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Scaffold hopping in the oxadiazole antibiotic structure leads to more active compounds

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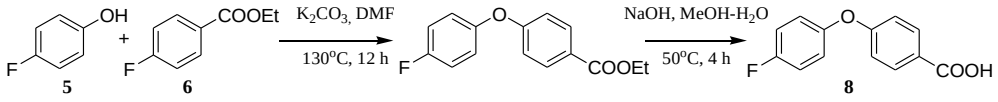
1. Synthesis of target compounds.

1.1. General experimental information.

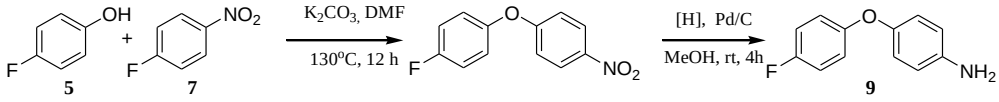
All reactions were carried out in glassware with magnetic stirring. Solvents and commercial reagents were used without additional purification. Visualization on TLC (analytical thin layer chromatography) was achieved by the use of UV light (254 nm) and treatment with phosphomolybdic acid ethanol solution followed by heating. TLC was performed on Imid Ltd Sorbfil plates. Unless otherwise noted, yields refer to chromatographically and spectroscopically pure compounds. Mass spectra were recorded using Shimadzu LCMS 2020 system with ESI. High resolution mass spectra (HRMS) were recorded using a Bruker microTOF spectrometer (ionization by electrospray, positive ions detection). Proton and carbon magnetic resonance spectra (^{1}H NMR at 300 MHz and ^{13}C NMR at 75 MHz) were recorded on a Bruker DPX-300 spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.25 ppm, DMSO-d_6 at 2.49 ppm; ^{13}C NMR: $CDCl_3$ at 77.00 ppm, DMSO-d_6 at 39.50 ppm). NMR data are represented as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant in Hertz (Hz). Melting points were measured with a Buchi B-520 melting point apparatus and were not corrected.

*4-(4-Fluorophenoxy)benzoic acid (**8**)*



Solid K_2CO_3 (13.8 g, 0.1 mol) was added to a solution of 4-fluorophenol **5** (5 g, 0.0445 mol) and ethyl 4-fluorobenzoate **6** (6.8 g, 0.04 mol) in DMF (50 ml), and this was stirred at 130 °C for 12 hours. The reaction mass was cooled to room temperature, poured into water, and extracted with ethyl acetate (3 times 150 ml each). The combined organic phases were evaporated, and the residue was dissolved in MeOH (100 ml). Then 15% aqueous solution of NaOH (25 ml) was added, stirred at 50 °C for 4 hours, the volatiles were evaporated, and the residue was dissolved in water (50 ml) and acidified with 10% HCl. The precipitate that formed was filtered and dried at 10 Torr. Yield 7.9 g (86%), white solid, m.p. 176-176.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.85 (s, 1H), 7.94 (d, *J* = 8.7 Hz, 2H), 7.29 (t, *J* = 8.7 Hz, 2H), 7.21 – 7.14 (m, 2H), 7.00 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d6) δ 166.84 (s), 161.39 (s), 159.02 (d, *J* = 244.0 Hz), 151.05, 131.79, 125.30, 122.16 (d, *J* = 8.6 Hz), 117.12, 116.89. LCMS (ESI): m/z (M+ H^+) calcd, 233.1 Da; found, 233.2 Da.

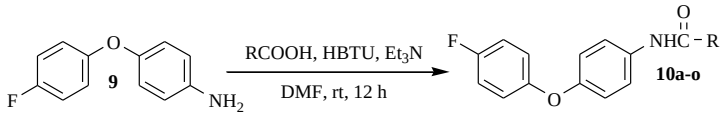
*4-(4-Fluorophenoxy)aniline (**9**)*



Solid K_2CO_3 (13.8 g, 0.1 mol) was added to a solution of 4-fluorophenol **5** (5 g, 0.0445 mol) and 4-fluoronitrobenzene **7** (6.7 g, 0.04 mol) in DMF (50 ml), and this was stirred at 130 °C for 12

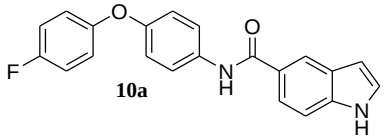
hours. The reaction mass was cooled to room temperature, poured into water, and extracted with ethyl acetate (3 times 150 ml each). The combined organic phases were evaporated, the residue was dissolved in MeOH (100 ml), and 10% Pd/C (0.2 g) was added, and this was hydrogenated at 1 atm H_2 for 4 hours. Then the reaction mixture was filtered through a celite layer, the filtrate was evaporated, and the resulting solid was triturated with Et_2O and filtered. Yield 6.6 g (82%), gray solid, m.p. 66-66.5 °C. ^{1}H NMR (300 MHz, DMSO-d6) δ 8.78 (s, 1H), 5.28 (s, 2H), 3.94 (d, *J* = 13.0 Hz, 2H), 2.69 (t, *J* = 11.6 Hz, 2H), 2.26 – 2.02 (m, 1H), 1.66 (dd, *J* = 19.6, 8.9 Hz, 2H), 1.54 – 1.22 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.26 (d, *J* = 237.5 Hz), 155.15, 146.08, 145.53, 120.67, 118.13 (d, *J* = 8.3 Hz), 116.17 (d, *J* = 23.2 Hz), 114.97. LCMS (ESI): m/z ($M+H^+$) calcd, 204.0 Da; found, 204.2 Da.

1.2. General procedure for *N*-[4-(4-fluorophenoxy)phenyl] carboxamide (10) preparation.



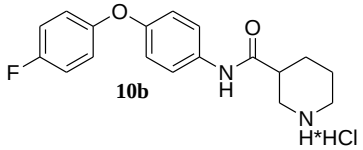
To a solution of the corresponding *N*-Boc-protected amino carboxylic acid (0.82 mmol, 1 eq) in DMF (10 ml), HBTU (0.37 g, 0.98 mmol, 1.2 eq), amine **9** (0.73 mmol, 0.9 eq), and Et_3N (0.1 g, 0.98 mmol, 1.2 eq) were added sequentially. The reaction mixture was stirred overnight, poured into water (25 ml), and the precipitate that formed was filtered off, dried, and triturated with Et_2O. The precipitate was filtered off, dissolved in dioxane (5 ml) and cooled to 0 °C. Then 4 M HCl/dioxane solution (5 ml) was added dropwise, and this was stirred overnight. The precipitate that formed was filtered off and recrystallized from EtOH.

*N-[4-(4-Fluorophenoxy)phenyl]-1H-indole-5-carboxamide, LK1632 (**10a**)*



Yield 0.156 g (55%), white solid, m.p. 176-176.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.20 (s, 1H), 7.94 (s, 1H), 7.73 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.62 (d, *J* = 8.9 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.06 – 6.93 (m, 6H), 6.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.98, 159.02 (d, *J* = 244.0 Hz), 153.88, 153.27, 137.74, 133.78, 127.66, 126.53, 125.89, 122.06, 121.08, 120.02 (d, *J* = 8.2 Hz), 119.10, 116.24 (d, *J* = 23.3 Hz), 111.32. HRMS (ESI), m/z calcd $C_{21}H_{16}FN_2O_2$ [$M+H^+$] 347.1195 Da, found 347.1196 Da.

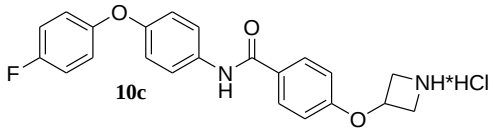
*N-[4-(4-Fluorophenoxy)phenyl]piperidine-3-carboxamide hydrochloride, LK1771, (**10b**)*



Yield 0.149 g (52%), white solid, m.p. 235-235.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.41 (s, 1H), 9.17 (d, *J* = 64.1 Hz, 2H), 7.63 (d, *J* = 8.9 Hz, 2H), 7.19 (t, *J* = 8.8 Hz, 2H), 7.08 – 6.88 (m,

4H), 3.39 (s, 1H), 3.23 (dd, *J* = 36.3, 10.7 Hz, 2H), 3.08 – 2.71 (m, 3H), 2.04 (d, *J* = 10.7 Hz, 1H), 1.89 – 1.51 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.95, 158.32 (d, *J* = 238.9 Hz), 153.71 (d, *J* = 2.3 Hz), 152.71, 135.18, 121.40, 120.21 (d, *J* = 8.4 Hz), 119.31, 116.84 (d, *J* = 23.4 Hz), 44.48, 43.23, 26.71, 21.48. HRMS (ESI), m/z calcd $C_{18}H_{20}FN_2O_2$ [M+H$^+$] 315.1508 Da, found 315.1508 Da.

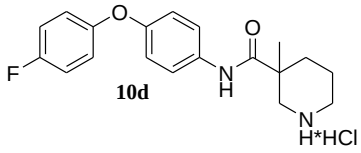
*4-(Azetidin-3-yloxy)-N-[4-(4-fluorophenoxy)phenyl]benzamide hydrochloride, LK1813 (**10c**)*



10c

Yield 0.169 g (50%), white solid, m.p. 208-208.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.22 (s, 1H), 9.56 (s, 2H), 7.99 (d, *J* = 8.7 Hz, 2H), 7.79 (d, *J* = 9.0 Hz, 2H), 7.21 (t, *J* = 8.8 Hz, 2H), 7.10 – 6.91 (m, 6H), 5.34 – 5.00 (m, 1H), 4.47 (s, 2H), 4.01 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.92, 158.67, 158.35 (d, *J* = 239.0 Hz), 153.70 (d, *J* = 2.3 Hz), 152.91, 135.45, 130.26, 128.59, 122.52, 120.31 (d, *J* = 8.4 Hz), 119.11 (s), 116.86 (d, *J* = 23.3 Hz), 114.86, 67.83, 52.37. HRMS (ESI), m/z calcd $C_{22}H_{20}FN_2O_3$ [M+H$^+$] 379.1457 Da, found 379.1457 Da.

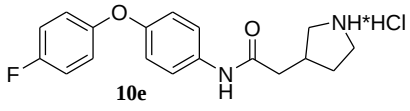
*N-[4-(4-Fluorophenoxy)phenyl]-3-methylpiperidine-3-carboxamide hydrochloride, LK1815 (**10d**)*



10d

Yield 0.098 g (33%), white solid, m.p. 231-231.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.95 (s, 1H), 9.49 (s, 1H), 7.95 (s, 1H), 7.69 (d, *J* = 9.0 Hz, 2H), 7.21 (t, *J* = 8.8 Hz, 2H), 7.10 – 6.90 (m, 4H), 3.53 – 3.42 (m, 2H), 3.05 (d, *J* = 11.3 Hz, 1H), 2.79 (dd, *J* = 20.7, 10.3 Hz, 2H), 2.32 (d, *J* = 15.9 Hz, 1H), 1.76 (d, *J* = 13.6 Hz, 1H), 1.64 (t, *J* = 12.8 Hz, 1H), 1.56 – 1.39 (m, 1H), 1.32 (s, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.84, 158.36 (d, *J* = 239.0 Hz), 153.60 (d, *J* = 2.2 Hz), 153.17, 134.74, 123.11 – 122.63 (m), 120.35 (d, *J* = 8.5 Hz), 119.00, 116.91 (d, *J* = 23.3 Hz), 66.74, 49.53, 43.14, 41.70, 31.82, 23.34, 19.95. HRMS (ESI), m/z calcd $C_{19}H_{22}FN_2O_2$ [M+H$^+$] 329.1665 Da, found 329.1666 Da.

*N-[4-(4-Fluorophenoxy)phenyl]-2-pyrrolidin-3-ylacetamide hydrochloride, LK1816 (**10e**)*

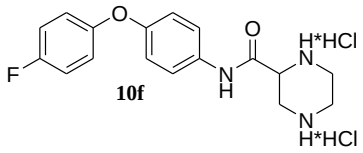


10e

Yield 0.101 g (35%), white solid, m.p. 226-226.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.18 (s, 1H), 9.12 (d, *J* = 38.7 Hz, 2H), 7.61 (d, *J* = 9.0 Hz, 2H), 7.25 – 7.15 (m, 2H), 7.04 – 6.91 (m, 4H), 3.77 – 3.62 (m, 1H), 3.48 (dd, *J* = 8.3, 4.4 Hz, 1H), 3.28 – 2.98 (m, 3H), 2.81 (dd, *J* = 18.5, 6.9 Hz, 1H), 2.67 – 2.53 (m, 2H), 2.16 – 1.98 (m, 1H), 1.58 (dq, *J* = 17.0, 8.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.82, 158.29 (d, *J* = 238.8 Hz), 153.73 (d, *J* = 2.3 Hz), 152.48, 135.35,

121.19, 120.16 (d, *J* = 8.4 Hz), 119.36, 116.87 (d, *J* = 23.3 Hz), 49.38, 44.43, 34.86, 30.09. HRMS (ESI), m/z calcd $C_{18}H_{20}FN_2O_2$ [M+H$^+$] 315.1508 Da, found 315.1508 Da.

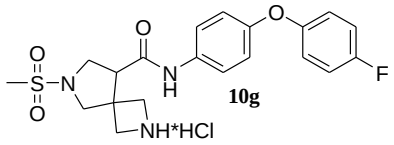
*N-[4-(4-Fluorophenoxy)phenyl]piperazine-2-carboxamide dihydrochloride LK1817 (**10f**)*



10f

Yield 0.158 g (50%), white solid, m.p. 248-248.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.25 (s, 1H), 10.07 (s, 3H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.21 (t, *J* = 8.7 Hz, 2H), 7.09 – 6.93 (m, 4H), 4.45 (d, *J* = 9.0 Hz, 1H), 3.99 (d, *J* = 13.5 Hz, 1H), 3.52 – 3.30 (m, 10H), 3.22 (t, *J* = 12.6 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.94, 158.45 (d, *J* = 239.2 Hz), 153.62, 153.38 (d, *J* = 2.2 Hz), 133.87, 121.92, 120.51 (d, *J* = 8.4 Hz), 119.32, 116.95 (d, *J* = 23.3 Hz), 66.74, 53.78, 42.27. HRMS (ESI), m/z calcd $C_{17}H_{19}FN_3O_2$ [M+H$^+$] 316.1461 Da, found 316.1462 Da.

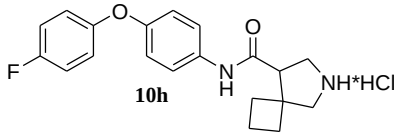
*N-[4-(4-fluorophenoxy)phenyl]-6-(methylsulfonyl)-2,6-diazaspiro[3.4]octane-8-carboxamide hydrochloride, LK1819 (**10g**)*



10g

Yield 0.101 g (27%), white solid, m.p. 173-174 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.81 (s, 1H), 9.27 (s, 2H), 7.68 (d, *J* = 9.0 Hz, 2H), 7.31 – 7.11 (m, 2H), 7.06 – 6.92 (m, 4H), 4.17 – 3.86 (m, 4H), 3.76 – 3.54 (m, 4H), 2.96 (s, *J* = 12.6 Hz, 3H).; ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.11, 158.36 (d, *J* = 238.9 Hz), 153.67 (d, *J* = 2.2 Hz), 153.04, 134.79, 121.70, 120.25 (d, *J* = 8.5 Hz), 119.35, 116.87 (d, *J* = 23.4 Hz), 55.77, 55.64, 50.37, 49.64, 45.57, 34.38. HRMS (ESI), m/z calcd $C_{20}H_{23}FN_3O_4S$ [M+H$^+$] 420.1393 Da, found 420.1393 Da.

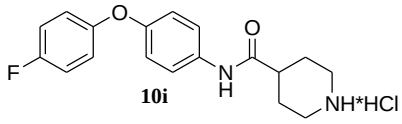
*N-[4-(4-Fluorophenoxy)phenyl]-6-azaspiro[3.4]octane-8-carboxamide hydrochloride, LK1820 (**10h**)*



10h

Yield 0.12g (39%), white solid, m.p. 222-222.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.62 (s, 1H), 9.45 (d, *J* = 113.1 Hz, 1H), 7.66 (d, *J* = 8.9 Hz, 2H), 7.26 – 7.10 (m, 2H), 7.06 – 6.93 (m, 4H), 3.30 – 3.11 (m, 5H), 2.30 – 2.03 (m, 3H), 1.94 – 1.75 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.89, 158.41 (d, *J* = 234.8 Hz), 153.59 (d, *J* = 2.3 Hz), 153.03, 134.82, 121.63, 120.38 (d, *J* = 8.5 Hz), 119.25, 116.87 (d, *J* = 23.3 Hz), 54.14, 52.07, 48.46, 46.20, 32.85, 26.37, 15.83. HRMS (ESI), m/z calcd $C_{20}H_{22}FN_2O_2$ [M+H$^+$] 341.1665 Da, found 341.1665 Da.

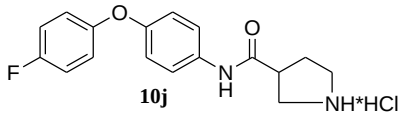
*N-[4-(4-Fluorophenoxy)phenyl]piperidine-4-carboxamide hydrochloride, LK1827 (**10i**)*



10i

Yield 0.171 g (66%), white solid, m.p. 206-206.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.95 (d, *J* = 115.9 Hz, 2H), 7.63 (d, *J* = 8.9 Hz, 2H), 7.19 (t, *J* = 8.8 Hz, 2H), 7.06 – 6.85 (m, 4H), 3.32 (d, *J* = 20.0 Hz, 8H), 2.89 (d, *J* = 11.0 Hz, 2H), 2.67 (t, *J* = 10.7 Hz, 1H), 2.05 – 1.72 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.31, 158.30 (d, *J* = 238.9 Hz), 153.76 (d, *J* = 2.2 Hz), 152.56, 135.41, 121.35, 120.17 (d, *J* = 8.4 Hz), 119.32, 116.83 (d, *J* = 23.3 Hz), 42.74, 25.46. HRMS (ESI), m/z calcd $C_{18}H_{20}FN_2O_2$ [M+H$^+$] 315.1508 Da, found 315.1508 Da.

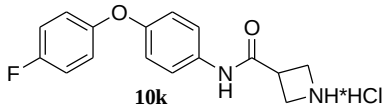
*N-[4-(4-Fluorophenoxy)phenyl]pyrrolidine-3-carboxamide hydrochloride, LK1823 (**10j**)*



10j

Yield 0.069 g (25%), white solid, m.p. 202-202.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.46 (s, 1H), 9.38 (d, *J* = 89.7 Hz, 2H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.19 (t, *J* = 8.7 Hz, 2H), 7.08 – 6.82 (m, 4H), 3.47 – 3.08 (m, 5H), 2.25 (dd, *J* = 13.1, 6.5 Hz, 1H), 2.04 (dd, *J* = 14.3, 7.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.40, 158.35 (d, *J* = 239.0 Hz), 153.66 (d, *J* = 2.3 Hz), 152.81, 135.15, 121.43, 120.26 (d, *J* = 8.5 Hz), 119.30, 116.86 (d, *J* = 23.4 Hz), 47.14, 45.11, 43.38, 29.30. HRMS (ESI), m/z calcd $C_{17}H_{18}FN_2O_2$ [M+H$^+$] 301.1352 Da, found 301.1352 Da.

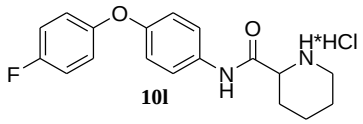
*N-[4-(4-Fluorophenoxy)phenyl]azetidine-3-carboxamide hydrochloride, LK1824 (**10k**)*



10k

Yield 0.084 g (32%), white solid, m.p. 141-141.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.48 (s, 1H), 9.24 (d, *J* = 142.6 Hz, 2H), 7.65 (d, *J* = 9.0 Hz, 2H), 7.26 – 7.14 (m, 2H), 7.05 – 6.92 (m, 4H), 4.18 – 3.98 (m, 4H), 3.83 (p, *J* = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.73, 158.34 (d, *J* = 238.9 Hz), 153.59 (d, *J* = 2.3 Hz), 152.85, 134.97, 121.34, 120.29 (d, *J* = 8.5 Hz), 119.32, 116.89 (d, *J* = 23.3 Hz), 47.59, 36.21. HRMS (ESI), m/z calcd $C_{16}H_{16}FN_2O_2$ [M+H$^+$] 287.1195 Da, found 287.1198 Da.

*N-[4-(4-Fluorophenoxy)phenyl]piperidine-2-carboxamide hydrochloride, LK1825 (**10l**)*

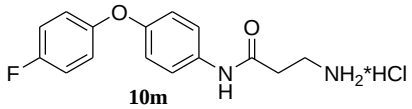


10l

Yield 0.086 g (30%), white solid, m.p. 215-215.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.13 (d, *J* = 195.3 Hz, 2H), 7.66 (d, *J* = 8.9 Hz, 2H), 7.21 (t, *J* = 8.7 Hz, 2H), 7.08 – 6.94 (m, 4H), 4.03 – 3.85 (m, 1H), 3.25 (d, *J* = 12.3 Hz, 1H), 2.94 (s, 1H), 2.26 (d, *J* = 10.9 Hz, 1H), 1.87 – 1.42 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.46, 158.38 (d, *J* = 239.0 Hz), 153.53 (d, *J* = 2.2 Hz), 153.17, 134.41, 121.49, 120.35 (d, *J* = 8.4 Hz), 119.45, 116.91 (d, *J* = 23.4 Hz),

57.92, 43.67, 27.49, 22.04, 21.59. HRMS (ESI), m/z calcd $C_{18}H_{20}FN_2O_2$ [M+H$^+$] 315.1508 Da, found 315.1508 Da.

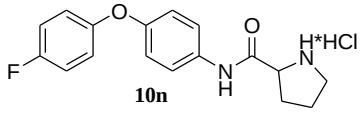
*N^1-[4-(4-Fluorophenoxy)phenyl]-β-alanilamide hydrochloride, LK1826 (**10m**)*



10m

Yield 0.17 g (67%), white solid, m.p. 155-155.5 °C. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 10.38 (s, 1H), 8.04 (s, 3H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.20 (t, *J* = 8.5 Hz, 2H), 6.99 (dd, *J* = 14.8, 6.4 Hz, 4H), 3.13 – 2.95 (m, 2H), 2.81 – 2.65 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 168.50 (s), 158.33 (d, *J* = 238.9 Hz), 153.69 (s), 152.66 (s), 135.18 (s), 121.31 (s), 120.25 (d, *J* = 8.4 Hz), 119.27 (s), 116.86 (d, *J* = 23.3 Hz), 35.37 (s), 33.53 (s). HRMS (ESI), m/z calcd $C_{15}H_{16}FN_2O_2$ [M+H$^+$] 275.1195 Da, found 275.1190 Da.

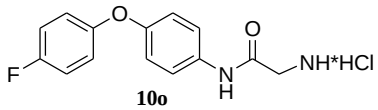
*N-[4-(4-Fluorophenoxy)phenyl]pyrrolidine-2-carboxamide hydrochloride, LK1828 (**10n**)*



10n

Yield 0.096 g (35%), white solid, m.p. 203-203.5 °C. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 10.99 (s, 1H), 10.06 (s, 1H), 8.68 (s, 1H), 7.65 (d, *J* = 9.0 Hz, 2H), 7.28 – 7.14 (m, 2H), 7.08 – 6.94 (m, 4H), 4.39 (s, 1H), 3.26 (s, 2H), 2.45 – 2.32 (m, 1H), 1.93 (d, *J* = 3.2 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 166.98, 158.42 (d, *J* = 239.1 Hz), 153.46 (d, *J* = 2.3 Hz), 153.30, 134.33, 121.58, 120.44 (d, *J* = 8.5 Hz), 119.36, 116.93 (d, *J* = 23.4 Hz), 59.86, 46.03, 30.14, 24.01. HRMS (ESI), m/z calcd $C_{17}H_{18}FN_2O_2$ [M+H$^+$] 301.1352 Da, found 301.1352 Da.

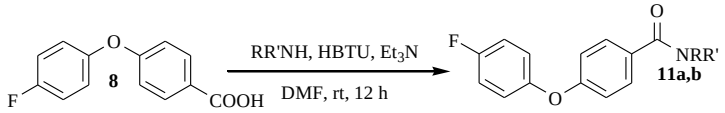
*N^1-[4-(4-Fluorophenoxy)phenyl]glycinamide hydrochloride, LK1829 (**10o**)*



10o

Yield 0.155 g (64%), white solid, m.p. 232-232.5 °C. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 10.88 (s, 1H), 8.31 (s, 3H), 7.64 (d, *J* = 8.9 Hz, 2H), 7.21 (t, *J* = 8.8 Hz, 2H), 7.08 – 6.88 (m, 4H), 3.78 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 164.89, 158.41 (d, *J* = 239.1 Hz), 153.52 (d, *J* = 2.3 Hz), 153.10, 134.48, 121.31, 120.40 (d, *J* = 8.5 Hz), 119.38, 116.88 (d, *J* = 23.4 Hz), 41.30. HRMS (ESI), m/z calcd $C_{14}H_{14}FN_2O_2$ [M+H$^+$] 261.1039 Da, found 261.1040 Da.

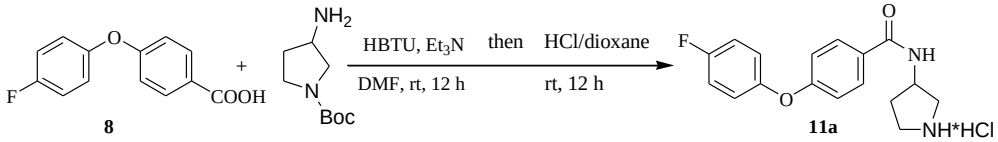
1.3. General procedure for 4-(4-fluorophenoxy)benzamide (11) preparation.



To a solution of acid **8** (0.82 mmol, 1 eq) in DMF (10 ml), HBTU (0.37 g, 0.98 mmol, 1.2 eq), the corresponding mono-Boc-protected diamine (0.73 mmol, 0.9 eq), and Et_3N (0.1 g, 0.98 mmol, 1.2 eq) were added sequentially. The reaction mixture was stirred overnight, poured into

water (25 ml), and the precipitate that formed was filtered off, dried, and triturated with Et_2O. The precipitate was filtered off, dissolved in dioxane (5 ml) and cooled to 0 °C. Then 4 M HCl/dioxane solution (5 ml) was added dropwise, and this was stirred overnight. The precipitate that formed was filtered off and recrystallized from EtOH.

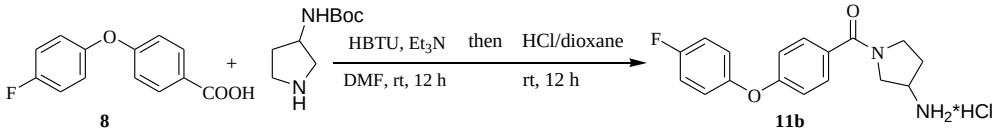
*4-(4-Fluorophenoxy)-N-pyrrolidin-3-ylbenzamide hydrochloride LK1762 (**11a**)*



8 **11a**

Yield 0.121 g (44%), white solid, m.p. 191-191.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.44 (d, *J* = 40.1 Hz, 2H), 8.77 (d, *J* = 6.7 Hz, 1H), 7.98 (t, *J* = 9.7 Hz, 2H), 7.27 (t, *J* = 8.7 Hz, 2H), 7.18 – 7.10 (m, 2H), 7.00 (d, *J* = 8.7 Hz, 4H), 4.65 – 4.47 (m, 1H), 3.41 – 3.11 (m, 5H), 2.30 – 2.11 (m, 1H), 1.99 (dt, *J* = 12.9, 5.9 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.02, 160.42 (d, *J* = 0.5 Hz), 159.14 (d, *J* = 240.4 Hz), 157.55, 152.04 (d, *J* = 2.5 Hz), 130.19, 128.97, 121.99 (d, *J* = 8.6 Hz), 117.39 (d, *J* = 4.6 Hz), 117.11, 49.62, 49.33, 43.90, 30.57. HRMS (ESI), m/z calcd $C_{17}H_{18}FN_2O_2$ [M+H$^+$] 301.1352 Da, found 301.1352 Da.

*1-[4-(4-Fluorophenoxy)benzoyl]pyrrolidin-3-amine hydrochloride LK1763 (**11b**)*



8 **11b**

Yield 0.066 g (24%), white solid, m.p. 197-197.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44 (d, *J* = 28.8 Hz, 3H), 7.58 (d, *J* = 8.1 Hz, 2H), 7.28 (t, *J* = 8.7 Hz, 2H), 7.15 (dd, *J* = 9.0, 4.5 Hz, 2H), 7.00 (d, *J* = 8.7 Hz, 2H), 3.92 – 3.32 (m, 4H), 2.30 – 1.92 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.18, 159.08, 159.06 (d, *J* = 240.5 Hz), 152.01, 131.46, 129.86, 121.97 (d, *J* = 8.5 Hz), 117.34, 117.19 (d, *J* = 23.4 Hz), 48.90, 46.87, 44.91, 30.36. HRMS (ESI), m/z calcd $C_{17}H_{18}FN_2O_2$ [M+H$^+$] 301.1352 Da, found 301.1352 Da.

2. Antibacterial activity evaluation.

Testing was conducted against the following microorganisms: *Enterococcus faecalis* (ATCC 29812), *Staphylococcus aureus* (ATCC 25912), *Klebsiella pneumoniae* (ATCC 19882), *Acinetobacter baumannii* (948®, patient-derived strain from the Pasteur Institute own collection), *Pseudomonas aeruginosa* (ATCC 27853), and *Enterobacter cloacae* (ATCC 13047) for compounds **10a-o**, **11a,b** and ciprofloxacin (employed as a positive control) using the Kirby–Bauer disk diffusion test[S1] under the Standard Operating Procedure of The European Committee on Antimicrobial Susceptibility Testing (EUCAST)[S2]. Paper disks bearing 5 mg of the tested compounds were used. Solutions of tested compounds made up in DMSO (1 mg per 10 ml) were prepared and diluted to a total volume of 1 ml with deionized water. Aliquots of the resulting solutions (5 μl each) were added to a Petri dish containing Muller–Hilton agar that was inoculated with a bacterial suspension (McFarland OD 1/4 0.5). After the compound solution has dried off, the Petri dish was incubated at 37 °C for 18 h. The bacterial growth inhibition zone diameter around the disc with ciprofloxacin or the compounds' dried solution circular spot indicated the general susceptibility to a drug being assessed. Thereupon, minimum inhibitory concentrations (MIC, μg/mL) were determined using serial broth dilutions[S3]. The experiment was carried out in sterile Nunc 96-well plates with Nunclon Sphera surface. All measurements were done in triplicate according to ISO standard 20776-2.

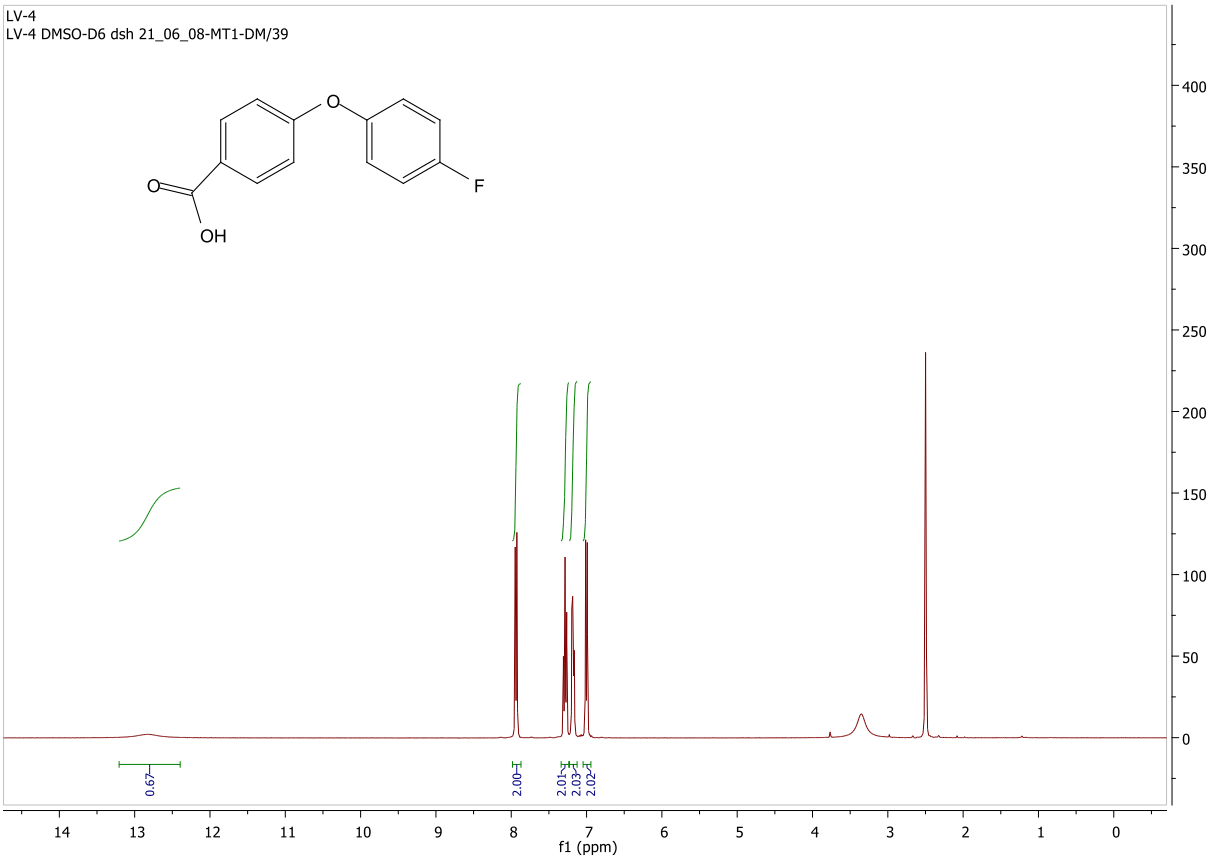
The most active compound **10g** (LK1819) was screened against a panel of MRSA multiresistant clinical isolates using the same methods. The results are given in Table S1.

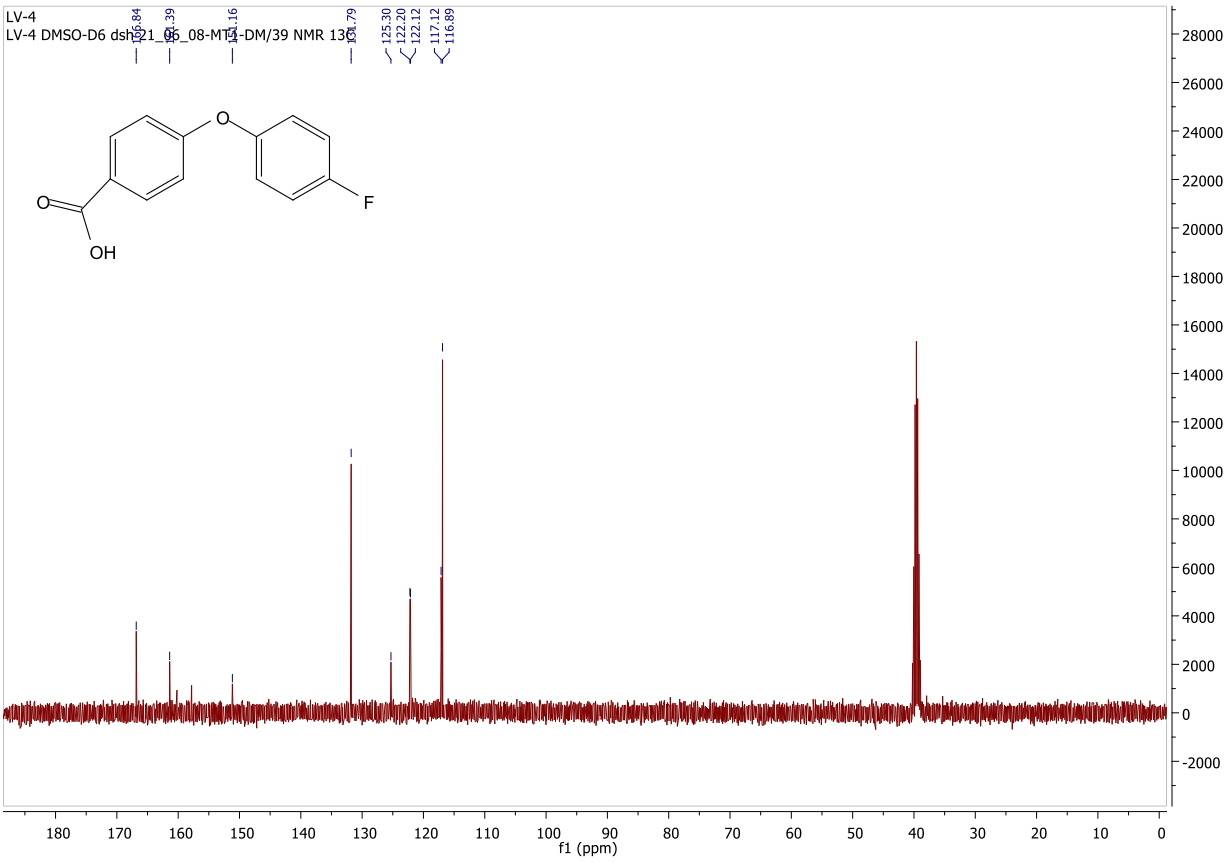
Table S1 Anti-MRSA activity of LK1819 (**10g**).

S.Aureus strain clinical isolate	Inhibition zone (mm) at 3 μg ml^{-1}	MIC (μg ml^{-1})	MIC control (ciprofloxacin)	Comment
2692	9	0.75	n.t.	R
4225	11	0.375	n.t.	R
5436	9	0.75	32	R
8316	14	0.75	n.t.	R
7854	10	0.75	16	R
2713	9	0.75	n.t.	R
7135	9	0.75	n.t.	R
966	9	0.093	1	S
2598	9	0.093	0.5	R
4844	9	0.093	0.5	S
6041	11	0.75	16	R
3014	14	0.75	n.t.	R
4687	12	0.1875	n.t.	S
4624	9	0.1875	0.5	S
4724	7	0.75	0.5	S
1516	11	0.093	0.5	S
R is multiresistant MRSA strain; S is susceptible strain.				

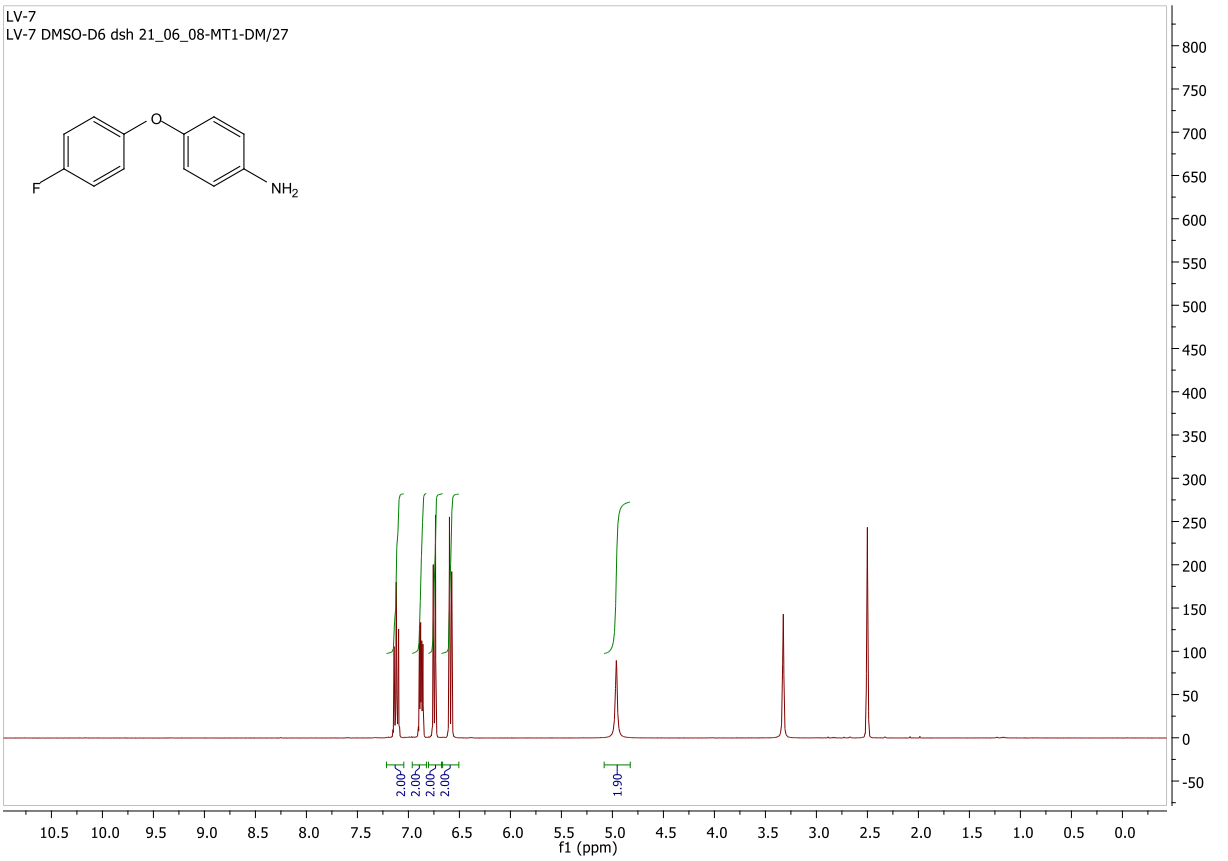
3. Copies of ^{1}H and ^{13}C NMR spectra

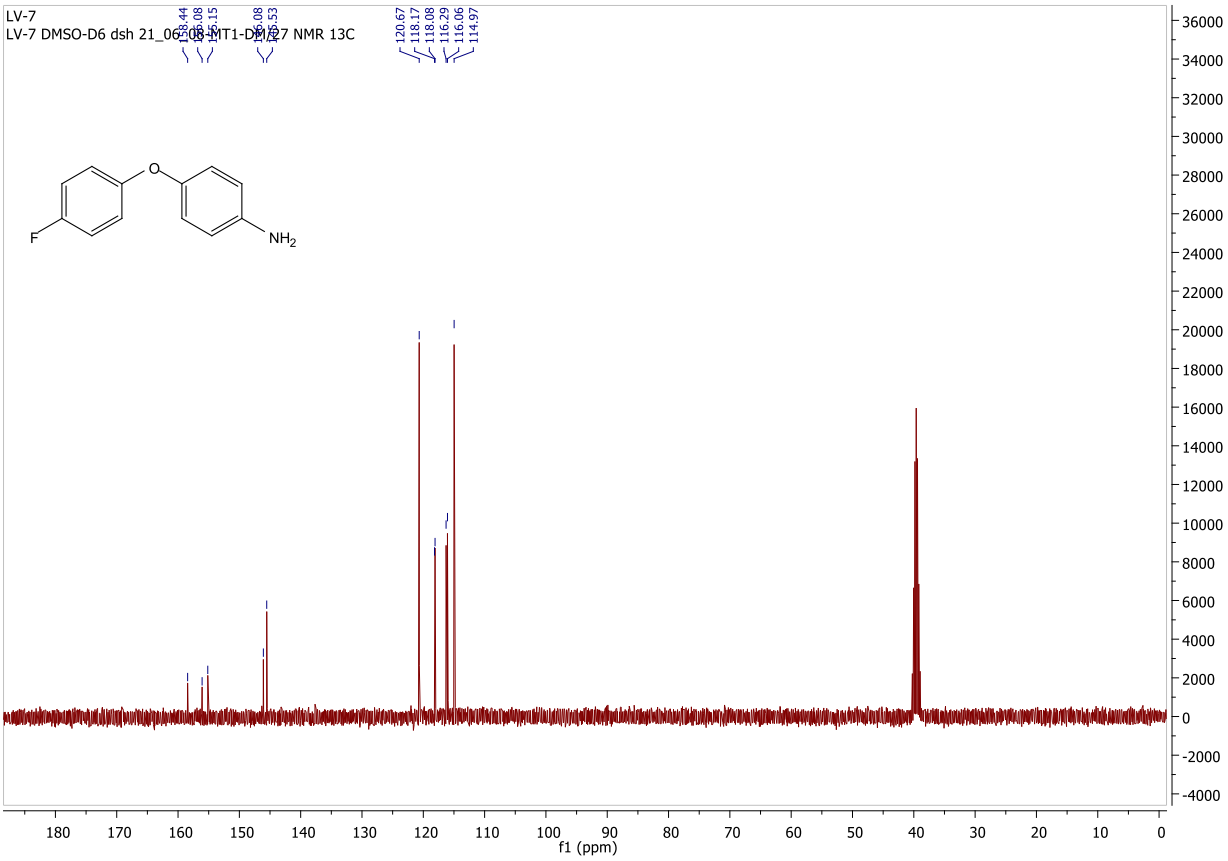
^{1}H and ^{13}C NMR spectra of compound **8**



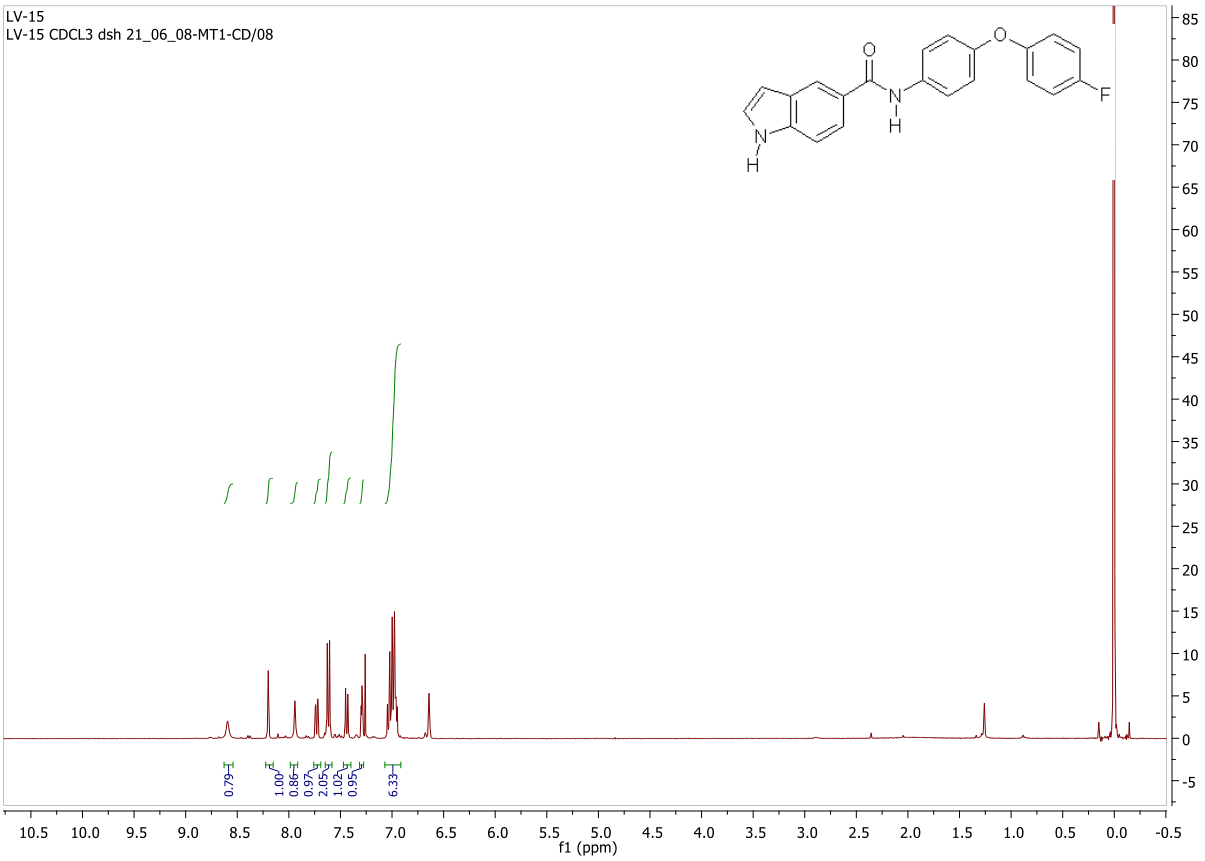


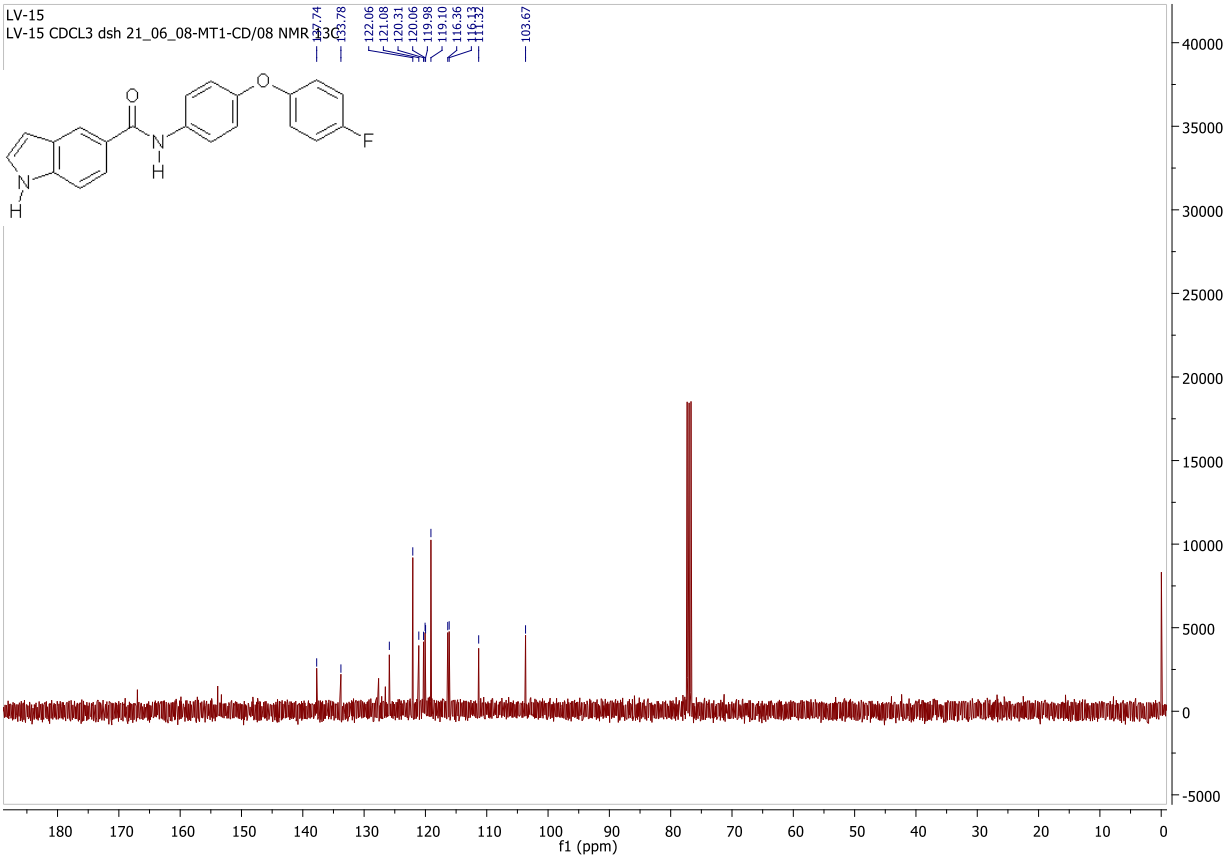
^{1}H and ^{13}C NMR spectra of compound **9**



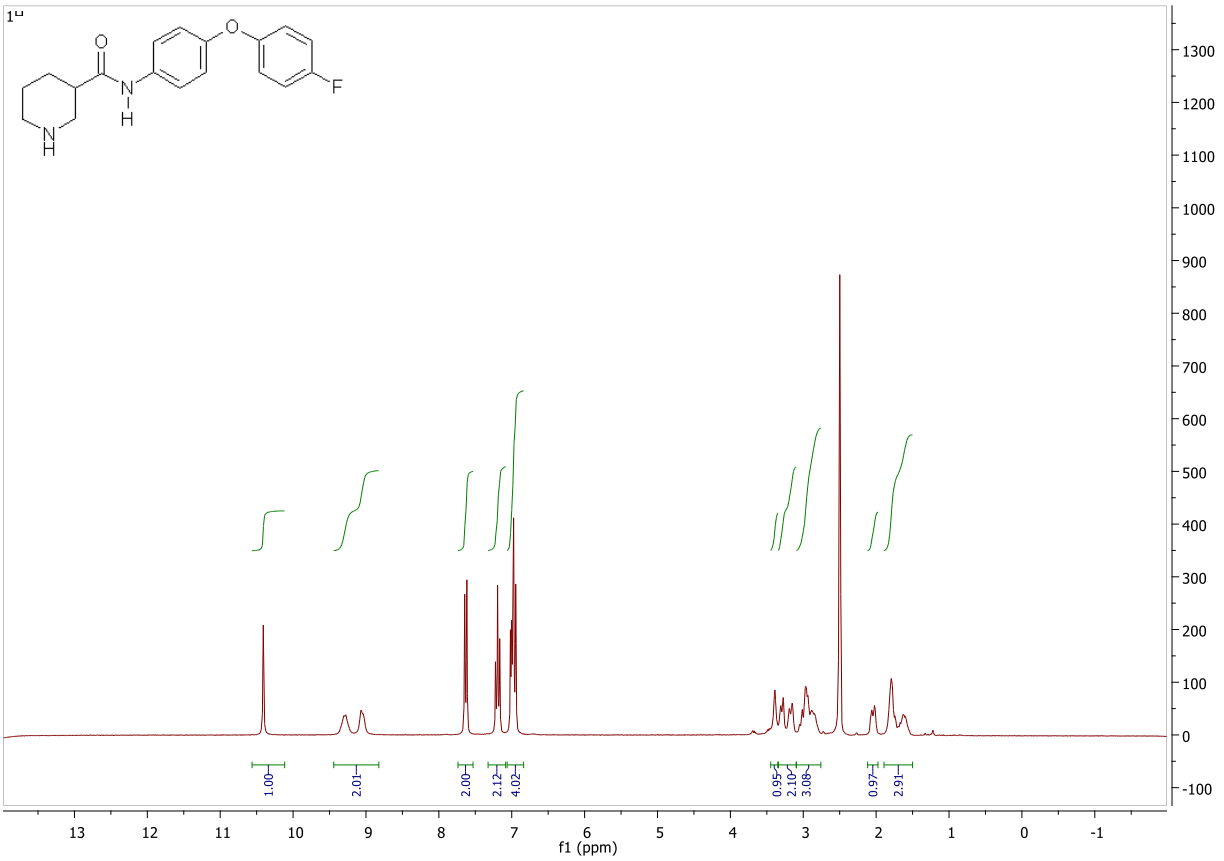


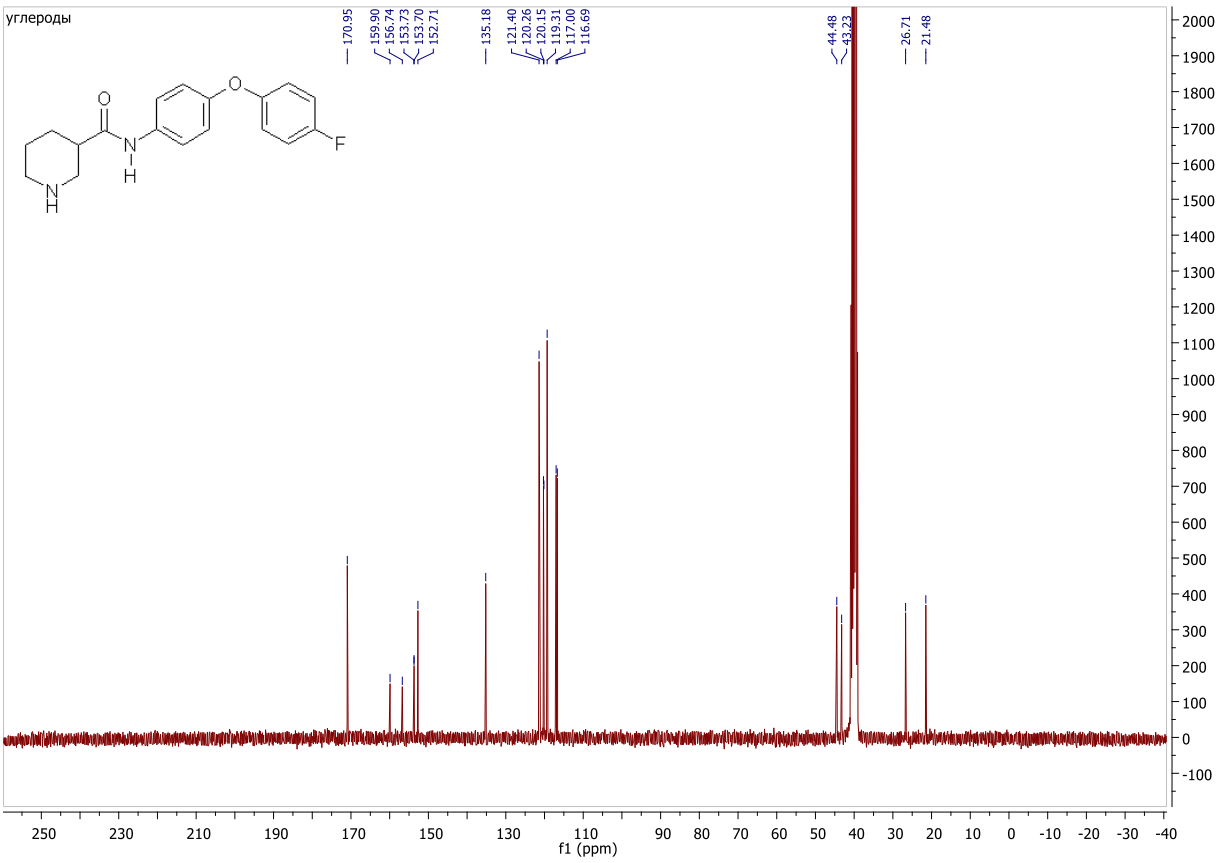
^{1}H and ^{13}C NMR spectra of compound **10a**



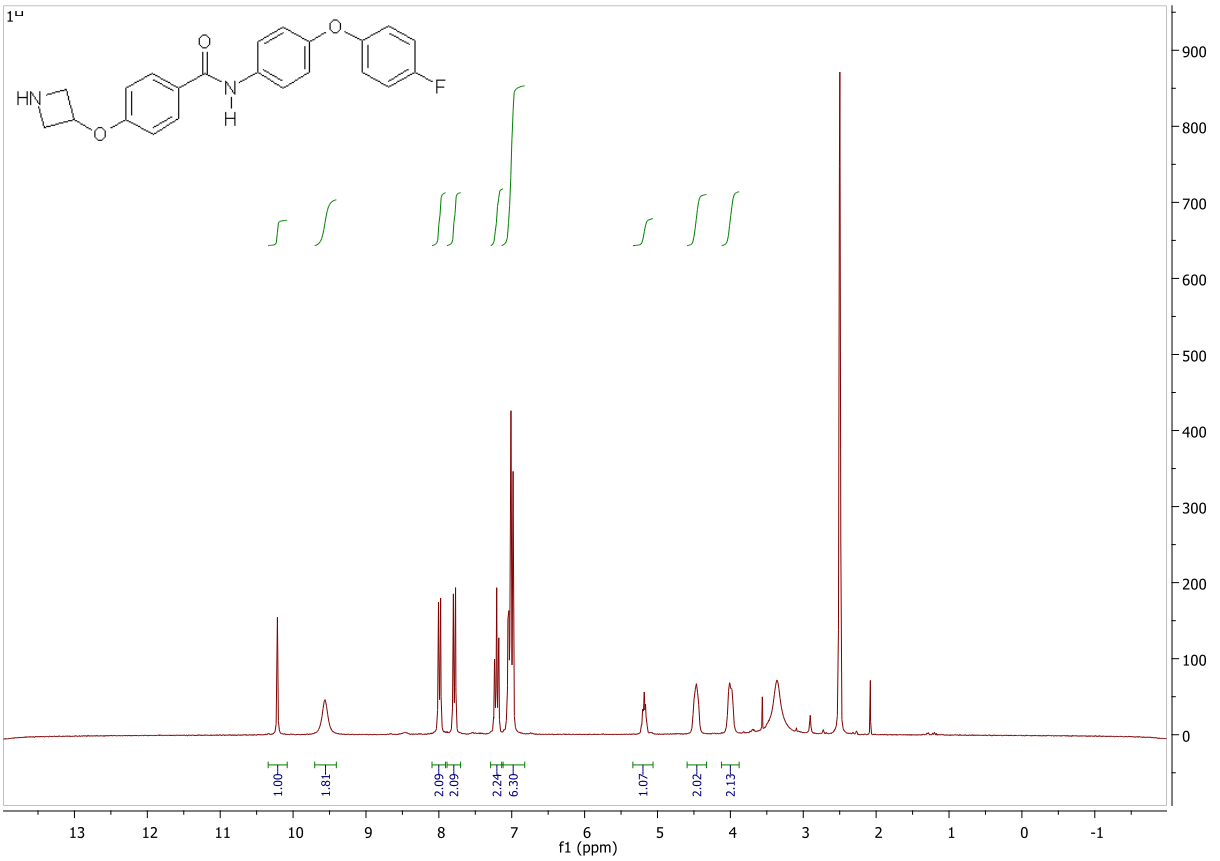


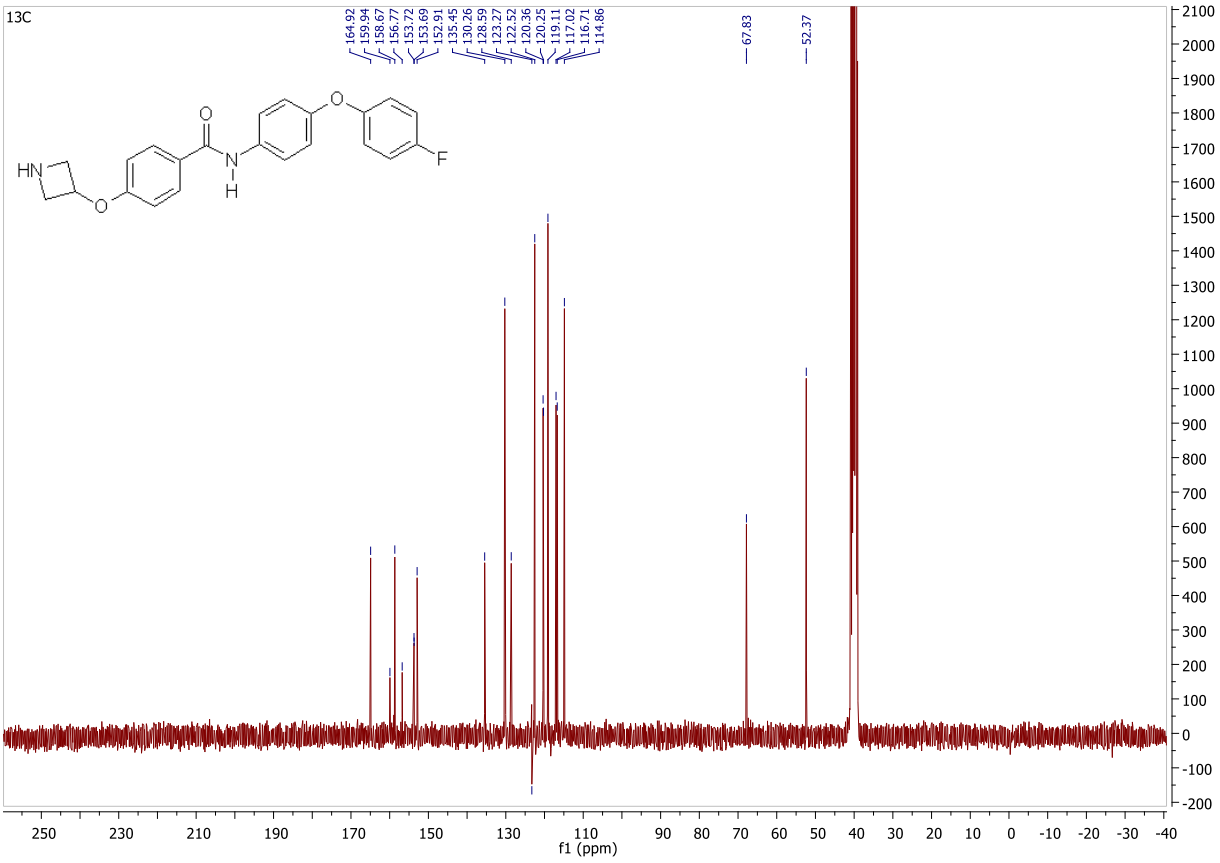
^{1}H and ^{13}C NMR spectra of compound **10b**



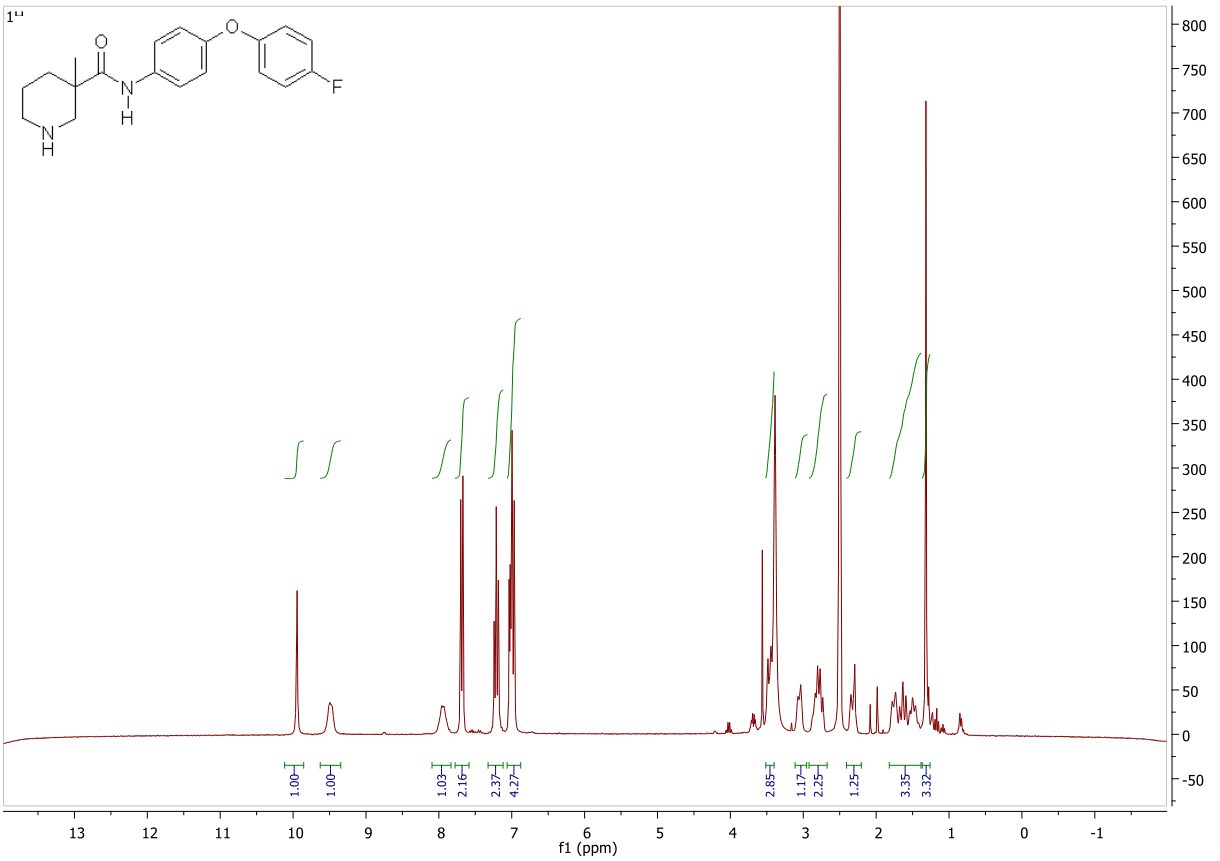


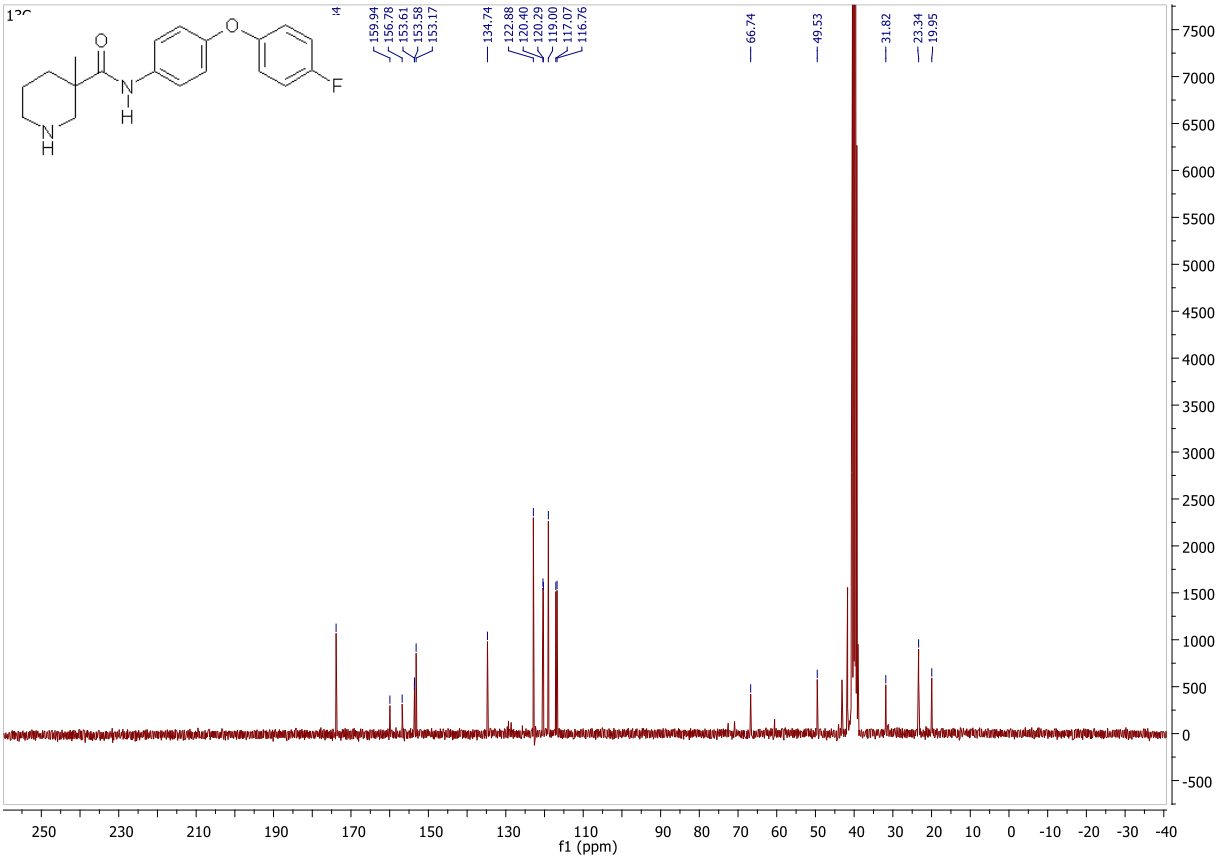
^{1}H and ^{13}C NMR spectra of compound **10c**



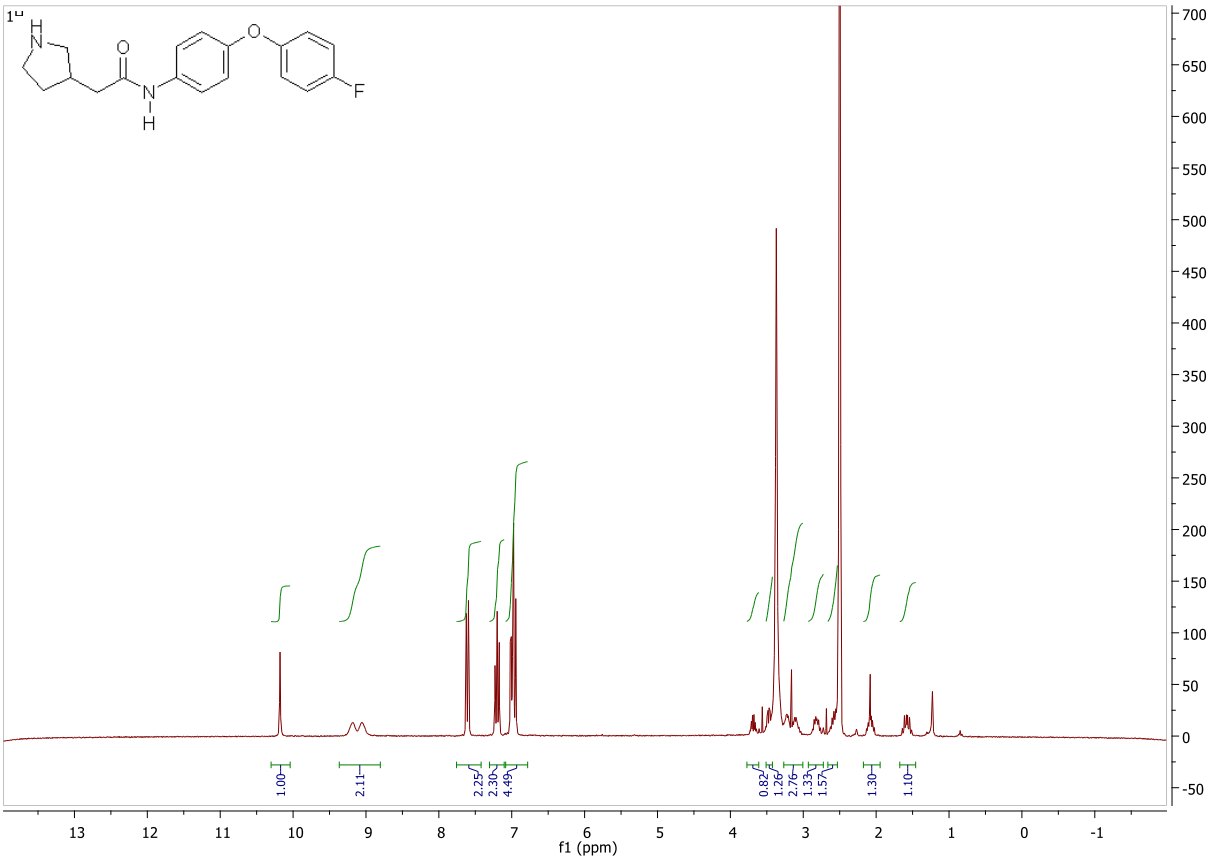


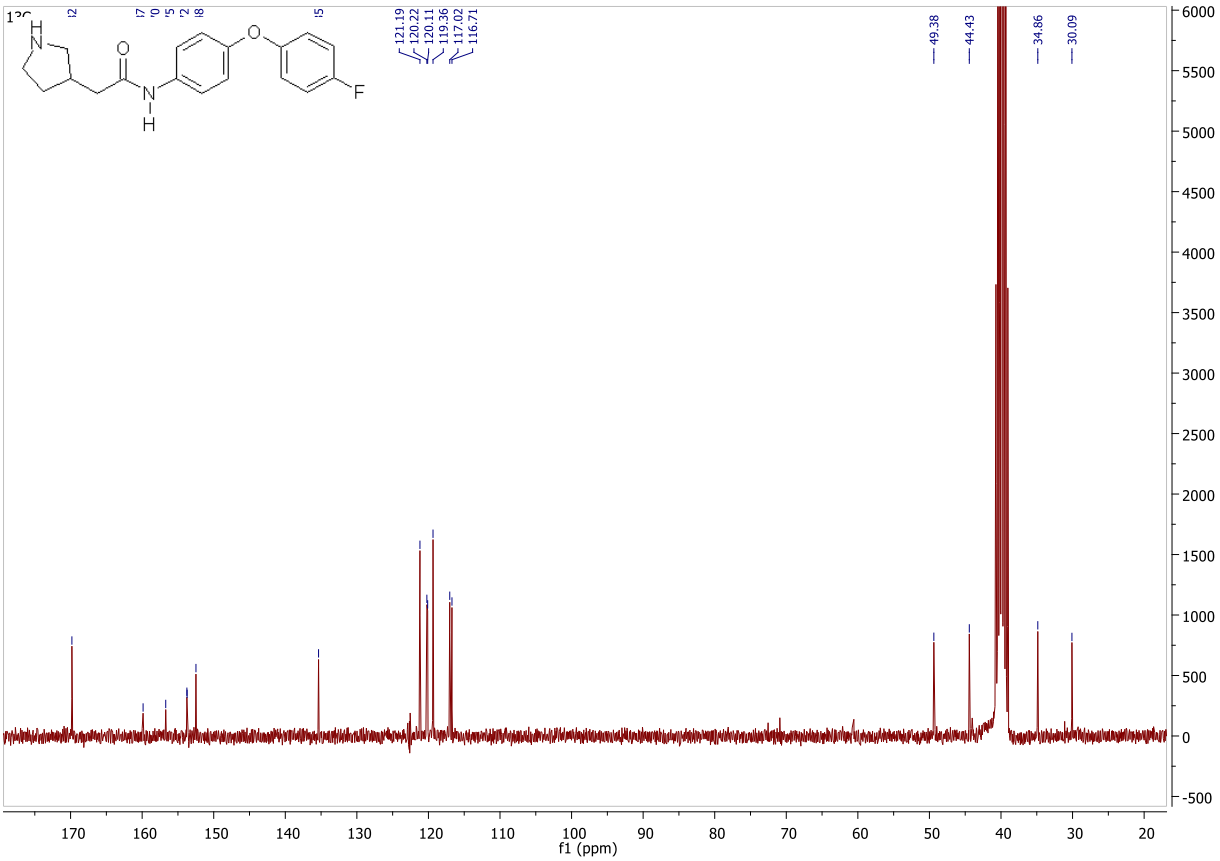
^{1}H and ^{13}C NMR spectra of compound **10d**



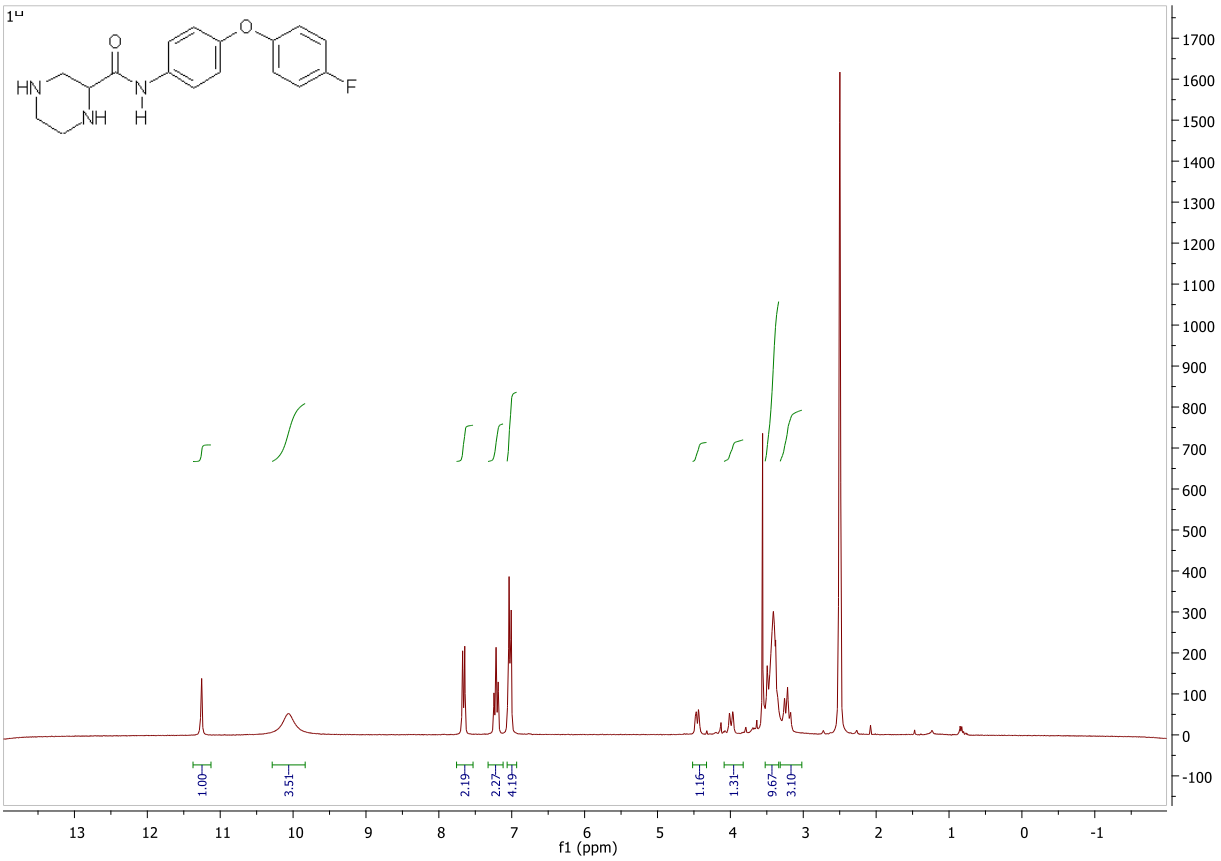


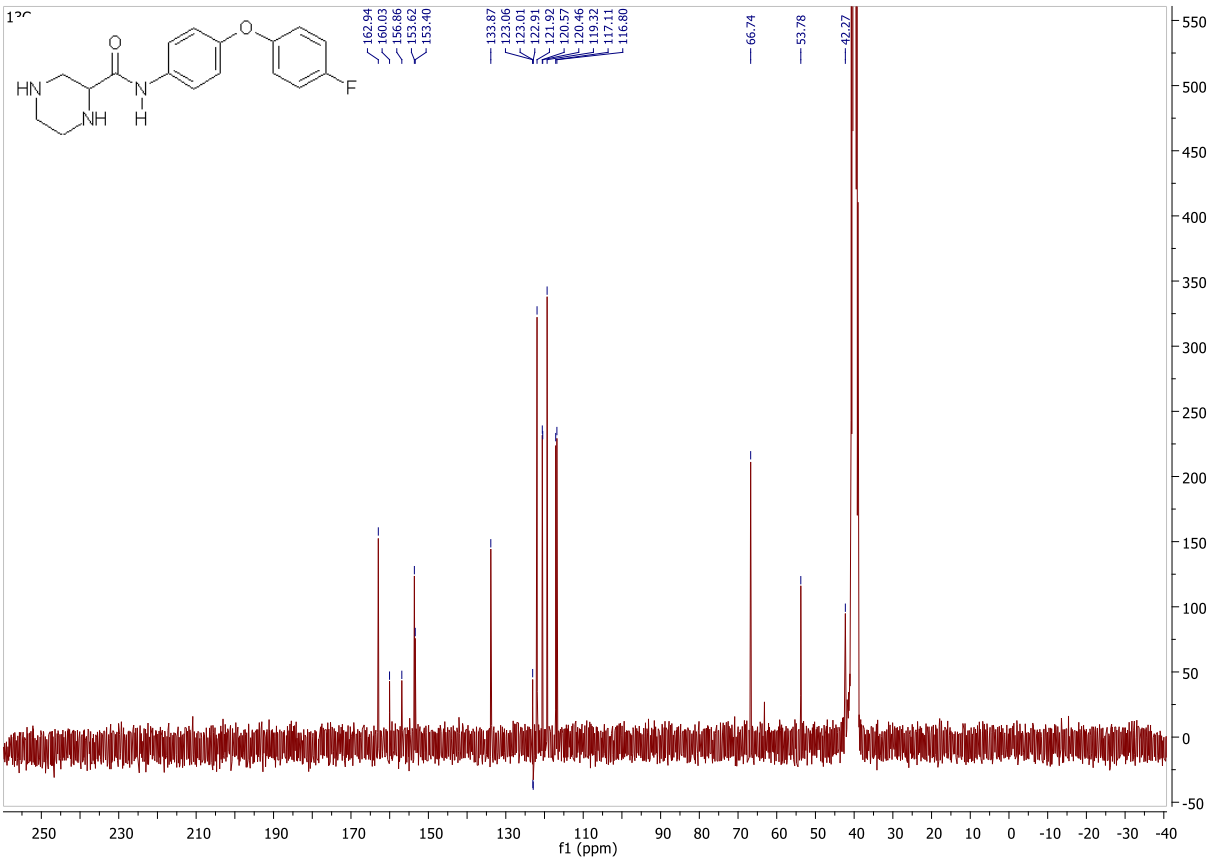
^{1}H and ^{13}C NMR spectra of compound **10c**



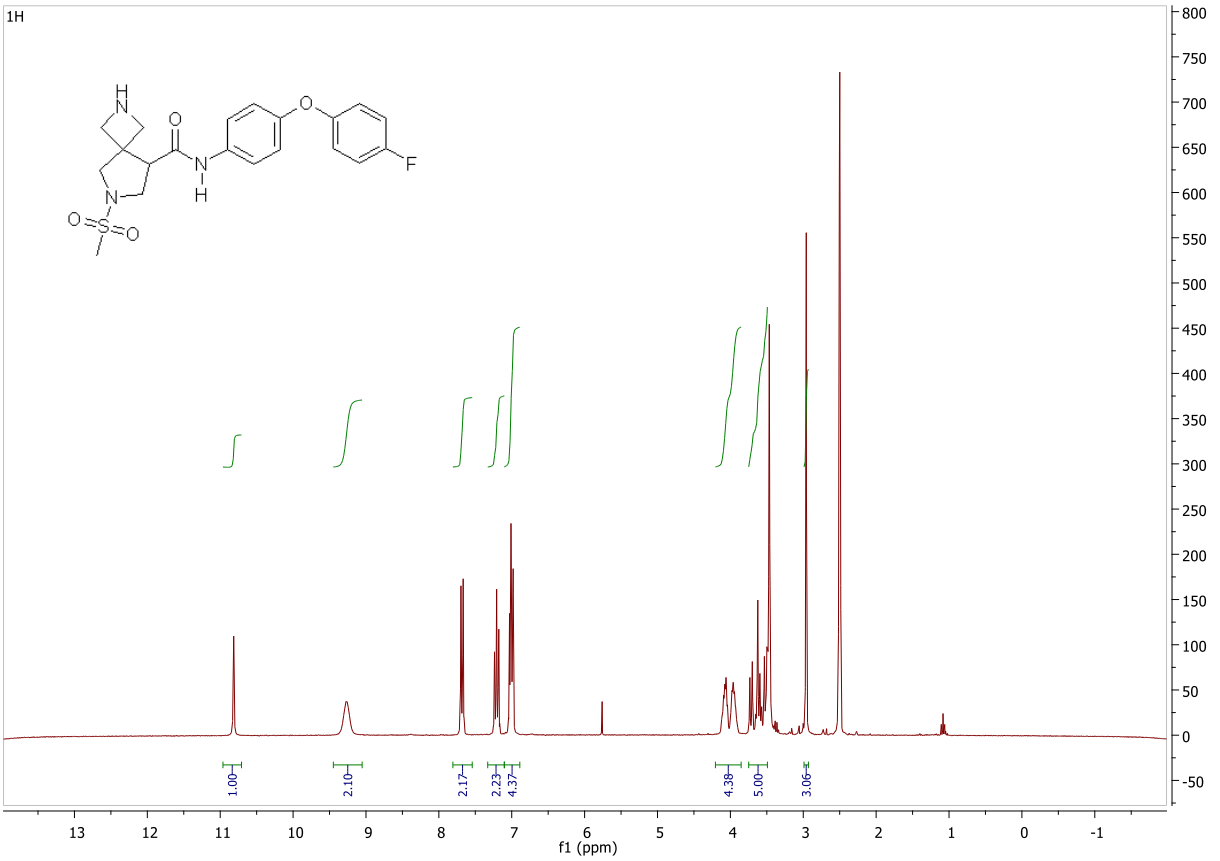


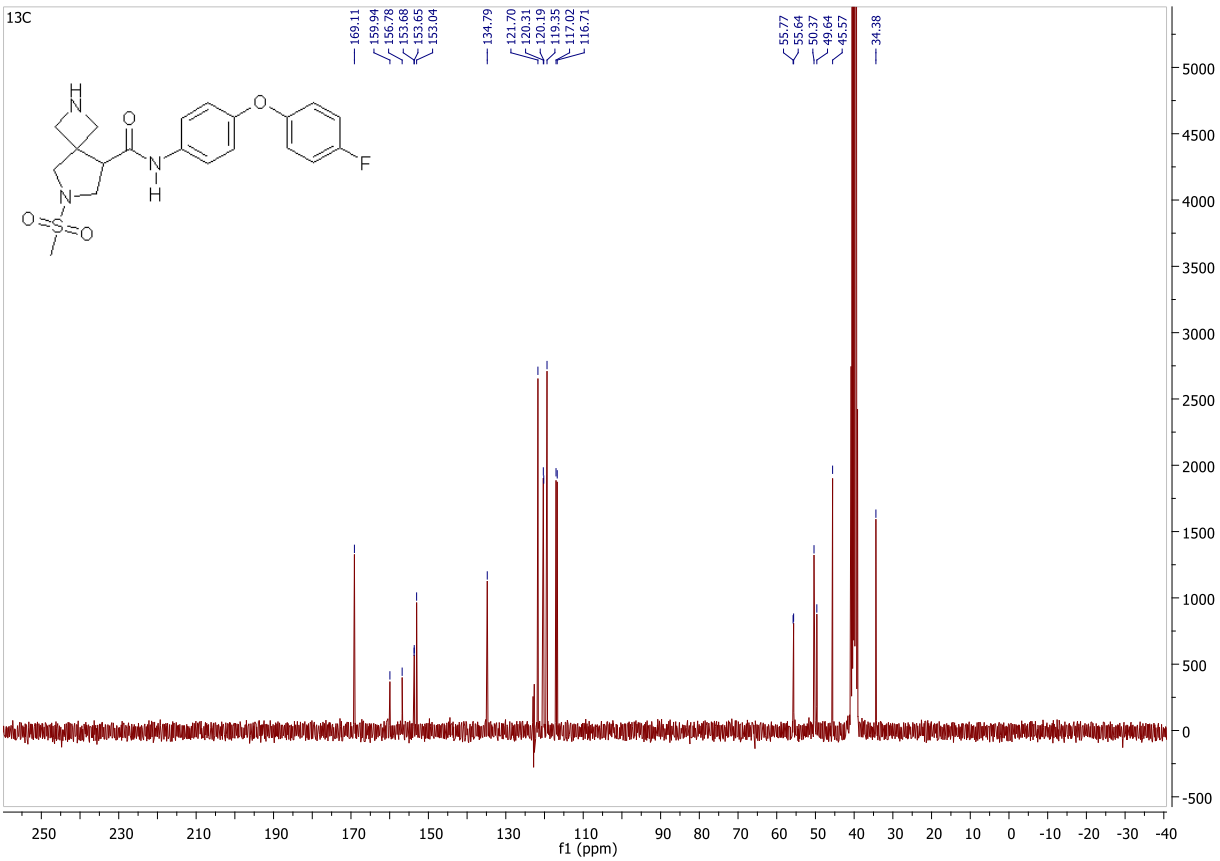
^{1}H and ^{13}C NMR spectra of compound **10f**



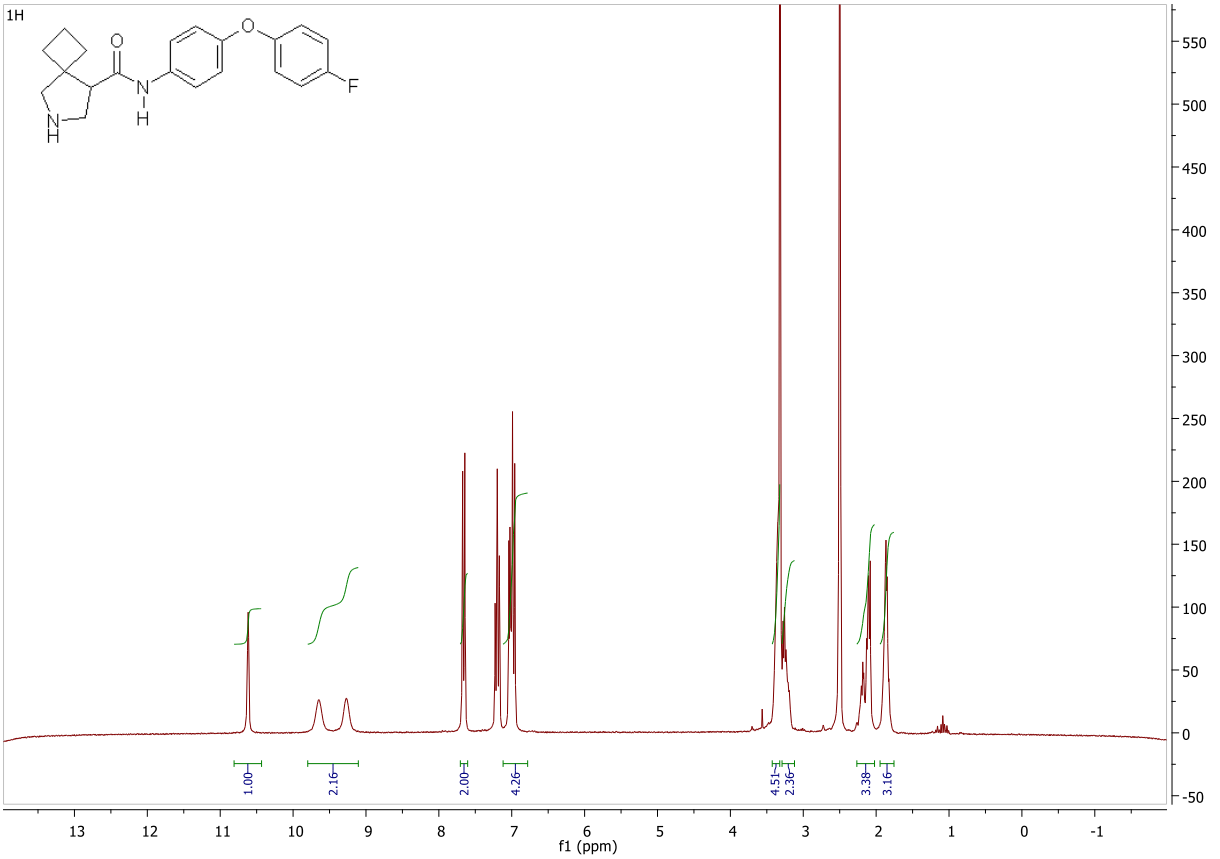


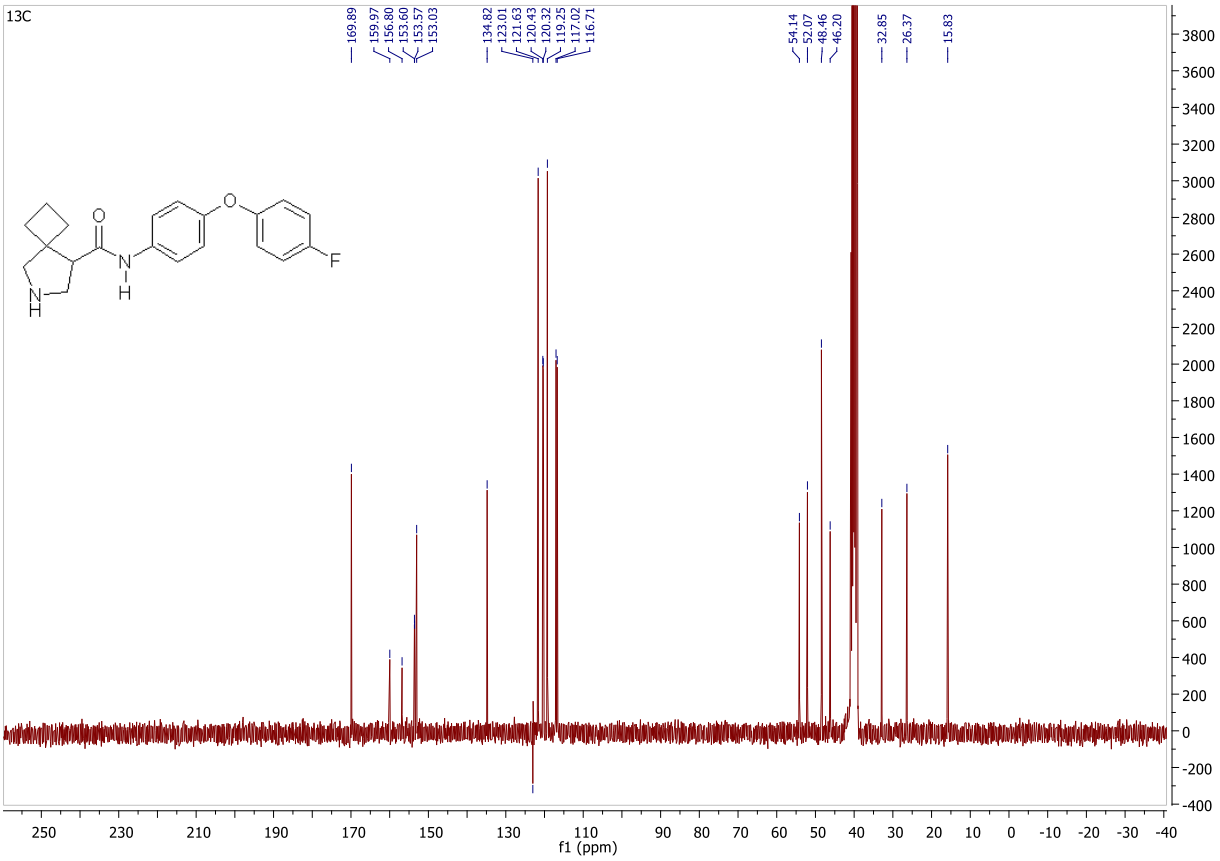
^{1}H and ^{13}C NMR spectra of compound **10g**



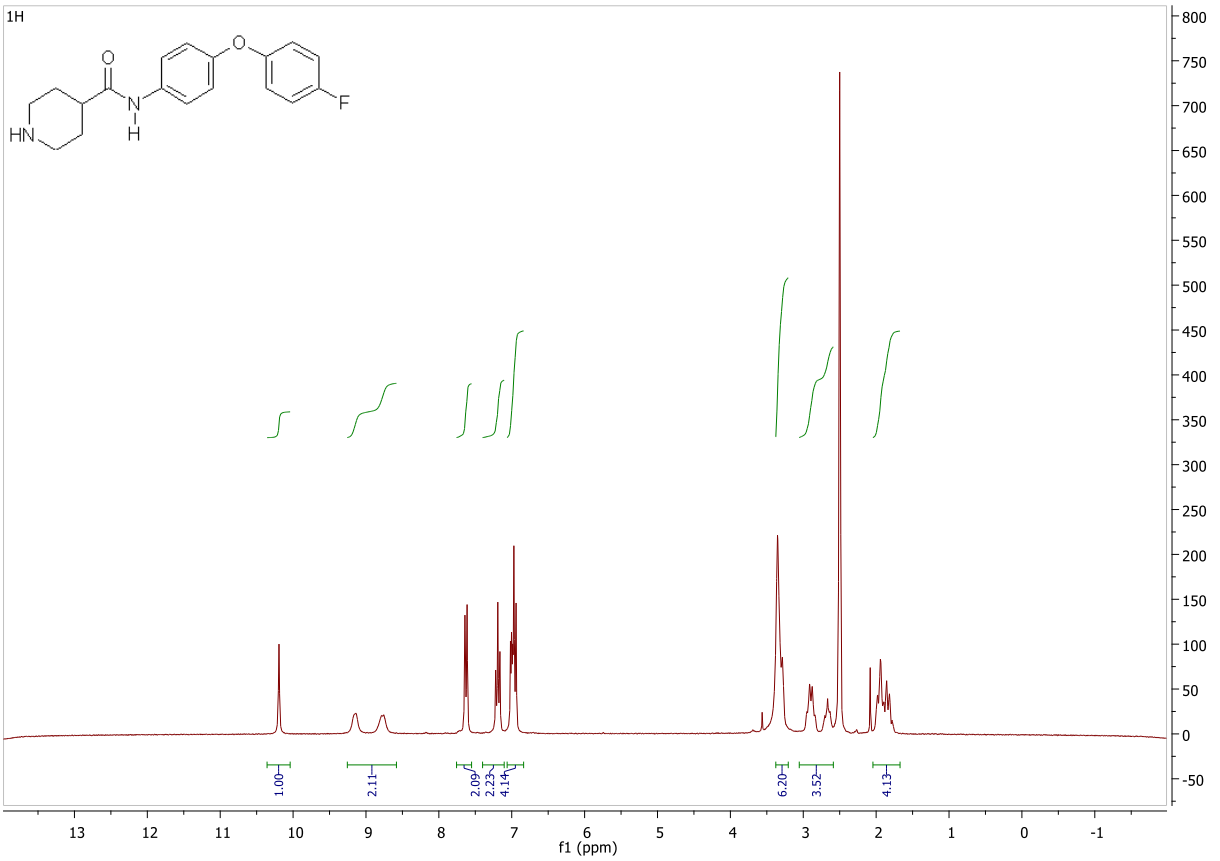


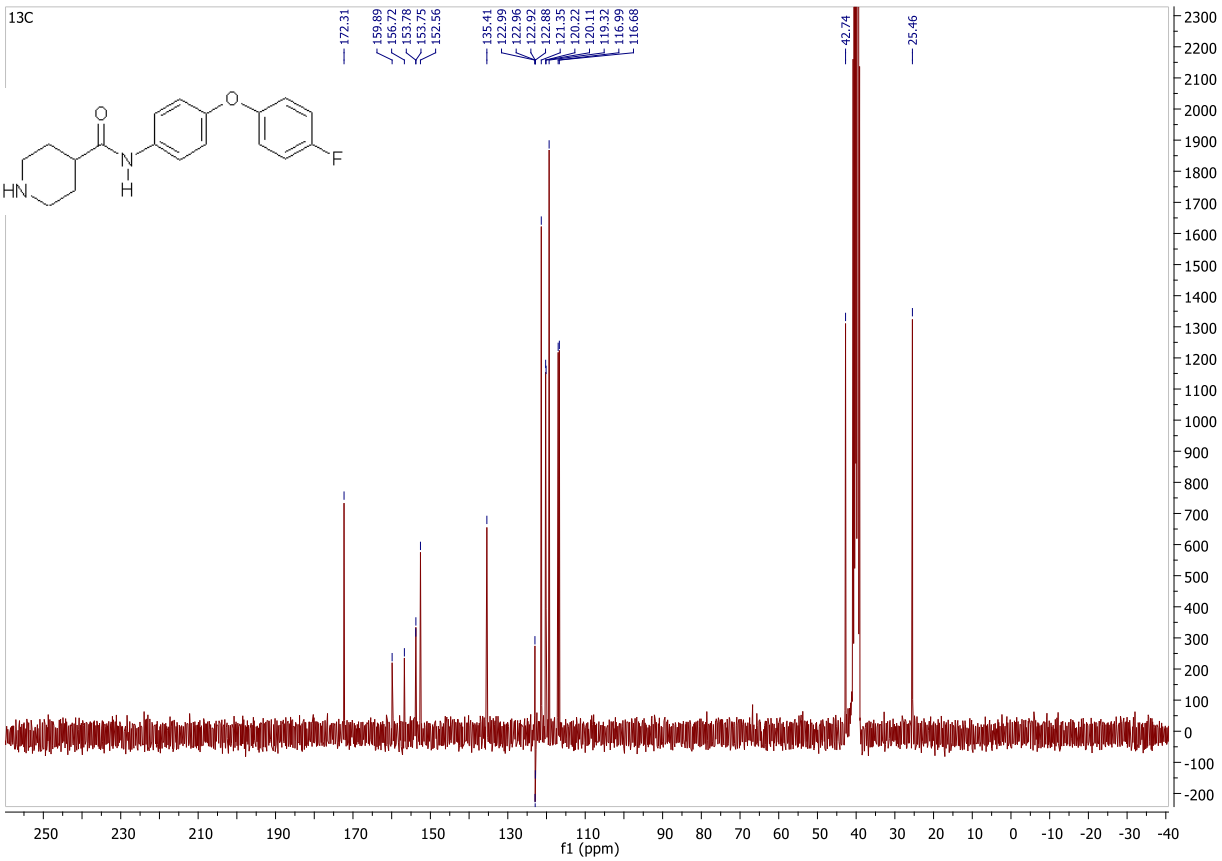
^{1}H and ^{13}C NMR spectra of compound **10h**



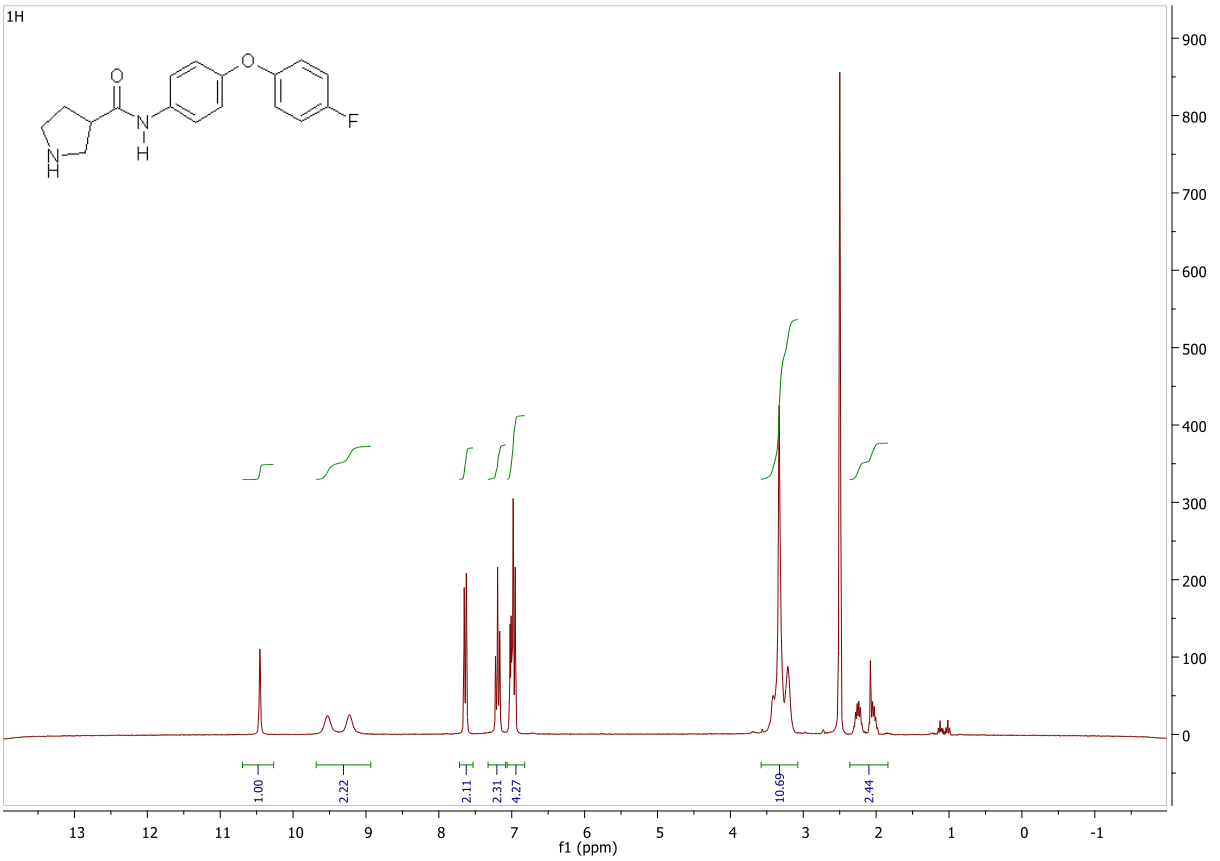


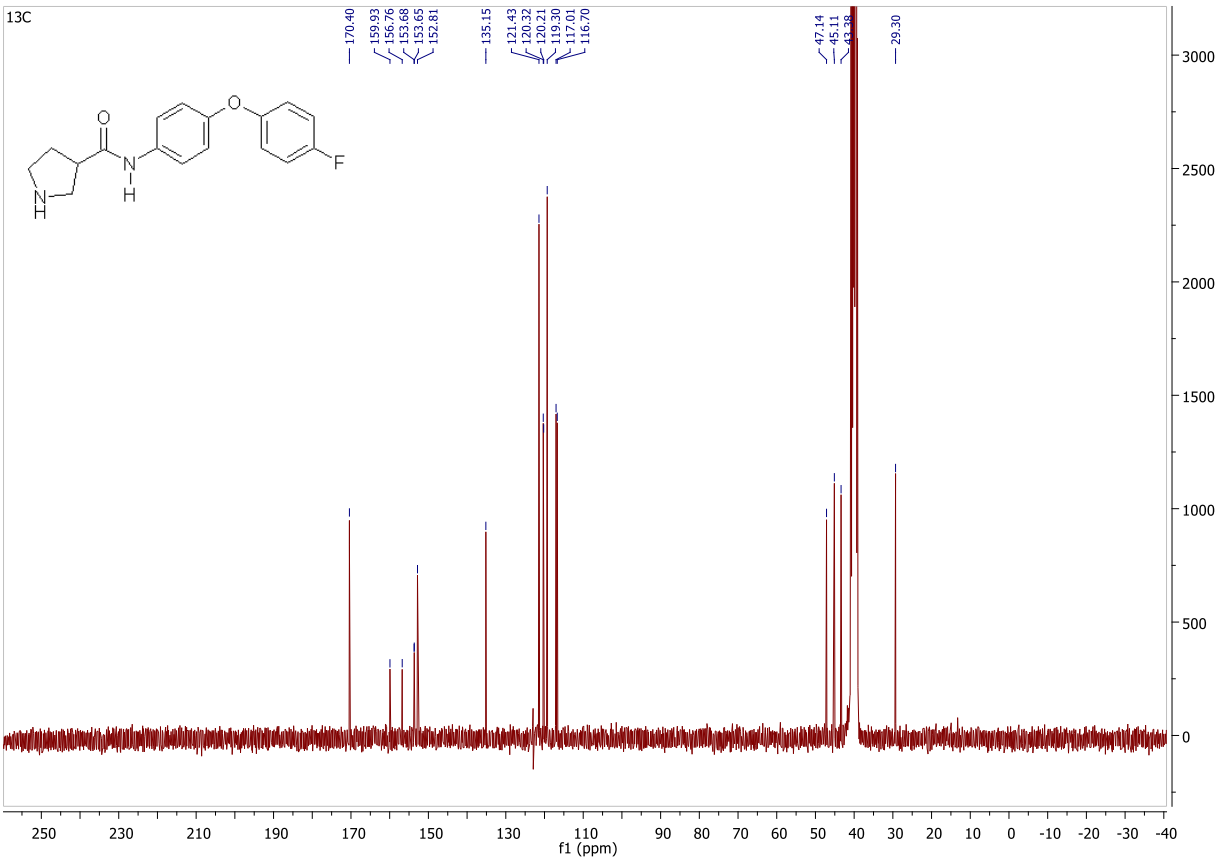
^{1}H and ^{13}C NMR spectra of compound **10i**



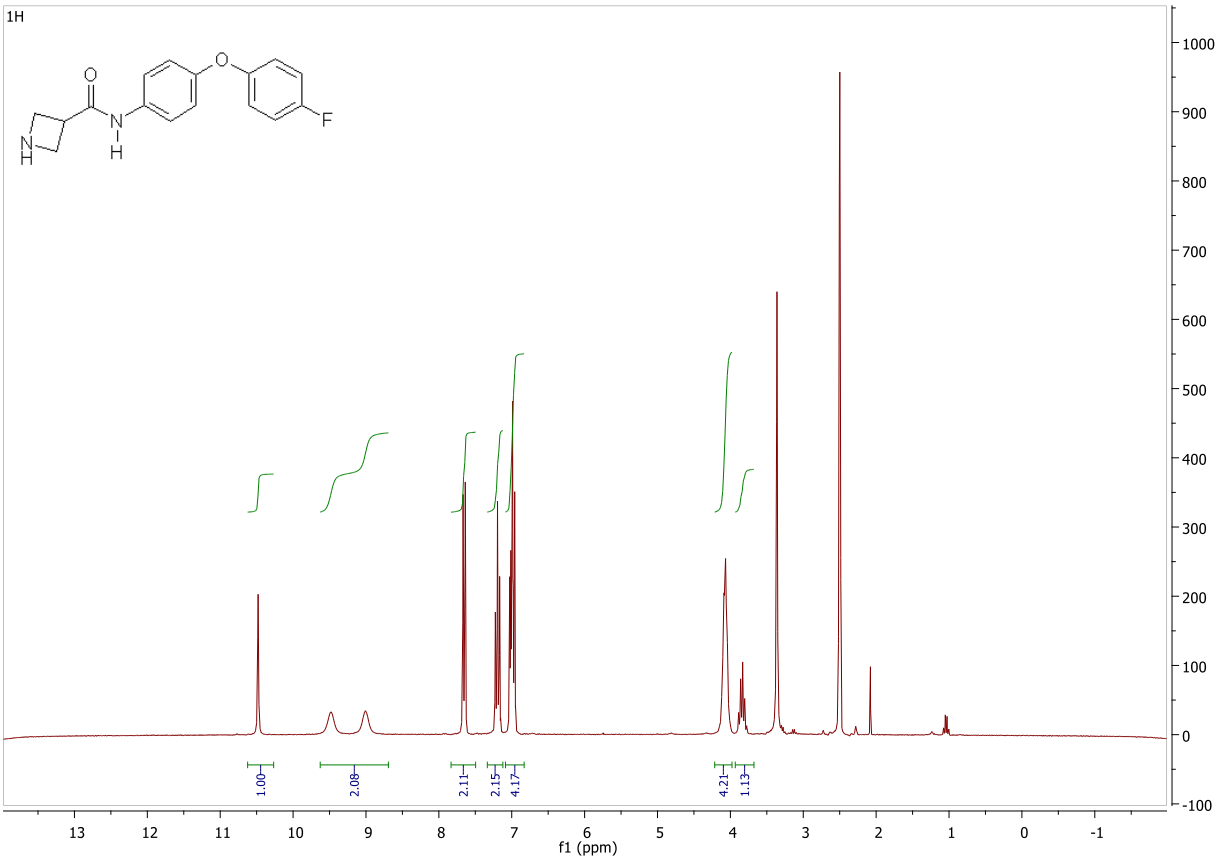


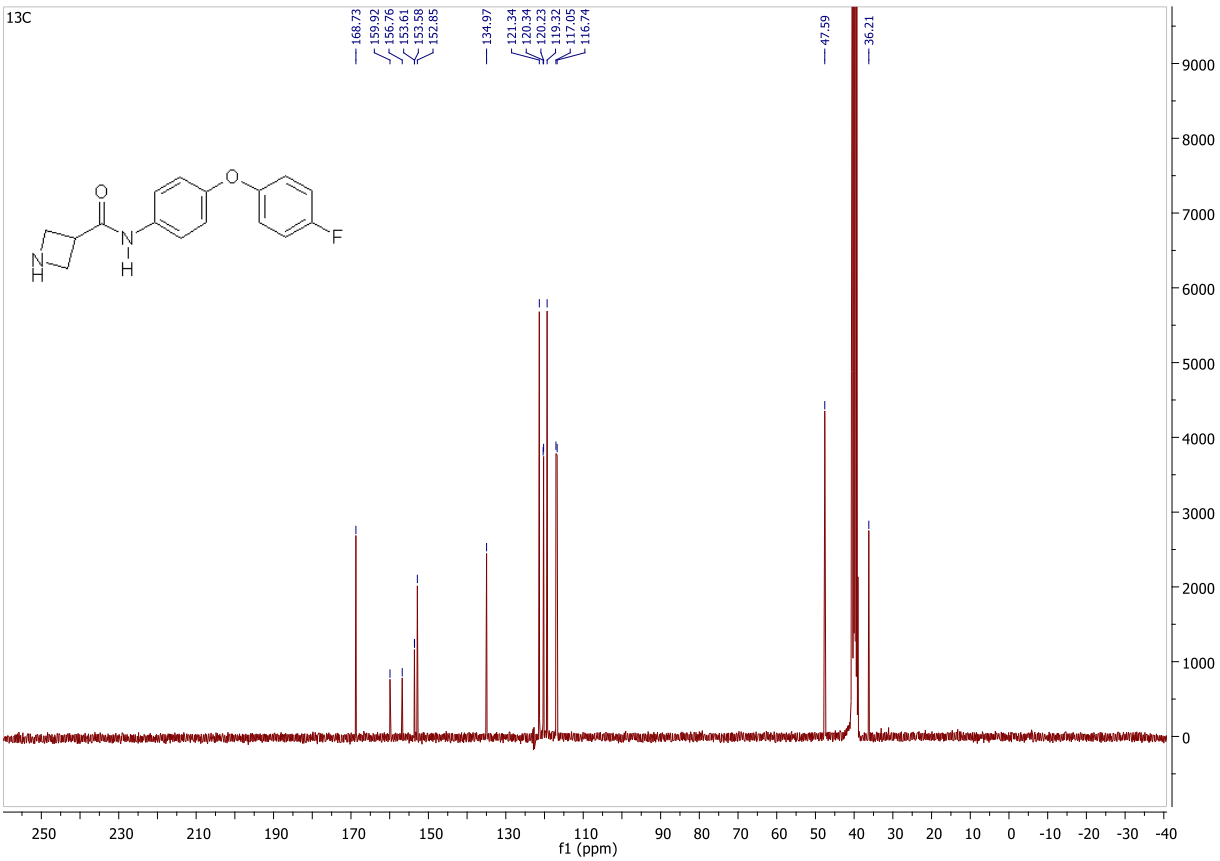
^{1}H and ^{13}C NMR spectra of compound **10j**



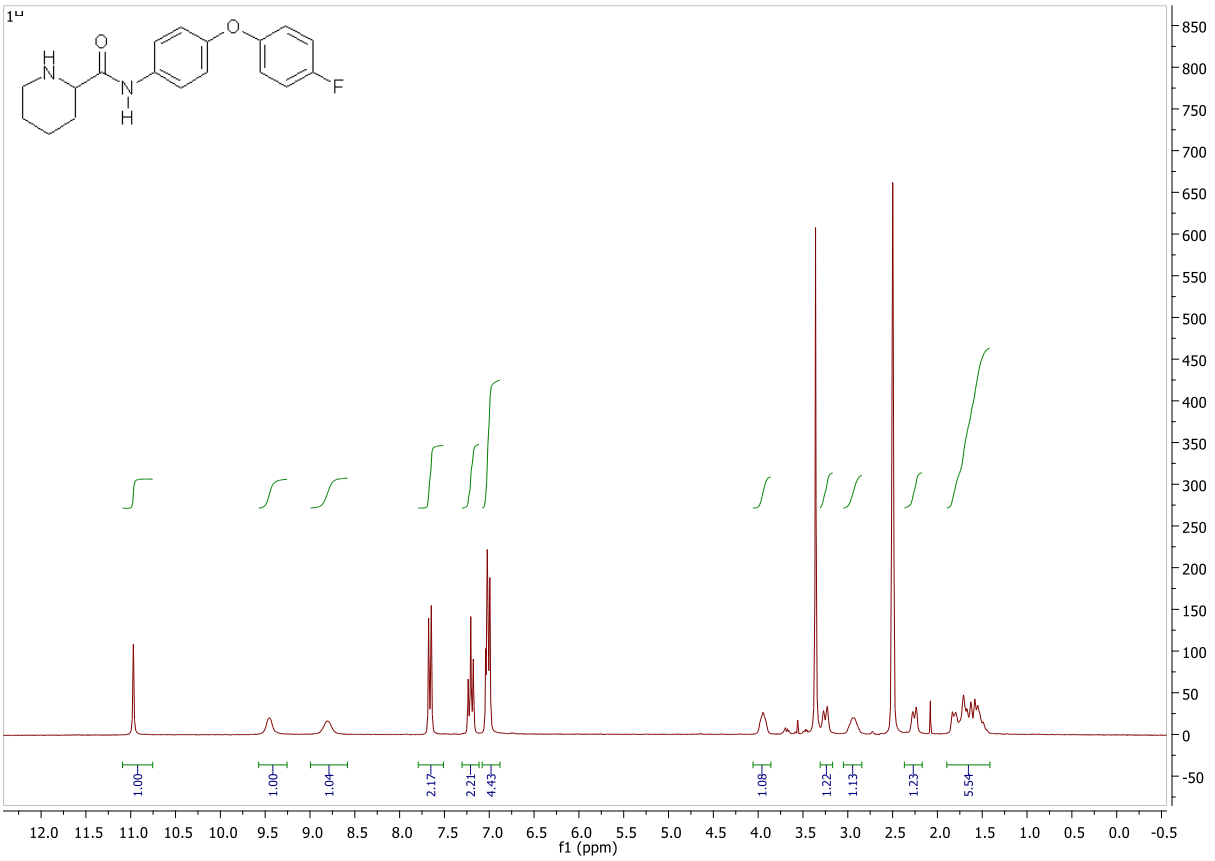


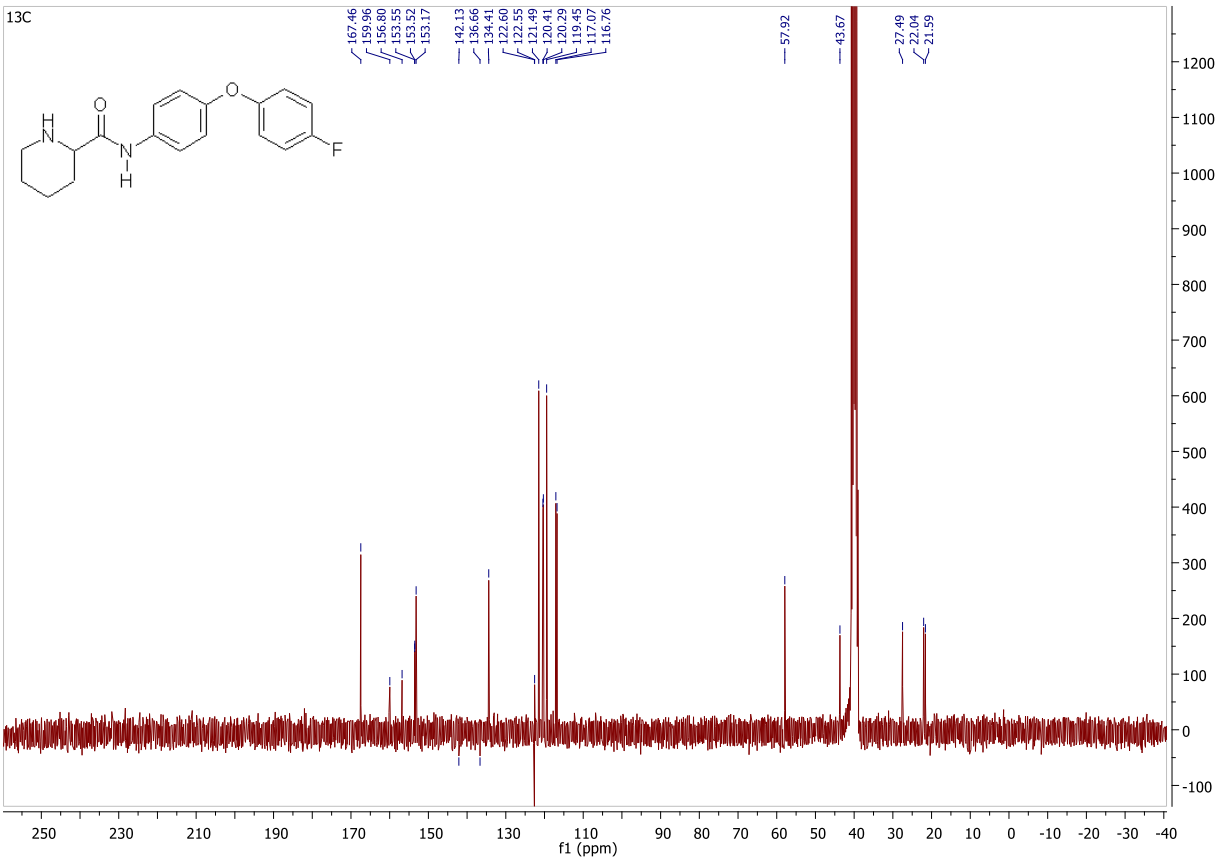
^{1}H and ^{13}C NMR spectra of compound **10k**



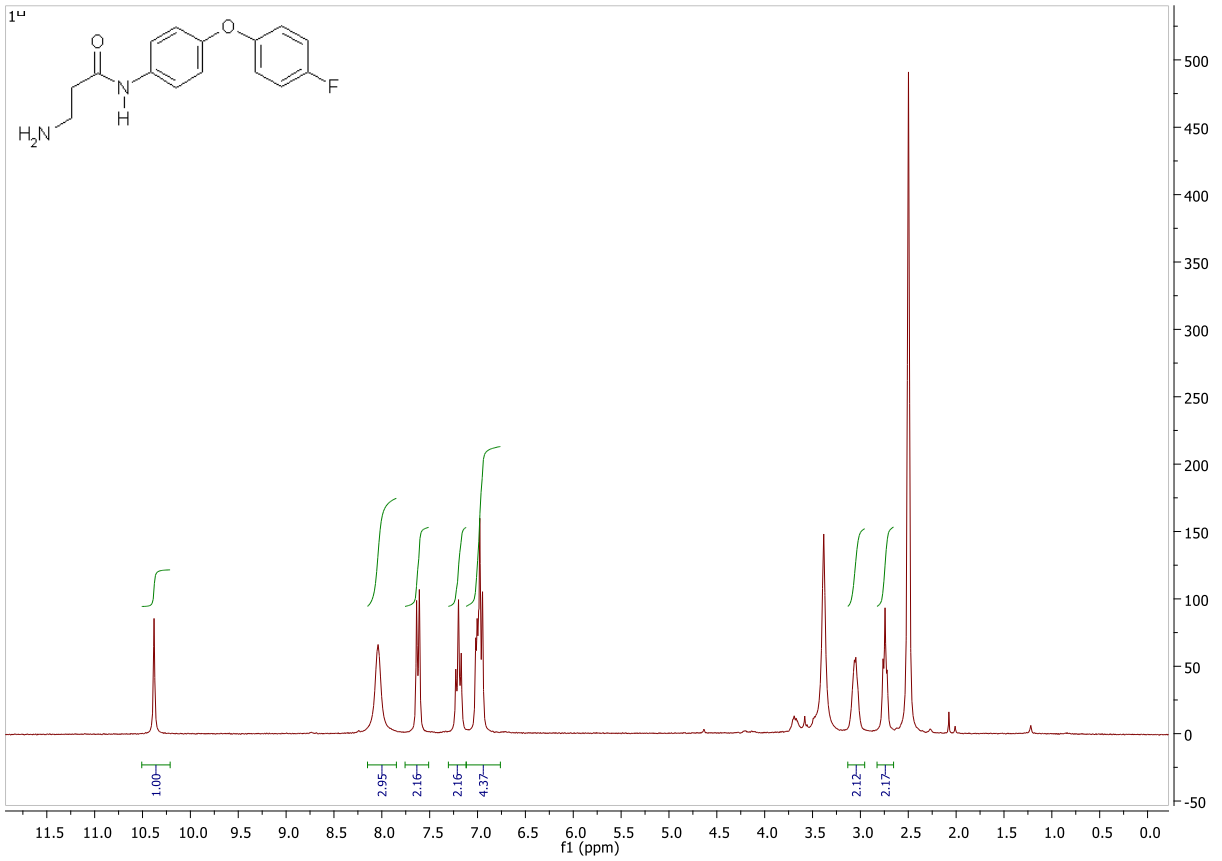


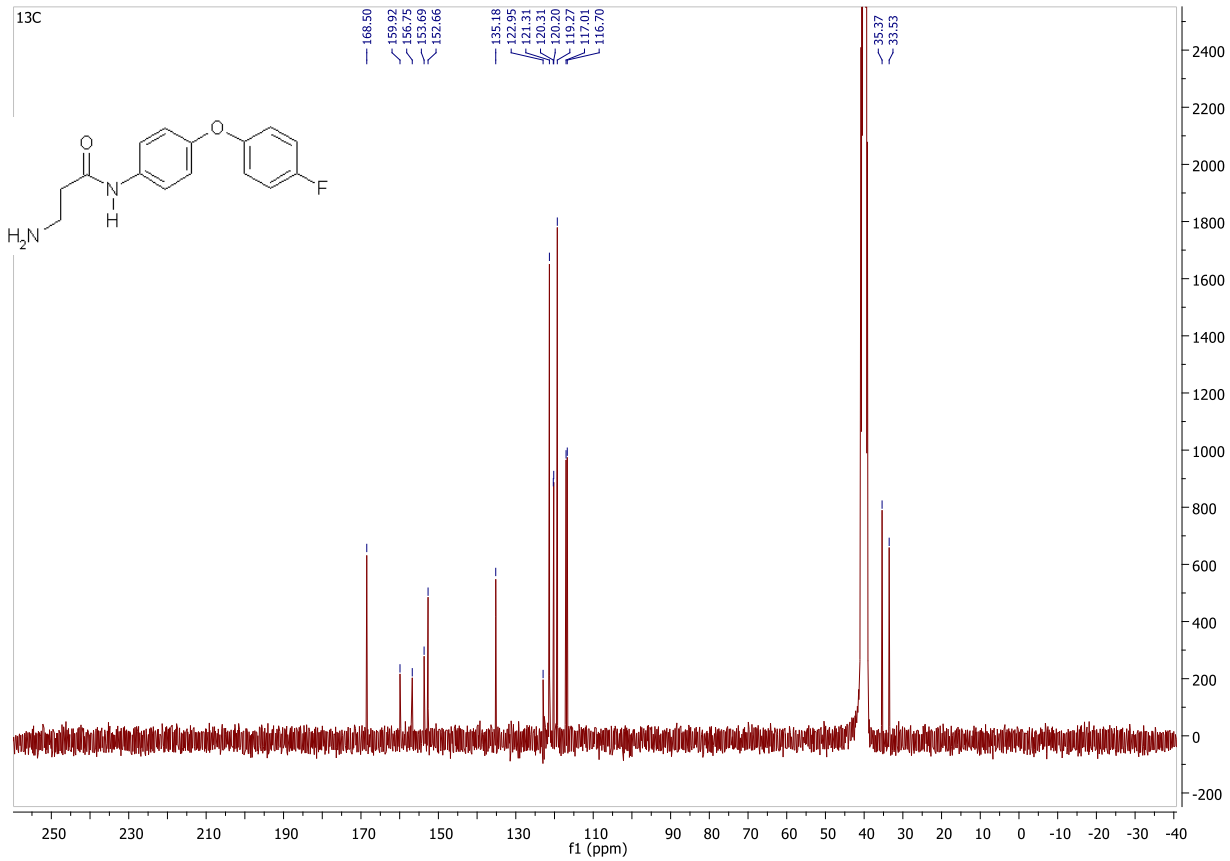
^{1}H and ^{13}C NMR spectra of compound **10l**



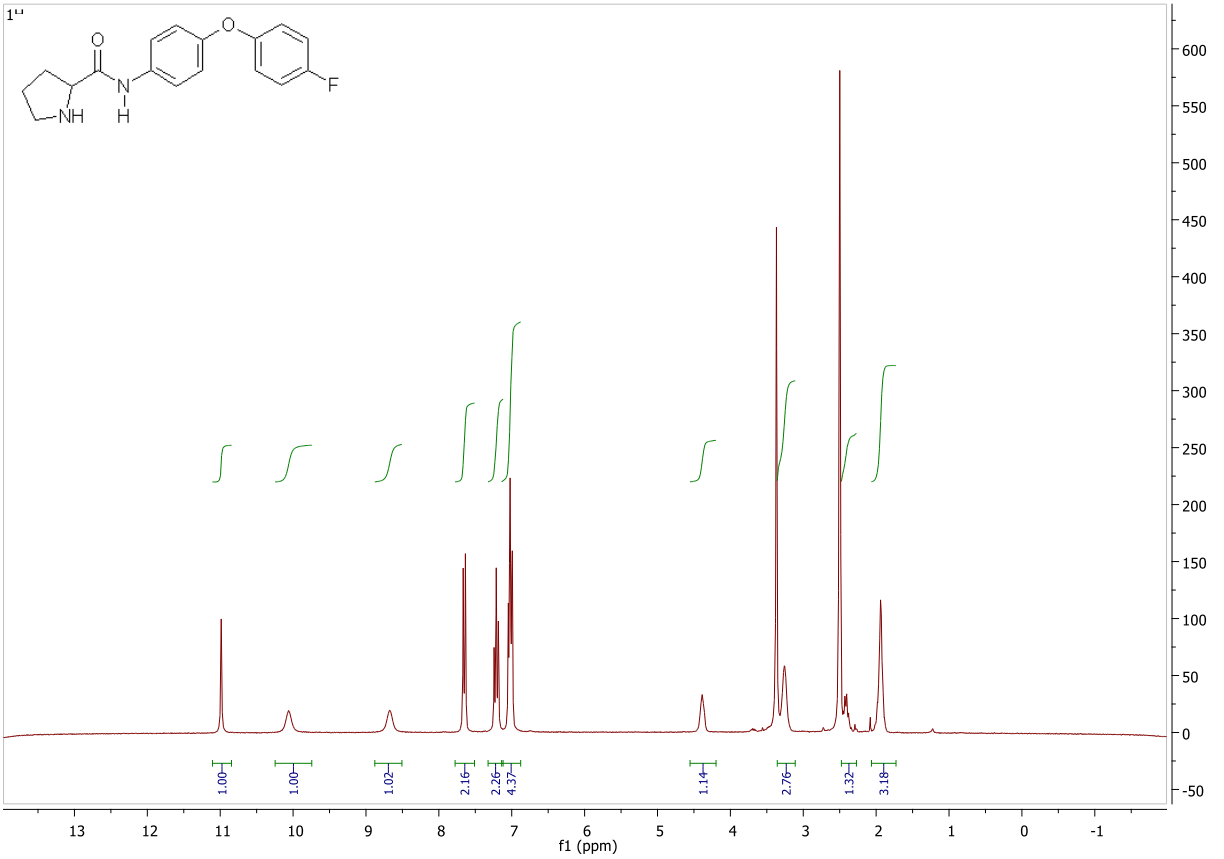


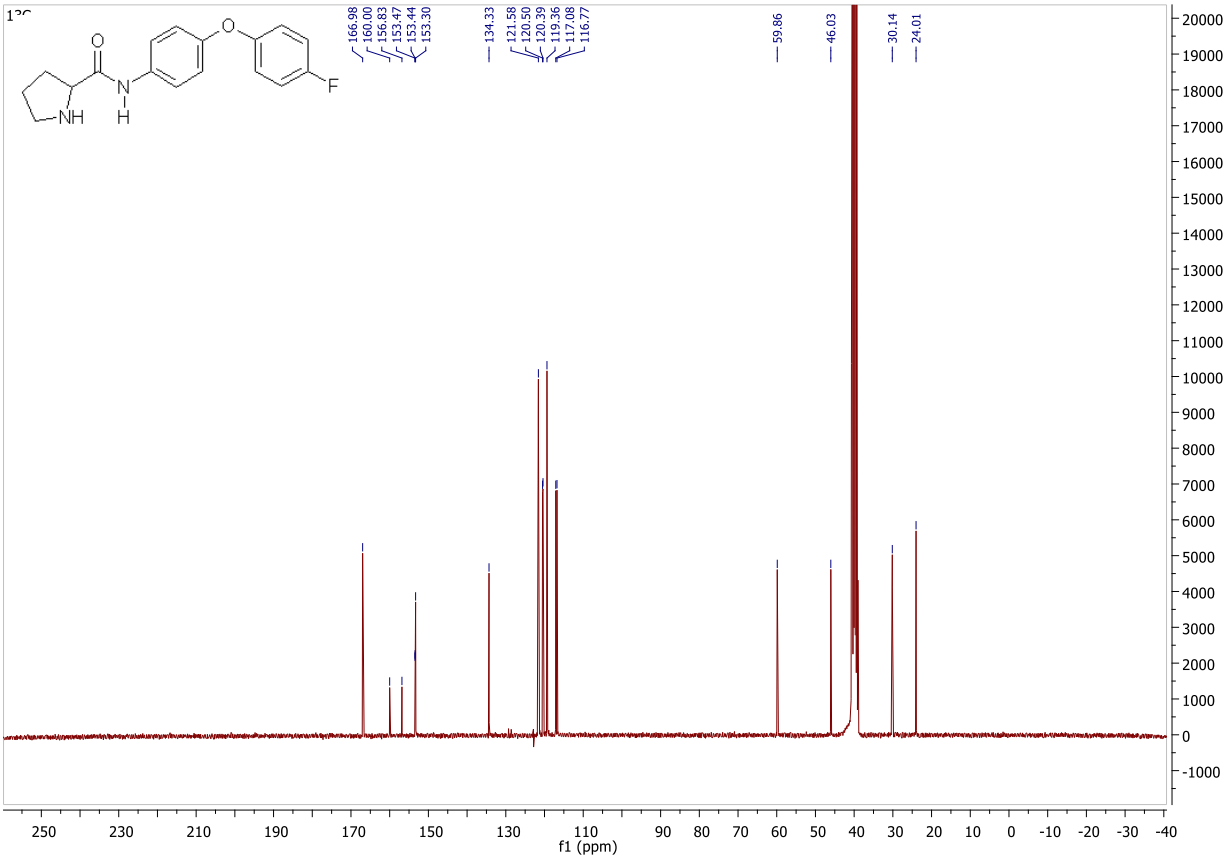
^{1}H and ^{13}C NMR spectra of compound **10m**



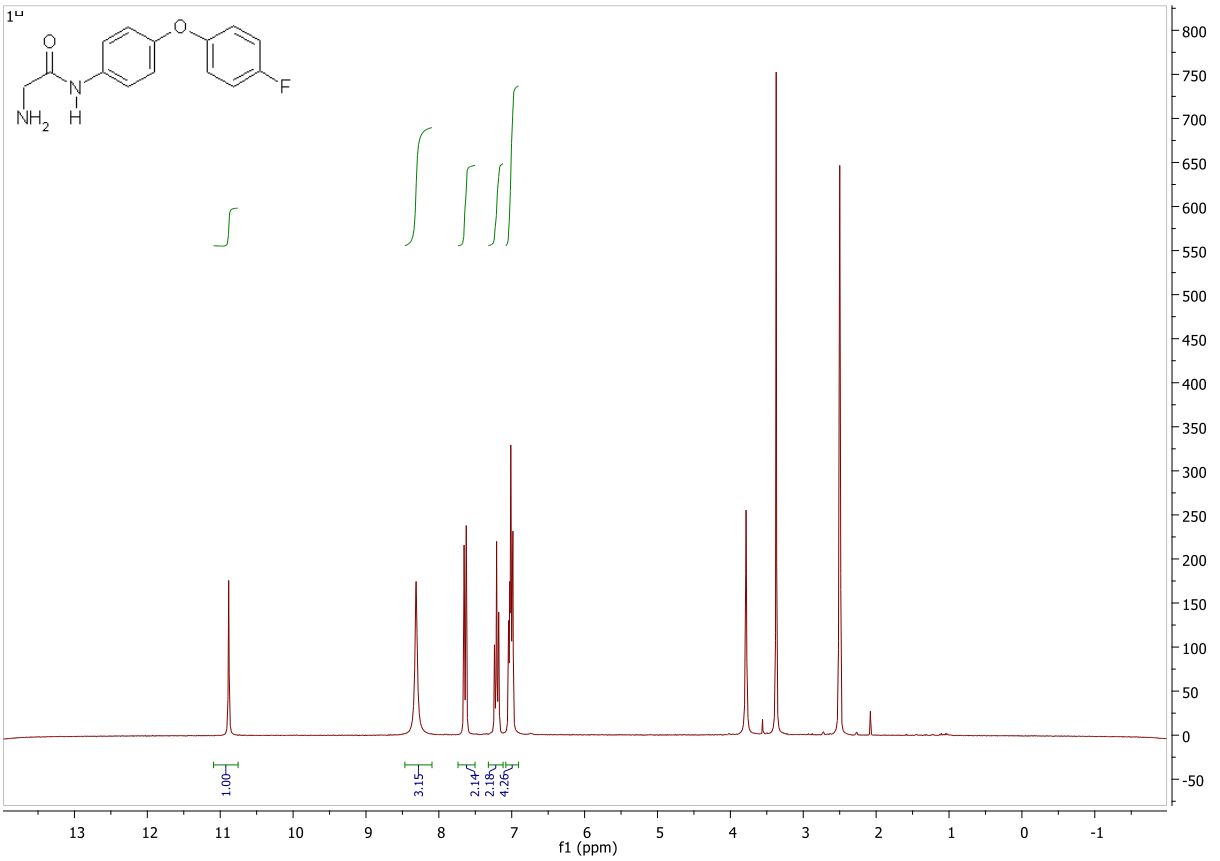


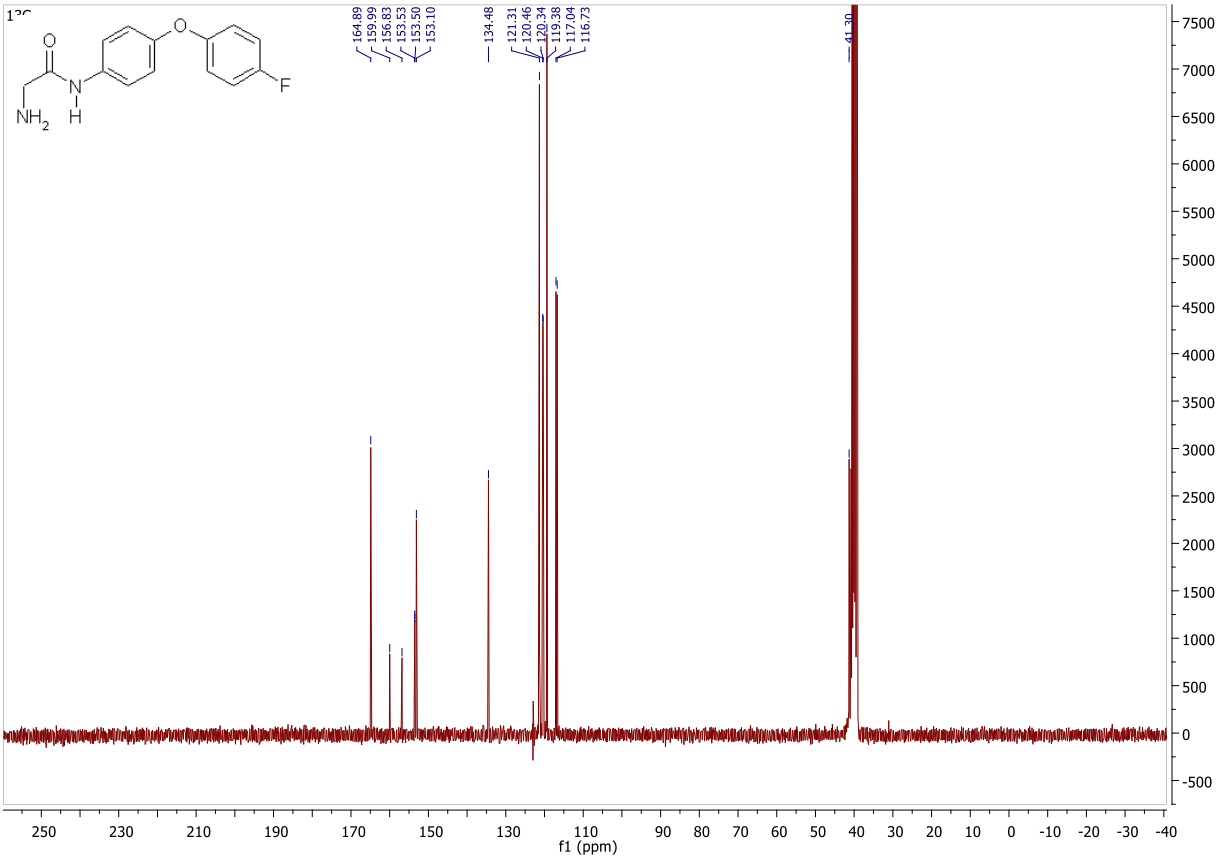
^{1}H and ^{13}C NMR spectra of compound **10n**



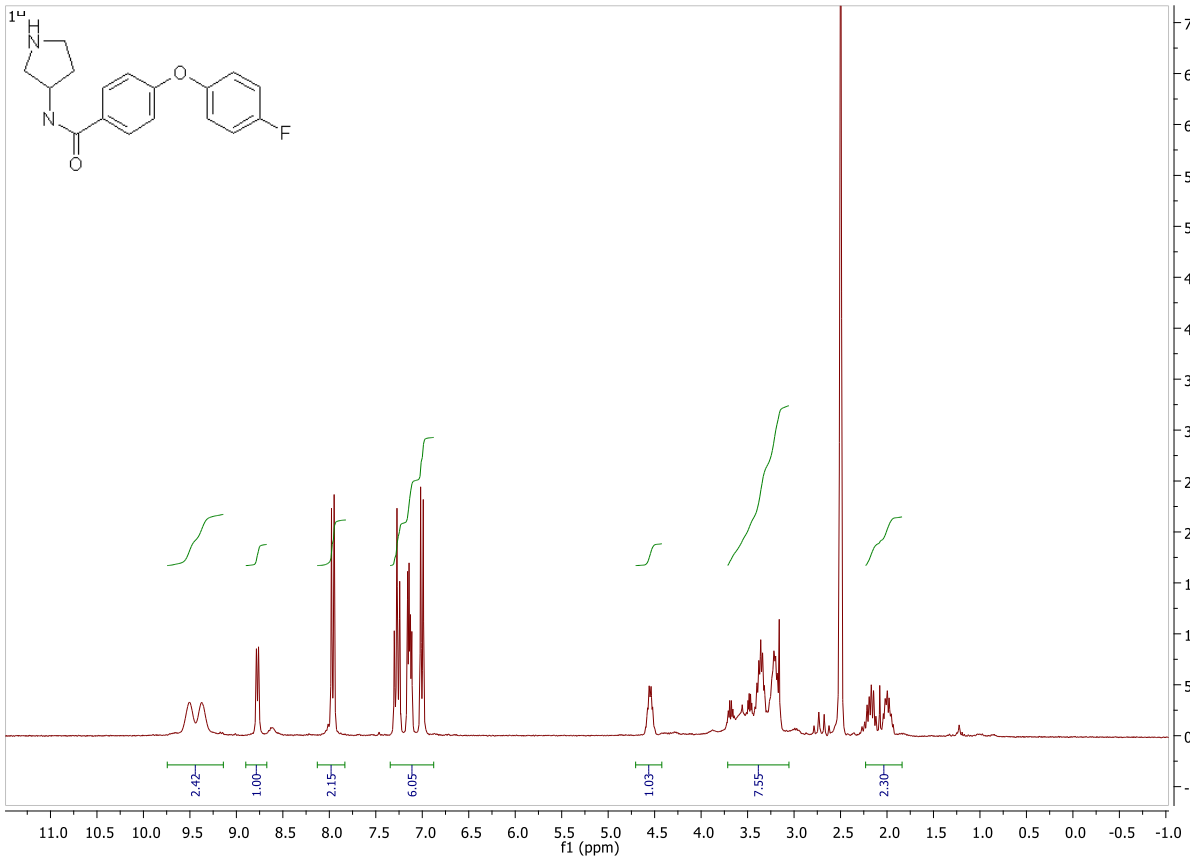


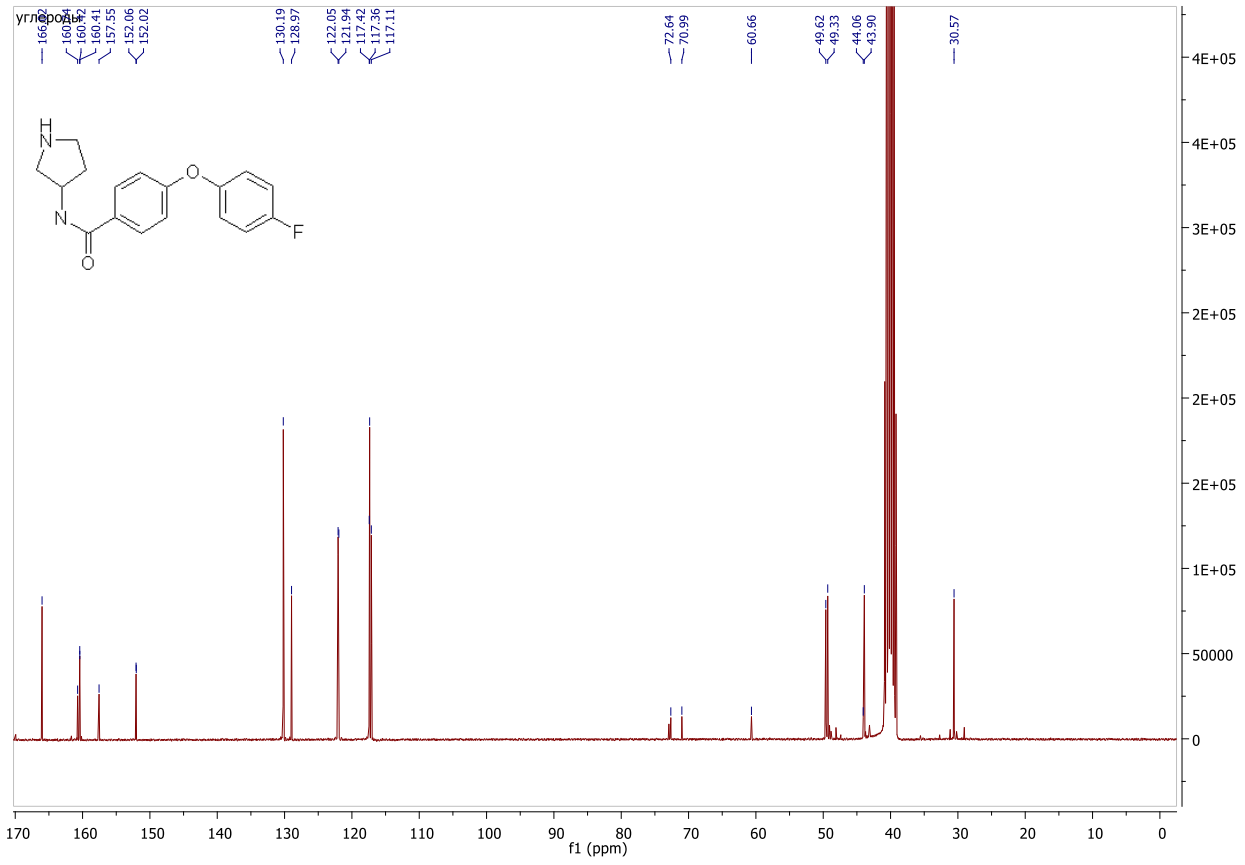
^{1}H and ^{13}C NMR spectra of compound **10o**



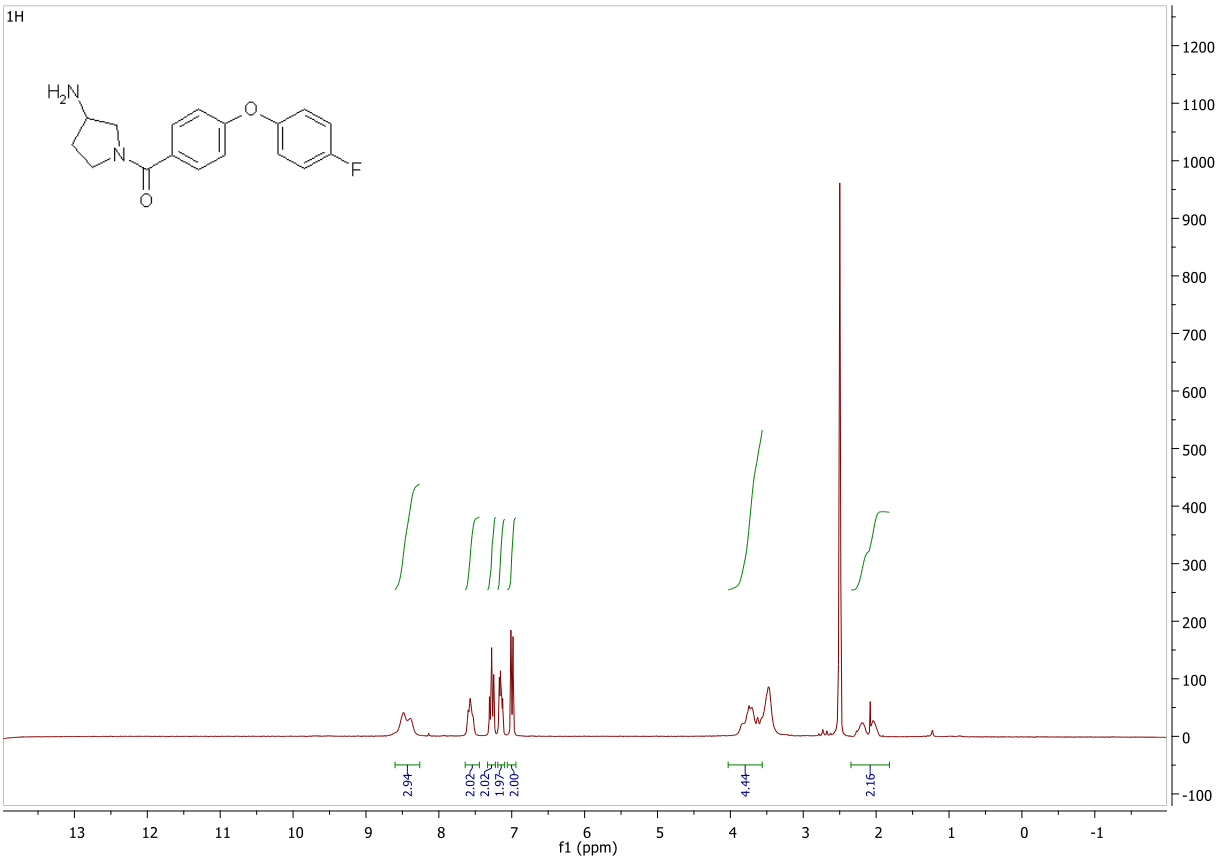


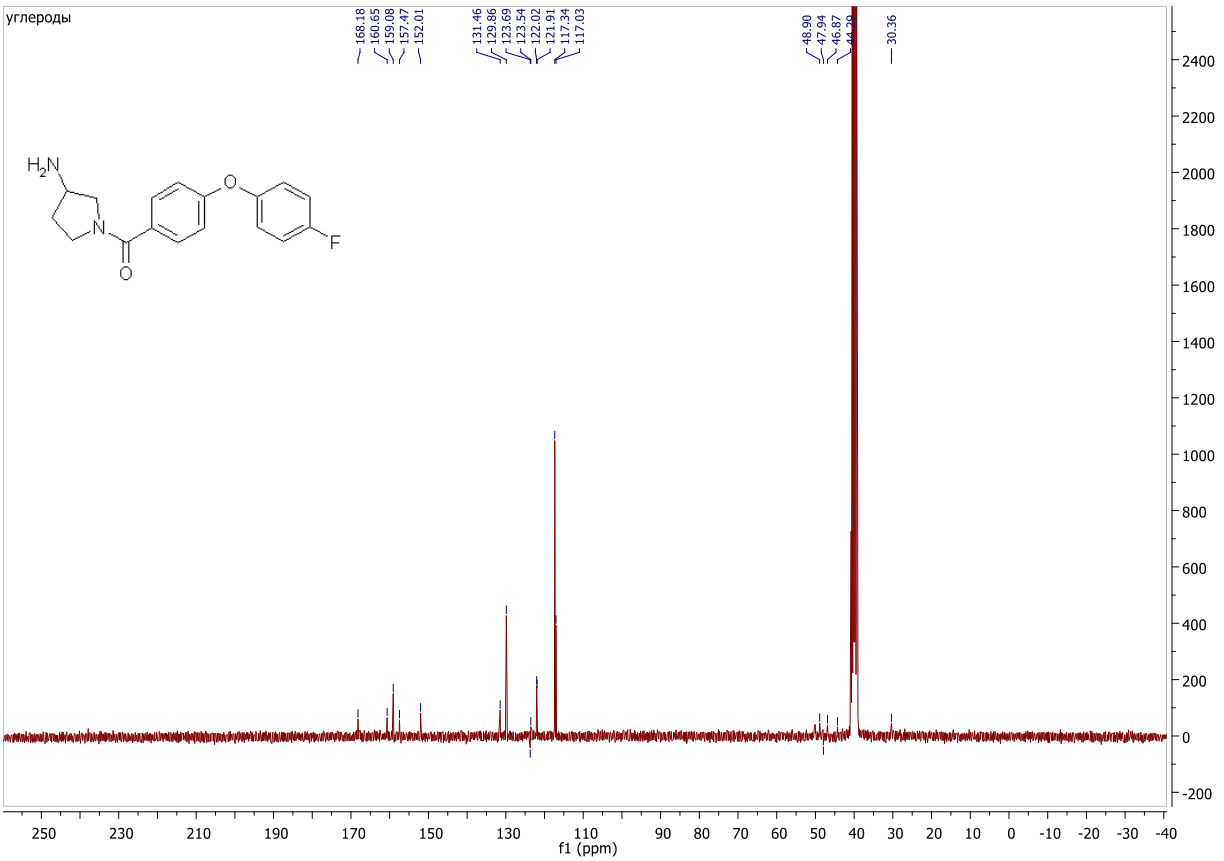
^{1}H and ^{13}C NMR spectra of compound **11a**





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





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