Supporting Information

One-pot synthesis of diverse *N,N'*-disubstituted guanidines from *N*-chlorophthalimide, isocyanides and amines via *N*-phthaloylguanidines

András Demjén,[a,b] Anikó Angyal,[a,b] János Wölfling,[b] László G. Puskás,[a] and Iván Kanizsai[a]*

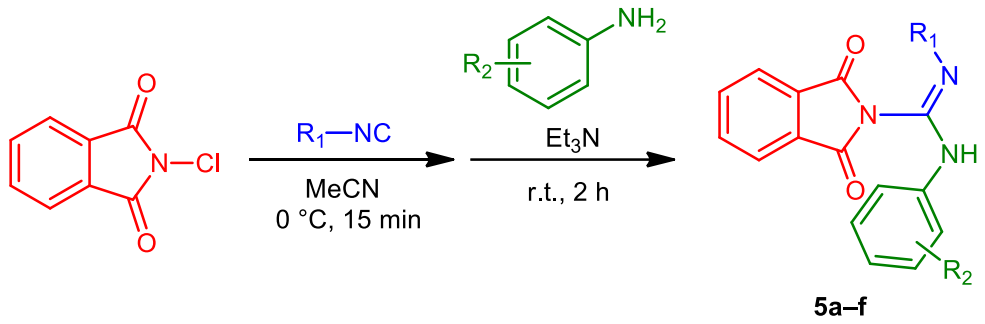
[a] AVIDIN Ltd., Alsó kikötő sor 11/D, Szeged, H-6726, Hungary
Phone: (+36)-62-202-107; e-mail: i.kanizsai@avidinbiotech.com
[b] Department of Organic Chemistry, University of Szeged, Dóm tér 8, Szeged, H-6720, Hungary

Contents

1. General information

All NMR spectra were recorded in deuterated solvents at 298 K on a Bruker Avance 500 spectrometer. All chemical shifts (δ) are reported in ppm relative to the internal standard (TMS) or the residual solvent signal. In case of ^{19}F-NMR, hexafluorobenzene was used as reference compound. The following abbreviations are used for NMR multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad, with coupling constants (*J*) given in Hertz (Hz). Melting points were determined on a Stuart SMP10 apparatus and are uncorrected. Optical rotation was measured on an Optical Activity AA-55 polarimeter (Optical Activity Ltd.). $[\alpha]_D$ value is given in 10^{-1} deg cm^2 g^{-1} and the concentration in the parenthesis is given in g 100^{-1} mL^{-1}. HPLC-MS analysis was performed on an Agilent 1200 Series equipment with a Waters SQ detector (ESI, operated in positive mode) with Luna C18(2) column (100 Å, 10 μm, 250 x 4.6 mm, Phenomenex). HRMS spectra were recorded on a Thermo Scientific Q Exactive Plus mass spectrometer using HESI ion source. Samples (5 μL from 1 μg/ml solution) were injected to the MS using flow injection method (200 μL/min, water:MeCN 1:1, 0.1% TFA). TLC was performed on aluminum sheets coated with silica gel 60 F_{254}. (Merck, 1.05554). Visualization was done under UV light (254 nm) or by using potassium permanganate dip or Dragendorff's reagent. Column chromatography was carried out using silica gel (Merck, 60 Å, 0.063–0.200 mm) or neutral alumina (Merck, 90 Å, 0.063–0.200 mm, activity stage I). Flash column chromatography was performed on a Teledyne Isco CombiFlash Rf system using RediSep Rf columns. Aromatic isocyanides (4-fluorophenyl isocyanide; 4-nitrophenyl isocyanide; 4-methoxyphenyl isocyanide; 3,4,5-trimethoxyphenyl isocyanide) were obtained according to a known procedure.[1] All other reagents and solvents were commercially available and were used without further purification.

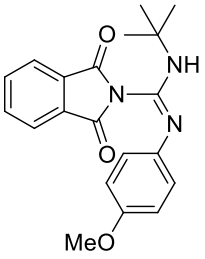
2. Synthesis and analytical data of *N*-phthaloylguanidines 5a–f



General remarks

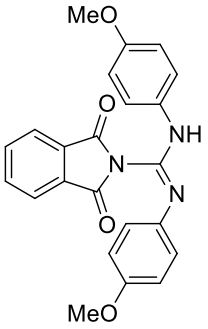
- Application of methanol or ethanol in any phase of the isolation procedure are not tolerated. (Ring-opened products were observed).
- Each product required individual conditions for column chromatography. (Various combinations of mobile/stationary phases resulted in no or unsatisfying amount of the corresponding *N*-phthaloylguanidine, probably due to strong or irreversible binding to the solid phase).
- In order to evaluate the identification of *N*-phthaloylguanidines, performing two TLCs with different conditions (eg. silica gel, hexane:EtOAc and toluene:MeCN) simultaneously are recommended. Visualization of TLC by Dragendorff's reagent is also advised (products result in orange spots).

_N_-(*tert*-Butyl)-_N'_-(4-methoxyphenyl)-1,3-dioxoisoindoline-2-carboximidamide (5a)



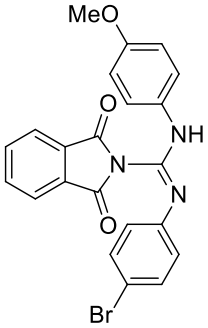
To a cooled suspension of *N*-chlorophthalimide (1.0 mmol, 182 mg) in anhydrous acetonitrile (2 mL) *tert*-butyl isocyanide (1.1 mmol, 124 µL) was added and stirred at 0 °C for 15 min. Then triethylamine (1.0 mmol, 140 µL) and subsequently *p*-anisidine (1.2 mmol, 148 mg) was added and the reaction mixture was allowed to warm to room temperature. After stirring for 2 h, the reaction mixture was concentrated in vacuo and purified by column chromatography on neutral alumina (THF:cyclohexane, 0:100–10:90 gradient) to afford pure **5a** (240 mg, 68%). Light yellow solid, m.p. 147–148 °C; R_f = 0.44 (hexane:EtOAc = 2:1), R_f = 0.47 (toluene:MeCN = 9:1); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.80 (s, 4H), 6.93 (s, 1H), 6.62 (d, *J* = 8.3 Hz, 2H), 6.55 (d, *J* = 8.3 Hz, 2H), 3.55 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.5, 154.5, 142.0, 136.5, 134.8, 131.0, 123.5, 121.8, 113.7, 54.9, 51.0, 28.1; HRMS (ESI) m/z calculated for $C_{20}H_{22}N_3O_3$ $[M+H]^+$ 352.1661, found 352.1659.

***N*,*N*'-Bis(4-methoxyphenyl)-1,3-dioxoisoindoline-2-carboximidamide (5b)**



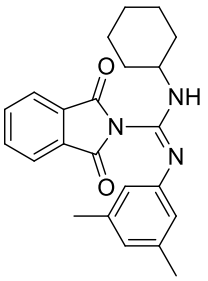
To a cooled suspension of *N*-chlorophthalimide (1.0 mmol, 182 mg) in anhydrous acetonitrile (2 mL) 4-methoxyphenyl isocyanide (1.1 mmol, 146 mg) was added and stirred at 0 °C for 15 min. Then triethylamine (1.0 mmol, 140 µL) and subsequently *p*-anisidine (1.2 mmol, 148 mg) was added and the reaction mixture was allowed to warm to room temperature. After stirring for 2 h, the reaction mixture was poured into aqueous HCl solution (30 mL, 0.5 M) and extracted with chloroform (3 x 50 mL). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone:hexane, 1:30–1:5 gradient) to afford pure **5b** (125 mg, 31%). Light yellow solid, m.p. 156–157 °C; R_f = 0.21 (hexane:EtOAc = 2:1), R_f = 0.32 (toluene:MeCN = 9:1); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.92 – 7.83 (m, 4H), 7.65 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 6.65 (d, *J* = 8.5 Hz, 2H), 3.72 (s, 3H), 3.58 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.4, 155.1, 154.9, 140.8, 135.3, 135.1, 133.0, 130.7, 124.0, 121.7, 119.8, 114.1, 113.9, 55.3, 55.0; HRMS (ESI) m/z calculated for $C_{23}H_{20}N_3O_4$ $[M+H]^+$ 402.1454, found 402.1456.

***N*'-(4-Bromophenyl)-*N*-(4-methoxyphenyl)-1,3-dioxoisoindoline-2-carboximidamide (5c)**



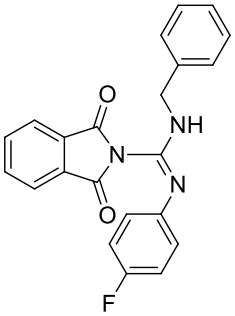
To a cooled suspension of *N*-chlorophthalimide (1.0 mmol, 182 mg) in anhydrous acetonitrile (2 mL) 4-methoxyphenyl isocyanide (1.1 mmol, 146 mg) was added and stirred at 0 °C for 15 min. Then triethylamine (1.0 mmol, 140 µL) and subsequently 4-bromoaniline (1.2 mmol, 206 mg) was added and the reaction mixture was allowed to warm to room temperature. After stirring for 2 h, the reaction mixture was concentrated in vacuo and purified by column chromatography on silica gel (acetone:hexanes, 1:30–1:10 gradient). Further purification by column chromatography on silica gel (MeCN:toluene, 0:100–1:50 gradient) was necessary to obtain **5c** in acceptable purity (127 mg, 28%). Pale yellow solid, m.p. 170–171 °C; R_f = 0.28 (hexane:EtOAc = 2:1), R_f = 0.42 (toluene:MeCN = 9:1); ^{1}H NMR and ^{13}C NMR spectra display signals for two tautomers in a ratio of 1:1. Chemical shifts are given for the tautomeric mixture: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.81 (s, 1H), 9.69 (s, 1H), 7.96 – 7.83 (m, 8H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.6 Hz, 2H), 6.68 – 6.61 (m, 4H), 3.72 (s, 3H), 3.58 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.3, 155.3, 155.2, 147.1, 140.3, 139.0, 135.5, 135.1, 132.5, 131.7, 131.5, 130.6, 130.6, 124.1, 123.2, 121.5, 120.3, 120.0, 115.0, 114.1, 114.0, 55.3, 55.0; HRMS (ESI) m/z calculated for $C_{22}H_{17}BrN_3O_3$ $[M+H]^+$ 450.0453, 452.0433, found 450.0452, 452.0431.

***N*-Cyclohexyl-*N*'-(3,5-dimethylphenyl)-1,3-dioxoisoindoline-2-carboximidamide (5d)**



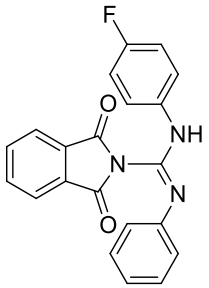
To a cooled suspension of *N*-chlorophthalimide (1.0 mmol, 182 mg) in anhydrous acetonitrile (2 mL) cyclohexyl isocyanide (1.1 mmol, 138 μL) was added and stirred at 0 °C for 15 min. Then triethylamine (1.0 mmol, 140 μL) and subsequently 3,5-dimethylaniline (1.2 mmol, 150 μL) was added and the reaction mixture was allowed to warm to room temperature. After stirring for 2 h, the reaction mixture was concentrated in vacuo and purified by column chromatography on silica gel (1,4-dioxane:hexanes, 1:50–1:15 gradient) to afford pure **5d** (110 mg, 29%). White solid, m.p. 201–202 °C; R_f = 0.56 (hexane:EtOAc = 2:1), R_f = 0.52 (toluene:MeCN = 9:1); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.87 – 7.78 (m, 4H), 7.17 (d, *J* = 7.2 Hz, 1H), 6.40 (s, 1H), 6.24 (s, 2H), 3.73 – 3.59 (m, 1H), 2.01 (s, 6H), 1.99 – 1.93 (m, 2H), 1.73 – 1.64 (m, 2H), 1.59 – 1.48 (m, 1H), 1.38 – 1.15 (m, 5H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.5, 148.5, 137.2, 137.1, 135.0, 130.9, 123.7, 123.6, 119.0, 49.9, 31.5, 25.4, 24.0, 20.9; HRMS (ESI) m/z calculated for $C_{23}H_{26}N_3O_2$ $[M+H]^+$ 376.2025, found 376.2022.

***N*-Benzyl-*N*'-(4-fluorophenyl)-1,3-dioxoisoindoline-2-carboximidamide (5e)**



To a cooled suspension of *N*-chlorophthalimide (1.0 mmol, 182 mg) in anhydrous acetonitrile (2 mL) benzyl isocyanide (1.1 mmol, 134 μL) was added and stirred at 0 °C for 15 min. Then triethylamine (1.0 mmol, 140 μL) and subsequently 4-fluoroaniline (1.2 mmol, 114 μL) was added and the reaction mixture was allowed to warm to room temperature. After stirring for 2 h, the reaction mixture was concentrated in vacuo, then purification by column chromatography on silica gel (acetone:hexanes, 1:50–1:10 gradient) followed by recrystallization (n-hexane/diethyl ether mixture, overnight) afforded pure **5e** (178 mg, 48%). Grey solid, m.p. 112–114 °C; R_f = 0.44 (hexane:EtOAc = 2:1), R_f = 0.47 (toluene:MeCN = 9:1); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.92 (t, *J* = 5.7 Hz, 1H), 7.88 – 7.82 (m, 4H), 7.46 (d, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.27 (t, *J* = 7.4 Hz, 1H), 6.90 (t, *J* = 8.6 Hz, 2H), 6.67 – 6.59 (m, 2H), 4.56 (d, *J* = 5.5 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.4, 158.0 (d, *J* = 239.0 Hz), 144.7, 139.2, 138.4, 135.2, 130.8, 128.3, 127.3, 126.9, 123.8, 122.5 (d, *J* = 6.4 Hz), 115.1 (d, *J* = 22.1 Hz), 45.0; ^{19}F NMR (471 MHz, DMSO-d_6) δ -124.1; HRMS (ESI) m/z calculated for $C_{22}H_{17}FN_3O_2$ $[M+H]^+$ 374.1305, found 374.1301.

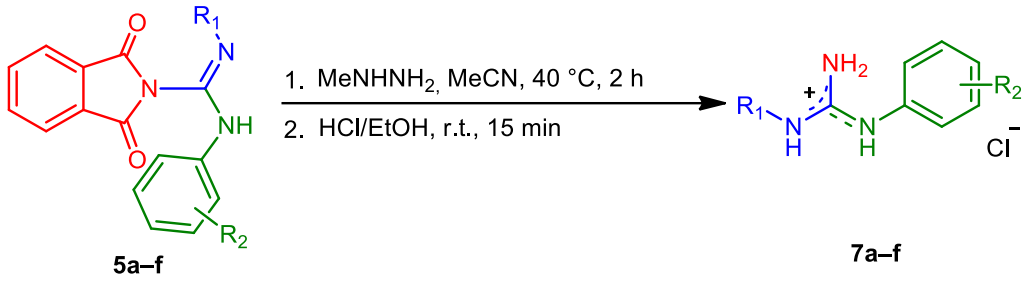
***N*-(4-Fluorophenyl)-1,3-dioxo-*N*'-phenylisoindoline-2-carboximidamide (5f)**



To a cooled suspension of *N*-chlorophthalimide (1.0 mmol, 182 mg) in anhydrous acetonitrile (2 mL) 4-fluorophenyl isocyanide (1.1 mmol, 133 mg) was added and stirred at 0 °C for 15 min. Then triethylamine (1.0 mmol, 140 μL) and subsequently aniline (1.2 mmol, 110 μL) was added and the reaction mixture was allowed to warm to room temperature. After stirring for 2 h, the reaction mixture was poured into aqueous HCl solution (30 mL, 0.5 M) and extracted with chloroform (3 x 50 mL). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by column chromatography on silica gel (acetone:hexanes, 1:30–1:5 gradient) to afford pure **5f** (109 mg, 30%). White solid, m.p. 157–158 °C; R_f = 0.40 (hexane:EtOAc = 2:1), R_f = 0.43 (toluene:MeCN = 9:1); ^{1}H NMR and ^{13}C NMR spectra display signals for two tautomers in a ratio of 1:1. Chemical shifts are given for the tautomeric mixture: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.82 (s, 1H), 9.78 (s, 1H), 7.93 – 7.85 (m, 8H), 7.78 – 7.74 (m, 2H), 7.72 (d, *J* = 8.1 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 8.7 Hz, 2H), 7.13 (t, *J* = 7.5 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.98 (t, *J* = 8.6 Hz, 2H), 6.88 (t, *J* = 7.4 Hz, 1H), 6.78 – 6.69 (m, 4H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.3, 158.4 (d, *J* = 237.8 Hz), 157.8 (d, *J* = 240.4 Hz), 147.4, 144.0, 139.4, 136.0, 135.7, 135.4, 135.2, 130.6, 129.0, 128.7, 124.1, 123.1, 123.0, 122.2 (d, *J* = 7.9 Hz), 120.8, 120.1 (d, *J* = 6.9 Hz), 118.5, 115.5 (d, *J* = 18.3 Hz), 115.4 (d, *J* = 17.9 Hz); ^{19}F NMR (471 MHz, DMSO-d_6) δ -122.2, -123.3; HRMS (ESI) m/z calculated for $C_{21}H_{15}FN_3O_2$ $[M+H]^+$ 360.1148, found 360.1146.

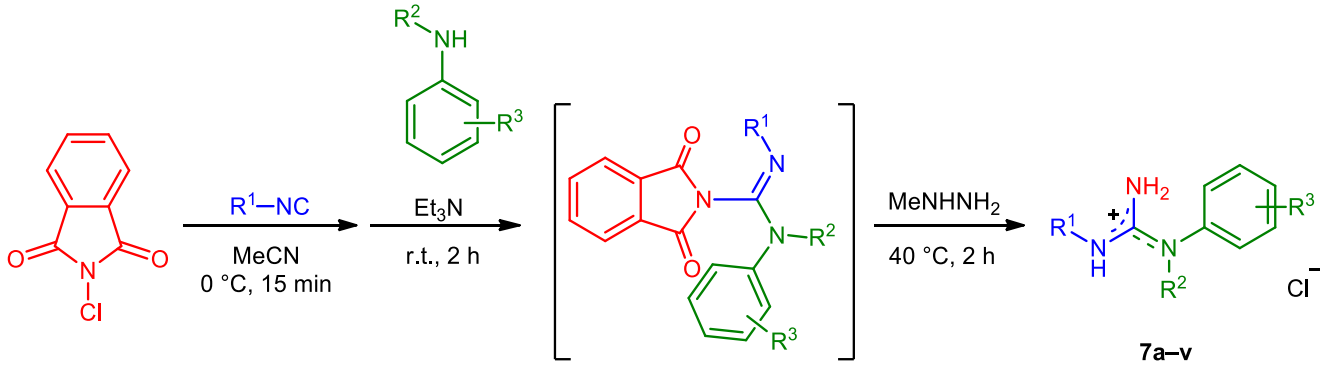
3. Synthesis and analytical data of guanidines 7a–v

*3.1. Synthesis of guanidines **7a–f** from N-phthaloylguanidines **5a–f** (General procedure A)*



Methylhydrazine (0.375 mmol, 20 μL) was added to a solution of *N*-phthaloylguanidine **5a**–**f** (0.25 mmol) in acetonitrile (0.5 mL). After stirring at 40 °C for 2 h, the reaction mixture was cooled to room temperature. Then HCl in ethanol (1 M, 0.75 mmol, 0.75 mL) was added and the stirring was continued for 15 min. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel (methanol:chloroform, 0:100–1:10 gradient) to afford pure **7a**–**f**.

*3.2. One-pot three-step synthesis of guanidines **7a–v** (General procedure B)*

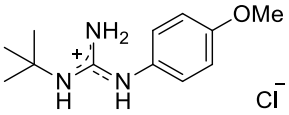


To a cooled suspension of *N*-chlorophthalimide (1.0 mmol, 182 mg) in anhydrous acetonitrile (2 mL) isocyanide (1.1 mmol) was added and stirred at 0 °C for 15 min. Then triethylamine (1.0 mmol, 140 μL) and subsequently the corresponding aniline (1.2 mmol) was added and the reaction mixture was allowed to warm to room temperature. After stirring for 2 h, methylhydrazine (1.5 mmol, 79 μL) was added, and the stirring was continued at 40 °C for 2 h. Then the reaction mixture was poured into aqueous NaOH solution (30 mL, 1 M) and extracted with chloroform (4 x 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated in vacuo until the complete removal of the solvent and triethylamine. The residue was purified by flash column chromatography on neutral alumina (RediSep Rf; EtOAc:hexanes 0:100–100:0 gradient, then eluent switch to methanol:chloroform 0:100–1:10 gradient) to afford the pure guanidine base, which was then treated with HCl in ethanol (1 M, 2–3 equiv.) and stirred at room temperature for 15 min. Finally, evaporation to dryness followed by trituration with *n*-hexane or diisopropyl ether or diethyl ether (if necessary) gave pure guanidine hydrochlorides **7a**–**v**.

*Further remarks (for the one-pot three-step synthesis of guanidines **7a–v**)*

- Application of the isolation protocol described in *General Procedure A* resulted in guanidines with triethylamine hydrochloride impurity.
- Most of the undesired products were eluted in the first stage of flash column chromatography (EtOAc:hexane). In most cases, the guanidines were eluted only in the second stage (methanol:chloroform).
- Visualization of TLC by Dragendorff's reagent is advised (products result in orange spots).
- Extensive drying at 50–60 °C was crucial (otherwise sticky solids were obtained).

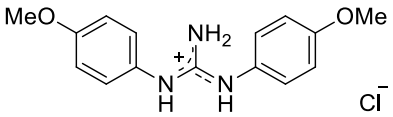
1-(*tert*-Butyl)-2-(4-methoxyphenyl)guanidine hydrochloride (7a)



According to *General procedure A*, pure **7a** was obtained as white solid (63 mg, 98%), m.p. 180 °C; R_f = 0.29 (chloroform:methanol = 9:1 + 1% AcOH).

According to *General procedure B*, pure **7a** was obtained as white solid (178 mg, 69%), m.p. 179–180 °C; R_f = 0.29 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.52 (s, 1H), 8.07 (s, 1H), 7.30 (s, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 3.75 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.9, 154.4, 128.1, 127.0, 114.8, 55.4, 51.7, 28.8; HRMS (ESI) m/z calculated for $C_{12}H_{20}N_3O$ $[M+H]^+$ 222.1606, found 222.1600.

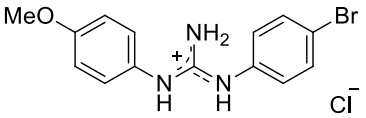
1,2-Bis(4-methoxyphenyl)guanidine hydrochloride (7b)



According to *General procedure A*, pure **7b** was obtained as white solid (72 mg, 94%), m.p. 191 °C; R_f = 0.41 (chloroform:methanol = 9:1 + 1% AcOH).

According to *General procedure B*, pure **7b** was obtained as grey solid (126 mg, 41%), m.p. 190–191 °C; R_f = 0.41 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.83 (s, 1H), 9.78 (br s, 1H), 7.61 (s, 2H), 7.21 (d, J = 8.4 Hz, 4H), 6.98 (d, J = 8.4 Hz, 4H), 3.75 (s, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.0, 155.1, 127.8, 127.0, 114.8, 55.4; HRMS (ESI) m/z calculated for $C_{15}H_{18}N_3O_2$ $[M+H]^+$ 272.1399, found 272.1396.

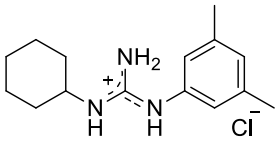
2-(4-Bromophenyl)-1-(4-methoxyphenyl)guanidine hydrochloride (7c)



According to *General procedure A*, pure **7c** was obtained as white solid (86 mg, 96%), m.p. 194–195 °C; R_f = 0.52 (chloroform:methanol = 9:1 + 1% AcOH).

According to *General procedure B*, pure **7c** was obtained as white solid (122 mg, 34%), m.p. 194–195 °C; R_f = 0.52 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.27 (s, 1H), 10.12 (s, 1H), 7.90 (s, 2H), 7.58 (d, *J* = 8.1 Hz, 2H), 7.29 – 7.18 (m, 4H), 6.97 (d, *J* = 8.3 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (126 MHz DMSO-d_6) δ 158.0, 154.6, 135.3, 132.4, 127.7, 126.7, 126.4, 118.6, 114.8, 55.5; HRMS (ESI) m/z calculated for $C_{14}H_{15}BrN_3O$ $[M+H]^+$ 320.0393, found 320.0396.

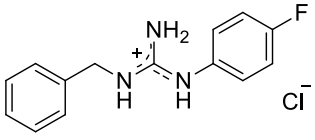
1-Cyclohexyl-2-(3,5-dimethylphenyl)guanidine hydrochloride (7d)



According to *General procedure A*, pure **7d** was obtained as white solid (67 mg, 96%), m.p. 146 °C; R_f = 0.43 (chloroform:methanol = 9:1 + 1% AcOH).

According to *General procedure B*, pure **7d** was obtained as light yellow solid (157 mg, 56%), m.p. 145–146 °C; R_f = 0.43 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.83 (s, 1H), 8.16 (s, 1H), 7.65 (s, 2H), 6.88 (s, 1H), 6.80 (s, 2H), 3.72 – 3.45 (m, 1H), 2.25 (s, 6H), 1.91 – 1.78 (m, 2H), 1.74 – 1.63 (m, 2H), 1.52 (dd, *J* = 10.9, 6.3 Hz, 1H), 1.36 – 1.18 (m, 4H), 1.19 – 1.09 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.0, 138.8, 135.5, 127.6, 49.7, 32.1, 24.8, 24.0, 20.9; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.63 (s, 1H), 6.87 (s, 1H), 6.75 (s, 2H), 3.82 (s, 1H), 6.01 (s, 6H), 1.98 – 1.88 (m, 2H), 1.69 – 1.61 (m, 2H), 1.51 – 1.44 (m, 1H), 1.43 – 1.33 (m, 2H), 1.32 – 1.21 (m, 2H), 1.18 – 1.09 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.9, 139.5, 133.6, 129.0, 122.8, 50.4, 32.2, 24.7, 23.7, 20.7; HRMS (ESI) m/z calculated for $C_{15}H_{24}N_3$ $[M+H]^+$ 246.1965, found 246.1966.

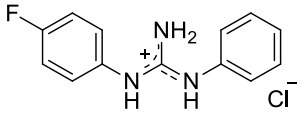
1-Benzyl-2-(4-fluorophenyl)guanidine hydrochloride (7e)



According to *General procedure A*, pure **7e** was obtained as white solid (68 mg, 97%), m.p. 58–60 °C; R_f = 0.27 (chloroform:methanol = 9:1 + 1% AcOH).

According to *General procedure B*, pure **7e** was obtained as light yellow solid (145 mg, 52%), m.p. 58–60 °C; R_f = 0.27 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.99 (s, 1H), 8.41 (s, 1H), 7.81 (s, 2H), 7.41 – 7.32 (m, 4H), 7.33 – 7.24 (m, 5H), 4.50 (d, *J* = 6.2 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.49 (d, *J* = 242.9 Hz), 155.5, 137.1, 131.6, 128.5, 127.55 (d, *J* = 7.6 Hz), 127.4, 127.3, 116.44 (d, *J* = 22.9 Hz), 44.3; ^{19}F NMR (471 MHz, DMSO-d_6) δ -117.9; HRMS (ESI) m/z calculated for $C_{14}H_{15}FN_3$ $[M+H]^+$ 244.1250, found 244.1247.

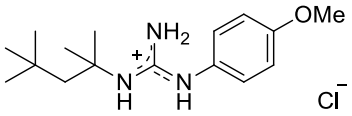
1-(4-Fluorophenyl)-2-phenylguanidine hydrochloride (7f)



According to *General procedure A*, pure **7f** was obtained as light yellow solid (64 mg, 96%), m.p. 125–126 °C; R_f = 0.38 (chloroform:methanol = 9:1 + 1% AcOH).

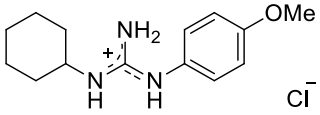
According to *General procedure B*, pure **7f** was obtained as beige solid (98 mg, 37%), m.p. 124–126 °C; R_f = 0.38 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.34 (s, 1H), 10.29 (s, 1H), 8.00 (s, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.37 – 7.31 (m, 2H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.27 – 7.21 (m, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.4 (d, *J* = 243.1 Hz), 154.5, 135. 7, 131.9, 129.6, 127.0 (d, *J* = 8.6 Hz), 126.3, 124.2, 116.34 (d, *J* = 22.7 Hz); ^{19}F NMR (471 MHz, DMSO-d_6) δ -118.2; HRMS (ESI) m/z calculated for $C_{13}H_{13}FN_3$ $[M+H]^+$ 230.1088, found 230.1089.

2-(4-Methoxyphenyl)-1-(2,4,4-trimethylpentan-2-yl)guanidine hydrochloride (7g)



According to *General procedure B*, pure **7g** was obtained as beige solid (188 mg, 60%), m.p. 160–161 °C; R_f = 0.45 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.14 (s, 1H), 7.86 (s, 1H), 7.18 (s, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.3 Hz, 2H), 3.75 (s, 3H), 1.72 (s, 2H), 1.40 (s, 6H), 1.00 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.0, 154.4, 127.9, 127.4, 114.9, 55.4, 55.2, 49.9, 31.4, 31.0, 29.8; HRMS (ESI) m/z calculated for $C_{16}H_{28}N_3O$ $[M+H]^+$ 278.2232, found 278.2229.

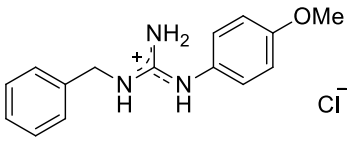
1-Cyclohexyl-2-(4-methoxyphenyl)guanidine hydrochloride (7h)



According to *General procedure B*, pure **7h** was obtained as white solid (145 mg, 51%), m.p. 145–147 °C; R_f = 0.34 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.46 (s, 1H), 7.90 (s, 1H), 7.41 (s, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 6.96 (d, *J* = 8.3 Hz, 2H), 3.73 (s, 3H), 3.58 – 3.45 (m, 1H), 1.88 – 1.77 (m, 2H), 1.73 – 1.63 (m, 2H), 1.57 – 1.48 (m, 1H), 1.31 – 1.18 (m, 4H), 1.16 – 1.08 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.9, 154.5, 127.8, 127.1,114.8, 55.4, 49.7, 32.2, 24.8, 24.1; HRMS (ESI) m/z calculated for $C_{14}H_{22}N_3O$ $[M+H]^+$ 248.1757, found 248.1758.

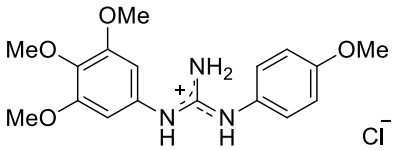
According to *General procedure C* (see below, chapter 5), pure **7h** was obtained as white solid (187 mg, 66%), m.p. 146–147 °C; R_f = 0.34 (chloroform:methanol = 9:1 + 1% AcOH).

1-Benzyl-2-(4-methoxyphenyl)guanidine hydrochloride (7i)



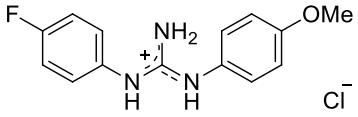
According to *General procedure B*, pure **7i** was obtained as beige oil (169 mg, 58%); R_f = 0.29 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.26 (s, 1H), 7.65 (s, 2H), 7.41 – 7.26 (m, 5H), 7.15 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 8.2 Hz, 2H), 4.47 (d, *J* = 6.0 Hz, 2H), 3.75 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.1, 155.7, 137.3, 128.6, 127.5, 127.4, 127.3, 127.2, 114.9, 55.5, 44.2; HRMS (ESI) m/z calculated for $C_{15}H_{18}N_3O$ $[M+H]^+$ 256.1450, found 256.1444.

2-(4-Methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)guanidine hydrochloride (7j)



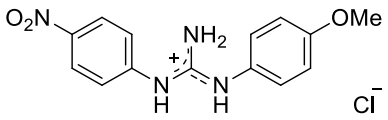
According to *General procedure B*, pure **7j** was obtained as grey solid (177 mg, 48%), m.p. 107–108 °C; R_f = 0.46 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.96 (s, 2H), 7.72 (s, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.2 Hz, 2H), 6.61 (s, 2H), 3.75 (s, 9H), 3.63 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.0, 154.8, 153.3, 136.0, 130.9, 127.8, 127.0, 114.8, 103.0, 60.0, 56.0, 55.4; HRMS (ESI) m/z calculated for $C_{17}H_{22}N_3O_4$ $[M+H]^+$ 332.1610, found 332.1607.

1-(4-Fluorophenyl)-2-(4-methoxyphenyl)guanidine hydrochloride (7k)



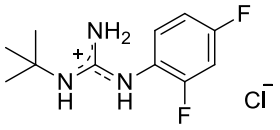
According to *General procedure B*, pure **7k** was obtained as beige solid (98 mg, 33%), m.p. 76–78 °C; R_f = 0.39 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.93 (s, 1H), 9.86 (s, 1H), 7.74 (s, 2H), 7.37 – 7.30 (m, 2H), 7.29 – 7.18 (m, 4H), 6.98 (d, *J* = 8.4 Hz, 2H), 3.75 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.43 (d, *J* = 243.0 Hz), 158.0, 155.0, 131.8, 127.7, 127.3 (d, *J* = 8.6 Hz), 126.9, 116.32 (d, *J* = 22.7 Hz), 114.8, 55.5; ^{19}F NMR (471 MHz, DMSO-d_6) δ -118.2; HRMS (ESI) m/z calculated for $C_{14}H_{25}FN_3O_1$ $[M+H]^+$ 260.1199, found 260.1195.

2-(4-Methoxyphenyl)-1-(4-nitrophenyl)guanidine hydrochloride (7l)



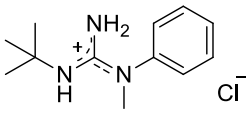
According to *General procedure B*, pure **7l** was obtained as beige solid (71 mg, 22%), m.p. 101–103 °C; R_f = 0.43 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.84 (s, 1H), 10.49 (s, 1H), 8.34 (s, 2H), 8.24 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 3.75 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.1, 154.0, 143.7, 143.4, 127.7, 126.3, 125.2, 122.5, 114.9, 55.5; HRMS (ESI) m/z calculated for $C_{14}H_{15}N_4O_3$ $[M+H]^+$ 287.1144, found 287.1141.

1-(*tert*-Butyl)-2-(2,4-difluorophenyl)guanidine hydrochloride (7m)



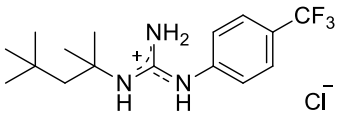
According to *General procedure B*, pure **7m** was obtained as grey solid (192 mg, 73%), m.p. 196–198 °C; R_f = 0.27 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.42 (s, 1H), 8.18 (s, 1H), 7.51 (s, 2H), 7.45 – 7.37 (m, 2H), 7.19 – 7.11 (m, 1H), 1.36 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.1 (dd, *J* = 246.5, 11.6 Hz), 157.4 (dd, *J* = 250.2, 13.3 Hz), 154.5, 130.46 (d, *J* = 10.3 Hz), 119.67 (dd, *J* = 12.5, 3.0 Hz), 112.26 (dd, *J* = 22.3, 2.5 Hz), 105.21 (t, *J* = 25.6 Hz), 51.9, 28.6; ^{19}F NMR (471 MHz, DMSO-d_6) δ -113.0, -119.4; HRMS (ESI) m/z calculated for $C_{11}H_{16}F_2N$ $[M+H]^+$ 228.1312, found 228.1307.

2-(*tert*-Butyl)-1-methyl-1-phenylguanidine hydrochloride (7n)



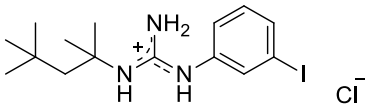
According to *General procedure B*, pure **7n** was obtained as white solid (159 mg, 66%), m.p. 120–121 °C; R_f = 0.10 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.85 (s, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.33 – 7.24 (m, 3H), 6.90 (s, 1H), 3.34 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.2, 142.6, 129.8, 127.1, 126.0, 52.8, 40.3, 28.6; HRMS (ESI) m/z calculated for $C_{12}H_{20}N_3$ $[M+H]^+$ 206.1652, found 206.1650.

2-(4-(Trifluoromethyl)phenyl)-1-(2,4,4-trimethylpentan-2-yl)guanidine hydrochloride (7o)



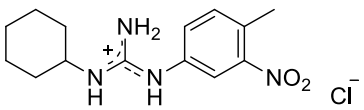
According to *General procedure B*, pure **7o** was obtained as white solid (193 mg, 55%), m.p. 159–160 °C; R_f = 0.51 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.21 (s, 1H), 8.46 (s, 1H), 7.84 (s, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 1.76 (s, 2H), 1.43 (s, 6H), 1.00 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.2, 140.9, 126.7 (q, *J* = 4.1 Hz), 125.0 (q, *J* = 34.3 Hz), 124.2 (q, *J* = 271.5 Hz), 122.7, 55.8, 50.1, 31.4, 31.0, 29.5; ^{19}F NMR (471 MHz, DMSO-d_6) δ -62.9; HRMS (ESI) m/z calculated for $C_{16}H_{25}F_2N_3$ $[M+H]^+$ 316.1995, found 316.1998.

2-(3-Iodophenyl)-1-(2,4,4-trimethylpentan-2-yl)guanidine hydrochloride (7p)



According to *General procedure B*, pure **7p** was obtained as white solid (263 mg, 64%), m.p. 155–156 °C; R_f = 0.56 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.28 (s, 1H), 7.75 – 7.39 (m, 4H), 7.16 (s, 2H), 1.71 (s, 2H), 1.38 (s, 6H), 0.97 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.5, 137.9, 134.3, 131.9, 131.5, 123.1, 95.2, 55.6, 50.2, 31.4, 31.0, 29.5; HRMS (ESI) m/z calculated for $C_{15}H_{25}IN_3$ $[M+H]^+$ 374.1088, found 374.1089.

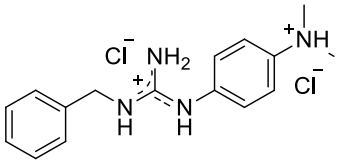
1-Cyclohexyl-2-(4-methyl-3-nitrophenyl)guanidine hydrochloride (7q)



According to *General procedure B*, pure **7q** was obtained as light beige solid (110 mg, 35%), m.p. 201–203 °C; R_f = 0.37 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.22 (s, 1H), 8.30 (s, 1H), 7.97 (s, 2H), 7.83 (s, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 3.73 – 3.53 (m, 1H), 1.89 – 1.80 (m, 2H), 1.73 – 1.64 (m, 2H), 1.57 – 1.50 (m, 1H), 1.35 – 1.19 (m, 4H), 1.18 – 1.09 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.9, 149.0, 135.2, 133.8, 50.1, 32.1, 24.8, 24.0, 19.1; ^{1}H NMR (500 MHz, MeOD-d_4) δ 7.88 (s, 1H), 7.54 – 7.44 (m, 2H), 3.62 – 3.46 (m, 1H), 2.56 (s, 3H), 2.04 – 1.96 (m, 2H), 1.85 – 1.76 (m, 2H), 1.70 – 1.61 (m, 1H), 1.49 – 1.31 (m, 4H), 1.29 – 1.18 (m, 1H); ^{13}C

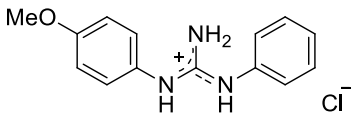
NMR (126 MHz, MeOD-d_4) δ 153.9, 149.2, 134.1, 133.6, 50.8, 31.8, 24.4, 23.9, 18.1; HRMS (ESI) m/z calculated for $C_{14}H_{21}N_4O_2$ $[M+H]^+$ 277.1659, found 277.1662.

1-Benzyl-2-(4-(dimethylamino)phenyl)guanidine hydrochloride (7r)



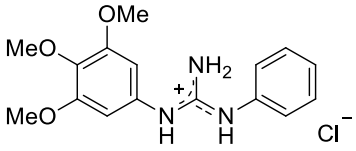
According to *General procedure B*, pure **7r** was obtained as deep purple solid (160 mg, 47%), m.p. 137–139 °C; R_f = 0.32 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.40 (s, 1H), 7.78 (s, 2H), 7.41 – 7.12 (m, 9H), 4.49 (s, 2H), 2.97 (s, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.3, 137.1, 128.6, 127.5, 127.3, 125.8, 44.4; ^{1}H NMR (500 MHz, MeOD-d_4) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.43 – 7.37 (m, 4H), 7.37 – 7.30 (m, 1H), 4.54 (s, 2H), 3.28 (s, 6H); ^{13}C NMR (126 MHz, MeOD-d_4) δ 155.0, 140.9, 135.5, 128.2, 127.3, 126.7, 125.9, 121.2, 45.0, 44.7; HRMS (ESI) m/z calculated for $C_{16}H_{21}N_4$ $[M+H]^+$ 269.1761, found 269.1764.

1-(4-Methoxyphenyl)-2-phenylguanidine hydrochloride (7s)



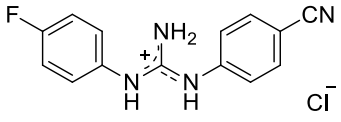
According to *General procedure B*, pure **7s** was obtained as grey solid (116 mg, 42%), m.p. 137–139 °C (Ref.[2] 139–140 °C); R_f = 0.40 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.10 (s, 1H), 9.98 (s, 1H), 7.80 (s, 2H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.30 – 7.16 (m, 5H), 6.97 (d, *J* = 8.4 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.0, 154.6, 135.7, 129.6, 127.8, 126.7, 126.2, 124.2, 114.8, 55.5; HRMS (ESI) m/z calculated for $C_{14}H_{16}N_3O$ $[M+H]^+$ 242.1288, found 242.1289.

2-Phenyl-1-(3,4,5-trimethoxyphenyl)guanidine hydrochloride (7t)



According to *General procedure B*, pure **7t** was obtained as beige solid (145 mg, 43%), m.p. 74–76 °C; R_f = 0.45 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.20 (s, 1H), 10.06 (s, 1H), 7.92 (s, 2H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.26 (t, *J* = 7.6 Hz, 1H), 6.63 (s, 2H), 3.75 (s, 6H), 3.64 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.3, 153.3, 136.0, 135.6, 130.9, 129.6, 126.3, 124.3, 102.8, 60.1, 56.0; HRMS (ESI) m/z calculated for $C_{16}H_{20}N_3O_3$ $[M+H]^+$ 302.1499, found 302.1502.

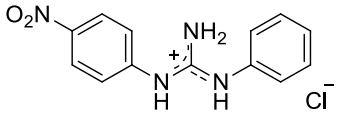
2-(4-Cyanophenyl)-1-(4-fluorophenyl)guanidine hydrochloride (7u)



According to *General procedure B*, pure **7u** was obtained as beige solid (79 mg, 27%), m.p. 186–187 °C; R_f = 0.36 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.64 (s, 1H), 10.46 (s, 1H), 8.34 (s, 2H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.41 – 7.33 (m, 2H), 7.32 – 7.22 (m, 2H);

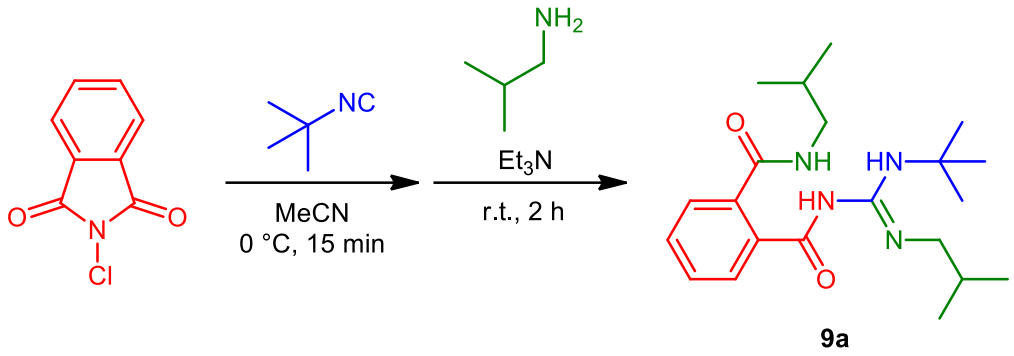
^{13}C NMR (126 MHz, DMSO-d_6) δ 160.4 (d, J = 243.4 Hz), 153.9, 141.1, 133.7, 131.7, 126.7 (d, J = 8.7 Hz), 123.1, 118.7, 116.4 (d, J = 22.8 Hz), 107.2; ^{19}F NMR (471 MHz, DMSO-d_6) δ -117.9; HRMS (ESI) m/z calculated for $C_{14}H_{12}FN_4$ $[M+H]^+$ 255.1041, found 255.1044.

1-(4-Nitrophenyl)-2-phenylguanidine hydrochloride (7v)



According to *General procedure B*, pure **7v** was obtained as yellow solid (102 mg, 35%), m.p. 113–115 °C; R_f = 0.42 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.03 (s, 1H), 10.79 (s, 1H), 8.56 (s, 2H), 8.24 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 7.42 (t, J = 7.7 Hz, 2H), 7.32 (d, J = 7.8 Hz, 2H), 7.26 (t, J = 7.4 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.6, 143.7, 143.4, 135.6, 129.6, 126.4, 125.2, 123.7, 122.4; HRMS (ESI) m/z calculated for $C_{13}H_{13}N_4O_2$ $[M+H]^+$ 257.1033, found 257.1035.

4. Synthesis and analytical data of guanidine 9a

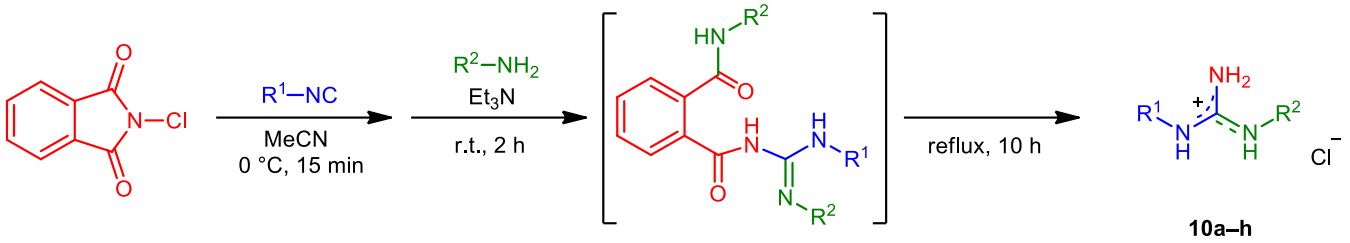


9a

***N*^{1}-(*N*-(*tert*-Butyl)-*N*'-isobutylcarbamimidoyl)-*N*^{2}-isobutylphthalamide (9a)**

To a cooled suspension of *N*-chlorophthalimide (1.0 mmol, 182 mg) in anhydrous acetonitrile (2 mL) *tert*-butyl isocyanide (1.1 mmol, 124 μL) was added and stirred at 0 °C for 15 min. Then triethylamine (1.0 mmol, 140 μL) and subsequently isobutylamine (1.2 mmol, 119 μL) was added and the reaction mixture was allowed to warm to room temperature. After stirring for 2 h, the residue was concentrated in vacuo and purified by column chromatography on silica gel (acetone:hexanes 1:10–1:4 gradient) to afford pure **9a** (142 mg, calculated for *N*-chlorophtalimide: 38%). White solid, m.p. 119 °C; R_f = 0.18 (hexane:EtOAc = 1:1); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.70 – 10.00 (two br s, 1H), 8.01 – 7.92 (m, 1H), 7.80 (s, 1H), 7.40 – 7.32 (m, 2H), 7.28 – 7.21 (m, 1H), 6.63 – 5.39 (two br s, 1H), 3.07 (br s, 2H), 2.96 (t, *J* = 6.3 Hz, 2H), 1.87 – 1.72 (m, 2H), 1.39 (s, 9H), 0.94 – 0.81 (m, 12H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.7, 139.1, 138.2, 128.8, 128.5, 128.2, 127.6, 48.0, 46.7, 29.4, 28.0, 20.4, 20.0; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.74 (m, 1H), 7.63 – 7.56 (m, 1H), 7.41 – 7.33 (m, 2H), 3.22 (d, *J* = 7.3 Hz, 2H), 2.99 – 2.79 (m, 1H), 1.95 – 1.78 (m, 2H), 1.43 (s, 9H), 0.99 (s, 6H), 0.96 – 0.91 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.4, 169.6, 138.8, 135.3, 128.7, 128.6, 128.4, 128.2, 48.3, 47.0, 29.4, 27.9, 19.9; ^{1}H NMR (500 MHz, acetone-d_6) δ 10.91 –10.32 (two br s, 1H), 7.83 (s, 1H), 7.52 – 7.42 (m, 2H), 7.41 – 7.33 (m, 2H), 5.95 – 5.19 (two br s, 1H), 3.40 – 3.00 (m, 2H), 3.15 (t, *J* = 6.3 Hz, 2H), 1.97 – 1.85 (m, 2H), 1.45 (s, 9H), 1.00 – 0.91 (m, 12H); ^{13}C NMR (126 MHz, acetone-d_6) δ 177.4, 168.9, 139.3, 136.9, 128.2, 128.1, 127.9, 127.8, 47.9, 46.7, 28.0, 19.4, 19.2; HRMS (ESI) m/z calculated for $C_{21}H_{35}N_4O_2$ $[M+H]^+$ 375.2760, found 375.2755.

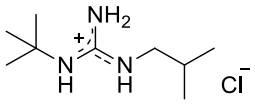
5. Synthesis and analytical data of guanidines 10a–h



General Procedure C

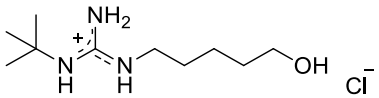
To a cooled suspension of *N*-chlorophthalimide (1.0 mmol, 182 mg) in anhydrous acetonitrile (2 mL) isocyanide (1.1 mmol) was added and stirred at 0 °C for 15 min. Then triethylamine (1.0 mmol, 140 µL) and subsequently primary amine (2.2 mmol) was added and the mixture was warmed to room temperature. After stirring for 2 h, the reaction mixture was warmed to reflux temperature and the stirring was continued for 10 h. Then the reaction mixture was poured into aqueous NaOH solution (30 mL, 1 M) and extracted with chloroform (4 x 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated in vacuo until the complete removal of the solvent and triethylamine. The residue was purified by flash column chromatography on neutral alumina (RediSep Rf; EtOAc:hexanes 0:100–100:0 gradient, then eluent switch to methanol:chloroform 0:100–1:10 gradient) to afford the pure guanidine base, which was then treated with HCl in ethanol (1 M, 2–3 equiv.) and stirred at room temperature for 15 min. Finally, evaporation to dryness followed by trituration with n-hexane or diisopropyl ether or diethyl ether (if necessary) gave the pure guanidine hydrochloride **10**.

2-(*tert*-Butyl)-1-isobutylguanidine hydrochloride (10a)



According to *General procedure C*, pure **10a** was obtained as grey solid (168 mg, 81%), m.p. 178–179 °C; R_f = 0.19 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.78 (s, 1H), 7.58 (t, *J* = 5.9 Hz, 1H), 7.28 (s, 2H), 2.97 (t, *J* = 6.3 Hz, 2H), 1.74 (m, *J* = 6.7 Hz, 1H), 1.30 (s, 9H), 0.87 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.1, 51.1, 48.2, 28.9, 27.7, 19.8; HRMS (ESI) m/z calculated for $C_9H_{22}N_3$ $[M+H]^+$ 172.1814, found 172.1809.

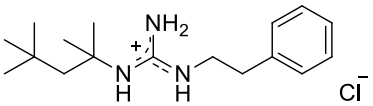
2-(*tert*-Butyl)-1-(5-hydroxypentyl)guanidine hydrochloride (10b)



According to *General procedure C*, pure **10b** was obtained as beige oil (190 mg, 80%); R_f = 0.07 (chloroform:methanol = 9:1 + 1% AcOH); 1H NMR (500 MHz, DMSO-*d6*) δ 7.53 (s, 1H), 7.35 (s, 1H), 7.23 (s, 2H), 3.40 – 3.31 (m, 2H), 3.15 – 3.06 (m, 2H), 1.47 – 1.35 (m, 4H), 1.28 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.9, 60.5, 51.1, 41.0, 32.0, 28.9, 28.3, 22.6; ^{1}H NMR (500 MHz, MeOD-d_4) δ 3.57 (t, *J* = 6.4 Hz,

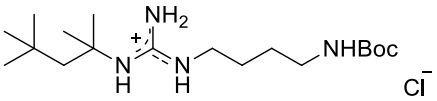
2H), 3.21 (t, *J* = 7.2 Hz, 2H), 1.67 – 1.51 (m, 4H), 1.49 – 1.40 (m, 2H), 1.40 (s, 9H); HRMS (ESI) m/z calculated for $C_{10}H_{24}N_3O$ $[M+H]^+$ 202.1919, found 202.1910.

1-Phenethyl-2-(2,4,4-trimethylpentan-2-yl)guanidine hydrochloride (10c)



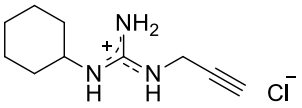
According to *General procedure C*, pure **10c** was obtained as white solid (225 mg, 72%), m.p. 136–137 °C; R_f = 0.35 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.75 (s, 1H), 7.43 (s, 1H), 7.32 (s, 2H), 7.30 – 7.25 (m, 4H), 7.23 – 7.17 (m, 1H), 3.41 (q, *J* = 6.9 Hz, 2H), 2.77 (t, *J* = 7.5 Hz, 2H), 1.63 (s, 2H), 1.30 (s, 6H), 0.93 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.8, 138.4, 128.9, 128.3, 126.4, 54.8, 50.0, 42.4, 34.7, 31.3, 31.0, 29.9; HRMS (ESI) m/z calculated for $C_{17}H_{30}N_3$ $[M+H]^+$ 276.2440, found 276.2437.

***tert*-Butyl (4-(2-(2,4,4-trimethylpentan-2-yl)guanidino)butyl)carbamate hydrochloride (10d)**



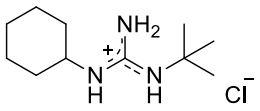
After the reaction was completed (according to *General procedure C*), the reaction mixture was concentrated in vacuo and purified by column chromatography on silica gel (methanol:chloroform 0:100–1:10 gradient) to afford pure **10d** as white solid (208 mg, 55%), m.p. 72–74 °C; R_f = 0.33 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.60 (s, 1H), 7.30 (s, 1H), 7.19 (s, 2H), 6.80 (t, *J* = 5.2 Hz, 1H), 3.12 (q, *J* = 6.2 Hz, 2H), 2.89 (q, *J* = 6.1 Hz, 2H), 1.65 (s, 2H), 1.44 – 1.37 (m, 4H), 1.35 (s, 9H), 1.33 (s, 6H), 0.94 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.6, 154.8, 77.4, 54.7, 49.8, 40.7, 31.3, 31.0, 30.0, 28.3, 26.7, 26.1; HRMS (ESI) m/z calculated for $C_{18}H_{39}N_4O_2$ $[M+H]^+$ 343.3073, found 343.3070.

2-Cyclohexyl-1-(prop-2-yn-1-yl)guanidine hydrochloride (10e)



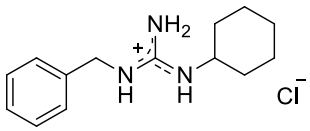
According to *General procedure C*, pure **10e** was obtained as grey solid (95 mg, 44%), m.p. 153–154 °C; R_f = 0.12 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.94 (s, 1H), 7.85 (s, 1H), 7.65 (s, 2H), 4.04 (dd, *J* = 6.1, 2.7 Hz, 2H), 3.47 – 3.39 (m, 1H), 3.37 (s, 1H), 1.81 – 1.73 (m, 2H), 1.71 – 1.59 (m, 2H), 1.58 – 1.45 (m, 1H), 1.35 – 1.02 (m, 5H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.0, 79.3, 74.86, 49.6, 32.2, 30.6, 24.8, 24.0; HRMS (ESI) m/z calculated for $C_{10}H_{18}N_3$ $[M+H]^+$ 180.1501, found 180.1498.

1-(*tert*-Butyl)-2-cyclohexylguanidine hydrochloride (10f)



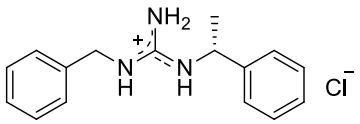
According to *General procedure C*, pure **10f** was obtained as white solid (150 mg, 64%), m.p. 247–248 °C; R_f = 0.24 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.63 (s, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.26 (s, 2H), 3.58 – 3.44 (m, 1H), 1.79 – 1.71 (m, 2H), 1.70 – 1.61 (m, 2H), 1.54 – 1.46 (m, 1H), 1.29 (s, 9H), 1.26 – 1.07 (m, 5H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.1, 51.2, 49.2, 32.2, 28.9, 24.9, 23.9; HRMS (ESI) m/z calculated for $C_{11}H_{24}N_3$ $[M+H]^+$ 198.1970, found 198.1961.

2-Benzyl-1-cyclohexylguanidine hydrochloride (10g)



According to *General procedure C*, pure **10g** was obtained as grey solid (190 mg, 71%), m.p. 225 °C; R_f = 0.24 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.62 (s, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.30 (d, *J* = 7.5 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 1H), 4.42 (d, *J* = 6.1 Hz, 2H), 3.55 – 3.45 (m, 1H), 1.81 – 1.72 (m, 2H), 1.70 – 1.61 (m, 2H), 1.55 – 1.46 (m, 1H), 1.34 – 1.04 (m, 5H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.1, 137.5, 128.5, 127.3, 127.1, 49.4, 43.9, 32.3, 24.9, 24.0; HRMS (ESI) m/z calculated for $C_{14}H_{22}N_3$ $[M+H]^+$ 232.1814, found 232.1806.

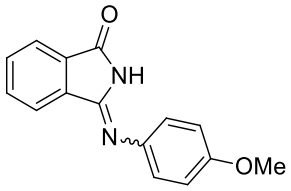
(*R*)-2-Benzyl-1-(1-phenylethyl)guanidine hydrochloride (10h)



According to *General procedure C*, pure **10h** was obtained as light beige solid (153 mg, 53%), m.p. 76–78 °C; $[\alpha]_D$ -40.2 (c 2.04 in $CHCl_3$); R_f = 0.24 (chloroform:methanol = 9:1 + 1% AcOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.48 (d, *J* = 8.2 Hz, 1H), 8.26 (t, *J* = 6.0 Hz, 1H), 7.68 (s, 2H), 7.38 – 7.30 (m, 4H), 7.32 – 7.21 (m, 4H), 7.20 – 7.13 (m, 2H), 4.93 (t, *J* = 7.4 Hz, 1H), 4.50 – 4.31 (m, 2H), 1.40 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.6, 143.0, 137.3, 128.5, 128.4, 127.3, 127.2, 127.0, 125.9, 50.4, 43.9, 23.3; HRMS (ESI) m/z calculated for $C_{16}H_{20}N_3$ $[M+H]^+$ 254.1652, found 254.1653.

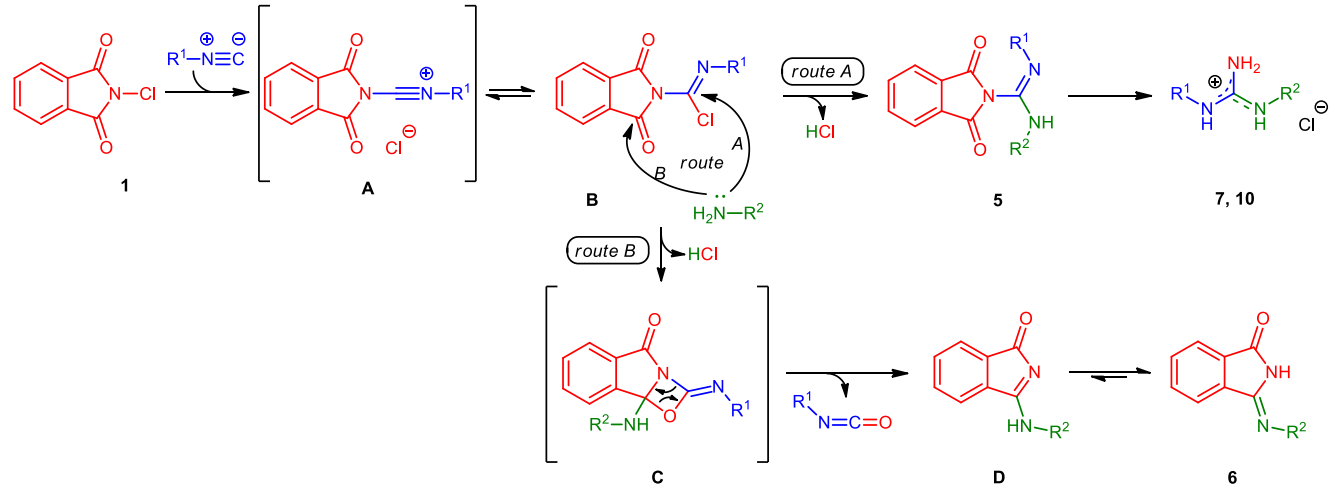
6. Synthesis and analytical data of isoindolinone 6a

3-((4-Methoxyphenyl)imino)isoindolin-1-one (6a)



To a cooled suspension of *N*-chlorophthalimide (1.0 mmol, 182 mg) in anhydrous dichloromethane (2 mL) *tert*-butyl isocyanide (1.1 mmol, 124 μL) was added and stirred at 0 °C for 15 min. Then *p*-anisidine (1.2 mmol, 148 mg) was added to the reaction mixture and allowed to warm to room temperature. After stirring for 2 h the mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetonitrile:toluene, 0:100–10:90 gradient) to afford pure **6a** (73 mg, 29%). Yellow solid, m.p. 143°C; R_f = 0.39 (hexane:EtOAc = 2:1), R_f = 0.43 (toluene:MeCN = 5:1); NMR spectra display signals for two isomers (*Z*/*E*, in a ratio of 1:0.12). *E*-*Z* isomerism of **6a** has been reported earlier.[3] Chemical shifts are given for the major (*Z*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.6 Hz, 1H), 7.94 (s, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 7.3 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 156.7, 148.1, 140.3, 135.8, 133.1, 131.7, 130.7, 123.0, 121.9, 121.9, 114.5, 55.1; HRMS (ESI) m/z calculated for $C_{15}H_{13}N_2O_2$ [M+H]+ 253.0977, found 253.0975.

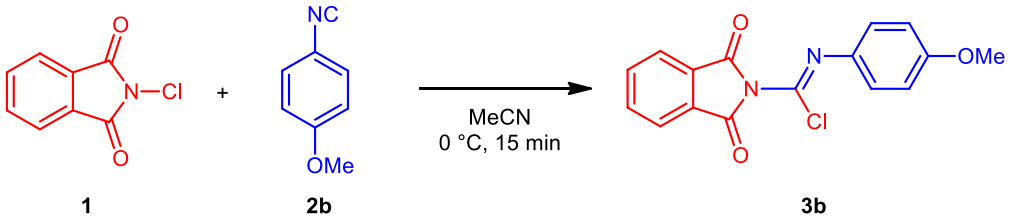
7. Mechanistic study



Scheme 1. Proposed mechanism

*7.1. Proof for the formation of intermediate **B***

A representative example of imidoyl chloride intermediate **B** was isolated and characterized to confirm the α-addition of isocyanide to *N*-chlorophthalimide (**1**) (Scheme 2, compound **3b**).



Scheme 2. Synthesis of imidoyl chloride **3b**

***N*-(4-Methoxyphenyl)-1,3-dioxoisoindoline-2-carbimidoyl chloride (3b)**

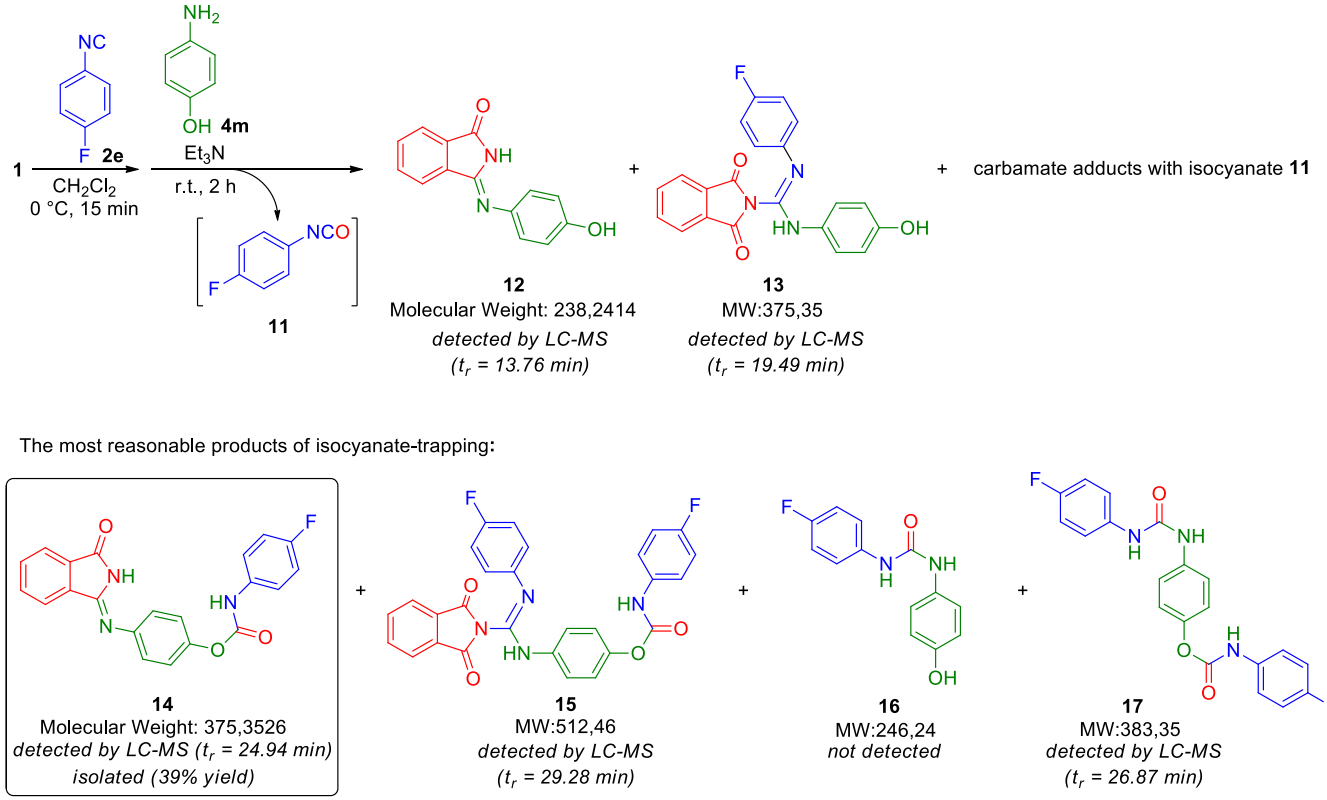
To a cooled suspension of *N*-chlorophthalimide (0.50 mmol, 91 mg) in anhydrous acetonitrile (1 mL) 4-methoxyphenyl isocyanide (0.55 mmol, 73 mg) was added and stirred at 0 °C for 15 min. The precipitated solid was filtered, washed with acetonitrile, then dried *in vacuo* to afford pure **3b** (45 mg, 29 %). White solid, m.p. 150–151 °C; R_f = 0.58 (hexane:EtOAc = 2:1); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.03 – 7.93 (m, 2H), 7.88 – 7.78 (m, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 3.84 (s, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 163.4, 157.9, 136.9, 134.7, 130.7, 124.1, 122.6, 113.8, 55.0; HRMS (ESI) m/z calculated for $C_{16}H_{12}ClN_2O_3$ $[M+H]^+$ 315.0536, 317.0507, found 315.0534, 317.0503.

7.2. Proof for the formation of isocyanate in „route B"

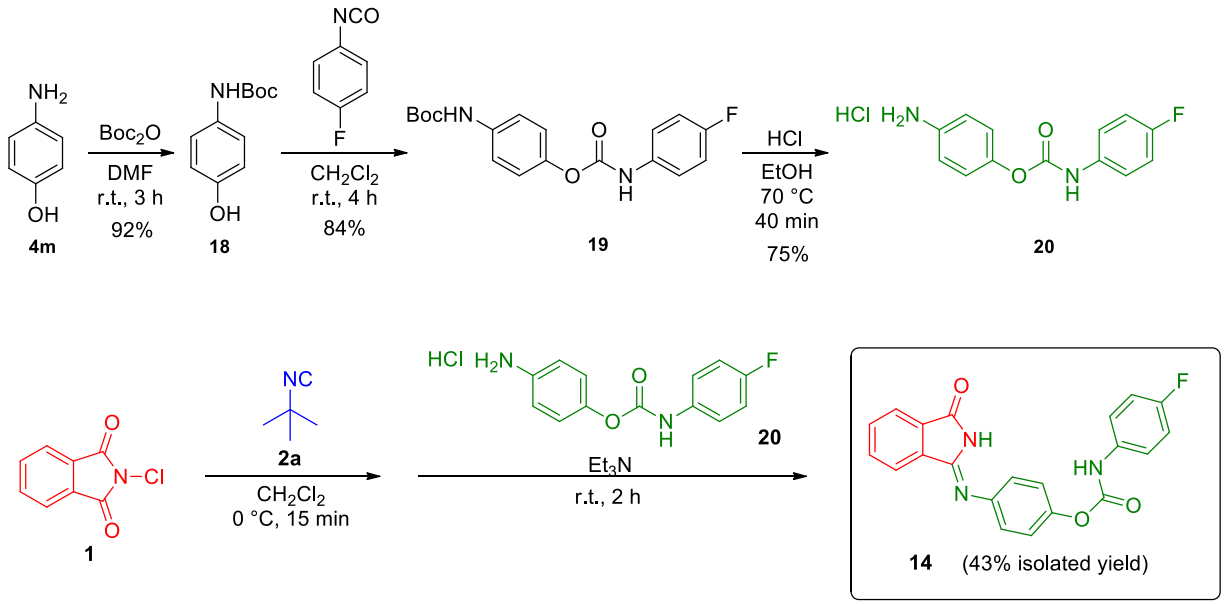
To support the proposed mechanism and confirm the formation of isocyanate by-product in "*route B"*, an experiment based on isocyanate trapping was designed (Scheme 3). When *N*-chlorophthalimide (**1**) was reacted with 4-fluorophenyl isocyanide (**2e**) and 4-aminophenol (**4m**) in the presence of triethylamine, we expected that,

- by using dichloromethane as solvent, the reaction would mainly proceed towards the formation of isocyanate **11** and isoindolinone **12** (*route B*), rather than guanidine **13** (*route A*),
- by applying 4-fluorophenyl isocyanide, a highly reactive aromatic isocyanate would be generated,
- besides products **12** and **13**, their (4-fluorophenyl)carbamate adducts would be also formed (confirming the formation of isocyanate).

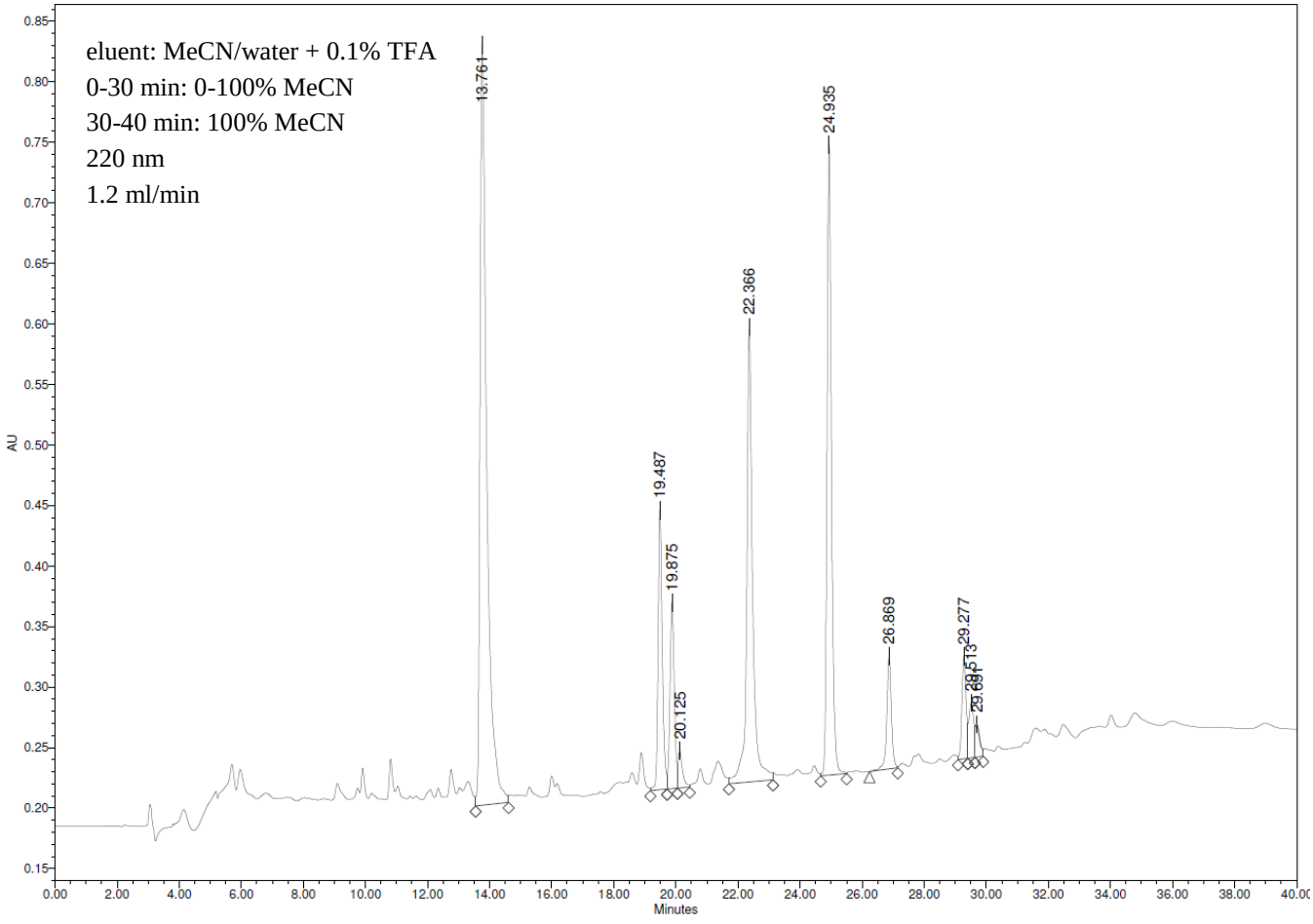
Analysis of the reaction mixture by LC-MS confirmed the presence of **12** and its isocyanate adduct **14** as main products (Scheme 5). Detection of compound **15** and **17** gave further proof for isocyanate formation. For synthetic evidence, compound **14** was isolated (39% yield) and characterized. In order to compare and validate its analytical (LC and NMR) data, product **14** was also synthesized from 4-aminophenyl (4-fluorophenyl)carbamate (**20**) (Scheme 4).

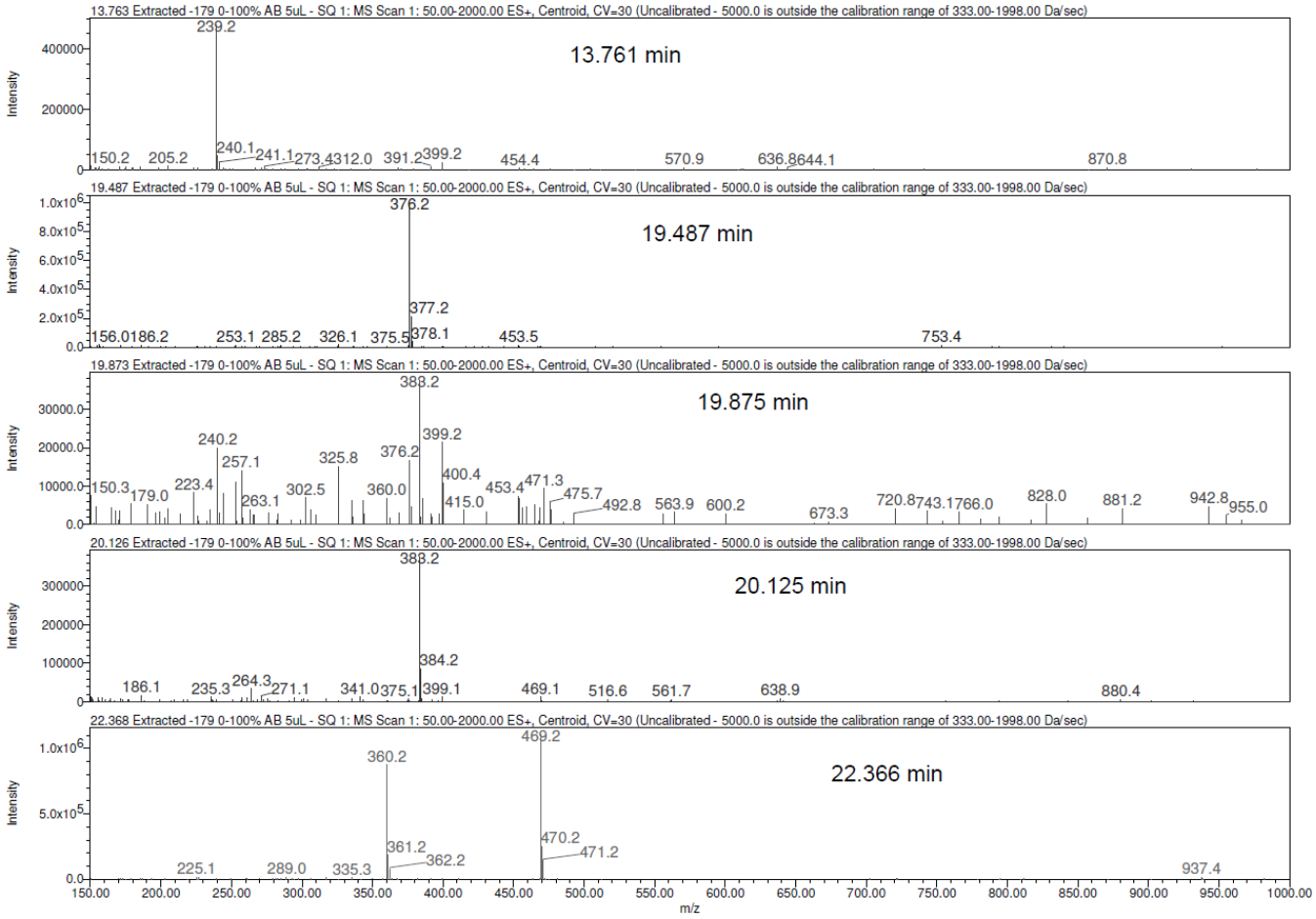


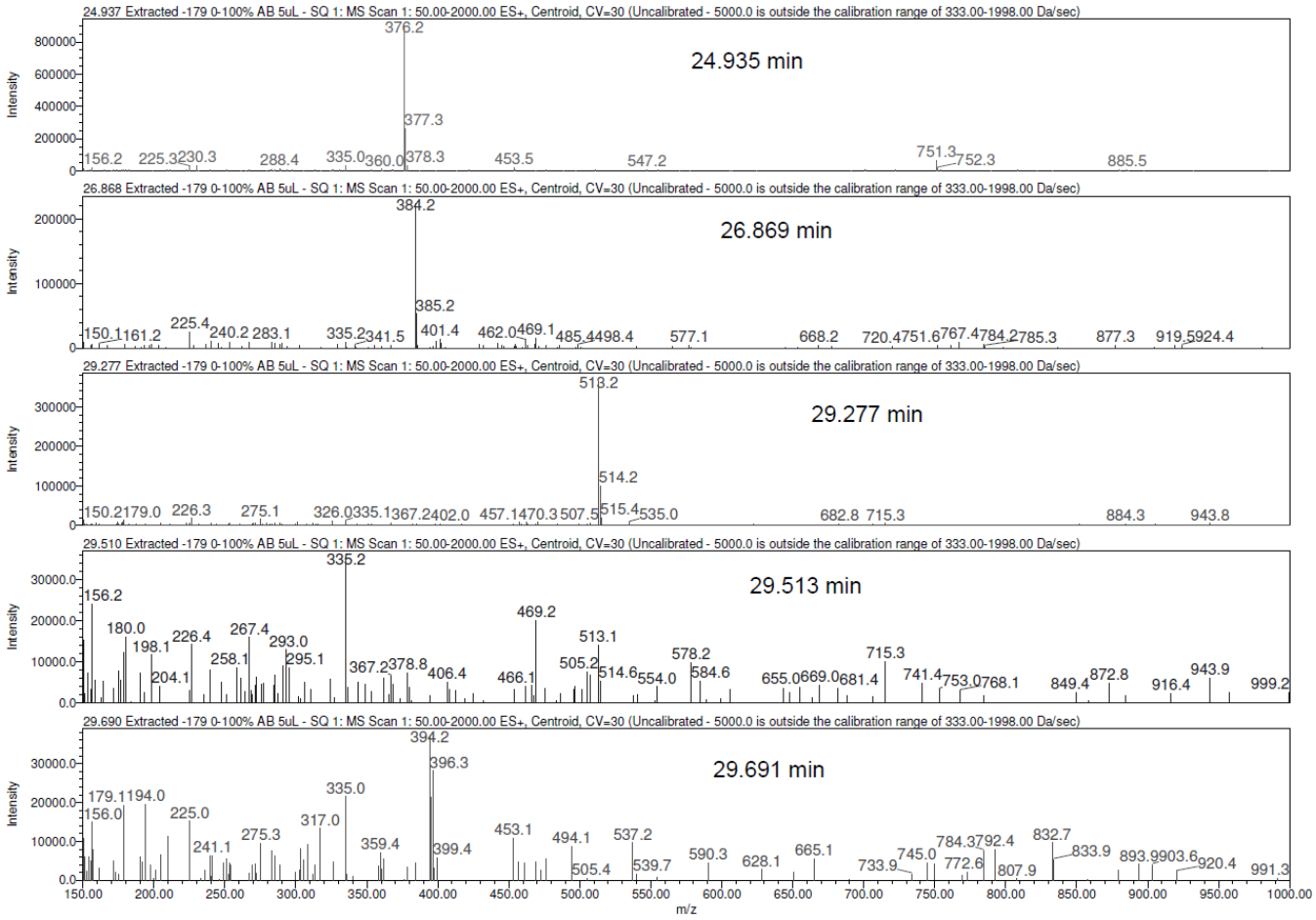
Scheme 3. The reaction designed for proving the formation of isocyanate by-product



Scheme 4. Alternative synthesis of **14**

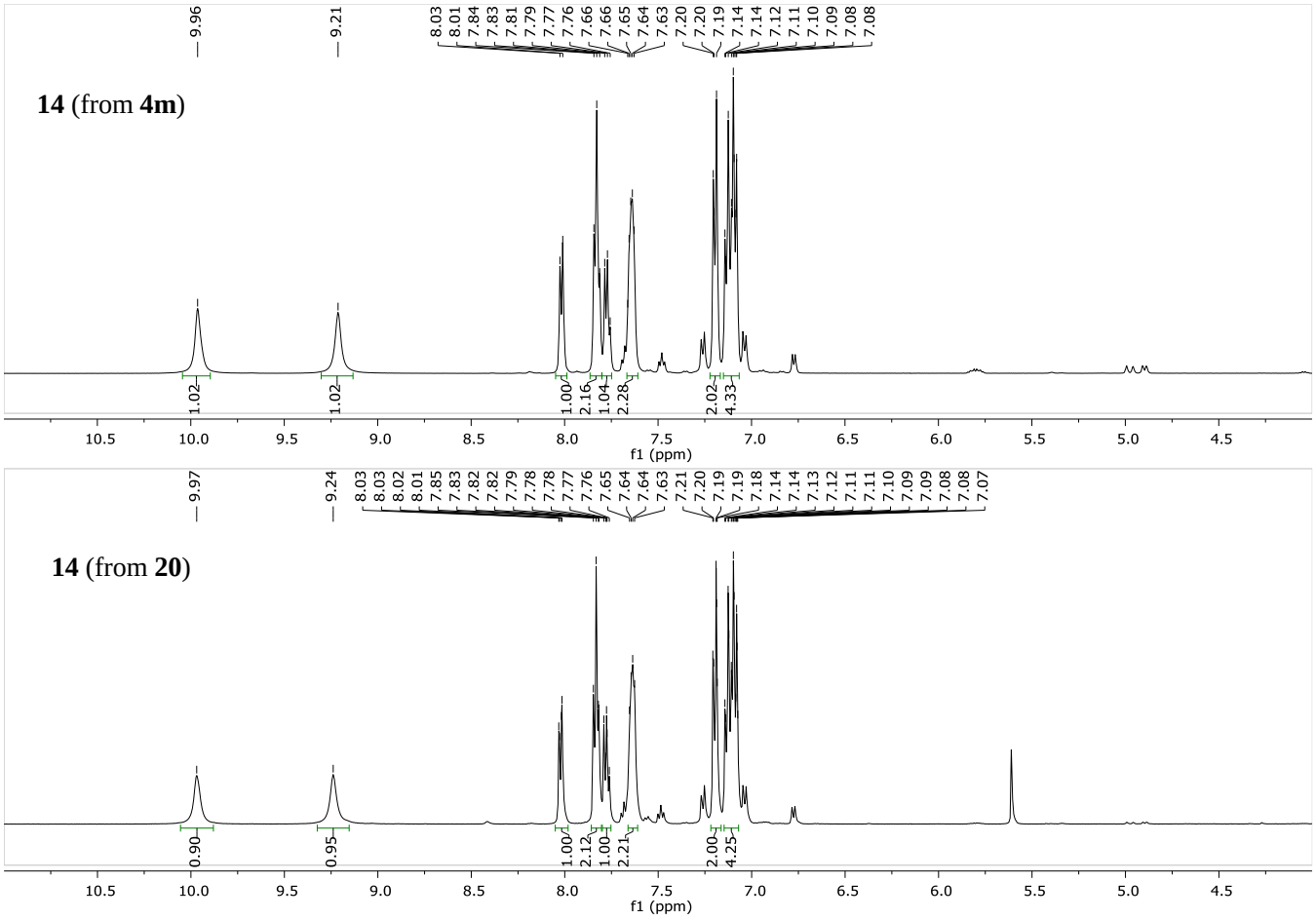



13.763 Extracted -179 0-100% AB 5uL - SQ 1: MS Scan 1: 50.00-2000.00 ES+, Centroid, CV=30 (Uncalibrated - 5000.0 is outside the calibration range of 333.00-1998.00 Da/sec)
13.761 min
19.487 Extracted -179 0-100% AB 5uL - SQ 1: MS Scan 1: 50.00-2000.00 ES+, Centroid, CV=30 (Uncalibrated - 5000.0 is outside the calibration range of 333.00-1998.00 Da/sec)
19.487 min
19.873 Extracted -179 0-100% AB 5uL - SQ 1: MS Scan 1: 50.00-2000.00 ES+, Centroid, CV=30 (Uncalibrated - 5000.0 is outside the calibration range of 333.00-1998.00 Da/sec)
19.875 min
20.126 Extracted -179 0-100% AB 5uL - SQ 1: MS Scan 1: 50.00-2000.00 ES+, Centroid, CV=30 (Uncalibrated - 5000.0 is outside the calibration range of 333.00-1998.00 Da/sec)
20.125 min
22.368 Extracted -179 0-100% AB 5uL - SQ 1: MS Scan 1: 50.00-2000.00 ES+, Centroid, CV=30 (Uncalibrated - 5000.0 is outside the calibration range of 333.00-1998.00 Da/sec)
22.366 min
Intensity
m/z


24.937 Extracted -179 0-100% AB 5uL - SQ 1: MS Scan 1: 50.00-2000.00 ES+, Centroid, CV=30 (Uncalibrated - 5000.0 is outside the calibration range of 333.00-1998.00 Da/sec)
24.935 min
26.868 Extracted -179 0-100% AB 5uL - SQ 1: MS Scan 1: 50.00-2000.00 ES+, Centroid, CV=30 (Uncalibrated - 5000.0 is outside the calibration range of 333.00-1998.00 Da/sec)
26.869 min
29.277 Extracted -179 0-100% AB 5uL - SQ 1: MS Scan 1: 50.00-2000.00 ES+, Centroid, CV=30 (Uncalibrated - 5000.0 is outside the calibration range of 333.00-1998.00 Da/sec)
29.277 min
29.510 Extracted -179 0-100% AB 5uL - SQ 1: MS Scan 1: 50.00-2000.00 ES+, Centroid, CV=30 (Uncalibrated - 5000.0 is outside the calibration range of 333.00-1998.00 Da/sec)
29.513 min
29.690 Extracted -179 0-100% AB 5uL - SQ 1: MS Scan 1: 50.00-2000.00 ES+, Centroid, CV=30 (Uncalibrated - 5000.0 is outside the calibration range of 333.00-1998.00 Da/sec)
29.691 min
Intensity
m/z

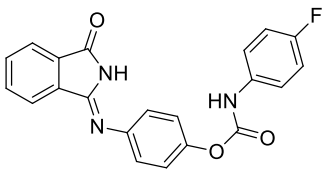
	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		13.761							9449731	36.32	628648	VV			Unknown	
2		19.487							2151746	8.27	231643	VV			Unknown	
3		19.875							1485970	5.71	154375	VV			Unknown	
4		20.125							305755	1.18	30934	VV			Unknown	
5		22.366							4957177	19.05	376439	VV			Unknown	
6		24.935							5167143	19.86	523417	VV			Unknown	
7		26.869							947141	3.64	93305	BV			Unknown	
8		29.277							785383	3.02	85076	VV			Unknown	
9		29.513							501100	1.93	45355	VV			Unknown	
10		29.691							266772	1.03	27050	VV			Unknown	

Scheme 5. LC-MS data



Scheme 6. Comparison of ^{1}H-NMR spectra (acetone-d_6) of **14** obtained by the two different synthetic strategy

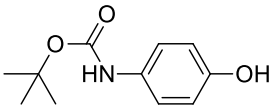
4-((3-Oxoisoindolin-1-ylidene)amino)phenyl (4-fluorophenyl)carbamate (14)



Synthesis according to Scheme 3. To a cooled suspension of *N*-chlorophthalimide (0.50 mmol, 91 mg) in anhydrous dichloromethane (1 mL) 4-fluorophenyl isocyanide (0.55 mmol, 68 mg) was added and stirred at 0 °C for 15 min. Then triethylamine (0.50 mmol, 70 µL) and subsequently 4-aminophenol (0.50 mmol, 55 mg) was added to the reaction mixture and allowed to warm to room temperature. After stirring for 2 h, sample (10 µL) was taken for LC-MS analysis, then the mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetonitrile:toluene, 0:100–10:90 gradient) to afford pure **14** (73 mg, 39%). Yellow solid, m.p. 215 – 216 °C; R_f = 0.56 (hexane:EtOAc = 1:1); R_f = 0.27 (toluene:MeCN = 5:1); ^{1}H-NMR (500 MHz, acetone-d_6) δ 9.96 (s, 1H), 9.21 (s, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.86 – 7.80 (m, 2H), 7.77 (t, *J* = 7.3 Hz, 1H), 7.67 – 7.61 (m, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.15 – 7.06 (m, 4H); ^{13}C-NMR (126 MHz, acetone-d_6) δ 168.0, 158.3 (d, *J* = 240.1 Hz), 151.6, 149.1, 147.2, 145.4, 136.3, 134.7, 132.9, 131.8, 131.2, 122.3, 122.3, 122.0, 121.7, 121.6, 120.0, 114.9 (d, *J* = 22.8 Hz); HRMS (ESI) m/z calculated for $C_{21}H_{15}FN_3O_3$ $[M+H]^+$ 376.1097, found 376.1096.

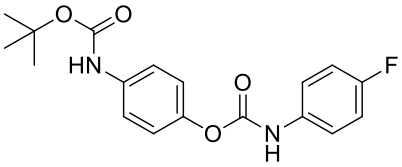
Synthesis according to Scheme 4. To a cooled suspension of *N*-chlorophthalimide (0.50 mmol, 91 mg) in anhydrous dichloromethane (1 mL) *tert*-butyl isocyanide (0.55 mmol, 62 µL) was added and stirred at 0 °C for 15 min. Then triethylamine (1.00 mmol, 140 µL) and subsequently 4-aminophenyl (4-fluorophenyl)carbamate hydrochloride (**20**) (0.50 mmol, 141.3 mg) was added to the reaction mixture and allowed to warm to room temperature. After stirring for 2 h, the mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetonitrile:toluene, 0:100–10:90 gradient) to afford pure **14** (81 mg, 43%). Yellow solid, m.p. 215 °C; R_f = 0.56 (hexane:EtOAc = 1:1); R_f = 0.27 (toluene:MeCN = 5:1); ^{1}H-NMR (500 MHz, acetone-d_6) δ 9.97 (s, 1H), 9.24 (s, 1H), 8.05 – 7.98 (m, 1H), 7.85 – 7.80 (m, 2H), 7.80 – 7.75 (m, 1H), 7.66 – 7.61 (m, 2H), 7.22 – 7.17 (m, 2H), 7.15 – 7.06 (m, 4H).

***tert*-Butyl (4-hydroxyphenyl)carbamate (18)**



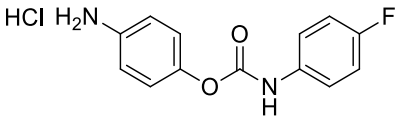
The preparation of **18** was based on a reported procedure.[4] Boc-anhydride (5.0 mmol, 1.09 g) was added to 4-aminophenol (5.0 mmol, 546 mg) in DMF (5 mL) and stirred at room temperature for 3 h. The reaction mixture was poured into water (100 mL) and the precipitated white solid was filtered off, washed with water and dried in vacuo to afford pure **18** (961 mg, 92%). White solid, m.p. 145 °C (decomp.) (Ref.[5] 146 °C).

***tert*-Butyl (4-(((4-fluorophenyl)carbamoyl)oxy)phenyl)carbamate (19)**



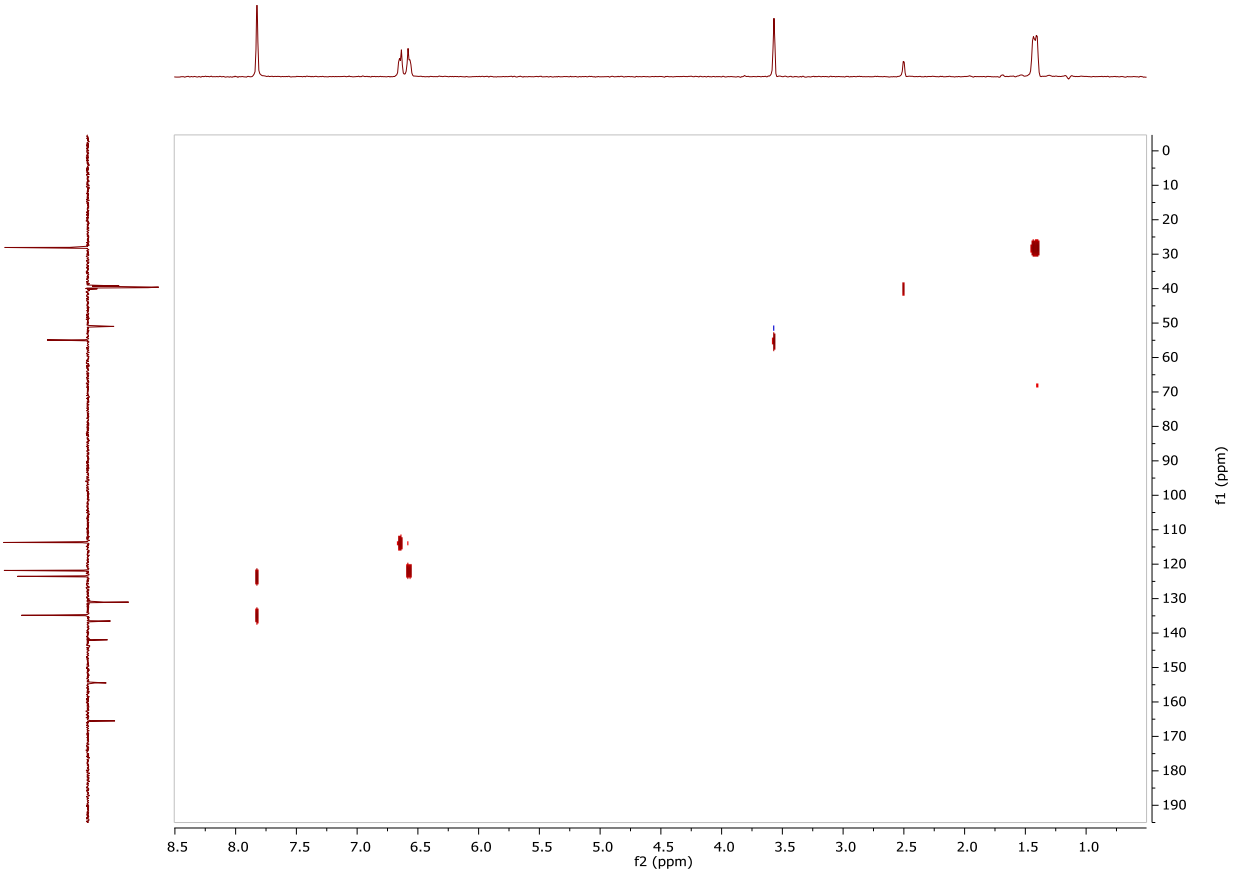
4-fluorophenyl isocyanate (2.2 mmol, 247 µL) was added dropwise to a solution of *tert*-butyl (4-hydroxyphenyl)carbamate (**18**) (2.0 mmol, 418 mg) and 4-dimethylaminopyridine (0.04 mmol, 5 mg) in dichloromethane (4 mL). After stirring the reaction mixture at room temperature for 4 h, the precipitated solid was filtered off, washed with cold dichloromethane and dried in vacuo to afford pure **19** (583 mg, 84%). White solid, m.p. 188 °C; R_f = 0.64 (hexane:EtOAc = 2:1); ^{1}H-NMR (500 MHz, DMSO-d_6) δ 10.18 (s, 1H), 9.36 (s, 1H), 7.52 – 7.41 (m, 4H), 7.14 (t, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 1.46 (s, 9H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 157.9 (d, *J* = 239.1 Hz), 152.9, 152.1, 145.1, 136.9, 135.1, 122.0, 120.1, 119.0, 115.5 (d, *J* = 22.5 Hz), 79.1, 28.1; HRMS (ESI) m/z calculated for $C_{18}H_{23}FN_3O_4$ $[M+H+NH_3]^+$ 364.1668, found 364.1671.

4-Aminophenyl (4-fluorophenyl)carbamate hydrochloride (20)

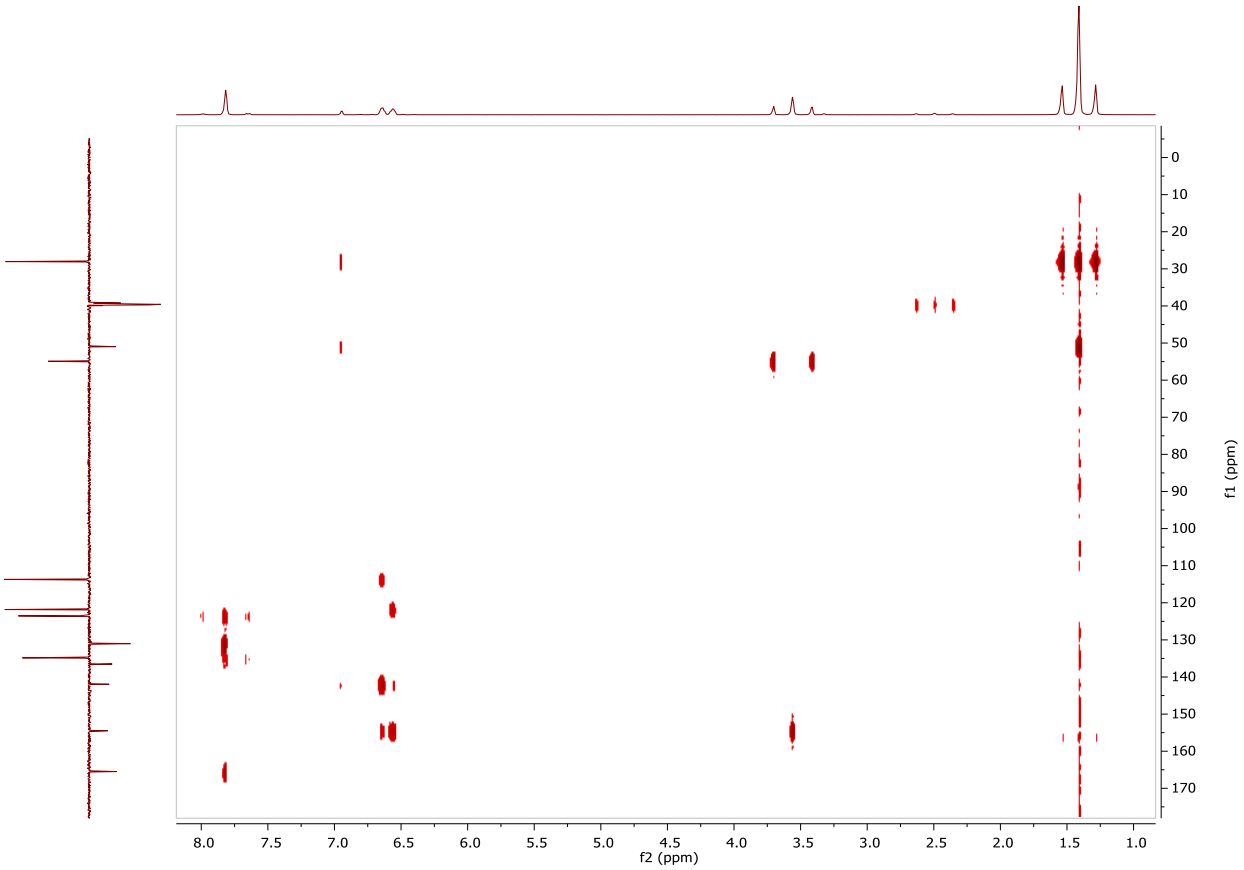


HCl in ethanol (6 mL, 1M) was added to *tert*-butyl (4-(((4-fluorophenyl)carbamoyl)oxy)phenyl)carbamate (**19**) (1.0 mmol, 346 mg). After strirring the reaction mixture at 70 °C for 40 min, the precipitated white solid was filtered off, washed with cold dichloromethane and dried in vacuo to afford pure **20** (213 mg, 75%). White solid, m.p. 252 – 253 °C; R_f = 0.39 (hexane:EtOAc = 1:1); ^{1}H-NMR (500 MHz, DMSO-d_6) δ 10.33 (s, 1H), 10.12 (br s, 2H), 7.53 – 7.45 (m, 2H), 7.37 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.16 (t, *J* = 8.9 Hz, 2H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 158.0 (d, *J* = 239.7 Hz), 151.6, 149.6, 134.8, 129.5, 124.2, 123.2, 120.2, (d, *J* = 7.2 Hz), 115.5 (d, *J* = 22.2 Hz); HRMS (ESI) m/z calculated for $C_{13}H_{12}FN_2O_2$ $[M+H]^+$ 247.0883, found 247.0880.

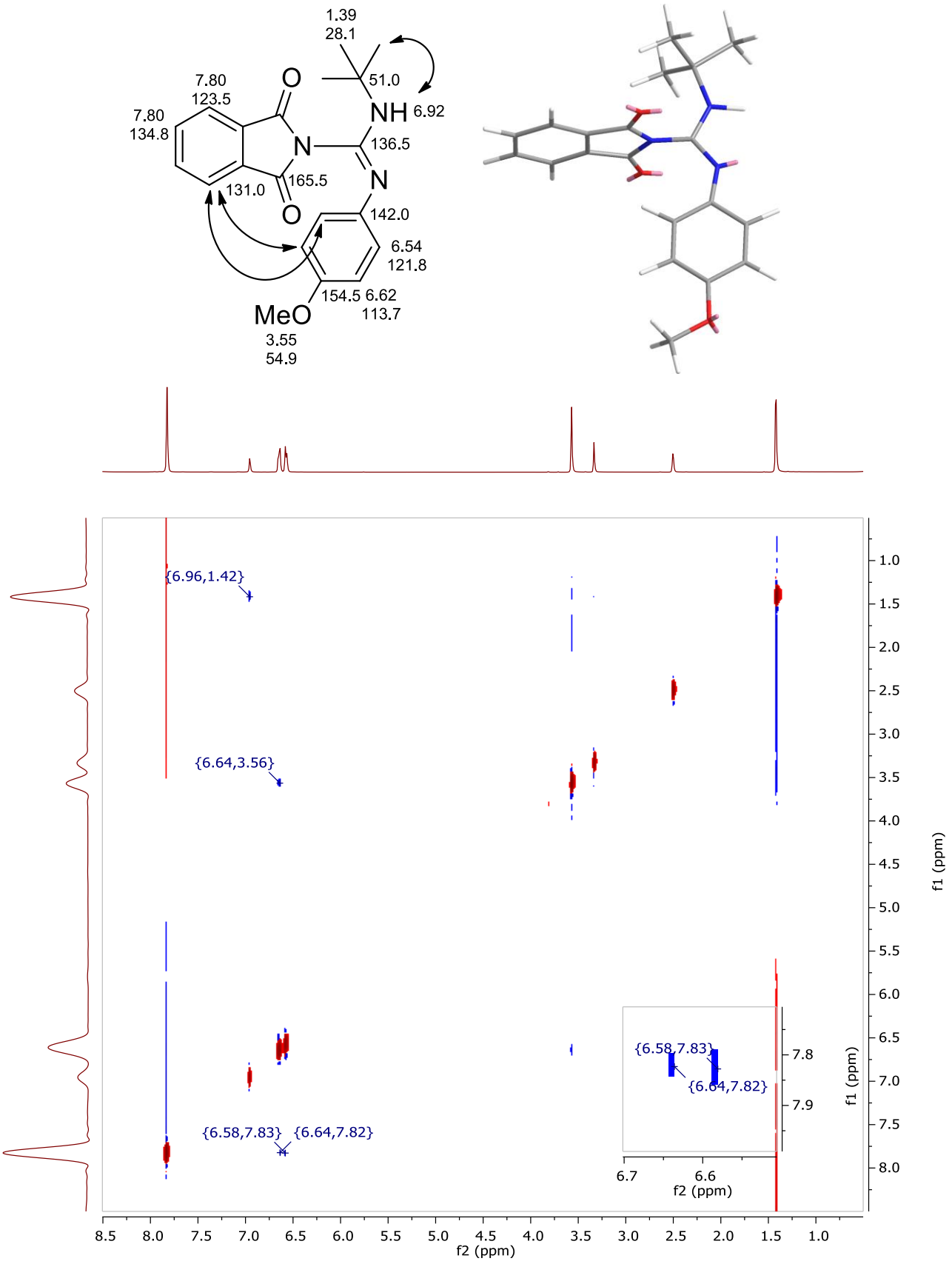
8. 2D NMR spectra of 5a



^{1}H-^{13}C HSQC spectrum of **5a** in DMSO-d_6

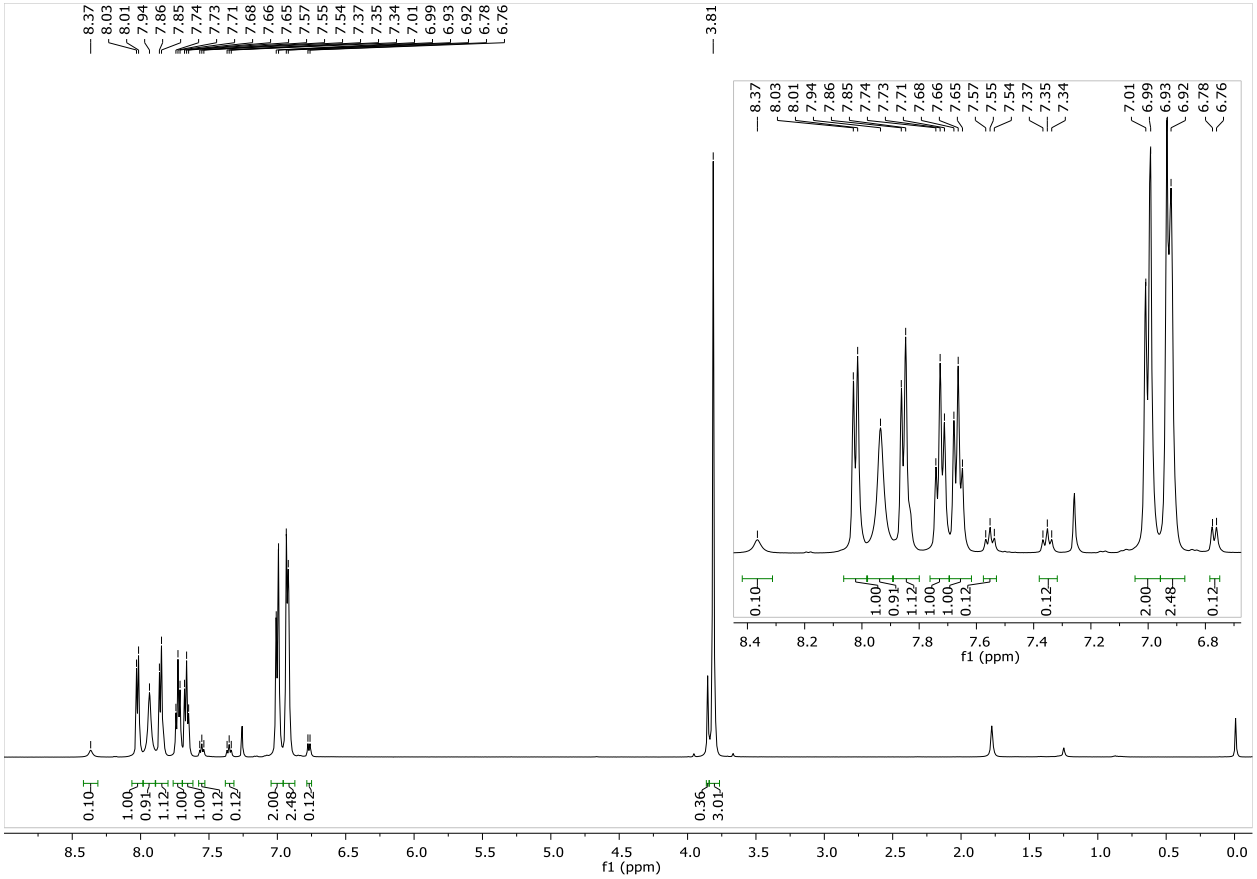


^{1}H-^{13}C HMBC spectrum of **5a** in DMSO-d_6

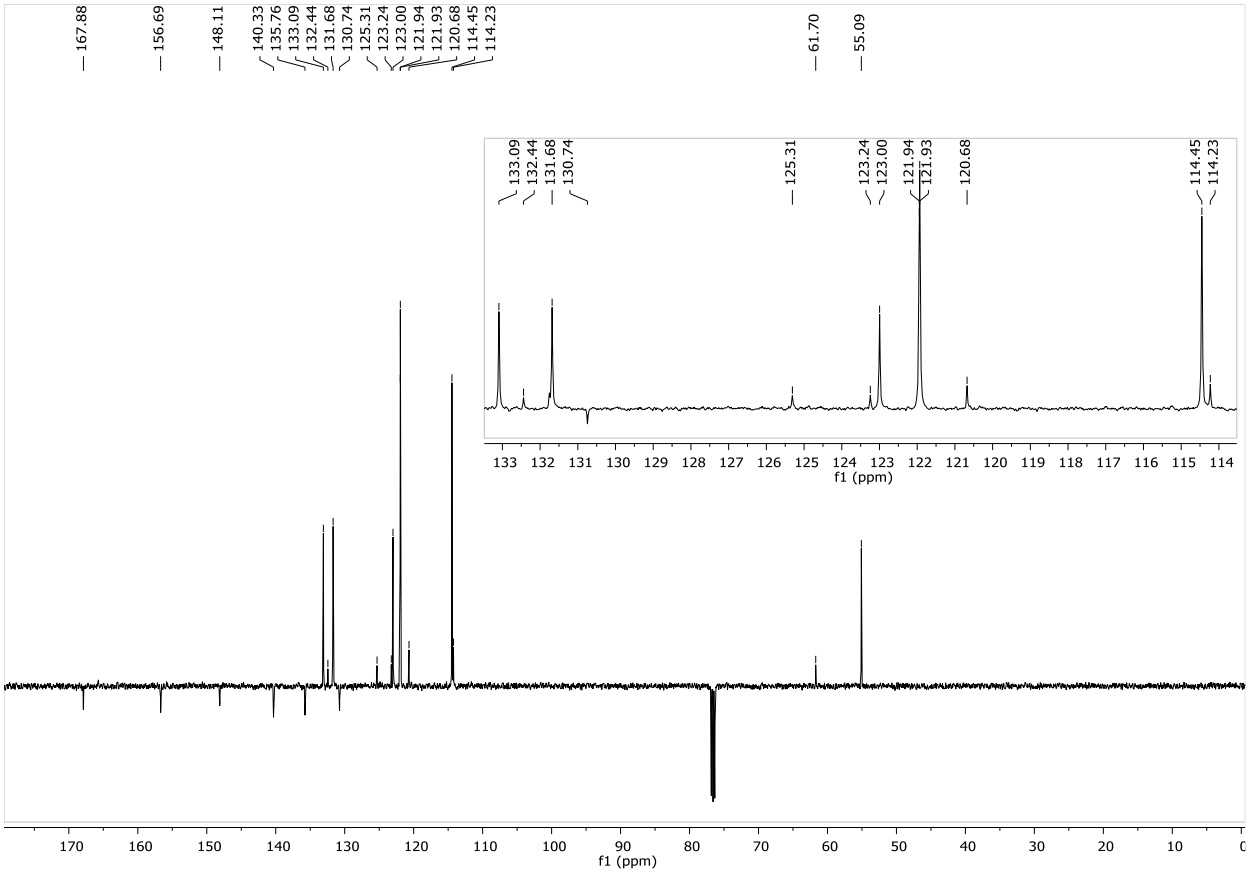


^{1}H-^{1}H NOESY spectrum of **5a** in DMSO-d_6

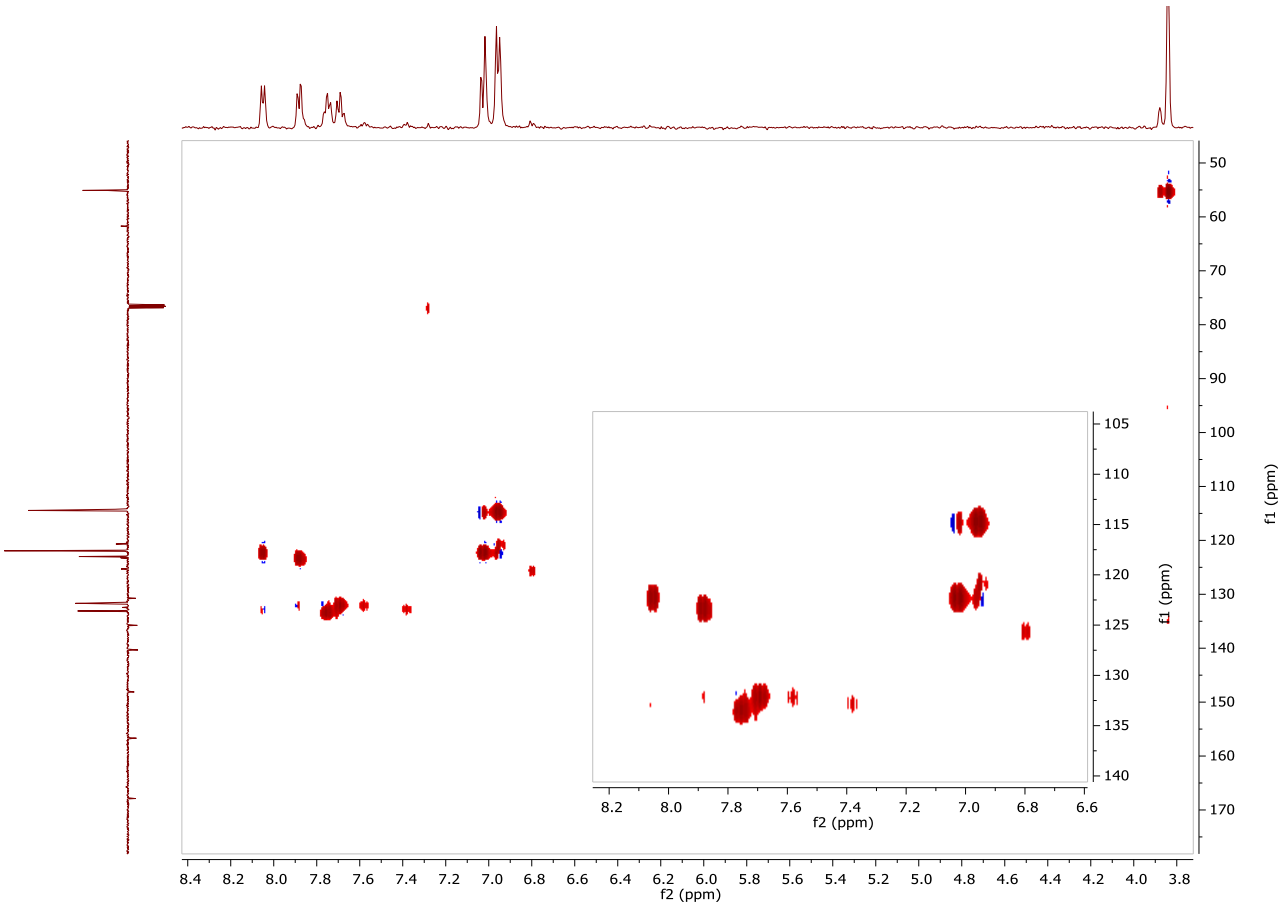
9. 1D and 2D NMR spectra of 6a



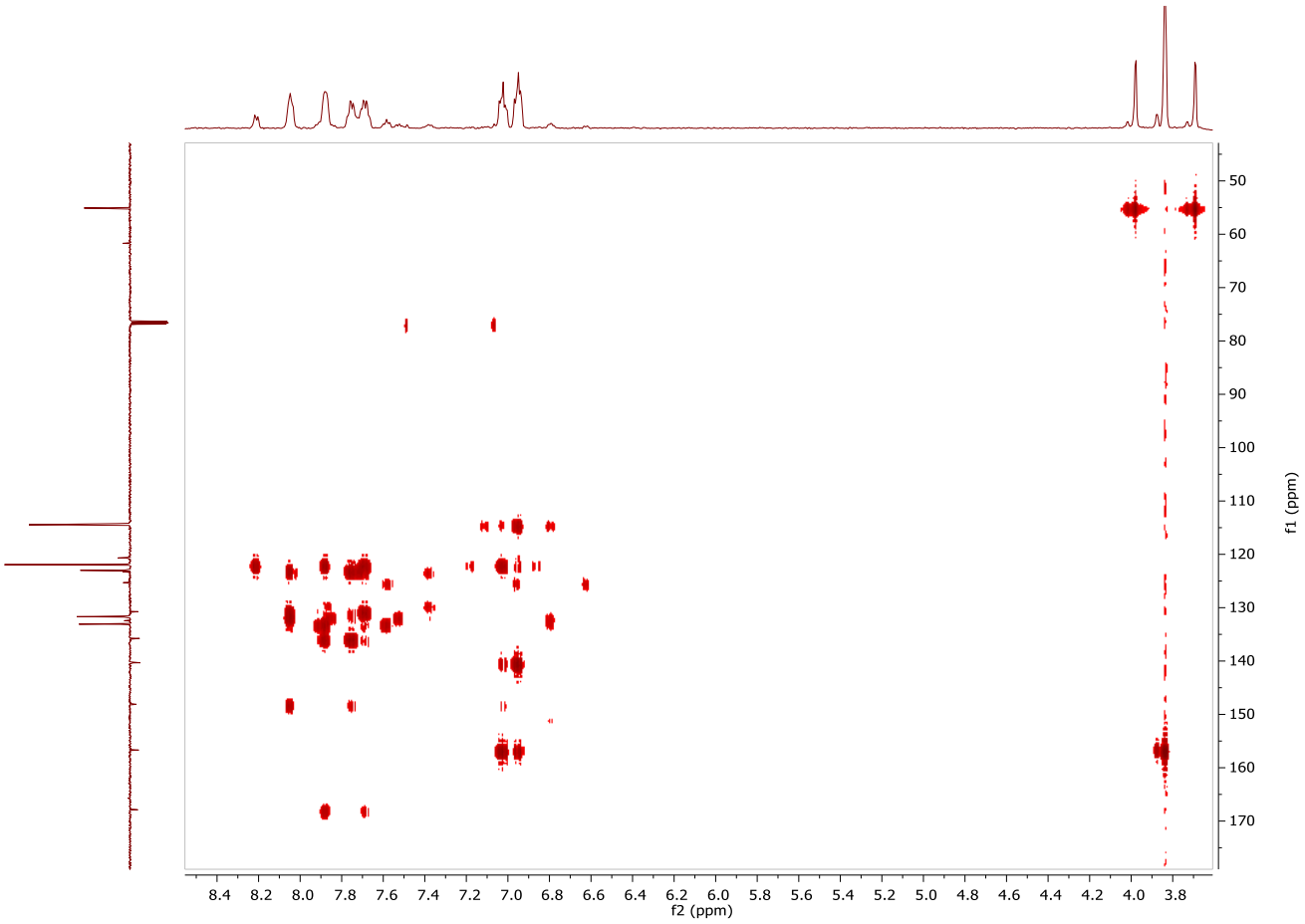
^{1}H-NMR (500 MHz, $CDCl_3$) spectrum of **6a**



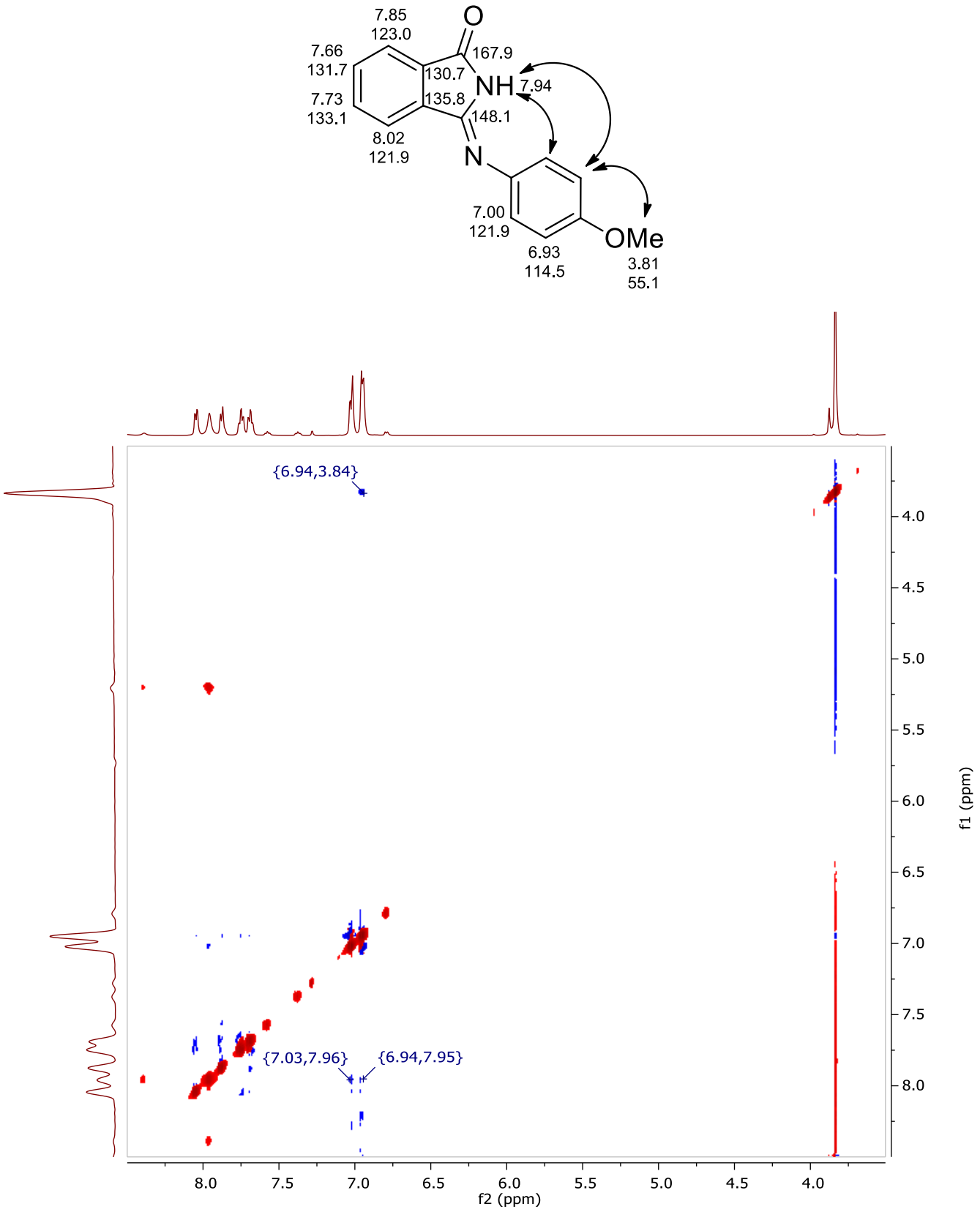
^{13}C-NMR (126 MHz, $CDCl_3$) spectrum of **6a**



^{1}H-^{13}C HSQC spectrum of **6a** in $CDCl_3$

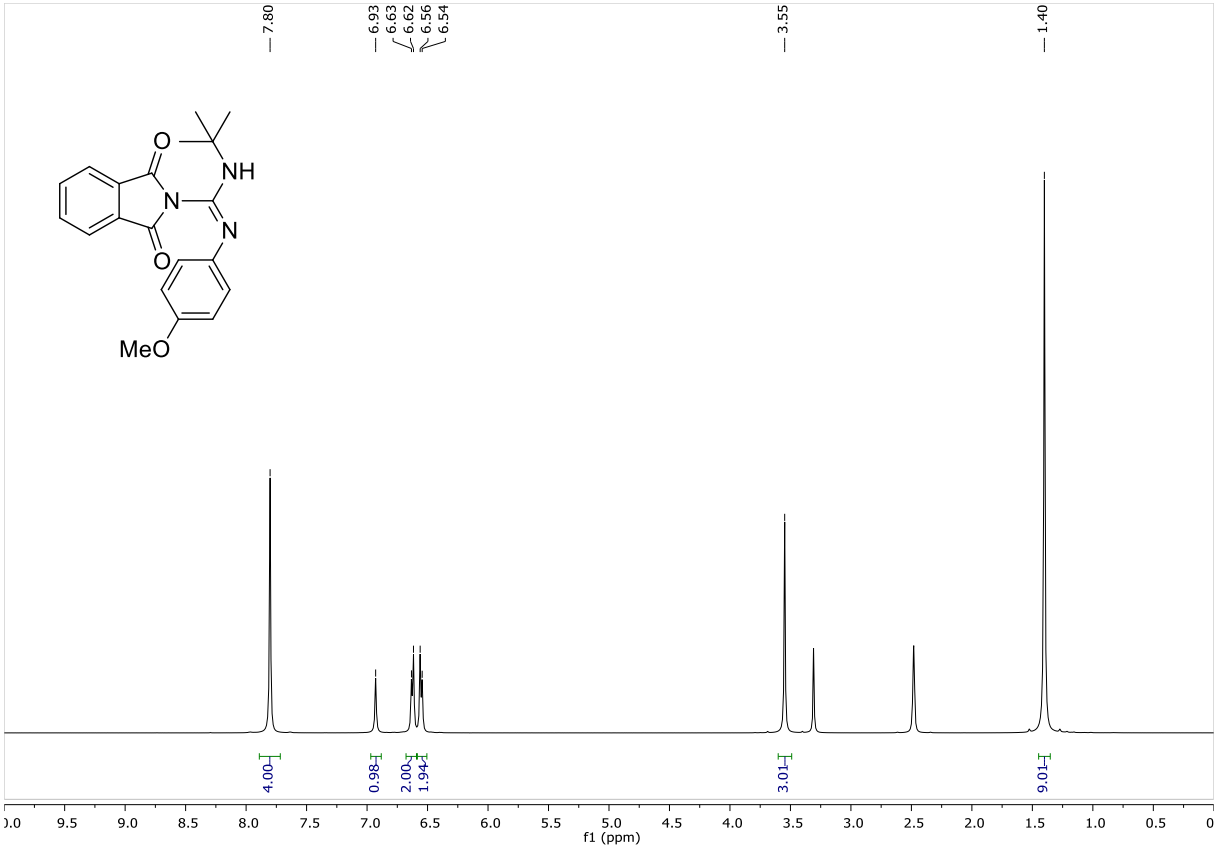


^{1}H-^{13}C HMBC spectrum of **6a** in $CDCl_3$

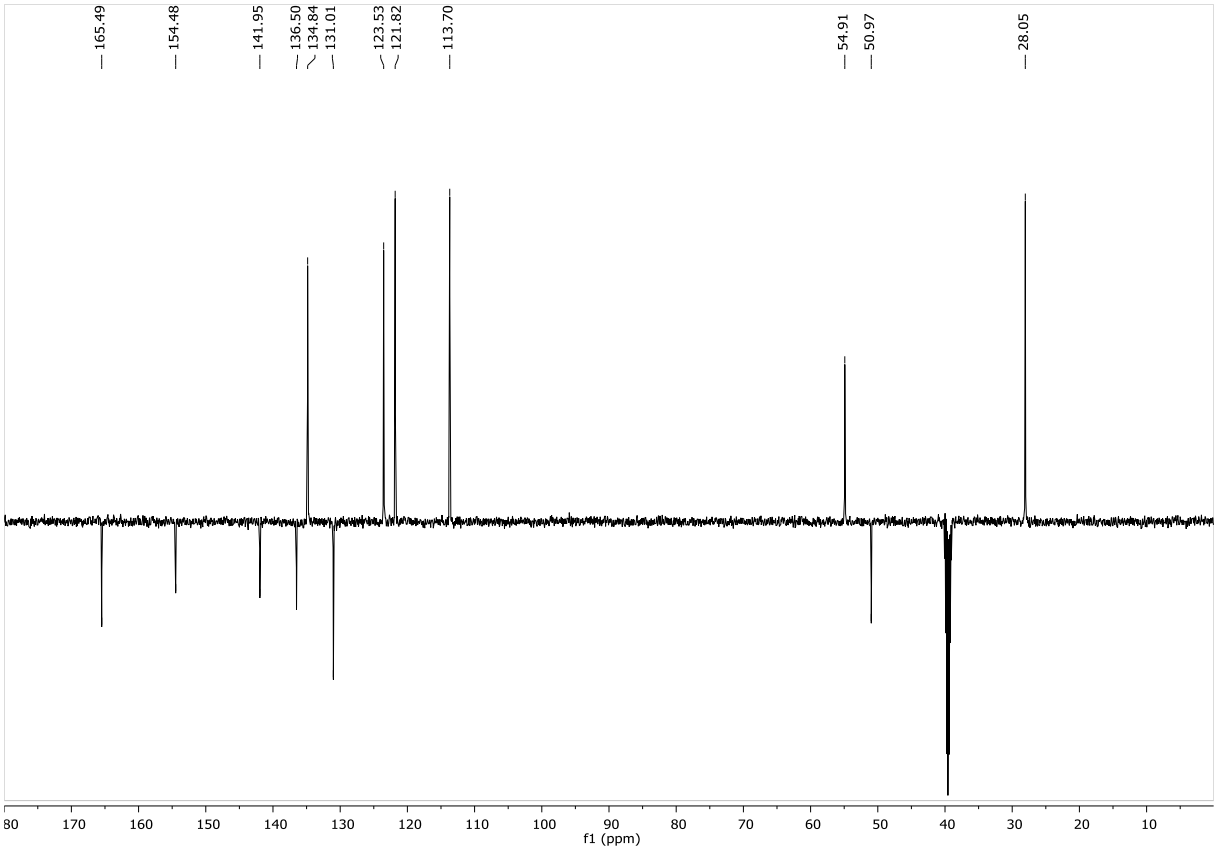


^{1}H-^{1}H NOESY spectrum of **6a** in $CDCl_3$

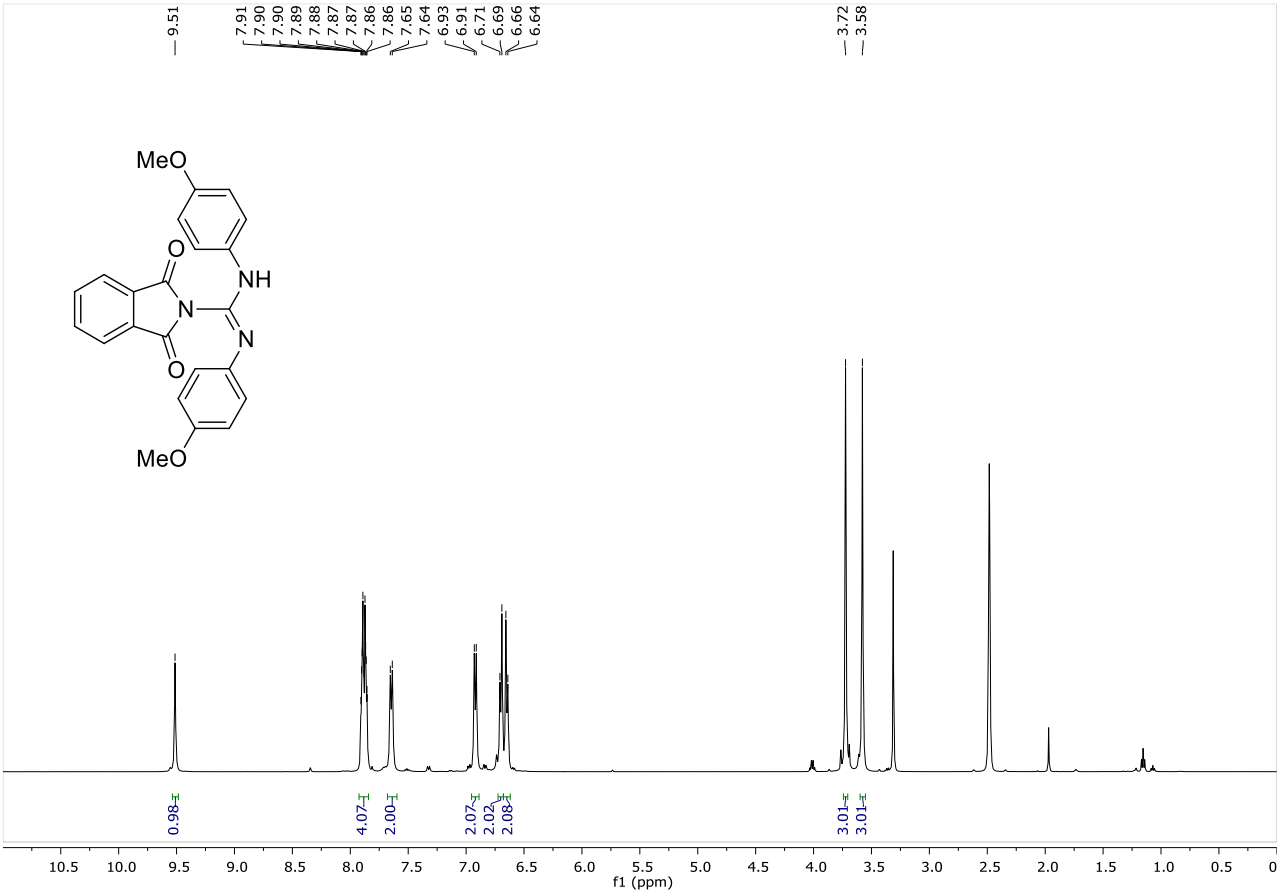
10. 1D NMR spectra of all compounds



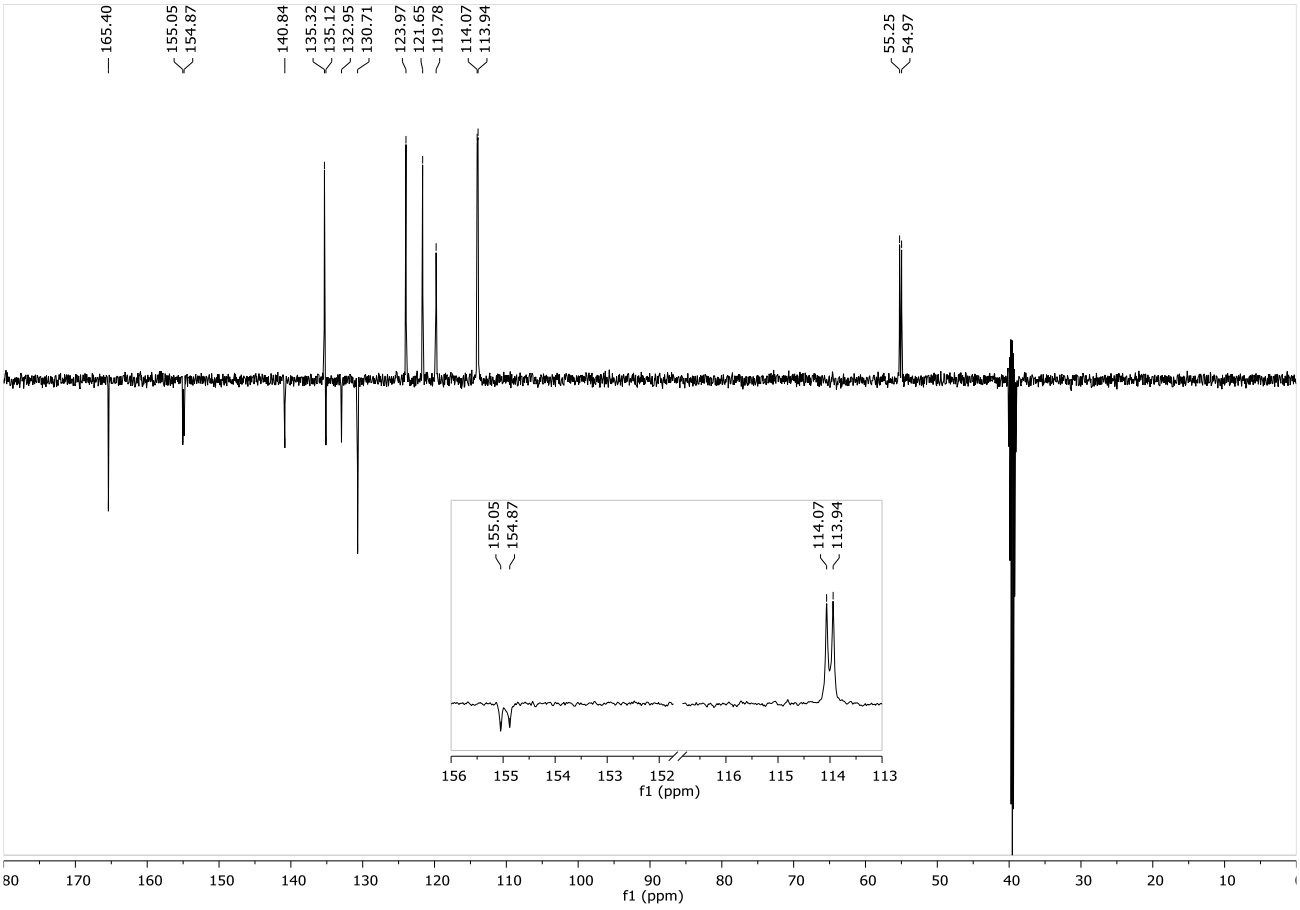
^{1}H-NMR spectrum of **5a** in DMSO-d_6



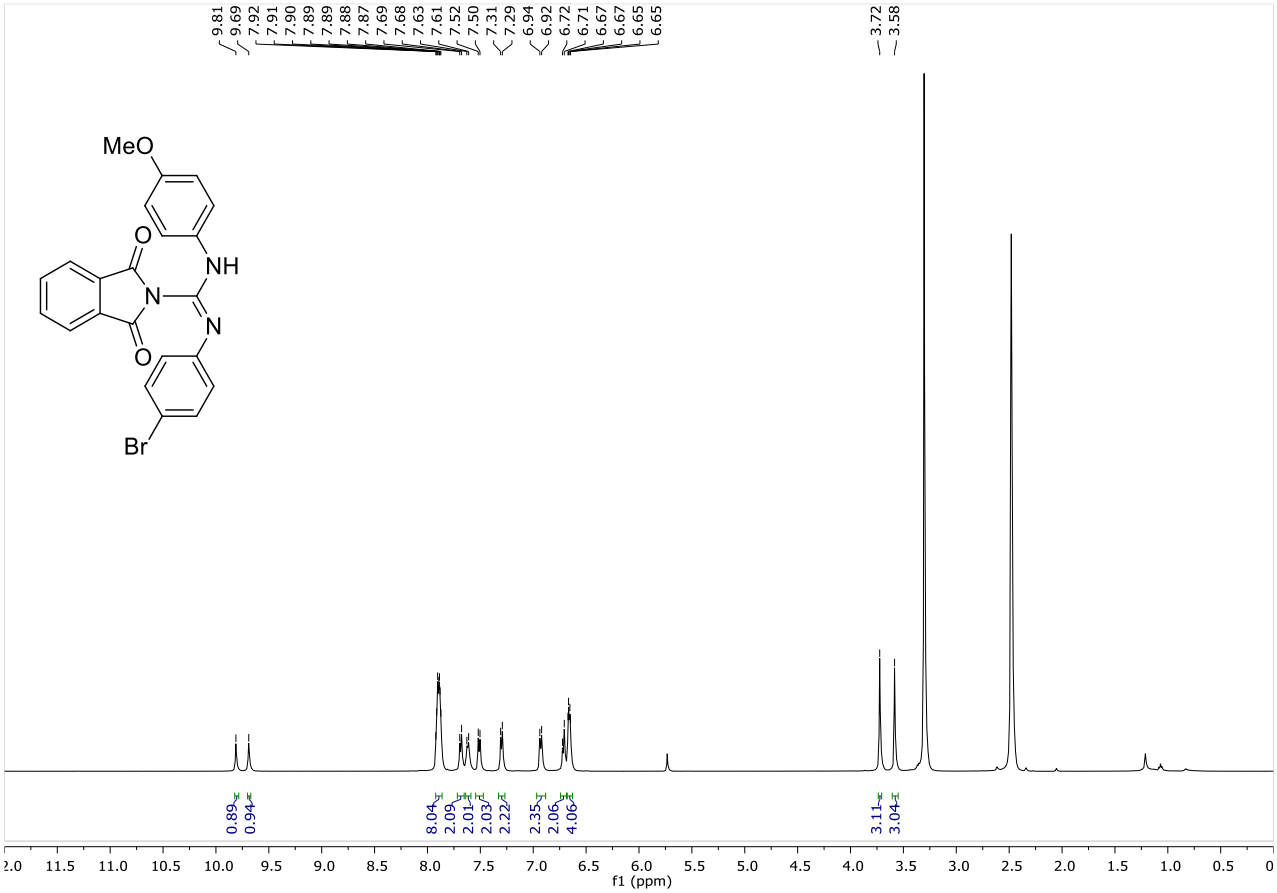
^{13}C-NMR spectrum of **5a** in DMSO-d_6



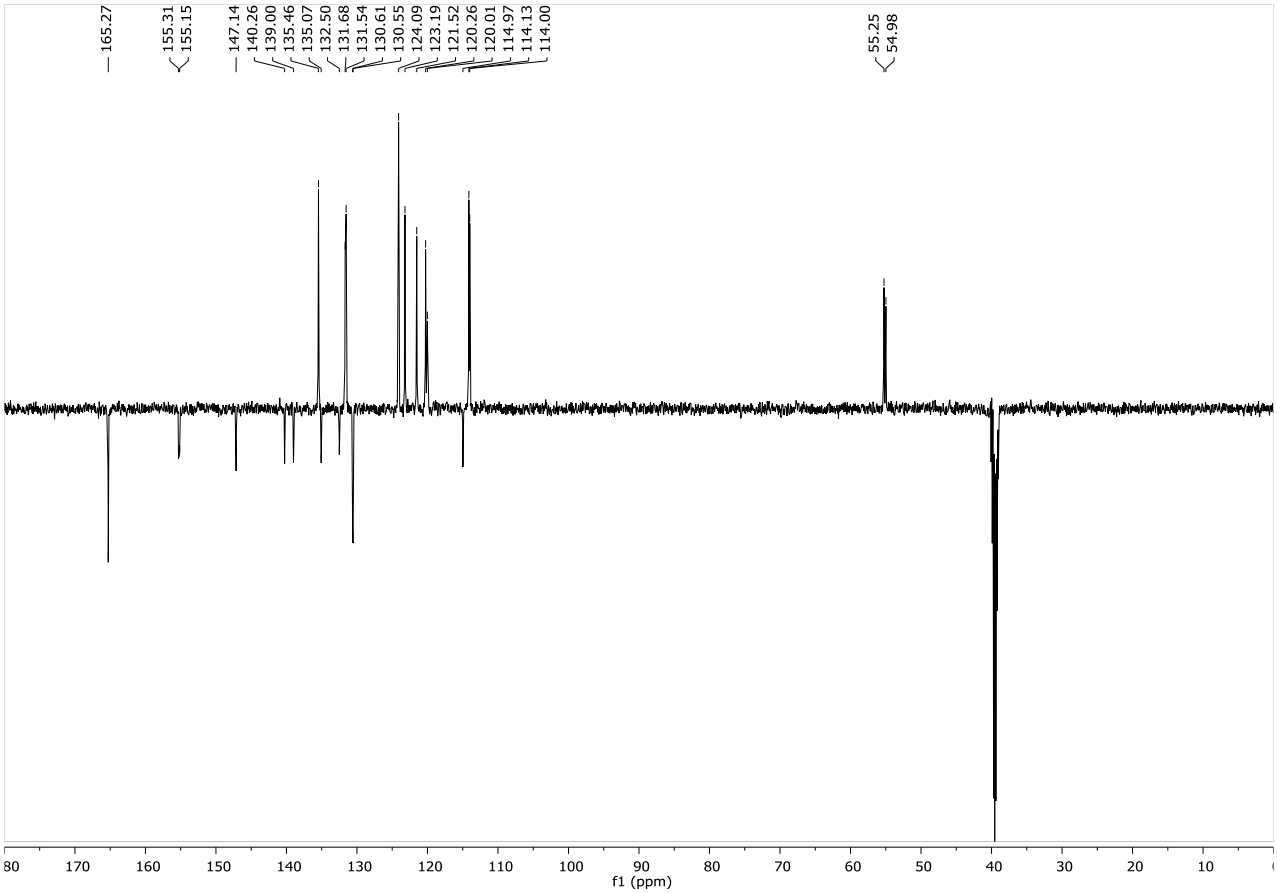
^{1}H-NMR spectrum of **5b** in DMSO-d_6



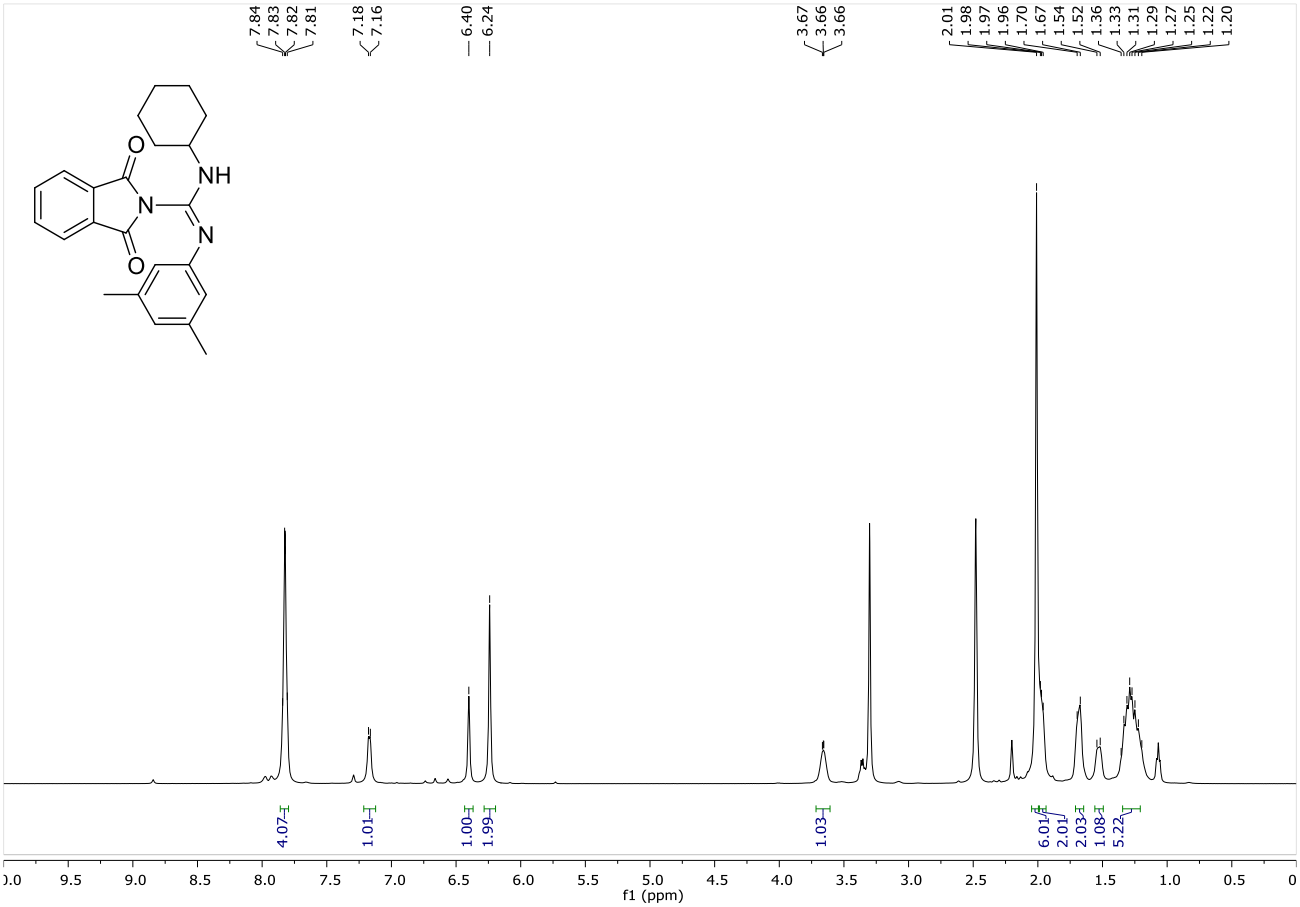
^{13}C-NMR spectrum of **5b** in DMSO-d_6



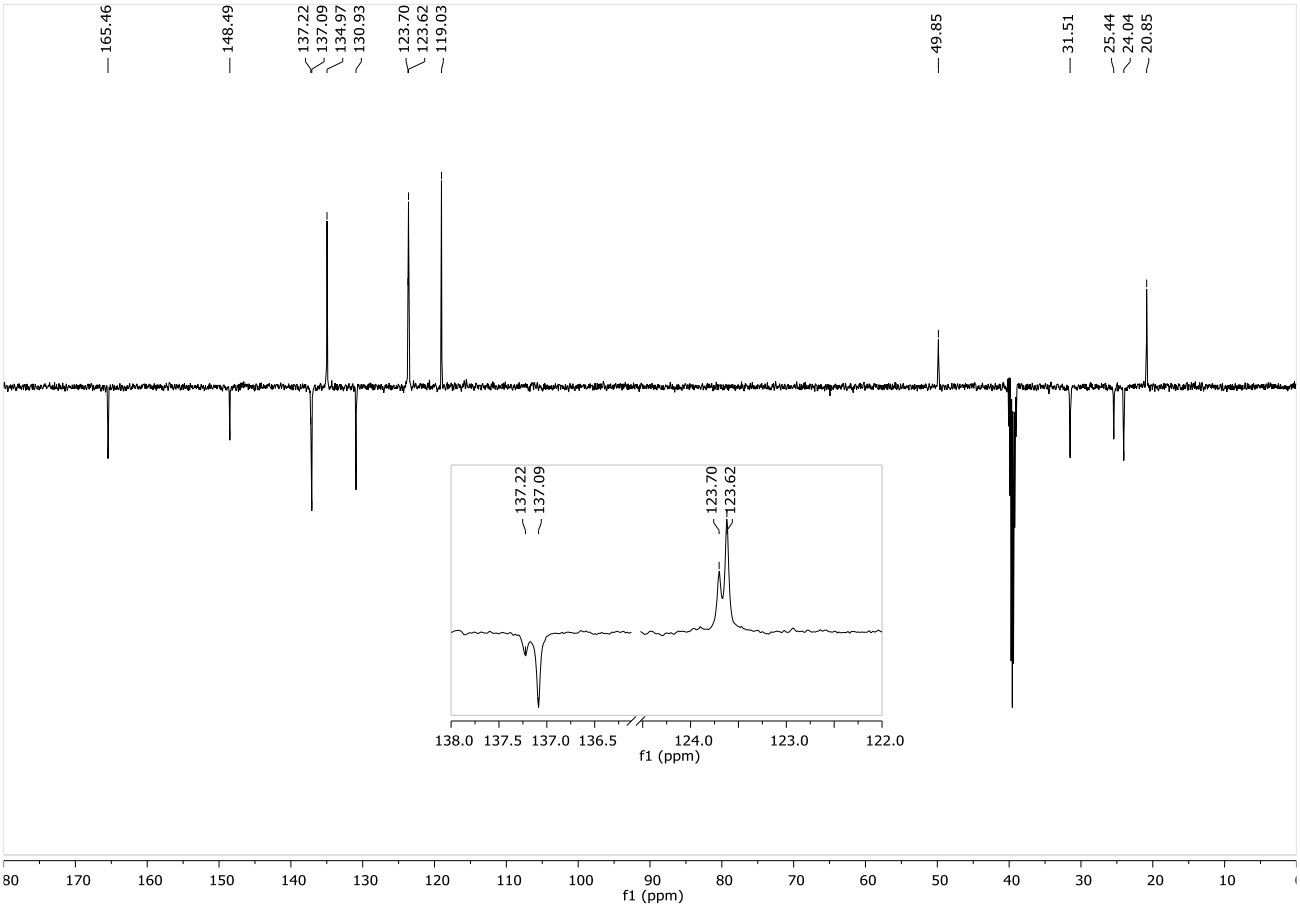
^{1}H-NMR spectrum of **5c** in DMSO-d_6



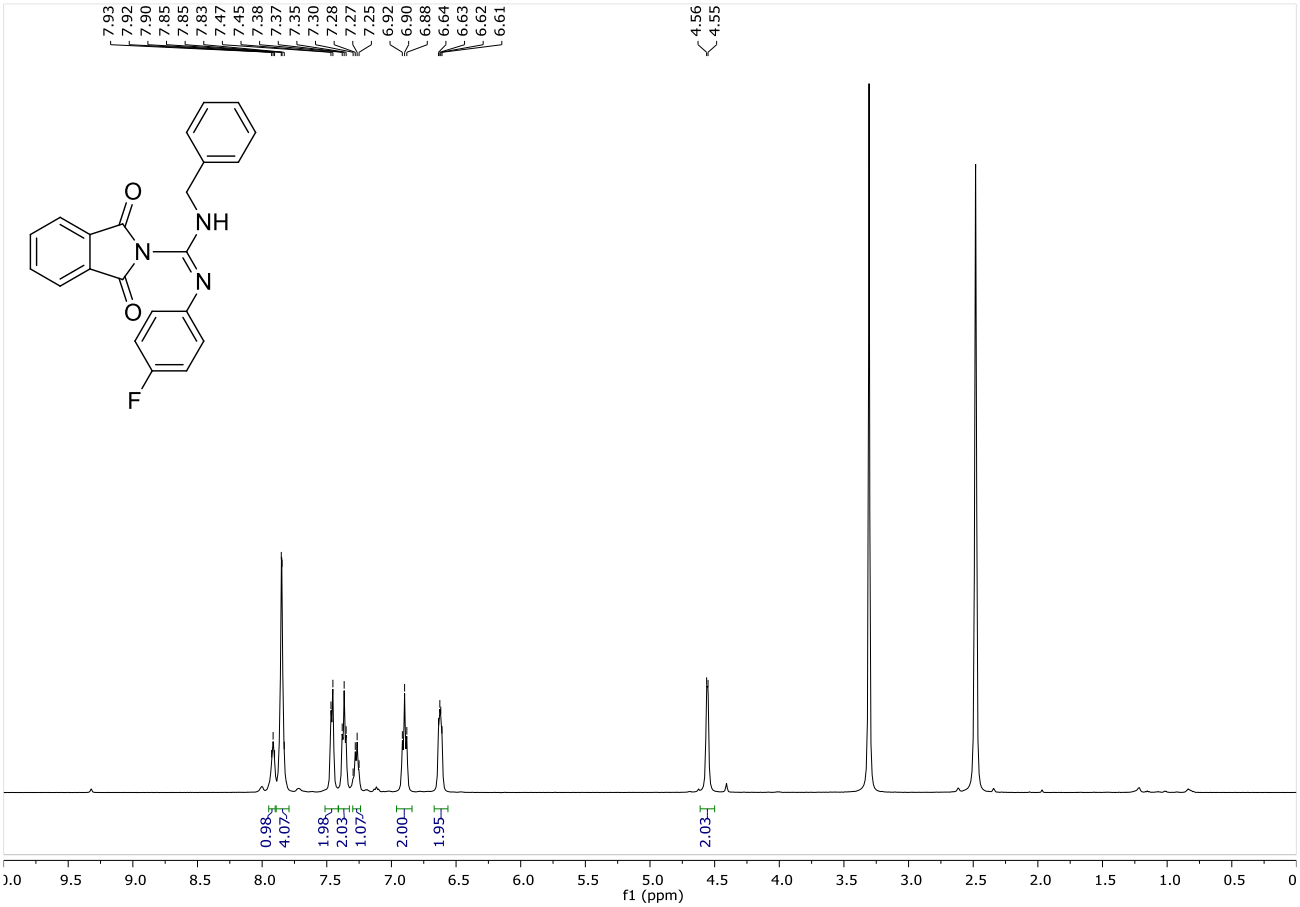
^{13}C-NMR spectrum of **5c** in DMSO-d_6



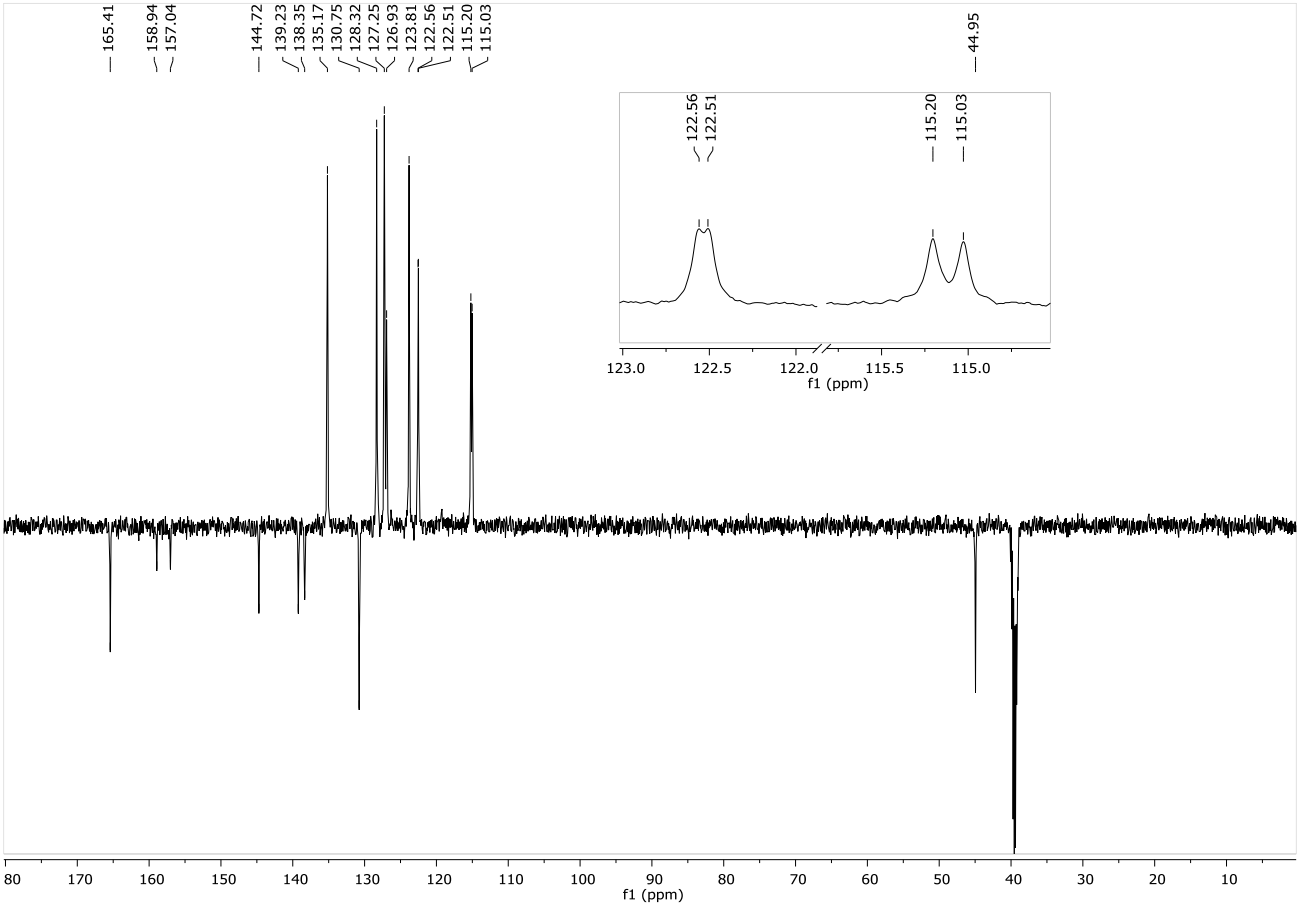
^{1}H-NMR spectrum of **5d** in DMSO-d_6



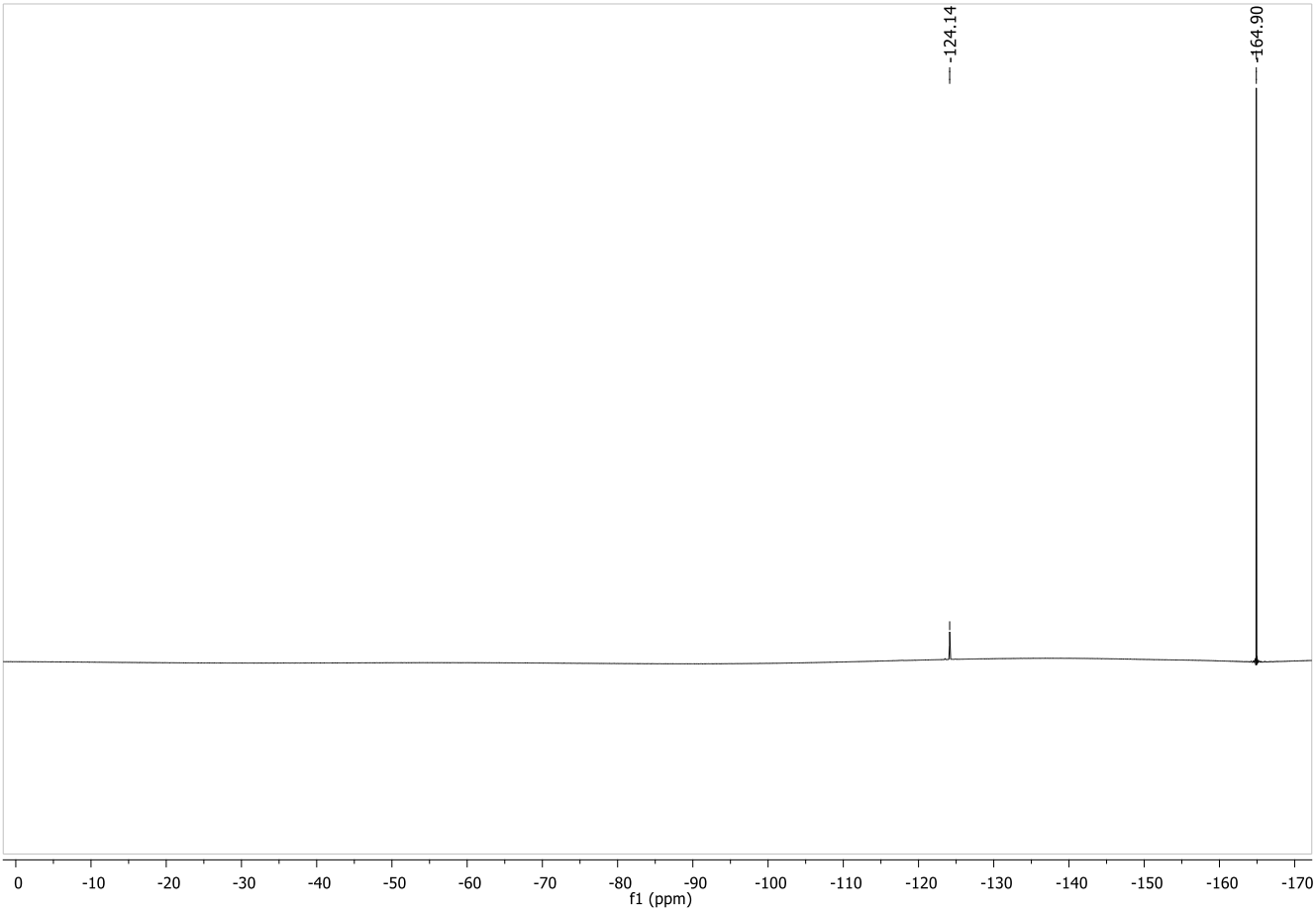
^{13}C-NMR spectrum of **5d** in DMSO-d_6



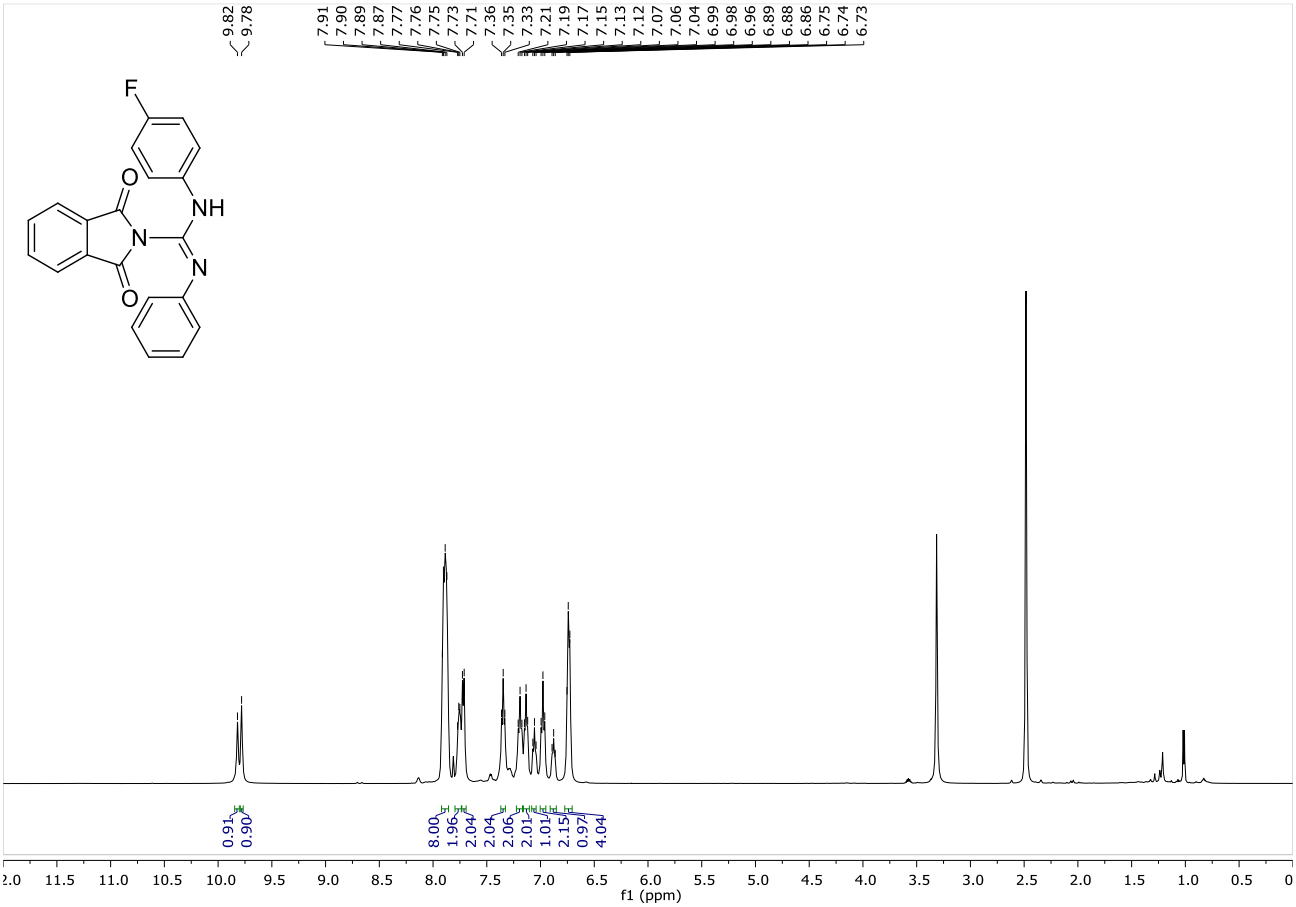
^{1}H-NMR spectrum of **5e** in DMSO-d_6



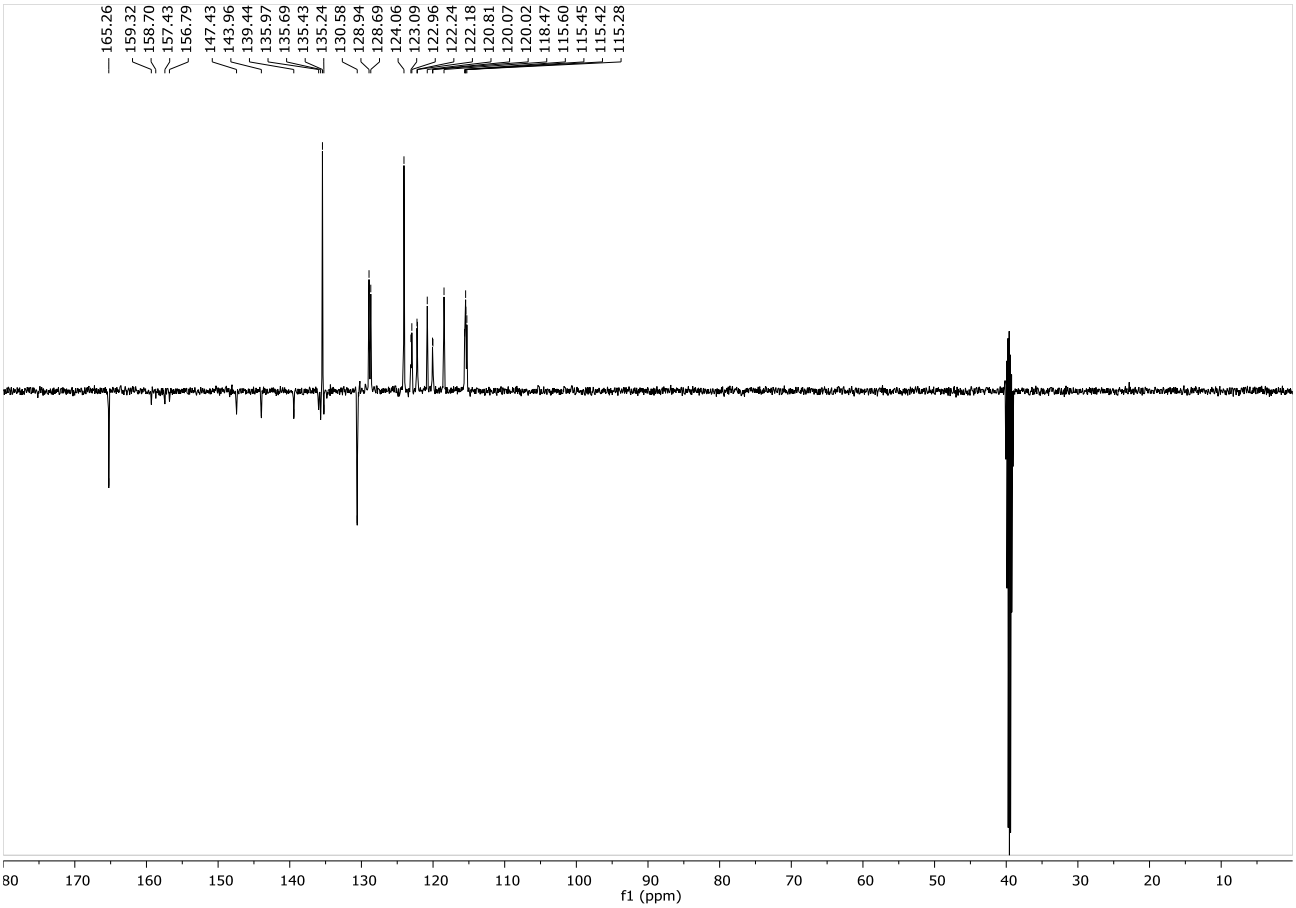
^{13}C-NMR spectrum of **5e** in DMSO-d_6



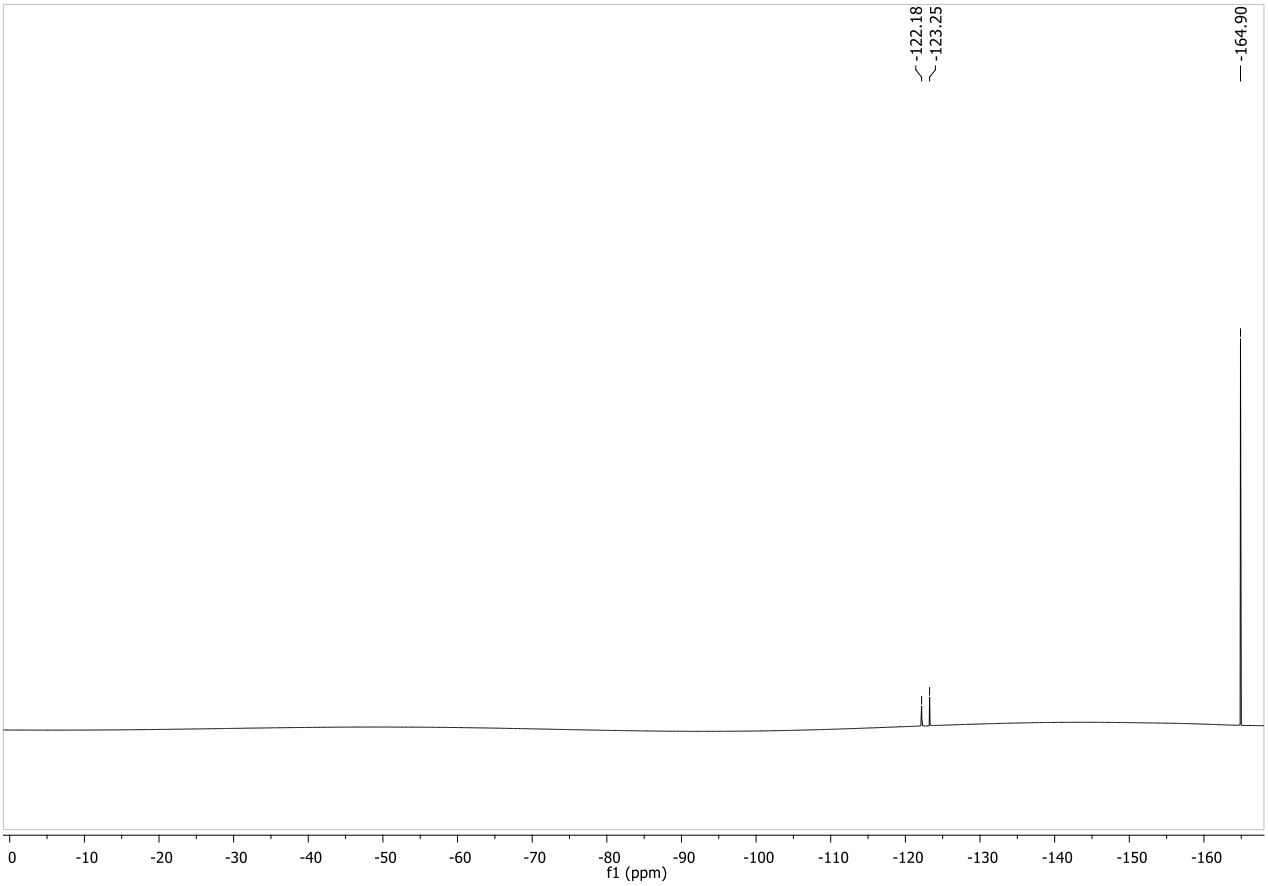
^{19}F-NMR spectrum of **5e** in DMSO-d_6



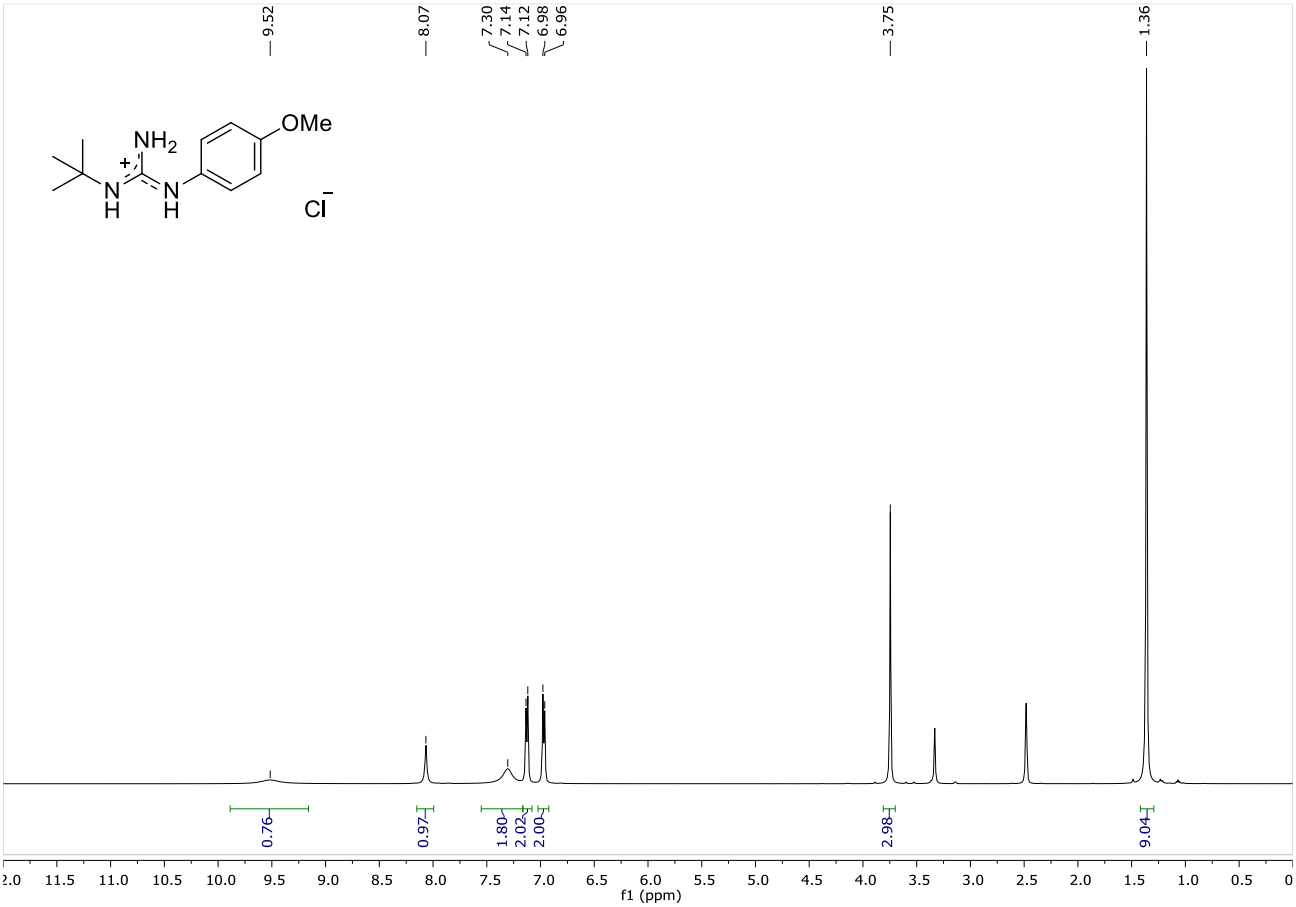
^{1}H-NMR spectrum of **5f** in DMSO-d_6



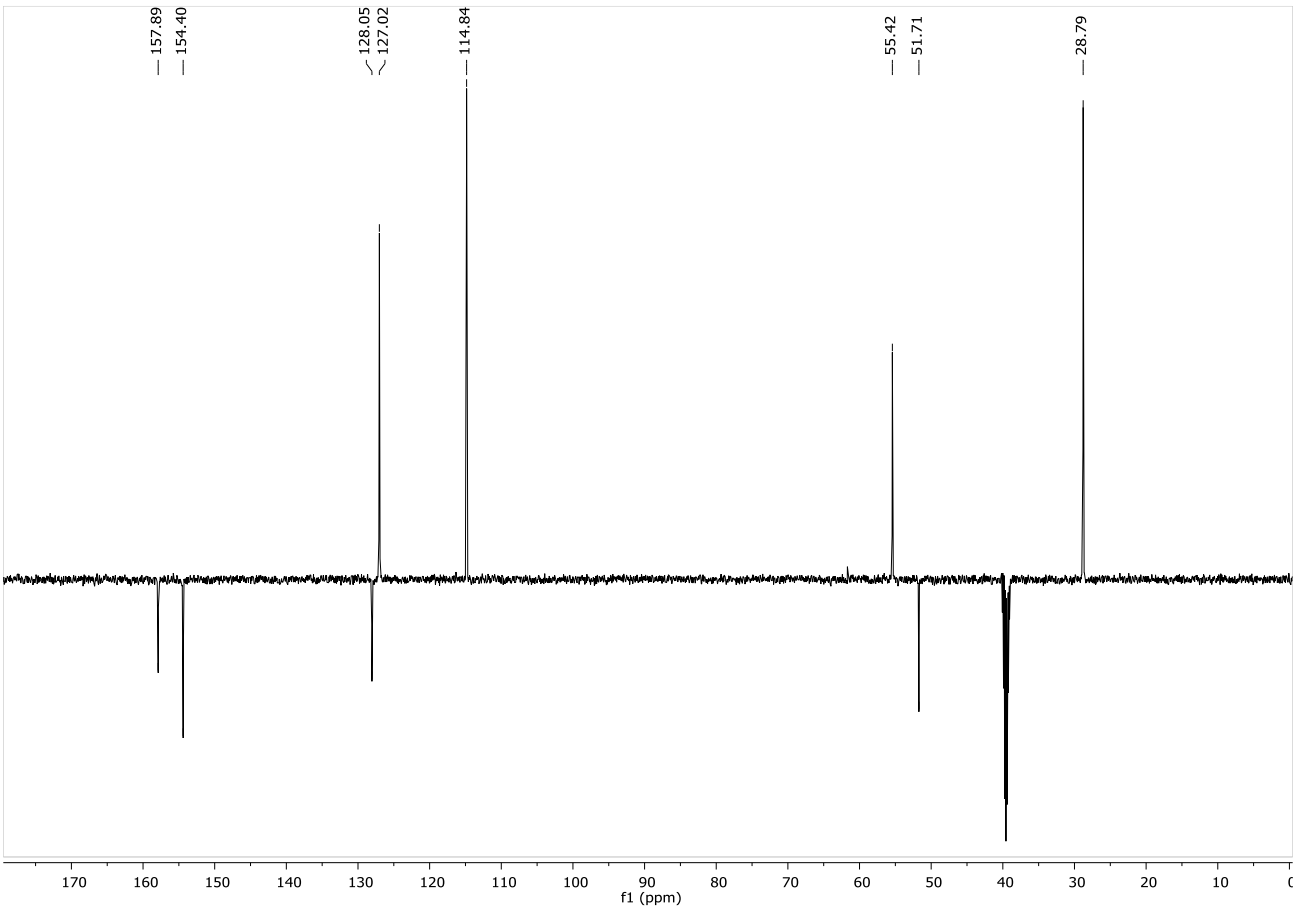
^{13}C-NMR spectrum of **5f** in DMSO-d_6



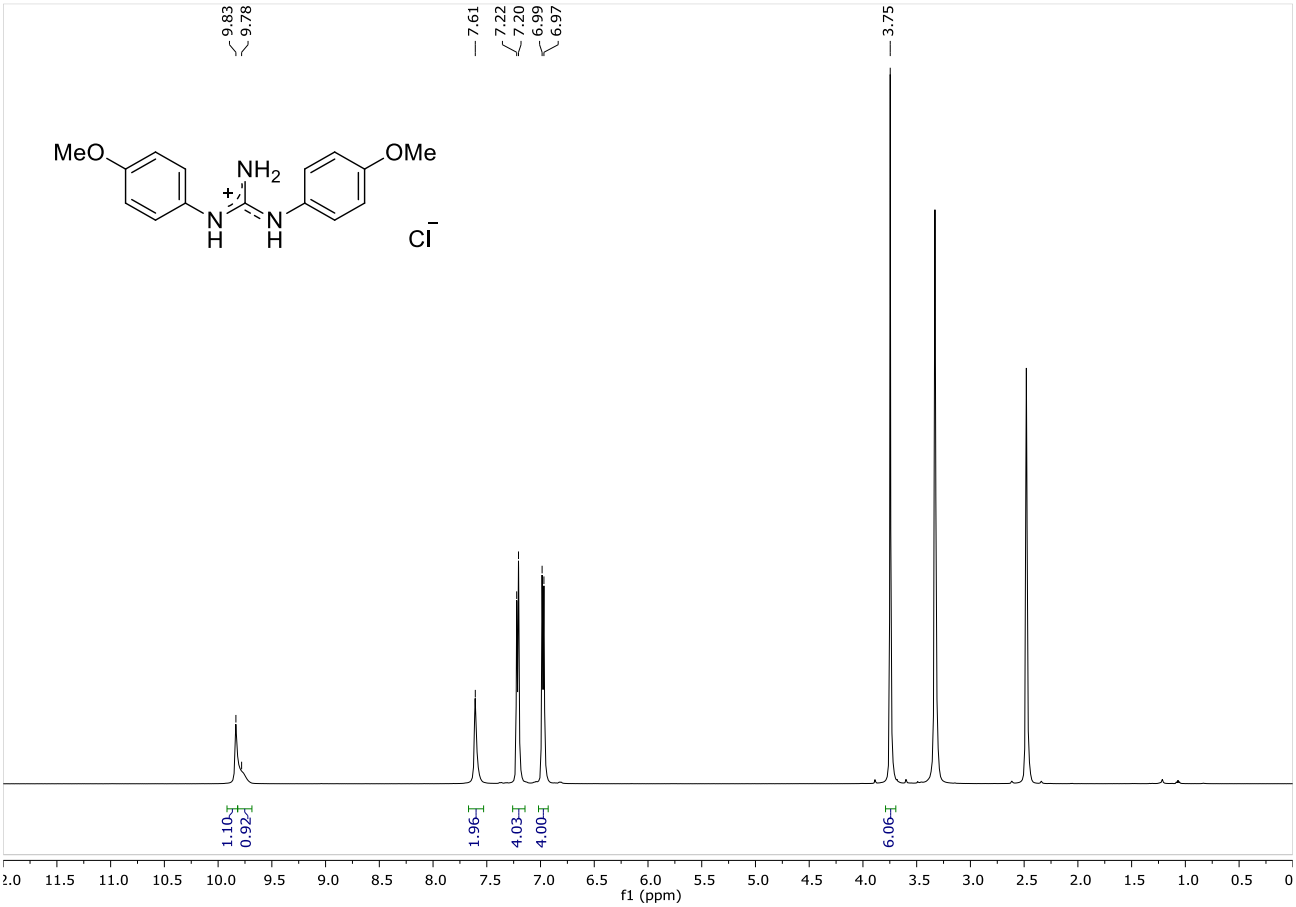
^{19}F-NMR spectrum of **5f** in DMSO-d_6



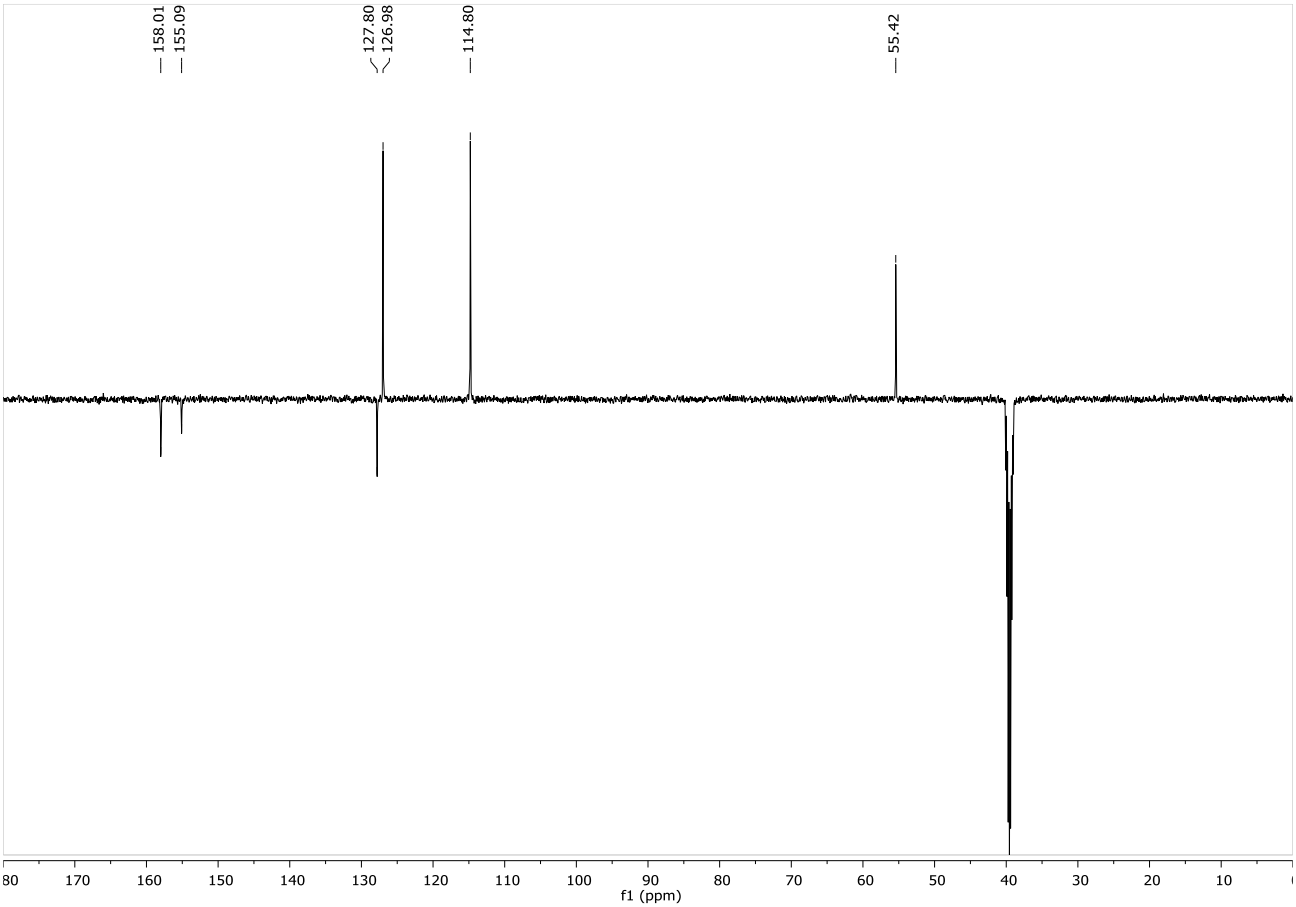
^{1}H-NMR spectrum of **7a** in DMSO-d_6



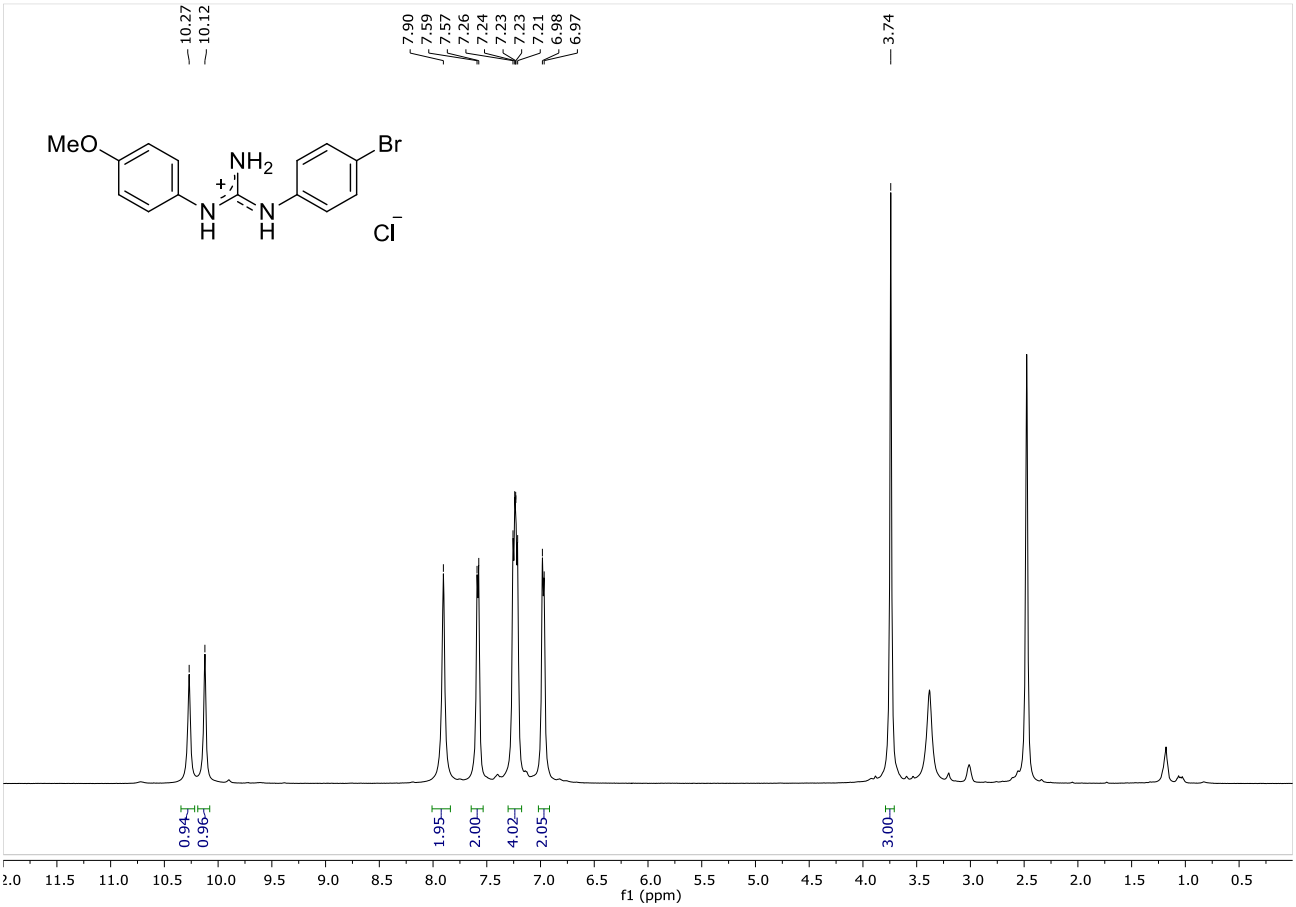
^{13}C-NMR spectrum of **7a** in DMSO-d_6



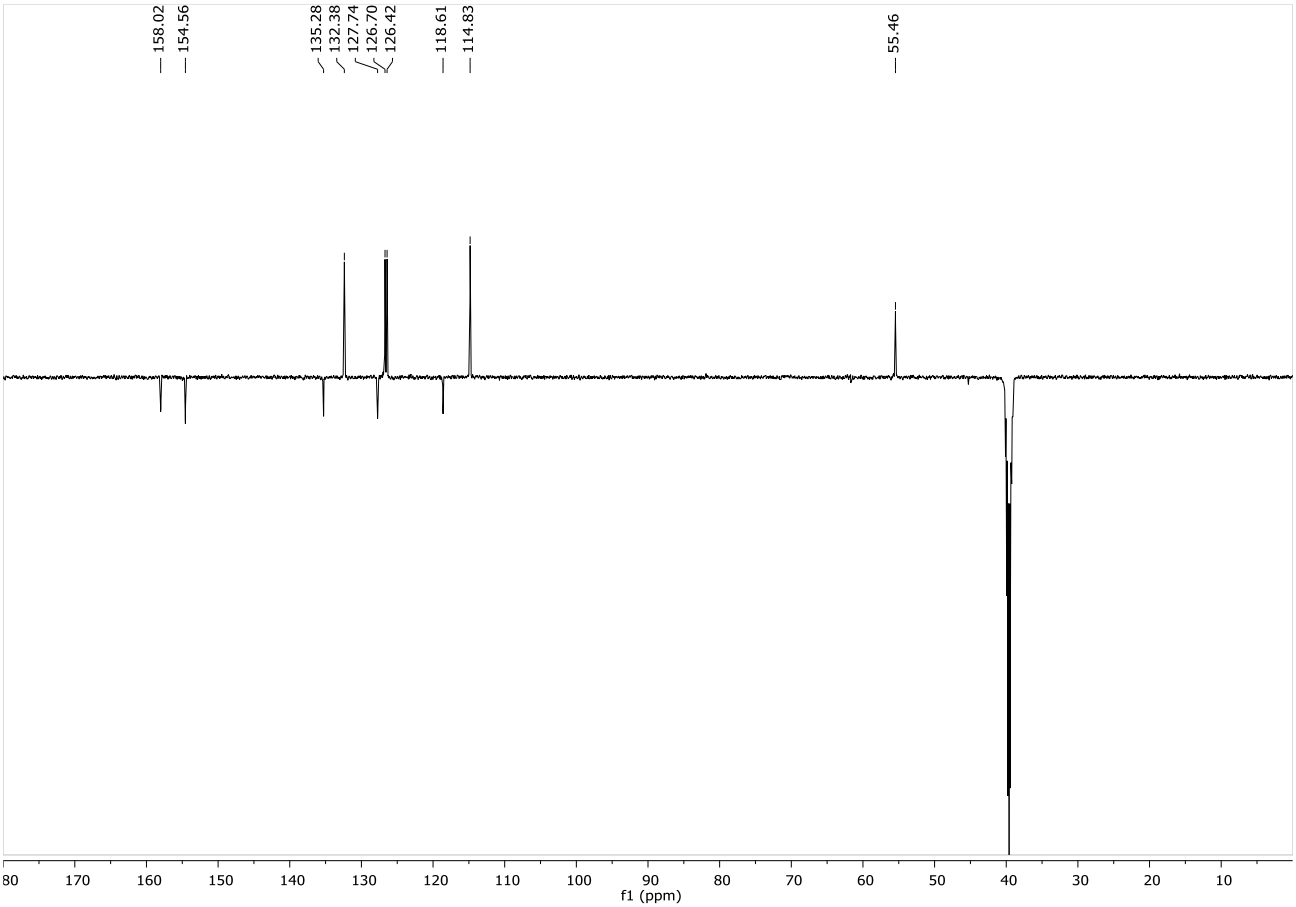
^{1}H-NMR spectrum of **7b** in DMSO-d_6



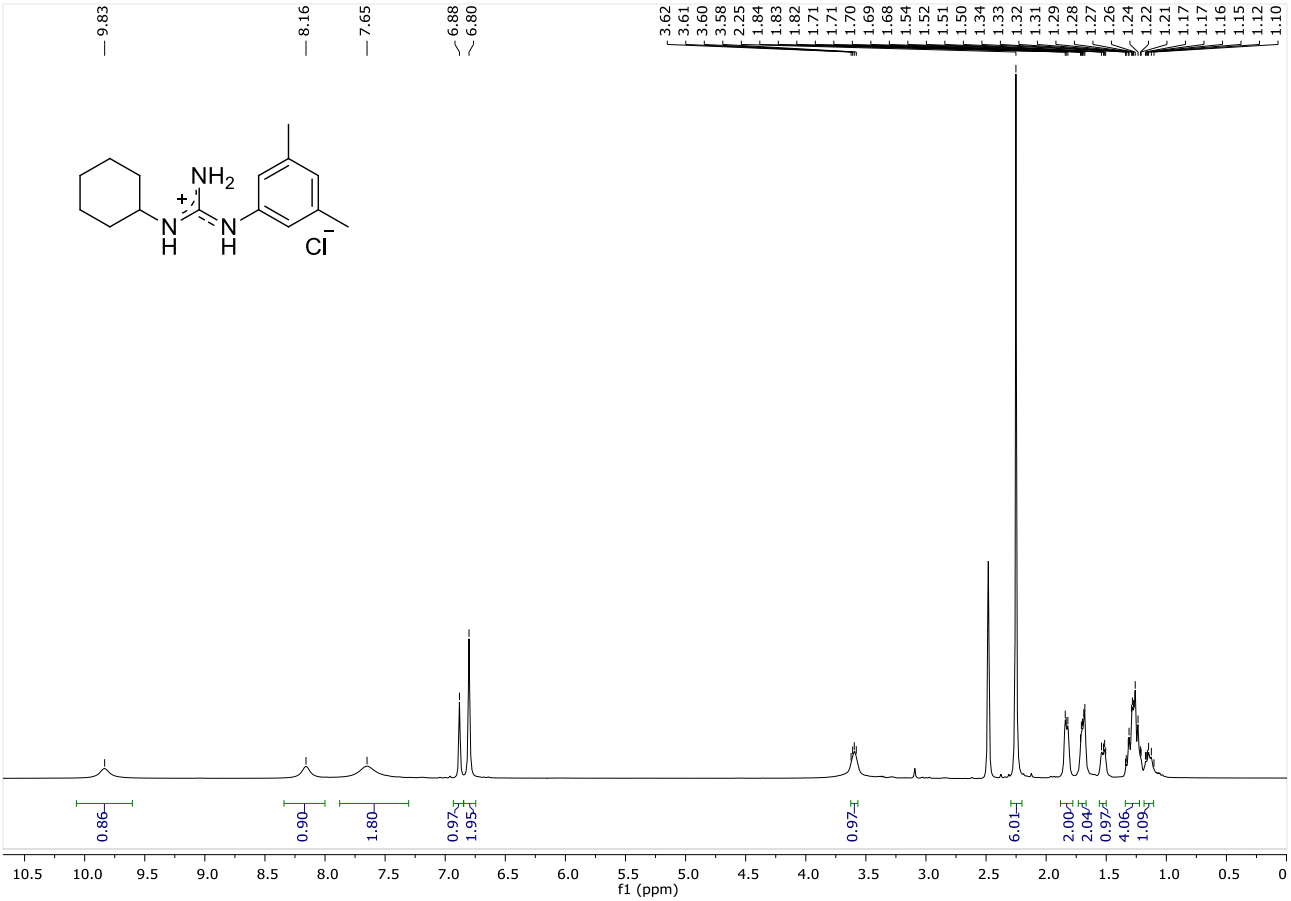
^{13}C-NMR spectrum of **7b** in DMSO-d_6



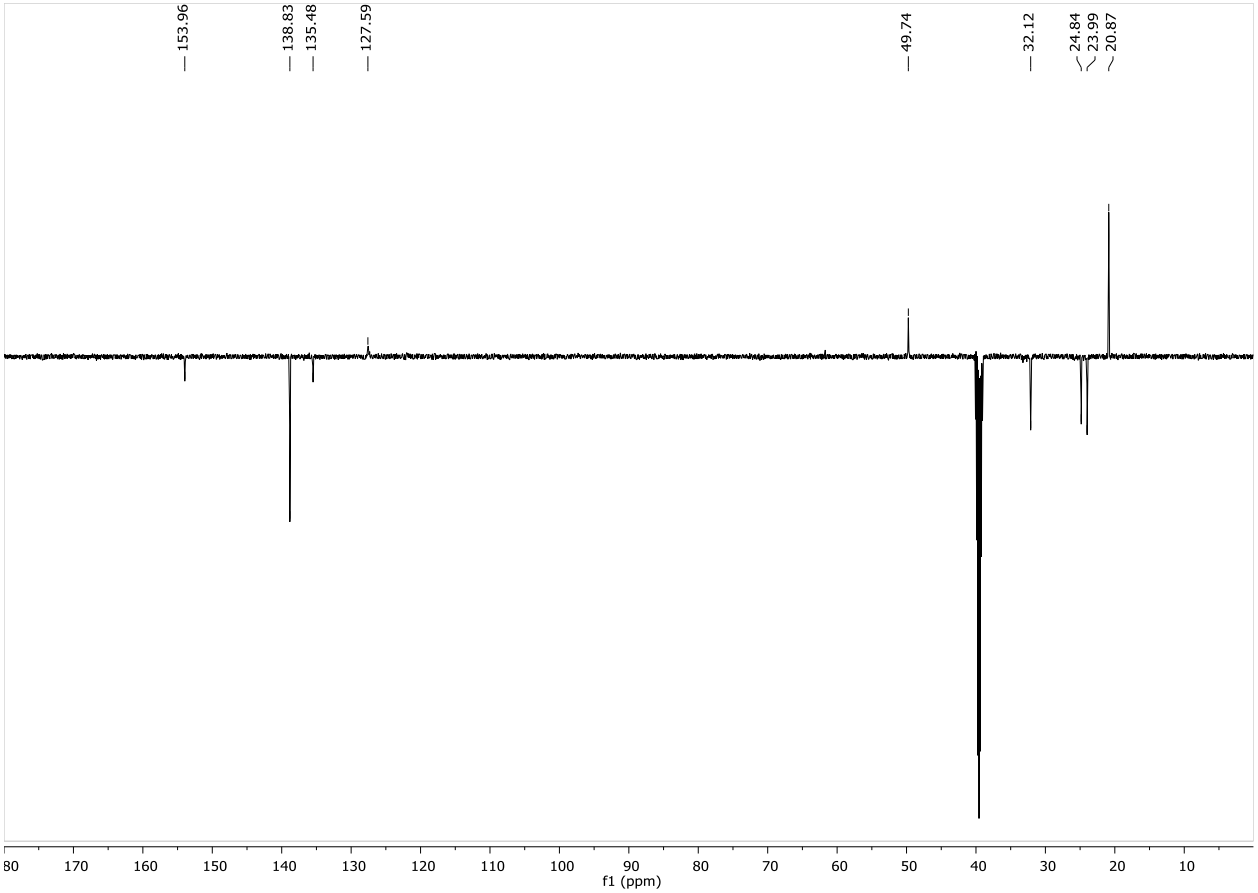
^{1}H-NMR spectrum of **7c** in DMSO-d_6



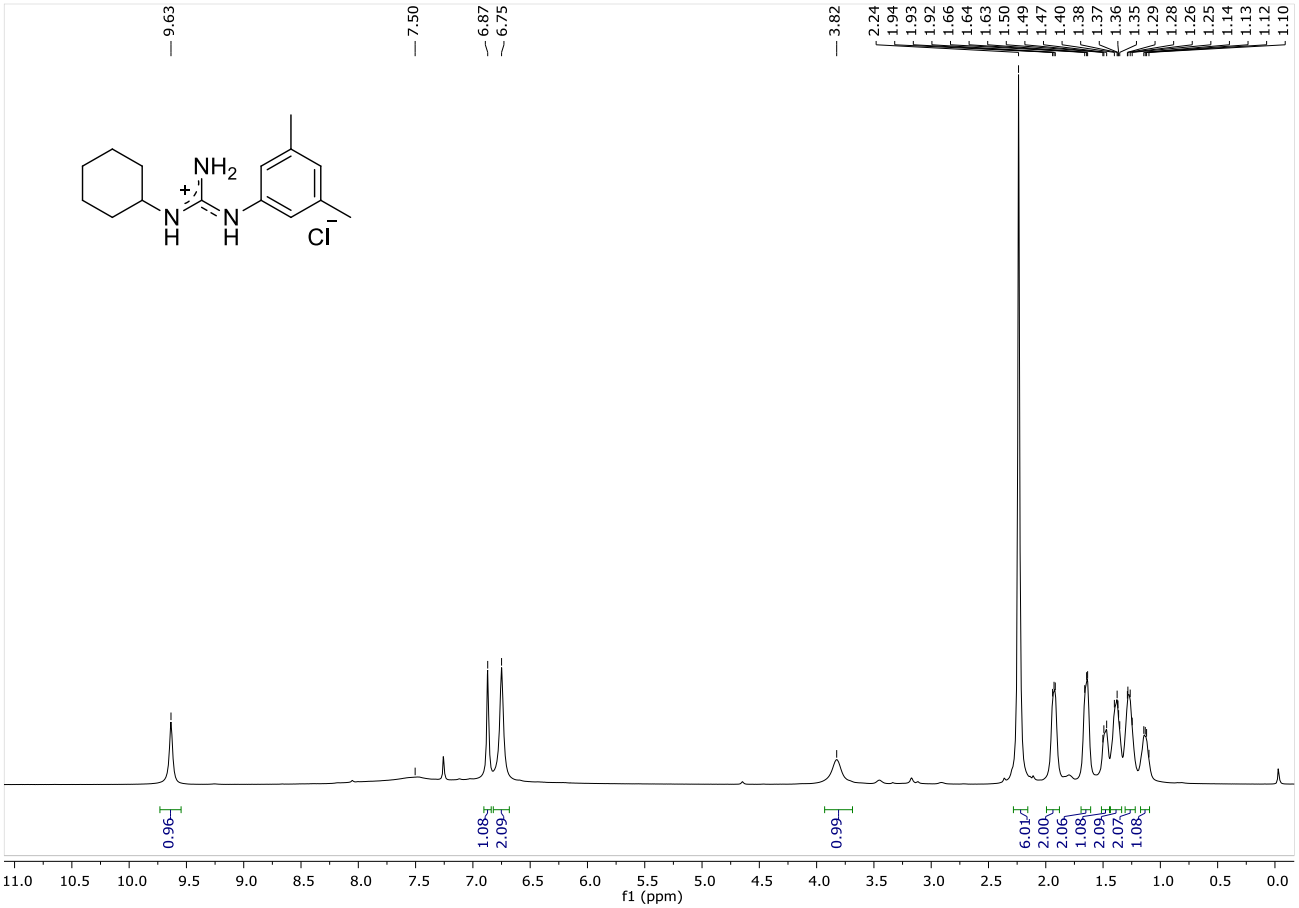
^{13}C-NMR spectrum of **7c** in DMSO-d_6



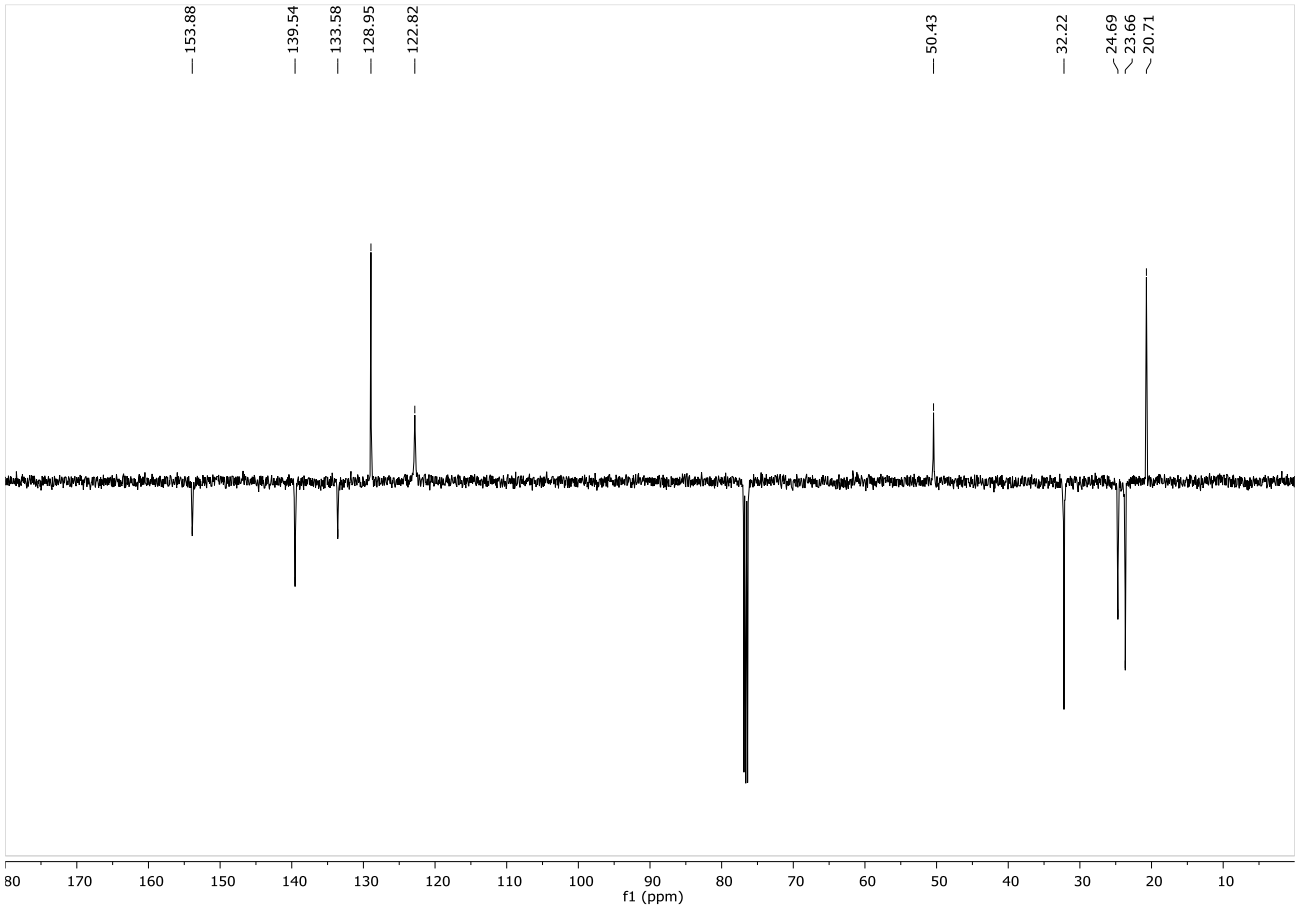
^{1}H-NMR spectrum of **7d** in DMSO-d_6



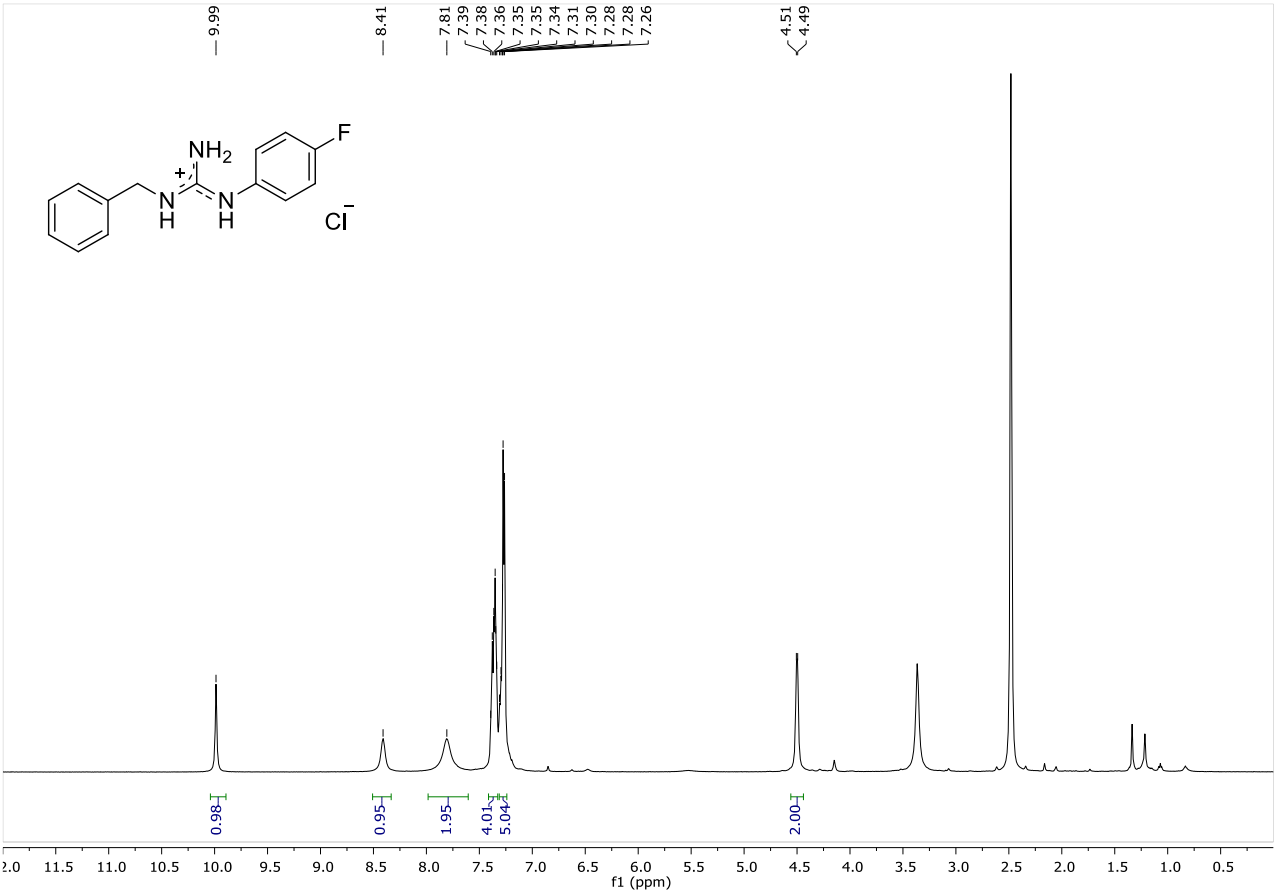
^{13}C-NMR spectrum of **7d** in DMSO-d_6



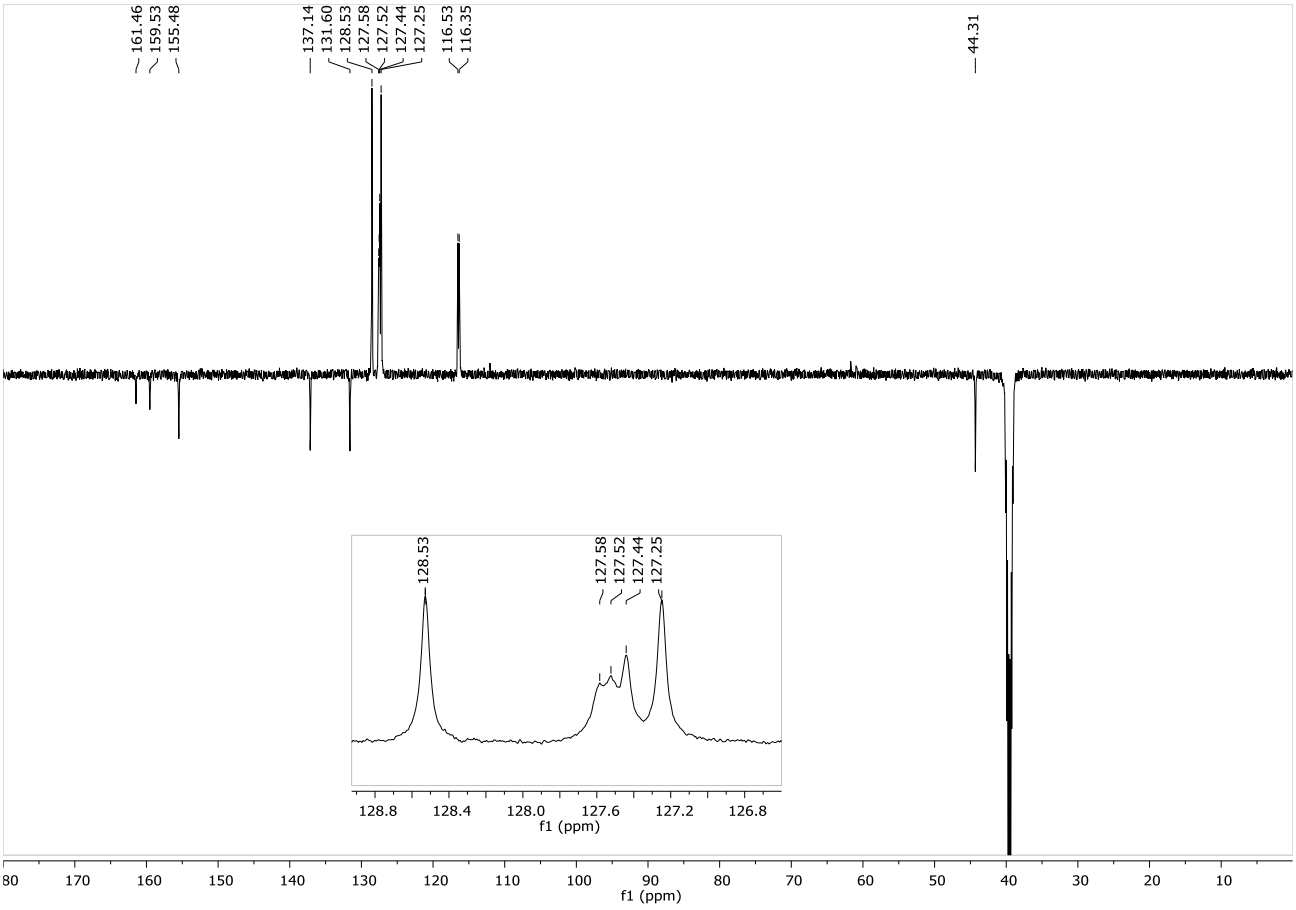
^{1}H-NMR spectrum of **7d** in $CDCl_3$



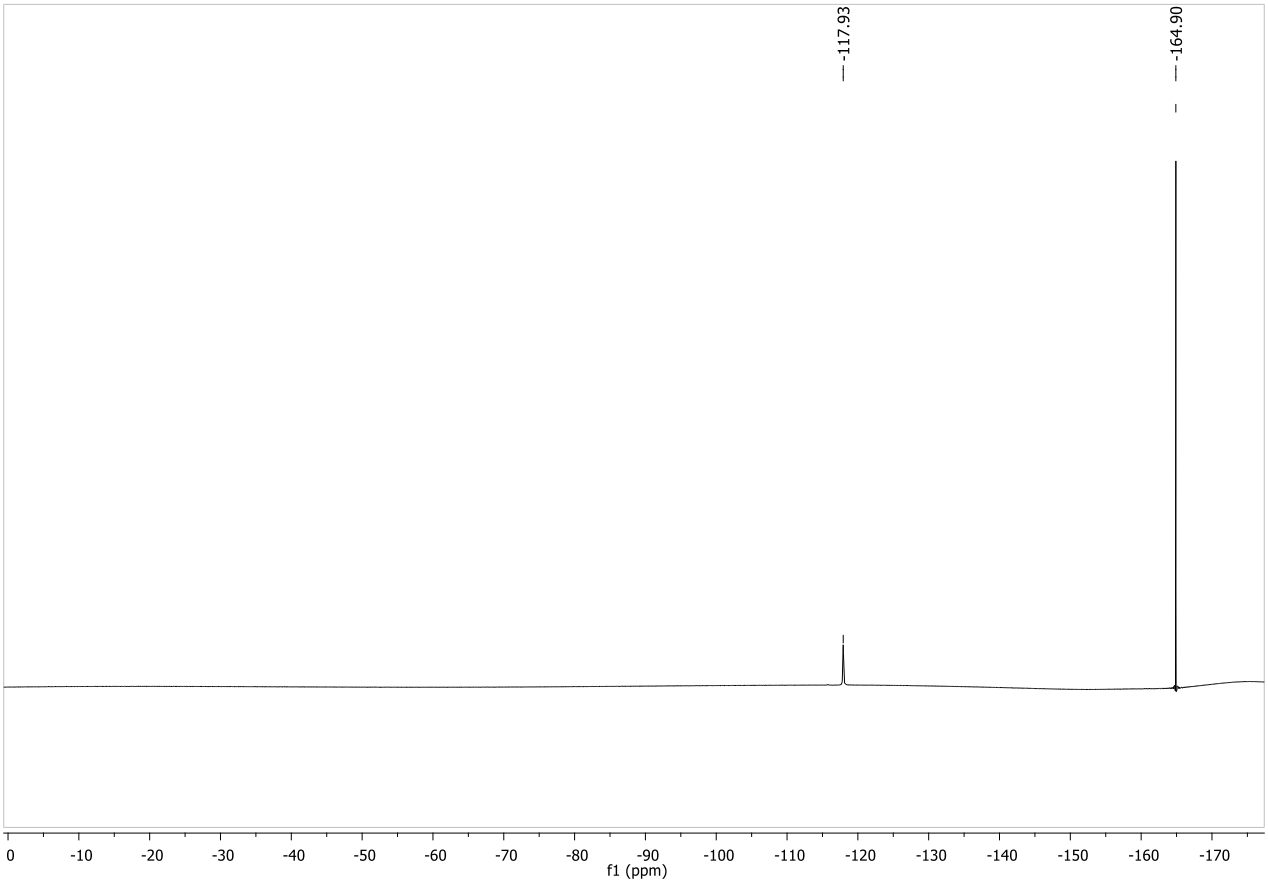
^{13}C-NMR spectrum of **7d** in $CDCl_3$



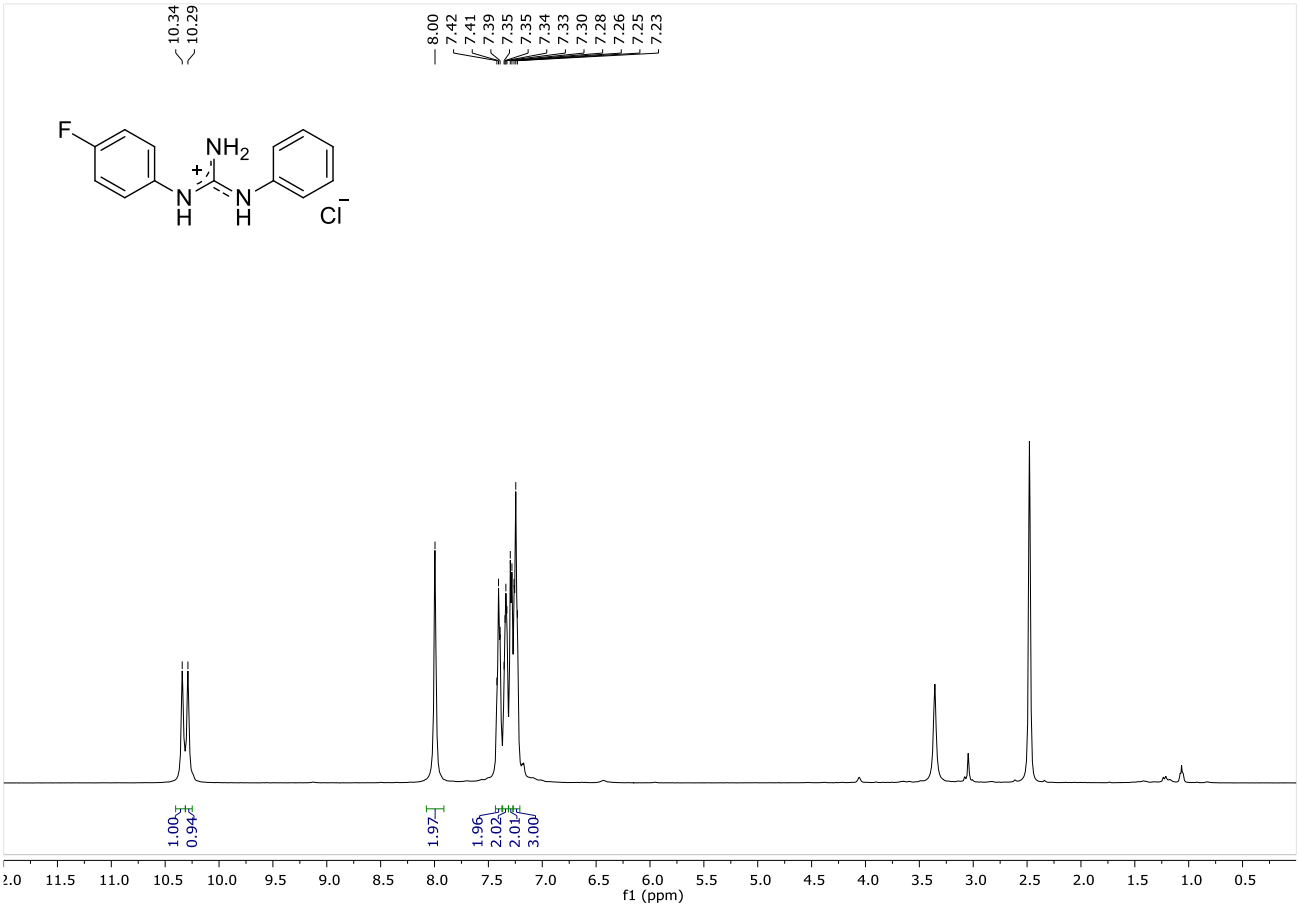
^{1}H-NMR spectrum of **7e** in DMSO-d_6



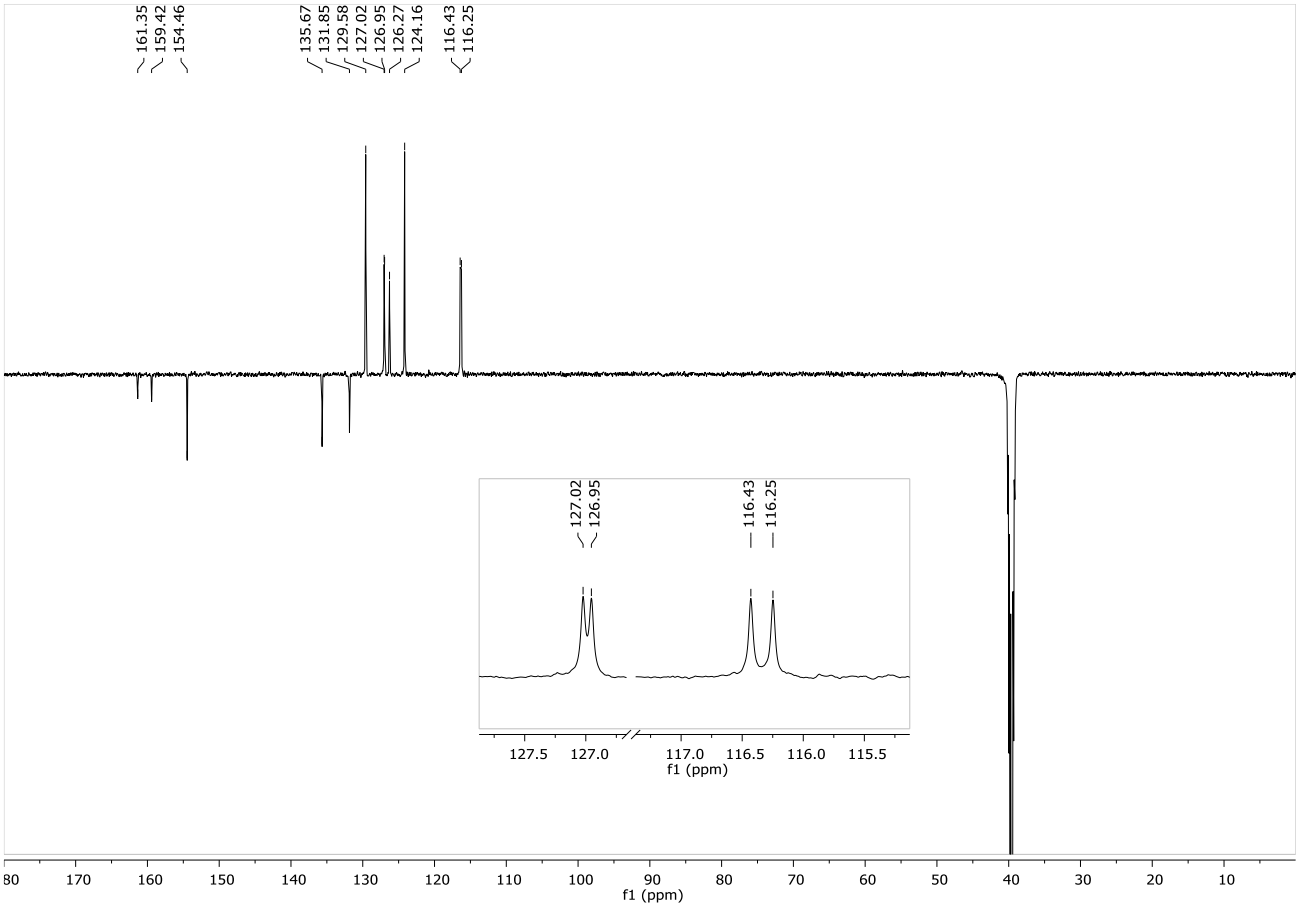
^{13}C-NMR spectrum of **7e** in DMSO-d_6



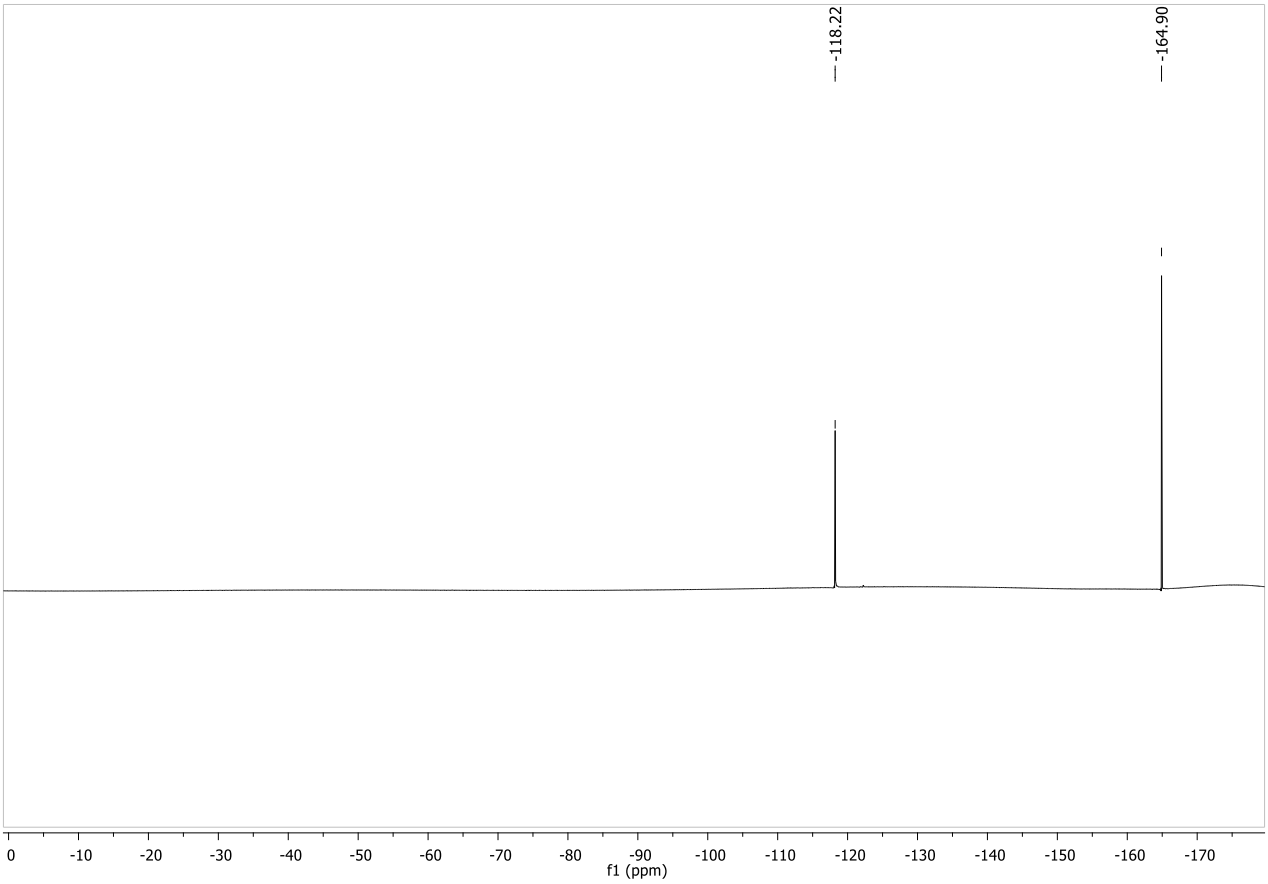
^{19}F-NMR spectrum of **7e** in DMSO-d_6



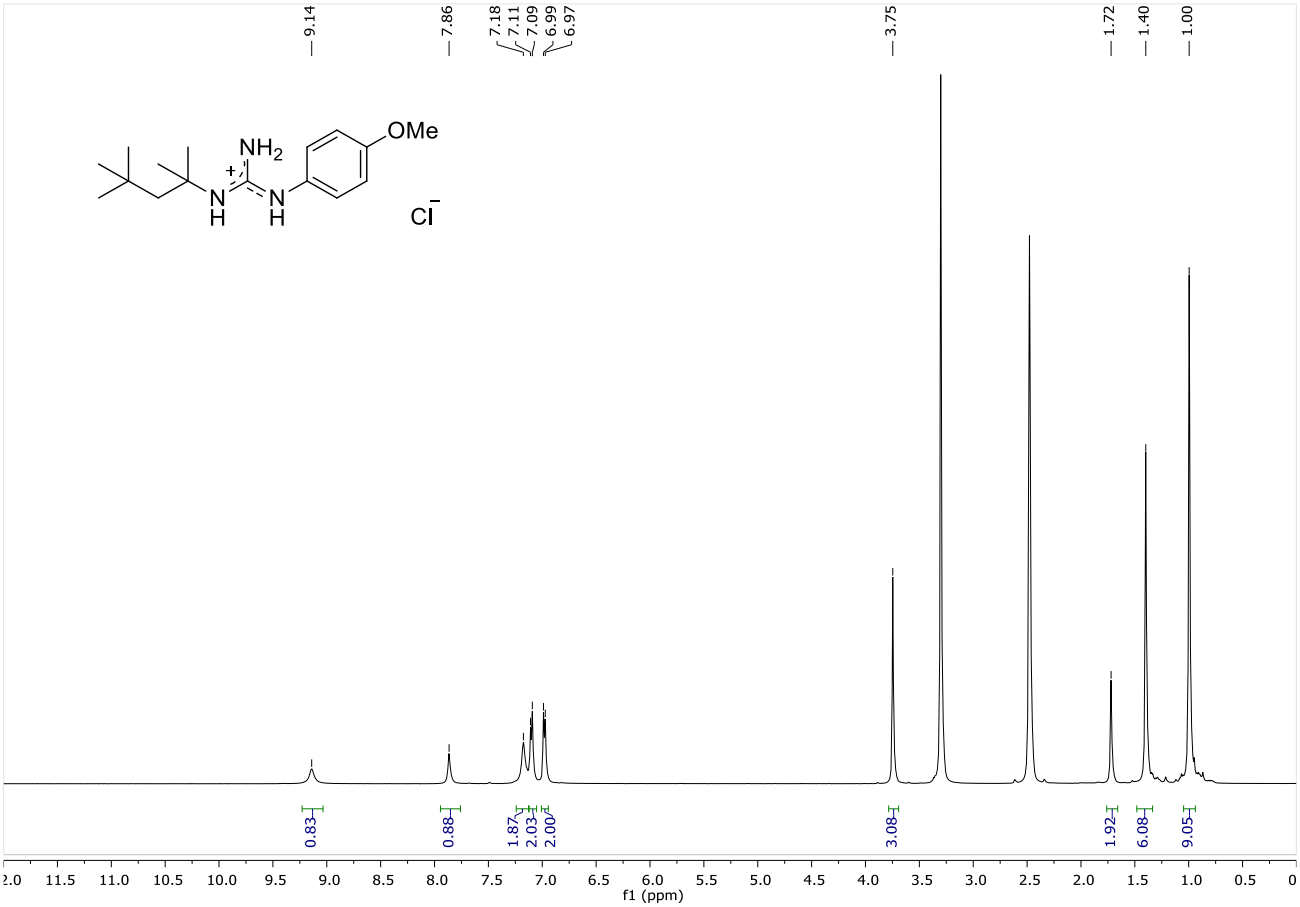
^{1}H-NMR spectrum of **7f** in DMSO-d_6



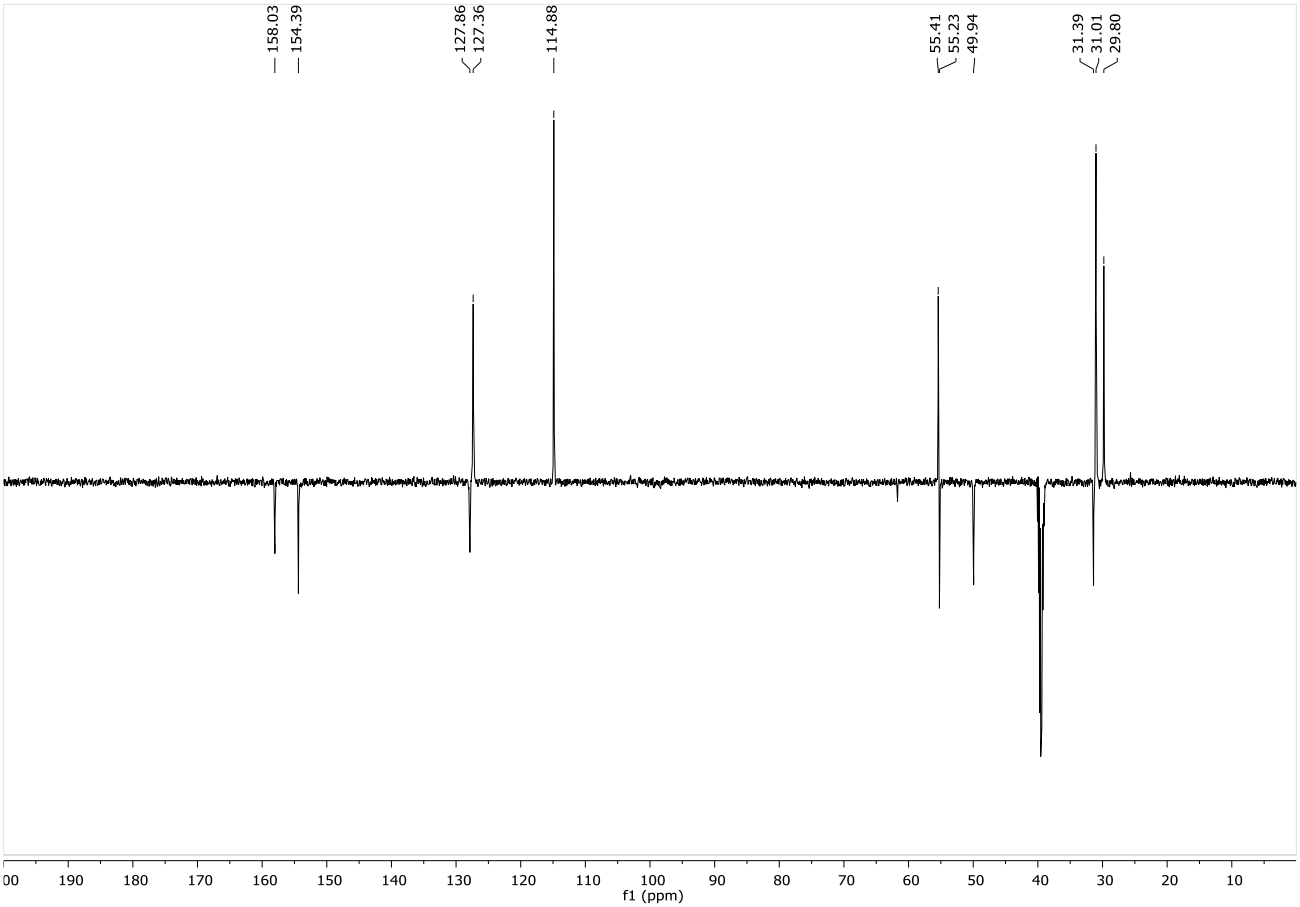
^{13}C-NMR spectrum of **7f** in DMSO-d_6



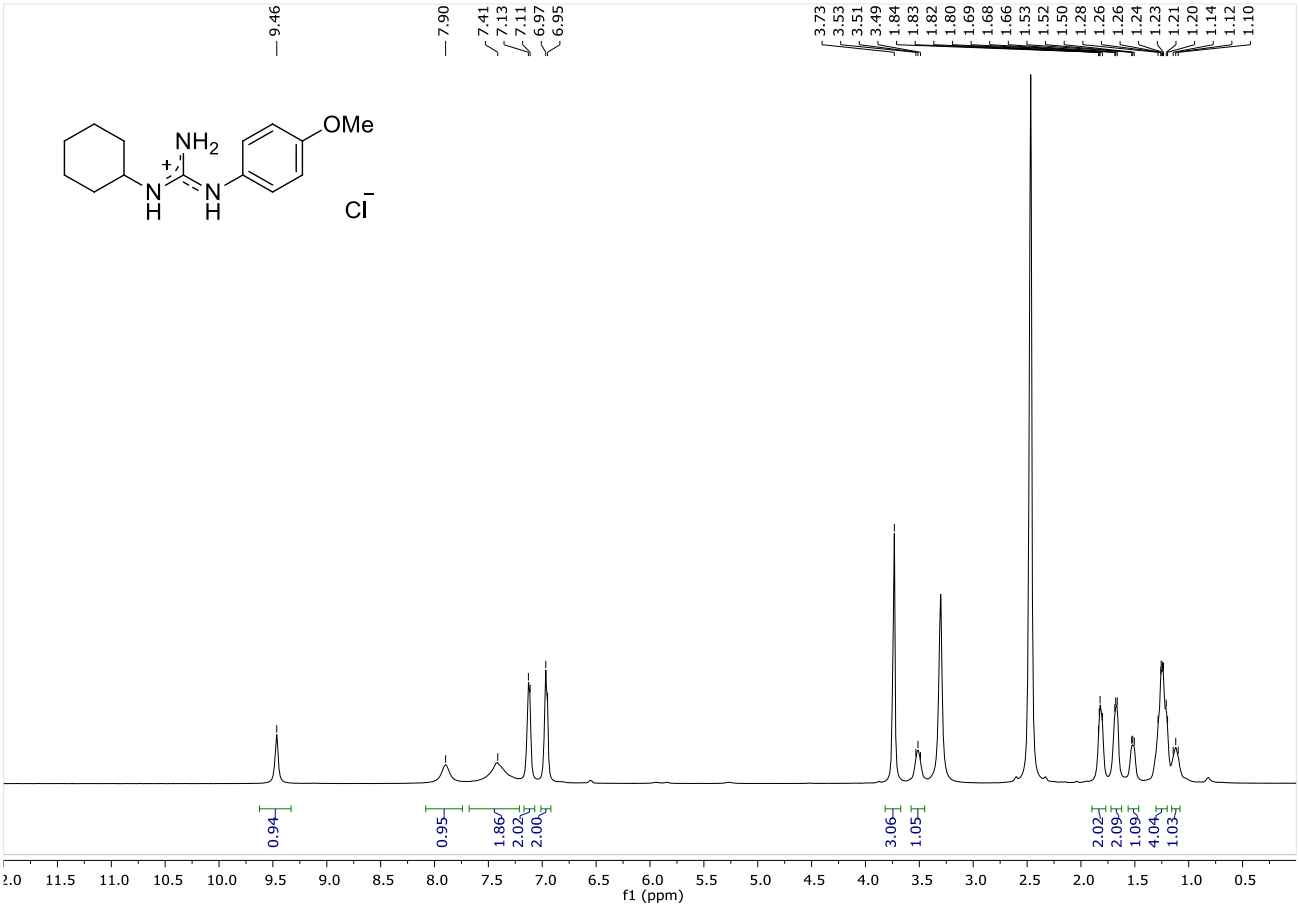
^{19}F-NMR spectrum of **7f** in DMSO-d_6



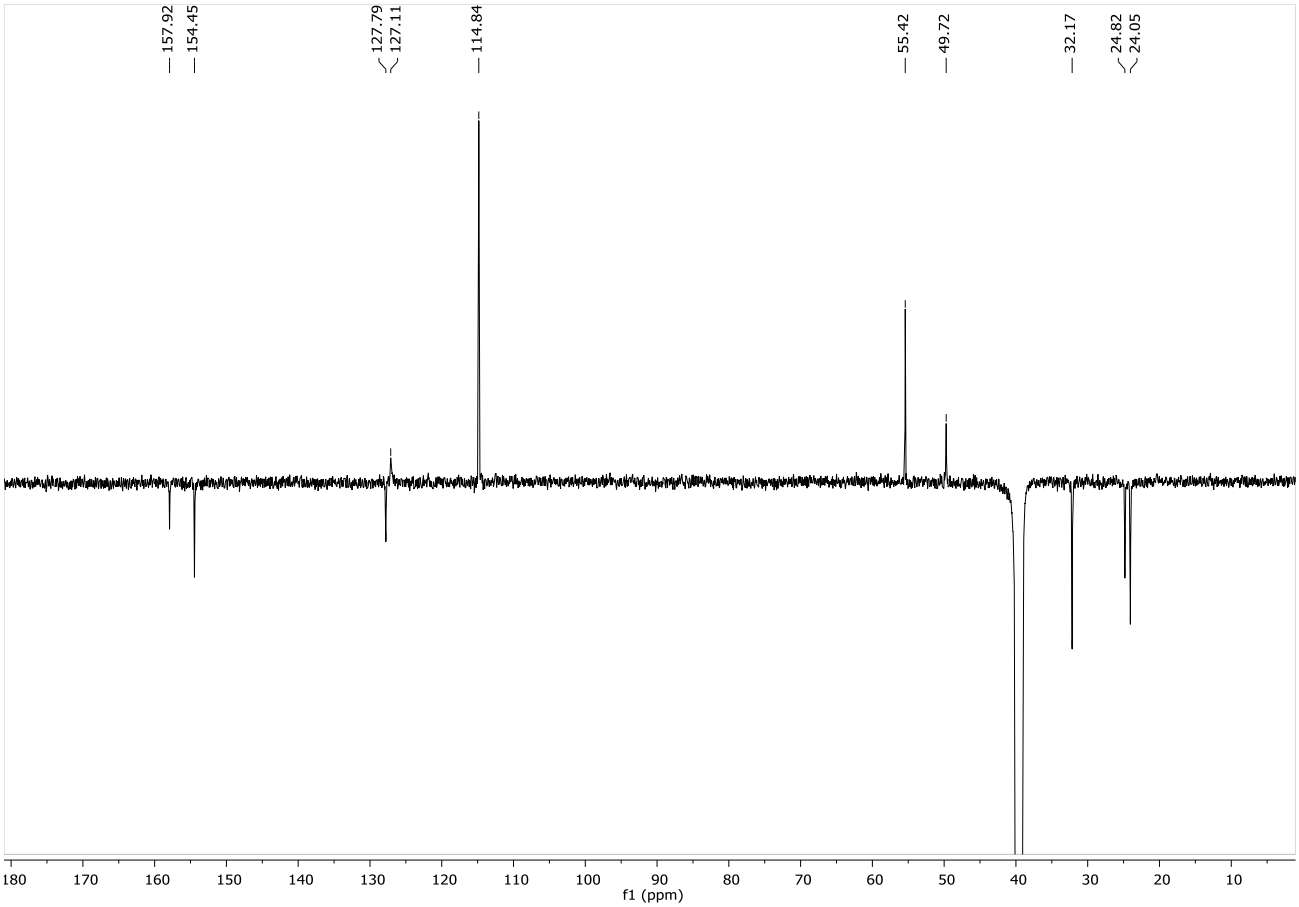
^{1}H-NMR spectrum of **7g** in DMSO-d_6



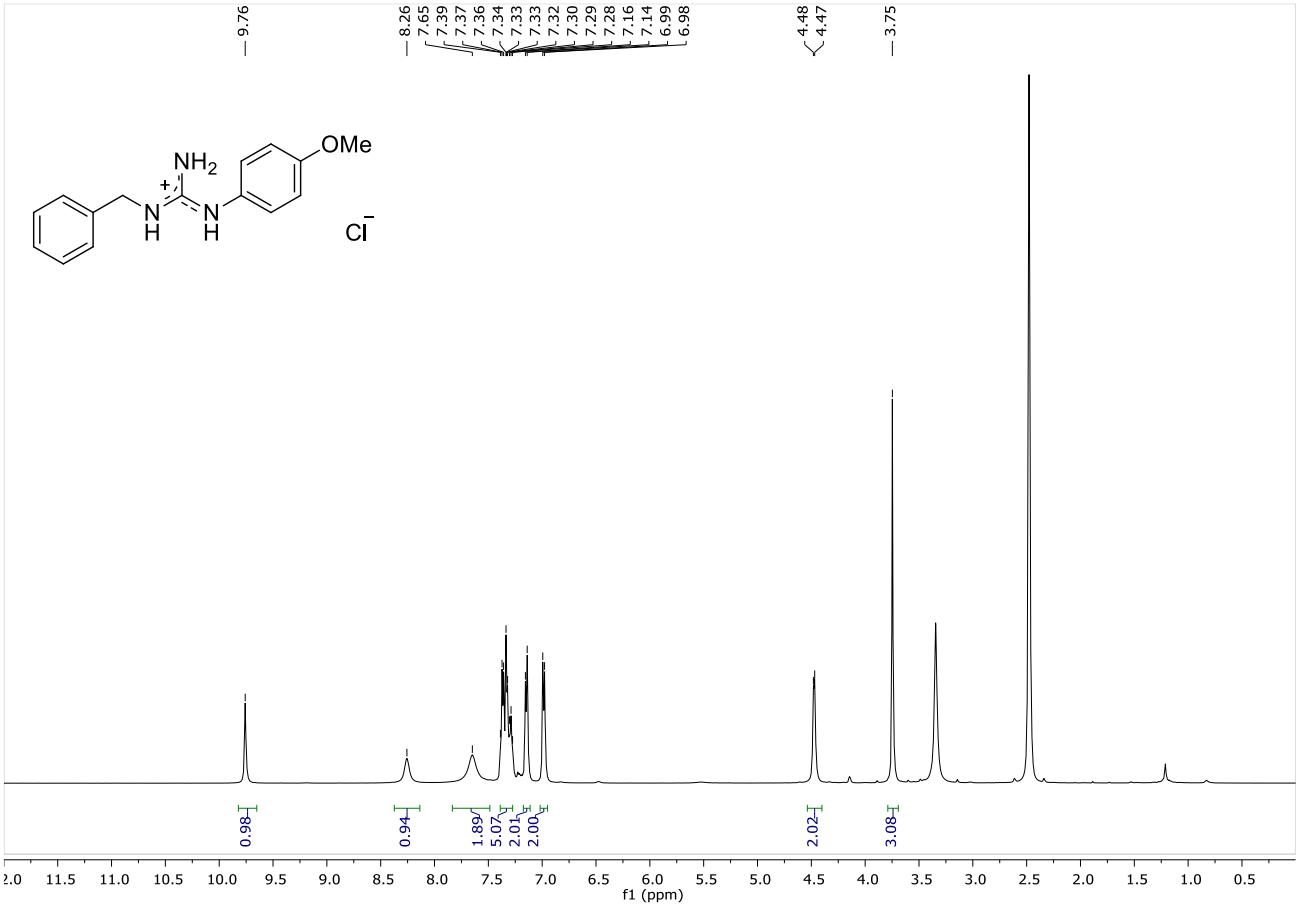
^{13}C-NMR spectrum of **7g** in DMSO-d_6



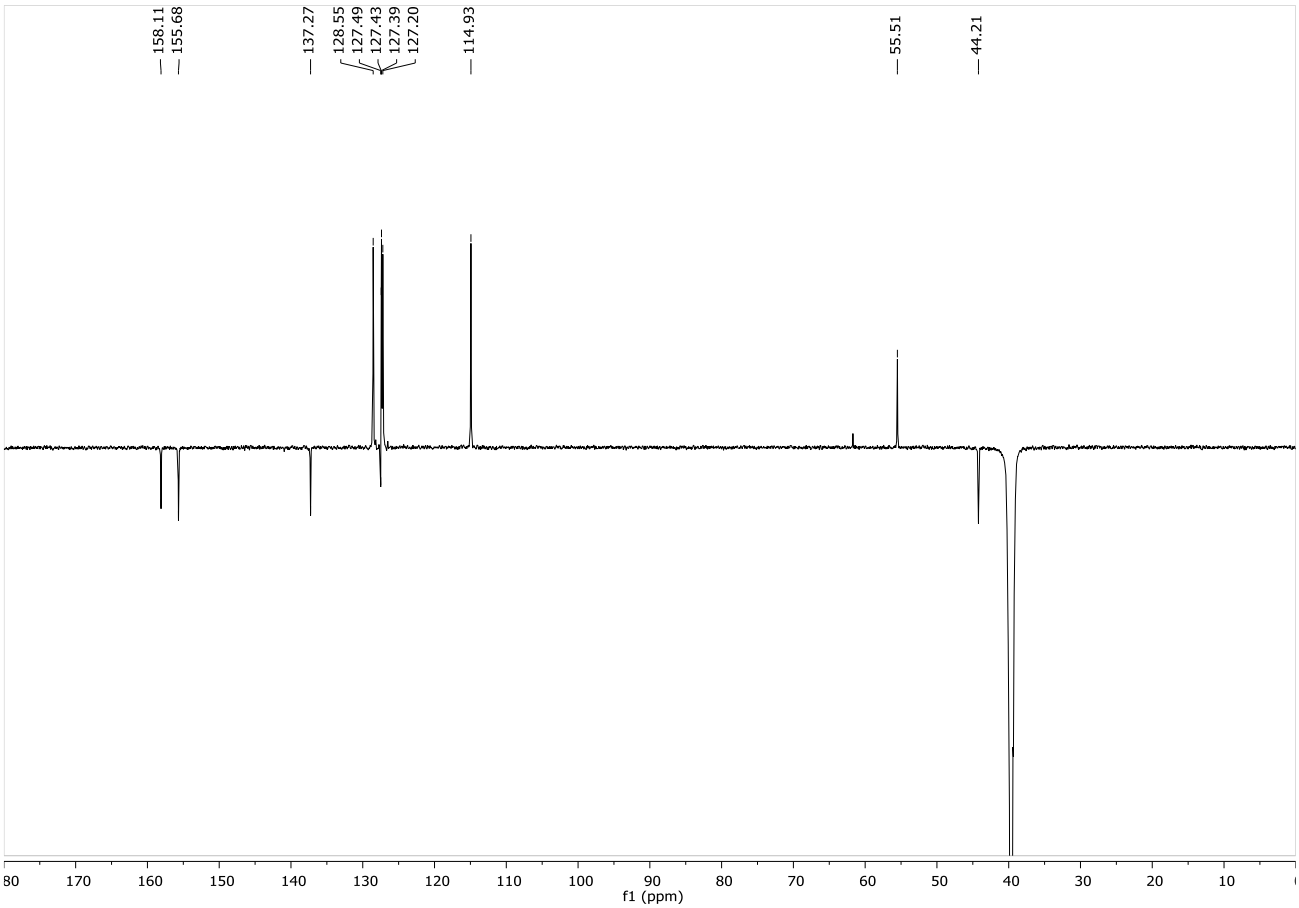
^{1}H-NMR spectrum of **7h** in DMSO-d_6



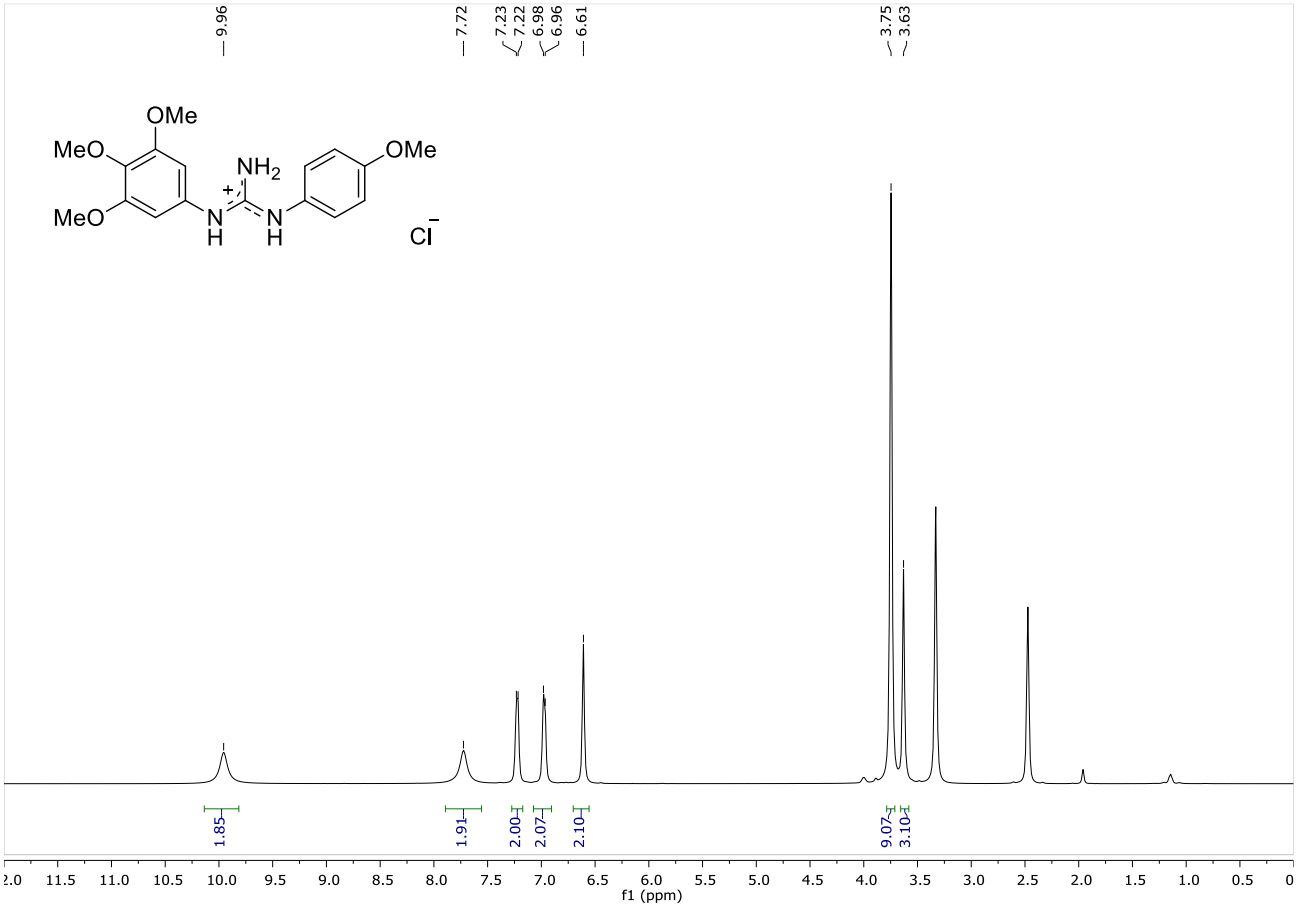
^{13}C-NMR spectrum of **7h** in DMSO-d_6



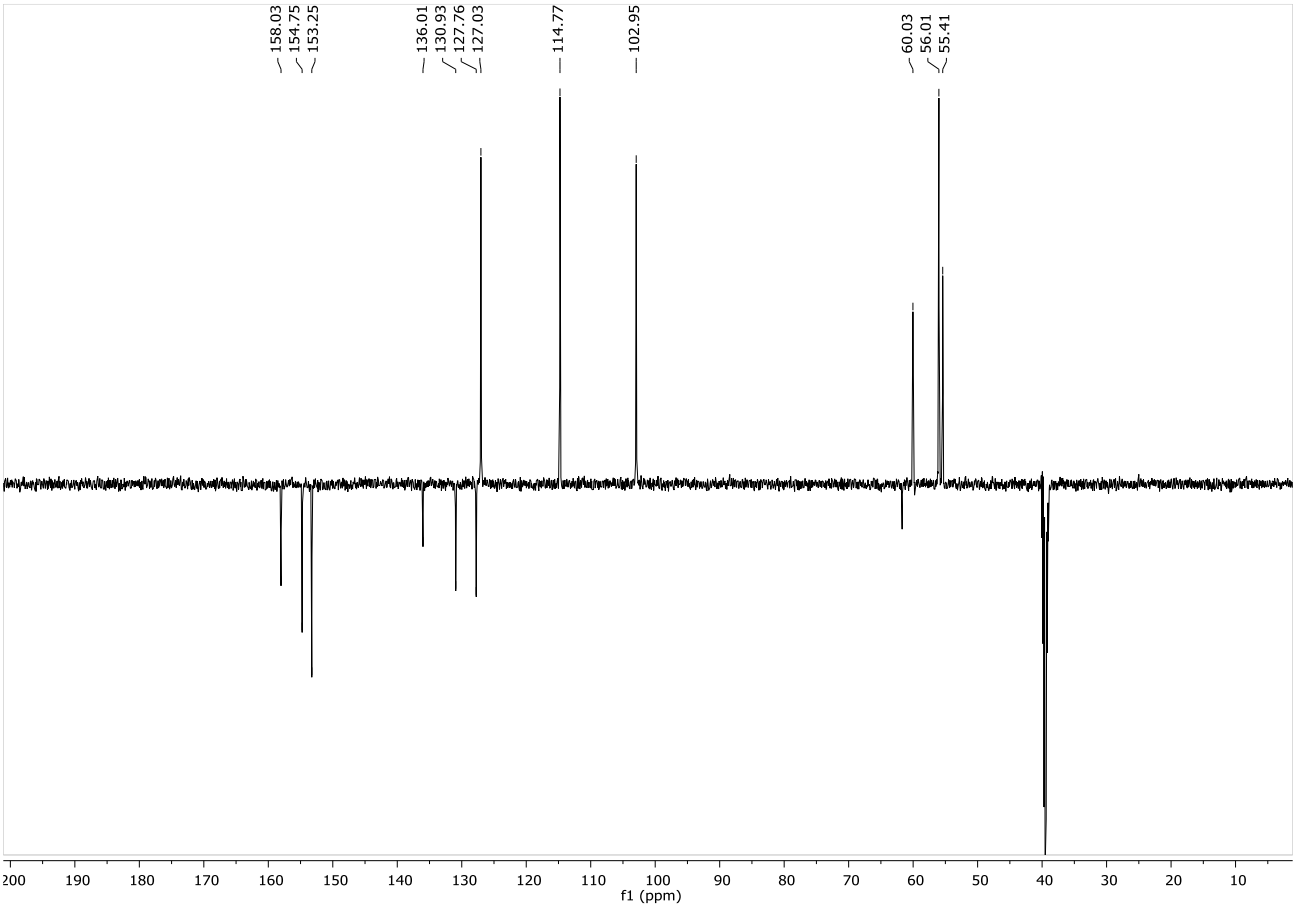
^{1}H-NMR spectrum of **7i** in DMSO-d_6



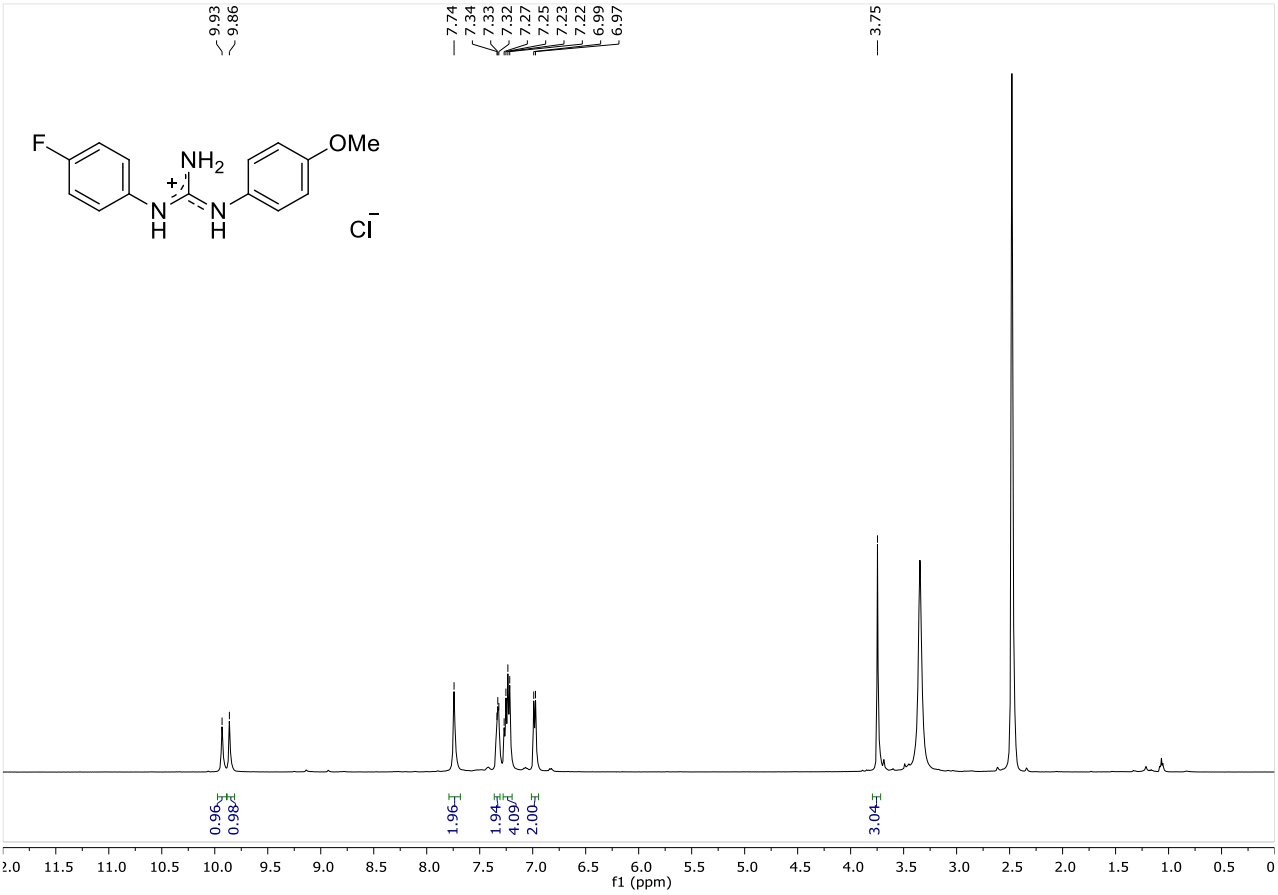
^{13}C-NMR spectrum of **7i** in DMSO-d_6



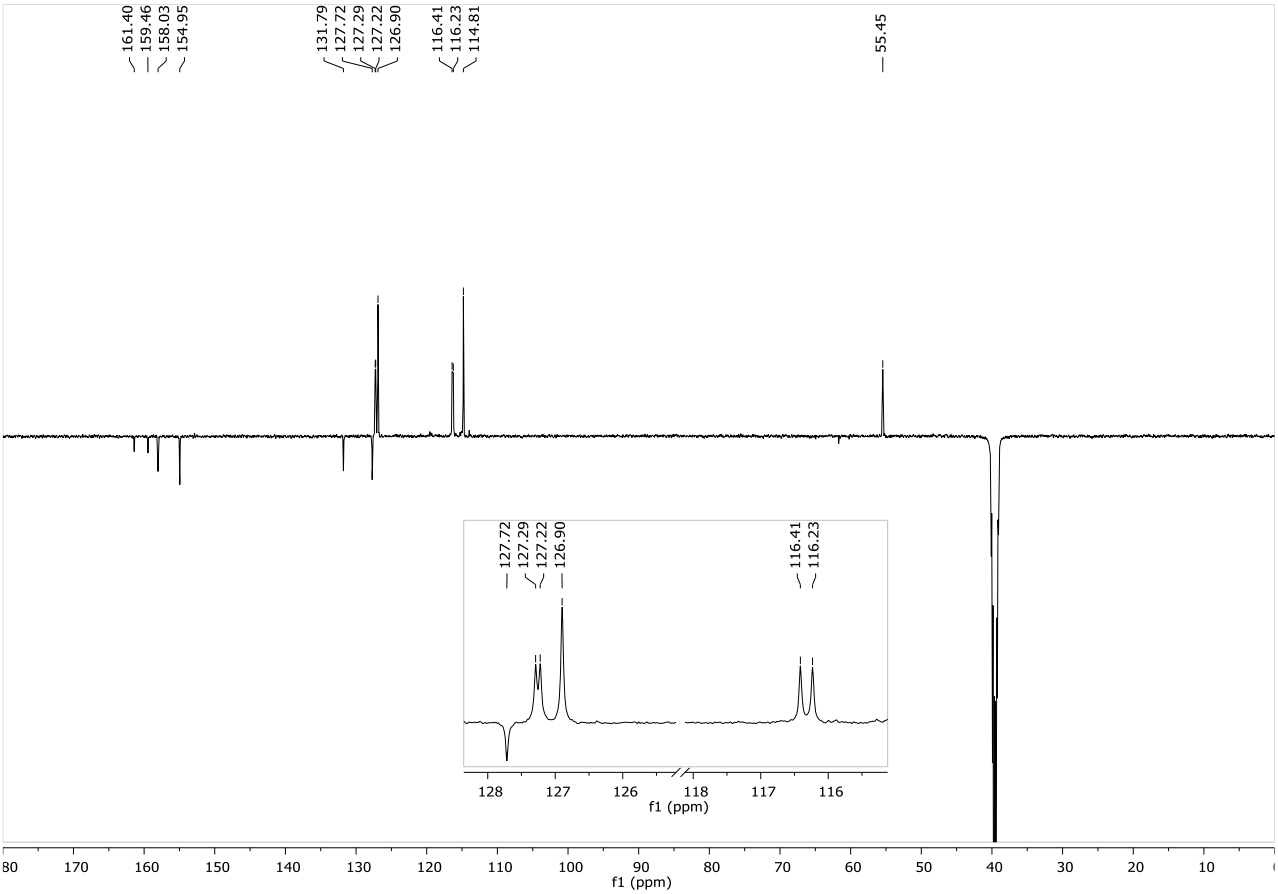
^{1}H-NMR spectrum of **7j** in DMSO-d_6



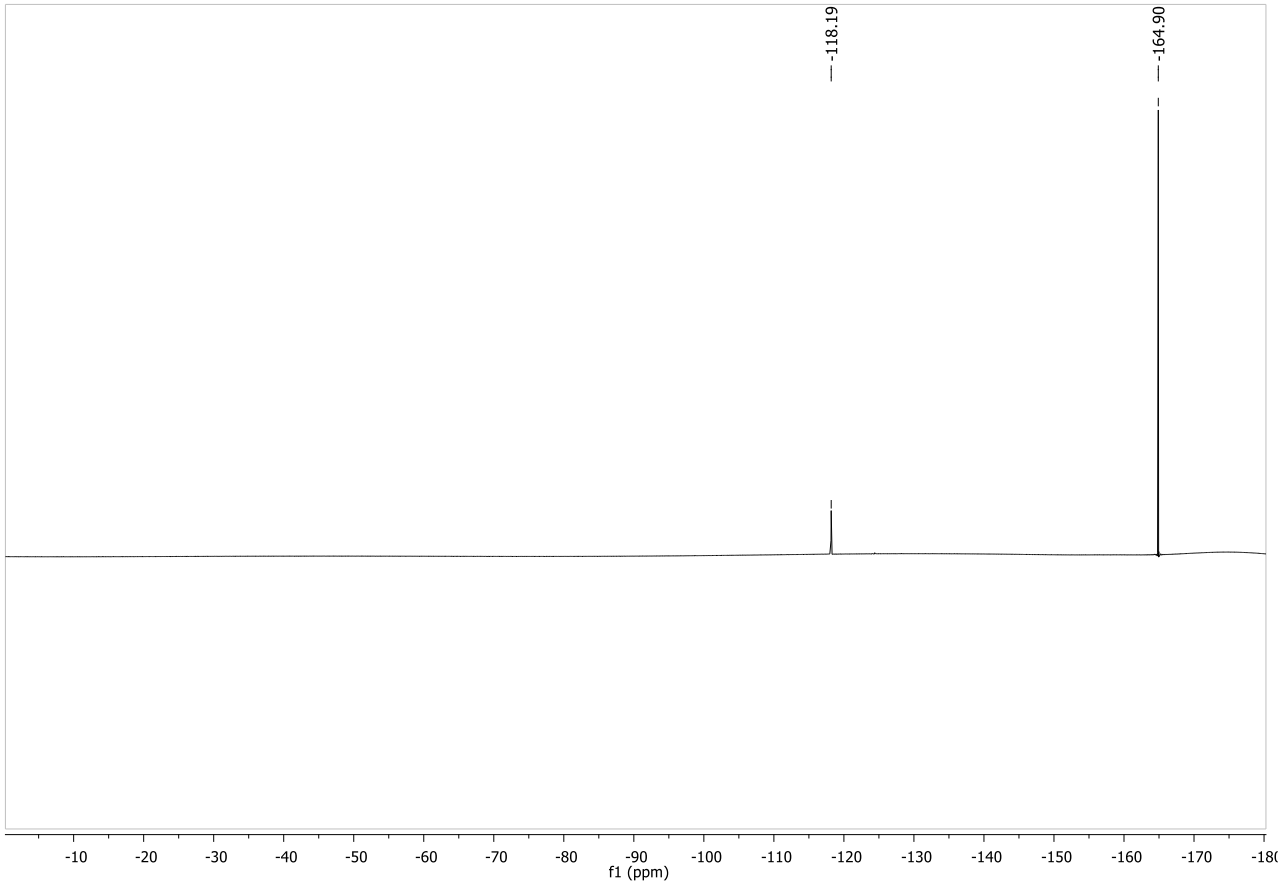
^{13}C-NMR spectrum of **7j** in DMSO-d_6



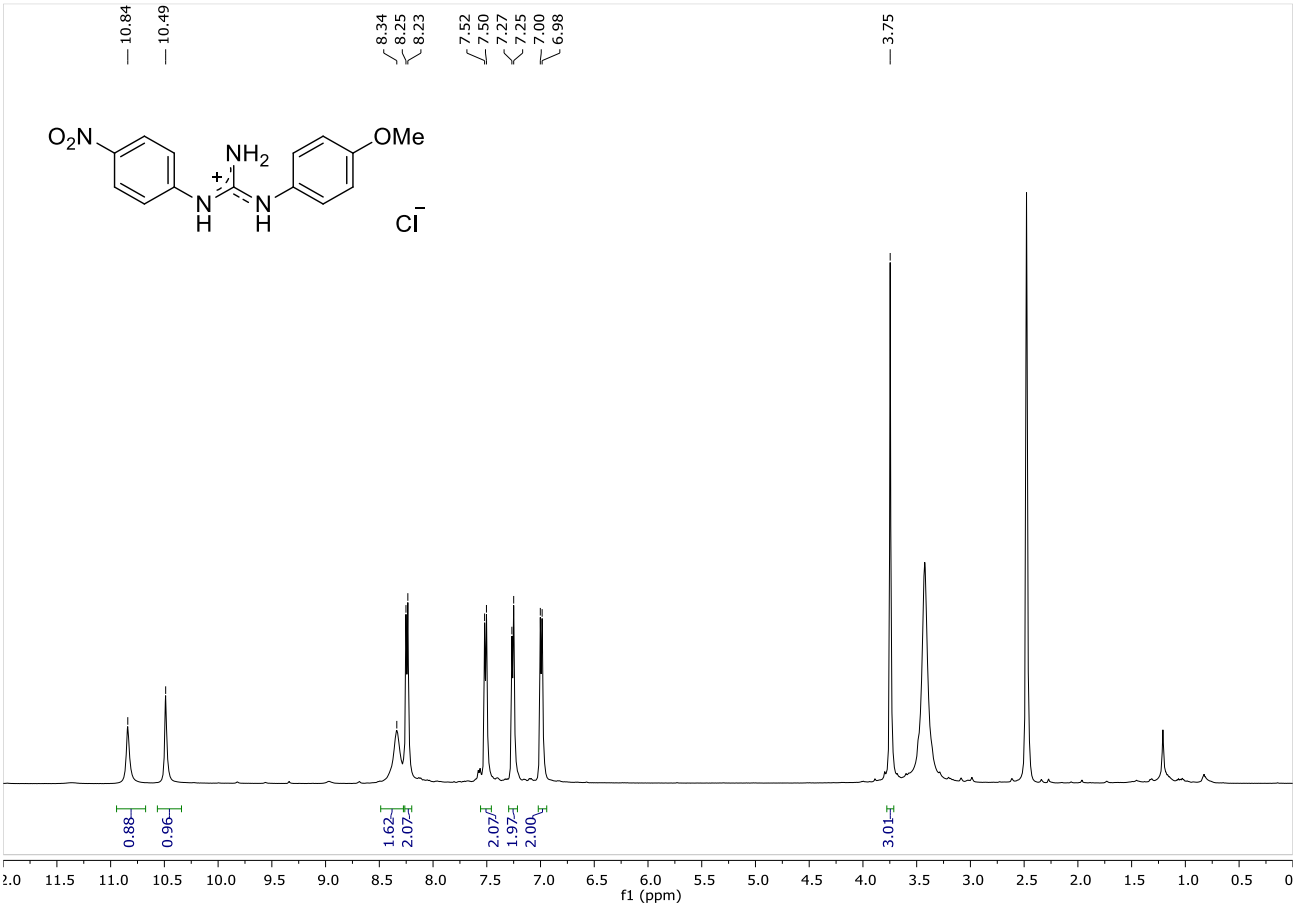
^{1}H-NMR spectrum of **7k** in DMSO-d_6



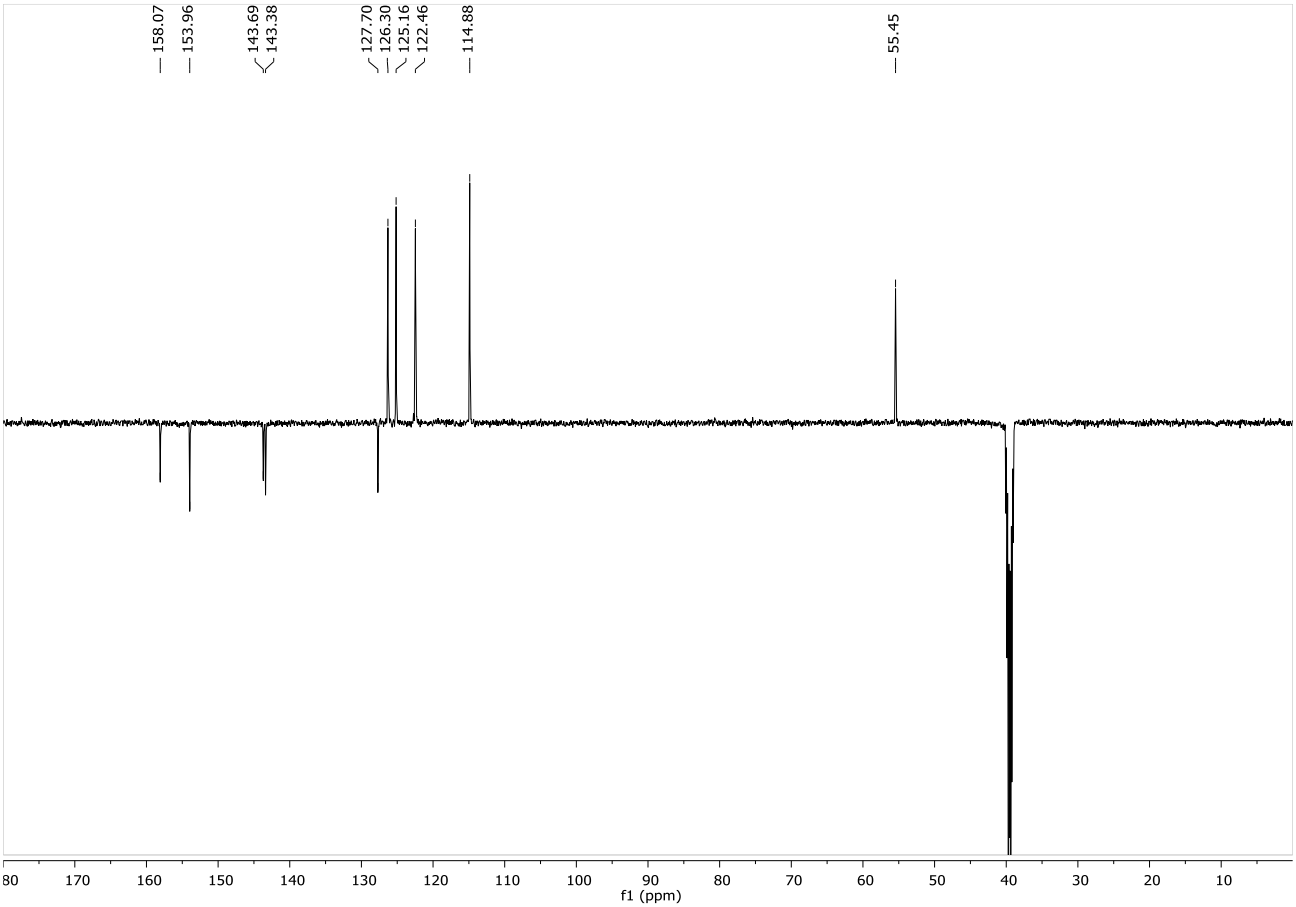
^{13}C-NMR spectrum of **7k** in DMSO-d_6



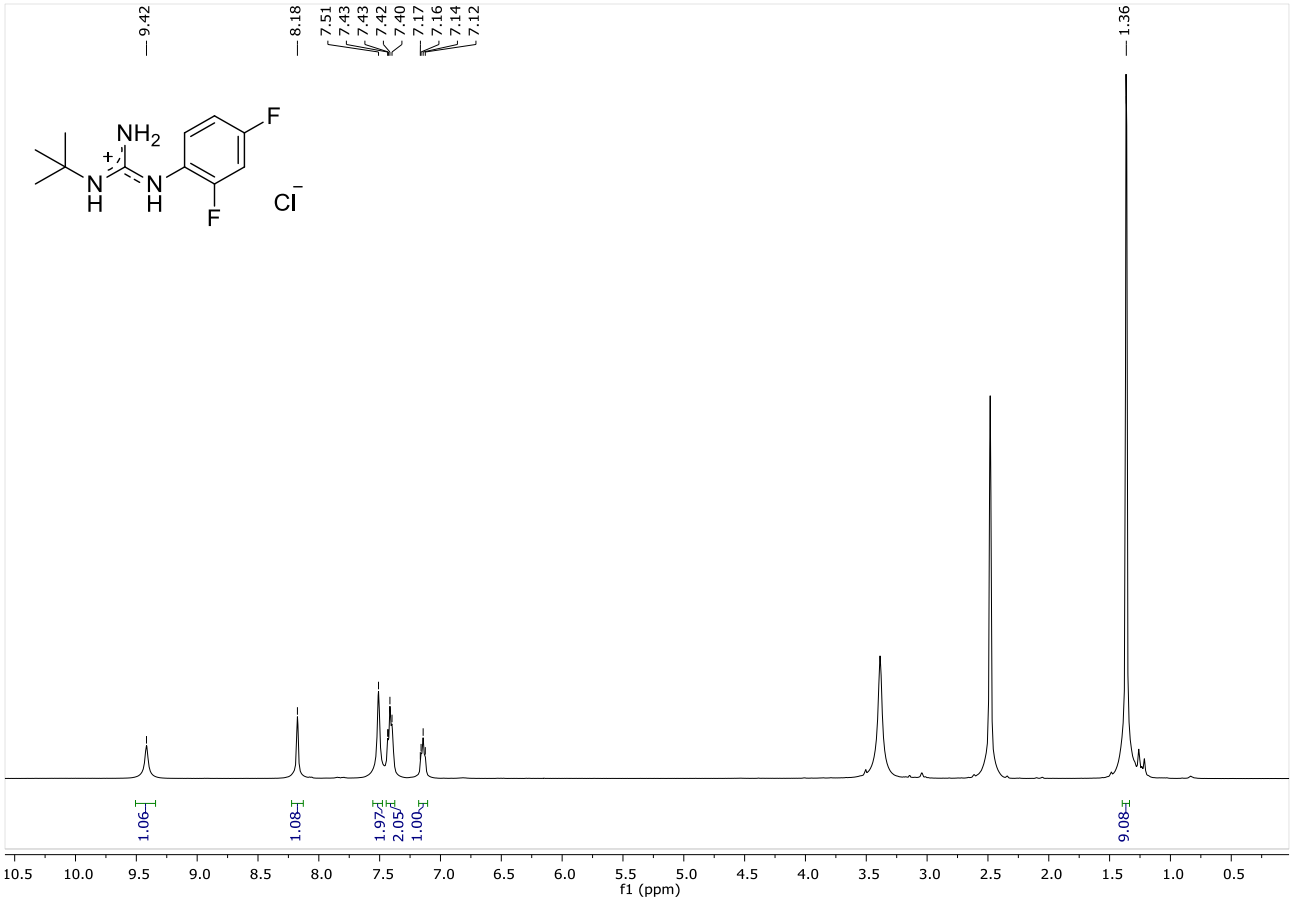
^{19}F-NMR spectrum of **7k** in DMSO-d_6



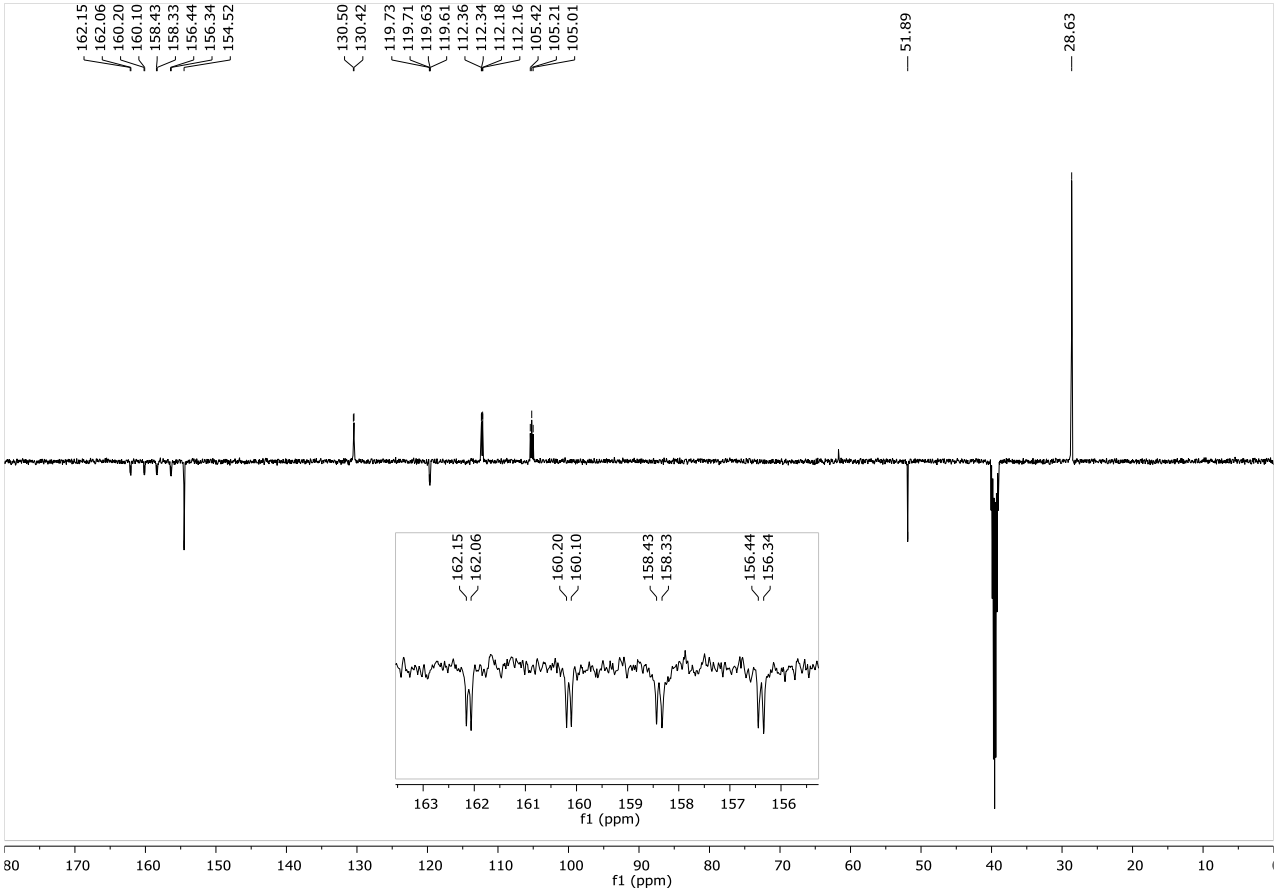
^{1}H-NMR spectrum of **7l** in DMSO-d_6



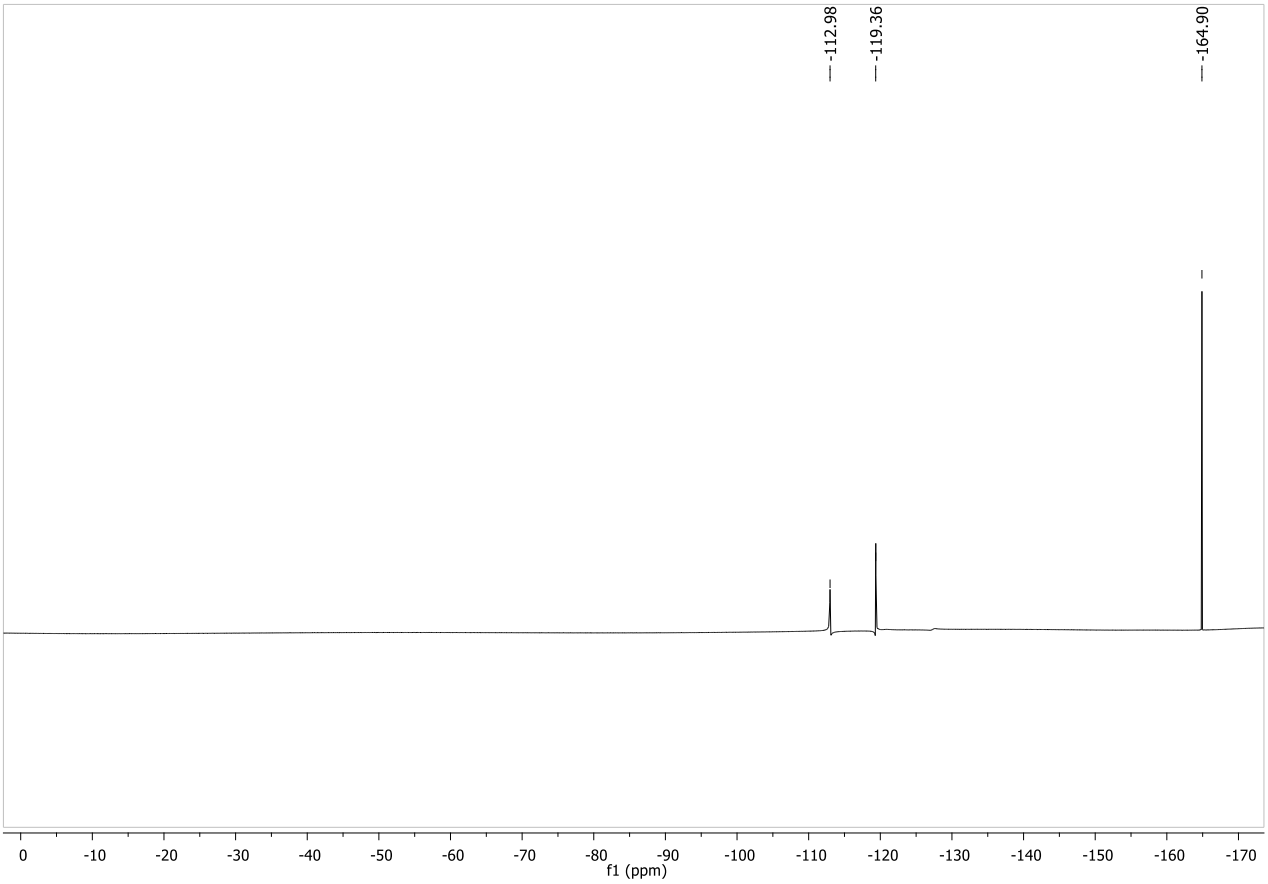
^{13}C-NMR spectrum of **7l** in DMSO-d_6



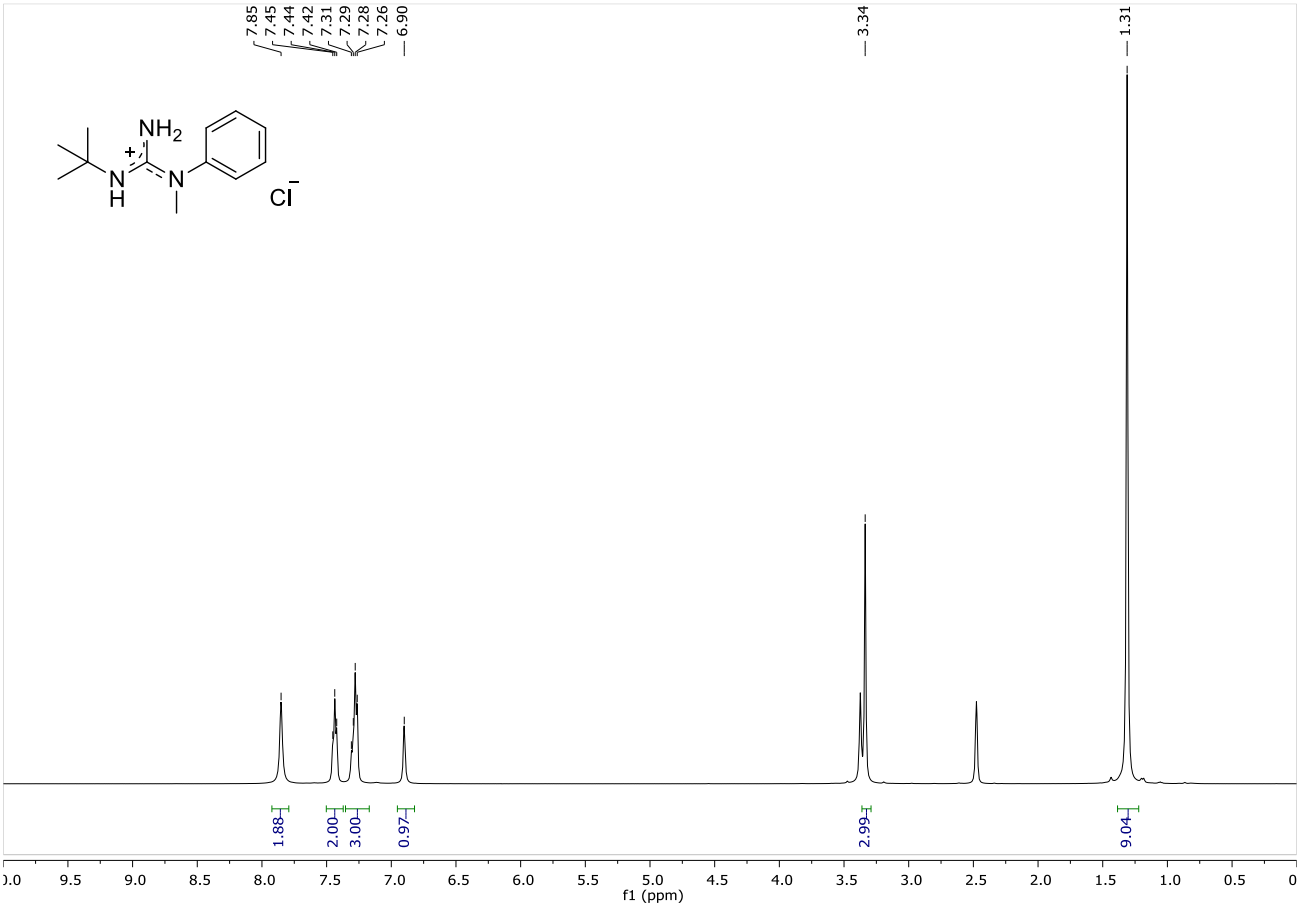
^{1}H-NMR spectrum of **7m** in DMSO-d_6



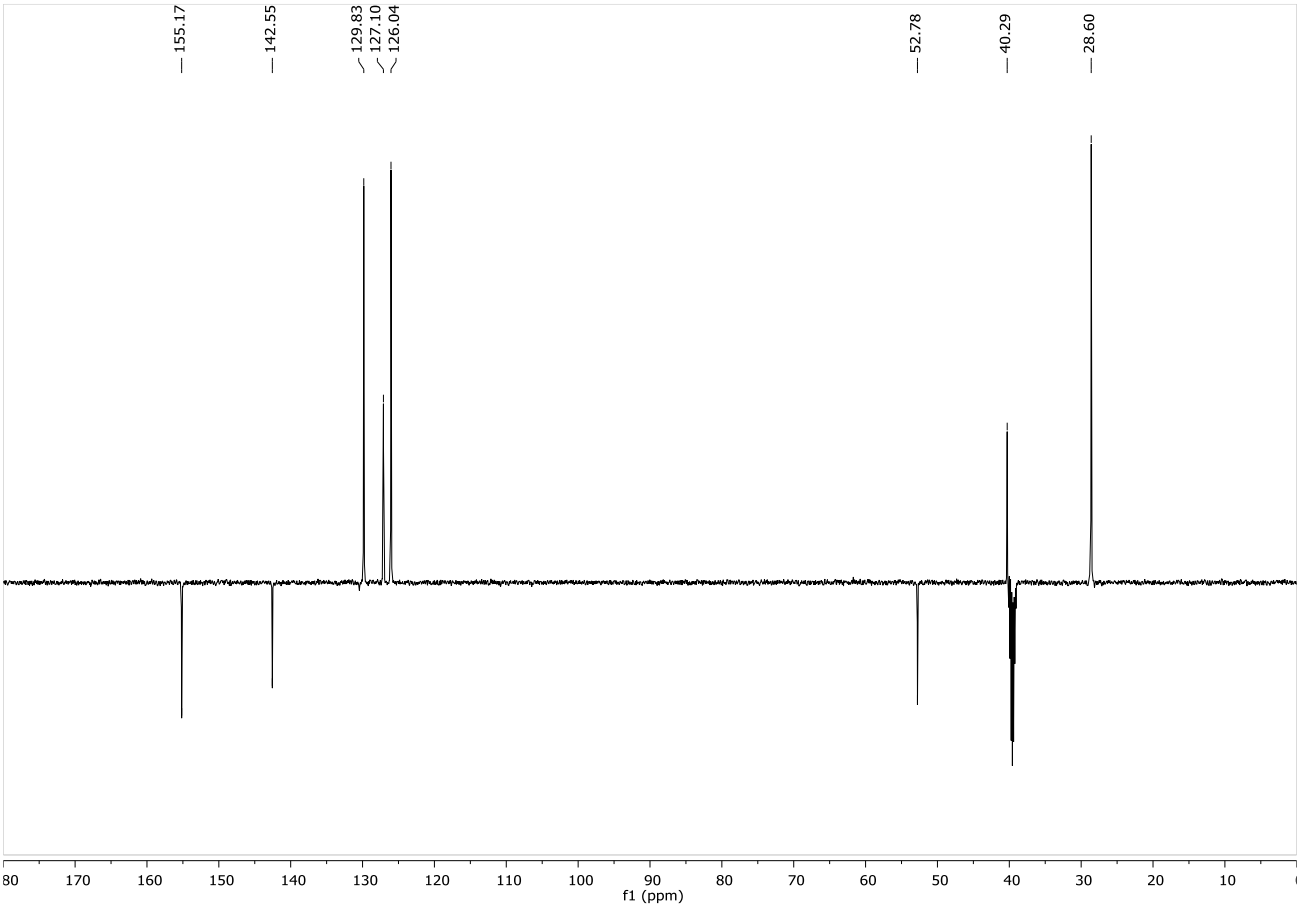
^{13}C-NMR spectrum of **7m** in DMSO-d_6



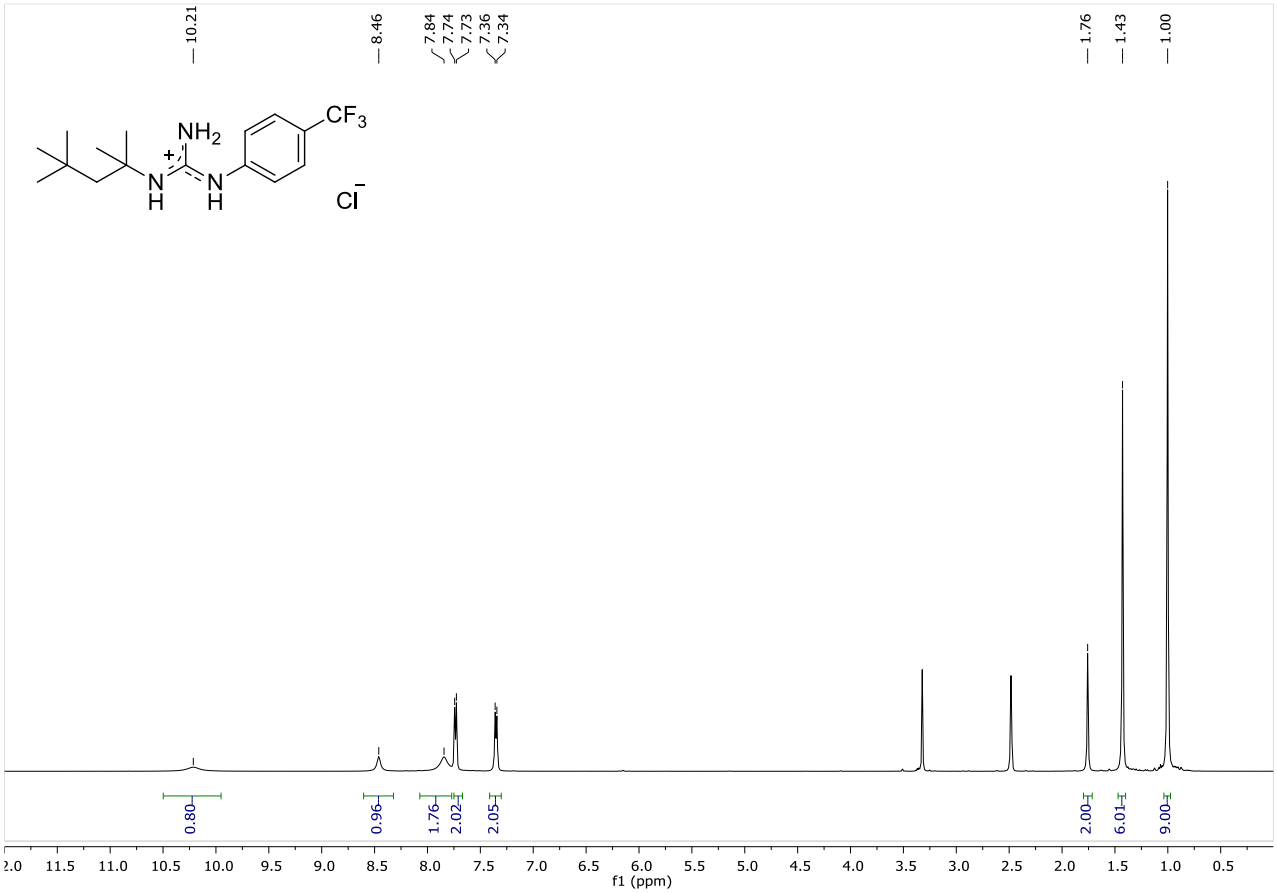
^{19}F-NMR spectrum of **7m** in DMSO-d_6



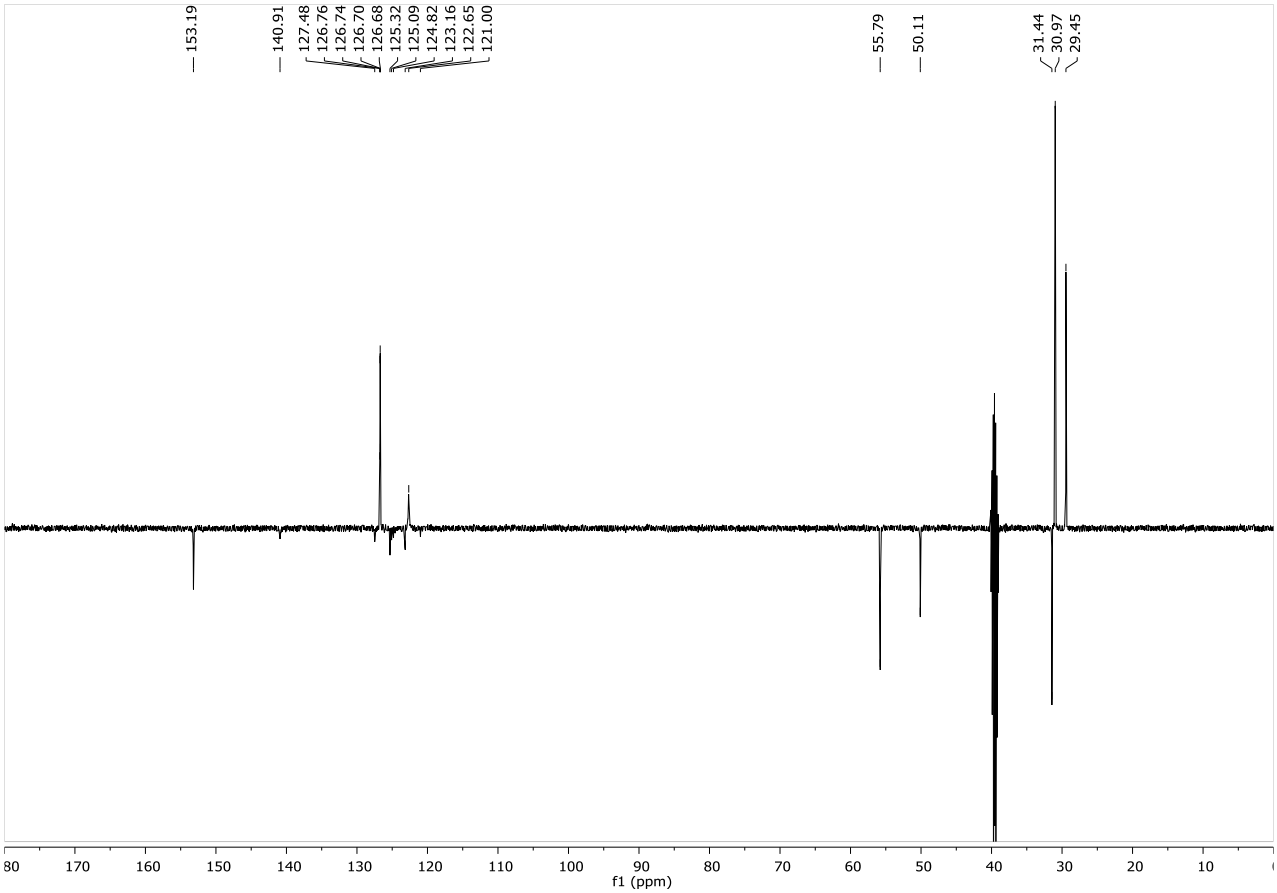
^{1}H-NMR spectrum of **7n** in DMSO-d_6



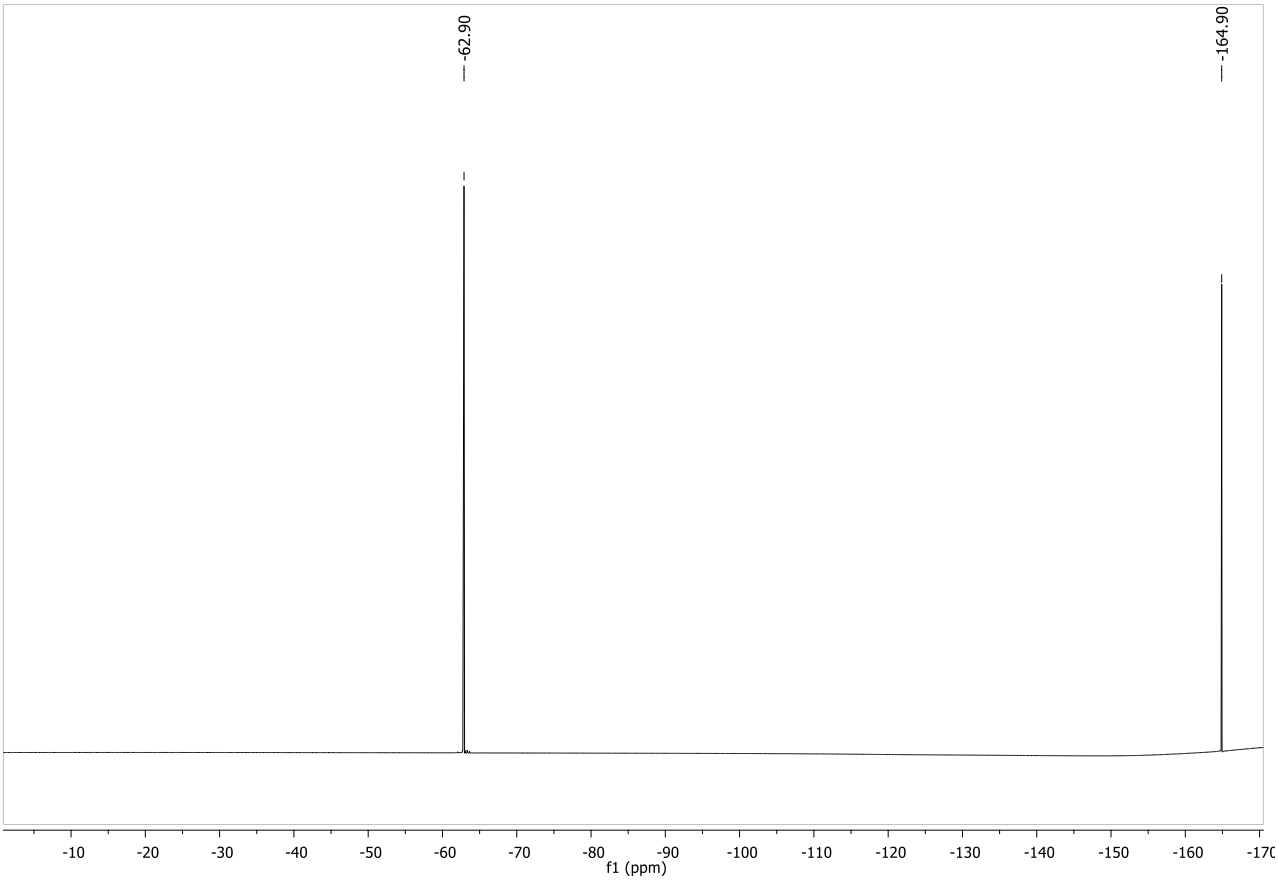
^{13}C-NMR spectrum of **7n** in DMSO-d_6



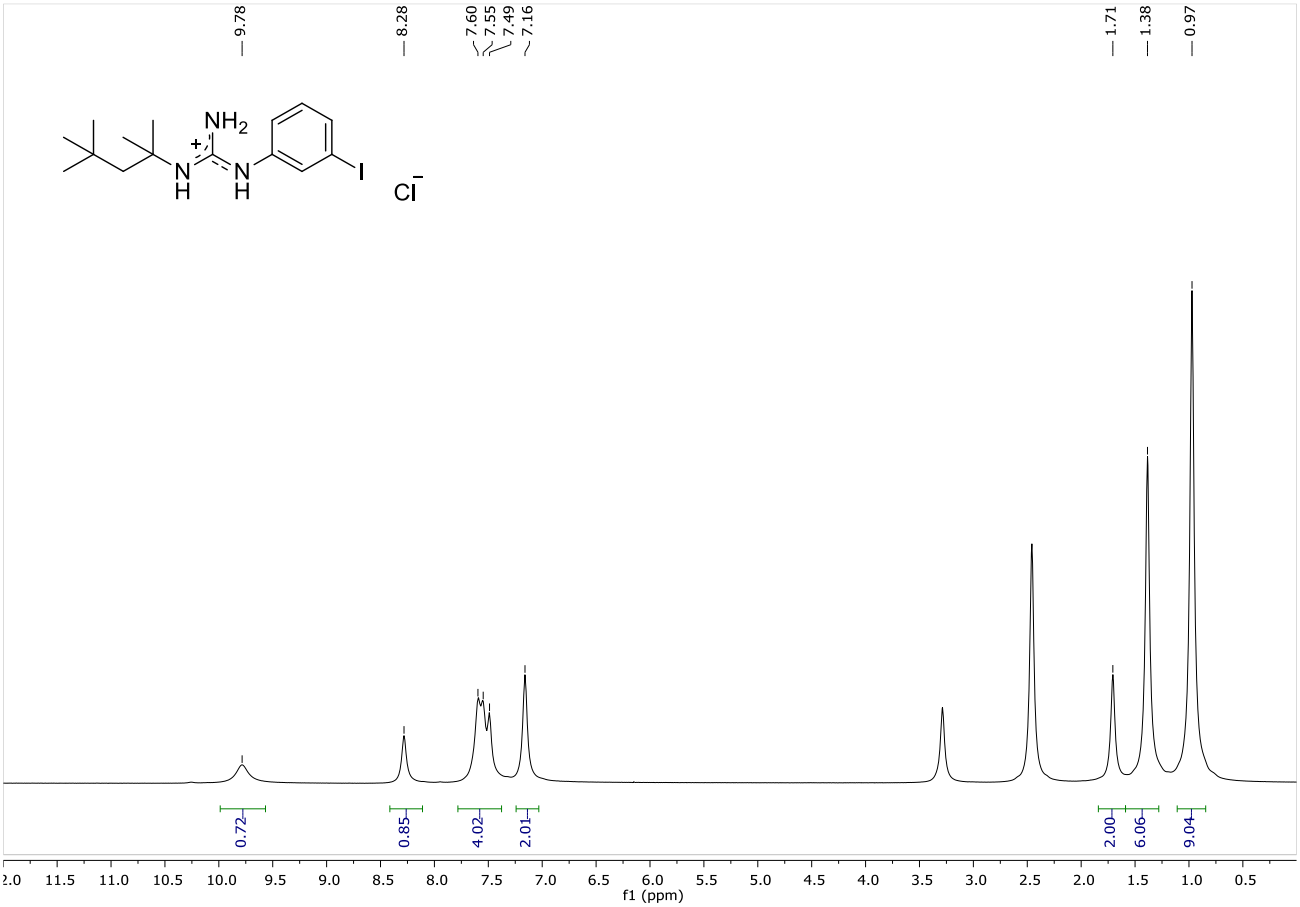
^{1}H-NMR spectrum of **7o** in DMSO-d_6



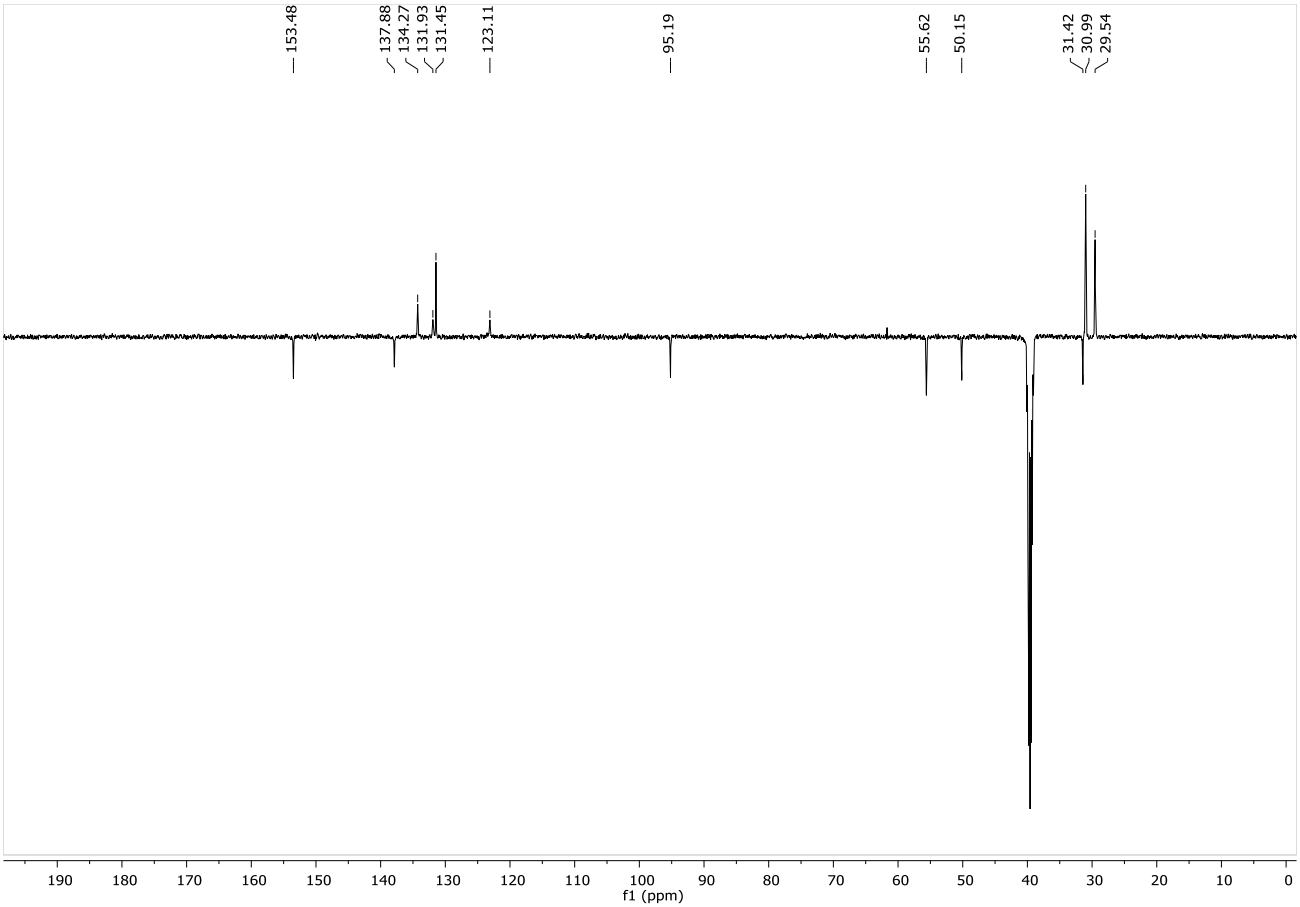
^{13}C-NMR spectrum of **7o** in DMSO-d_6



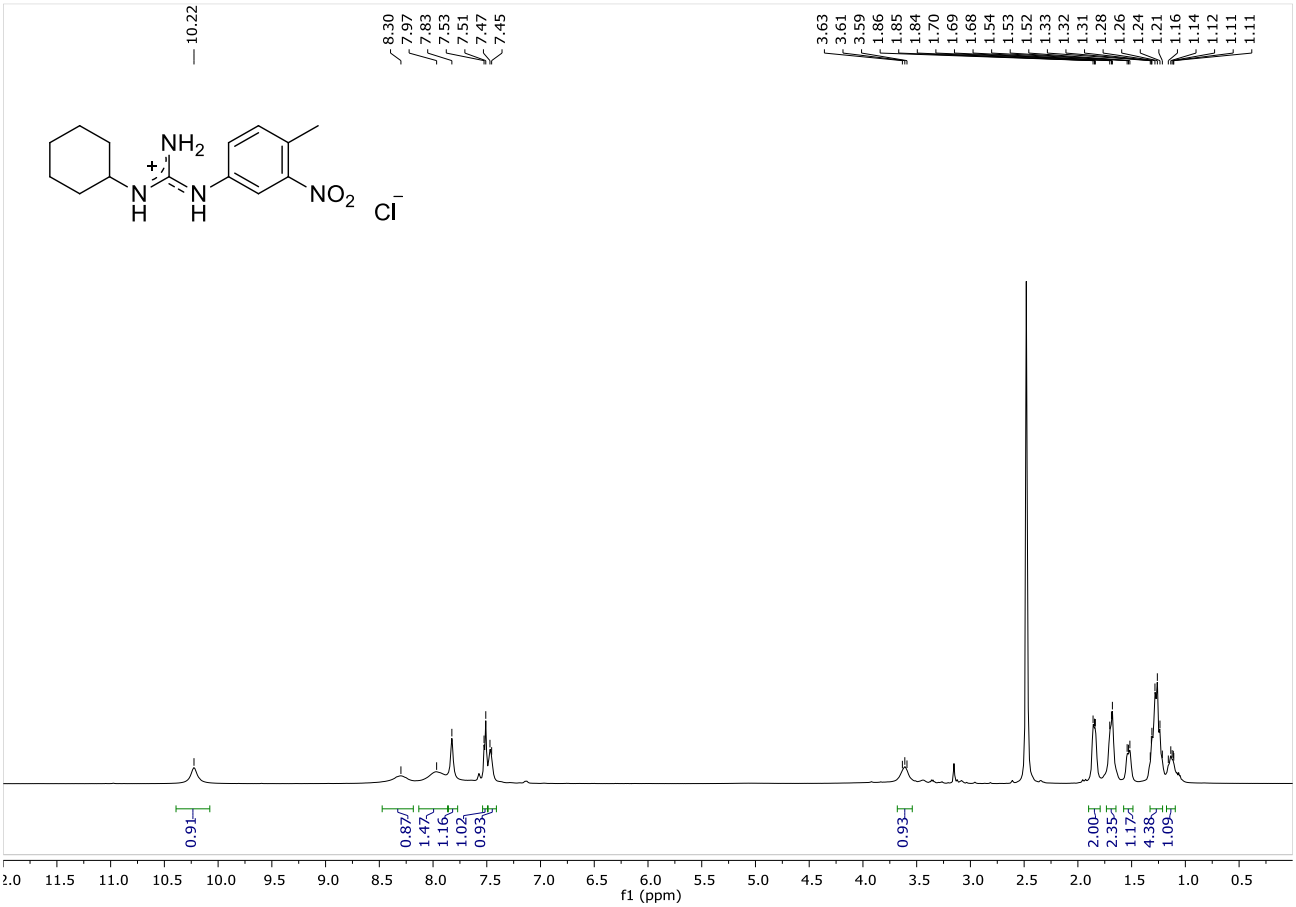
^{19}F-NMR spectrum of **7o** in DMSO-d_6



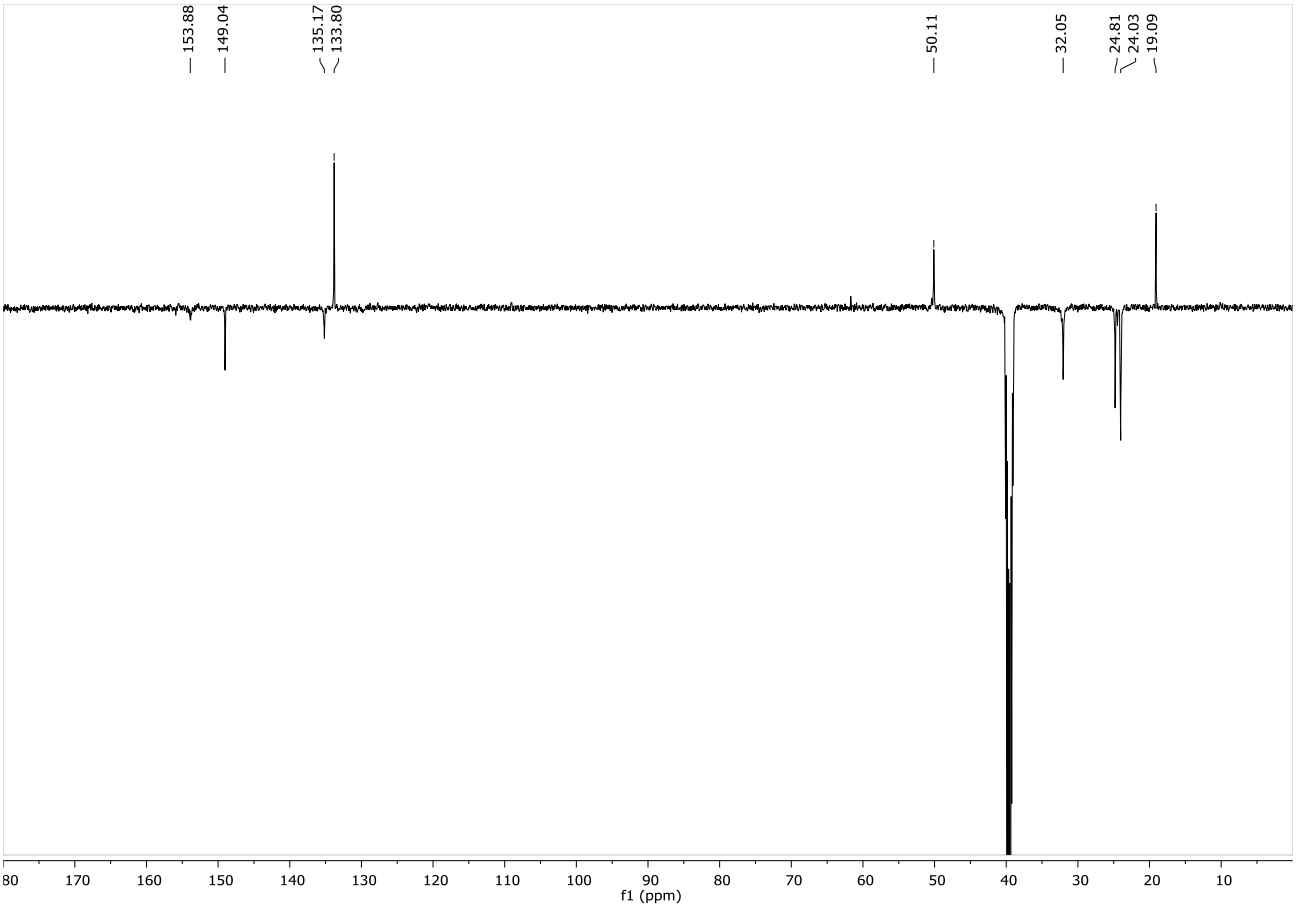
^{1}H-NMR spectrum of **7p** in DMSO-d_6



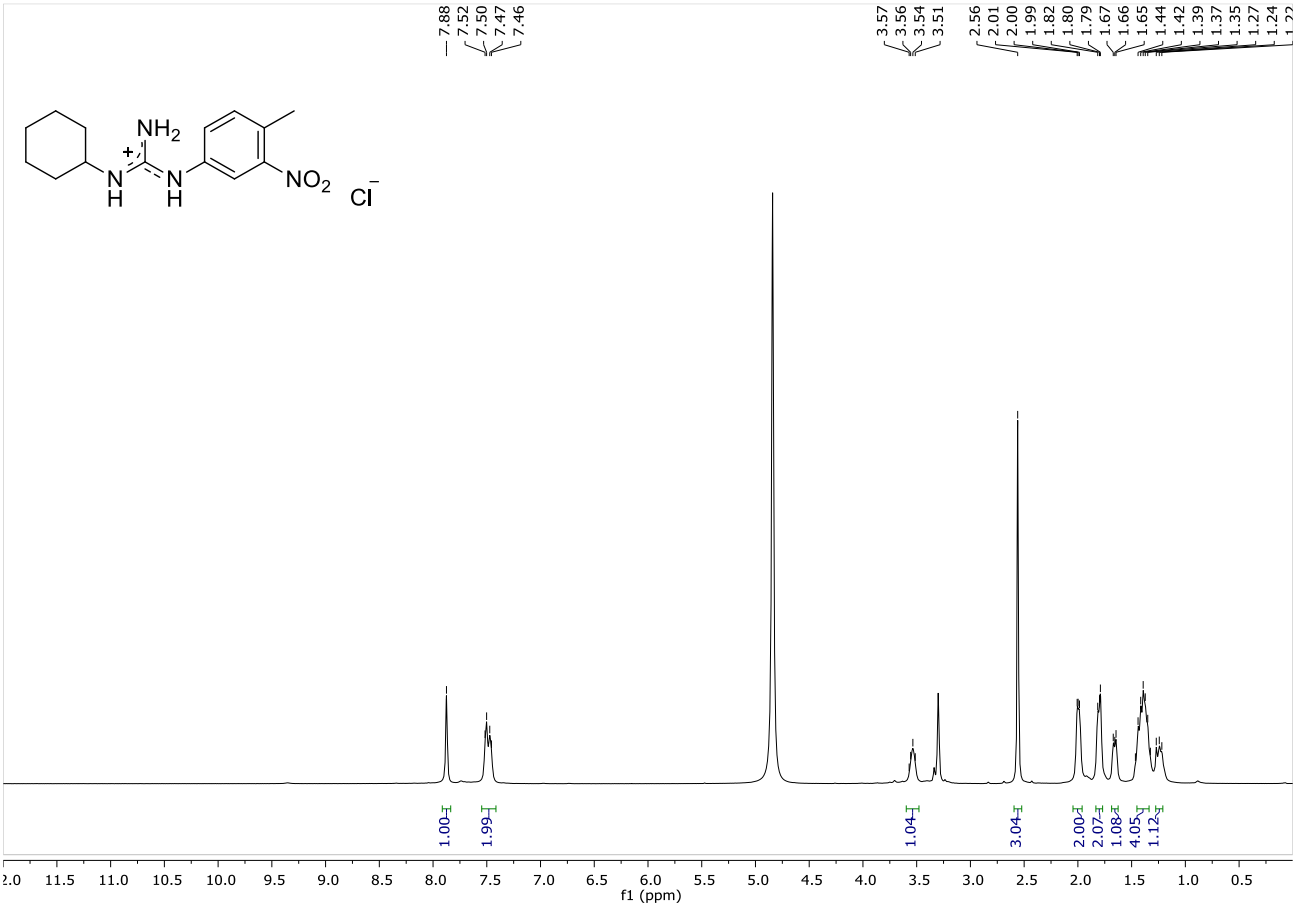
^{13}C-NMR spectrum of **7p** in DMSO-d_6



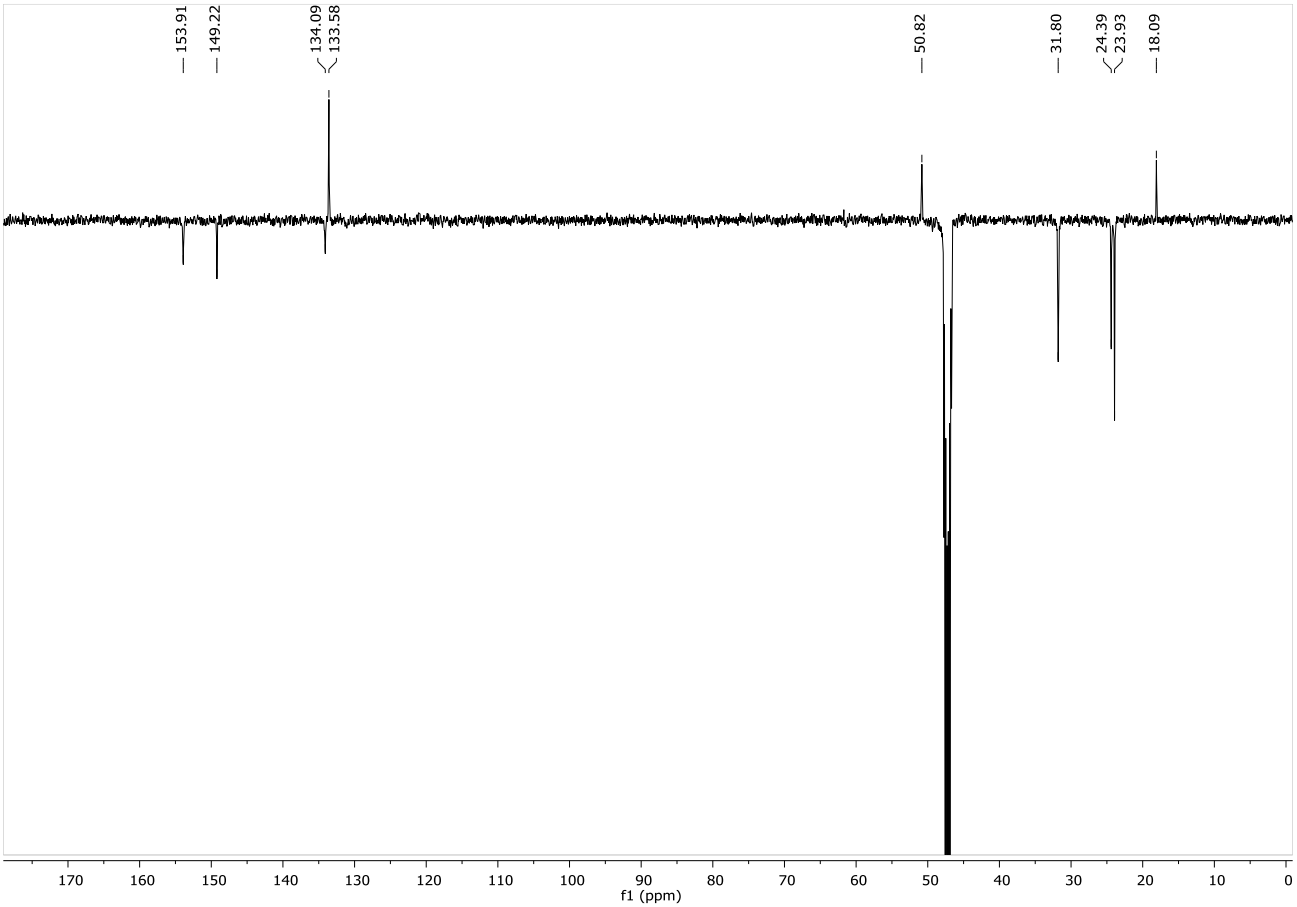
^{1}H-NMR spectrum of **7q** in DMSO-d_6



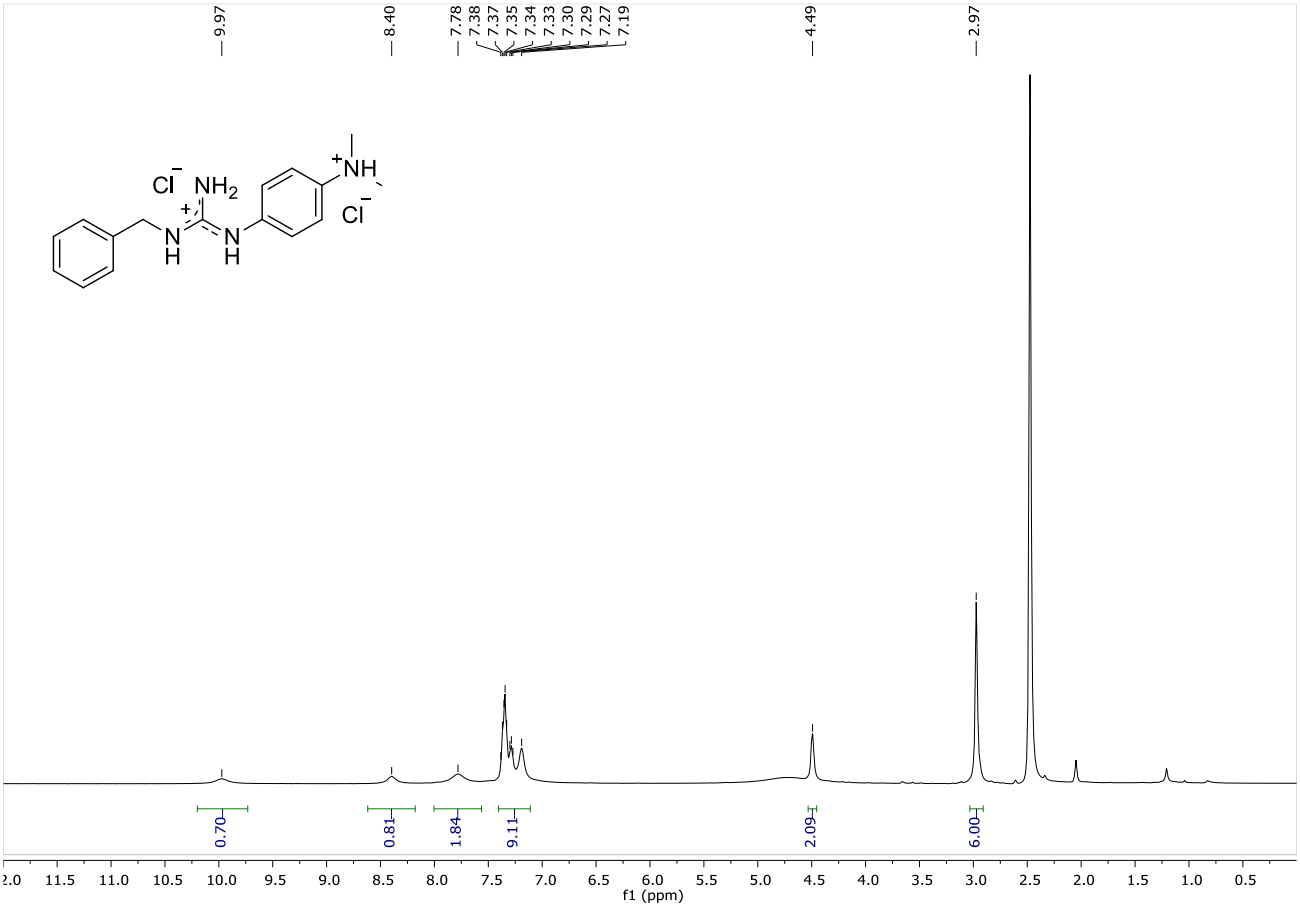
^{13}C-NMR spectrum of **7q** in DMSO-d_6



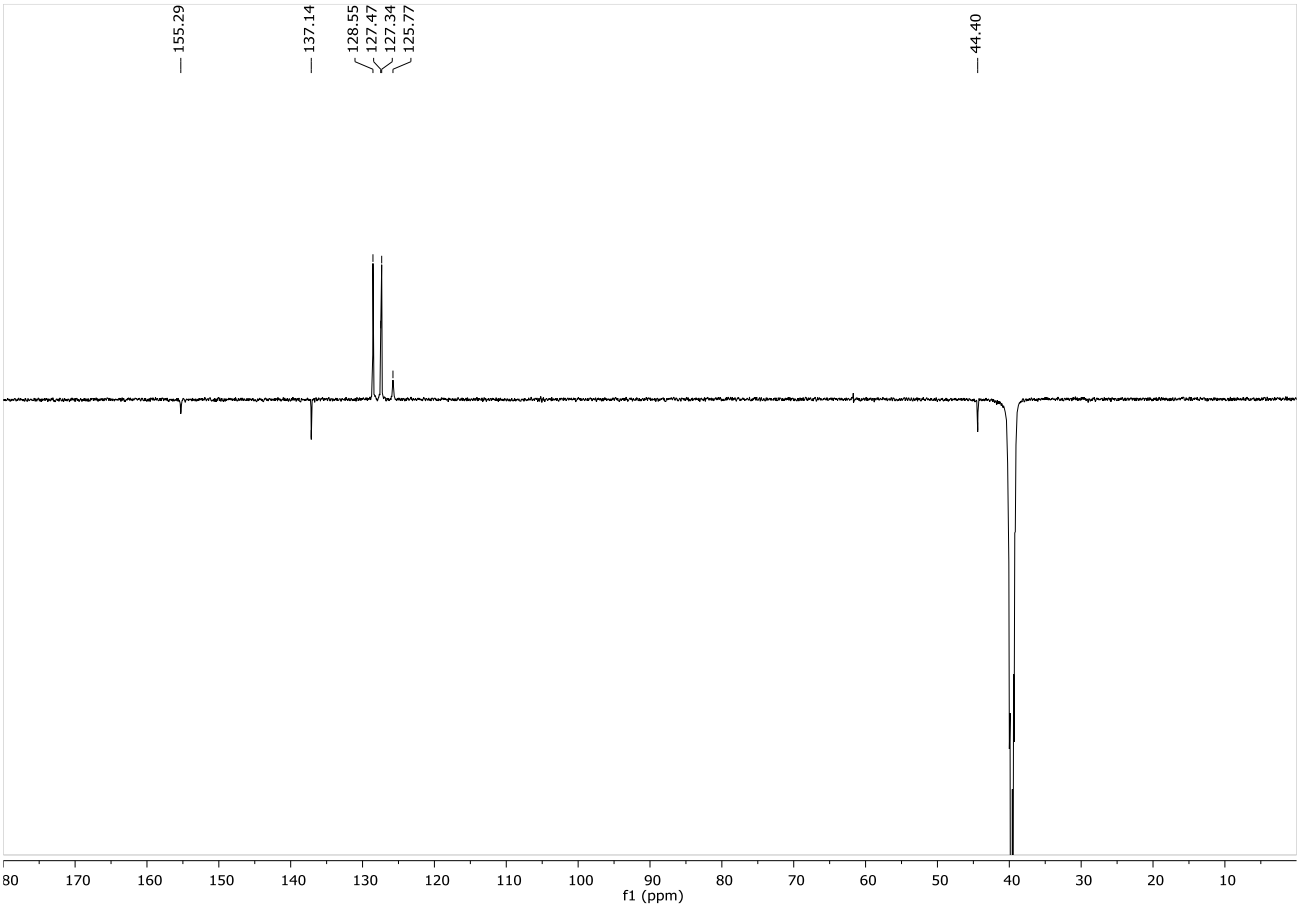
^{1}H-NMR spectrum of **7q** in MeOD-d_4



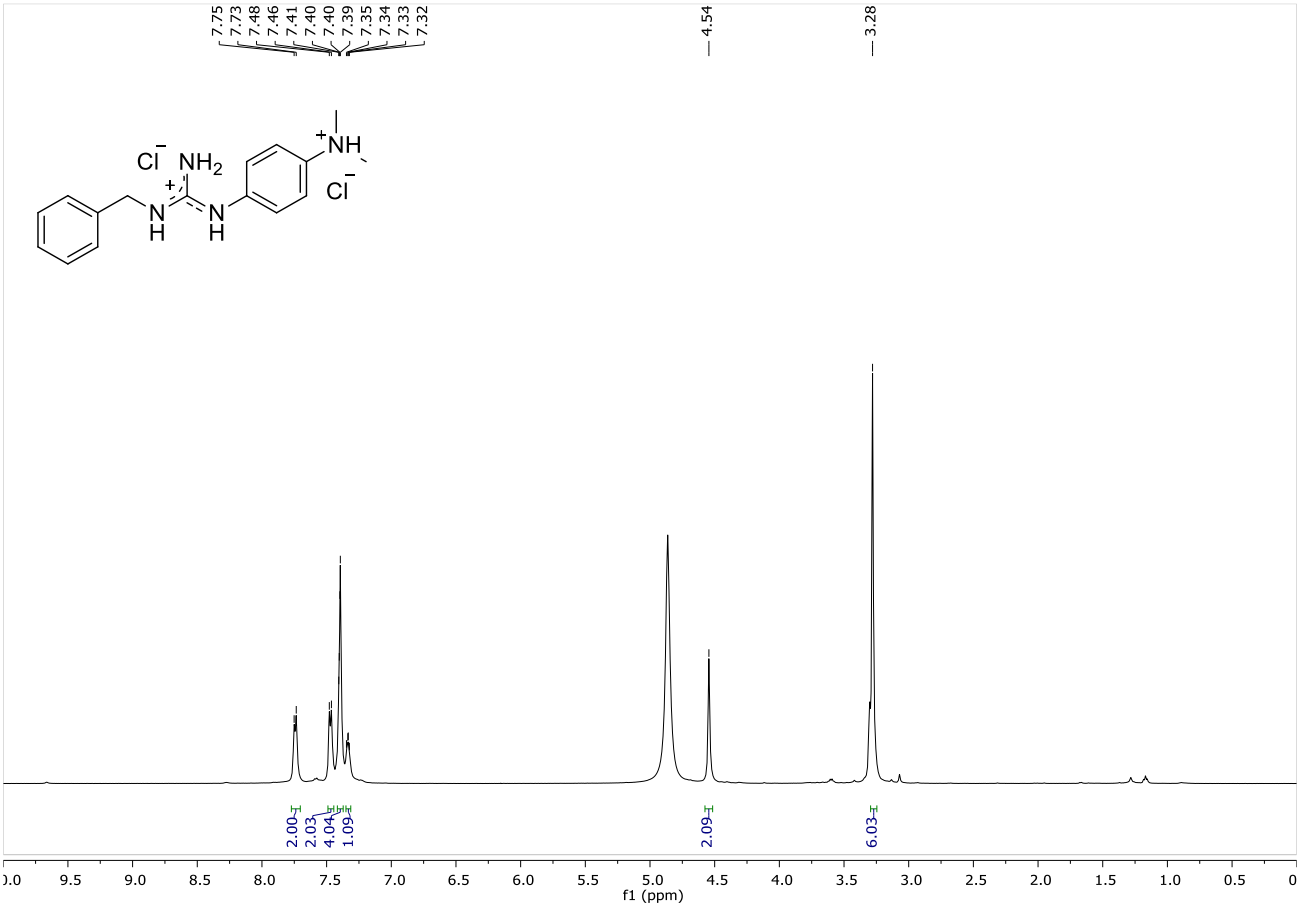
^{13}C-NMR spectrum of **7q** in MeOD-d_4



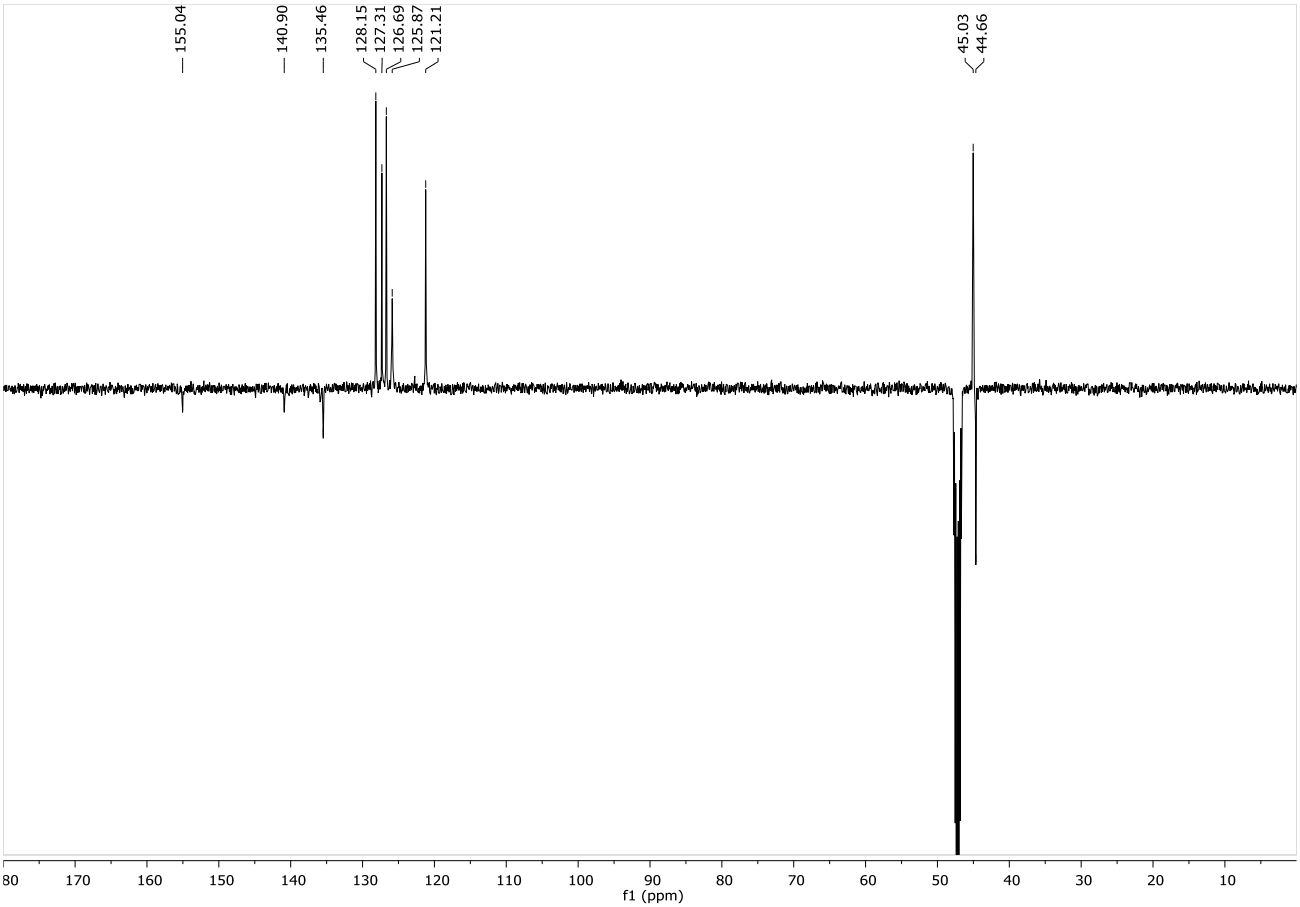
^{1}H-NMR spectrum of **7r** in DMSO-d_6



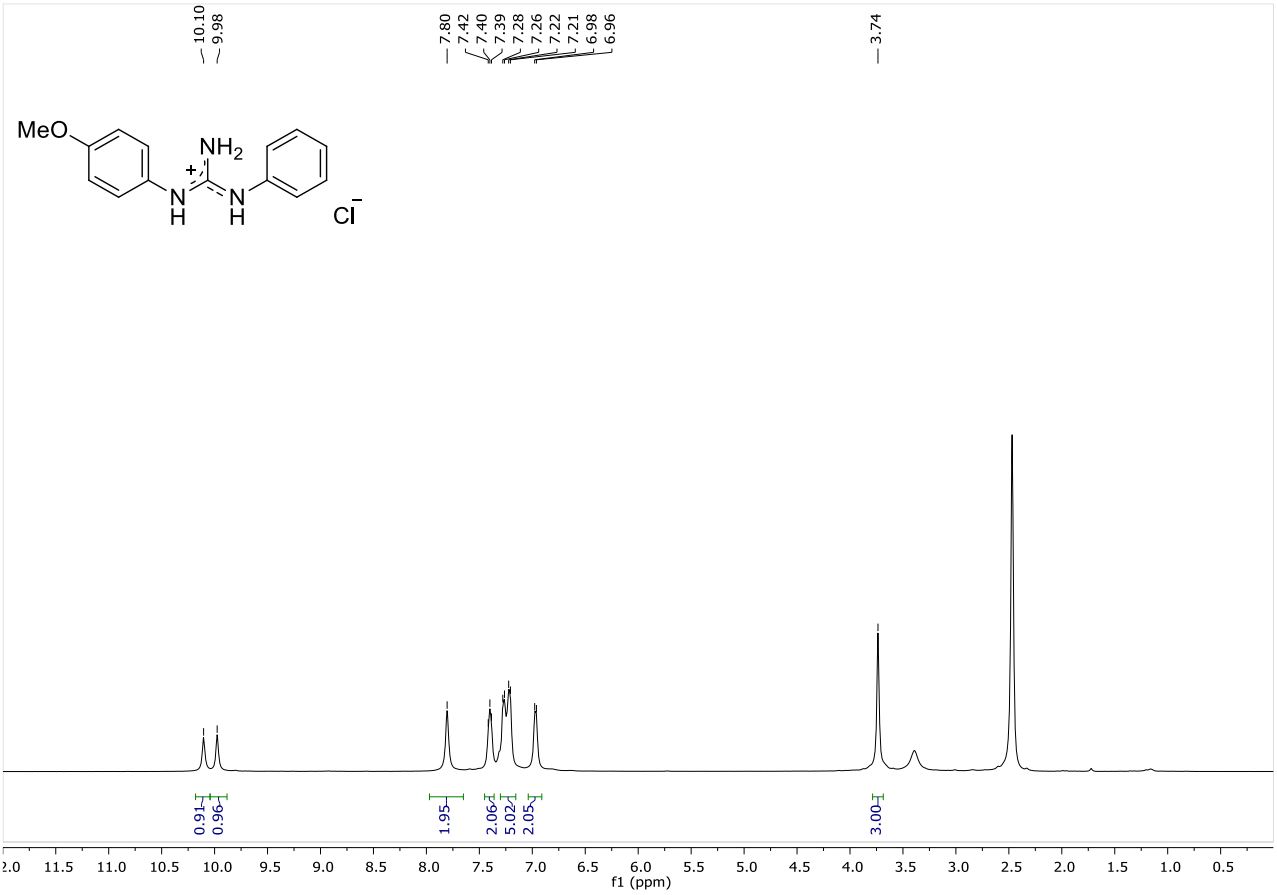
^{13}C-NMR spectrum of **7r** in DMSO-d_6



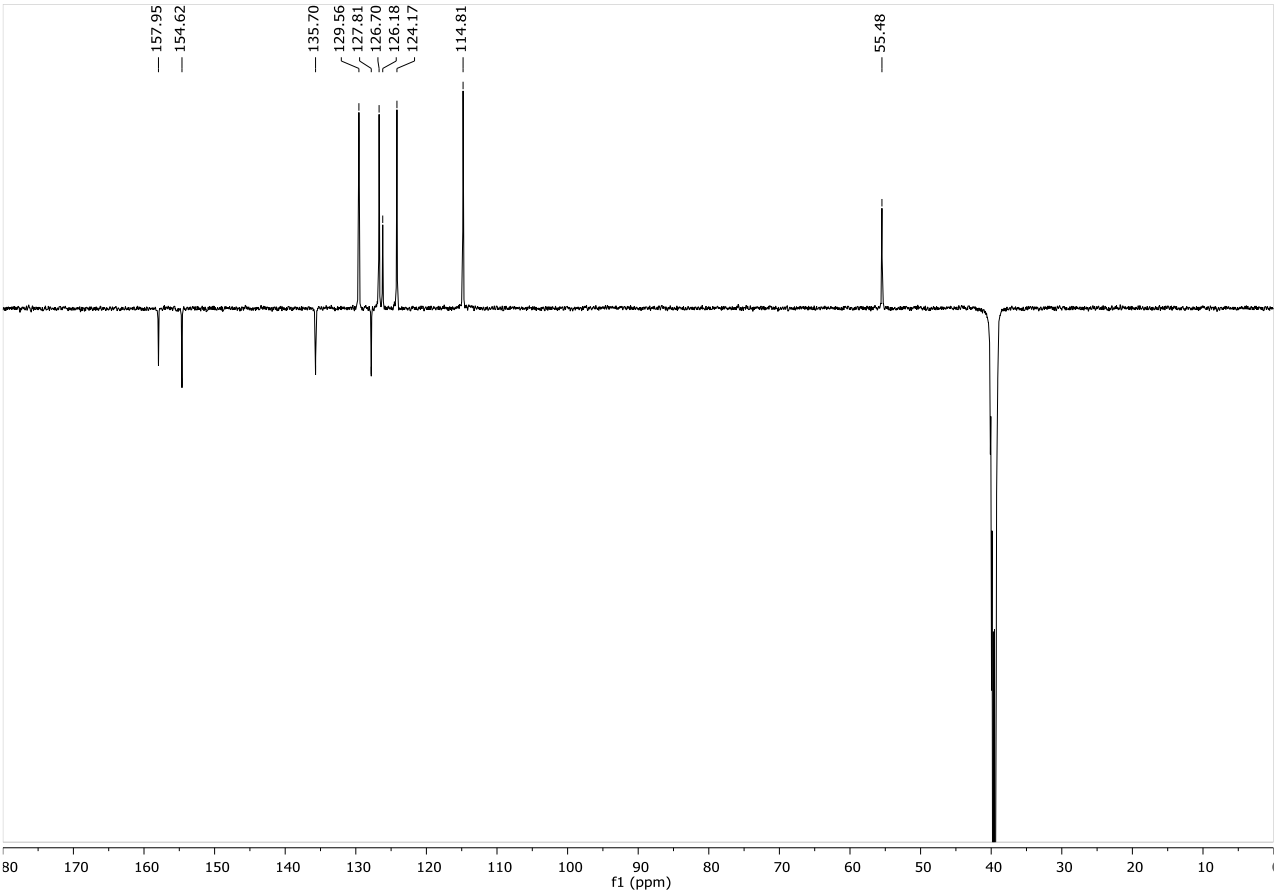
^{1}H-NMR spectrum of **7r** in MeOD-d_4



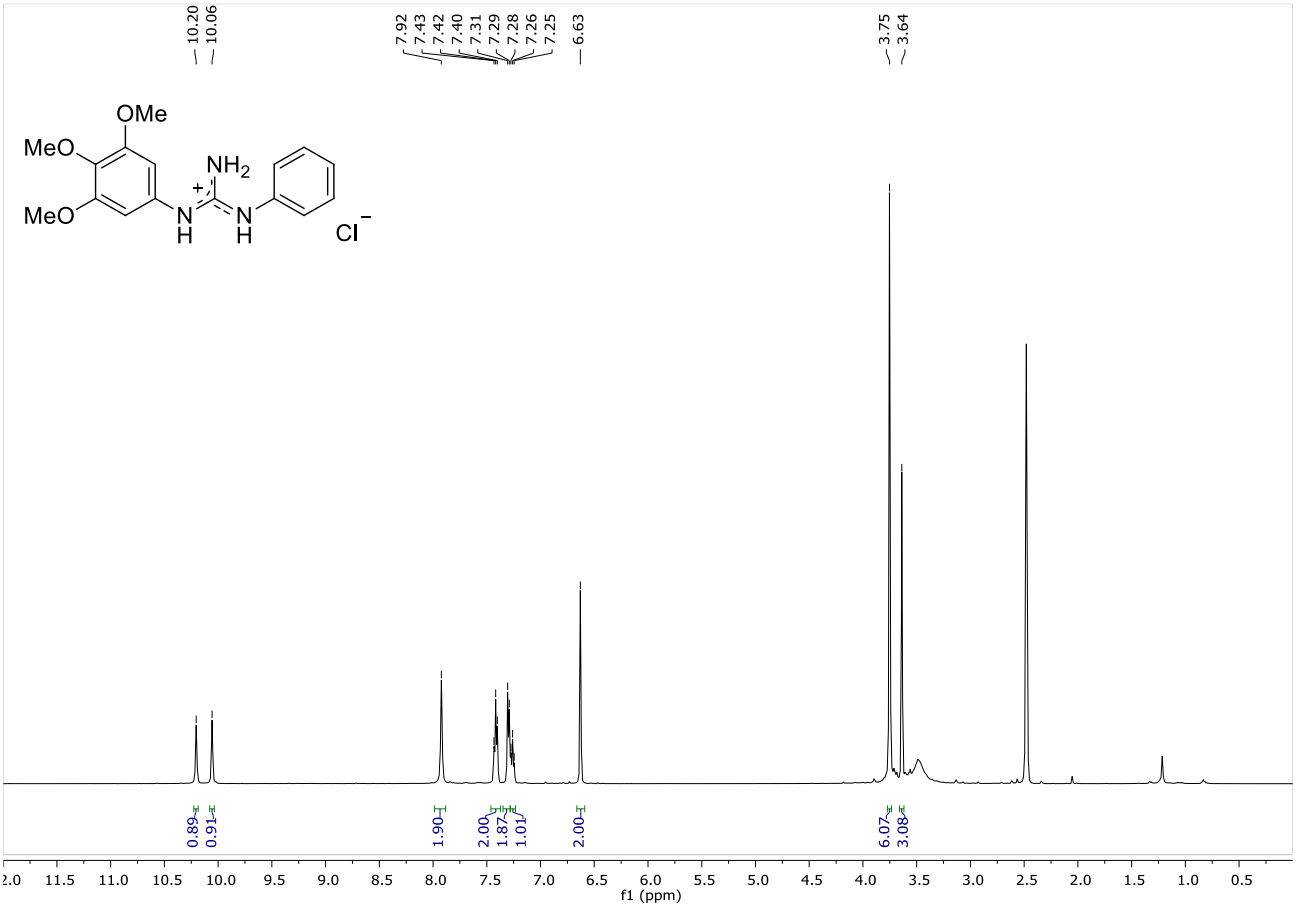
^{13}C-NMR spectrum of **7r** in MeOD-d_4



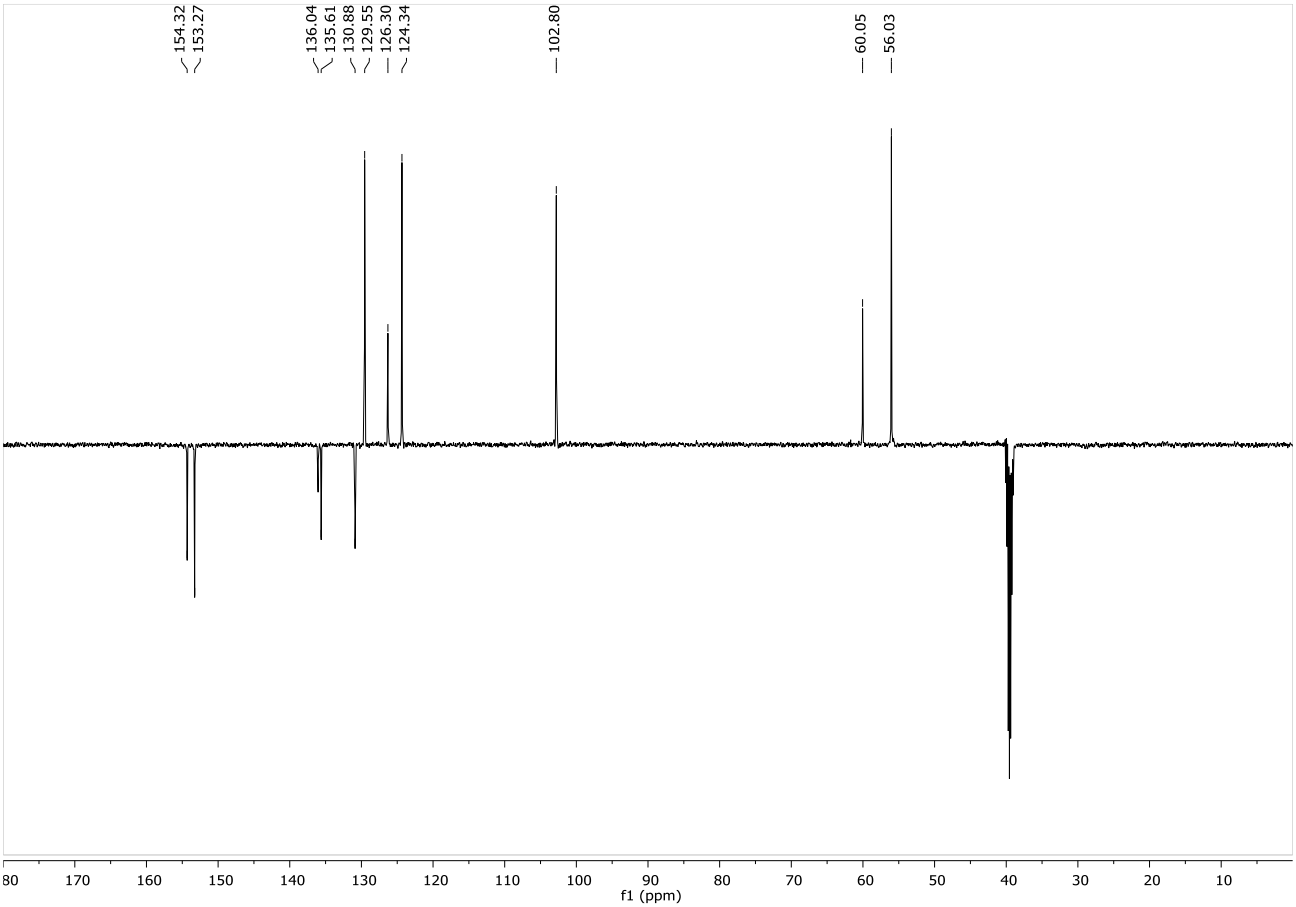
^{1}H-NMR spectrum of **7s** in DMSO-d_6



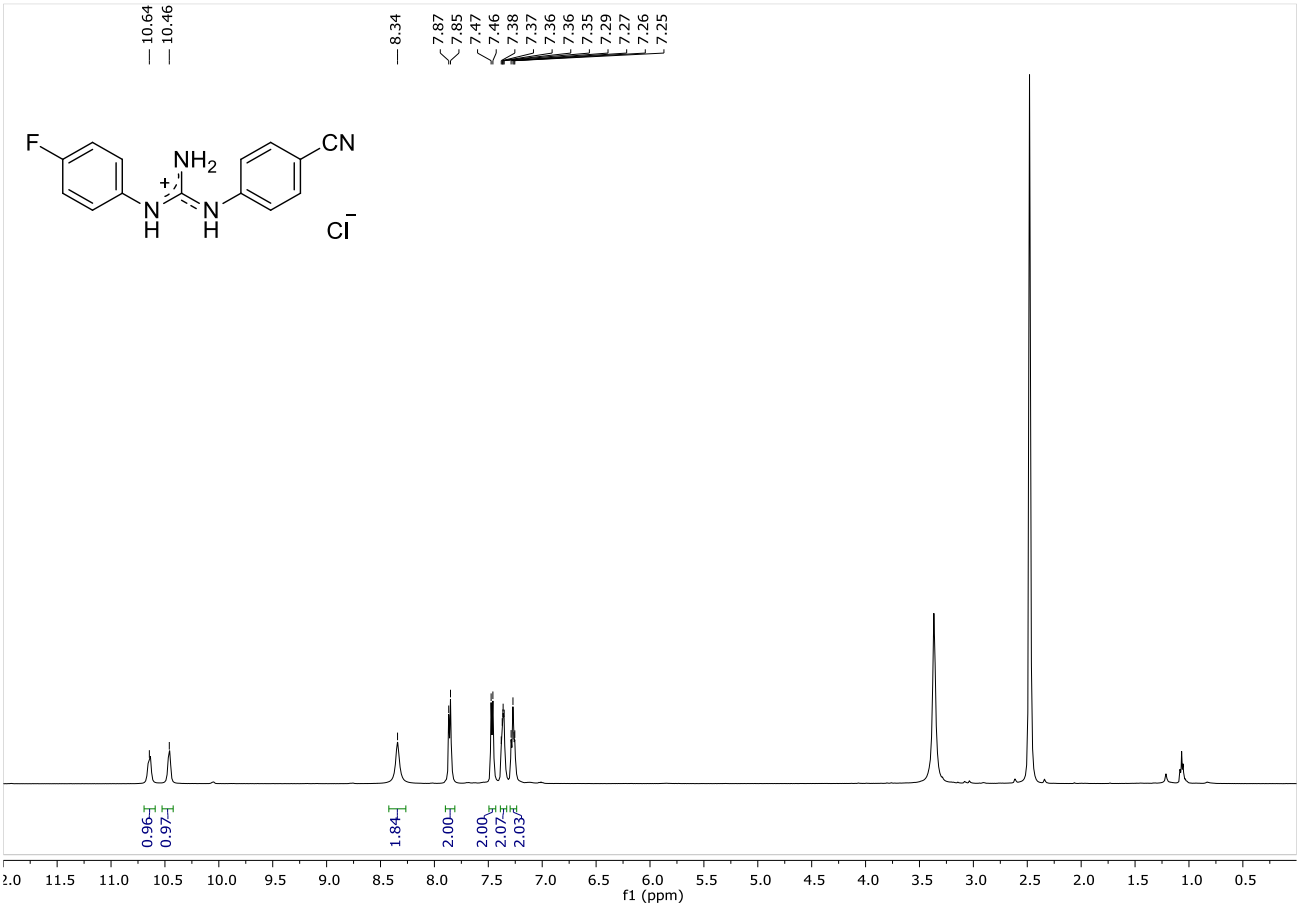
^{13}C-NMR spectrum of **7s** in DMSO-d_6



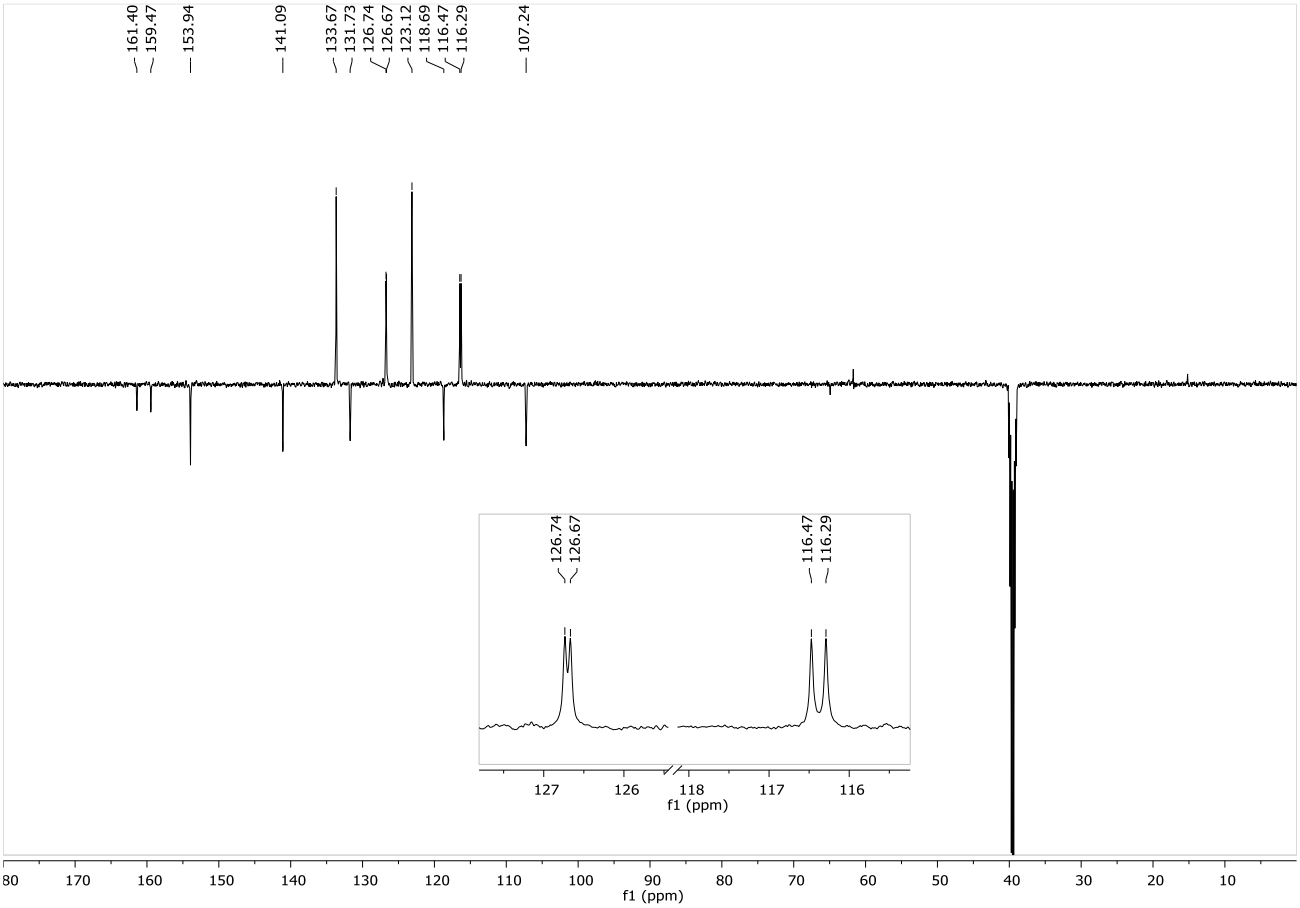
^{1}H-NMR spectrum of **7t** in DMSO-d_6



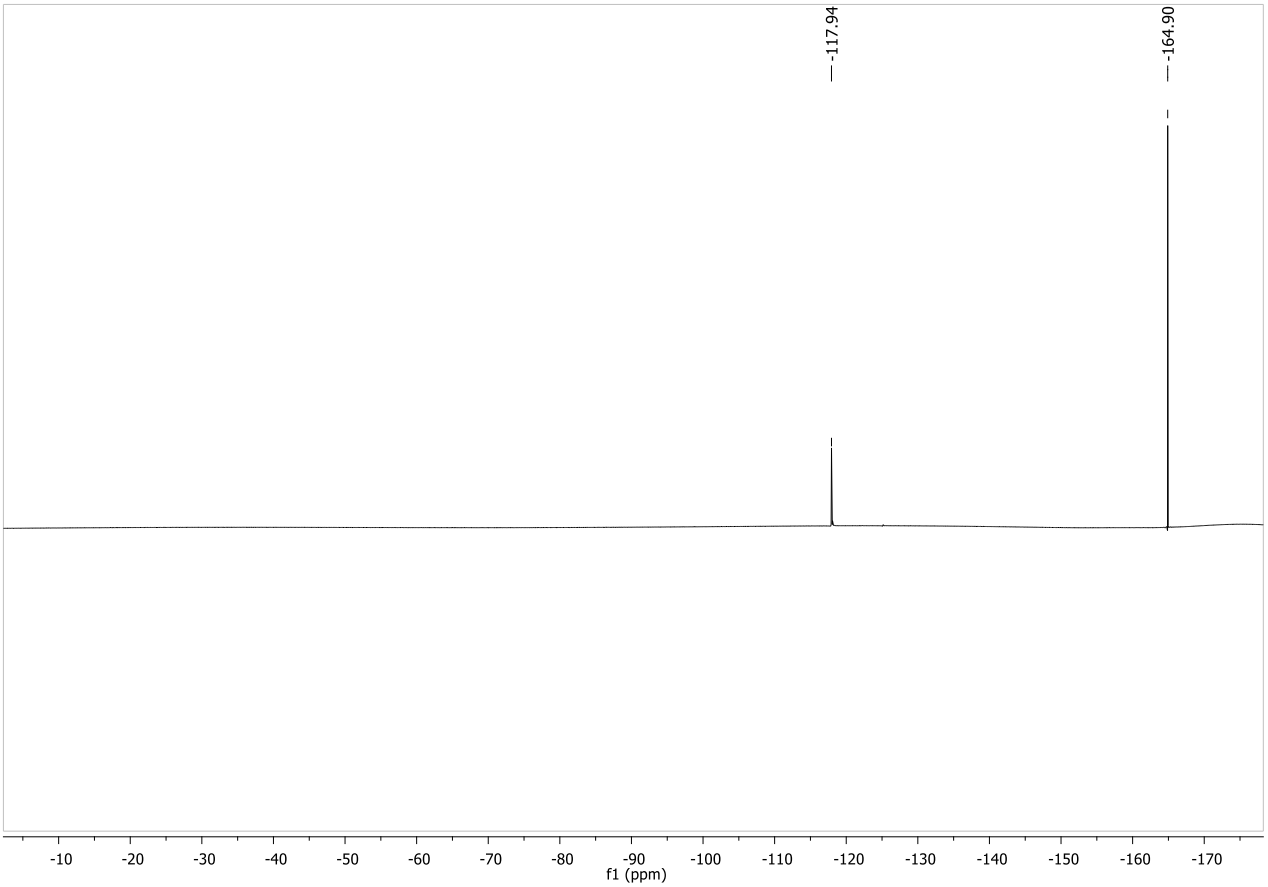
^{13}C-NMR spectrum of **7t** in DMSO-d_6



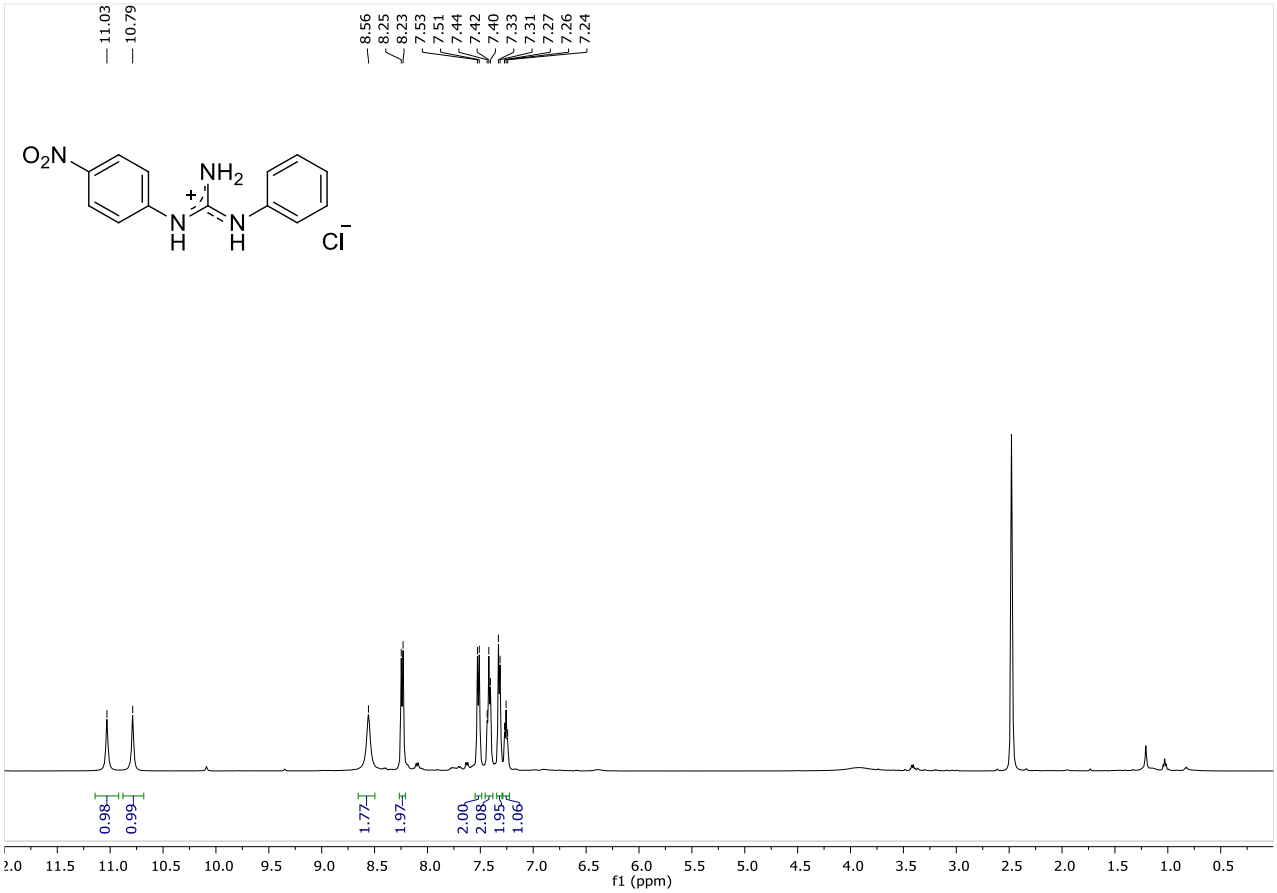
^{1}H-NMR spectrum of **7u** in DMSO-d_6



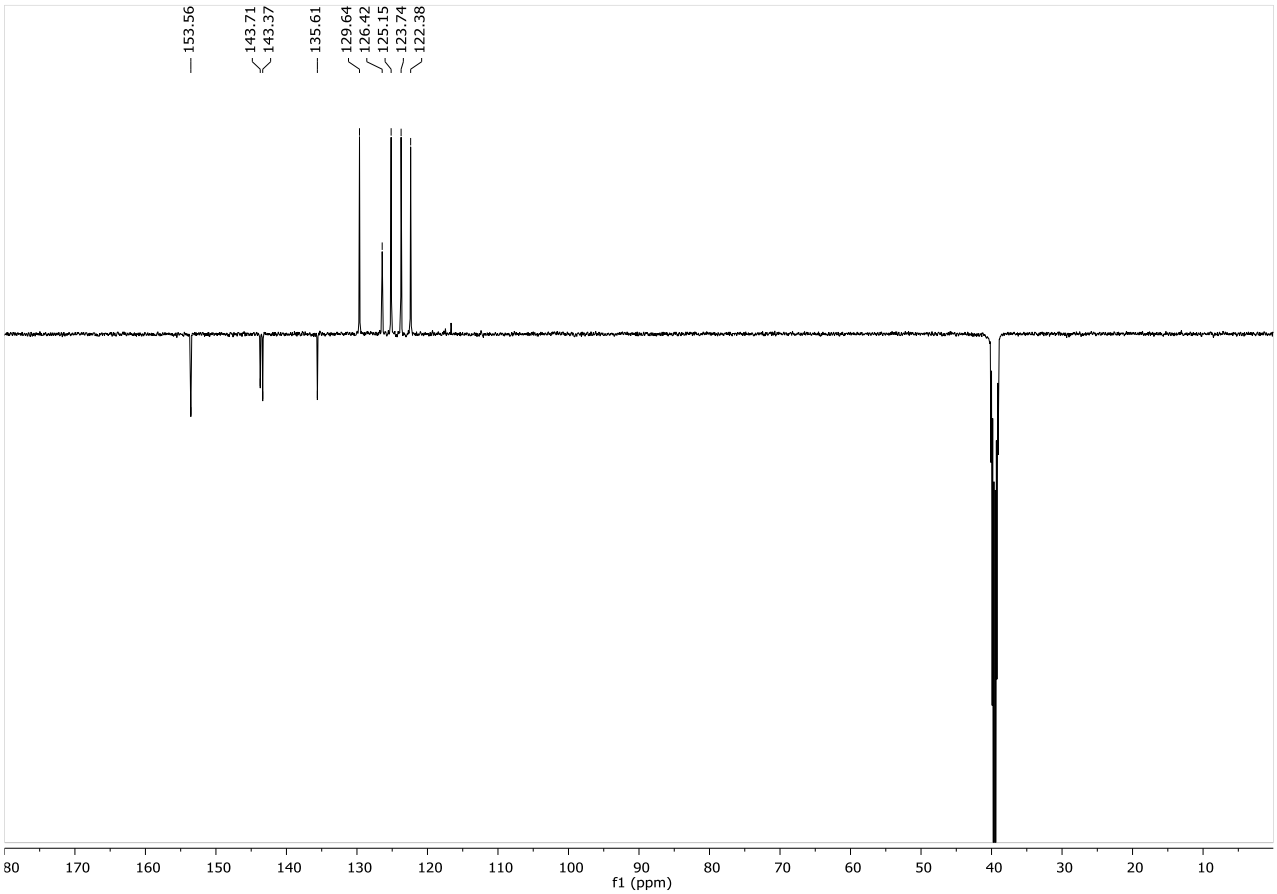
^{13}C-NMR spectrum of **7u** in DMSO-d_6



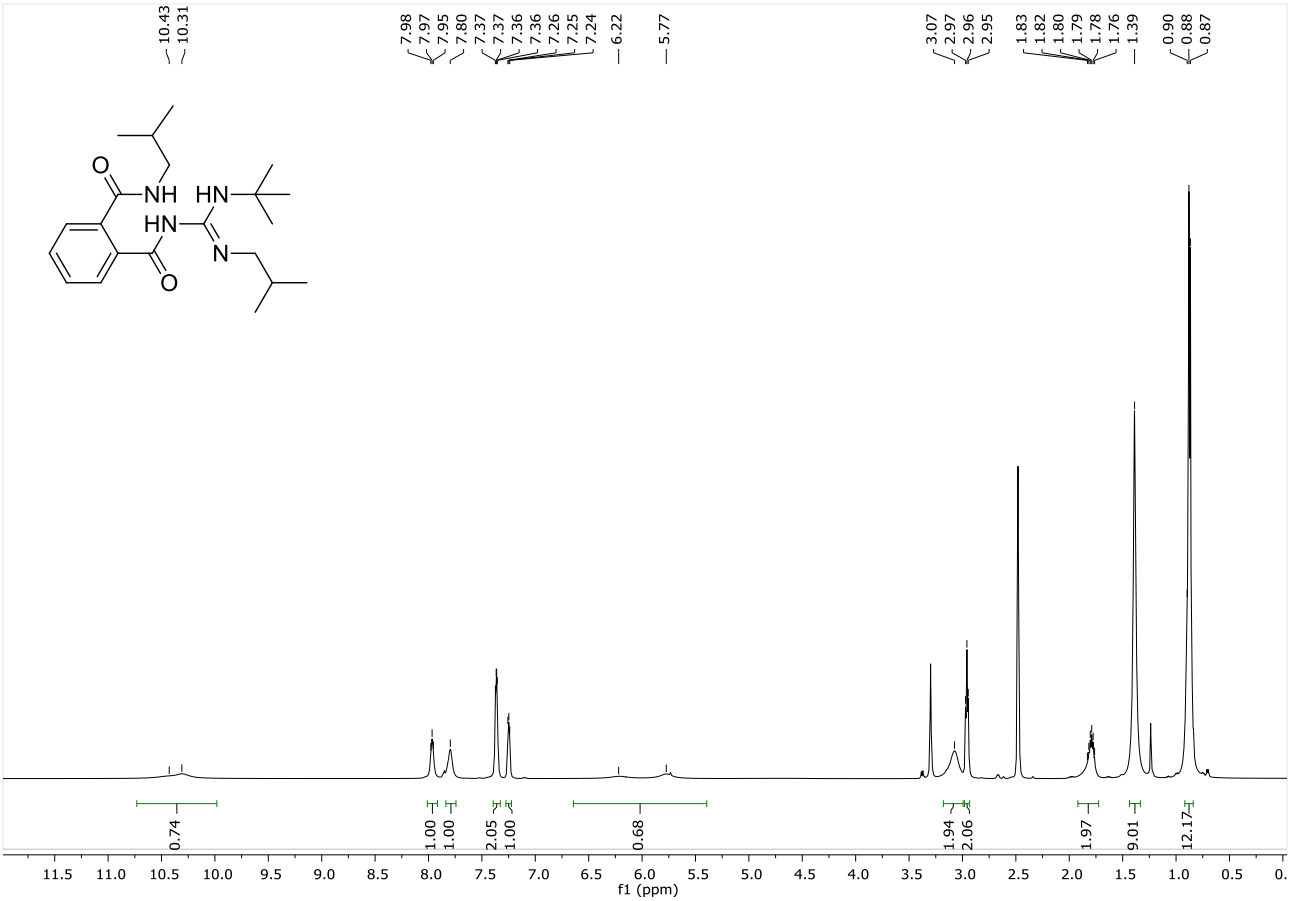
^{19}F-NMR spectrum of **7u** in DMSO-d_6



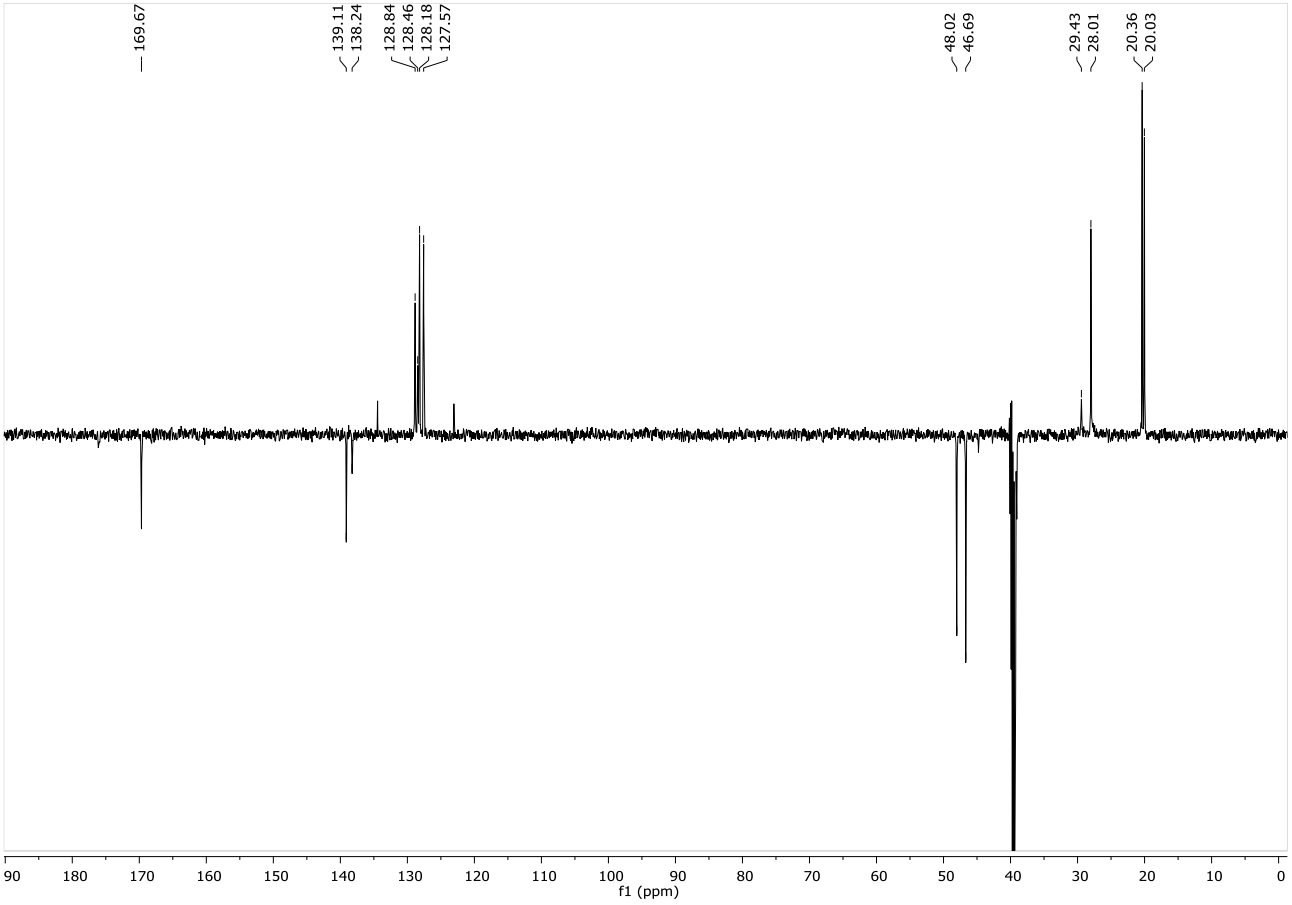
^{1}H-NMR spectrum of **7v** in DMSO-d_6



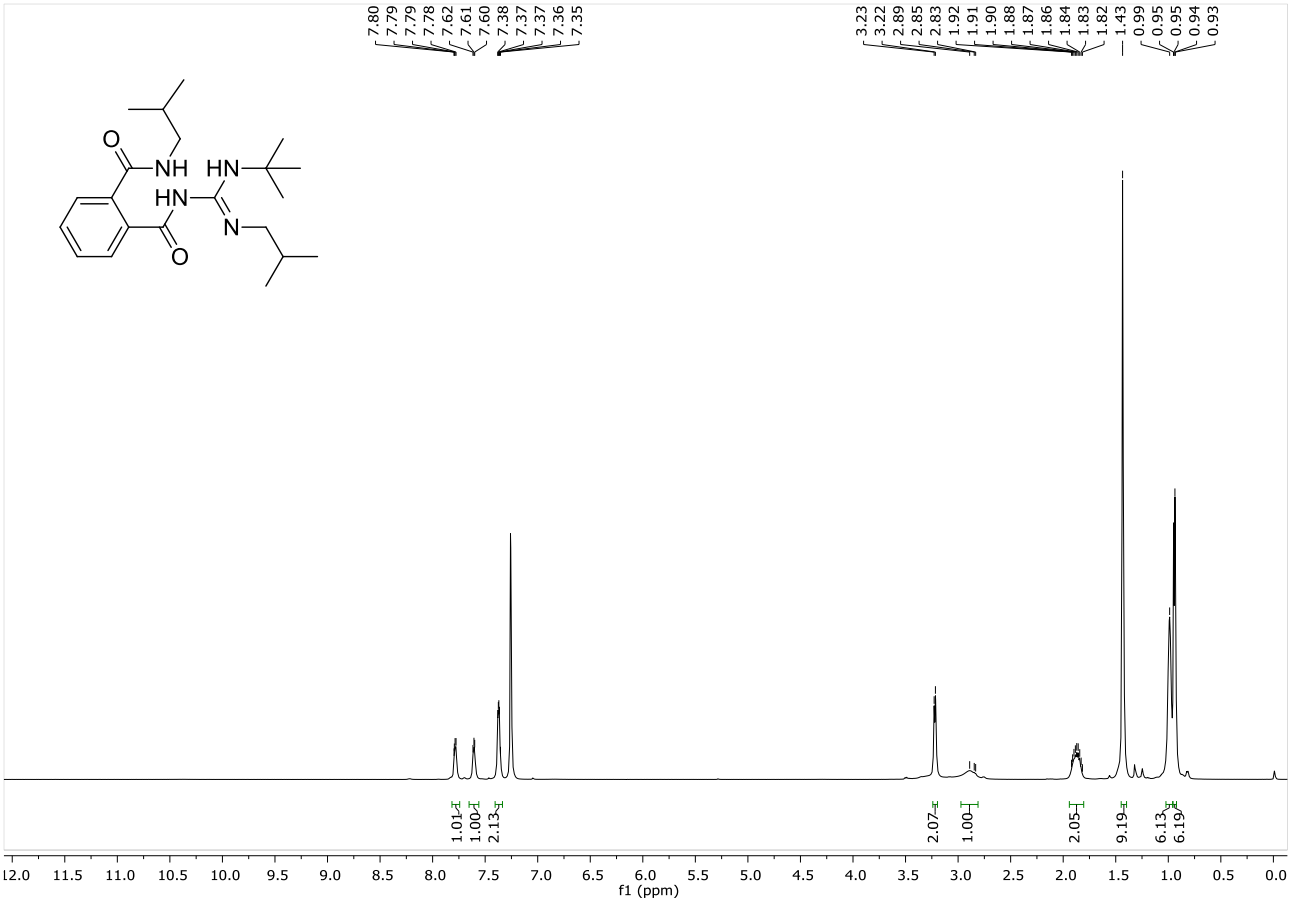
^{13}C-NMR spectrum of **7v** in DMSO-d_6



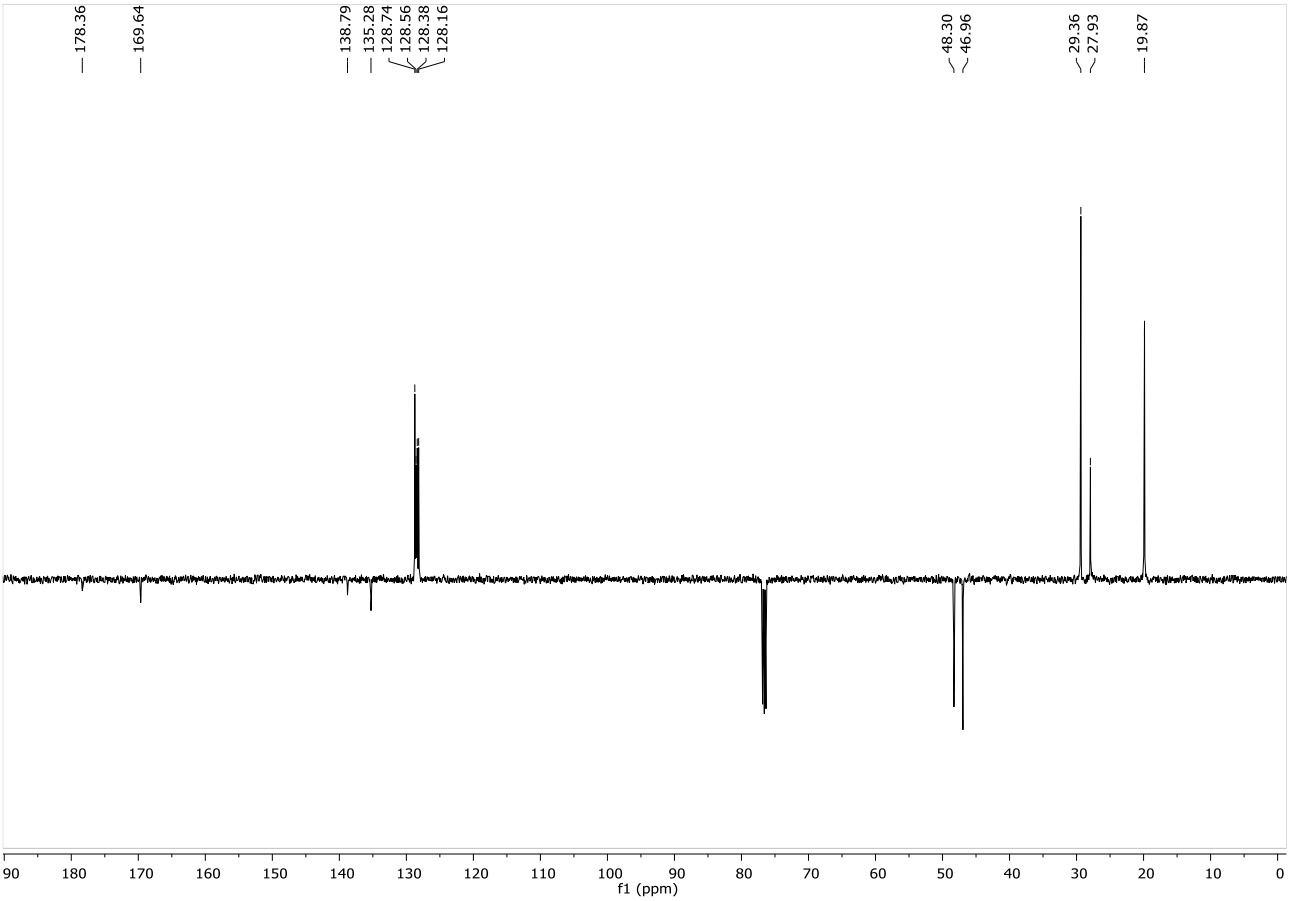
^{1}H-NMR spectrum of **9a** in DMSO-d_6



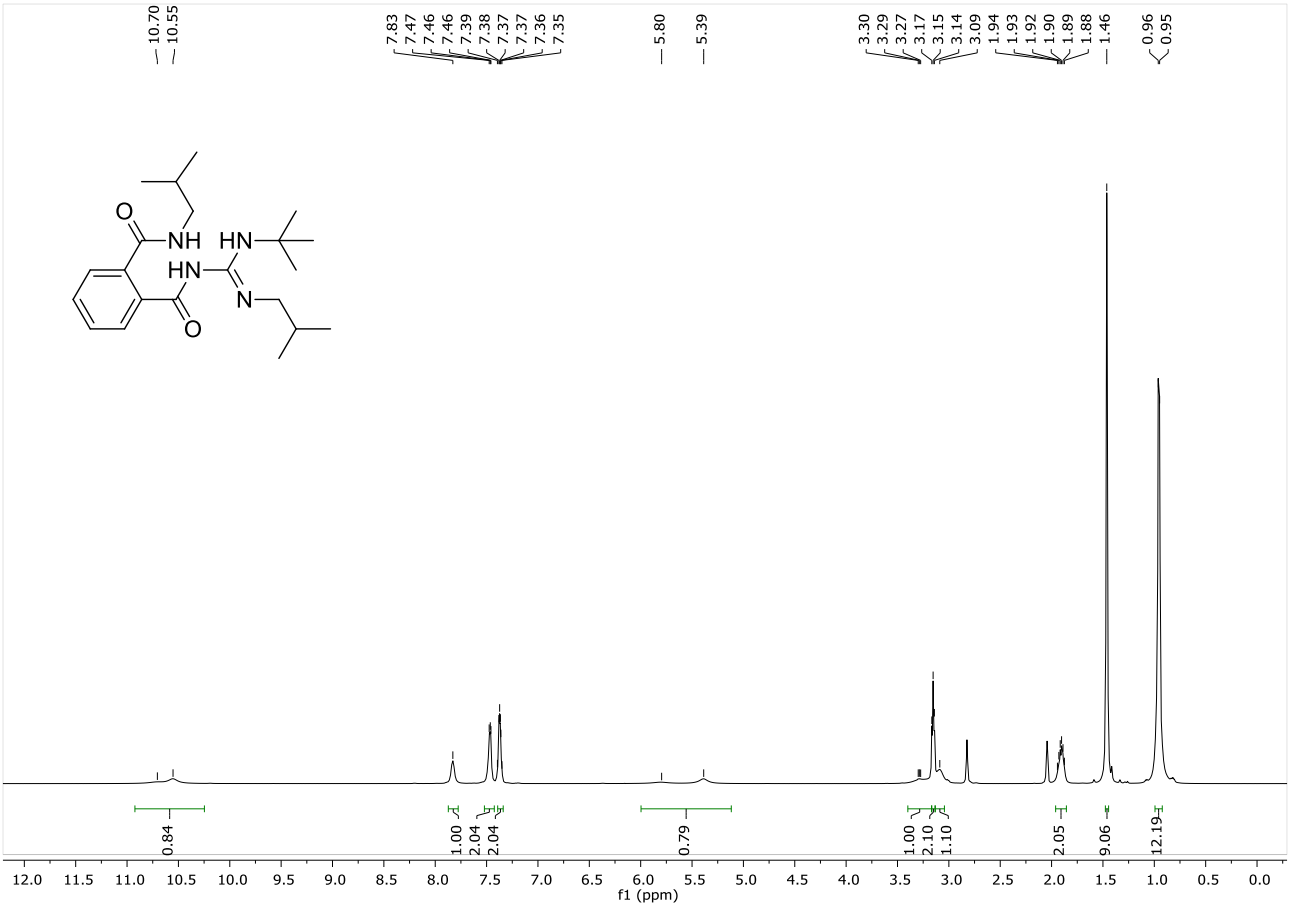
^{13}C-NMR spectrum of **9a** in DMSO-d_6



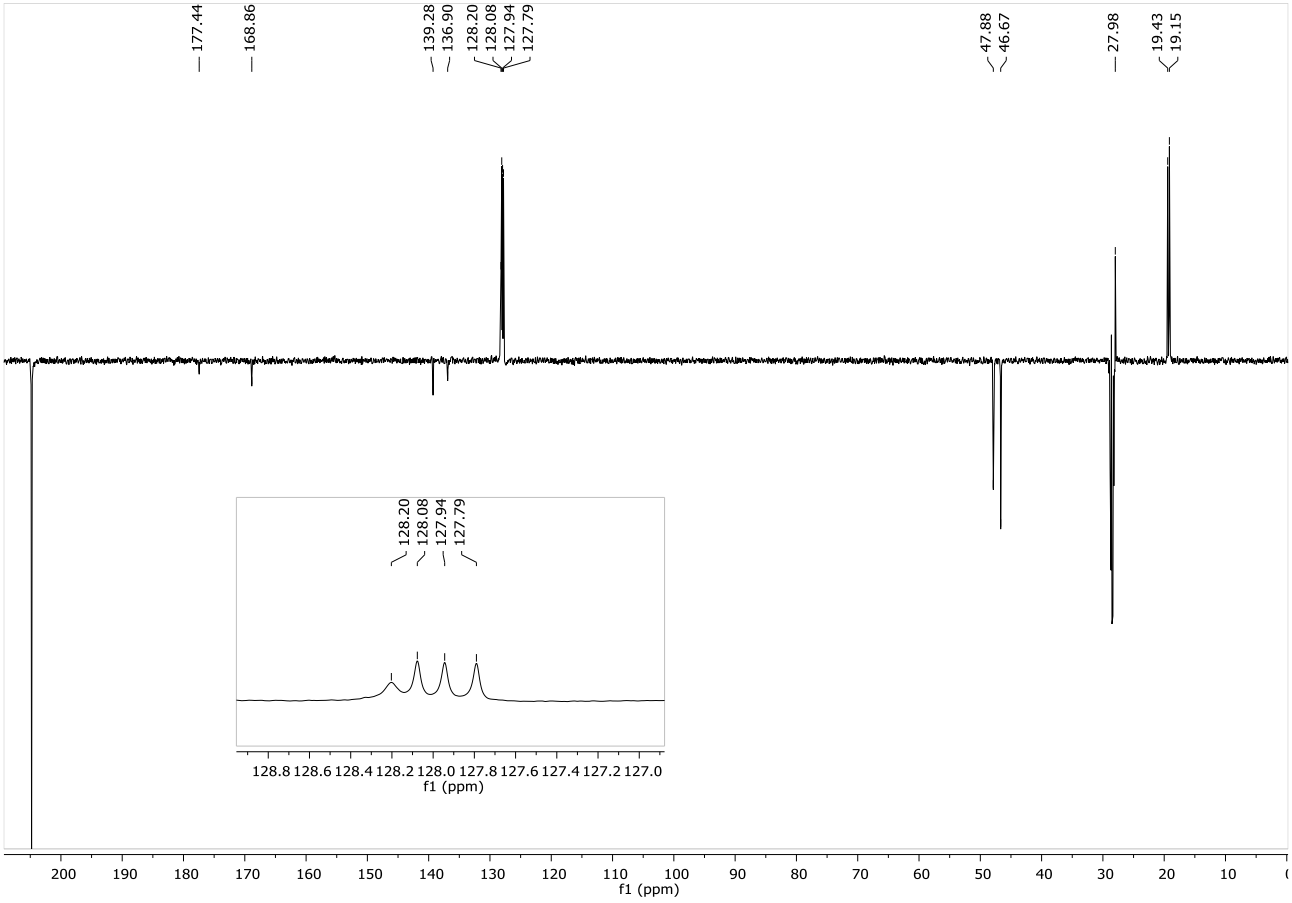
^{1}H-NMR spectrum of **9a** in $CDCl_3$



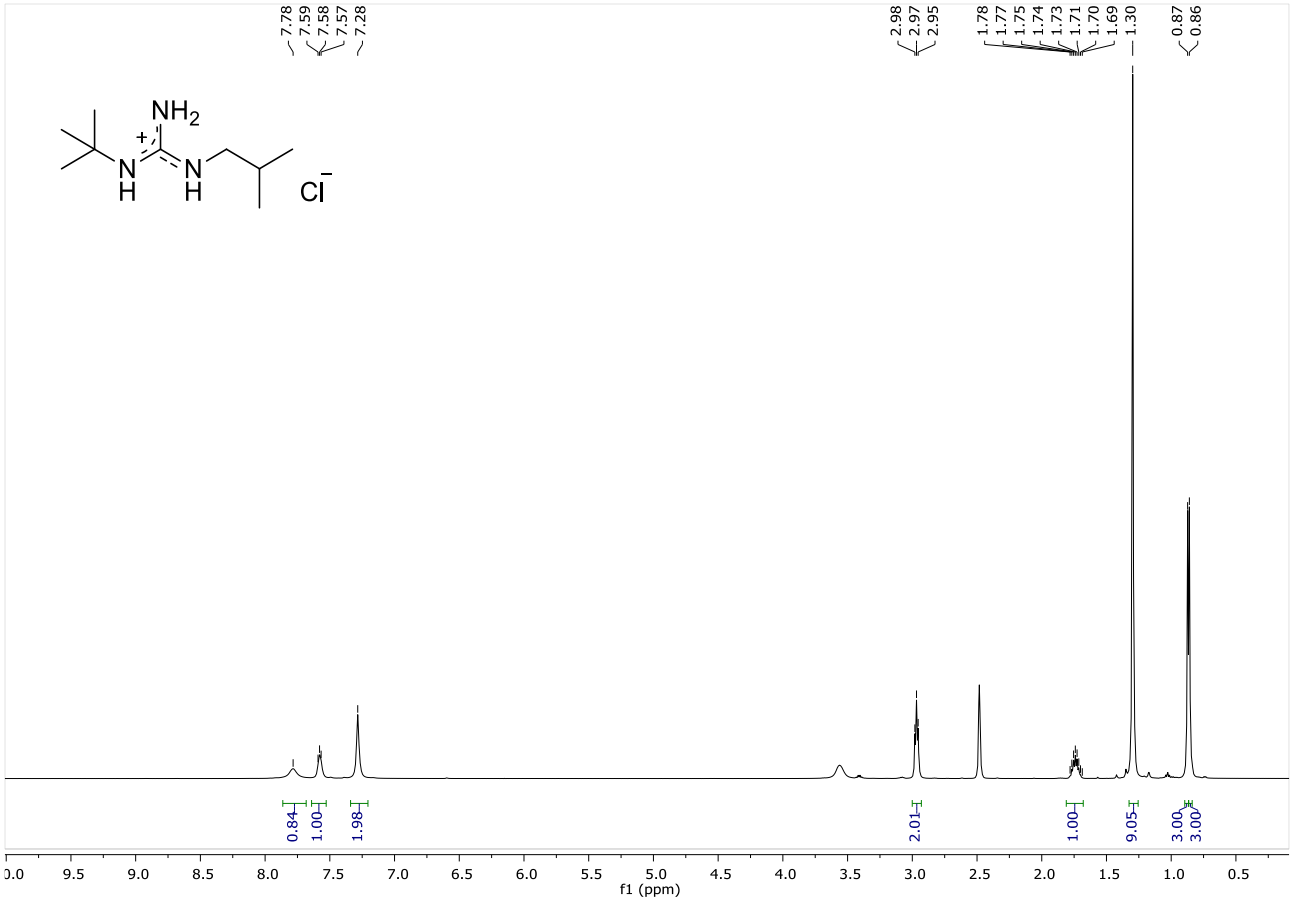
^{13}C-NMR spectrum of **9a** in $CDCl_3$



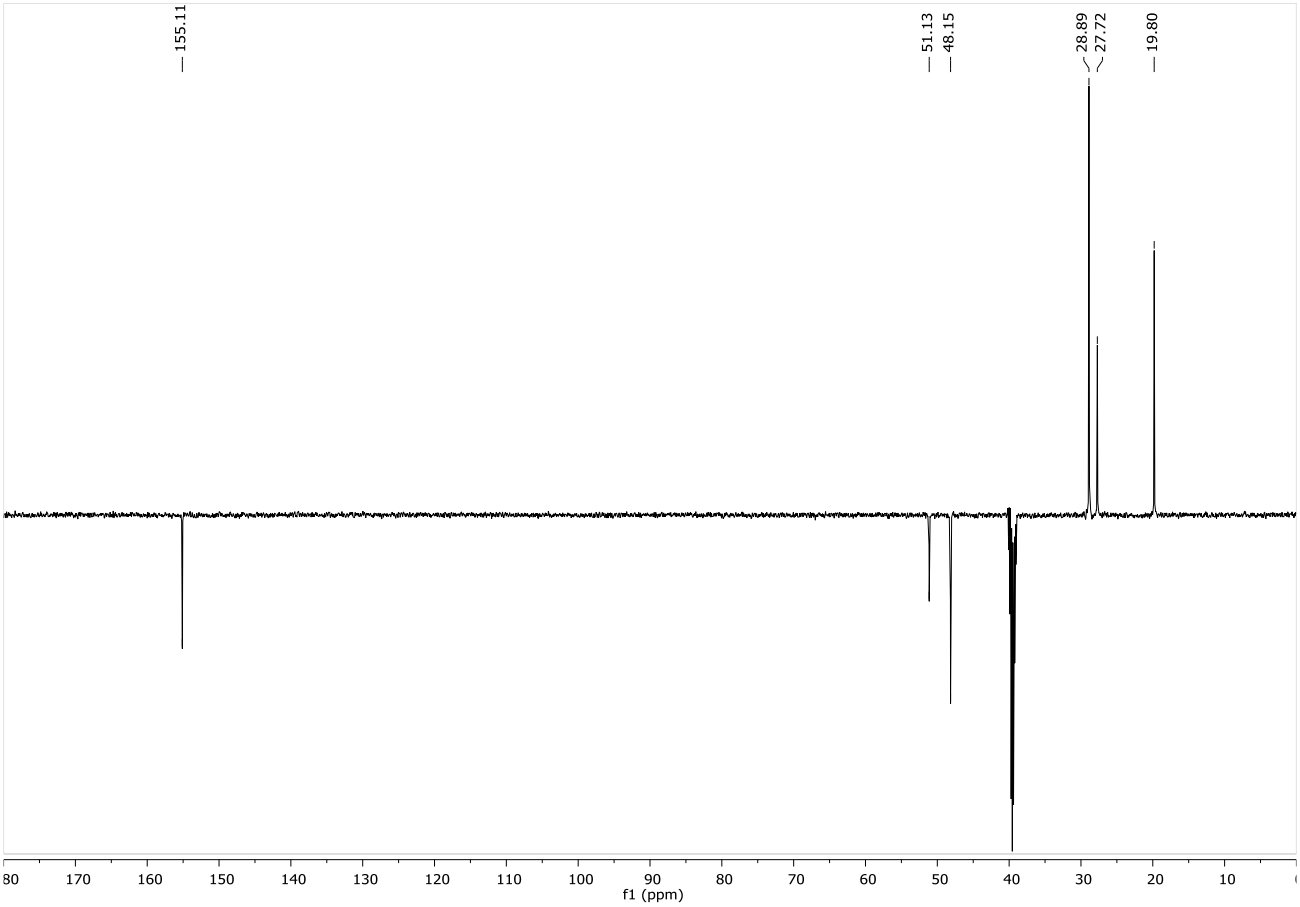
^{1}H-NMR spectrum of **9a** in acetone-d_6



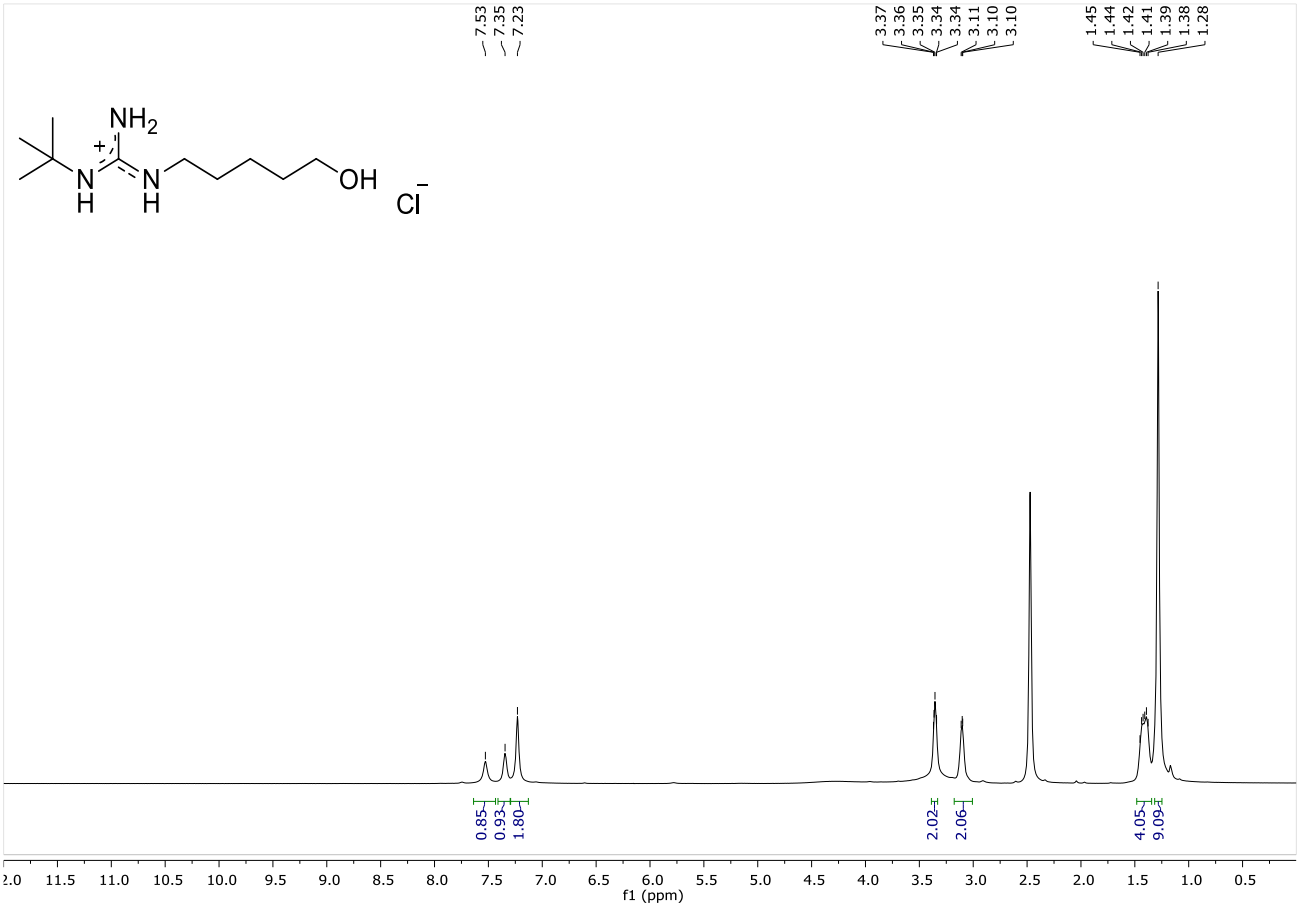
^{13}C-NMR spectrum of **9a** in acetone-d_6



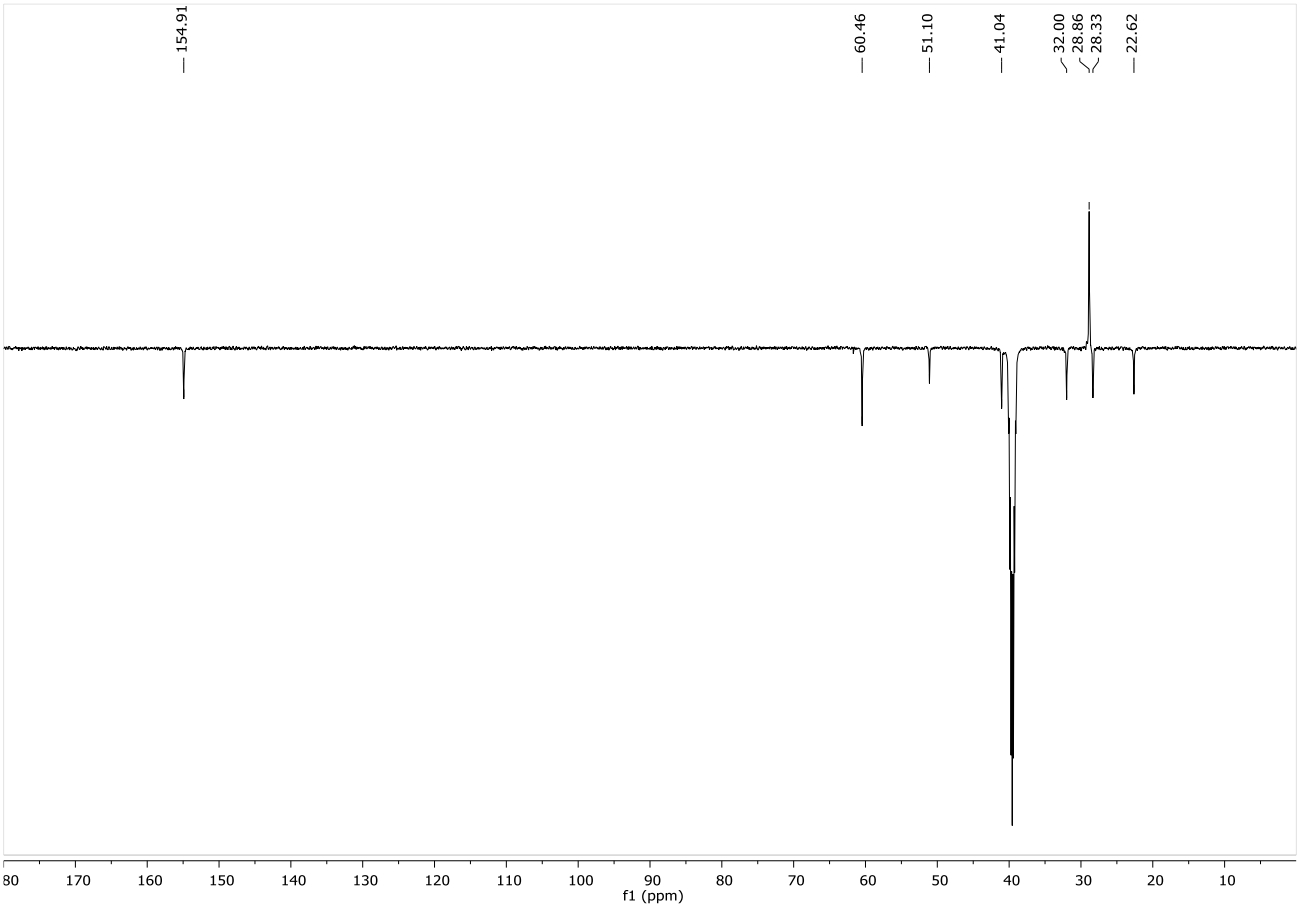
^{1}H-NMR spectrum of **10a** in DMSO-d_6



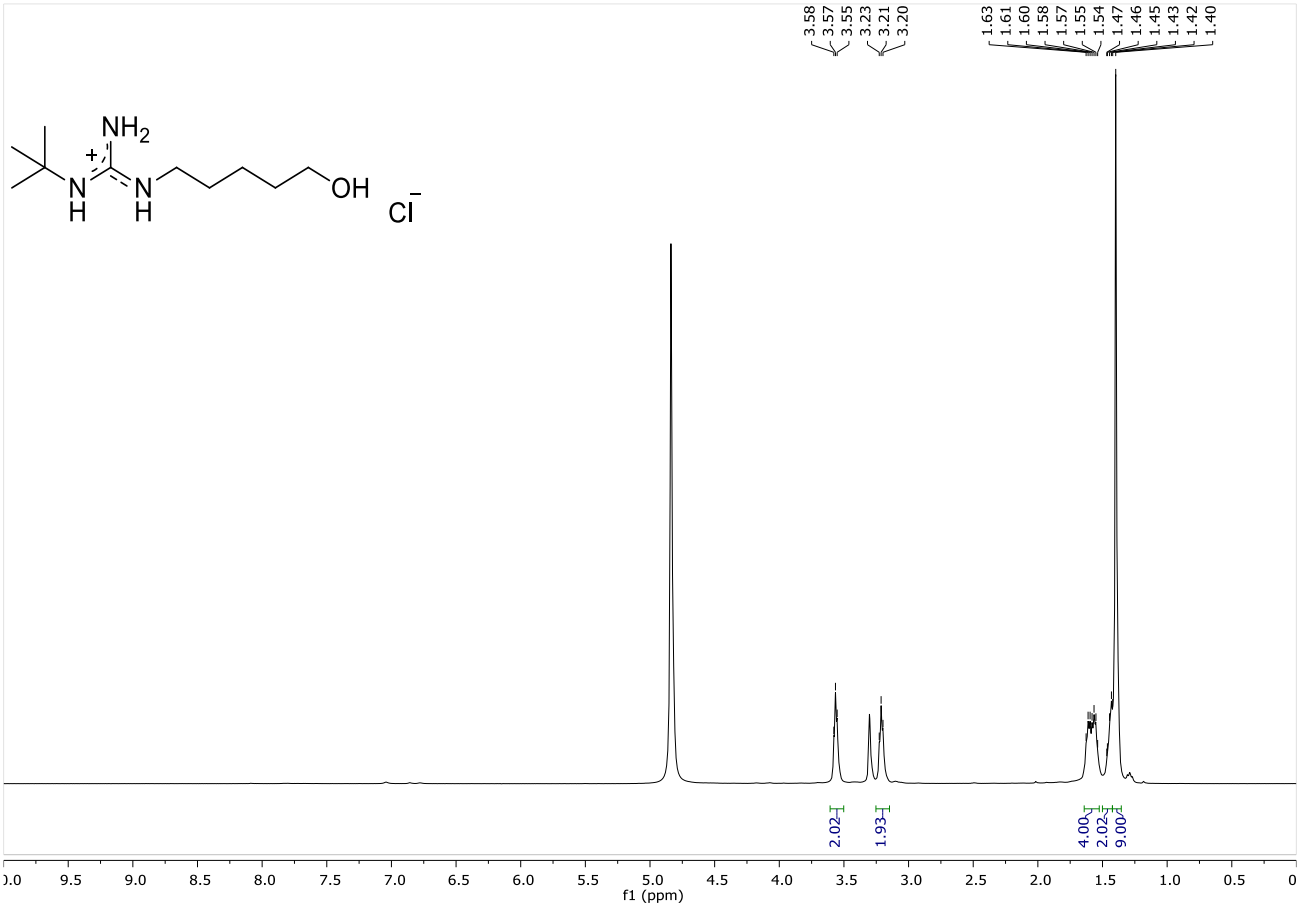
^{13}C-NMR spectrum of **10a** in DMSO-d_6



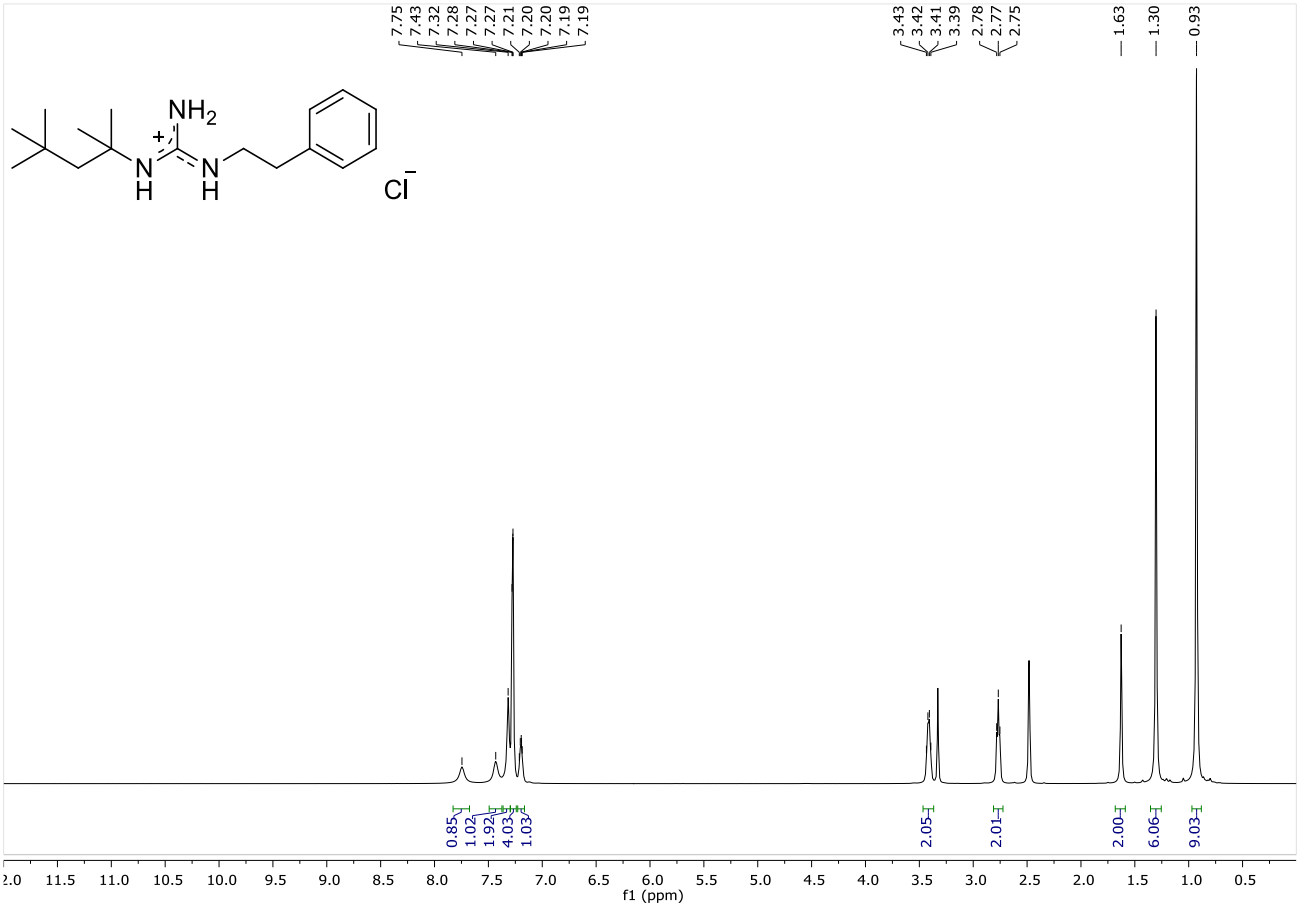
^{1}H-NMR spectrum of **10b** in DMSO-d_6



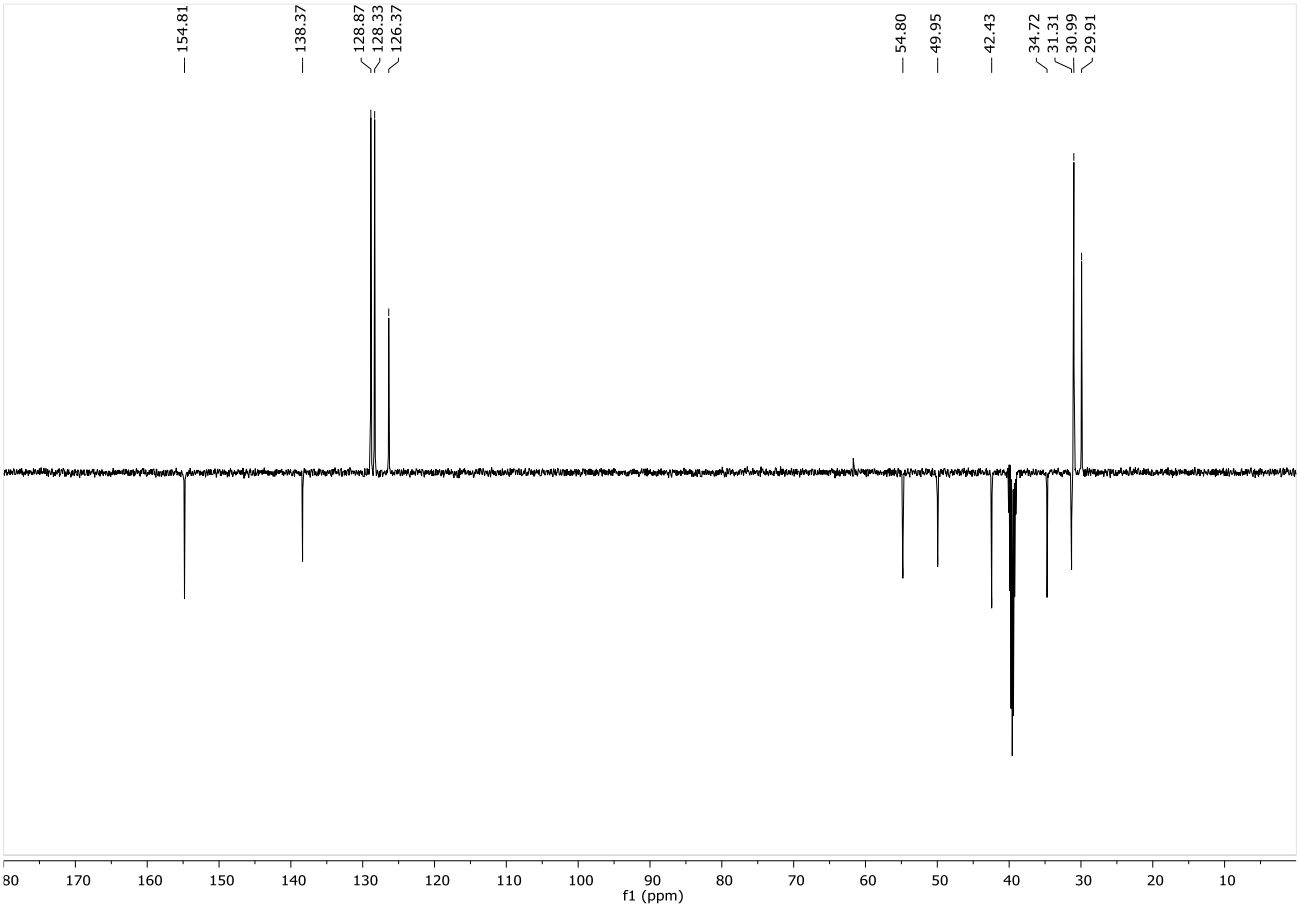
^{13}C-NMR spectrum of **10b** in DMSO-d_6



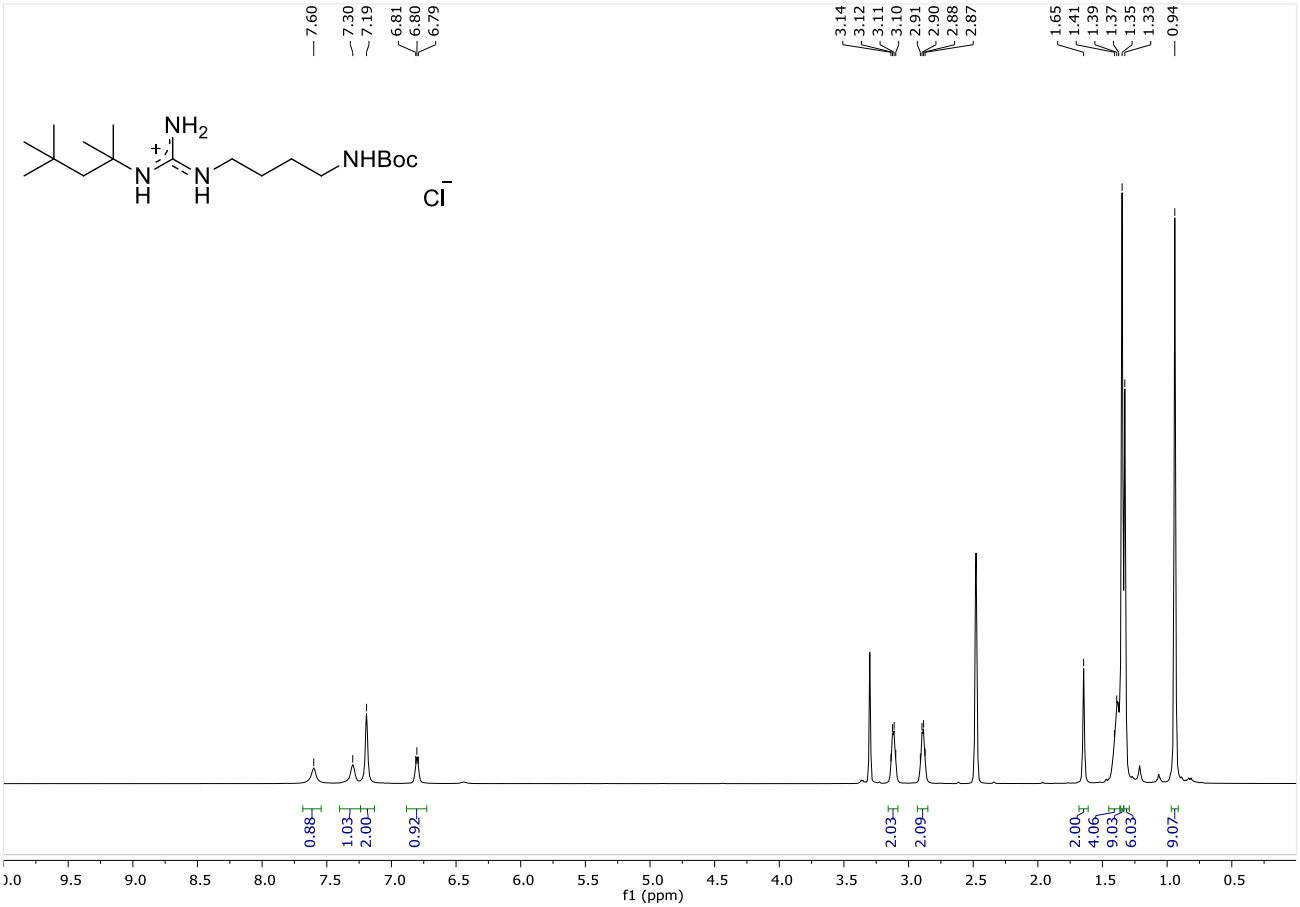
^{1}H-NMR spectrum of **10b** in MeOD-d_4



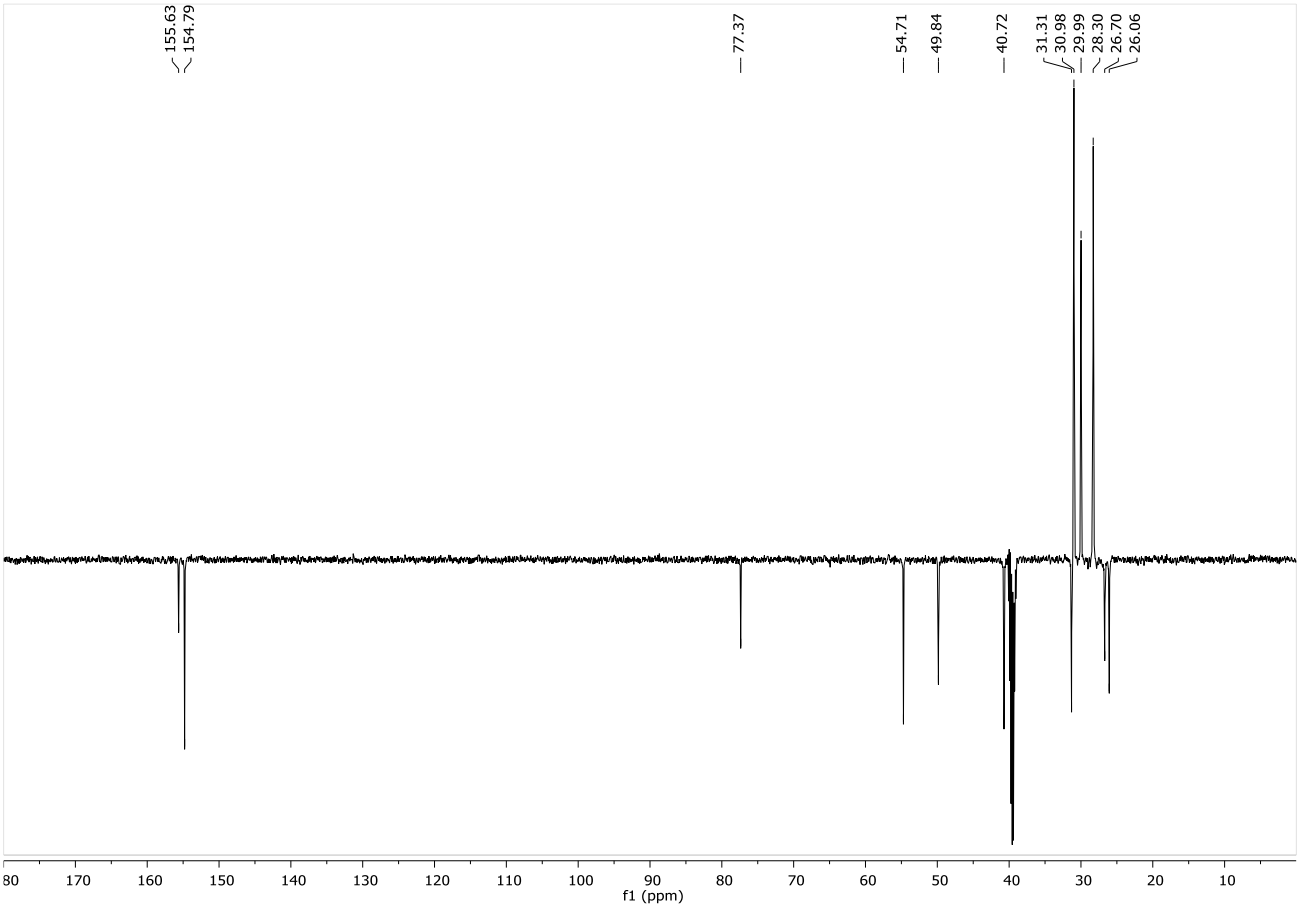
^{1}H-NMR spectrum of **10c** in DMSO-d_6



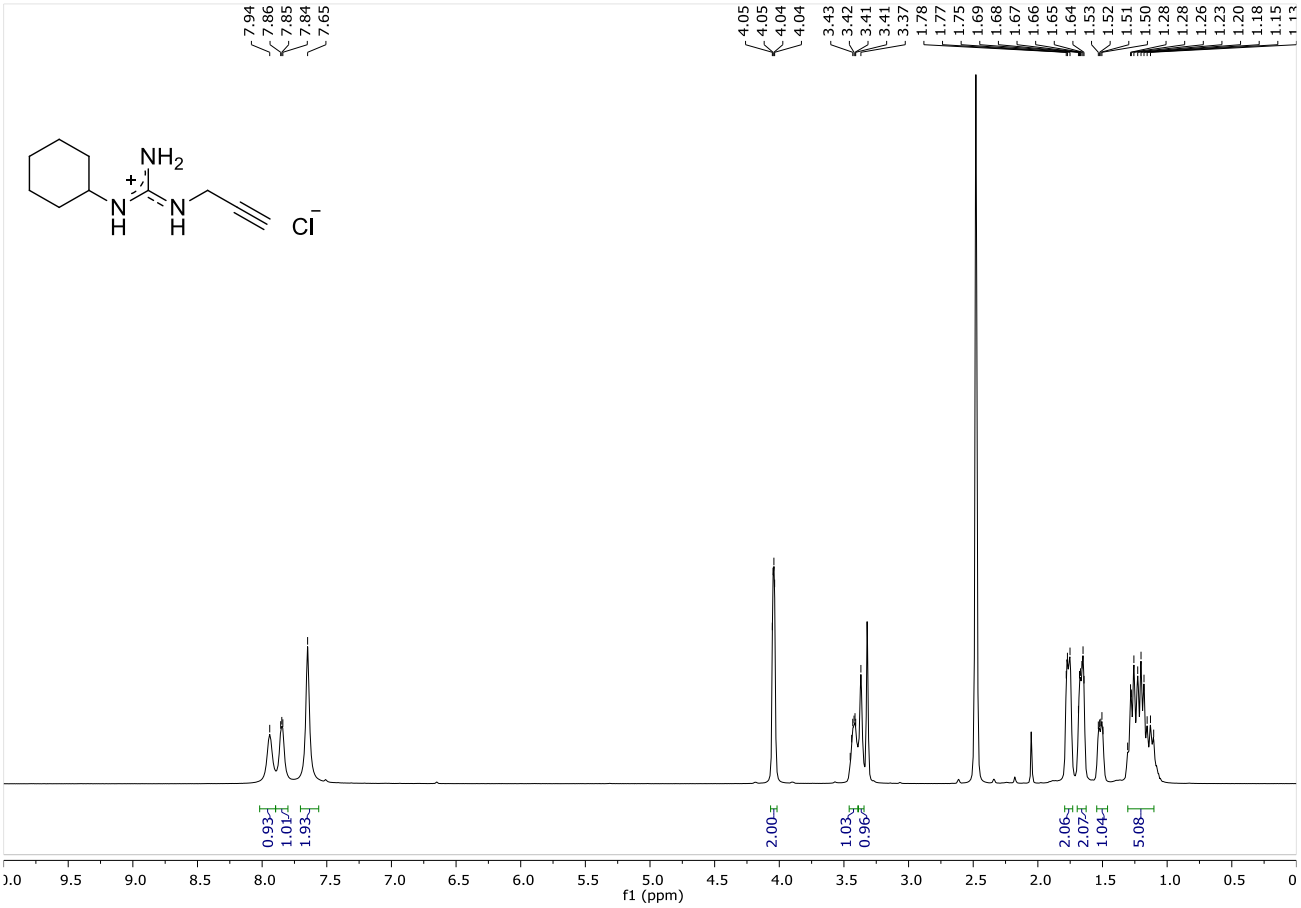
^{13}C-NMR spectrum of **10c** in DMSO-d_6



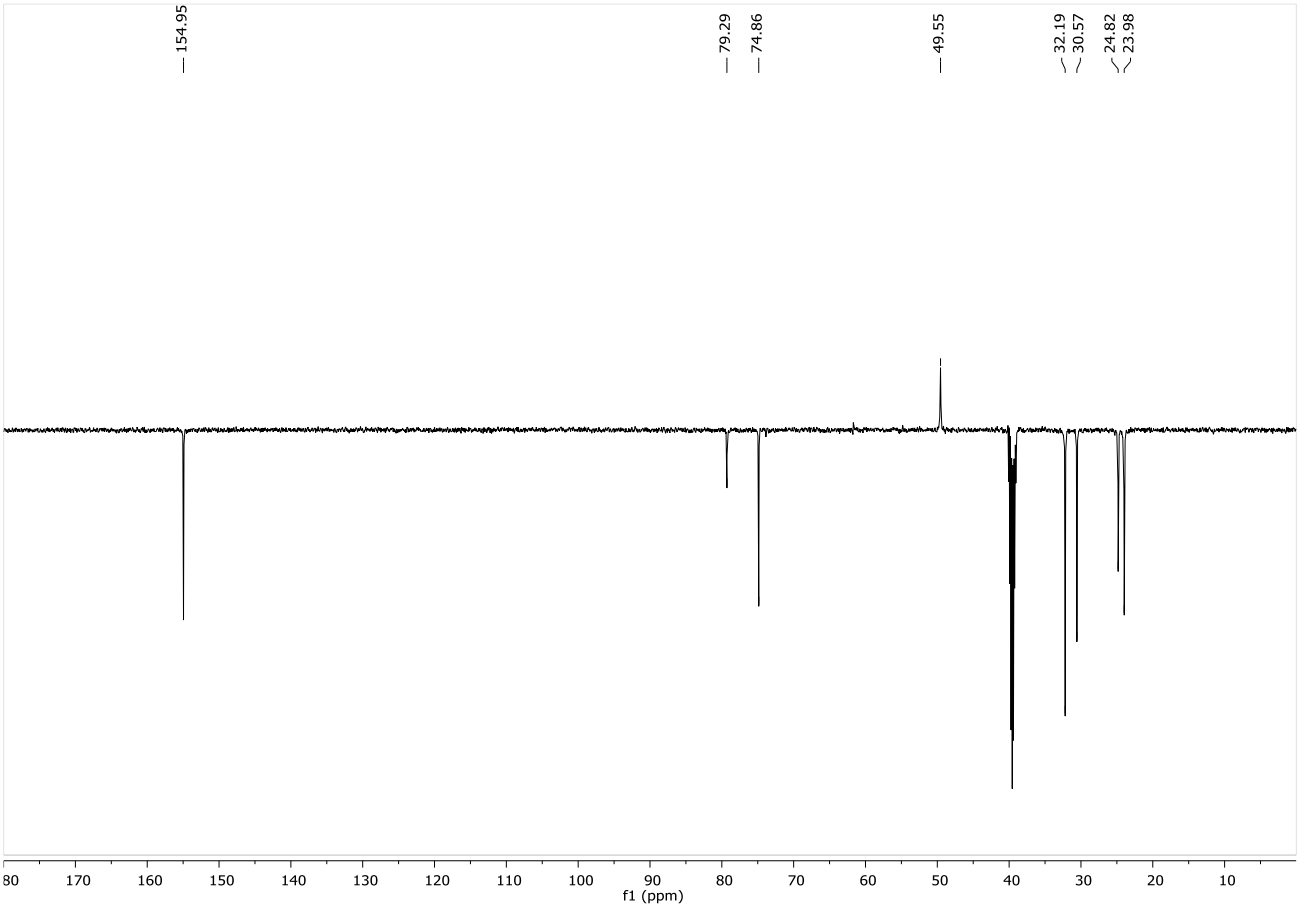
^{1}H-NMR spectrum of **10d** in DMSO-d_6



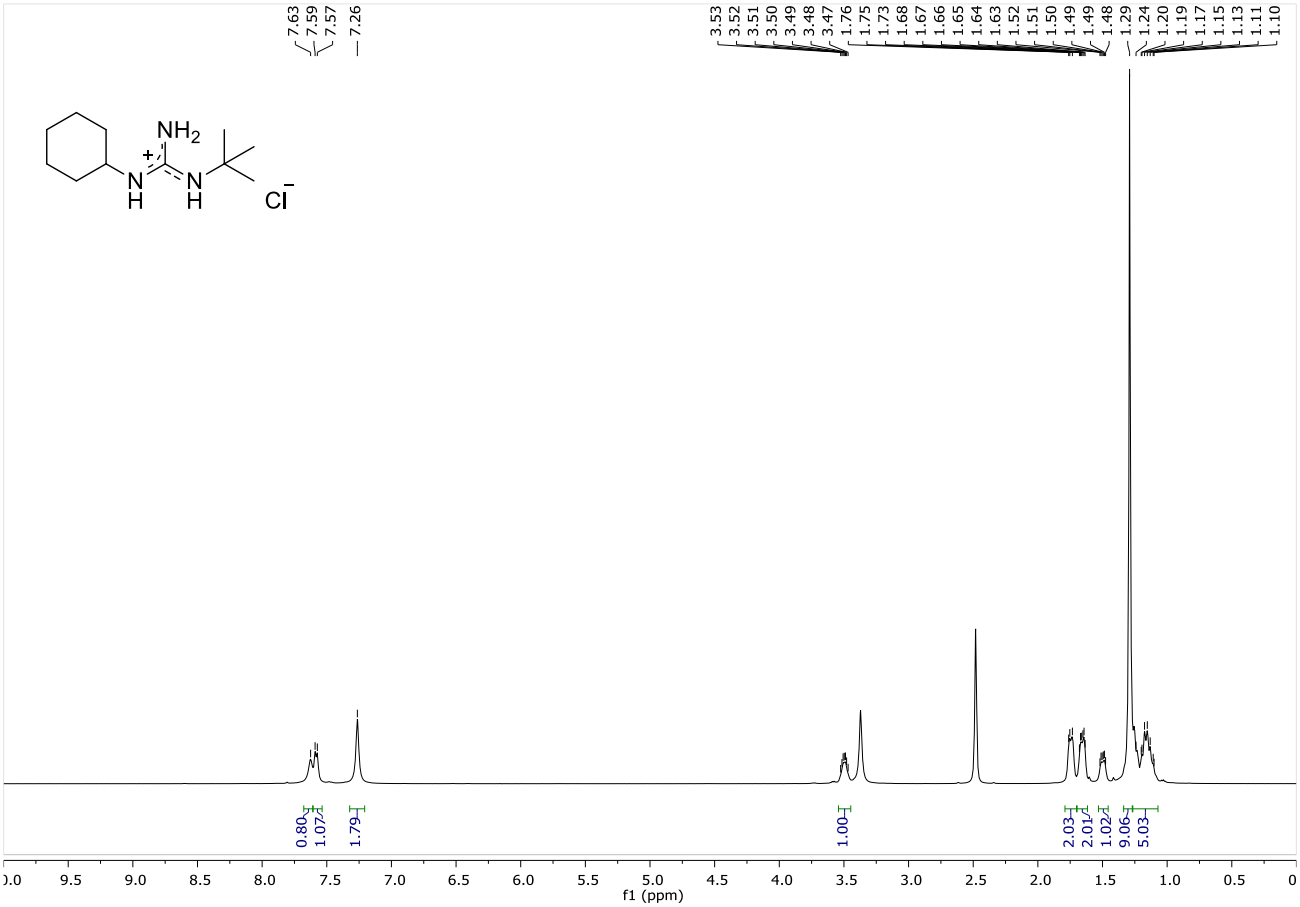
^{13}C-NMR spectrum of **10d** in DMSO-d_6



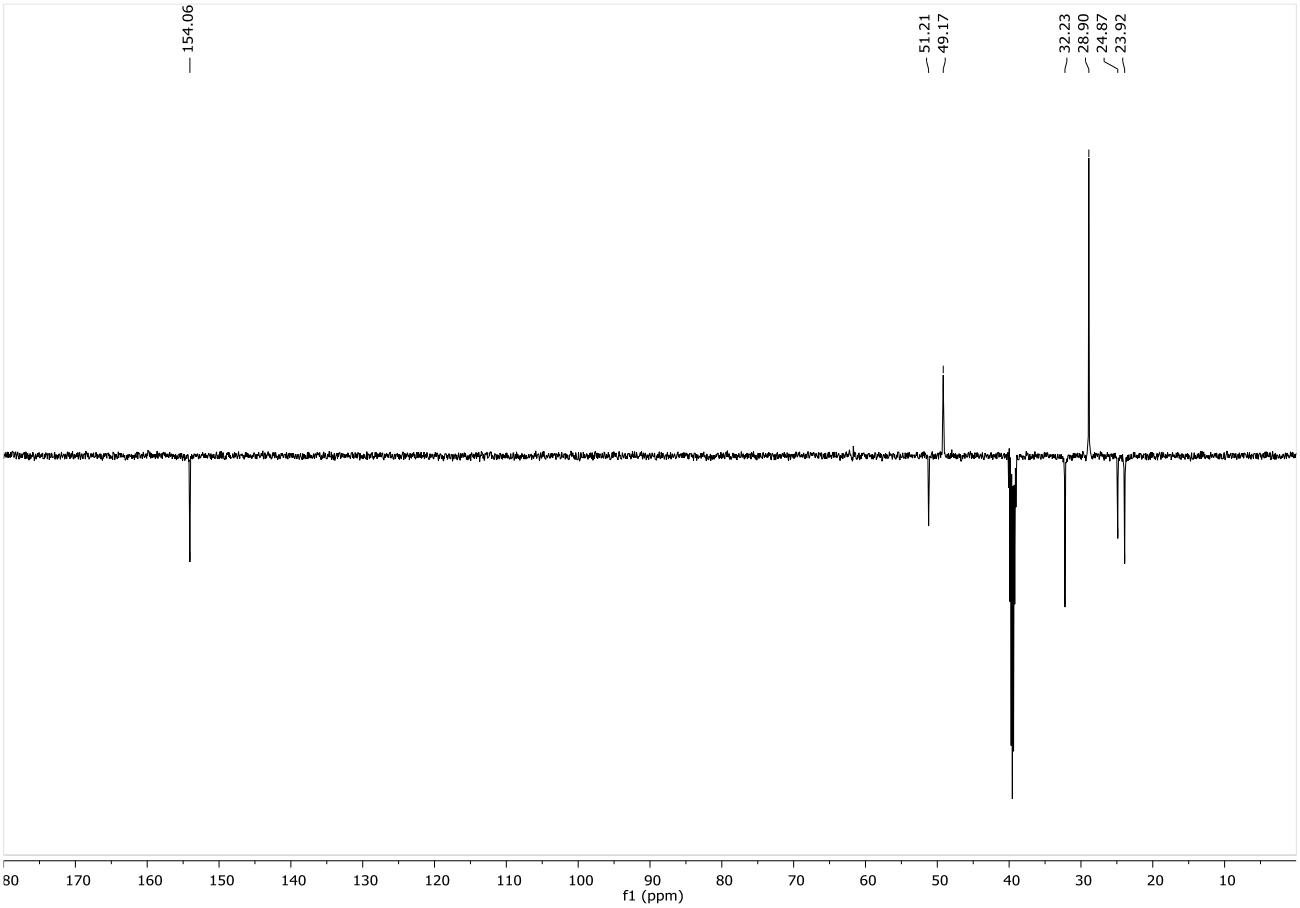
^{1}H-NMR spectrum of **10e** in DMSO-d_6



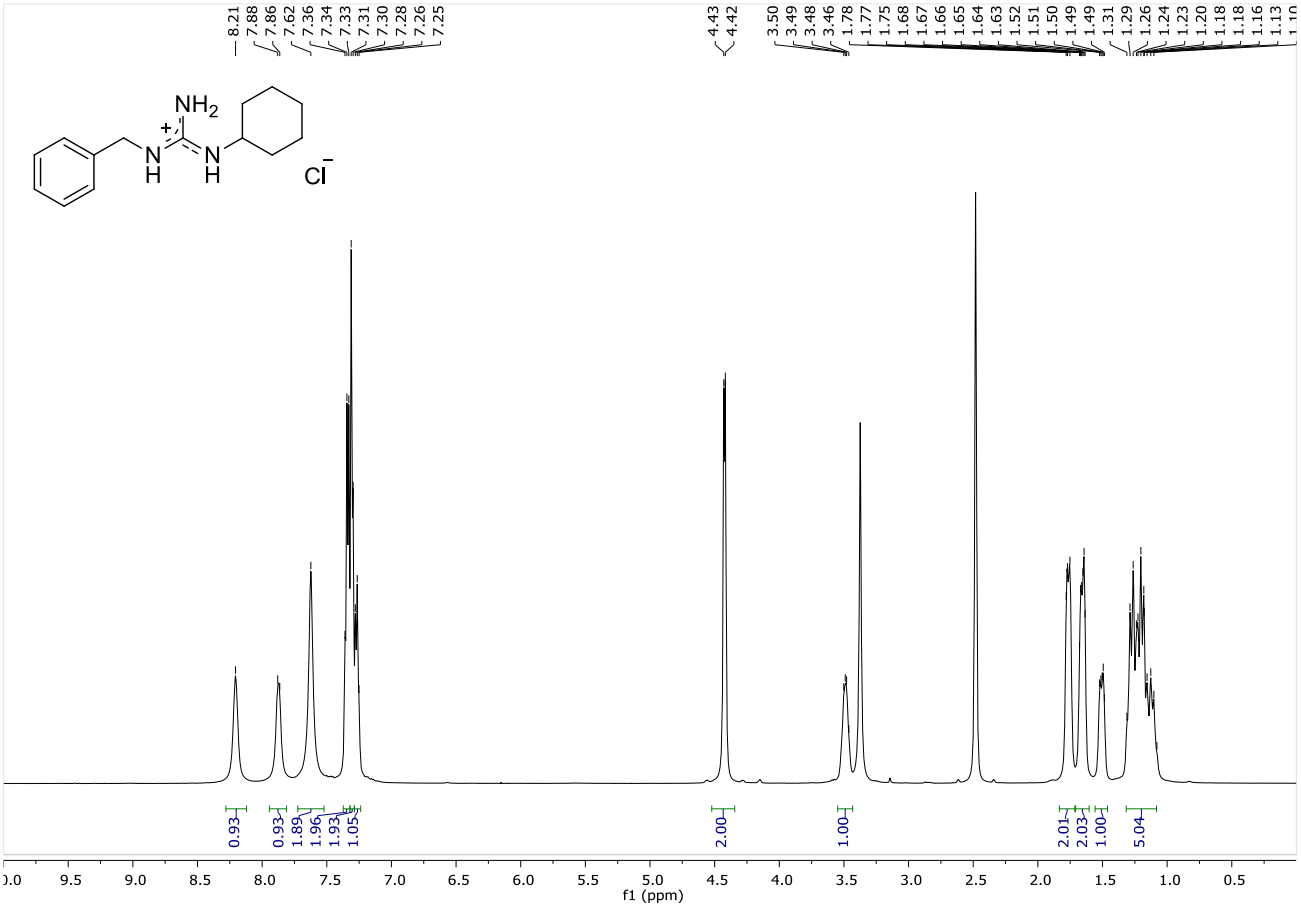
^{13}C-NMR spectrum of **10e** in DMSO-d_6



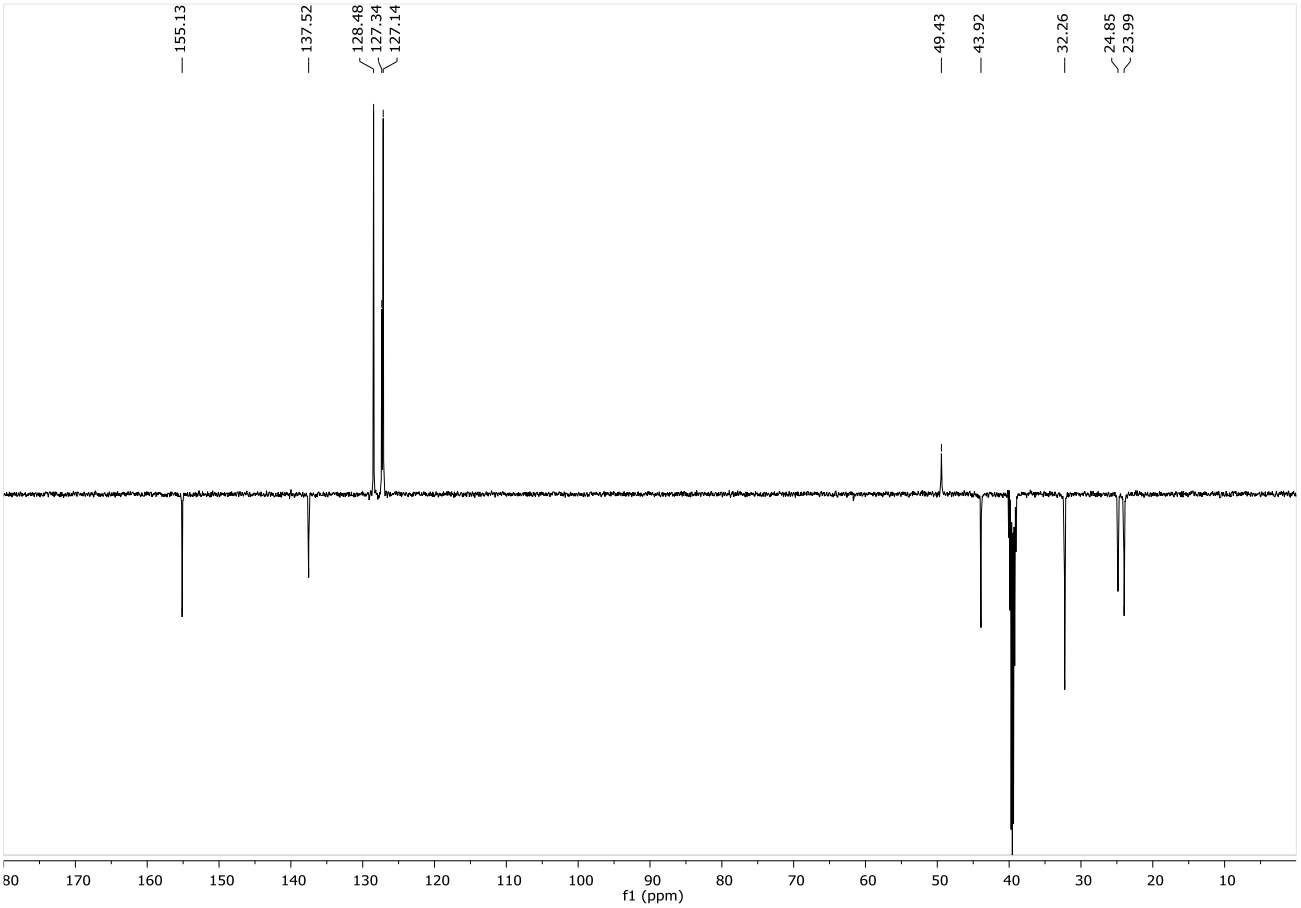
^{1}H-NMR spectrum of **10f** in DMSO-d_6



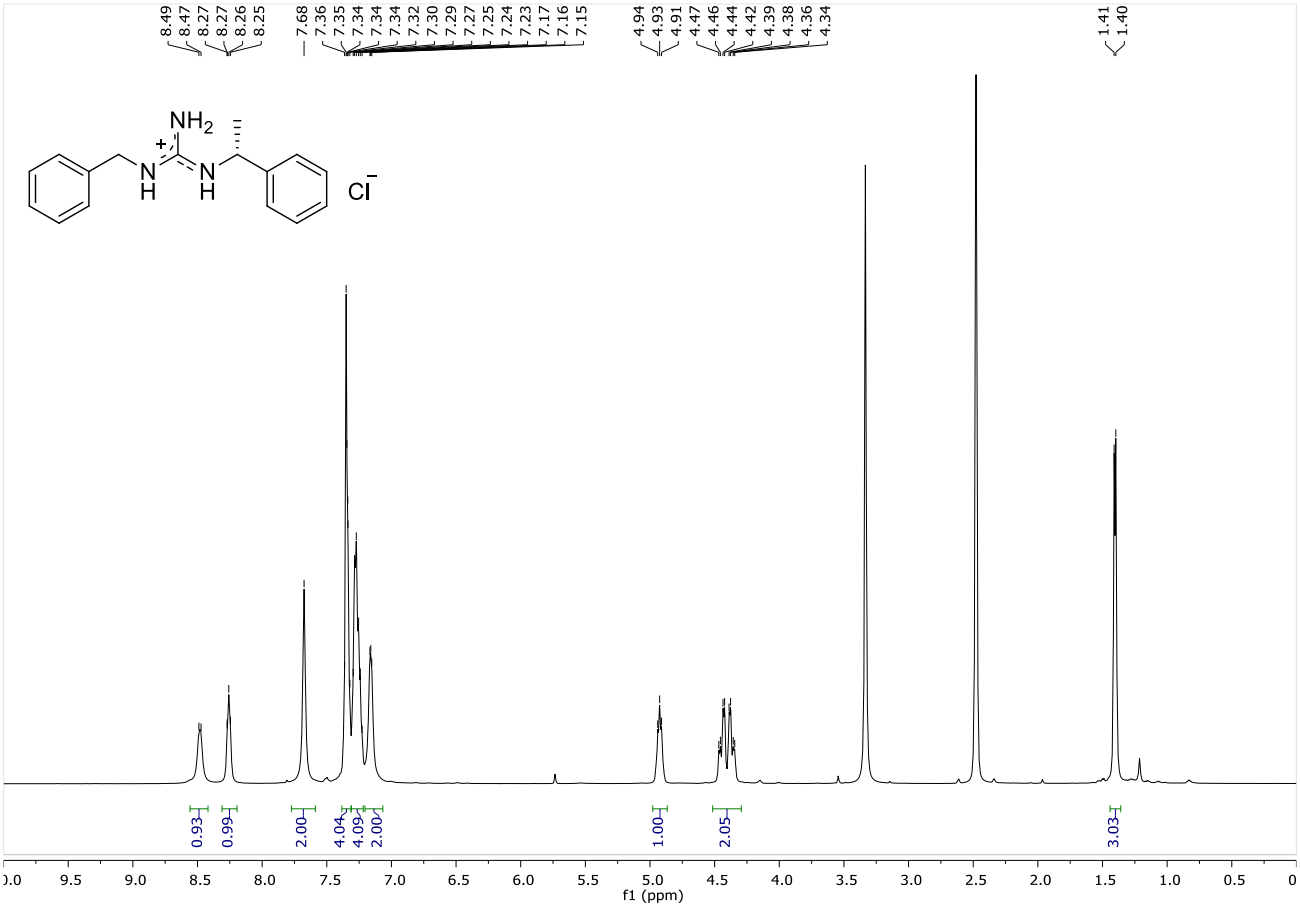
^{13}C-NMR spectrum of **10f** in DMSO-d_6



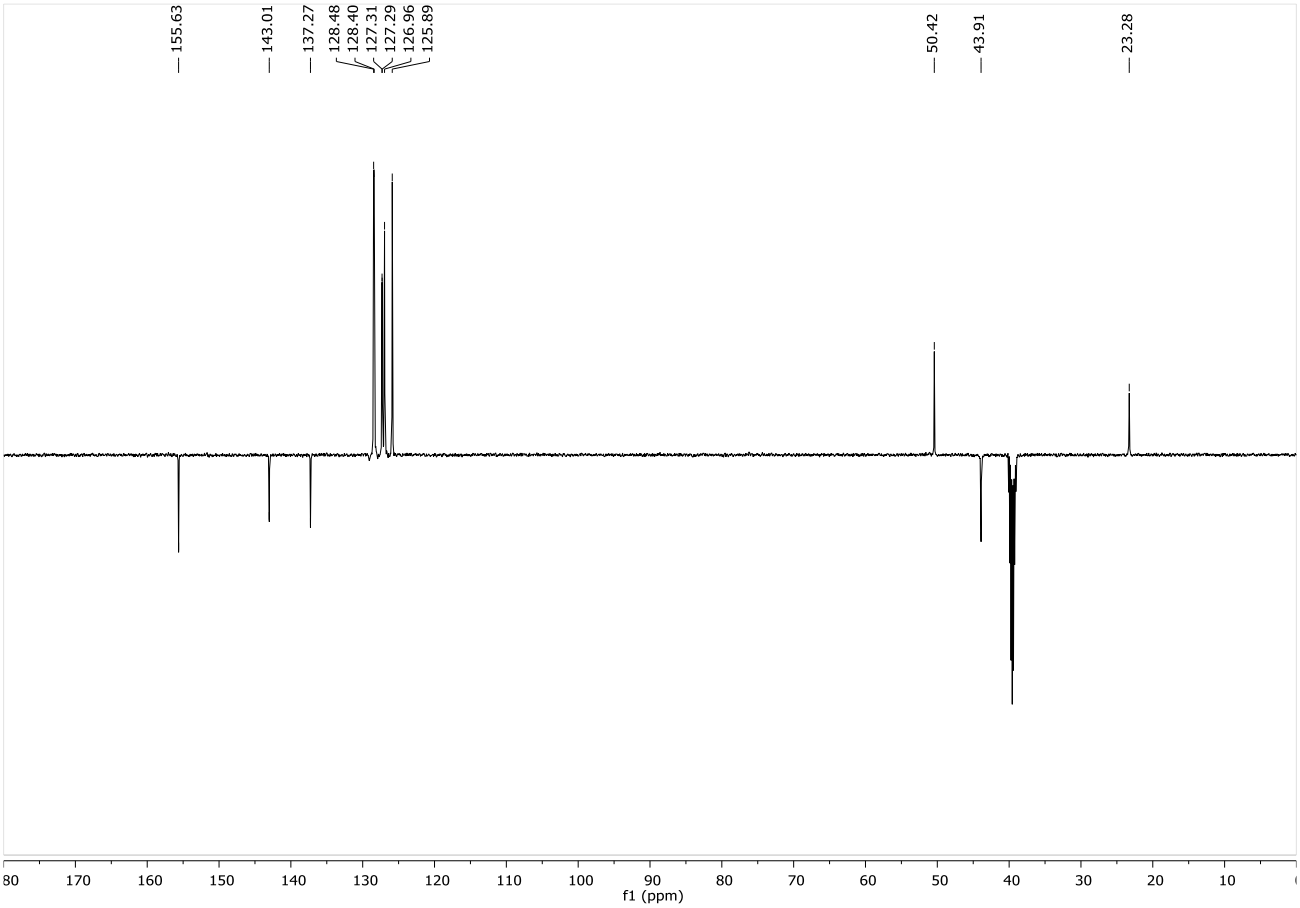
^{1}H-NMR spectrum of **10g** in DMSO-d_6



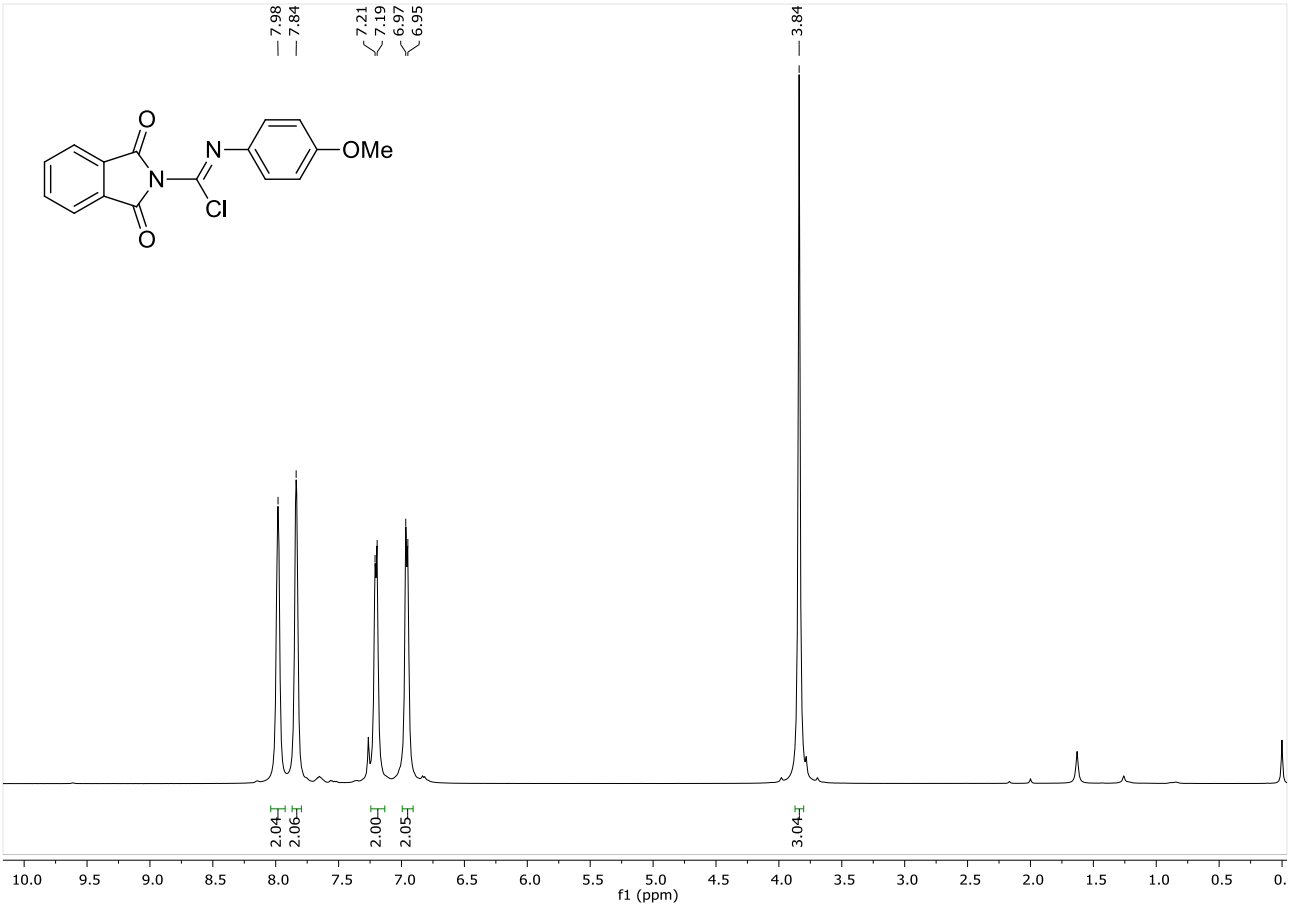
^{13}C-NMR spectrum of **10g** in DMSO-d_6



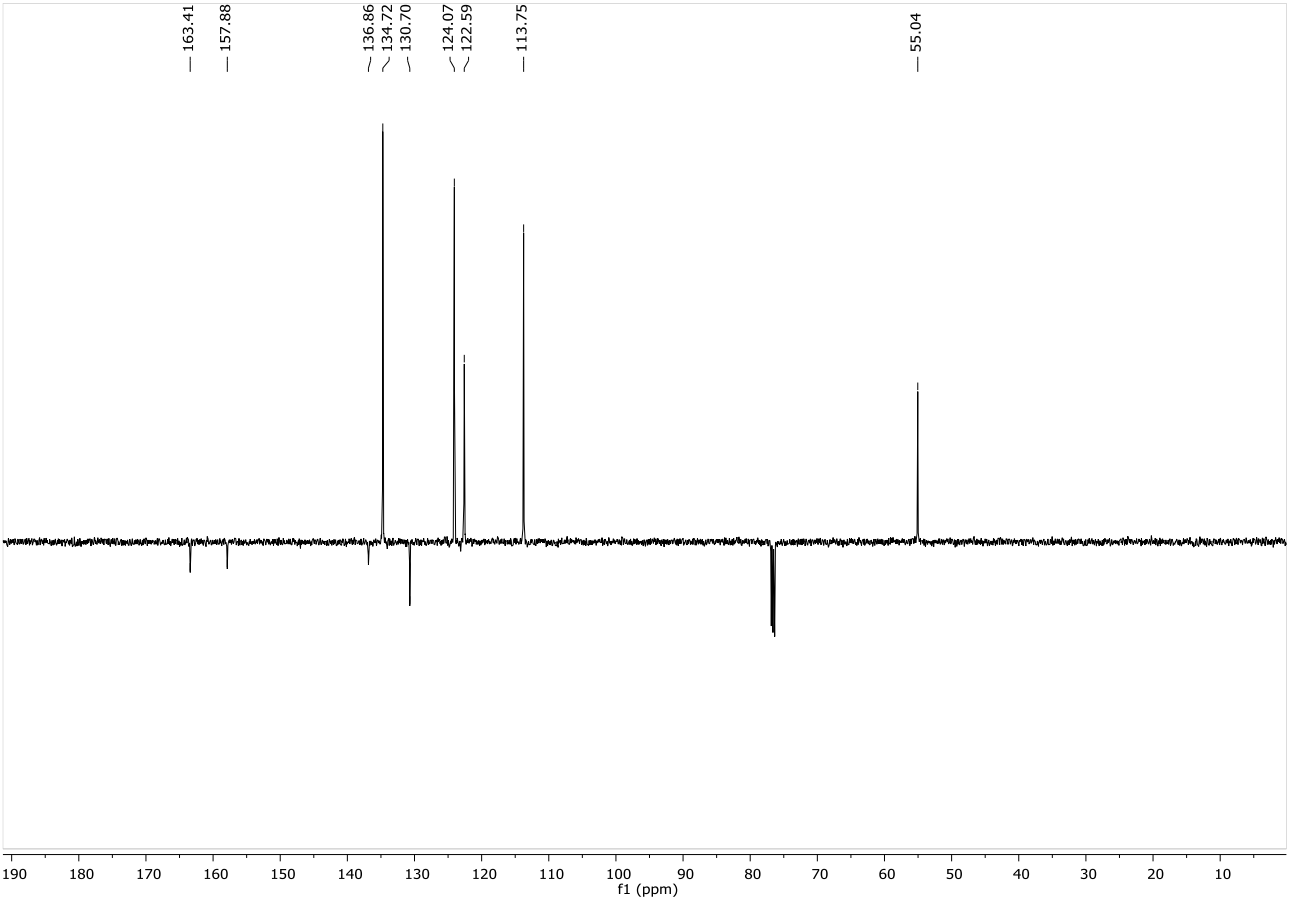
^{1}H-NMR spectrum of **10h** in DMSO-d_6



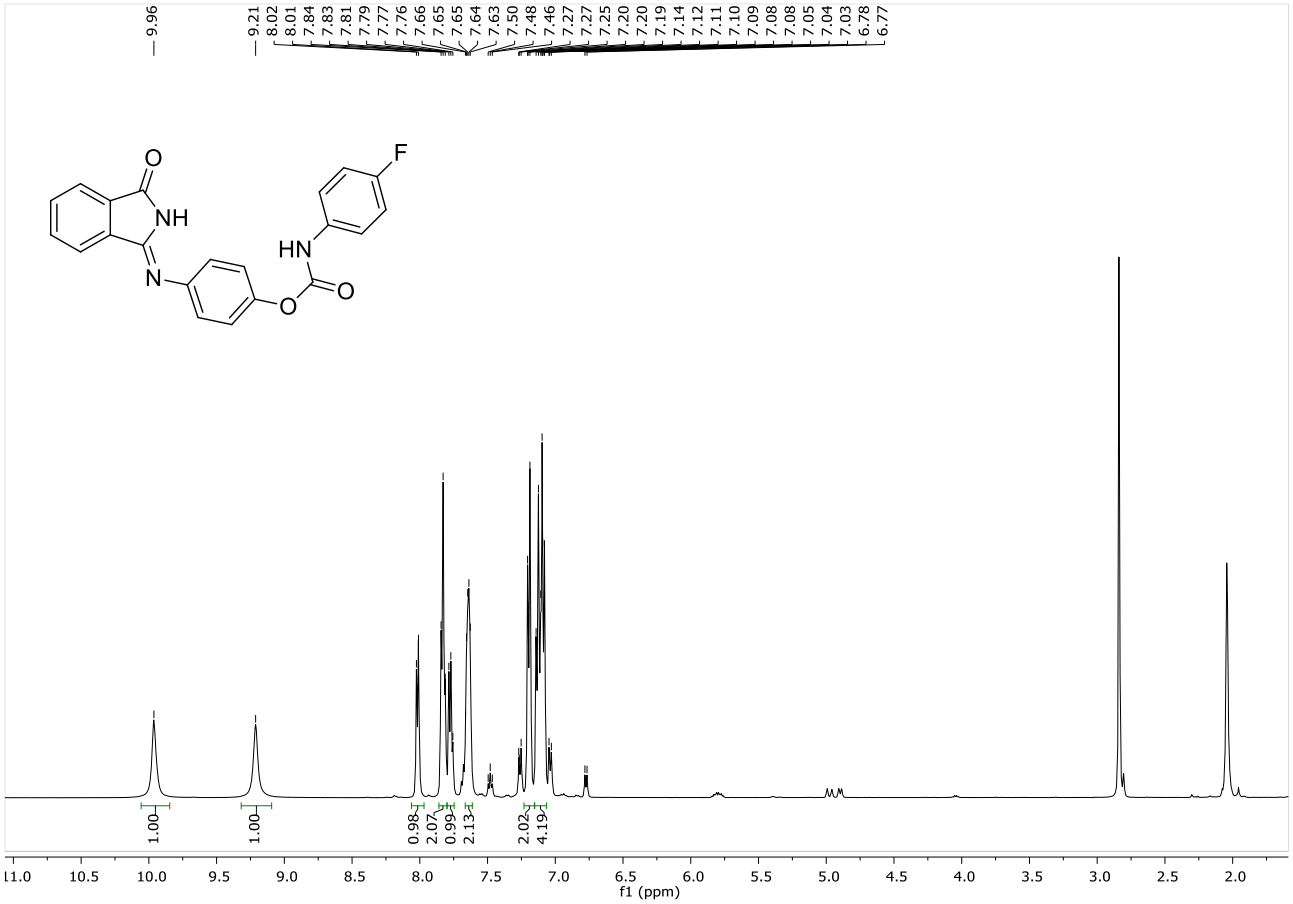
^{13}C-NMR spectrum of **10h** in DMSO-d_6



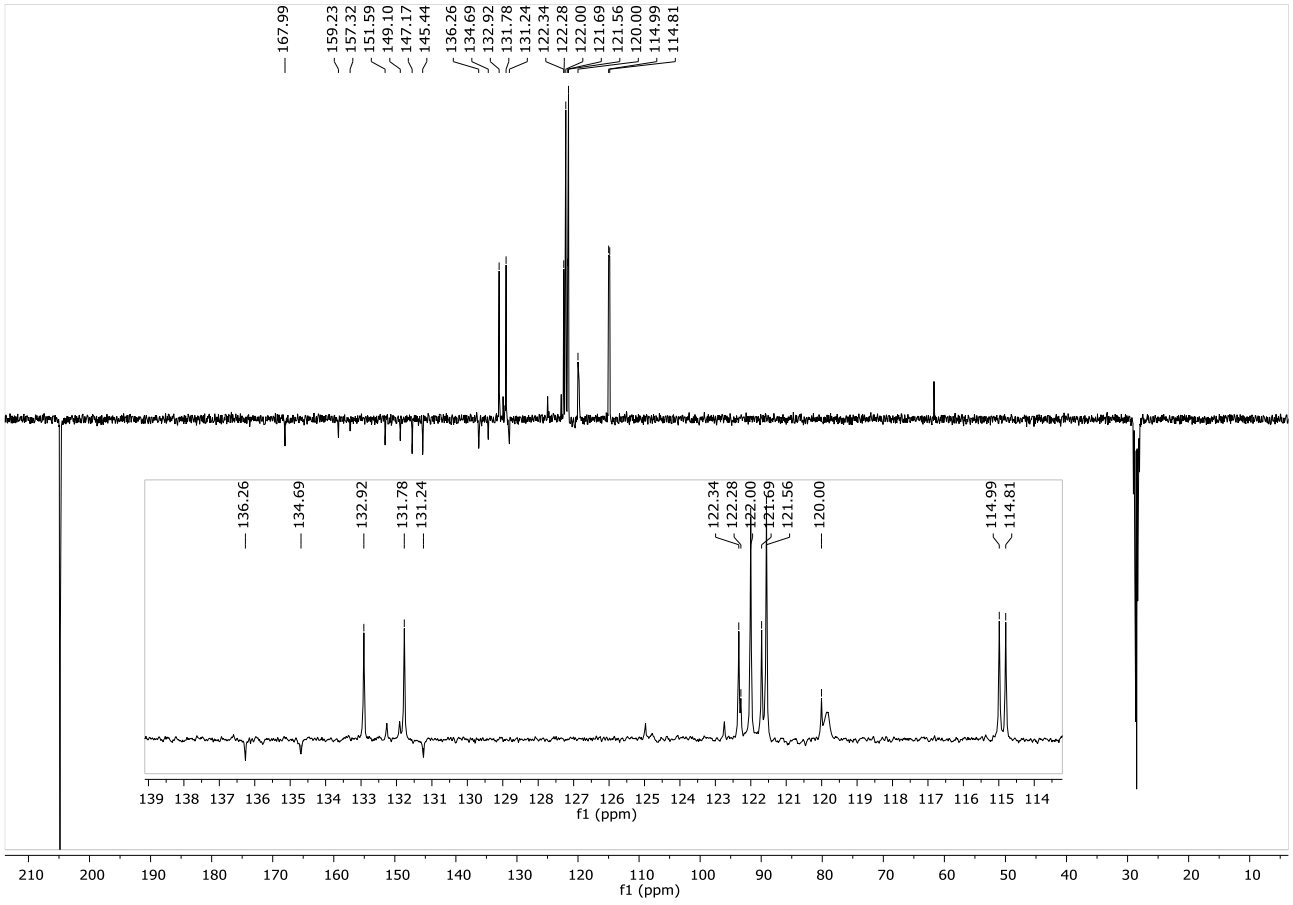
^{1}H-NMR spectrum of **3b** in $CDCl_3$



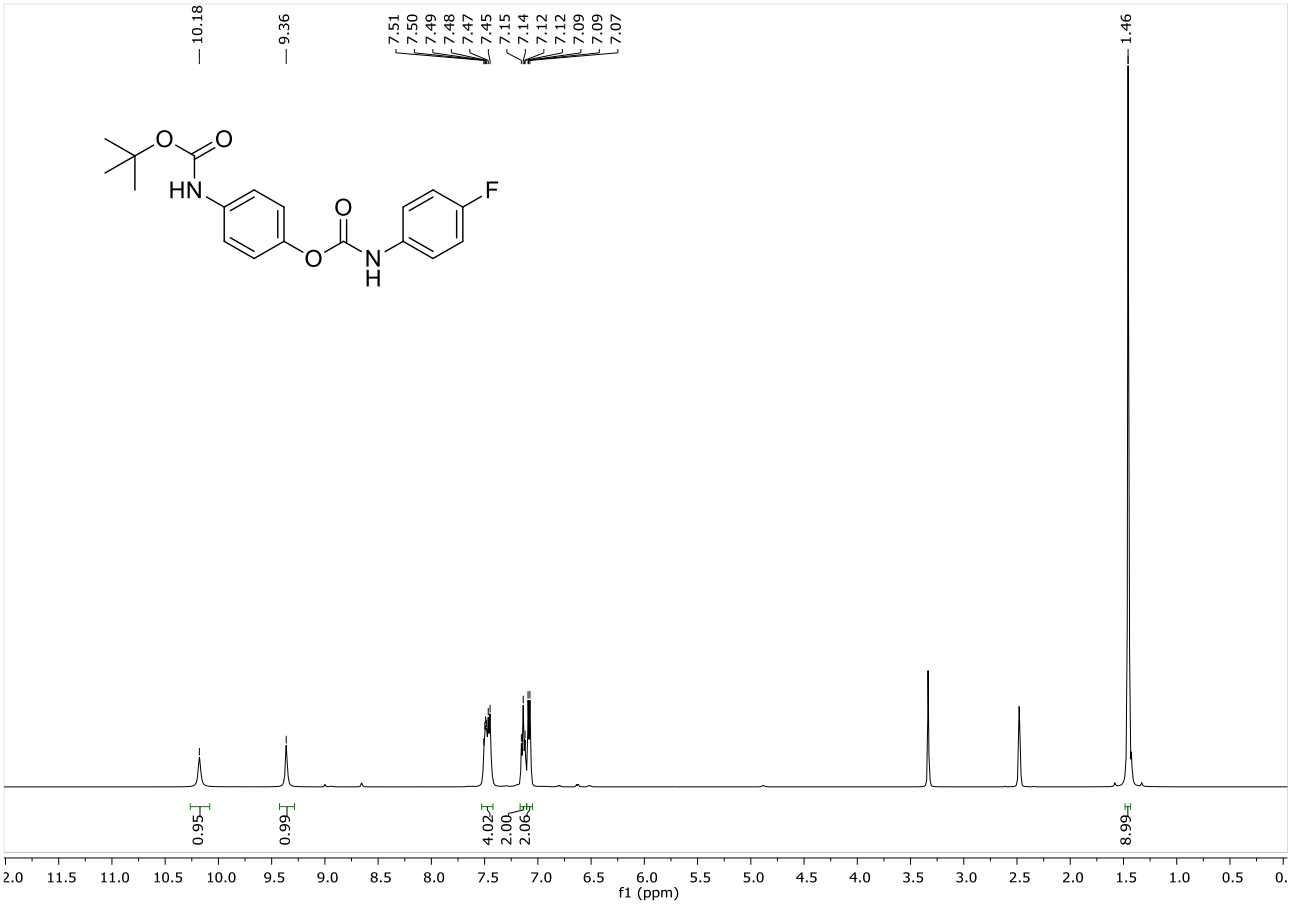
^{13}C-NMR spectrum of **3b** in $CDCl_3$



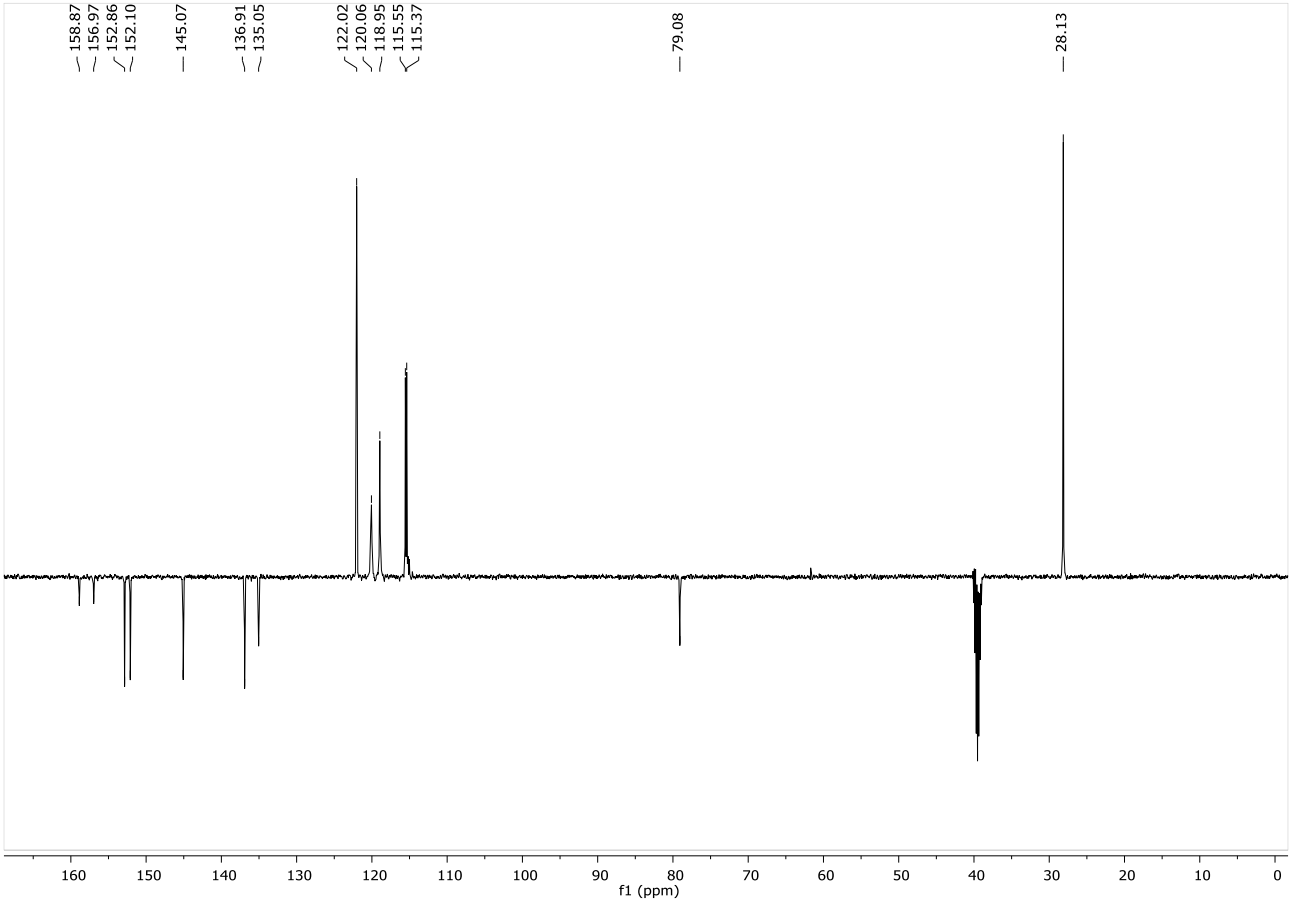
^{1}H-NMR spectrum of **14** in acetone-d_6



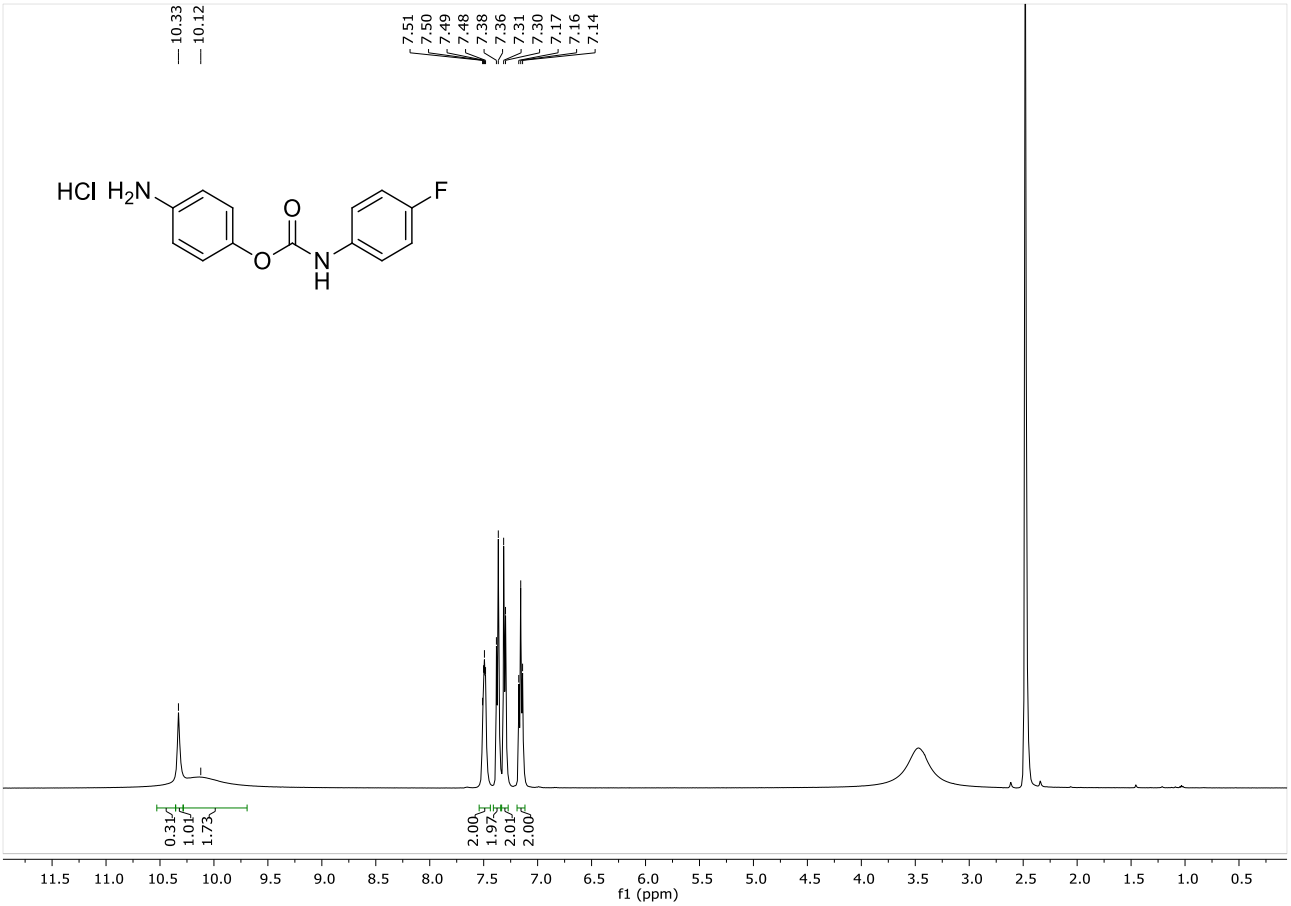
^{13}C-NMR spectrum of **14** in acetone-d_6



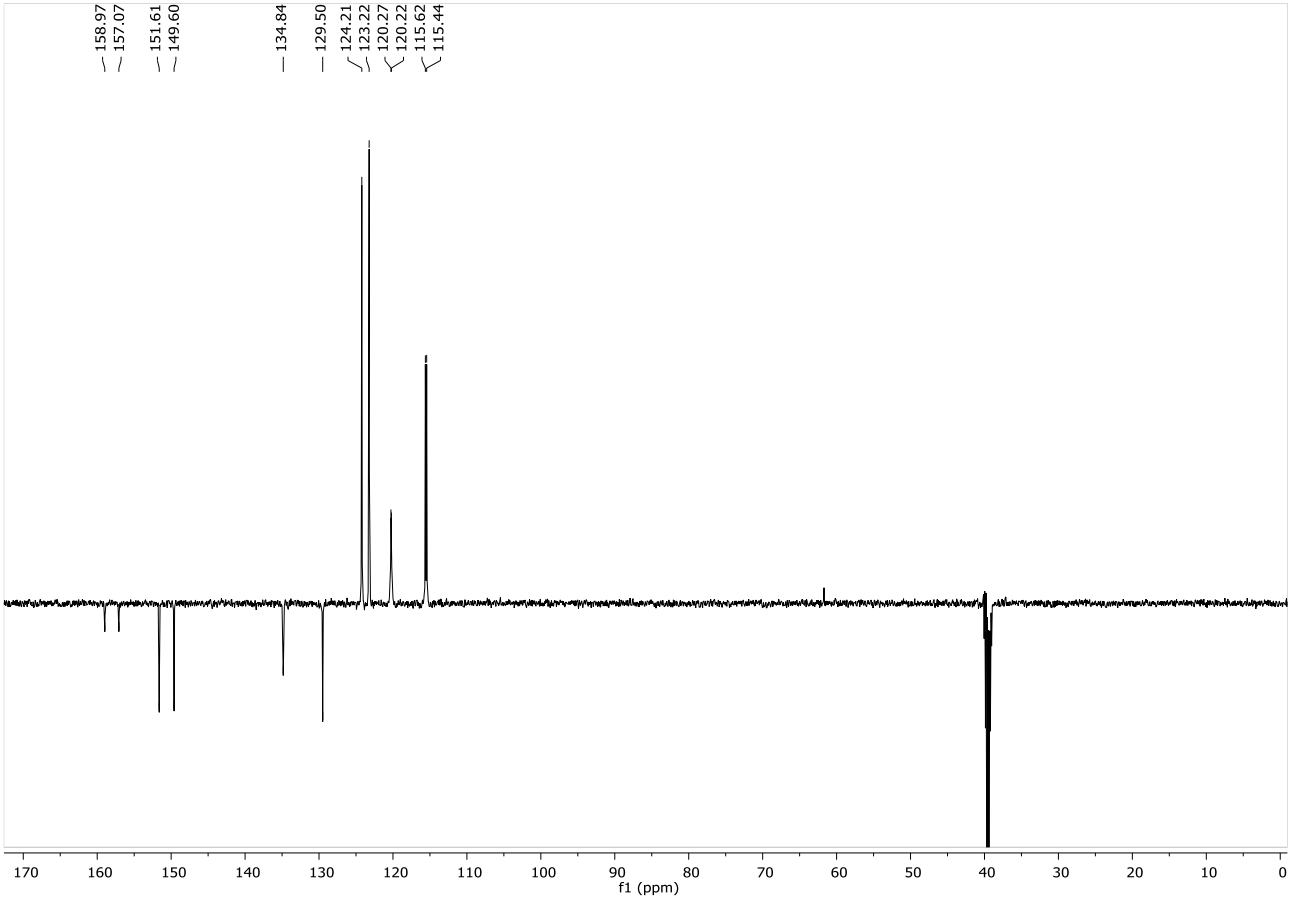
^{1}H-NMR spectrum of **19** in DMSO-d_6



^{13}C-NMR spectrum of **19** in DMSO-d_6



^{1}H-NMR spectrum of **20**in DMSO-d_6



^{13}C-NMR spectrum of **20** in DMSO-d_6

11. References

[1] a) R. Obrecht, R. Herrmann, I. Ugi, *Synthesis* **1985**, 400–402; b) S. Kamijo, T. Jin, Y. Yamamoto, *Angew. Chem.* **2002**, *114*, 1858–1860; c) J. C. A. Boeyens, L. M. Cook, Y. Ding, M. A. Fernandes, D. H. Reid, *Org. Biol. Chem.* **2003**, *1*, 2168–2172.

[2] C.-Y. Chen, H.-C. Lin, Y.-Y. Huang, K.-L. Chen, J.-J. Huang, M.-Y. Yeh, F. F. Wong, *Tetrahedron* **2010**, *66*, 1892–1897.

[3] S. Scherbakow, J. C. Namyslo, M. Gjikaj, A. Schmidt, *Synlett* **2009**, 1964–1968.

[4] T. Arnauld, J.-Y. Beaumal, F. Lefoulon, A. Petit, T. Renaud, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2217–2219.

[5] S. V. Chankeshwara, A. K. Chakraborti, *Org. Lett.* **2006**, *8*, 3259–3262.