ELECTRONIC SUPPORTING INFORMATION FOR

Azide-based in situ preparation of fused heterocyclic imines and their multicomponent reactions

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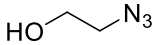
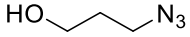
General information

NMR spectra were acquired with 400 MHz Bruker Avance III spectrometer (400.13 MHz for ^{1}H, 100.61 MHz for ^{13}C and 376.50 MHz for ^{19}F) in $CDCl_3$ or DMSO-d_6 and were referenced to residual solvent proton signals (δ_H = 7.26 and 2.50, respectively) and solvent carbon signals (δ_C = 77.16 and 39.52, respectively). Mass spectra were acquired with HRMS-ESI-qTOF spectrometer Nexera LCMS-9030 or MaXis II Bruker Daltonic GmbH (electrospray ionization mode, positive ions detection). TLC was performed on aluminium-backed pre-coated plates (0.25 mm) with silica gel 60 F254 with a suitable solvent system and was visualized using UV fluorescence. Flash column chromatography and normal-phase HPLC were carried out on compact preparative system ECOM ECS28P00, equipped with spectrophotometric detector. Column for preparative HPLC: YMC-Pack SIL-06, 5 μm, 250×20 mm. Some compounds were additionally purified by reverse-phase HPLC on Shimadzu LC-20AP. Column: Agilent Zorbax prepHT XDB-C18, 5 μm, 21.2 × 150 mm. All the commercially available solvents and reagents were used without additional purification if another isn't mentioned.

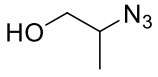
Preparation of azido-alcohols S1-S4 and their analytical data



2-Azidoethan-1-ol (S1): Sodium azide (5.85 g, 90 mmol) was added to the solution of 2-bromoethan-1-ol (3.750 g, 30 mmol) in water (30 mL) in a 250 mL round-bottom flask equipped with a magnetic stir bar and reflux condenser. The mixture was stirred for 20 hours at 80 °C, cooled down to room temperature and extracted with Et_2O (3x30 mL). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo* at 100 mbar. Yield 2.3 g (90%), colorless oil. The NMR data is in accordance with the previously reported one [1].

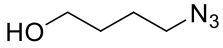


3-Azidopropan-1-ol (S2): Sodium azide (1.95 g, 30 mmol) was added to the solution of 3-bromopropane-1-ol (1.380 g, 10 mmol) in water (10 mL) in a 100 mL round-bottom flask equipped with a magnetic stir bar and reflux condenser. The mixture was stirred for 20 hours at 80 °C, cooled down to room temperature and extracted with Et_2O (3x20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo* at 100 mbar. Yield 1 g, (99%), transparent oil. The NMR data is in accordance with the previously reported one [2].



2-Azidopropan-1-ol (S3): Commercially available methyl 2-bromopropanoate (3.3 g, 20 mmol) was dissolved in 30 mL of acetone and added to the solution of sodium azide (3.9 g, 60 mmol) in 15 ml of water in a 250 mL round-bottom flask equipped with a magnetic stir bar. The reaction mixture was stirred at room temperature for 16 hours. After that acetone was evaporated and the product was extracted with DCM (3x15 mL), dried over Na_2SO_4 and concentrated *in vacuo* at 100 mbar. The obtained liquid was mixed with dry MeOH (915 mL) and

$NaBH_4$ (1.22 g, 34 mmol) was poured into the obtained solution at 0 °C. The reaction mixture was stirred at room temperature for 16 hours. After that acetone was evaporated and the product was extracted with DCM (3x15 mL), dried over Na_2SO_4 and concentrated *in vacuo* at 100 mbar to give yellowish transparent liquid (2g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 – 3.56 (m, 2H), 3.53 – 3.38 (m, 1H), 2.19 (s, 1H), 1.23 (d, *J* = 6.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 66.5, 59.5, 15.5. Several attempts to afford mass-spectra for **S3** failed.



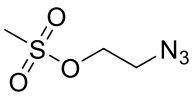
4-azidobutan-1-ol (S4): tetrahydrofuran (90 mL) was mixed with 20 mL of 48% HBr. The reaction mixture was stirred under refluxing for 16 hours, then cooled down to room temperature and saturated Na_2CO_3 (40 mL) was added. The product (4-bromobutan-1-ol) was extracted with $CHCl_3$, evaporated and used in the next step without additional purification.

4-Bromobutan-1-ol was mixed with 80 mL of water and NaN_3 (10.9 g, 0.17 mol) was added to the reaction mixture. The mixture was stirred for 20 hours at 80 °C, cooled down to room temperature and extracted with Et_2O (3x20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo* at 100 mbar. Yield 5.4 g, (84%), light yellow oil. The NMR data is in accordance with the previously reported one [3].

Preparation of azido-methanesulfonates S5-S8 and their analytical data

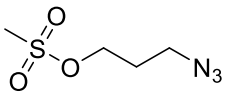
In a 250 mL round-bottom flask equipped with a magnetic stir bar corresponding alcohol (1.0 mol. eq.) was mixed with Et_3N (1.3 mol. eq.) in 1 mol. eq. of DCM. The flask was cooled down to 0 °C and methane sulfonyl chloride (1.1 mol. eq.) was added dropwise to a solution. The mixture was stirred for 30 min, then 1 volume of saturated $NaHCO_3$ solution was added and stirring was continued for additional 30 min at room temperature. Organic phase was separated, aqueous phase was extracted with DCM (2 times). Combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*.

2-Azidoethyl methanesulfonate (S5)



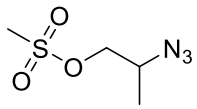
Yield 2.331g (83%, 16.95 mmol scale), yellowish oil. The NMR data is in accordance with the previously reported one [4].

3-Azidopropyl methanesulfonate (S6)



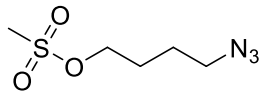
Yield 3.218g (90%, 20 mmol scale), colorless oil. The NMR data is in accordance with the previously reported one [4].

2-Azidopropyl methanesulfonate (S7)



Yield 533 mg (99%, 3 mmol scale), yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 – 4.17 (m, 1H), 4.16 – 4.06 (m, 1H), 3.90 – 3.77 (m, 1H), 3.08 (s, 3H), 1.31 (d, *J* = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 71.6, 55.9, 37.7, 15.7. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_4H_9N_3NaO_3S$ 202.0257; Found 202.0255.

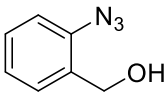
4-Azidobutyl methanesulfonate (S8)



Yield 6 g (66%, 50 mmol scale), orange oil. The NMR data is in accordance with the previously reported one [5].

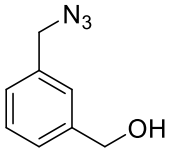
Preparation of azido benzyl alcohols S9, S10

(2-Azidophenyl)methanol (S9)



Commercially available 2-azidobenzaldehyde (294 mg, 2 mmol) was dissolved in 10 mL of dry MeOH plus 10 mL of dry DCM. $NaBH_4$ (83 mg, 2.2 mmol) was added slowly to the solution at 0 °C. Mixture was stirred at 0 °C for additional 15 minutes and then during 30 minutes at room temperature. Saturated $NaHCO_3$ (10 mL) was added, organic phase was separated and aqueous phase was extracted with DCM (2x30 mL). Combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give 240 mg (80%) of **S9** used in the next step without additional purification.

(3-(Azidomethyl)phenyl)methanol (S10)

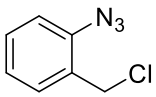


At the first step (3-(chloromethyl)phenyl)methanol was achieved *via* known literature protocol [6] from 1,3-phenylenedimethanol. At the second stage (3-(chloromethyl)phenyl)methanol (950 mg, 6 mmol) was dissolved in aquas acetone (8 mL of water + 10 mL of acetone). NaN_3 (975 mg, 15 mmol) was added to the obtained solution under stirring at room temperature. Stirring was continued for 16 hours. After that acetone was evaporated and the reaction mixture was extracted with DCM (3x15 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give 855 mg (87%) of colorless liquid of **S10** used in the next step without additional purification and characterization.

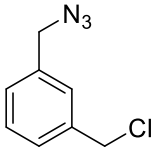
Preparation of azido benzyl chlorides S11, S12

$SOCl_2$ (1.2 mmol. equivalents) was slowly added to corresponding azido benzyl alcohol (1 mmol. equivalent) in 2.5 mL/1 mmol. equivalent of dry DCM at 0 °C and the mixture was stirred for 30 min. Reaction progress was controlled by TLC. After the reaction completion mixture was

concentrated *in vacuo*, re-evaporated with dry hexane and used in the next step without additional purification and characterization.



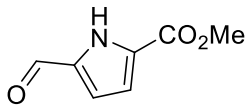
1-Azido-2-(chloromethyl)benzene (S11): Yield 662 mg (99%, scale 4 mmol), brown oil.



1-(Azidomethyl)-3-(chloromethyl)benzene (S12): Yield 351 mg (97%, scale 2 mmol), brown oil.

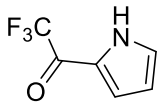
Preparation of substituted pyrroles S13-S16

Methyl 5-formyl-1*H*-pyrrole-2-carboxylate (S13)



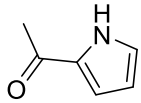
The solution of methyl 1*H*-pyrrole-2-carboxylate (4 g, 32 mmol) in dry DCE (10 mL) was added dropwise at 5 °C to the solution of dry DMF (3.7 mL, 48 mmol) and $POCl_3$ (4.5 mL, 48 mmol) in dry DCE (10 ml). The mixture was stirred for 1 hour at 5 °C and then refluxed for 15 minutes. The mixture was concentrated *in vacuo*, diluted with saturated $NaHCO_3$ (40 mL) solution and extracted with DCM (3x30 mL). Combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography in DCM–EA (1-50% of EA, 600 mL). Yield 2.6 g (53%), beige solid. The NMR data is in accordance with the previously reported one [7].

2,2,2-Trifluoro-1-(1*H*-pyrrol-2-yl)ethan-1-one (S14)



The solution of 1*H*-pyrrole (984 mg, 14.7 mmol) in dry DCM (5 mL) was added dropwise to the solution of TFAA (2.2 mL, 15.8 mmol) in dry DCM (5 mL) at -15 °C. The mixture was stirred at -15 °C for 1.5 hours and for 1 hour at room temperature. The mixture was washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. Yield 2.214 g (92%), lilac solid. The NMR data is in accordance with the previously reported one [8].

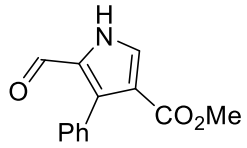
1-(1*H*-Pyrrol-2-yl)ethan-1-one (S15)



$POCl_3$ (2.8 mL, 30 mmol) was added dropwise to *N*,*N*-dimethylacetamide (2.8 mL, 30 mmol) at 0 °C. The mixture was allowed to warm up to room temperature and stirred until the Vilsmeier reagent was formed. The formed solid was dissolved in dry DCE (5 mL) and the solution was cooled down to 0 °C. 1*H*-pyrrole (1.7 mL, 25 mmol) was dissolved in dry DCE (10 mL) and added dropwise during 20 minutes at 0 °C. The mixture was refluxed for 30 minutes and cooled down to room temperature. Aqueous NaOAc (10.25 g, 125 mmol) was added to the mixture followed by refluxing for 30 minutes. The mixture was cooled down to room

temperature. The aqueous phase was extracted with DCM (3x40 mL). The combined organic phase was washed with saturated Na_2CO_3, brine, dried over Na_2SO_4 and concentrated *in vacuo*. Yield 2.22 g (81%), yellow solid. The NMR data is in accordance with the previously reported one [9].

Methyl 5-formyl-4-phenyl-1*H*-pyrrole-3-carboxylate (S16)

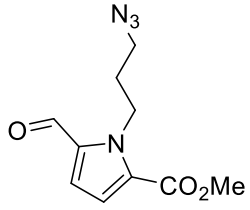


$POCl_3$ (506 mg, 3 mmol) was added dropwise to dry DMF (241 mg, 3.3 mmol) at 0 °C. The mixture was allowed to warm up to room temperature and stirred until the Vilsmeier reagent was formed. The formed solid was dissolved in dry DCE (2 mL) and the solution was cooled down to 0 °C. The solution of methyl 4-phenyl-1*H*-pyrrole-3-carboxylate (604 mg, 3 mmol) in 5 mL of dry DCE was added dropwise to the reaction mixture and stirring was continued at room temperature for 30 minutes. After that the mixture was refluxed for 30 minutes and cooled to 0 °C. The solution of NaOAc (1.31 g, 16 mmol) in water (3.6 mL) was added with vigorous stirring. The mixture was refluxed for 30 minutes and allowed to cool to room temperature. The mixture was diluted with water (15 mL) and extracted with DCM (3x20 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography in EtOAc system. Yield 549 mg (80%), beige solid. The NMR data is in accordance with the previously reported one [10].

General procedure for preparation of azido aldehydes and azido ketones 5a-r and their analytical data

In a screw-cap vial equipped with a magnetic stir bar the corresponding pyrrole (1 mol. eq) was dissolved in dry DMSO (2-4 mL) and K_2CO_3 (1.5 mol. eq) was added. The mixture was stirred in an ice-bath (carefully, do not allow solvent freezing) and the corresponding azido containing mesylate was added dropwise. After that the reaction vial was placed in a pre-heated to 50 °C oil bath or metal heating block for 16 hours. After the reaction completion mixture was diluted with water and extracted with DCM. Combined organic phase was washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography eluting with hexane-acetone (1-50% of acetone, 400-700 mL depending on the compound and reaction scale) was performed to achieve pure products **5a-r**.

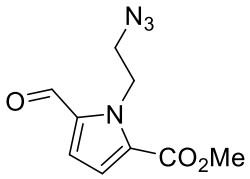
Methyl 1-(3-azidopropyl)-5-formyl-1*H*-pyrrole-2-carboxylate (5a)



Yield 503 mg (65%, 3.3 mmol scale), ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 6.96 (d, *J* = 4.3 Hz, 1H), 6.90 (d, *J* = 4.3 Hz, 1H), 4.92 – 4.85 (m, 2H), 3.89 (s, 3H), 3.36 (t, *J* = 6.9 Hz, 2H), 2.06 (p, *J* = 7.0 Hz, 2H). ^{13}C NMR (101

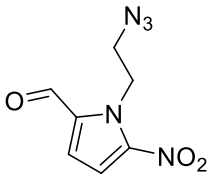
MHz, $CDCl_3$) δ 181.2, 161.2, 135.1, 129.4, 122.8, 117.4, 52.1, 49.0, 44.5, 30.6. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{10}H_{12}N_4NaO_3$ 259.0802; Found 259.0802.

Methyl 1-(2-azidoethyl)-5-formyl-1*H*-pyrrole-2-carboxylate (5b)



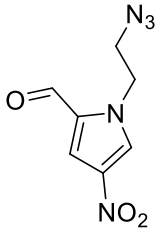
Yield 433 mg (98%, 2 mmol scale), light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 6.98 (d, *J* = 4.2 Hz, 1H), 6.94 (d, *J* = 4.3 Hz, 1H), 5.06 (t, *J* = 6.2 Hz, 2H), 3.88 (s, 3H), 3.60 (t, *J* = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 181.3, 161.3, 135.2, 129.7, 123.0, 117.7, 52.2, 51.9, 45.2. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_9H_{10}N_4NaO_3$ 245.0645 found 245.0646.

1-(2-Azidoethyl)-5-nitro-1*H*-pyrrole-2-carbaldehyde (5c)



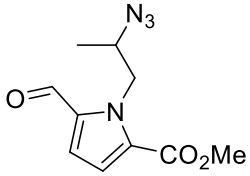
Yield 186 mg (89%, 1 mmol scale), red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.26 (s, 1H), 6.78 (s, 1H), 3.78 (t, *J* = 5.2 Hz, 2H), 2.95 (t, *J* = 5.2 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.8, 136.0, 129.7, 129.6, 118.0, 50.3, 48.5. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_7H_7N_5NaO_3$ 232.0441; Found 232.0442.

1-(2-Azidoethyl)-4-nitro-1H-pyrrole-2-carbaldehyde (5d)



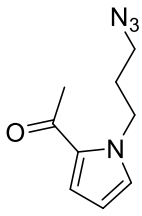
Yield 168 mg (70%, 1.1 mmol scale), light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.77 (s, 1H), 7.48 (d, *J* = 1.7 Hz, 1H), 4.56 – 4.42 (m, 2H), 3.74 – 3.64 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 180.3, 137.2, 130.3, 129.7, 118.7, 51.2, 49.5. Several attempts to afford mass-spectra for **5d** failed.

Methyl 1-(2-azidopropyl)-5-formyl-1*H*-pyrrole-2-carboxylate (5e)



Yield 75 mg (10%, 3 mmol scale), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 6.98 (d, *J* = 4.2 Hz, 1H), 6.94 (d, *J* = 4.2 Hz, 1H), 5.09 – 5.01 (m, 1H), 4.78 (dd, *J* = 13.5, 4.4 Hz, 1H), 3.88 (s, 3H), 3.83 – 3.76 (m, 1H), 1.31 (d, *J* = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 181.4, 161.4, 135.3, 129.7, 123.0, 117.7, 58.9, 52.1, 50.2, 16.9. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{10}H_{12}N_4NaO_3$ 259.0802; Found 259.0801.

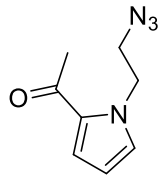
1-(1-(3-Azidopropyl)-1*H*-pyrrol-2-yl)ethan-1-one (5f)



Yield 482 mg (46%, 5.5 mmol scale). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 – 6.94 (m, 1H), 6.89 – 6.82 (m, 1H), 6.18 – 6.12 (m, 1H), 4.39 (t, *J* = 6.8 Hz, 2H), 3.25 (t, *J* = 6.5 Hz, 2H), 2.43 (s, 3H), 2.08 – 1.95 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ

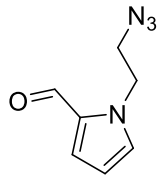
188.4, 130.7, 130.2, 120.7, 108.4, 48.5, 46.9, 30.4, 27.3. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_9H_{12}N_4NaO$ 215.0903; Found 215.0903.

1-(1-(2-Azidoethyl)-1*H*-pyrrol-2-yl)ethan-1-one (5g)



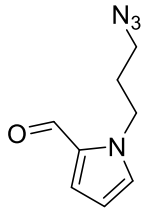
Yield 101 mg (57%, 1 mmol scale), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 – 6.99 (m, 1H), 6.93 – 6.89 (m, 1H), 6.23 – 6.16 (m, 1H), 4.48 – 4.42 (m, 2H), 3.60 (t, *J* = 5.6 Hz, 2H), 2.44 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 188.7, 131.4, 130.0, 121.3, 108.7, 52.1, 49.2, 27.3. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_8H_{11}N_4O$ 179.0927; Found 179.0924.

1-(2-Azidoethyl)-1*H*-pyrrole-2-carbaldehyde (5h)



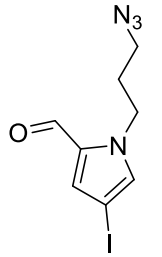
Yield 153 mg (95%, 1 mmol scale), light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.00 (d, *J* = 3.3 Hz, 2H), 6.31 – 6.23 (m, 1H), 4.50 – 4.34 (m, 2H), 3.62 (t, *J* = 5.5 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.7, 132.5, 131.1, 125.9, 110.2, 52.0, 48.6. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_7H_9N_4O^+$ 165.0771; Found 165.0767.

1-(3-Azidopropyl)-1*H*-pyrrole-2-carbaldehyde (5i)



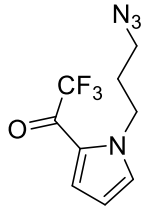
Yield 328 mg (35%, 5 mmol scale), pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 6.99 – 6.92 (m, 2H), 6.25 – 6.21 (m, 1H), 4.38 (t, *J* = 6.8 Hz, 2H), 3.26 (t, *J* = 6.4 Hz, 2H), 2.03 (p, *J* = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.4, 131.8, 131.4, 125.3, 109.9, 48.4, 46.3, 30.3. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_8H_{11}N_4O$ 179.0927; Found 179.0925.

1-(3-Azidopropyl)-4-iodo-1*H*-pyrrole-2-carbaldehyde (5j)



Yield 209 mg (30%, 2.3 mmol scale), light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 – 9.44 (m, 1H), 7.04 – 7.01 (m, 1H), 6.99 (s, 1H), 4.37 (t, *J* = 6.8 Hz, 2H), 3.29 (t, *J* = 6.4 Hz, 2H), 2.01 (p, *J* = 6.7 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 178.6, 135.7, 133.0, 131.2, 60.7, 48.2, 46.5, 30.3. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_8H_9IN_4NaO$ 326.9713; Found 326.9713.

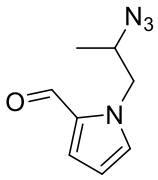
1-(1-(3-Azidopropyl)-1*H*-pyrrol-2-yl)-2,2,2-trifluoroethan-1-one (5k)



Yield 386 mg (43%, 3.6 mmol scale), light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 1H), 7.13 – 7.09 (m, 1H), 6.33 – 6.25 (m, 1H), 4.42 (t, *J* = 6.8 Hz, 2H), 3.30 (t, *J* = 6.3 Hz, 2H), 2.03 (p, *J* = 6.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.95 (q, *J* = 35.5 Hz), 134.8, 124.97 (q, *J* = 4.2 Hz), 124.1, 121.66 – 112.39 (m),

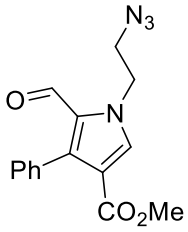
110.6, 48.3, 47.4, 30.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -71.2. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_9H_9F_3N_4NaO$ 269.0621; Found 269.0621.

1-(2-Azidopropyl)-1*H*-pyrrole-2-carbaldehyde (5l)



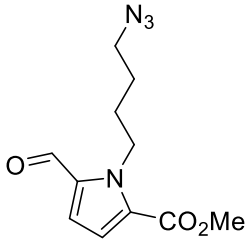
Yield 100 mg (56%, 1 mmol scale), light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.02 – 6.96 (m, 2H), 6.30 – 6.24 (m, 1H), 4.55 (dd, *J* = 13.6, 3.7 Hz, 1H), 4.05 – 3.97 (m, 1H), 3.93 – 3.84 (m, 1H), 1.28 (d, *J* = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.7, 132.6, 131.4, 125.8, 110.2, 58.6, 53.9, 17.1. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_8H_{11}N_4O$ 179.0927; Found 179.0923.

Methyl 1-(2-azidoethyl)-5-formyl-4-phenyl-1*H*-pyrrole-3-carboxylate (5m)



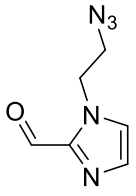
Yield 295 mg (99%, 1 mmol scale), light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (d, *J* = 0.8 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.46 – 7.34 (m, 5H), 4.53 – 4.47 (m, 2H), 3.73 – 3.69 (m, 5H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 181.8, 163.5, 141.4, 135.2, 131.2, 131.0, 128.7, 128.4, 127.8, 114.7, 51.5, 51.3, 49.5. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{14}N_4NaO_3$ 321.0958; Found 321.0965.

Methyl 1-(4-azidobutyl)-5-formyl-1*H*-pyrrole-2-carboxylate (5n)



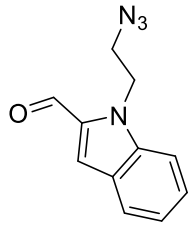
Yield 577 mg (68%, 3.4 mmol scale), light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 6.95 (d, *J* = 4.2 Hz, 1H), 6.89 (d, *J* = 4.3 Hz, 1H), 4.86 – 4.80 (m, 2H), 3.88 (s, 3H), 3.32 (t, *J* = 6.9 Hz, 2H), 1.87 – 1.78 (m, 2H), 1.70 – 1.60 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 181.2, 161.2, 135.1, 129.3, 122.7, 117.3, 52.0, 51.2, 46.1, 28.8, 26.0. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{11}H_{15}N_4O_3$ 251.1139; Found 251.1142.

1-(2-Azidoethyl)-1*H*-imidazole-2-carbaldehyde (5o)



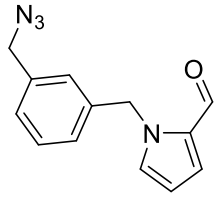
Yield 933 mg (52%, 11 mmol scale), yellow transparent liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, *J* = 0.8 Hz, 1H), 7.22 (s, 1H), 7.16 (s, 1H), 4.48 – 4.42 (m, 2H), 3.64 – 3.56 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 182.1, 142.9, 131.7, 127.1, 51.2, 46.8. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_6H_8N_5O$ 166.0723; Found 166.0720.

1-(2-Azidoethyl)-1*H*-indole-2-carbaldehyde (5p)



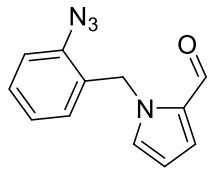
Yield 101 mg (62%, 0.77 mmol scale), light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.52 – 7.42 (m, 2H), 7.34 (s, 1H), 7.24 – 7.18 (m, 1H), 4.71 (t, *J* = 5.9 Hz, 2H), 3.69 (t, *J* = 5.9 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 182.8, 140.9, 135.2, 127.6, 126.6, 123.7, 121.5, 119.1, 110.6, 51.7, 44.1. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{11}H_{10}N_4NaO$ 237.0747; Found 237.0747.

1-(3-(Azidomethyl)benzyl)-1*H*-pyrrole-2-carbaldehyde (5q)



Yield 87 mg (36%, 1 mmol scale), light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 – 9.52 (m, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.08 (s, 1H), 7.02 – 6.95 (m, 2H), 6.33 – 6.26 (m, 1H), 5.58 (s, 2H), 4.30 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.7, 138.5, 136.1, 131.6, 131.5, 129.4, 127.6, 127.3, 127.0, 125.1, 110.4, 54.7, 51.9. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{13}H_{12}N_4NaO$ 263.0903; Found 263.0904.

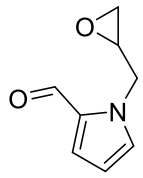
1-(2-Azidobenzyl)-1*H*-pyrrole-2-carbaldehyde (5r)



Yield 386 mg (85%, 2 mmol scale), beige solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 – 9.54 (m, 1H), 7.35 – 7.28 (m, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.08 – 7.00 (m, 1H), 6.99 – 6.91 (m, 2H), 6.28 – 6.24 (m, 1H), 5.53 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 179.6, 137.8, 131.9, 131.7, 129.3, 129.2, 129.0, 125.2, 124.9, 118.2, 110.2, 47.5. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{12}H_{11}N_4O$ 227.0927; Found 227.0930.

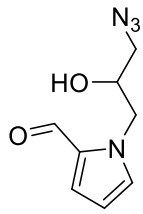
Preparation of 1-(3-Azido-2-hydroxypropyl)-1*H*-pyrrole-2-carbaldehyde 5s and its analytical data

1-(Oxiran-2-ylmethyl)-1*H*-pyrrole-2-carbaldehyde (S17)



To the stirred solution of 1H-pyrrole-2-carbaldehyde (0.95 g, 10 mmol) in dry DMF (8 mL) K_2CO_3 (3.45 g, 35 mmol) and 2-(chloromethyl)oxirane (1.39g, 15 mmol) were added. The mixture was heated to 50 °C and stirring was continued for 6 hours. After that the solvent was evaporated at 55 °C, diluted with water (20 mL) and extracted with diethyl ether (3*15 mL). The combined organic phases were washed with brine and evaporated to dryness. Pure 1-(oxiran-2-ylmethyl)-1H-pyrrole-2-carbaldehyde was achieved through flash column chromatography eluting with DCM to give 720 mg (48%) of yellowish liquid. The obtained product was used in the next step without additional purification.

1-(3-Azido-2-hydroxypropyl)-1*H*-pyrrole-2-carbaldehyde (5t)

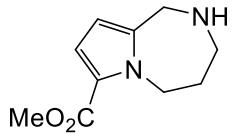


To the stirred solution of 1-(oxiran-2-ylmethyl)-1H-pyrrole-2-carbaldehyde (700 mg, 4.6 mmol) in THF (2 mL) - H_2O (20 mL) mixed solvent NaN_3 (715 mg, 11 mmol) was added. The reaction was conducted at 65 °C during 3 hours under microwave irradiation (Microwave Synthesizer CEM Discover® 2.0, sealed vessel was used). After that it was extracted with DCM (2*15 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The final product **5t** was purified *via* flash column chromatography eluting with DCM-acetone (0-15%, total volume 400 mL) to give 602 mg (68%) of yellowish transparent liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (d, *J* = 0.9 Hz, 1H), 7.03 (s, 1H), 7.01 – 6.97 (m, 1H), 6.31 – 6.24 (m, 1H), 4.51 (dd, *J* = 14.0, 3.9 Hz, 1H), 4.36 – 4.25 (m, 1H), 4.15 – 4.02 (m, 1H), 3.41 (dd, *J* = 12.6, 4.5 Hz, 1H), 3.30 (dd, *J* = 12.6, 6.0 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 180.3, 133.3, 131.7, 126.2, 110.4, 70.7, 54.0, 51.9. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_8H_{10}N_4NaO_2$ 217.0696; Found 217.0696.

General procedure for preparation of 6a-s and their analytical data

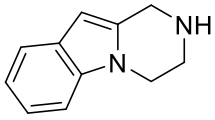
In a screw-cap vial equipped with a magnetic stir bar corresponding azido aldehyde **5a-t** (0.5 mmol) and PPh_3 (0.6 mmol) were mixed in 2 mL of dry MeOH. The resulting mixture was placed in a pre-heated to 65 °C oil bath or metal heating block for 1 hour followed by addition of $NaBH_4$ (0.75 mmol) and refluxing for additional 1 hour at 65 °C. After evaporation of solvent in vacuo the crude reaction mixtures were dissolved in 10 mL of 1M HCl and washed twice with ethyl acetate (2*10 mL). After that 1.5 g of K_2CO_3 was added, the mixtures were extracted with ethyl acetate (3*10 mL) and evaporated to give pure compounds **6a-j**, **6l**, **6o**. Compound **7r** was isolated as hydrochloride salt (the crude product was dissolved in 2 mL of Et_2O with 1 mL of acetone, saturated with HCl (gas) during 10 minutes, the obtained precipitate was centrifuged and dried on rotary evaporator to give pure compound). Several compounds were purified *via* RP-HPLC (MeCN-water + 0.1% TFA; gradient 5-70% of MeCN in 50 min, 40 °C; 12 mL/min) to give pure products **6k**, 6**m, 6n**, 6**p**, 6**q**, **6s**.

Methyl 2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepine-7-carboxylate (6a)



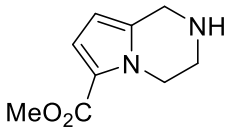
Yield 95 mg (98%), light yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, *J* = 3.9 Hz, 1H), 5.96 (d, *J* = 3.9 Hz, 1H), 4.77 (s, 1H), 3.87 (s, 2H), 3.79 (s, 3H), 3.21 – 3.12 (m, 2H), 1.83 – 1.74 (m, 2H), 1.48 (s, 2H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.1, 143.5, 122.1, 117.2, 107.5, 52.2, 51.1, 46.7, 45.8, 31.6. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{10}H_{15}N_2O_2^+$ 195.1128; Found 195.1128.

1,2,3,4-Tetrahydropyrazino[1,2-*a*]indole (6b)



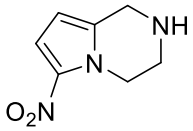
Yield 80 mg (93%), yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.09 – 6.95 (m, 2H), 6.12 (s, 1H), 4.04 (s, 2H), 3.94 (t, J = 5.6 Hz, 2H), 3.17 (t, J = 5.6 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 135.9, 135.7, 127.5, 119.8, 119.3, 119.3, 108.8, 95.1, 43.6, 43.0, 42.2. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{11}H_{13}N_2^+$ 173.1073; Found 173.1068.

Methyl 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-6-carboxylate (6c)



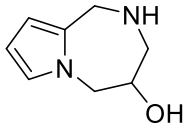
Yield 82 mg (91%), light yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, J = 3.9 Hz, 1H), 5.90 (d, J = 3.9 Hz, 1H), 4.36 (t, J = 5.6 Hz, 2H), 4.12 (s, 2H), 3.79 (s, 3H), 3.27 (t, J = 5.6 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.6, 134.8, 121.0, 117.4, 104.5, 50.9, 45.8, 44.2, 43.6. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_9H_{13}N_2O_2^+$ 181.0972; Found 181.0970.

6-Nitro-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine (6d)



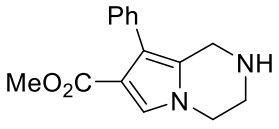
Yield 73 mg (87%), brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 1.5 Hz, 1H), 6.35 (s, 1H), 3.97 (s, 2H), 3.94 (t, J = 5.6 Hz, 2H), 3.27 – 3.20 (m, 2H), 1.68 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 136.8, 128.4, 120.3, 99.8, 46.1, 43.3, 43.2. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_7H_{10}N_3O_2^+$ 168.0768; Found 168.0767.

2,3,4,5-Tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-4-ol (6e)



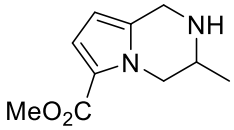
Yield 64 mg (84%), light beige powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (s, 1H), 6.01 – 5.92 (m, 2H), 4.16 – 4.03 (m, 2H), 3.92 (d, J = 15.3 Hz, 1H), 3.84 (s, 1H), 3.65 (d, J = 15.3 Hz, 1H), 3.22 (dd, J = 13.5, 4.4 Hz, 1H), 3.00 (d, J = 13.6 Hz, 1H), 2.43 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 134.3, 124.0, 107.4, 106.5, 66.9, 57.4, 54.3, 46.7. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_8H_{13}N_2O^+$ 153.1022; Found 153.1022.

Methyl 8-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-7-carboxylate (6f)



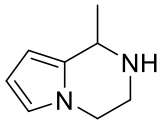
Yield 106 mg (83%), white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.35 – 7.27 (m, 2H), 7.26 – 7.18 (m, 3H), 3.91 (t, J = 5.5 Hz, 2H), 3.75 (s, 2H), 3.58 (s, 3H), 3.03 (t, J = 5.5 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.2, 134.3, 129.8, 127.4, 127.0, 126.0, 125.7, 118.6, 111.3, 50.3, 45.3, 42.7, 42.4. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{17}N_2O_2^+$ 257.1285; Found 257.1277.

Methyl 3-methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-6-carboxylate (6g)



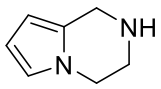
Yield 81 mg (83%), yellow powder. ^{1}H NMR (400 MHz, CDCl3) δ 6.90 (d, *J* = 3.9 Hz, 1H), 5.85 (d, *J* = 3.9 Hz, 1H), 4.60 (dd, *J* = 13.5, 3.9 Hz, 1H), 4.18 – 3.99 (m, 2H), 3.77 (s, 3H), 3.63 – 3.49 (m, 1H), 3.17 – 3.07 (m, 1H), 1.25 (d, *J* = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.7, 134.4, 120.8, 117.7, 104.3, 52.0, 50.9, 49.0, 44.1, 19.8. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{10}H_{15}N_2O_2^+$ 195.1128; Found 195.1131.

1-Methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine (6h)



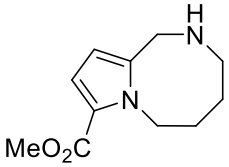
Yield 53 mg (79%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (s, 1H), 6.19 – 6.09 (m, 1H), 5.96 – 5.82 (m, 1H), 4.05 (q, *J* = 6.5 Hz, 1H), 3.94 – 3.88 (m, 2H), 3.38 – 3.30 (m, 1H), 3.23 – 3.13 (m, 1H), 1.44 (d, *J* = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 132.8, 119.0, 107.7, 102.4, 49.5, 45.3, 43.3, 21.3. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_8H_{13}N_2^+$ 137.1073; Found 137.1065.

1,2,3,4-Tetrahydropyrrolo[1,2-*a*]pyrazine (6i)



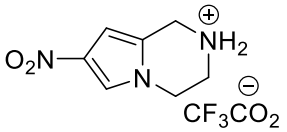
Yield 45 mg (74%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (s, 1H), 6.15 (t, *J* = 2.9 Hz, 1H), 5.84 (s, 1H), 4.04 (s, 2H), 3.92 (t, *J* = 5.6 Hz, 2H), 3.22 (t, *J* = 5.6 Hz, 2H), 1.83 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 127.2, 118.9, 107.8, 102.4, 45.4, 43.9 (2C). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_7H_{11}N_2^+$ 123.0917; Found 123.0918.

Methyl 1,2,3,4,5,6-hexahydropyrrolo[1,2-*a*][1,4]diazocine-8-carboxylate (6j)



Yield 53 mg (51%), white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.79 (d, *J* = 3.9 Hz, 1H), 6.03 (d, *J* = 3.9 Hz, 1H), 4.30 – 4.22 (m, 2H), 3.70 (s, 3H), 3.64 (s, 2H), 2.59 (t, *J* = 5.5 Hz, 2H), 1.78 (p, *J* = 7.8 Hz, 2H), 1.47 (p, *J* = 6.7 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.5, 139.3, 120.6, 116.9, 108.7, 50.7, 48.2, 45.1, 45.0, 29.5, 26.5. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{11}H_{17}N_2O_2^+$ 209.1285; Found 209.1287.

7-Nitro-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine (6k)



Yield 71 mg (50%), light brown crystals. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 7.24 (d, *J* = 1.6 Hz, 1H), 6.12 (s, 1H), 3.91 – 3.82 (m, 4H), 3.20 – 3.08 (m, 2H), 2.16 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$ + DMSO-d_6) δ 135.2, 120.8, 120.3, 100.3, 40.8, 39.4, 39.2. ^{19}F NMR (376 MHz, $CDCl_3$ + DMSO-d_6) δ -74.7. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_7H_{10}N_3O_2^+$ 168.0768; Found 168.0768.

Crystallographic data for compound 6k

X-ray Single Crystal analysis was performed on XtaLAB Synergy diffractometer with monochromated CuKα radiation. The crystal was kept at 100 K during data collection. Using Olex2[11], the structures were solved with the SHELXT[12] structure solution program using Intrinsic Phasing and refined with the SHELXL[13] refinement package using Least Squares minimization. CCDC 2359994 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk/.

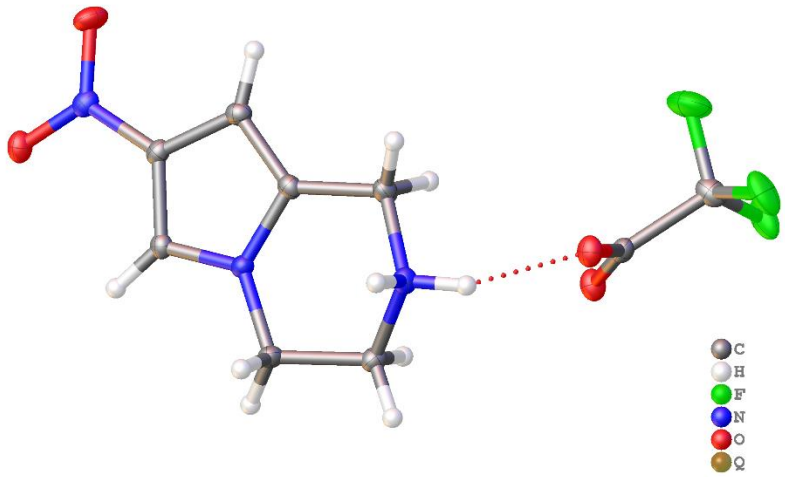
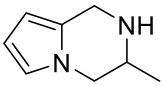


Figure S1. Crystal structure of compound **6k** (ORTEP plot, 50% probability level).

Table 1 Crystal data and structure refinement for compound 7k.	
Identification code	048-010_PPS-102
Empirical formula	$C_6H_{6.67}F_2N_2O_{2.67}$
Formula weight	187.47
Temperature/K	100.00(10)
Crystal system	triclinic
Space group	P-1
a/Å	6.2237(2)
b/Å	8.6358(3)
c/Å	10.4449(4)
α/°	90.670(3)
β/°	96.664(3)
γ/°	95.213(3)
Volume/Å^3	555.14(3)
Z	3
ρ_{calc}g/cm^3	1.682
μ/mm^{-1}	1.457
F(000)	288.0

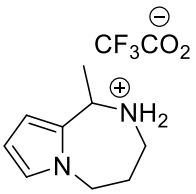
Crystal size/mm^3	0.2 × 0.18 × 0.16
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.526 to 156.688
Index ranges	-7 ≤ h ≤ 7, -10 ≤ k ≤ 10, -13 ≤ l ≤ 13
Reflections collected	6488
Independent reflections	2297 [R_{int} = 0.0183, R_{sigma} = 0.0186]
Data/restraints/parameters	2297/0/172
Goodness-of-fit on F^2	1.042
Final R indexes [I>=2σ (I)]	R_1 = 0.0321, wR_2 = 0.0827
Final R indexes [all data]	R_1 = 0.0332, wR_2 = 0.0836
Largest diff. peak/hole / e Å^{-3}	0.27/-0.30

3-Methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine (6l)



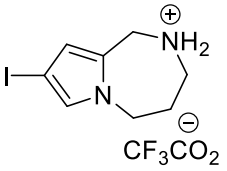
Yield 33 mg (49%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (s, 1H), 6.14 (t, *J* = 3.0 Hz, 1H), 5.88 – 5.79 (m, 1H), 4.15 – 4.00 (m, 2H), 3.94 (dd, *J* = 11.8, 4.0 Hz, 1H), 3.49 (t, *J* = 11.2 Hz, 1H), 3.24 – 3.13 (m, 1H), 1.77 (s, 2H), 1.24 (d, *J* = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 126.7, 118.6, 108.0, 102.2, 51.8, 49.3, 43.6, 19.7. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_8H_{13}N_2^+$ 137.1073; Found 137.1074.

1-Methyl-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepine (6m)



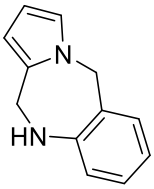
Yield 61 mg (46%), white powder. 1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 6.31 – 6.26 (m, 1H), 5.78 (s, 1H), 5.61 – 5.57 (m, 1H), 4.01 (q, *J* = 6.7 Hz, 1H), 3.85 – 3.67 (m, 2H), 3.16 – 3.07 (m, 1H), 2.95 – 2.84 (m, 1H), 1.77 – 1.67 (m, 1H), 1.61 – 1.49 (m, 1H), 1.37 (d, *J* = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$ + DMSO-d_6) δ 128.0, 123.0, 108.5, 105.8, 50.2, 47.2, 47.1, 26.2, 15.9. ^{19}F NMR (376 MHz, $CDCl_3$ + DMSO-d_6) δ -73.9. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_9H_{15}N_2^+$ 151.1230; Found 151.1227.

8-Iodo-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepine (6n)



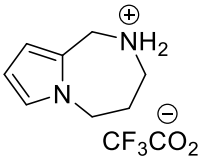
Yield 85 mg (45%), white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H), 7.04 – 6.99 (m, 1H), 6.31 (s, 1H), 4.28 (s, 2H), 4.20 – 4.14 (m, 2H), 3.33 – 3.26 (m, 2H), 1.92 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 128.2, 127.2, 117.5, 57.1, 48.0, 47.4, 42.2, 26.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ -73.5. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_8H_{12}IN_2^+$ 263.0040; Found 263.0032.

10,11-Dihydro-5*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine (6o)



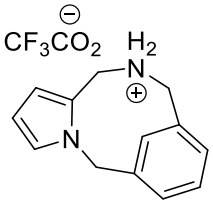
Yield 35 mg (38%), brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 – 6.96 (m, 2H), 6.72 – 6.66 (m, 1H), 6.63 (t, *J* = 7.4 Hz, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 6.04 (q, *J* = 2.7 Hz, 2H), 5.19 (s, 2H), 4.46 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.7, 131.1, 130.0, 129.0, 120.7, 120.2, 117.9, 117.8, 106.3, 105.8, 51.8, 40.9. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{12}H_{13}N_2^+$ 185.1073; Found 185.1073.

2,3,4,5-Tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepine (6p)



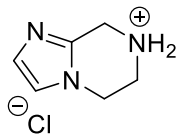
Yield 46 mg (37%), light yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (s, 2H), 6.87 – 6.81 (m, 1H), 6.17 (m, 1H), 5.92 – 5.87 (m, 1H), 4.29 (s, 2H), 4.19 – 4.12 (m, 2H), 3.33 – 3.27 (m, 2H), 1.94 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 124.4, 123.9, 111.2, 106.0, 48.1, 47.1, 42.9, 26.9. ^{19}F NMR (376 MHz, DMSO-d_6) δ -73.5. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_8H_{13}N_2^+$ 137.1073; Found 137.1071.

2,3-Dihydro-1*H*,9*H*-4,8-(metheno)pyrrolo[1,2-*a*][1,4]diazacycloundecine (6q)



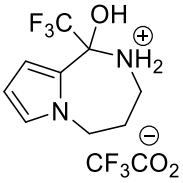
Yield 39 mg (35%), yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.35 (s, 1H), 7.42 – 7.29 (m, 2H), 6.95 (d, *J* = 27.0 Hz, 2H), 6.67 (d, *J* = 6.8 Hz, 1H), 6.36 (s, 1H), 6.18 – 6.10 (m, 1H), 5.08 (s, 2H), 4.15 (s, 2H), 3.65 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 138.9, 131.6, 129.5, 129.0, 127.2, 125.9, 124.1, 122.7, 111.9, 107.8, 49.2, 49.1, 39.2. ^{19}F NMR (376 MHz, DMSO-d_6) δ -73.5. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{13}H_{15}N_2^+$ 199.1230; Found 199.1230.

5,6,7,8-Tetrahydroimidazo[1,2-*a*]pyrazin-7-ium chloride (6r)



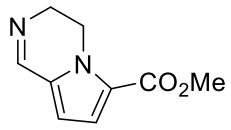
Yield 49 mg (62%), white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (d, *J* = 1.8 Hz, 1H), 7.69 (d, *J* = 1.8 Hz, 1H), 4.60 (s, 2H), 4.46 (t, *J* = 5.4 Hz, 2H), 3.65 (t, *J* = 5.5 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 137.6, 121.5, 119.8, 41.9, 39.3, 38.5. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_6H_{10}N_3^+$ 124.0869; Found 124.0870.

1-(Trifluoromethyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-ol (6s)



Yield 67 mg (40%), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 2H), 7.32 – 7.27 (m, 1H), 7.17 (s, 1H), 6.35 – 6.26 (m, 1H), 4.42 (t, *J* = 6.8 Hz, 2H), 3.02 (s, 2H), 2.20 – 2.11 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.01 (q, *J* = 35.6 Hz), 135.3, 125.66 (q, *J* = 4.4 Hz), 123.9, 117.15 (q, *J* = 290.1 Hz), 111.2, 46.8, 37.0, 29.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -71.2, -76.0. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_9H_{13}F_3N_2O^+$ 221.0896; Found 221.0896.

Preparation and analytical data of methyl 3,4-dihydropyrrolo[1,2-*a*]pyrazine-6-carboxylate (6c')



In a screw-cap vial equipped with a magnetic stir bar corresponding azido aldehyde **5b** (0.7 mmol) and PBu_3 (0.84 mmol) were mixed in 2 mL of dry MeOH. The resulting mixture was placed in a pre-heated to 65 °C oil bath or metal heating block for 1 hour. After that the reaction mixture was cooled down to room temperature, evaporated and purified *via* column chromatography eluting with hexane-acetone (1-50% of acetone, 600 mL) to give 79 mg (62%) of **6c'**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.24 (d, *J* = 4.4 Hz, 1H), 7.09 (d, *J* = 4.4 Hz, 1H), 4.90 – 4.75 (m, 2H), 4.16 (t, *J* = 6.9 Hz, 2H), 3.95 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.0, 154.6, 132.1, 125.3, 124.8, 119.6, 52.9, 41.9, 41.8. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_9H_{11}N_2O_2^+$ 179.0815; Found 179.0817.

General procedure for preparation of CCR-products 8a-c, 10a, b and 12 and their analytical data

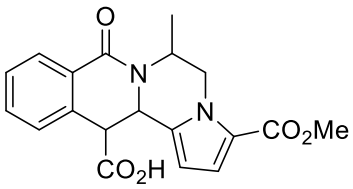
Procedure A: In a screw-cap vial equipped with a magnetic stir bar corresponding azido aldehydes (0.5 mmol) and PPh_3 (0.6 mmol) were mixed in 1 mL of dry MeCN. The resulting mixture was placed in a pre-heated to 65 °C oil bath or metal heating block for 1 hour. After this time homophthalic anhydride **7** (0.5 mmol for compound **8e** and 0.75 mmol for compounds **8a-d**) was added and the mixture was refluxed for additional 16 hour at 80 °C. Compounds **8b, 8c**, **8e** precipitated from the rection mixtures and pure products were achieved *via* crystallization from MTBE or diethyl ether. Compounds **8a** and **8d** were purified *via* preparative HPLC eluting with DCM-acetone (0-50% of acetone, total volume 500 mL).

Procedure B: In a screw-cap vial equipped with a magnetic stir bar corresponding azido aldehydes (0.5 mmol) and PPh_3 (0.6 mmol) were mixed in1 mL of dry toluene. The resulting mixture was placed in a pre-heated to 65 °C oil bath or metal heating block for 1 hour. After this time 3-aryl glutaconic acid anhydride **9** (0.75 mmol) was added and the mixture was refluxed for additional 16 hour at 80 °C. After that the solvent was evaporated and pure products were achieved *via* preparative HPLC eluting with hexane-acetone (0-50% of acetone, total volume 600 mL).

Procedure C: In a screw-cap vial equipped with a magnetic stir bar azido aldehyde **5b** (0.5 mmol) and PPh_3 (0.6 mmol) were mixed in1 mL of dry DCE. The resulting mixture was placed in a pre-heated to 65 °C oil bath or metal heating block for 1 hour. After this time 1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,3(4*H*)-dione **11** (0.75 mmol) was added and the mixture and stirring continued for additional 16 hours at 30 °C. After that the solvent was evaporated, the reaction mixture was diluted with 2 mL of dry DCM in a screw-cup vial equipped with a magnetic stir bar and CDI (0.75 mmol) was added. The vial was stirred at 30 °C for 30 minutes and 1 drop of dry MeOH was

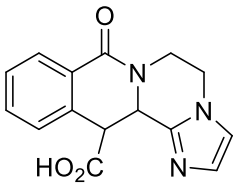
added. The heating was continued for 16 hours. Pure product was achieved *via* preparative HPLC eluting with hexane-acetone (0-50% of acetone, total volume 550 mL).

6-Methyl-8-oxo-5,6,13,13*a*-tetrahydro-8*H*-pyrrolo[2',1':3,4]pyrazino[1,2-*b*]isoquinoline-13-carboxylic acid (8a)



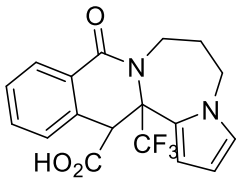
Yield 127 mg (86%, procedure A), white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.49 (s, 1H), 7.99 (d, J = 7.0 Hz, 1H), 7.67 – 7.57 (m, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 6.90 (d, J = 4.0 Hz, 1H), 6.08 (d, J = 4.0 Hz, 1H), 5.33 (d, J = 10.2 Hz, 1H), 5.20 – 5.07 (m, 1H), 4.71 – 4.59 (m, 1H), 4.33 (dd, J = 13.6, 4.3 Hz, 1H), 4.27 (d, J = 10.3 Hz, 1H), 3.75 (s, 3H), 1.05 (d, J = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 172.4, 162.1, 160.6, 135.4, 132.8, 132.7, 128.1, 128.0, 127.7, 126.1, 121.6, 117.2, 106.1, 51.0, 51.0, 50.8, 48.7, 43.5, 40.4. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{19}N_2O_5^+$ 355.1288; Found 355.1280.

8-Oxo-5,6,13,13*a*-tetrahydro-8*H*-imidazo[2',1':3,4]pyrazino[1,2-*b*]isoquinoline-13-carboxylic acid (8b)



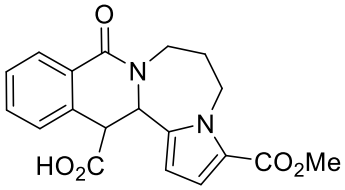
Yield 91 mg (64%, procedure A), white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H), 7.97 (d, J = 7.4 Hz, 1H), 7.63 – 7.52 (m, 2H), 7.52 – 7.44 (m, 1H), 7.17 (s, 1H), 6.97 – 6.88 (m, 1H), 5.33 (d, J = 4.4 Hz, 1H), 4.83 – 4.73 (m, 1H), 4.44 (d, J = 4.4 Hz, 1H), 4.30 – 4.17 (m, 1H), 3.95 (td, J = 11.8, 3.6 Hz, 1H), 3.40 – 3.26 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 170.4, 162.3, 141.7, 135.0, 132.2, 128.6, 128.2, 128.0, 127.9, 127.8, 118.7, 52.8, 47.3, 42.7, 38.3. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{14}N_3O_3^+$ 284.1030; Found 284.1032.

9-Oxo-14*a*-(trifluoromethyl)-6,7,14,14*a*-tetrahydro-5*H*,9*H*-pyrrolo[2',1':3,4][1,4]diazepino[1,2-*b*]isoquinoline-14-carboxylic acid (8c)



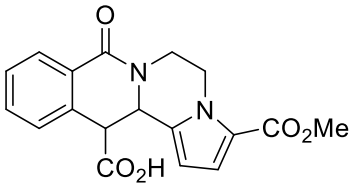
Yield 98 mg (54%, procedure A), white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.09 (s, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.51 (t, J = 7.2 Hz, 1H), 7.44 (d, J = 7.4 Hz, 1H), 7.38 (t, J = 7.4 Hz, 1H), 6.72 (s, 1H), 6.33 (s, 1H), 5.92 – 5.80 (m, 1H), 4.91 (s, 1H), 4.86 – 4.71 (m, 1H), 4.15 – 4.04 (m, 1H), 4.05 – 3.91 (m, 1H), 3.18 – 3.07 (m, 1H), 2.01 (s, 1H), 1.97 – 1.85 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 169.3, 163.9, 134.0, 132.5, 127.9, 127.9, 127.6, 127.0, 126.0, 124.79 (q, J = 289.3 Hz), 124.4, 111.9, 106.4, 67.51 (q, J = 27.5 Hz), 49.9, 47.4, 41.2, 26.5. ^{19}F NMR (376 MHz, DMSO-d_6) δ -66.9. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{16}F_3N_2O_3^+$ 365.1108; Found 365.1108.

3-(Methoxycarbonyl)-9-oxo-6,7,14,14*a*-tetrahydro-5*H*,9*H*-pyrrolo[2',1':3,4][1,4]diazepino[1,2-*b*]isoquinoline-14-carboxylic acid (8d)



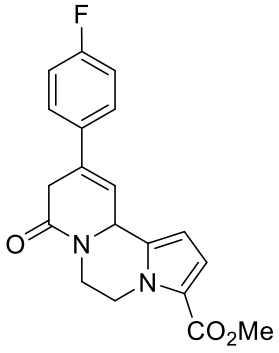
Yield 91 mg (51%, procedure A), light yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 8.96 (s, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.83 – 6.67 (m, 2H), 6.56 (t, *J* = 6.2 Hz, 1H), 5.78 (d, *J* = 3.7 Hz, 1H), 4.95 – 4.85 (m, 1H), 4.76 (d, *J* = 3.6 Hz, 1H), 4.66 (s, 1H), 4.03 (d, *J* = 13.3 Hz, 1H), 3.58 (s, 1H), 3.35 (t, *J* = 13.0 Hz, 1H), 2.92 (s, 3H), 2.37 (t, *J* = 12.2 Hz, 1H), 1.24 (d, *J* = 12.2 Hz, 1H), 0.94 (q, *J* = 11.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$ + DMSO-d_6) δ 170.2, 159.9, 159.6, 138.8, 134.2, 130.5, 128.0, 126.4, 126.1, 125.9, 120.5, 114.7, 105.7, 53.6, 49.4, 46.0, 44.4, 43.3, 26.3. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{19}N_2O_5^+$ 355.1288; Found 355.1288.

3-(Methoxycarbonyl)-8-oxo-5,6,13,13*a*-tetrahydro-8*H*-pyrrolo[2',1':3,4]pyrazino[1,2-*b*]isoquinoline-13-carboxylic acid (8e)



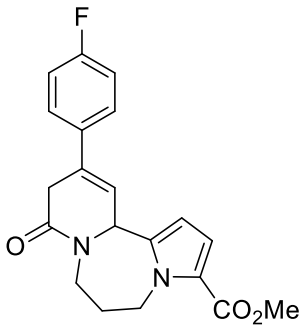
Yield 72 mg (42%, procedure A), white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.46 (s, 1H), 7.98 (d, *J* = 7.5 Hz, 1H), 7.66 – 7.53 (m, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 4.0 Hz, 1H), 6.15 (d, *J* = 3.9 Hz, 1H), 5.45 (d, *J* = 8.0 Hz, 1H), 4.73 – 4.58 (m, 2H), 4.38 (d, *J* = 8.0 Hz, 1H), 4.24 – 4.10 (m, 1H), 3.72 (s, 3H), 3.47 – 3.35 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 172.4, 162.6, 160.5, 134.9, 134.2, 132.6, 128.0, 127.8, 127.3, 127.2, 121.6, 116.9, 105.4, 54.1, 51.0, 48.8, 43.8, 40.5. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{16}N_2NaO_5^+$ 363.0951; Found 363.0947.

Methyl 10-(4-fluorophenyl)-8-oxo-5,6,9,11*a*-tetrahydro-8*H*-pyrido[1,2-*a*]pyrrolo[2,1-*c*]pyrazine-3-carboxylate (10a)



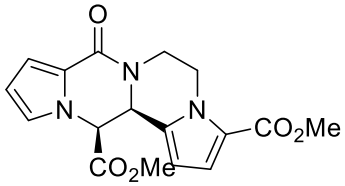
Yield 107 mg (78%, procedure B), light yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.35 (m, 2H), 7.13 – 7.04 (m, 2H), 6.98 (d, *J* = 4.0 Hz, 1H), 6.31 (s, 1H), 6.14 – 6.08 (m, 1H), 5.55 – 5.47 (m, 1H), 5.15 – 5.05 (m, 1H), 4.78 – 4.69 (m, 1H), 4.25 – 4.12 (m, 1H), 3.81 (s, 3H), 3.49 – 3.28 (m, 2H), 3.25 – 3.13 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.9, 162.9 (d, *J* = 248.1 Hz), 161.5, 134.3, 134.2 (d, *J* = 3.1 Hz), 132.5, 127.0 (d, *J* = 8.1 Hz), 122.0, 117.8, 117.2, 115.8 (d, *J* = 21.6 Hz), 104.5, 55.1, 51.3, 44.4, 39.6, 33.9. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -113.1. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{18}FN_2O_3^+$ 341.1296; Found 341.1294.

Methyl 11-(4-fluorophenyl)-9-oxo-6,7,10,12*a*-tetrahydro-5*H*,9*H*-pyrido[1,2-*a*]pyrrolo[2,1-*c*][1,4]diazepine-3-carboxylate (10b)



Yield 105 mg (60%, procedure B), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.38 (m, 2H), 7.09 (t, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 4.0 Hz, 1H), 6.37 – 6.31 (m, 1H), 5.95 (d, *J* = 3.9 Hz, 1H), 5.81 (dd, *J* = 14.8, 5.8 Hz, 1H), 5.22 (d, *J* = 5.2 Hz, 1H), 5.06 – 4.96 (m, 1H), 4.08 – 3.95 (m, 1H), 3.80 (s, 3H), 3.43 – 3.21 (m, 2H), 3.01 – 2.89 (m, 1H), 2.09 – 1.96 (m, 1H), 1.91 – 1.75 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.3, 162.9 (d, *J* = 248.1 Hz), 161.8, 138.8, 135.8, 134.1 (d, *J* = 3.5 Hz), 127.0 (d, *J* = 8.1 Hz), 118.4, 118.4, 116.8, 115.8 (d, *J* = 21.6 Hz), 107.6, 55.5, 51.3, 47.0, 45.0, 35.3, 28.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.2. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{20}FN_2O_3^+$ 355.1452; Found 355.1454.

Dimethyl (13*SR*,13*aRS*)-8-oxo-5,6,13,13*a*-tetrahydro-8*H*-pyrrolo[1,2-*a*]pyrrolo[1',2':4,5]pyrazino[2,1-*c*]pyrazine-3,13-dicarboxylate (12)



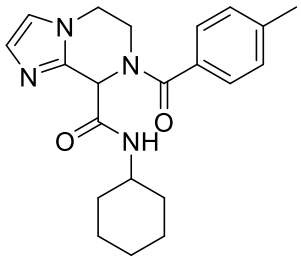
Yield 48 mg (28%, procedure C), light orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 – 7.01 (m, 1H), 7.00 (d, *J* = 4.1 Hz, 1H), 6.87 – 6.81 (m, 1H), 6.36 – 6.28 (m, 1H), 6.16 (d, *J* = 4.1 Hz, 1H), 5.55 (d, *J* = 4.3 Hz, 1H), 5.06 (d, *J* = 4.3 Hz, 1H), 5.01 (dt, *J* = 13.6, 2.6 Hz, 1H), 4.88 (dt, *J* = 13.7, 2.9 Hz, 1H), 4.09 – 3.99 (m, 1H), 3.82 (s, 3H), 3.47 (s, 3H), 3.26 – 3.15 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.5, 161.4, 158.6, 128.9, 124.1, 123.8, 122.3, 118.0, 115.3, 111.2, 106.1, 60.9, 54.1, 53.0, 51.3, 44.4, 38.1. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{18}N_3O_5^+$ 344.1241; Found 344.1251.

General procedure for preparation of Ugi and azido-Ugi products 13a,b and 14a and their analytical data

In a screw-cap vial equipped with a magnetic stir bar corresponding azido aldehydes (0.5 mmol) and PPh_3 (0.6 mmol) were mixed in1 mL of dry CF_3CH_2OH. The resulting mixture was placed in a pre-heated to 65 °C oil bath or metal heating block for 1 hour.

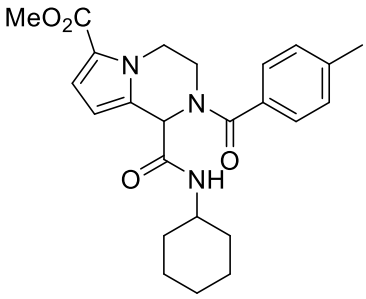
After this time 4-methylbenzoic acid (for Ugi reaction; 0.5 mmol) or azidotrimethylsilane (for azido-Ugi reaction; 0.5 mmol) and isocyanocyclohexane (0.5 mmol) were added and the mixture was stirring for additional 16 hour at 30 °C. After that the solvent was evaporated and pure compounds were achieved *via* preparative HPLC eluting with hexane-acetone (0-50% of acetone, total volume 500 mL).

_N_-Cyclohexyl-7-(4-methylbenzoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-8-carboxamide (13a)



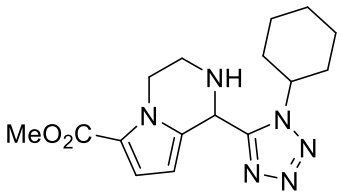
Yield 99 mg (54%), orange oil. ^{1}H NMR (400 MHz, DMSO-d_6; 80 °C) δ 7.72 (s, 1H), 7.36 (d, J = 7.9 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H), 7.15 (s, 1H), 6.97 (s, 1H), 5.73 (s, 1H), 4.14 – 4.07 (m, 2H), 4.02 (td, J = 11.9, 4.2 Hz, 1H), 3.66 (s, 1H), 3.61 – 3.50 (m, 1H), 2.37 (s, 3H), 1.79 (d, J = 8.9 Hz, 1H), 1.71 – 1.57 (m, 3H), 1.53 (d, J = 11.6 Hz, 1H), 1.36 – 1.15 (m, 5H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6; 80 °C) δ 170.0, 165.0, 139.2, 132.1, 128.6, 127.5, 126.5, 118.9, 78.7, 47.7, 43.3, 31.6, 31.5, 24.7, 23.7, 23.6, 20.4. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{27}N_4O_2^+$ 367.2129; Found 367.2129.

Methyl 1-(cyclohexylcarbamoyl)-2-(4-methylbenzoyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-6-carboxylate (13b)



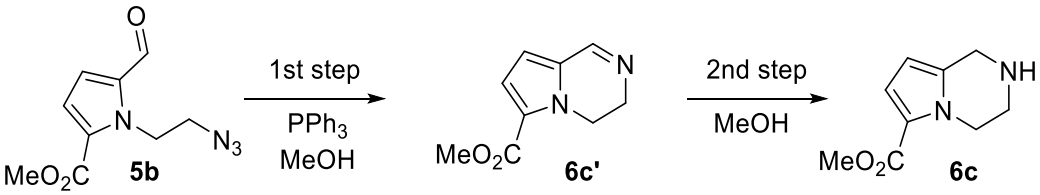
Yield 87 mg (41%), light beige solid. ^{1}H NMR (400 MHz, DMSO-d_6; 80 °C) δ 7.94 (s, 1H), 7.34 (d, J = 7.7 Hz, 2H), 7.28 (d, J = 7.8 Hz, 2H), 6.87 (d, J = 4.0 Hz, 1H), 6.25 (d, J = 3.8 Hz, 1H), 5.71 (s, 1H), 4.68 – 4.56 (m, 1H), 4.24 – 4.14 (m, 1H), 3.97 (t, J = 10.0 Hz, 1H), 3.74 (s, 3H), 3.55 (d, J = 8.8 Hz, 1H), 2.37 (s, 3H), 1.82 – 1.63 (m, 4H), 1.56 (d, J = 11.1 Hz, 1H), 1.37 – 1.14 (m, 5H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6; 80 °C) δ 169.9, 167.3, 160.1, 139.2, 132.2, 131.1, 128.6, 126.5, 120.7, 116.7, 106.1, 50.3, 47.5, 43.7, 31.7, 31.6, 24.8, 23.9, 23.9, 20.4. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{24}H_{30}N_3O_4^+$ 424.2231; Found 424.2227.

Methyl 1-(1-cyclohexyl-1*H*-tetrazol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-6-carboxylate (14a)



Yield 44 mg (30%), light orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (d, J = 4.1 Hz, 1H), 5.82 (s, 1H), 5.65 – 5.55 (m, 1H), 4.69 (dt, J = 13.5, 3.0 Hz, 1H), 4.25 – 4.11 (m, 2H), 3.81 (s, 3H), 3.48 – 3.41 (m, 1H), 3.31 – 3.21 (m, 1H), 2.29 (s, 1H), 2.06 – 1.97 (m, 1H), 1.96 – 1.83 (m, 2H), 1.80 – 1.69 (m, 2H), 1.67 – 1.58 (m, 1H), 1.52 – 1.44 (m, 1H), 1.34 – 1.13 (m, 2H), 1.07 – 0.93 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.6, 153.7, 131.4, 122.0, 117.6, 106.4, 58.9, 51.3, 49.7, 45.9, 43.0, 33.0, 32.0, 25.6, 25.5, 24.9. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{22}N_6NaO_2^+$ 353.1696; Found 353.1689.

Table S1. Screening of reaction's conditions for one-pot formation of tetrahydropyrrolo[1,2-*a*]pyrazine **6c**.

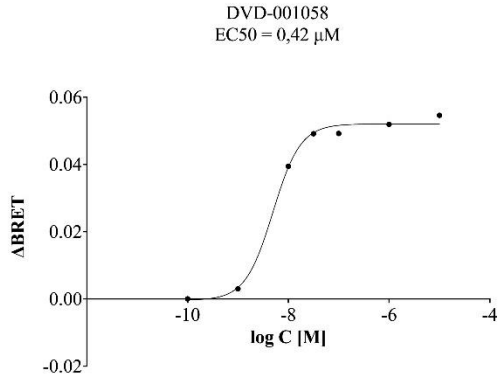


Entry	1st step		2nd step		Isolated yield of **6c**, %
	Time, h	t °C	Time, h	t °C	
1	1	65	1	65	90
2	1	30	1	65	83
3	16	30	1	65	91

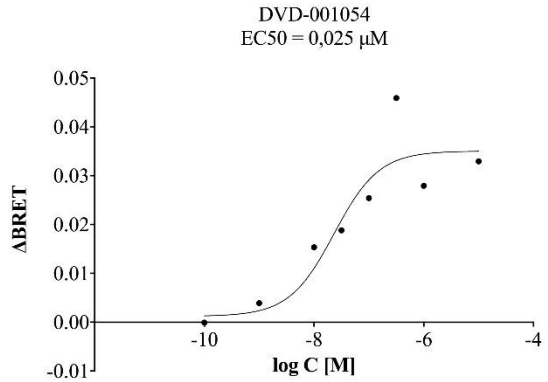
hTAAR1agonistic activity

To perform bioluminescence resonance energy transfer (BRET)-based in vitro screening CHO-K1 cells were transiently co-transfected with plasmids encoding *h*TAAR1 (constructed in our laboratory based on freely available pcDNA3.1 plasmid vector) and a cyclic adenosine monophosphate (cAMP) BRET biosensor EPAC (chimeric cAMP-binding protein containing *R. reniformis* luciferase and yellow fluorescent protein chains) using Lipofectamine® 2000 reagent (ThermoFisher).The cells were then plated in a 96-well white opaque plates (Corning) at 50-80×104 cells per well. On the following day, culture medium was removed and 80 µl of Hank's balanced salt solution containing calcium and magnesium, and 2 mM 3-isobutyl-1-methylxanthine (Sigma) as phosphodiesterase inhibitor, was added to each well followed by addition of 10 µl 50 µM coelenterazine-H solution (Promega) as *R. reniformis* luciferase substrate. After 10-min incubation, either 10 µl of vehicle or 10× concentrated solutions of compounds to be tested (1 µM final amount), or 1 µM of tyramine hydrochloride (Sigma) as positive control were added into corresponding wells. After additional 5-min incubation, luminescence readings were collected using Mithras LB943 multimodal plate reader (Berthold Technologies). The BRET signal is determined by calculating the ratio of the light intensity emitted at 505 to 555 nm to the light intensity emitted at 465 to 505 nm. To confirm specificity of the BRET signal for active compounds, parallel screening on mock-transfected (without hTAAR1- encoding vector) cells was carried out. For compounds considered active, separate dose-response experiments were performed in order to calculate the EC50 values. Curves were fitted applying non-linear regression models on GraphPad Prism 7.0 (GraphPad Software).

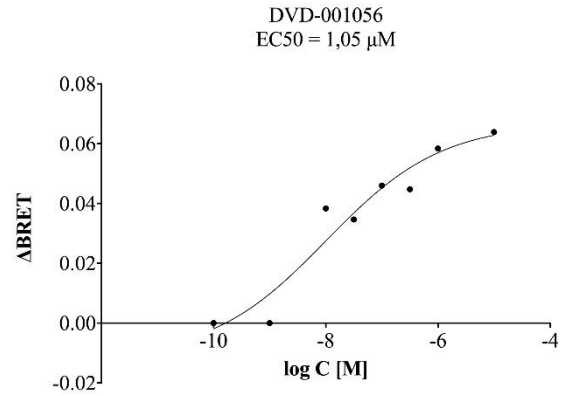
Dose response curve, compound 7a (DVD001058)



Dose response curve, compound 7m (DVD001054)



Dose response curve, compound 7s (DVD001056)



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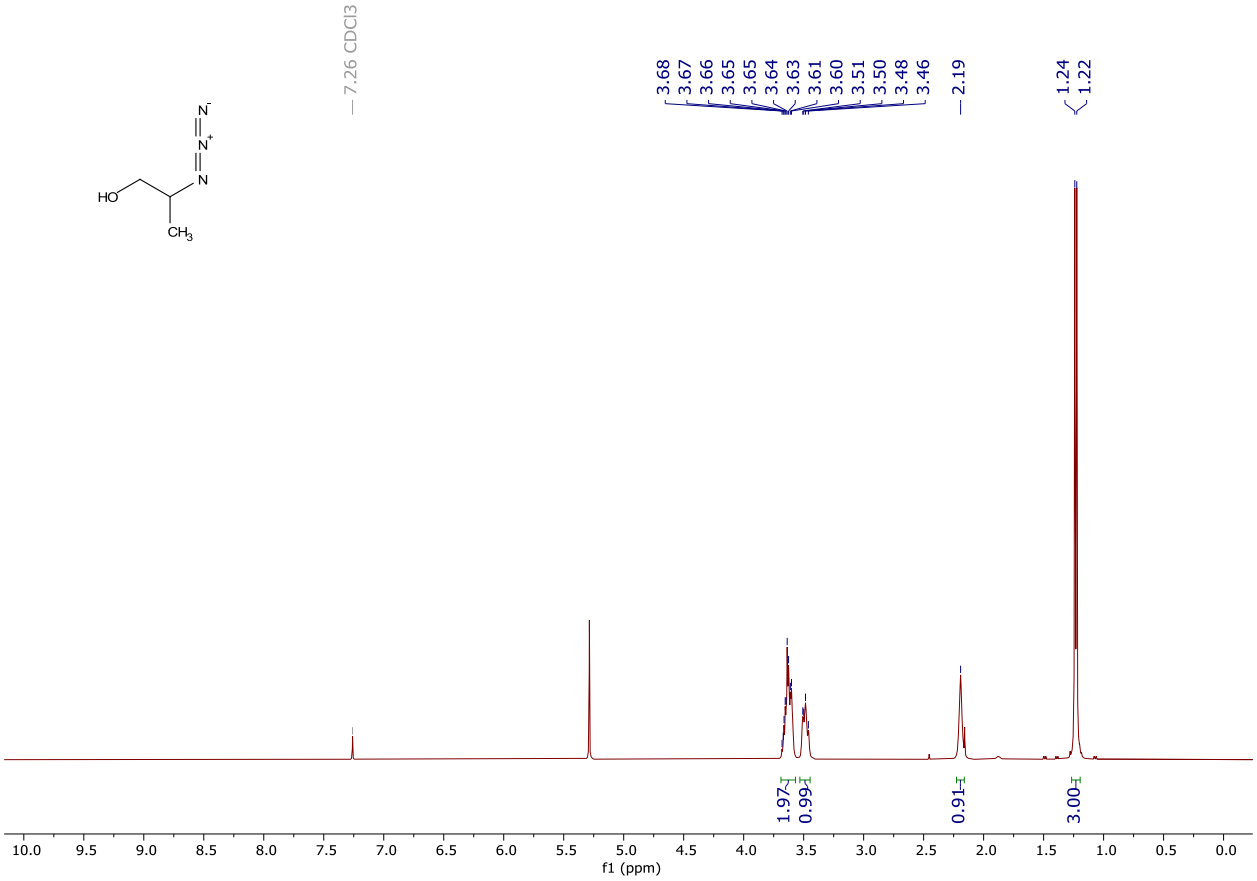
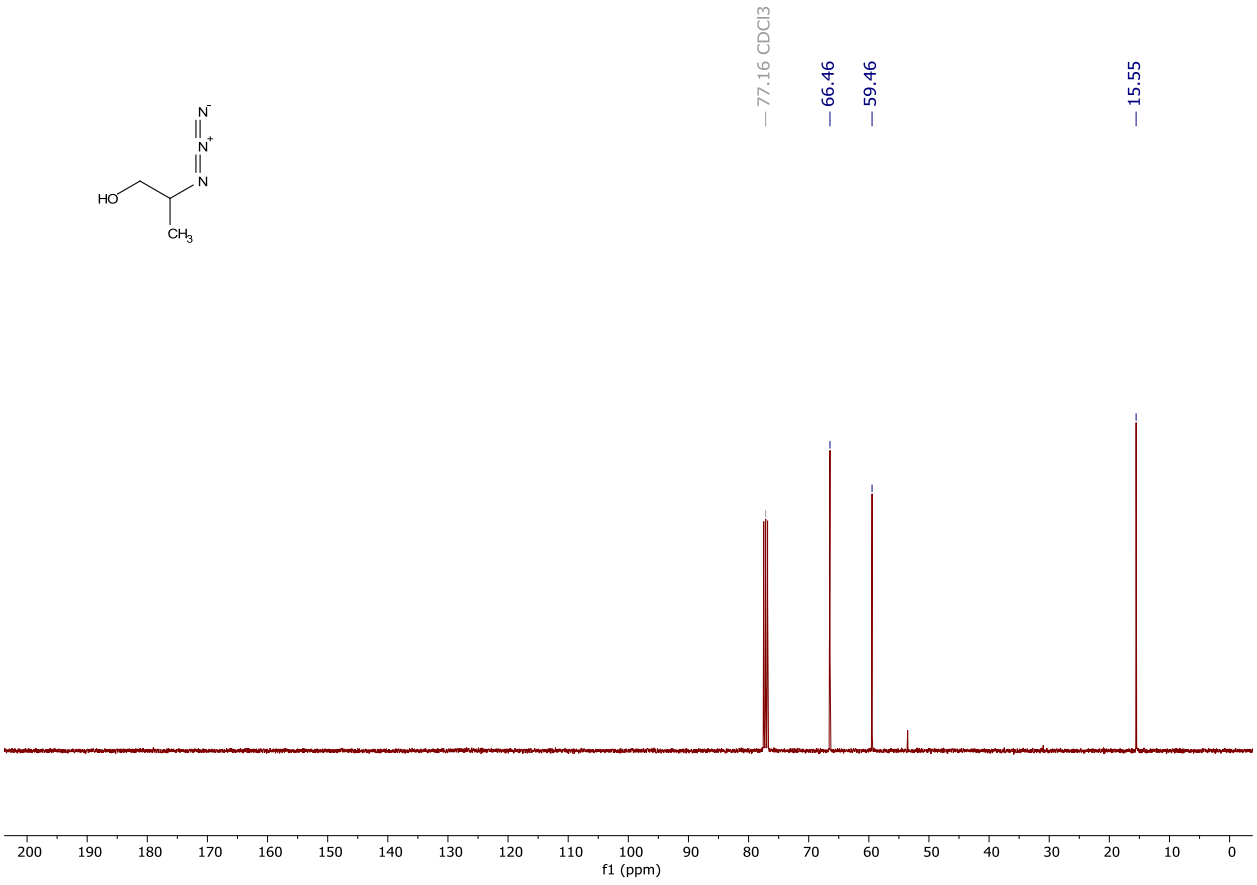
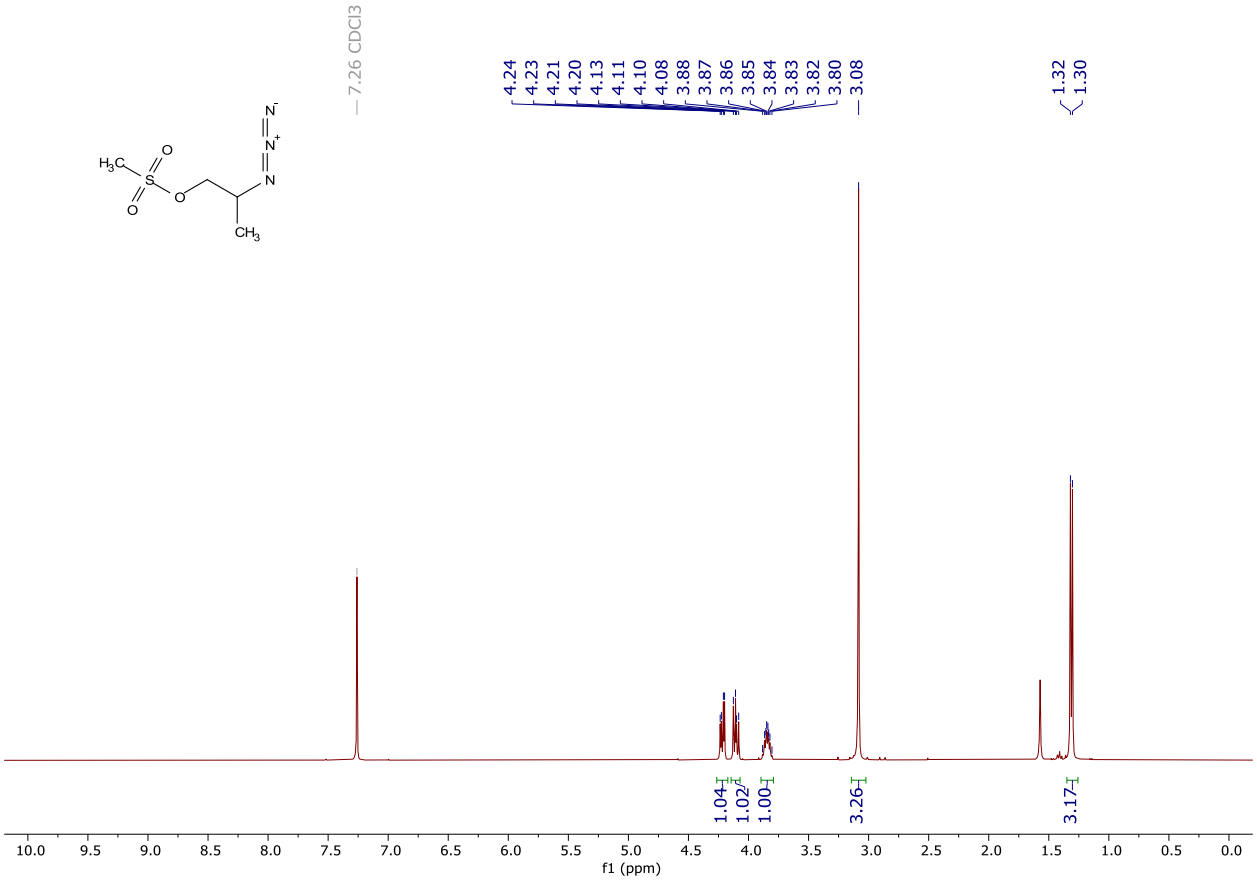
Copies of ^{1}H and ^{13}C NMR spectra

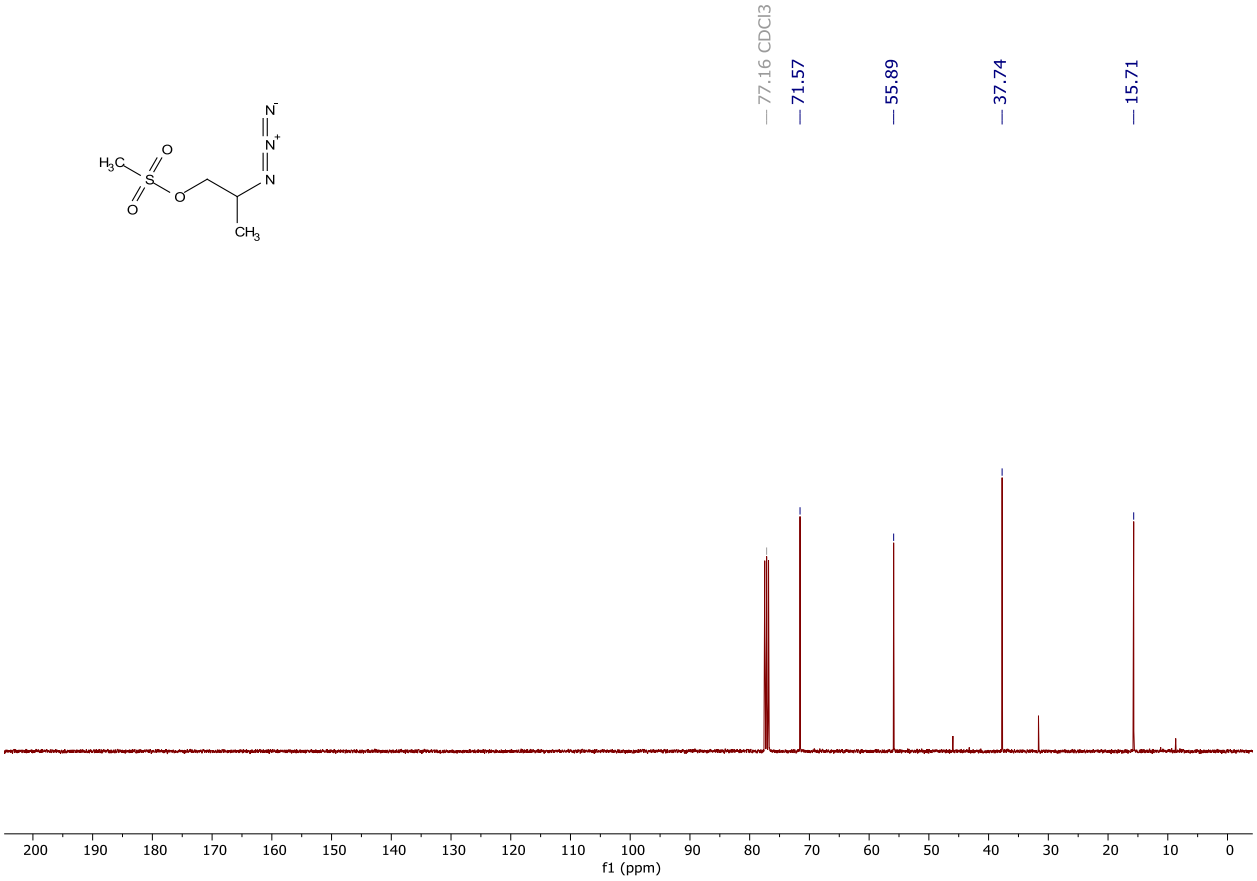
^{1}H and ^{13}C spectra of compound **S3**



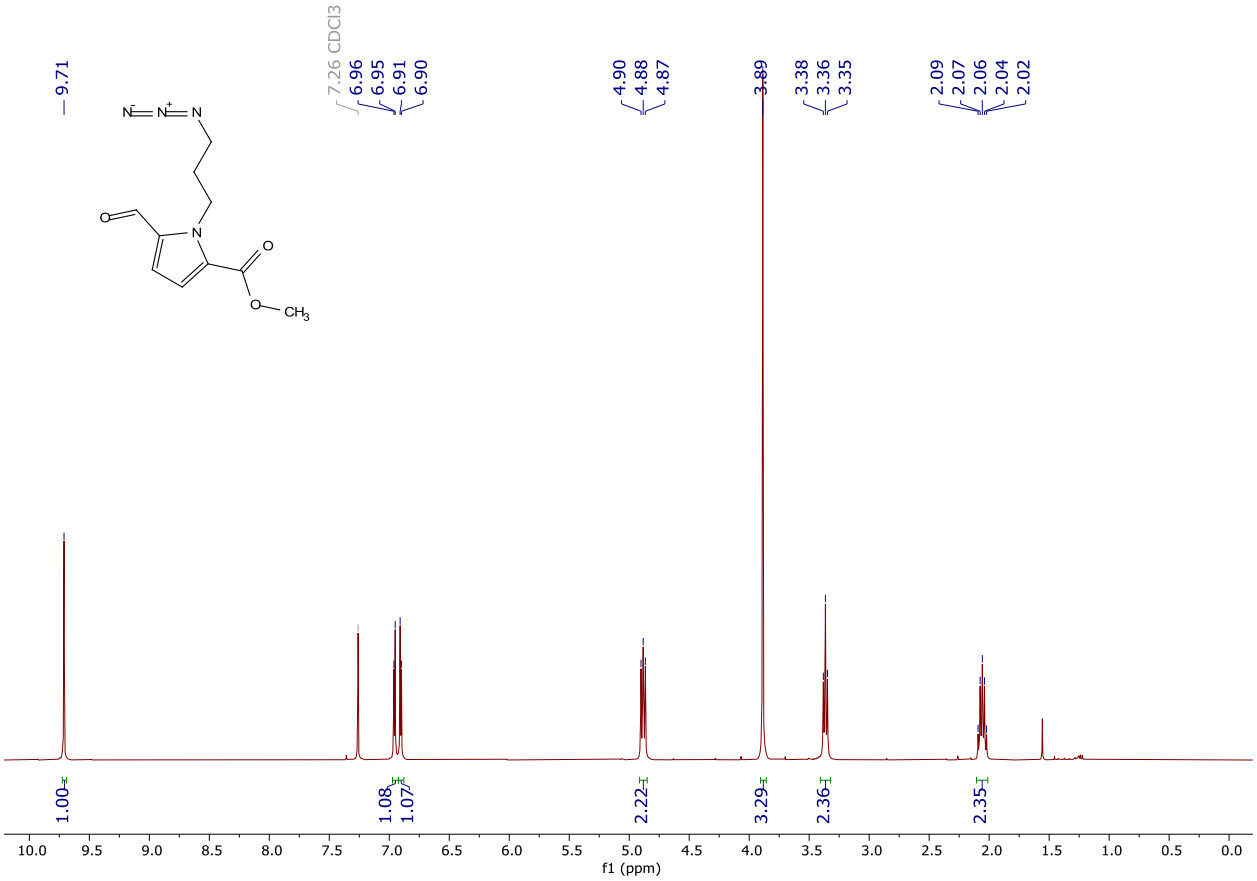


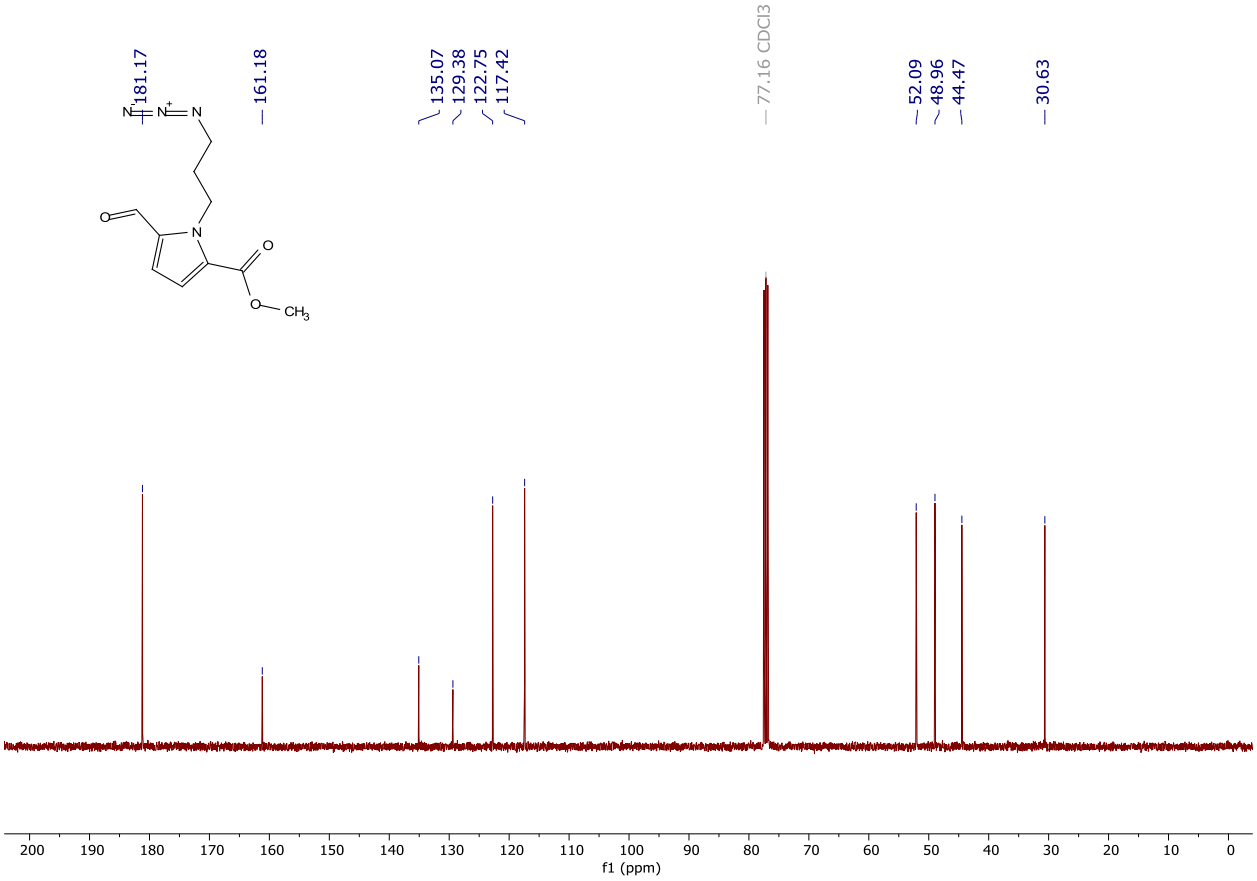
^{1}H and ^{13}C spectra of compound **S7**





^{1}H and ^{13}C spectra of compound **5a**





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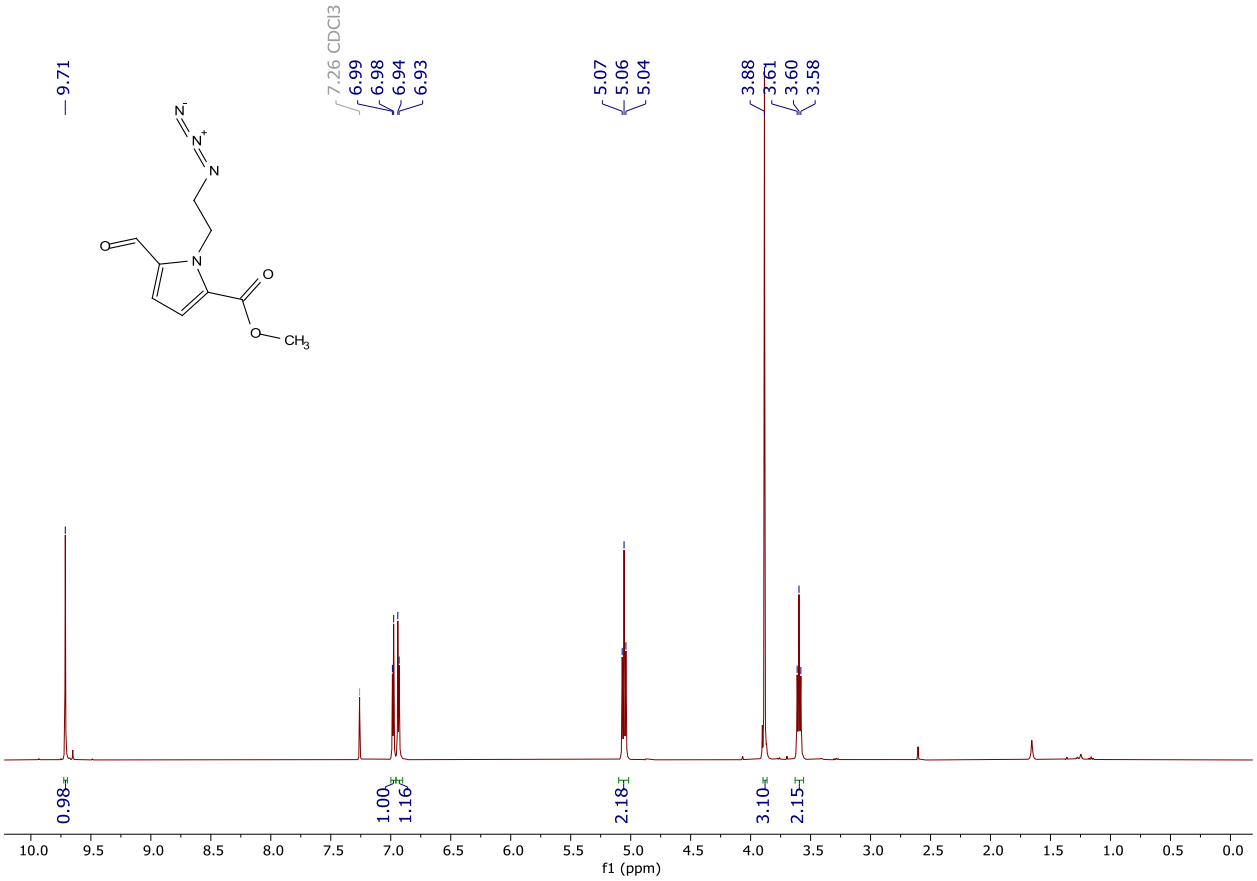
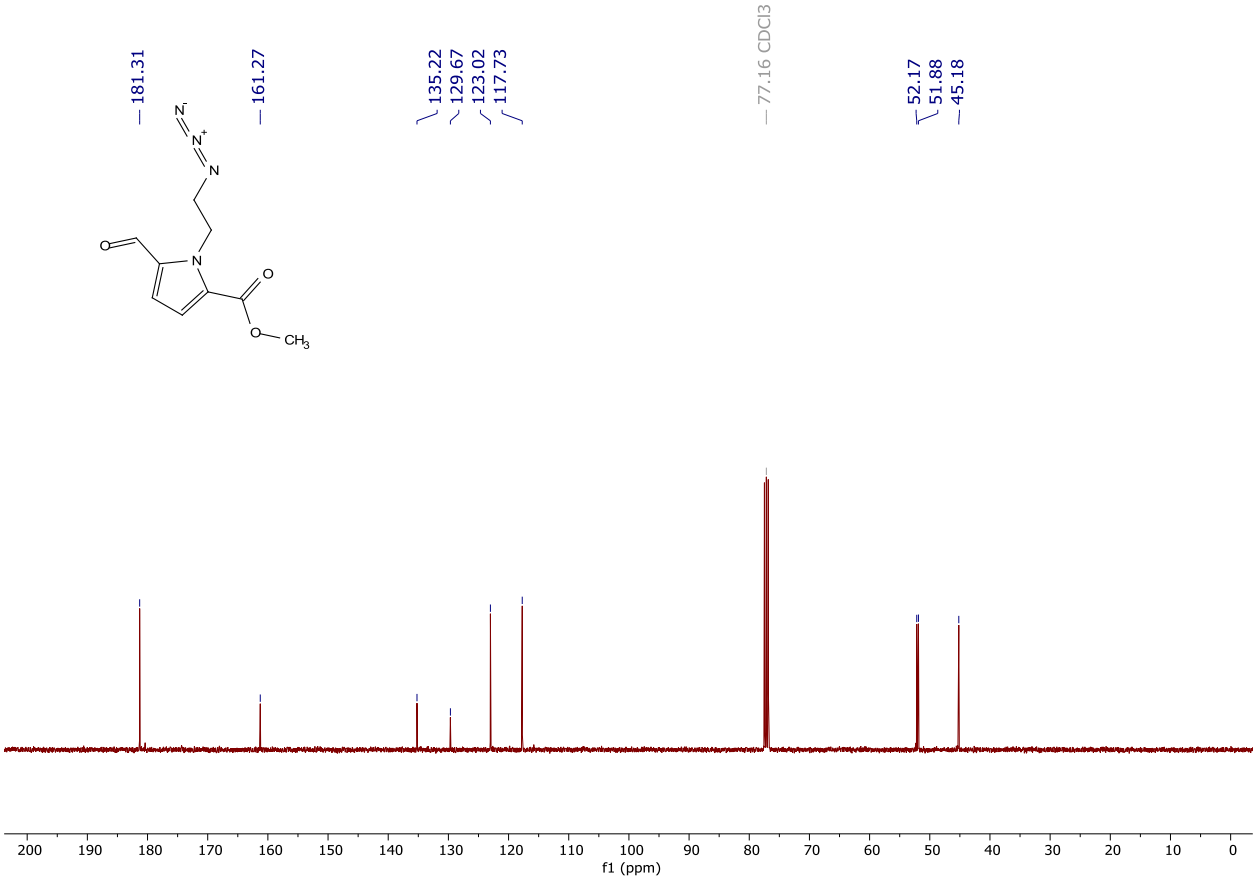
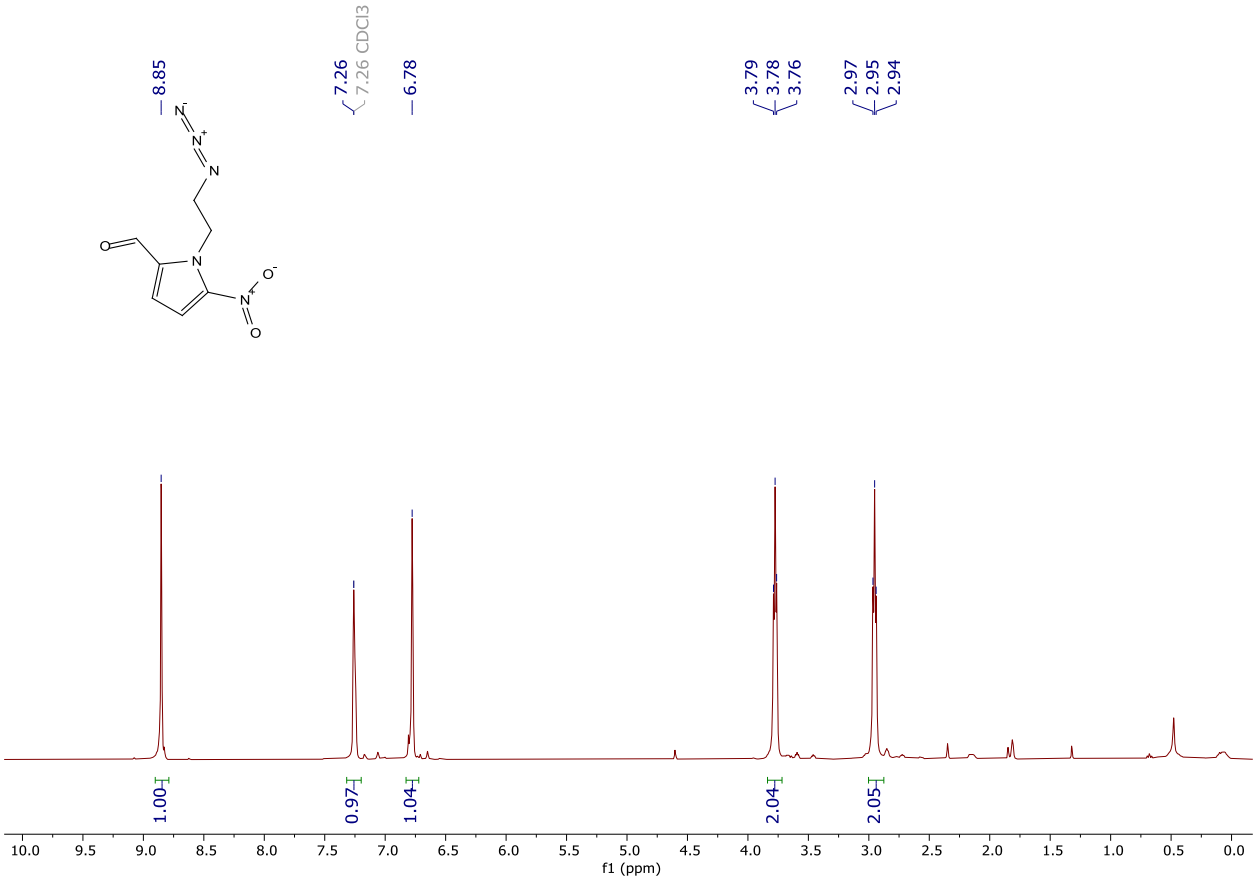
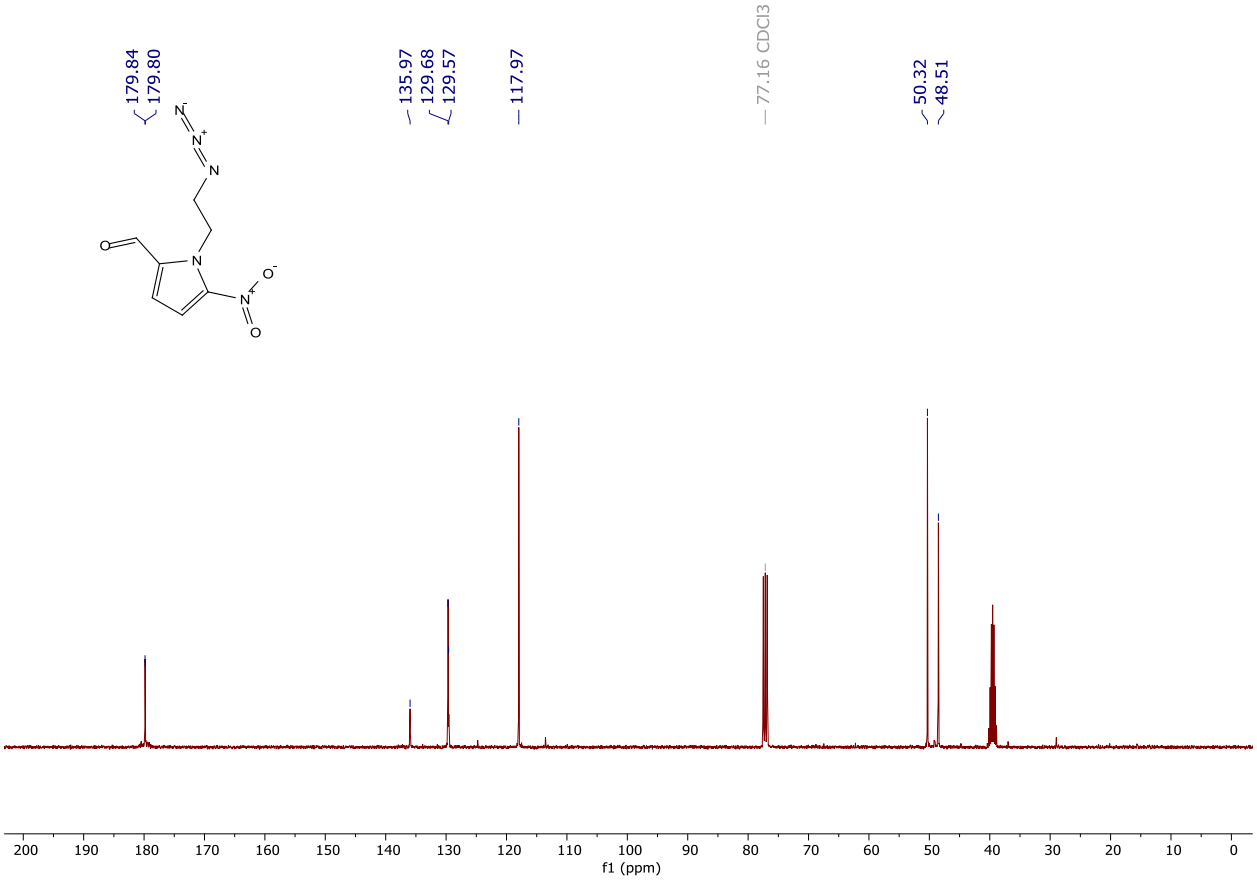




^{1}H and ^{13}C spectra of compound **5c**





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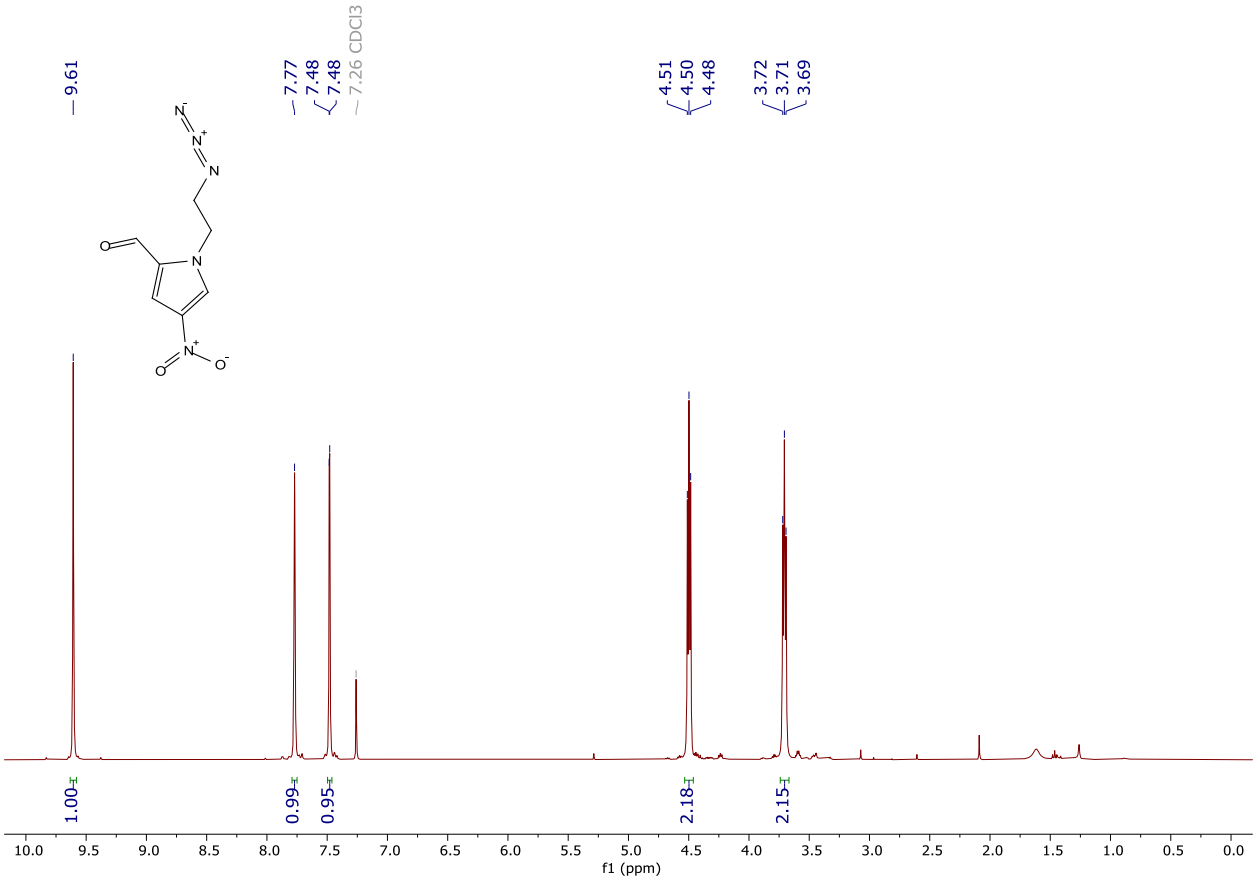
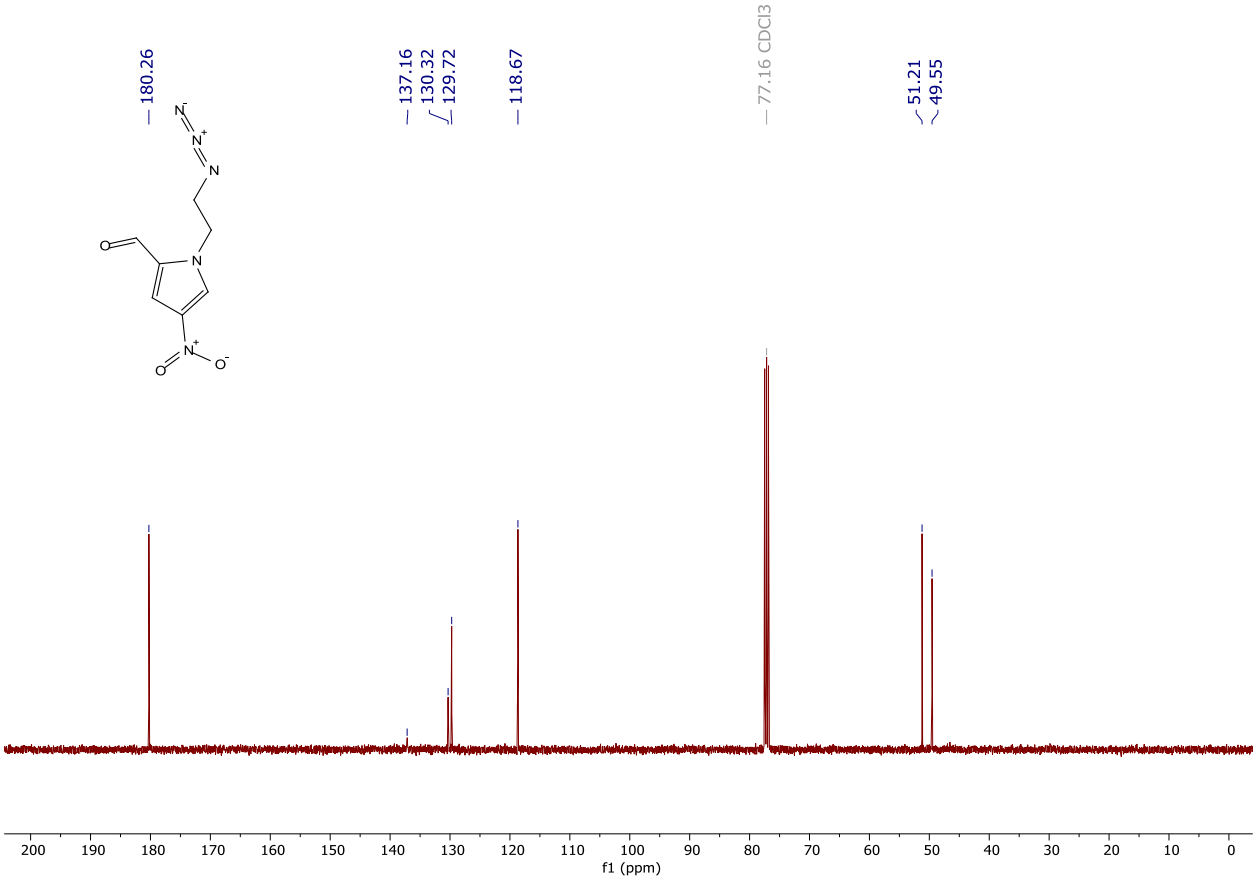
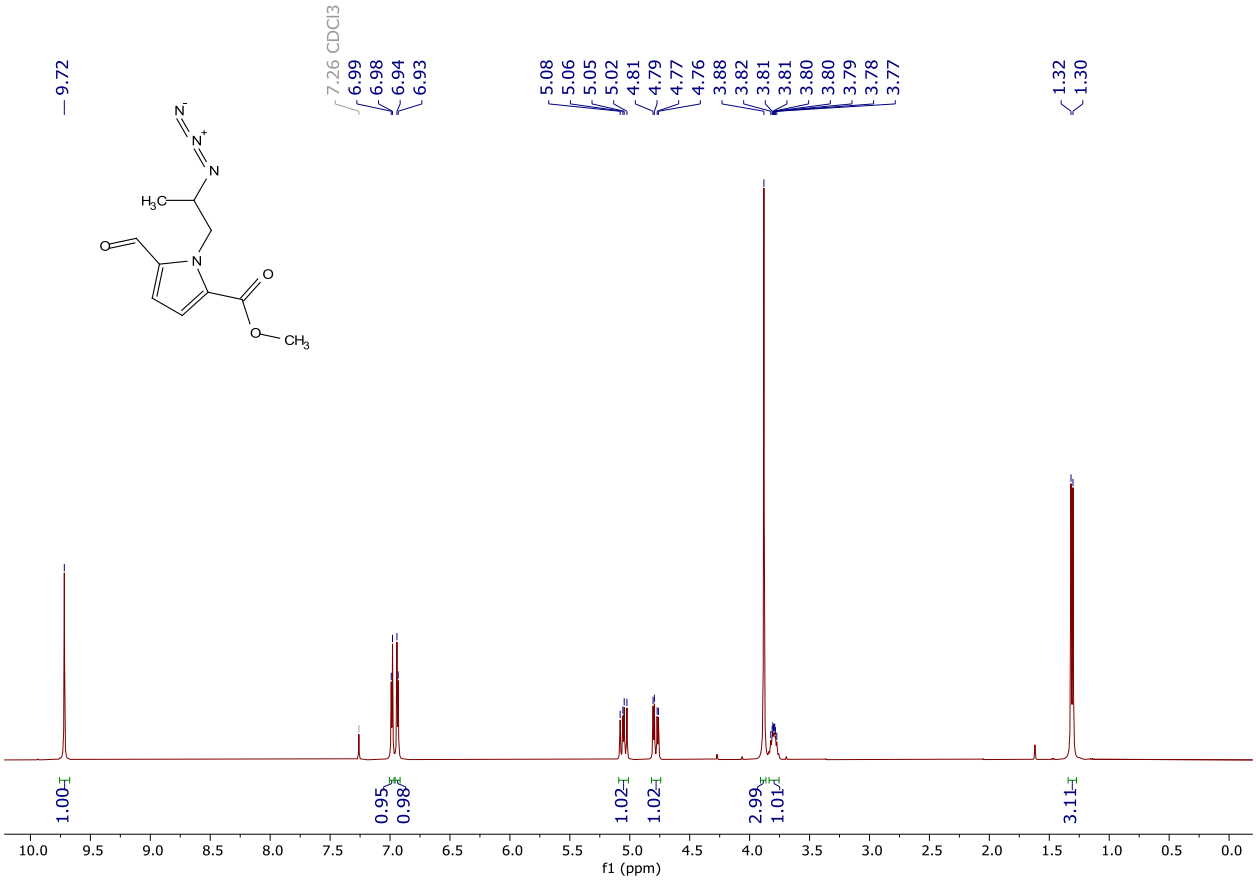
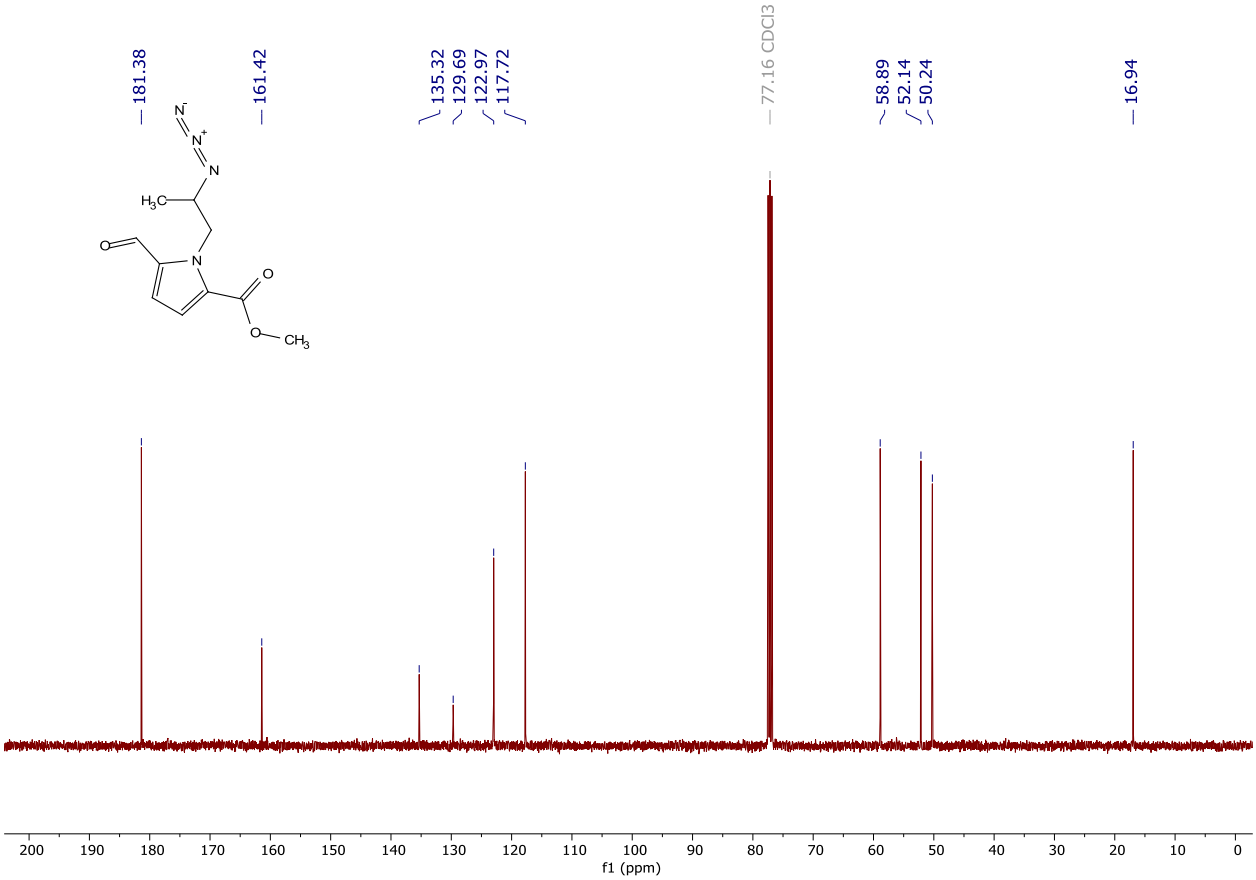


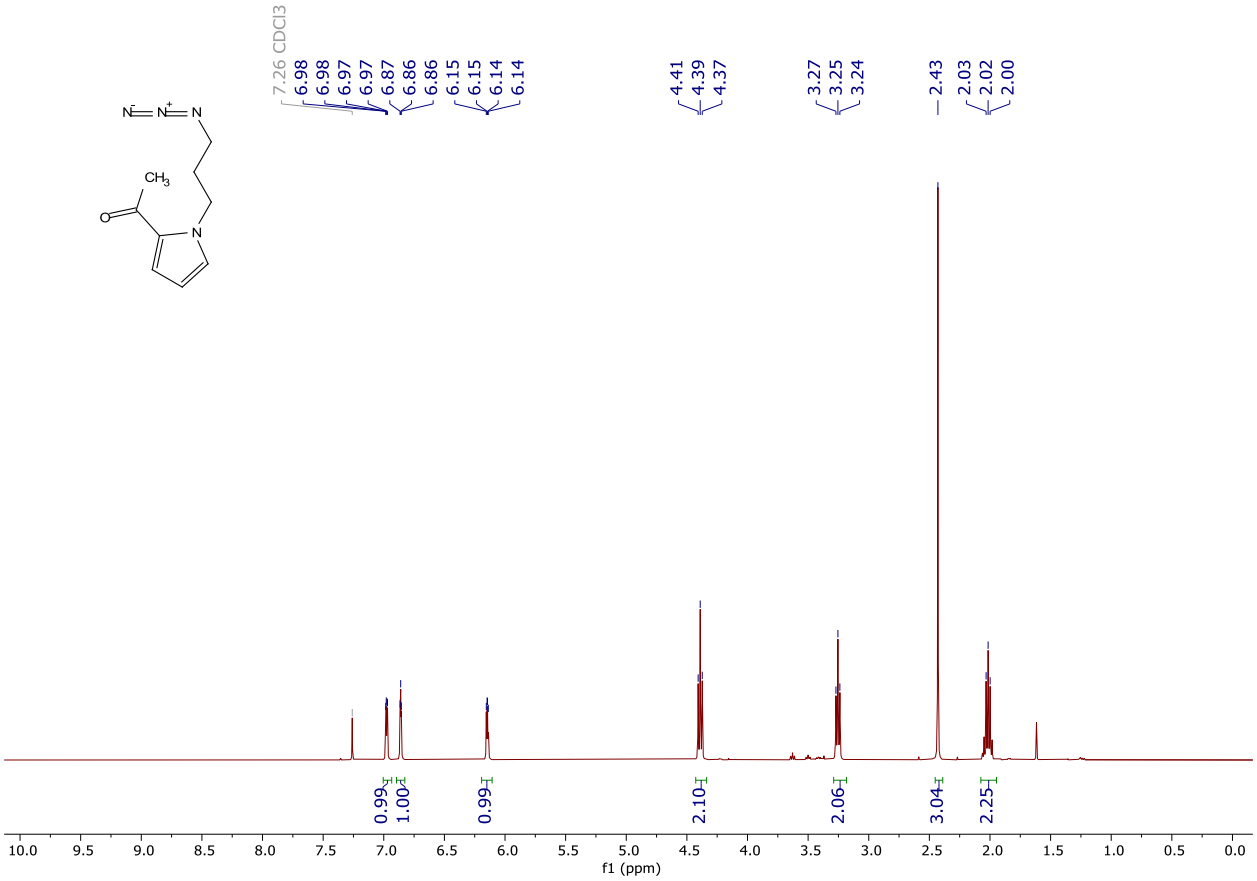


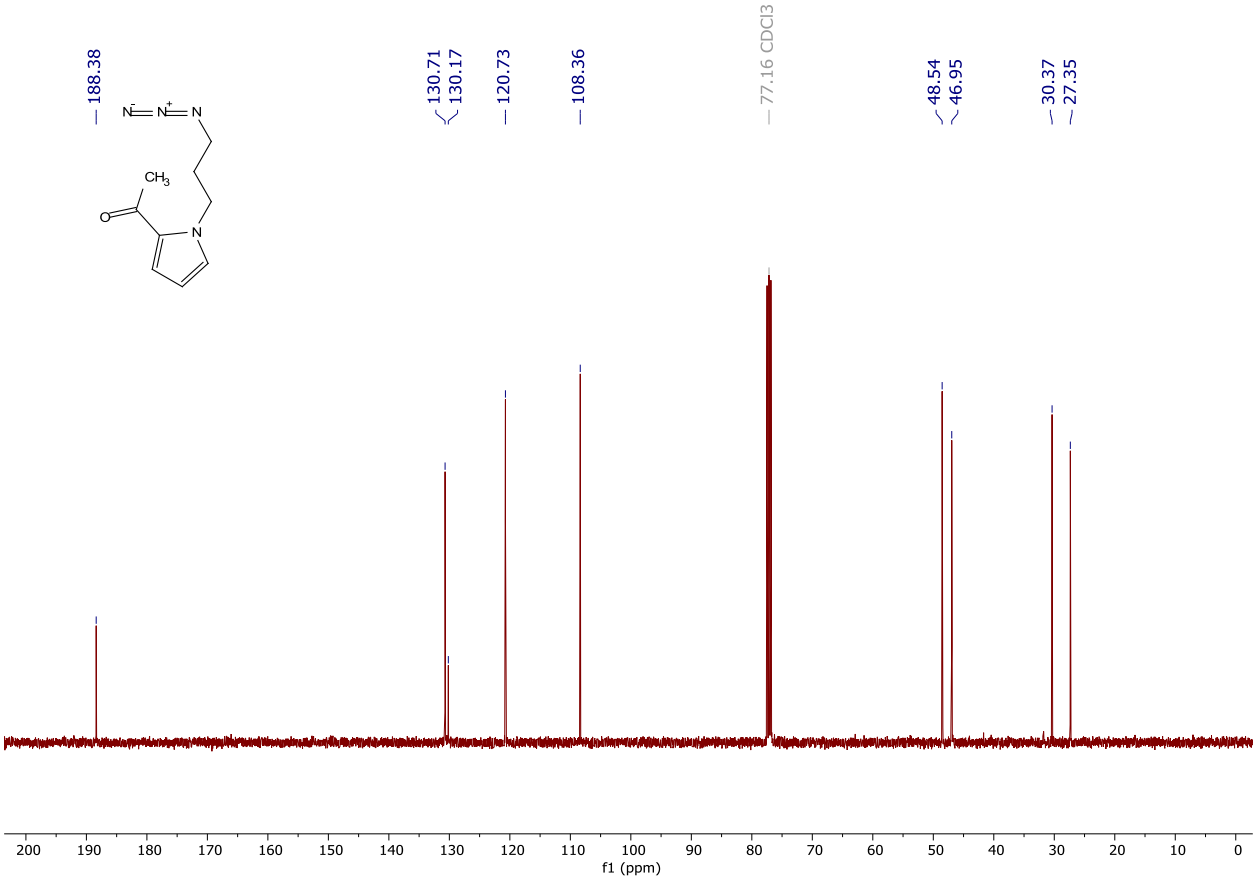
^{1}H and ^{13}C spectra of compound **5e**



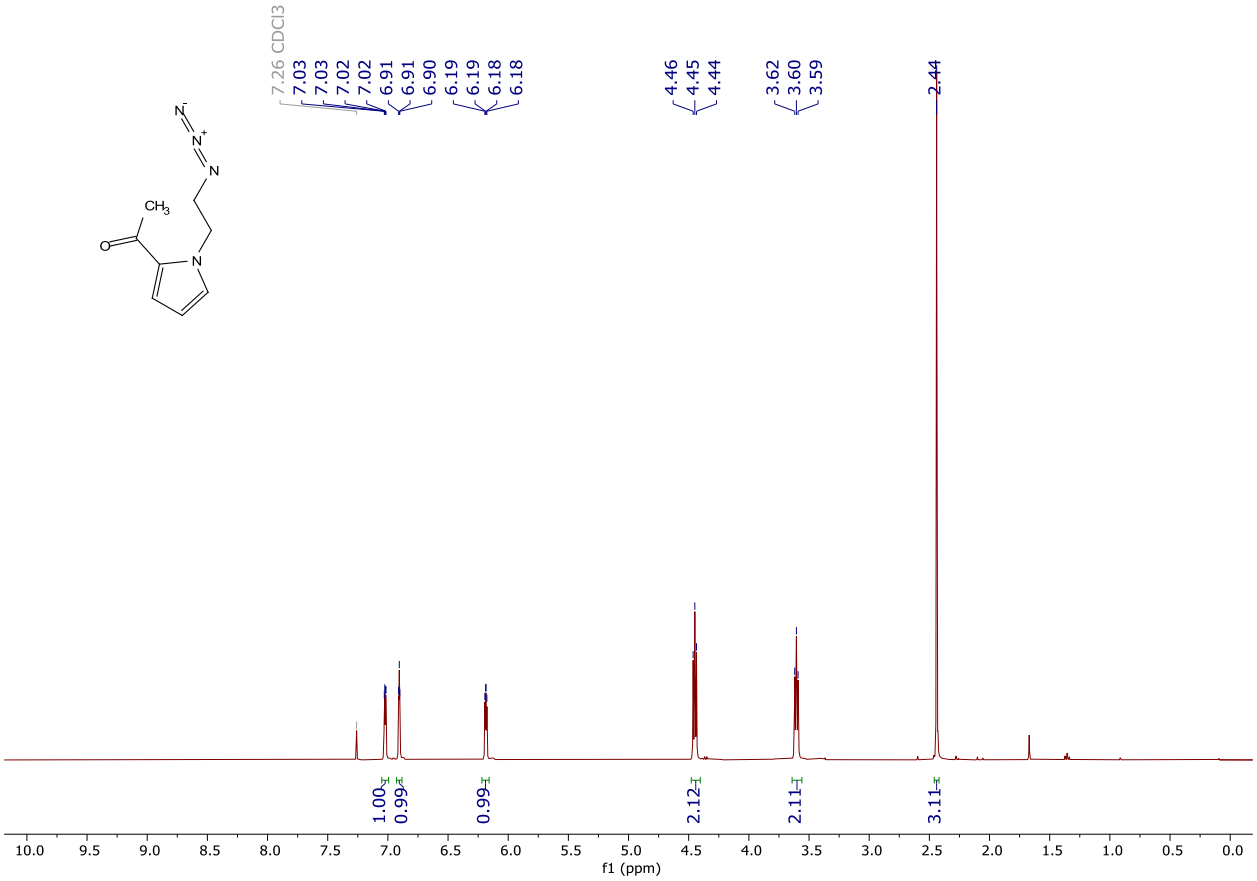


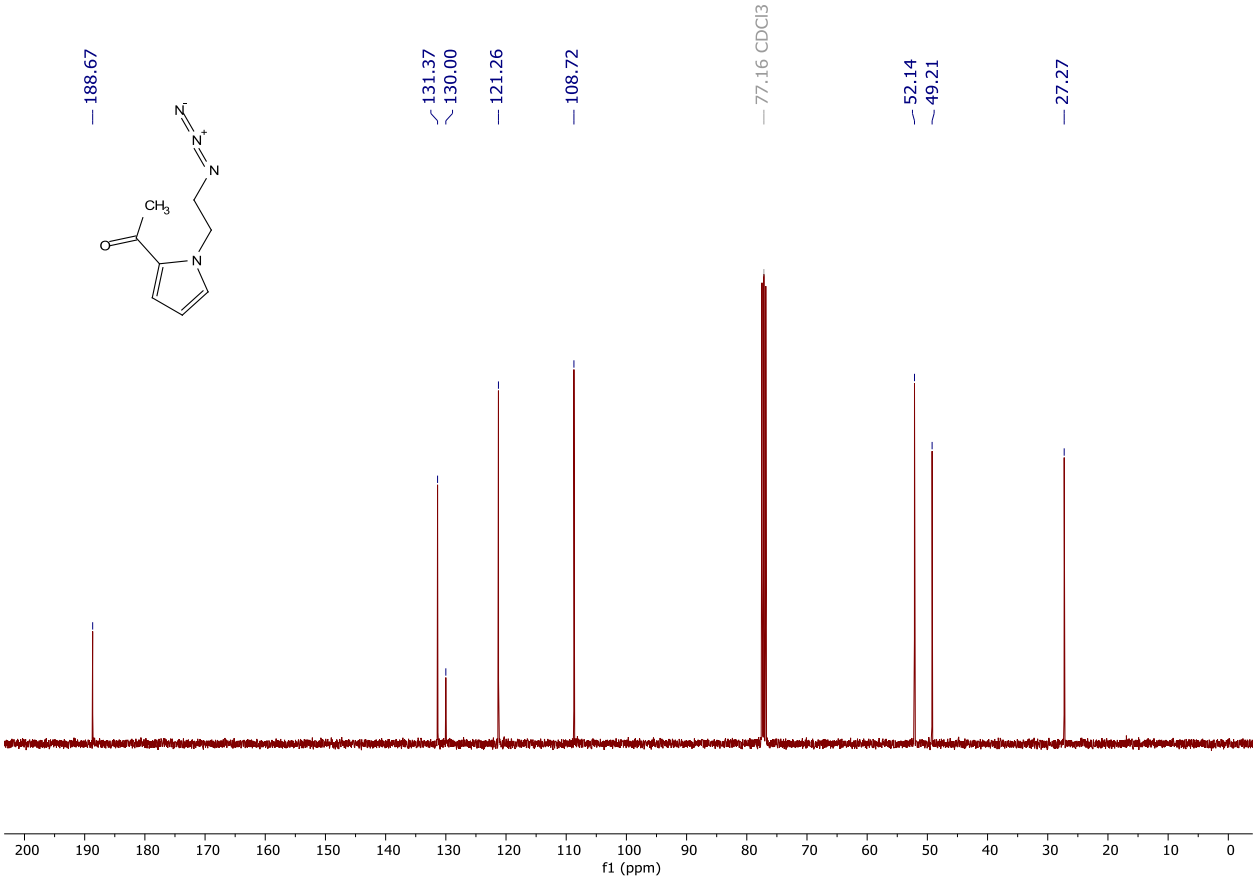
^{1}H and ^{13}C spectra of compound **5f**





^{1}H and ^{13}C spectra of compound **5g**





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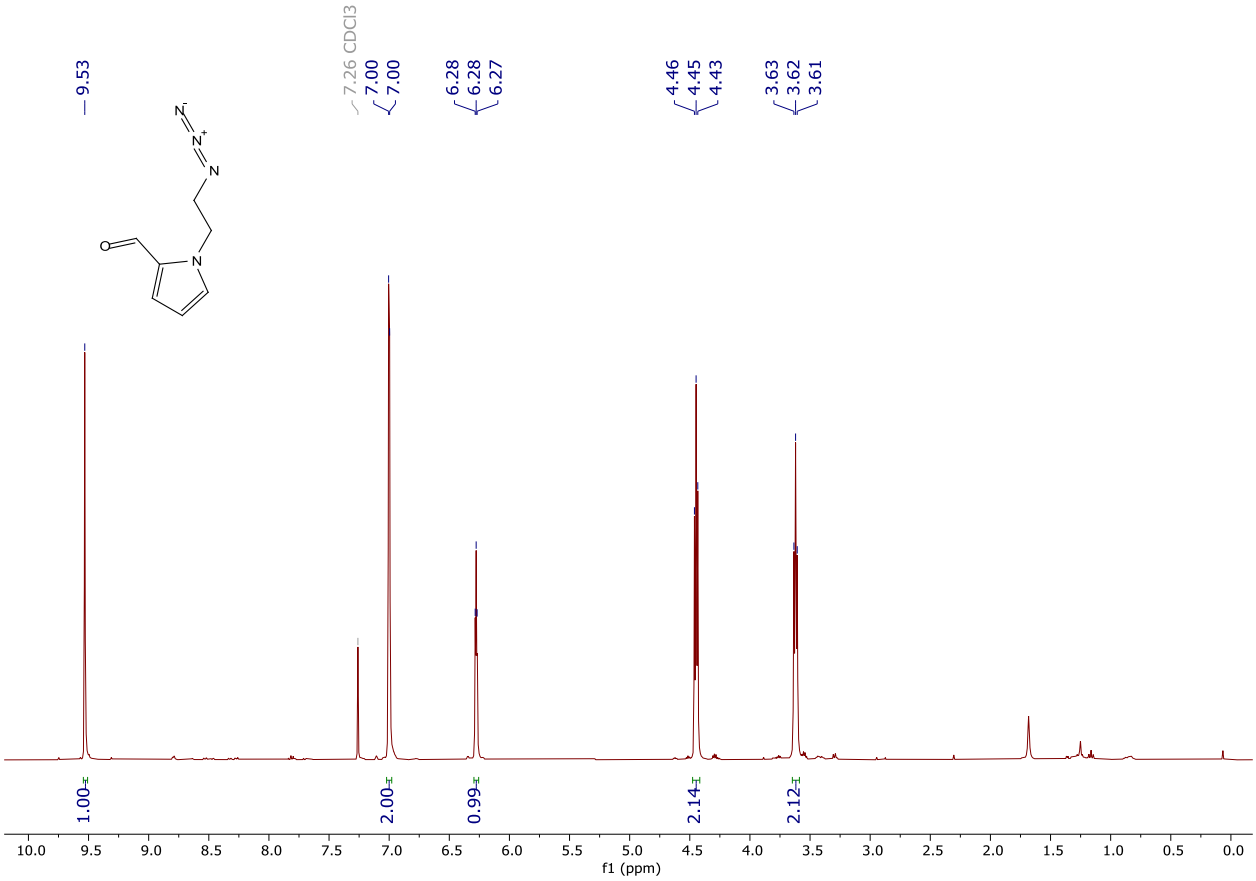

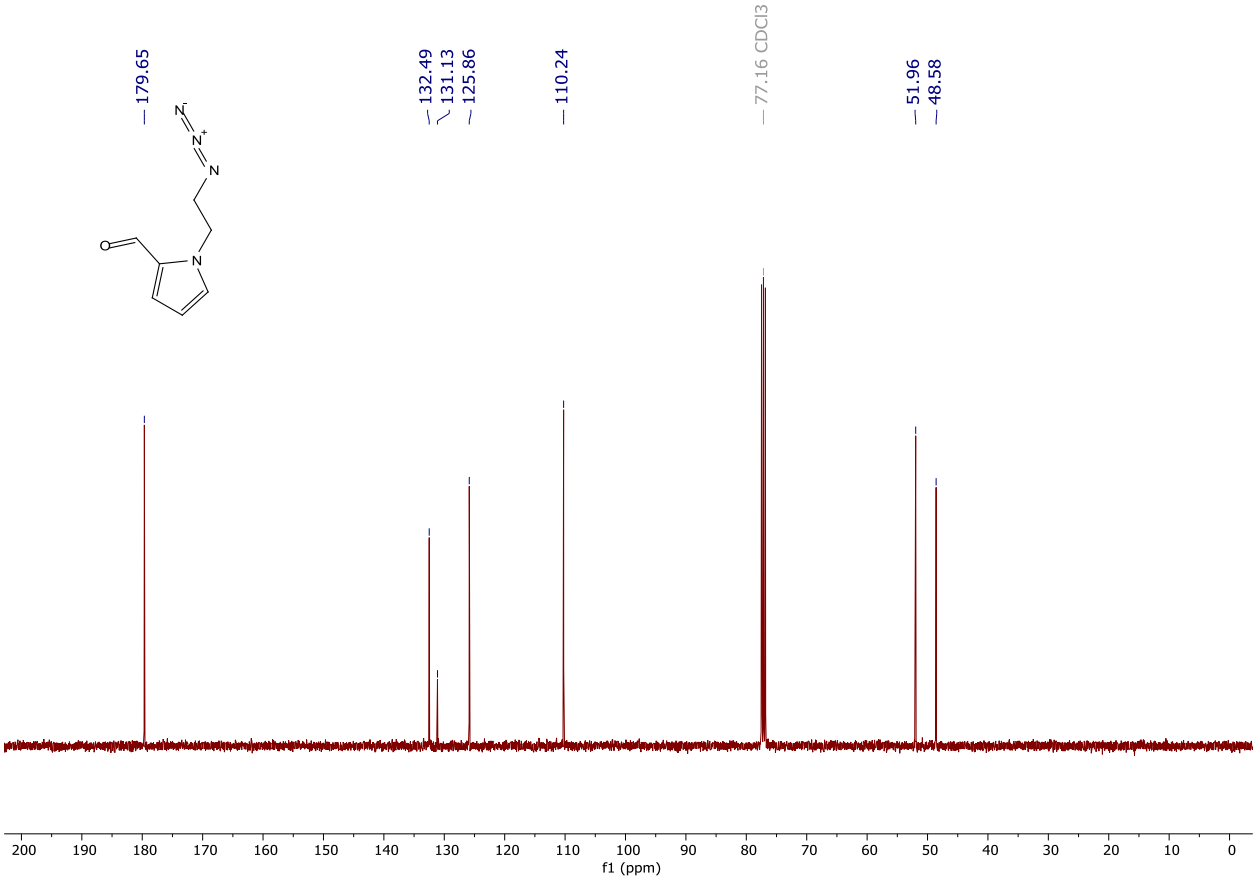

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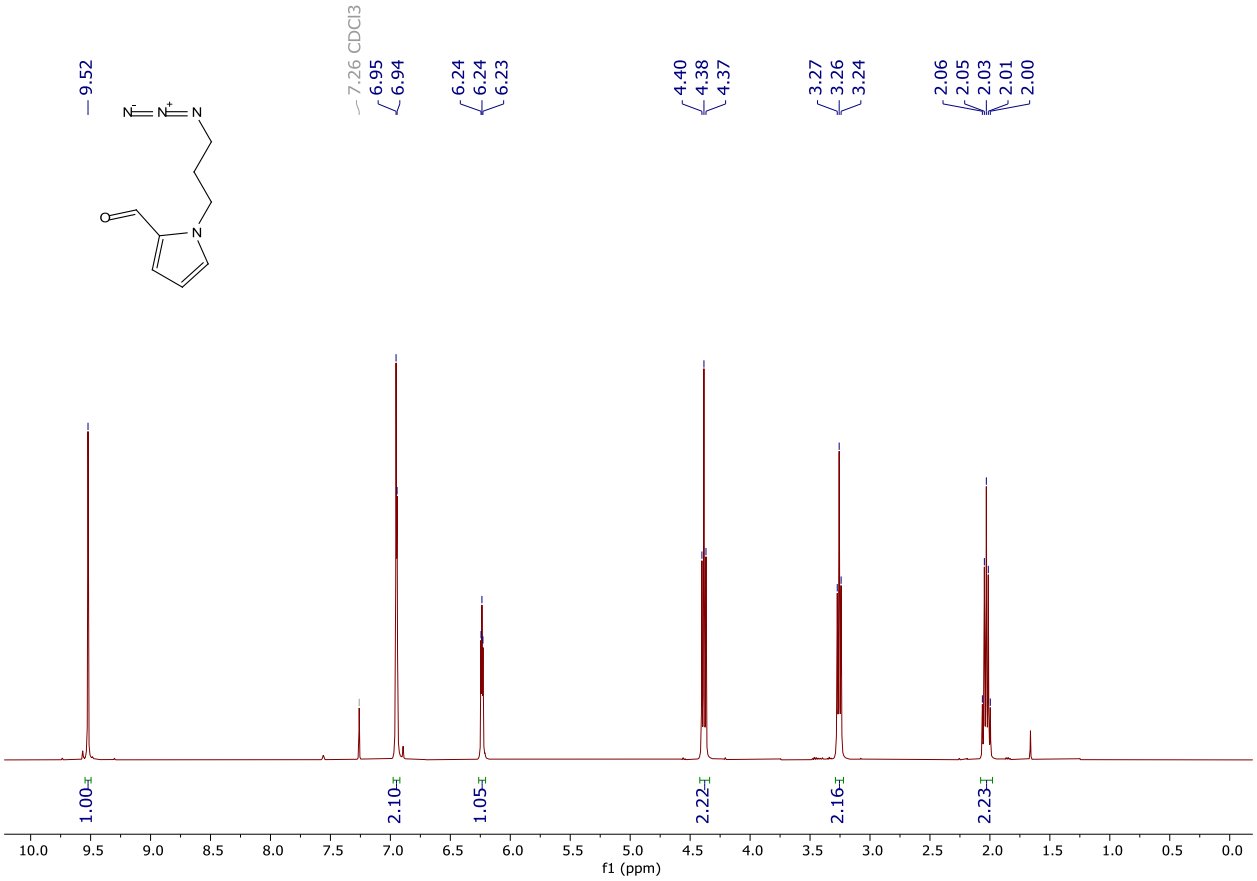
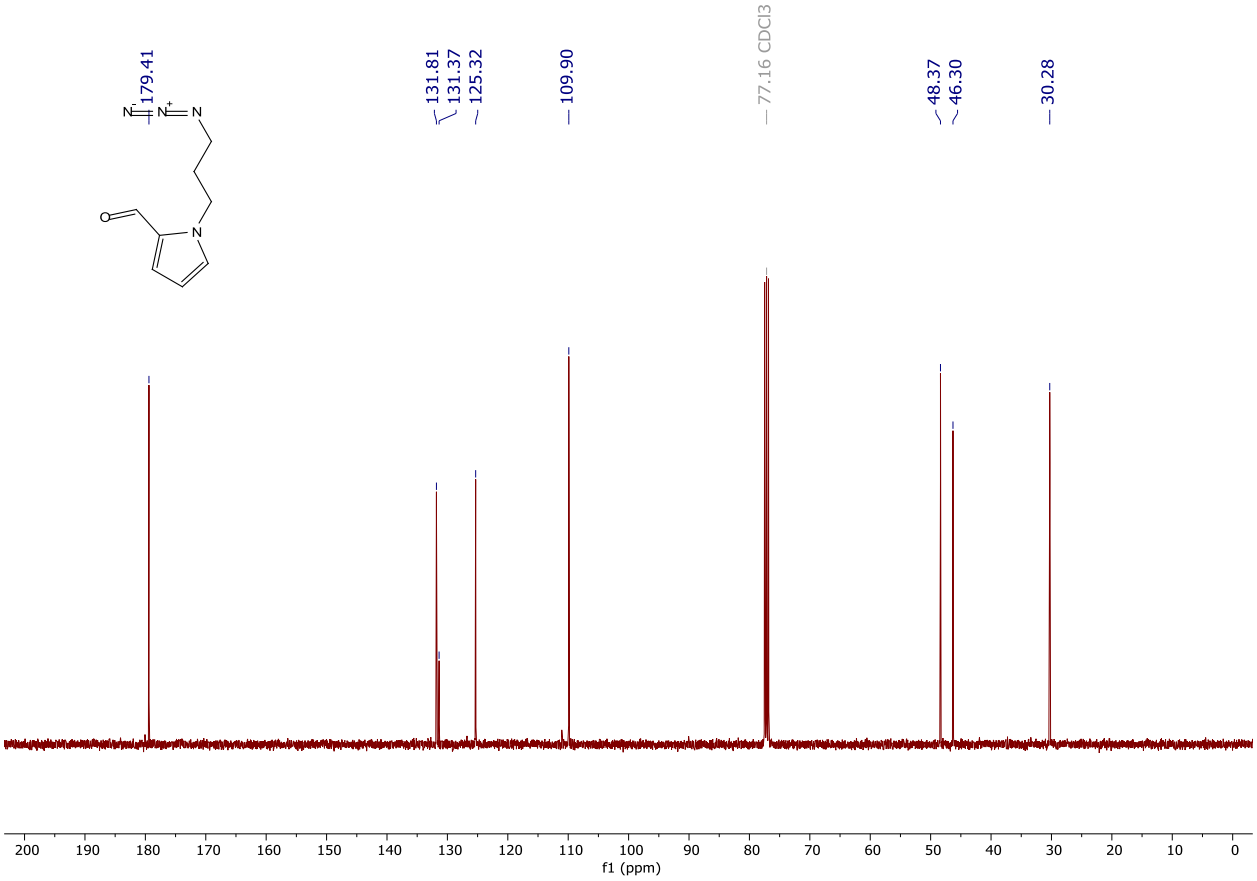
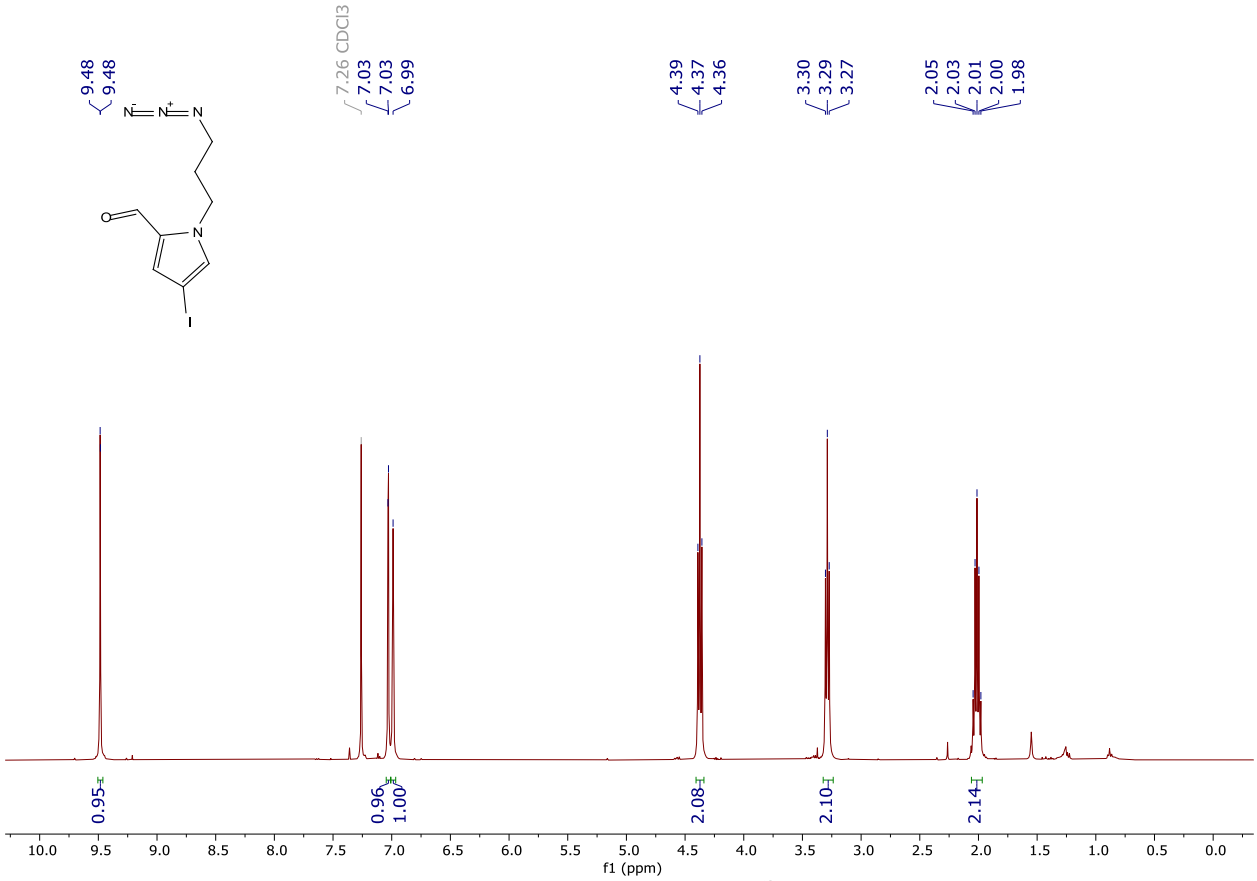
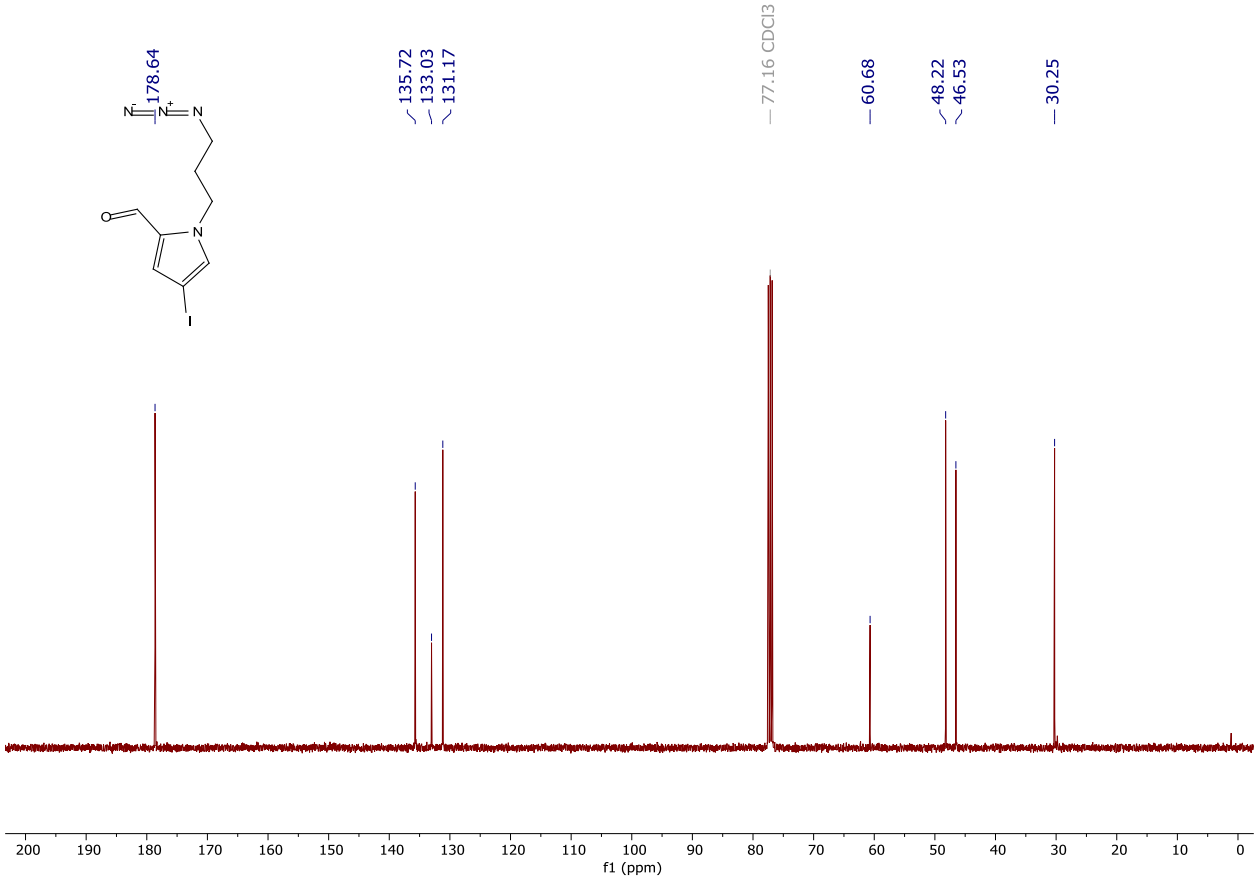


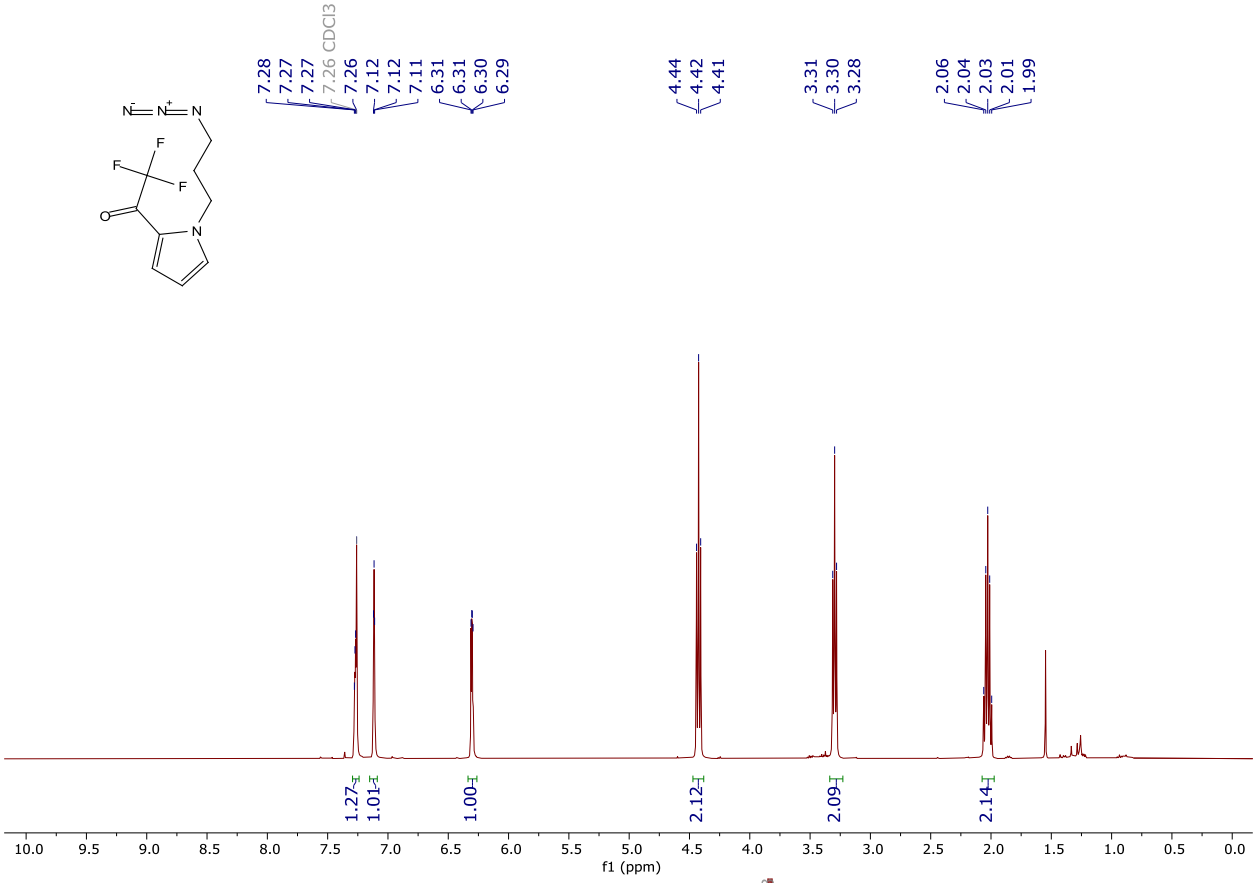


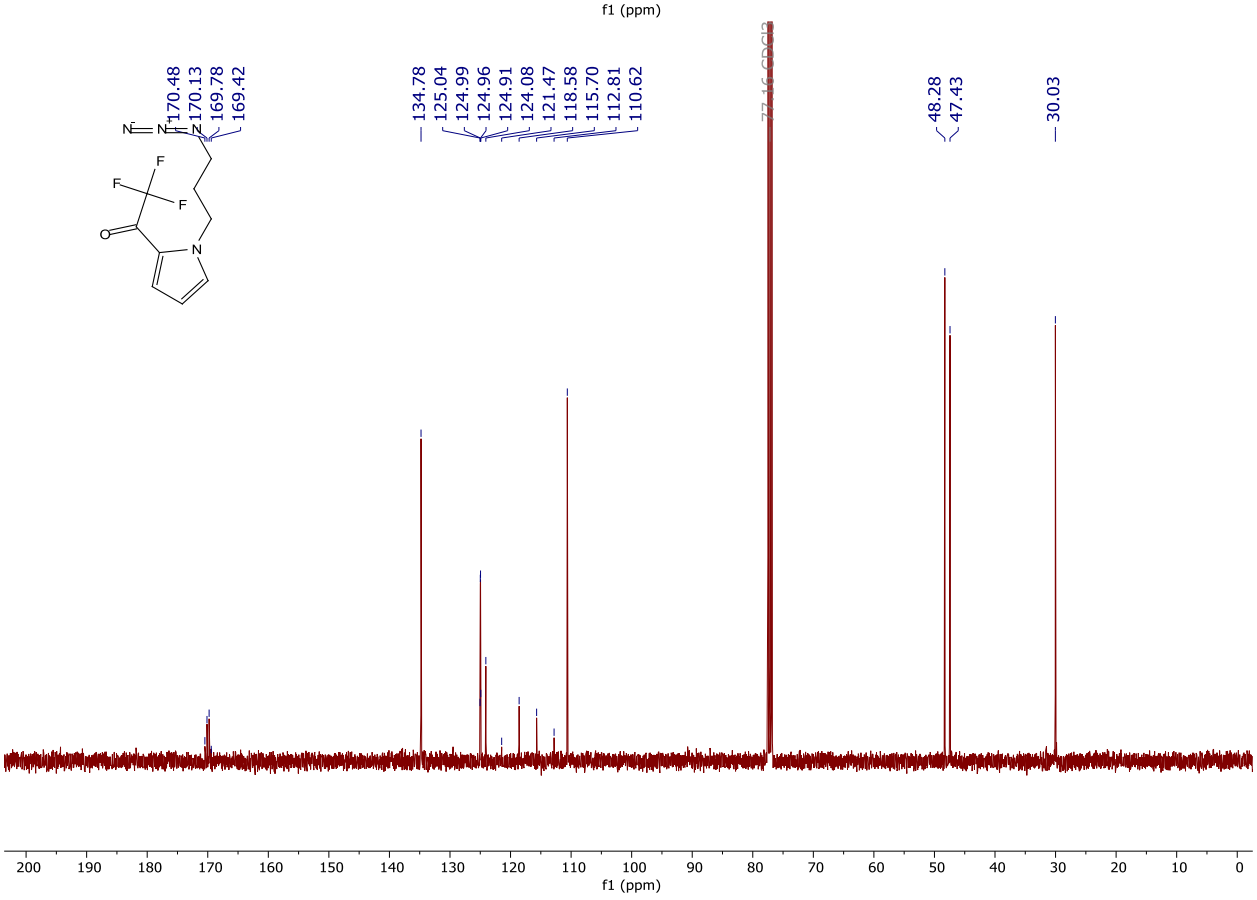
^{1}H and ^{13}C spectra of compound **5j**

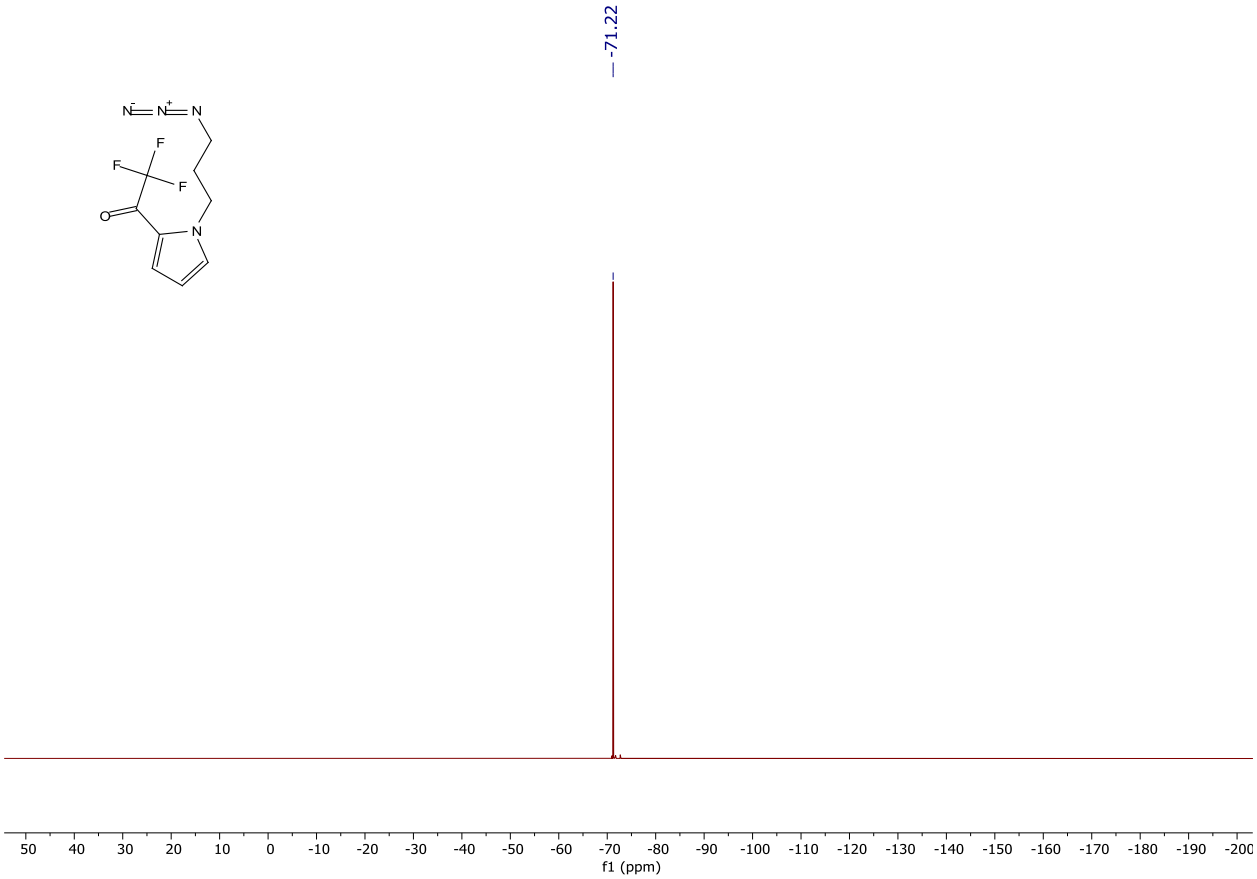




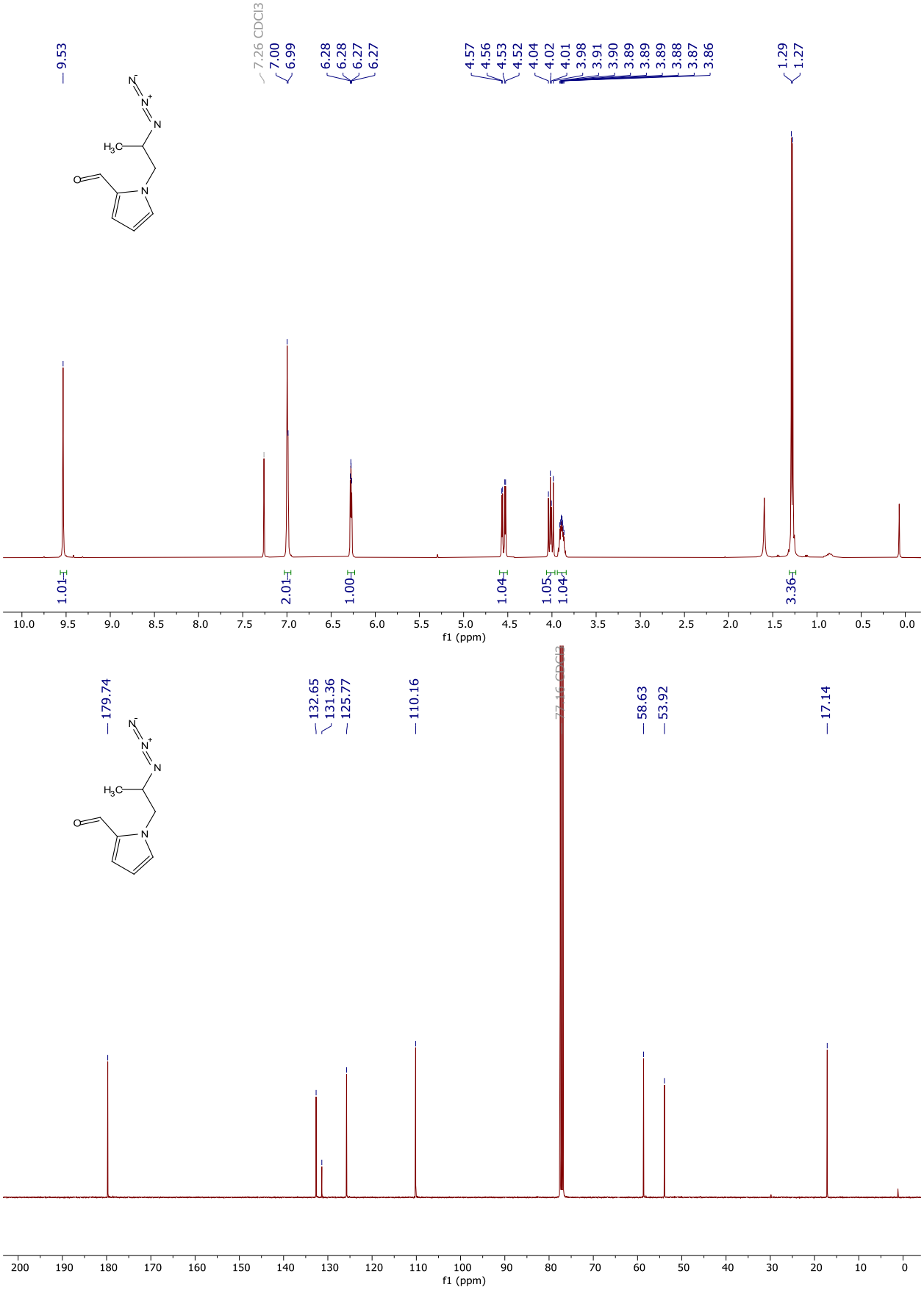
^{1}H, ^{13}C and ^{19}F spectra of compound **5k**






-71.22
F
F
F
O
N
50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

^{1}H and ^{13}C spectra of compound **5l**



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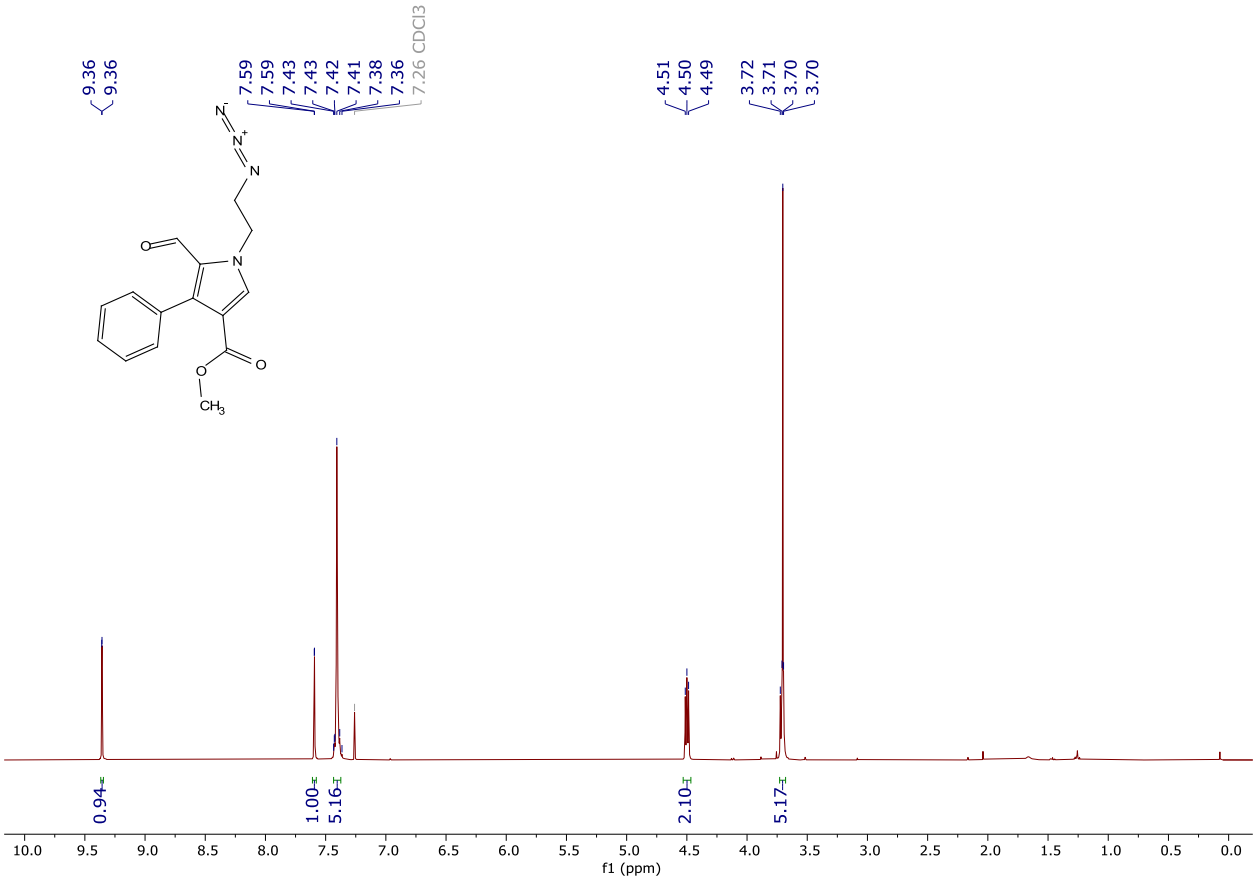
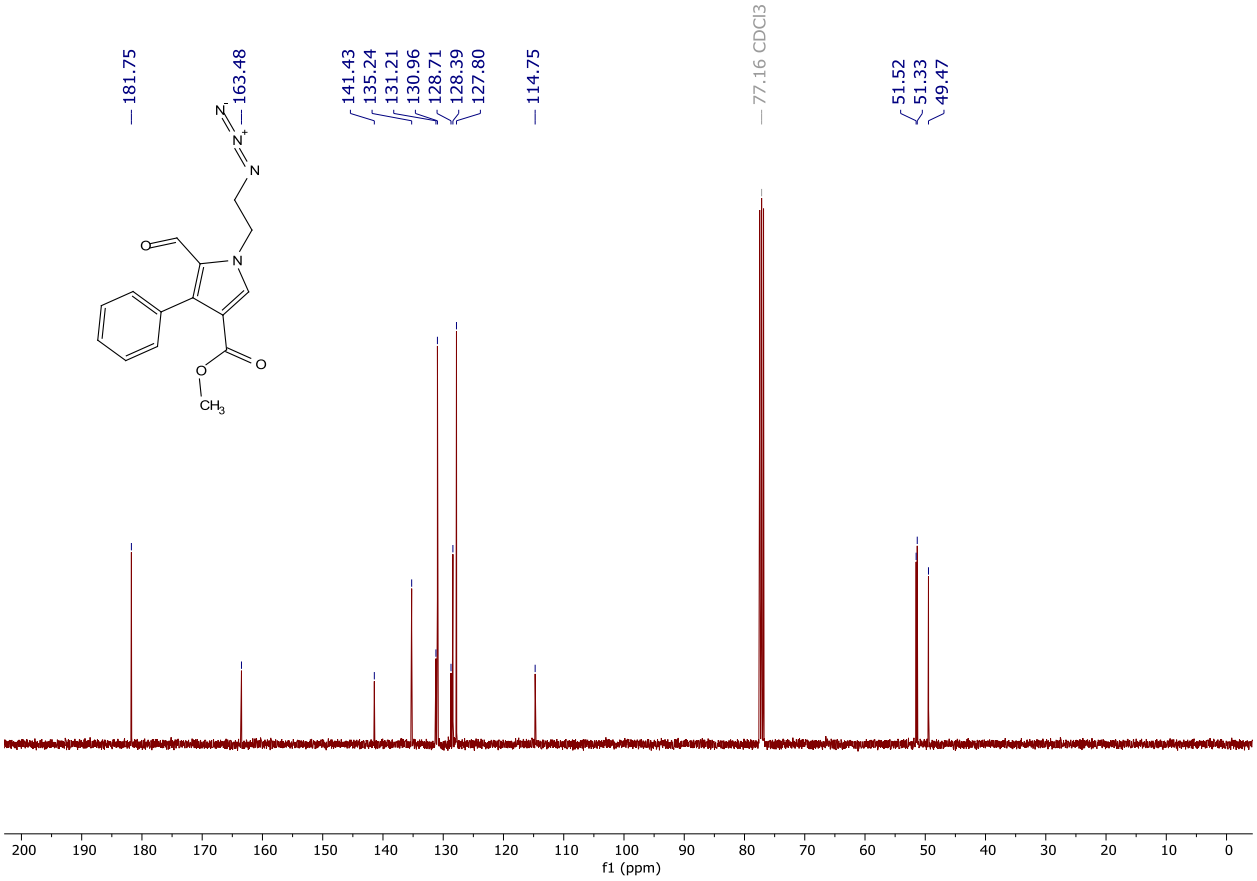
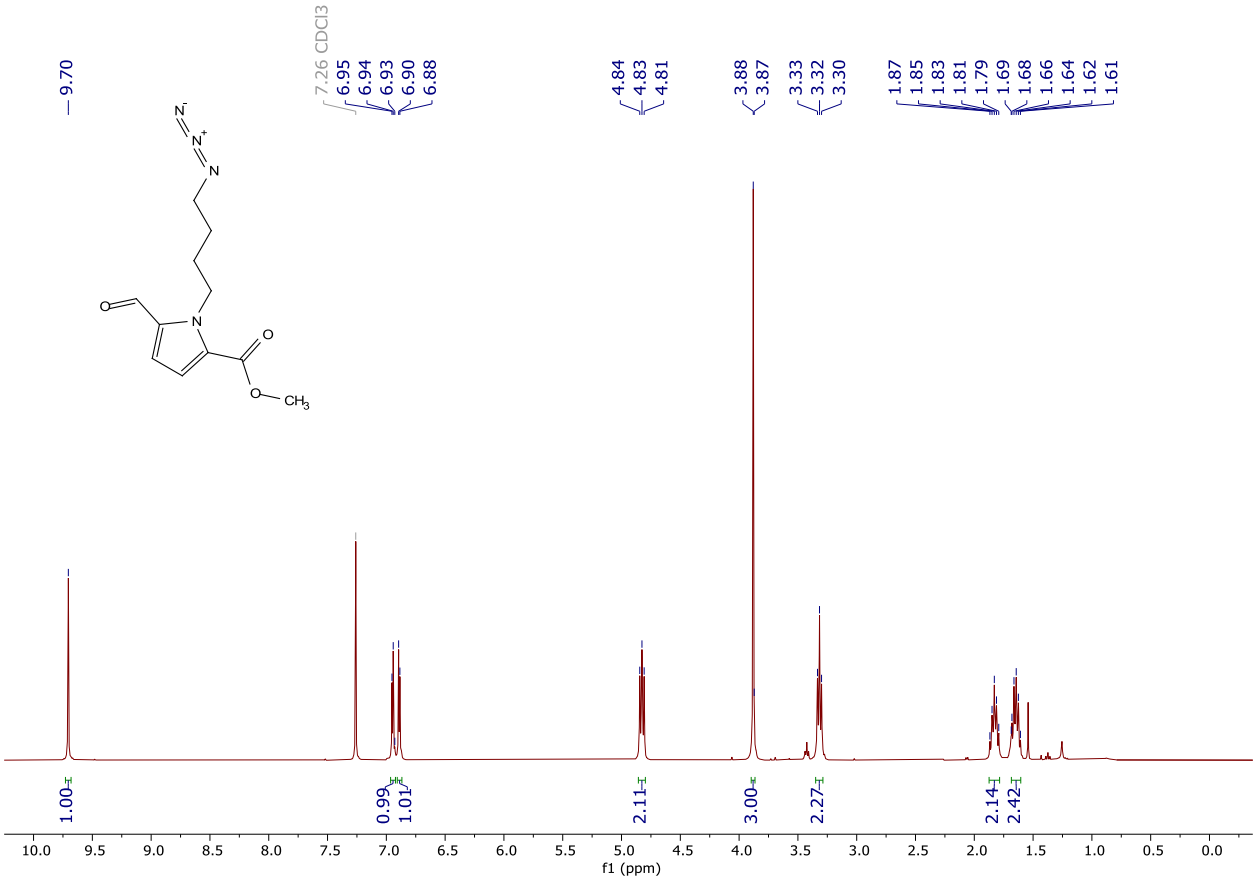
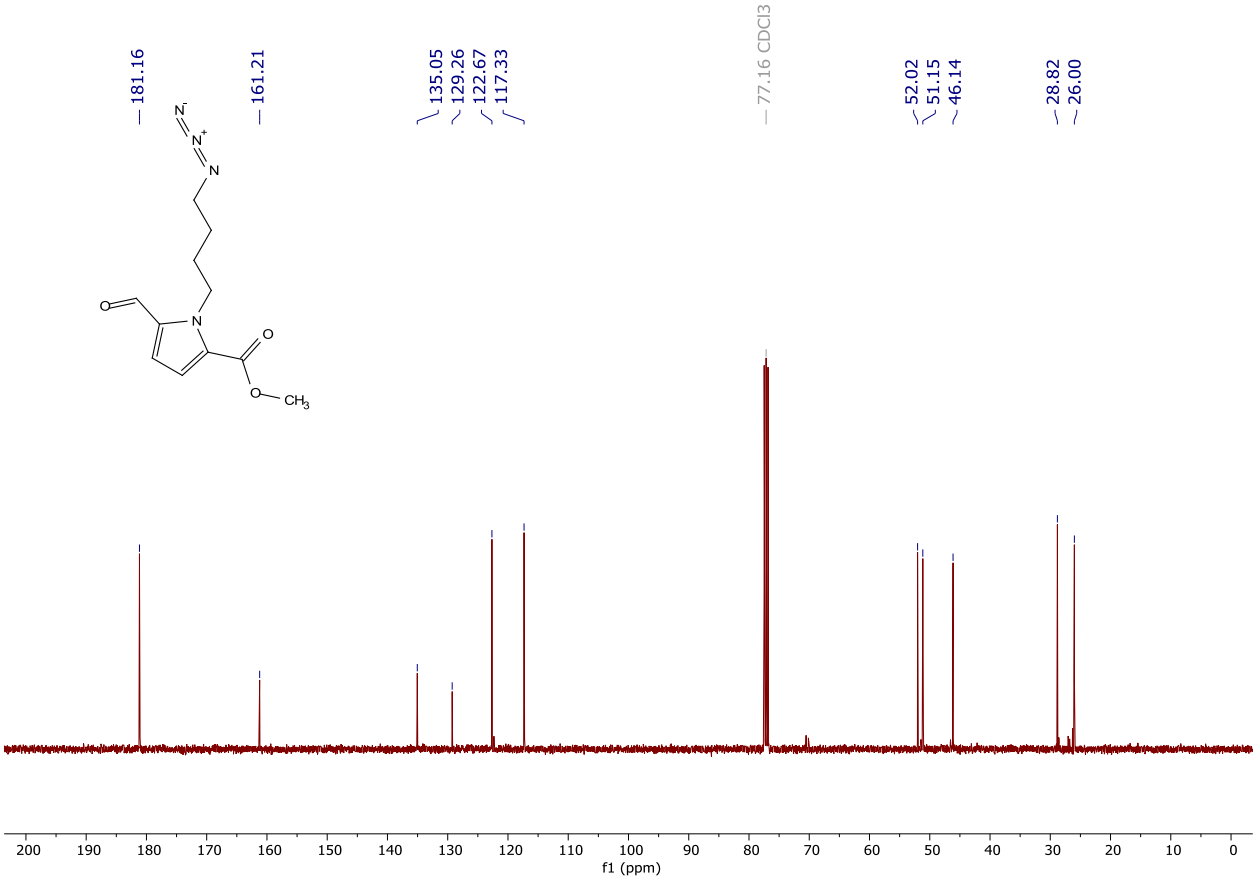


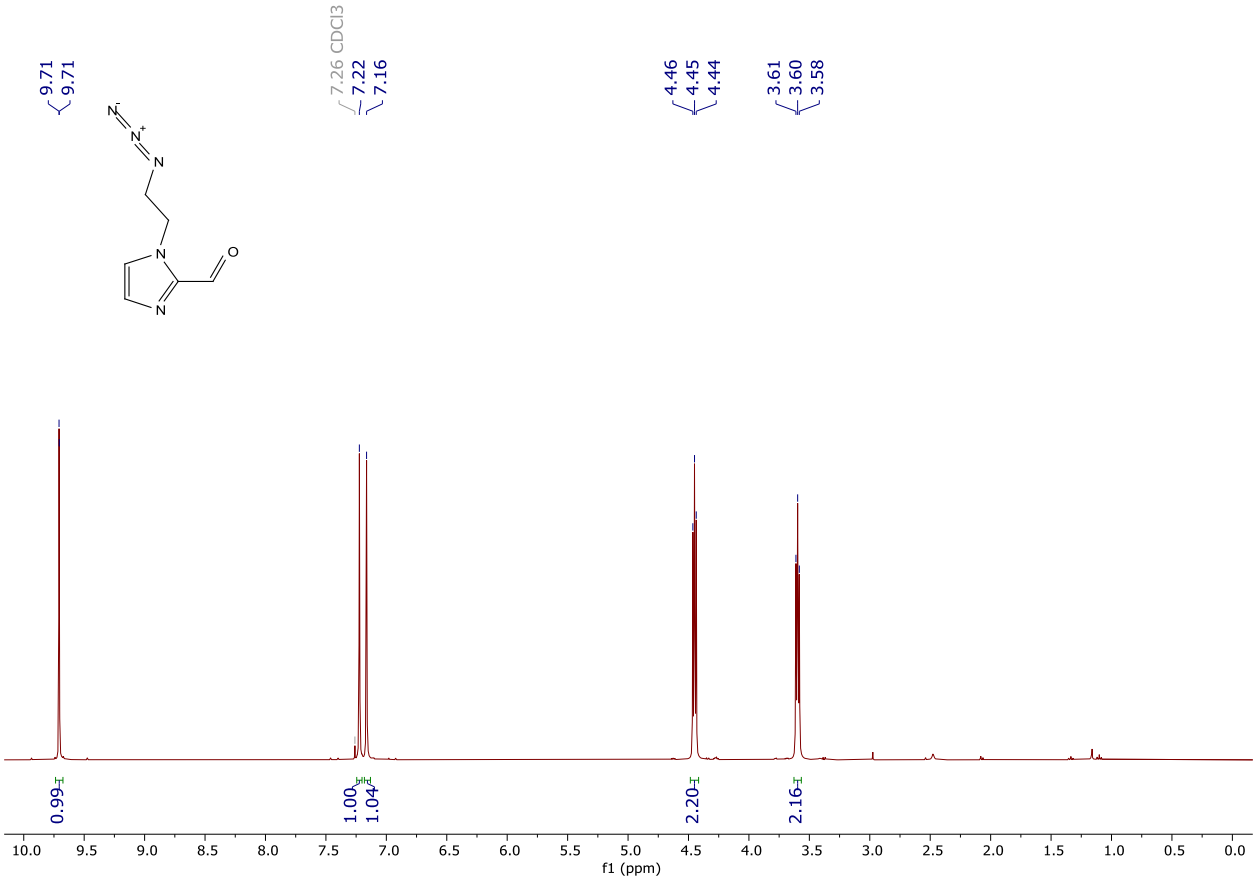


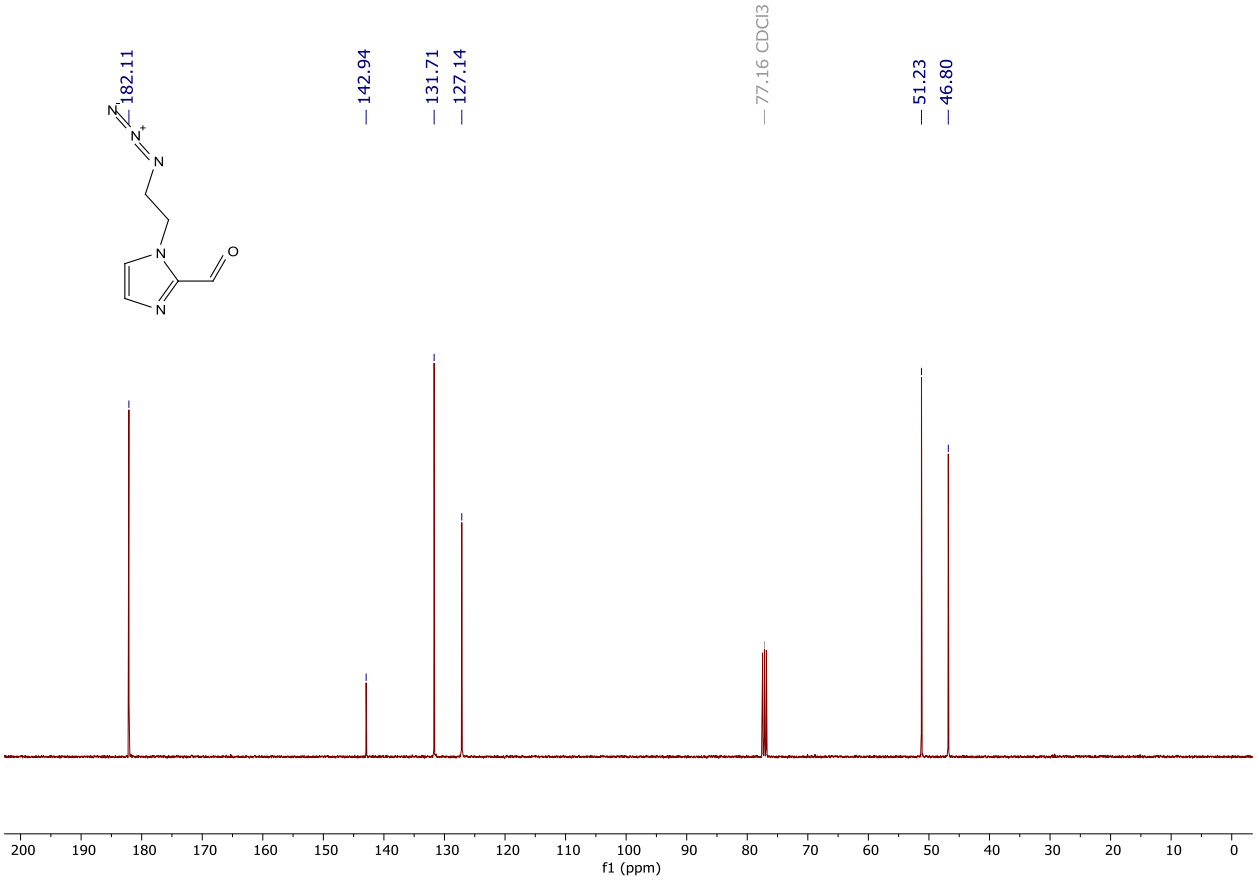
^{1}H and ^{13}C spectra of compound **5n**





^{1}H and ^{13}C spectra of compound **5o**





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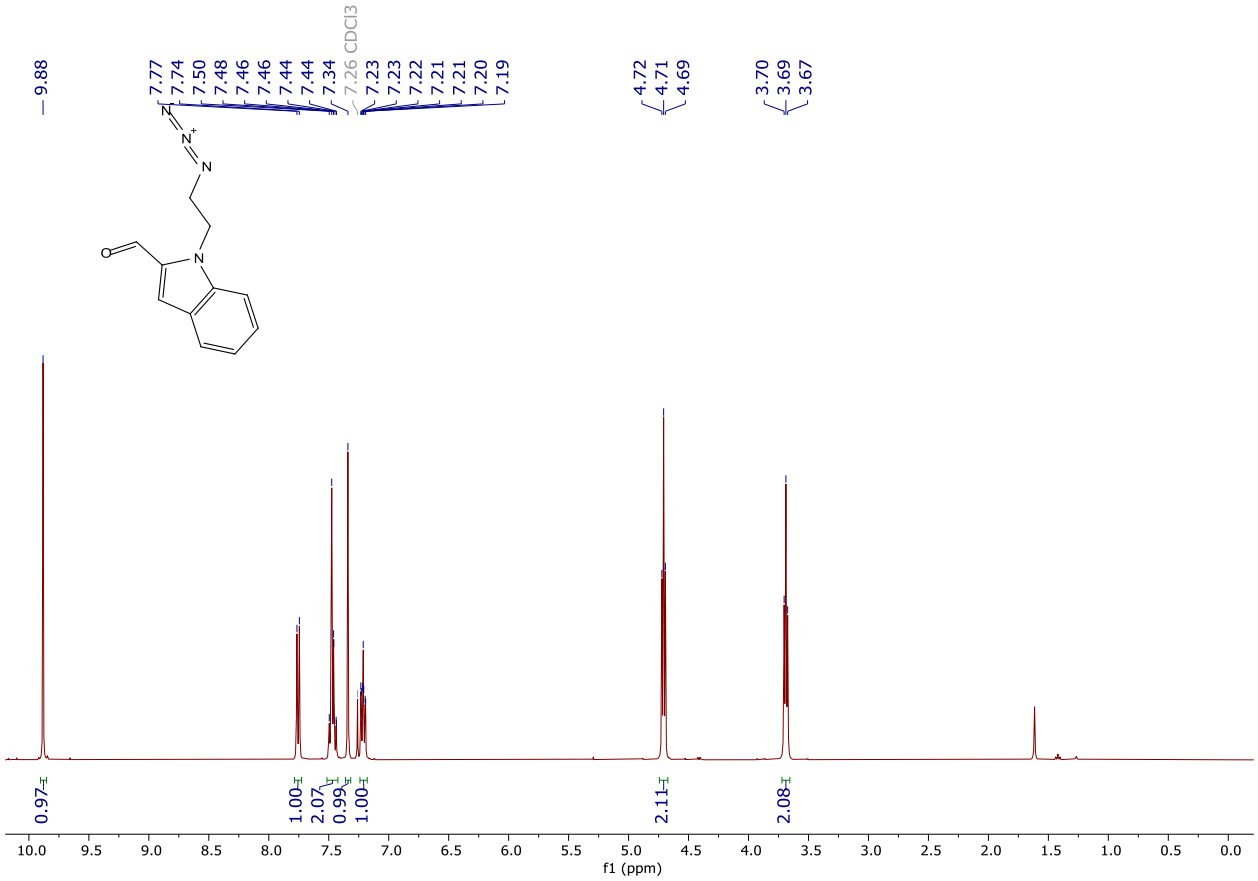

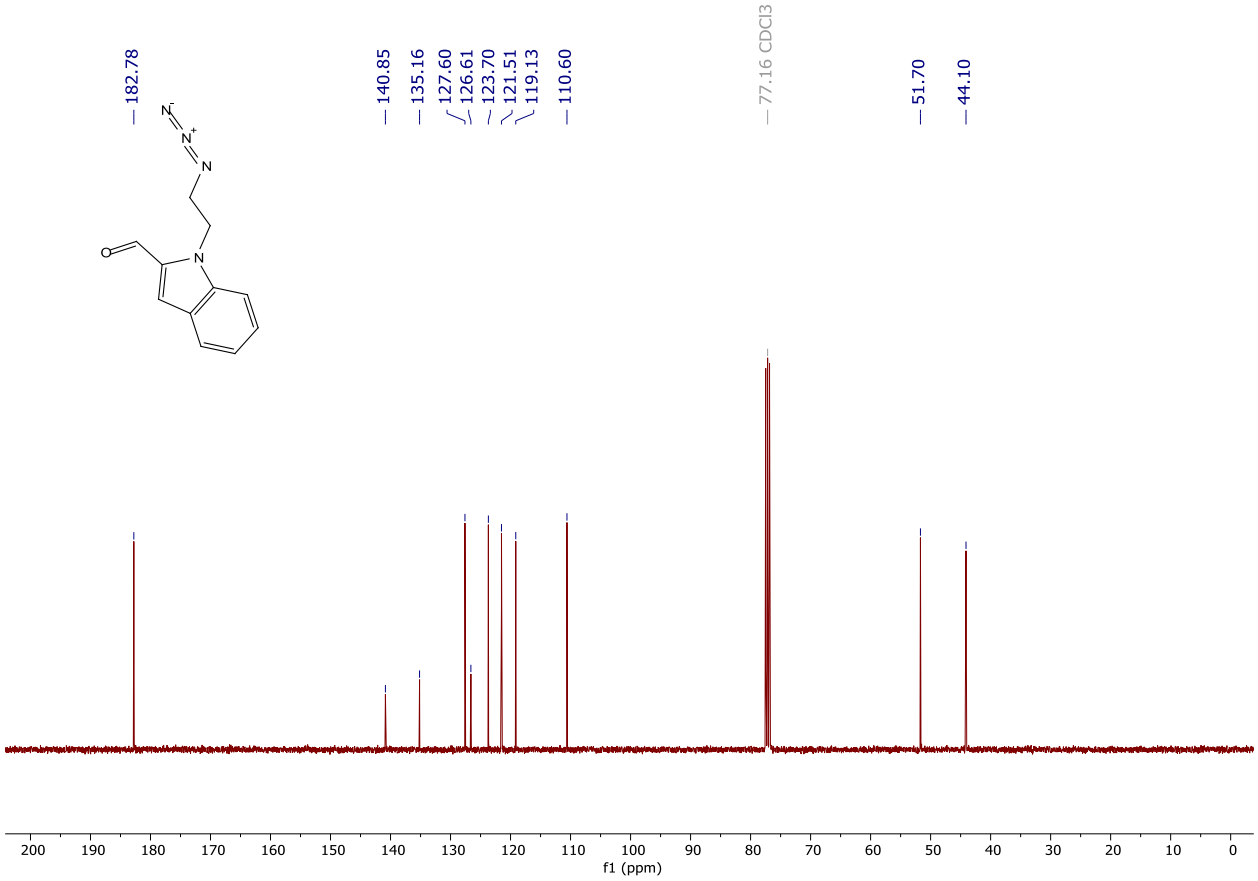

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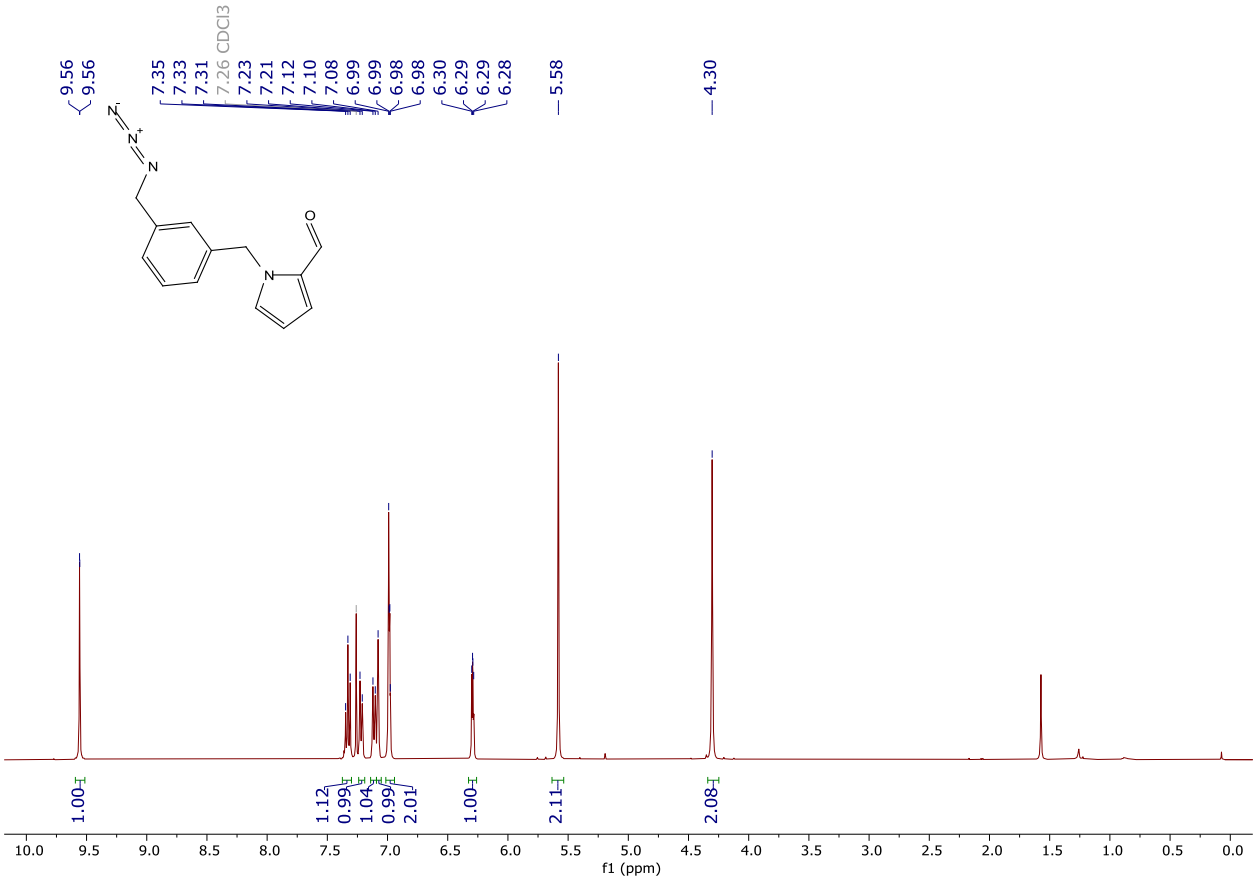

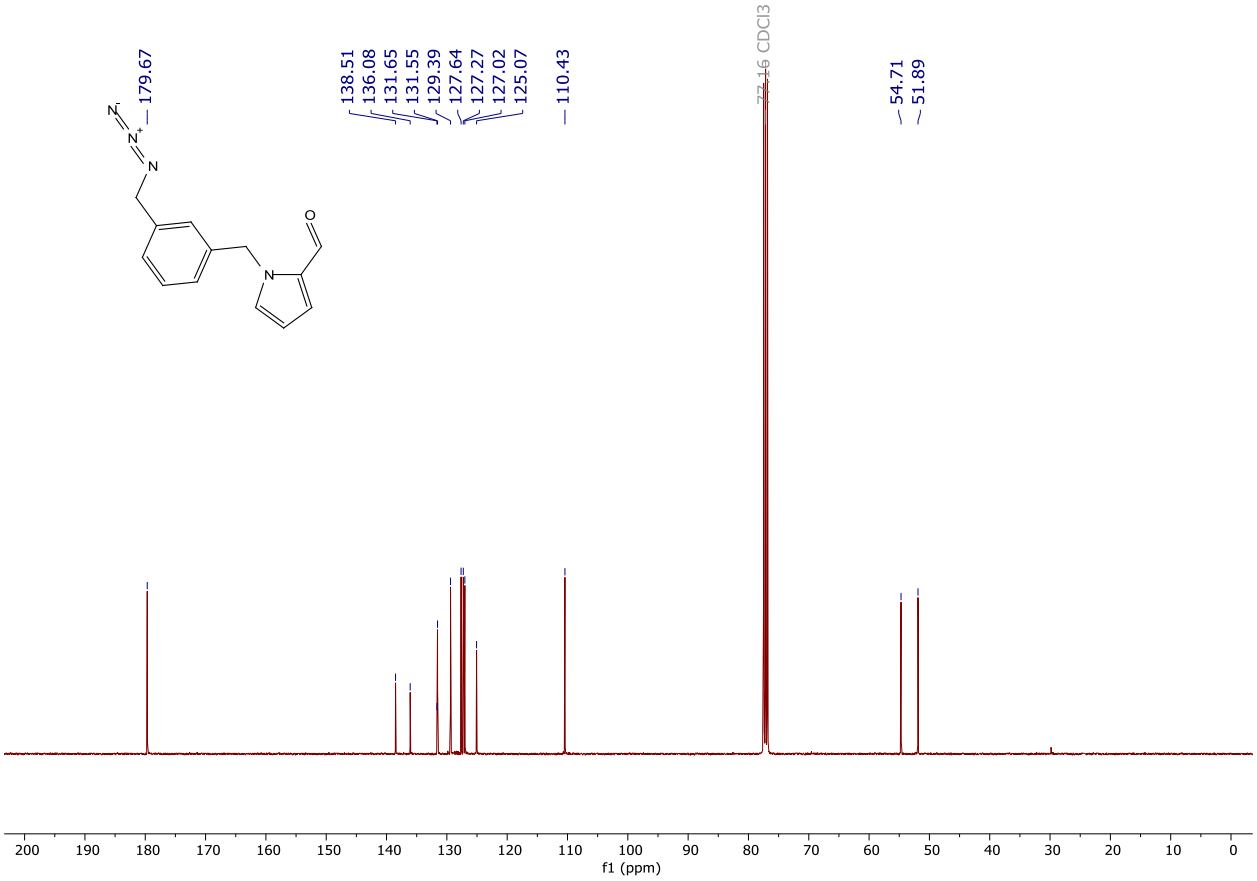

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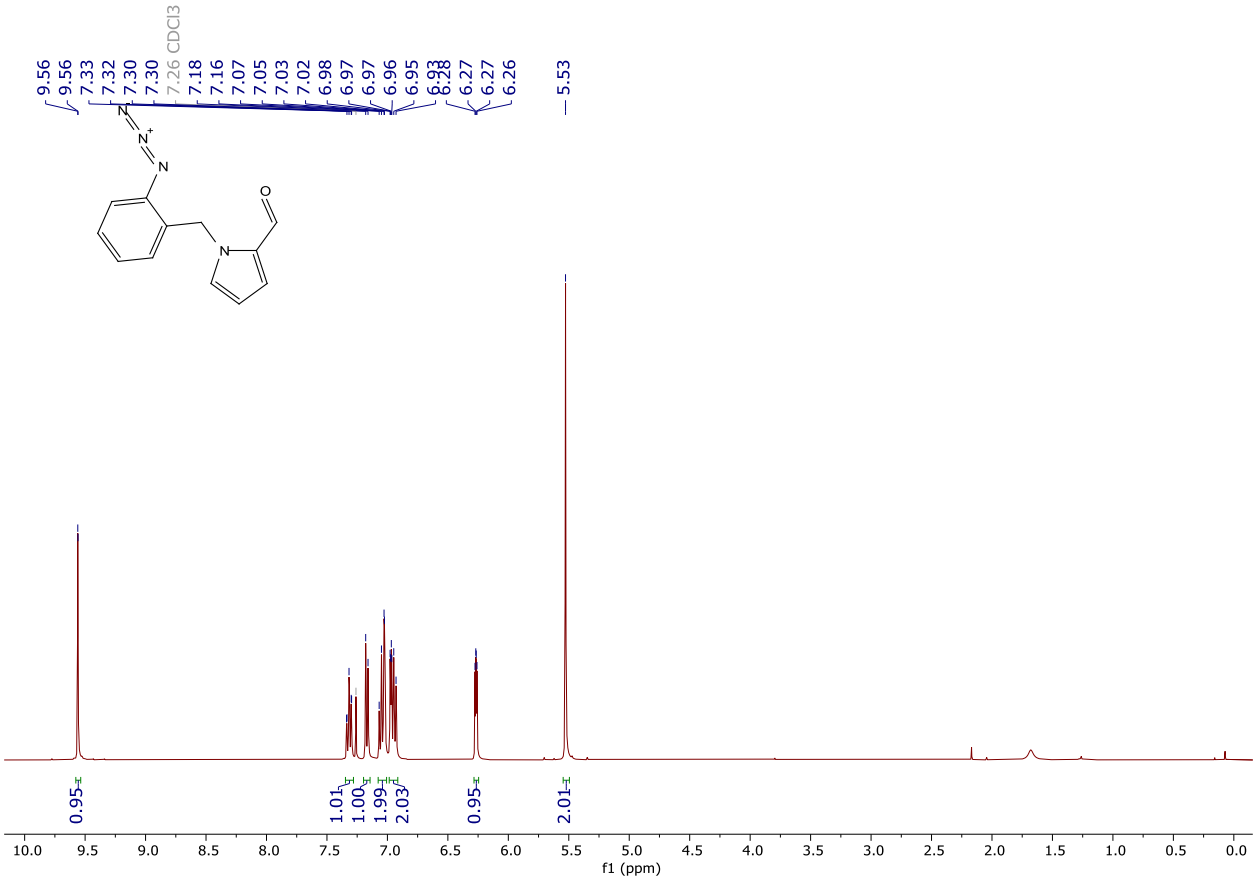

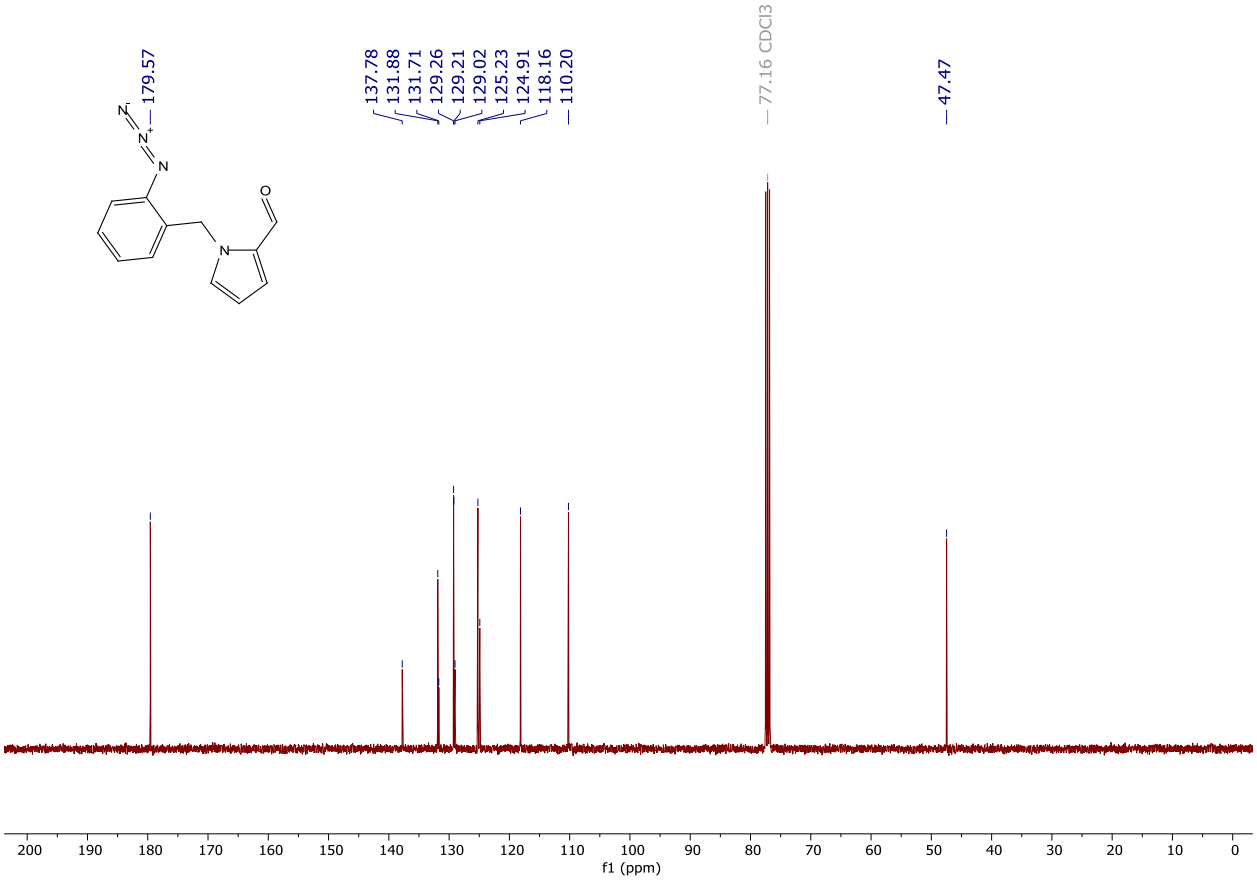

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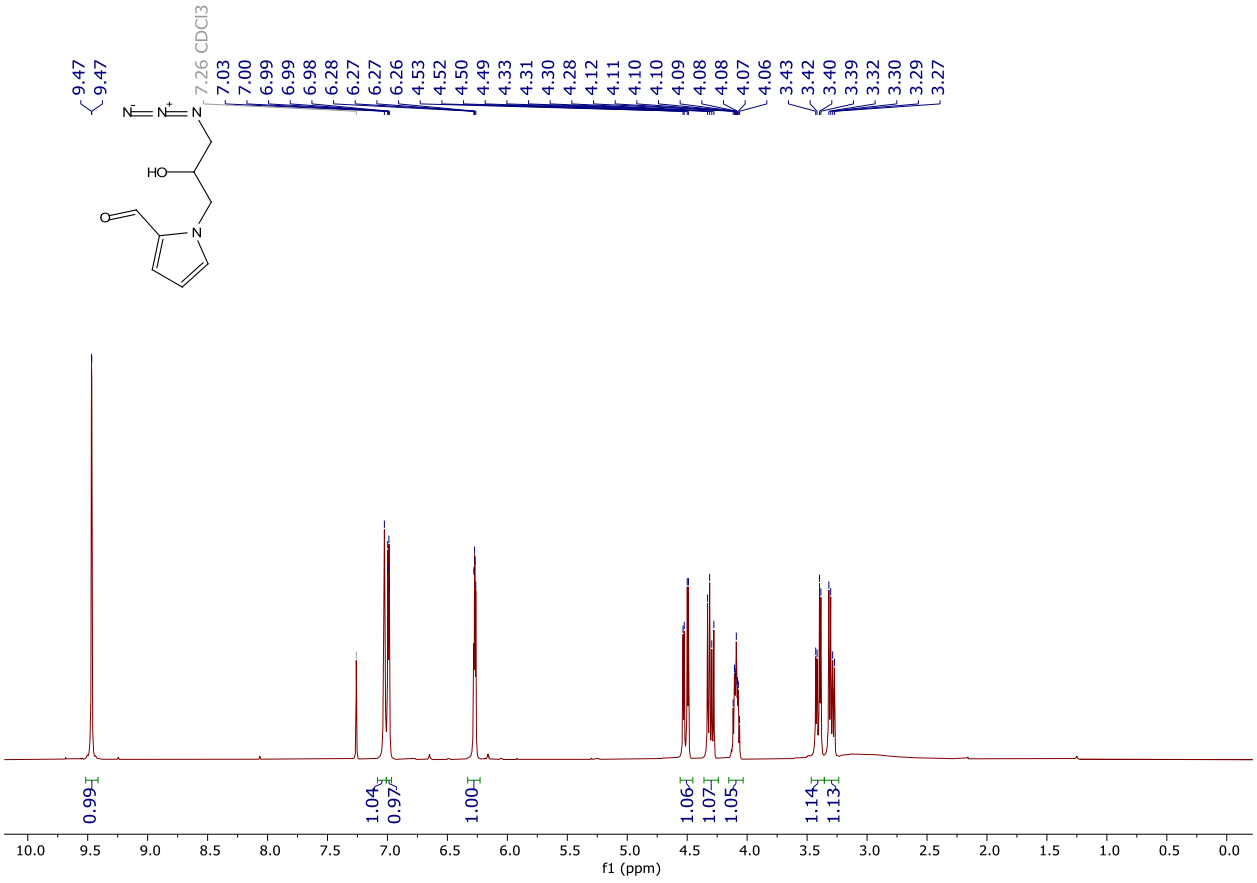
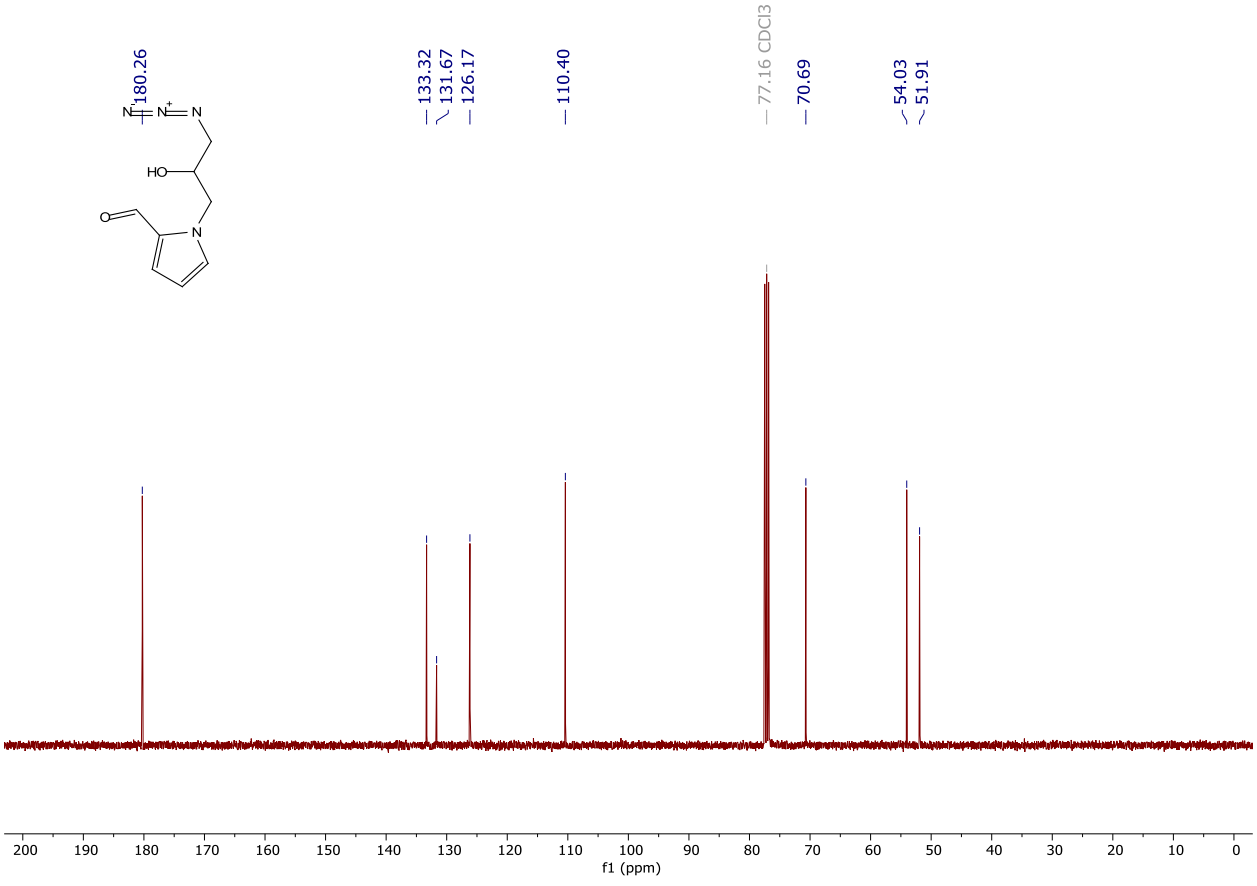
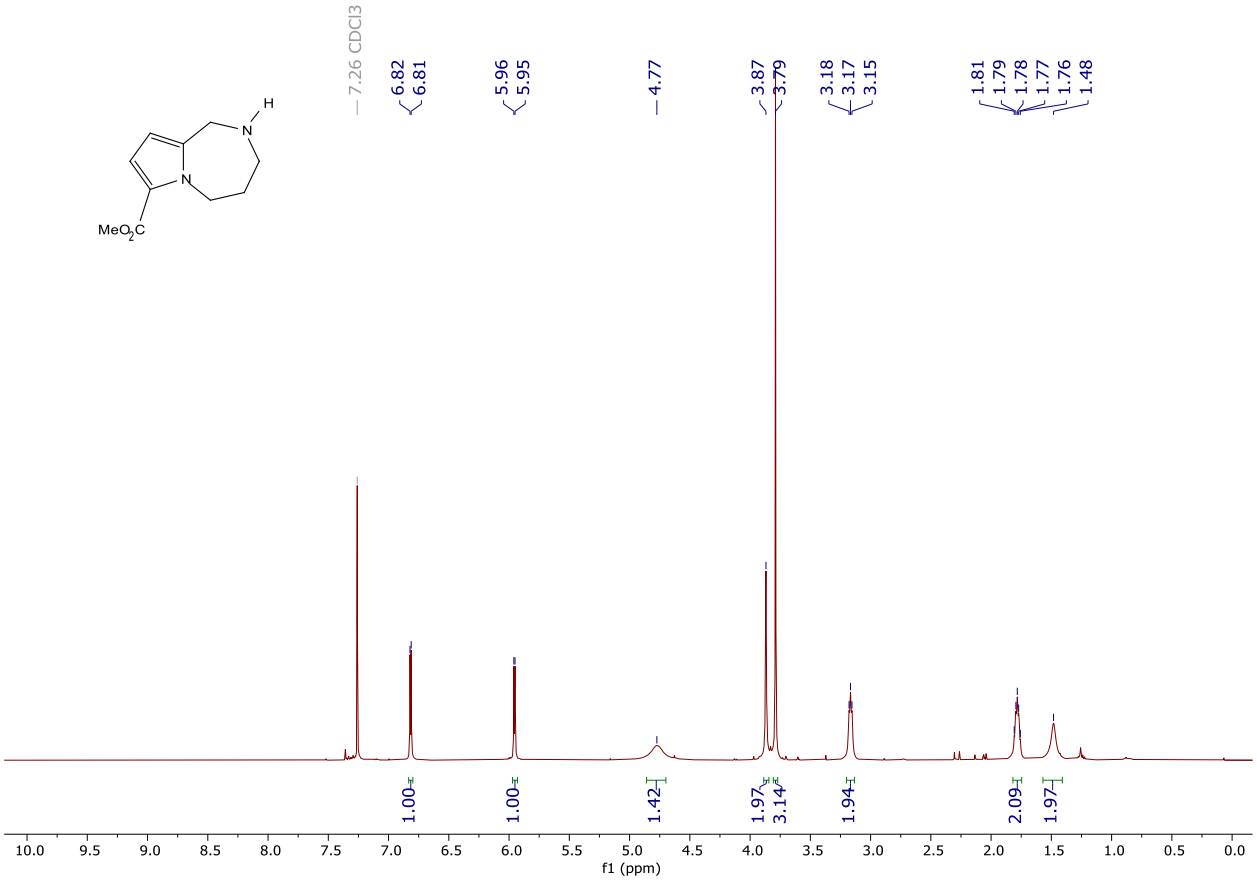
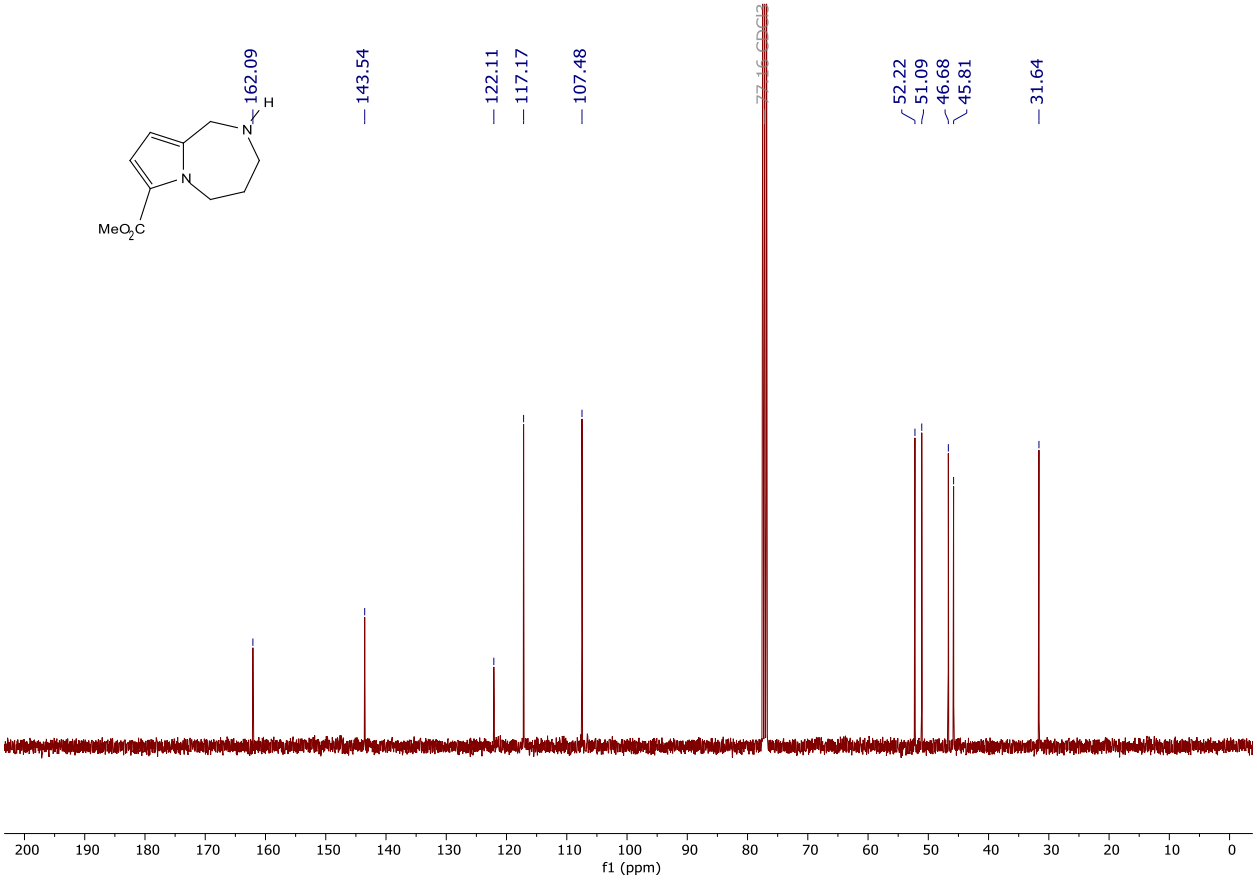


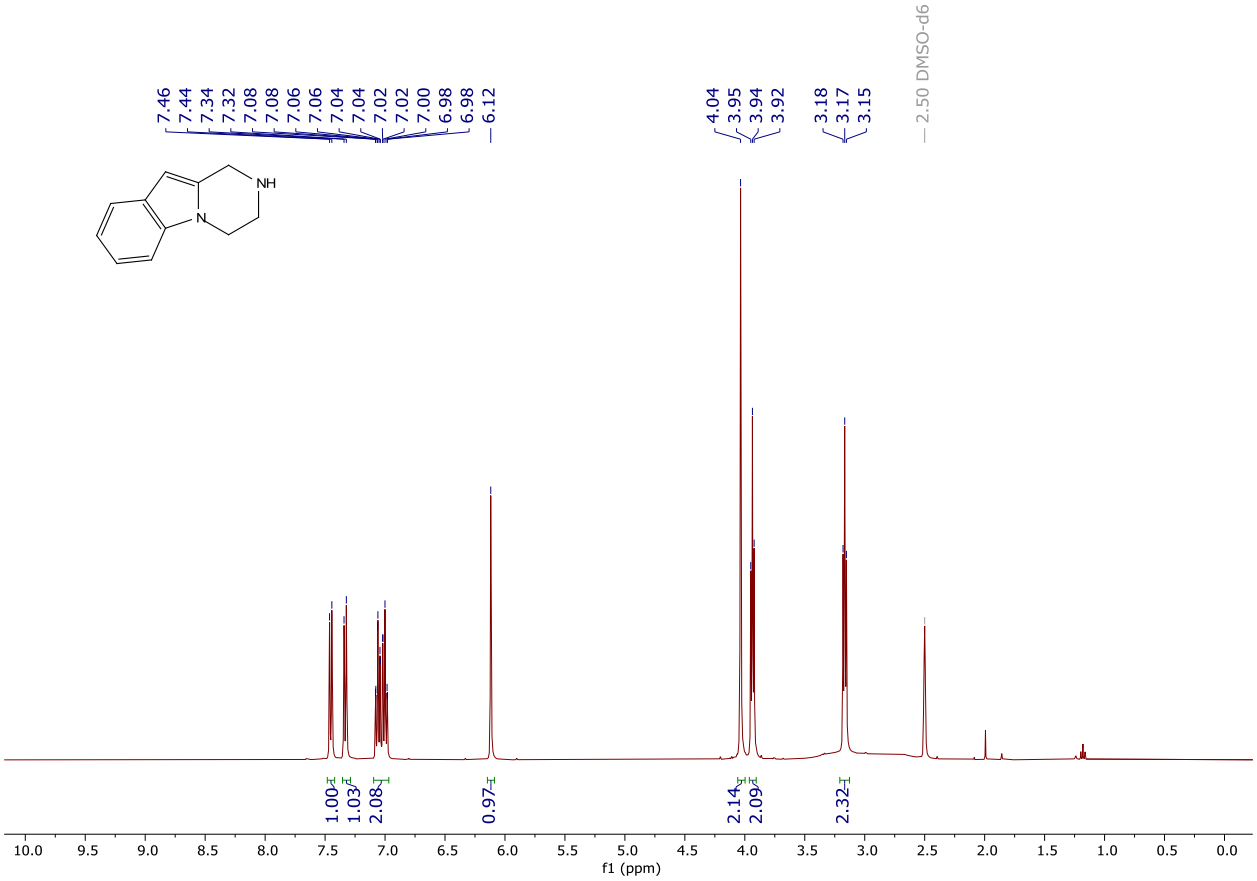


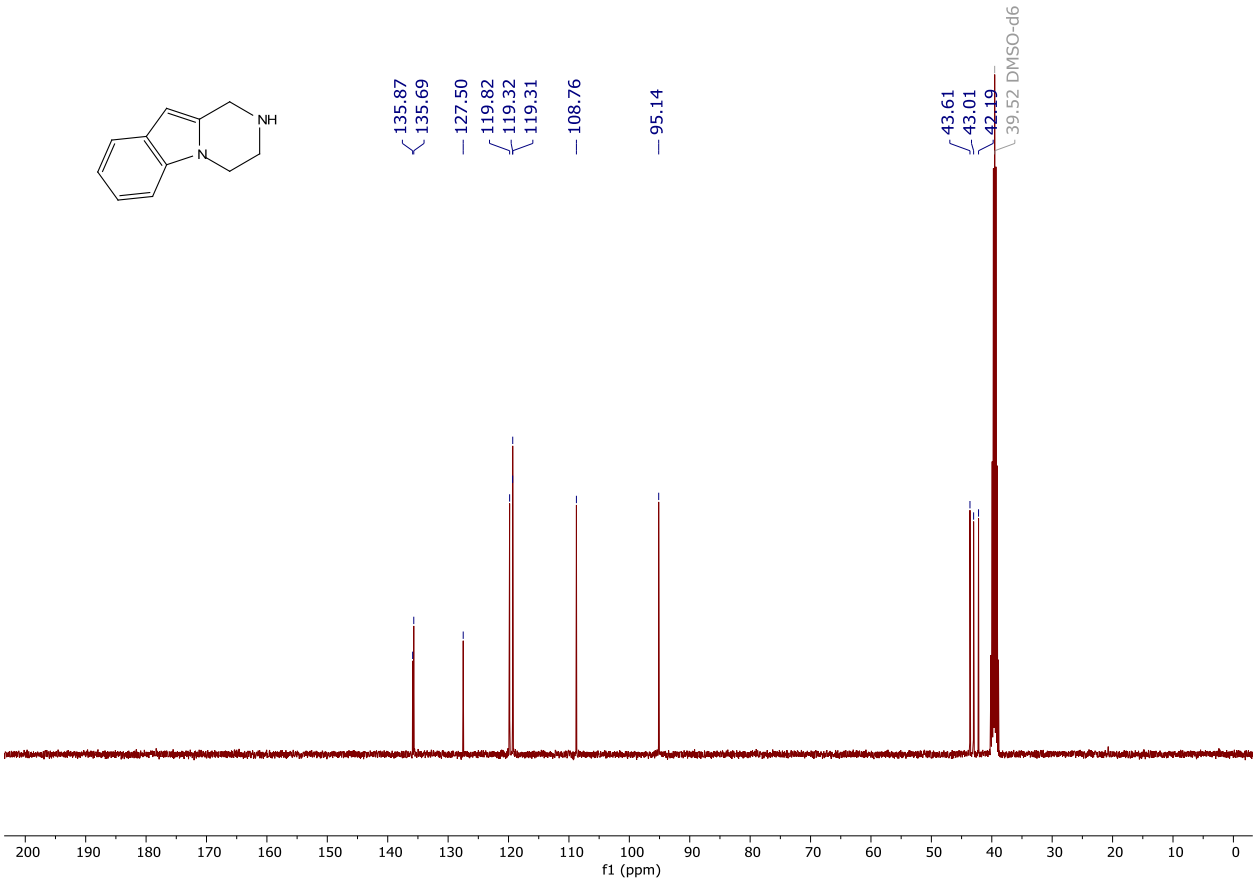
^{1}H and ^{13}C spectra of compound **6a**



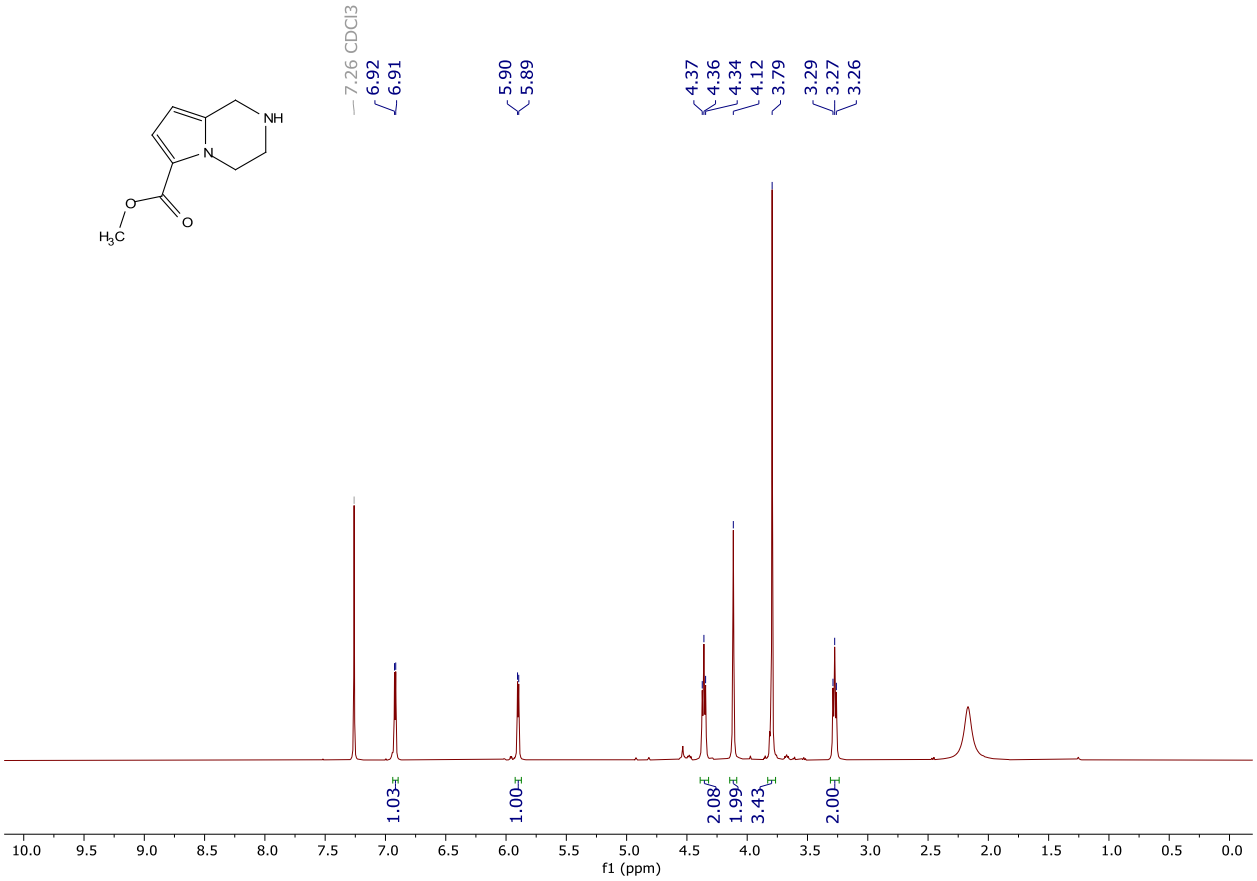


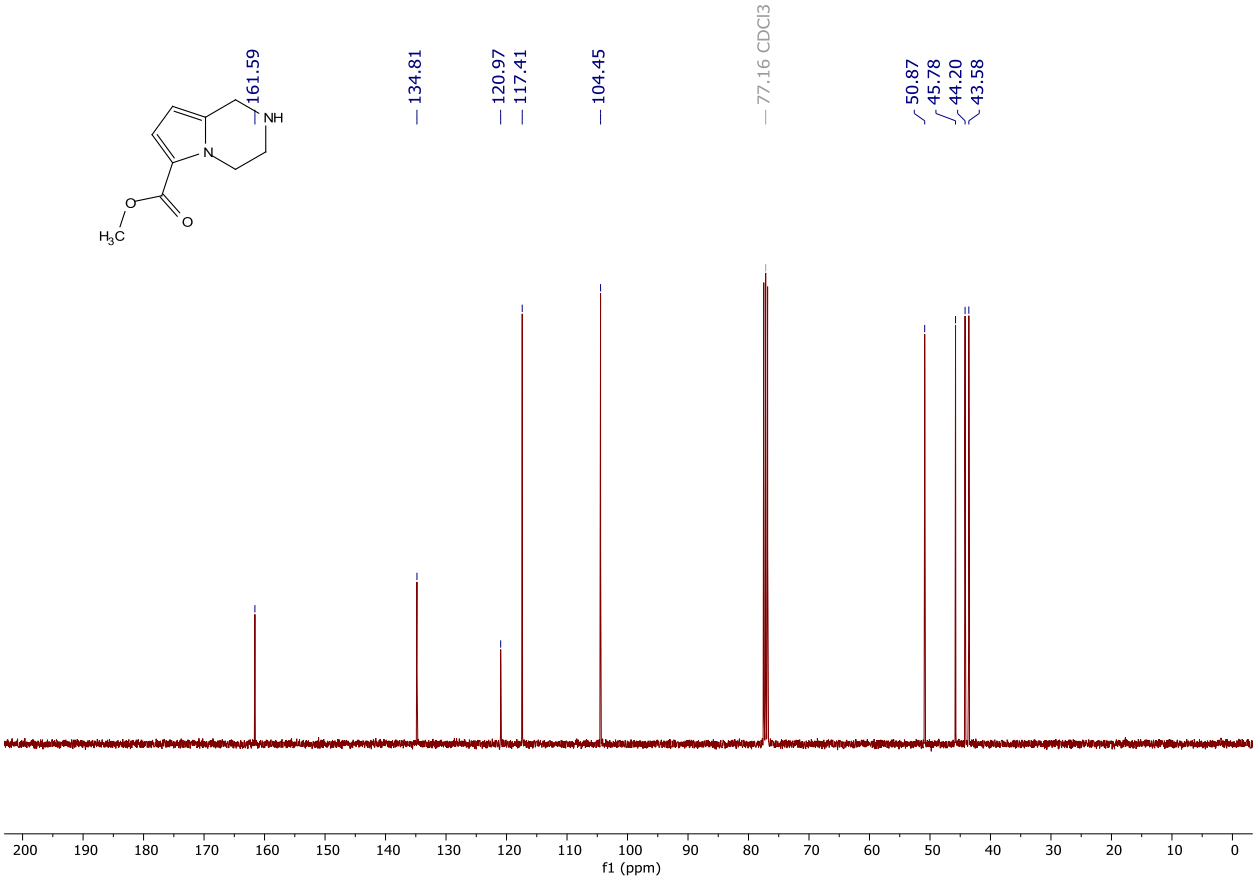
^{1}H and ^{13}C spectra of compound **6b**



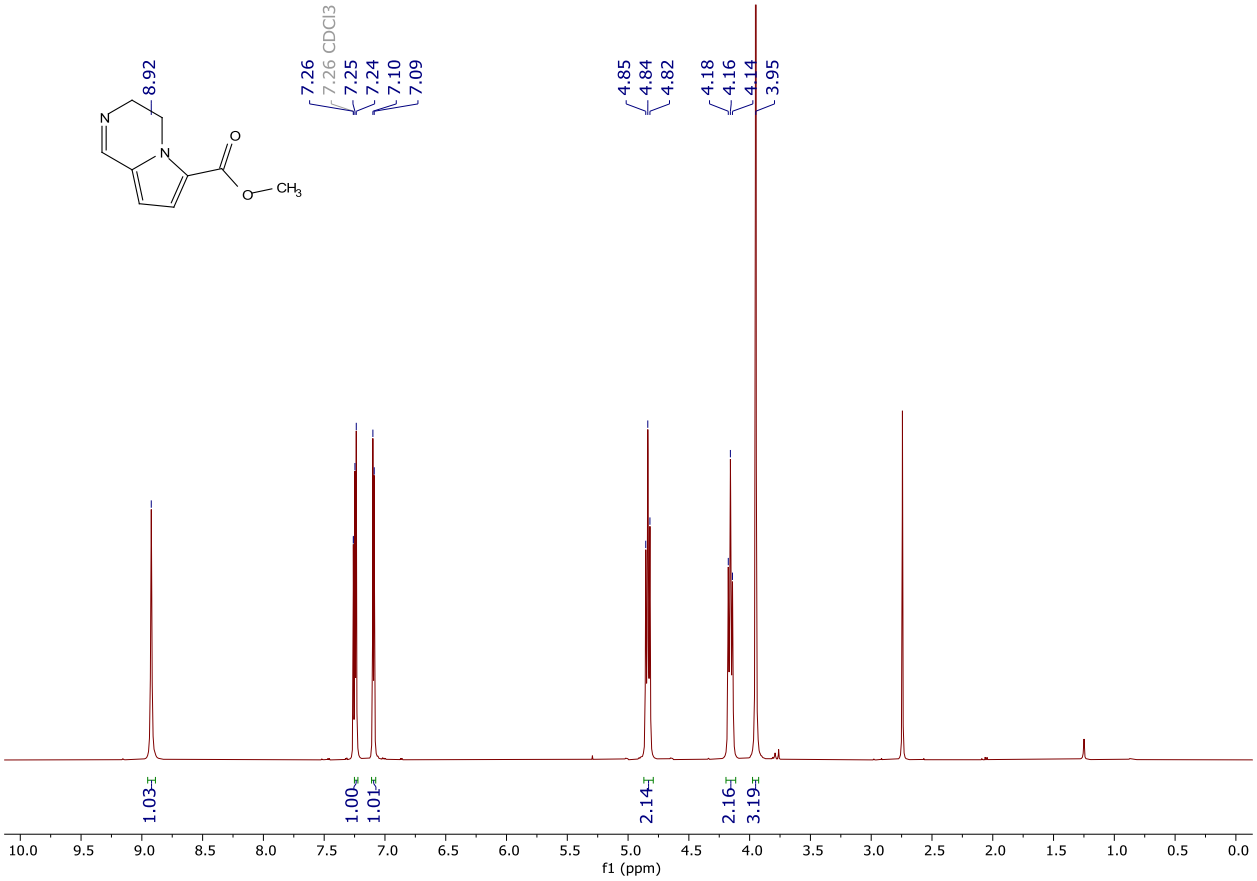


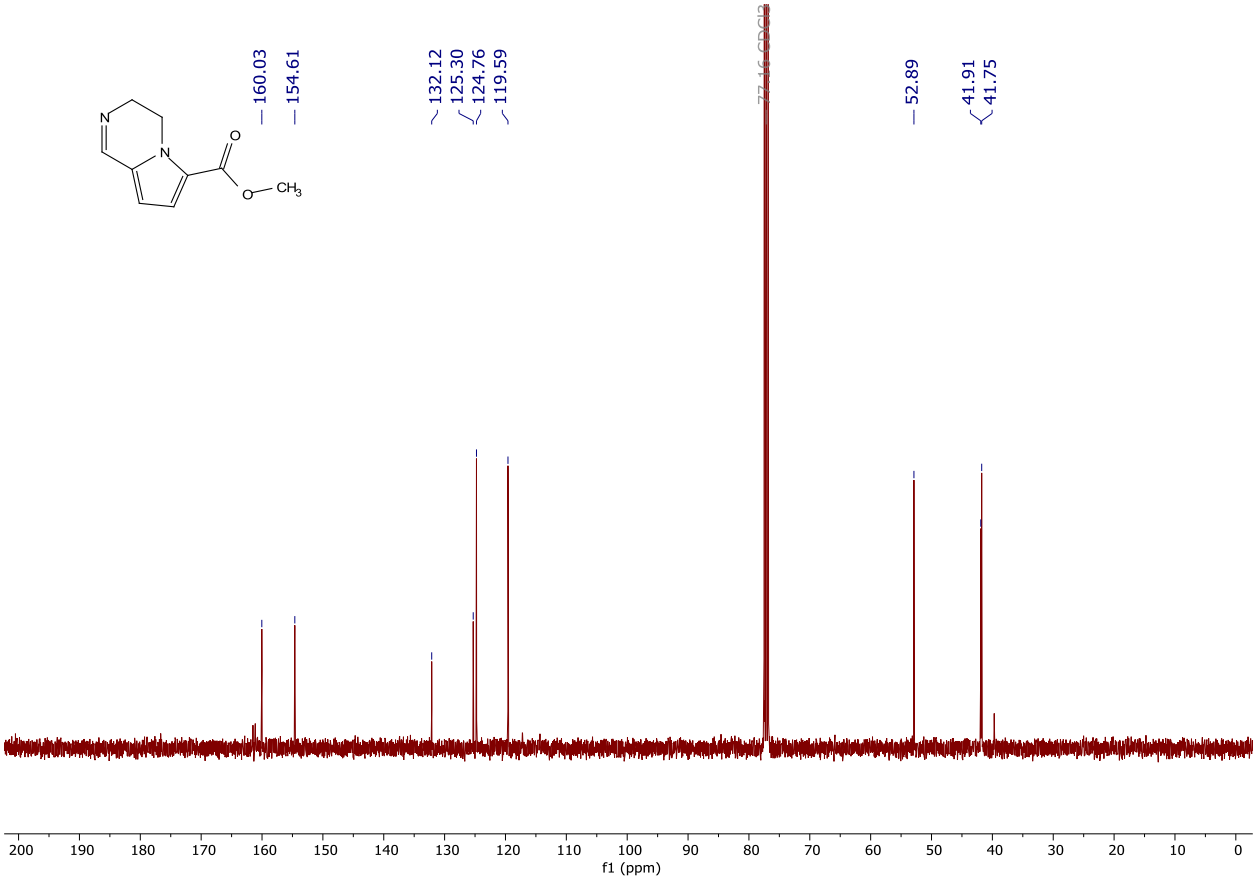
^{1}H and ^{13}C spectra of compound **6c**



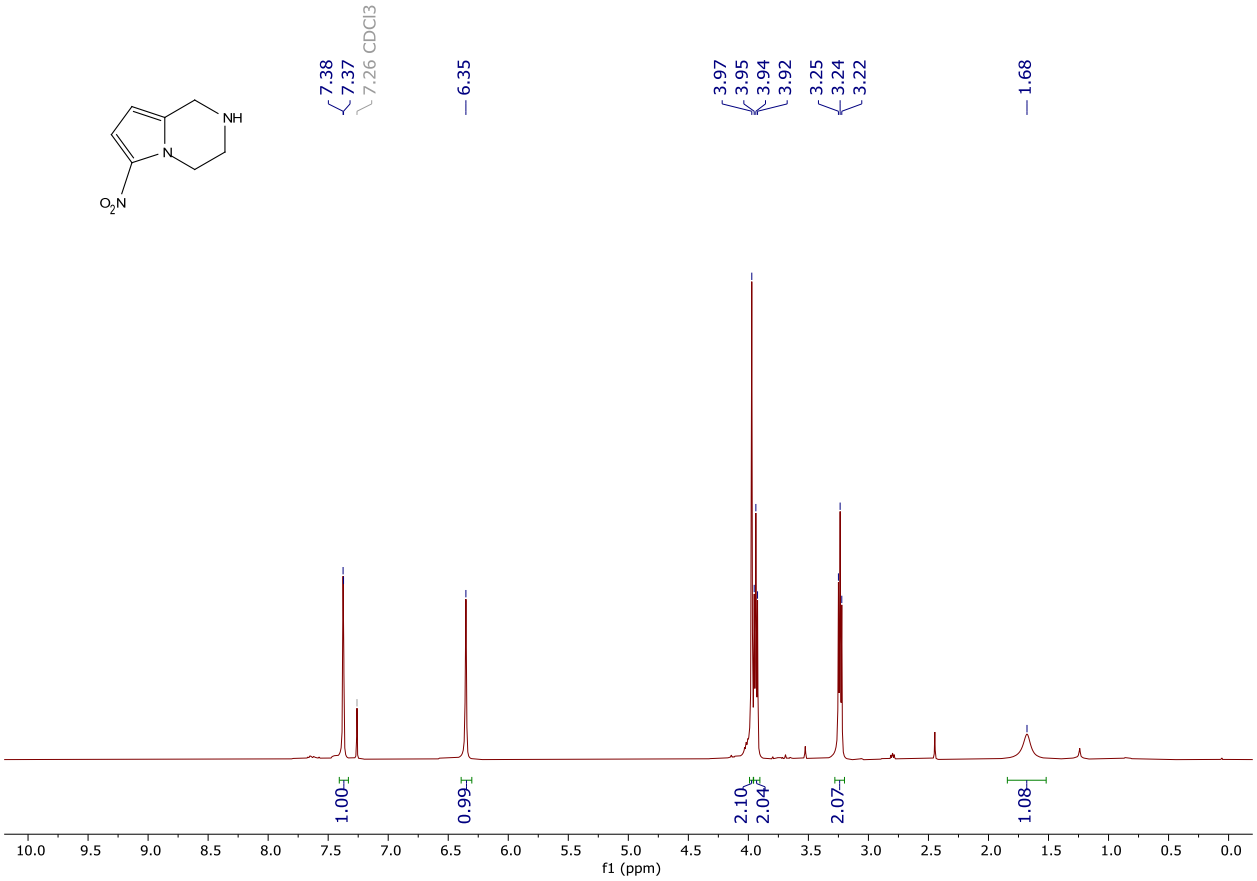


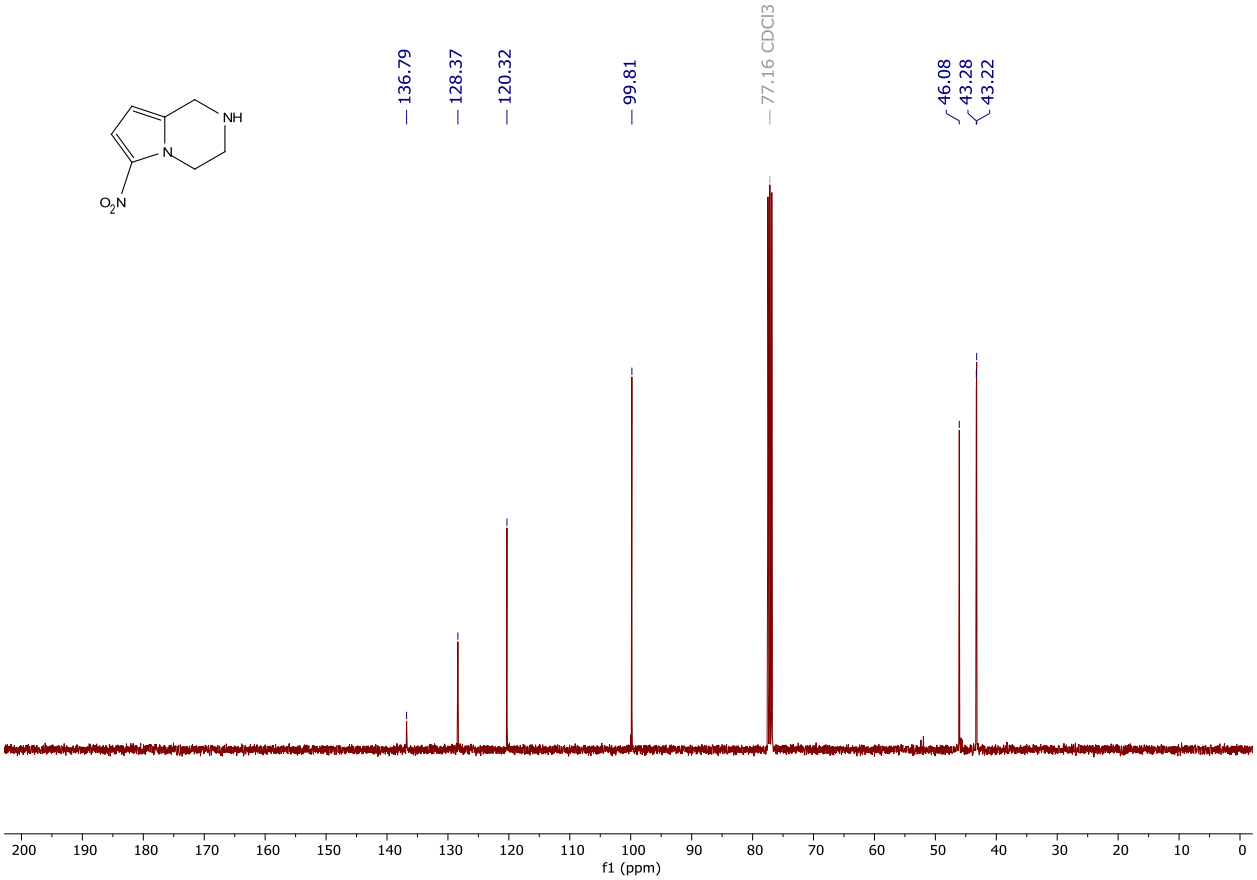
^{1}H and ^{13}C spectra of compound **6c'**



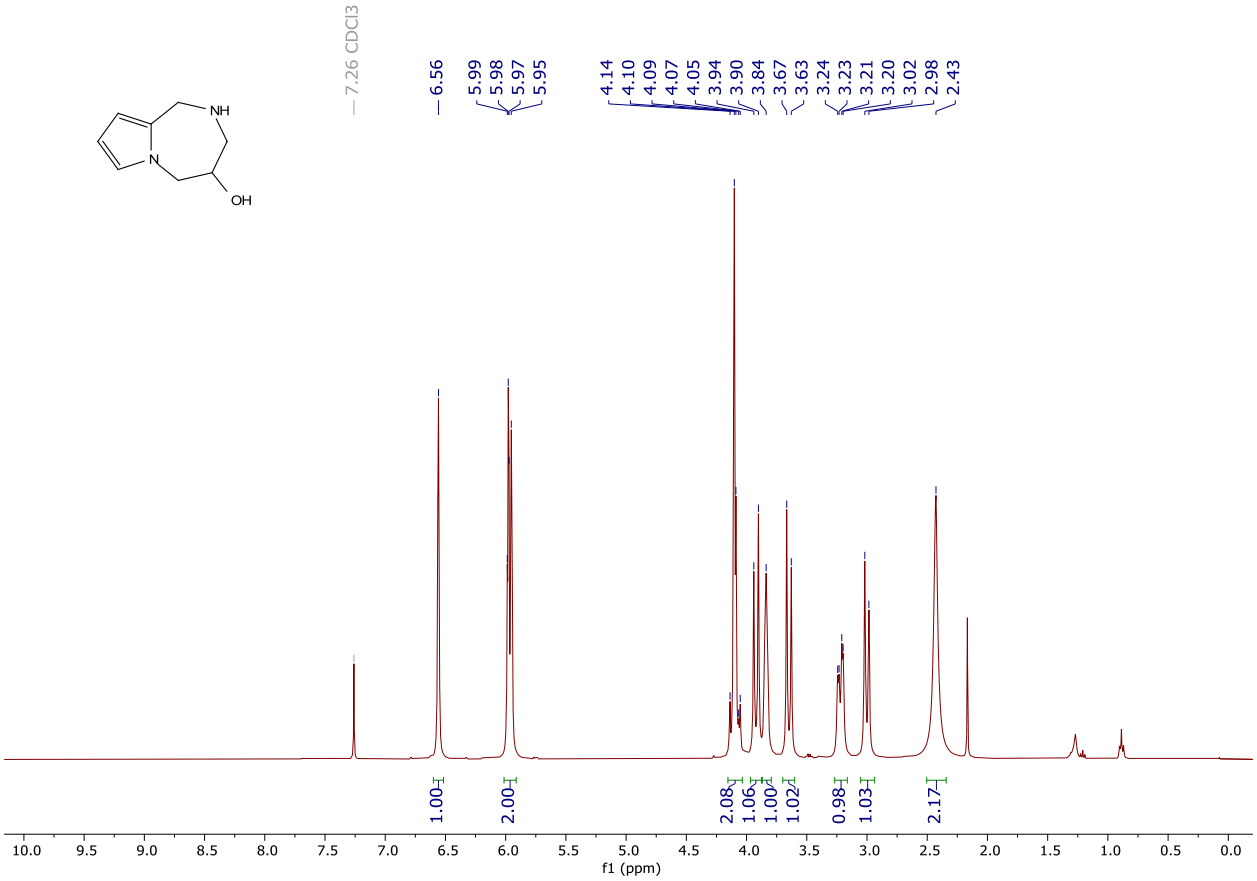


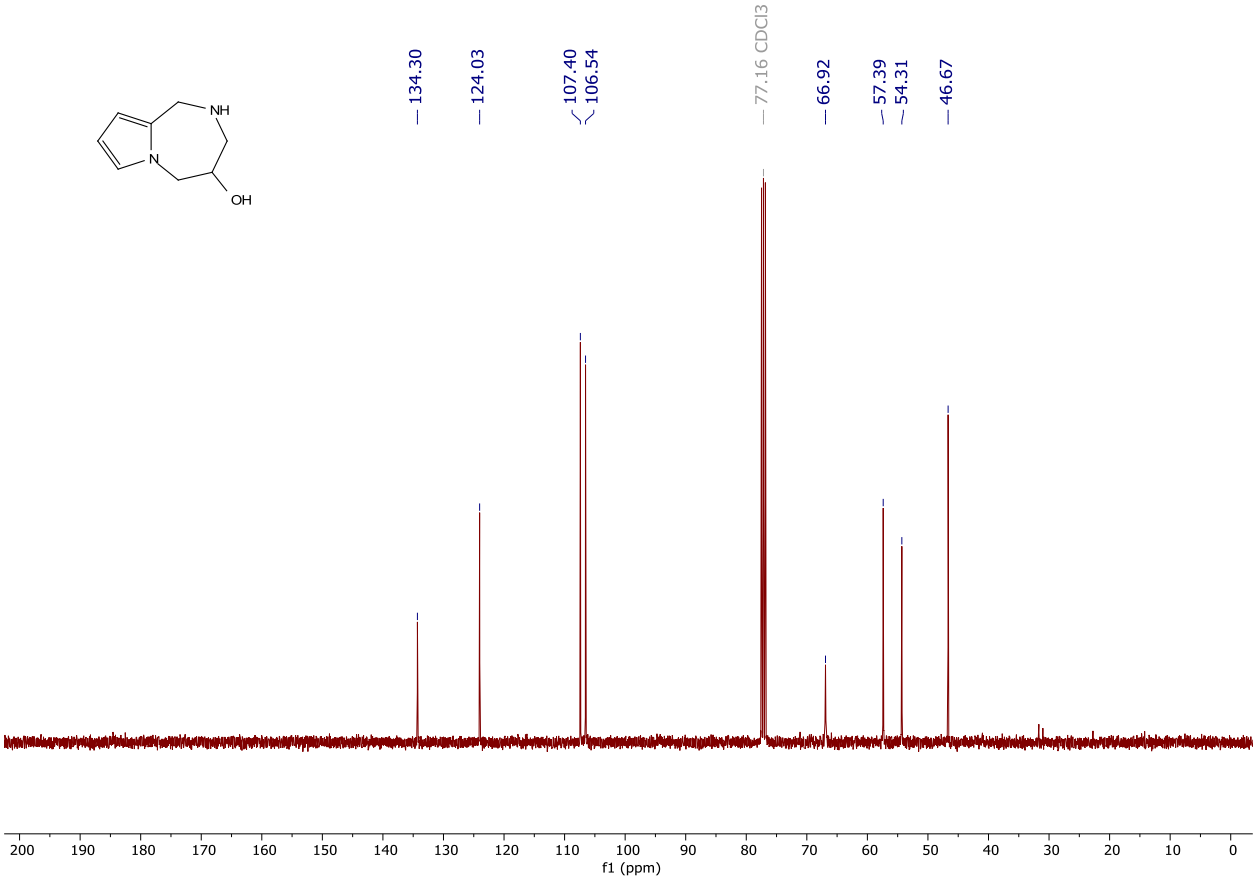
^{1}H and ^{13}C spectra of compound **6d**



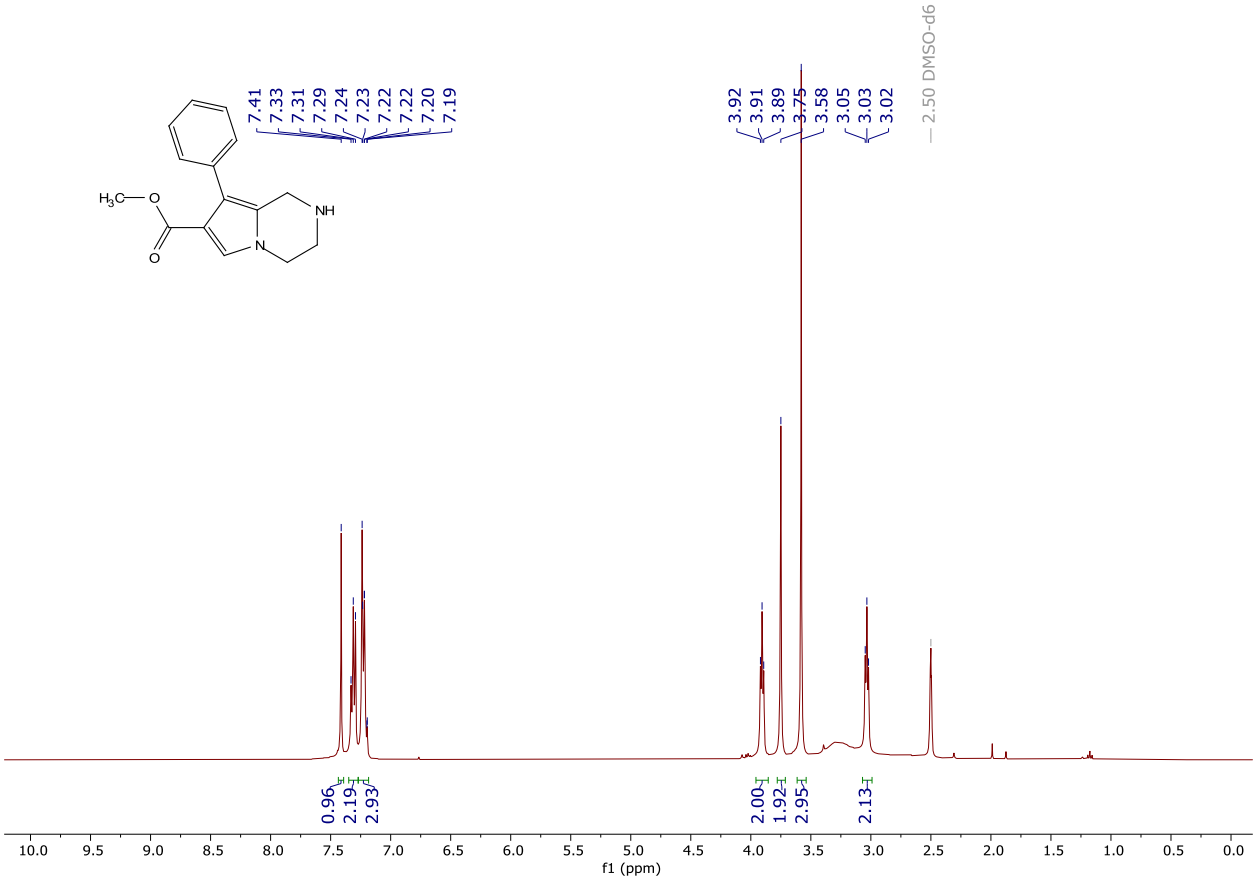


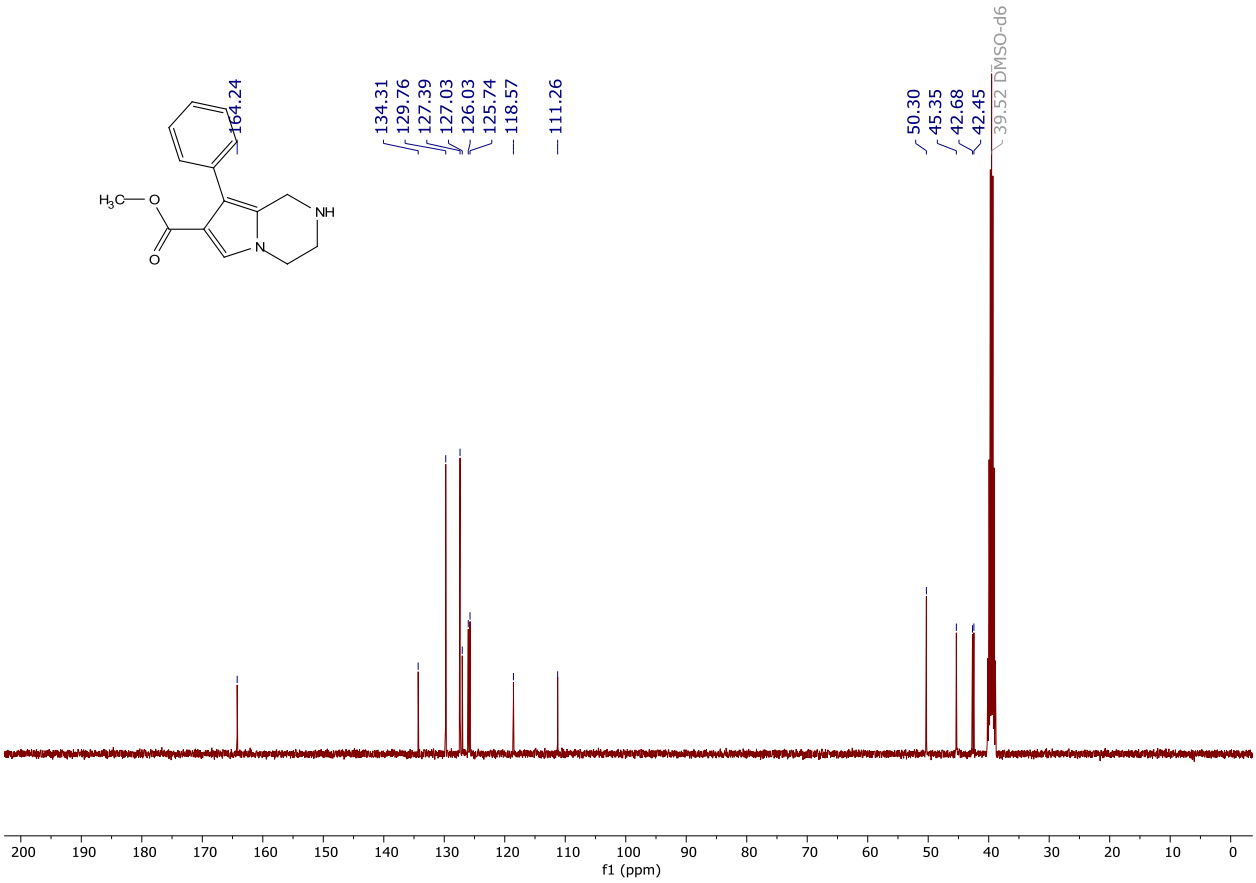
^{1}H and ^{13}C spectra of compound **6e**



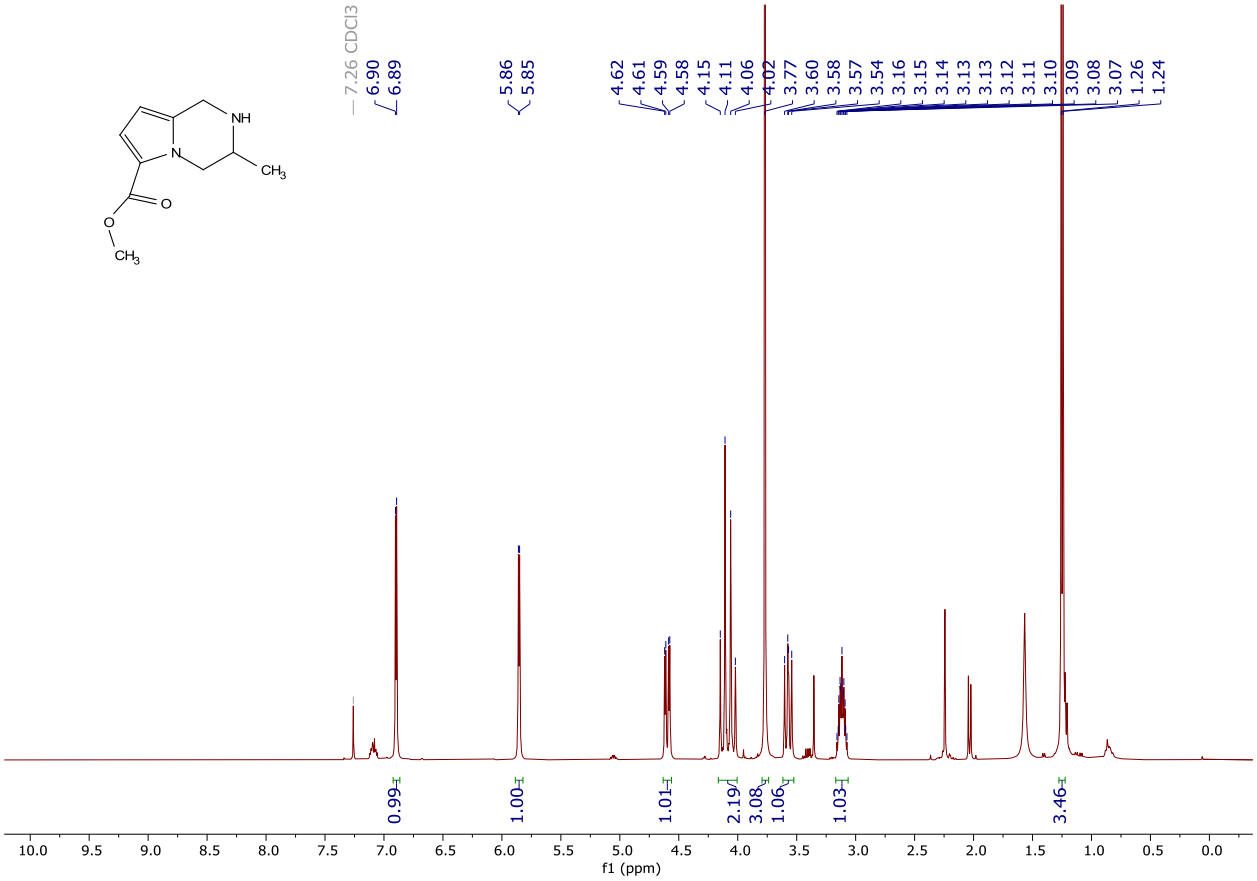


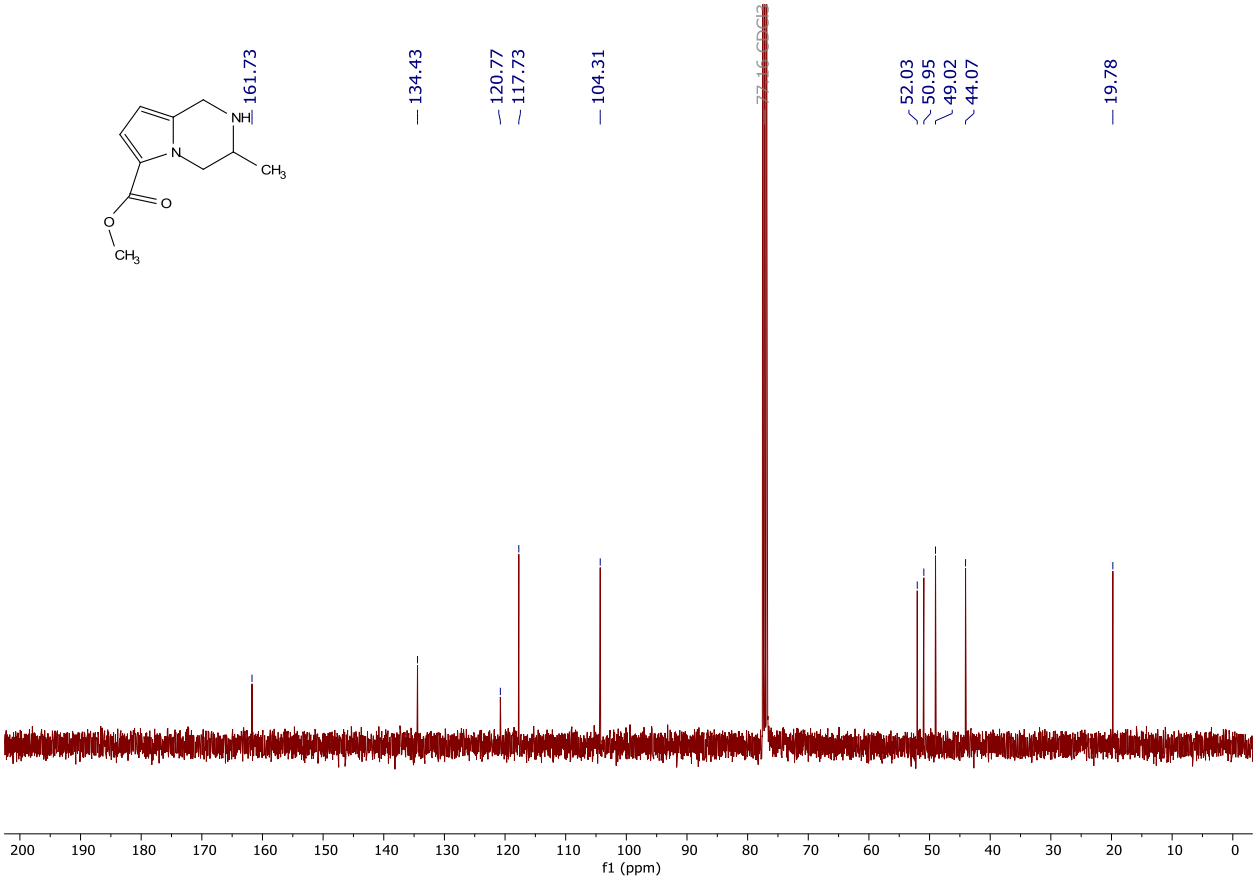
^{1}H and ^{13}C spectra of compound **6f**



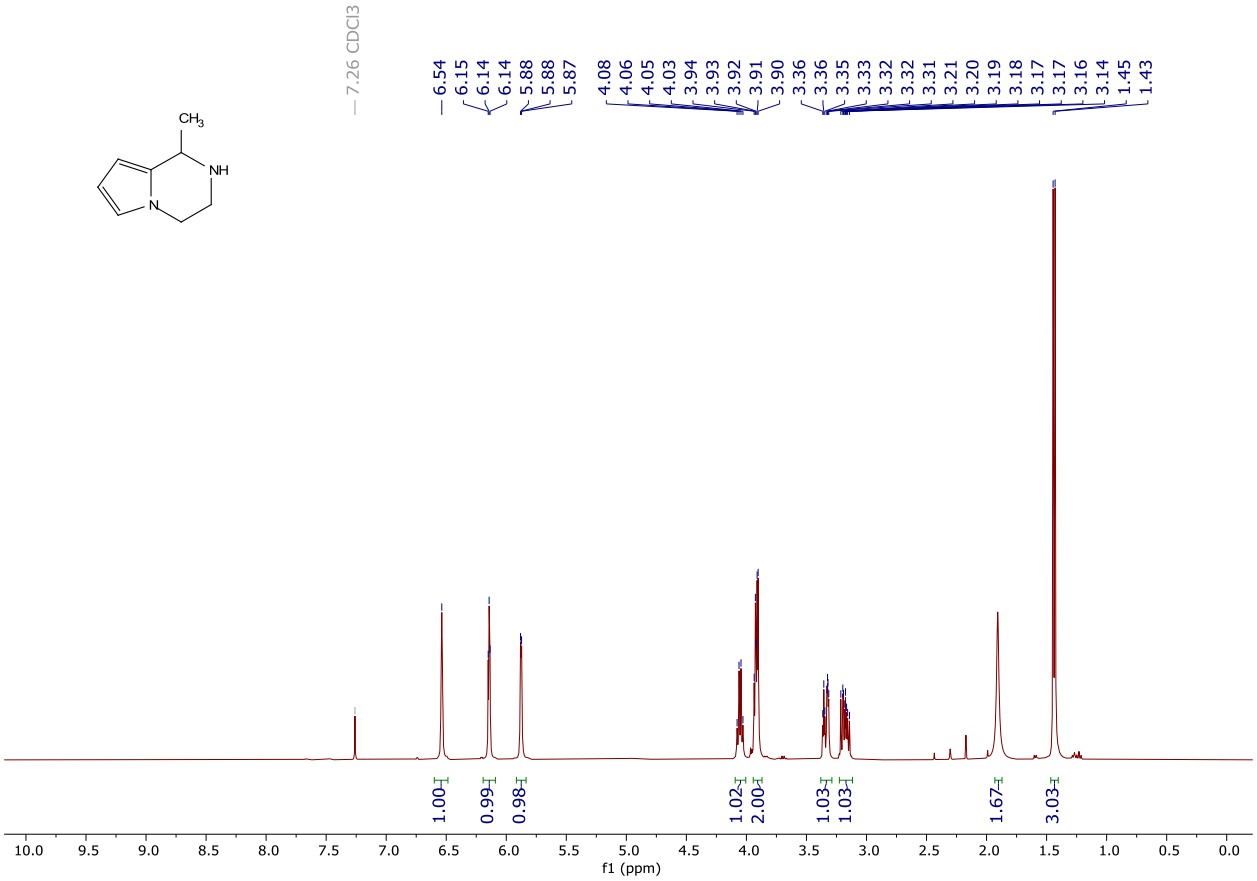


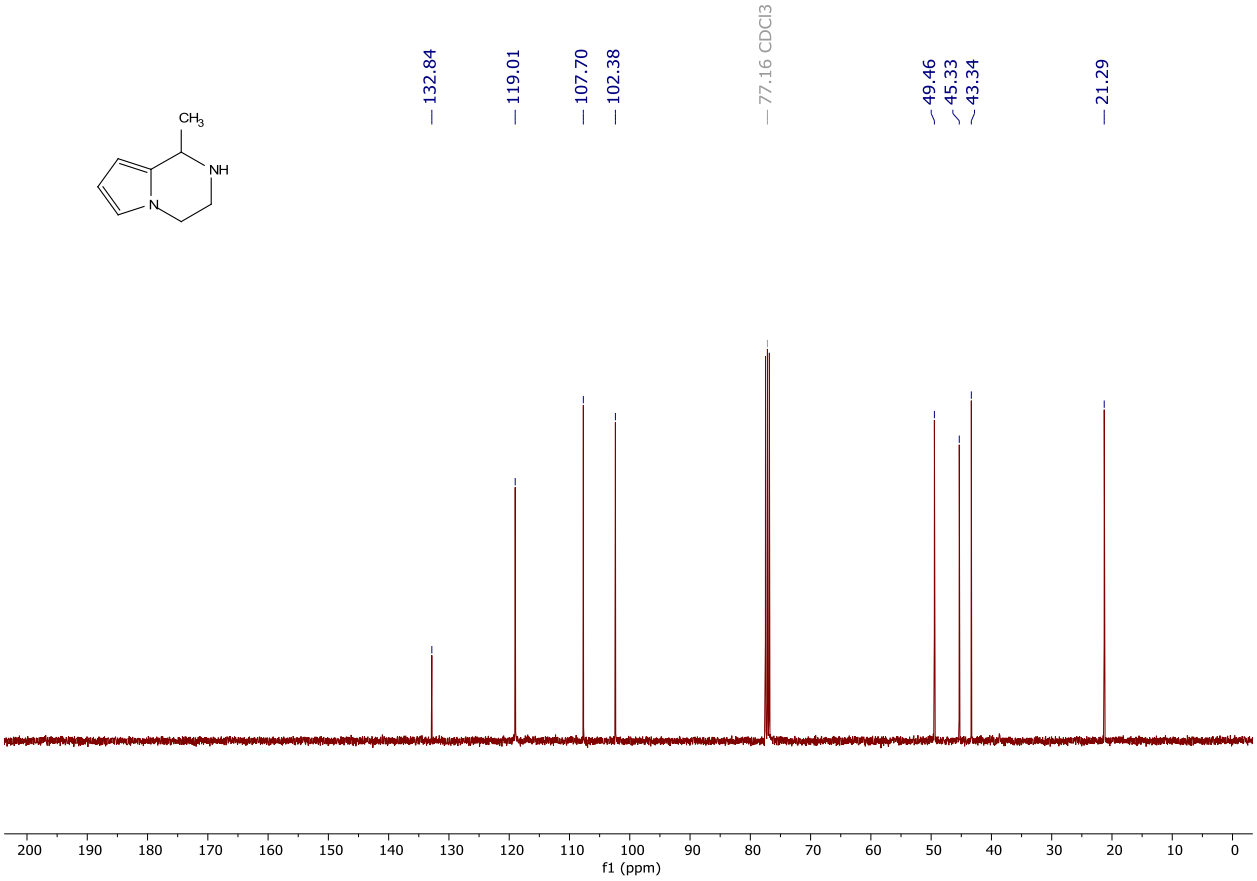
^{1}H and ^{13}C spectra of compound **6g**



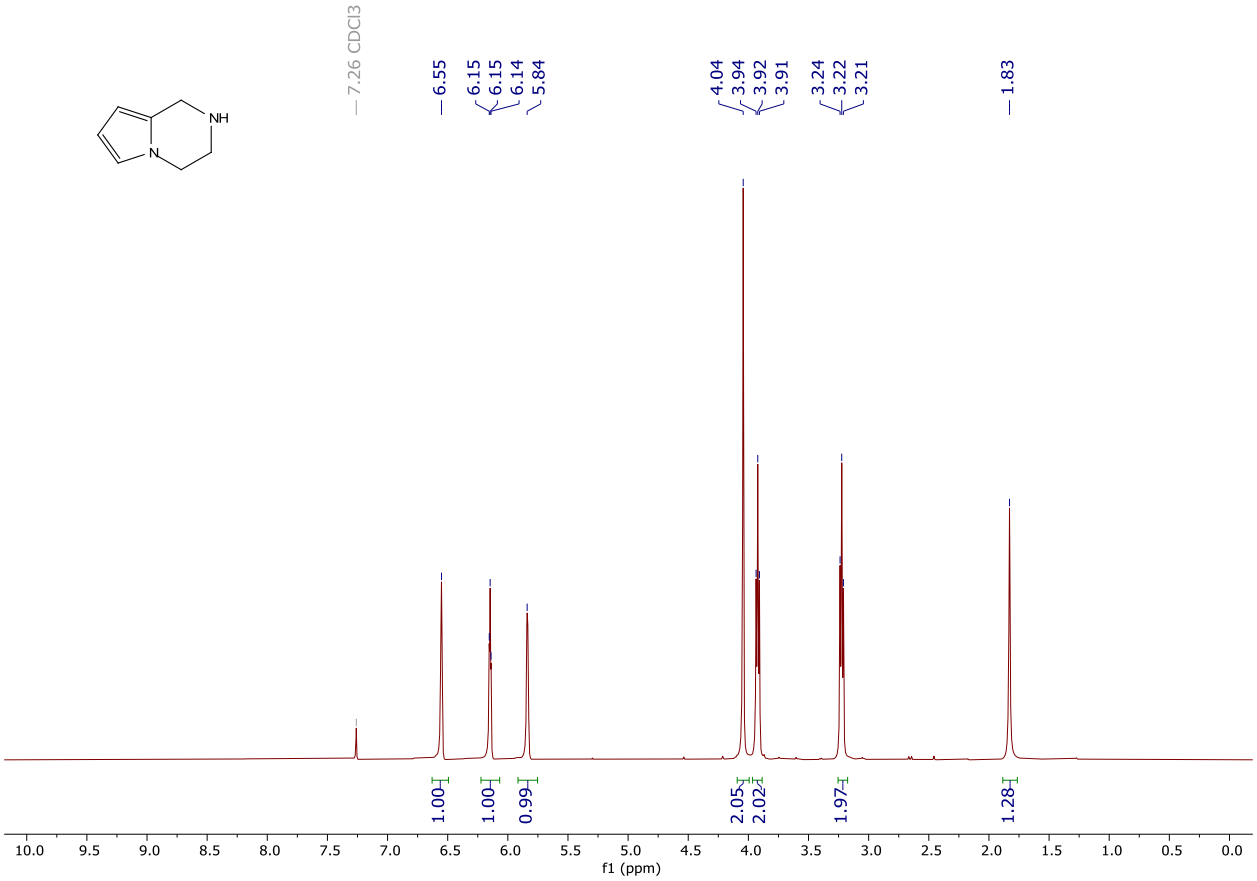


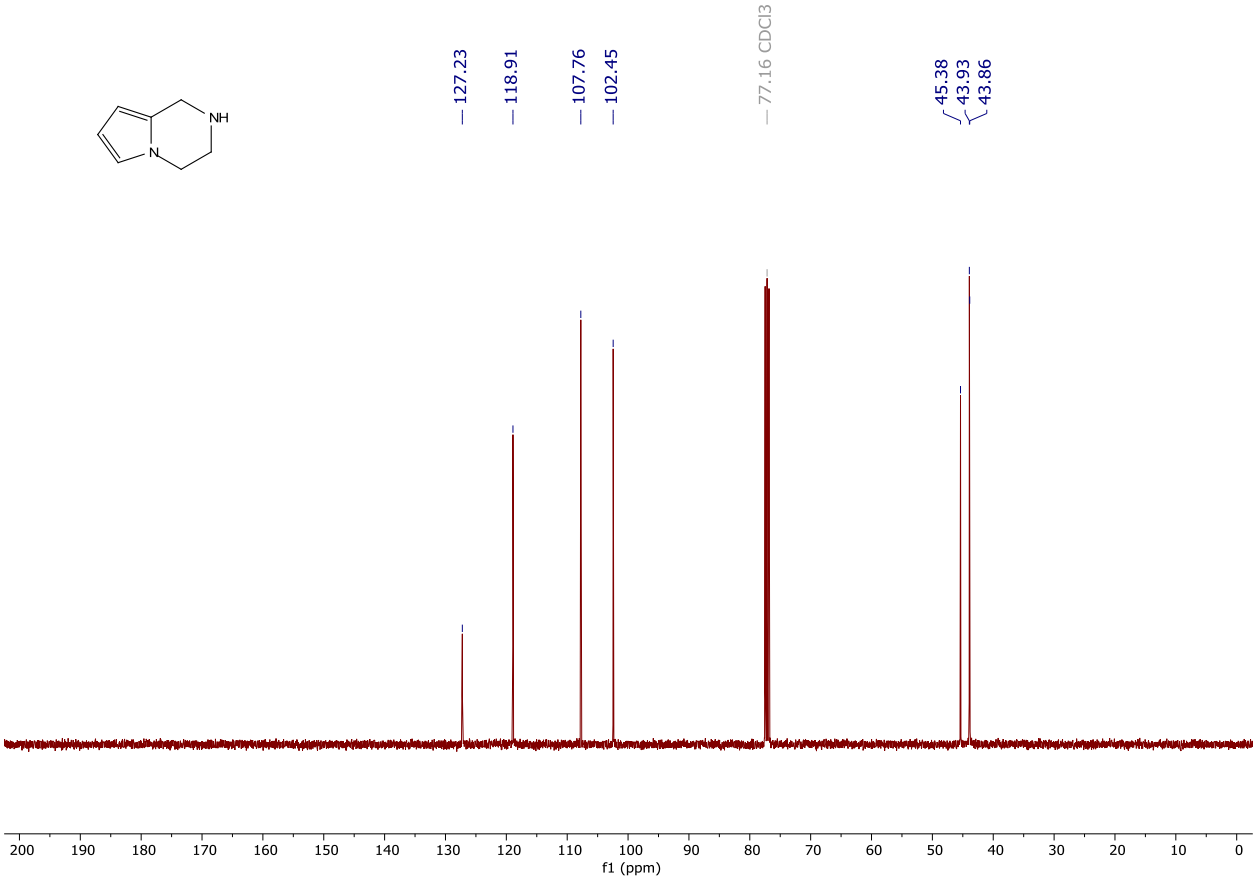
^{1}H and ^{13}C spectra of compound **6h**



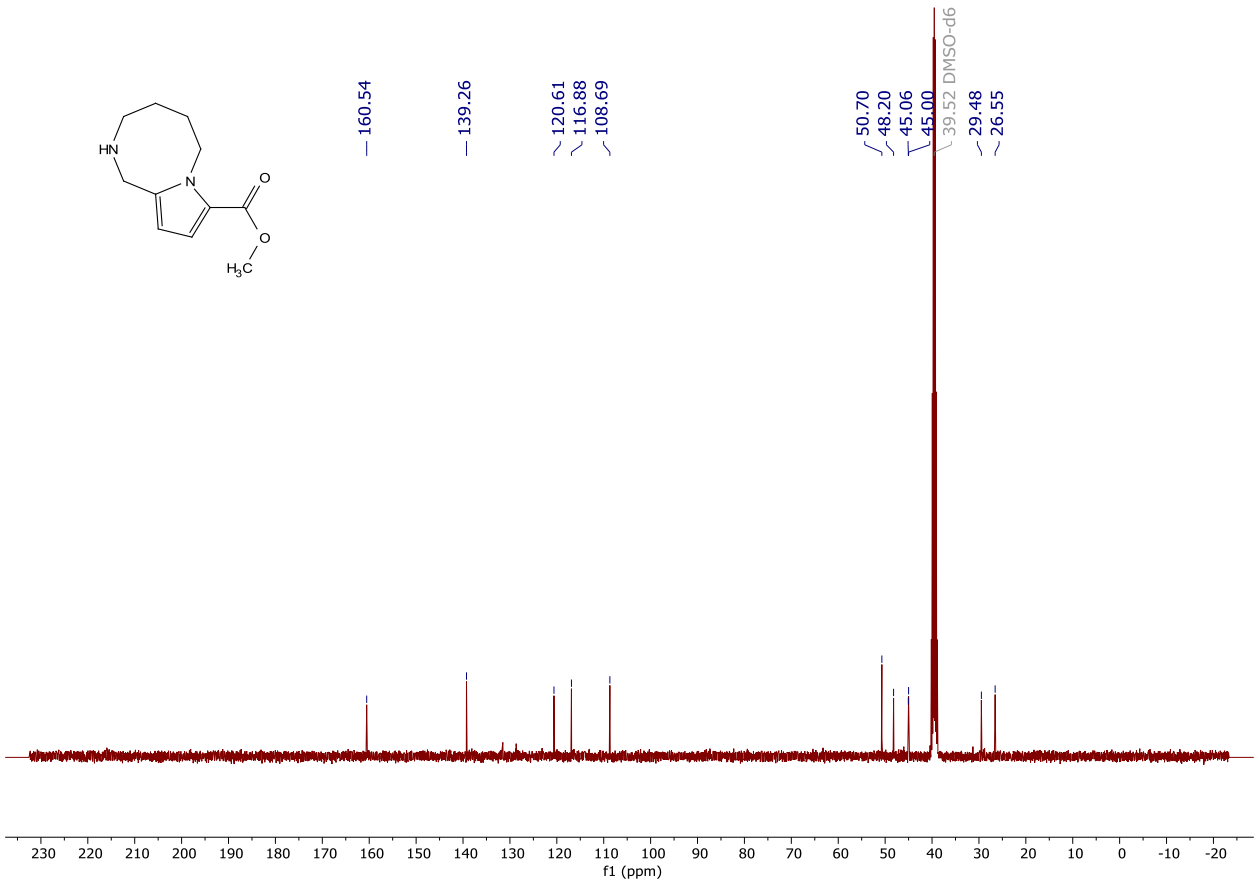


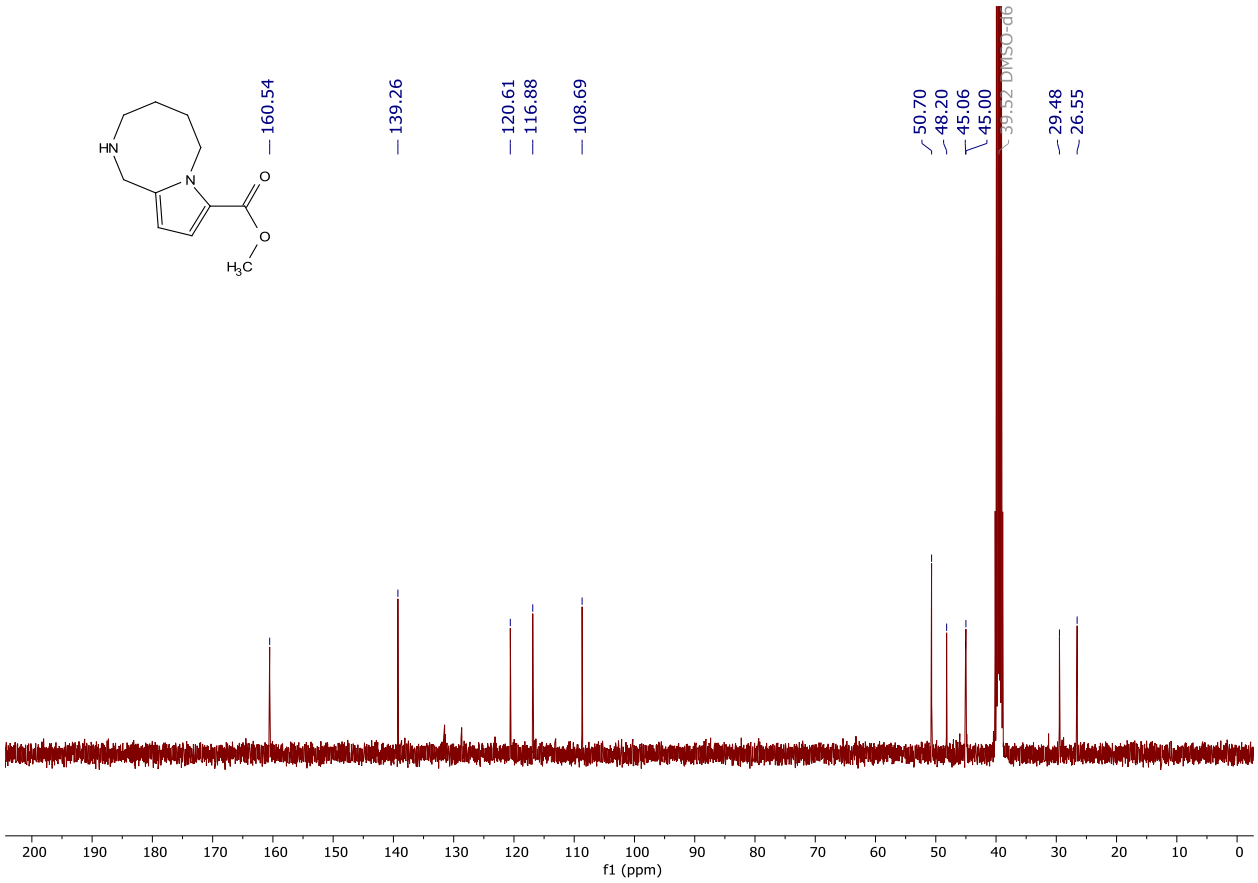
^{1}H and ^{13}C spectra of compound **6i**



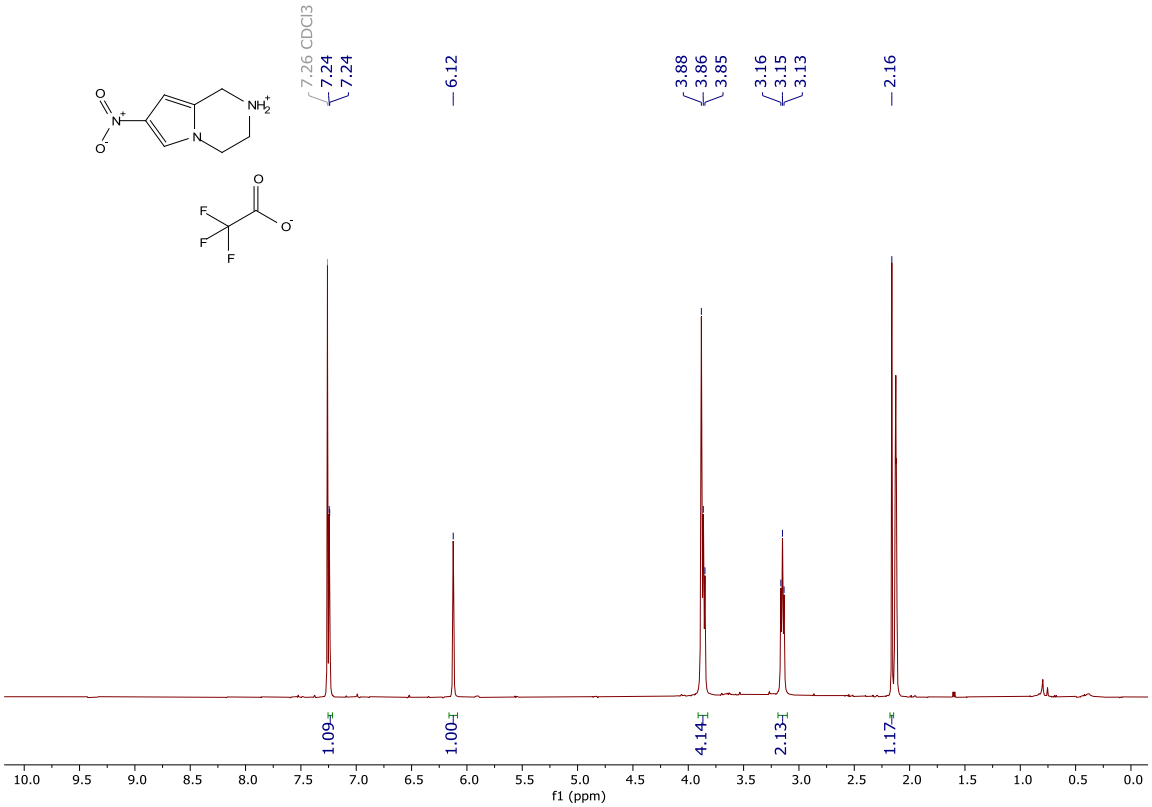


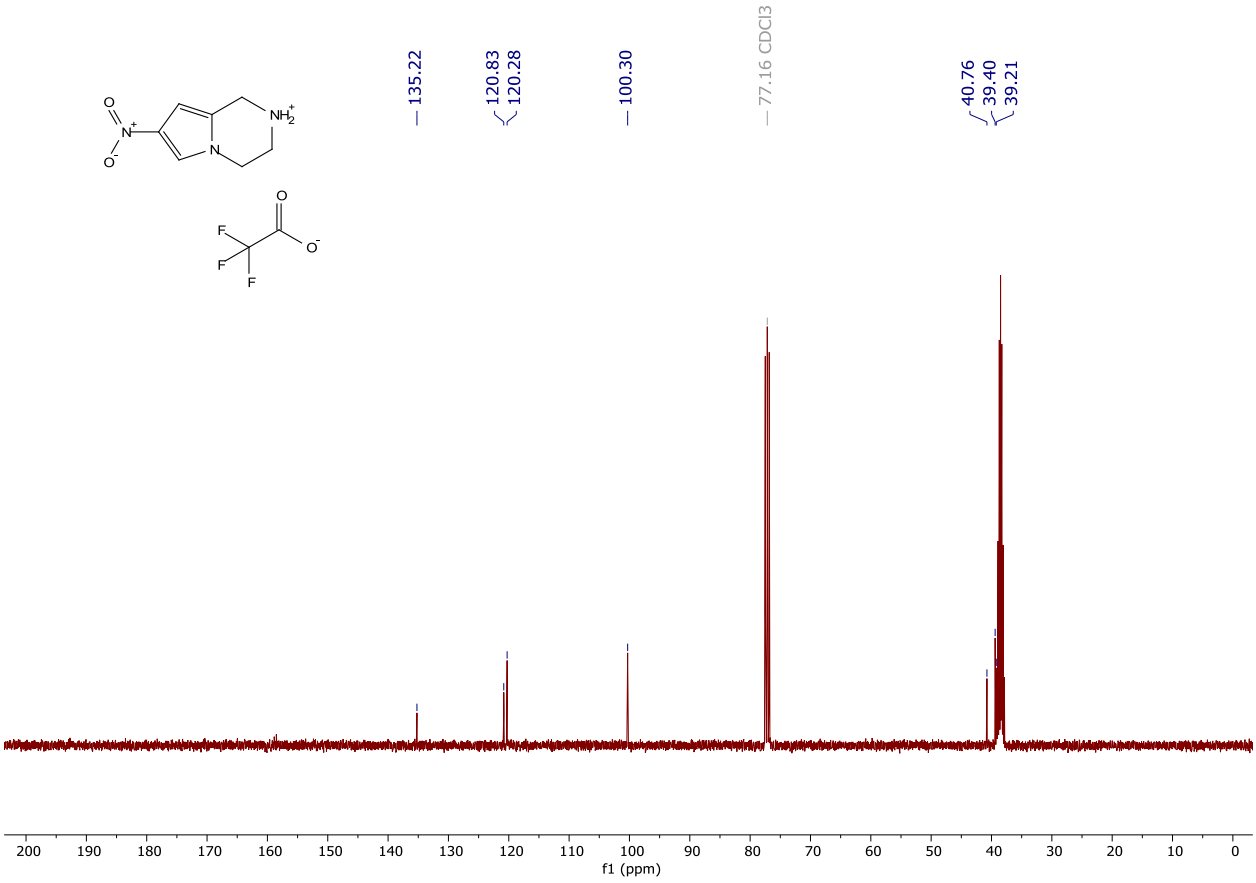
^{1}H and ^{13}C spectra of compound **6j**

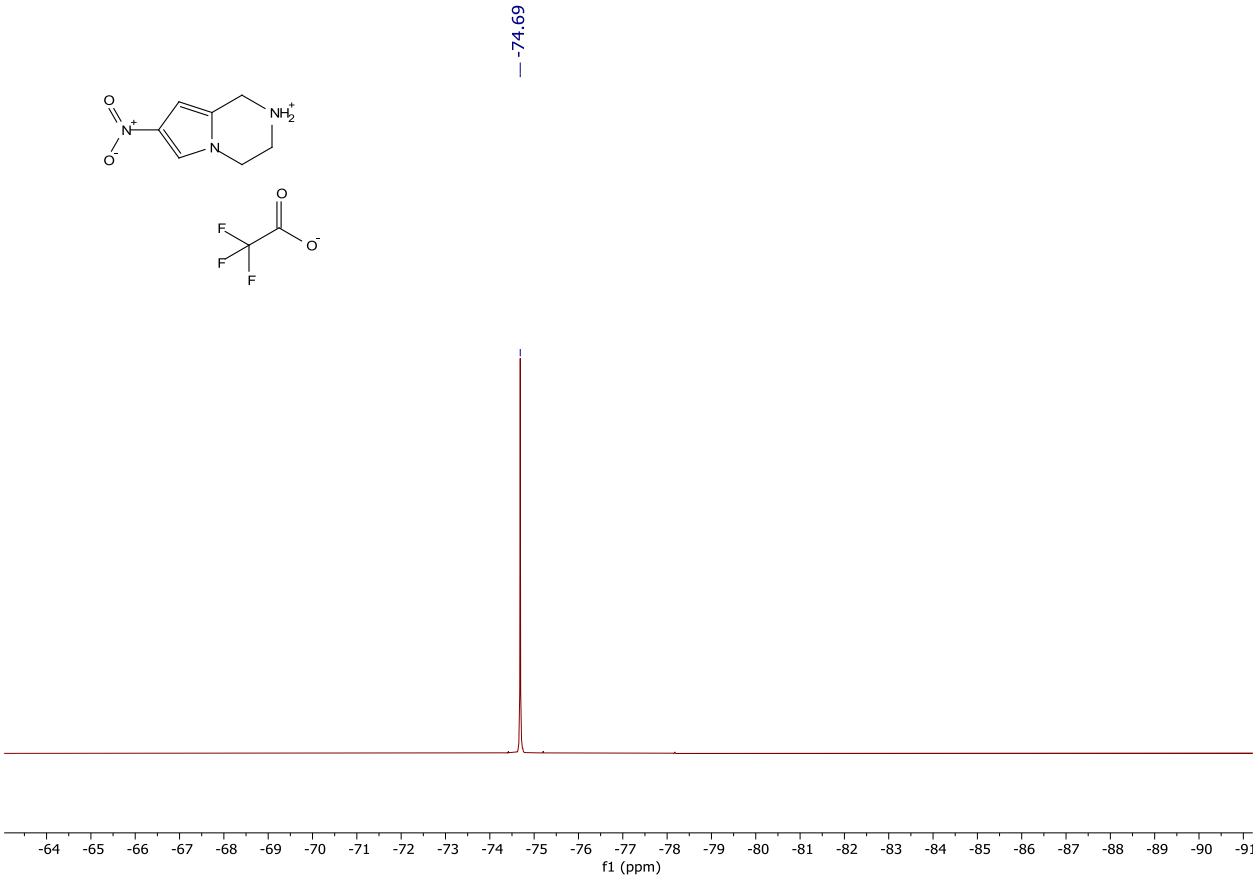




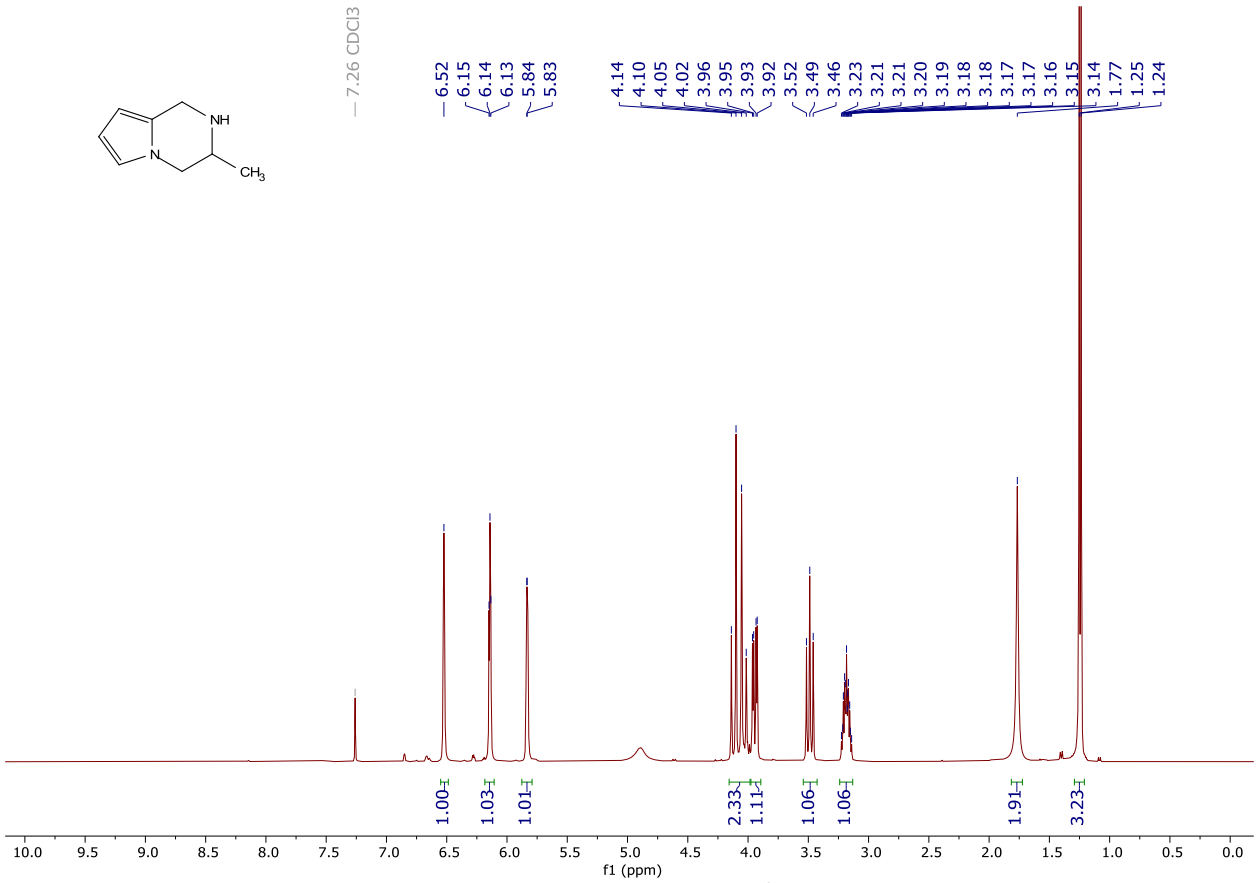
^{1}H, ^{13}C and ^{19}F spectra of compound **6k**

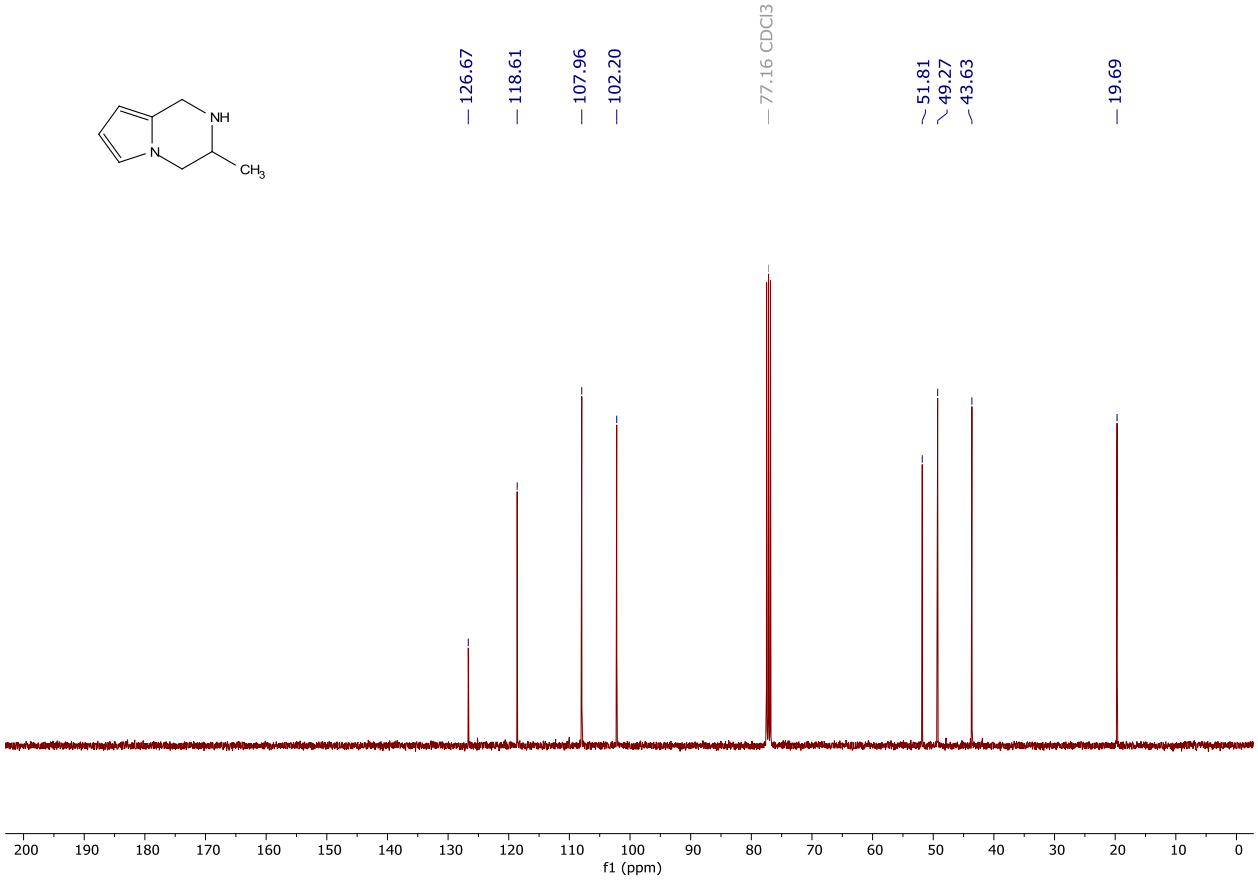




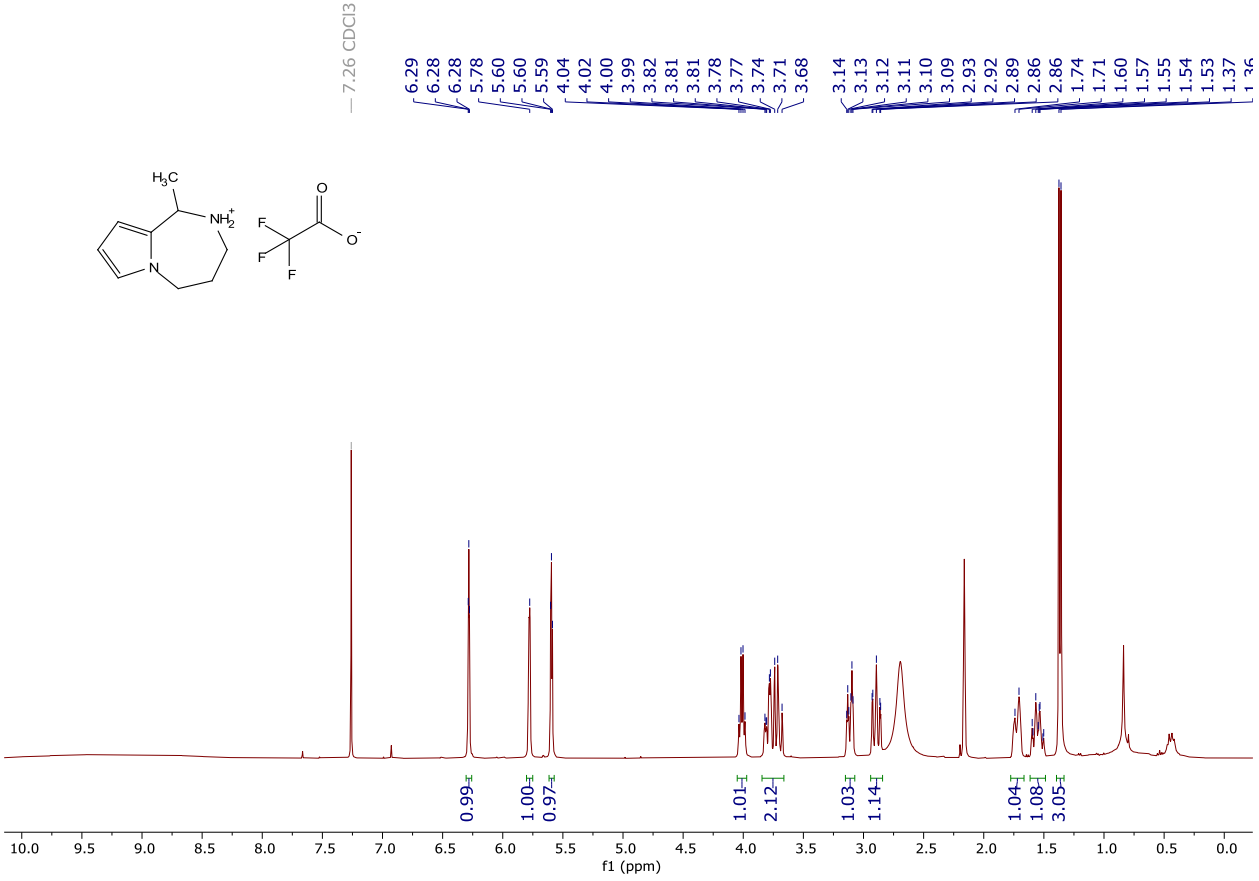

-74.69
O
N+
O-
NH2+
N
O
F
F
F
O-
-64 -65 -66 -67 -68 -69 -70 -71 -72 -73 -74 -75 -76 -77 -78 -79 -80 -81 -82 -83 -84 -85 -86 -87 -88 -89 -90 -91
f1 (ppm)

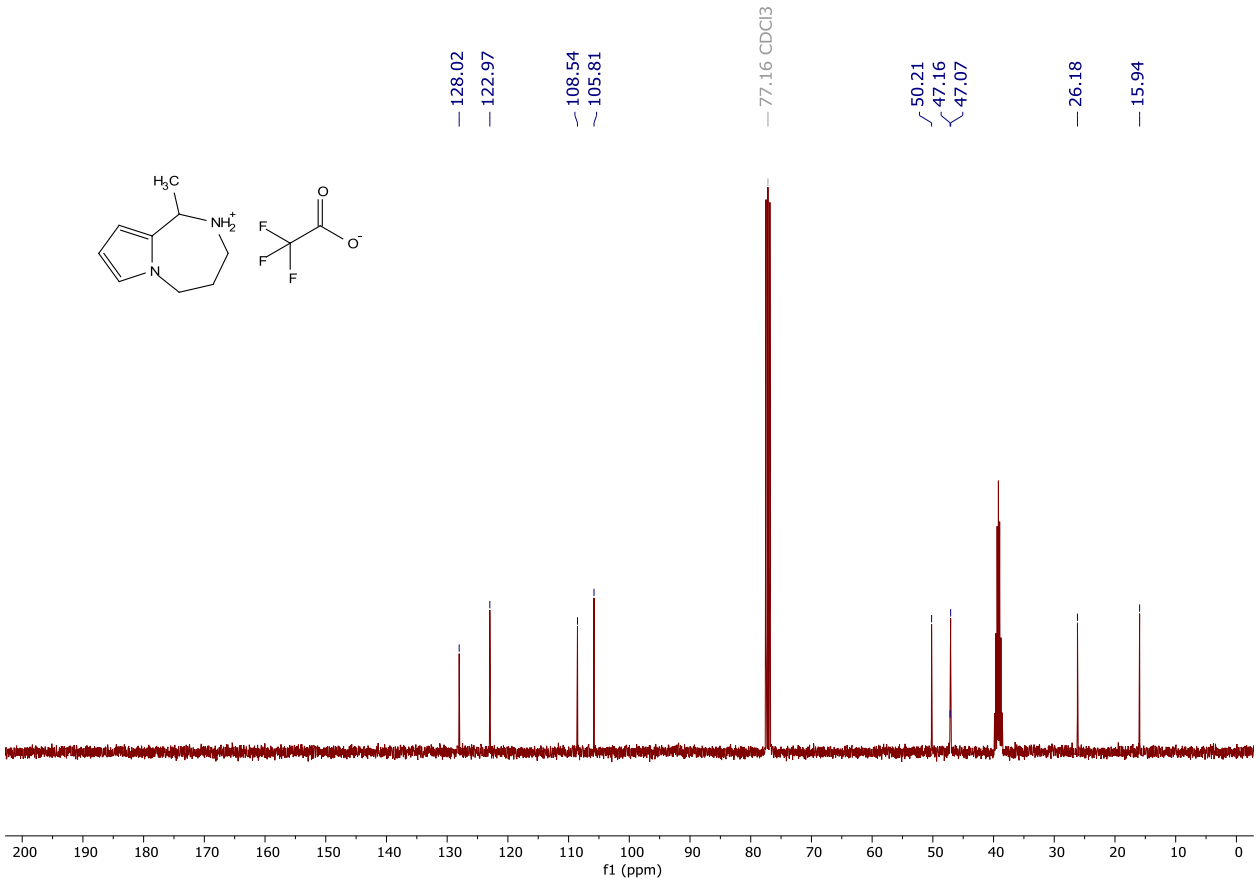
^{1}H, ^{13}C and ^{19}F spectra of compound **6l**

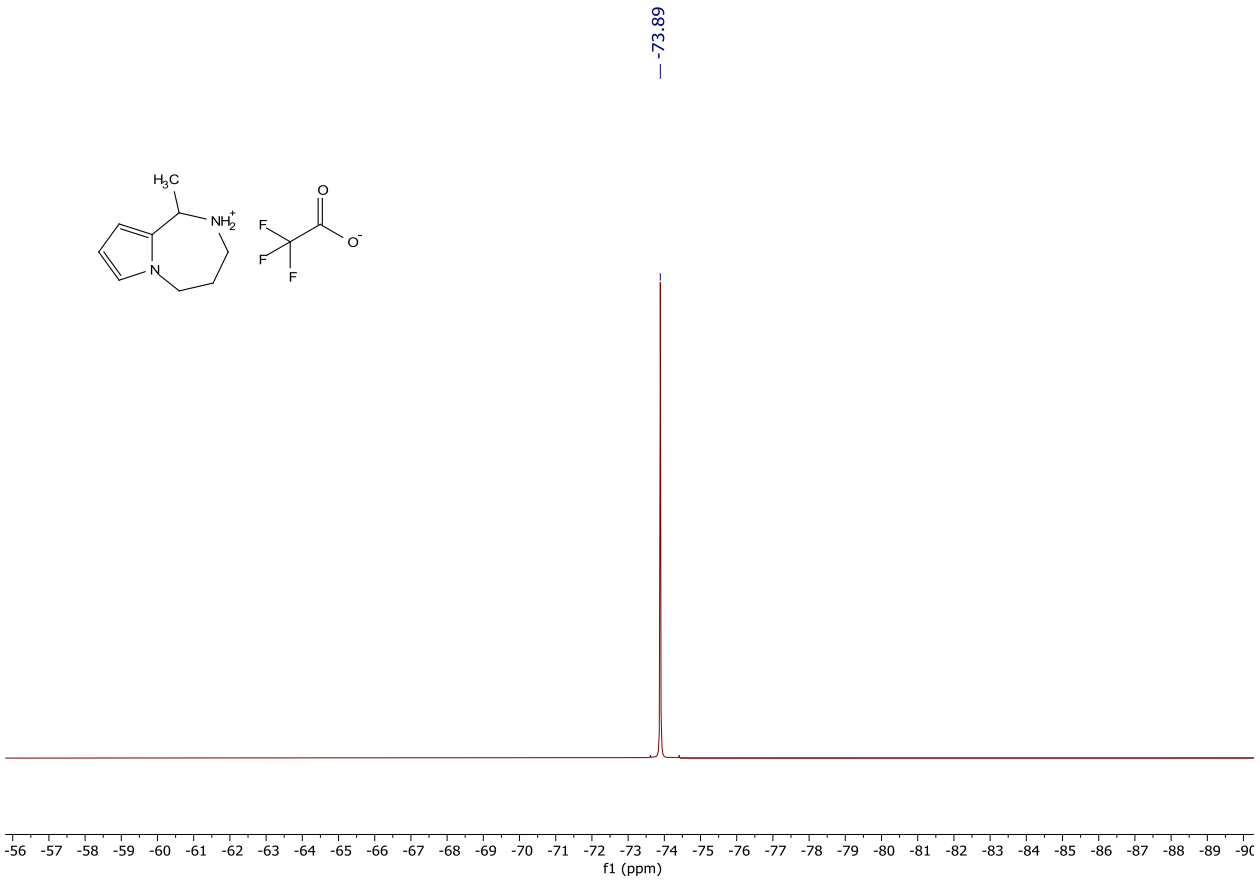




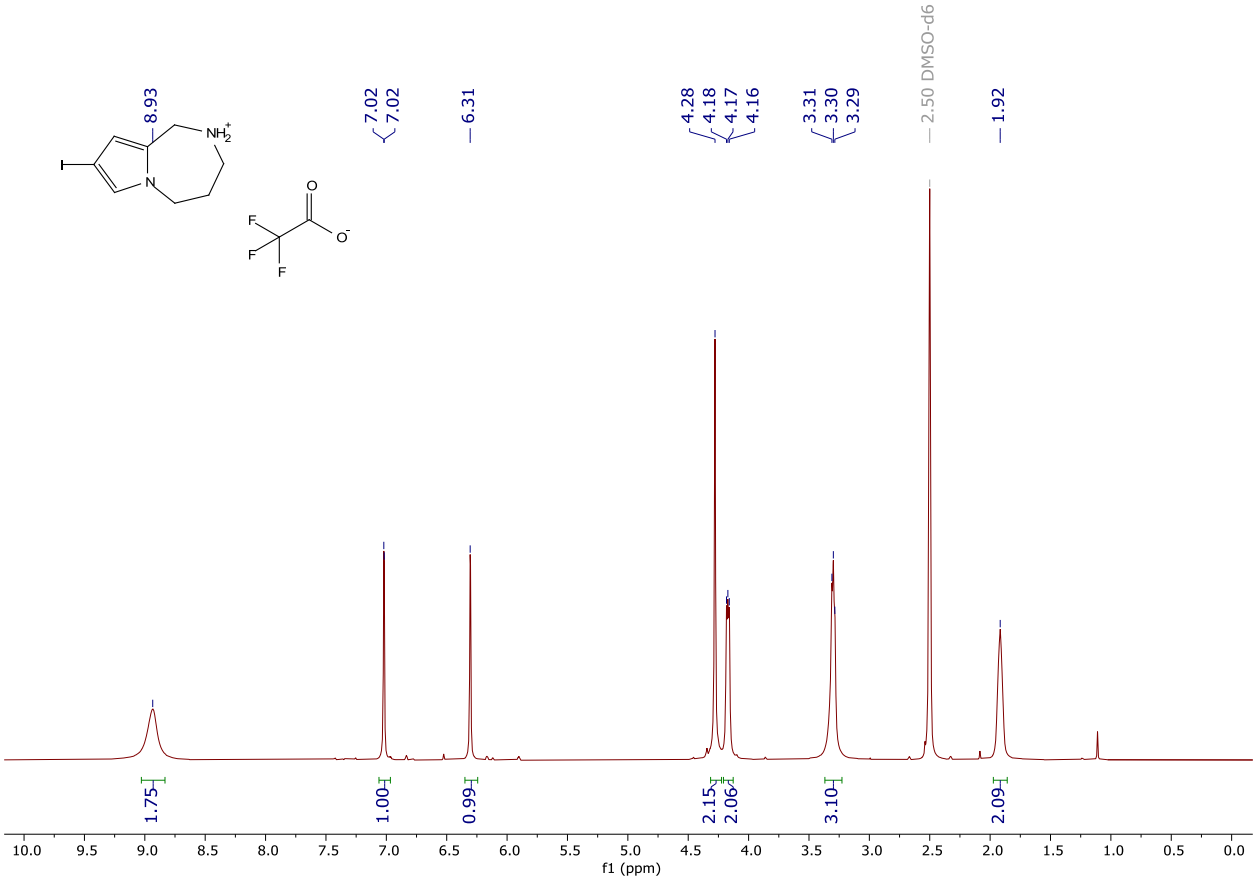
^{1}H, ^{13}C and ^{19}F spectra of compound **6m**

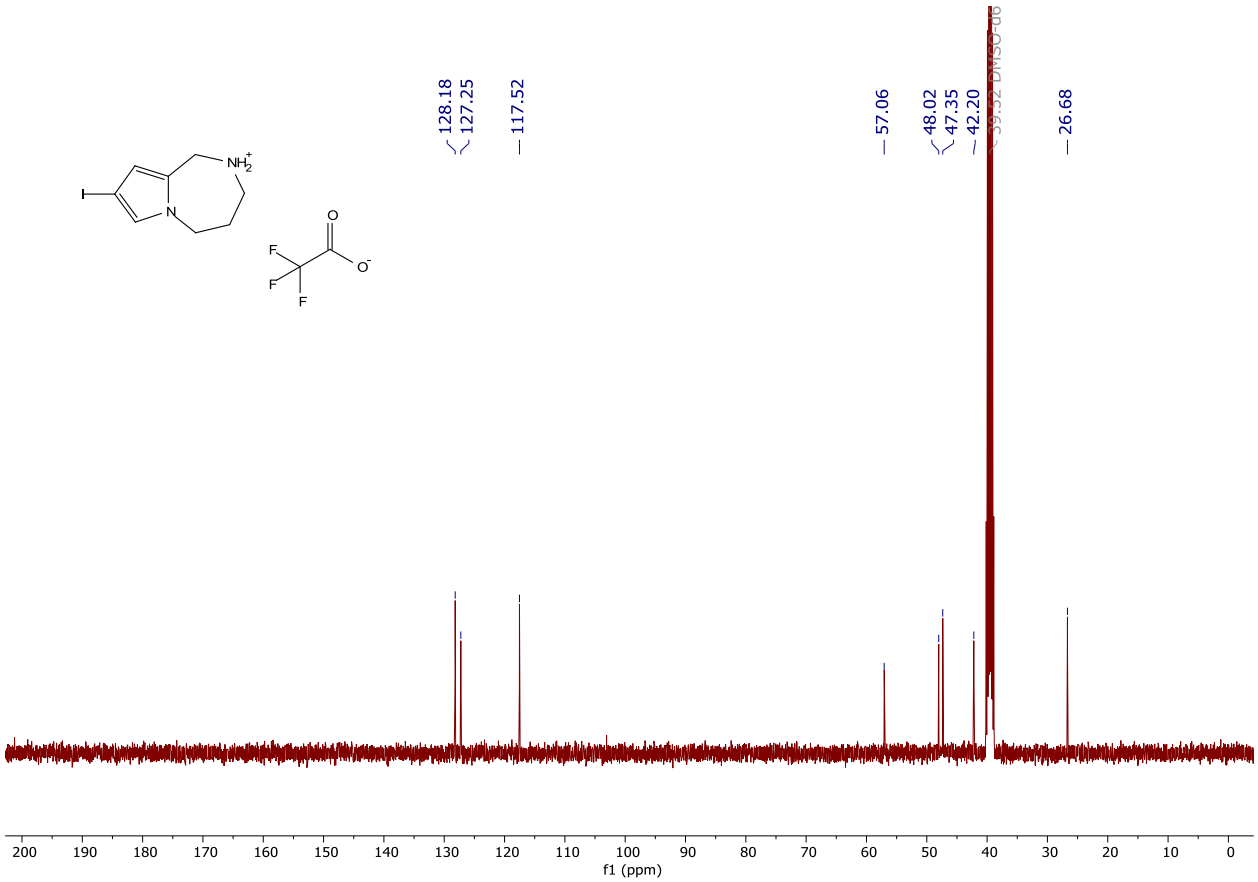


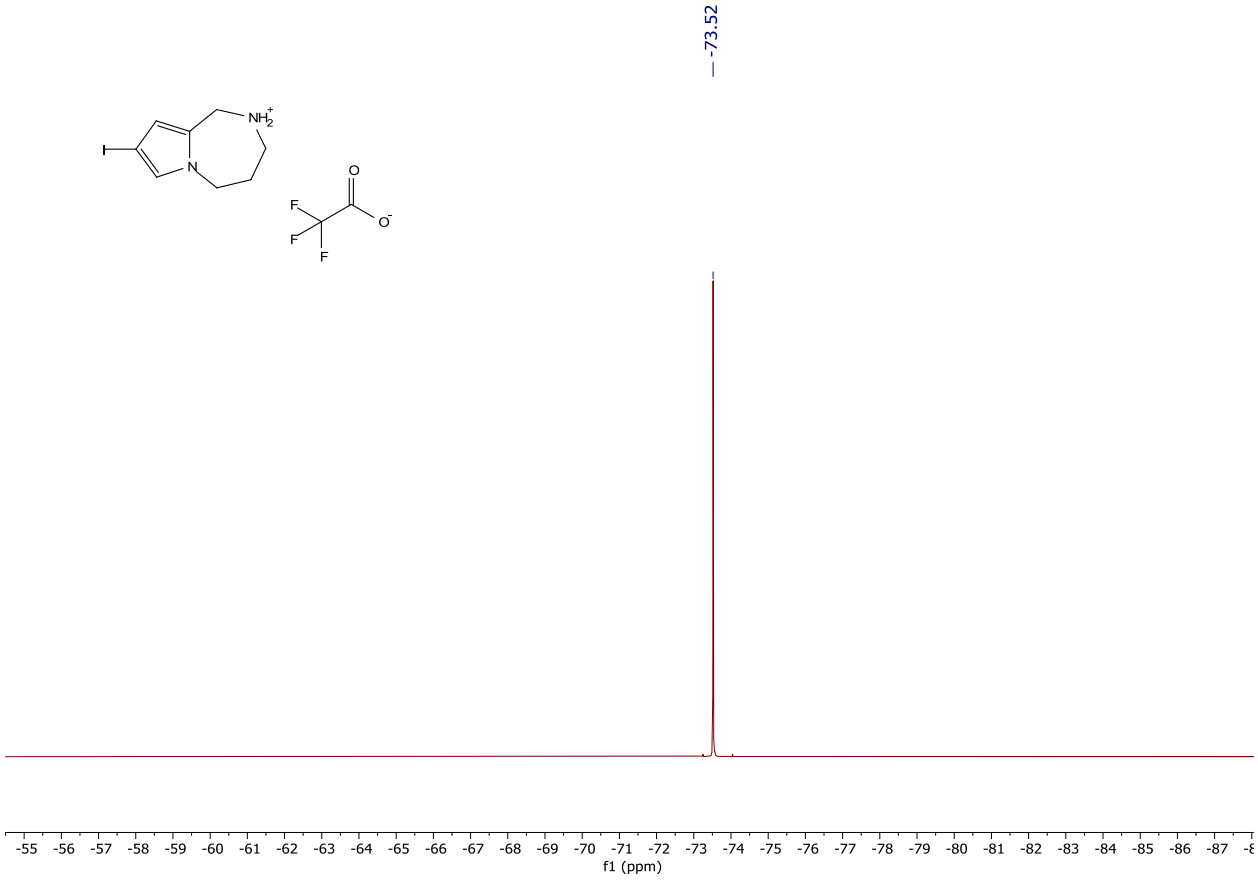

128.02
122.97
108.54
105.81
77.16 CDCl3
50.21
47.16
47.07
26.18
15.94
f1 (ppm)


-73.89
f1 (ppm)

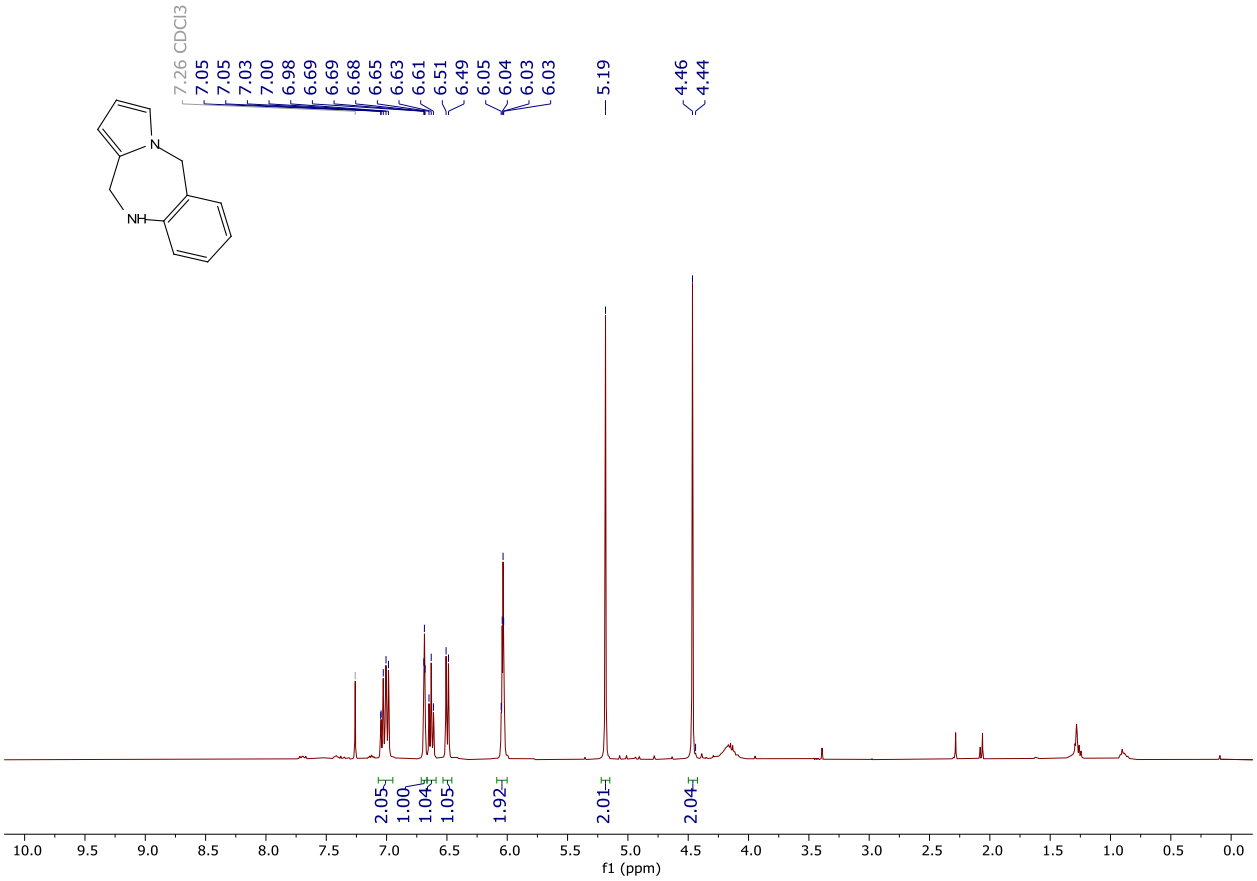
^{1}H, ^{13}C and ^{19}F spectra of compound **6n**

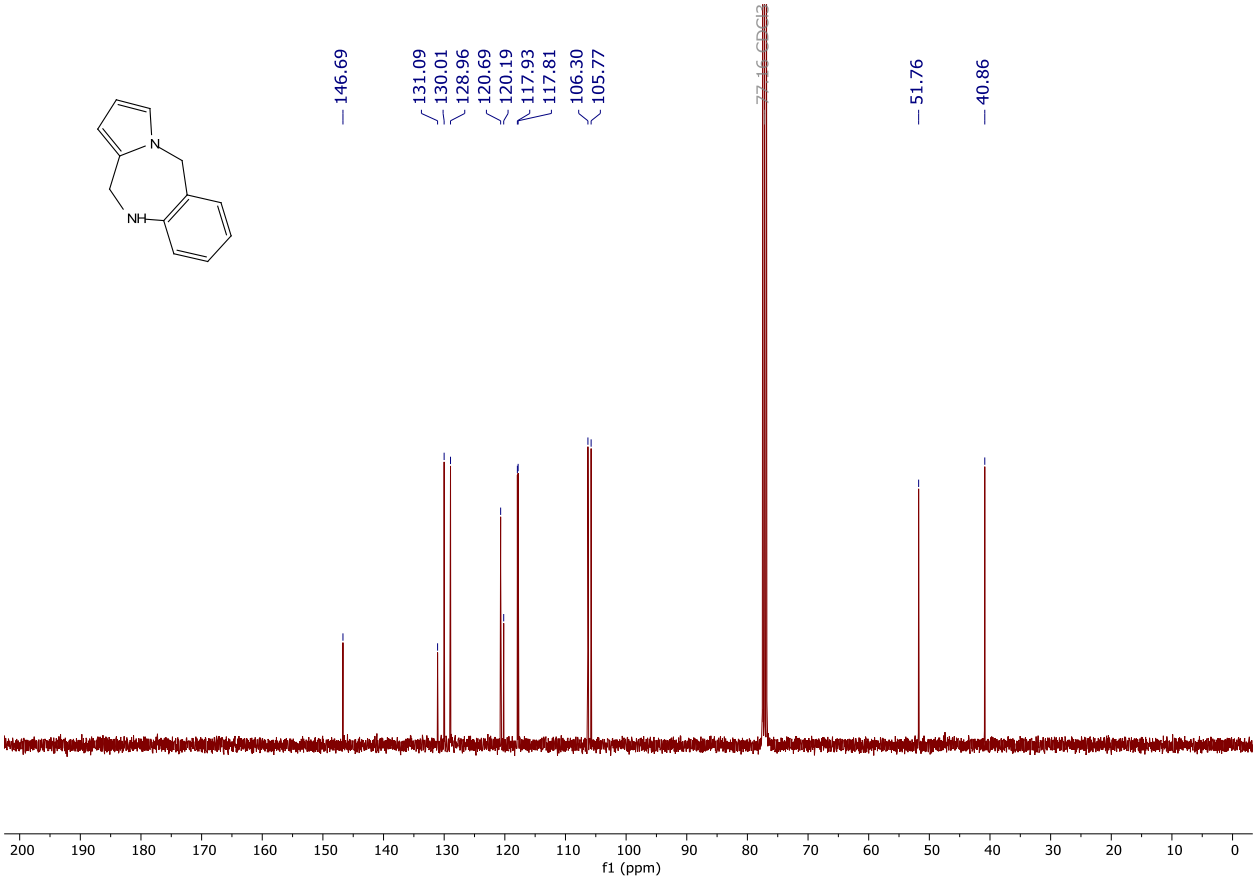



128.18
127.25
117.52
57.06
48.02
47.35
42.20
39.52 DMSO
26.68
f1 (ppm)

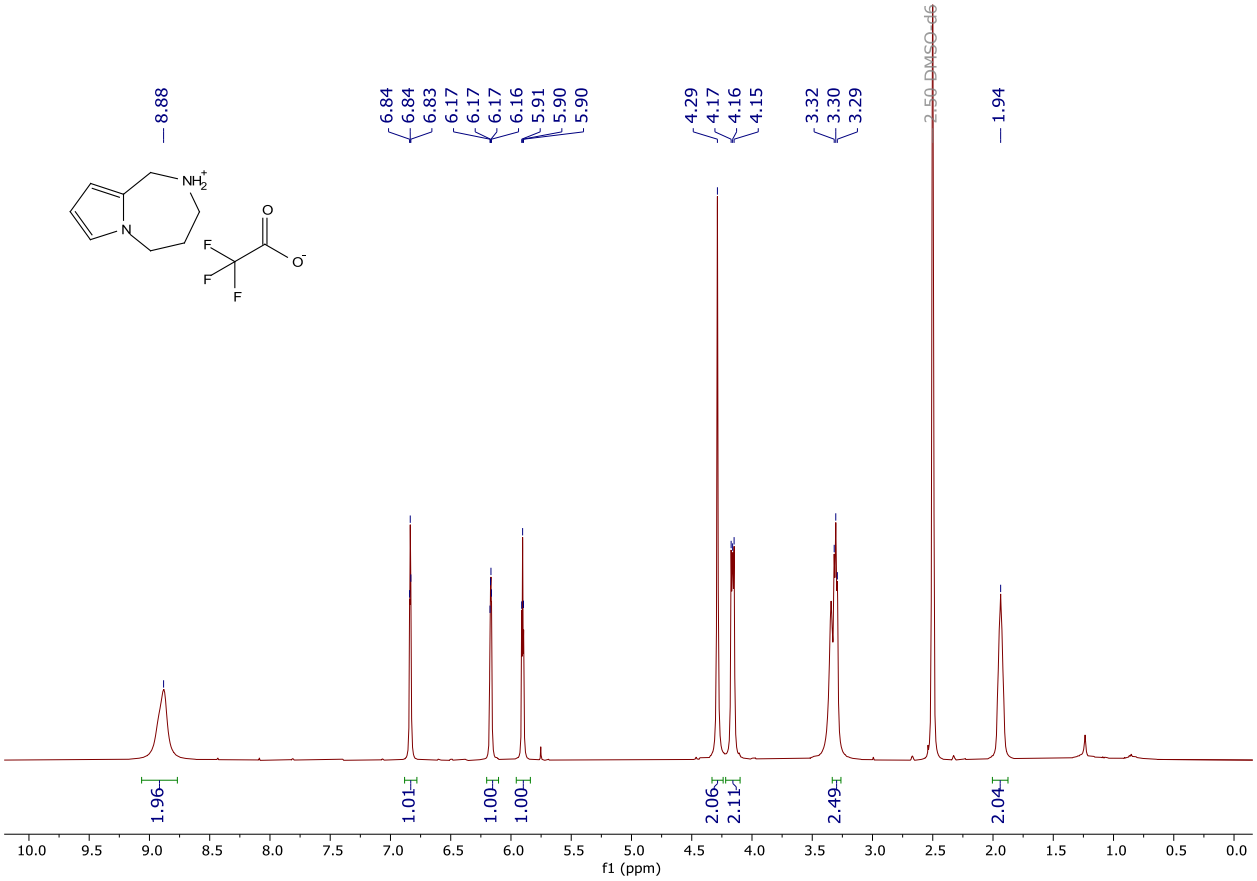

-73.52
f1 (ppm)

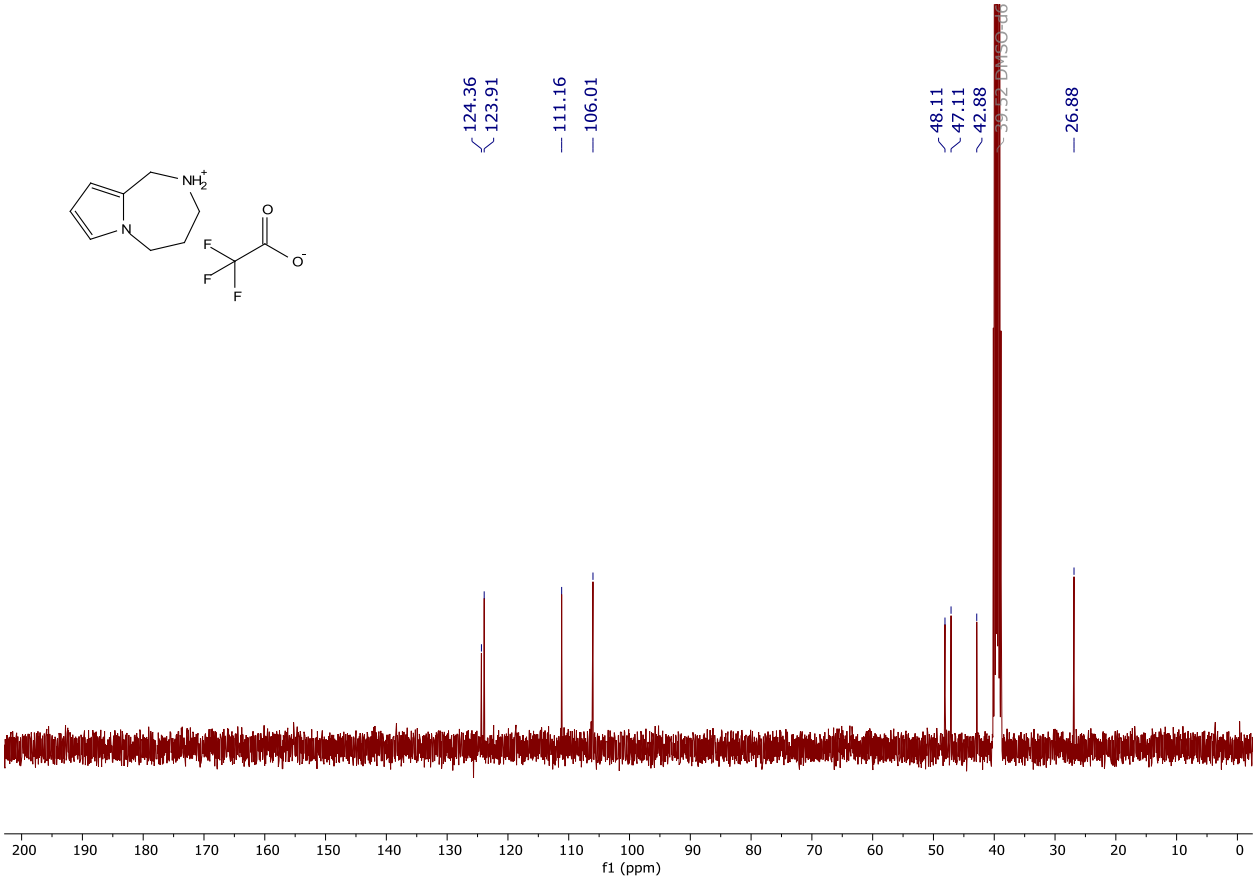
^{1}H and ^{13}C spectra of compound **6o**

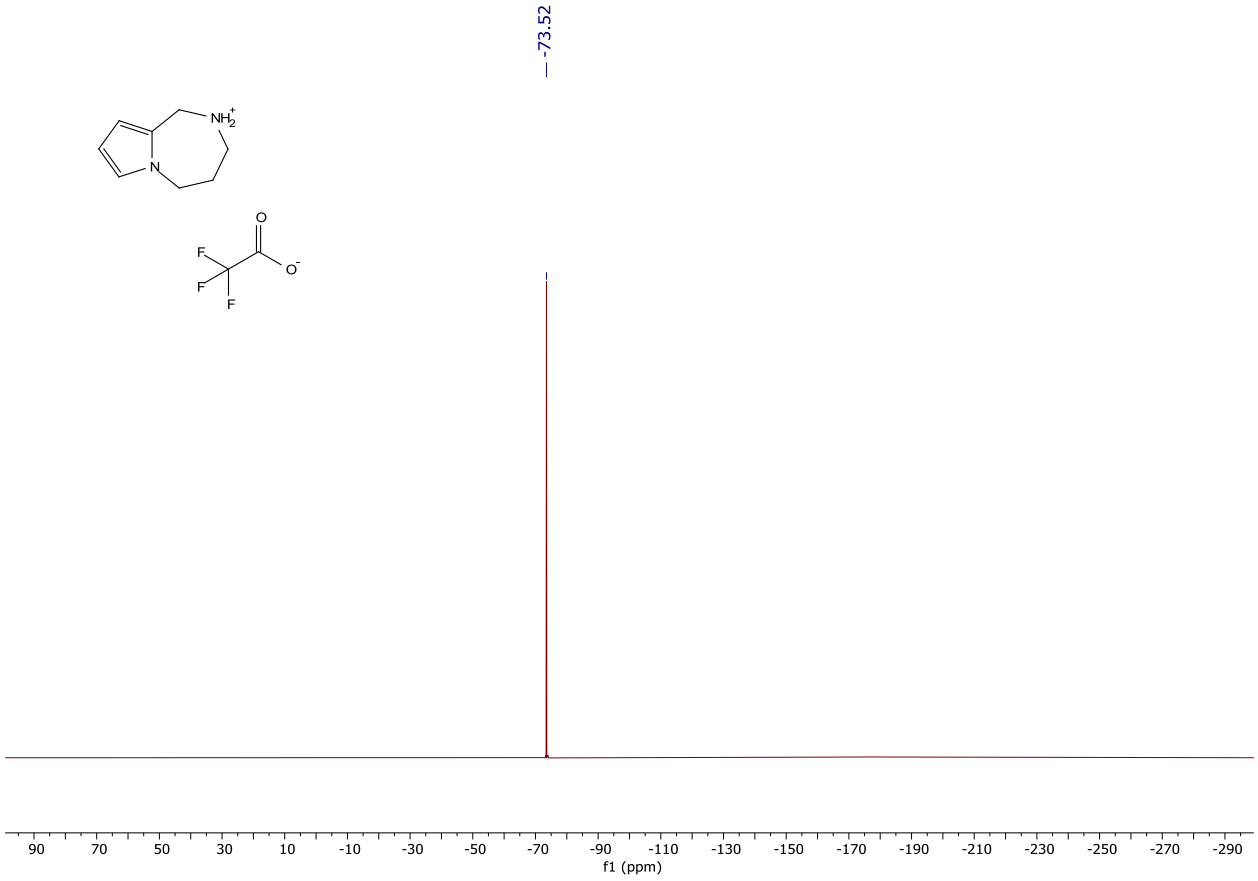




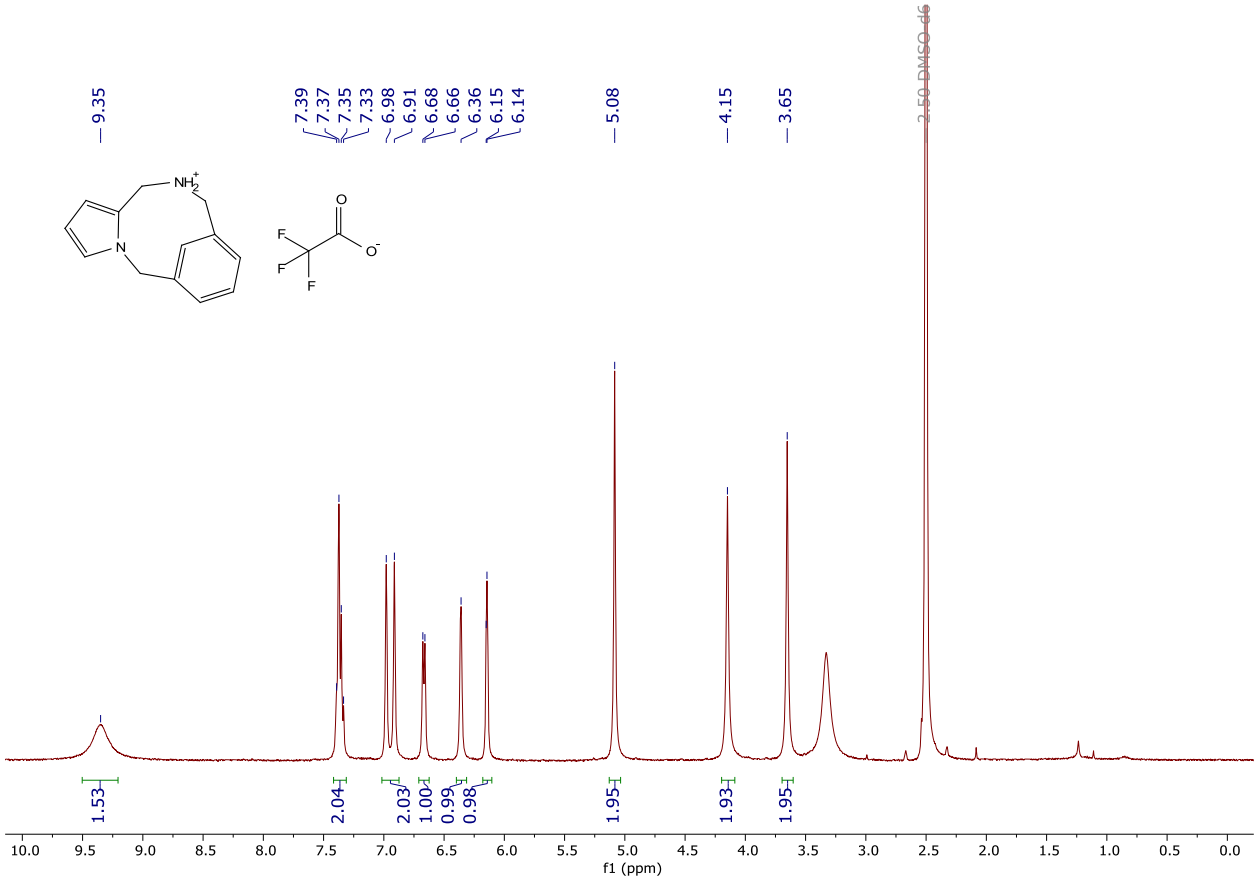
^{1}H, ^{13}C and ^{19}F spectra of compound **6p**

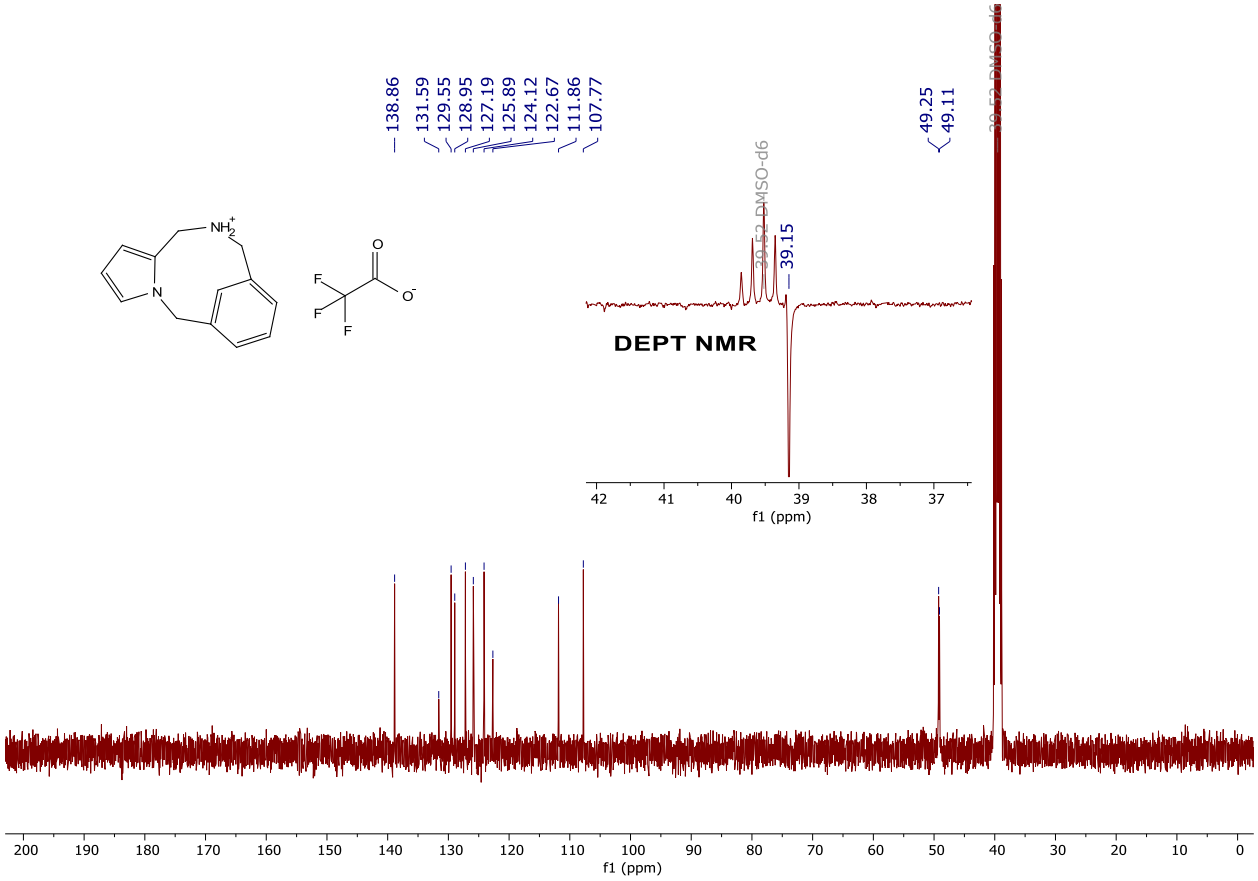


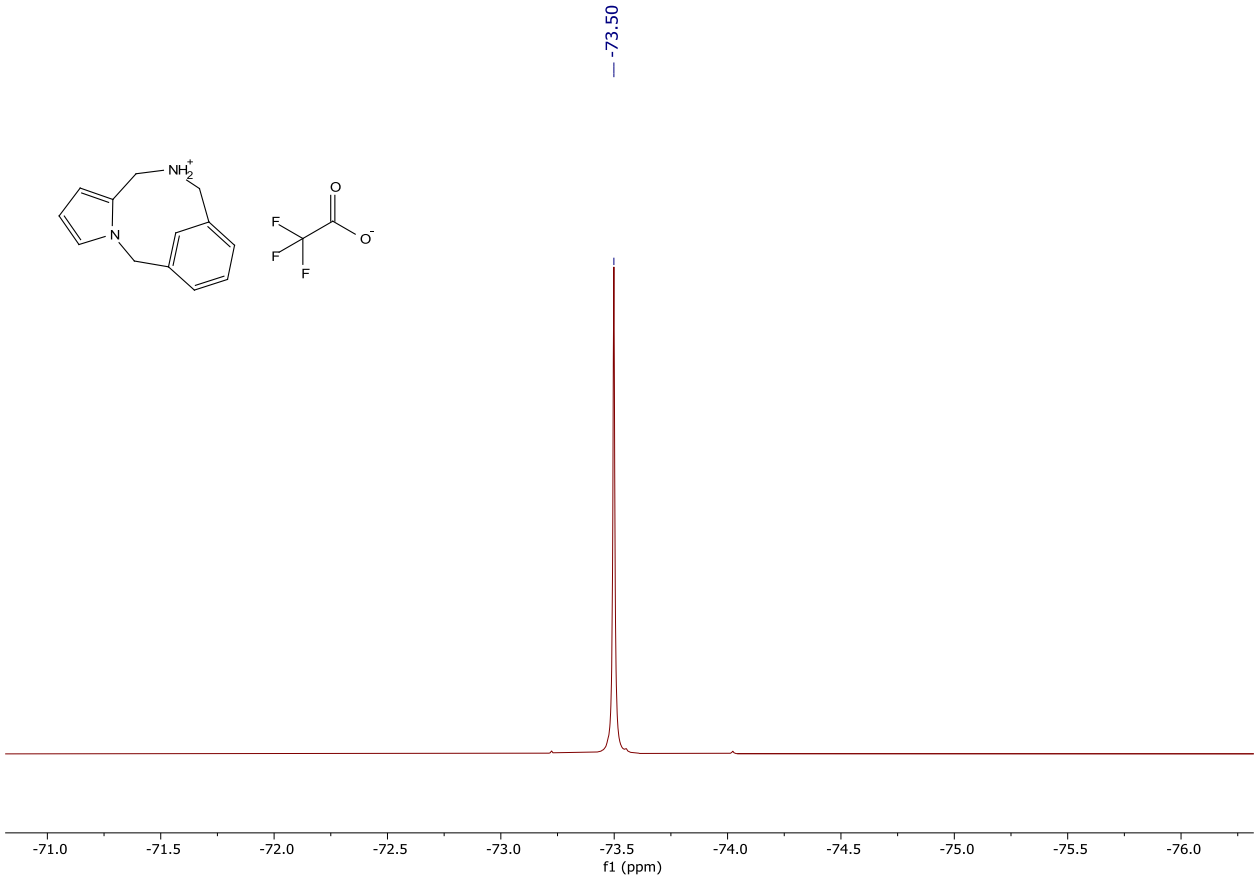



-73.52
NH2+
N
O
O-
F
F
F
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
-250
-270
-290
f1 (ppm)

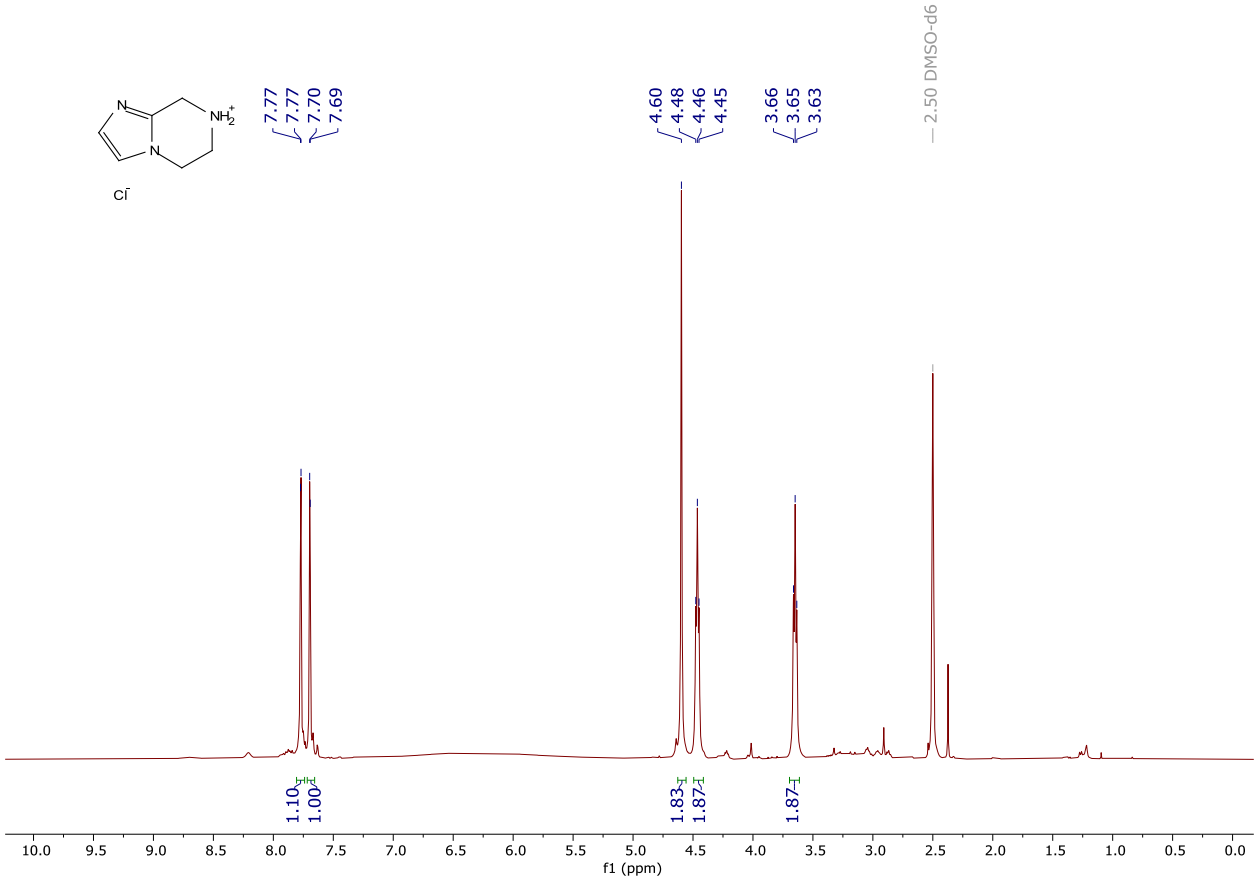
^{1}H, ^{13}C and ^{19}F spectra of compound **6q**

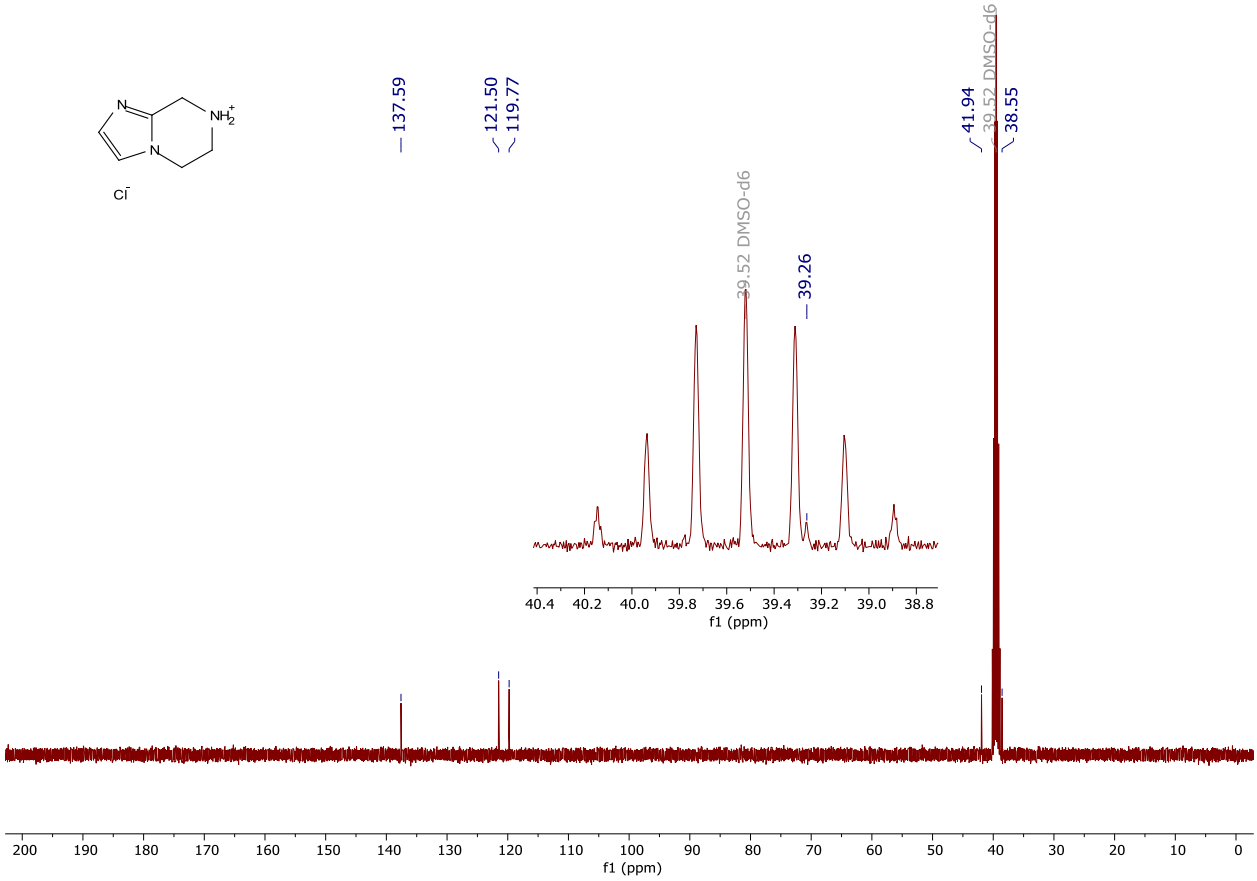




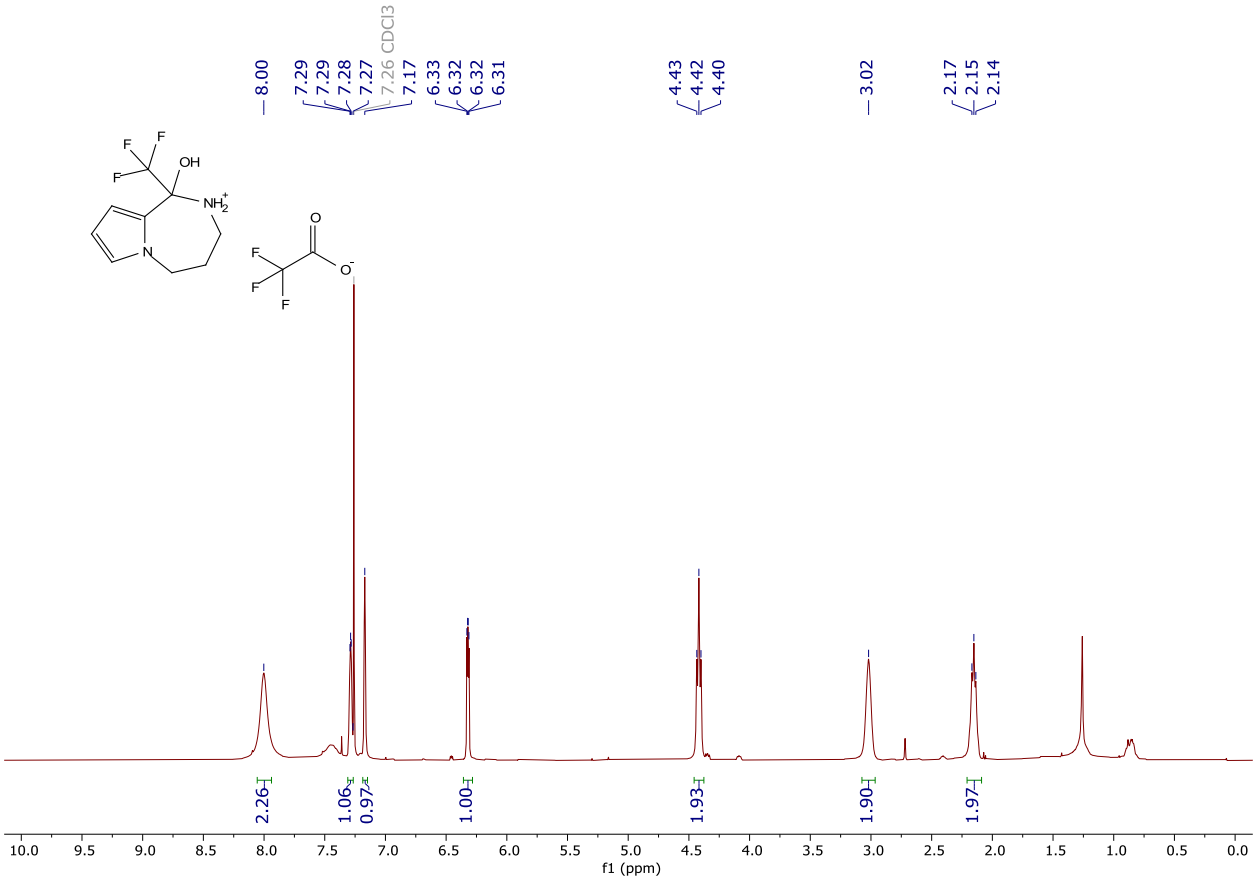

-73.50
NH2+
N
O
F
F
F
O-
-71.0
-71.5
-72.0
-72.5
-73.0
-73.5
-74.0
-74.5
-75.0
-75.5
-76.0
f1 (ppm)

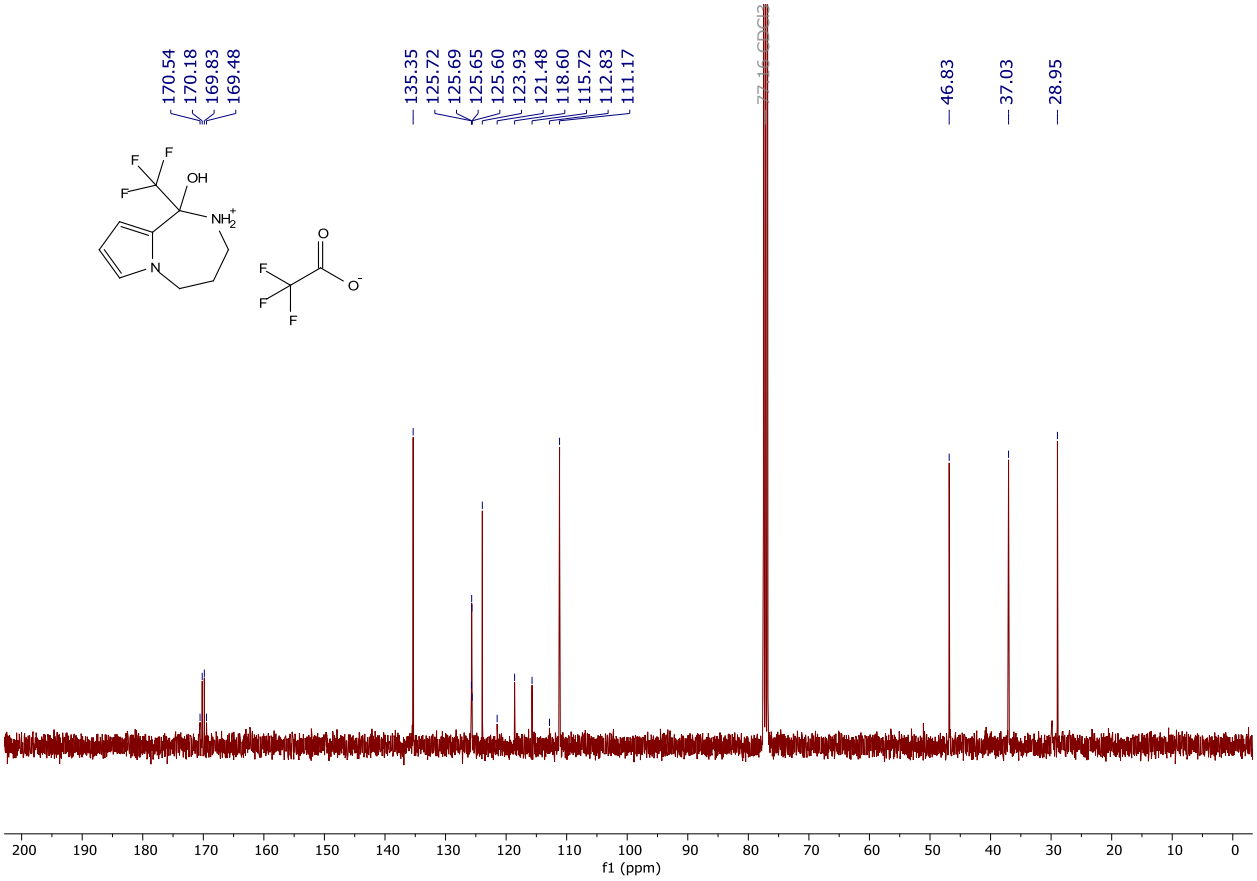
^{1}H and ^{13}C spectra of compound **6r**

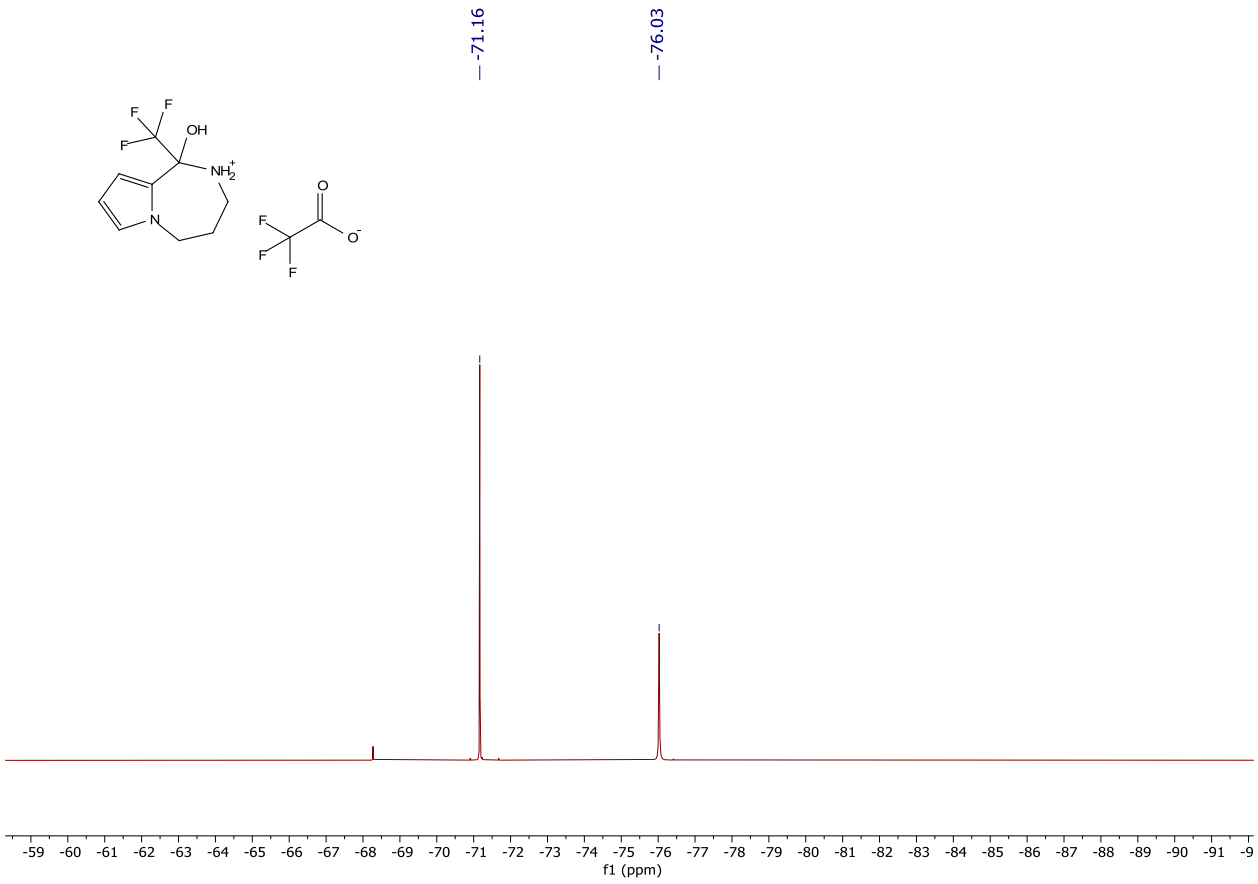




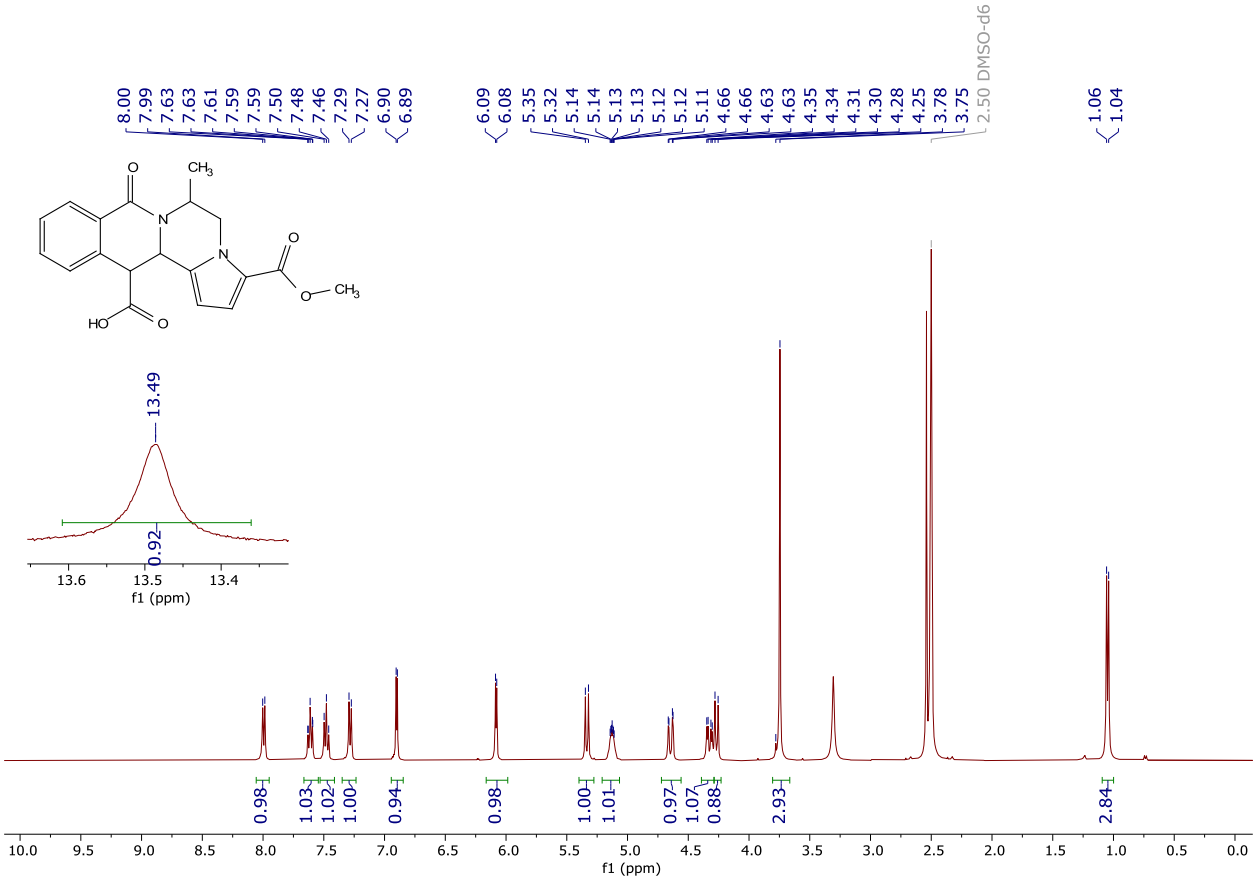
^{1}H, ^{13}C and ^{19}F spectra of compound **6s**

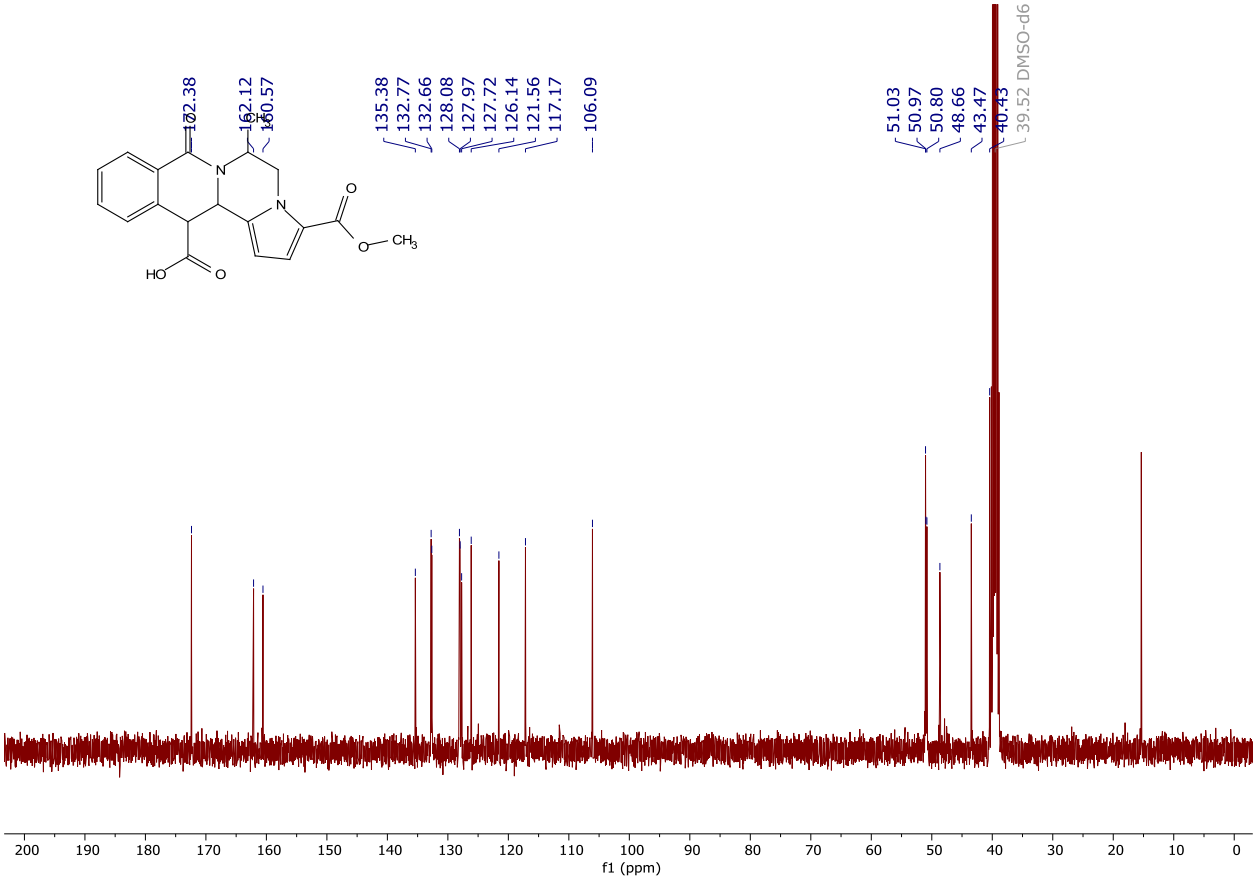




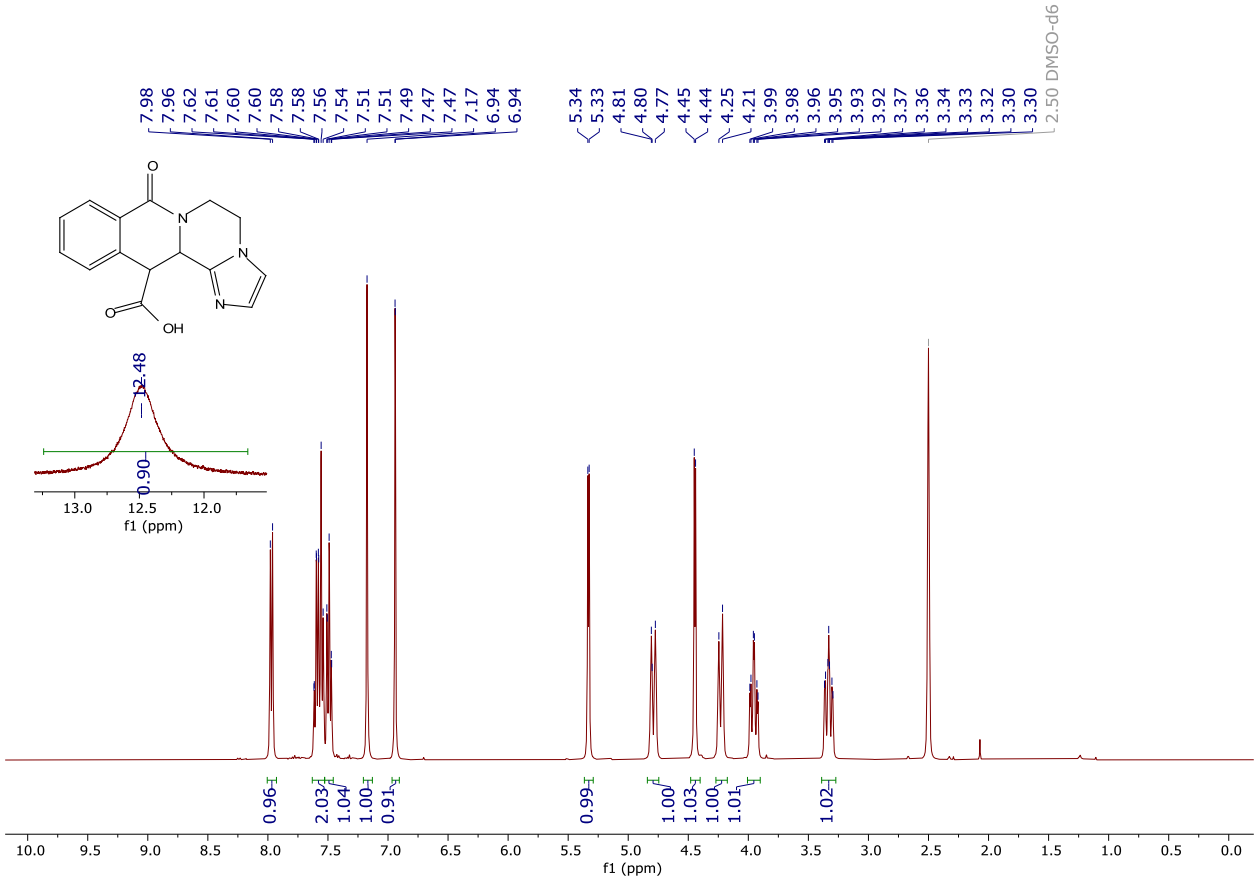

-71.16
-76.03
F
F
F
OH
NH2+
N
O
O-
F
F
F
-59 -60 -61 -62 -63 -64 -65 -66 -67 -68 -69 -70 -71 -72 -73 -74 -75 -76 -77 -78 -79 -80 -81 -82 -83 -84 -85 -86 -87 -88 -89 -90 -91 -9
f1 (ppm)

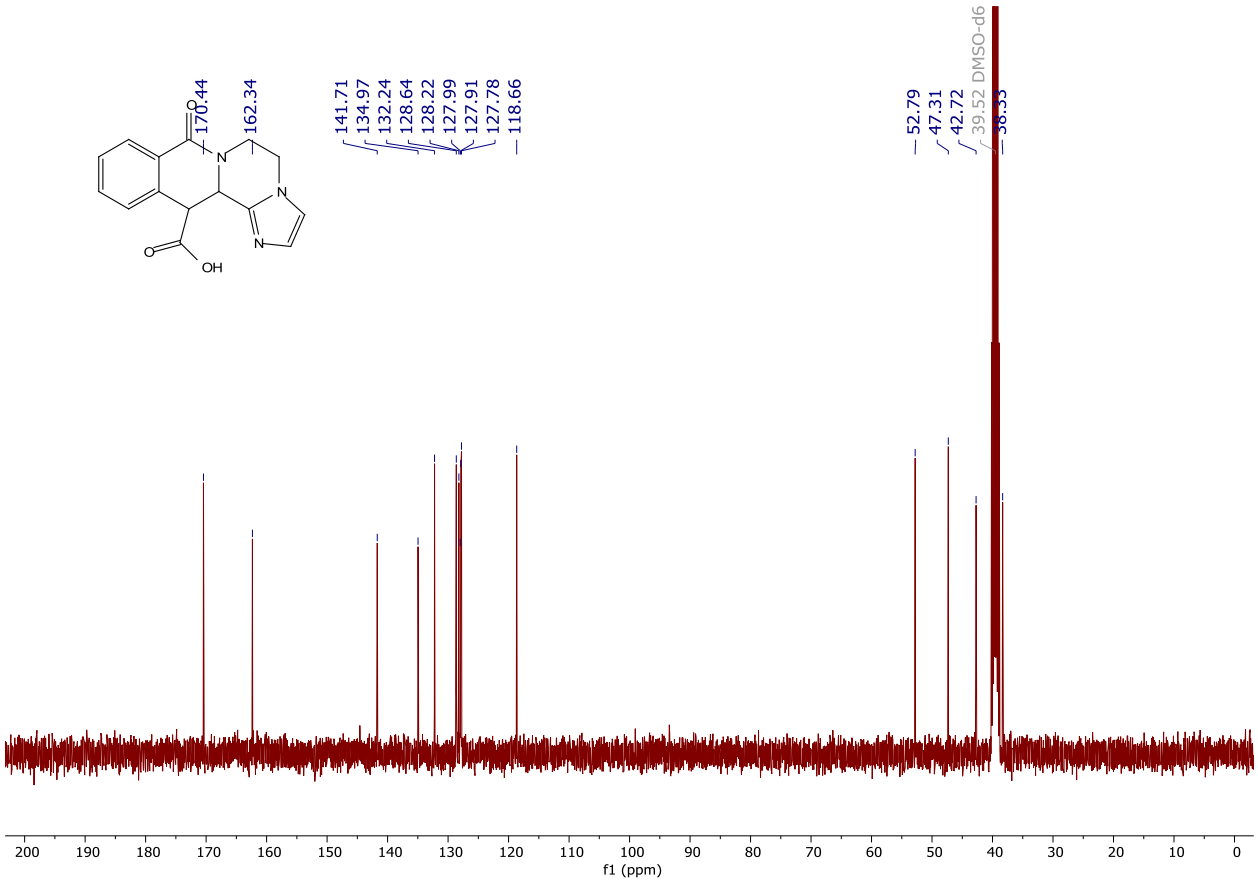
^{1}H and ^{13}C spectra of compound **8a**



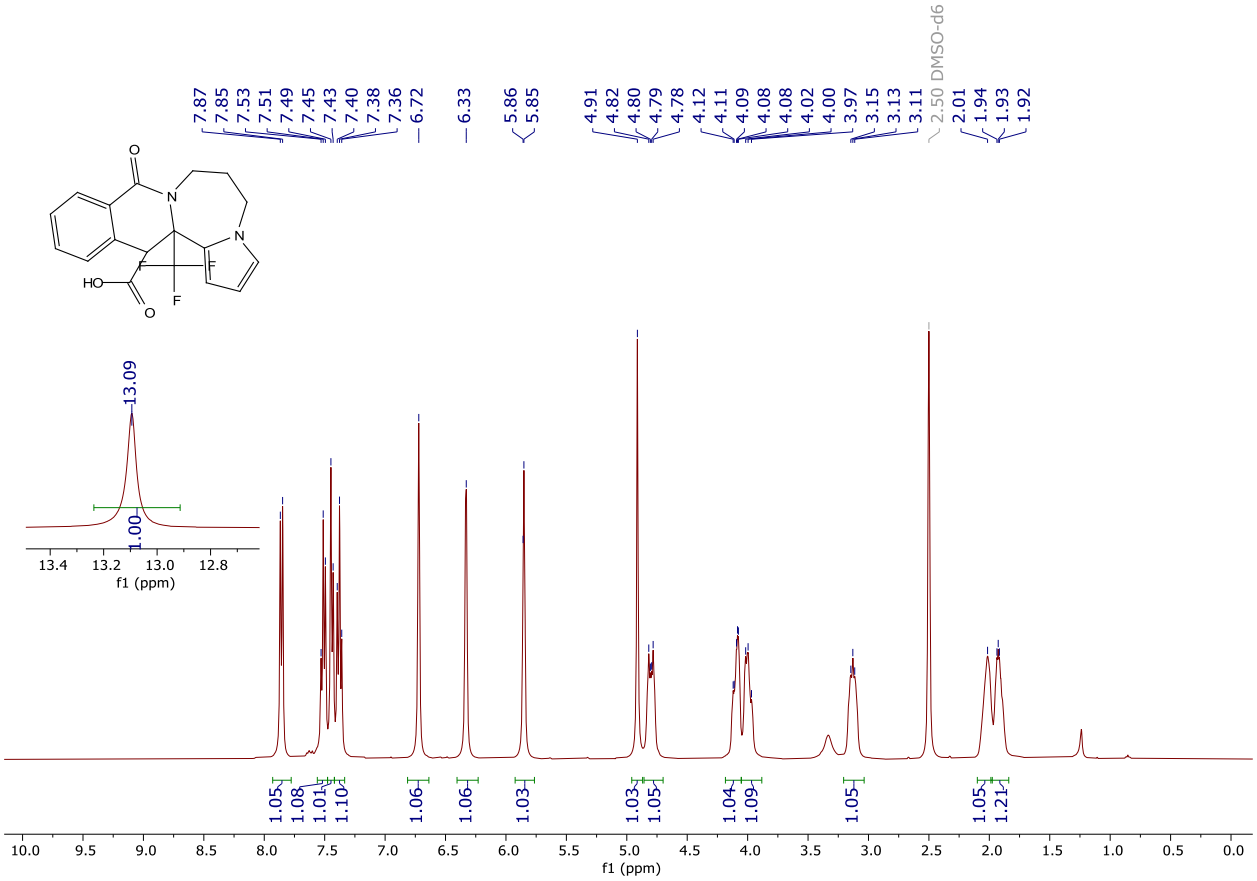


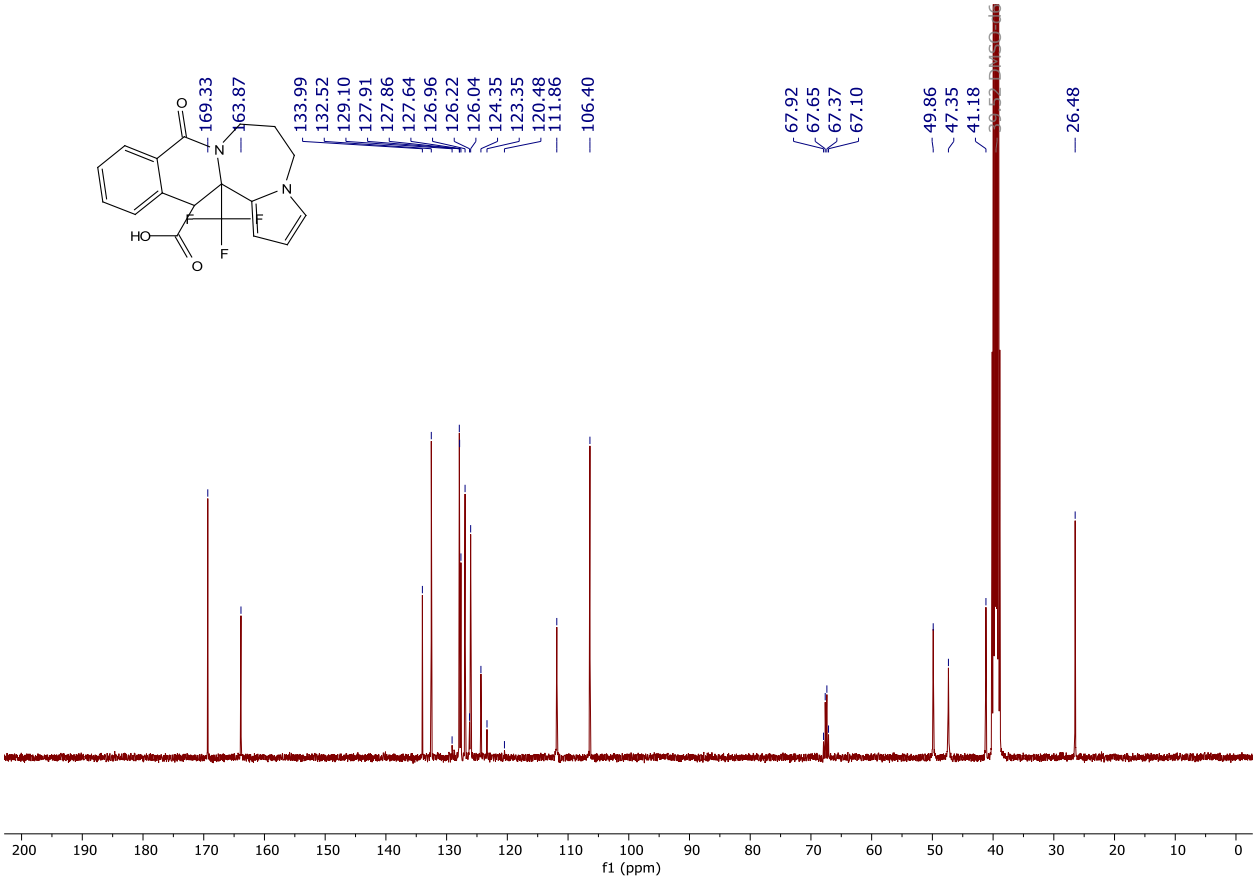
^{1}H and ^{13}C spectra of compound **8b**

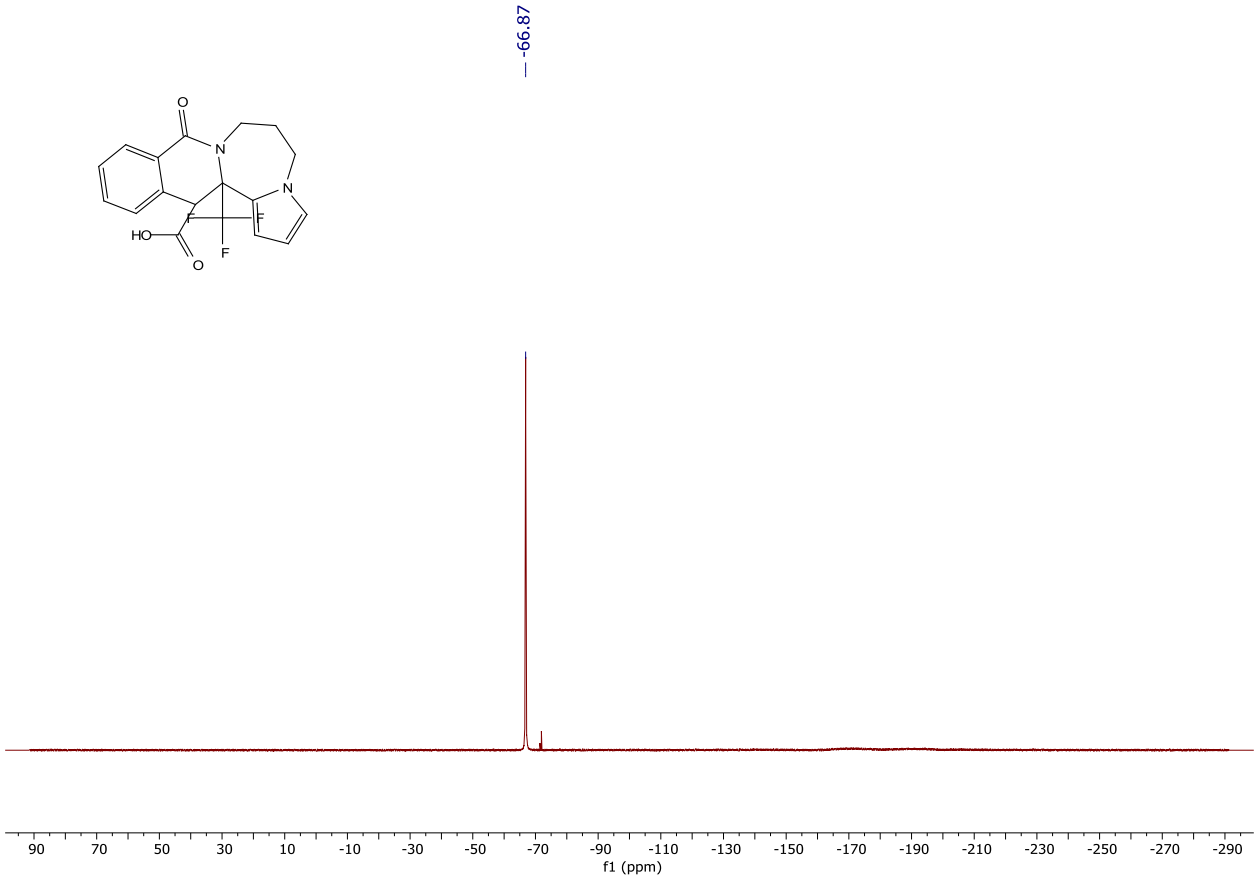




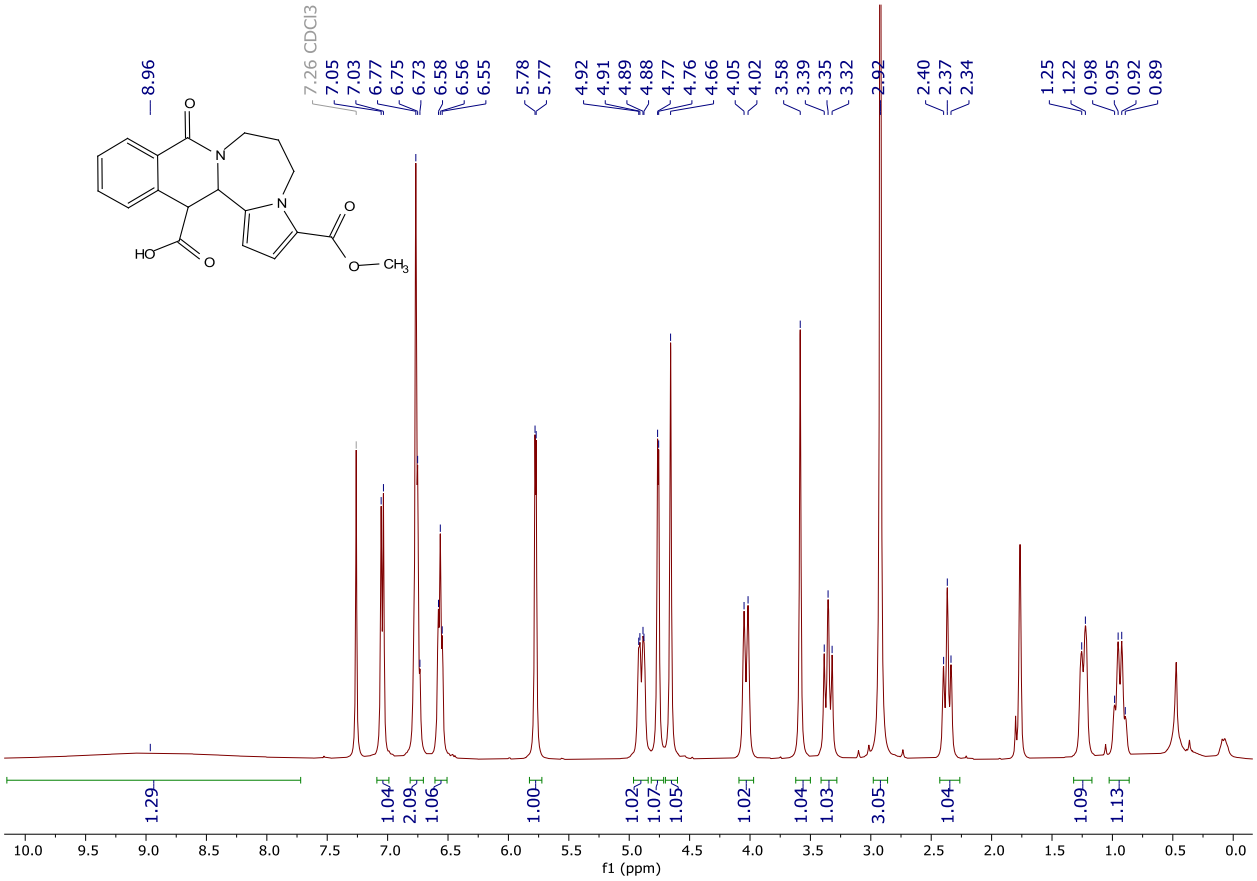
^{1}H, ^{13}C and ^{19}F spectra of compound **8c**

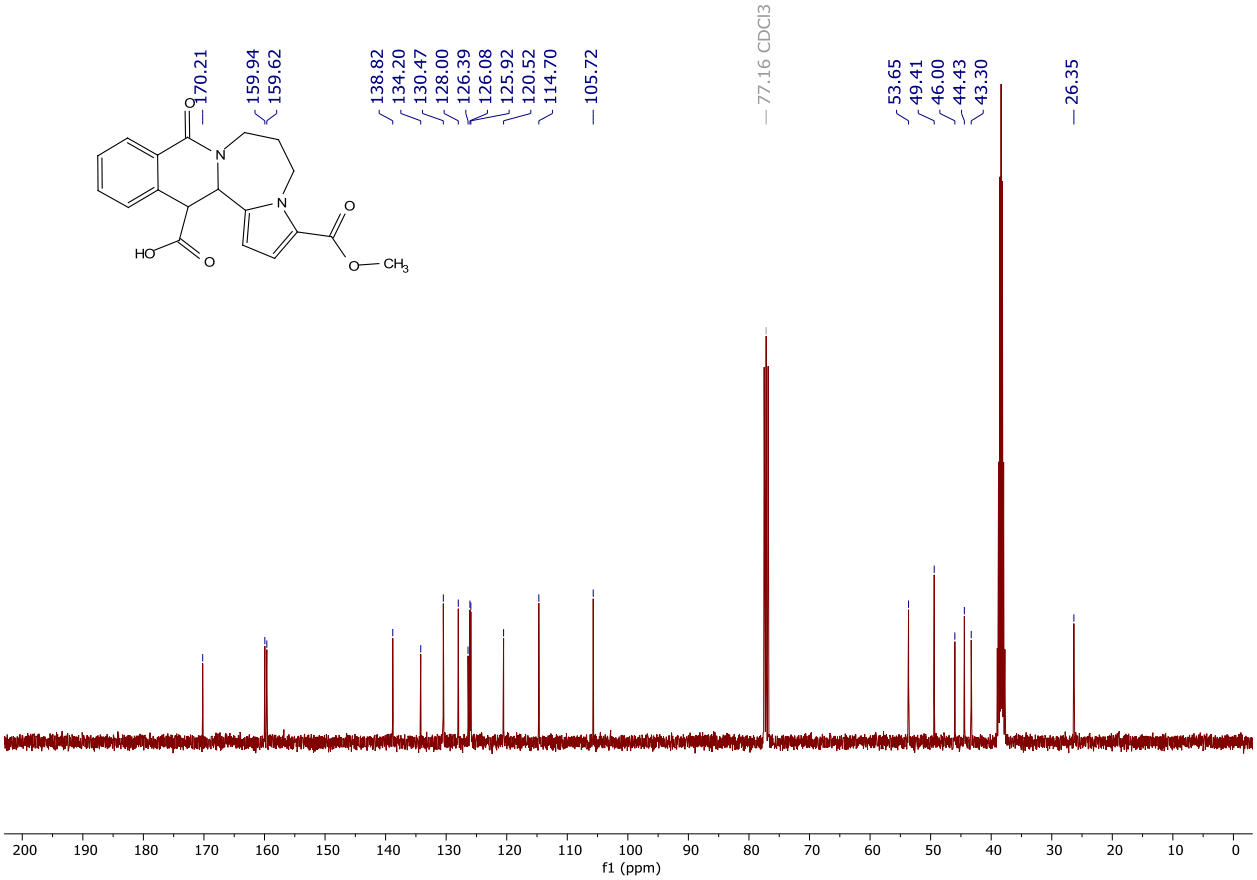




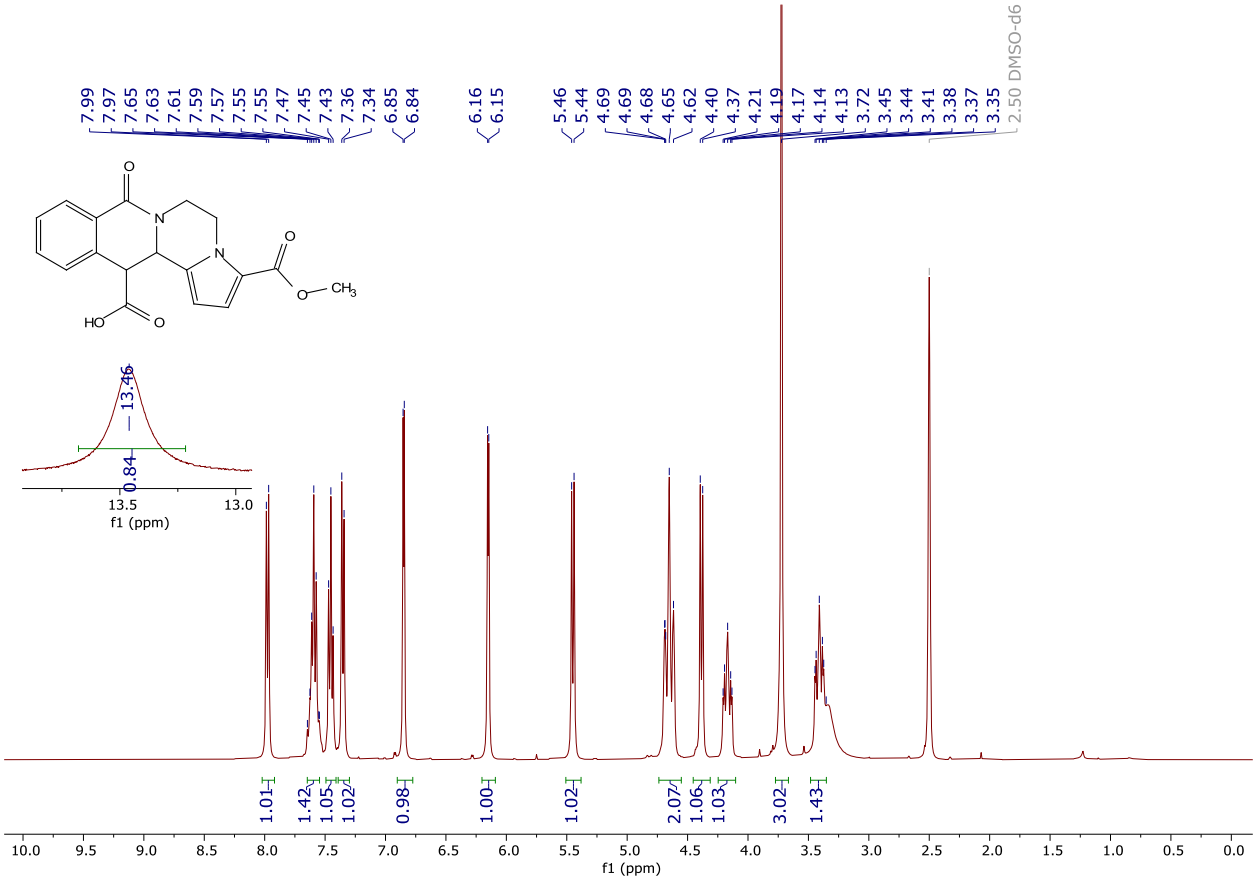

-66.87
O
N
N
F
F
F
HO
O
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
-250
-270
-290
f1 (ppm)

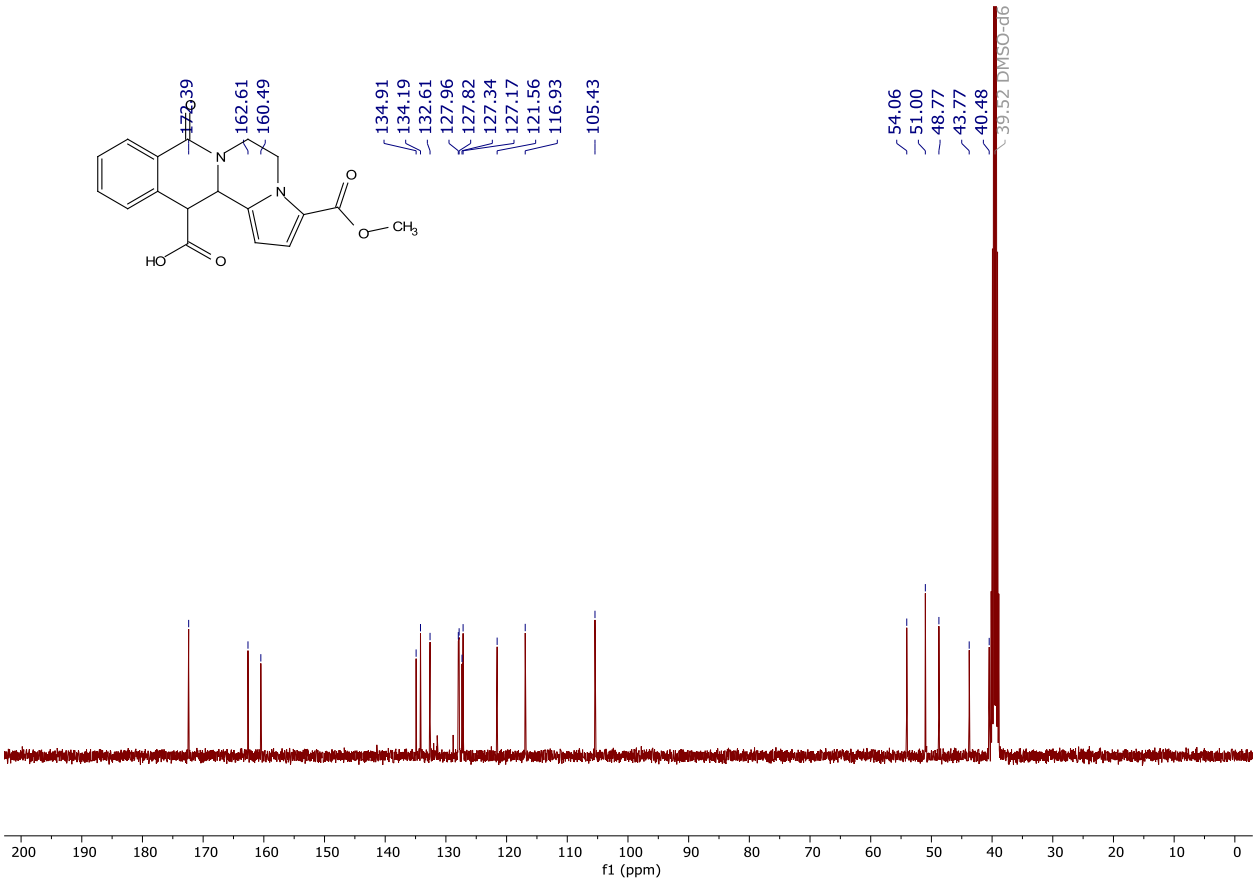
^{1}H and ^{13}C spectra of compound **8d**



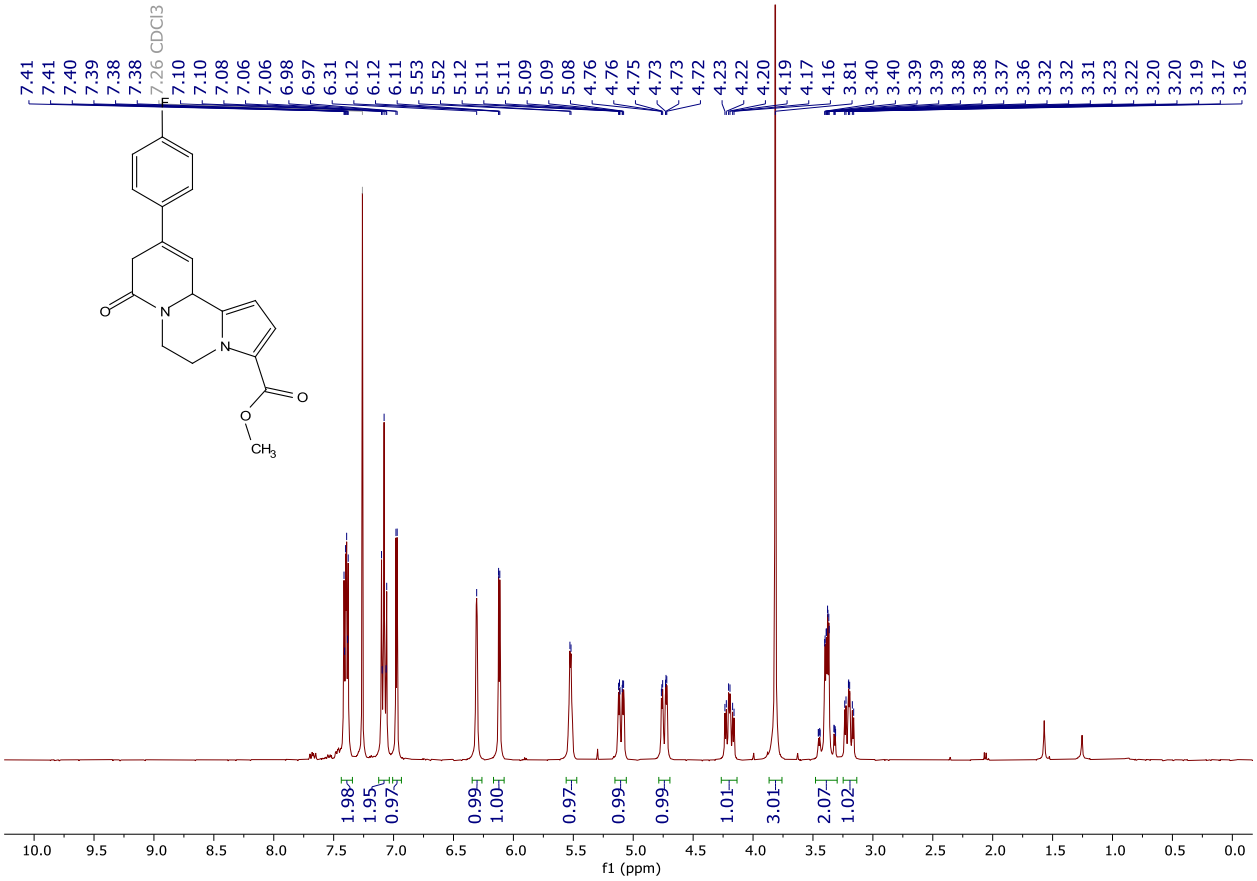


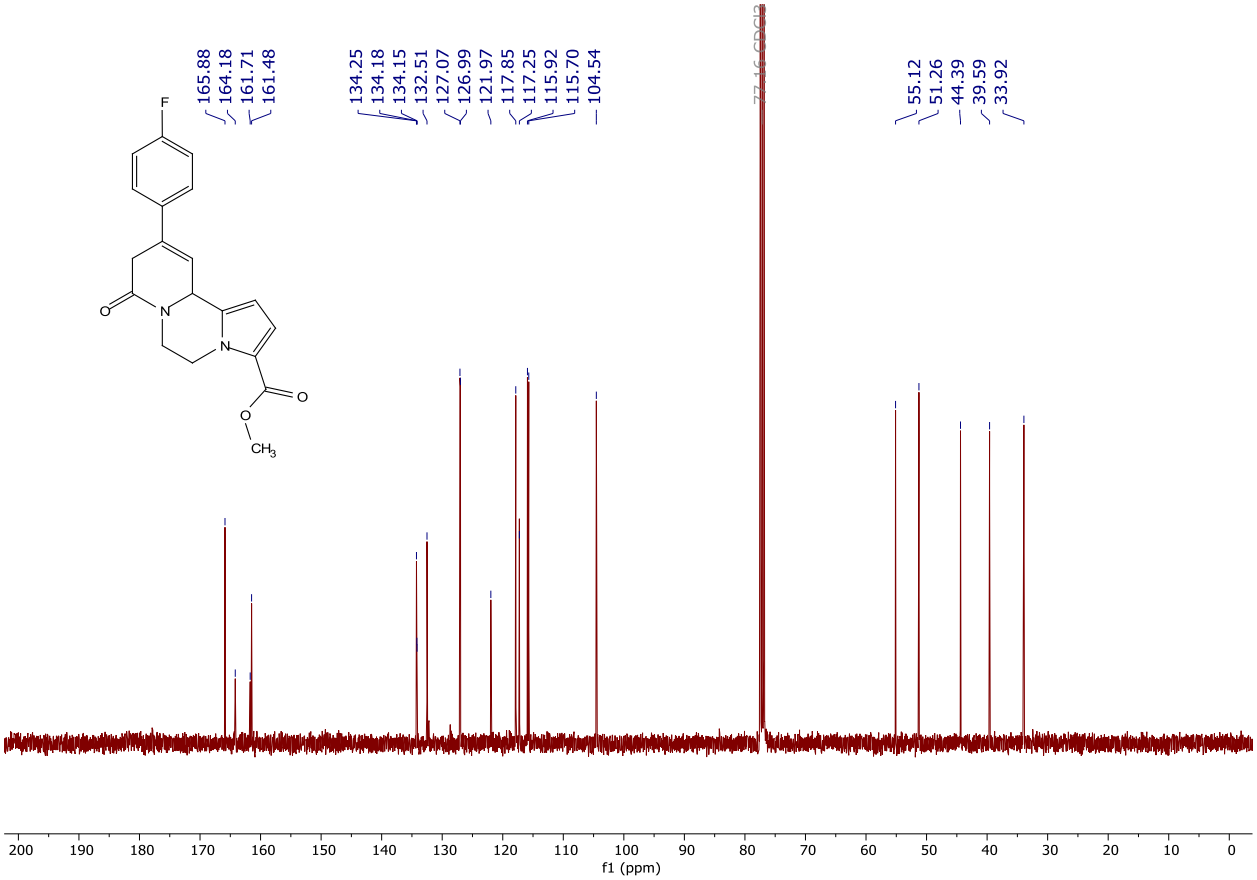
^{1}H and ^{13}C spectra of compound **8e**

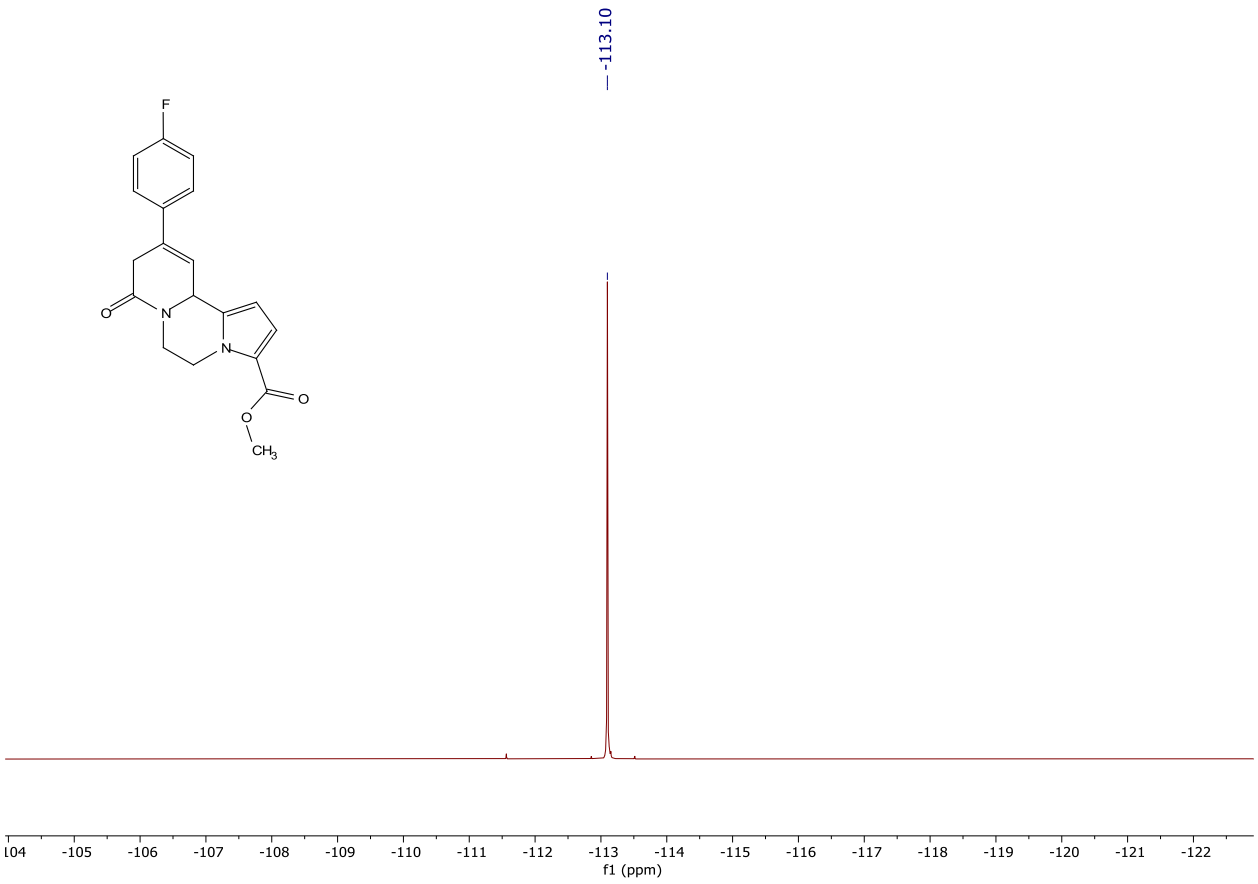




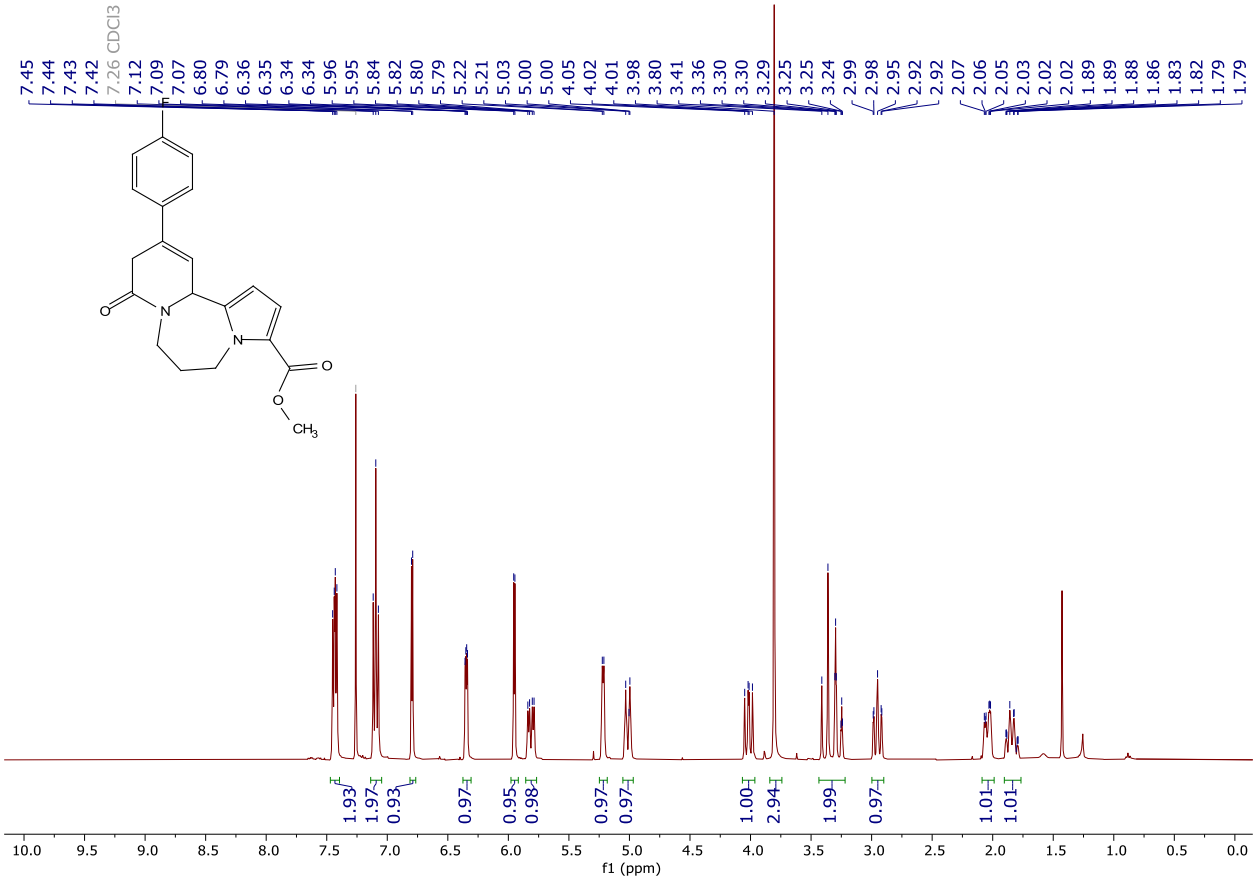
^{1}H, ^{13}C and ^{19}F spectra of compound **10a**

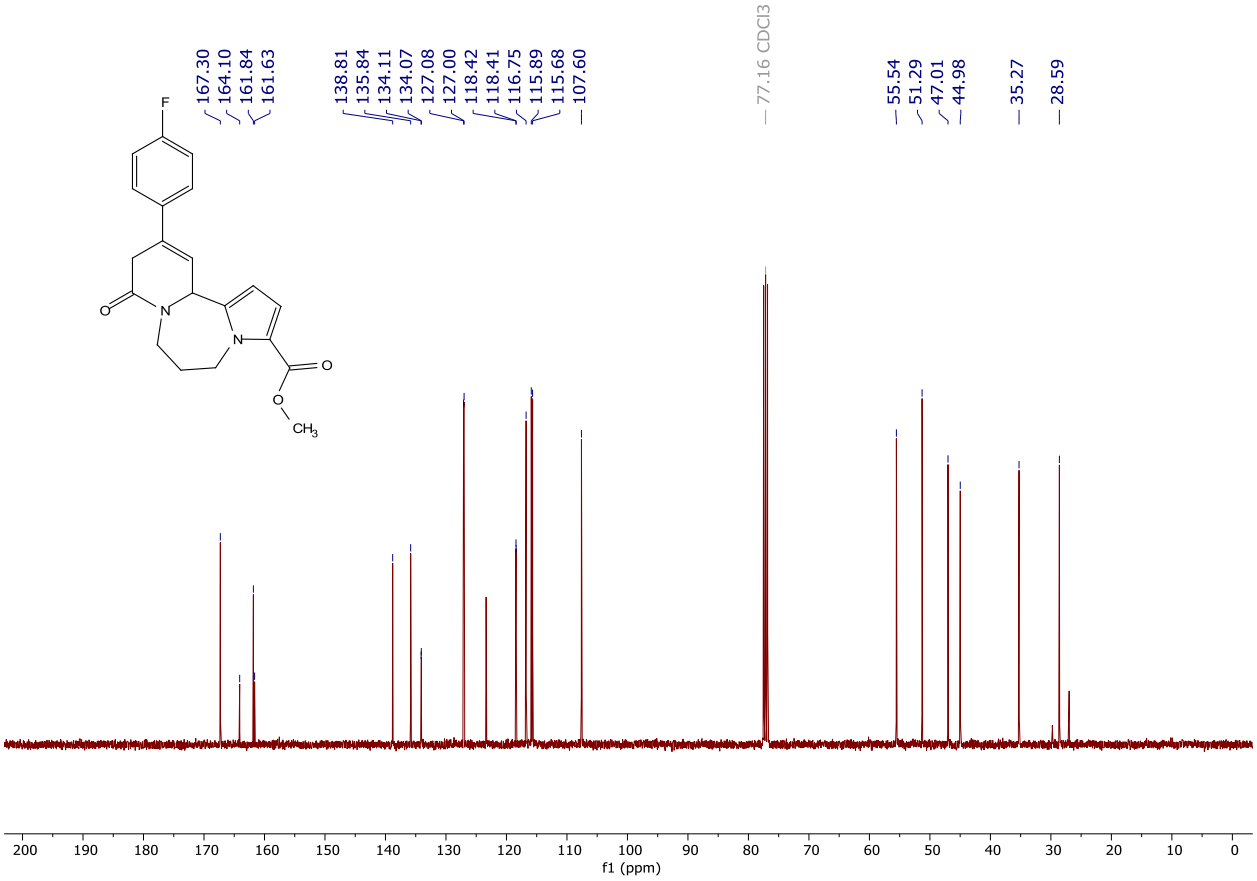


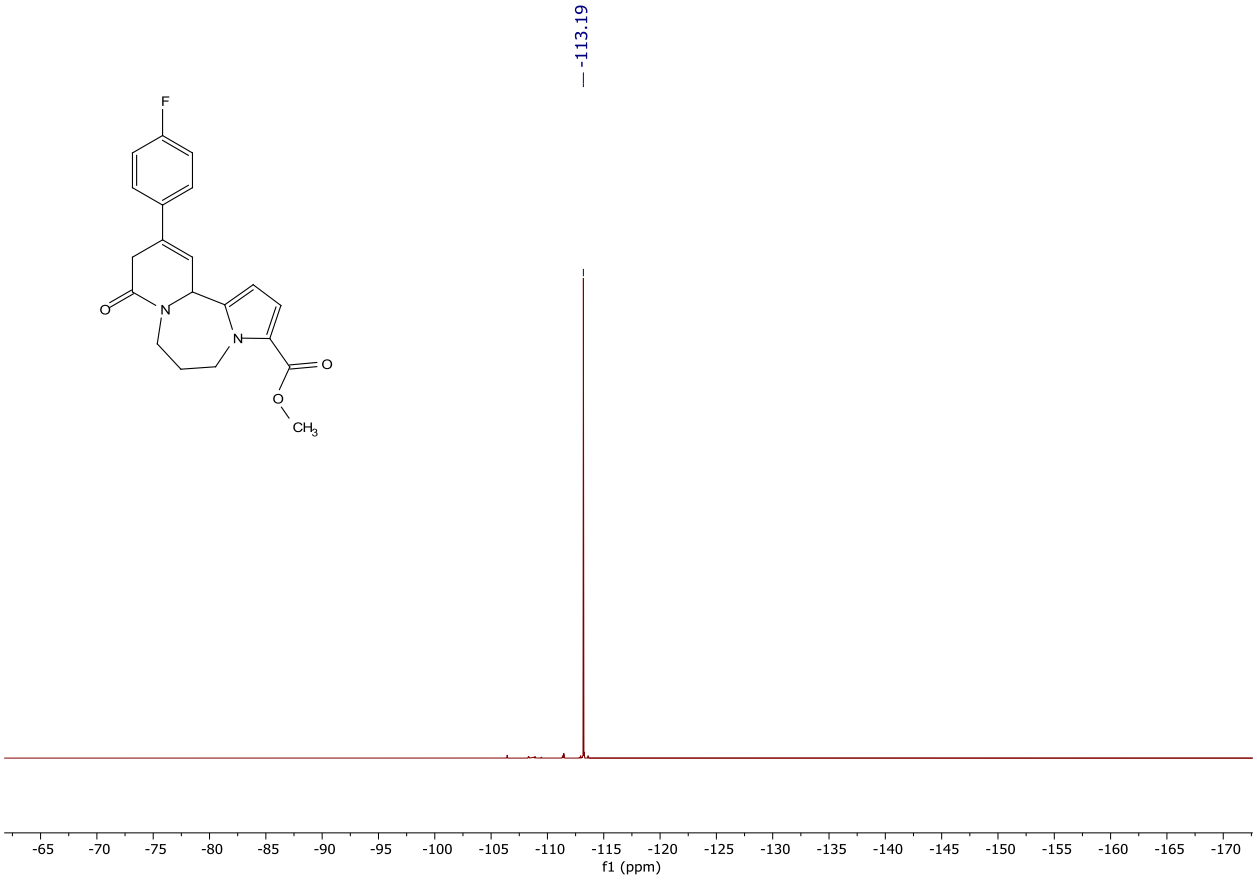



-113.10
F
O
N
N
O
O
CH3
-104
-105
-106
-107
-108
-109
-110
-111
-112
-113
-114
-115
-116
-117
-118
-119
-120
-121
-122
f1 (ppm)

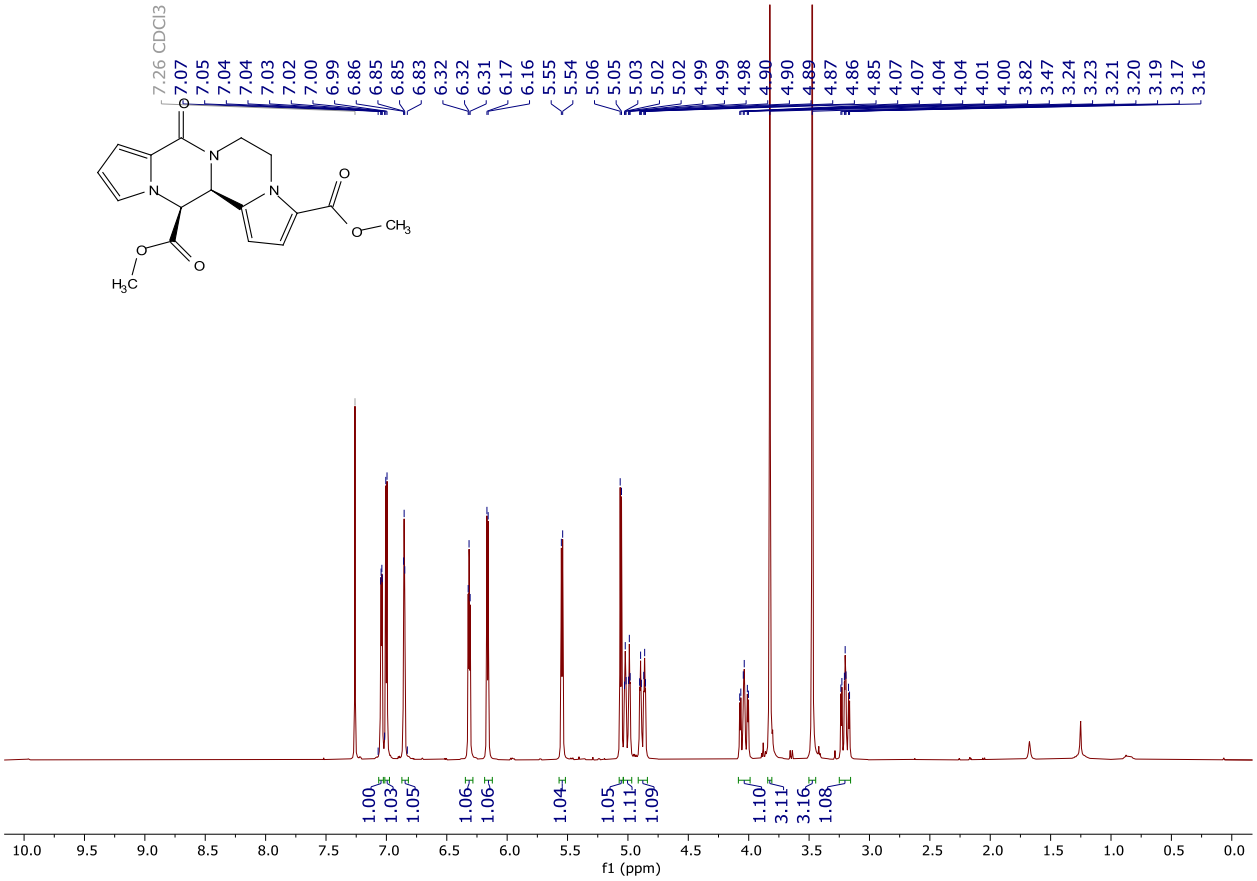
^{1}H, ^{13}C and ^{19}F spectra of compound **10b**

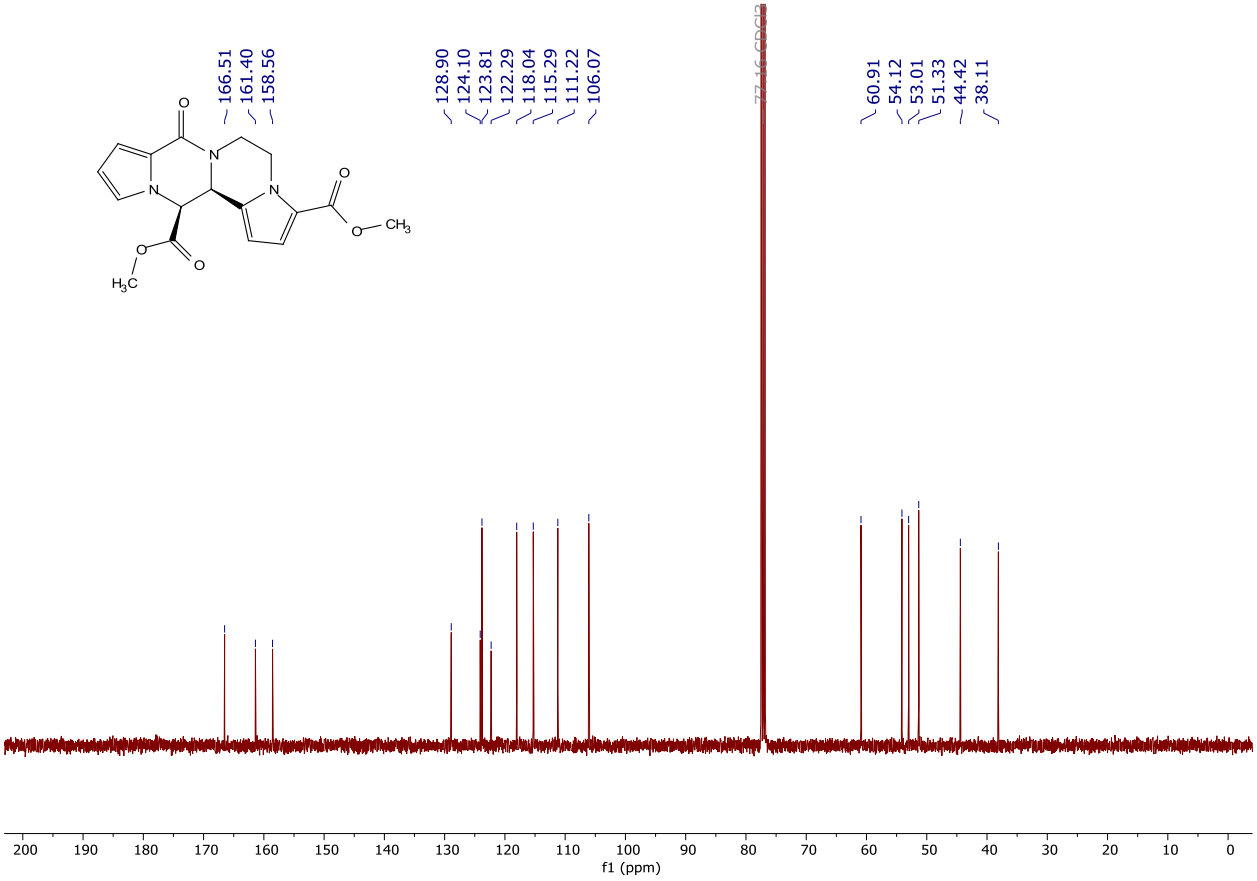




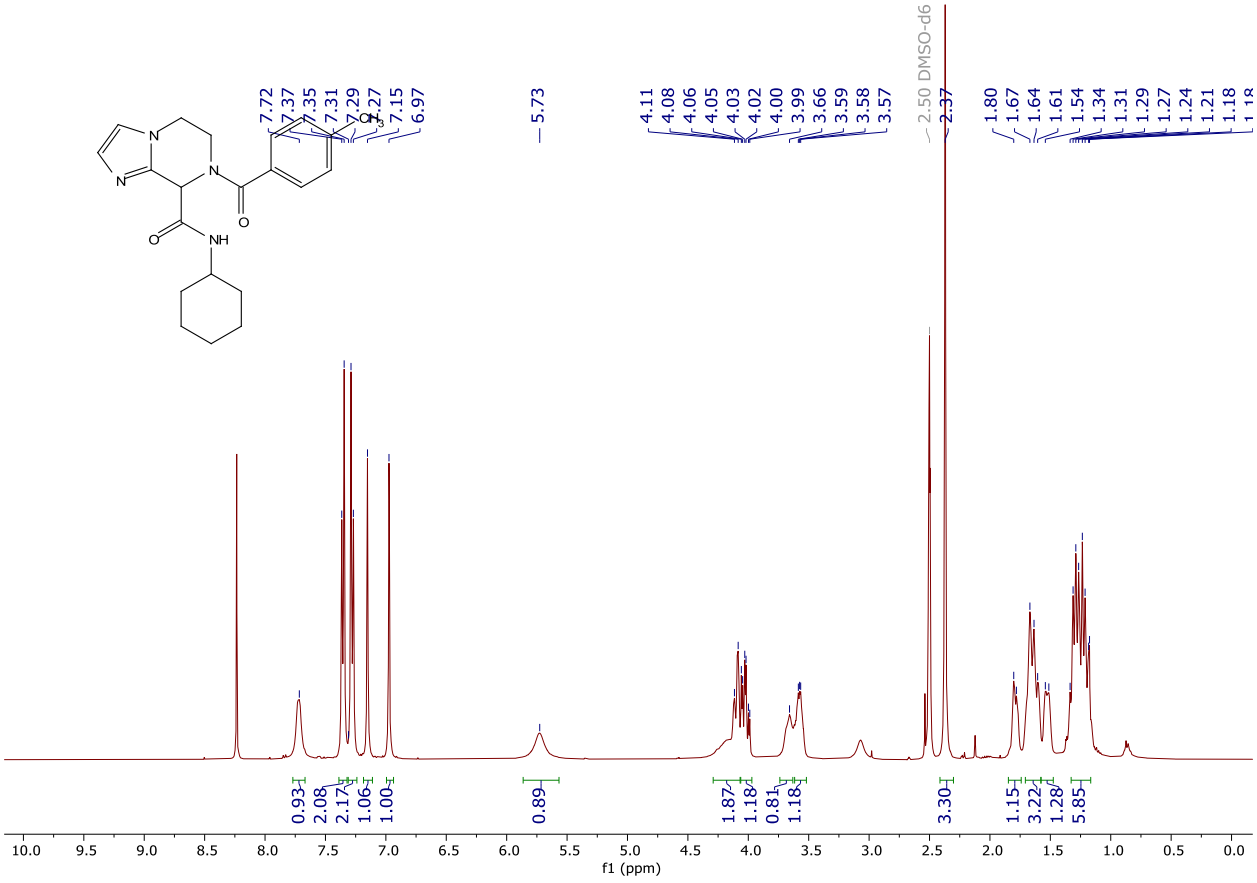

-113.19
F
O
N
N
O
O
CH3
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
-165
-170
f1 (ppm)

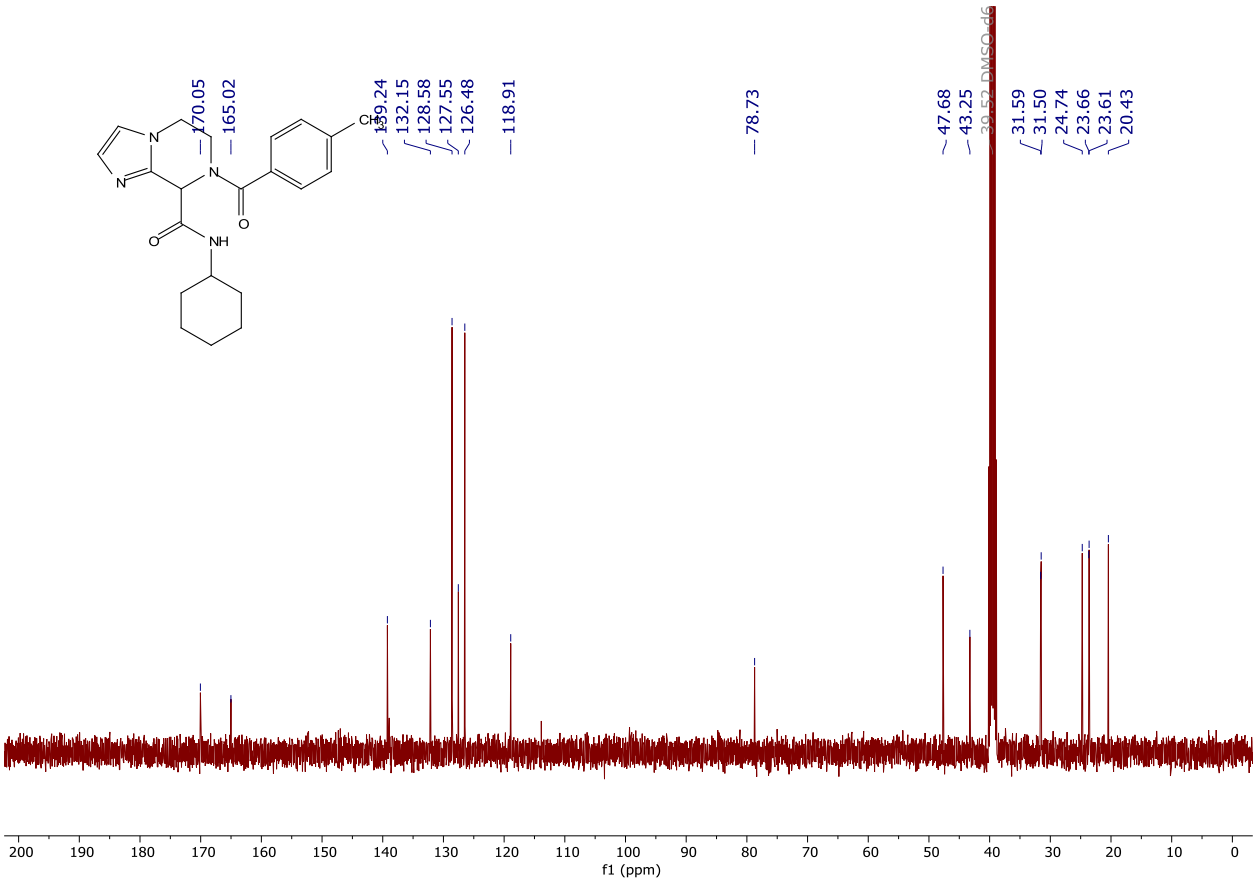
^{1}H and ^{13}C spectra of compound **12**



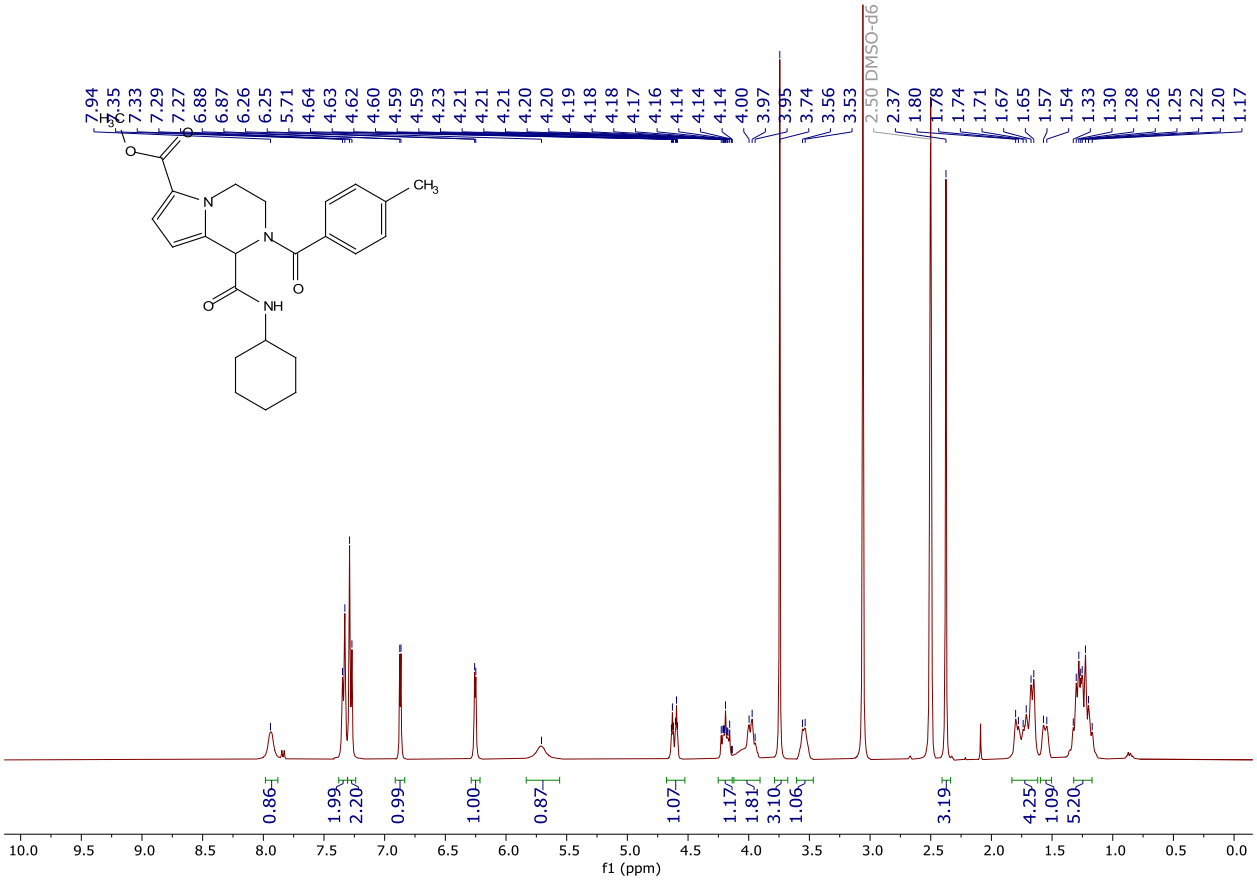


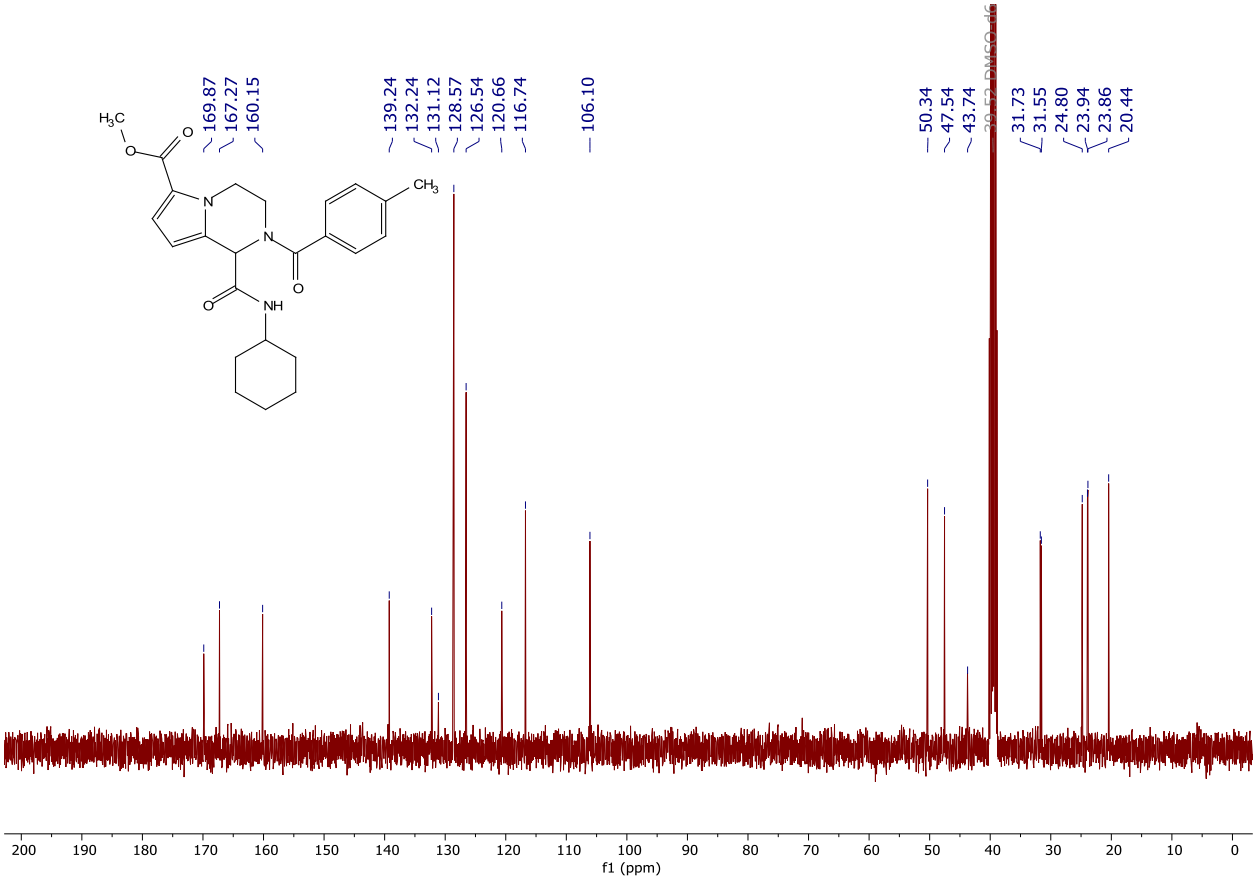
^{1}H and ^{13}C spectra of compound **13a**





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





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