Supporting Information for

Structurally Diverse Arene-Fused Ten-Membered Lactams Accessed via Imidazoline Ring Expansion

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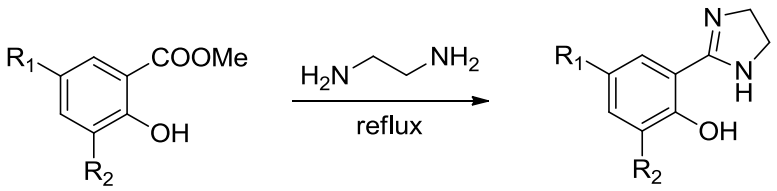
1. General Information

All commercial reagents and solvents were used without further purification, unless otherwise noted. DMF for the synthesis was distilled over CaH_2 and stored under nitrogen over freshly activated molecular sieves 4Å. Potassium carbonate was dried at 200 ^oC for 5 hours prior to use. Analytical thin-layer chromatography was carried out on Silufol UV-254 silica gel plates using appropriate mixtures of ethyl acetate and hexane. Compounds were visualized with short-wavelength UV light. NMR spectra were recorded on a 400 MHz and 300 MHz spectrometers; 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 microTOF spectrometers (ESI ionization). Melting points were determined in open capillary tubes and are not corrected. Single-crystal X-ray diffraction experiments were carried out using a diffractometer with monochromated MoKα radiation. The structures had been solved by the ShelXS[1] and Superflip[2] structure solution programs using Direct Methods and Charge Flipping, respectively, and refined by means of the ShelXL program, incorporated in the OLEX2 program package.[3]

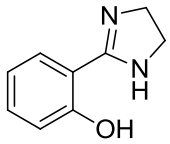
1. SHELXL, G.M. Sheldrick, Acta Cryst. (2008). A64, 112−122;
2. J. Appl. Cryst. (2007) 40, 786−790;
3. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, OLEX2: a complete structure solution, refinement and analysis program. J. Appl. Cryst. (2009) 42, 339−341.

2. Experimental procedures and analytical data

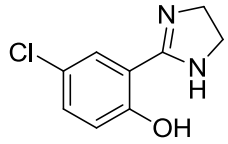
2.1. Preparation of imidazolines 14a-d.



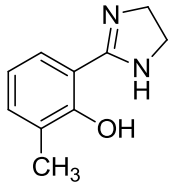
General Procedure 1: Respective methyl ester **13a-d** (25 mmol) was suspended in ethylene diamine (6.68 ml, 100 mmol) and the mixture was heated at reflux with vigorous stirring for 3 h. The mixture was cooled to 10 °C and the resulting precipitate was filtered off, washed with water, air-dried and crystallized from isopropanol to provide the analytically pure title compound.



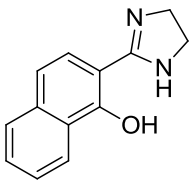
2-(4,5-Dihydro-1*H*-imidazol-2yl)phenol (14a) was synthesized according to General Procedure 1 starting from methyl salicylate (3.804 g, 25 mmol) in 74% (3.004 g, 18 mmol) yield; yellow solid; **mp** 206-213 °C. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 10.75-11.25 (br.s, 1H, ArOH), 7.55 (d, *J*= 7.9 Hz, 1H, H_{Ar}), 7.26 (m, 1H, H_{Ar}), 6.77 (d, *J*= 8.1 Hz, 1H, H_{Ar}), 6.68 (t, *J*= 7.7 Hz, 1H, H_{Ar}), 3.70 (br.s, 4H, $H_{Imidazolin}$) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.6, 163.7, 133.1, 127.8, 118.5, 116.3, 110.9, 47.3 ppm. **HRMS** (ESI), m/z calcd for $C_9H_{10}N_2O_3$ $[M+H]^+$ 162.0793, found 162.0781.



4-Chloro-2-(4,5-dihydro-1*H*-imidazol-2-yl)phenol (14b) was synthesized according to General Procedure 1 starting from methyl 5-chloro-2-hydroxybenzoate (4.665 g, 25 mmol) in 63% (3.096 g, 16 mmol) yield; yellow solid; **mp** 245-248 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.63 (d, *J*= 2.8 Hz, 1H, H_{Ar}), 7.18 (dd, *J*= 9.1, 2.8 Hz, 1H, H_{Ar}), 6.65 (d, *J*= 9.1 Hz, 1H, H_{Ar}), 3.73 (s, 4H, $H_{Imidazolin}$) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.4, 165.8, 133.3, 127.2, 122.4, 116.9, 110.3, 46.2 ppm. **HRMS** (ESI), m/z calcd for $C_9H_9ClN_2O$ $[M+H]^+$ 196.0403, found 196.0409.



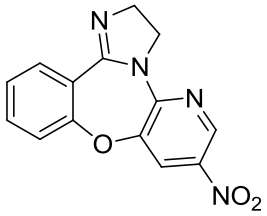
2-(4,5-Dihydro-1*H*-imidazol-2-yl)-6-methylphenol (14c) was synthesized according to General Procedure 1 starting from methyl 2-hydroxy-3-methylbenzoate (4.154 g, 25 mmol) in 58% (2.555 g, 15 mmol) yield; yellow solid; **mp** 229-232 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.43 (d, *J*= 7.6 Hz, 1H, H_{Ar}), 7.17 (d, *J*= 7.6 Hz, 1H, H_{Ar}), 6.62 (t, *J*= 7.6 Hz, 1H, H_{Ar}), 3.70 (s, 4H, $H_{Imidazolin}$), 2.13 (s, 3H, $ArCH_3$) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.9, 161.8, 133.5, 126.6, 125.5, 116.0, 110.2, 47.4, 16.5 ppm. **HRMS** (ESI), m/z calcd for $C_{10}H_{12}N_2O$ $[M+H]^+$ 176.0950, found 176.0957.



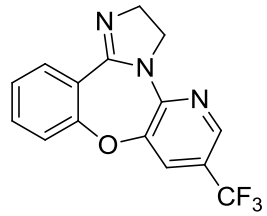
2-(4,5-Dihydro-1*H*-imidazol-2-yl)naphthalen-1-ol (14d) was synthesized according to General Procedure 1 starting from methyl 1-hydroxy-2-naphthoate (5.055 g, 25 mmol) in 47% (2.493 g, 12 mmol) yield; yellow solid; **mp** >300 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.28 (d, *J*= 8.1 Hz, 1H, H_{Ar}), 7.54 (d, *J*= 7.9 Hz, 1H, H_{Ar}), 7.35-7.38 (m, 2H, H_{Ar}), 7.27 (t, *J*= 7.5 Hz, 1H, H_{Ar}), 6.55 (d, *J*= 8.9 Hz, 1H, H_{Ar}), 3.78 (s, 4H, $H_{Imidazolin}$). ppm. **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.5, 158.2, 136.0, 129.9, 127.4, 125.8, 125.5, 124.4, 123.5, 118.4, 109.2, 47.2 ppm. **HRMS** (ESI), m/z calcd for $C_{13}H_{12}N_2O$ $[M+H]^+$ 212.0950, found 212.0962.

2.2. Preparation of imidazoline-fused [1,4]oxazepines

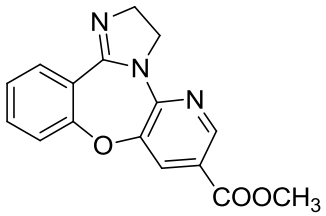
All the imidazoline-fused [1,4]oxazepines were prepared according to our previously published method (Karamysheva et al. *Tetrahedron Lett.* **2015**, *56*, 5632-5636, reference 15 in the article).



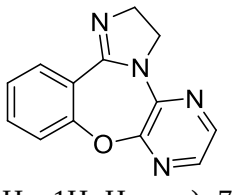
7-Nitro-2,3-dihydrobenzo[*f*]imidazo[1,2-*d*]pyrido[3,2-*b*][1,4]oxazepine (10a) was synthesized starting from **14a** (162 mg, 1.000 mmol), 2,3-dichloro-5-nitropyridine (192 mg, 1.000 mmol) and K_2CO_3 (414 mg, 3.000 mmol) in 87% (245 mg, 0.868 mmol) yield; colorless solid; **mp** 207-209 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.02 (d, *J*= 2.4 Hz, 1H, H_{Py}), 8.51 (d, *J*= 2.4 Hz, 1H, H_{Py}), 7.92 (dd, *J*= 7.9, 1.7 Hz, 1H, H_{Ar}), 7.61-7.69 (m, 1H, H_{Ar}), 7.55 (dd, *J*= 7.9, 1.7 Hz, 1H), 7.31-7.98 (m, 1H, H_{Ar}), 4.24 (t, *J*= 9.9 Hz, 2H, $H_{Imidazoline}$), 4.04 (t, *J*= 9.9 Hz, 2H, $H_{Imidazoline}$). ppm. **^{13}C NMR** (100 MHz, DMSO-d_6) δ 155.4, 154.7, 150.6, 141.7, 141.4, 138.8, 134.3, 131.4, 126.5, 124.3, 121.6 (2C), 52.4, 49.9 ppm. **HRMS** (ESI), m/z calcd for $C_{14}H_{10}N_4O_3$ $[M+H]^+$ 282.0753, found 282.0771.



7-(Trifluoromethyl)-2,3-dihydrobenzo[*f*]imidazo[1,2-*d*]pyrido[3,2-*b*][1,4] oxazepine (10b) was synthesized starting from **14a** (162 mg, 1.000 mmol), 2,3-dichloro-5-(trifluoromethyl)pyridine (215 mg, 1.000 mmol) and K_2CO_3 (414 mg, 3.000 mmol) in 55% (168 mg, 0.551 mmol) yield; grey solid; **mp** 115-119 °C. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.54 (d, *J*= 1.9 Hz, 1H, H_{Py}), 8.16 (d, *J*= 1.9 Hz, 1H, H_{Py}), 7.92-7.96 (m, 1H, H_{Ar}), 7.55-7.59 (m, 1H, H_{Ar}), 7.45-7.51 (m, 1H, H_{Ar}), 7.31-7.38 (m, 1H, H_{Ar}), 4.20 (t, *J*= 9.2 Hz, 2H, $H_{Imidazoline}$), 3.00 (t, *J*= 9.2 Hz, 2H, $H_{Imidazoline}$) ppm. **^{13}C NMR** (75 MHz, DMSO-d_6) δ 155.3, 155.0, 149.1, 142.1, 141.7, 133.8, 130.9, 126.0 (d, *J*= 6.9 Hz), 125.9, 123.4 (d, *J*= 271.3 Hz), 121.2, 119.3, 118.9, 51.6, 49.1 ppm. **HRMS** (ESI), m/z calcd for $C_{15}H_{10}F_3N_3O$ $[M+H]^+$ 305.0776, found 305.0783.

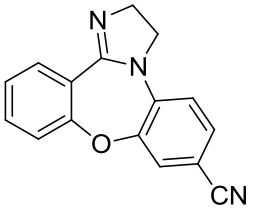


Methyl 2,3-dihydrobenzo[*f*]imidazo[1,2-*d*]pyrido[3,2-*b*][1,4]oxazepine-7-carboxylate (10c) was synthesized starting from **14a** (162 mg, 1.000 mmol), methyl 5,6-dichloronicotinate (206 mg, 1.000 mmol) and K_2CO_3 (414 mg, 3.000 mmol) in 72% (209 mg, 0.708 mmol) yield; grey solid; mp 115-119 °C. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.66 (d, *J*= 1.7 Hz, 1H, H_{Py}), 8.09 (d, *J*= 1.7 Hz, 1H, H_{Py}), 7.91 (d, *J*= 7.9 Hz, 1H, H_{Ar}), 7.60 (t, *J*= 7.6 Hz, 1H, H_{Ar}), 7.50 (d, *J*= 7.7 Hz, 1H, H_{Ar}), 7.32 (t, *J*= 7.8 Hz, 1H, H_{Ar}), 4.19 (t, *J*= 8.7 Hz, 2H, $H_{Imidazoline}$), 3.99 (t, *J*= 8.7 Hz, 2H, $H_{Imidazoline}$), 3.85 (s, 3H, $COOCH_3$) ppm. **^{13}C NMR** (75 MHz, DMSO-d_6) δ 165.5, 157.6, 146.2, 143.8, 142.9, 137.7, 133.3x2, 129.5, 126.8, 122.2, 121.1, 115.2, 52.3, 50.3, 49.0 ppm. **HRMS** (ESI), m/z calcd for $C_{16}H_{13}N_3O_3$ $[M+H]^+$ 295.0957, found 295.0978.

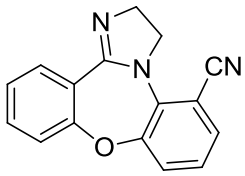


2,3-Dihydrobenzo[*f*]imidazo[1,2-*d*]pyrazino[2,3-*b*][1,4]oxazepine (10d) was synthesized starting from **14a** (162 mg, 1.000 mmol), 2,3-dichloropyrazine (149 mg, 1.000 mmol) and K_2CO_3 (414 mg, 3.000 mmol) in 71% (168 mg, 0.706 mmol) yield; colorless solid; **mp** 141-144 °C. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.21 (d, *J*= 2.8 Hz, 1H, $H_{Pyrazine}$), 7.96 (d, *J*= 7.8 Hz, 1H, H_{Ar}), 7.89 (d, *J*= 2.8 Hz, 1H, $H_{Pyrazine}$), 7.60 (t, *J*= 7.4 Hz, 1H, H_{Ar}), 7.40 (d, *J*= 8.4 Hz, 1H, H_{Ar}), 7.32 (t, *J*= 7.4 Hz, 1H, H_{Ar}), 4.13 (t, *J*= 8.4 Hz, 2H, $H_{Imidazoleine}$), 3.99 (t,

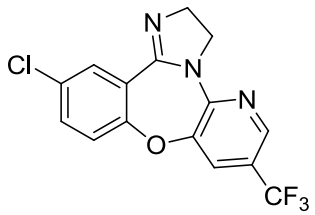
J= 8.4 Hz, 2H, $H_{Imidazoline}$) ppm. **^{13}C NMR** (75 MHz, DMSO-d_6) δ 154.8, 153.6, 148.3, 142.3, 139.9, 133.8, 133.8, 130.9, 125.9, 121.4, 120.9, 51.9, 48.8 ppm. **HRMS** (ESI), m/z calcd for $C_{13}H_{10}N_4O$ $[M+H]^+$ 238.0855, found 238.0869.



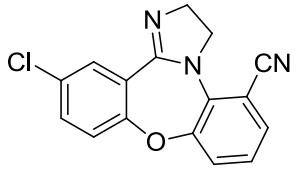
2,3-Dihydrodibenzo[*b,f*]imidazo[1,2-*d*][1,4]oxazepine-7-carbonitrile (10e) was synthesized starting from **14a** (162 mg, 1.000 mmol), 4-chloro-3-nitrobenzonitrile (182 mg, 1.000 mmol) and K_2CO_3 (414 mg, 3.000 mmol) in 54% (141 mg, 0.539 mmol) yield; yellow solid; **mp** 142-145 °C. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.79-7.87 (m, 2H, H_{Ar}), 7.63-7.71 (m, 1H, H_{Ar}), 7.55-7.63 (m, 1H, H_{Ar}), 7.42 (d, *J*= 8.1 Hz, 1H, H_{Ar}), 7.30 (t, *J*= 7.3 Hz, 1H, H_{Ar}), 7.21 (d, *J*= 8.1 Hz, 1H, H_{Ar}), 3.93–4.17 (m, 4H, $H_{Imidazoline}$) ppm. **^{13}C NMR** (75 MHz, DMSO-d_6) δ 156.4, 156.1, 147.2, 138.1, 133.5, 130.7, 129.7, 125.8, 125.1, 122.1, 120.9, 118.4, 118.2, 103.7, 51.9, 49.9 ppm. **HRMS** (ESI), m/z calcd for $C_{16}H_{11}N_3O$ $[M+H]^+$ 261.0902 found 261.0910.



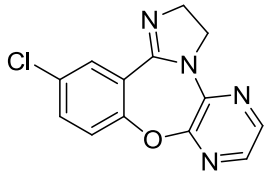
2,3-Dihydrodibenzo[*b,f*]imidazo[1,2-*d*][1,4]oxazepine-5-carbonitrile (10f) was synthesized starting from **14a** (162 mg, 1.000 mmol), 2,3-difluorobenzonitrile (139 mg, 1.000 mmol) and K_2CO_3 (414 mg, 3.000 mmol) in 61% (159 mg, 0.608 mmol) yield; colorless solid; **mp** 156-158 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (dd, *J*= 7.7, 1.6 Hz, 1H, H_{Ar}), 7.42-7.52 (m, 3H, H_{Ar}), 7.26-7.31 (m, 1H, H_{Ar}), 7.23 (d, *J*= 8.1 Hz, 1H, H_{Ar}), 7.10 (t, *J*= 7.7 Hz, 1H, H_{Ar}), 4.53 (t, *J*= 9.6 Hz, 2H, $H_{Imidazoline}$), 4.19 (t, *J*= 9.6 Hz, 2H, $H_{Imidazoline}$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.7, 157.9, 152.0, 136.9, 133.2, 131.5, 130.8, 126.8, 126.1, 124.4, 122.9, 120.3, 117.5, 104.9, 52.9, 51.4 ppm. **HRMS** (ESI), m/z calcd for $C_{16}H_{11}N_3O$ $[M+H]^+$ 261.0902 found 261.0917.



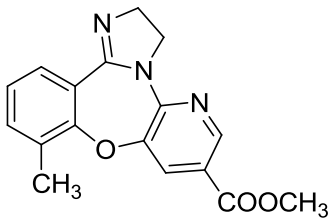
12-Chloro-7-(trifluoromethyl)-2,3-dihydrobenzo[*f*]imidazo[1,2-*d*]pyrido [3,2-*b*][1,4]oxazepine (10g) was synthesized starting from **14b** (197 mg, 1.000 mmol), 2,3-dichloro-5-(trifluoromethyl)pyridine (215 mg, 1.000 mmol) and K_2CO_3 (414 mg, 3.000 mmol) in 67% (228 mg, 0.671 mmol) yield; colorless solid; **mp** 173-175 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.52 (d, *J*= 1.5 Hz, 1H, H_{Py}), 8.10 (d, *J*= 1.5 Hz, 1H, H_{Py}), 7.89 (d, *J*= 2.7 Hz, 1H, H_{Ar}), 7.66 (dd, *J*= 8.7, 2.7 Hz, 1H, H_{Ar}), 7.50 (d, *J*= 8.7 Hz, 1H, H_{Ar}), 4.21 (t, *J*= 9.5 Hz, 2H, $H_{Imidazoline}$), 4.02 (t, *J*= 9.5 Hz, 2H, $H_{Imidazoline}$) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6) δ 159.8, 157.2, 146.5, 143.0, 142.9, 141.2, 134.9, 129.3 (q), 125.7, 124.3 (d, *J*= 107.8 Hz), 123.3 (d, *J*= 272.9 Hz), 122.0, 113.6, 51.6, 41.6. ppm. **HRMS** (ESI), m/z calcd for $C_{15}H_9ClF_3N_3O$ $[M+H]^+$ 339.0386, found 339.03397.



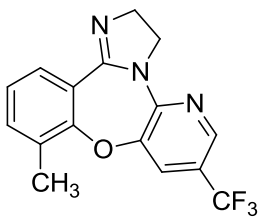
12-Chloro-2,3-dihydrodibenzo[*b,f*]imidazo[1,2-*d*][1,4]oxazepine-5-carbonitrile (10h) was synthesized starting from **14b** (197 mg, 1.000 mmol), 2,3-difluorobenzonitrile (139 mg, 1.000 mmol) and K_2CO_3 (414 mg, 3.000 mmol) in 64% (189 mg, 0.639 mmol) yield; colorless solid; **mp** 175-178 ^oC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ δ 7.81 (d, *J*= 2.6 Hz, 1H, H_{Ar}), 7.48 (dd, *J*= 3.7, 1.5 Hz, 1H, H_{Ar}), 7.46 (dd, *J*= 3.7, 1.5 Hz, 1H, H_{Ar}), 7.43 (d, *J*= 2.6 Hz, 1H, H_{Ar}), 7.41 (d, *J*= 2.6 Hz, 1H, H_{Ar}), 7.18 (d, *J*= 8.6 Hz, 1H, H_{Ar}), 7.11 (t, *J*= 7.9 Hz, 1H, H_{Ar}), 4.53 (t, *J*= 9.6 Hz, 2H, $H_{Imidazoline}$), 4.19 (t, *J*= 9.6 Hz, 2H, $H_{Imidazoline}$) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6) δ 154.8, 153.6, 148.3, 142.3, 139.9, 133.8, 133.8, 130.9, 125.9, 121.4, 120.9, 51.9, 48.8 ppm. **HRMS** (ESI), m/z calcd for $C_{16}H_{10}ClN_3O$ $[M+H]^+$ 295.0512, found 295.0519.



12-Chloro-2,3-dihydrobenzo[*f*]imidazo[1,2-*d*]pyrazino[2,3-*b*][1,4]oxazepine (10i) was synthesized starting from **14b** (197 mg, 1.000 mmol), 2,3-dichloropyrazine (149 mg, 1.000 mmol) and K_2CO_3 (414 mg, 3.000 mmol) in 66% (189 mg, 0.660 mmol) yield; colorless solid; **mp** 158-161 ^oC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (d, *J*= 2.6 Hz, 1H, $H_{Pyrazine}$), 8.09 (d, *J*= 2.6 Hz, 1H, $H_{Pyrazine}$), 7.87 (d, *J*= 2.7 Hz, 1H, H_{Ar}), 7.48 (dd, *J*= 8.7, 2.7 Hz, 1H, H_{Ar}), 7.37 (d, *J*= 8.7 Hz, 1H, H_{Ar}), 4.27 (t, *J*= 9.1 Hz, 2H, $H_{Imidazoline}$), 4.15 (t, *J*= 9.1 Hz, 2H, $H_{Imidazoline}$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.4, 152.7, 148.8, 142.2, 139.7, 134.4, 133.6, 131.3, 130.7, 123.2, 121.9, 51.8, 49.2 ppm. **HRMS** (ESI), m/z calcd for $C_{13}H_9ClN_4O$ $[M+H]^+$ 272.0465, found 272.0473.

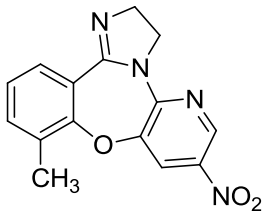


Methyl 10-methyl-2,3-dihydrobenzo[*f*]imidazo[1,2-*d*]pyrido[3,2-*b*][1,4]oxazepine-7-carboxylate (10j) was synthesized starting from **14c** (176 mg, 1.000 mmol), methyl 5,6-dichloronicotinate (206 mg, 1.000 mmol) and K_2CO_3 (414 mg, 3.000 mmol) in 41% (127 mg, 0.410 mmol) yield; colorless solid; **mp** 173-175 ^oC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.75 (d, *J*= 1.8 Hz, 1H, H_{Py}), 8.02 (d, *J*= 1.8 Hz, 1H, H_{Py}), 7.82 (d, *J*= 7.7 Hz, 1H, H_{Ar}), 7.38 (d, *J*= 7.7 Hz, 1H, H_{Ar}), 7.14 (t, *J*= 7.7 Hz, 1H, H_{Ar}), 4.30 (t, *J*= 9.0 Hz, 2H, $H_{Imidazoline}$), 4.11 (t, *J*= 9.0 Hz, 2H, $H_{Imidazoline}$), 3.94 (s, 3H, $COOCH_3$), 2.56 (s, 3H, $ArCH_3$) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6) δ 164.4, 159.8, 149.4, 146.6, 144.9, 136.8, 133.8, 131.8, 130.2, 126.1, 125.6, 124.2, 53.1, 51.9, 50.3, 16.8 ppm. **HRMS** (ESI), m/z calcd for $C_{17}H_{15}N_3O_3$ $[M+H]^+$ 309.1113, found 309.1126.



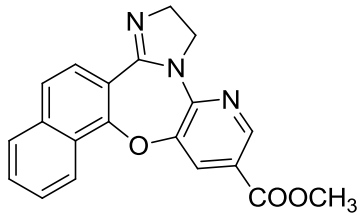
10-Methyl-7-(trifluoromethyl)-2,3-dihydrobenzo[*f*]imidazo[1,2-*d*]pyrido[3,2-*b*][1,4]oxazepine (10k) was synthesized starting from **14c** (176 mg, 1.000 mmol), 2,3-dichloro-5-(trifluoromethyl)pyridine (215 mg, 1.000 mmol) and K_2CO_3 (414 mg, 3.000 mmol) in 53% (129 mg, 0.527 mmol) yield; colorless solid; **mp** 142-144 ^oC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (s, 1H, H_{Py}), 7.88 (d, *J*= 7.7 Hz, 1H, H_{Ar}), 7.67 (s, 1H, H_{Py}), 7.40 (d, *J*= 7.7 Hz, 1H, H_{Ar}), 7.17 (t, *J*= 7.7 Hz, 1H, H_{Ar}), 4.31 (t,

J= 9.4 Hz, 1H, $H_{Imidazoline}$), 4.13 (t, *J*= 9.4 Hz, 1H, $H_{Imidazoline}$), 2.54 (s, 3H, $ArCH_3$). ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.1, 154.2, 149.4, 142.9, 141.4 (q), 135.1, 129.9, 129.7 (d, J = 206.9 Hz), 129.3, 125.7 (q), 125.5, 123.3 (d, J = 271.5 Hz), 121.2, 120.6, 51.4, 49.4, 16.5 ppm. **HRMS** (ESI), m/z calcd for $C_{16}H_{12}F_3N_3O$ $[M+H]^+$ 319.0932, found 319.0941.



10-Methyl-7-nitro-2,3-dihydrobenzo[*f*]imidazo[1,2-*d*]pyrido[3,2-*b*][1,4] oxazepine (10l) was synthesized starting from **14c** (176 mg, 1.000 mmol), 2,3-dichloro-5-nitropyridine (192 mg, 1.000 mmol) and K_2CO_3 (414 mg, 3.000 mmol) in 68% (201 mg, 0.678 mmol) yield; colorless solid; **mp** 200-203 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.01 (d, *J*= 2.1 Hz, 1H, H_{Py}), 8.21 (d, *J*= 2.1 Hz, 1H, H_{Py}), 7.86 (d, *J*= 7.6 Hz, 1H, H_{Ar}), 7.42 (d, *J*= 7.4 Hz, 1H, H_{Ar}), 7.18 (t, *J*= 7.6 Hz, 1H, H_{Ar}), 4.34 (t, *J*= 9.0 Hz, 2H, $H_{Imidazoline}$), 4.16 (t, *J*= 9.0 Hz, 2H, $H_{Imidazoline}$), 2.56 (s, 3H, $ArCH_3$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.2, 153.7, 150.8, 141.7, 141.2, 138.6, 135.3, 130.0, 129.3, 125.7, 123.6, 121.1, 51.8, 49.8, 16.4 ppm. **HRMS** (ESI), m/z calcd for $C_{15}H_{12}N_4O_3$ $[M+H]^+$ 296.0909, found 296.0917.

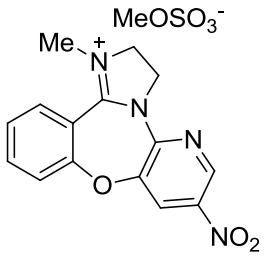
Methyl 2,3-dihydroimidazo[1,2-*d*]naphtho[2,1-*f*]pyrido[3,2-*b*][1,4]oxazepine-7-carboxylate (10m)



was synthesized starting from **14d** (212 mg, 1.000 mmol), methyl 5,6-dichloronicotinate (206 mg, 1.000 mmol) and K_2CO_3 (414 mg, 3.000 mmol) in 40% (138 mg, 0.400 mmol) yield; yellow solid; **mp** 215-218 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.79 (d, *J*= 1.8 Hz, 1H, H_{Py}), 8.61 (d, *J*= 8.2 Hz, 1H, H_{Ar}), 8.20 (d, *J*= 1.8 Hz, 1H, H_{Py}), 8.06 (t, *J*= 8.8 Hz, 1H, H_{Ar}), 7.88 (t, *J*= 9.5 Hz, 1H, H_{Ar}), 7.63-7.78 (m, 3H, H_{Ar}), 4.41 (t, *J*= 9.3 Hz, 2H, $H_{Imidazoline}$), 4.19 (t, *J*= 9.3 Hz, 2H, $H_{Imidazoline}$), 3.96 (s, 3H, $COOCH_3$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.9, 157.9, 153.1, 149.3, 146.6, 142.8, 136.8, 130.9, 129.3, 128.9, 127.9, 127.5, 126.2, 125.4, 122.8, 121.3, 115.5, 52.4, 50.6, 49.3 ppm. **HRMS** (ESI), m/z calcd for $C_{20}H_{15}N_3O_3$ $[M+H]^+$ 345.1113, found 345.1120.

2.3. Screening of reaction conditions for quaternization imidazoline-fused [1,4]oxazepine 10a.

Compound **10a** (30.0 mg, 0.106 mmol) and an alkylating agent (0.213 mmol) were combined in dry solvent in a glass test tube with a screw cap. The reaction was monitored by TLC (ethyl acetate/hexane 8:2). After completion of the reaction, the mixture was concentrated *in vacuo*, diluted with 3 mL of Et_2O. The crystals of compound **11a** thus formed were filtered and air-dried.



1-Methyl-7-nitro-2,3-dihydrobenzo[*f*]imidazo[1,2-*d*]pyrido[3,2-*b*][1,4]oxaze-pin-1-ium methyl sulfate (11a) yellow solid; **mp** >300 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.22 (d, *J*= 2.3 Hz, 1H, H_{Py}), 8.92 (d, *J*= 2.3 Hz, 1H, H_{Py}), 8.02-7.96 (m, 1H, H_{Ar}), 7.94 (dd, *J*= 8.1, 1.3 Hz, 1H, H_{Ar}), 7.84 (d, *J*= 8.1 Hz, 1H, H_{Ar}),

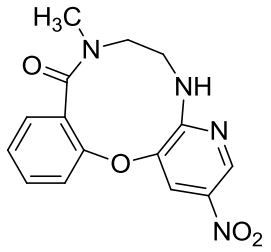
7.63 (t, *J*= 7.7 Hz, 1H, H_{Ar}), 4.69-4.55 (m, 2H, $H_{Imidazoline}$), 4.33 (t, *J*= 10.3 Hz, 2H, $H_{Imidazoline}$), 3.52 (s, 3H, N^+CH_3), 3.38 (s, 3H, SO_2OCH_3). ppm. **^{13}C NMR** (100 MHz, DMSO-d_6) δ 160.8, 157.8, 147.9, 144.7, 143.2, 142.0, 138.6, 132.6, 127.5, 126.7, 123.0, 114.9, 53.3, 51.9, 48.3, 38.1 ppm. **HRMS** (ESI), m/z calcd for $C_{16}H_{16}N_4O_7S$ $[M+H]^+$ 408.0740, found 408.0763.

2.4. Optimization of reaction conditions for the ring expansion 11a→12a.

Compound **11a** (15.0 mg, 0.106 mmol) was added to the prepared basic solution. The reaction was monitored by TLC (ethyl acetate/hexane 8:2). After completion of the reaction, the mixture was concentrated *in vacuo*, water (2 mL) and EtOAc (2 mL) were added to the residue. The organic layer was separated, washed with water, brine, dried over Na_2SO_4 and purified by column chromatography eluting with EtOAc-C_6H_{14} 6:4.

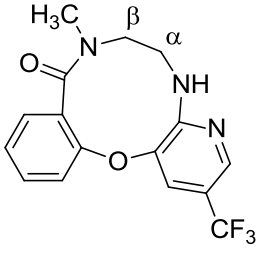
2.5. One-pot preparation of compounds 12a-q.

General Procedure 2: To a solution of respective imidazoline-fused [1,4]oxazepine **10a-m** (0.140 mmol) in acetonitrile (9.5 mL) dimethyl sulfate (23 µl, 0.280 mmol) or diethyl sulfate (36 µl, 0.280 mmol) was added. The resulting mixture was stirred overnight at room temperature (dimethyl sulfate) or at reflux (diethyl sulfate). Then 0.2% aqueous solution K_2CO_3 (9.5 mL, 0.140 mmol) was added at room temperature. After 6 h, EtOAc (2x4 mL) were added. The organic layer was separated, washed with water, brine, dried over Na_2SO_4 and purified by column chromatography eluting with an appropriate gradient of EtOAc in C_6H_{14}.



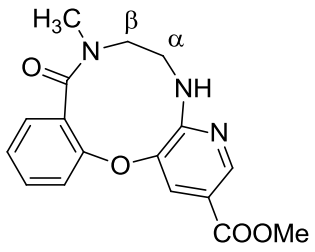
8-Methyl-2-nitro-7,8-dihydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]oxadiazecin-9(6*H*)-one (12a) was synthesized according to General Procedure 2 starting from **10a** (40 mg, 0.140 mmol) in 76% (33 mg, 0.105 mmol) yield; colorless solid; R_f ($EtOAc/C_6H_{14}$ = 1/1): 0.49; **mp** 173-176 °C. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.83 (d, *J*= 2.3 Hz, 1H, H_{Py}), 8.05 (d, *J*= 1.9 Hz, 1H, H_{Py}), 7.40-7.50 (m, 1H, H_{Ar}), 7.12-7.36 (m, 4H, NH+H_{Ar}), 3.74-3.92 (br.s, 1H, β-CH), 3.34-3.64 (m, 3H, α-CH+β-CH), 2.75 (s, 3H, NCH_3) ppm. **^{13}C NMR** (75 MHz, DMSO-d_6) δ 167.5, 157.9, 152.1, 142.7, 136.2, 135.4, 131.3, 130.0, 125.2, 125.0, 123.9, 118.8, 52.7, 43.2, 33.7 ppm. **HRMS** (ESI), m/z calcd for $C_{15}H_{14}N_4O_4$ $[M+H]^+$ 314.1015, found 314.1027.

Using the same protocol, compound **12a** was prepared from compound **10a** (1,040 mg, 3.700 mmol) in 78% (903 mg, 2.89 mmol) yield.

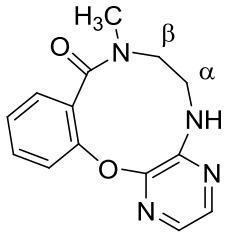


8-Methyl-2-(trifluoromethyl)-7,8-dihydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7] oxadiazecin-9(6*H*)-one (12b) was synthesized according to General Procedure 2 starting from **10b** (43 mg, 0.140 mmol), in 71% (34 mg, 0.101 mmol) yield; yellow solid; R_f ($EtOAc/C_6H_{14}$ = 1/1): 0.53; **mp** 129-132 °C. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.27 (s, 1H, H_{Py}), 7.74 (d, *J*= 1.7 Hz, 1H, H_{Py}), 7.47-7.38 (m,

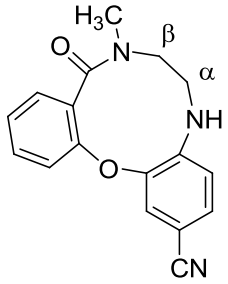
1H, H_{Ar}), 7.17-7.03 (m, 3H, H_{Ar}), 6.24-6.38 (br.s, 1H, NH), 3.72-3.91 (br.s, 1H, β-CH), 3.26-3.52 (m, 3H, α-CH+β-CH), 2.72 (s, 3H, NCH_3) ppm. **^{13}C NMR** (75 MHz, DMSO-d_6) δ 167.5, 156.8, 151.9, 142.18 (q), 136.7, 130.9, 129.6, 127.8, 124.8, 124.4 (d, *J*= 271.1 Hz), 123.4, 118.2, 115.3 (q), 53.6, 43.5, 33.4 ppm. **HRMS** (ESI), m/z calcd for $C_{16}H_{14}F_3N_3O_2$ $[M+H]^+$ 337.1038, found 337.1051.



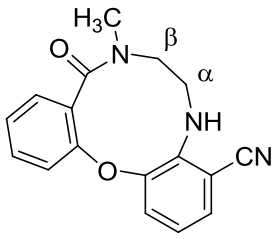
Methyl 8-methyl-9-oxo-6,7,8,9-tetrahydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]oxadiazecine-2-carboxylate (12c) was synthesized according to General Procedure 2 starting from **10c** (41 mg, 0.140 mmol), in 65% (30 mg, 0.092 mmol) yield; yellow solid; $\boldsymbol{R_f}$ ($EtOAc/C_6H_{14}$ = 1/1): 0.58; **mp** 105-108 °C. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.48 (d, *J*= 1.6 Hz, 1H, H_{Py}), 7.69 (d, *J*= 1.6 Hz, 1H, H_{Py}), 7.42 (dd, *J*= 10.4, 4.2 Hz, 1H, H_{Ar}), 7.07-7.19 (m, 3H, H_{Ar}), 6.48-6.59 (br.s, 1H, NH), 3.79 (m, 4H, $COOCH_3$+ β-CH), 3.37-3.55 (m, 3H, α-CH+β-CH), 2.73 (s, 3H, NCH_3) ppm. **^{13}C NMR** (75 MHz, DMSO-d_6) δ 167.5, 165.3, 157.1, 152.3, 147.1, 136.5, 131.1, 130.4, 129.9, 125.0, 123.7, 118.4, 115.9, 53.2, 52.2, 43.3, 33.6 ppm. **HRMS** (ESI), m/z calcd for $C_{17}H_{17}N_3O_4$ $[M+H]^+$ 327.1219, found 327.1234.



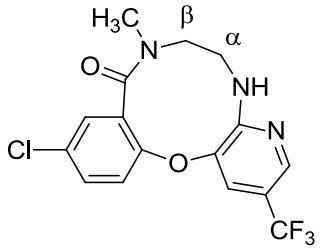
8-Methyl-7,8-dihydro-5*H*-benzo[*i*]pyrazino[2,3-*b*][1,4,7]oxadiazecin-9(6*H*)-one (12d) was synthesized according to General Procedure 2 starting from **10d** (33 mg, 0.140 mmol), in 75% (28 mg, 0.104 mmol) yield; yellow solid; $\boldsymbol{R_f}$ ($EtOAc/C_6H_{14}$ = 1/1): 0.53; **mp** 120-123 °C. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.92 (d, *J*= 2.6 Hz, 1H, $H_{Pyrazine}$), 7.51 (d, *J*= 2.6 Hz, 1H, $H_{Pyrazine}$), 7.39-7.48 (m, 1H, H_{Ar}), 7.12-7.28 (m, 3H, H_{Ar}), 6.36 (t, *J* = 6.5 Hz, 1H, NH), 3.55-3.66 (m, 2H, β-CH), 3.42-3.50 (m, 2H, α-CH), 2.75 (s, 3H, NCH_3) ppm. **^{13}C NMR** (75 MHz, DMSO-d_6) δ 167.5, 151.9, 149.7, 145.5, 140.0, 131.2 130.1 (2C), 125.6, 123.9, 118.7, 52.5, 42.5, 33.9 ppm. **HRMS** (ESI), m/z calcd for $C_{14}H_{14}N_4O_2$ $[M+H]^+$ 270.1117, found 270.1126.



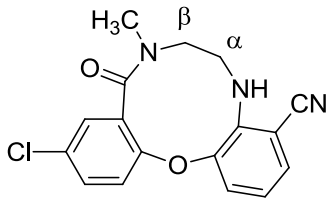
8-Methyl-9-oxo-6,7,8,9-tetrahydro-5*H*-dibenzo[*b,i*][1,4,7]oxadiazecine-2-carbonitrile (12e) was synthesized according to General Procedure 2 starting from **10e** (37 mg, 0.140 mmol), in 51% (21 mg, 0.072 mmol) yield; yellow solid; $\boldsymbol{R_f}$ ($EtOAc/C_6H_{14}$ = 1/1): 0.57; **mp** 119-122 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, *J*= 1.8 Hz, 1H, H_{Ar}), 7.34-7.41 (m, 2H, H_{Ar}), 7.21 (dd, *J*= 7.6, 1.8 Hz, 1H, H_{Ar}), 7.10 (t, *J*= 7.6, 1H, H_{Ar}), 7.05 (d, *J*= 8.4 Hz, 1H, H_{Ar}), 6.89 (d, *J*= 8.4 Hz, 1H, H_{Ar}), 4.27-4.41 (br.s, 1H, NH), 3.55-3.68 (m, 2H, β-CH), 3.40-3.52 (m, 1H, α-CH), 3.20-3.34 (m, 1H, α-CH), 2.84 (s, 1H, NCH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.3, 154.2, 146.6, 143.0, 131.4, 130.5, 129.2, 128.5, 125.1, 124.2, 120.5, 117.6, 114.0, 101.4, 53.1, 46.2, 33.9 ppm. **HRMS** (ESI), m/z calcd for $C_{17}H_{15}N_3O_2$ $[M+H]^+$ 293.1164, found 293.1179.



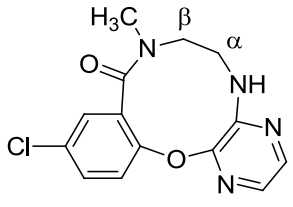
8-Methyl-9-oxo-6,7,8,9-tetrahydro-5*H*-dibenzo[*b,i*][1,4,7]oxadiazecine-4-carbonitrile (12f) was synthesized according to General Procedure 2 starting from **10f** (37 mg, 0.140 mmol), in 57% (23 mg, 0.078 mmol) yield; yellow solid; R_f (EtOAc/C_6H_{14} = 1/1): 0.53; **mp** 140-143 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39-7.27 (m, 4H, H_{Ar}), 7.12 (t, *J*= 7.5 Hz, 1H, H_{Ar}), 6.83-6.93 (m, 2H, H_{Ar}), 4.46-4.28 (br.s, 1H, NH), 3.55-3.79 (m, 3H, β-CH+α-CH), 3.31-3.35 (m, 1H α-CH), 2.99 (s, 3H, NCH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.1, 153.1, 145.8, 143.2, 130.9, 130.2, 129.9, 129.5, 125.1, 123.2, 120.1, 117.1, 114.8, 101.6, 53.9, 46.9, 33.2 ppm. **HRMS** (ESI), m/z calcd for $C_{17}H_{15}N_3O_2$ $[M+H]^+$ 293.1164, found 293.1172.



11-Chloro-8-methyl-2-(trifluoromethyl)-7,8-dihydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]oxadiazecin-9(6*H*)-one (12g) was synthesized according to General Procedure 2 starting from **10g** (48 mg, 0.140 mmol), in 70% (36 mg, 0.097 mmol) yield; yellow solid; R_f (EtOAc/C_6H_{14} = 1/1): 0.47; **mp** 117-120 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 (s, 1H, H_{Py}), 7.59 (d, *J*= 1.9 Hz, 1H, H_{Py}), 7.33 (dd, *J*= 8.9, 2.6 Hz, 1H, H_{Ar}), 7.18 (d, *J*= 2.6 Hz, 1H, H_{Ar}), 7.01 (d, *J*= 8.9 Hz, 1H, H_{Ar}), 4.43-4.52 (t, *J*= 11.9 Hz, 1H, NH), 4.07-4.20 (m, 1H, β-CH), 3.58-3.71 (m, 1H, β-CH), 3.39-3.53 (m, 1H, α-CH), 3.25-3.38 (m, 1H, α-CH), 2.83 (s, 3H, NCH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.4, 155.6, 150.0, 142.3 (q), 136.5, 130.9, 128.9, 128.5, 127.9 (q), 125.3, 123.4 (d, *J* = 271.4 Hz), 119.1, 118.4 (d, *J* = 33.7 Hz), 54.2, 43.9, 33.5 ppm. **HRMS** (ESI), m/z calcd for $C_{16}H_{13}ClF_3N_3O_2$ $[M+H]^+$ 371.0648, found 371.0654.

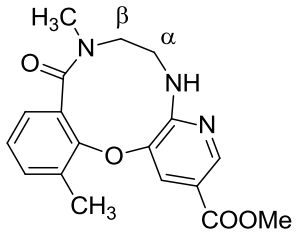


11-chloro-8-methyl-9-oxo-6,7,8,9-tetrahydro-5H-dibenzo[b,i][1,4,7]oxadiazecine-4-carbonitrile (12h) was synthesized according to General Procedure 2 starting from **10h** (41 mg, 0.140 mmol), in 59% (27 mg, 0.083 mmol) yield; yellow solid; R_f (EtOAc/C_6H_{14} = 1/1): 0.50; **mp** 155-158 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (dd, *J*= 7.9, 1.5 Hz, 1H, H_{Ar}), 7.36 (d, *J*= 2.6 Hz, 1H, H_{Ar}), 7.33 (dd, *J*= 7.9, 1.5 Hz, 1H, H_{Ar}), 7.27 (dd, *J*= 8.8, 2.6 Hz, 1H, H_{Ar}), 6.91 (t, *J*= 7.9 Hz, 1H, H_{Ar}), 6.80 (d, *J*= 8.8 Hz, 1H, H_{Ar}), 4.38 (t, *J* = 6.3 Hz, 1H, NH), 3.67-3.77 (m, 2H, β-CH), 3.52-3.65 (m, 1H, α-CH), 3.33-3.48 (s, 1H, α-CH), 2.99 (s, 3H, NCH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.6, 151.8, 145.6, 143.0, 130.7, 130.4, 129.7, 129.3, 128.4, 126.6, 120.3, 116.9, 116.2, 101.8, 53.9, 46.9, 33.3 ppm. **HRMS** (ESI), m/z calcd for $C_{17}H_{14}ClN_3O_2$ $[M+H]^+$ 327.7650, found 327.7664.

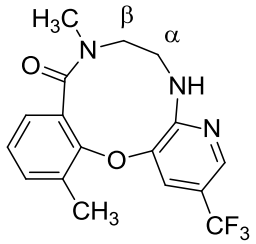


11-Chloro-8-methyl-7,8-dihydro-5*H*-benzo[*i*]pyrazino[2,3-*b*][1,4,7]oxadiazecin-9(6*H*)-one (12i) was synthesized according to General Procedure 2 starting from **10i** (38 mg, 0.140 mmol), in 58% (24 mg, 0.079 mmol) yield; R_f (EtOAc/C_6H_{14} = 1/1): 0.50; yellow solid; **mp** 130-133 °C. **^{1}H NMR** (400

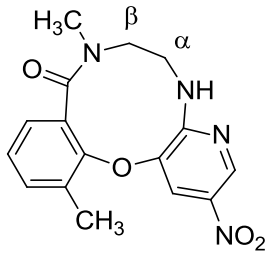
MHz, $CDCl_3$) δ 7.96 (d, *J*= 2.5 Hz, 1H, $H_{Pyrazine}$), 7.70 (d, *J*= 2.5 Hz, 1H, $H_{Pyrazine}$), 7.24-7.37 (m, 3H, H_{Ar}), 4.63 (br.s, 1H, NH), 3.70-3.86 (br.s, 2H, β-CH), 3.47-3.62 (br.s, 2H, α-CH), 2.92 (s, 3H, NCH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.6, 150.1, 148.9, 145.4, 139.8, 131.8, 130.9, 129.8, 128.9, 126.3, 119.3, 53.1, 43.4, 33.9 ppm. **HRMS** (ESI), m/z calcd for $C_{14}H_{13}ClN_4O_2$ $[M+H]^+$ 304.0727, found 304.0739.



Methyl 8,13-dimethyl-9-oxo-6,7,8,9-tetrahydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]oxadiazecine-2-carboxylate (12j) was synthesized according to General Procedure 2 starting from **10j** (43 mg, 0.140 mmol), in 61% (29 mg, 0.085 mmol) yield; yellow solid; R_f (EtOAc/C_6H_{14} = 1/1): 0.54; **mp** 159-162 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.66 (d, *J*= 1.9 Hz, 1H, H_{Py}), 7.88 (d, *J*= 1.9 Hz, 1H, H_{Py}), 7.29 (d, *J*= 7.6 Hz, 1H, H_{Ar}), 7.02 (t, *J*= 7.6 Hz, 1H, H_{Ar}), 6.95 (dd, *J*= 7.6, 1.5 Hz, 1H, H_{Ar}), 4.53 (d, *J*= 10.9 Hz, 1H, NH), 4.25-4.38 (m, 1H, β-CH), 3.86 (s, 3H, $COOCH_3$), 3.74-3.84 (m, 1H, β-CH), 3.40-3.49 (m, 1H, α-CH), 3.17-3.27 (m, 1H, α-CH), 2.75 (s, 3H, NCH_3), 2.42 (s, 3H, $ArCH_3$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.3, 165.4, 155.7, 149.0, 146.9, 137.7, 132.3, 129.8, 129.5, 126.8, 123.1, 122.9, 118.2, 53.9, 51.8, 42.6, 33.7, 17.2 ppm. **HRMS** (ESI), m/z calcd for $C_{18}H_{19}N_3O_4$ $[M+H]^+$ 341.1376, found 341.1389.

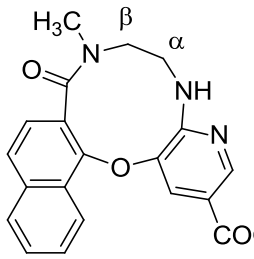


8,13-Dimethyl-2-(trifluoromethyl)-7,8-dihydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]oxadiazecin-9(6*H*)-one (12k) was synthesized according to General Procedure 2 starting from **10k** (45 mg, 0.140 mmol), in 70% (34 mg, 0.097 mmol) yield; yellow solid; R_f (EtOAc/C_6H_{14} = 1/1): 0.54; **mp** 112-115 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 (d, *J*= 0.8 Hz, 1H, H_{Py}), 7.58 (d, *J*= 2.0 Hz, 1H, H_{Py}), 7.29 (d, *J*= 7.6 Hz, 1H, H_{Ar}), 7.01 (t, *J*= 7.6 Hz, 1H, H_{Ar}), 6.91 (dd, *J*= 7.6, 1.3 Hz, 1H, H_{Ar}), 4.29-4.39 (m, 1H, β-CH), 4.06 (d, *J* = 11.4 Hz, 1H, NH), 3.71-3.82 (m, 1H, β-CH), 3.27-3.35 (m, 1H α-CH), 3.20 (dd, *J* = 14.7, 2.4 Hz, 1H, α-CH), 2.72 (s, 3H, NCH_3), 2.42 (s, 3H, $ArCH_3$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.2, 155.2, 148.5, 141.7 (q), 137.7, 132.3, 129.4, 126.5 (2C), 123.6 (d, *J*= 271.2 Hz), 122.9 (2C), 118.5 (d, *J*= 33.4 Hz), 54.3, 42.9, 33.4, 17.2 ppm. **HRMS** (ESI), m/z calcd for $C_{17}H_{16}F_3N_3O_2$ $[M+H]^+$ 351.1195, found 351.1203.

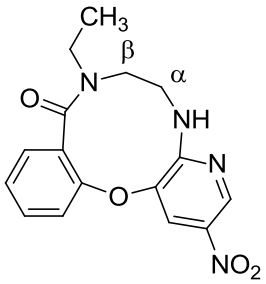


8,13-dimethyl-2-nitro-7,8-dihydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7]oxadiazecin-9(6*H*)-one (12l) was synthesized according to General Procedure 2 from **10l** (41 mg, 0.140 mmol), in 79% (36 mg, 0.109 mmol) yield; colorless solid; R_f (EtOAc/C_6H_{14} = 1/1): 0.50; **mp** 185-188 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.91 (d, *J*= 2.3 Hz, 1H, H_{Py}), 8.06 (d, *J*= 2.3 Hz, 1H, H_{Py}), 7.32 (d, *J*= 7.3 Hz, 1H, H_{Ar}), 7.06 (t, *J*= 7.3 Hz, 1H, H_{Ar}), 6.98 (d, *J*= 7.3 Hz, 1H, H_{Ar}), 4.65 (d, *J*= 10.4 Hz, 1H, NH), 4.24-4.37 (m, 1H, β-CH), 3.73-3.86 (m, 1H, β-CH), 3.54 (d, *J*= 14.7 Hz, 1H, α-CH), 3.27 (dd, *J*= 14.7, 3.2 Hz, 1H, α-CH), 2.77 (s, 3H, $NHCH_3$), 2.44 (s, 3H, $ArCH_3$) ppm. **^{13}C NMR**

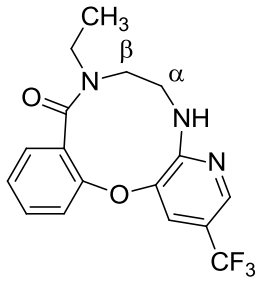
(100 MHz, $CDCl_3$) δ 168.2, 156.4, 148.6, 141.7, 137.3, 137.1, 132.7, 129.7, 127.0, 123.9, 123.6, 123.3, 53.4, 42.7, 33.9, 17.1 ppm. **HRMS** (ESI), m/z calcd for $C_{16}H_{16}N_4O_4$ $[M+H]^+$ 328.1172, found 328.1190.



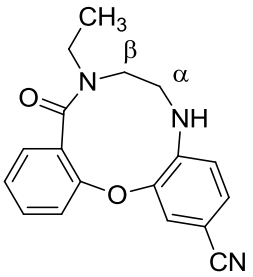
Methyl 8-methyl-9-oxo-6,7,8,9-tetrahydro-5*H*-naphtho[2,1-*i*]pyrido[3,2-*b*][1,4,7]oxadiazecine-2-carboxylate (12m) was synthesized according to General Procedure 2 starting from **10m** (48 mg, 0.140 mmol), in 64% (34 mg, 0.090 mmol) yield; yellow solid; $\boldsymbol{R_f}$ (EtOAc/C_6H_{14} = 1/1): 0.47; **mp** 181-183 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.69 (d, *J*= 1.9 Hz, 1H, H_{Py}), 8.43-8.48 (m, 1H, H_{Ar}), 7.98 (d, *J*= 1.9 Hz, 1H, H_{Py}), 7.87-7.92 (m, 1H, H_{Ar}), 7.61-7.69 (m, 3H, H_{Ar}), 7.18 (d, *J*= 8.5 Hz, 1H, H_{Ar}), 5.04 (br.s, 1H, NH), 4.28-4.37 (m, 1H, β-CH), 3.87 (s, 3H, $COOCH_3$), 3.74-3.86 (m, 1H, β-CH), 3.50 (d, *J*= 14.6 Hz, 1H, α-CH), 3.22-3.31 (m, 1H, α-CH), 2.84 (s, 3H, $NHCH_3$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.5, 165.3, 156.7, 153.1, 148.4, 146.6, 144.0, 136.8, 132.4, 129.3, 127.5, 126.7 (2), 126.1, 125.4, 123.2, 120.7, 117.5, 53.8, 52.3, 42.6, 33.4 ppm. **HRMS** (ESI), m/z calcd for $C_{21}H_{19}N_3O_4$ $[M+H]^+$ 377.1376, found 377.1385.



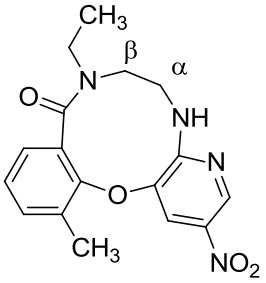
8-Ethyl-2-nitro-7,8-dihydro-5H-benzo[*i*]pyrido[3,2-*b*][1,4,7]oxadiazecin-9(6*H*)-one (12n) was synthesized according to General Procedure 2 starting from **10a** (40 mg, 0.140 mmol), in 48% (22 mg, 0.067 mmol) yield; colorless solid; $\boldsymbol{R_f}$ (EtOAc/C_6H_{14} = 1/1): 0.59; **mp** 142-145 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.93 (d, *J*= 2.2 Hz, 1H, H_{Py}), 8.15 (d, *J*= 2.2 Hz, 1H, H_{Py}), 7.38-7.45 (m, 1H, H_{Ar}), 7.12-7.21 (m, 3H, H_{Ar}), 4.83-4.91 (br.s, 1H, NH), 4.11-4.26 (br.s, 1H, β-CH), 3.34-3.70 (m, 4H, α-CH+β-CH+N$\underline{CH_2}CH_3$), 2.66-2.82 (br.s, 1H, α-CH), 1.16 (t, *J*= 7.2 Hz, 3H, $NCH_2\underline{CH_3}$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.4, 157.2, 150.8, 142.0, 136.9, 136.1, 131.1, 129.6, 125.5, 124.1, 123.8, 118.4, 50.2, 44.0, 40.1, 12.6 ppm. **HRMS** (ESI), m/z calcd for $C_{16}H_{16}N_4O_4$ $[M+H]^+$ 328.1172, found 328.1189.



8-Ethyl-2-(trifluoromethyl)-7,8-dihydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7] oxadiazecin-9(6*H*)-one (12o) was synthesized according to General Procedure 2 starting from **10b** (43 mg, 0.140 mmol), in 41% (20 mg, 0.057 mmol) yield; yellow solid; $\boldsymbol{R_f}$ (EtOAc/C_6H_{14} = 1/1): 0.57; **mp** 107-110 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (s, 1H, H_{Py}), 7.62 (d, *J*= 1.8 Hz, 1H, H_{Py}), 7.35-7.42 (m, 1H), 7.22 (dd, *J*= 8.3, 1.7 Hz, 1H, H_{Ar}), 7.10-7.18 (m, 1H, H_{Ar}), 7.05 (d, *J*= 8.3 Hz, 1H, H_{Ar}), 4.67-4.83 (br.s, 1H, NH), 3.99-4.15 (br.s, 1H, β-CH), 3.33-3.77 (m, 4H, α-CH+β-CH+N$\underline{CH_2}CH_3$), 2.74-2.89 (m, 1H, α-CH), 1.17 (t, *J*= 7.2 Hz, 3H, $NCH_2\underline{CH_3}$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.5, 156.2, 151.4, 142.0 (q), 136.6, 130.8, 129.5, 128.2 (q), 124.3, 123.5 (d, *J* = 271.3 Hz), 123.3, 118.2 (d, *J* = 33.4 Hz), 117.1, 50.8, 44.7, 39.8, 12.6 ppm. **HRMS** (ESI), m/z calcd for $C_{17}H_{16}F_3N_3O_2$ $[M+H]^+$ 351.1195, found 351.1203.

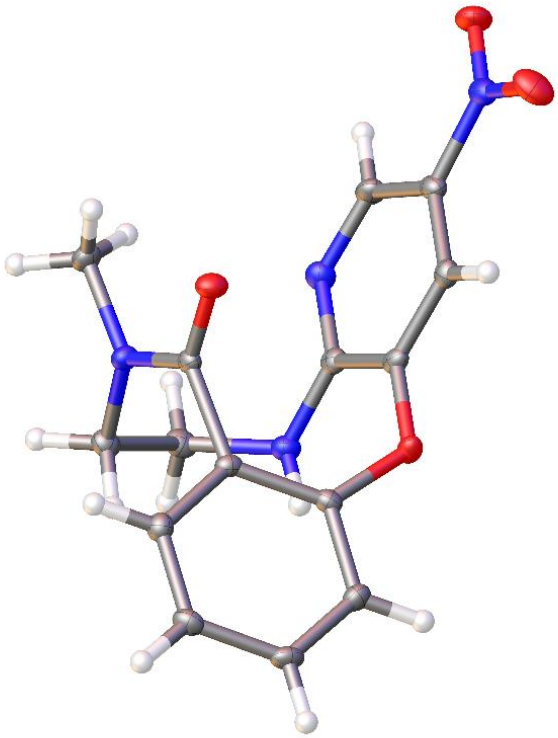


8-Ethyl-9-oxo-6,7,8,9-tetrahydro-5H-dibenzo[b,i][1,4,7]oxadiazecine-2-carbonitrile (12p) was synthesized according to General Procedure 2 starting from **10e** (37 mg, 0.140 mmol), in 37% (15 mg, 0.049 mmol) yield; yellow solid; $\boldsymbol{R_f}$ (EtOAc/C_6H_{14} = 1/1): 0.56; **mp** 87-100°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d, *J*= 1.9 Hz, 1H, H_{Ar}), 7.32-7.48 (m, 2H, H_{Ar}), 7.20 (dd, *J*= 7.6, 1.9 Hz, 1H, H_{Ar}), 7.10-7.13 (m, 1H, H_{Ar}), 7.00 (dd, *J*= 8.4, 0.6 Hz, 1H, H_{Ar}), 6.84 (d, *J*= 8.4 Hz, 1H, H_{Ar}), 3.86-3.98 (br.s, 1H, NH), 3.27-3.68 (m, 5H, α-CH+β-CH+N$\underline{CH_2}CH_3$), 2.73-2.87 (m, 1H, α-CH), 1.17 (t, *J*= 7.1 Hz, 3H, $NCH_2\underline{CH_3}$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.6, 152.1, 146.7), 141.7, 130.8, 130.5, 129.4, 128.3, 124.2, 122.9, 118.9, 118.1, 116.5, 102.2, 51.0, 46.8, 39.8, 12.6 ppm. **HRMS** (ESI), m/z calcd for $C_{18}H_{17}N_3O_2$ $[M+H]^+$ 307.1321, found 307.1338.



8-Ethyl-13-methyl-2-nitro-7,8-dihydro-5*H*-benzo[*i*]pyrido[3,2-*b*][1,4,7] oxadiazecin-9(6*H*)-one (12q) was synthesized according to General Procedure 2 starting from **10l** (41 mg, 0.140 mmol), in 51% (24 mg, 0.070 mmol) yield; colorless solid; $\boldsymbol{R_f}$ (EtOAc/C_6H_{14} = 1/1): 0.57; **mp** 151-154 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.91 (d, *J*= 2.2 Hz, 1H, H_{Py}), 8.09 (d, *J*= 2.2 Hz, 1H, H_{Py}), 7.90 (d, *J*= 8.3 Hz, 1H, H_{Ar}), 7.31 (d, *J*= 7.3 Hz, 1H, H_{Ar}), 7.05 (t, *J*= 7.3 Hz, 1H, H_{Ar}), 4.57 (d, *J* = 8.7 Hz, 1H, NH), 4.22-4.37 (m, 2H, β-CH), 3.61-3.74 (m, 1H, α-CH), 3.34-3.59 (m, 2H, N$\underline{CH_2}CH_3$), 3.33 (dd, *J*= 14.8, 3.3 Hz, 1H, α-CH), 2.44 (s, 3H, $ArCH_3$), 1.13 (t, *J*= 7.1 Hz, 3H, $CH_2\underline{CH_3}$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.4, 156.3, 148.7, 141.4, 137.1, 137.0, 132.7, 129.4, 127.1, 123.8, 123.5, 123.3, 50.4, 45.0, 39.9, 17.1, 12.6. **HRMS** (ESI), m/z calcd for $C_{17}H_{18}N_4O_4$ $[M+H]^+$ 342.1328, found 342.1335.

3. Crystallographic data for compound 12a.

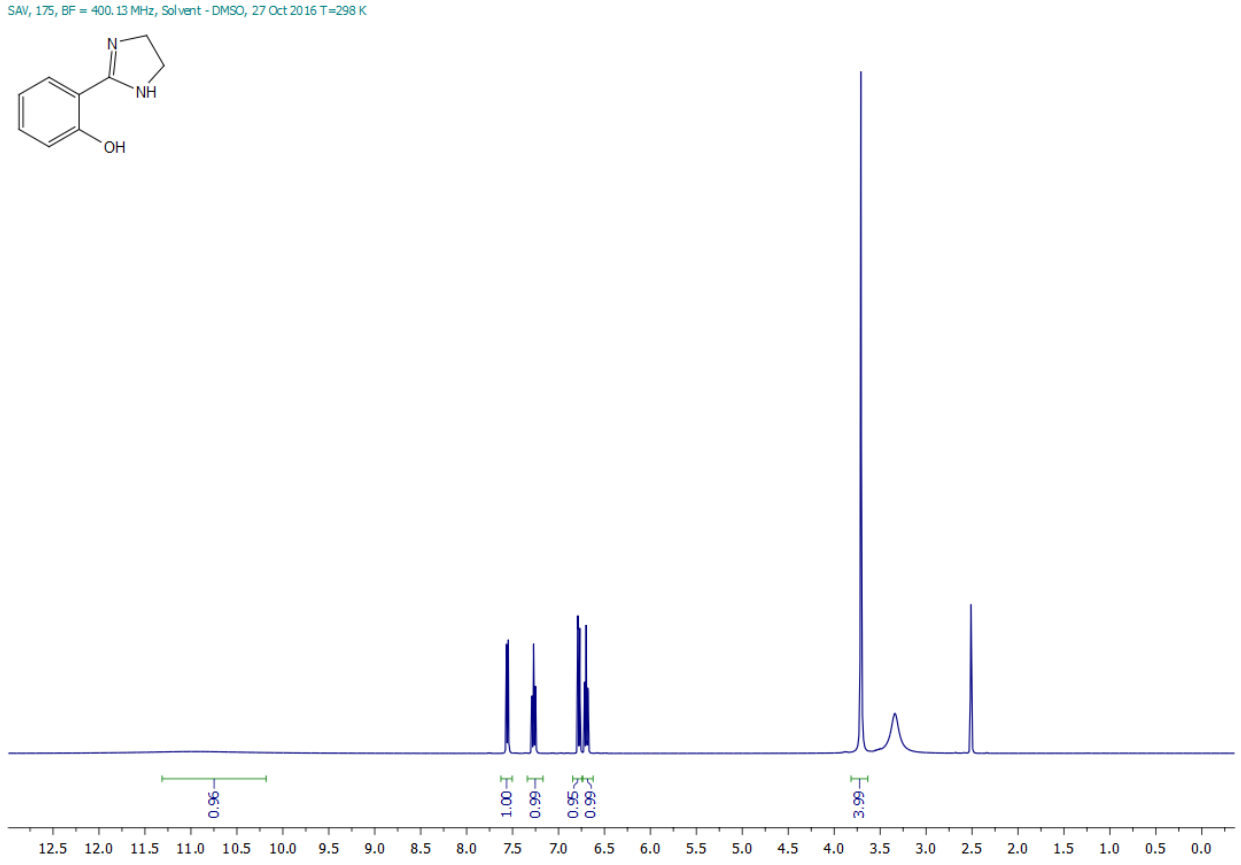


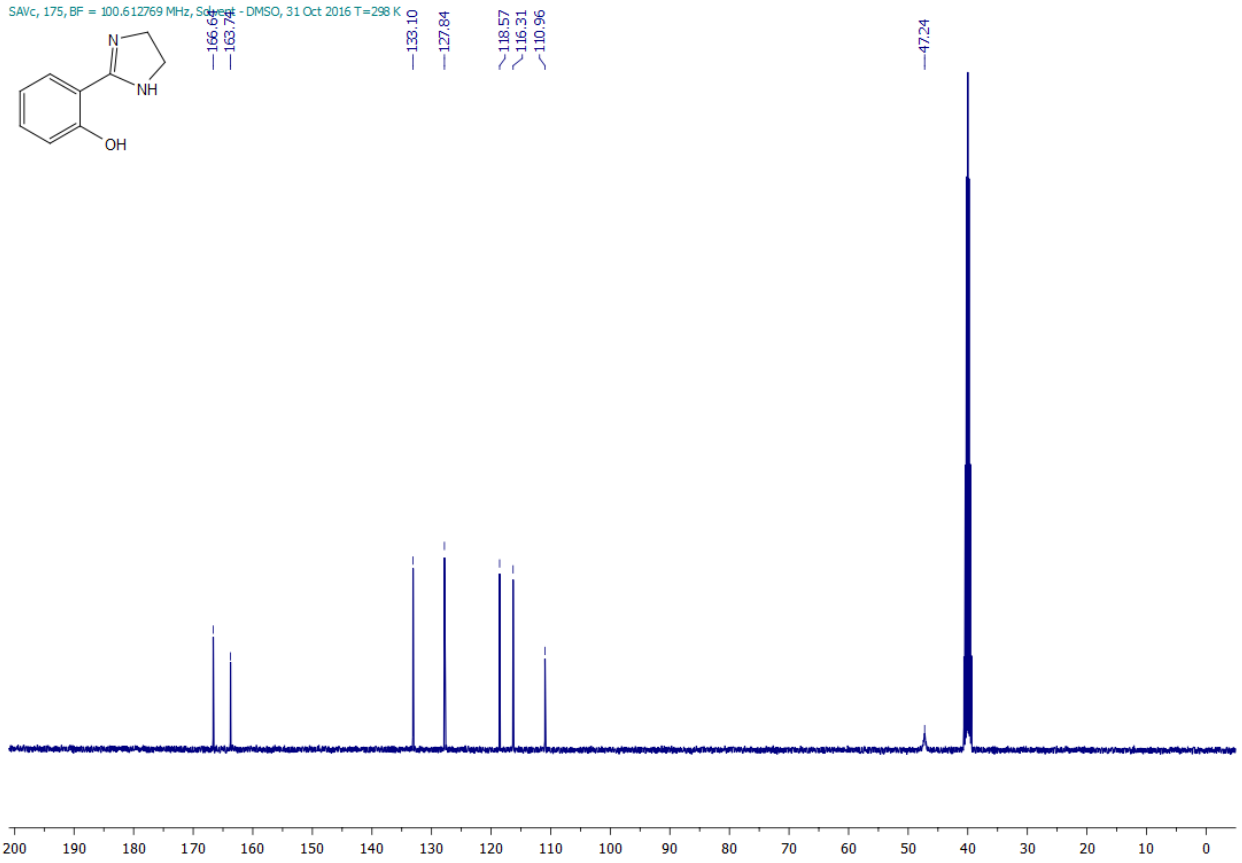
Crystal data and structure refinement for 12a.

Empirical formula	$C_{15}H_{14}N_4O_4$	ρ_{calc} g/cm^3	1.320
Formula weight	314.30	μ/mm^{-1}	0.099
Temperature/K	293(2)	F(000)	1148
Crystal system	orthorhombic	Radiation	MoKα (λ = 0.71073)
Space group	Pbca	2Θ range for data collection/°	5.18 to 54.96
a/Å	15.0497(7)	Index ranges	-19 ≤ h ≤ 15, -14 ≤ k ≤ 12, -21 ≤ l ≤ 18
b/Å	11.1392(5)		
c/Å	16.514(5)	Reflections collected	11083
α/°	90.00	Independent reflections	3167 [R_{int} =0.0299, R_{sigma} =0.0327]
β/°	99.00	Goodness-of-fit on F^2	1.062
γ/°	90.00	Final R indexes [I>=2σ (I)]	R_1 = 0.0415, wR_2 = 0.0967
Volume/Å3	2768.5(8)	Final R indexes [all data]	R_1 = 0.0532, wR_2 = 0.1032
Z	7	**CCDC**	1520950

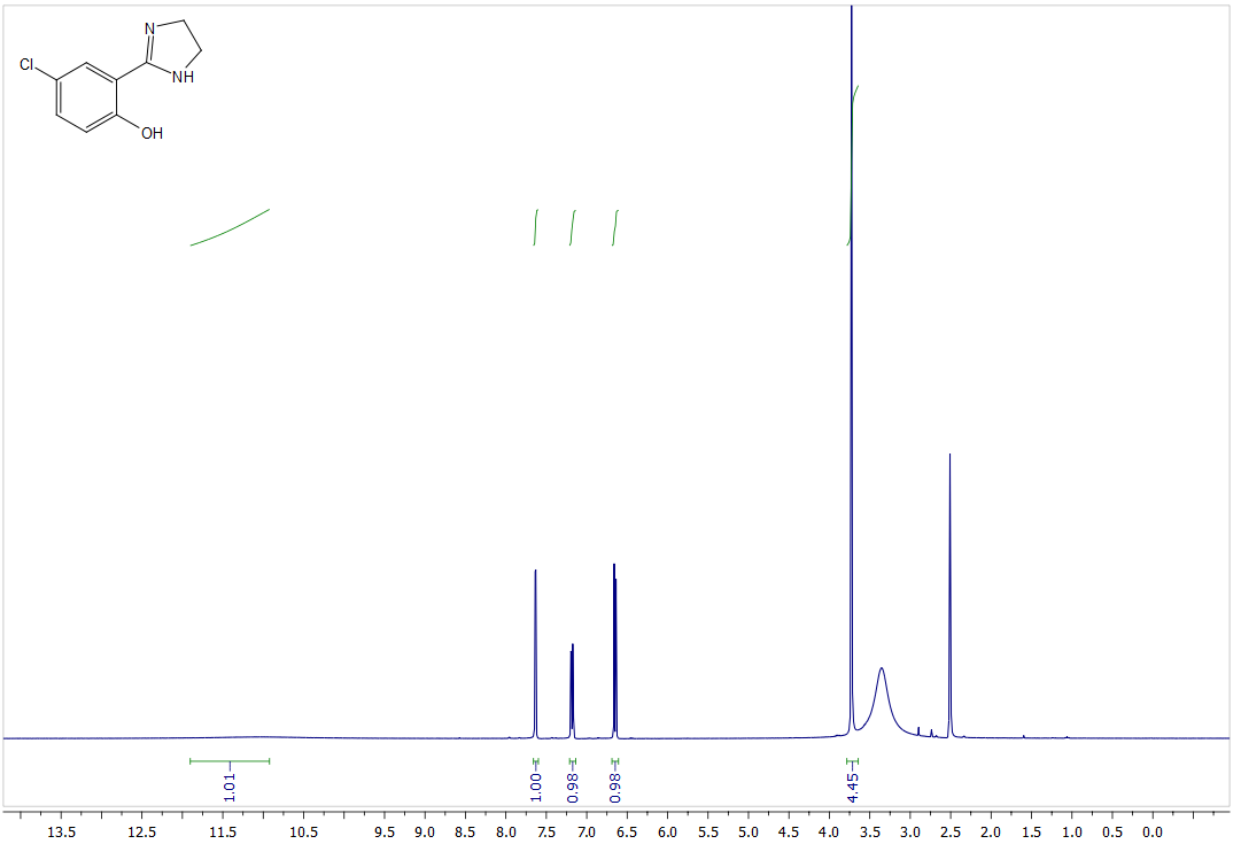
4. Copies of ^{1}H and ^{13}C NMR spectra.

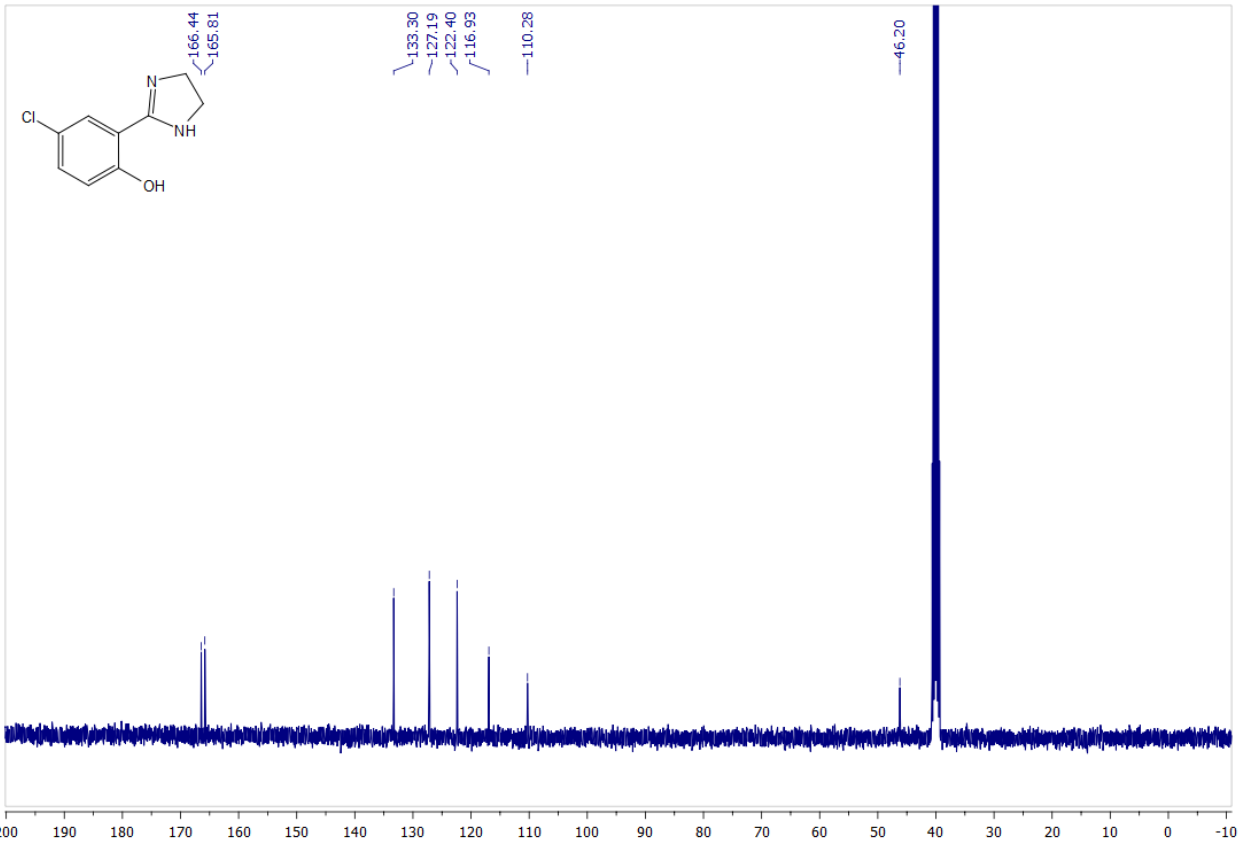
^{1}H and ^{13}C NMR spectra of compound 14a



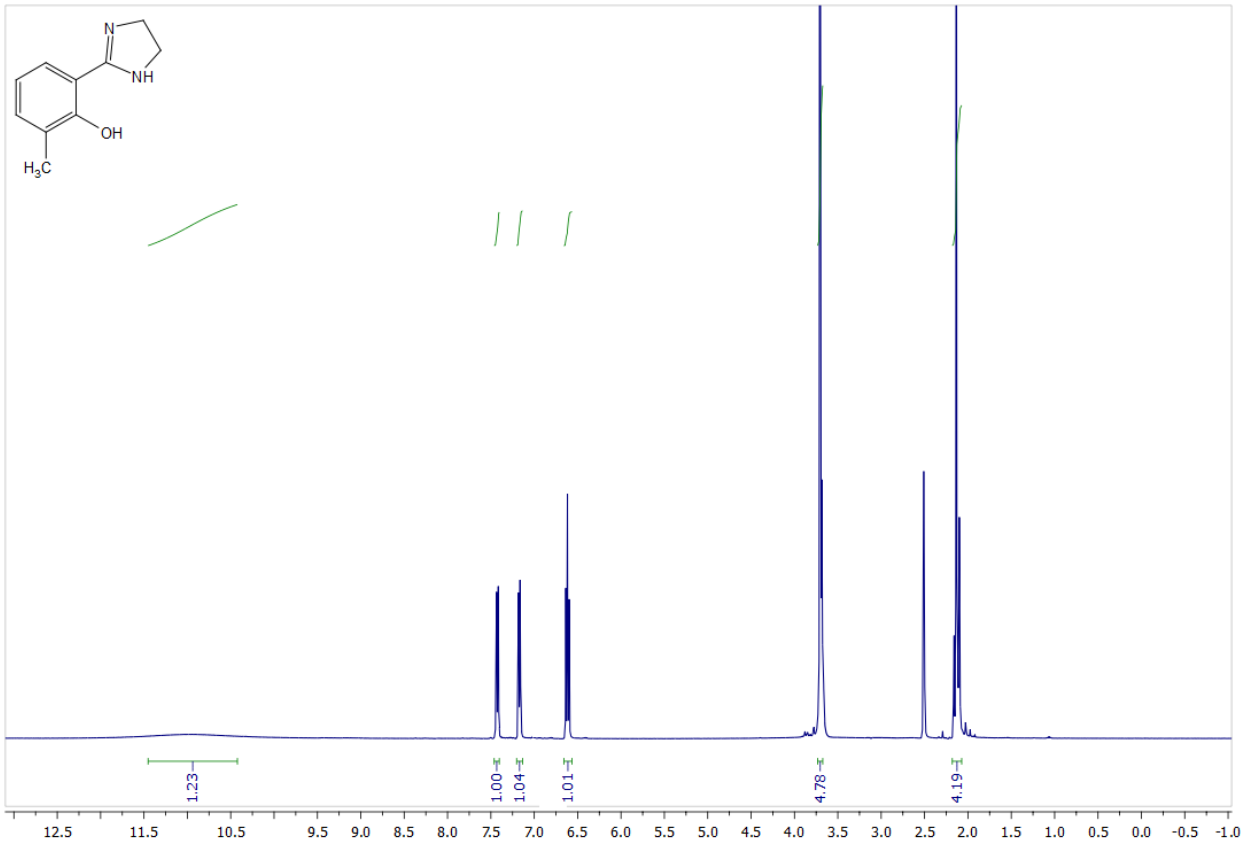


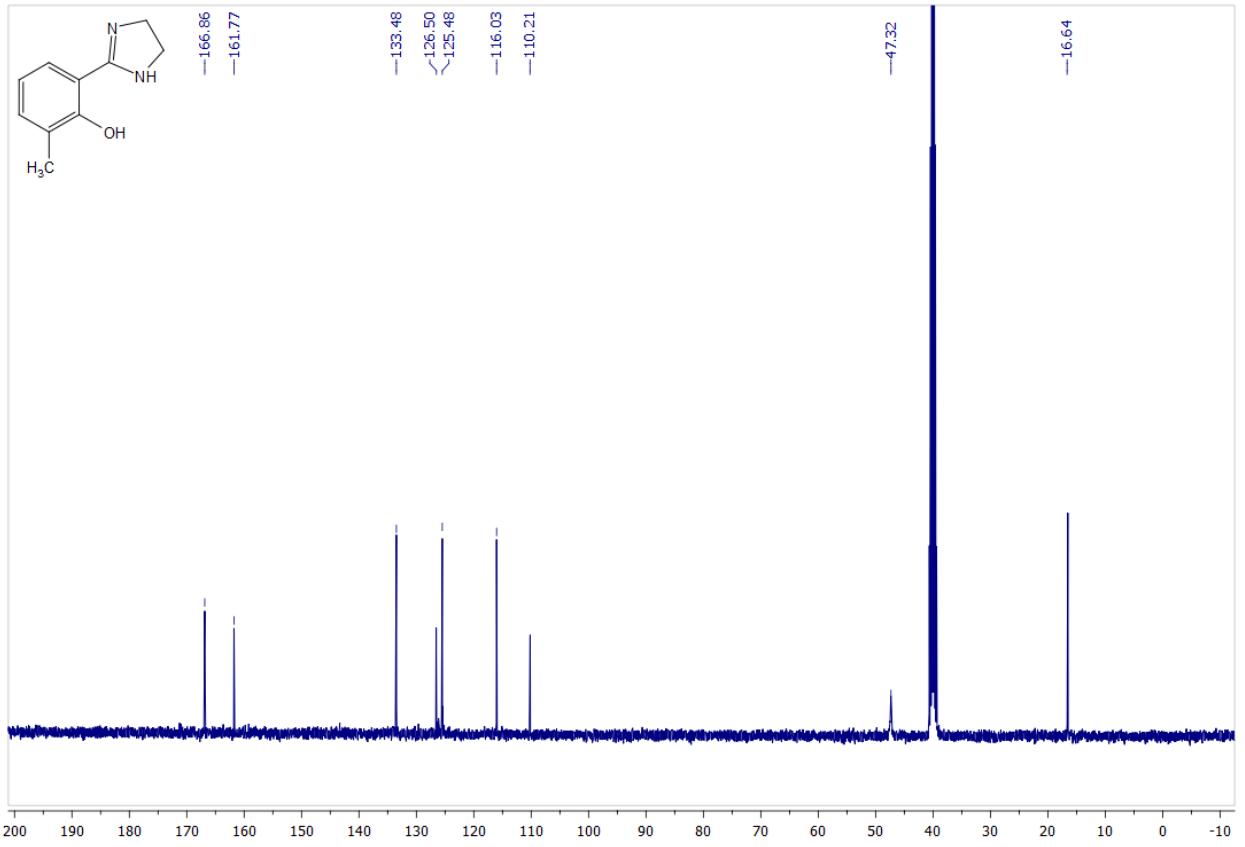
***[1]H and [13]C NMR spectra of compound 14b**



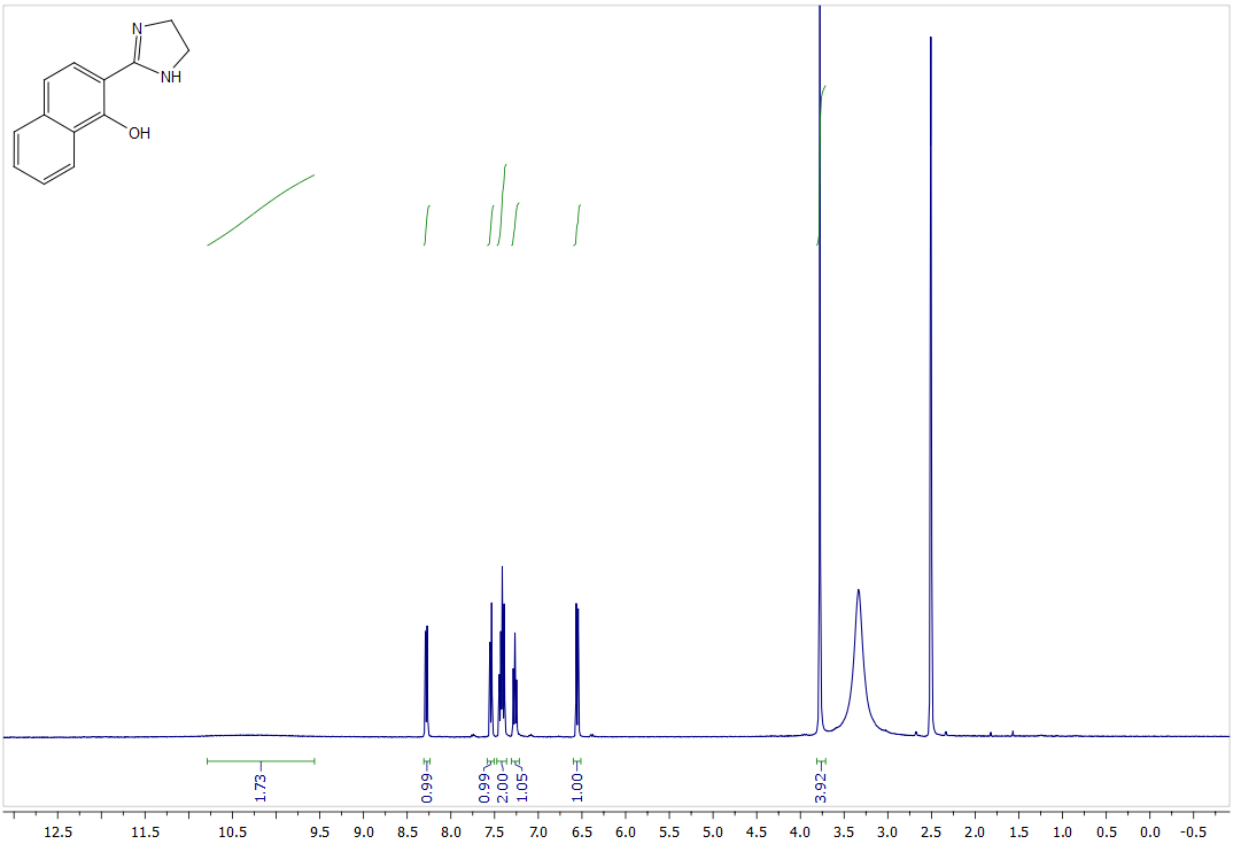


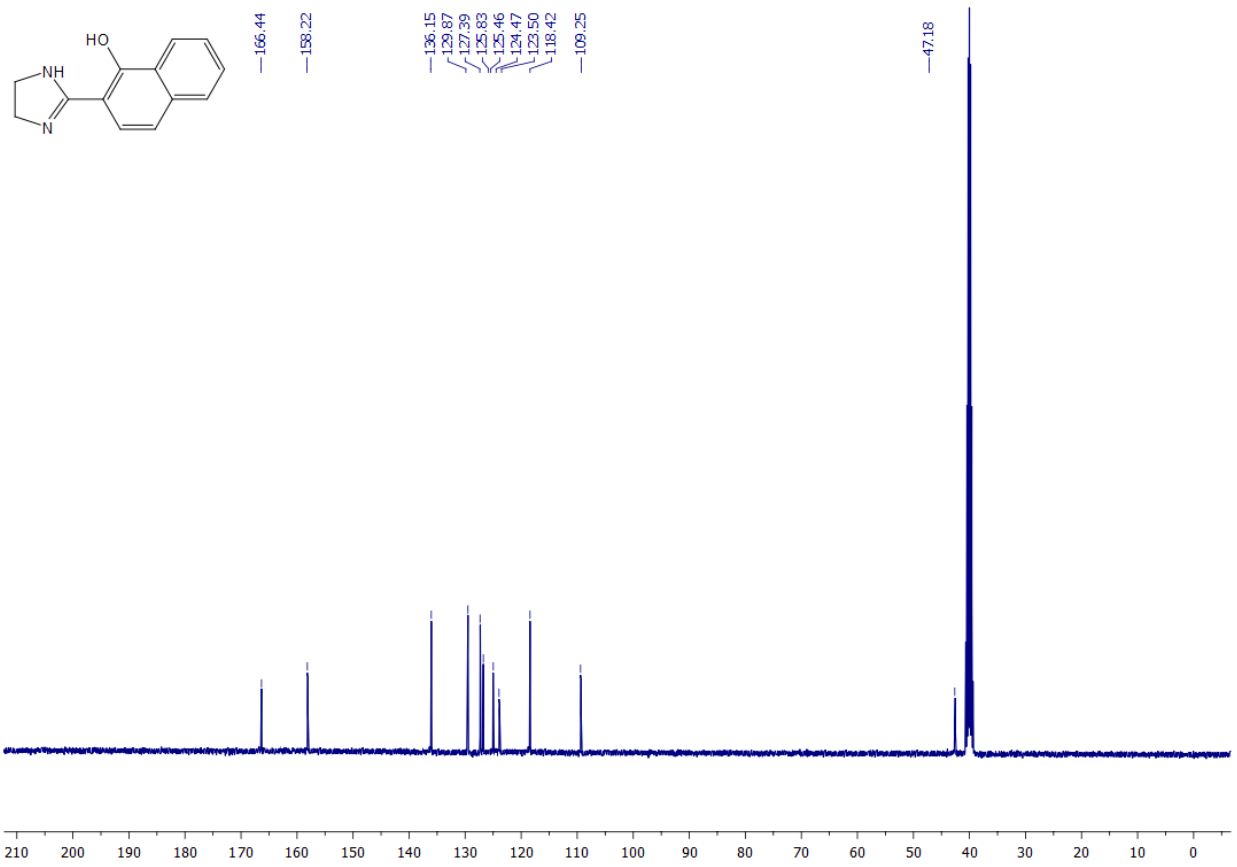
^{1}H and ^{13}C NMR spectra of compound 14c



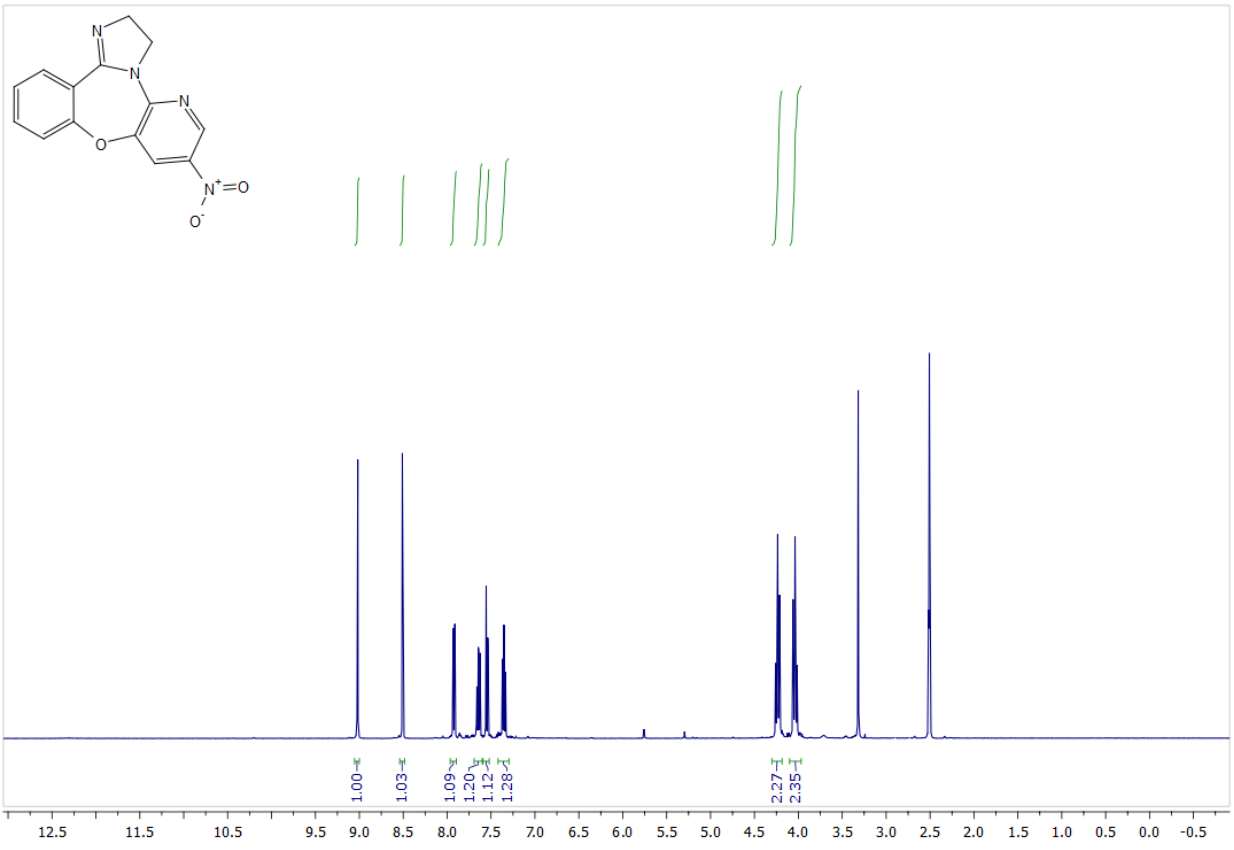


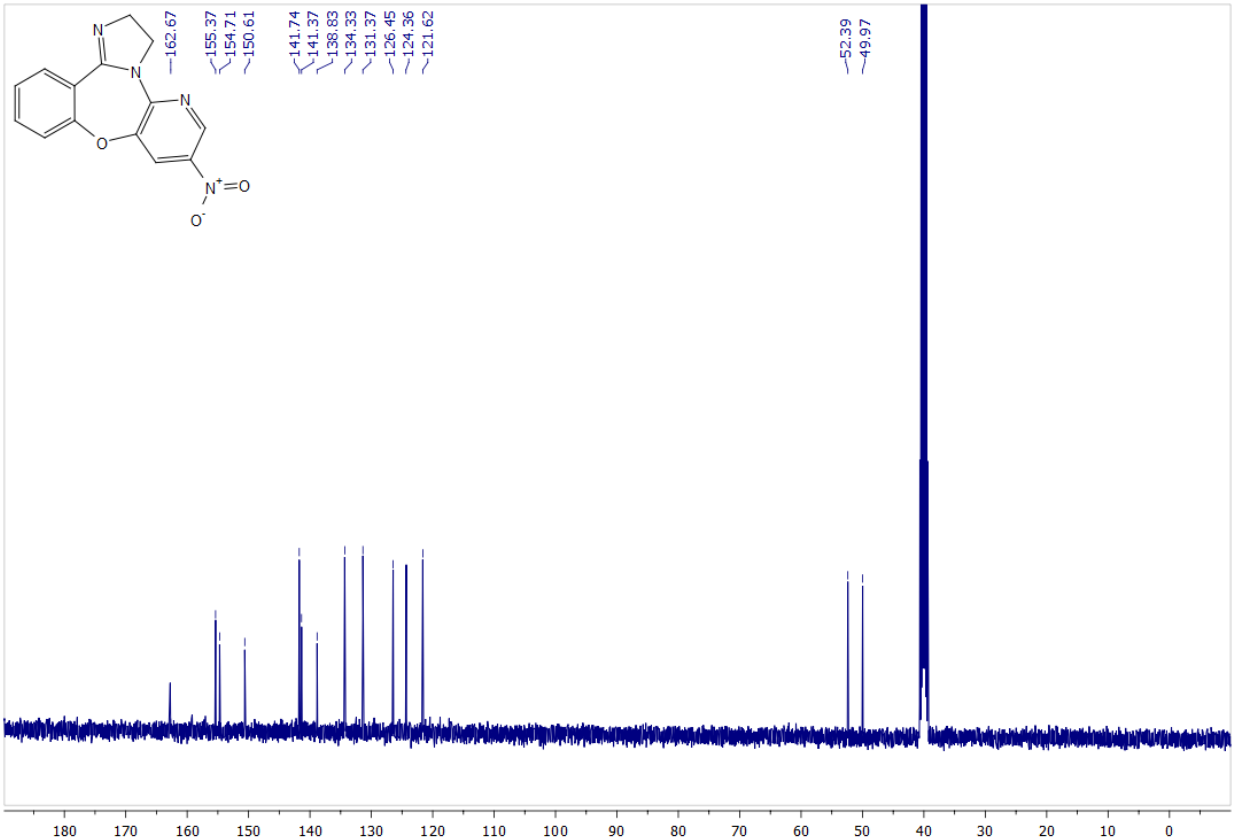
^{1}H and ^{13}C NMR spectra of compound 14d



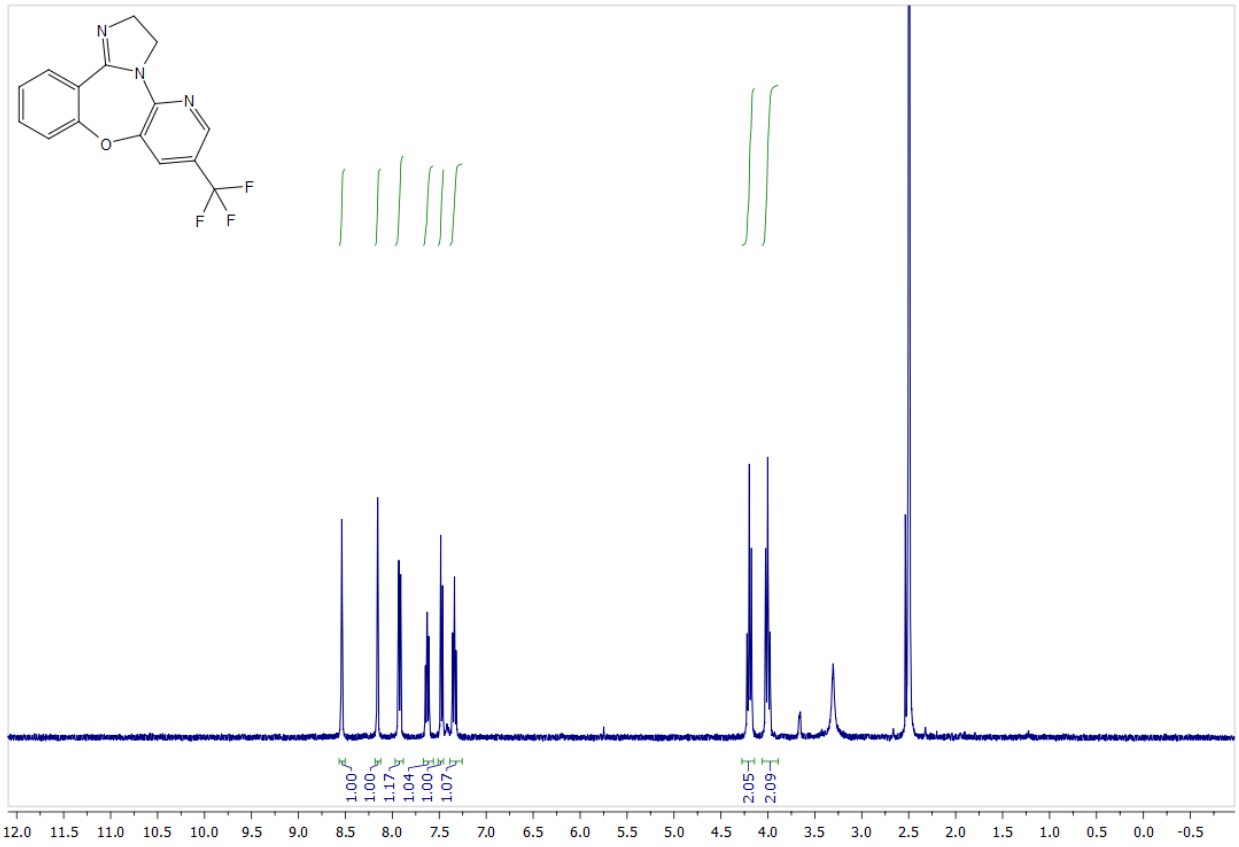


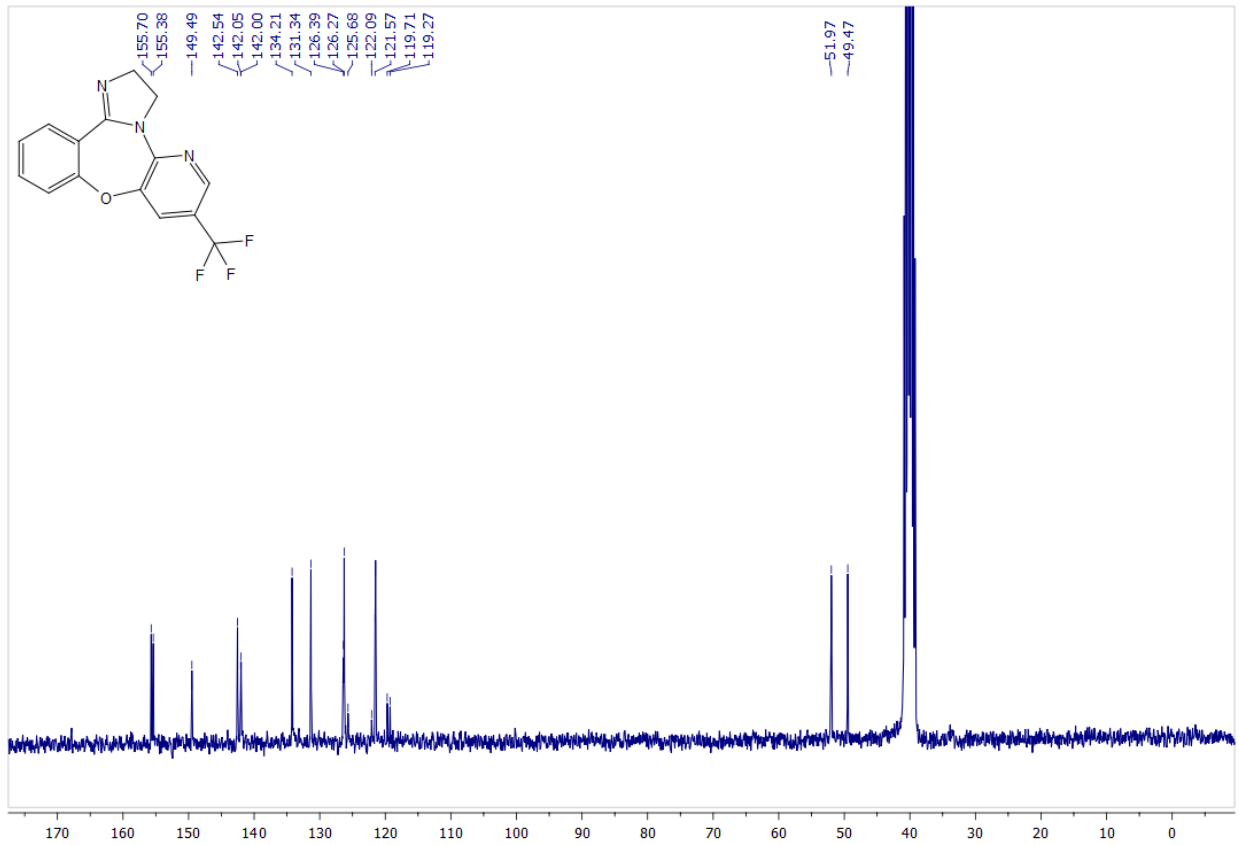
^{1}H and ^{13}C NMR spectra of compound 10a



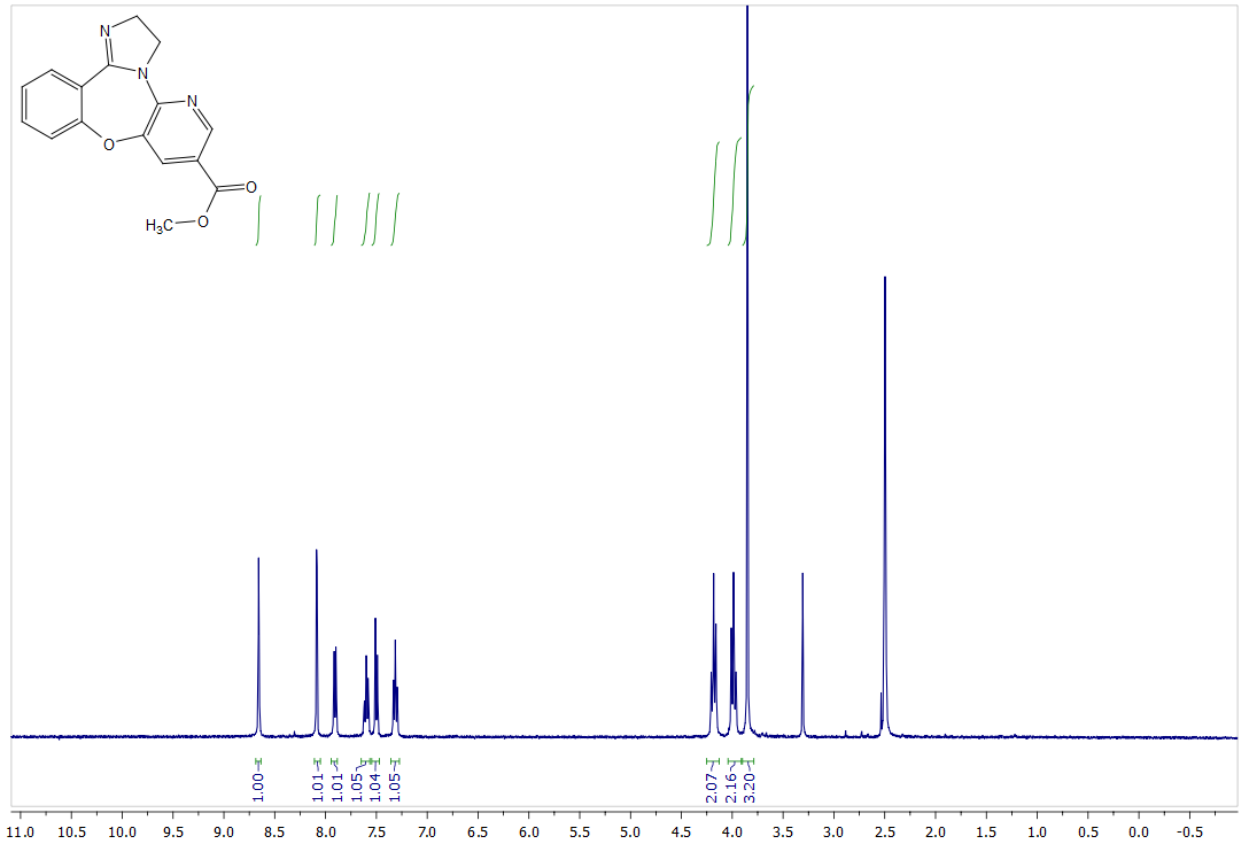


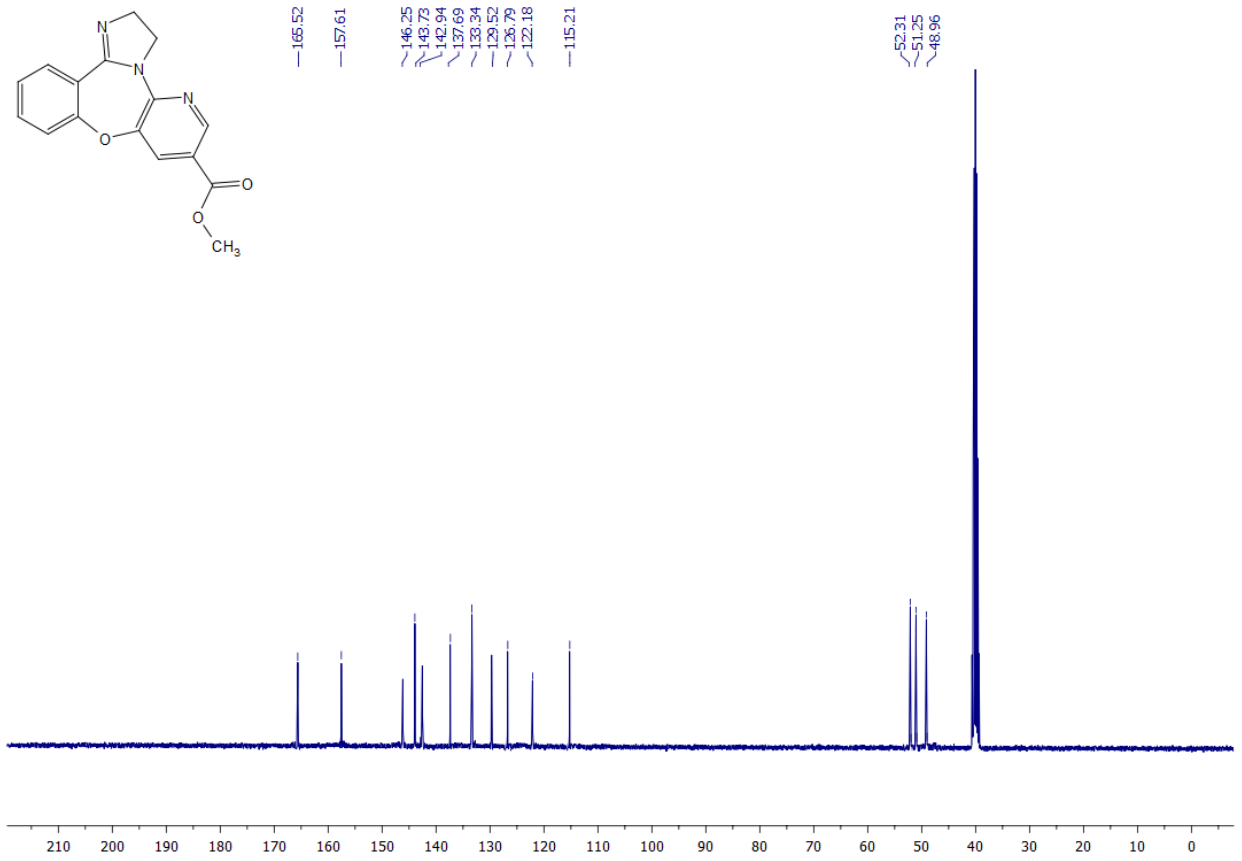
^{1}H and ^{13}C NMR spectra of compound 10b



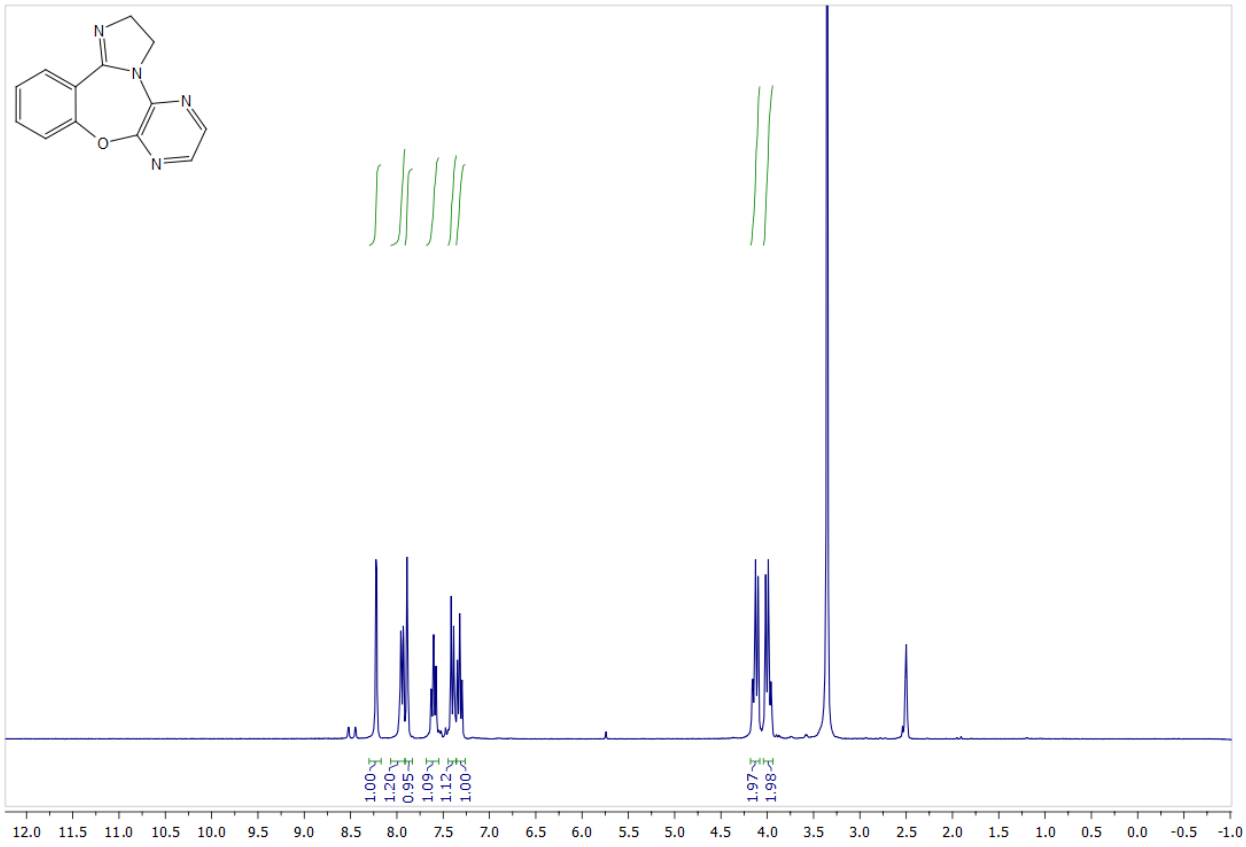


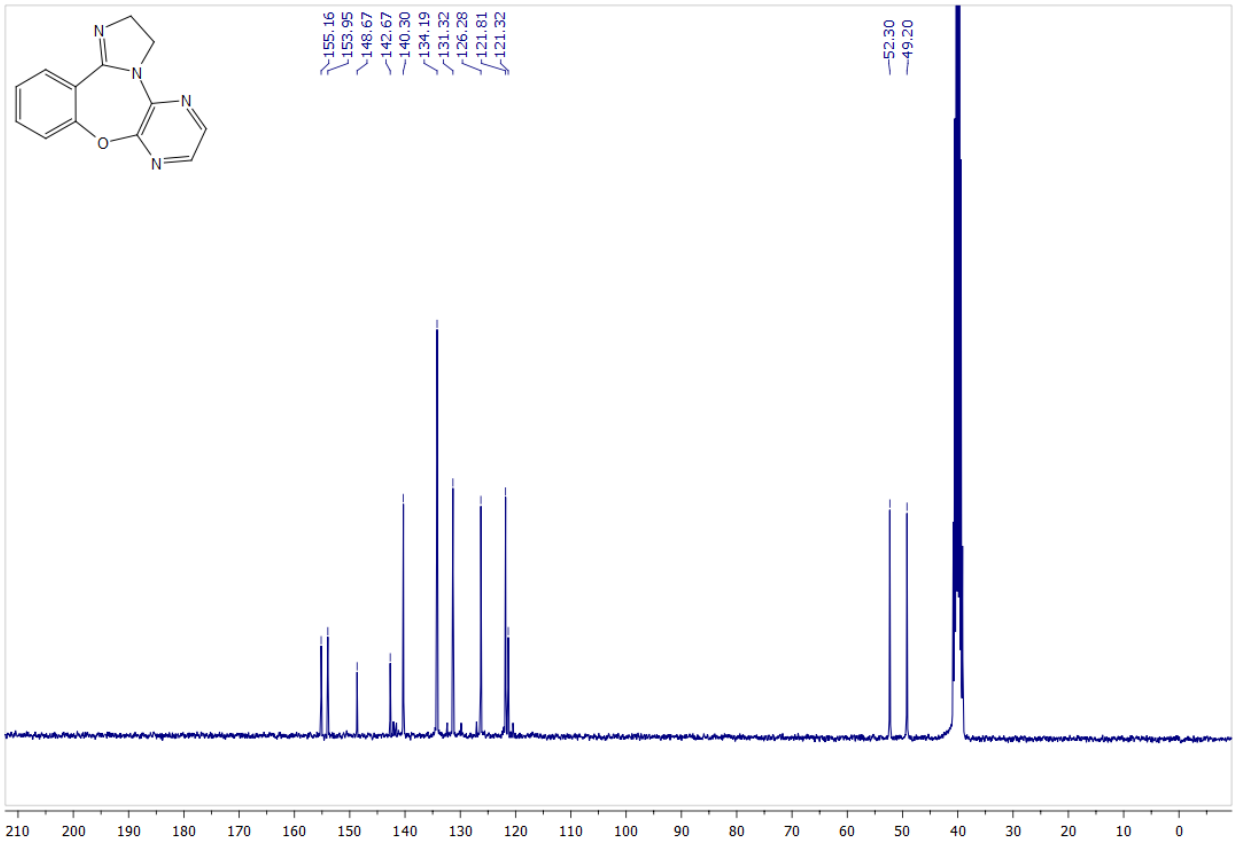
^{1}H and ^{13}C NMR spectra of compound 10c



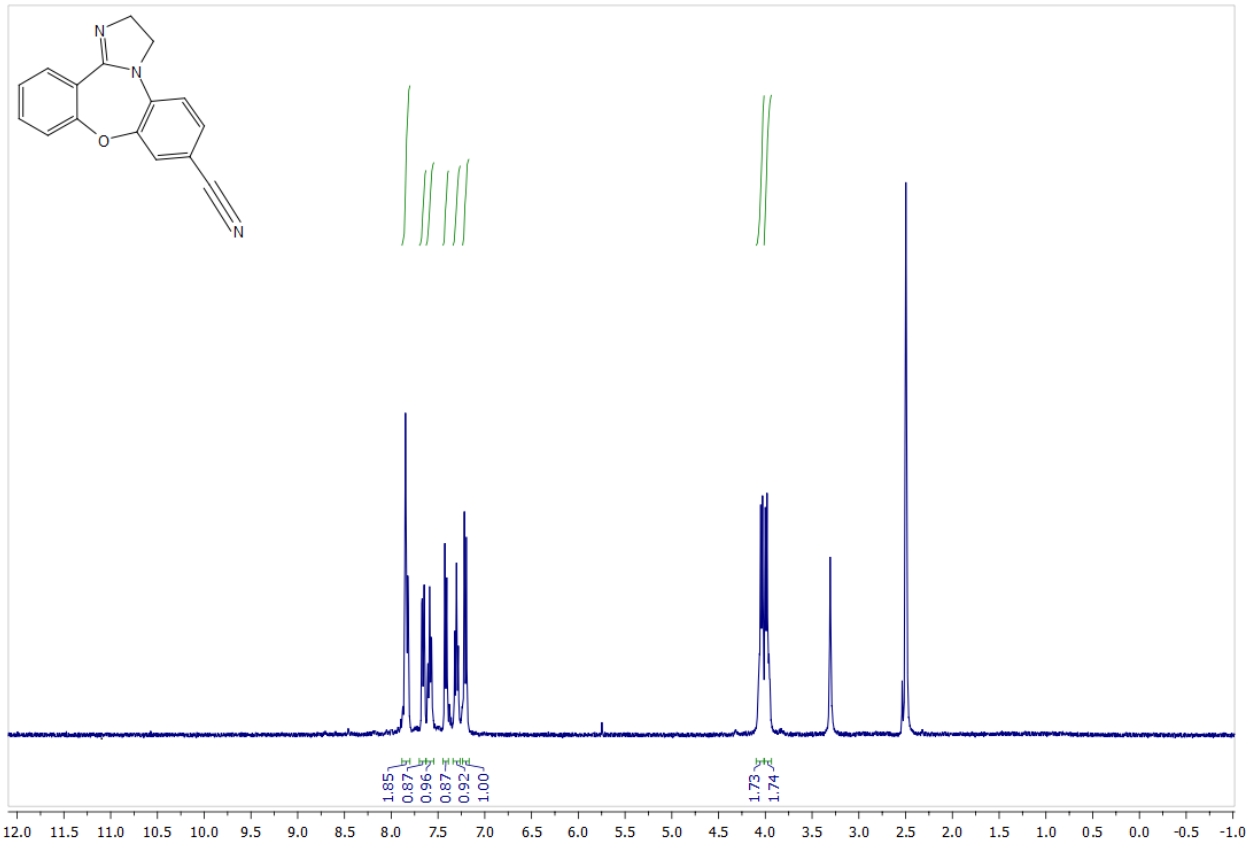


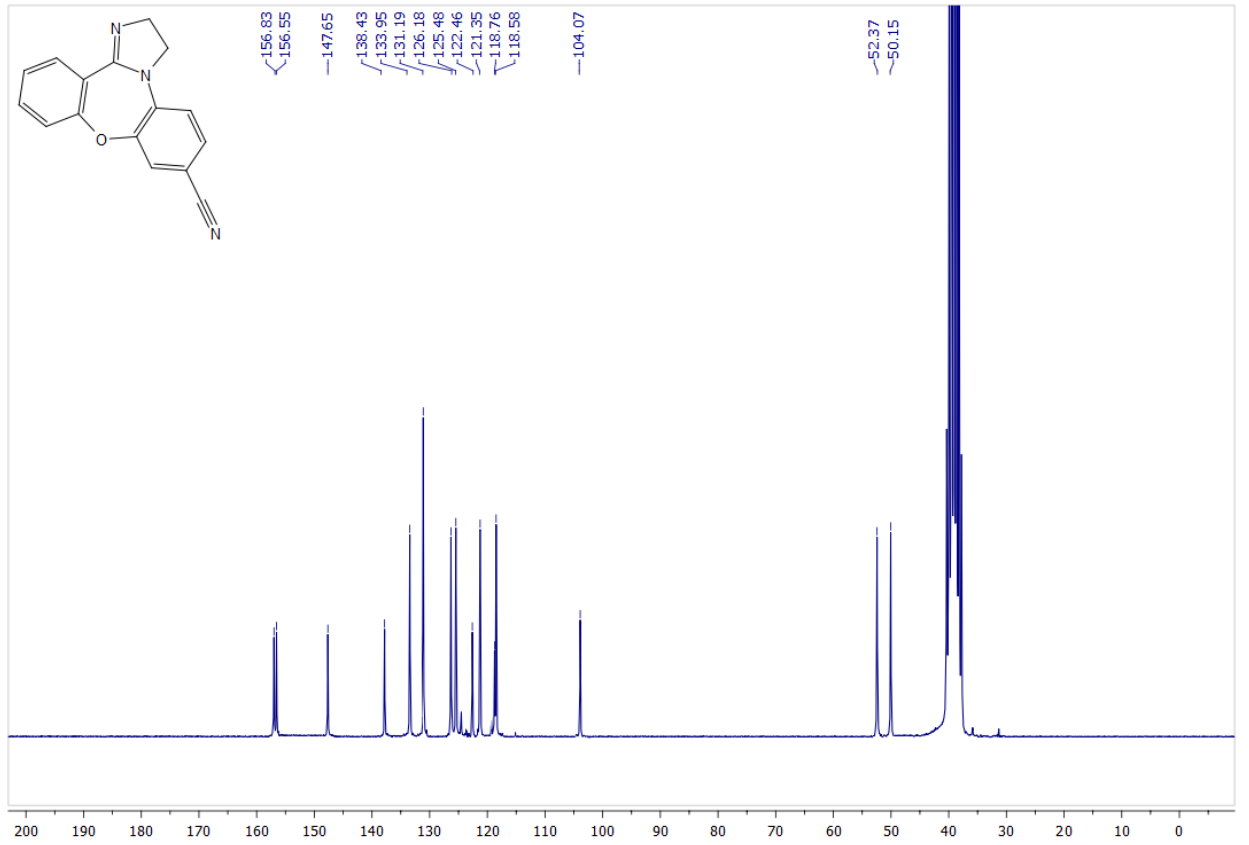
^{1}H and ^{13}C NMR spectra of compound 10d



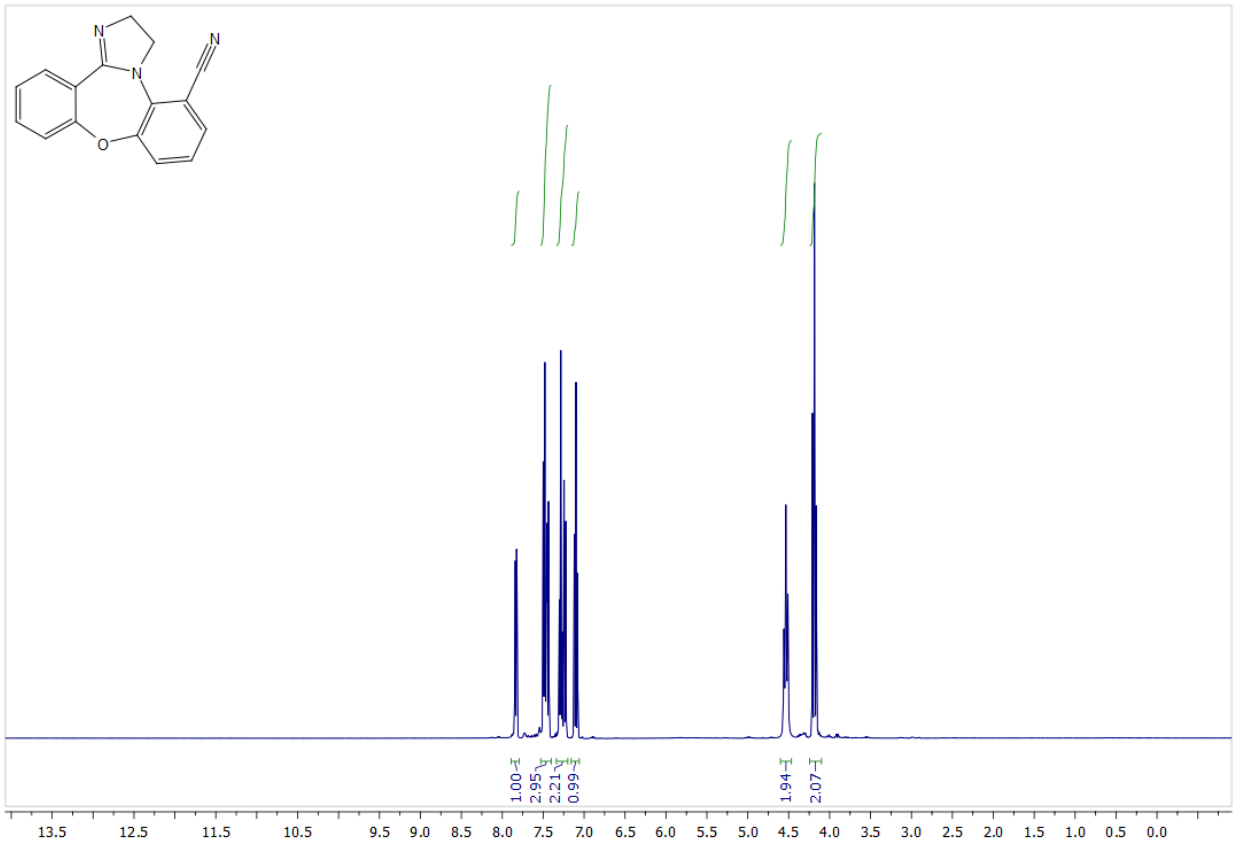


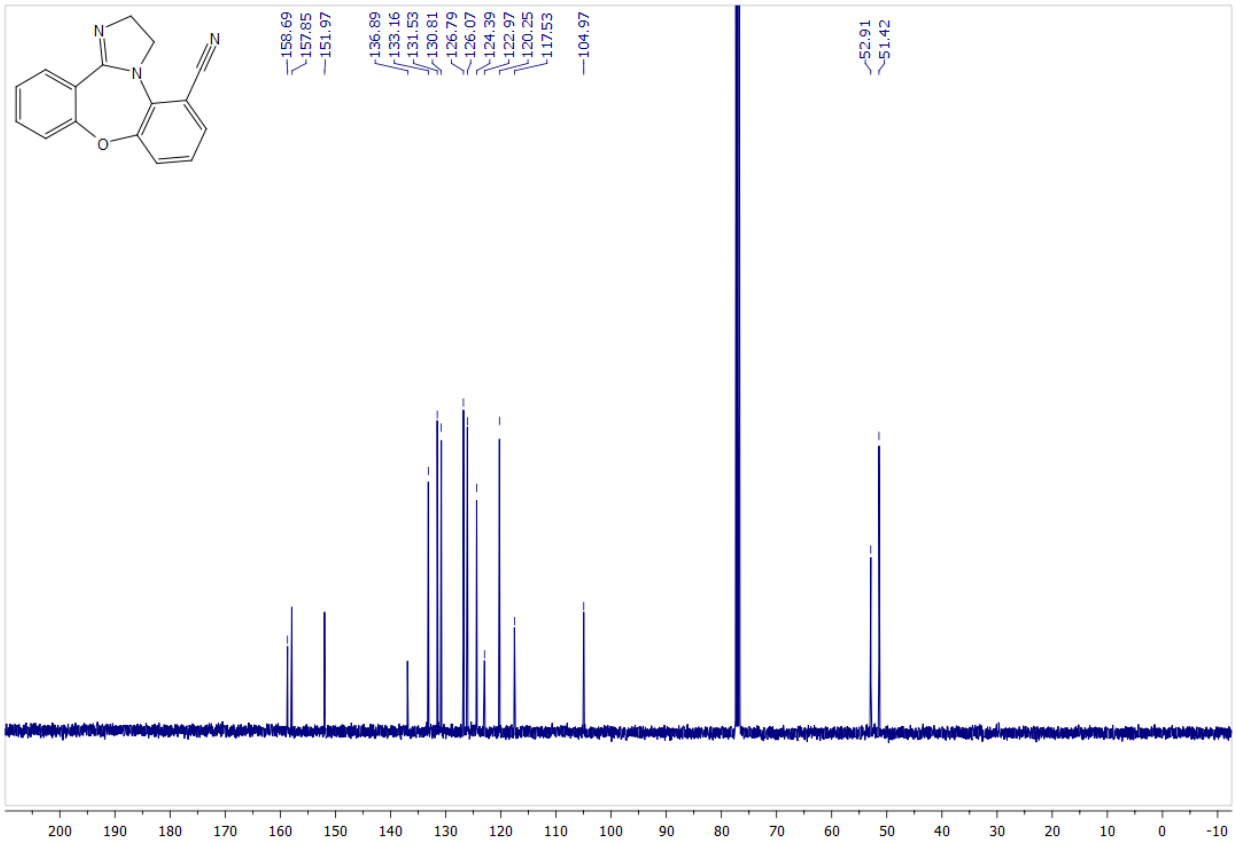
^{1}H and ^{13}C NMR spectra of compound 10e



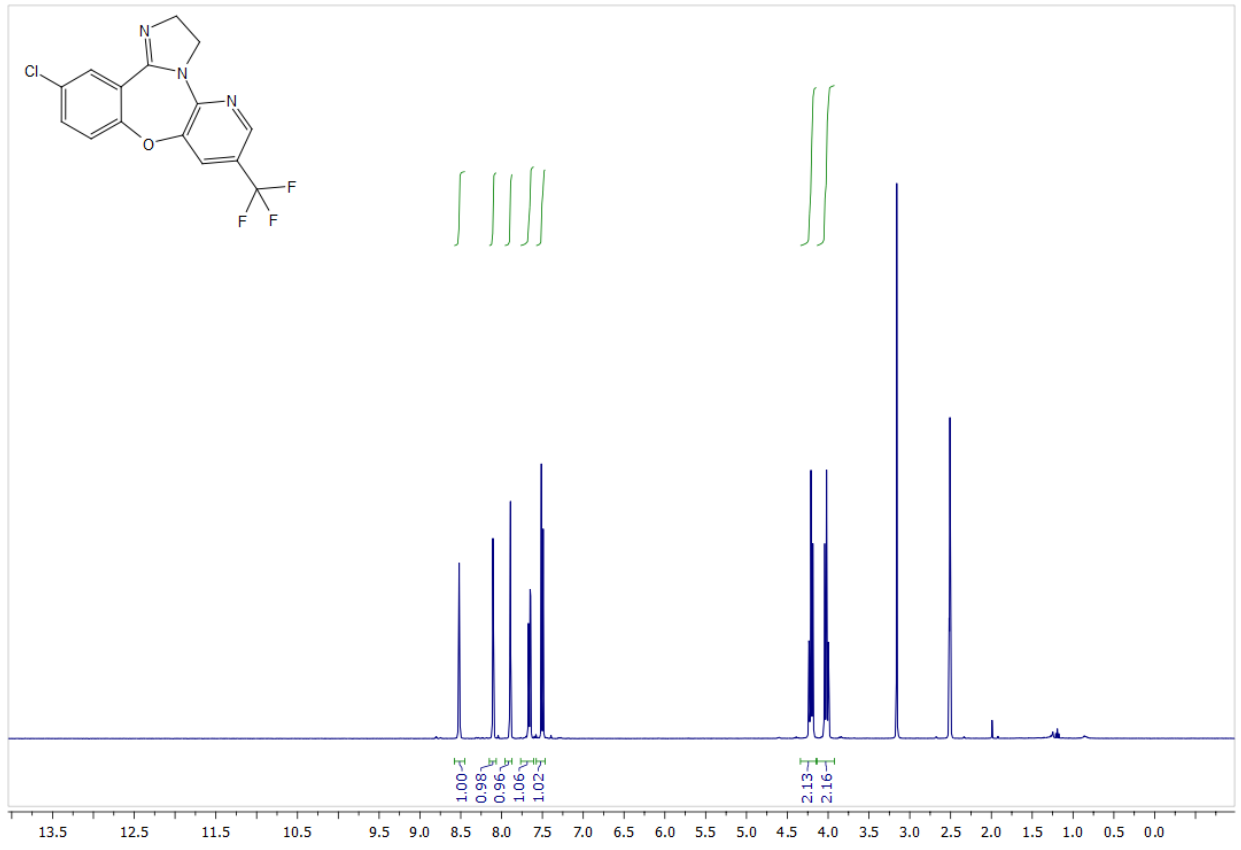


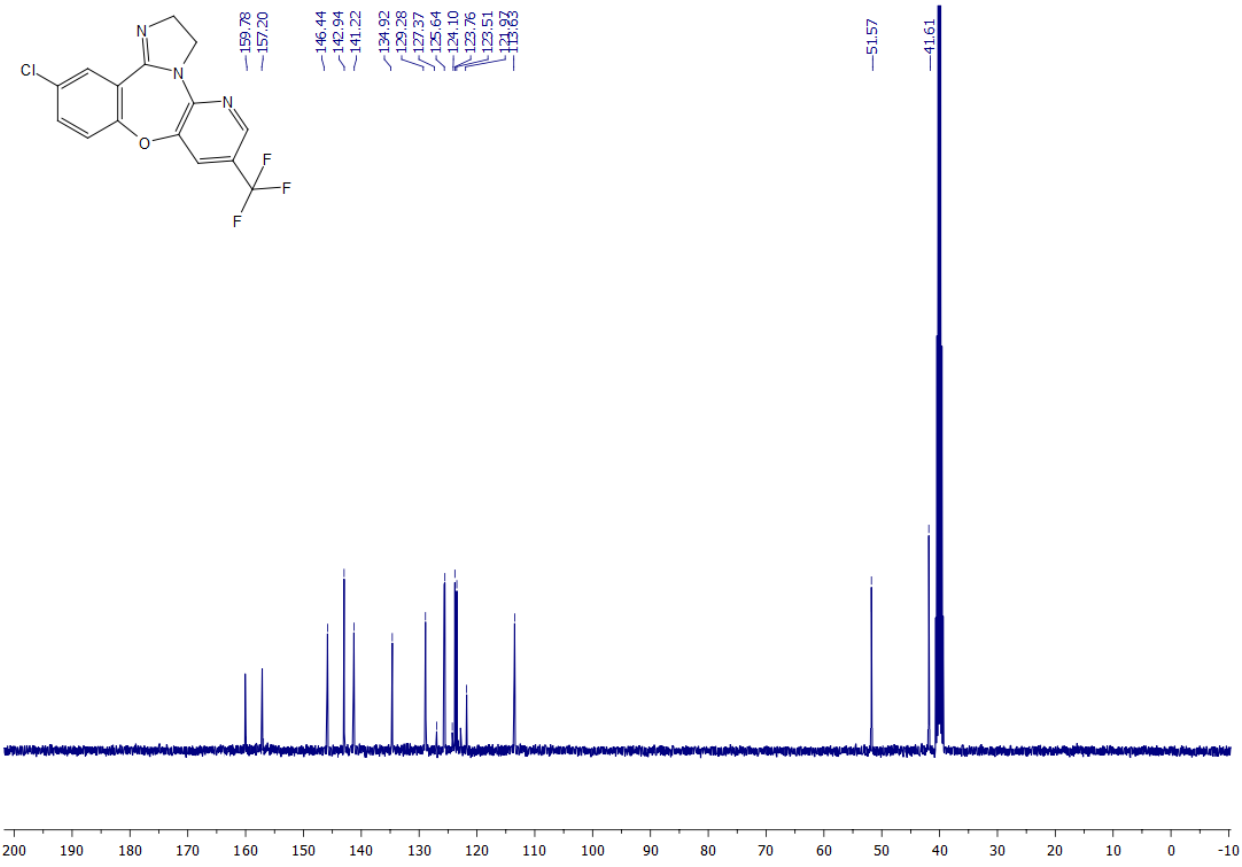
^{1}H and ^{13}C NMR spectra of compound 10f



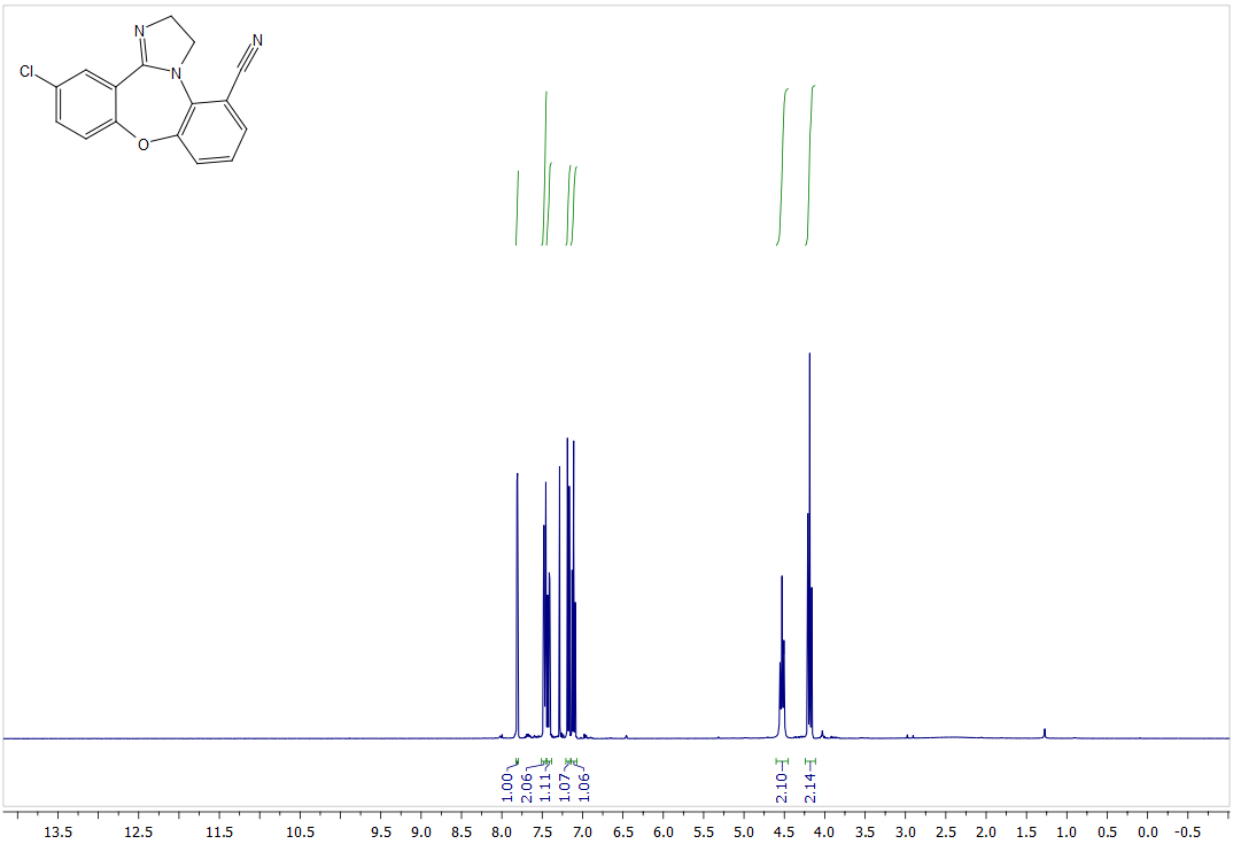


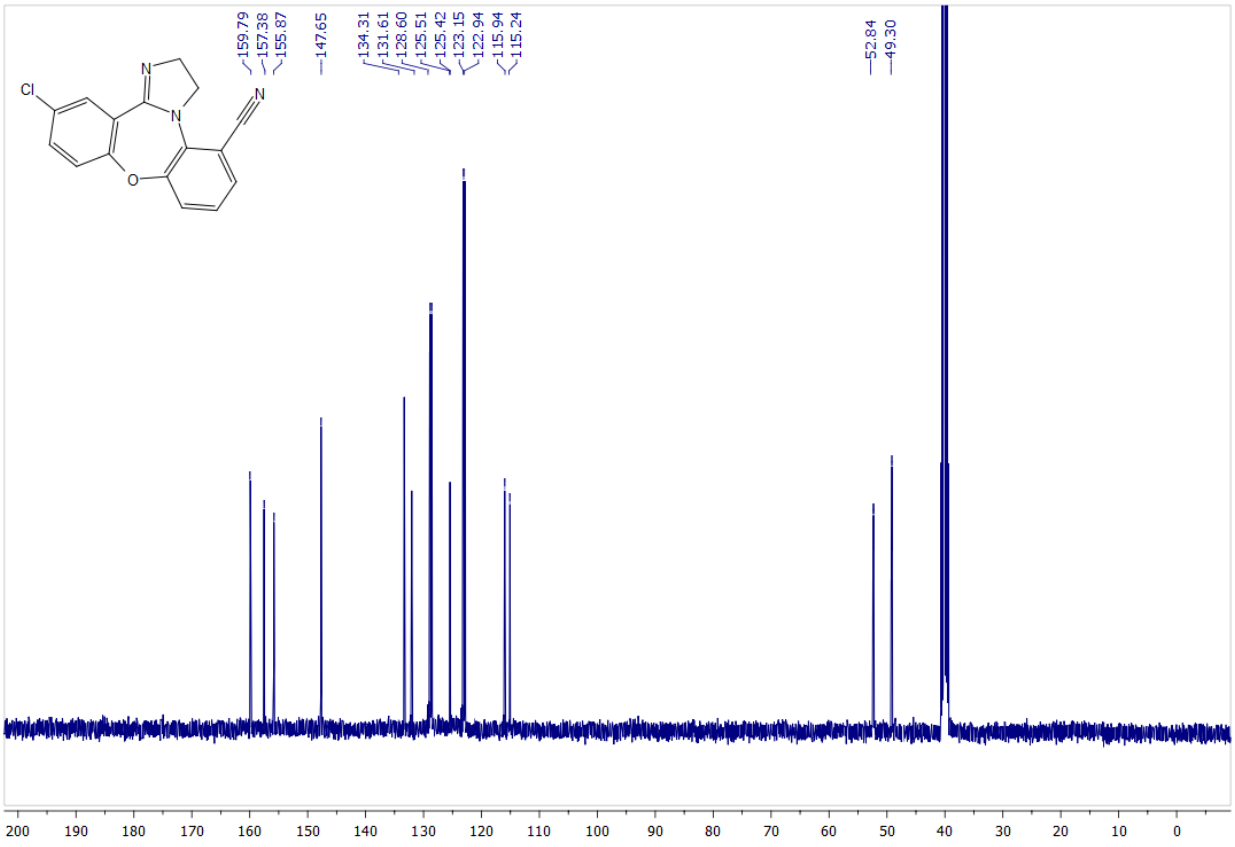
^{1}H and ^{13}C NMR spectra of compound 10g



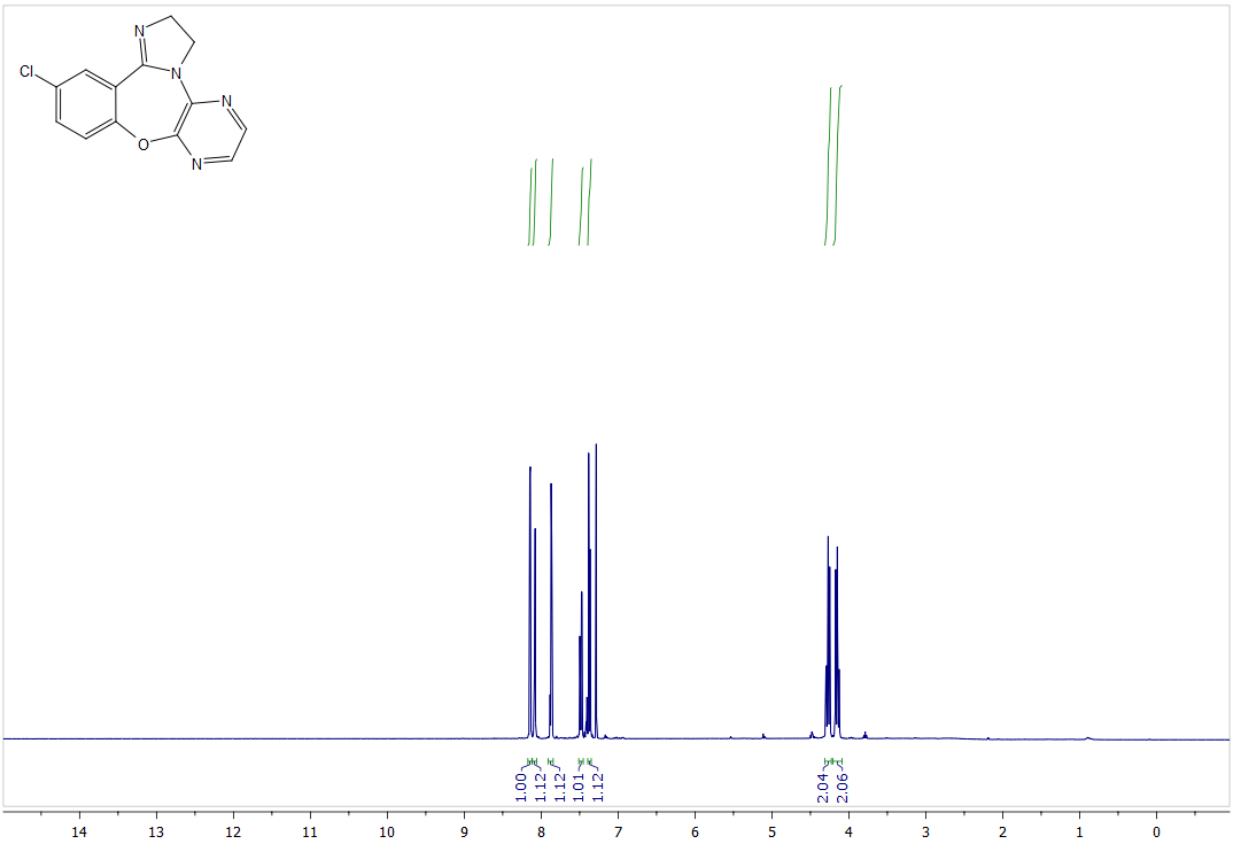


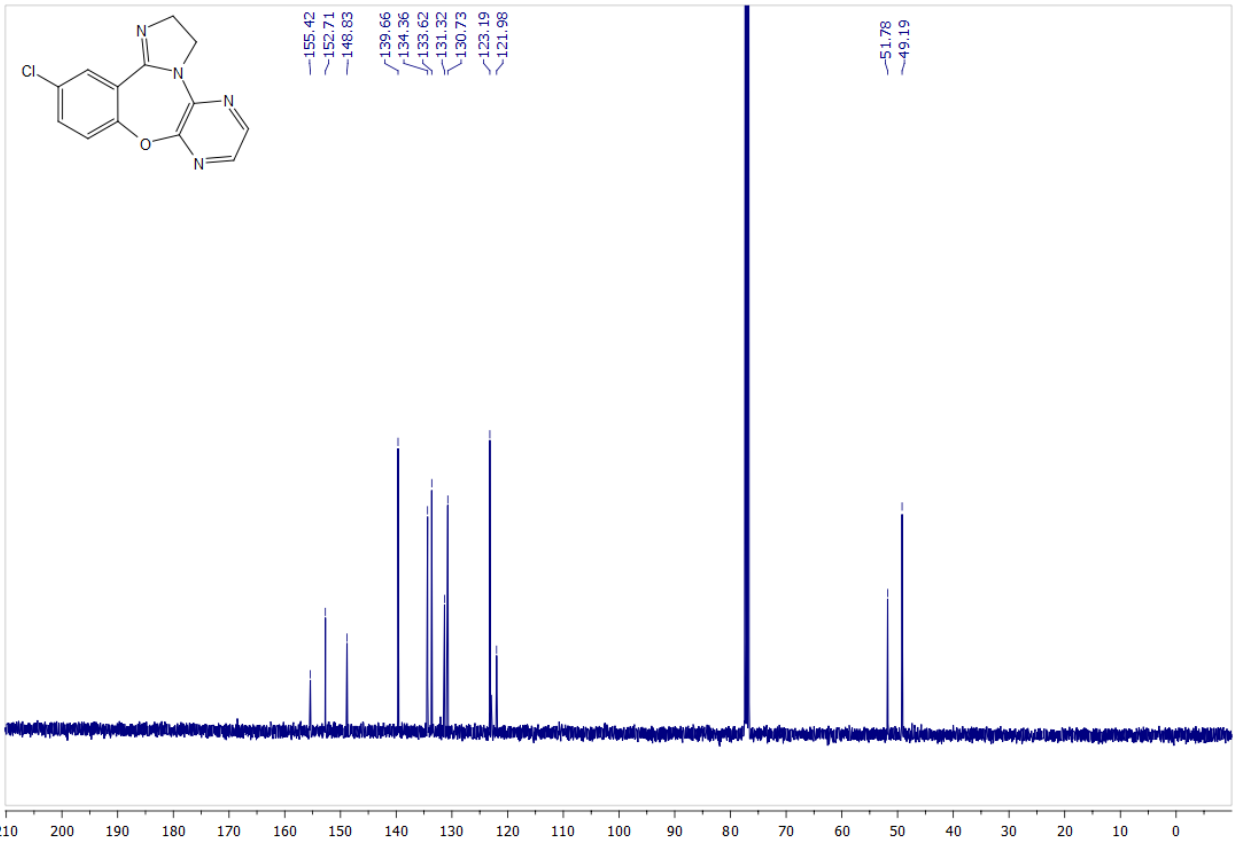
^{1}H and ^{13}C NMR spectra of compound 10h



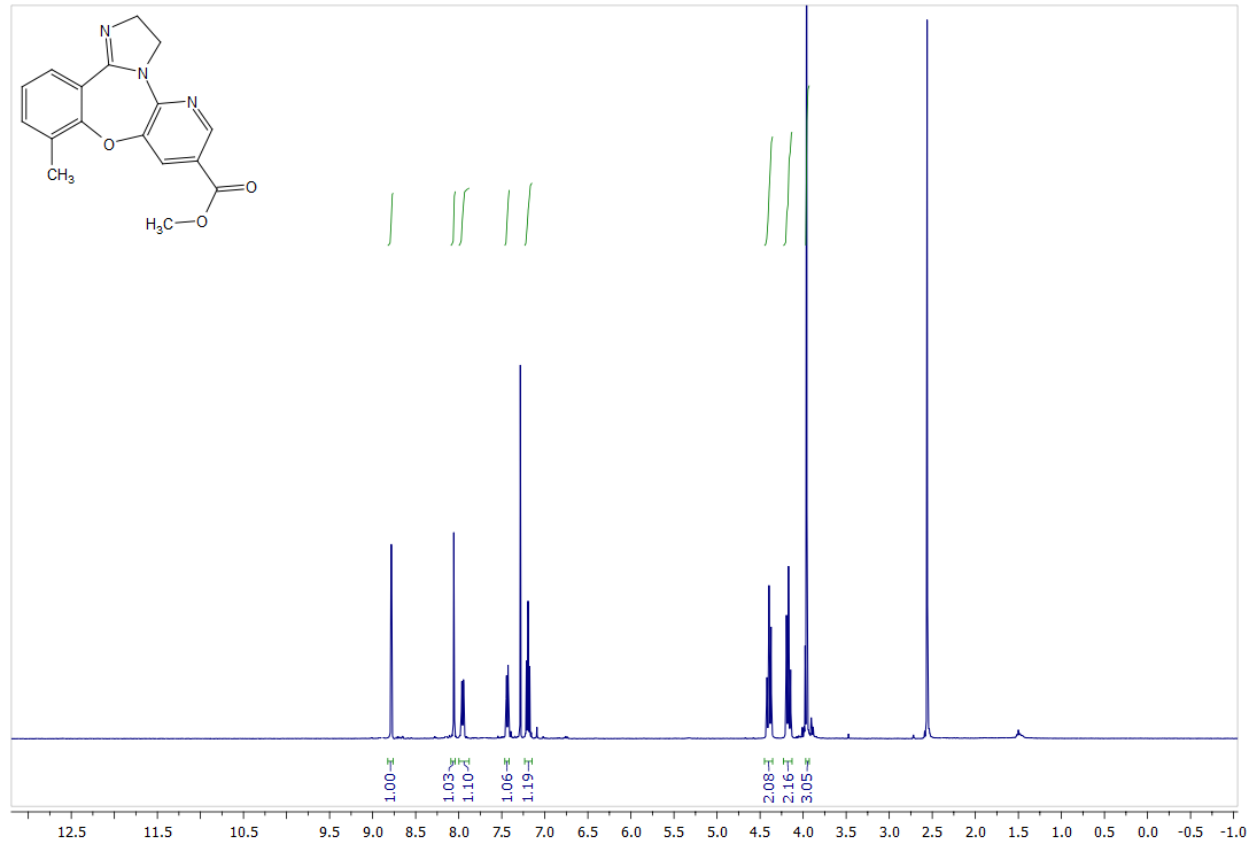


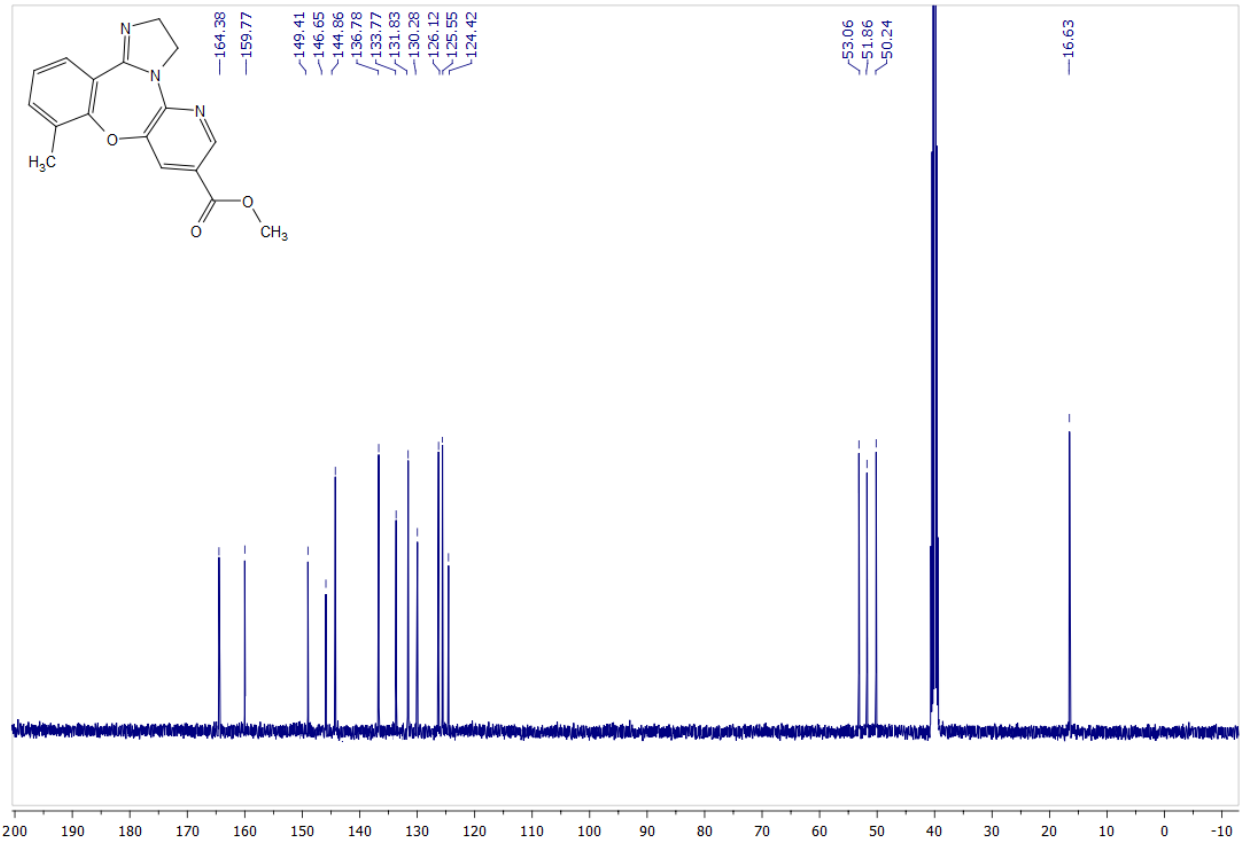
^{1}H and ^{13}C NMR spectra of compound 10i



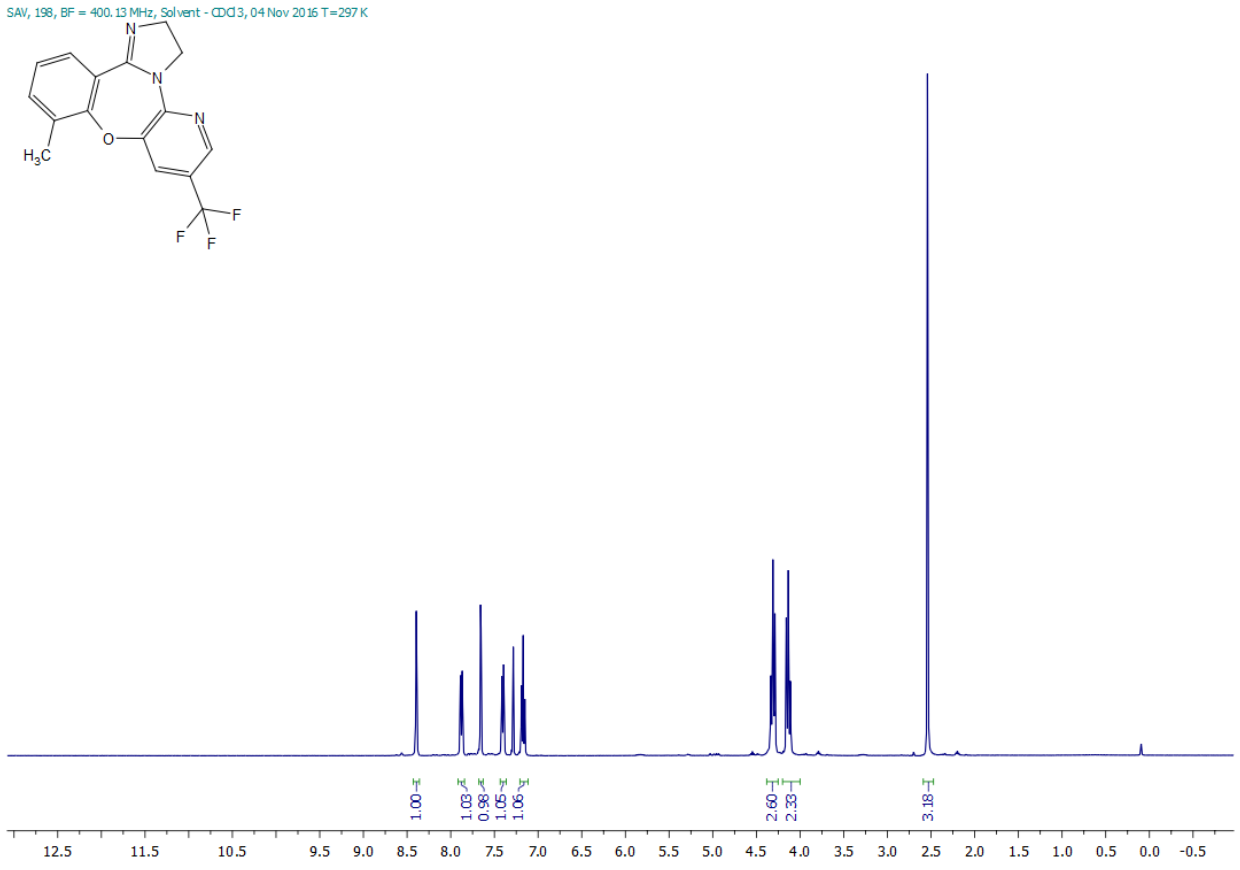


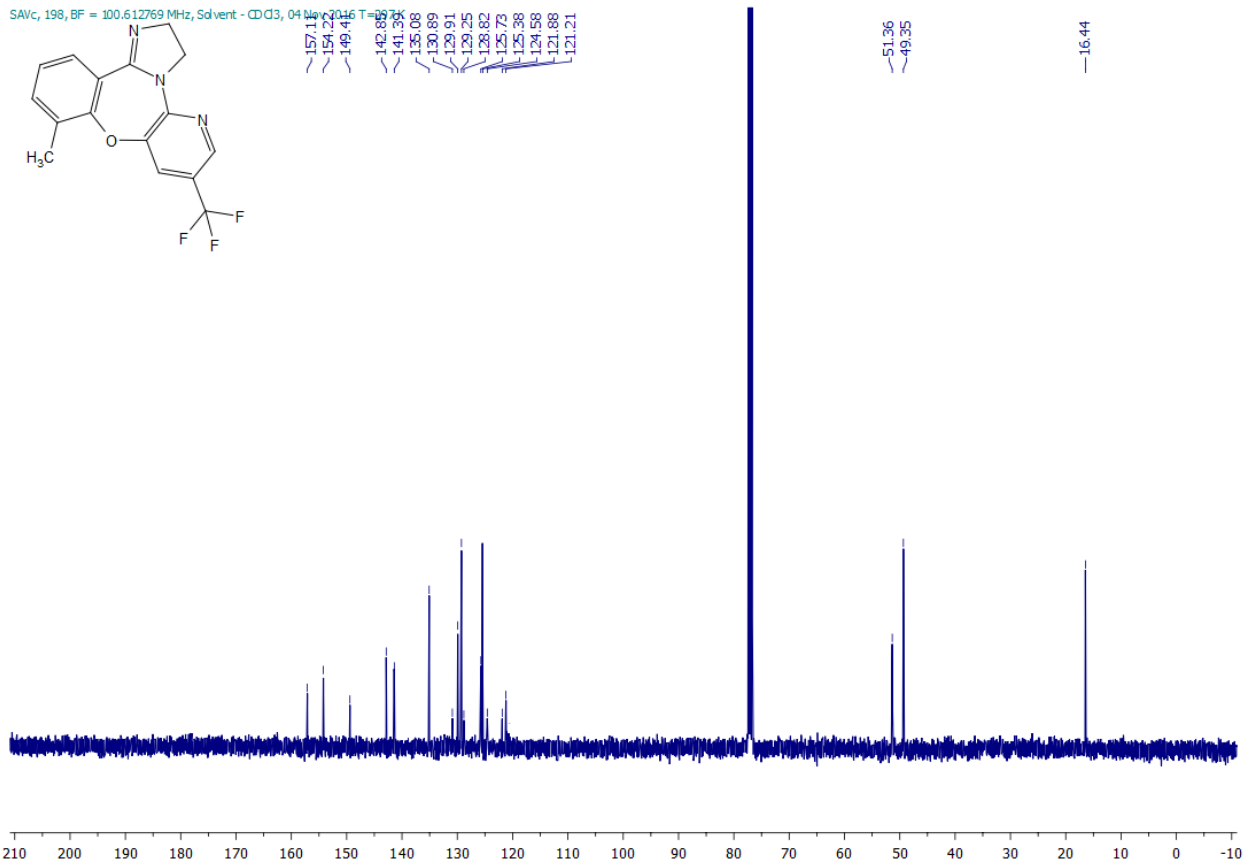
^{1}H and ^{13}C NMR spectra of compound 10j



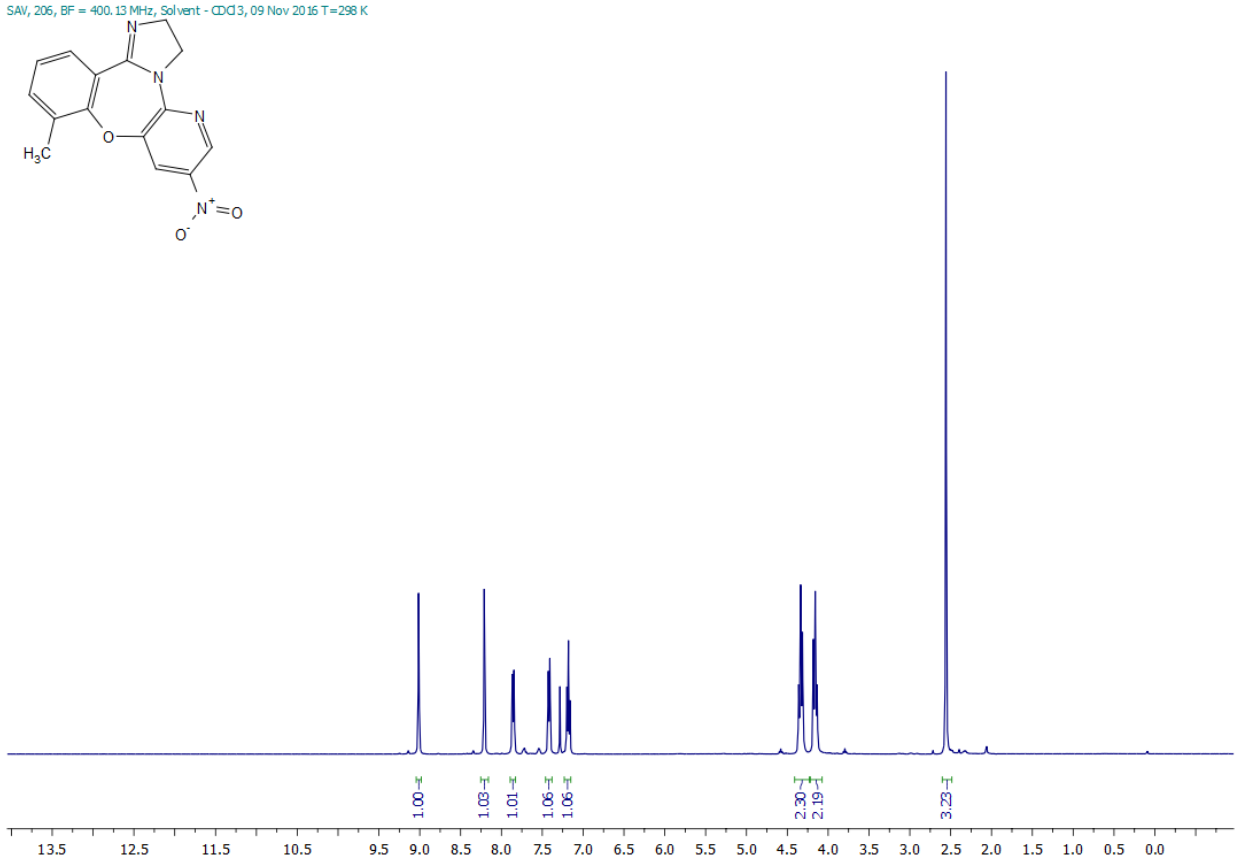


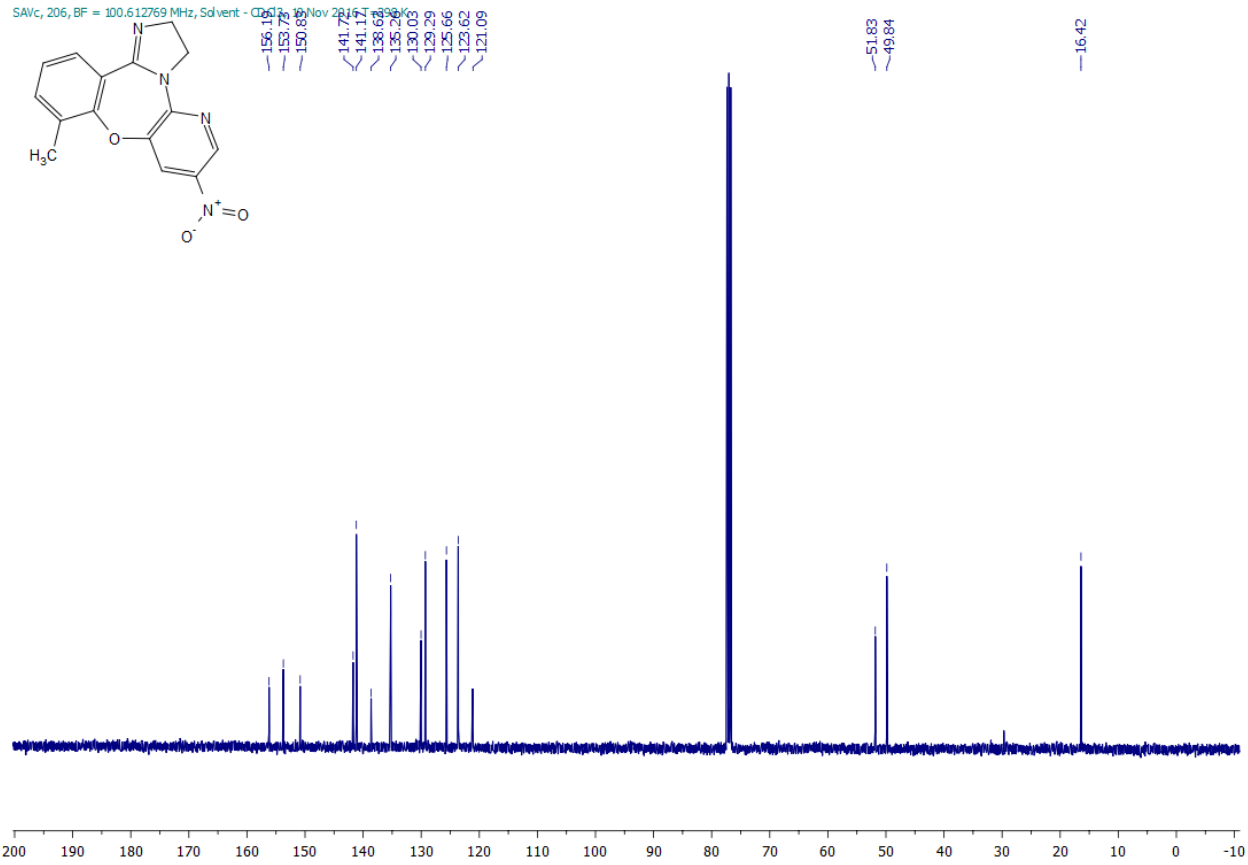
^{1}H and ^{13}C NMR spectra of compound 10k



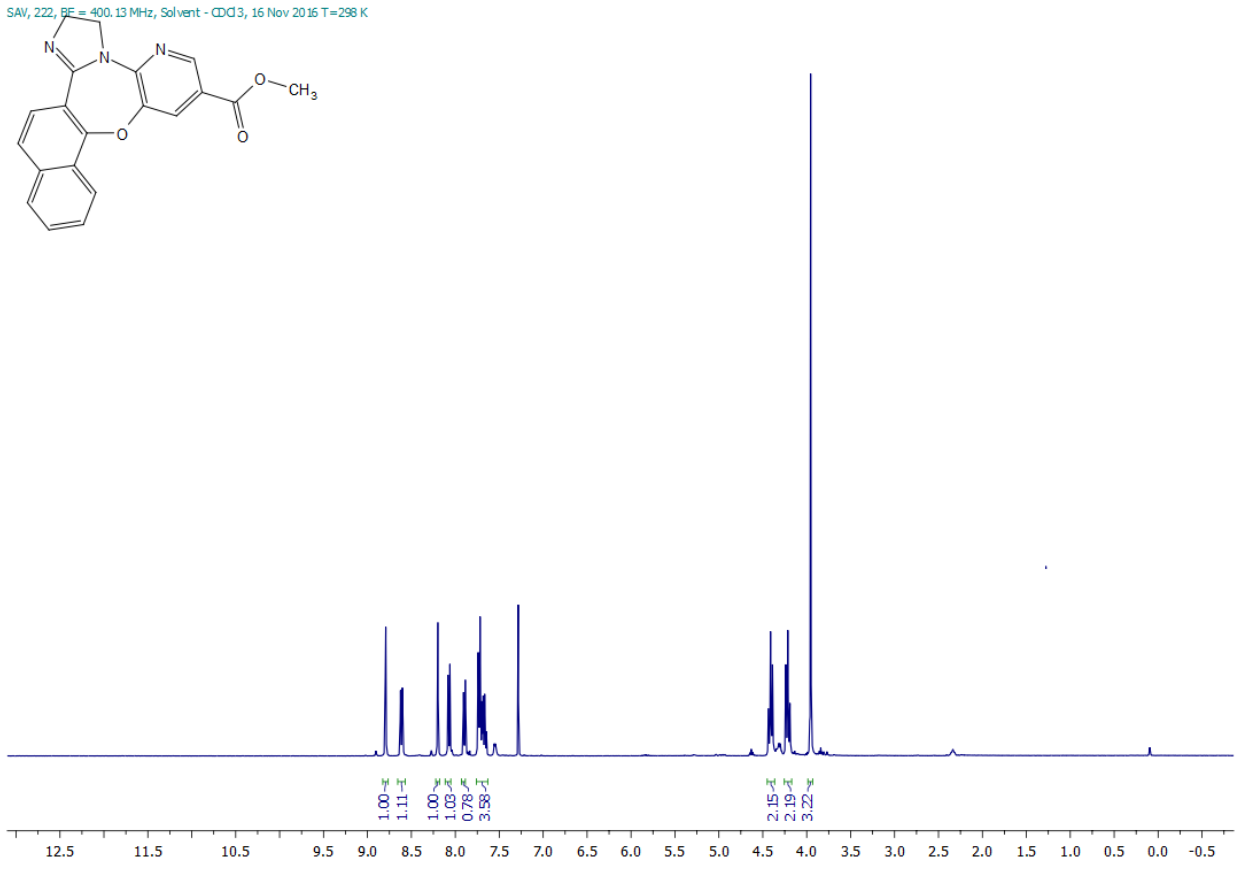


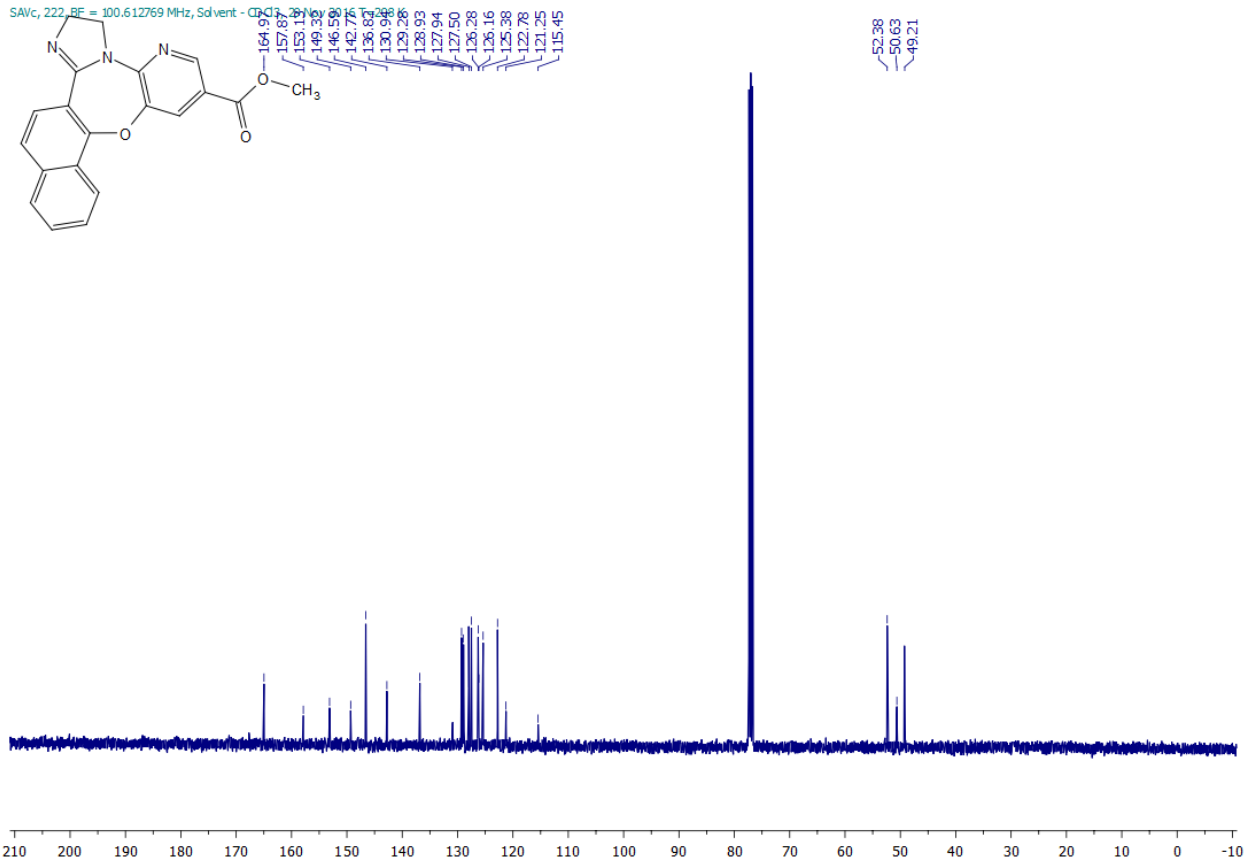
^{1}H and ^{13}C NMR spectra of compound 10l



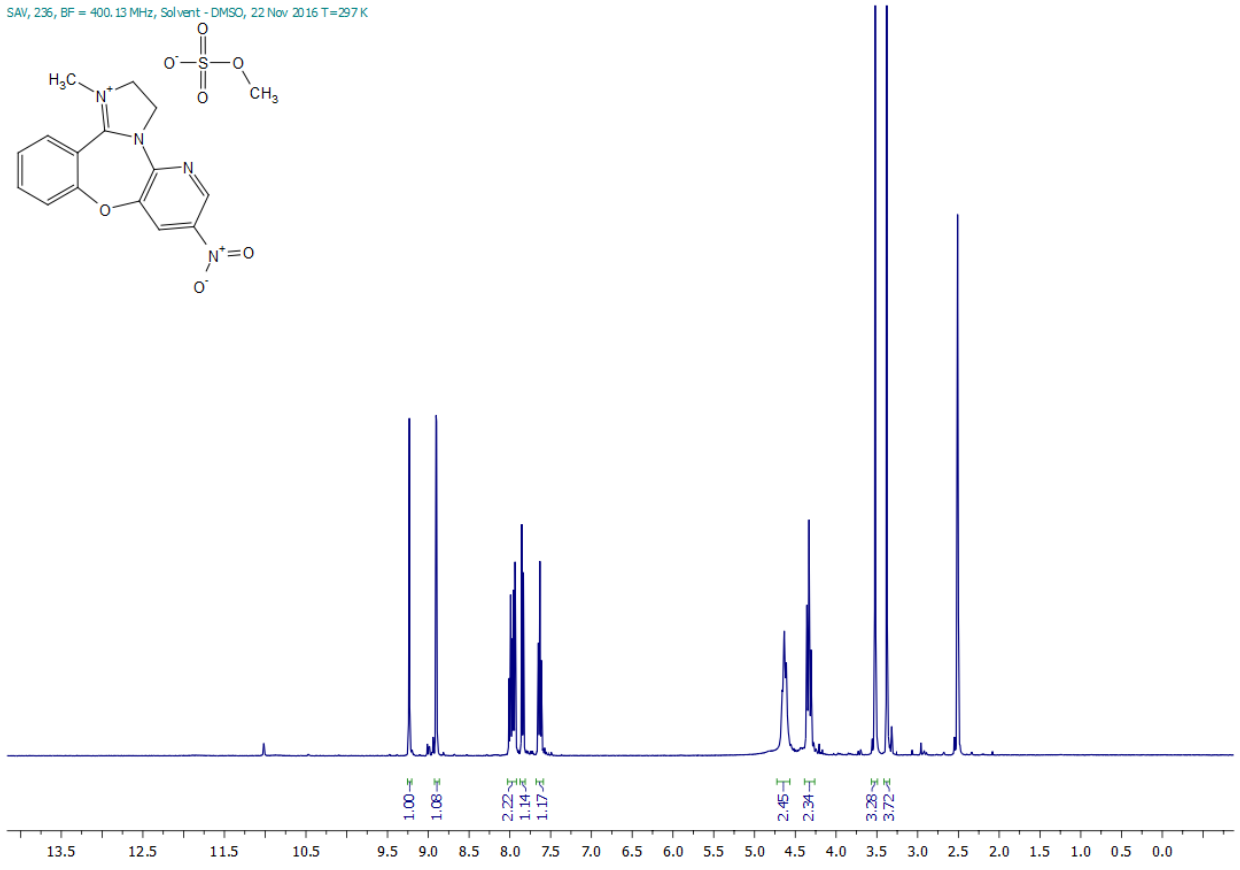


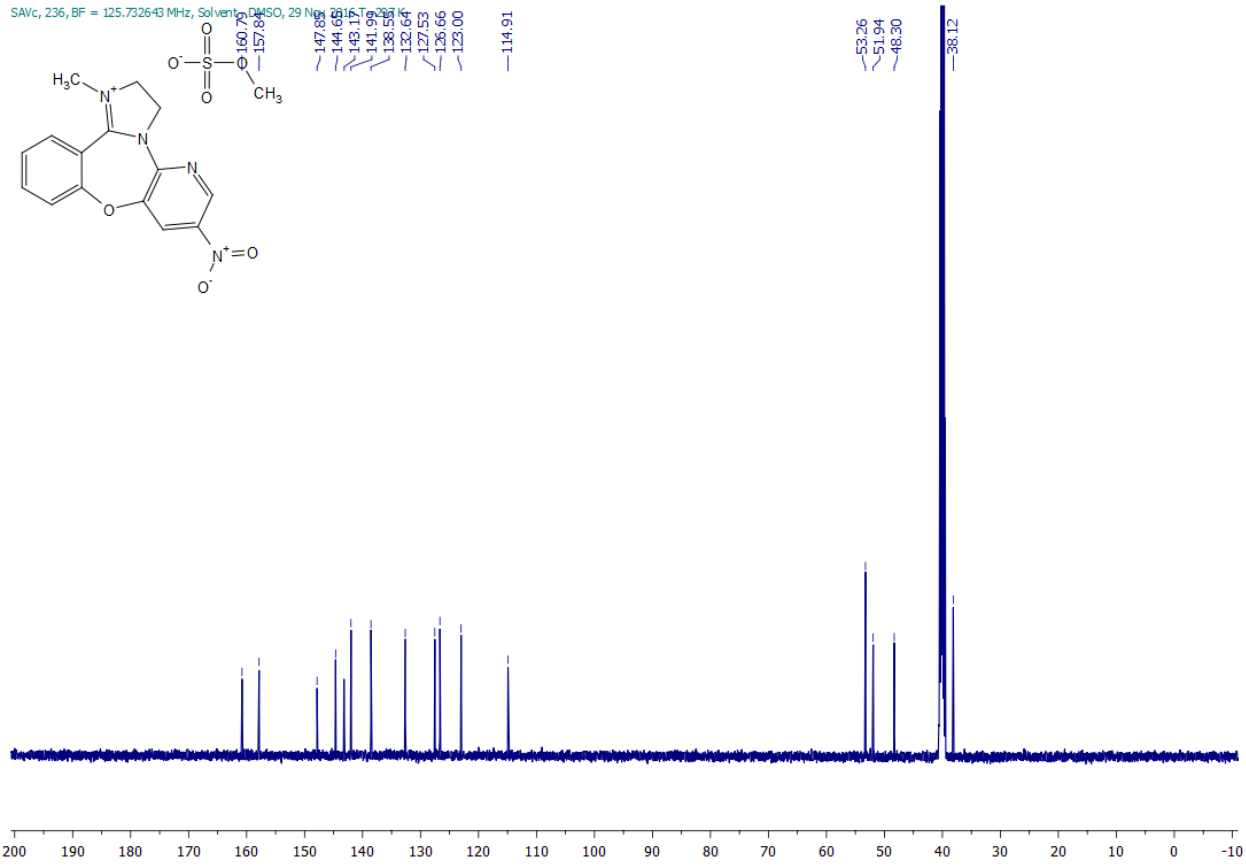
^{1}H and ^{13}C NMR spectra of compound 10m



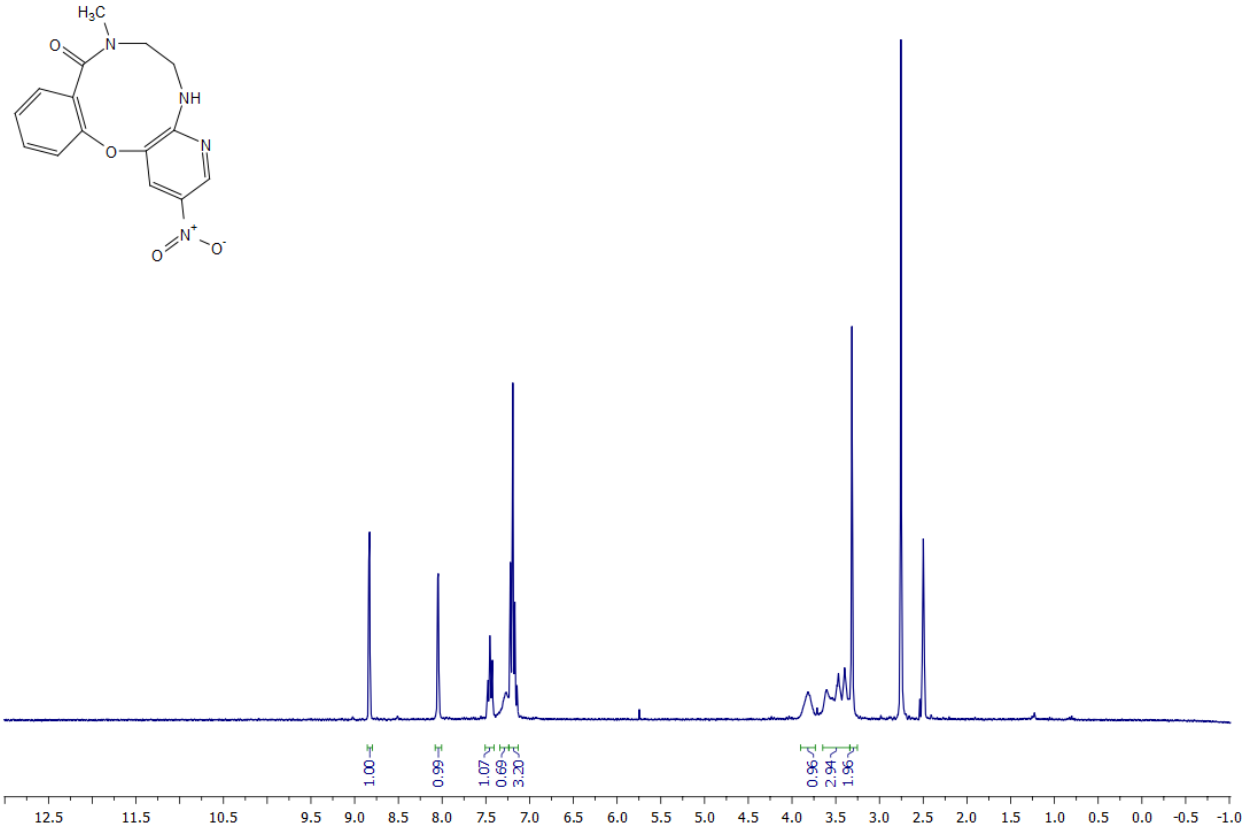


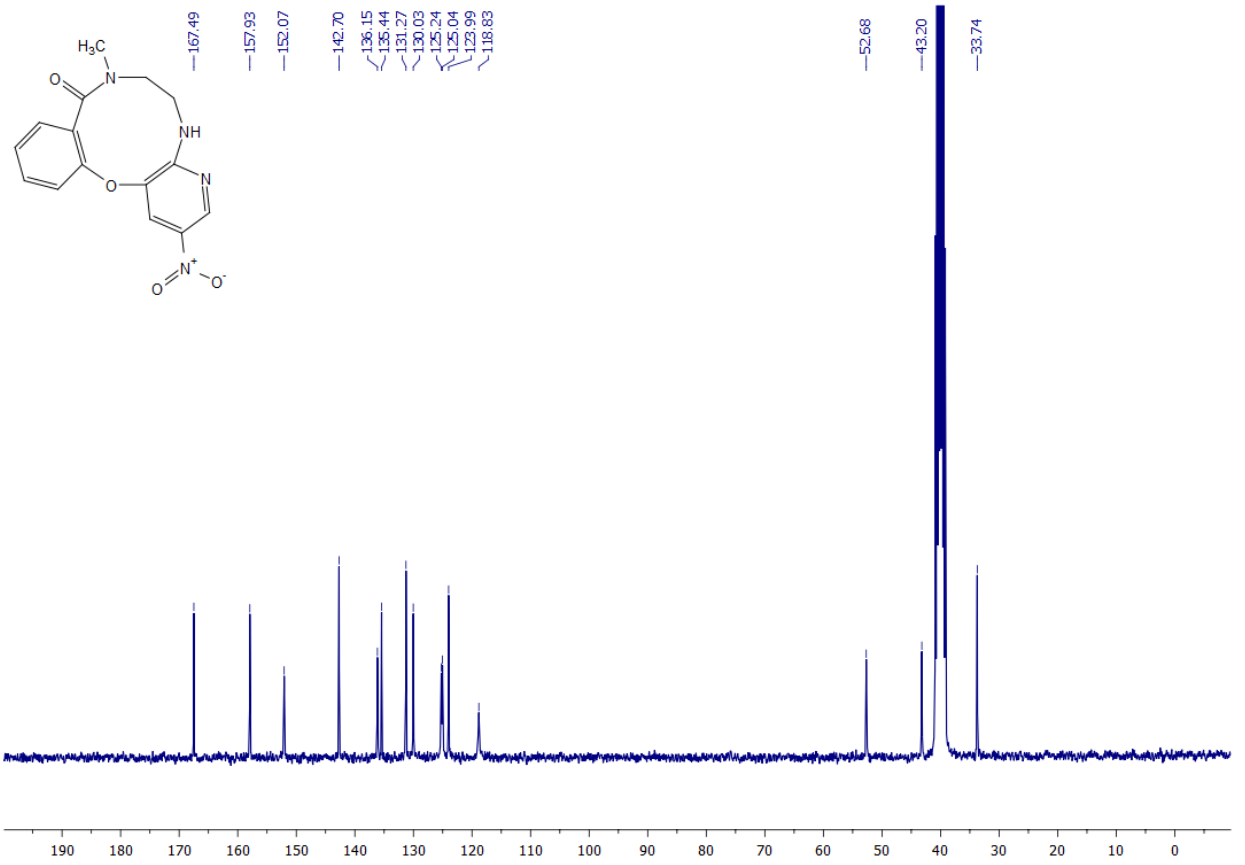
^{1}H and ^{13}C NMR spectra of compound 11a



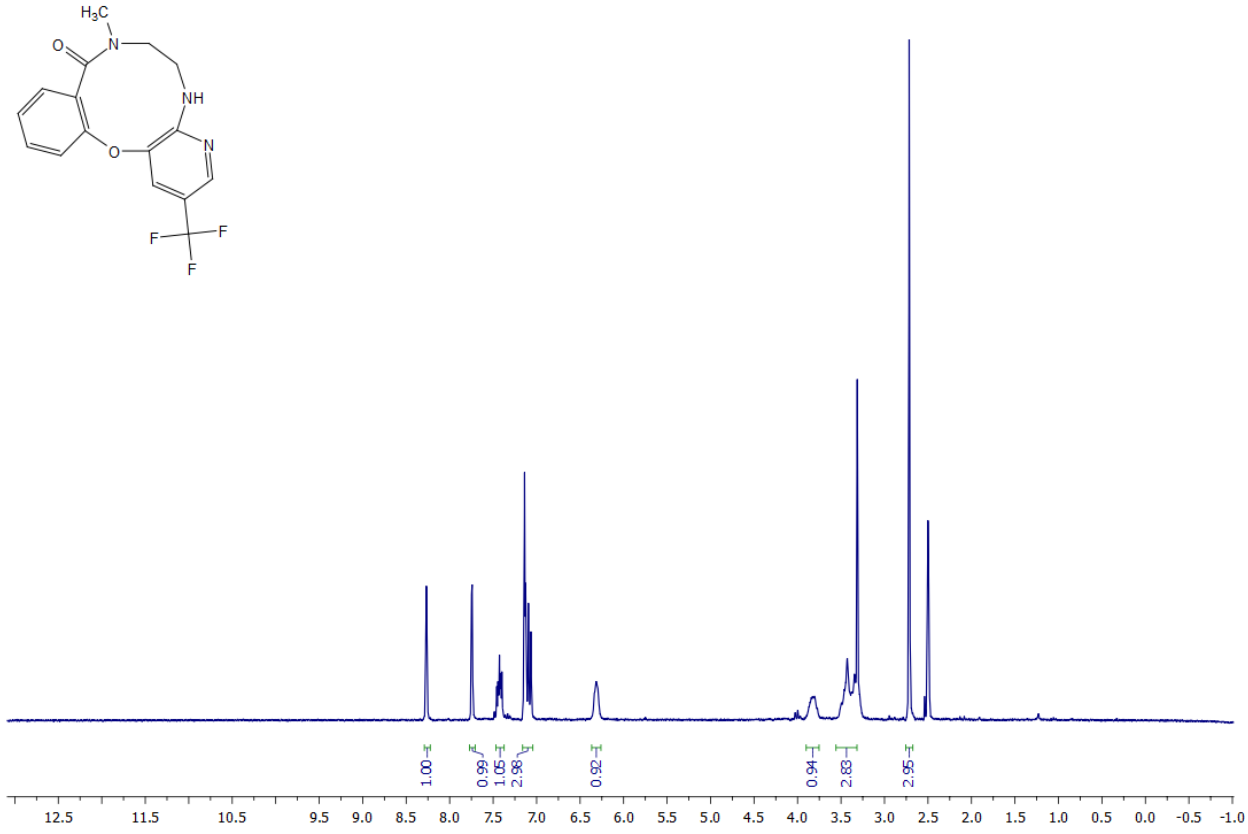


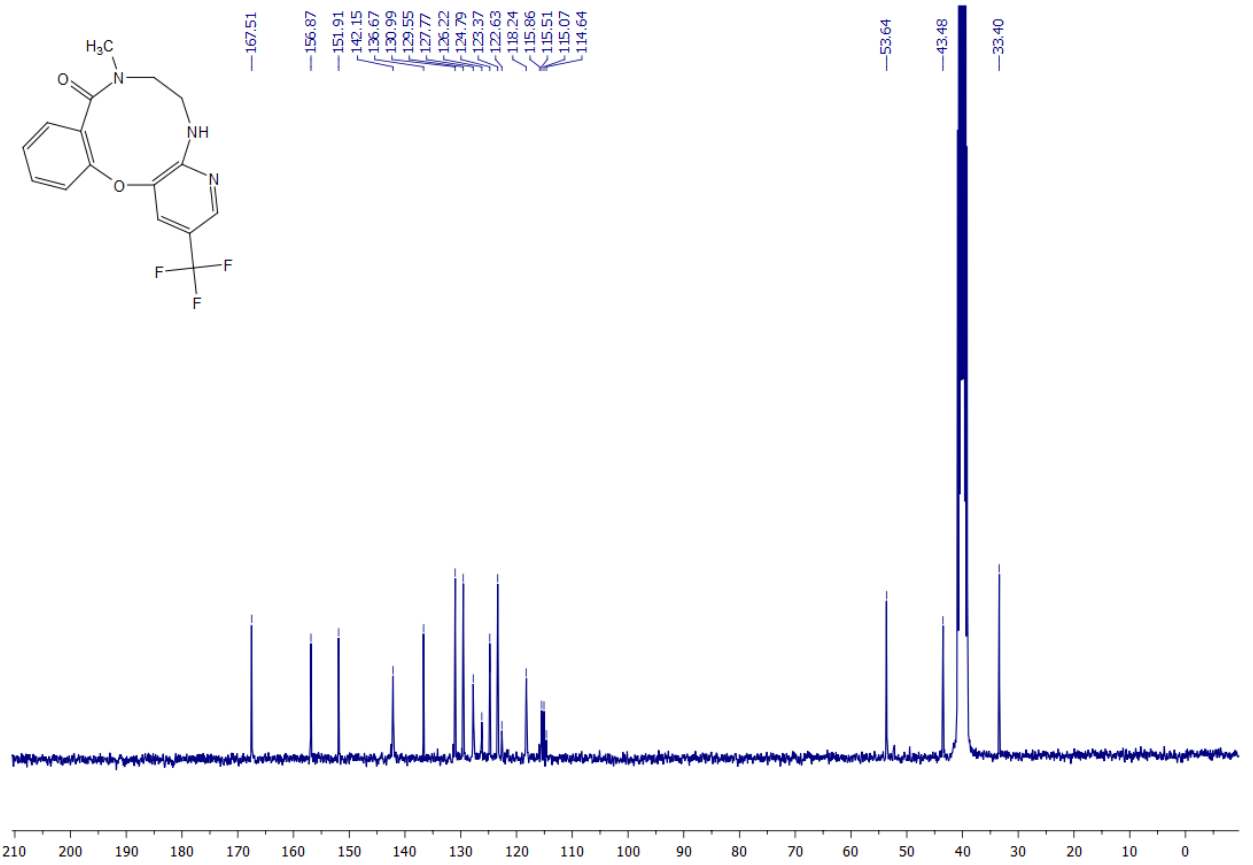
^{1}H and ^{13}C NMR spectra of compound 12a



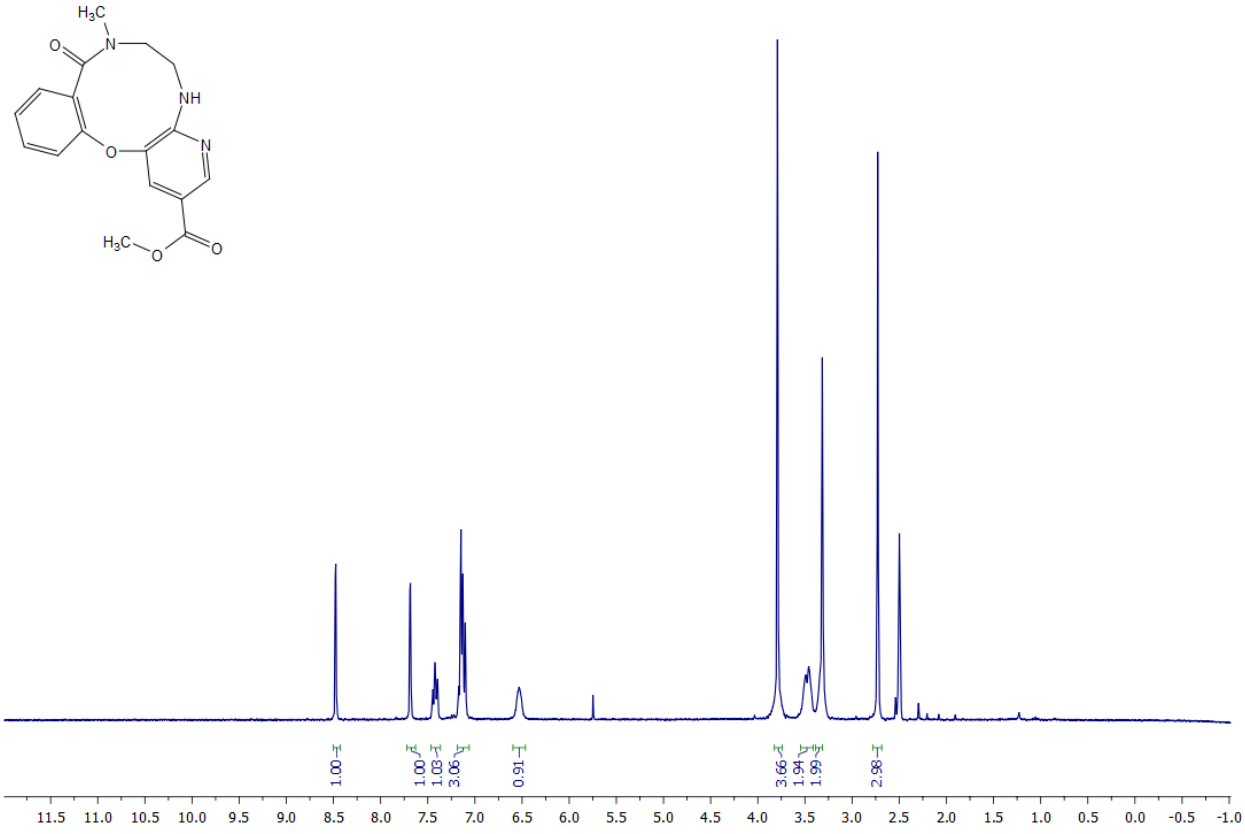


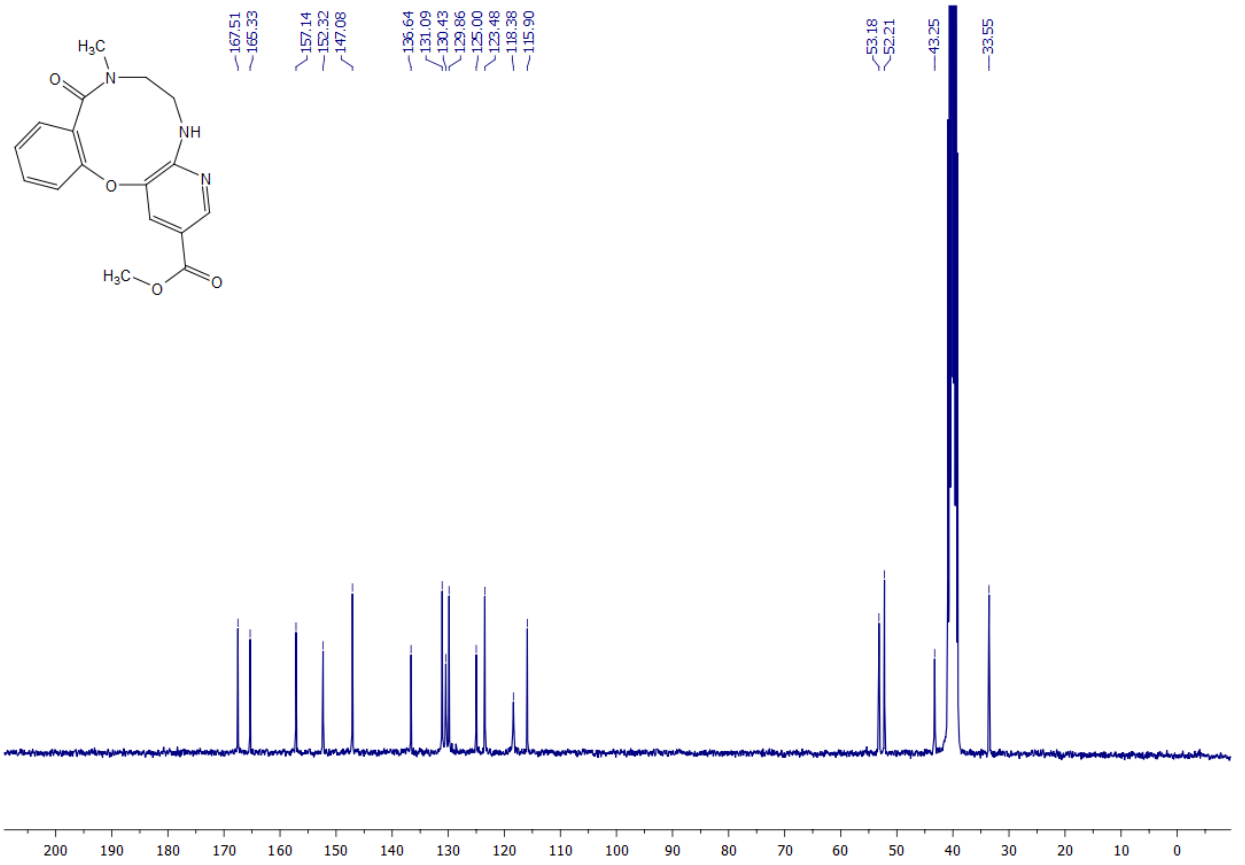
^{1}H and ^{13}C NMR spectra of compound 12b



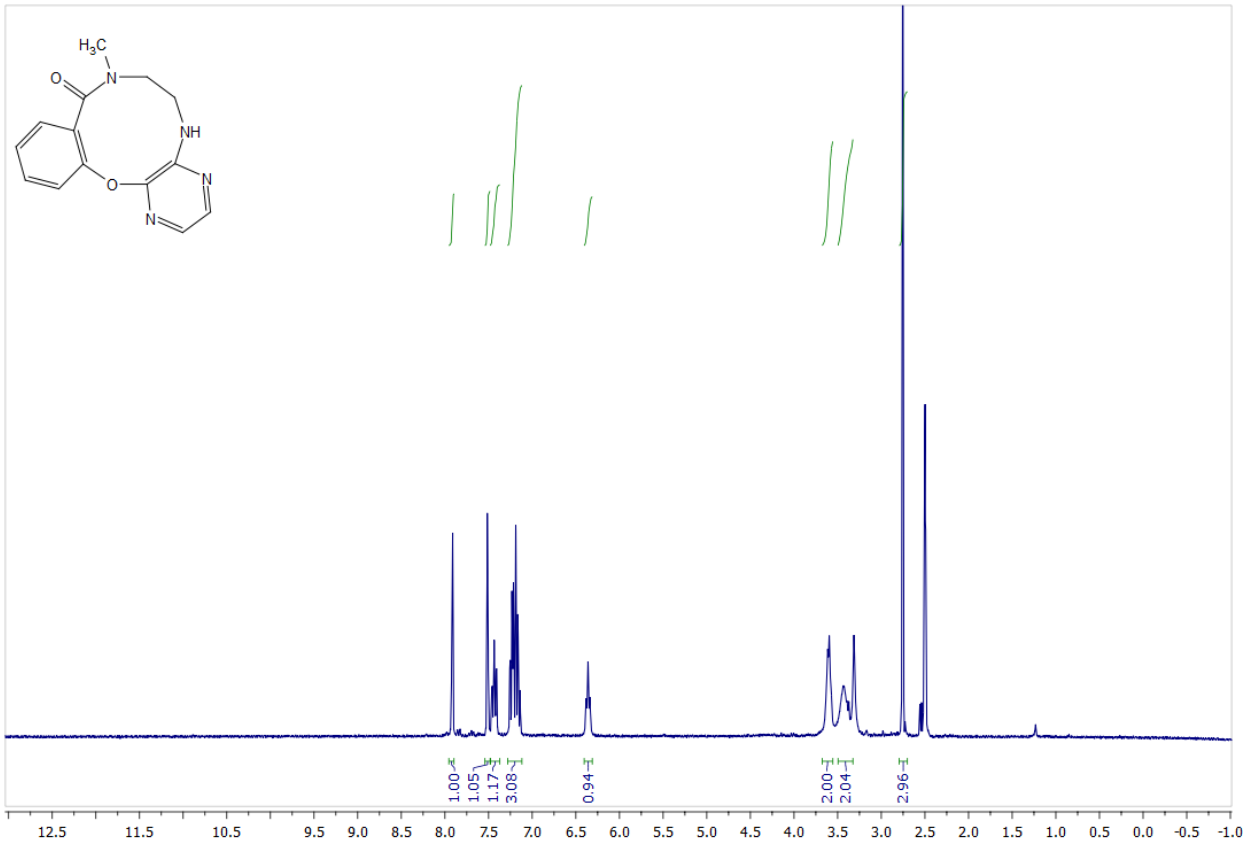


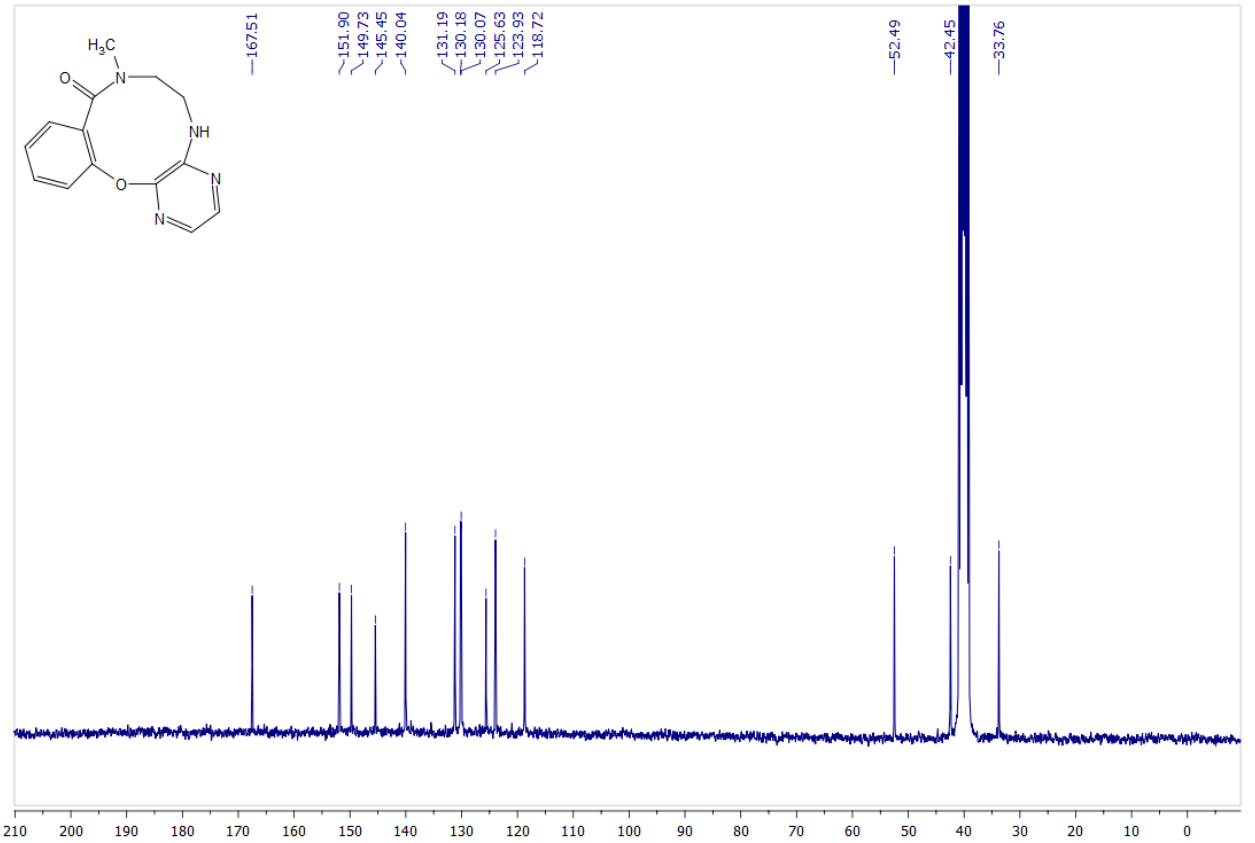
^{1}H and ^{13}C NMR spectra of compound 12c



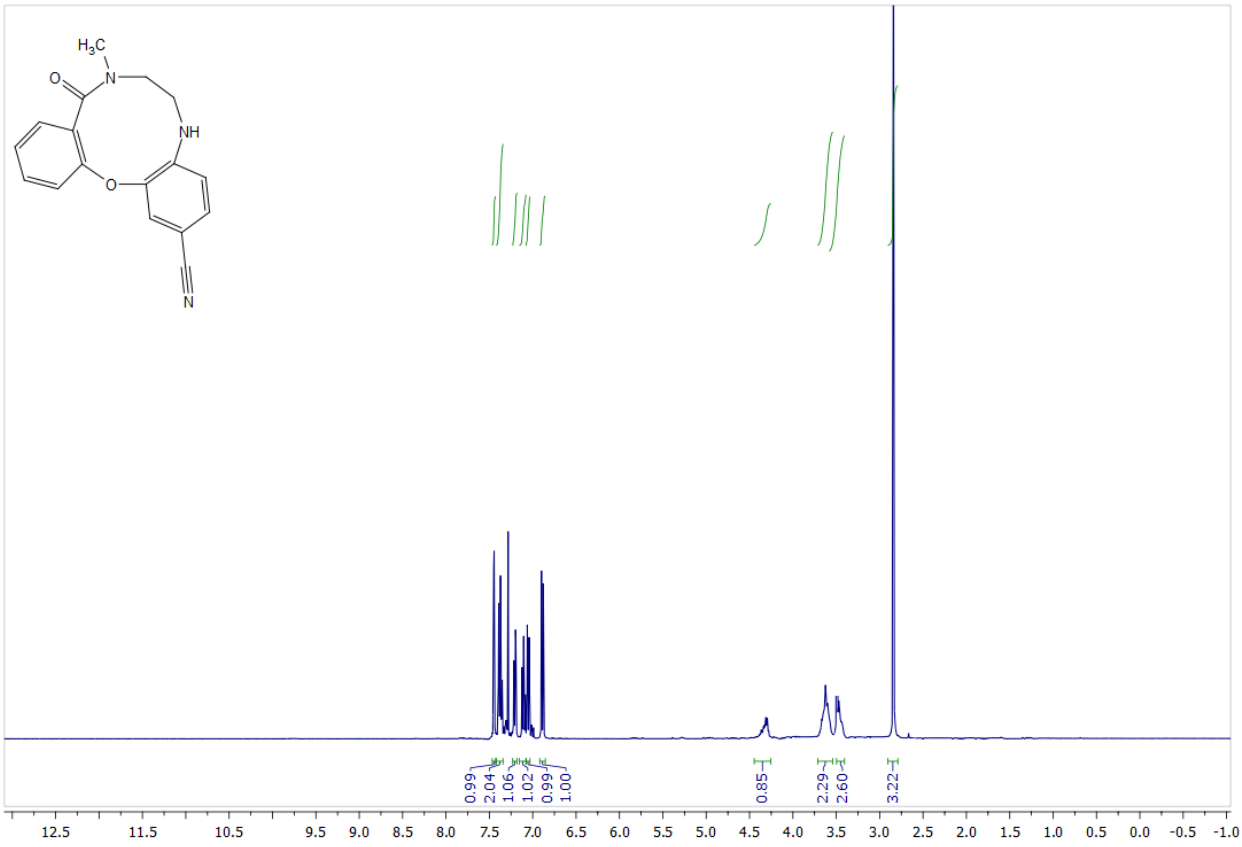


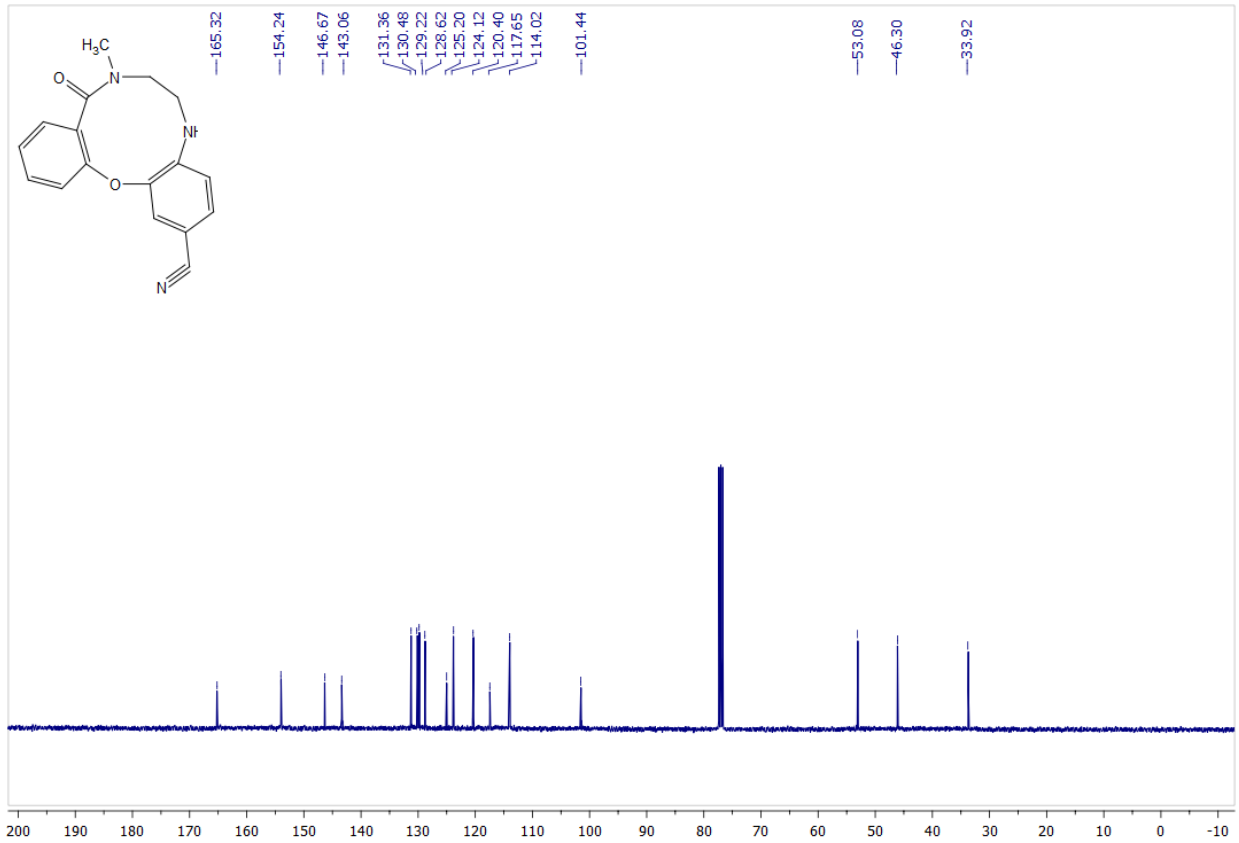
^{1}H and ^{13}C NMR spectra of compound 12d



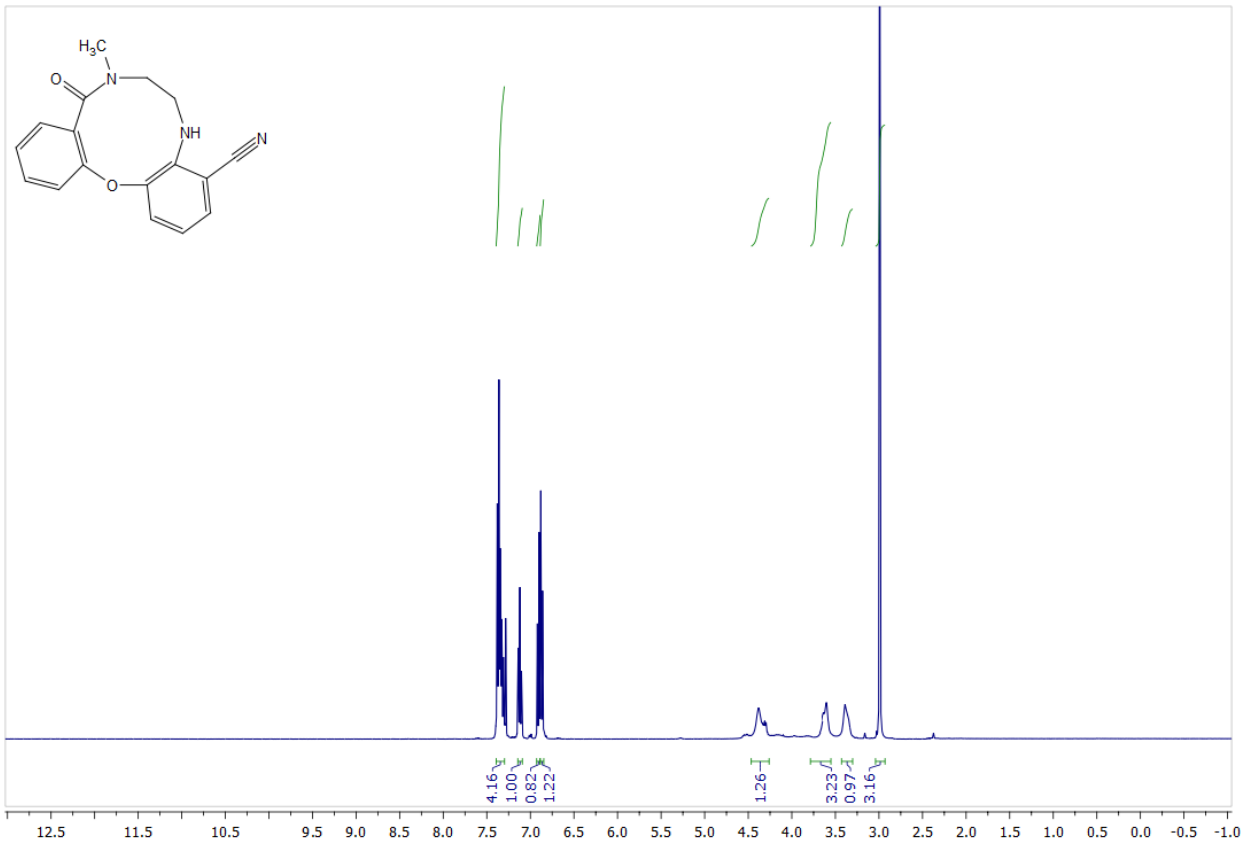


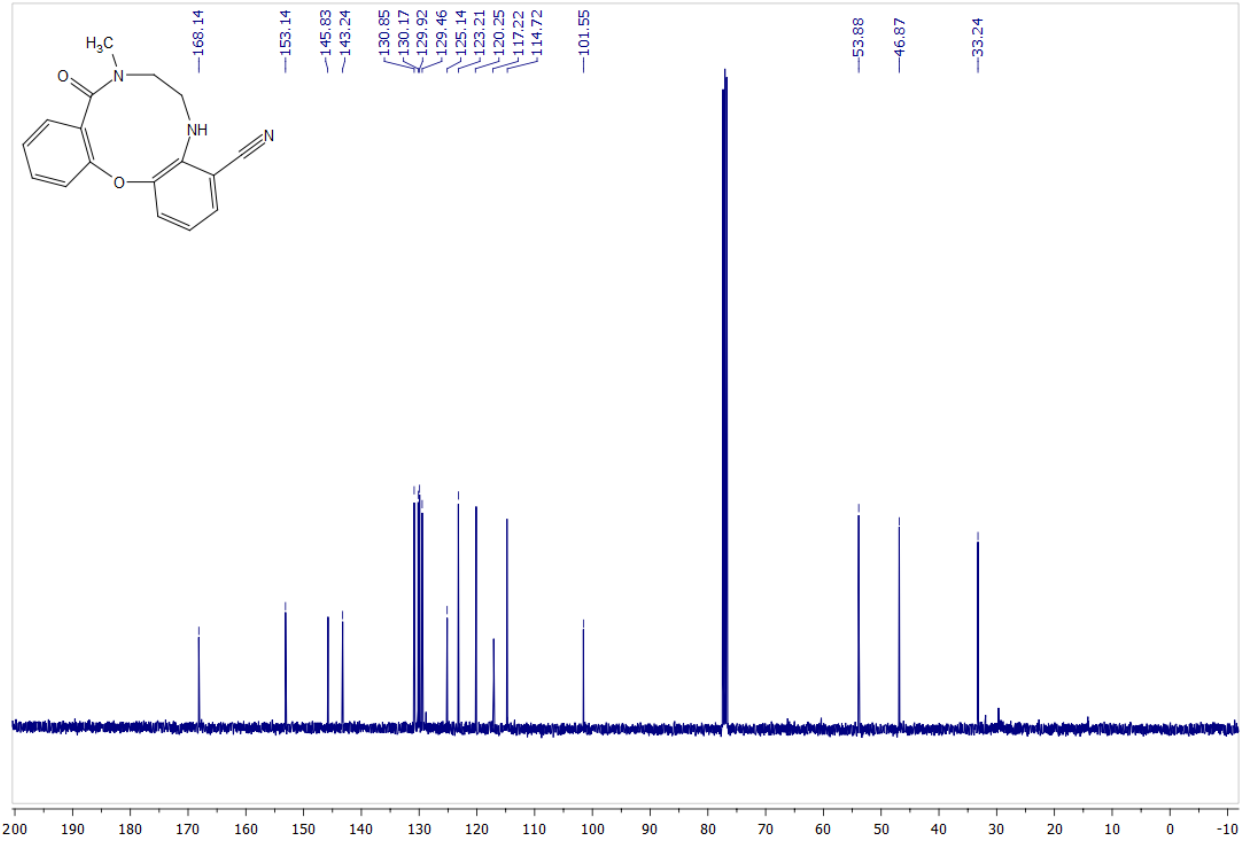
^{1}H and ^{13}C NMR spectra of compound 12e



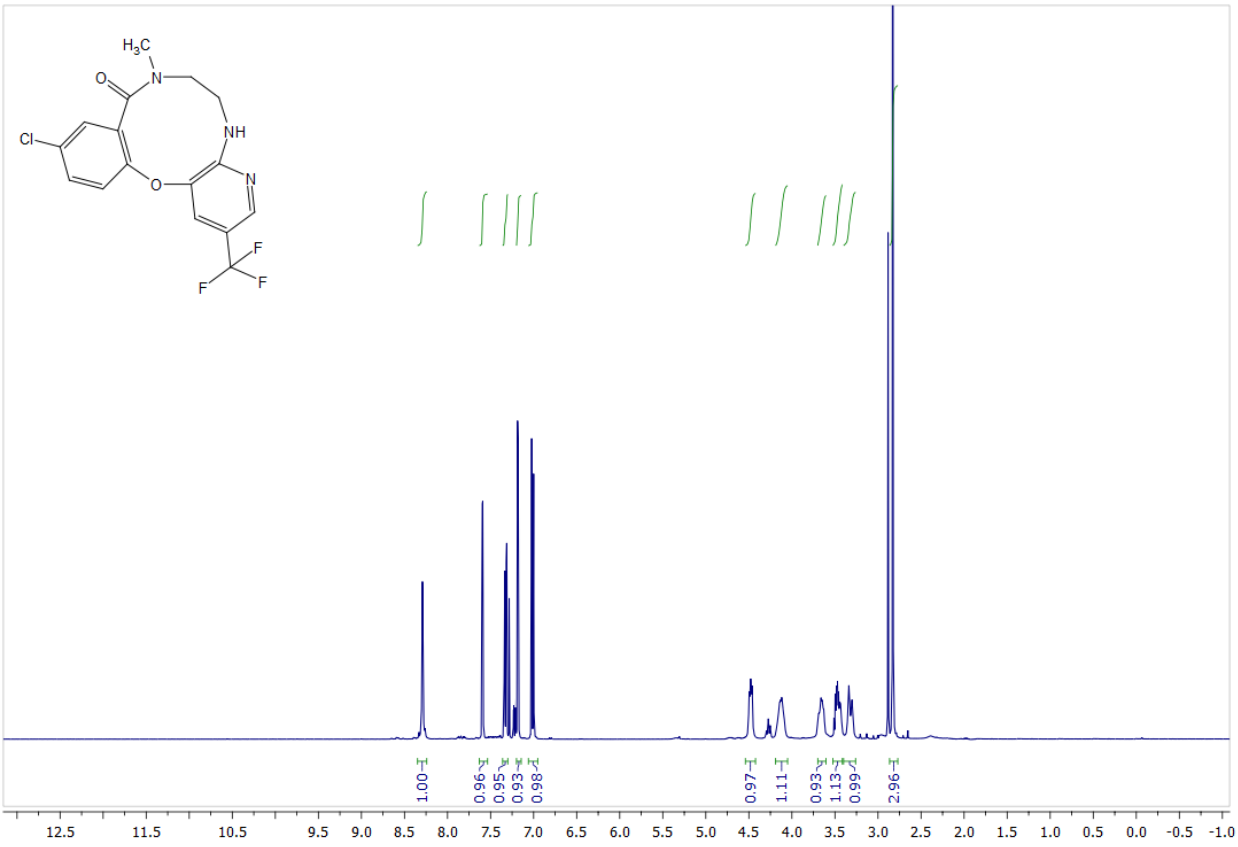


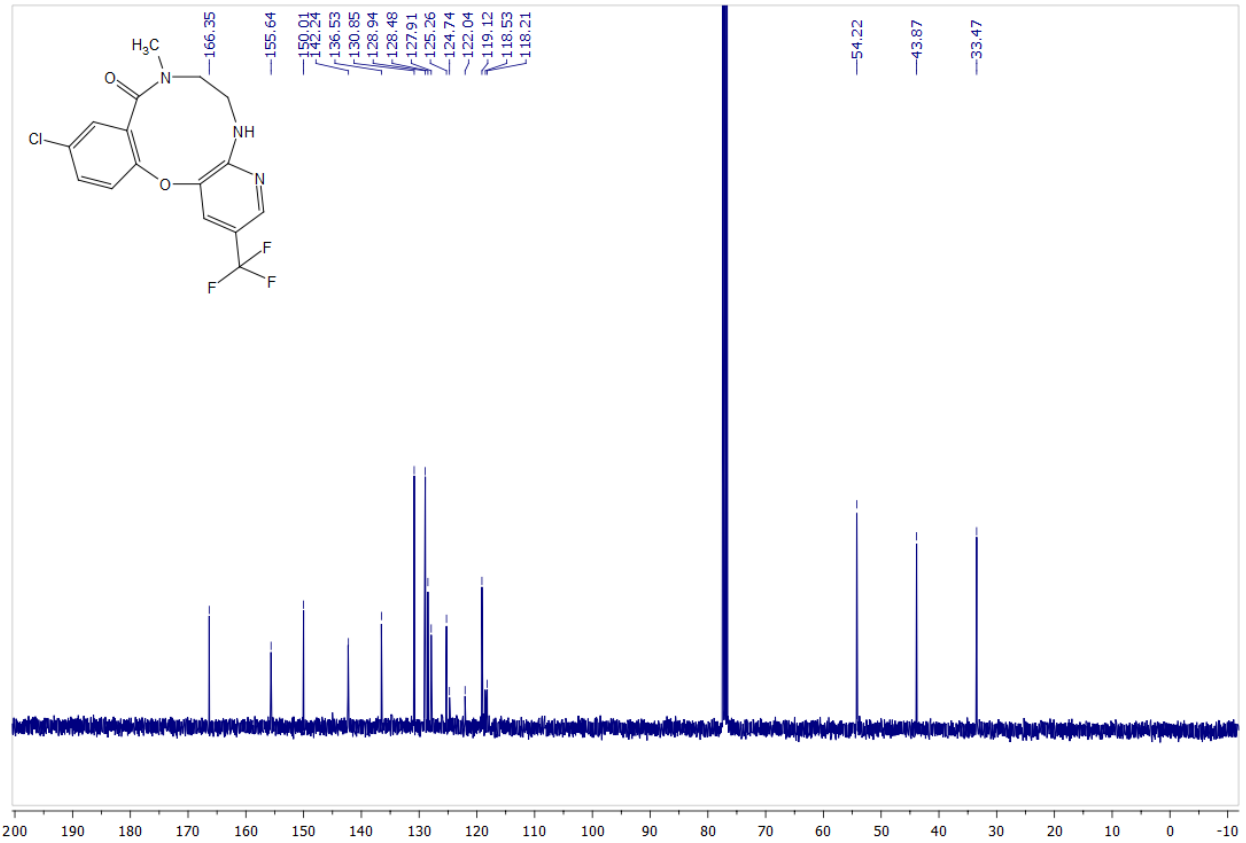
^{1}H and ^{13}C NMR spectra of compound 12f



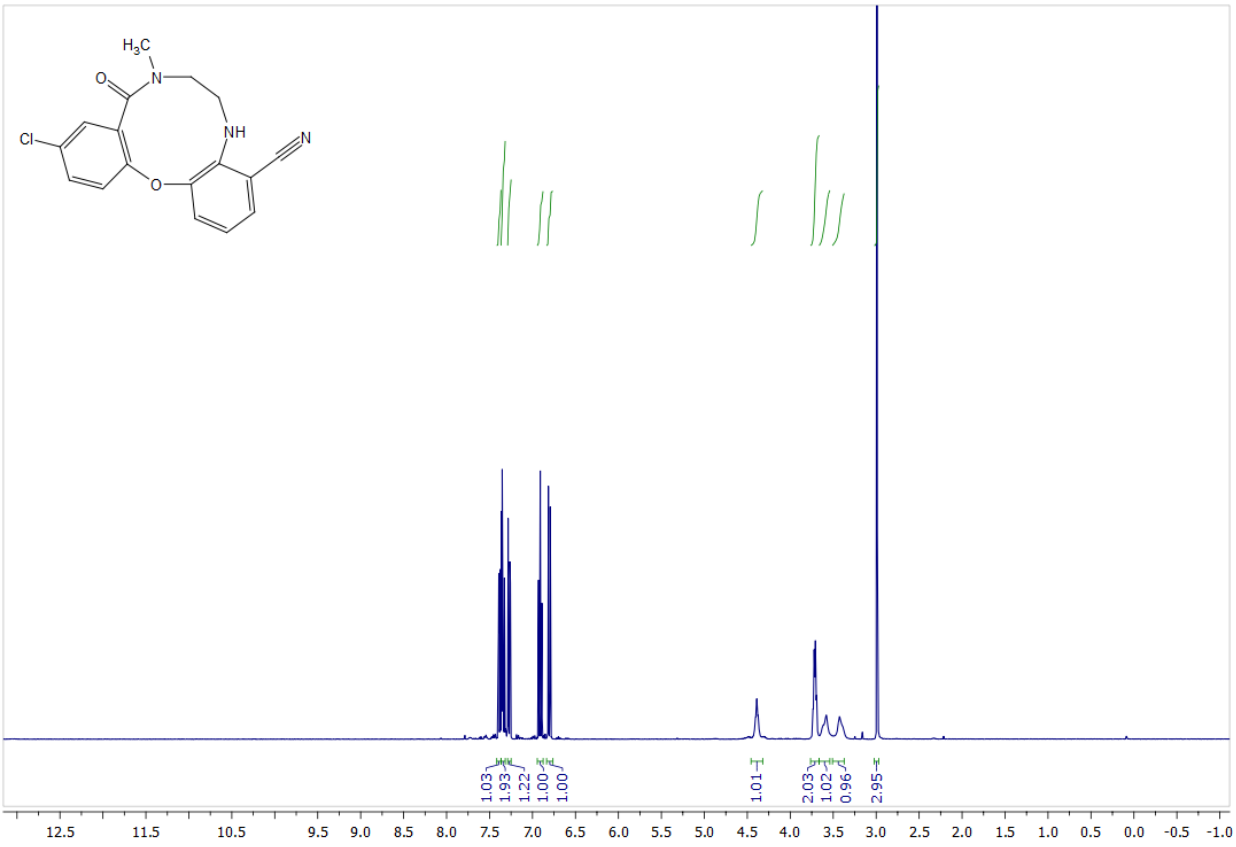


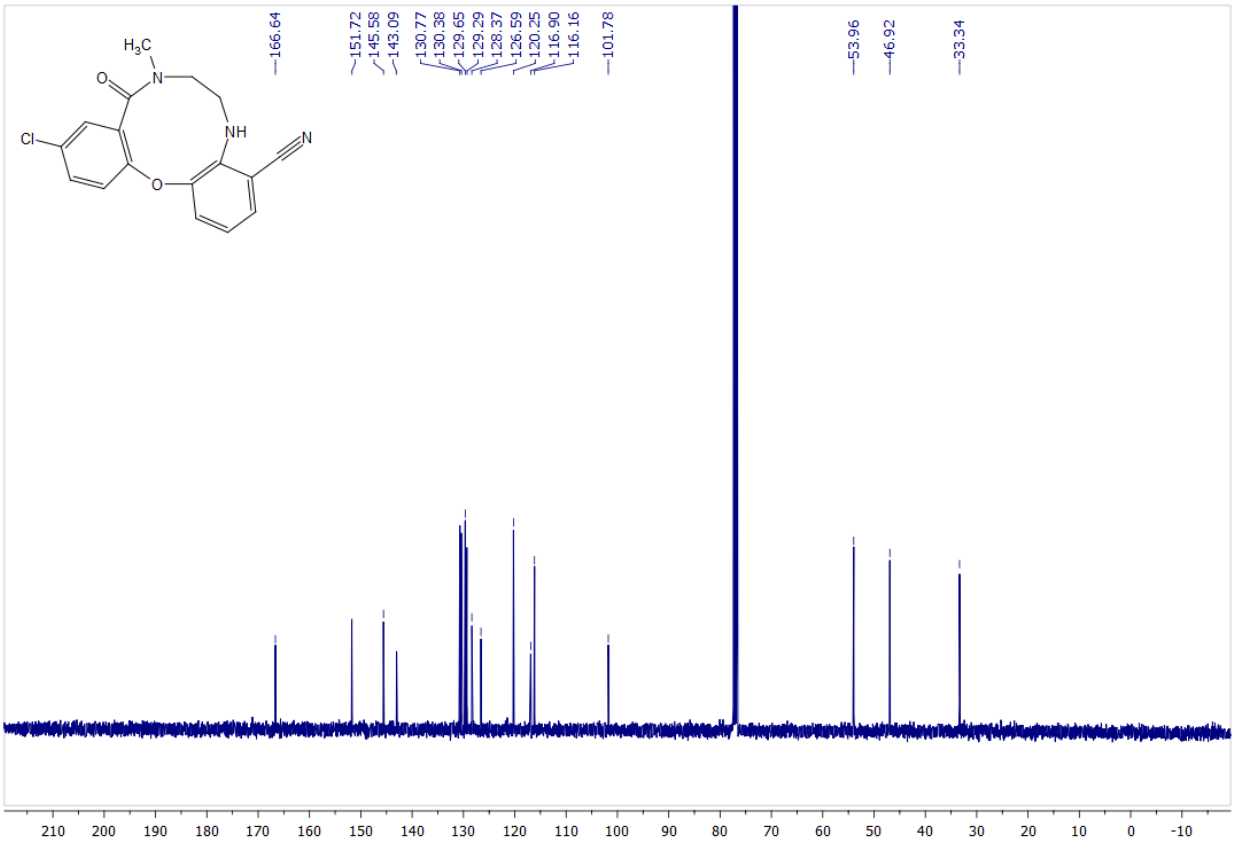
^{1}H and ^{13}C NMR spectra of compound 12g



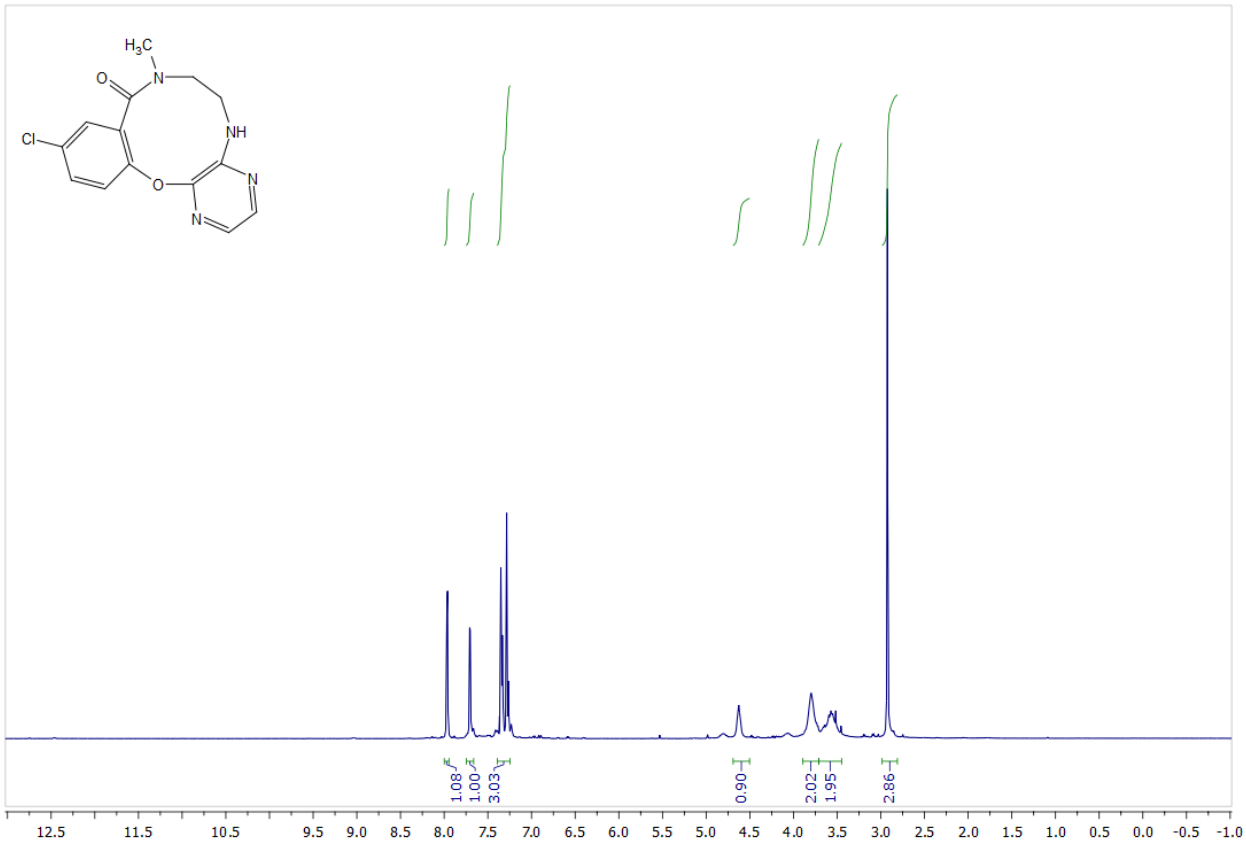


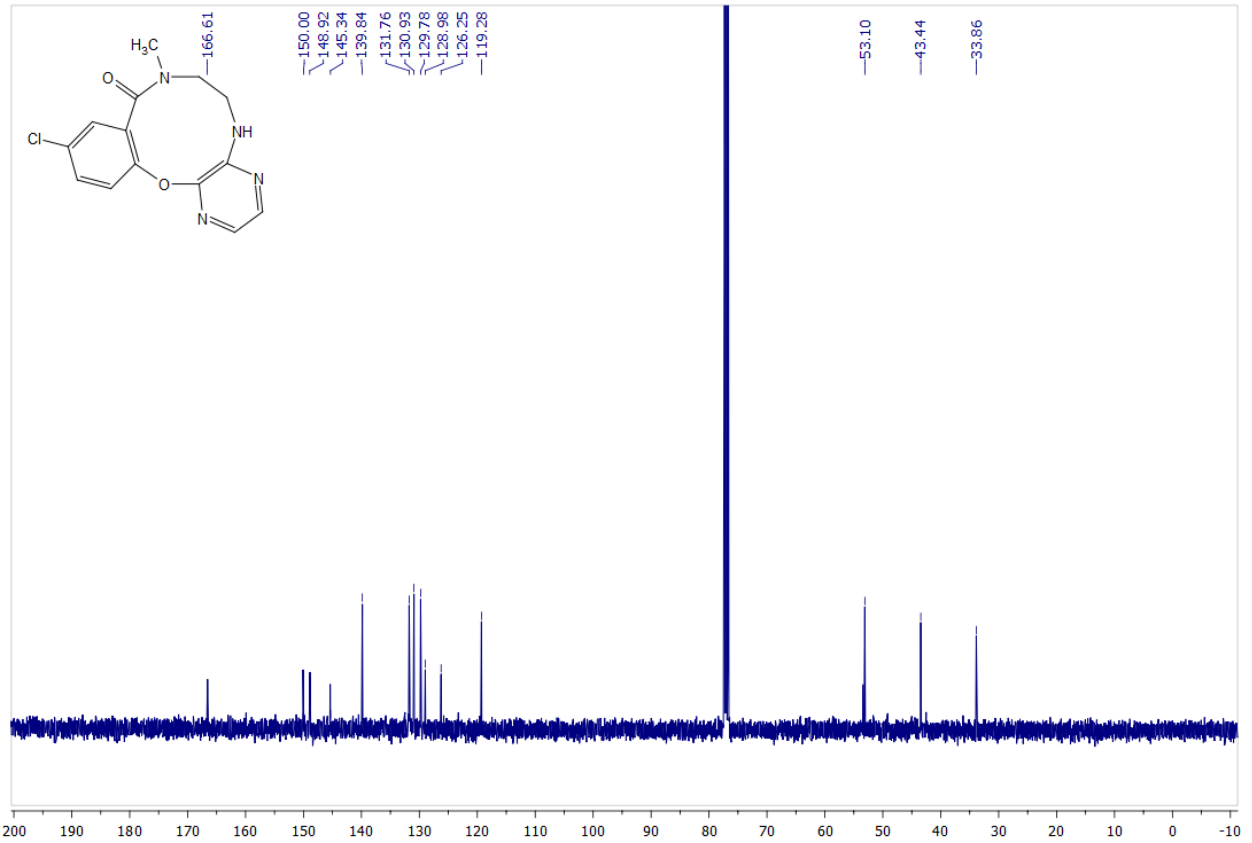
^{1}H and ^{13}C NMR spectra of compound 12h



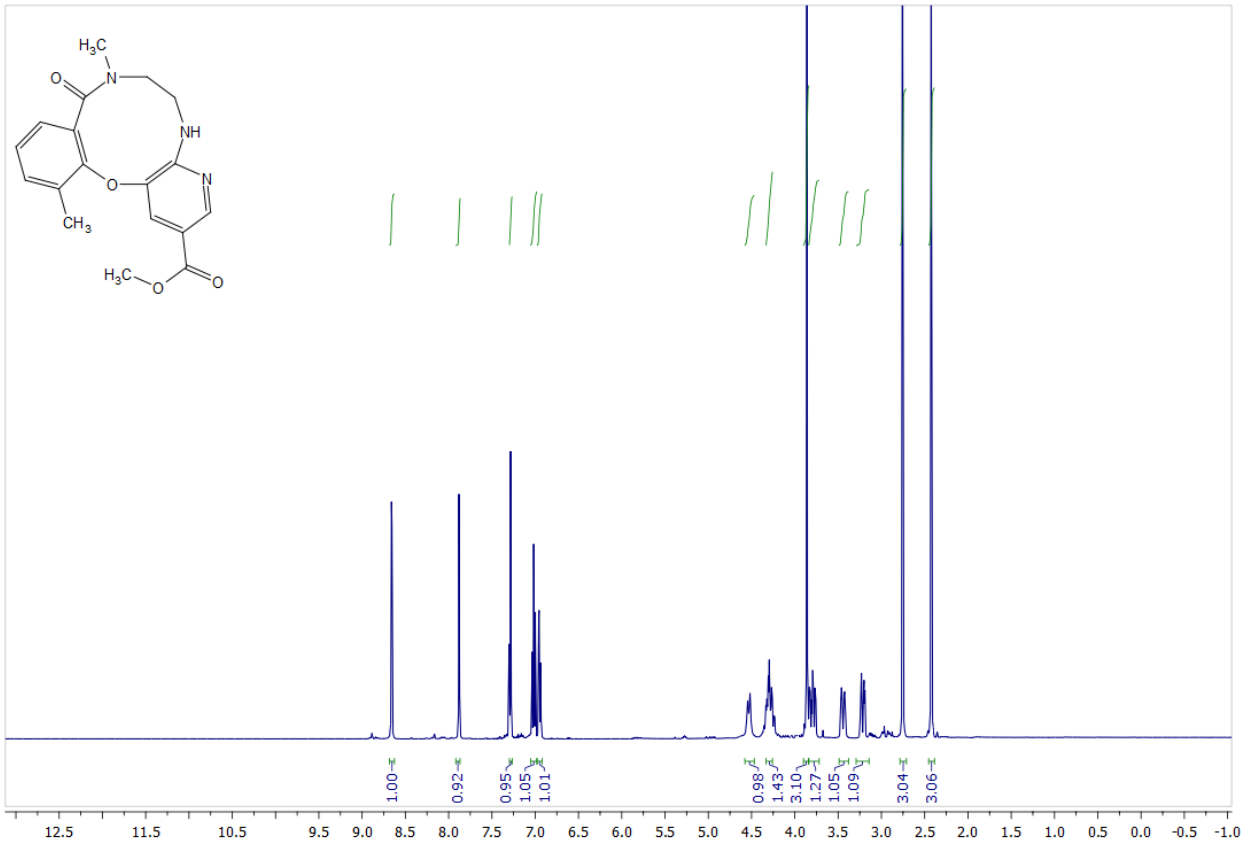


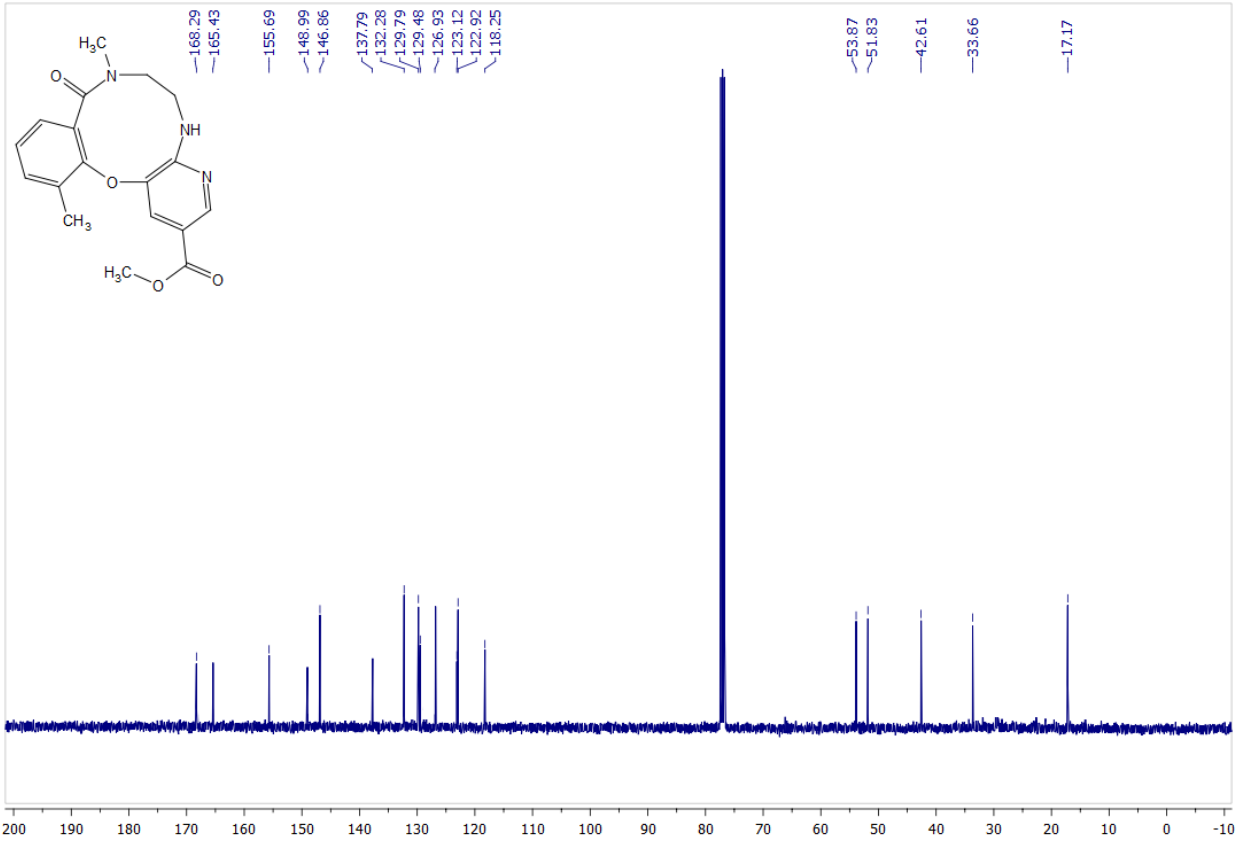
^{1}H and ^{13}C NMR spectra of compound 12i



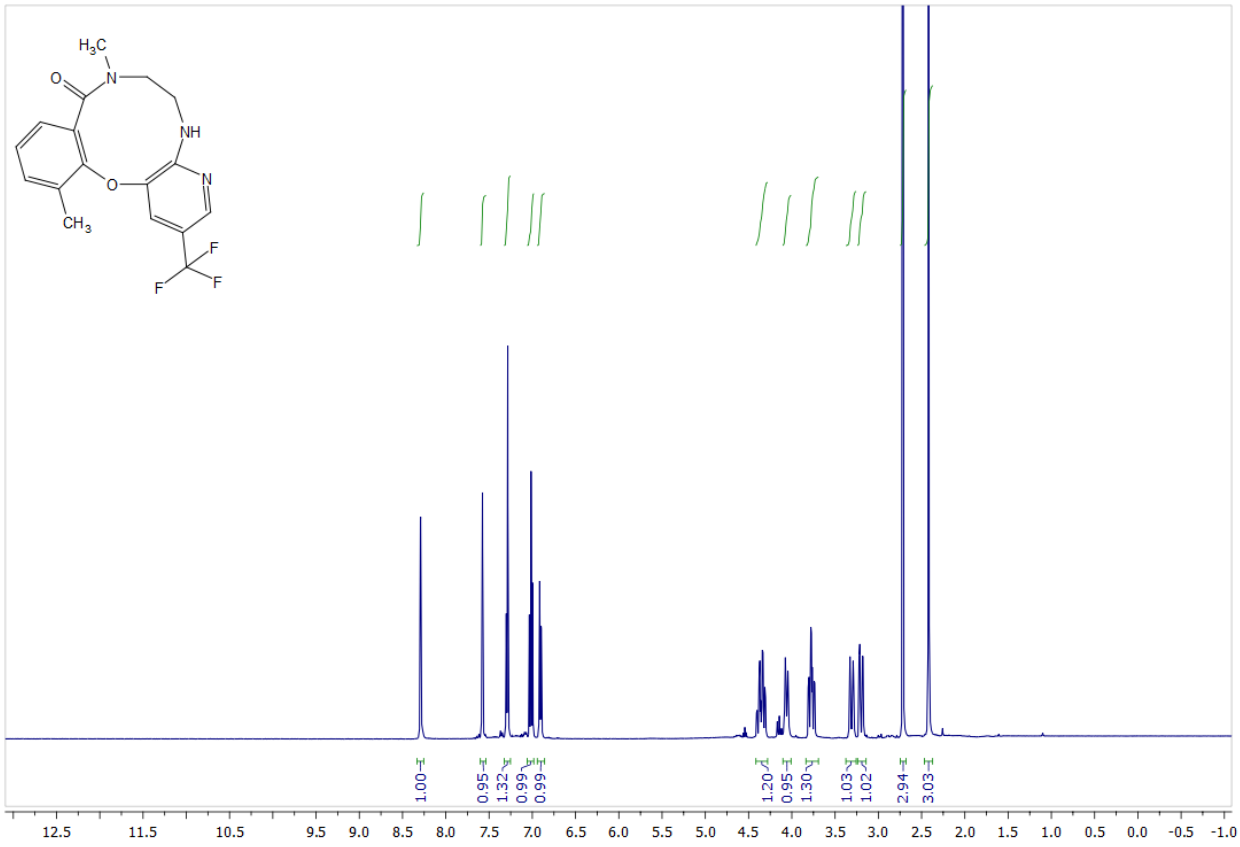


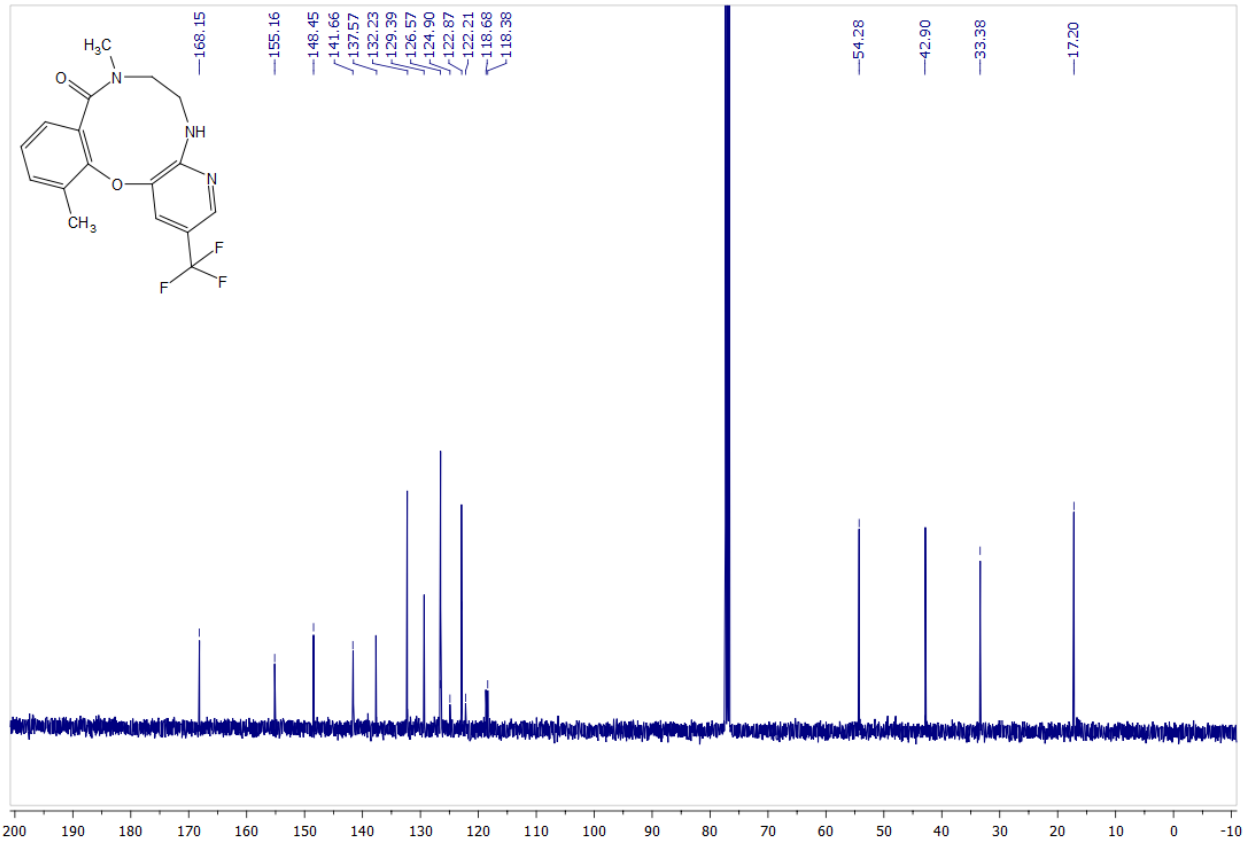
^{1}H and ^{13}C NMR spectra of compound 12j



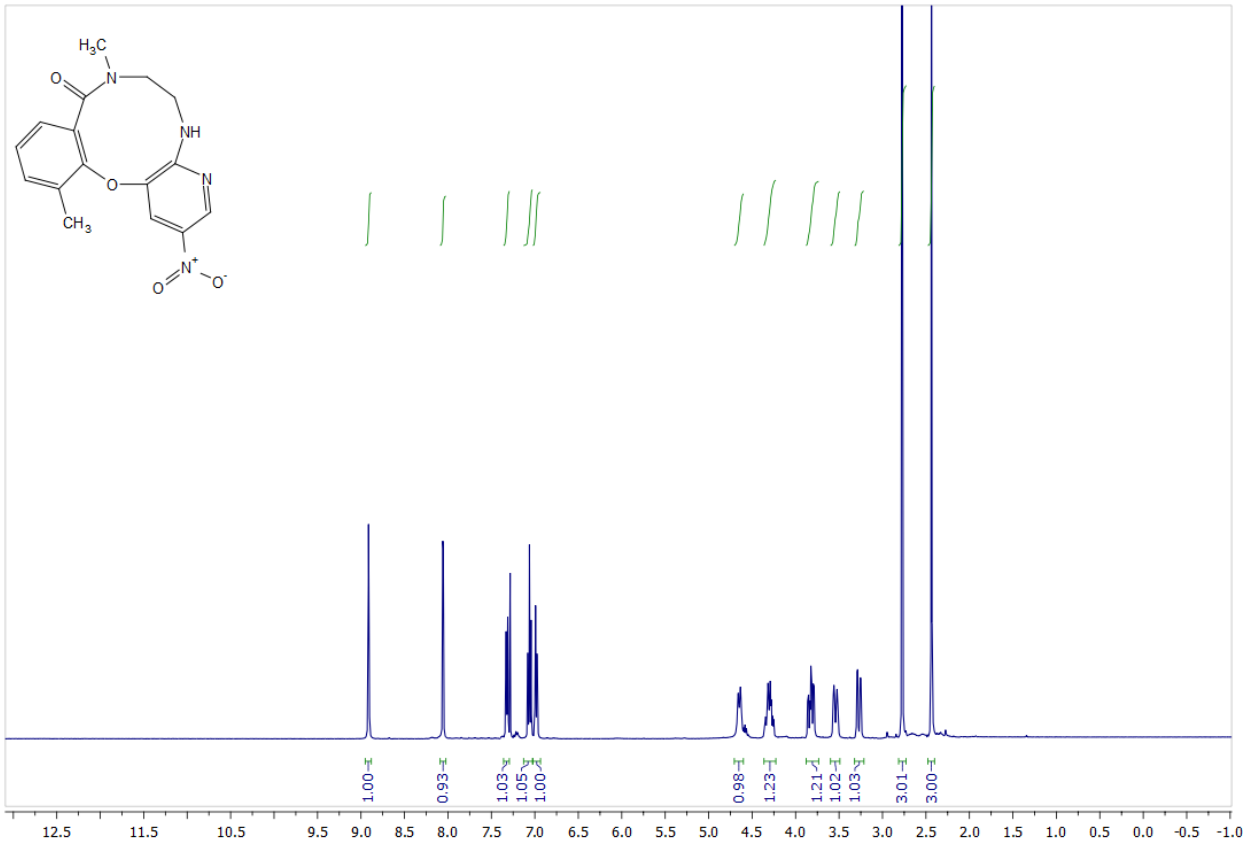


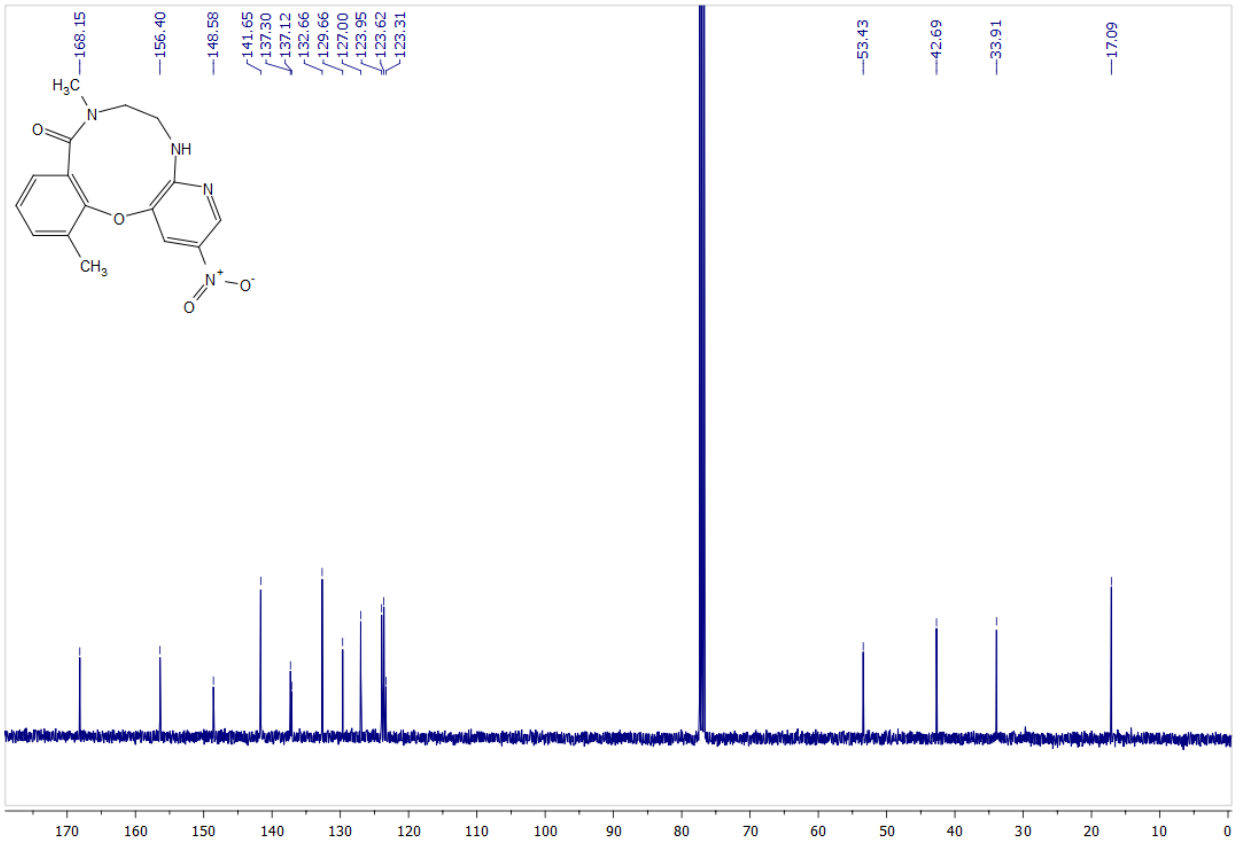
^{1}H and ^{13}C NMR spectra of compound 12k



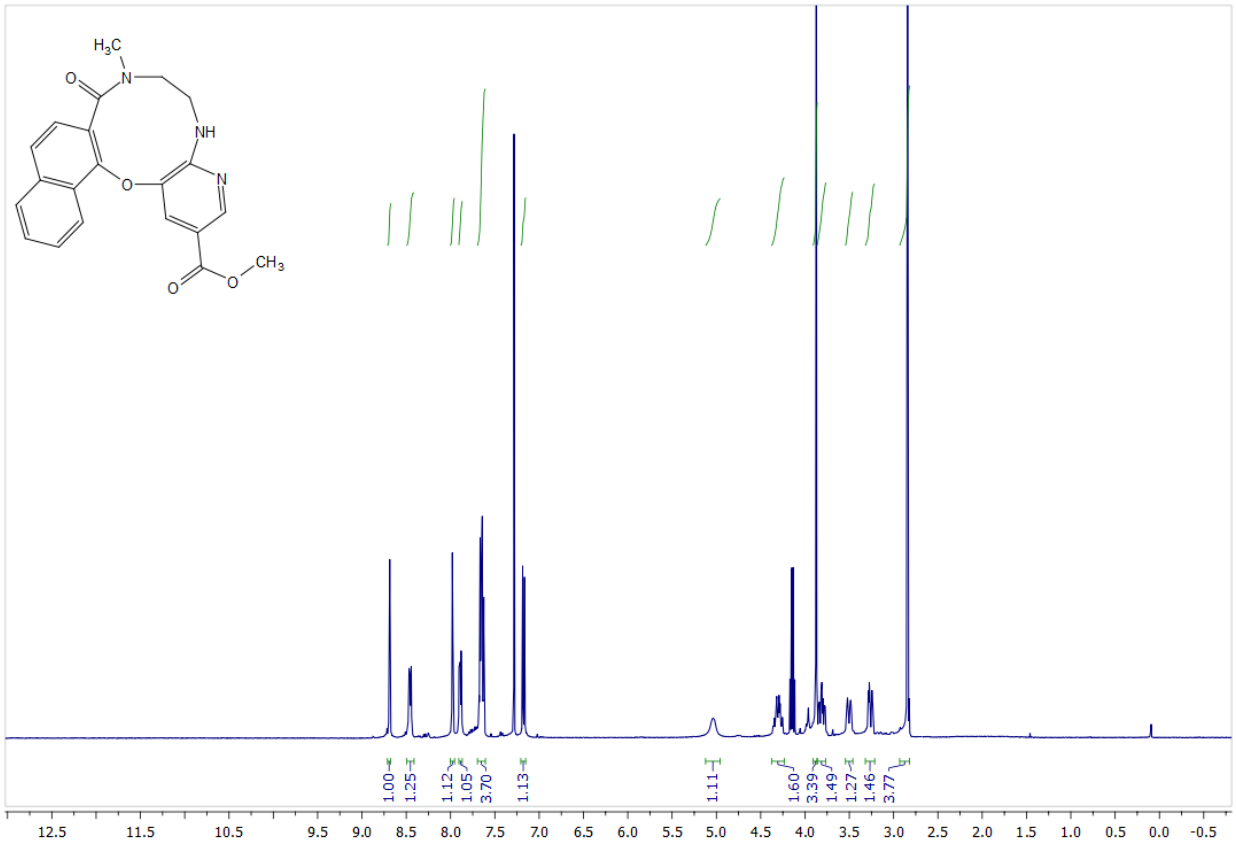


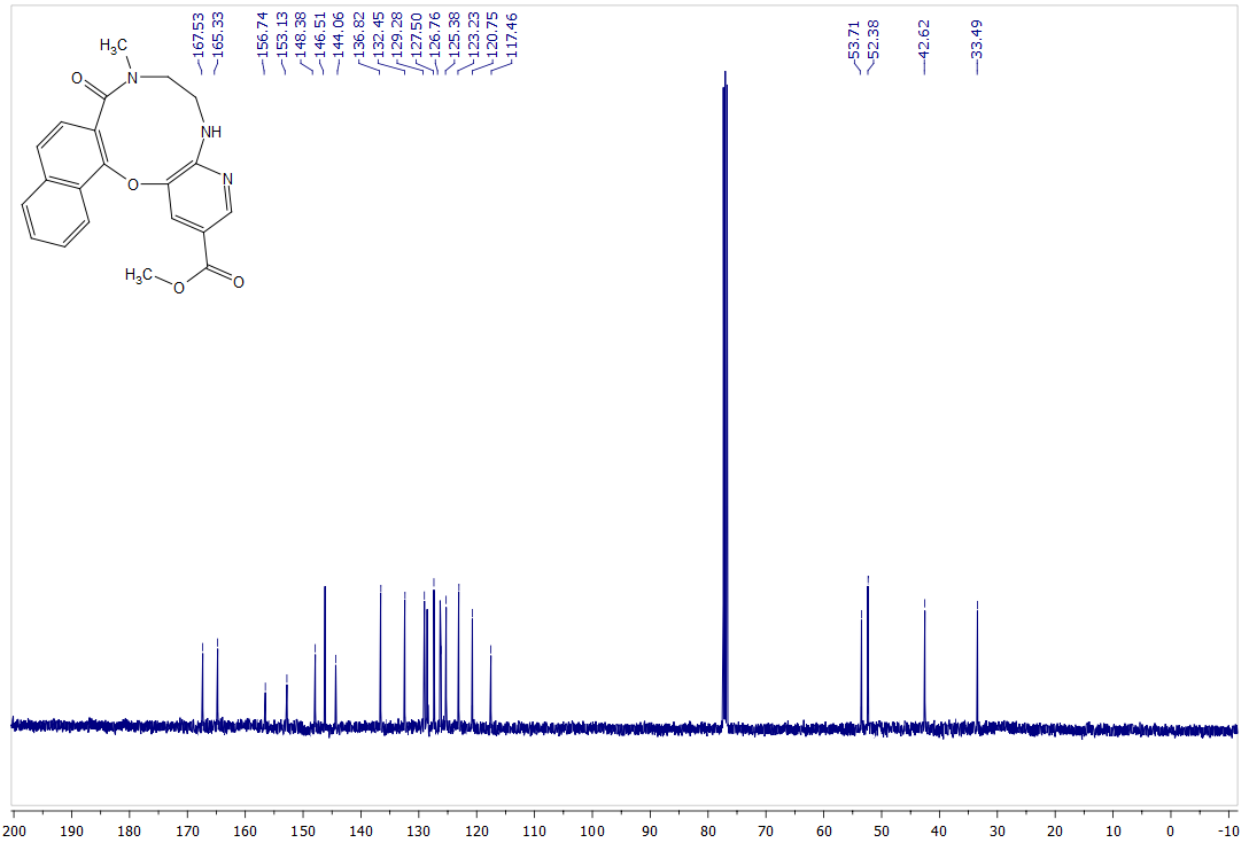
^{1}H and ^{13}C NMR spectra of compound 12l



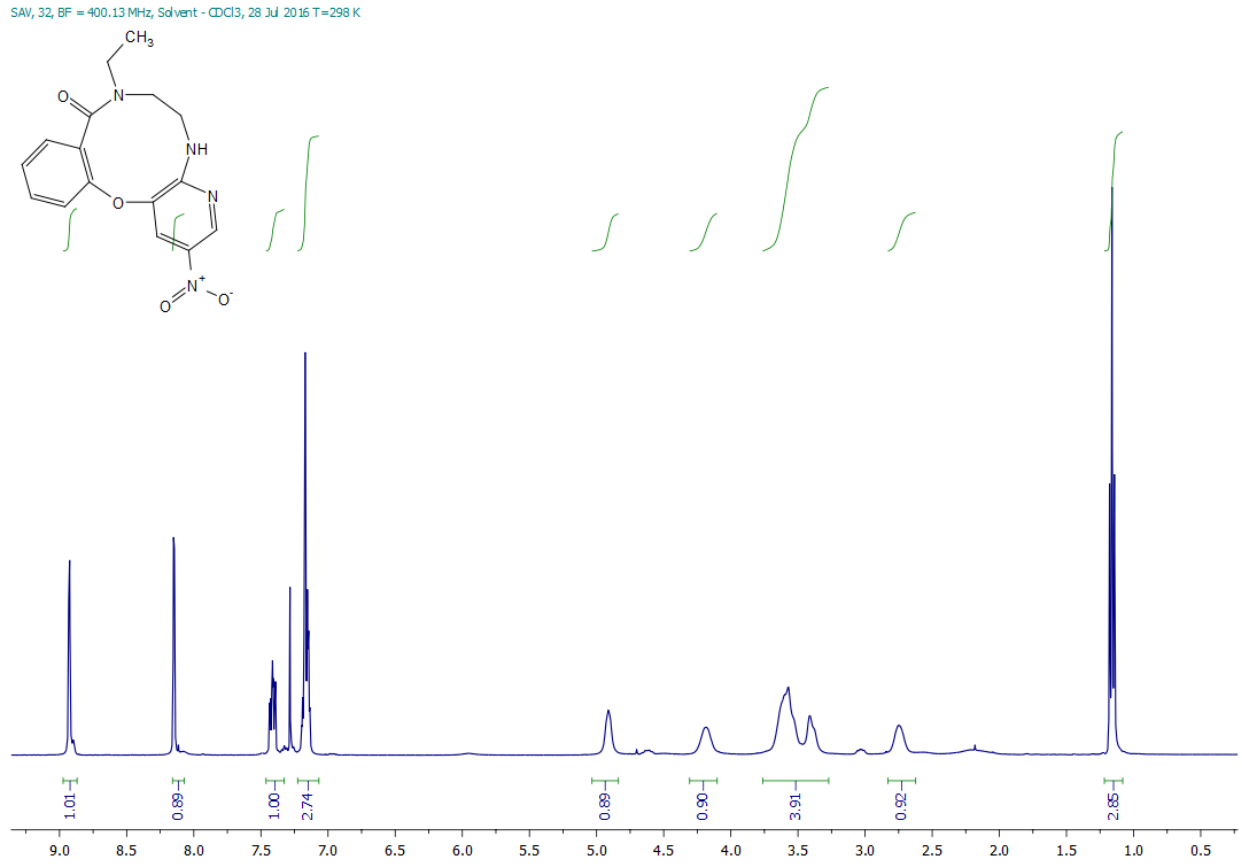


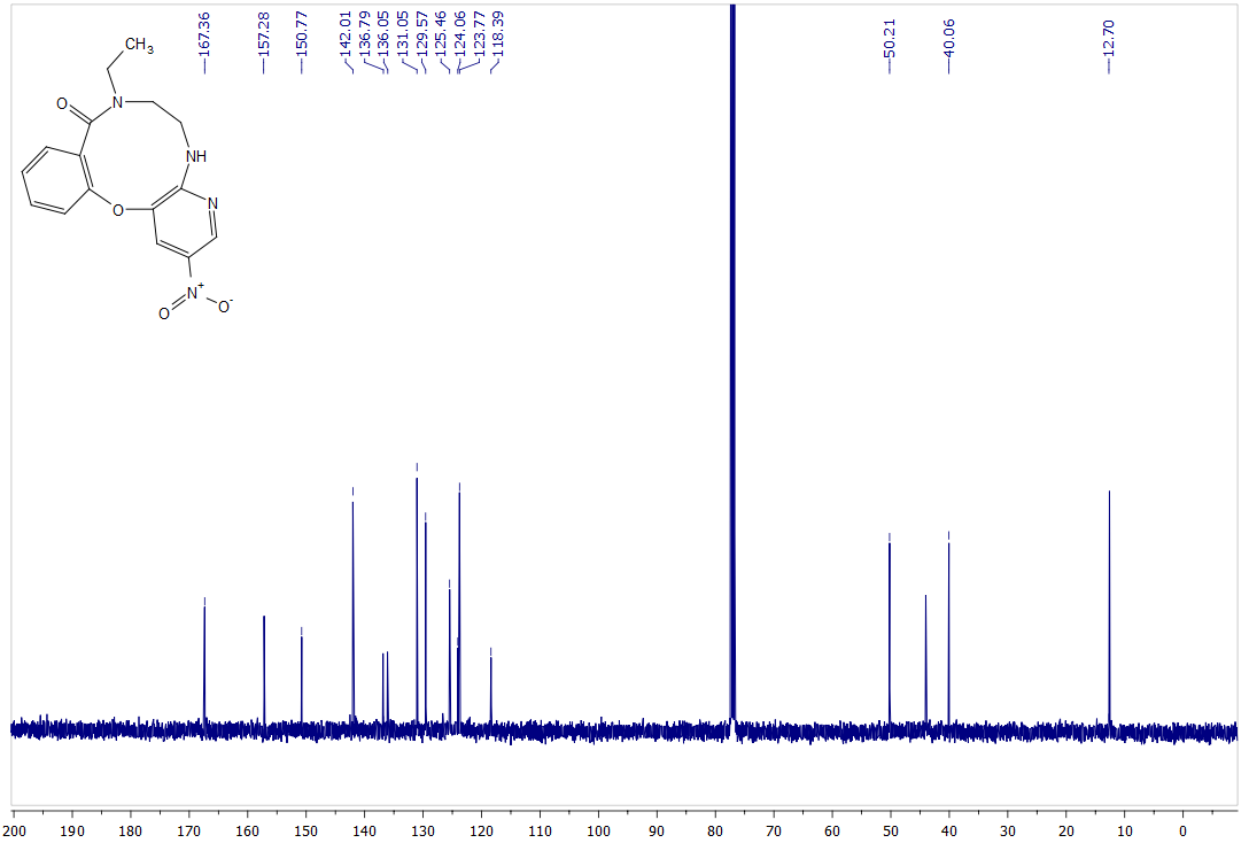
^{1}H and ^{13}C NMR spectra of compound 12m



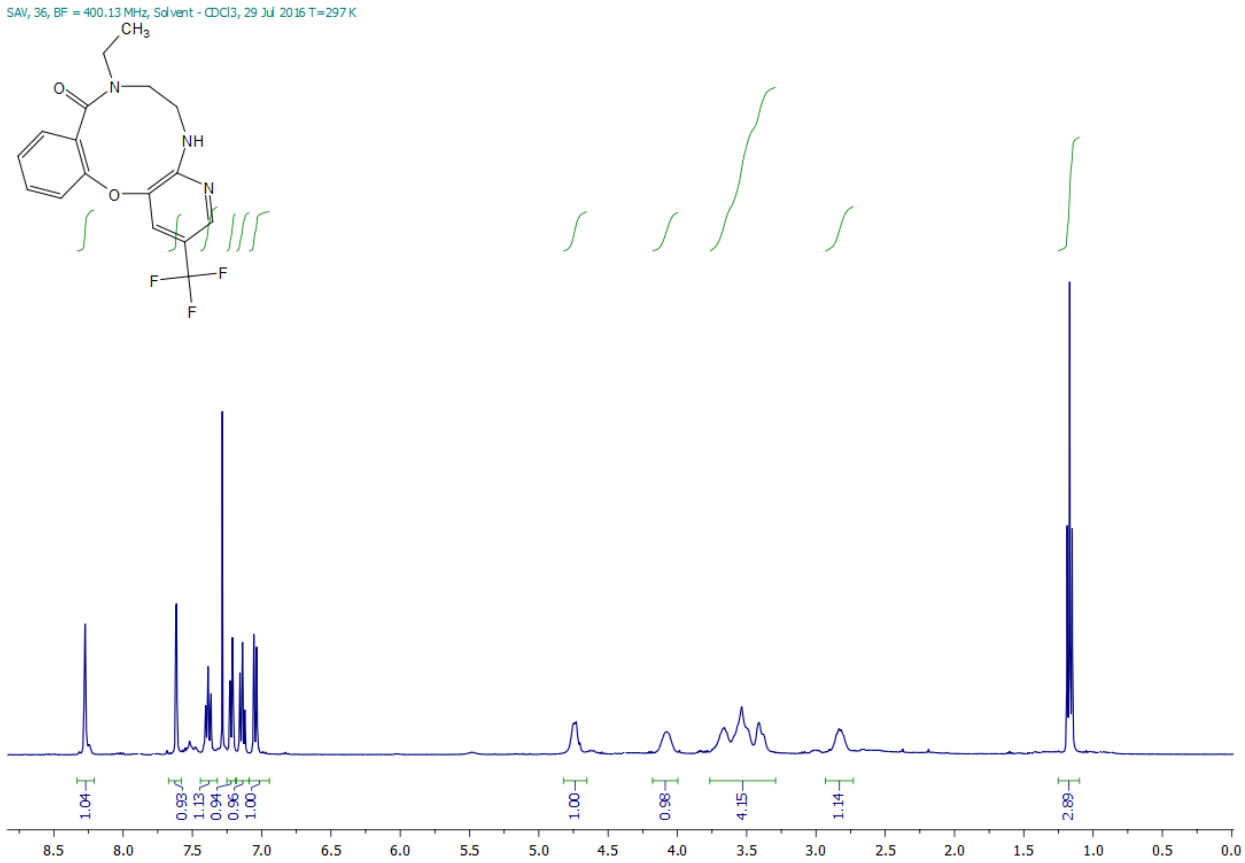


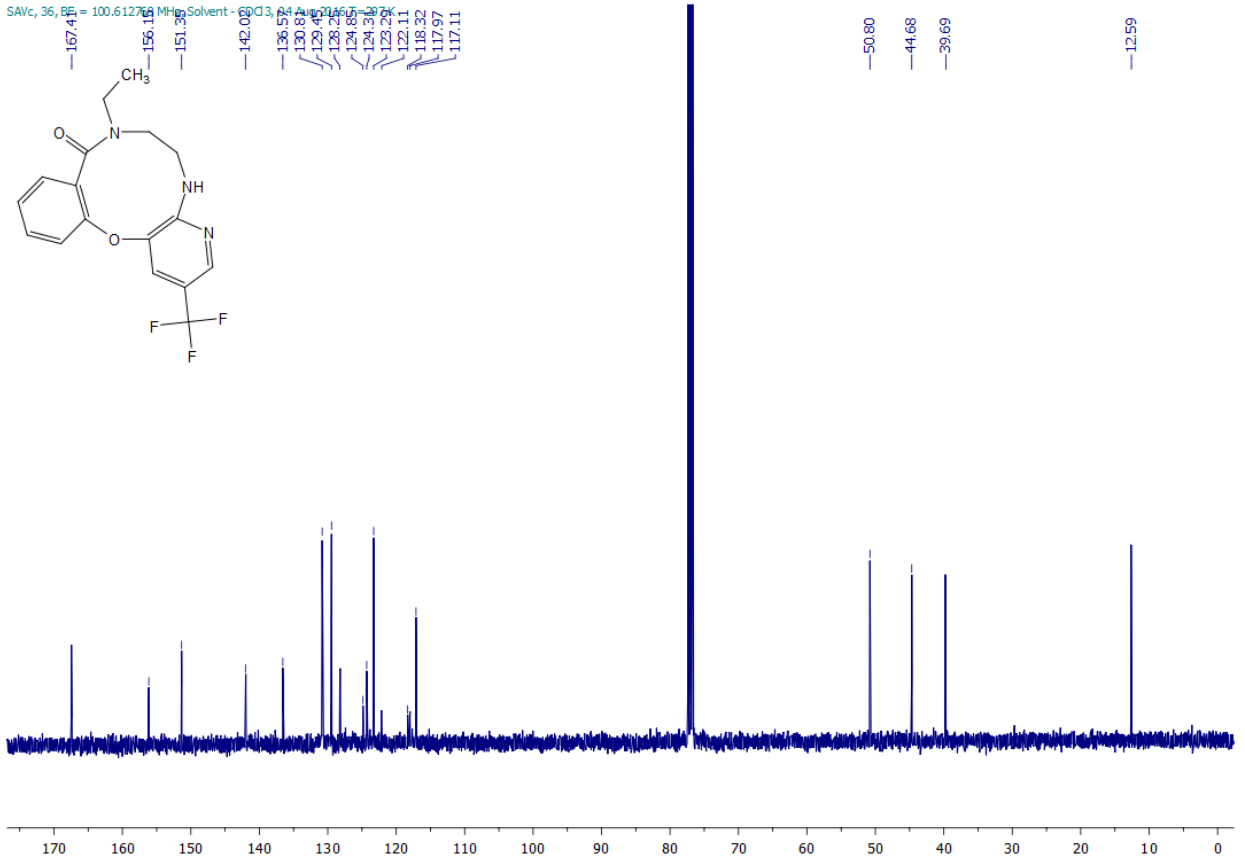
H and ^{13}C NMR spectra of compound 12n



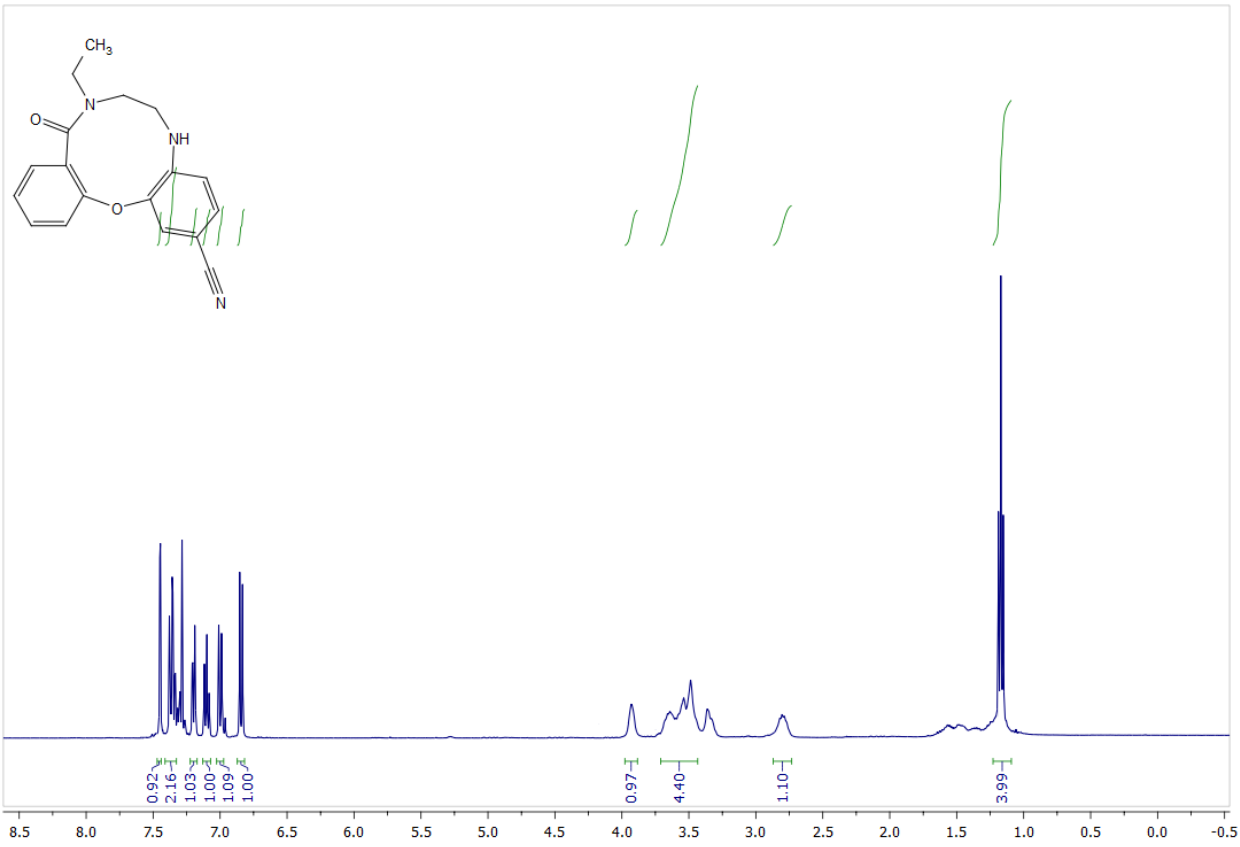


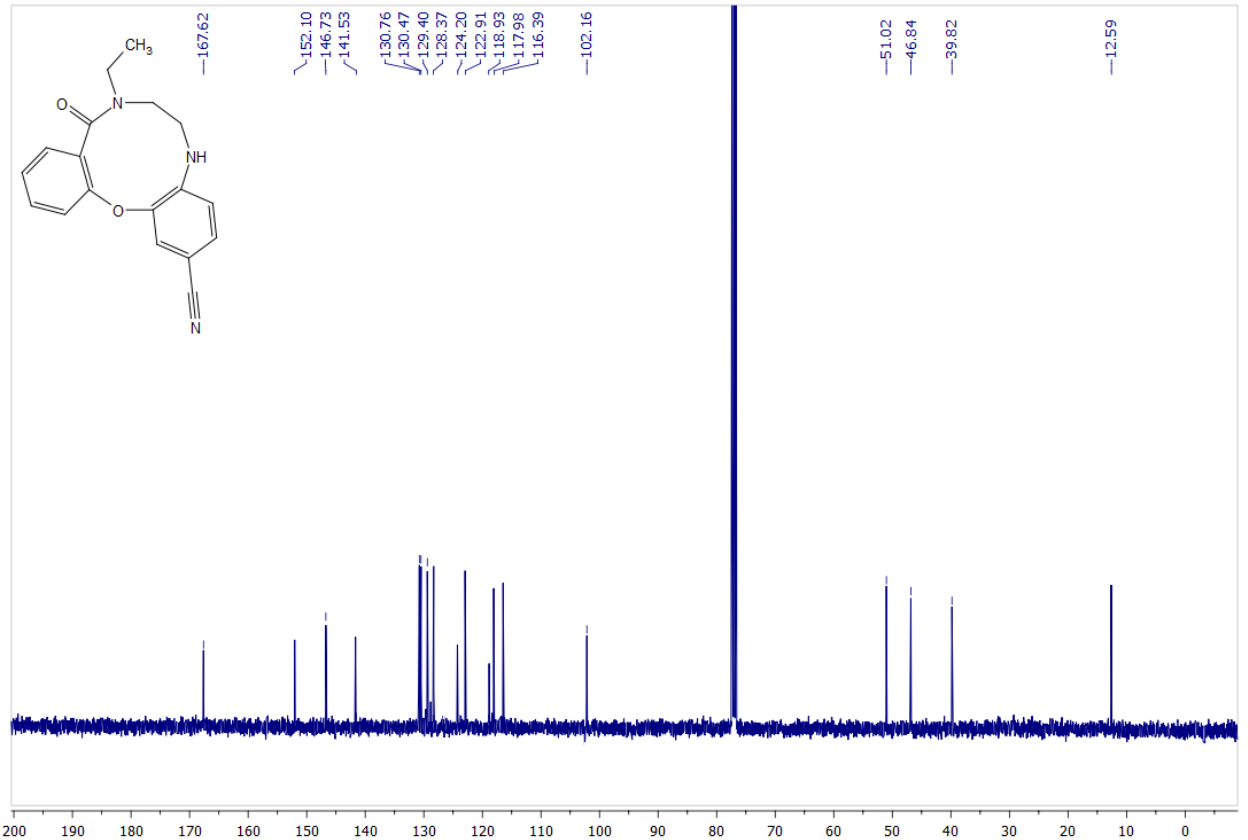
^{1}H and ^{13}C NMR spectra of compound 12o





^{1}H and ^{13}C NMR spectra of compound 12p





^{1}H and ^{13}C NMR spectra of compound 12q