Seeking potent anti-tubercular agents: Design and synthesis of subsituted-*N*-(6-(4-(pyrazine-2-carbonyl)piperazine/homopiperzine-1-yl)pyridin-3-yl)benzamide derivatives as anti-tubercular agents

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1. Materials and methods

All chemical reagents and solvents are purchased from Aldrich, Alfa Aesar, Finar. The solvents and reagents were of LR grade. All the solvents were dried and distilled before use. Thin-layer chromatography (TLC) was carried out on aluminium-supported silica gel plates (Merck 60 F254) with visualization of components by UV light (254 nm). Column chromatography was carried out on silica gel (Merck 100-200 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 101 MHz respectively using a Bruker AV 400 spectrometer (Bruker CO., Switzerland) in $CDCl_3$ and DMSO-*d6* solution with tetramethylsilane as the internal standard and chemical shift values (δ) were given in ppm. ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-*d6*. The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. Melting points were determined on an electro thermal melting point apparatus (Stuart-SMP30) in open capillary tubes and are uncorrected. Elemental analyses were performed by ElementarAnalysensysteme GmbH vario MICRO cube CHN Analyzer. Mass spectra (ESI-MS) were recorded on Schimadzu MS/ESI mass spectrometer.

Biological assay: *In vitro* anti-mycobacterial activity of the compounds was evaluated by a luminometric assay based on a *M. tuberculosis* H37Ra laboratory strain transformed with a pSMT1 luciferase reporter plasmid (H37Ra-lux). A twofold serial dilution of each compound was made in complete 7H9 broth with final concentrations ranging from 128 to 0.125 µm. Volumes of 100 µl of the serial dilutions were added in triplicate to black, flat-bottomed 96-well plates. As a positive control, isoniazid, a first-line anti-mycobacterial drug, was included. The mycobacterial suspension was made by thawing a frozen glycerol stock of H37Ra-lux and, subsequently, diluting it in complete H9 broth to obtain a suspension with 10,000 relative light units (RLU)/ml. A volume of 100 µl of bacteria was added to each well. All of the outer-perimeter wells were filled with 200 µl of sterile deionized water to minimize evaporation of the medium in the test wells during incubation. After 7 days, the bacterial replication was analyzed by luminometry. To evoke a luminescent signal, 25 µl of 1% n-decanal in ethanol was added to each well, where after light emission was measured.

Materials and methods of docking: Docking studies were carried out using Schrödinger software (Version 2019-1, Schrödinger) installed on Intel Xenon W 3565 processor and Ubuntu enterprise version 18.04 as the operating system. Targeted ligands were drawn in ChemDraw 18.0. The result of the docking results was analyzed with the help of XP Visualiser (Version 2019-1, Schrödinger).

Ligand preparation: The ligands used as inputs for docking were sketched using ChemDraw software and cleaned up the structure for the bond alignment; ligands were incorporated into the workstation, the energy was minimized using OPLS3e force field in Ligprep (Version 2019-1, Schrödinger). This minimization helps to assign bond orders, the addition of the hydrogens to the ligands and conversion of 2D to 3D structure for the docking studies. The generated output file (best conformations of the ligands) was used for docking studies.

Receptor grid generation: A receptor grid was generated around the protein by picking the inhibitory ligand (X-ray pose of the ligand in the protein). The centroid of the ligand is selected to create a grid box around it, and Vander Waal radius of receptor atoms was scaled to 1.00 Å with a partial atomic charge of 0.25.

Protein preparation: Protein was prepared using the protein preparation wizard (Version 2019-1, Schrödinger). Hydrogen atom was added to the proteins and charges were assigned. Generated Het states using Epik at pH 7.0 ±2.0. Pre-process the protein and refine, modify the protein by analyzing the workspace, water molecules and other heteroatoms were examined and the non-significant atoms were excluded from the crystal structure of the protein. Finally, the protein was minimized using OPLS3e force filed. A grid was created by considering co-crystal ligand, which is included in the active site of the selected target pantothenate synthetase (PDB-3IUB) from *Mycobacterium tuberculosis*.

Chemistry: Chemicals and solvents were procured from commercial source. The solvents and reagents were of LR grade and if necessary purified before use. Thin-layer chromatography (TLC) was carried out on aluminium-supported silica gel plates (Merck

60 F254) with visualization of components by UV light (254 nm). Column chromatography was carried out on silica gel (Merck 100-200 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 101 MHz respectively using a Bruker AV 400 spectrometer (Bruker CO., Switzerland) in $CDCl_3$ and DMSO-d_6 solution with tetramethylsilane as the internal standard and chemical shift values (δ) were given in ppm. Melting points were determined on an electro thermal melting point apparatus (Stuart-SMP30) in open capillary tubes and are uncorrected. Elemental analyses were performed by Elementar Analysensysteme GmbH vario MICRO cube CHN Analyzer.

2. General Procedure and analytivcal Data

Representative procedure for the synthesis of compounds 2a and 2b

A solution of 2-chloro-5-nitropyridine (**1**) (5.0 g, 31.53 mmol) in DMF, 1-Boc-piperazine/1-Boc-homopiperazine (6.4 g, 44.75 mmol) and *N*,*N*-diisopropylethylamine (16.5 mL, 94.9 mmol) was stirred for 4 h at 110 °C. Once completion of the reaction, as indicated by TLC, the reaction was quenched with cold water, solid was filtrated and washed with water and hexane to get the compound **2a** and **2b.**

Compound 2a: Yellow solid (9.0 g, Yield: 92%); Melting point of **2a**: 168-170 °C; ESI-MS showed 309.16 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO) δ 8.97 (s, 1H), 8.25 (dd, J = 9.6, 2.9 Hz, 1H), 6.94 (d, J = 9.6 Hz, 1H), 3.83 – 3.72 (m, 4H), 3.51 – 3.41 (m, 4H), 1.43 (s, 9H).

Compound 2b: Yellow solid (8.9g, Yield: 89%); Melting point of **2b**: 157-159 °C; ESI-MS showed 323.20 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO) δ 8.97 (s, 1H), 8.21 (dd, J = 9.2, 2.6 Hz, 1H), 6.86 (d, J = 9.6 Hz, 1H), 4.05 – 3.65 (m, 4H), 3.63 – 3.43 (m, 2H), 3.33 – 3.30 (m, 2H), 1.77 (q, 2H), 1.25 (s, 9H).

Representative procedure for the synthesis of compound 3a and 3b

tert-butyl 4-(5-nitropyridin-2-yl)piperazine-1-carboxylate/*tert*-butyl 4-(5-nitropyridin-2-yl)-1,4-diazepane-1-carboxylate (**2a/2b**) (9.0 g, 1.0 equiv.) was added in CH_2Cl_2 and cooled to 0 °C, After 5 min, 4N HCl in dioxane (4.5 ml) was added and warmed at rt for 12 h. After completion of the reaction, as indicated by TLC, the reaction was concentrated in vacuo and washed with n-pentane. Compounds **3a** and **3b** were obtained in excellent yield ~98% as yellow solids.

Compound 3a: Pale yellow solid (7.1 g, Yield: 98%); Melting point of **3a**: 84-86 °C (salt free compound); ESI-MS showed 209.20 $(M+H)^+$. ^1H NMR (400 MHz, DMSO) δ 9.69 (bs, 2H), 8.99 (s, 1H), 8.39 – 8.22 (m, 1H), 7.04 (d, *J* = 9.6 Hz, 1H), 4.45 – 4.38 (m, 4H), 4.11 – 3.95 (m, 4H).

Compound 3b: Pale yellow solid (7.20g, Yield: 100%); Melting point of **3b**: 79-81 °C (salt free compound); ESI-MS showed 223.20 $(M+H)^+$. ^1H NMR (400 MHz, DMSO) δ 9.47 (bs, 2H), 8.99 (s, 1H), 8.27 (dd, *J* = 9.6, 2.8 Hz, 1H), 6.90 (d, *J* = 9.6 Hz, 1H), 3.93-3.96 (m, 4H), 3.34 – 3.07 (m, 4H), 2.12 (q, 2H).

Representative procedure for the synthesis of compounds 4a and 4b

EDC·HCl (1.20 equiv) and *N*, *N*- diisopropylethylamine (2.5 equiv.) were added to a solution of compound **3a** (1 equiv.), pyrazinoic acid (1 equiv.) and HOBt (1.2 equiv.) in DMF and stirred for 24 h at room temperature under nitrogen. Once completion of the reaction, as indicated by TLC, the reaction was quenched with cold water and extracted with ethyl acetate. The organic layers were collected, washed with saturated brine solution, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resultant crude product was purified by column chromatography [ethyl acetate / hexane (30 - 40%)] to get the compound **4a** and **4b.**

Compound 4a: Yellow gummy solid; Yield: 83%; ESI-MS showed 315.16 $(M+H)^+$. **Compound 4b:** Yellow gummy solid; Yield: 73%; ESI-MS showed 329.20 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO) δ 8.91 (s, 1H), 8.61 – 8.52 (m, 3H), 8.11 (dd, *J* = 9.6, 2.9 Hz, 1H), 6.79 (d, *J* = 9.6 Hz, 1H), 3.88 – 3.63 (m, 4H), 3.50 – 3.08 (m, 4H).

Compound 4b: Yellow gummy solid; Yield: 73%; ESI-MS showed 329.20 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO) δ 8.92 (s, 1H), 8.67 – 8.56 (m, 3H), 8.17 (dd, *J* = 9.6, 2.9 Hz, 1H), 6.85 (d, *J* = 9.6 Hz, 1H), 3.83 – 3.71 (m, 4H), 3.60 – 3.03 (m, 4H), 1.78 (q, 2H).

Representative procedure for the synthesis of compounds 5a and 5b

To stirred suspension of an appropriate nitro compound **4a** (1 equiv) and 10% Pd-C (0.2-0.3 g) in methanol. H_2 was added at a pressure 60 psi in hydrogenation shaker for 6 h at room temperature. Once completion of the reaction, as indicated by TLC, the reaction mixture was filtered through celite and washed with excess of methanol. The combined filtrate washings were evaporated under reduced pressure. Crude residue was washed with hexane and diethyl ether to get compound **5**a and **5b** as solids. These two compounds directly taken to next step without further purification.

Compound 5a: Dark black and gummy solid; Yield: 82%; ESI-MS showed 285.16 $(M+H)^+$.

Compound 5b: Dark brown and gummy solid; Yield: 70%; ESI-MS showed 399.20 $(M+H)^+$.

Representative procedure for the synthesis of compounds 6a-n

EDC,HCl (1.20 equiv) and *N*, *N*- diisopropylethylamine (2.5 equiv.) were added to a solution of compound **5a** (1 equiv.), substituted benzoic acid (1.2 equiv.) and HOBt (1.2 equiv.) in DCM and stirred for 24 h at room temperature under nitrogen. Once completion of the reaction, as indicated by TLC, the reaction was quenched with cold water and extracted with DCM. The organic layers were collected, washed with saturated brine solution, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resultant

crude product was purified by column chromatography [methanol / DCM (2 - 5%)] to get the compound **6**. Yields of **6a-n**: 65-93%. Similar procedure was followed to get the titled compounds **7a-m** from **5b**.

3. X-ray crystallographic studies:

Single Crystal X-ray crystallographic structure of compounds 6d, 6f and 6n: The suitable crystals of compound **6d**, **6f** and **6n**, for single crystal X-ray diffraction (SCXRD) analysis were grown from the mixture of 40% methanol in dichloromethane. The SCXRD measurements were performed on the Rigaku XtaLAB P200 diffractometer using graphite monochromated Cu-Kα radiation (λ = 1.54184 Å). The data was collected and reduced using CrysAlisPro (Rigaku Oxford Diffraction) software. The data collection was carried out at 100 K and the structures were solved using Olex2 with the ShelX structure solution program using Direct Methods and refined with the ShelXL refinement package using Least Squares minimizationThe CCDC numbers for the structures of **6d**, **6f** and **6n** are 1979945, 1979944 and 1979943 respectively.

The structure of **6n** crystallizes in monoclinic P21/c space group with $C_{19}H_{18}N_8O_2$ empirical formula. The terminal pyrazine ring in the structure is disordered over 2 positions with 0.60 and 0.40 occupancies. Moreover, the carbonyl oxygen adjacent to this pyrazine ring is also disordered over 2 positions with 0.34 and 0.66 occupancies **(Figure 1**). However, such disorder was not observed in the case of compounds **6d** and **6f** with the empirical formulas $C_{22}H_{20}N_2O_2Cl$ and $C_{21}H_{19}N_7O_4$ and, respectively.

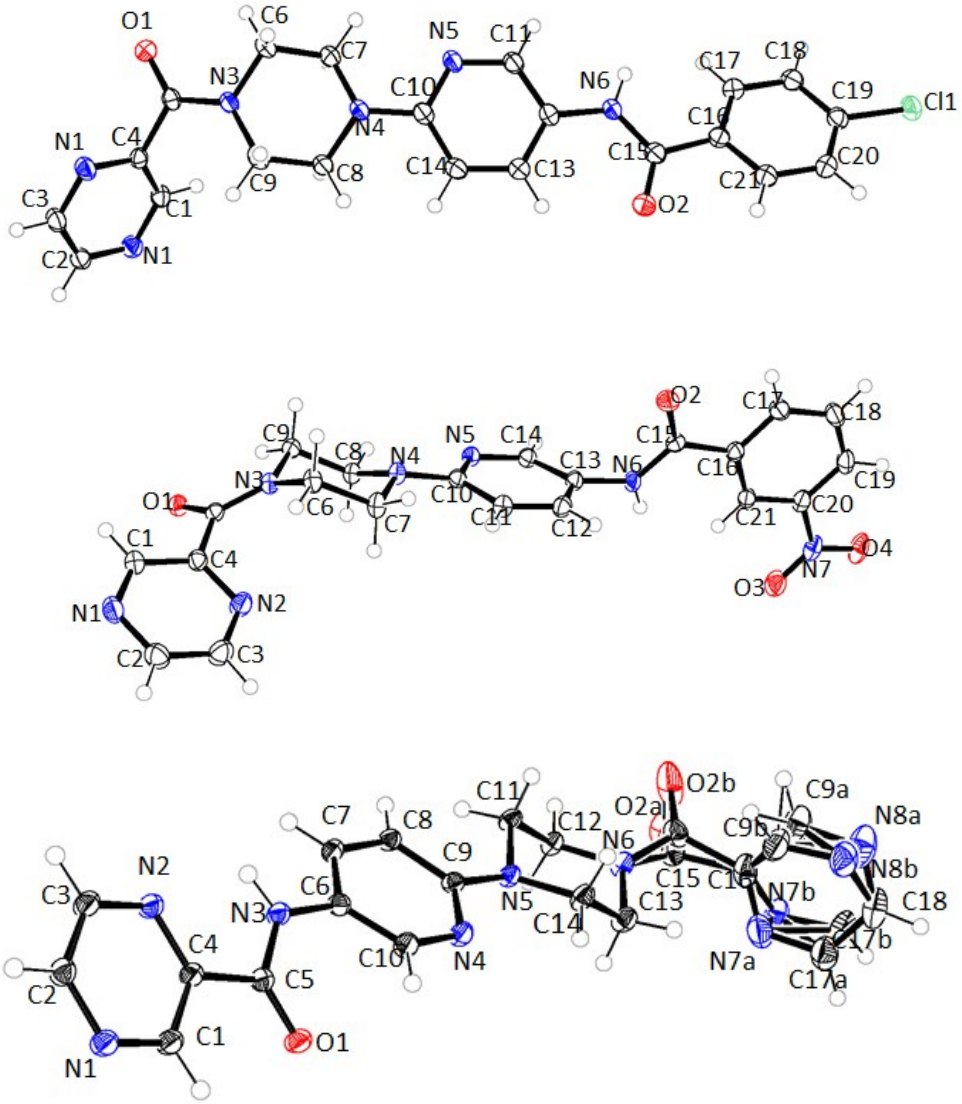


Figure 1. ORTEP diagram of compound **6d** (top), **6f** (middle) and **6n**) (bottom).

4. ***Spectral data:***

Analytical data for the final compounds:

N-(6-(4-(pyrazine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)benzamide **(6a)** : Off white solid (88%); m.p. 137-139 °C; IR (KBr) υ_{max} / cm^{-1} 3573, 3032, 2923, 1675, 1445, , 1052. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.90 (d, J = 1.5 Hz, 1H), 8.78 (d, J = 2.6 Hz, 1H), 8.71 (dd, J = 2.5, 1.5 Hz, 1H), 8.49 (d, J = 2.5 Hz, 1H), 8.03 – 7.90 (m, 3H), 7.64 – 7.49 (m, 3H), 6.91 (d, J = 9.1 Hz, 1H), 3.84 – 3.77 (m, 2H), 3.65 – 3.48 (m, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.7, 165.3, 156.0, 149.7, 146.0, 145.0, 143.7, 140.8, 135.0, 132.0, 131.7, 128.9, 128.0, 127.5, 107.5, 46.6, 45.9, 45.3, 41.90. EI-MS *m/z* 389.17 $(M+H)^+$; Anal. calcd for $C_{21}H_{20}N_6O_2$: (%) C, 64.94; H, 5.20; N, 21.64; Found: C, 64.95; H, 5.21; N, 21.65.

4-methoxy-*N*-(6-(4-(pyrazine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)benzamide **(6b)** : White solid (87%); m.p. 188-190 °C; (KBr) υ_{max} / cm^{-1} 3579, 3029, 2853, 1687, 1408, 1344, 500. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.90 (d, J = 1.5 Hz, 1H), 8.79 (d, J = 2.6 Hz, 1H), 8.72 (dd, J = 2.6, 1.5 Hz, 1H), 8.49 (d, J = 2.6 Hz, 1H), 7.97 – 7.91 (m, 2H), 7.90 (s, 1H), 7.78 – 7.73 (m, 2H), 6.92 (d, J = 9.1 Hz, 1H), 3.83 (s, 3H), 3.81 – 3.76 (m, 2H), 3.63 – 3.48 (m, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.3, 165.1, 162.3, 155.9, 149.7, 146.0, 145.0, 143.7, 140.8, 131.7, 129.9, 127.7, 127.1, 114.0, 107.5, 55.9, 46.6, 46.0, 45.3, 41.9. EI-MS *m/z* 418.18 $(M+H)^+$; Anal. Calcd for $C_{22}H_{22}N_6O_2$: (%) C, 63.15; H, 5.31; N, 20.08; Found: C, 63.17; H, 5.32; N, 20.09.

4-(tert-butyl)-*N*-(6-(4-(pyrazine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)benzamide **(6c)** : White solid (91%); m.p. 156-158 °C; IR (KBr) υ_{max} / cm^{-1} 3576, 3031, 2925, 1685, 1421, 1330, 1050. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.90 (d, J = 1.5 Hz, 1H), 8.78 (d, J = 2.6 Hz, 1H), 8.71 (dd, J = 2.5, 1.5 Hz, 1H), 8.48 (d, J = 2.6 Hz, 1H), 7.98 – 7.85 (m, 3H), 7.58 – 7.50 (m, 2H), 6.90 (d, J = 9.1 Hz, 1H), 3.81 (dd, J = 13.1, 8.4 Hz, 2H), 3.67 – 3.46 (m, 6H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ

165.3, 163.7, 152.1, 149.0, 146.2, 145.1, 143.7, 140.8, 134.1, 131.9, 131.7, 130.1, 127.3, 125.1, 107.5, 46.6, 45.9, 45.2, 41.9, 35.9, 30.8. EI-MS *m/z* 445.27 $(M+H)^+$; Anal. calcd for $C_{25}H_{28}N_6O_2$: (%) C, 67.56; H, 6.35; N, 18.92; Found: C, 67.57; H, 6.37; N, 18.93.

4-chloro-*N*-(6-(4-(pyrazine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)benzamide **(6d)** : Light yellow solid (81%); m.p. 144-146 °C; IR (KBr) υ_{max} / cm^{-1} 3585, 3031, 2922, 1675, 1532, 1372, 1027, 575. ^1H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H), 8.90 (d, *J* = 1.3 Hz, 1H), 8.78 (d, *J* = 2.5 Hz, 1H), 8.71 (dd, *J* = 2.4, 1.5 Hz, 1H), 8.47 (d, *J* = 2.5 Hz, 1H), 8.04 – 7.91 (m, 3H), 7.61 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 9.1 Hz, 1H), 3.83 – 3.75 (m, 2H), 3.57 (ddd, *J* = 22.2, 7.7, 4.1 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.3, 164.6, 156.1, 149.7, 146.0, 145.0, 143.7, 140.8, 136.8, 133.7, 131.7, 130.1, 128.9, 127.3, 107.5, 46.6, 46.27 – 45.97 (m), 45.6, 41.9. EI-MS *m/z* 423.87 $(M+H)^+$; Anal. Calcd for $C_{21}H_{19}ClN_6O_2$: (%) C, 59.65; H, 4.54; N, 19.87; Found: C, 59.66; H, 4.54; N, 19.88.

4-bromo-*N*-(6-(4-(pyrazine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)benzamide **(6e)** : White solid (90%); m.p. 119-121 °C; IR (KBr) υ_{max} / cm^{-1} 3590, 3021, 2843, 1687, 1410, 1340, 570. ^1H NMR (400 MHz, DMSO-d_6) *δ* 10.26 (s, 1H), 8.90 (d, *J* = 1.5 Hz, 1H), 8.78 (d, *J* = 2.6 Hz, 1H), 8.72 (dd, *J* = 2.6, 1.5 Hz, 1H), 8.47 (d, *J* = 2.6 Hz, 1H), 7.97 – 7.91 (m, 2H), 7.90 (s, 1H), 7.78 – 7.72 (m, 2H), 6.92 (d, *J* = 9.1 Hz, 1H), 3.81 – 3.76 (m, 2H), 3.64 – 3.48 (m, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) *δ* 165.3, 164.7, 156.1, 149.7, 146.0, 145.0, 143.7, 140.8, 134.1, 131.9, 131.7, 130.1, 127.3, 125.8, 107.5, 46.6, 45.9, 45.3, 41.9. EI-MS *m/z* 468.08 $(M+H)^+$ 469.07 $(M+H)^{+2}$; Anal. Calcd for $C_{21}H_{19}BrN_6O_2$: (%) C, 53.97; H, 4.10; N, 17.98; Found: C, 53.98; H, 4.11; N, 17.99.

3-nitro-*N*-(6-(4-(pyrazine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)benzamide **(6f)** : Yellow solid (82%); m.p. 202-203 °C; IR (KBr) υ_{max} / cm^{-1} 3590, 3021, 2833, 1515, 1679, 1410, 1340, 1120, 1061. ^1H NMR (400 MHz, DMSO-d_6) ^1H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H), 8.90 (d, *J* = 1.2 Hz, 1H), 8.83 – 8.76 (m, 2H), 8.74 – 8.69 (m, 1H), 8.50 (d, *J* = 2.4 Hz, 1H), 8.47 – 8.39 (m, 2H), 7.96 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.85 (t, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 9.1 Hz, 1H), 3.83 – 3.77 (m, 2H), 3.66 – 3.51

(m, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.4, 163.6, 156.2, 149.6, 148.2, 146.0, 144.9, 143.7, 140.9, 136.3, 134.5, 131.9, 130.7, 127.6, 126.7, 122.7, 107.5, 46.6, 45.8, 45.2, 41.9. EI-MS *m/z* 434.15 $(M+H)^+$; Anal. calcd for $C_{21}H_{19}N_7O_4$: (%) C, 58.19; H, 4.42; N, 22.63; Found: C, 58.20; H, 4.43; N, 22.64.

3-bromo-*N*-(6-(4-(pyrazine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)benzamide **(6g)** : White solid (76%); m.p. 246-248 °C; IR (KBr) υ_{max} / cm^{-1} 3595, 3059, 2933, 1680, 1412, 1357, 1279, 1045, 612. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.90 (d, *J* = 1.5 Hz, 1H), 8.78 (d, *J* = 2.6 Hz, 1H), 8.71 (dd, *J* = 2.5, 1.5 Hz, 1H), 8.48 (d, *J* = 2.6 Hz, 1H), 8.14 (t, *J* = 1.7 Hz, 1H), 8.00 – 7.90 (m, 2H), 7.80 (ddd, *J* = 8.0, 1.9, 0.9 Hz, 1H), 7.50 (t, *J* = 7.9 Hz, 1H), 6.92 (d, *J* = 9.1 Hz, 1H), 3.84 – 3.76 (m, 2H), 3.65 – 3.50 (m, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.3, 164.1, 156.1, 149.7, 146.0, 145.0, 143.7, 140.8, 137.1, 134.7, 131.7, 131.1, 130.6, 127.2, 122.2, 107.5, 46.6, 45.9, 45.2, 41.9. EI-MS *m/z* 467.09 $(M+H)^+$; 469.08 $(M+H)^{+2}$; Anal. Calcd for $C_{21}H_{19}BrN_6O_2$: (%) C, 53.98; H, 4.10; N, 17.98; Found: C, 53.99; H, 4.11; N, 17.99.

2-methyl-*N*-(6-(4-(pyrazine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)benzamide **(6h)** : Brown solid (80%); m.p. 165-167 °C; IR (KBr) υ_{max} / cm^{-1} 3542, 3027, 2832, 1675, 1424, 1365, 1034, 1020^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.90 (s, 1H), 8.78 (d, *J* = 2.4 Hz, 1H), 8.71 (s, 1H), 8.47 (d, *J* = 2.3 Hz, 1H), 7.95 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.34 – 7.25 (m, 2H), 6.90 (d, *J* = 9.1 Hz, 1H), 3.79 (d, *J* = 5.0 Hz, 2H), 3.63 – 3.55 (m, 4H), 3.50 (d, *J* = 2.8 Hz, 2H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) *δ* 168.0, 165.3, 155.9, 149.7, 146.0, 145.0, 143.7, 140.0, 137.4, 135.8, 131.0, 130.8, 130.1, 127.8, 127.7, 126.1, 107.7, 46.6, 46.1, 45.4, 41.9, 19.8. EI-MS *m/z* 403.20 $(M+H)^+$; Anal. calcd for $C_{22}H_{22}N_6O_2$: (%) C, 65.66; H, 5.52; N, 20.89; Found: C, 65.67; H, 5.53; N, 20.90.

2-iodo-*N*-(6-(4-(pyrazine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)benzamide **(6i)** : White solid (89%); m.p. 165-167 °C; (KBr) υ_{max} / cm^{-1} 3599, 3027, 2834, 1677, 1412, 1343, 1043, 615. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.90 (d, *J* = 1.3 Hz, 1H), 8.78 (d, *J* = 2.5 Hz, 1H), 8.74 – 8.69 (m, 1H), 8.44 (d, *J* = 2.4 Hz, 1H), 7.97 – 7.90 (m, 2H), 7.50 (q, *J* = 7.2 Hz, 2H), 7.26 – 7.20 (m, 1H), 6.92 (d, *J* = 9.1 Hz, 1H), 3.83 – 3.77 (m, 2H), 3.63 – 3.55 (m, 4H), 3.53 – 3.48 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) *δ* 168.0, 165.3, 155.9, 146.0, 145.0, 143.7, 140.0, 137.4, 135.8, 131.0, 130.8, 130.0, 127.8, 127.3, 122.3, 107.7, 93.8, 46.6, 46.1, 45.4, 41.9. EI-MS *m/z* 515.08 $(M+H)^{+}$; Anal. calcd for $C_{21}H_{19}IN_6O_2$: (%) C, 49.05; H, 3.73; N, 16.34; Found: C, 49.07; H, 3.75; N, 16.35.

2-bromo-6-chloro-*N*-(6-(4-(pyrazine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)benzamide (**6j**) : P-7 Pale yellow solid (87%); m.p. 150-152 °C; IR (KBr) υ_{max} / cm^{-1} 3582, 3022, 2973, 1671, 1422, 1332, 1055, 680. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (s, 1H), 8.90 (d, *J* = 1.3 Hz, 1H), 8.78 (d, *J* = 2.5 Hz, 1H), 8.71 (dd, *J* = 2.5, 1.5 Hz, 1H), 8.42 (d, *J* = 2.6 Hz, 1H), 7.91 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.84 (d, *J* = 2.4 Hz, 1H), 7.71 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 6.92 (d, *J* = 9.1 Hz, 1H), 3.82 – 3.78 (m, 2H), 3.64 – 3.55 (m, 4H), 3.53 – 3.49 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.3, 163.5, 156.2, 149.7, 146.0, 145.0, 143.7, 139.9, 138.9, 134.3, 132.2, 131.9, 130.8, 129.9, 127.2, 120.4, 107.7, 46.6, 45.9, 45.3, 41.9. EI-MS *m/z* 501.04 $(M+H)^{+}$; 503.06 $(M+H)^{+2}$; Anal. Calcd for $C_{21}H_{18}BrClN_6O_2$: (%) C, 50.27; H, 3.64; N, 16.75; Found: C, 50.28; H, 3.65; N, 16.76.

4-bromo-2-chloro-*N*-(6-(4-(pyrazine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)benzamide (**6k**): Light brown solid (80%); m.p.147-149 °C; ; IR (KBr) υ_{max} / cm^{-1} 3575, 30311, 2925, 1673, 1402, 1043, 560. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (s, 1H), 8.90 (s, 1H), 8.78 (d, *J* = 2.3 Hz, 1H), 8.71 (s, 1H), 8.42 (d, *J* = 2.2 Hz, 1H), 7.91 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.84 (d, *J* = 2.1 Hz, 1H), 7.71 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 6.92 (d, *J* = 9.1 Hz, 1H), 3.80 (s, 2H), 3.66 – 3.54 (m, 5H), 3.51 (d, *J* = 4.6 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) *δ* 165.4, 161.8, 156.2, 148.7, 148.2, 147.0, 145.4, 145.0, 144.7, 143.9, 143.8, 141.0, 131.7, 126.6, 107.4, 46.6, 45.7, 45.2, 41.8. EI-MS *m/z* 501.04 $(M+H)^{+}$; 503.06 $(M+H)^{+2}$; Anal. Calcd for $C_{21}H_{18}BrClN_6O_2$: (%) C, 50.27; H, 3.64; N, 16.75; Found: C, 50.28; H, 3.65; N, 16.76.

2,4-dichloro-*N*-(6-(4-(pyrazine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)benzamide **(6l)** :Off solid (80%); m.p.197-199 °C; IR (KBr) υ_{max} / cm^{-1} 3595, 3029, 2945, 1683, 1422, 1053, 560. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.95 (d, J = 1.5 Hz, 1H), 8.88 (d, J = 2.5 Hz, 1H), 8.73 (dd, J = 2.6, 1.5 Hz, 1H), 8.46 (d, J = 2.6 Hz, 1H), 7.89 (dd, J = 9.1, 2.7 Hz, 1H), 7.80 (d, J = 2.4 Hz, 1H), 7.69 (dd, J = 8.6, 2.4 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 6.92 (d, J = 9.1 Hz, 1H), 3.78 (t, J = 5.2 Hz, 2H), 3.60 – 3.49 (m, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.4, 161.8, 156.2, 148.7, 148.2, 147.0, 145.4, 145.0, 144.7, 143.9, 143.8, 141.0, 131.7, 126.6, 107.4, 46.6, 45.7, 45.2, 41.8. EI-MS *m/z* 558.10 $(M+H)^+$; Anal. Calcd for $C_{21}H_{18}Cl_2N_6O_2$: (%) C, 55.16; H, 3.97; N, 18.38; Found: C, 55.18; H, 3.98; N, 18.39.

N-(6-(4-(pyrazine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)isonicotinamide **(6m)** : Off white solid (83%); m.p. 212-213 °C; IR (KBr) υ_{max} / cm^{-1} 3510, 3021, 2865, 1670, 1410, 1340, 1060. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.72 (s, 1H), 8.93 (d, J = 2.5 Hz, 2H), 8.91 (d, J = 1.6 Hz, 2H), 8.80 (dd, J = 2.5, 1.7 Hz, 2H), 8.78 (d, J = 2.6 Hz, 1H), 8.70 (dd, J = 2.6, 1.5 Hz, 1H), 8.66 (d, J = 2.7 Hz, 1H), 8.07 (dd, J = 9.1, 2.7 Hz, 1H), 6.90 (d, J = 9.1 Hz, 1H), 3.79 (dd, J = 6.6, 4.2 Hz, 2H), 3.63 (dd, J = 6.6, 4.2 Hz, 2H), 3.60 – 3.53 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.5, 162.9, 156.1, 149.7, 146.1, 145.3 145.1, 143.7, 143.6, 140.9, 131.2, 126.2, 121.2, 107.5, 46.7, 45.8, 45.1, 41.9. EI-MS *m/z* 389.19 $(M+H)^+$; Anal. calcd for $C_{21}H_{20}N_6O_2$: (%) C, 64.94; H, 5.19; N, 21.64; Found: C, 64.95; H, 5.21; N, 21.65.

N-(6-(4-(pyrazine-2-carbonyl)piperazin-1-yl)pyridin-3-yl)pyrazine-2-carboxamide **(6n)** : Off white solid (87%); m.p. 205-206 °C; (KBr) υ_{max} / cm^{-1} 3525, 3025, 2867, 16775, 1412, 1363, 1022. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 10.73 (s, 1H), 9.28 (d, J = 1.5 Hz, 1H), 8.93 (d, J = 2.5 Hz, 1H), 8.90 (d, J = 1.5 Hz, 1H), 8.80 (dd, J = 2.5, 1.5 Hz, 1H), 8.78 (d, J = 2.6 Hz, 1H), 8.71 (dd, J = 2.5, 1.5 Hz, 1H), 8.63 (d, J = 2.6 Hz, 1H), 8.32 (d, J = 1.5 Hz, 1H), 8.07 (dd, J = 9.1, 2.7 Hz, 1H), 6.92 (d, J = 9.1 Hz, 1H), 3.82 – 3.77 (m, 2H), 3.67 – 3.50 (m, 7H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.3, 161.9, 156.1, 149.7, 148.1, 146.0, 145.4, 145.0, 144.4, 143.7, 143.7, 141.0, 131.6, 126.6, 107.4, 46.6, 45.8, 45.2, 41.9. EI-MS *m/z* 391.16 $(M+H)^+$; Anal. calcd for $C_{19}H_{18}N_8O_2$: (%) C, 58.45; H, 4.65; N, 28.70; Found: C, 58.46; H, 4.67; N, 28.71.

N-(6-(4-(pyrazine-2-carbonyl)-1,4-diazepan-1-yl)pyridin-3-yl)benzamide **(7a)** : White solid (86%); m.p. 147-149 °C; IR (KBr) υ_{max} / cm^{-1} 3610, 3019, 2917, 1668, 1484, 1326, 1032. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 8.91 (d, J = 1.5 Hz, 1H), 8.76 (d, J = 2.6 Hz, 1H), 8.71 (dd, J = 2.6, 1.5 Hz, 1H), 8.47 (d, J = 2.8 Hz, 1H), 7.97 – 7.91 (m, 3H), 7.90 (s, 1H), 7.78 – 7.72 (m, 2H), 6.92 (d, J = 9.2 Hz, 1H), 3.71 – 3.66 (m, 8H), 2.44 – 2.18 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.8, 163.7, 152.2, 148.9, 147.9, 145.2, 143.6, 140.7, 134.5, 131.9, 131.7, 130.2, 127.8, 125.8, 107.7, 67.3, 56.4, 52.1, 49.1, 29.7. EI-MS *m/z* 403.19 $(M+H)^+$; Anal. calcd for $C_{22}H_{22}N_6O_2$: (%) C, 65.66; H, 5.51; N, 20.88; Found: C, 65.67; H, 5.52; N, 20.89.

4-ethoxy-*N*-(6-(4-(pyrazine-2-carbonyl)-1,4-diazepan-1-yl)pyridin-3-yl)benzamide **(7b)** : Brown solid (88%); m.p. 207-209 °C; IR (KBr) υ_{max} / cm^{-1} 3560, 3021, 2835, 1684, 1411, 1365, 1024. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.98 (d, J = 1.6 Hz, 1H), 8.73 (d, J = 2.5 Hz, 2H), 8.57 (d, J = 2.6 Hz, 1H), 7.90 (dd, J = 9.2, 2.3 Hz, 3H), 7.10 – 7.01 (m, 2H), 6.90 (d, J = 9.0 Hz, 1H), 4.15 – 4.07 (m, 2H), 3.79 – 3.75 (m, 4H), 3.60 – 3.54 (m, 4H), 3.50 – 3.45 (m, 2H), 1.31 (t, J = 7.0, 1.5 Hz, 3H).^{13}C NMR (101 MHz, DMSO-d_6) δ 165.3, 165.2, 161.6, 155.6, 149.7, 146.1, 145.0, 143.7, 140.2, 132.0, 129.9, 127.7, 126.9, 114.5, 107.8, 63.9, 58.8, 55.4, 46.6, 46.0, 45.4, 41.3, 28.1, 15.0. EI-MS *m/z* 446.21 $(M+H)^+$; Anal. calcd for $C_{24}H_{26}N_6O_3$: (%) C, 64.57; H, 5.87; N, 18.82; Found: C, 64.58; H, 5.88; N, 18.83.

4-(tert-butyl)-*N*-(6-(4-(pyrazine-2-carbonyl)-1,4-diazepan-1-yl)pyridin-3-yl)benzamide **(7c)** :Off white solid (83%); m.p. 228-230 °C; IR (KBr) υ_{max} / cm^{-1} 3573, 3029, 2912, 1672, 1420, 1335, 1066. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 8.93 (d, J = 1.5 Hz, 1H), 8.78 (d, J = 2.6 Hz, 1H), 8.71 (dd, J = 2.6, 1.5 Hz, 1H), 8.57 (d, J = 2.6 Hz, 1H), 7.87 – 7.91 (m, 2H), 7.91 (s, 1H), 7.76 – 7.70 (m, 2H), 6.91 (d, J = 9.1 Hz, 1H), 3.68 – 3.62 (m, 8H), 2.54 – 2.38 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.2, 164.6, 153.1, 148.9, 145.8, 145.0, 143.9, 141.1, 134.2, 131.7, 131.2, 130.2, 127.7, 125.4, 107.7, 67.3, 55.4, 53.8, 46.9, 38.7, 35.1, 30.2, 25.6. EI-MS *m/z* 458.25 $(M+H)^+$; Anal. calcd for $C_{26}H_{30}N_6O_2$: (%) C, 68.11; H, 6.59; N, 18.33; Found: C, 68.13; H, 6.60; N, 18.34.

4-chloro-*N*-(6-(4-(pyrazine-2-carbonyl)-1,4-diazepan-1-yl)pyridin-3-yl)benzamide **(7d)** : White solid (77%); m.p. 240-242 °C; IR (KBr) υ_{max} / cm^{-1} 3575, 3039, 2940, 1684, 1412, 13495, 1188, 1021, 782. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 8.76 – 8.65 (m, 2H), 8.64(dd, J = 9.1, 2.8 Hz, 1H), 8.00 – 7.58 (m, 3H), 7.55 – 7.51 (m, 2H), 6.72 (dd, J = 9.2, 2.4 Hz, 1H), 3.84 – 3.50 (m, 8H), 1.93 (q, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.5, 164.8, 156.2, 149.8, 146.4, 145.5, 143.1, 140.8, 136.8, 133.7, 131.8, 129.2, 128.4, 127.7, 107.5, 55.9, 53.4, 50.7, 47.8, 25.8. EI-MS *m/z* 436.14 $(M+H)^{+}$; Anal. calcd for $C_{22}H_{21}ClN_6O_2$: (%) C, 60.48; H, 4.84; N, 19.25; Found: C, 60.49; H, 4.85; N, 19.50.

4-bromo-*N*-(6-(4-(pyrazine-2-carbonyl)-1,4-diazepan-1-yl)pyridin-3-yl)benzamide **(7e)** :

White solid (90%); m.p. 119-121 °C; IR (KBr) υ_{max} / cm^{-1} 3590, 3021, 2843, 1687, 1410, 1340, 570. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.79 – 8.68 (m, 2H), 8.65(dd, J = 9.1, 2.8 Hz, 1H), 8.42 – 8.34 (m, 1H), 7.98 – 7.90 (m, 2H), 7.89 (m, 1H), 7.79 – 7.74 (m, 2H), 6.73 (dd, J = 9.2, 2.4 Hz, 1H), 3.85 – 3.52 (m, 8H), 1.96 (q, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.7, 166.6, 164.6, 154.5, 150.4, 150.1, 145.9, 144.3, 143.5, 141.4, 134.2, 132.1, 131.9, 130.1, 125.8, 125.6, 105.7, 48.4, 47.7, 46.2, 45.2, 29.5. EI-MS *m/z* 481.19 $(M+H)^{+}$ 483.21 $(M+H)^{+2}$; Anal. Calcd for $C_{22}H_{21}BrN_6O_2$: (%) C, 54.91; H, 4.40; N, 17.46; Found: C, 54.93; H, 4.42; N, 17.47.

3-nitro-*N*-(6-(4-(pyrazine-2-carbonyl)-1,4-diazepan-1-yl)pyridin-3-yl)benzamide **(7f)** : Yellow solid (78%); m.p. 212-213 °C; IR (KBr) υ_{max} / cm^{-1} 3591, 3041, 2893, 1689, 1411, 1351, 1120, 1061. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 8.90-8.76 (m, 2H), 8.63(s, 1H) 8.51-8.32 (m, 4H) 7.97 – 7.90 (m, 2H), 6.73 (d, J = 9.3 Hz, 1H), 3.85-3.32 (m, 8H), 1.97 (p, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.3, 168.1, 159.4, 154.9, 153.0, 150.6, 149.0, 148.2, 146.1, 141.3, 139.2,136.8, 135.4, 131.3, 127.5, 110.55, 53.32, 52.8, 59.0, 50.0, 29.3. EI-MS *m/z* 447.18 $(M+H)^{+}$; Anal. calcd for $C_{22}H_{21}N_7O_4$: (%) C, 59.05; H, 4.73; N, 21.91; Found: C, 58.20; H, 4.43; N, 22.64.

3-bromo-*N*-(6-(4-(pyrazine-2-carbonyl)-1,4-diazepan-1-yl)pyridin-3-yl)benzamide **(7g)** : White solid (71%); m.p. 246-248 °C; IR (KBr) υ_{max} / cm^{-1} 3590, 3050, 2931, 1682, 1410, 1333, 1276, 1035, 615. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.87 (d, J = 1.6 Hz, 1H), 8.76 (d, J = 2.6 Hz, 1H), 8.70 (dd, J = 2.6, 1.6 Hz, 1H), 8.49 (d, J = 2.6 Hz, 1H), 8.24 (t, J = 1.8 Hz, 1H), 7.99 – 7.90 (m, 2H), 7.83 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 7.54 (t, J = 7.9 Hz, 1H), 6.93 (d, J = 9.1 Hz, 1H), 3.57 3– 3.50 (m, 4H), 3.45 – 3.37 (m, 6H), 1.85(p, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.5, 168.3, 159.3, 155.1, 154.9, 152.9, 150.5, 149.1, 148.1, 141.2, 139.1, 136.9, 135.2, 131.3, 130.1, 127.6, 110.4, 53.1, 52.6, 51.8, 50.1, 30.0. EI-MS *m/z* 480.09 $(M+H)^{+}$; 482.08 $(M+H)^{+2}$; Anal. Calcd for $C_{22}H_{21}BrN_6O_2$: (%) C, 54.91; H, 4.40; N, 17.46; Found: C, 54.92; H, 4.41; N, 17.48.

2-iodo-*N*-(6-(4-(pyrazine-2-carbonyl)-1,4-diazepan-1-yl)pyridin-3-yl)benzamide **(7h)** : Off white solid (80%); m.p. 226-228 °C; IR (KBr) υ_{max} / cm^{-1} 3581, 3032, 2916, 1689, 1417, 1325, 1130, 1060, 634. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.92 (d, J = 1.5 Hz, 1H), 8.88 (d, J = 2.6 Hz, 1H), 8.80 – 8.71 (m, 2H), 7.95 (dd, J = 9.0, 2.7 Hz, 2H), 7.49 (dd, J = 8.5, 6.6 Hz, 1H), 7.35 (d, J = 7.6 Hz, 2H), 6.91 (d, J = 9.1 Hz, 1H), 3.82 – 3.78 (m, 2H), 3.59 (t, 4H), 3.50 – 3.41 (m, 2H), 1.77(p, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.0, 165.3, 155.9, 146.0, 145.0, 143.7, 139.9, 137.4, 135.8, 131.0, 130.8, 130.1 127.8, 127.3, 122.3, 107.7, 93.8, 57.0, 53.2, 50.9, 47.2, 25.9. EI-MS *m/z* 528.17 $(M+H)^{+}$; Anal. calcd for $C_{22}H_{21}IN_6O_2$: (%) C, 50.01; H, 4.02; N, 15.91; Found: C, 50.03 H, 4.04; N, 15.92.

4-bromo-2-chloro-*N*-(6-(4-(pyrazine-2-carbonyl)-1,4-diazepan-1-yl)pyridin-3-yl)benzamide **(7i)** : White solid (77%); m.p. 221-223 °C; IR (KBr) υ_{max} / cm^{-1} 3560, 3029, 2864, 1686, 1415, 1323, 1109, 1031, 623. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.87-8.76 (dd, J = 2.6, 1.5 Hz, 2H), 8.52 (s, 1H), 7.90 (dd, J = 9.1, 2.7 Hz, 1H), 7.87 (d, J = 2.4 Hz, 1H), 7.69 (dd, J = 8.6, 2.4 Hz, 1H), 7.57 (d, J = 8.6 Hz, 1H), 6.73 (d, J = 9.1 Hz, 1H), 3.80-3.41 (m, 8H), 1.73 (p, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.4, 161.8, 156.2, 148.7, 148.2, 147.0, 145.4, 145.0, 144.7, 143.9, 143.8, 140.9, 131.7, 126.6, 107.4, 57.0, 53.2, 50.9, 47.2,

29.8. EI-MS *m/z* 514.06 $(M+H)^+$; 516.08 $(M+H)^{+2}$; Anal. Calcd for $C_{22}H_{20}BrClN_6O_2$: (%) C, 51.23; H, 3.92; N, 16.29; Found: C, 51.24; H, 3.93; N, 16.30.

2,4-dichloro-*N*-(6-(4-(pyrazine-2-carbonyl)-1,4-diazepan-1-yl)pyridin-3-yl)benzamide **(7j)** : Off white solid (80%); m.p.197-199 °C; IR (KBr) υ_{max} / cm^{-1} 3597, 3028, 2947, 1687, 1427, 1023, 569. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 8.89 (m. 2H), 8.78 (d, J = 2.5 Hz, 1H), 8.73 (dd, J = 2.6, 1.5 Hz, 1H), 87.89-7.5 (m, 3H), 7.42 (m, 1H), 7.78 (d, J = 2.4 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 9.0 Hz, 1H), 3.89 – 3.36 (m, 8H), 1.71(p, 2H) ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.4, 161.8, 156.2, 148.7, 148.2 147.0, 145.4, 146.0, 145.7, 143.9, 143.8, 141.0, 132.9, 126.7, 109.4, 58.9, 54.2, 51.9, 48.2, 32.8. EI-MS *m/z* 470.12 $(M+H)^+$; Anal. Calcd for $C_{22}H_{20}Cl_2N_6O_2$: (%) C, 56.06; H, 4.28; N, 17.83; Found: C, 56.08; H, 4.29; N, 17.84.

N-(6-(4-(pyrazine-2-carbonyl)-1,4-diazepan-1-yl)pyridin-3-yl)pyrazine-2-carboxamide **(7k)** : Brown solid (79%); m.p. 135-136 °C; IR (KBr) υ_{max} / cm^{-1} 3572, 3021, 2915, 1677, 1454, 1350, 1090. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.67 (s, 1H), 9.30 (d, J = 1.6 Hz, 1H), 8.94 (d, J = 2.7 Hz, 1H), 8.89 (d, J = 1.5 Hz, 1H), 8.81 (dd, J = 2.5, 1.7 Hz, 1H), 8.75 (d, J = 2.6 Hz, 1H), 8.70 (dd, J = 2.6, 1.7 Hz, 1H), 8.64 (d, J = 2.6 Hz, 1H), 8.17 (dd, J = 9.1, 2.7 Hz, 1H), 6.90 (d, J = 9.1 Hz, 1H), 3.66 – 3.60 (m, 8H), 2.47 – 2.28 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.5, 162.0, 157.0, 149.8, 148.2, 146.2, 145.3, 145.2, 144.7, 143.3, 143.0, 140.6, 130.1, 126.6, 109.1, 67.3, 56.4, 52.8, 49.9, 28.7. EI-MS *m/z* 405.17 $(M+H)^+$; Anal. calcd for $C_{20}H_{20}N_8O_2$: (%) C, 59.40; H, 4.98; N, 27.71; Found: C, 59.42; H, 4.90; N, 27.72.

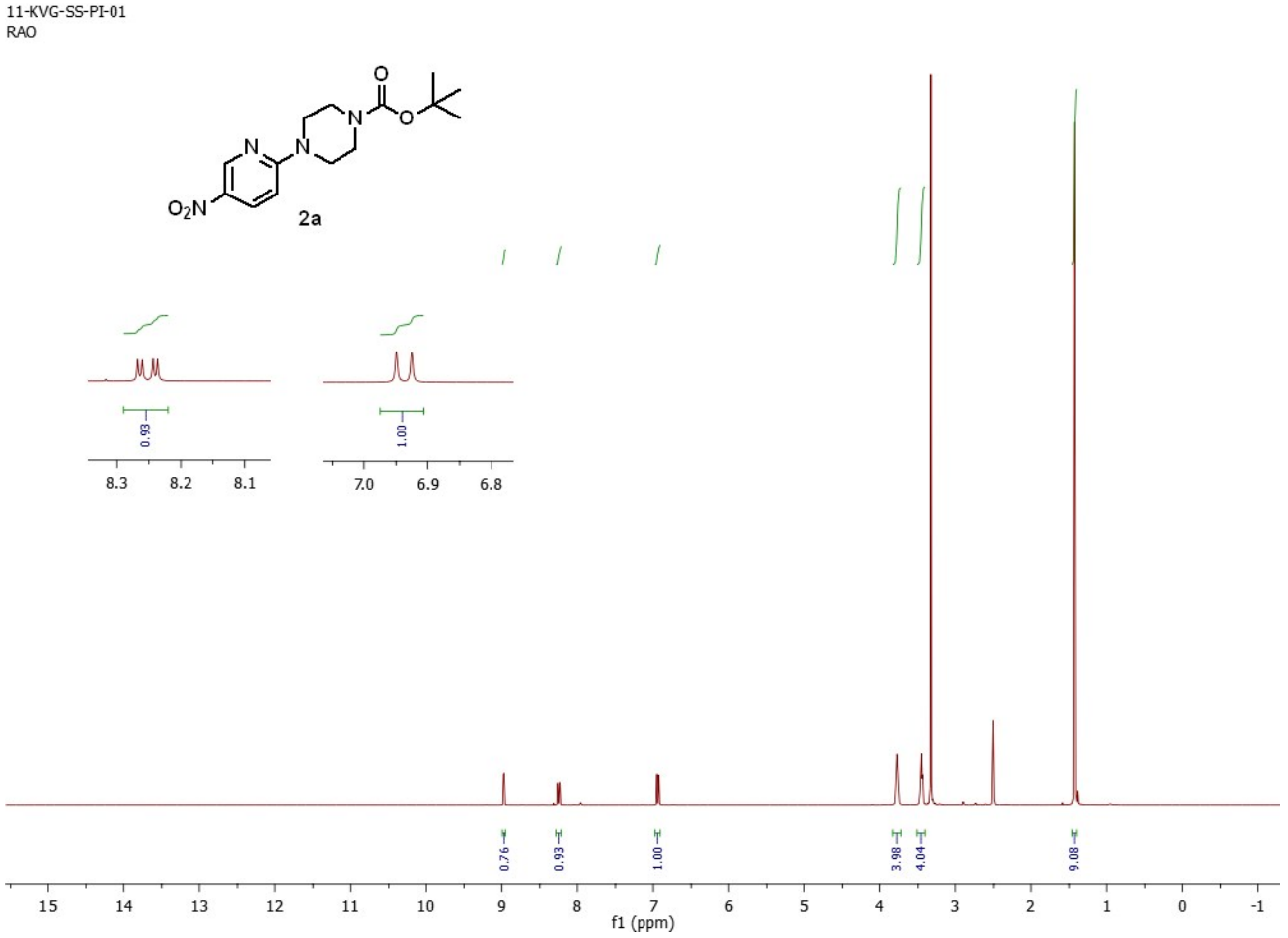
N-(6-(4-(pyrazine-2-carbonyl)-1,4-diazepan-1-yl)pyridin-3-yl)isonicotinamide **(7l)** : White solid (82%); m.p. 139-141 °C; IR (KBr) υ_{max} / cm^{-1} 3585, 3029, 2840, 1684, 1415, 1342, 1070. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 8.93 (d, J = 2.5 Hz, 2H), 8.91 (d, J = 1.6 Hz, 2H), 8.81 (dd, J = 2.5, 1.7 Hz, 2H), 8.78 (d, J = 2.5 Hz, 1H), 8.70 (dd, J = 2.6, 1.6 Hz, 1H), 8.66 (d, J = 2.7 Hz, 1H), 8.07 (dd, J = 9.1, 2.5 Hz, 1H), 6.89 (d, J = 9.2 Hz, 1H), 3.69 – 3.51 (m, 2H), 3.51 (t, 2H), 3.40 – 3.33 (m, 6H), 1.88(p, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.5, 162.9, 156.0, 149.7, 146.3, 145.3, 145.1, 143.7, 143.6, 140.9, 131.2, 126.2, 121.2,

107.5, 67.3, 55.4, 53.8, 46.9, 25.6. EI-MS *m/z* 404.18 $(M+H)^+$; Anal. calcd for $C_{21}H_{21}N_7O_2$: (%) C, 62.53; H, 5.25; N, 24.31; Found: C, 62.54; H, 5.26; N, 24.33.

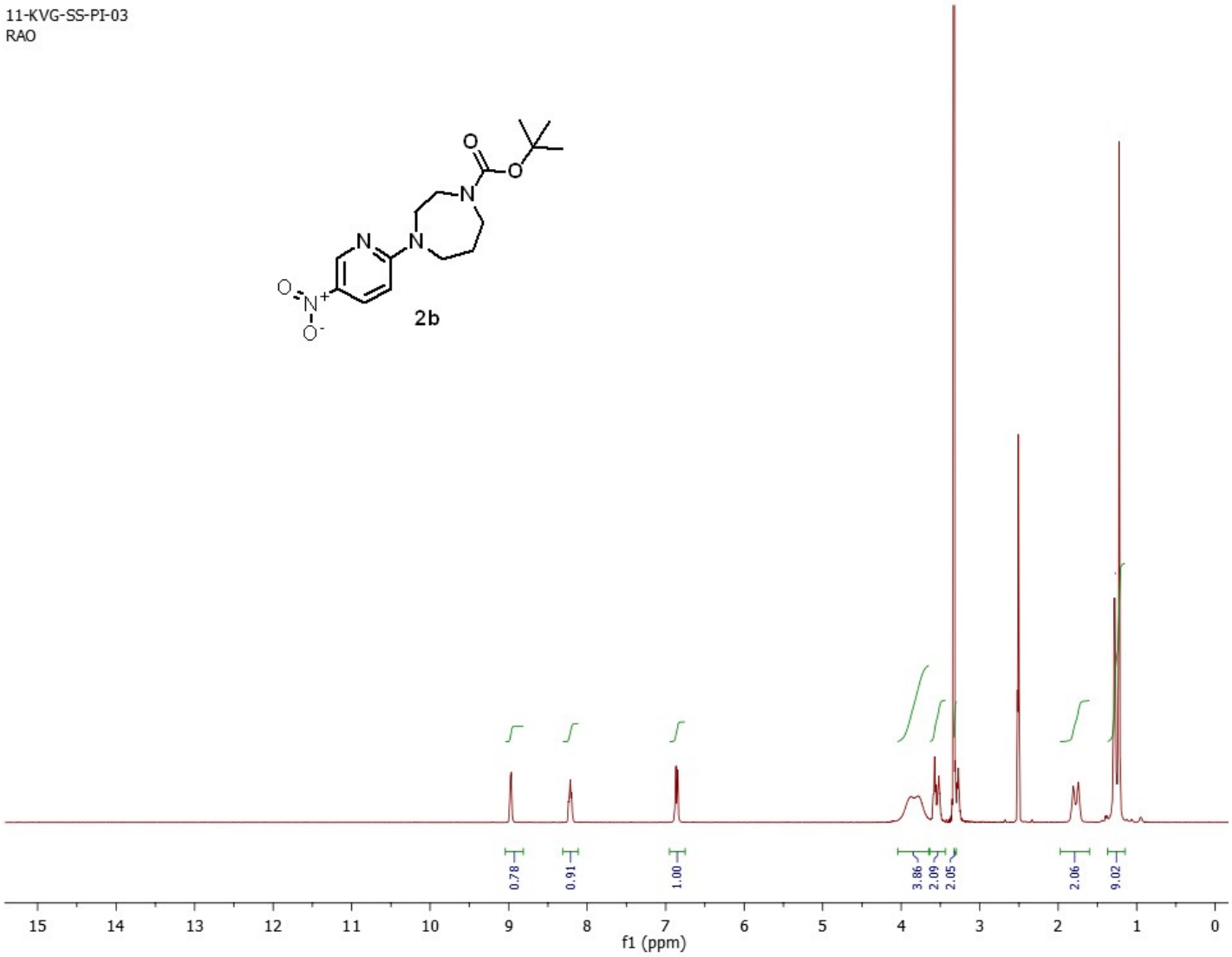
2-chloro-6-fluoro-*N*-(6-(4-(pyrazine-2-carbonyl)-1,4-diazepan-1-yl)pyridin-3-yl)benzamide **(7m)** : Off white solid (81%); m.p. 198-199 °C; IR (KBr) υ_{max} / cm^{-1} 3594, 3042, 2913, 1687, 1412, 1036, 654. ^1H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 8.90 (d, J = 1.6 Hz, 1H), 8.80 (d, J = 2.5 Hz, 1H), 8.74 (dd, J = 2.6, 1.6 Hz, 1H), 8.50 (d, J = 2.6 Hz, 1H), 7.61 – 7.44 (m, 4H), 6.92 (d, J = 9.1 Hz, 1H), 3.67 – 3.52 (m, 4H), 3.55 – 3.47 (m, 6H), 1.87(p, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.7, 164.6, 159.3, 156.2, 149.6, 146.3, 145.1, 143.4, 141.8, 137.8, 136.7, 135.7, 131.2, 129.2, 128.1, 127.2, 113.2, 58.2, 56.2, 52.9, 46.2, 30.8. EI-MS *m/z* 454.14 $(M+H)^+$; Anal. calcd for $C_{22}H_{20}ClFN_6O_2$: (%) C, 58.09; H, 4.43; N, 18.49; Found: C, 58.10; H, 4.44; N, 18.50.

^{1}H and ^{13}C NMR spectra's

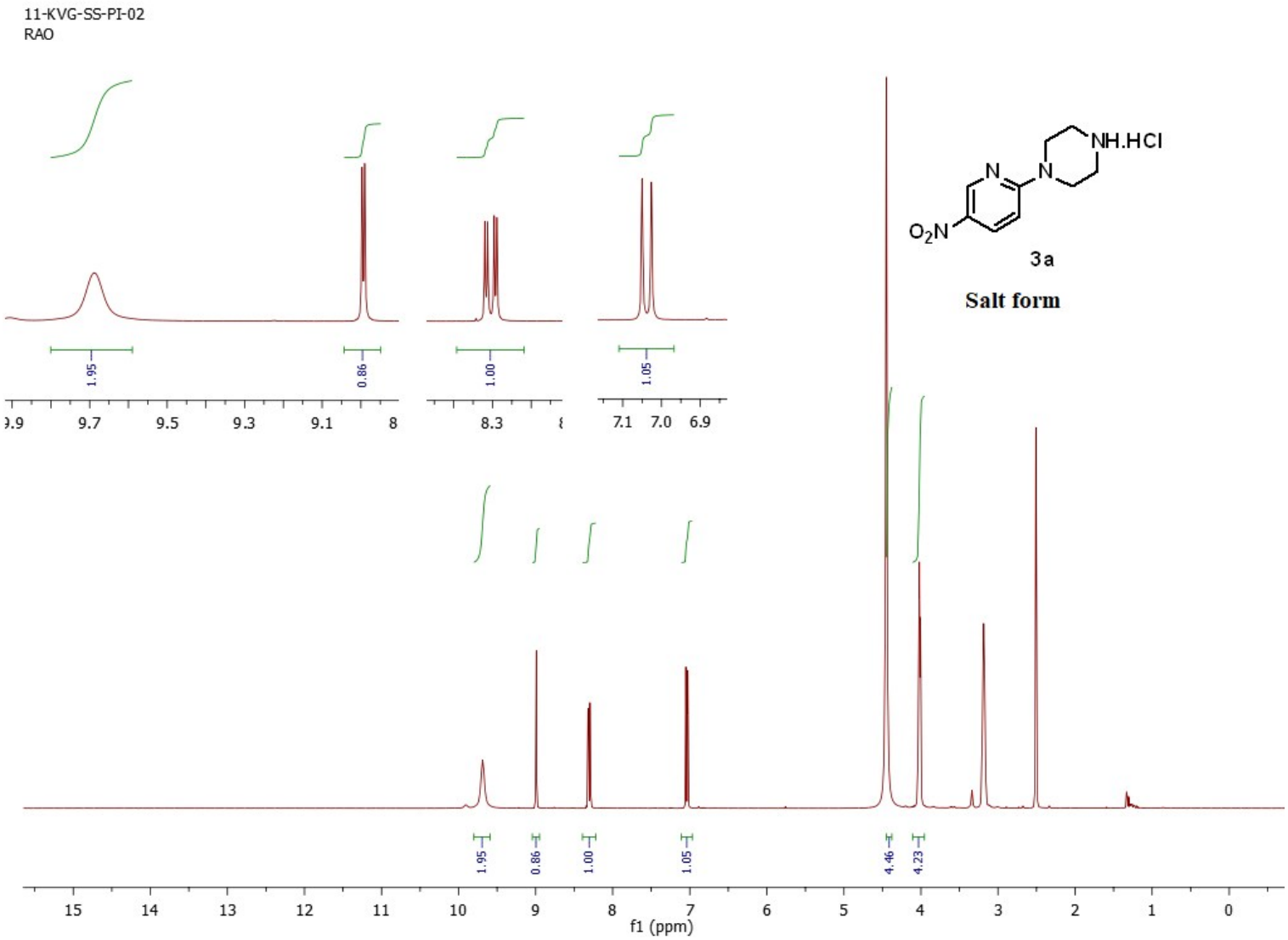
^{1}H and ^{13}C NMR spectras of intermediate compounds and final compounds:



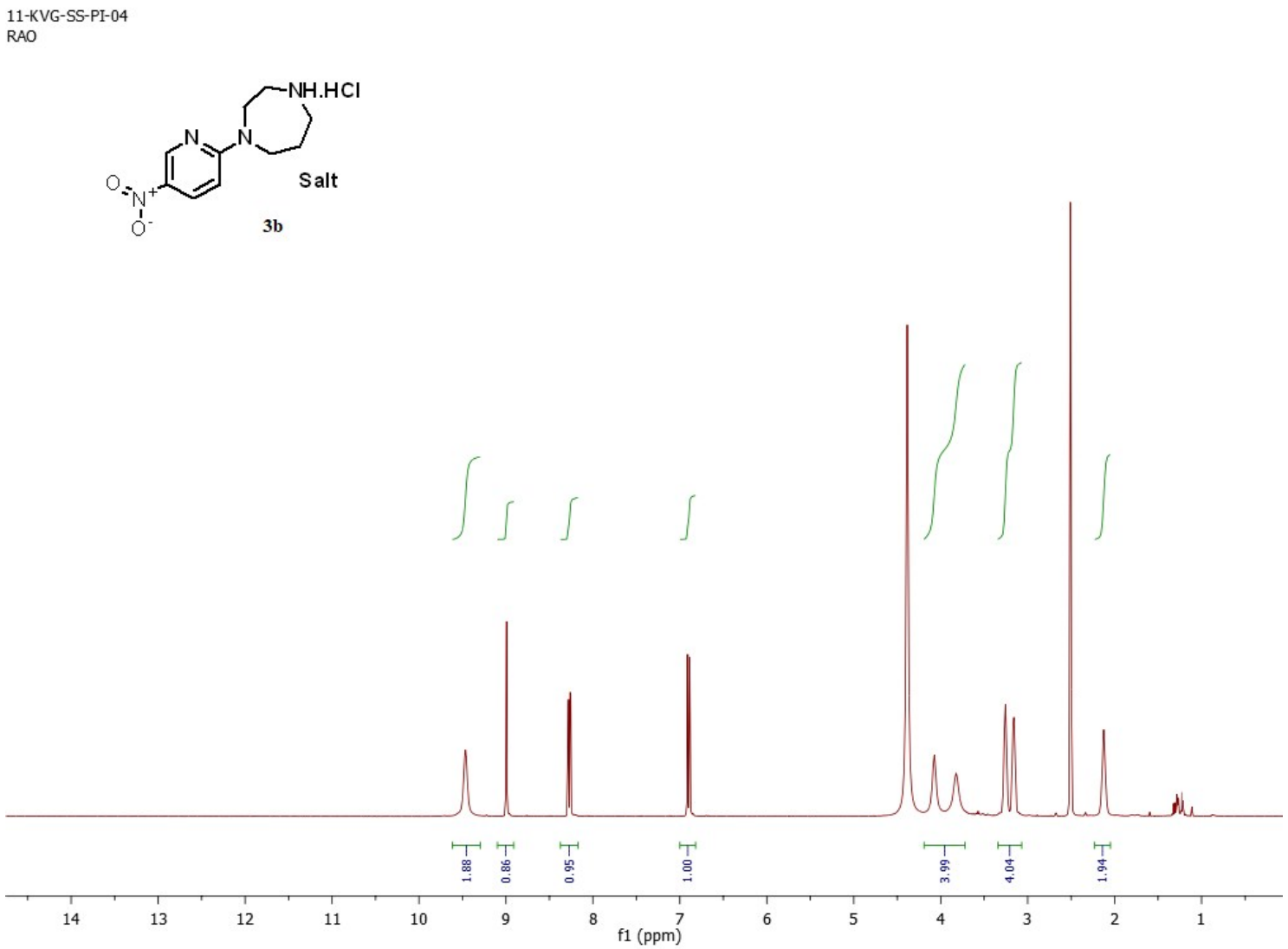
$^{1}HNMR$ of 2a


11-KVG-SS-PI-03
RAO
2b
0.78
0.91
1.00
3.86
2.09
2.05
2.06
9.02
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

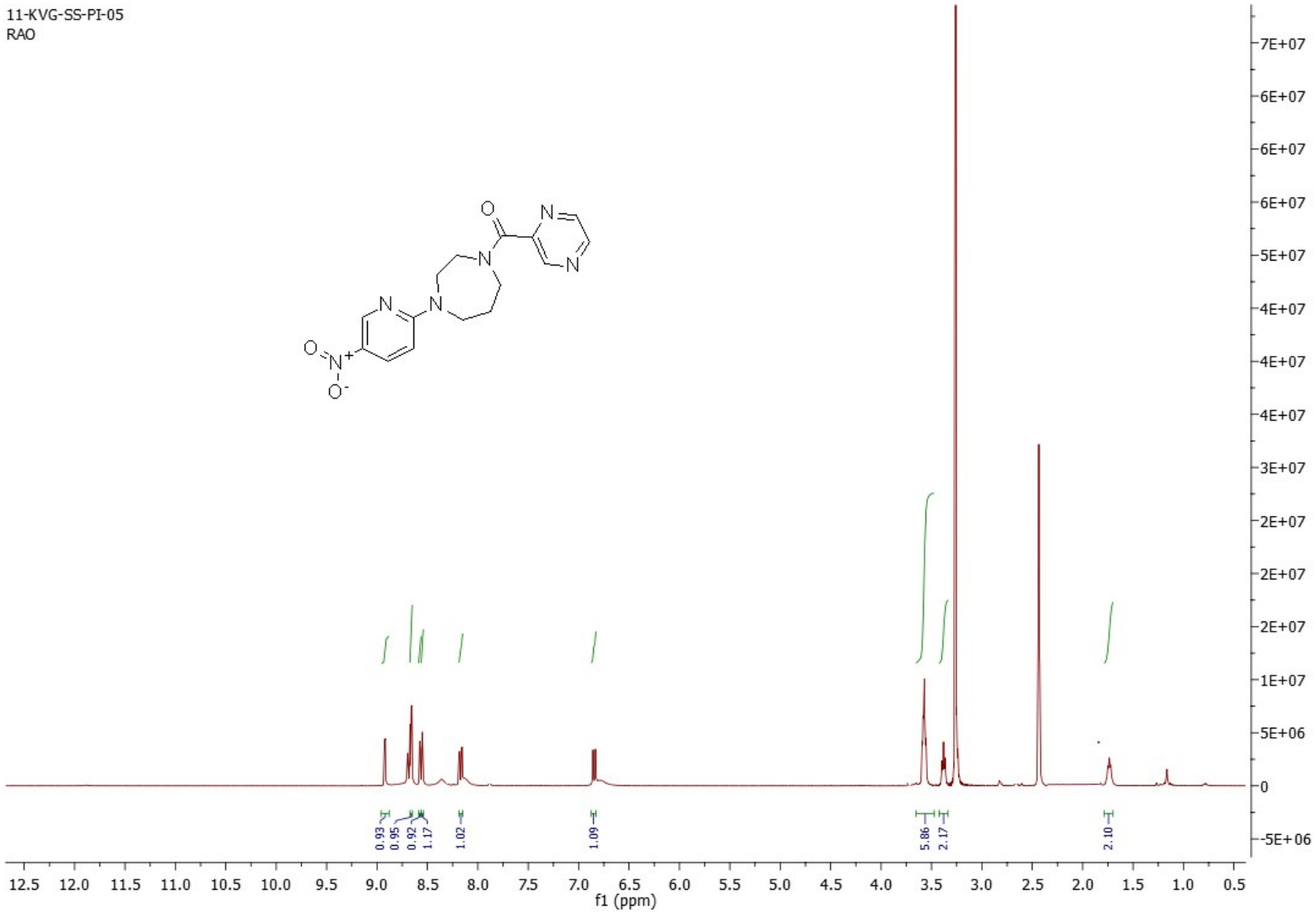
^{1}HNMR of 2b


11-KVG-SS-PI-02
RAO
NH.HCl
N
N
O_2N
3a
Salt form
1.95
0.86
1.00
1.05
4.46
4.23
f1 (ppm)

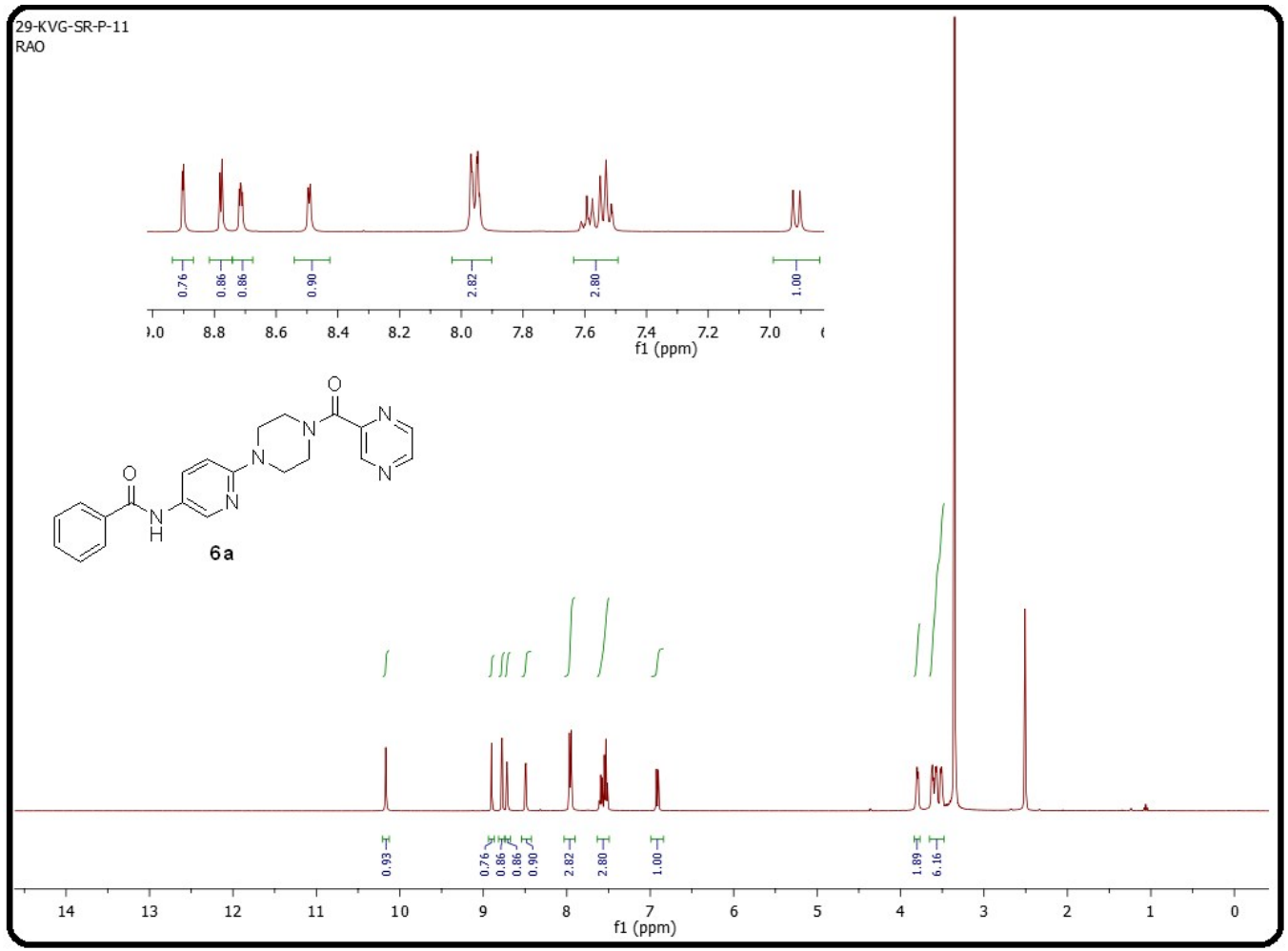
^{1}HNMR of 3a


11-KVG-SS-PI-04
RAO
NH.HCl
Salt
3b
1.88
0.86
0.95
1.00
3.99
4.04
1.94
14
13
12
11
10
9
8
7
6
5
4
3
2
1
f1 (ppm)

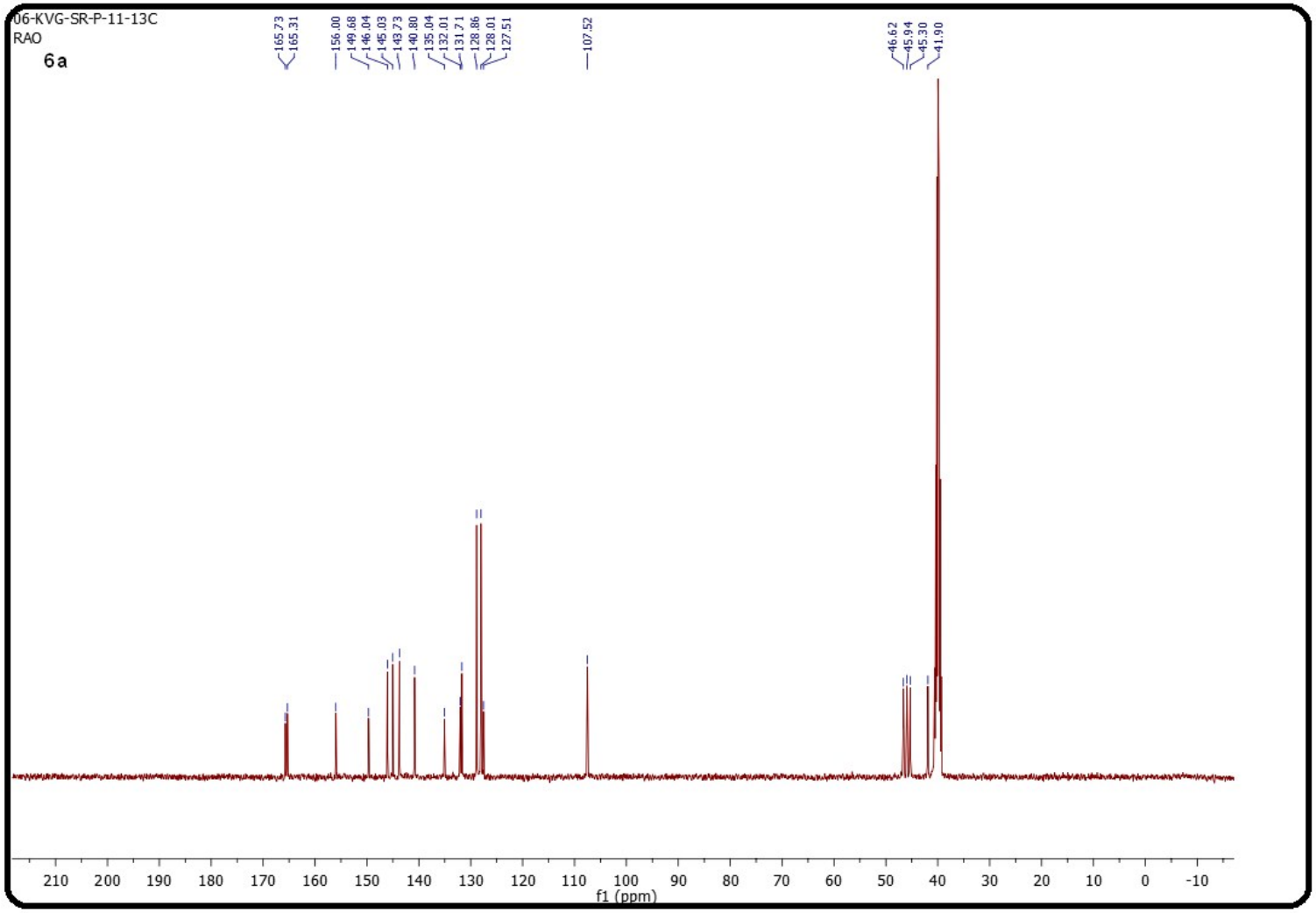
^{1}HNMR of 3b


11-KVG-SS-PI-05
RAO
7E+07
6E+07
6E+07
6E+07
5E+07
4E+07
4E+07
4E+07
3E+07
2E+07
2E+07
2E+07
1E+07
5E+06
0
-5E+06
0.93
0.95
0.92
1.17
1.02
1.09
5.86
2.17
2.10
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

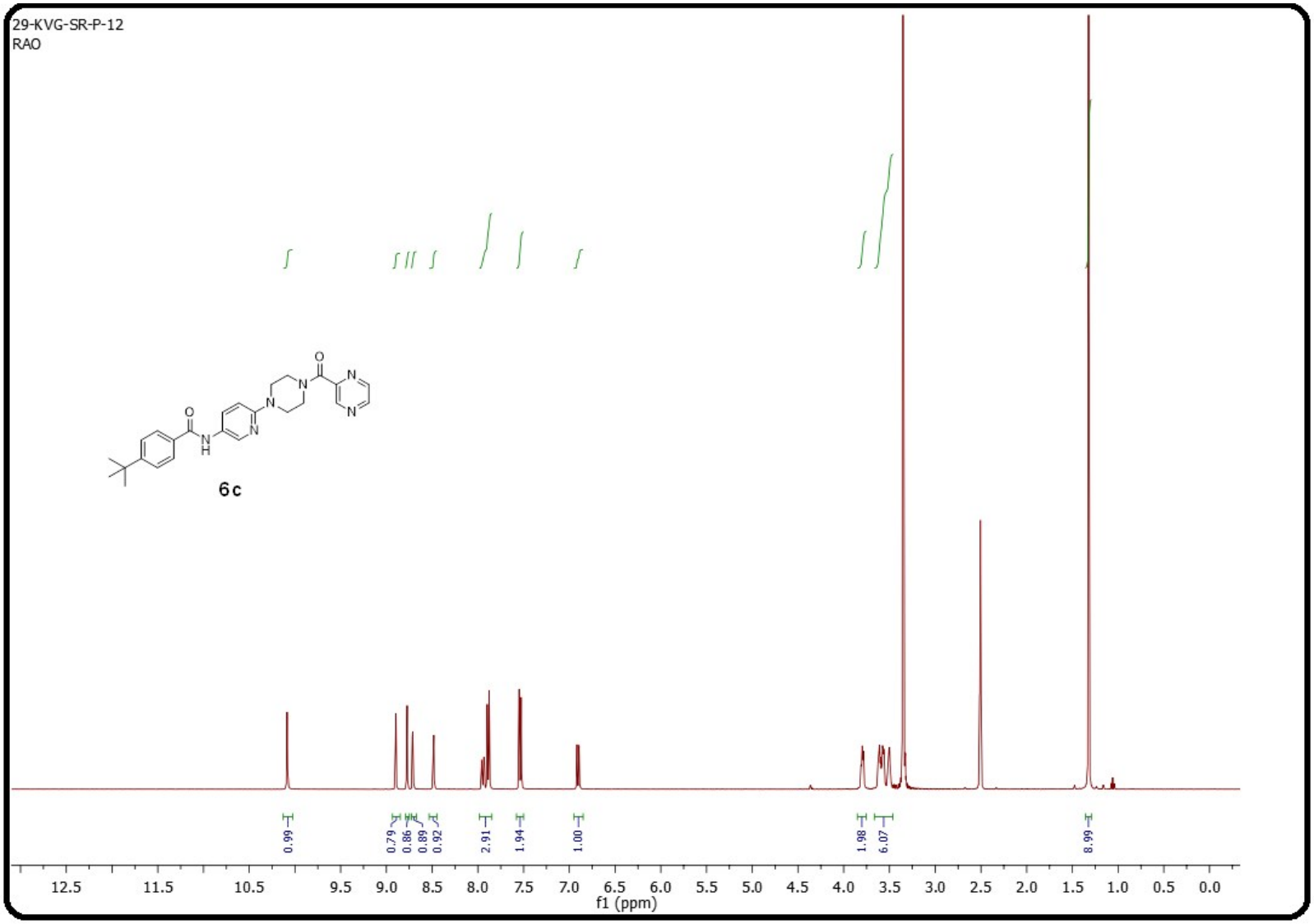
1HNMR of 4b



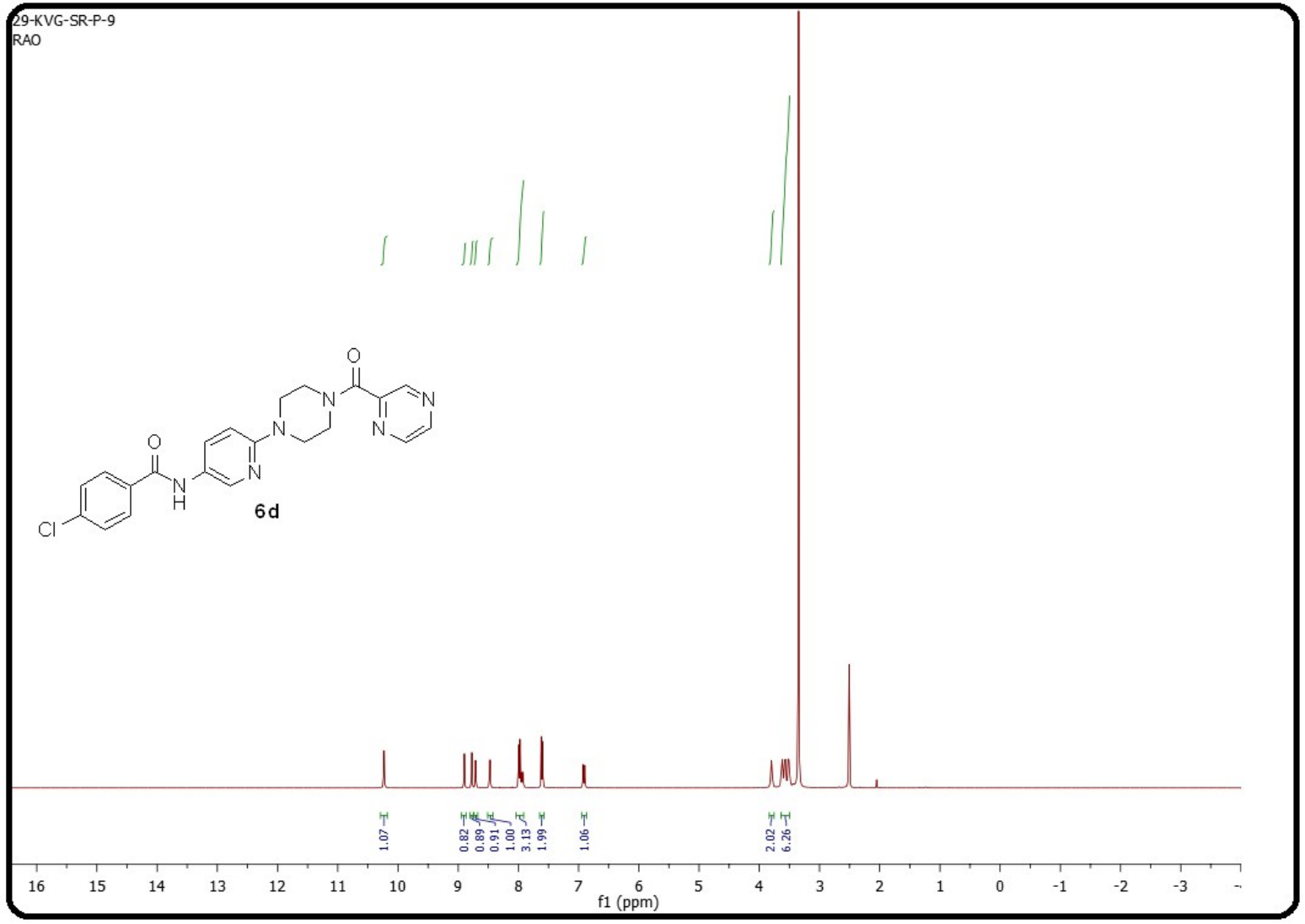
[1]HNMR of **6a**


06-KVG-SR-P-11-13C
RAO
6a
165.73
165.31
156.00
149.68
146.04
145.03
143.73
140.80
135.04
132.01
131.71
128.86
128.01
127.51
107.52
46.62
45.94
45.30
41.90
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

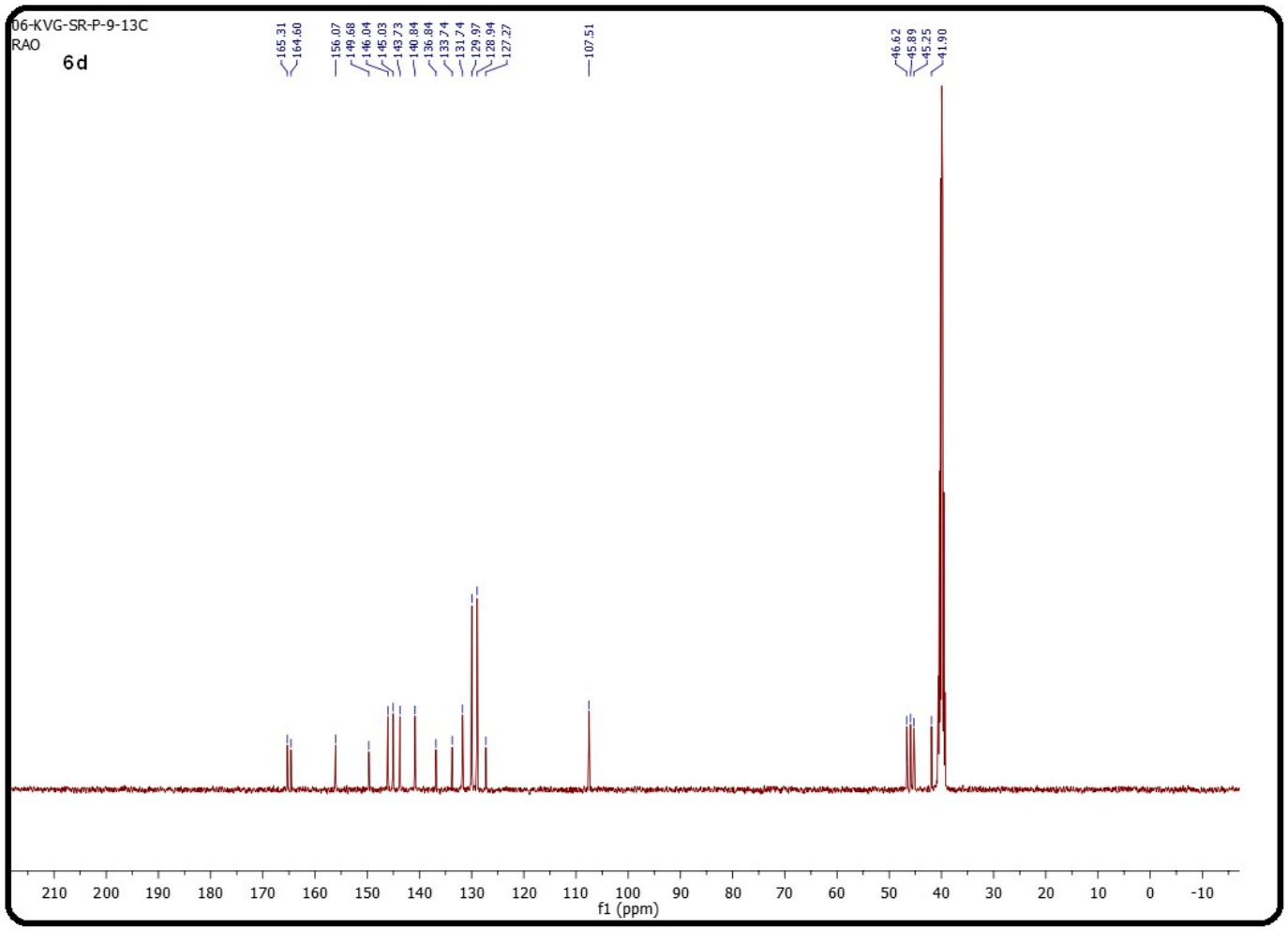
^{13}CNMR of **6a**


29-KVG-SR-P-12
RAO
6c
0.99
0.79
0.86
0.89
0.92
2.91
1.94
1.00
1.98
6.07
8.99
12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

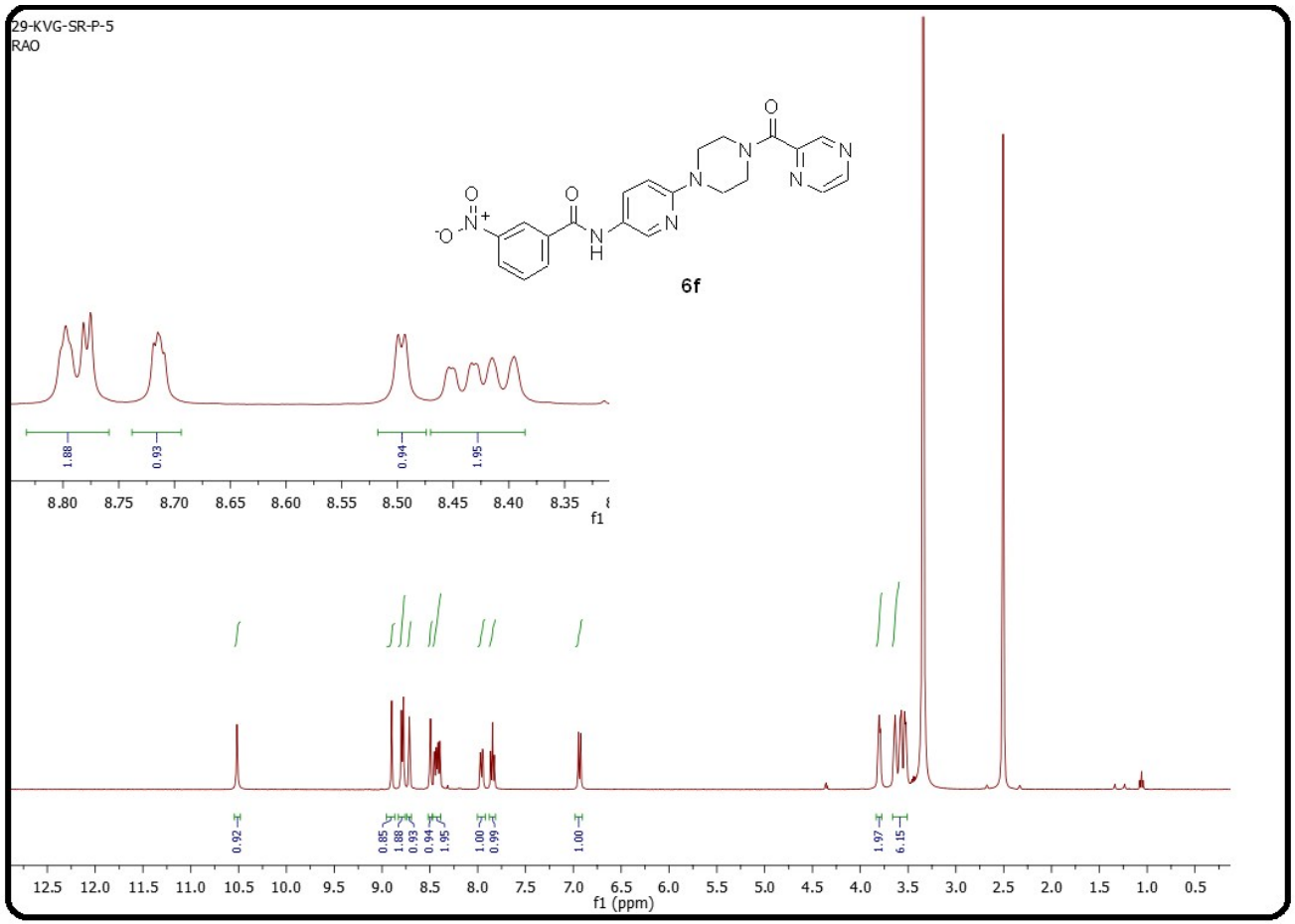
^{1}HNMR of **6c**



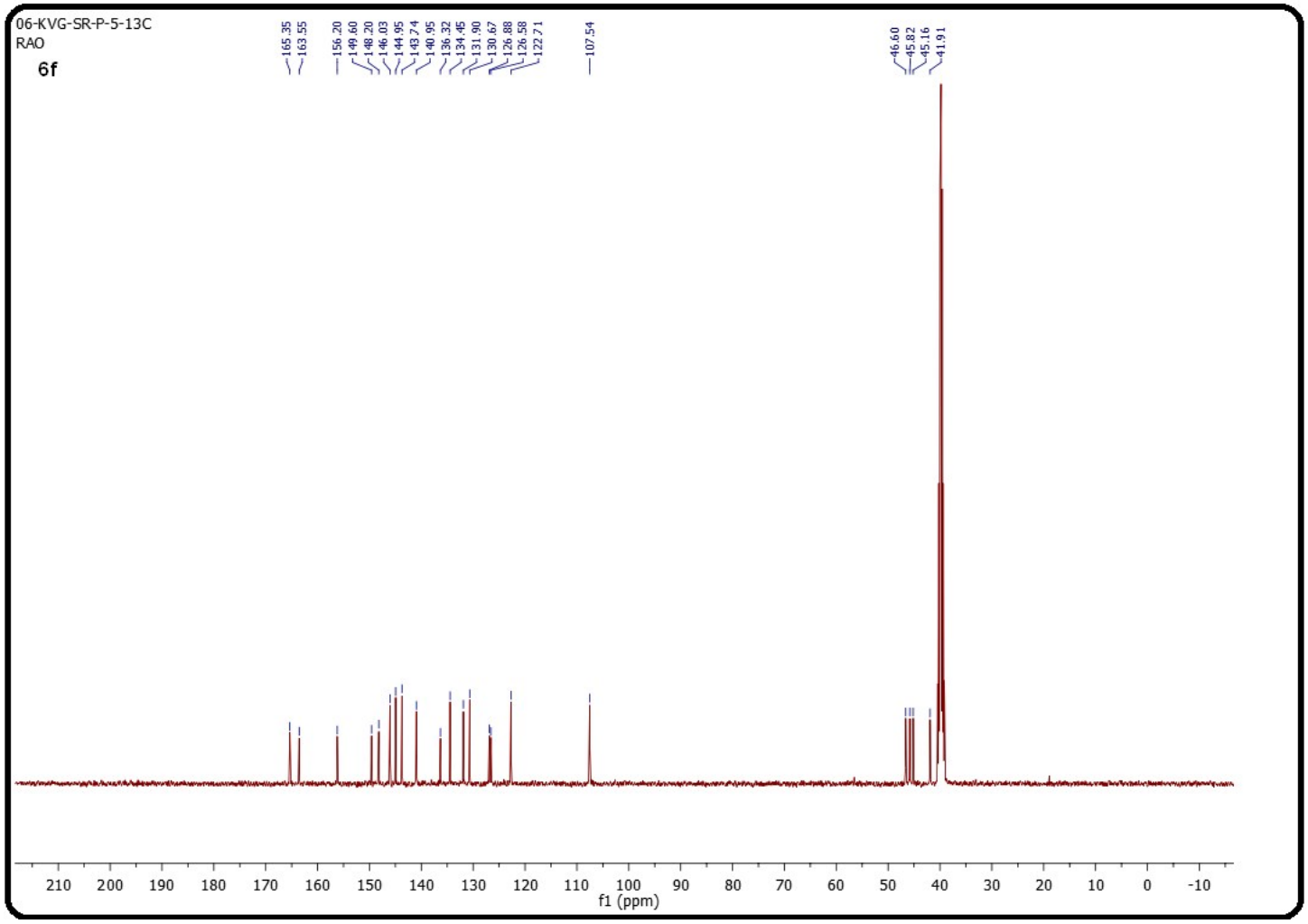
^{1}HNMR of **6d**


06-KVG-SR-P-9-13C
RAO
6d
165.31
164.60
156.07
149.68
146.04
145.03
143.73
140.84
136.84
133.74
131.74
129.97
128.94
127.27
107.51
46.62
45.89
45.25
41.90
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

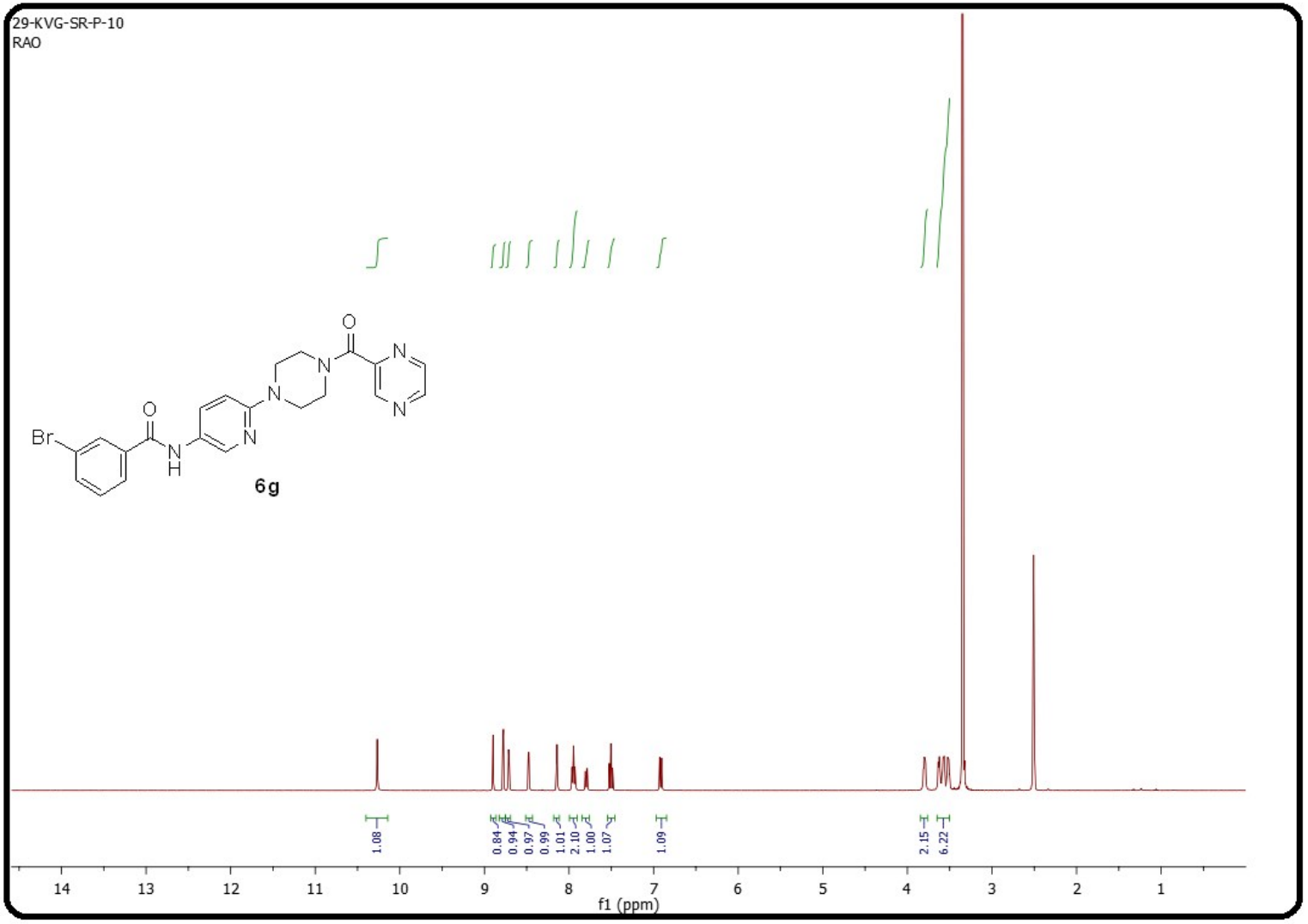
^{13}CNMR of **6d**



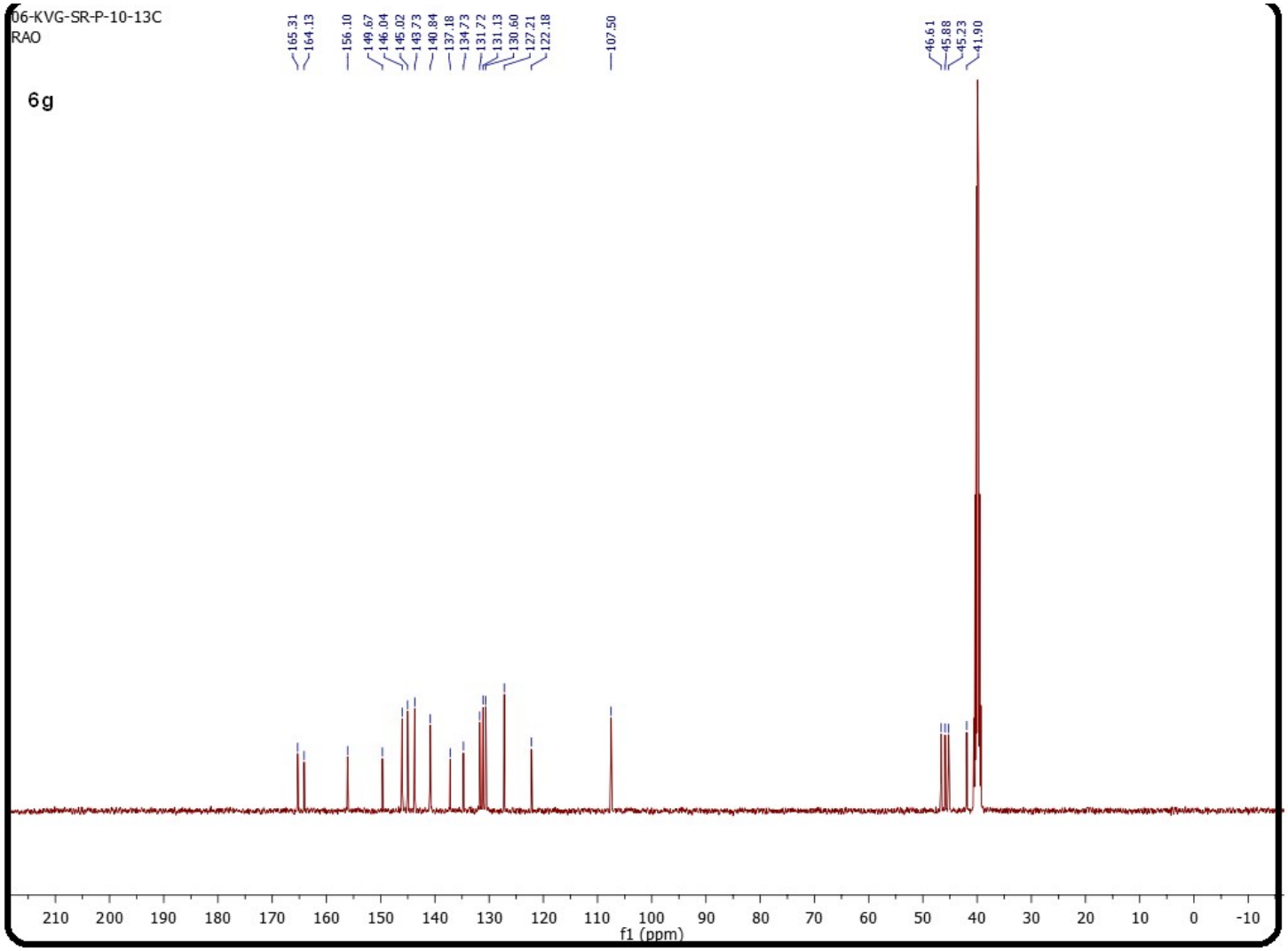
^{13}HNMR of **6f**


06-KVG-SR-P-5-13C
RAO
6f
165.35
163.55
156.20
149.60
148.20
146.03
144.95
143.74
140.95
136.32
134.45
131.90
130.67
126.88
126.58
122.71
107.54
46.60
45.82
45.16
41.91
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

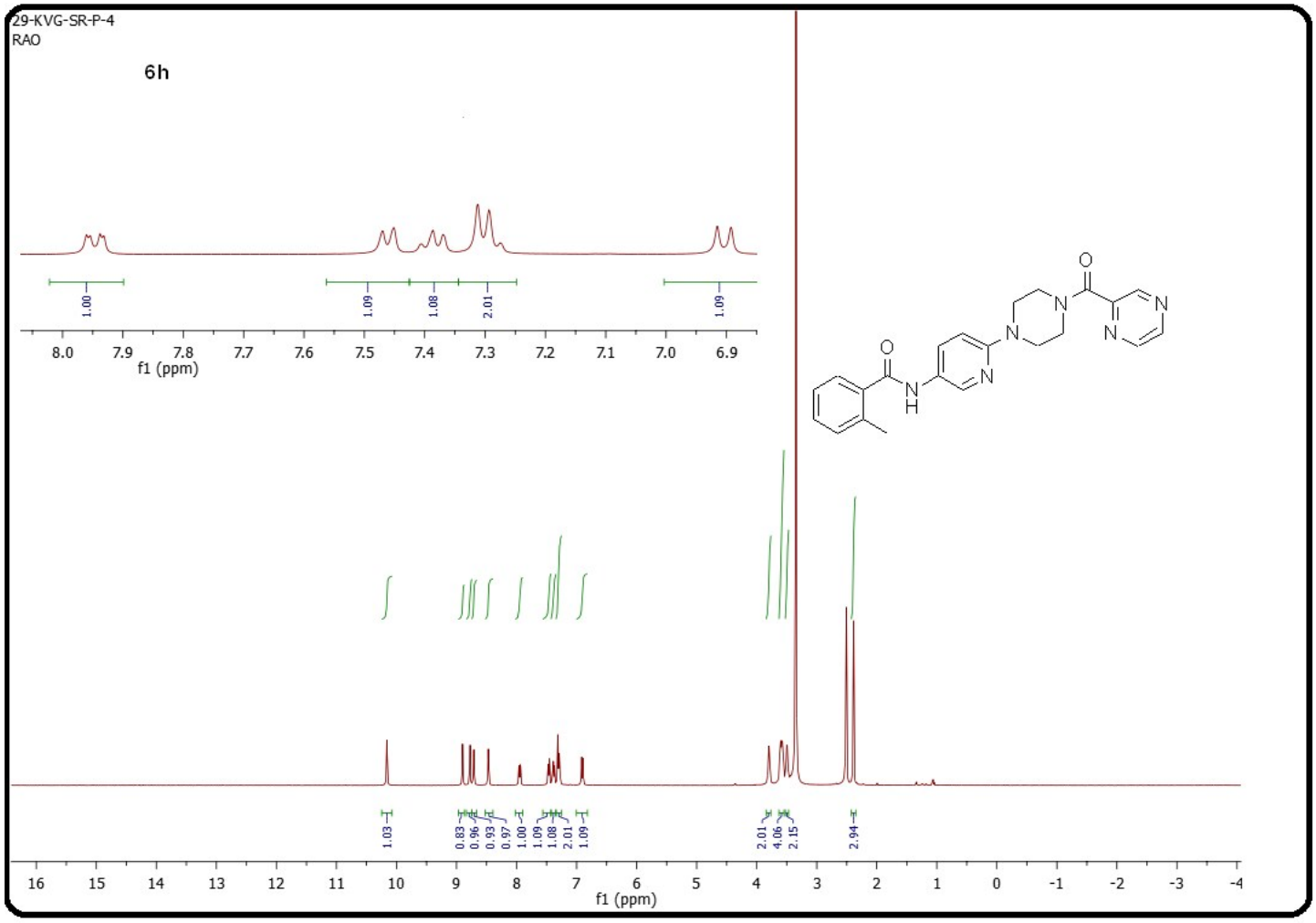
^{13}CNMR of **6f**


29-KVG-SR-P-10
RAO
6g
1.08
0.84
0.94
0.97
0.99
1.01
2.10
1.00
1.07
1.09
2.15
6.22
f1 (ppm)

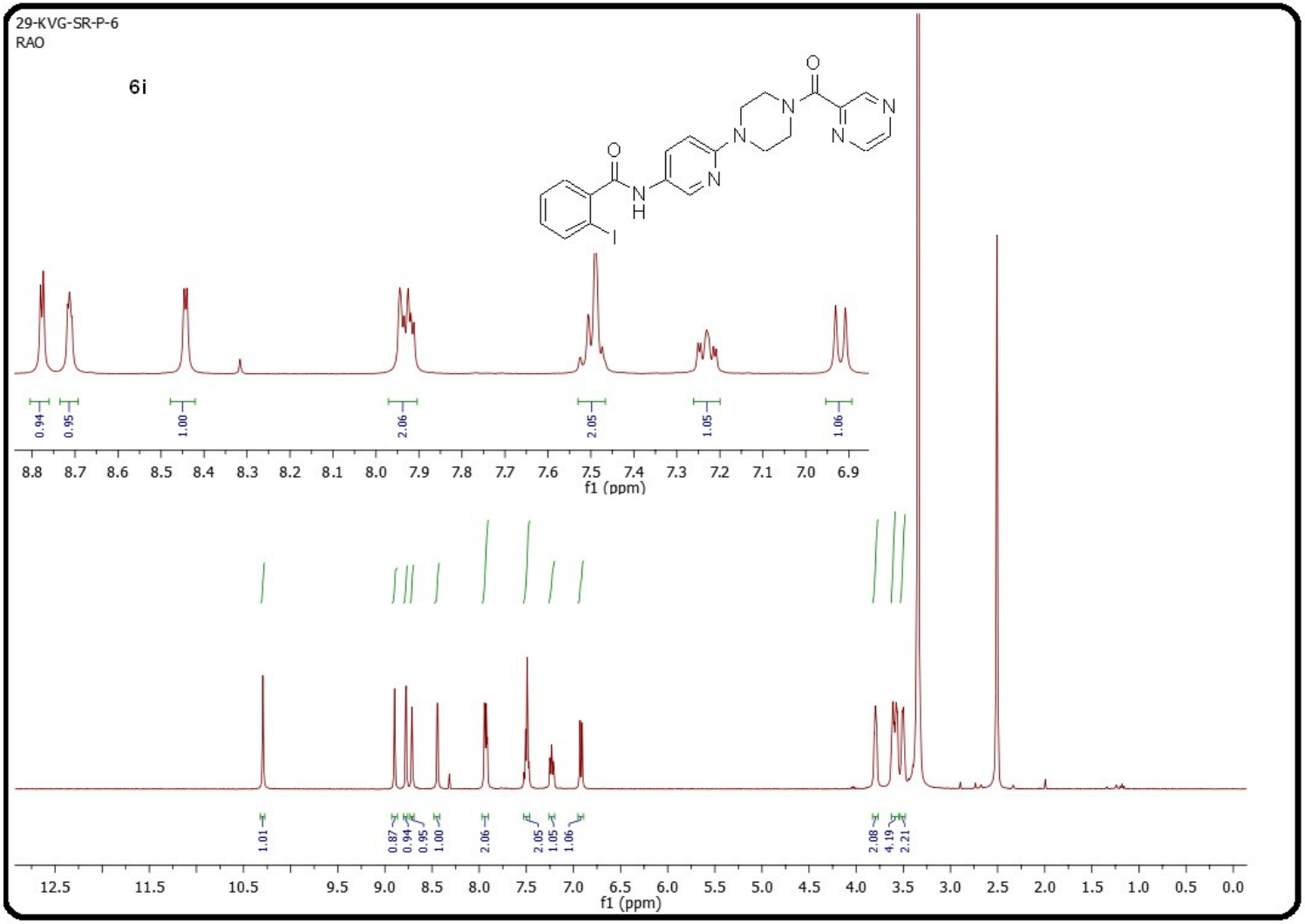
^{1}HNMR of **6g**


06-KVG-SR-P-10-13C
RAO
6g
165.31
164.13
156.10
149.67
146.04
145.02
143.73
140.84
137.18
134.73
131.72
131.13
130.60
127.21
122.18
107.50
46.61
45.88
45.23
41.90
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

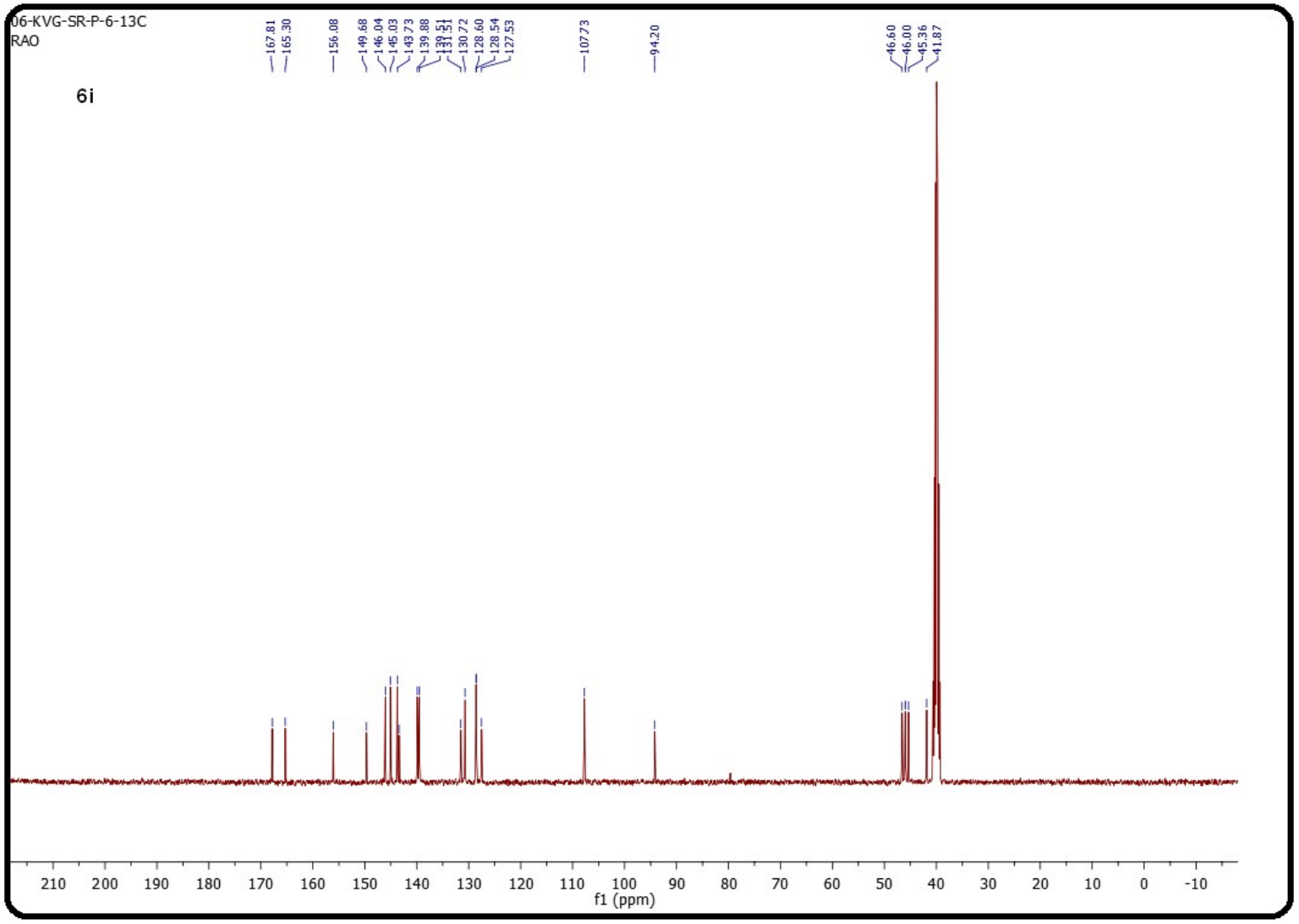
^{13}CNMR of **6g**



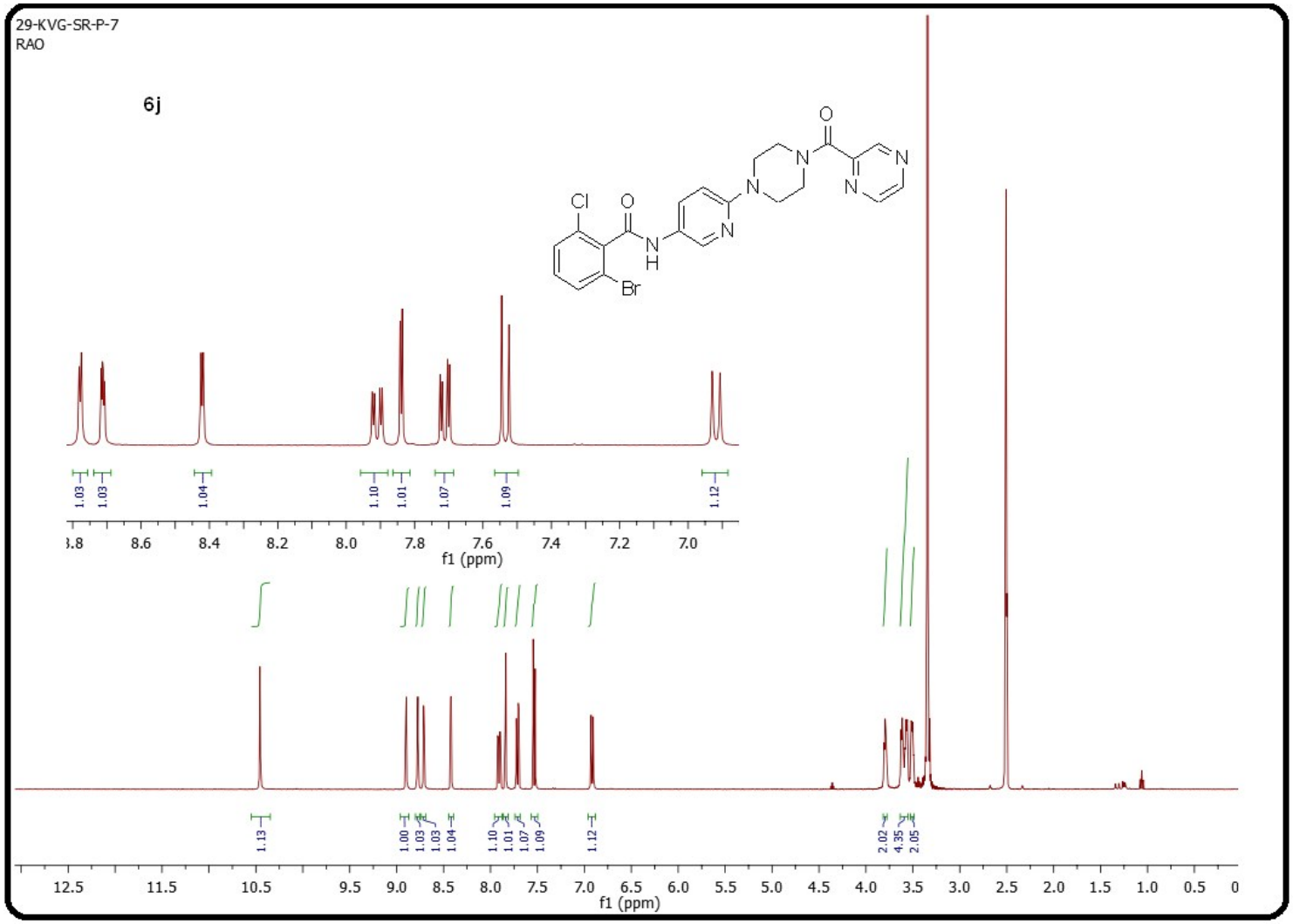
^{1}HNMR of **6h**



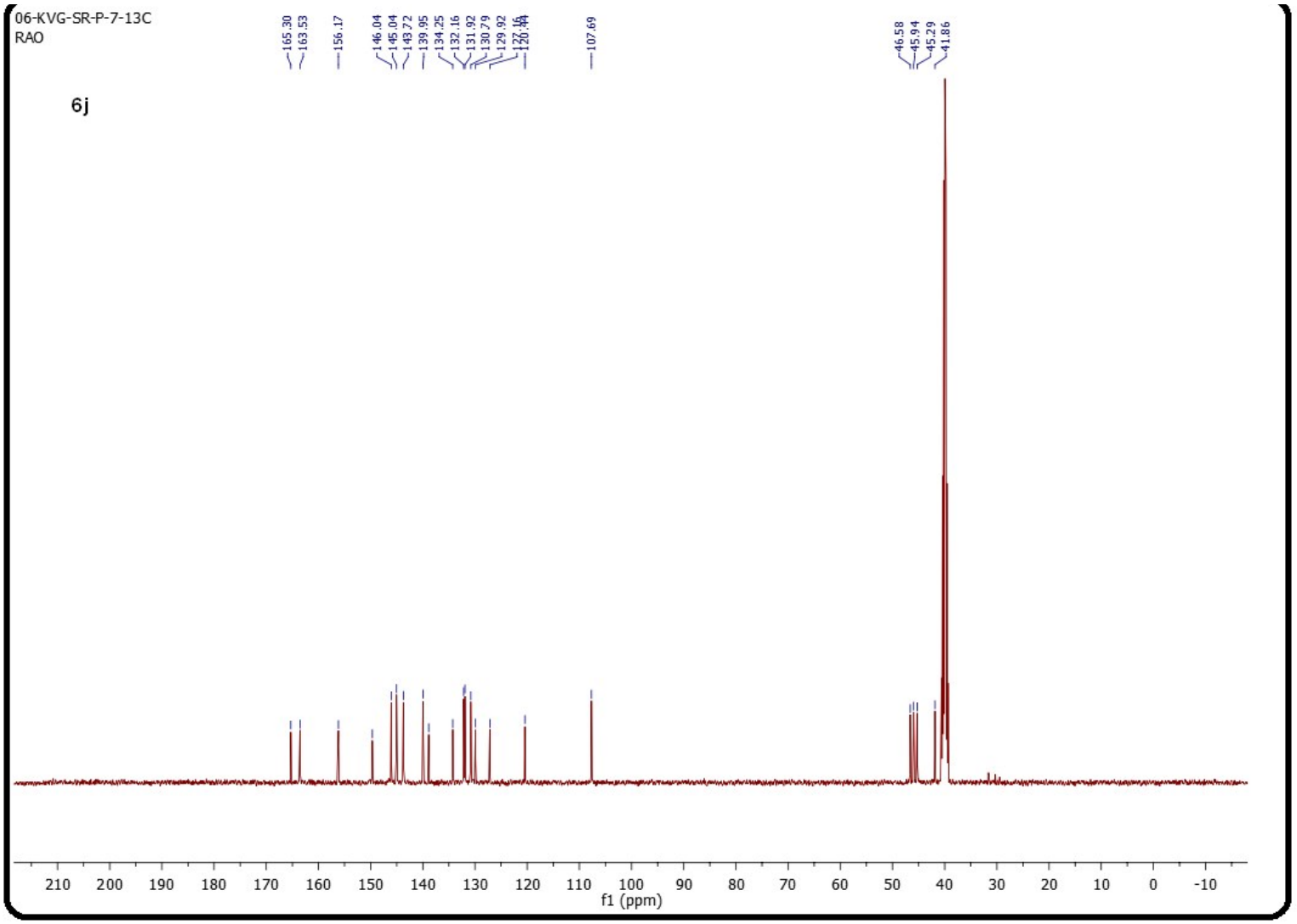
^{1}HNMR of **6i**


06-KVG-SR-P-6-13C
RAO
6i
167.81
165.30
156.08
149.68
146.04
145.03
143.73
139.88
131.51
130.72
128.60
128.54
127.53
107.73
94.20
46.60
46.00
45.36
41.87
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

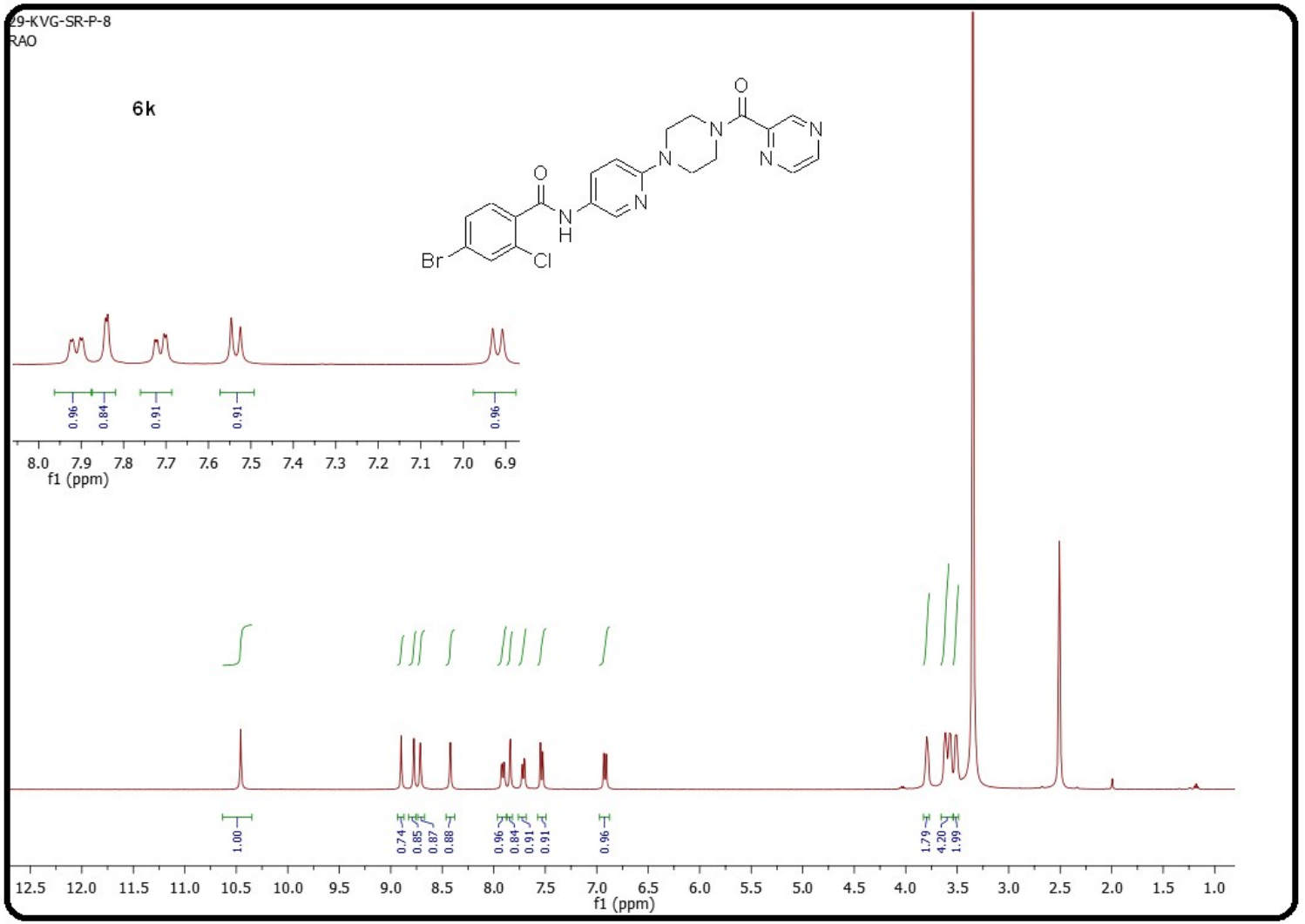
^{13}CNMR of **6i**



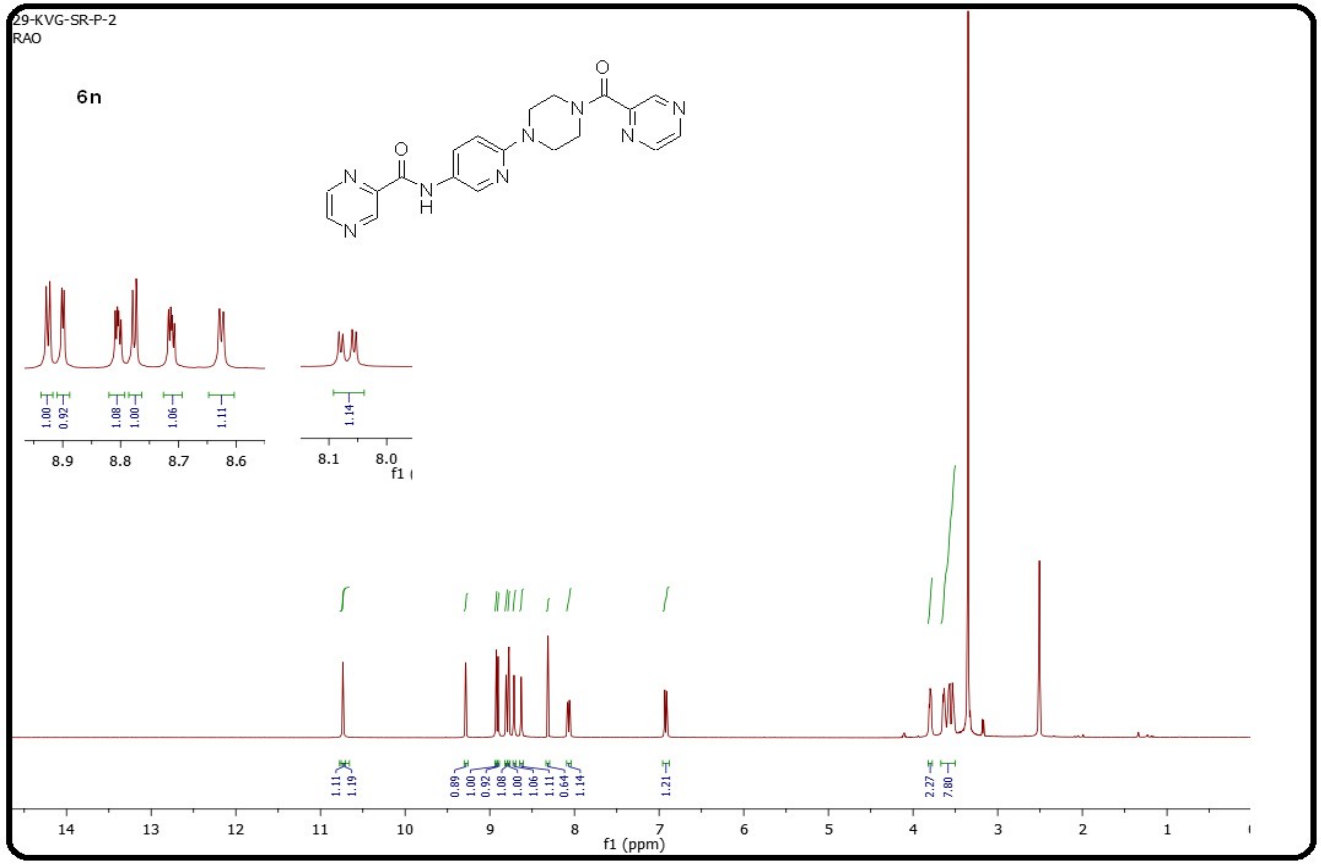
^{1}HNMR of **6j**


06-KVG-SR-P-7-13C
RAO
6j
165.30
163.53
156.17
146.04
145.04
143.72
139.95
134.25
132.16
131.92
130.79
129.92
107.69
46.58
45.94
45.29
41.86
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

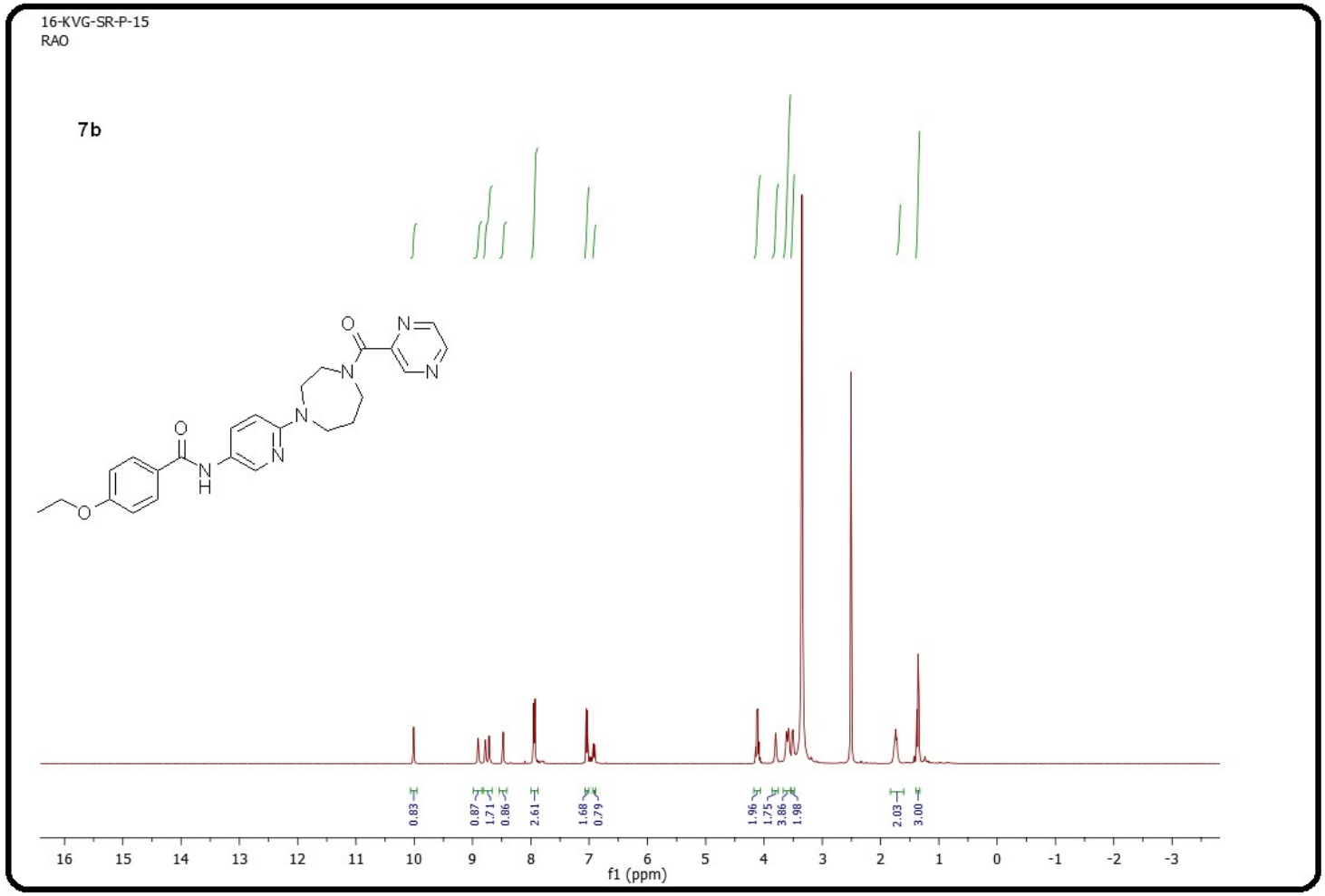
^{13}CNMR of **6j**


29-KVG-SR-P-8
RAO
6k
O
N
N
N
N
O
N
H
Br
Cl
0.96
0.84
0.91
0.91
0.96
8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9
f1 (ppm)
1.00
0.74
0.85
0.87
0.88
0.96
0.84
0.91
0.91
0.96
1.79
4.20
1.99
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

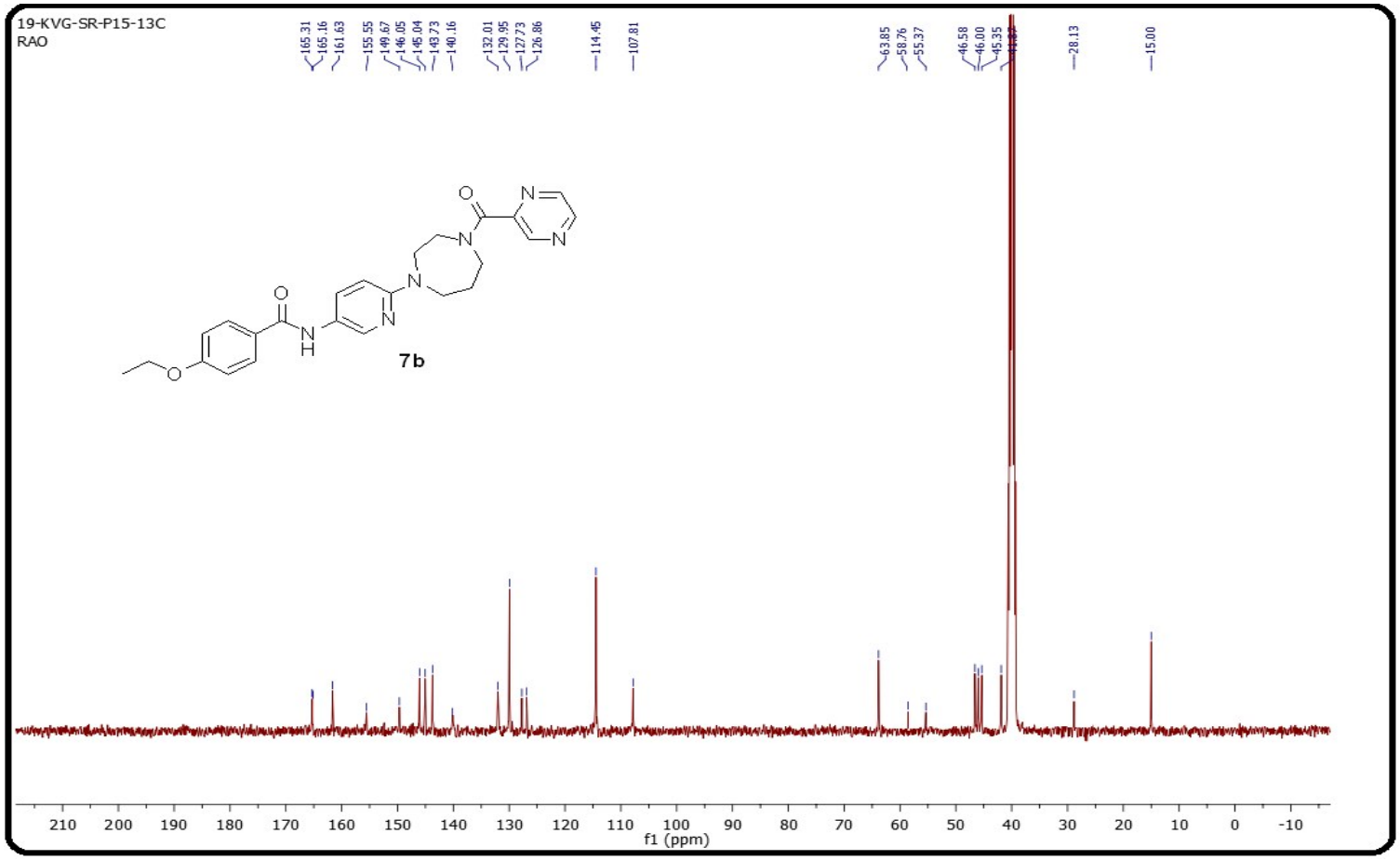
^{1}HNMR of **6k**



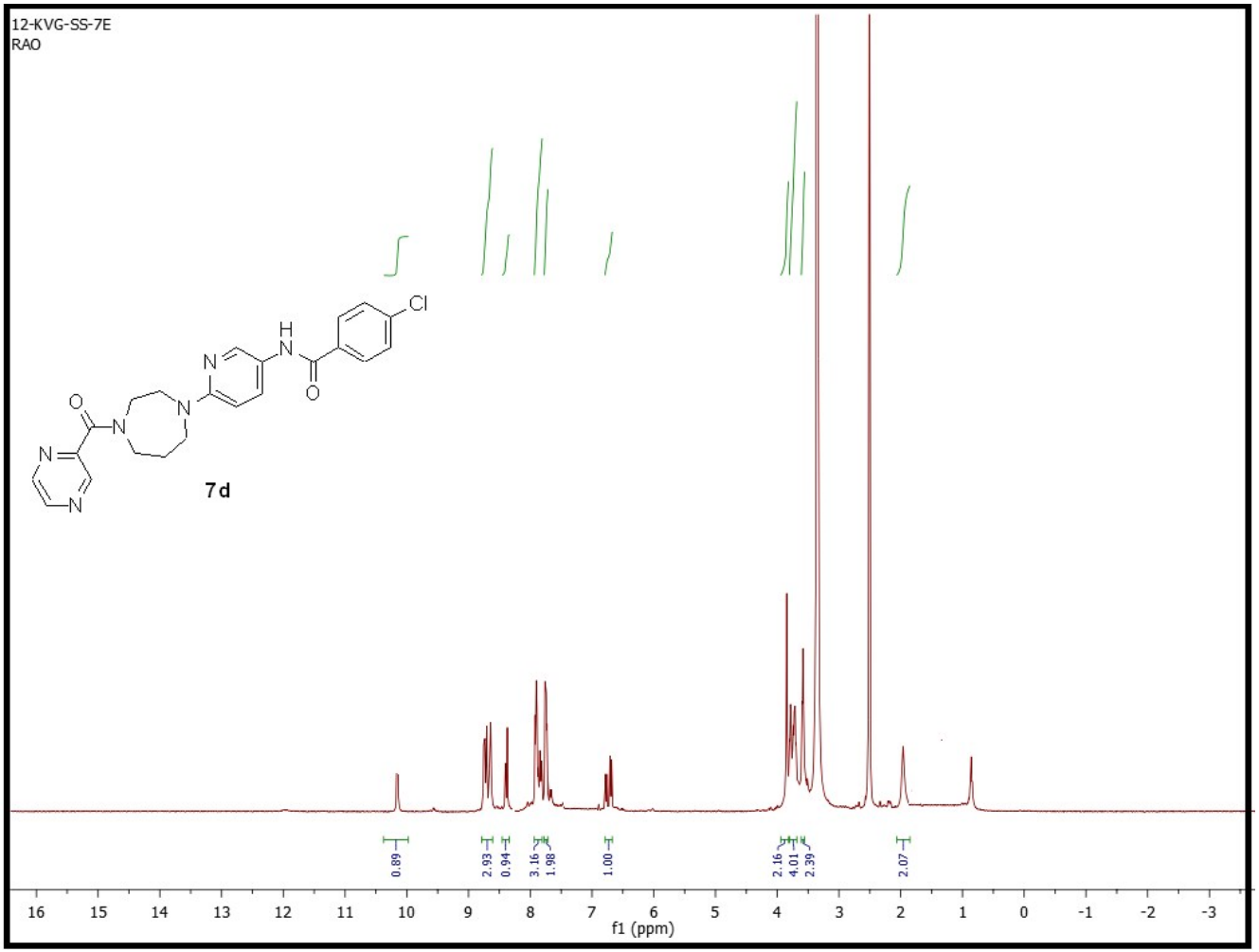
^{1}HNMR of **6n**


16-KVG-SR-P-15
RAO
7b
0.83
0.87
1.71
0.86
2.61
1.68
0.79
1.96
1.75
3.86
1.98
2.03
3.00
f1 (ppm)

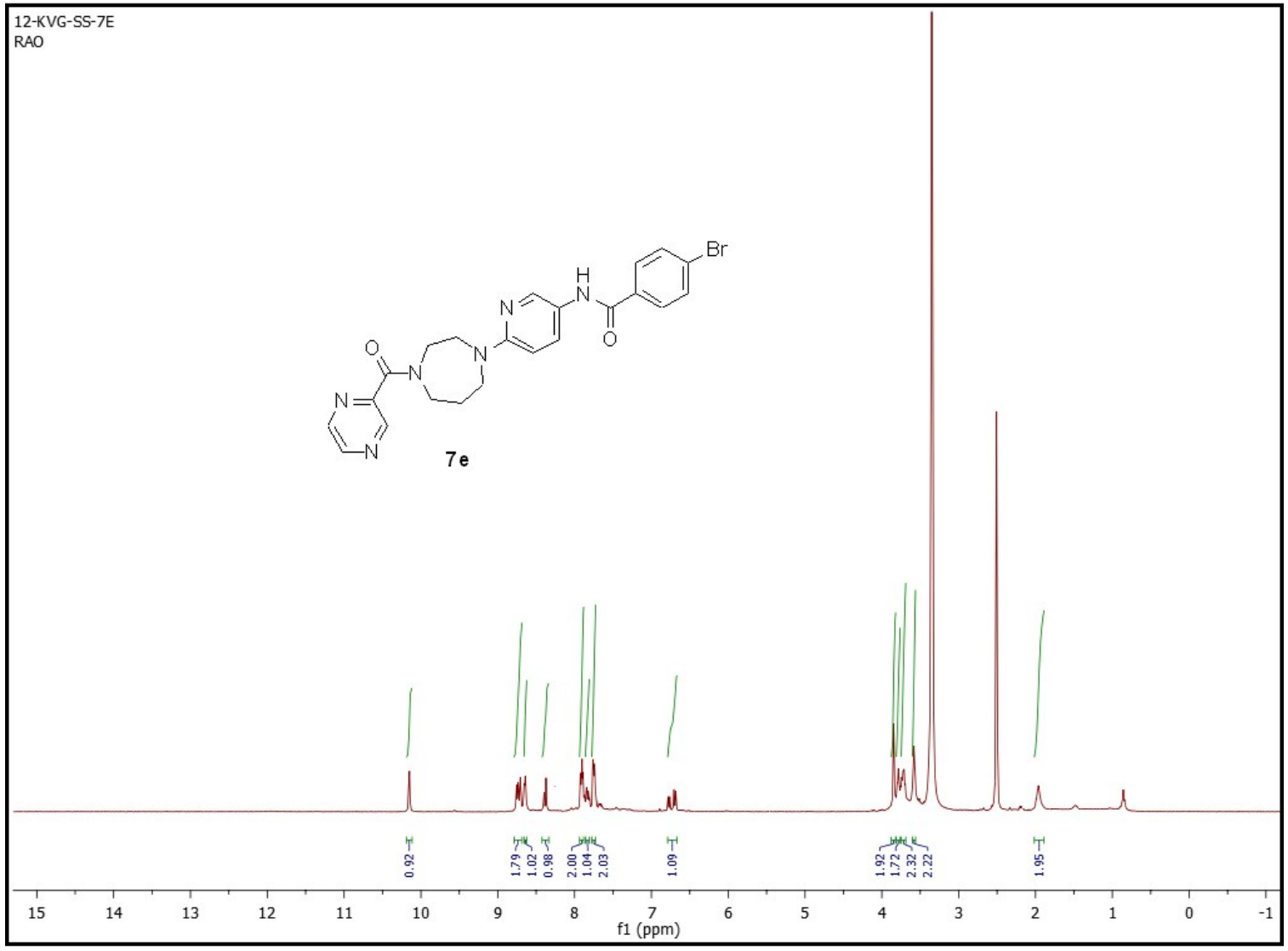
^{1}HNMR of **7b**


19-KVG-SR-P15-13C
RAO
165.31
165.16
161.63
155.55
149.67
146.05
145.04
143.73
140.16
132.01
129.95
127.73
126.86
114.45
107.81
63.85
58.76
55.37
46.58
46.00
45.35
28.13
15.00
7b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

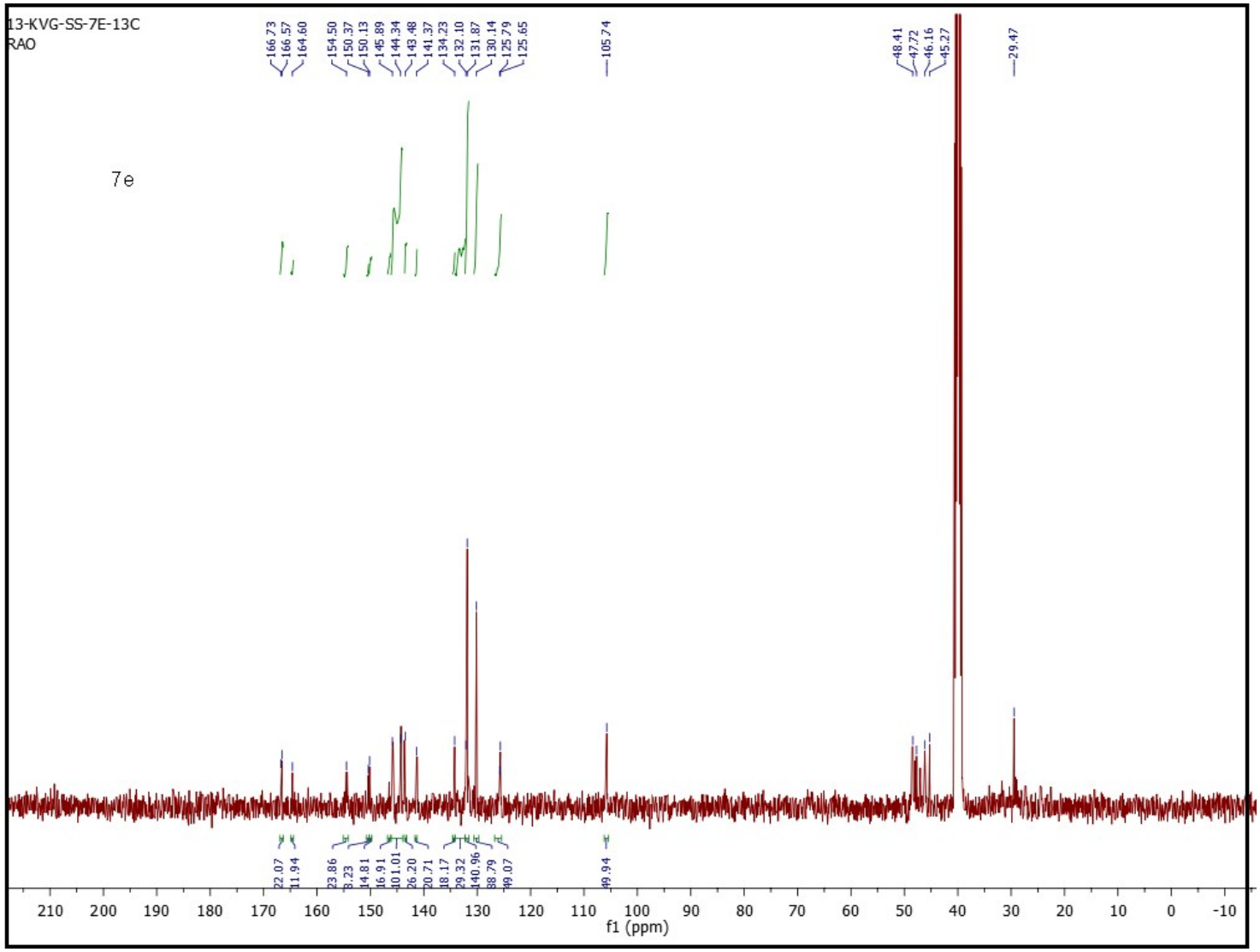
^{13}CNMR of **7b**



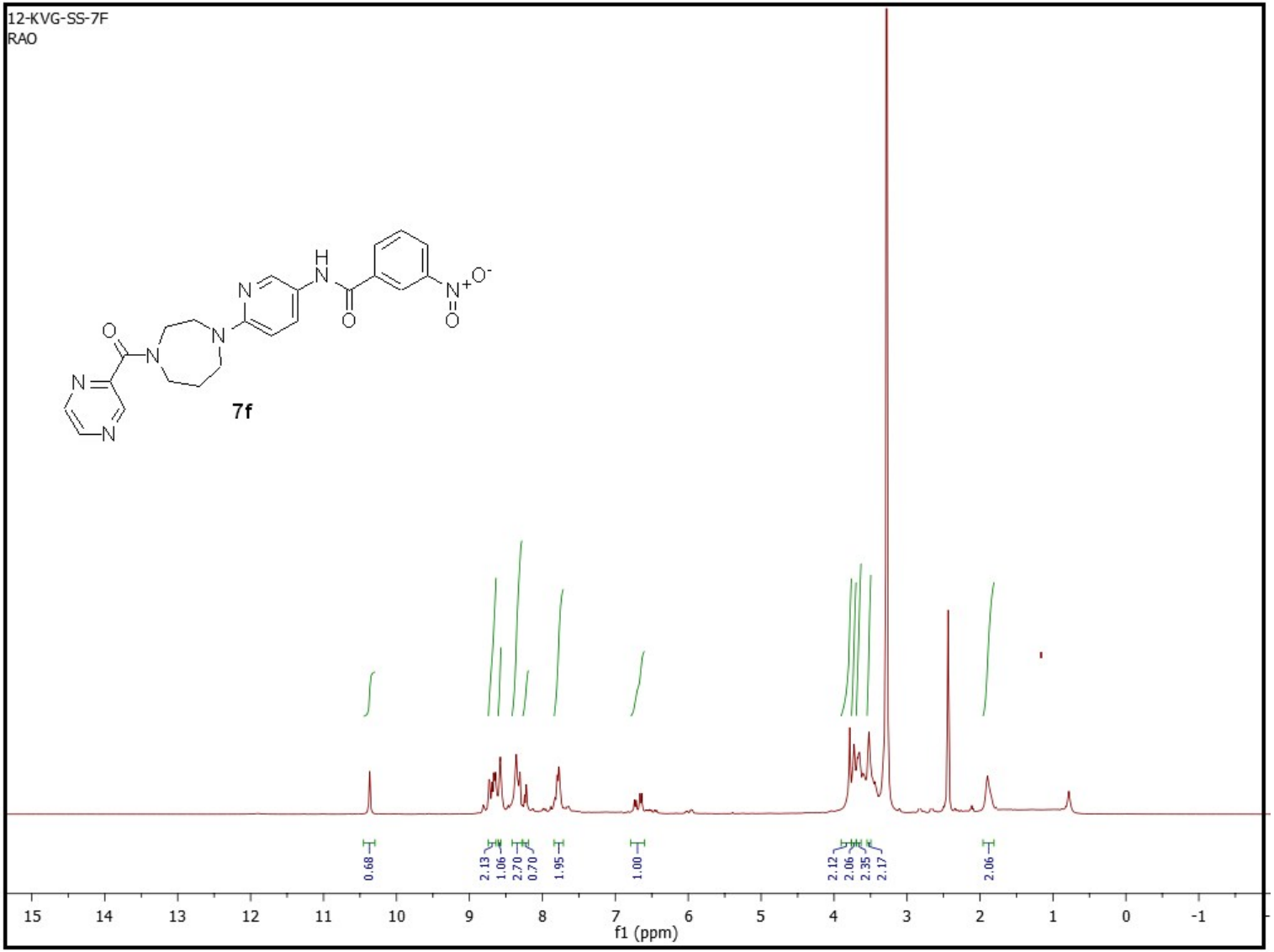
[1]HNMR of 7d


12-KVG-SS-7E
RAO
Br
H
N
O
N
N
N
O
N
7e
0.92
1.79
1.02
0.98
2.00
1.04
2.03
1.09
1.92
1.72
2.32
2.22
1.95
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

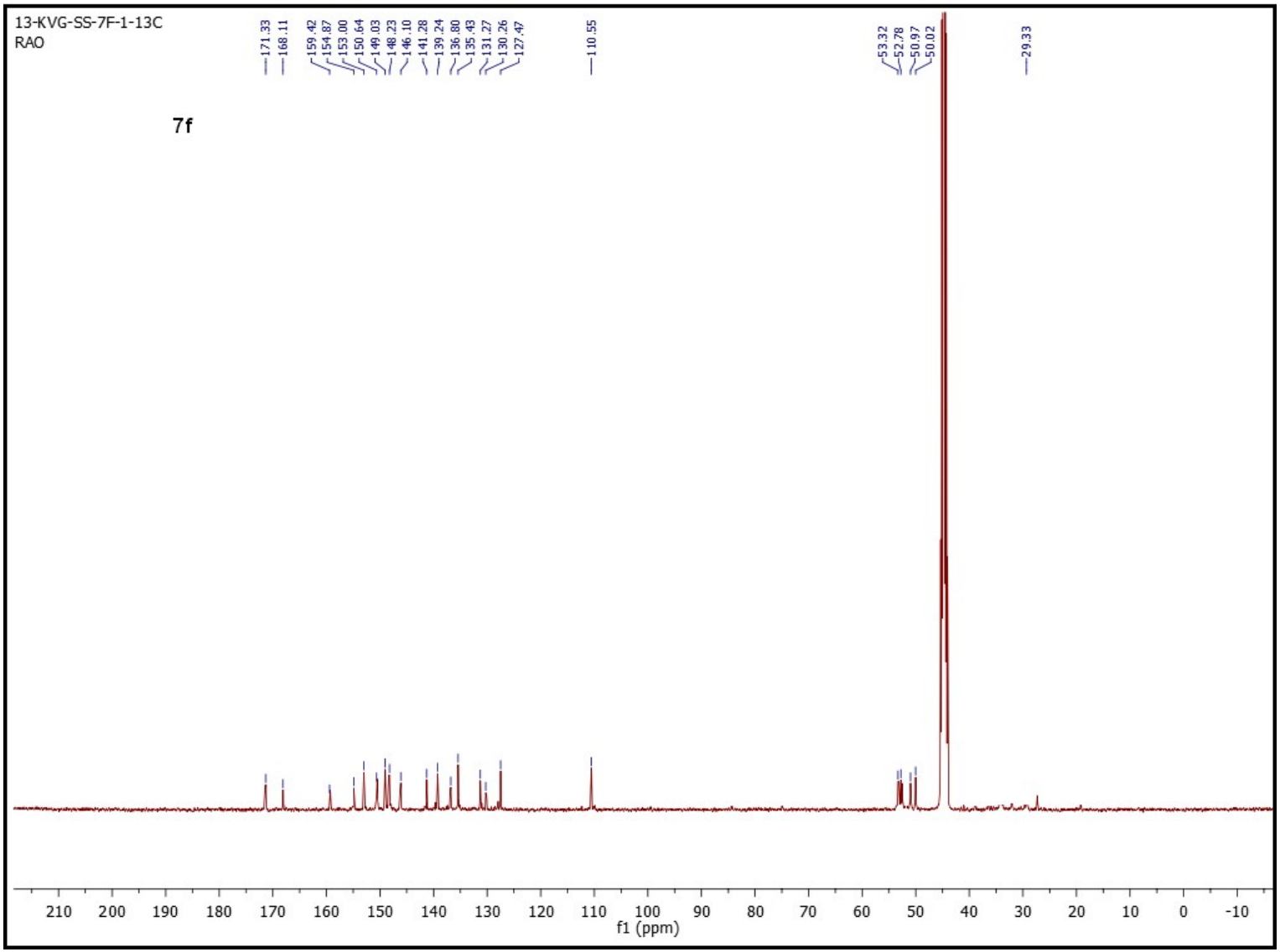
^{1}HNMR of 7e


13-KVG-SS-7E-13C
RAO
7e
166.73
166.57
164.60
154.50
150.37
150.13
145.89
144.34
143.48
141.37
134.23
132.10
131.87
130.14
125.79
125.65
105.74
48.41
47.72
46.16
45.27
29.47
22.07
11.94
23.86
8.23
14.81
16.91
101.01
26.20
20.71
18.17
29.32
140.96
88.79
49.07
49.94
f1 (ppm)

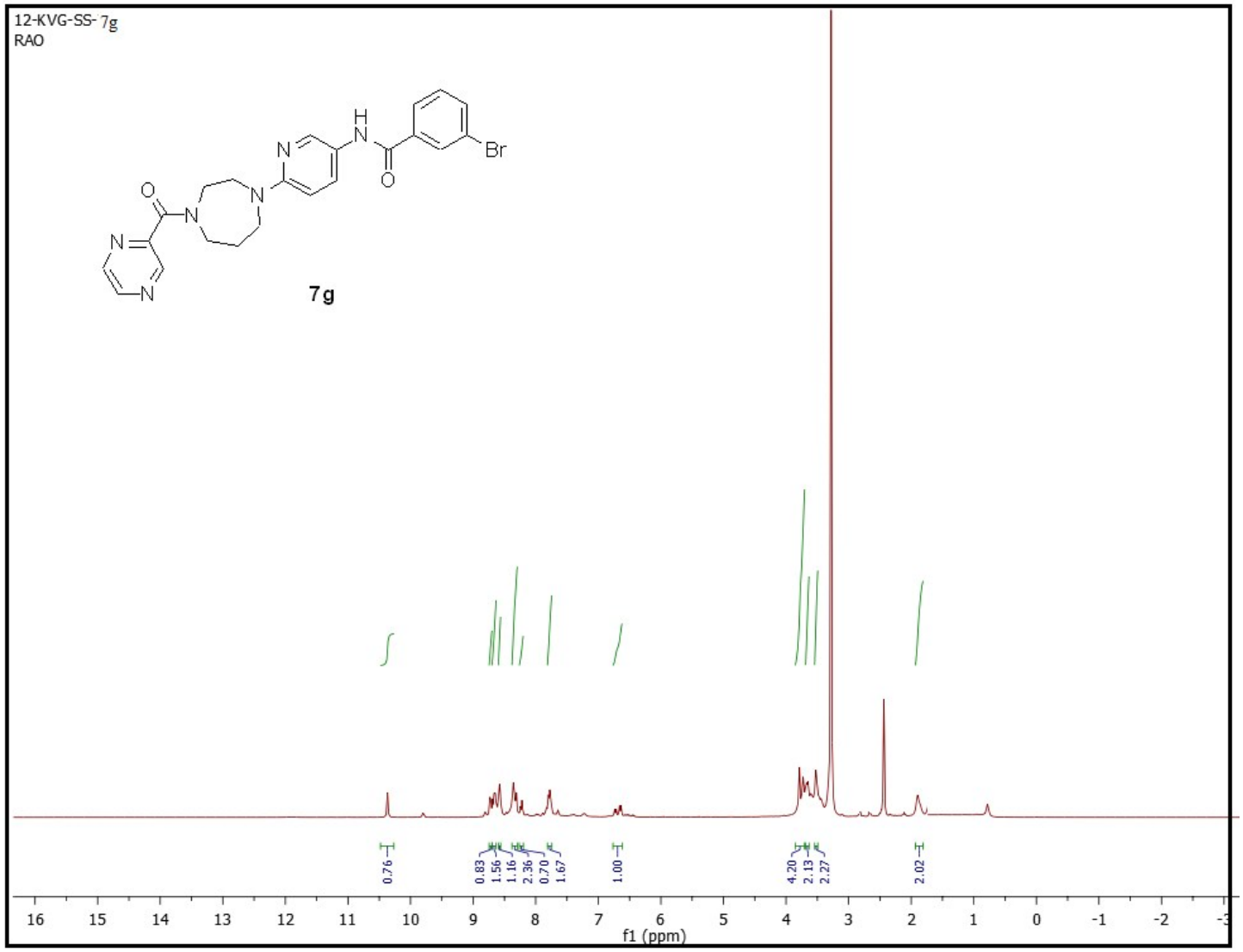
^{13}CNMR of 7e


12-KVG-SS-7F
RAO
7f
0.68
2.13
1.06
2.70
0.70
1.95
1.00
2.12
2.06
2.35
2.17
2.06
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

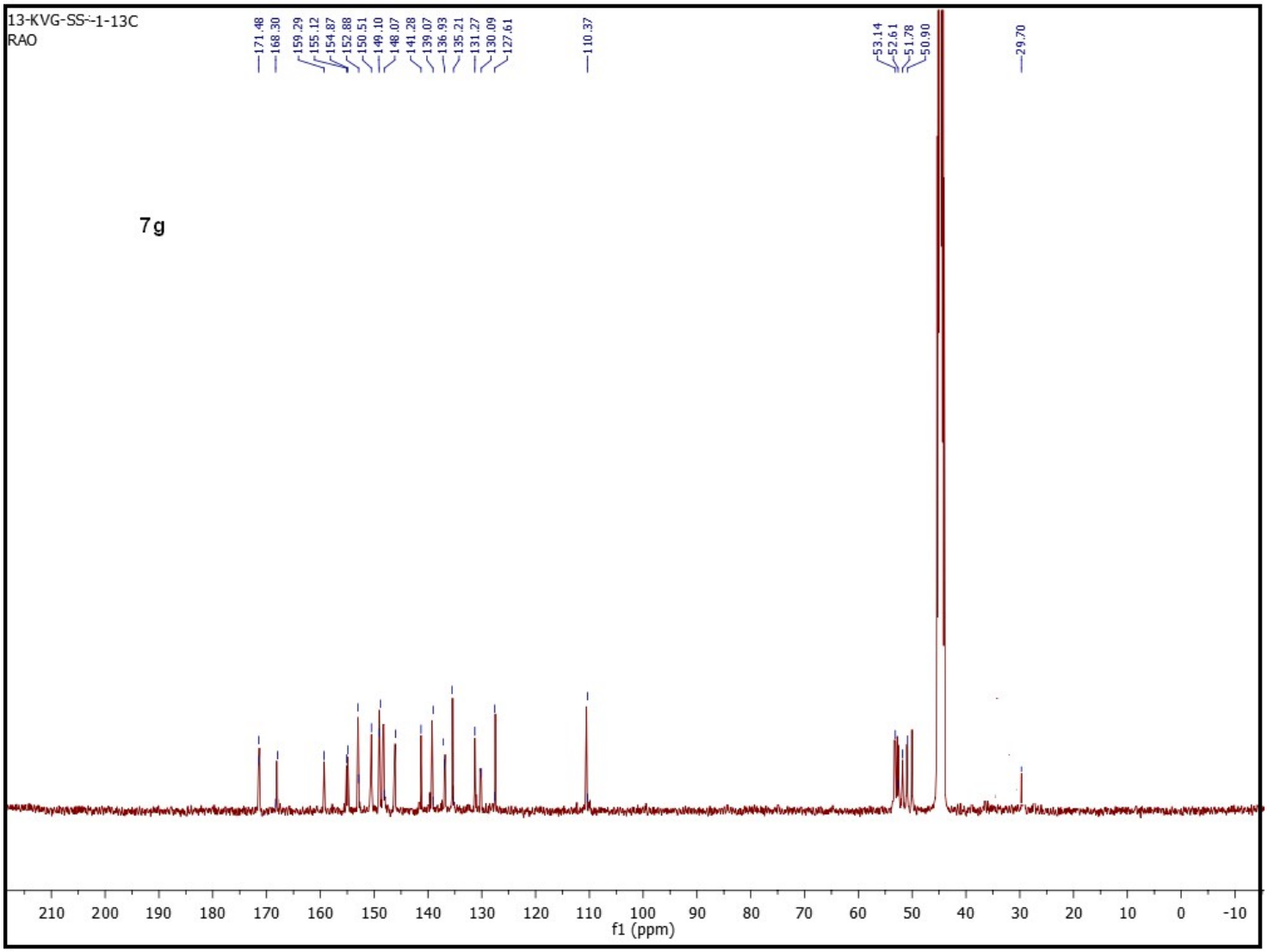
^{1}HNMR of 7f


13-KVG-SS-7F-1-13C
RAO
7f
171.33
168.11
159.42
154.87
153.00
150.64
149.03
148.23
146.10
141.28
139.24
136.80
135.43
131.27
130.26
127.47
110.55
53.32
52.78
50.97
50.02
29.33
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

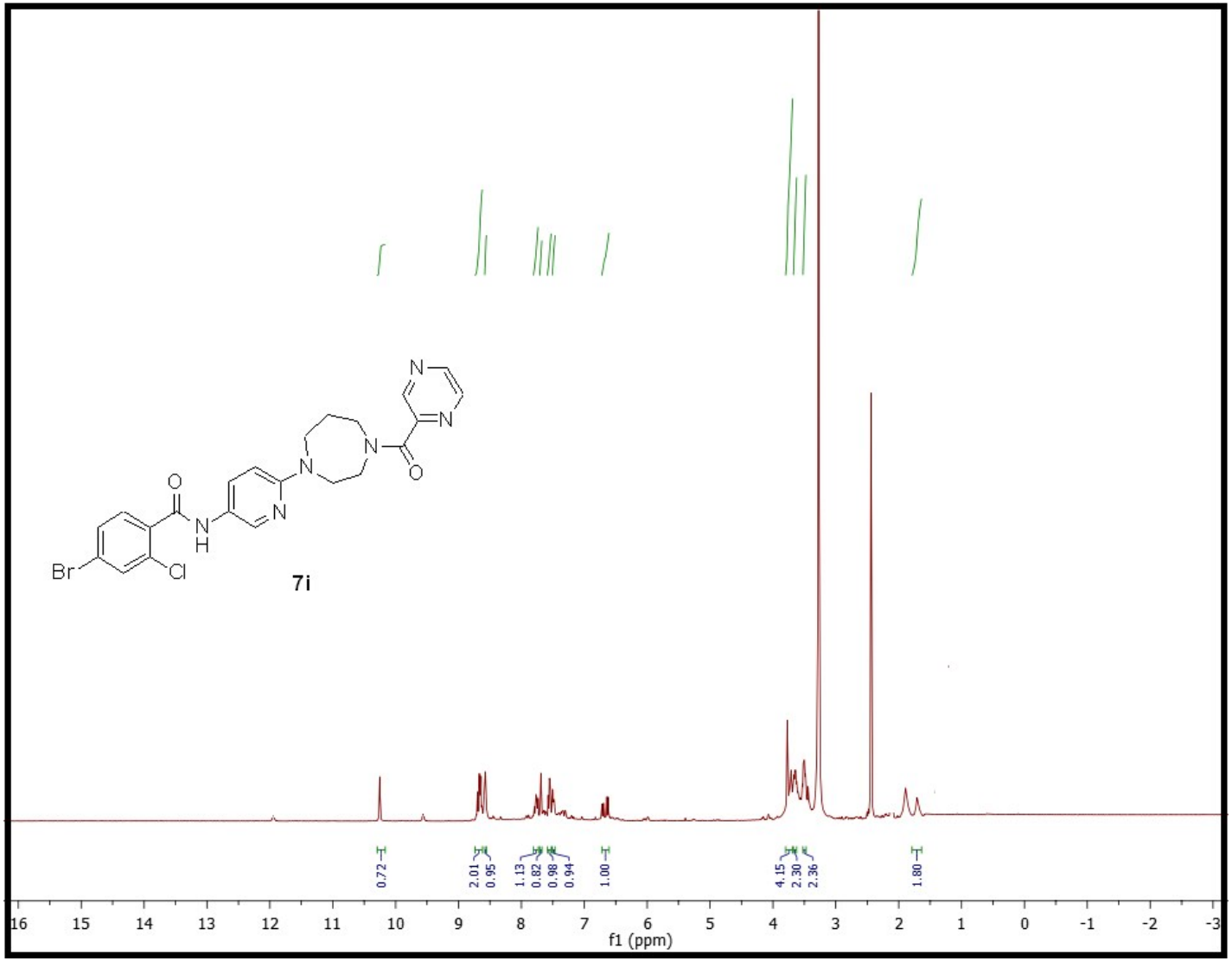
^{13}CNMR of 7f


12-KVG-SS- 7g
RAO
7g
0.76
0.83
1.56
1.16
2.36
0.70
1.67
1.00
4.20
2.13
2.27
2.02
f1 (ppm)

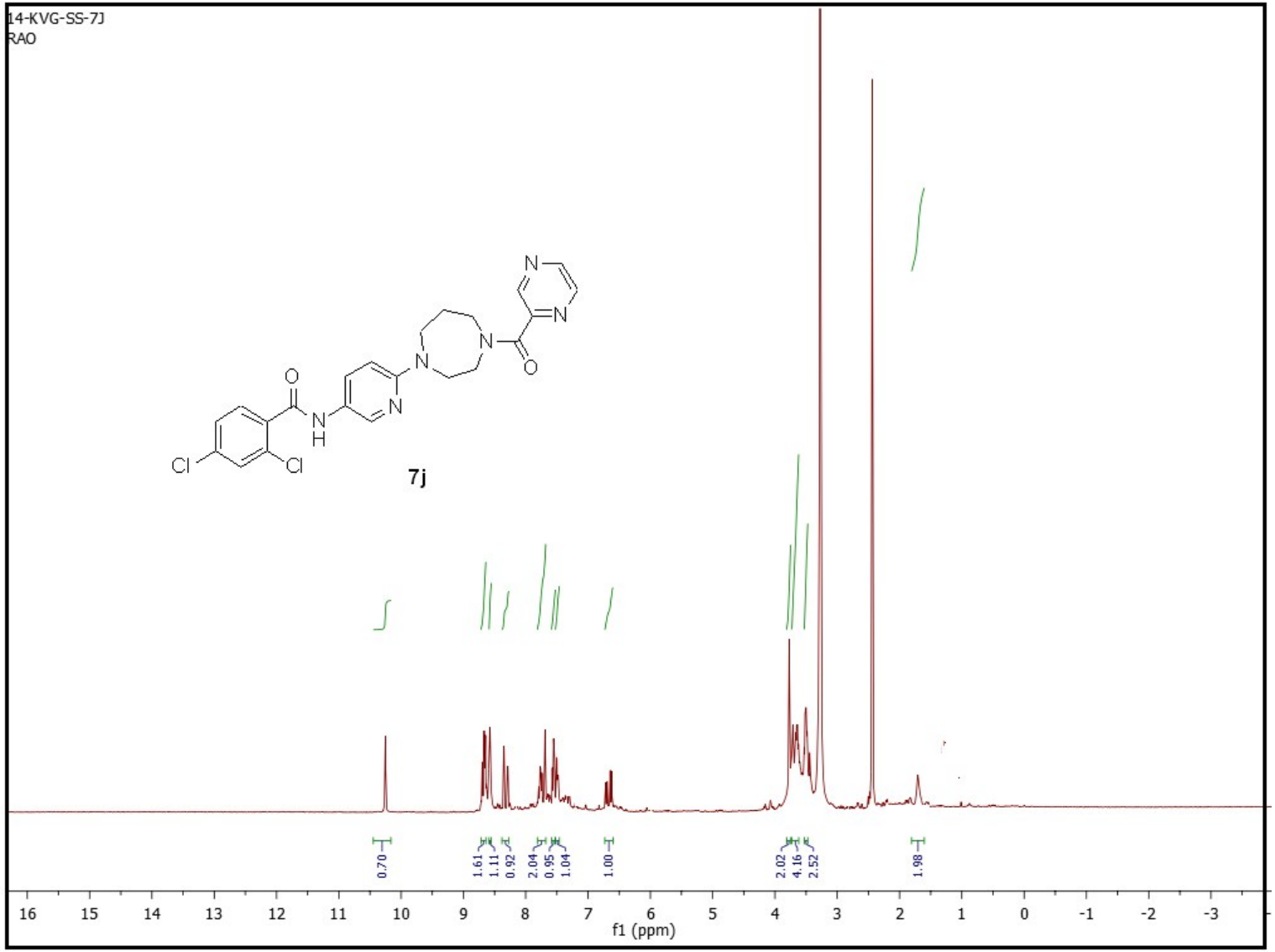
^{1}HNMR of 7g


13-KVG-SS-1-13C
RAO
7g
171.48
168.30
159.29
155.12
154.87
152.88
150.51
149.10
148.07
141.28
139.07
136.93
135.21
131.27
130.09
127.61
110.37
53.14
52.61
51.78
50.90
29.70
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

^{13}CNMR of 7g

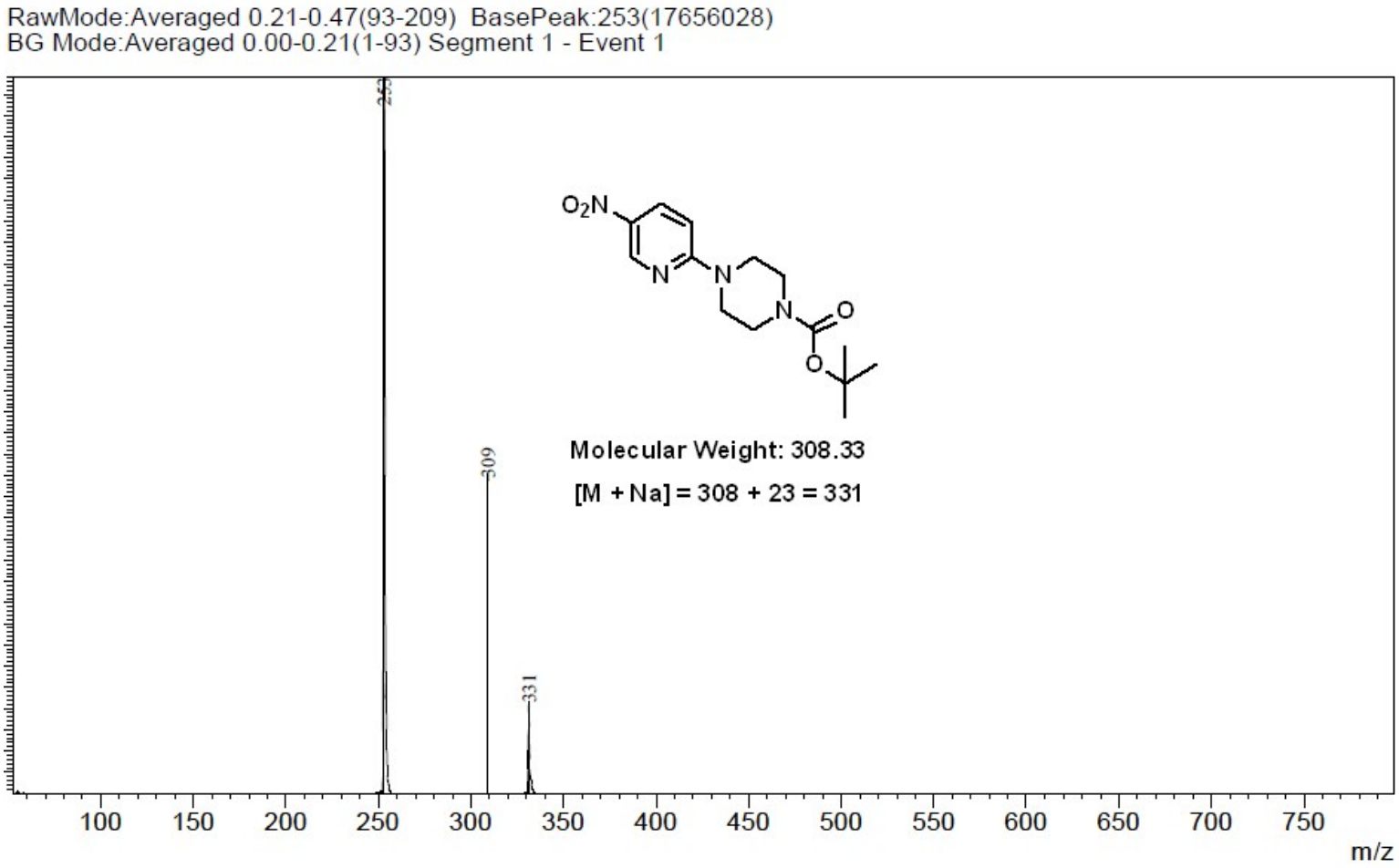


^{1}HNMR of 7i

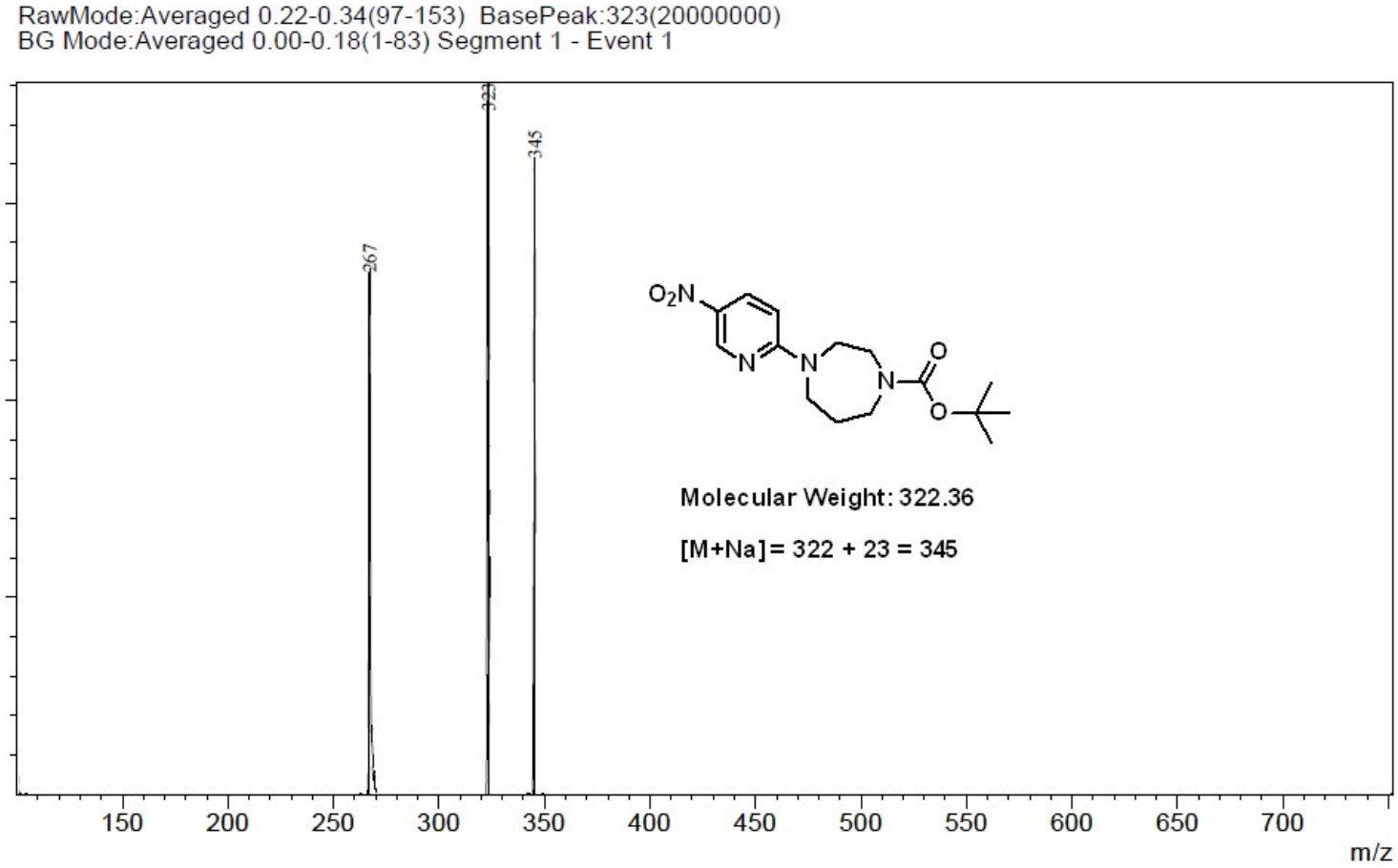

14-KVG-SS-7J
RAO
7j
0.70
1.61
1.11
0.92
2.04
0.95
1.04
1.00
2.02
4.16
2.52
1.98
f1 (ppm)

^{1}HNMR of 7j

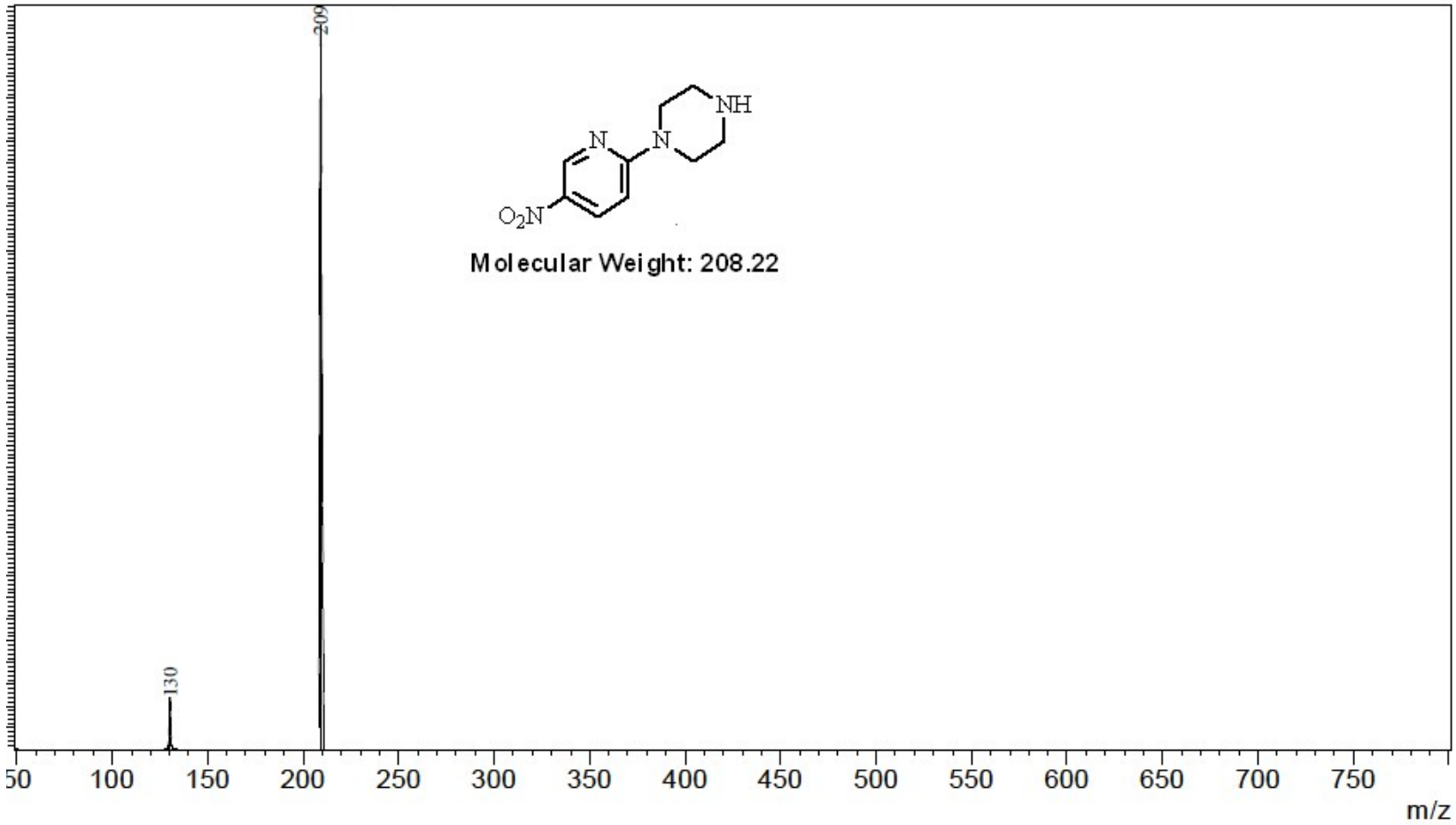
Mass spectras



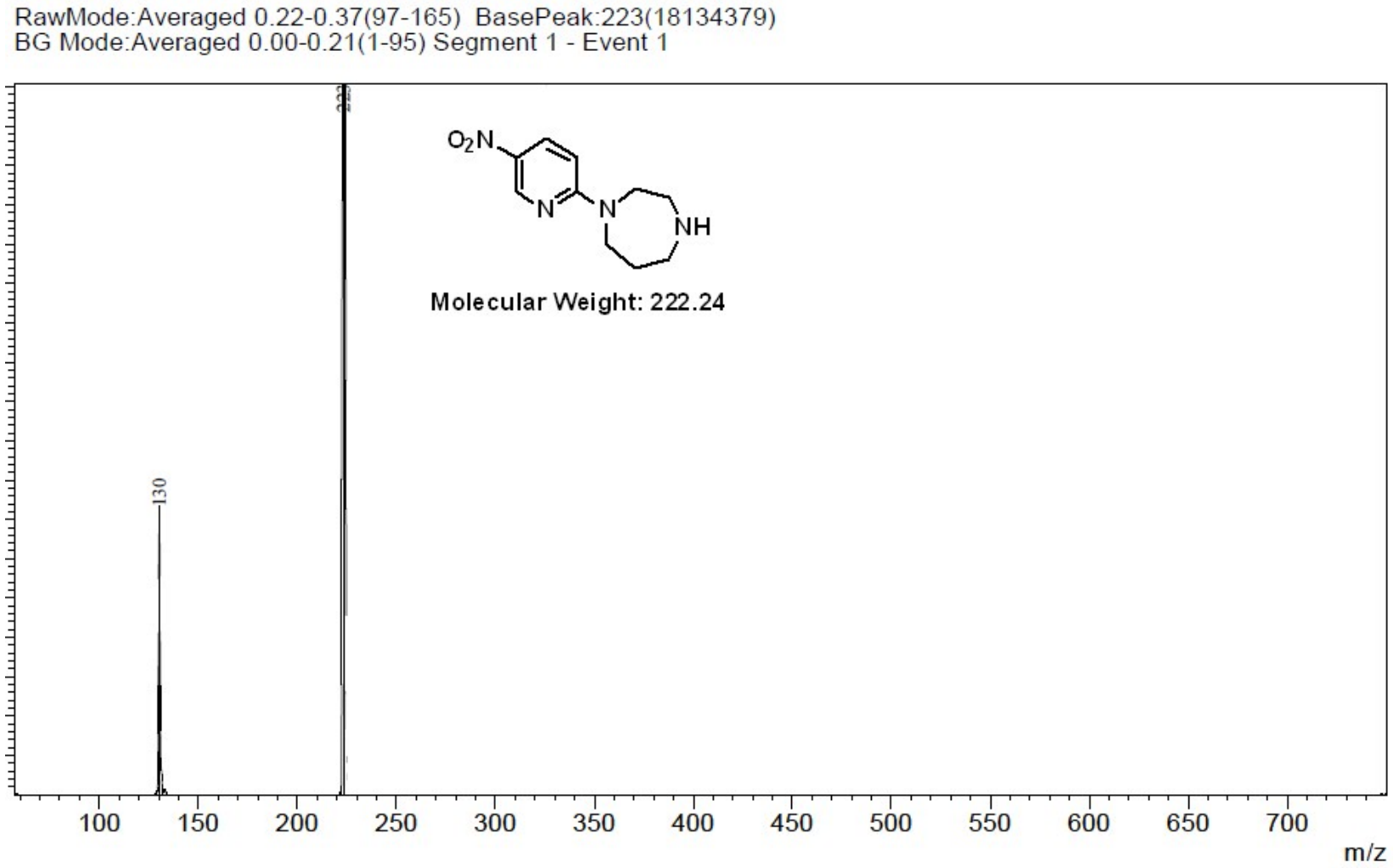
Mass spectra of 2a



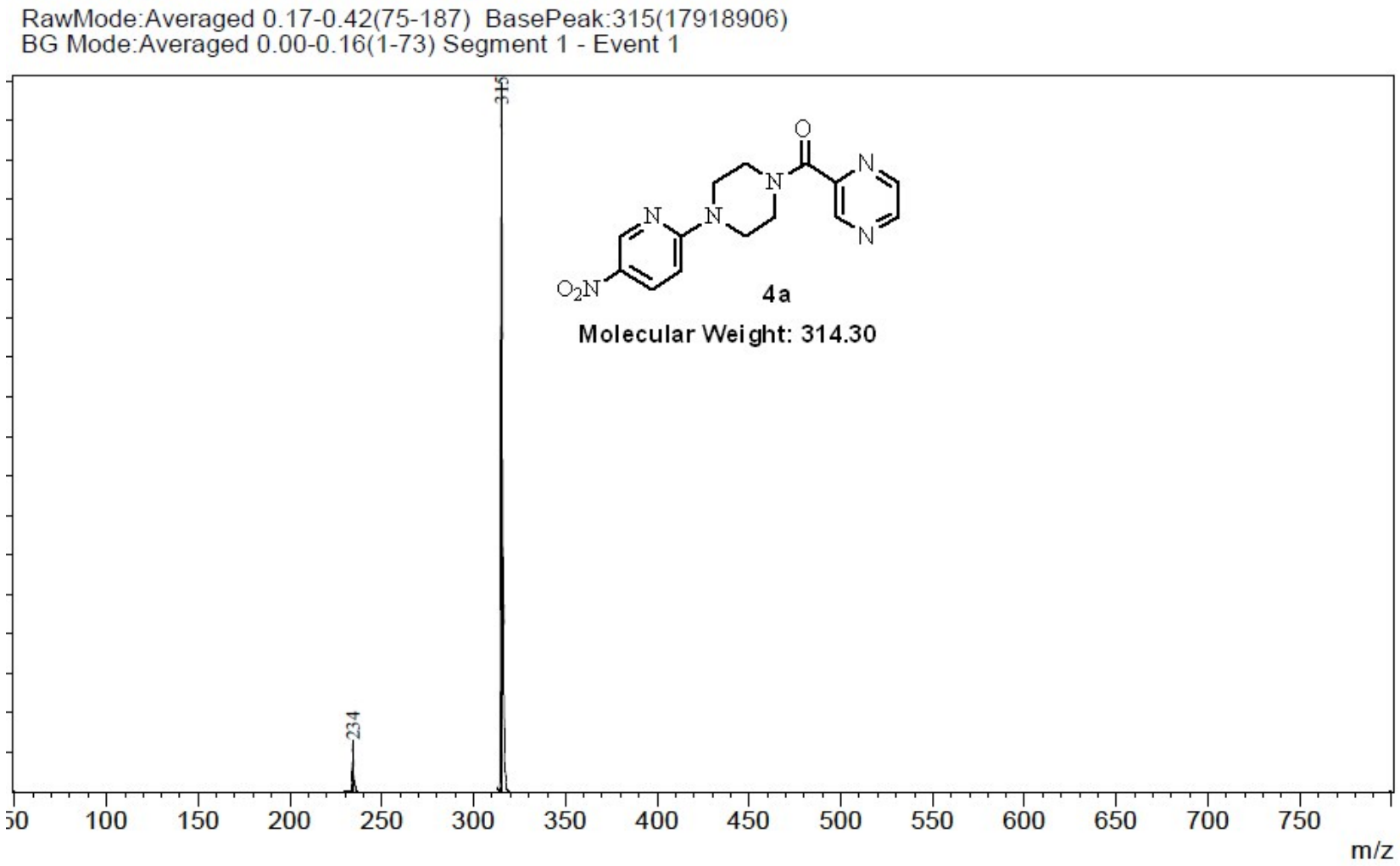
Mass spectra of 2b



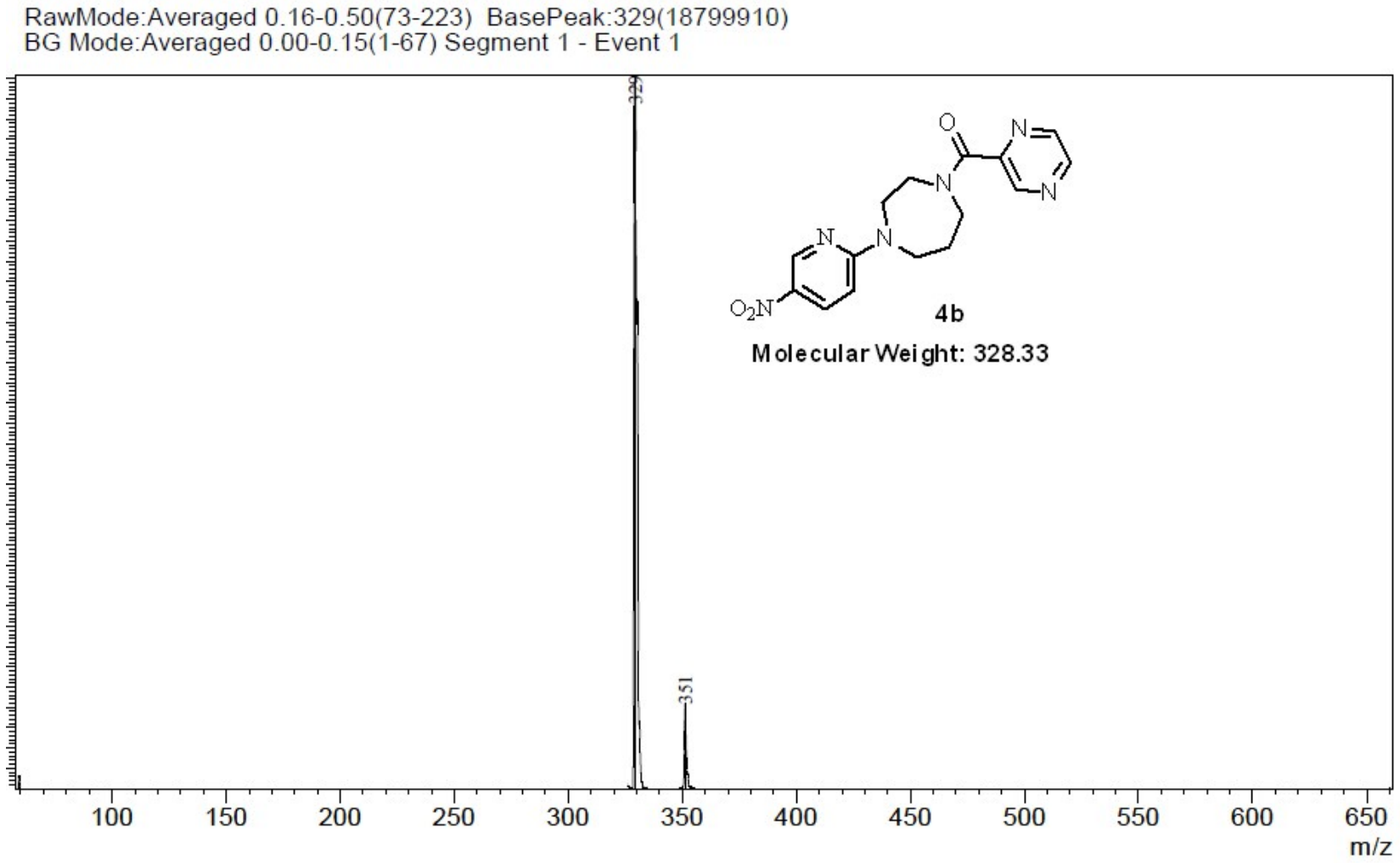
Mass spectra of 3a



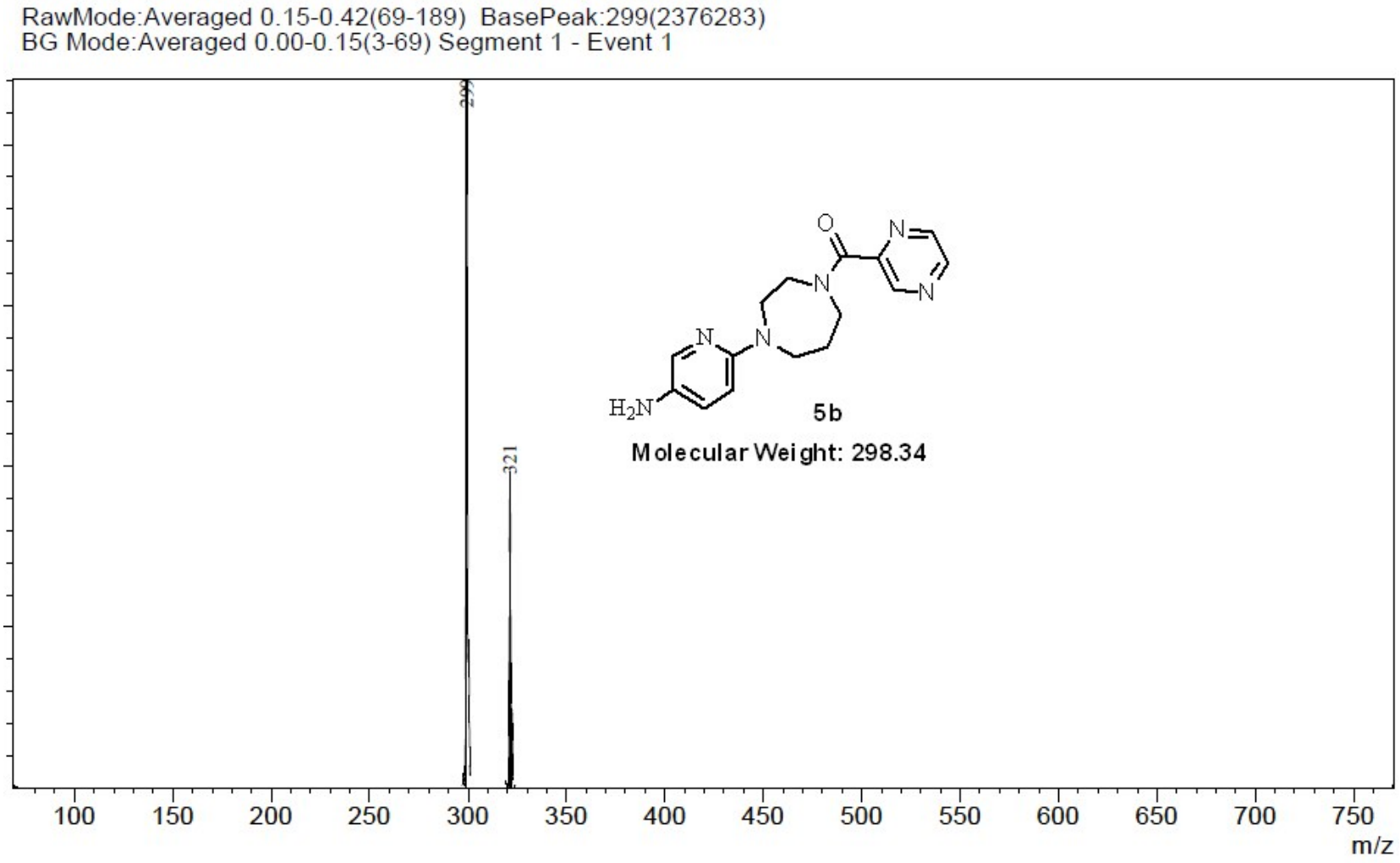
Mass spectra of 3b



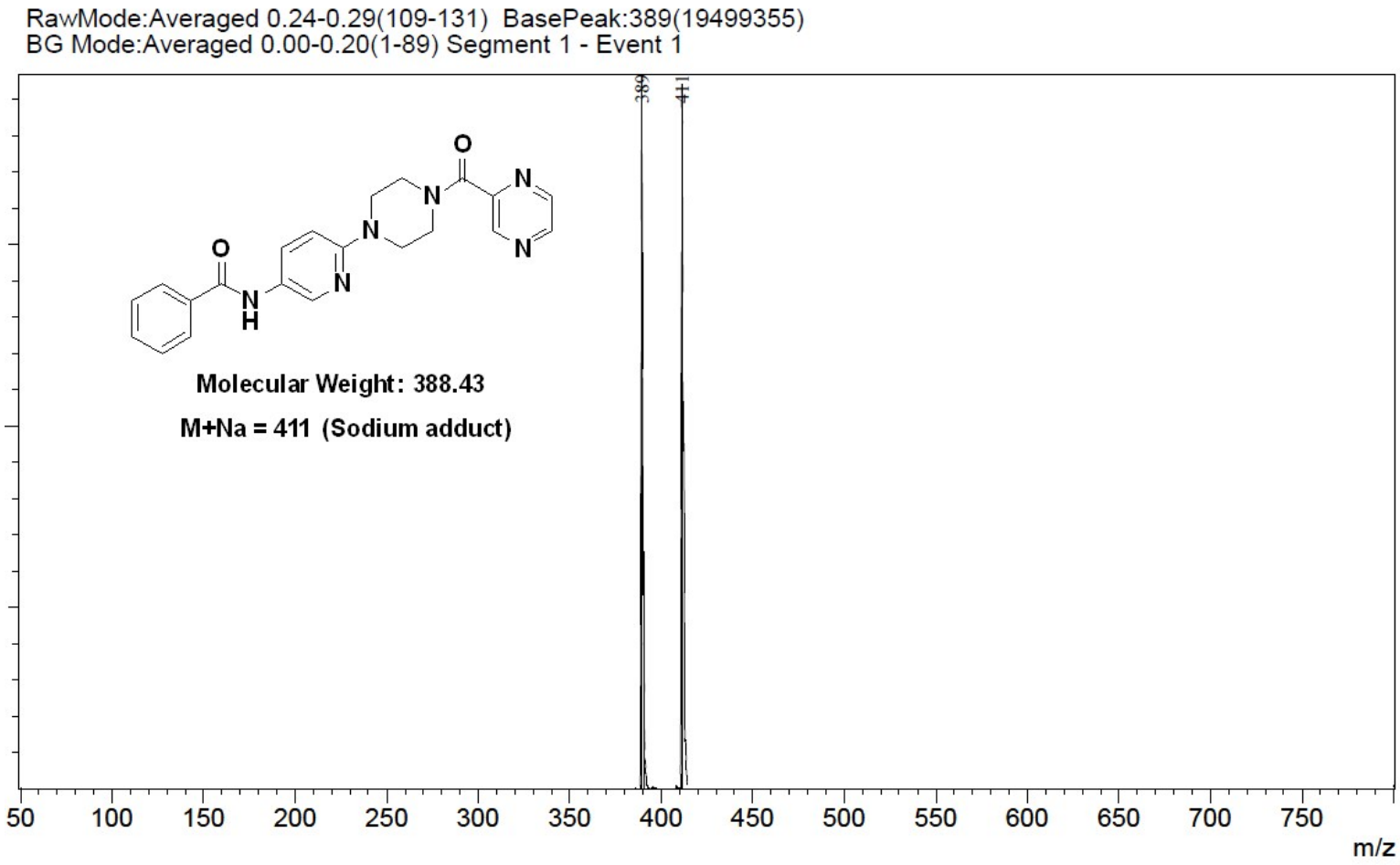
Mass spectra of 4a



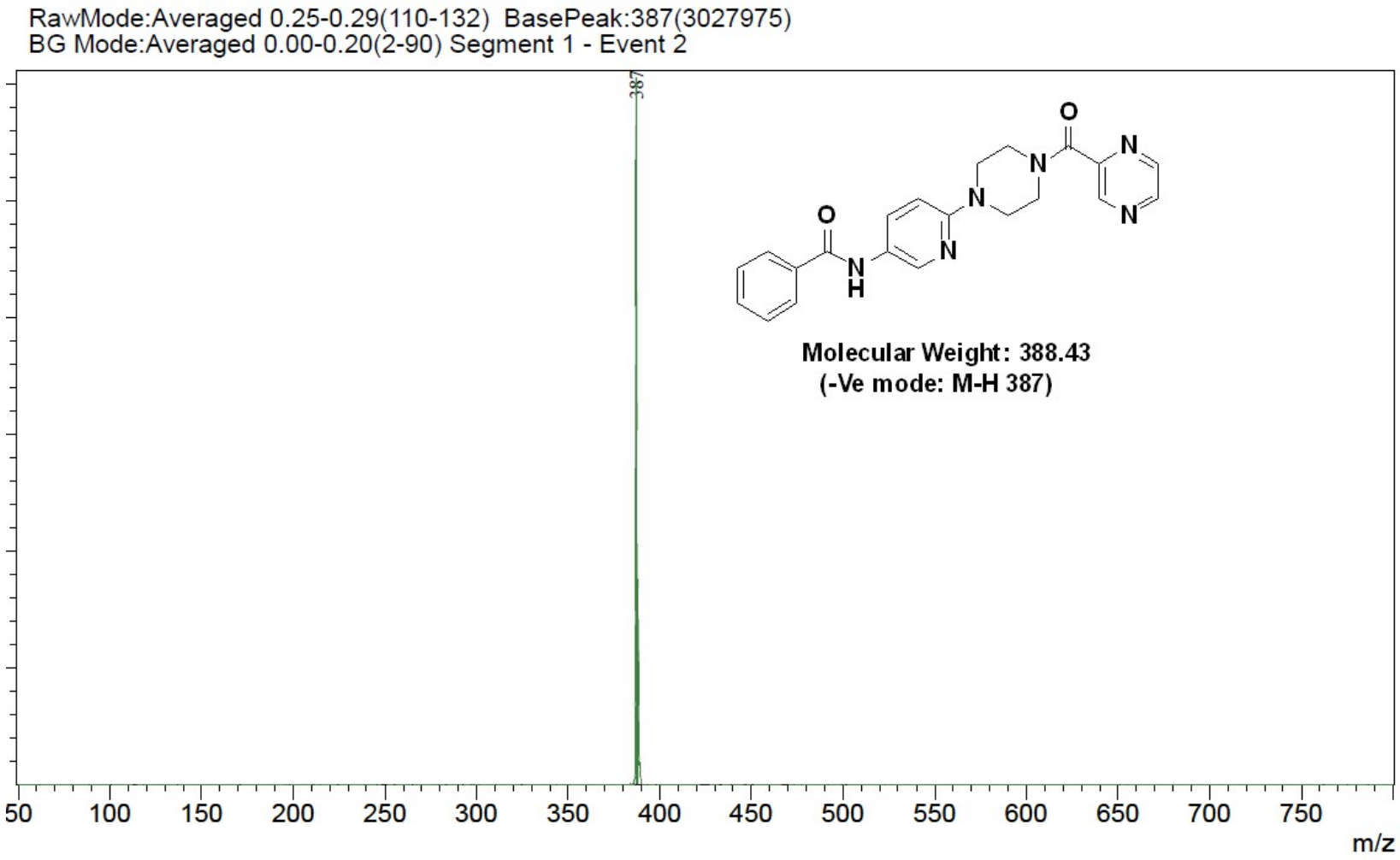
Mass spectra of 4b



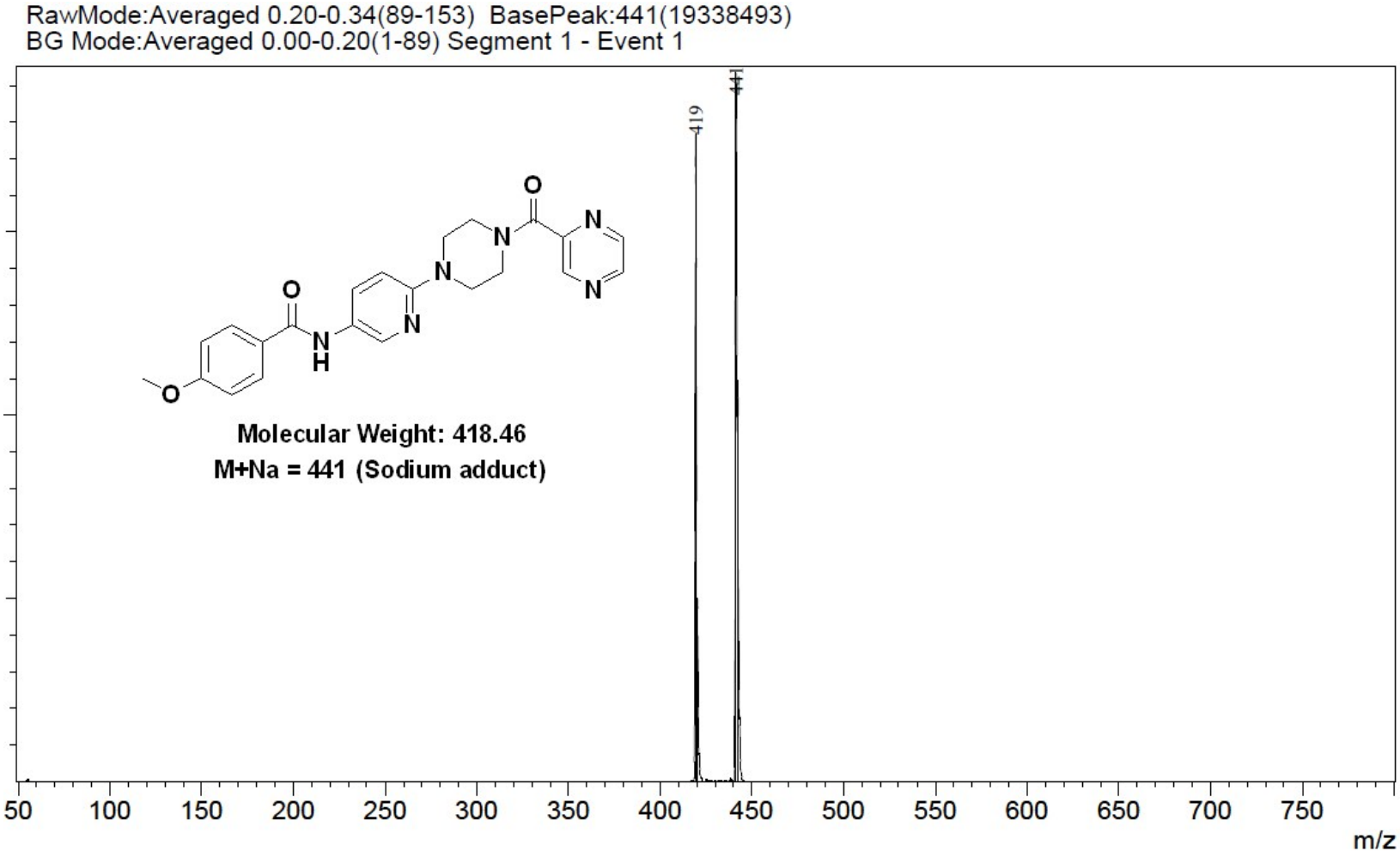
Mass spectra of 5b



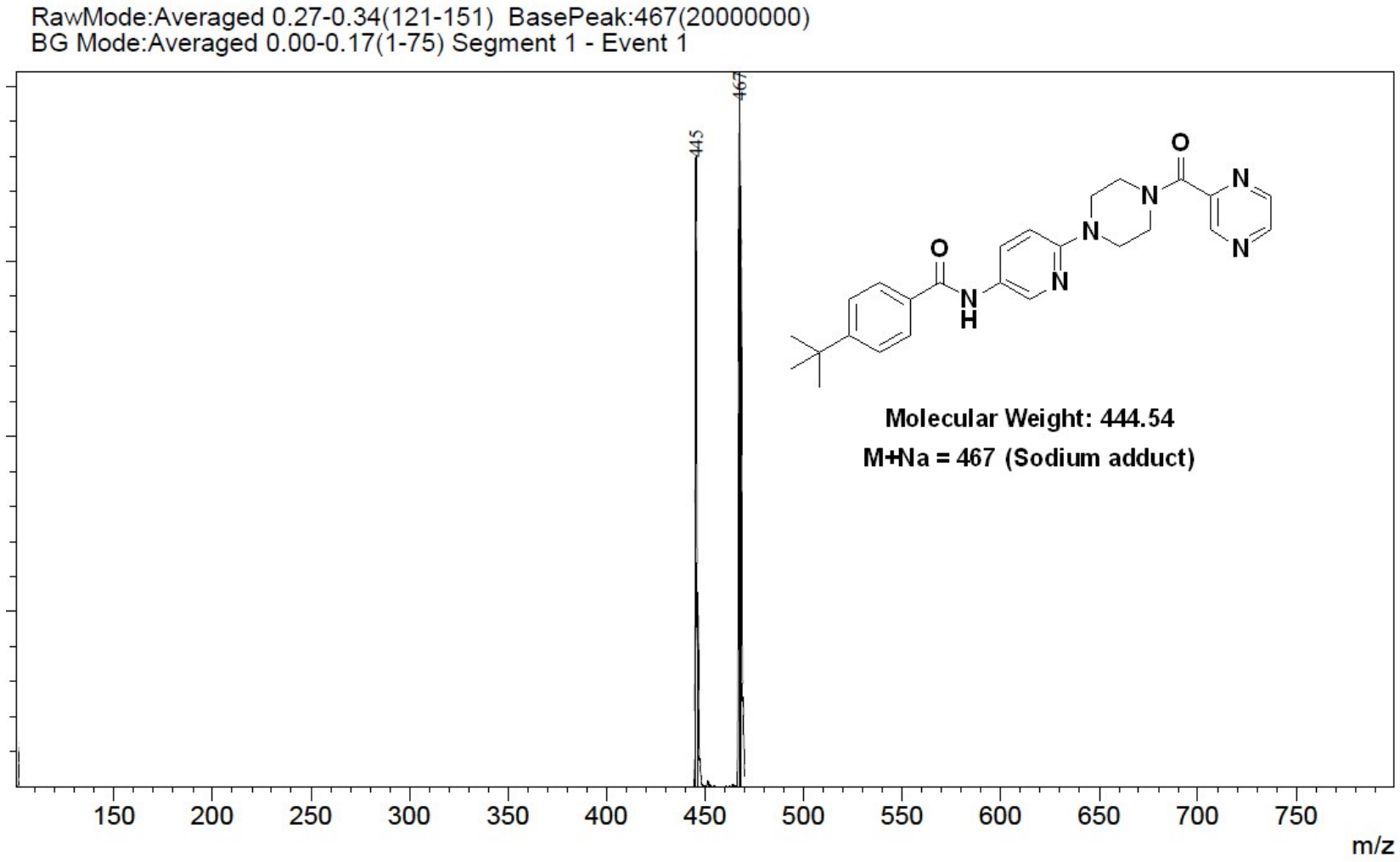
Positive mode of Mass spectra of 6a



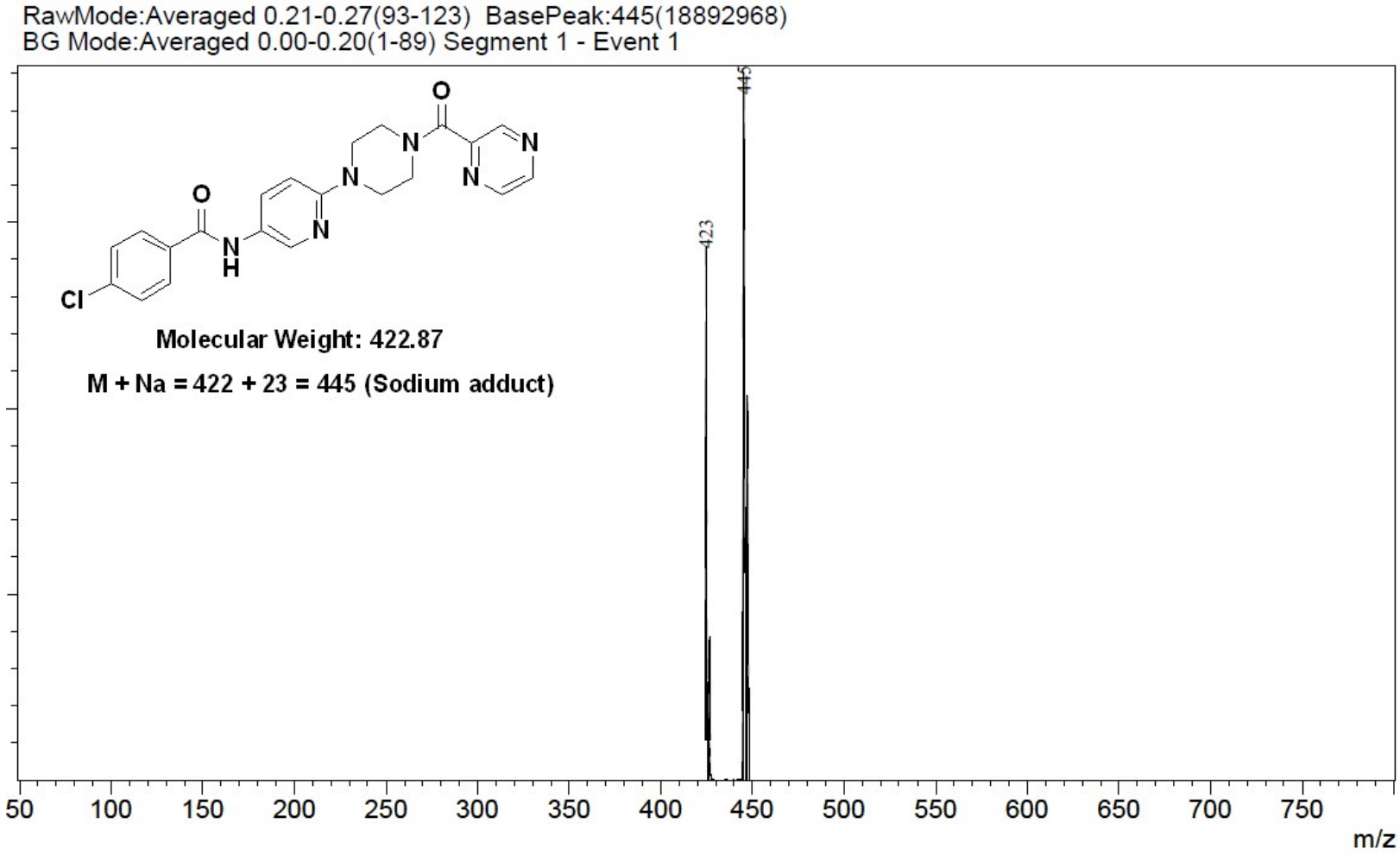
Negative mode of Mass spectra of 6a



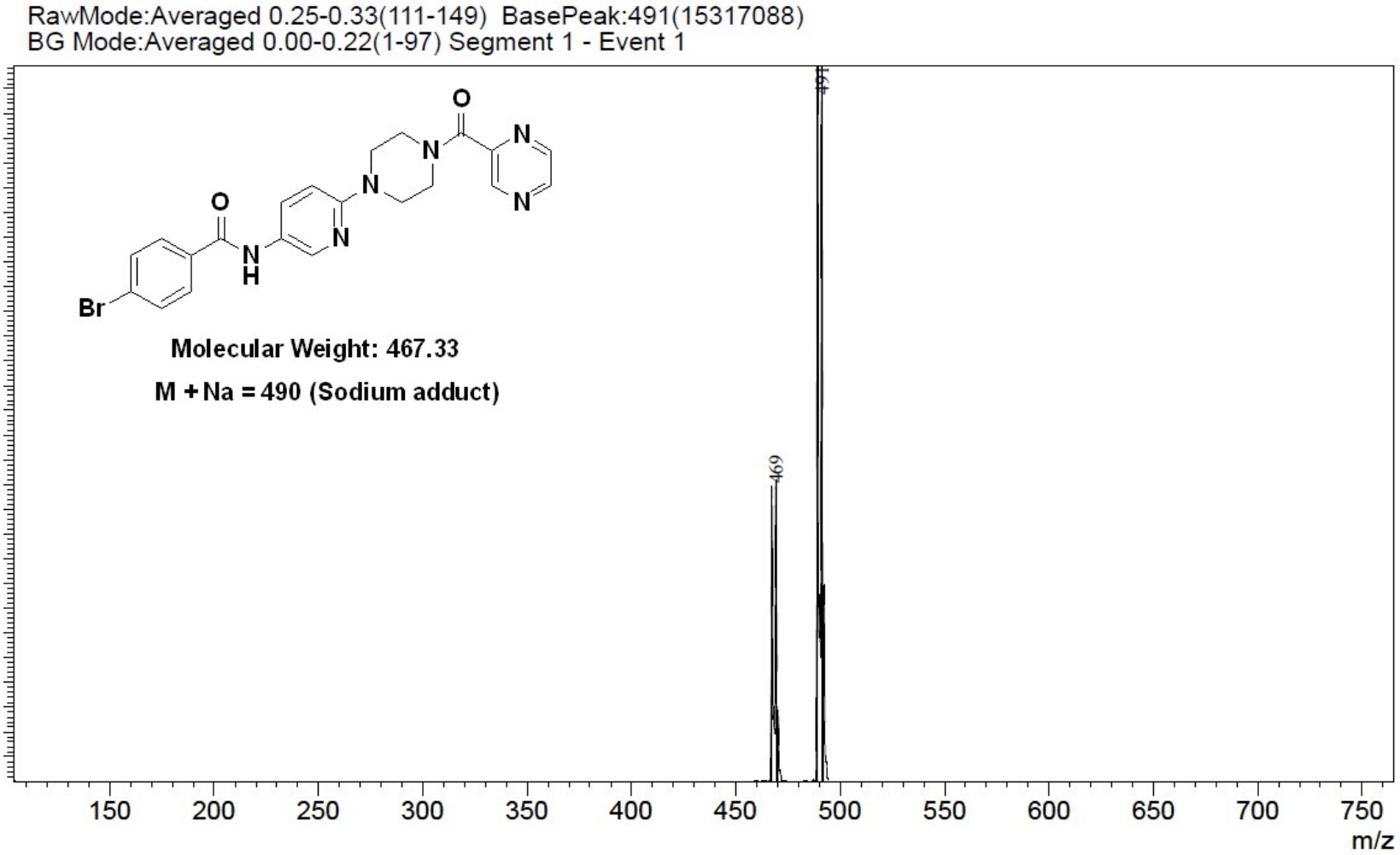
Mass spectra of 6b



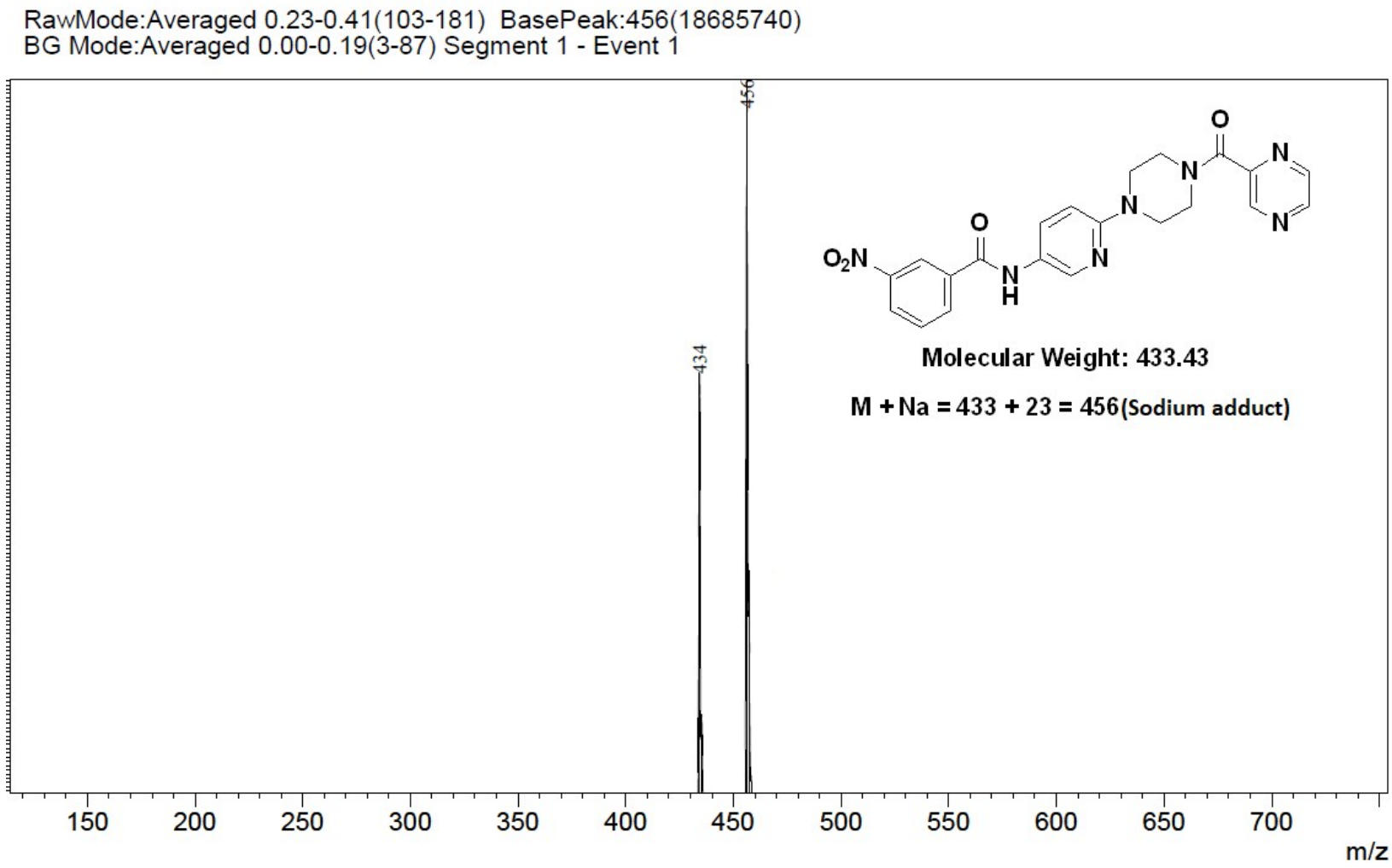
Mass spectra of 6c



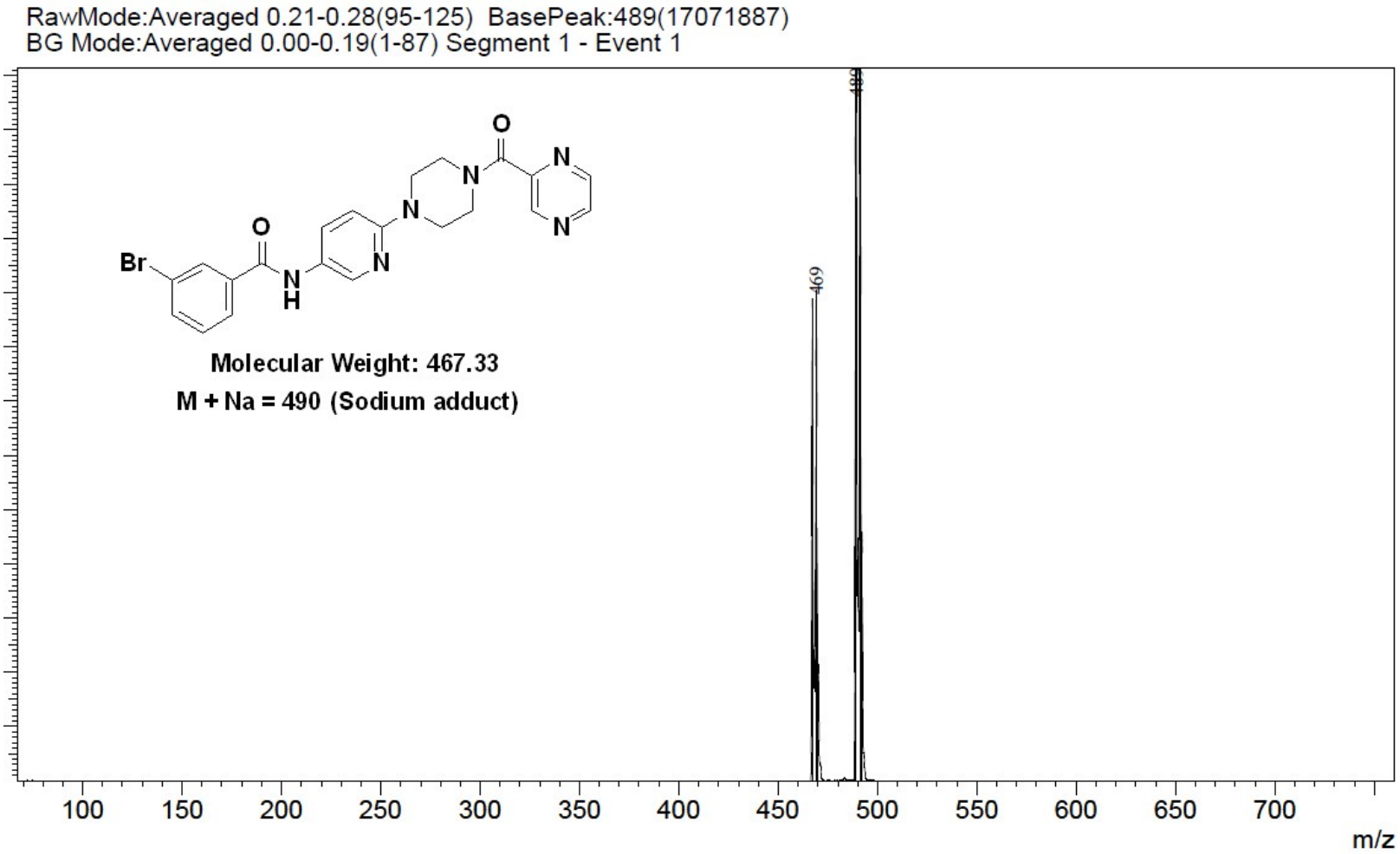
Mass spectra of 6d



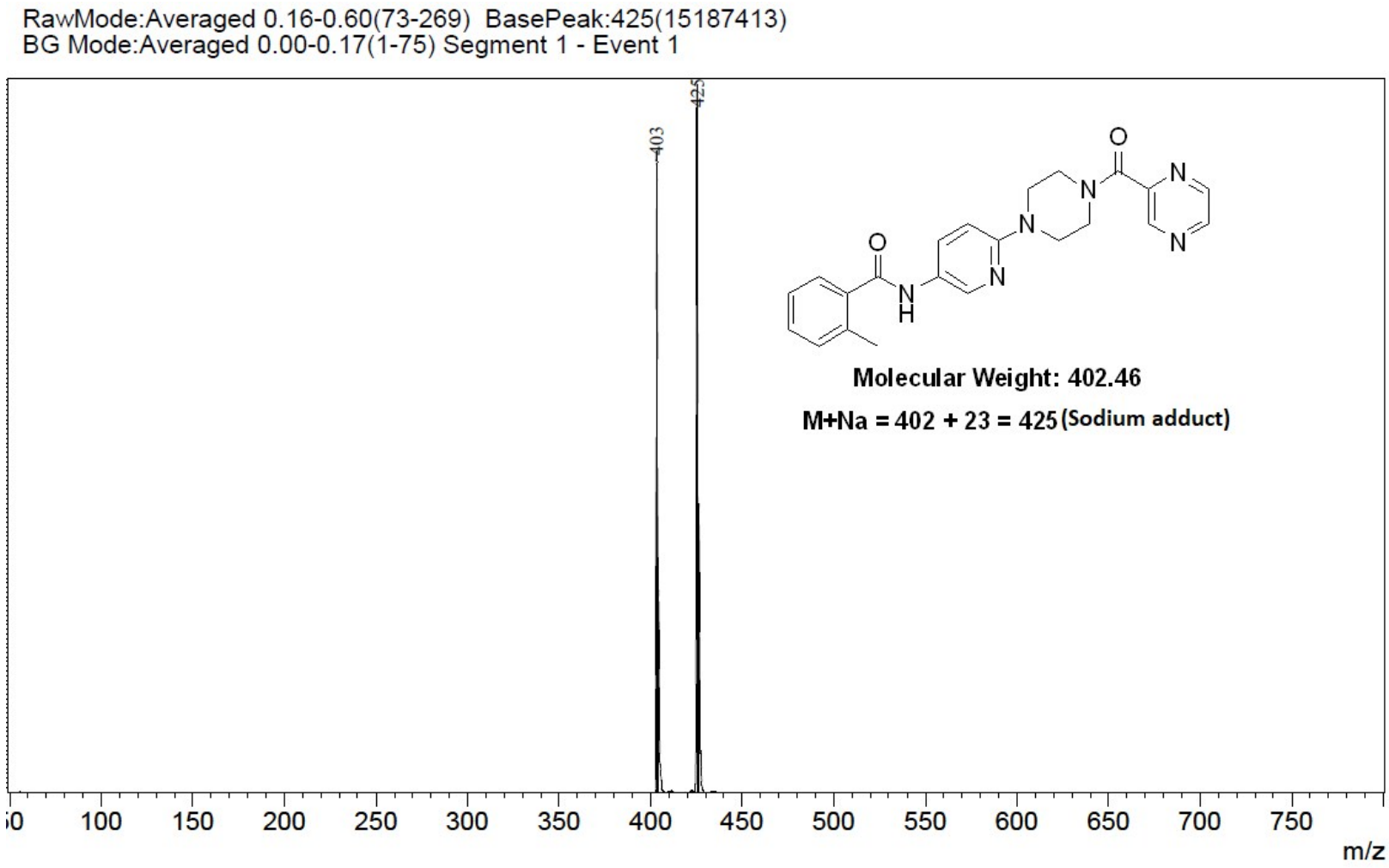
Mass spectra of 6e



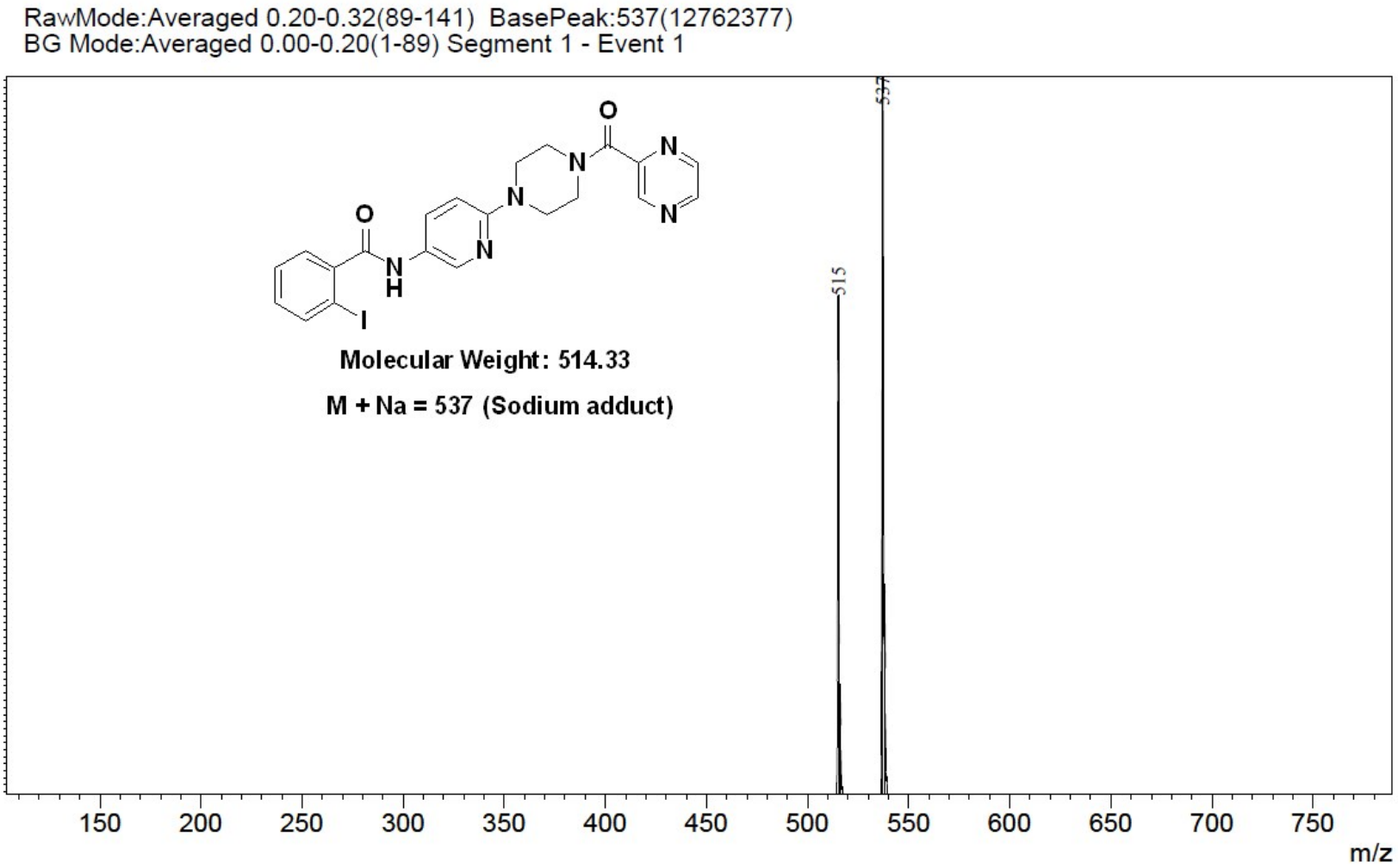
Mass spectra of 6f



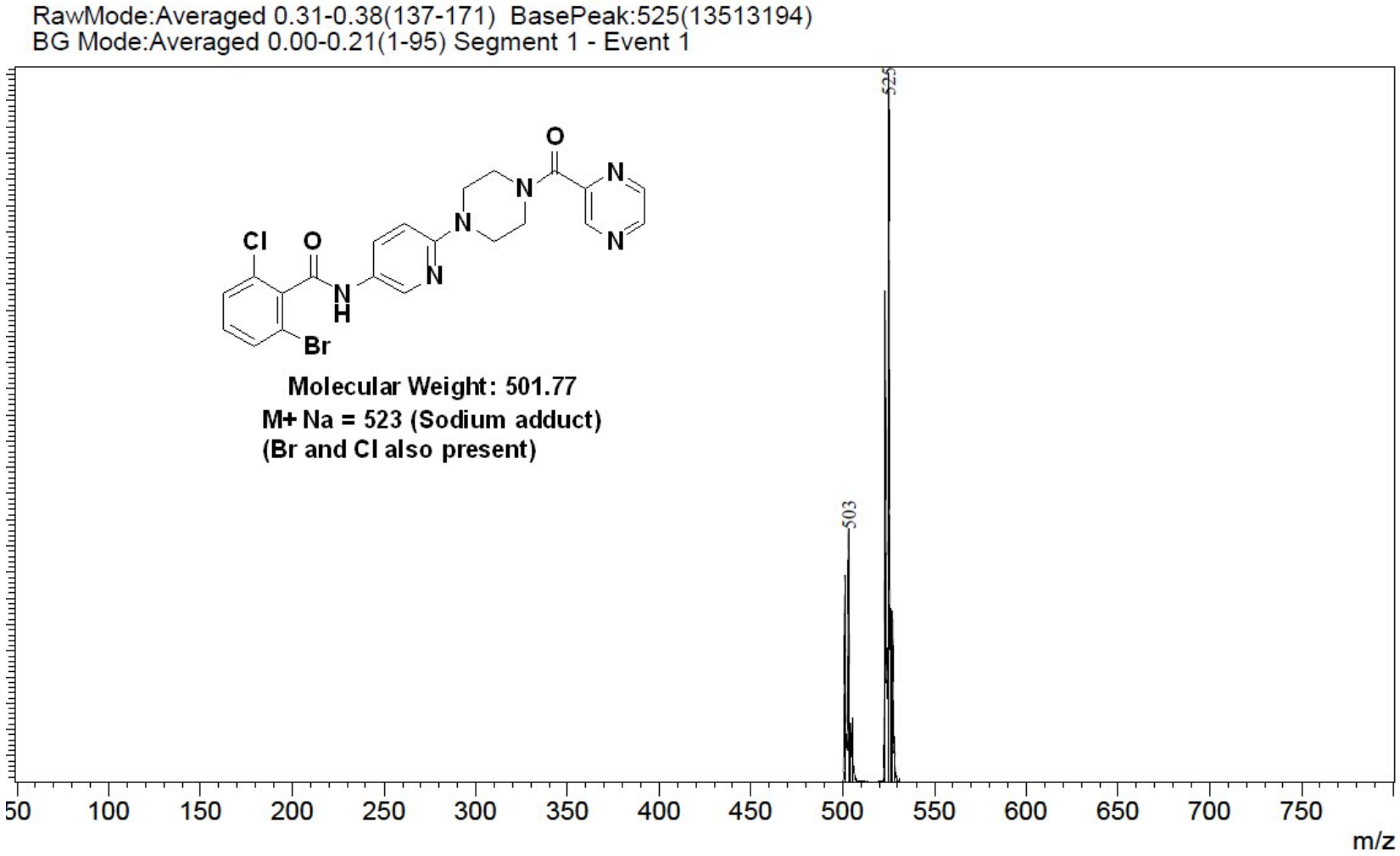
Mass spectra of 6g



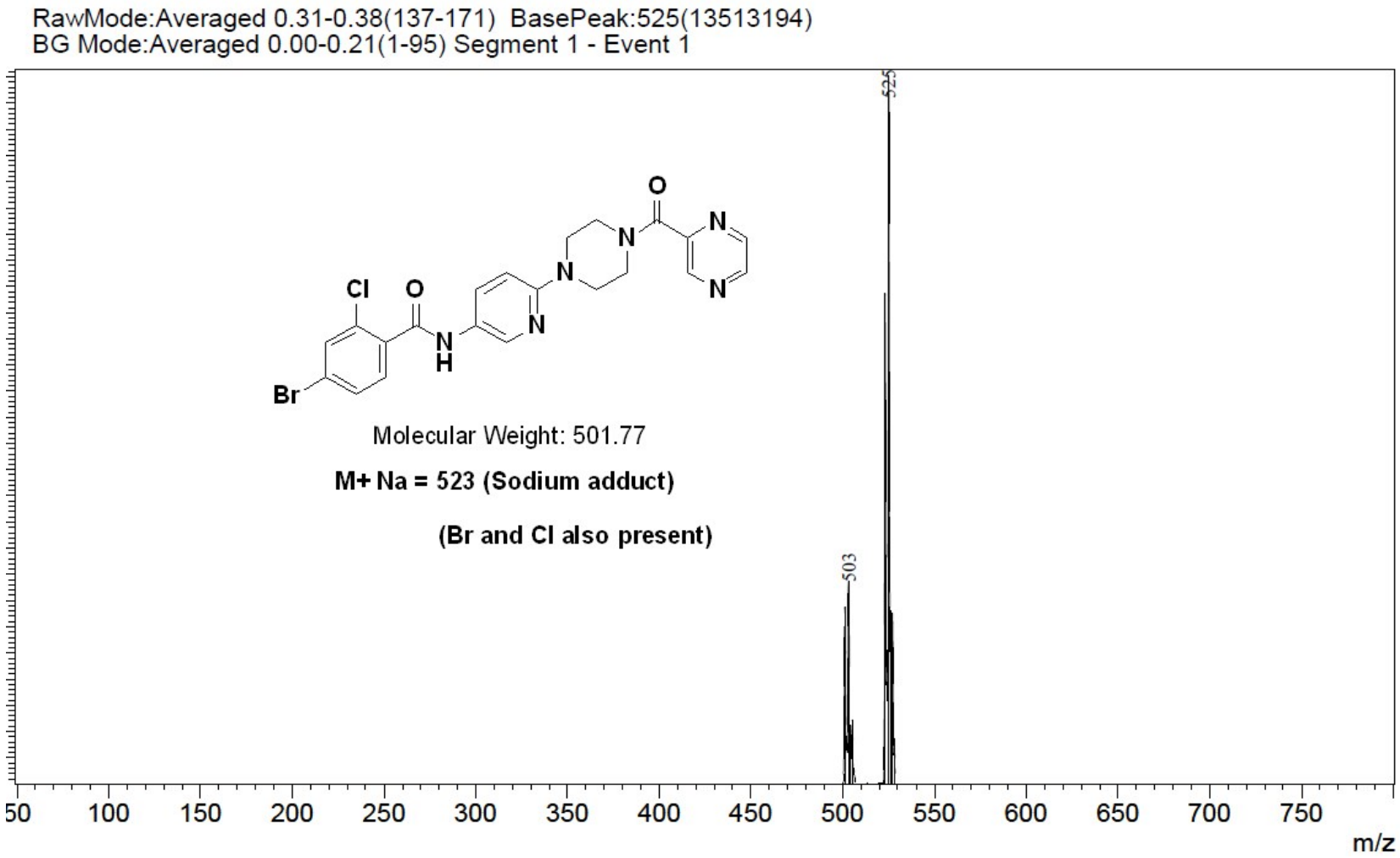
Mass spectra of 6h



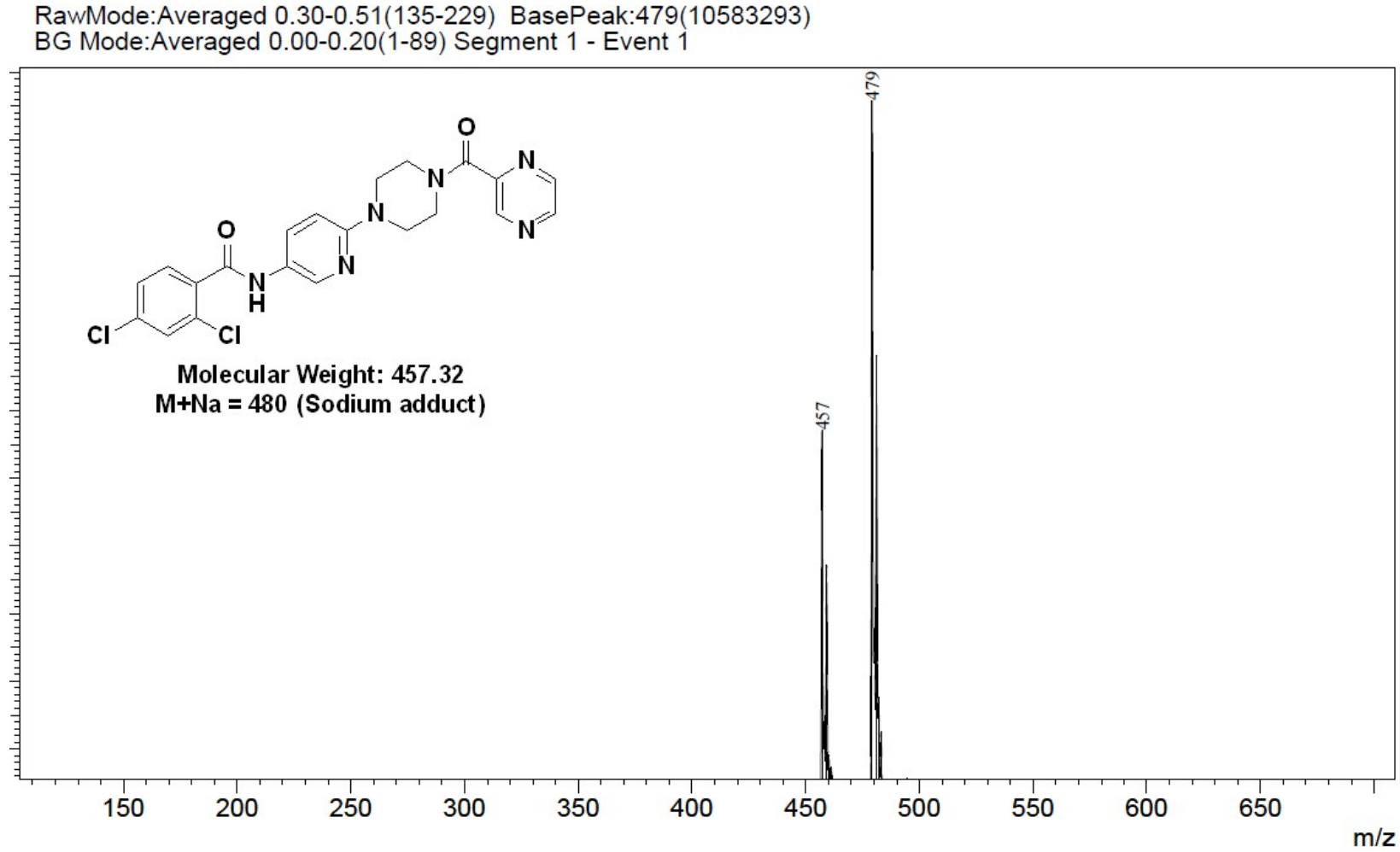
Mass spectra of 6i



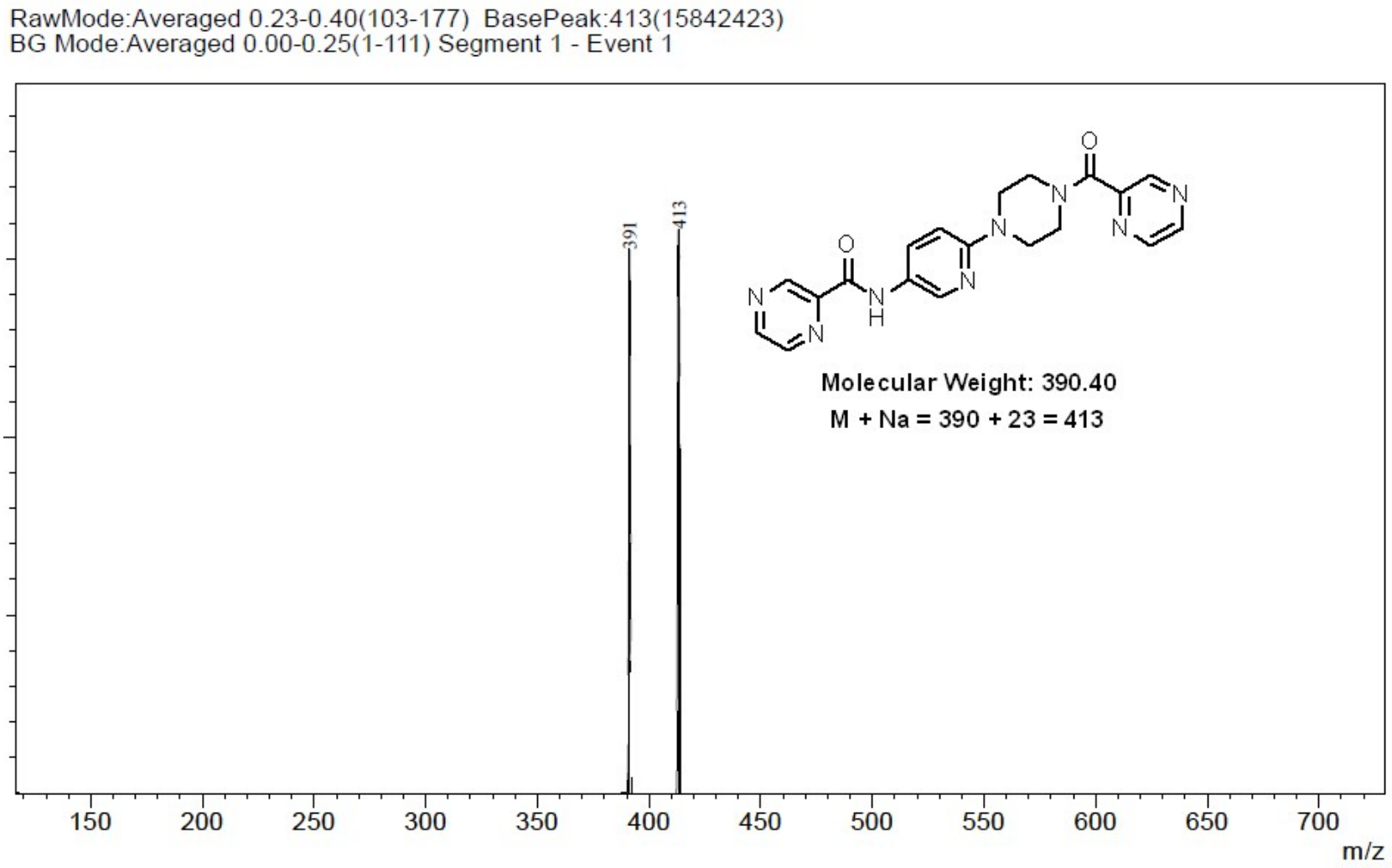
Mass spectra of 6j



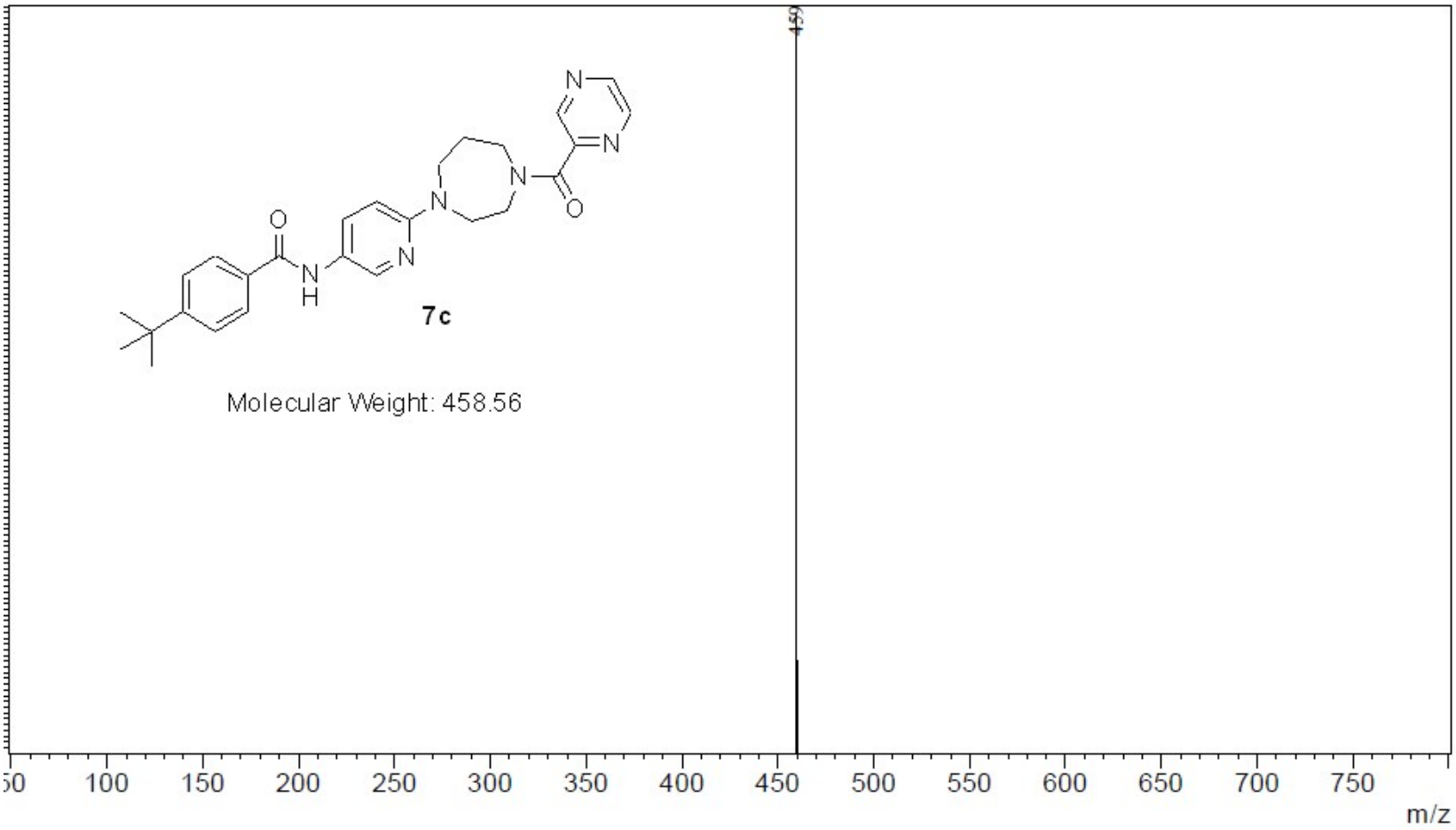
Mass spectra of 6k



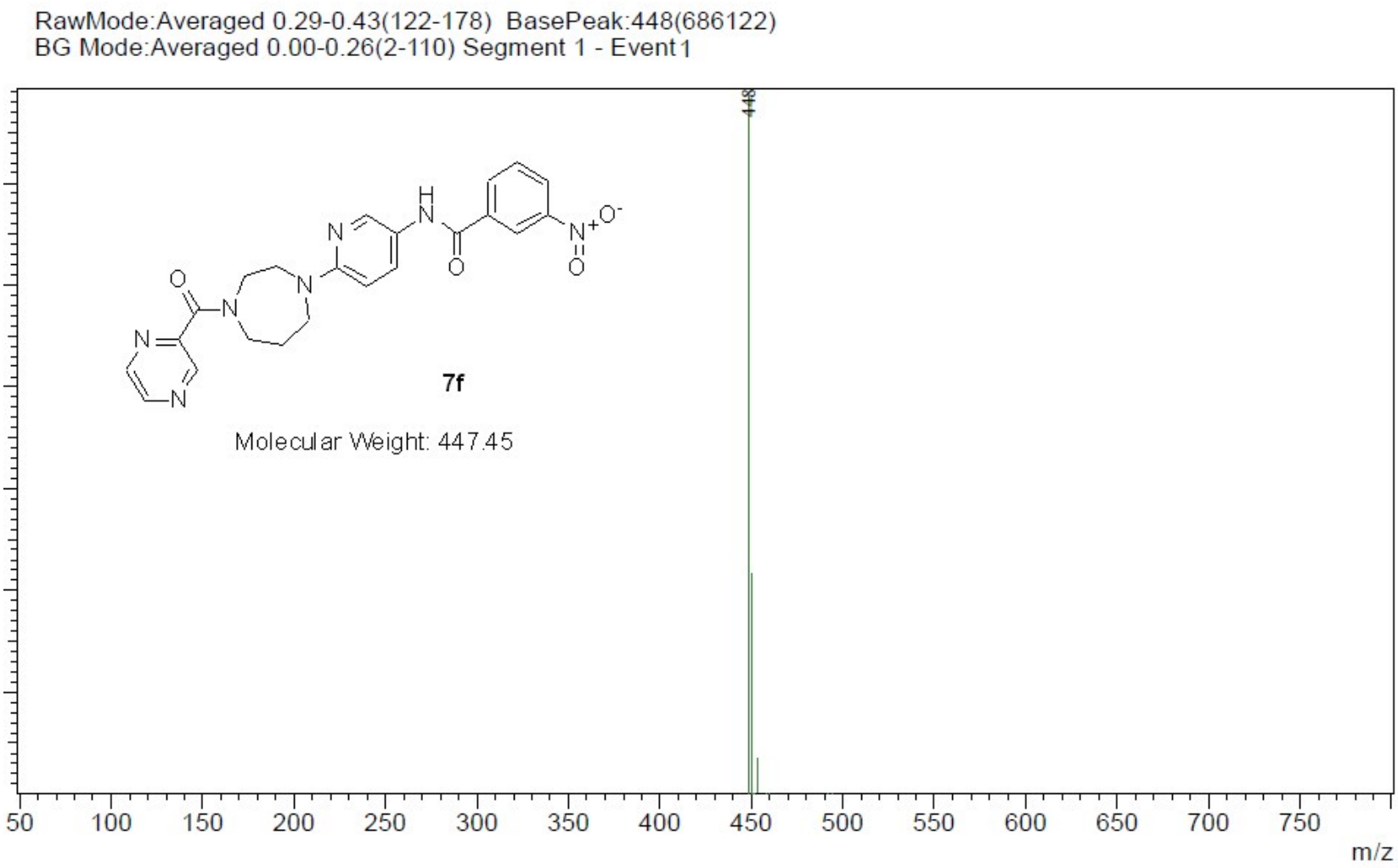
Mass spectra of 6l



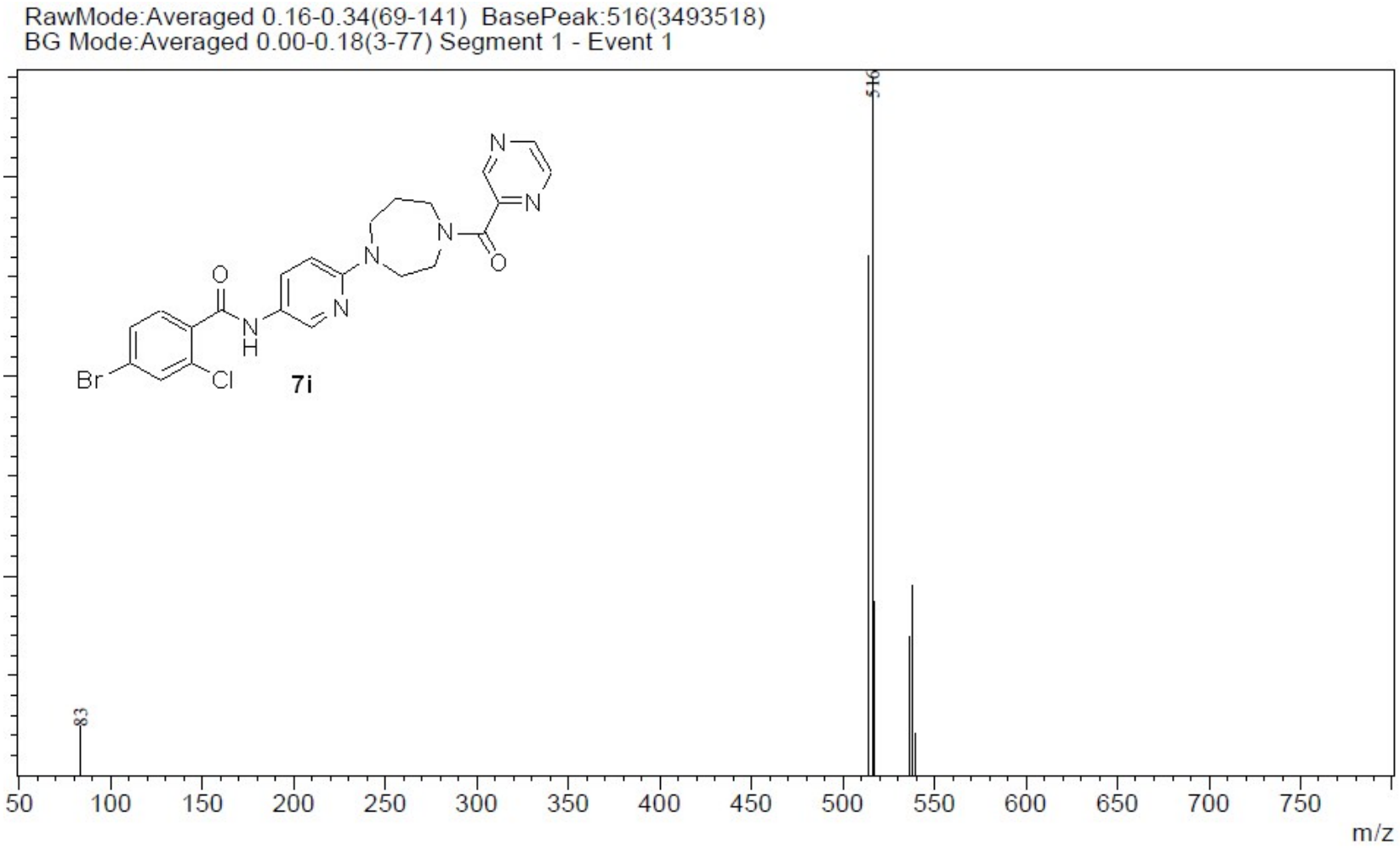
Mass spectra of 6n



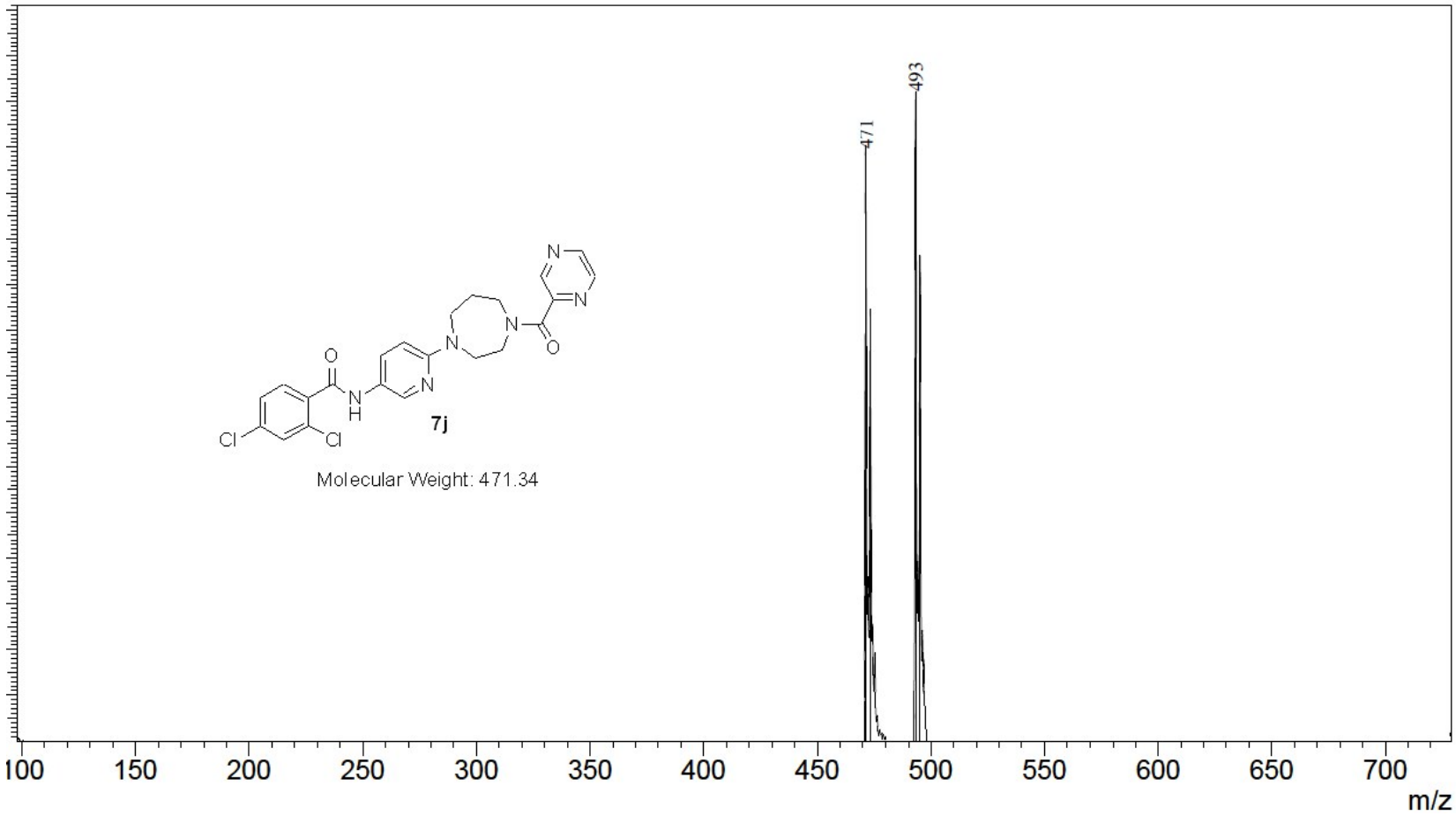
Mass spectra of 7c



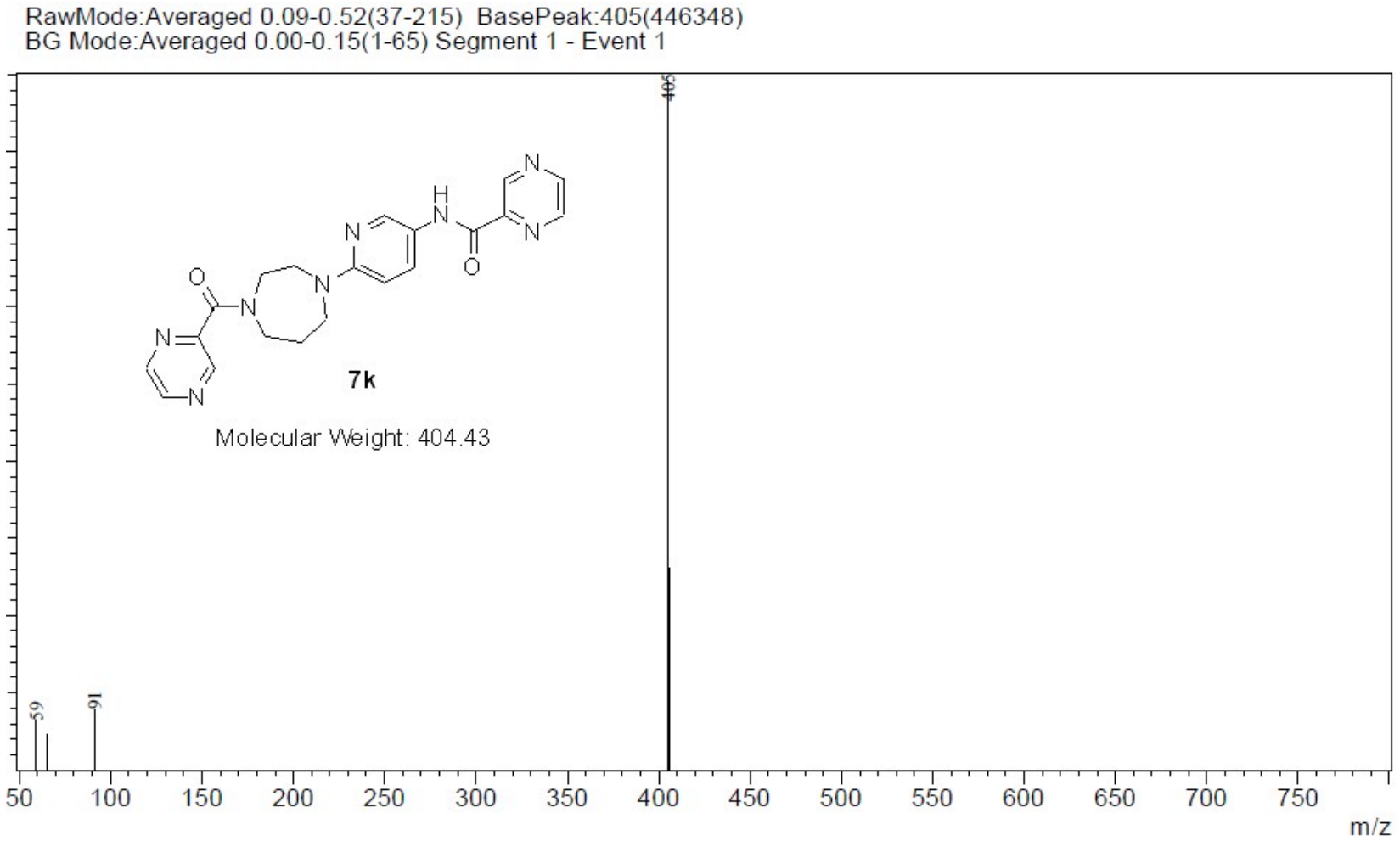
Mass spectra of 7f



Mass spectra of 7i



Mass spectra of 7j



Mass spectra 7k