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Supporting Information

Biocatalytic synthesis of oxadiazole thioethers and evaluation of their antitumor activity

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1. Experimental section

1.1. Chemistry

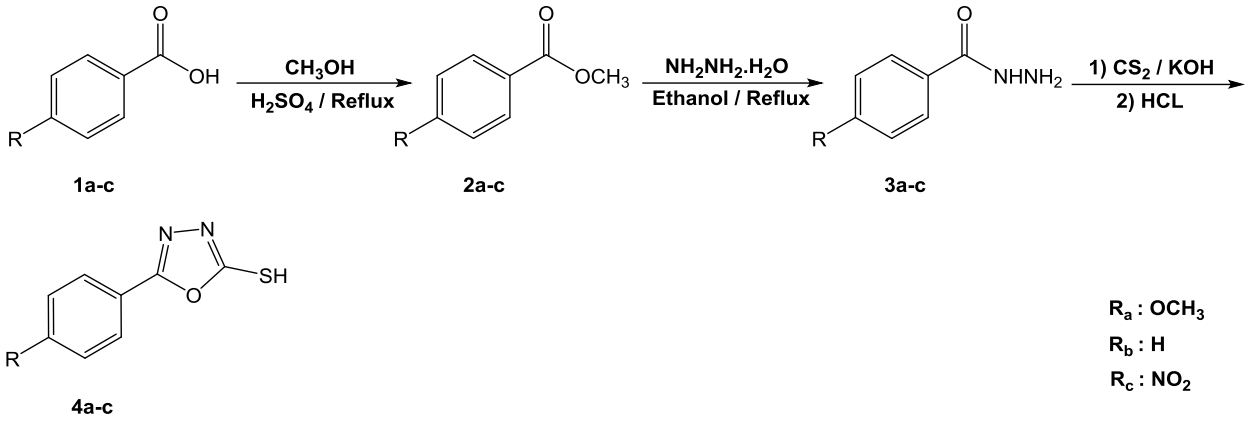
All chemicals and reagents used in the current study were of analytical grade. Novozym 435 was a generous gift from Novozymes (Denmark). Porcine pancreas lipase, *Thermomyces lanuginosus* lipase, *Aspergillus niger* lipase, and bovine serum albumin (BSA) were purchased from Sigma-Aldrich. Progress of the reactions was monitored by thin layer chromatography (TLC, performed on pre-coated Merck silica gel 60 F_{254} plates). The compounds were purified by preparative TLC (home-made plates 20*20 cm with silica gel 60 F_{254}, Merck) using a mixture of ethyl acetate and *n*-hexane as a mobile phase. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer (300 MHz and 75 MHz, respectively) using $CDCl_3$ and DMSO-*d6* with TMS as internal reference. Melting points were determined on a Thermo Scientific 9100 apparatus. Mass spectra were recorded via an Agilent Technologies (HP) 5973 mass spectrometer.

1.2. Synthesis of 5-phenyl-1,3,4-oxadiazole-2-thiols (4a-c)

The 5-phenyl-1,3,4-oxadiazole-2-thiols (**4a-c**) were synthesized according to previous reports [1-3] with some modifications (Scheme 1). Exemplified with **4c**, a mixture of 4-methoxybenzoic acid (40 mmol, 4.4 mL), sulfuric acid 95-97% (5.2 mL), and methanol (60 mL) was heated to 80 °C under reflux for 24 h. Excess solvent was removed by vacuum evaporation, and an aqueous solution of saturated sodium bicarbonate was added to neutralize the acid. Then, the methyl benzoate product was extracted with ethyl acetate.

In the next step, the synthesized methyl 4-methoxybenzoate (30 mmol, 4.98 g) and excess hydrazine hydrate (90 mmol, 2.88 mL) was mixed with absolute ethanol (50 mL) and refluxed overnight. After completion of the reaction, the reaction mixture was concentrated to a reduced volume *in vacuo*, and the product subsequently recovered by filtration. Excess hydrazine was removed by washing the product on the filter with water.

Finally, the synthesized 4-methoxybenzohydrazide (18.3 mmol, 3.04 g), solubilized in a mixture of absolute ethanol and water (5:1), was reacted with carbon disulfide (36 mmol, 2.2 mL) in presence of potassium hydroxide (32 mmol, 1.8 g) at 90 °C under reflux for 24 h. After reducing the volume *in vacuo*, pH was adjusted to 2-3 with 1 M HCl. The formed precipitate was then collected by filtration and found to be pure by TLC (*n*-hexane/ethyl acetate, 8:1-6:1) and NMR analysis. Overall yield of 5-(4-nitrophenyl)-1,3,4-oxadiazole-2-thiol (**4c**) was 83%.



Scheme 1. Synthesis of 5-(4-methoxyphenyl)-1,3,4-oxadiazole-2-thiol (**4a**, 80%), 5-phenyl-1,3,4-oxadiazole-2-thiol (**4b**, 78%), and 5-(4-nitrophenyl)-1,3,4-oxadiazole-2-thiol (**4c**, 83%).

1.3.1. Typical procedure for synthesis of 2,5-disubstituted-1,3,4-oxadiazole thioethers

A reaction mixture containing 5-(4-methoxyphenyl)-1,3,4-oxadiazole-2-thiol (**4a**) (0.1 mmol, 0.02 g), 4-chlorobenzaldehyde (**5b**) (0.2 mmol, 0.028 g), ethyl butyryl acetate (**6a**) (0.2 mmol, 32 µL), enzyme (30 mg Novozym 435), acetonitrile (485 µL), H_2O (15 µL) and aniline (5 µL) was stirred at room temperature. The reaction was incubated for 24 h and the progress was monitored using TLC (*n*-hexane/ethyl acetate, 8:1-6:1). Thereupon, the enzyme was filtered from the reaction, and the mixture was purified using preparative TLC (*n*-hexane/ethyl acetate, 8:1-6:1). Finally, the desired product **7c** was recrystallized from ethanol. Analytical data of all compounds are provided in the Supporting Information.

1.3.2. Structure-characterization of compound 7c

The 1,3,4-oxadiazole thioether product (**7c**) was characterized by NMR spectroscopy (Figure 1). A doublet of doublets (dd) signal at δ_H = 6.23 ppm was assigned to the proton H_a linked to the chiral center, whereas two signals at δ_H = 3.2 ppm and δ_H = 3.6 ppm indicated the two protons H_{b1} and H_{b2}. According to the splitting pattern and coupling constants of H_a (dd, J = 8.7, 6.0 Hz), it was concluded that the two diastereotopic protons were vicinal to H_a; H_{b1} (dd, J = 17.7, 8.7 Hz) and H_{b2} (dd, J = 17.7, 6.0 Hz). The NMR spectra showed no ethyl ester signals, indicating that the ethyl ester part of the compound is converted to a carboxylic acid during the reaction, which

subsequently decarboxylates. As further confirmation, the mass spectrometry (MS) result corresponded to the theoretical molecular weight of compound **7c**.

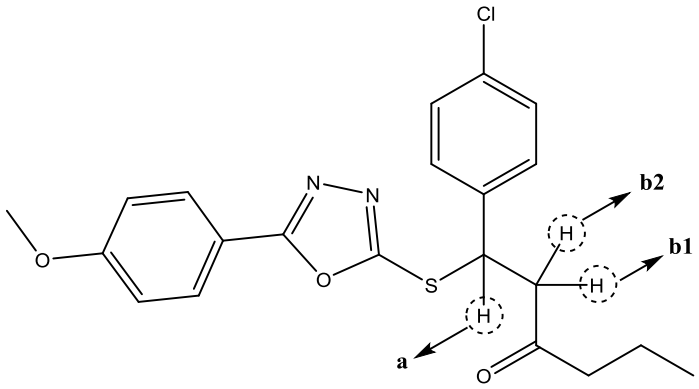


Figure 1. The 1,3,4-oxadiazole thioether product (**7c**).

1.4. Anti-proliferation assay

To assess the cytotoxicity effects of the synthesized compounds, an MTT-based colorimetric assay was performed. In brief, HepG2 (human liver cancer) and HT-29 (human colorectal cancer) cell lines were cultured in appropriate media, supplemented with 5% of heat-activated fetal bovine serum (FBS), and penicillin/streptomycin. For the MTT assay, a proper number of cells was added to the 96-well plate. Following overnight incubation (at 37°C with 5% CO_2), the synthesized compounds were added at different concentrations to the plate, including Doxorubicin as reference. The plate was further incubated for 48 h, before the MTT solution (0.5 mg/mL) was added to each well. The plate was finally incubated for approximately 2 h at 37 °C. Subsequently, the medium was discarded, and DMSO was added to each well to solubilize formed formazan crystals. The absorbance was measured using an ELISA plate reader at 570 nm. The data are presented as mean ± SEM. The IC50 value is defined as the concentration at which the viability of the cells is reduced by 50%.

1.5. Computational methods

1.5.1. ADME prediction

In silico ADME properties of compounds **7f** and **7g** were studied using SwissADME (http://www.swissadme.ch/) to predict their physicochemical properties, lipophilicity, water solubility, pharmacokinetics, and drug-likeness.

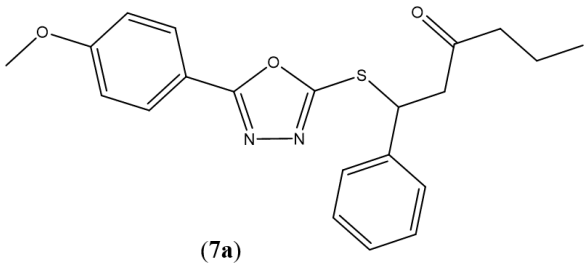
1.5.2. Molecular modeling

Molecular docking studies were carried out using Maestro 11.5, available in the Schrödinger suites software (version 2018-1). The human thymidylate synthase crystal structure (PDB: 6QXG) was retrieved from Protein Data Bank. The protein structure was prepared by adding hydrogen atoms, bonds, and charges using the protein preparation wizard in Maestro. Crystallographic water molecules and other unnecessary hetero atoms were deleted. Then, the structure was minimized using an OPLS3 force field [4]. The receptor grid generation panel in Glide (Grid-based Ligand Docking with Energetics) was used to generate the grid box of the co-crystallized ligand defining the active site (x: 39.67, y: -33.85, z: 19.16). The 2D structures of the compounds were drawn and converted to 3D, which were subsequently refined by the LigPrep module in Maestro. Ligands with different chiralities were generated using an OPLS3 force field for energy minimization. Molecular docking calculation was conducted using the Glide application in extra precision (XP) mode without applying any constraints [5]. The co-crystallized ligand of the receptor was redocked into the TS binding pocket with a low RMSD (0.52 Å), validating the docking procedure.

2. Characterization data of compounds 7a-l:

1-{[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-1-phenylhexan-3-one:

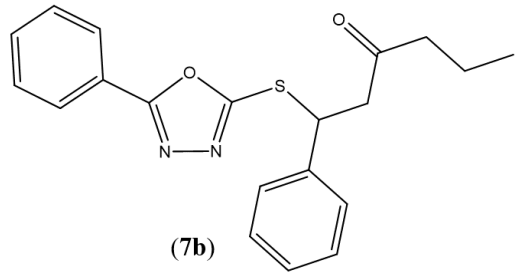
White powder (yield: 73%); mp: 103 °C; ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.90 – 7.81 (d, 2H), 7.52 (d, *J* = 7.0 Hz, 2H), 7.36 (q, *J* = 6.6 Hz, 3H), 7.02 – 6.95 (m, 2H), 6.27 (dt, *J* = 8.9, 4.2 Hz, 1H), 3.88 (d, *J* = 3.2 Hz, 3H), 3.68 – 3.56 (m, 1H), 3.22 (dd, *J* = 17.4, 5.4 Hz, 1H), 2.45 (q, *J* = 5.4, 3.4 Hz, 2H), 1.60 (q, *J* = 10.7, 9.0 Hz, 2H), 0.91 – 0.83 (m, 3H). ^{13}CNMR (75 MHz, Chloroform-*d*) δ 210.8, 180.3, 167.5, 164.1, 141.8, 133.5, 133.3, 133.0, 132.1, 119.6, 119.3, 62.3, 60.2, 50.8, 49.6, 21.8, 18.3. MS (EI, m/z) = 382.3 $[M]^+$ (calculated: 382.5). Anal. Calcd for $C_{21}H_{22}N_2O_3S$: C = 65.95, H = 5.80, N = 7.32; Found: C = 65.91, H = 5.86, N = 7.28.



(**7a**)

1-phenyl-1-{[5-phenyl-1,3,4-oxadiazol-2-yl]sulfanyl}hexan-3-one:

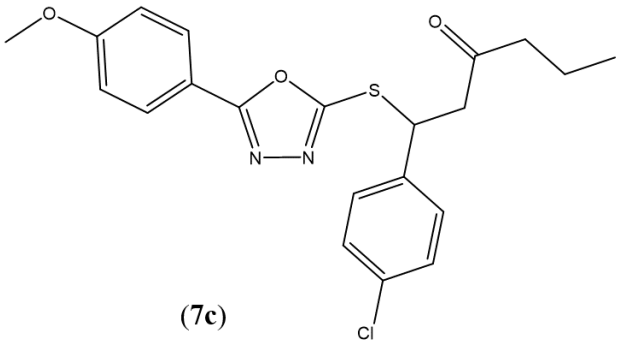
White powder (yield: 70%); mp: 81 °C; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.99 – 7.90 (m, 2H), 7.53 (dq, *J* = 8.0, 3.3, 2.2 Hz, 5H), 7.37 (q, *J* = 7.5, 7.0 Hz, 3H), 6.29 (dd, *J* = 9.2, 5.5 Hz, 1H), 3.66 (dd, *J* = 17.6, 9.2 Hz, 1H), 3.23 (dd, *J* = 17.6, 5.6 Hz, 1H), 2.46 (t, *J* = 7.2 Hz, 2H), 1.62 (p, *J* = 7.3 Hz, 2H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}CNMR (75 MHz, Chloroform-*d*) δ 206.1, 175.9, 159.3, 137.0, 132.3, 129.1, 128.9, 128.7, 127.4, 126.4, 122.5, 57.7, 46.1, 44.9, 17.1, 13.6. MS (EI, m/z) = 352.2 $[M]^+$ (calculated: 352.5). Anal. Calcd for $C_{20}H_{20}N_2O_2S$: C = 68.16, H = 5.72, N = 7.95; Found: C = 68.19, H = 5.72, N = 7.91.



(**7b**)

1-(4-chlorophenyl)-1-{[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}hexan-3-one:

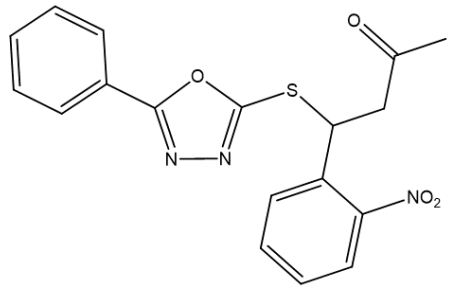
White crystal (yield: 78%); mp: 97 °C; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.88 – 7.81 (m, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.35 – 7.27 (m, 2H), 7.01 – 6.93 (m, 2H), 6.23 (dd, *J* = 8.7, 6.0 Hz, 1H), 3.88 (s, 3H), 3.60 (dd, *J* = 17.7, 8.7 Hz, 1H), 3.21 (dd, *J* = 17.7, 6.0 Hz, 1H), 2.45 (td, *J* = 7.2, 1.9 Hz, 2H), 1.60 (q, *J* = 7.3 Hz, 2H), 0.86 (d, *J* = 7.4 Hz, 3H). ^{13}CNMR (75 MHz, Chloroform-*d*) δ 205.8, 175.6, 162.9, 159.5, 135.5, 134.6, 129.0, 128.9, 128.3, 114.7, 114.6, 56.9, 55.6, 46.0, 44.9, 17.1, 13.6. MS (EI, m/z) = 416.2 $[M]^+$ (calculated: 416.9). Anal. Calcd for $C_{21}H_{21}ClN_2O_3S$: C = 60.50, H = 5.08, N = 6.72; Found: C = 60.43, H = 5.12, N = 6.79.



(**7c**)

4-(2-nitrophenyl)-4-{[5-phenyl-1,3,4-oxadiazol-2-yl]sulfanyl}butan-2-one:

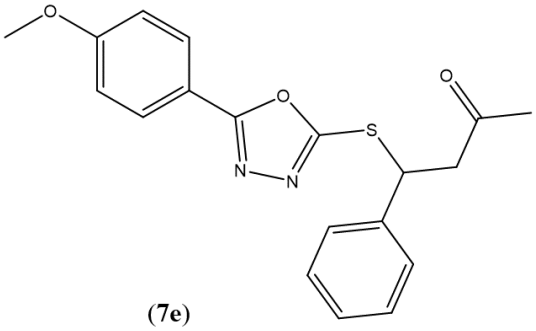
White powder (yield: 82%); mp: 193 °C; ^{1}HNMR (300 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 8.1 Hz, 1H), 7.95 (d, *J* = 7.4 Hz, 2H), 7.64 – 7.45 (m, 6H), 6.70 (dd, *J* = 11.0, 3.1 Hz, 1H), 3.77 (dd, *J* = 17.9, 10.9 Hz, 1H), 3.31 (dd, *J* = 17.7, 3.1 Hz, 1H), 2.29 (s, 3H).^{13}CNMR (75 MHz, Chloroform-*d*) δ 202.8, 176.3, 159.3, 148.4, 133.9, 133.4, 132.6, 129.2, 128.0, 126.5, 125.0, 122.3, 54.2, 46.8, 29.7. MS (EI, m/z) = 369.1 $[M]^+$ (calculated: 369.4). Anal. Calcd for $C_{18}H_{15}N_3O_4S$: C = 58.53, H = 4.09, N = 11.38; Found: C = 58.47, H = 4.21, N = 11.41.



(**7d**)

4-{[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-4-phenylbutan-2-one:

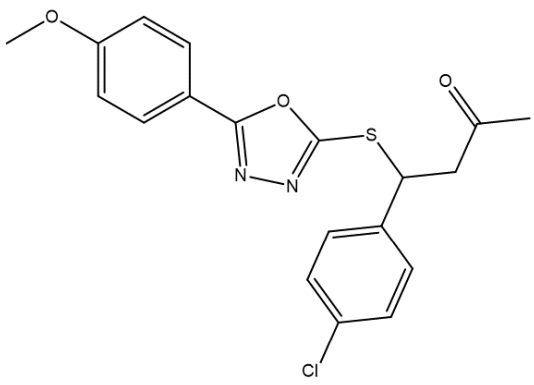
Brownish powder (yield: 72%); mp: 95 °C; ^{1}HNMR (300 MHz, Chloroform-d) δ 7.90 – 7.84 (m, 2H), 7.57 – 7.50 (m, 2H), 7.41 – 7.32 (m, 3H), 7.02 – 6.96 (m, 2H), 6.26 (dd, J = 8.5, 5.5 Hz, 1H), 3.89 (s, 3H), 3.67 (dd, J = 17.5, 8.9 Hz, 1H), 3.32 – 3.19 (m, 1H), 2.23 (s, 3H). ^{13}CNMR (75 MHz, DMSO-d6) δ 205.3, 175.4, 163.0, 159.4, 137.9, 129.2, 128.7, 127.4, 115.4, 114.6, 57.6, 56.1, 46.7, 30.3. MS (EI, m/z) = 354.2 $[M]^+$ (calculated: 354.4). Anal. Calcd for $C_{19}H_{18}N_2O_3S$: C = 64.39, H = 5.12, N = 7.90; Found: C = 64.41, H = 5.15, N = 7.86.



(**7e**)

4-(4-chlorophenyl)-4-{[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}butan-2-one:

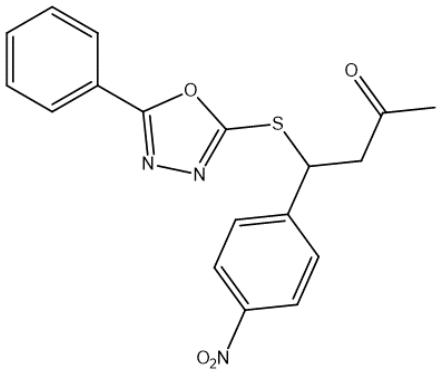
White powder (yield: 77%); mp: 107 °C; ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.85 (dd, *J* = 7.6, 3.8 Hz, 2H), 7.46 (dd, *J* = 7.4, 3.7 Hz, 2H), 7.32 (dd, *J* = 5.9, 2.7 Hz, 2H), 6.98 (dd, *J* = 7.6, 3.7 Hz, 2H), 6.28 – 6.15 (m, 1H), 3.88 (d, *J* = 3.2 Hz, 3H), 3.61 (dt, *J* = 12.8, 6.2 Hz, 1H), 3.25 (dt, *J* = 17.7, 5.2 Hz, 1H), 2.21 (d, *J* = 3.3 Hz, 3H). ^{13}CNMR (75 MHz, DMSO-d_6) δ 205.1, 175.4, 163.0, 159.5, 136.9, 133.4, 129.4, 129.2, 128.7, 115.4, 114.5, 57.0, 56.1, 46.5, 30.3. MS (EI, m/z) = 388.2 $[M]^+$ (calculated: 388.9). Anal. Calcd for $C_{19}H_{17}ClN_2O_3S$: C = 58.69, H = 4.41, N = 7.20; Found: C = 58.64, H = 4.45, N = 7.22.



(**7f**)

4-(4-nitrophenyl)-4-{[5-phenyl-1,3,4-oxadiazol-2-yl]sulfanyl}butan-2-one:

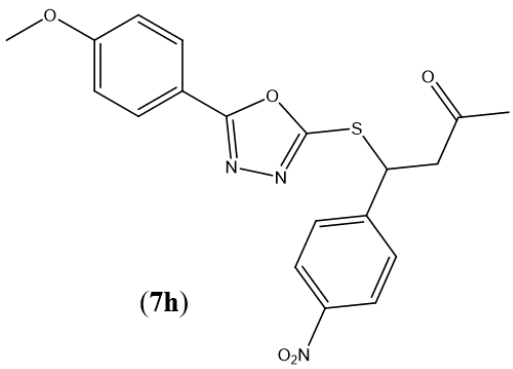
Brownish crystal (yield: 70%); mp: 132 °C; ^{1}HNMR (300 MHz, Chloroform-*d*) δ 8.23 (d, *J* = 8.4 Hz, 2H), 7.94 (d, *J* = 7.5 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.54 (q, *J* = 10.6, 7.2 Hz, 3H), 6.34 (t, *J* = 7.3 Hz, 1H), 3.69 (dd, *J* = 18.0, 8.5 Hz, 1H), 3.34 (dd, *J* = 18.1, 6.0 Hz, 1H), 2.26 (d, *J* = 3.4 Hz, 3H). ^{13}CNMR (75 MHz, Chloroform-*d*) δ 207.6, 180.7, 164.4, 152.6, 148.4, 137.4, 133.9, 133.3, 131.2, 128.8, 126.8, 61.6, 51.4, 34.9. MS (EI, m/z) = 369.2 $[M]^+$ (calculated: 369.4). Anal. Calcd for $C_{18}H_{15}N_3O_4S$: C = 58.53, H = 4.09, N = 11.38; Found: C = 58.47, H = 4.21, N = 11.41.



(**7g**)

4-{[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-4-(4-nitrophenyl)butan-2-one:

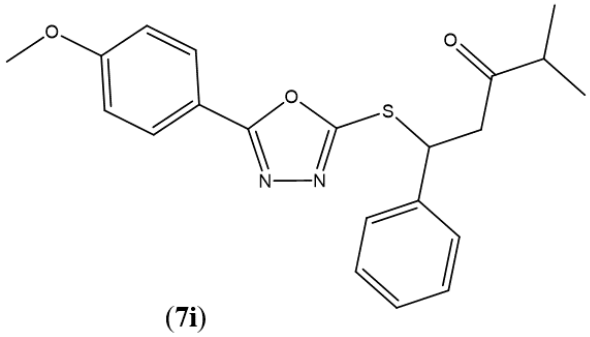
White powder (yield: 75%); mp: 147 °C; ^{1}HNMR (300 MHz, Chloroform-*d*) δ 8.17 – 8.09 (m, 2H), 7.82 – 7.73 (m, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 6.96 – 6.88 (m, 2H), 6.21 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.79 (s, 3H), 3.59 (dd, *J* = 18.0, 8.5 Hz, 1H), 3.23 (dd, *J* = 18.1, 6.0 Hz, 1H), 2.15 (s, 3H). ^{13}CNMR (75 MHz, DMSO-d_6) δ 204.9, 175.7, 163.1, 159.6, 147.7, 145.1, 128.9, 128.8, 124.3, 115.4, 114.5, 57.2, 56.1, 46.5, 30.2. MS (EI, m/z) = 399.2 $[M]^+$ (calculated: 399.4). Anal. Calcd for $C_{19}H_{17}N_3O_5S$: C = 57.13, H = 4.29, N = 10.52; Found: C = 57.20, H = 4.22, N = 10.45.



(**7h**)

1-{[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-4-methyl-1-phenylpentan-3-one:

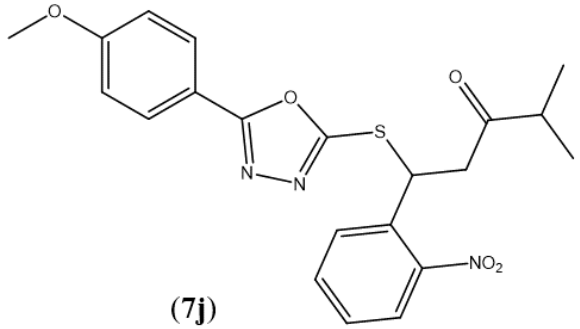
White powder (yield: 65%); mp: 131 °C; ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.92 – 7.81 (m, 2H), 7.54 – 7.45 (m, 2H), 7.36 (q, *J* = 7.3, 6.9 Hz, 3H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.26 (dd, *J* = 9.2, 5.4 Hz, 1H), 3.88 (s, 3H), 3.72 (dd, *J* = 17.8, 9.3 Hz, 1H), 3.24 (dd, *J* = 17.7, 5.4 Hz, 1H), 2.66 (hept, *J* = 7.0 Hz, 1H), 1.11 (t, *J* = 7.1 Hz, 6H). ^{13}CNMR (75 MHz, Chloroform-*d*) δ 209.6, 175.6, 162.7, 159.3, 137.1, 128.8, 128.5, 128.2, 127.4, 114.9, 114.5, 77.4, 77.0, 76.6, 57.6, 55.5, 43.9, 41.0, 18.1, 17.9. MS (EI, m/z) = 382.3 $[M]^+$ (calculated: 382.5). Anal. Calcd for $C_{21}H_{22}N_2O_3S$: C = 65.95, H = 5.80, N = 7.32; Found: C = 66.05, H = 5.77, N = 7.36.



(**7i**)

1-{[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-4-methyl-1-(2-nitrophenyl)pentan-3-one:

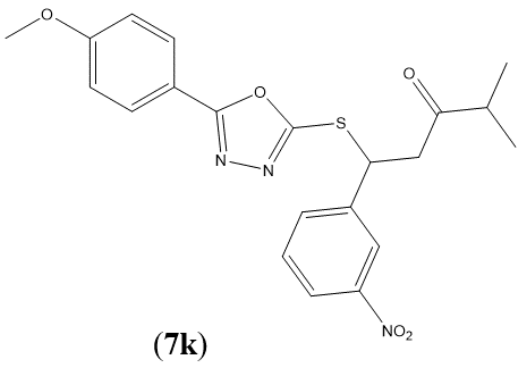
Light-brown powder (yield: 94%); mp: 126 °C; ^{1}HNMR (300 MHz, Chloroform-*d*) δ 8.08 – 7.98 (m, 1H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.66 – 7.54 (m, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.08 – 6.96 (m, 2H), 6.68 (dd, *J* = 10.9, 3.0 Hz, 1H), 3.89 (s, 2H), 3.81 (dd, *J* = 18.0, 10.9 Hz, 1H), 3.28 (dd, *J* = 18.0, 3.1 Hz, 1H), 2.73 (hept, *J* = 6.8 Hz, 1H), 1.17 (t, *J* = 6.7 Hz, 6H). ^{13}CNMR (75 MHz, Chloroform-*d*) δ 213.6, 180.8, 167.6, 164.0, 153.1, 138.5, 138.5, 133.8, 133.0, 132.9, 129.6, 119.4, 60.3, 58.7, 48.5, 45.4, 23.1, 22.7. MS (EI, m/z) = 427.3 $[M]^+$ (calculated: 427.5). Anal. Calcd for $C_{21}H_{21}N_3O_5S$: C = 59.00, H = 4.95, N = 9.83; Found: C = 58.96, H = 4.93, N = 9.89.



(**7j**)

1-{[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-4-methyl-1-(3-nitrophenyl)pentan-3-one:

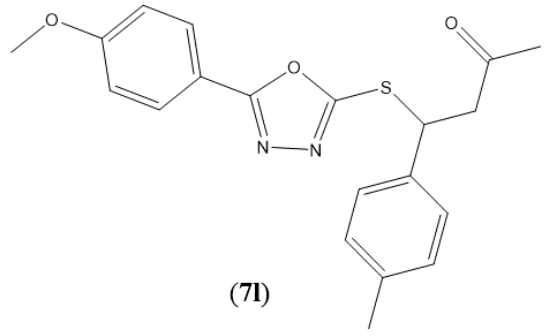
Yellowish crystal (yield: 79%); mp: 146 °C; ^{1}HNMR (300 MHz, Chloroform-*d*) δ 8.41 – 8.29 (m, 1H), 8.22 – 8.10 (m, 1H), 7.93 – 7.78 (m, 3H), 7.56 (t, *J* = 8.0 Hz, 1H), 6.97 (dd, *J* = 8.6, 3.3 Hz, 2H), 6.33 (dd, *J* = 8.7, 5.9 Hz, 1H), 3.86 (d, *J* = 4.1 Hz, 3H), 3.78 – 3.64 (m, 1H), 3.34 (dd, *J* = 18.2, 5.9 Hz, 1H), 2.68 (hept, *J* = 6.9 Hz, 1H), 1.11 (dd, *J* = 9.6, 6.8 Hz, 6H). ^{13}CNMR (75 MHz, Chloroform-*d*) δ 213.9, 180.4, 167.7, 164.4, 153.1, 143.8, 138.9, 134.7, 133.1, 128.3, 126.9, 119.4, 119.2, 61.5, 60.3, 48.3, 45.7, 22.8, 22.6. MS (EI, m/z) = 427.2 $[M]^+$ (calculated: 427.5). Anal. Calcd for $C_{21}H_{21}N_3O_5S$: C = 59.00, H = 4.95, N = 9.83; Found: C = 58.98, H = 4.93, N = 9.90.



(**7k**)

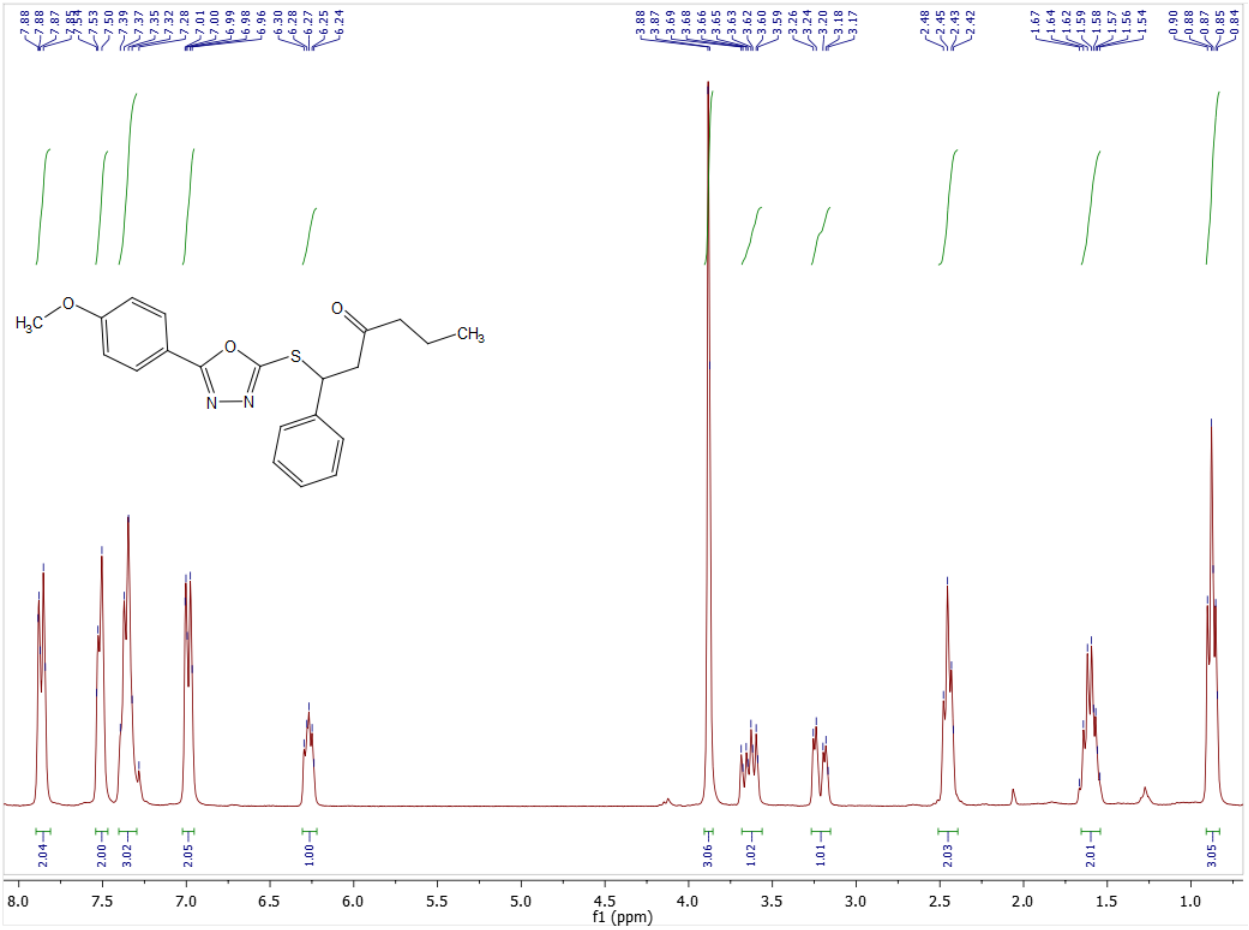
4-{[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}-4-(p-tolyl)butan-2-one:

White powder (yield: 73%); mp: 97 °C; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 8.9 Hz, 2H), 7.42 (d, *J* = 7.7 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 6.99 (d, *J* = 8.9 Hz, 2H), 6.23 (dd, *J* = 8.9, 5.7 Hz, 1H), 3.88 (s, 3H), 3.64 (dd, *J* = 17.6, 8.9 Hz, 1H), 3.26 (dd, *J* = 17.4, 5.7 Hz, 1H), 2.34 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 203.83, 175.54, 162.77, 159.39, 138.57, 133.96, 129.51, 128.34, 127.39, 114.89, 114.55, 57.43, 55.56, 46.90, 30.22, 21.19. MS (EI, m/z) = 369.2 $[M]^+$ (calculated: 368.5). Anal. Calcd for $C_{20}H_{20}N_2O_3S$: C = 65.20, H = 5.47, N = 7.60; Found: C = 65.17, H = 5.48, N = 7.63.

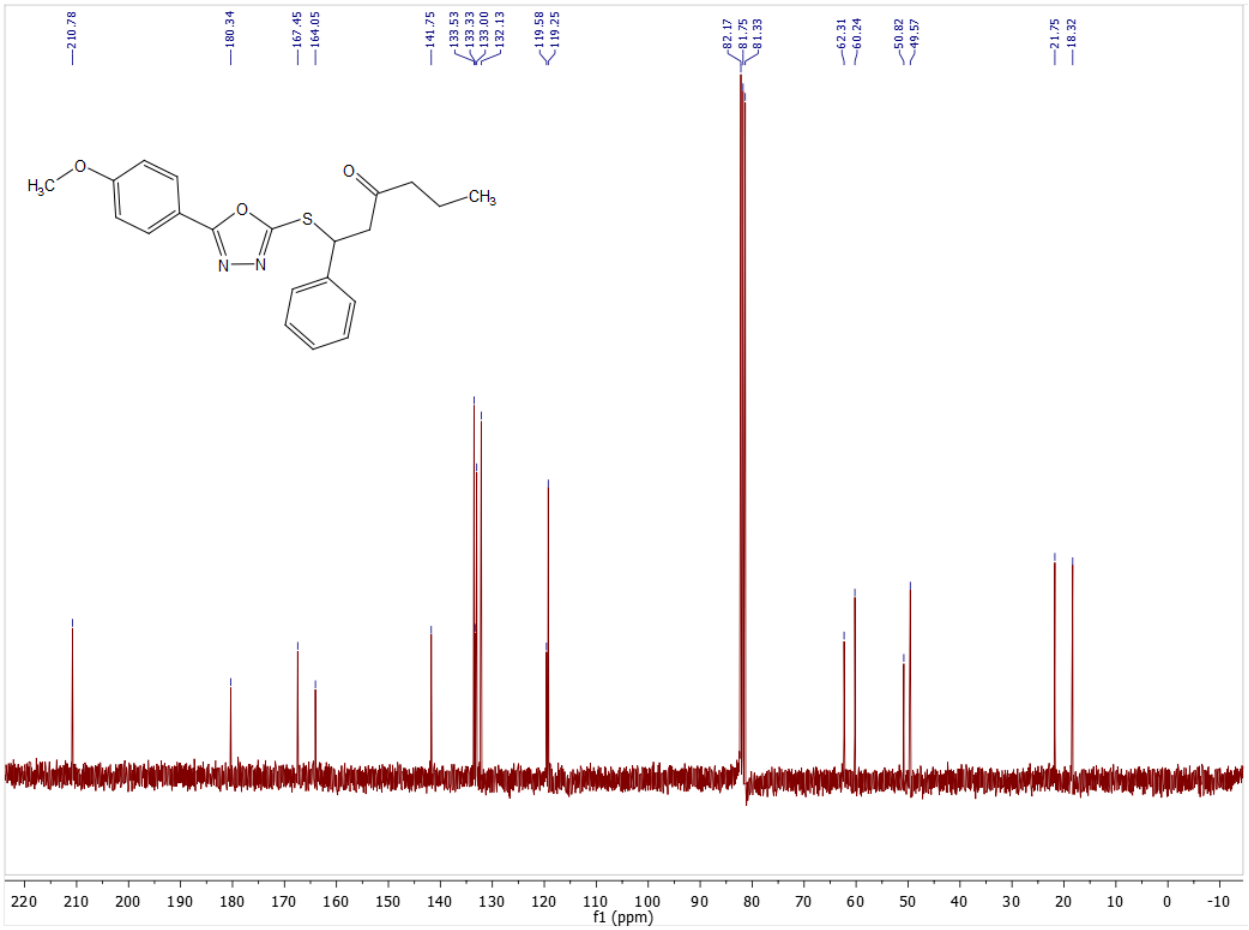


(**7l**)

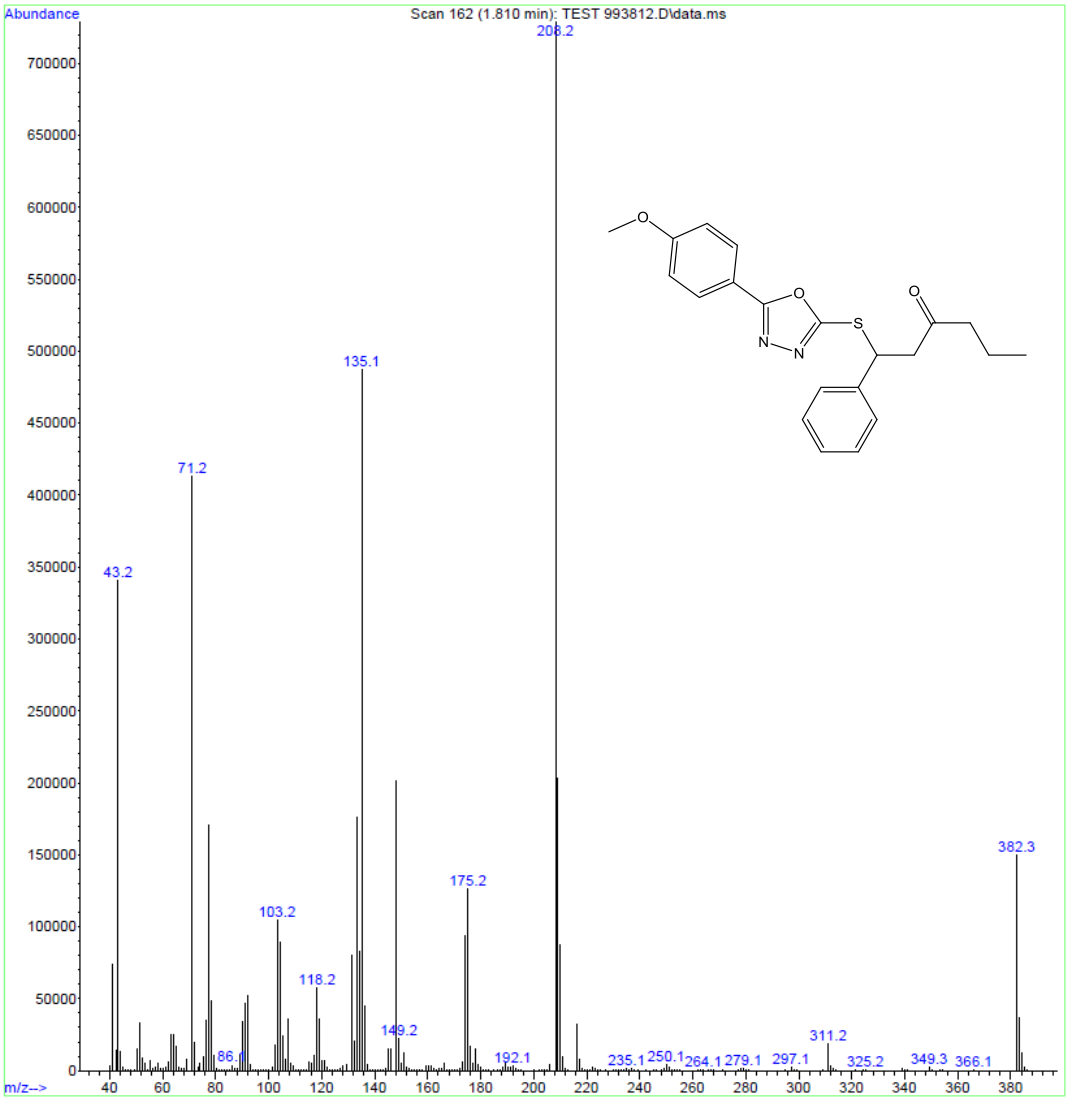
3. Spectral data of compounds 7a-l (^{1}HNMR, ^{13}C NMR, and mass spectrometry):



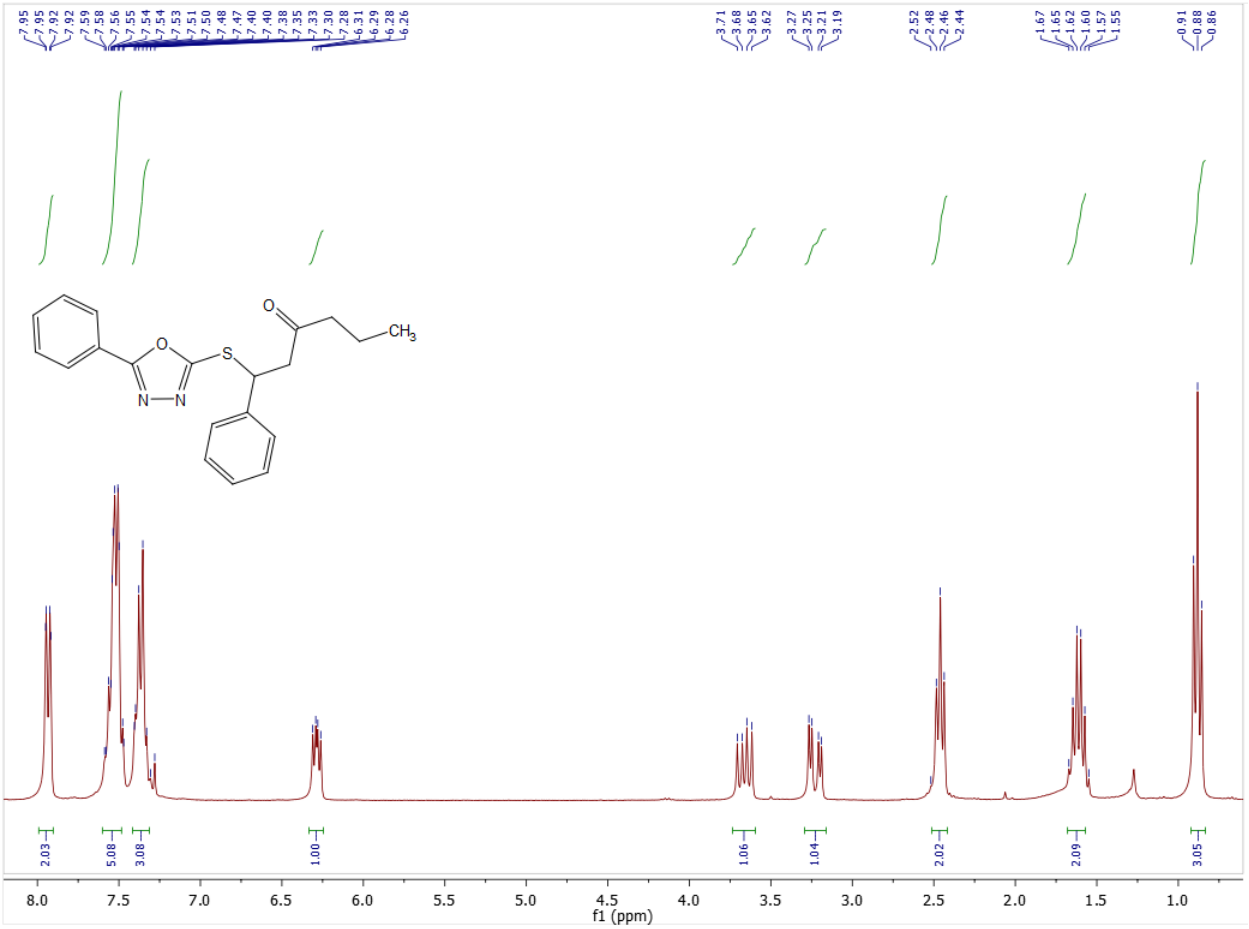
^{1}H NMR of **7a** in $CDCl_3$



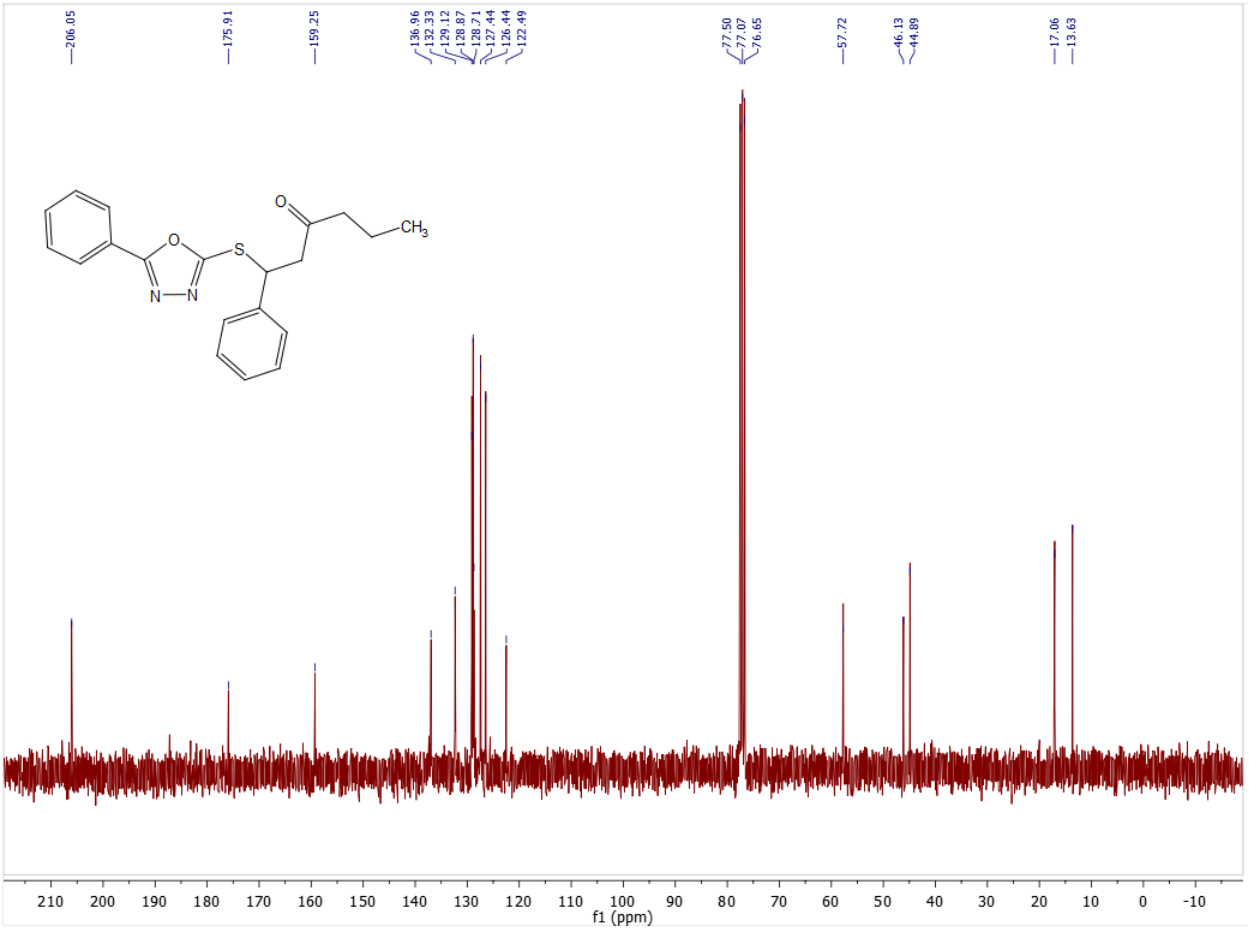
^{13}C NMR of **7a** in $CDCl_3$



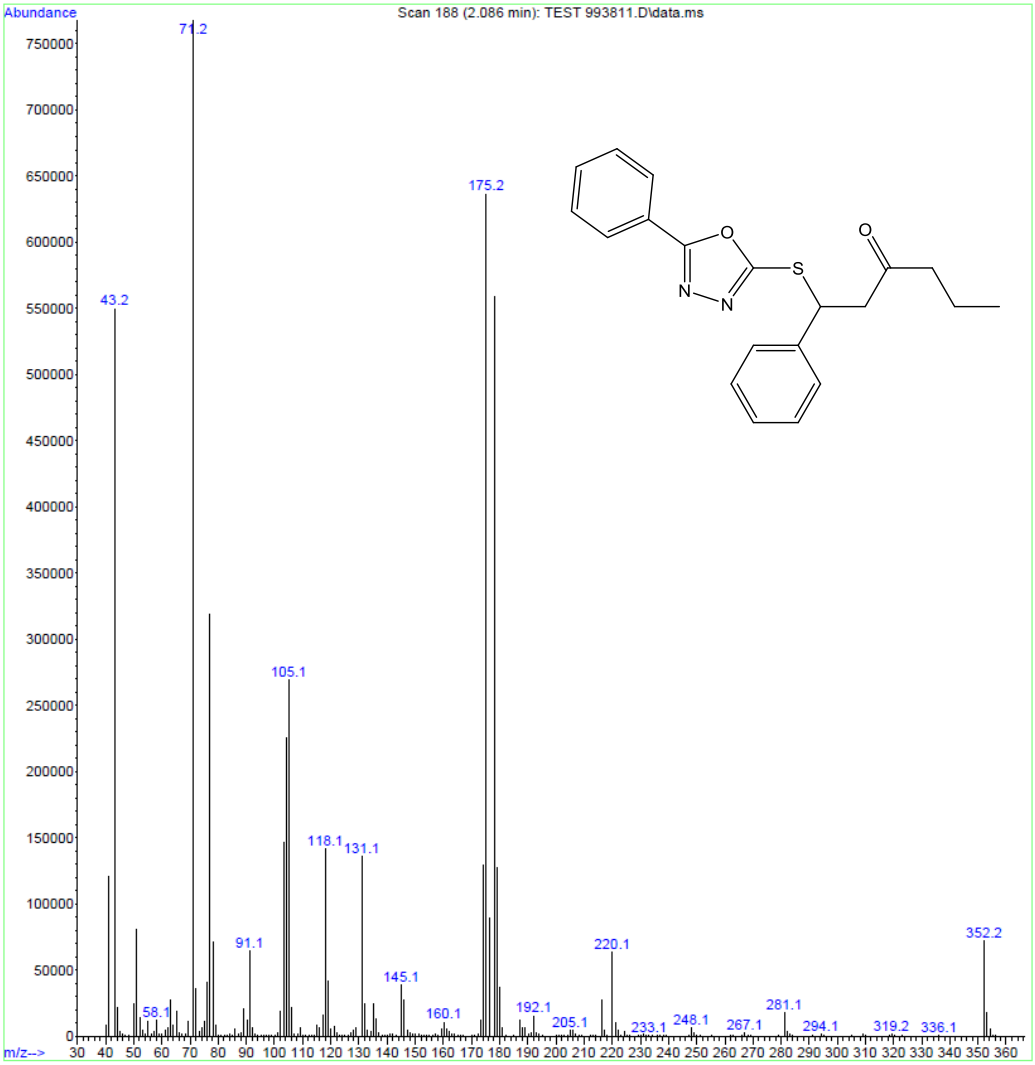
Mass spectrum of **7a**



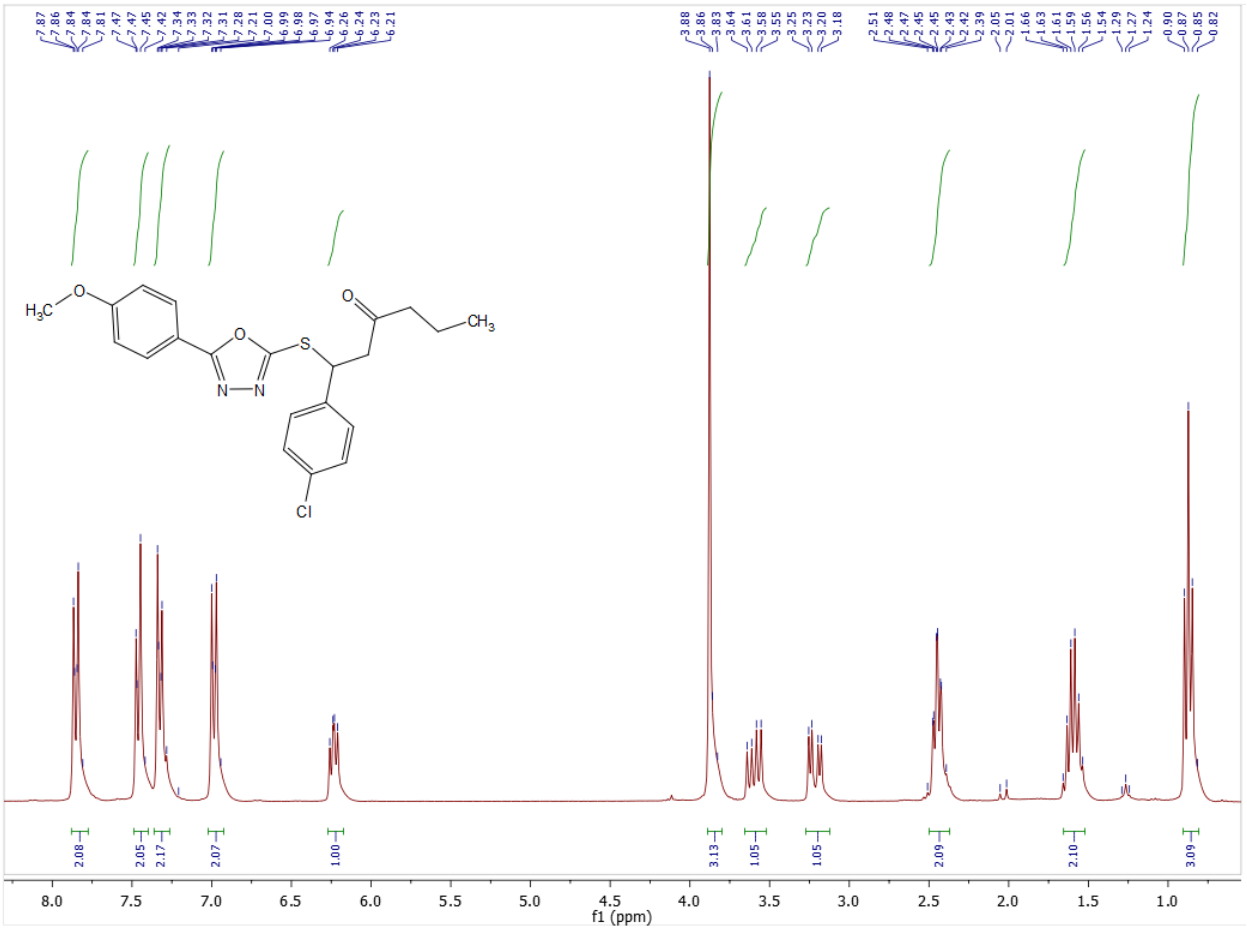
^{1}H NMR of **7b** in $CDCl_3$



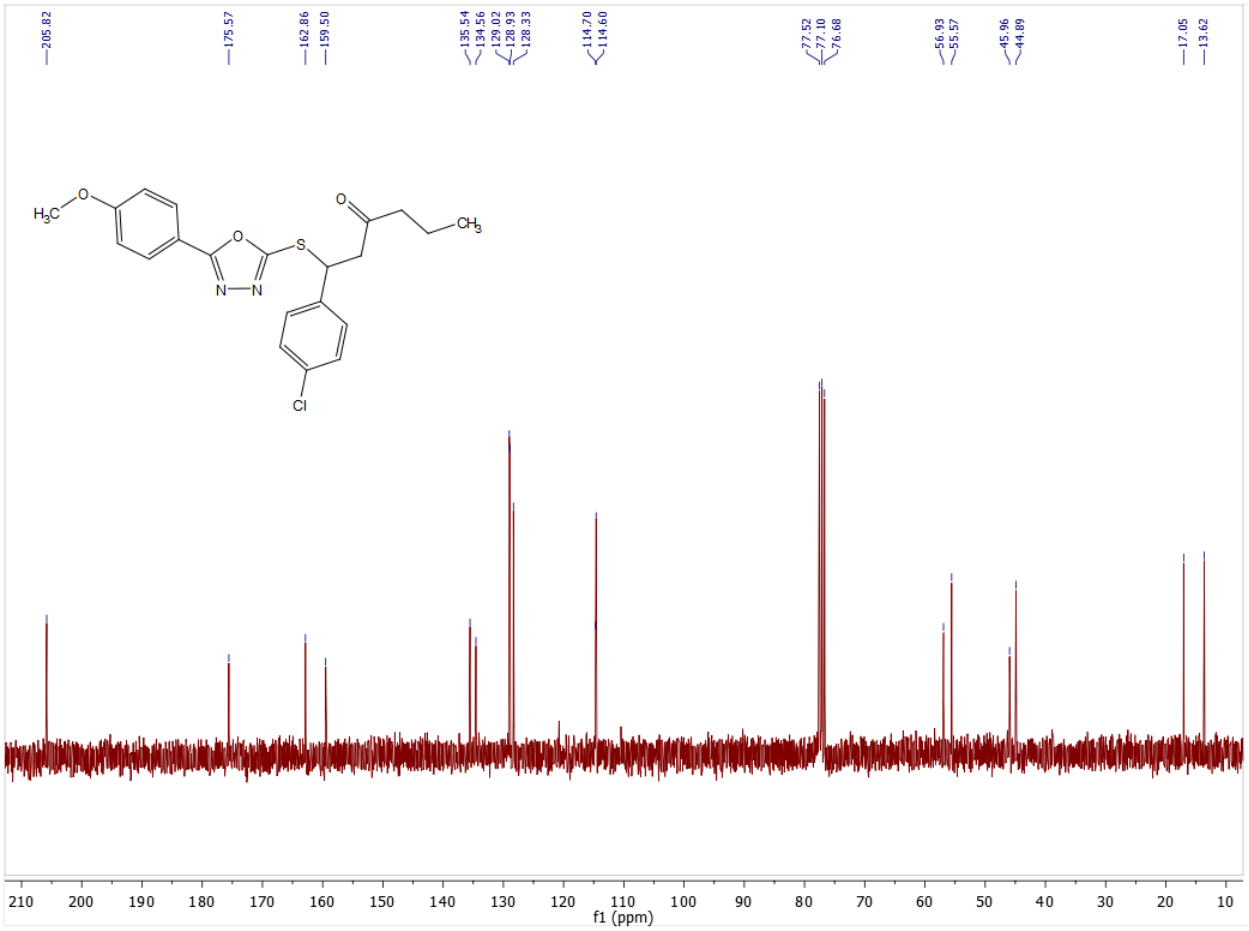
^{13}C NMR of **7b** in $CDCl_3$



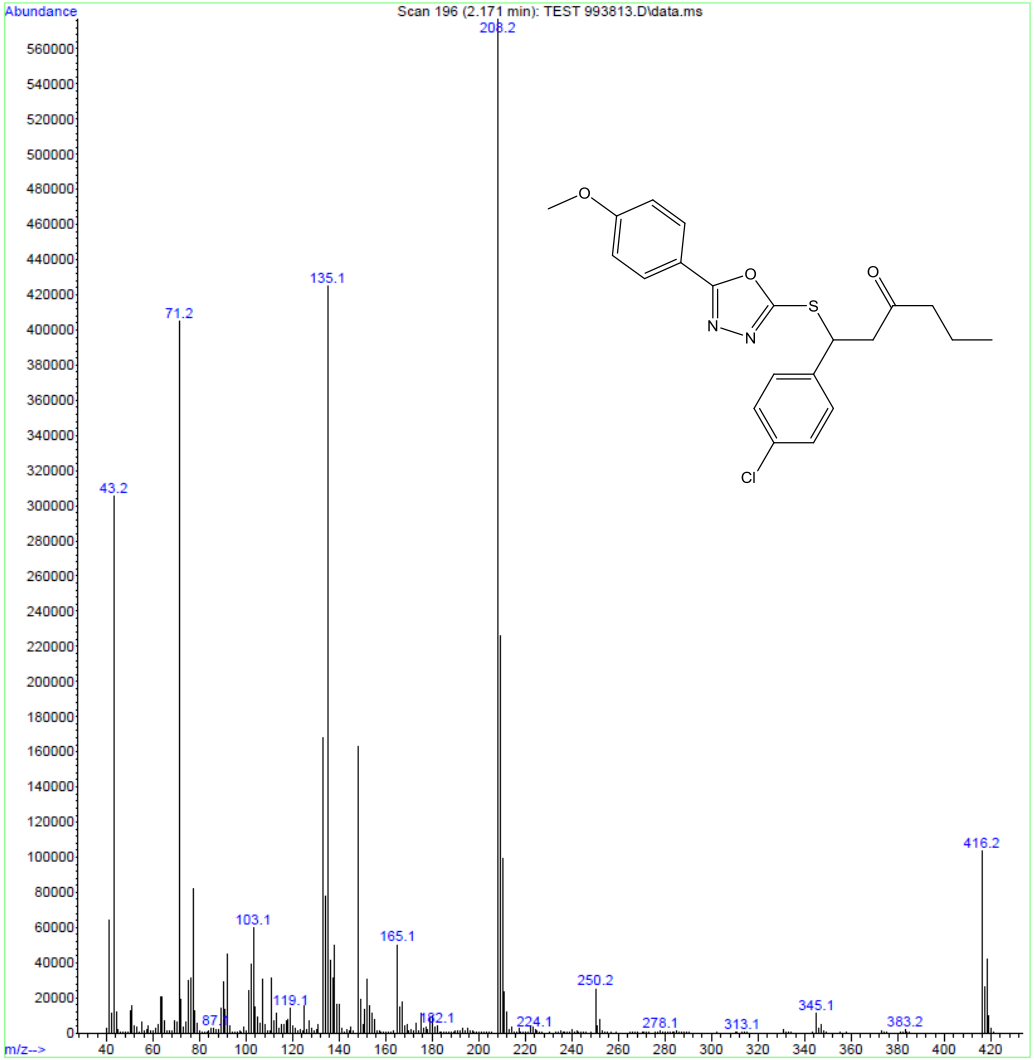
Mass spectrum of **7b**



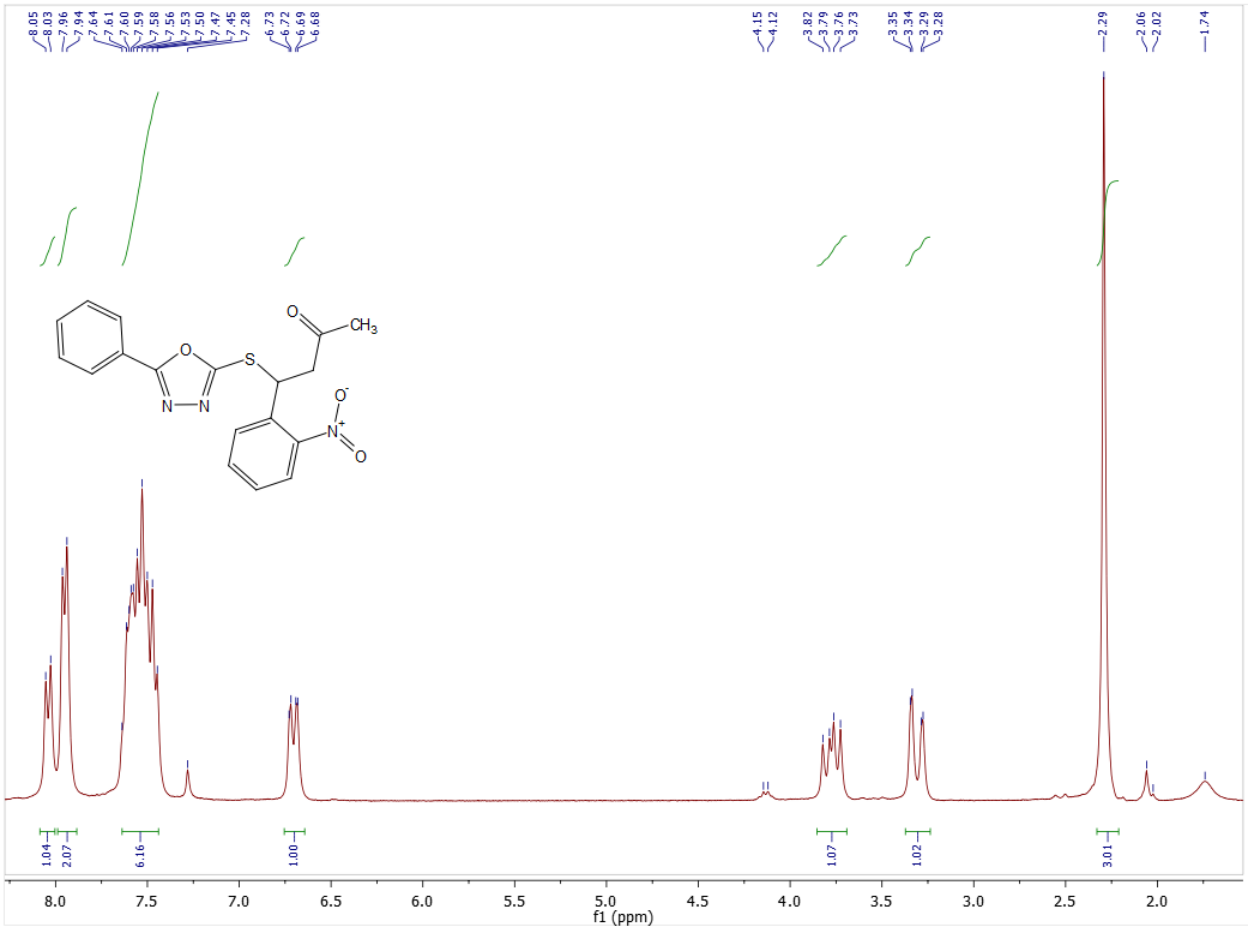
^{1}H NMR of **7c** in $CDCl_3$



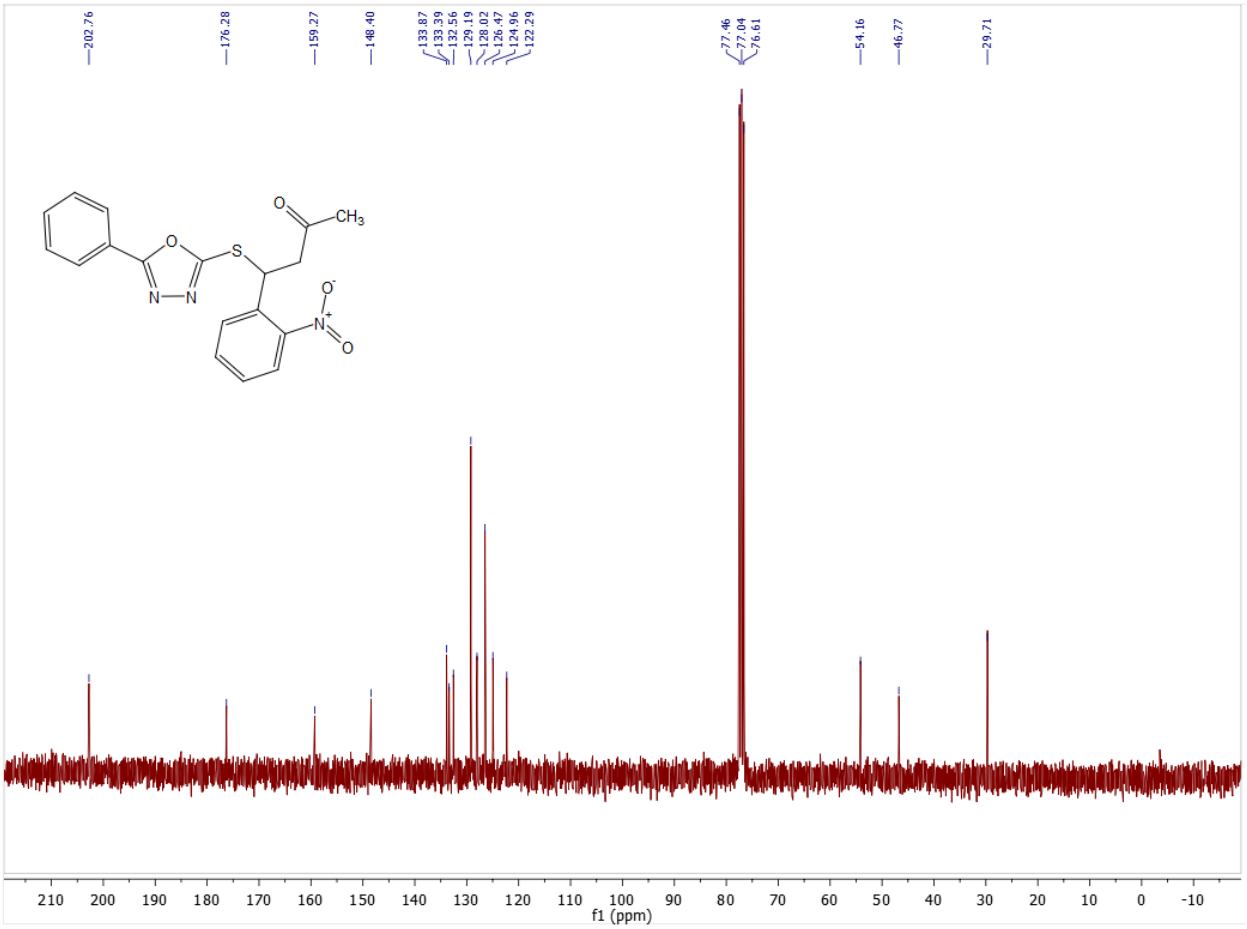
^{13}C NMR of **7c** in $CDCl_3$



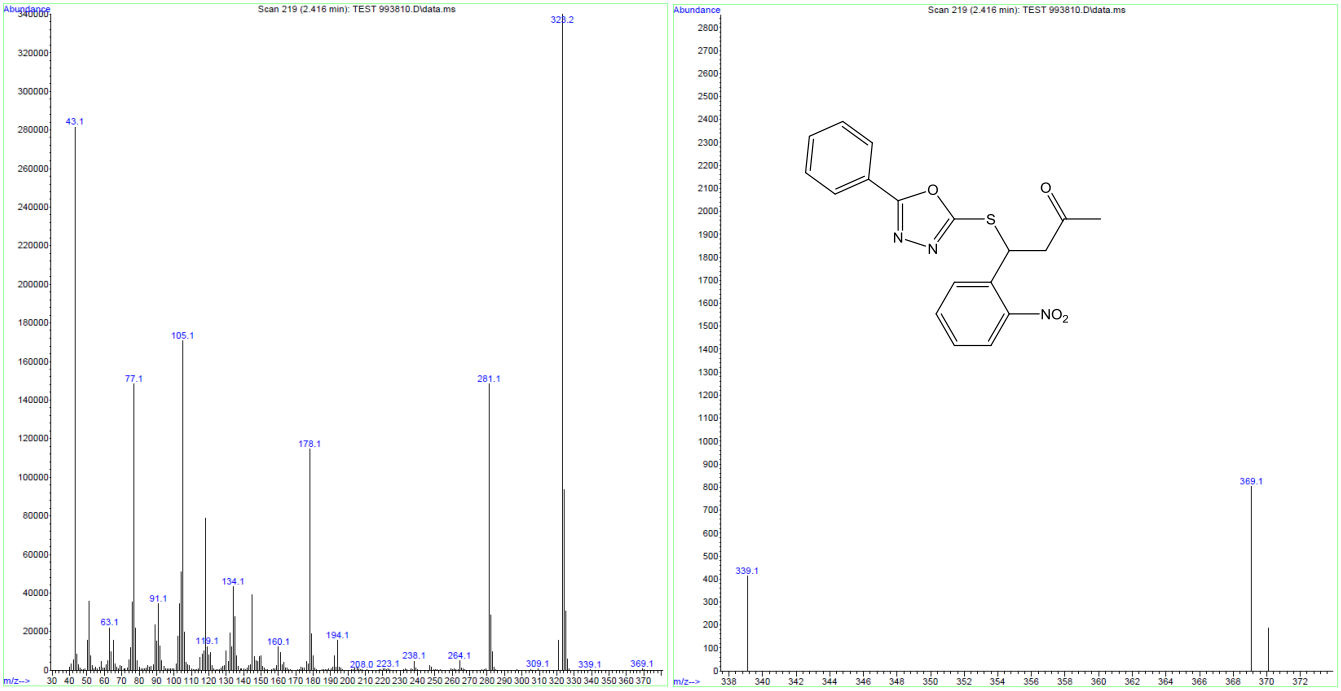
Mass spectrum of **7c**



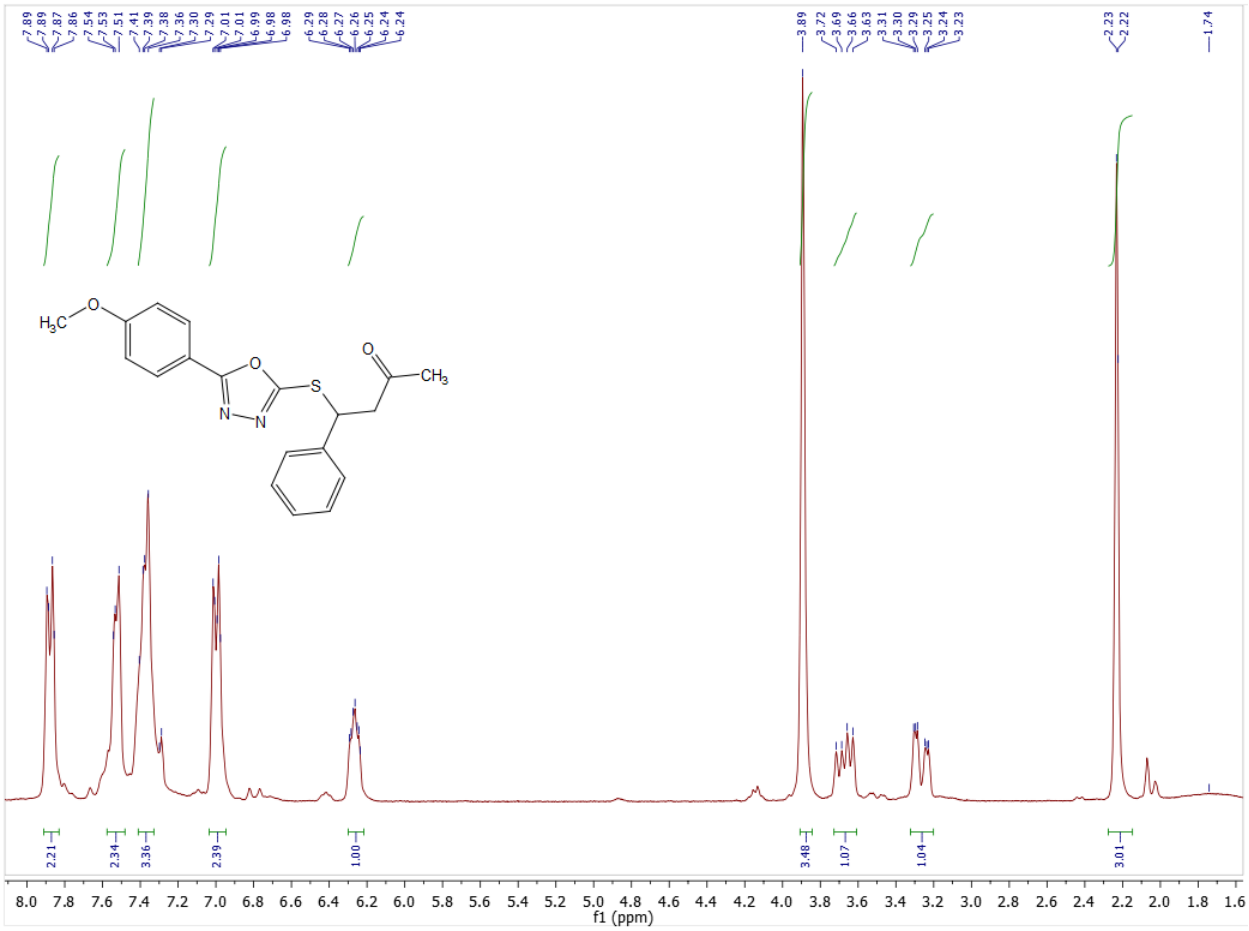
^{1}H NMR of **7d** in $CDCl_3$



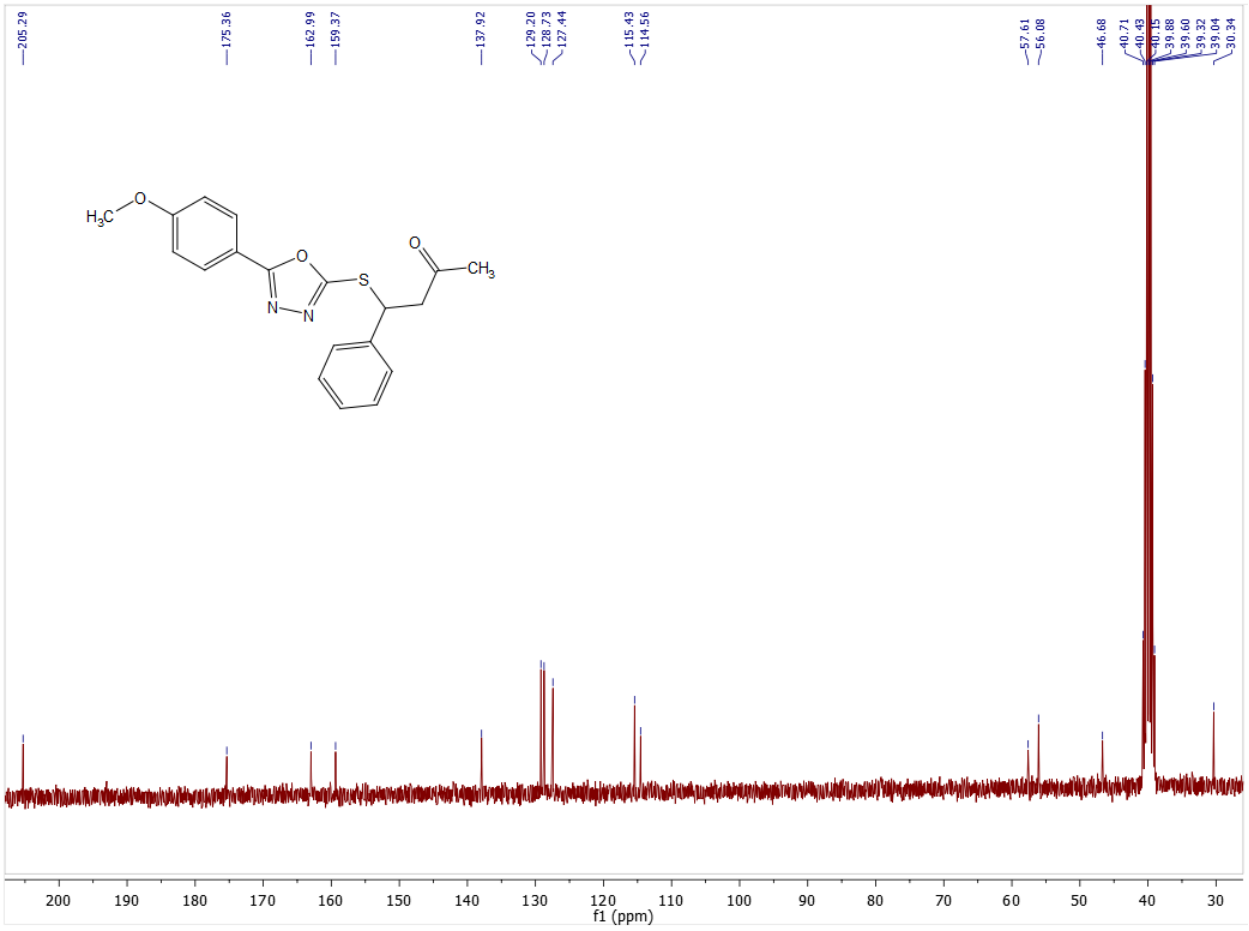
^{13}C NMR of **7d** in $CDCl_3$



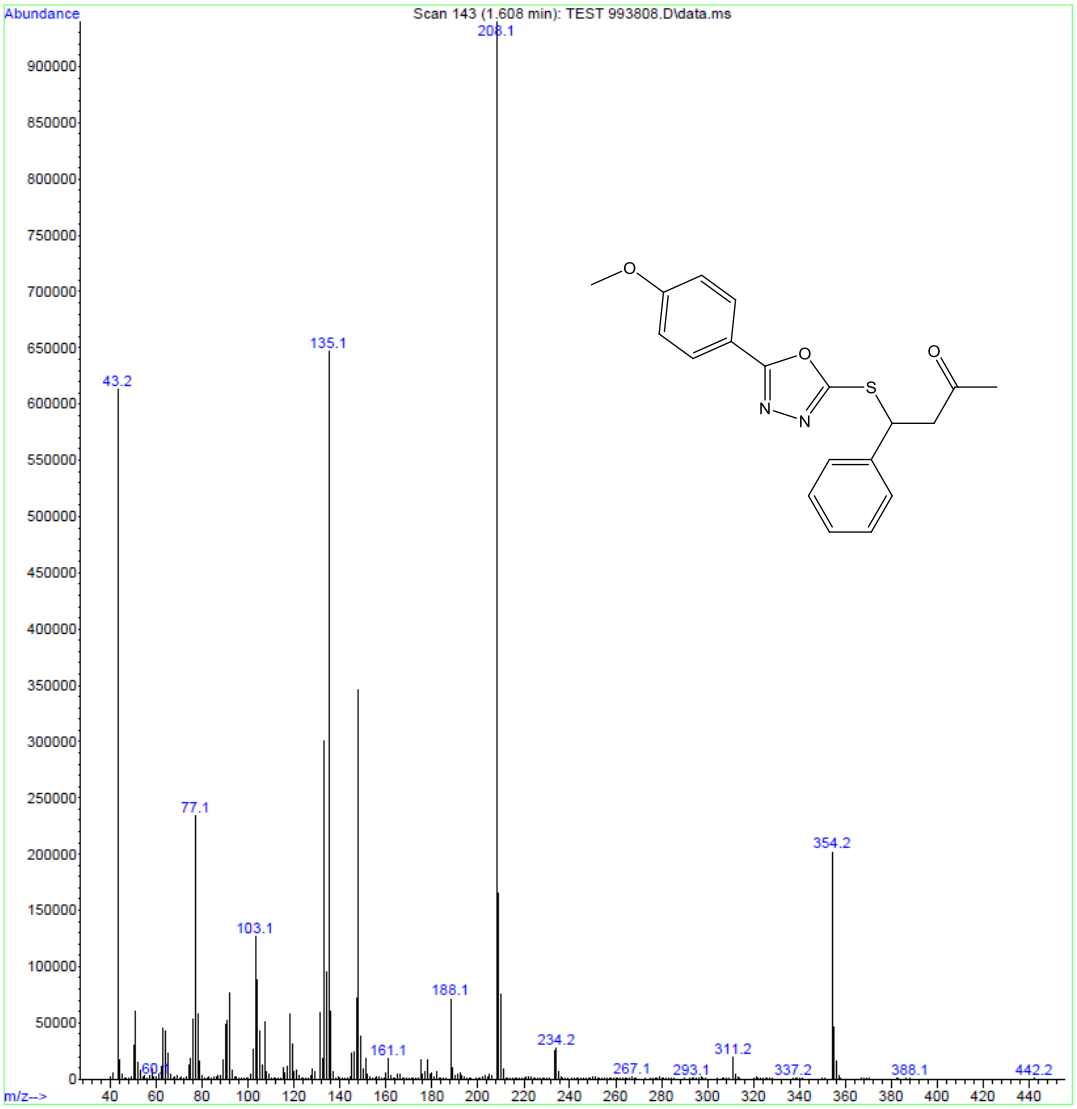
Mass spectrum of **7d**



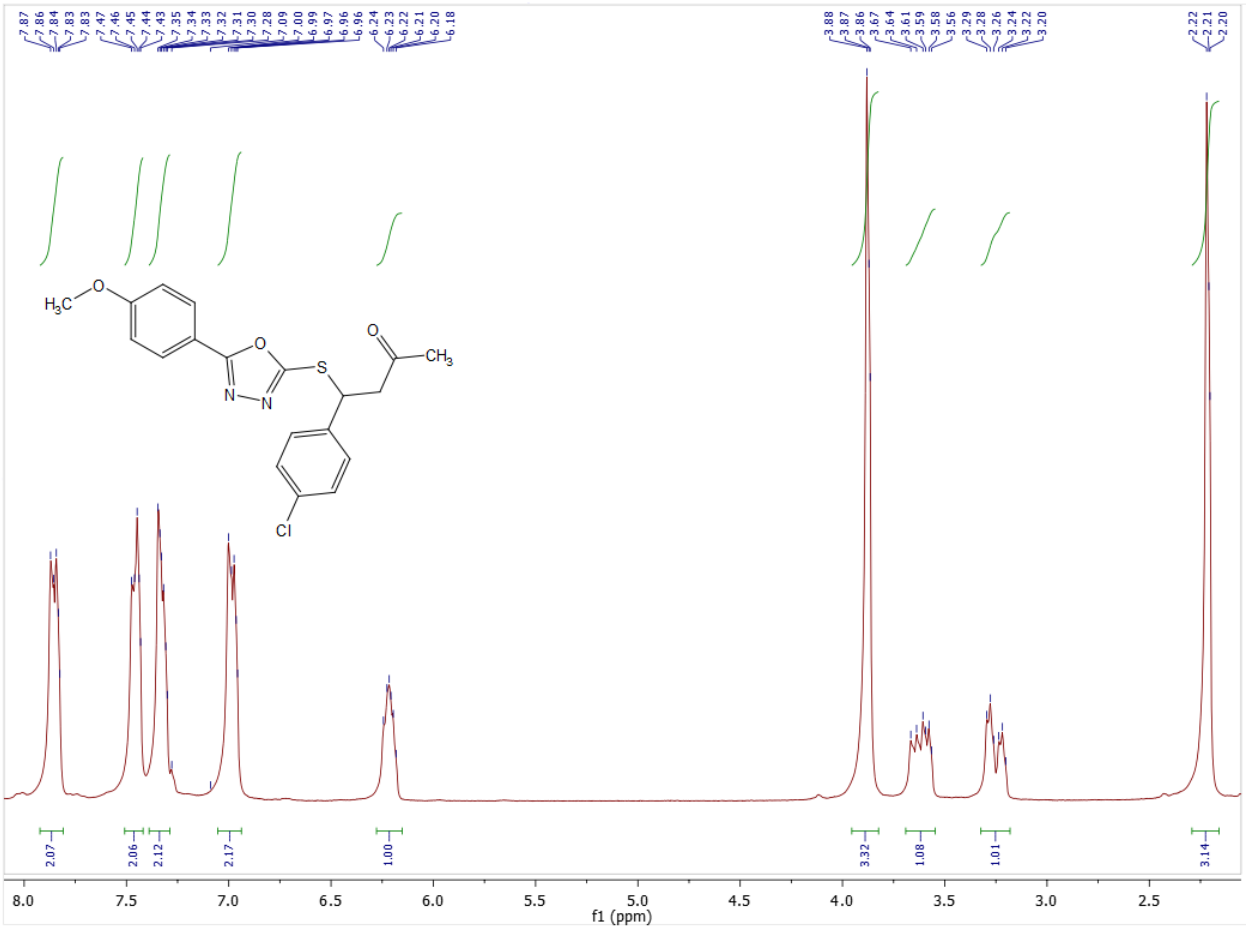
^{1}H NMR of **7e** in $CDCl_3$



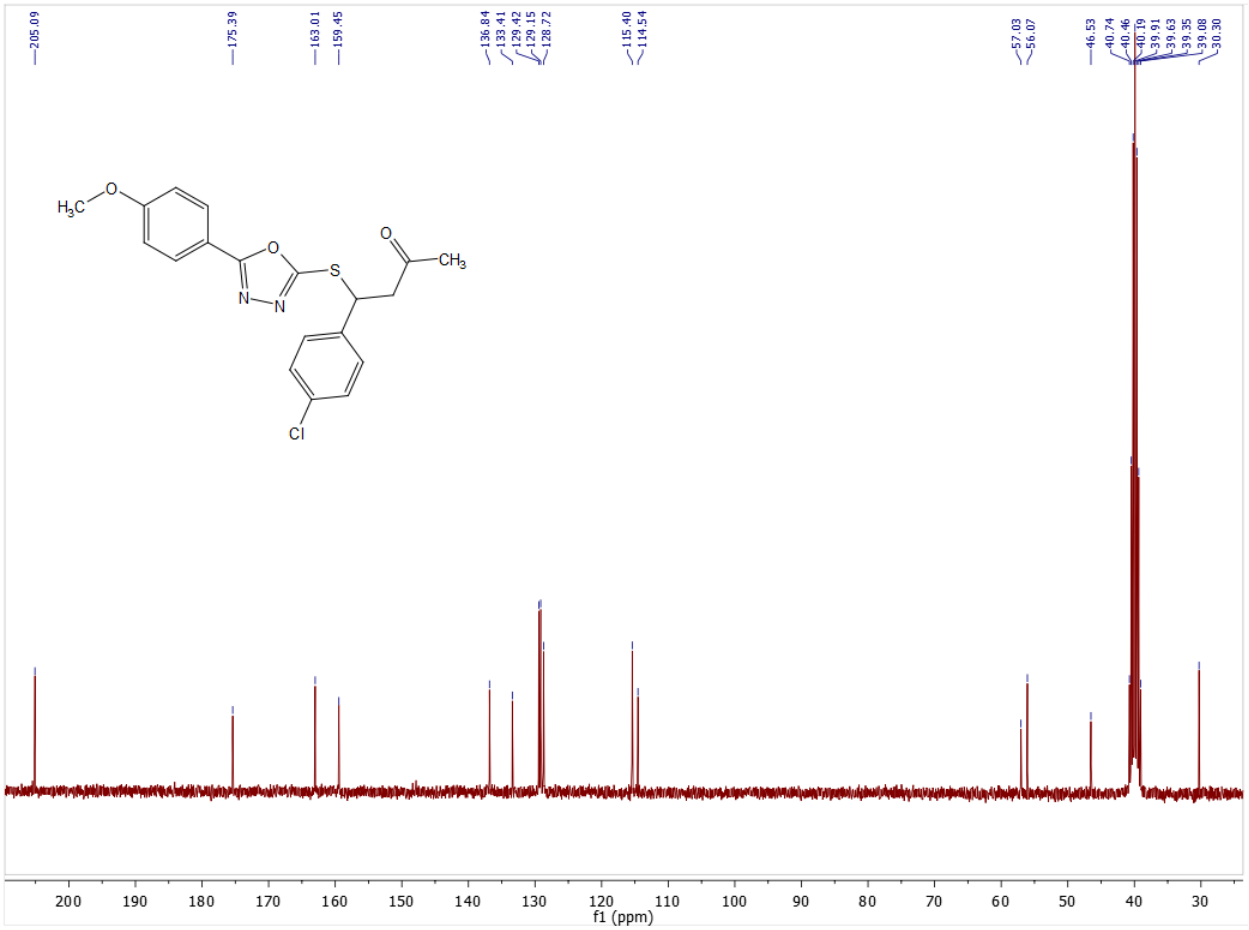
^{13}C NMR of **7e** in DMSO



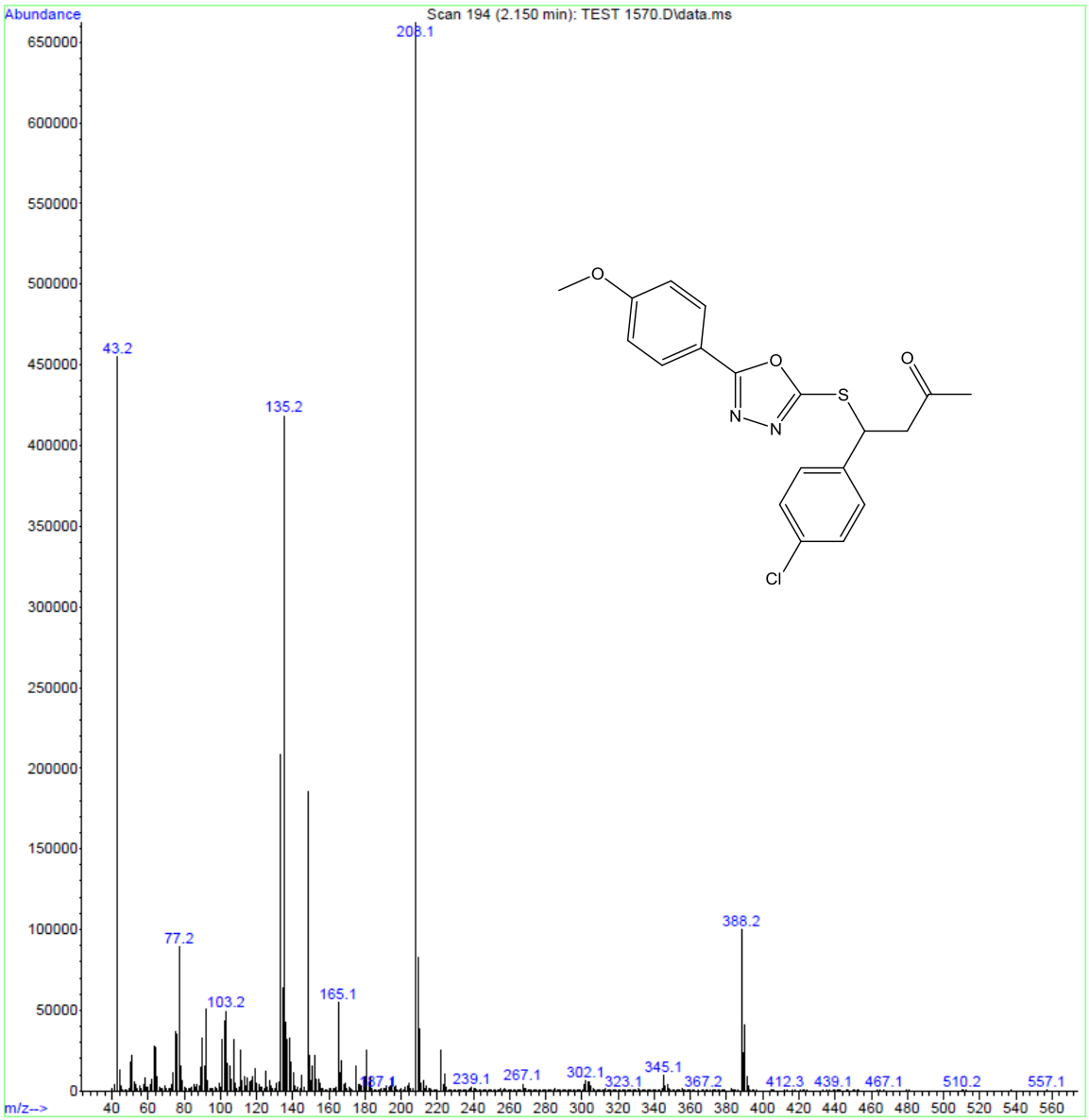
Mass spectrum of **7e**



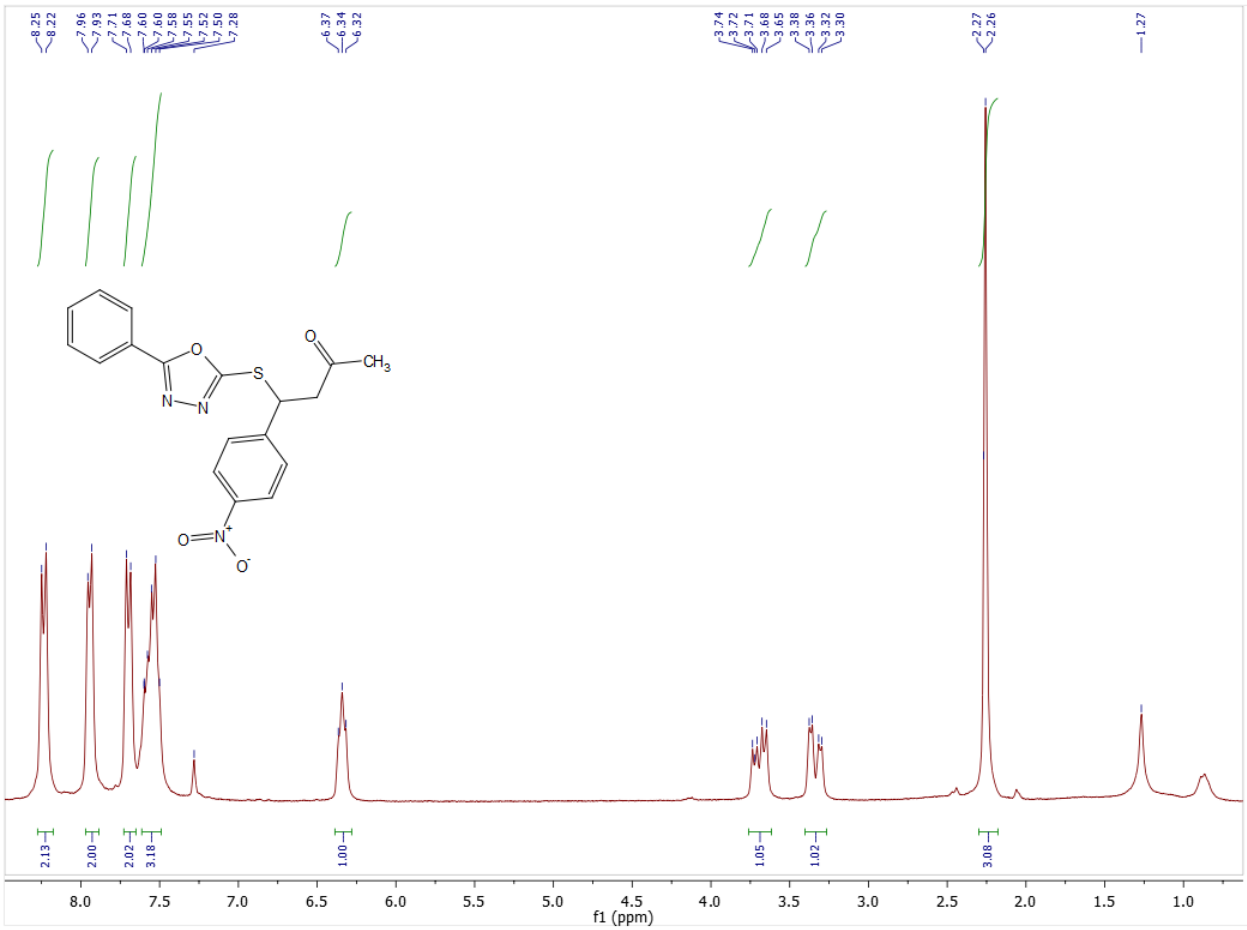
^{1}H NMR of **7f** in $CDCl_3$



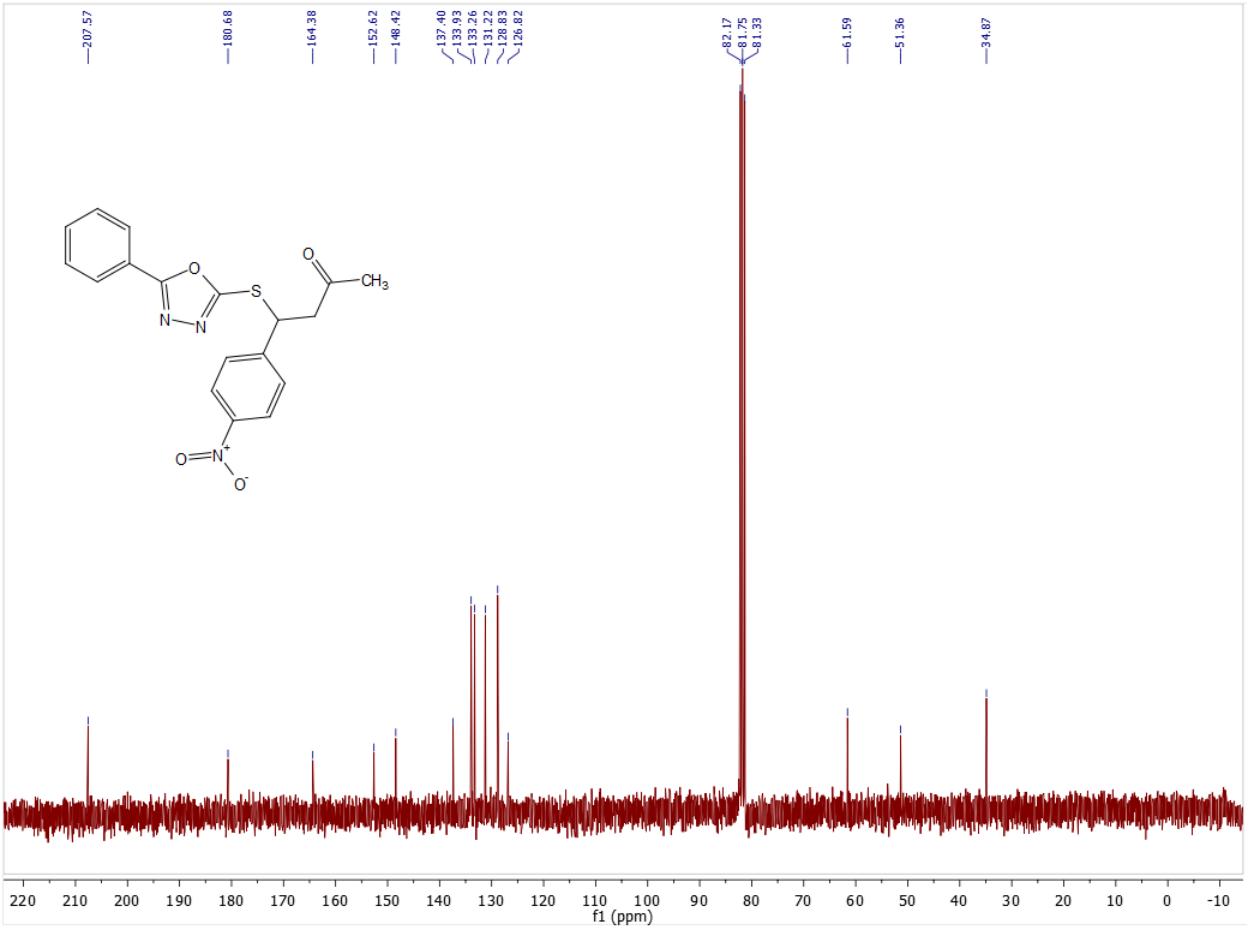
^{13}C NMR of **7f** in DMSO



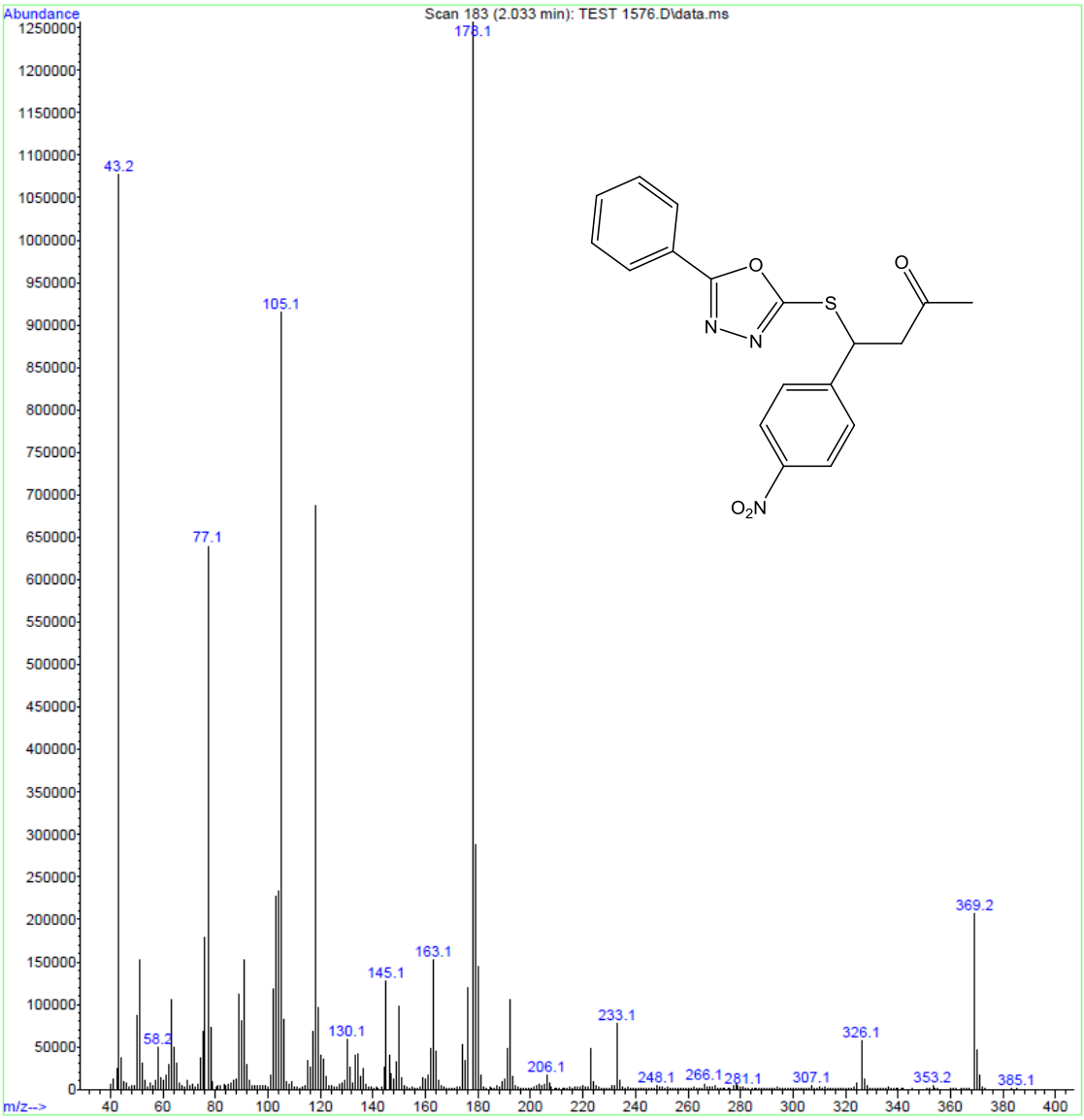
Mass spectrum of **7f**



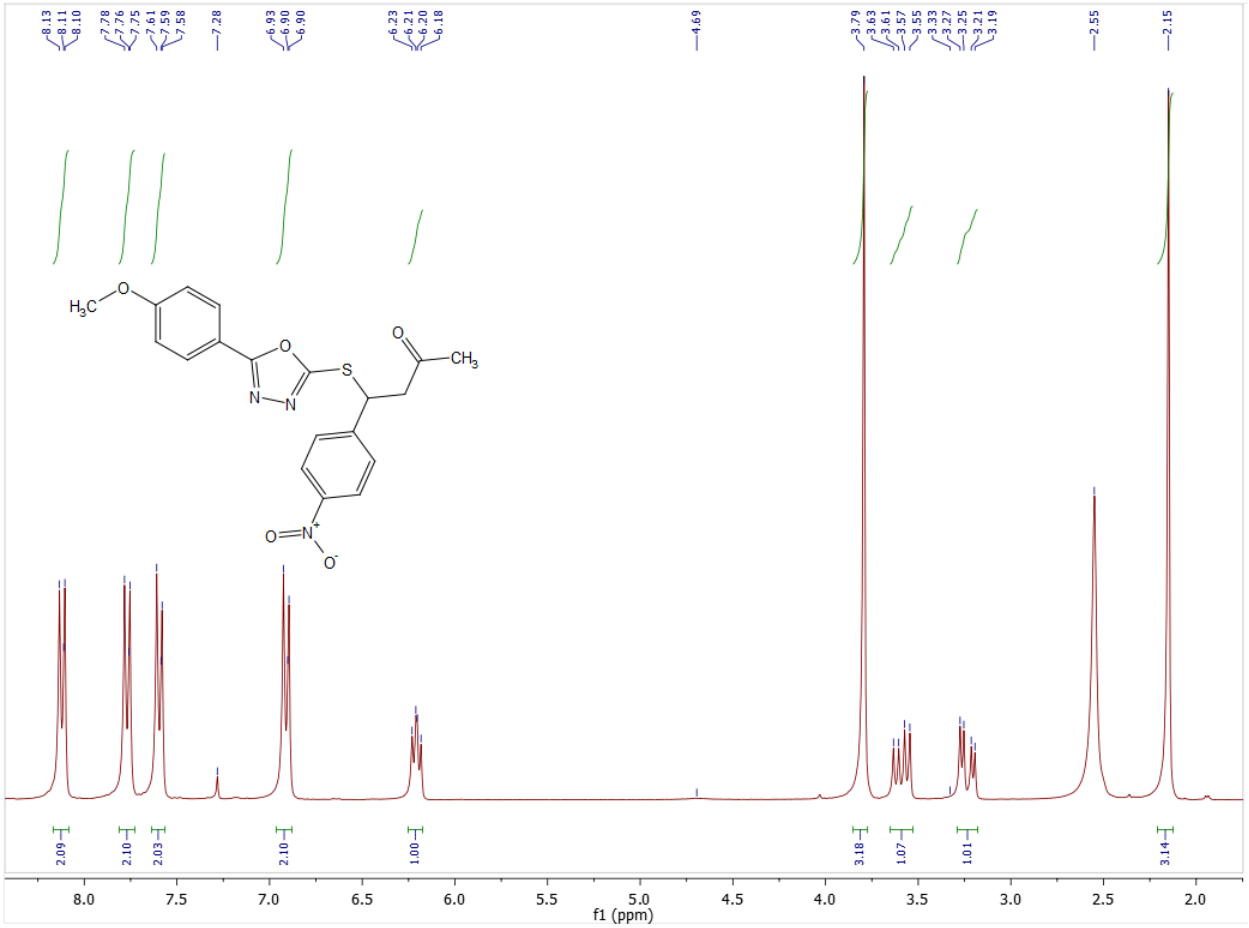
^{1}H NMR of **7g** in $CDCl_3$



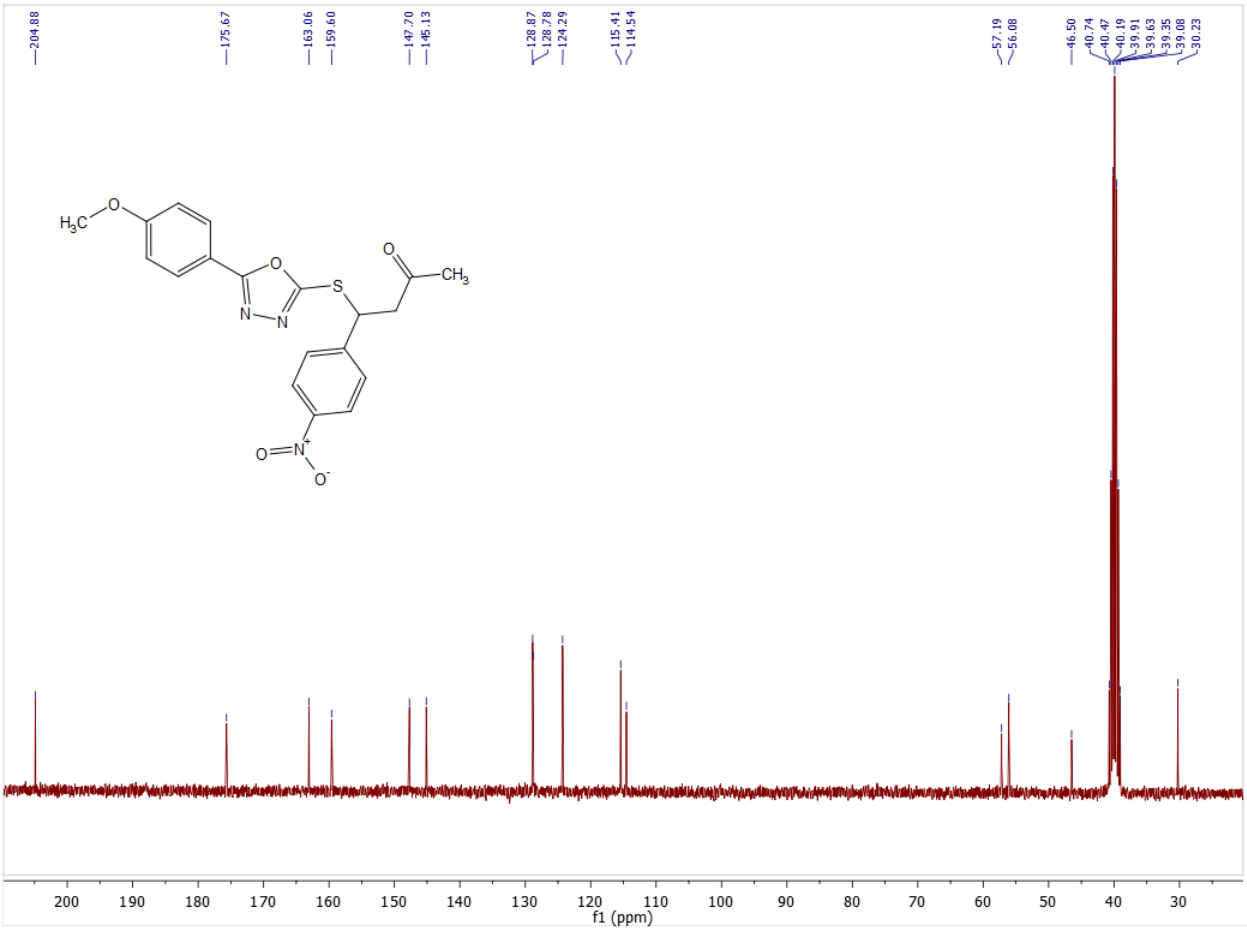
^{13}C NMR of **7g** in $CDCl_3$



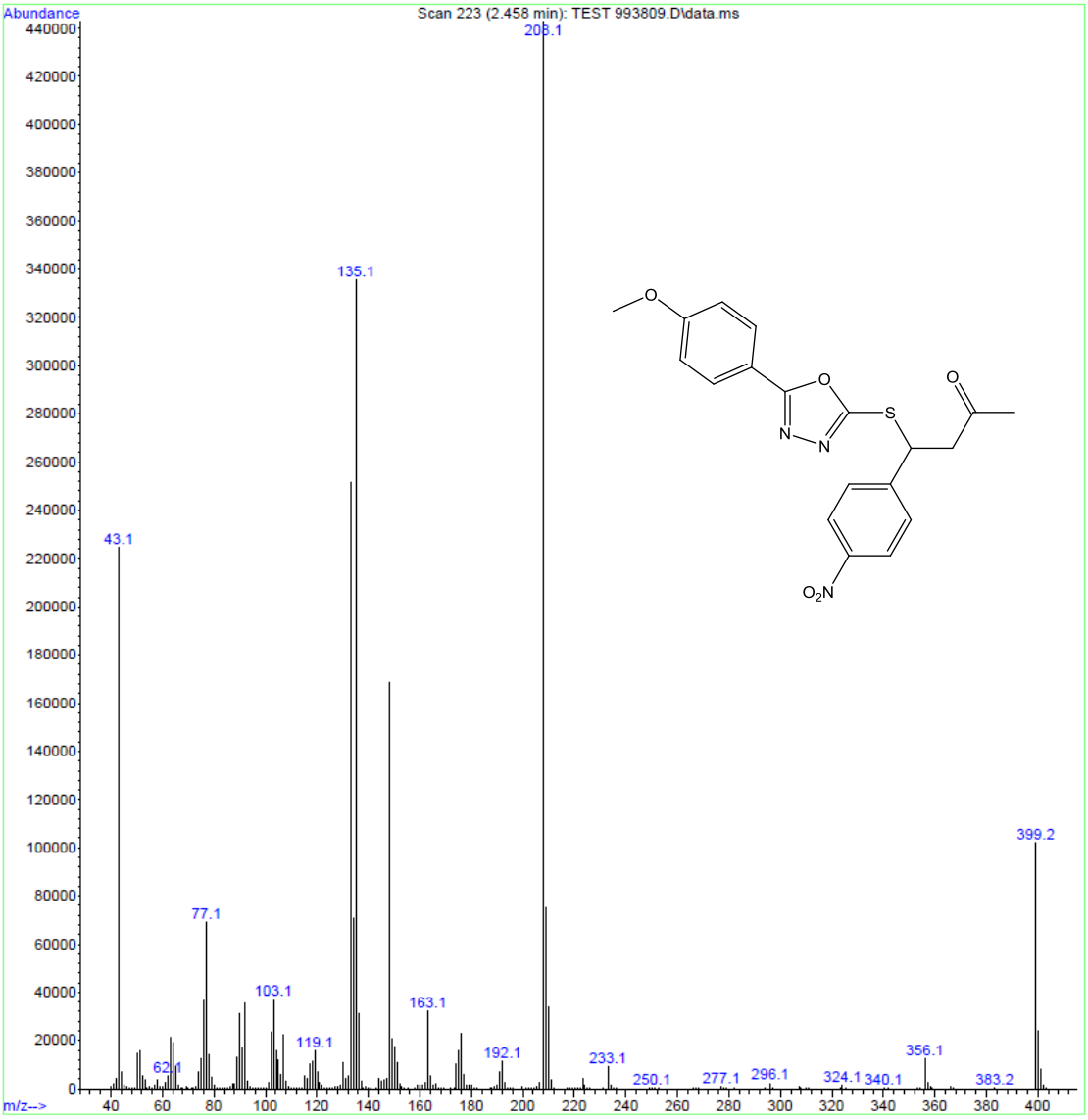
Mass spectrum of **7g**



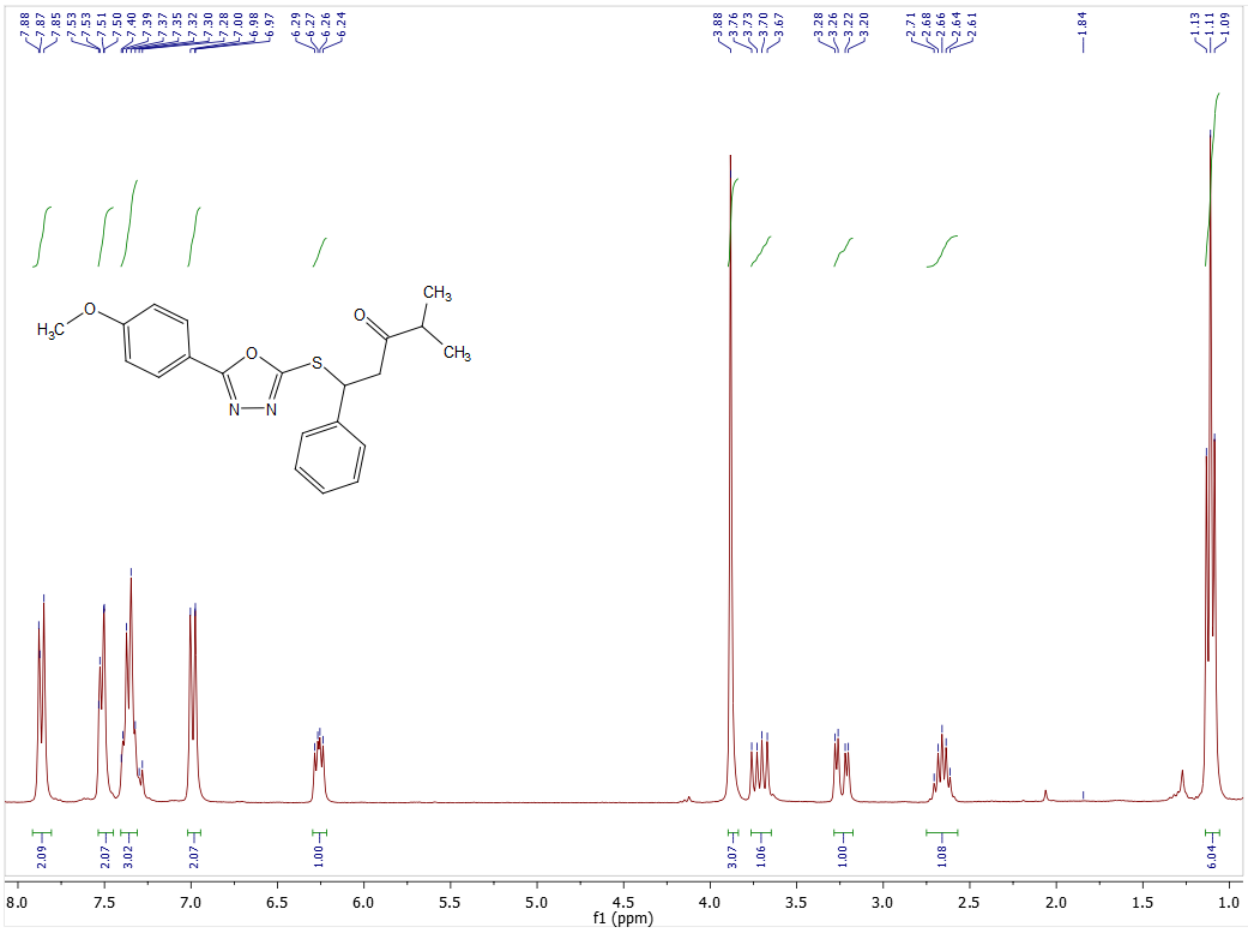
^{1}H NMR of **7h** in $CDCl_3$



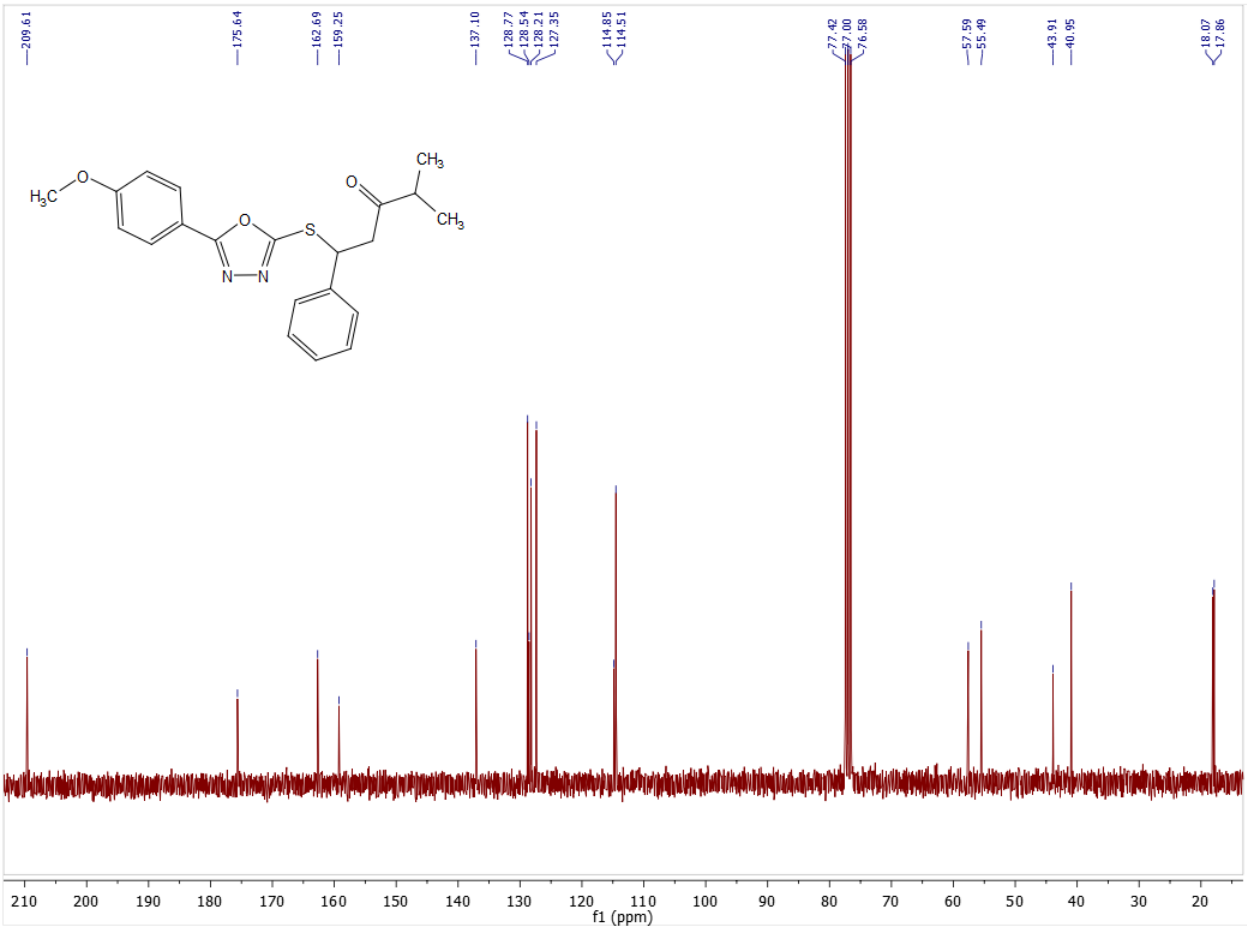
^{13}C NMR of **7h** in DMSO



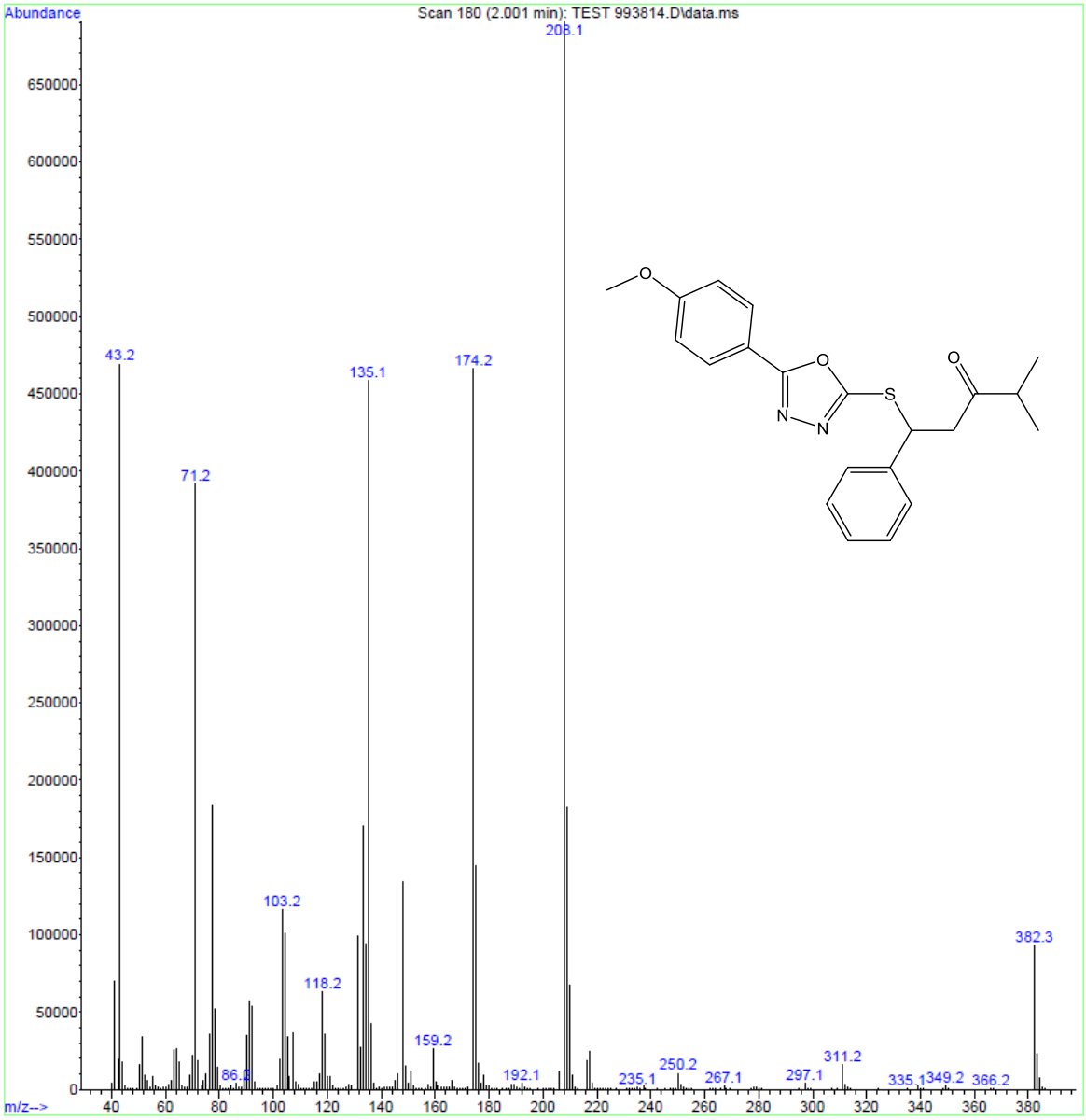
Mass spectrum of **7h**



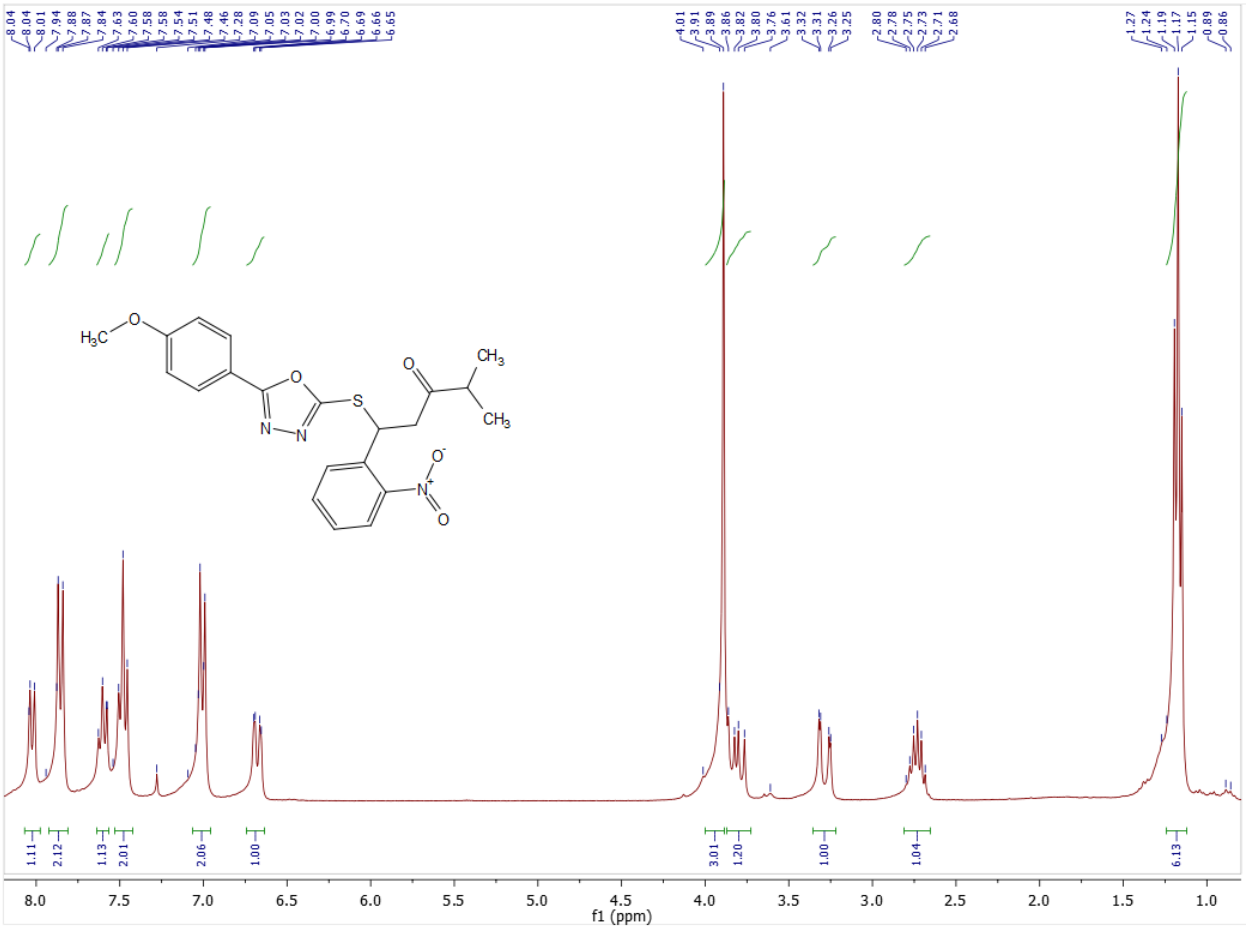
^{1}H NMR of **7i** in $CDCl_3$



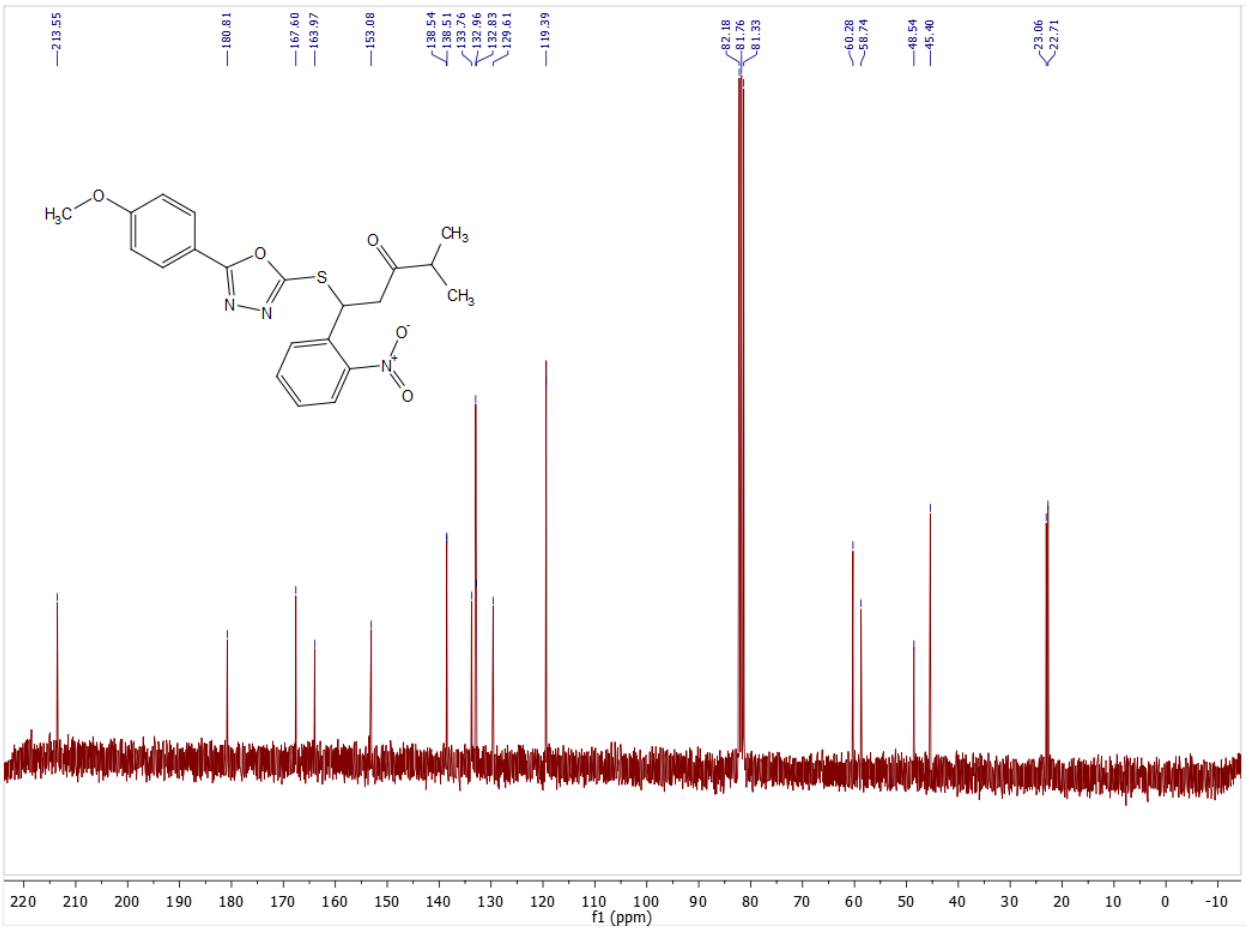
^{13}C NMR of **7i** in $CDCl_3$



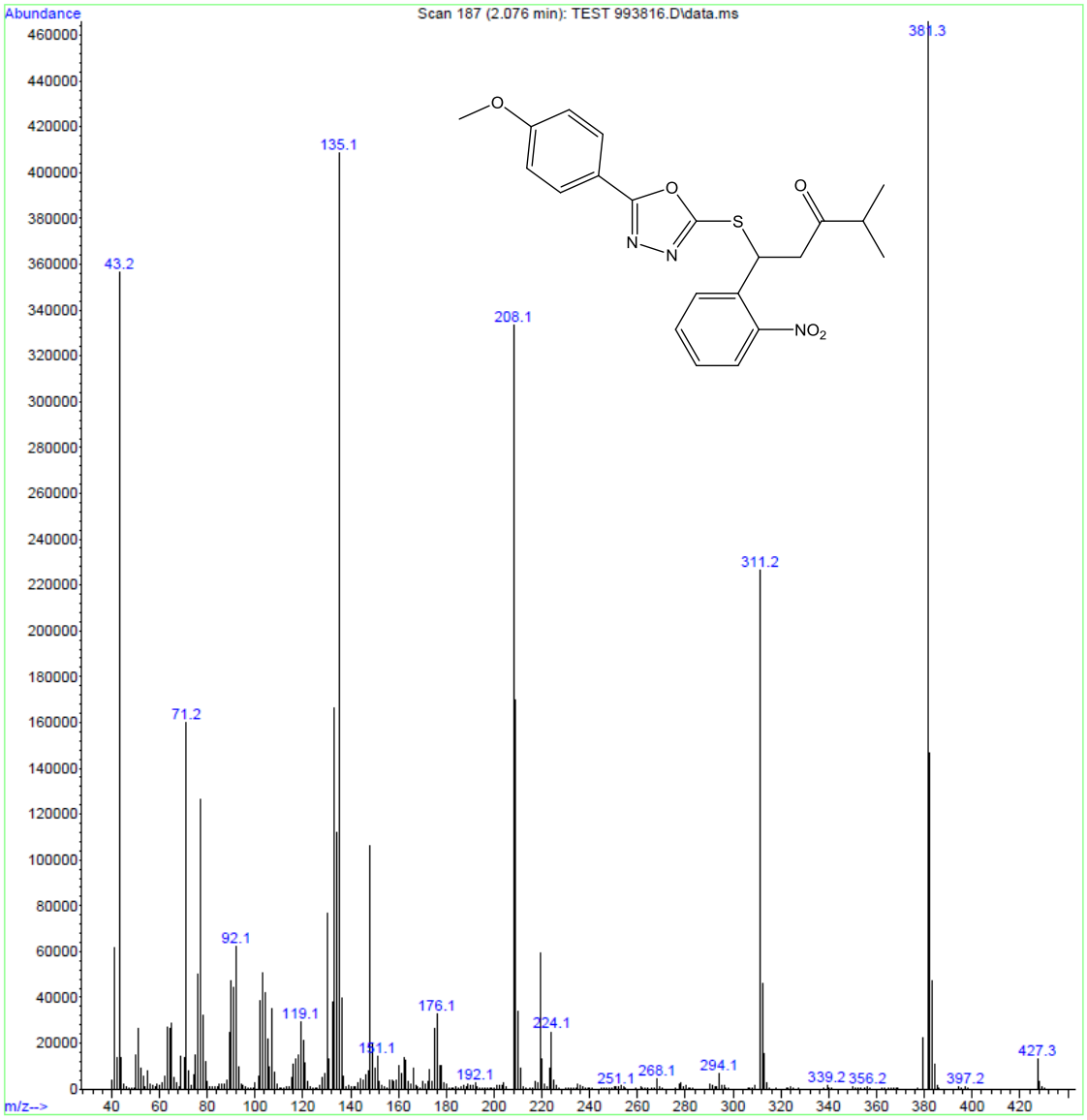
Mass spectrum of **7i**



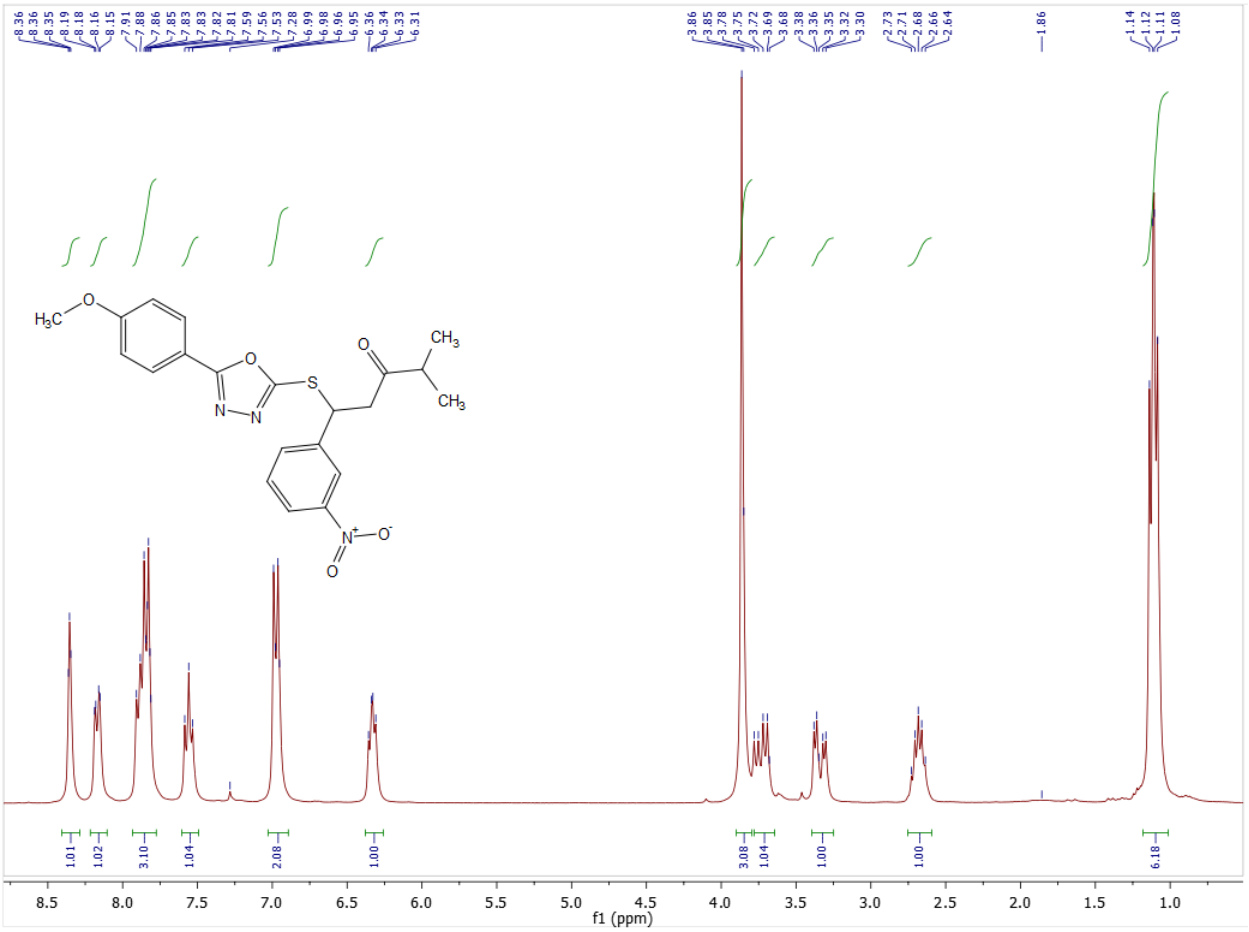
^{1}H NMR of **7j** in $CDCl_3$



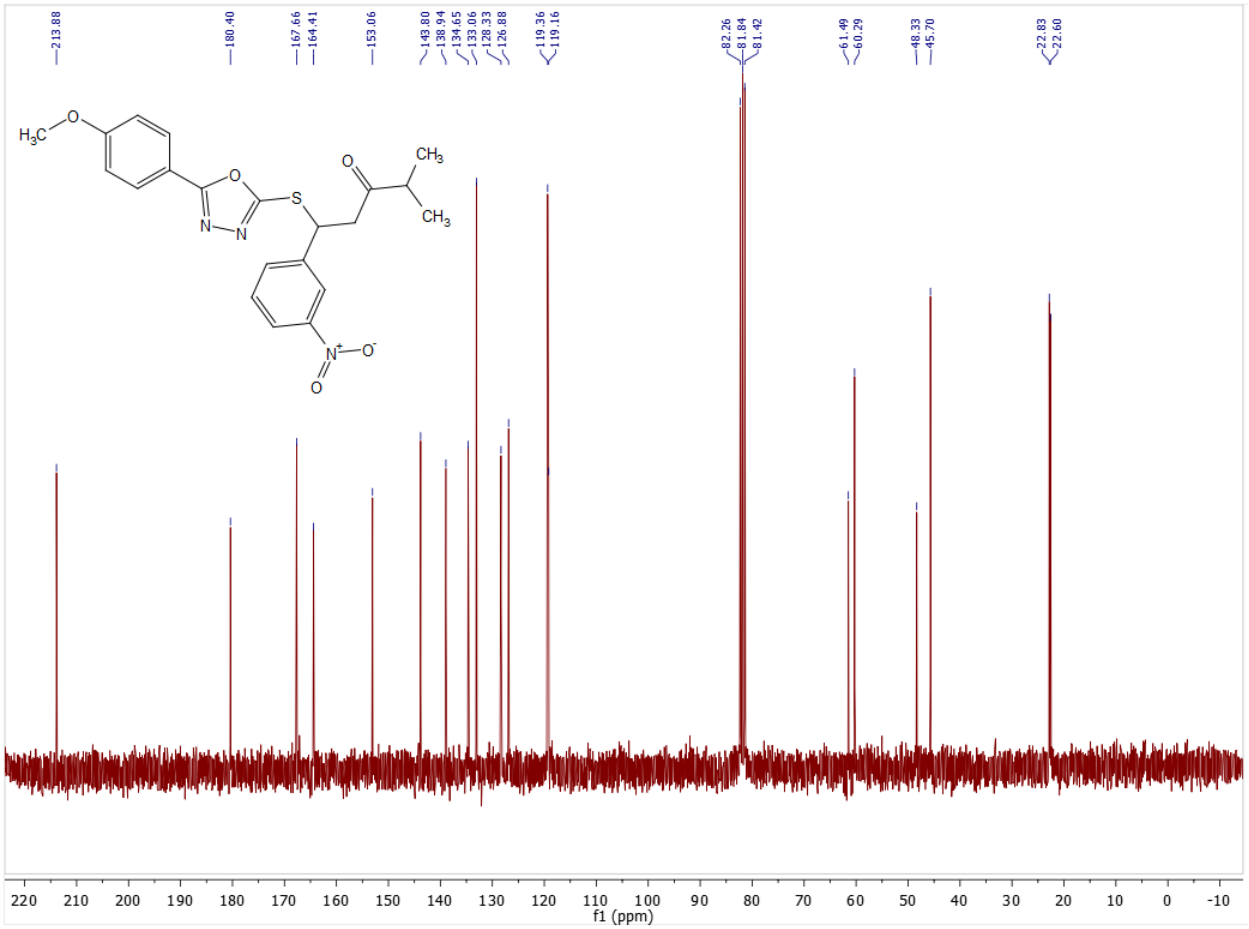
^{13}C NMR of **7j** in $CDCl_3$



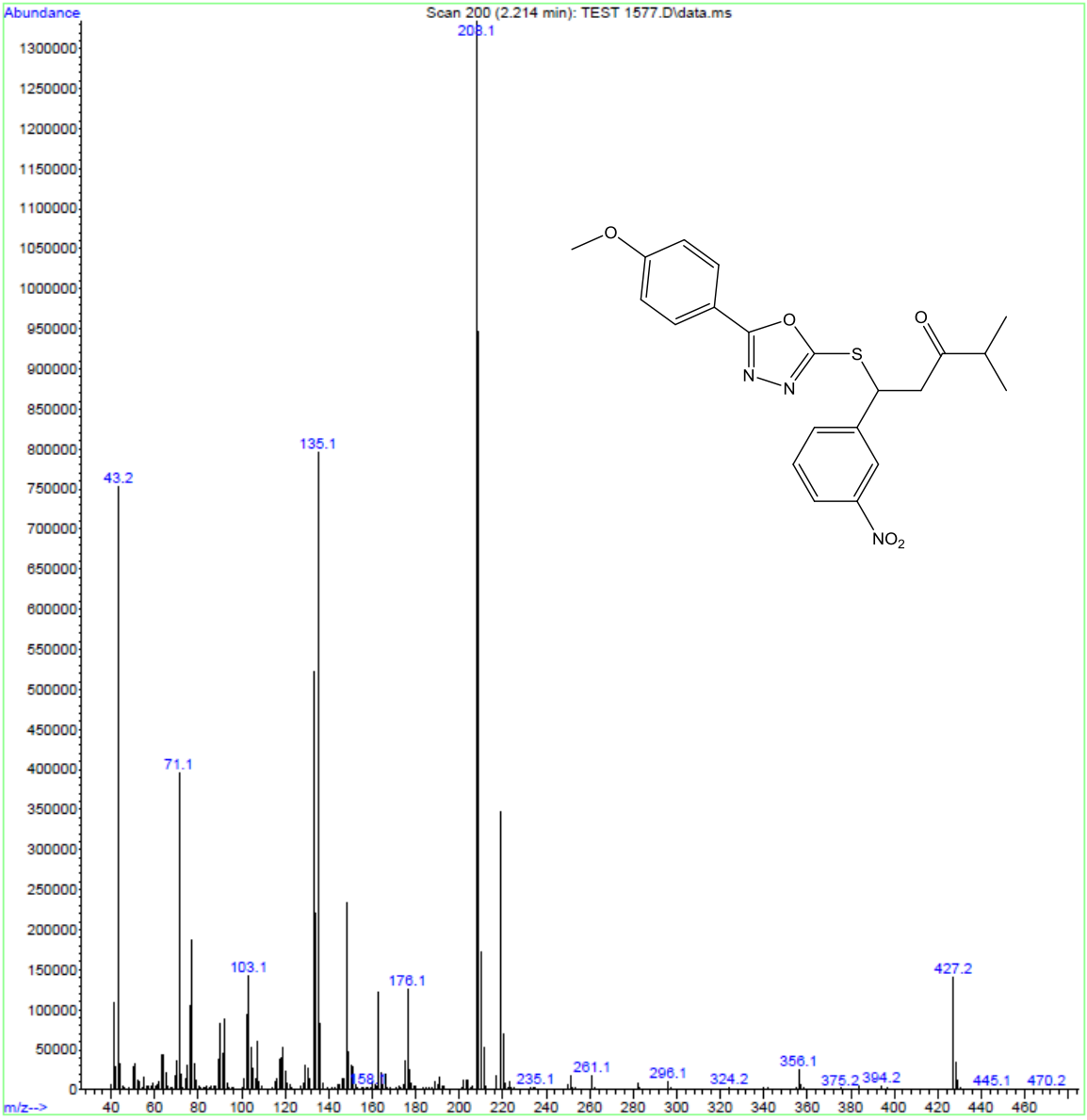
Mass spectrum of **7j**



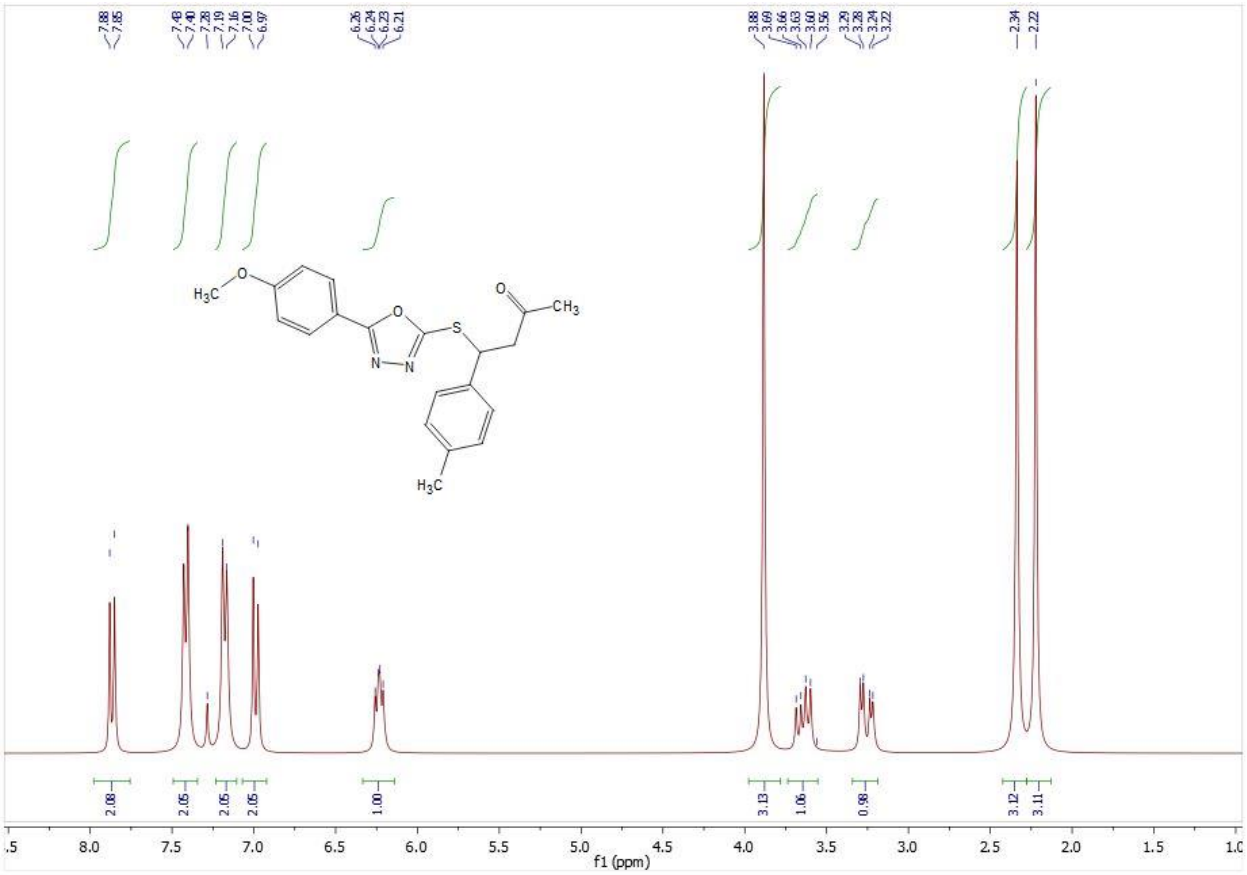
^{1}H NMR of **7k** in $CDCl_3$



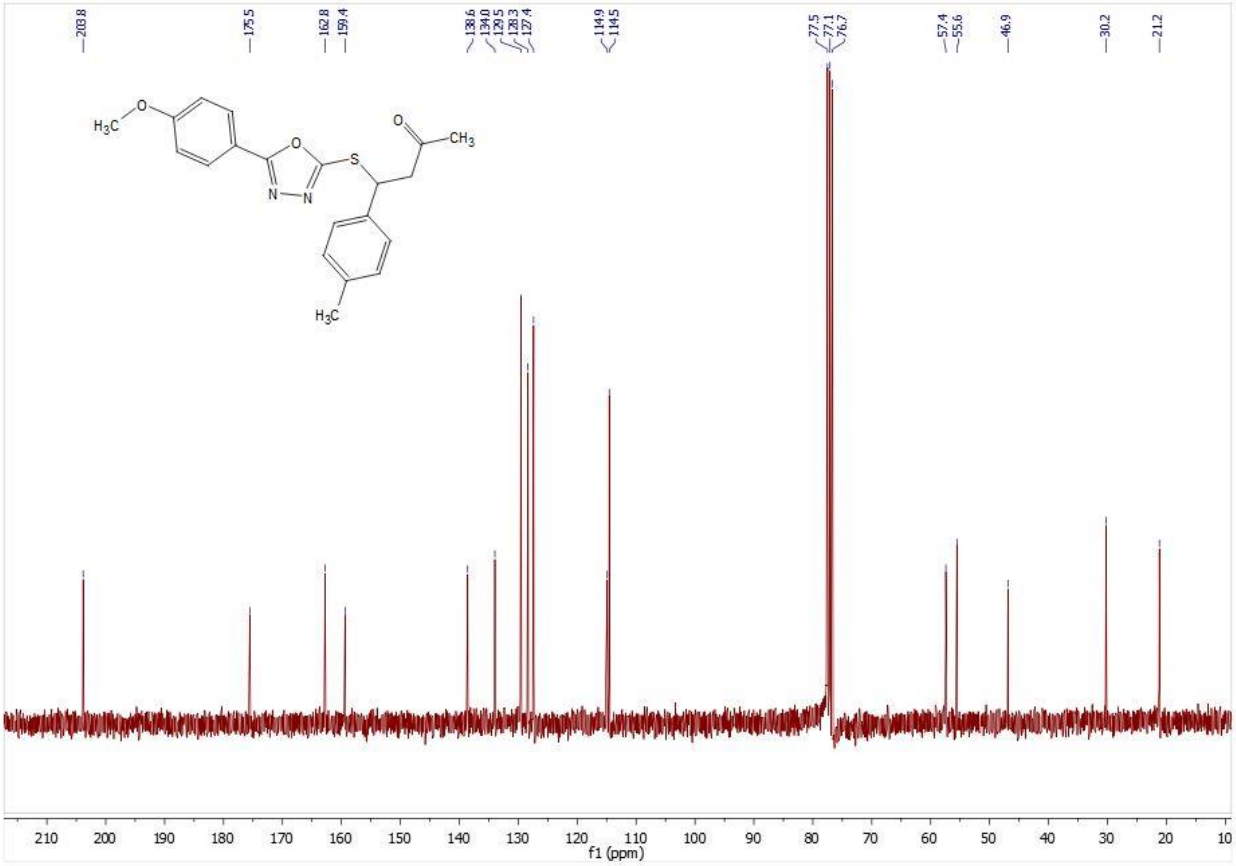
^{13}C NMR of **7k** in $CDCl_3$



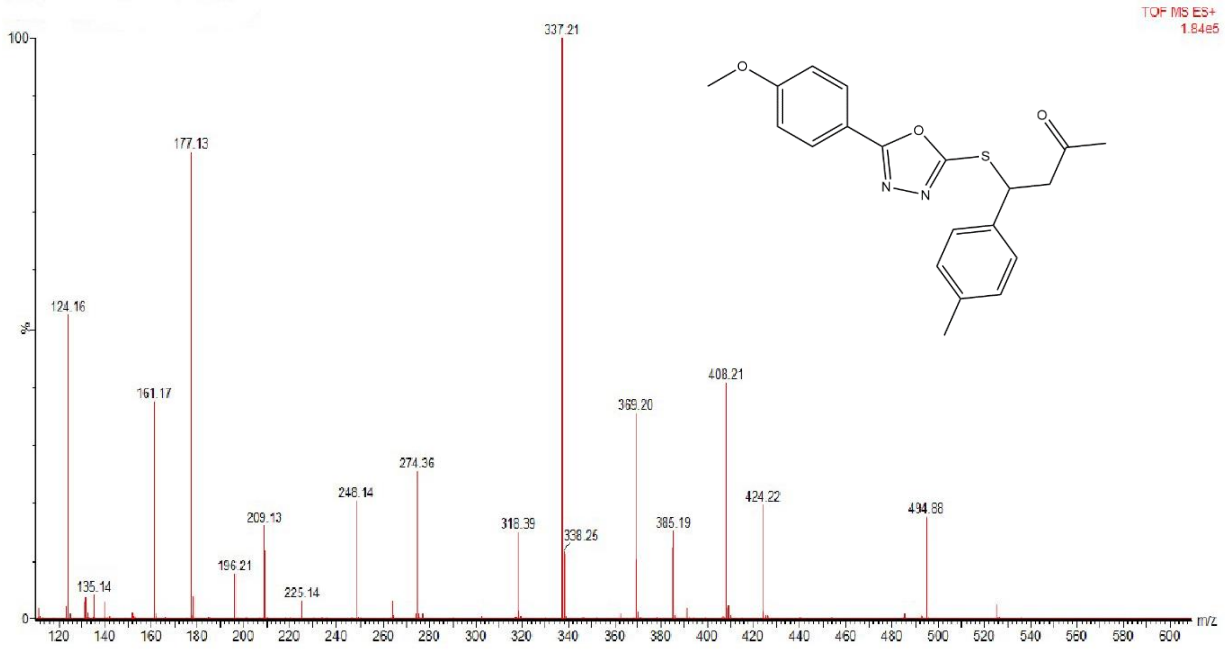
Mass spectrum of **7k**



^{1}H NMR of **7l** in $CDCl_3$



^{13}C NMR of **7l** in $CDCl_3$



Mass spectrum of **7l**

4. References

1. L. Ma, Y. Xiao, C. Li, Z.-L. Xie, D.-D. Li, Y.-T. Wang, H.-T. Ma, H.-L. Zhu, M.-H. Wang and Y.-H. Ye, *Bioorg. Med. Chem.*, 2013, **21**, 6763-6770.
2. H. S. Abd-Ellah, M. Abdel-Aziz, M. E. Shoman, E. A. Beshr, T. S. Kaoud and A.-S. F. Ahmed, *Bioorg. Chem.*, 2016, **69**, 48-63.
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5. 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, *J. Med. Chem.*, 2006, **49**, 6177-6196.