Supplementary information

Synthesis and pharmacological evaluation of 1,3-diaryl substituted pyrazole based (thio)urea derivatives as potent antimicrobial agents against multi-drug resistant *Staphylococcus aureus* and *Mycobacterium tuberculosis*

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Contents

1. Materials and methods:

All the chemicals and solvents were purchased from commercial providers and were used without any further purification. The reactions were monitored by thin layer chromatography (TLC) on precoated Merck 60 F_{254} silica gel (0.5 mm) aluminium plates with visualization under UV light (254 nm). Column chromatography was performed using silica gel 60-120 or 100- 200 mesh, wherever required. ^{1}H and ^{13}C spectra were obtained on Bruker Avance 500 spectrometer (500 and 125 MHz for ^{1}H and ^{13}C NMR, respectively) using DMSO-d_6 as a solvent. Chemical shifts (δ) are reported in ppm referenced to the internal standard, TMS (δ 0.00 for ^{1}H NMR and ^{13}C NMR) or DMSO-d_6 (δ 2.50 for ^{1}H NMR and 39.5 for ^{13}C NMR). Spin multiplicities are reported as s (singlet), brs (broad singlet), d (doublet), dd (double doublet), t (triplet), q (quartet) and m (multiplet). Coupling constant (J) values are reported in hertz (Hz). Carbon-Fluorine coupling is denoted by J_{CF} in ^{13}C spectra of compounds with fluorine group. HRMS was recorded with Agilent QTOF mass spectrometer 6540 series instrument and were performed in ESI techniques at 70 eV.[1] Stuart® SMP30 apparatus used for determination of melting points.

1.1 General procedure A for the synthesis of intermediate 4-(3-Aryl-1H-pyrazol-1-yl) aniline, 5a-i:

A mixture of 5g of appropriate acetophenone **1** (1 equiv.) and 10 mL of dimethylformamide-dimethyl acetal (3 equiv.) was heated under reflux for 15-20 h. After completion of the reaction as indicated by TLC, solvent was evaporated under reduced pressure, and to the residue, 50 ml of ice-cold water was added; the obtained precipitate was filtered and oven-dried to give intermediates **2a-i** (1-Aryl-3-dimethylaminoprop-2-enones) as yellow solids in 80-90% yields which were carried to next step without any further purification. 5g of appropriate 3-dimethylamino-1-(aryl) prop-2-en-1-one **2a-i** (1 equiv.) was dissolved in ethanol, and hydrazine hydrate (2 equiv.) was added. The reaction mixture was refluxed for 4 h. Upon completion, the residual solvent was removed using rota evaporator, and the resultant solid was poured onto the crushed ice. The precipitate formed was filtered off, washed with ice-cold water and oven-dried providing the C3-substituted pyrazole derivatives **3a-i** in 85-90 % yields which were pure enough to be used in the subsequent reactions. A mixture of appropriate intermediates **3a-i** (1 equiv.), 1-fluoro, 4-

nitro benzene (1.3 equiv.) and potassium carbonate (2 equiv.) in DMF was heated at 110 °C for 15 h. After completion, the reaction mixture was allowed to cool to ambient temperature, followed by the addition of crushed ice. The resultant yellow solid was filtered off, washed with ice-cold water and purified by recrystallization from chloroform and hexane to give the target 1-(4-nitrophenyl)-3-aryl-1H-pyrazole intermediates **4a-i** in 85-95 % yields. 2g of appropriate 1-(4-nitrophenyl)-3-aryl-1H-pyrazole intermediate **4a-i** (1 equiv.) was dissolved in 30 ml of EtOH (15 mL) and water (15 mL) solvent mixture to which Fe powder (8 equiv.), and acetic acid (catalytic amount) were added one after another. The resulting mixture was stirred at 80 °C for 2 h. After completion of the reaction, as monitored by tlc, the reaction mixture was cooled to room temperature and subjected to celite filtration. The filtrate obtained was extracted with ethyl acetate (15 mL × 2). The combined organic layers were then washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was later purified by recrystallization with chloroform and hexane to give the corresponding amine intermediate **5a-i** in 70-75 % yields. Intermediate **5a** was reported in the literature cited above. Characterization data for the newly synthesized intermediates **5b-i** is given below.

4-(3-(Naphthalen-2-yl)-1H-pyrazol-1-yl)aniline (5b)

Off-white solid, Yield 75 %; mp: 155-157 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.43 (S, 1H, P2), 8.33 (d, *J* = 2.1 Hz, 1H, C1), 8.10 (d, *J* = 8.5 Hz, 1H, C3), 7.98 (t, *J* = 6.5 Hz, 2H, C6, 7), 7.93 (d, *J* = 7.8 Hz, 1H, C5), 7.57 (d, *J* = 8.6 Hz, 2H, C4, 8), 7.51 (dd, *J* = 16.8, 8.0 Hz, 2H, C2', 6'), 7.08 (d, *J* = 2.1 Hz, 1H, P1), 6.70 (d, *J* = 8.6 Hz, 2H, C3', 5'), 5.28 (s, 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.00, 148.05, 133.73, 133.02, 131.15, 130.17, 129.18, 128.64, 128.45, 128.11, 126.88, 126.35, 124.29, 123.96, 120.48, 114.47, 105.02; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{19}H_{16}N_3$ 286.1344; observed 286.1335.

4-(3-(Pyridin-3-yl)-1H-pyrazol-1-yl)aniline (5c)

Beige solid, Yield 67 %; mp: 162-164 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.10 (d, *J* = 1.6 Hz, 1H, P2), 8.53 (dd, *J* = 4.7, 1.6 Hz, 1H, C2), 8.33 (d, *J* = 2.4 Hz, 1H, C4), 8.26 – 8.22 (m, 1H, C5), 7.53 (d, *J* = 8.8 Hz, 2H, C2', 6'), 7.46 (dd, *J* = 8.2, 5.1 Hz, 1H, C6), 7.05 (d, *J* = 2.4 Hz, 1H, P1), 6.68 (d, *J* = 8.8 Hz, 2H, C3', 5'), 5.29 (s, 1H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 149.05,

148.35, 148.21, 146.98, 132.80, 129.94, 129.36, 124.31, 120.58, 114.41, 105.08; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{14}H_{13}N_4$ 237.1140; observed 237.1143

4-(3-(4-Chlorophenyl)-1H-pyrazol-1-yl)aniline (5d)

White solid, Yield 70 %; mp: 148-150 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.29 (d, *J* = 2.4 Hz, 1H, P2), 7.91 (d, *J* = 8.6 Hz, 1H, C2', 6'), 7.50 (dd, *J* = 10.9, 8.7 Hz, 4H, C2, 3, 5, 6), 6.96 (d, *J* = 2.4 Hz, 1H, P1), 6.67 (d, *J* = 8.8 Hz, 2H, C3', 5'), 5.27 (s, 1H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 149.91, 148.10, 132.54, 132.50, 130.04, 129.23, 129.17, 127.35, 120.48, 114.45, 104.85; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{15}H_{13}ClN_3$ 270.0798; found 270.0790

4-(3-(4-Methoxyphenyl)-1H-pyrazol-1-yl)aniline (5e)

Off-white solid, Yield 75 %; mp: 147--149 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.50 (s, 1H, P2), 8.09 (d, *J* = 9.6 Hz, 1H, C2), 8.04 (d, *J* = 2.1 Hz, 1H, C6), 7.81 (d, *J* = 8.7 Hz, 2H, C2', 6'), 7.71 (dd, *J* = 8.9, 2.3 Hz, 1H, C3), 7.42 (d, *J* = 8.9 Hz, 1H, C5), 7.03 (d, *J* = 8.7 Hz, 2H, C3', 5'), 6.51 (d, *J* = 9.6 Hz, 1H, P1), 5.41 (s, 2H, NH_2), 3.80 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.99, 148.02, 147.89, 130.24, 129.27, 128.31, 127.83, 122.19, 120.97, 120.39, 114.47, 112.36, 108.54, 55.92; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{16}H_{16}N_3O$ 266.1293; found 266.1284

4-(3-(4-Methylphenyl)-1H-pyrazol-1-yl)aniline (5f)

White solid, Yield 73 %; mp: 148--150 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.24 (d, *J* = 2.4 Hz, 1H, P2), 7.78 (d, *J* = 8.1 Hz, 2H, C2, 6), 7.51 (d, *J* = 8.8 Hz, 2H, C2', 6'), 7.24 (d, *J* = 7.9 Hz, 2H, C3, 5), 6.87 (d, *J* = 2.4 Hz, 1H, P1), 6.67 (d, *J* = 8.8 Hz, 2H, C3', 5'), 5.25 (s, 2H, NH_2), 2.34 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.12, 147.89, 137.29, 130.91, 130.24, 129.70, 128.85, 125.62, 120.36, 114.48, 104.40, 21.31; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{16}H_{16}N_3$ 250.1344; found 250.1342

4-(3-(2,4-Dichlorophenyl)-1H-pyrazol-1-yl)aniline (5g)

Light yellow solid, Yield 73 %; mp: 162-164 °C;^{1}H NMR (500 MHz, DMSO-d_6) δ 8.33 (d, *J* = 2.5 Hz, 1H, P2), 7.92 (d, *J* = 8.5 Hz, 1H, C6), 7.71 (d, *J* = 2.2 Hz, 1H, C5), 7.54 – 7.50 (m, 3H, C2', 6', C2), 6.94 (d, *J* = 2.4 Hz, 1H, P1), 6.67 (d, *J* = 8.8 Hz, 2H, C3', 5'), 5.30 (s, 2H, NH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 148.31, 147.60, 133.24, 132.30, 132.06, 131.33, 130.16, 129.82,

128.51, 128.02, 120.68, 114.43, 108.19; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{15}H_{12}Cl_2N_3$ 304.0408; found 304.0398

4-(3-(3,4,5-Trimethoxyphenyl)-1H-pyrazol-1-yl)aniline (5h)

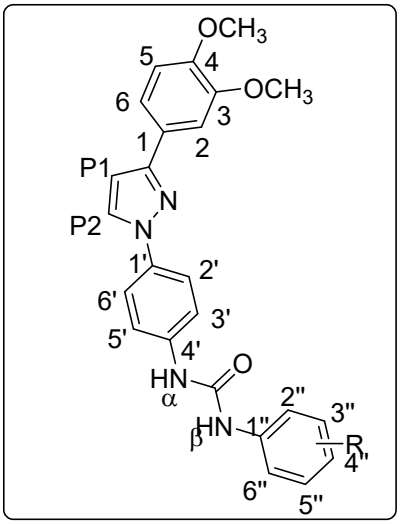
Beige solid, Yield 66 %; mp: 152-154 °C;^{1}H NMR (500 MHz, DMSO-d_6) δ 8.25 (d, *J* = 2.4 Hz, 1H, P2), 7.53 (d, *J* = 8.8 Hz, 2H, C2', 6'), 7.18 (s, 2H, C2, 6), 6.95 (d, *J* = 2.4 Hz, 1H, P1), 6.68 (d, *J* = 8.8 Hz, 2H, C3', 5'), 5.25 (s, 2H, NH_2), 3.87 (s, 6H, C3, 5-$(OCH_3)_2$), 3.70 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.65, 151.14, 147.95, 137.74, 130.19, 129.41, 128.93, 120.49, 114.47, 104.86, 103.13, 60.56, 56.39; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{19}H_{16}N_3$ 326.1504; found 326.1500

4-(3-Phenyl-1H-pyrazol-1-yl)aniline (5i)

White solid, Yield 73 %; mp: 148--150 °C;^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (d, *J* = 2.3 Hz, 1H, P2), 7.89 (d, *J* = 7.3 Hz, 2H, C2', 6'), 7.52 (d, *J* = 8.7 Hz, 2H, C3, 5), 7.43 (t, *J* = 7.6 Hz, 2H, C2, 6), 7.33 (t, *J* = 7.3 Hz, 1H, C4), 6.92 (d, *J* = 2.3 Hz, 1H, P1), 6.67 (d, *J* = 8.7 Hz, 2H, C3', 5'), 5.26 (s, 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.06, 147.99, 133.65, 130.18, 129.14, 129.00, 128.06, 125.69, 120.43, 114.47, 104.66; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{19}H_{16}N_3$ 236.1187; found 236.1183

1.2 General procedure B for the synthesis of urea and thiourea derivatives 6-10:

A mixture of equimolar quantities of appropriate pyrazole amine (**5a-i)** and corresponding isocyanate/ isothiocyanates in 5 ml acetonitrile was stirred at room temperature for 12 h. After completion of the reaction, obtained solids were filtered and washed with methanol to give crude products, which were then purified by recrystallization with methanol and chloroform to afford target compounds **6-10** in 90-95 % yields. All newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR and HRMS (ESI).



1-(4-(3-(3,4-Dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)-3-(4-methoxyphenyl)thiourea(6a)

Off-white solid, yield 89 %, mp: 162-164 ºC; FT-IR (cm^{-1}): 3391, 3421, 3201, 3000, 2926, 2836, 1610, 1546, 1513, 1170; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.91 (s, 1H, β-NH), 9.84 (s, 1H, α-NH), 8.49 (d, *J* = 2.3 Hz, 1H, P2), 7.85 (d, *J* = 8.8 Hz, 2H, C2', 6'), 7.63 (d, *J* = 8.6 Hz, 2H, C3', 5'), 7.50 (s, 1H, C2), 7.46 (d, *J* = 8.3 Hz, 1H, C6), 7.36 (d, *J* = 8.7 Hz, 2H, C2'', 6''), 7.03 (d, *J* = 8.3 Hz, 1H, C5), 6.99 (d, *J* = 2.2 Hz, 1H, P1), 6.93 (d, *J* = 8.8 Hz, 2H, C3'', 5''), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3), 3.76 (s, 3H, c4''-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.38, 157.08, 152.27, 149.40, 149.36, 138.01, 136.53, 132.56, 129.51, 126.50, 126.11, 125.12, 118.66, 118.56, 114.19, 112.37, 109.46, 105.45, 56.02, 56.01, 55.71; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{25}H_{25}N_4O_3S$ 461.1647; observed 461.1622

1-(3-Bromophenyl)-3-(4-(3-(3,4-dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)thiourea(6b)

Beige solid, yield 86 %, mp: 163-165 ºC; FT-IR (cm^{-1}): 3440, 3287, 3011, 2929, 2832, 1587, 1513, 1420, 1315, 1170; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.07 (s, 1H, β-NH), 9.96 (s, 1H, α-NH), 8.51 (d, *J* = 2.0 Hz, 1H, P2), 7.88 (d, *J* = 8.7 Hz, 2H, C2', 6'), 7.84 (s, 1H, C2''), 7.60 (d, *J* = 8.6 Hz, 2H, C3', 5'), 7.50 (s, 1H, C2), 7.47 (d, *J* = 7.8 Hz, 2H, C4'', C6''), 7.36 – 7.28 (m, 2H, C5'', C6), 7.04 (d, *J* = 8.3 Hz, 1H, C5), 7.00 (d, *J* = 2.1 Hz, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.11, 152.34, 149.40, 149.38, 141.67, 137.54, 136.84, 130.80, 129.54, 127.39, 126.29, 126.07, 125.27, 122.83, 121.40, 118.79 , 118.57 , 112.36, 109.45, 105.53, 56.01,56.00; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{22}BrN_4O_2S$ 509.0646; observed 509.0631.

1-(4-(3-(3,4-Dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)-3-(p-tolyl)thiourea(6c)

white solid, yield 85 %, mp: 230-232 ºC; FT-IR (cm^{-1}): 3376, 3194, 3011, 2929, 2829, 1509, 1476, 1315, 1271, 1047; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.78 (s, 1H, β-NH), 9.76 (s, 1H, α-NH), 8.49 (s, 1H, P2), 7.86 (d, *J* = 7.8 Hz, 2H, C2', 6'), 7.62 (d, *J* = 7.7 Hz, 2H, C3', 5'), 7.51 (s, 1H, C2), 7.46 (d, *J* = 7.5 Hz, 1H, C6), 7.37 (d, *J* = 7.0 Hz, 2H, C2'', 6''), 7.17 (d, *J* = 7.1 Hz, 2H, C3'', 5''), 7.04 (d, *J* = 7.9 Hz, 1H, C5), 6.99 (s, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3), 2.30 (s, 3H, C4''-CH3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.16, 152.29, 149.43, 149.40, 137.94, 137.20, 136.61, 134.29, 129.51, 129.44, 126.13, 125.16, 124.41, 118.69, 118.58, 112.42, 109.52, 105.46, 56.04, 21.00; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{25}H_{25}N_4O_2S$ 445.1698; observed 445.1682

1-(3-Chlorophenyl)-3-(4-(3-(3,4-dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)thiourea(6d)

white solid, yield 88 %, mp: 163-165 ºC; FT-IR (cm^{-1}): 3477, 3283, 3112, 3011, 2829, 1587, 1513, 1315, 1252, 1088; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.05 (s, 1H, β-NH), 9.96 (s, 1H, α-NH), 8.50 (d, *J* = 2.5 Hz, 1H, P2), 7.88 (d, *J* = 8.9 Hz, 2H, C2', 6'), 7.73 (t, *J* = 1.9 Hz, 1H, C2''), 7.62 (d, *J* = 8.9 Hz, 2H, C3', 5'), 7.51 (d, *J* = 1.9 Hz, 1H, C2), 7.46 (dd, *J* = 8.3, 1.9 Hz, 1H, C6), 7.43 (d, *J* = 8.9 Hz, 1H, C5''), 7.37 (t, *J* = 8.0 Hz, 1H, C6''), 7.20 (d, *J* = 8.8 Hz, 1H, C4''), 7.03 (d, *J* = 8.4 Hz, 1H, C5), 7.00 (d, *J* = 2.5 Hz, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.15, 152.36, 149.41, 141.54, 137.55, 136.87, 133.04, 130.53, 129.56, 126.09, 125.32, 124.54, 123.49, 122.44, 118.81, 118.59, 112.37, 109.46, 105.54, 56.02; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{22}ClN_4O_2S$ 465.1152; observed 465.1133

1-(4-(3-(3,4-Dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)-3-(4-fluorophenyl)thiourea(6e)

Off-white solid, yield 90 %, mp: 150-153 ºC; FT-IR (cm^{-1}): 3444, 3198, 3015, 2832, 1505, 1353, 1248, 1114; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.95 (s, 1H, β-NH), 9.86 (s, 1H, α-NH), 8.50 (d, *J* = 2.5 Hz, 1H, P2), 7.86 (d, *J* = 9.0 Hz, 2H, C2', 6'), 7.61 (d, *J* = 8.8 Hz, 2H, C3', 5'), 7.53 – 7.48 (m, 3H, C2, 2'', 6''), 7.46 (dd, *J* = 8.3, 2.0 Hz, 1H, C6), 7.19 (t, *J* = 8.9 Hz, 2H, C3'', 5''), 7.03 (d, *J* = 8.4 Hz, 1H, C5), 6.99 (d, *J* = 2.5 Hz, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3);^{13}C NMR (125 MHz, DMSO-d_6) δ 180.51, 159.68 (d, *J* = 241.5 Hz), 152.32, 149.40,

149.37, 137.75, 136.72, 136.17 (d, *J* = 2.5 Hz), 129.52, 126.75 (d, *J* = 8.2 Hz), 126.09, 125.25, 118.74, 118.57, 115.56 (d, *J* = 22.6 Hz)., 112.36, 109.45, 105.49, 56.01, 55.99; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{22}FN_4O_2S$ 449.1447; observed 449.1447

1-(4-Chlorophenyl)-3-(4-(3-(3,4-dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)thiourea(6f)

White solid, yield 90 %, mp: 184-186 ºC; FT-IR (cm^{-1}): 3473, 3257, 3101, 2933, 2832, 1591, 1472, 1312, 1174; ^1H NMR (500 MHz, DMSO-d_6) δ 9.97 (s, 1H, β-NH), 9.91 (s, 1H, α-NH), 8.50 (d, *J* = 2.5 Hz, 1H, P2), 7.87 (d, *J* = 8.9 Hz, 2H, C2', 6'), 7.61 (d, *J* = 8.8 Hz, 2H, C3', 5'), 7.54 (d, *J* = 8.7 Hz, 2H, C2'', 6''), 7.50 (d, *J* = 1.8 Hz, 1H, C2), 7.46 (dd, *J* = 8.3, 1.8 Hz, 1H, C6), 7.41 (d, *J* = 8.8 Hz, 2H, C3'', 5''), 7.03 (d, *J* = 8.4 Hz, 1H, C5), 6.99 (d, *J* = 2.5 Hz, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 180.23, 152.34, 149.43, 138.92, 137.66, 136.80, 129.53, 128.80, 126.13, 125.80, 125.24, 118.78, 118.60, 112.45, 109.57, 105.50, 56.04; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{22}ClN_4O_2S$ 465.1152; observed 465.1133

1-(4-Cyanophenyl)-3-(4-(3-(3,4-dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)thiourea(6g)

Off-white solid, yield 87 %, mp: 173-175 ºC; FT-IR (cm^{-1}): 3436, 3272, 3138, 2989, 2266, 1584, 1520, 1252, 1109, 1025; ^1H NMR (500 MHz, DMSO-d_6) δ 10.25 (s, 2H, α, β-NH), 8.51 (d, *J* = 2.1 Hz, 1H, P2), 7.89 (d, *J* = 8.7 Hz, 2H, C2', 6'), 7.80 (s, 4H, C2'', C3'', 5'', 6''), 7.63 (d, *J* = 8.6 Hz, 2H, C3', 5'), 7.50 (s, 1H, C2), 7.46 (d, *J* = 8.2 Hz, 1H, C6), 7.04 (d, *J* = 8.3 Hz, 1H, C5), 7.00 (d, *J* = 2.2 Hz, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.87, 152.40, 149.45, 144.59, 137.36, 137.01, 133.20, 129.57, 126.10, 125.24, 122.87, 119.54, 118.84, 118.61, 112.45, 109.58, 105.86, 105.56, 56.05; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{25}H_{22}N_5O_2S$ 456.1494; observed 456.1483.

1-(4-(3-(3,4-Dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)-3-(4-(trifluoromethyl)phenyl)thiourea(6h)

Off-white solid, yield 85 %, mp: 172-175 ºC; FT-IR (cm^{-1}): 3350, 3265, 3209, 2844, 1535, 1472, 1319, 1241, 1162; ^1H NMR (500 MHz, DMSO-d_6) ^1H NMR (500 MHz, DMSO) δ 10.16 (s, 1H, β-NH), 10.15 (s, 1H, α-NH), 8.50 (d, *J* = 2.5 Hz, 1H, P2), 7.89 (d, *J* = 8.9 Hz, 2H, C2', 6'), 7.78 (d, *J* = 8.5 Hz, 2H, C3'', 5''), 7.70 (d, *J* = 8.7 Hz, 2H, C2'', 6''), 7.64 (d, *J* = 7.3 Hz, 2H, C3',

5'), 7.50 (d, *J* = 1.9 Hz, 1H, C2), 7.46 (dd, *J* = 8.3, 1.9 Hz, 1H, C6), 7.03 (d, *J* = 6.5 Hz, 1H, C5), 7.00 (d, *J* = 2.5 Hz, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.11, 152.37, 149.41, 149.39, 143.83, 137.51, 136.91, 126.08 (q, *J* = 4.3 Hz),125.94, 125.27, 124.43 (q, *J* = 31.7 Hz), 123.65 (d, *J* = 34.3 Hz), 123.36, 120.56 (d, *J* = 268.0 Hz).118.79, 118.58, 113.45, 112.35, 109.46, 105.53, 56.00, 55.98; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{25}H_{22}F_3N_4O_2S$ 499.1415; observed 499.1402.

1-(4-(3-(3,4-Dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)-3-(4-nitrophenyl)thiourea(6i)

Yellow solid, yield 85 %, mp: 160-162 ºC; FT-IR (cm^{-1}): 3384, 3257, 3123, 2959, 1595, 1546, 1513, 1457, 1326, 1252, 1174; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.43 (s, 1H, β-NH), 10.37 (s, 1H, α-NH), 8.51 (s, 1H, P2), 8.23 (d, *J* = 8.9 Hz, 2H, C3'', 5''), 7.89 (dd, *J* = 17.2, 8.0 Hz, 4H, C2', 6', 2'', 6''), 7.65 (d, *J* = 6.7 Hz, 2H, C3', 5'), 7.51 (s, 1H, C2), 7.47 (d, *J* = 8.1 Hz, 1H, C6), 7.04 (d, *J* = 8.3 Hz, 1H, C5), 7.01 (d, *J* = 2.0 Hz, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.83, 152.41, 149.42, 146.69, 142.84, 137.27, 137.08, 129.58, 126.06, 125.25, 124.88, 122.11, 118.85, 118.60, 112.39, 109.51, 105.59, 56.03, 56.02; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{22}N_5O_4S$ 476.1392; observed 476.1373.

1-(4-(3-(3,4-Dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)-3-(naphthalen-1-yl)thiourea(6j)

Beige solid, yield 85 %, mp: 168-170 ºC; FT-IR (cm^{-1}): 3391, 3291, 3190, 3000, 2832, 1595, 1431, 1394, 1244, 1140; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.93 (s, 1H, β-NH), 9.84 (s, 1H, α-NH), 8.49 (d, *J* = 2.6 Hz, 1H, P2), 8.03 – 7.97 (m, 2H, C5'', 8''), 7.88 (dd, *J* = 7.5, 1.6 Hz, 1H, C4''), 7.87 – 7.84 (m, 2H, C2', 6'), 7.66 (d, *J* = 8.9 Hz, 2H, C3', 5'), 7.62 – 7.53 (m, 4H, C2'', 3'', 6'', 7''), 7.50 (d, *J* = 1.9 Hz, 1H, C2), 7.46 (dd, *J* = 8.3, 2.0 Hz, 1H, C6), 7.03 (d, *J* = 6.2 Hz, 1H, C5), 6.99 (d, *J* = 2.5 Hz, 1H, P1), 3.85 (s, 3H, C3-OCH_3), 3.80 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 181.83, 152.31, 149.43, 149.40, 138.02, 136.76, 135.50, 134.43, 130.44, 129.52, 128.61, 127.28, 126.68, 126.59, 126.15, 126.12, 125.87, 125.60, 123.59, 118.61, 118.59, 112.42, 109.52, 105.49, 56.04, 56.03, 40.51, 40.34, 40.18, 40.01, 39.84, 39.68, 39.51; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{28}H_{25}N_4O_2S$ 481.1698; found 481.1679.

1-Cyclohexyl-3-(4-(3-(3,4-dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)thiourea(6k)

Off-white solid, yield 85 %, mp: 83-85 ºC; FT-IR (cm^{-1}): 3384, 3272, 2926, 2851, 1703, 1606, 1513, 1244, 1021; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.44 (s, 1H, α-NH), 8.47 (d, *J* = 2.4 Hz, 1H, P2), 7.83 (d, *J* = 8.9 Hz, 2H, C2', 6'), 7.67 (brs, 1H, β-NH), 7.60 (d, *J* = 8.7 Hz, 2H, C3', 5'), 7.50 (d, *J* = 1.8 Hz, 1H, C2), 7.45 (dd, *J* = 8.3, 1.8 Hz, 1H, C6), 7.03 (d, *J* = 8.4 Hz, 1H, C5), 6.98 (d, *J* = 2.5 Hz, 1H, P1), 4.12 (s, 1H, C1''), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3), 1.93 (d, *J* = 10.1 Hz, 2H, C2'', 6''), 1.75 – 1.65 (m, 2H, C2'', 6''), 1.58 (d, *J* = 12.7 Hz, 1H, C4''), 1.37 – 1.22 (m, 4H, C3'', 5''), 1.21 – 1.13 (m, 1H, C4''); ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.74, 152.21, 149.42, 149.37, 138.02, 136.15, 129.43, 126.16, 124.02, 118.75, 118.55, 112.41, 109.48, 105.38, 56.03, 52.63, 32.34, 25.64, 24.99; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{29}N_4O_2S$ 437.2011; observed 437.2024.

1-(4-(3-(3,4-Dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)-3-phenylthiourea(6l)

Pale-yellow solid, yield 87 %, mp: 143-145 ºC; FT-IR (cm^{-1}): 3406, 3265, 3123, 2933, 2832, 1632, 1513, 1423, 1244; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.92 (s, 1H, β-NH), 9.88 (s, 1H, α-NH), 8.50 (d, *J* = 2.5 Hz, 1H, P2), 7.87 (d, *J* = 9.3 Hz, 2H, C2', 6'), 7.63 (d, *J* = 7.4 Hz, 2H, C3', 5'), 7.50 (dd, *J* = 4.8, 2.7 Hz, 3H, C2, 2'', 6''), 7.46 (dd, *J* = 8.3, 1.9 Hz, 1H, C6), 7.36 (t, *J* = 7.9 Hz, 2H, C3'', 5''), 7.15 (t, *J* = 7.4 Hz, 1H, C4''), 7.03 (d, *J* = 8.4 Hz, 1H, C5), 7.00 (d, *J* = 2.5 Hz, 1H, P1), 3.85 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.12, 152.30, 149.39, 149.36, 139.84, 137.84, 136.64, 129.52, 128.96, 128.91, 126.07, 125.23, 125.16, 125.00, 124.90, 124.17, 124.11, 118.71, 118.57, 112.36, 109.43, 105.49, 56.01, 56.00; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{23}N_4O_2S$ 431.1541; observed 431.1521

1-(4-(3-(3,4-Dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)-3-(3-methoxyphenyl)thiourea(6m)

yellow solid, yield 85 %, mp: 153-155 ºC; FT-IR (cm^{-1}): 3362, 3302, 3172, 2996, 1599, 1543, 1513, 1423; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.88 (s, 1H, β-NH), 9.85 (s, 1H, α-NH), 8.49 (d, *J* = 2.5 Hz, 1H, P2), 7.86 (d, *J* = 8.9 Hz, 2H, C2', 6'), 7.62 (d, *J* = 8.8 Hz, 2H, C3', 5'), 7.51 (d, *J* = 1.7 Hz, 1H, C2), 7.46 (dd, *J* = 8.3, 1.8 Hz, 1H, C6), 7.26 (t, *J* = 8.1 Hz, 1H, C5''), 7.21 (s, 1H, C6''), 7.06 (d, *J* = 9.6 Hz, 1H, C2''), 7.03 (d, *J* = 8.4 Hz, 1H, C5), 6.99 (d, *J* = 2.4 Hz, 1H, P1), 6.73 (dd, *J* = 8.2, 2.1 Hz, 1H, C4''), 3.86 (s, 3H, C3-OCH_3), 3.80 (d, *J* = 10.5 Hz, 3H, C4-OCH_3), 3.76 (s, 3H, C3''-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.92, 159.78, 152.30, 149.40, 149.37, 140.95, 137.81, 136.68, 129.76, 129.52, 126.08, 125.23, 118.69, 118.56, 116.08, 112.36,

110.35, 109.69, 109.44, 105.49, 56.00, 55.56; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{25}H_{25}N_4O_3S$ 461.1647; observed 461.1631.

1-(4-(3-(3,4-Dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)-3-heptylthiourea(6n)

Off-white solid, yield 85 %, mp: 90-92 ºC; FT-IR (cm^{-1}): 3443, 3284, 2934, 1215, 1189, 853, 771, 764; ^1H NMR (500 MHz, DMSO-d_6) δ 9.56 (brs, 1H, β-NH), 8.48 (d, *J* = 2.3 Hz, 1H, P2), 7.84 (d, *J* = 8.8 Hz, 2H, C2', 6'), 7.79 (brs, 1H, α-NH), 7.55 (d, *J* = 8.8 Hz, 2H, C3', 5'), 7.50 (d, *J* = 1.4 Hz, 1H, C2), 7.46 (dd, *J* = 8.3, 1.6 Hz, 1H, C6), 7.03 (d, *J* = 8.4 Hz, 1H, C5), 6.99 (d, *J* = 2.4 Hz, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.80 (s, 3H, C4-OCH_3), 3.47 (s, 2H, C1''), 1.55 (m, C2''), 1.29 (m, 8H, C3''-C6''), 0.88 (t, *J* = 6.6 Hz, 3H, C7'') ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.80, 152.24, 149.39, 149.35, 137.76, 136.31, 129.44, 126.11, 124.34, 118.86, 118.54, 112.34, 109.41, 105.41, 55.99, 44.35, 31.74, 28.94, 26.88, 22.55, 14.44. HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{25}H_{33}N_4O_2S$ 453.2324; observed 453.2330

1-(4-(3-(3,4-Dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)-3-(3,5-dimethylphenyl)thiourea(6o)

Off-white solid, yield 85 %, mp: 230-232 ºC; FT-IR (cm^{-1}): 3295, 3157, 3000, 2832, 1632, 1509, 1341, 1244; ^1H NMR (500 MHz, DMSO-d_6) δ 9.78 (s, 1H, β-NH), 9.72 (s, 1H, α-NH), 8.49 (d, *J* = 2.3 Hz, 1H, P2), 7.86 (d, *J* = 8.8 Hz, 2H, C2', 6'), 7.61 (d, *J* = 8.7 Hz, 2H, C3', 5'), 7.50 (s, 1H, C2), 7.46 (d, *J* = 8.2 Hz, 1H, C6), 7.10 (s, 2H, C2'', 6''), 7.03 (d, *J* = 8.3 Hz, 1H, C5), 6.99 (d, *J* = 2.3 Hz, 1H, P1), 6.80 (s, 1H, C4''), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3), 2.27 (s, 6H, C3'', 5''); ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.05, 152.31, 149.44, 149.40, 139.55, 138.06, 137.96, 136.66, 129.50, 126.67, 126.14, 125.28, 121.95, 118.68, 118.59, 112.41, 109.52, 105.46, 56.04, 56.02, 21.44; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{26}H_{27}N_4O_2S$ 459.1854; observed 459.1858

1-benzyl-3-(4-(3-(3,4-Dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)thiourea(6p)

Beige solid, yield 85 %, mp: 144-146 ºC; FT-IR (cm^{-1}): 3417, 3283, 3117, 1646, 1515, 1345, 1244, 1112; ^1H NMR (500 MHz, DMSO-d_6) δ 9.70 (s, 1H, β-NH), 8.48 (d, *J* = 2.5 Hz, 1H, P2), 8.23 (s, 1H, α-NH), 7.86 (d, *J* = 8.9 Hz, 2H, C2', 6'), 7.58 (d, *J* = 7.3 Hz, 2H, C3', 5'), 7.50 (d, *J* = 1.9 Hz, 1H, C2), 7.46 (dd, *J* = 8.3, 1.9 Hz, 1H, C6), 7.37 (s, 2H, C3'', 5''), 7.36 (s, 2H, C2'', 6''), 7.31-7.25 (m, 1H, C4''), 7.03 (d, *J* = 8.4 Hz, 1H, C5), 6.98 (d, *J* = 2.5 Hz, 1H, P1), 4.77 (d, *J* = 5.2

Hz, 2H, CH2), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 181.39, 152.29, 149.43, 149.39, 139.45, 137.59, 136.58, 129.49, 128.77, 127.92, 127.37, 126.12, 124.83, 118.91, 118.57, 112.41, 109.50, 105.46, 56.04, 47.69; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{25}H_{25}N_4O_2S$ 445.1698; observed 445.1710

1-(2,4-Dimethoxyphenyl)-3-(4-(3-(3,4-dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)thiourea(6q)

Off-white solid, yield 85 %, mp: 150-152 ºC; FT-IR (cm^{-1}): 3481, 3142, 2981, 2832, 1602, 1558, 1509, 1271, 1021; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.74 (s, 1H, β-NH), 9.08 (s, 1H, α-NH), 8.49 (d, *J* = 2.1 Hz, 1H, P2), 7.85 (d, *J* = 8.7 Hz, 2H, C2', 6'), 7.66 (d, *J* = 8.6 Hz, 2H, C3', 5'), 7.54 (d, *J* = 8.6 Hz, 1H, C6''), 7.50 (s, 1H, C2), 7.46 (d, *J* = 8.3 Hz, 1H, C6), 7.03 (d, *J* = 8.3 Hz, 1H, C5), 6.99 (d, *J* = 2.1 Hz, 1H, P1), 6.66 (d, *J* = 7.7 Hz, 1H, C3''), 6.54 (dd, *J* = 8.7, 2.2 Hz, 1H, C5''), 3.86 (s, 3H, C3-OCH_3), 3.84 (s, 3H, C2''-OCH_3), 3.81 (s, 3H, C4-OCH_3), 3.79 (s, 3H, C4''-OCH_3); ^{13}C NMR (125 MHz, DMSO) δ 180.51, 158.78, 154.48, 152.28, 149.43, 149.39, 138.04, 136.54, 129.50, 128.47, 126.14, 125.13, 120.87, 118.61, 118.58, 112.41, 109.52, 105.44, 104.72, 99.42, 56.20, 56.04, 56.02, 55.83; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{26}H_{27}N_4O_4S$ 491.1753; observed 491.1782

1-(2,4-Difluorophenyl)-3-(4-(3-(3,4-dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)thiourea(6r)

Beige solid, yield 85 %, mp: 230-232 ºC; FT-IR (cm^{-1}): 3450, 3323, 3000, 2951, 1610, 1536, 1484, 1211; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.05 (s, 1H, β-NH), 9.46 (s, 1H, α-NH), 8.50 (d, *J* = 3.9 Hz, 1H, P2), 7.88 (d, *J* = 8.9 Hz, 2H, C2', 6'), 7.62 (d, *J* = 5.9 Hz, 2H, C3', 5'), 7.60-7.54 (m, 1H, C6''), 7.50 (d, *J* = 1.9 Hz, 1H, C2), 7.46 (dd, *J* = 8.3, 2.0 Hz, 1H, C6), 7.37-7.31 (m, 1H, C5''), 7.13 – 7.08 (m, 1H, C3''), 7.03 (d, *J* = 8.4 Hz, 1H, C5), 6.99 (d, *J* = 2.5 Hz, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 181.54, 160.64 (dd, *J* = 245.2, 11.7 Hz), 157.42 (dd, *J* = 249.3, 13.3 Hz), 152.35, 149.43, 149.41, 137.57, 136.89, 130.86 (dd, *J* = 9.5, 2.2 Hz), 129.54, 126.09, 125.35, 124.17 (dd, *J* = 11.8, 3.4 Hz), 118.77, 118.59, 112.41, 111.58 (dd, *J* = 21.9, 3.4 Hz), 109.51, 105.52, 104.78 (t, *J* = 27.0, 24.2 Hz), 56.04, 56.02; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{21}F_2N_4O_2S$ 467.1353; observed 467.1357

1-(3-Chloro-4-fluorophenyl)-3-(4-(3-(3,4-dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)thiourea(6s)

white solid, yield 85 %, mp: 165-167 ºC; FT-IR (cm^{-1}): 3242, 3134, 3041, 2922, 1621, 1550, 1472, 1338, 1249, 1140; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.04 (S, 1H, β-NH), 9.90 (s, 1H, α-NH), 8.51 (d, *J* = 2.5 Hz, 1H, P2), 7.88 (d, *J* = 8.9 Hz, 2H, C2', 6'), 7.79 (dd, *J* = 6.8, 2.3 Hz, 1H, C2''), 7.60 (d, *J* = 8.9 Hz, 2H, C3', 5'), 7.50 (d, *J* = 1.9 Hz, 1H, C2), 7.46 (dd, *J* = 8.3, 1.9 Hz, 1H, C6), 7.42 (d, *J* = 5.6 Hz, 2H, C5'', 6''), 7.03 (d, *J* = 8.4 Hz, 1H, C5), 7.00 (d, *J* = 2.5 Hz, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.50, 154.71 (d, *J* = 244.3 Hz), 152.35, 149.40 (d, *J* = 1.9 Hz), 137.46, 137.16 (d, *J* = 3.2 Hz), 136.92, 129.55, 126.66, 126.41, 126.07, 125.42, 125.21 (d, *J* = 6.8 Hz), 119.18 (d, *J* = 18.5 Hz), 118.81, 118.57, 116.95 (d, *J* = 21.9 Hz), 112.39, 109.48, 105.54, 56.02; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{21}ClFN_4O_2S$ 483.1057; observed 483.1029

1-(3,5-Bis(trifluoromethyl)phenyl)-3-(4-(3-(3,4-dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)thiourea(6t)

white solid, yield 85 %, mp: 166-168 ºC; FT-IR (cm^{-1}): 3276, 3190, 3015, 2937, 1610, 1550, 1517, 1468, 1274, 1133; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.40 (s, 1H, β-NH), 10.26 (s, 1H, α-NH), 8.53 (d, *J* = 1.8 Hz, 1H, P2), 8.29 (s, 2H, C2'', 6''), 7.92 (d, *J* = 8.6 Hz, 2H, C2', 6'), 7.82 (s, 1H, C4''), 7.60 (d, *J* = 8.5 Hz, 2H, C3', 5'), 7.50 (s, 1H, C2), 7.47 (d, *J* = 8.2 Hz, 1H, C6), 7.04 (d, *J* = 8.4 Hz, 1H, C5), 7.01 (d, *J* = 1.9 Hz, 1H, C2), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 180.36, 152.44, 149.42, 142.31, 137.30, 136.90, 130.49(dd, *J* = 33.0 Hz), 129.61, 126.03, 125.68, 124.82, 124.06,(dd, *J* = 7.5, 5.1 Hz), 122.65, 119.00, 118.59, 117.41 (dd, *J* = 8.1, 5.6 Hz), 112.37, 109.47, 105.62, 56.00; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{26}H_{21}F_6N_4O_2S$ 567.1289; observed 567.1276

1-(3,4-Dichlorophenyl)-3-(4-(3-(3,4-dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)urea(7a)

White solid, yield 90 %, mp: 198-200 ºC; FT-IR (cm^{-1}): 3362, 3280, 3060, 3004, 2832, 1602, 1558, 1513, 1218; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.03 (s, 1H, β-NH), 8.96 (s, 1H, α-NH), 8.44 (d, *J* = 2.5 Hz, 1H, P2), 7.91 (d, *J* = 2.4 Hz, 1H, C2''), 7.83 (d, *J* = 9.0 Hz, 2H, C2', 6'), 7.60 (d, *J* =

8.9 Hz, 2H, C3', 5'), 7.54 (d, *J* = 8.8 Hz, 1H, C5''), 7.49 (d, *J* = 1.8 Hz, 1H, C6), 7.45 (dd, *J* = 8.3, 1.9 Hz, 1H, C2), 7.36 (dd, *J* = 8.8, 2.5 Hz, 1H, C6''), 7.03 (d, *J* = 8.4 Hz, 1H, C5), 6.96 (d, *J* = 2.5 Hz, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.79, 152.05, 149.39, 149.30, 140.41, 137.84, 134.99, 131.51, 131.06, 129.32, 126.20, 123.63, 119.83, 119.71, 119.30, 118.90, 118.50, 112.37, 109.44, 105.23, 56.02, 56.00; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{22}Cl_2N_4O_3$ 483.0990; observed 483.0978

1-(4-(3-(3,4-Dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)-3-(3-(trifluoromethyl)phenyl)urea(7b)

Off-white solid, yield 85 %, mp: 186-188 ºC; FT-IR (cm^{-1}): 3302, 3060, 2955, 1666, 1602, 1558, 1517, 1218, 1025; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.10 (s, 1H, β-NH), 8.97 (s, 1H, α-NH), 8.46 (d, *J* = 2.4 Hz, 1H, P2), 8.05 (s, 1H, C2''), 7.83 (d, *J* = 8.9 Hz, 2H, C2', 6'), 7.62 (d, *J* = 8.9 Hz, 2H, C3', 5'), 7.60 (s, 1H, C6''), 7.53 (t, *J* = 7.9 Hz, 1H, C5''), 7.49 (d, *J* = 1.8 Hz, 1H, C6'), 7.46 (dd, *J* = 8.3, 1.8 Hz, 1H, C2), 7.33 (d, *J* = 7.6 Hz, 1H, C4''), 7.03 (d, *J* = 8.4 Hz, 1H, C5), 6.97 (d, *J* = 2.4 Hz, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.80 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.98, 152.04, 149.40, 149.30, 141.03, 137.93, 134.96, 130.40, 130.01 (q, *J* = 31.6 Hz), 129.32, 126.21, 124.70 (q, *J* = 272.6 Hz) 122.38, 119.68, 119.31, 118.60 (q, *J* = 3.8 Hz), 118.50, 114.65 (q, *J* = 3.6 Hz). 112.37, 109.45, 105.23, 56.02, 56.00; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{25}H_{22}F_3N_4O_3$ 483.1644; observed 483.1631.

1-(4-(3-(3,4-Dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)-3-(o-tolyl)urea(7c)

Off-white solid, yield 89 %, mp: 219-221 ºC; FT-IR (cm^{-1}): 3306, 3145, 3071, 2832, 1643, 1558, 1517, 1420, 1252, 1218; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.19 (s, 1H, β-NH), 8.44 (s, 1H, α-NH), 7.97 (s, 1H, P2), 7.87 (d, *J* = 7.6 Hz, 1H, C6''), 7.83 (d, *J* = 7.9 Hz, 2H, C2', 6'), 7.62 (d, *J* = 7.9 Hz, 2H, C3', 5'), 7.50 (s, 1H, C2), 7.46 (d, *J* = 7.5 Hz, 1H, C6), 7.26 – 7.11 (m, 2H, C3'', 5''), 7.03 (d, *J* = 7.9 Hz, 1H, C5), 6.97 (s, 2H, P1, C4''), 3.87 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3), 2.27 (s, 3H, C2''-CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.13, 151.99, 149.43, 149.32, 138.51, 137.81, 134.61, 130.68, 129.24, 128.11, 126.65, 126.28, 123.25, 121.63, 119.39, 119.13, 118.51, 112.43, 109.50, 105.16, 56.04, 56.03, 18.35; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{25}H_{25}N_4O_3$ 429.1926; observed 429.1917

N-((4-(3-(3,4-Dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)carbamoyl)benzenesulfonamide(7d)

Off-white solid, yield 85 %, mp: 193-195 ºC; FT-IR (cm^{-1}): 3324, 3235, 3000, 1651, 1520, 1453, 1252, 1155, 1021; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.81 (s, 1H, α-NH), 9.04 (s, 1H, β-NH), 8.44 (d, *J* = 2.4 Hz, 1H, P2), 8.00 (d, *J* = 7.5 Hz, 2H, C2'', 6''), 7.80 (d, *J* = 8.9 Hz, 2H, C2', 6'), 7.72 (t, *J* = 7.4 Hz, 1H, C4''), 7.66 (t, *J* = 7.6 Hz, 2H, C3'', 5''), 7.49 (s, 1H, C6), 7.47 (s, 2H, C3', 5'), 7.44 (dd, *J* = 8.4, 1.8 Hz, 1H, C2), 7.02 (d, *J* = 8.3 Hz, 1H, C5), 6.96 (d, *J* = 2.4 Hz, 1H, P1), 3.85 (s, 3H, C3-OCH_3), 3.80 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.18, 149.32, 149.02, 147.76, 132.32, 130.26, 129.43, 128.88, 126.54, 126.02, 120.38, 118.29, 114.53, 112.35, 109.27, 104.36, 55.97; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{23}N_4O_5S$ 479.1389; observed 479.1374

1-(4-(3-(3,4-Dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)-3-(2-methoxyphenyl)urea(7e)

Off-white solid, yield 90 %, mp: 131-133 ºC; FT-IR (cm^{-1}): 3298, 3131, 3078, 2832, 1643, 1595, 1528, 1256, 1218; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.48 (s, 1H, α-NH), 8.44 (d, *J* = 2.4 Hz, 1H, P2), 8.27 (s, 1H, β-NH), 8.16 (dd, *J* = 7.9, 1.4 Hz, 1H, C6''), 7.82 (d, *J* = 8.9 Hz, 2H, C2', 6'), 7.59 (d, *J* = 8.9 Hz, 2H, C3', 5'), 7.49 (d, *J* = 1.8 Hz, 1H, C6), 7.45 (dd, *J* = 8.3, 1.8 Hz, 1H, C2), 7.06 – 7.01 (m, 2H, C4'', C5''), 6.99 – 6.95 (m, 2H, C5, C3''), 6.92 (dd, *J* = 11.0, 4.3 Hz, 1H, P1), 3.90 (s, 3H, C2''-OCH_3), 3.86 (s, 3H, C4-OCH_3), 3.81 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.83, 151.98, 149.39, 149.28, 148.13, 138.44, 134.61, 129.25, 129.06, 126.23, 122.35, 121.04, 119.40, 119.01, 118.78, 118.48, 112.36, 111.21, 109.41, 105.17, 56.25, 56.01, 55.99; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{25}H_{25}N_4O_4$ 445.1875; observed 445.1865.

1-Benzyl-3-(4-(3-(3,4-dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)urea(7f)

Beige solid, yield 85 %, mp: 175-177 ºC; FT-IR (cm^{-1}): 3369, 3309, 3198, 2937, 1646, 1606, 1554, 1517, 1218; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.78 (s, 1H, α-NH), 8.40 (d, *J* = 2.4 Hz, 1H, P2), 7.75 (d, *J* = 8.9 Hz, 2H, C2', 6'), 7.54 (d, *J* = 8.9 Hz, 2H, C3', 5'), 7.48 (d, *J* = 1.8 Hz, 1H, C6), 7.44 (dd, *J* = 8.3, 1.8 Hz, 1H, C2), 7.38 – 7.30 (m, 4H, C2'', 3'', 5'', 6''), 7.25 (t, *J* = 9.2, 4.4 Hz, 1H, C4''), 7.02 (d, *J* = 8.4 Hz, 1H, C5), 6.94 (d, *J* = 2.4 Hz, 1H, P1), 6.70 (t, *J* = 5.9 Hz, 1H, β-NH), 4.33 (d, *J* = 5.8 Hz, 2H, CH_2), 3.85 (s, 3H, C3-OCH_3), 3.80 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz,

DMSO-d_6) δ 155.67, 151.86, 149.38, 149.25, 140.80, 139.15, 134.13, 129.19, 128.79, 127.59, 127.20, 126.28, 119.27, 118.75, 118.45, 112.37, 109.43, 105.06, 56.01, 56.00, 43.22; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{25}H_{25}N_4O_3$ 429.1926; observed 429.1921

1-(3-Chloro-4-methylphenyl)-3-(4-(3-(3,4-dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)urea(7g)

white solid, yield 90 %, mp: 229-231 ºC; FT-IR (cm^{-1}): 3347, 3287, 3142, 2959, 1651, 1610, 1517, 1431, 1244; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.72 (s, 1H, β-NH), 8.66 (s, 1H, α-NH), 8.27 (d, *J* = 1.6 Hz, 1H, P2), 7.65 (d, *J* = 8.4 Hz, 2H, C2', 6'), 7.55 (s, 1H, C2''), 7.43 (d, *J* = 8.4 Hz, 2H, C3', 5'), 7.32 (s, 1H, C2), 7.29 (d, *J* = 6.8 Hz, 1H, C6), 7.13 – 7.01 (m, 2H, C5'', 6''), 6.86 (d, *J* = 8.1 Hz, 1H, C5), 6.80 (d, *J* = 1.6 Hz, 1H, P1), 3.69 (s, 3H, C3-OCH_3), 3.64 (s, 3H, C4-OCH_3), 2.11 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.90, 152.01, 149.39, 149.29, 139.31, 138.11, 134.81, 133.60, 131.66, 129.29, 128.78, 126.22, 119.50, 119.31, 118.66, 118.49, 117.51, 112.36, 109.43, 105.20, 56.02, 56.00, 19.29; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{25}H_{24}ClN_4O_3$ 463.1536; observed 463.1522

1-(2,4-Dichlorophenyl)-3-(4-(3-(3,4-dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)urea(7h)

Off-white solid, yield 88 %, mp: 126-128 ºC; FT-IR (cm^{-1}): 3280, 2989, 2932, 1714, 1640, 1584, 1517, 1222; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.61 (s, 1H, β-NH), 8.44 (d, *J* = 11.0 Hz, 2H, α-NH, C3''), 8.23 (d, *J* = 8.9 Hz, 1H, P2), 7.85 (d, *J* = 8.5 Hz, 2H, C2', 6'), 7.65 (s, 1H, C5''), 7.60 (d, *J* = 8.5 Hz, 2H, C3', 5'), 7.49 (s, 1H, C6), 7.43 (dd, *J* = 21.3, 8.2 Hz, 2H, C6'', C6), 7.03 (d, *J* = 8.2 Hz, 1H, C5), 6.97 (s, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.45, 152.07, 149.38, 149.29, 138.40, 137.78, 135.03, 132.09, 129.30, 128.62, 126.17, 124.11, 120.85, 120.13, 119.47, 119.40, 118.51, 112.34, 109.39, 105.25, 56.00, 55.98; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{22}Cl_2N_4O_3$ 483.0990; observed 483.0966

1-(4-(3-(3,4-Dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)-3-(3-fluorophenyl)urea(7i)

white solid, yield 88 %, mp: 216-218 ºC; FT-IR (cm^{-1}): 3302, 3078, 1647, 1550, 1513, 1215, 1140, 1025; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.95 (s, 1H, β-NH), 8.91 (s, 1H, α-NH), 8.45 (d, *J* = 2.5 Hz, 1H, P2), 7.83 (d, *J* = 8.9 Hz, 2H, C2', 6'), 7.60 (d, *J* = 8.9 Hz, 2H, C3', 5'), 7.55 – 7.50 (m, 1H, C2''), 7.49 (d, *J* = 1.8 Hz, 1H, C6), 7.45 (dd, *J* = 8.3, 1.9 Hz, 1H, C2), 7.32 (dd, *J* = 15.2,

8.1 Hz, 1H, C5''), 7.15 (dd, *J* = 8.2, 1.1 Hz, 1H, C6''), 7.03 (d, *J* = 8.4 Hz, 1H, C5), 6.97 (d, *J* = 2.5 Hz, 1H, P1), 6.80 (td, *J* = 8.5, 2.5 Hz, 1H, C4''), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.88 (d, *J* = 240.7 Hz), 152.86, 152.03, 149.39, 149.29, 142.00 (d, *J* = 11.4 Hz), 138.00, 134.88, 130.81 (d, *J* = 9.8 Hz),, 129.31, 126.20, 119.57, 119.33, 118.50, 114.47 (d, *J* = 1.9 Hz), 112.37, 109.43, 108.68 (d, *J* = 21.0 Hz), 105.40 (d, *J* = 26.6 Hz), 105.21, 56.01, 55.99; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{22}FN_4O_3$ 433.1675; observed 433.1669

1-(2,4-Difluorophenyl)-3-(4-(3-(3,4-dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)urea(7j)

Off-white solid, yield 85 %, mp: 215-217 ºC; FT-IR (cm^{-1}): 3309, 3250, 3078, 2840, 1640, 1558, 1513, 1423, 1271, 1144; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.18 (s, 1H, β-NH), 8.54 (d, *J* = 1.9 Hz, 1H, α-NH), 8.45 (d, *J* = 2.5 Hz, 1H, P2), 8.11 (td, *J* = 9.2, 6.2 Hz, 1H, C6''), 7.83 (d, *J* = 9.0 Hz, 2H, C2', 6'), 7.59 (d, *J* = 9.0 Hz, 2H, C3', 5'), 7.49 (d, *J* = 1.9 Hz, 1H, C6), 7.45 (dd, *J* = 8.3, 1.9 Hz, 1H, C2), 7.34 (ddd, *J* = 11.6, 8.9, 2.9 Hz, 1H, C5''), 7.07 (ddd, *J* = 8.4, 2.7, 1.4 Hz, 1H, C3''), 7.03 (d, *J* = 8.4 Hz, 1H, C5), 6.97 (d, *J* = 2.5 Hz, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.80 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.35 (dd, *J* = 241.4, 11.5 Hz), 152.78, 152.73 (dd, *J* = 245.0, 12.3 Hz), 152.03, 149.39, 149.30, 137.99, 134.87, 129.29, 126.21, 124.48 (dd, *J* = 10.9, 3.4 Hz), 122.57 (dd, *J* = 8.8, 2.4 Hz), 119.37, 119.30, 118.49, 112.36, 111.53 (dd, *J* = 21.6, 3.2 Hz), 109.43, 105.21, 104.27 (dd, *J* = 26.4, 24.0 Hz).56.01, 55.99; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{21}F_2N_4O_3$ 451.1581; observed 451.1567

1-(4-(3-(3,4-Dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)-3-(2,6-dimethylphenyl)urea(7k)

White solid, yield 90 %, mp: 235-237 ºC; FT-IR (cm^{-1}): 3332, 3268, 3008, 2832, 1647, 1550, 1509, 1259, 1218, 1025; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.92 (s, 1H, β-NH), 8.43 (d, *J* = 2.4 Hz, 1H, α-NH), 7.82 – 7.75 (m, 3H, P2, C2', 6'), 7.60 (d, *J* = 8.9 Hz, 2H, C3', 5'), 7.49 (d, *J* = 1.5 Hz, 1H, C6), 7.45 (dd, *J* = 8.3, 1.7 Hz, 1H, C2), 7.12 – 7.05 (m, 3H, C3'',4'', 5''), 7.02 (d, *J* = 8.4 Hz, 1H, C5), 6.96 (d, *J* = 2.4 Hz, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.80 (s, 3H, C4-OCH_3), 2.22 (d, *J* = 12.8 Hz, 6H, $(CH_3)_2$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.59, 151.90, 149.39, 149.27, 138.97, 136.06, 135.75, 134.33, 129.20, 128.21, 126.47, 126.26, 119.24, 118.99, 118.47, 112.37, 109.43, 105.10, 56.02, 56.00, 18.76; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{26}H_{27}N_4O_3$ 443.2083; observed 443.2075

1-(3-Chlorophenyl)-3-(4-(3-(3,4-dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)urea(7l)

white solid, yield 85 %, mp: 203-205 ºC; FT-IR (cm^{-1}): 33.03, 3231, 3000, 1643, 1550, 1510, 1214, 1122, 1025; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.94 (s, 1H, α-NH), 8.93 (s, 1H, β-NH), 8.45 (d, *J* = 2.5 Hz, 1H, P2), 7.83 (d, *J* = 8.9 Hz, 2H, C2', 6'), 7.74 (t, *J* = 1.8 Hz, 1H, C5''), 7.60 (d, *J* = 8.9 Hz, 2H, C3', 5'), 7.49 (d, *J* = 1.8 Hz, 1H, C6), 7.45 (dd, *J* = 8.3, 1.8 Hz, 1H, C2), 7.35 – 7.27 (m, 2H, C2'', 6''), 7.06 – 7.01 (m, 2H, C5, C4''), 6.97 (d, *J* = 2.4 Hz, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.85, 152.03, 149.38, 149.29, 141.68, 137.98, 134.90, 133.68, 130.89, 129.31, 126.19, 122.00, 119.59, 119.32, 118.50, 118.10, 117.20, 112.37, 109.43, 105.22, 56.02, 56.00; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{22}ClN_4O_3$ 449.1380; observed 449.1367

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-(3-(3,4-dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)urea(7m)

Off-white solid, yield 90 %, mp: 150-152 ºC; FT-IR (cm^{-1}): 3287, 3000, 2929, 2832, 1736, 1640, 1554, 1513, 1218, 1118; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (s, 1H, β-NH), 9.02 (s, 1H, α-NH), 8.46 (d, *J* = 2.5 Hz, 1H, P2), 8.14 (d, *J* = 2.4 Hz, 1H, C2''), 7.83 (d, *J* = 8.9 Hz, 2H, C2', 6'), 7.67 (dd, *J* = 8.8, 2.4 Hz, 1H, C5''), 7.62 (t, *J* = 8.7 Hz, 3H, C3', 5', 6''), 7.49 (d, *J* = 1.8 Hz, 1H, C6), 7.45 (dd, *J* = 8.3, 1.8 Hz, 1H, C2), 7.03 (d, *J* = 8.4 Hz, 1H, C5), 6.97 (d, *J* = 2.4 Hz, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.80 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.88, 152.06, 149.39, 149.30, 138.78 (q, *J* = 255.0 Hz), 135.06, 132.47, 129.32, 127.19 (q, *J* = 30.5 Hz) 126.19, 124.39, 123.59, 122.82, 122.22, 119.84, 119.29, 118.50, 117.29 (q, *J* = 5.4 Hz), 112.35, 109.45, 105.23, 56.01, 55.98; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{25}H_{21}ClF_3N_4O_3$ 517.1254; observed 517.1243

1-(2,5-Dichlorophenyl)-3-(4-(3-(3,4-dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)urea(7n)

Pale yellow solid, yield 90 %, mp: 228-230 ºC; FT-IR (cm^{-1}): 3466, 3261, 3063, 1647, 1587, 1517, 1420, 1256, 1218; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.69 (d, *J* = 5.7 Hz, 1H, β-NH), 8.50 (s, 1H, α-NH), 8.47 (d, *J* = 2.5 Hz, 1H, P2), 8.36 (d, *J* = 2.5 Hz, 1H, C6''), 7.86 (d, *J* = 9.0 Hz, 2H, C2', 6'), 7.61 (d, *J* = 9.0 Hz, 2H, C3', 5'), 7.52 (d, *J* = 8.6 Hz, 1H, C4''), 7.50 (d, *J* = 1.9 Hz, 1H, C6), 7.46 (dd, *J* = 8.3, 1.9 Hz, 1H, C2), 7.11 (dd, *J* = 8.6, 2.5 Hz, 1H, C3''), 7.03 (d, *J* = 8.4 Hz, 1H, C5), 6.97 (d, *J* = 2.5 Hz, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3); ^{13}C NMR

(125 MHz, DMSO-d_6) δ 152.37, 152.08, 149.40, 149.31, 137.67, 137.61, 135.12, 132.42, 131.01, 129.32, 126.18, 123.17,120.56, 120.43, 119.52, 119.38,118.51, 112.37, 109.43, 105.28, 56.02, 56.00; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{21}Cl_2N_4O_3$ 483.0990; observed 483.0971

1-(2,3-Dichlorophenyl)-3-(4-(3-(3,4-dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)urea(7o)

Beige msolid, yield 90 %, mp: 211-213 ºC; FT-IR (cm^{-1}): 3309, 3063, 2933, 2832, 1658, 1587, 1517, 1416, 1218, 1029; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.65 (s, 1H, β-NH), 8.52 (s, 1H, α-NH), 8.46 (d, *J* = 2.5 Hz, 1H, P2), 8.20 (dd, *J* = 8.1, 1.5 Hz, 1H, C6''), 7.85 (d, *J* = 8.9 Hz, 2H, C2', 6'), 7.61 (d, *J* = 8.9 Hz, 2H, C3', 5'), 7.49 (d, *J* = 1.8 Hz, 1H, C6), 7.45 (dd, *J* = 8.3, 1.9 Hz, 1H, C2), 7.35 (t, 1H, C5''), 7.31 (dd, *J* = 8.0, 1.6 Hz, 1H, C4''), 7.03 (d, *J* = 8.4 Hz, 1H, C5), 6.97 (d, *J* = 2.5 Hz, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.80 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.43, 152.06 , 149.38, 149.29, 138.42 , 137.78 , 135.03, 132.09 , 129.30, 128.63, 126.17, 124.09, 120.81, 120.09, 119.46, 119.39, 118.50, 112.33, 109.39, 105.25, 56.00, 55.98; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{21}Cl_2N_4O_3$ 483.0990; observed 483.0969.

1-(4-(3-(3,4-Dimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)-3-phenylurea(7p)

Off-white solid, yield 85 %, mp: 230-232 ºC; FT-IR (cm^{-1}): 3298, 3004, 2933, 2840, 1647, 1550, 1513, 1136, 1025; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.83 (s, 1H, β-NH), 8.70 (s, 1H, α-NH), 8.44 (d, *J* = 2.5 Hz, 1H, P2), 7.81 (d, *J* = 9.0 Hz, 2H, C2', 6'), 7.60 (d, *J* = 9.0 Hz, 2H, C3', 5'), 7.49 (d, *J* = 1.9 Hz, 2H, C2'', 6''), 7.47 (s, 1H, C6), 7.45 (dd, *J* = 8.3, 2.0 Hz, 1H, C2), 7.33 – 7.27 (m, 2H, C3'', 5''), 7.03 (d, *J* = 8.4 Hz, 1H, C5), 6.99 (t, *J* = 7.4 Hz, 1H, C4''), 6.96 (d, *J* = 2.5 Hz, 1H, P1), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.00, 151.98, 149.39, 149.28, 140.10, 138.32, 134.68, 129.28, 126.23, 122.38, 119.34, 118.75, 118.48, 112.37, 109.43, 105.17, 56.01, 56.00; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{23}N_4O_3$ 415.1770; observed 415.1765.

1-(3,4-Dichlorophenyl)-3-(4-(3-(naphthalen-2-yl)-1H-pyrazol-1-yl)phenyl)urea(8a)

Brown solid, yield 90 %, mp: 210-212 ºC; FT-IR (cm^{-1}): 3295, 2922, 2855, 1720, 1640, 1580, 1543, 1472, 1226, 1125; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.06 (s, 1H, β-NH), 9.01 (s, 1H, α-NH), 8.54 (d, *J* = 2.4 Hz, 1H, P2), 8.46 (s, 1H, C1), 8.14 (dd, *J* = 8.5, 1.2 Hz, 1H, C5), 8.00 (d, *J* = 8.2 Hz, 2H, C4, 8), 7.94 (d, *J* = 8.3 Hz, 1H, C3), 7.93 (d, *J* = 2.5 Hz, 1H, C2''), 7.89 (d, *J* = 8.9 Hz,

2H, C2', 6'), 7.64 (d, *J* = 8.9 Hz, 2H, C3', 5'), 7.58 – 7.49 (m, 3H, C 6, 7, 5''), 7.38 (dd, *J* = 8.8, 2.3 Hz, 1H, C6''), 7.18 (d, *J* = 2.4 Hz, 1H, P1); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.79, 151.91, 140.39, 138.10, 134.92, 133.68, 133.16, 131.53, 131.06, 130.78, 129.70, 128.74, 128.52, 128.14, 126.96, 126.54, 124.33, 124.28, 123.66, 119.85, 119.72, 119.48, 118.91, 105.86; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{26}H_{19}Cl_2N_4O$ 473.0935; observed 473.0929.

1-(3,4-Dichlorophenyl)-3-(4-(3-(pyridin-3-yl)-1H-pyrazol-1-yl)phenyl)urea(8b)

Beige solid, yield 85 %, mp: 257-258 ºC; FT-IR (cm^{-1}): 3339, 3287, 3037, 1710, 1595, 1546, 1513, 1185; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.14 (s, 1H, α-NH), 9.05 (s, 1H, β-NH), 9.00 (s, 1H, C2), 8.56 (d, *J* = 4.1 Hz, 1H, P2), 8.54 (s, 1H, C6), 8.28 (d, *J* = 7.7 Hz, 1H, C4), 7.91 (s, 1H, C2''), 7.85 (d, *J* = 8.6 Hz, 2H, C2', 6'), 7.62 (d, *J* = 8.6 Hz, 2H, C3', 5'), 7.53 (d, *J* = 8.7 Hz, 1H, C5''), 7.49 (t, *J* = 7.5, 4.9 Hz, 1H, C5), 7.36 (d, *J* = 7.1 Hz, 1H, C2''), 7.14 (d, *J* = 1.7 Hz, 1H, P1); 13C NMR (125 MHz, DMSO-d_6) δ 152.77, 149.36, 149.30, 147.14, 140.37, 138.29, 134.73, 133.00, 131.53, 131.04, 129.84, 129.05, 124.34, 123.68, 119.85, 119.68, 119.60, 118.90, 105.89; HRMS-QTOF (ESI): m/z calcd. for [M+H]+ $C_{21}H_{16}Cl_2N_5O$ 424.0731; observed 424.0730.

1-(4-(3-(4-Chlorophenyl)-1H-pyrazol-1-yl)phenyl)-3-(3,4-dichlorophenyl)urea(8c)

White solid, yield 90 %, mp: 249-251 ºC; FT-IR (cm^{-1}): 3280, 3082, 2922, 1617, 1584, 1517, 1468, 1304, 1248, 1121; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.04 (s, 1H, β-NH), 8.98 (s, 1H, α-NH), 8.50 (d, *J* = 2.5 Hz, 1H, P2), 7.95 (d, *J* = 8.6 Hz, 2H, C2, 6), 7.91 (d, *J* = 2.4 Hz, 1H, C2''), 7.84 (d, *J* = 9.0 Hz, 2H, C2', 6'), 7.61 (d, *J* = 9.0 Hz, 2H, C3', 5'), 7.53 (t, *J* = 8.9 Hz, 3H, C3, 5, 5''), 7.36 (dd, *J* = 8.8, 2.5 Hz, 1H, C6''), 7.05 (d, *J* = 2.5 Hz, 1H, P1); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.77, 150.81, 140.37, 138.17, 134.79, 132.87, 132.18, 131.52, 131.05, 129.75, 129.24, 127.54, 123.66, 119.85, 119.68, 119.49, 118.90, 105.69; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{22}H_{16}Cl_3N_4O$ 457.0389; observed 457.0380

1-(3,4-Dichlorophenyl)-3-(4-(3-(4-methoxyphenyl)-1H-pyrazol-1-yl)phenyl)urea(8d)

Off-white solid, yield 88 %, mp: 224-226 ºC; FT-IR (cm^{-1}): 3268, 3442, 3086, 1640, 1558, 1468, 1379, 1129, 1025; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.03 (s, 1H, β-NH), 8.96 (s, 1H, α-NH), 8.44 (d, *J* = 2.0 Hz, 1H, P2), 7.91 (d, *J* = 1.9 Hz, C2''), 7.85 (d, *J* = 8.6 Hz, 2H, C2', 6'), 7.82 (d, *J* = 8.8 Hz, 2H, C2, 6), 7.60 (d, *J* = 8.7 Hz, 2H, C3', 5'), 7.53 (d, *J* = 8.8 Hz, 1H, C5''), 7.36 (dd,

J = 8.7, 2.0 Hz, 1H, C6''), 7.02 (d, *J* = 8.6 Hz, 2H, C3, 5), 6.92 (d, *J* = 2.0 Hz, 1H, P1), 3.81 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.61, 152.78, 151.87, 140.40, 137.84, 135.00, 131.53, 131.03, 129.30, 127.19, 125.95, 123.64, 119.83, 119.71, 119.25, 118.88, 114.58, 104.99, 55.59; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{23}H_{19}Cl_2N_4O_2$ 453.0885; observed 453.0874

1-(3,4-Dichlorophenyl)-3-(4-(3-(p-tolyl)-1H-pyrazol-1-yl)phenyl)urea(8e)

White solid, yield 87 %, mp: 241-243 ºC; FT-IR (cm^{-1}): 3373, 3302, 3276, 1635, 1576, 1550, 1472, 1379, 1230, 1125; ^1H NMR (500 MHz, DMSO-d_6) δ 9.03 (s, 1H, β-NH), 8.96 (s, 1H, α-NH), 8.46 (d, *J* = 2.5 Hz, 1H, P2), 7.91 (d, *J* = 2.5 Hz, 1H, C2''), 7.85 – 7.80 (m, 4H, C2', 6', 2, 6), 7.62 – 7.58 (m, 2H, C3', 5'), 7.54 (d, *J* = 8.8 Hz, 1H, C5''), 7.36 (dd, *J* = 8.8, 2.5 Hz, 1H, C6''), 7.27 (d, *J* = 7.9 Hz, 2H, C3, 5), 6.97 (d, *J* = 2.5 Hz, 1H, P1), 2.36 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.78, 152.02, 140.40, 137.94, 137.67, 134.99, 131.53, 131.03, 130.56, 129.75, 129.35, 125.79, 123.67, 119.87, 119.72, 119.35, 118.90, 105.26, 21.32; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{23}H_{19}Cl_2N_4O$ 437.0936; observed 437.0929

1-(3,4-Dichlorophenyl)-3-(4-(3-(2,4-dichlorophenyl)-1H-pyrazol-1-yl)phenyl)urea(8f)

White solid, yield 90 %, mp: 249-251 ºC; FT-IR (cm^{-1}): 3295, 3082, 2661, 1722, 1640, 1550, 1472, 1230, 1043; ^1H NMR (500 MHz, DMSO-d_6) δ 9.05 (s, 1H, β-NH), 9.01 (s, 1H, α-NH), 8.55 (d, *J* = 2.1 Hz, 1H, P2), 7.94 (d, *J* = 8.4 Hz, 1H, C6), 7.91 (d, *J* = 2.1 Hz, 1H, C2''), 7.84 (d, *J* = 8.8 Hz, 2H, C2', 6'), 7.75 (d, *J* = 1.5 Hz, 1H, C3), 7.61 (d, *J* = 8.8 Hz, 2H, C3', 5'), 7.54 (d, *J* = 8.7 Hz, 2H, C5, 5''), 7.36 (dd, *J* = 8.8, 2.1 Hz, 1H, C6''), 7.02 (d, *J* = 2.2 Hz, 1H, P1); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.76, 148.59, 140.36, 138.41, 134.62, 133.58, 132.48, 132.19, 131.52, 131.06, 131.04, 130.22, 129.02, 128.09, 123.69, 119.87, 119.74, 119.68, 118.92, 108.93; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{22}H_{15}Cl_4N_4O$ 492.9970; observed 492.9964

1-(3,4-Dichlorophenyl)-3-(4-(3-(3,4,5-trimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)urea(8g)

Beige solid, yield 85 %, mp: 175-177 ºC; FT-IR (cm^{-1}): 3280, 3082, 2922, 2851, 2370, 1617, 1517, 1304, 1248, 1121; ^1H NMR (500 MHz, DMSO-d_6) δ 9.02 (s, 1H, β-NH), 8.97 (s, 1H, α-NH), 8.47 (s, 1H, P2), 7.91 (s, 1H, C2''), 7.84 (d, *J* = 8.1 Hz, 2H, C2', 6'), 7.61 (d, *J* = 8.1 Hz, 2H, C3', 5'), 7.54 (d, *J* = 8.6 Hz, 1H, C5''), 7.36 (d, *J* = 7.5 Hz, 1H, C6''), 7.21 (s, 2H, C2, 6), 7.05 (s, 1H, P1), 3.88 (s, 6H, C3, 5-$(OCH_3)_2$), 3.71 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ

153.67, 152.78, 152.01, 140.39, 137.97, 134.92, 131.52, 131.05, 129.42, 129.00, 123.66, 119.84, 119.70, 119.43, 118.91, 105.73, 103.31, 60.57, 56.44; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{25}H_{23}Cl_2N_4O_4$ 513.1096; observed 513.1083

1-(3,4-Dichlorophenyl)-3-(4-(3-phenyl-1H-pyrazol-1-yl)phenyl)urea(8h)

Off-white solid, yield 90 %, mp: 209-211 ºC; FT-IR (cm^{-1}): 3280, 3056, 2836, 1647, 1580, 1513, 1412, 1226, 1118; ^1H NMR (500 MHz, DMSO-d_6) δ 9.05 (s, 1H, β-NH), 8.99 (s, 1H, α-NH), 8.49 (d, *J* = 2.1 Hz, 1H, P2), 7.94 (s, 1H, C2''), 7.92 (s, 2H, C2, 6), 7.84 (d, *J* = 8.7 Hz, 2H, C2', 6'), 7.61 (d, *J* = 8.6 Hz, 2H, C3', 5'), 7.54 (d, *J* = 8.7 Hz, 1H, C5''), 7.46 (t, 2H, C3, 5), 7.37 (d, *J* = 7.1 Hz, 2H, 6'', 4), 7.03 (d, *J* = 2.1 Hz, 1H, P1); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.78, 151.95, 140.39, 138.03, 134.92, 133.29, 131.52, 131.05, 129.52, 129.20, 128.40, 125.86, 123.66, 119.84, 119.70, 119.42, 118.90, 105.52; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{22}H_{17}Cl_2N_4O$ 423.0779; observed 423.0771

1-(2,4-Difluorophenyl)-3-(4-(3-(naphthalen-2-yl)-1H-pyrazol-1-yl)phenyl)urea(9a)

Brown solid, yield 85 %, mp: 280-282 ºC; FT-IR (cm^{-1}): 3298, 3067, 1736, 1606, 1561, 1517, 1218, 1144; ^1H NMR (500 MHz, DMSO-d_6) δ 9.21 (s, 1H, β-NH), 8.56 (s, 1H, α-NH), 8.54 (d, *J* = 2.4 Hz, 1H, P2), 8.46 (s, 1H, C1), 8.17 – 8.08 (m, 2H, C6'', 5), 8.00 (d, *J* = 8.2 Hz, 2H, C4, 8), 7.94 (d, *J* = 7.7 Hz, 1H, C3), 7.89 (d, *J* = 8.9 Hz, 2H, C2', 6'), 7.63 (d, *J* = 8.9 Hz, 2H, C3', 5'), 7.58 – 7.50 (m, 2H, C7, 5''), 7.37-7.30 (m, 1H, 3''), 7.18 (d, *J* = 2.4 Hz, 1H, P1), 7.08 (t, *J* = 8.7 Hz, 1H, C6); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.36 (dd, *J* = 240.4, 11.4 Hz), 152.78, 152.77 (dd, *J* = 237.5, 7.2 Hz),151.89, 138.24, 134.81, 133.68, 133.16, 130.79, 129.68, 128.73, 128.51, 128.14, 126.95, 126.53, 124.48 (dd, *J* = 9.6, 4.0 Hz), 124.33, 124.28, 122.58 (dd, *J* = 8.5, 3.1 Hz), , 119.56, 119.31, 111.54 (dd, *J* = 21.3, 1.9 Hz), , 105.84, 104.29 (dd, *J* = 25.7, 24.5 Hz); HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{26}H_{19}F_2N_4O$ 441.1526; observed 441.1507

1-(2,4-Difluorophenyl)-3-(4-(3-(pyridin-3-yl)-1H-pyrazol-1-yl)phenyl)urea(9b)

Off-white solid, yield 85 %, mp: 269-271 ºC; FT-IR (cm^{-1}): 3295, 3149, 1710, 1654, 1610, 1543, 1517, 1312, 1185; ^1H NMR (500 MHz, DMSO-d_6) δ 9.19 (s, 1H, β-NH), 9.14 (d, *J* = 1.7 Hz, 1H, α-NH), 8.56 (dd, *J* = 4.7, 1.4 Hz, 1H, P2), 8.54 (d, *J* = 2.5 Hz, 2H, C6'', C2), 8.28 (dt, *J* = 8.0, 3.9, 2.0 Hz, 1H, C5), 8.10 (td, *J* = 9.2, 6.2 Hz, 1H, C4), 7.85 (d, *J* = 9.0 Hz, 2H, C2', 6'), 7.61 (d, *J* = 9.0 Hz, 2H, C3', 5'), 7.49 (ddd, *J* = 7.9, 4.8, 0.6 Hz, 1H, C6), 7.36-7.30 (m, 1H, C5''), 7.14

(d, *J* = 2.5 Hz, 1H, C3''), 7.10 – 7.04 (m, 1H, P1);^{13}C NMR (125 MHz, DMSO-d_6) δ 157.39 (dd, *J* = 241.3, 11.5 Hz), 152.77, 152.76 (dd, *J* = 244.9, 12.3 Hz),, 149.37, 149.29, 147.13, 138.42, 134.62, 133.01, 129.85, 129.05, 124.37, 122.62 (dd, *J* = 9.1, 2.6 Hz),, 119.69, 119.29, 111.54 (dd, *J* = 21.6, 3.3 Hz), 105.89, 104.28 (dd, *J* = 26.7, 23.9 Hz); HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{21}H_{16}F_2N_5O$ 392.1323; observed 392.1372

1-(4-(3-(4-Chlorophenyl)-1H-pyrazol-1-yl)phenyl)-3-(2,4-difluorophenyl)urea(9c)

White solid, yield 90 %, mp: 220-222 ºC; FT-IR (cm^{-1}): 3280, 3086, 2922, 1640, 1606, 1505, 1423, 1312, 1140, 1099; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.18 (s, 1H, β-NH), 8.53 (d, *J* = 1.9 Hz, 1H, α-NH), 8.49 (d, *J* = 2.5 Hz, 1H, P2), 8.14 – 8.06 (m, 1H, C6''), 7.95(d, *J* = 8.6 Hz, 2H, C2, 6), 7.83 (d, *J* = 9.0 Hz, 2H, C2', 6'), 7.60(d, *J* = 9.0 Hz, 2H, C3', 5'), 7.52 (d, *J* = 8.6 Hz, 2H, C3, 5), 7.36-7.30 (m, 1H, C5''), 7.10 – 7.06 (m, 1H, C3''), 7.05 (d, *J* = 2.5 Hz, 1H, P1); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.39 (dd, *J* = 241.2, 11.3 Hz), 152.77, 152.76 (dd, *J* = 245.0, 12.7 Hz) 151.84, 151.74, 150.81, 138.30, 134.69, 132.87, 132.19, 129.75, 129.25, 127.55, 124.43 (dd, *J* = 11.3, 3.4 Hz),, 122.63 (dd, *J* = 8.9, 2.5 Hz), 119.58, 119.30, 111.64, 111.54 (dd, *J* = 21.8, 3.2 Hz), 105.68, 104.28 (dd, *J* = 27.0, 23.8 Hz); HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{22}H_{16}ClF_2N_4O$ 425.0980; observed 425.0973

1-(2,4-Difluorophenyl)-3-(4-(3-(4-methoxyphenyl)-1H-pyrazol-1-yl)phenyl)urea(9d)

Off-white solid, yield 85 %, mp: 220-222 ºC; FT-IR (cm^{-1}): 3287, 3086, 3008, 2959, 2832, 1651, 1606, 1558, 1517, 1252, 1133; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.17 (s, 1H, β-NH), 8.54 (d, *J* = 1.7 Hz, 1H, α-NH), 8.44 (d, *J* = 5.4 Hz, 1H, P2), 8.11 (dt, *J* = 11.4, 5.7 Hz, 1H, C6''), 8.02 (dd, *J* = 7.7, 1.6 Hz, 1H, C3''), 7.84 (d, *J* = 9.0 Hz, 2H, C2', 6'), 7.60 (d, *J* = 9.0 Hz, 2H, C3', 5'), 7.37-7.30 (m, 2H, C2, 6), 7.13 (d, *J* = 8.1 Hz, 1H, C5''), 7.09 – 7.02 (m, 2H, C3, 5), 6.97 (d, *J* = 2.4 Hz, 1H, P1), 3.90 (s, 3H, OCH_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.35 (dd, *J* = 241.4, 11.6 Hz), 157.13, 152.78, 152.73 (dd, *J* = 244.7, 12.2 Hz), 148.99, 138.09, 134.87, 129.63, 128.45, 128.31, 124.49 (dd, *J* = 10.7, 3.3 Hz), 122.55 (dd, *J* = 9.0, 2.3 Hz), 121.85, 121.01, 119.47, 119.31, 112.40, 111.52 (dd, *J* = 21.9, 3.0 Hz), 109.30, 104.26 (dd, *J* = 26.6, 24.0 Hz)., 55.95; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{23}H_{19}F_2N_4O_2$ 421.1476; observed 421.1476.

1-(2,4-Difluorophenyl)-3-(4-(3-(p-tolyl)-1H-pyrazol-1-yl)phenyl)urea(9e)

Off-white solid, yield 86 %, mp: 223-225 ºC; FT-IR (cm^{-1}): 3272, 3086, 2926, 1714, 1606, 1509, 1420, 1300, 1140, 1095; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.17 (s, 1H, β-NH), 8.54 (d, *J* = 2.0 Hz, 1H, α-NH), 8.46 (d, *J* = 2.5 Hz, 1H, P2), 8.10 (td, *J* = 9.2, 6.2 Hz, 1H, C6''), 7.84-7.80 (m, 4H, C2', 6', 2, 6), 7.59 (d, *J* = 9.0 Hz, 2H, C3', 5'), 7.35-7.31 (m, 1H, C5''), 7.26 (d, *J* = 7.9 Hz, 2H, C3, 5), 7.10 – 7.04 (m, 1H, C3''), 6.97 (d, *J* = 2.5 Hz, 1H, P1), 2.36 (s, 3H, CH3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.36 (dd, *J* = 241.6, 11.7 Hz), 152.78, 152.74 (dd, *J* = 244.7, 12.3 Hz),151.99, 138.08, 137.68, 134.87, 130.56, 129.75, 129.34, 125.79, 124.48 (dd, *J* = 10.7, 3.3 Hz), 122.57 (dd, *J* = 9.0, 2.7 Hz), 119.42, 119.31, 111.52 (dd, *J* = 21.6, 3.2 Hz), 105.26, 104.26 (dd, *J* = 26.8, 24.0 Hz)., 21.32; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{23}H_{19}F_2N_4O$ 405.1527; observed 405.1520

1-(4-(3-(2,4-Dichlorophenyl)-1H-pyrazol-1-yl)phenyl)-3-(2,4-difluorophenyl)urea(9f)

White solid, yield 88 %, mp: 230-232 ºC; FT-IR (cm^{-1}): 3291, 3081, 1632, 1558, 1509, 1423, 1230, 1140, 1099, 1039; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (d, *J* = 5.0 Hz, 1H, β-NH), 8.55 (d, *J* = 1.9 Hz, 1H, α-NH), 8.54 (d, *J* = 2.5 Hz, 1H, P2), 8.14 – 8.06 (m, 1H, C6''), 7.94 (d, *J* = 8.4 Hz, 1H, C6), 7.84 (d, *J* = 9.0 Hz, 2H, C2', 6'), 7.74 (d, *J* = 2.1 Hz, 1H, C5), 7.61 (d, *J* = 9.0 Hz, 2H, C3', 5'), 7.54 (dd, *J* = 8.4, 2.1 Hz, 1H, C3), 7.36-7.30 (m, 1H, C5''), 7.10-7.04 (m, 1H, C3''), 7.02 (d, *J* = 2.5 Hz, 1H, P1); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.38 (dd, *J* = 241.7, 11.7 Hz), 152.75, 152.74 (dd, *J* = 244.8, 12.3 Hz), 148.57, 138.54, 134.50, 133.58, 132.48, 132.20, 131.06, 130.23, 129.01, 128.10, 124.44 (dd, *J* = 10.8, 3.4 Hz), 122.58 (dd, *J* = 8.9, 2.4 Hz), 119.81, 119.27, 111.53 (dd, *J* = 21.6, 3.2 Hz),, 108.93, 104.28 (dd, *J* = 26.9, 23.9 Hz); HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{22}H_{15}Cl_2F_2N_4O$ 459.0591; observed 459.0571.

1-(2,4-Difluorophenyl)-3-(4-(3-(3,4,5-trimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)urea(9g)

Off-white solid, yield 85 %, mp: 242-244 ºC; FT-IR (cm^{-1}): 3280, 3145, 3067, 2937, 2836, 1647, 1602, 1558, 1517, 1133; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.18 (s, 1H, β-NH), 8.53 (d, *J* = 1.7 Hz, 1H, α-NH), 8.47 (d, *J* = 2.5 Hz, 1H, P2), 8.10 (td, *J* = 9.2, 6.2 Hz, 1H, C6''), 7.84 (d, *J* = 9.0 Hz, 2H, C2', 6'), 7.60 (d, *J* = 9.0 Hz, 2H, C3', 5'), 7.36-7.29 (m, 1H, 5''), 7.21 (s, 2H, C2, 6), 7.10 – 7.06 (m, 1H, C3''), 7.05 (d, *J* = 2.4 Hz, 1H, P1), 3.88 (s, 6H, C3, 4-$(OCH_3)_3$), 3.71 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.36 (dd, *J* = 239.1, 9.0 Hz), 153.68, 152.79(dd, *J* = 256.6, 11.8 Hz), 152.77, 151.99, 138.13, 138.00, 134.80, 129.39, 129.01, 124.47 (dd, *J* = 10.9, 3.3 Hz), 122.59 (dd, *J* = 9.2, 1.6 Hz), 119.50, 119.29, 111.52 (dd, *J* = 21.5, 3.4 Hz),

105.70, 104.26 (dd, *J* = 26.9, 23.7 Hz), 103.33, 60.57, 56.44; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{25}H_{23}F_2N_4O_4$ 481.1687; observed 481.1725

1-(2,4-Difluorophenyl)-3-(4-(3-phenyl-1H-pyrazol-1-yl)phenyl)urea(9h)

Off-white solid, yield 88 %, mp: 264-266 ºC; FT-IR (cm^{-1}): 3276, 3093, 3000, 1643, 1514, 1233, 1140, 1096; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.19 (s, 1H, β-NH), 8.55 (s, 1H, α-NH), 8.49 (s, 1H, P2), 8.11 (s, 1H, C6''), 7.89 (d, *J* = 46.0 Hz, 4H, C2', 6', 2, 6), 7.54 (d, *J* = 72.8 Hz, 4H, C3', 5', 3, 5), 7.36 (s, 2H, C5'', C4), 7.08 (s, 1H, C3''), 7.03 (s, 1H, P1);^{13}C NMR (125 MHz, DMSO-d_6) δ 157.37 (dd, *J* = 241.6, 11.7 Hz), 152.77, 152.75 (dd, *J* = 244.8, 12.3 Hz), 151.94, 138.17, 134.82, 133.30, 129.51, 129.20, 128.40, 125.85, 124.47 (dd, *J* = 10.6, 3.5 Hz), 122.60 (dd, *J* = 8.7, 2.2 Hz), 119.50, 119.30, 111.54 (dd, *J* = 21.5, 3.2 Hz), 105.51, 104.28 (dd, *J* = 27.0, 23.8 Hz); HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{22}H_{17}F_2N_4O$ 391.1370; observed 391.1367

1-Benzyl-3-(4-(3-(naphthalen-2-yl)-1H-pyrazol-1-yl)phenyl)urea(10a)

Brown solid, yield 90 %, mp: 241-243 ºC; FT-IR (cm^{-1}): 3298, 3142, 3049, 1628, 1572, 1513, 1300, 1230, 1043; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.77 (s, 1H, β-NH), 8.51 (d, *J* = 2.5 Hz, 1H, C1), 8.45 (d, *J* = 0.8 Hz, 1H, P2), 8.12 (dd, *J* = 8.5, 1.7 Hz, 1H, C8), 8.02 – 7.98 (m, 2H, C2', 6'), 7.94 (d, *J* = 7.8 Hz, 1H, C4), 7.82 (d, *J* = 9.0 Hz, 2H, C5, 3), 7.58 (d, *J* = 9.5 Hz, 2H, C6, 7), 7.56 – 7.50 (m, 2H, C3', 5'), 7.38 – 7.31 (m, 4H, C2'', 3'', 5'', 6''), 7.28 – 7.24 (m, 1H, C4''), 7.16 (d, *J* = 2.5 Hz, 1H, P1), 6.69 (t, *J* = 6.0 Hz, 1H, α-NH), 4.34 (d, *J* = 5.9 Hz, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.67, 151.74, 140.80, 139.40, 134.10, 133.69, 133.14, 130.86, 129.58, 128.80, 128.72, 128.51, 128.14, 127.62, 127.22, 126.94, 126.50, 124.29, 124.27, 119.47, 118.80, 105.70, 43.26; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{27}H_{23}N_4O$ 419.1871; observed 419.1828

1-Benzyl-3-(4-(3-(pyridin-3-yl)-1H-pyrazol-1-yl)phenyl)urea(10b)

Off-white solid, yield 85 %, mp: 225-227 ºC; FT-IR (cm^{-1}): 3306, 3104, 3026, 2914, 1733, 1610, 1554, 1509, 1315, 1248; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.13 (d, *J* = 1.6 Hz, 1H, β-NH), 8.78 (s, 1H, C2), 8.56 (dd, *J* = 4.7, 1.5 Hz, 1H, C4), 8.51 (d, *J* = 2.5 Hz, 1H, P2), 8.27 (td, *J* = 8.0 Hz, 1H, C6), 7.79 (d, *J* = 9.0 Hz, 2H, C2', 6'), 7.57 (d, *J* = 9.0 Hz, 2H, C3', 5'), 7.51 – 7.47 (m, 1H, C5), 7.38 – 7.31 (m, 4H, C2'', 3'', 5'', 6''), 7.29 – 7.23 (m, 1H, C4''), 7.13 (d, *J* = 2.5 Hz, 1H, P1),

6.69 (t, *J* = 5.9 Hz, 1H, α-NH), 4.33 (d, *J* = 5.9 Hz, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.64, 149.32, 149.12, 147.11, 140.78, 139.57, 133.89, 132.98, 129.74, 129.11, 128.79, 127.61, 127.22, 124.35, 119.58, 118.74, 105.75, 43.24; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{22}H_{20}N_5O$ 370.1667; observed 370.1677

1-Benzyl-3-(4-(3-(4-chlorophenyl)-1H-pyrazol-1-yl)phenyl)urea(10c)

White solid, yield 88 %, mp: 243-245 ºC; FT-IR (cm^{-1}): 3302, 3149, 3063, 2922, 2657, 1644, 1602, 1561, 1230; ^1H NMR (500 MHz, DMSO-d_6) δ 8.76 (s, 1H, β-NH), 8.46 (d, *J* = 2.5 Hz, 1H, P2), 7.94 (d, *J* = 8.5 Hz, 2H, C2', 6'), 7.77 (d, *J* = 8.9 Hz, 2H, C3', 5'), 7.56 (d, *J* = 9.0 Hz, 2H, C2, 6), 7.51 (d, *J* = 8.5 Hz, 2H, C3, 5), 7.38 – 7.30 (m, 4H, C2'', 3'', 5'', 6''), 7.26 (dd, *J* = 9.3, 4.3 Hz, 1H, C4''), 7.04 (d, *J* = 2.4 Hz, 1H, P1), 6.68 (t, *J* = 5.9 Hz, 1H, α-NH), 4.33 (d, *J* = 5.9 Hz, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.64, 150.64, 140.78, 139.46, 133.95, 132.80, 132.25, 129.63, 129.23, 128.79, 127.61, 127.51, 127.21, 119.47, 118.75, 105.54, 43.24; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{23}H_{20}ClN_4O$ 403.1325; observed 403.1320

1-Benzyl-3-(4-(3-(4-methoxyphenyl)-1H-pyrazol-1-yl)phenyl)urea(10d)

Off-white solid, yield 89 %, mp: 221-223 ºC; FT-IR (cm^{-1}): 3309, 3063, 3000, 2840, 2545, 1602, 1505, 1248, 1118, 1028; ^1H NMR (500 MHz, DMSO-d_6) δ 8.73 (s, 1H, β-NH), 8.40 (d, *J* = 2.5 Hz, 1H, P2), 7.84(d, *J* = 8.9 Hz, 2H, C2', 6'), 7.75(d, *J* = 9.0 Hz, 1H, C3', 5'), 7.54(d, *J* = 9.1 Hz, 2H, C2, 6), 7.39 – 7.31 (m, 4H, C2'', 3'', 5'', 6''), 7.28 – 7.23 (m, 1H, C4''), 7.01 (d, *J* = 8.9 Hz, 2H, C3, 5), 6.91 (d, *J* = 2.5 Hz, 1H, P1), 6.67 (t, *J* = 6.0 Hz, 1H, α-NH), 4.33 (d, *J* = 5.9 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.57, 155.66, 151.69, 140.80, 139.13, 134.16, 129.20, 128.79, 127.61, 127.21, 127.15, 126.02, 119.23, 118.77, 114.57, 104.83, 55.60, 43.24; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{23}N_4O_2$ 399.1821; observed 399.1833

1-Benzyl-3-(4-(3-(p-tolyl)-1H-pyrazol-1-yl)phenyl)urea(10e)

White solid, yield 86 %, mp: 225-227 ºC; FT-IR (cm^{-1}): 3302, 1640, 1602, 1558, 1513, 1312, 1230, 1114, 1043; ^1H NMR (500 MHz, DMSO-d_6) δ 8.72 (s, 1H, β-NH), 8.42 (d, *J* = 2.5 Hz, 1H, P2), 7.81 (d, *J* = 8.1 Hz, 2H, C2', 6'), 7.75 (d, *J* = 9.0 Hz, 2H, C3', 5'), 7.55 (d, *J* = 9.1 Hz, 2H, C2, 6), 7.38 – 7.29 (m, 4H, C2'', 3'', 5'', 6''), 7.26 (m, 3H, C3, 5, 4''), 6.95 (d, *J* = 2.5 Hz, 1H, P1), 6.66 (t, *J* = 6.0 Hz, 1H, α-NH), 4.33 (d, *J* = 5.9 Hz, 2H, CH_2), 2.35 (s, 3H, CH_3); ^{13}C NMR (125

MHz, DMSO-d_6) δ 155.67, 155.67, 151.85, 140.79, 139.24, 137.61, 134.16, 130.63, 129.74, 129.24, 128.79, 128.67, 127.61, 127.61, 127.47, 127.21, 127.02, 125.77, 119.34, 118.80, 105.10, 43.27, 21.32; MS (ESI): m/z $[M+H]^+$ $C_{24}H_{23}N_4O$ 383; observed 383

1-Benzyl-3-(4-(3-(2,4-dichlorophenyl)-1H-pyrazol-1-yl)phenyl)urea(10f)

White solid, yield 90 %, mp: 224-226 ºC; FT-IR (cm^{-1}): 3302, 3063, 2926, 2877, 1632, 1554, 1513, 1304, 1230, 1125; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.77 (s, 1H, β-NH), 8.51 (d, *J* = 2.5 Hz, 1H, C6), 7.93 (d, *J* = 6.8 Hz, 1H, P2), 7.77 (d, *J* = 2.5 Hz, 2H, C2', 6') 7.74 (d, *J* = 2.2 Hz, 1H, C5), 7.56(d, *J* = 9.1 Hz, 2H, C3', 5'), 7.53 (dd, *J* = 8.5, 2.2 Hz, 1H, C3), 7.38 – 7.30 (m, 4H, C2'', 3'', 5'', 6''), 7.28 – 7.23 (m, 1H, C4''), 7.00 (d, *J* = 2.5 Hz, 1H, P1), 6.69 (t, *J* = 6.0 Hz, 1H, α-NH), 4.33 (d, *J* = 5.9 Hz, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.63, 148.40, 140.77, 139.69, 133.77, 133.52, 132.45, 132.18, 131.11, 130.21, 128.90, 128.79, 128.08, 127.61, 127.21, 119.70, 118.74, 108.80, 43.24; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{23}H_{19}Cl_2N_4O$ 437.0935; observed 437.0888

1-Benzyl-3-(4-(3-(3,4,5-trimethoxyphenyl)-1H-pyrazol-1-yl)phenyl)urea(10g)

Off-white solid, yield 85 %, mp: 191-193 ºC; FT-IR (cm^{-1}): 3302, 1662, 1710, 1513, 1466, 1353, 1215, 1121; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.75 (s, 1H, β-NH), 8.43 (d, *J* = 2.4 Hz, 1H, P2), 7.77 (d, *J* = 8.9 Hz, 2H, C2', 6'), 7.56 (d, *J* = 8.9 Hz, 2H, C3', 5'), 7.38 – 7.31 (m, 4H, C2'', 3'', 5'', 6''), 7.28 – 7.24 (m, 1H, C4''), 7.20 (s, 2H, C2, 6), 7.03 (d, *J* = 2.4 Hz, 1H, P1), 6.68 (t, *J* = 5.9 Hz, 1H, α-NH), 4.33 (d, *J* = 5.8 Hz, 2H, CH_2), 3.88 (s, 6H, C3, 5), 3.71 (s, 3H, C4); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.67, 153.67, 151.84, 140.79, 139.30, 137.90, 134.07, 129.29, 129.09, 128.79, 127.60, 127.21, 119.41, 118.76, 105.57, 103.24, 60.56, 56.40, 43.24; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{26}H_{27}N_4O_4$ 459.2032; observed 459.2031.

1-Benzyl-3-(4-(3-phenyl-1H-pyrazol-1-yl)phenyl)urea(10h)

Off-white solid, yield 90 %, mp: 212-214 ºC; FT-IR (cm^{-1}): 3306, 3063, 3034, 1632, 1558, 1513, 1308, 1218, 1125; ^{1}H NMR (500 MHz, DMSO) δ 8.75 (s, 1H, β-NH), 8.45 (d, *J* = 1.7 Hz, 1H, P2), 7.92 (d, *J* = 7.4 Hz, 2H, C2, 6), 7.77 (d, *J* = 8.7 Hz, 2H, C2', 6'), 7.56 (d, *J* = 8.7 Hz, 2H, C3', 5'), 7.45 (t, *J* = 7.5 Hz, 2H, C3, 5), 7.39 – 7.30 (m, 5H, C2'', 3'', 5'', 6'', C4''), 7.27 (t, *J* = 6.6 Hz, 1H, C4), 7.00 (d, *J* = 1.7 Hz, 1H, P1), 6.68 (t, *J* = 5.6 Hz, 1H, α-NH), 4.33 (d, *J* = 5.5 Hz, 2H, CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.65, 151.77, 140.79, 139.33, 134.08, 133.35,

129.40, 129.19, 128.79, 128.34, 127.61, 127.21, 125.83, 119.39, 118.76, 105.36, 43.24; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{23}H_{21}N_4O$ 369.1715; observed 369.1708

1.3 Synthesis of 4-(4-(3,4-Dimethoxyphenyl)-1H-1, 2, 3-triazol-1-yl) aniline, 14:

To a mixture of 3,4-Dimethoxybenzaldehyde **11** (1 equiv.) and carbon tetrabromide (2 equiv.) in dichloromethane at 0 °C was added triphenylphosphine (4 equiv.). The reaction mixture is then allowed to stir at room temperature for 1 h. Then the reaction was quenched with water (40 mL) and extracted with dichloromethane (20 mL X 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure and further purified by silica gel column chromatography eluting at EA: Hex 1:6 to afford the desired dibromo alkene in 90% yield as a colourless oil which is then used in the next step au such without any further purification. To a stirred solution of dibromo alkene (1 equiv.) in anhydrous acetonitrile was added DBU (4 equiv.) dropwise over a period of 10 min. at room temperature and continued to stir at the same temperature for 16 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was cooled to 0 °C and quenched with the 5N aqueous HCl (10 mL) and extracted with ethyl acetate (20 mL X 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain alkyne **12** in 70 % as a colourless oil. Alkyne **12** (1 equiv.) and 4-nitrophenyl azide (2 equiv.) were dissolved in a mixture of DMF: H2O (10:0.5) followed by the addition of CuSO4.5H_2O (0.2 equiv.) and sodium ascorbate (0.4 equiv.). The resulting mixture was allowed to stir for 15 h at rt. After completion of the reaction, the reaction mixture was poured into crushed ice and the precipitate formed was vacuum filtered and dried in oven to furnish crude triazole nitrophenyl intermediate **13** in 87 % yield, which is used in the next step without any further purification. Reduction of nitro intermediate was carried out according to the general procedure B, resulting in the formation of triazole aniline **14** as pale yellow solid in 75 % yield.

1.4 Synthesis of urea derivatives, 15a-c:

Intermediate **14**(synthesis detailed in supporting information) was treated according to general procedure B with isocyanates (3,4-dichlorophenyl, 2,4-difluorophenyl and benzyl) to yield the compounds **15a-c** in 90-95% yields.

1-(3,4-Dichlorophenyl)-3-(4-(4-(3,4-dimethoxyphenyl)-1H-1,2,3-triazol-1-yl)phenyl)urea(15a)

Beige solid, yield 85 %, mp: 218-220 ºC; FT-IR (cm^{-1}): 3339, 3287, 3213, 3145, 3086, 2955, 1742, 1591, 1554, 1502; ^{1}H NMR (500 MHz, DMSO) δ 9.14 (s, 1H, β-NH), 9.12 (s, 1H, α-NH), 9.09 (s, 1H, triazole), 7.92 (s, 1H, C2''), 7.86 (d, *J* = 8.3 Hz, 2H, C2', 6'), 7.71 (d, *J* = 8.3 Hz, 2H, C3', 5'), 7.54 (d, *J* = 12.1 Hz, 2H, C5'', 6''), 7.50 (d, *J* = 8.2 Hz, 1H, C6), 7.37 (d, *J* = 7.8 Hz, 1H, C2), 7.08 (d, *J* = 8.2 Hz, 1H, C5), 3.87 (s, 3H, C3-OCH_3), 3.82 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.73, 149.56, 149.34, 147.76, 140.25, 140.13, 131.64, 131.54, 131.06, 123.84, 123.59, 121.14, 119.96, 119.66, 119.09, 118.99, 118.25, 112.64, 109.53, 56.04; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{23}H_{20}Cl_2N_5O_3$ 484.0943; observed 484.0932

1-(2,4-Difluorophenyl)-3-(4-(4-(3,4-dimethoxyphenyl)-1H-1,2,3-triazol-1-yl)phenyl)urea(15b)

Off-white solid, yield 90 %, mp: 221-223 ºC; FT-IR (cm^{-1}): 3369, 3265, 3075, 2967, 2840, 1710, 1606, 1556, 1505, 1267; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.32 (s, 1H, β-NH), 9.15 (s, 1H, α-NH), 8.61 (s, 1H, triazole), 8.09 (dd, *J* = 15.3, 9.1 Hz, 1H, C2''), 7.86 (d, *J* = 8.8 Hz, 2H, C2', 6'), 7.69 (d, *J* = 8.8 Hz, 2H, C3', 5'), 7.52 (s, 1H, C5''), 7.50 (d, *J* = 8.3 Hz, 1H, C6''), 7.39 – 7.29 (m, 1H, C2), 7.08 (d, *J* = 8.2 Hz, 2H, C5, 6), 3.86 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.50 (dd, *J* = 241.7, 11.7 Hz), 152.87 (dd, *J* = 245.0, 12.3 Hz), 152.74, 149.54, 149.32, 147.76, 140.24, 131.52, 124.31 (dd, *J* = 10.8, 3.3 Hz), 123.56, 122.75 (dd, *J* = 9.0, 2.5 Hz), 121.23, 119.28, 119.11, 118.22, 112.62, 111.57 (dd, *J* = 21.7, 3.3 Hz), 109.47, 104.33 (dd, *J* = 26.9, 23.8 Hz)., 56.03; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{23}H_{20}F_2N_5O_3$ 452.1534; observed 452.1531.

1-Benzyl-3-(4-(4-(3,4-dimethoxyphenyl)-1H-1,2,3-triazol-1-yl)phenyl)urea(15c)

Beige solid, yield 88 %, mp: 230-232 ºC; FT-IR (cm^{-1}): 3332, 3149, 3060, 2933, 2836, 1636, 1602, 1502, 1215; ^{1}H NMR (500 MHz, DMSO) δ 9.12 (s, 1H, β-NH), 8.90 (s, 1H, triazole), 7.79 (d, *J* = 8.8 Hz, 2H, C2', 6'), 7.65 (d, *J* = 8.8 Hz, 2H, C3', 5'), 7.52 (s, 1H, C2), 7.49 (d, *J* = 8.2 Hz, 1H, C5), 7.40 – 7.31 (m, 4H, C2'', 3'', 5'', 6''), 7.26 (t, *J* = 6.5 Hz, 1H, C4''), 7.08 (d, *J* = 8.3 Hz, 1H, C6), 6.76 (t, *J* = 5.7 Hz, 1H, α-NH), 4.34 (d, *J* = 5.6 Hz, 2H, CH_2), 3.86 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C4-OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.56, 149.54, 149.30, 147.70, 141.36,

140.68, 130.77, 128.80, 127.62, 127.24, 123.63, 121.09, 119.05, 118.74, 118.20, 112.61, 109.48, 56.02, 43.26; HRMS-QTOF (ESI): m/z calcd. for $[M+H]^+$ $C_{24}H_{24}N_5O_3$ 430.1879; observed 430.1878.

Bacterial strains and media:

The panel of bacteria consist of *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 29213), *Klebsiella peumoniae* (BAA-1705), *Acinetobacter baumannii* (BAA 1605) and *Pseudomonas aeruginosa* (ATCC 27853). NRS 100, NRS 119, NRS 129, NRS 186, NRS 191, NRS 192, NRS 193, NRS 194, NRS 198 are MRSA strains, while VRS1, VRS4, VRS12 are VRSA strains. These strains were procured from BEI/NARSA/ATCC (Biodefense and Emerging Infections Research Resources Repository/ Network on Antimicrobial Resistance in *Staphylococcus aureus*/American Type Culture Collection, USA). These strains are usually cultivated on Mueller-Hinton Agar (MHA). A single colony was picked from the MHA plate, inoculated in Mueller-Hinton cation supplemented broth II (CA-MHB) and incubated overnight at 37 °C while shaking for 18–24 h to get the starter culture. *M. tuberculosis H37Rv* ATCC 27294 was cultured in Middlebrook 7H9 (Difco, Becton, NJ, USA) media supplemented with 10% (v/v) ADC (Bovine Serum Albumin, Dextrose, NaCl), 0.2% (v/v) glycerol and 0.05% (v/v) Tween-80 (ADC-Tween-80).

1.5 Antibiotic susceptibility testing against ESKAP (*E. coli, S. aureus*, *K. Pneuminiae*, *A. baumannii*, and *P. aeruginosa)* pathogen panel:

Antibiotic susceptibility testing was carried out on the newly synthesized compounds by determining the Minimum Inhibitory Concentration (MIC) with reference to the standard CLSI guidelines.[2, 3] MIC is defined as the minimum concentration of compound at which visible bacterial growth is inhibited. Bacterial cultures were grown in Mueller-Hinton cation-supplemented broth (CA-MHB). The Optical density (OD_{600}) of the cultures was measured, followed by dilution for ~10^6 CFU/mL. Bacterial inoculum was added into a series of test wells in a microtiter plate that contained various concentrations of the compound under test ranging from 64 to 0.25 µg/mL. Controls, i.e., cells alone and media alone (without compound and cells) and levofloxacin were used as a reference standard. Plates were incubated at 37 °C for 16-18 h, followed by observations of MIC values by the absence or

presence of visible growth. For each compound, MIC determinations were performed independently thrice using duplicate samples each time.

1.6 Antibiotic susceptibility testing against pathogenic mycobacteria:

Antimycobacterial susceptibility testing for newly synthesized compounds was carried out by REMA employing the broth dilution method.[4] A total of 10 mg/ml stock solutions of test and control compounds were prepared in DMSO and stored at −20°C. Mycobacterial cultures were inoculated in Middlebrook 7H9 enriched (Difco, Becton) media supplemented with 10% ADC-Tween-80 (bovine serum albumin, dextrose, 0.2% glycerol, and 0.05% Tween-80) and OD600 of cultures was measured, followed by dilution to achieve ∼106 CFU/ml. The final test concentration ranged from 64 to 0.03 μg/ml prepared by a two-fold serial diluted fashion from stock solution with 2.5 ml of each concentration added per well of a 96-well round bottom microtiter plate. Later, 97.5 ml of bacterial suspension was added to each well containing the test compound, along with appropriate controls. Presto blue (Thermo Fisher) resazurin-based dye was used for the visual identification of active compounds.[5] MIC of active compounds was determined as the lowest concentration of compounds that inhibited visible growth after the incubation period. The MIC results evaluated were obtained from one among the concentration of 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, and >64 mg/ml of test solution. MIC was detected on the basis of the visual colour change of the culture medium from blue to pink. The lowest concentration that prevents this colour change was recorded as MIC, the determination of which was performed in triplicate, and the consistent MIC value obtained was reported as the final analyzed MIC; that is, the MIC result reported is the one obtained twice or three times out of three times the experiment. The MIC plates were incubated at 37°C for 7 days for Mtb and 48 h for other mycobacterial pathogens.

1.7 Time-kill Studies:

Time-kill studies were performed in sterile 5 ml muller hinton broth (MHB) dispensed in autoclaved screw-capped tubes. Ciprofloxacin at 0.125 μg/ml (MIC) and the test compound 7a at its 0.25 μg/ml (MIC), 1 μg/ml (4X MIC) and 2 μg/ml (8X MIC) were assessed for kill kinetics against *S. aureus* ATCC 29213. The inoculum was prepared from overnight grown culture on muller hinton agar (MHA) plate by suspending well-isolated colonies of culture in

sterile normal saline (NaCl, 0.85% w/v), and the turbidity of suspension was adjusted to an OD_{600} of 0.08 (≈ 10^8 CFU/ml of *E.coli*). Fifty microlitres of this inoculum was added to respective screw-capped tubes containing with different concentrations of the drug compounds so that the final inoculum reached to 10^6 CFU/ml in each tube. CFU/ml was determined by a serial dilution method on MHA plates at 0 (inoculum control), 2, 4, 8, 10, 12 and 24 h of incubation at 37°C. Killing curves were constructed by plotting the Log_{10} CFU/ml versus time over 24 h. The assay was performed in triplicate.[6]

1.8 Characterization of the Supercoiling Activity of Gyrase: pUC19 containing DH5α strain of *E. coli* was grown to saturation by incubating at 37°C in LB media supplemented with 50 µg/mL of ampicillin. The overnight grown cells were pelleted down at 6000 rpm for 10 min and re-suspended in fresh LB media to an OD_{600} of 2.0. The adjusted suspensions were treated with DMSO, Ciprofloxacin (01.25 µg/ml i.e. MIC) and test compound, 7a at 1 µg/ml (4X MIC) and 2 µg/ml (8X MIC) followed by incubation at 37°C with 200 rpm for 90 minutes. For determining the supercoiling states of pUC19 DNA after treatment, cells were harvested and pUC19 was extracted from all the treated samples using a Qiagen QIAprep spin miniprep kit (Qiagen). The extracted plasmids were quantified using nanodrop, and 300 ng of plasmid from each sample was separated by electrophoresis in 0.8% agarose at 80 V for 30 min for determination of topological states.[7]

1.9 Cell cytotoxicity assay:

The active newly synthesized compounds were screened for their cell toxicity against Vero cells (ATCC CCL-81 cells obtained from ATCC, USA) using MTT assay. ~10^3 cells/ well were seeded in 96 well plate and incubated at 37 °C with a 5% CO_2 atmosphere. After 24 h, the compound was added ranging from 100 to 5 mg/L and incubated for 72 h at 37 °C with 5% CO_2 atmosphere. After the incubation was over, MTT was added at 5 mg/L in each well, and incubated at 37 ^oC for further 4 h, residual medium was discarded, 0.1 mL of DMSO was added to solubilize the formazan crystals, and OD was taken at 540 nm for the calculation of CC_{50}. CC_{50} is defined as the lowest concentration of compound, which leads to a 50% reduction in cell viability.

1.10 Molecular docking studies:

Molecular docking studies were performed using the glide docking module of Schrödinger suite 20-2. The structure coordinates of DNA gyrase in complex with ciprofloxacin (PDB: 2XCT) were obtained from the RCSB.[8] The protein was prepared using the Protein Preparation Wizard[9] of the Schrödinger suite by adding hydrogens, bond orders were assigned, and water molecules were removed within 5 Å around the co-crystal. The protein structure was minimized using the OPLS-3e force field. The grid for docking was generated by taking the centroid of the co-crystal validated by re-docking of co-crystal to an RMSD of 0.92. Compound **7a was** drawn and prepared using LigPrep, and was docked at the active site of gyrase using the GLIDE module[10].

1.11 *In vitro* metabolic stability test:

Pooled human liver microsomes, 100 mM phosphate buffer pH 7.4, test compounds were added together to reach a final concentration of 0.52 mg/mL of pooled human liver microsomes, 1 µM of test compounds and 0.1% of DMSO. This mixture was preincubated for 5 min at 37 °C followed by the addition of 50 µL of 10 mM NADPH for initiating the reaction and adjusted to a final volume of 500 µL. Incubation of test compounds in human liver microsomes was performed in duplicate to assess the metabolic stability. In addition, a positive control (testosterone) was included to ensure the satisfactory performance of the drug and negative control (without NADPH) to determine loss of compound due to thermal instability. The mixture was incubated for 0, 10, 30, 45, and 60 min. The positive and negative controls were incubated for 60 min only. The metabolic reaction was halted by adding an equal volume of chilled acetonitrile containing internal standard (tolbutamide, 200 ng/mL) at the appropriate time points. Then the samples were centrifuged at 4000 rpm for 10 min at 4 °C, and the supernatant was subjected to further analysis by LC-MS/MS. The line slope was determined by plotting the ln peak area ratio (compound peak area/ internal standard peak area) against incubation time. Subsequently, half-life and intrinsic clearance were calculated using the equations below [11]:

$$Elimination\ rate\ constant\ (k) = (-\ slope)$$

$$Half\ life\ (t_{½}) = \frac{0.693}{k}$$

$$Intrinsic\ clearance\ (CL_{int}) = \frac{V\ \times 0.693}{t_{½}}$$

Where, $$V = \frac{Incubation\ volume\ (\mu L)}{Microsomal\ protein\ (mg) in\ incubation}$$

Liquid chromatography coupled to mass spectrometry (LC-MS) analysis was carried out using the Agilent 1200 series LC system (Agilent Technologies, Santa Clara, California, USA), hyphenated to quadrupole time of flight (Q-TOF) mass spectrometer (6540 series, Agilent Technologies). The study was carried out in positive mode under electrospray ionization (ESI). The typical operating source conditions for MS scan of test compounds and IS were optimized as the fragmentor voltage was set at 120 V, the capillary at 4500 V, the skimmer at 70 V, nitrogen was used as the drying (320 °C, 10 L/min) and nebulizing gas (40 psig). All the spectra were recorded under identical experimental conditions. Before analysis, internal calibration was carried out using an ESI-L tuning mix (Agilent Technologies). Then, the data were acquired and evaluated using Mass Hunter Workstation software.

Chromatographic separation of the test compound and IS was achieved on the Waters ACQUITY UPLC® BEH C18 column (2.1 × 100 mm, 1.7 µm). The mobile phase components 0.1% formic acid in water (A) and acetonitrile (B) were used in the following gradient elution method (T, min/ACN, %): 0.0–0.0/5, 0.0–3.0/80, 3.0–6.0/80, 6.0–7.0/5, 7.0–10.0/5. This 10 min gradient method included 6 min for elution and 4 min for equilibration. The flow rate was set at 0.4 mL/min, and the column temperature was 40 ± 2 ºC. Auto-sampler temperature and injection volumes were 5 ± 0.8 ºC and 10 µL, respectively. Extracted ion chromatograms are used to obtain peak areas of test compounds and IS.

1.12 Kinetic aqueous solubility assay:

Solubility assay was performed in DMSO (n=3) and buffer (n = 3) by spiking 5 µL of compound (mother stock) into 245 µL of matrices as per the reported procedure.[12] Then the samples were incubated in Eppendorf thermomixer for 16 h at 1300 rpm. After incubation, aqueous samples were filtered by Millipore filters and both the aqueous and DMSO samples were transferred to HPLC vials. The samples were then subjected to HPLC analysis. Solubility in mg/mL was calculated by comparing the area of peak obtained in aqueous with organic.

Chromatographic separation was performed on an XBridge C18 column (250 mm × 4.6 mm, 5 µm) with a gradient mobile phase of 0.1% formic acid:acetonitrile (20:80) at 1 mL/min flow rate and run time of 5 min.

$$Solubility\ (\mu M) = \frac{Average\ peak\ area\ in\ aqueous}{Average\ peak\ area\ in\ organic} \times Assay\ concentration$$

$$Solubility\ (mg/mL) = \frac{Solubility\ in\ \mu M\ \times Molecular\ weight}{1000\ \times 1000}$$

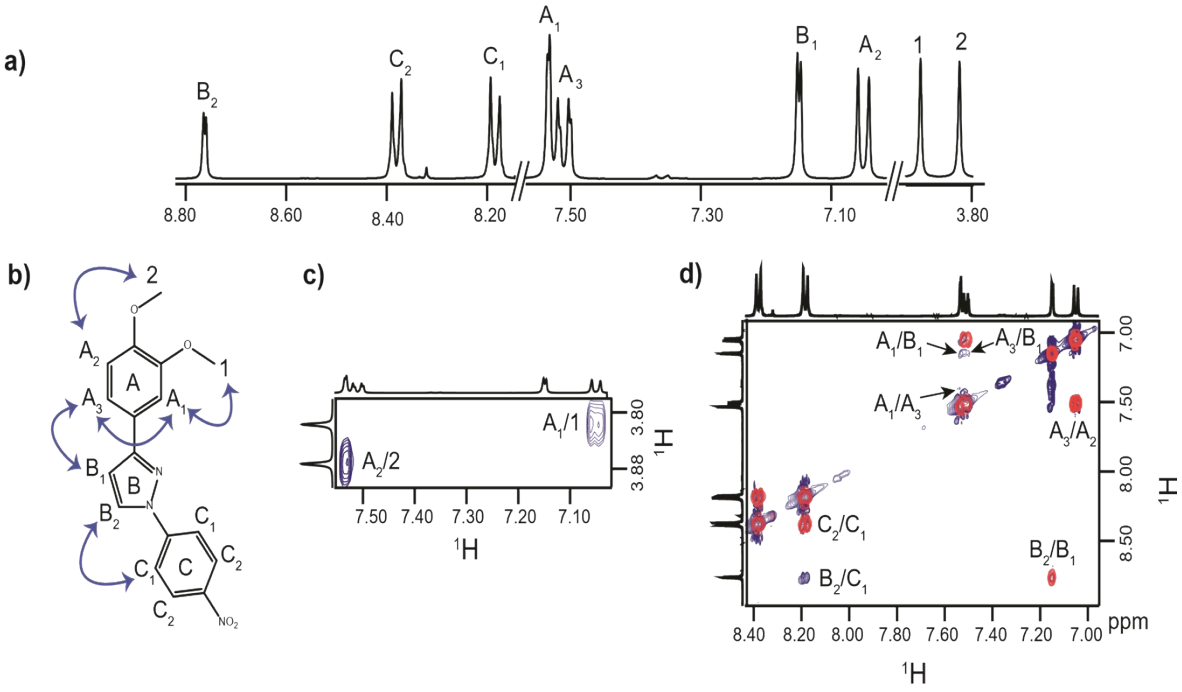


Figure S1. Compound 4a: (a) Complete 1D ^{1}H NMR spectrum at 500 MHz in DMSO-d6. (b) Chemical Structure of compound 4a illustrating the key characteristic NOEs with double edged blue arrows. (C) Partial ROESY spectrum highlighting 1↔A_1 and 2↔A_2. (d) Partial overlay of COSY (red), ROESY(blue) spectra highlighting A_3↔B_1, B_2↔C_1 NOEs.

Table ST1: Antibacterial screening results for compounds 5-10 and 15a-c

Sl. No.	Compound Code	MIC (µg/mL)				
		S.aureus **ATCC 29213**	***E.coli**** **ATCC 25922**	***K.pneumoniae**** **BAA 1705**	***A.baumannii**** **BAA 1605**	***P.aeruginosa**** **ATCC 27853**

1.	5a	**64**	>64	>64	>64	>64
2.	5b	>64	>64	>64	>64	>64
3.	5c	>64	>64	>64	>64	>64
4.	5d	>64	>64	>64	>64	>64
5.	5e	>64	>64	>64	>64	>64
6.	5f	>64	>64	>64	>64	>64
7.	5g	**64**	>64	>64	>64	>64
8.	5h	>64	>64	>64	>64	>64
9.	5i	**64**	>64	>64	>64	>64
10.	6a	>64	>64	>64	>64	>64
11.	6b	**64**	>64	>64	>64	>64
12.	6c	>64	>64	>64	>64	>64
13.	6d	>64	>64	>64	>64	>64
14.	6e	>64	>64	>64	>64	>64
15.	6f	>64	>64	>64	>64	>64
16.	6g	>64	>64	>64	>64	>64
17.	6h	**2**	>64	>64	>64	>64
18.	6i	>64	>64	>64	>64	>64
19.	6j	>64	>64	>64	>64	>64
20.	6k	>64	>64	>64	>64	>64
21.	6l	>64	>64	>64	>64	>64
22.	6m	>64	>64	>64	>64	>64
23.	6n	>64	>64	>64	>64	>64
24.	6o	>64	>64	>64	>64	>64
25.	6p	>64	>64	>64	>64	>64
26.	6q	>64	>64	>64	>64	>64
27.	6r	>64	>64	>64	>64	>64
28.	6s	>64	>64	>64	>64	>64
29.	6t	**1**	>64	>64	>64	>64
30.	7a	**0.25**	>64	>64	>64	>64
31.	7b	>64	>64	>64	>64	>64

32.	7c	>64	>64	>64	>64	>64
33.	7d	>64	>64	>64	>64	>64
34.	7e	>64	>64	>64	>64	>64
35.	7f	>64	>64	>64	>64	>64
36.	7g	>64	>64	>64	>64	>64
37.	7h	>64	>64	>64	>64	>64
38.	7i	>64	>64	>64	>64	>64
39.	7j	>64	>64	>64	>64	>64
40.	7k	>64	>64	>64	>64	>64
41.	7l	**2**	>64	>64	>64	>64
42.	7m	**2**	>64	>64	>64	>64
43.	7n	>64	>64	>64	>64	>64
44.	7o	>64	>64	>64	>64	>64
45.	8a	>64	>64	>64	>64	>64
46.	8b	>64	>64	>64	>64	>64
47.	8c	>64	>64	>64	>64	>64
48.	8d	>64	>64	>64	>64	>64
49.	8e	>64	>64	>64	>64	>64
50.	8f	>64	>64	>64	>64	>64
51.	8g	>64	>64	>64	>64	>64
52.	8h	>64	>64	>64	>64	>64
53.	9a	>64	>64	>64	>64	>64
54.	9b	>64	>64	>64	>64	>64
55.	9c	>64	>64	>64	>64	>64
56.	9d	>64	>64	>64	>64	>64
57.	9e	>64	>64	>64	>64	>64
58.	9f	>64	>64	>64	>64	>64
59.	9g	>64	>64	>64	>64	>64
60.	9h	>64	>64	>64	>64	>64
61.	10a	>64	>64	>64	>64	>64
62.	10b	>64	>64	>64	>64	>64

63.	10c	>64	>64	>64	>64	>64
64.	10d	>64	>64	>64	>64	>64
65.	10e	>64	>64	>64	>64	>64
66.	10f	>64	>64	>64	>64	>64
67.	10g	>64	>64	>64	>64	>64
68.	10h	>64	>64	>64	>64	>64
69.	15a	**4**	>64	>64	>64	>64
70.	15b	>64	>64	>64	>64	>64
71.	15c	>64	>64	>64	>64	>64
72.	Levofloxacin	0.25	0.0156	64	8	1

**E.coli: Escherichia coli; S.aureus: Staphylococcus aureus; K.pneumoniae: Klebsiella pneumoniae; A.baumannii: Acinetobacter baumannii; P.aeruginosa: Pseudomonas aeruginosa.*

Table ST2. Antimycobacterial screening results for compounds 5-10 and 15a-c

Sl. No.	**Compound Code**	**MIC (µg/mL)**			
		M. tuberculosis H37Rv ATCC 27294	***M. abscessus ATCC 19977***	***M. fortuitum ATCC 6841***	***M. chelonae ATCC 35752***
1.	5a	**8**	>64	>64	>64
2.	5b	**16**	>64	>64	>64
3.	5c	**64**	>64	>64	>64
4.	5d	**16**	>64	>64	>64
5.	5e	**32**	>64	>64	>64
6.	5f	**64**	>64	>64	>64
7.	5g	**32**	>64	>64	>64
8.	5h	**32**	>64	>64	>64
9.	5i	**16**	>64	>64	>64
10.	6a	**8**	>64	>64	>64
11.	6b	**16**	>64	>64	>64

12.	6c	**64**	>64	>64	>64
13.	6d	**16**	>64	>64	>64
14.	6e	**2**	>64	>64	>64
15.	6f	**8**	>64	>64	>64
16.	6g	**32**	>64	>64	>64
17.	6h	**2**	>64	>64	>64
18.	6i	**16**	>64	>64	>64
19.	6j	**16**	>64	>64	>64
20.	6k	**16**	>64	>64	>64
21.	6l	**8**	>64	>64	>64
22.	6m	**16**	>64	>64	>64
23.	6n	**4**	>64	>64	>64
24.	6o	**8**	>64	>64	>64
25.	6p	**8**	>64	>64	>64
26.	6q	**32**	>64	>64	>64
27.	6r	**16**	>64	>64	>64
28.	6s	**16**	>64	>64	>64
29.	6t	**16**	>64	>64	>64
30.	7a	**32**	>64	>64	>64
31.	7b	**8**	>64	>64	>64
32.	7c	**16**	>64	>64	>64
33.	7d	**16**	>64	>64	>64
34.	7e	**32**	>64	>64	>64
35.	7f	**1**	>64	>64	>64
36.	7g	**4**	>64	>64	>64
37.	7h	**16**	>64	>64	>64
38.	7i	**32**	>64	>64	>64
39.	7j	**1**	>64	>64	>64
40.	7k	>64	>64	>64	>64
41.	7l	**16**	>64	>64	>64
42.	7m	**4**	>64	>64	>64

43.	7n	>64	>64	>64	>64
44.	7o	**16**	>64	>64	>64
45.	8a	**64**	>64	>64	>64
46.	8b	**16**	>64	>64	>64
47.	8c	**8**	>64	>64	>64
48.	8d	**32**	>64	>64	>64
49.	8e	>64	>64	>64	>64
50.	8f	>64	>64	>64	>64
51.	8g	>64	>64	>64	>64
52.	8h	**64**	>64	>64	>64
53.	9a	>64	>64	>64	>64
54.	9b	**8**	>64	>64	>64
55.	9c	>64	>64	>64	>64
56.	9d	**8**	>64	>64	>64
57.	9e	>64	>64	>64	>64
58.	9f	>64	>64	>64	>64
59.	9g	**8**	>64	>64	>64
60.	9h	>64	>64	>64	>64
61.	10a	**64**	>64	>64	>64
62.	10b	**8**	>64	>64	>64
63.	10c	>64	>64	>64	>64
64.	10d	>64	>64	>64	>64
65.	10e	>64	>64	>64	>64
66.	10f	64	>64	>64	>64
67.	10g	**0.5**	>64	**1**	**1**
68.	10h	>64	>64	>64	>64
69.	15a	>64	>64	>64	>64
70.	15b	**8**	>64	>64	>64
71.	15c	**16**	>64	>64	>64
72.	Isoniazid	0.03	NT	NT	NT
73.	Rifampicin	0.06	NT	NT	NT

74.	Streptomycin	1	NT	NT	NT
75.	Ethambutol	2	NT	NT	NT

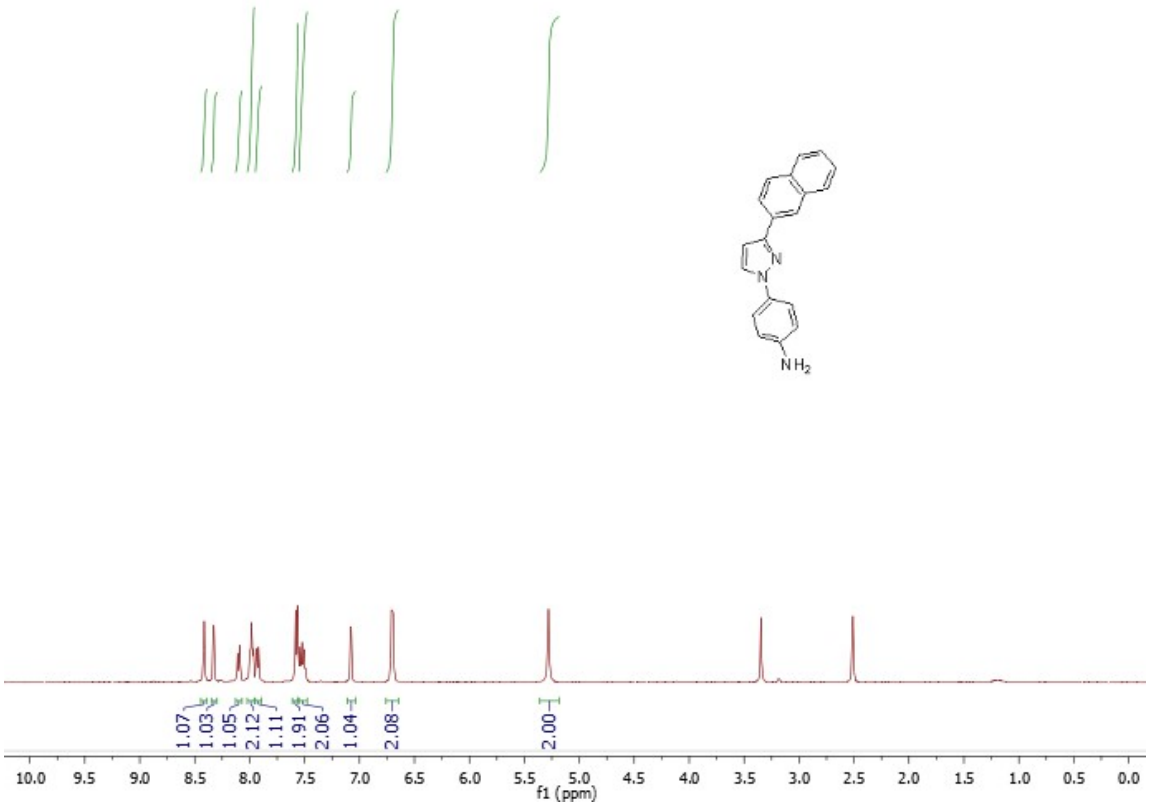
Table ST3 GLIDE docking results of compounds, 5-10 and 15a-c

Ligand ID	Docking Score	Interactions			
		Hydrogen bond	π - π	π - cation	Halogen bond
6a	4.938	-	DG-8, DG-9, DC-13	-	-
6b	5.489	DG-8	DG-8, DG-9	ARG458	-
6c	5.075	-	DG-8, DG-9	-	-
6d	5.640	ARG-1122	DG-8, DG-9, DC-13	-	-
6e	6.082	DG-8	DG-8, DG-9	ARG-458	-
6f	6.413	ARG-1122	DG-8, DG-9, DC-13	-	-
6g	6.407	ARG-1122	DG-8, DG-9	ARG-458	-
6h	5.633	DG-9	DG-9, DC-13	-	-
6i	5.449	-	DG-8, DG-13	-	-
6j	6.805	DG-8	DG-8, DG-9	ARG-458	-
6k	6.842	DT-10	DG-8, DC-13	-	-
6l	5.476	DC-12	DG-8, DG-9, DC-13	-	-
6m	5.830	-	DG-8, DG-9, DC-13	ARG458	-
6n	5.004	-	-	ARG458	-
6o	4.443	-	-		-
6p	6.496	DC-12, ARG-1122	DG-8, DG-9, DC-13, DA-11	-	-
6q	5.474	-	DG-8, DG-9, DA-11	-	-
6r	6.545	ARG-1122	DG-8, DG-9, DC-13	-	-
6s	6.117	ARG-1122	DG-8, DG-9, DC-13	-	-
6t	5.793	ARG-1122	DG-8, DG-9	-	-
7a	6.343	-			
7b	5.988	-	DG-8, DG-9, DC-12	-	-
7c	4.810	DT-10	DG-8, DG-9, DT-10	ARG458	-
7d	4.511	-	DG-8, DG-9	-	-
7e	4.970	ARG1122	DG-8, DG-9	-	-

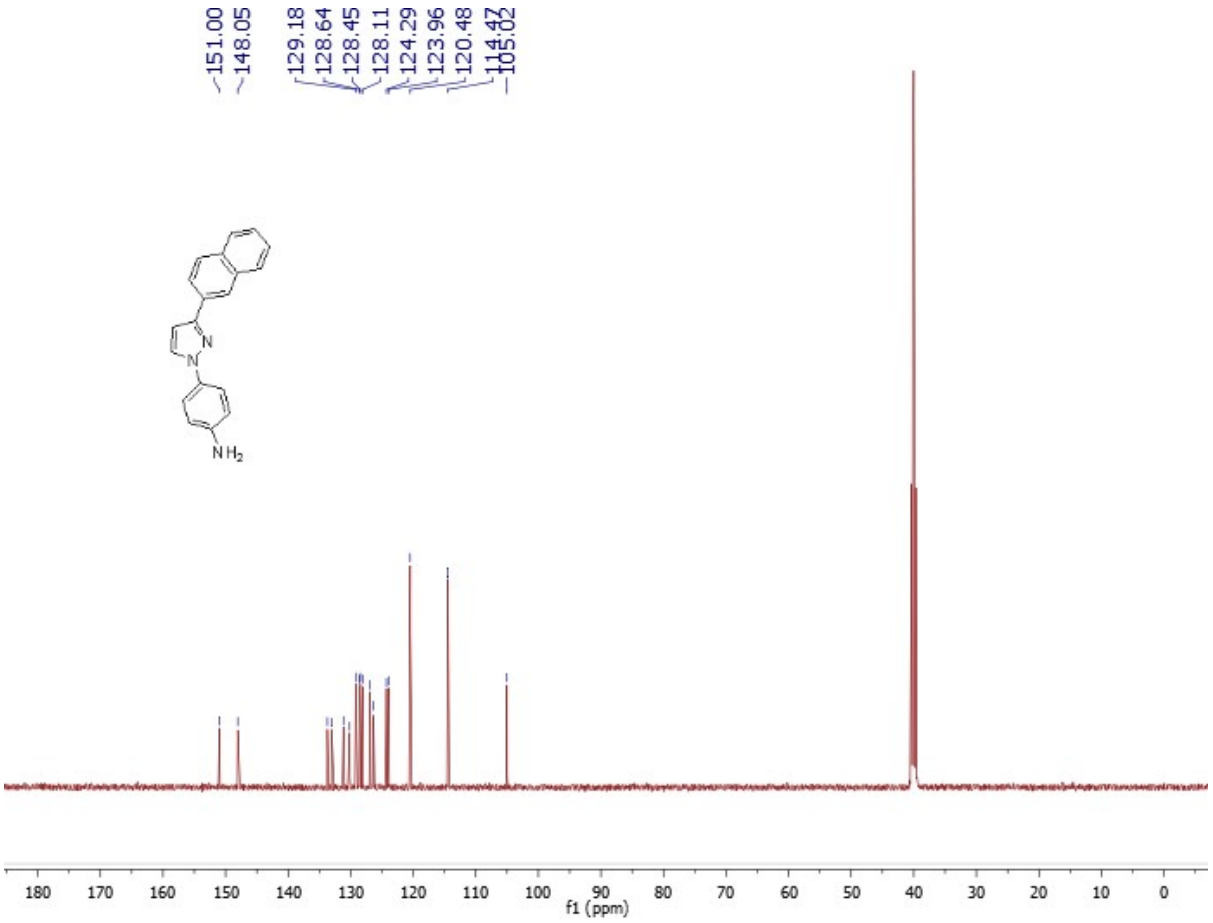
7f	7.175	DG-8	DG-9	DC-13	-
7g	5.401	DT-10	DG-8, DG-9	-	ASN476
7h	4.785	DG-9	DG-8, DG-9	ARG458	-
7i	5.112	DC-13	DG-8, DG-9	-	-
7j	4.185	DG-9	DG-8, DG-9	ARG458	-
7k	5.094	DT-10	DG-8, DG-9	-	ARG458
7l	4.956	-	DG-8, DG-9	-	-
7m	5.186	DT-10	DG-8, DG-9, DC-13	-	-
7n	4.902	-	DG-8, DG-9		ARG458
7o	5.512	-	DG-9, DT-8	ARG1122	-
7p	4.778	-	DG-9, DT-8, PHE1123	-	-
8a	5.060	DG-9	DG-8, DG-9	DC-12	ARG458
8b	5.815	ARG1122, ARG458, DC-12	DG-8, DG-9, DC-13	-	-
8c	5.821	DC-12	DG-8, DG-9, DC-12, DC-13	-	-
8d	5.984	DG-9	DG-8, DG-9	ARG458	SER1084
8e	5.468	DC-12, ARG458	DG-8, DG-9, DC-13	-	-
8f	4.556	-	DG-8	ARG458	-
8g	6.287	-	DG-8, DG-9, DC-13	ARG458	ASN475, ASN476
8h	5.675	DC-12, ARG458	DG-8, DG-9, DC-13	-	-
9a	5.594	DG-8	DG-8, DG-9	-	-
9b	5.437	DG-9	DG-8, DG-9	-	-
9c	6.289	-	DG-8, DG-9, DC-12	-	-
9d	4.157	-	DG-8, DG-9, DC-13	ARG458	-
9e	5.717	DC-13	DG-8, DG-9	-	-
9f	3.931		DG-8, DG-9, DC-13	ARG458	
9g	4.864	DC-12	DG-8, DG-9,	-	-
9h	5.112	-	DG-8, DG-9, DC-13	-	-
10a	6.254	-	DG-8, DG-9	-	-
10b	6.047	ARG458	DG-9	ARG458	-
10c	5.579	-	DG-9	ARG458	-
10d	6.962	DG-8	DG-8, DG-9	-	-
10e	4.681	-	DG-9, DT-8, PHE1123	ARG1122	-
10f	6.120	DT-10	DG-8, DG-9, DC-13	ARG458	ARG-1122

10g	5.494	-	DG-8, DG-9	-	-
10h	5.954	-	DG-9	ARG458	-
15a	5.194	-	DG-8, DG-9	-	-
15b	5.976	-	DG-9, DT8, DA-13	-	-
15c	4.930	-	DT-8, PHE1123	ARG1122	-

2. **^{1}H, ^{13}C and HRMS spectra of intermediates, 5b-i**

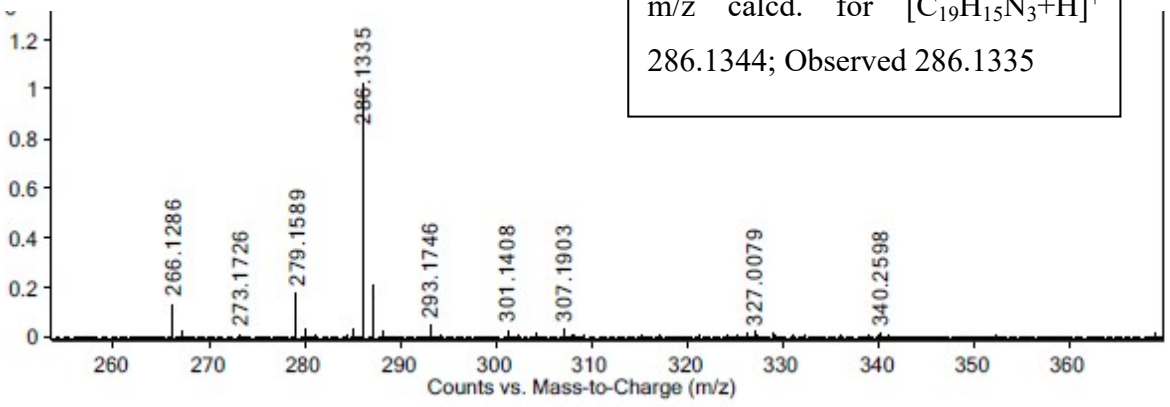


^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **5b**

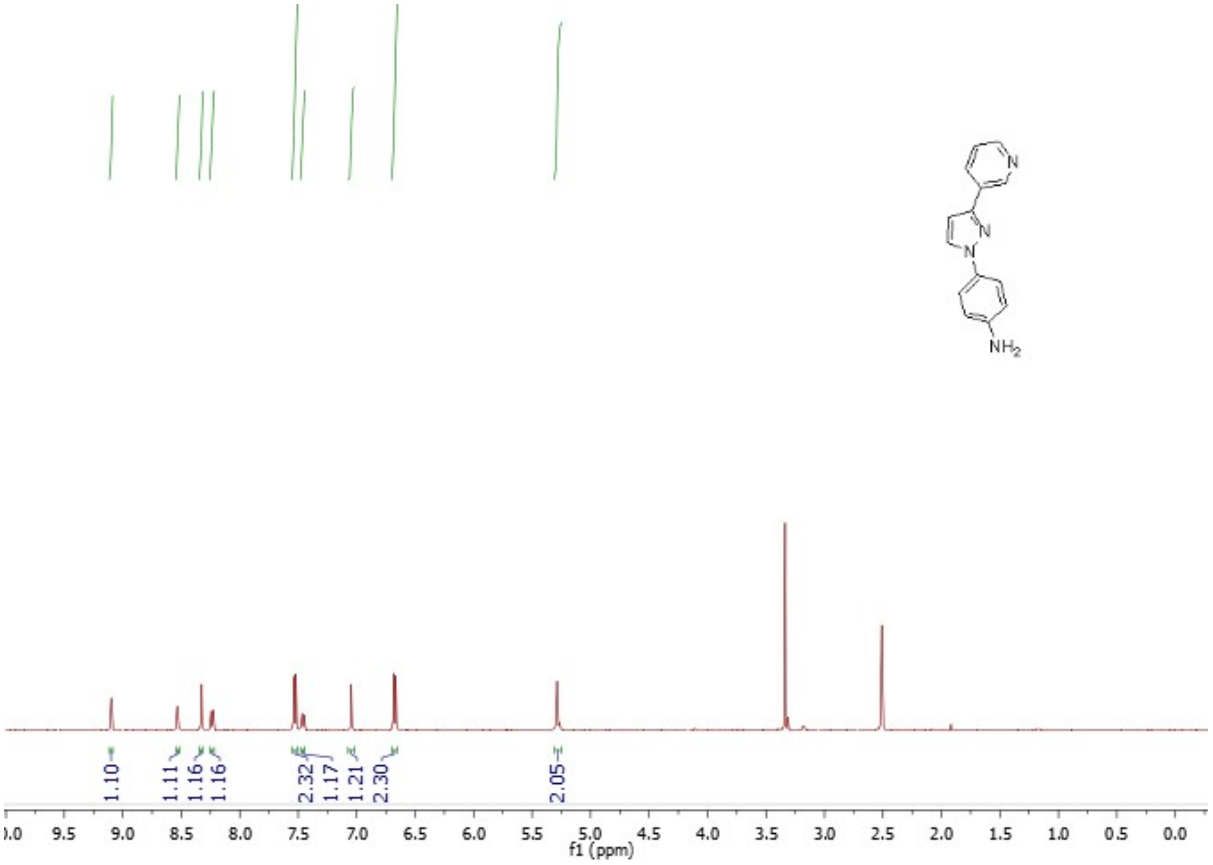


^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **5b**

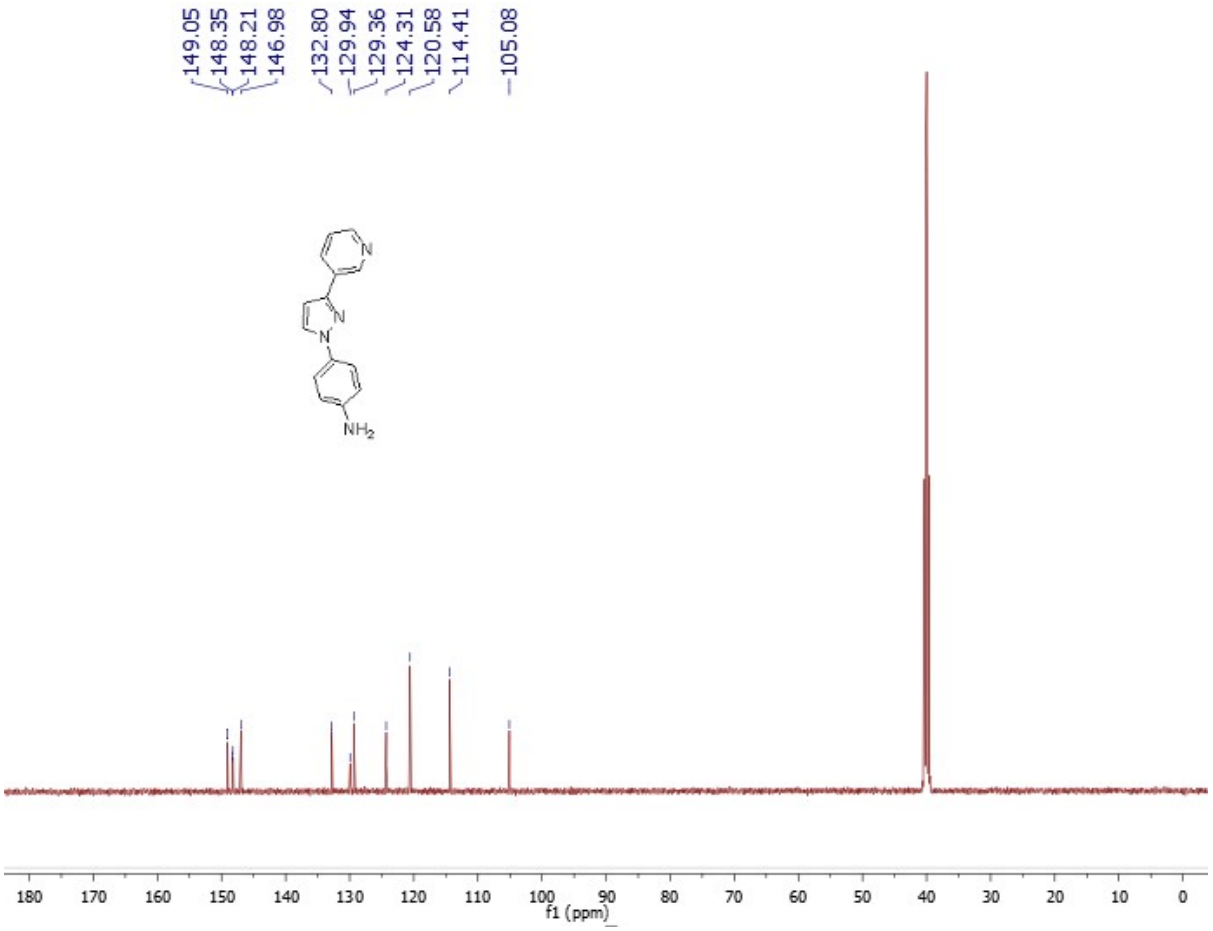
m/z calcd. for $[C_{19}H_{15}N_3+H]^+$ 286.1344; Observed 286.1335



Mass spectrum of compound **5b**

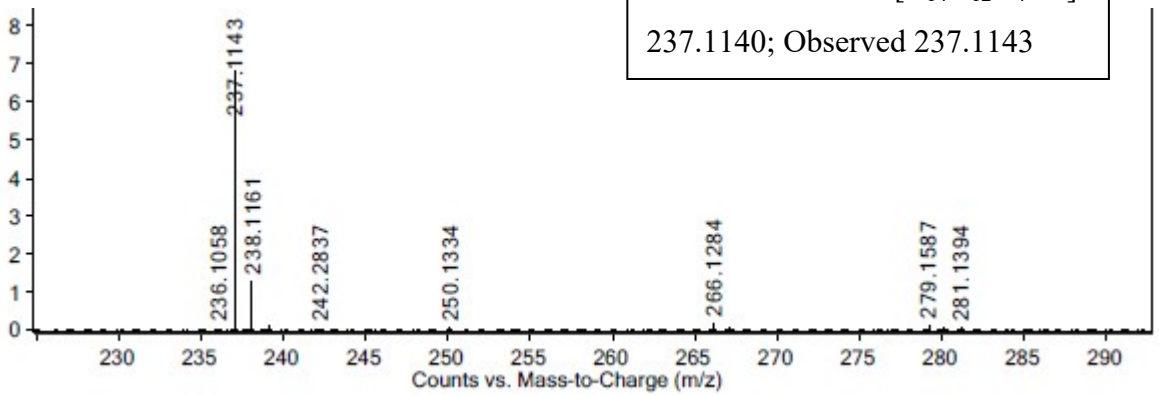


^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **5c**

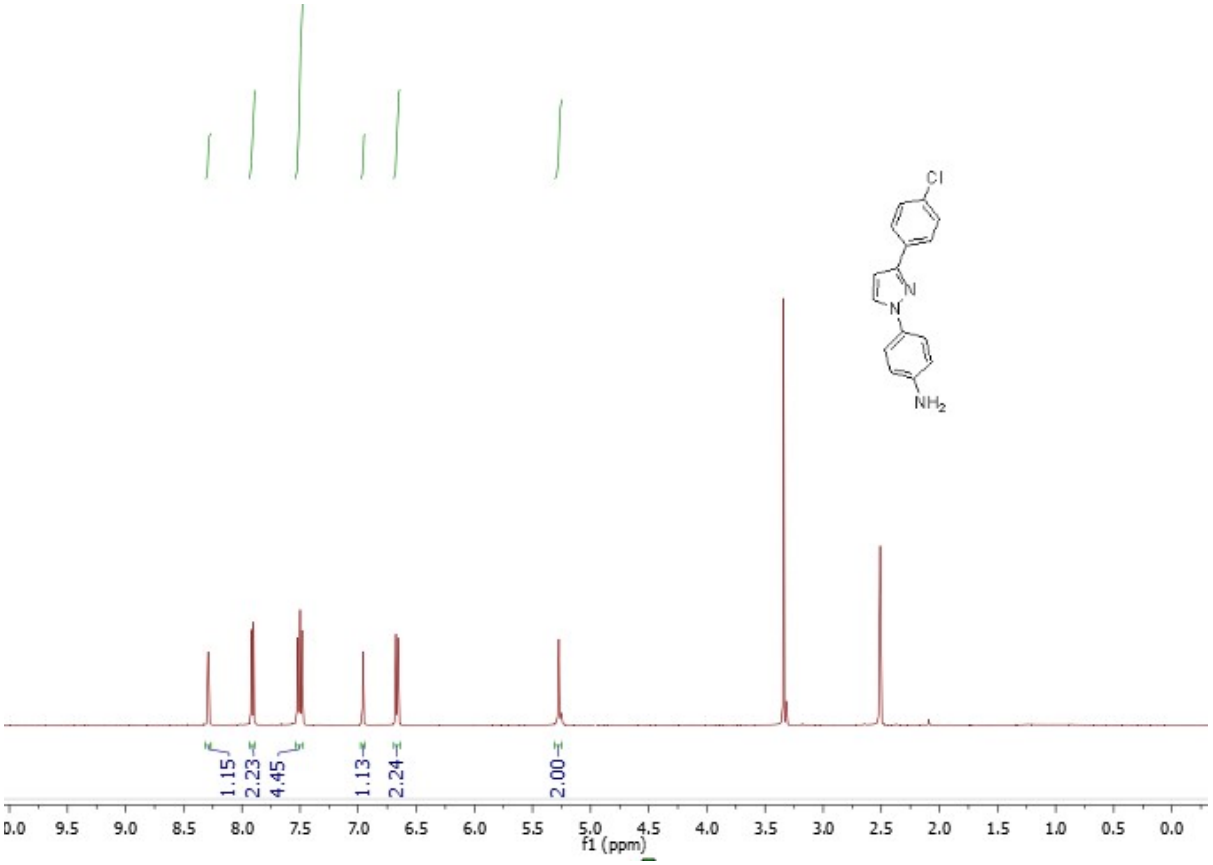


^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **5c**

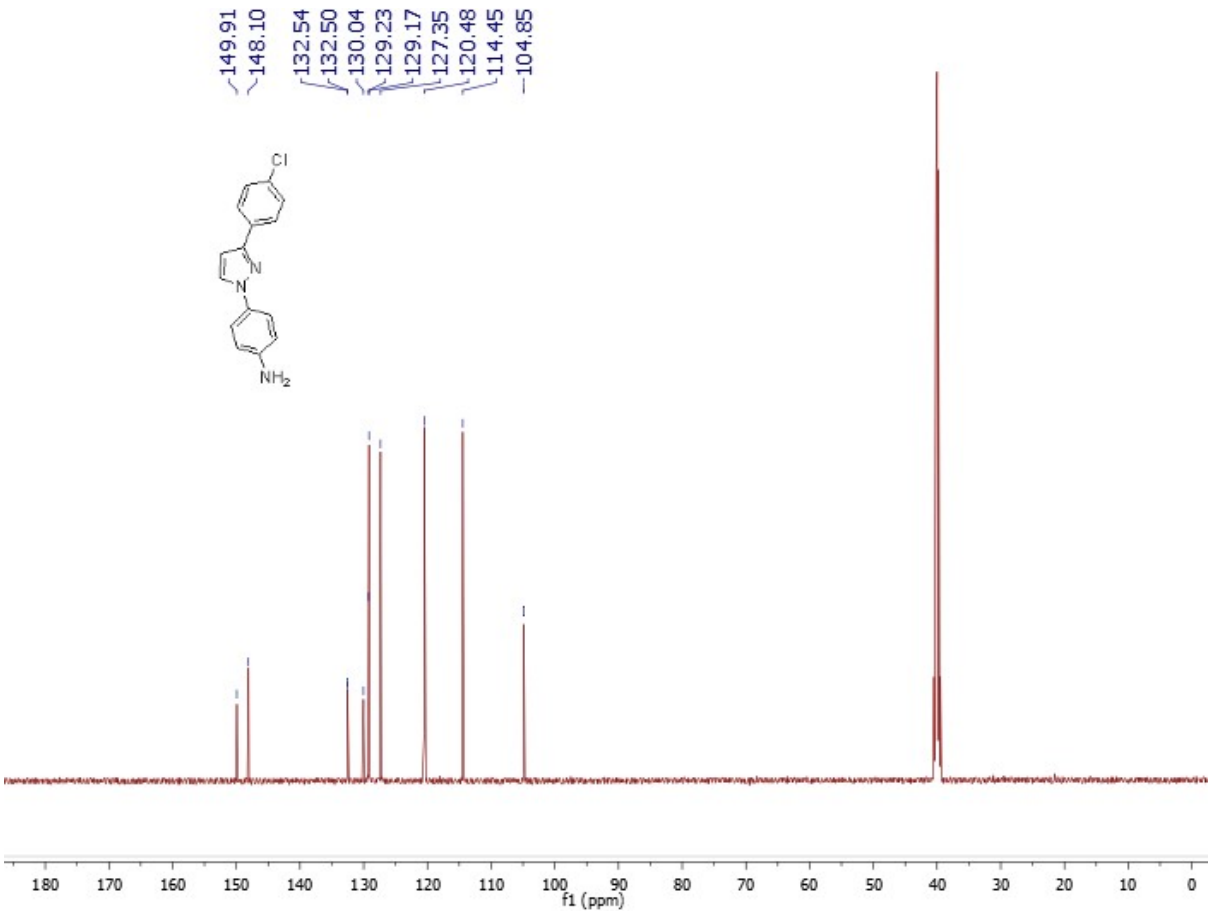
m/z calcd. for $[C_{14}H_{12}N_4+H]^+$ 237.1140; Observed 237.1143



Mass spectrum of compound **5c**

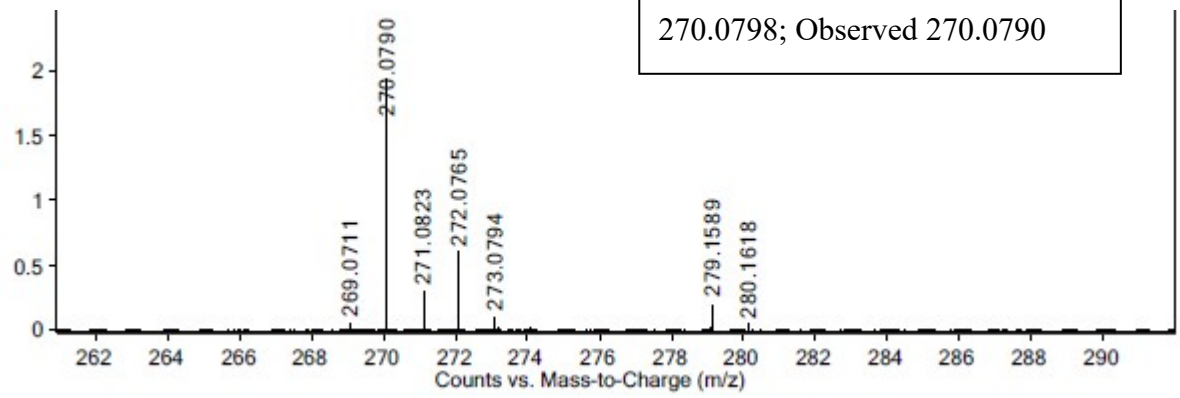


^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **5d**

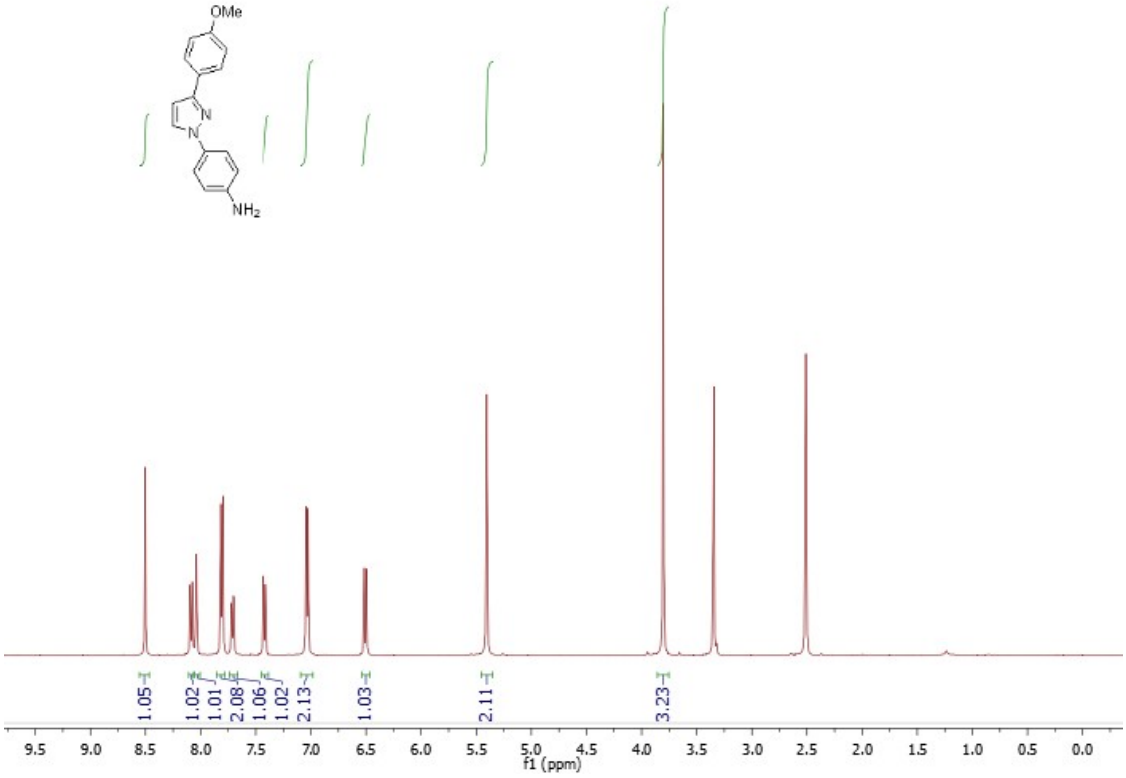


^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **5d**

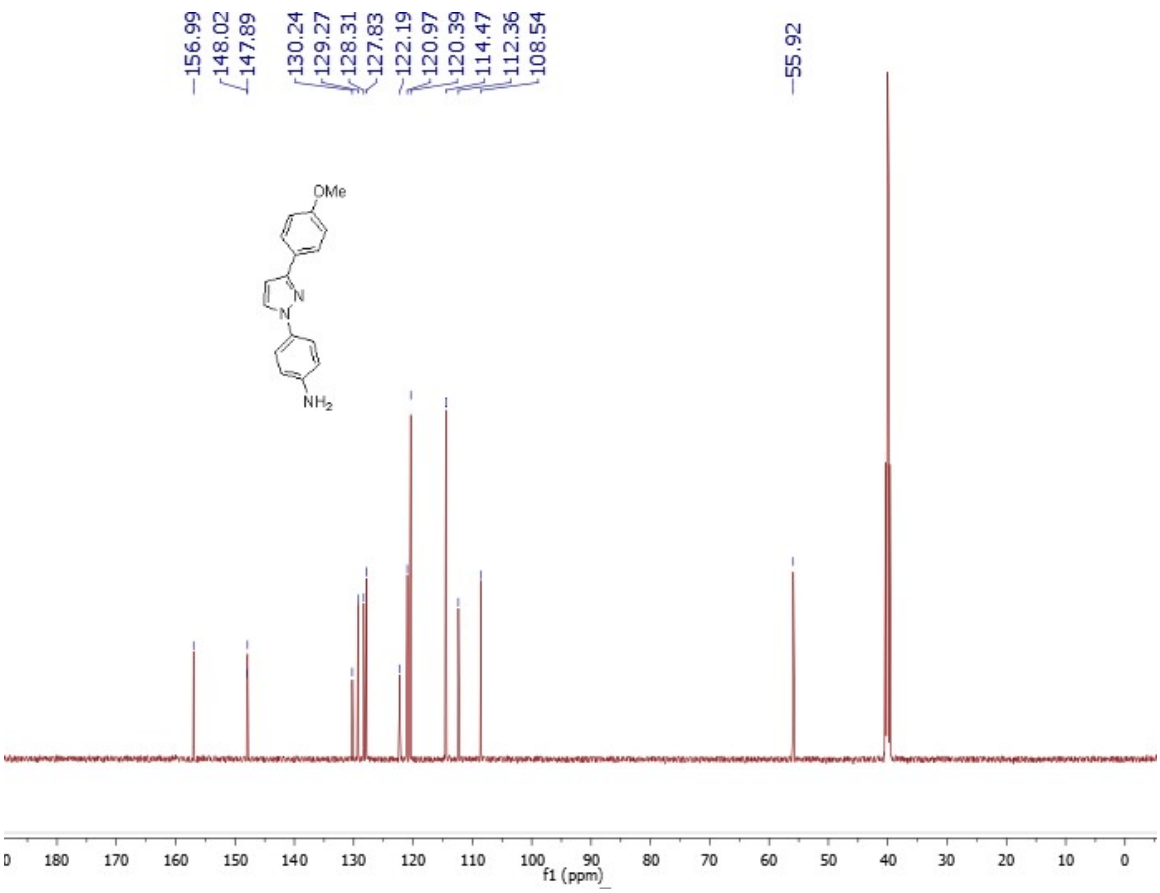
m/z calcd. for $[C_{15}H_{12}ClN_3+H]^+$ 270.0798; Observed 270.0790



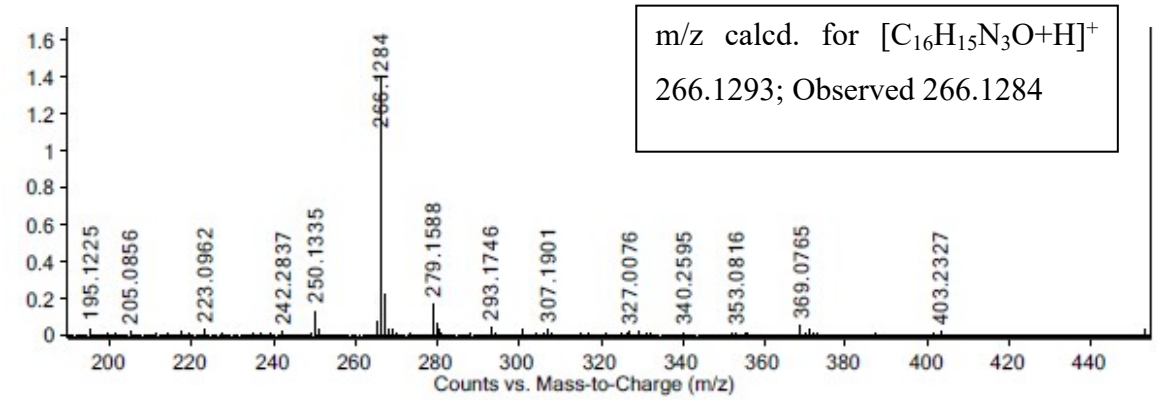
Mass spectrum of compound **5d**



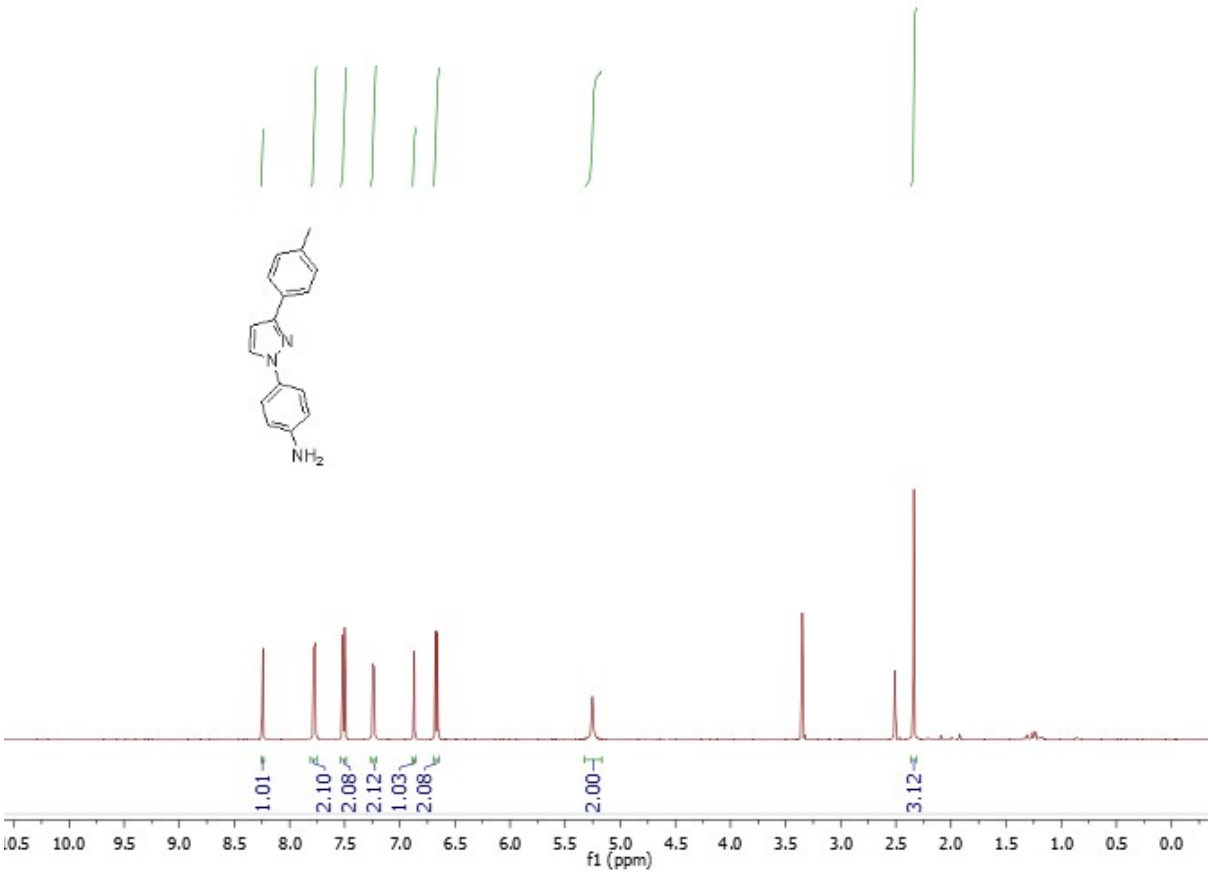
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **5e**



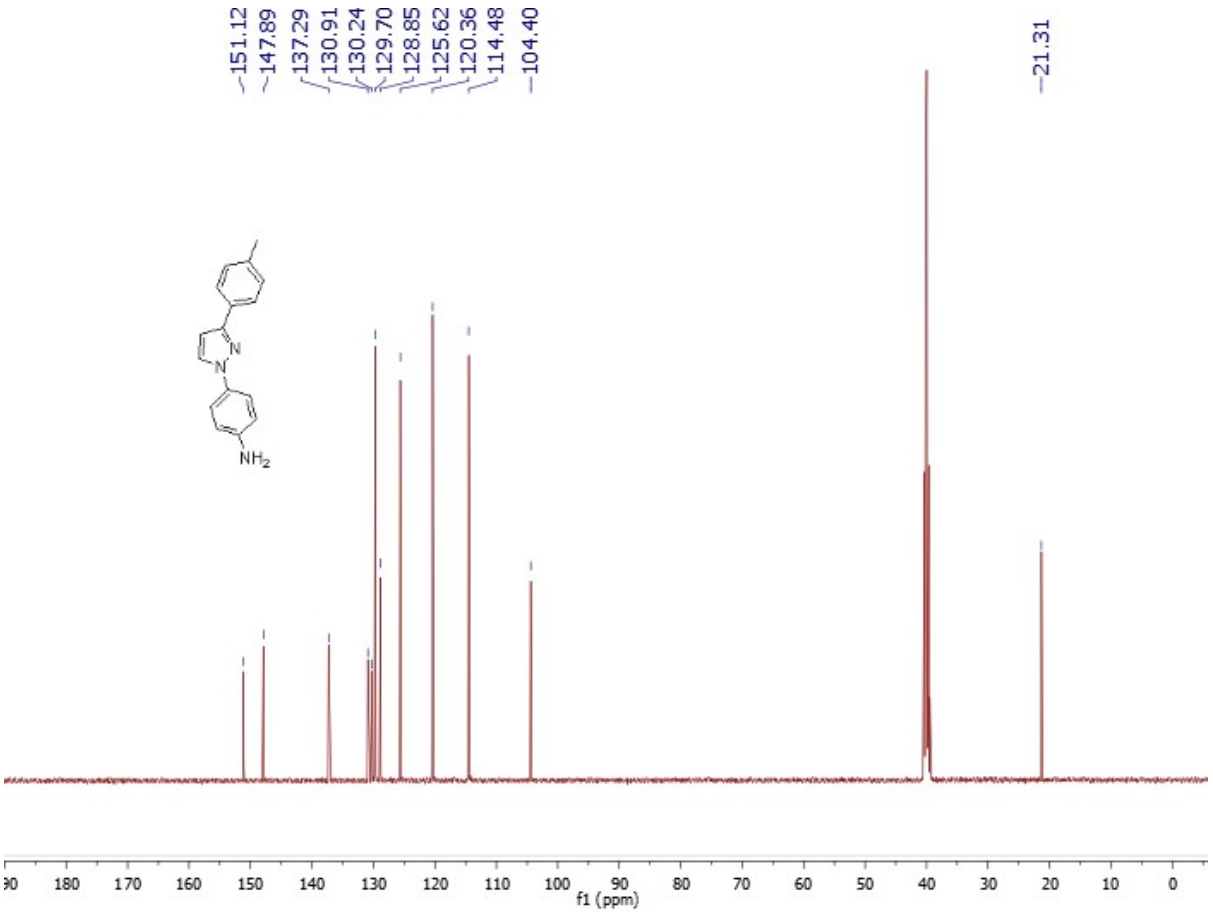
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **5e**



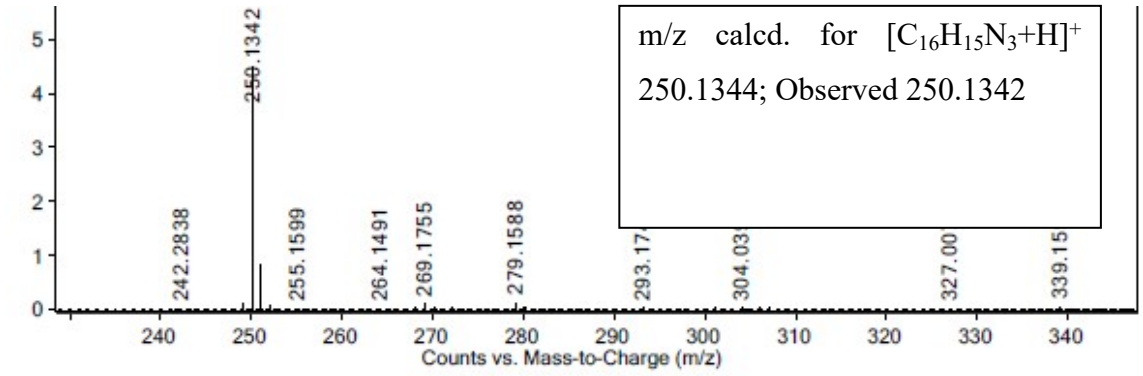
Mass spectrum of compound **5e**



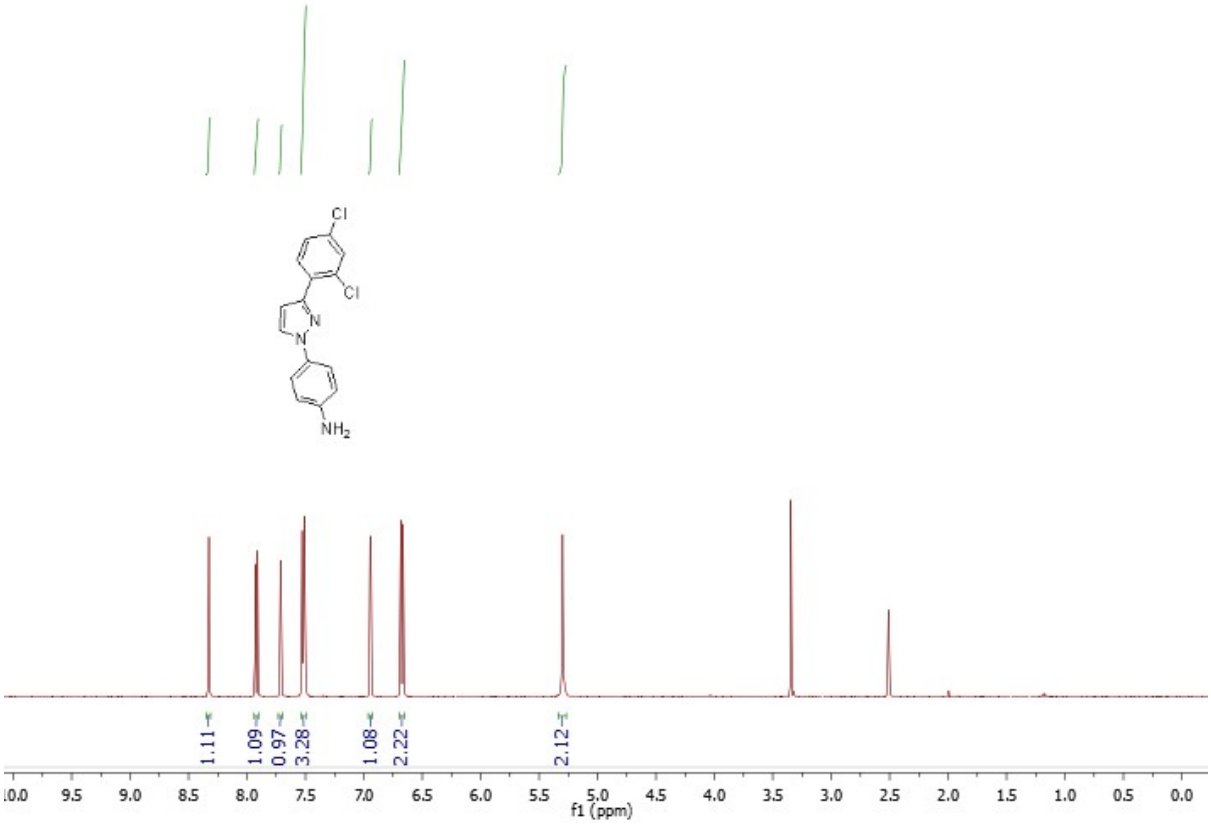
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **5f**



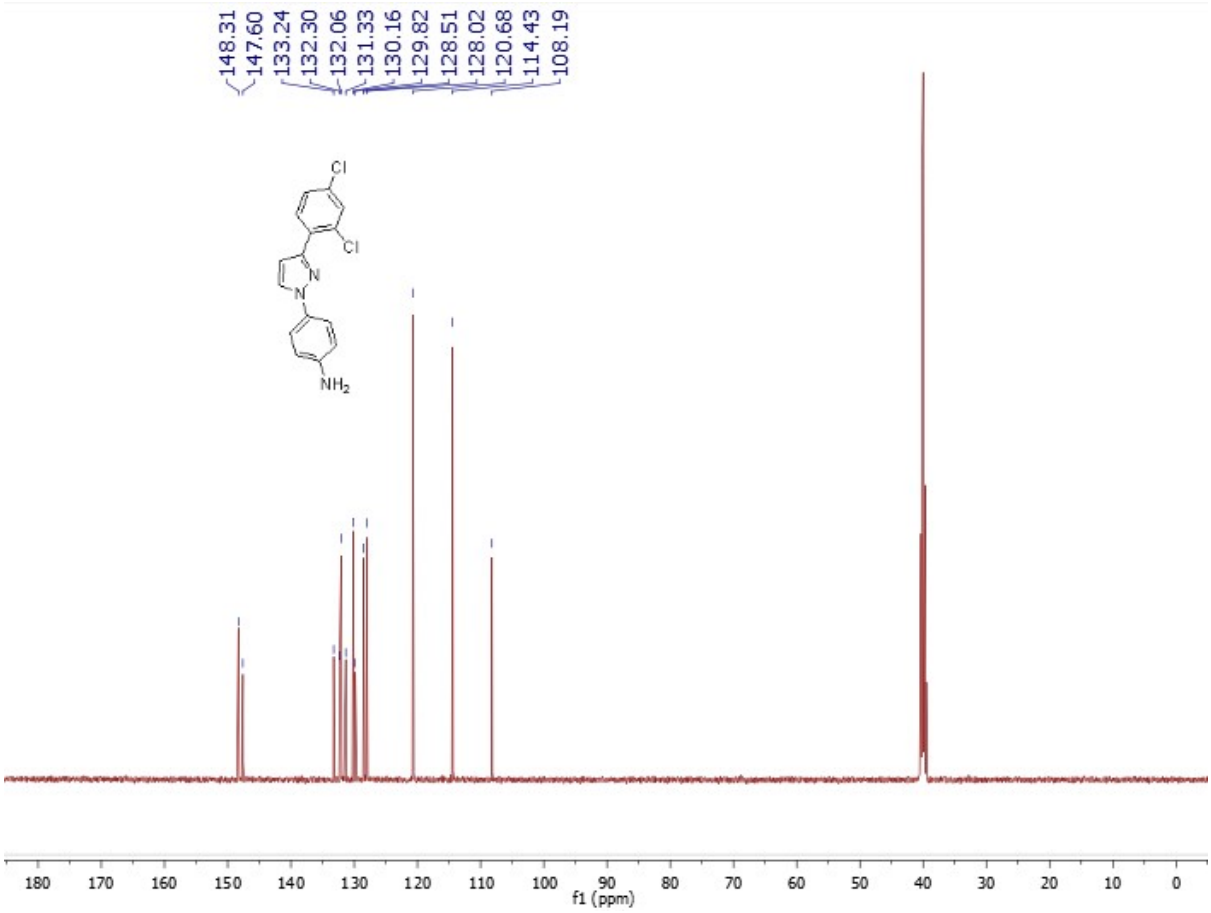
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **5f**



Mass spectrum of compound **5f**

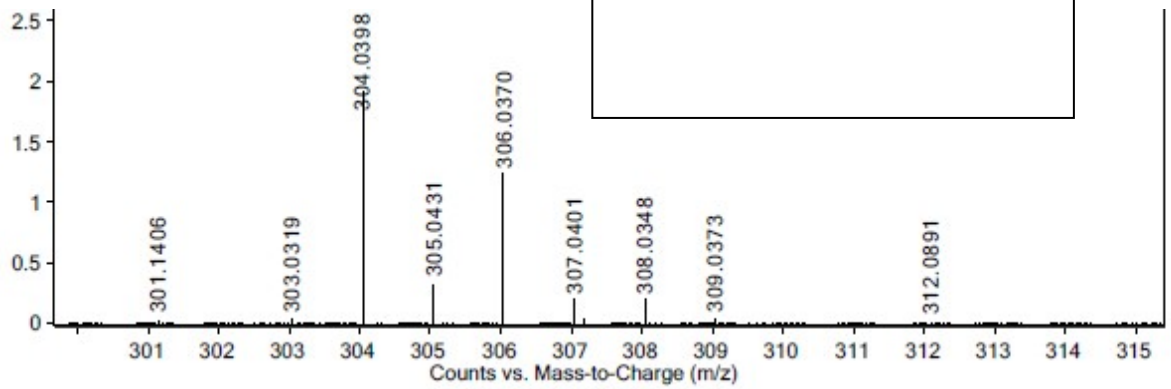


^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **5g**

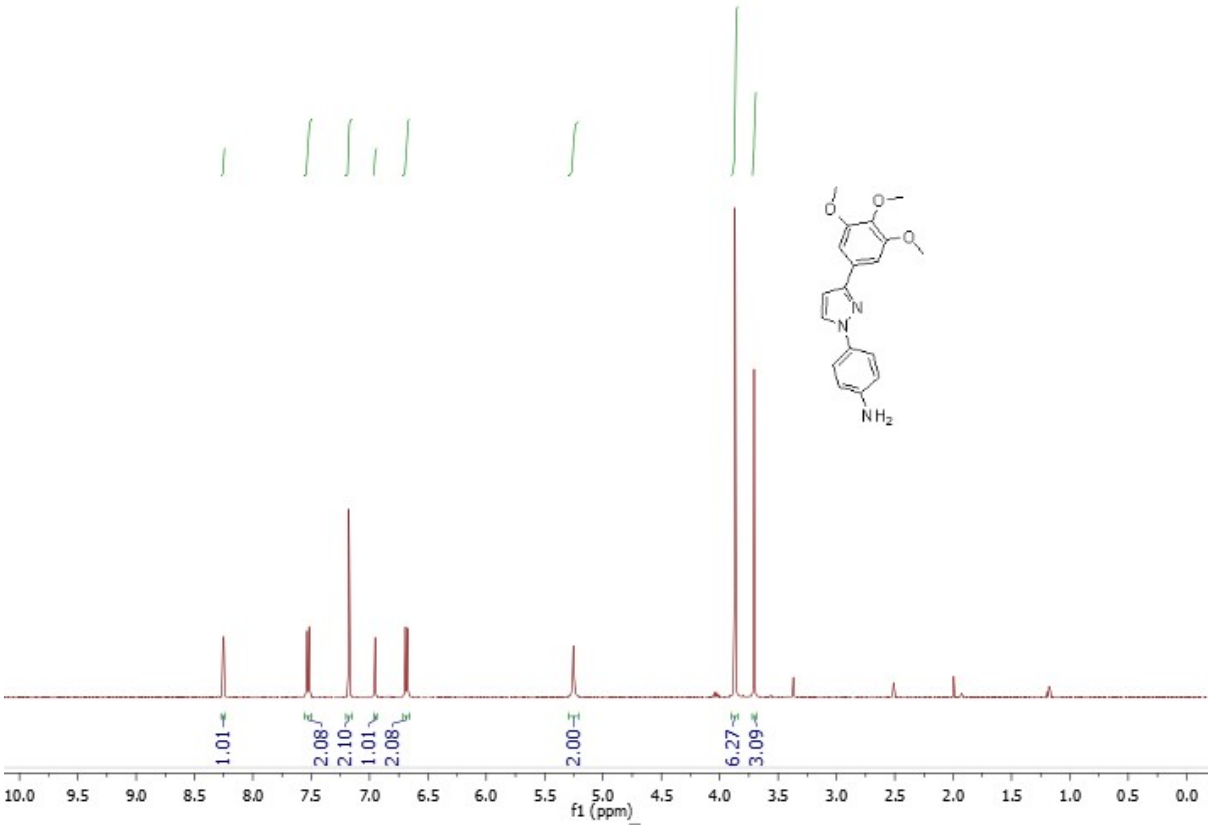


^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **5g**

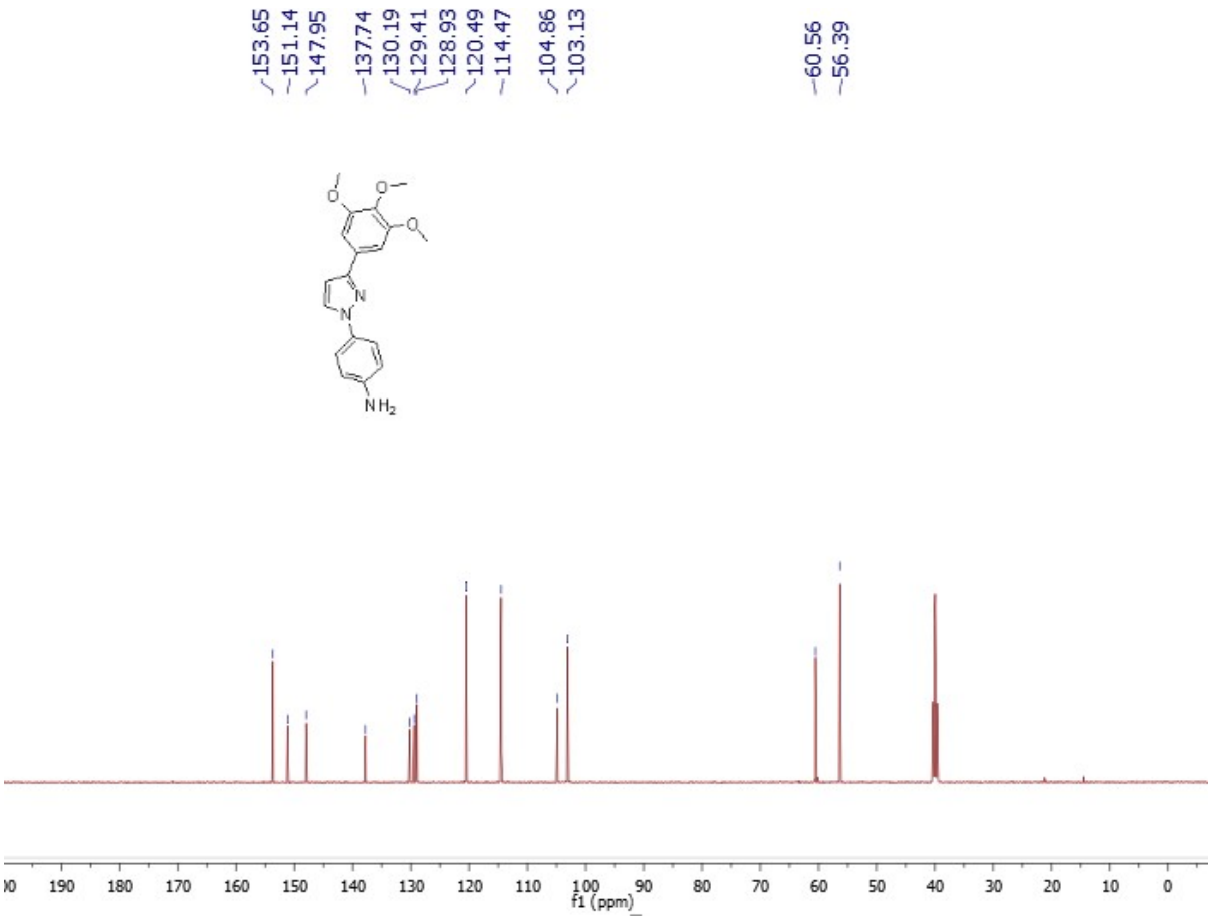
m/z calcd. for $[C_{15}H_{11}Cl_2N_3+H]^+$ 304.0408; Observed 304.0398



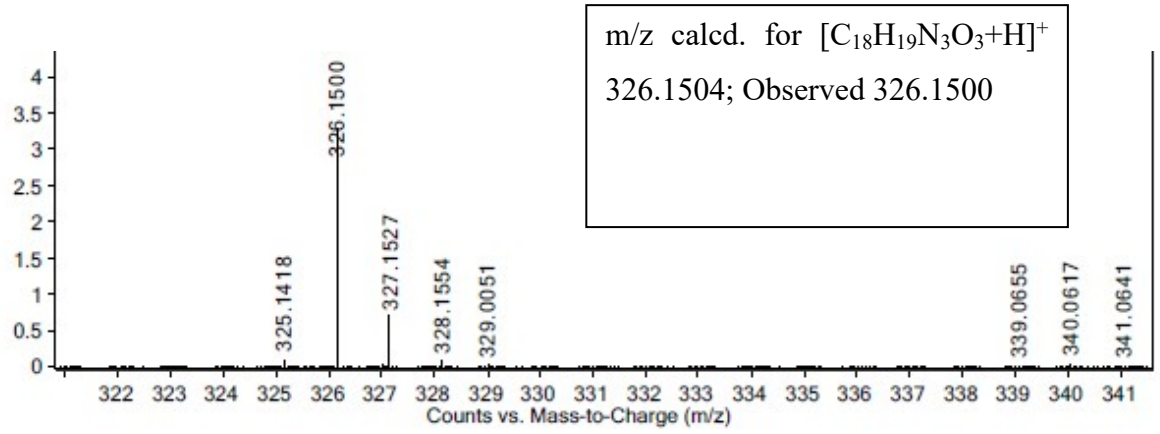
Mass spectrum of compound **5g**



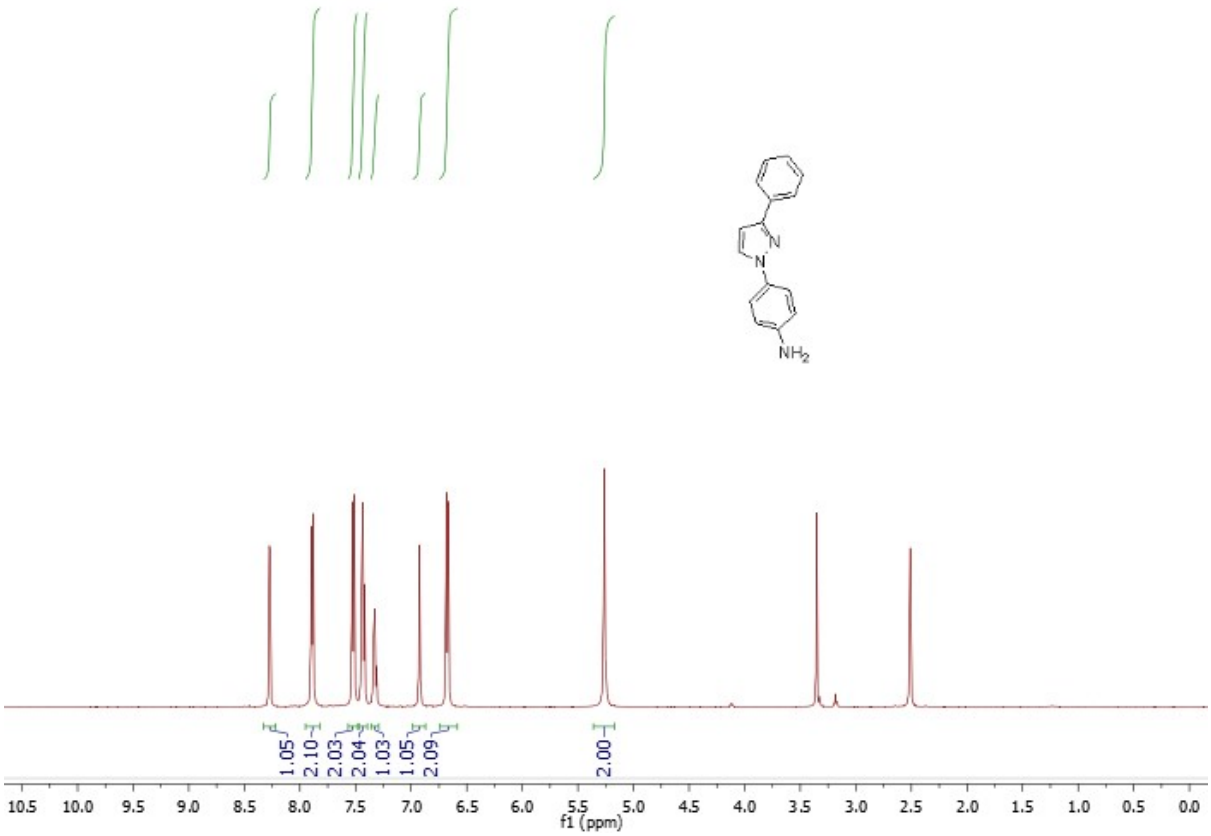
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **5h**



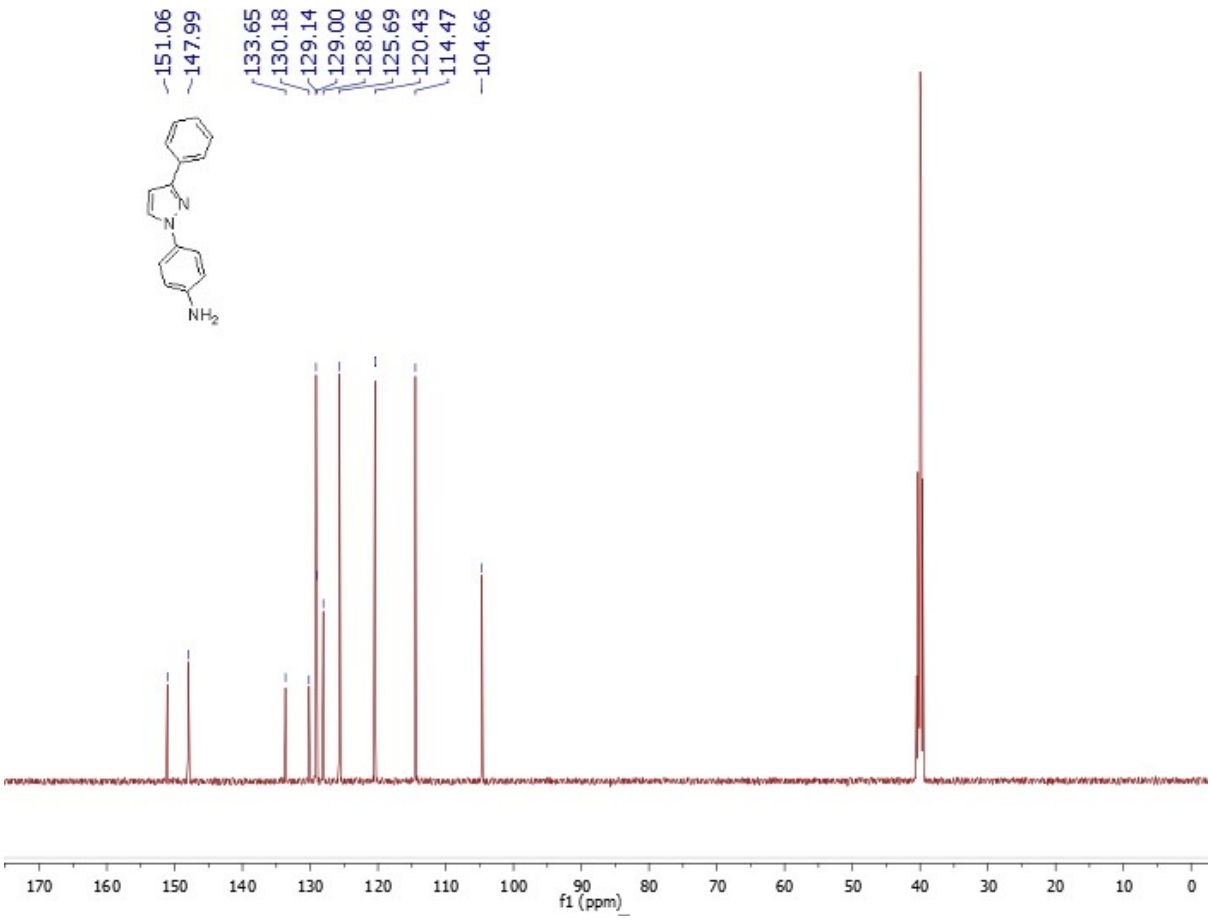
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **5h**



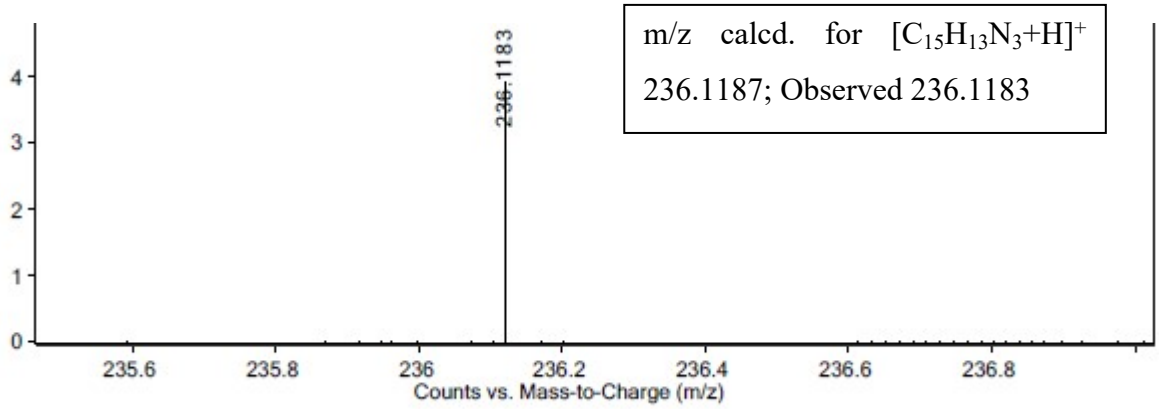
Mass spectrum of compound **5h**



^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **5i**



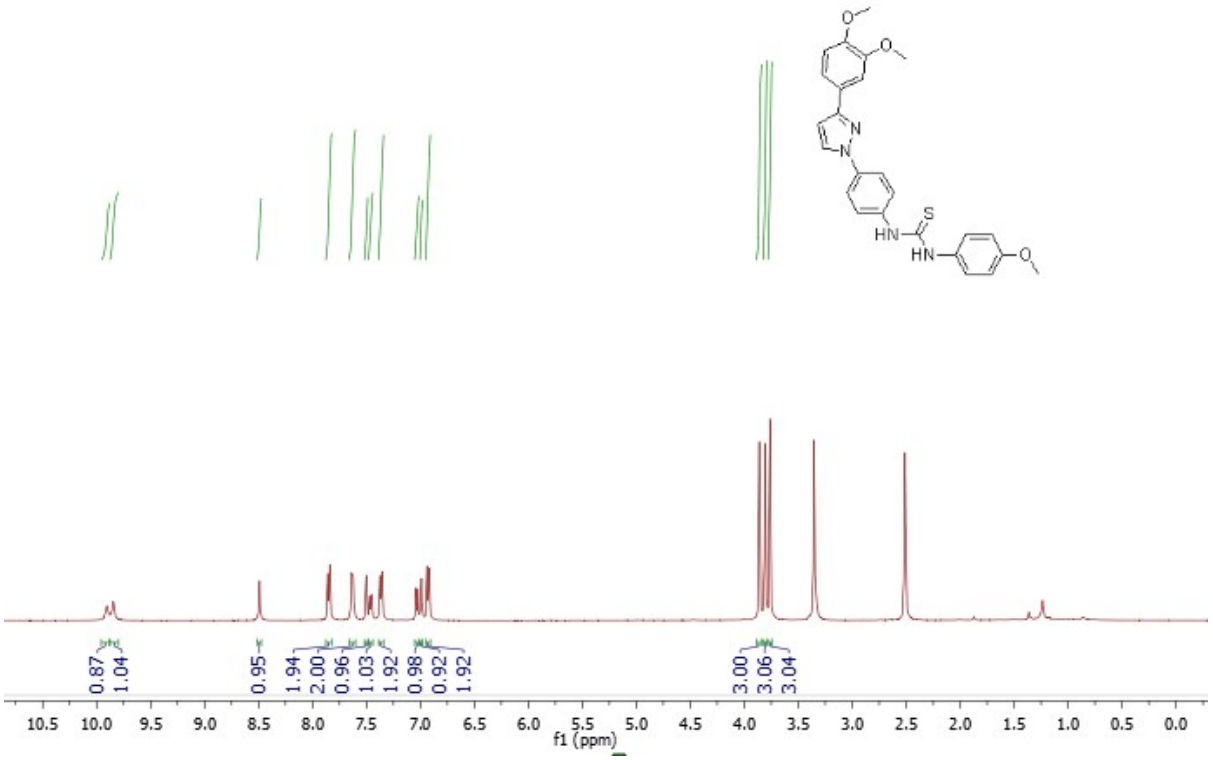
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **5i**



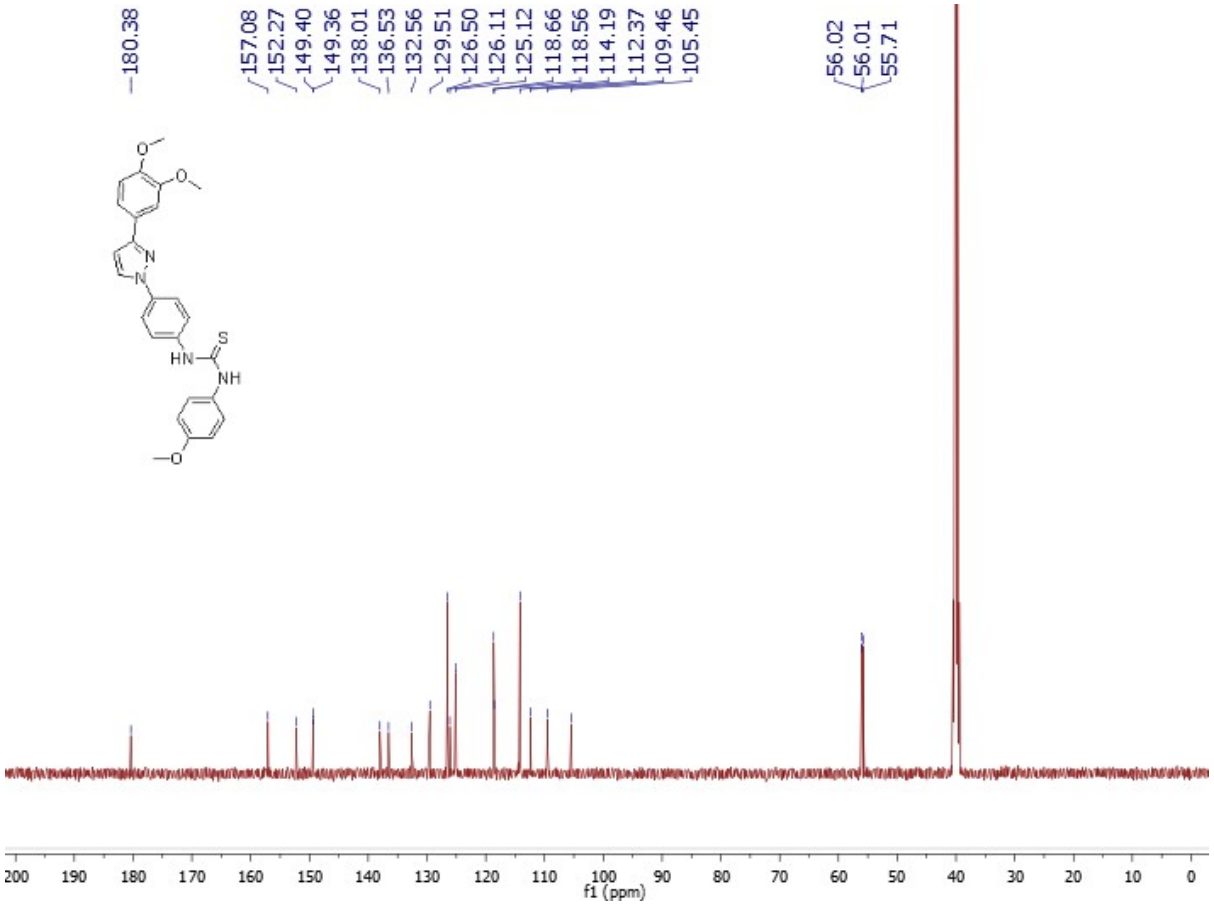
m/z calcd. for $[C_{15}H_{13}N_3+H]^+$ 236.1187; Observed 236.1183

Mass spectrum of compound **5i**

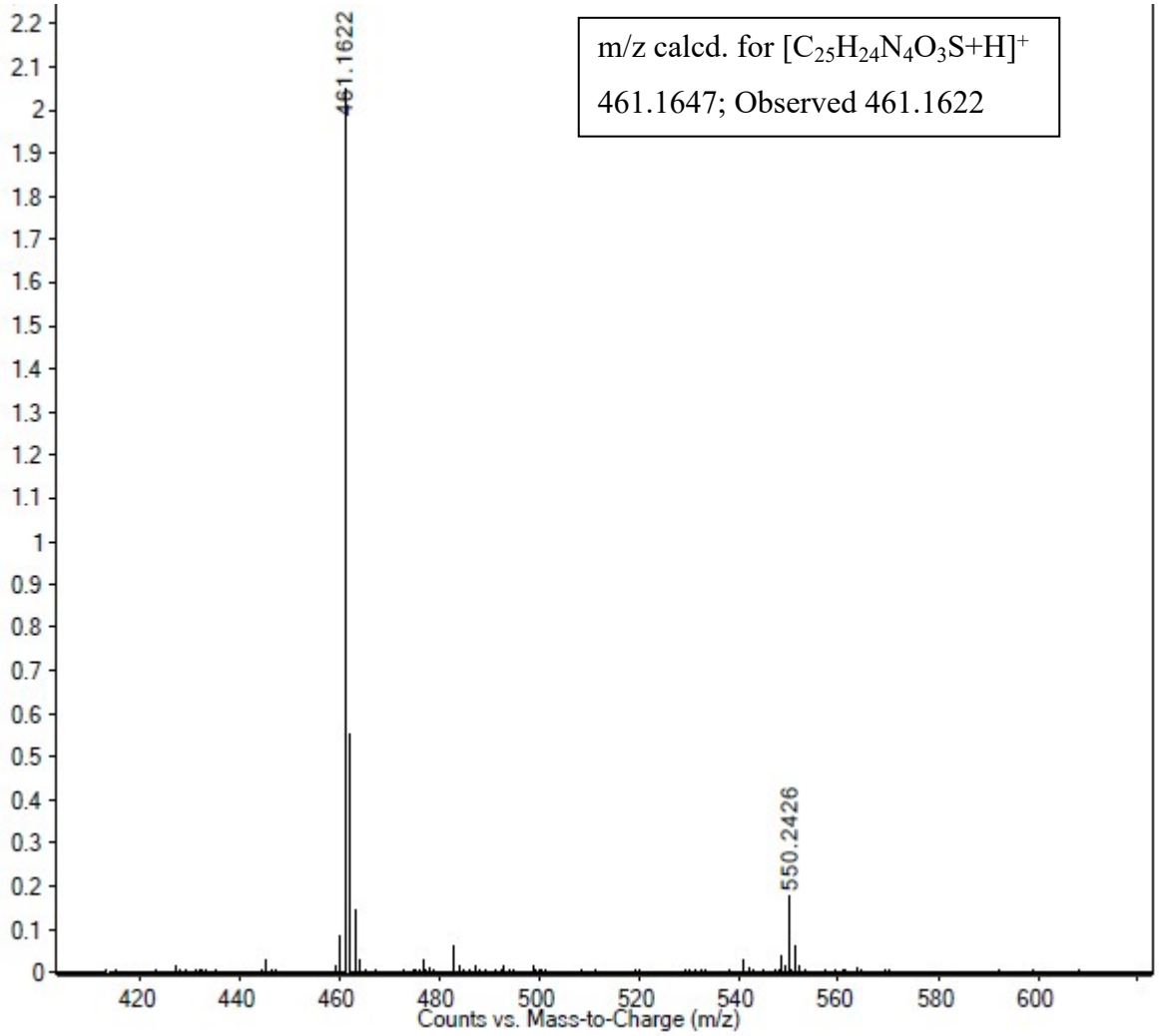
3. **^{1}H, ^{13}C and HRMS spectra of final compounds, 6-10, 15a-c**



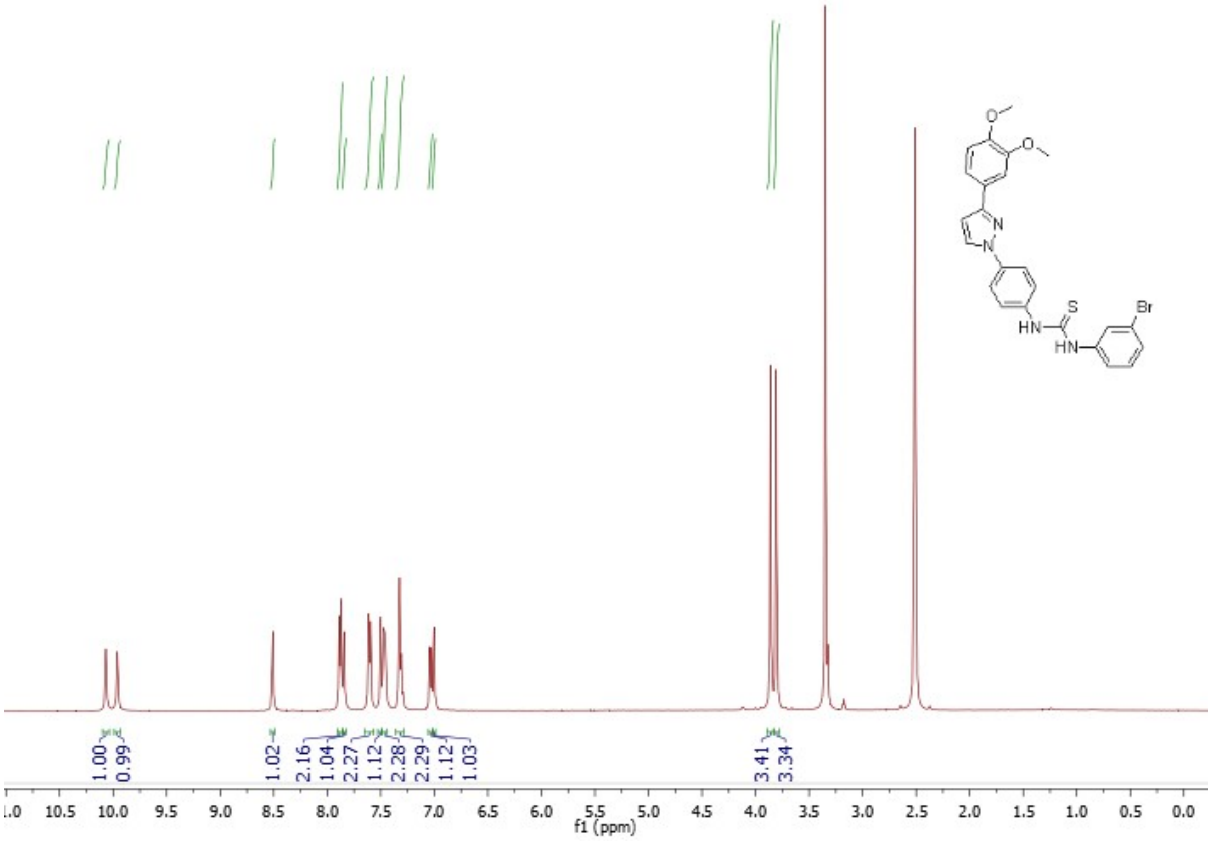
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6a**



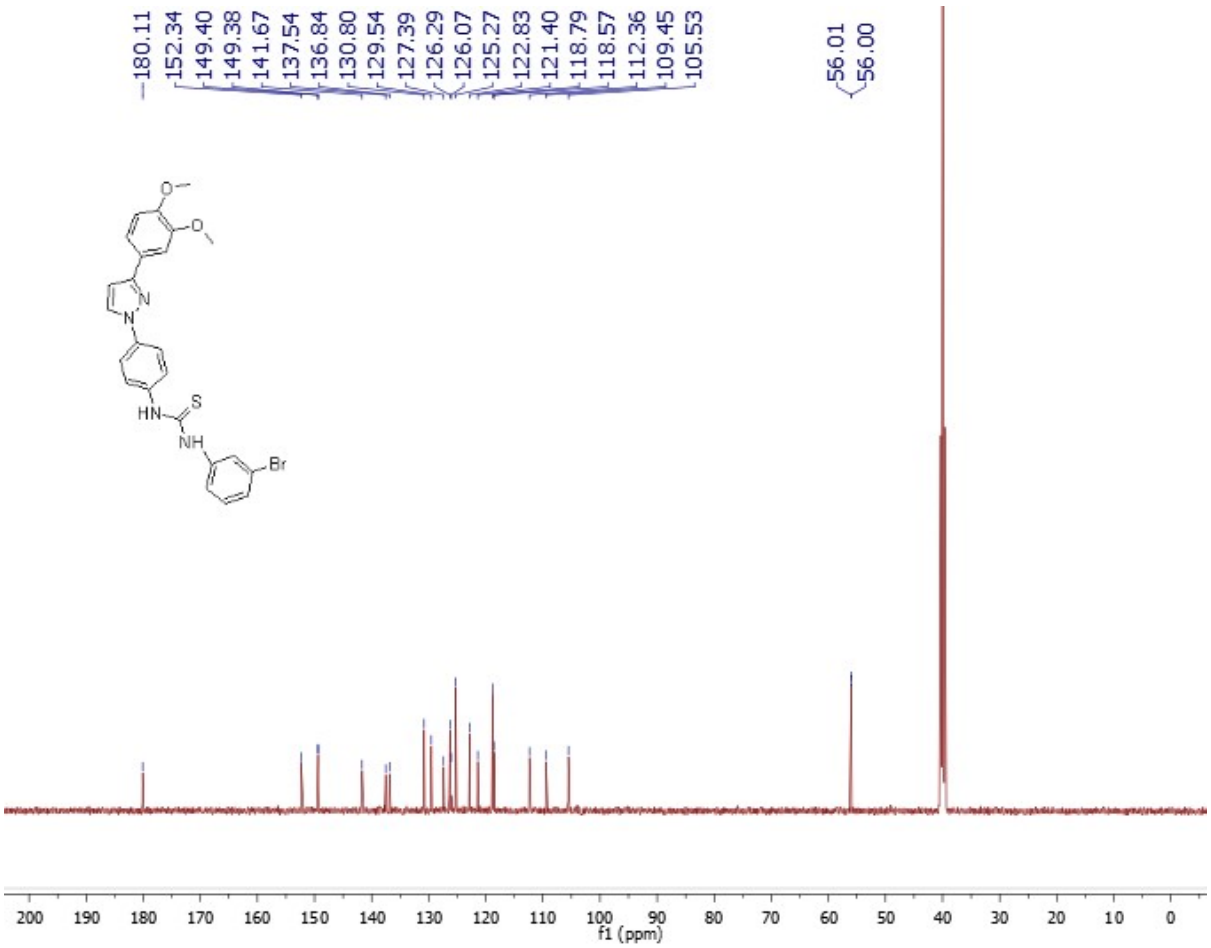
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6a**



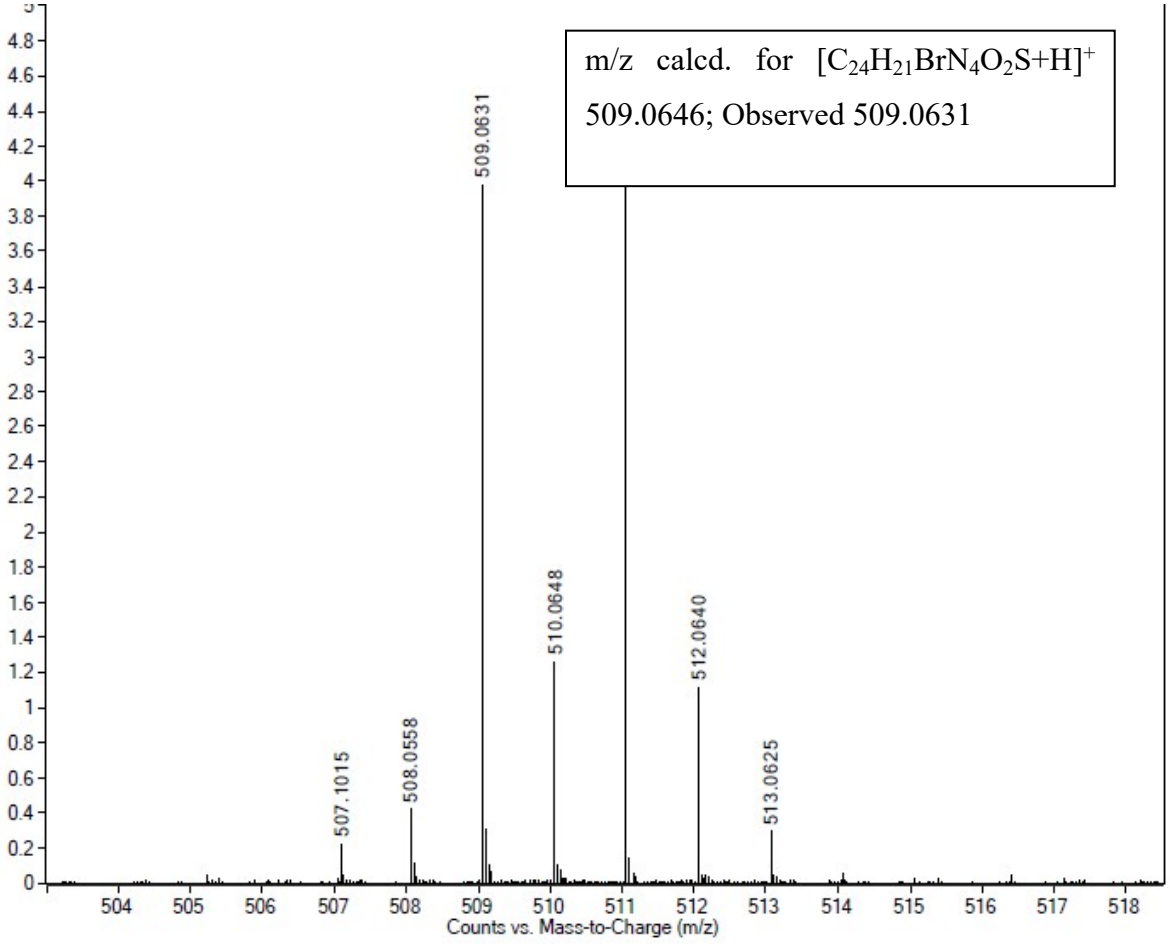
Mass spectrum of compound **6a**



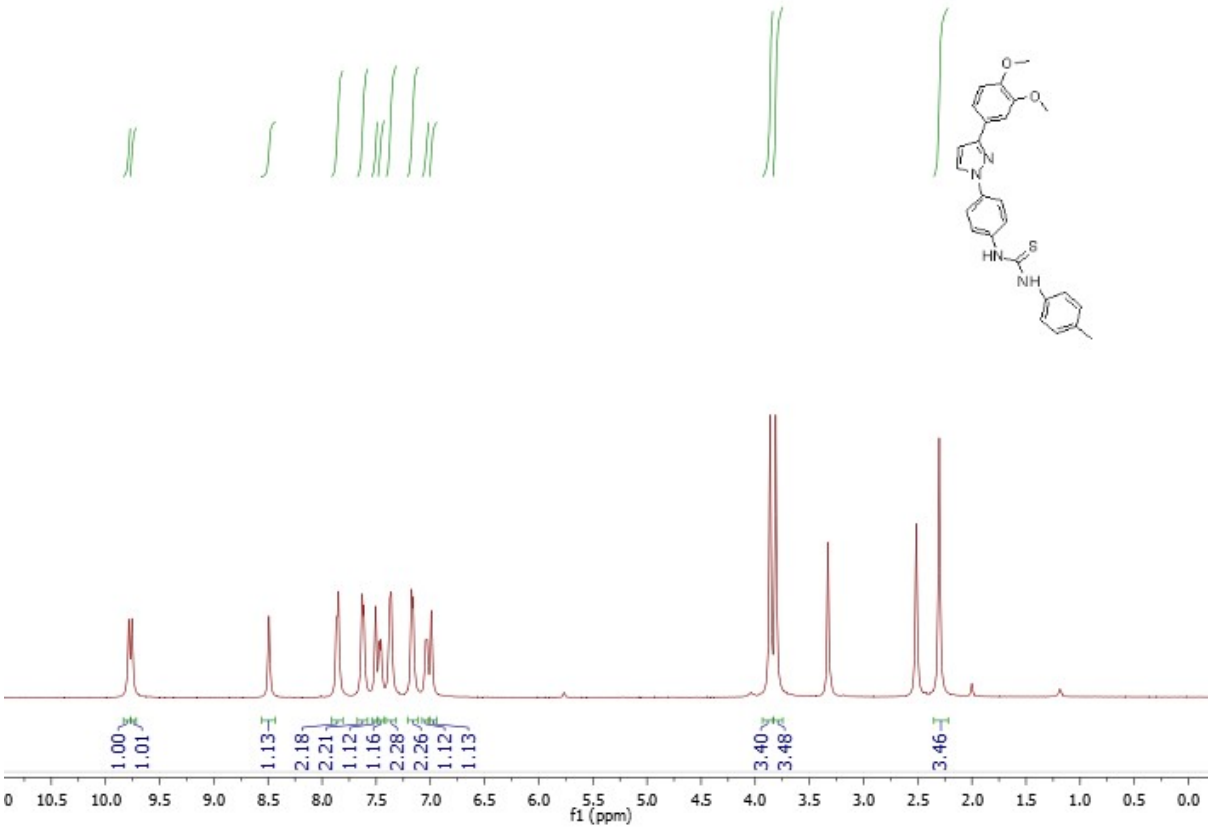
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6b**



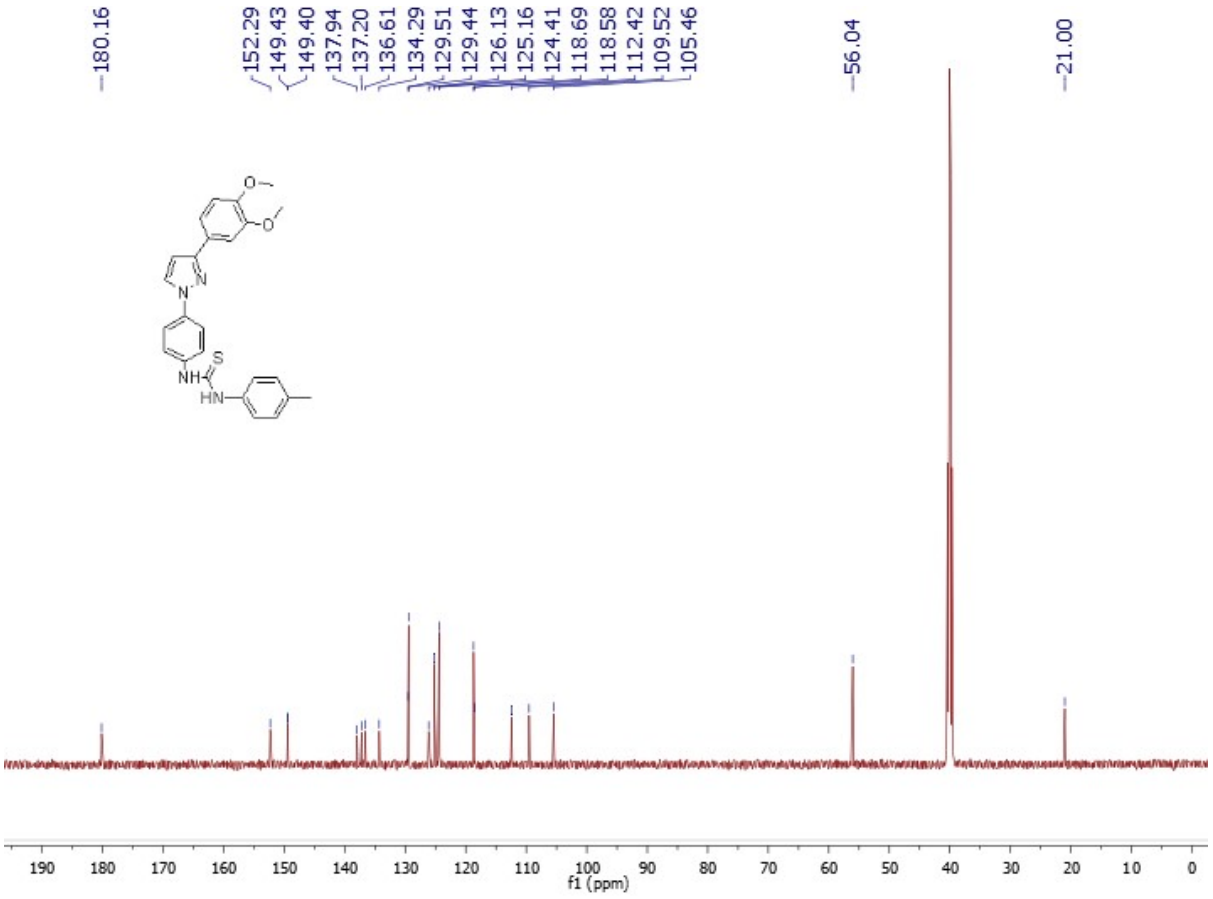
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6b**



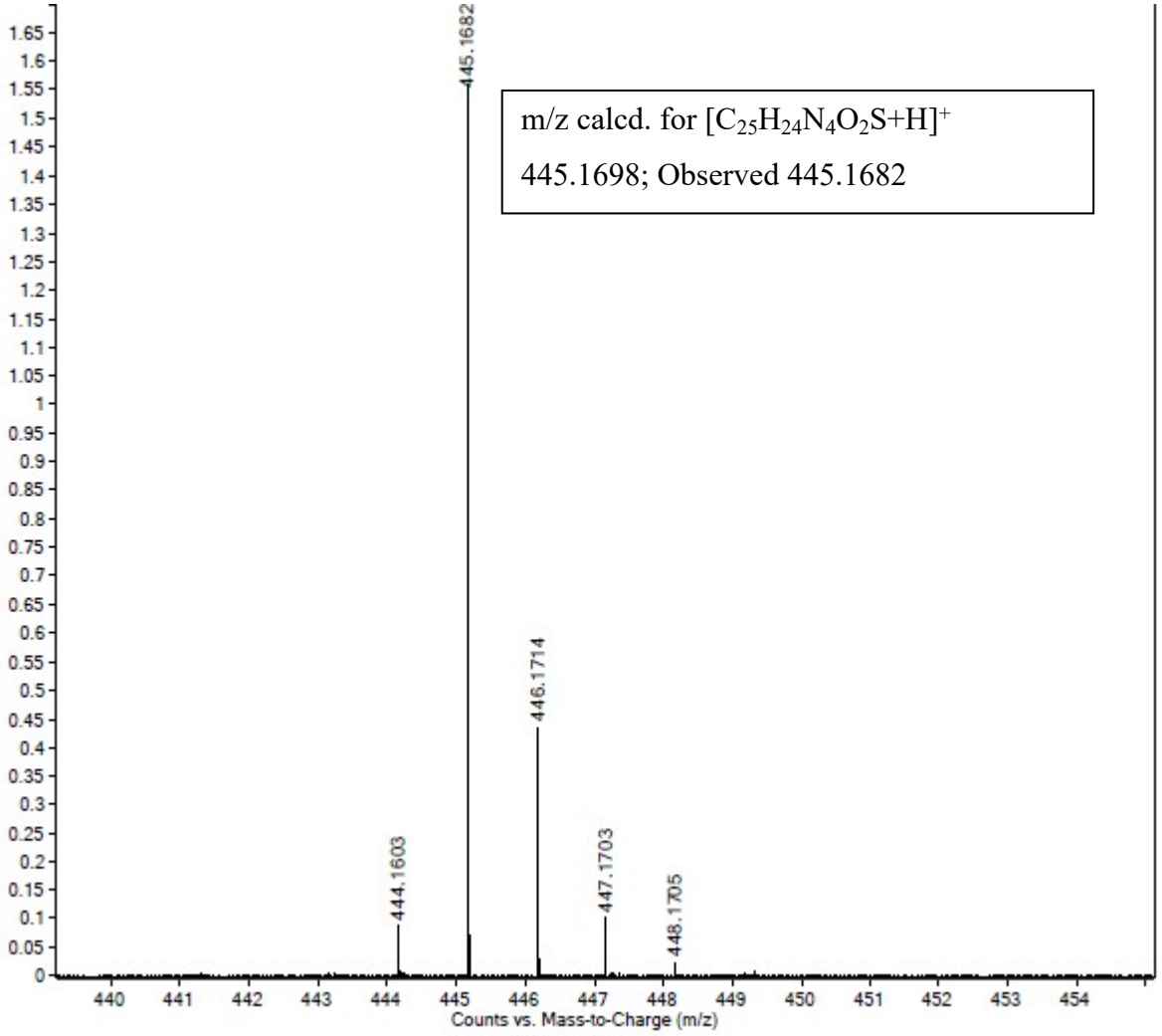
Mass spectrum of compound **6b**



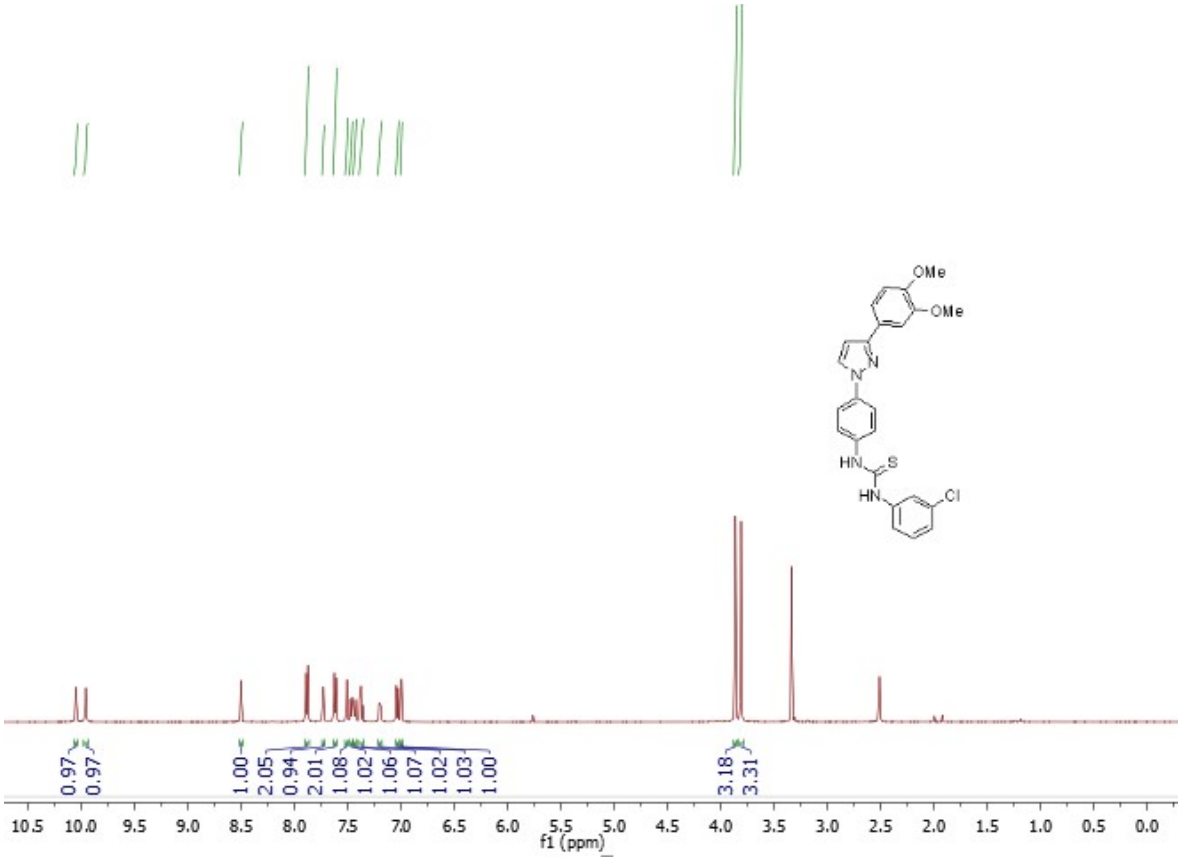
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6c**



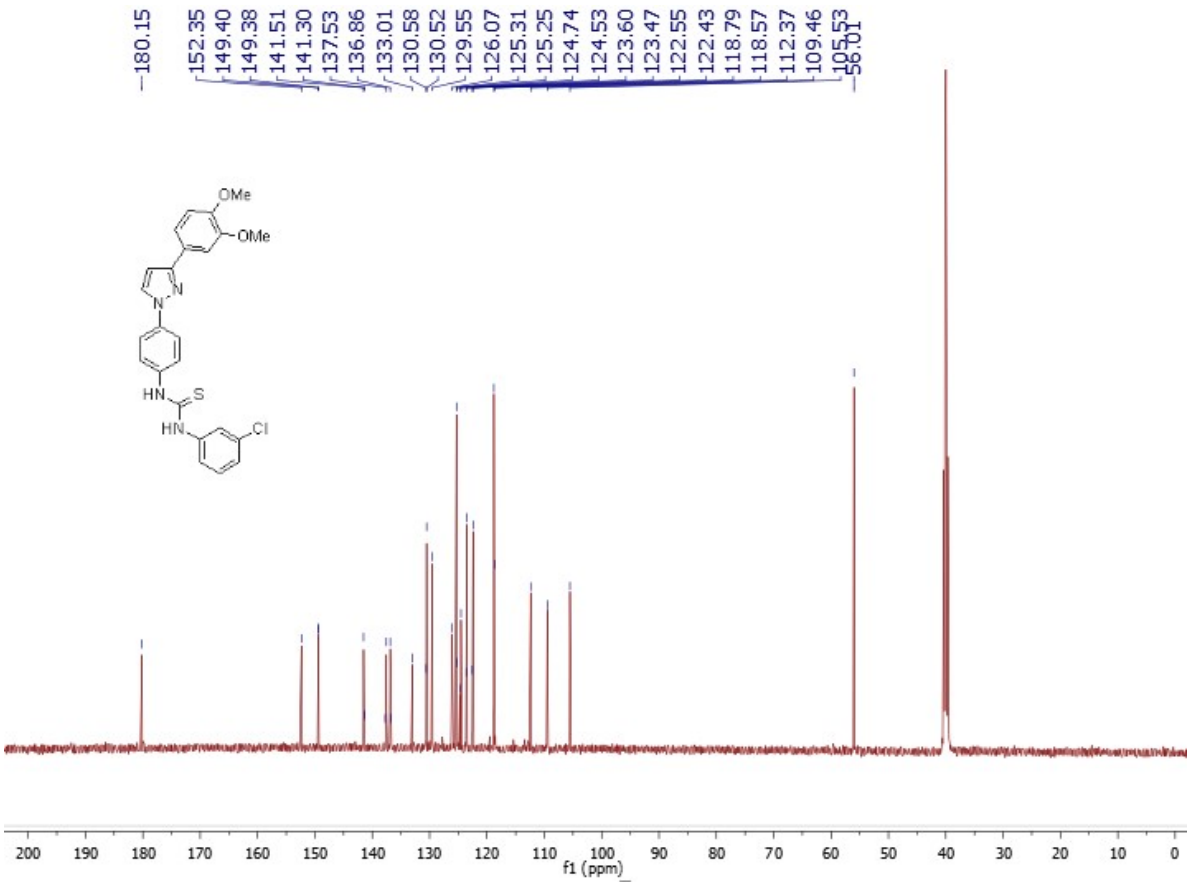
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6c**



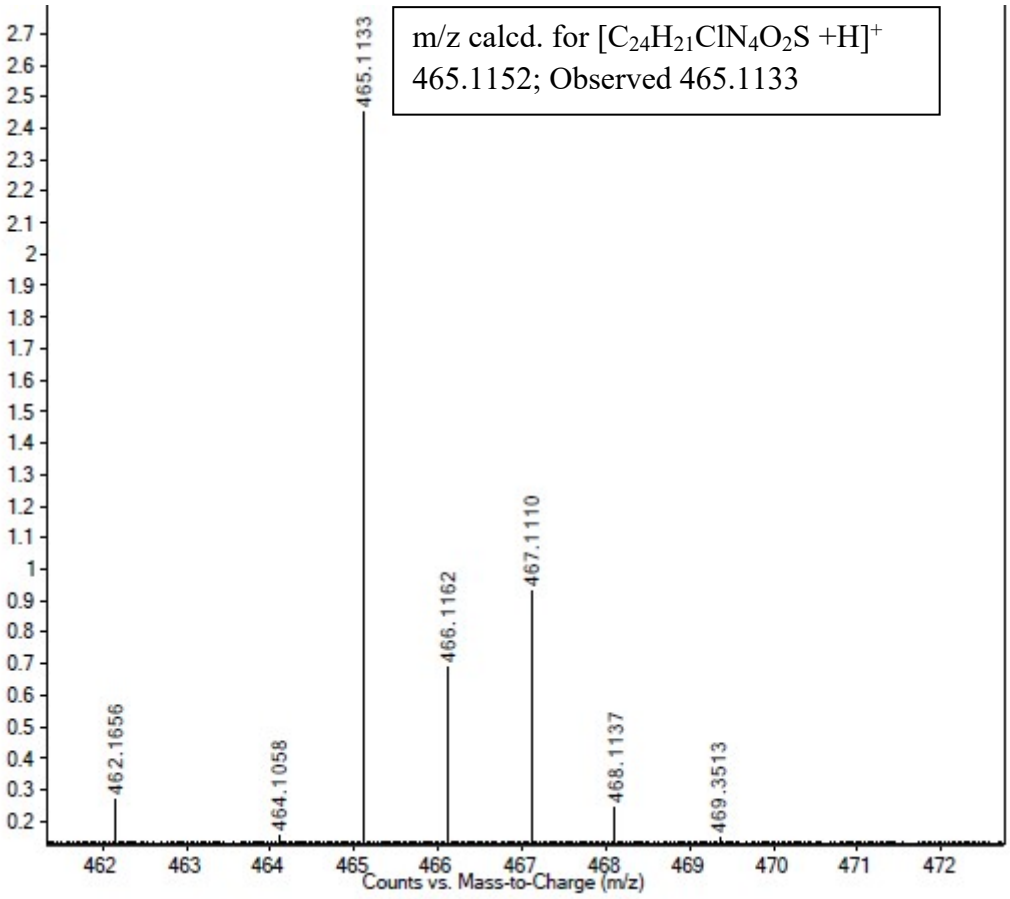
Mass spectrum of compound **6c**



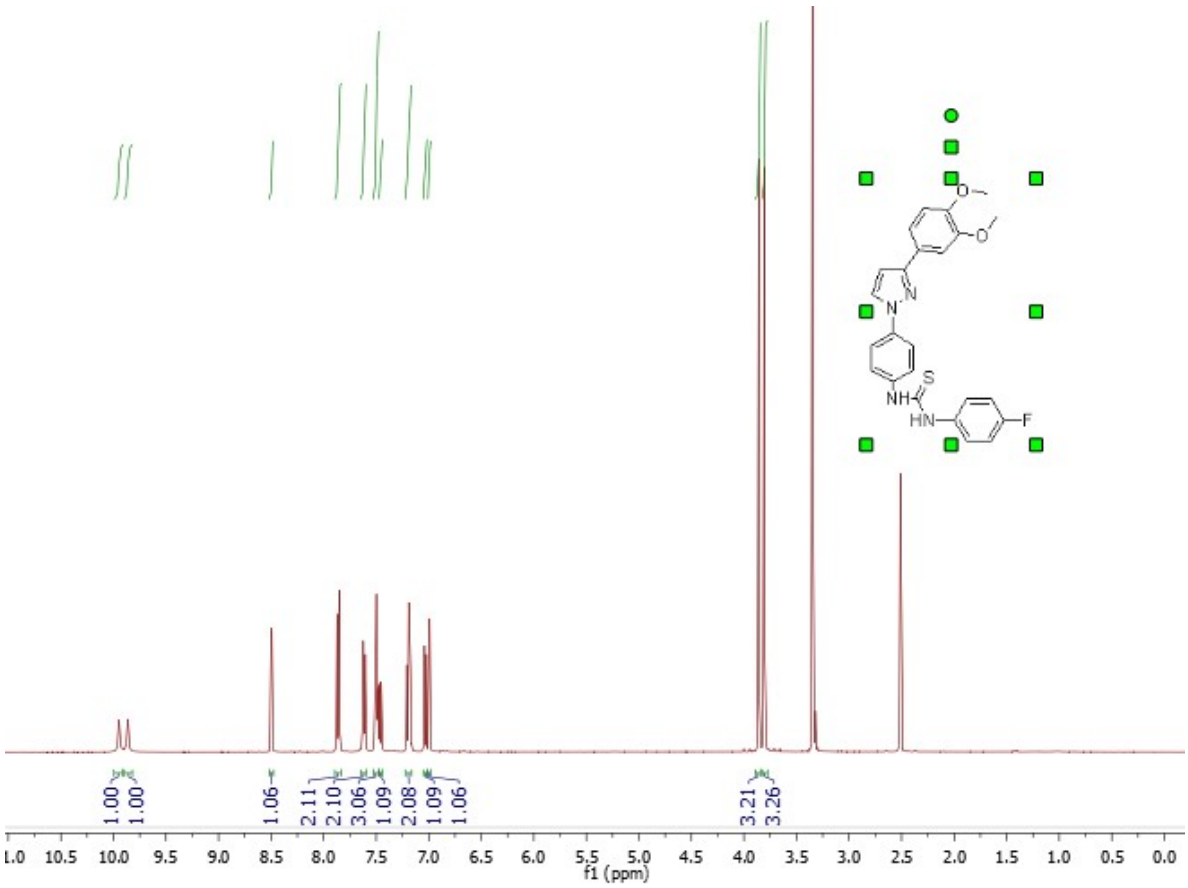
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6d**



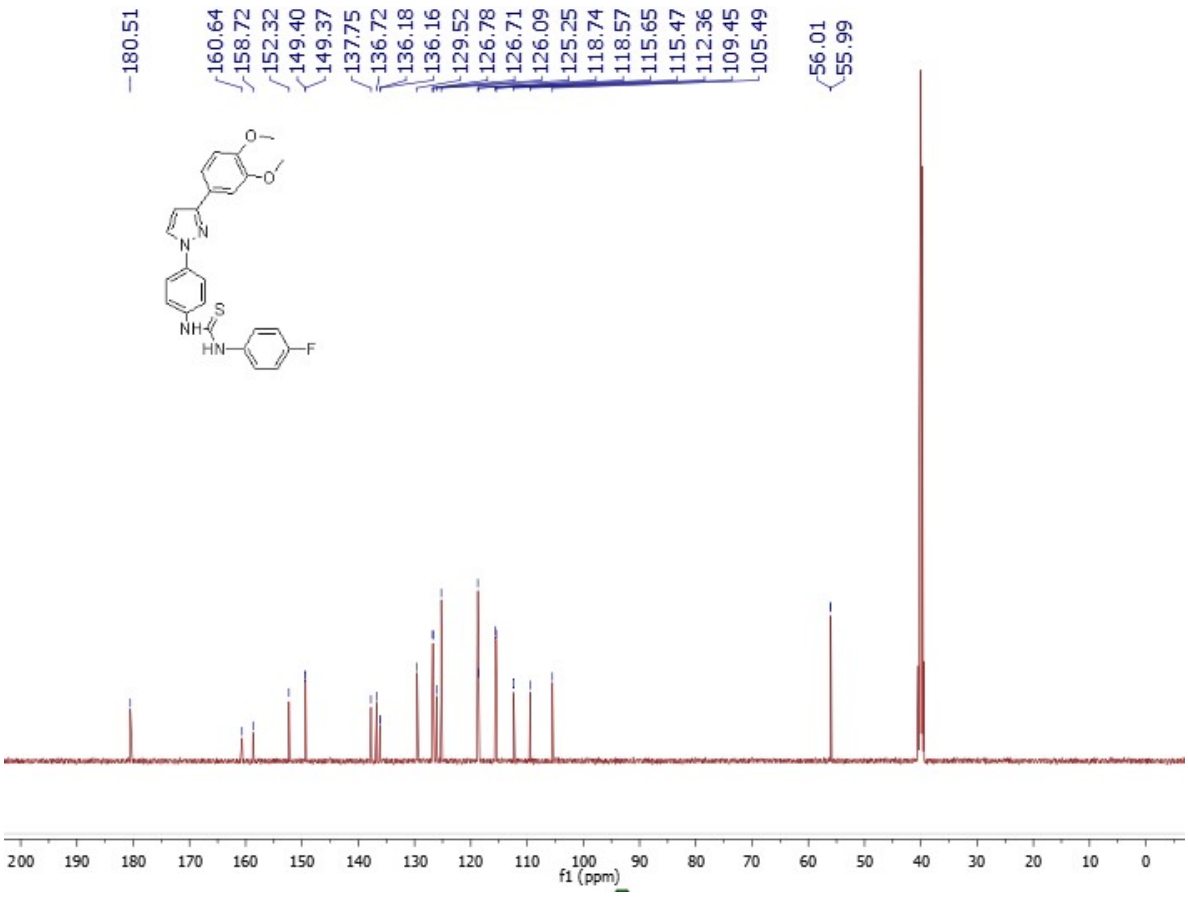
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6d**



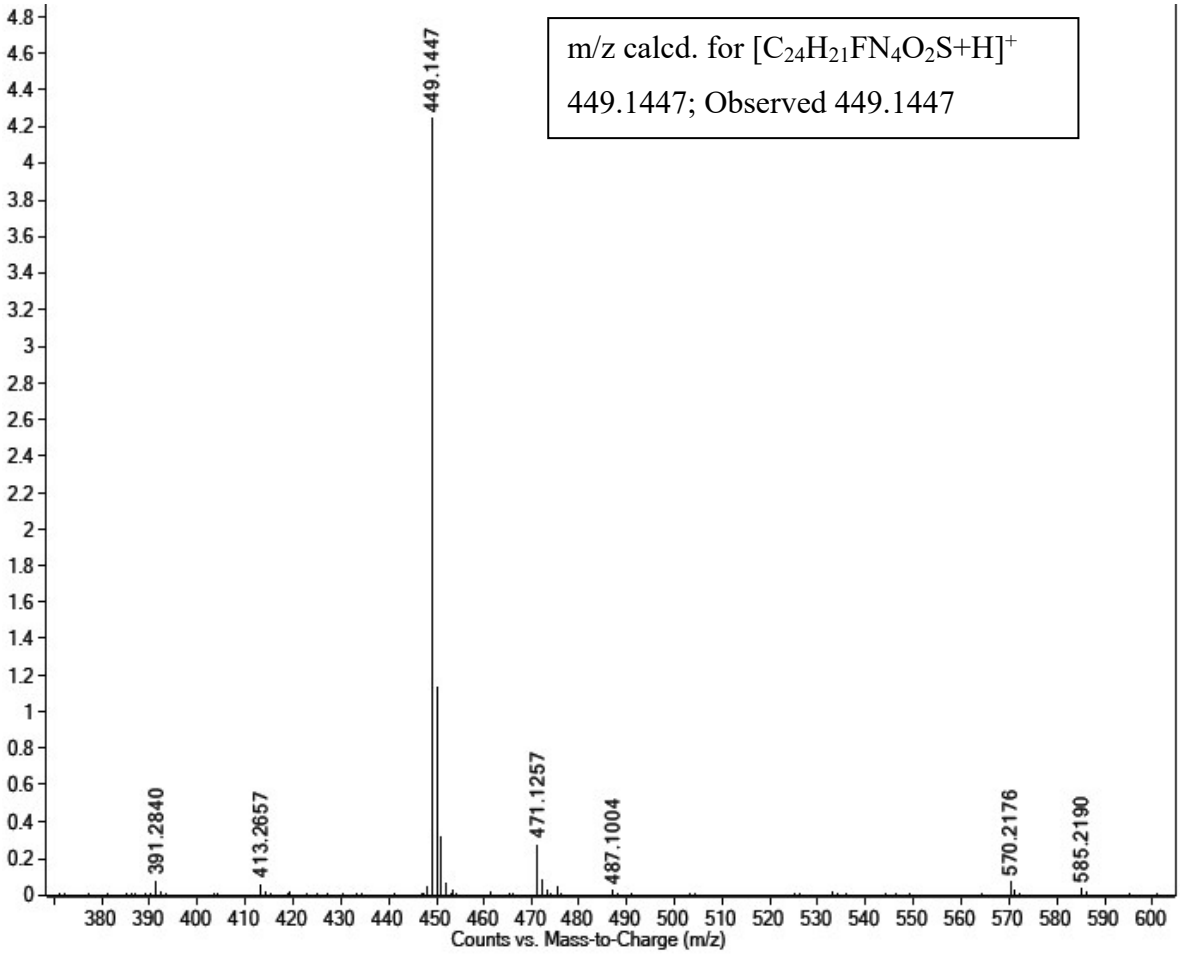
Mass spectrum of compound **6d**



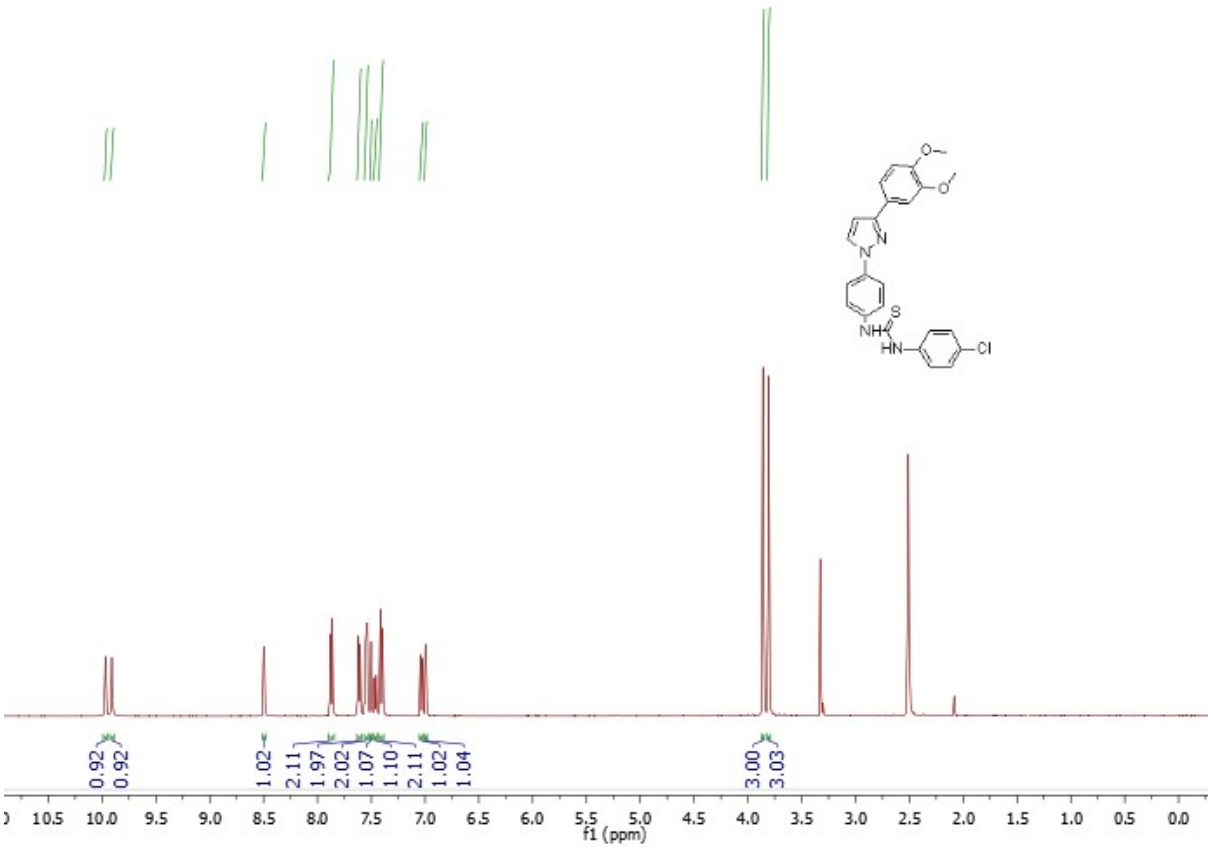
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6e**



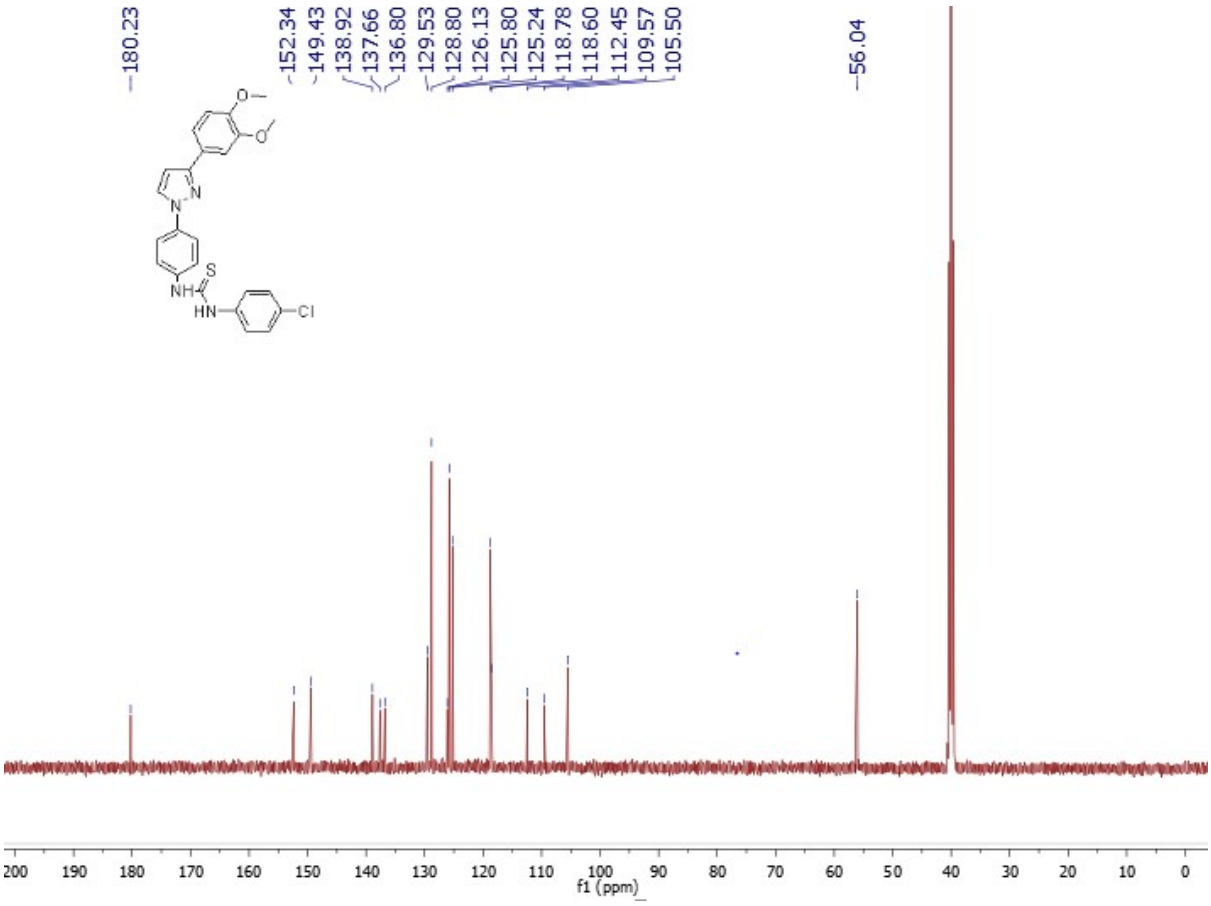
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6e**



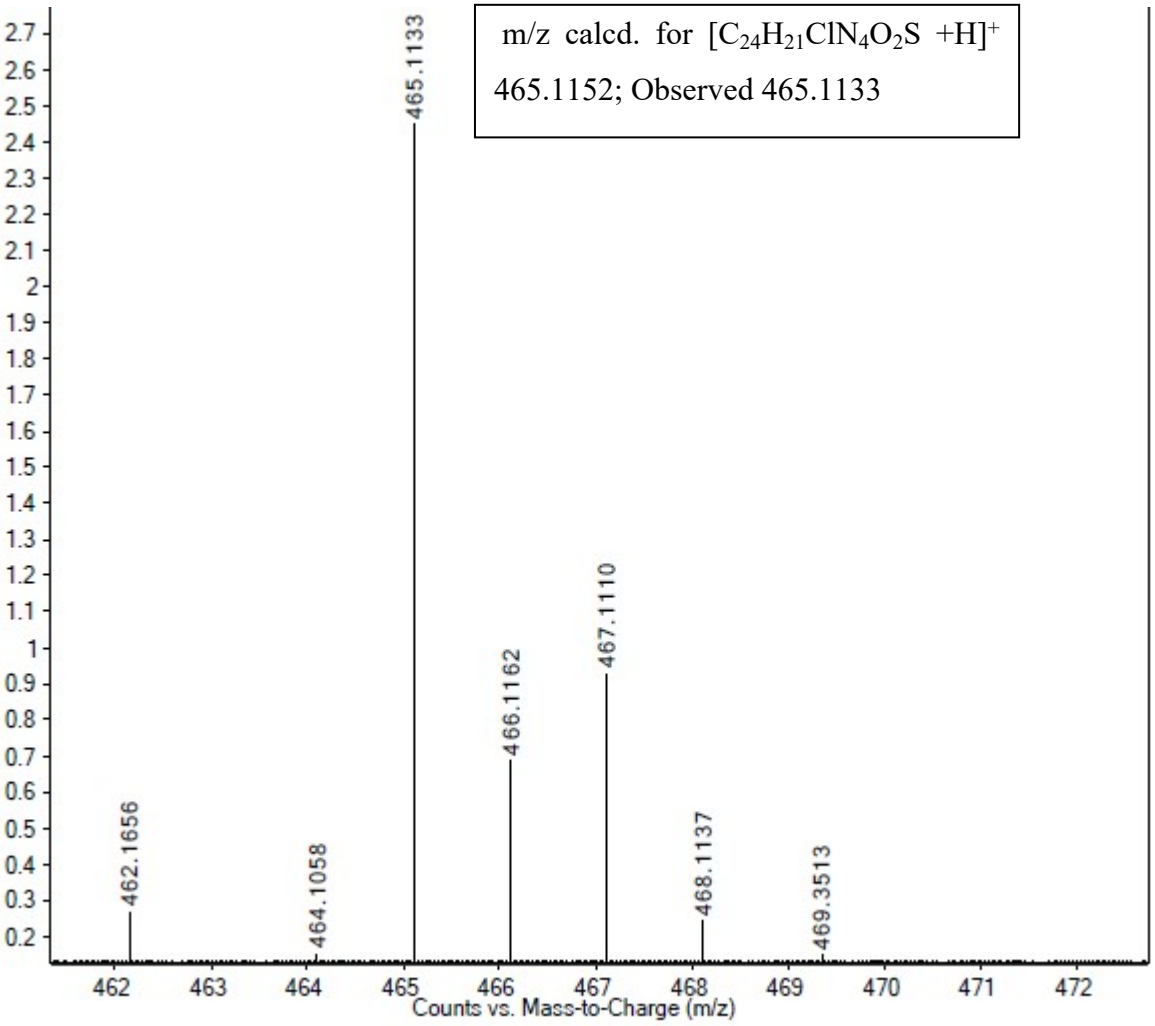
Mass spectrum of compound **6e**



^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6f**

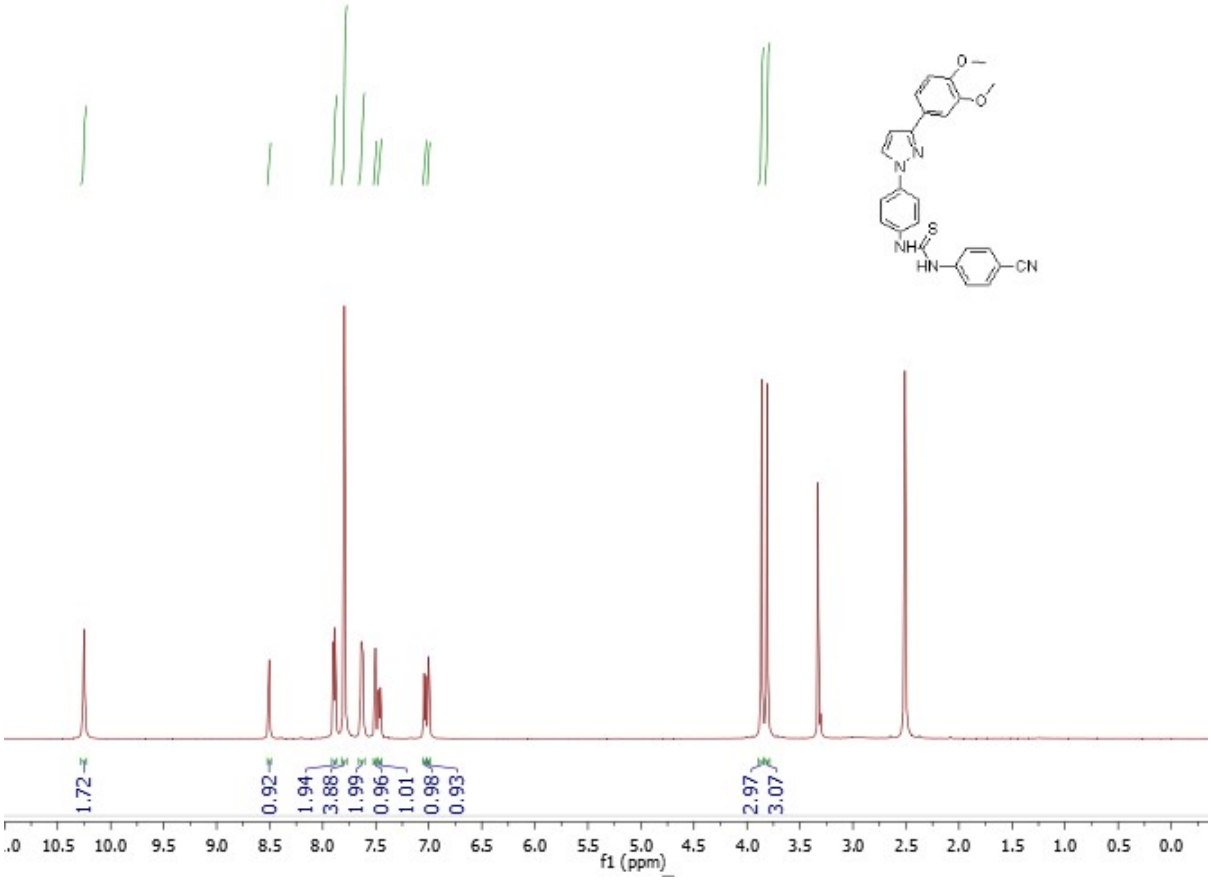


^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6f**

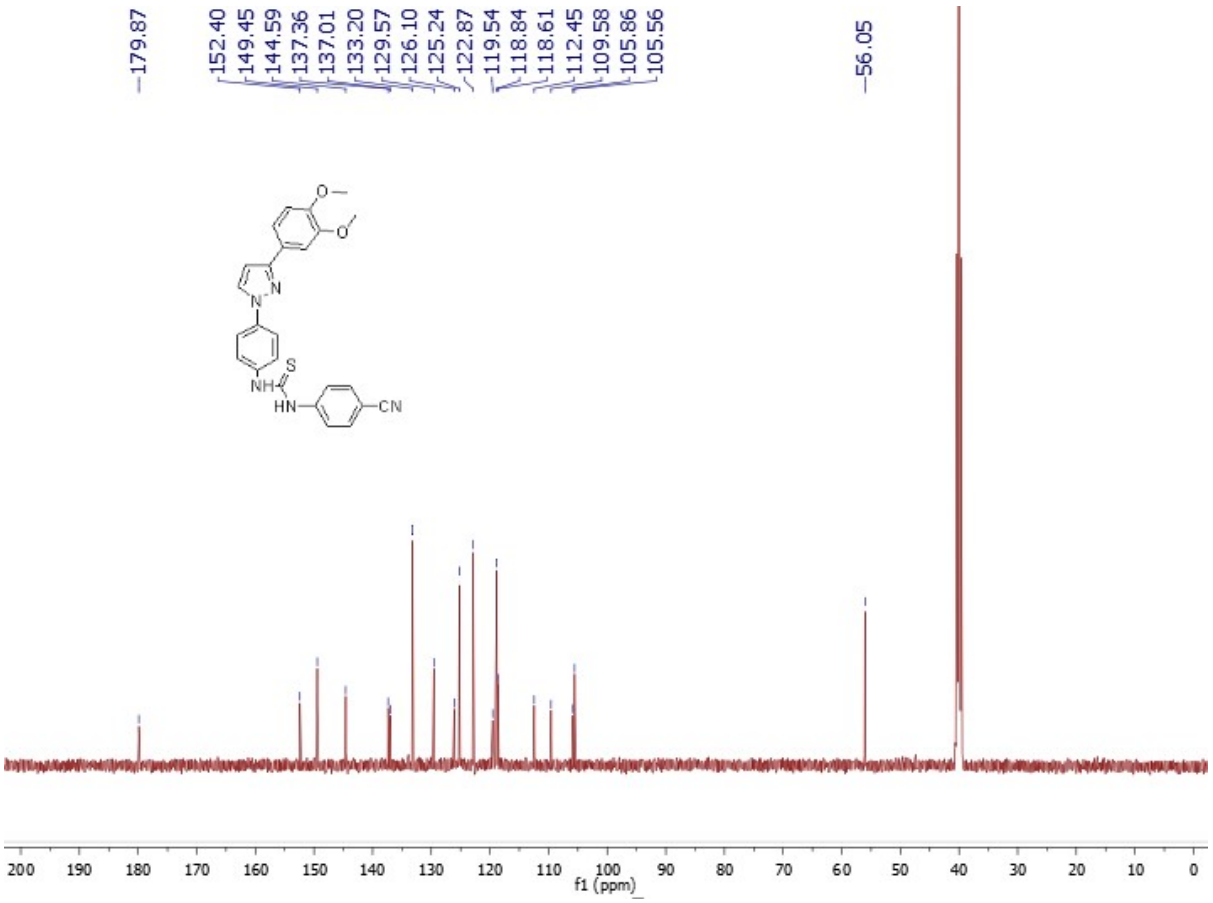


M

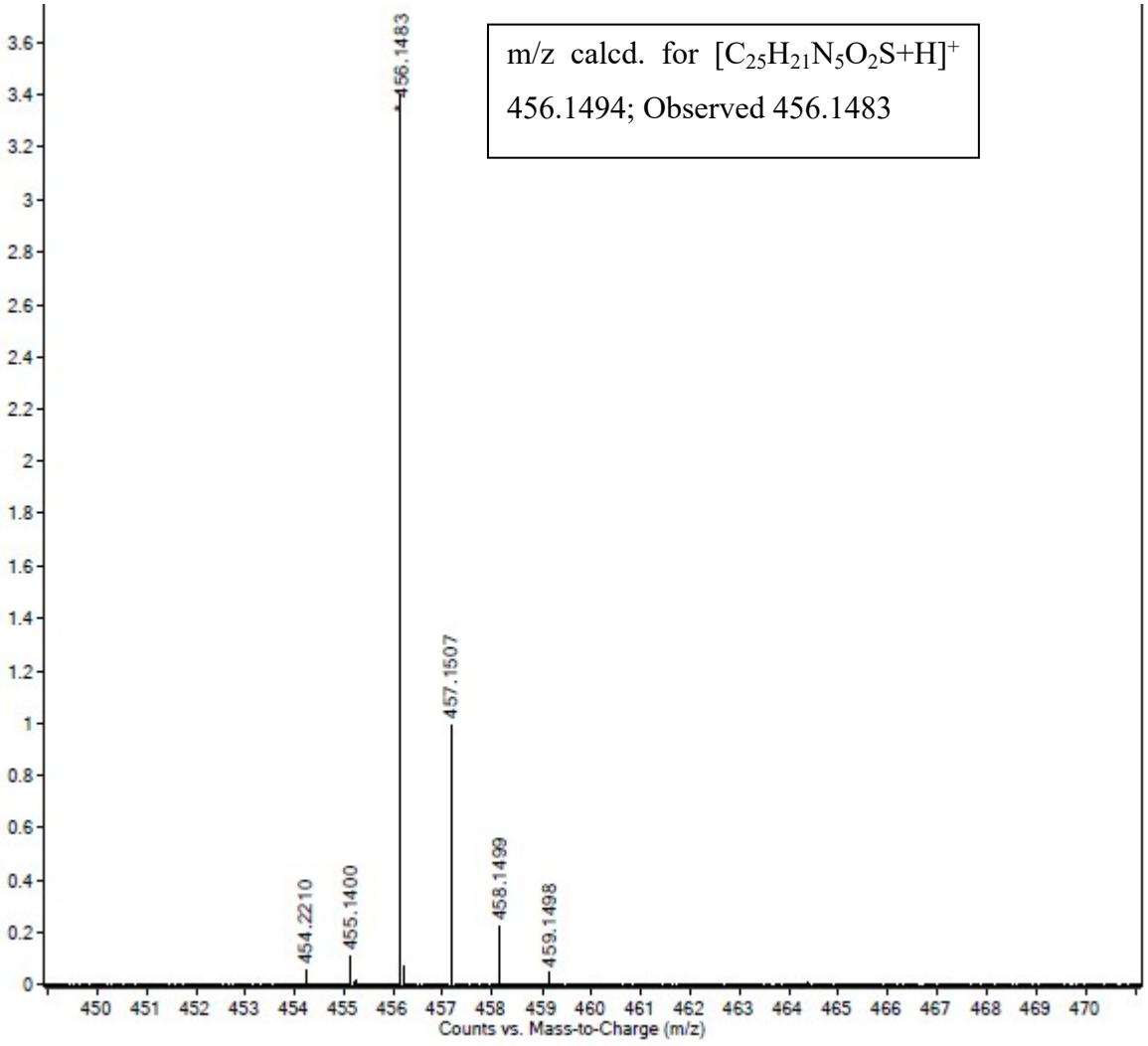
ass spectrum of compound **6f**



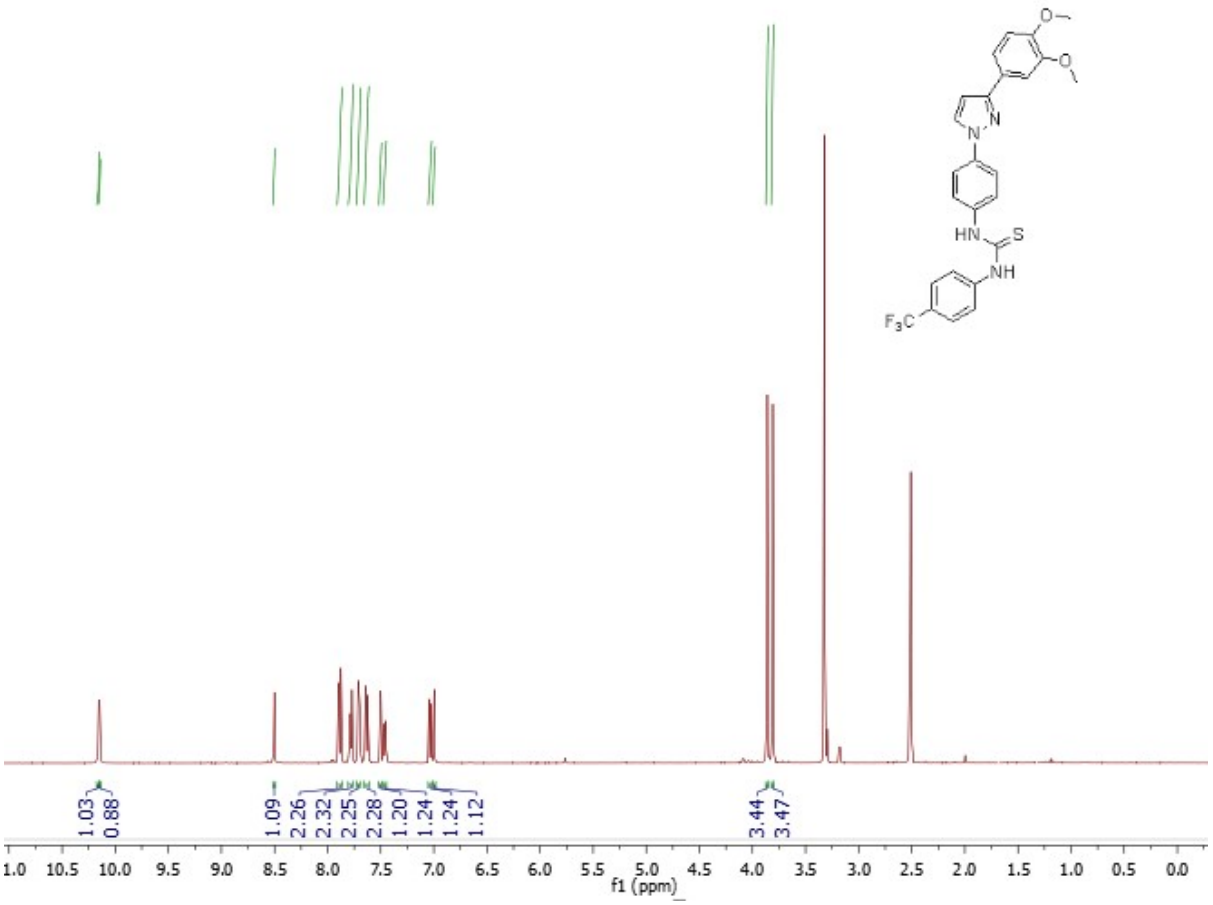
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6g**



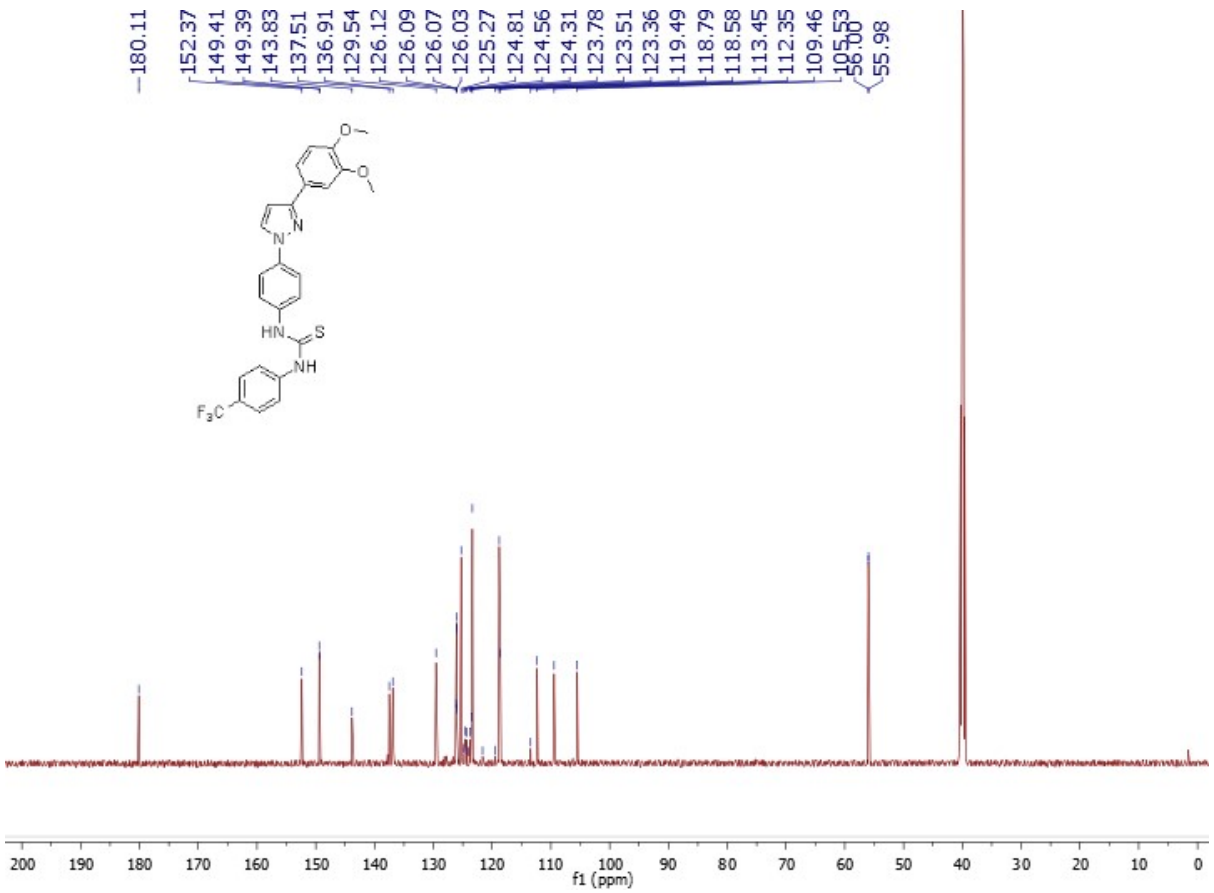
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6g**



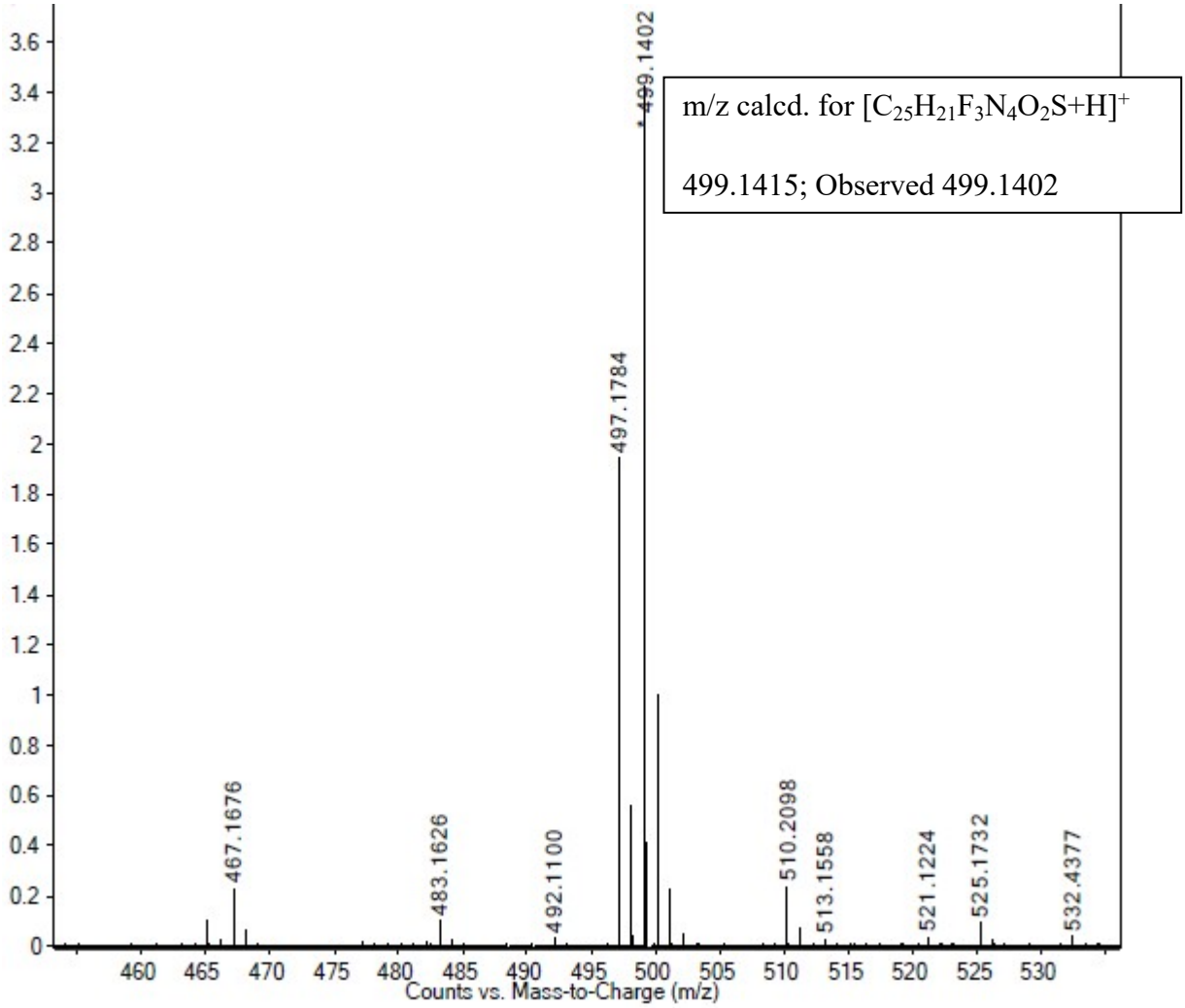
Mass spectrum of compound **6g**



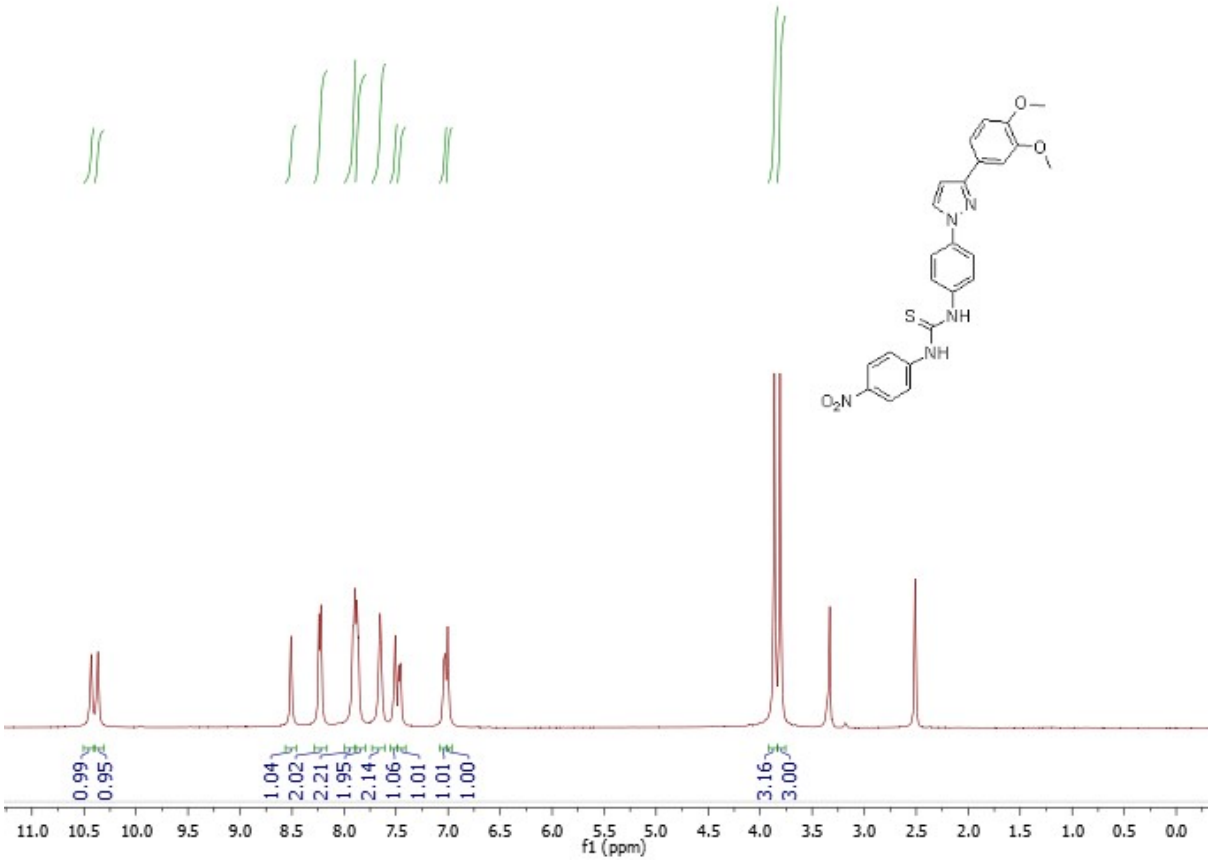
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6h**



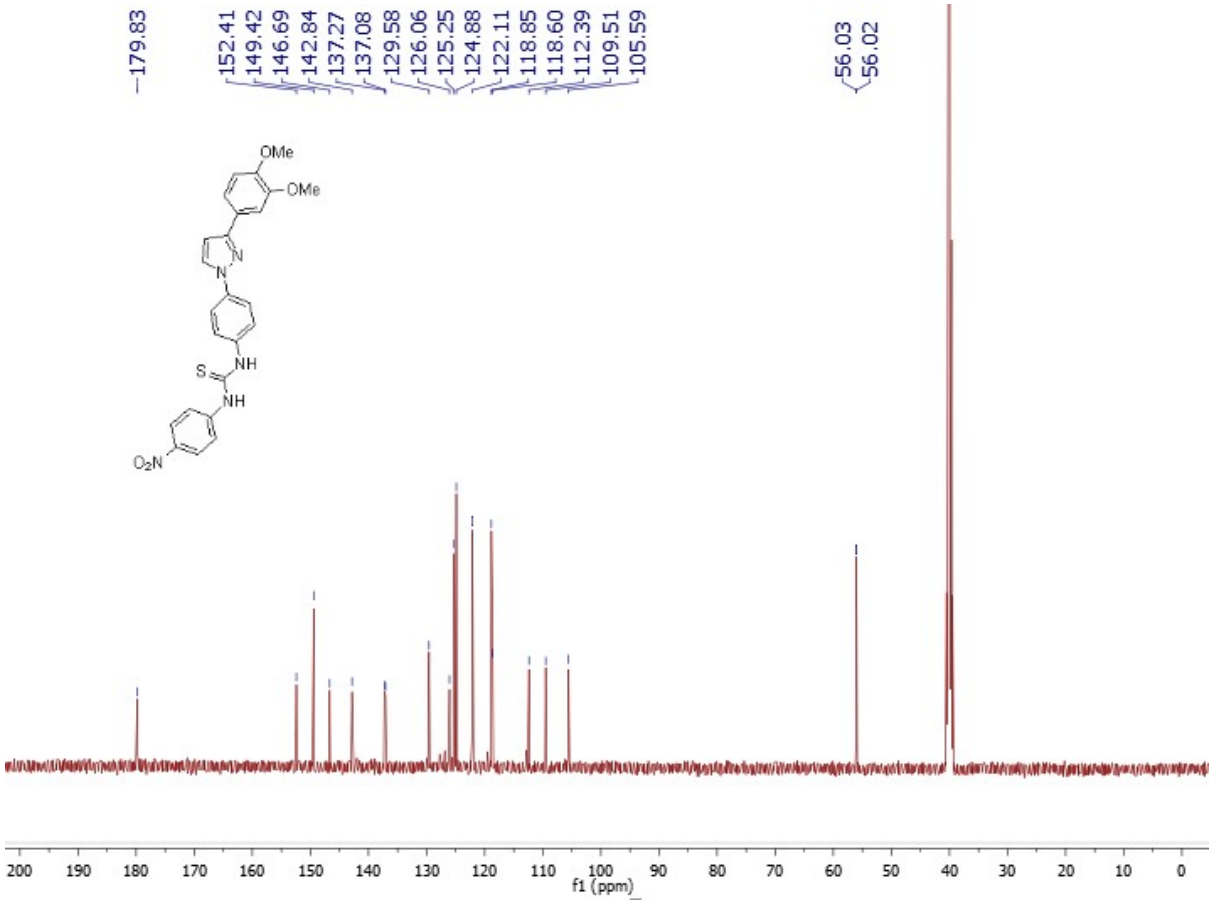
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6h**



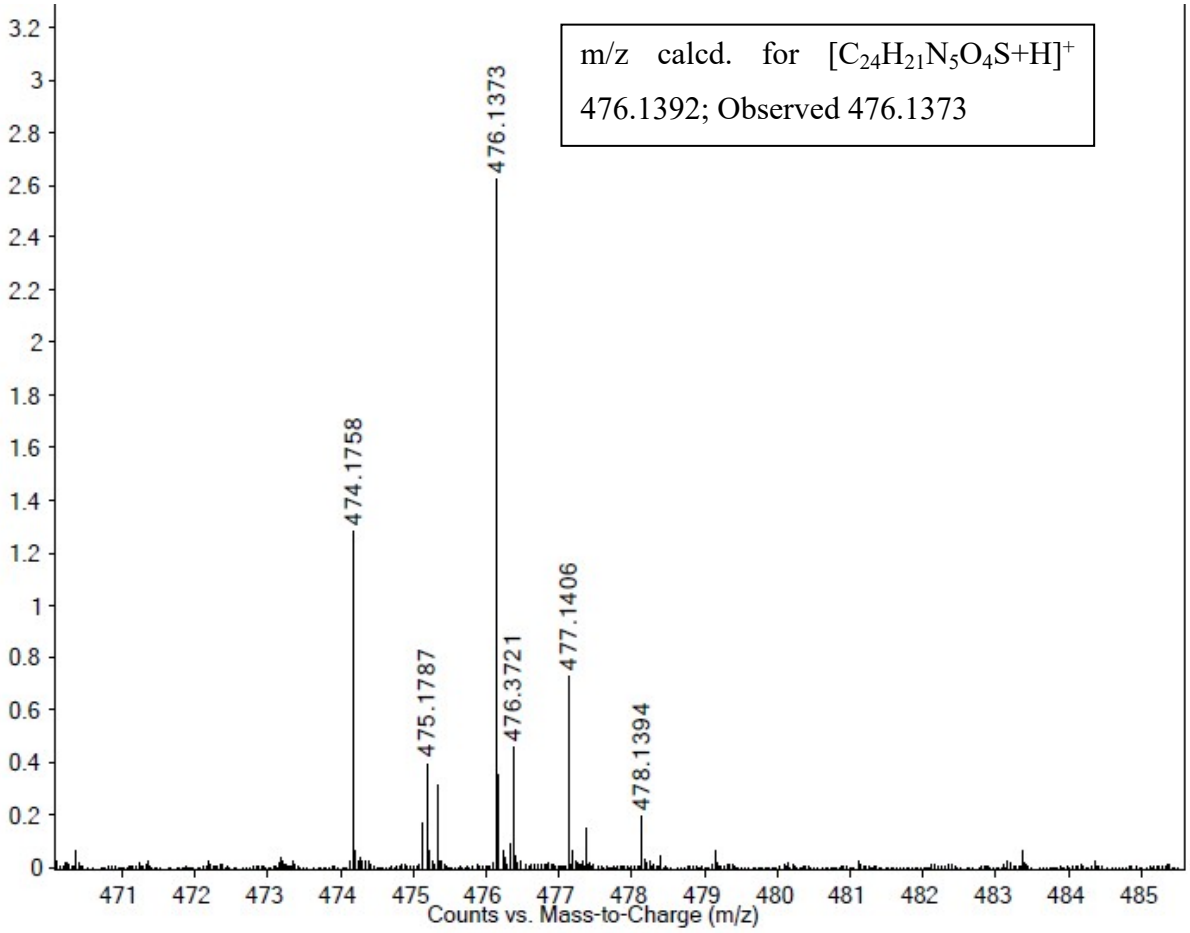
Mass spectrum of compound **6h**



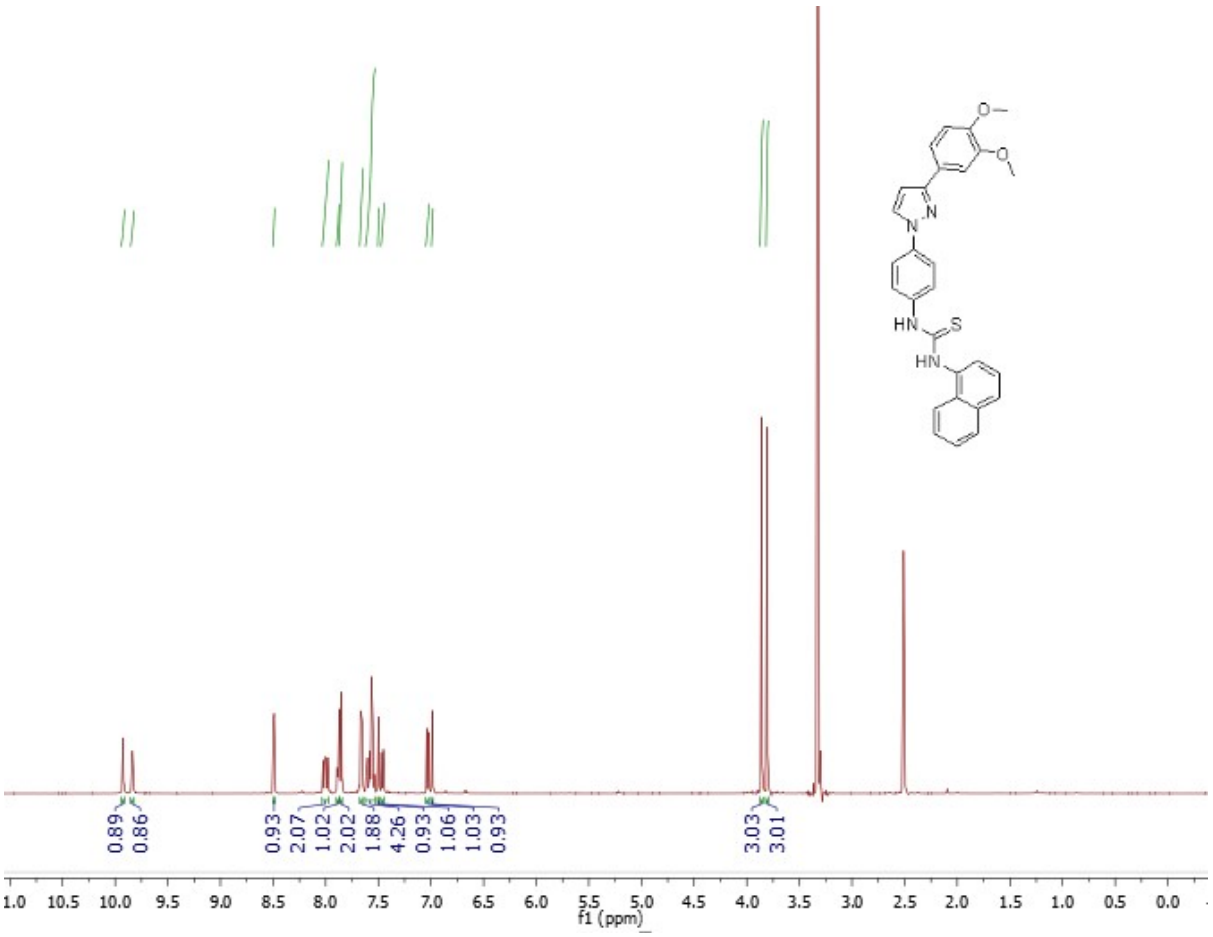
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6i**



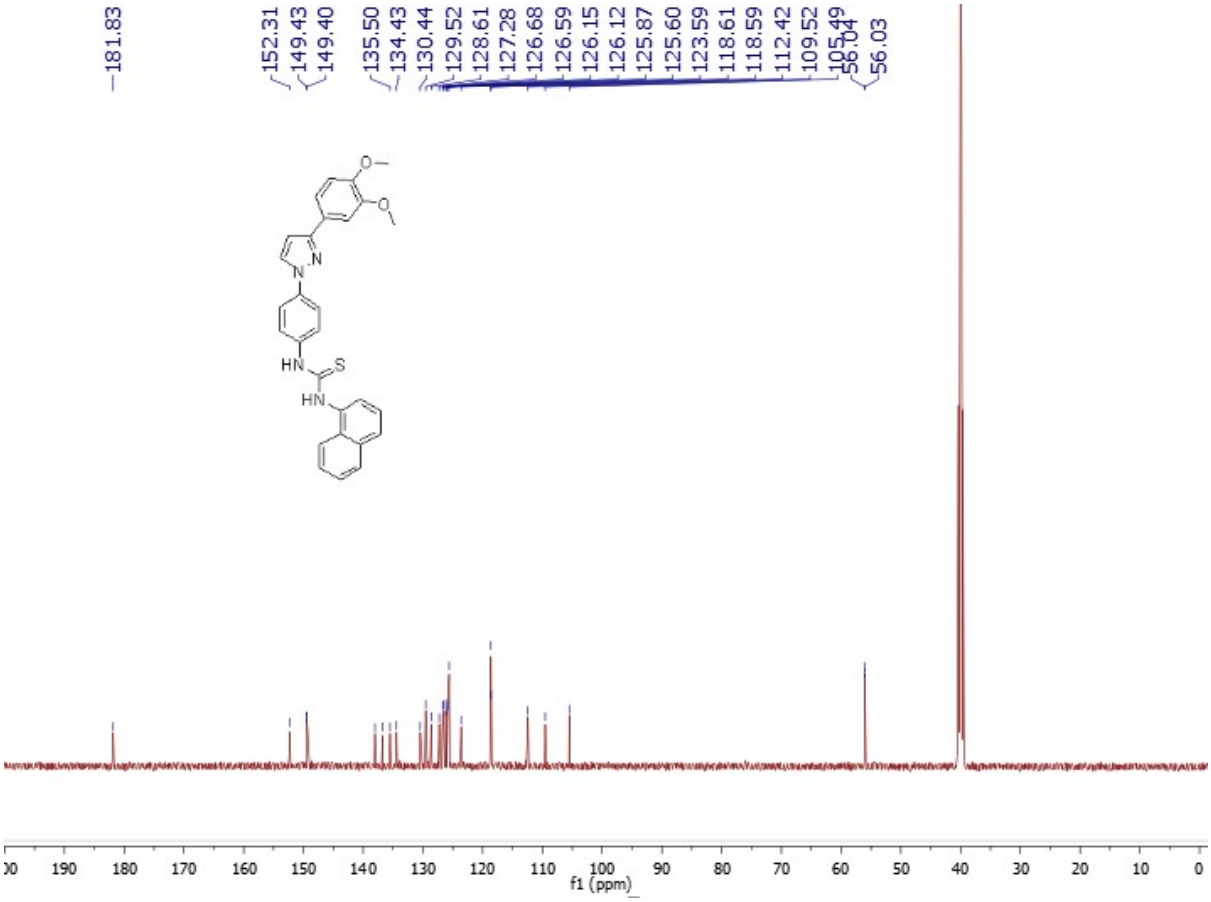
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6i**



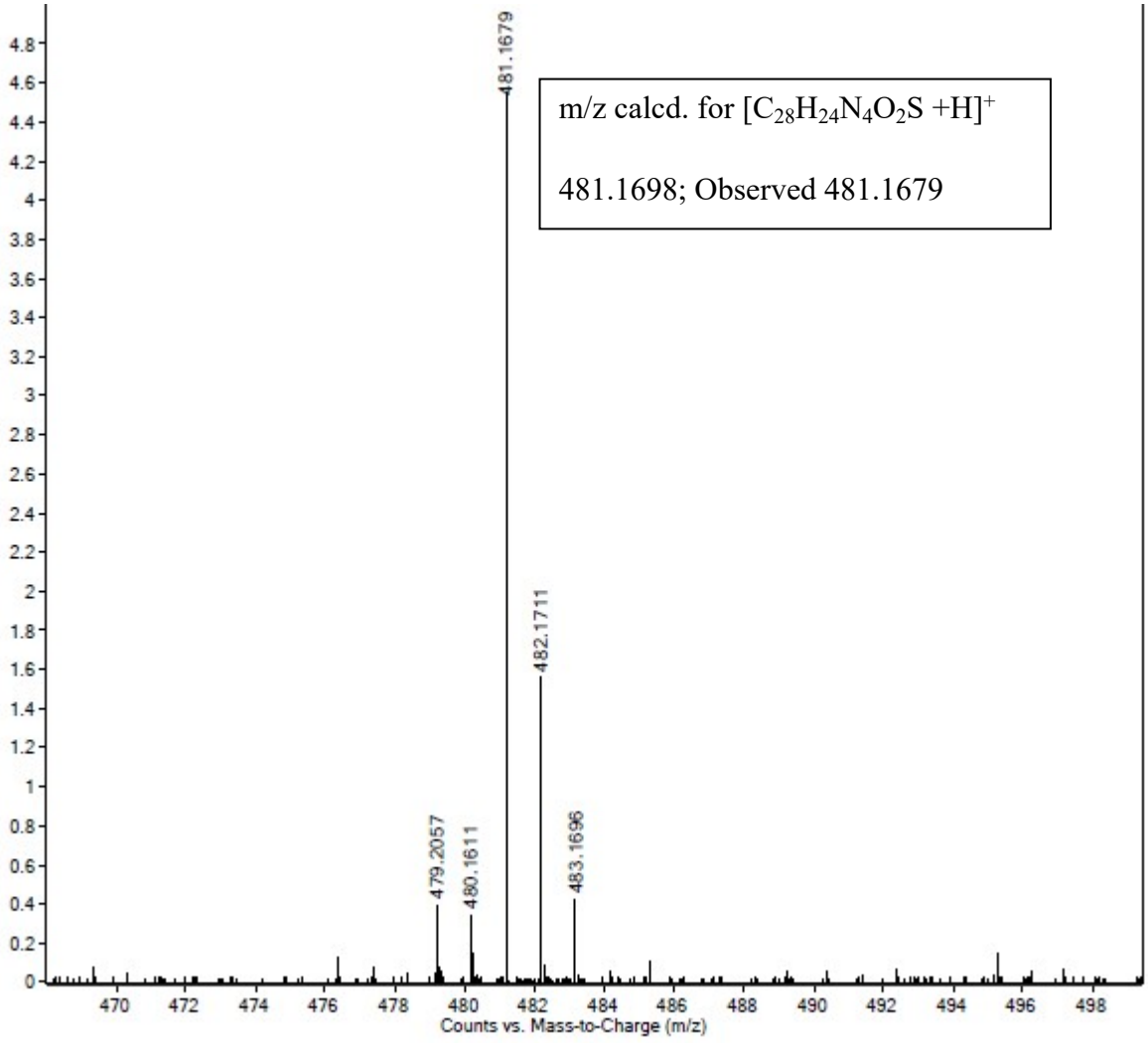
Mass spectrum of compound **6i**



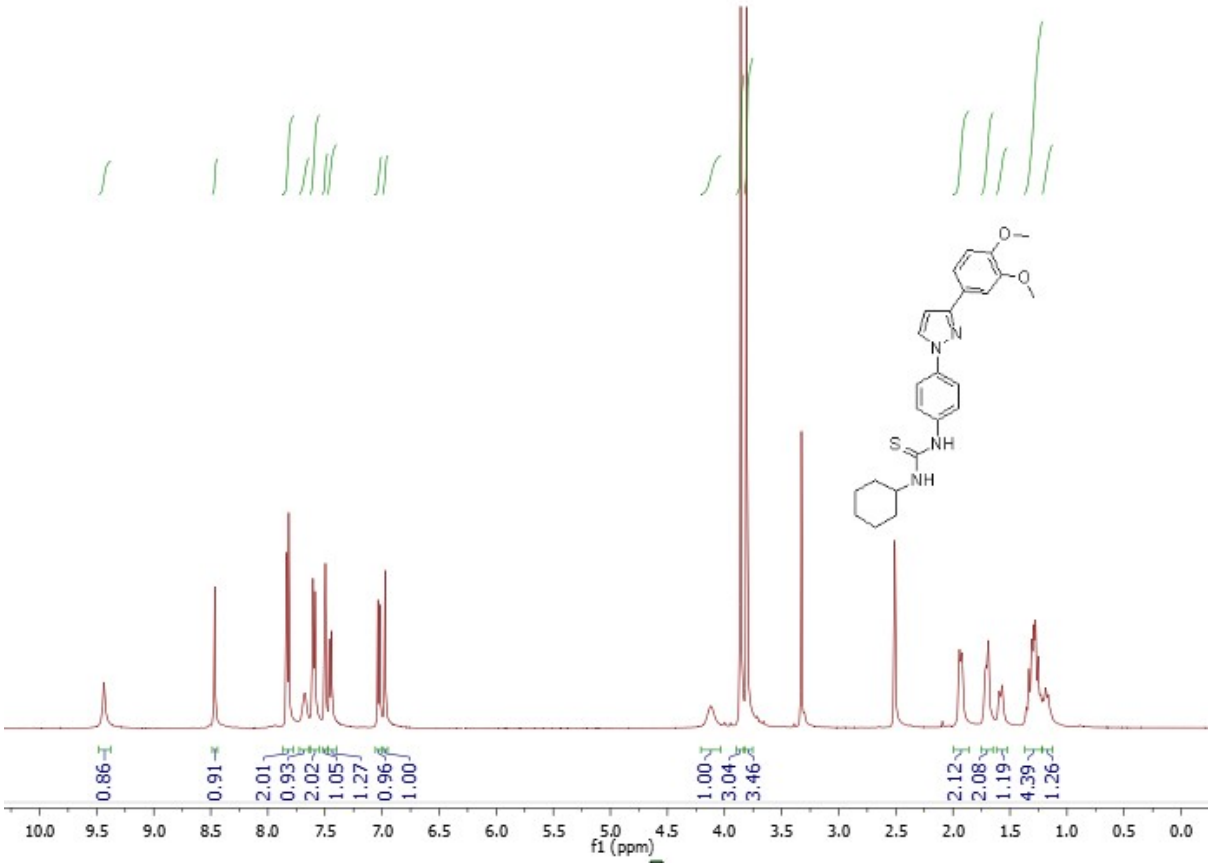
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6j**



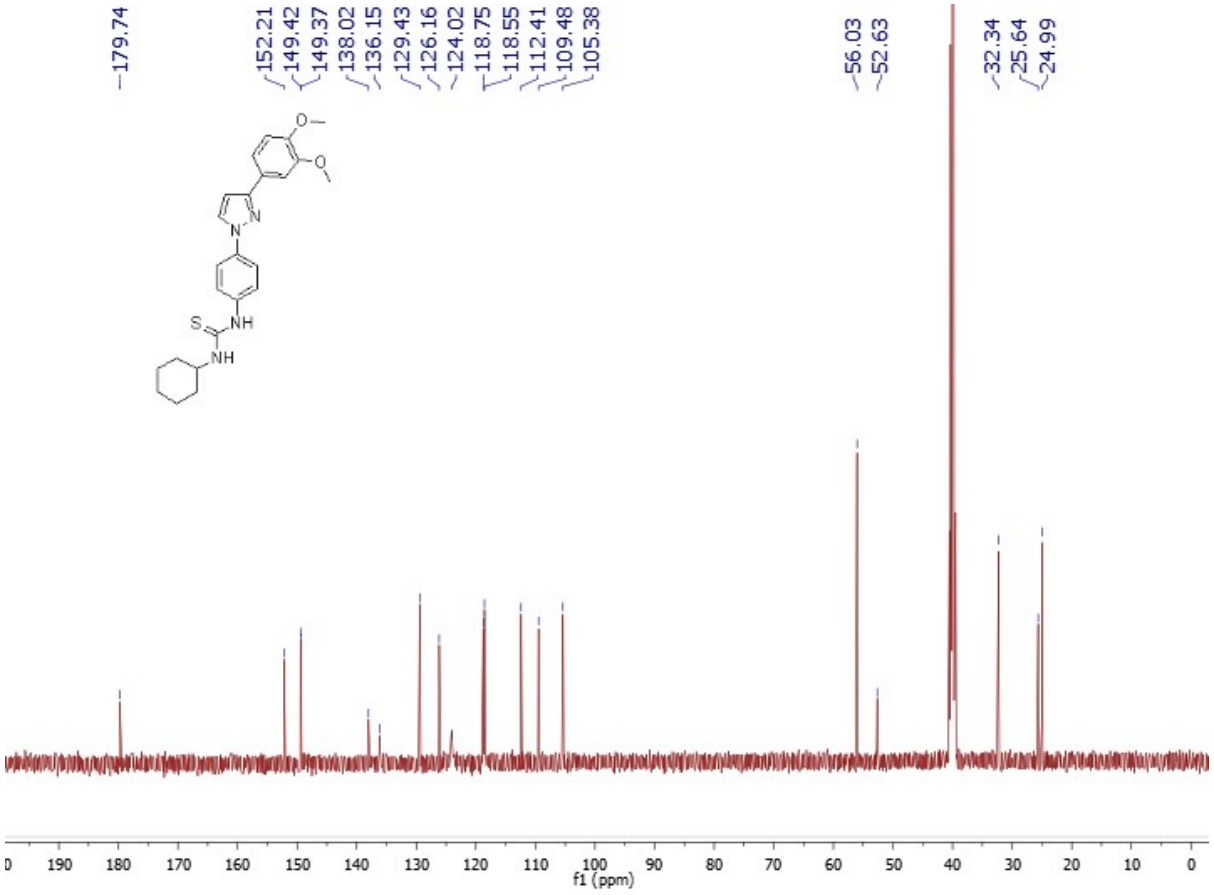
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6j**



Mass spectrum of compound **6j**

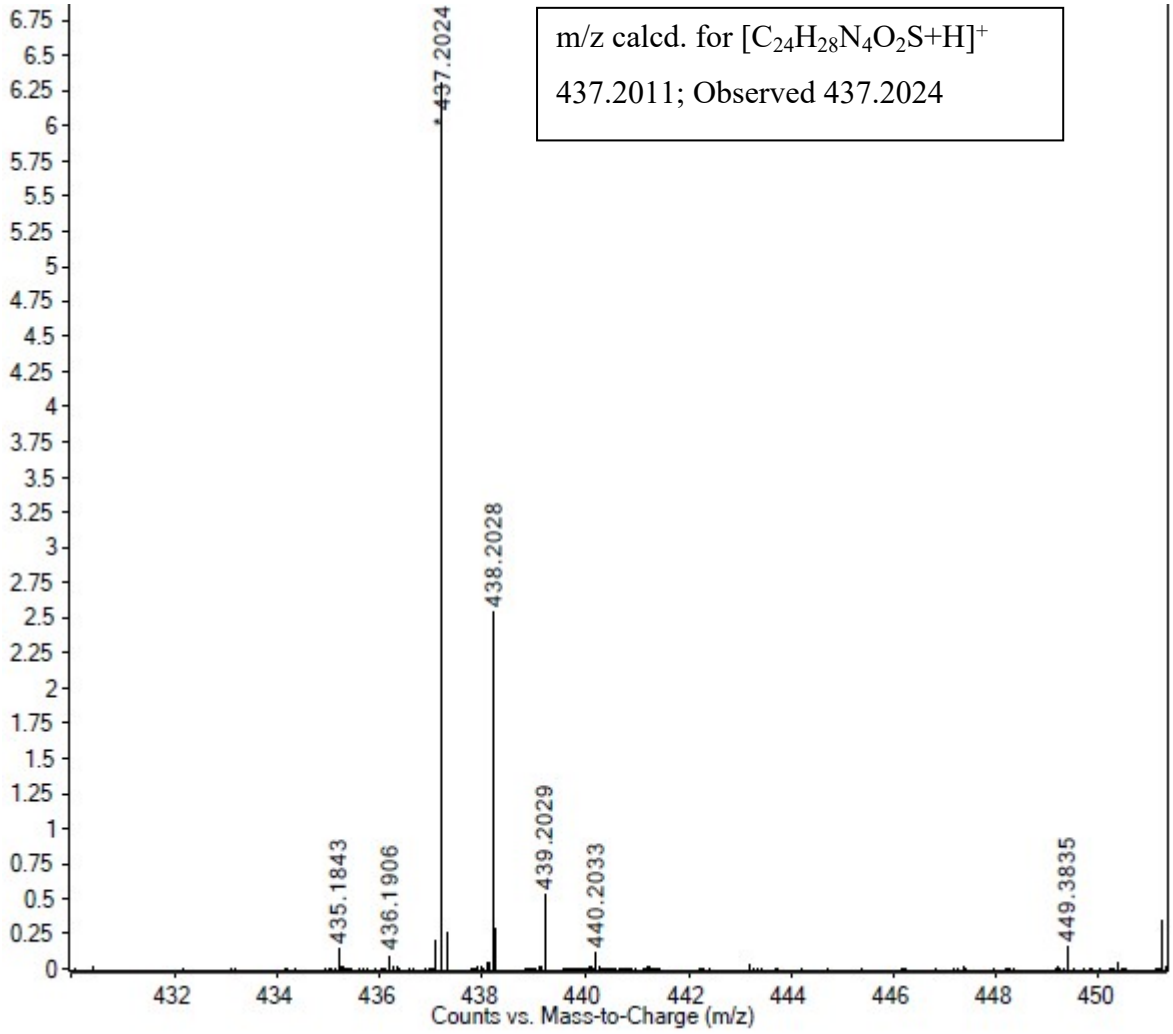


^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6k**

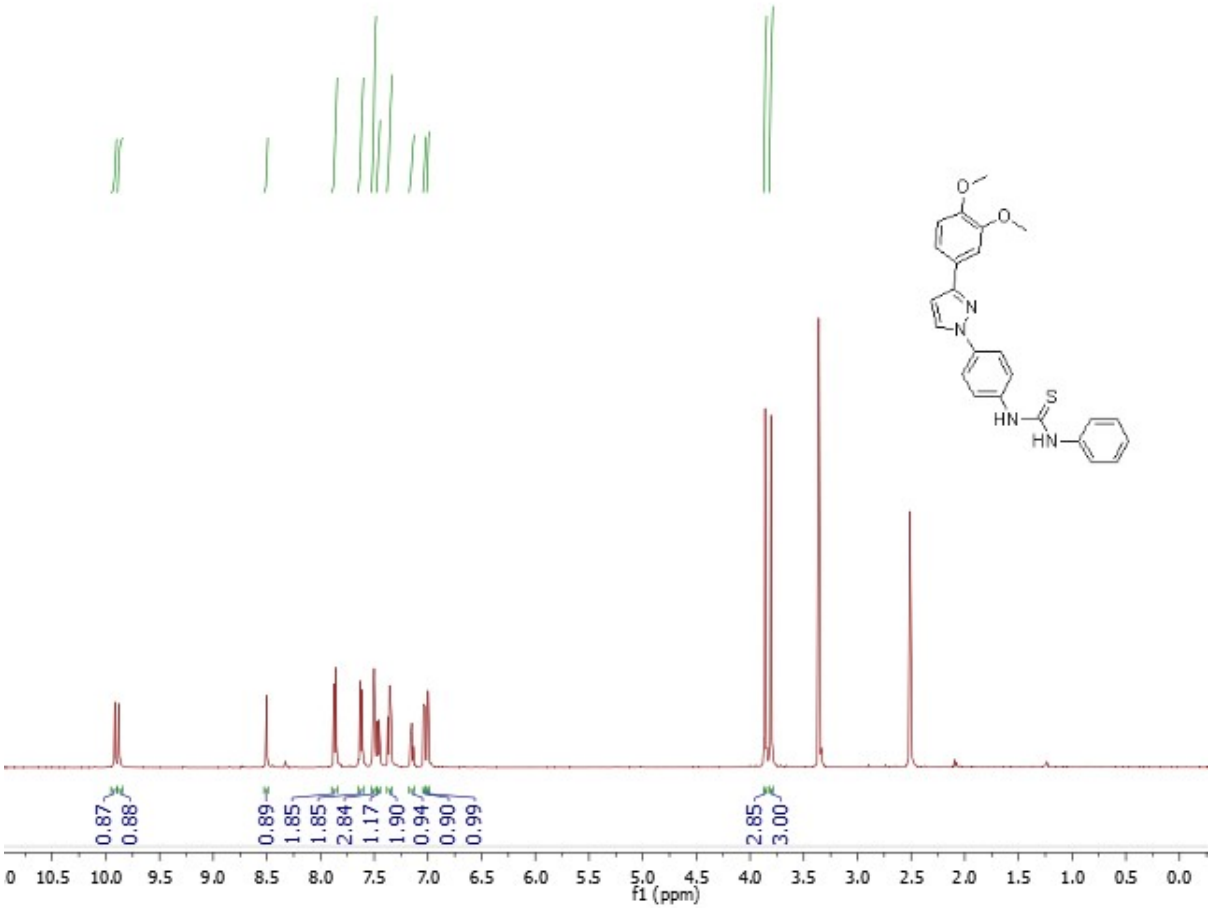


^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6k**

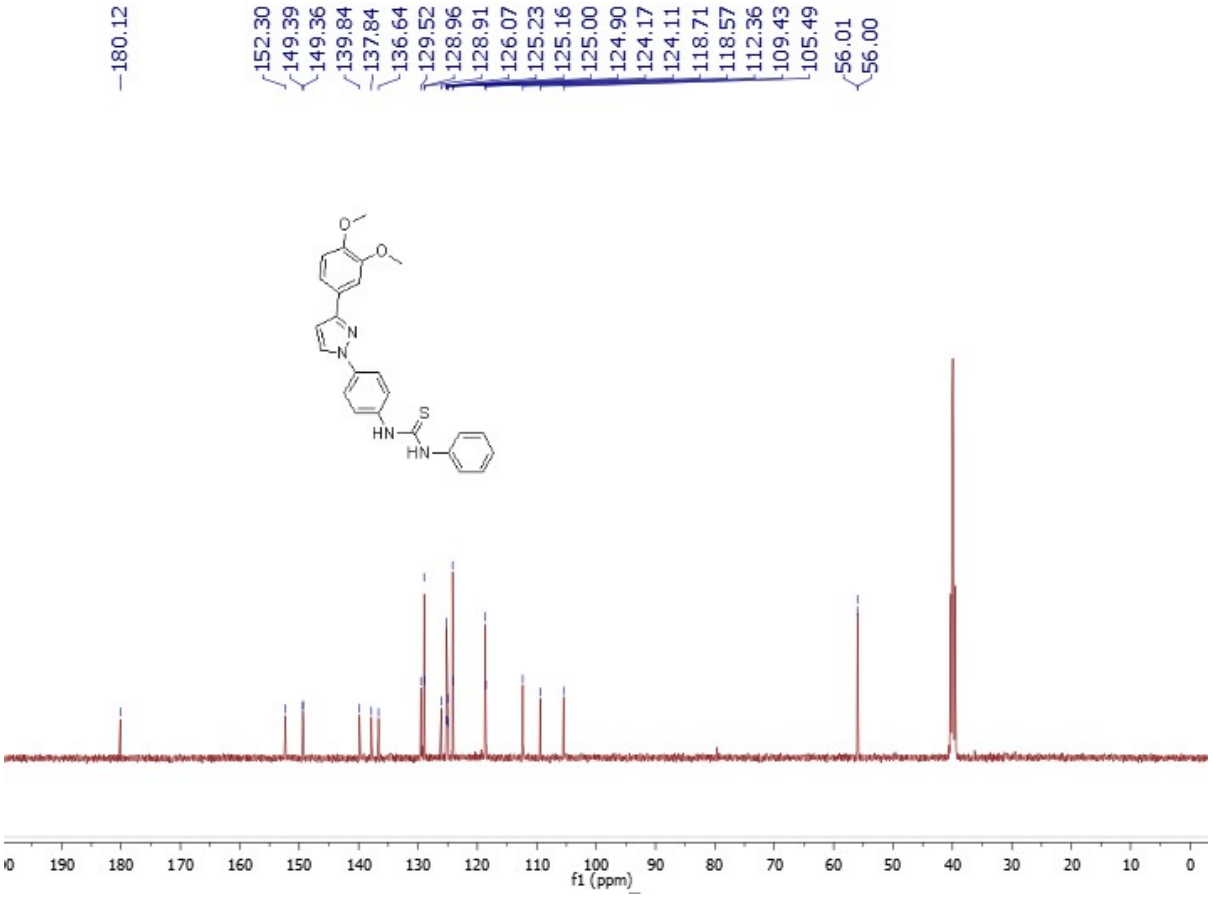
s



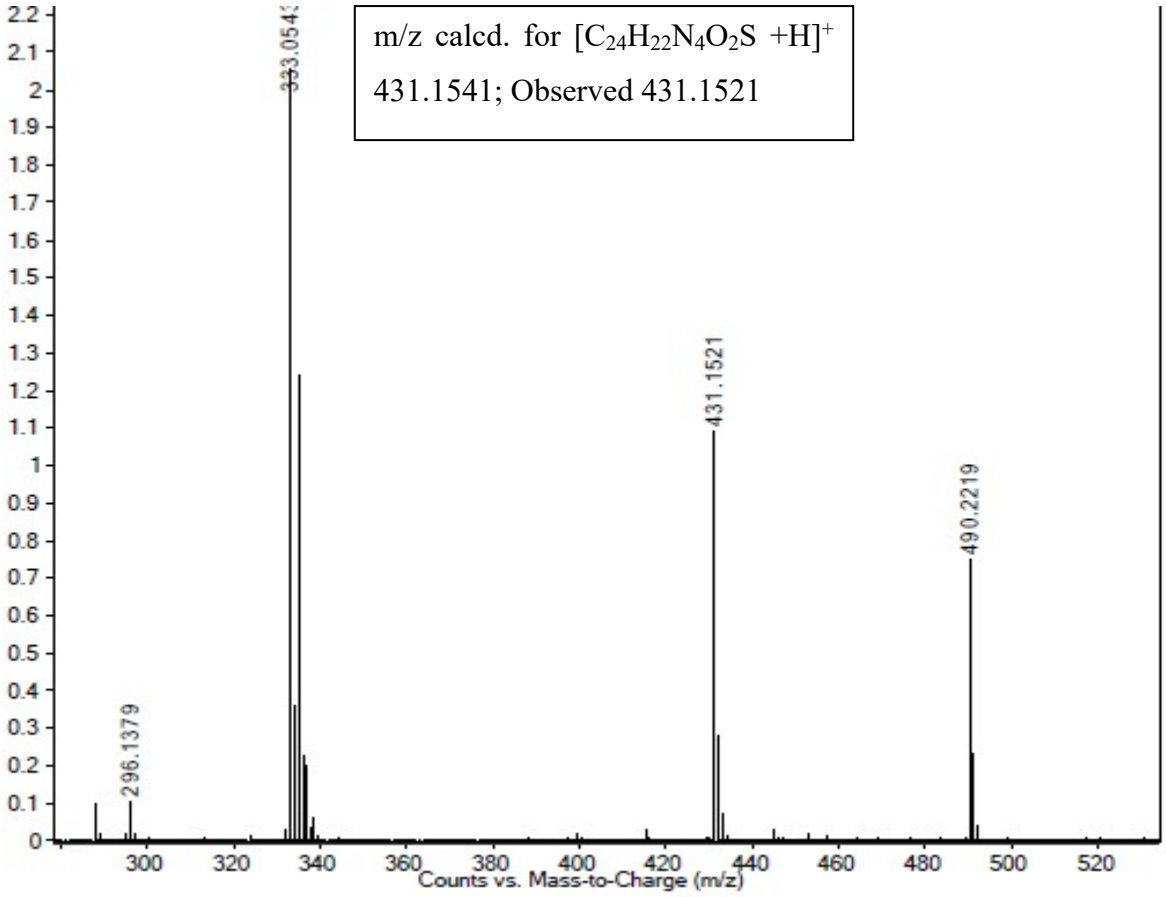
Mass spectrum of compound **6k**



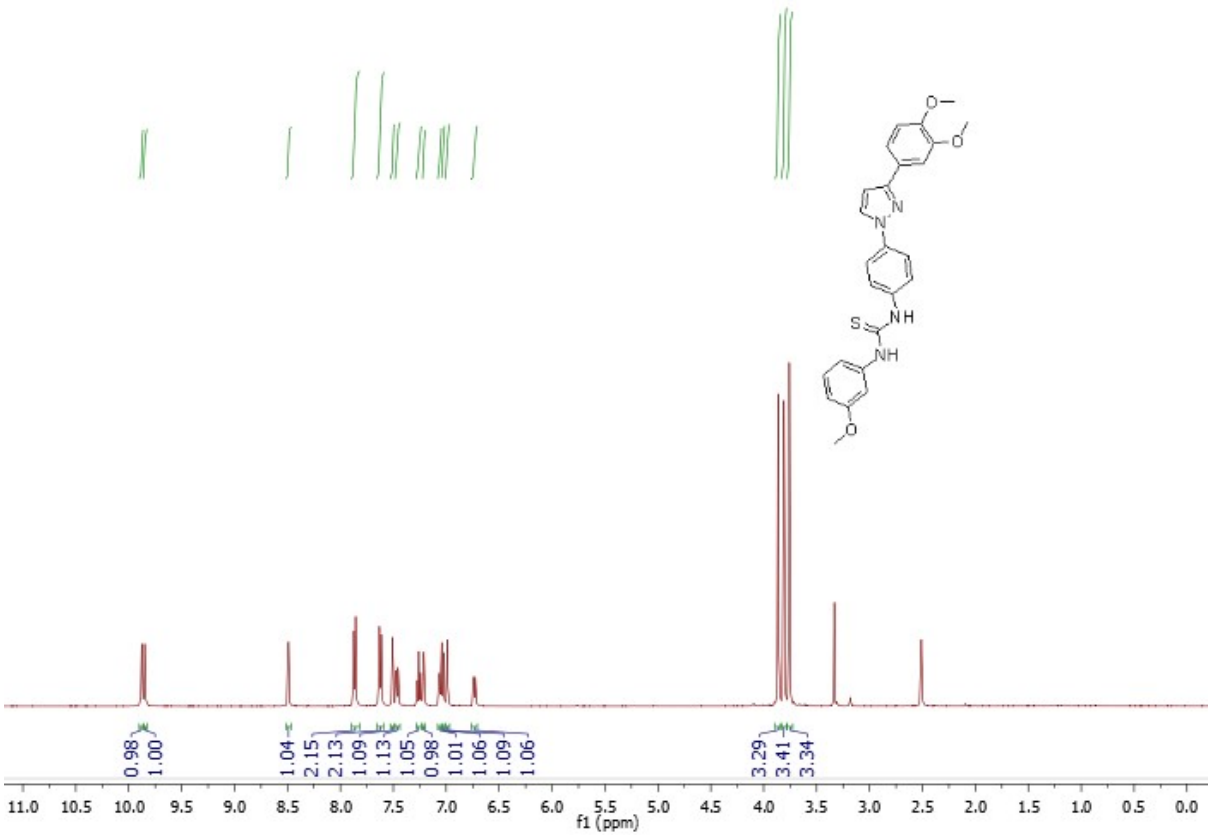
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6l**



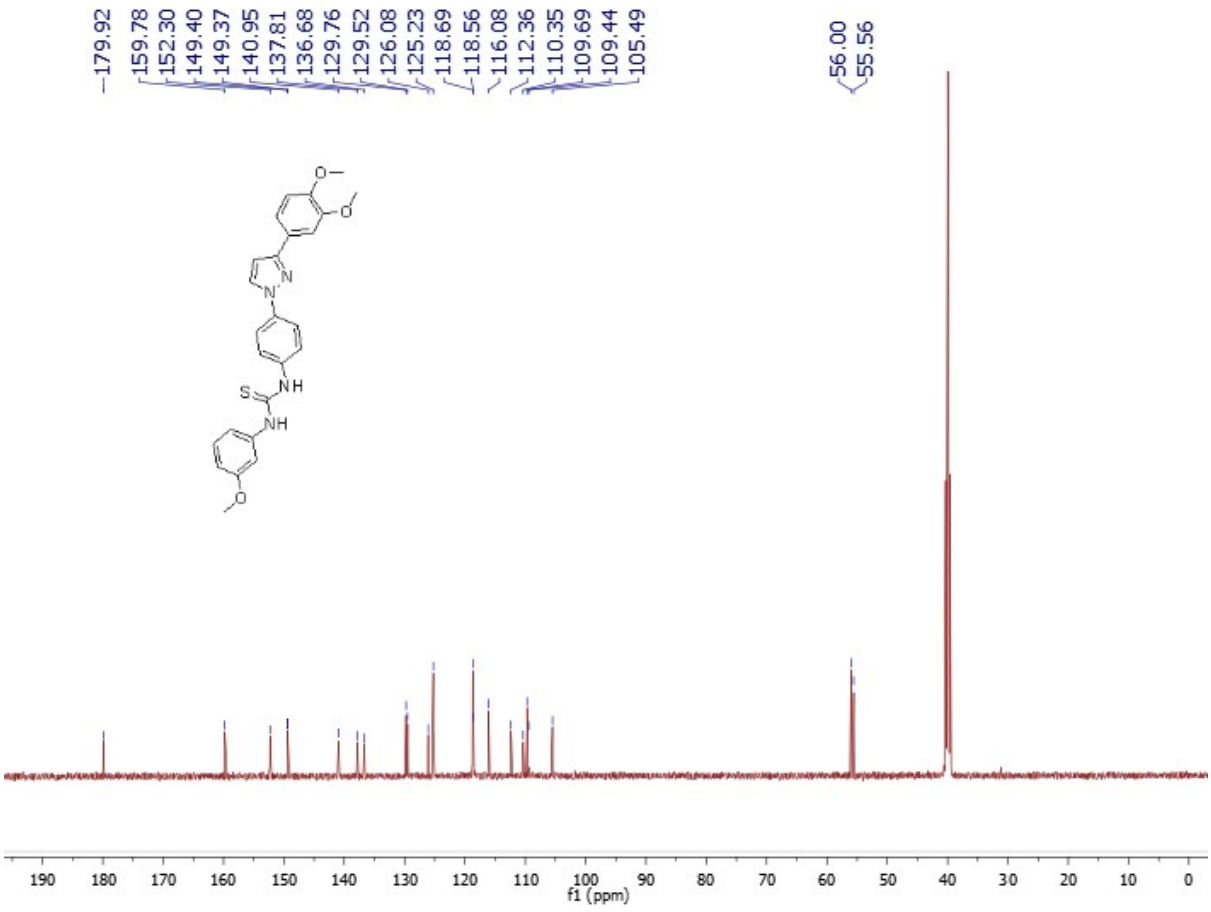
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6l**



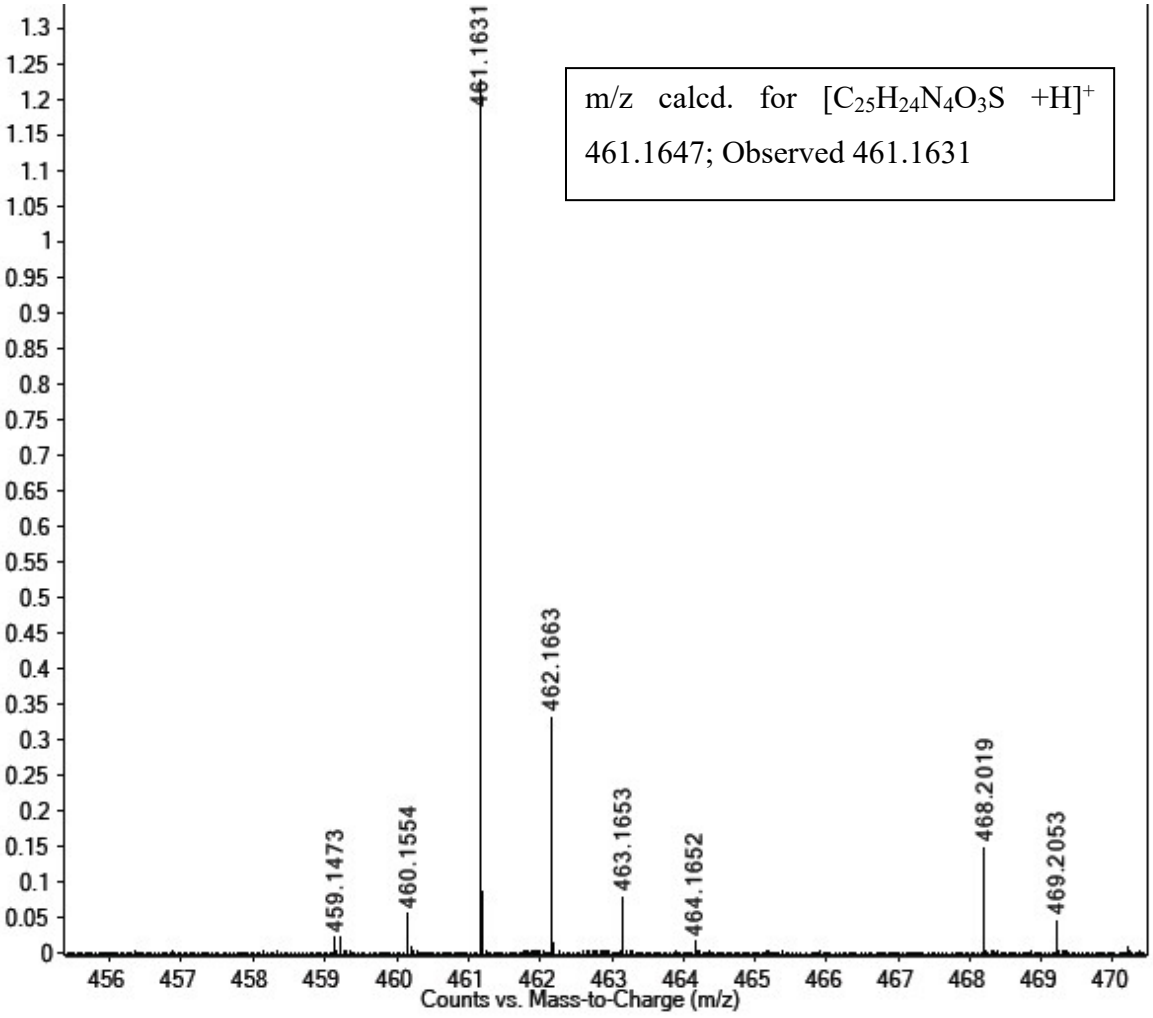
Mass spectrum of compound **6l**



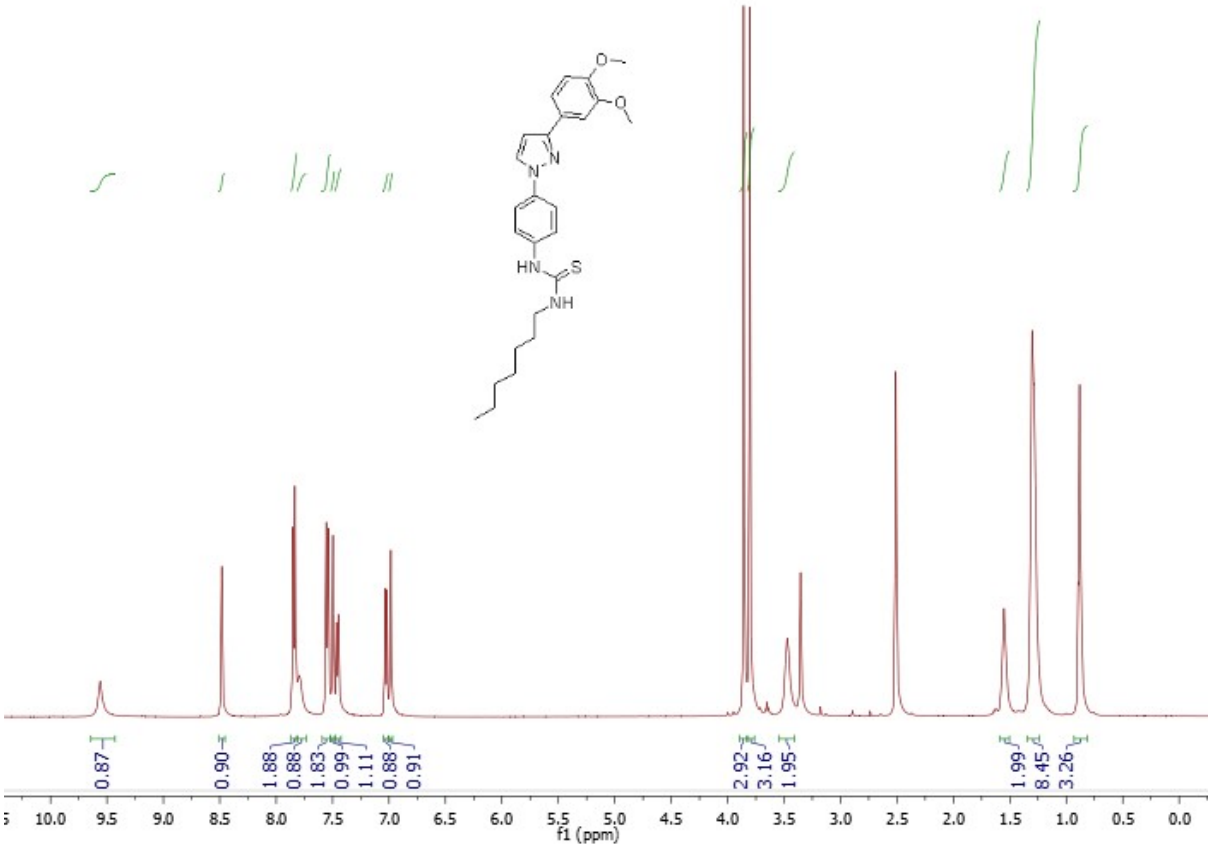
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6m**



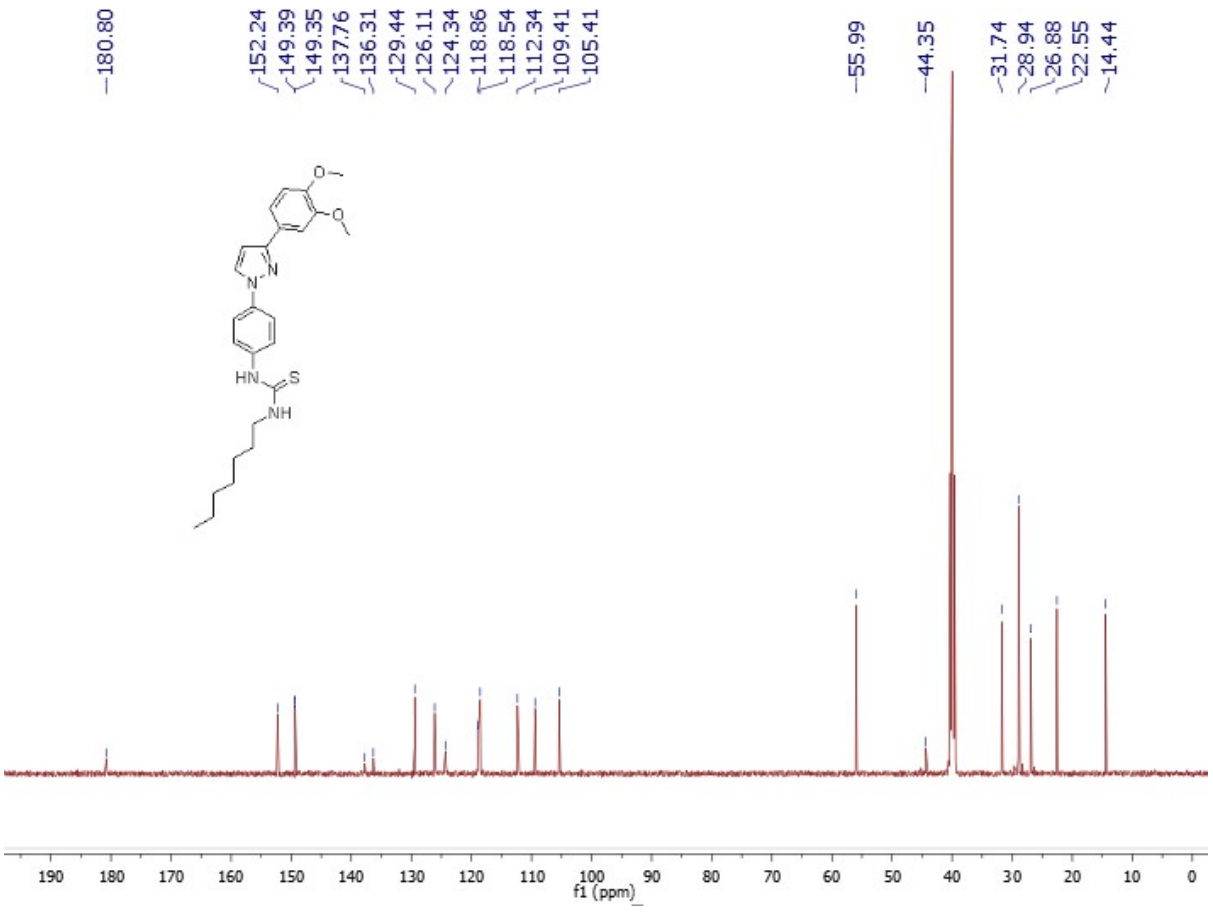
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6m**



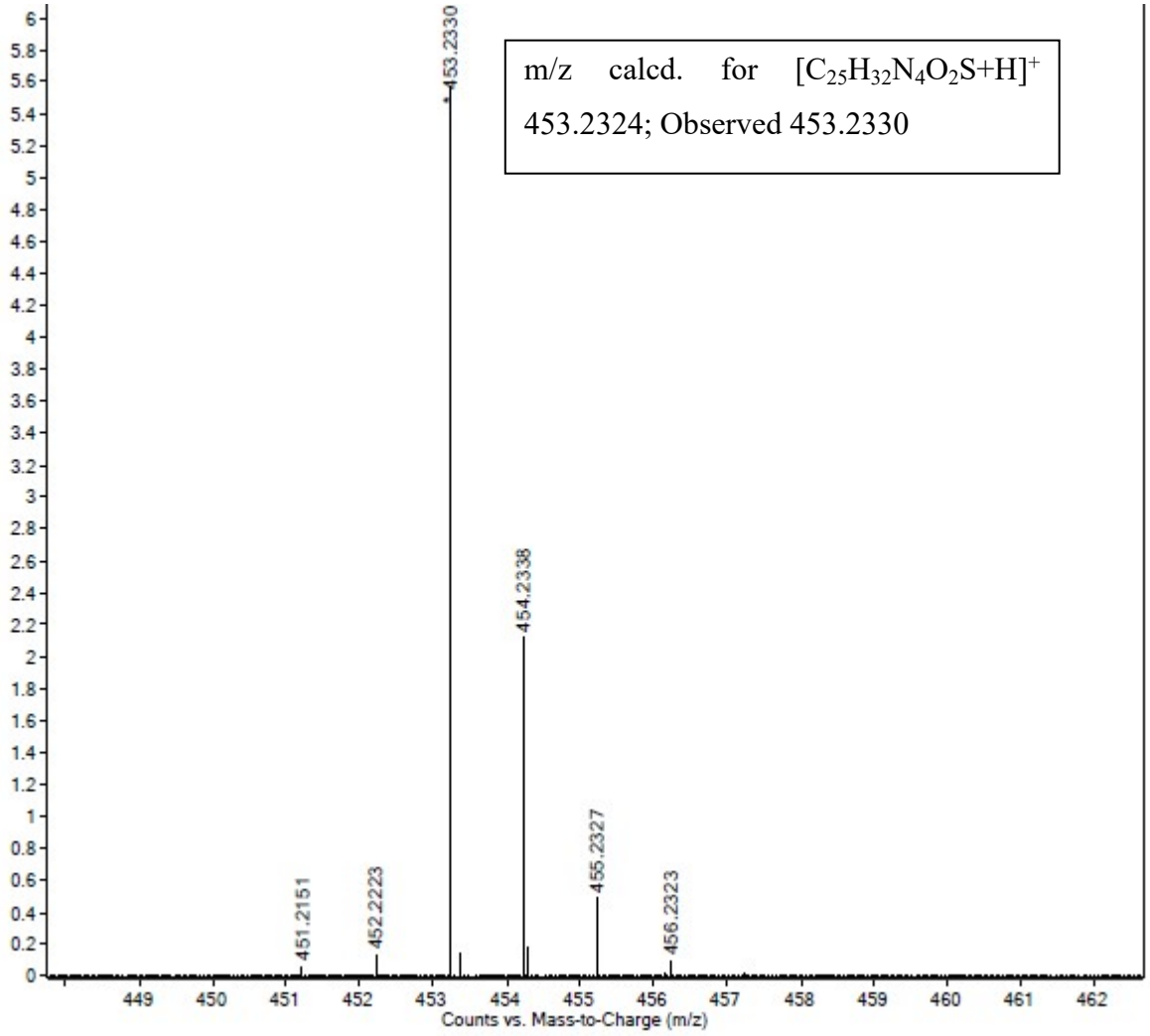
Mass spectrum of compound **6m**



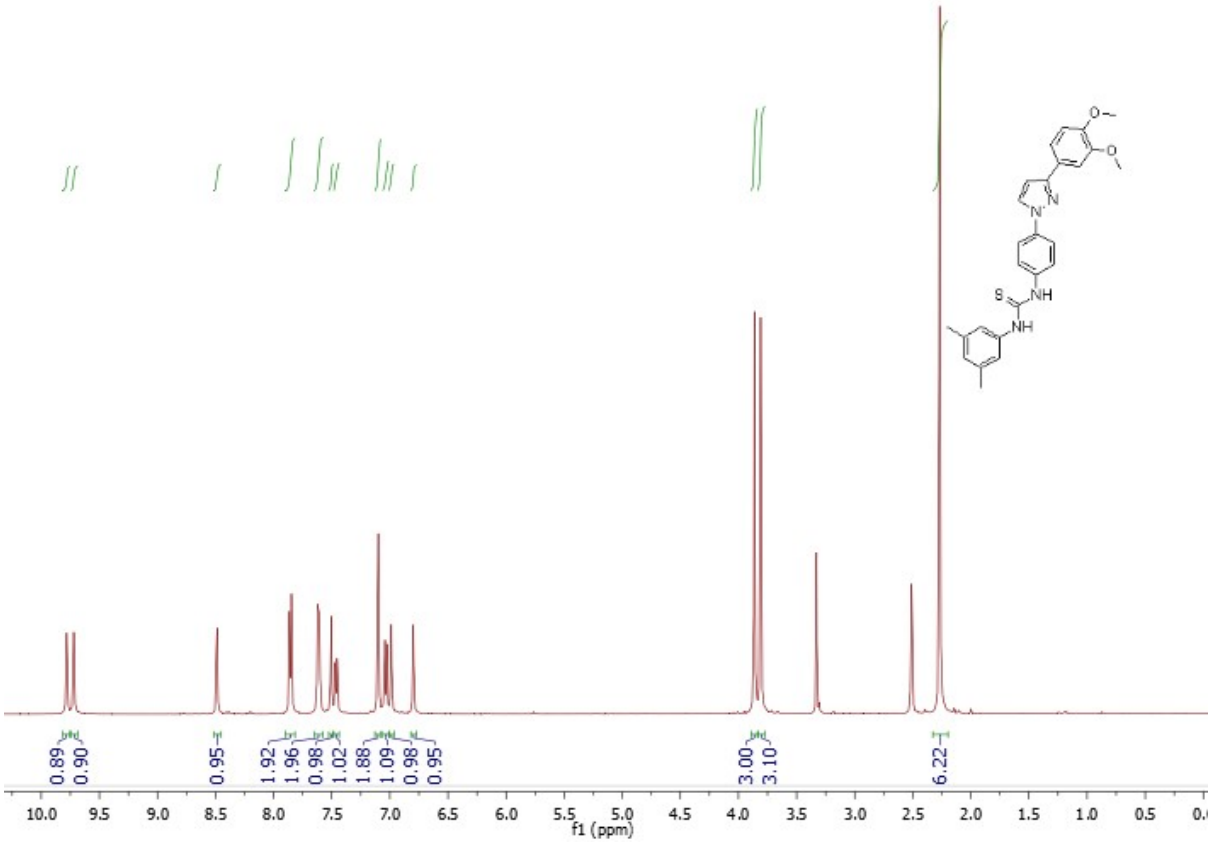
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6n**



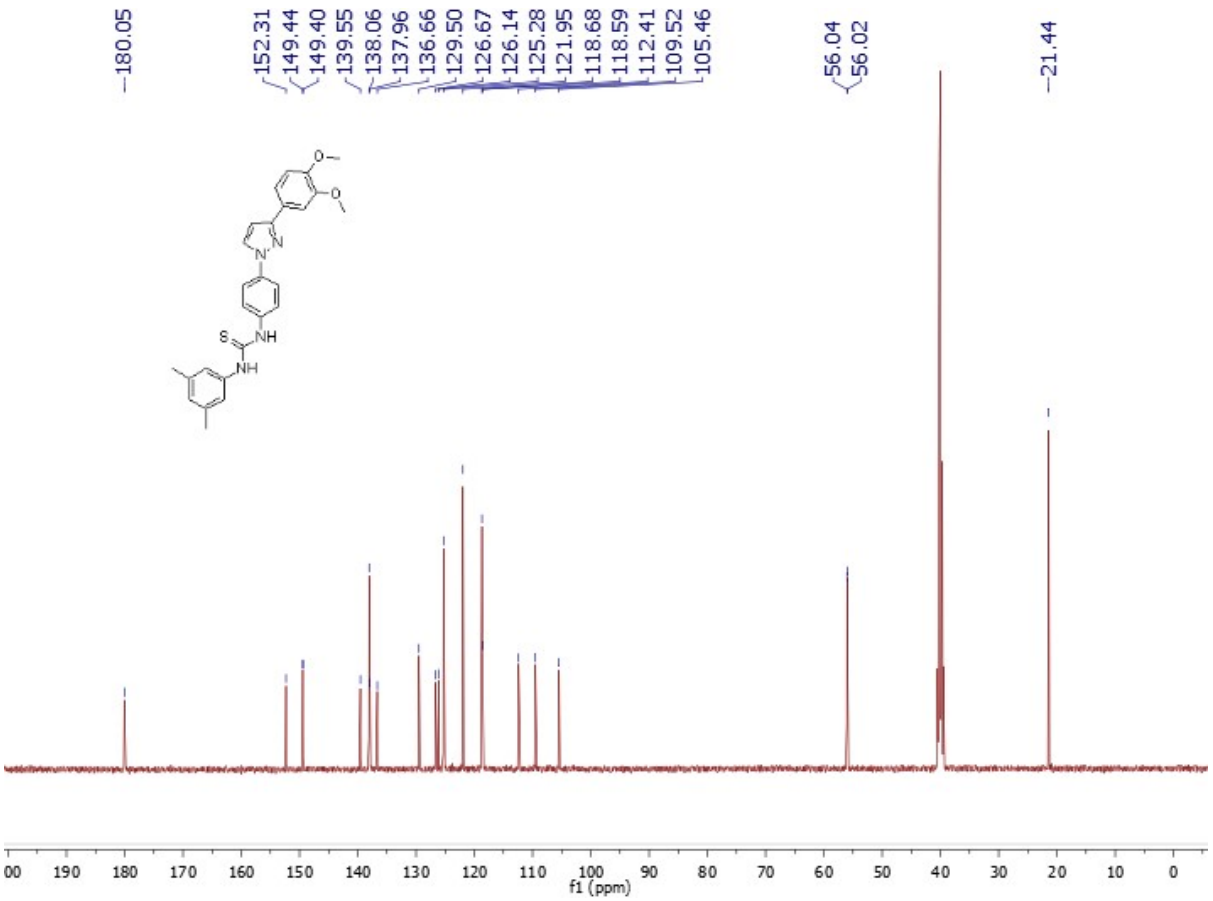
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6n**



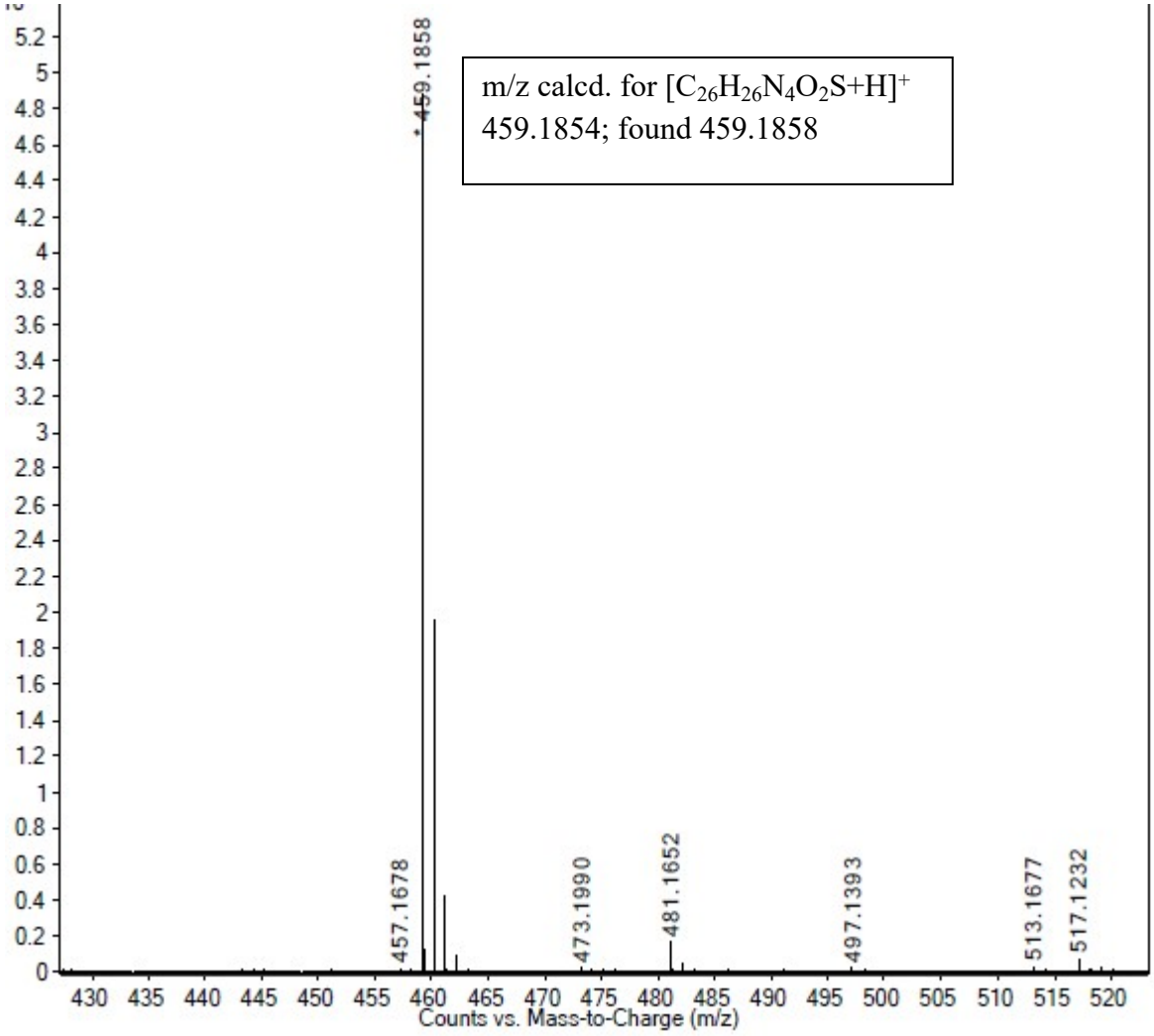
Mass spectrum of compound **6n**



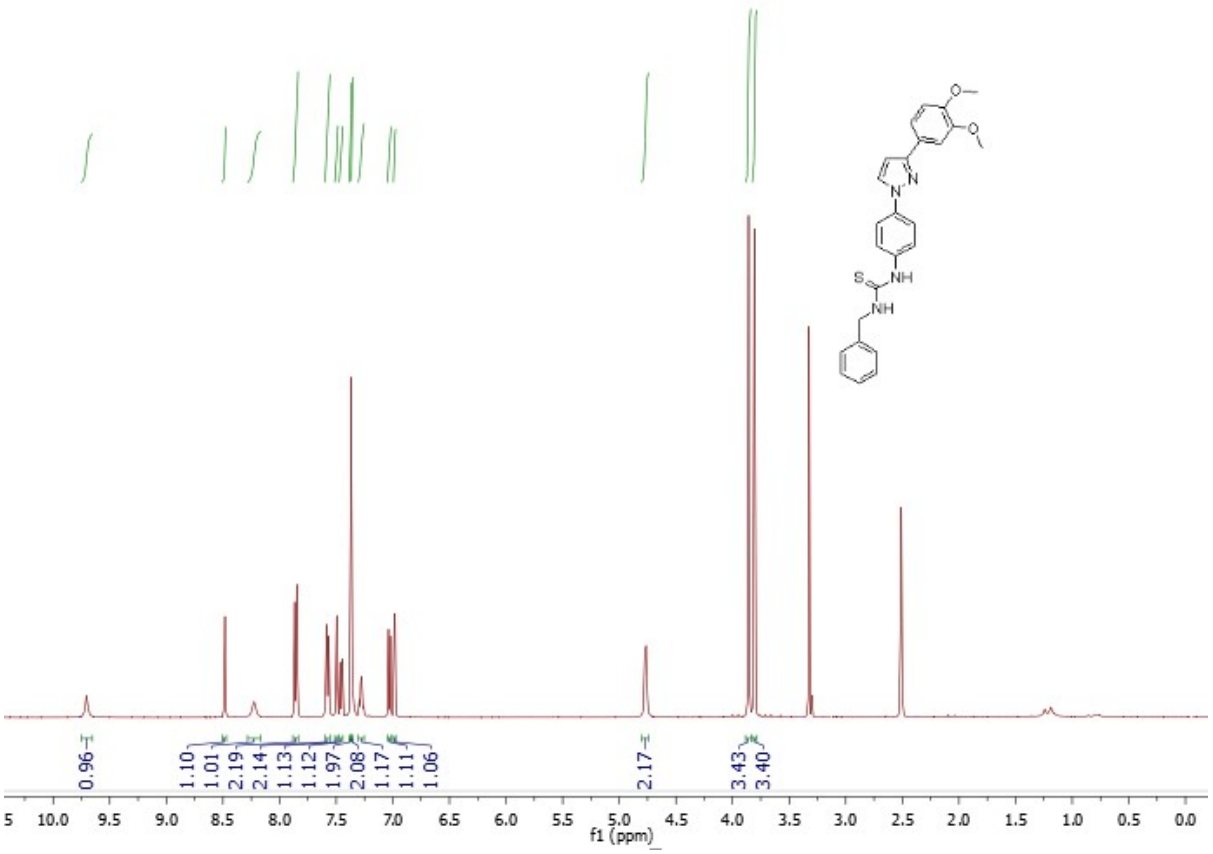
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6o**



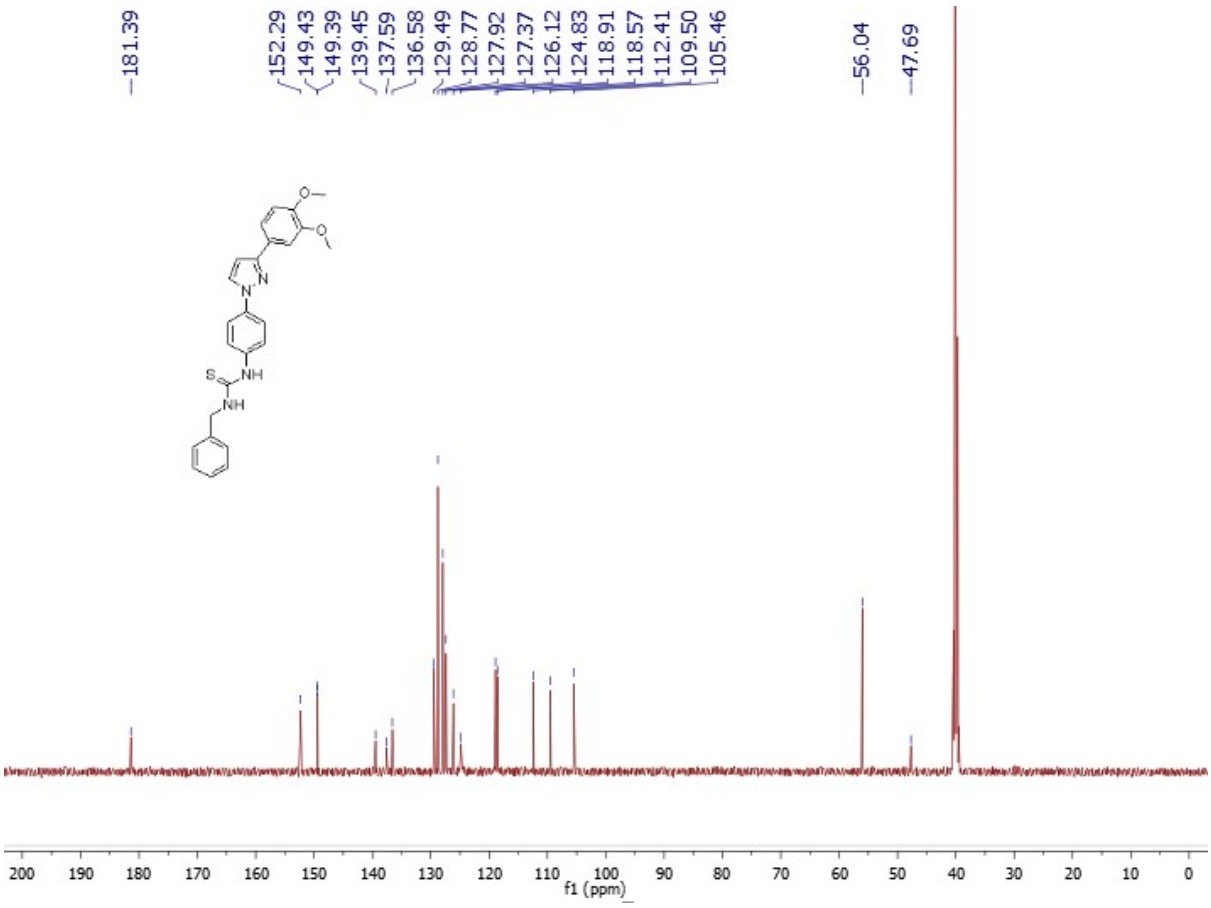
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6o**



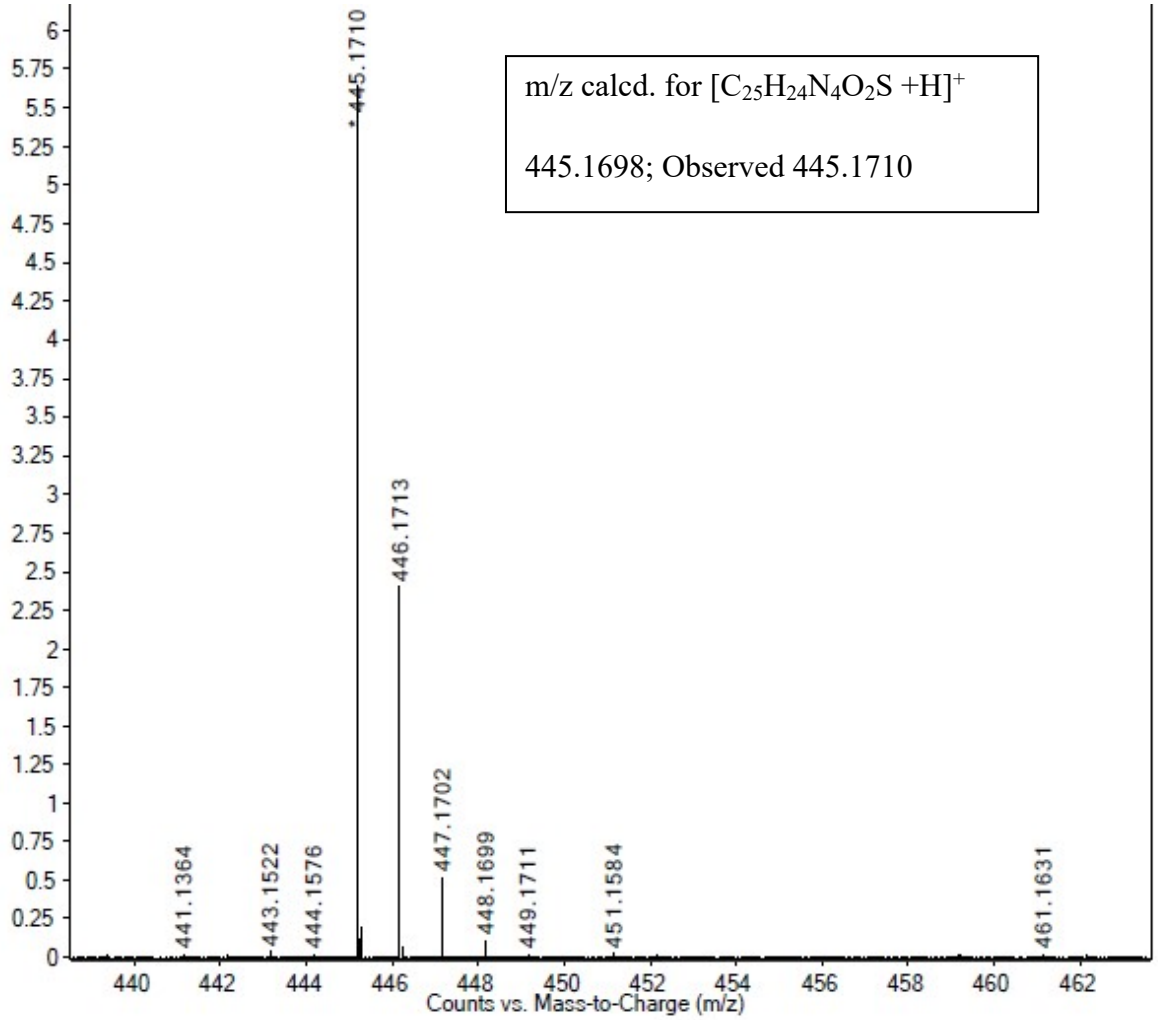
Mass spectrum of compound **6o**



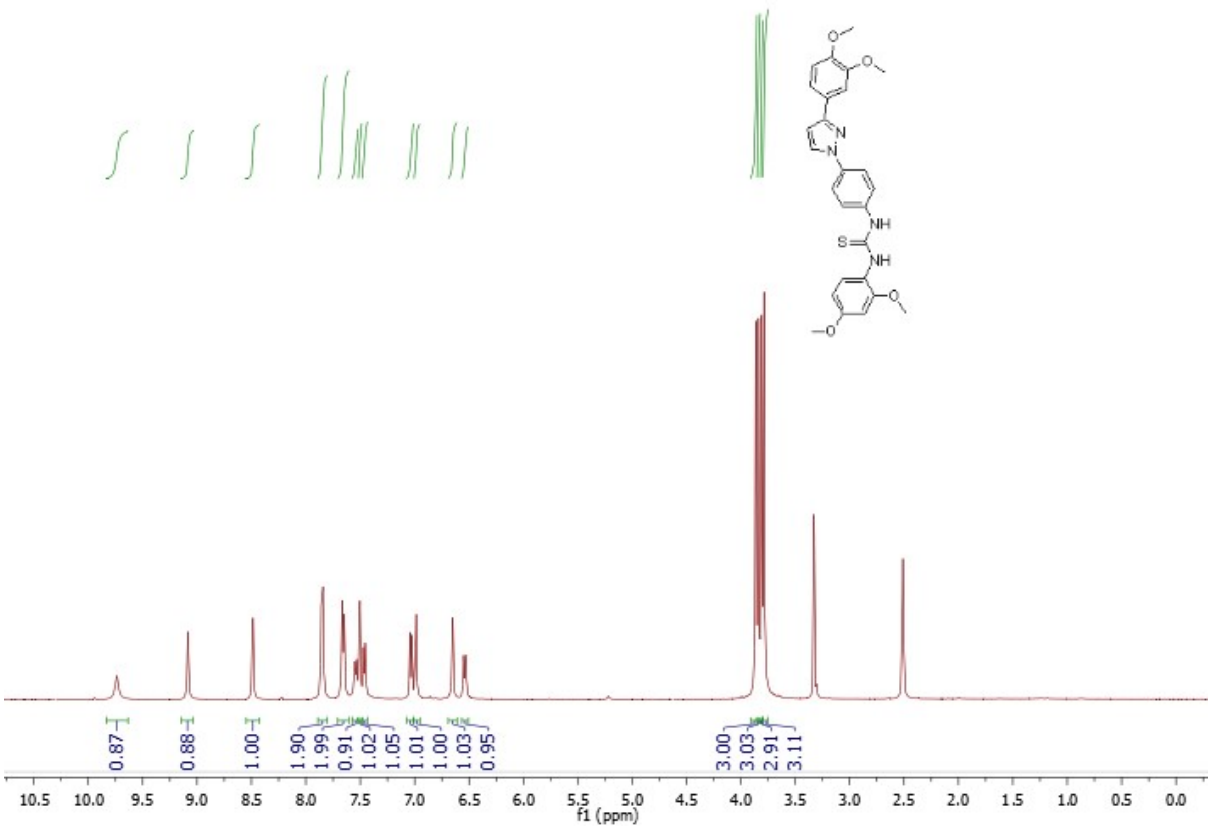
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6p**



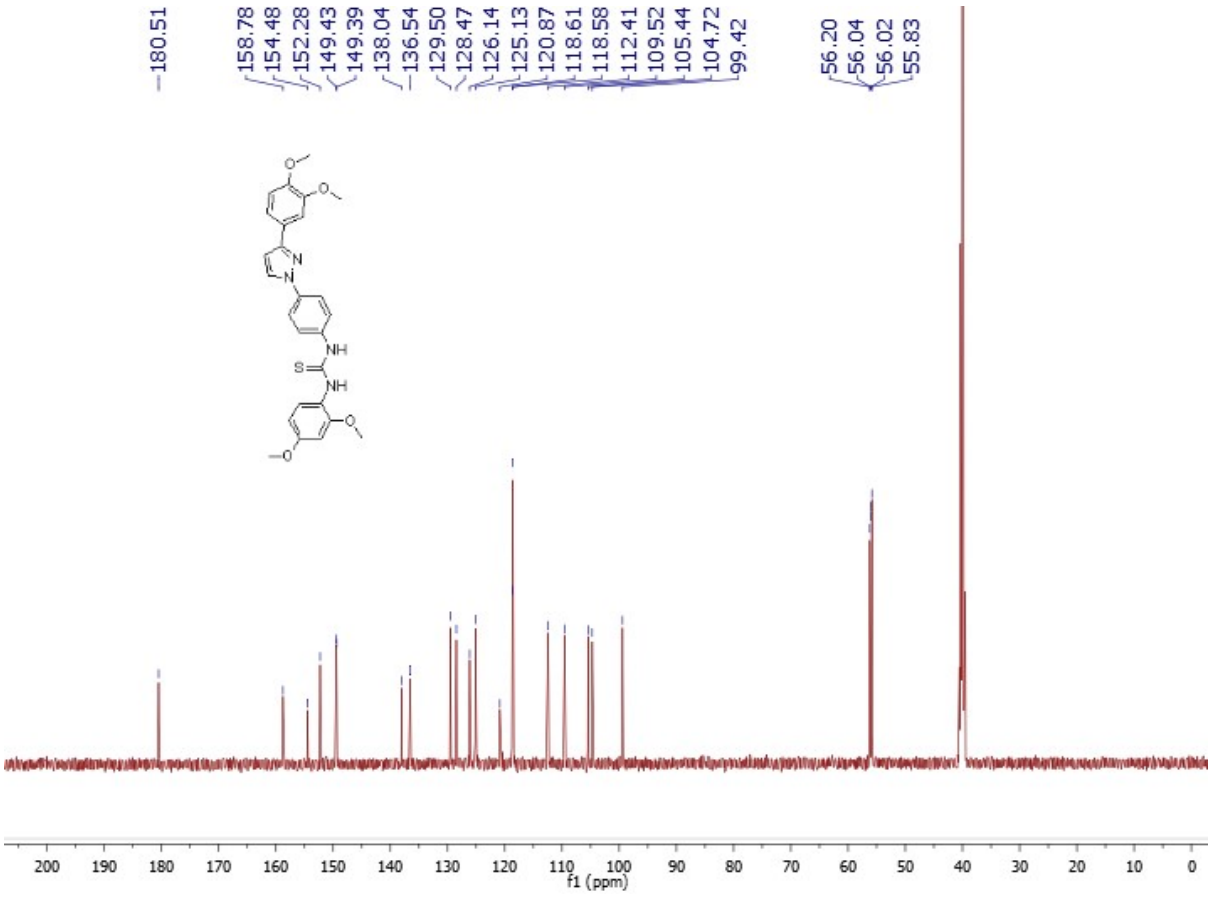
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6p**



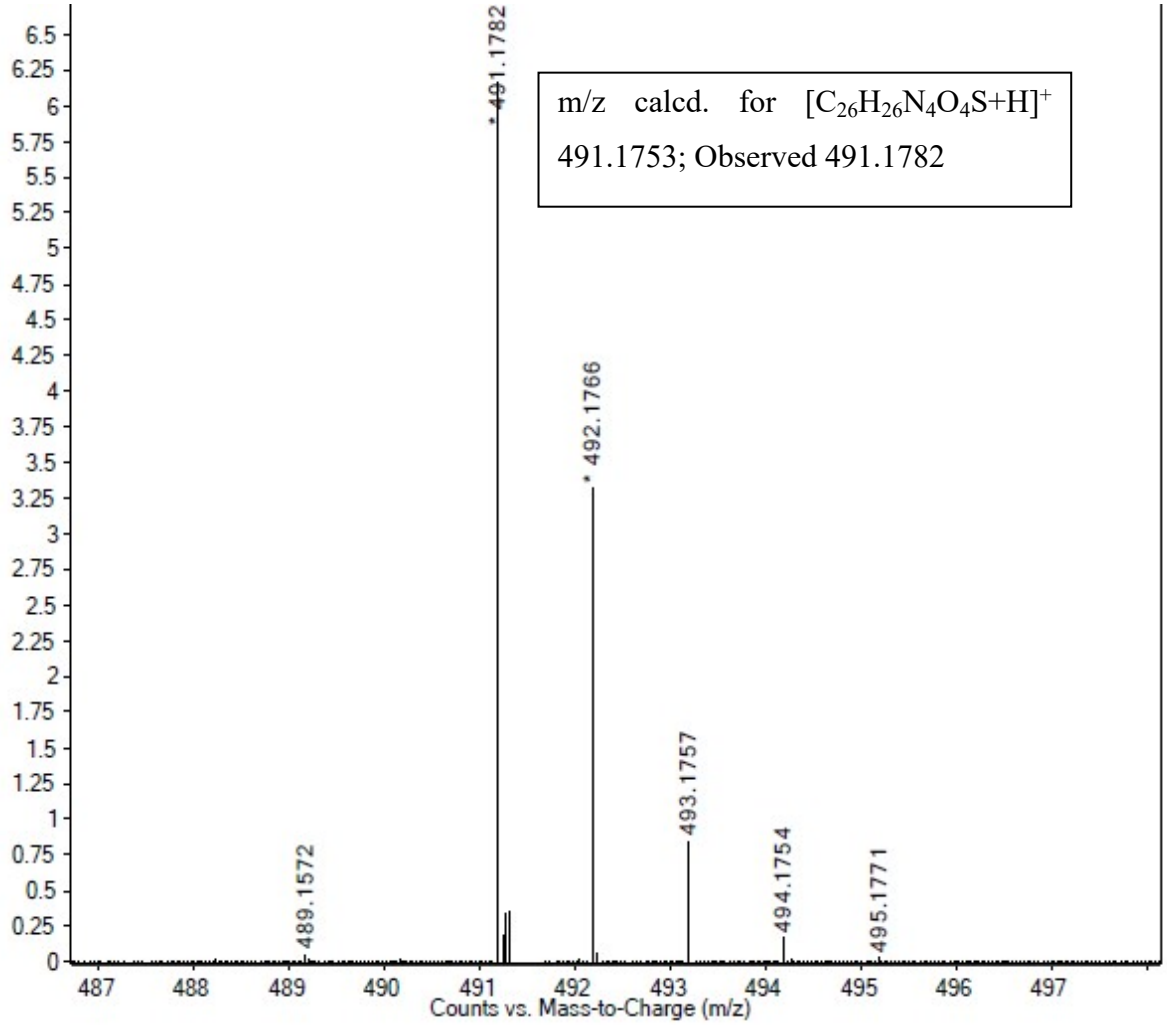
Mass spectrum of compound **6p**



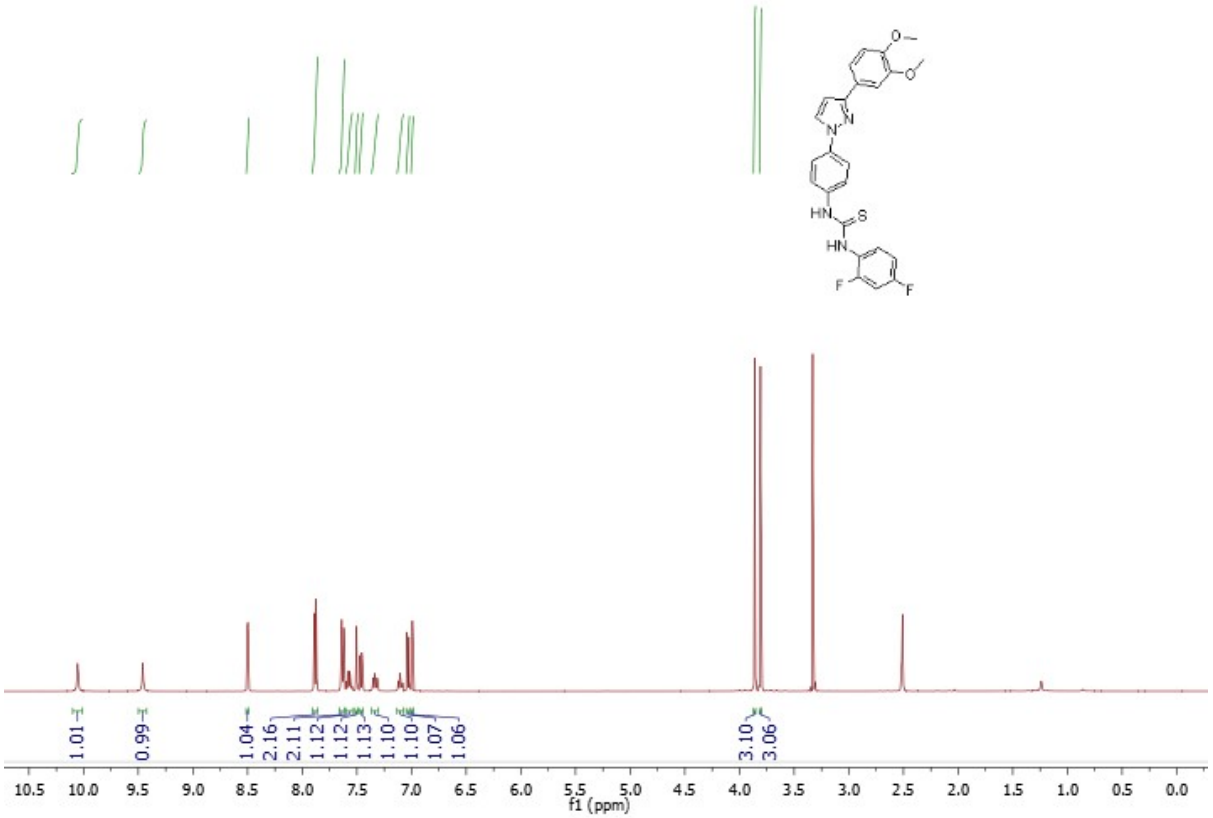
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6q**



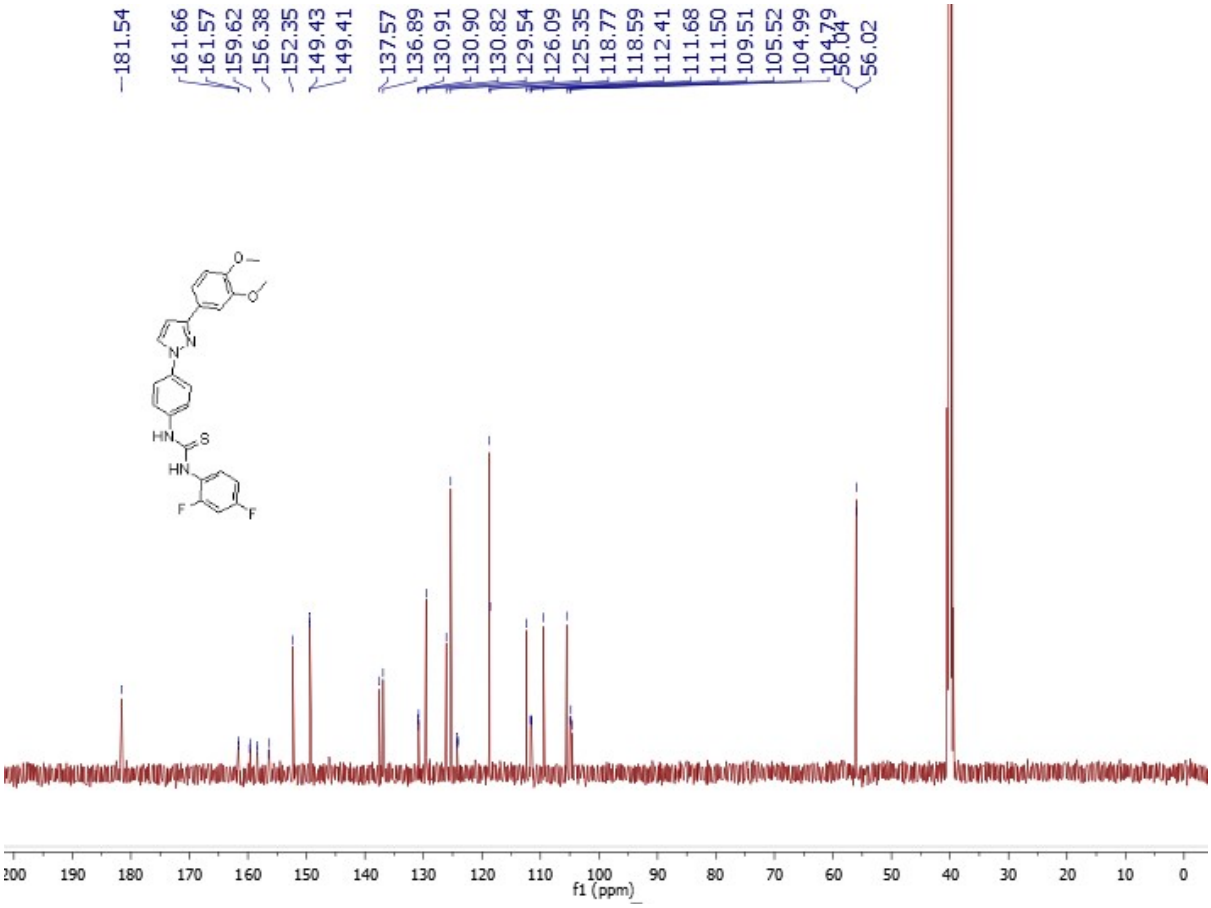
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6q**



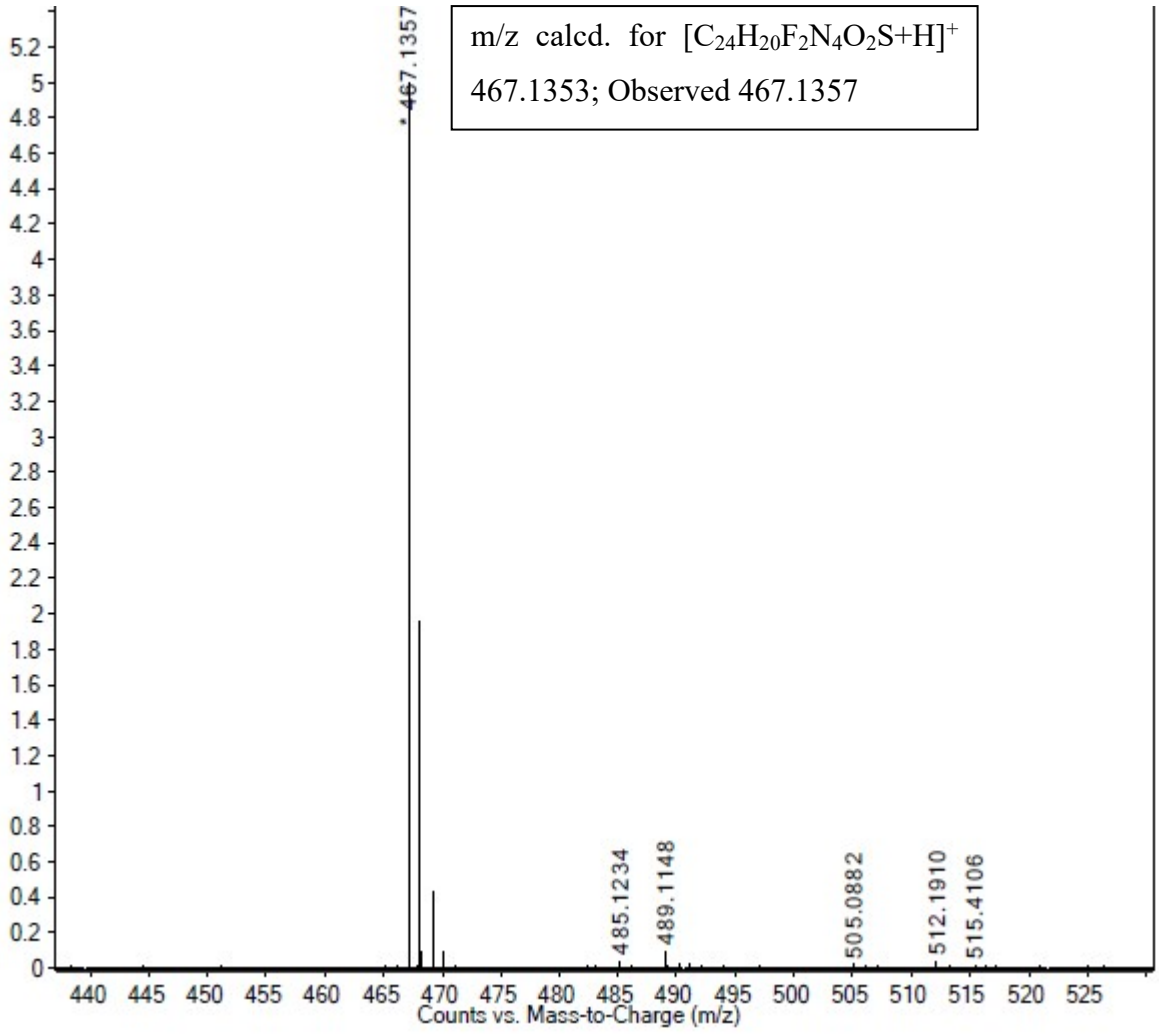
Mass spectrum of compound **6q**



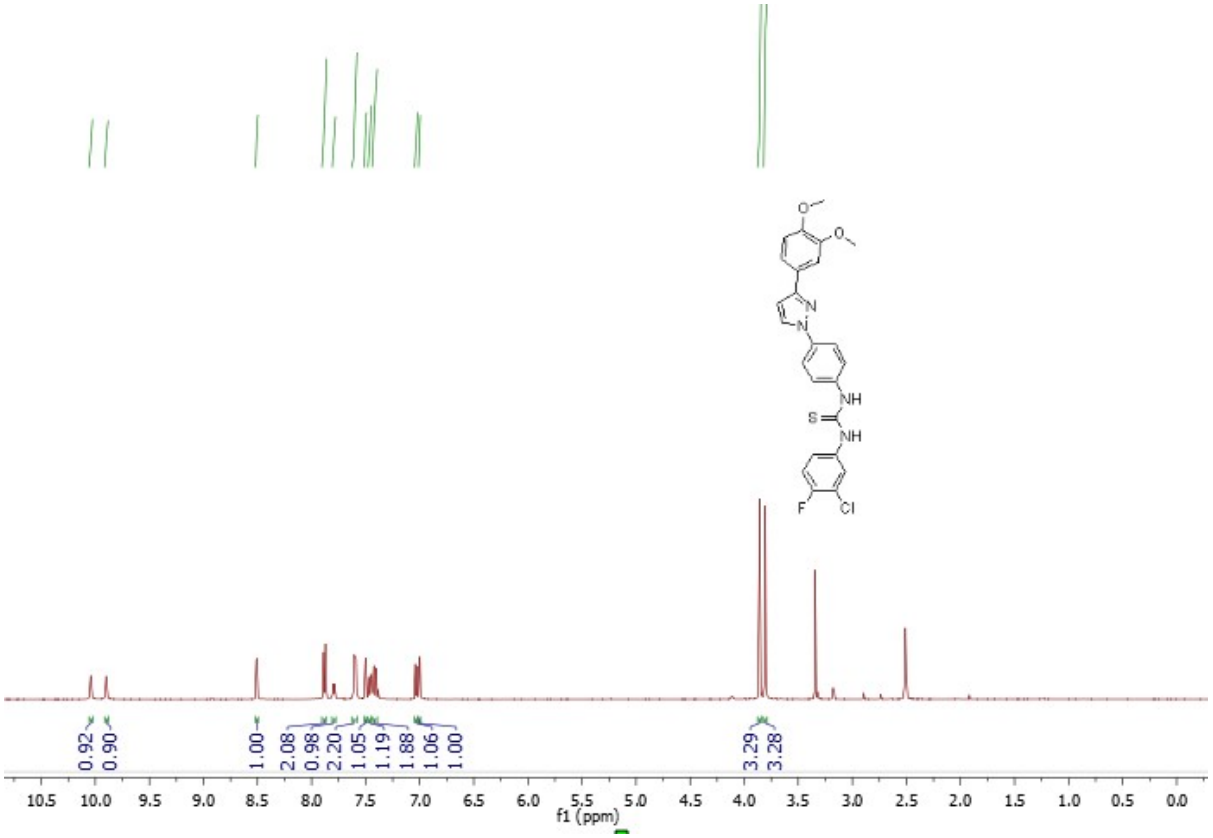
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6r**



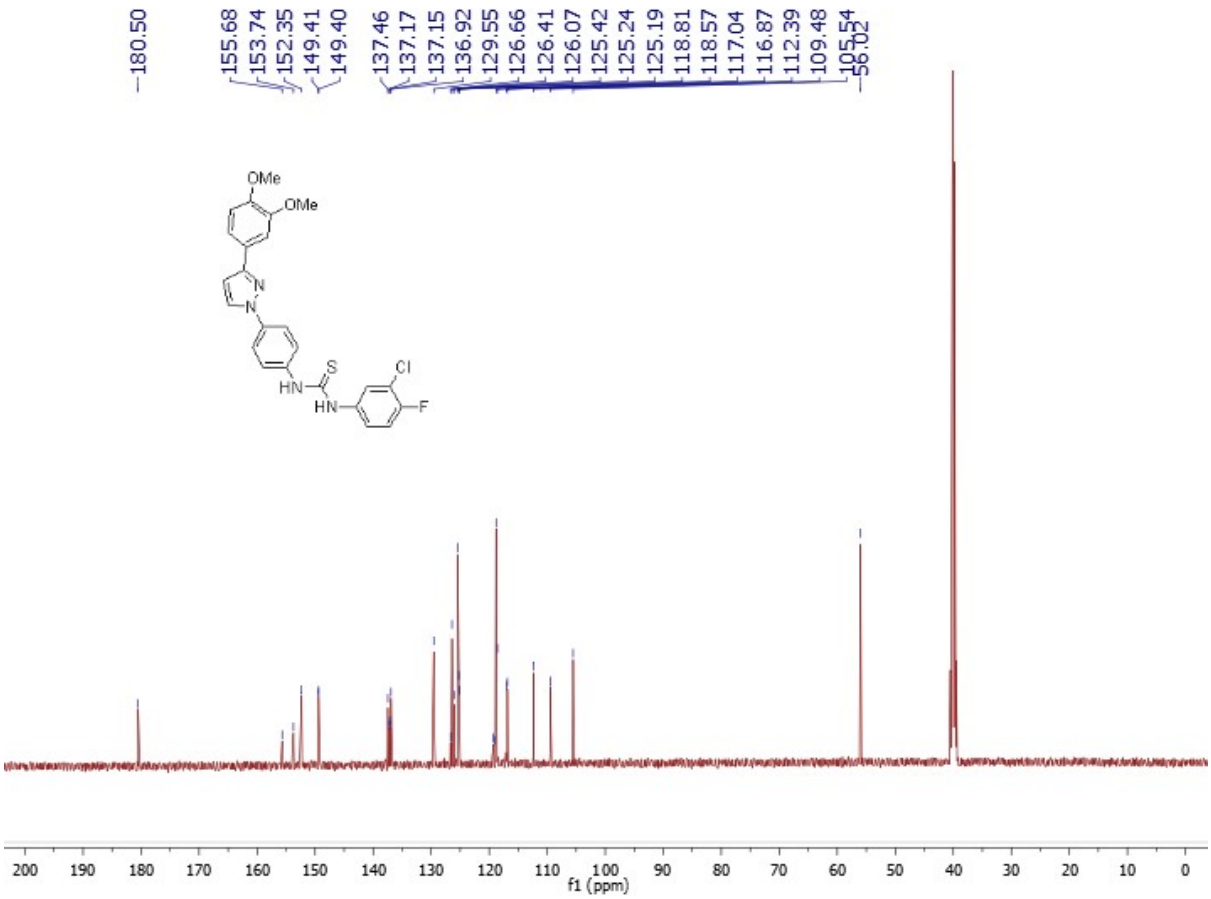
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6r**



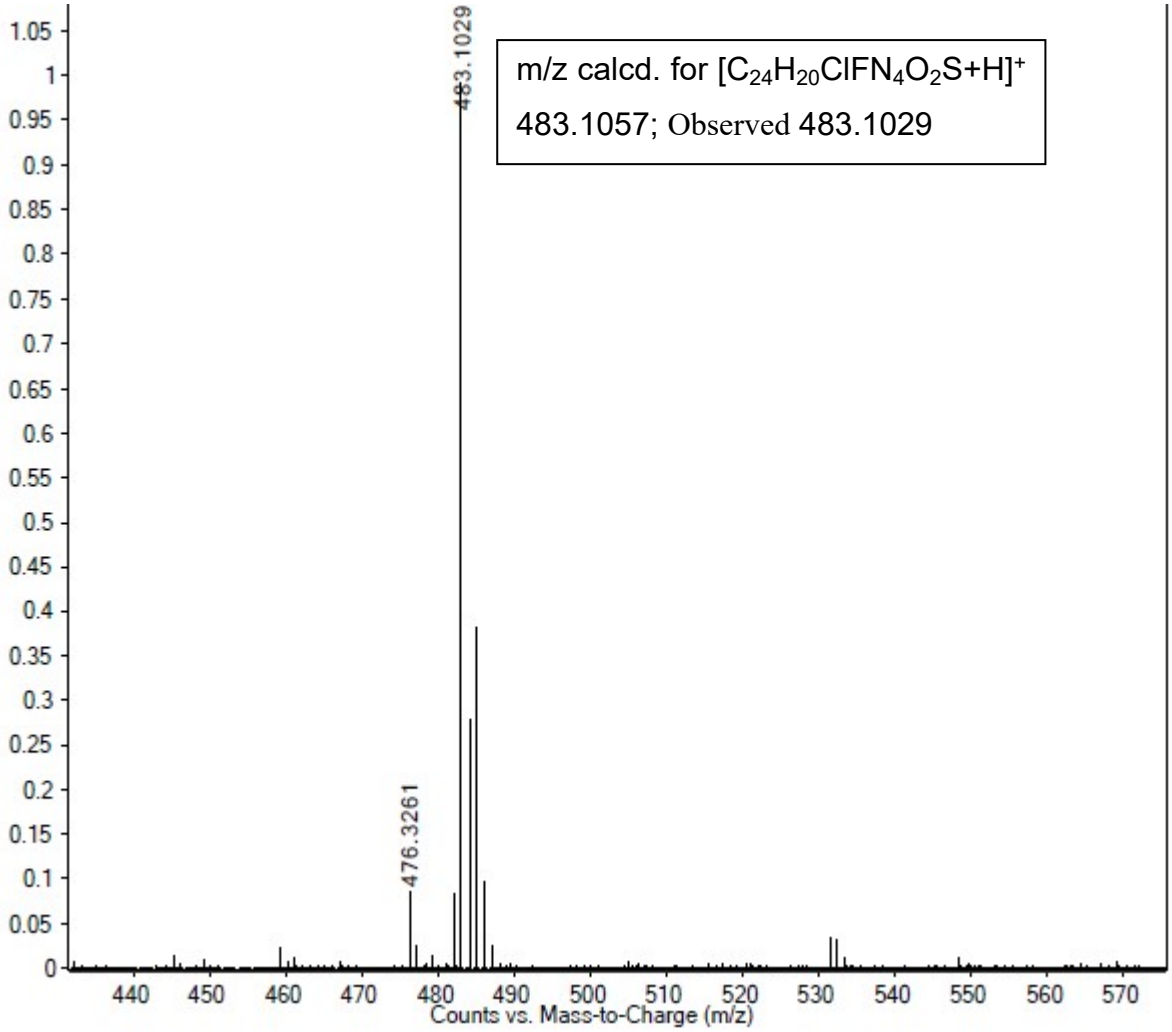
Mass spectrum of compound **6r**



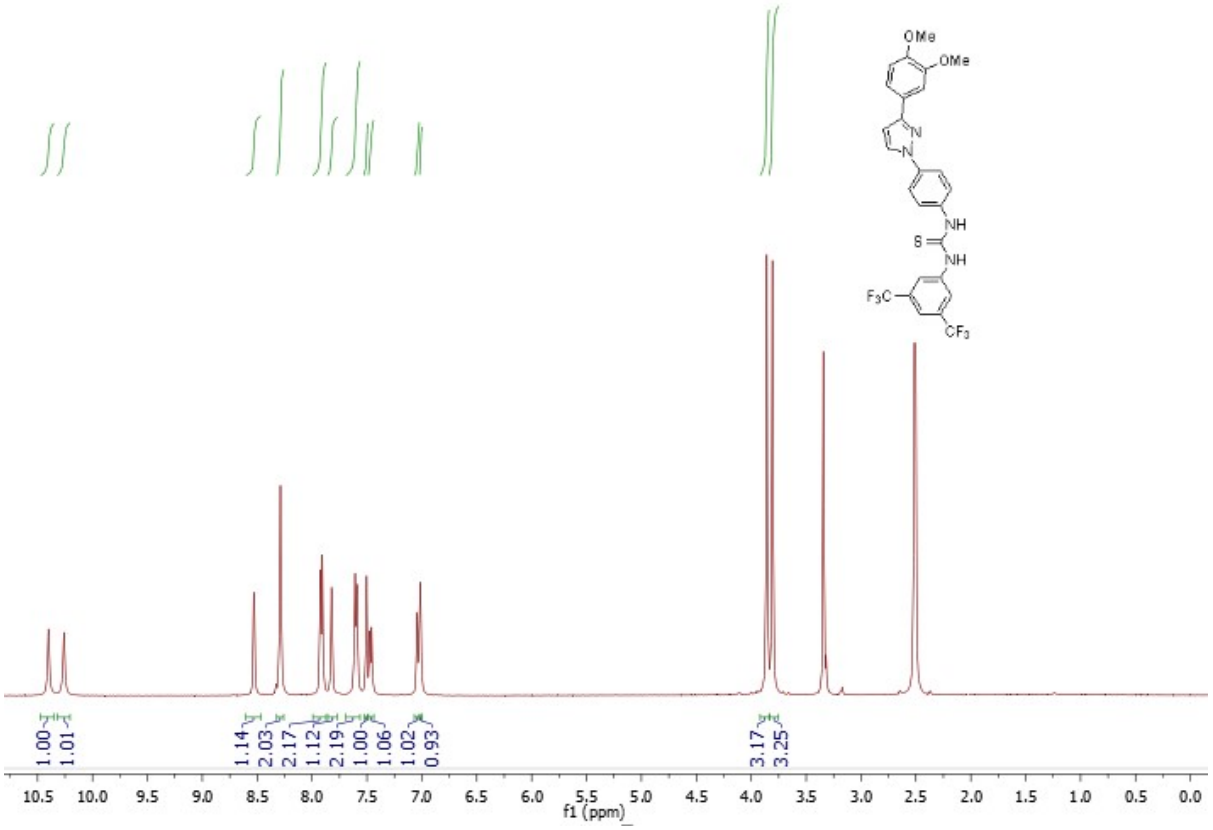
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6s**



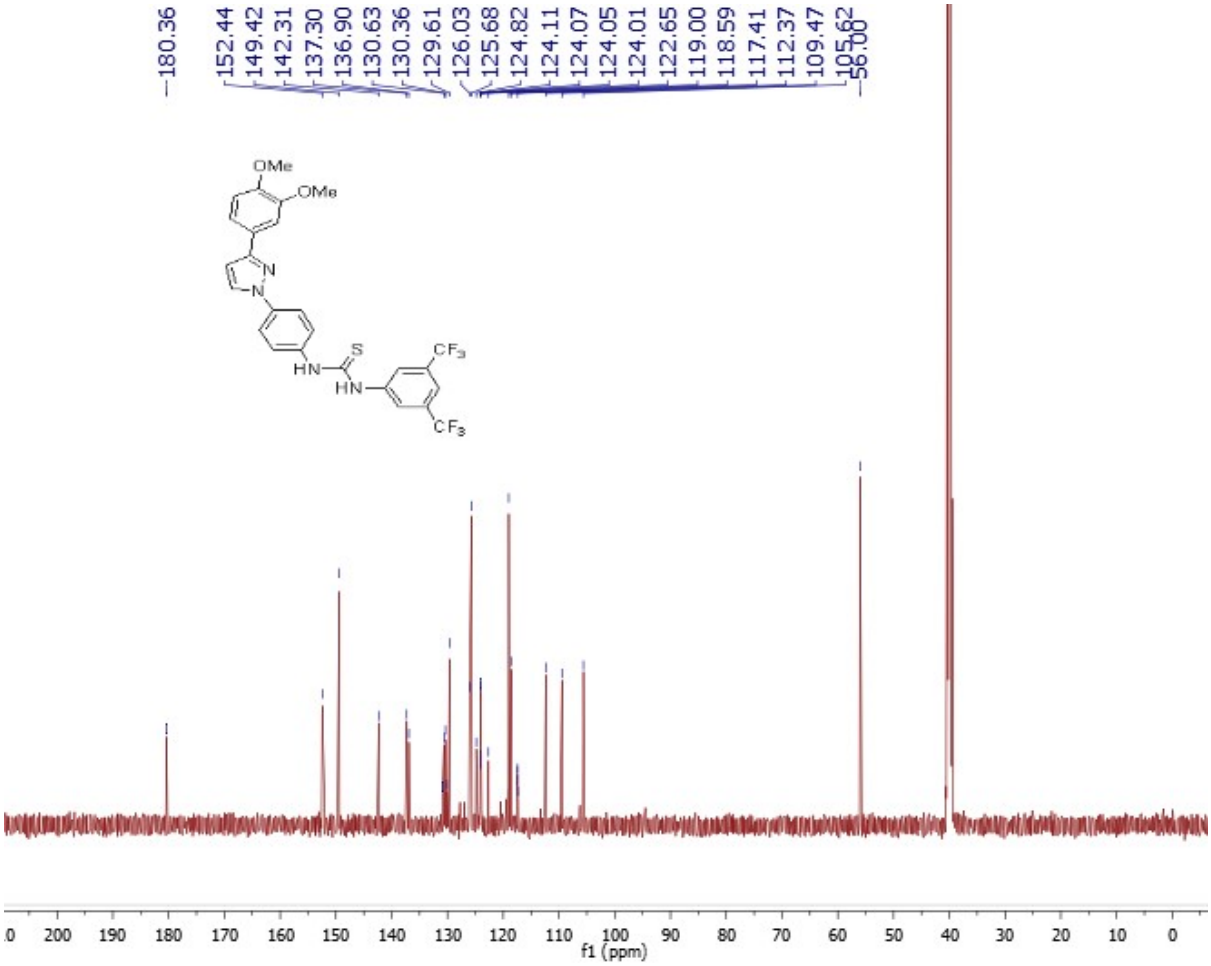
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6s**



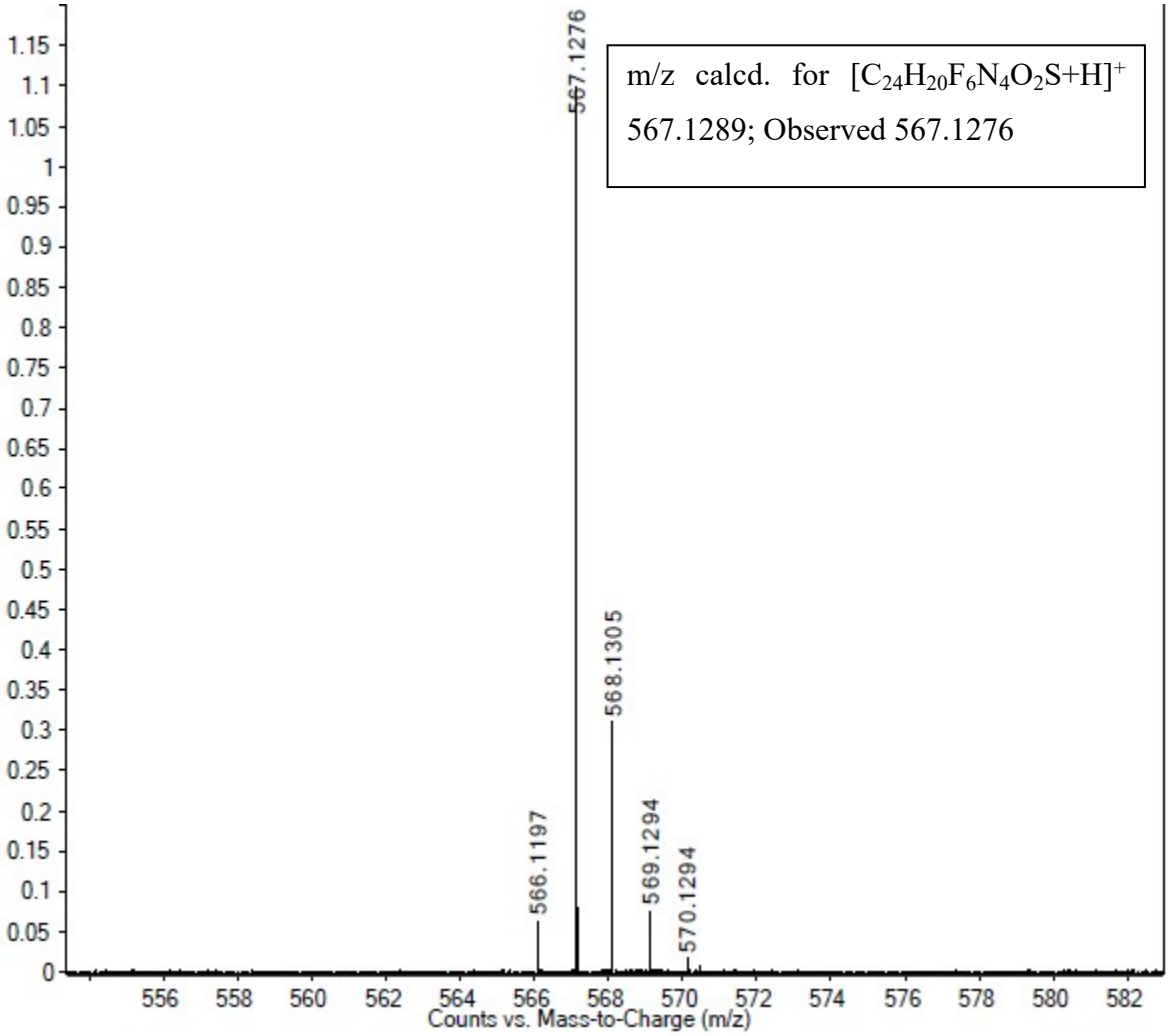
Mass spectrum of compound **6s**



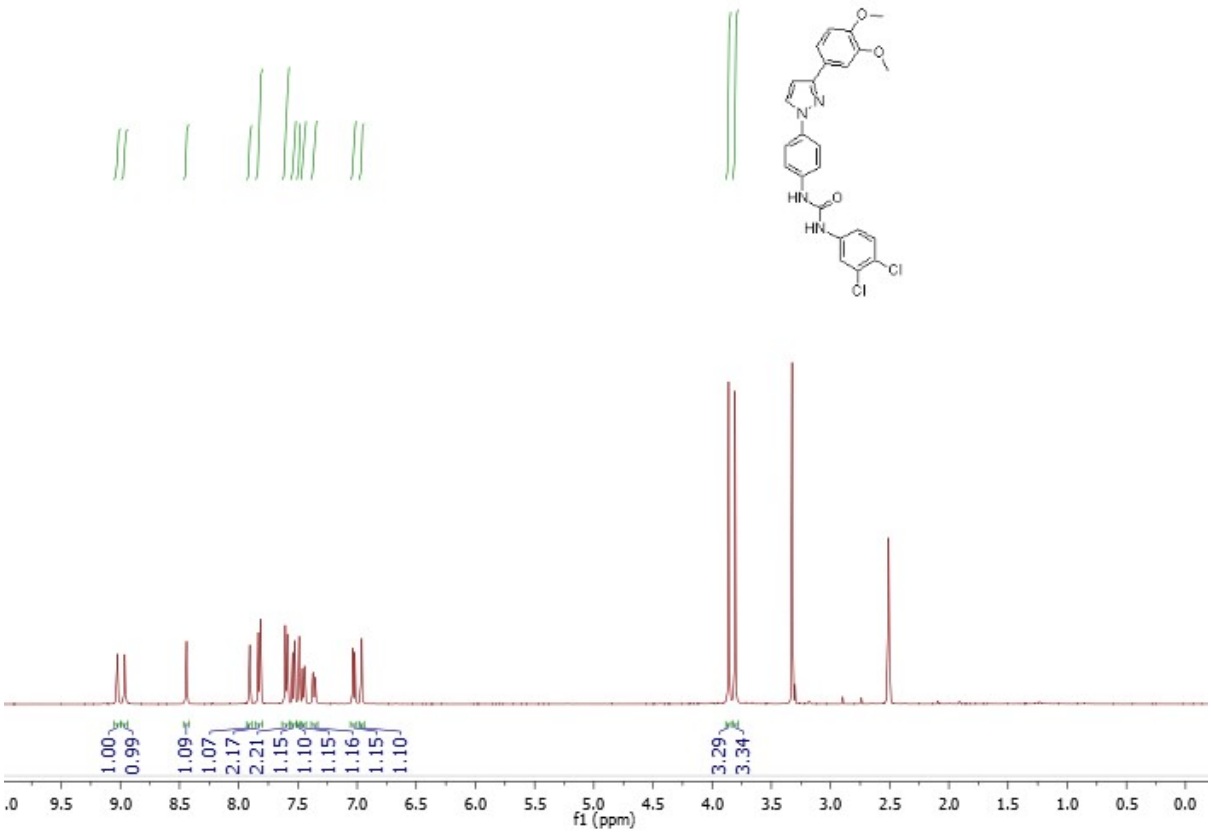
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **6t**



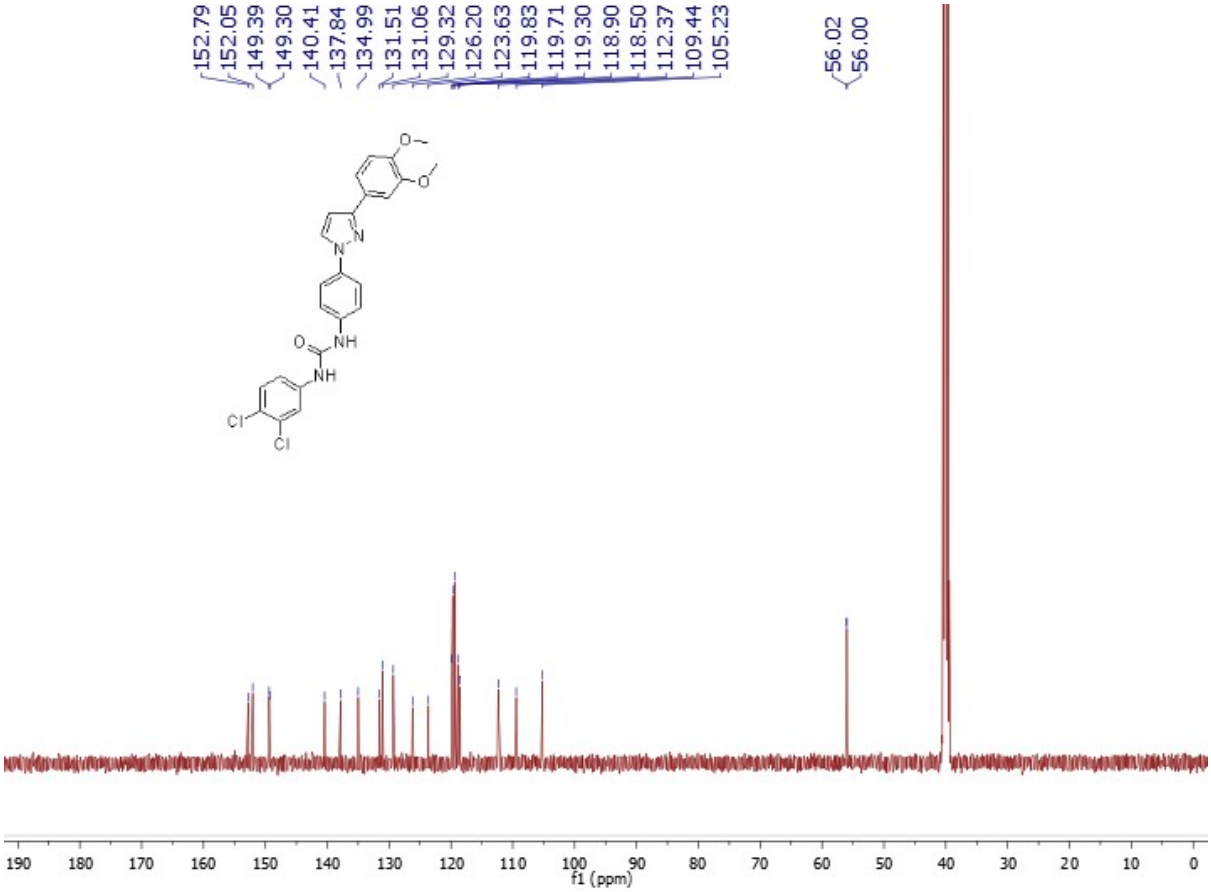
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **6t**



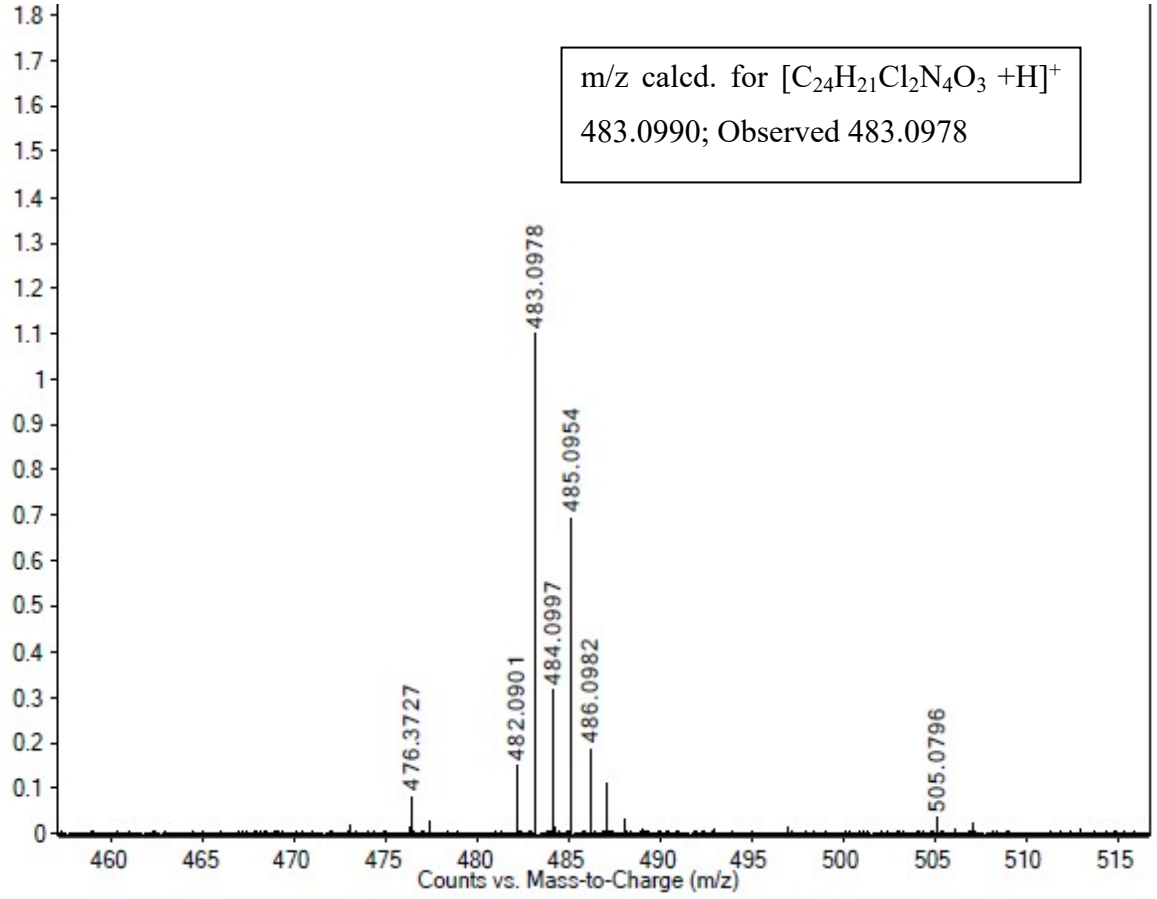
Mass spectrum of compound **6t**



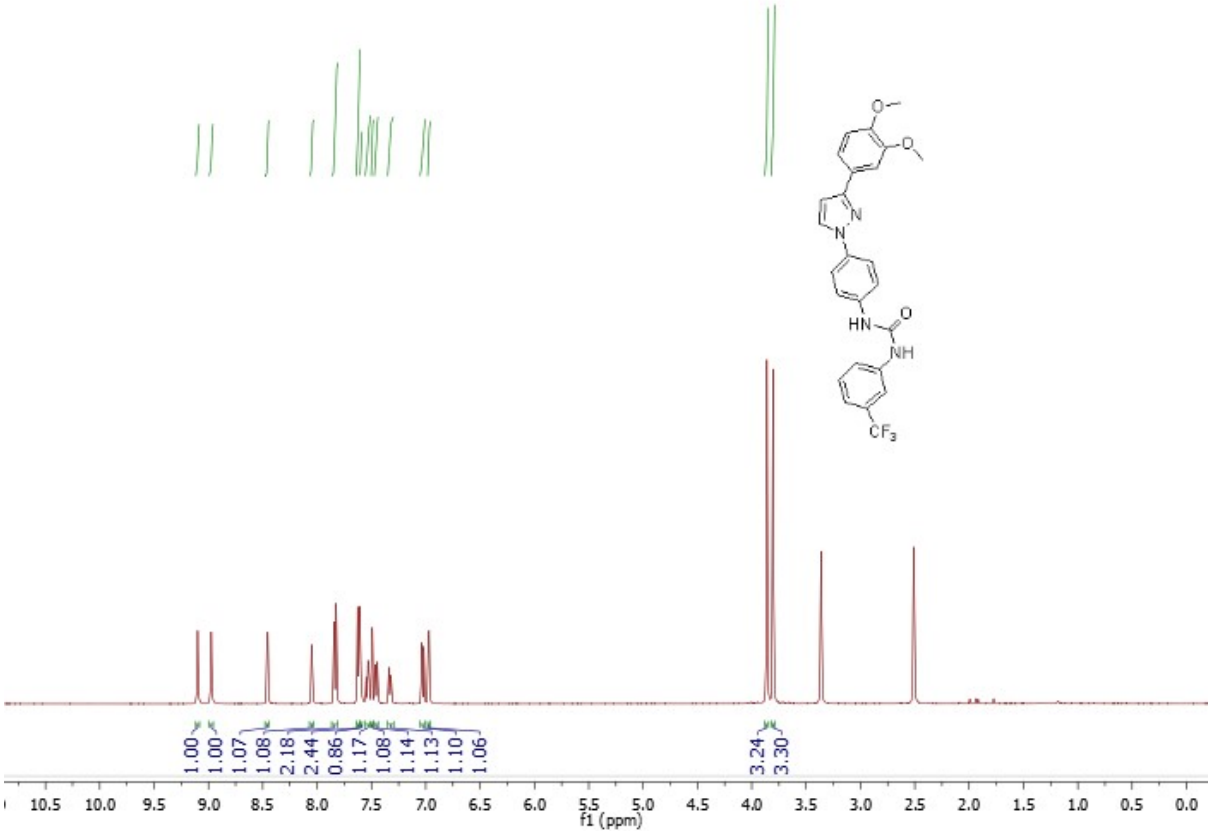
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **7a**



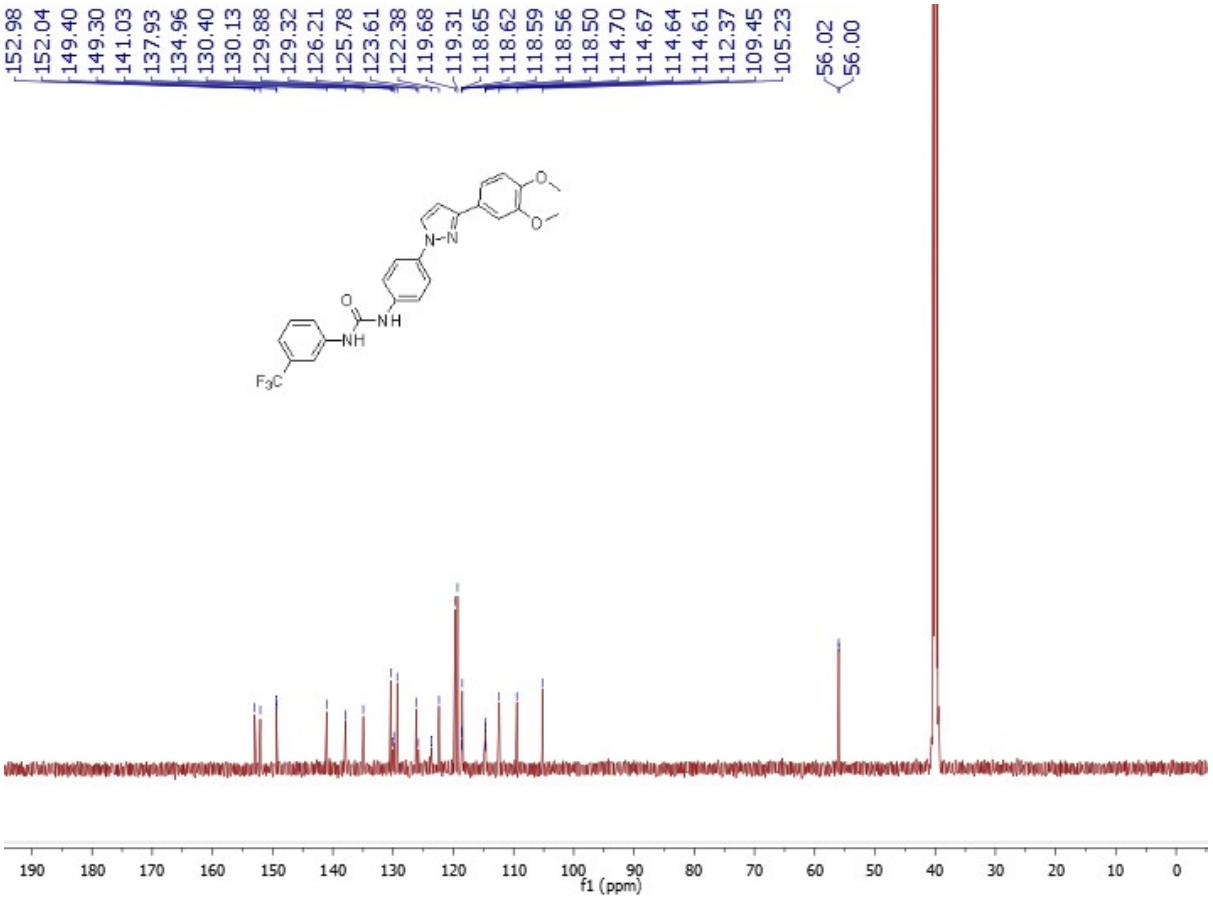
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **7a**



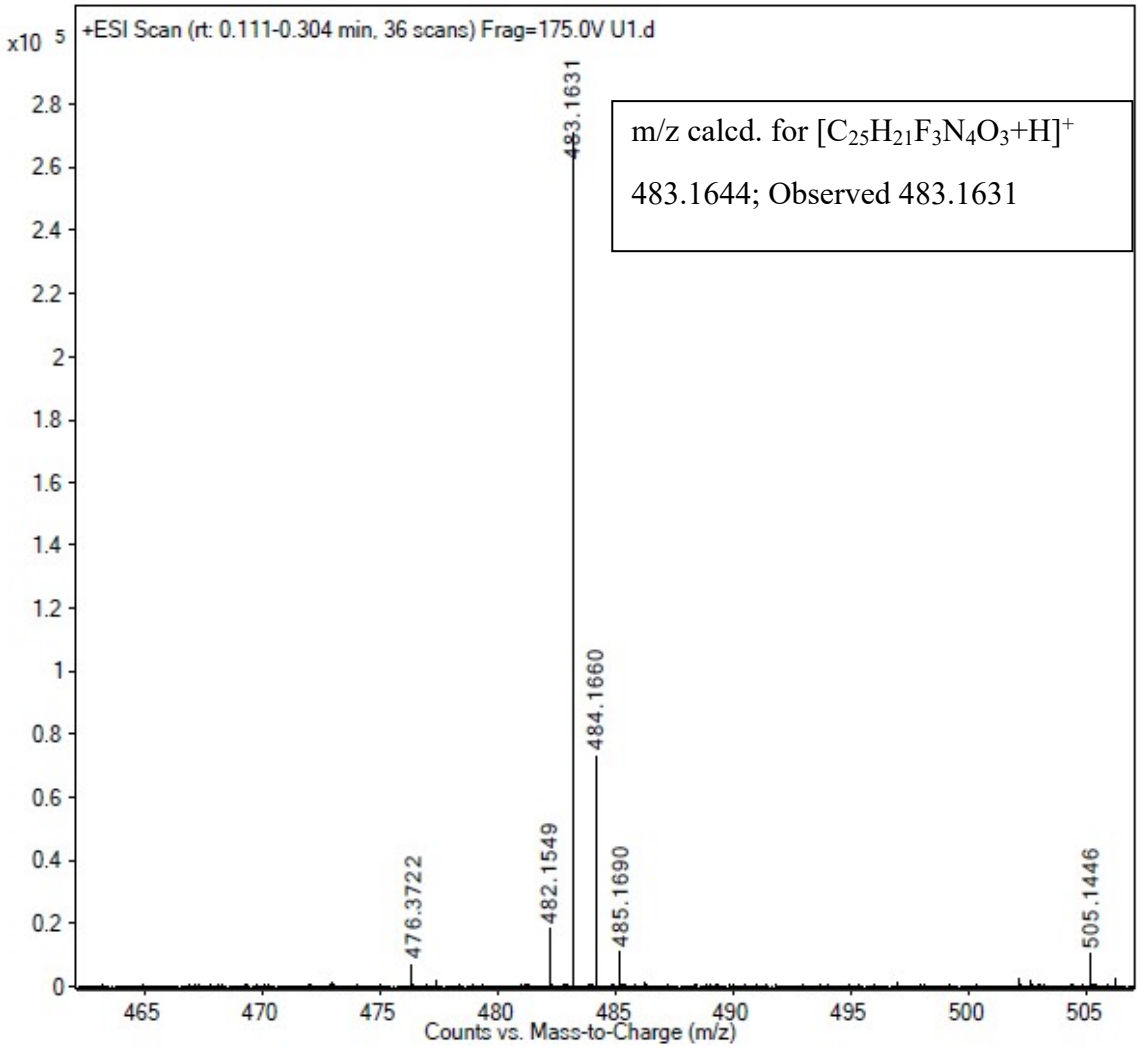
Mass spectrum of compound **7a**



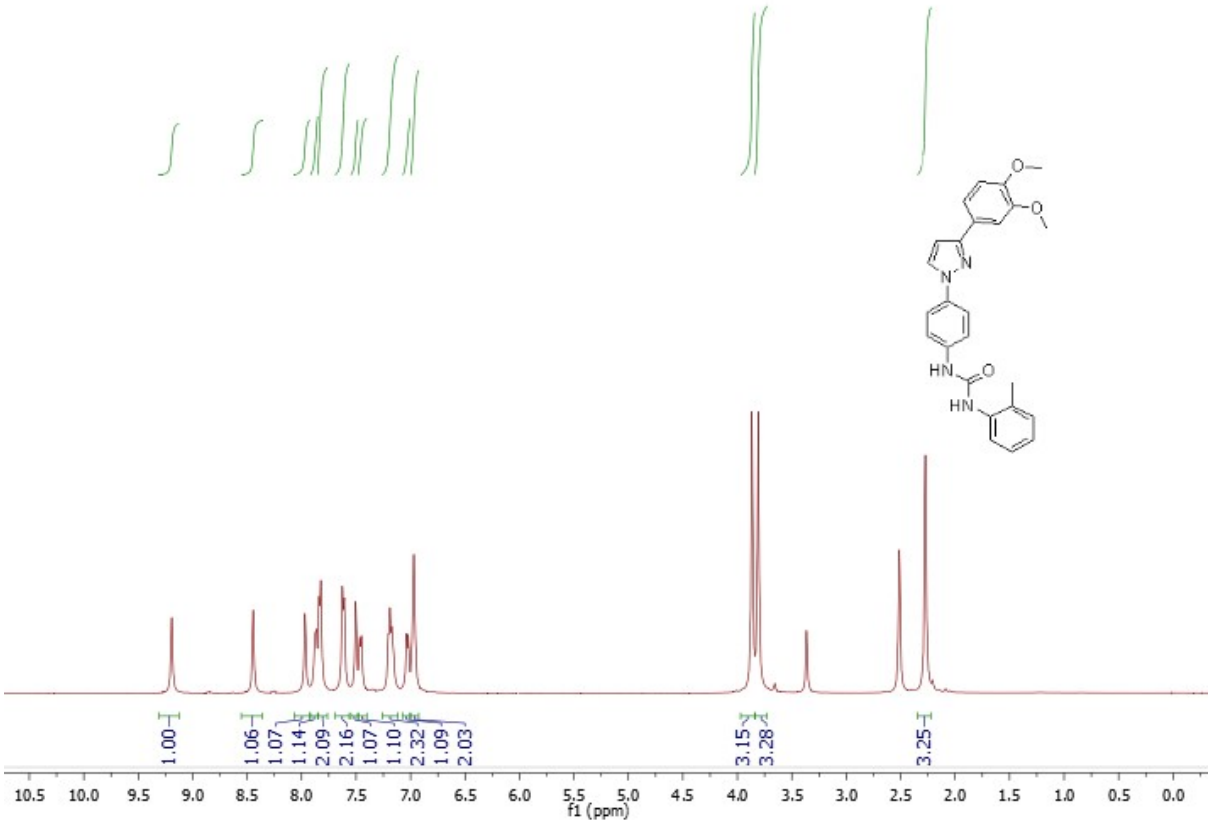
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **7b**



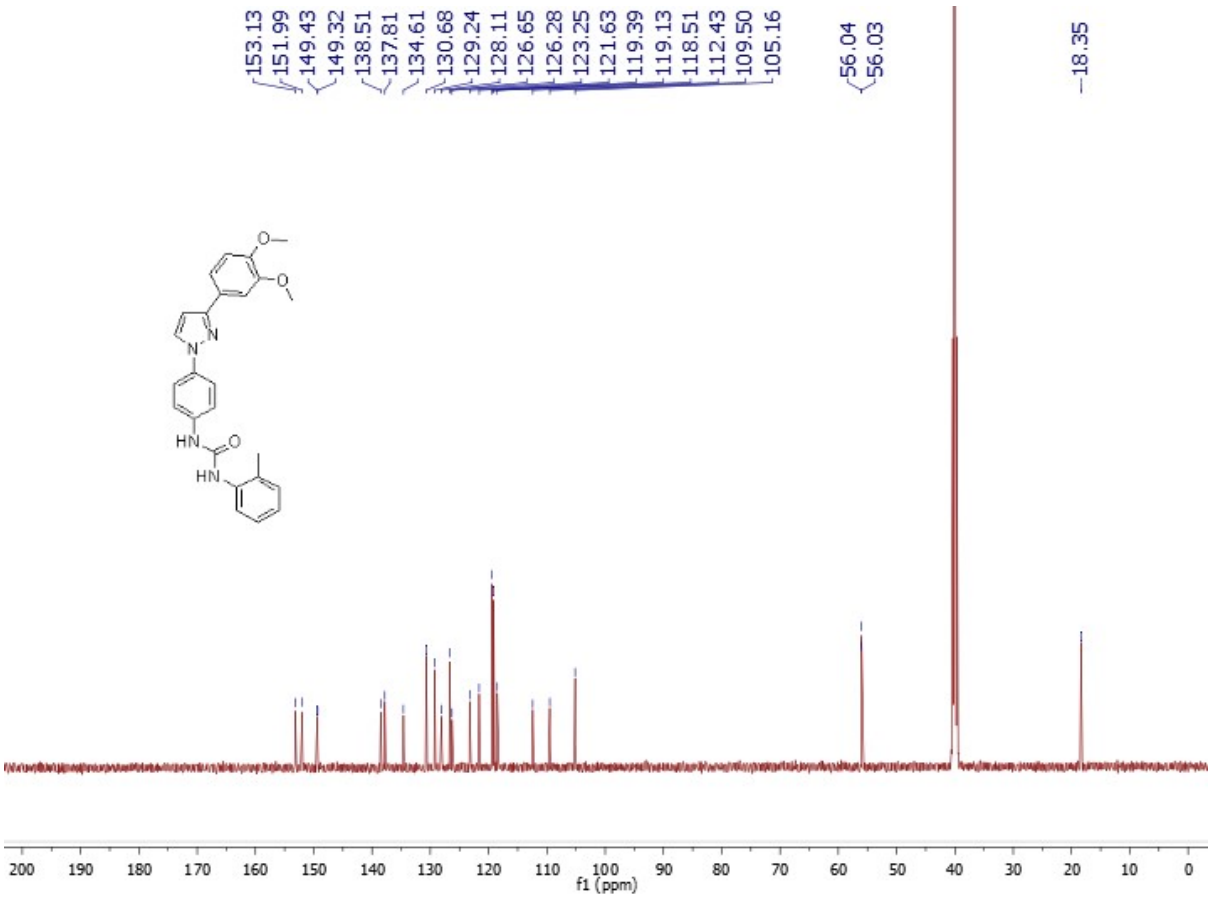
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **7b**



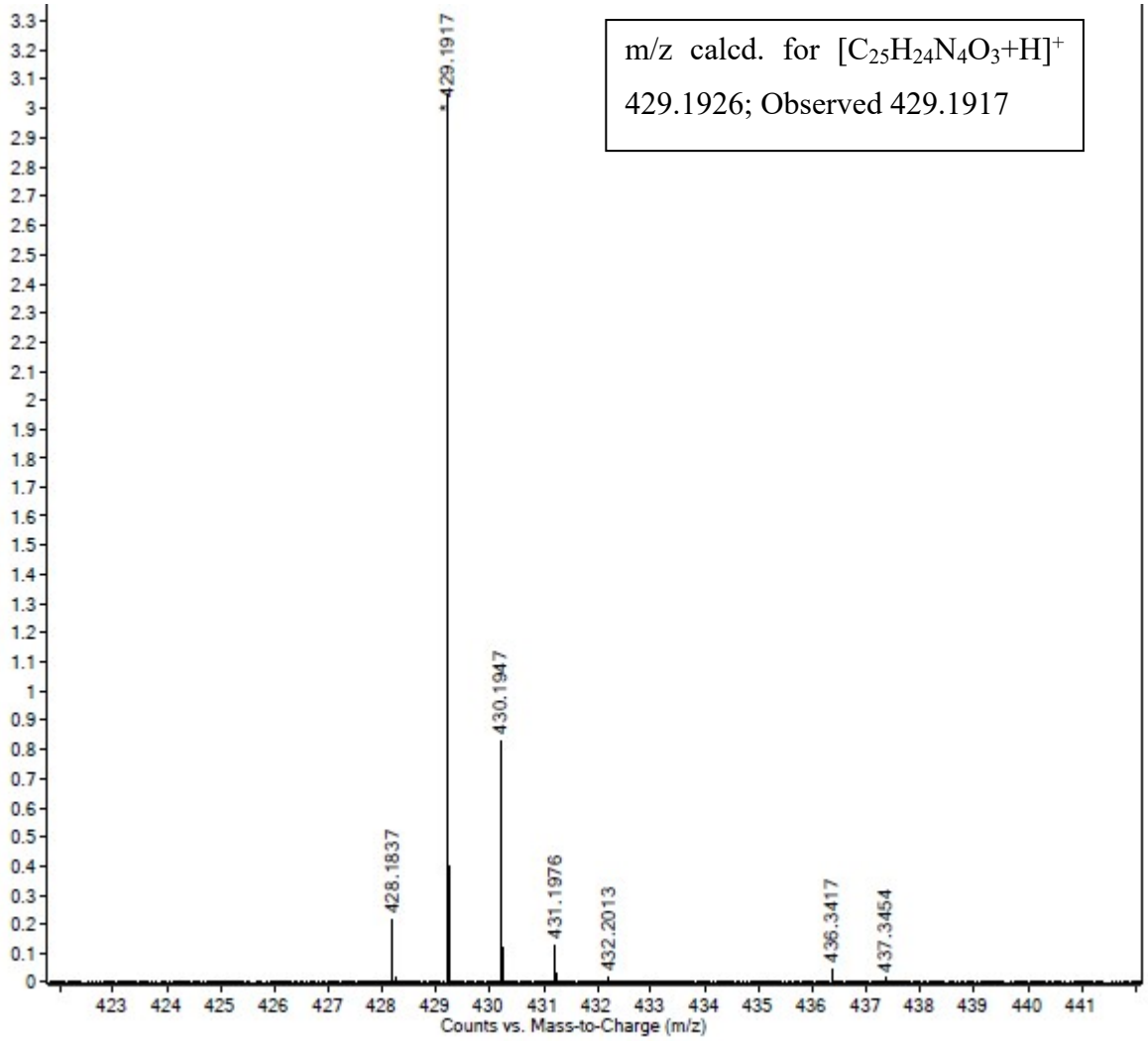
Mass spectrum of compound **7b**



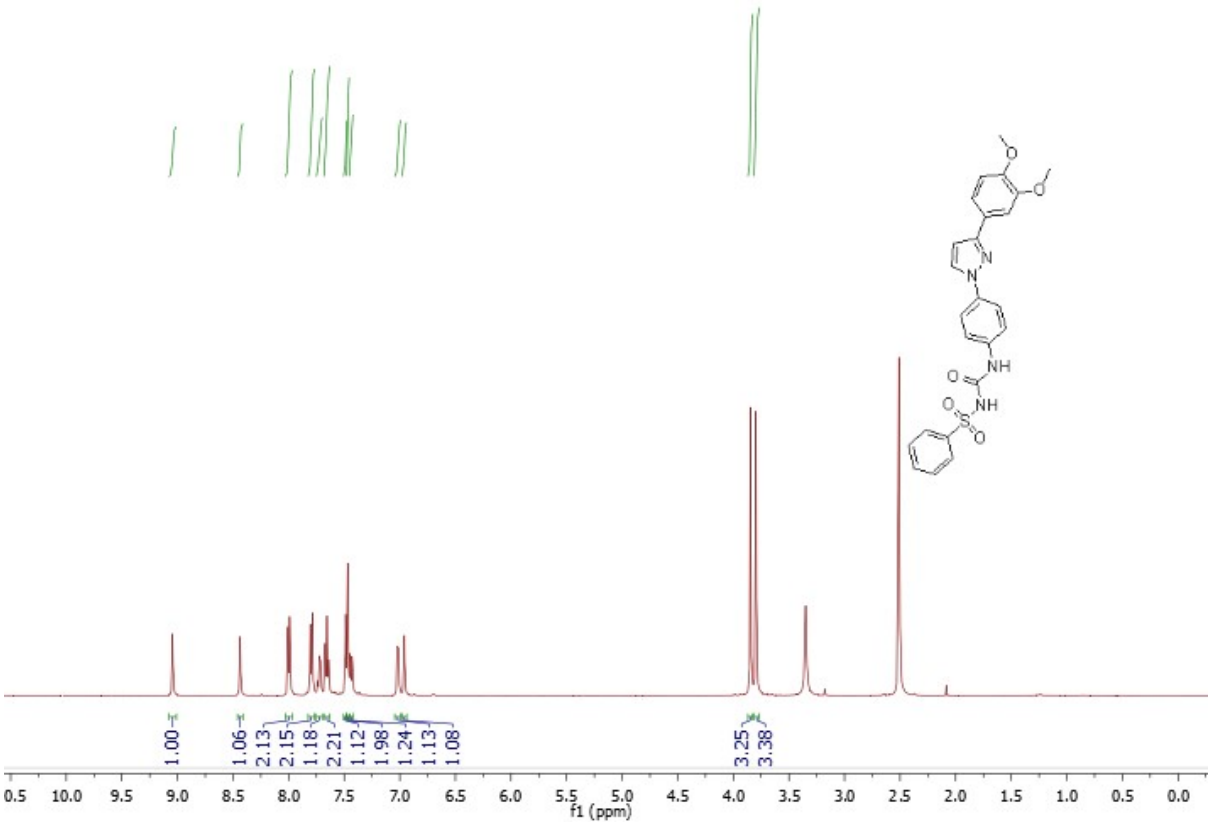
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **7c**



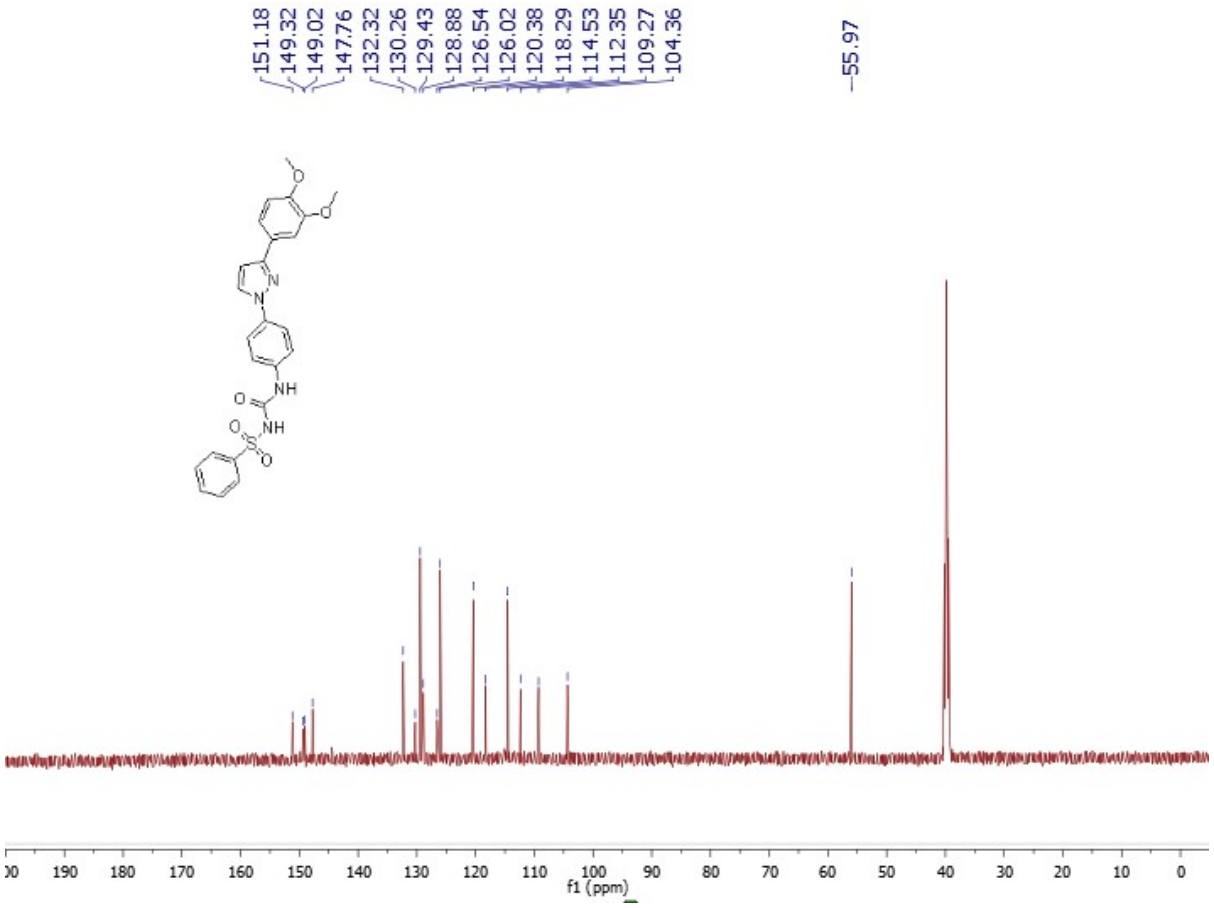
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **7c**



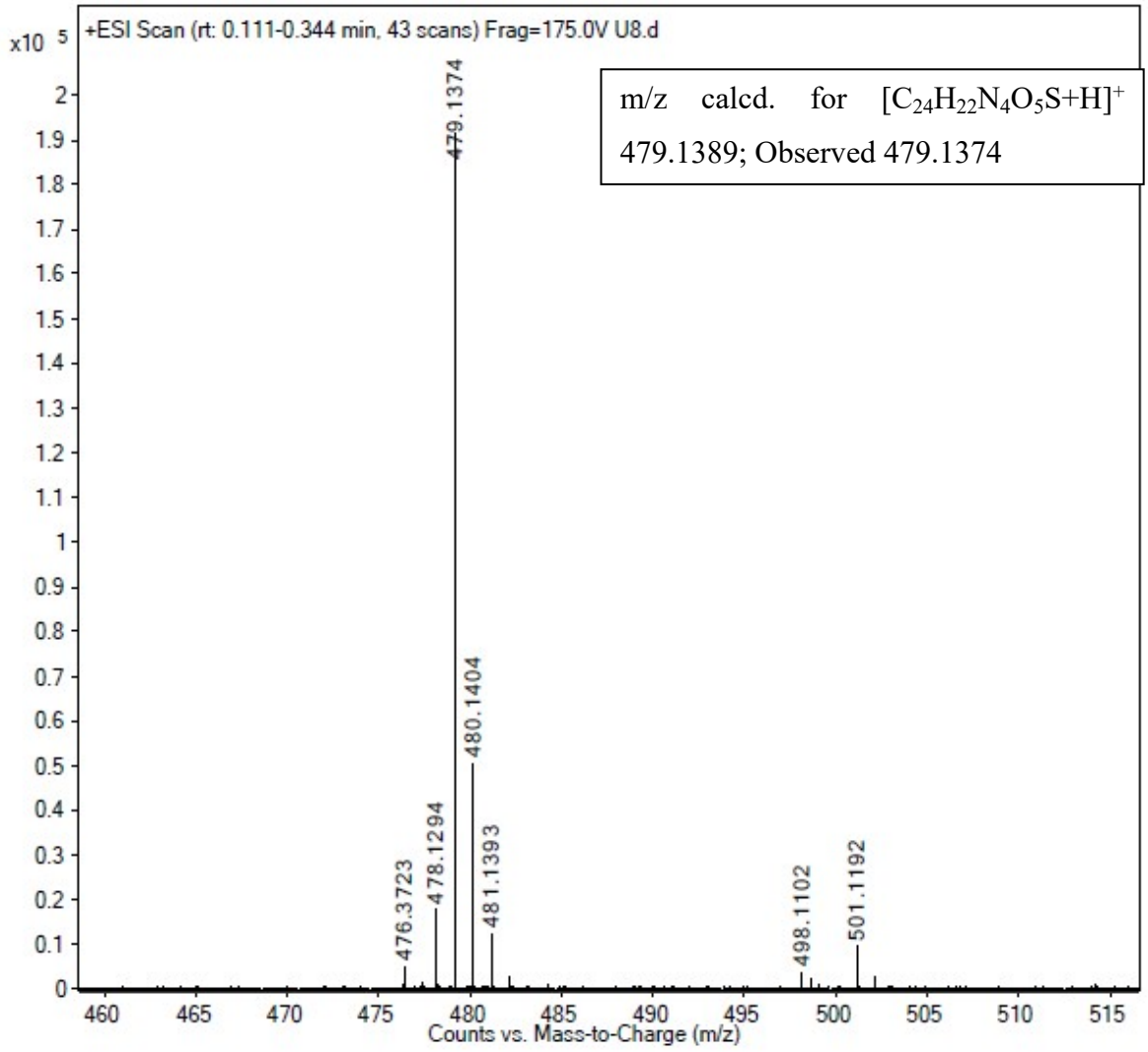
Mass spectrum of compound **7c**



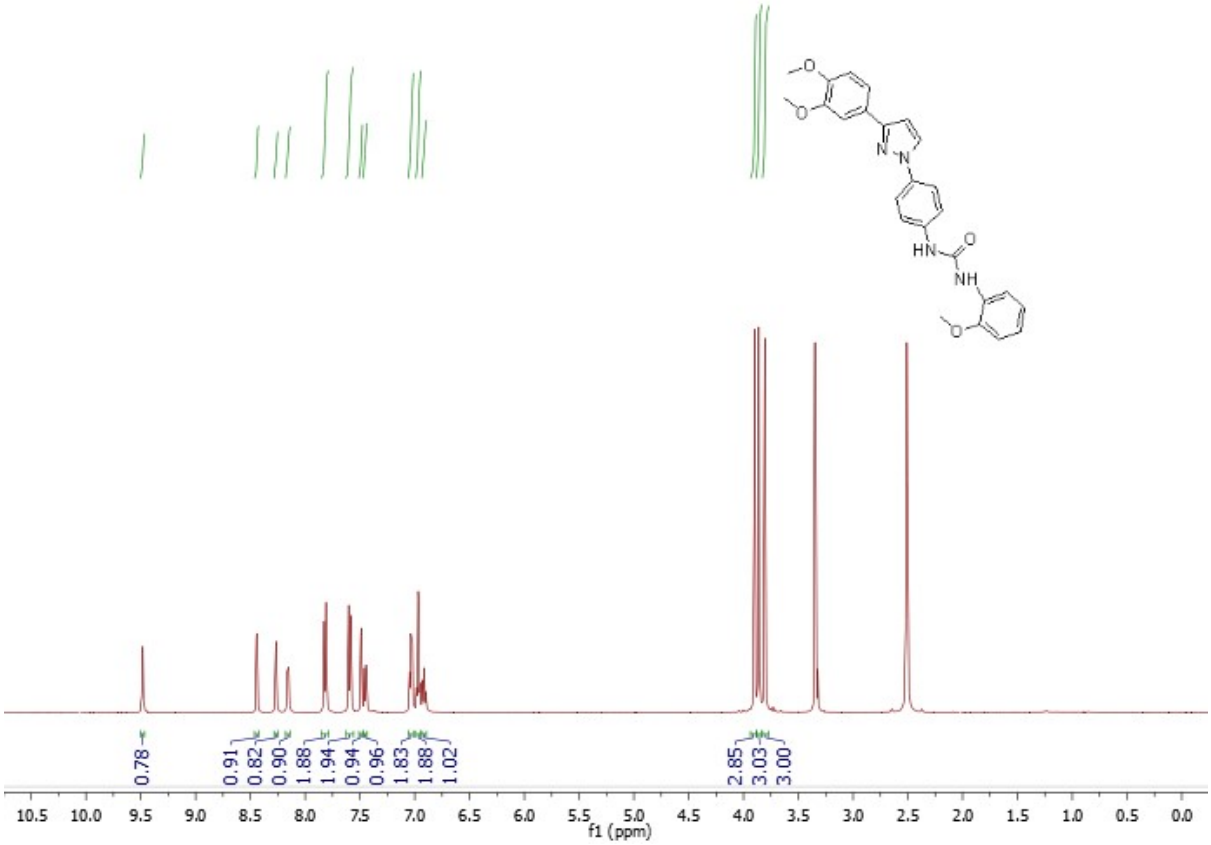
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **7d**



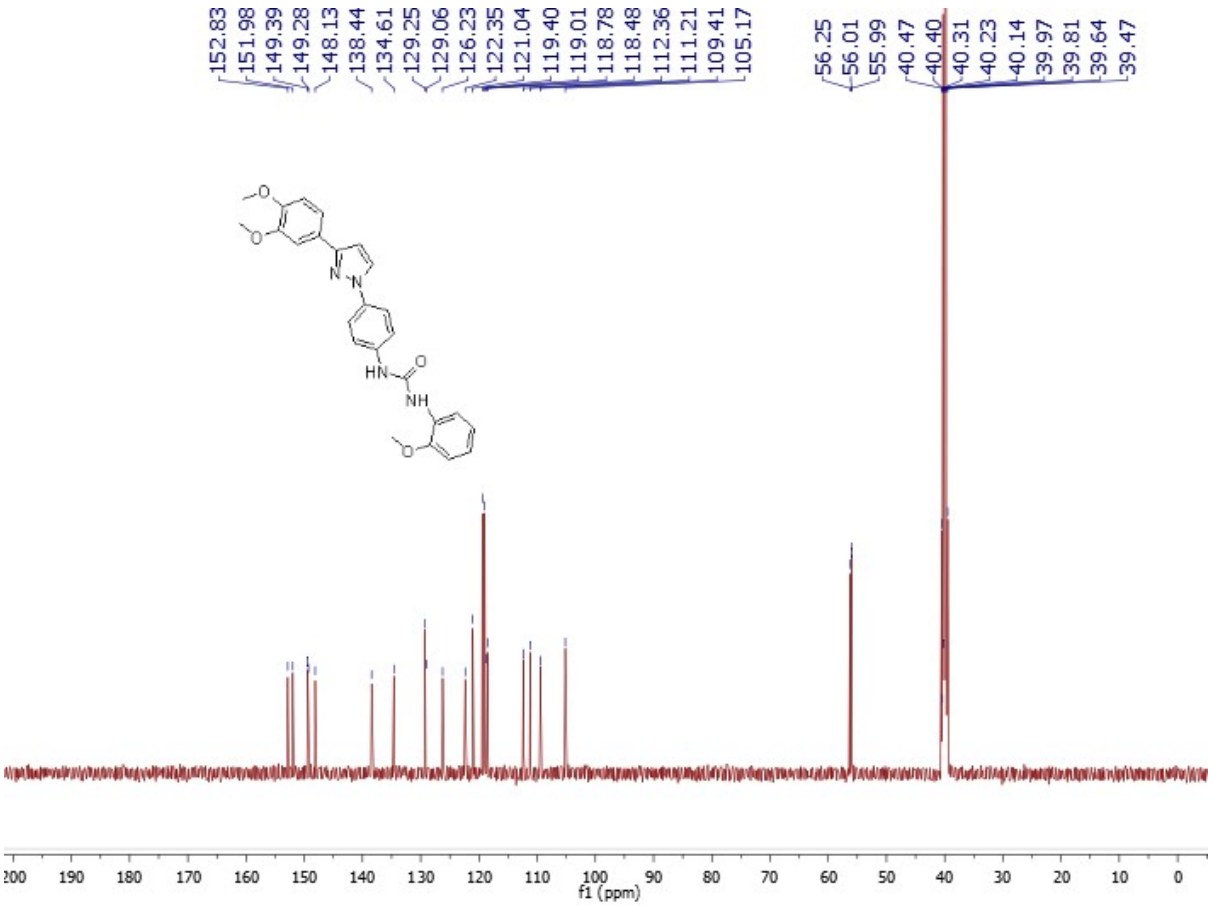
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **7d**



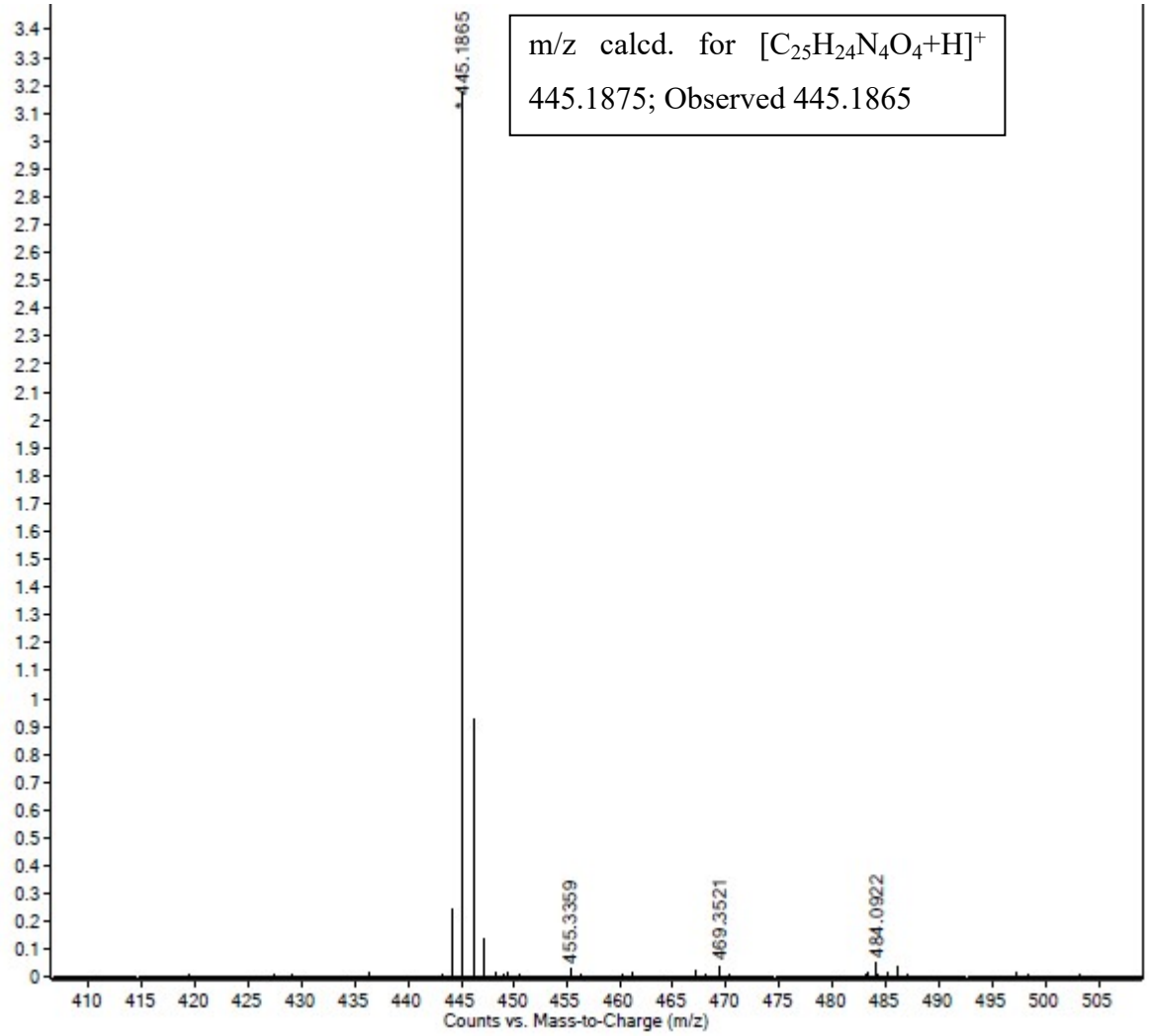
Mass spectrum of compound **7d**



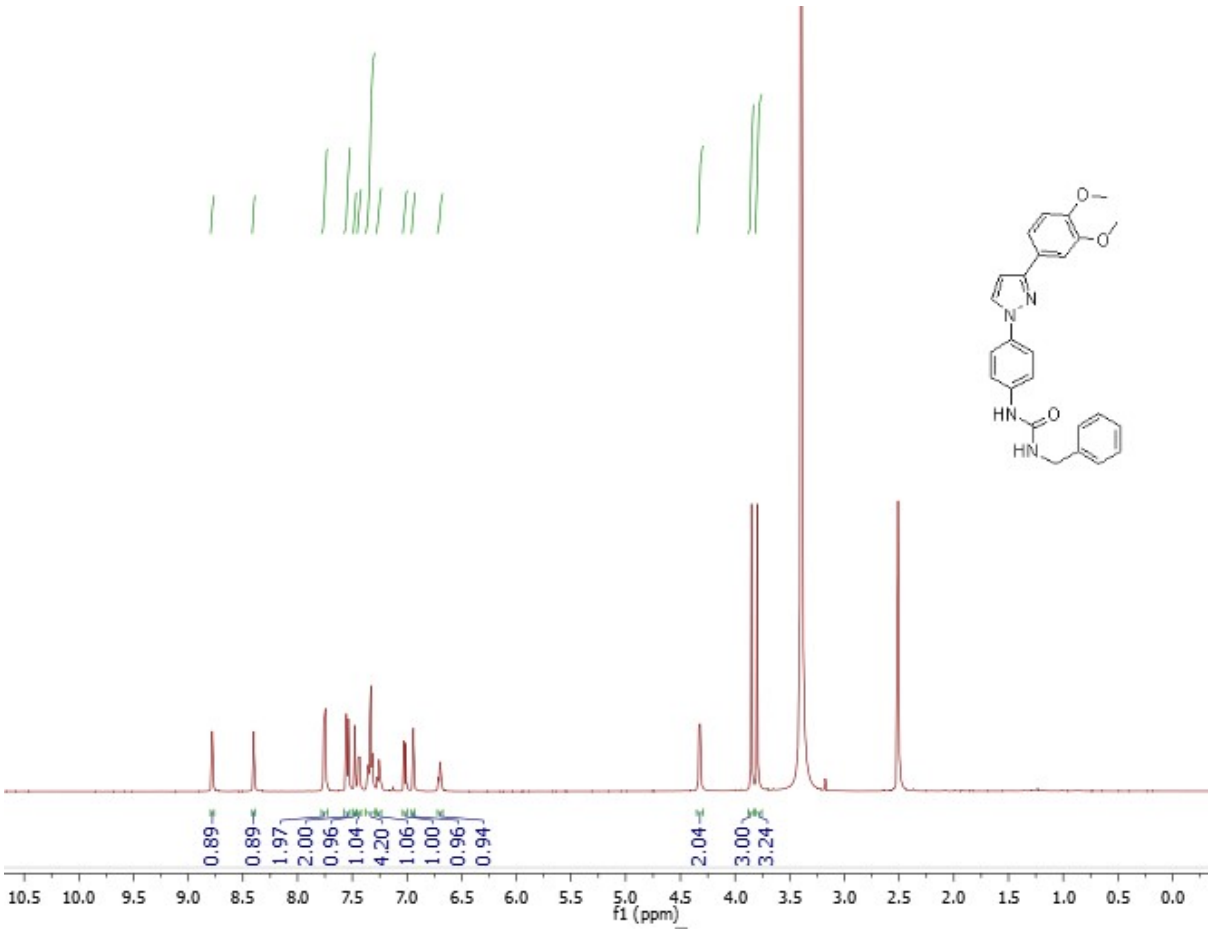
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **7e**



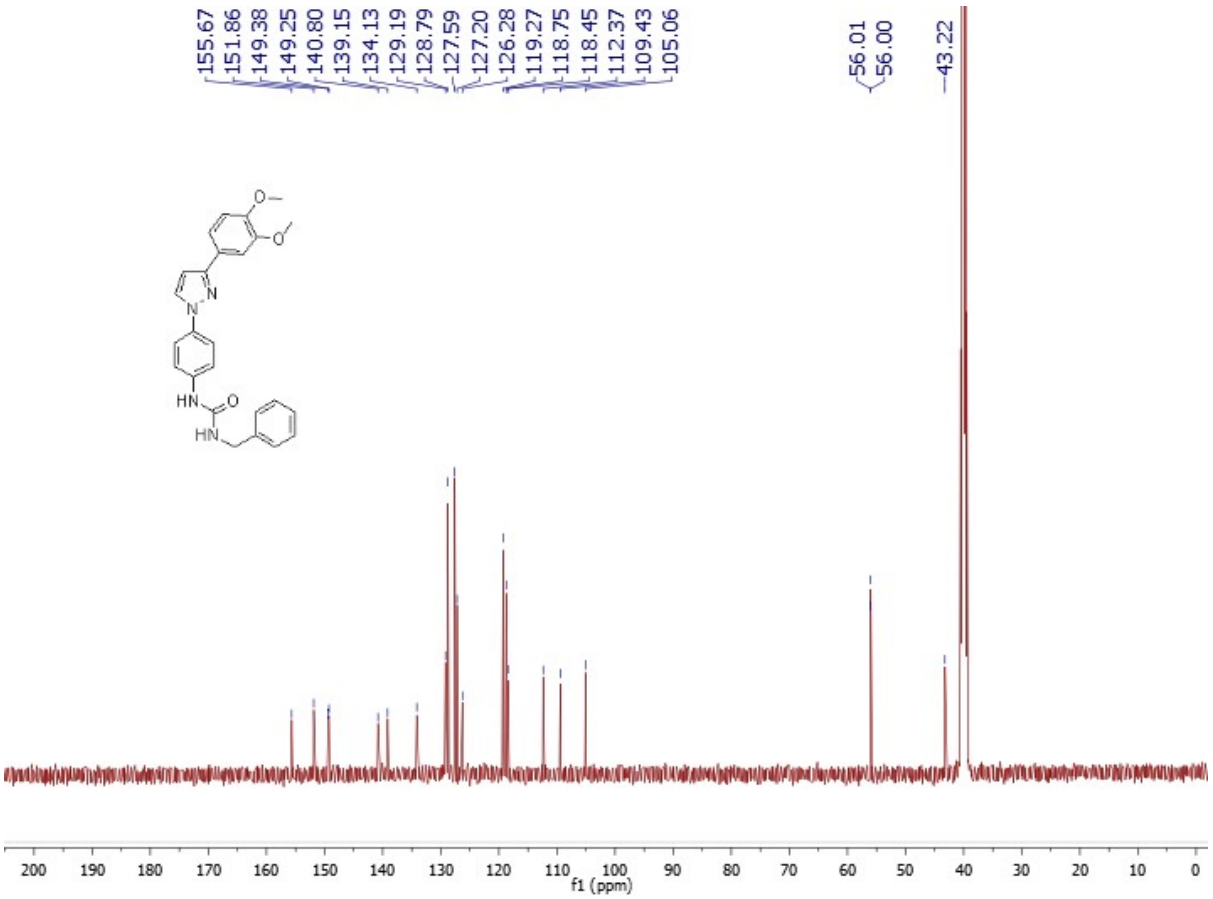
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **7e**



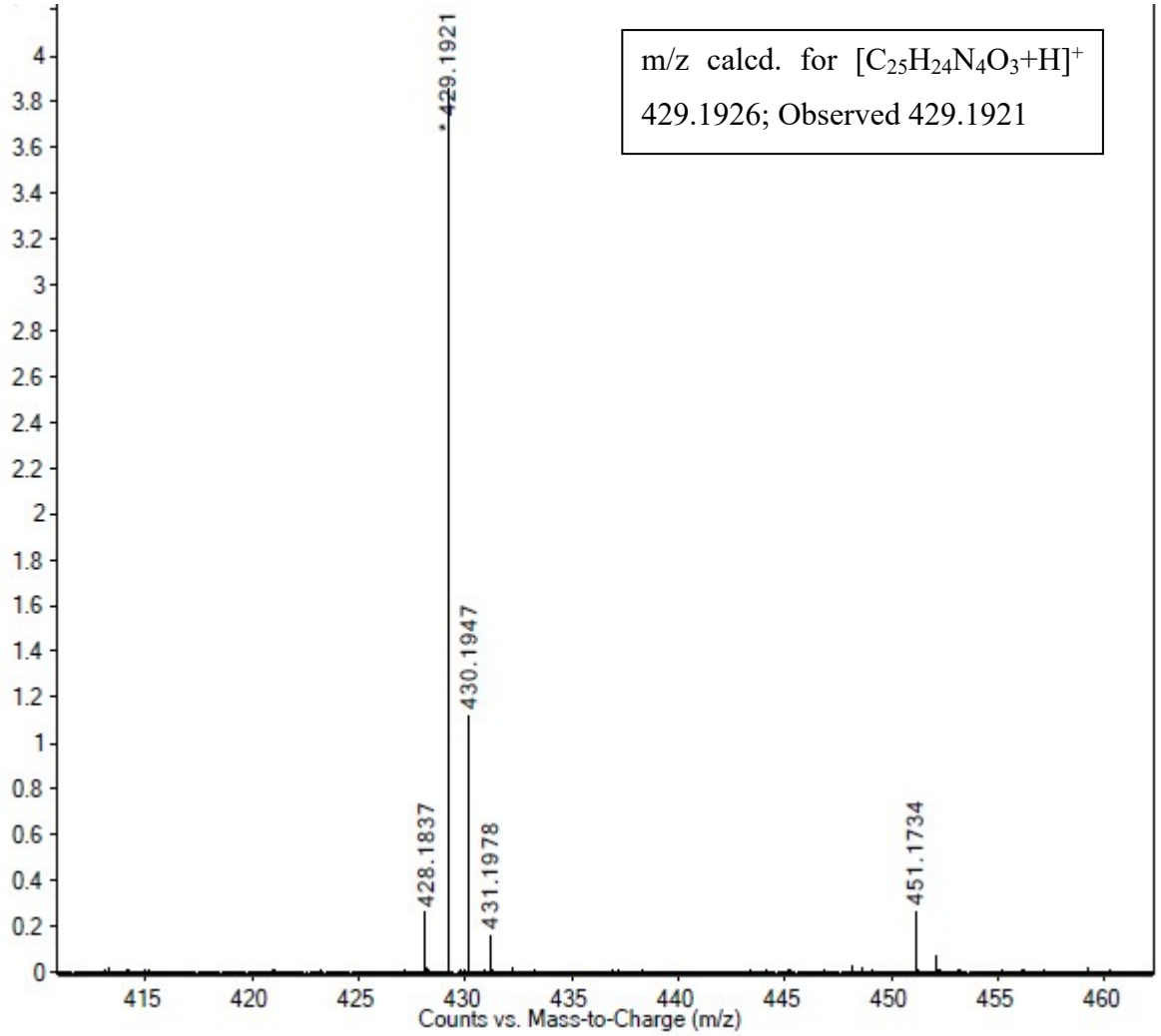
Mass spectrum of compound **7e**



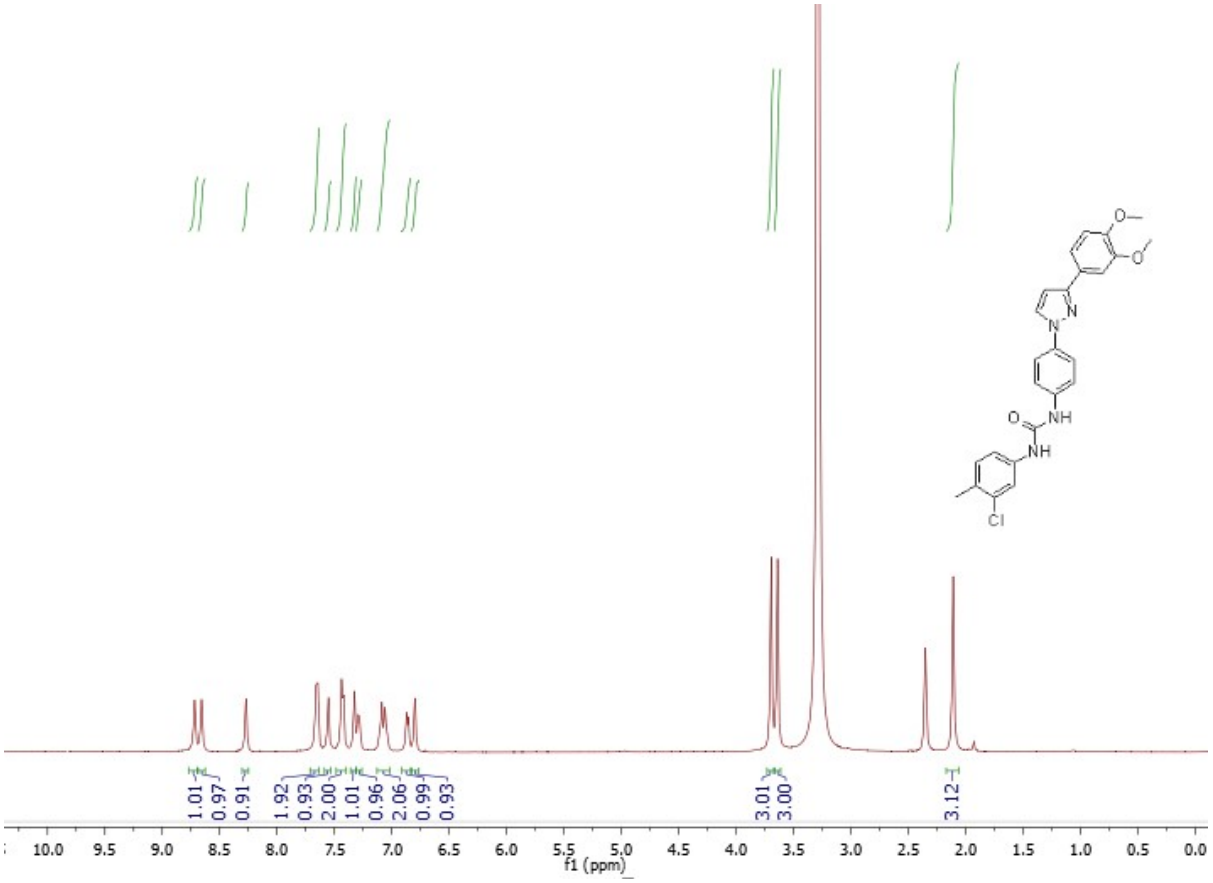
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **7f**



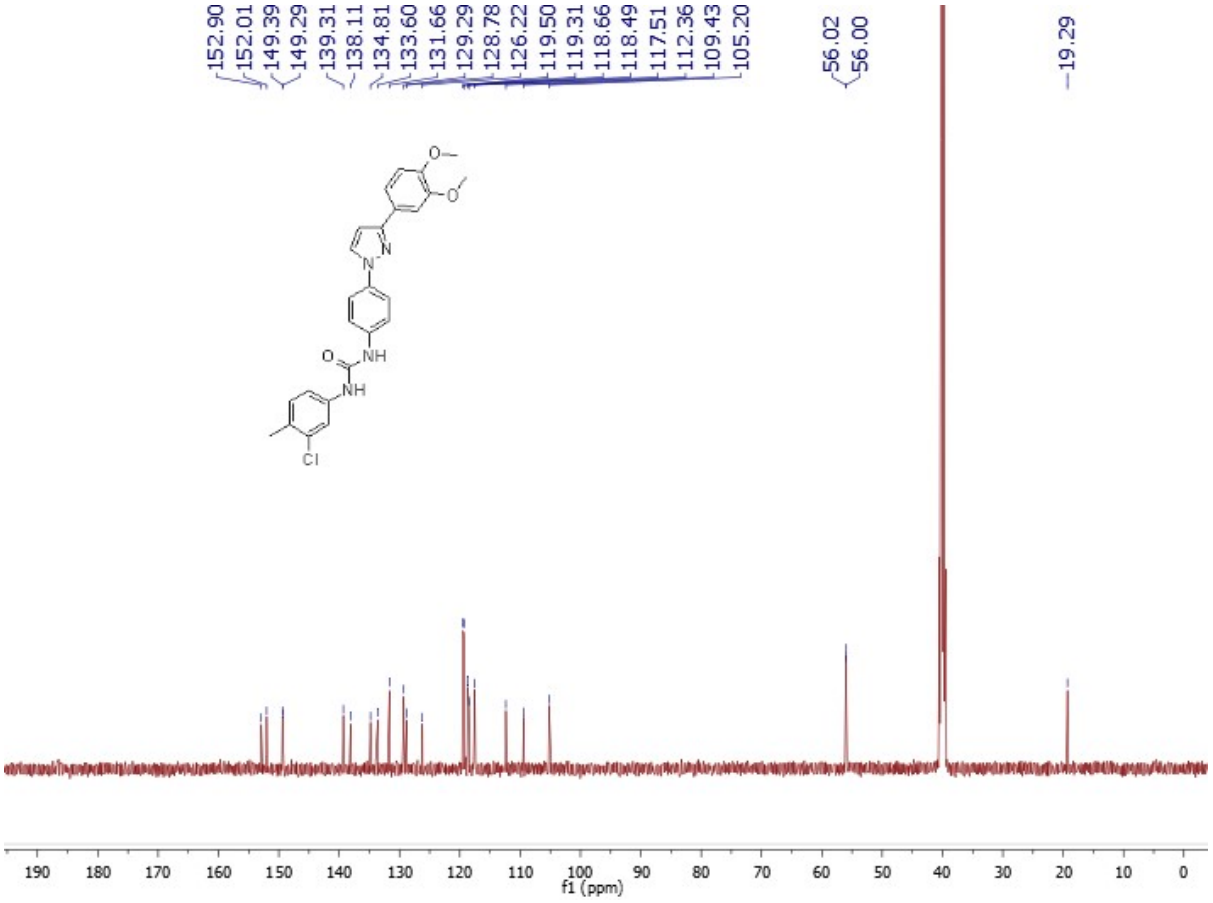
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **7f**



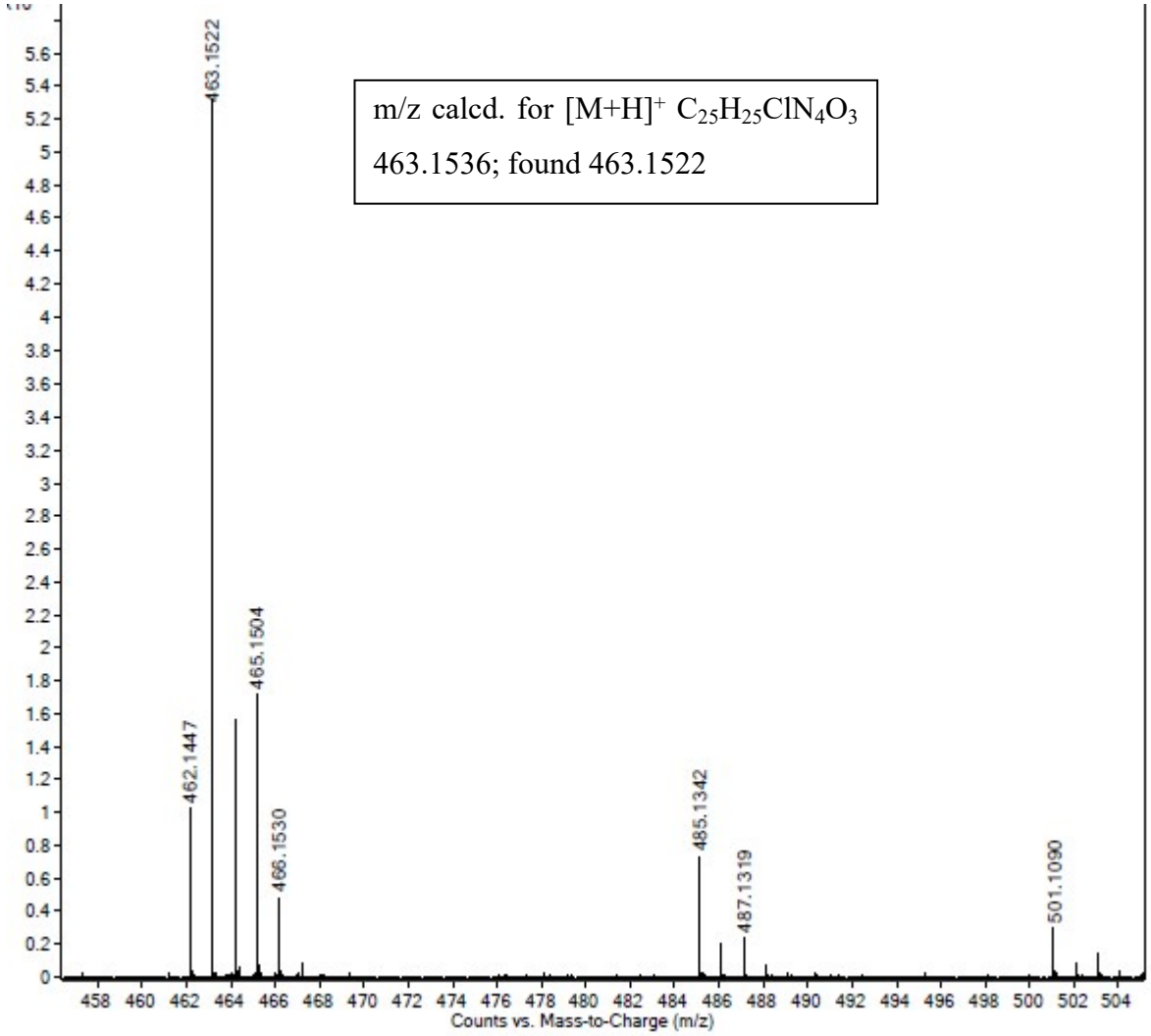
Mass spectrum of compound **7f**



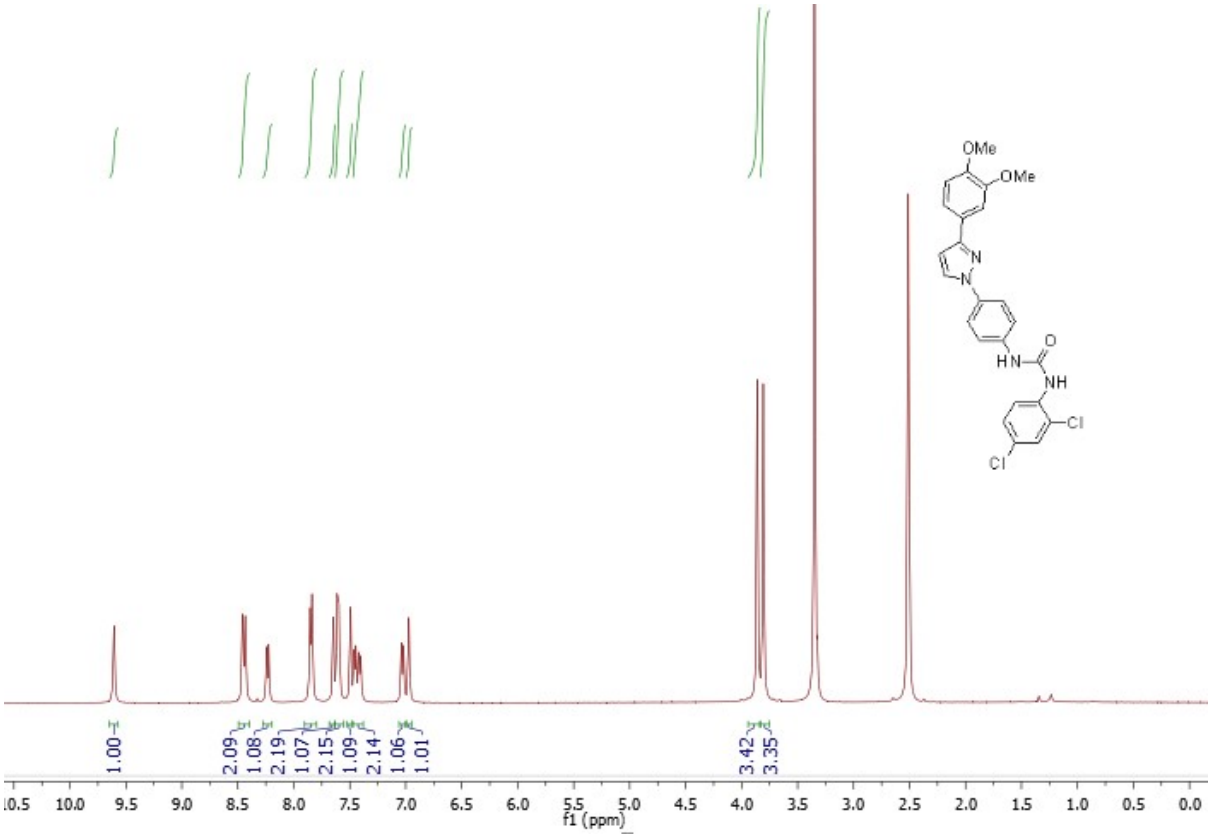
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **7g**



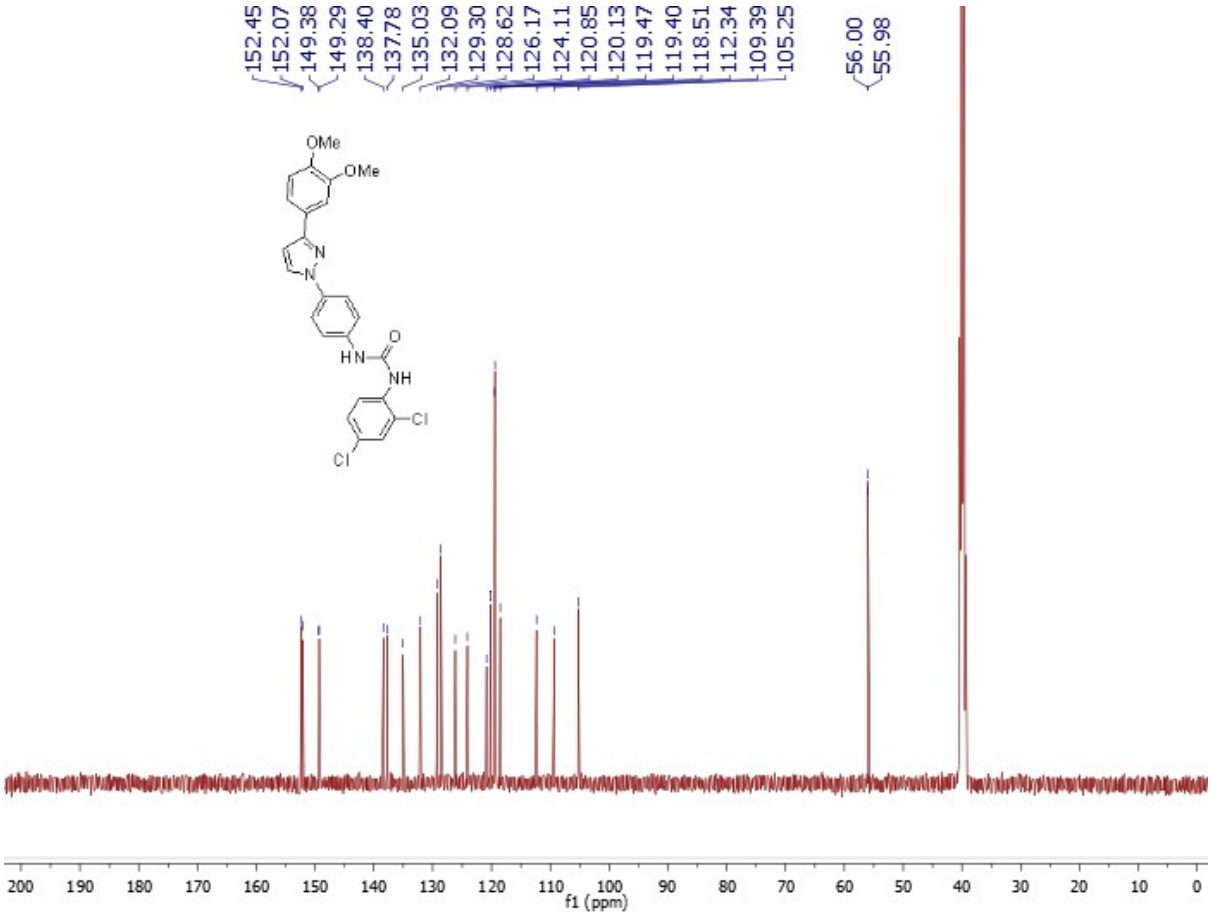
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **7g**



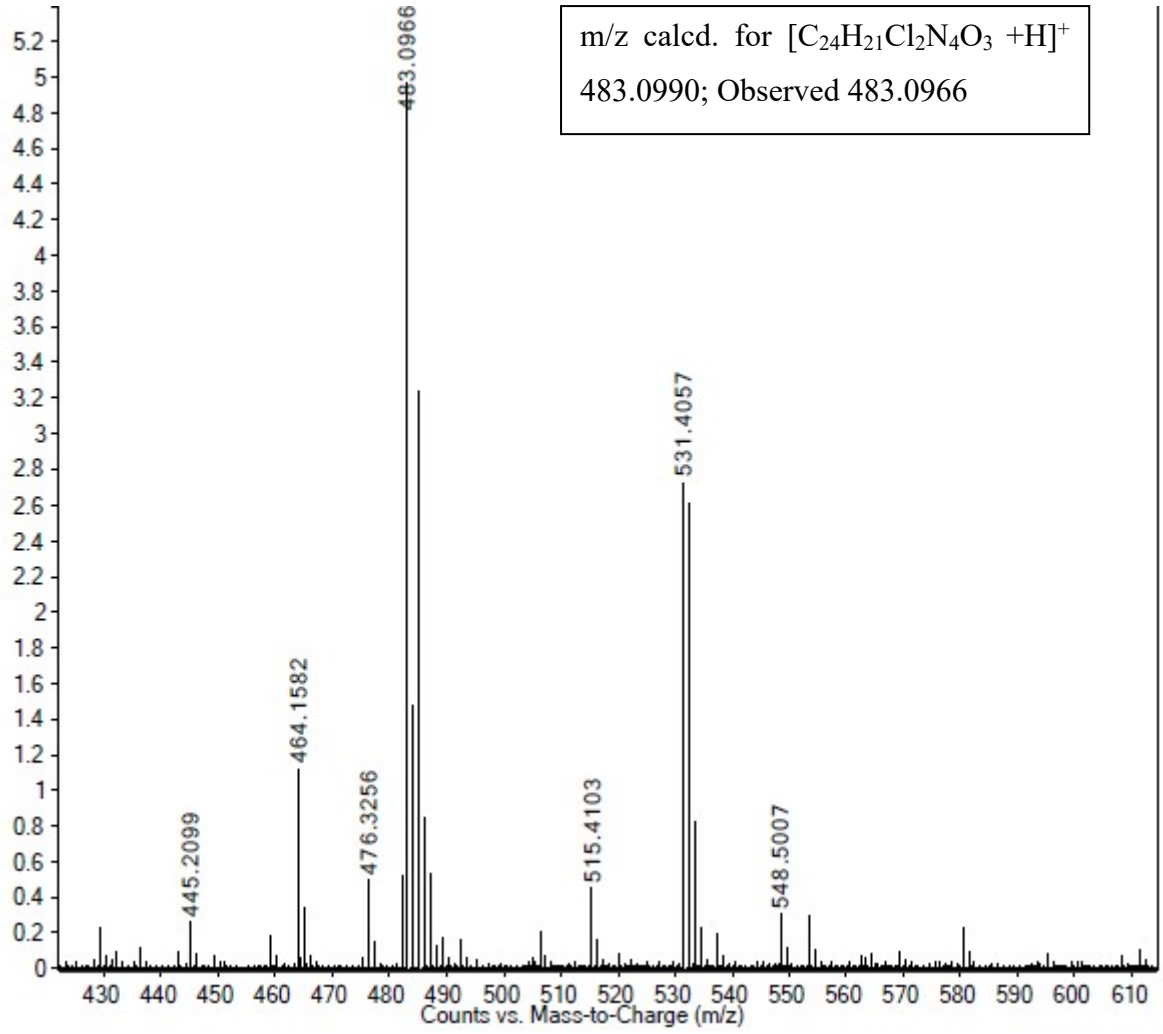
Mass spectrum of compound **7g**



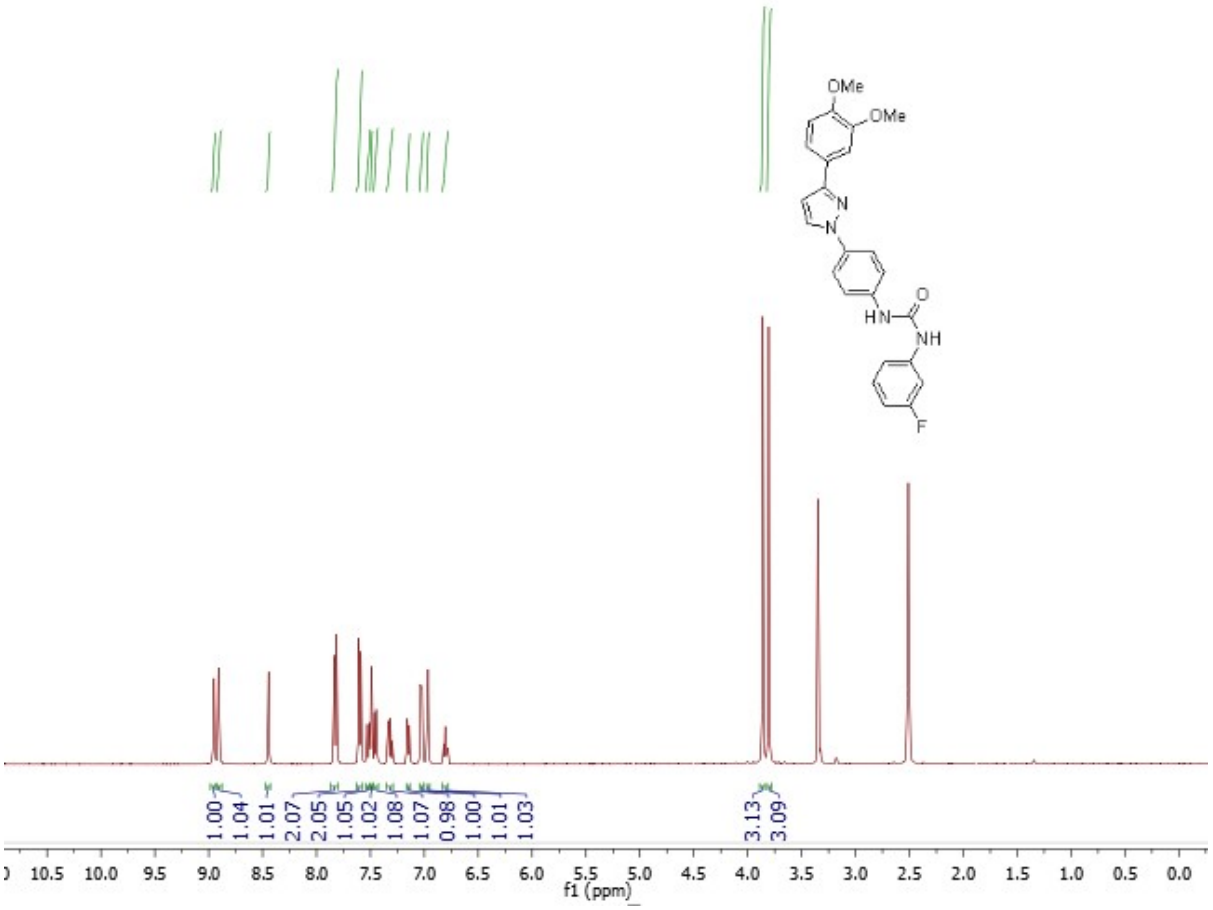
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **7h**



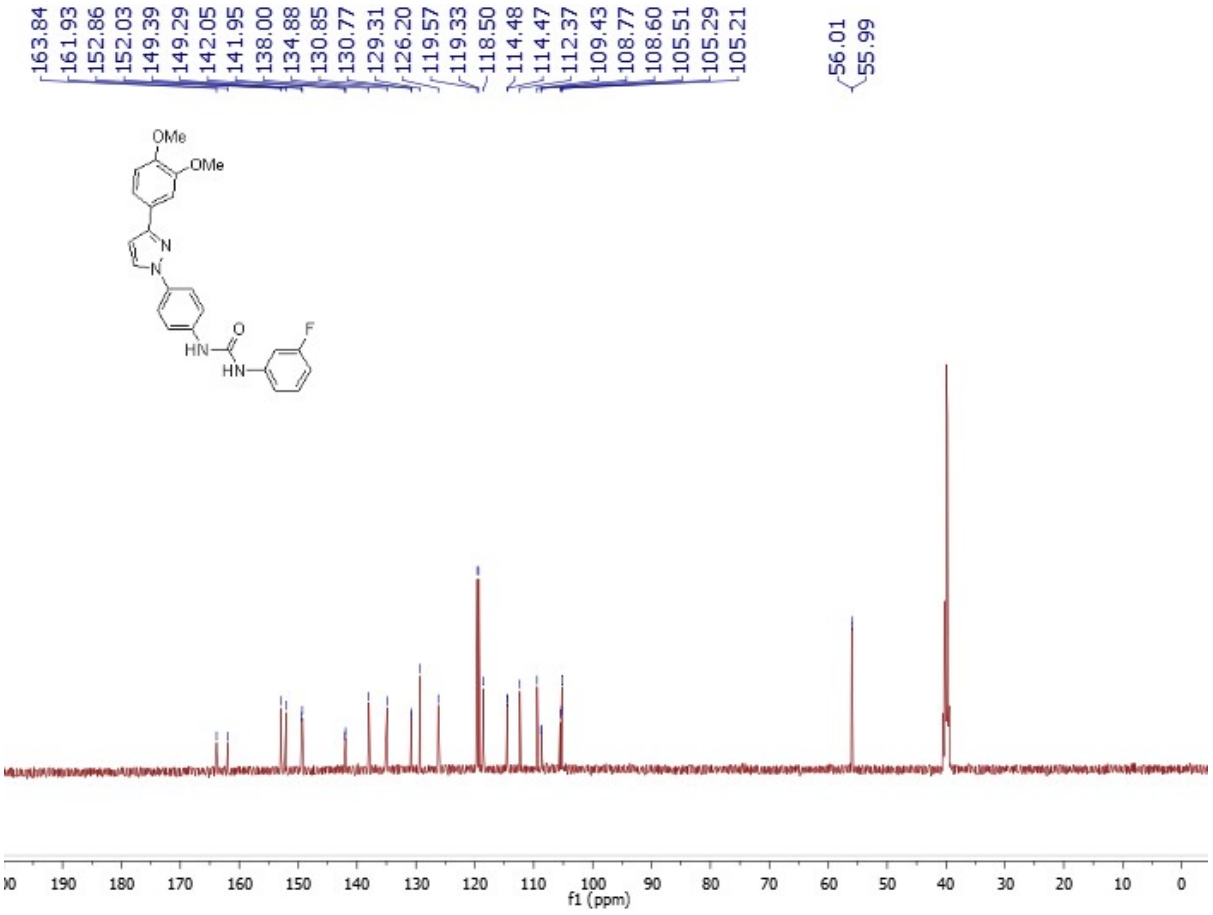
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **7h**



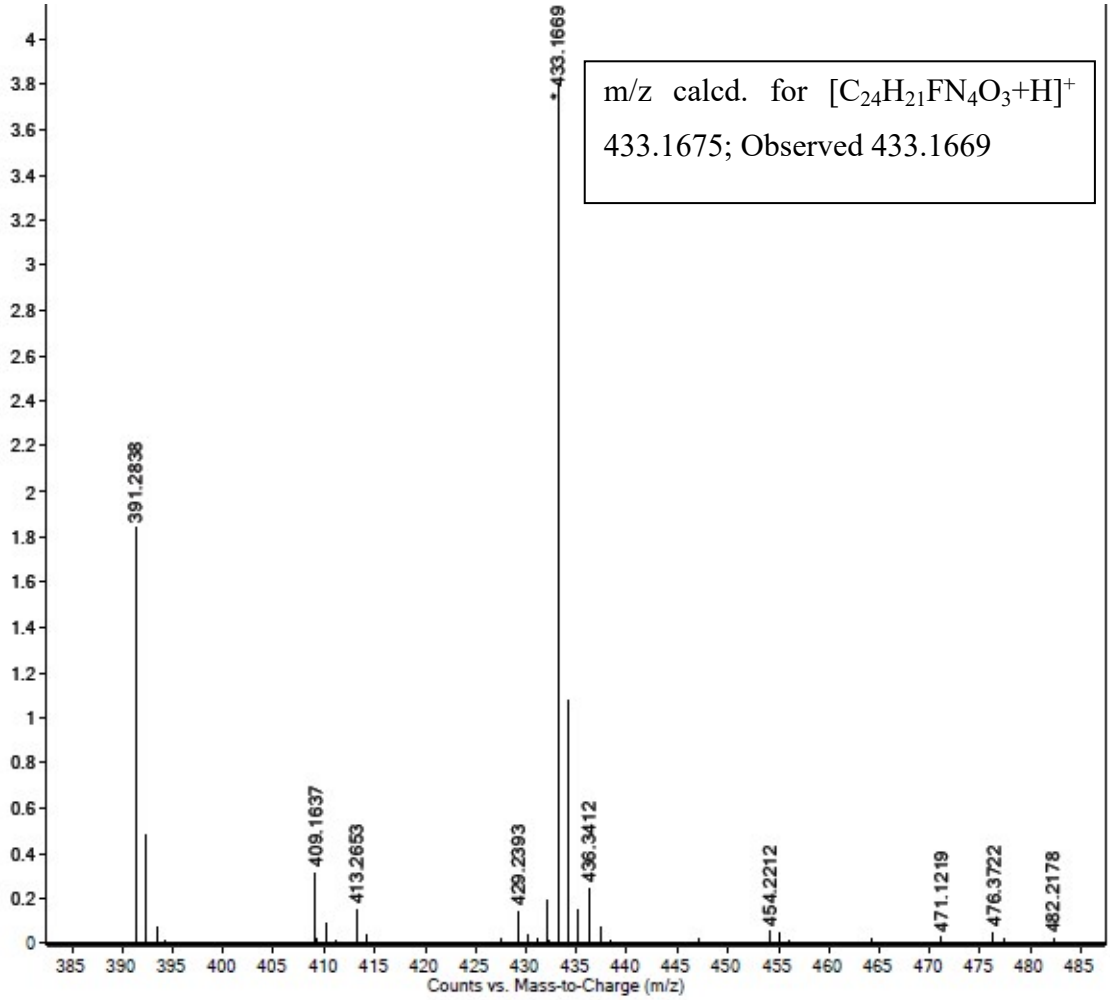
Mass spectrum of compound **7h**



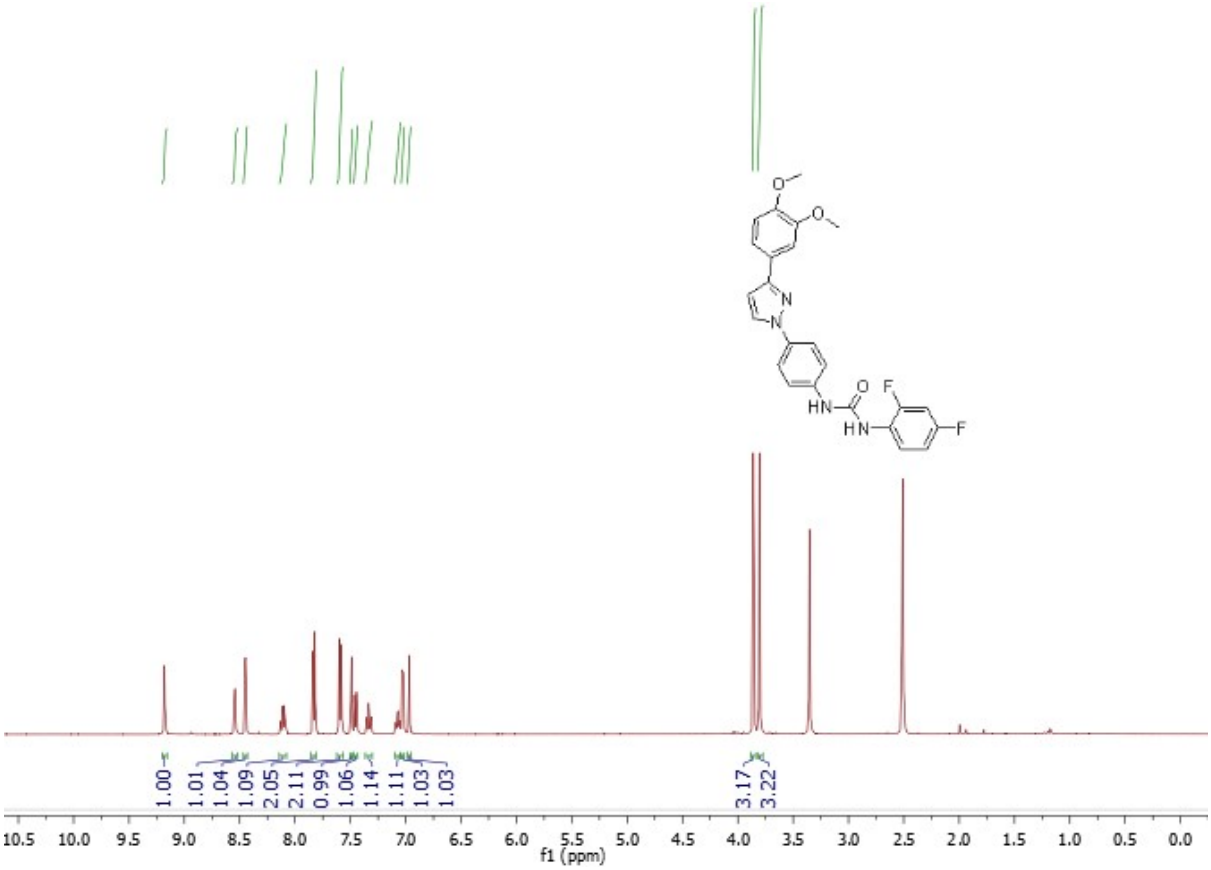
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **7i**



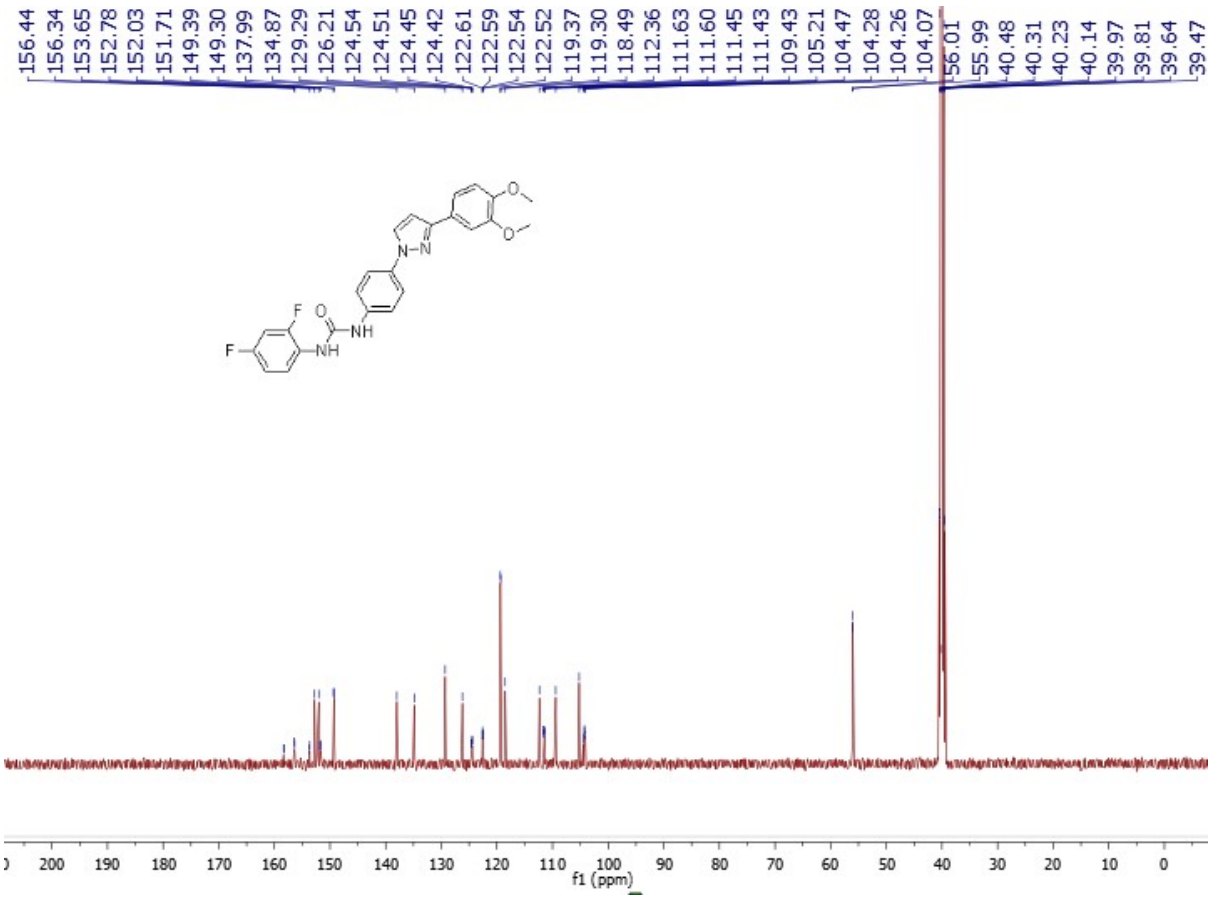
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **7i**



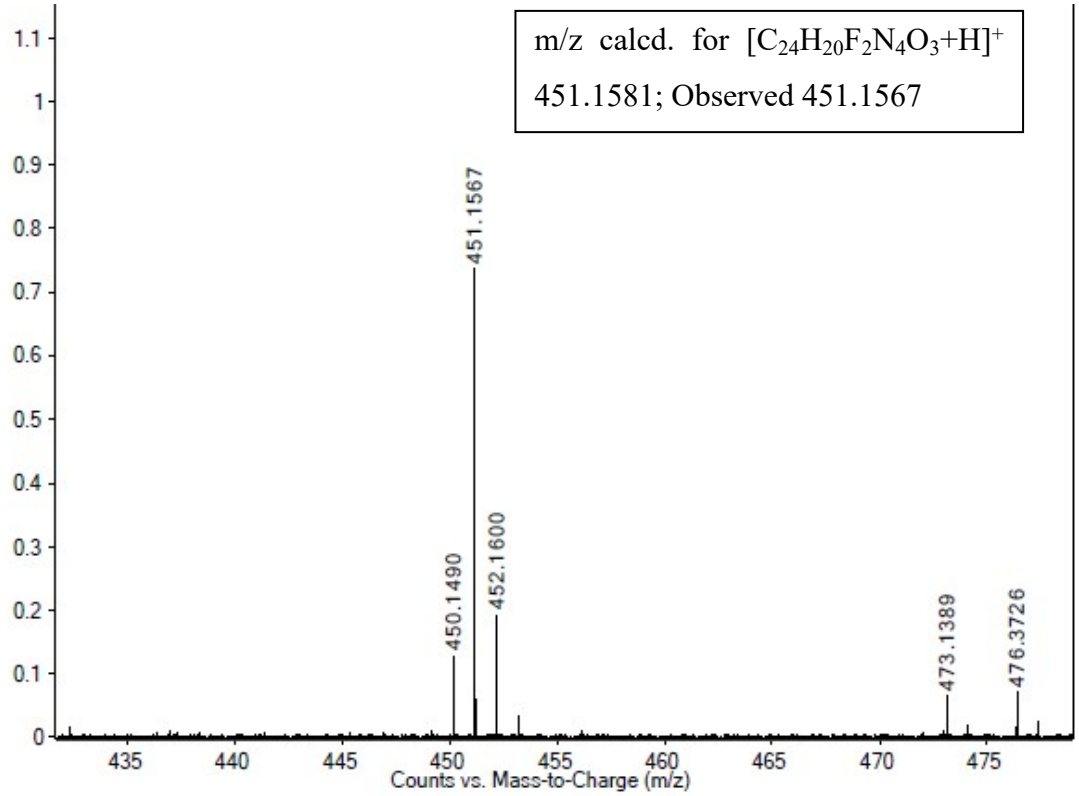
Mass spectrum of compound **7i**



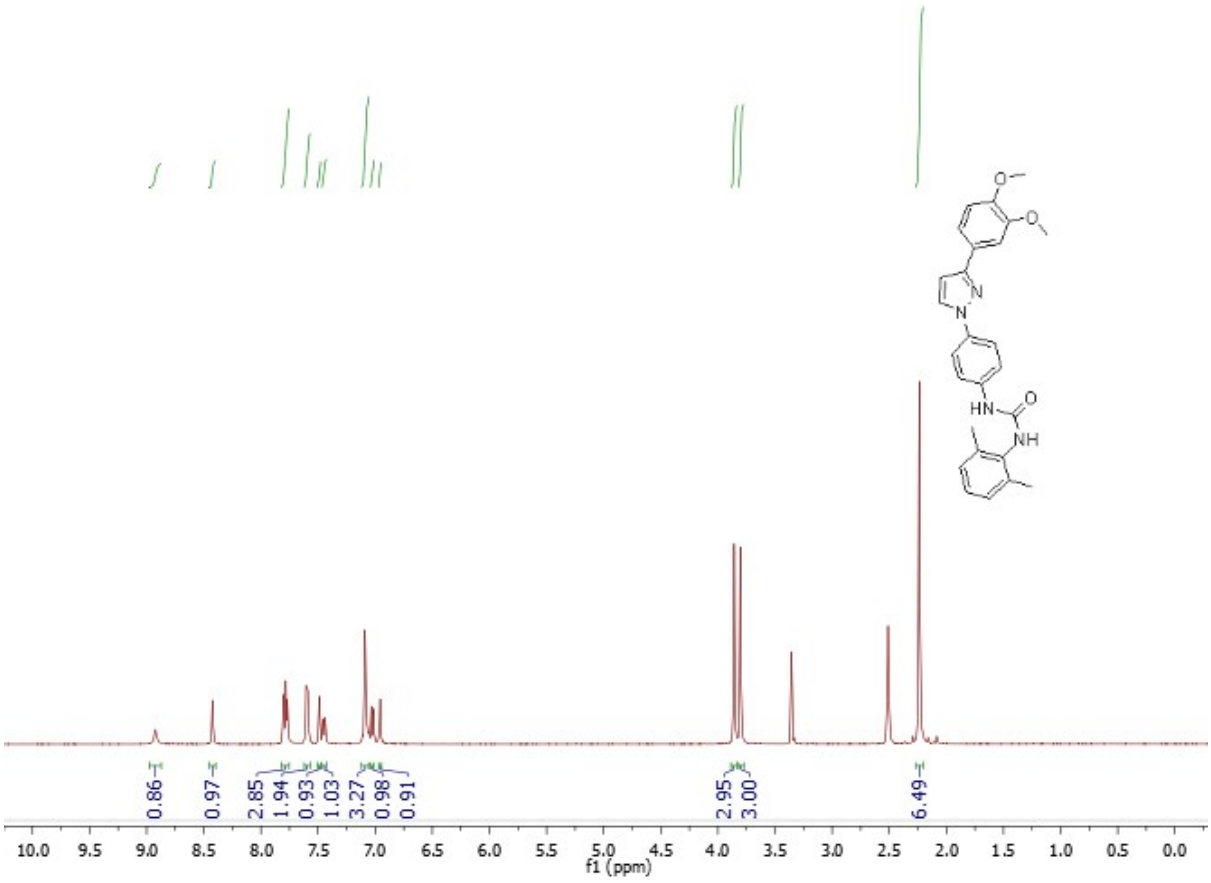
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **7j**



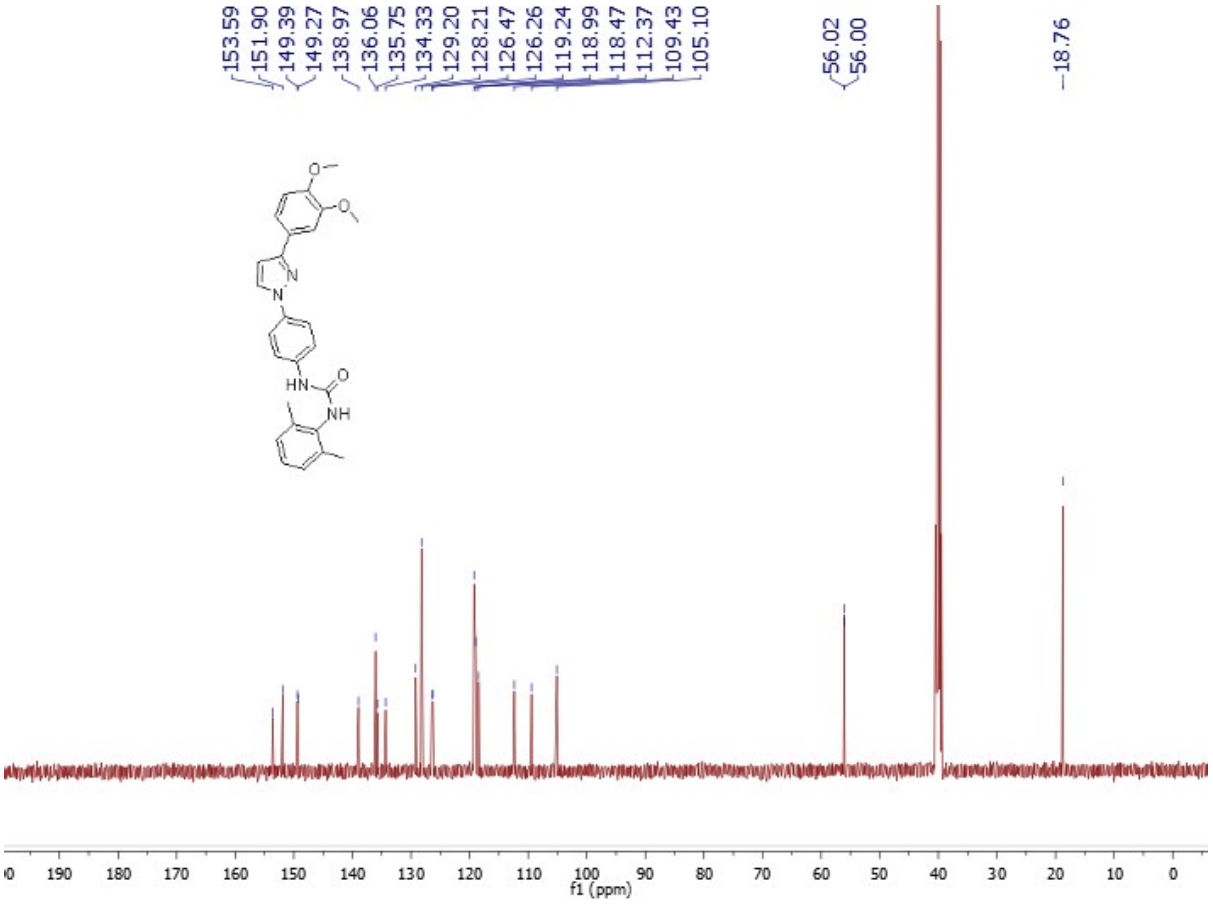
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **7j**



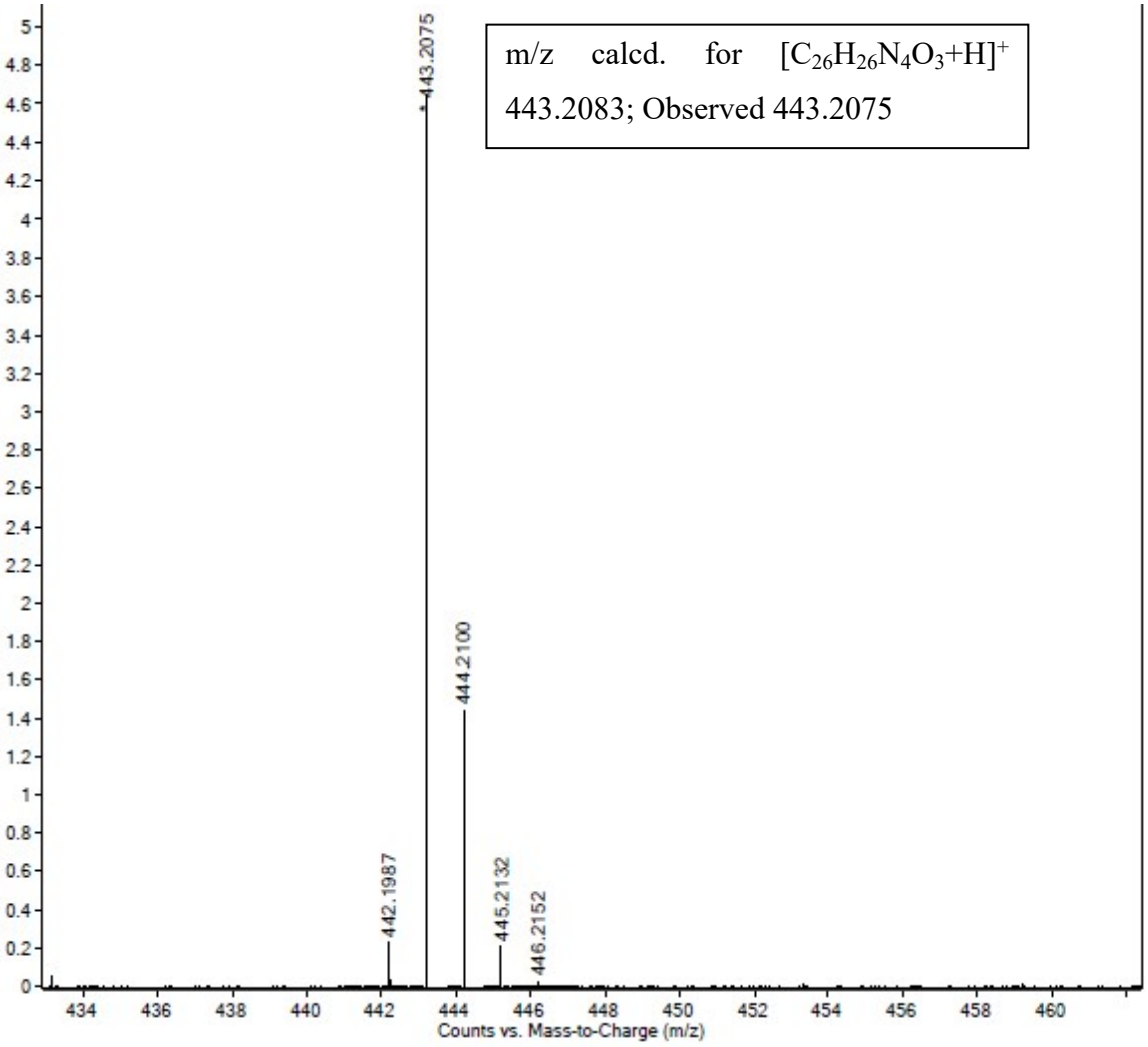
Mass spectrum of compound **7j**



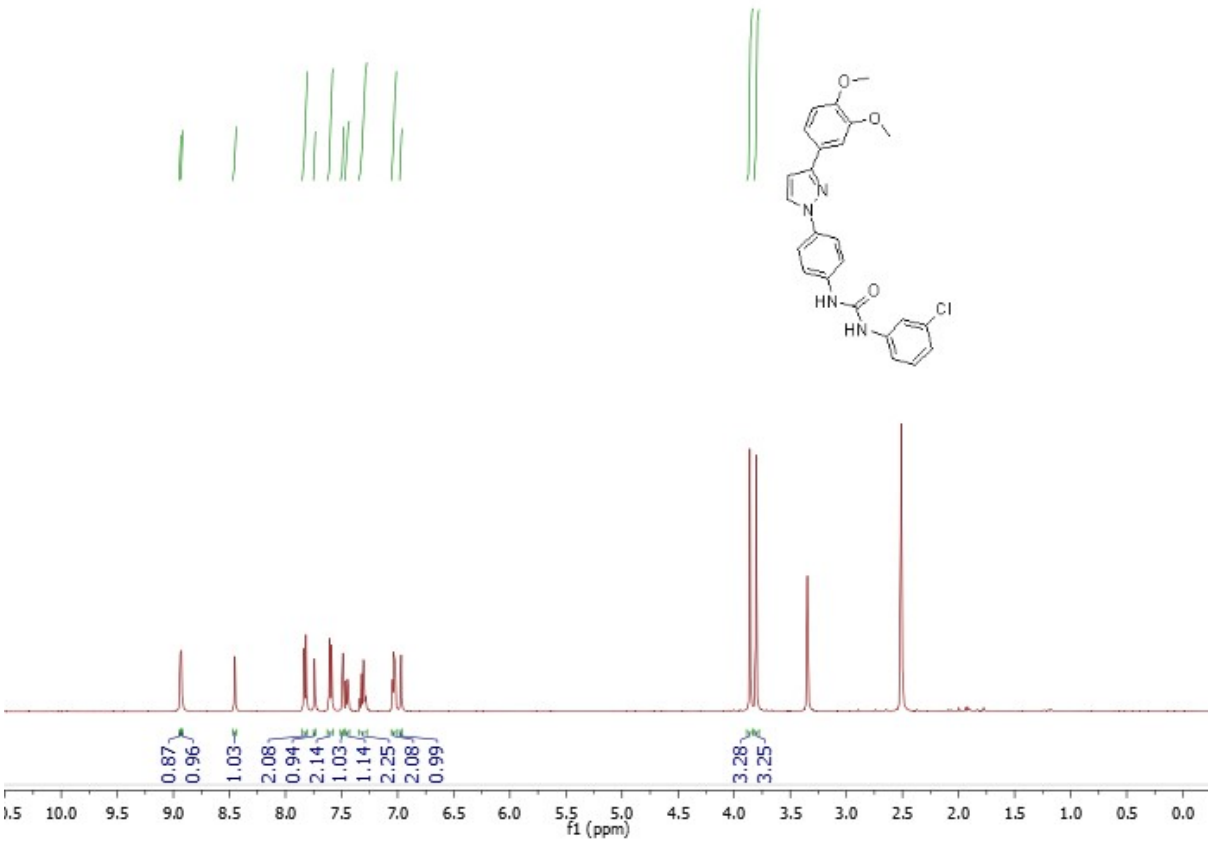
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **7k**



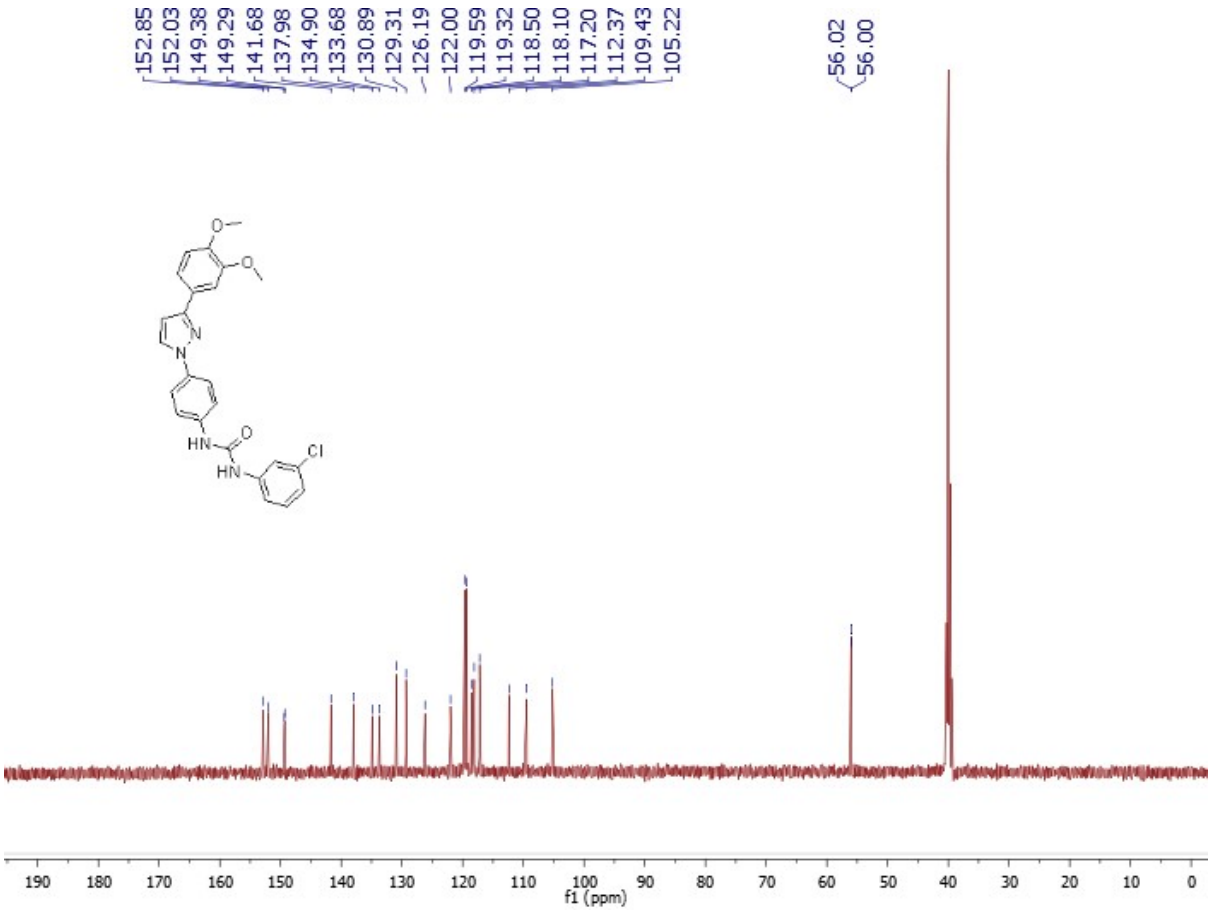
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **7k**



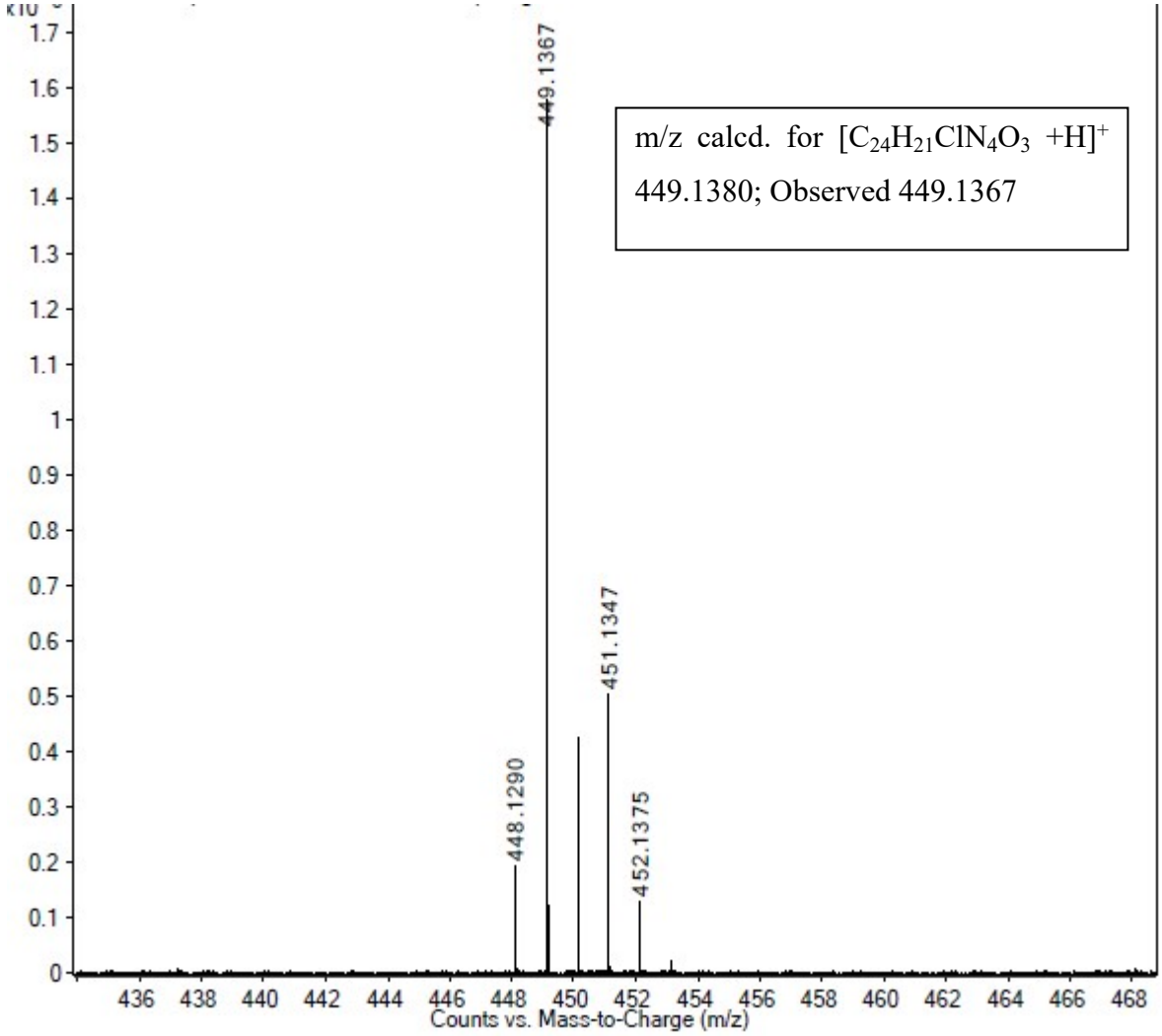
Mass spectrum of compound **7k**



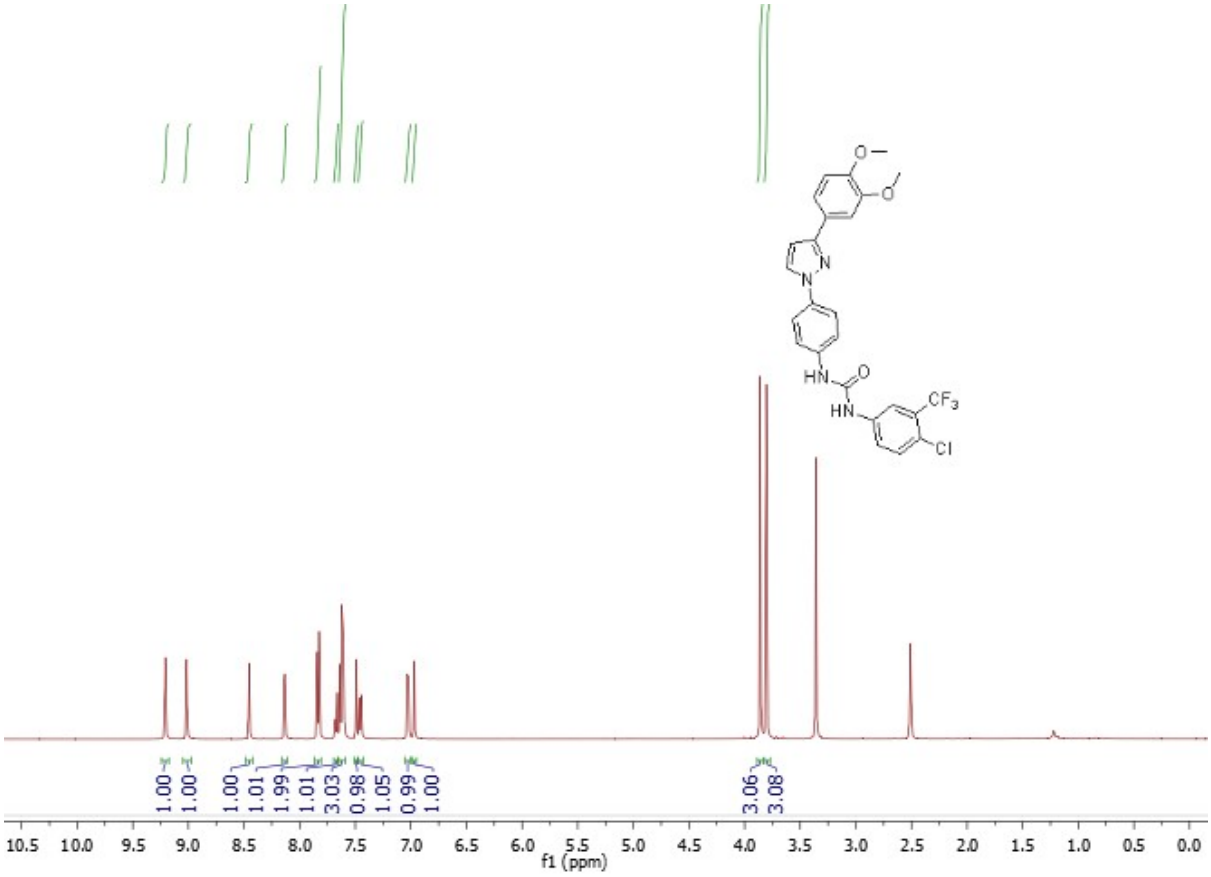
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **7l**



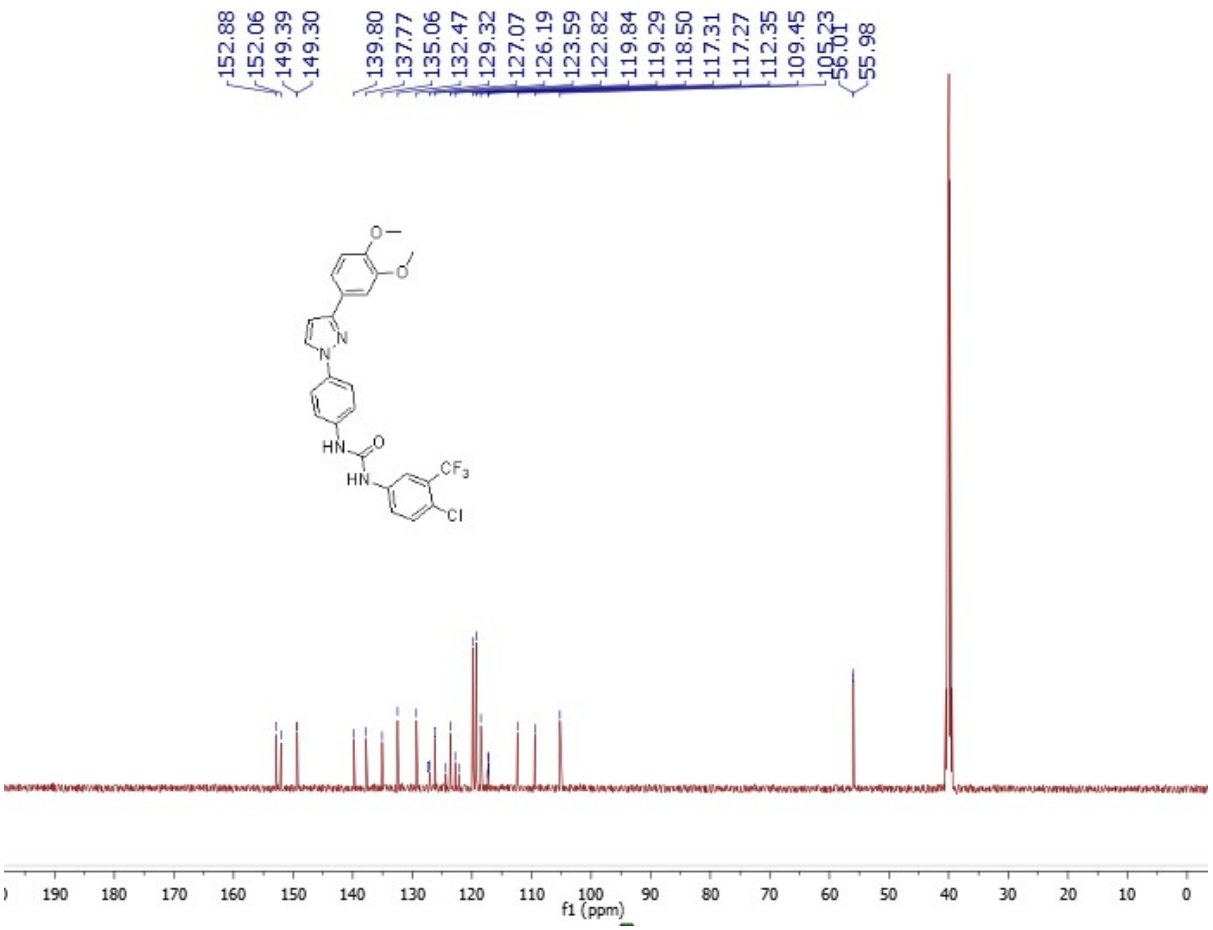
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **7l**



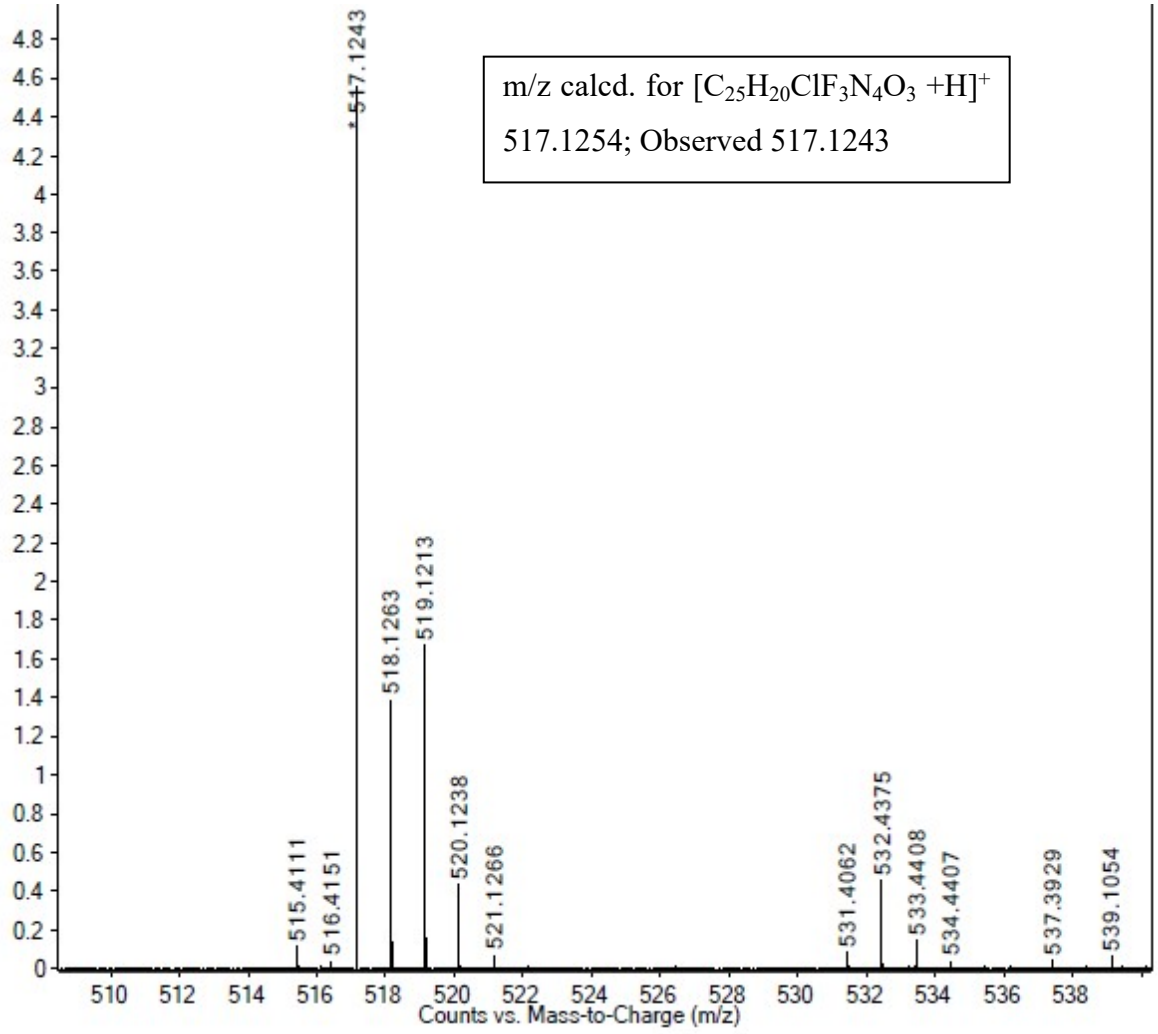
Mass spectrum of compound **7l**



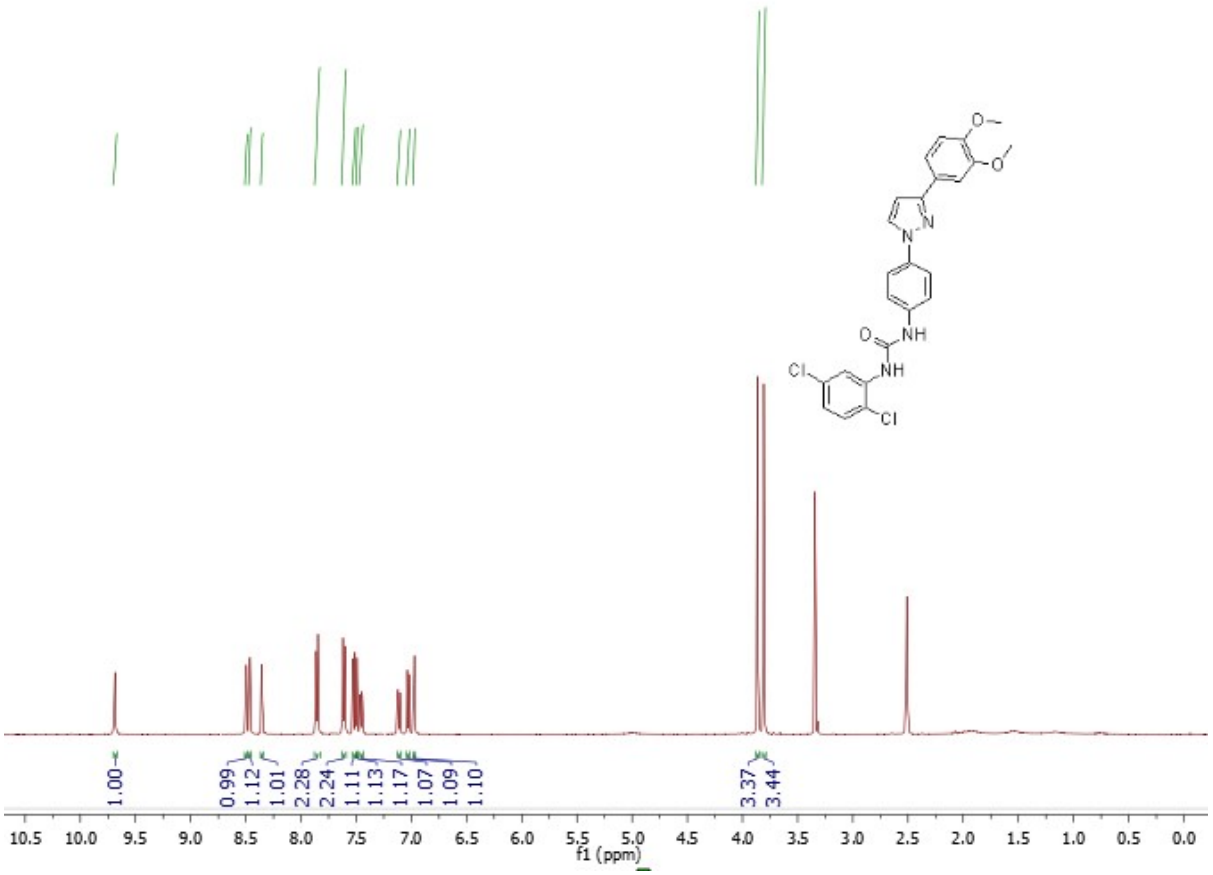
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **7m**



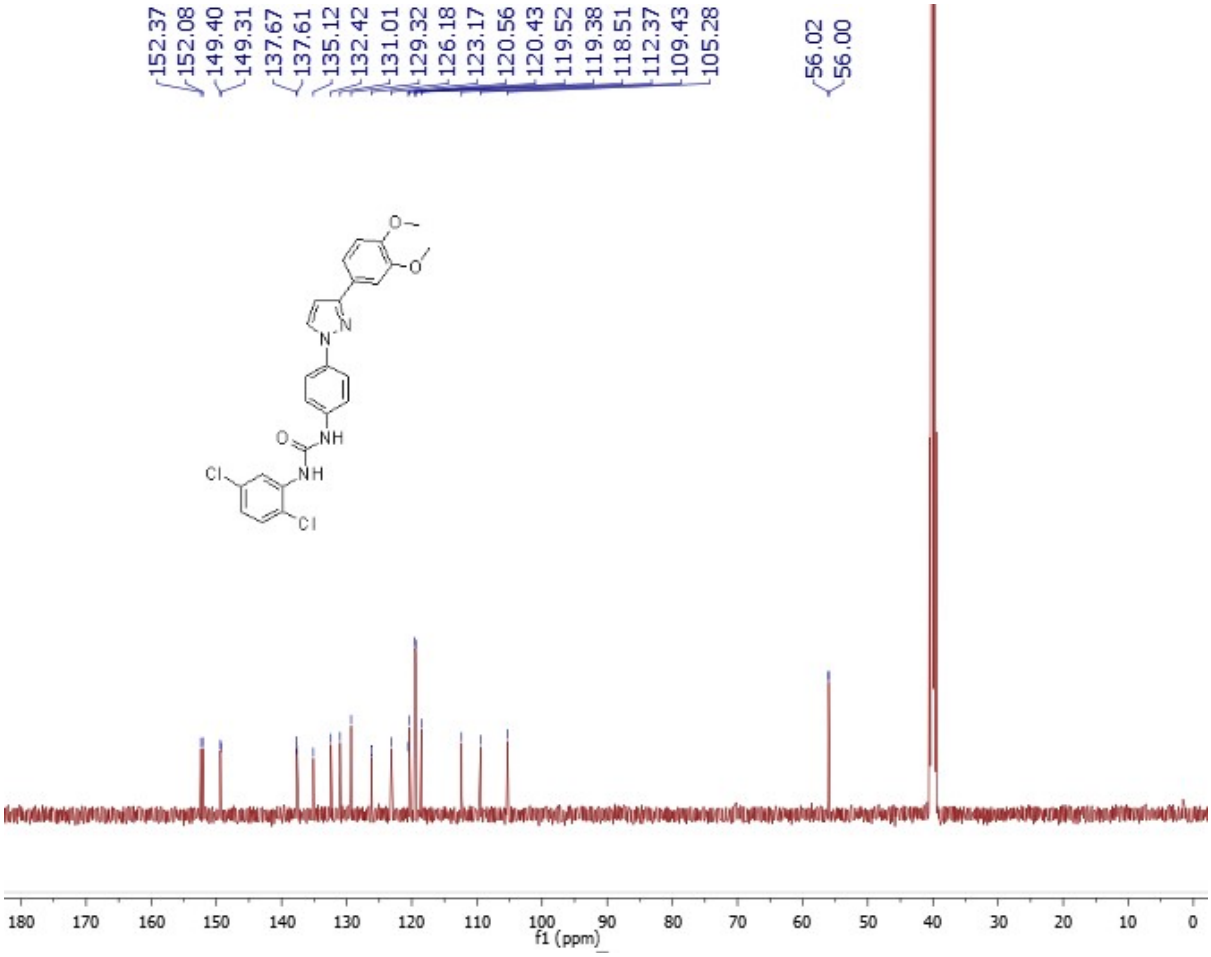
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **7m**



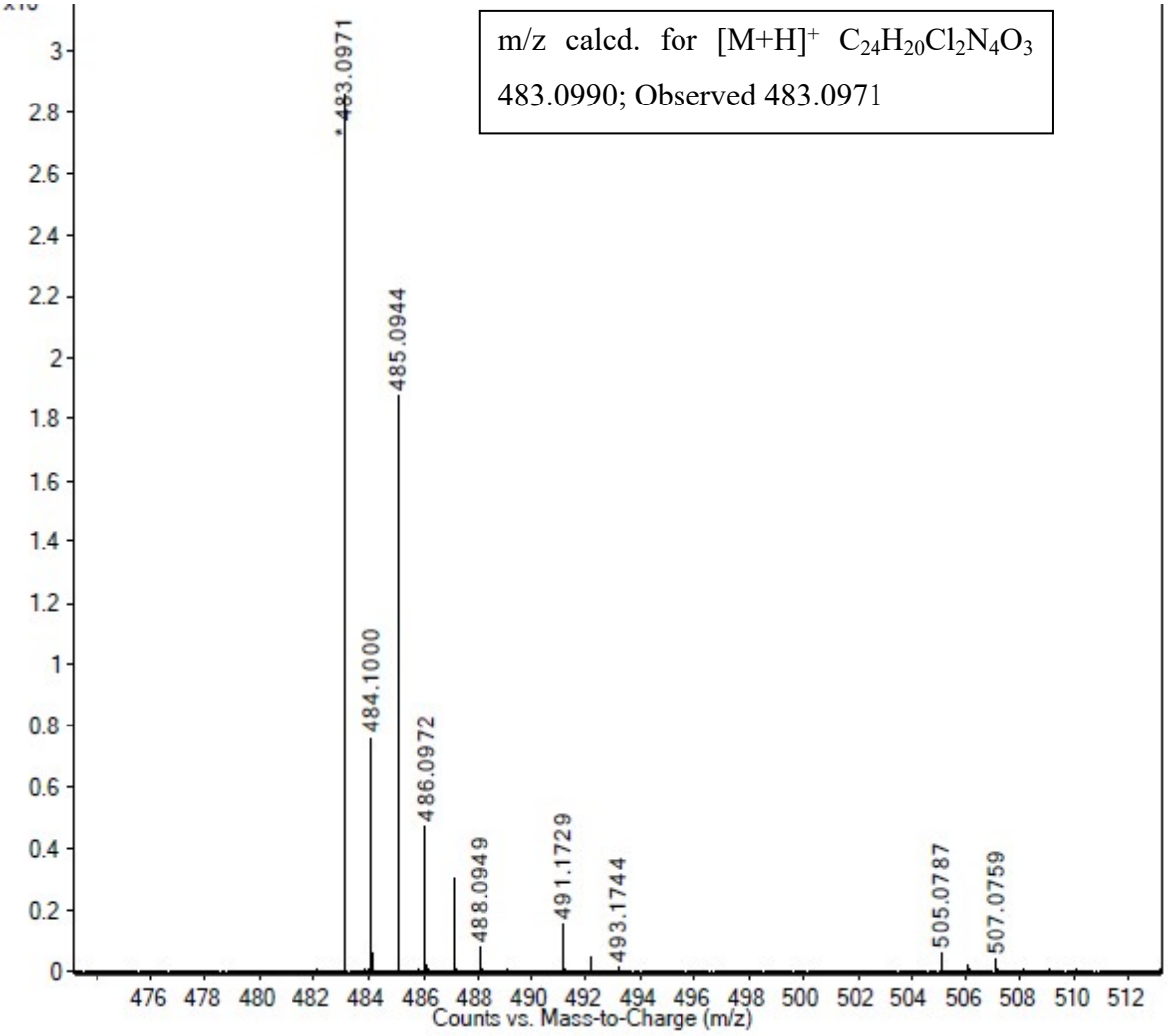
Mass spectrum of compound **7m**



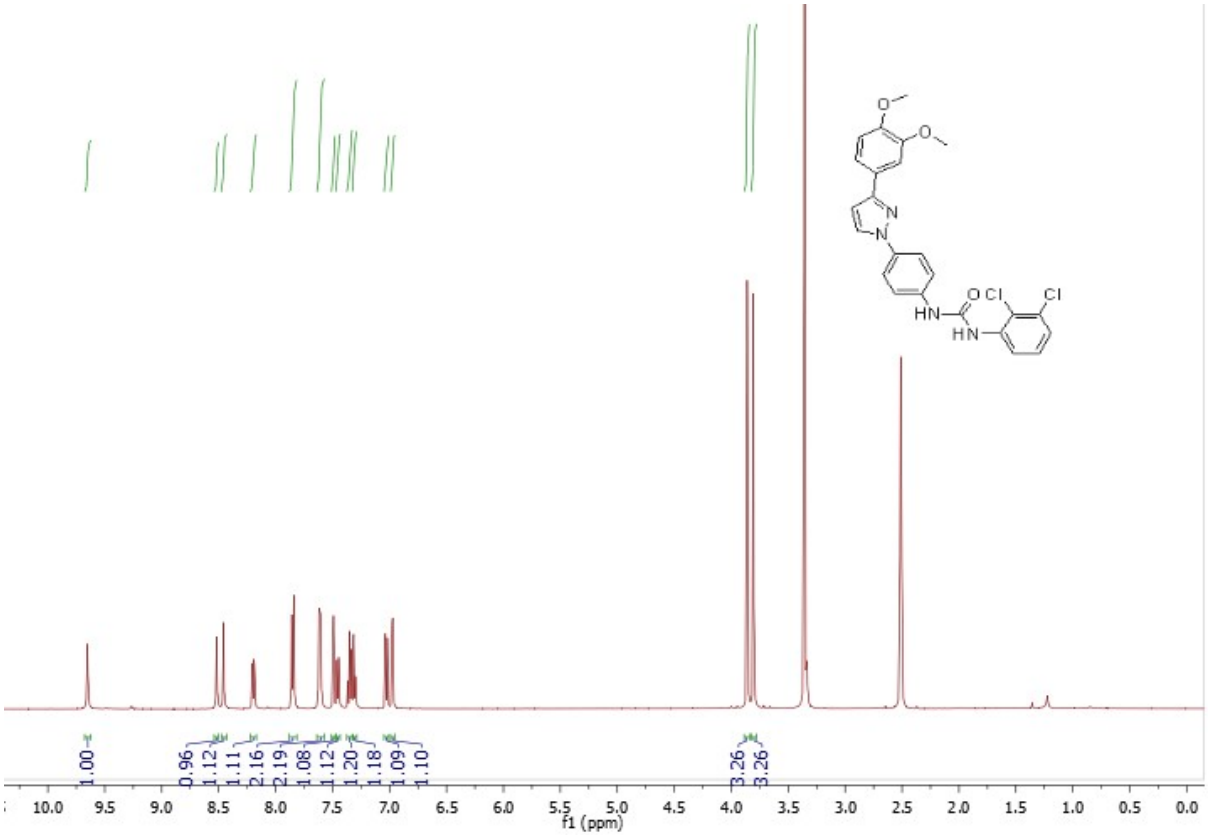
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **7n**



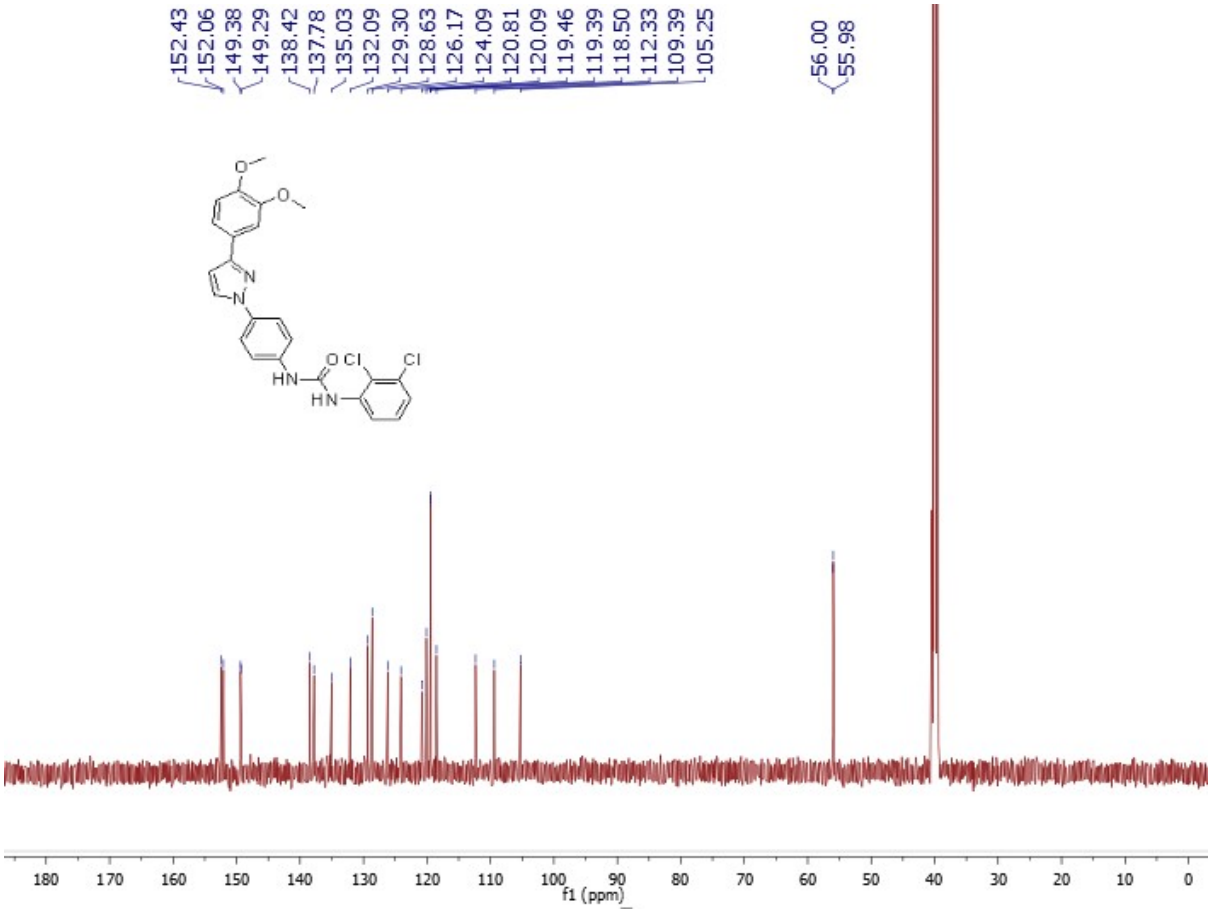
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **7n**



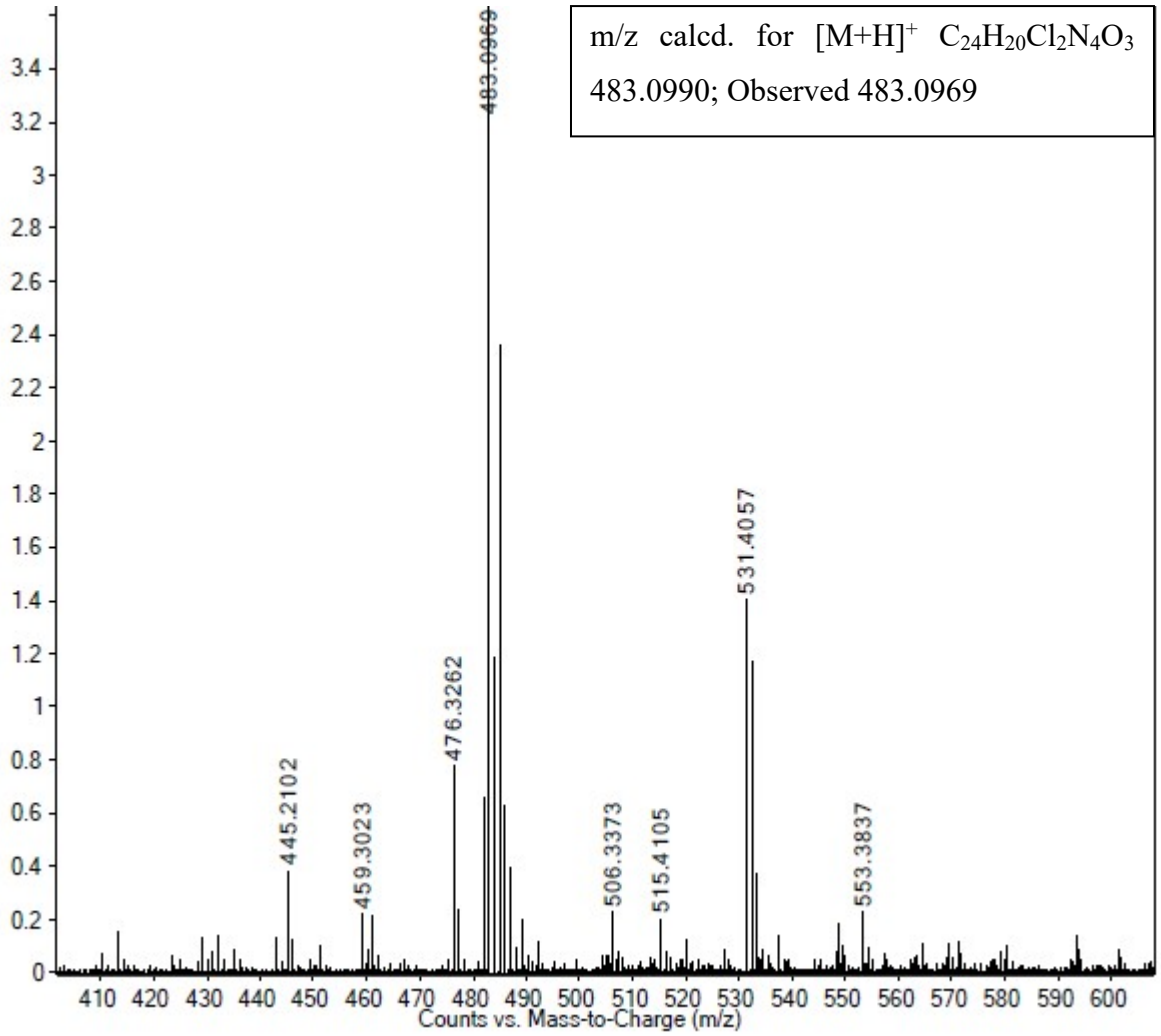
Mass spectrum of compound **7n**



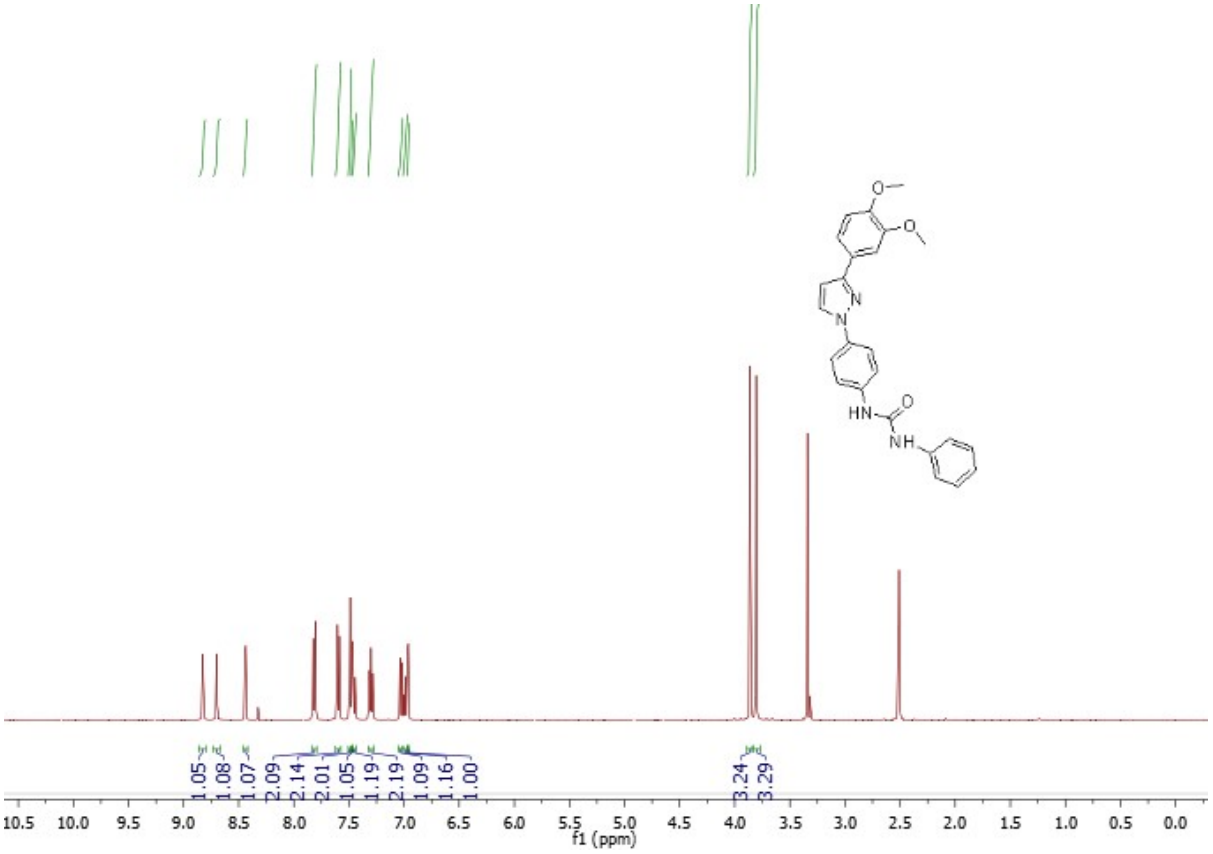
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **7o**



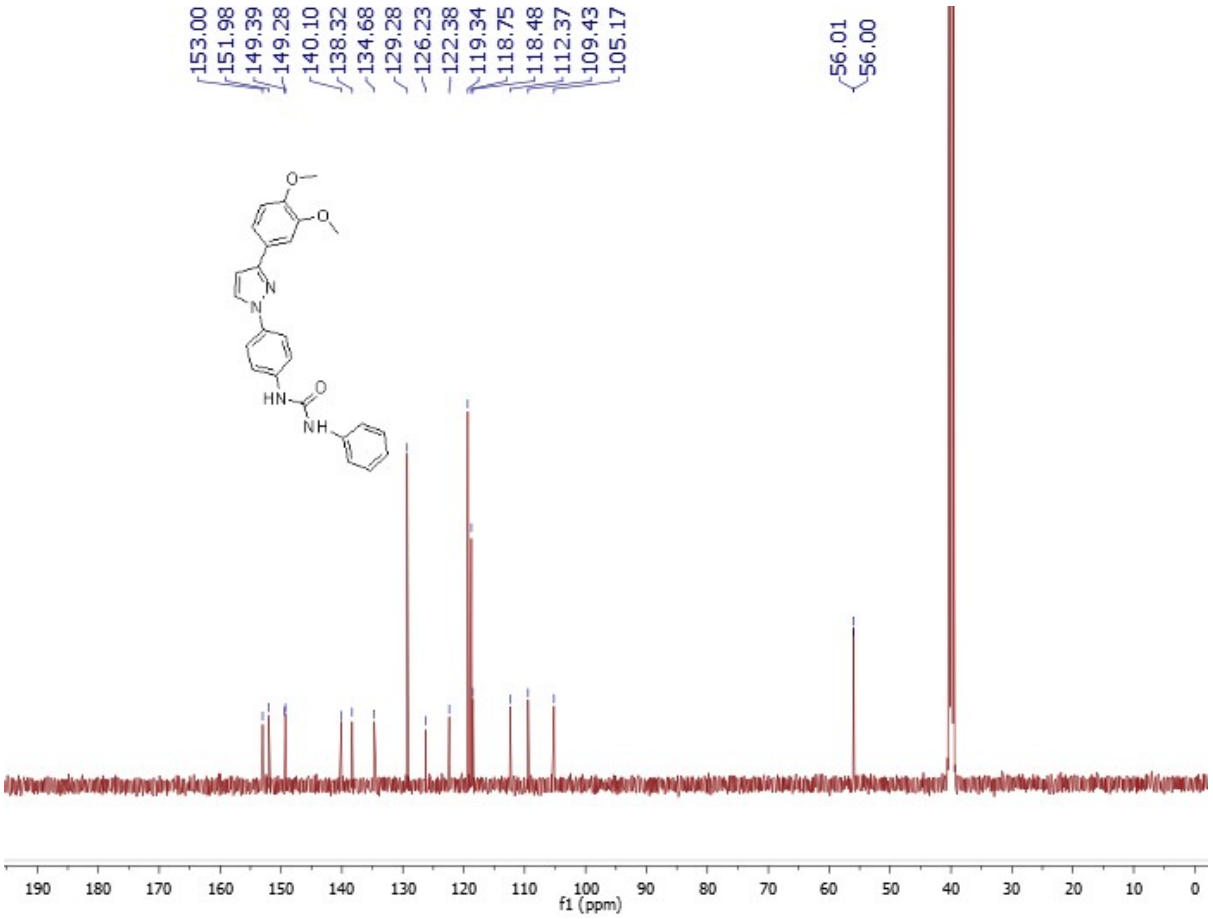
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **7o**



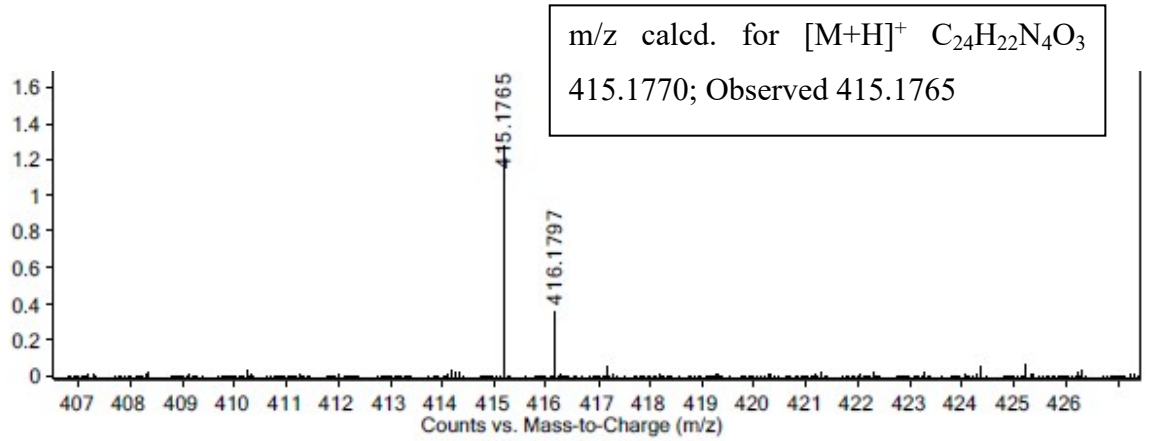
Mass spectrum of compound **7o**



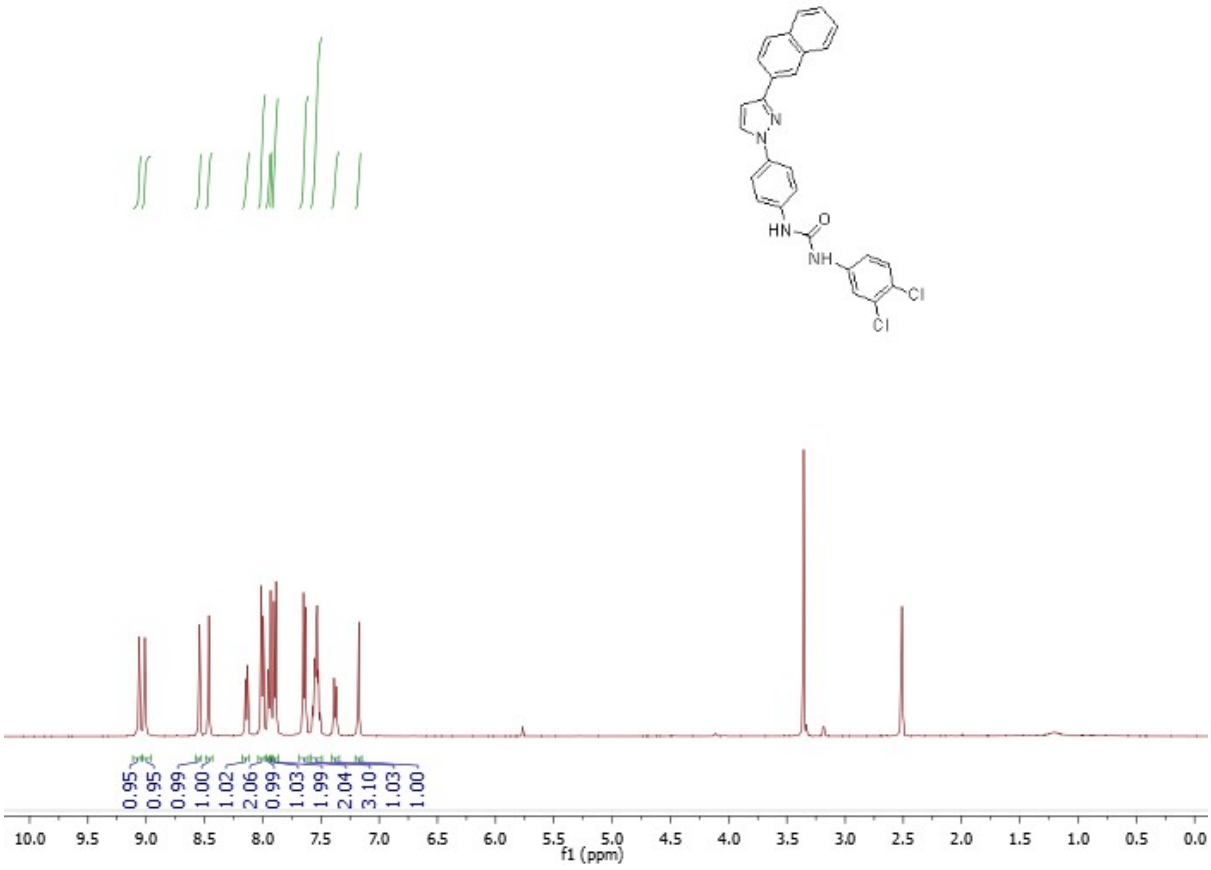
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **7p**



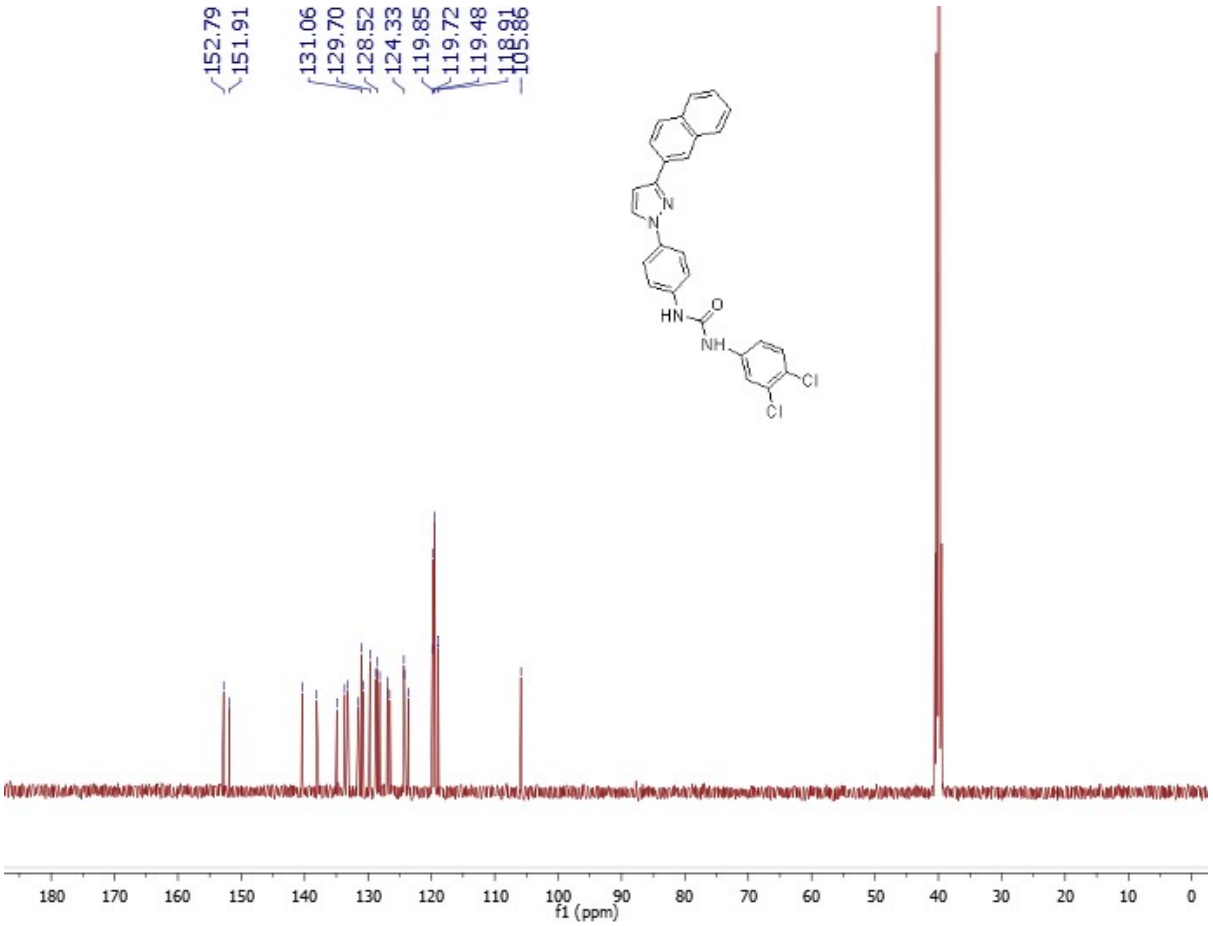
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **7p**



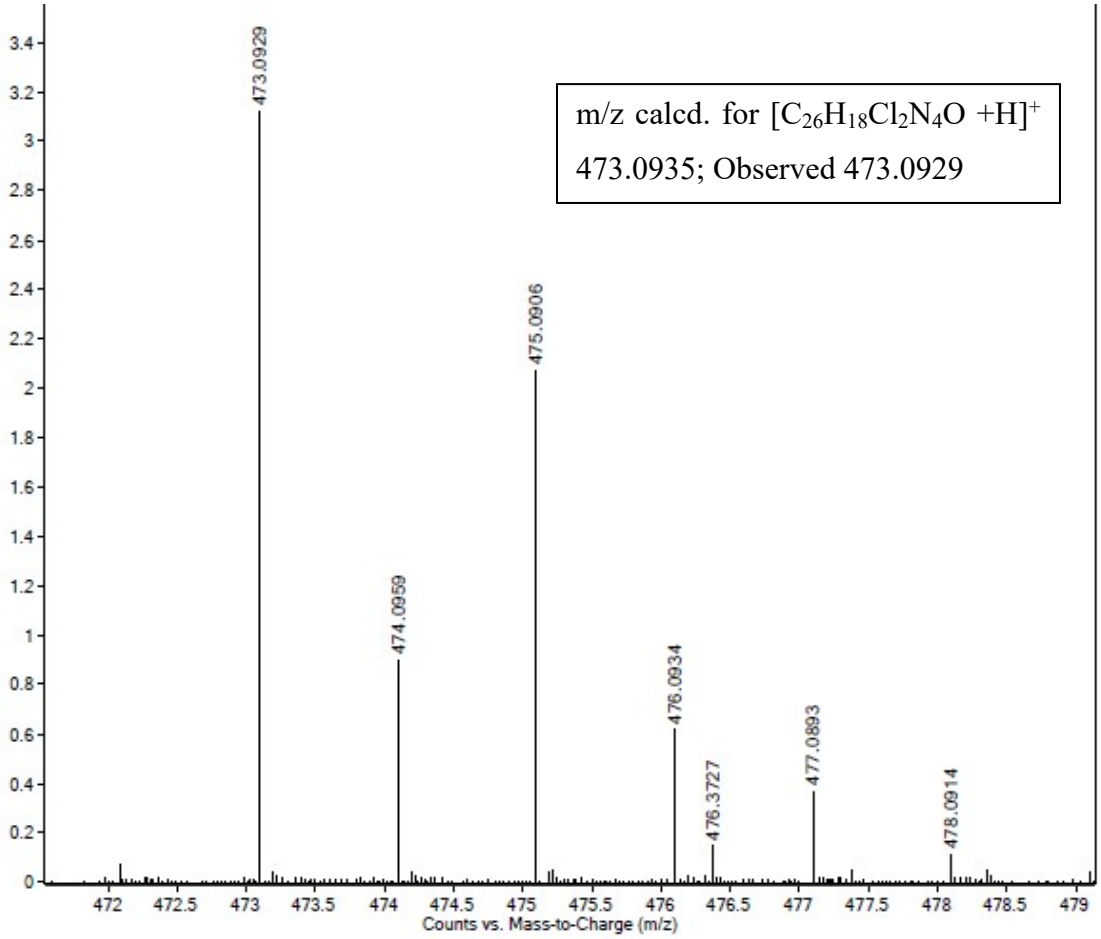
Mass spectrum of compound **7p**



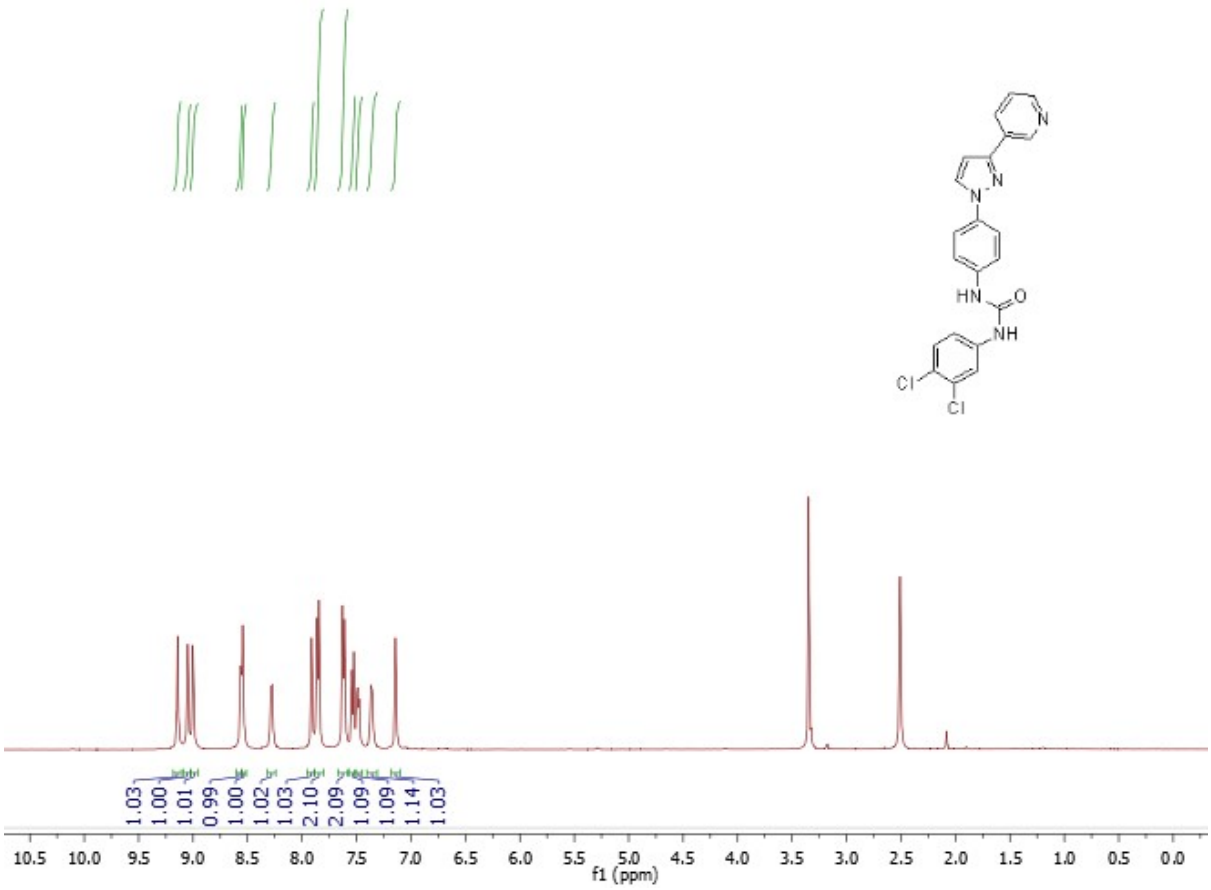
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **8a**



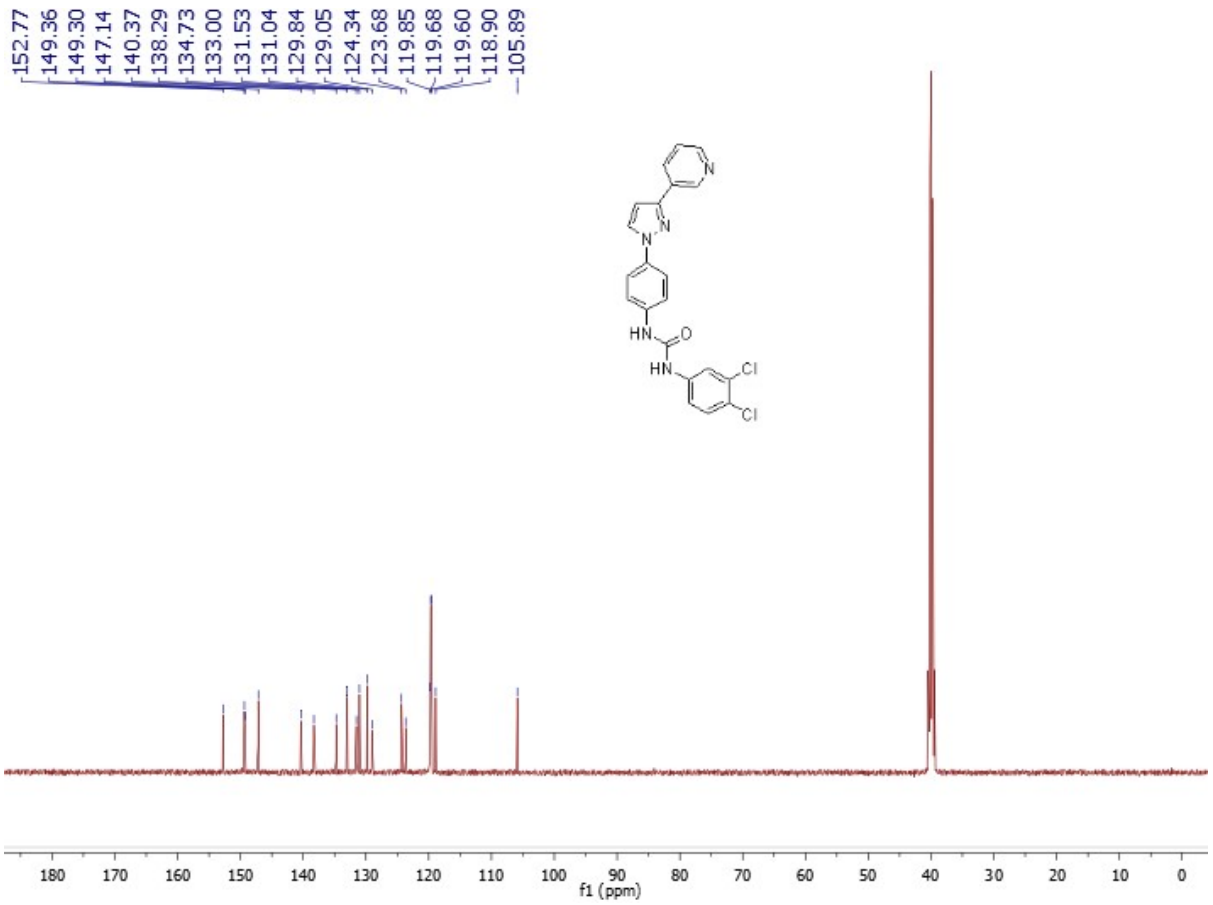
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **8a**



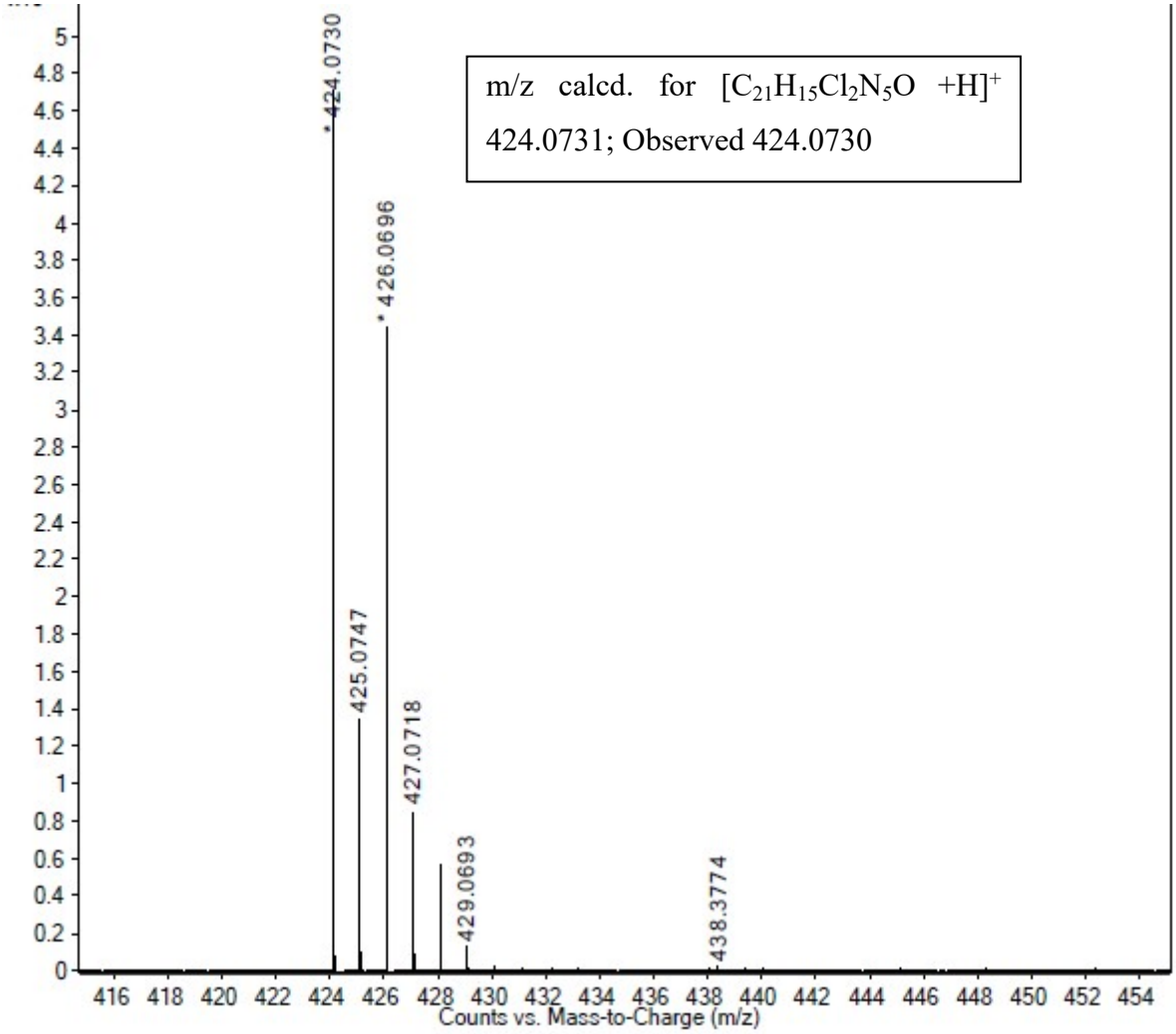
Mass spectrum of compound **8a**



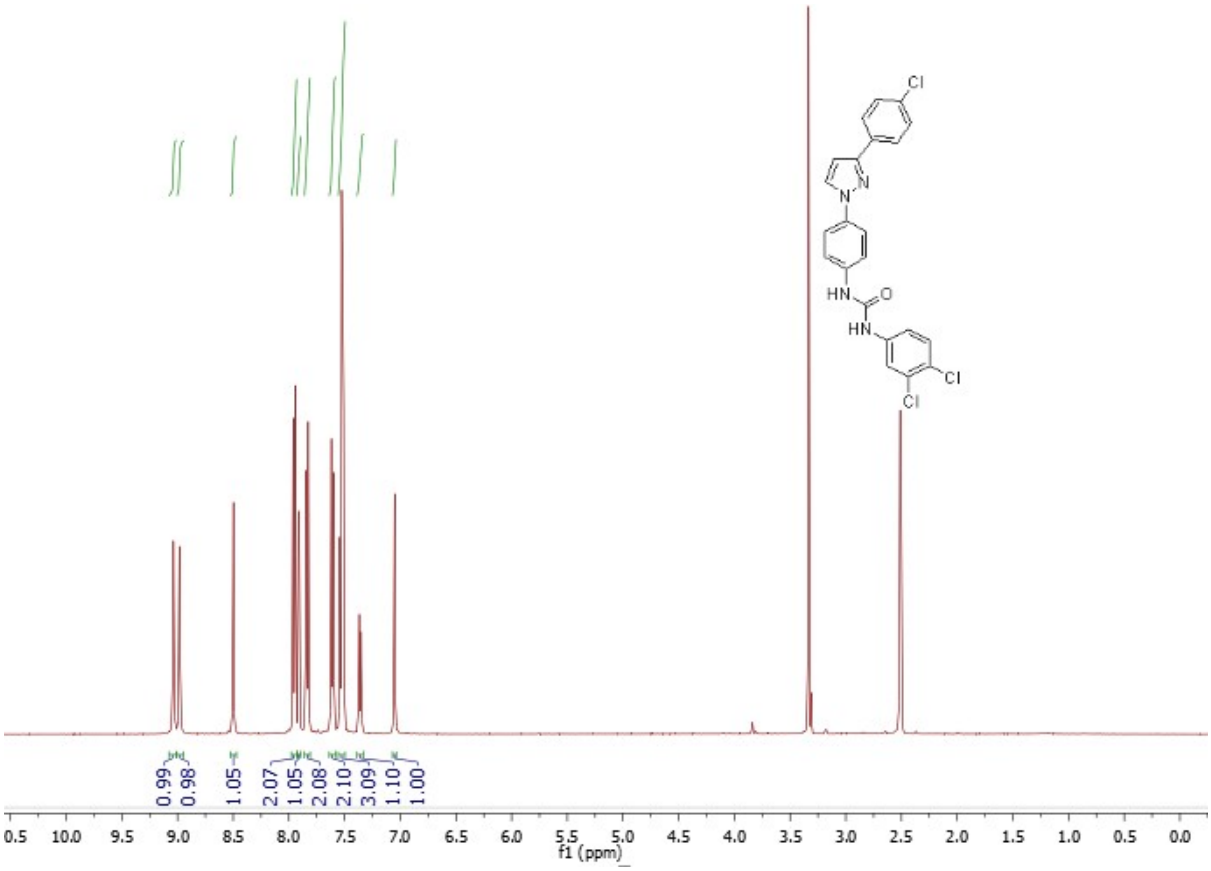
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **8b**



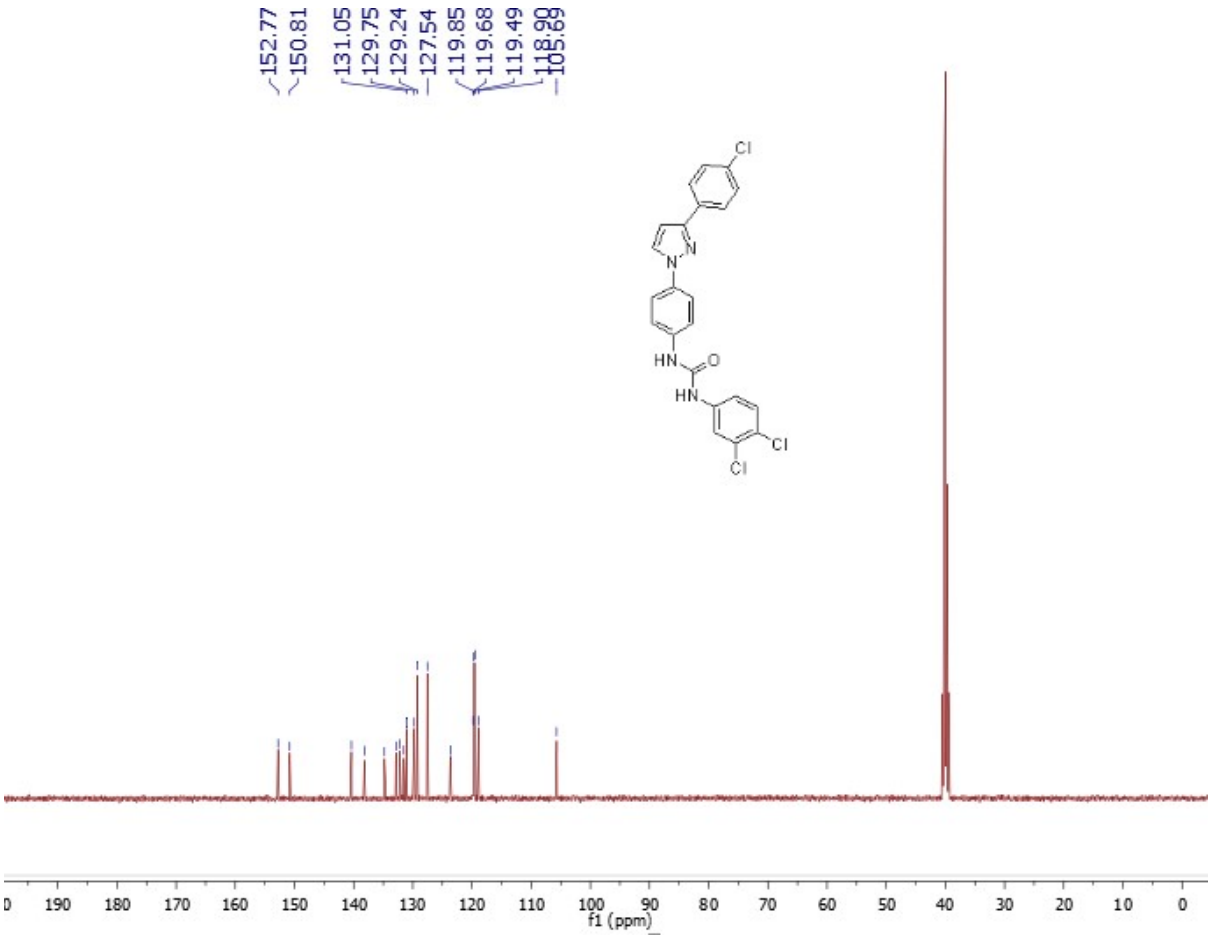
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **8b**



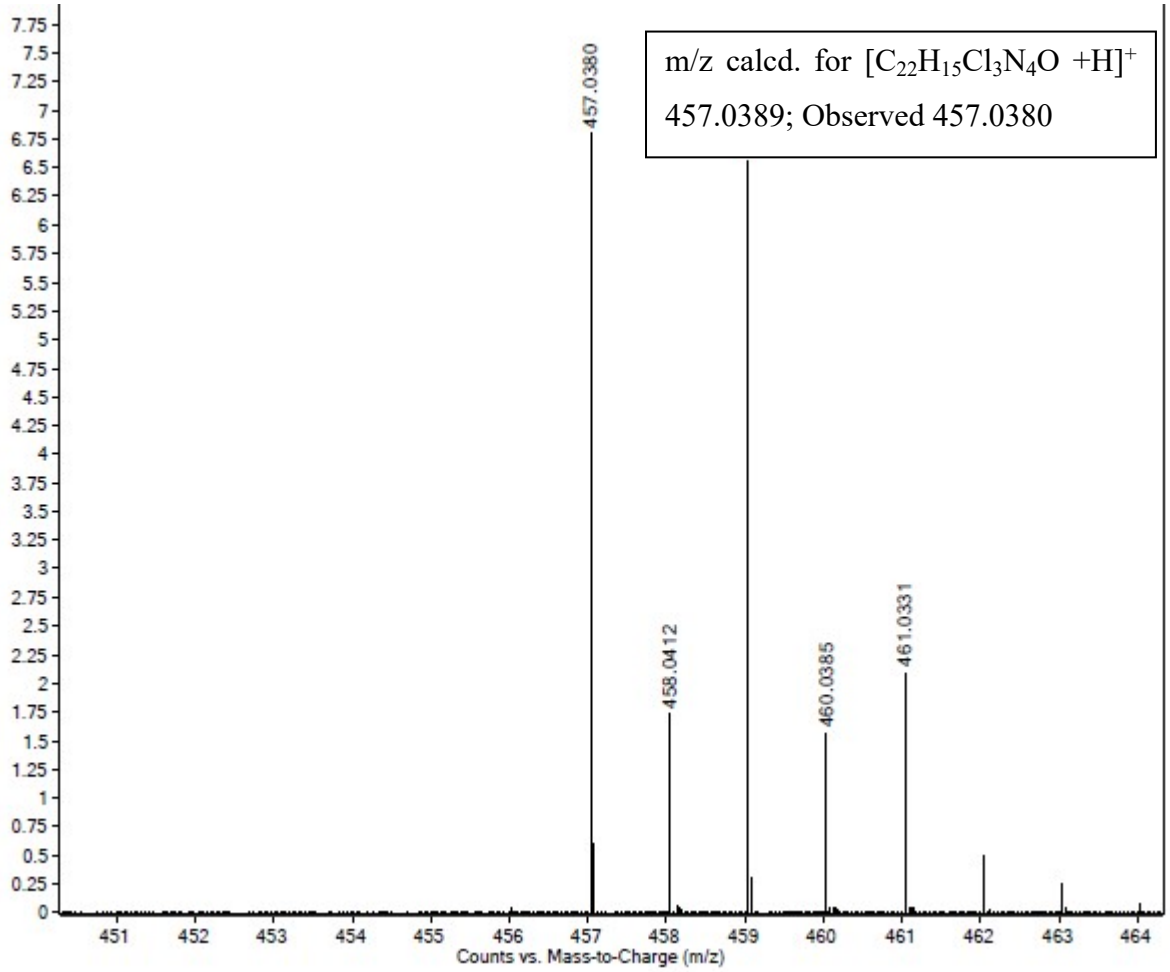
Mass spectrum of compound **8b**



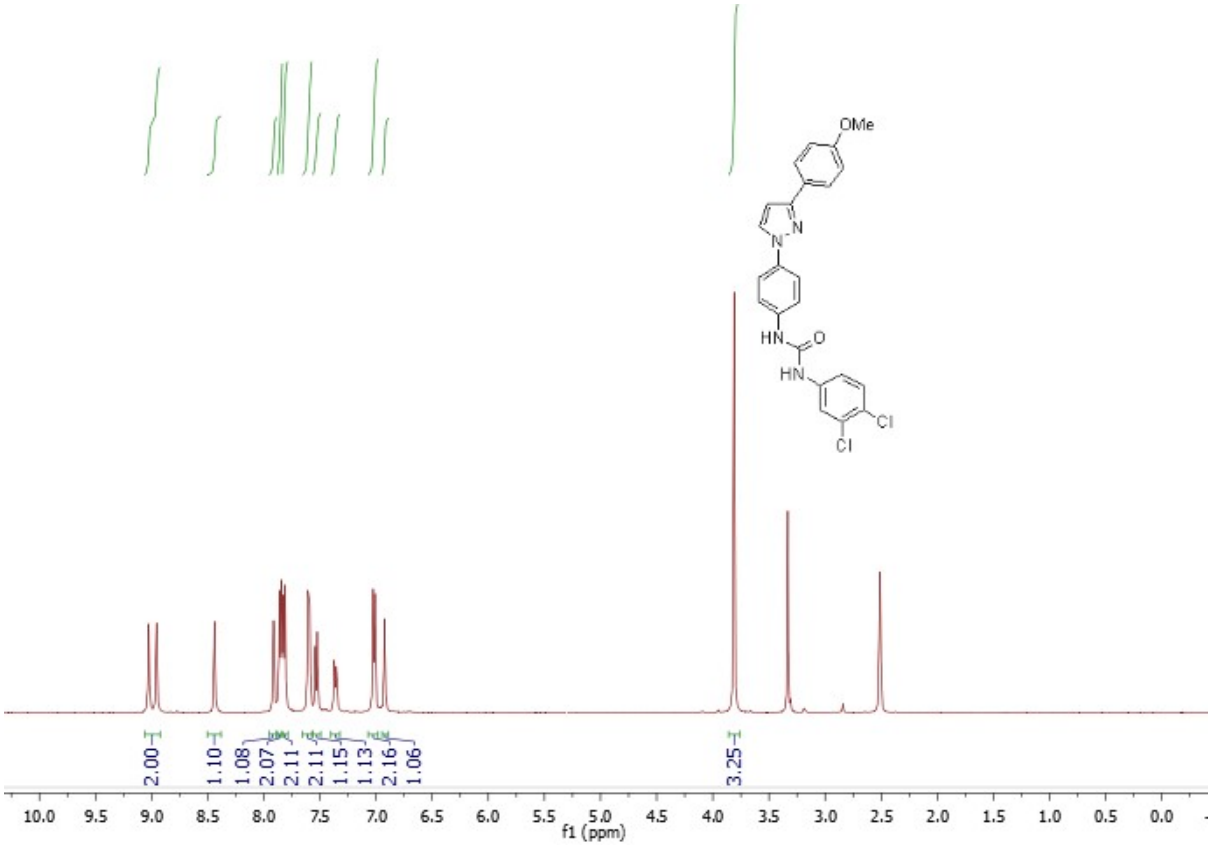
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **8c**



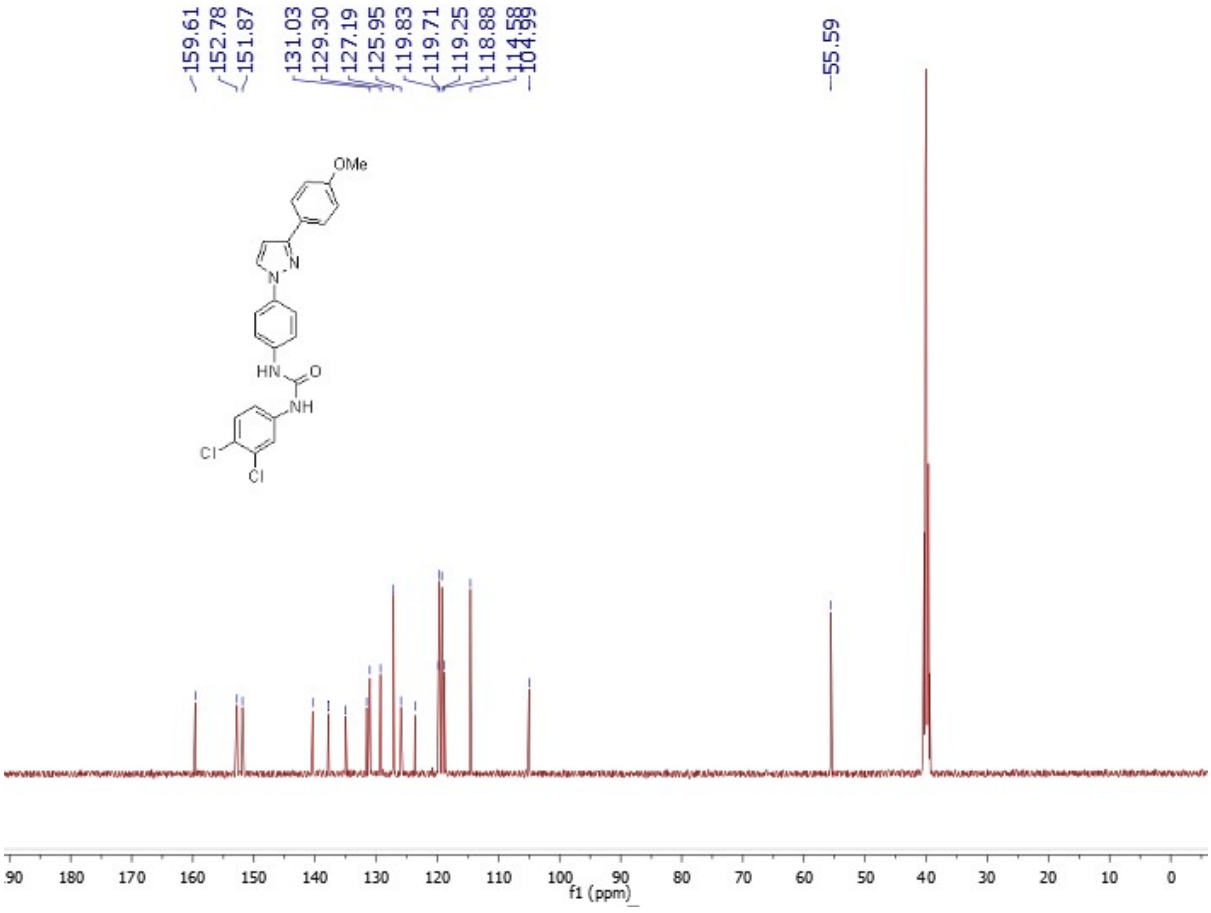
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **8c**



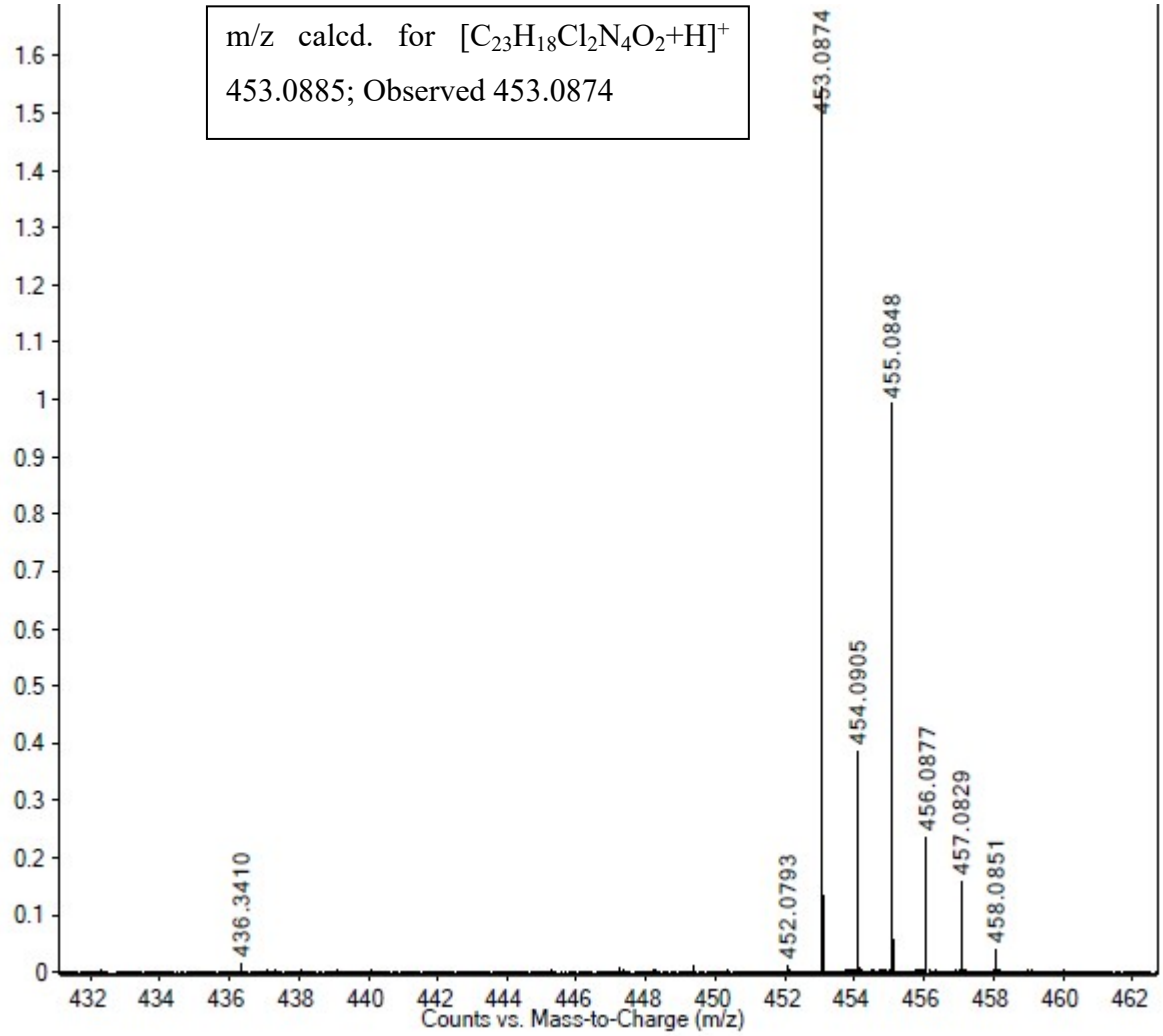
Mass spectrum of compound **8c**



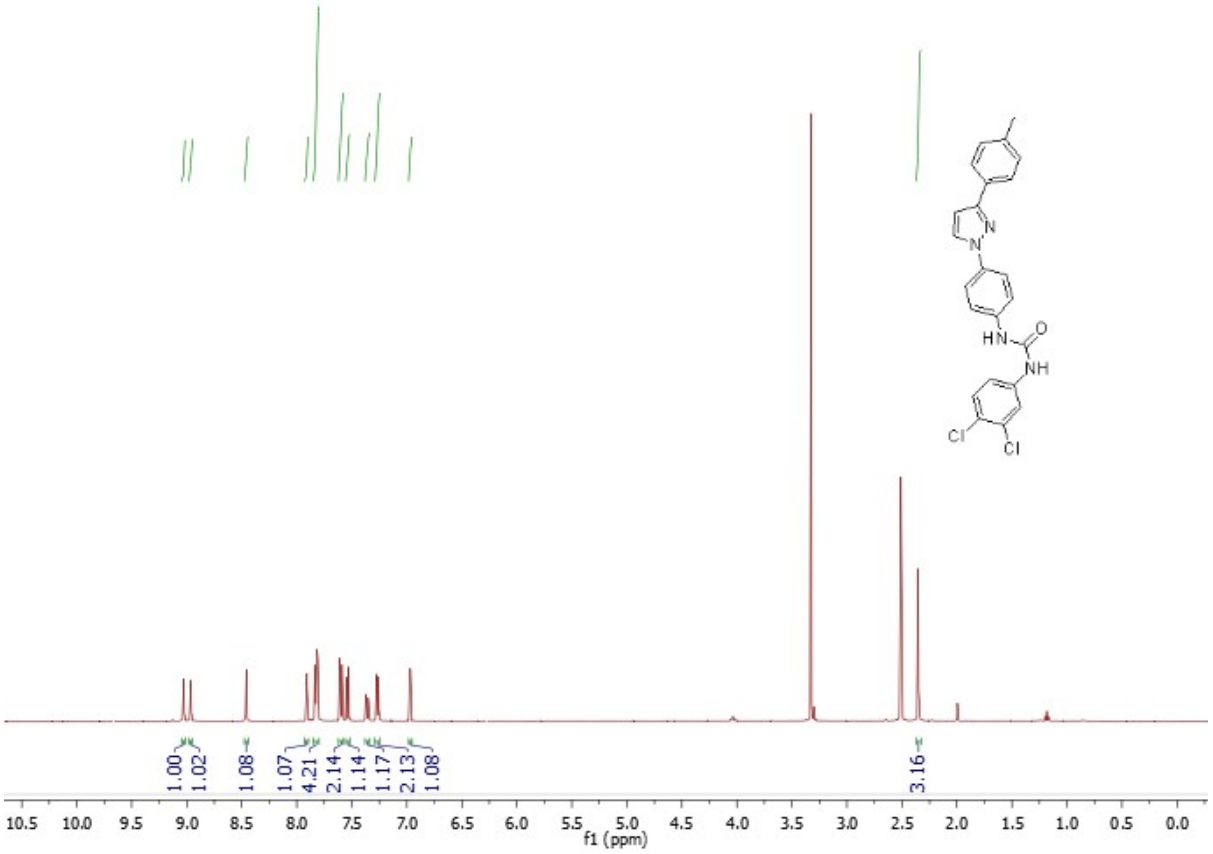
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **8d**



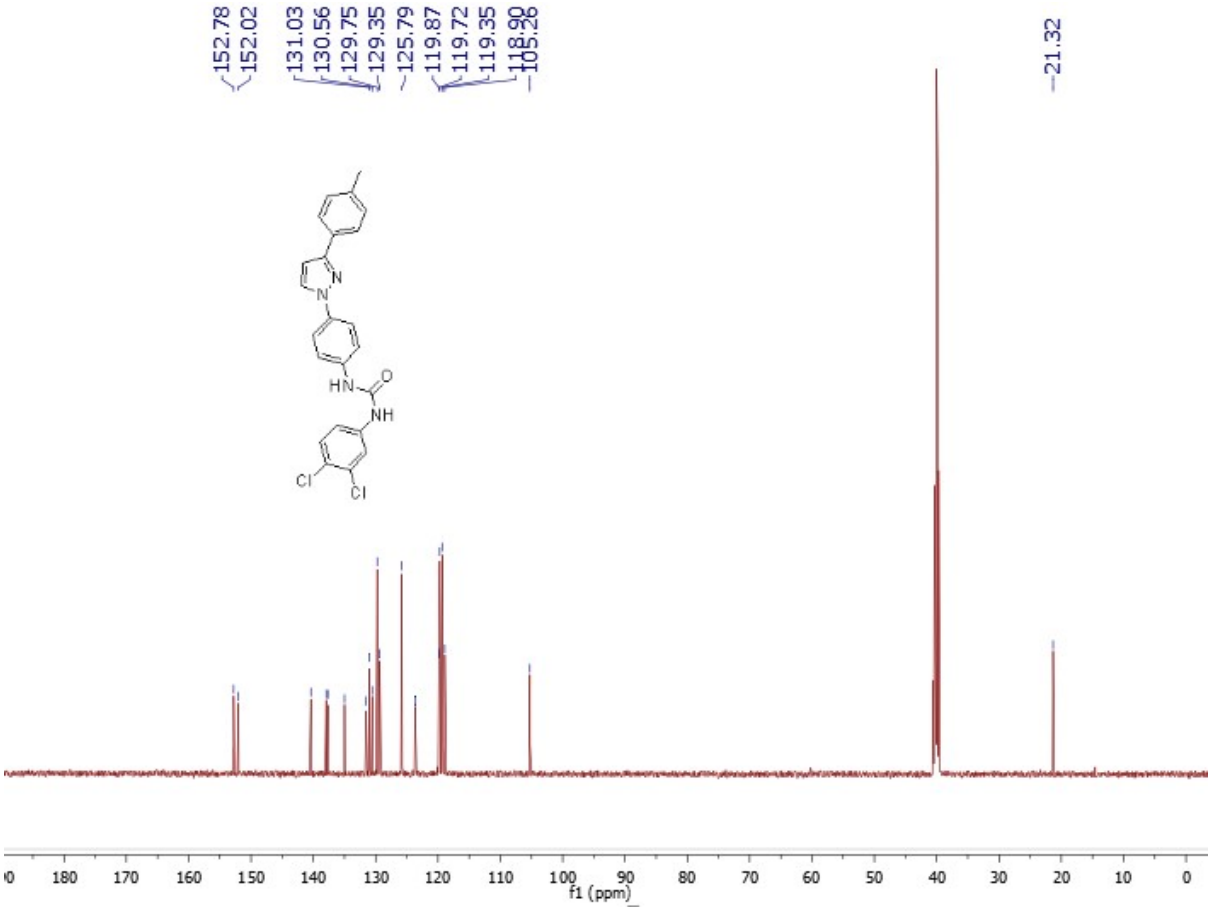
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **8d**



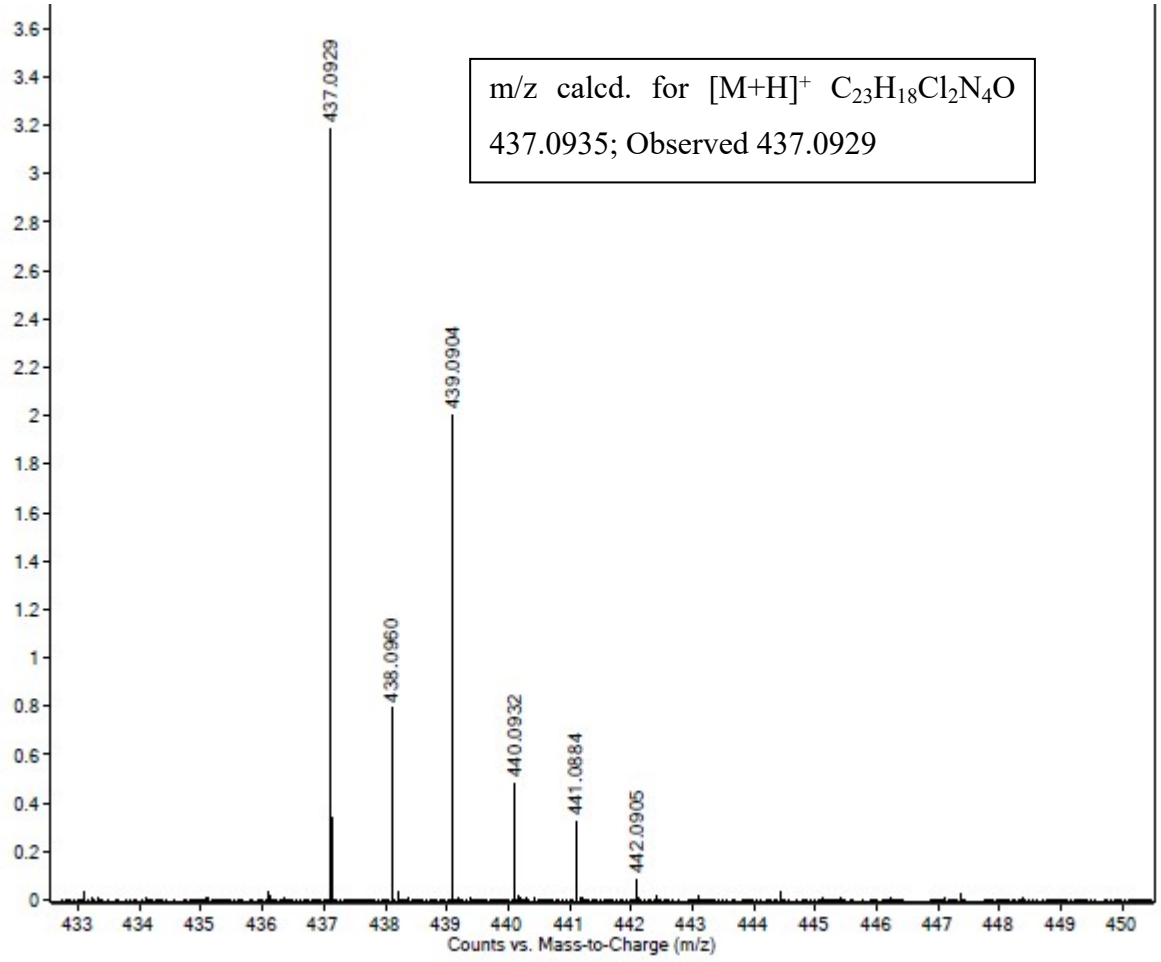
Mass spectrum of compound **8d**



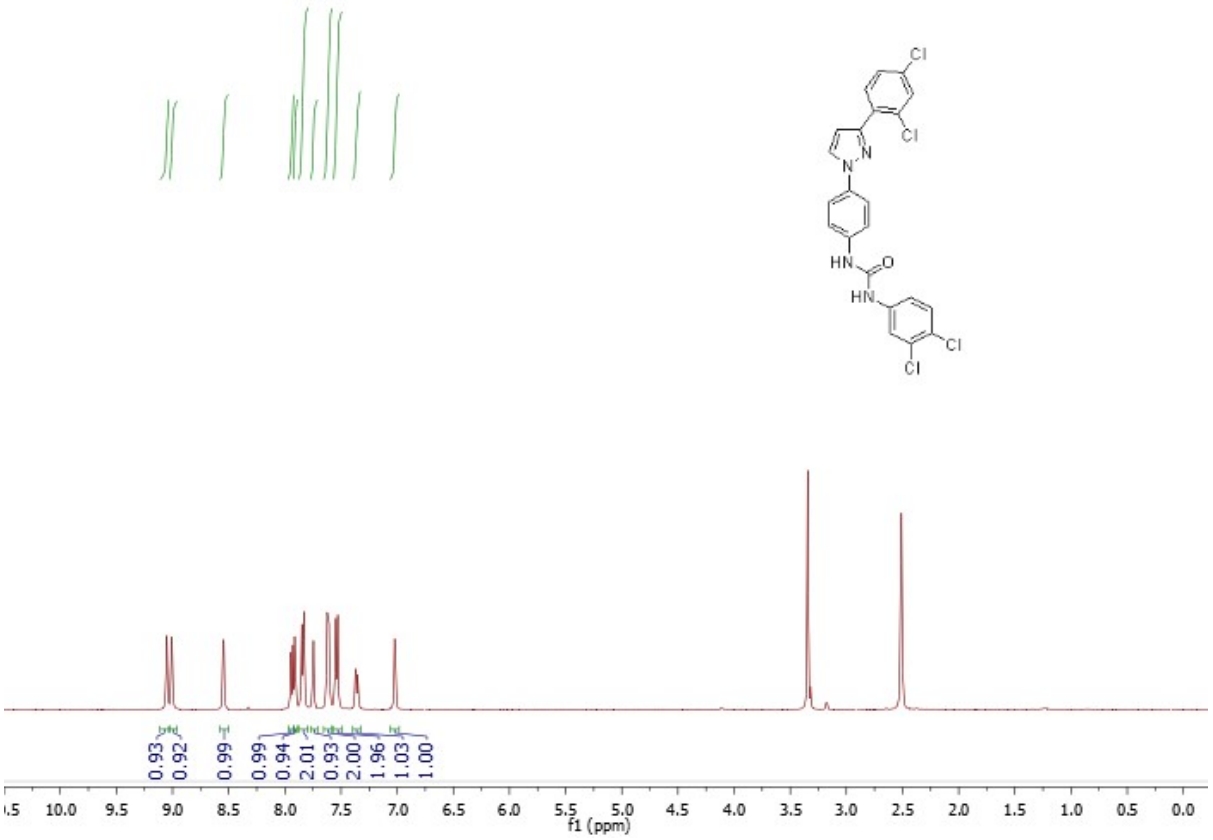
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **8e**



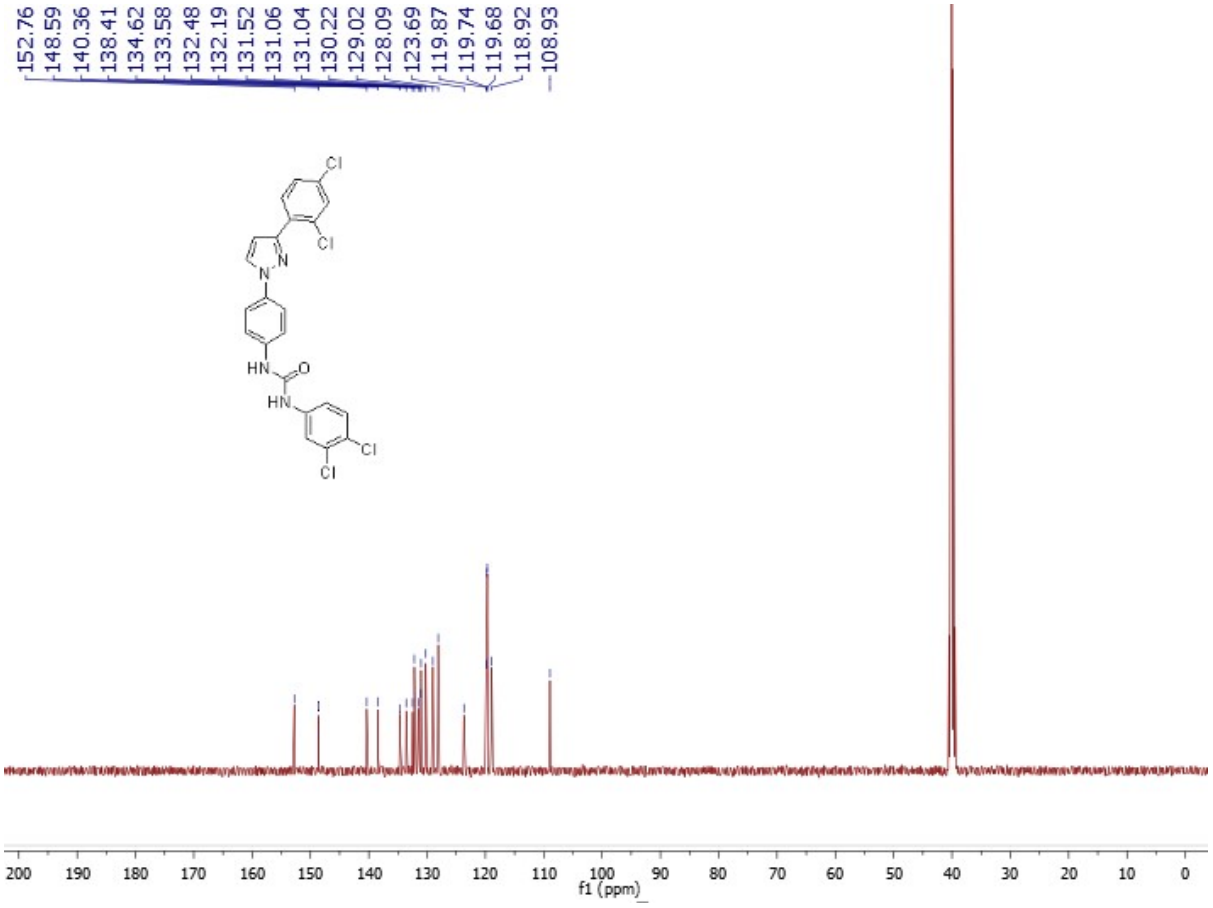
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **8e**



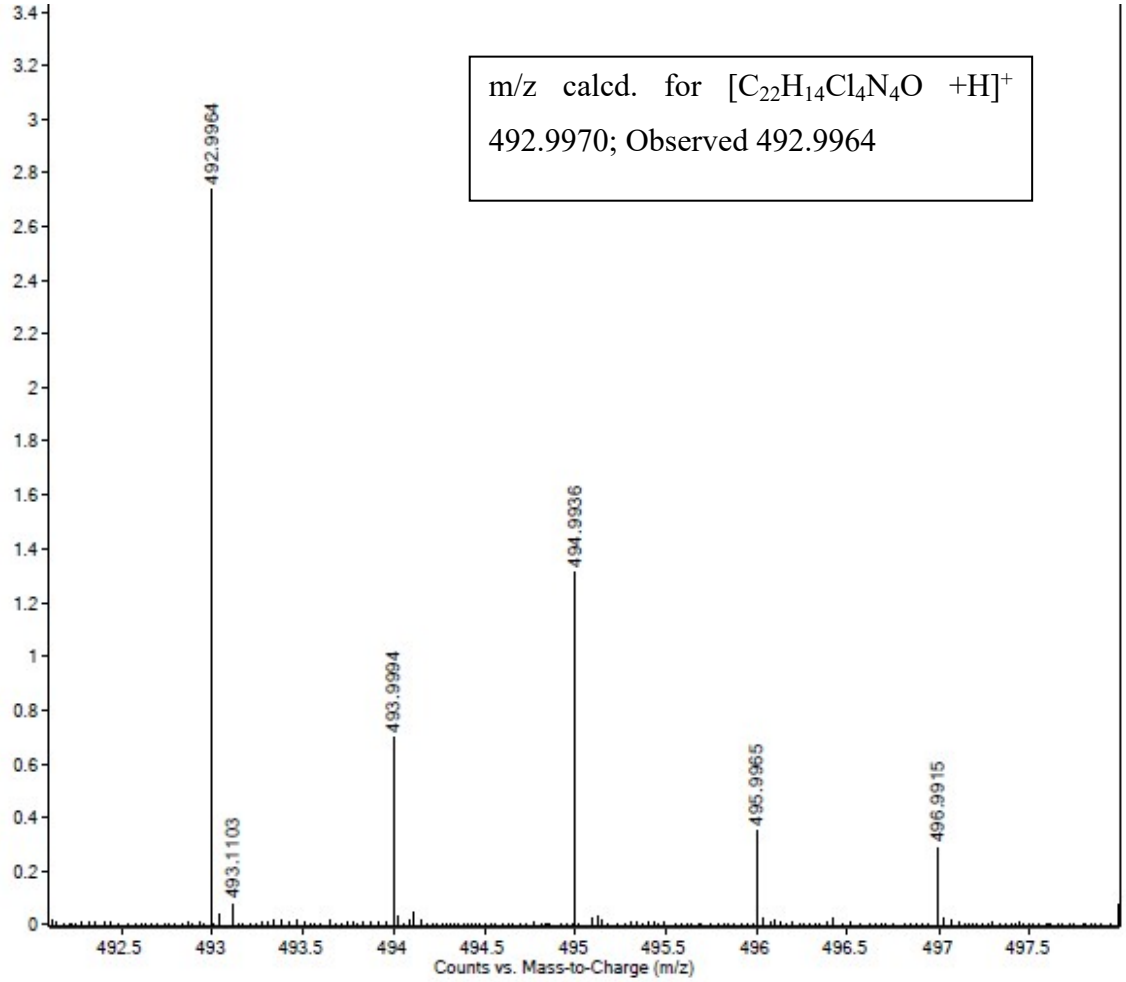
Mass spectrum of compound **8e**



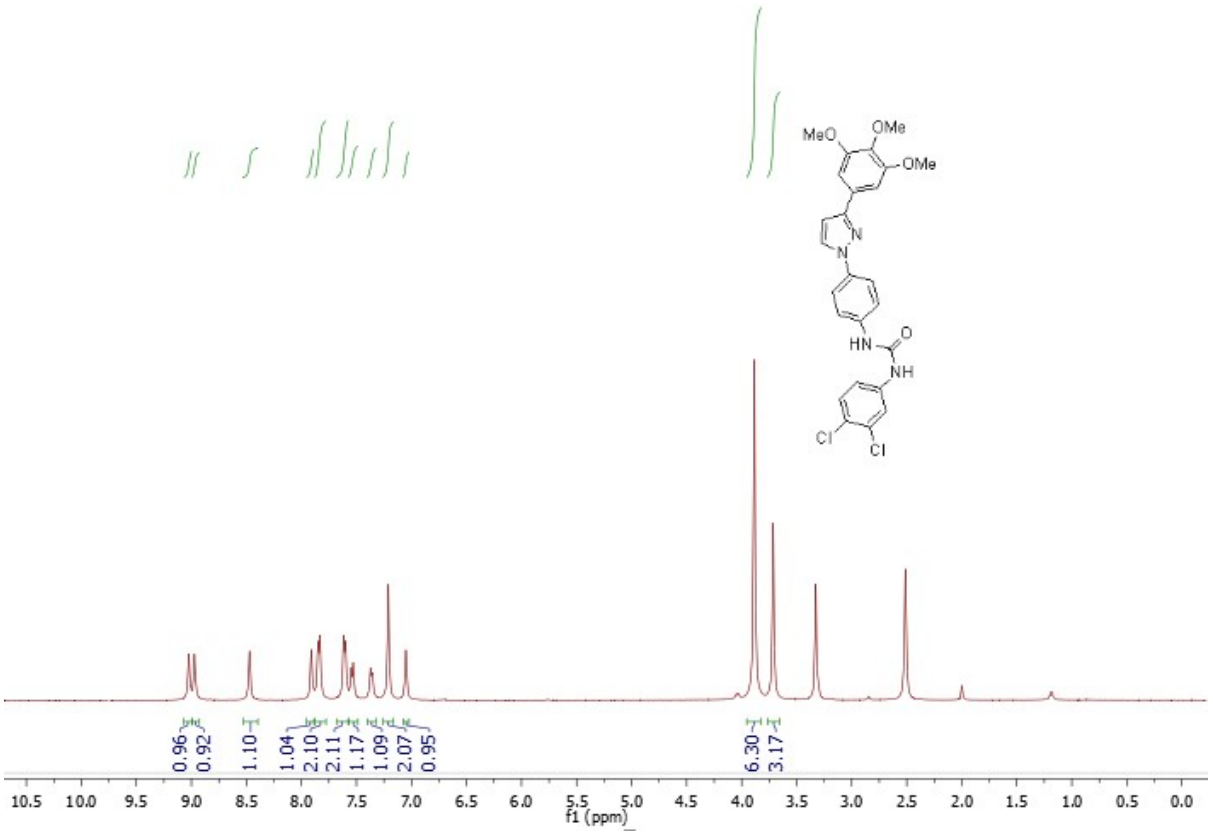
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **8f**



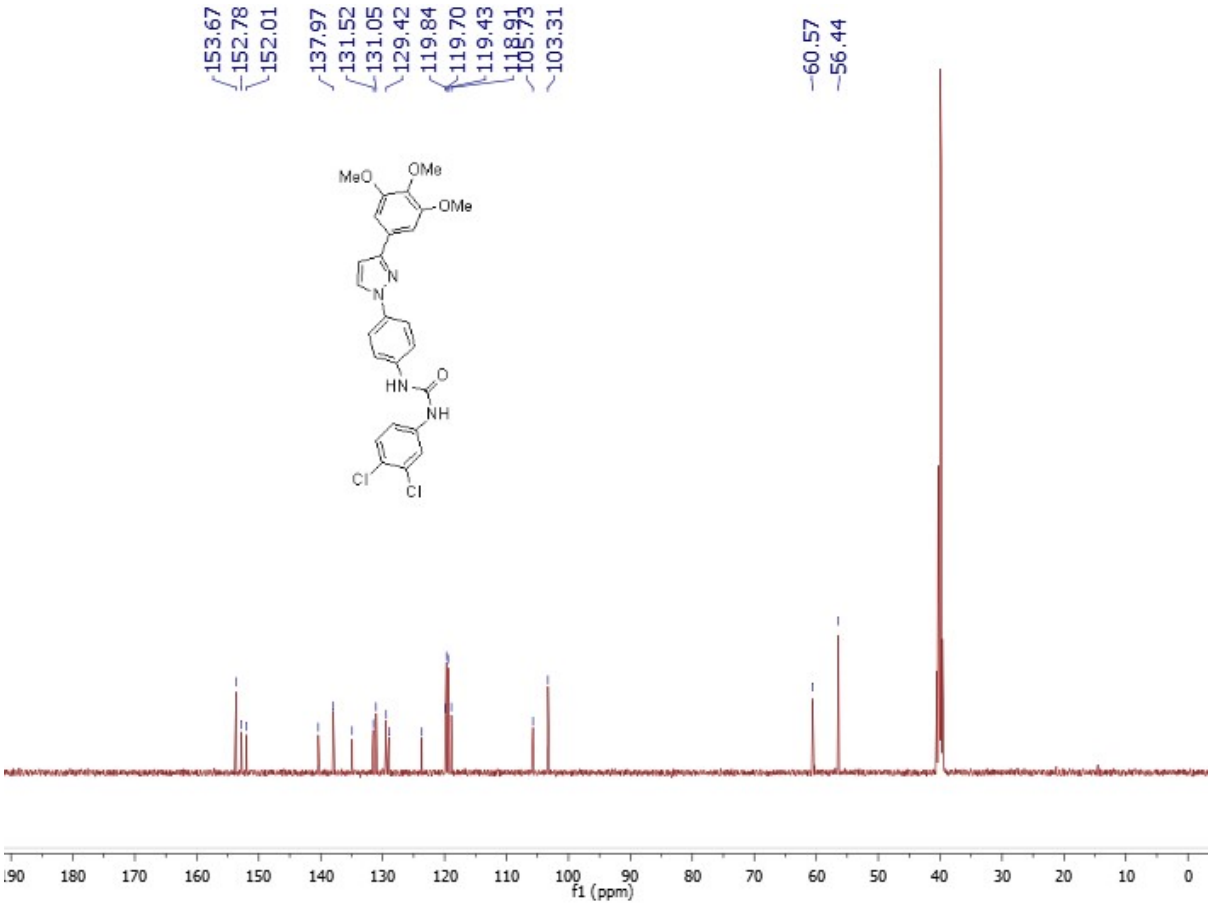
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **8f**



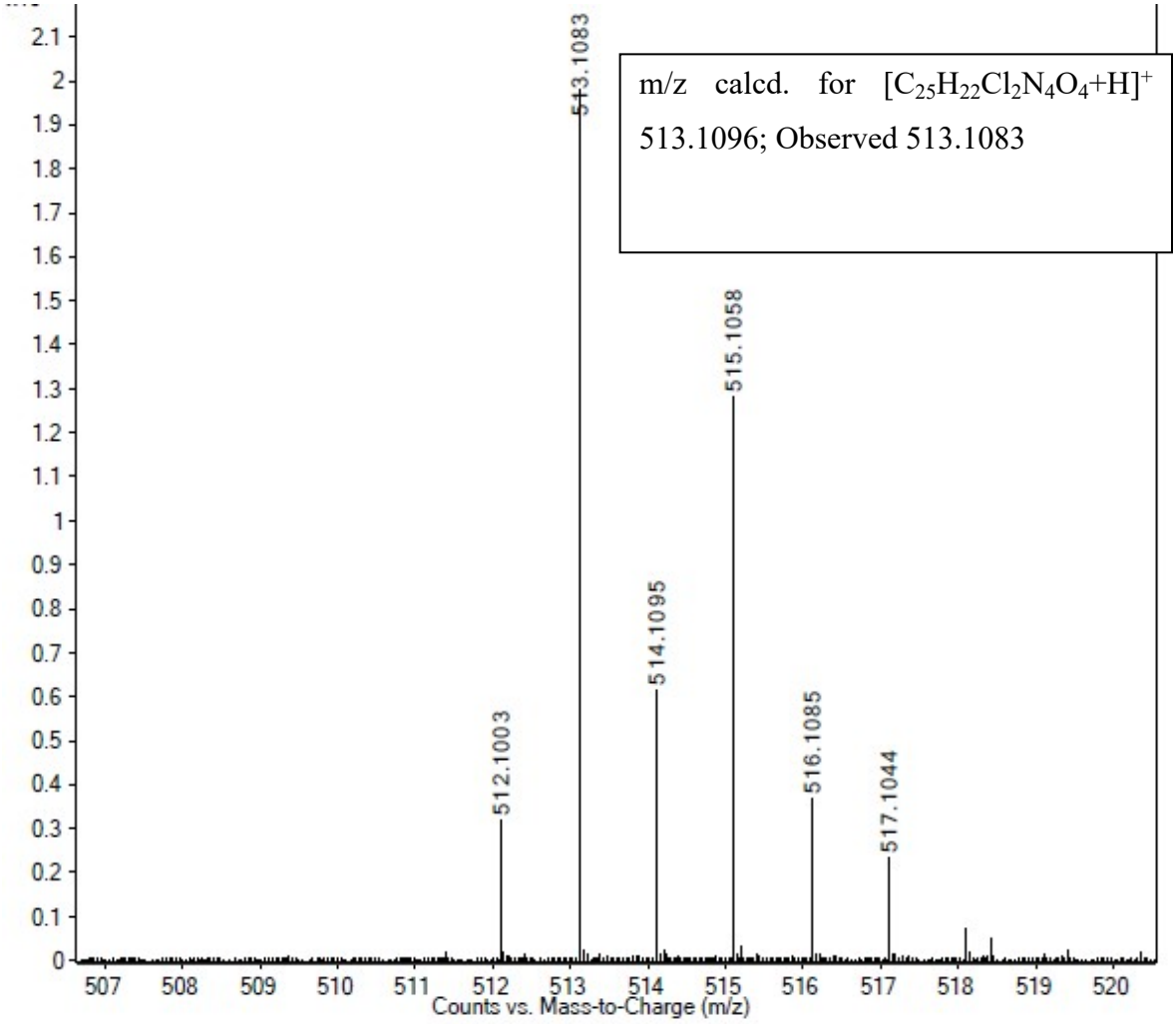
Mass spectrum of compound **8f**



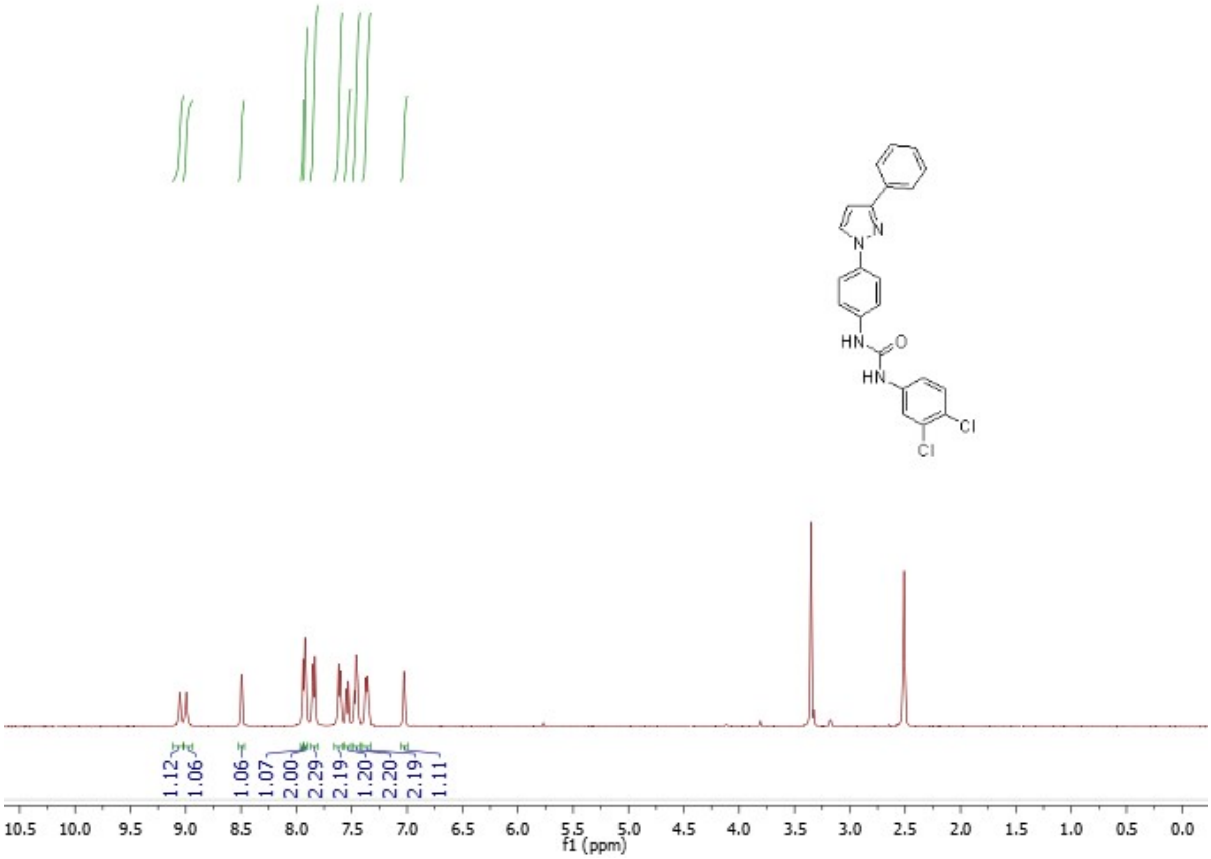
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **8g**



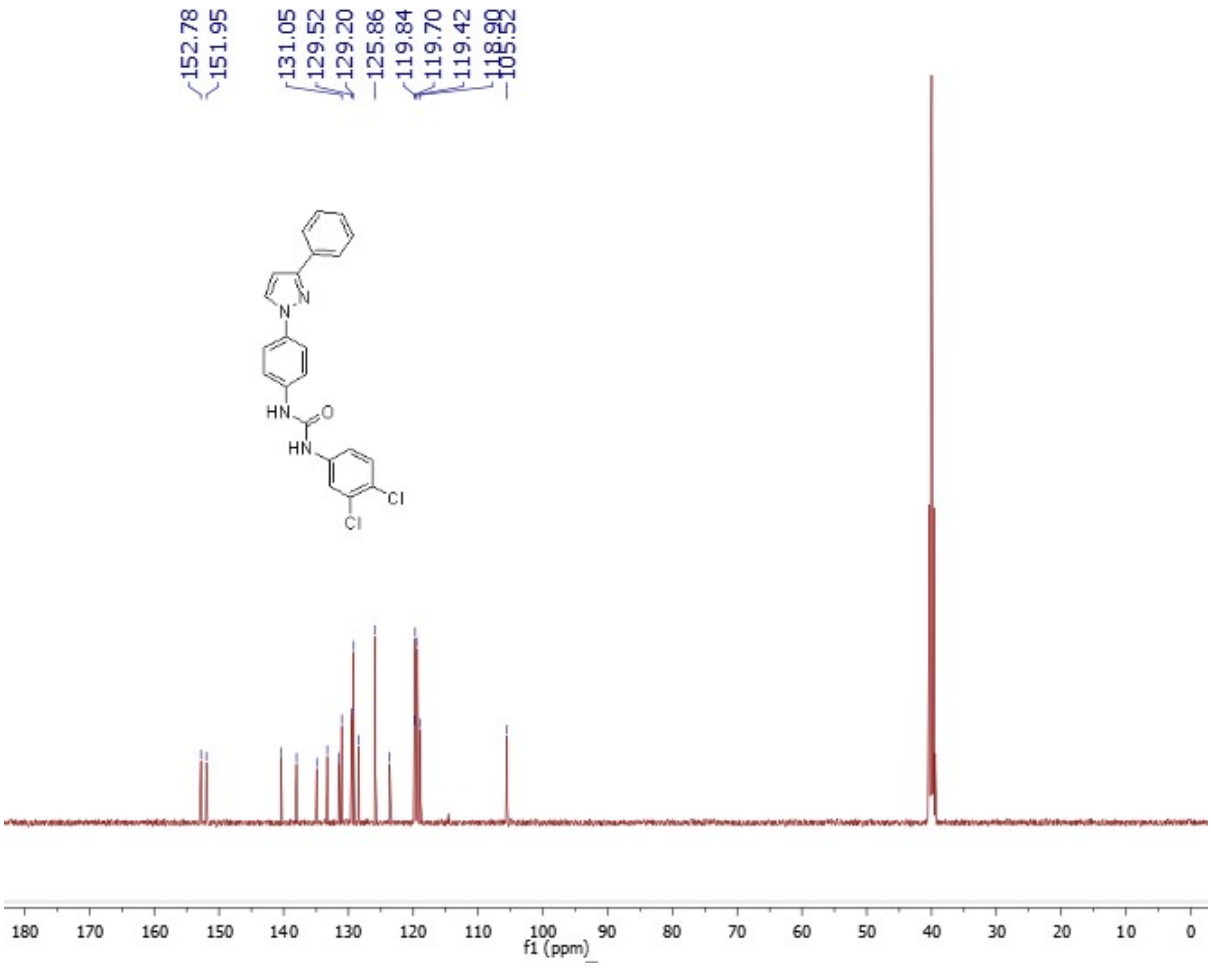
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **8g**



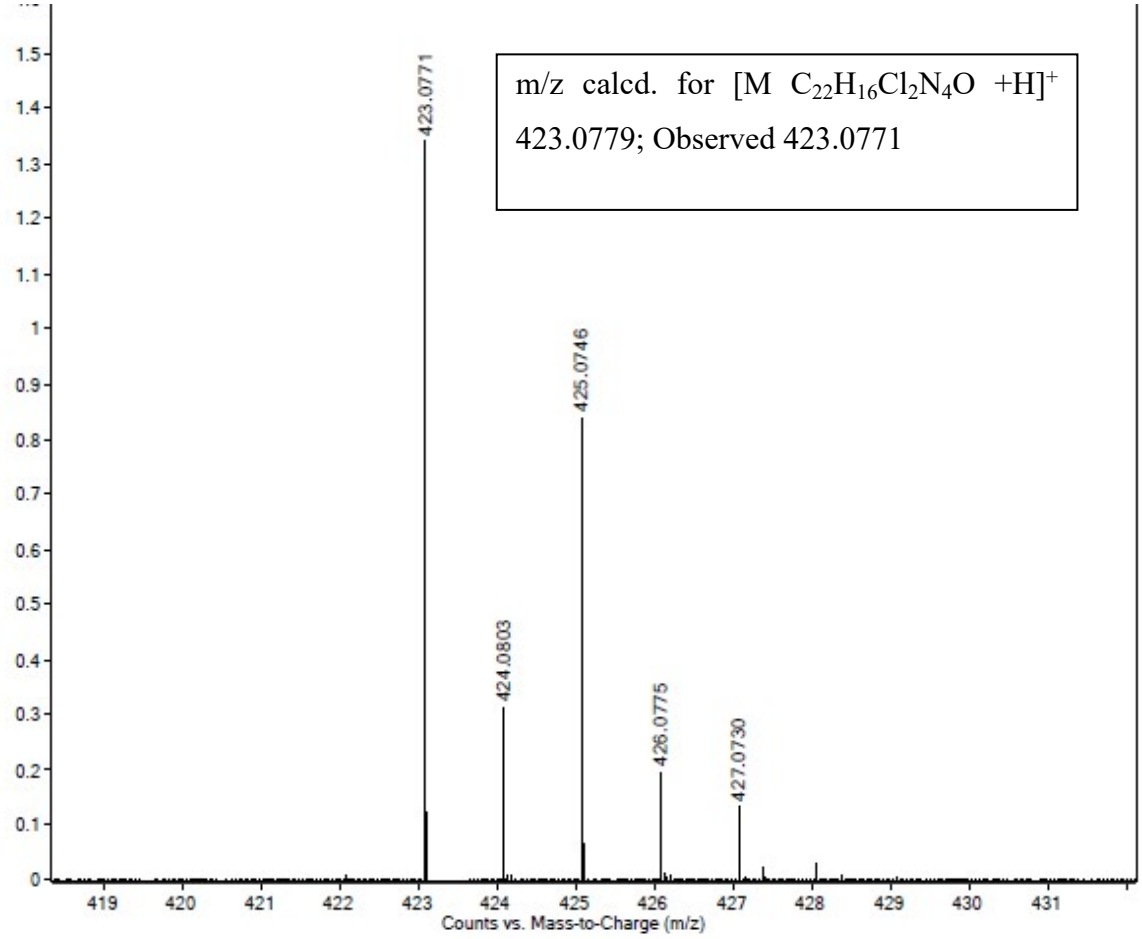
Mass spectrum of compound **8g**



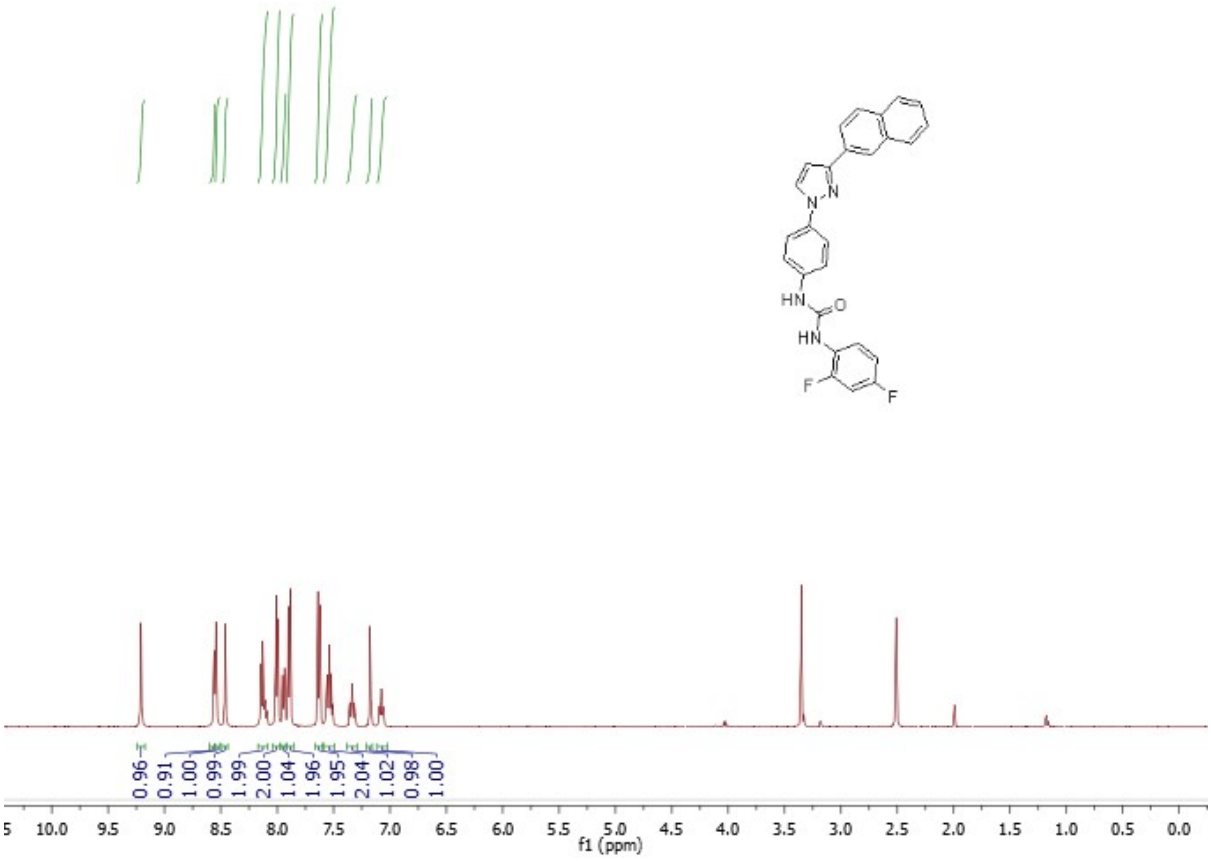
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **8h**



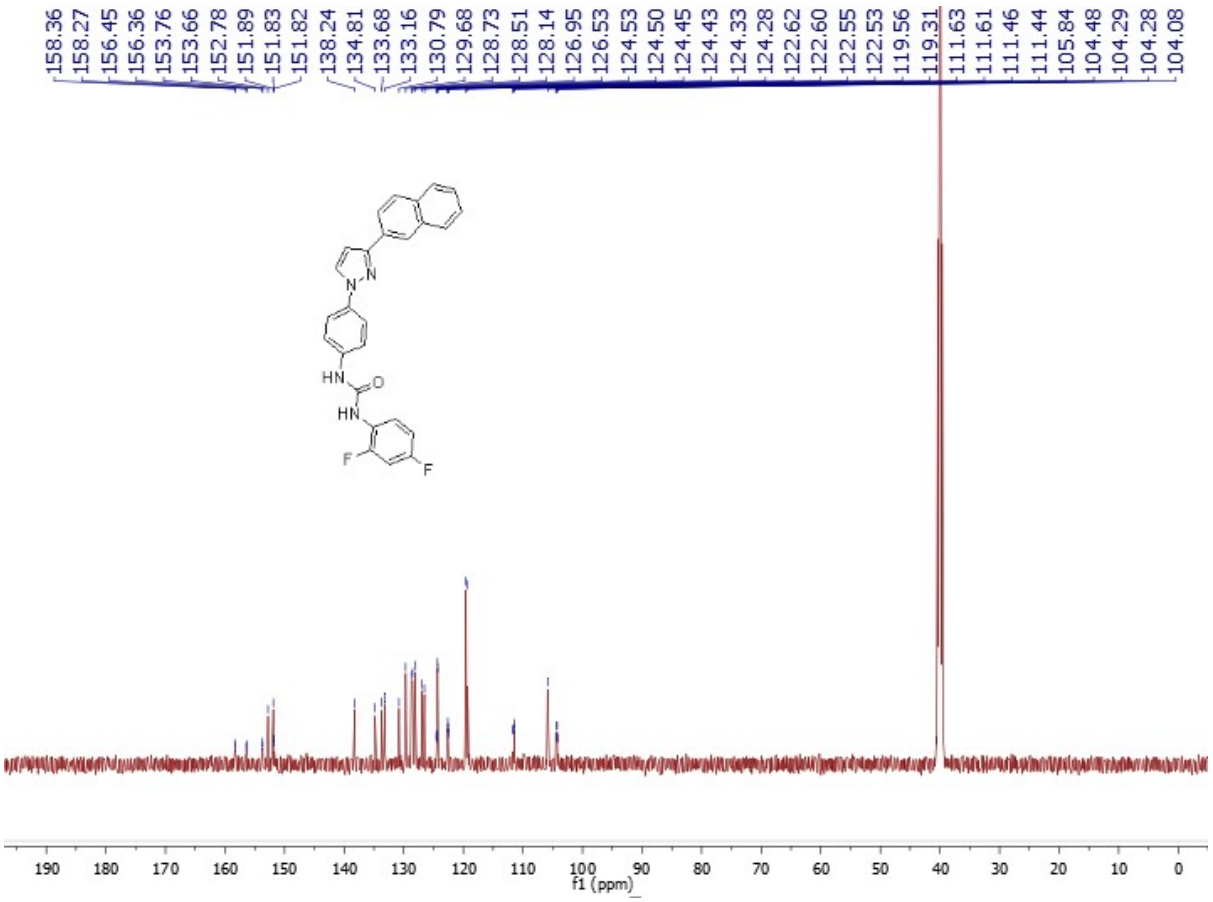
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **8h**



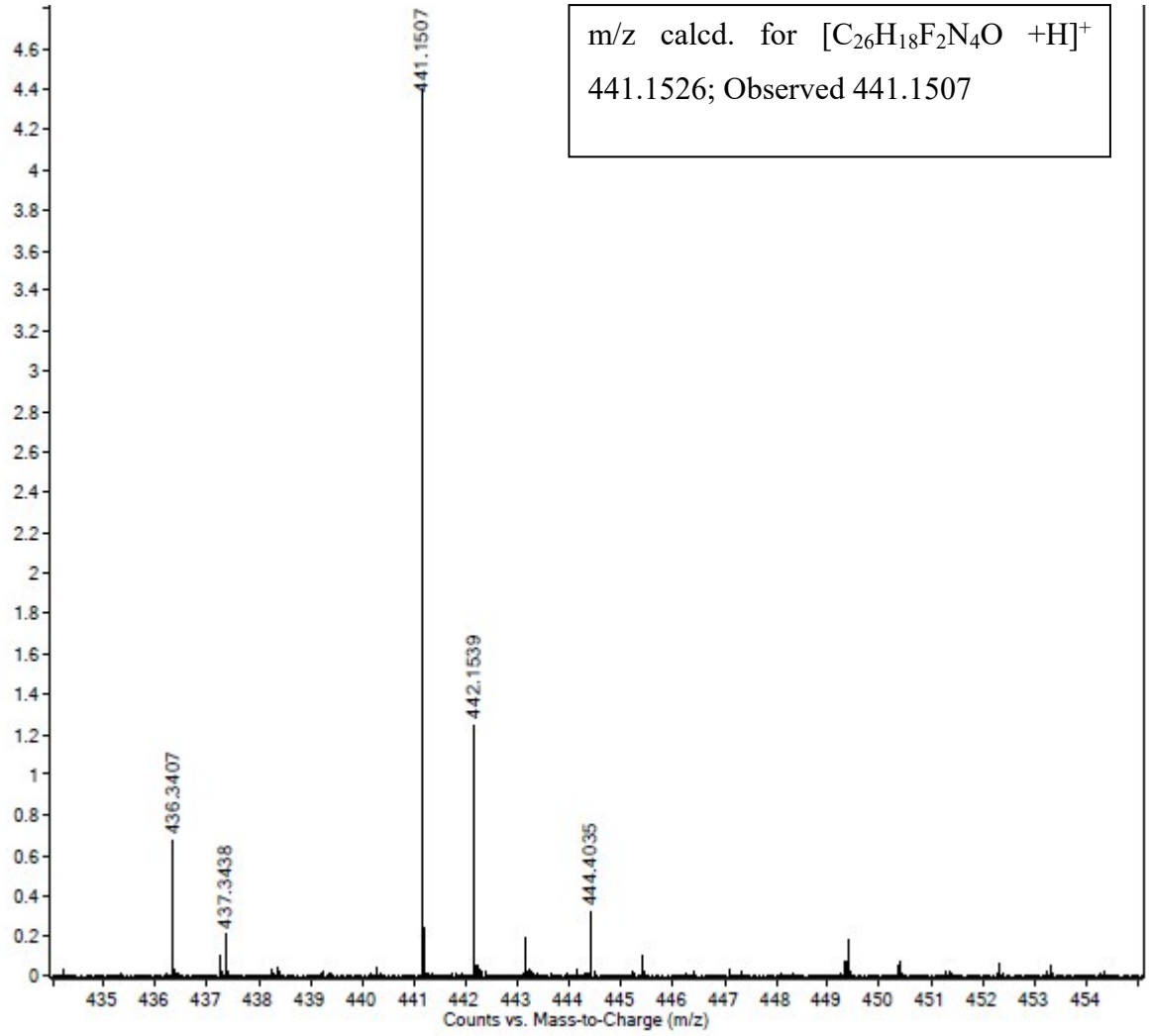
Mass spectrum of compound **8h**



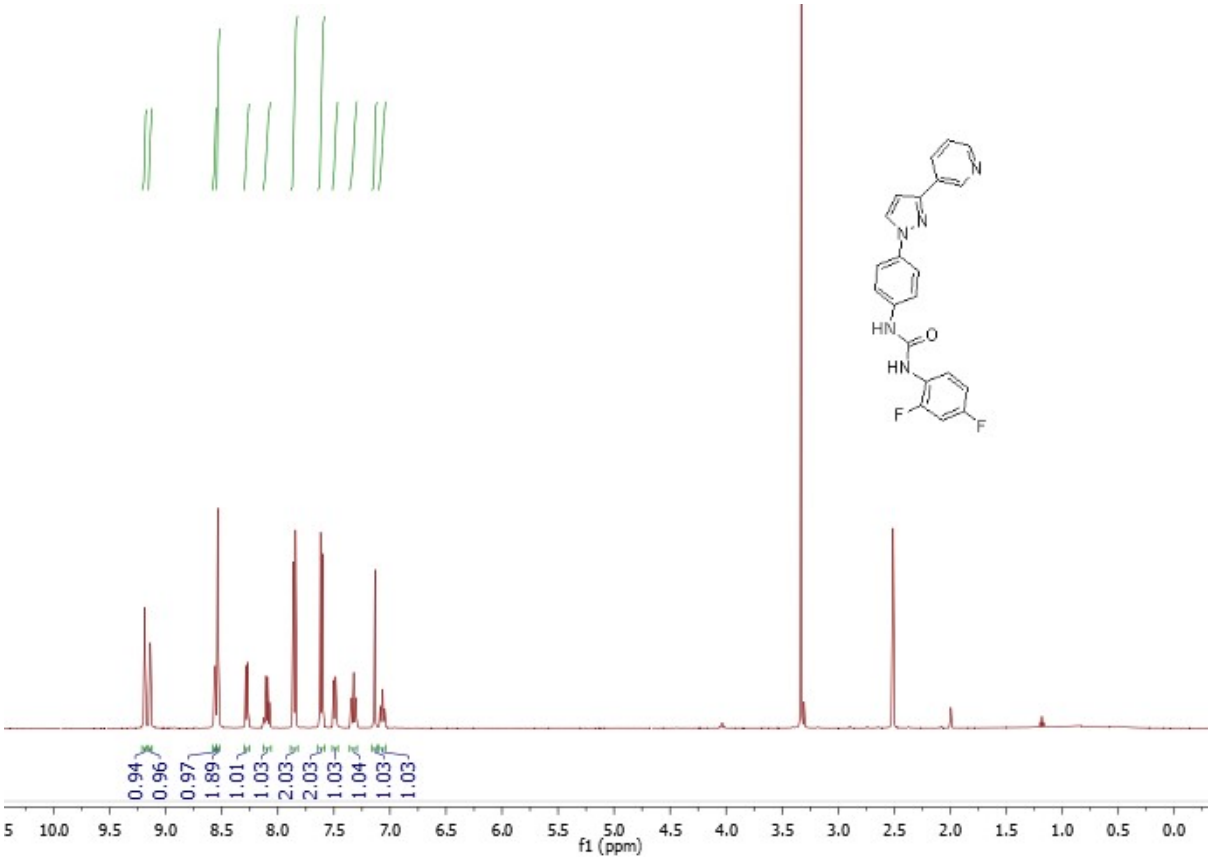
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **9a**



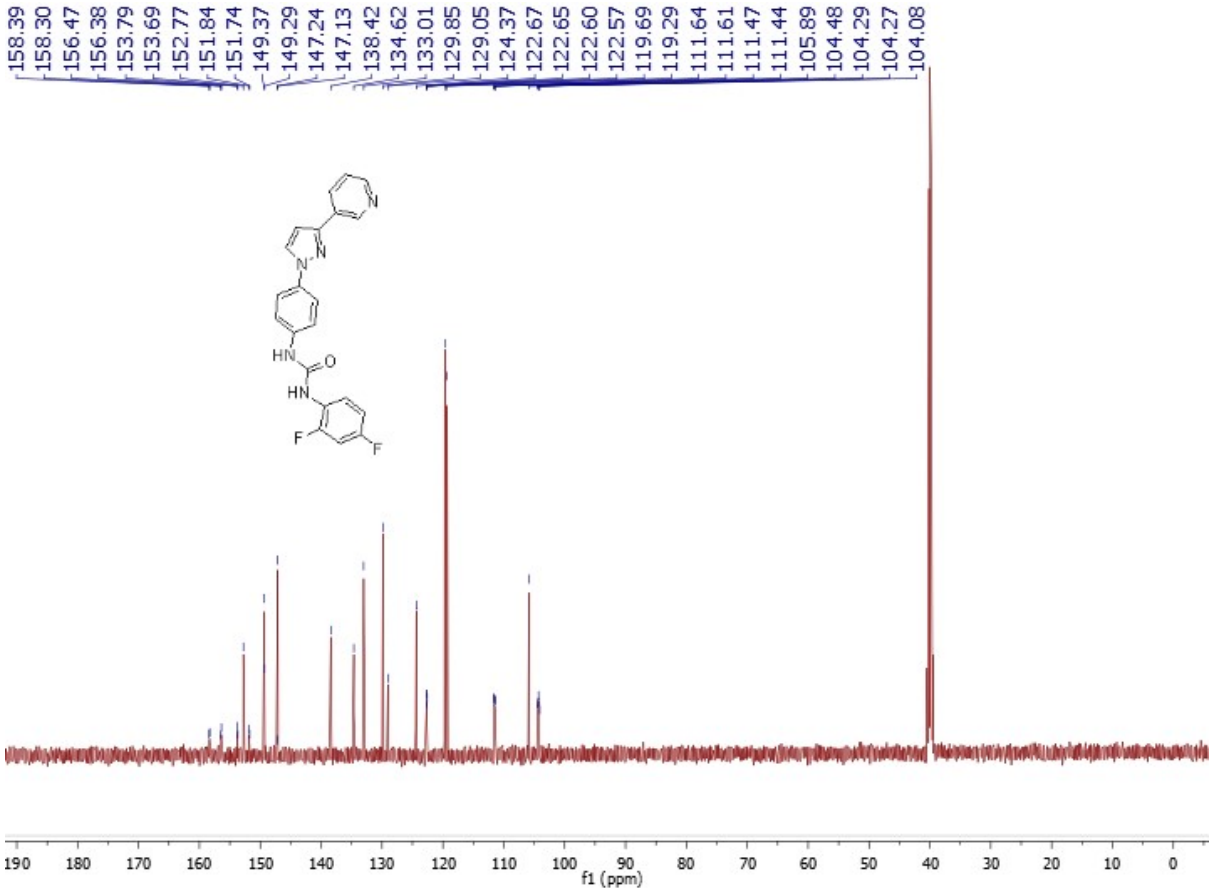
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **9a**



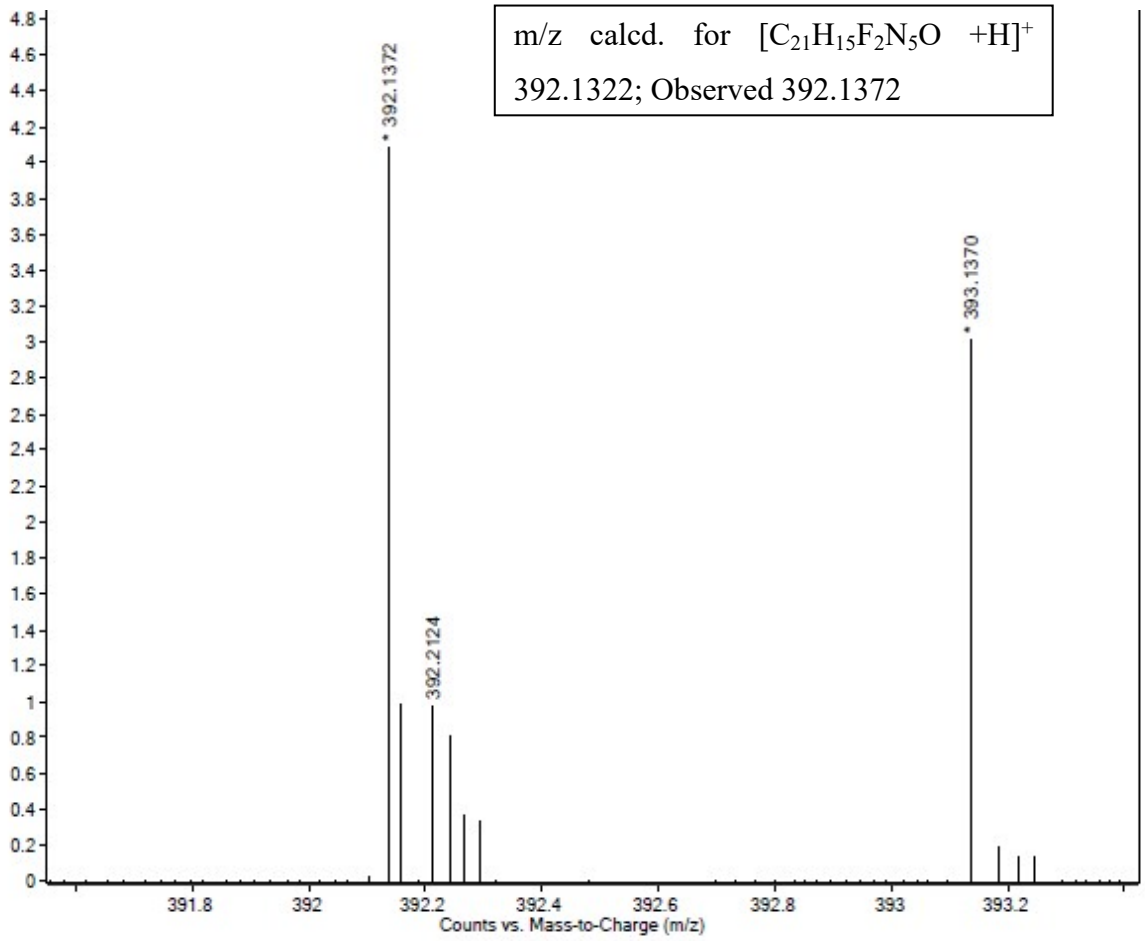
Mass spectrum of compound **9a**



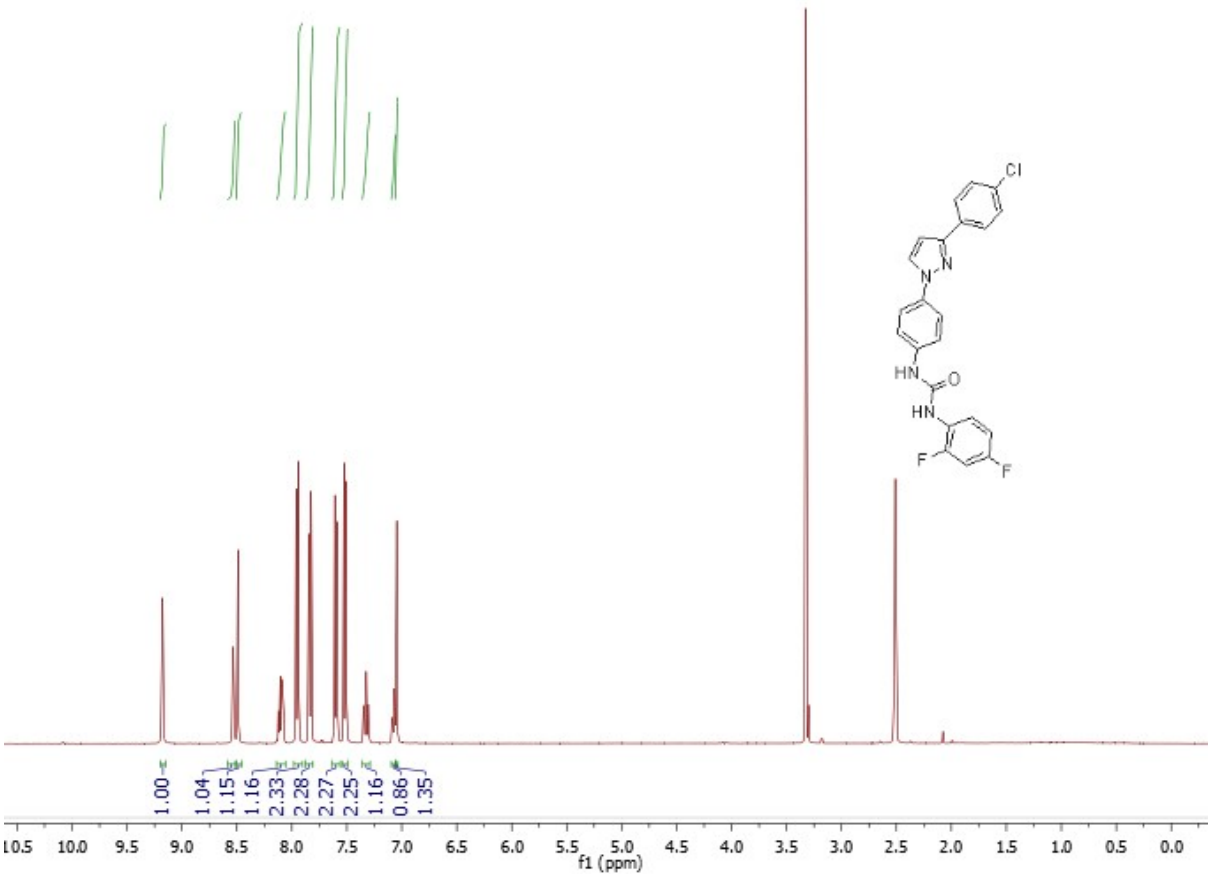
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **9b**



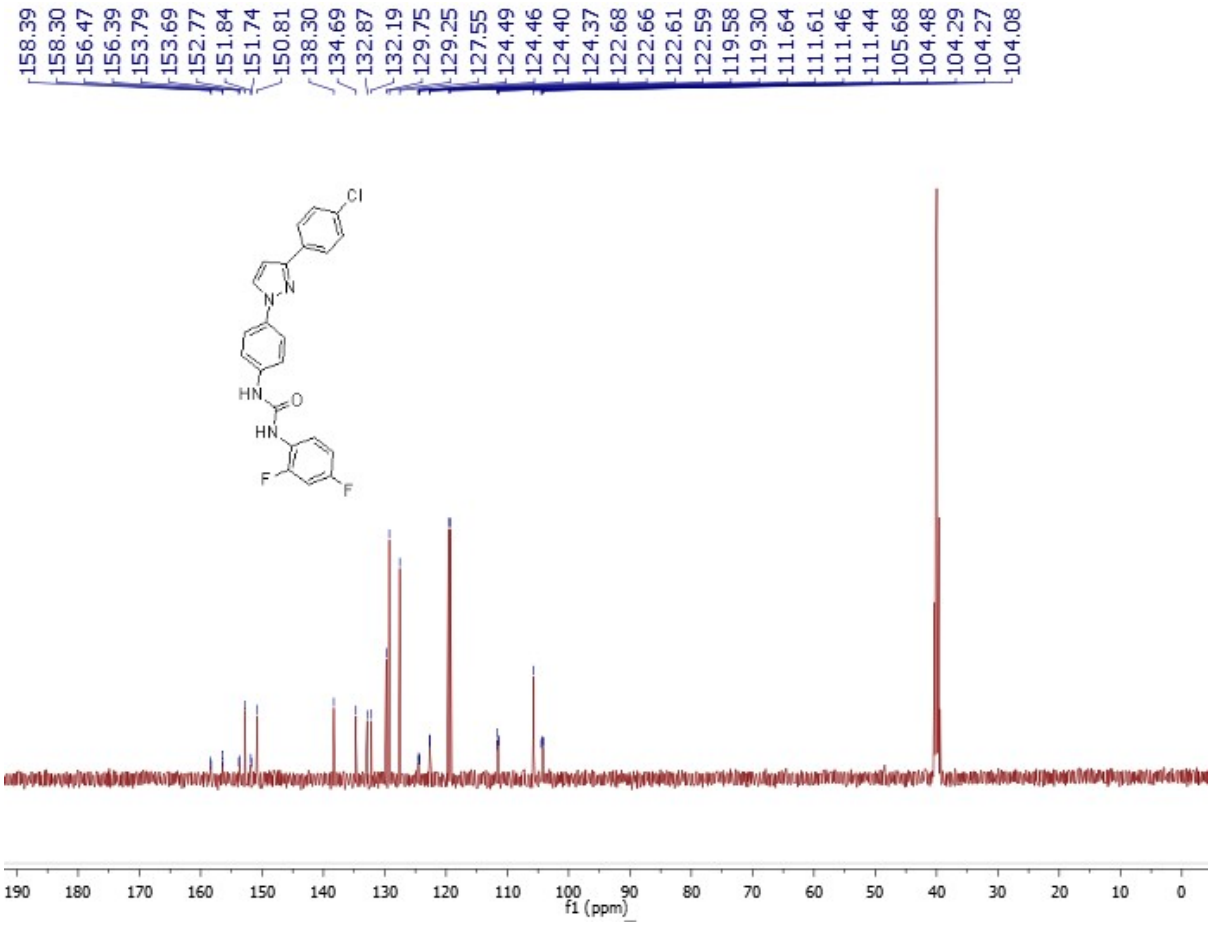
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **9b**



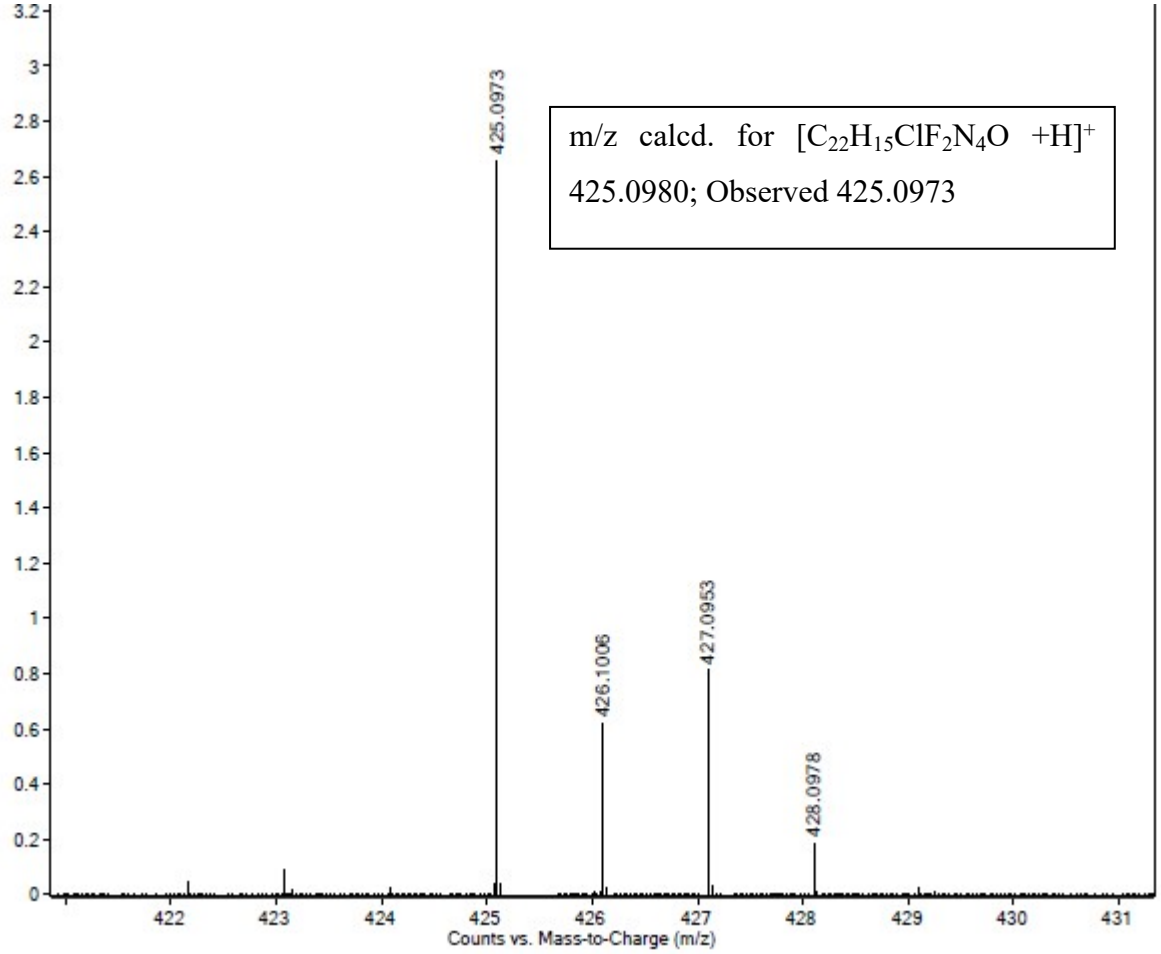
Mass spectrum of compound **9b**



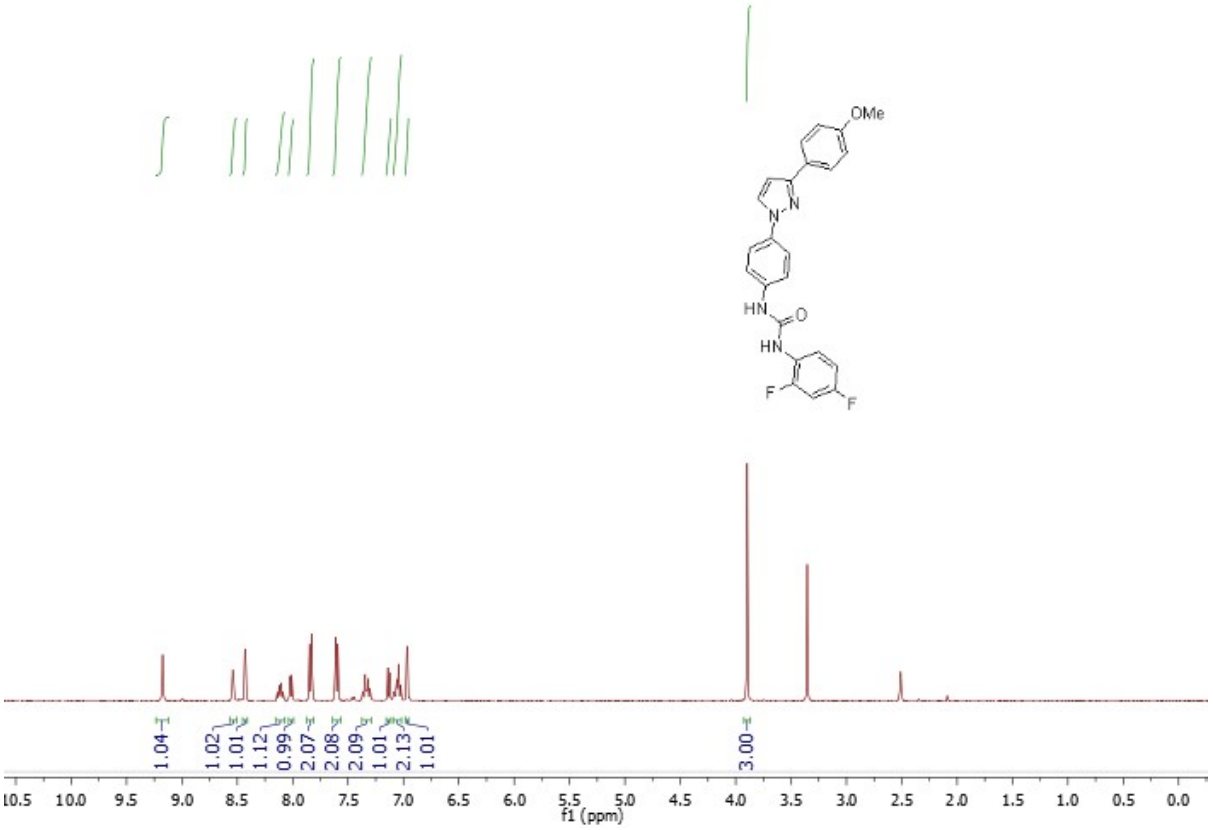
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **9c**



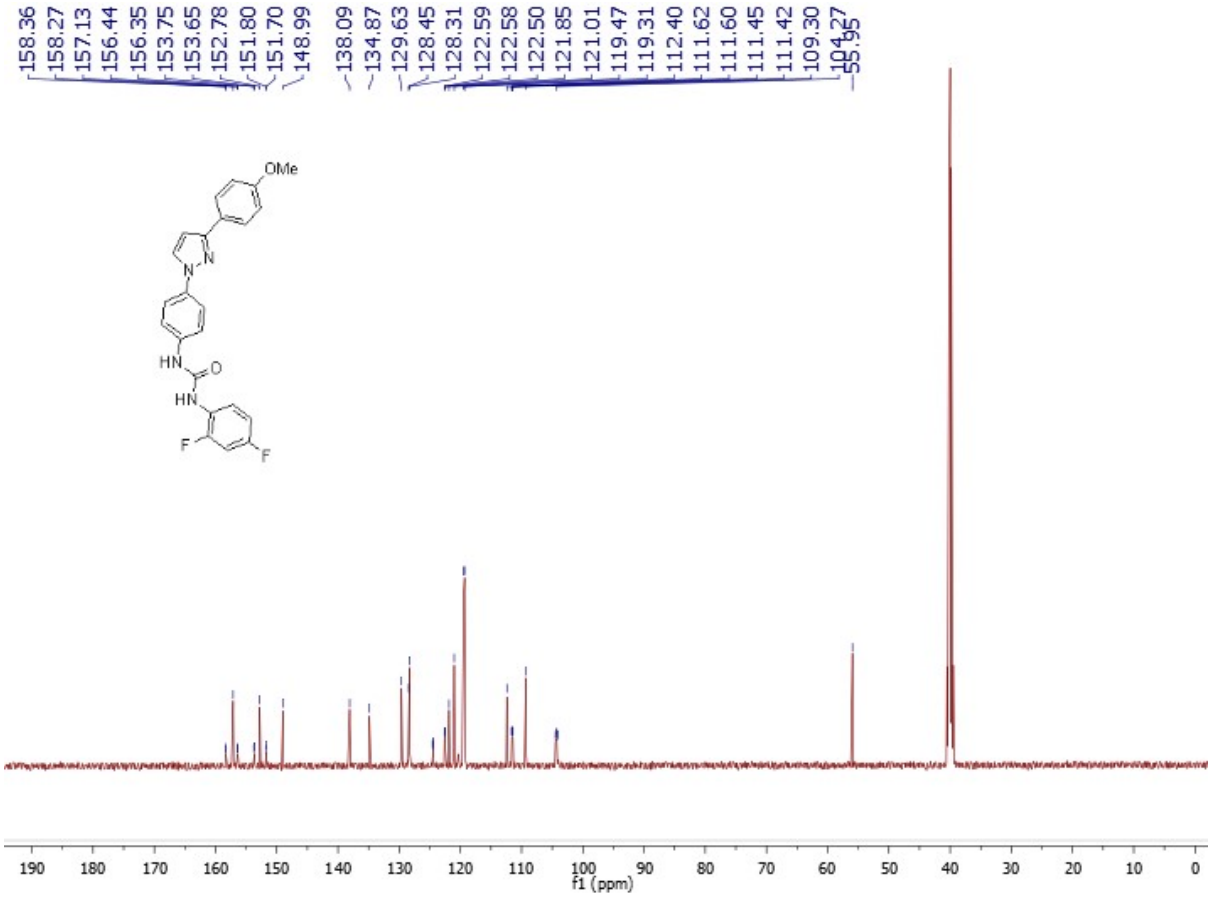
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **9c**



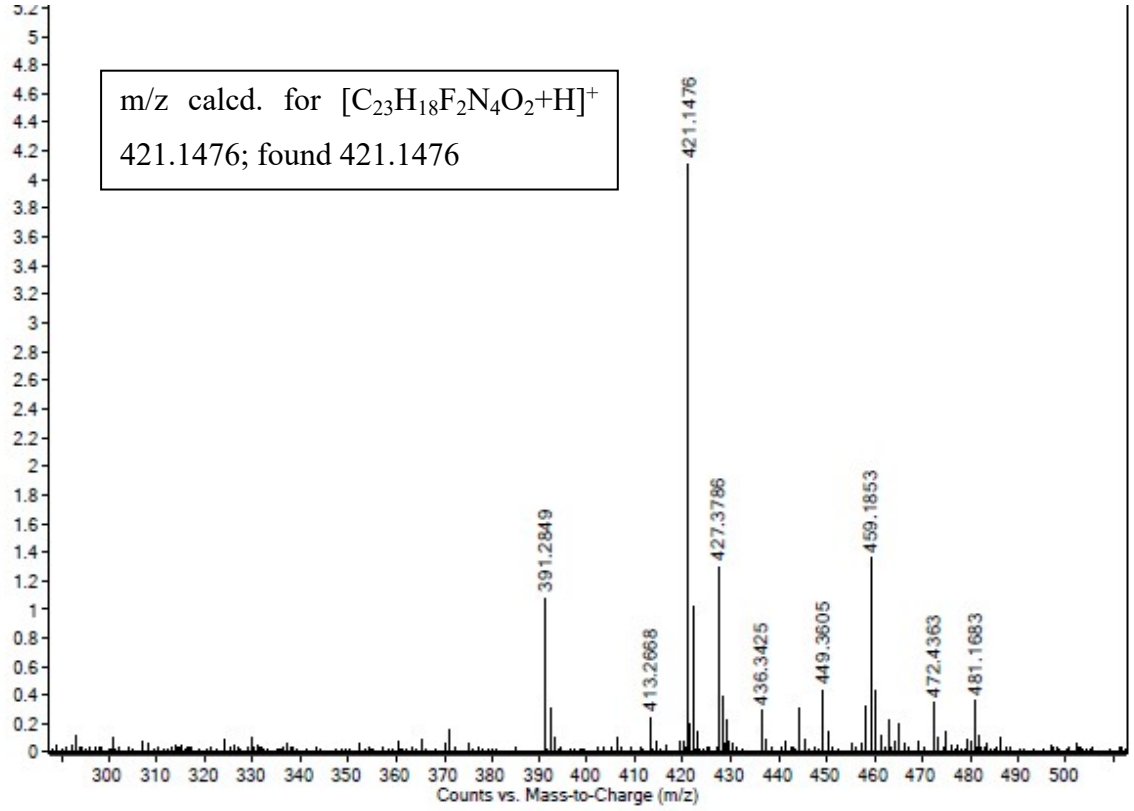
Mass spectrum of compound **9c**



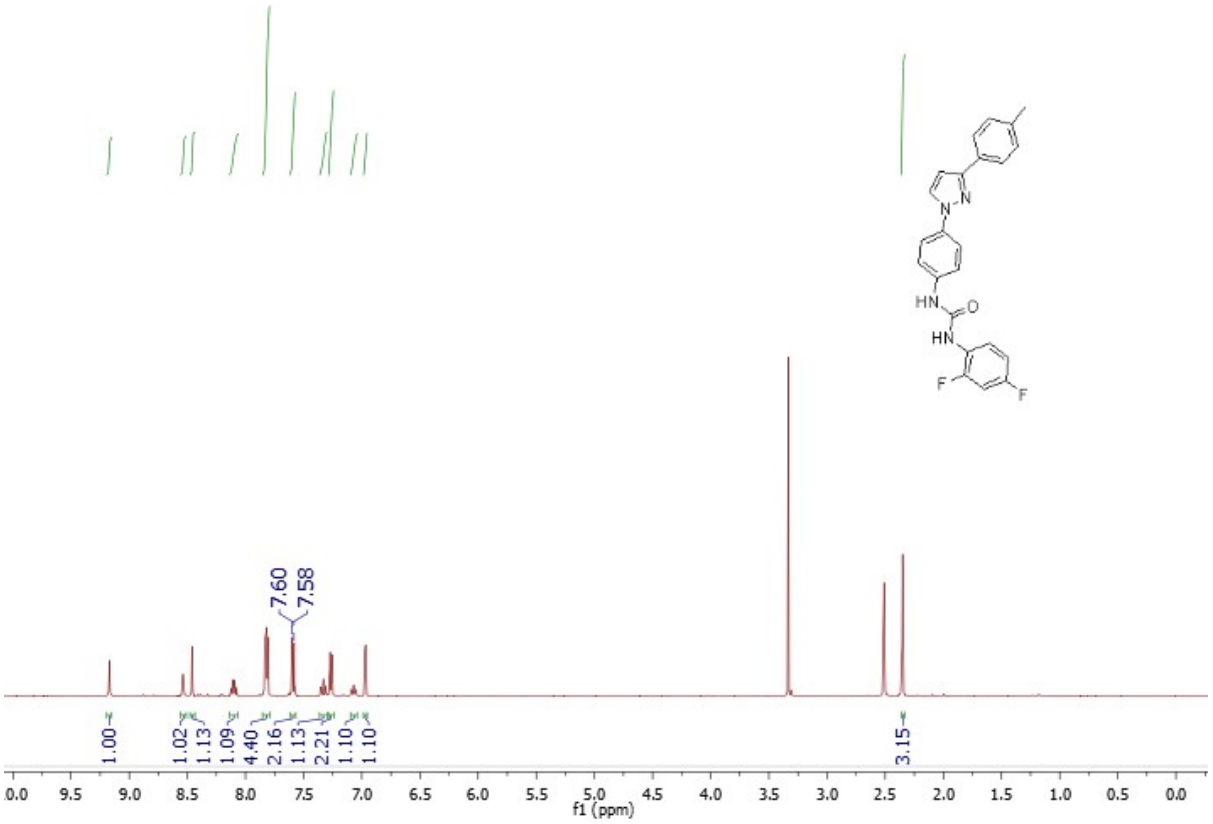
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **9d**



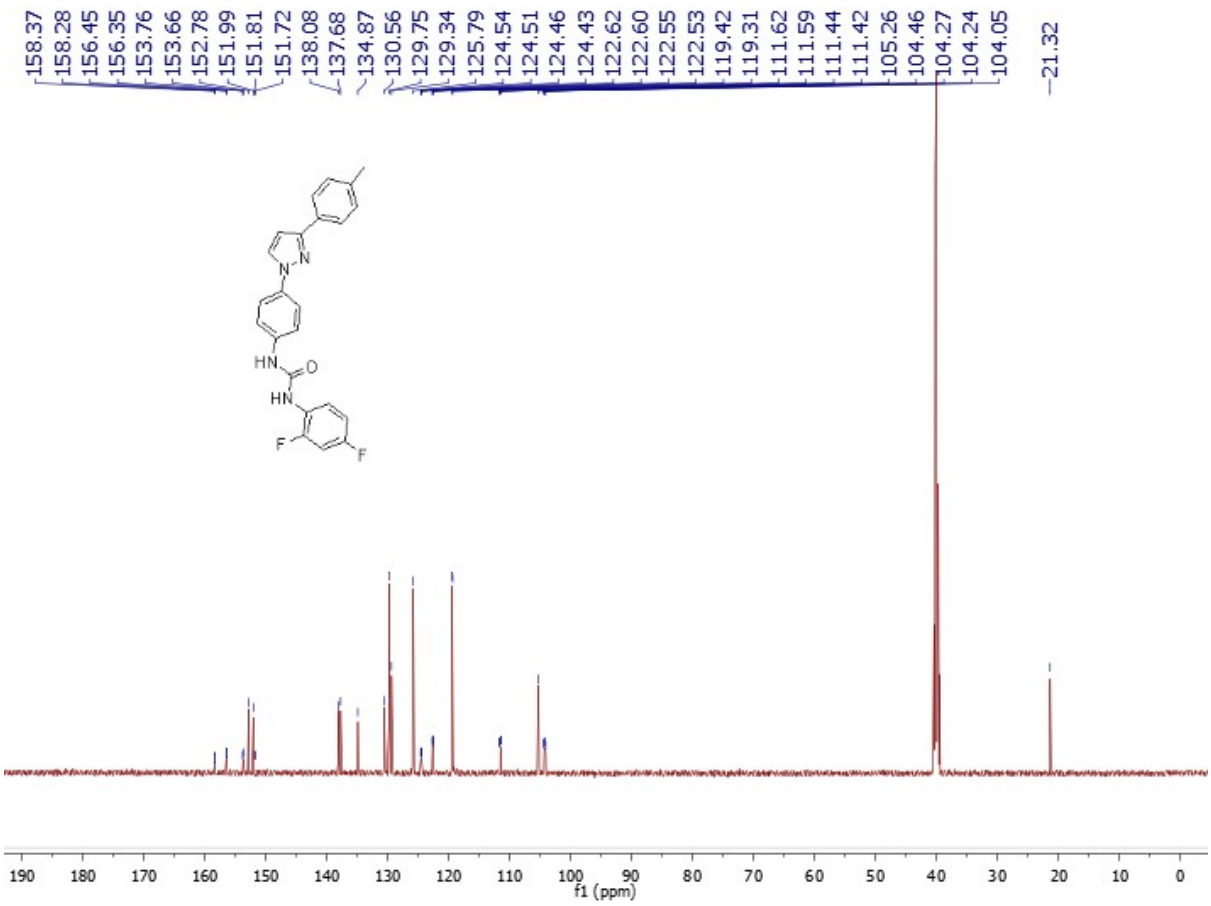
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **9d**



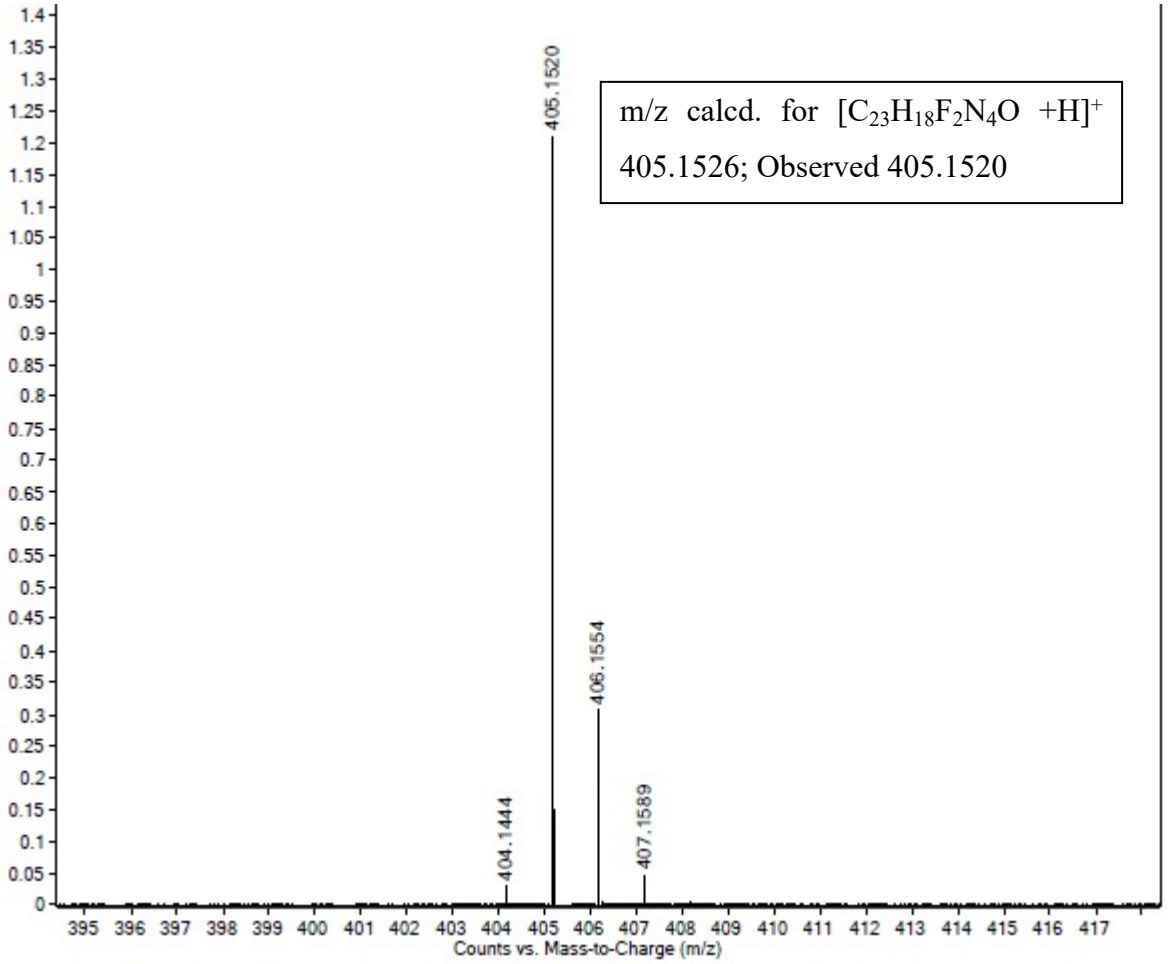
Mass spectrum of compound **9d**



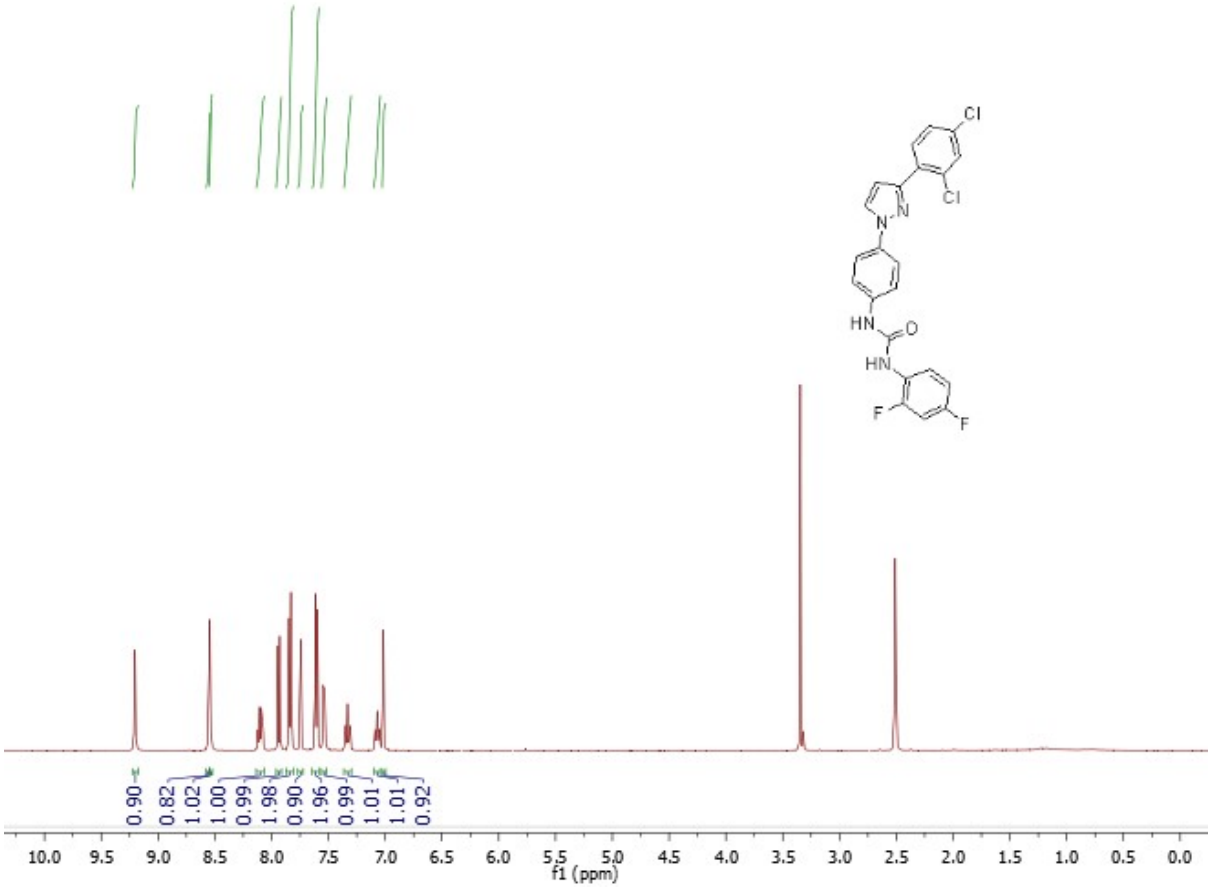
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **9e**



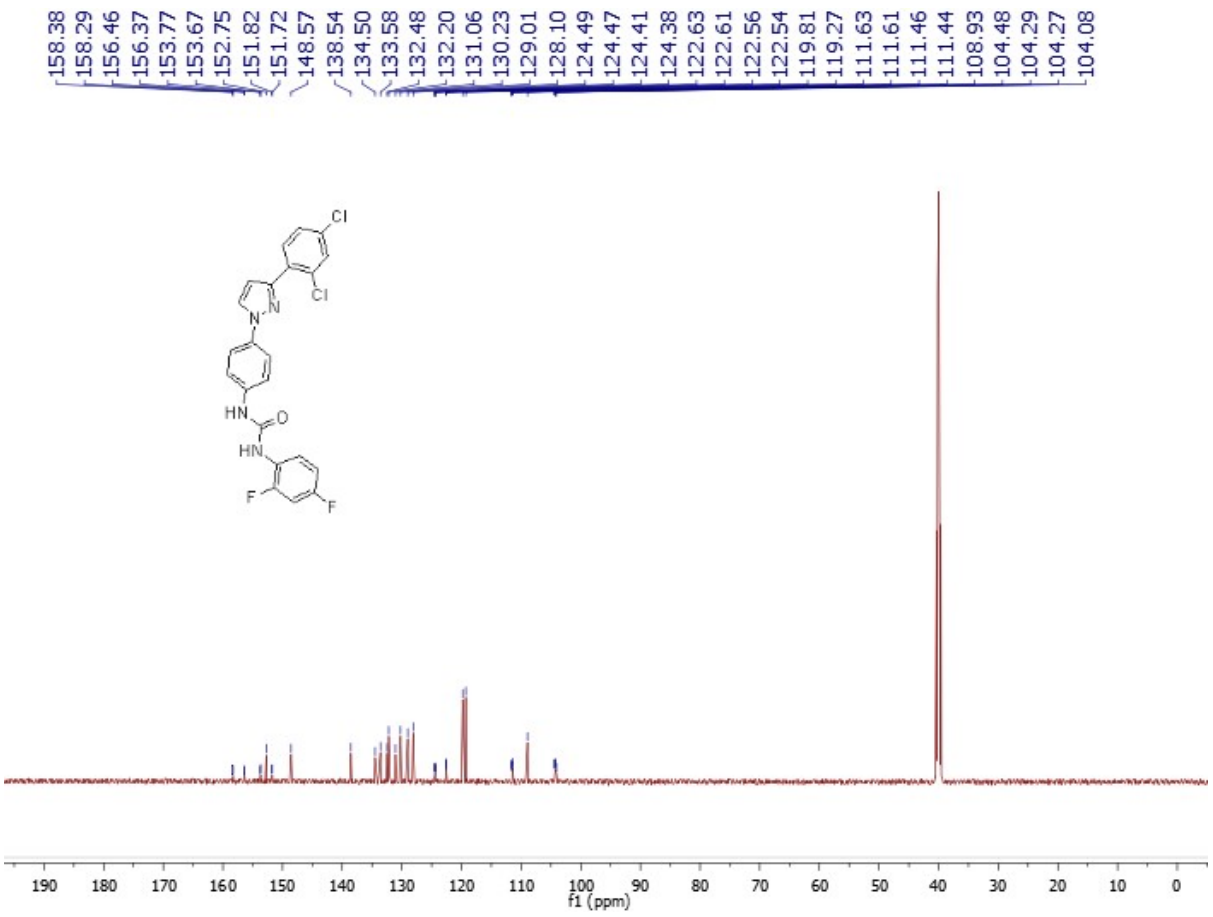
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **9e**



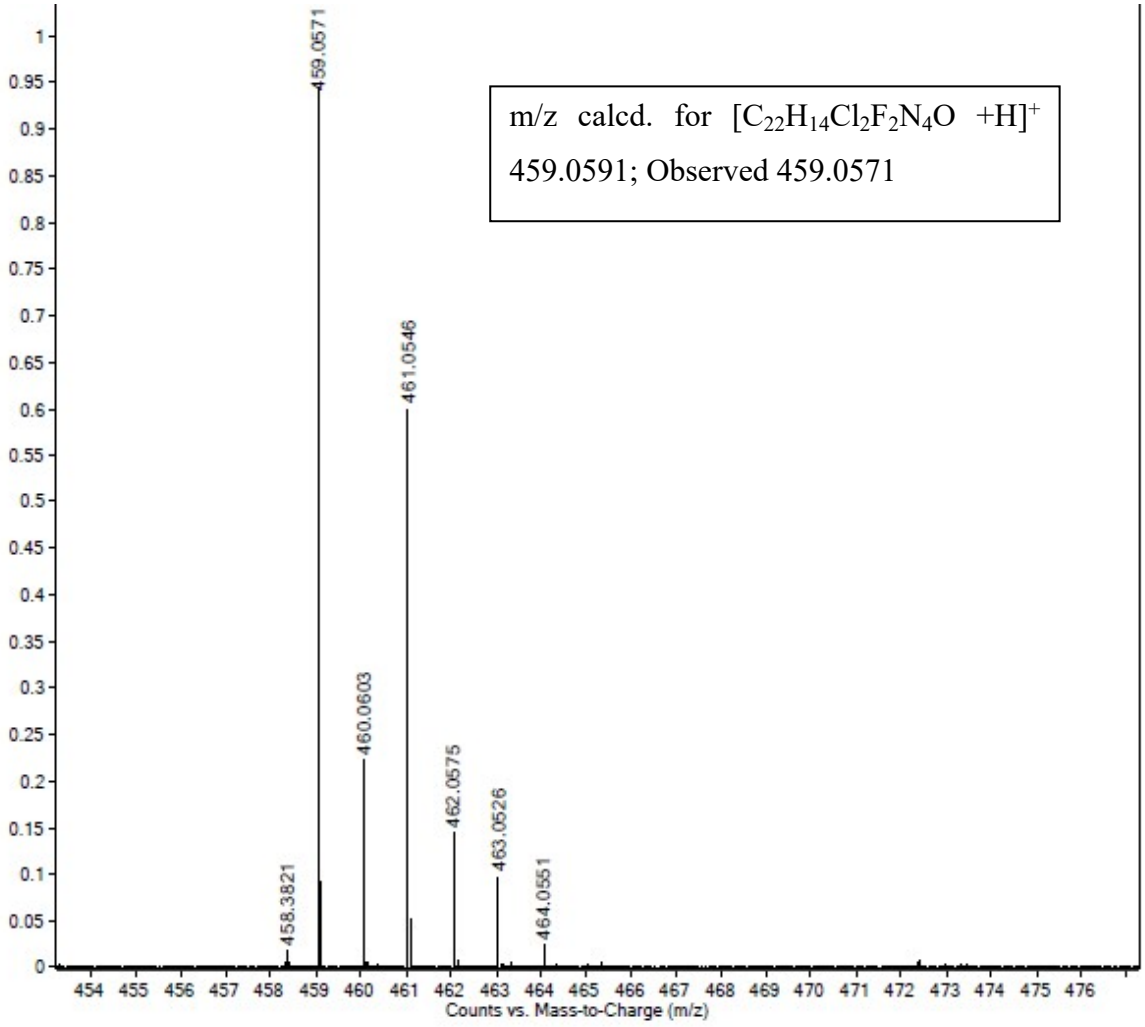
Mass spectrum of compound **9e**



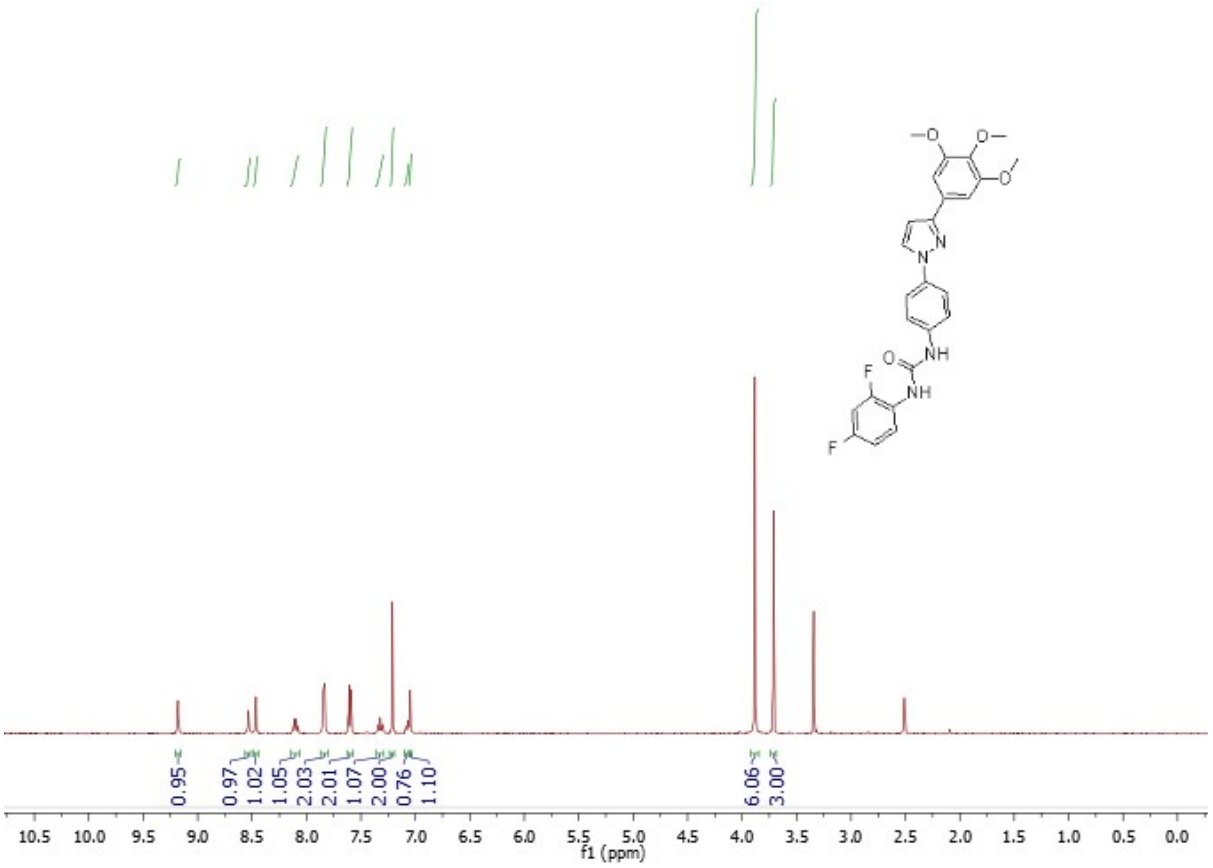
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **9f**



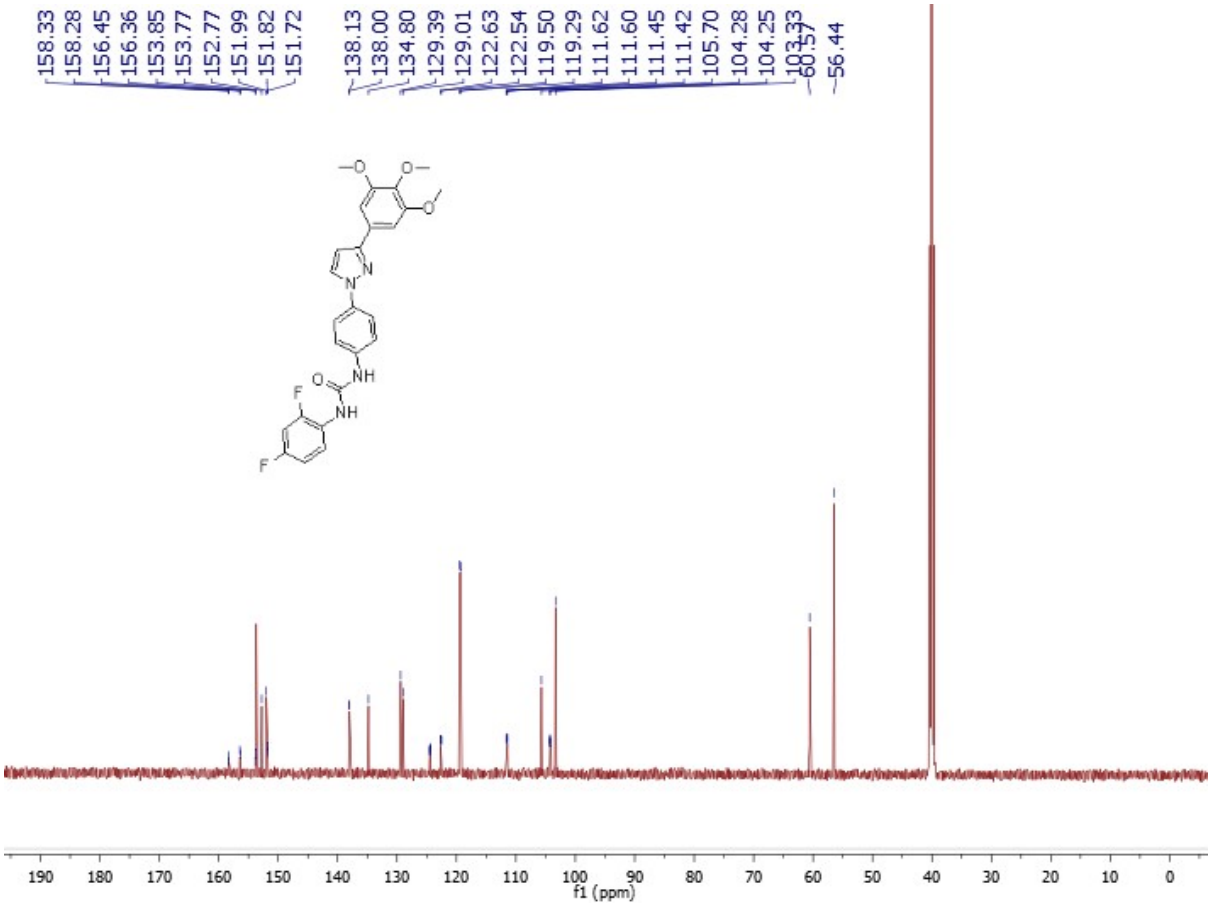
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **9f**



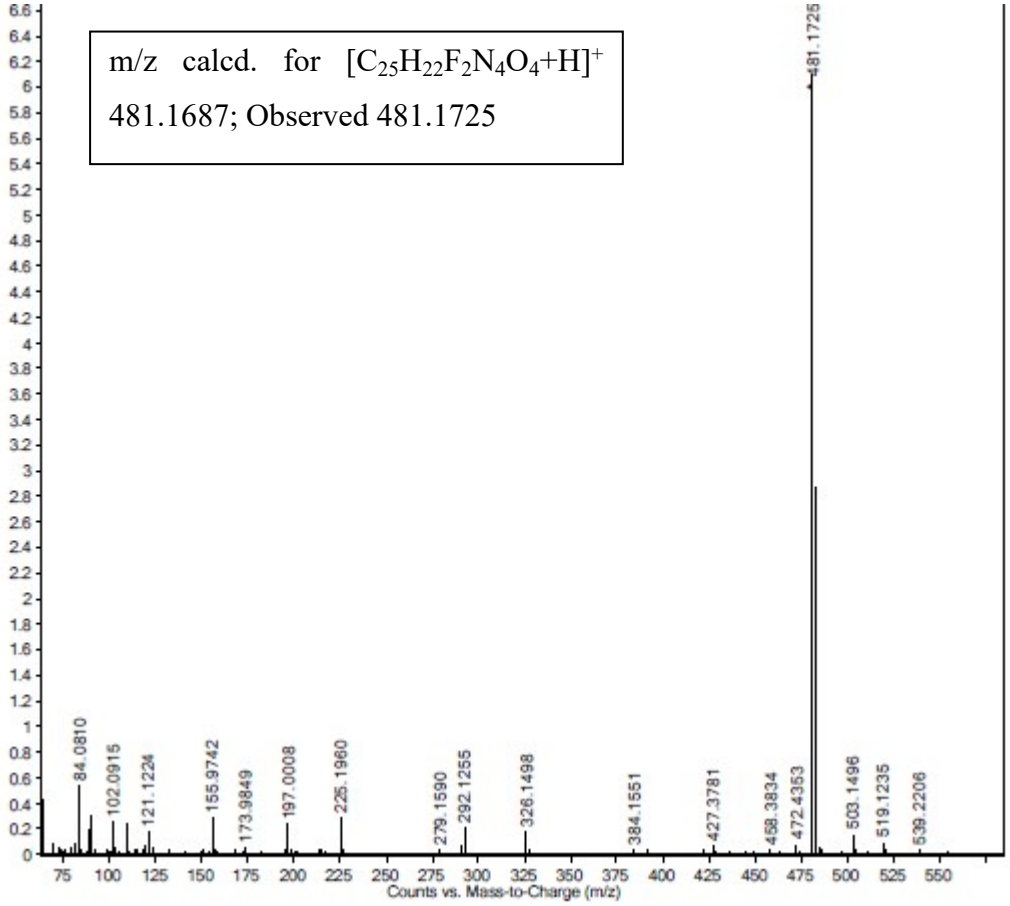
Mass spectrum of compound **9f**



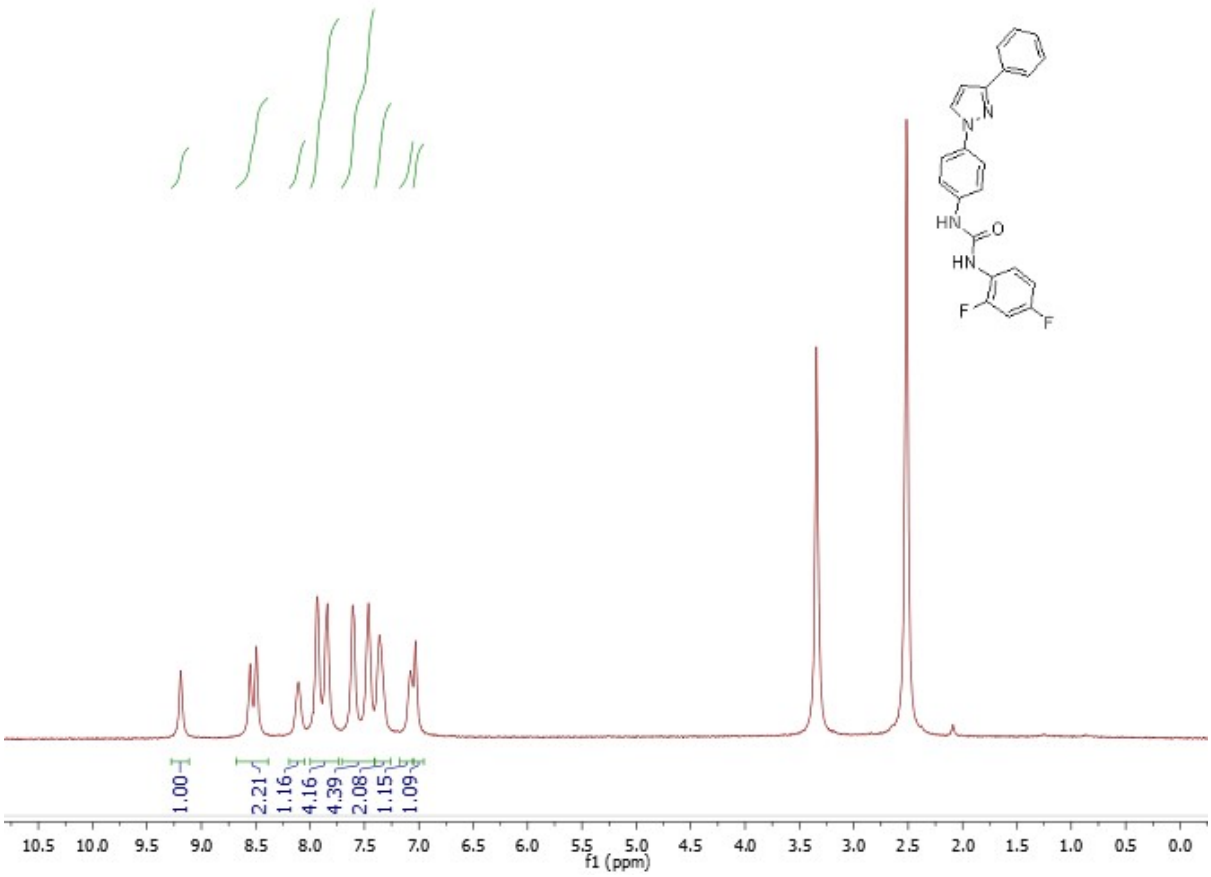
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **9g**



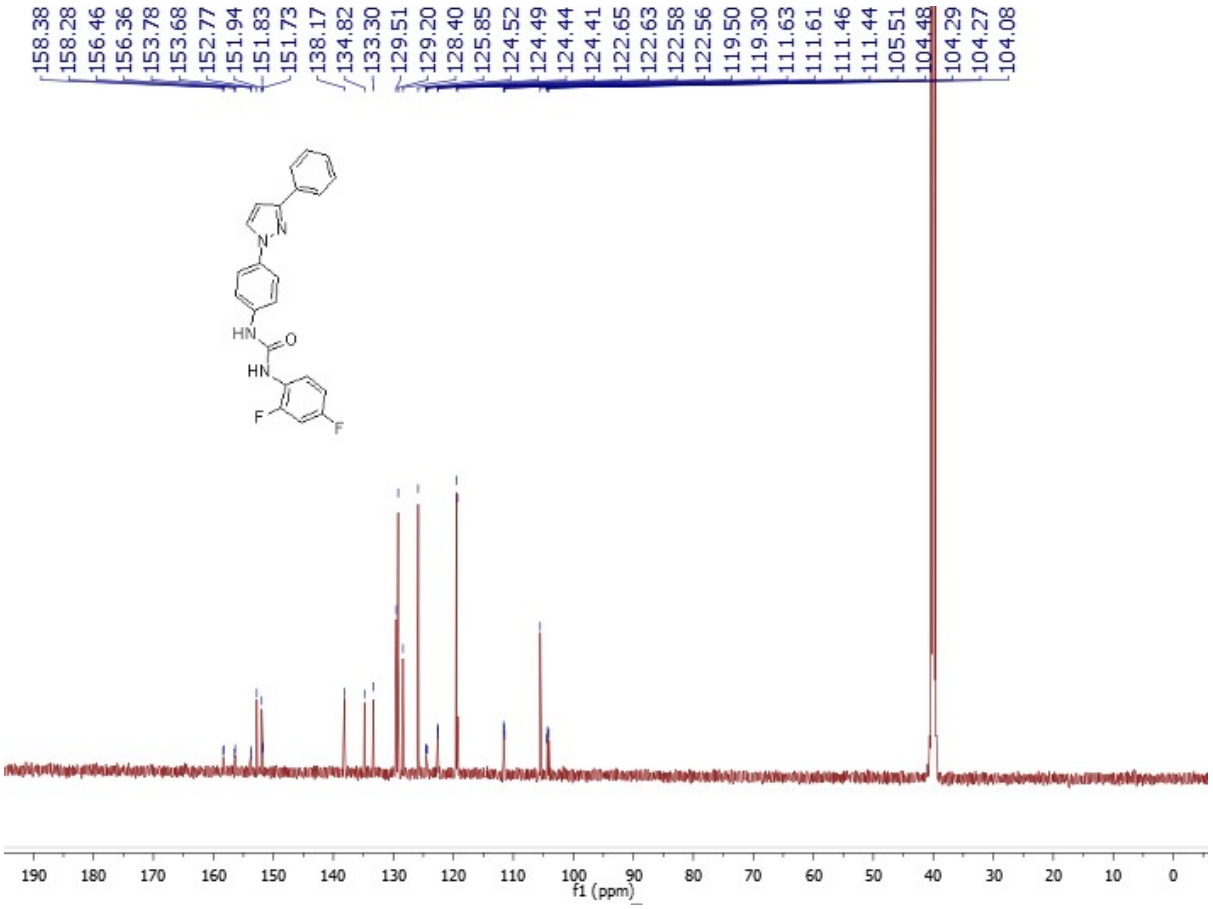
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **9g**



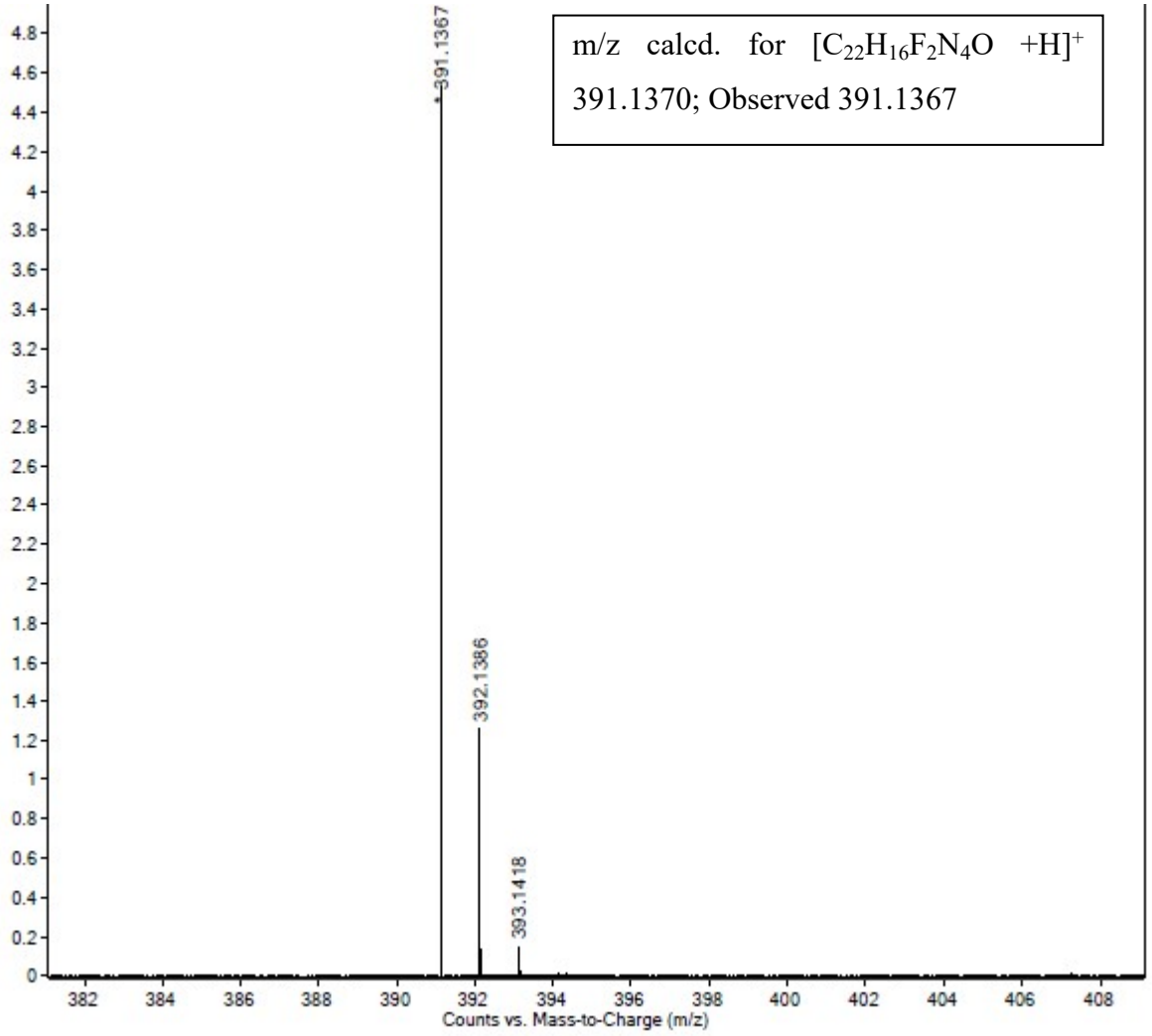
Mass spectrum of compound **9g**



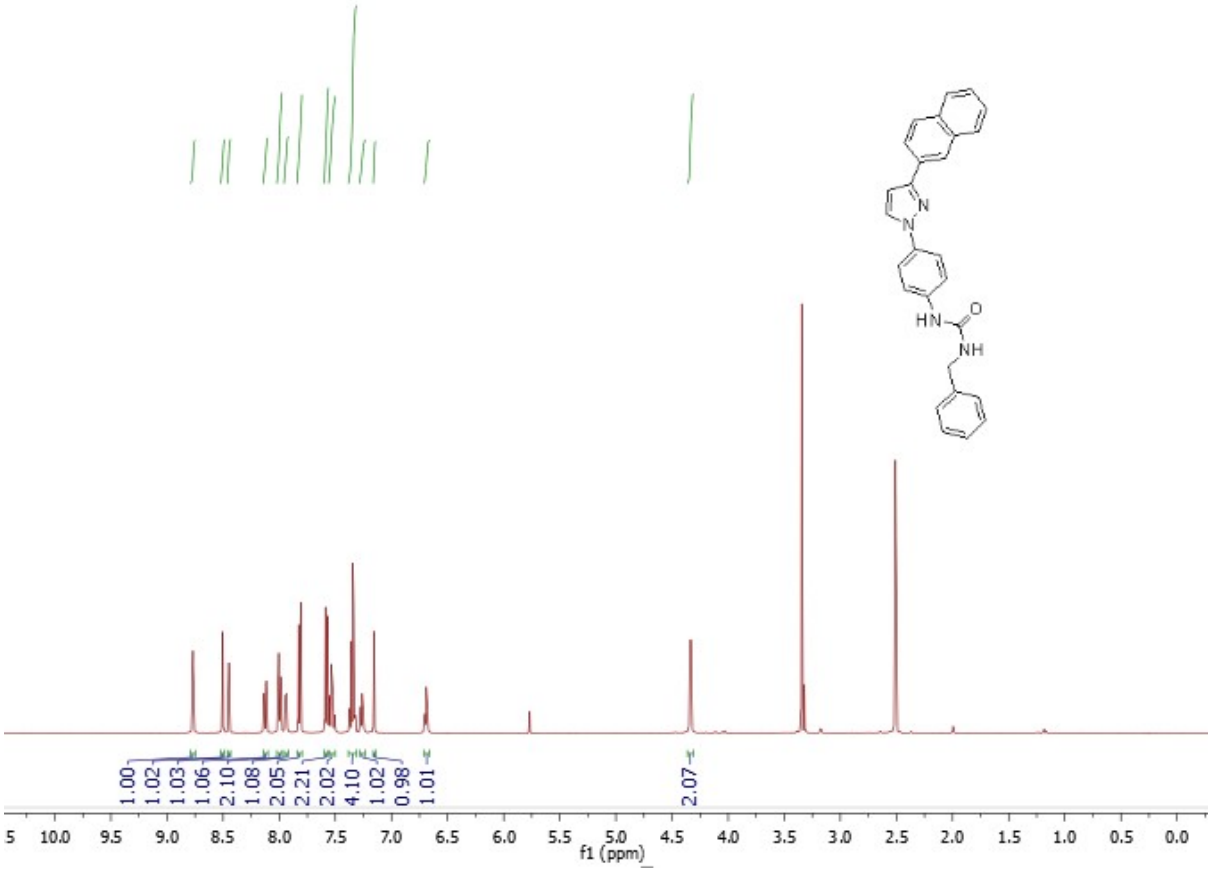
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **9h**



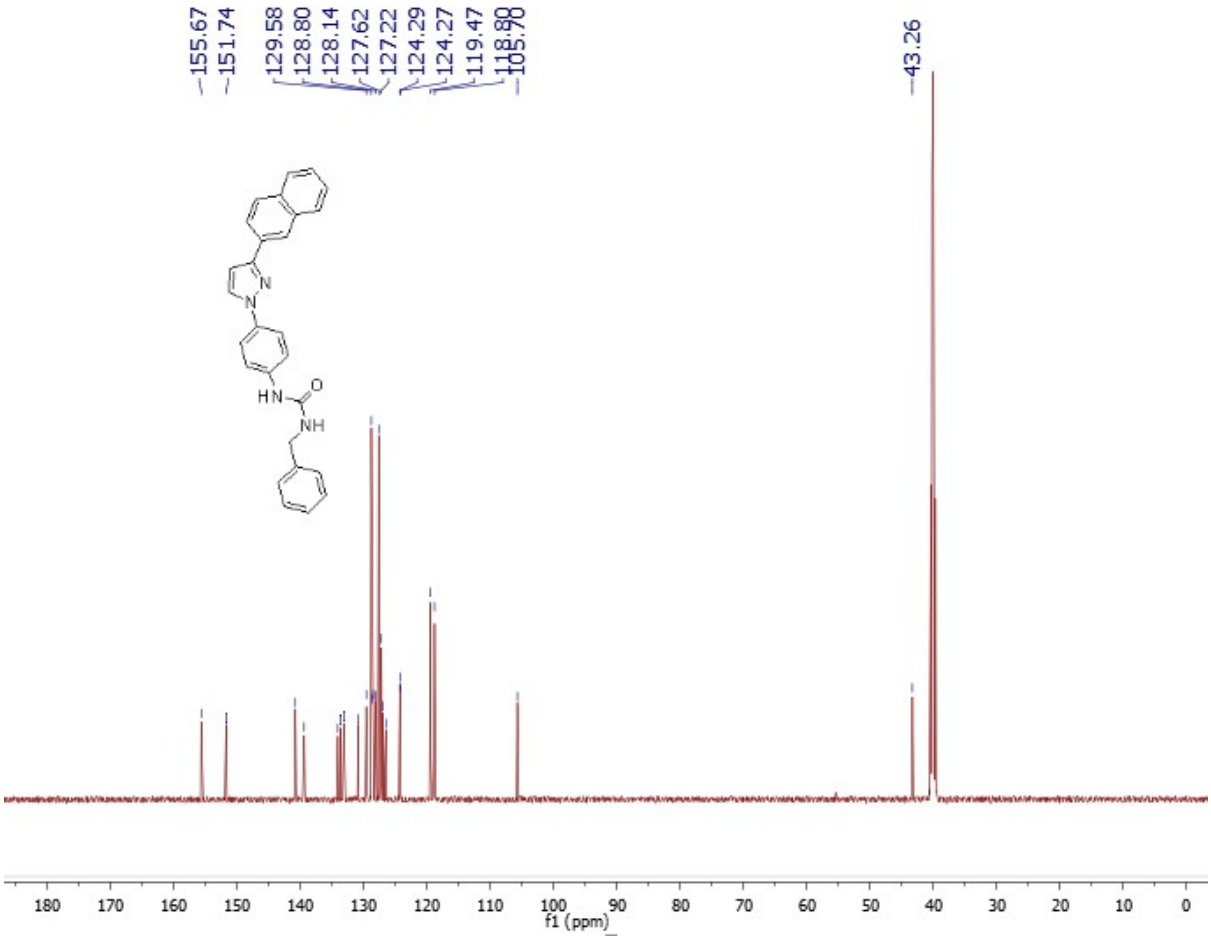
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **9h**



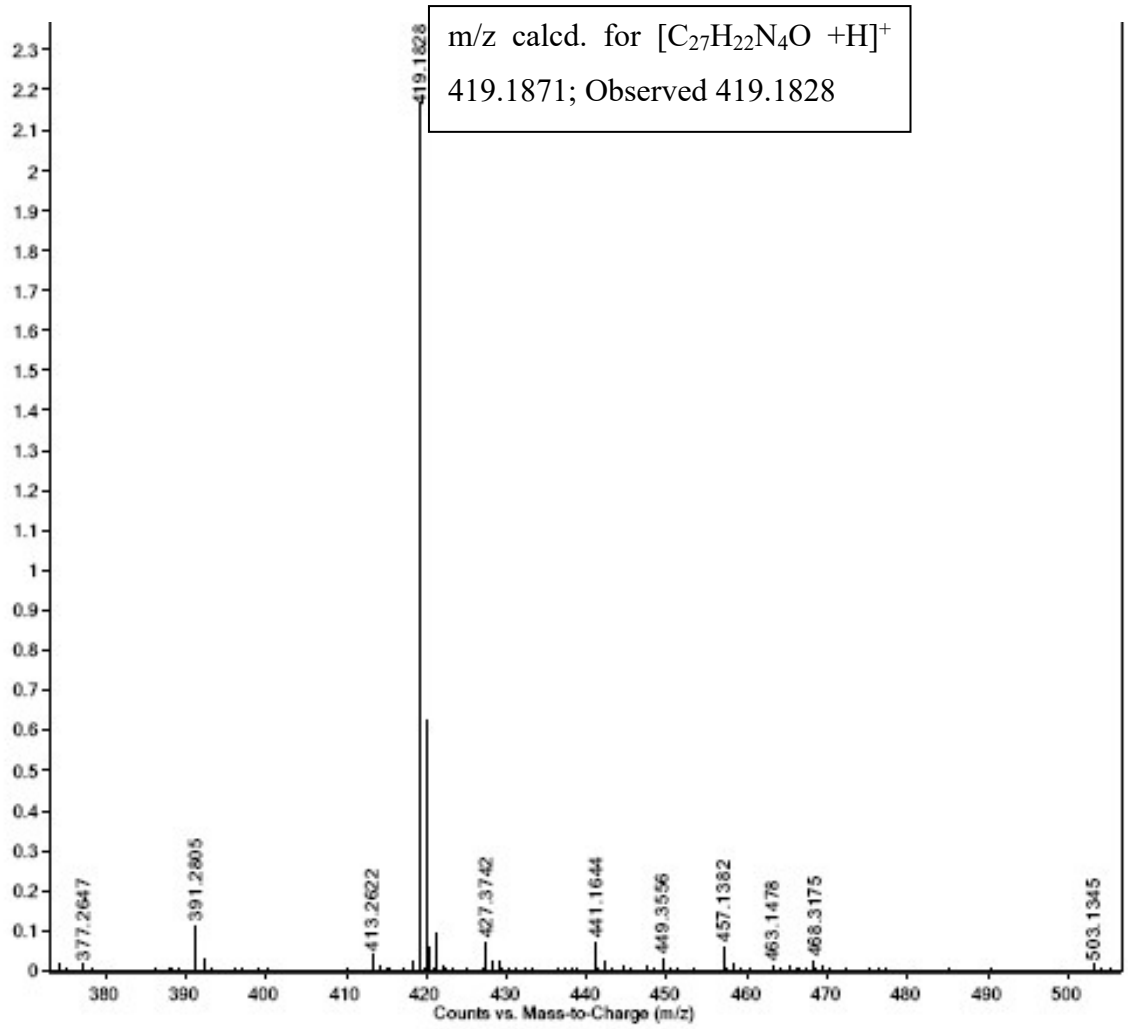
Mass spectrum of compound **9h**



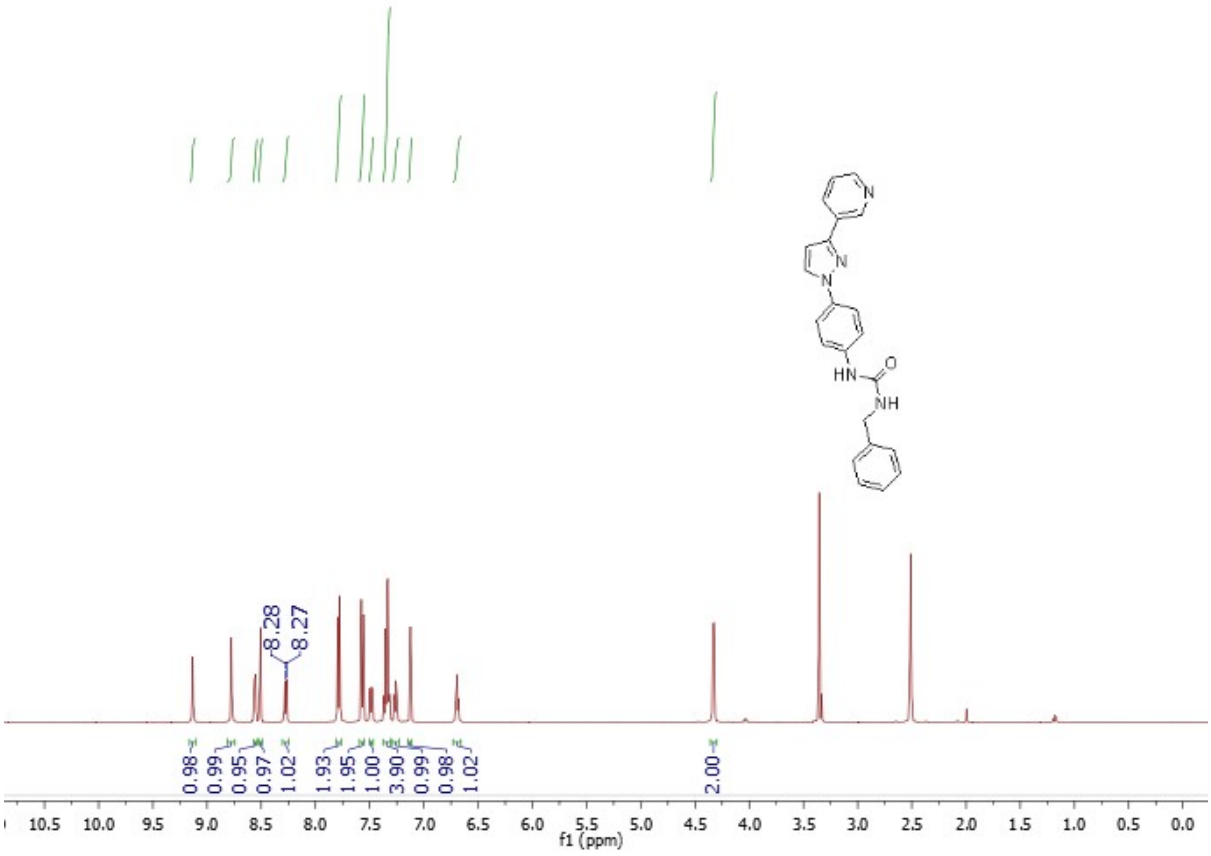
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **10a**



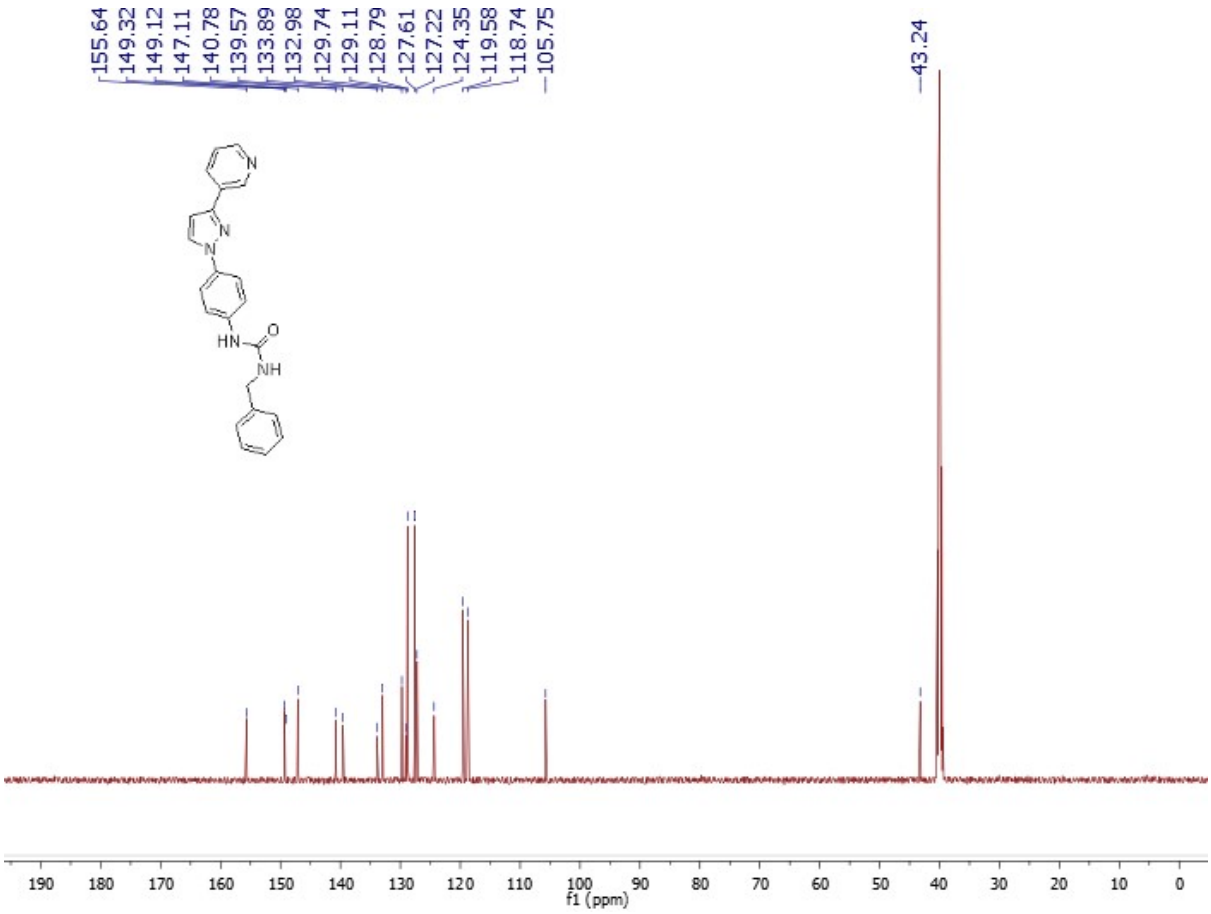
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **10a**



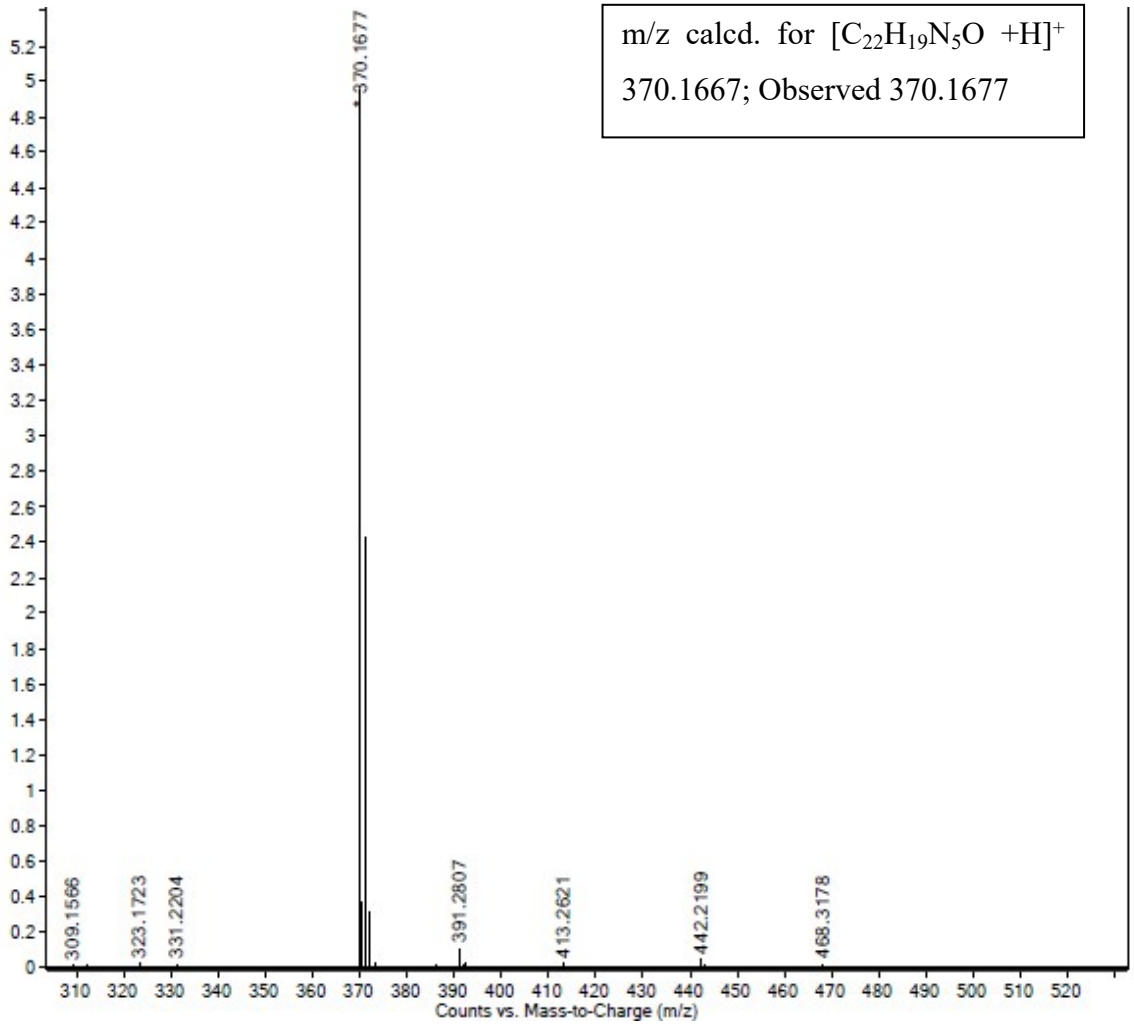
Mass spectrum of compound **10a**



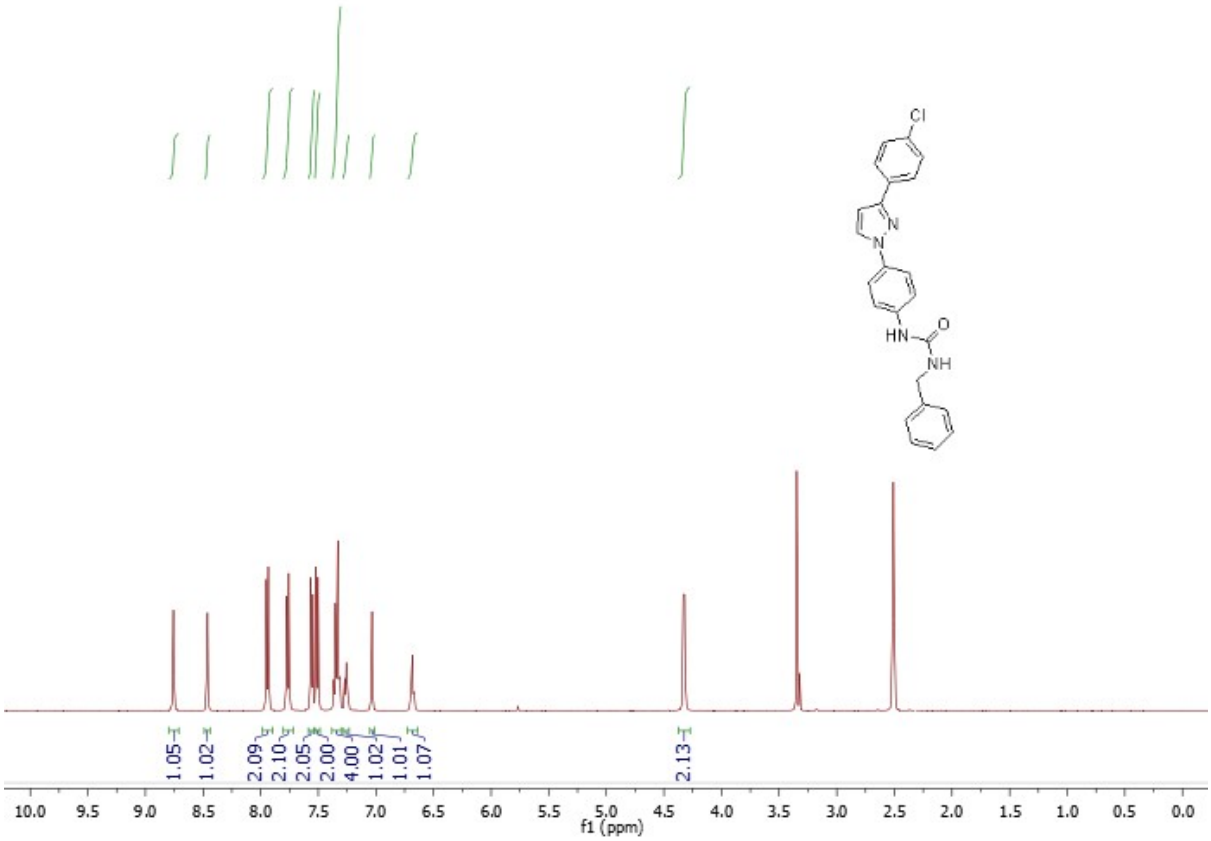
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **10b**



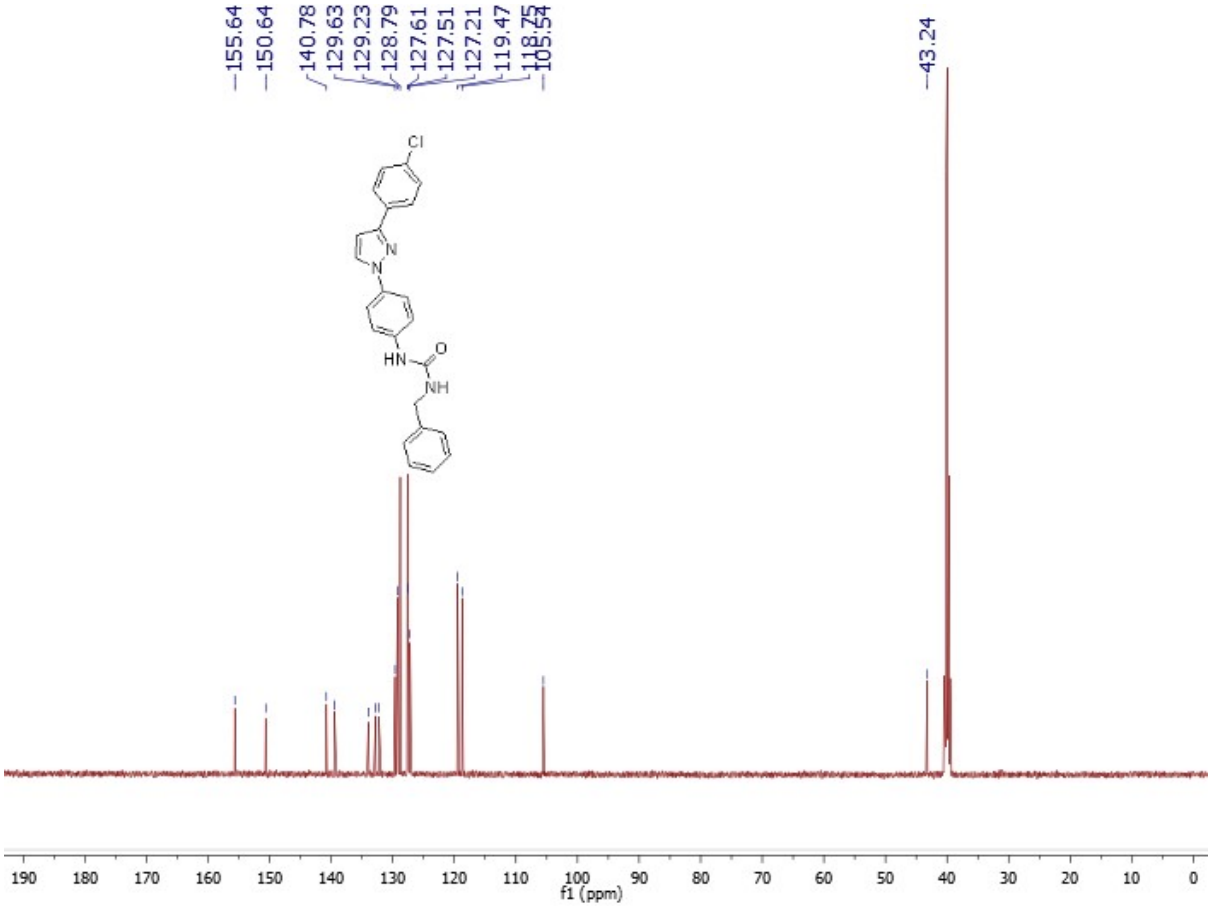
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **10b**



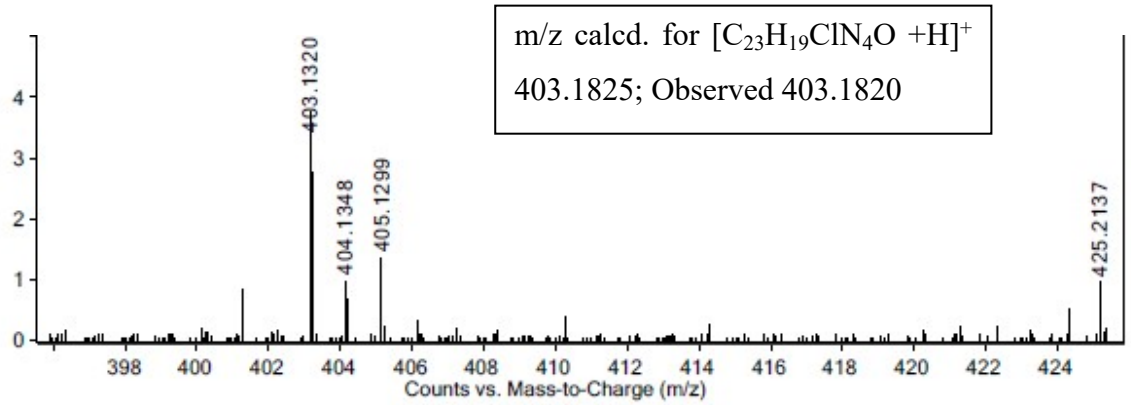
Mass spectrum of compound **10b**



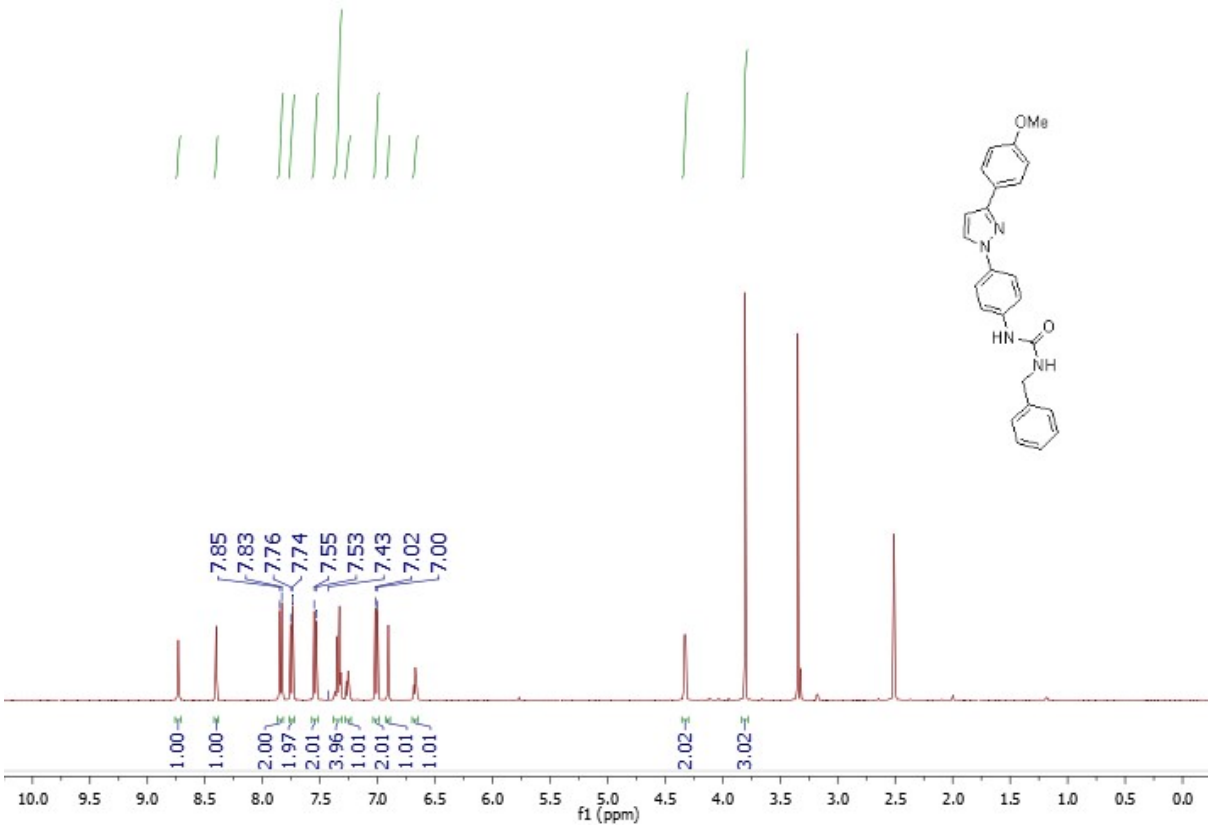
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **10c**



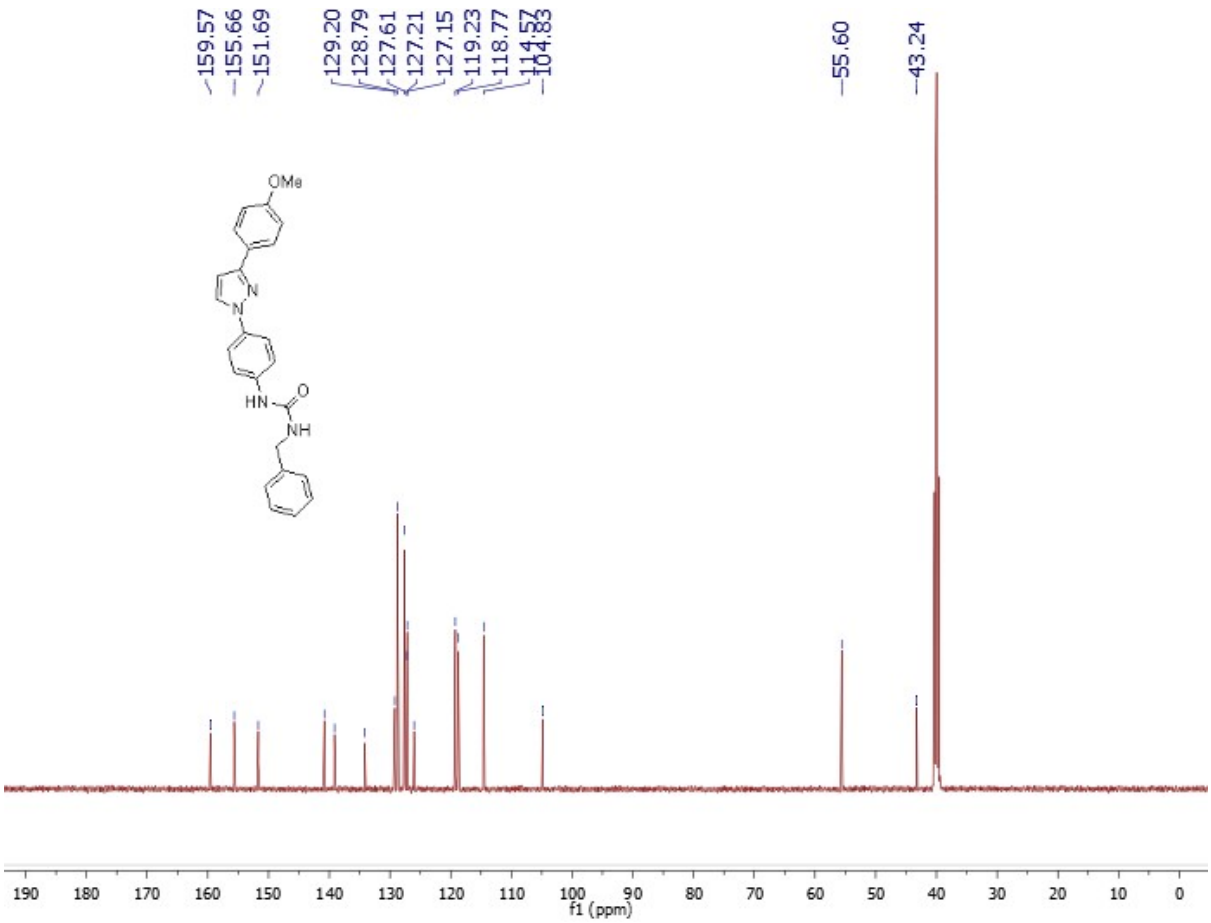
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **10c**



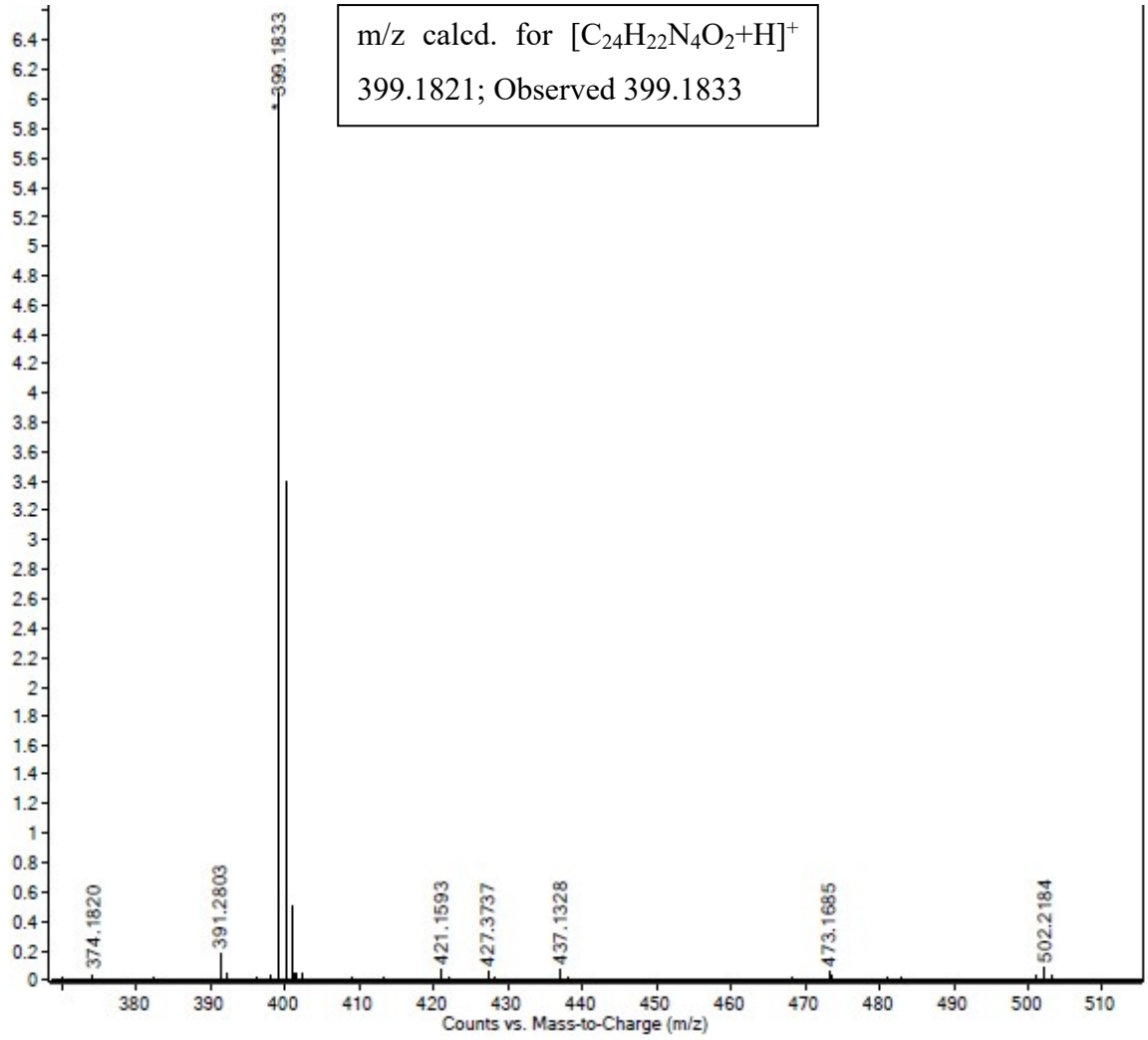
Mass spectrum of compound **10c**



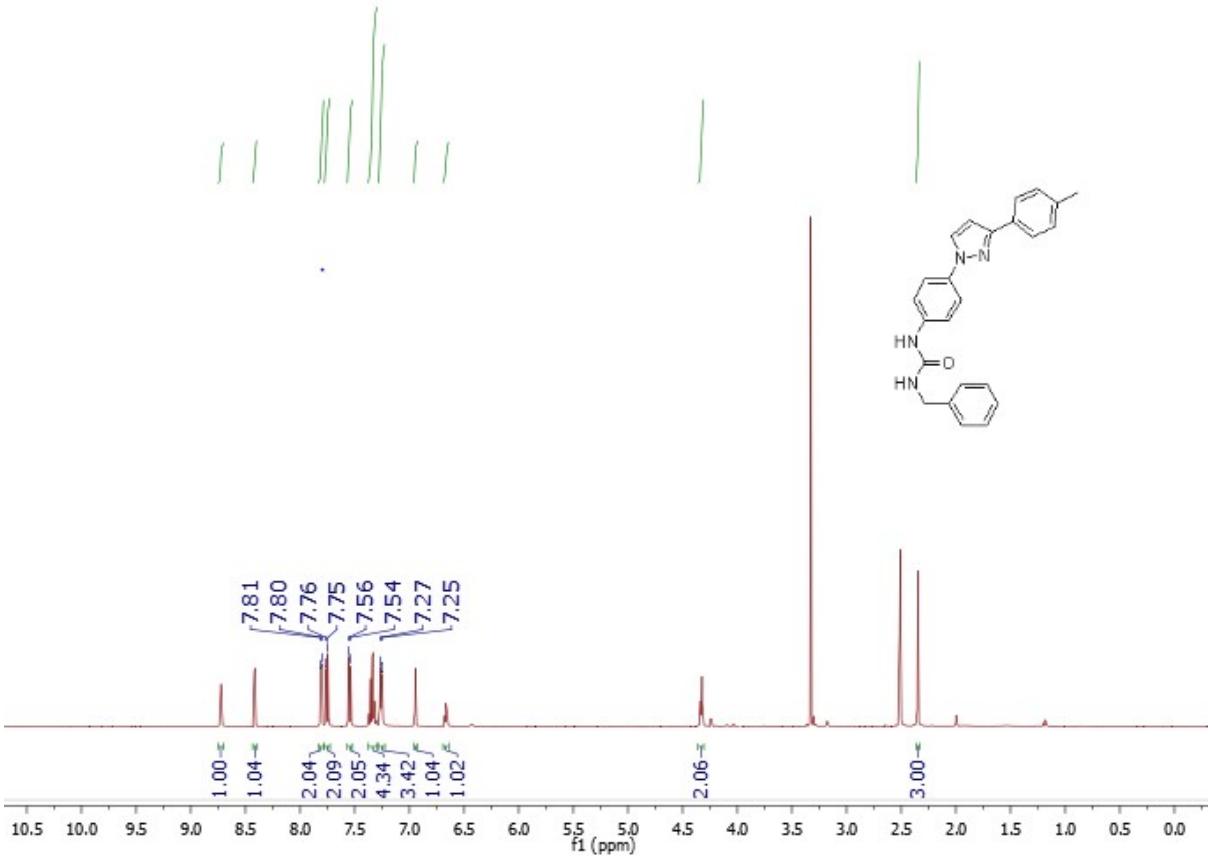
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **10d**



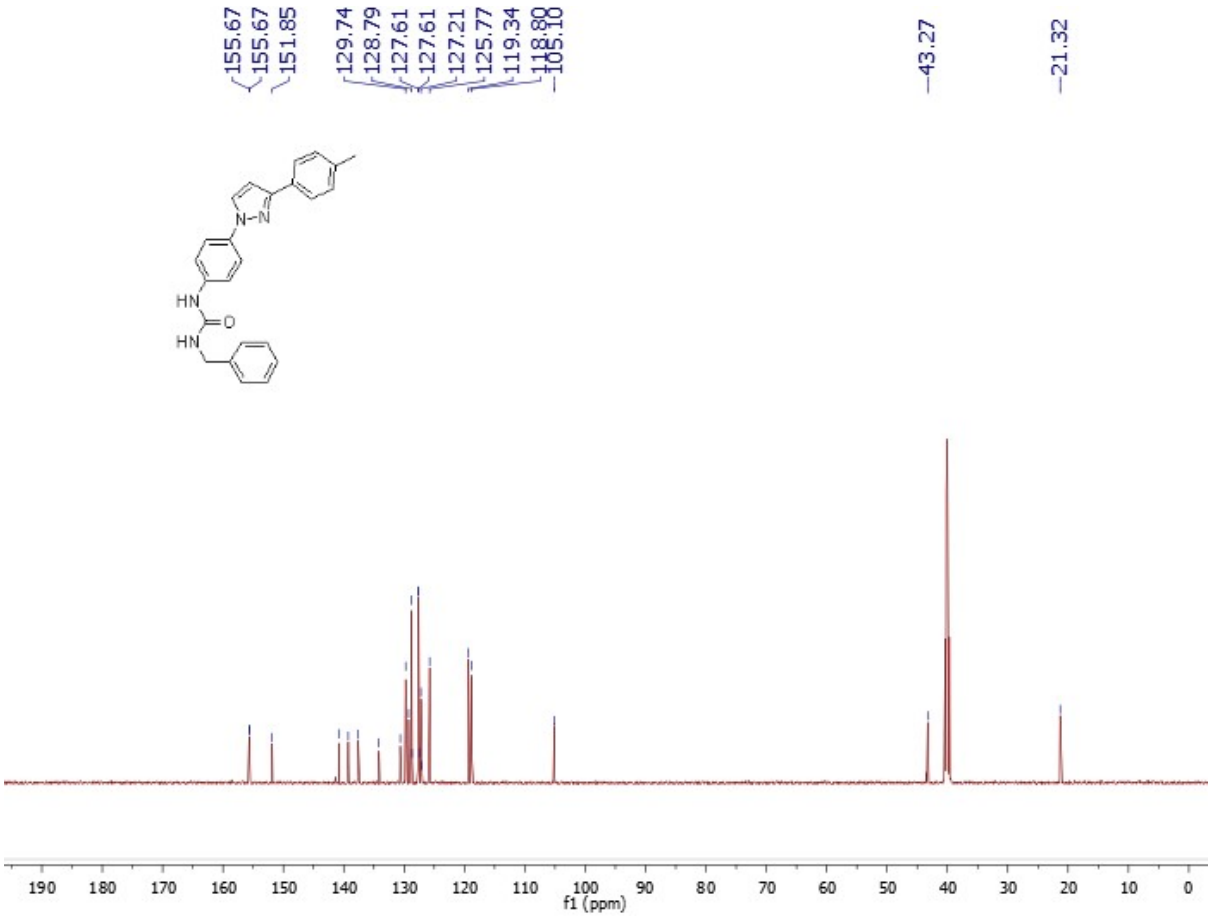
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **10d**



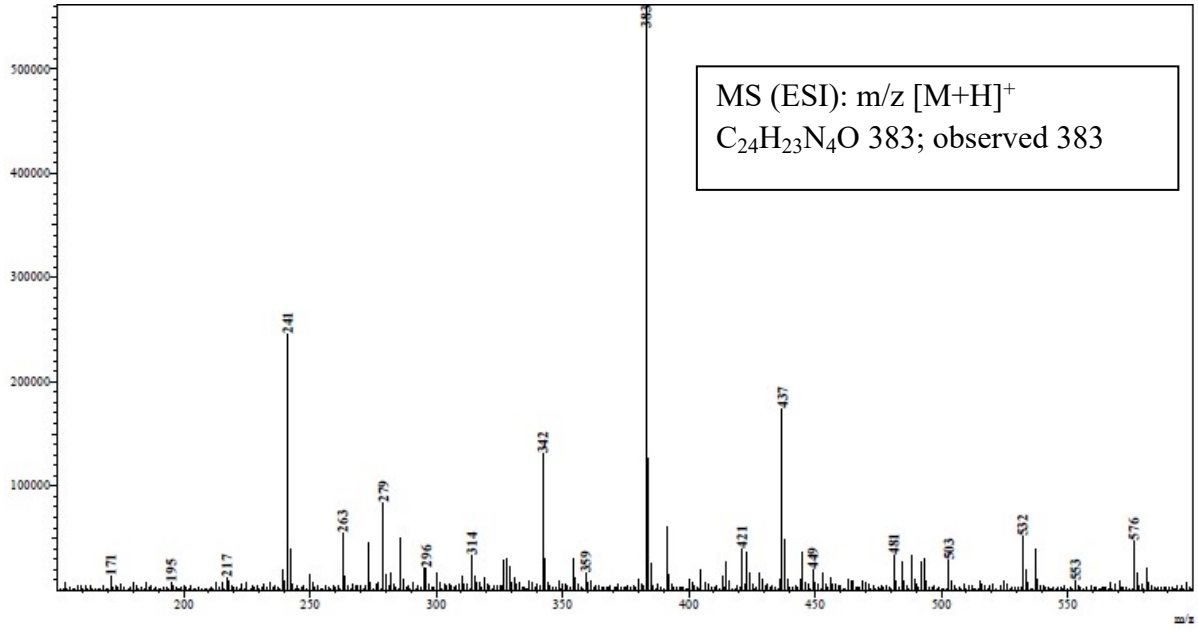
Mass spectrum of compound **10d**



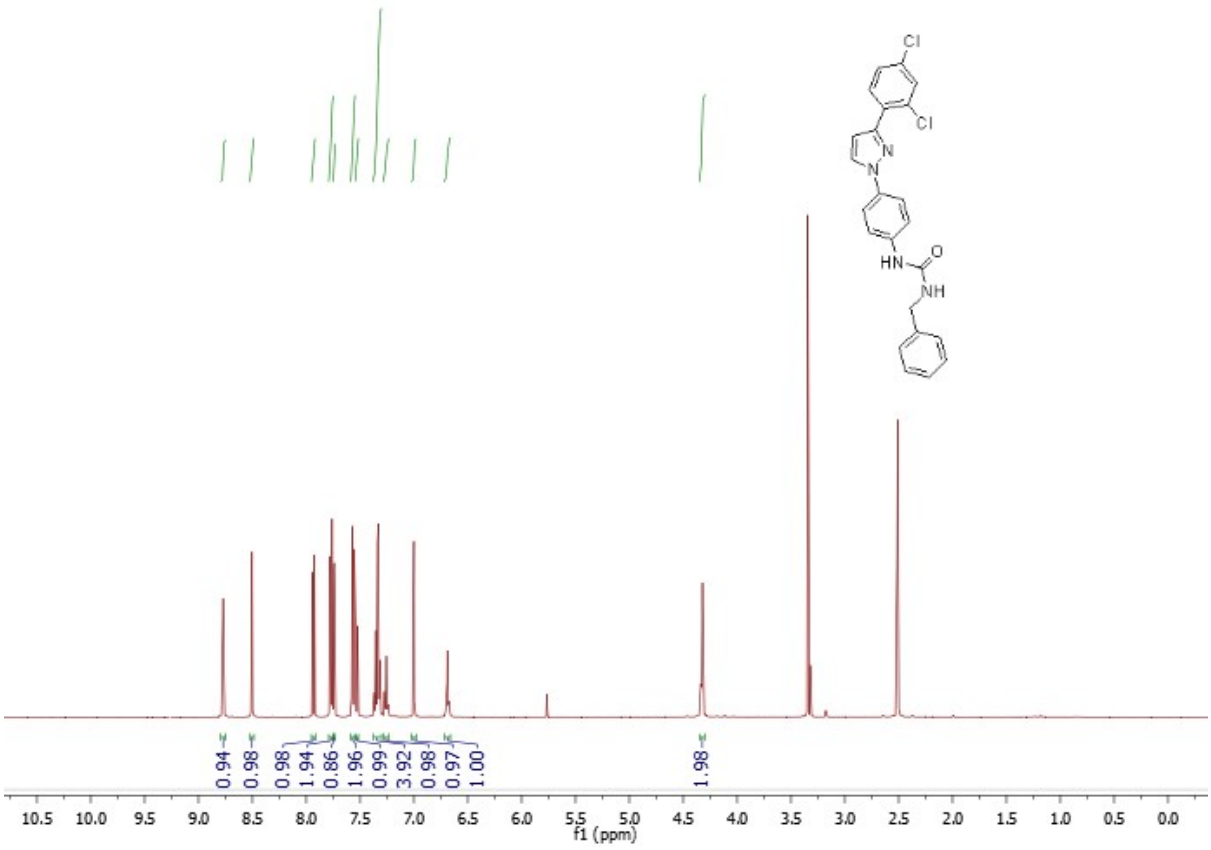
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **10e**



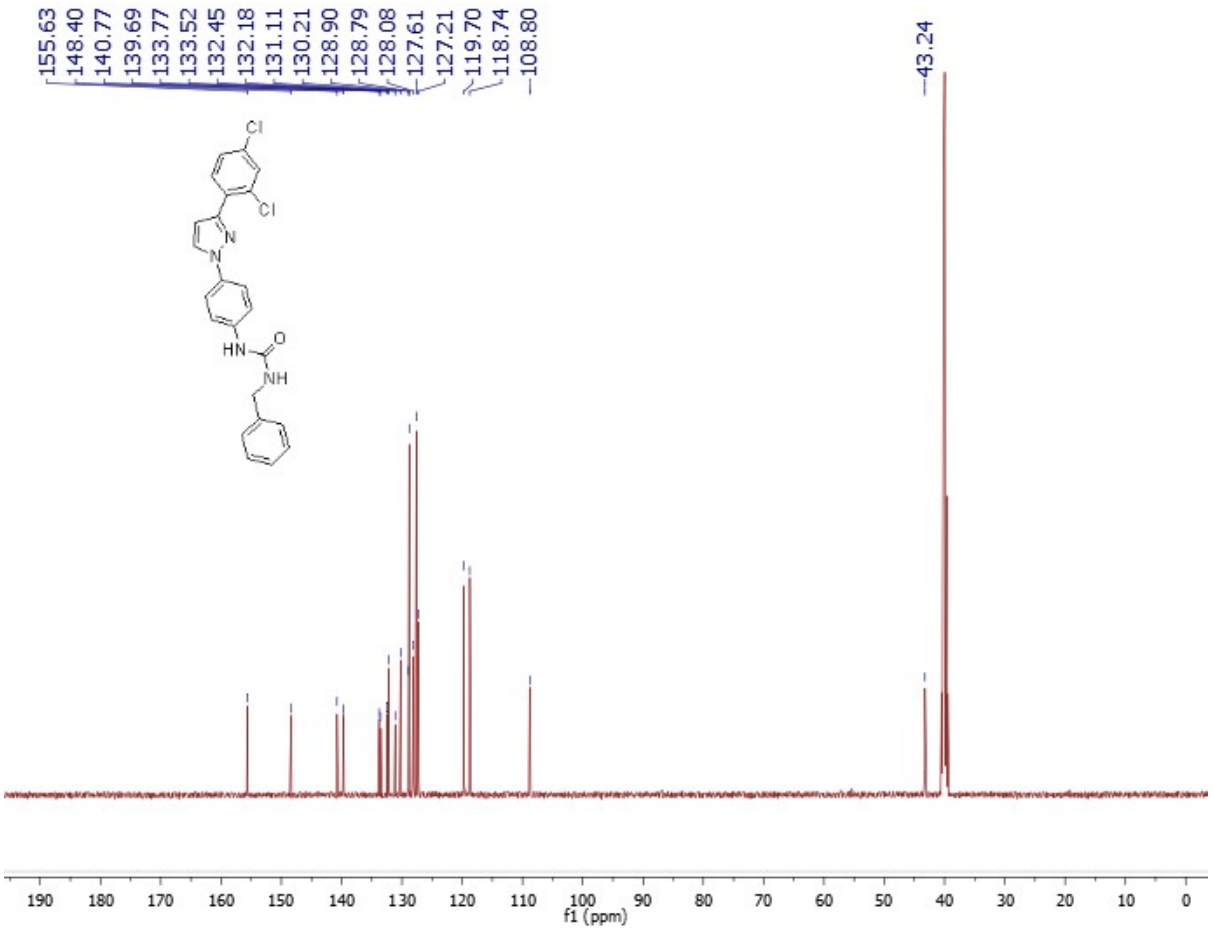
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **10e**



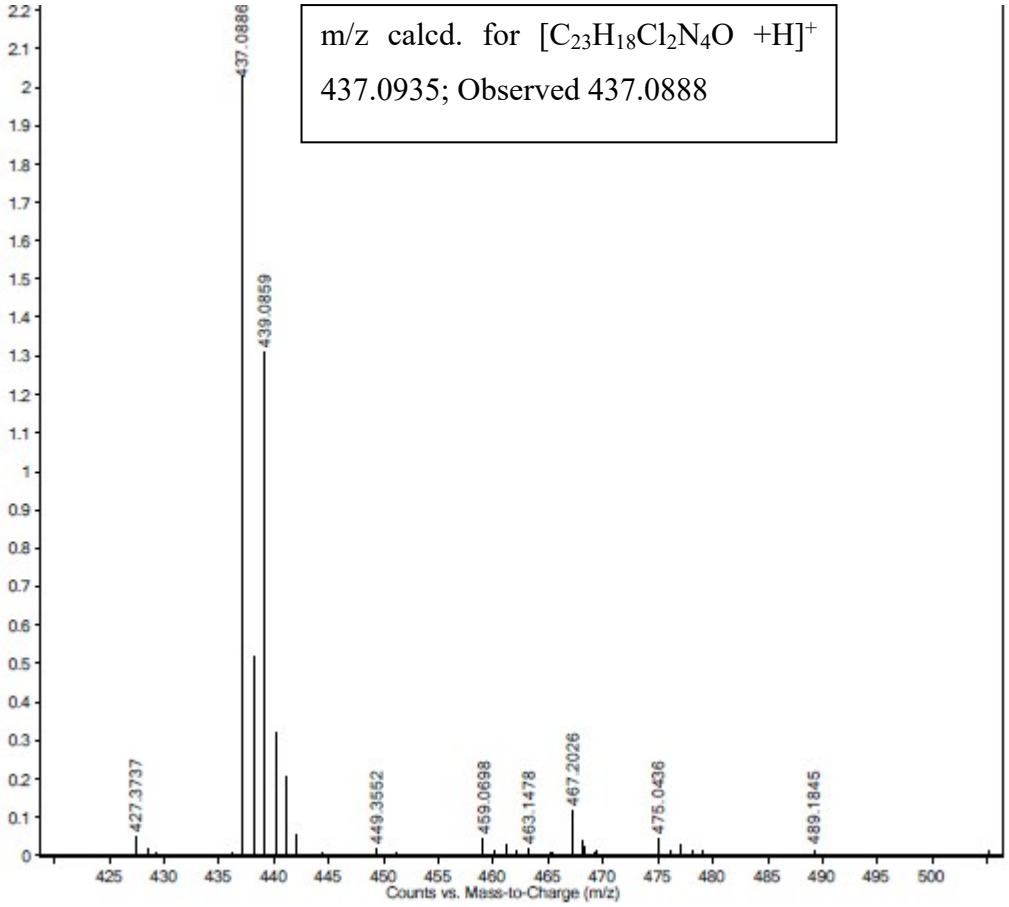
Mass spectrum of compound **10e**



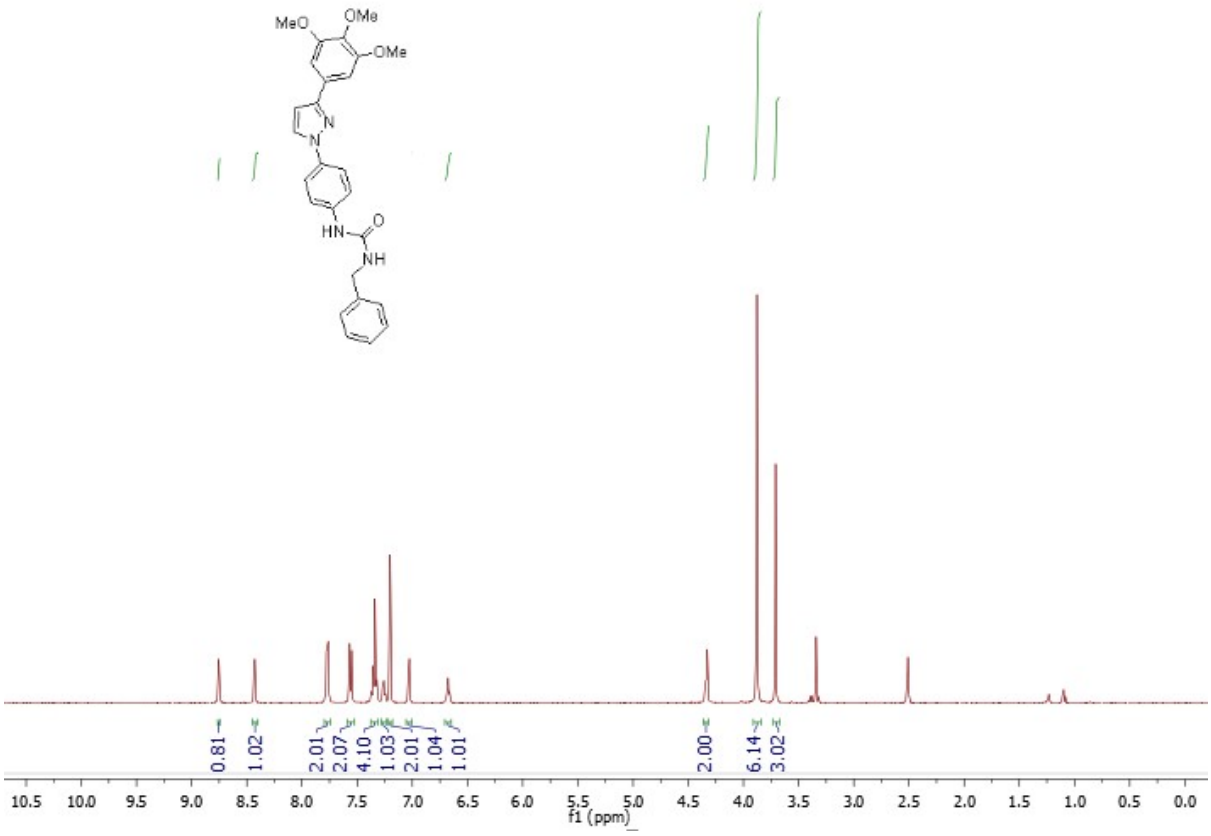
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **10f**



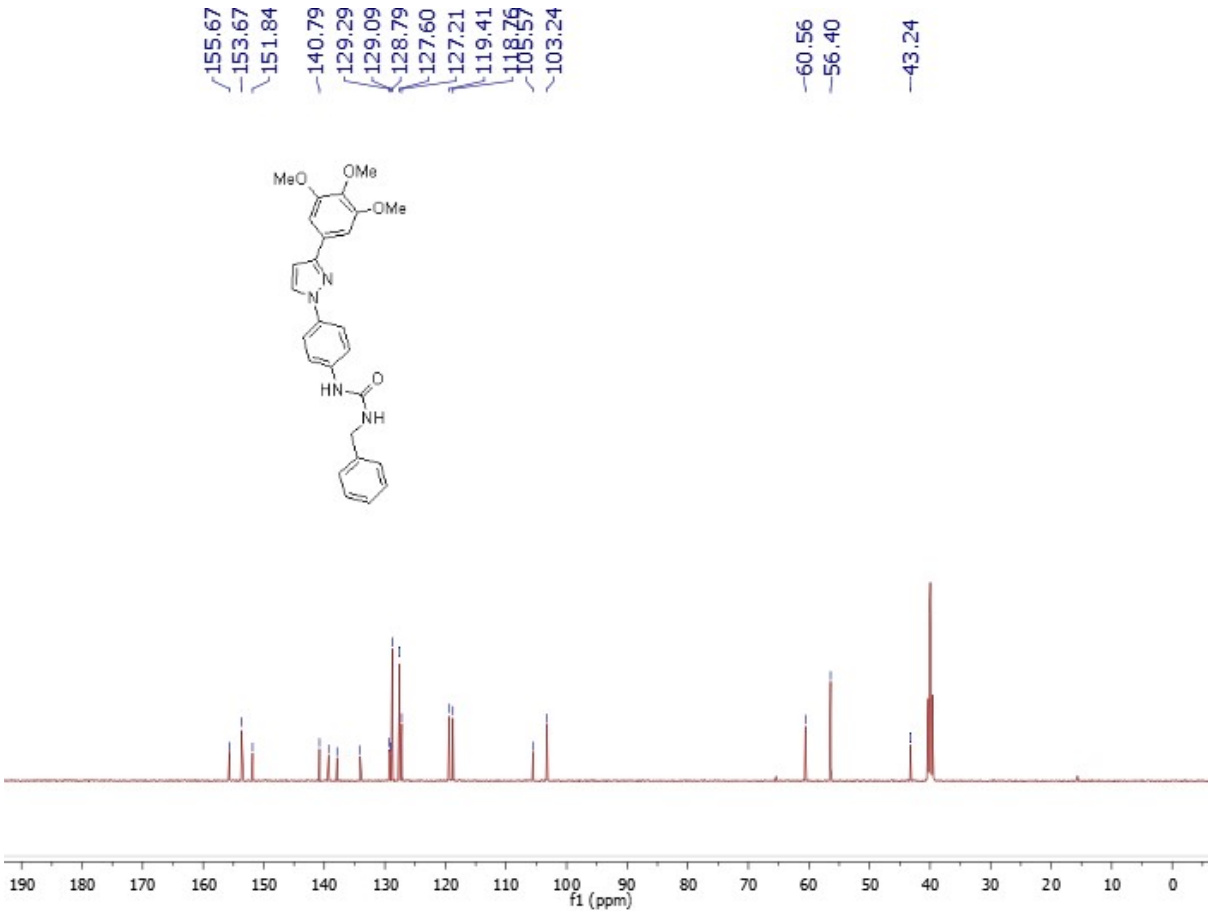
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **10f**



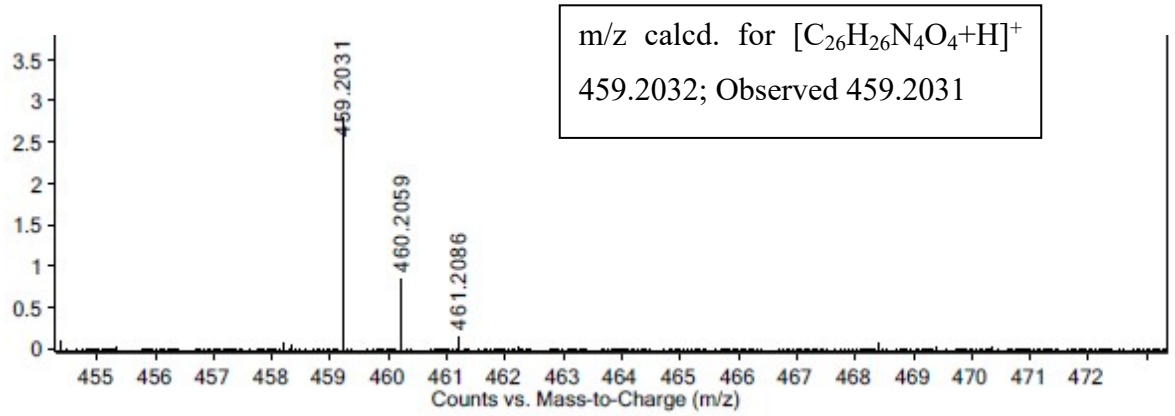
Mass spectrum of compound **10f**



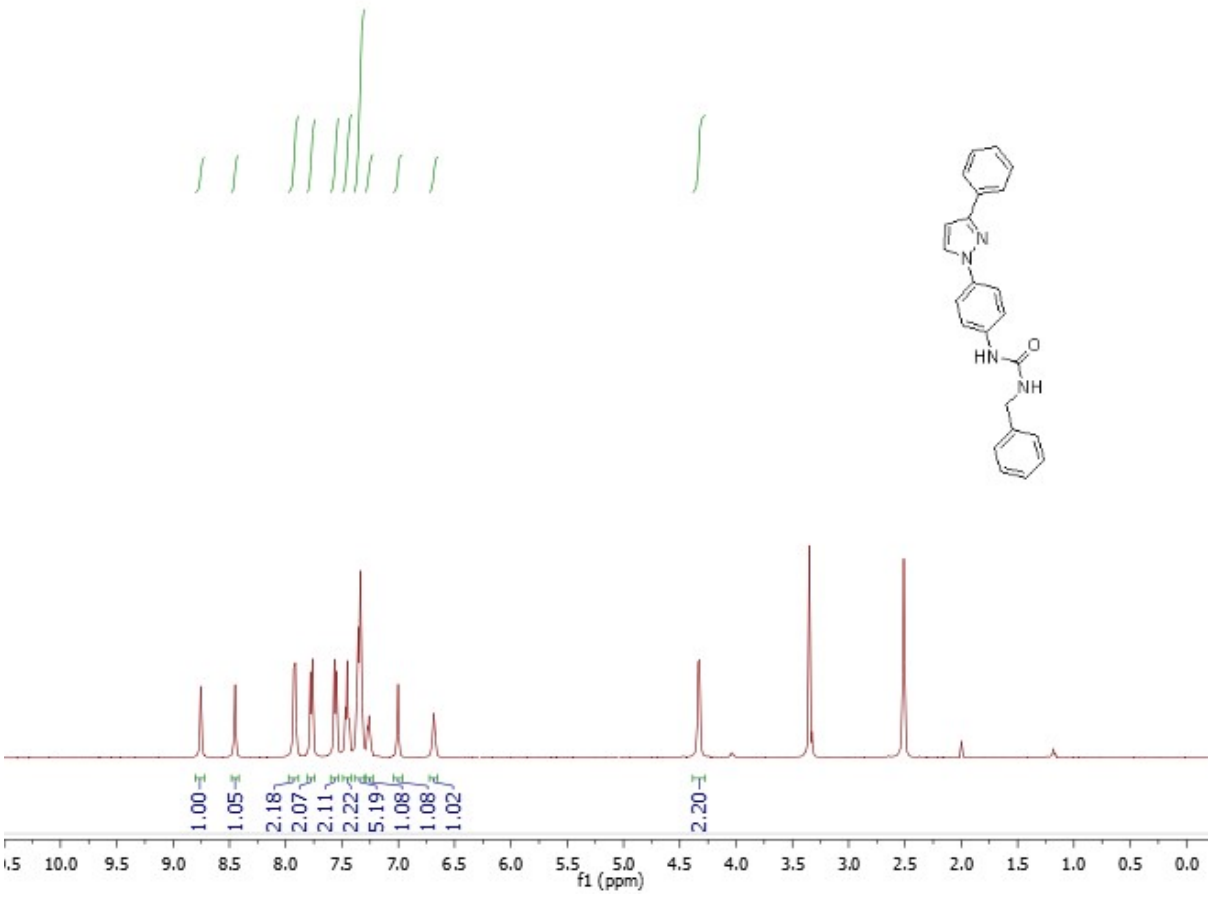
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **10g**



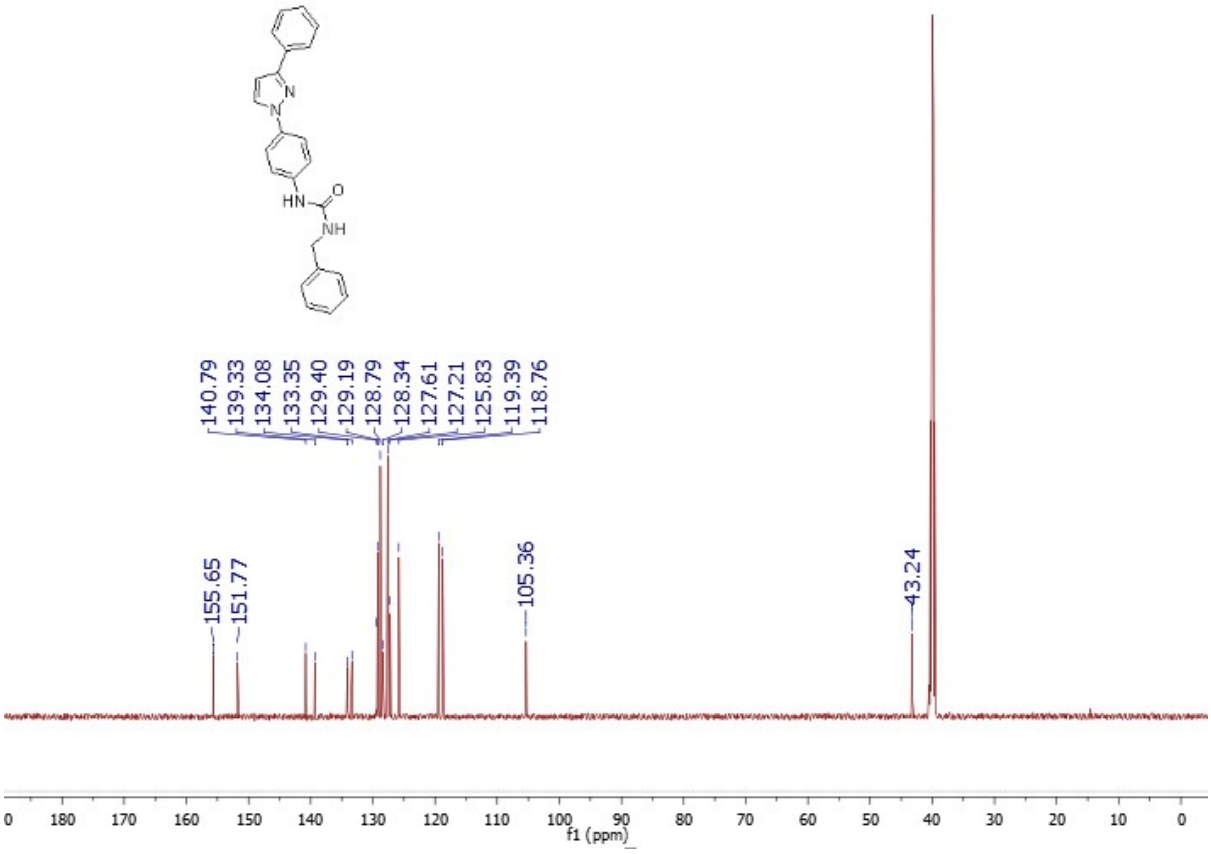
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **10g**



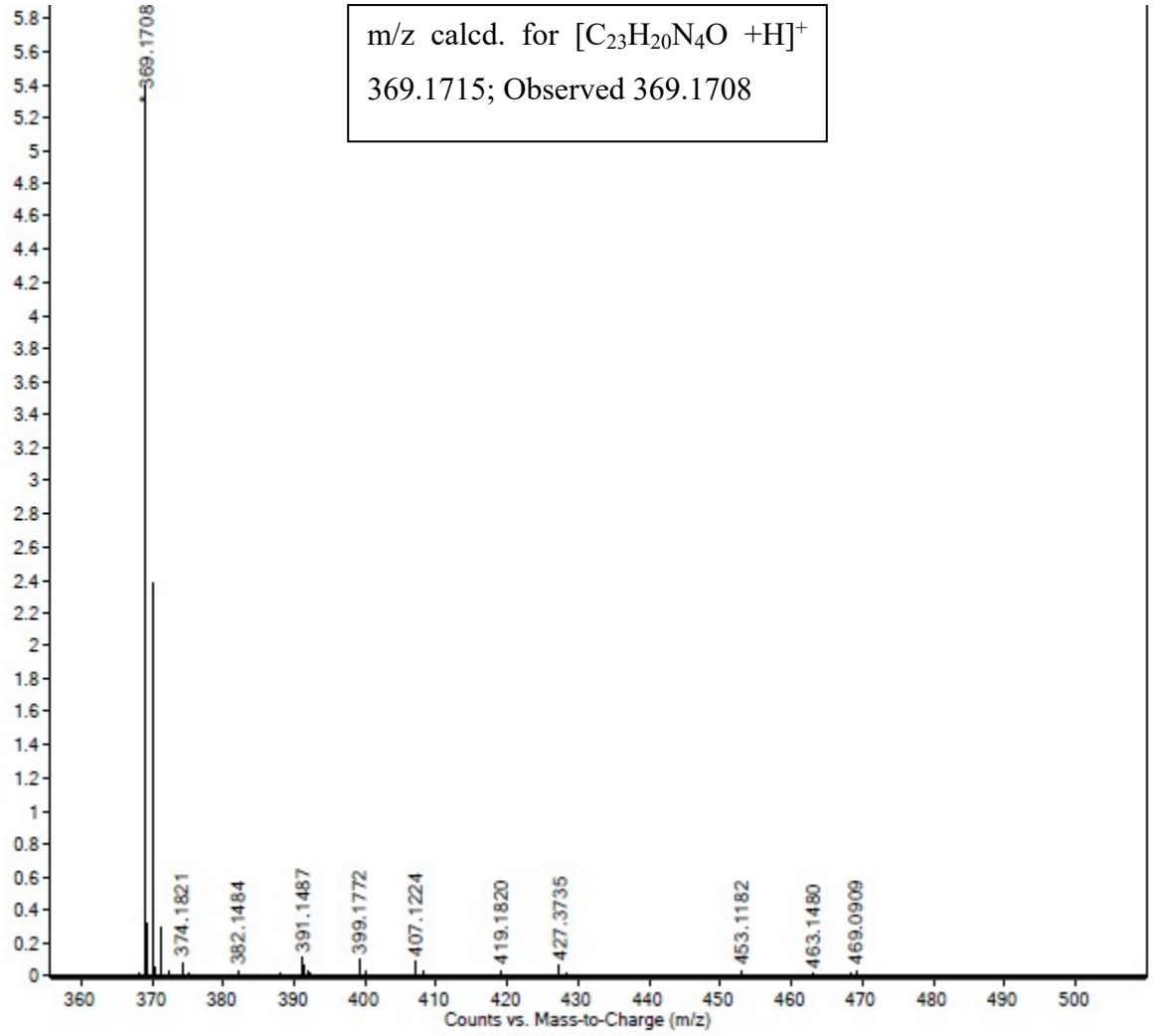
Mass spectrum of compound **10g**



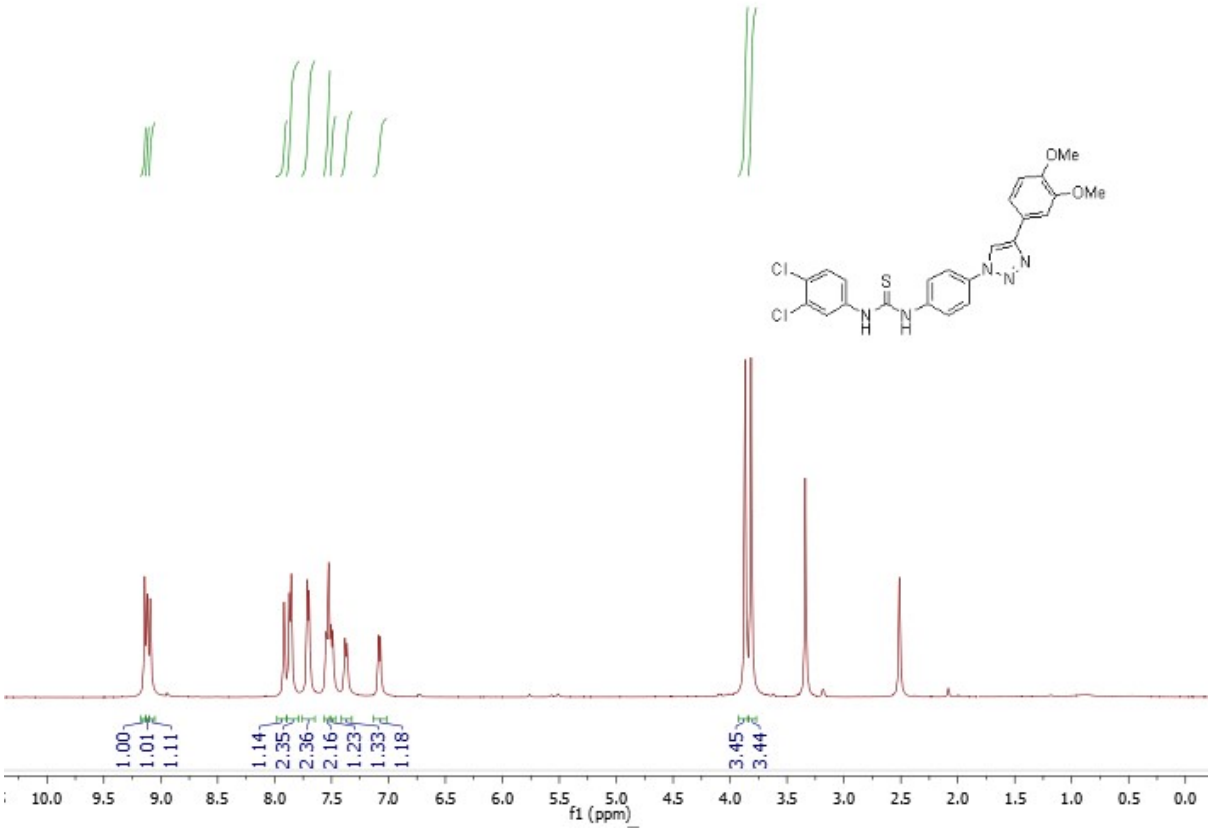
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **10h**



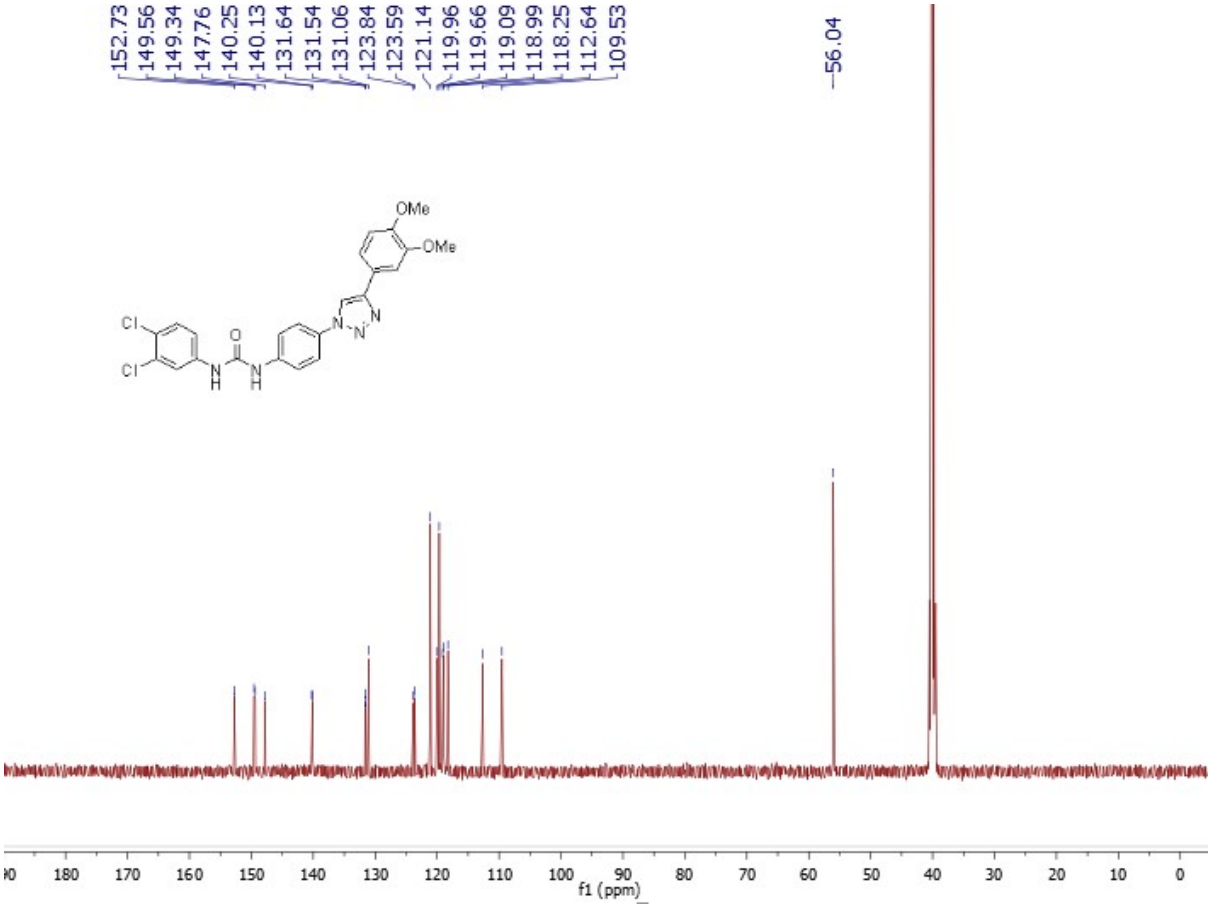
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **10h**



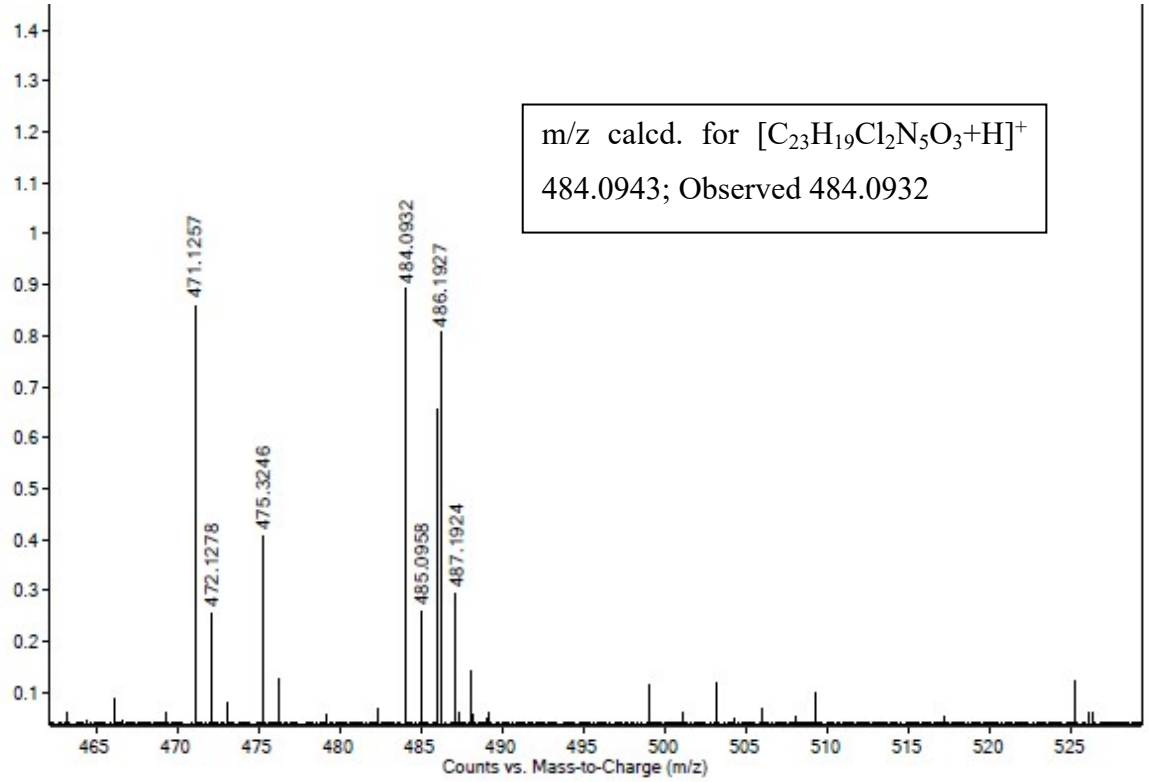
Mass spectrum of compound **10h**



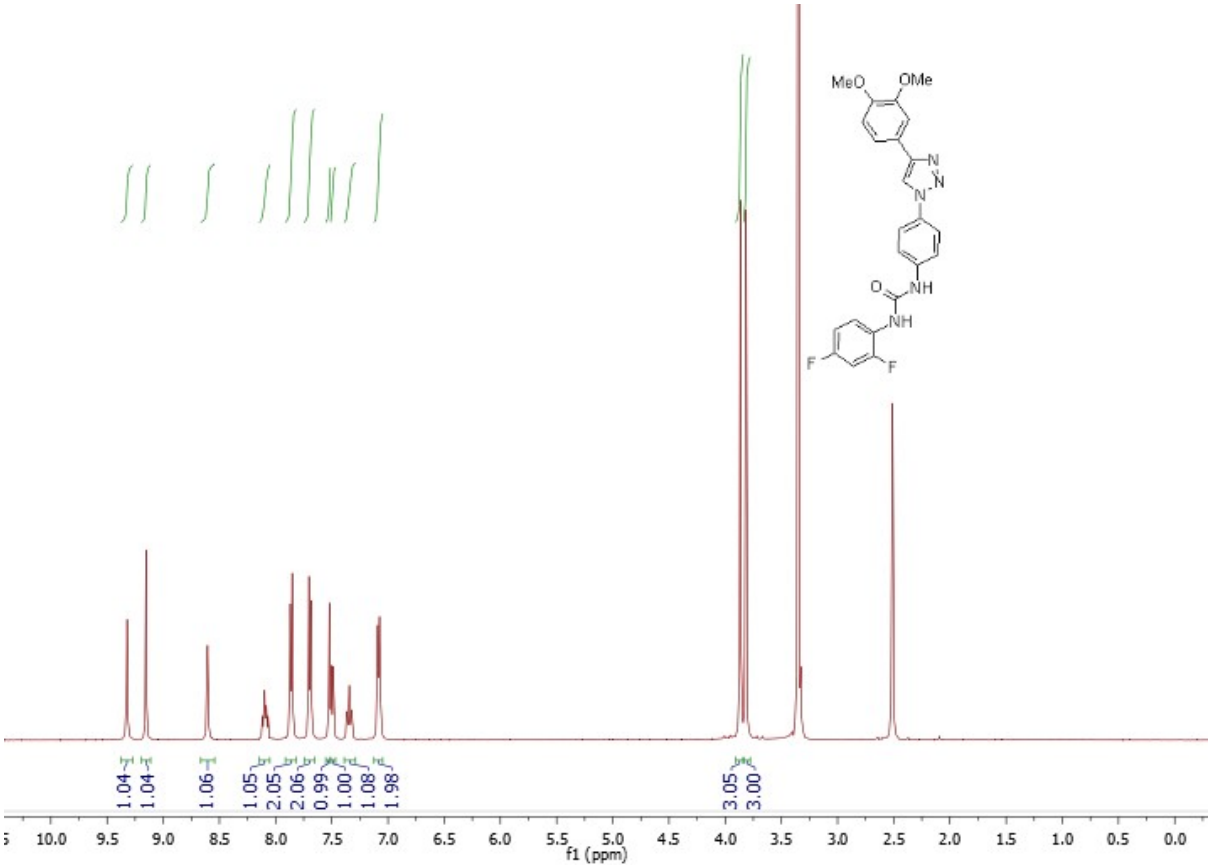
^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **15a**



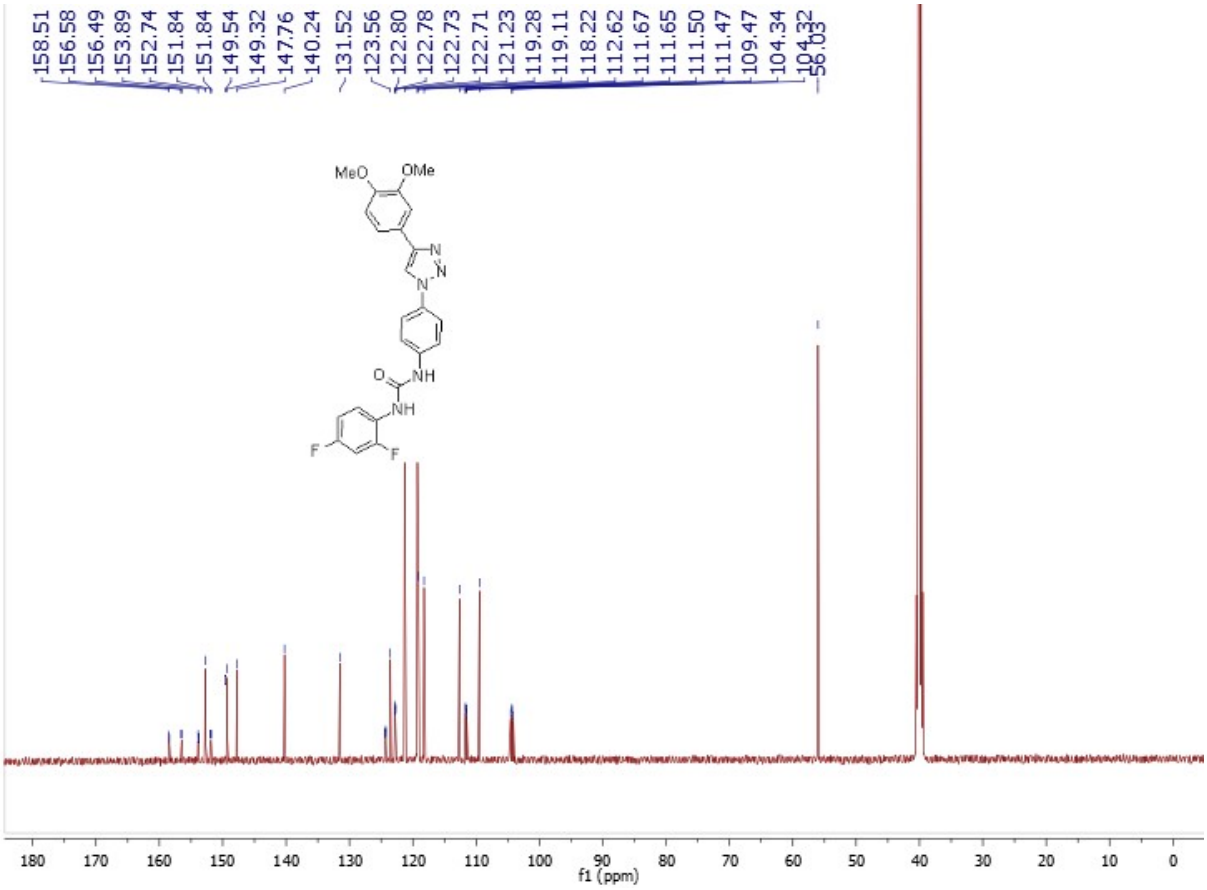
^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **15a**



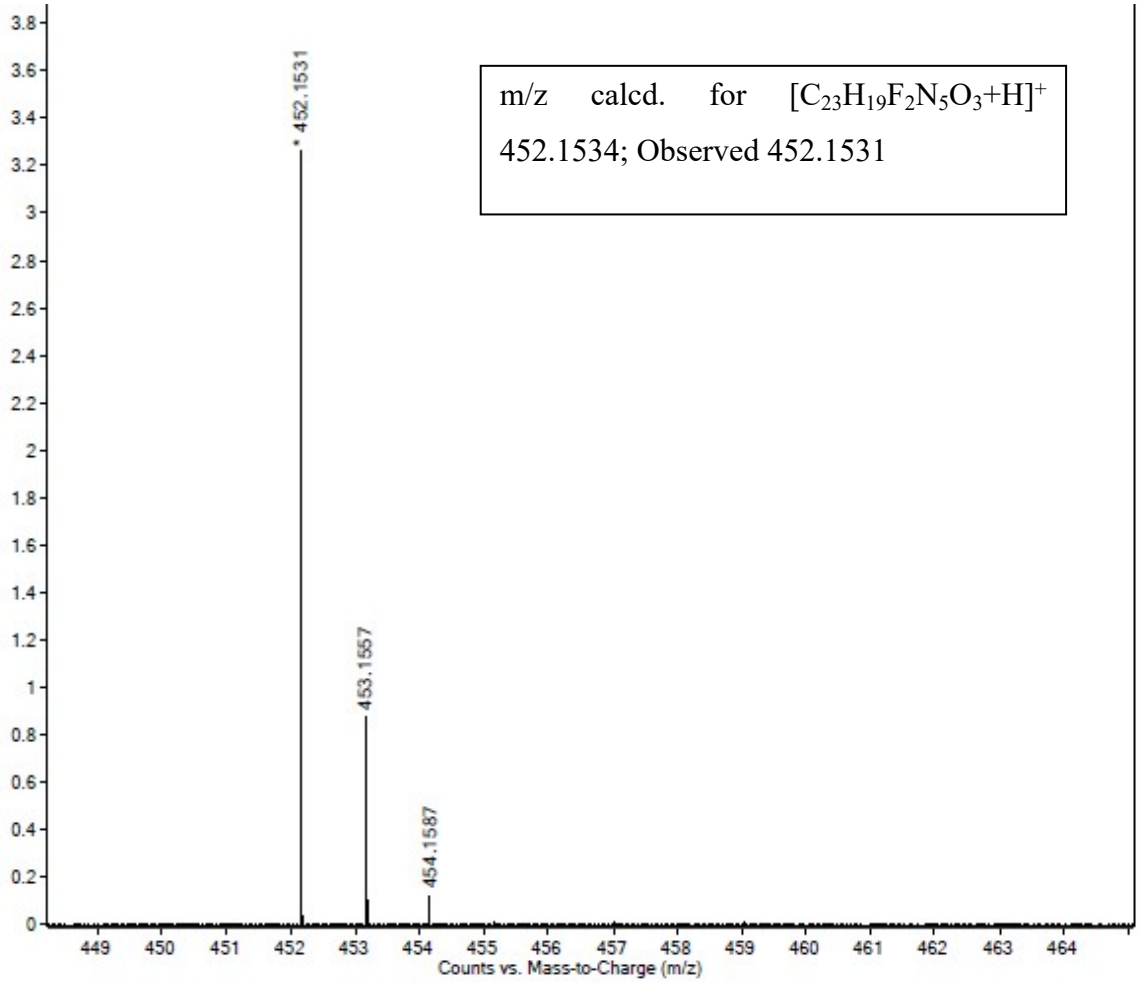
Mass spectrum of compound **15a**



^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound1 **15b**

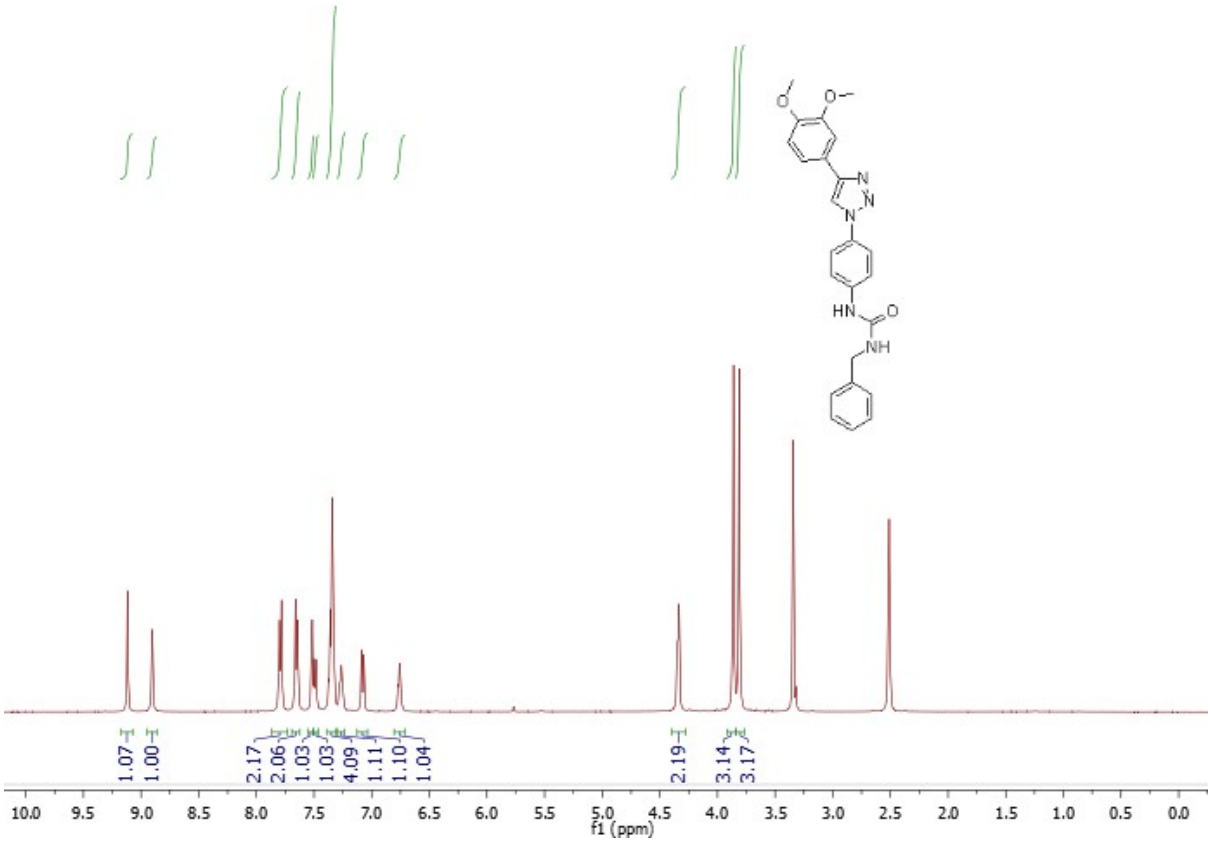


^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **15b**

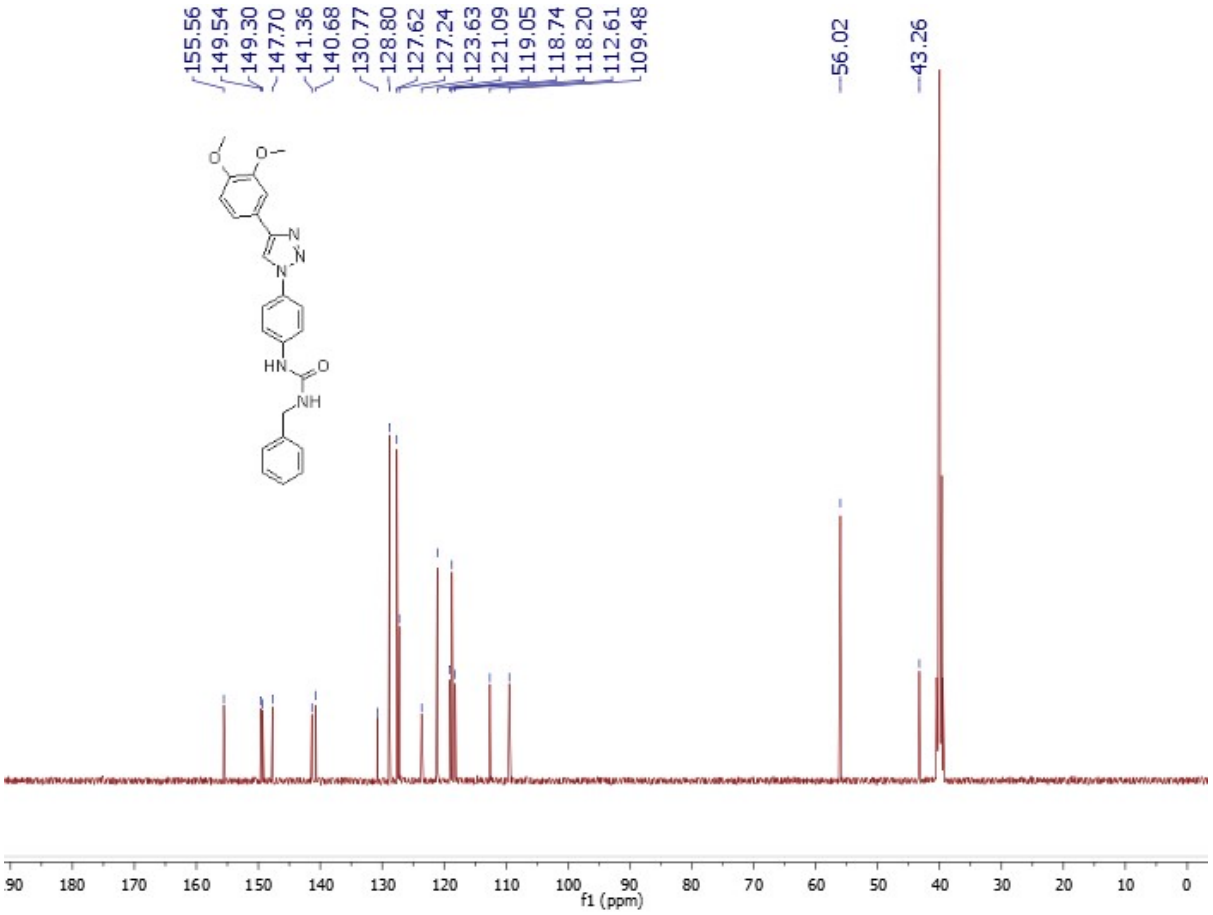


m/z calcd. for $[C_{23}H_{19}F_2N_5O_3+H]^+$ 452.1534; Observed 452.1531

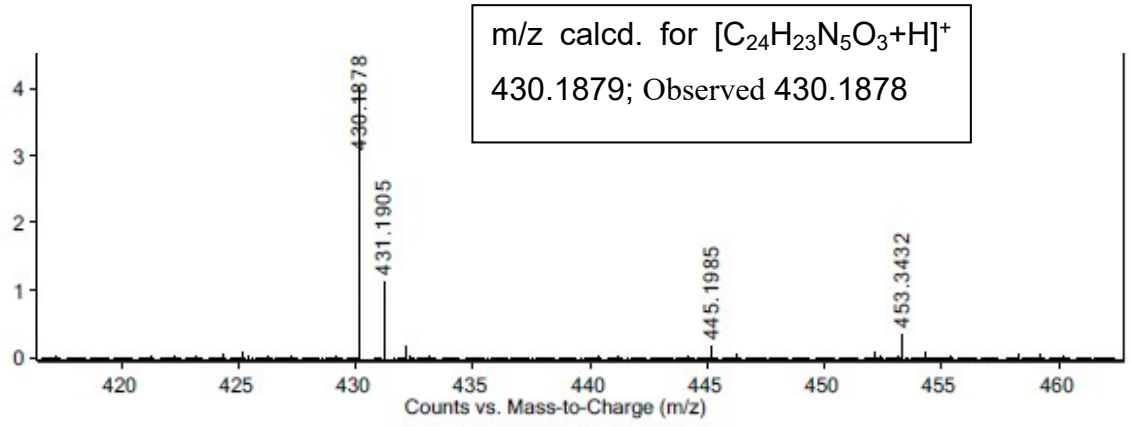
Mass spectrum of compound **15b**



^{1}H NMR (500 MHz, DMSO-d_6) spectrum of compound **15c**



^{13}C NMR (125 MHz, DMSO-d_6) spectrum of compound **15c**



Mass spectrum of compound **15c**

1. S. K. Sahoo, M. N. Ahmad, G. Kaul, S. Nanduri, A. Dasgupta, S. Chopra and V. M. Yaddanapudi, *RSC Medicinal Chemistry*, 2022, **13**, 585-593. DOI: 10.1039/D1MD00387A
2. J. H. Jorgensen and J. F. Hindler, *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 2007, **44**, 280-286. DOI: 10.1086/510431
3. P. Wayne, *Approved standard M7-A7. Clinical and Laboratory Standards Institute*, 2006.
4. I. Wiegand, K. Hilpert and R. E. W. Hancock, *Nature Protocols*, 2008, **3**, 163-175. DOI: 10.1038/nprot.2007.521
5. N. K. Taneja and J. S. Tyagi, *Journal of Antimicrobial Chemotherapy*, 2007, **60**, 288-293. DOI: 10.1093/jac/dkm207
6. N. P. Kalia, P. Mahajan, R. Mehra, A. Nargotra, J. P. Sharma, S. Koul and I. A. Khan, *Journal of Antimicrobial Chemotherapy*, 2012, **67**, 2401-2408. DOI: 10.1093/jac/dks232
7. M. Rajendram, K. A. Hurley, M. H. Foss, K. M. Thornton, J. T. Moore, J. T. Shaw and D. B. Weibel, *ACS Chemical Biology*, 2014, **9**, 1312-1319. DOI: 10.1021/cb500154m
8. B. D. Bax, P. F. Chan, D. S. Eggleston, A. Fosberry, D. R. Gentry, F. Gorrec, I. Giordano, M. M. Hann, A. Hennessy, M. Hibbs, J. Huang, E. Jones, J. Jones, K. K. Brown, C. J. Lewis, E. W. May, M. R. Saunders, O. Singh, C. E. Spitzfaden, C. Shen, A. Shillings, A. J. Theobald, A. Wohlkonig, N. D. Pearson and M. N. Gwynn, *Nature*, 2010, **466**, 935-940. DOI: 10.1038/nature09197.
9. S. Release, *Journal*, 2020.
10. R. A. Friesner, R. B. Murphy, M. P. Repasky, L. L. Frye, J. R. Greenwood, T. A. Halgren, P. C. Sanschagrin and D. T. Mainz, *Journal of medicinal chemistry*, 2006, **49**, 6177-6196. DOI: 10.1021/jm051256o.
11. S. N. R. Gajula, N. Nadimpalli and R. Sonti, *Drug Metabolism Reviews*, 2021, **53**, 459-477. DOI: 10.1080/03602532.2021.1970178.
12. S. Kumar Sahoo, S. Maddipatla, S. Nageswara Rao Gajula, M. Naiyaz Ahmad, G. Kaul, S. Nanduri, R. Sonti, A. Dasgupta, S. Chopra and V. Madhavi Yaddanapudi, *Bioorganic & Medicinal Chemistry*, 2022, **64**, 116777. DOI: 10.1016/j.bmc.2022.116777.