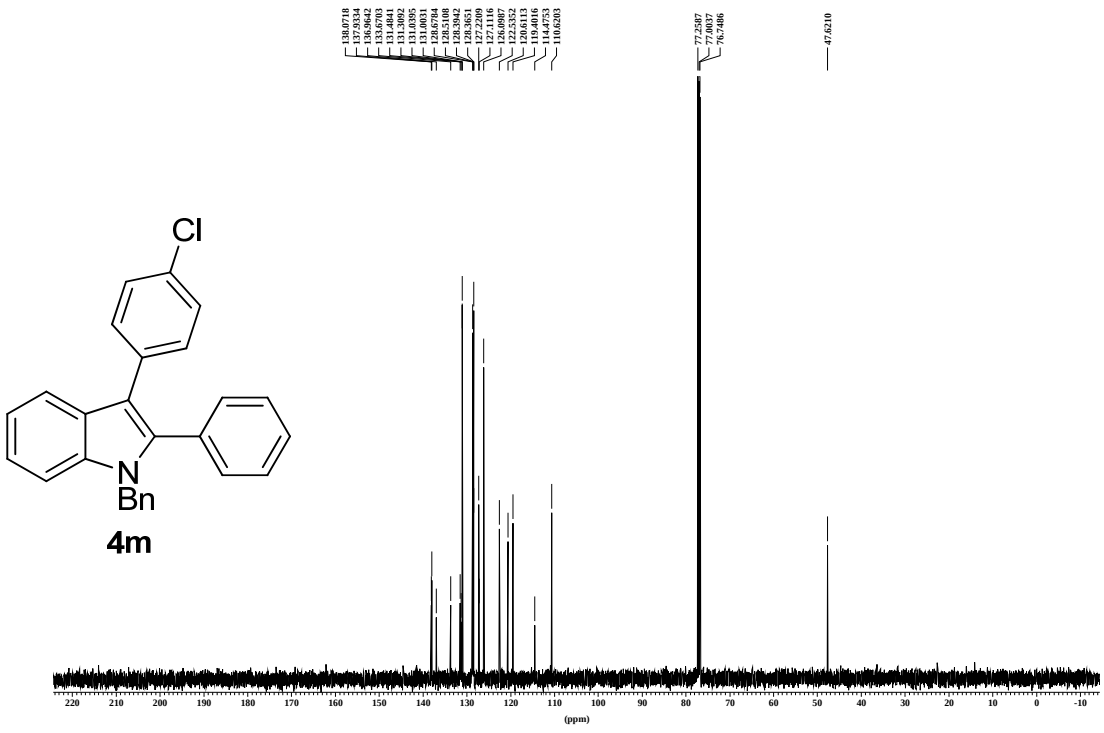

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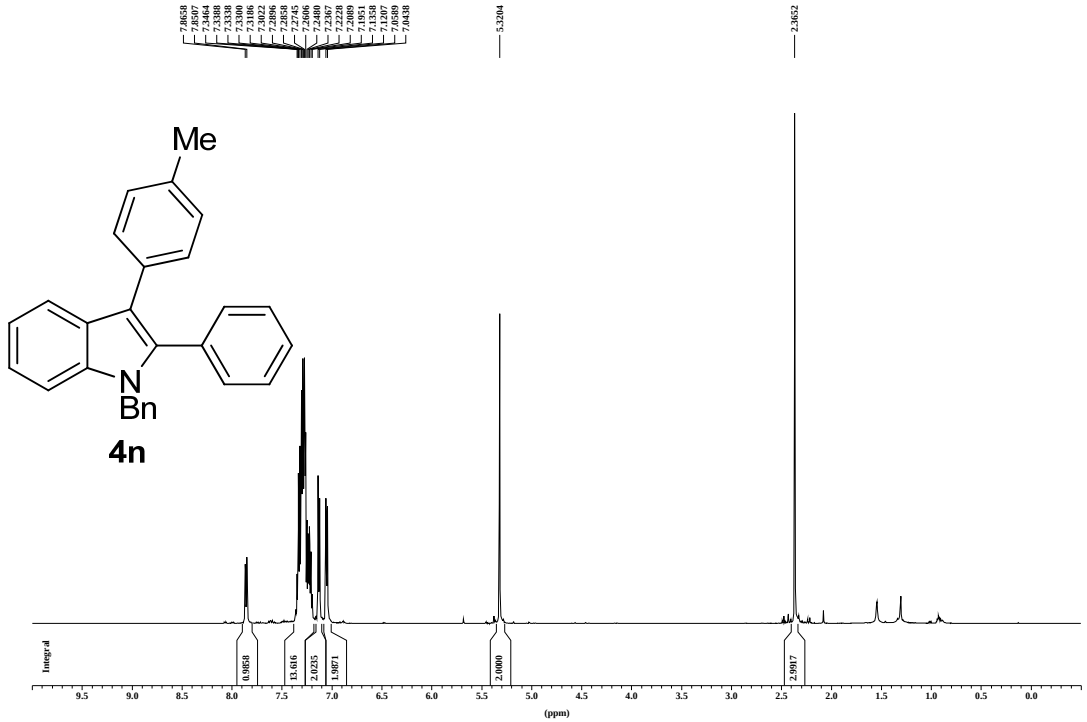
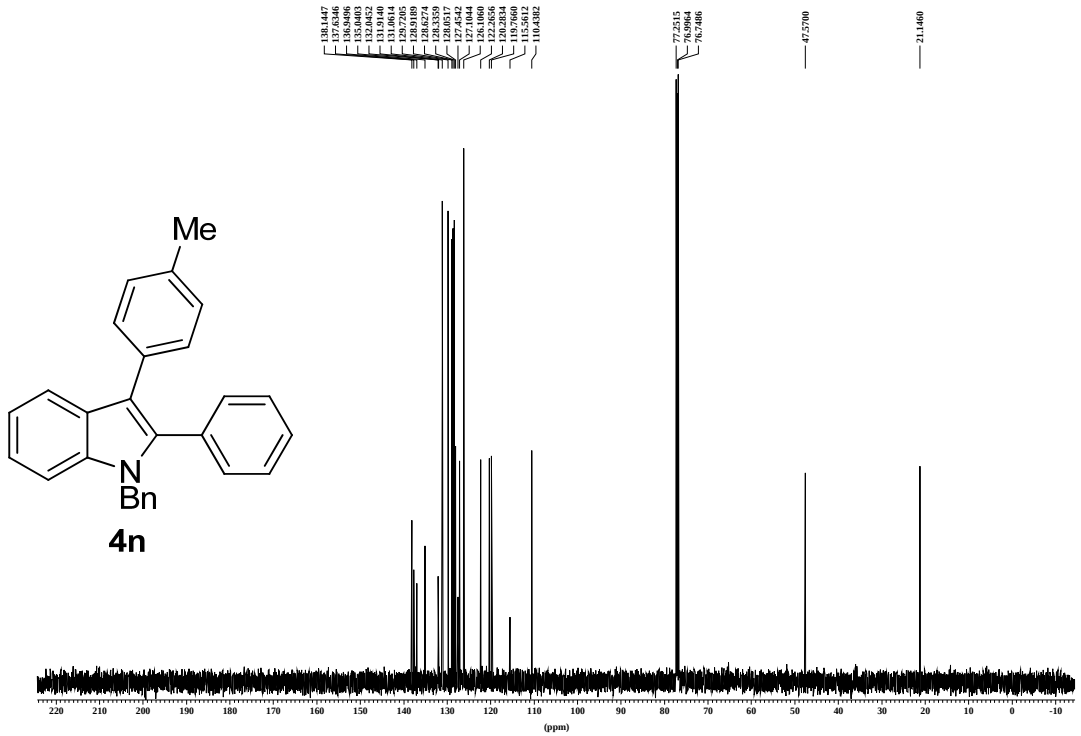


13C AMX500 dxw1213-4 1972C



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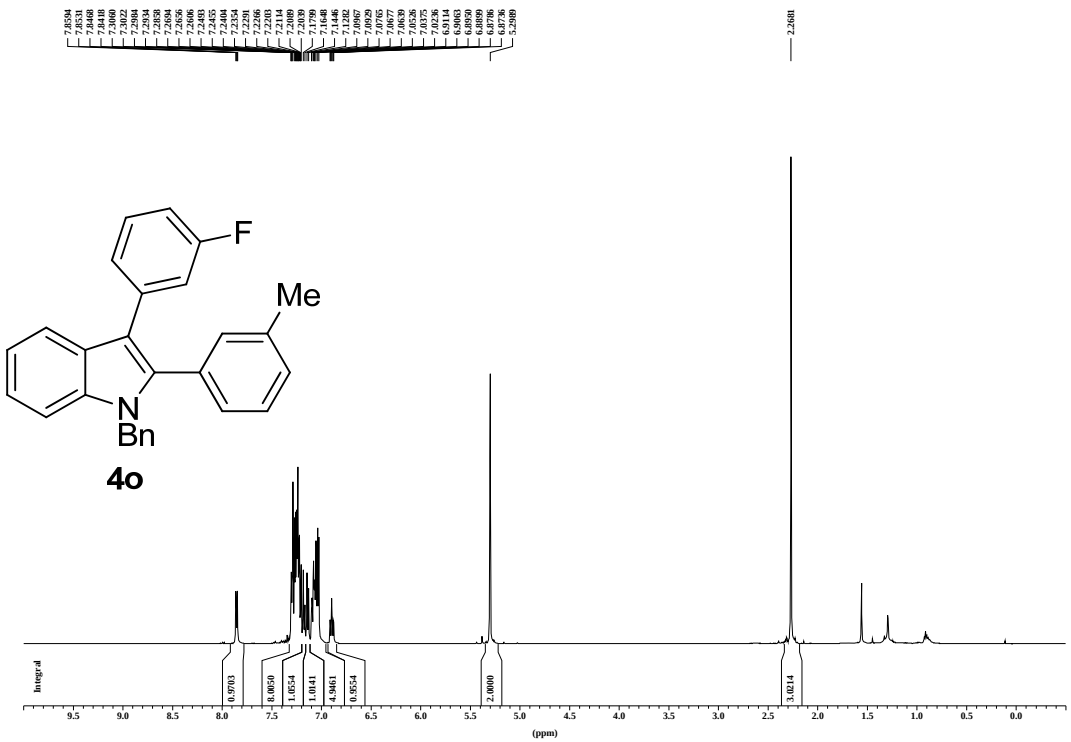
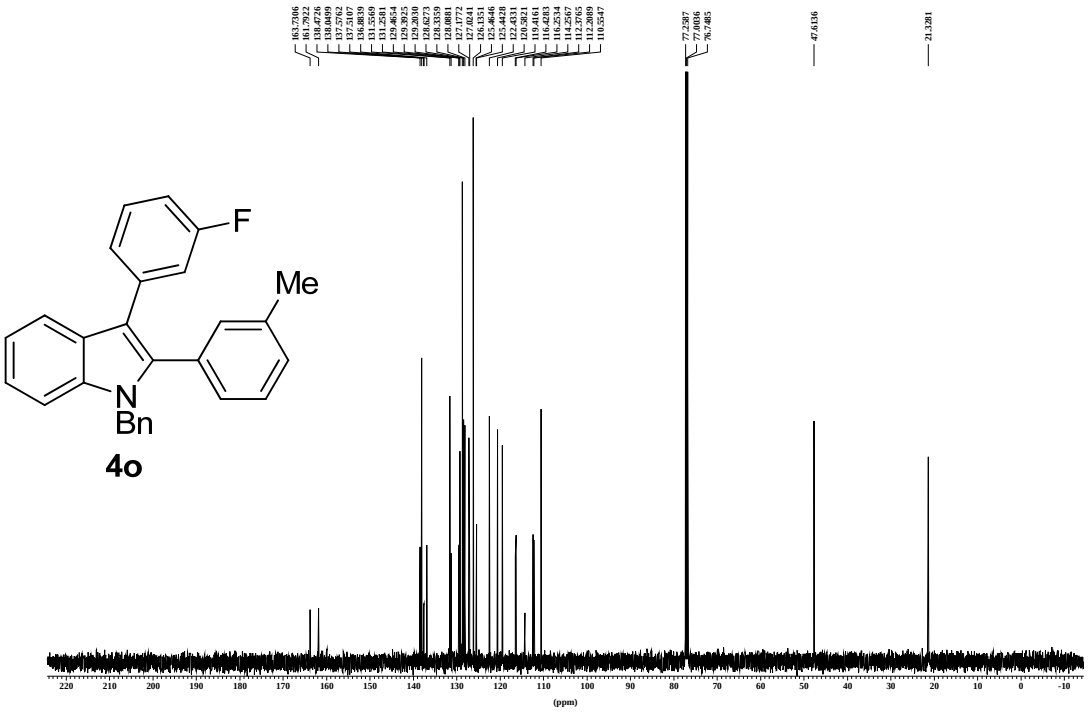


13C AMX500 dxw1231-6 1993C



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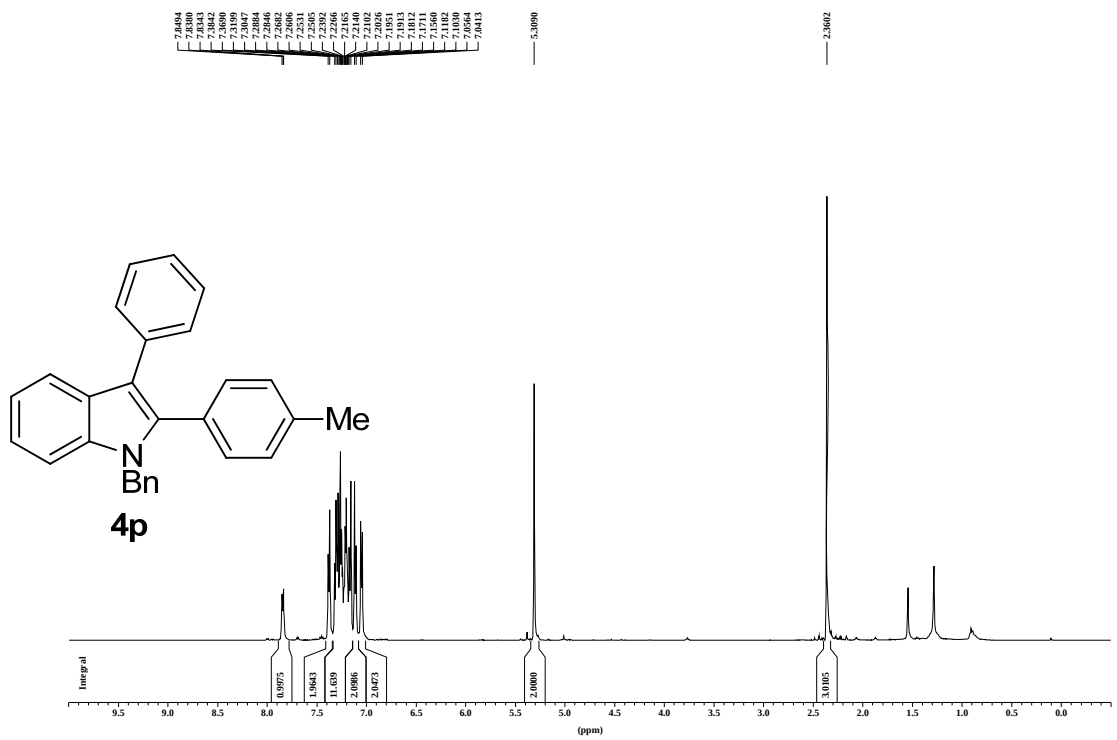

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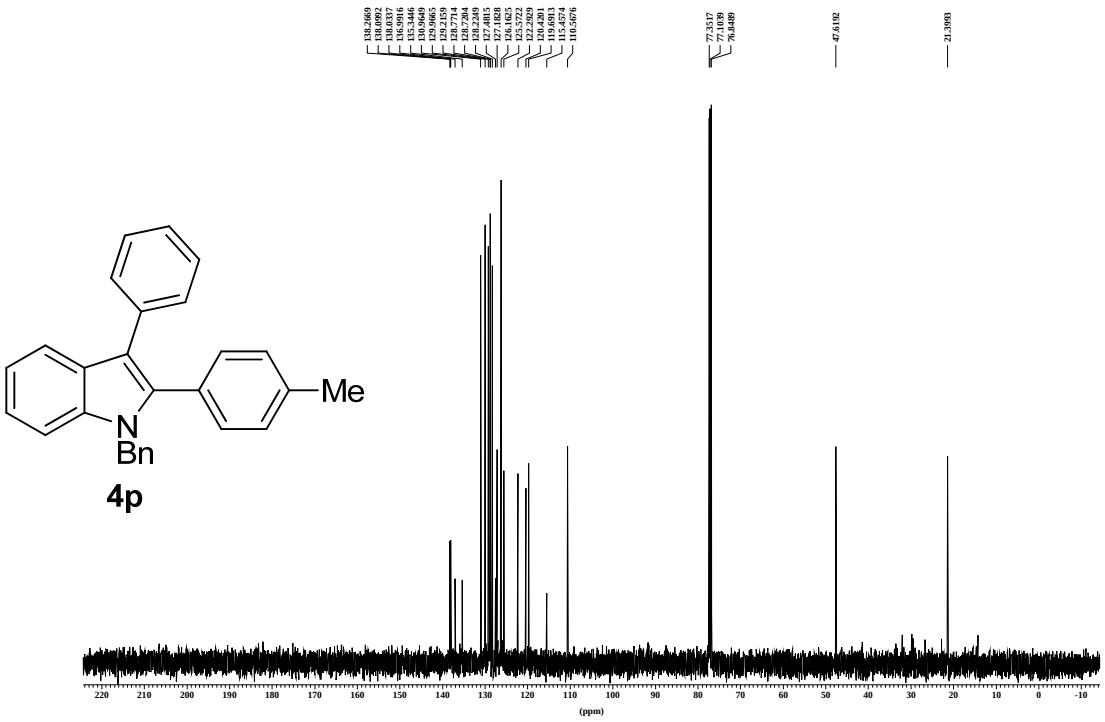

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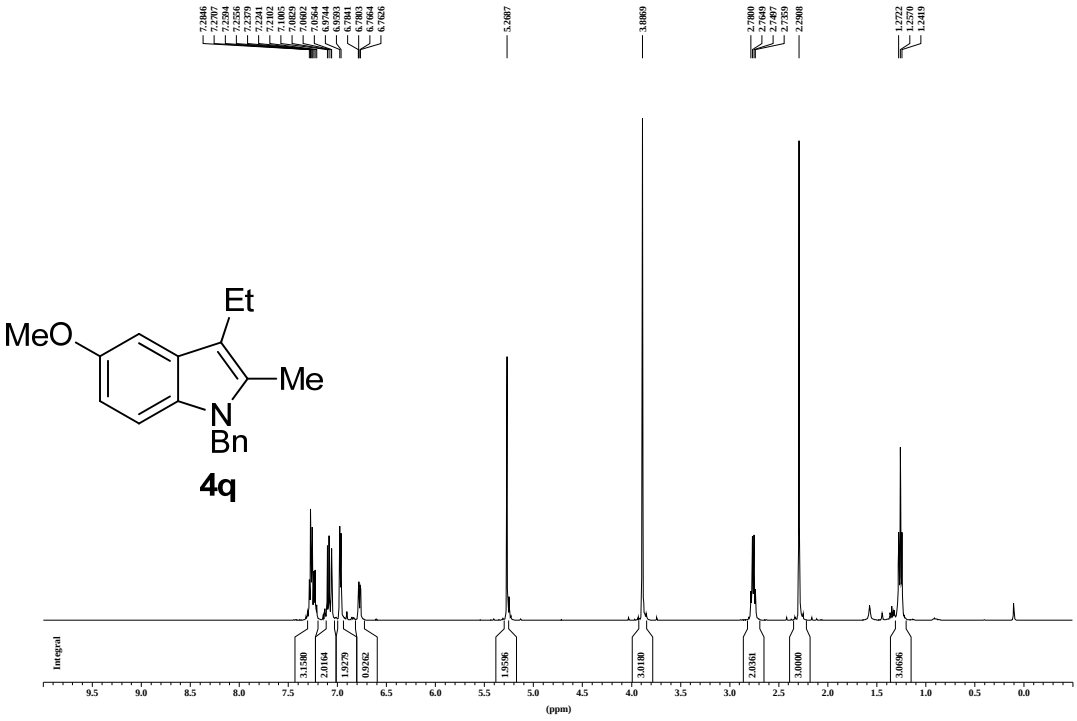

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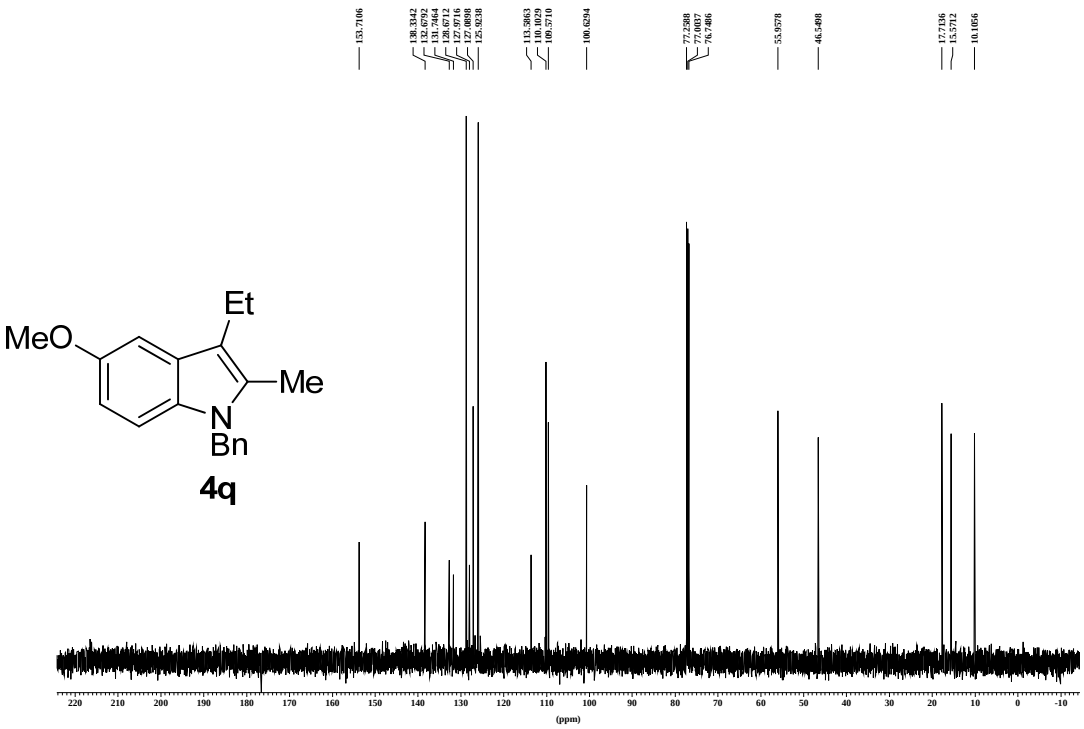

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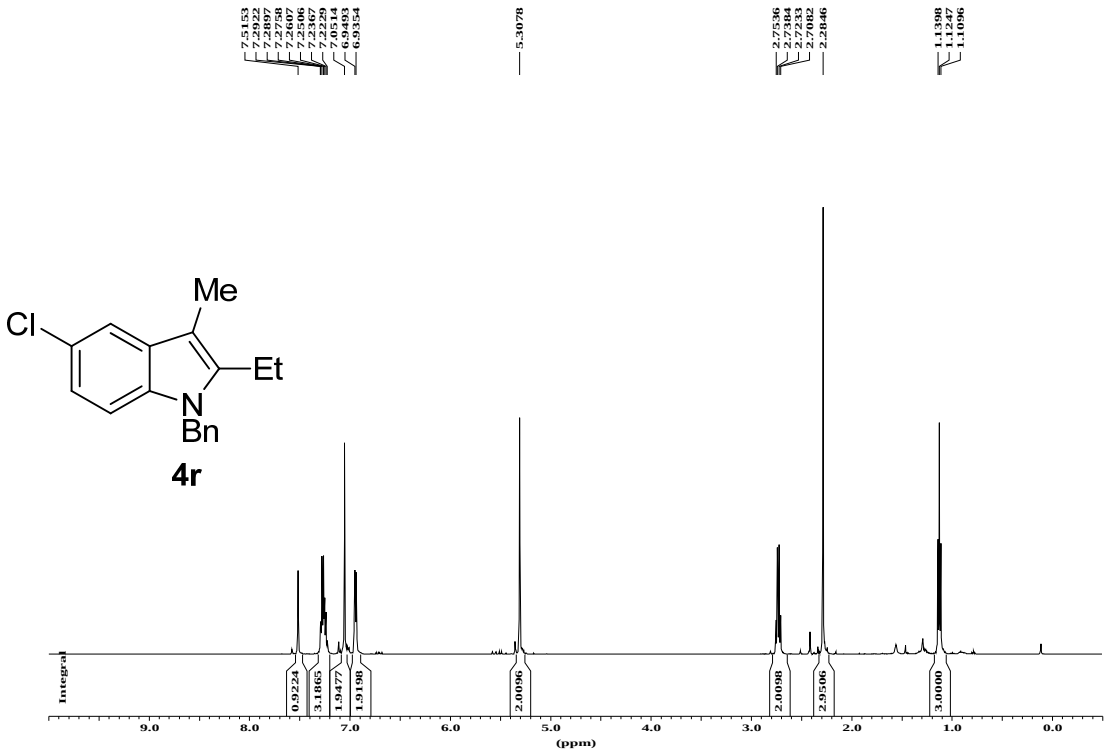

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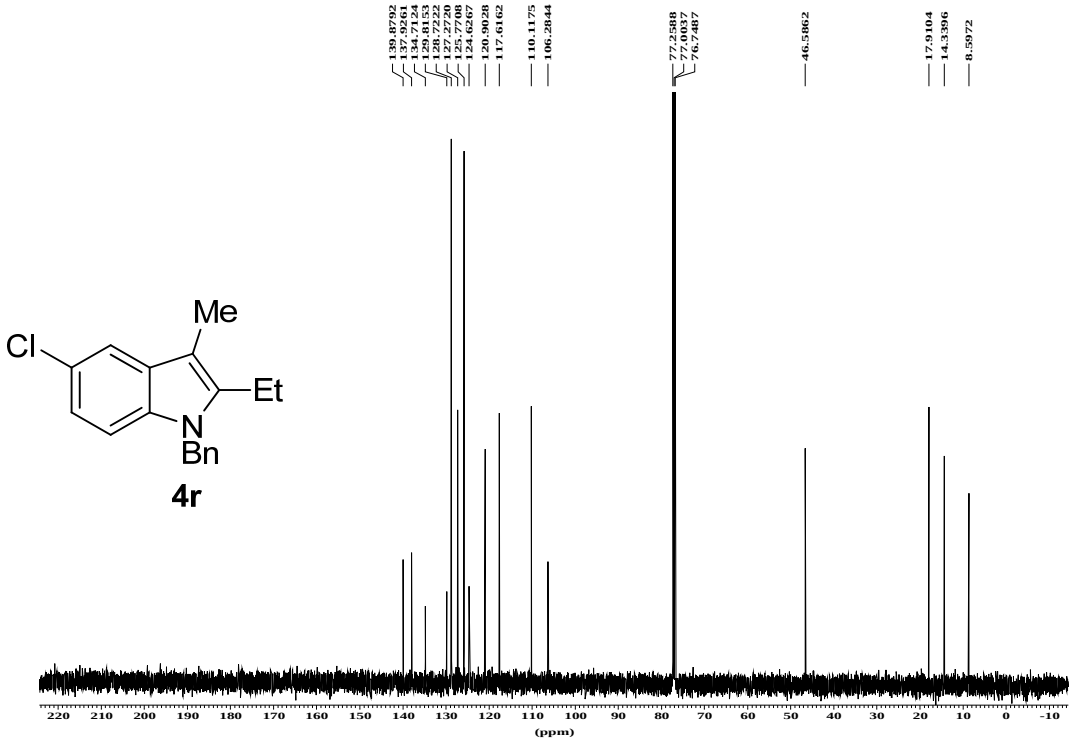

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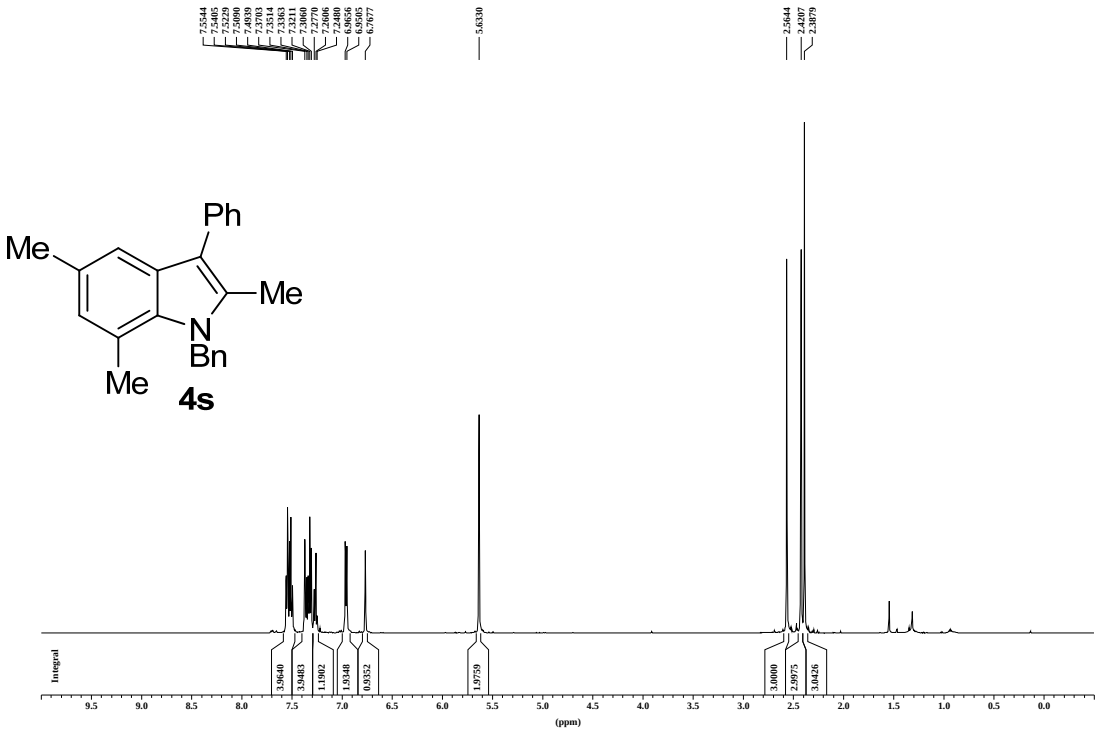

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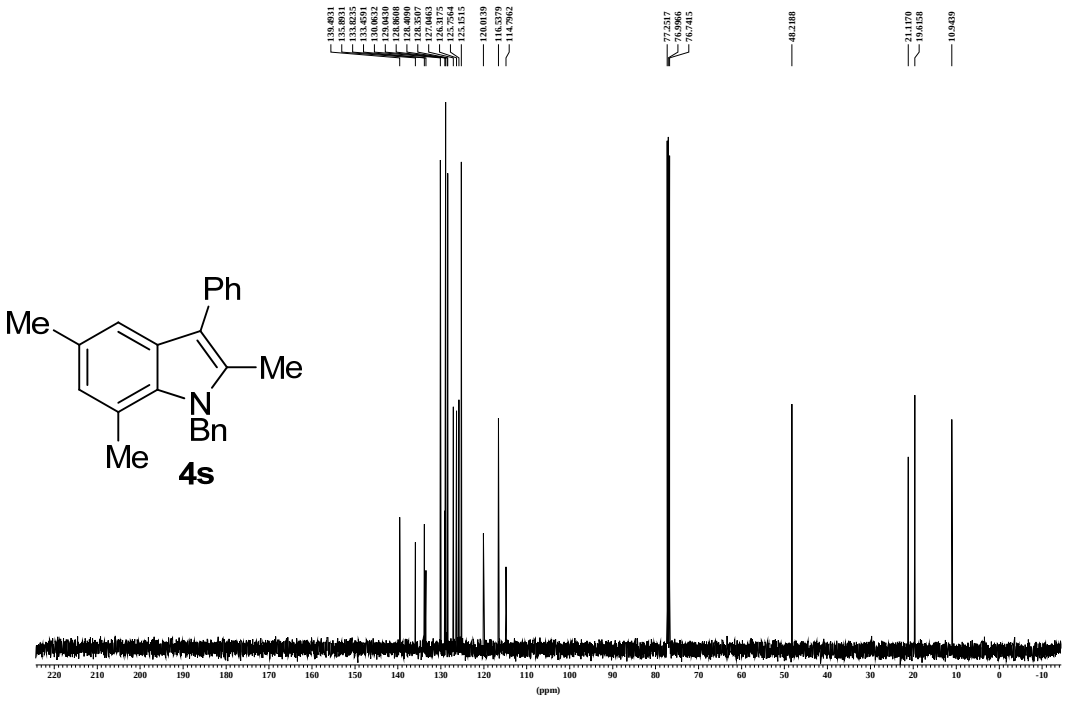

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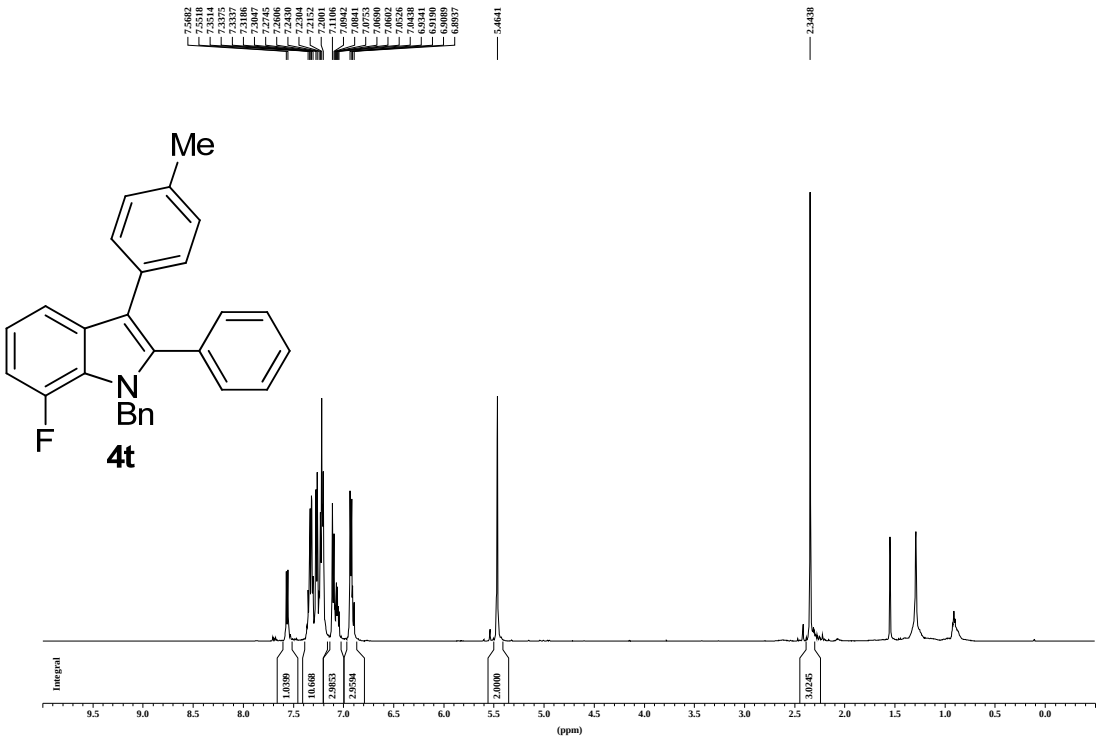
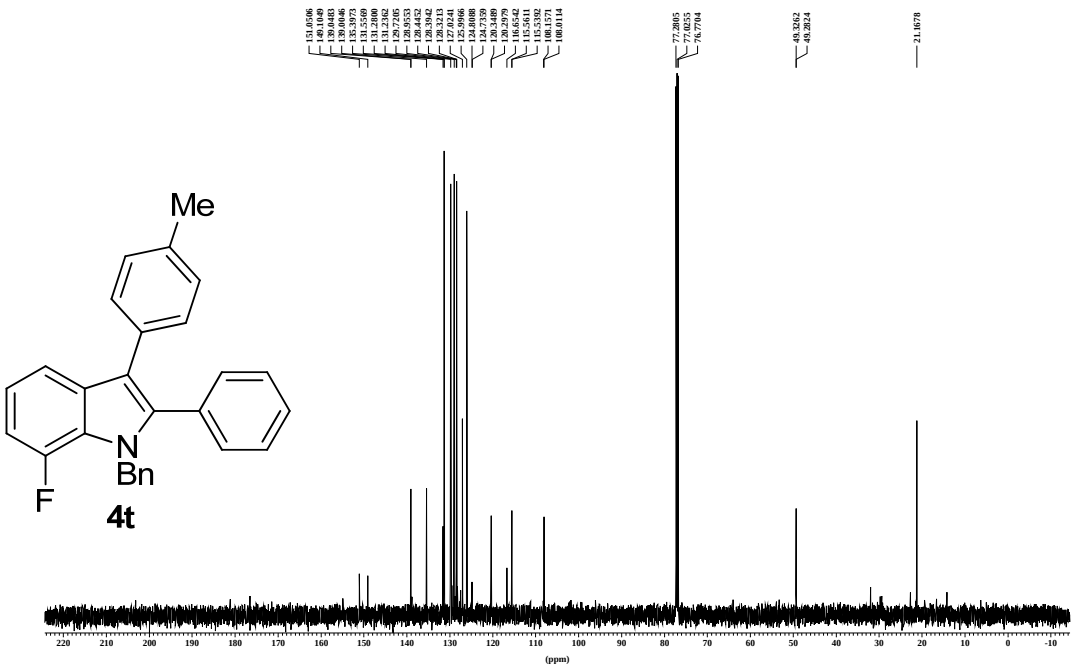


13C AMX500 dxw1231-10 1985C



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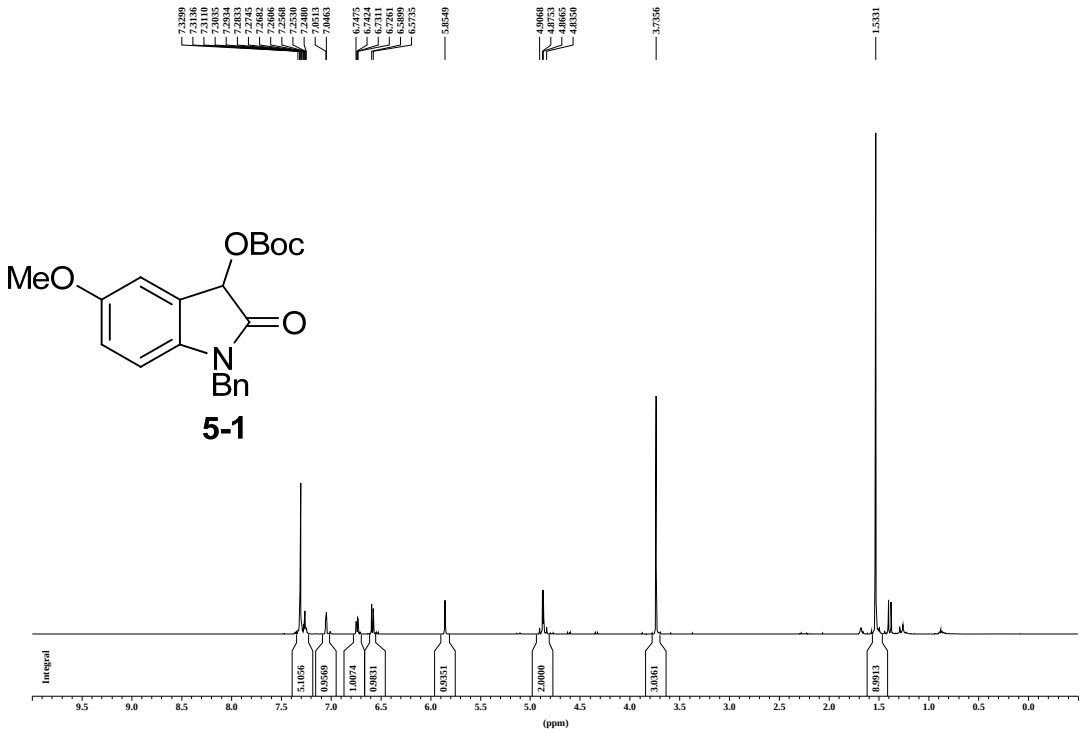

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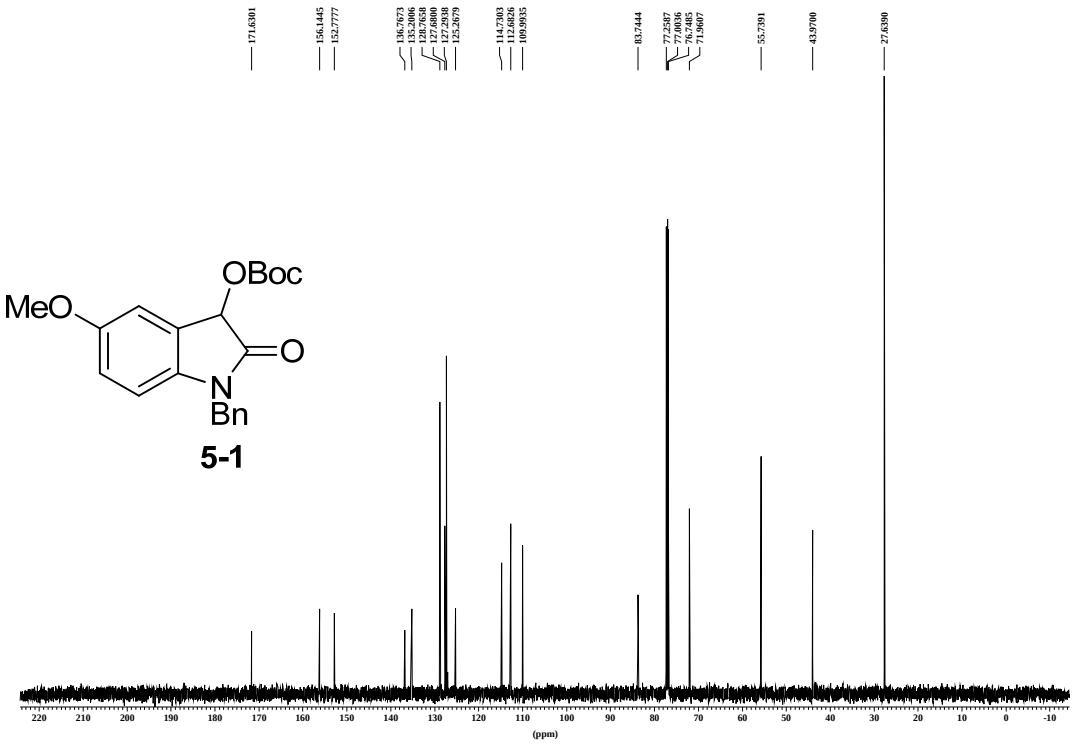

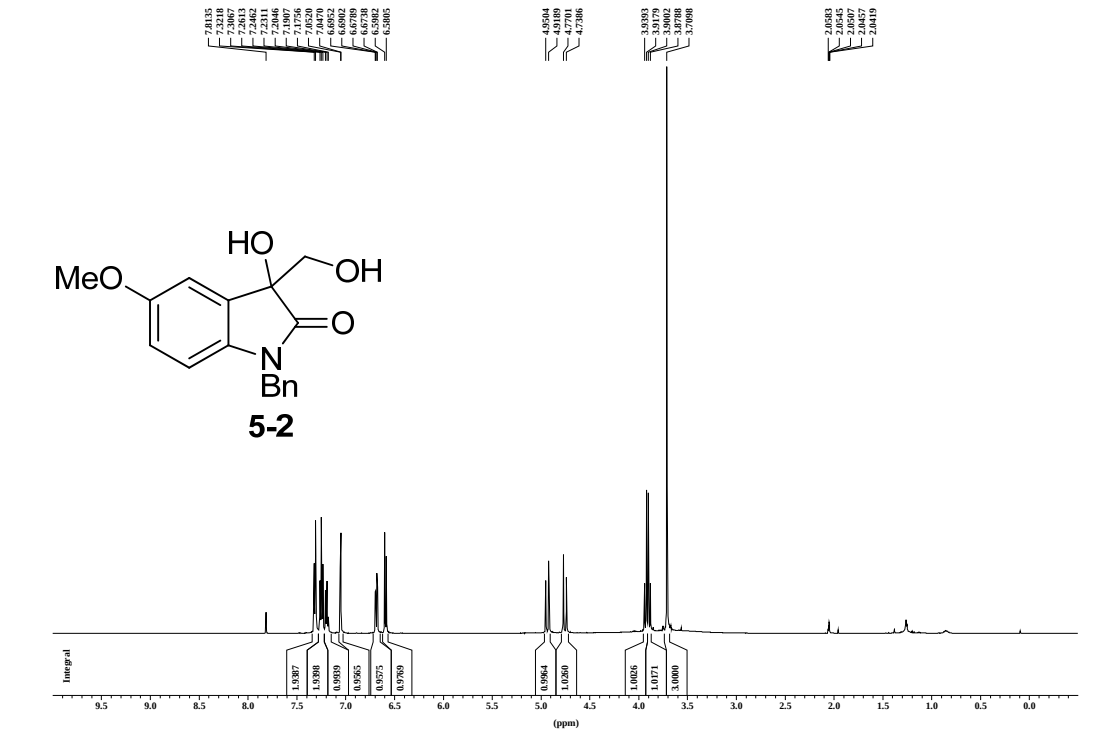
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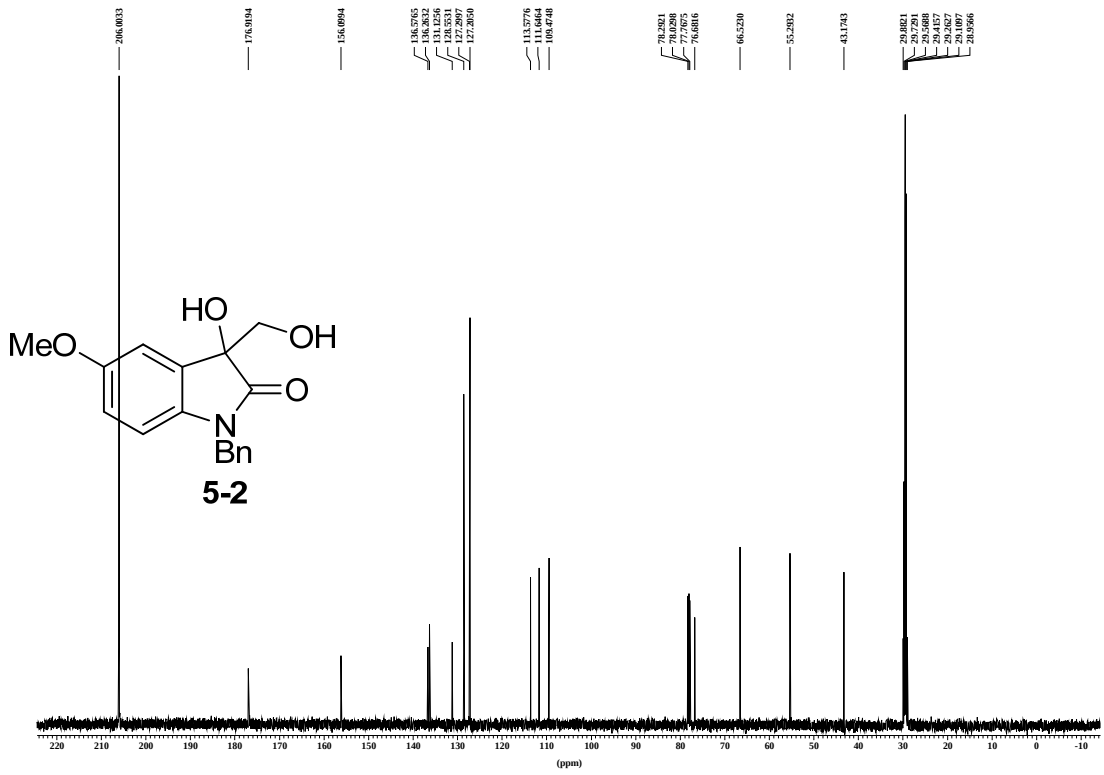
OH
MeO
O
N
Bn
5-2
Integral
(ppm)


HO
OH
MeO
O
N
Bn
5-2
(ppm)

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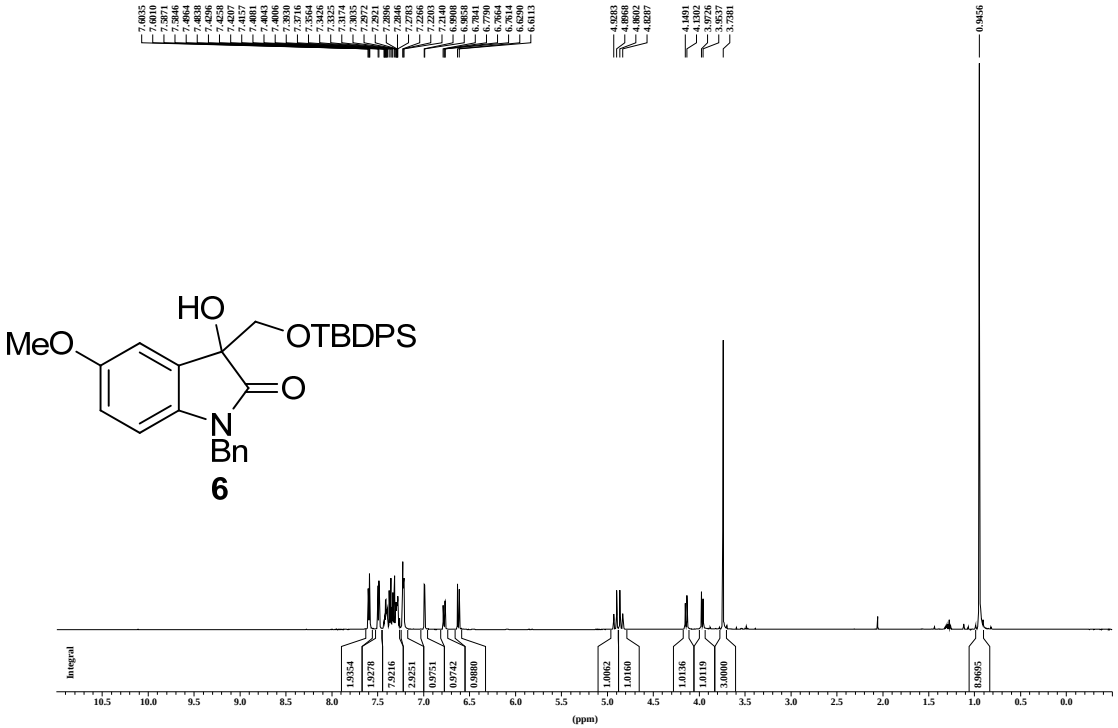

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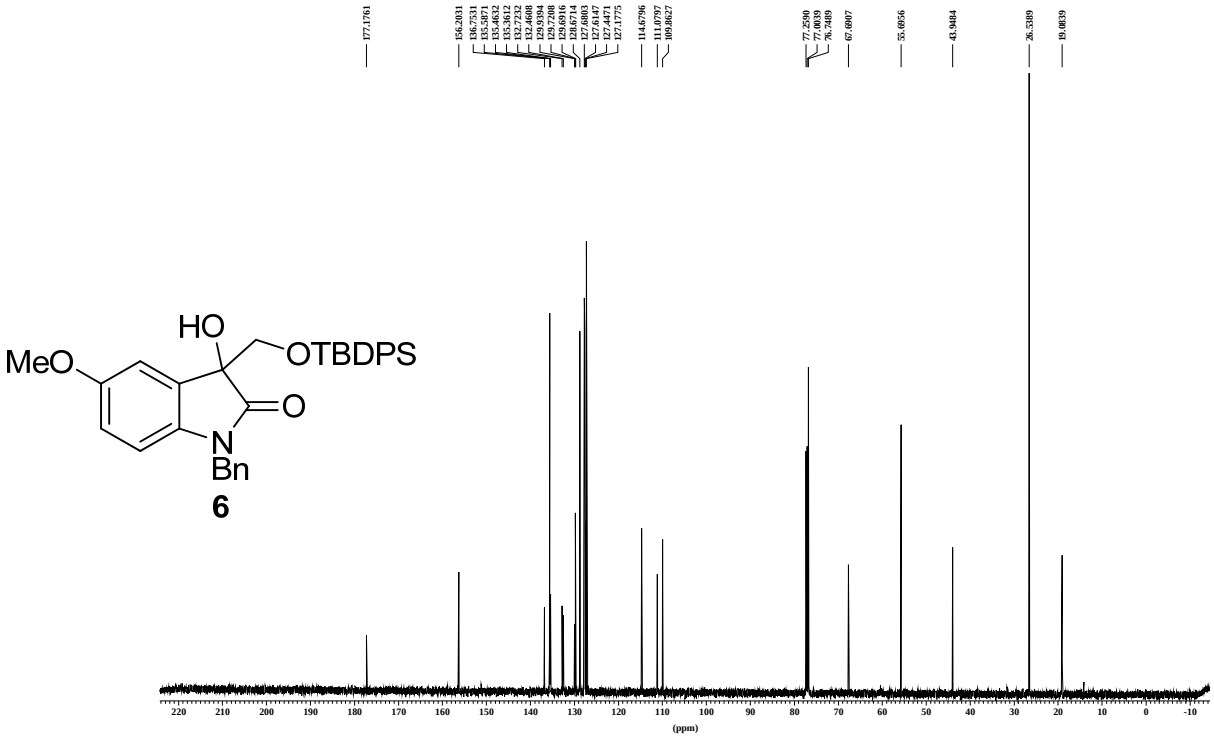
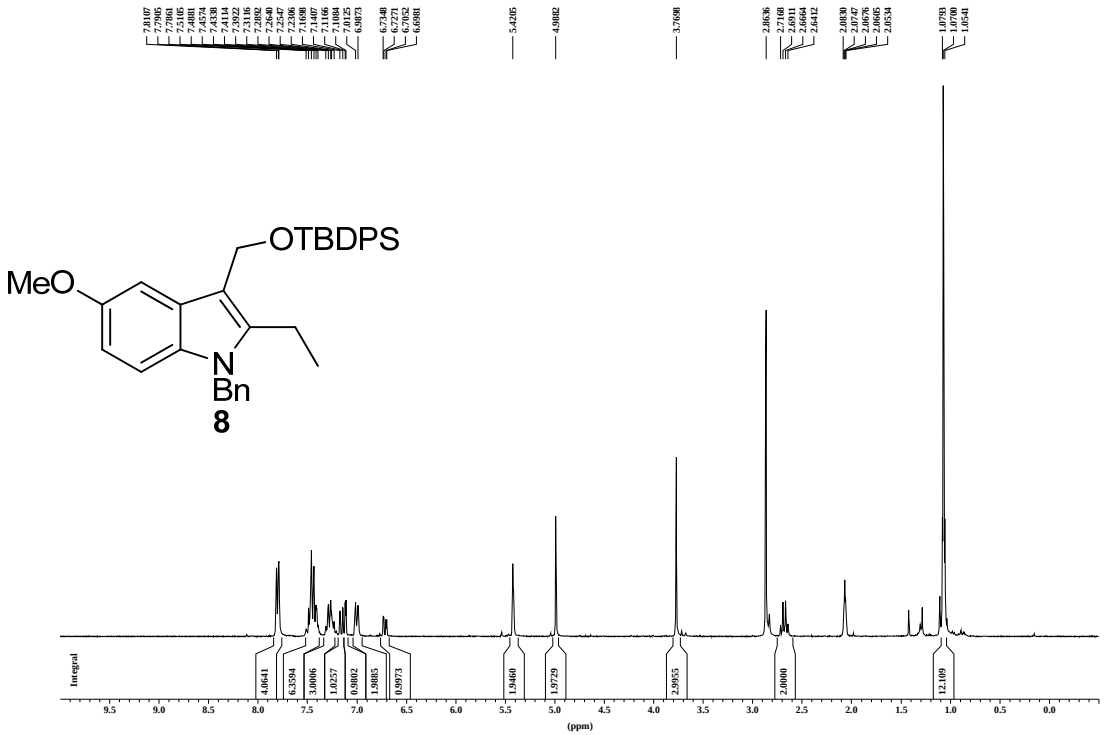


1H normal range AC300



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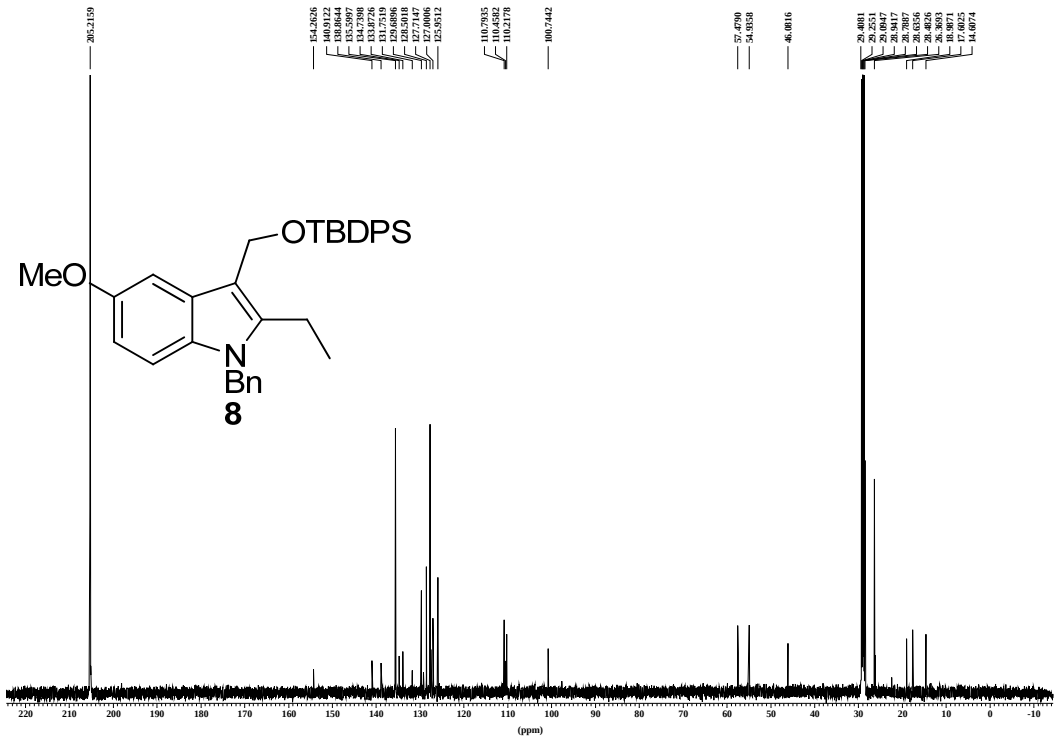

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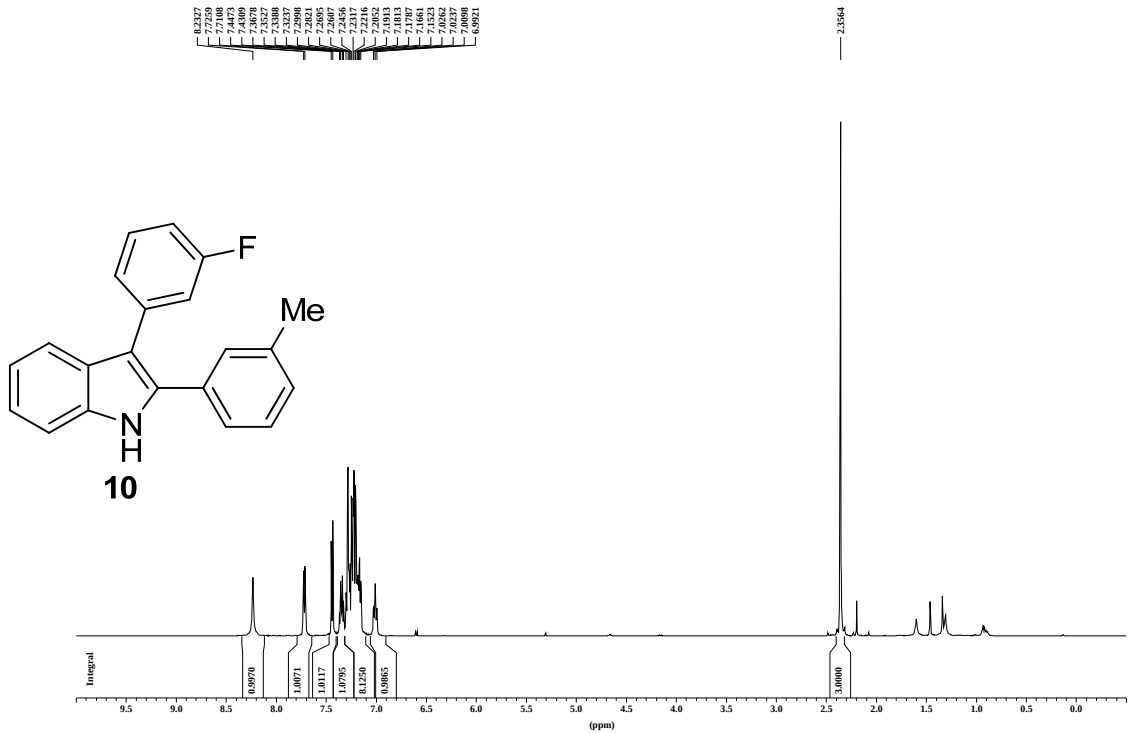

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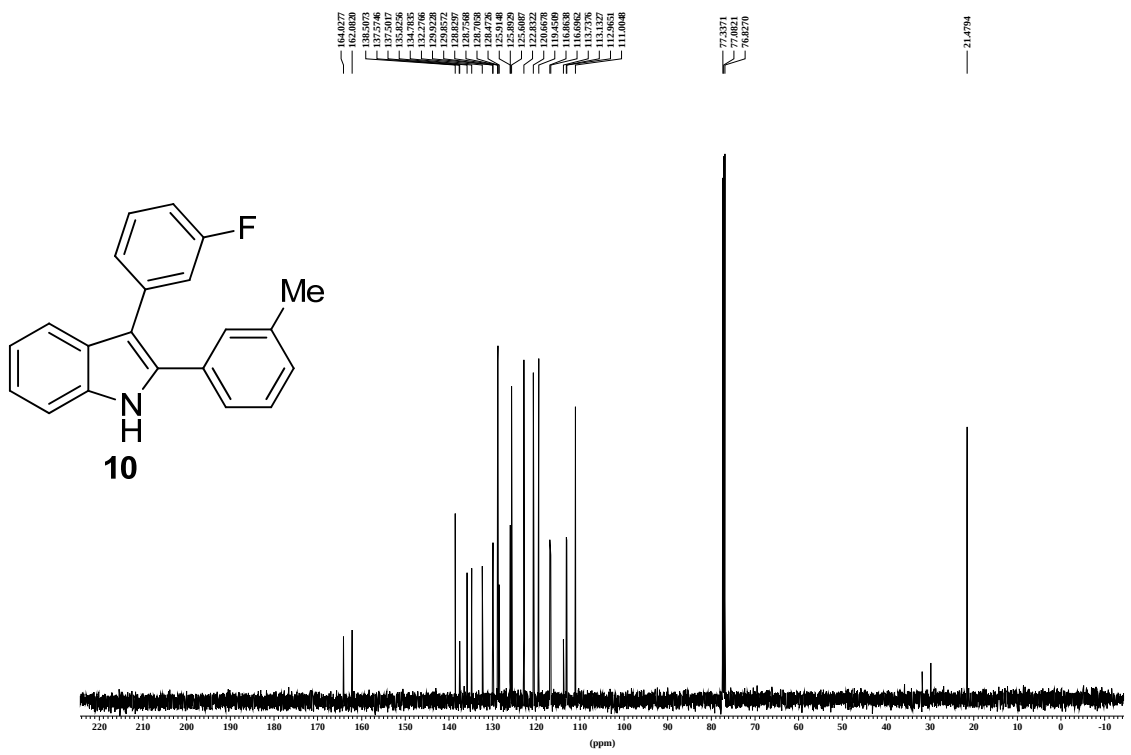
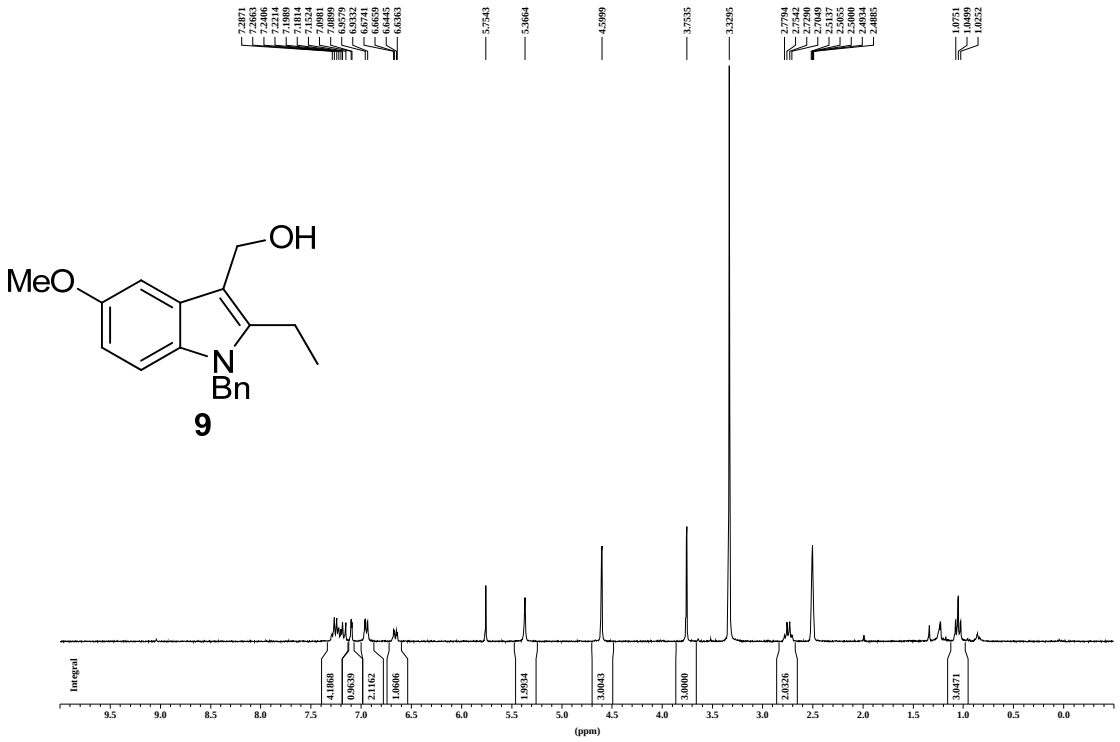


1H normal range AC300 ja17dxw-1



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