AZAINDOLE SYNTHESIS THROUGH DUAL ACTIVATION CATALYSIS WITH N-HETEROCYCLIC CARBENES

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Supporting Information

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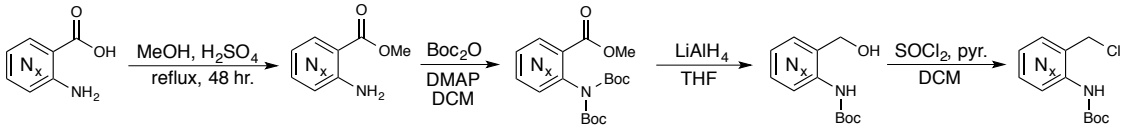
General Information

All reactions were carried out under a nitrogen atmosphere in oven-dried glassware with magnetic stirring. 1,4-dioxane was dried over 4 Å molecular sieves and sparged with nitrogen gas for 1 hour before use. Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.[1] Purification of select reaction products was carried out by flash chromatography using EM Reagent or Silicycle silica gel 60 (230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and ceric ammonium nitrate stain, anisaldehyde stain, or potassium permanganate stain followed by heating. Infrared spectra were recorded on a Bruker Tensor 37 FT-IR spectrometer. 1H-NMR spectra were recorded on a Bruker Avance 500 MHz w/ direct cryoprobe (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm, d6-DMSO 2.50 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration). Proton-decoupled ^{13}C-NMR spectra were recorded on a Bruker Avance 500 MHz w/ direct cryoprobe (126 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm, d6-DMSO at 39.5 ppm). Mass spectra data were obtained on a Waters Acquity Single Quadrupole ESI Spectrometer.

All aldehydes were purchased from commercial sources (Sigma-Aldrich, Acros, Oakwood) and purified immediately before use. Aldehydes were purified by dissolving in diethyl ether, washing with saturated sodium carbonate, followed by drying and concentration. Nicotinic acids were purchased from Oakwood or AK Scientific and used without further purification.

[1] [1] D. D. Perrin, W. L. Armarego, Purification of Laboratory Chemicals; 3rd Ed., Pergamon Press, Oxford. 1988.

4.2 Procedure for Synthesis of N-Boc amino picolyl chlorides

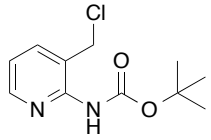


To a suspension of aminopicolinic acid derivative (1.0 equiv) in distilled methanol (0.6 M) in a roundbottom flask was slowly added sulfuric acid (Aq. 1.0 M, 4.15 equiv). The mixture was refluxed for 20 h and then cooled to ambient temperature, concentrated to a volume of 5 mL, and transferred to a mixture of ice and ammonium hydroxide (25% w/w) causing precipitation. The precipitate was taken up in ethyl acetate, dried with sodium sulfate, filtered, and the solvent removed *in vacuo* to afford the *O*-methyl amino-picolinate. This material was used without further purification.

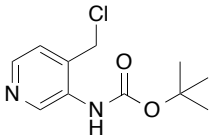
After further drying under a stream of air, the *O*-methyl amino-picolinate derivative (1.0 equiv) was slowly added to a roundbottom flask containing di-*t*-butyl dicarbonate (2.5 equiv), 4-dimethylamino-pyridine (0.1 equiv), and dichloromethane (0.1 M). The reaction was stirred under nitrogen until ^{1}H NMR showed complete conversion (usually 48 h) to the desired di-Boc protected product. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (gradient, 15-35% EtOAc/Hexanes) to afford *O*-methyl-N-di-Boc-amino-picolinate derivative as a white solid.

To a solution of *O*-methyl-di-Boc-amino-picolinate derivative (1.0 equiv) in tetrahydrofuran (0.36 M) at 0 °C was added lithium aluminum hydride (2.0 equiv, 0.5 M in THF). The reaction was stirred at 0 °C for 2 h, then warmed to 23 °C and stirred for an additional 30 min. Once complete (LCMS analysis), the reaction mixture was cooled to 0 °C and transferred dropwise to a saturated solution of sodium potassium tartrate (10 equiv) cooled to –10 °C. To the solution was added ethyl acetate (10 equiv), and then the solution was allowed to warm to room temperature and was let stir for 1 h. The mixture was transferred to a separatory funnel, and the aqueous and organic layers separated. The aqueous layer was then extracted twice with ethyl acetate, and the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and the solvent was removed *in vacuo* to afford crude product. If necessary, products were purified via flash column chromatography (gradient, 25-60% EtOAC/hexanes) to afford pure N-Boc amino picolyl alcohol derivatives.

To a roundbottom flask containing the N-Boc amino picolyl alcohol derivative (1 equiv) in dichloromethane (0.2 M) cooled to 0 °C under nitrogen atmosphere was added pyridine (1.1 equiv) followed by dropwise addition of thionyl chloride (1.05 equiv). The reaction was allowed to warm to ambient temperature with stirring. Upon consumption of the alcohol starting material (TLC or ^{1}H NMR analysis, typically 0.5–2 h), the reaction was quenched by addition of aqueous sodium bicarbonate (3:1 of sat. bicarbonate (aq):DI water) and transferred to a separatory flask. The organic portion was removed and the aqueous extracted (DCM x 3). The combined organic portions were dried over anhydrous sodium sulfate, solvent removed *in vacuo* to yield crude product. If necessary, the crude material was purified by flash column chromatography (gradient, 35–90% EtOAc/hexanes) to yield analytically pure desired product.

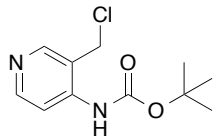


2-(*tert*-butoxycarbonyl)amino-3-chloromethyl pyridine (1a): Prepared according to the general procedure from 2-amino-3-pyridinecarboxylic acid. The unpurified residue did not require further purification, thus affording picolyl chloride **1a** as a white solid (2.15 g, 51% yield over four steps from 2-aminonicotinic acid, average of 3 syntheses). Analytical data for **1a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 4.0 Hz, 1H), 7.82 (dd, J = 7.7, 1.8 Hz, 1H), 7.21 (s, 1H), 7.15 (dd, J = 7.7, 4.8 Hz, 1H), 4.68 (s, 2H), 1.52 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 152.8, 148.9, 148.3, 139.1, 125.7, 120.9, 81.4, 42.8, 28.2; IR (ATR) cm^{-1} 3164, 2980, 2938, 1723, 1554, 1519, 1451, 1392, 1368, 1157, 798; LRMS (ESI); Mass calculated for $C_{11}H_{15}ClN_2O_2$ $[M+1]^+$: 243; found 243.

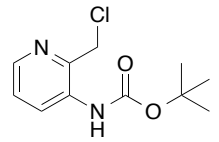


3-(*tert*-butoxycarbonyl)amino-4-chloromethyl pyridine (SI-1b). Prepared according to the general procedure from 3-amino-4-pyridinecarboxylic acid. After chlorination, the crude residue was purified by flash column chromatography (gradient, 35%-90%

EtOAc/hexanes), thus affording picolyl chloride **SI-1b** as a thick red oil (460 mg, 33% yield over four steps from 3-Amino-isonicotinic acid). **SI-1b** tended to decompose significantly within 1 week even under positive N_2 pressure; we found that storage in a static N_2 atmosphere at –30 °C satisfactorily limited decomposition. Analytical data for **1d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.38 (d, J = 4.9, 1H), 6.58 (s, 1H), 4.56 (s, 2H), 1.54 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 145.8, 145.4, 136.1, 132.9, 123.5, 81.7, 41.7, 28.2; IR (ATR) cm^{-1} 3152, 2983, 2932, 1725, 1587, 1523, 1375, 1249, 1151, 772; LRMS (ESI); Mass calculated for $C_{11}H_{15}ClN_2O_2$ $[M+1]^+$: 243; found 243.

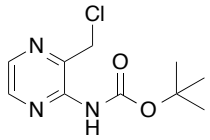


4-(*tert*-butoxycarbonyl)amino-3-chloromethyl pyridine (SI-1c). Prepared according to the general procedure from 4-amino-3-pyridinecarboxylic acid. After chlorination, the crude residue was purified by flash column chromatography (gradient, 35%-90% EtOAc/hexanes), thus affording picolyl chloride **SI-1c** as a white solid (540 mg, 69% yield over four steps from 4-aminonicotinic acid, average of 2 syntheses). Analytical data for **SI-1c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, J = 5.7 Hz, 1H), 8.40 (s, 1H), 8.07 (d, J = 5.8 Hz, 1H), 7.04 (s, 1H), 4.61 (s, 2H), 1.55 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.7, 150.3, 144.8, 119.6, 113.5, 82.26, 41.2, 28.2; IR (ATR) cm^{-1} 3153, 2978, 2935, 1725, 1594, 1451, 1421, 1238, 1155, 819; LRMS (ESI); Mass calculated for $C_{11}H_{15}ClN_2O_2$ $[M+1]^+$: 243; found 243.



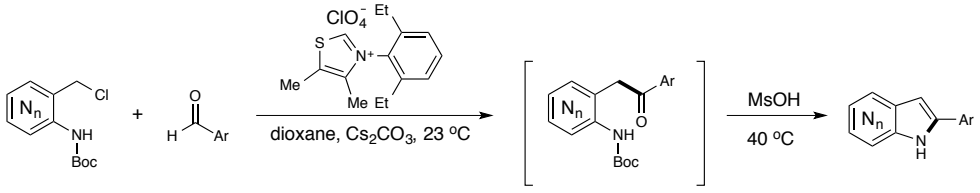
3-(*tert*-butoxycarbonyl)amino-2-chloromethyl pyridine (SI-1d). Prepared according to the general procedure from 3-amino-2-pyridinecarboxylic acid. After the chlorination step, the unpurified residue was purified by flash column chromatography (35%-90%) EtOAc/hexanes, thus affording picolyl chloride **1b** as a thick red oil that crystallized upon refrigeration at 0 °C (3.79 g, 55% yield over four steps from 2-aminopicolinic acid,

average of 2 syntheses). Analytical data for **1b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.6 Hz, 1H), 8.26 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.30 (dd, *J* = 8.4, 4.7 Hz, 1H), 6.83 (s, 1H), 4.76 (s, 2H), 1.54 (s, 8H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 152.6, 143.8, 134.1, 129.5, 124.5, 81.7, 44.9, 28.2; IR (ATR) cm^{-1} 3349, 2983, 1726, 1692, 1509, 1367, 1247, 1093; LRMS (ESI); Mass calculated for $C_{11}H_{15}ClN_2O_2$ $[M+1]^+$: 243; found 243.



3-(*tert*-butoxycarbonyl)amino-2-chloromethyl pyrazine (SI-1e). Prepared according to the general procedure from 3-amino-2-pyrazinecarboxylic acid. After chlorination, the crude residue was purified by flash column chromatography (gradient, 35%-90% EtOAc/hexanes), thus affording picolyl chloride **1e** as a pale brown solid (210 mg, 28% yield over four steps from 3-Amino-2 pyrazinecarboxylic acid). Analytical data for **1e:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 2.5, 1H), 8.34 (d, *J* = 2.5, 1H), 7.06 (s, 1H), 4.81 (s, 2H), 1.55 (d, *J* = 2.9, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.7, 146.1, 143.8, 142.7, 140.0, 82.2, 44.2, 28.2; IR (ATR) cm^{-1} 3230, 2980, 2965, 1697, 1534, 1518, 1439, 1233, 1178, 1040, 967; LRMS (ESI): Mass calculated for $C_{10}H_{14}ClN_3O_2$ $[M+1]^+$: 244; found 244.

4.3 General Procedure for Reaction of Aryl Aldehydes with N-Boc amino picolyl chlorides.

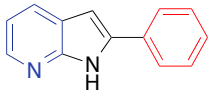


Part I: An oven-dried, screw-capped 2 dram vial equipped with a magnetic stirbar was taken into a nitrogen-filled glovebox at which time picolyl chloride (0.41 mmol, 1.0 equiv), thiazolium salt C (0.082 mmol, 0.2 equiv), cesium carbonate (0.49 mmol, 1.2 equiv) were added. Solid aryl aldehydes (0.49 mmol, 1.2 equiv) were also added in the glovebox. The vial was capped with a septum cap, removed from the drybox and put

under positive N_2 pressure. Into the vial were then successively added 1,4-dioxane (4.10 mL, 0.10 M) and liquid aryl aldehyde (0.492 mmol, 1.2 equiv) via syringe. The reaction was stirred at room temperature until consumption of the benzyl chloride was observed by ^{1}H NMR spectroscopy or for 36 h (usually complete within 36 h).

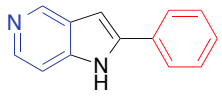
Part II: Under positive N_2 pressure with venting, methanesulfonic acid (0.222 mL, 7.5 equiv) was added dropwise with evolution of carbon dioxide. The reaction was stirred at ambient temperature or at 40 °C until consumption of the intermediate ketone was observed (^{1}H-NMR analysis or TLC, usually 12 h). The reaction was diluted with dichloromethane (3 mL) and transferred to separatory funnel containing aqueous sodium bicarbonate (3:1 sat. sodium bicarbonate/DI water, 15 mL). The reaction vessel was rinsed with dichloromethane (3 x 2 mL) and water (2 x 2 mL) and transferred to a separatory funnel. After shaking vigorously with venting, the organic phase was separated and the aqueous phase was back extracted with dichloromethane (3 x 10 mL). The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and the solvent removed *in vacuo*. Four methods of purification were used as necessary: A) flash chromatography on silica gel with ethyl acetate/hexanes/triethylamine (gradient, 49%/49%/2% to 80%/18%/2%) or B) flash chromatography on silica gel with methanol/dichloromethane (gradient, 1%/99% to 15%/85%). C) dissolution in 2 mL dichloromethane and recrystallization via slow addition of 6 mL hexanes or D) flash chromatography on silica gel with methanole/dichloromethane (gradient, 1%/99% to 15%/85%), combination of fractions containing desired product, removal of solvent *in vacuo* followed by recrystallization in 2 mL DCM via slow addition of 6mL hexanes. After each recrystallization, the precipitate was washed with a 1:1 mixture of DCM:hexane to afford the desired azaindoles in high purity.

*Note: Sonication was often necessary to improve the solubility of compounds in DMSO-*d*6.

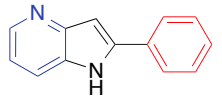


2-phenyl-1*H*-pyrrolo[2,3-b]pyridine (4). Prepared according to the general procedure starting from picolyl chloride (**1a**) (100 mg, 0.41 mmol) and benzaldehyde (52.5 mg, 0.49

mmol). The unpurified residue was purified by Method A to yield **4** as a white powder (56mg, 90%). Analytical data for **4:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.29 (s, 1H), 8.32 (dd, *J* = 4.8, 1.5 Hz, 2H), 7.97 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.92 – 7.86 (m, 5H), 7.53 (t, *J* = 7.7 Hz, 5H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.11 (dd, *J* = 7.8, 4.8 Hz, 2H), 6.80 (d, *J* = 1.8 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.0, 142.1, 139.4, 132.4, 129.0, 128.7, 128.2, 125.8, 122.3, 116.1, 97.4; IR (ATR) cm^{-1} 3146, 3032, 2918, 1716, 1542, 1457, 1364, 1224, 1195, 904; Mp: 214–217 °C; LRMS (ESI): Mass calculated for $C_{13}H_{10}N_2$ $[M+1]^+$: 195; found 195.

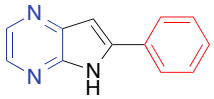


2-phenyl-1*H*-pyrrolo[3,2-c]pyridine (**5**). Prepared according to the general procedure starting from picolyl chloride (**SI-1c**) (100 mg, 0.41 mmol) and benzaldehyde (52.5 mg, 0.49 mmol). The unpurified residue was purified by Method C to afford **5** as a light yellow crystals (70 mg, 87%). Analytical data for **5**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.01 (s, 1H), 8.82 (s, 1H), 8.17 (d, *J* = 5.6 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.37 (q, *J* = 7.4, 6.6 Hz, 2H), 7.04 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 142.9, 140.4, 138.9, 131.4, 129.0, 128.1, 125.7, 125.3, 106.6, 97.5; IR (ATR) cm^{-1} 3430, 3052, 2822, 1615, 1431, 1228, 1191, 1125, 918; Mp: 260 °C (decomposition); LRMS (ESI): Mass calculated for $C_{13}H_{10}N_2$ $[M+1]^+$: 195; found 195.

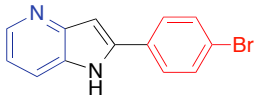


2-phenyl-1*H*-pyrrolo[3,2-b]pyridine (6). Prepared according to the general procedure starting from picolyl chloride (**SI-1d**) (100 mg, 0.41 mmol) and benzaldehyde (52.5 mg, 0.49 mmol). The unpurified residue was purified by Method C to afford **6** as an off white powder (74 mg, 92%). Analytical data for **6**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.83 (s, 1H), 8.33 (t, *J* = 3.1 Hz, 1H), 7.96 (d, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.11 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 147.4, 143.3, 141.3, 132.0, 130.3, 129.4, 128.7, 125.8, 118.5, 117.1, 99.6; IR (ATR) cm^{-1} 3449, 3050, 2820,

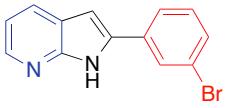
1544, 1430, 1223, 1132, 910; Mp: 251–254 °C; LRMS (ESI): Mass calculated for $C_{13}H_{10}N_2$ $[M+1]^+$: 195; found 195.



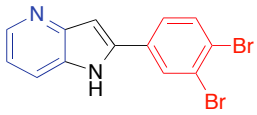
2-phenyl-5-*H*-pyrrolo[2,3-b]pyrazine (7). Prepared according to the general procedure starting from picolyl chloride (**SI-1e**) (100 mg, 0.41 mmol) and benzaldehyde (52.5 mg, 0.49 mmol). The unpurified residue was purified by Method C to afford **7** as a light brown powder (72 mg, 90%). Analytical data for **7**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.50 (s, 1H), 8.35 (s, 1H), 8.20 (s, 1H), 8.03 (d, J = 7.6 Hz, 2H), 7.53 (t, J = 7.7 Hz, 2H), 7.44 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 2.3 Hz, 1H^{13}C NMR (126 MHz, DMSO-d_6) δ 143.1, 143.0, 140.3, 138.5, 136.8, 130.9, 129.1, 129.1, 125.9, 97.5; IR (ATR) cm^{-1} 3133, 3050, 1473, 1456, 1401, 1349, 1219, 925; Mp: 214 – 216 °C; LRMS (ESI): Mass calculated for $C_{11}H_9N_3$ $[M+1]^+$: 196; found 196.



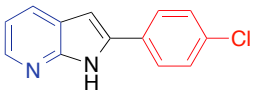
2-(4-bromophenyl)-1*H*-pyrrolo[3,2-b]pyridine (8). Prepared according to the general procedure starting from picolyl chloride (**SI-1d**) (100 mg, 0.41 mmol) and 4-bromobenzaldehyde (91 mg, 0.49 mmol). The unpurified residue was purified by Method C to afford **8** as a brown powder (97 mg, 86%). Analytical data for **8**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.85 (s, 1H), 8.33 (d, J = 4.5 Hz, 1H), 7.90 (d, J = 8.1 Hz, 2H), 7.77 (d, J = 8.2 Hz, 1H), 7.71 (d, J = 8.2 Hz, 2H), 7.12 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 146.7, 143.1, 139.6, 131.9, 130.9, 130.0, 128.3, 127.3, 121.3, 118.2, 116.9, 99.7; IR (ATR) cm^{-1} 3412, 3208, 1664, 1508, 1100, 1049, 1024, 825, 702; Mp: 219–219 °C; LRMS (ESI): Mass calculated for $C_{13}H_9BrN_2$ $[M+1]^+$: 273; found 273.



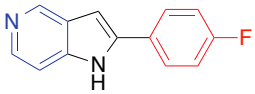
2-(3-bromophenyl)-1*H*-pyrrolo[2,3-b]pyridine (9). Prepared according to the general procedure starting from picolyl chloride (**1a**) (100 mg, 0.41 mmol) and 3-bromobenzaldehyde (91 mg, 0.49 mmol). The unpurified residue was purified by Method C to afford **9** as light brown needles (93 mg, 84%). Analytical data for **9**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.2 (s, 1H), 8.2 (dd, J = 4.8, 1.7 Hz, 1H), 8.2 (d, J = 2.0 Hz, 1H), 7.9 (dd, J = 7.8, 1.8 Hz, 2H), 7.5 (dd, J = 7.9, 1.9 Hz, 1H), 7.4 (t, J = 7.9 Hz, 1H), 7.1 (dd, J = 7.8, 4.7 Hz, 1H), 7.0 (d, J = 1.9 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 149.6, 143.4, 136.4, 133.9, 131.0, 130.5, 128.2, 127.7, 124.2, 122.4, 120.6, 116.2, 98.3. IR (ATR) cm^{-1} 3152, 3097, 2941, 2873, 1589, 1474, 1390, 1359, 1220, 1170, 1117, 972, 803; Mp: 190–193°C; LRMS (ESI): Mass calculated for $C_{13}H_9BrN_2$ $[M+1]^+$: 273; found 273.



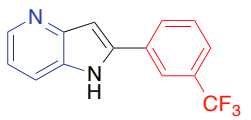
2-(3,4-dibromophenyl)-1*H*-pyrrolo[3,2-b]pyridine (10). Prepared according to the general procedure starting from picolyl chloride (**SI-1d**) (100 mg, 0.41 mmol) and 3,4-dibromobenzaldehyde (130 mg, 0.49 mmol). The unpurified residue was purified by Method C to afford **10** as an off-white powder (127 mg, 88%). Analytical data for **10**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.04 (s, 1H), 8.66 (s, 1H), 8.38 (dd, J = 4.6, 1.4 Hz, 1H), 7.89 (s, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 2.1 Hz, 1H), 7.17 (dd, J = 8.2, 4.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 150.3, 146.2, 143.6, 138.5, 137.7, 130.4, 119.4, 118.7, 117.8, 101.9; IR (ATR) cm^{-1} 3238, 3084, 1728, 1650, 1443, 1357, 1278, 1013, 933, 826, 773; Mp: 260 °C (decomposition); LRMS (ESI): Mass calculated for $C_{13}H_8Br_2N_2$ $[M+1]^+$: 351; found 351.



2-(4-chlorophenyl)-1*H*-pyrrolo[2,3-b]pyridine (11). Prepared according to the general procedure starting from picolyl chloride (**1a**) (100 mg, 0.41 mmol) and 4-chlorobenzaldehyde (69.5 mg, 0.49 mmol). The unpurified residue was purified by Method C to afford **11** as a pale yellow powder (79 mg, 84%). Analytical data for **11**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.18 (s, 1H), 8.25 – 8.20 (m, 1H), 7.95 (td, J = 8.5, 1.8, 3H), 7.53 (d, J = 8.6, 1H), 7.07 (dd, J = 7.8, 4.7, 1H), 6.96 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 149.7, 143.1, 136.9, 132.4, 130.5, 128.9, 128.0, 127.0, 120.8, 116.1, 97.7; IR (ATR) cm^{-1} 3070, 3056, 2980, 1730, 1448, 1372, 1330, 1158, 1130, 745; Mp: 215–217 °C; LRMS (ESI): Mass calculated for $C_{13}H_9ClN_2$ $[M+1]^+$: 229; found 229.

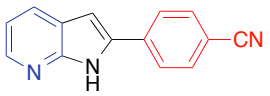


2-(4-fluorophenyl)-1*H*-pyrrolo[3,2-c]pyridine (12). Prepared according to the general procedure starting from picolyl chloride (**SI-1c**) (100 mg, 0.41 mmol) and 4-fluorobenzaldehyde (61.4 mg, 0.49 mmol). The unpurified residue was purified by Method C to afford **12** as an off-white powder (69 mg, 79%). Analytical data for **12**:^{1}H NMR (500 MHz, DMSO) δ 11.99 (s, 1H), 8.82 (s, 1H), 8.17 (d, J = 5.7, 1H), 7.97 – 7.92 (m, 2H), 7.39 – 7.32 (m, 3H), 7.02 (s, 1H). ^{13}C NMR (126 MHz, DMSO) δ 163.36, 161.41, 143.29, 140.84 (d, J = 4.1), 138.49, 128.53 (d, J = 3.1), 127.95 (d, J = 8.2), 126.18, 116.44 (d, J = 21.7), 107.06, 98.07; IR (ATR) cm^{-1} 3356, 3104, 3072, 2970, 2706, 1640, 1586, 1499, 1302, 1232, 1161, 1099, 1026, 927; Mp: 252–255 °C; LRMS (ESI): Mass calculated for $C_{13}H_9FN_2$ $[M+1]^+$: 213; found 213.

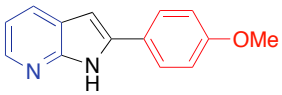


2-(3-(trifluoromethyl)phenyl)-1*H*-pyrrolo[3,2-b]pyridine (13). Prepared according to the general procedure starting from picolyl chloride (**SI-1d**) (100 mg, 0.41 mmol) and 3-(trifluoromethyl)benzaldehyde (86 mg, 0.49 mmol). The unpurified residue was purified by Method D to afford **13** as a pale brown powder (93 mg, 86%). Analytical data for **13**:

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.97 (s, 1H), 8.34 (dd, J = 4.6, 1.5, 1H), 8.29 (s, 1H), 8.27 – 8.23 (m, 1H), 7.79 (dt, J = 8.2, 1.2, 1H), 7.73 (dd, J = 5.0, 1.5, 2H), 7.26 (dd, J = 2.2, 0.9, 1H), 7.14 (dd, J = 8.1, 4.6, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 146.6, 143.3, 138.9, 132.7, 130.1, 129.8, 129.4, 125.2, 124.5 (d, J = 4.0 Hz), 123.1, 121.5 (d, J = 4.0 Hz), 118.4, 117.2, 100.5; IR (ATR) cm^{-1} 3392, 3134, 3060, 2886, 2830, 2766, 1417, 1322, 1282, 1273, 1162, 1109, 940; Mp: 218–220 °C; LRMS m/z 263 (M+1). LRMS (ESI): Mass calculated for $C_{14}H_9F_3N_2$ $[M+1]^+$: 263; found 263.

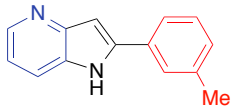


2-(4-cyanophenyl)-1*H*-pyrrolo[2,3-b]pyridine (14). Prepared according to the general procedure starting from picolyl chloride (**1a**) (100 mg, 0.41 mmol) and 4-formylbenzonitrile (64.8 mg, 0.49 mmol). The unpurified residue was purified by Method C to afford **14** as a tan powder (75 mg, 83%). Analytical data for **14**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.34 (s, 1H), 8.28 (dd, J = 4.7, 1.6 Hz, 1H), 8.13 (d, J = 8.5 Hz, 1H), 8.00 (dd, J = 7.8, 1.6 Hz, 1H), 7.92 (d, J = 8.7 Hz, 2H), 7.16 (s, 1H), 7.10 (dd, J = 7.9, 4.7 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 149.9, 144.1, 136.1, 136.0, 132.8, 128.7, 125.7, 120.60 , 118.9, 116.4, 109.8, 99.9; IR (ATR) cm^{-1} 3396, 3127, 2090, 2978, 2874, 2224, 1604, 1487, 1331, 1280, 817; Mp: 240 °C (decomposition); LRMS (ESI): Mass calculated for $C_{14}H_9N_3$ $[M+1]^+$: 220; found 220.

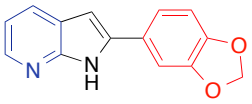


2-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-b]pyridine (15). Prepared according to the general procedure starting from picolyl chloride (**1a**) (100 mg, 0.41 mmol) and 4-methoxybenzaldehyde (63.7 mg, 0.49 mmol). The unpurified residue was purified by Method A to afford **15** as a white powder (74 mg, 80%). Analytical data for **17**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.01 (s, 1H), 8.17 (s, 1H), 7.88 (m, 3H), 7.03 (m, 3H), 6.77 (s, 1H), 3.80 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.2, 149.6, 142.1, 138.4, 127.2, 126.7, 124.2, 121.1, 115.9, 114.3, 95.7, 55.2; IR (ATR) cm^{-1} 3111, 2950, 2902, 1625,

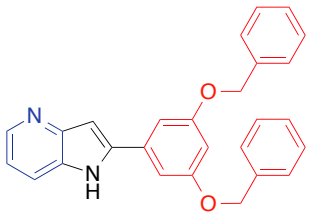
1498, 1431, 1222, 1191, 1125, 1041, 993; Mp: 192–195 °C; LRMS (ESI): Mass calculated for $C_{14}H_{12}N_2O$ $[M+1]^+$: 225; found 225.



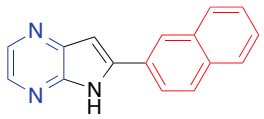
2-(3-methylphenyl)-1*H*-pyrrolo[3,2-b]pyridine (16). Prepared according to the general procedure starting from picolyl chloride (**SI-1d**) (100 mg, 0.41 mmol) and 3-methylbenzaldehyde (59.4 mg, 0.49 mmol). The unpurified residue was purified by Method A to afford **16** as a tan powder (63 mg, 73%). Analytical data for **16**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.73 (s, 1H), 8.30 (dd, J = 4.6, 1.4, 1H), 7.78 – 7.69 (m, 3H), 7.38 (t, J = 7.6, 1H), 7.21 – 7.17 (m, 1H), 7.08 (dd, J = 8.1, 4.6, 1H), 7.03 (d, J = 2.0, 1H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 146.9, 142.8, 141.0, 138.1, 131.5, 129.8, 128.9, 128.8, 125.9, 122.6, 118.0, 116.5, 99.0, 21.1; IR (ATR) cm^{-1} 3053, 2952, 2861, 2812, 1476, 1355, 1230, 1059, 973, 817; Mp: 214–217 °C; LRMS (ESI): Mass calculated for $C_{14}H_{12}N_2$ $[M+1]^+$: 209; found 209.



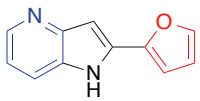
2-(benzo[d][1,3]dioxol-5-yl)-1*H*-pyrrolo[2,3-b]pyridine (17). Prepared according to the general procedure starting from picolyl chloride (**1a**) (100 mg, 0.41 mmol) and benzo[d][1,3]dioxole-5-carbaldehyde (74.2 mg, 0.49 mmol). The unpurified residue was purified by Method C to afford **17** as a pale tan powder (78 mg, 78%). Analytical data for **17**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.98 (s, 1H), 8.17 (dd, J = 4.7, 1.6 Hz, 1H), 7.88 (dd, J = 7.8, 1.6 Hz, 1H), 7.53 (d, J = 1.8 Hz, 1H), 7.46 (dd, J = 8.1, 1.8 Hz, 1H), 7.05 – 7.00 (m, 2H), 6.82 (d, J = 2.1 Hz, 1H), 6.07 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 149.5, 147.9, 147.2, 142.3, 138.2, 127.4, 125.8, 121.0, 119.2, 115.9, 108.7, 105.7, 101.2, 96.3; IR (ATR) cm^{-1} 3150, 3090, 3018, 2932, 2878, 1592, 1495, 1364, 1280, 1170, 1118, 1118, 969; Mp: 239–241 °C; LRMS (ESI): Mass calculated for $C_{16}H_{10}N_2O_2$ $[M+1]^+$: 239; found 239.



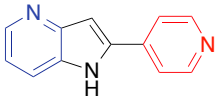
2-(3,5-(dibenzyloxy)phenyl)-1*H*-pyrrolo[3,2-b]pyridine (18). Prepared according to the general procedure starting from picolyl chloride (**SI-1d**) (100 mg, 0.41 mmol) and 3,5-bis(benzyloxy)benzaldehyde (157 mg, 0.49 mmol). The unpurified residue was purified by method C to afford **18** as an off white powder (144 mg, 86%). Analytical Data for **18**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.31 (dd, J = 4.7, 1.4 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 7.3 Hz, 4H), 7.42 (t, J = 7.5 Hz, 4H), 7.35 (t, J = 7.3 Hz, 2H), 7.23 (d, J = 2.2 Hz, 2H), 7.13 – 7.08 (m, 2H), 6.70 (t, J = 2.2 Hz, 1H), 5.19 (s, 4H). ^{13}C NMR (126 MHz, DMSO) δ 160.43, 147.21, 143.40, 141.02, 137.39, 133.90, 130.23, 128.93, 128.38, 128.30, 118.48, 117.23, 105.06, 102.29, 100.20 (s, 1H), 69.97; IR (ATR) cm^{-1} 3090, 2888, 2160, 1594, 1448, 1366, 1265, 1160, 1055, 1030, 845; Mp: 212–214 °C; LRMS (ESI): Mass calculated for $C_{27}H_{23}N_2O_2$ $[M+1]^+$: 407; found 407.



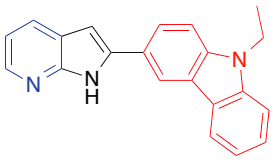
2-(napthalen-2-yl)-5-*H*-pyrrolo[2,3-b]pyrazine (19). Prepared according to the general procedure starting from picolyl chloride (**SI-1e**) (100 mg, 0.41 mmol) and 2-napthaldehyde (77.0 mg, 0.49 mmol). The unpurified residue was purified by method C to afford **19** as a brown powder (86 mg, 85%). Analytical Data for **19**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.56 (s, 1H), 8.54 (s, 1H), 8.30 (d, J = 2.6 Hz, 1H), 8.15 (d, J = 2.6 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 7.97 (d, J = 8.6 Hz, 1H), 7.90 (dd, J = 7.4, 4.0 Hz, 2H), 7.55 – 7.46 (m, 2H), 7.22 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 143.3, 143.0, 140.4, 138.5, 136.9, 133.0, 129.6, 128.5, 128.3, 127.7, 126.9, 126.8, 124.7, 123.8, 98.2; IR (ATR) cm^{-1} 3110, 3059, 2938, 2853, 1553, 1406, 1349, 1223, 1128, 1069, 931, 836; Mp: 220 °C (decomposition); LRMS (ESI): Mass calculated for $C_{16}H_{11}N_3$ $[M+1]^+$: 246; found 246.



2-(4-furyl)-1-*H*-pyrrolo[3,2-b]pyridine (20). Prepared according to the general procedure starting from picolyl chloride (**SI-1d**) (100 mg, 0.41 mmol) and furan-2-carbaldehyde (47.5 mg, 0.49 mmol). The unpurified residue was purified by method A to afford **20** as a tan powder (59 mg, 78%). Analytical Data for **20**: ^{1}H NMR (500 MHz, DMSO) δ 11.80 (s, 1H), 8.30 (d, *J* = 4.6, 2H), 7.84 (d, *J* = 1.7, 2H), 7.72 (d, *J* = 8.1, 2H), 7.09 (dd, *J* = 8.2, 4.6, 2H), 7.00 (d, *J* = 3.4, 2H), 6.80 (s, 2H), 6.67 (dd, *J* = 3.4, 1.8, 2H). ^{13}C NMR (126 MHz, DMSO) δ 147.0, 146.5, 143.4, 143.0, 132.3, 129.4, 118.0, 116.7, 112.1, 107.5, 97.8; IR (ATR) cm^{-1} 3404, 3116, 3053, 2678, 1613, 1523, 1413, 1350, 1226, 1013, 914; Mp: 241–243 °C; LRMS (ESI); Mass calculated for $C_{11}H_8N_2O$ $[M+1]^+$: 185; found 185.



2-(4-pyridyl)-1-*H*-pyrrolo[3,2-b]pyridine (21). Prepared according to the general procedure starting from picolyl chloride (**SI-1d**) (100 mg, 0.41 mmol) and isonicotinaldehyde (53.0 mg, 0.49 mmol). The unpurified residue was purified by method D to afford **21** as a tan powder (40 mg, 50%). Analytical Data for **21**: ^{1}H NMR (500 MHz, DMSO) δ 12.04 (s, 1H), 8.66 (s, 2H), 8.38 (dd, *J* = 4.6, 1.4, 1H), 7.90 (d, *J* = 6.2, 2H), 7.82 (d, *J* = 8.1, 1H), 7.36 (d, *J* = 2.1, 1H), 7.17 (dd, *J* = 8.2, 4.5, 1H). ^{13}C NMR (126 MHz, DMSO) δ 150.8, 146.7, 144.1, 139.0, 138.1, 130.9, 119.8, 119.3, 118.3, 102.3; IR (ATR) cm^{-1} 3083, 3028, 2961, 2738, 1603, 1557, 1449, 1348, 1277, 1068, 928; Mp: 243–246 °C; LRMS (ESI); Mass calculated for $C_{12}H_9N_3$ $[M+1]^+$: 196; found 196.

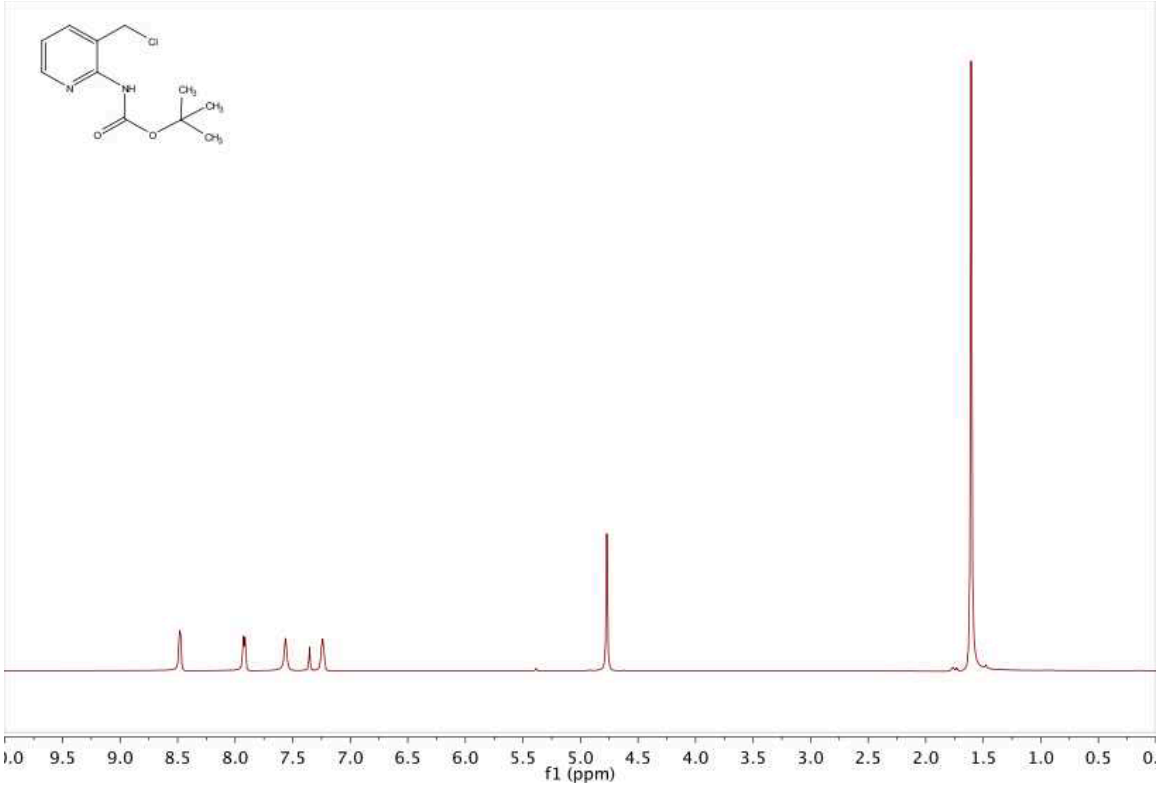


9-ethyl-3-(1*H*-pyrrolo[2,3-b]pyridine-2-yl)-9*H*-carbazole (22). Prepared according to the general procedure starting from picolyl chloride (**1a**) (100 mg, 0.41 mmol) and 9-

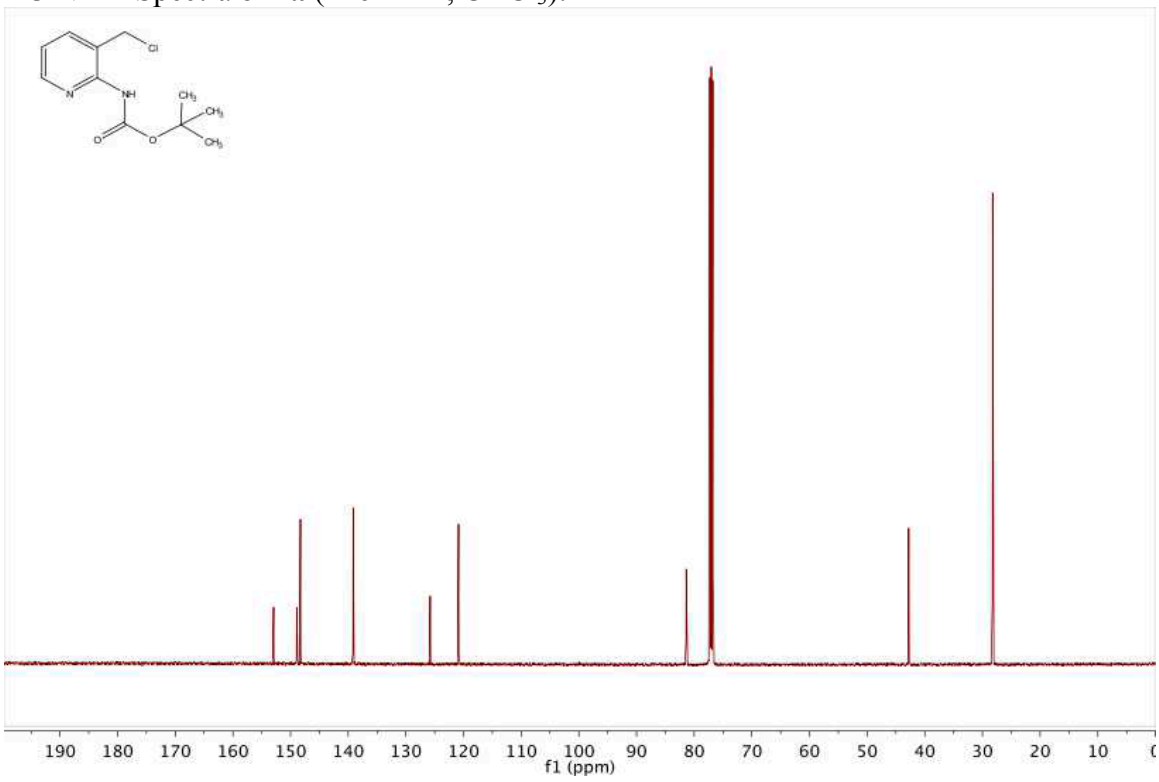
ethyl-9*H*-carbazole-3-carbaldehyde (110 mg, 0.49 mmol). The unpurified residue was purified by Method D to afford **22** as a brown powder (76 mg, 60%). Analytical data for **22**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.1 (d, J = 2.3 Hz, 1H), 8.8 (d, J = 1.8 Hz, 1H), 8.2 – 8.2 (m, 2H), 8.1 (dd, J = 8.5, 1.8 Hz, 1H), 7.9 (dd, J = 7.7, 1.5 Hz, 1H), 7.7 (d, J = 8.6 Hz, 1H), 7.6 (d, J = 8.2 Hz, 1H), 7.5 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 7.3 – 7.2 (m, 1H), 6.9 (d, J = 2.1 Hz, 1H), 4.5 (d, J = 7.2 Hz, 2H), 1.3 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 149.7, 141.9, 140.0, 139.7, 139.3, 127.0, 126.0, 123.6, 122.5, 122.5, 122.2, 121.3, 120.4, 119.1, 117.4, 115.8, 109.5, 109.4, 95.5, 37.1, 13.7; IR (ATR) cm^{-1} 3430, 3204, 3126, 3061, 2970, 2892, 1630, 1475, 1271, 1281, 1232, 1160, 823; Mp: 236–238 °C; LRMS (ESI); Mass calculated for $C_{21}H_{17}N_3$ $[M+1]^+$: 312; found 312.

4.4 Selected NMR Spectra

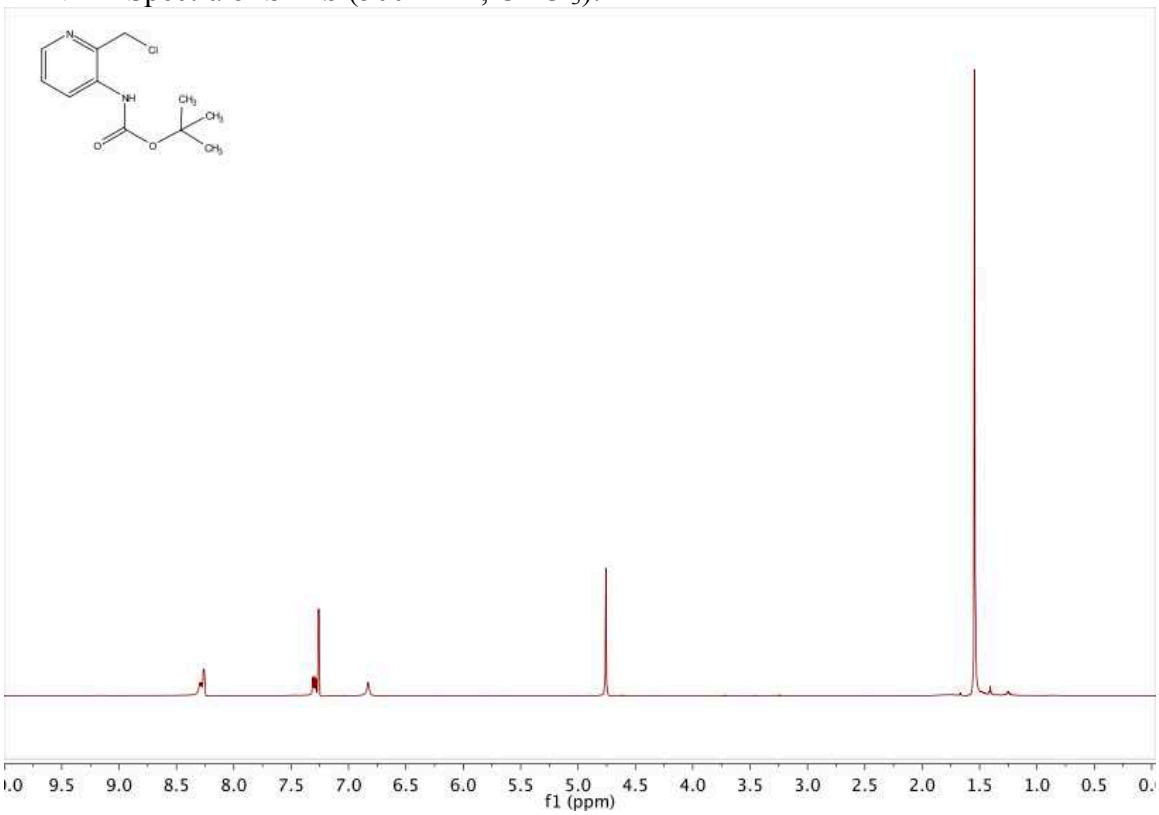
^{1}H NMR Spectra of **1a** (500 MHz, $CDCl_3$):



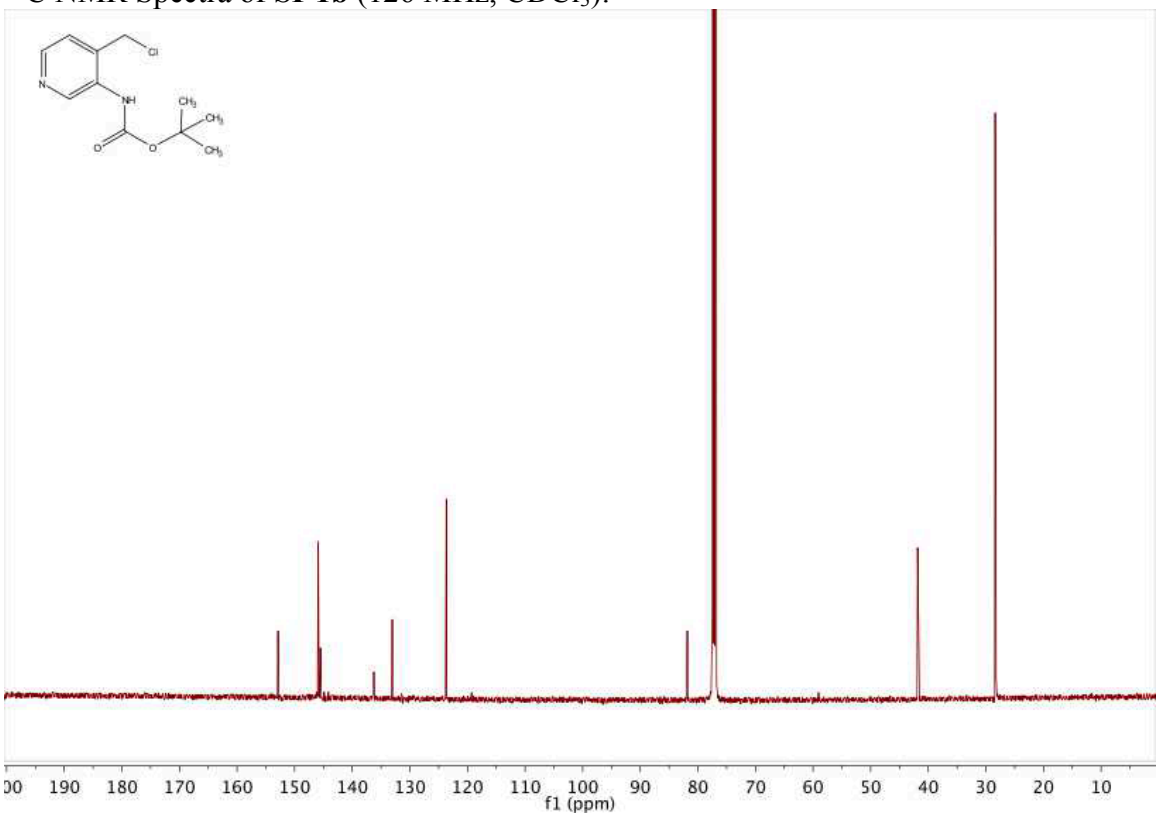
^{13}C NMR Spectra of **1a** (126 MHz, $CDCl_3$):



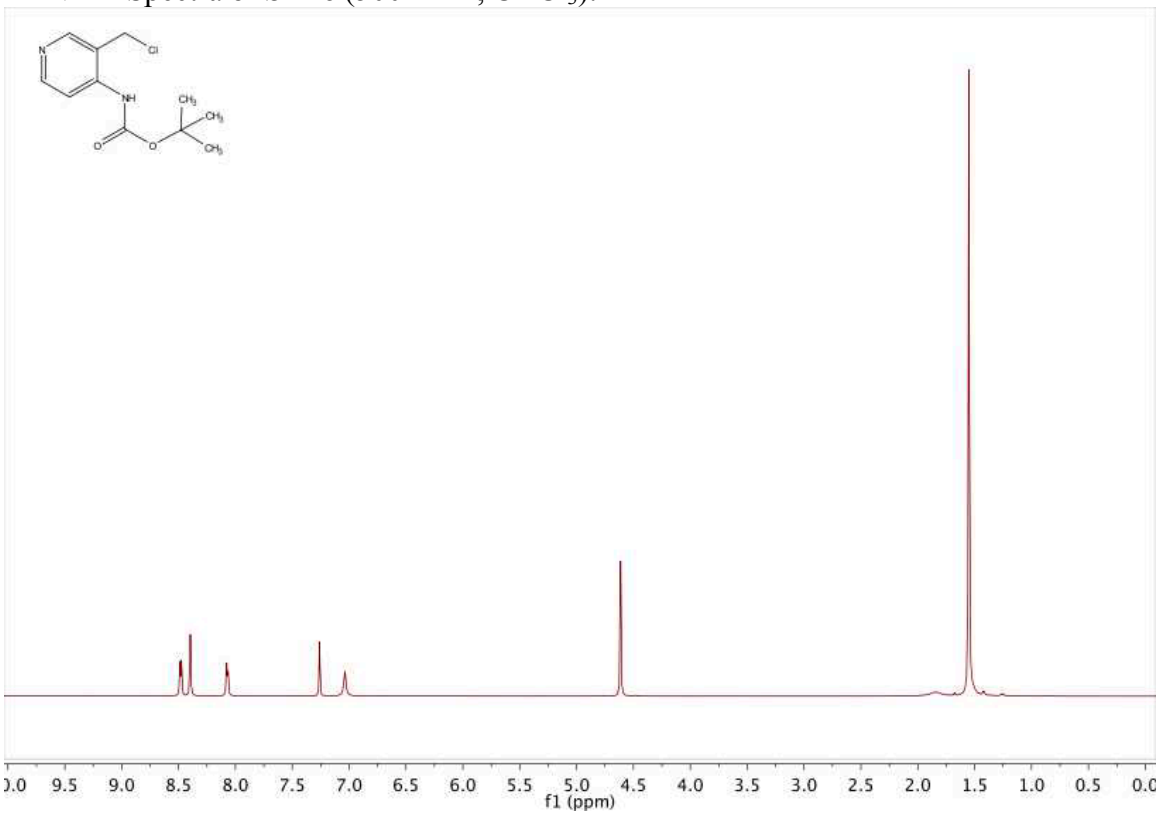
^{1}H NMR Spectra of **SI-1b** (500 MHz, $CDCl_3$):



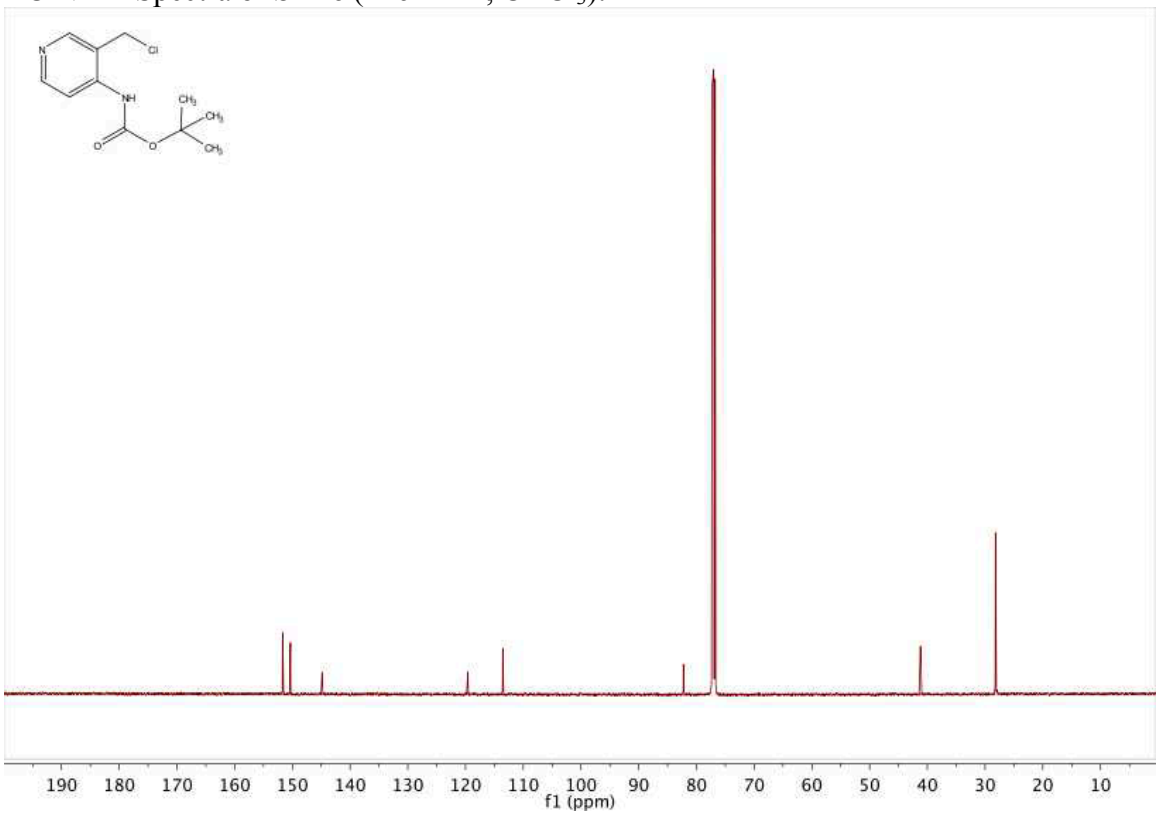
^{13}C NMR Spectra of **SI-1b** (126 MHz, $CDCl_3$):



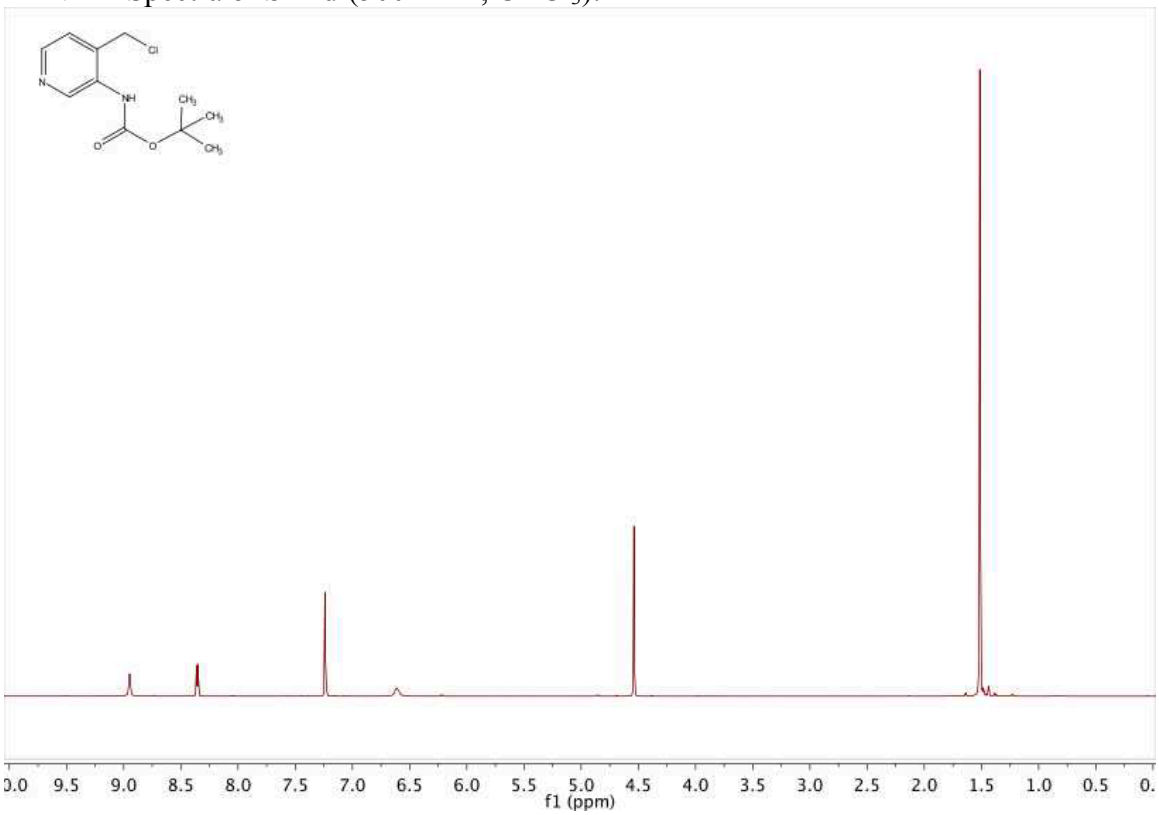
^{1}H NMR Spectra of **SI-1c** (500 MHz, $CDCl_3$):



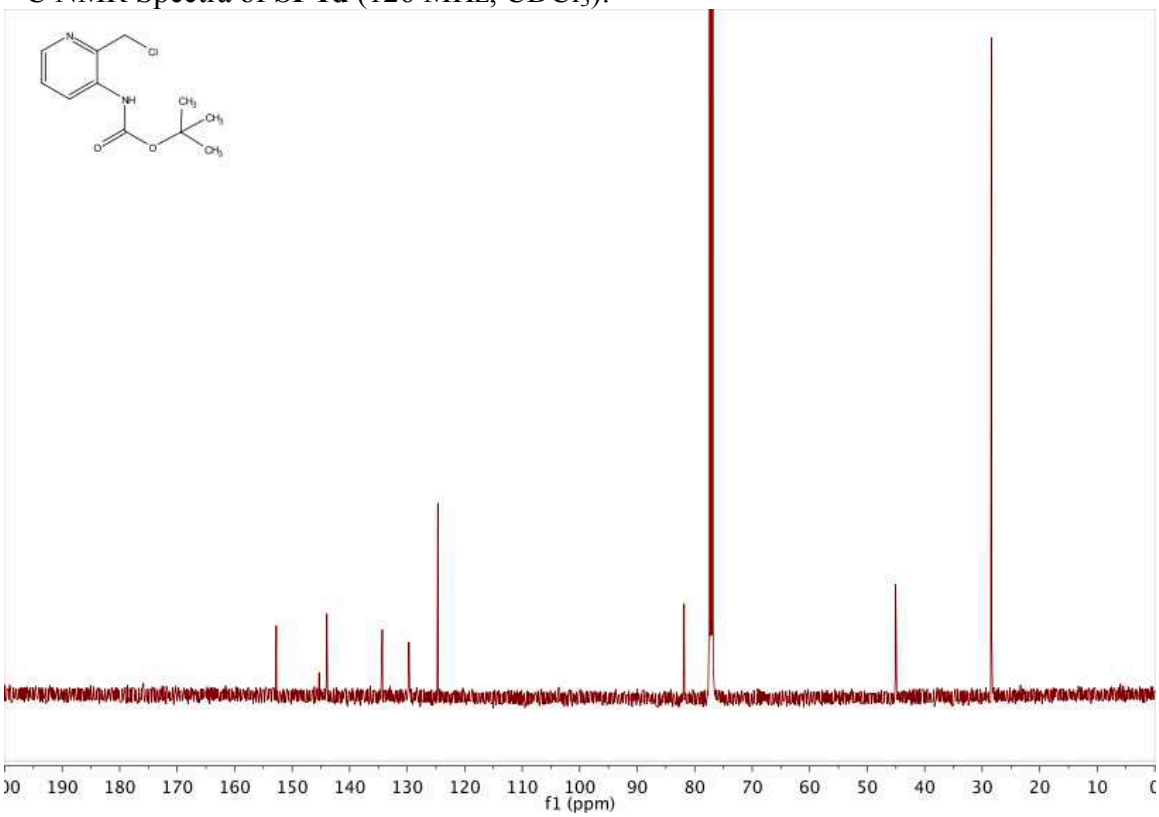
^{13}C NMR Spectra of **SI-1c** (126 MHz, $CDCl_3$):



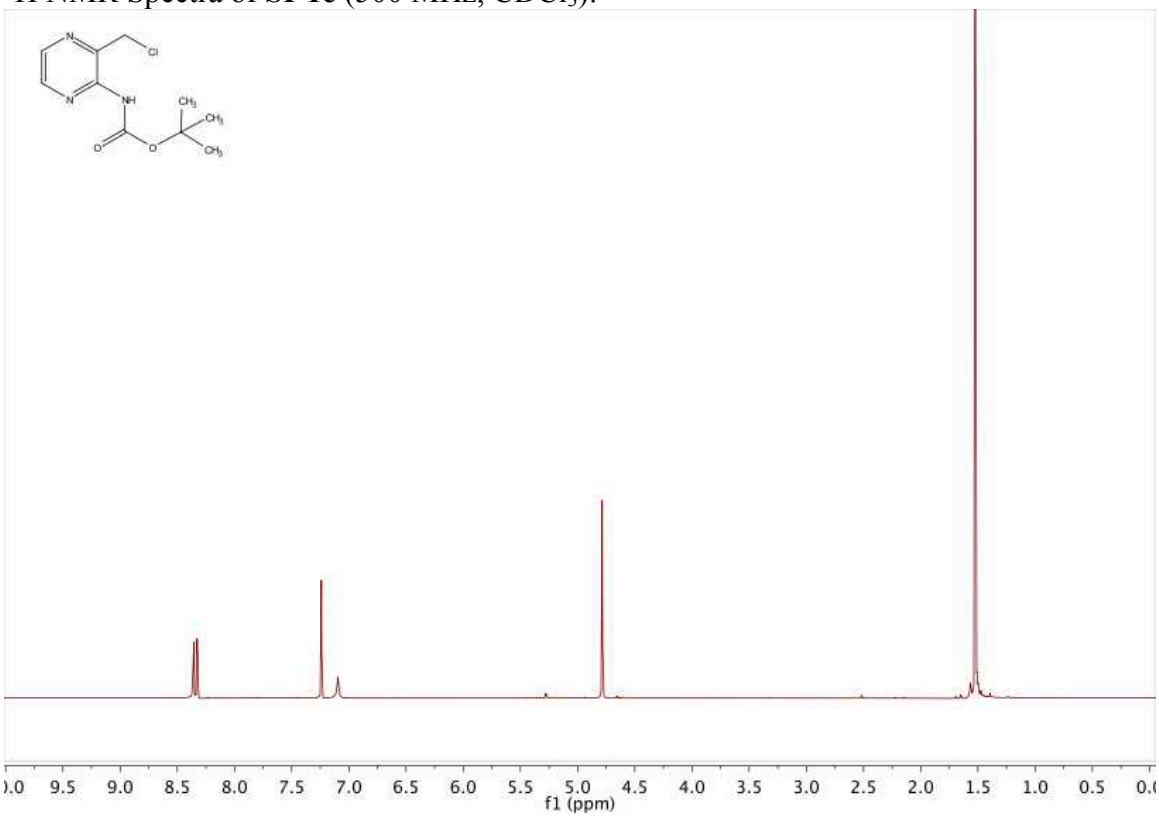
^{1}H NMR Spectra of **SI-1d** (500 MHz, $CDCl_3$):



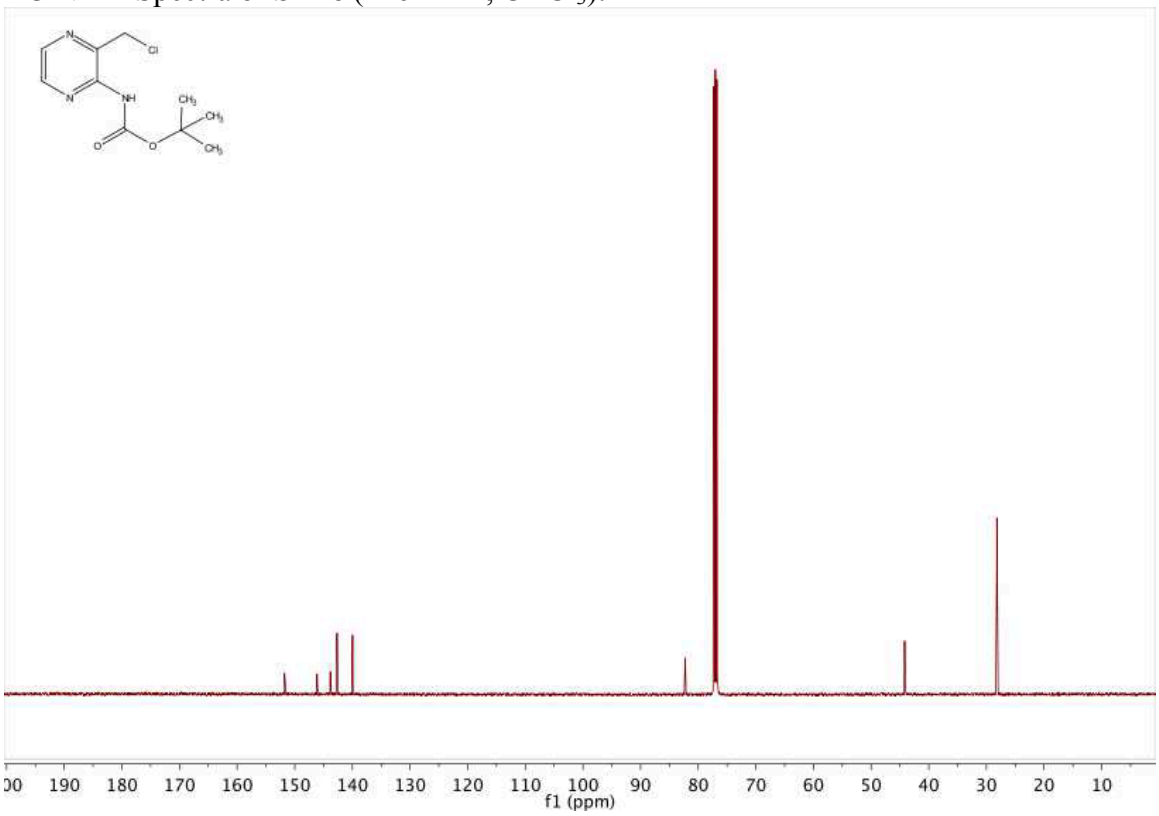
^{13}C NMR Spectra of **SI-1d** (126 MHz, $CDCl_3$):



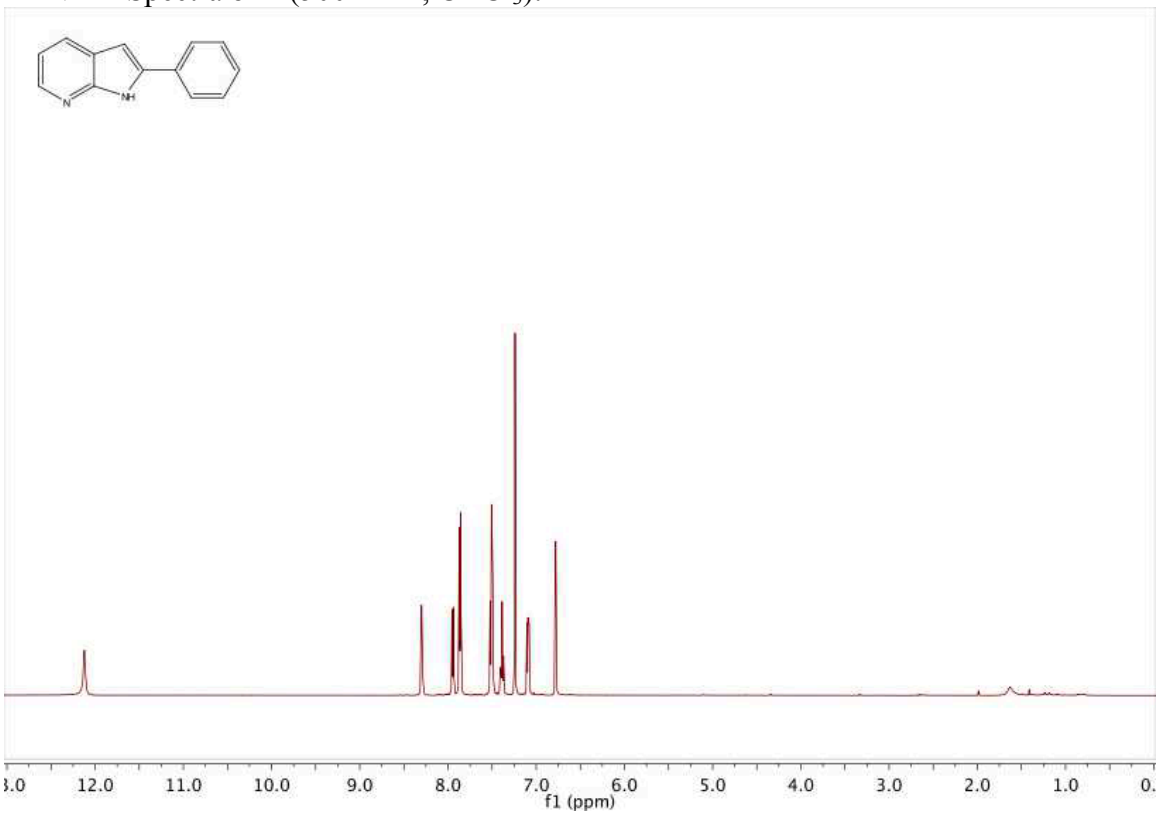
^{1}H NMR Spectra of **SI-1e** (500 MHz, $CDCl_3$):



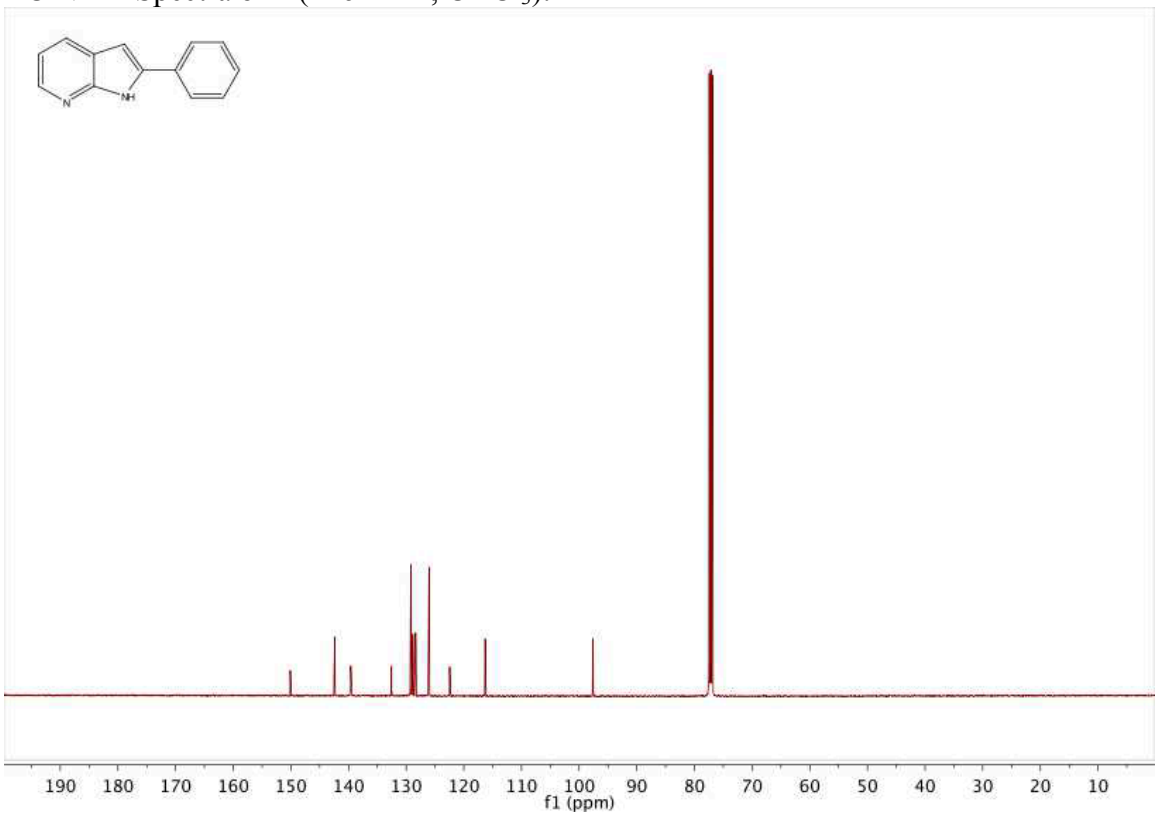
^{13}C NMR Spectra of **SI-1e** (126 MHz, $CDCl_3$):



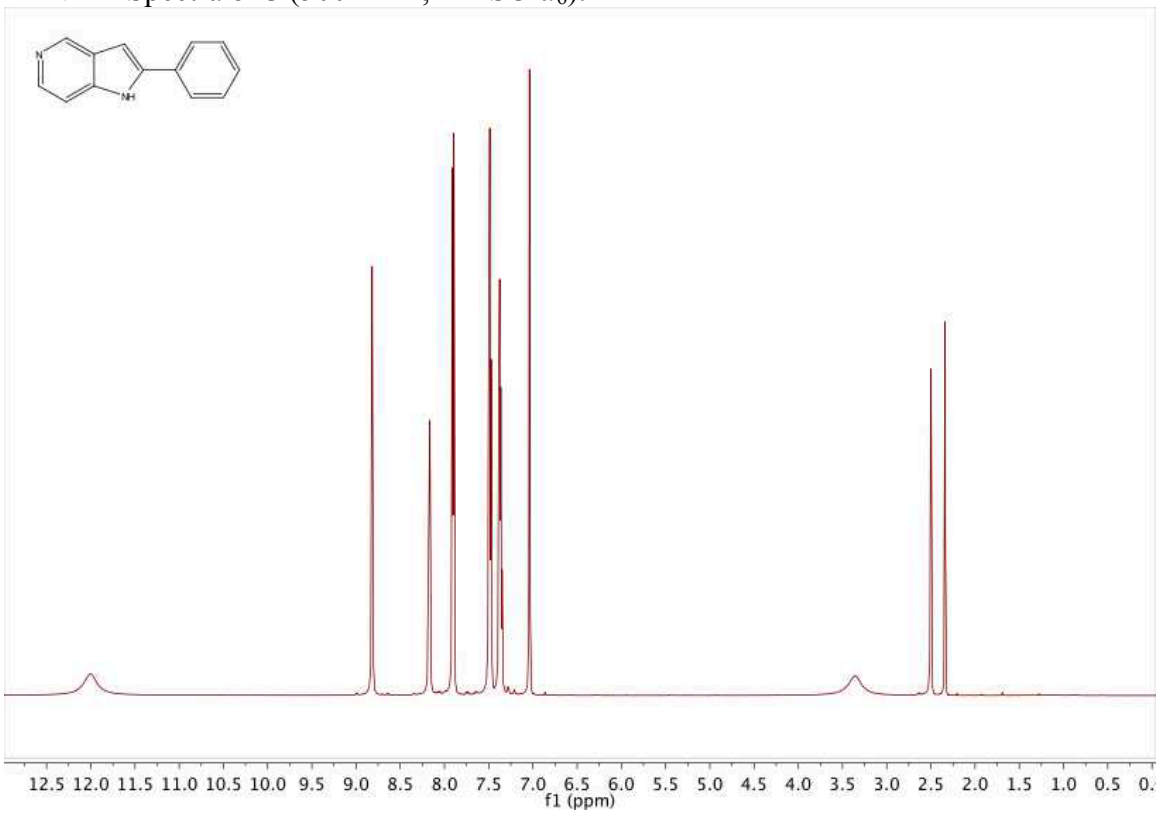
^{1}H NMR Spectra of **4** (500 MHz, $CDCl_3$):



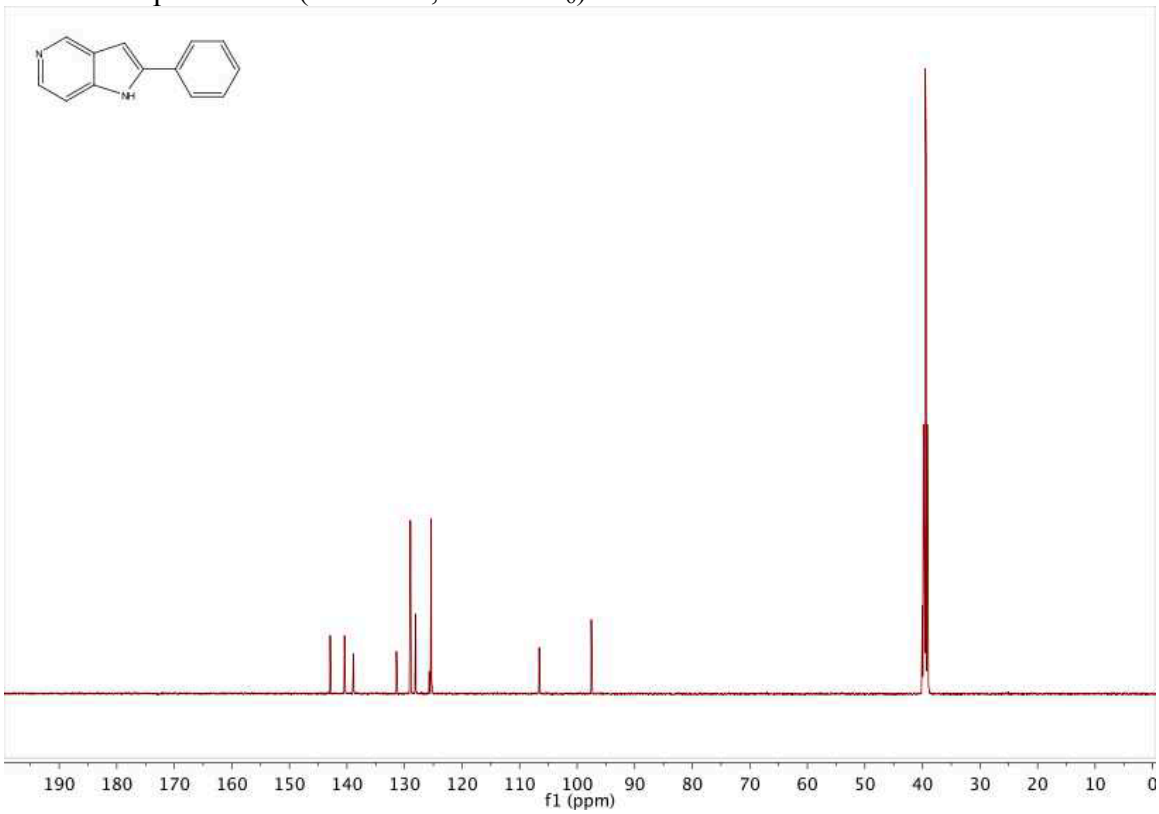
^{13}C NMR Spectra of **4** (126 MHz, $CDCl_3$):



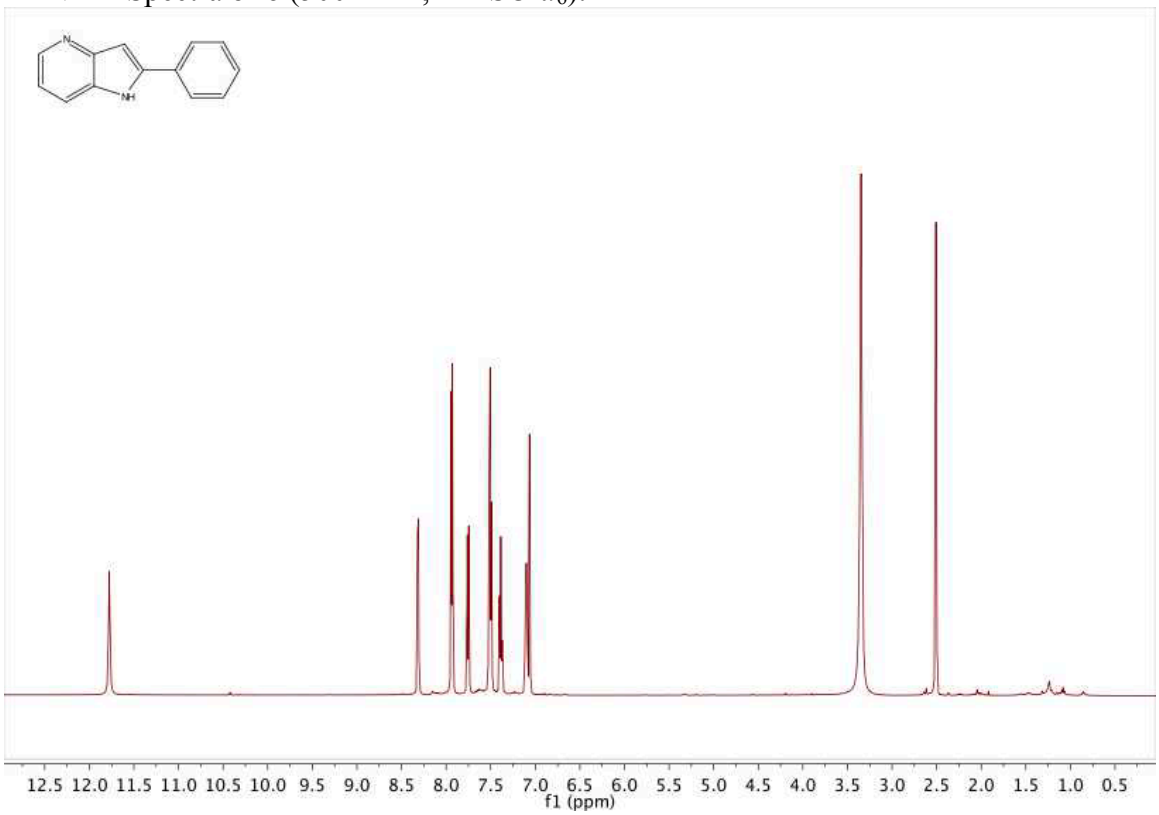
^{1}H NMR Spectra of **5** (500 MHz, DMSO-d_6):



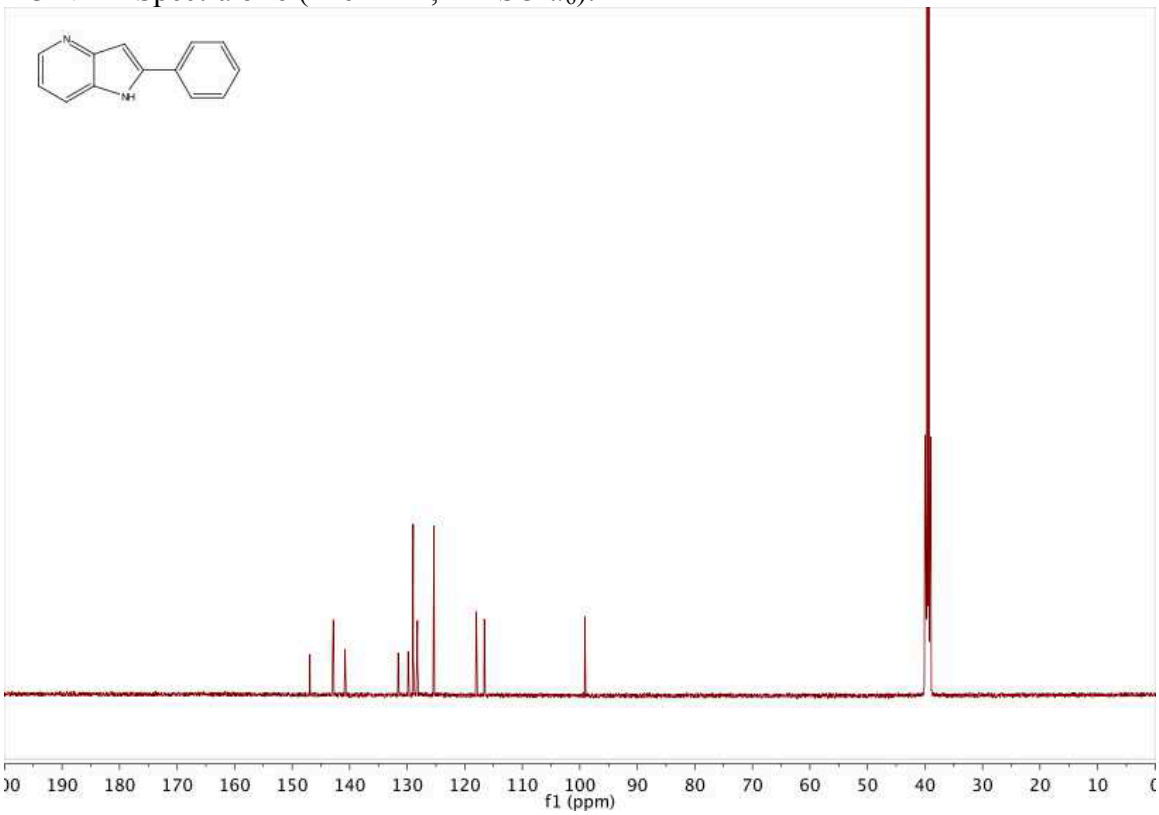
^{13}C NMR Spectra of **5** (126 MHz, DMSO-d_6):



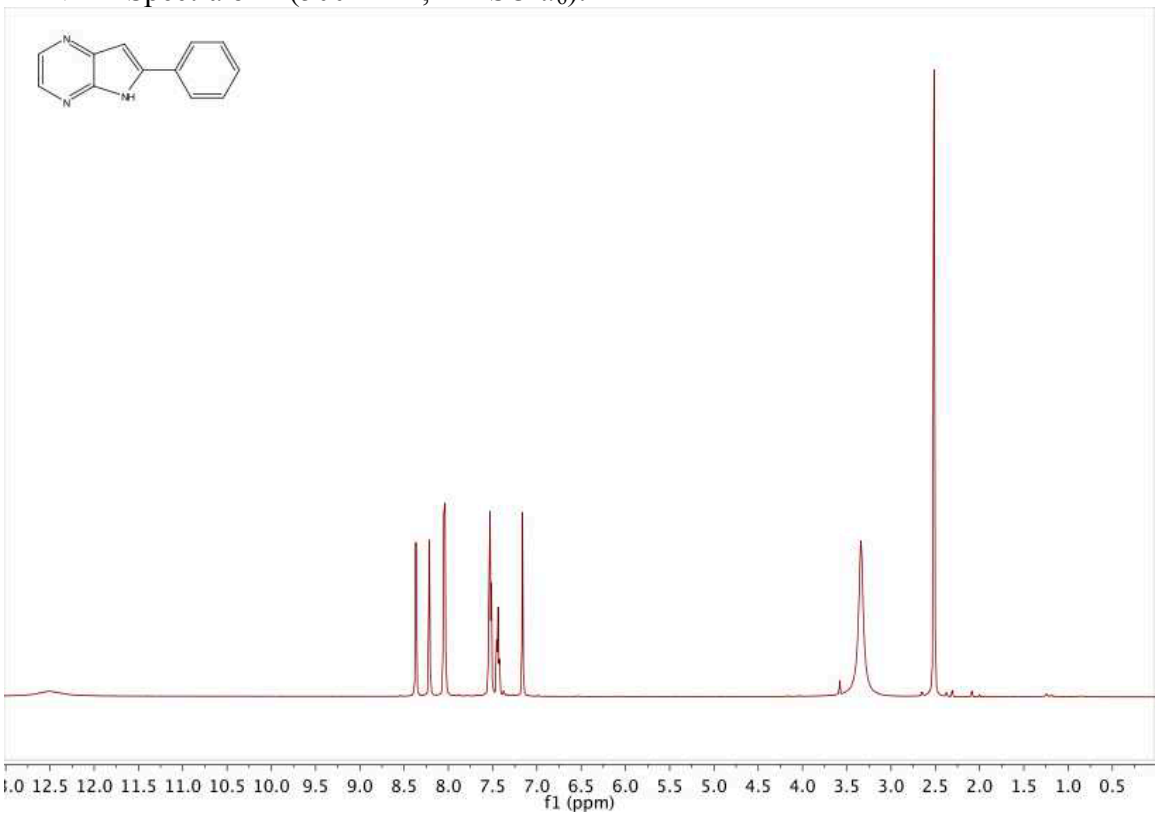
^{1}H NMR Spectra of **6** (500 MHz, DMSO-d_6):



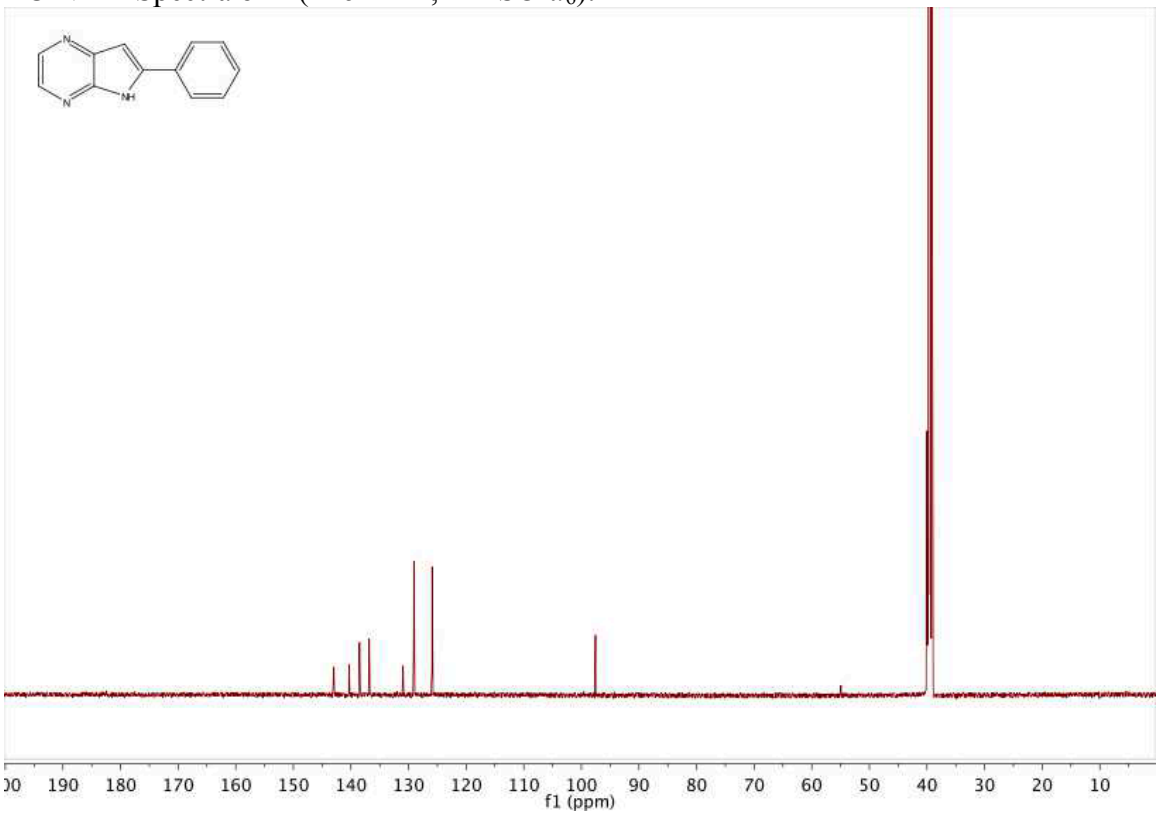
^{13}C NMR Spectra of **6** (126 MHz, DMSO-d_6):



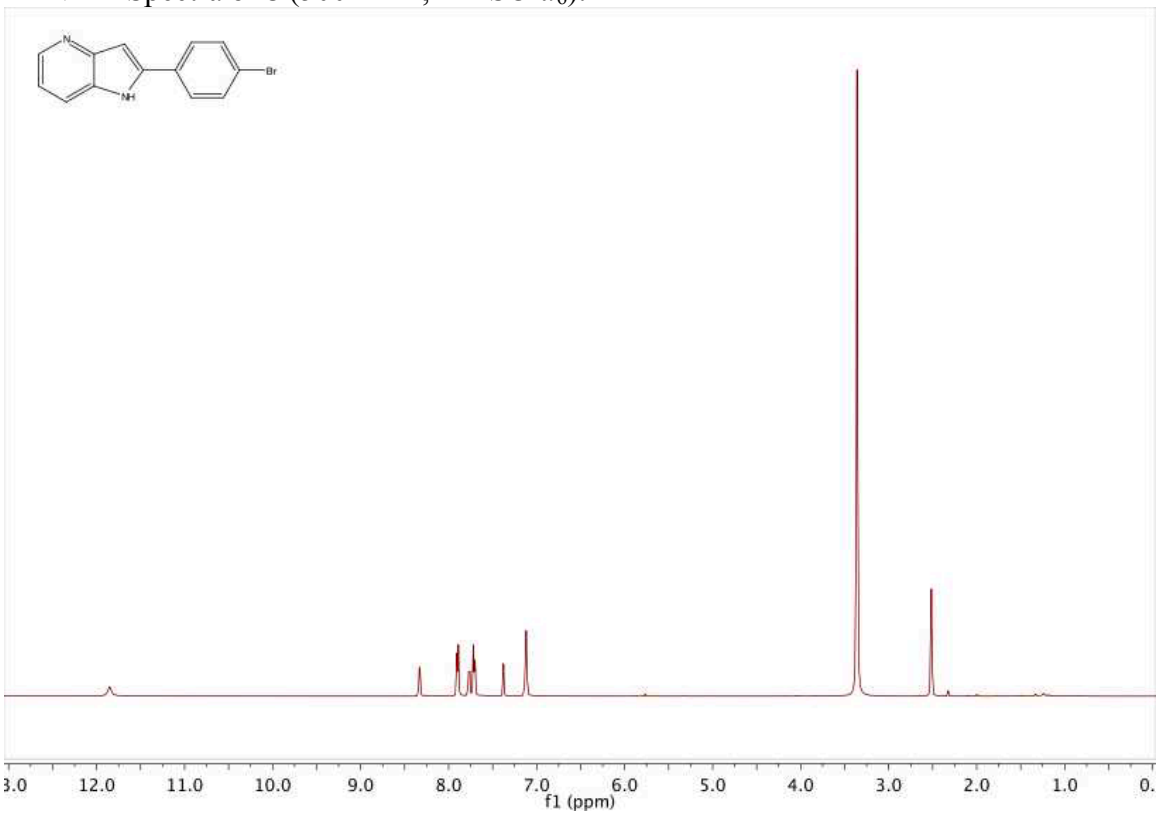
^{1}H NMR Spectra of **7** (500 MHz, DMSO-d_6):



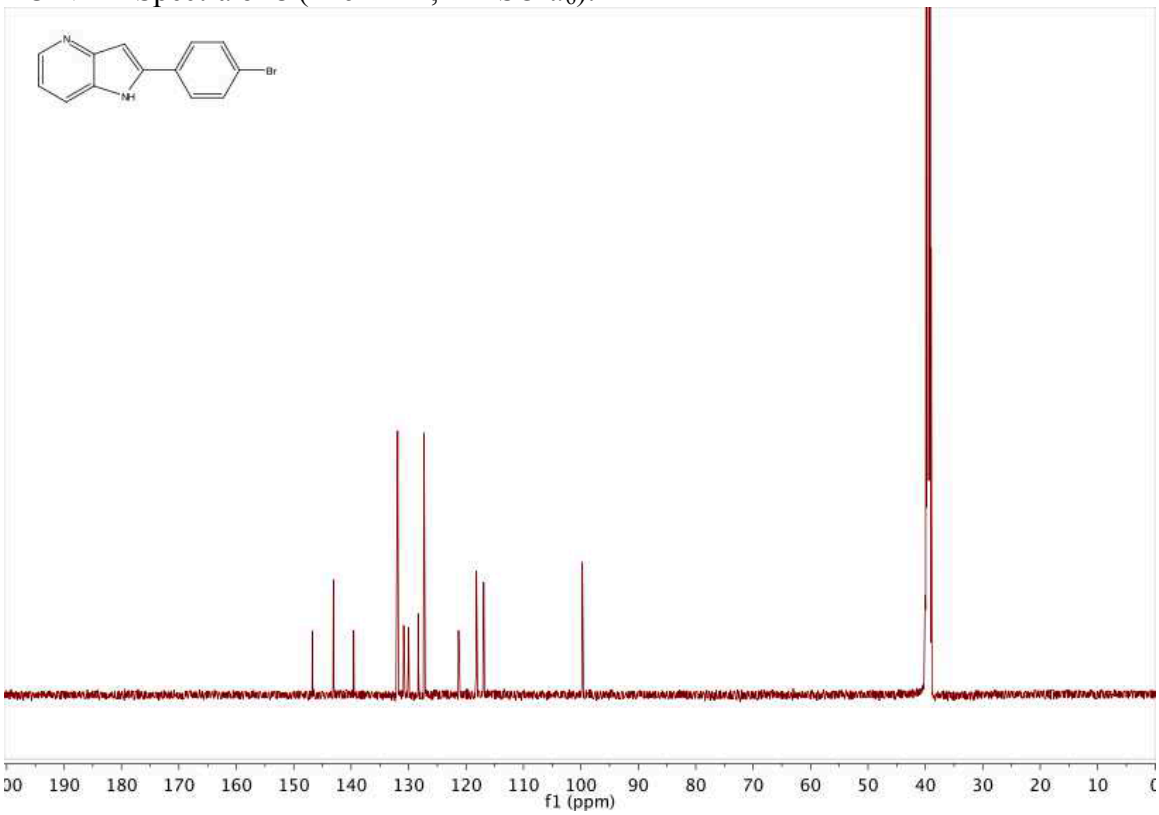
^{13}C NMR Spectra of **7** (126 MHz, DMSO-d_6):



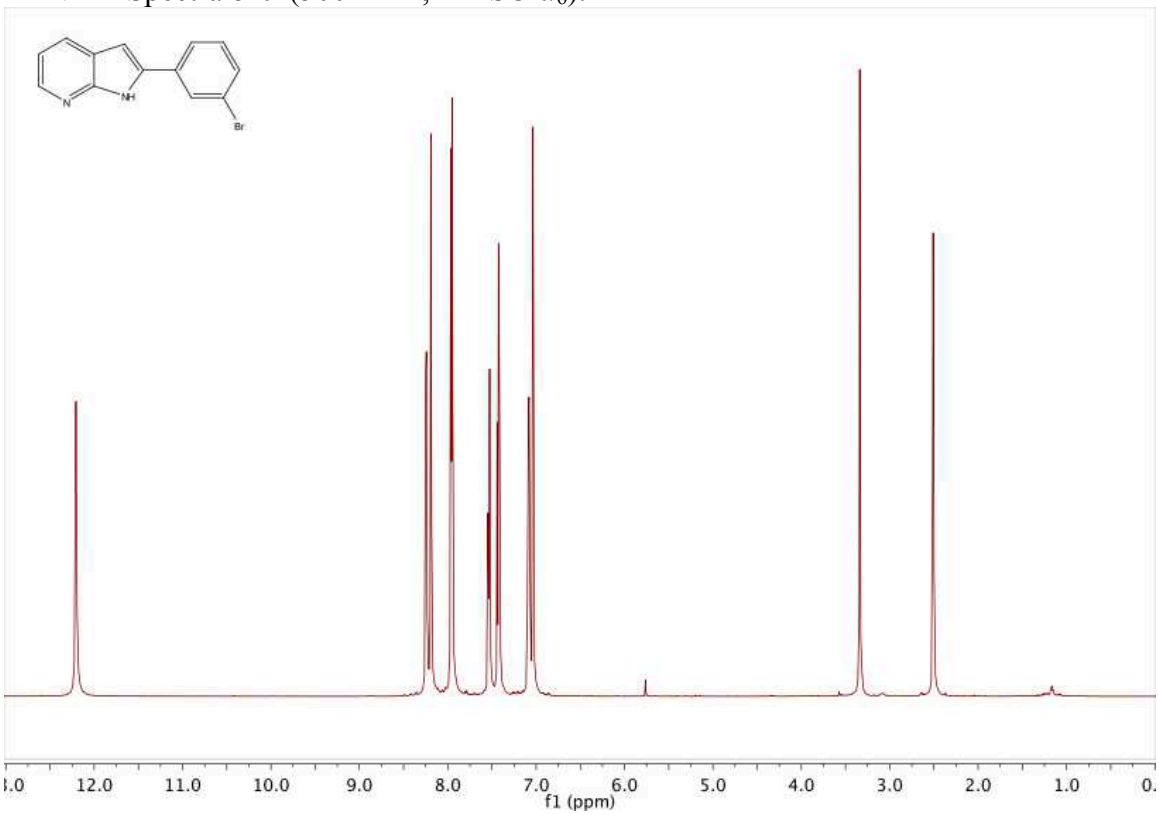
^{1}H NMR Spectra of **8** (500 MHz, DMSO-d_6):



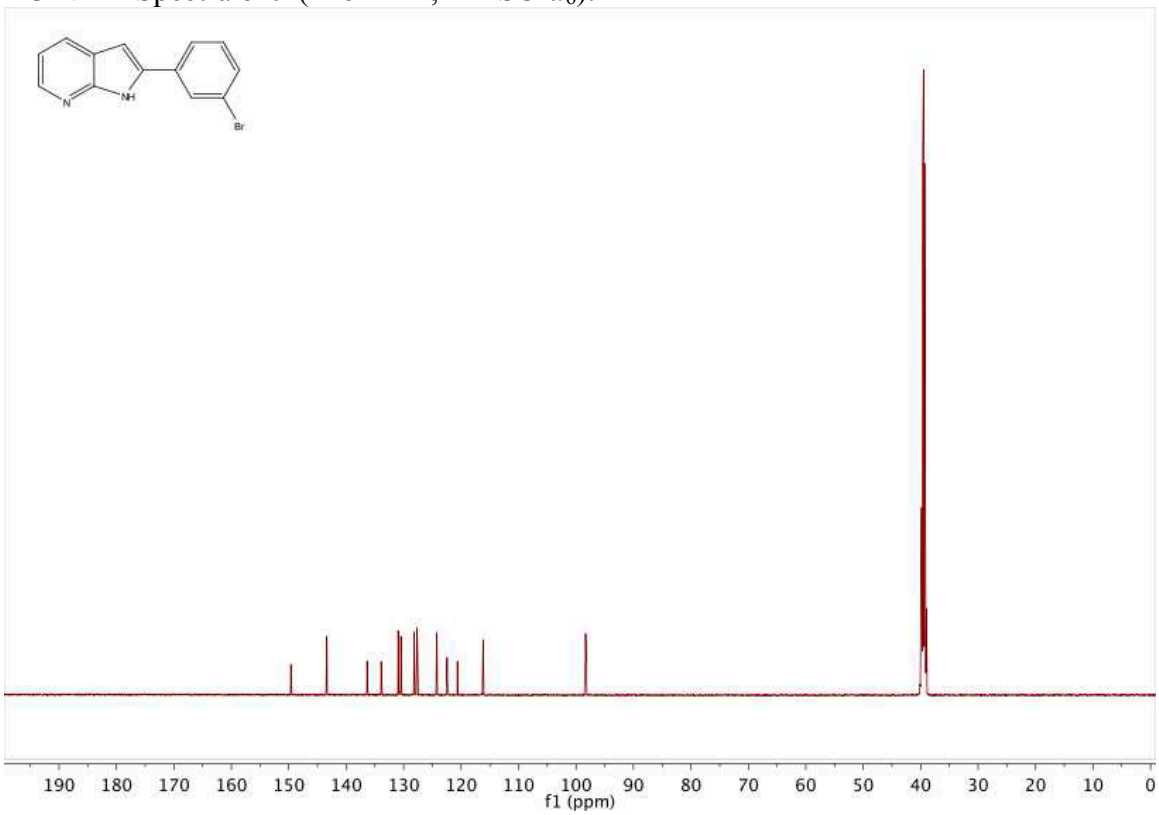
^{13}C NMR Spectra of **8** (126 MHz, DMSO-d_6):



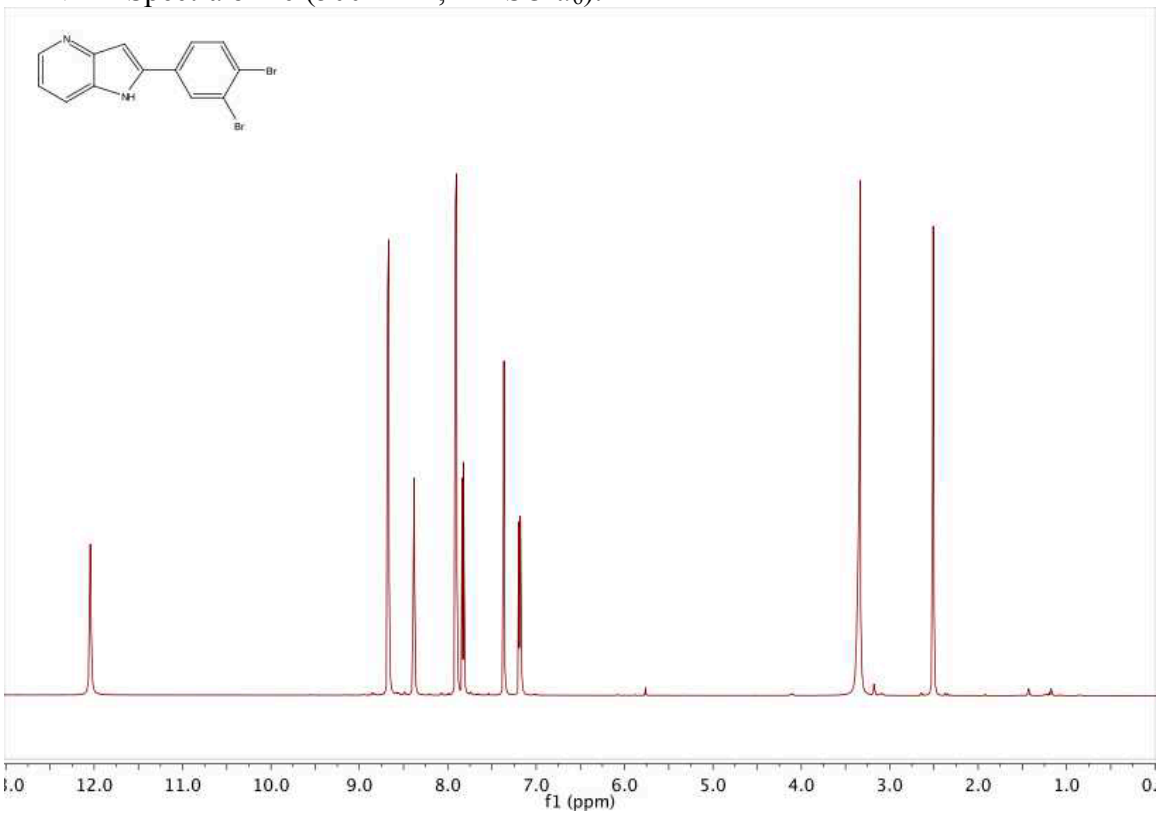
^{1}H NMR Spectra of **9** (500 MHz, DMSO-d_6):



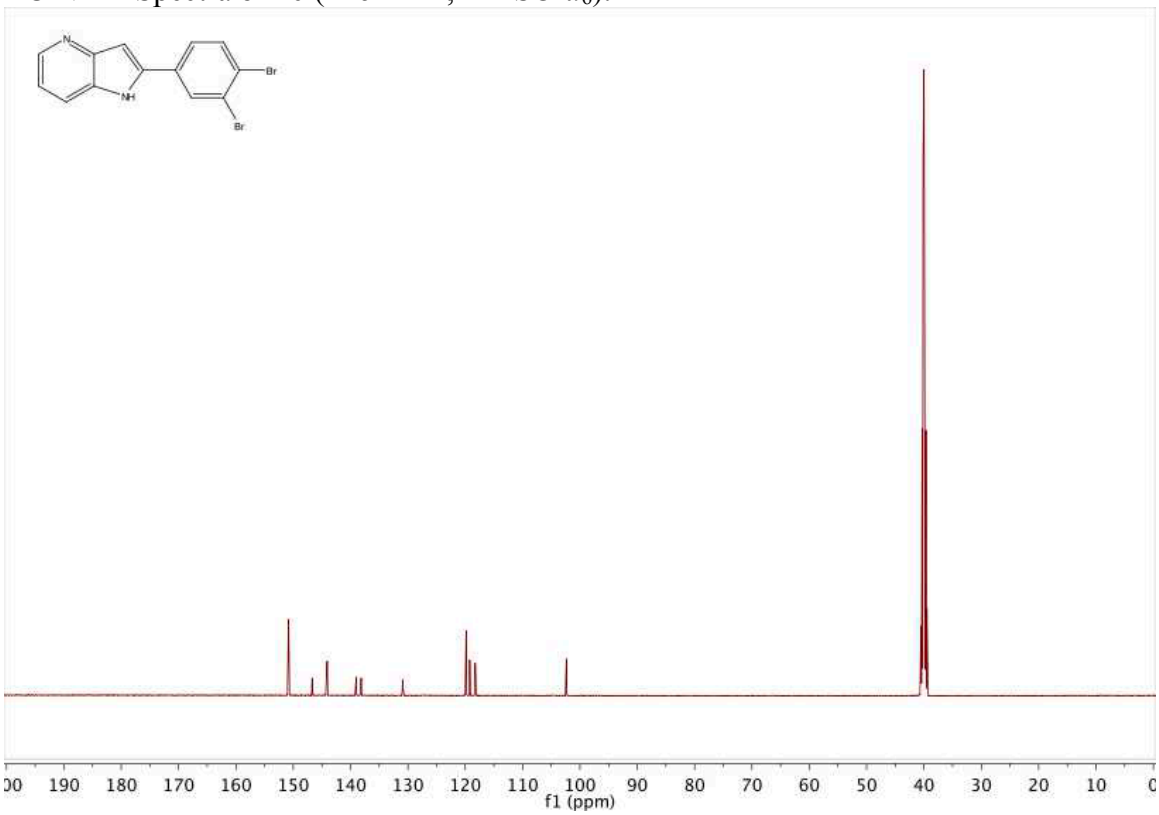
^{13}C NMR Spectra of **9** (126 MHz, DMSO-d_6):



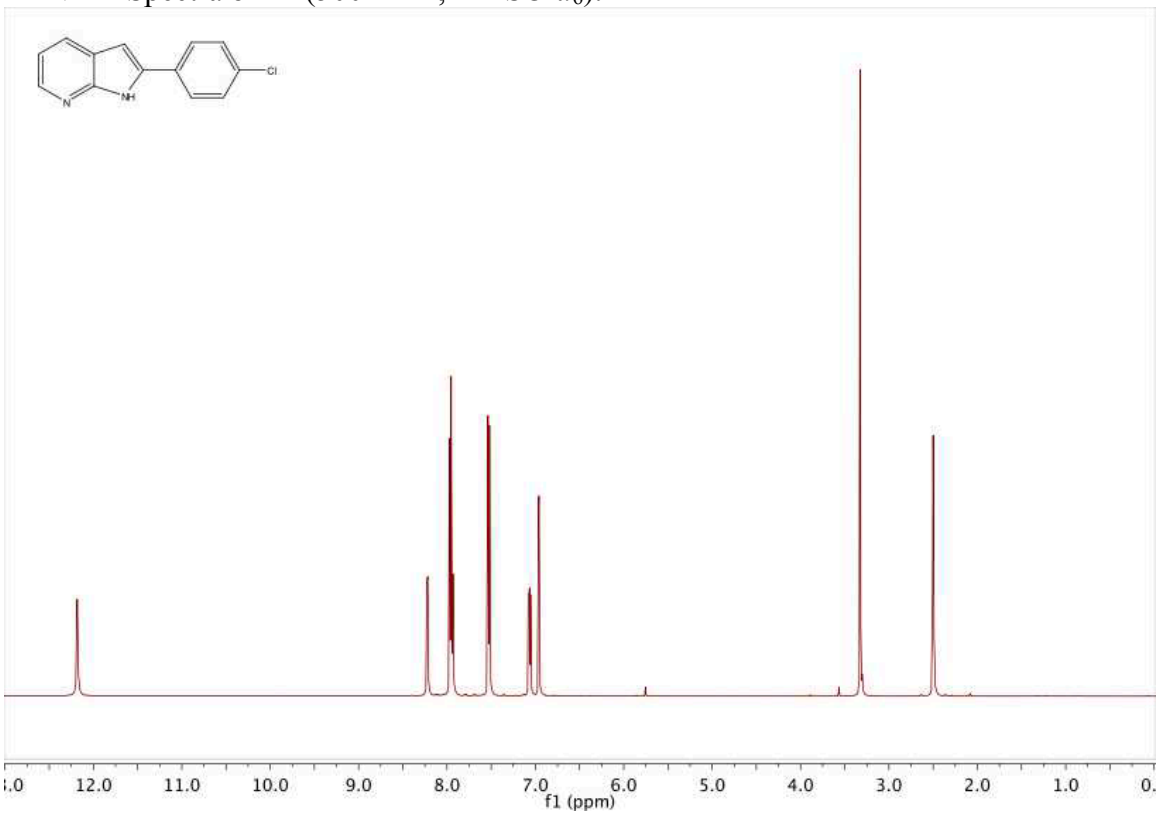
^{1}H NMR Spectra of **10** (500 MHz, DMSO-d_6):



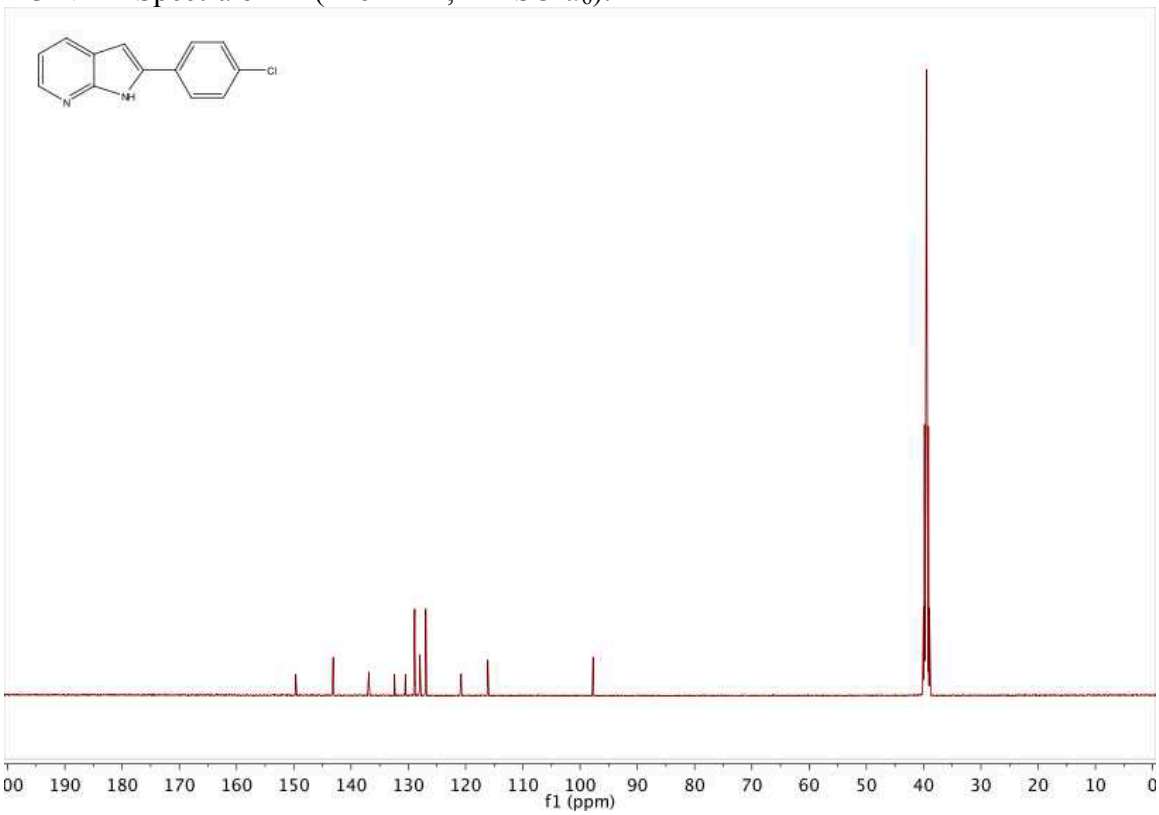
^{13}C NMR Spectra of **10** (126 MHz, DMSO-d_6):



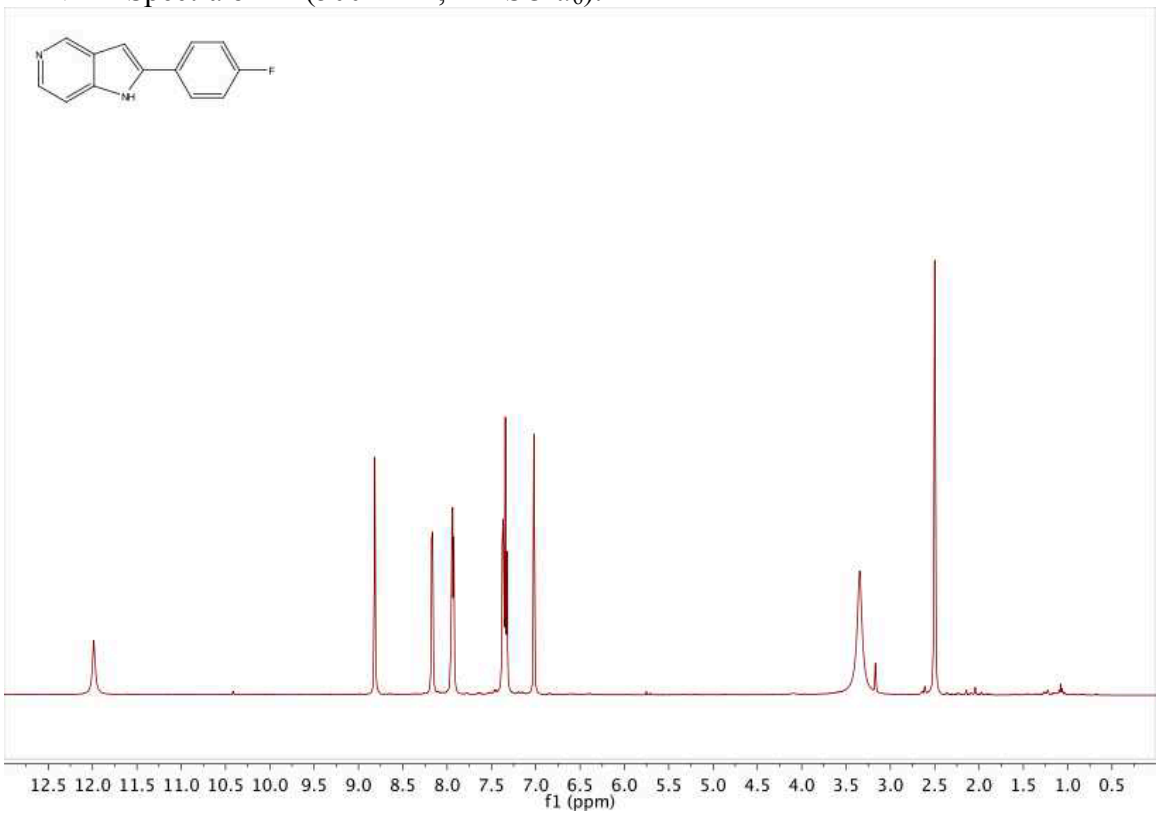
^{1}H NMR Spectra of **11** (500 MHz, DMSO-d_6):



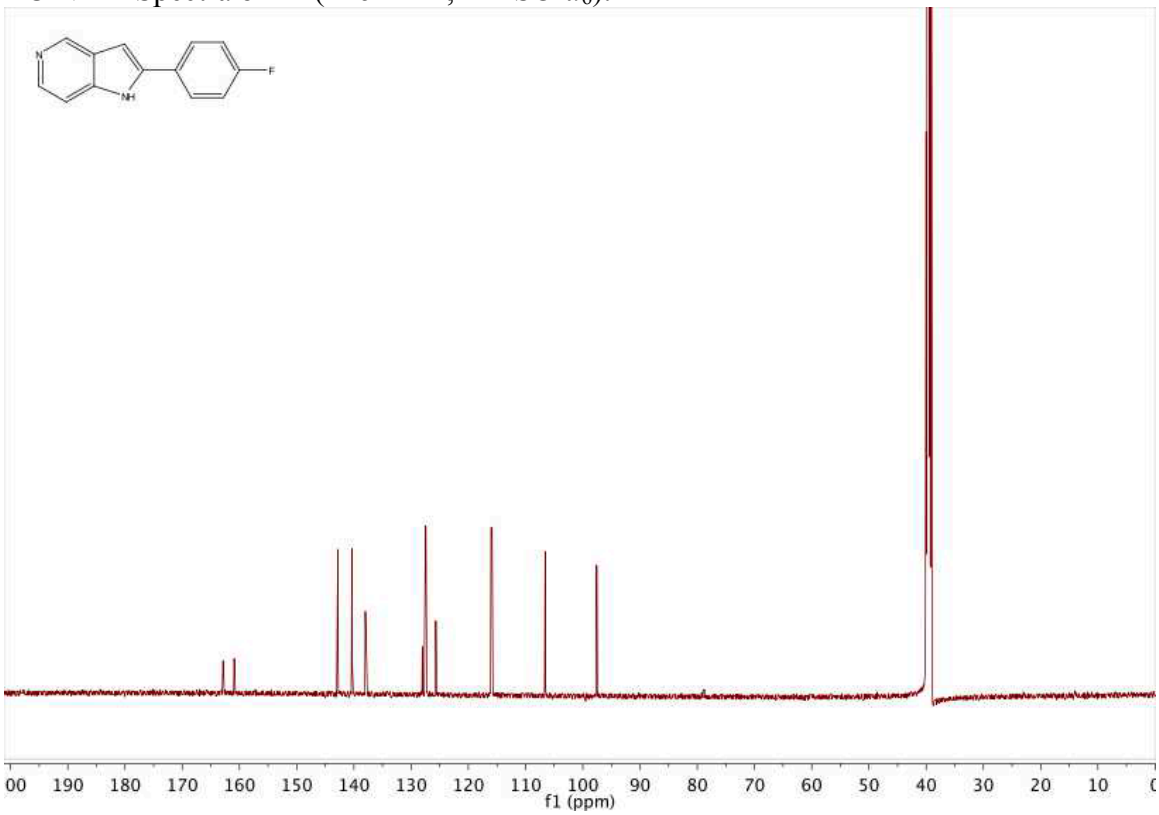
^{13}C NMR Spectra of **11** (126 MHz, DMSO-d_6):



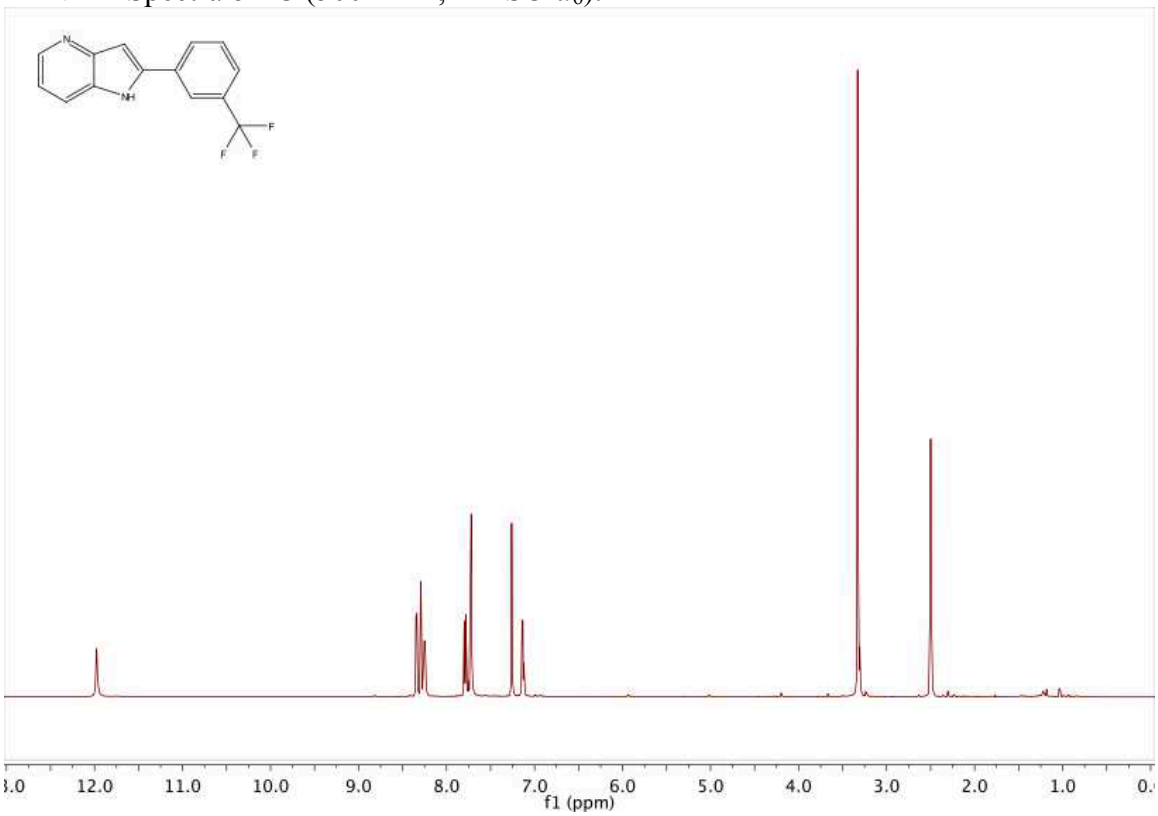
^{1}H NMR Spectra of **12** (500 MHz, DMSO-d_6):



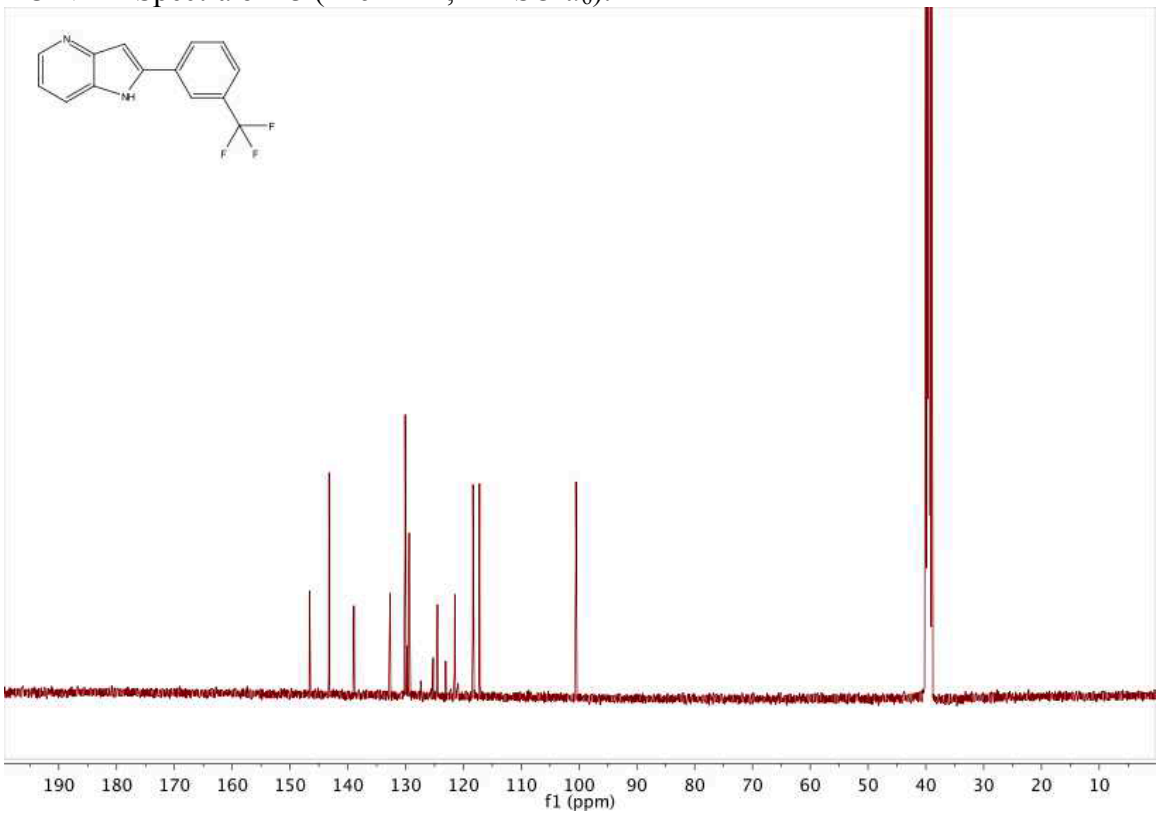
^{13}C NMR Spectra of **12** (126 MHz, DMSO-d_6):



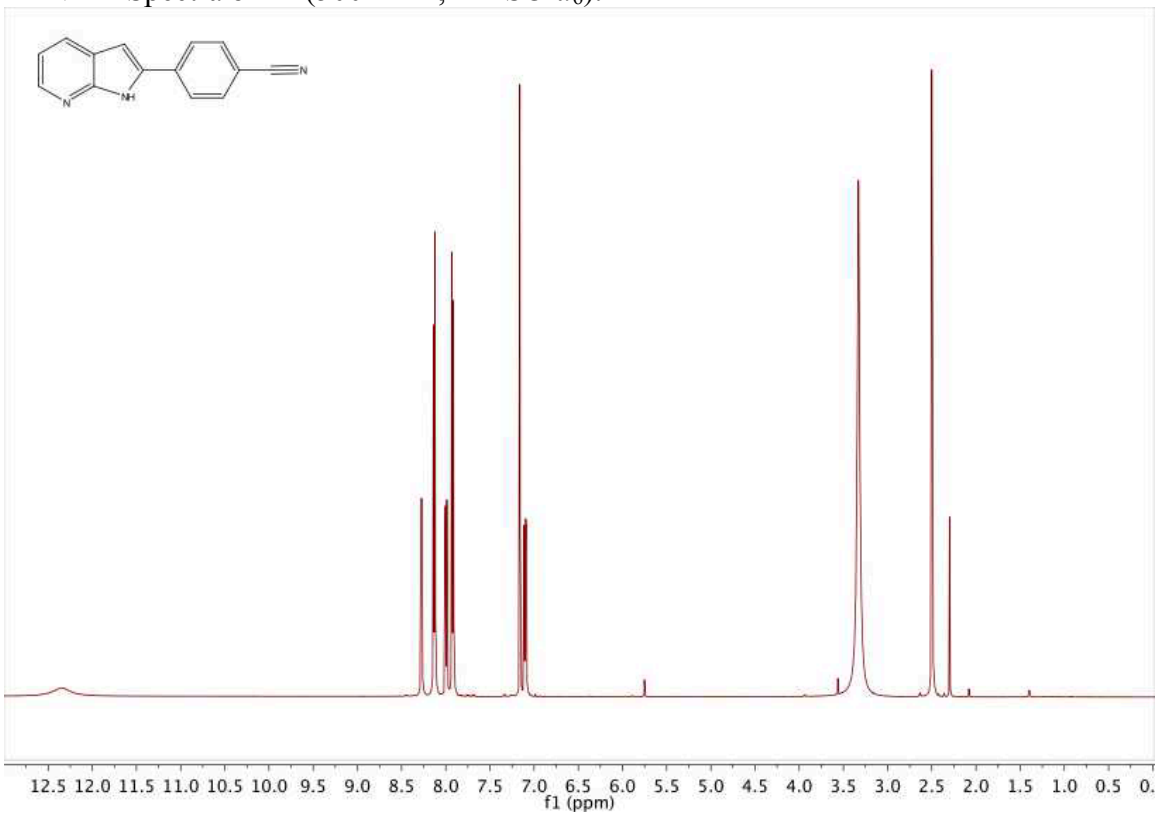
^{1}H NMR Spectra of **13** (500 MHz, DMSO-d_6):



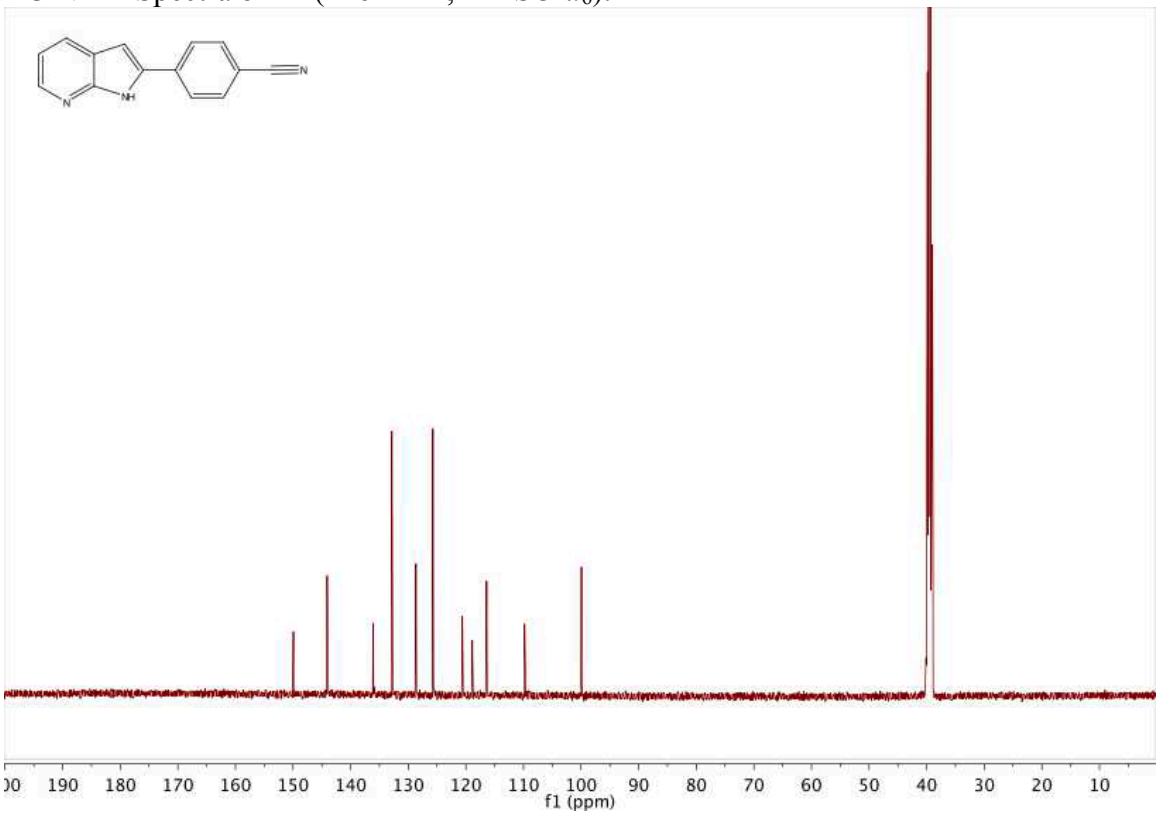
^{13}C NMR Spectra of **13** (126 MHz, DMSO-d_6):



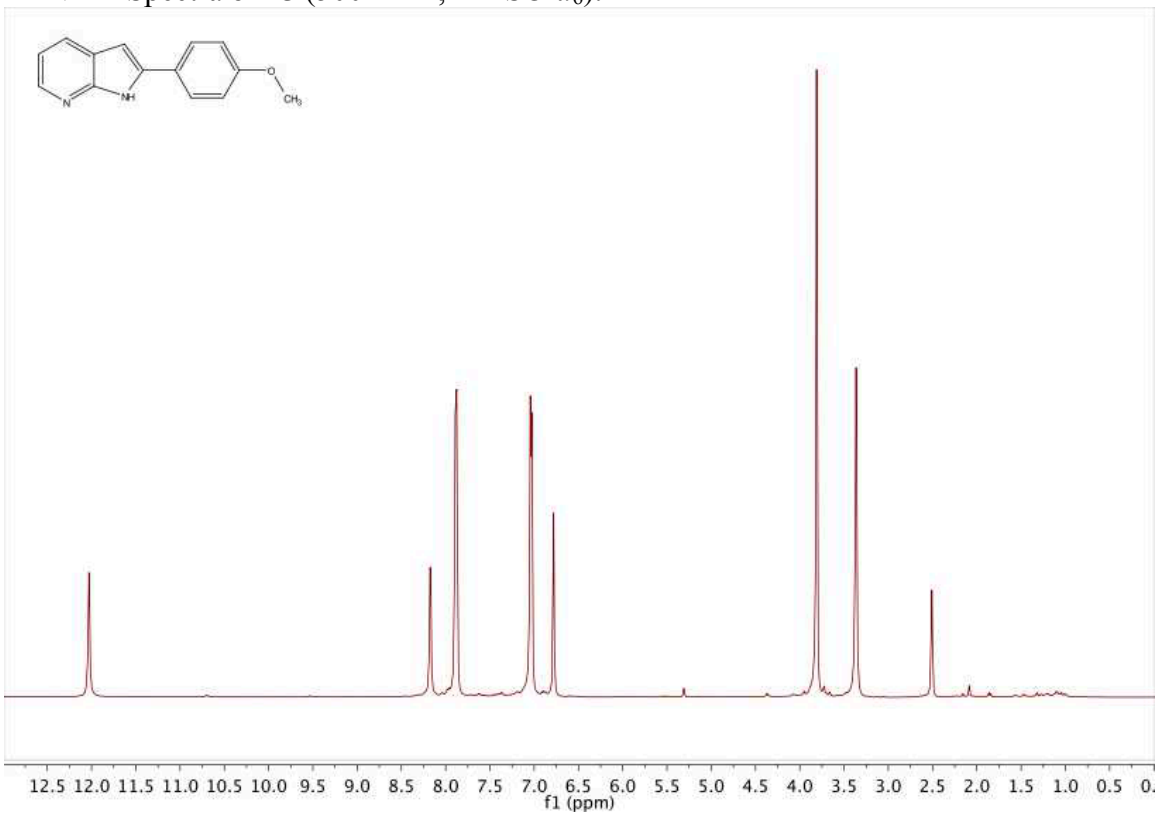
^{1}H NMR Spectra of **14** (500 MHz, DMSO-d_6):



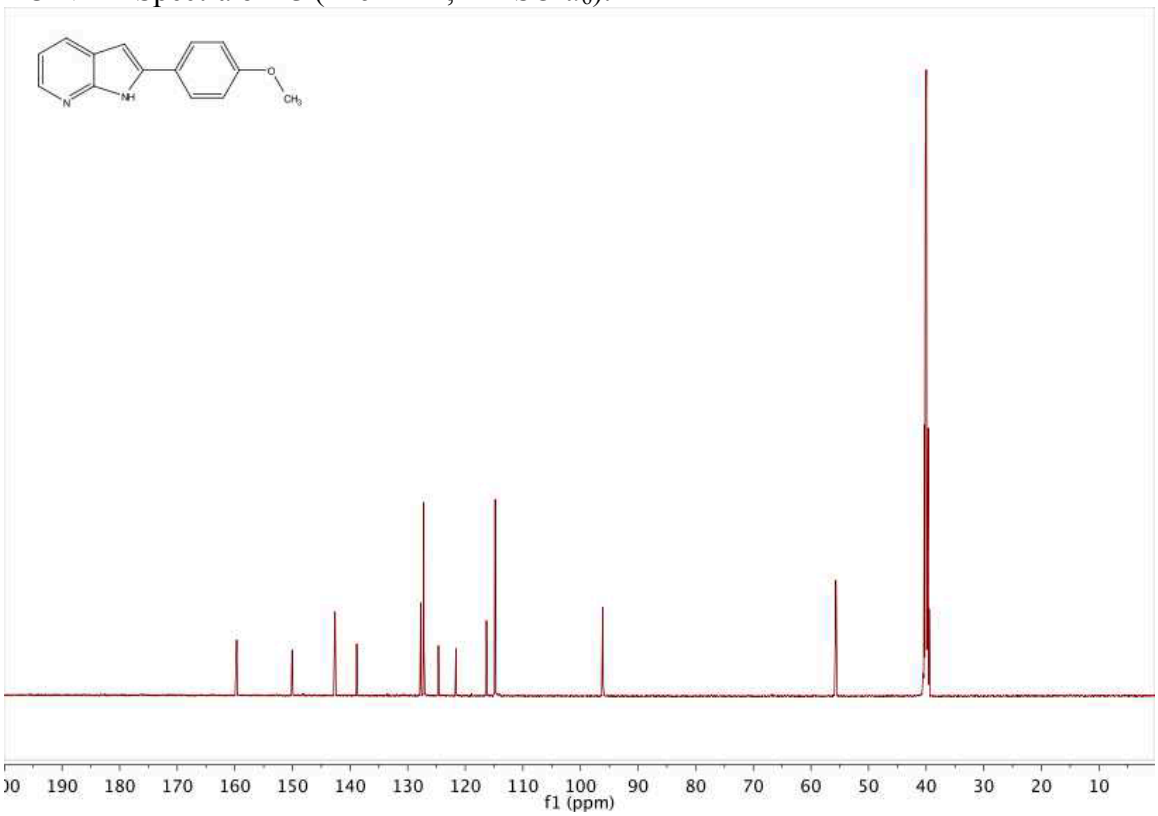
^{13}C NMR Spectra of **14** (126 MHz, DMSO-d_6):



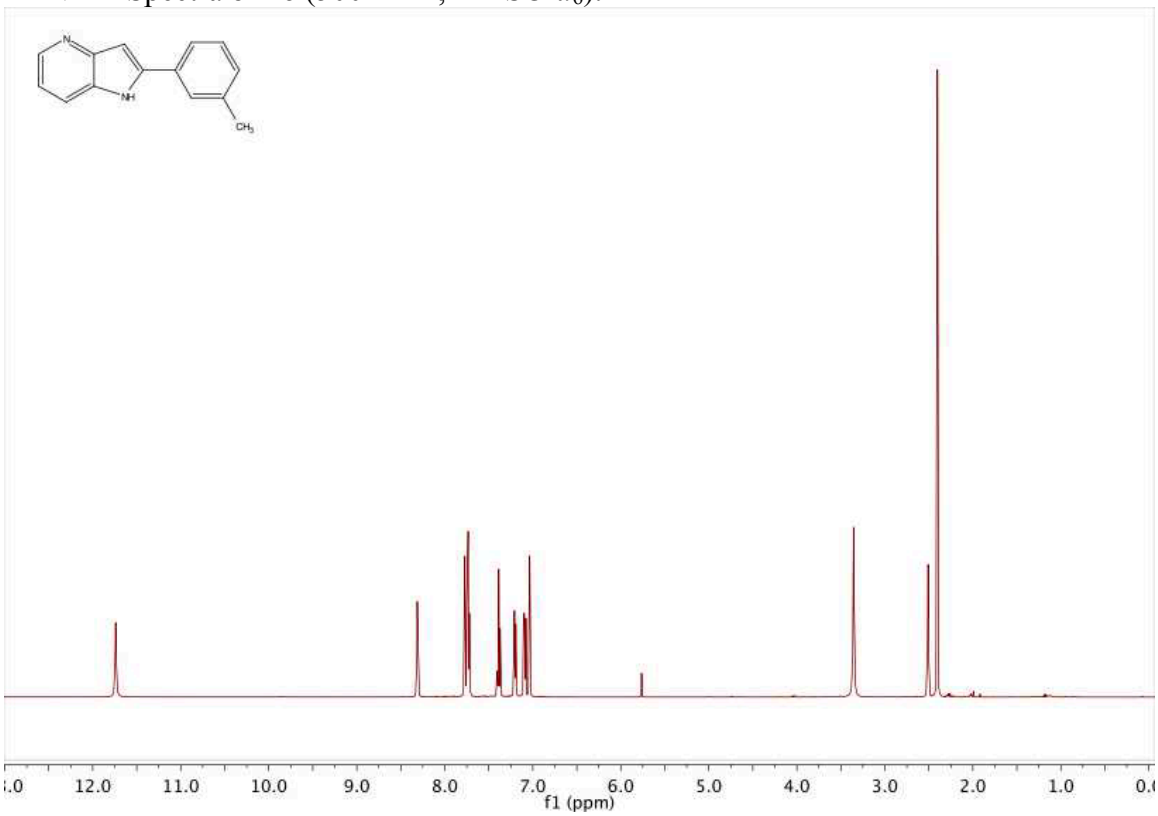
^{1}H NMR Spectra of **15** (500 MHz, DMSO-d_6):



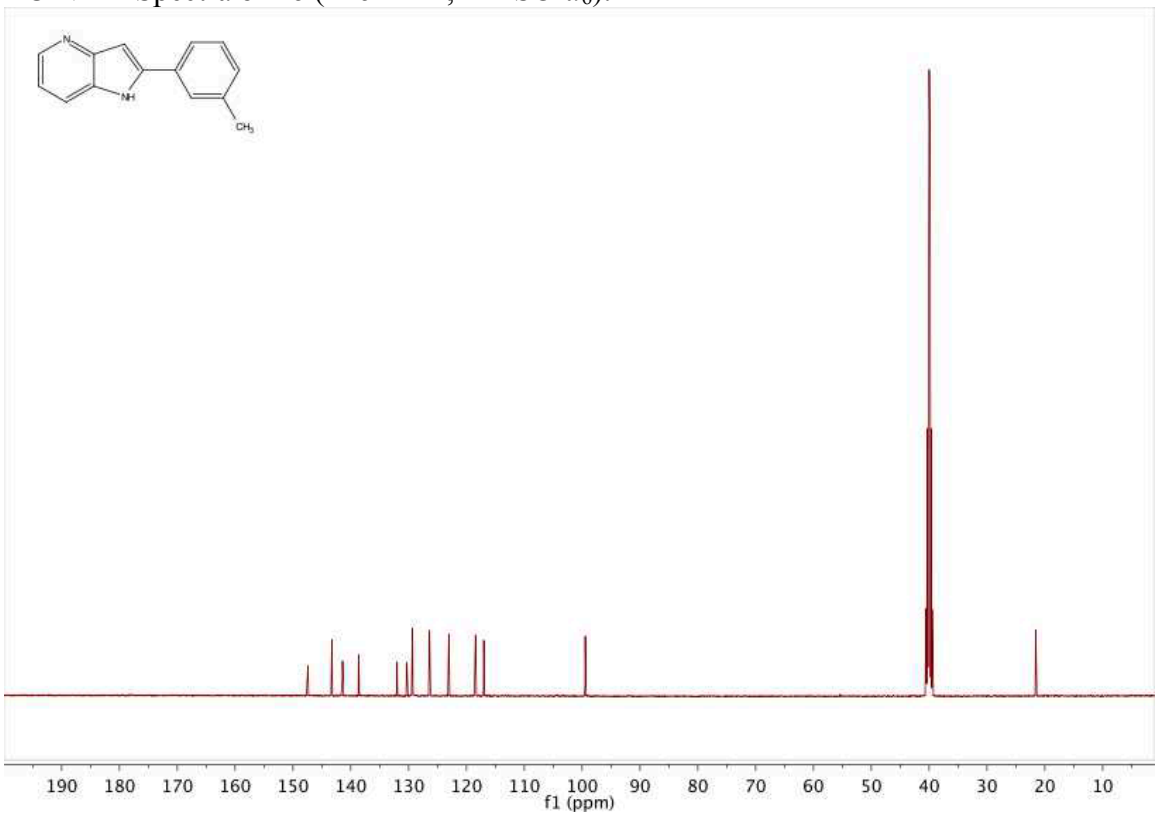
^{13}C NMR Spectra of **15** (126 MHz, DMSO-d_6):



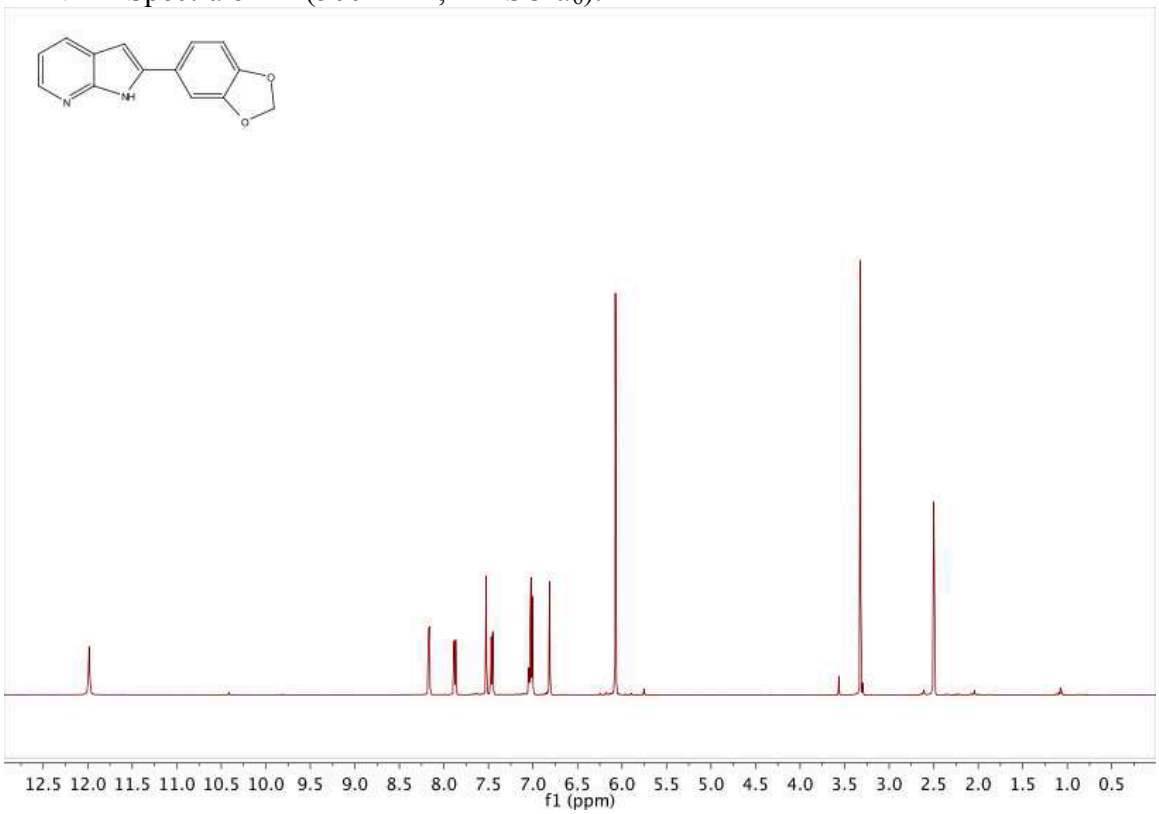
^{1}H NMR Spectra of **16** (500 MHz, DMSO-d_6):



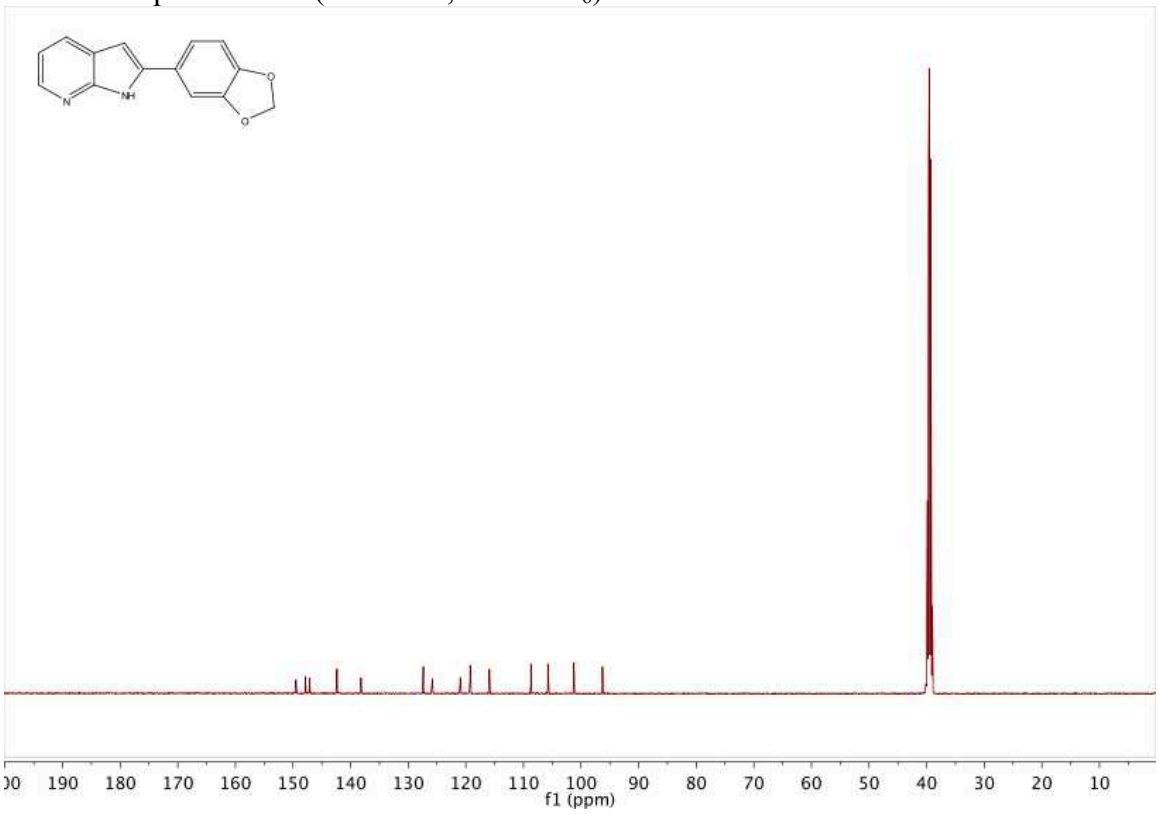
^{13}C NMR Spectra of **16** (126 MHz, DMSO-d_6):



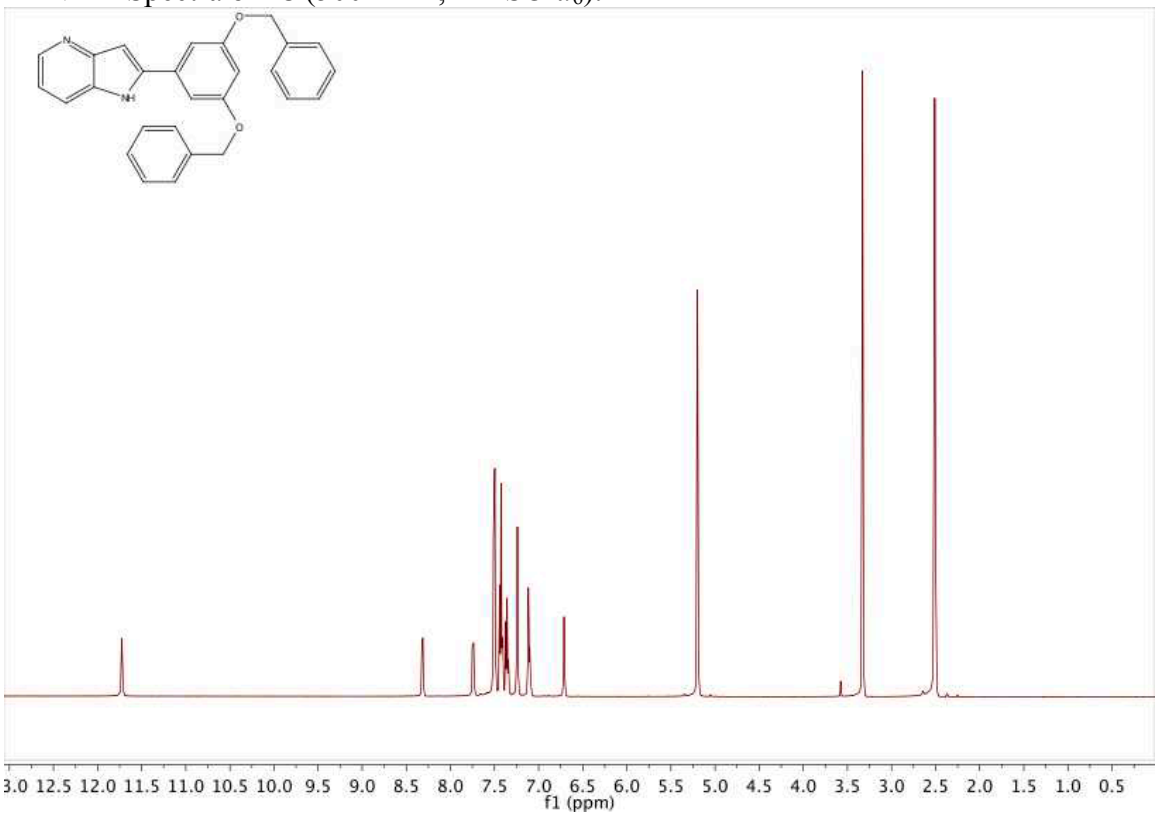
^{1}H NMR Spectra of **17** (500 MHz, DMSO-d_6):



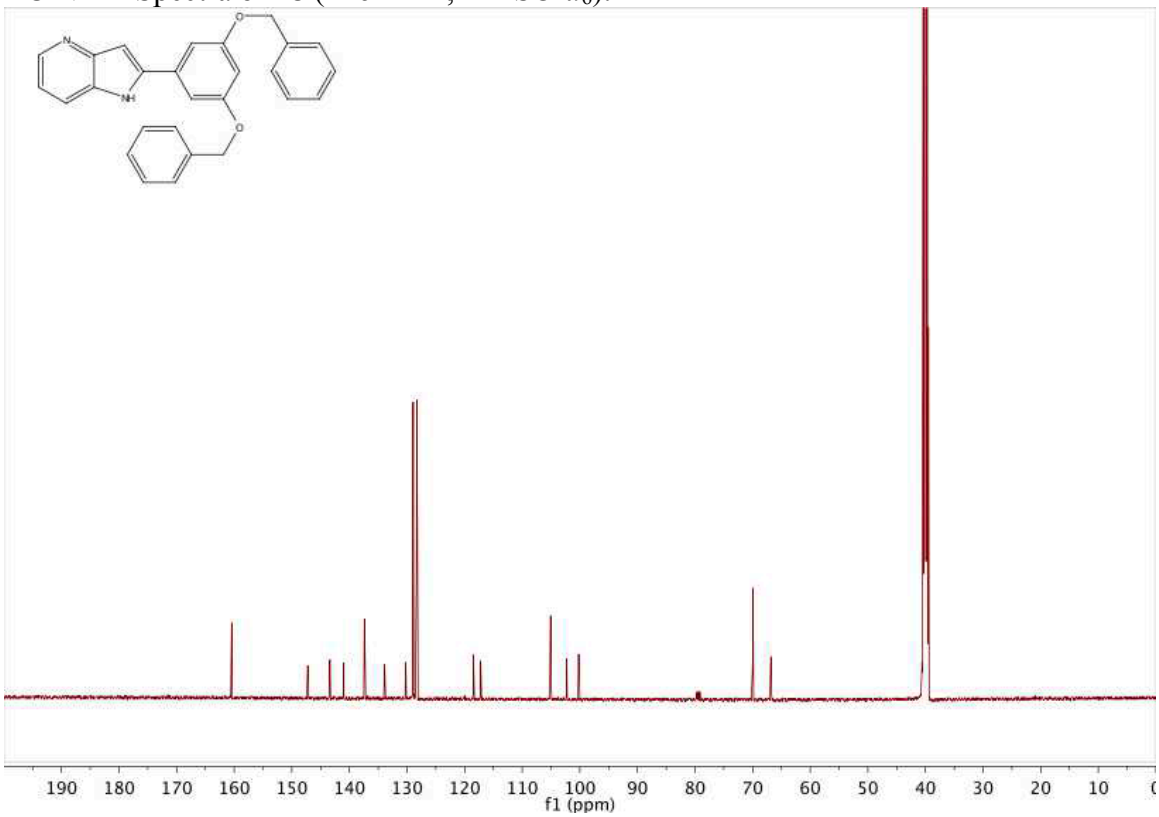
^{13}C NMR Spectra of **17** (126 MHz, DMSO-d_6):



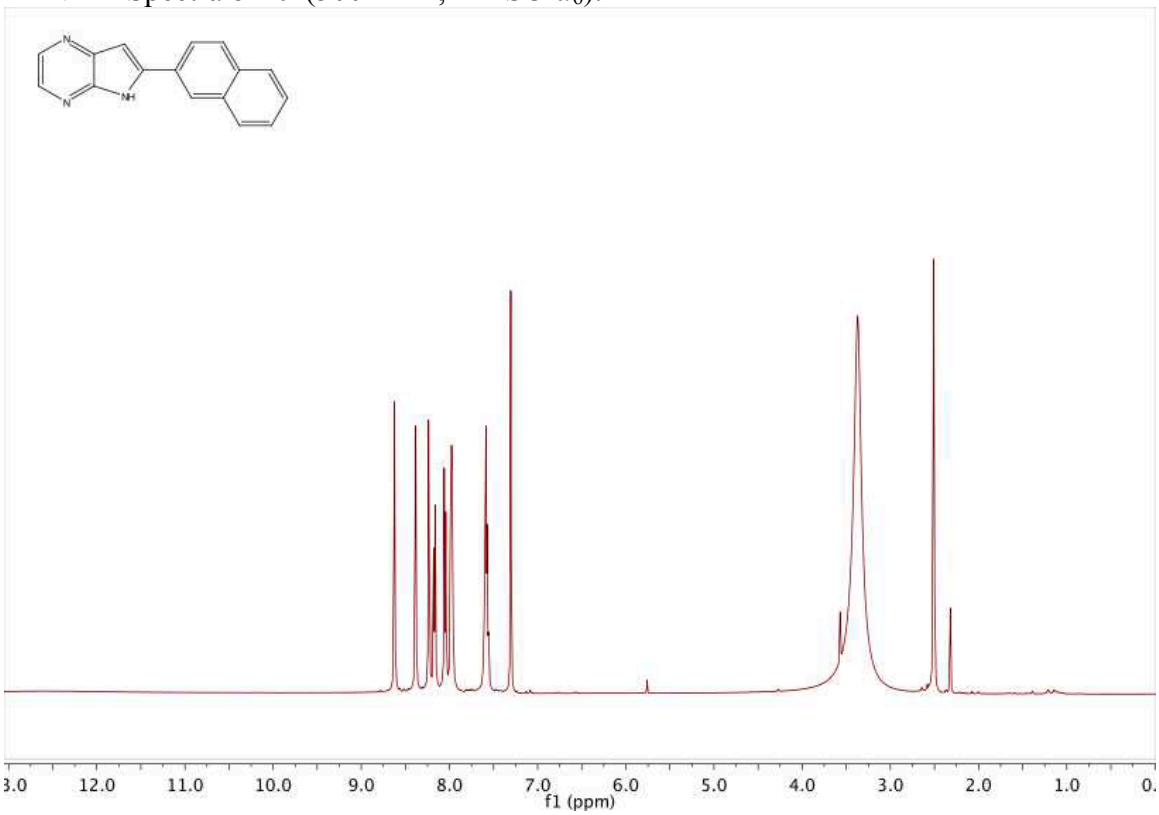
^{1}H NMR Spectra of **18** (500 MHz, DMSO-d_6):



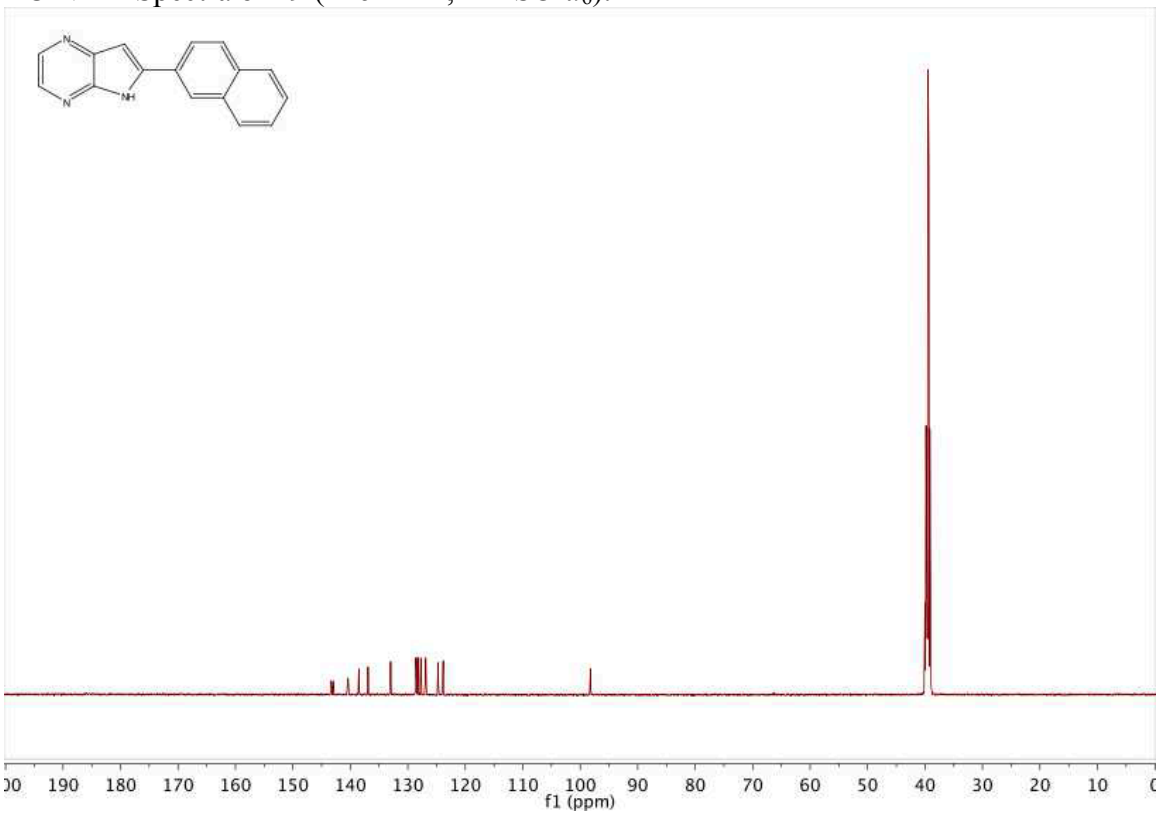
^{13}C NMR Spectra of **18** (126 MHz, DMSO-d_6):



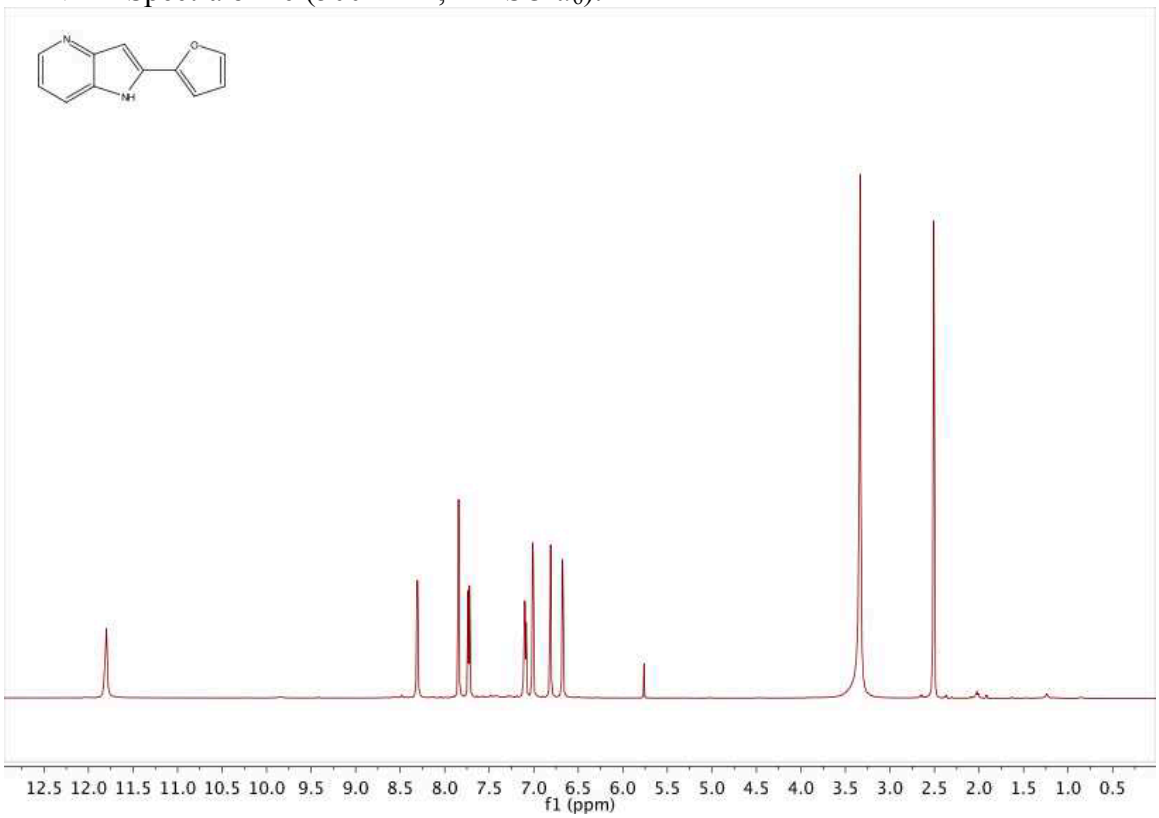
^{1}H NMR Spectra of **19** (500 MHz, DMSO-d_6):



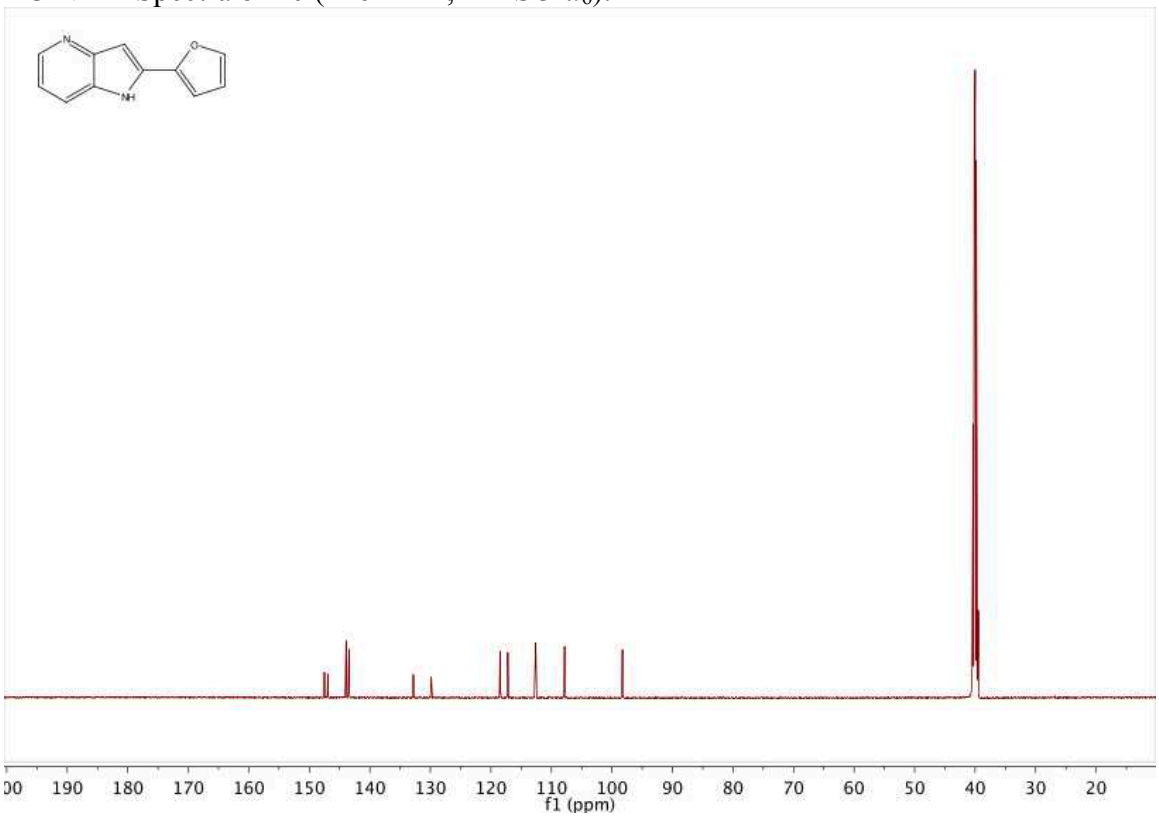
^{13}C NMR Spectra of **19** (126 MHz, DMSO-d_6):



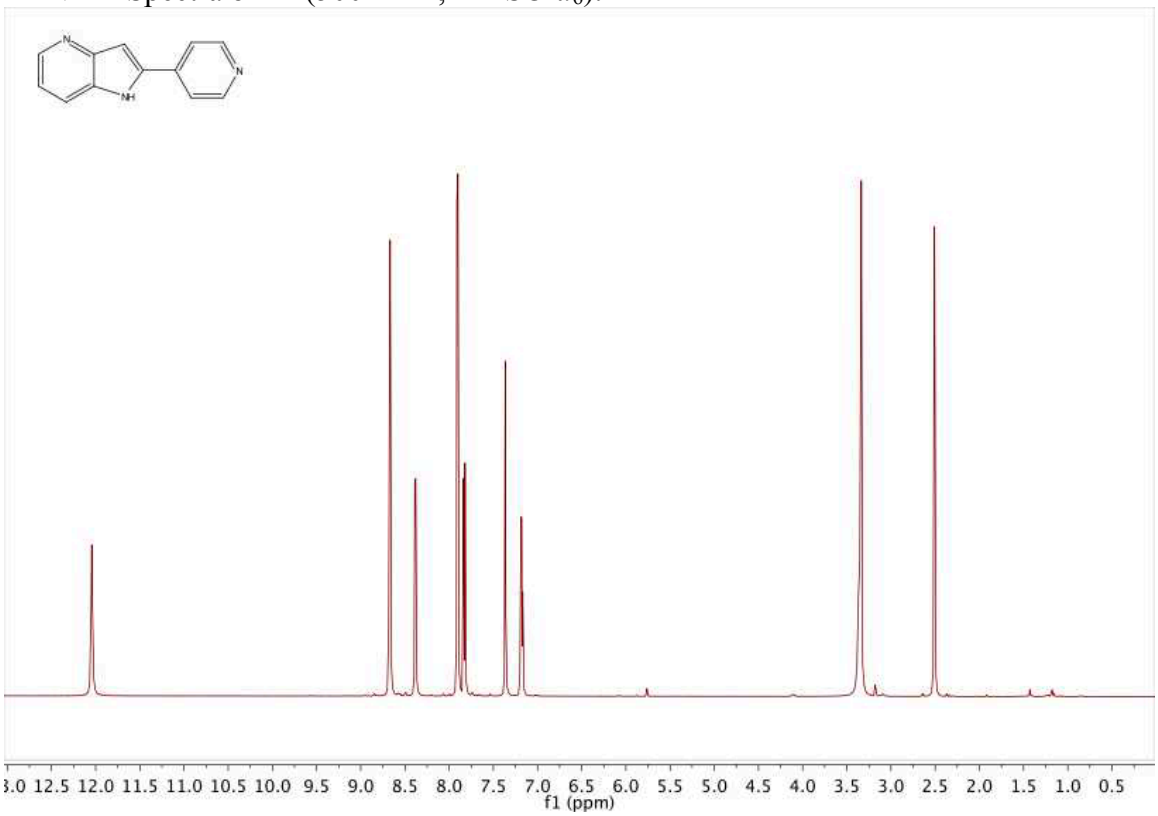
^{1}H NMR Spectra of **20** (500 MHz, DMSO-d_6):



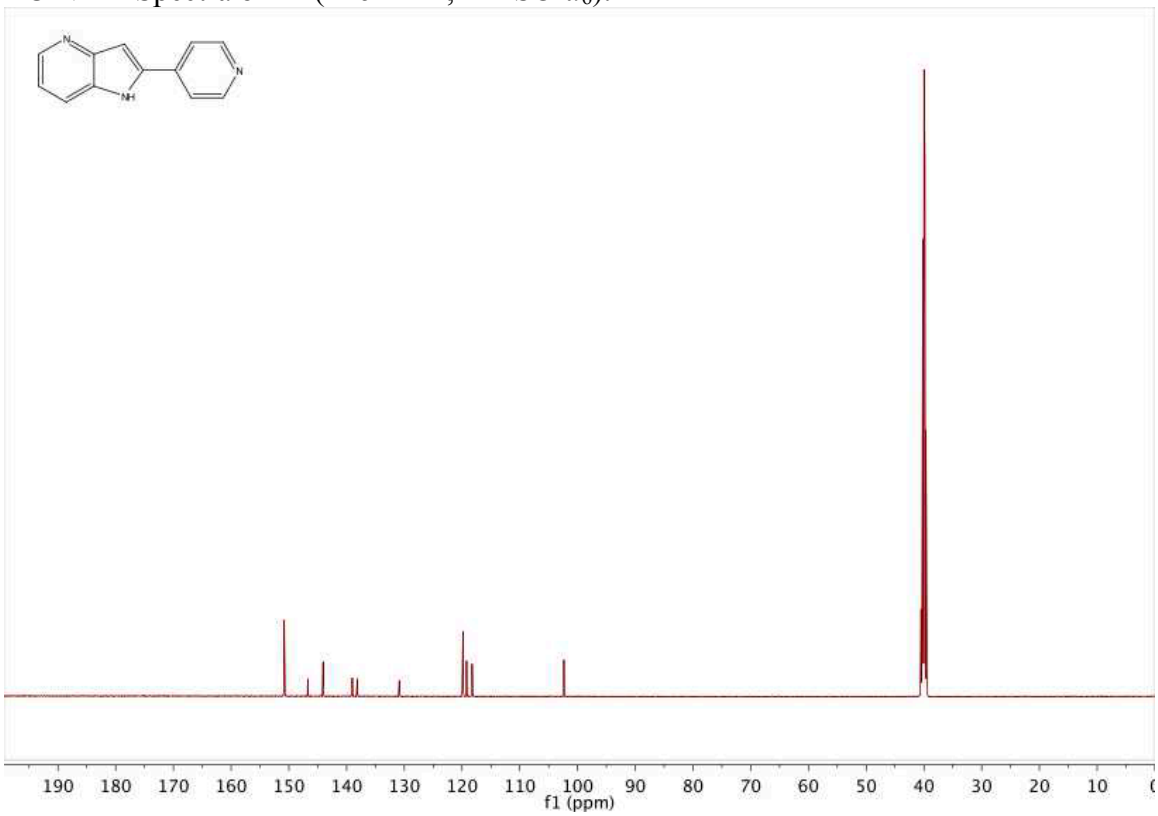
^{13}C NMR Spectra of **20** (126 MHz, DMSO-d_6):



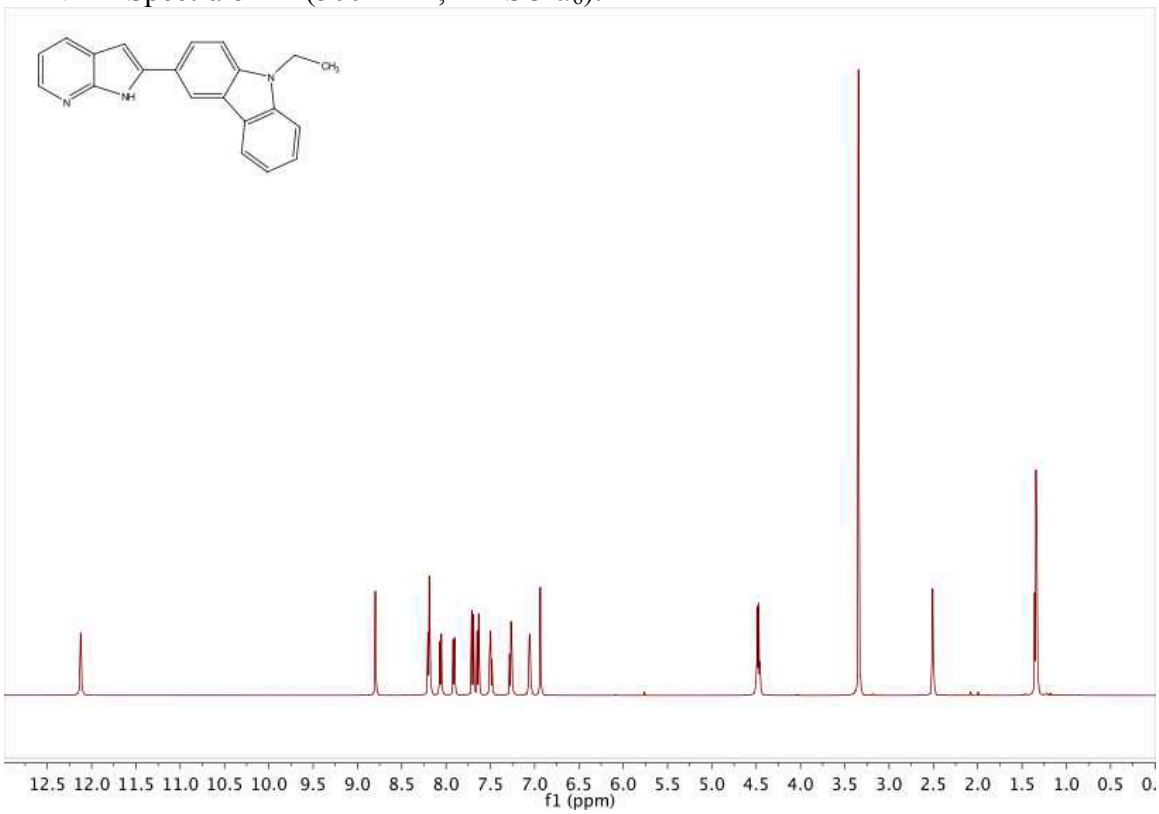
^{1}H NMR Spectra of **21** (500 MHz, DMSO-d_6):



^{13}C NMR Spectra of **21** (126 MHz, DMSO-d_6):



^{1}H NMR Spectra of **22** (500 MHz, DMSO-d_6):



^{13}C NMR Spectra of **22** (126 MHz, DMSO-d_6):