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Supporting Information

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An Expedient Strategy for the Synthesis of Novel Heterocycles and Tryptamines

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Supporting Information

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General Methods

Reactions were carried out under an argon atmosphere in oven-dried glassware that was allowed to cool to room temperature under high vacuum. Diethyl ether (Et_2O), tetrahydrofuran (THF) and *i*Pr_2NH were dried and purified from a solvent system by the published procedure,[1] unless otherwise mentioned. Solutions of anhydrous $LaCl_3$•2LiCl in dry THF (distilled from Na/benzophenone) were prepared as reported,[2] stored over activated 4Å molecular sieves, and titrated for protic content against *t*BuLi using 1,10-phenanthroline as endpoint indicator. *N*-Boc-pyrrolidin-3-one (**A**) was prepared following the literature report.[3] Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, and either ninhydrin, cerium sulfate, cerium ammonium molybdate, or potassium permanganate staining solutions and heat as developing agents. Flash column chromatography was performed using E. Merck silica gel (60, particle size 0.040–0.063 mm). Nuclear magnetic resonance (NMR) spectra were recorded using Bruker DRX-600, AV-600 and DRX-500 spectrometers. Spectra were calibrated using the residual ^1H chemical shift in $CDCl_3$ (7.26 ppm), CD_3CN (1.94 ppm) or CD_3OD (3.30 ppm), which were used as the internal reference standards for ^1H NMR, and $CDCl_3$ (77.0 ppm), CD_3CN (1.4 ppm) or CD_3OD (49.0 ppm) for ^{13}C NMR spectra. Coupling constants are reported in Hz. The following abbreviations were used to explain multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet, br = broad. IR spectra were recorded on a Perkin-Elmer Spectrum 100 FT-IR spectrometer or a Perkin-Elmer Spectrum One FTIR spectrometer with diamond ATR accessory. Bands were designated as s (strong), m (medium), w (weak), and br (broad). Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on an API 100 Perkin Elmer SCIEX single quadrupole mass spectrometer at 4000 V emitter voltage or an Agilent ESI TOF (time of flight) mass spectrometer at 3500 V emitter voltage. High-resolution mass spectra (HRMS) were recorded on a VGZAB-ZSE mass spectrometer using ESI. Melting points are uncorrected and were recorded on a Buchi B-540 or Thomas Scientific uni-melt™ capillary melting point apparatus.

Experimental Procedures

General procedure A: Formation of spirocarbamates.

An oven-dried, two-necked 50 mL round-bottom flask equipped with a thermometer, to monitor internal temperature, was loaded with the *N*-Boc-aniline (3.00 mmol). After evacuating and then backfilling the flask with argon (3 ×), Et_2O (10 mL) was added, and the reaction mixture was cooled to –40 ºC in an acetone/dry ice bath. *t*BuLi (1.7 M in pentane, 4.2 mL, 7.2 mmol, 2.4 equiv) was injected into the flask at such a rate that the internal temperature was kept below –10 ºC. The resulting solution was stirred at that temperature and for the duration specified for each compound. Once arene lithiation had proceeded to >95 % (as monitored by ^{1}H NMR spectroscopic analysis)[4] the reaction mixture was cooled to –70 ºC (internal temperature, acetone/dry ice) and treated with $LaCl_3$•2LiCl[2] (0.33 M in THF, 12.0 mL, 4.00 mmol, 1.3 equiv), so that the internal temperature was maintained below –70 ºC. The reaction mixture was then allowed to stir for 5 min at temperatures below –70 ºC,[5] after which time *N*-Boc-pyrrolidin-3-one[3] (1.0 M in THF, 3.6 mL, 3.6 mmol, 1.2 equiv) was rapidly introduced. The mixture was then allowed to warm to room temperature over 1 h. *t*BuOK (34 mg, 0.30 mmol, 0.10 equiv) was then added, and the reaction mixture was heated for 4 h in a 70 ºC oil bath. Standard work-up involved cooling to room temperature and pouring into a stirring mixture of EtOAc (50 mL), aqueous HCl (2 M, 15 mL) and saturated aqueous NH_4Cl solution (50 mL). After 5 min, the phases were separated, and the aqueous layer was further extracted with EtOAc (50 mL and 25 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The title spirocarbamates were then isolated following flash column chromatography on silica gel using the eluent systems described for each compound. A non-aqueous work-up procedure was also employed as follows: After the spirocyclization was completed, the reaction mixture was cooled to room temperature, silica gel (15 g) was added along with CH_2Cl_2 (20 mL). The resulting slurry was filtered through a plug of silica, eluting with EtOAc (250 mL), and the combined organic filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel as described above.

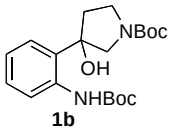
General procedure B: Ring-opening of spirocarbamates/acid-catalyzed tryptamine formation.

To a solution of spirocarbamate[6] (0.10 mmol, 1.0 equiv) in THF (3.0 mL) were successively added *t*BuOK (13.5 mg, 0.12 mmol, 1.2 equiv) and TIPS-Cl[7] (26 µL, 0.12 mmol, 1.2 equiv) under argon. The reaction mixture was then allowed to stir until *N*-silylation was complete, typically for 30–120 min.[8] The mixture was then cooled to an internal temperature of –50 ºC (dry ice/acetone) and treated dropwise with freshly prepared LDA (1.0 M in THF, 0.50 mL, 0.50 mmol, 5.0 equiv) while the internal temperature was kept below –50 ºC. The reaction was allowed to proceed at –50 to –20 ºC until the starting material was completely consumed, as evidenced by TLC. The reaction mixture was then quenched by sequential addition of saturated aqueous NH_4Cl (2 mL), H_2O (2 mL) and brine (2 mL). The aqueous layer was extracted with EtOAc (3 × 4 mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Unless specified otherwise, the crude mixture was then redissolved in CH_2Cl_2 (5 mL) and stirred in the presence of TFA (0.5 mL) at ambient temperature until all enamine was converted to baseline material, as indicated by TLC analysis (EtOAc:hexanes 1:1). The reaction mixture was diluted with H_2O (5 mL), and washed with Et_2O (3 × 3 mL). The aqueous layer was then rendered basic (pH ~ 12–13) using NaOH pellets, and extracted with $CHCl_3$ or CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the corresponding tryptamine, which could be further purified by flash column chromatography on silica gel using MeOH:CH_2Cl_2 mixtures containing 0.5 % Et_3N as eluent. An alternate method to obtain analytically pure tryptamine follows: The crude enamine was dissolved in CH_2Cl_2 (5 mL) and stirred in the presence of TFA (0.05 mL) until all starting enamine was consumed, typically 30–90 min, as indicated by TLC analysis (EtOAc:hexanes 1:1). The reaction mixture was then quenched with aqueous saturated $NaHCO_3$ until the pH rose above 7, and extracted with $CHCl_3$ or CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the *N*-Boc tryptamine, which was purified by flash column chromatography on silica gel using EtOAc:hexanes mixtures as eluent. Then the purified *N*-Boc tryptamine was dissolved in CH_2Cl_2 (3 mL) and treated with TFA (0.3 mL). The reaction mixture was stirred until all starting *N*-Boc compound was converted to baseline product, as

evidenced by TLC analysis (EtOAc:hexanes 1:1), typically for 5–30 min. The reaction mixture was diluted with H_2O (5 mL) and washed with Et_2O (3 × 3 mL). The aqueous layer was then rendered basic (pH ~ 12–13) by the addition of NaOH pellets, and extracted with $CHCl_3$ or CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the analytically pure tryptamine.

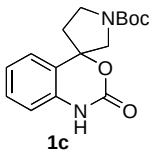
Characterization Data

***tert*-Butyl 3-(2-(*tert*-butoxycarbonylamino)phenyl)-3-hydroxypyrrolidine-1-carboxylate (1b).** This compound was prepared according to general procedure A and starting with *N*-Boc aniline **1a** by performing the lithiation for 4 h at –10 ºC, but omitting both the addition of *t*BuOK and heating, prior to work-up. Flash column chromatography (silica gel, EtOAc:hexanes 1:3) afforded carbinol **1b** (851 mg, 75 %) as a white solid. **1b**: R_f = 0.37 (silica gel, EtOAc:hexanes 1:1); mp 173–174 ºC (CH_2Cl_2/hexanes); IR (film): ν_{max} = 3311 (m, br), 2978 (m), 2932 (m), 1723 (m), 1668 (s), 1449 (m), 1422 (s), 1365 (m), 1242 (m), 1160 (s), 1139 (s), 749 (m) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, ca. 1:1 mixture of rotamers): δ = 8.37 (br s, 0.5 H), 8.27 (br s, 0.5 H), 7.95–7.90 (m, 1 H), 7.30–7.28 (m, 1 H), 7.22–7.16 (m, 1 H), 7.02–7.00 (m, 1 H), 3.92–3.75 (m, 1 H), 3.59–3.45 (m, 3 H), 3.32 (br s, 0.5 H), 3.07 (br s, 0.5 H), 2.49–2.25 (m, 2 H), 1.53 (s, 9 H), 1.45 ppm (s, 9 H); ^{13}C NMR[9] (150 MHz, $CDCl_3$): δ = 154.6, 153.4, 137.8, 131.0, 130.7, 129.0, 125.0, 123.1, 122.6, 80.8, 80.3, 79.9, 79.7, 56.7, 56.2, 44.3, 43.5, 37.1, 36.4, 28.5, 28.4 ppm; HRMS [ESI]: calcd for $C_{20}H_{30}N_2O_5^+$ [M + Na^+]: 401.2047, found 401.2051.



1b

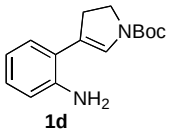
***tert*-Butyl 2-oxo-1,2-dihydrospiro[benzo[*d*][1,3]oxazine-4,3'-pyrrolidine]-1'-carboxylate (1c).** This compound was prepared according to general procedure A and starting with *N*-Boc aniline **1a** by performing the lithiation for 4 h at –10 ºC. Flash column chromatography (silica gel, EtOAc:hexanes 1:2 → 2:1) afforded spirocarbamate **1c** (657 mg, 72 %) as a white solid. **1c**: R_f = 0.32 (silica gel, EtOAc:hexanes 1:1); mp 176–177 ºC (EtOAc); IR (film): ν_{max} = 3256 (b), 2971 (b), 1724 (s), 1678 (s), 1599 (w), 1417 (s), 1325 (m), 1243 (m), 1168 (w), 1023 (m), 754 (s), 738 (m), 608 (m) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, ca. 1:1 mixture of rotamers): δ = 9.30 (s, 0.5 H, NH), 9.26 (s, 0.5 H, NH), 7.30 (t, *J* = 7.7 Hz, 1 H), 7.17 (d, *J* = 7.2 Hz, 1 H), 7.10 (t, *J* = 7.5 Hz, 1 H), 6.93 (d, *J* = 7.5 Hz, 1 H), 4.03 (d, *J* = 12.7 Hz, 0.5 H), 3.96 (d, *J* = 12.3 Hz, 0.5 H), 3.79–3.73 (m, 2 H), 3.69–3.64 (m, 1 H), 2.53–2.47 (m, 1 H), 2.38–2.29 (m, 1 H), 1.50 (s, 4.5 H), 1.48 ppm (s, 4.5 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 154.2, 154.0, 152.0, 135.0, 134.9, 129.9, 123.8, 123.2, 120.3, 120.2, 114.9,



1c

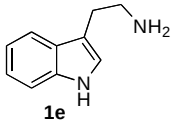
89.5, 88.7, 80.0, 79.9, 57.1, 56.5, 44.4, 44.1, 38.1, 37.2, 28.5 ppm; HRMS [ESI]: calcd for $C_{16}H_{20}N_2O_4^+$ [M + Na^+]: 327.1315, found 327.1320.

***tert*-Butyl 4-(2-aminophenyl)-2,3-dihydro-1*H*-pyrrole-1-carboxylate (1d).** To a solution of spirocarbamate **1c** (32.7 mg, 0.10 mmol, 1.0 equiv) in THF (3.0 mL) were successively added *t*BuOK (13.5 mg, 0.12 mmol, 1.2 equiv) and TBSCl (18 mg, 0.12 mmol, 1.2 equiv) at room temperature. The reaction mixture was then allowed to stir until *N*-silylation was complete, as evidenced by ^{1}H NMR spectroscopic analysis. The mixture was then cooled to –50 ºC (internal temperature, dry ice/acetone) and treated dropwise with freshly prepared LDA (1.0 M in THF, 0.50 mL, 0.50 mmol, 5.0 equiv) while the internal temperature was kept below –50 ºC. The reaction was allowed to proceed at –50 to –30 ºC until the starting material was completely consumed, as evidenced by TLC analysis. The mixture was then quenched by the sequential addition of saturated aqueous NH_4Cl solution (2 mL), H_2O (2 mL) and brine (2 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, EtOAc:hexanes 1:3, containing 0.5 % Et_3N) afforded enamine **1d** (20 mg, 77 %) as a white solid. **1d**: R_f = 0.75 (silica gel, EtOAc:hexanes 1:1); mp 124–125 ºC (EtOAc); IR (film): ν_{max} = 3421 (w), 3333 (w), 3218 (w), 3131 (w), 2967 (m), 2930 (m), 1713 (m), 1675 (s), 1455 (w), 1422 (s), 1349 (w), 1269 (m), 1165 (s), 1150 (s), 906 (m), 749 (m) cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN, ca. 1:1 mixture of rotamers): δ = 7.02 (d, *J* = 7.6 Hz, 1 H), 6.97 (t, *J* = 6.5 Hz, 1 H), 6.90 (br s, 1 H), 6.72 (d, *J* = 7.9 Hz, 1 H), 6.68 (t, *J* = 7.4 Hz, 1 H), 4.17 (br s, 2 H), 3.77–3.72 (m, 2 H), 3.03–2.95 (m, 2 H), 1.47 ppm (s, 9 H); ^{13}C NMR (150 MHz, CD_3CN): δ = 153.0, 152.4, 146.0, 128.4, 128.3, 128.1, 127.4, 127.1, 121.8, 119.9, 119.9, 119.1, 117.0, 80.9, 80.7, 45.7, 45.2, 33.3, 32.2, 28.6 ppm; HRMS [ESI]: calcd for $C_{15}H_{21}N_2O_2^+$ [M + H^+]: 261.1598, found 261.1603.



1d

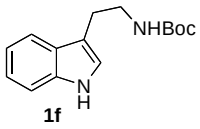
2-(1*H*-Indol-3-yl)ethanamine (1e). Following general procedure B for tryptamine formation starting with spirocarbamate **1c**, tryptamine **1e** (12.2 mg, 76 %) was obtained as a white solid. Tryptamine **1e** was also obtained starting with enamine **1d** according to the following procedure: To a solution of **1d** (130 mg, 0.50 mmol) in CH_2Cl_2



1e

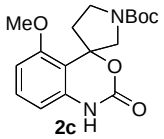
(20 mL) at 0 ºC was added TFA (2.0 mL) dropwise. The resulting solution was warmed to room temperature and stirred for 2 h. The reaction mixture was concentrated under reduced pressure and diluted with saturated aqueous $NaHCO_3$ solution until the pH rose above 7. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford tryptamine **1e** as a white solid (78.5 mg, 98 %). Characterization data were identical to those previously reported.[10]

***tert*-Butyl 2-(1*H*-indol-3-yl)ethyl carbamate (1f).** To a stirred solution of enamine **1d** (130 mg, 0.50 mmol) in CH_2Cl_2 (20 mL) at 0 ºC was added HCl (conc., 1 drop). The resulting solution was allowed to warm to room temperature with stirring over 2 h. The reaction mixture was treated with saturated aqueous $NaHCO_3$ solution until the pH rose above 7. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford tryptamine **1f** (128 mg, 98 %) as a white solid. Characterization data were identical to those previously reported.[11]



1f

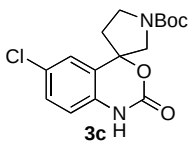
***tert*-Butyl 5-methoxy-2-oxo-1,2-dihydrospiro[benzo[*d*][1,3]oxazine-4,3'-pyrrolidine]-1'-carboxylate (2c).** This compound was prepared according to general procedure A and starting with *N*-Boc aniline **2a** by performing the lithiation for 2 h between –20 and –15 ºC. Flash column chromatography (silica gel, EtOAc:hexanes 1:2 → 2:1) afforded spirocarbamate **2c** (762 mg, 76 %) as a white solid. **2c**: R_f = 0.24 (silica gel, EtOAc:hexanes 1:1); mp 172–173 ºC (CH_2Cl_2/hexanes); IR (film): ν_{max} = 2967 (b), 1720 (s), 1686 (s), 1403 (s), 1379 (s), 1368 (s), 1247 (m), 1174 (w), 1146 (m), 1105 (w), 1045 (w), 781 (w), 759 (m) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, ca. 1:1 mixture of rotamers): δ = 9.32 (s, 0.5 H, NH), 9.28 (s, 0.5 H, NH), 7.21 (t, *J* = 8.1 Hz, 1 H), 6.61 (d, *J* = 8.7 Hz, 1 H), 6.52 (d, *J* = 7.9 Hz, 1 H), 4.16 (d, *J* = 12.3 Hz, 0.5 H), 4.02 (d, *J* = 12.3 Hz, 0.5 H), 3.85 (s, 1.5 H), 3.84 (s, 1.5 H), 3.86–3.61 (m, 3 H), 2.93–2.83 (m, 1 H), 2.26 (d, *J* = 6.2 Hz, 0.5 H), 2.24 (d, *J* = 6.2 Hz, 0.5 H), 1.50 (s, 4.5 H), 1.47 ppm (s, 4.5 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 155.6, 154.4, 154.3, 150.9, 136.0, 136.0, 130.4, 107.9, 106.6, 106.3, 91.2, 90.4, 79.5, 79.5, 56.7, 56.1, 55.7, 44.3,



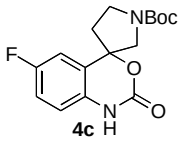
2c

44.1, 37.4, 36.7, 29.6, 28.5 ppm; HRMS [ESI]: calcd for $C_{17}H_{22}N_2O_5^+$ [M + Na^+]: 357.1421, found 357.1425.

***tert*-Butyl 6-chloro-2-oxo-1,2-dihydrospiro[benzo[*d*][1,3]oxazine-4,3'-pyrrolidine]-1'-carboxylate (3c).** This compound was prepared according to general procedure A and starting with *N*-Boc aniline **3a** by performing the lithiation for 2 h between –20 and –15 ºC. Flash column chromatography (silica gel, EtOAc:hexanes 1:2 → 2:1) afforded spirocarbamate **3c** (822 mg, 81 %) as a white solid. **3c**: R_f = 0.30 (silica gel, EtOAc:hexanes 1:1); mp 147–148 ºC (CH_2Cl_2/hexanes); IR (film): ν_{max} = 2971 (b), 1717 (s), 1673 (s), 1497 (w), 1409 (s), 1365 (m), 1153 (s), 1031 (m), 878 (w), 814 (m) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, ca. 1:1 mixture of rotamers): δ = 9.74 (s, 0.5 H, NH), 9.71 (s, 0.5 H, NH), 7.26 (d, *J* = 8.4 Hz, 1 H), 7.16 (s, 1 H), 6.90 (d, *J* = 8.4 Hz, 1 H), 4.01 (d, *J* = 12.7 Hz, 0.5 H), 3.94 (d, *J* = 12.6 Hz, 0.5 H), 3.75–3.63 (m, 3 H), 2.51–2.46 (m, 1 H), 2.35–2.28 (m, 1 H), 1.49 (s, 4.5 H), 1.47 ppm (s, 4.5 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 154.2, 154.0, 151.8, 133.6, 133.6, 129.9, 129.0, 123.5, 121.8, 116.3, 89.1, 88.2, 80.2, 80.1, 57.0, 56.5, 44.3, 44.0, 37.9, 37.2, 28.5, 28.4 ppm; HRMS [ESI]: calcd for $C_{16}H_{19}ClN_2O_4^+$ [M + Na^+]: 361.0926, found 361.0927.

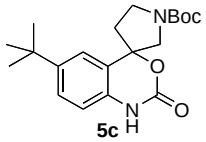


***tert*-Butyl 6-fluoro-2-oxo-1,2-dihydrospiro[benzo[*d*][1,3]oxazine-4,3'-pyrrolidine]-1'-carboxylate (4c).** This compound was prepared according to general procedure A and starting with *N*-Boc aniline **4a** by performing the lithiation for 2 h between –20 and –15 ºC. Flash column chromatography (silica gel, EtOAc:hexanes 1:2 → 2:1) afforded spirocarbamate **4c** (676 mg, 70 %) as a white solid. **4c**: R_f = 0.28 (silica gel, EtOAc:hexanes 1:1); mp 165–166 ºC (CH_2Cl_2/hexanes); IR (film): ν_{max} = 3258 (b), 2970 (b), 1724 (s), 1672 (s), 1501 (m), 1413 (s), 1320 (w), 1164 (m), 1126 (w), 1027 (s), 876 (w), 864 (w), 727 (w), 562 (m) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, ca. 1:1 mixture of rotamers): δ = 9.51 (s, 0.5 H, NH), 9.49 (s, 0.5 H, NH), 7.03–7.00 (m, 1 H), 6.93–6.90 (m, 2 H), 4.03 (d, *J* = 12.7 Hz, 0.5 H), 3.96 (d, *J* = 12.6 Hz, 0.5 H), 3.77–3.61 (m, 3 H), 2.52–2.48 (m, 1 H), 2.36–2.28 (m, 1 H), 1.50 (s, 4.5 H), 1.48 ppm (s, 4.5 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.1 (d, *J* = 243.2 Hz, CF), 154.2, 154.0, 151.9, 131.1, 131.1, 121.9, 121.9, 116.8, 116.6, 116.3, 116.3, 110.6,

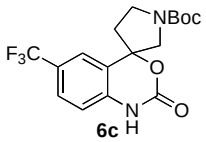


110.6, 110.5, 110.5, 88.9, 88.1, 80.2, 80.1, 56.9, 56.4, 44.3, 44.0, 37.8, 37.1, 28.5 ppm; HRMS [ESI]: calcd for $C_{16}H_{19}FN_2O_4^+$ [M + Na^+]: 345.1221, found 345.1225.

***tert*-Butyl 6-*tert*-butyl-2-oxo-1,2-dihydrospiro[benzo[*d*][1,3]oxazine-4,3'-pyrrolidine]-1'-carboxylate (5c).** This compound was prepared according to general procedure A and starting with *N*-Boc aniline **5a** by performing the lithiation for 4 h between –15 and –10 ºC. Flash column chromatography (silica gel, EtOAc:hexanes 1:2 → 2:1) provided spirocarbamate **5c** (800 mg, 74 %) as a white solid. **5c**: R_f = 0.41 (silica gel, EtOAc:hexanes 1:1); mp 200 ºC (CH_2Cl_2/hexanes); IR (film): ν_{max} = 3271 (b), 2954 (b), 1735 (s), 1669 (m), 1508 (m), 1405 (m), 1252 (w), 1154 (w), 1021 (m), 827 (m) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, ca. 1:1 mixture of rotamers): δ = 9.43 (s, 0.5 H, NH), 9.39 (s, 0.5 H, NH), 7.31 (d, *J* = 6.4 Hz, 1 H), 7.15 (d, *J* = 5.3 Hz, 1 H), 6.87 (d, *J* = 8.2 Hz, 1 H), 4.01 (d, *J* = 12.6 Hz, 0.5 H), 3.96 (d, *J* = 12.7 Hz, 0.5 H), 3.82 (d, *J* = 12.6 Hz, 0.5 H), 3.78–3.68 (m, 2 H), 3.65 (d, *J* = 12.7 Hz, 0.5 H), 2.53–2.46 (m, 1 H), 2.40–2.28 (m, 1 H), 1.51 (s, 4.5 H), 1.48 (s, 4.5 H), 1.34 (s, 4.5 H), 1.29 ppm (s, 4.5 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 154.3, 154.0, 152.2, 147.1, 132.5, 132.4, 126.9, 126.8, 119.8, 119.7, 119.6, 119.6, 114.6, 89.7, 89.0, 79.9, 79.8, 57.2, 56.5, 44.5, 44.1, 38.3, 37.2, 34.5, 31.4, 28.5 ppm; HRMS [ESI]: calcd for $C_{20}H_{28}N_2O_4^+$ [M + Na^+]: 383.1941, found 383.1946.

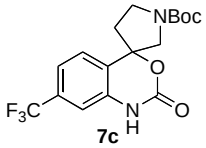


***tert*-Butyl 2-oxo-6-(trifluoromethyl)-1,2-dihydrospiro[benzo[*d*][1,3]oxazine-4,3'-pyrrolidine]-1'-carboxylate (6c).** This compound was prepared according to general procedure A and starting with *N*-Boc aniline **6a** by performing the lithiation for 4 h between –35 and –15 ºC, and 2 h between –15 and –8 ºC. Flash column chromatography (silica gel, EtOAc:hexanes 1:2 → 2:1) afforded spirocarbamate **6c** (804 mg, 72 %) as a white solid. **6c**: R_f = 0.40 (silica gel, EtOAc:hexanes 1:1); mp 212–213 ºC (CH_2Cl_2/hexanes); ν_{max} = 3218 (b), 2980 (b), 1723 (s), 1657 (m), 1417 (m), 1367 (m), 1328 (s), 1266 (m), 1156 (s), 1110 (s), 1073 (m), 1040 (s), 877 (w), 830 (m), 760 (w), cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, ca. 1:1 mixture of rotamers): δ = 9.63 (s, 0.5 H, NH), 9.62 (s, 0.5 H, NH), 7.59 (d, *J* = 8.3 Hz, 1 H), 7.44 (s, 1 H), 7.04 (d, *J* = 8.3 Hz, 1 H), 4.07 (d, *J* = 12.7 Hz, 0.5 H), 4.00 (d, *J* = 12.7 Hz, 0.5 H), 3.76–3.68 (m, 3 H), 2.54 (d, *J* =



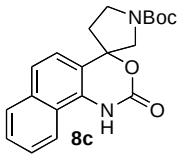
13.6 Hz, 0.5 H), 2.53 (d, J = 13.3 Hz, 0.5 H), 2.43–2.36 (m, 1 H), 1.51 (s, 4.5 H), 1.49 ppm (s, 4.5 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 154.2, 153.9, 151.5, 138.0, 138.0, 127.3, 126.2, 125.9, 123.7 (**C**F_3, q, $J_{C\text{-}F}$ = 270 Hz), 120.7, 115.3, 89.3, 88.5, 80.3, 80.2, 57.1, 56.6, 44.3, 44.0, 38.0, 37.3, 28.4 ppm; HRMS [ESI]: calcd for $C_{17}H_{19}F_3N_2O_4^+$ [M + Na^+]: 395.1189, found 395.1193.

***tert*-Butyl 2-oxo-7-(trifluoromethyl)-1,2-dihydrospiro[benzo[*d*][1,3]oxazine-4,3'-pyrrolidine]-1'-carboxylate (7c).** This compound was prepared according to general procedure A and starting with *N*-Boc aniline **7a** by performing the lithiation for 2 h between –20 and –15 ºC. Flash column chromatography (silica gel, EtOAc:hexanes 1:2 → 2:1) afforded spirocarbamate **7c** (822 mg, 74 %) as a white solid. **7c**: R_f = 0.22 (silica gel, EtOAc:hexanes 1:2); mp 205–206 ºC (CH_2Cl_2/hexanes); IR (film): ν_{max} = 3197 (b), 2978 (b), 1723 (s), 1687 (m), 1658 (s), 1411 (m), 1335 (m), 1243 (s), 1127 (s), 1071 (m), 1043 (m), 878 (s) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, ca. 1:1 mixture of rotamers): δ = 9.63 (s, 0.5 H, NH), 9.61 (s, 0.5 H, NH), 7.37 (d, J = 8.0 Hz, 1 H), 7.31 (d, J = 8.0 Hz, 1 H), 7.20 (s, 1 H), 4.07 (d, J = 12.7 Hz, 0.5 H), 3.99 (d, J = 12.6 Hz, 0.5 H), 3.80–3.68 (m, 3 H), 2.54 (d, J = 12.5 Hz, 0.5 H), 2.53 (d, J = 12.7 Hz, 0.5 H), 2.39–2.33 (m, 1 H), 1.51 (s, 4.5 H), 1.48 ppm (s, 4.5 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 154.3, 154.0, 152.2, 147.1, 132.5, 132.4, 126.9, 122.9 (**C**F_3, q, $J_{C\text{-}F}$ = 265 Hz), 119.8, 119.7, 119.6, 119.6, 114.6, 89.7, 89.0, 79.9, 79.8, 57.2, 56.5, 44.5, 44.1, 38.3, 37.2, 34.5, 31.4, 28.5 ppm; HRMS [ESI]: calcd for $C_{17}H_{19}F_3N_2O_4^+$ [M + Na^+]: 395.1189, found 395.1194.



7c

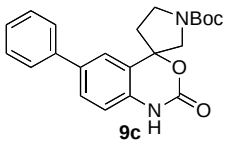
***tert*-Butyl 2-oxo-1,2-dihydrospiro[naphtho[1,2-d][1,3]oxazine-4,3'-pyrrolidine]-1'-carboxylate (8c).** This compound was prepared according to general procedure A and starting with *N*-Boc aniline **8a** by performing the lithiation for 4 h between –15 and –10 ºC. Flash column chromatography (silica gel, EtOAc:hexanes 1:2 → 2:1) afforded spirocarbamate **8c** (839 mg, 79 %) as a white solid. **8c**: R_f = 0.25 (silica gel, EtOAc:hexanes 1:2); mp 211–212 ºC (CH_2Cl_2/hexanes); IR (film): ν_{max} = 3227 (b), 2975 (b), 1709 (s), 1690 (s), 1405 (m), 1380 (m), 1366 (m), 1167 (m), 1145 (m), 812 (w), 756 (m), 741 (m), 666 (w) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, ca. 1:1 mixture of rotamers): δ = 10.21 (s, 0.5 H, NH), 10.14 (s, 0.5 H, NH), 8.28 (d, J = 8.6 Hz, 0.5 H), 8.26 (d, J = 8.7 Hz, 0.5



8c

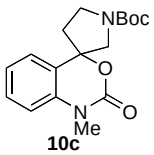
H), 7.84 (d, *J* = 8.0 Hz, 1 H), 7.68 (dt, *J* = 7.5, 7.3 Hz, 1 H), 7.61 (t, *J* = 8.3 Hz, 1 H), 7.56 (t, *J* = 7.8 Hz, 1 H), 7.28–7.25 (m, 1 H), 4.02 (d, *J* = 12.7 Hz, 0.5 H), 4.06 (d, *J* = 12.6, 0.5 H), 3.89 (d, *J* = 12.8 Hz, 0.5 H), 3.87–3.68 (m, 2 H), 3.81 (d, *J* = 12.7 Hz, 0.5 H), 2.62–2.56 (m, 1 H), 2.48–2.41 (m, 1 H), 1.56 (s, 4.5 H), 1.49 ppm (s, 4.5 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 154.3, 154.2, 152.3, 133.8, 130.6, 130.6, 128.4, 127.5, 127.4, 127.1, 123.9, 121.6, 120.6, 120.0, 115.0, 89.8, 89.0, 80.0, 79.9, 57.1, 56.6, 44.5, 44.2, 38.3, 37.4, 28.5 ppm; HRMS [ESI]: calcd for $C_{20}H_{22}N_2O_4^+$ [M + Na^+]: 377.1472, found 377.1476.

***tert*-Butyl 2-oxo-6-phenyl-1,2-dihydrospiro[benzo[*d*][1,3]oxazine-4,3'-pyrrolidine]-1'-carboxylate (9c).** This compound was prepared according to general procedure A and starting with *N*-Boc aniline **9a** by performing the lithiation for 3 h between –15 and –10 ºC. Flash column chromatography (silica gel, EtOAc:hexanes 1:3) afforded spirocarbamate **9c** (912 mg, 80 %) as a white solid. **9c**: R_f = 0.13 (silica gel, EtOAc:hexanes 1:2); mp 232–233 ºC (dec.) (CH_2Cl_2/hexanes); IR (film): ν_{max} = 3220 (b), 2974 (m), 2913 (m), 2866 (m), 1708 (s), 1686 (s), 142 (m), 1365 (m), 1132 (w), 1044 (w), 768 (m) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$:DMSO-d_6 1:1, ca. 1:1 mixture of rotamers): δ = 10.19 (s, 1 H), 7.46 (br d, *J* = 7.2 Hz, 2 H), 7.41 (d, *J* = 8.2 Hz, 1 H), 7.34 (t, *J* = 7.4 Hz, 2 H), 7.31 (s, 1 H), 7.24 (t, *J* = 7.3 Hz, 1 H), 6.96 (d, *J* = 8.2 Hz, 1 H), 3.85 (d, *J* = 12.3 Hz, 0.5 H), 3.83 (d, *J* = 12.3 Hz, 0.5 H), 3.67 (d, *J* = 12.5 Hz, 0.5 H), 3.62–3.58 (m, 2.5 H), 2.40–2.32 (m, 2 H), 1.40 (s, 4.5 H), 1.37 ppm (s, 4.5 H); ^{13}C NMR (150 MHz, $CDCl_3$:DMSO-d_6 1:1): δ = 153.0, 152.8, 149.5, 138.9, 135.0, 134.3, 127.8, 126.2, 125.6, 125.6, 120.7, 120.6, 119.6, 119.5, 87.6, 86.7, 78.5, 78.4, 56.0, 55.5, 43.4, 43.1, 36.7, 35.9, 27.4 ppm; HRMS [ESI]: calcd for $C_{22}H_{25}N_2O_4^+$ [M + H^+]: 381.1809, found 381.1816.



9c

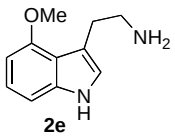
***tert*-Butyl 1-methyl-2-oxo-1,2-dihydrospiro[benzo[*d*][1,3]oxazine-4,3'-pyrrolidine]-1'-carboxylate (10c).** This compound was prepared according to general procedure A and starting with *N*-Boc aniline **1a** by performing the lithiation for 4 h at –10 ºC. Following the addition of *t*BuOK and heating to 60–70 ºC for 4 h, the reaction mixture was cooled to room temperature and treated with iodomethane (0.37 mL, 6.0 mmol, 2.0 equiv). After standard aqueous work-up, flash column chromatography (silica gel,



10c

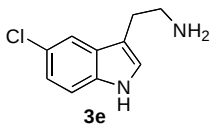
EtOAc:hexanes 1:3) afforded spirocarbamate **10c** (680 mg, 71 %) as a viscous yellow oil. **10c**: R_f = 0.39 (silica gel, EtOAc:hexanes 1:1); IR (film): ν_{max} = 2975 (w), 2931 (w), 2893 (w), 1717 (s), 1694 (s), 1606 (w), 1598 (w), 1403 (m), 1365 (m), 1158 (m), 1145 (m), 756 (m) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, ca. 1:1 mixture of rotamers): δ = 7.34 (t, *J* = 7.8 Hz, 1 H), 7.17 (br d, *J* = 7.2 Hz, 1 H), 7.09 (t, *J* = 7.5 Hz, 1 H), 6.95 (d, *J* = 8.1 Hz, 1 H), 3.91 (d, *J* = 12.5 Hz, 0.5 H), 3.83 (d, *J* = 12.4 Hz, 0.5 H), 3.72-3.56 (m, 3 H), 3.38 (s, 1.5 H), 3.36 (s, 1.5 H), 2.40–2.25 (m, 2 H), 1.44 (s, 4.5 H), 1.42 ppm (s, 4.5 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 154.1, 153.9, 151.4, 151.3, 137.5, 137.4, 123.4, 122.9, 122.8, 122.7, 113.4, 87.0, 86.2, 79.8, 79.7, 56.2, 55.6, 44.2, 43.9, 36.8, 36.3, 31.3, 28.4 ppm; HRMS [ESI]: calcd for $C_{17}H_{23}N_2O_4^+$ [M + H^+]: 319.1652, found 319.1648.

2-(4-Methoxy-1*H*-indol-3-yl)ethanamine (2e). Tryptamine **2e** was prepared according to general procedure B starting with spirocarbamate **2c** (16.0 mg, 84 %) as a light yellow oil. Characterization data for **2e** were identical to those previously reported.[12]



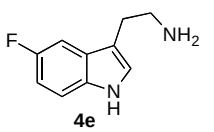
2e

2-(5-Chloro-1*H*-indol-3-yl)ethanamine (3e). Tryptamine **3e** was prepared according to general procedure B starting with spirocarbamate **3c** (16.6 mg, 80 %) as a light yellow oil. **3e**: ^1H NMR (600 MHz, CD_3CN): δ = 9.18 (br s, 1 H), 7.58 (d, *J* = 1.5 Hz, 1 H), 7.36 (d, *J* = 8.7 Hz, 1 H), 7.13 (d, *J* = 1.3 Hz, 1 H), 7.08 (dd, *J* = 8.7, 1.8 Hz, 1 H), 2.86 (t, *J* = 6.9 Hz, 2 H), 2.77 ppm (t, *J* = 6.9 Hz, 2 H); ^{13}C NMR (150 MHz, CD_3CN): δ = 135.8, 129.7, 125.1, 124.7, 121.4, 118.8, 114.3, 113.5, 43.6, 30.2 ppm; the melting point and IR spectral data for **3e** were identical to those previously reported.[13]



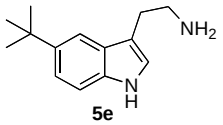
3e

2-(5-Fluoro-1*H*-indol-3-yl)ethanamine (4e). Tryptamine **4e** was prepared according to general procedure B starting with spirocarbamate **4c** (12.6 mg, 71 %) as a light yellow oil. **4e**: HRMS [ESI]: calcd for $C_{10}H_{12}FN_2^+$ [M + H^+]: 179.0979, found 179.0972. The ^1H NMR spectroscopic data for **4e** were identical to those previously reported.[14]



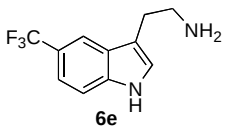
4e

2-(5-*tert*-Butyl-1*H*-indol-3-yl)ethanamine (5e). This tryptamine was prepared according to general procedure B starting with spirocarbamate **5c** (14.3 mg, 66%) as a light yellow oil. Characterization data for **5e** were identical to those previously reported.[15]



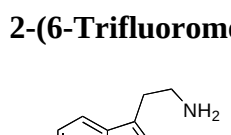
5e

2-(5-Trifluoromethyl-1*H*-indol-3-yl)ethanamine[16] **(6e).** This tryptamine was prepared according to general procedure B starting with spirocarbamate **6c** (15.5 mg, 68%) as a light yellow oil. **6e**: IR (film) ν_{max} = 3343 (br, m), 2976 (m), 2922 (m), 2844 (m), 1379 (br, w), 1121 (s), 1091 (m), 1060 (m), 1033 (m), 972 (s) cm^{-1}; ^1H NMR (600 MHz, CD_3OD): δ = 7.89 (s, 1 H), 7.48 (d, *J* = 8.4 Hz, 1 H), 7.35 (d, *J* = 8.7 Hz, 1 H), 7.25 (s, 1 H), 3.01–2.95 ppm (m, 4 H); ^{13}C NMR (150 MHz, CD_3OD): δ = 139.8, 128.2, 126.4, 126.0, 122.1 (q, $J_{C\text{-}F}$ = 31 Hz), 119.1 (q, $J_{C\text{-}F}$ = 3.3 Hz), 117.1 (q, $J_{C\text{-}F}$ = 4.4 Hz), 114.4, 112.9, 43.0, 28.6 ppm; HRMS [ESI]: calcd for $C_{11}H_{12}F_3N_2^+$ [M + H^+]: 229.0947, found 229.0948.



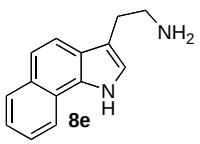
6e

2-(6-Trifluoromethyl-1*H*-indol-3-yl)ethanamine (7e). This tryptamine was prepared according to general procedure B starting with spirocarbamate **7c** (17.6 mg, 77 %) as a light yellow oil. **7e**: IR (film) ν_{max} = 3356 (w), 3320 (w), 2943 (m), 2922 (m), 2865 (m), 2844 (w), 1454 (w), 1346 (br, m), 1054 (s), 1033 (s), 1014 (s), 832 (m) cm^{-1}; ^1H NMR (600 MHz, CD_3CN): δ = 9.48 (br s, 1 H), 7.75–7.72 (m, 2 H), 7.31 (dd, *J* = 8.5, 1.1 Hz, 1 H), 7.29 (d, *J* = 2.3 Hz, 1 H), 2.91 (t, *J* = 6.4 Hz, 2 H), 2.86 ppm (t, *J* = 6.4 Hz, 2 H); ^{13}C NMR (150 MHz, CD_3CN): δ = 136.2, 131.0, 126.6 (**C**F_3, q, $J_{C\text{-}F}$ = 269 Hz), 126.8, 123.5 ($\mathbf{C}_{Ar}CF_3$, q, $J_{C\text{-}F}$ = 31 Hz), 120.2, 115.8 (q, $J_{C\text{-}F}$ = 4 Hz), 114.7, 109.7 (q, $J_{C\text{-}F}$ = 4 Hz), 43.4, 29.7 ppm; HRMS [ESI]: calcd for $C_{11}H_{12}F_3N_2^+$ [M + H^+]: 229.0947, found 229.0947.



7e

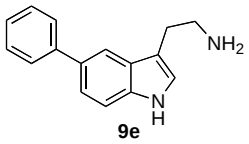
2-(1*H*-Benzo[*g*]indol-3-yl)ethanamine (8e). This tryptamine was prepared according to general procedure B starting from spirocarbamate **8c** (8.6 mg, 41%) as a light yellow oil. **8e**: IR (film) ν_{max} = 3356 (w), 3320 (w), 2967 (m), 2923 (m), 2865 (m), 2844 (m), 1270 (w), 1054 (s), 1033 (s), 1012 (s) cm^{-1}; ^1H NMR (600 MHz,



8e

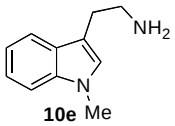
CD_3CN): δ = 10.00 (br s, 1 H), 8.16 (dd, *J* = 8.2, 3.3 Hz, 1 H), 7.92 (dd, *J* = 8.2, 2.8 Hz, 1 H), 7.71 (dd, *J* = 8.2, 3.3 Hz, 1 H), 7.57–7.50 (m, 1 H), 7.48 (dd, *J* = 8.6, 3.3 Hz, 1 H), 7.45–7.39 (m, 1 H), 7.17 (t, *J* = 2.5 Hz, 1 H), 2.98–2.94 (m, 2 H), 2.91 ppm (dt, *J* = 5.9, 3.4 Hz, 2 H); ^{13}C NMR (150 MHz, CD_3CN): δ = 131.3, 129.5, 126.4, 124.7, 123.2, 121.8, 121.2, 120.5, 120.2, 118.4, 116.2, 43.9, 30.1 ppm; HRMS [ESI]: calcd for $C_{14}H_{15}N_2^+$ [M + H^+]: 211.1230, found 211.1230.

2-(4-Phenyl-1*H*-indol-3-yl)ethanamine (9e). This tryptamine was prepared according to general procedure B starting from spirocarbamate **9c** (20.5 mg, 87%), as a light yellow oil. **9e**: IR (film) ν_{max} = 3355 (w), 3259 (w), 2967 (m), 2923 (m), 2844 (w), 2827 (w), 1678 (w), 1271 (m), 1054 (s), 1033 (s), 1014 (s) cm^{-1}; ^1H NMR (600 MHz, CD_3CN): δ = 9.21 (br s, 1 H), 7.83 (s, 1 H), 7.68 (dd, *J* = 8.4, 1.2 Hz, 2 H), 7.46 (d, *J* = 8.2 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 7.43 (dt, *J* = 8.4, 1.2 Hz, 2 H), 7.30 (tt, *J* = 7.2, 1.2 Hz, 1 H), 7.13 (d, *J* = 0.9 Hz, 1 H), 2.97 (t, *J* = 6.6 Hz, 2 H), 2.91 ppm (t, *J* = 6.8 Hz, 2 H); ^{13}C NMR (150 MHz, CD_3CN): δ = 143.6, 137.3, 133.0, 129.8, 129.2, 128.1, 127.3, 124.6, 122.0, 118.0, 114.3, 112.7, 43.3, 29.3 ppm; HRMS [ESI]: calcd for $C_{16}H_{17}N_2^+$ [M + H^+]: 237.1386, found 237.1384.



9e

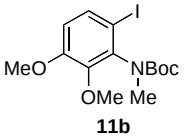
(1-Methylindol-3-yl)-ethanamine (10e). To a solution of *N*-methyl spirocarbamate **10c** (21 mg, 0.0663 mmol, 1.0 equiv) in THF (2 mL) at –50 ºC (internal temperature, dry ice/acetone) was added dropwise freshly prepared LDA (1.0 M in THF, 0.26 mL, 0.26 mmol, 3.9 equiv). After stirring for 1 h at –50 ºC, the reaction mixture was quenched at –50 ºC with saturated aqueous NH_4Cl solution (5 mL), the layers were separated, and the aqueous phase was extracted with Et_2O (2 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was then redissolved in CH_2Cl_2 (3 mL), treated at room temperature with TFA (0.3 mL), and stirred for 1 h. After concentration under reduced pressure, the crude residue was treated with saturated aqueous $NaHCO_3$ solution until the pH rose above 7. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford tryptamine **10e** (7.5 mg, 65 %) as a light yellow



10e

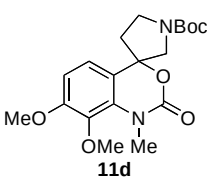
oil. **10e**: HRMS [ESI]: calcd for $C_{11}H_{15}N_2^+$ [M + H^+]: 175.1230, found 175.1227. The NMR spectral data of this compound were identical to those previously reported.[17]

***tert*-Butyl 6-iodo-2,3-dimethoxyphenyl(methyl)carbamate (11b).** 6-Iodo-2,3-dimethoxyaniline[18] (**11a**, 1.40 g, 5.00 mmol, 1.0 equiv) was transformed to its *N*-Boc derivative according to a literature procedure.[19] To a solution of the so obtained *N*-Boc aniline (1.89 g, 5.00 mmol, 1.0 equiv) in THF (30 mL) at 0 ºC was carefully added solid NaH (60% in oil, 300 mg, 7.50 mmol, 1.5 equiv). After hydrogen evolution had ceased, MeI (0.62 mL, 10.0 mmol, 2.0 equiv) was added drowise at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (25 mL) and diluted with EtOAc (100 mL). The aqueous phase was further extracted with EtOAc (2 × 20 mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, EtOAc:hexanes 1:3) afforded *N*-Boc aniline **11b** (1.22 g, 62% yield over two steps) as light beige prisms. **11b**: R_f = 0.72 (silica gel, EtOAc:hexanes 1:1); mp 103–104 ºC (EtOAc:hexanes); IR (film) ν_{max} = 2974 (w), 2937 (w), 2837 (w), 1699 (s), 1571 (m), 1473 (m), 1422 (m), 1354 (s), 1255 (m), 1150 (s), 1067 (m), 1006 (m), 1014 (s), 832 (m) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, ca. 3:1 mixture of rotamers, peaks for the major rotamer reported): δ = 7.50 (d, *J* = 9.0 Hz, 1 H), 6.65 (d, *J* = 8.8 Hz, 1 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.09 (s, 3 H), 1.39 ppm (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 154.2, 153.8, 146.6, 139.7, 132.9, 113.1, 89.2, 80.1, 60.8, 56.1, 35.3, 28.4 ppm; HRMS [ESI]: calcd for $C_{14}H_{21}INO_4^+$ [M + H^+]: 394.0510, found 394.0509.



11b

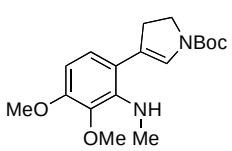
***tert*-Butyl 7,8-dimethoxy-1-methyl-2-oxo-1,2-dihydrospiro[benzo[*d*][1,3]oxazine-4,3'-pyrrolidine]-1'-carboxylate (11d).** To a solution of *N*-Boc aniline **11b** (1.22 g, 3.10 mmol, 1.0 equiv) in THF (10 mL) at –70 ºC (internal temperature, dry ice/acetone) was added *i*PrMgCl•LiCl (1.0 M in THF, 3.4 mL, 3.4 mmol, 1.1 equiv) dropwise. Once iodine-lithium exchange had proceeded to >95 % conversion, as determined by ^1H NMR spectroscopic analysis, the reaction mixture was carefully treated with $LaCl_3$•2LiCl (0.33 M in THF, 10.3 mL, 3.40 mmol, 1.1 equiv) and stirred at –70 ºC (internal temperature, dry ice/acetone) for 1 h. A solution of *N*-Boc-pyrrolidin-3-one



11d

(**A**, 1.0 M in THF, 3.10 mL, 3.10 mmol, 1.0 equiv) was rapidly introduced. The reaction mixture was stirred at –70 ºC for 1 h and then allowed to warm to room temperature. Silica gel (10 g) was added to the crude reaction mixture followed by CH_2Cl_2 (20 mL). The resulting slurry was filtered through a plug of silica and eluted with EtOAc (250 mL). The solution was concentrated under reduced pressure and the residue was purified by flash column chromatography (silica gel, EtOAc:hexanes 1:2) to afford the corresponding 3-hydroxypyrrolidine **11c** (1.06 g, 78 % yield) as a white foamy solid. To the solution of **11c** (1.06 g, 2.42 mmol, 1.0 equiv) in CH_2Cl_2 (48 mL) was added TFA (18 μL, 0.24 mmol, 0.10 equiv) at 0 ºC. The resulting mixture was allowed to stir at 0 ºC for 1 h before it was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted into CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash column chromatography (silica gel, EtOAc:hexanes 1:2) afforded spirocarbamate **11d** (925 mg, 96 % yield) as a light yellow oil. **11d**: R_f = 0.22 (silica gel, EtOAc:hexanes 1:1); IR (film) ν_{max} = 2970 (b), 1733 (s), 1685 (s), 1406 (s), 1370 (s), 1368 (s), 1217 (m), 1151 (w), 1122 (m), 1015 (w), 1017 (w), 781 (m) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, ca. 1:1 mixture of rotamers): δ = 6.87 (d, *J* = 8.5 Hz, 1 H), 6.68 (d, *J* = 8.6 Hz, 1 H), 3.89 (s, 3 H), 3.85–3.57 (m, 4 H), 3.78 (s, 3 H), 3.56 (s, 1.5 H), 3.55 (s, 1.5 H), 2.35–2.25 (m, 2 H), 1.48 (s, 4.5 H), 1.46 ppm (s, 4.5 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 150.0, 149.8, 149.6, 149.0, 148.9, 134.0, 134.0, 127.3, 127.2, 115.6, 115.5, 113.1, 113.1, 102.9, 81.9, 81.3, 75.5, 75.4, 56.8, 51.6, 51.0, 50.5, 39.8, 39.4, 31.8, 31.3, 31.2, 24.0 ppm; HRMS [ESI]: calcd for $C_{19}H_{26}N_2O_6^+$ [M + Na^+]: 401.1683, found 401.1687.

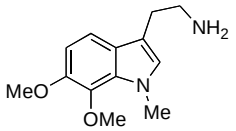
***tert*-Butyl 4-(3,4-dimethoxy-2-(methylamino)phenyl)-2,3-dihydro-1*H*-pyrrole-1-carboxylate (11e).** To a solution of *N*-methyl spirocarbamate **11d** (400 mg, 1.00 mmol, 1.0 equiv) in THF (20 mL) at –50 ºC (internal temperature, dry ice/acetone) was added dropwise freshly prepared LDA (1.0 M in THF, 1.1 mL, 1.1 mmol, 1.1 equiv). The reaction mixture was warmed to –30 ºC and stirred for 3 h, before it was quenched at that temperature with saturated NH_4Cl aqueous solution (15 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under



11e

reduced pressure. Flash column chromatography (silica gel, EtOAc:hexanes 1:3) afforded enamine **11e** (33 mg, 92 % yield) as a light yellow oil. **11e**: R_f = 0.69 (silica gel, EtOAc:hexanes 1:1); IR (film) ν_{max} = 2930 (b), 1674 (s), 1455 (m), 1426 (s), 1366 (m), 1270 (m), 1251 (m), 1165 (m), 1043 (w), 907 (w), 750 (s) cm^{-1}; ^1H NMR (600 MHz, CD_3CN): δ = 6.96 (br s, 0.5 H), 6.91 (br s, 0.5 H), 6.81 (d, *J* = 8.7 Hz, 1 H), 6.51 (d, *J* = 8.6 Hz, 1 H), 4.17 (br s, 1 H), 3.80 (s, 3 H), 3.77–3.73 (m, 2 H), 3.73 (s, 3 H), 2.96–2.89 (m, 2 H), 2.70 (s, 3 H), 1.47 ppm (s, 9 H); ^{13}C NMR (150 MHz, CD_3CN): δ = 151.8, 142.9, 140.3, 126.4, 123.4, 119.9, 119.1, 105.0, 91.2, 79.5, 60.1, 55.5, 44.9, 34.1, 30.9, 27.7 ppm; HRMS [ESI]: calcd for $C_{18}H_{26}N_2O_4^+$ [M + Na^+]: 357.1785, found 357.1788.

2-(6,7-Dimethoxy-1-methyl-1*H*-indol-3-yl)ethanamine (11f). To a solution of enamine **11e**



11f

(71 mg, 0.2 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) was added TFA (1.5 μL, 0.020 mmol, 0.10 equiv) dropwise at 0 ºC. The reaction mixture was allowed to warm to room temperature and stirred for 2 h before it was concentrated under reduced pressure. To the crude residue was added saturated aqueous $NaHCO_3$ solution until the pH rose above 7. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford tryptamine **11f** (45 mg, 96 % yield) as a light yellow oil. The ^1H NMR spectrum of this compound was identical to the previously reported values[20] and indicated ≥95 % purity.

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[4] A reaction aliquot (~0.1 mL) was quenched into 0.5 mL CD_3OD, and the ^1H NMR (400, 500 or 600 MHz, CD_3OD) was recorded. Complete disappearance of the *ortho*-proton signal indicated > 98 % *D* incorporation.

[5] Longer transmetallation time led to erosion in deuteration and yield, and to the formation of unidentified side-products.

[6] Pure starting materials were required for successful spirocycle ring opening.

[7] Since it was more convenient to transfer small amounts of TIPS-Cl than TBS-Cl under inert atmosphere, the former was favored throughout this work.

[8] A reaction aliquot (~0.2 mL) could be evaporated under reduced pressure and analyzed by ^1H NMR (CD_3CN); however, the authors found 1–2 h to be a reliable reaction time.

[9] The presence of more ^{13}C signals than the number of carbon atoms in this and other compounds in this series is attributed to the presence of rotamers.

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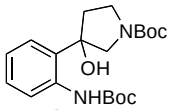
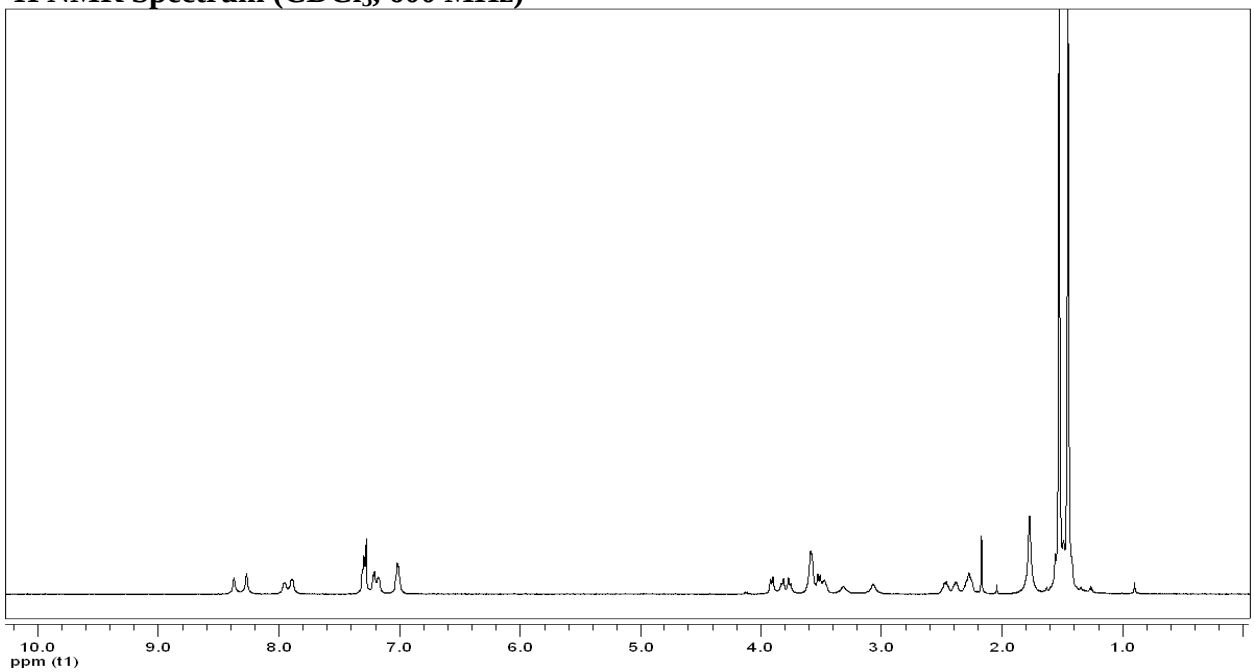
New Compounds NMR Spectra

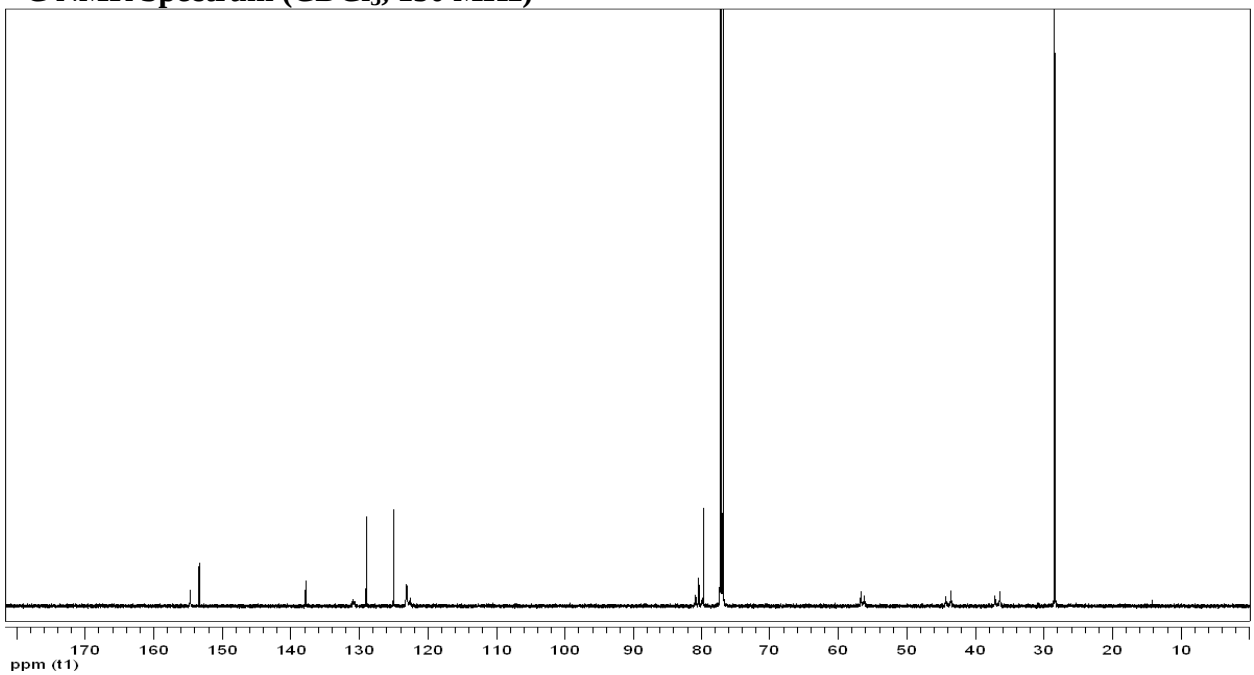


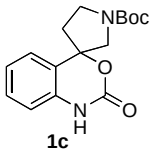
1b

^{1}H NMR Spectrum ($CDCl_3$, 600 MHz)



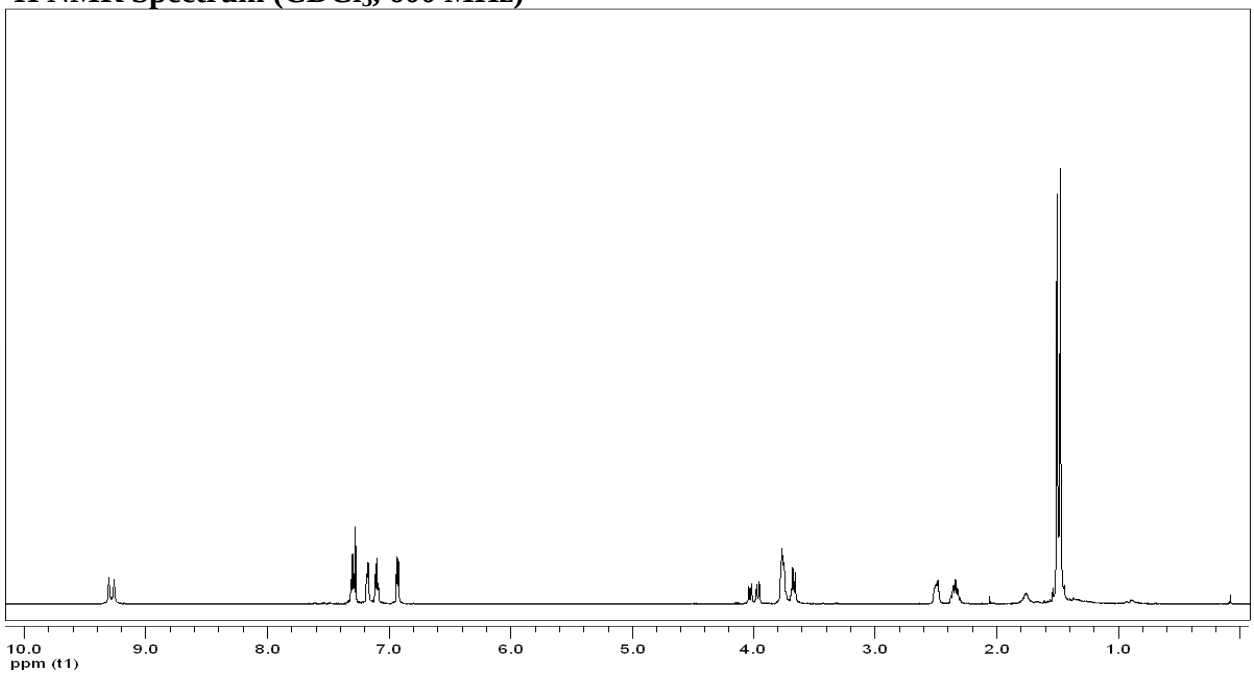
^{13}C NMR Spectrum ($CDCl_3$, 150 MHz)



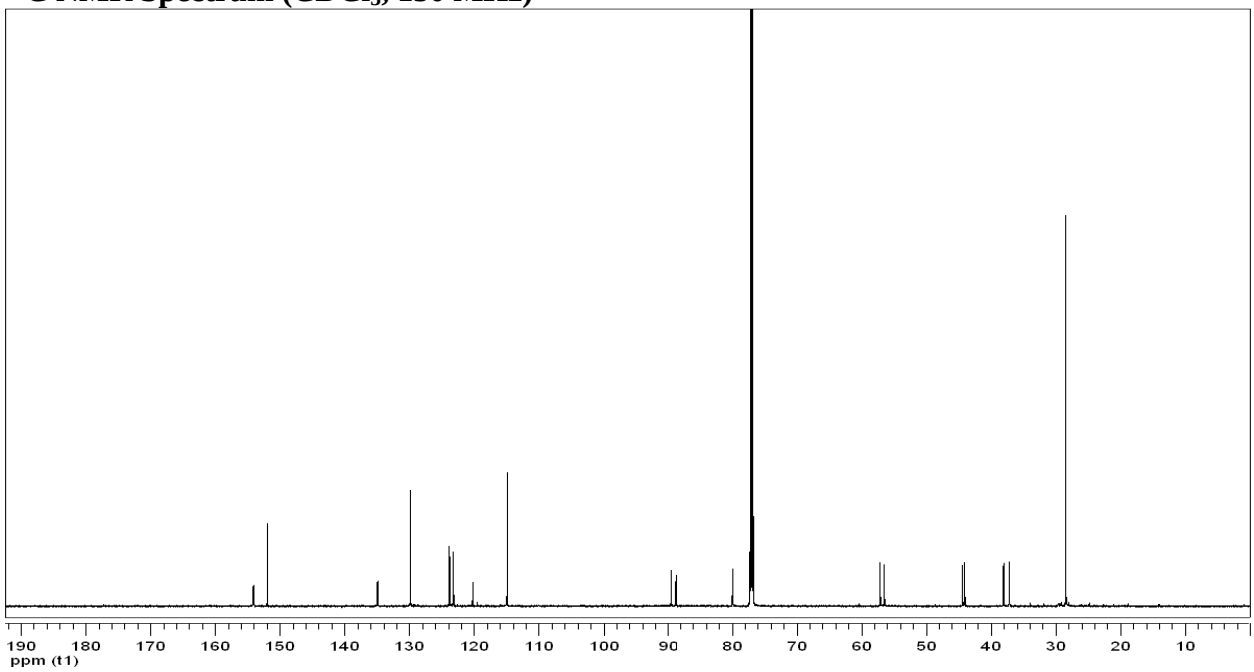


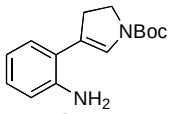
1c

^{1}H NMR Spectrum ($CDCl_3$, 600 MHz)



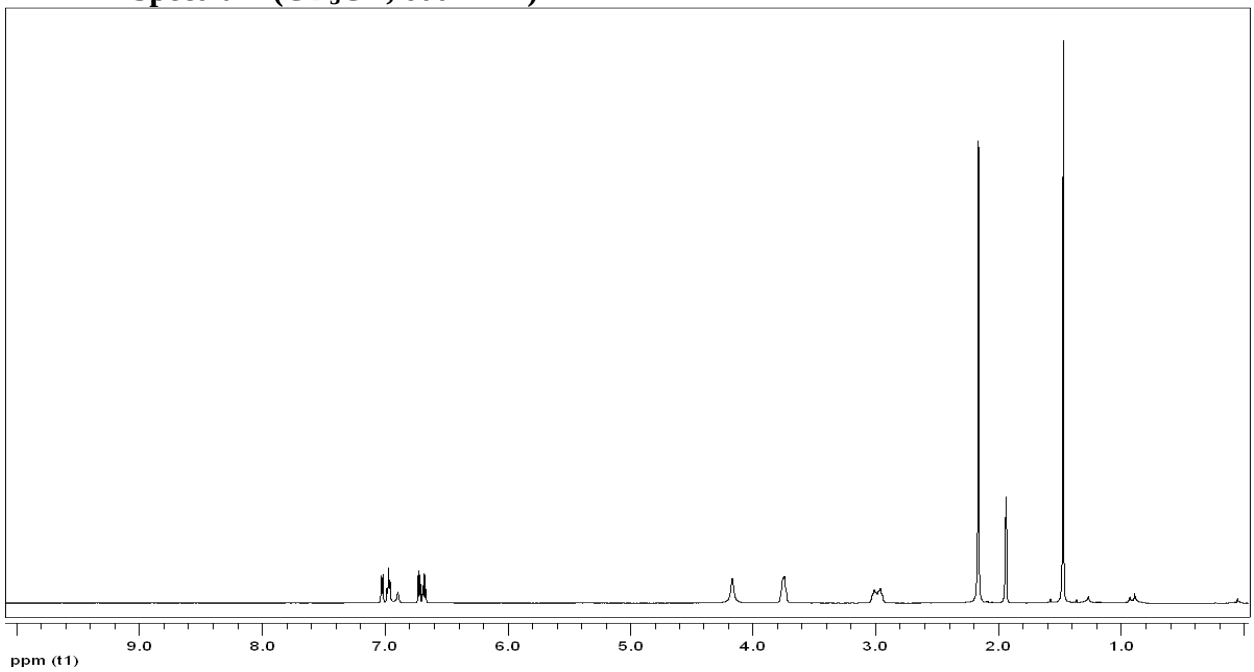
^{13}C NMR Spectrum ($CDCl_3$, 150 MHz)



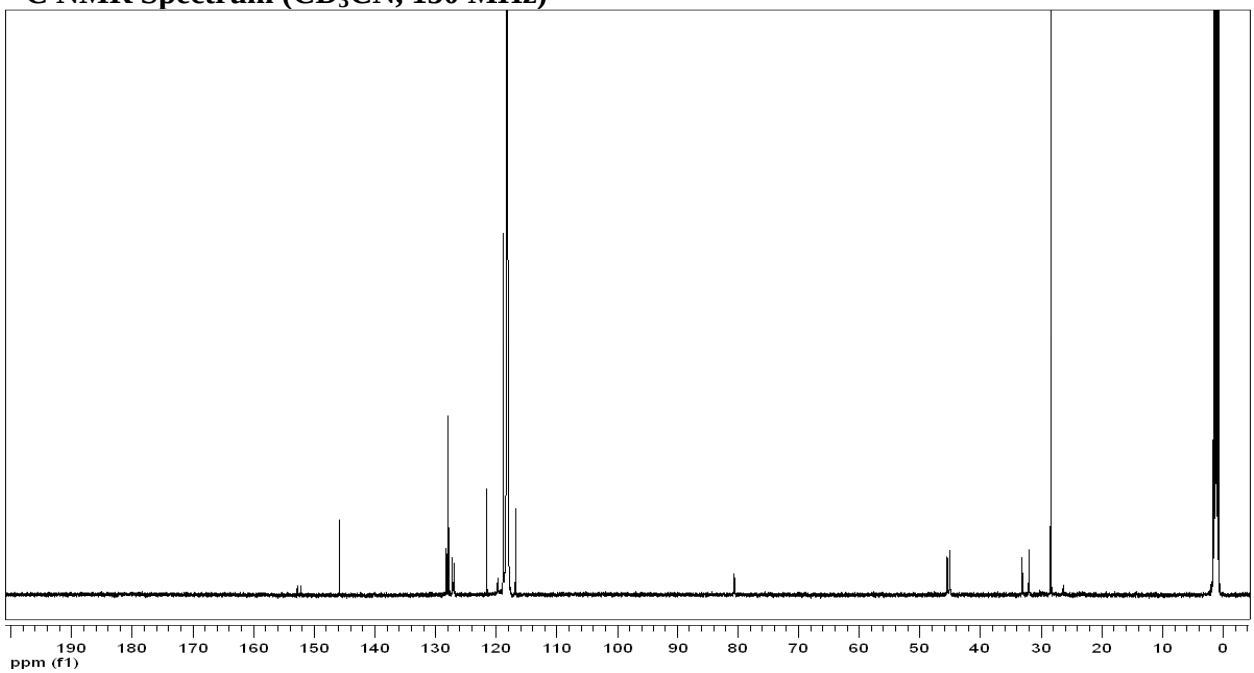


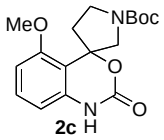
1d

^{1}H NMR Spectrum (CD_3CN, 600 MHz)



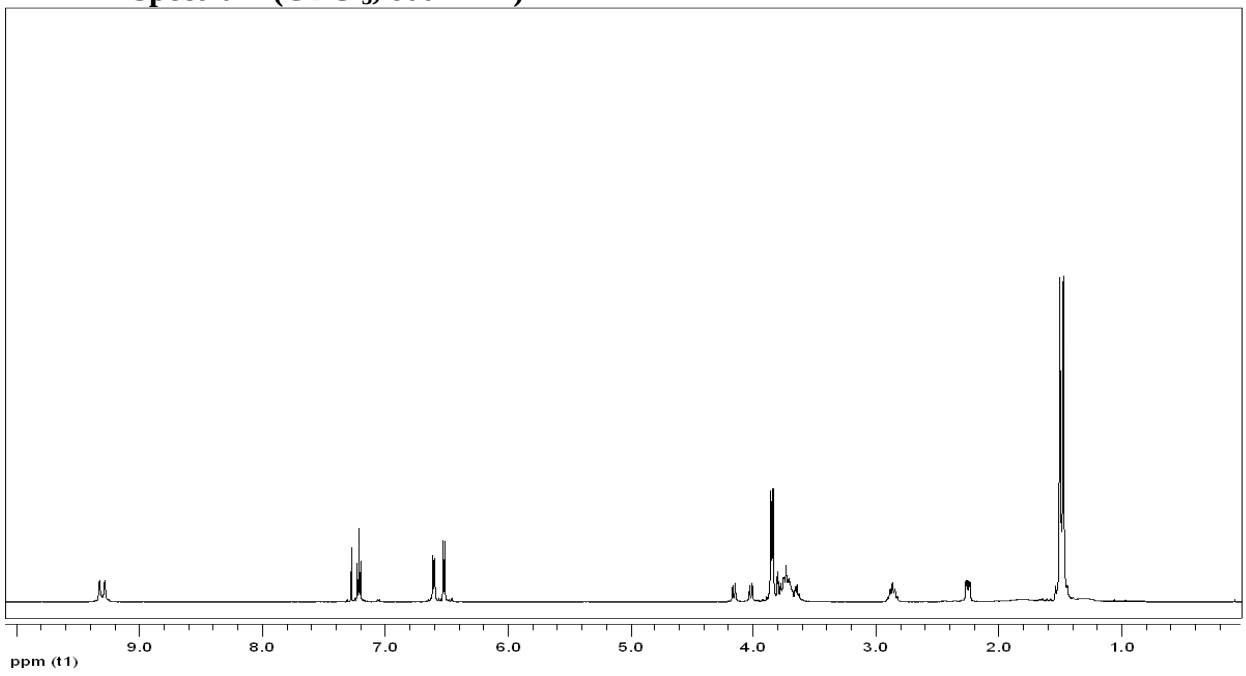
^{13}C NMR Spectrum (CD_3CN, 150 MHz)



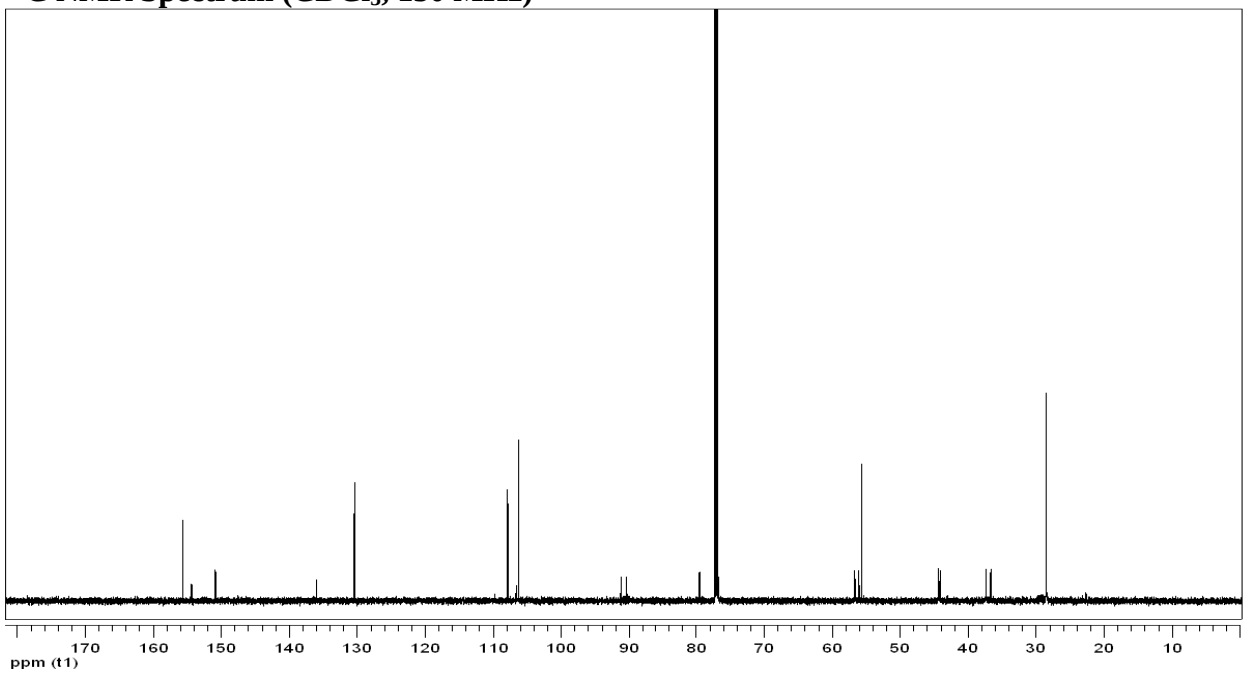


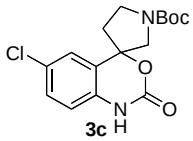
2c

^{1}H NMR Spectrum ($CDCl_3$, 600 MHz)



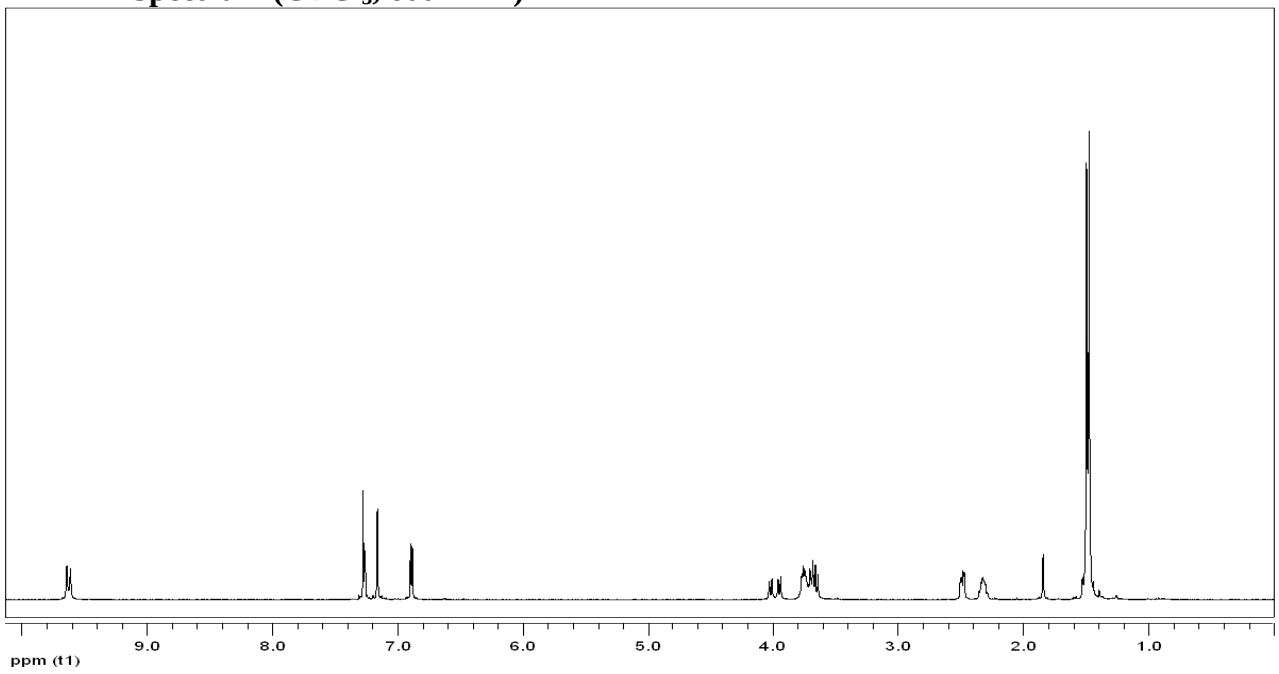
^{13}C NMR Spectrum ($CDCl_3$, 150 MHz)





3c

^{1}H NMR Spectrum ($CDCl_3$, 600 MHz)



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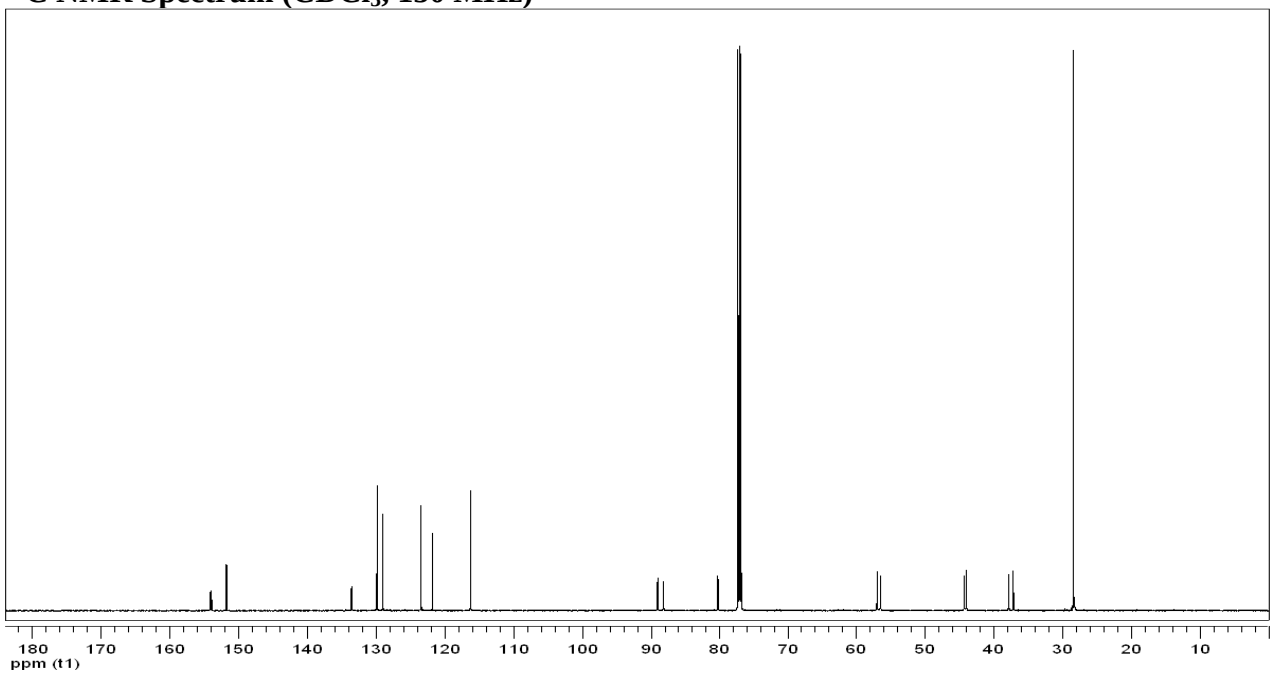
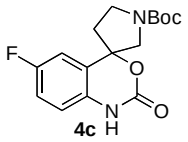
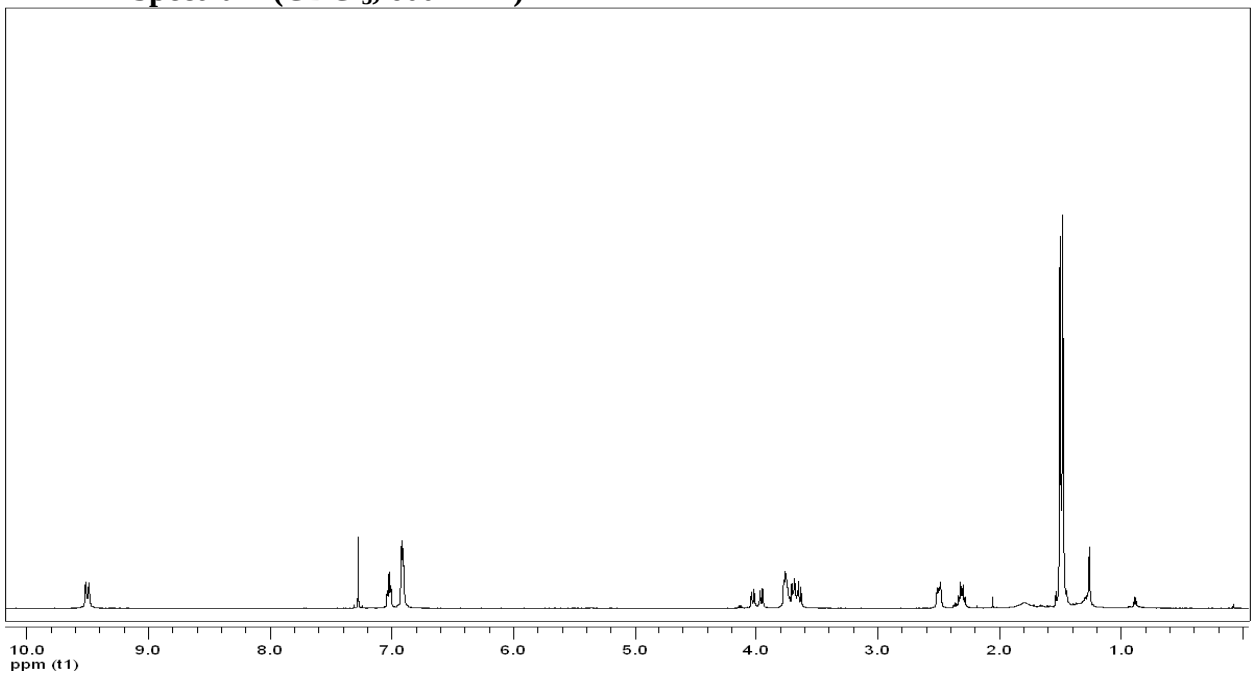


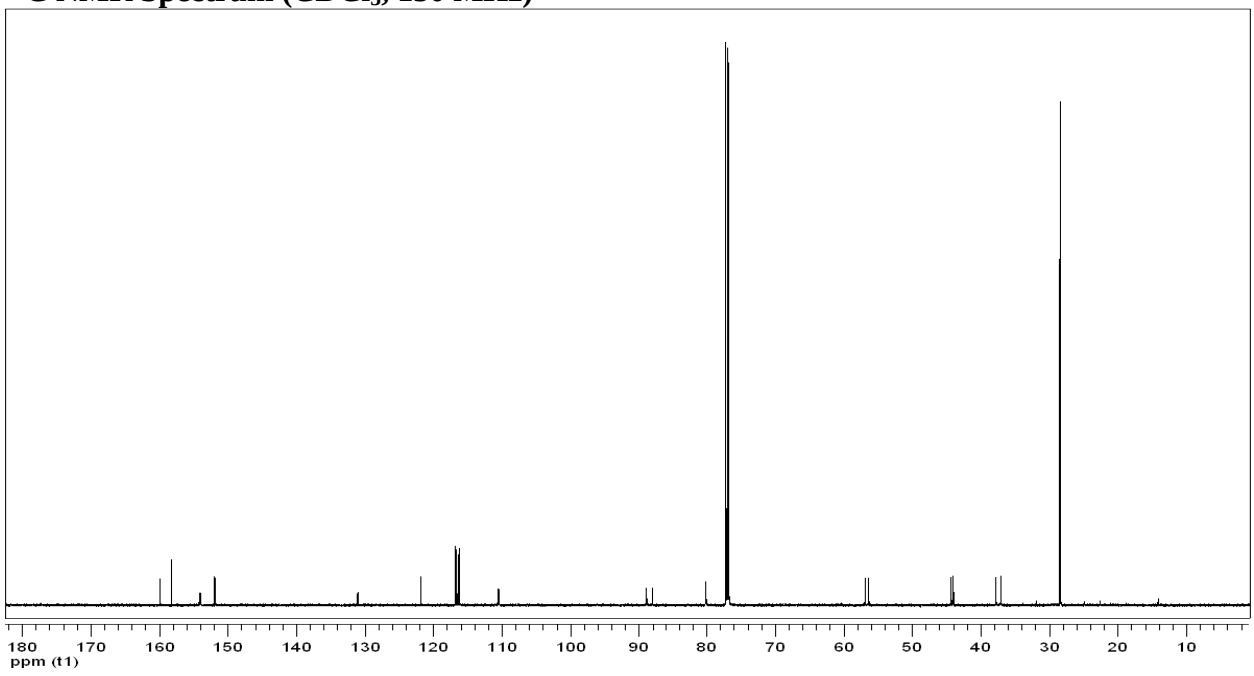


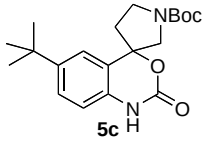
4c

^{1}H NMR Spectrum ($CDCl_3$, 600 MHz)



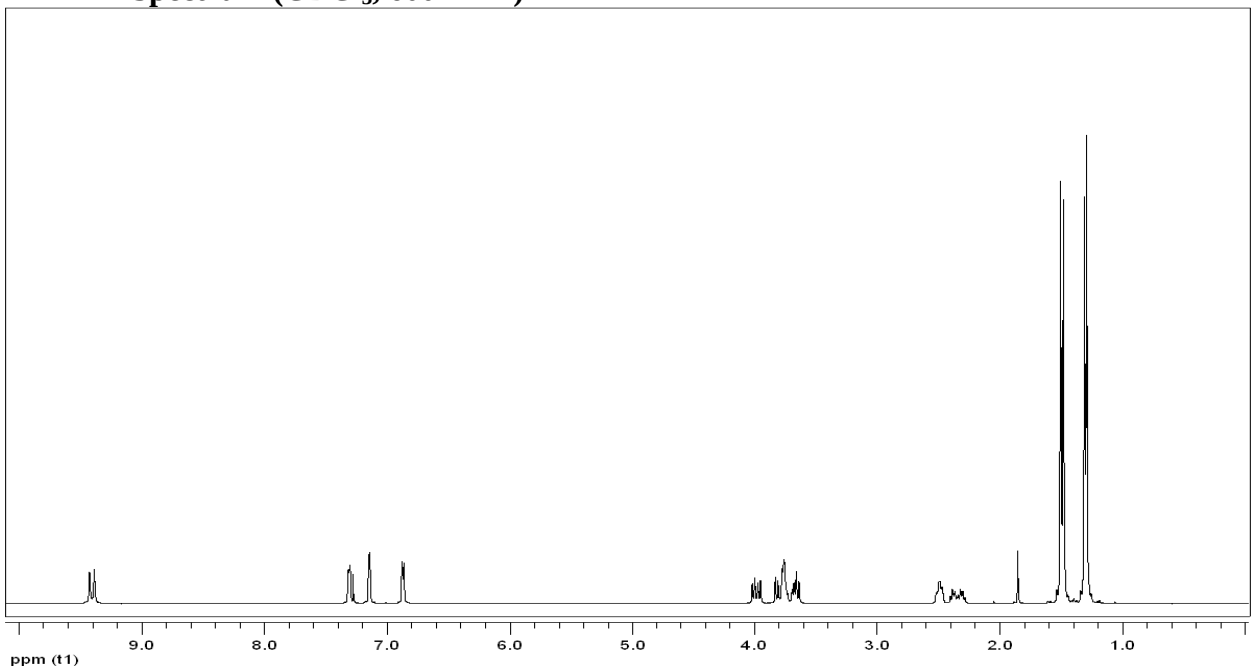
^{13}C NMR Spectrum ($CDCl_3$, 150 MHz)



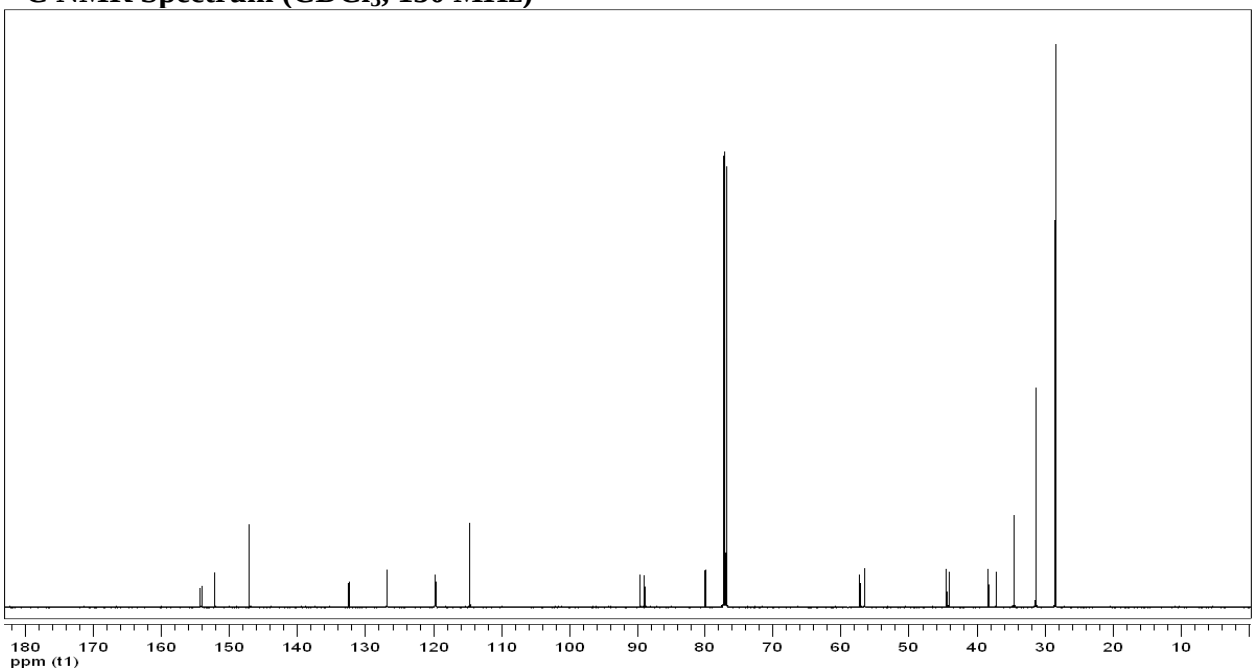


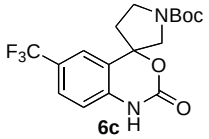
5c

^{1}H NMR Spectrum ($CDCl_3$, 600 MHz)



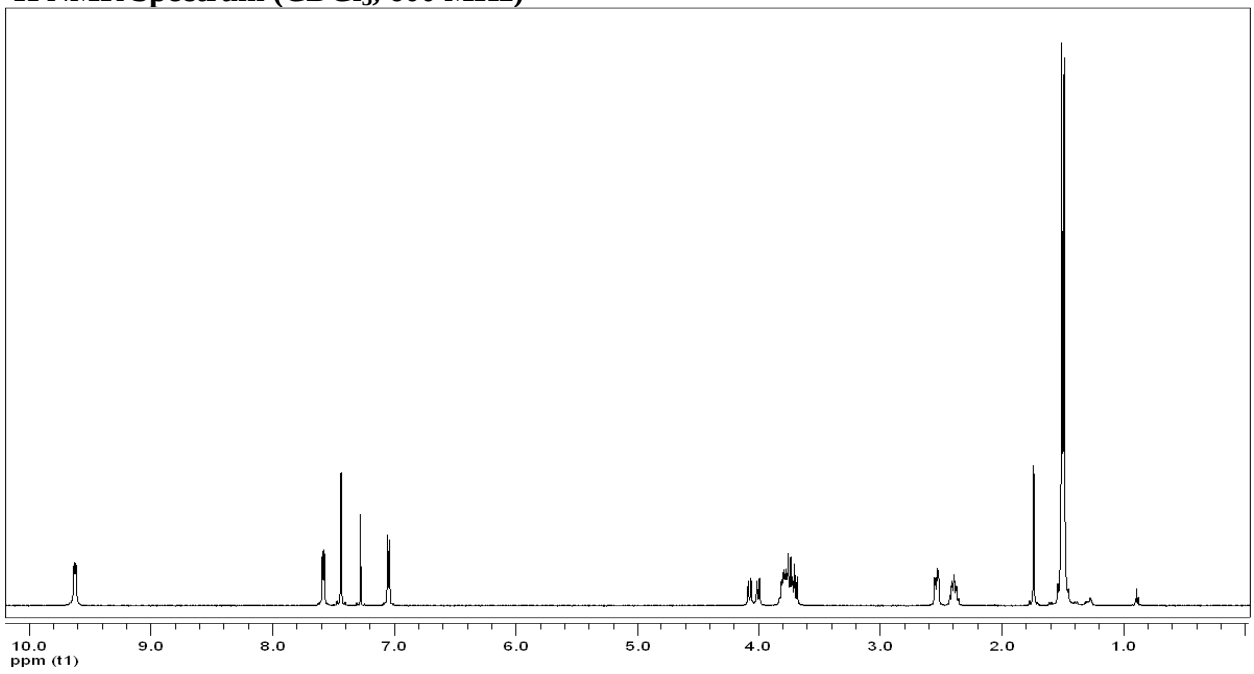
^{13}C NMR Spectrum ($CDCl_3$, 150 MHz)



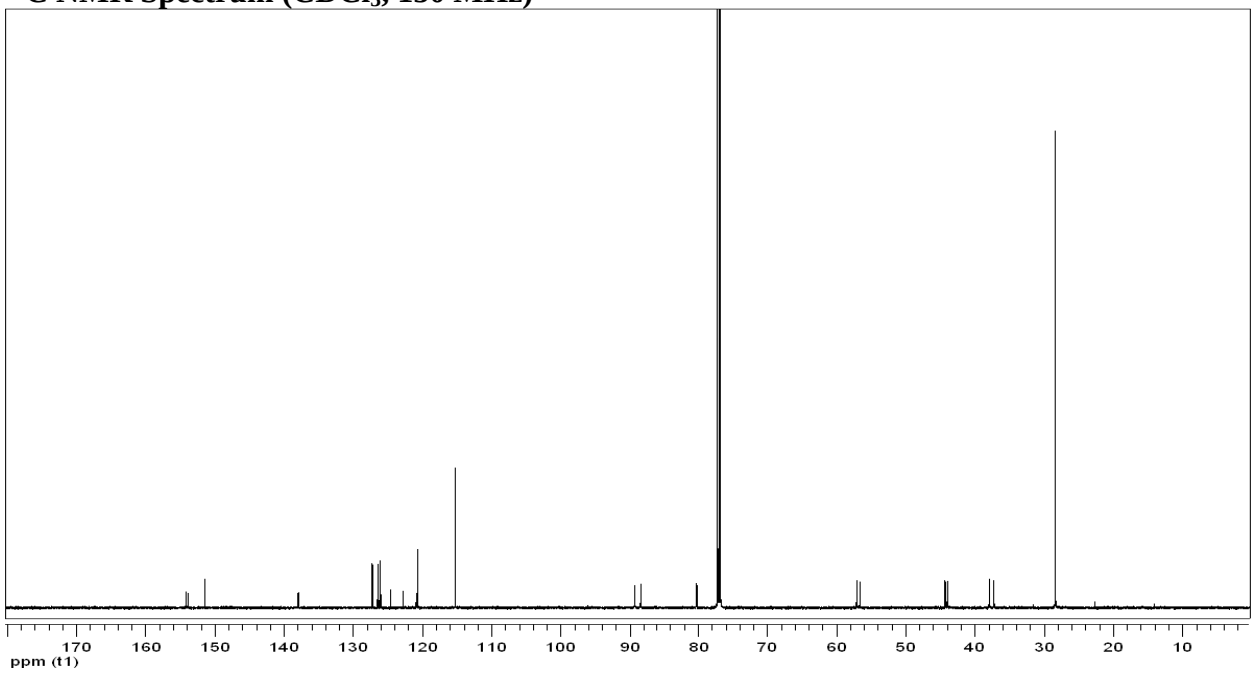


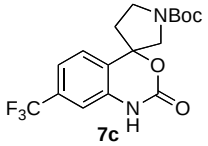
6c

^{1}H NMR Spectrum ($CDCl_3$, 600 MHz)



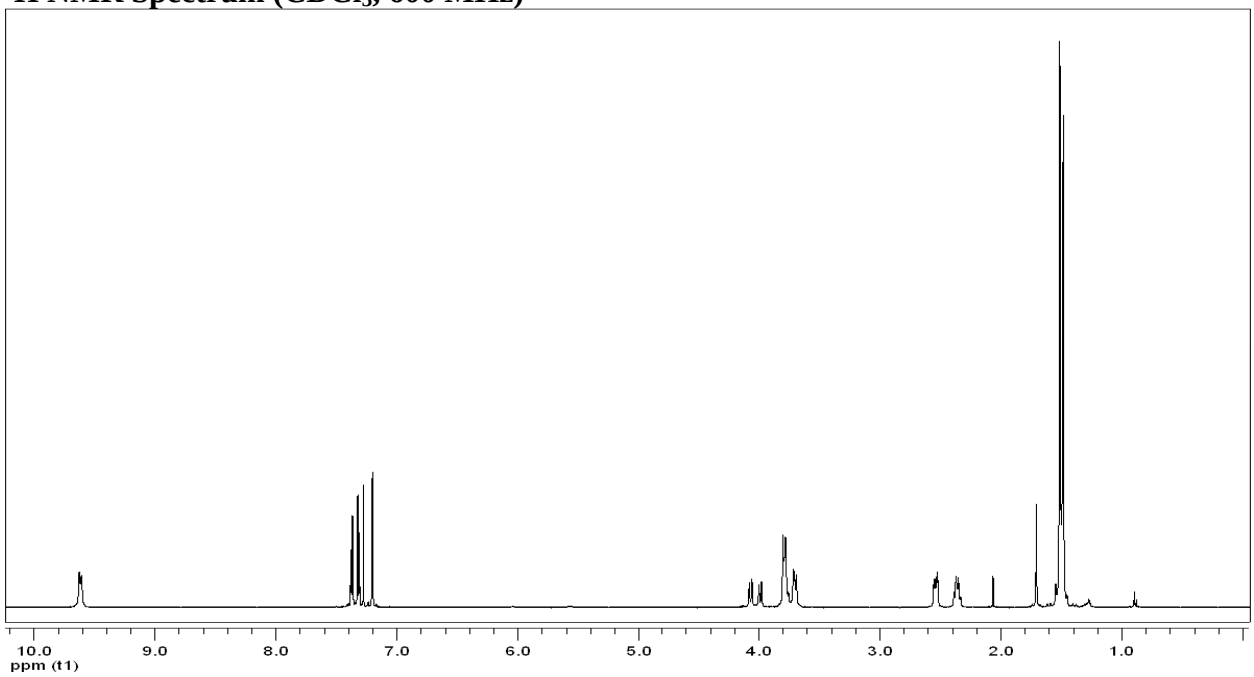
^{13}C NMR Spectrum ($CDCl_3$, 150 MHz)



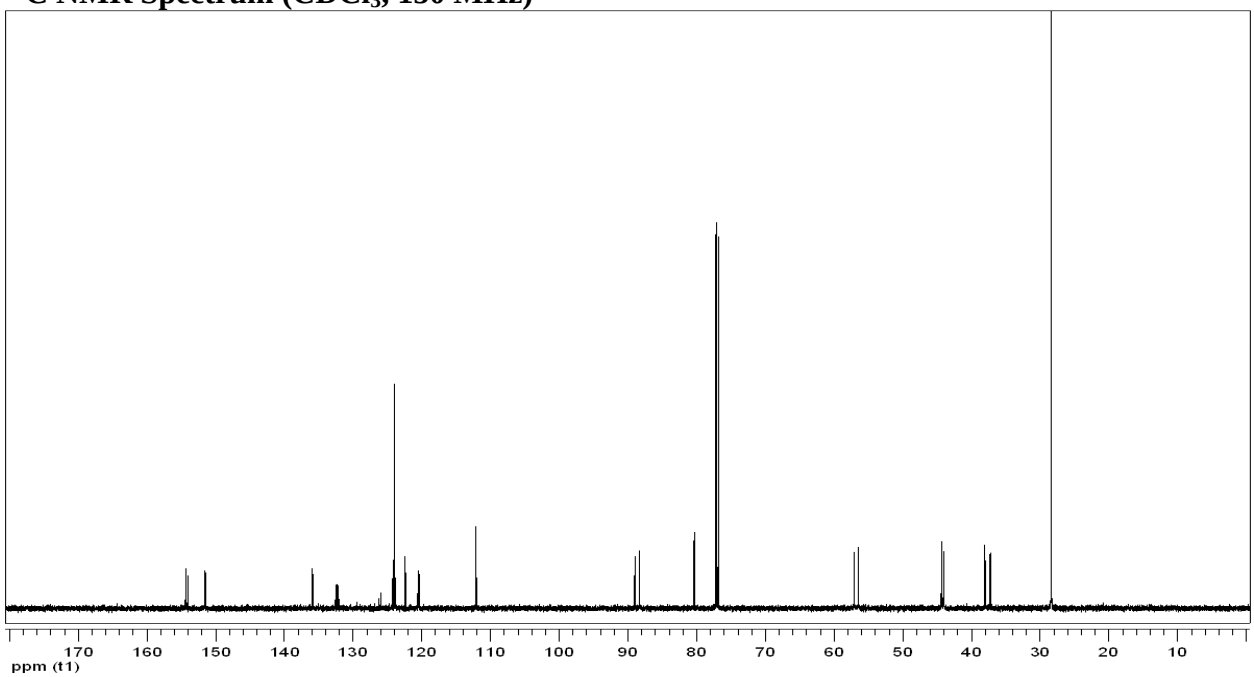


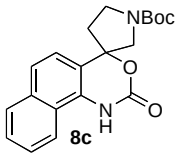
7c

^{1}H NMR Spectrum ($CDCl_3$, 600 MHz)



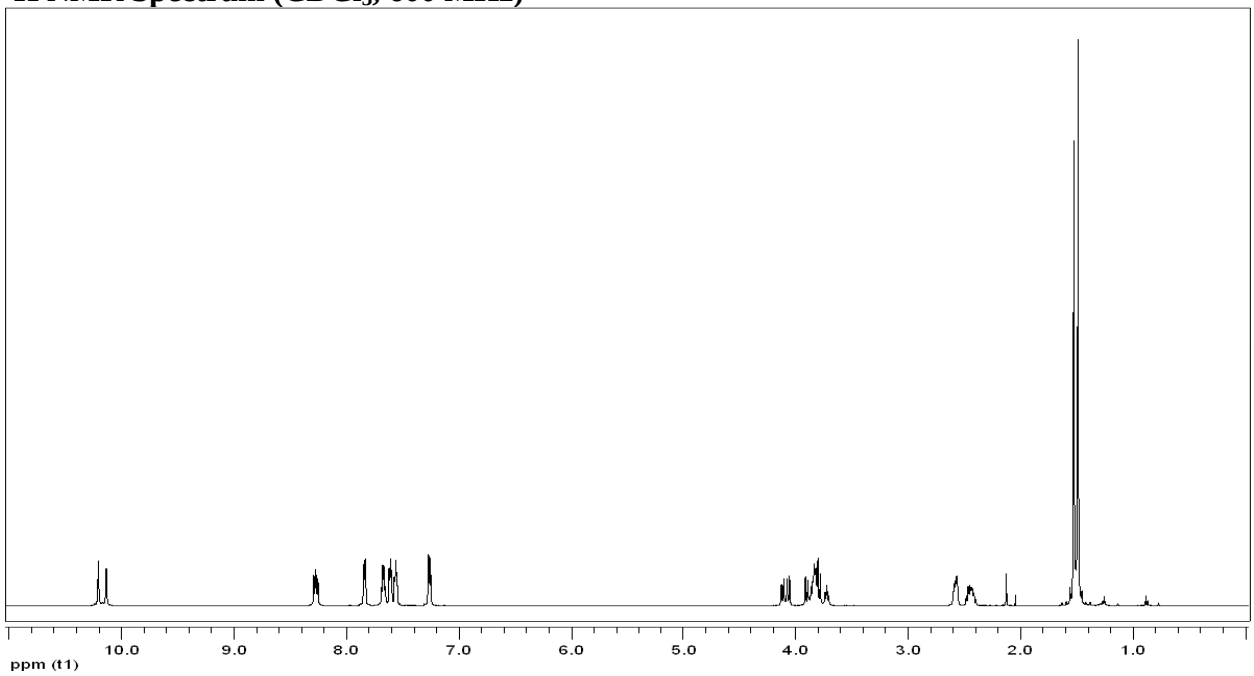
^{13}C NMR Spectrum ($CDCl_3$, 150 MHz)



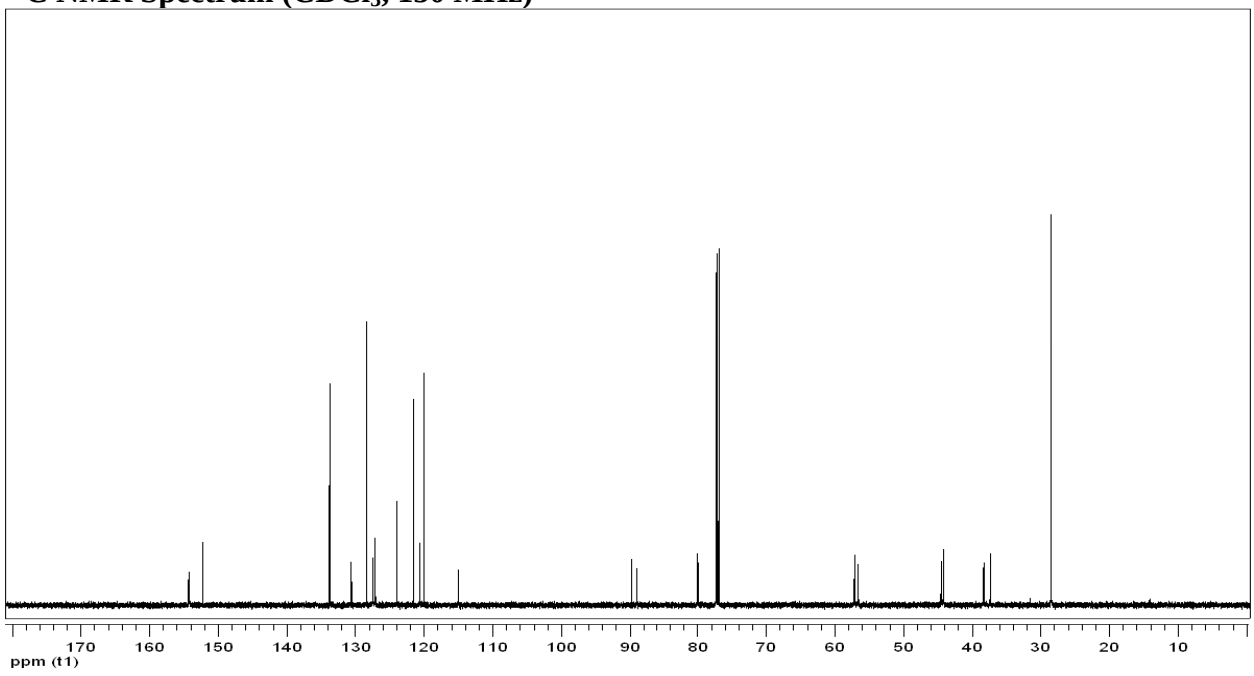


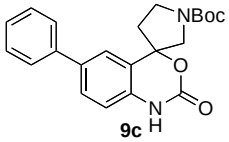
8c

^{1}H NMR Spectrum ($CDCl_3$, 600 MHz)



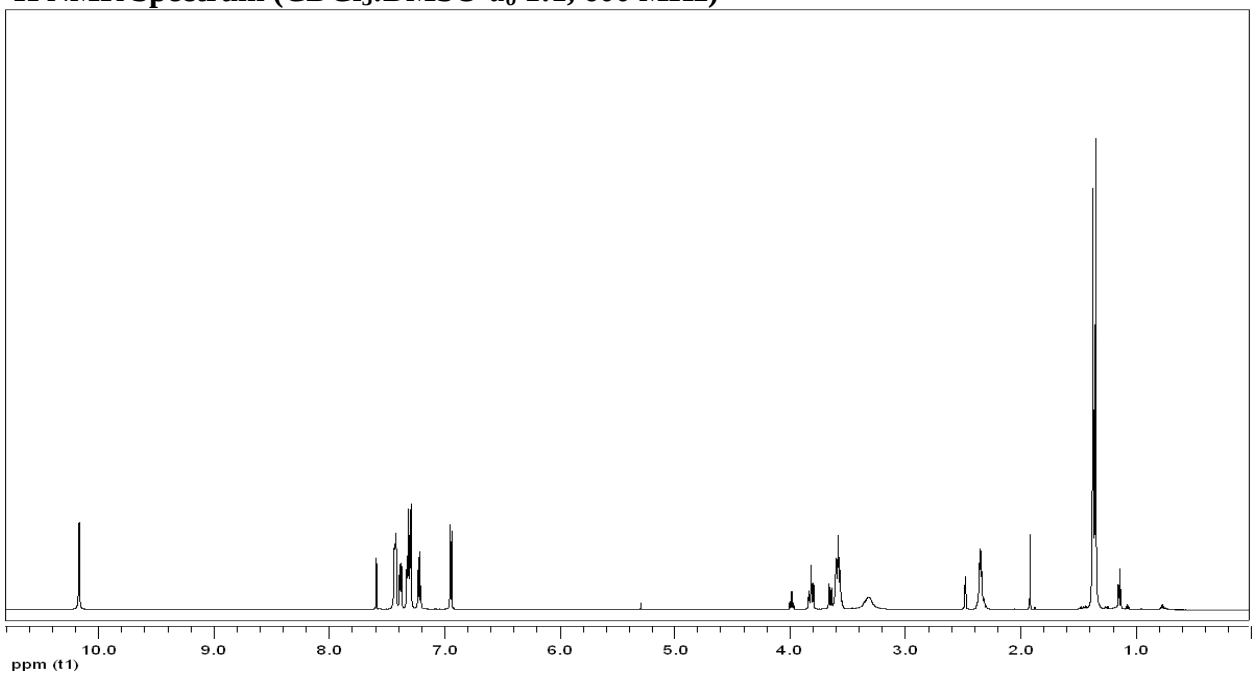
^{13}C NMR Spectrum ($CDCl_3$, 150 MHz)



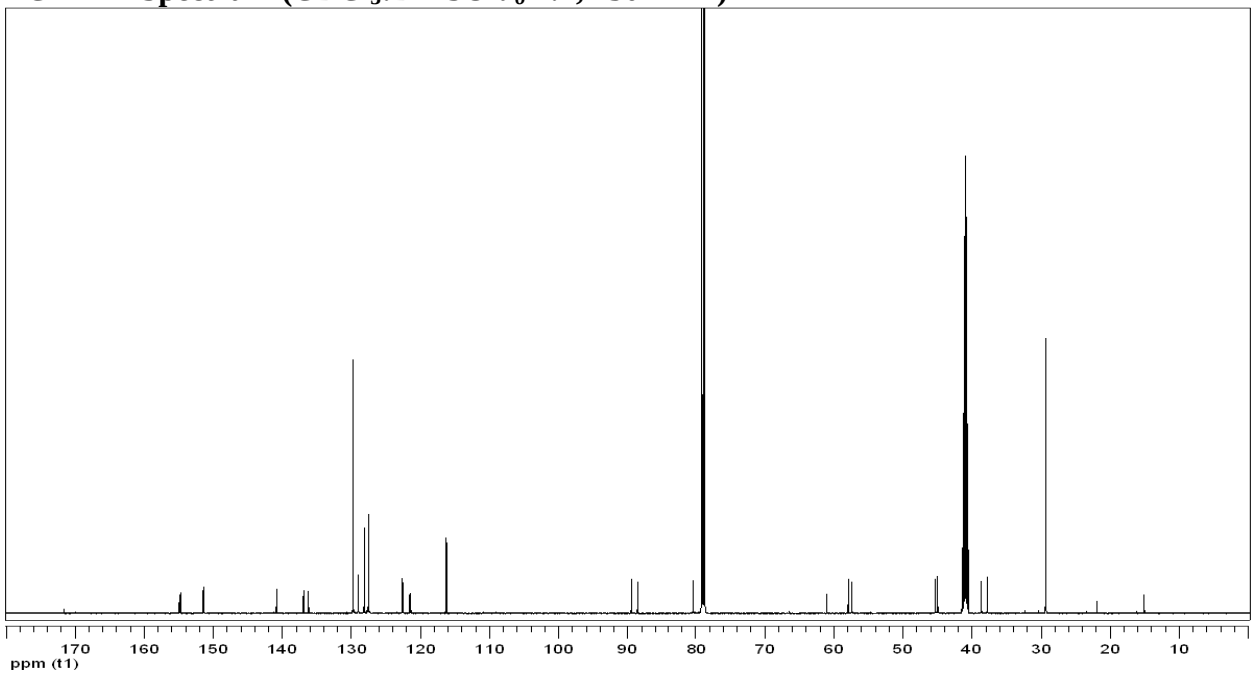


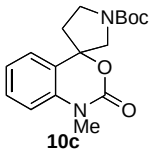
9c

^{1}H NMR Spectrum ($CDCl_3$:DMSO-d_6 1:1, 600 MHz)



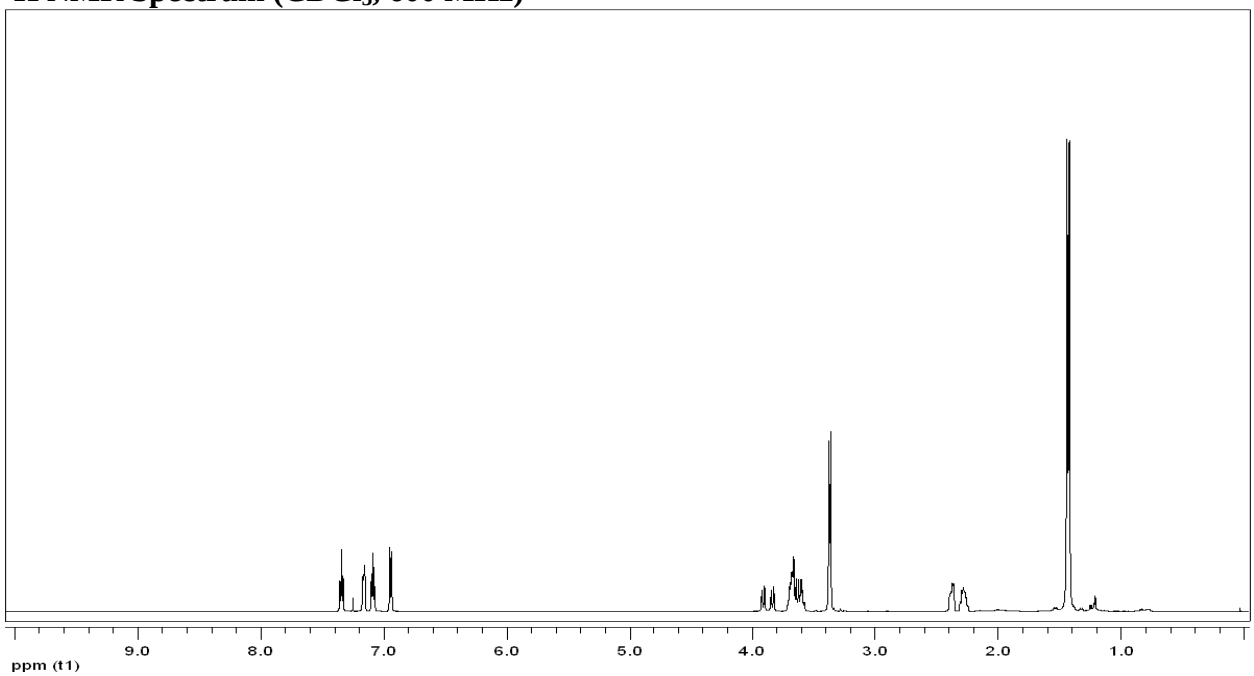
^{13}C NMR Spectrum ($CDCl_3$:DMSO-d_6 1:1, 150 MHz)



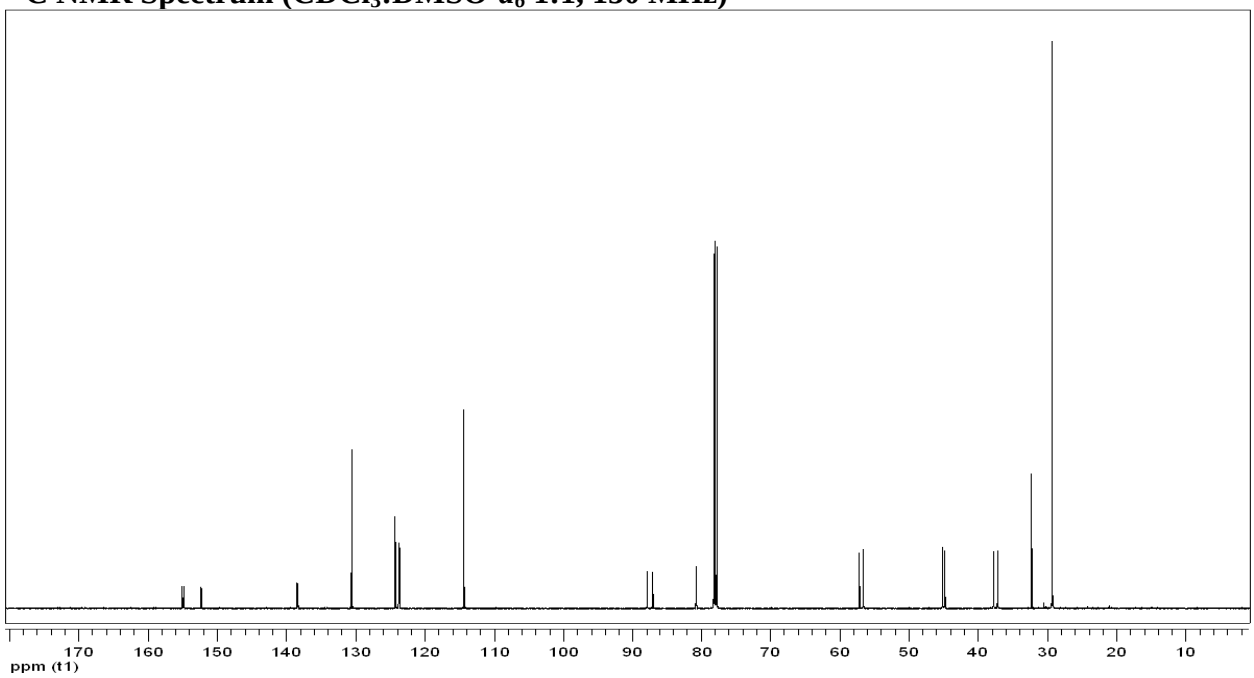


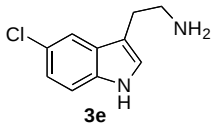
10c

^{1}H NMR Spectrum ($CDCl_3$, 600 MHz)



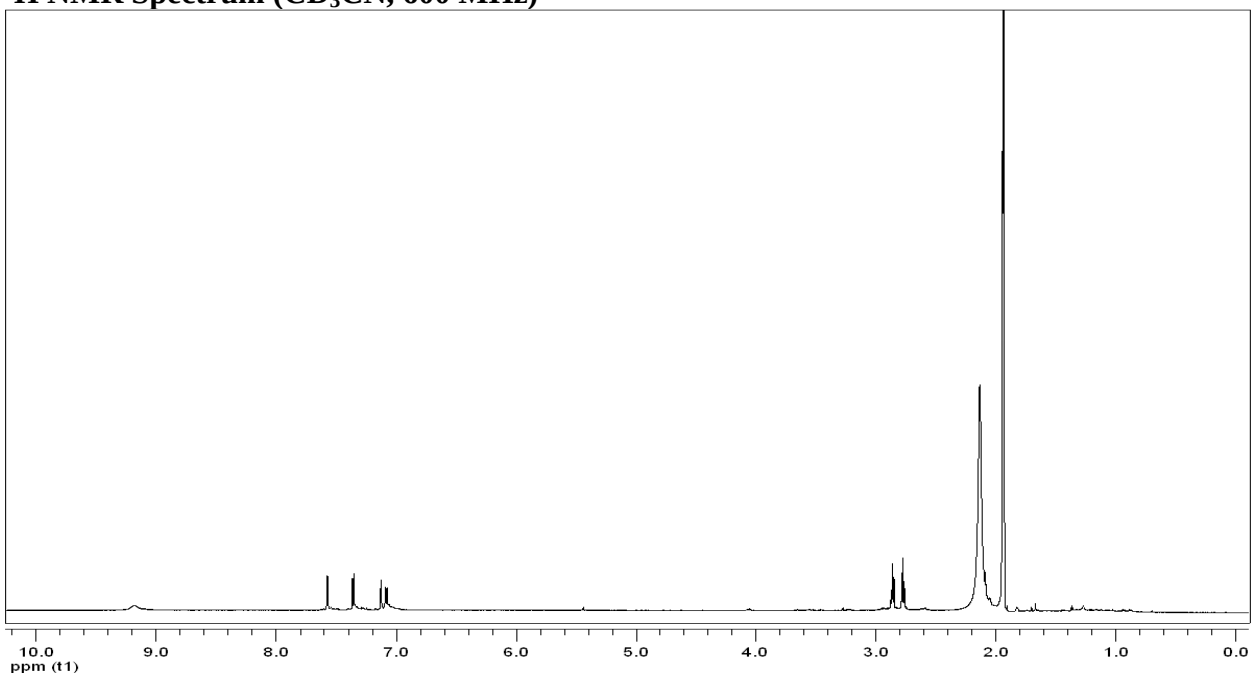
^{13}C NMR Spectrum ($CDCl_3$:DMSO-d_6 1:1, 150 MHz)



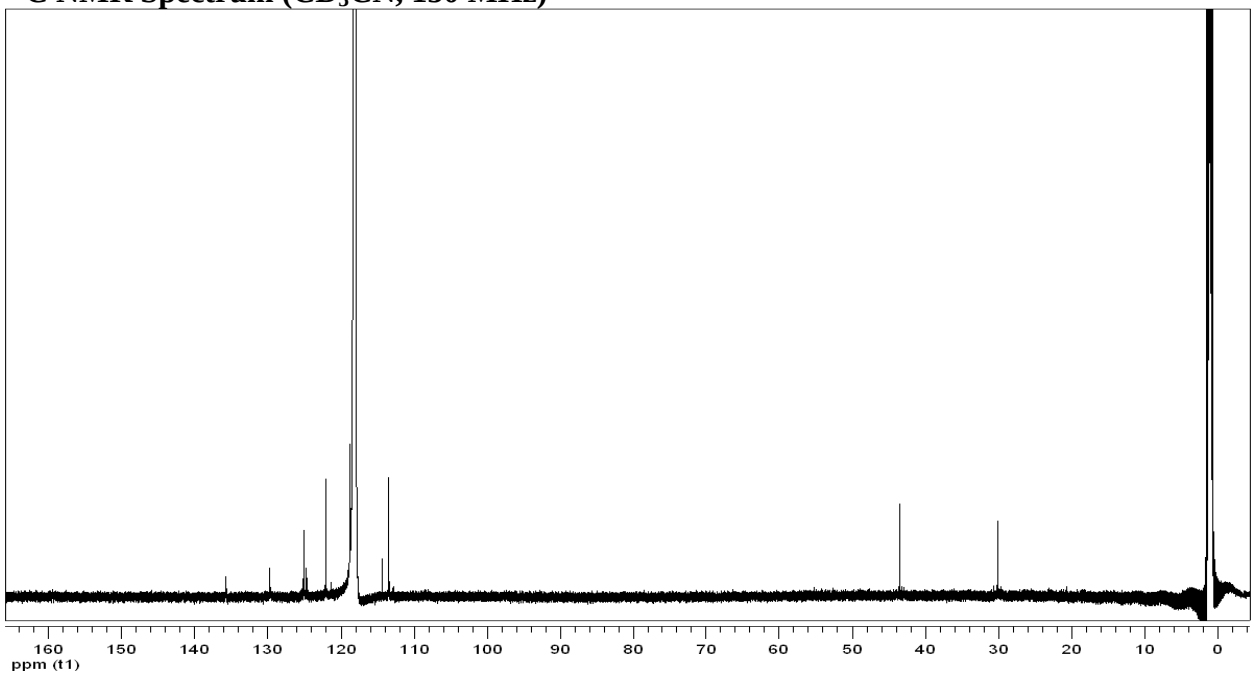


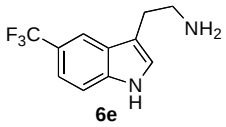
3e

^{1}H NMR Spectrum (CD_3CN, 600 MHz)



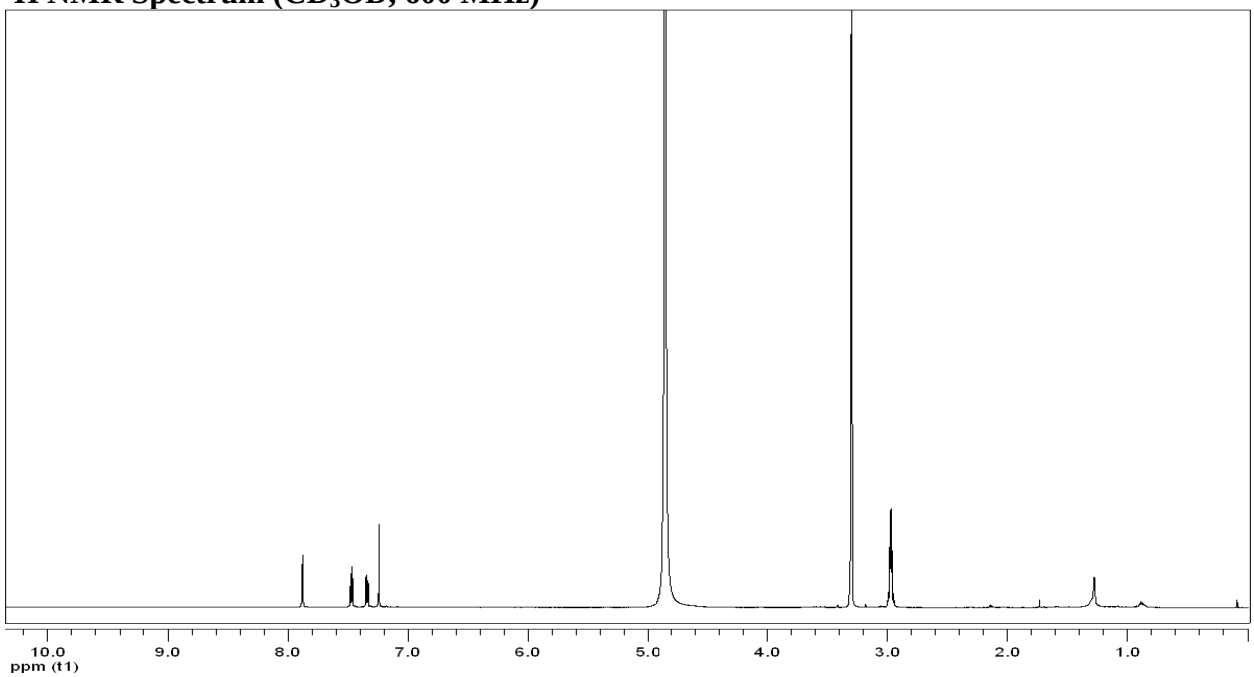
^{13}C NMR Spectrum (CD_3CN, 150 MHz)



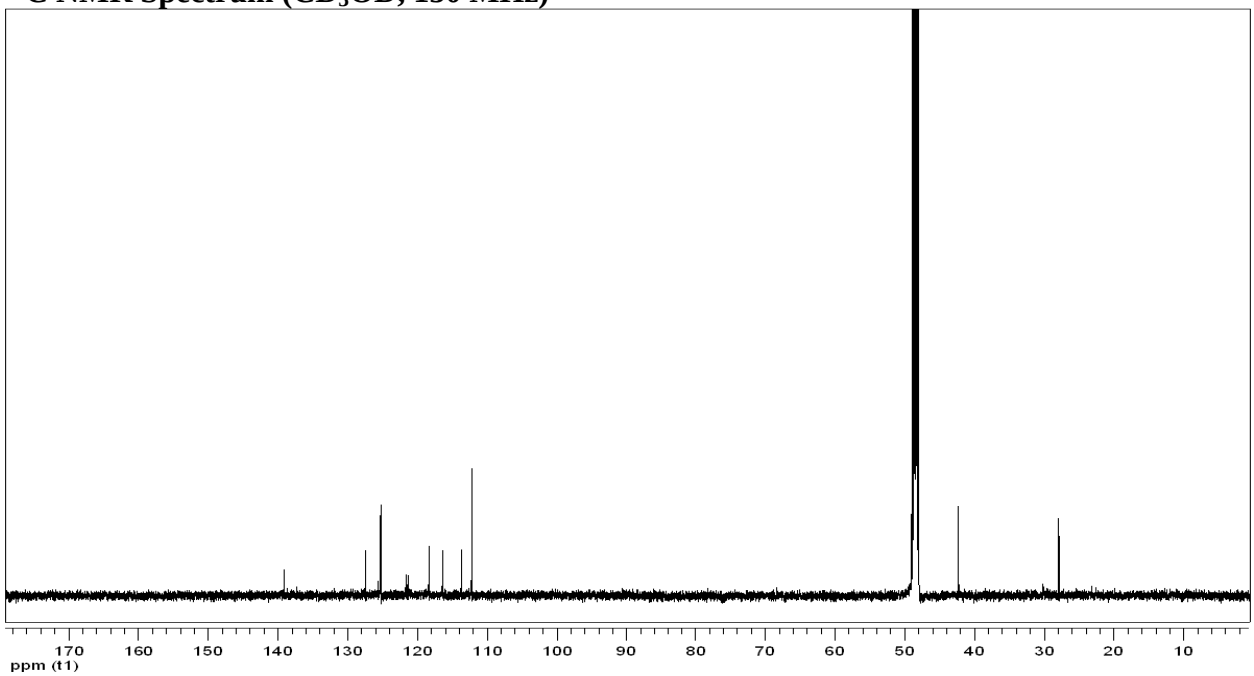


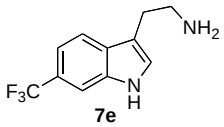
6e

^{1}H NMR Spectrum (CD_3OD, 600 MHz)



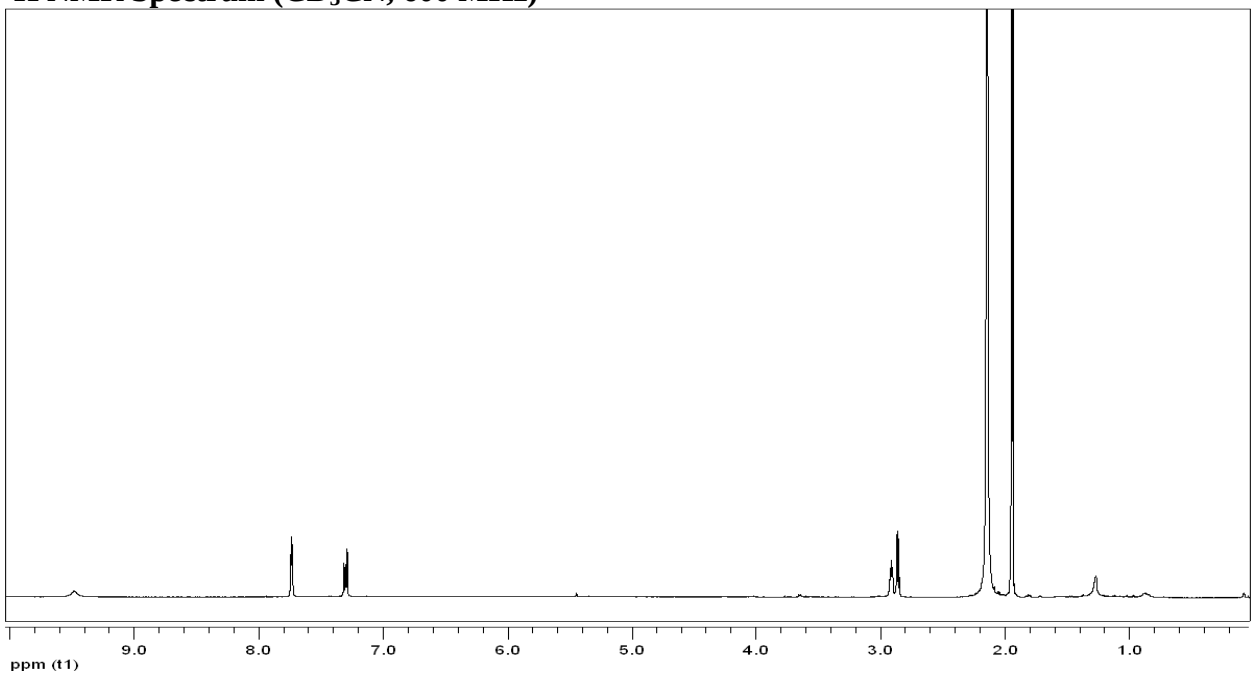
^{13}C NMR Spectrum (CD_3OD, 150 MHz)



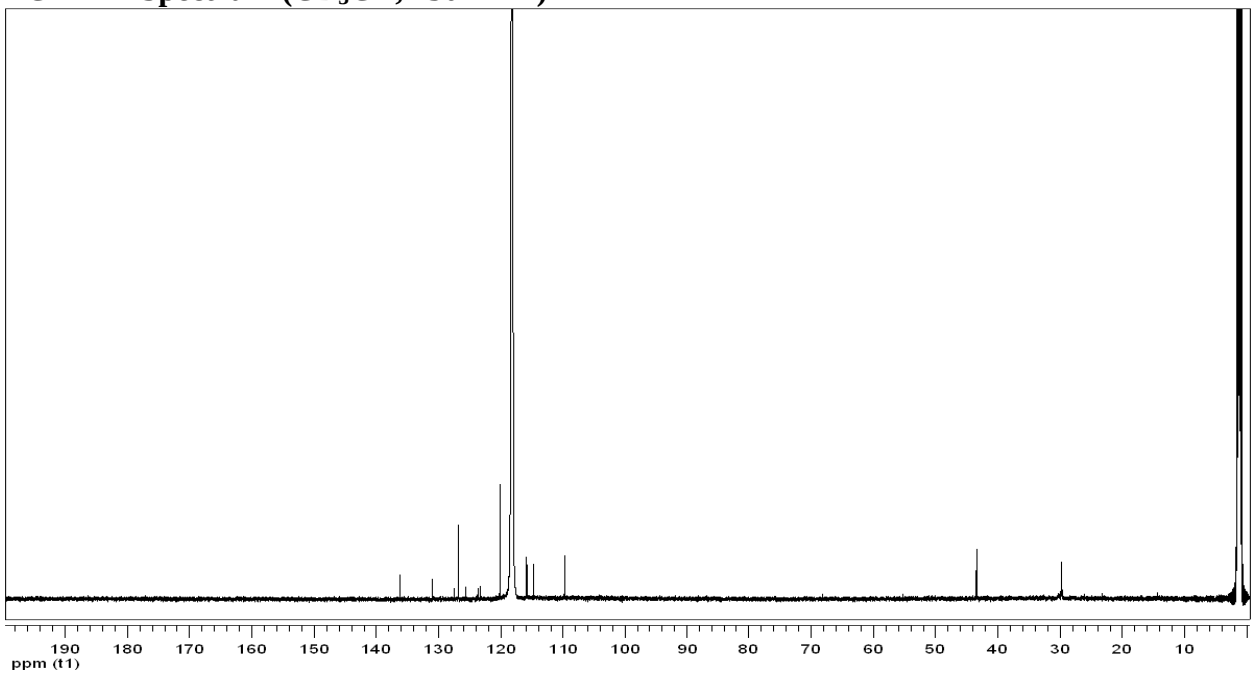


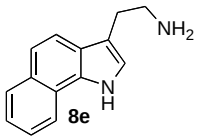
7e

^{1}H NMR Spectrum (CD_3CN, 600 MHz)



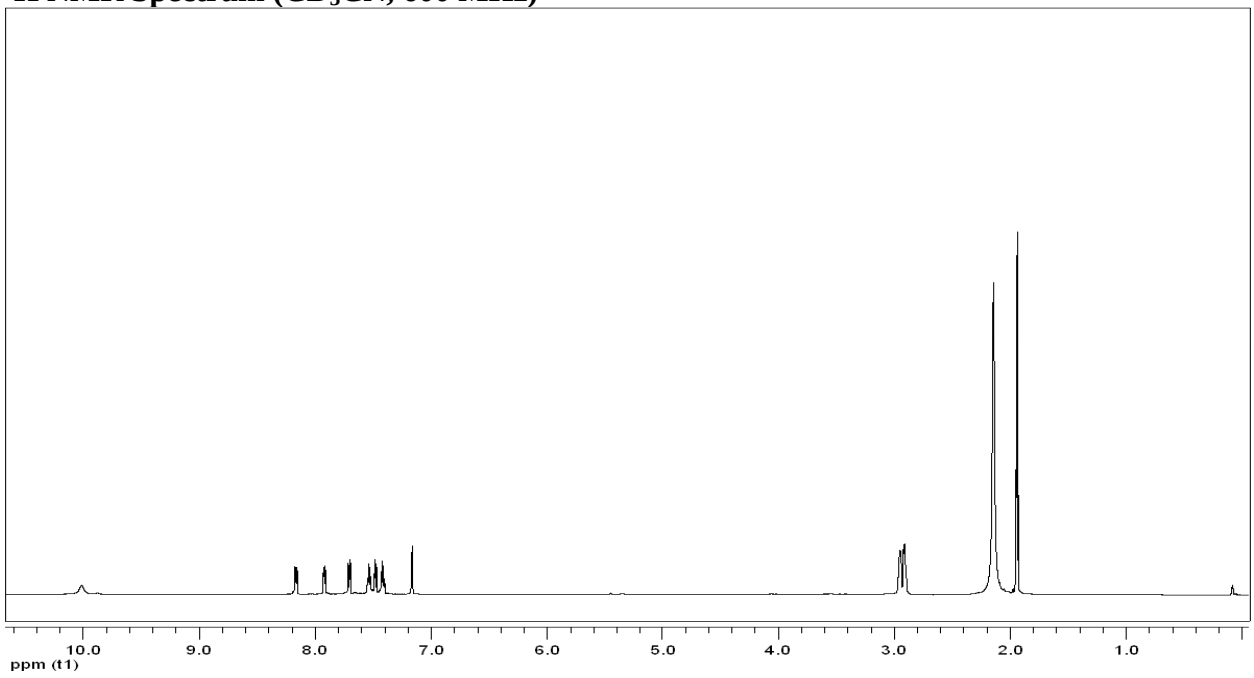
^{13}C NMR Spectrum (CD_3CN, 150 MHz)



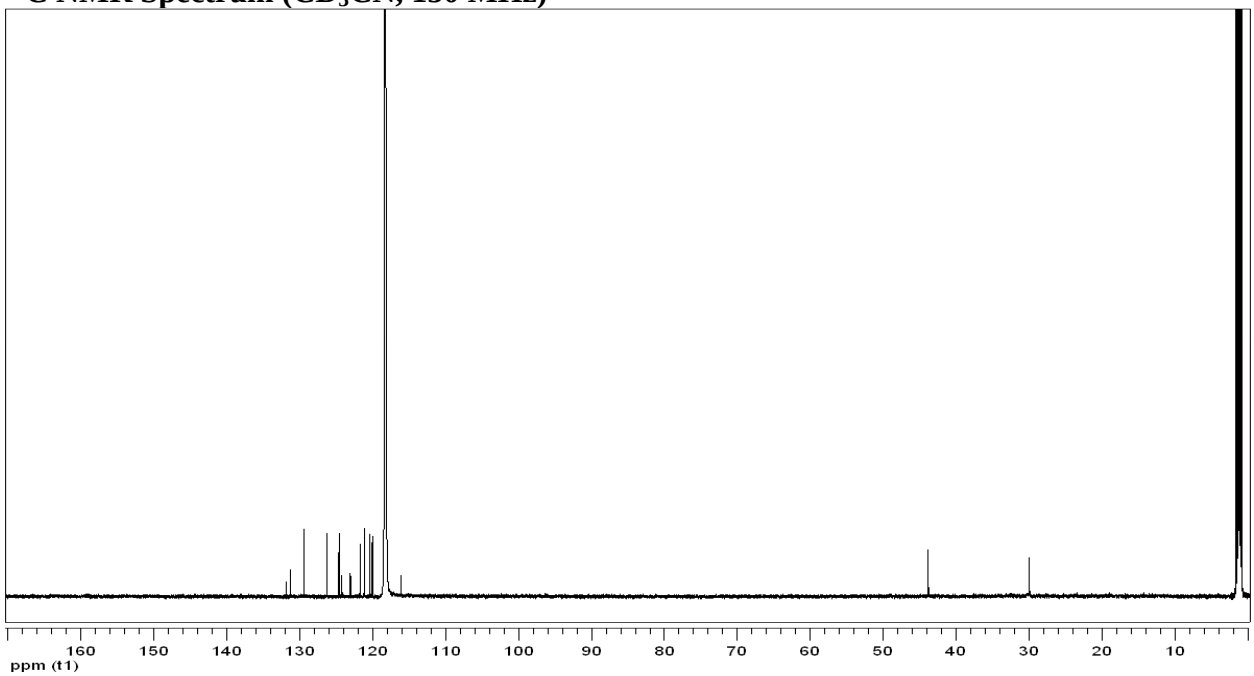


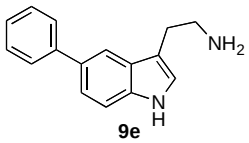
8e

^{1}H NMR Spectrum (CD_3CN, 600 MHz)



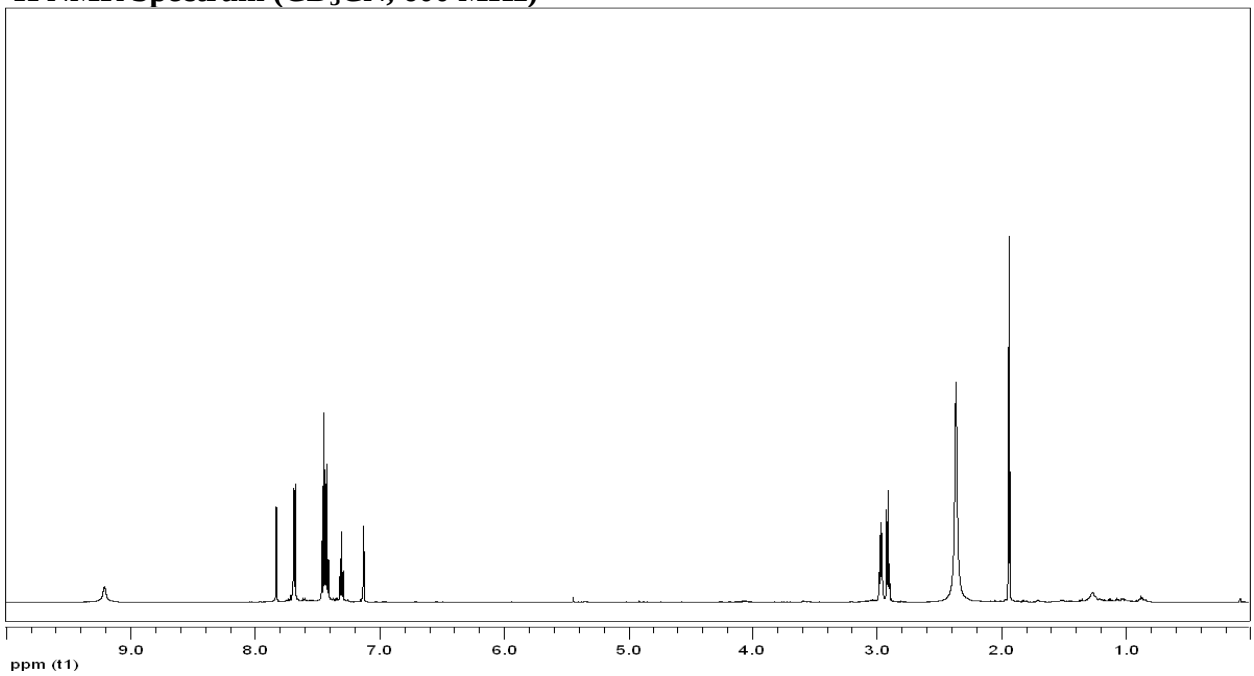
^{13}C NMR Spectrum (CD_3CN, 150 MHz)



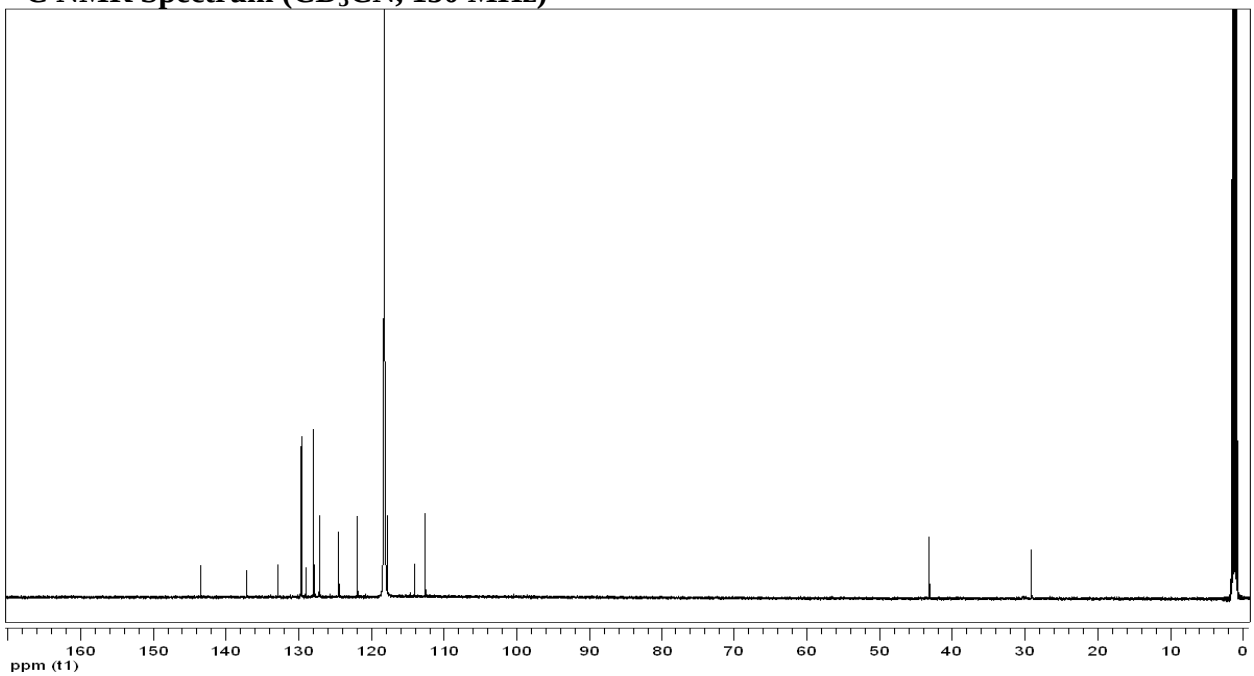


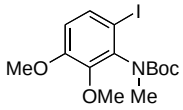
9e

^{1}H NMR Spectrum (CD_3CN, 600 MHz)



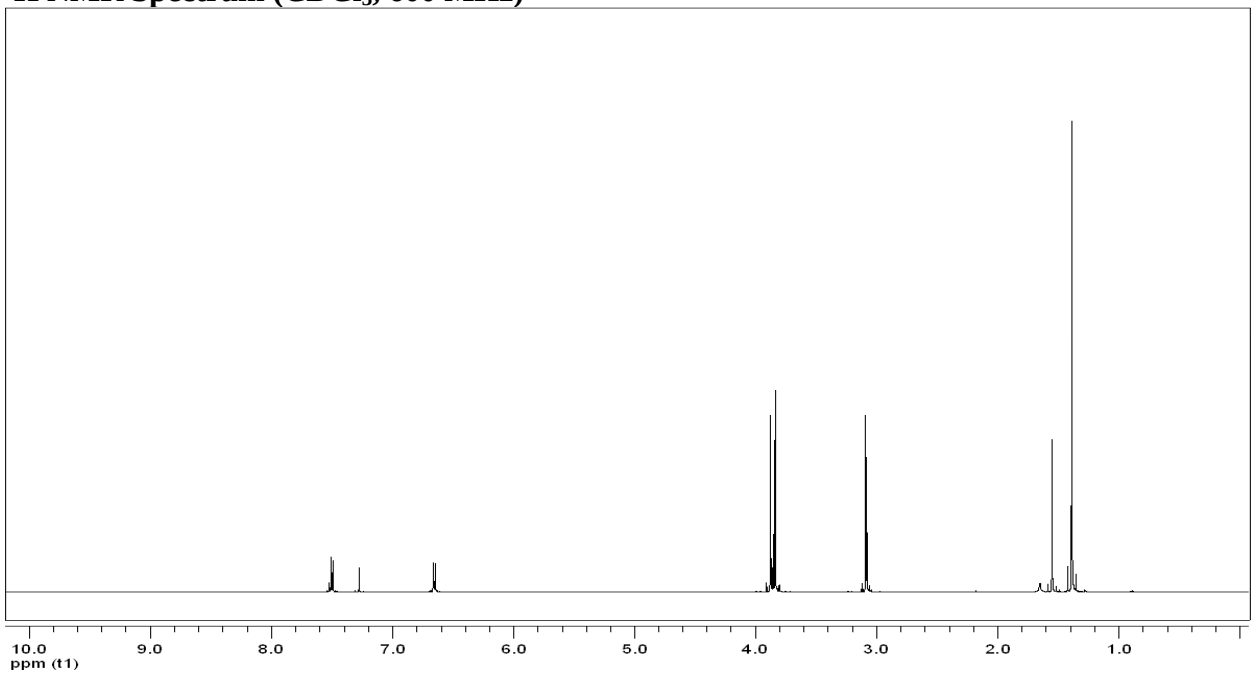
^{13}C NMR Spectrum (CD_3CN, 150 MHz)



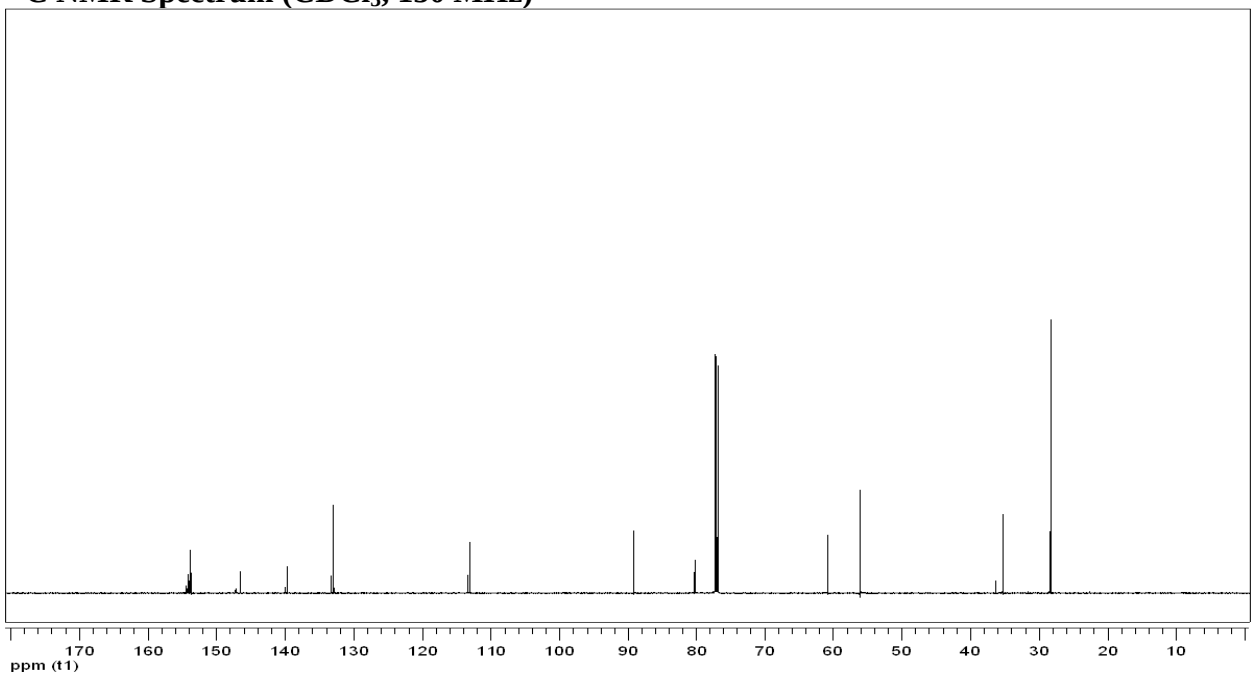


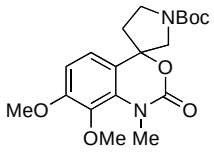
11b

^{1}H NMR Spectrum ($CDCl_3$, 600 MHz)



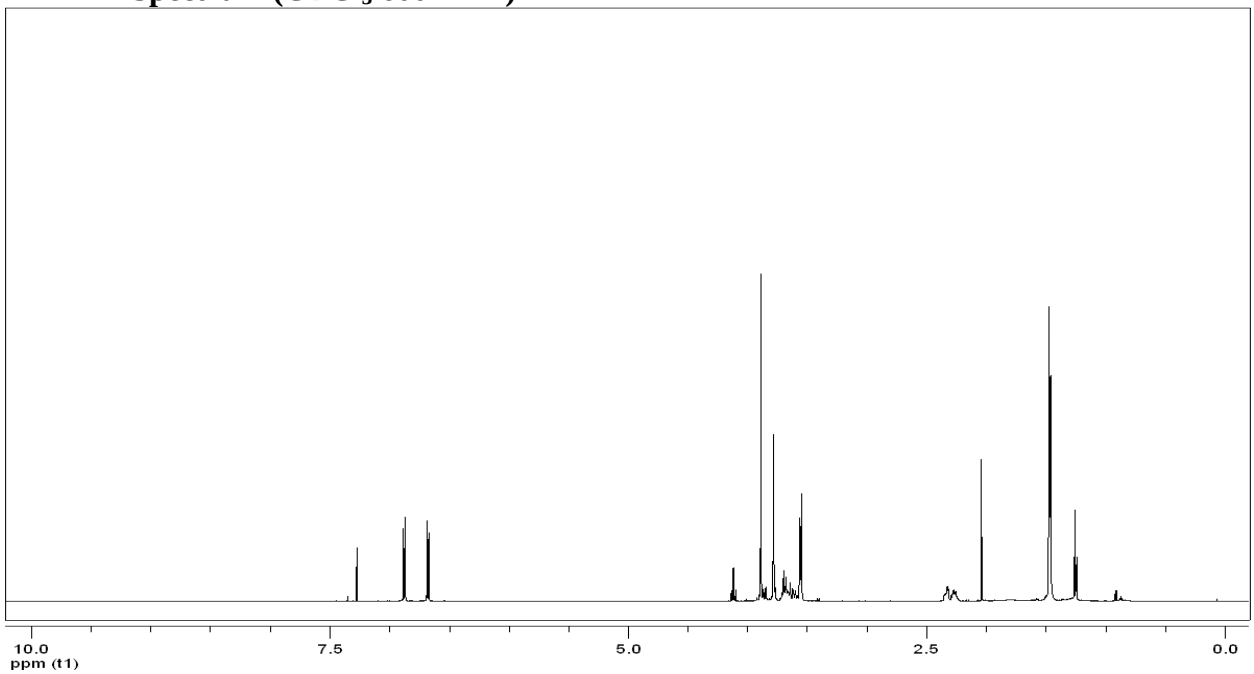
^{13}C NMR Spectrum ($CDCl_3$, 150 MHz)



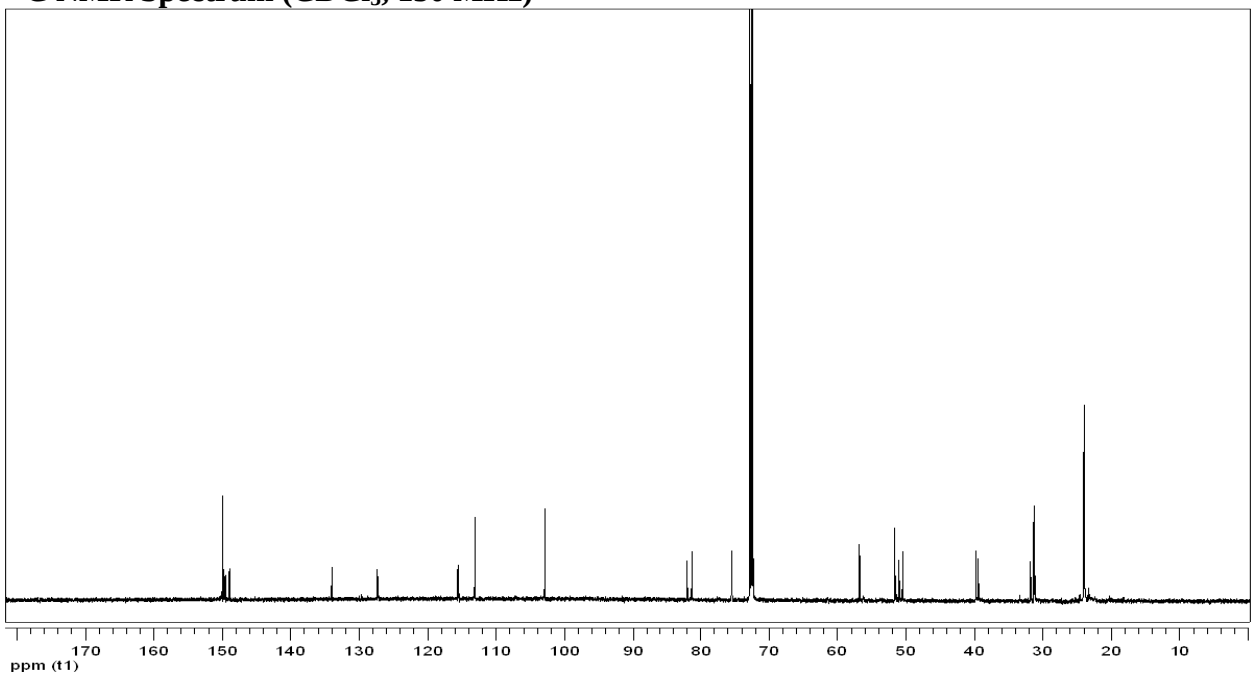


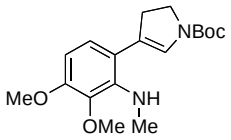
11d

^{1}H NMR Spectrum ($CDCl_3$ 600 MHz)



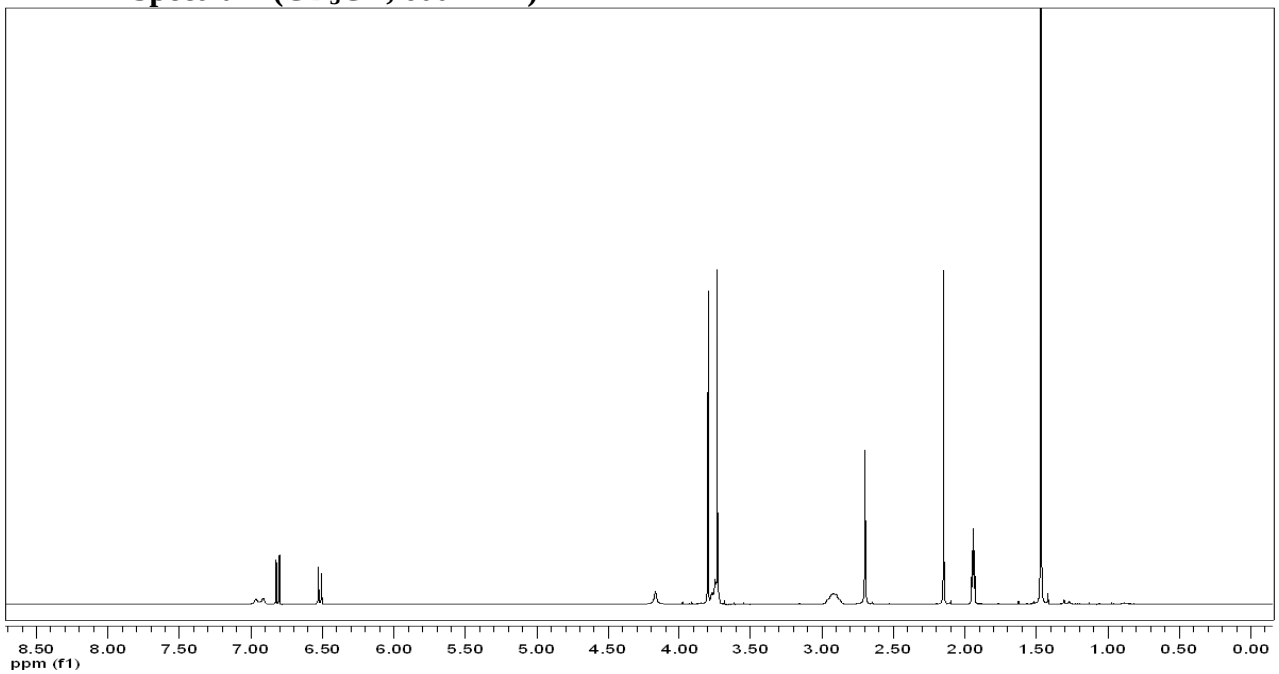
^{13}C NMR Spectrum ($CDCl_3$, 150 MHz)





11e

^{1}H NMR Spectrum (CD_3CN, 600 MHz)



^{13}C NMR Spectrum (CD_3CN, 150 MHz)