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Novel medium-sized di(het)areno-fused 1,4,7-(oxa)thiadiazecines as probes for aminergic receptors

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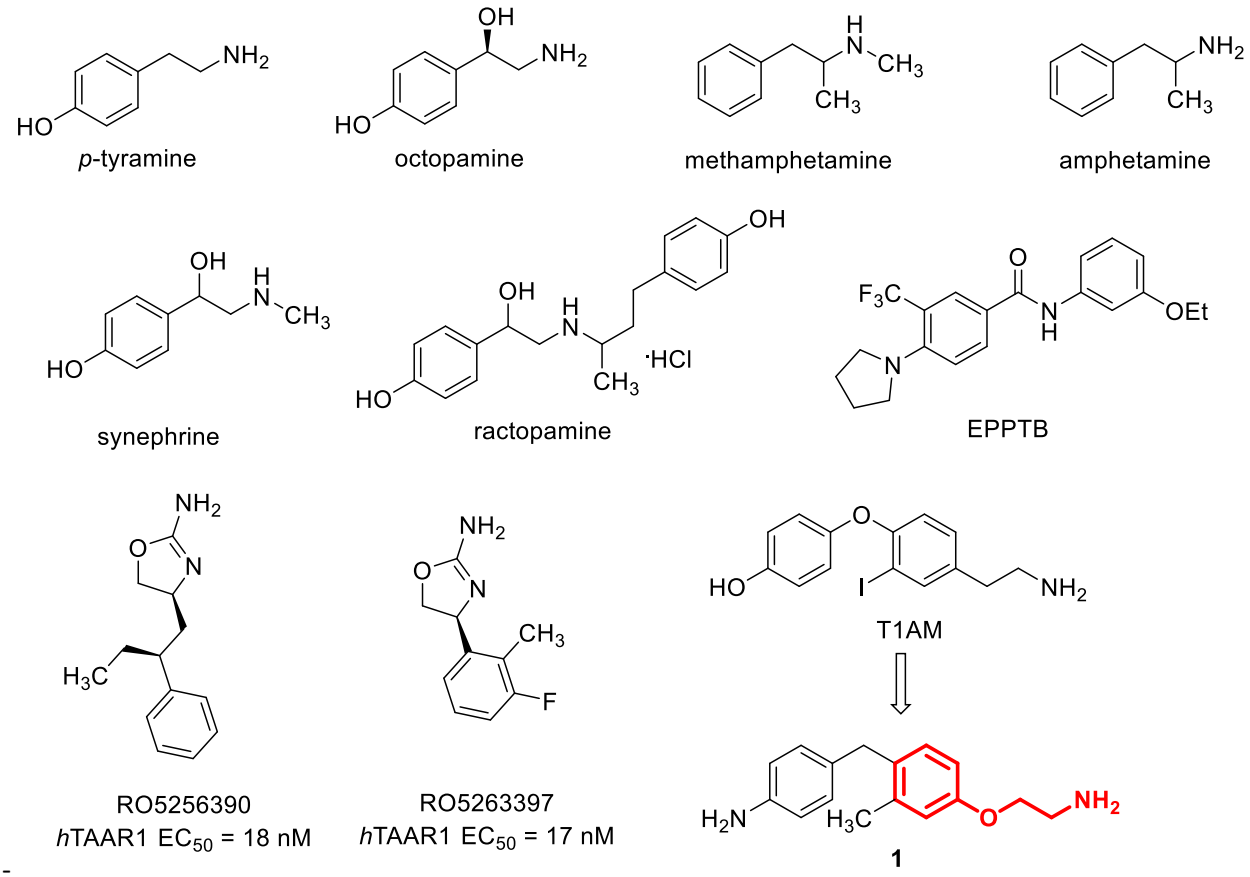


Figure S1. Known TAAR1 ligands.

Experimental part

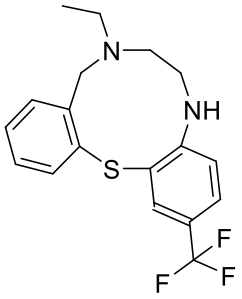
General considerations

All commercial reagents and solvents were used without further purification, unless otherwise noted. THF for the synthesis was distilled over Na and stored under nitrogen over freshly activated molecular sieves 4Å. NMR spectra were recorded on a Bruker Avance III 400 spectrometer (^{1}H: 400.13 MHz; ^{13}C: 100.61 MHz; chemical shifts are reported as parts per million (δ, ppm)); the residual solvent peaks were used as internal standards: 7.28 and 2.50 ppm for 1H in $CDCl_3$ and DMSO-d_6 respectively, 40.01 and 77.02 ppm for ^{13}C in DMSO-d_6 and $CDCl_3$ respectively. Mass spectra were recorded on a Bruker Maxis HRMS-ESI-qT spectrometer (ESI ionization). Melting points were determined in open capillary tubes on Stuart SMP30 Melting Point Apparatus. Analytical thin-layer chromatography was carried out on Silufol UV-254 silica gel plates using an appropriate mixtures of ethyl acetate and hexane. Compounds were visualized with short-wavelength UV light. Column chromatography was performed on silica gel 60 (230-400 mesh).

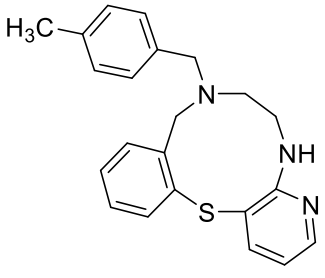
General procedure for preparation of compounds 3a-i (GP1).

The solution of lactam **2** (0.060 mmol) in THF (1 ml) was added dropwise to a solution of $LiAlH_4$ (14 mg, 0.36 mmol) and $AlCl_3$ (24 mg, 0.18 mmol) in diethyl ether (1 ml) at 0 °C. The resulting mixture was stirred for 24 h at room temperature. The reaction mixture was quenched with cold water (2 ml). The aqueous phase was extracted with CH_2Cl_2, the organic phase was washed with water (4×5 ml), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using an appropriate gradient of ethyl acetate in hexanes (2:5) as eluent.

8-Ethyl-2-trifluoromethyl-6,7,8,9-tetrahydro-5*H*-dibenzo[*b,i*][1,4,7]thiadiazecine (3a): The title compound was synthesized from 8-ethyl-2-trifluoromethyl-5,6,7,8-tetrahydro-9*H*-dibenzo[*b,i*][1,4,7]thiadiazecin-9-one (22 mg, 0.060 mmol) according to GP1. Yield 9 mg (44%), colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 1.6 Hz, 1H, Ar), 7.59 (dd, J = 7.8, 1.6 Hz, 1H, Ar), 7.45 (dd, J = 8.5, 2.3 Hz, 1H, Ar), 7.35 – 7.22 (m, 2H, Ar), 7.02 (dd, J = 7.4, 1.8 Hz, 1H, Ar), 6.95 (t, J = 5.6 Hz, 1H, NH), 4.70 (s, 2H, CH_2), 4.31 – 4.26 (m, 2H, CH_2), 3.47 – 3.41 (m, 2H, CH_2), 3.09 – 3.01 (m, 2H, CH_2), 1.12 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.0, 138.4, 133.1, 131.6 (q, J = 3.9 Hz), 129.3, 128.7, 127.2, 126.9 (q, J = 3.6 Hz), 126.1, 124.3 (q, J = 270.3 Hz), 119.7, 117.8 (q, J = 32.4 Hz), 115.5, 42.2, 37.1, 35.5, 24.5, 11.7 ppm; HRMS (ESI), *m/z* calcd for $C_{18}H_{20}F_3N_2S$ $[M+H]^+$ 353.1294, found 353.1297.



8-(4-Methylbenzyl)-6,7,8,9-tetrahydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]thiadiazecine (3b): The title compound was synthesized from 8-(4-methylbenzyl)-5,6,7,8-tetrahydro-9*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]thiadiazecin-9-one (23 mg, 0.060 mmol) according to GP1. Yield 12 mg (58%), dark oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (dd, J = 5.0, 1.8 Hz, 1H, Py), 7.76 (dd, J = 7.3, 1.8 Hz, 1H, Py), 7.28 (s, 2H, Ar), 7.26 – 7.08 (m, 8H, Ar), 7.03 – 6.97 (m, 1H, Ar), 6.59 (dd, J = 7.3, 5.0 Hz, 1H, Py), 6.46 – 6.34 (br. s, 1H, NH), 4.81 (s, 2H, CH_2), 3.59 (s, 2H, CH_2), 3.48 (q, J = 5.4 Hz, 2H), 2.76 – 2.65 (m, 2H, CH_2), 2.37 (s, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.0, 148.9, 144.2, 140.1, 136.4, 134.4, 130.0, 129.2 (2C), 129.1, 129.0,



128.6, 128.1 (2C), 126.9, 112.2, 63.6, 53.0, 48.0, 40.7, 21.1 ppm; HRMS (ESI), *m/z* calcd for $C_{22}H_{24}N_3S$ $[M+H]^+$ 362.1685, found 362.1687.

8-Ethyl-6,7,8,9-tetrahydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]thiadiazecine (3c): The title compound was synthesized from 8-ethyl-5,6,7,8-tetrahydro-9*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]thiadiazecin-9-one (18 mg, 0.060 mmol) according to GP1. Yield 6 mg (36%), colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (dd, J = 4.8, 1.6 Hz, 1H, Py), 7.90 (dd, J = 7.8, 1.8 Hz, 1H, Ar), 7.65 (dd, J = 8.0, 1.6 Hz, 1H, Py), 7.50 (td, J = 7.8, 1.8 Hz, 1H, Ar), 7.35 – 7.07 (m, 3H, Ar+Py), 5.95 (br. s, 1H, NH), 4.81 (s, 2H, CH_2), 4.39 – 4.26 (m, 2H, CH_2), 3.63 – 3.58 (m, 2H, CH_2), 3.32 (q, J = 7.19 Hz, 2H, CH_2), 1.13 (t, J = 7.19 Hz, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.5, 148.8, 148.1, 134.0 (2C), 132.8, 132.7, 130.5, 125.8, 121.7, 119.6, 51.6, 46.6, 43.6, 40.0, 13.6 ppm; HRMS (ESI), *m/z* calcd for $C_{16}H_{20}N_3S$ $[M+H]^+$ 286.1372, found 286.1373.

8-Ethyl-2-(pyrrolidin-1-ylsulfonyl)-6,7,8,9-tetrahydro-5*H*-benzo[*i*]pyrido[3,2-*b*]-[1,4,7]thiadiazecine (3d): The title compound was synthesized from 8-ethyl-2-(pyrrolidin-1-ylsulfonyl)-5,6,7,8-tetrahydro-9*H*-benzo[*i*]pyrido-[3,2-*b*][1,4,7]thiadiazecin-9-one (26 mg, 0.060 mmol) according to GP1. Yield 7 mg (27%), colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.43 (d, J = 2.3 Hz, 1H, Py), 8.06 (d, J = 2.3 Hz, 1H, Py), 7.45 (dd, J = 8.2, 1.3 Hz, 1H, Ar), 7.39 – 7.35 (m, 1H, Ar), 7.26 (td, J = 7.4, 1.3 Hz, 1H, Ar), 6.97 (dd, J = 7.4, 1.5 Hz, 1H), 6.05 (br. s, 1H, NH), 3.87 – 3.77 (m, 2H, CH_2), 3.49 (s, 3H, CH_3), 3.17 – 3.08 (m, 4H, 2CH_2), 2.54 – 2.41 (m, 2H, CH_2), 1.89 – 1.43 (m, 4H, 2CH_2), 0.85 (t, J = 7.4 Hz, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.3, 160.7, 149.7, 143.8, 138.5, 133.5, 130.6, 130.0, 129.9, 127.9, 115.3, 51.1 (2C), 46.5, 42.1, 39.8, 32.6 (2C), 13.8 ppm; HRMS (ESI), *m/z* calcd for $C_{20}H_{27}N_4O_2S_2$ $[M+H]^+$ 419.1570, found 419.1568.

(8-Methyl-6,7,8,9-tetrahydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]thiadiazecin-2-yl)methanol (3e): The title compound was synthesized from methyl 8-methyl-9-oxo-6,7,8,9-tetrahydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]thiadiazecine-2-carboxylate (21 mg, 0.060 mmol) according to GP1. Yield 11 mg (61%), colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 2.1 Hz, 1H, Py), 7.87 (dd, J = 7.4, 1.9 Hz, 1H, Ar), 7.71 (d, J = 2.1 Hz, 1H, Py), 7.54 (dd, J = 7.4, 1.6 Hz, 1H, Ar), 7.47 – 7.33 (m, 2H, Ar), 6.04 (br. s, 1H, NH), 4.70 (s, 2H, CH_2), 4.33 (t, J = 6.0 Hz, 2H, CH_2) 3.93 (s, 2H, CH_2), 3.57 – 3.51 (m, 2H, CH_2), 2.72 (s, 3H, CH_3), 2.21 (br. s, 1H, OH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.3, 162.2, 151.3, 143.4, 131.8, 129.8, 129.0, 128.6 (2C), 127.2, 116.2 63.4, 52.3, 46.8, 41.0, 32.8 ppm; HRMS (ESI), *m/z* calcd for $C_{16}H_{20}N_3OS$ $[M+H]^+$ 302.1322, found 302.1320.

8-(2-Fluorobenzyl)-6,7,8,9-tetrahydro-5*H*-benzo[*i*]pyrazino[2,3-*b*][1,4,7]thiadiazecine (3f): The title compound was synthesized from methyl 8-(2-fluorobenzyl)-5,6,7,8-tetrahydro-9*H*-benzo[*i*]pyrazino[2,3-*b*][1,4,7]thiadiazecin-9-one (23 mg, 0.060 mmol) according to GP1. Yield 9 mg (39%), colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 2.5 Hz, 1H, $H_{Pyrazine}$), 7.70 (d, J = 2.5 Hz, 1H, $H_{Pyrazine}$), 7.38 (dd, J = 8.1, 1.3 Hz, 1H, Ar), 7.20 (dt, J = 7.3, 1.5 Hz, 2H, Ar), 7.22 (dd, J = 7.5, 1.4 Hz, 1H, Ar), 7.17 – 7.05 (m, 2H, Ar), 6.97 (dd, J = 7.7, 1.5 Hz, 1H, Ar), 5.53 (t, J = 4.9 Hz, 1H, NH), 4.79 (s, 2H, CH_2), 4.78 (s, 2H, CH_2), 4.46 (t, J = 5.6 Hz, 2H, CH_2), 3.35 – 3.31 (m, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.0, 154.6, 150.5, 137.0, 131.4 (d, J = 150.2 Hz), 129.1, 126.3, 125.1 (d, J = 4.5 Hz), 124.8, 124.7 (d, J = 8.2 Hz), 124.1, 123.3, 122.2,

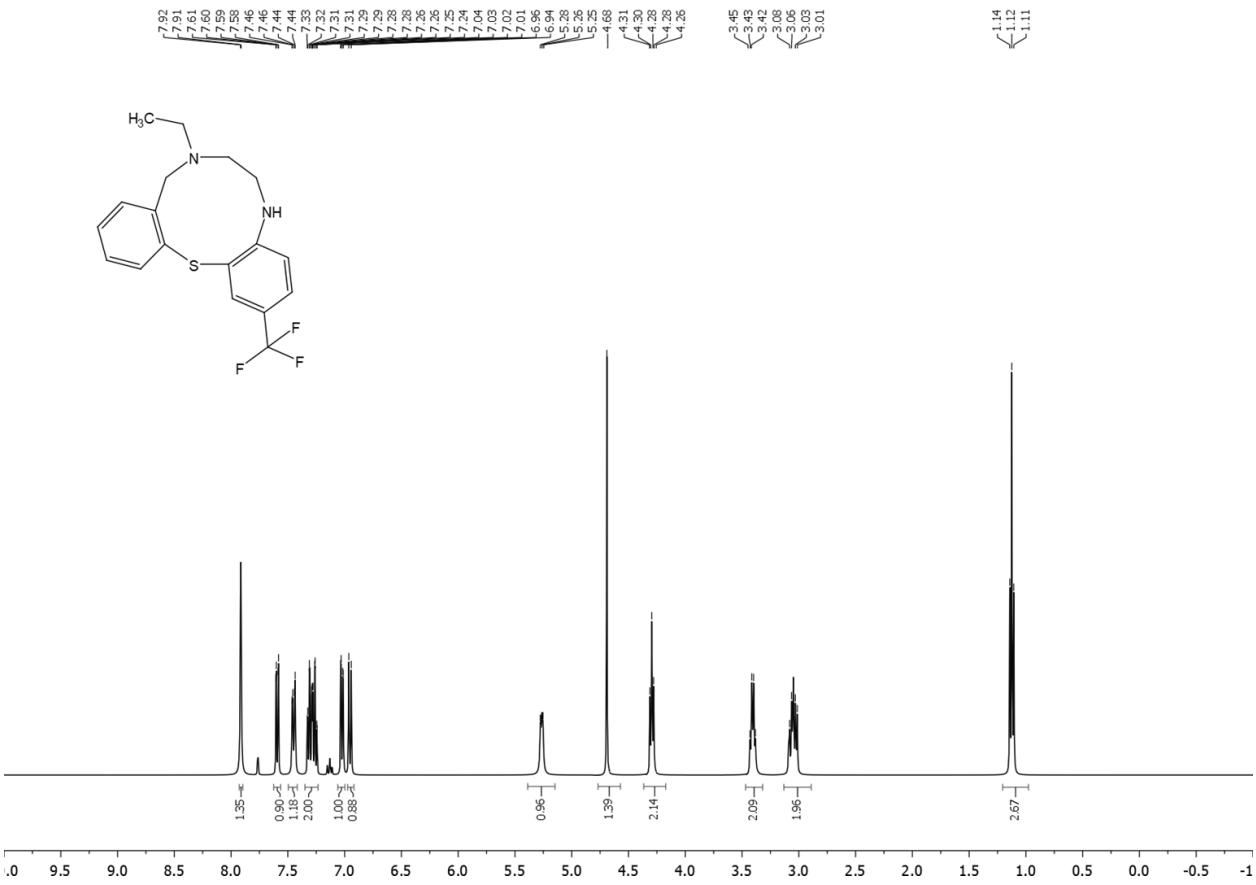
120.05 (d, *J* = 3.7 Hz), 119.6 (d, *J* = 14.5 Hz), 110.7 (d, *J* = 21.0 Hz), 46.3, 35.9 (2C), 30.0 ppm; HRMS (ESI), *m/z* calcd for $C_{20}H_{20}FN_4S$ $[M+H]^+$ 367.1387, found 367.1387.

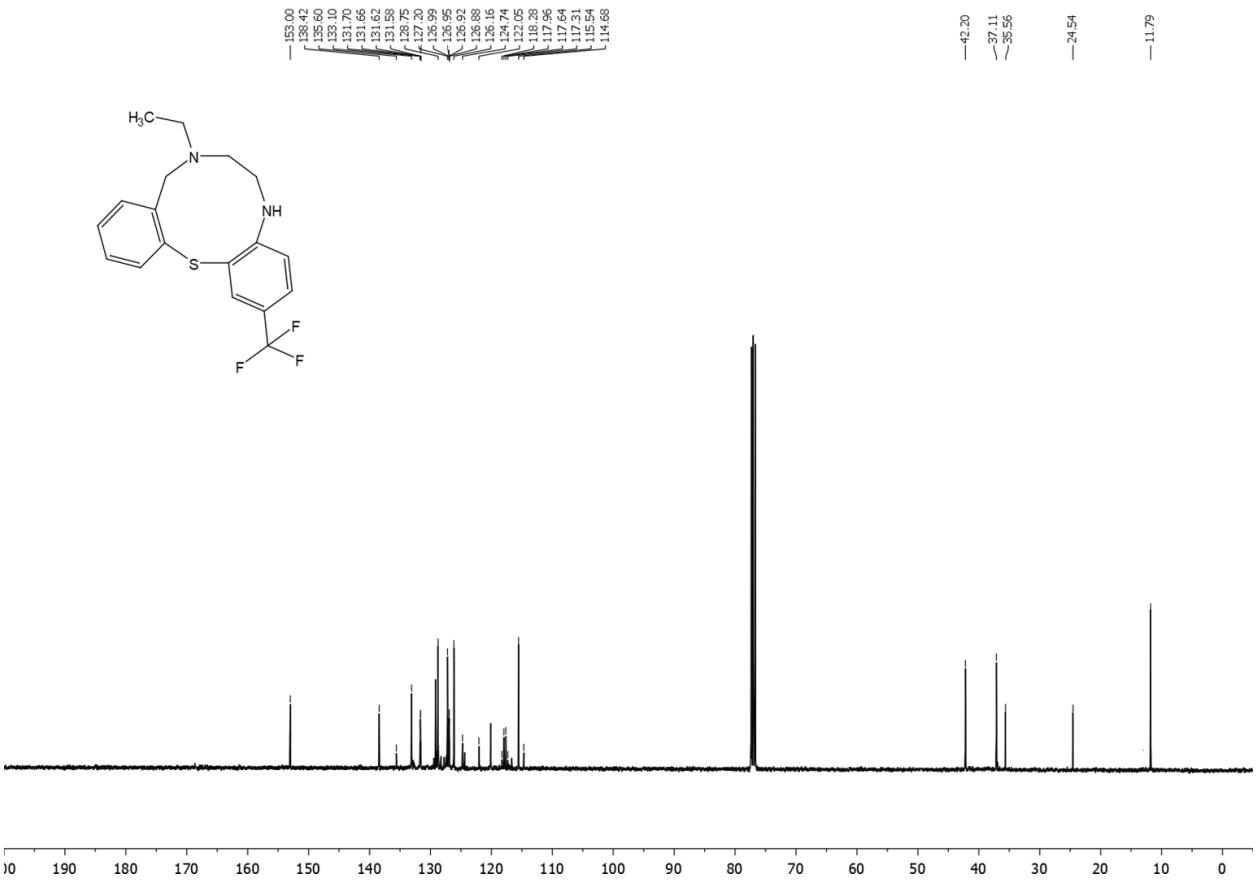
6,7,8,9-Tetrahydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]thiadiazecine (3g): The title compound was synthesized from methyl 5,6,7,8-tetrahydro-9*H*-benzo[*i*]pyrido[3,2-*b*]-[1,4,7]thiadiazecin-9-one (16 mg, 0.060 mmol) according to GP1. Yield 9 mg (61%), colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (dd, *J* = 4.9, 1.7 Hz, 1H, Py), 7.49 (dd, *J* = 7.8, 1.7 Hz, 1H, Py), 7.26 – 7.20 (m, 2H, Ar), 7.11 – 6.97 (m, 2H, Ar), 6.76 (dd, *J* = 7.8, 4.9 Hz, 1H, Py), 4.87 (br, s, 1H, NH), 3.95 (s, 2H), 3.45 (q, *J* = 6.6 Hz, 2H), 2.90 (t, *J* = 6.3 Hz, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.2, 154.6, 144.3, 138.3, 132.4, 131.2, 128.7, 123.3, 120.0, 114.4, 114.1, 49.4, 47.9, 43.6 ppm; HRMS (ESI), *m/z* calcd for $C_{14}H_{16}N_3S$ $[M+H]^+$ 258.1059, found 258.1056.

11-Chloro-6,7,8,9-tetrahydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]oxadiazecine (3h): The title compound was synthesized from methyl 11-chloro-5,6,7,8-tetrahydro-9*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]oxadiazecin-9-one (17 mg, 0.060 mmol) according to GP1. Yield 10 mg (57%), colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (dd, *J* = 4.6, 1.5 Hz, 1H, Py), 7.84 (d, *J* = 2.7 Hz, 1H, Ar), 7.58 (dd, *J* = 8.1, 1.5 Hz, 1H, Py), 7.43 (dd, *J* = 8.6, 2.7 Hz, 1H, Ar), 7.20 – 7.11 (m, 2H, Ar+Py), 5.56 (t, *J* = 5.5 Hz, 1H, NH), 4.79 (s, 2H, CH_2), 4.41 (t, *J* = 5.8 Hz, 2H, CH_2), 3.68 – 3.46 (m, 2H, CH_2) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 157.9, 155.9, 148.5, 147.6, 145.0, 133.6, 132.2, 129.8, 127.6, 121.6, 120.9, 46.9, 42.7, 39.8 ppm; HRMS (ESI), *m/z* calcd for $C_{14}H_{15}ClN_3O$ $[M+H]^+$ 292.0670, found 292.0667.

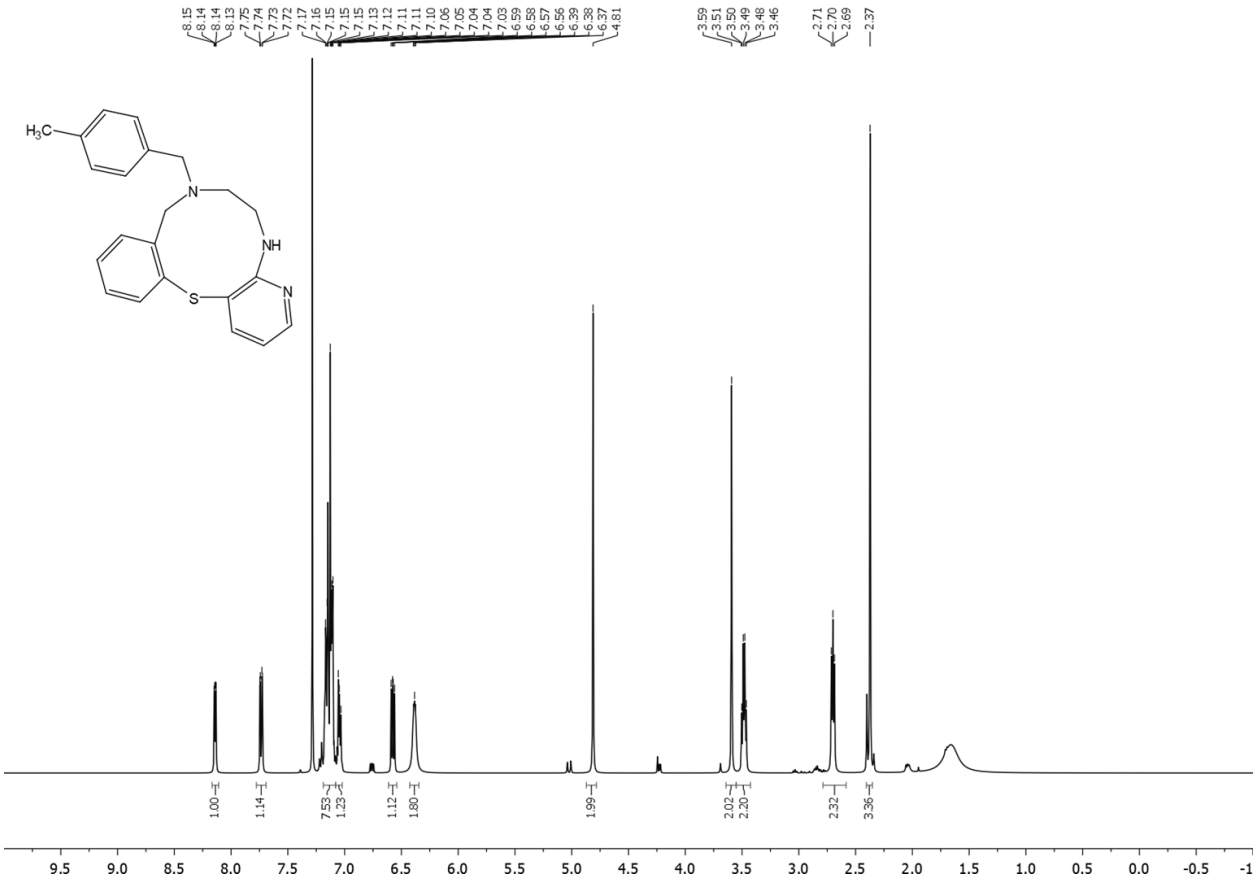
2-Trifluoromethyl-6,7,8,9-tetrahydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]oxadiazecine (3i): The title compound was synthesized from methyl 2-trifluoromethyl-5,6,7,8-tetrahydro-9*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]oxadiazecin-9-one (19 mg, 0.060 mmol) according to GP1. Yield 8 mg (43%), dark oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, *J* = 2.1 Hz, 1H, Py), 7.89 (dd, *J* = 7.8, 1.7 Hz, 1H, Ar), 7.80 (d, *J* = 2.1 Hz, 1H, Py), 7.54 (ddd, *J* = 8.1, 7.6, 1.7 Hz, 1H, Ar), 7.31 (td, *J* = 7.6, 1.2 Hz, 1H, Ar), 7.25 (dd, *J* = 8.1, 1.2 Hz, 1H, Ar), 6.87 – 6.69 (br. s, 1H, NH), 4.24 (s, 2H, CH_2), 3.21 (t, *J* = 6.3 Hz, 2H, CH_2), 2.52 – 2.47 (m, 2H, CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.8, 154.0, 147.8, 141.7 (q, *J* = 4.2 Hz), 134.2, 132.6 (2C), 127.2, 126.2, 126.0, 124.4, 122.7 (q, *J* = 267.7 Hz), 52.8, 43.0, 41.6 ppm; HRMS (ESI), *m/z* calcd for $C_{15}H_{15}F_3N_3O$ $[M+H]^+$ 310.1162, found 310.1160.

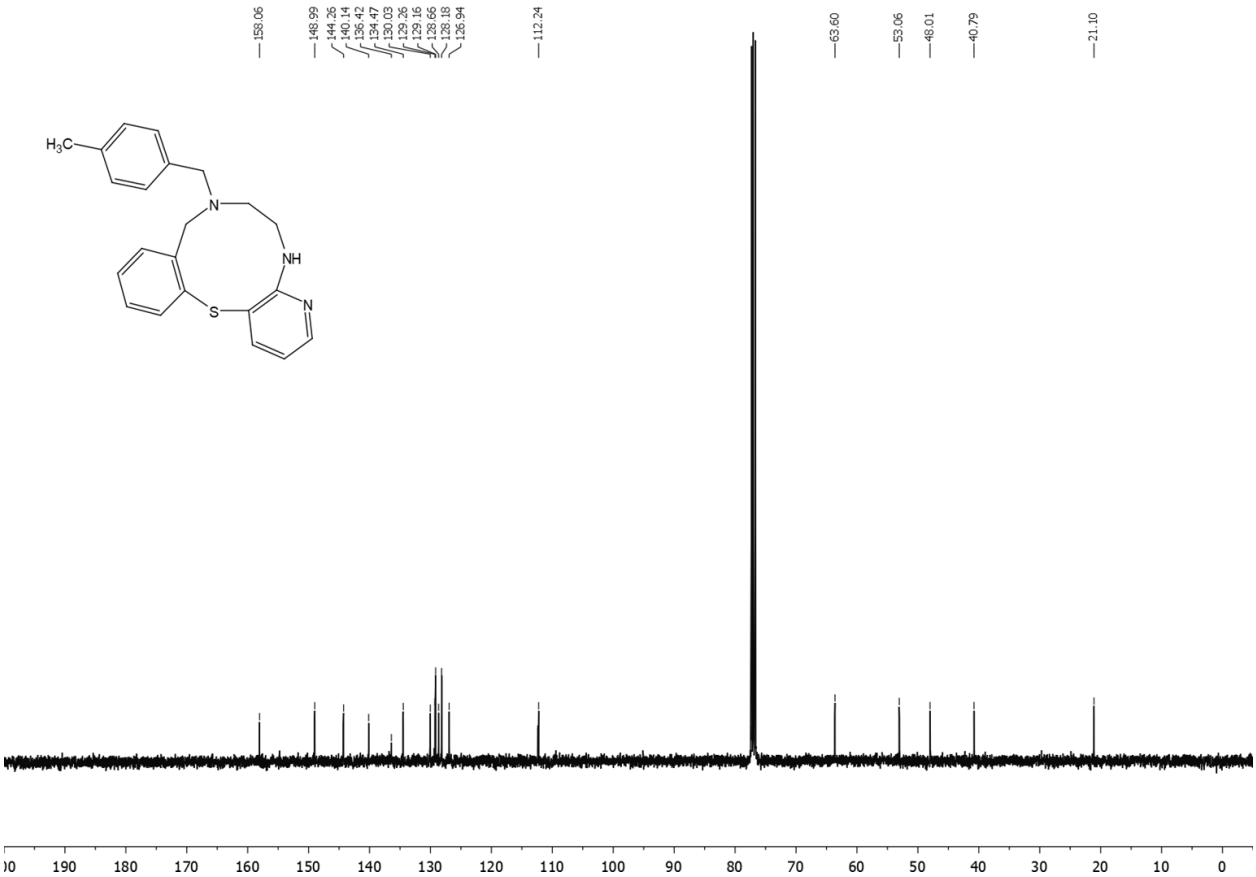
^{1}H and ^{13}C NMR spectra of compound 3a



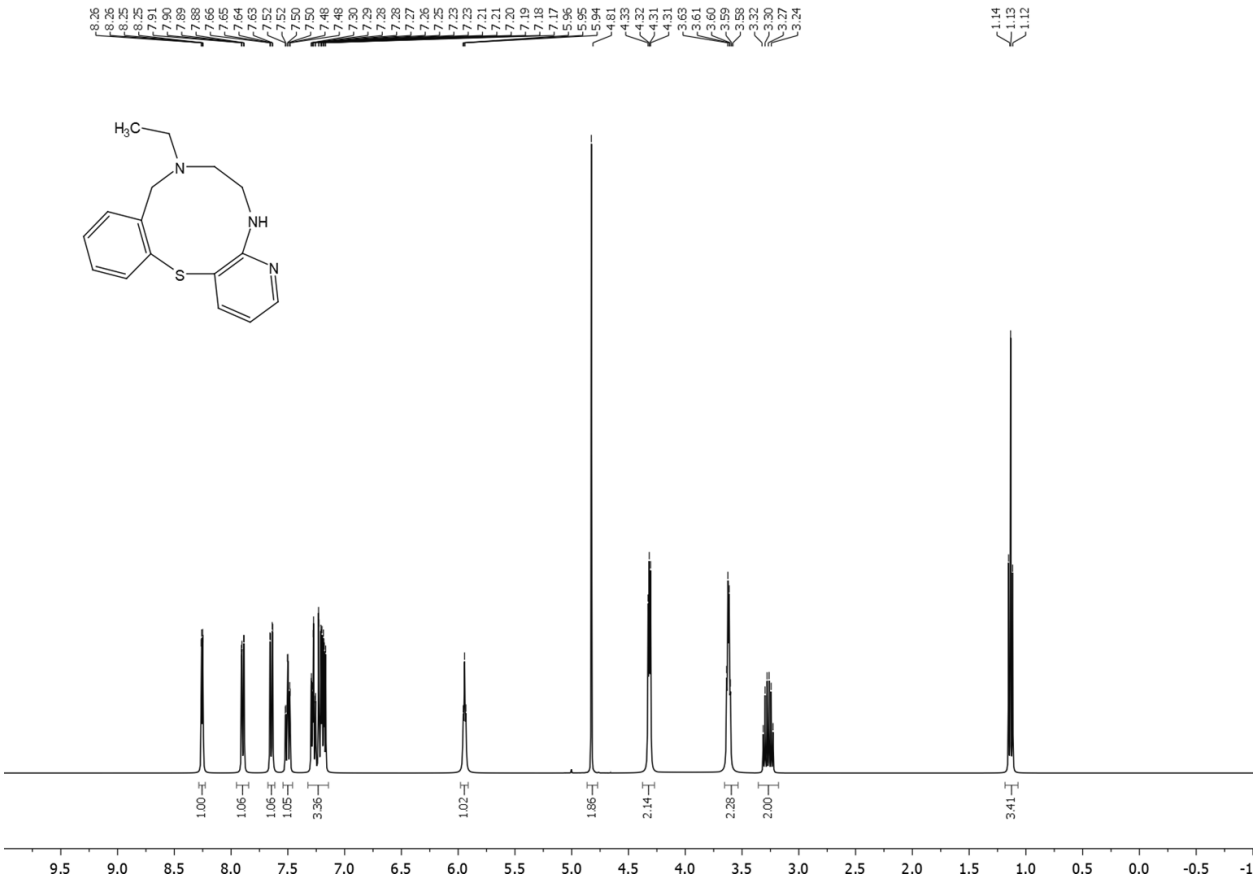


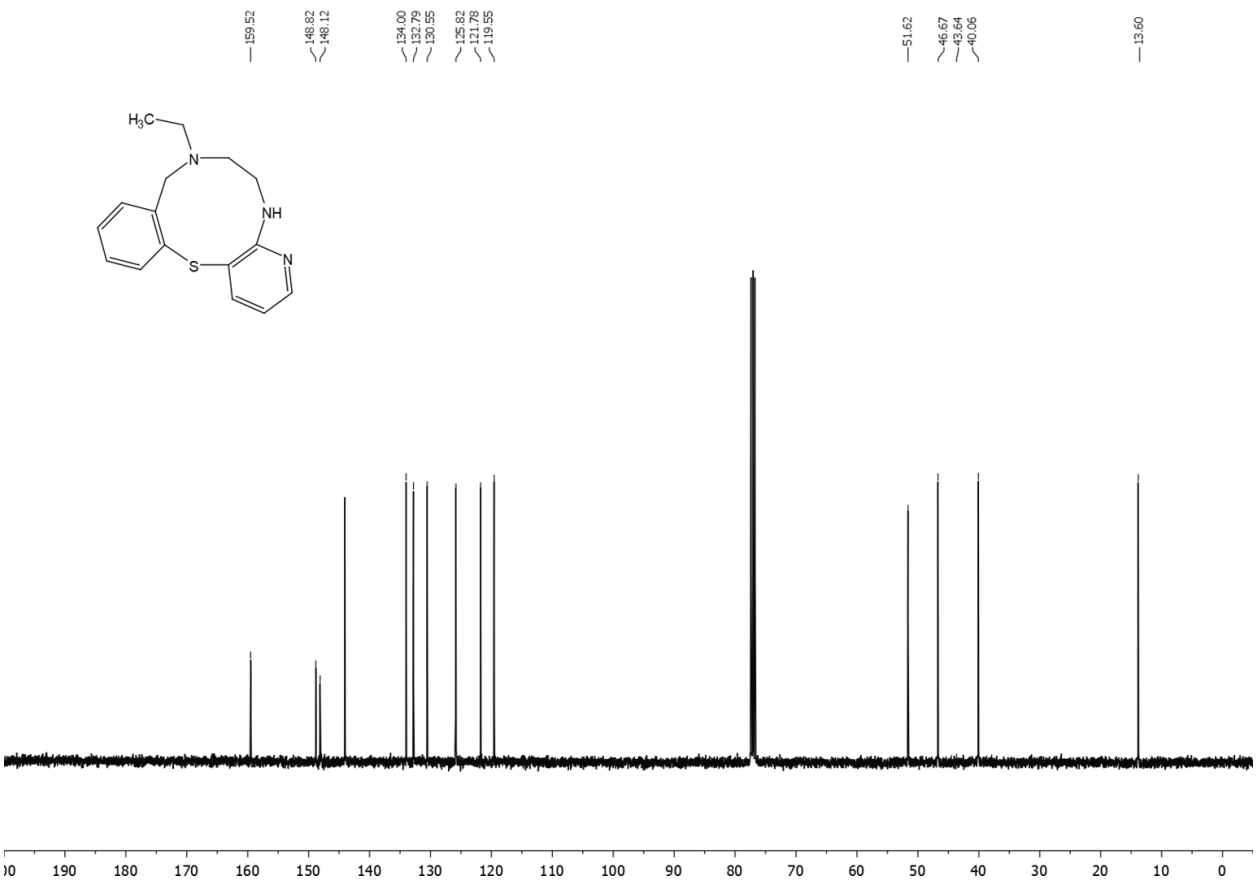
^{1}H and ^{13}C NMR spectra of compound 3b



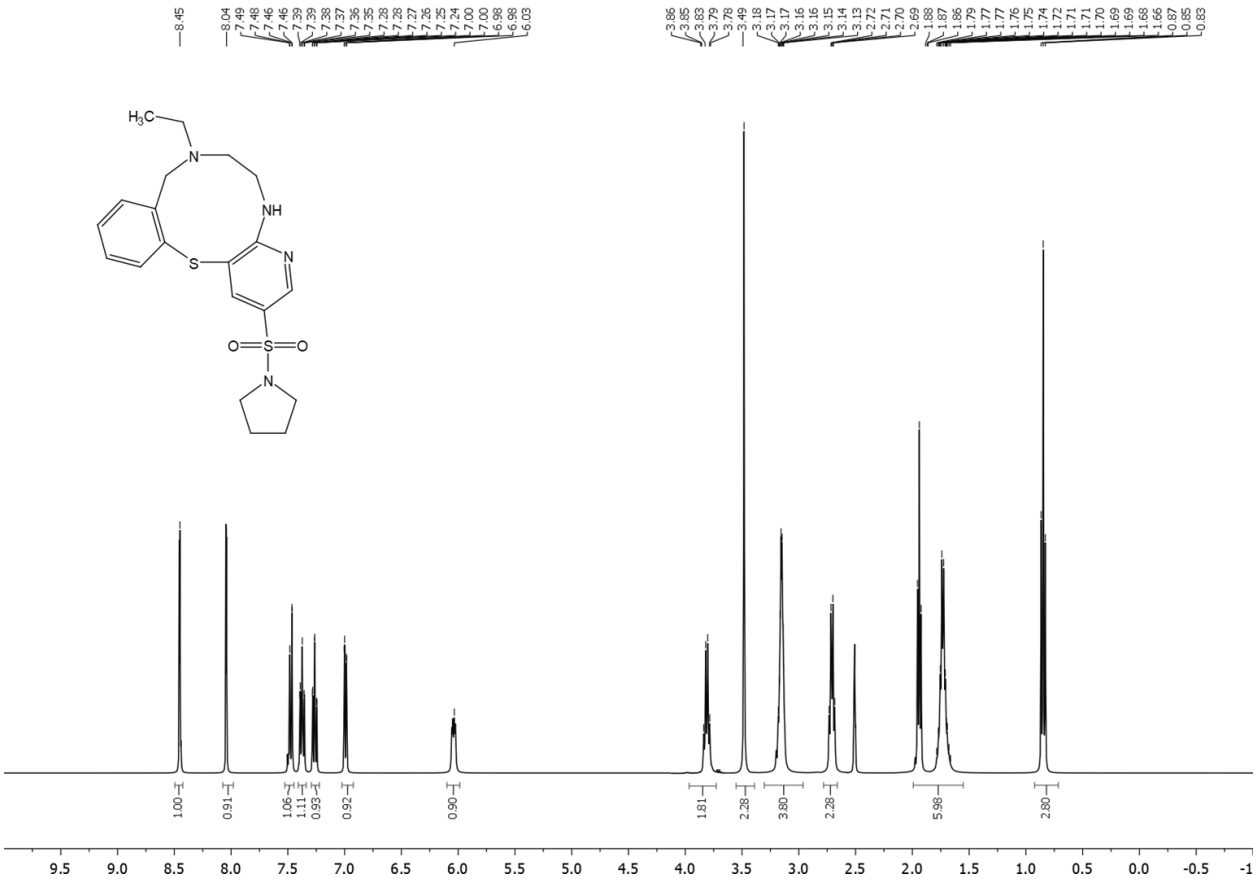


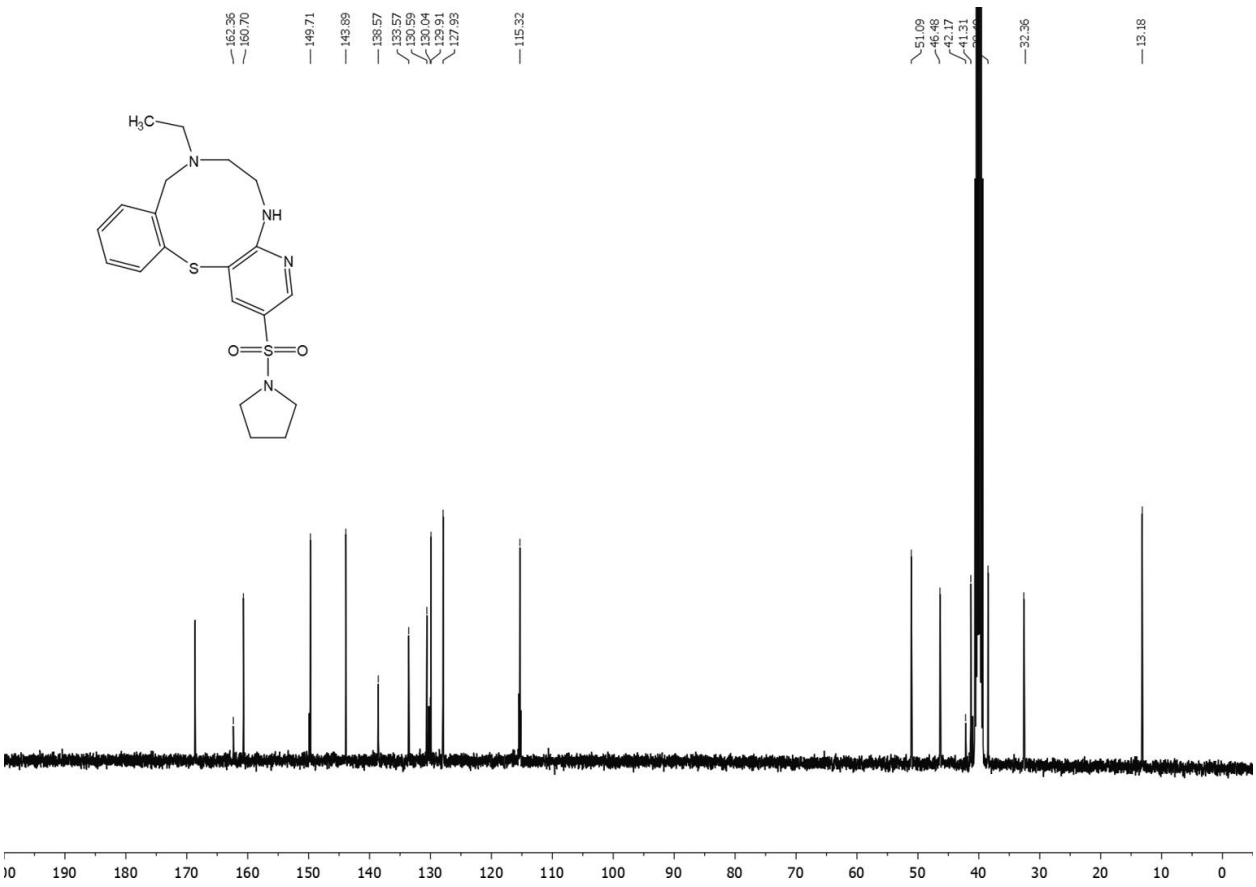
^{1}H and ^{13}C NMR spectra of compound 3c



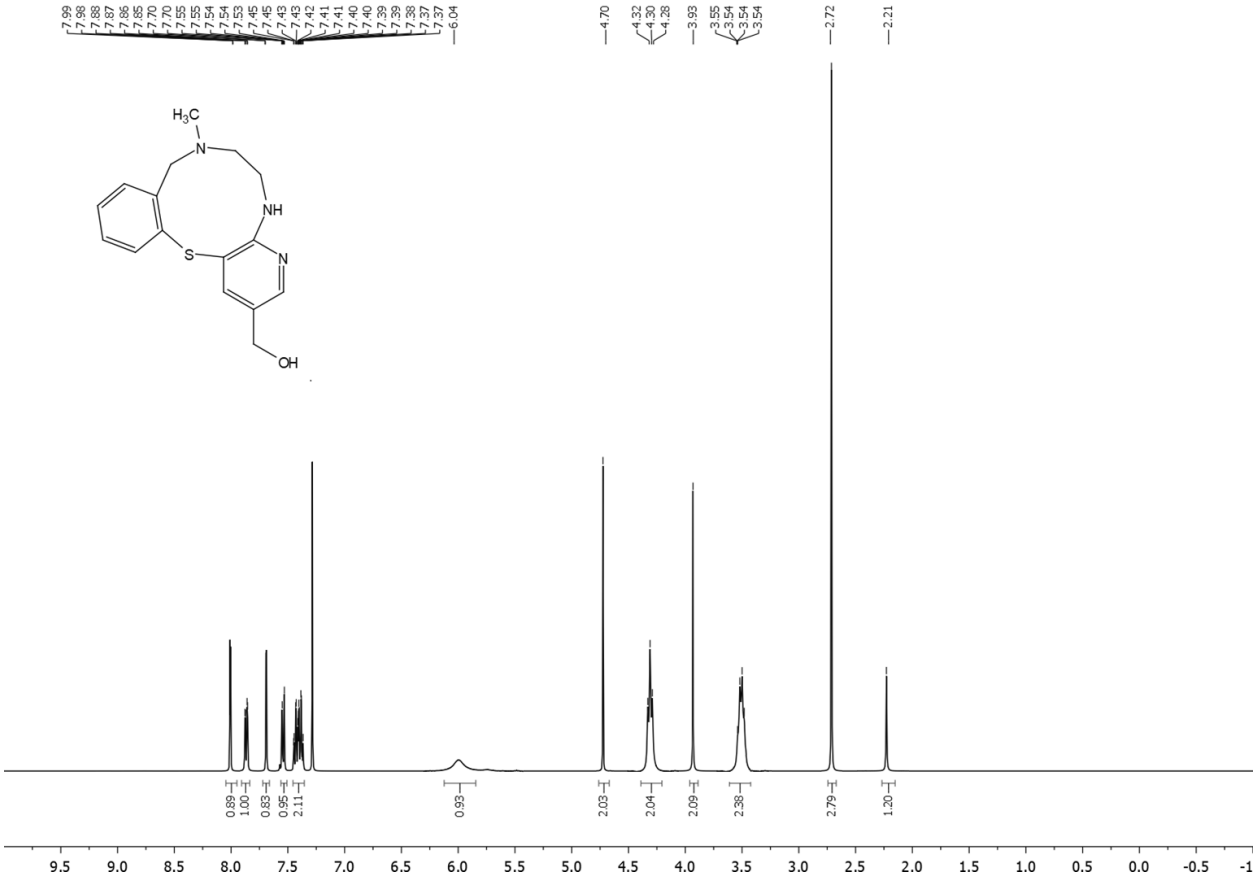


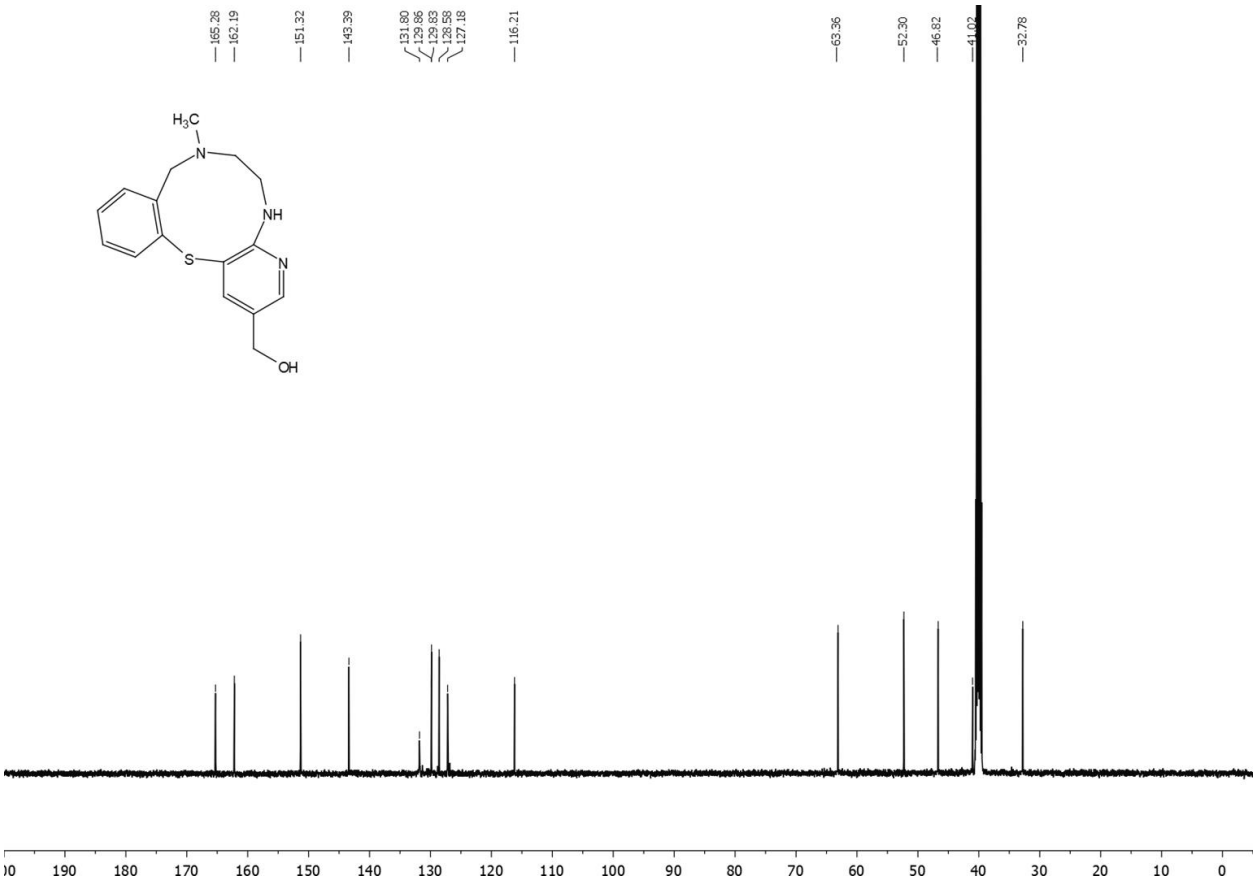
^{1}H and ^{13}C NMR spectra of compound 3d



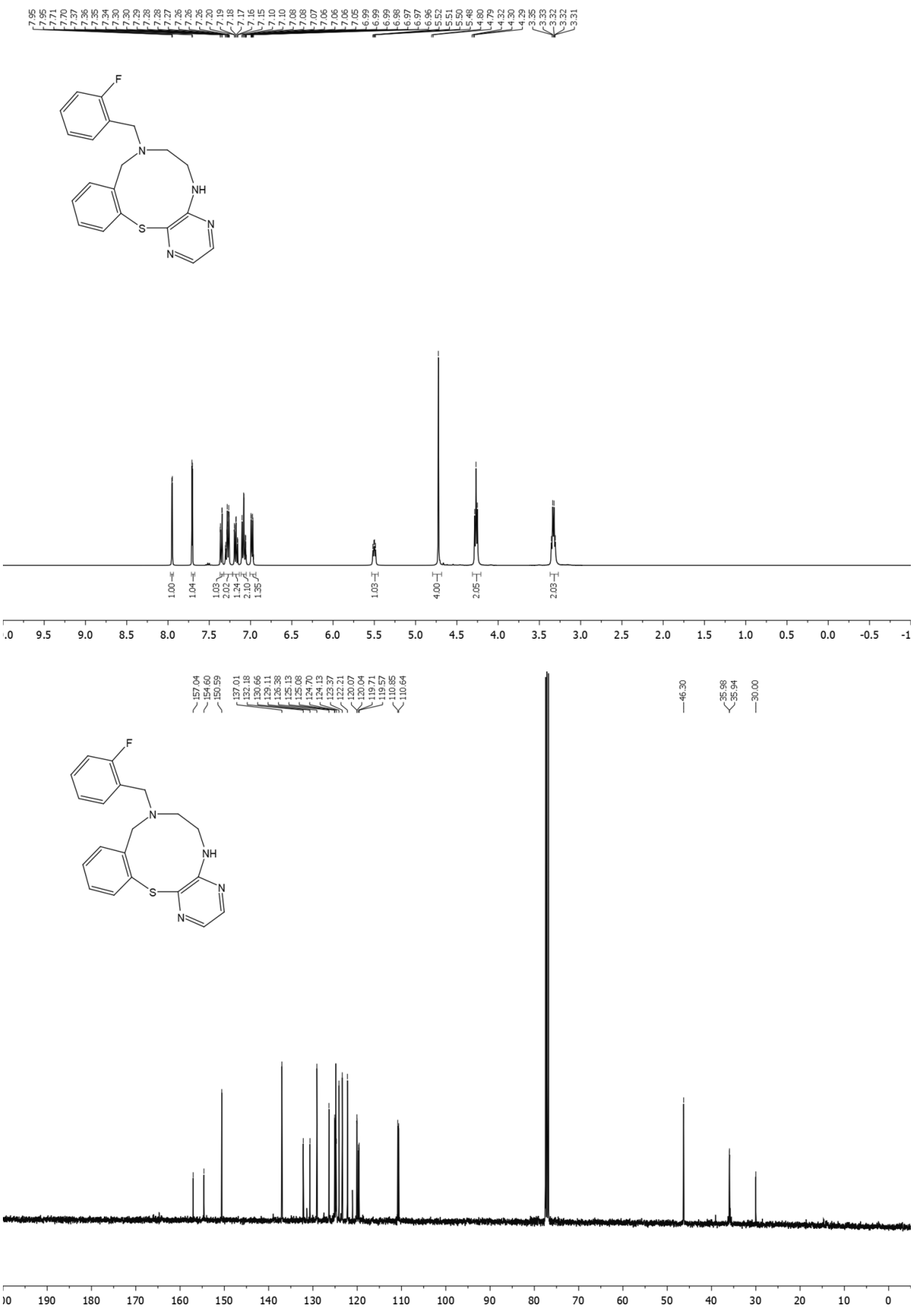


^{1}H and ^{13}C NMR spectra of compound 3e

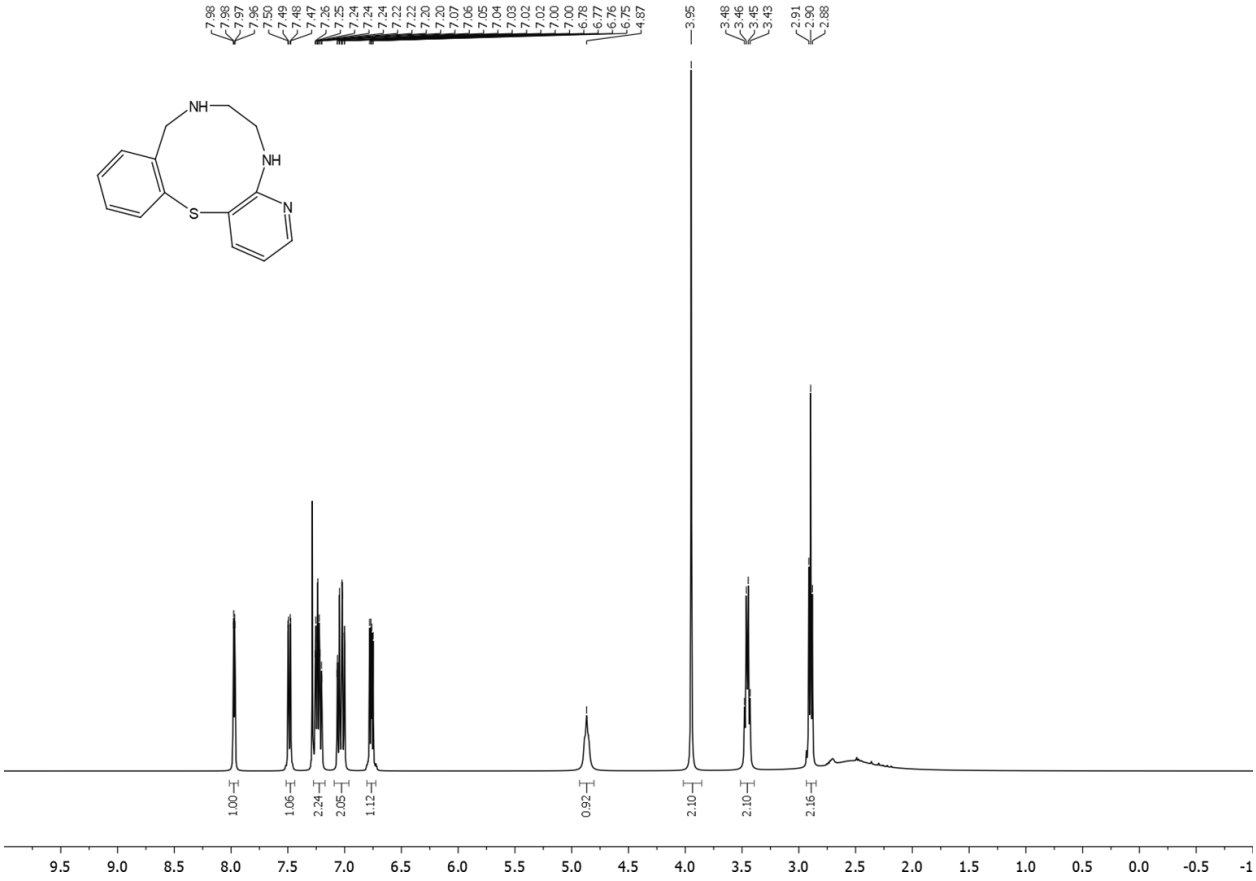


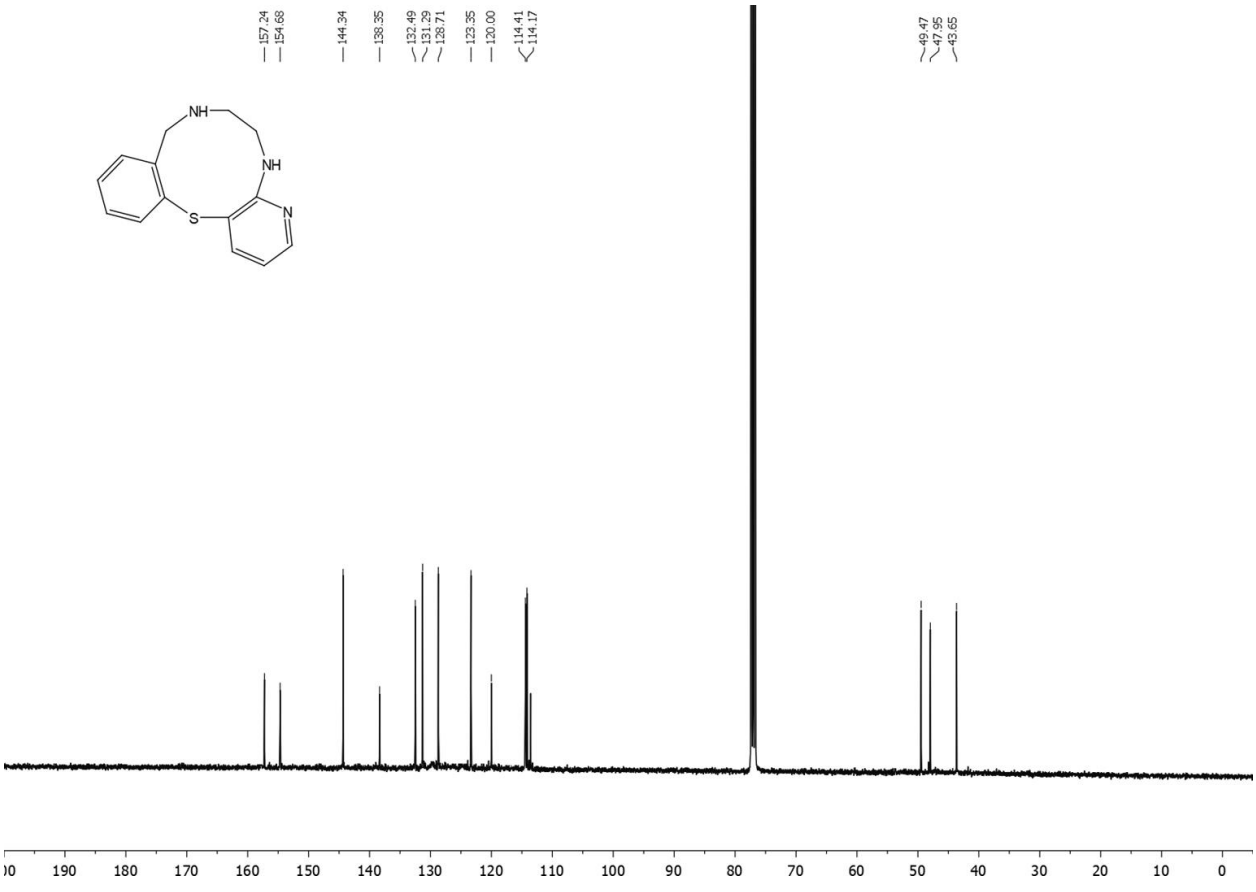


^{1}H and ^{13}C NMR spectra of compound 3f

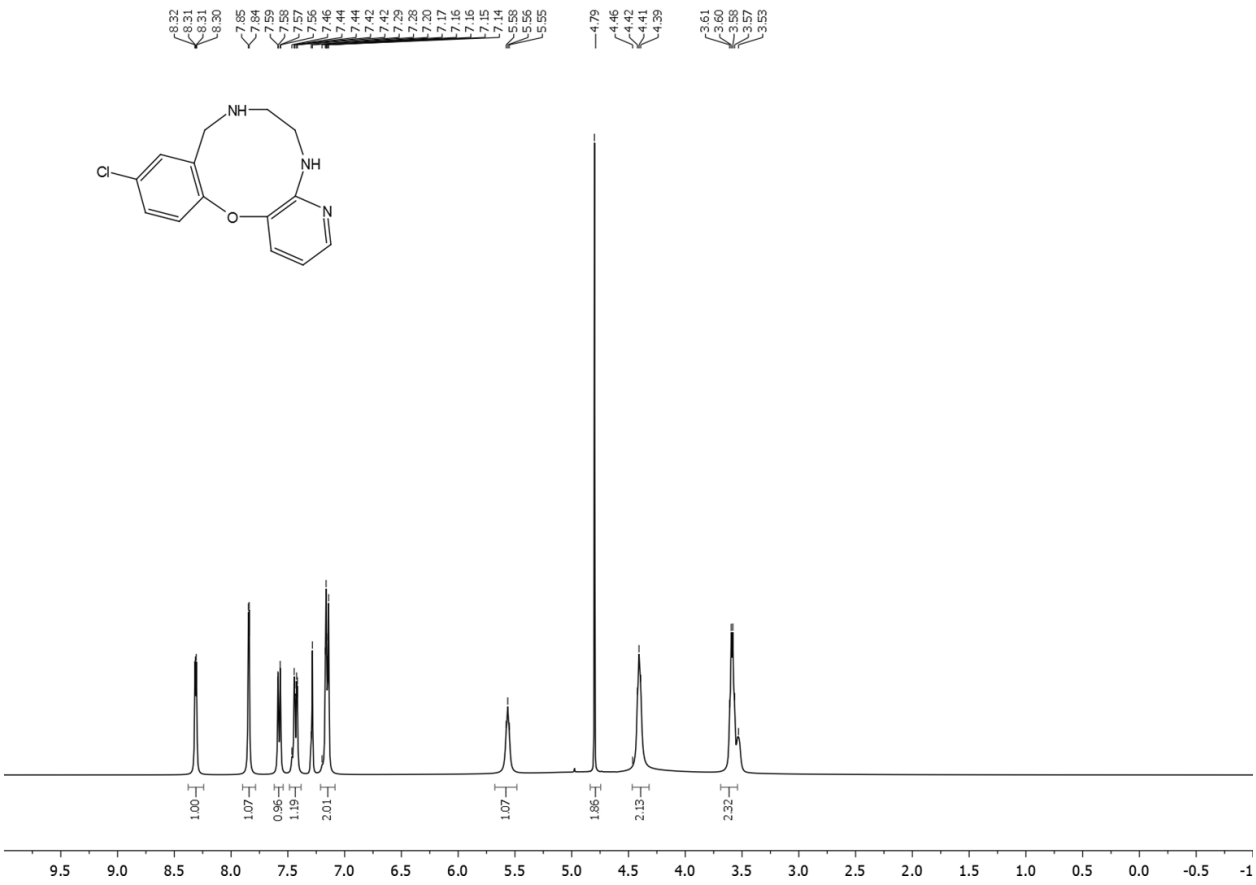


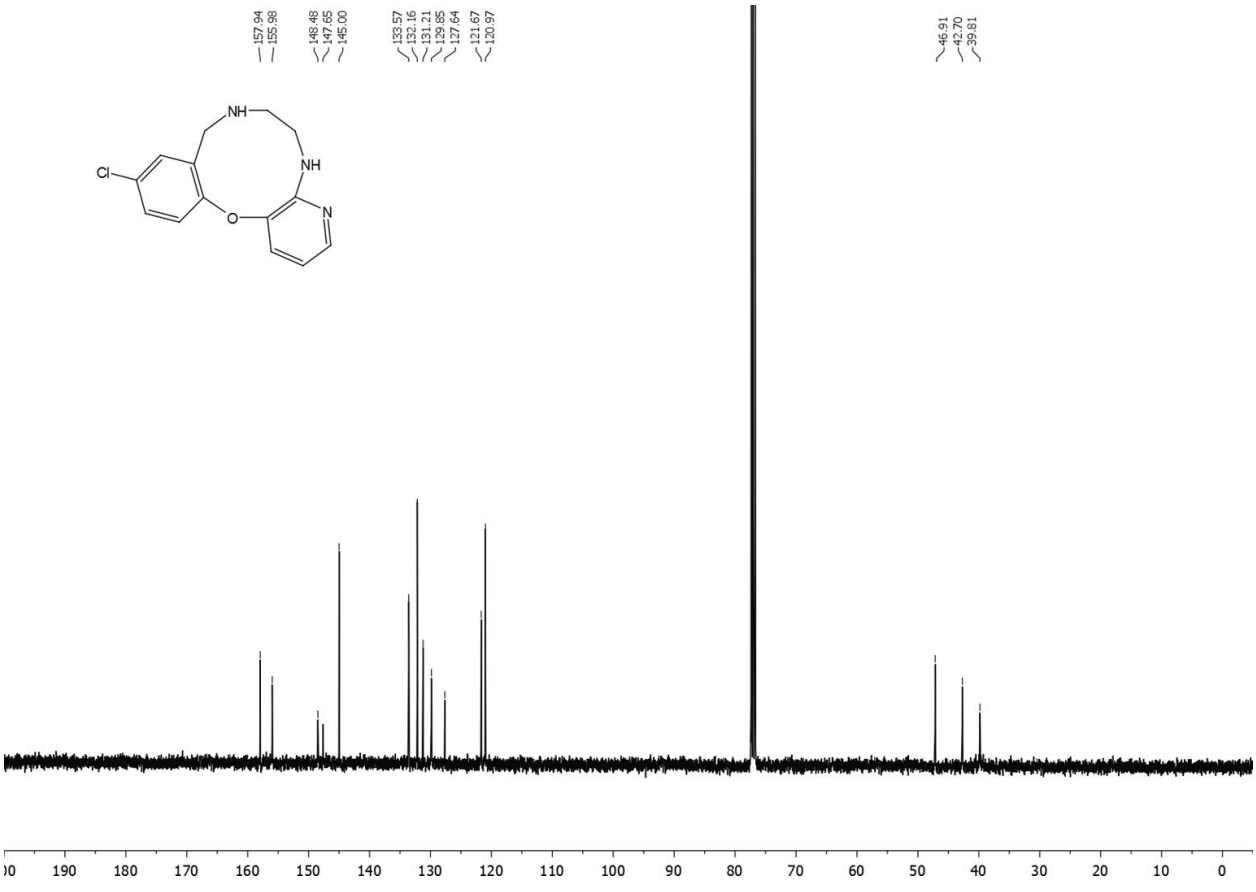
^{1}H and ^{13}C NMR spectra of compound 3g





^{1}H and ^{13}C NMR spectra of compound 3h





^{1}H and ^{13}C NMR spectra of compound 3i