Electronic Supplementary Material (ESI) for RSC Medicinal Chemistry.

Design, Synthesis, and Antibacterial Activity of *N*-(Trifluoromethyl)phenyl Substituted Pyrazole Derivatives

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General consideration

All of the reactions were carried out under air atmosphere in round-bottom flasks using commercially available solvents, reagents, and substrates from Fisher Scientific (Hanover Park, IL, USA.) and Oakwood chemical (Estill, SC, USA) and used the chemicals directly without any further purification or drying. Varian Mercury NMR spectrometer was used to record ^{1}H and ^{13}C NMR spectra (300 MHz for ^{1}H and 75MHz for ^{13}C) and Brucker Apex II-FTMS system was used to record High Resolution Mass Spectrometry (HRMS) data. Chemical shifts (^{1}H and ^{13}C) are reported in parts per million (ppm) referenced to the residual solvent peak, and abbreviations used to describe the peak signals in ^{1}H and ^{13}C NMR data are s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), br (broad), and m (multiplet).

Experimental procedure

Synthesis of 4-[4-formyl-1-[4-(trifluoromethyl)phenyl]pyrazol-3-yl]benzoic acid (1). A solution of **c**ommercially available 4-(trifluoromethyl)phenylhydrazine (1.76 g, 10 mmol) and 4-acetylbenzoic acid (1.64 g, 10 mmol) in 50 ml dry ethanol in a round-bottom flask was refluxed for 12 h and the solvent was evaporated in vacuo. The solid hydrazone was further dried for 30 min under vacuum to remove the traces of solvent. The solid hydrazone was dissolved in *N,N*-dimethyl formamide (DMF) and cooled under ice. Phosphorous (V) oxychloride ($POCl_3$, 50 mmol) was added dropwise through the septum. The reaction mixture was brought to room temperature for 30 minutes and further heated to 80 ^{o}C for 6 h. The reaction mixture was poured onto ice and stirred for 12 h. The solid precipitate was filtered and washed with water repeatedly followed by drying to get the pure product (**1**).

Synthesis of 4-trifluoromethylphenyl-substituted pyrazole derived aniline derivatives (2-31): 4-Trifluoromethyl phenyl substituted pyrazole-derived aniline derivatives were synthesized by reacting the aldehyde containing pyrazole (**1**, 1 mmol) with commercially available substituted aniline (1.05 mmol), which was refluxed in toluene for 8 hrs. The resulting mixture was isolated and dissolved in methanol, then cooling the mixture at 0 ^{o}C. Ten minutes later, $NaBH_4$ (3 mmol) was added portion-wise to the reaction mixture and stirred for 8 hours. Hydrochloric acid solution (10%) was poured onto the reaction mixture to precipitate the product. Filtration followed by washing with water gave the pure product.

Minimum inhibitory concentration (MIC): MIC values were determined by following the recommended methodology by the Clinical and Laboratory Standards Institute by using the broth microdilution method in 96 well plates. MIC for each compound was determined in triplicates using fresh cultures from different days and values were confirmed with at least two exact occurrences.

IC_{50} for HEK293: Resazurin cell viability assay was used to determine IC_{50} values of the compounds against the Human Embryonic Kidney cell line (HEK293 - ATCC). Cells (6000 cells per well) were plated in 96-well black

plate in Eagle's Minimum Essential Medium (EMEM) containing 10% Fetal Bovine Serum (FBS) and incubated at 37 °C in the presence of 5% carbon dioxide for 24 h. After incubation, a range of concentrations of test antibiotics was treated in designated wells in triplicates and incubated for additional 24 hours. The next day, resazurin (0.15 mg/mL) was added to each well and incubated for additional 4 h. The plate was then read at 560 nm with emission detected at 590 nm using Bio Tek™ Cytation™5 plate reader. Microsoft Excel® for Office 365 MSO was used to determine the percentage viability of the HEK cells, and IC_{50} values were determined through data processing using Graphpad Prism 7 for Windows, Version 7.04.

Time Kill Assay: Exponential phase bacterial culture was diluted to ~5×10^6 CFU/mL in sterile Cation Adjusted Muller Hinton Broth (CAMHB) and exposed to 4×MIC concentrations of compounds and vancomycin as a control drug. Aliquots were collected every two hours starting from 0 hours of treatment, serially diluted 10-fold in sterile PBS and plated on Trypticase Soy Agar (TSA) plate containing 5% sheep blood (FisherScientific) by using the 6 × 6 drop plate method. The plates were incubated at 35 °C for 18-20 hours before doing a viable CFU/ml plate count.

Biofilm eradication studies: Experiments consisted of three phases: production of a biofilm on the pegs, treatment of biofilms with compounds, and growth phase to detect surviving cells from the treated biofilms.

To prepare the biofilm, bacteria from an overnight plate culture were suspended to a 0.5 McFarland turbidity then diluted 1:100 in a CAMHB containing 1% glucose. Bacteria suspension (150 µL) was inoculated into the CBD wells and incubated at 35 °C for 24 h to establish the bacterial biofilm. After incubation, the lid was removed, and the biofilm was washed three times by dipping into phosphate buffered saline (PBS) in a fresh 96-well plate to remove non-adherent cells. The lid with biofilms was transferred to a different 96-well plate, termed the "challenge plate," containing 200 µL 2-fold serial dilutions of the test compounds in PBS. The challenge plate was then incubated for 24 h at 35 °C. Following incubation, the lid of the challenge plate was removed and placed into fresh medium to obtain MBEC values as follows. The CBD lid (with attached pegs/treated biofilms) was transferred to a new 96-well plate containing 180 µL fresh CAMHB with 1% glucose and incubated at 35 °C for 24 h to allow viable bacteria from biofilms to seed the wells and proliferate, resulting in turbidity at the end of the incubation period. MBEC value for a compound was the lowest test concentration that resulted in eradicated biofilms i.e., wells that had no turbidity after the final incubation. Minimum bactericidal concentrations (MBC) could also be estimated by removing 20 µL from each well of the challenge plate, and transferring these planktonic cells into a fresh 96-well plate containing 180 µL of CAMHB containing 1% glucose and incubating overnight at 35 °C. The MBC value for a compound was the lowest concentration that gave no visible turbidity after incubation.

Persisters kill assay and time-dependent persister kill assay: Stationary phase cultures of *S. aureus* were obtained by growing bacteria in CAMHB in an orbital shaking incubator at 200 rpm at 35 °C for 24 h. Bacteria were washed in 1×PBS thrice by centrifugation for 2 min at 10,000 g. The cells were then diluted to ~ 5×10^8

CFU/mL (confirmed by plate count). The diluted persister cells with the desired concentration of antibiotics were taken in each well-marked sterile 10×75 plastic tubes in triplicates and incubated at 35 °C with shaking at 200 rpm.

For persister killing assays, an aliquot was taken from each tube, diluted 10 fold and plated on TSA plate containing 5% sheep blood by using the 6 × 6 drop plate method incubated for 18-20 hours before colony count. For time-dependent persister kill assays, aliquots were taken hourly, plated, and incubated, and colony counts were done.

Macromolecular Synthesis (MMS) Inhibition Assay: MMS inhibition assay was carried out using *S. aureus* ATCC 2913. Cells were grown on TSA plates containing 5% sheep blood at 35 °C. Isolated colonies were used to inoculate broth medium as described below for each assay. For each macromolecular synthesis reaction, *S. aureus* ATCC 29213 was exposed to 0.25, 0.5, 1, 2, 4, 8, and 16-fold of the broth microdilution MIC of compound **25**. Positive controls for each study were dosed at 8xMIC. A "no drug" control was included for all experiments.

Nucleic acid (DNA and RNA) synthesis: When cells reached an early exponential phase in CAMHB, 100 µL of culture was added to triplicate 1.5 mL microfuge tubes containing various concentrations of the compound (**25**) or control antibiotics (2.5 µL) at 40x, the required final concentration. Following a 30 min pre-incubation at room temperature to allow for drug inhibition of a pathway, either [^{3}H] thymidine, at 3.0 µCi per tube for DNA synthesis or [^{3}H] uridine, at 0.5 µCi per tube for RNA synthesis was added. Reactions were allowed to proceed at room temperature for 30 min and then stopped by adding 6 µL of cold 100% trichloroacetic acid (TCA). After 30 mins, the TCA-precipitated material was filtered through glass fiber filters followed by three washes with 5 ml of 5% TCA and two washes with 5 mL of ethanol. After drying, the filters were placed in scintillation vials, liquid scintillation fluid was added, and counts were determined using a Perkin Elmer Tri-Carb 4810TR Liquid Scintillation Analyzer.

Protein synthesis: Exponential phase cells in CAMHB were resuspended in M9 minimal medium (MEM) and 100 µL of culture was added to 1.5 mL microfuge tubes containing various concentrations of test compounds and the control as described above. [^{3}H] leucine was added at 3.0 µCi per tube. Reactions were allowed to proceed at room temperature for 40 min and then stopped by adding 12 µL of cold 50% TCA/20% casamino acids. Reactions were incubated on ice for 30 min and the TCA-precipitated material was filtered and further processed as described above in the nucleic acid inhibition assay.

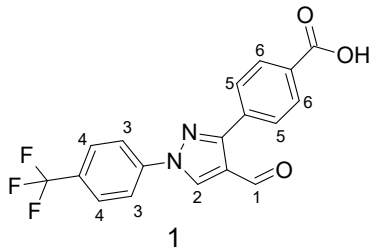
Cell wall synthesis. Bacterial culture with different concentrations of compound **25** was prepared as described above for protein synthesis studies. [^{14}C]*N*-Actylglucosamine (0.4 µCi/reaction) was added to each tube and incubated for 45 min in a 37 °C heating block. Reactions were stopped through the addition of 100 µL of 8% SDS to each tube. Each sample was then heated at 95 °C for 30 min, and filtered using pre-wet nitrocellulose membrane filters (0.8 µM). The filters were dried then placed into scintillation vials to determine the counts as described above.

Lipid synthesis: Bacterial suspensions with different concentrations of the test compound (**25**) and the positive control were prepared as described above for nucleic acid synthesis studies. [^{3}H]-Glycerol was added at 0.5 µCi

per reaction. Reactions were allowed to proceed at room temperature for 50 min and then stopped through the addition of 373 µL chloroform/methanol (1:2), followed by vortexing for 20 s. Chloroform (125 µL) was then added to each reaction and vortexed followed by the addition of 125 µL dH_2O and vortexing. Reactions were centrifuged at 13,000 rpm in a microfuge for 10 min, and then 150 µL of the organic phase was transferred to a scintillation vial and allowed to dry in a fume hood for at least 1 h. Liquid scintillation fluid was added and samples were counted using a Perkin Elmer Tri-Carb 4810TR Liquid Scintillation Analyzer.

Experimental Data

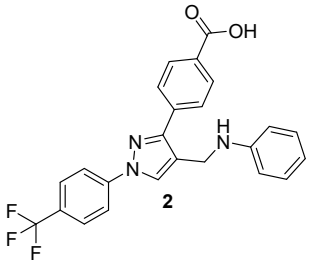
4-[4-formyl-1-[4-(trifluoromethyl)phenyl]pyrazol-3-yl]benzoic acid (**1**). Light beige solid (353 mg; 97%);



1

^{1}H NMR, 300 MHz (DMSO-d_6): δ 9.99 (s, 1H, H-1), 9.49 (s, 1H, H-2), 8.20 (d, *J* = 8.3 Hz, 2H, H-4), 8.05 (s, 4H, H-5 & H-6), 7.91 (d, *J* = 8.5 Hz, 2H, H-3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 184.9, 167.4, 152.3, 141.6, 136.5, 135.4, 131.7, 129.9, 129.2, 128.3 ($^2J_{C\text{-}F}$ = 32.1 Hz), 127.4 ($^3J_{C\text{-}F}$ = 3.6 Hz), 124.3 ($^1J_{C\text{-}F}$ = 270.3 Hz) 123.3, 120.0. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{18}H_{11}F_3N_2O_3$ $[M+H]^+$ = 361.0795, found 361.0791.

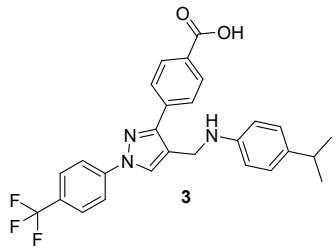
4-[4-(anilinomethyl)-1-[4-(trifluoromethyl)phenyl]pyrazol-3-yl]benzoic acid



2

(2). White solid (299 mg, 68%); IR (KBr pellet, cm^{-1}): 2651, 1693, 1228; ^{1}H NMR, 300 MHz (DMSO-d_6): δ 8.92 (s, 1H), 8.10 (d, *J* = 8.0 Hz, 2H), 8.03 (d, *J* = 7.5 Hz, 2H), 7.92 (d, *J* = 8.1 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 7.2 Hz, 2H), 7.00- 6.93 (m, 3H), 4.45 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4, 151.4, 142.3, 136.6, 131.2, 130.7, 130.0, 129.7, 128.1, 127.5 ($^3J_{C\text{-}F}$ = 3.5 Hz), 127.1 ($^2J_{C\text{-}F}$ = 32.0 Hz), 124.5 ($^1J_{C\text{-}F}$ = 270.2 Hz) 123.8, 122.7, 120.1, 119.0, 117.3, 41.8. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{24}H_{18}F_3N_3O_2$ $[M+H]^+$ = 438.1424, found 438.1428.

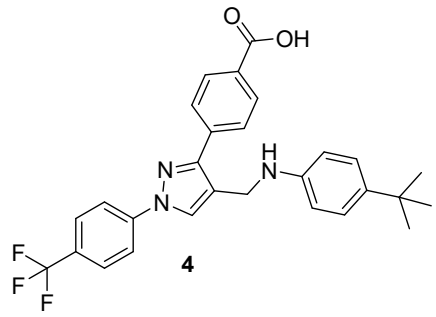
4-[4-[(4-isopropylanilino)methyl]-1-[4-(trifluoromethyl) phenyl]pyrazol-3-yl]benzoic acid (**3**). White solid; **(**389 mg, 81%); IR (KBr pellet, cm^{-1}): 2961, 1686, 1214; ^{1}H NMR, 300 MHz (DMSO-d_6): δ 8.99 (s, 1H), 8.09 (d, *J* = 8.4 Hz, 2H), 7.96-7.94 (m, 4H), 7.71 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 7.09-7.06 (m, 2H), 4.53 (s, 2H), 2.82- 2.77 (m, 1H), 1.13 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, DMSO- d_6): δ



3

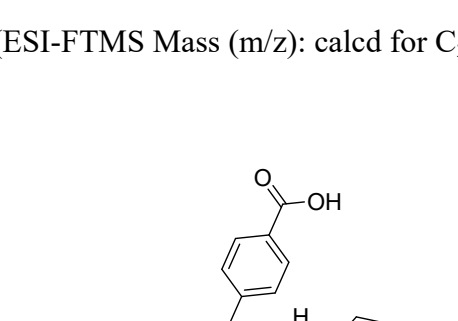
167.4, 152.1, 148.5, 142.1, 136.6, 134.6, 132.3, 130.7, 129.9, 128.3, 127.7, 127.6 ($^3J_{C\text{-}F}$ = 3.3 Hz), 126.7 ($^2J_{C\text{-}F}$ = 32.1 Hz), 124.4 ($^1J_{C\text{-}F}$ = 270.1 Hz), 122.8, 119.1, 113.8, 44.6, 33.3, 24.0. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{27}H_{24}F_3N_3O_2$ $[M+H]^+$ = 480.1893, found 480.1885.

4-[4-[(4-tert-butylanilino)methyl]-1-[4-(trifluoromethyl)phenyl]pyrazol-3-yl]benzoic acid (**4**). Yellow solid; (466 mg, 94%); IR (KBr pellet, cm^{-1}): 3415, 2965, 1694, 1220; ^{1}H NMR, 300 MHz (DMSO-d_6): δ 9.03 (s, 1H), 8.07 (d, *J* = 8.3 Hz, 2H), 7.94- 7.93 (m, 4H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H),7.13- 7.09 (m, 2H), 4.54 (s, 2H), 1.20 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4, 151.8, 142.2, 136.3, 132.0, 130.7, 129.9, 129.4, 129.2, 128.2, 127.8, 127.6 ($^3J_{C\text{-}F}$ = 3.5 Hz),127.2 ($^2J_{C\text{-}F}$ = 32.0 Hz), 126.5, 124.5 ($^1J_{C\text{-}F}$ = 270.1 Hz), 123.3, 119.0, 43.4, 34.5, 31.4. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{28}H_{26}F_3N_3O_2$ $[M+H]^+$ = 494.2050, found 494.2043.



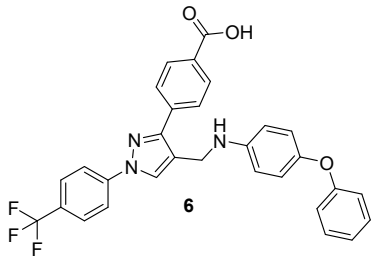
4

4-[4-[(4-methoxyanilino)methyl]-1-[4-(trifluoromethyl)phenyl]pyrazol-3-yl]benzoic acid (**5**). Light grey solid (362 mg, 77%); IR (KBr pellet, cm^{-1}): 3391, 2936, 1693, 1255; ^{1}H NMR, 300 MHz (DMSO-d_6): δ 9.00 (s, 1H), 8.08 (d, *J* = 8.2 Hz, 2H), 7.95 (d, *J* = 6.8 Hz, 4H), 7.68 (d, *J* = 7.8 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 4.54 (s, 2H), 3.69 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4, 152.0, 142.1, 136.2, 132.1, 130.7, 129.9, 129.2, 128.3, 127.6 ($^3J_{C\text{-}F}$ = 3.5 Hz), 126.7 ($^2J_{C\text{-}F}$ = 32.1 Hz), 124.9, 124.5 ($^1J_{C\text{-}F}$ = 270.1 Hz) 120.1, 119.1, 115.2, 115.0, 55.7, 44.6. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{25}H_{20}F_3N_3O_3$ $[M+H]^+$ = 468.1530, found 468.1525.



5

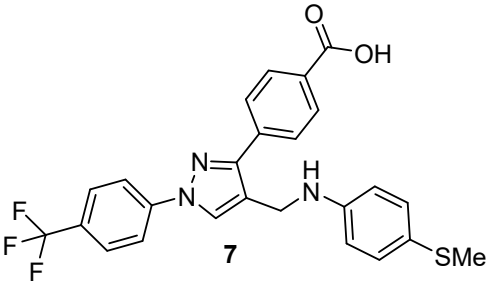
4-[4-[(4-phenoxyanilino)methyl]-1-[4-(trifluoromethyl)phenyl]pyrazol-3-yl]benzoic acid (**6**). White solid (425 mg, 80%); IR (KBr pellet, cm^{-1}): 3456, 2764, 1686, 1255; ^{1}H NMR, 300 MHz (DMSO-d_6): δ 8.94 (s, 1H), 8.11 (d, *J* = 8.2 Hz, 2H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.09- 7.06 (m, 3H), 6.90 (t, *J* = 8.8 Hz, 4H),



6

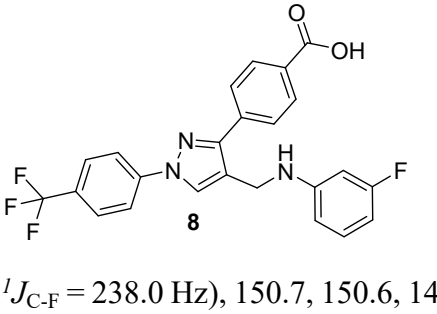
4.48 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4, 157.6, 151.4, 142.3, 136.6, 131.5, 130.7, 130.6, 130.4, 130.0, 128.1, 127.5, ($^{3}J_{C\text{-}F}$ = 3.4 Hz), 127.1 ($^{2}J_{C\text{-}F}$ = 31.9 Hz), 124.5 ($^{1}J_{C\text{-}F}$ = 270.2 Hz), 124.4, 120.3, 120.1, 119.4, 119.0, 118.6, 118.3, 42.3. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{30}H_{22}F_3N_3O_3$ $[M+H]^+$ = 530.1686, found 530.1688.

4-[4-[(4-methylsulfanylanilino)methyl]-1-[4-(trifluoromethyl)phenyl]pyrazol-3-yl]benzoic acid (**7**). Light beige solid (341 mg, 70%); IR (KBr pellet, cm^{-1}): 3210, 2725, 1698, 1246; ^{1}H NMR, 300 MHz (DMSO-d_6): δ 8.86 (s, 1H), 8.11 (d, *J* = 8.4 Hz, 2H), 8.00 (d, *J* = 8.1 Hz, 2H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 2H), 4.39 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4, 151.4, 142.3, 136.6, 131.3, 130.7, 130.4, 130.0, 129.2, 129.0, 128.1, 127.5 ($^{3}J_{C\text{-}F}$ = 3.6 Hz), 127.0 ($^{2}J_{C\text{-}F}$ = 32.1 Hz), 124.5 ($^{1}J_{C\text{-}F}$ = 270.2), 124.3, 120.1, 118.9, 41.5, 16.8. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{25}H_{20}F_3N_3O_2S$ $[M+H]^+$ = 484.1301, found 484.1301.



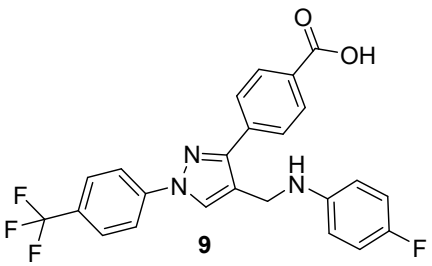
7

4-[4-[(3-fluoroanilino)methyl]-1-[4-(trifluoromethyl)phenyl]pyrazol-3-yl]benzoic acid (**8**). Light beige solid (381 mg, 83%); IR (KBr pellet, cm^{-1}): 2667, 1693, 1226; ^{1}H NMR, 300 MHz (DMSO-d_6): δ 8.80 (s, 1H), 8.14 (d, *J* = 8.4 Hz, 2H), 8.02 (d, *J* = 8.3 Hz, 2H), 7.95-7.89 (m, 4H), 7.11- 7.08 (m, 1H), 6.46 (t, *J* = 8.4 Hz, 2H), 6.36-6.28 (m, 1H), 4.32 (s, 2H); ^{13}C NMR (75MHz, DMSO-d_6): δ 167.5, 163.8 (d,$^{1}J_{C\text{-}F}$ = 238.0 Hz), 150.7, 150.6, 142.4, 136.9, 130.8, 130.7, 130.3, 130.1, 127.8, 127.4 ($^{3}J_{C\text{-}F}$ = 3.4), 126.6 ($^{2}J_{C\text{-}F}$ = 31.8 Hz), 124.5 ($^{1}J_{C\text{-}F}$ = 270.0 Hz), 120.4, 118.8, 109.3, 102.9 (d,$^{2}J_{C\text{-}F}$ = 21.1 Hz), 99.3 (d,$^{2}J_{C\text{-}F}$ = 24.5 Hz), 38.6. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{24}H_{17}F_4N_3O_2$ $[M+H]^+$ = 456.1330, found 456.1327.



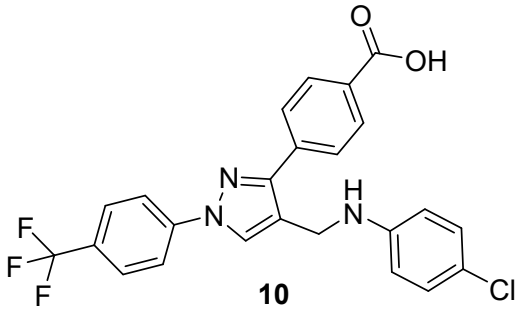
8

4-[4-[(4-fluoroanilino)methyl]-1-[4-(trifluoromethyl)phenyl]pyrazol-3-yl]benzoic acid (**9**). Light beige solid (386 mg, 84%); IR (KBr pellet, cm^{-1}): 3480, 2806, 1710, 1242; ^{1}H NMR, 300 MHz (DMSO-d_6): δ 8.90 (s, 1H), 8.09 (d, *J* = 8.3 Hz, 2H), 7.98 (d, *J* = 7.9 Hz, 2H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 4H), 4.37 (s, 2H); ^{13}C



9

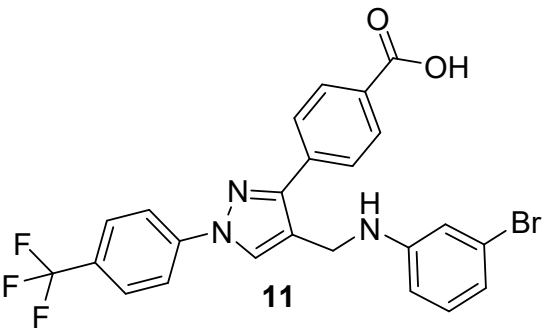
NMR (75MHz, DMSO-d_6): δ 167.4, 151.3, 142.3, 139.7, 136.6, 131.2, 130.7, 130.0, 129.9, 128.1, 127.5 ($^3J_{C\text{-}F}$ = 3.3 Hz), 127.0 ($^2J_{C\text{-}F}$ = 32.0 Hz), 124.5 ($^1J_{C\text{-}F}$ = 270.0 Hz), 118.9, 117.5, 116.2 (d,$^2J_{C\text{-}F}$ = 22.3 Hz), 41.8. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{24}H_{17}F_4N_3O_2$ $[M+H]^+$ = 456.1330, found 456.1322.



10

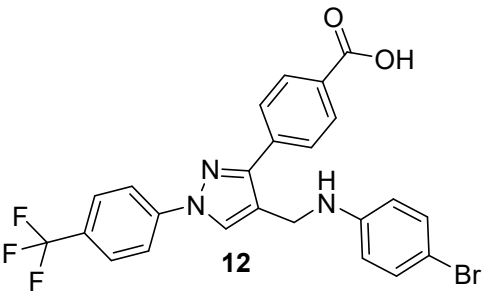
4-[4-[(4-chloroanilino)methyl]-1-[4-(trifluoromethyl)phenyl]pyrazol-3-yl]benzoic acid (**10**). Beige solid (338 mg, 71%); IR (KBr pellet, cm^{-1}): 2907, 1720, 1244; ^{1}H NMR, 300 MHz (DMSO-d_6): δ 8.81 (s, 1H), 8.12 (d, *J* = 8.3 Hz, 2H), 8.01 (d, *J* = 8.2 Hz, 2H), 7.90 (d, *J* = 8.2 Hz, 4H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 4.33 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.5, 150.9, 146.0, 142.4, 136.8, 130.6, 130.5, 130.1, 129.9, 129.1, 127.9, 127.4 ($^3J_{C\text{-}F}$ = 3.8 Hz), 126.7 ($^2J_{C\text{-}F}$ = 31.9 Hz), 124.5 ($^1J_{C\text{-}F}$ = 270.0 Hz), 121.8, 119.6, 118.8, 115.7. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{24}H_{17}ClF_3N_3O_2$ $[M+H]^+$ = 472.1034, 474.1007, found 472.1024.

4-[4-[(3-bromoanilino)methyl]-1-[4-(trifluoromethyl)phenyl]pyrazol-3-yl]benzoic acid (**11**). Light brown; (423 mg, 81%); IR (KBr pellet, cm^{-1}): 3415, 3096, 1694, 1228; ^{1}H NMR, 300 MHz (DMSO-d_6): δ 8.80 (s, 1H), 8.14 (d, *J* = 8.3 Hz, 2H), 8.03 (d, *J* = 8.3 Hz, 2H), 7.92 (t, *J* = 10.3 Hz, 4H), 7.04- 7.01 (m, 1H), 6.86 (s, 1H), 6.74- 6.69 (m, 2H), 4.32 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4, 150.7, 150.2, 142.4, 136.9, 134.9, 131.2, 130.7, 130.3, 130.1, 127.8, 127.4 ($^3J_{C\text{-}F}$ = 3.6 Hz), 126.7 ($^2J_{C\text{-}F}$ = 31.9 Hz), 124.5 ($^1J_{C\text{-}F}$ = 269.0 Hz), 120.4, 119.2, 118.8, 115.2, 111.9, 38.5. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{24}H_{17}BrF_3N_3O_2$ $[M+H]^+$ = 516.0529, 518.0510, found 516.0521.



11

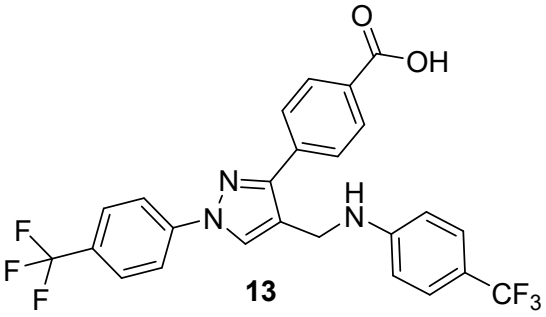
4-[4-[(4-bromoanilino)methyl]-1-[4-(trifluoromethyl)phenyl]pyrazol-3-yl]benzoic acid (**12**). Light beige solid (411 mg, 79%); IR (KBr pellet, cm^{-1}): 3399, 3029, 1702, 1245; ^{1}H NMR, 300 MHz (DMSO-d_6): δ 8.79 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 2H), 8.01 (d, *J* = 8.2 Hz, 2H), 7.90 (d, *J* = 8.7 Hz, 4H), 7.24 (d, *J* = 8.7 Hz,



12

2H), 6.69 (d, J = 8.7 Hz, 2H), 4.31 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.5, 150.8, 146.9, 142.4, 136.9, 131.9, 130.6, 130.4, 130.1, 129.9, 127.9, 127.4 ($^3J_{C\text{-}F}$ = 3.6 Hz), 126.7 ($^2J_{C\text{-}F}$ = 32.0 Hz), 124.5 ($^1J_{C\text{-}F}$ = 260.9 Hz), 120.0, 118.8, 115.7, 108.5. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{24}H_{17}BrF_3N_3O_2$ $[M+H]^+$ = 516.0529, 518.0510, found 516.0522.

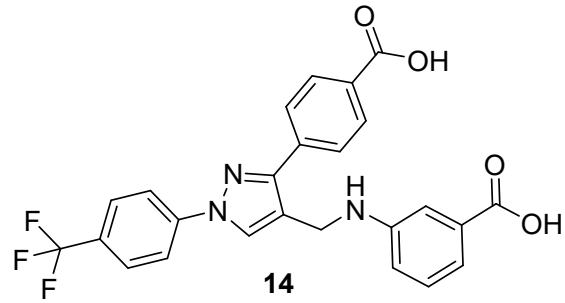
4-[4-[[4-(trifluoromethyl)anilino]methyl]-1-[4-(trifluoromethyl)phenyl]pyrazol-3-yl]-benzoic acid (**13**).



13

Light beige solid (421 mg, 83%); IR (KBr pellet, cm^{-1}): 3170, 2883, 1720, 1219; ^{1}H NMR, 300 MHz (DMSO-d_6): δ 8.79 (s, 1H), 8.14 (d, J = 8.3 Hz, 2H), 8.02 (d, J = 8.2 Hz, 2H), 7.91- 7.88 (m, 4H), 7.40 (d, J = 8.4 Hz, 2H), 7.27 (br, 1H), 6.78 (d, J = 8.3 Hz, 2H), 4.38 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4, 151.7, 150.7, 142.4, 136.9, 130.7, 130.3, 130.1, 127.8, 127.4 ($^3J_{C\text{-}F}$ = 3.6 Hz), 127.1 ($^2J_{C\text{-}F}$ = 24.0 Hz), 126.6 ($^3J_{C\text{-}F}$ = 4.1 Hz), 124.4 ($^1J_{C\text{-}F}$ = 270.2 Hz), 120.3, 118.9, 116.2 ($^2J_{C\text{-}F}$ = 31.5 Hz), 112.1, 38.2. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{25}H_{17}F_6N_3O_2$ $[M+H]^+$ = 506.1298, found 506.1307.

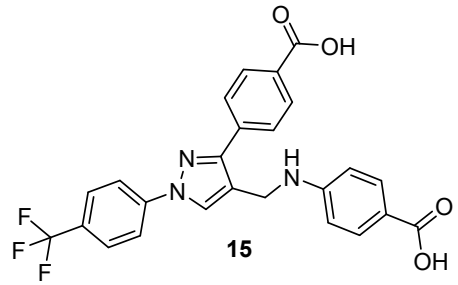
3-[[3-(4-carboxyphenyl)-1-[4-(trifluoromethyl)phenyl]pyrazol-4-yl]methylamino]benzoic acid (**14**).



14

Light beige solid (398 mg, 82%); IR (KBr pellet, cm^{-1}): 3073, 1693, 1170; ^{1}H NMR, 300 MHz (DMSO-d_6): δ 8.82 (s, 1H), 8.11 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 8.2 Hz, 2H), 7.89 (d, J = 8.1 Hz, 4H), 7.37 (s, 1H), 7.25 (t, J = 8.4 Hz, 2H), 7.03- 6.98 (m, 1H), 4.40 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.9, 167.4, 150.9, 146.9, 142.4, 136.8, 131.9, 130.7, 130.5, 130.1, 129.9, 129.6, 127.9, 127.4 ($^3J_{C\text{-}F}$ = 3.5 Hz), 126.9 ($^2J_{C\text{-}F}$ = 31.9 Hz), 124.5 ($^1J_{C\text{-}F}$ = 270.0 Hz), 119.6, 119.1, 118.9, 118.6, 115.3. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{25}H_{18}F_3N_3O_4$ $[M+H]^+$ = 482.1322, found 482.1318.

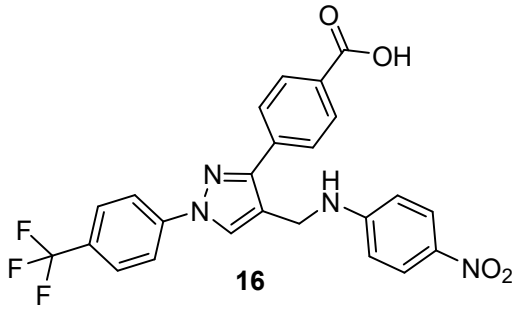
4-[4-[(4-carboxyanilino)methyl]-1-[4-(trifluoromethyl)phenyl]pyrzol-3-yl]benzoic acid (**15**).



15

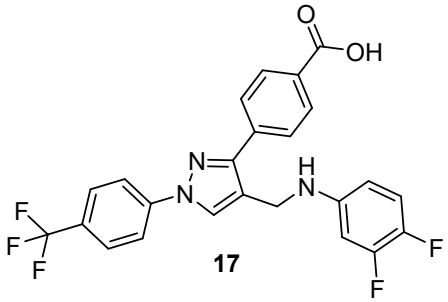
Light beige solid (461 mg, 95%); IR (KBr pellet,

cm^{-1}): 3396, 2980, 1682, 1174; ^{1}H NMR, 300 MHz (DMSO-d$_6$): δ 8.78 (s, 1H), 8.14 (d, *J* = 8.3 Hz, 2H), 8.03 (d, *J* = 8.3 Hz, 2H), 7.95- 7.88 (m, 4H), 7.70 (d, *J* = 8.5 Hz, 2H), 6.87 (br, 1H), 6.69 (d, *J* = 8.6 Hz, 2H), 4.39 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d$_6$): δ 167.9, 167.5, 152.5, 150.7, 142.4, 136.9, 131.5, 130.7, 130.1, 129.2, 127.8, 127.4 ($^{3}J_{C\text{-}F}$ = 3.6 Hz), 126.8 ($^{2}J_{C\text{-}F}$ = 31.9 Hz), 124.4 ($^{1}J_{C\text{-}F}$ = 270.1 Hz), 120.3, 118.8, 118.0, 111.7, 38.1. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{25}H_{18}F_3N_3O_4$ [M+H]$^+$ = 482.1322, found 482.1319.



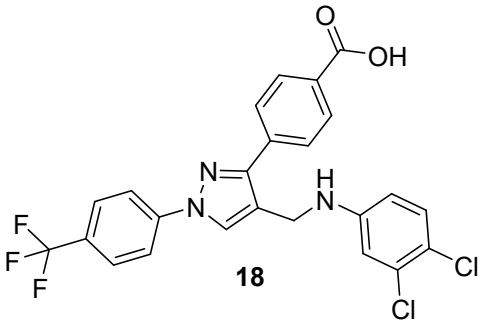
16

4-[4-[(4-nitroanilino)methyl]-1-[4-(trifluoromethyl)phenyl]pyrazol-3-yl]benzoic acid (**16**). Lime color solid; (332 mg, 68%)**;** IR (KBr pellet, cm^{-1}): 3396, 2983, 1682, 1226; ^{1}H NMR, 300 MHz (DMSO-d$_6$): δ 8.79 (s, 1H), 8.14 (d, *J* = 8.3 Hz, 2H), 8.02 (d, *J* = 7.7 Hz, 4H), 7.93- 7.88 (m, 4H), 7.69 (s, 1H), 6.75 (d, *J* = 9.0 Hz, 2H), 4.49 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d$_6$): δ 167.4, 154.5, 150.7, 142.3, 136.8, 136.6, 130.7, 130.4, 130.2, 127.8, 127.4 ($^{3}J_{C\text{-}F}$ = 3.2 Hz), 126.9 ($^{2}J_{C\text{-}F}$ = 30.7 Hz), 126.6, 124.5 ($^{1}J_{C\text{-}F}$ = 264.7 Hz), 119.5, 118.9, 111.7, 38.1. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{24}H_{17}F_3N_4O_4$ [M+H]$^+$ = 483.1275, found 483.1271.



17

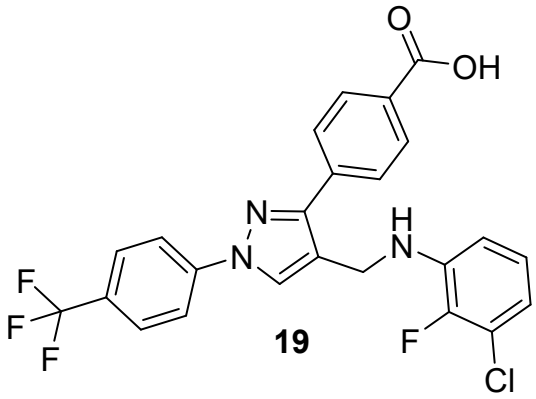
4-[4-[(3,4-difluoroanilino)methyl]-1-[4-(trifluoromethyl)phenyl]pyrzol-3-yl]benzoic acid (**17**). Light beige (398 mg, 84%); IR (KBr pellet, cm^{-1}): 3404, 3199, 1728, 1210; ^{1}H NMR, 300 MHz (DMSO-d$_6$): δ 8.78 (s, 1H), 8.14 (d, *J* = 8.3 Hz, 2H), 8.02 (d, *J* = 8.2 Hz, 2H), 7.96- 7.88 (m, 4H), 7.15-7.12 (m, 1H), 6.69- 6.63 (m, 1H), 6.45 (d, *J* = 8.7 Hz, 1H), 6.25 (br, 1H), 4.28 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d$_6$): δ 167.5, 150.7, 150.3 (dd, $J_{C\text{-}F}$ = 13.2, 246.2 Hz), 146.5 (d, $^{3}J_{C\text{-}F}$ = 8.9 Hz), 142.4, 141.7 (dd, $J_{C\text{-}F}$ = 12.9, 237.2 Hz), 136.9, 130.7, 130.3, 130.1, 127.8, 127.4 ($^{3}J_{C\text{-}F}$ = 3.6 Hz), 126.8 ($^{2}J_{C\text{-}F}$ = 31.9 Hz), 124.5 ($^{1}J_{C\text{-}F}$ = 270.1 Hz), 120.5, 118.8, 117.8 (d, $^{2}J_{C\text{-}F}$ = 16.7 Hz), 108.4, 100.8 (d, $^{2}J_{C\text{-}F}$ = 20.2 Hz), 38.9. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{24}H_{16}F_5N_3O_2$ [M+H]$^+$ = 474.1235, found 474.1238.



18

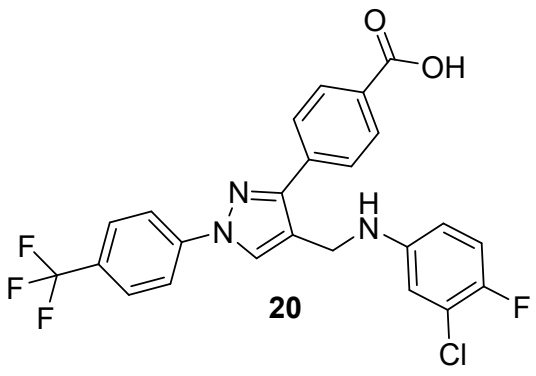
4-[4-[(3,4-dichloroanilino)methyl]-1-[4-(trifluoromethyl)phenyl]-pyrazol-3-yl]benzoic acid (**18**). White solid (439 mg, 86%); IR (KBr pellet, cm^{-1}): 3419, 2690, 1716, 1213; ^1H NMR, 300 MHz (DMSO-d_6): δ 8.76 (s, 1H), 8.14 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.1 Hz, 2H), 7.91 (t, J = 8.9 Hz, 4H), 7.28 (d, J = 8.7 Hz, 1H), 6.86 (s, 1H), 6.66 (dd, J = 2.3, 7.6 Hz, 1H), 6.53 (s, 1H), 4.32 (d, J = 4.3 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.5, 150.7, 148.9, 142.4, 136.9, 131.7, 130.9, 130.7, 130.1, 127.8, 127.4 ($^3J_{C\text{-}F}$ = 3.6 Hz), 126.8 ($^2J_{C\text{-}F}$ = 31.9 Hz), 124.5 ($^1J_{C\text{-}F}$ = 270.1 Hz) 123.8, 120.3, 118.9, 117.2, 113.4, 113.2, 38.4. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{24}H_{16}Cl_2F_3N_3O_2$ $[M+H]^+$ = 506.0644, 508.0616, found 506.0642.

4-[4-[(3-chloro-2-fluoro-anilino)methyl]-1-[4-(trifluoromethyl)phenyl]pyrazol-3-yl]benzoic acid (**19**). Light beige solid (434 mg, 88%); IR (KBr pellet, cm^{-1}): 3411, 2559, 1689, 1217; ^1H NMR, 300 MHz (DMSO-d_6): δ 8.66 (s, 1H), 8.12 (d, J = 8.2 Hz, 2H), 8.04 (d, J = 8.2 Hz, 2H), 7.93 (d, J = 8.3 Hz, 2H), 7.86 (d, J = 8.6 Hz, 2H), 6.92 (t, J = 8.1 Hz, 1H), 6.69 (d, J = 7.9 Hz, 2H), 4.44 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.5, 150.4, 146.7 (d,$^1J_{C\text{-}F}$ = 239.1 Hz), 142.4, 138.1 (d,$^3J_{C\text{-}F}$ = 11.2 Hz), 137.0, 130.6, 130.1, 129.8, 127.9, 127.3 ($^3J_{C\text{-}F}$ = 3.6 Hz), 126.7 ($^2J_{C\text{-}F}$ = 32.0 Hz), 125.7- 125.6 (m), 124.5 ($^1J_{C\text{-}F}$ = 270.0 Hz), 120.9, 119.5 (d,$^2J_{C\text{-}F}$ = 14.5 Hz), 118.8, 116.7, 111.5, 38.5. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{24}H_{16}ClF_4N_3O_2$ $[M+H]^+$ = 490.0940, 492.0912, found 490.0948.



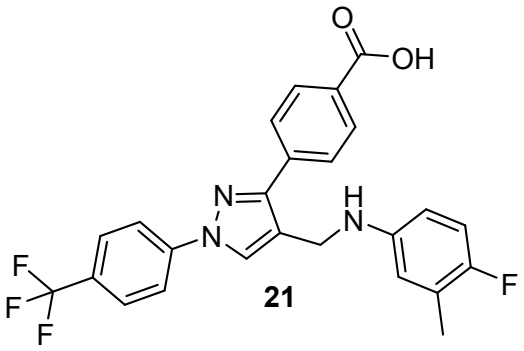
19

4-[4-[(3-chloro-4-fluoroanilino)methyl]-1-[4-(trifluoromethyl)phenyl]pyrazol-3-yl]benzoic acid (**20**). White solid (427 mg, 87%); IR (KBr pellet, cm^{-1}): 3214, 1695, 1255; ^1H NMR, 300 MHz (DMSO-d_6): δ 8.83 (s, 1H), 8.12 (d, J = 8.3 Hz, 2H), 8.01 (d, J = 8.1 Hz, 2H), 7.94 (d, J = 8.2 Hz, 4H), 7.15 (t, J = 9.0 Hz, 1H), 6.90 (s, 1H), 6.73 (d, J = 6.6 Hz, 2H), 4.33 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4, 150.9, 150.6 (d,$^1J_{C\text{-}F}$ = 234.4 Hz),

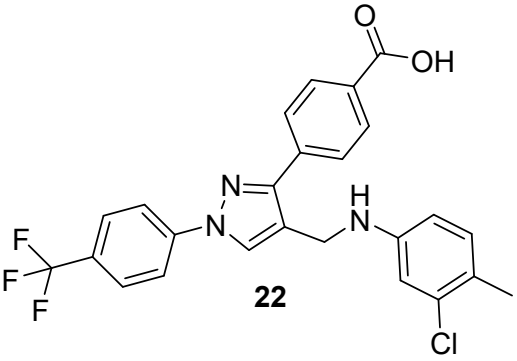


20

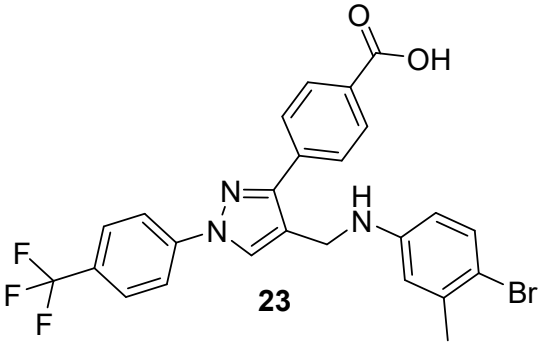
144.8, 142.2 , 136.8, 130.6 (d,$^{3}J_{C\text{-}F}$ = 8.8 Hz) , 130.1, 127.9, 127.4 ($^{3}J_{C\text{-}F}$ = 3.5 Hz), 126.9 ($^{2}J_{C\text{-}F}$ = 31.9 Hz), 124.5 ($^{1}J_{C\text{-}F}$ = 270.1 Hz), 120.0, 119.8, 119.5, 118.8, 117.4 (d,$^{2}J_{C\text{-}F}$ = 21.3 Hz), 114.7, 114.1, 38.6. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{24}H_{16}ClF_4N_3O_2$ $[M+H]^+$ = 490.0940, 492.0912, found 490.0941.



4-[4-[(4-fluoro-3-methylanilino)methyl]-1-[4-(trifluoromethyl)phenyl]pyrazol-3-yl]benzoic acid (**21**). White solid (353 mg, 75%); IR (KBr pellet, cm^{-1}): 3324, 2851, 1686, 1224; ^{1}H NMR, 300 MHz (DMSO-d_6): δ 8.91 (s, 1H), 8.10 (d, *J* = 8.5 Hz, 2H), 7.97 (d, *J* = 8.2 Hz, 2H), 7.92 (d, *J* = 8.7 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.00- 6.82 (m, 3H), 4.46 (s, 2H), 2.08 (s, 3H); ^{13}C NMR (75MHz, DMSO-d_6): δ 167.4, 151.5, 142.2, 136.5, 131.4, 130.7, 129.9, 128.1, 127.6, 127.5 ($^{3}J_{C\text{-}F}$ = 3.5 Hz), 127.1($^{2}J_{C\text{-}F}$ = 32.1 Hz), 125.4 (d,$^{2}J_{C\text{-}F}$ = 18.3 Hz), 124.5 ($^{1}J_{C\text{-}F}$ = 270.1 Hz), 122.7, 121.1, 119.0, 117.4, 116.9, 115.8 (d,$^{2}J_{C\text{-}F}$ = 23.3 Hz), 42.1, 14.7. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{25}H_{19}F_4N_3O_2$ $[M+H]^+$ = 470.1486, found 470.1485.



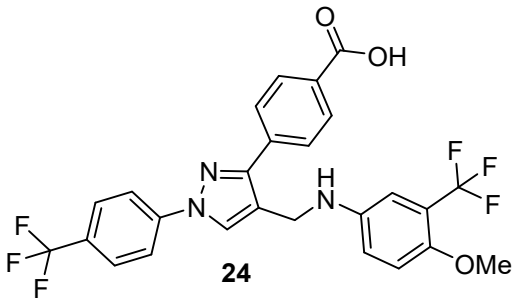
4-[4-[(3-chloro-4-methylanilino) methyl]-1-[4-(trifluoromethyl) phenyl]pyrazol-3-yl]benzoic acid (**22**). Light beige solid (433 mg, 89%); IR (KBr pellet, cm^{-1}): 3341, 2855, 1686, 1223; ^{1}H NMR, 300 MHz (DMSO-d_6): δ 8.89 (s, 1H), 8.10 (d, *J* = 8.3 Hz, 2H), 7.98 (d, *J* = 8.1 Hz, 2H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.81 (d, *J* = 7.7 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.93 (s, 1H), 6.77- 6.75 (m, 1H), 4.39 (s, 2H), 2.16- 2.0 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4, 151.2, 144.2, 142.3, 136.7, 133.9, 132.5, 131.8, 131.0, 130.7, 130.0, 129.2, 128.0, 127.4 ($^{3}J_{C\text{-}F}$ = 3.3 Hz), 126.9 ($^{2}J_{C\text{-}F}$ = 31.9 Hz), 124.5 ($^{1}J_{C\text{-}F}$ = 270.1 Hz), 118.9, 118.4, 116.1, 115.1, 19.1. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{25}H_{19}ClF_3N_3O_2$ $[M+H]^+$ = 486.1191, 488.1163, found 486.1198.



4-[4-[(4-bromo-3-methyl-anilino)methyl]-1-[4-(trifluoromethyl)phenyl]pyrazol-3-yl]benzoic acid (**23**). Light beige solid (399 mg, 75%); IR (KBr pellet, cm^{-1}): 2561, 1686, 1214;

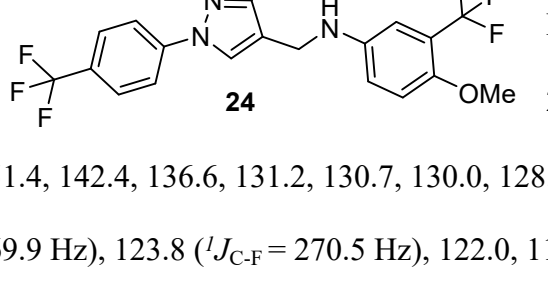
^{1}H NMR, 300 MHz (DMSO-d_6): δ 8.85 (s, 1H), 8.12 (d, J = 8.5 Hz, 2H), 8.00 (d, J = 8.2 Hz, 2H), 7.88 (t, J = 8.4 Hz, 4H), 7.26 (d, J = 8.5 Hz, 1H), 6.77 (s, 1H), 6.58 (d, J = 8.4 Hz, 1H), 4.34 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4, 151.0, 142.4, 137.8, 136.8, 133.6, 132.6, 130.7, 130.0, 129.9, 129.2, 127.9, 127.4 ($^3J_{C\text{-}F}$ = 3.4 Hz), 126.9 ($^2J_{C\text{-}F}$ = 32.1 Hz), 124.5 ($^1J_{C\text{-}F}$ = 269.9 Hz) 120.1, 119.4, 118.9, 117.1, 114.5, 23.0. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{25}H_{19}BrF_3N_3O_2$ $[M+H]^+$ = 530.0686, 532.0666, found 530.0688.

4-[4-[[4-methoxy-3-(trifluoromethyl)anilino] methyl]-1-[4-(trifluoromethyl) phenyl]pyrazol-3-yl]benzoic acid (**24**). White solid (383 mg, 71%); IR (KBr pellet, cm^{-1}): 3413, 3007, 1693, 1220; ^{1}H NMR, 300 MHz (DMSO-d_6): δ 8.87 (s, 1H), 8.11 (d, J = 8.5 Hz, 2H), 7.96 (d, J = 8.3 Hz, 2H), 7.92 (d, J = 8.7 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H), 7.14- 7.04 (m, 3H), 4.46 (s, 2H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4, 152.0, 151.4, 142.4, 136.6, 131.2, 130.7, 130.0, 128.0, 127.5 ($^3J_{C\text{-}F}$ = 3.4 Hz), 127.0 ($^2J_{C\text{-}F}$ = 32.0 Hz), 124.5 ($^1J_{C\text{-}F}$ = 269.9 Hz), 123.8 ($^1J_{C\text{-}F}$ = 270.5 Hz), 122.0, 118.9, 118.3, 117.7 ($^2J_{C\text{-}F}$ = 29.8 Hz), 115.7, 114.6, 56.8, 41.9. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{26}H_{19}F_6N_3O_3$ $[M+H]^+$ = 536.1403, found 536.1399.



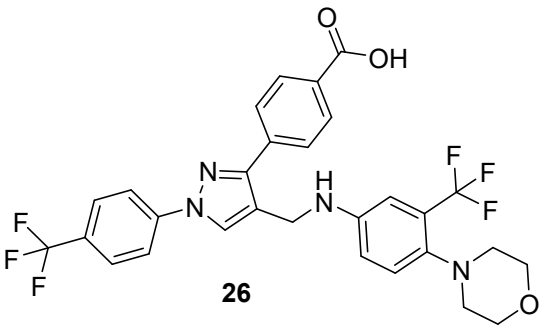
24

4-[4-[[4-bromo-3-(trifluoromethyl)anilino]methyl]-1-[4-(trifluoromethyl)phenyl]pyra-zol-3-yl]benzoic acid (**25**). Light beige solid (497 mg, 85%); IR (KBr pellet, cm^{-1}): 3214, 2859, 1693, 1233; ^{1}H NMR, 300 MHz (DMSO-d_6): δ 8.78 (s, 1H), 8.14 (d, J = 7.8 Hz, 2H), 8.03 (d, J = 7.8 Hz, 2H), 7.92 (t, J = 9.0 Hz, 4H), 7.51 (d, J = 8.3 Hz, 1H), 7.09 (s, 1H), 6.79 (s, 2H), 4.36 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.5, 150.7, 148.3, 142.4, 136.9, 135.7, 130.7, 130.2 ($^3J_{C\text{-}F}$ = 5.9 Hz), 129.9, 128.9 ($^2J_{C\text{-}F}$ = 29.9 Hz), 127.8, 127.4 ($^3J_{C\text{-}F}$ = 3.6 Hz), 126.8 ($^2J_{C\text{-}F}$ = 31.9 Hz), 124.5 ($^1J_{C\text{-}F}$ = 270.0 Hz), 123.6 ($^1J_{C\text{-}F}$ = 271.5 Hz), 120.1, 118.9, 116.8, 112.2, 102.9, 38.3. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{25}H_{16}BrF_6N_3O_2$ $[M+H]^+$ = 584.0403, 586.0384, found 584.0411.



25

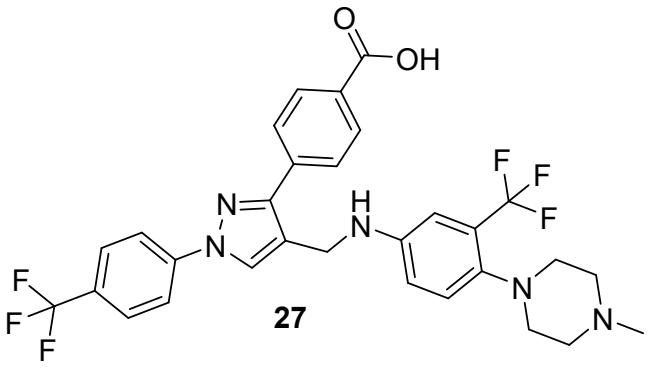
4-[4-[[4-morpholino-3-(trifluoromethyl)anilino] methyl]-1-[4-(trifluoromethyl)phenyl]pyrazol-3-yl]benzoic acid (**26**). Light



26

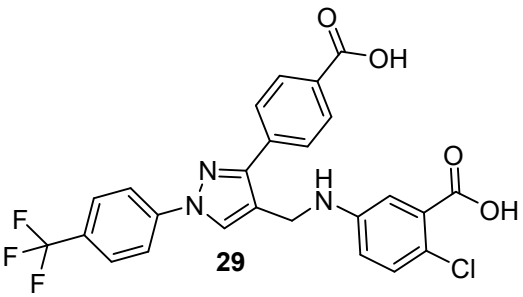
beige solid (388 mg, 76%); IR (KBr pellet, cm^{-1}): 3419, 2918, 1715, 1216; ^1H NMR, 300 MHz (DMSO-d_6): δ 8.78 (s, 1H), 8.13 (d, J = 8.2 Hz, 2H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.91 (t, *J* = 8.3 Hz, 4H), 7.35 (d, *J* = 8.5 Hz, 1H), 6.91 (d, *J* = 10.7 Hz, 2H), 4.35 (s, 2H), 2.72 (s, 4H), 2.49 (s, 5H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.5, 150.8, 146.0, 142.4, 141.3, 136.9, 131.1, 130.7, 130.3, 129.9, 127.9, 127.5 ($^3J_{C\text{-}F}$ = 9.8 Hz), 126.8 ($^2J_{C\text{-}F}$ = 32.6 Hz), 124.5 ($^1J_{C\text{-}F}$ = 264.6 Hz), 120.1, 118.9, 116.1, 110.8, 67.2, 54.1, 31.1. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{29}H_{24}F_6N_4O_3$ $[M+H]^+$ = 591.1825, found 591.1830.

4-[4-[[4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)anilino methyl]-1- [4- (trifluoro-methyl)phenyl]pyrazol-3-yl]benzoic acid (**27**). White solid (448 mg, 74%); IR (KBr pellet, cm^{-1}): 3412, 2967, 1701, 1231; ^1H NMR, 300 MHz (DMSO-d_6): δ 8.81 (s, 1H), 8.13 (d, *J* = 8.4 Hz, 2H), 8.01 (d, *J* = 8.2 Hz, 2H), 7.92 (d, *J* = 6.4 Hz, 4H), 7.30 (d, *J* = 7.5 Hz 1H), 6.97 (s, 2H), 4.36 (s, 2H), 3.40 (d, *J* = 10.6 Hz, 2H), 3.15 (d, *J* = 11.4 Hz, 2H), 3.05- 3.02 (m, 2H), 2.89 (d, *J* = 11.2 Hz, 2H), 2.79 (s, 2H), 2.49 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4, 150.8, 146.3, 142.4, 139.7, 136.9, 130.7, 130.4, 130.0, 127.9, 127.4 ($^3J_{C\text{-}F}$ = 3.7 Hz), 127.0 ($^3J_{C\text{-}F}$ = 7.7 Hz), 126.5 ($^2J_{C\text{-}F}$ = 23.4 Hz), 124.4 ($^1J_{C\text{-}F}$ = 260.0 Hz), 124.3 ($^1J_{C\text{-}F}$ = 254.8 Hz), 120.1, 118.9, 116.9,111.1, 53.5, 50.4, 42.4, 31.1. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{30}H_{27}F_6N_5O_2$ $[M+H]^+$ = 604.2142, found 604.2144.



27

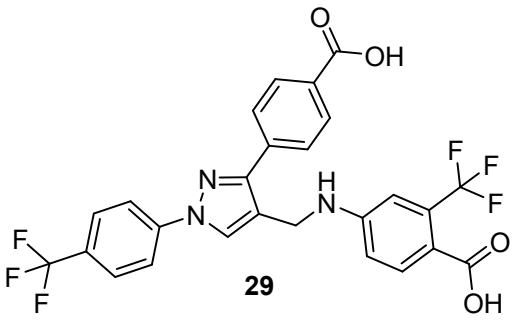
5-[[3-(4-carboxyphenyl)-1-[4-(trifluoromethyl)phenyl]pyrazol-4-yl]methylamino]-2-chloro-benzoic acid (**28**). Light beige solid (354 mg, 68%); IR (KBr pellet, cm^{-1}): 3248, 3091, 1727, 1281; ^1H NMR, 300 MHz (DMSO-d_6): δ 8.76 (s, 1H), 8.13 (d, *J* = 8.0 Hz, 2H), 8.02 (d, *J* = 7.2 Hz, 2H), 7.95- 7.88 (m, 4H), 7.21 (d, *J* = 8.5 Hz, 1H), 7.04 (s, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 6.48 (br, 1H), 4.32 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.7, 167.5, 150.7, 147.6, 142.4, 136.9, 132.1, 131.3, 130.7, 130.1, 129.3, 127.8, 127.4 ($^3J_{C\text{-}F}$ = 3.6 Hz), 126.8 ($^2J_{C\text{-}F}$



29

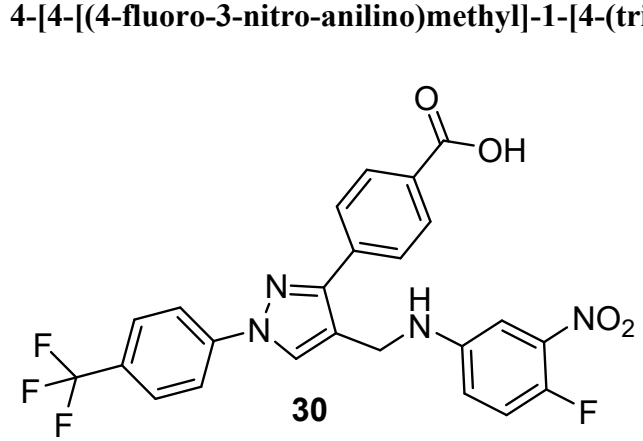
= 31.9 Hz), 124.5 ($^{1}J_{C\text{-}F}$ = 270.0 Hz), 120.5, 118.8, 118.0, 116.1, 114.4, 38.5. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{25}H_{17}ClF_3N_3O_4$ $[M+H]^+$ = 516.0932, 518.0905, found 516.0928.

4-[[3-(4-carboxyphenyl)-1-[4-(trifluoromethyl)phenyl]pyrazol-4-yl]methylamino]-2-(trifluoromethyl)benzoic acid (**29**). Light beige solid (367 mg, 66%); IR (KBr pellet, cm^{-1}): 3343, 2882, 1694, 1219; ^{1}H NMR, 300 MHz (DMSO-d_6): δ 8.77 (s, 1H), 8.13 (d, *J* = 8.3 Hz, 2H), 8.03 (d, *J* = 7.9 Hz, 2H), 7.91 (t, *J* = 9.2 Hz, 4H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.19 (s, 1H), 7.08 (s, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 4.45 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4, 167.0, 151.3, 150.7, 142.4, 136.8, 134.1, 130.7, 130.2, 129.7 ($^{2}J_{C\text{-}F}$ = 30.6 Hz), 127.8, 127.4 ($^{3}J_{C\text{-}F}$ = 4.0 Hz), 126.9 ($^{2}J_{C\text{-}F}$ = 31.9 Hz), 124.5 ($^{1}J_{C\text{-}F}$ = 270.1 Hz), 124.1 ($^{1}J_{C\text{-}F}$ = 271.3 Hz), 119.9, 118.9, 117.0, 113.0, 111.4, 38.0. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{26}H_{17}F_6N_3O_4$ $[M+H]^+$ = 550.1196, found 550.1186.



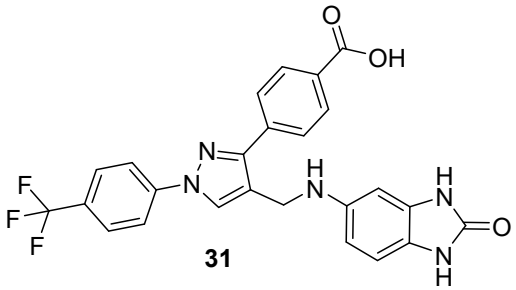
29

4-[4-[(4-fluoro-3-nitro-anilino)methyl]-1-[4-(trifluoromethyl) phenyl]pyrazol-3-yl]benzoic acid (30). Lime solid (432 mg, 86%); IR (KBr pellet, cm^{-1}): 3350,3003, 1697, 1331; ^{1}H NMR, 300 MHz (DMSO-d_6): δ 8.77 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 2H), 8.02 (d, *J* = 8.1 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.88 (d, *J* = 8.6 Hz, 2H), 7.34- 7.27 (m, 2H), 7.06-7.03 (m, 1H), 4.36 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.5, 150.7, 146.8 (d,$^{1}J_{C\text{-}F}$ = 248.3 Hz), 145.7, 142.4, 137.4 (d,$^{3}J_{C\text{-}F}$ = 8.2 Hz), 136.9, 130.7, 130.2, 130.1, 127.8, 127.4 ($^{3}J_{C\text{-}F}$ = 3.4 Hz), 126.8 ($^{2}J_{C\text{-}F}$ = 32.0 Hz), 124.5 ($^{1}J_{C\text{-}F}$ = 270.1 Hz), 120.1, 119.8 (d,$^{3}J_{C\text{-}F}$ = 6.8 Hz), 119.1 ($^{2}J_{C\text{-}F}$ = 21.5 Hz), 118.8, 107.3, 38.7. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{24}H_{16}F_4N_4O_4$ $[M+H]^+$ = 501.1180, found 501.1182.



30

4-[4-[[(2-oxo-1,3-dihydrobenzimidazol-5-yl)amino]methyl]-1-[4-(trifluoromethyl)-phenyl]pyrazol-3-yl] benzoic acid (**31**). Brown solid (362 mg, 73%); ^{1}H NMR, 300 MHz (DMSO-d_6): δ 10.68 (s, 2H), 8.97 (s, 1H), 8.08 (d, *J* = 8.6

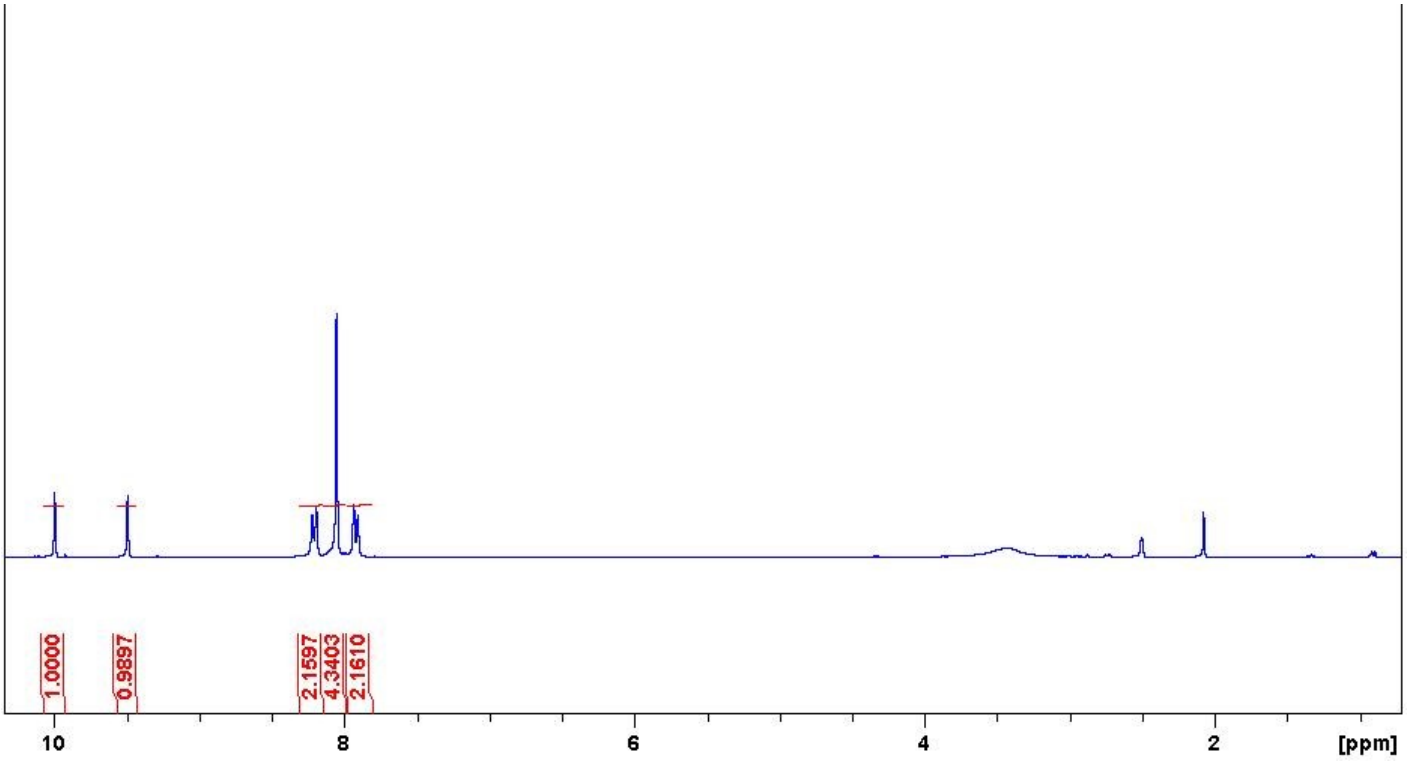


31

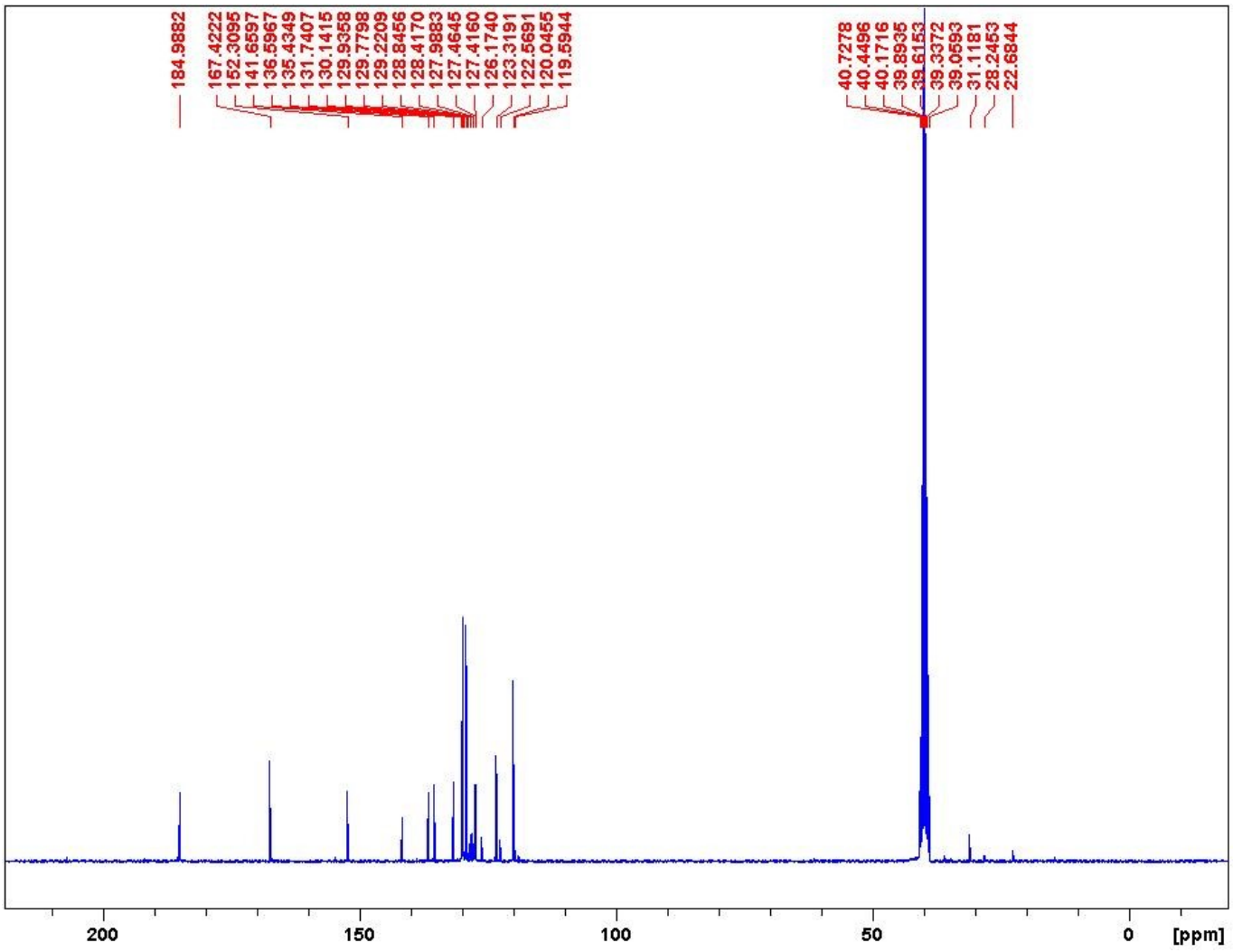
Hz, 2H), 7.94 (t, J = 7.0 Hz, 4H), 7.67 (d, J = 7.8 Hz, 2H), 6.78 (s, 3H), 4.54 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 185.1,167.4, 155.7, 152.4, 136.6, 135.4, 131.7, 130.6, 129.9, 129.7, 129.3, 128.3 ($^{2}J_{C\text{-}F}$ = 32.0 Hz), 128.2, 127.5 ($^{3}J_{C\text{-}F}$ = 3.9 Hz), 124.6, 120.9 ($^{1}J_{C\text{-}F}$ = 269.1 Hz), 120.1, 115.6, 109.3, 109.0, 104.1. HRMS (ESI-FTMS Mass (m/z): calcd for $C_{25}H_{18}F_3N_5O_3$ $[M+H]^+$ = 494.1435, found 494.1427.

NMR Spectra of Compounds

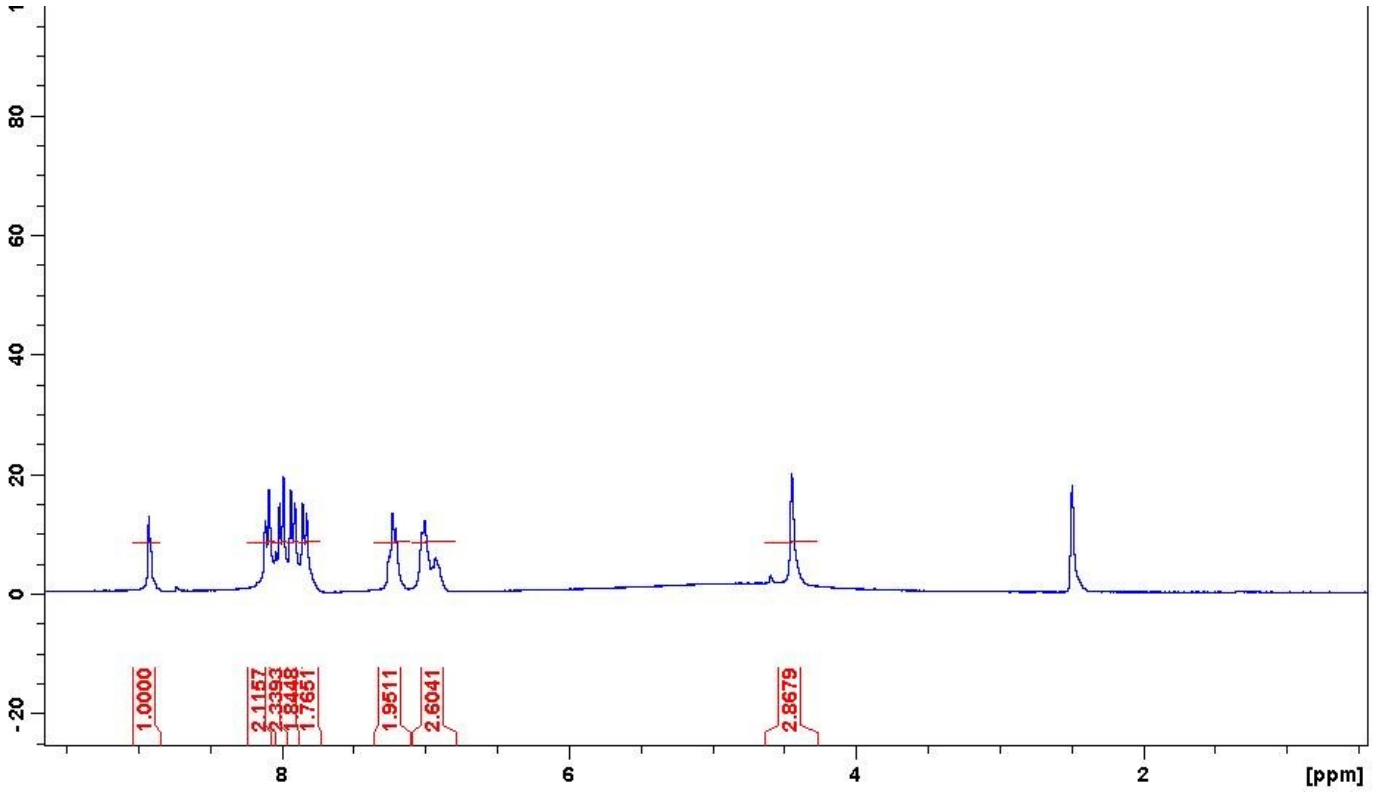
^{1}H NMR spectrum of compound **1**



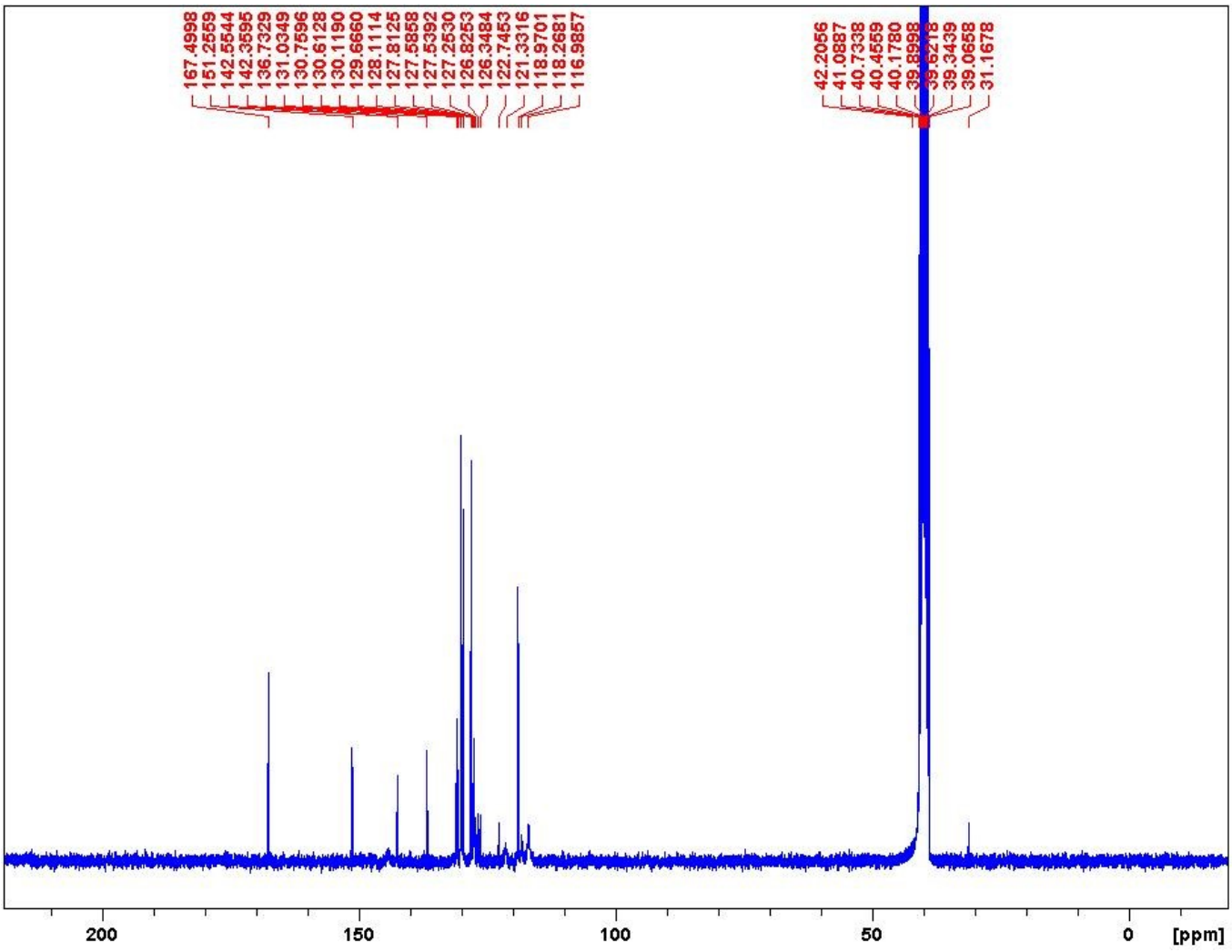
^{13}C NMR spectrum of compound **1**



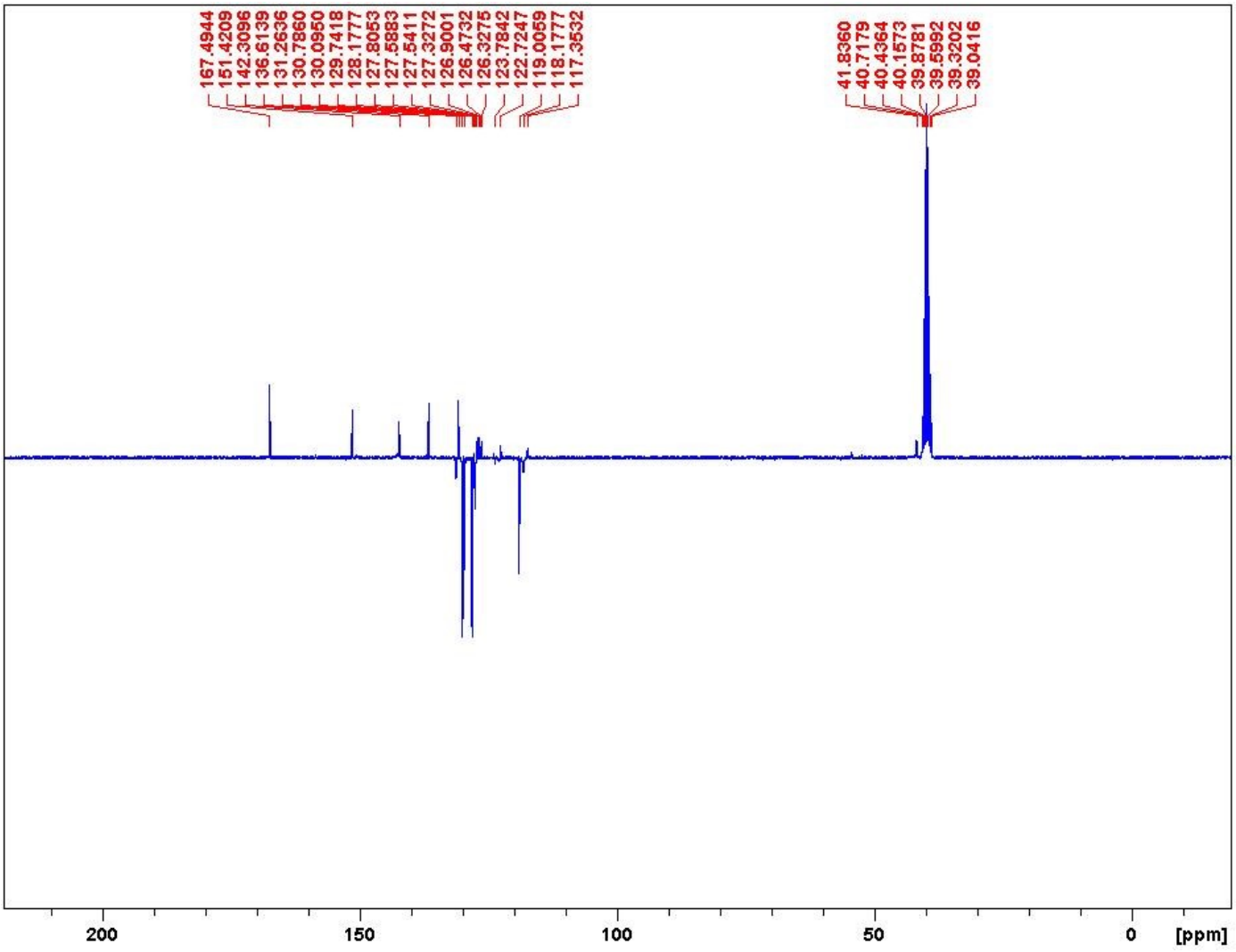
^{1}H NMR spectrum of compound **2**



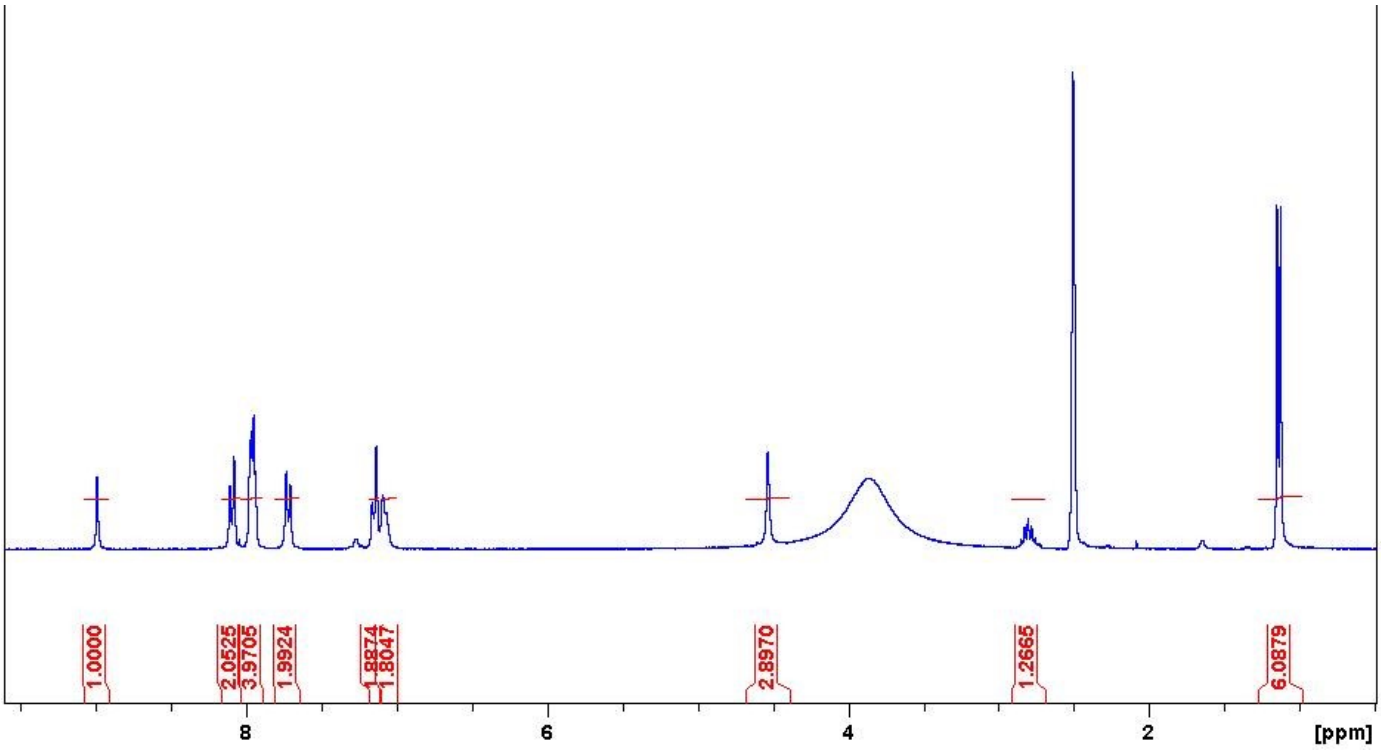
^{13}C NMR spectrum of compound **2**



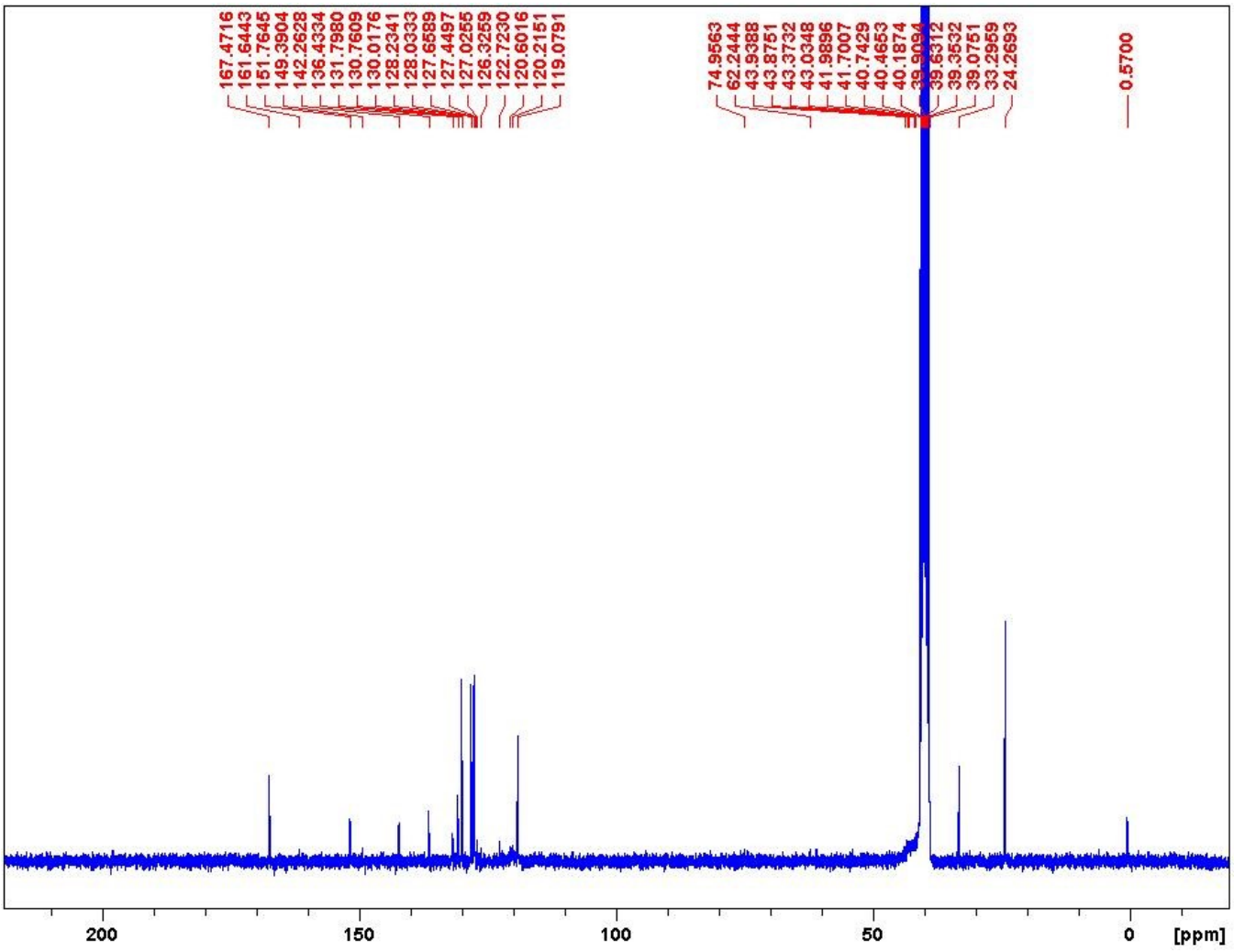
APT NMR spectrum of compound **2**


167.4944
151.4209
142.3096
136.6139
131.2636
130.7860
130.0950
129.7418
128.1777
127.8053
127.5883
127.5411
127.3272
126.9001
126.4732
126.3275
123.7842
122.7247
119.0059
118.1777
117.3532
41.8360
40.7179
40.4364
40.1573
39.8781
39.5992
39.3202
39.0416
200
150
100
50
0
[ppm]

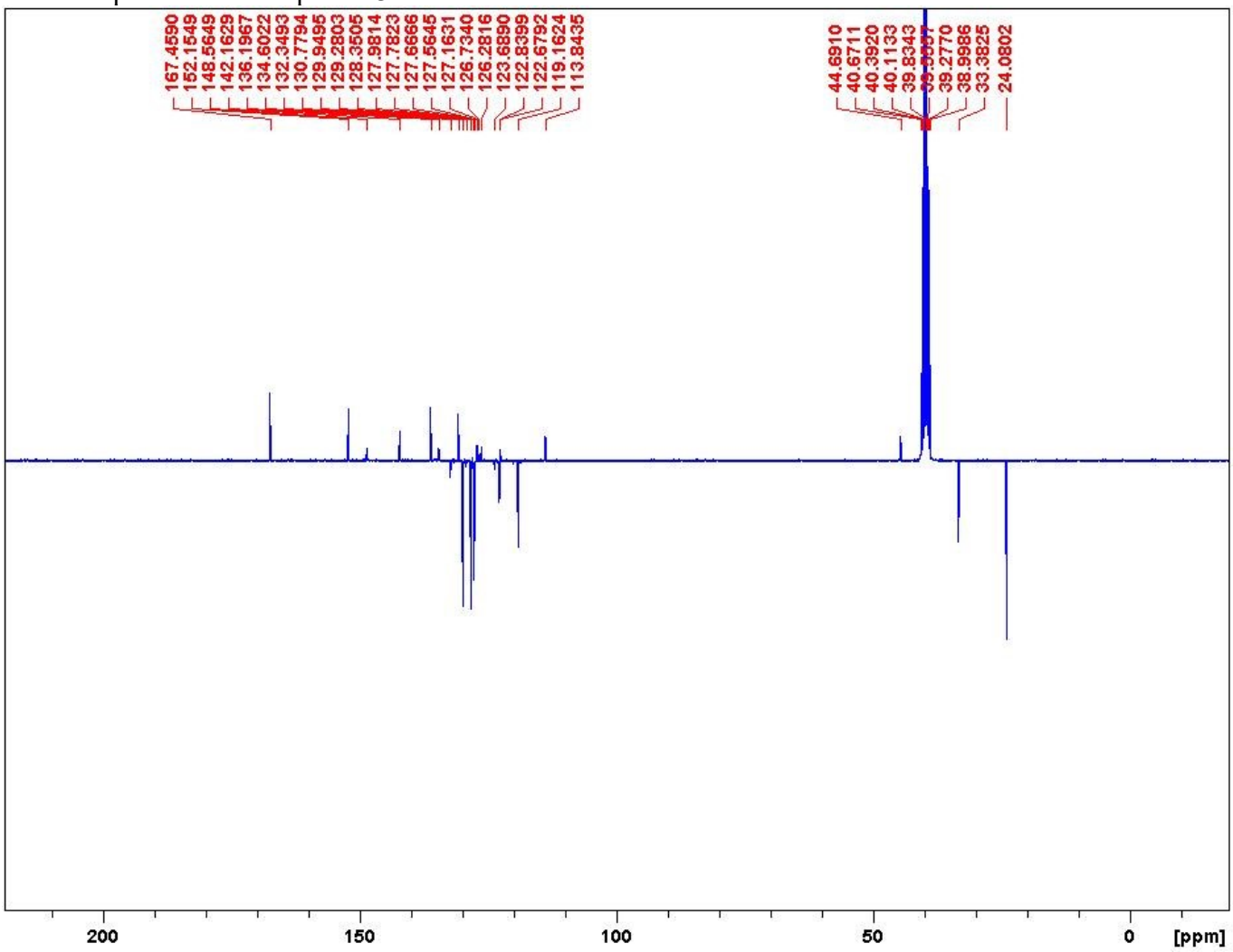
^{1}H NMR spectrum of compound **3**.



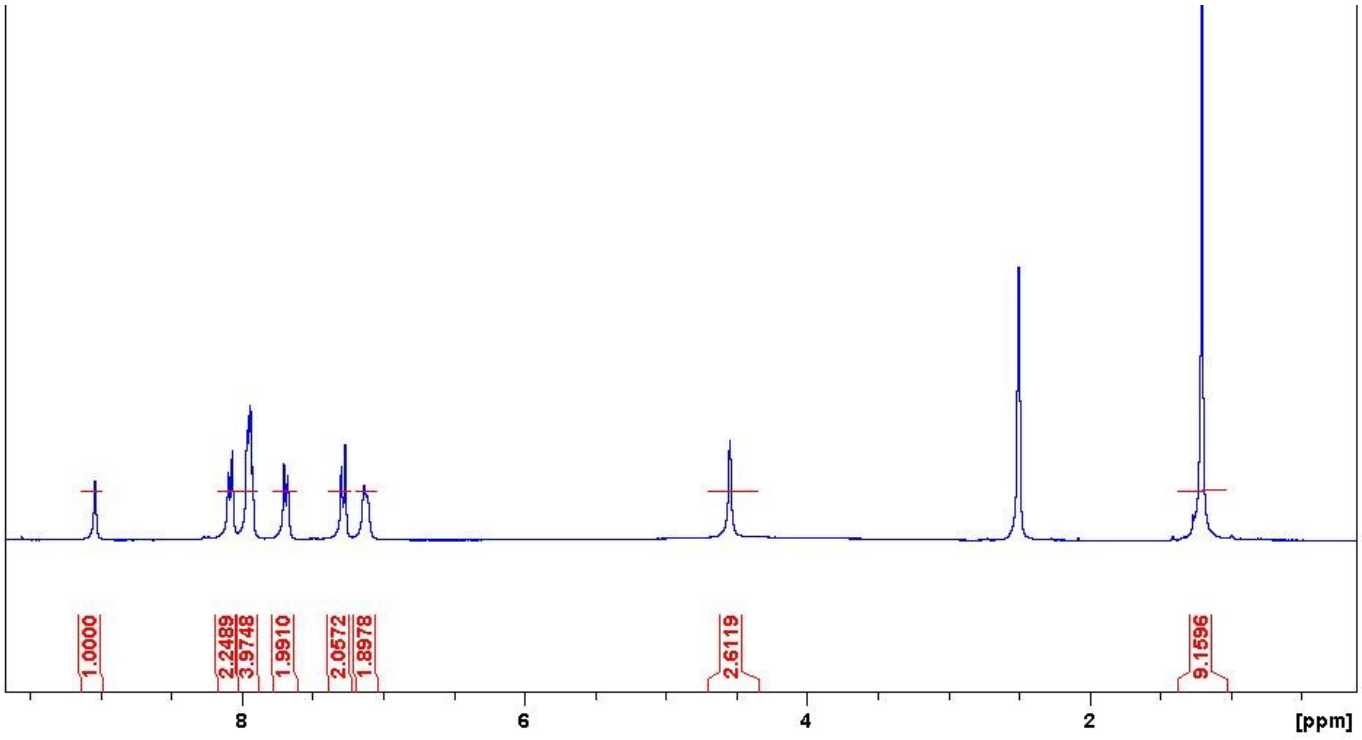
^{13}C NMR spectrum of compound **3**



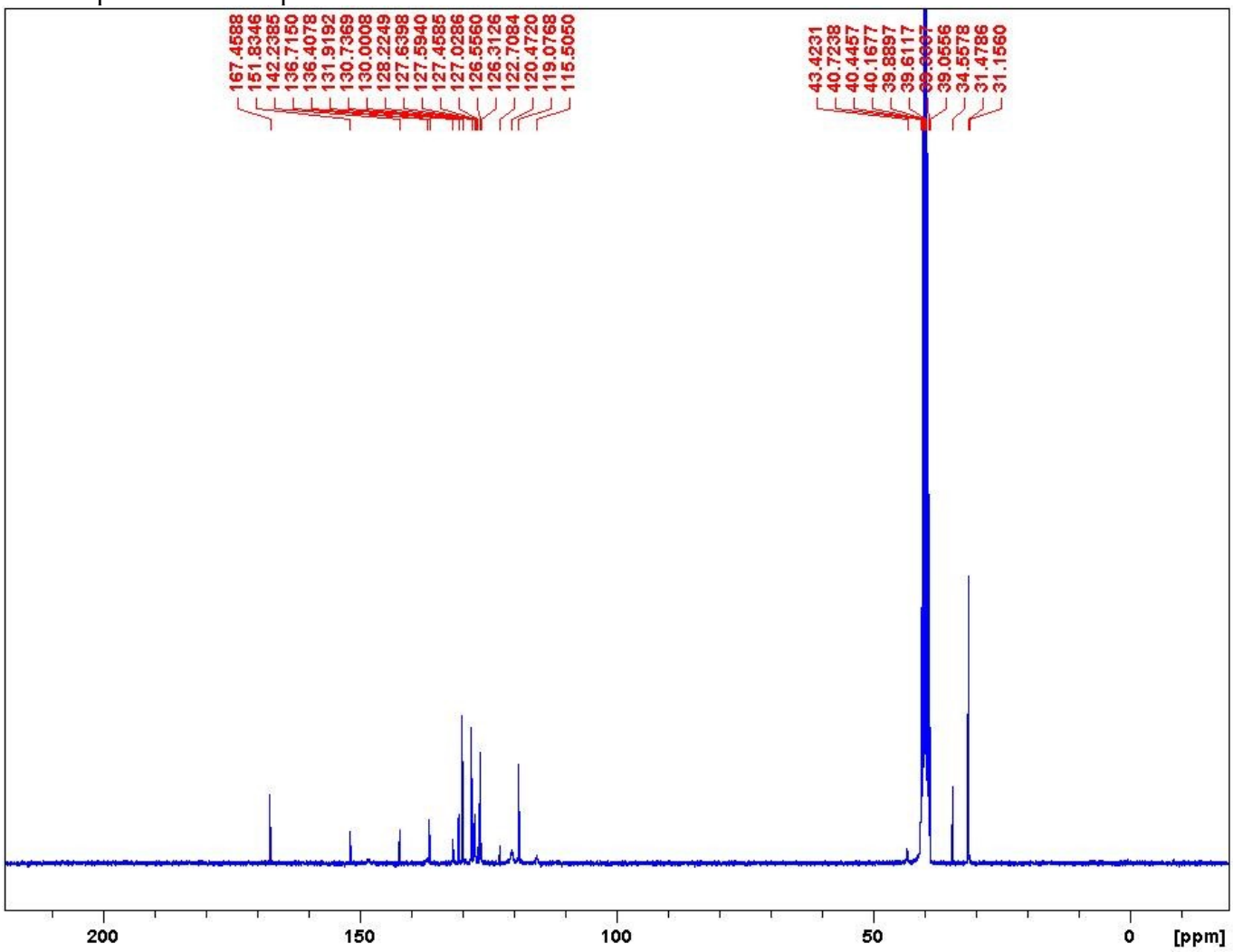
APT NMR spectrum of compound **3**



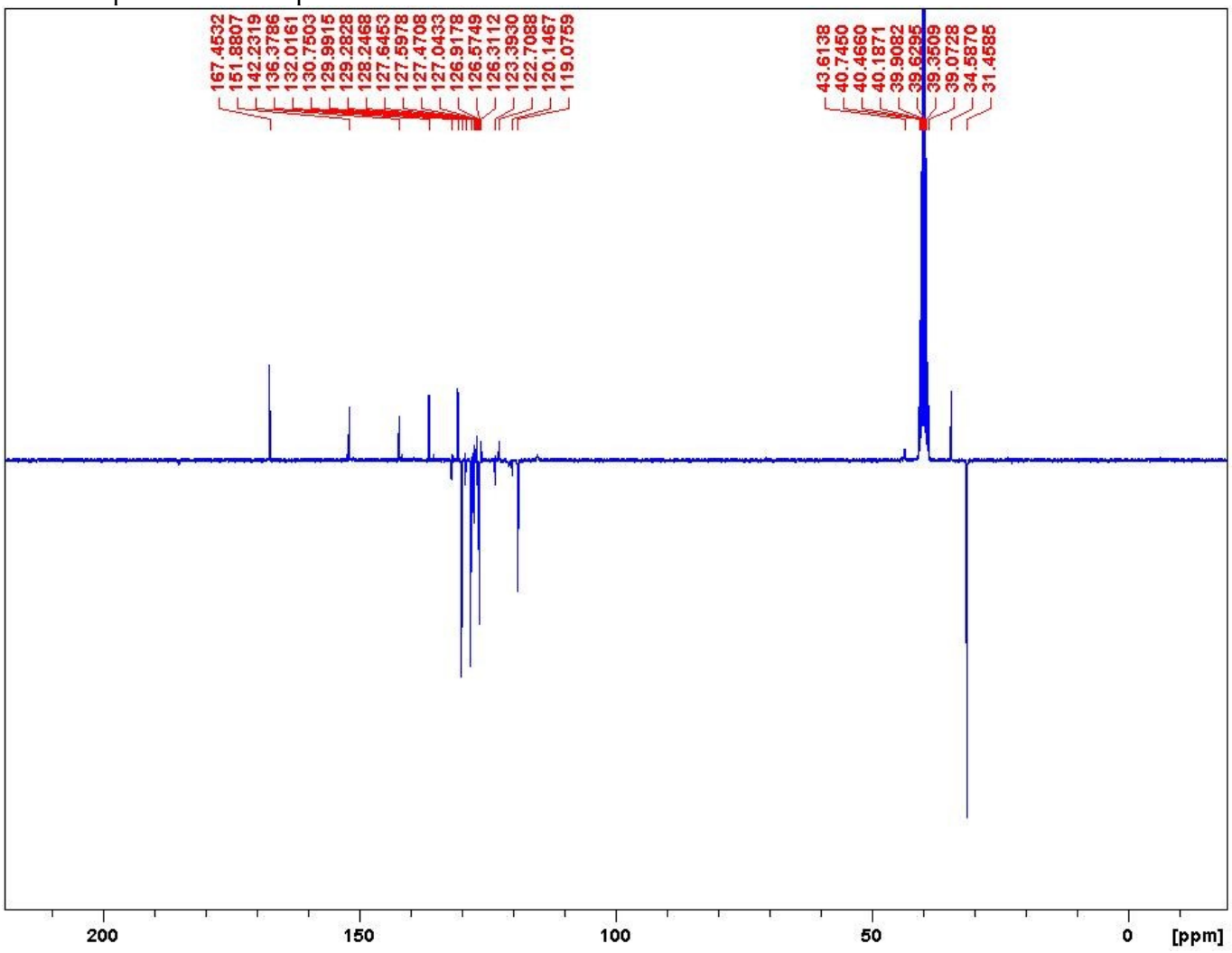
^{1}H NMR spectrum of compound **4**



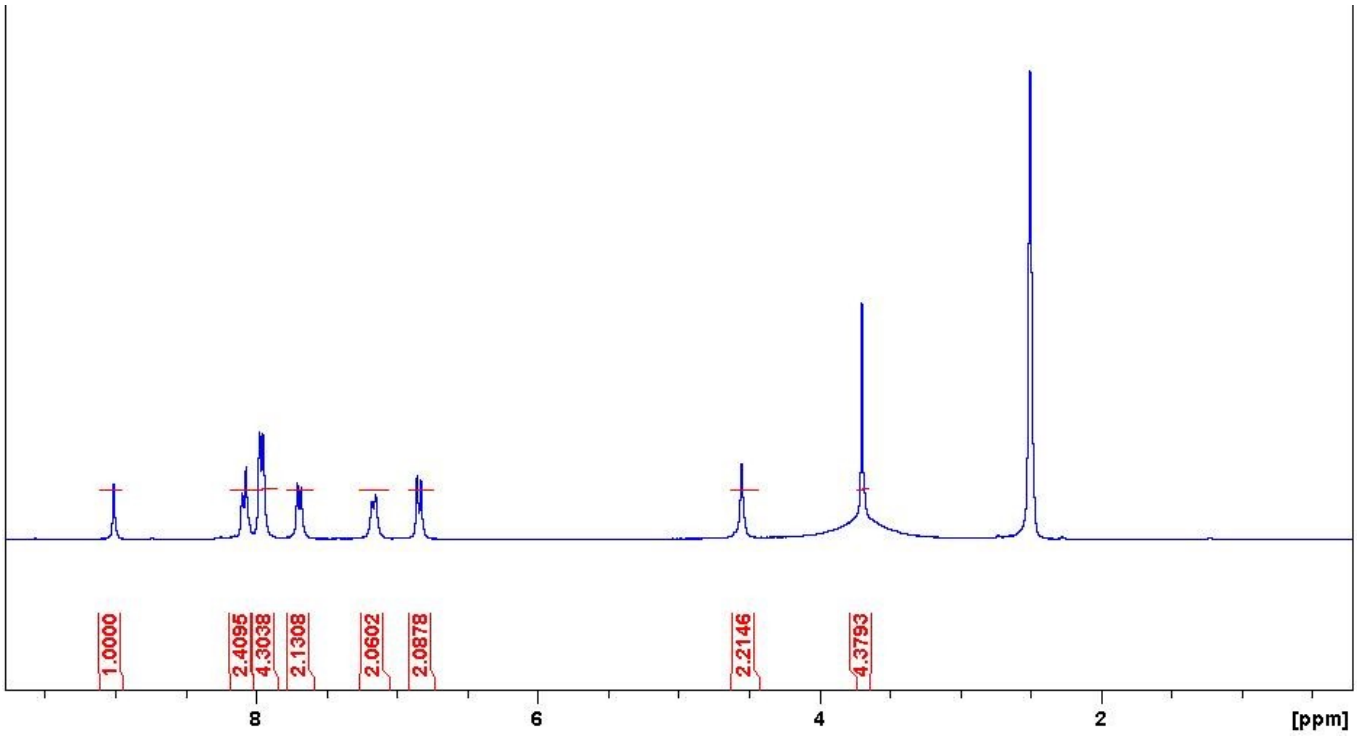
^{13}C NMR spectrum of compound **4**



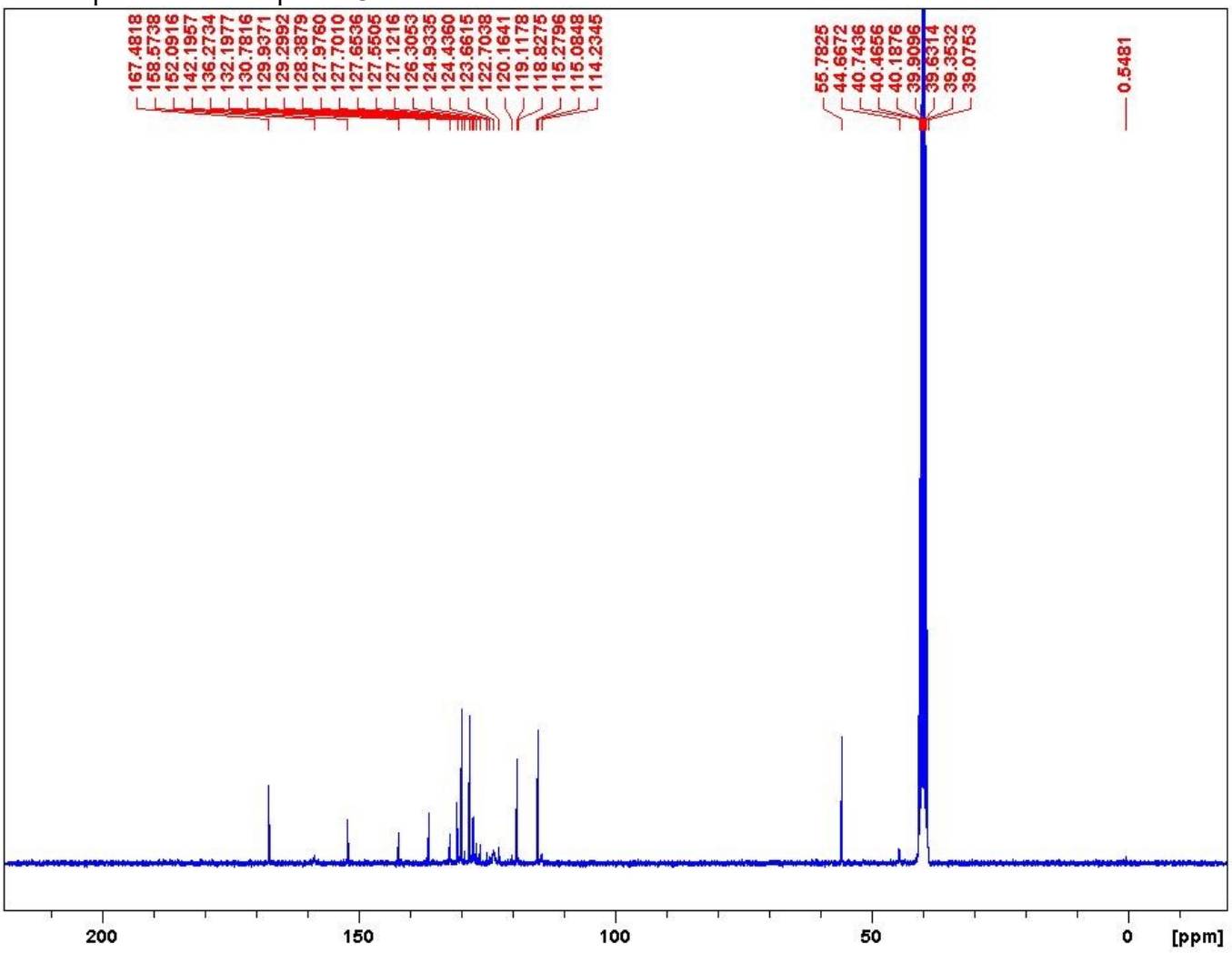
APT NMR spectrum of compound **4**



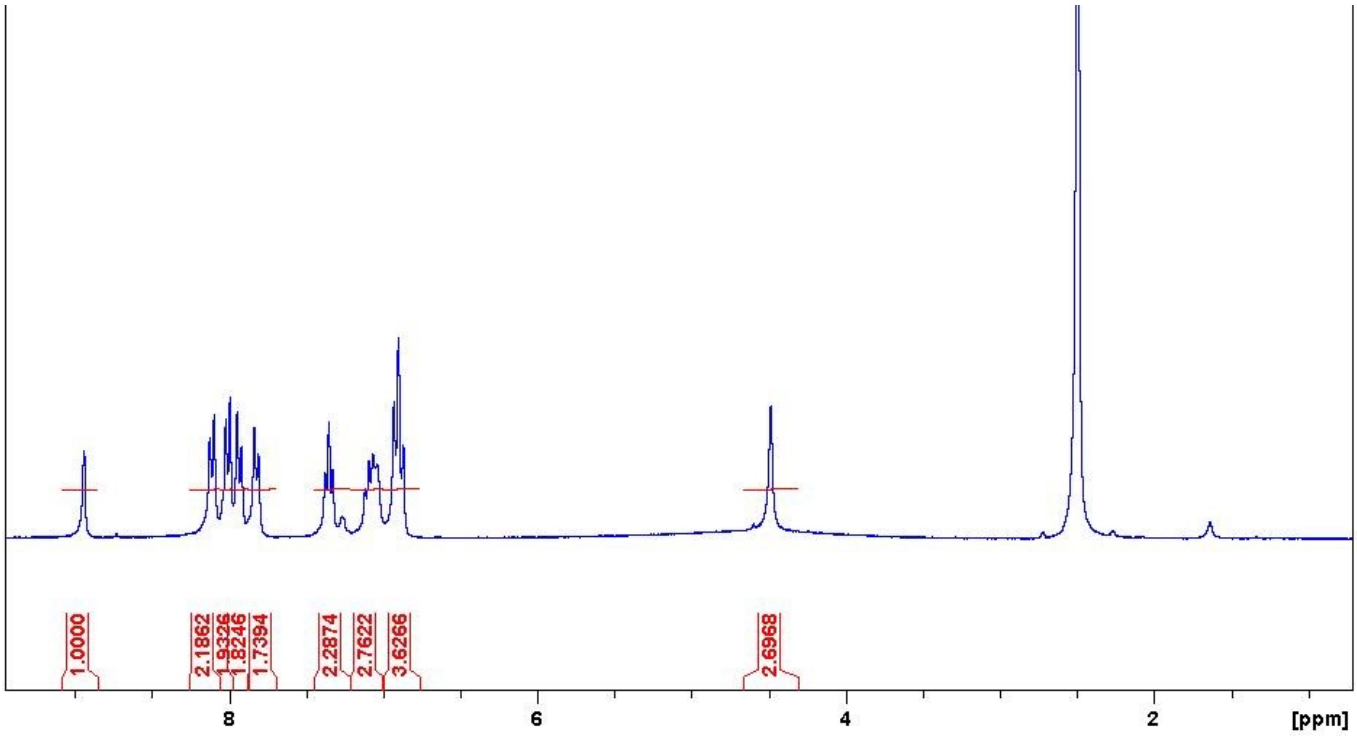
^{1}H NMR spectrum of compound **5**



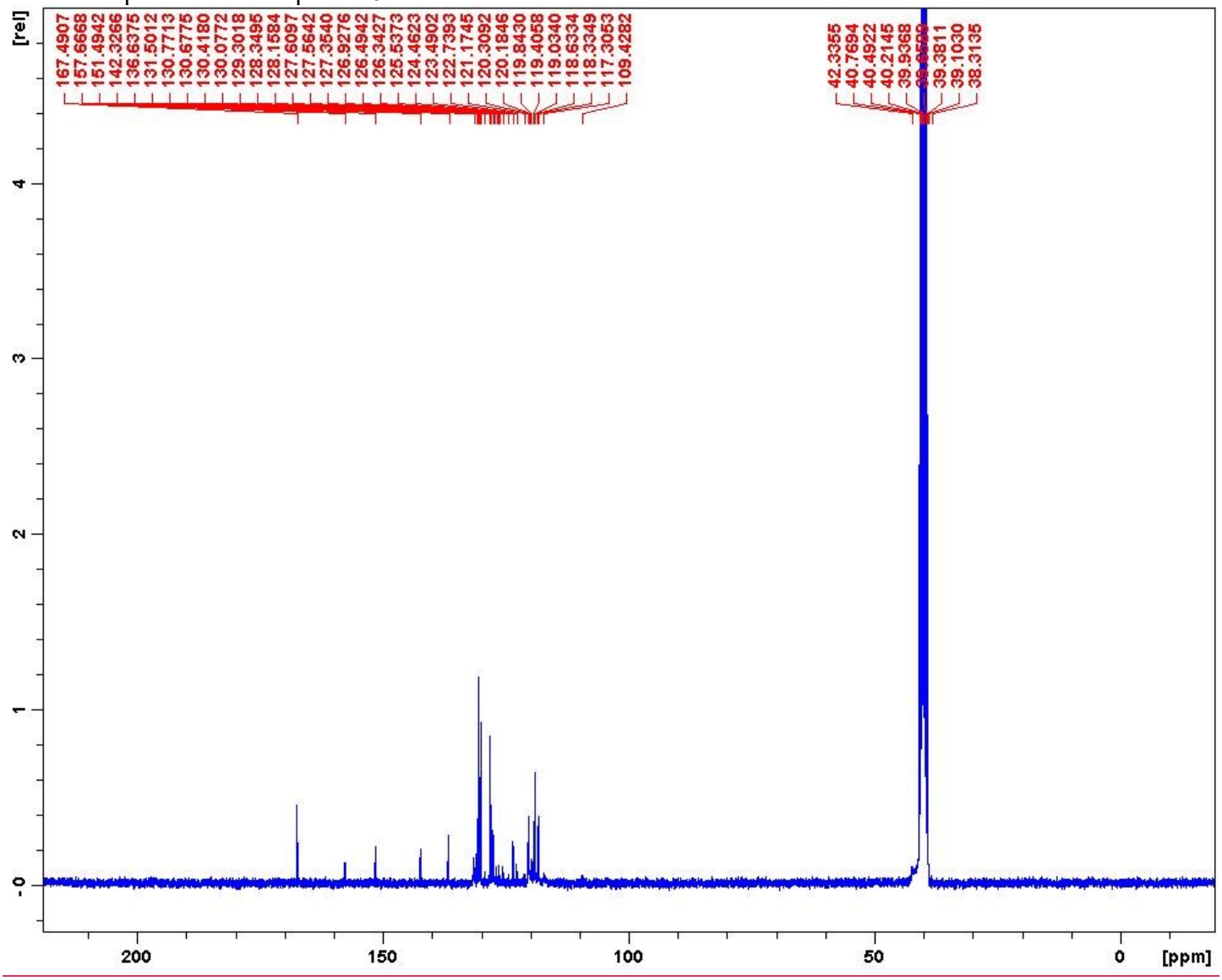
^{13}C NMR spectrum of compound **5**



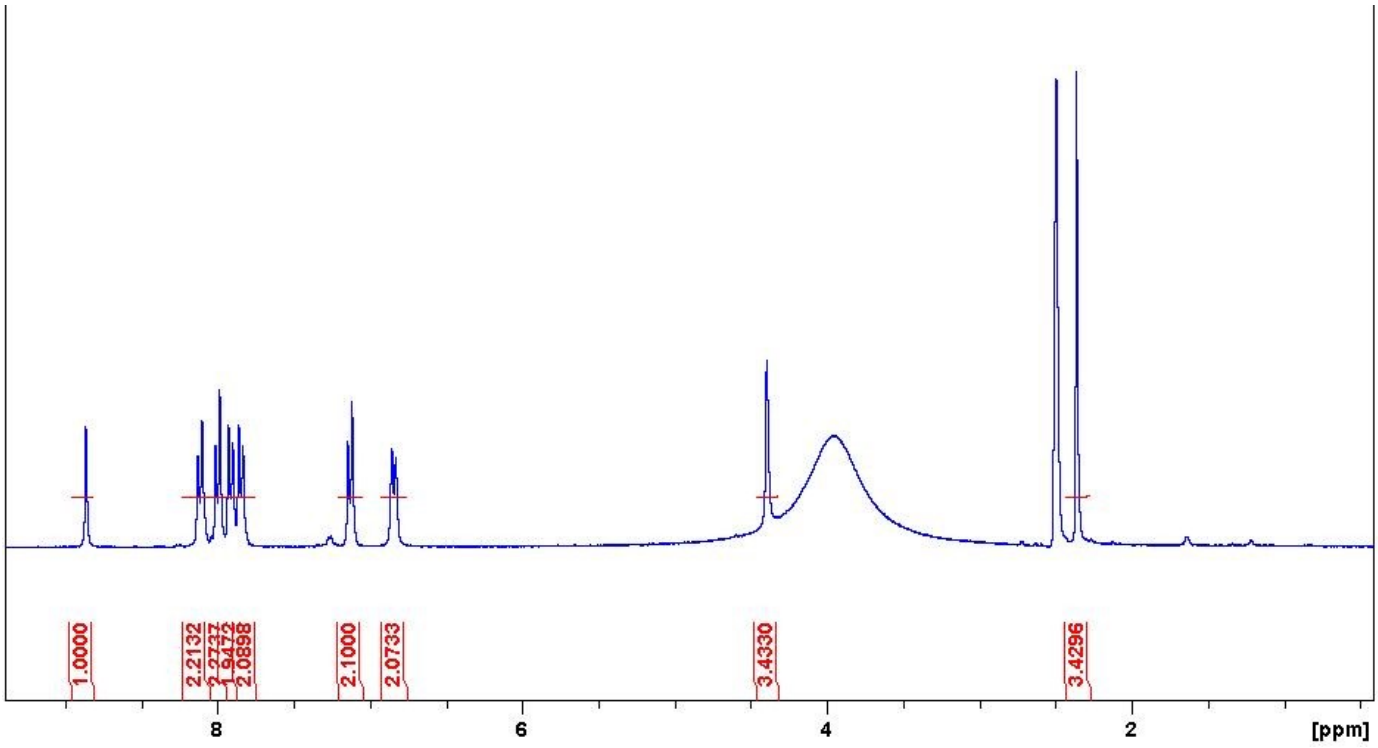
^{1}H NMR spectrum of compound **6**



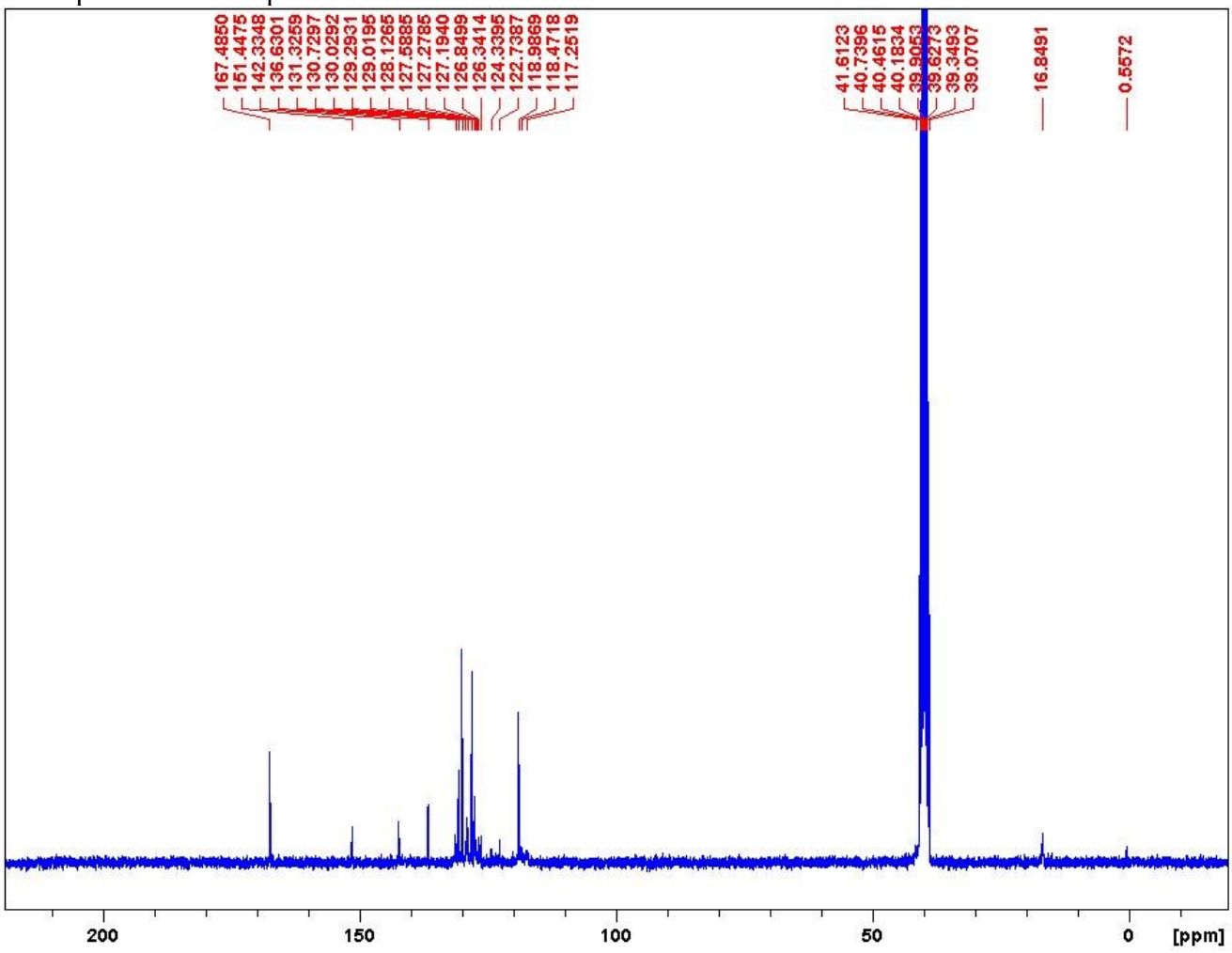
^{13}C NMR spectrum of compound **6**



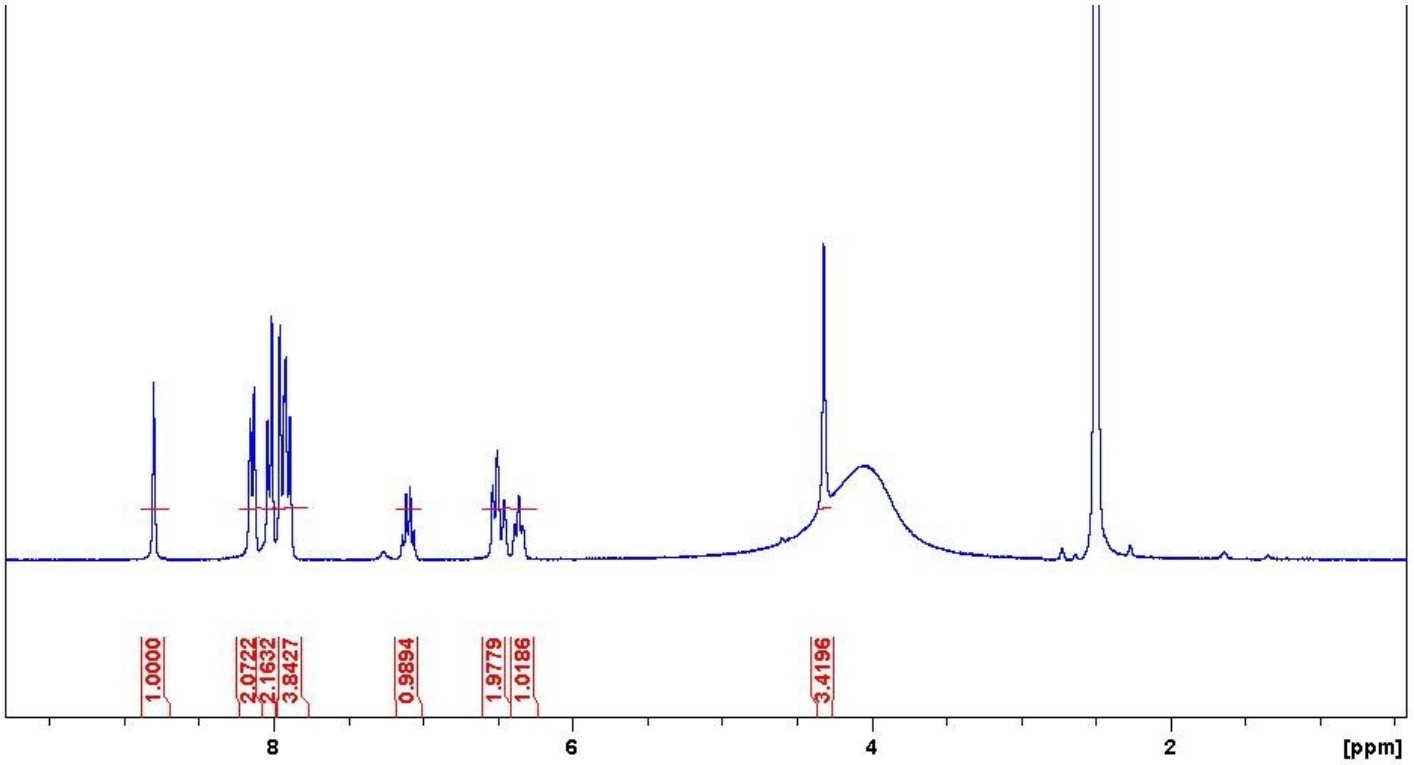
^{1}H NMR spectrum of compound **7**



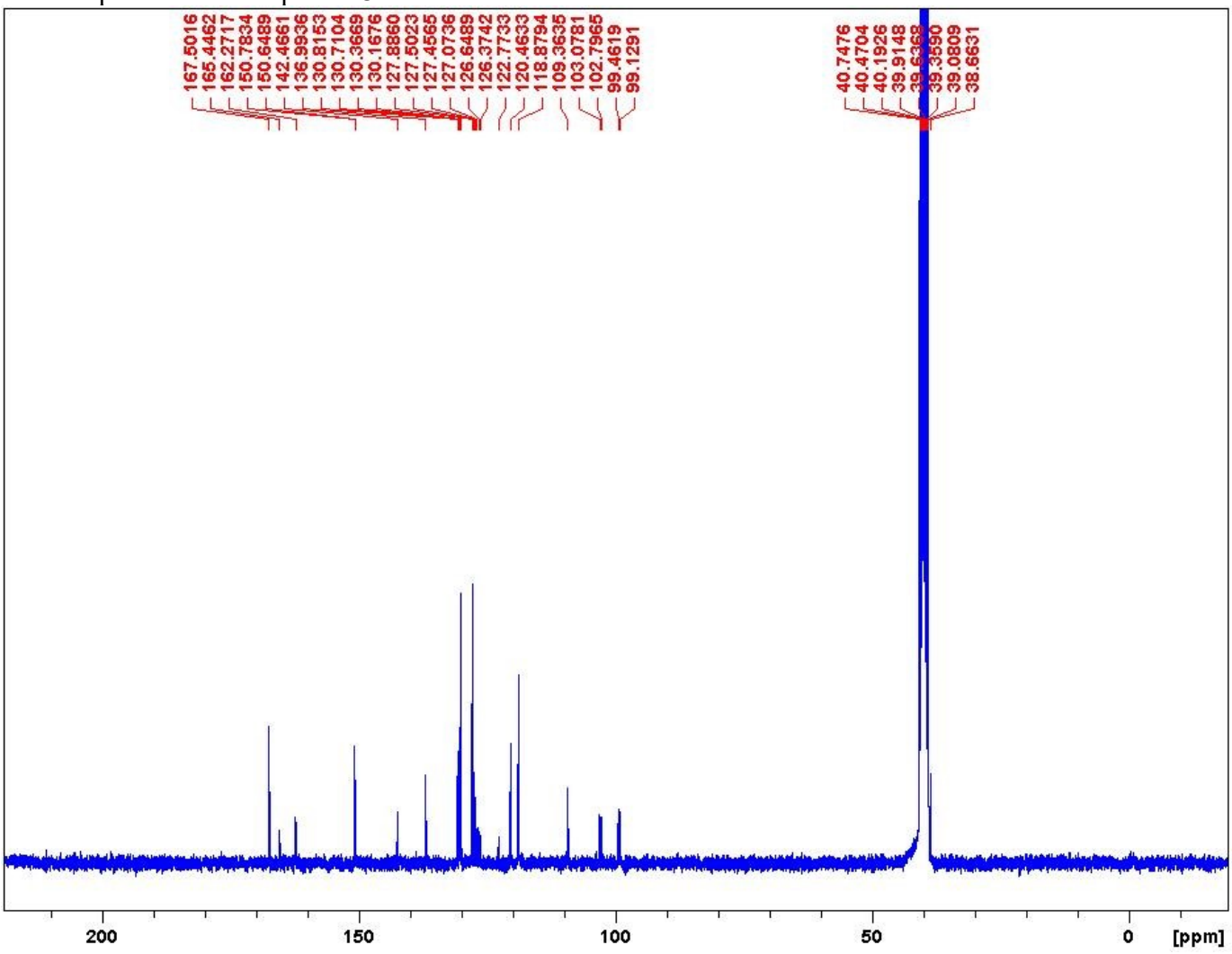
^{13}C NMR spectrum of compound **7**



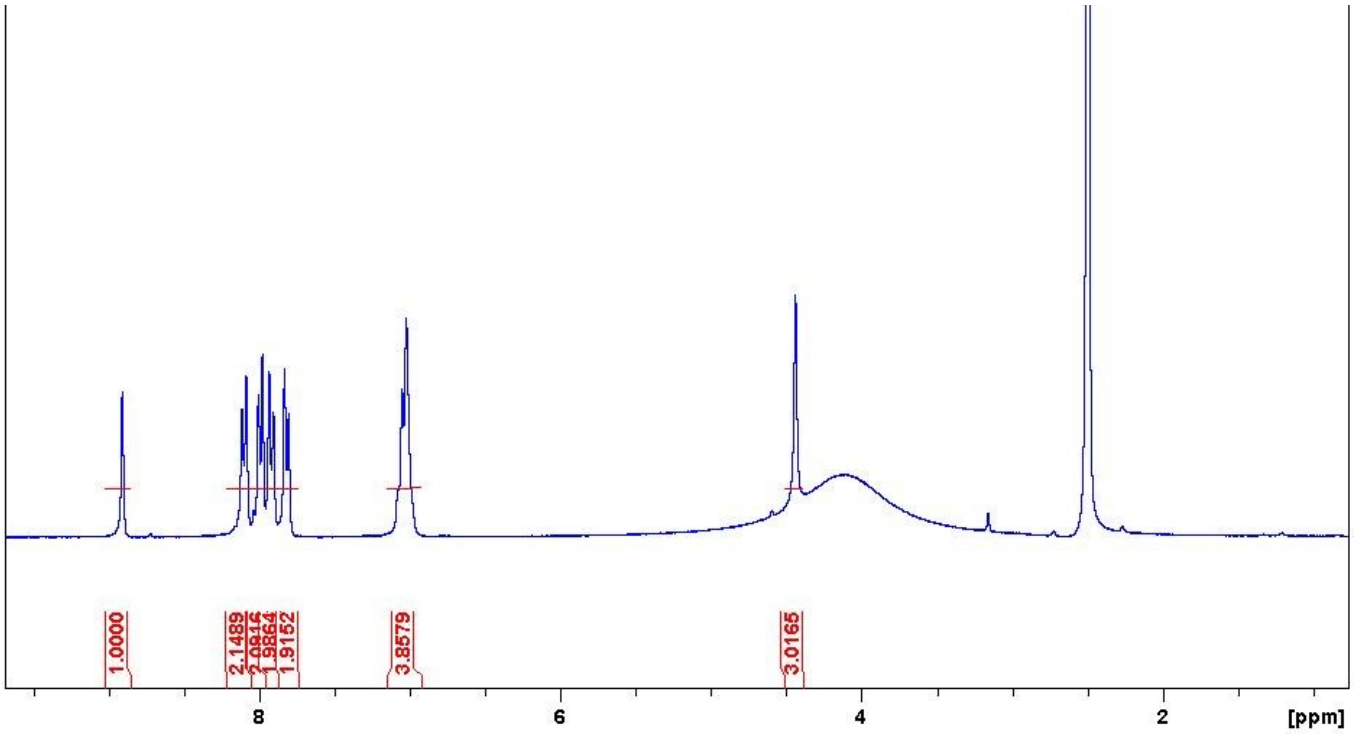
^{1}H NMR spectrum of compound **8**



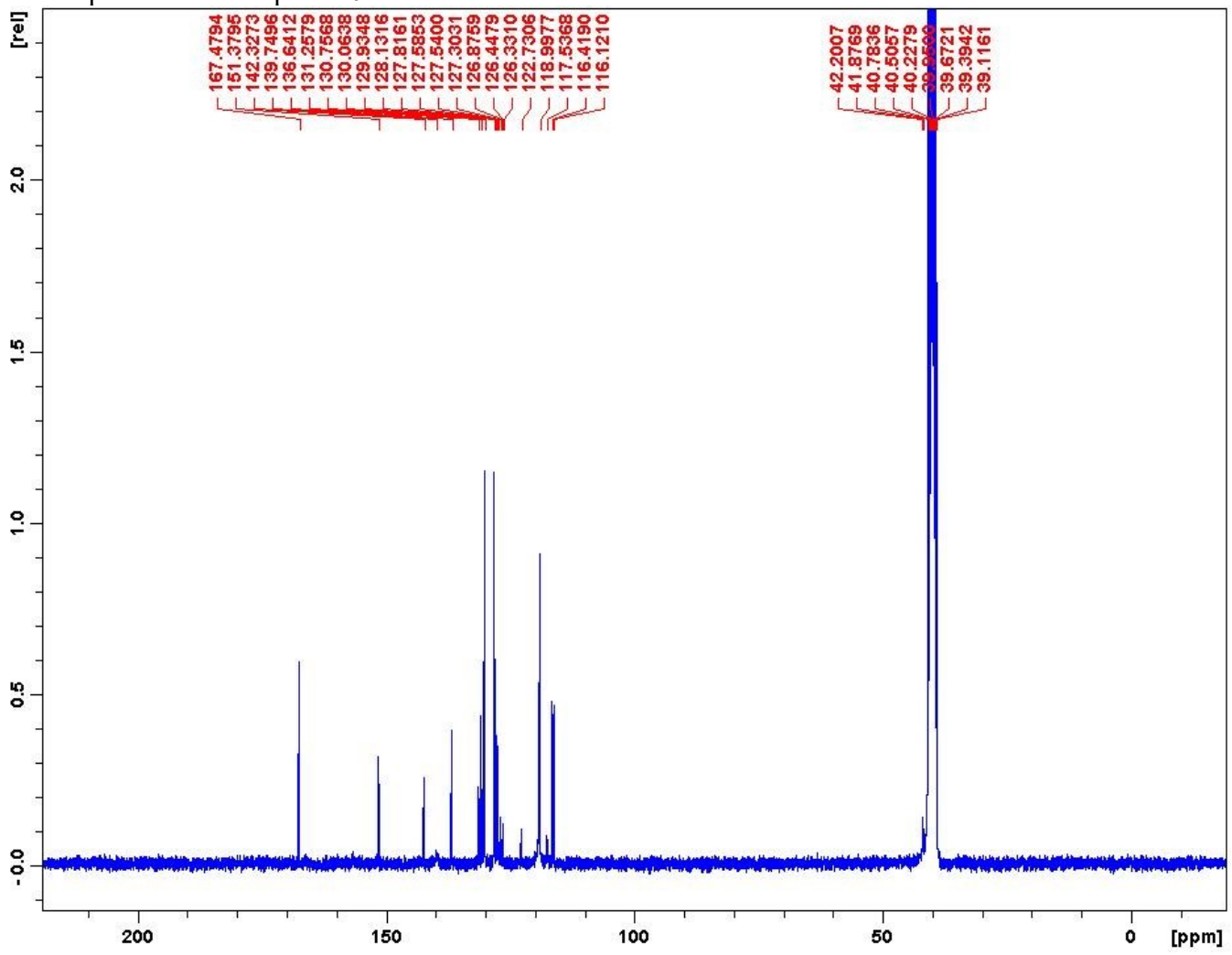
^{13}C NMR spectrum of compound **8**



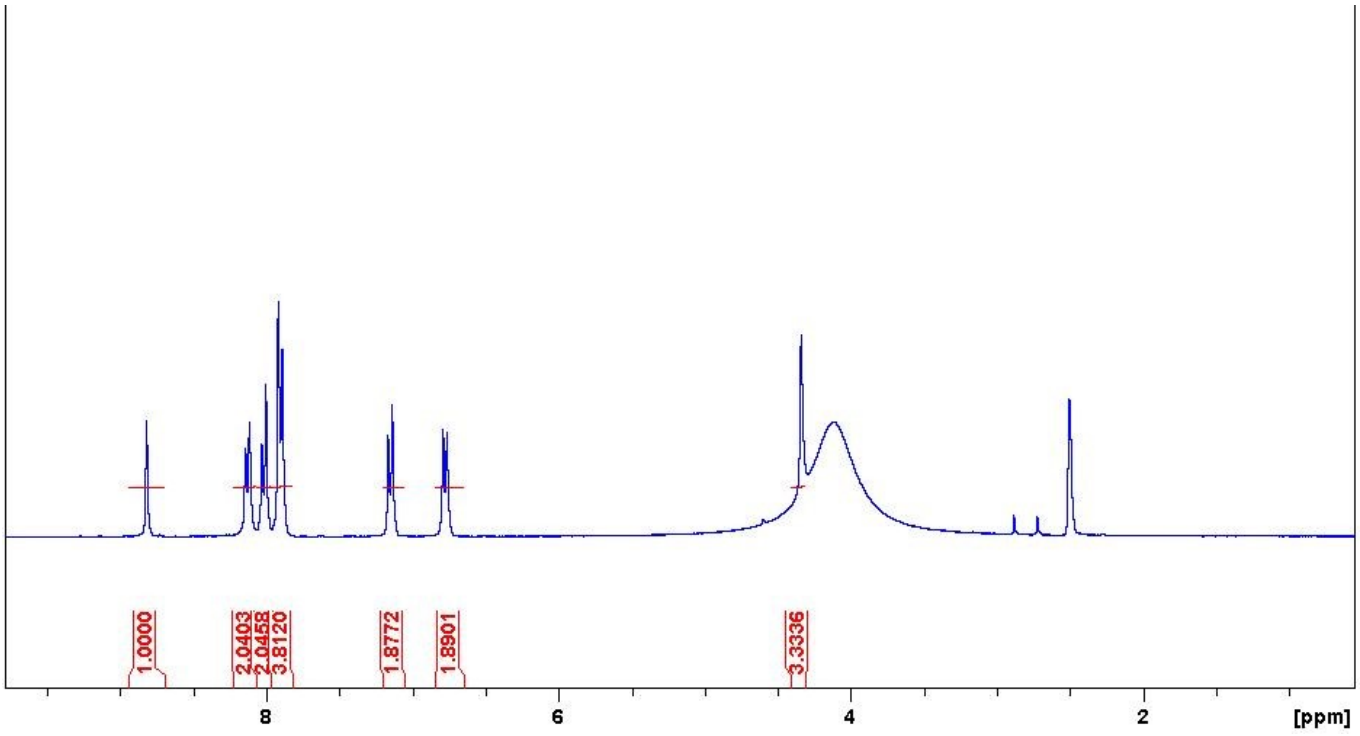
^{1}H NMR spectrum of compound **9**



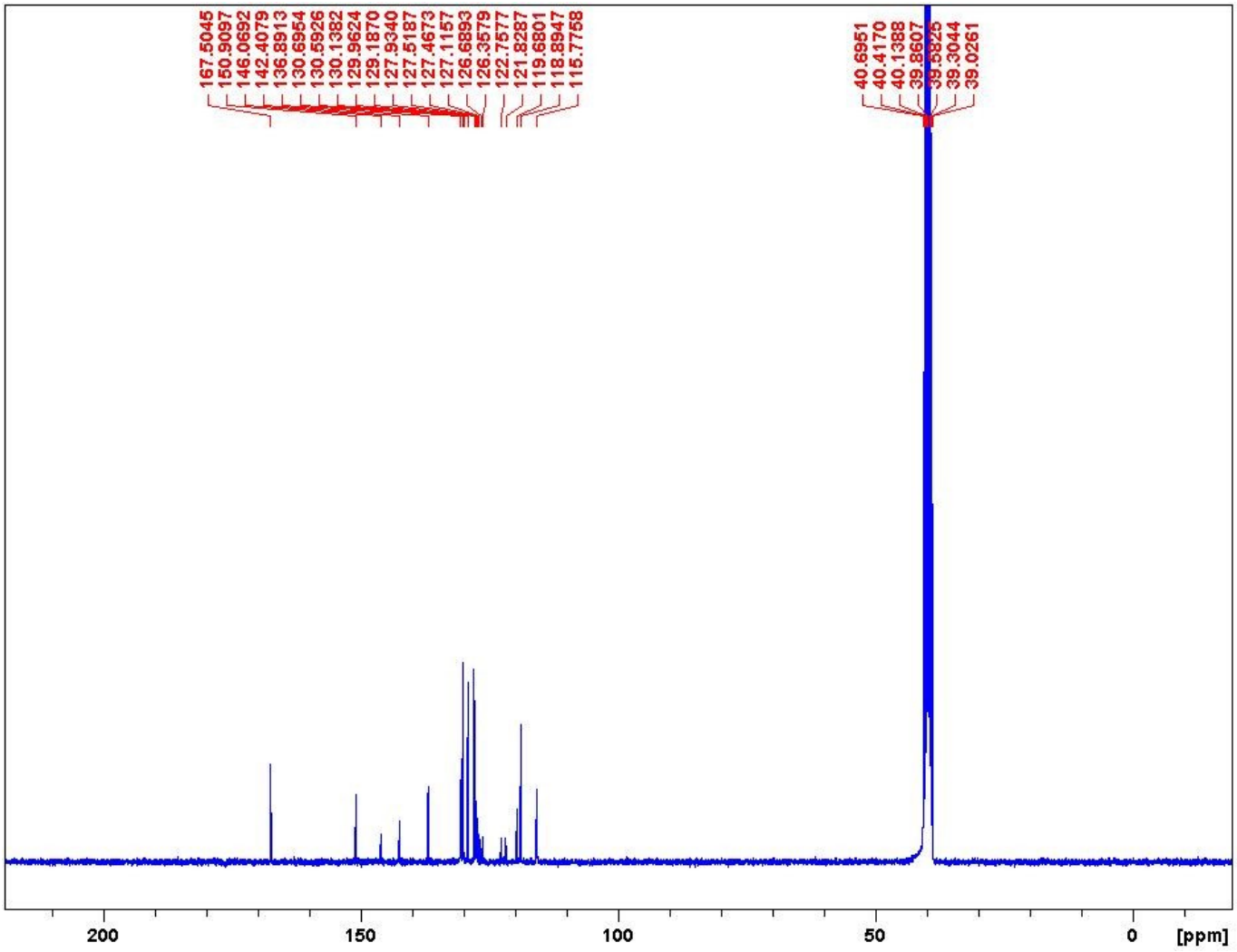
^{13}C NMR spectrum of compound **9**



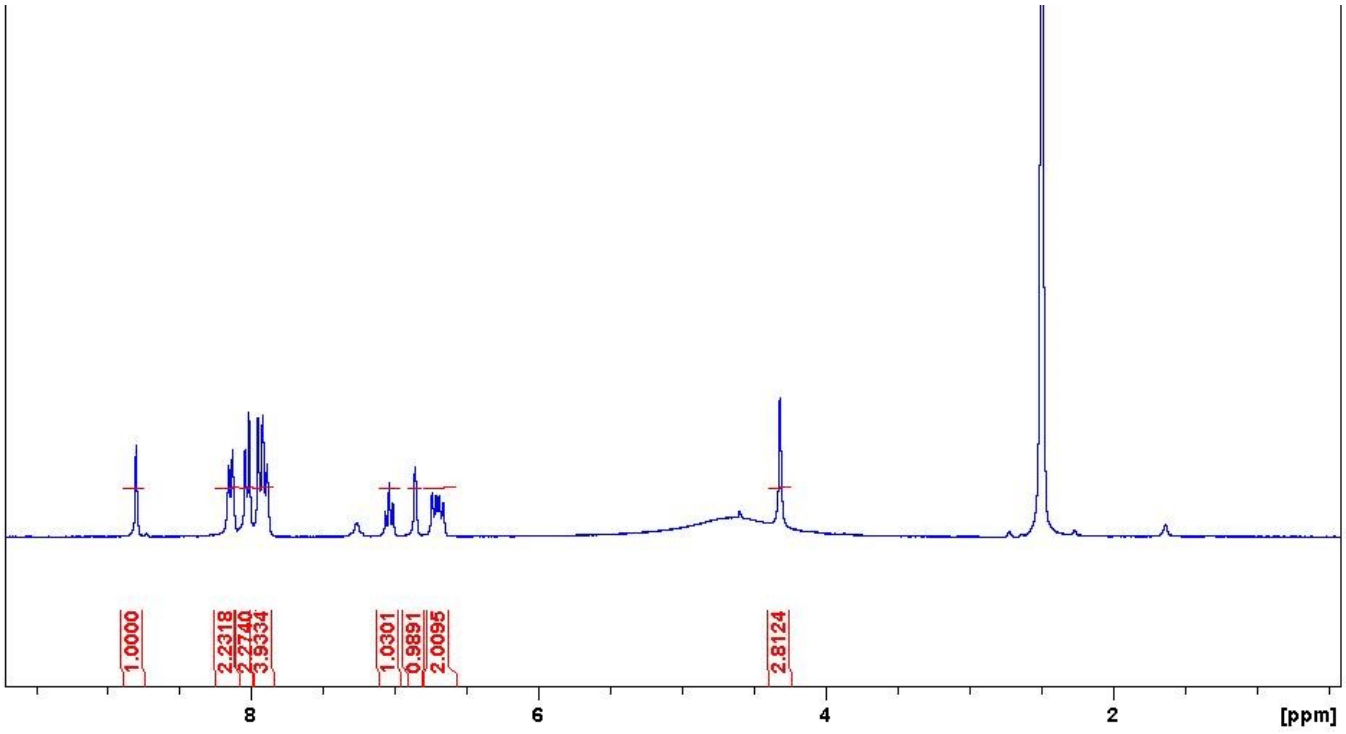
^{1}H NMR spectrum of compound **10**



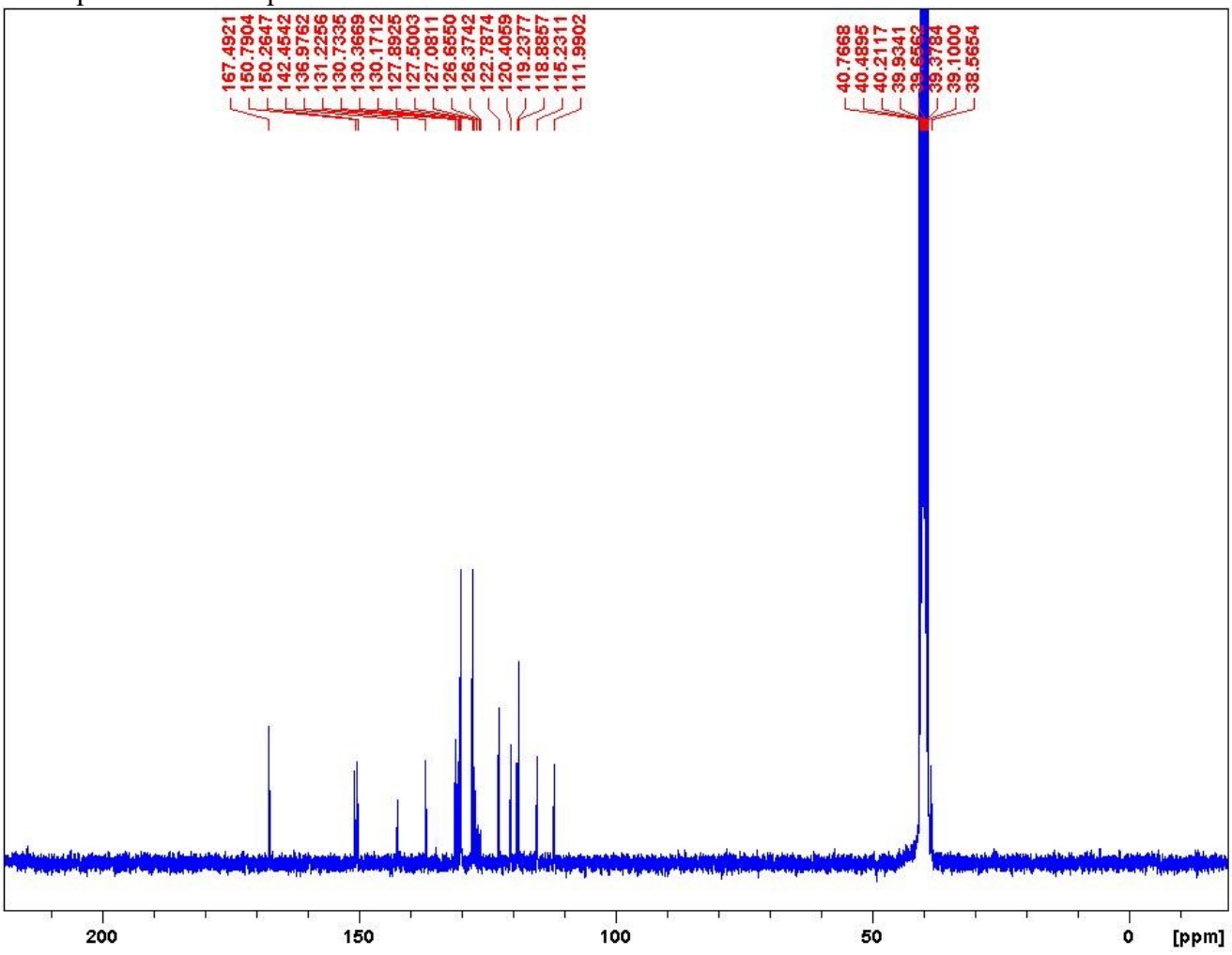
^{13}C NMR spectrum of compound **10**



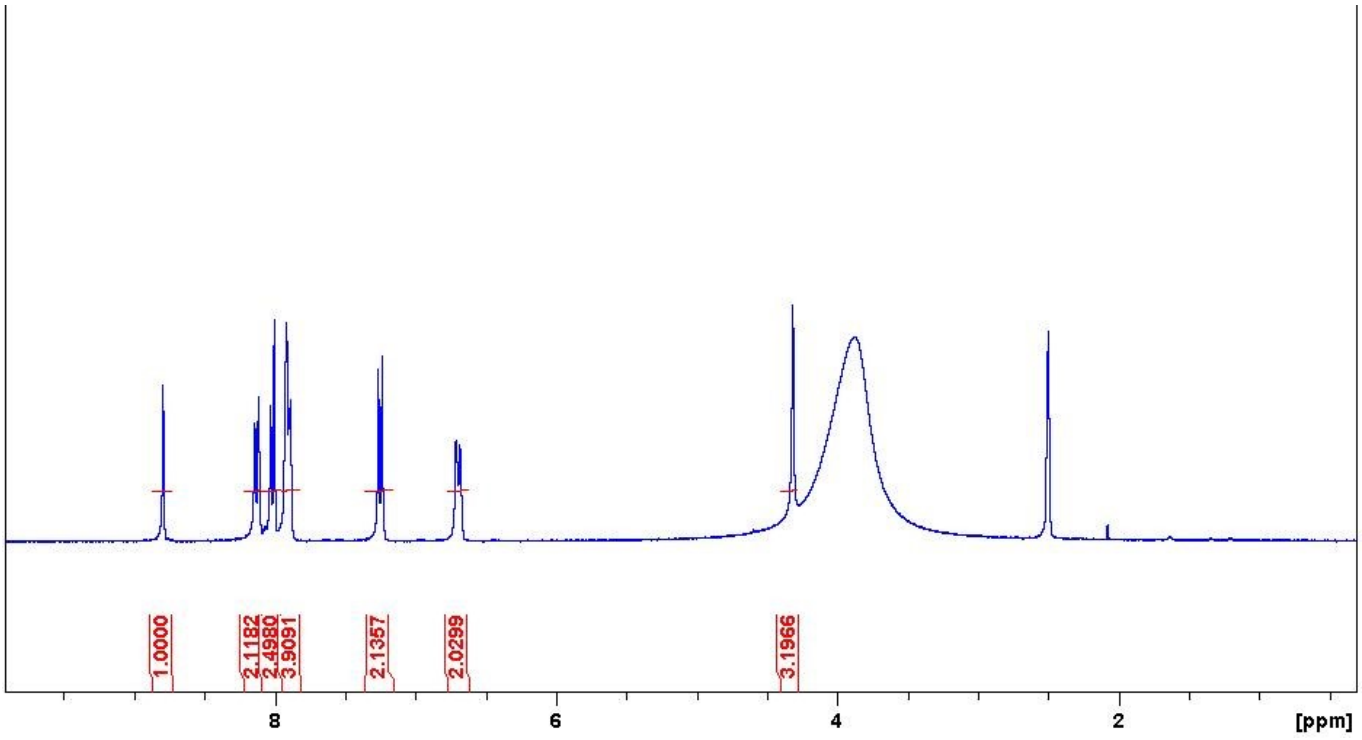
^{1}H NMR spectrum of compound **11**



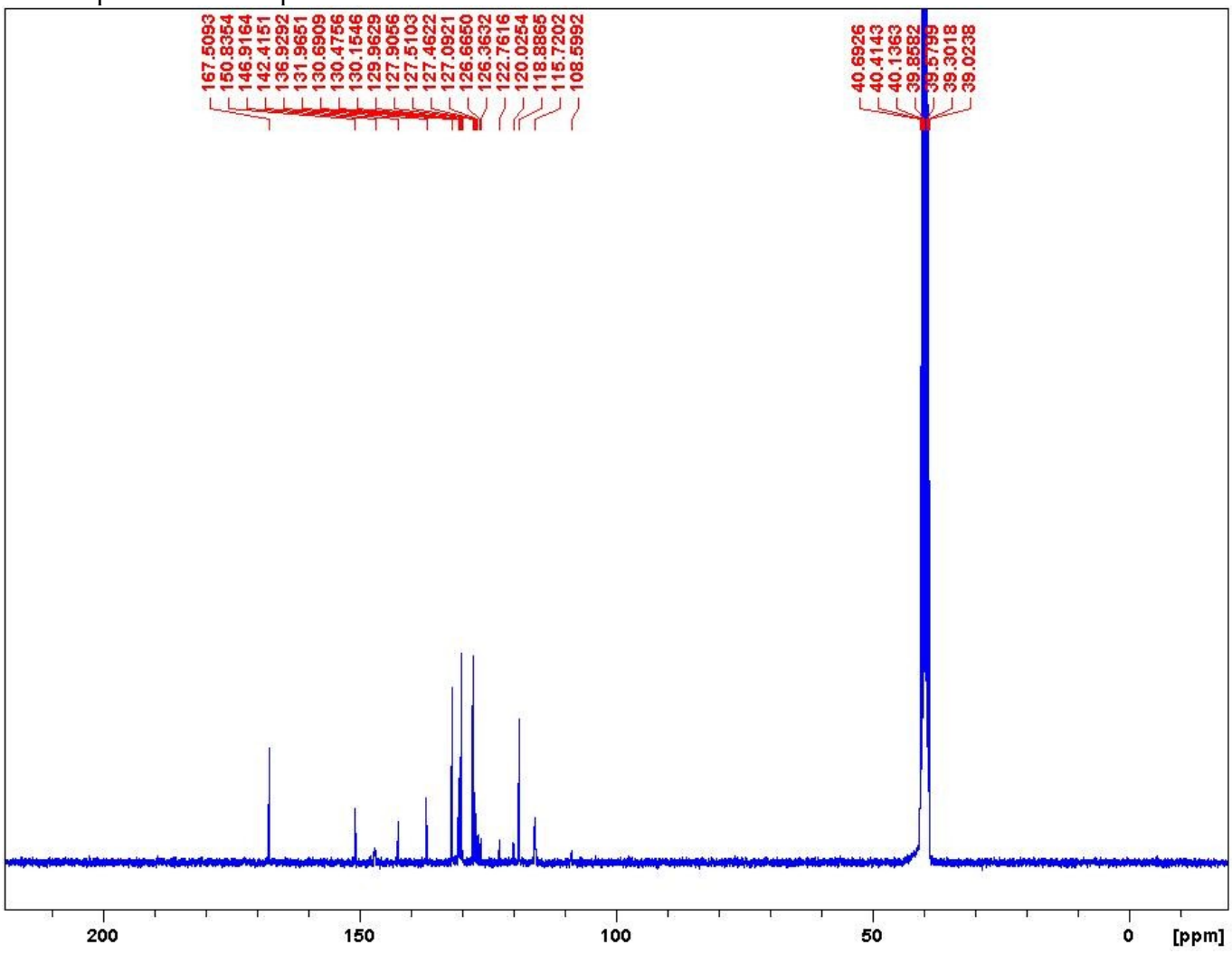
^{13}C NMR spectrum of compound **11**



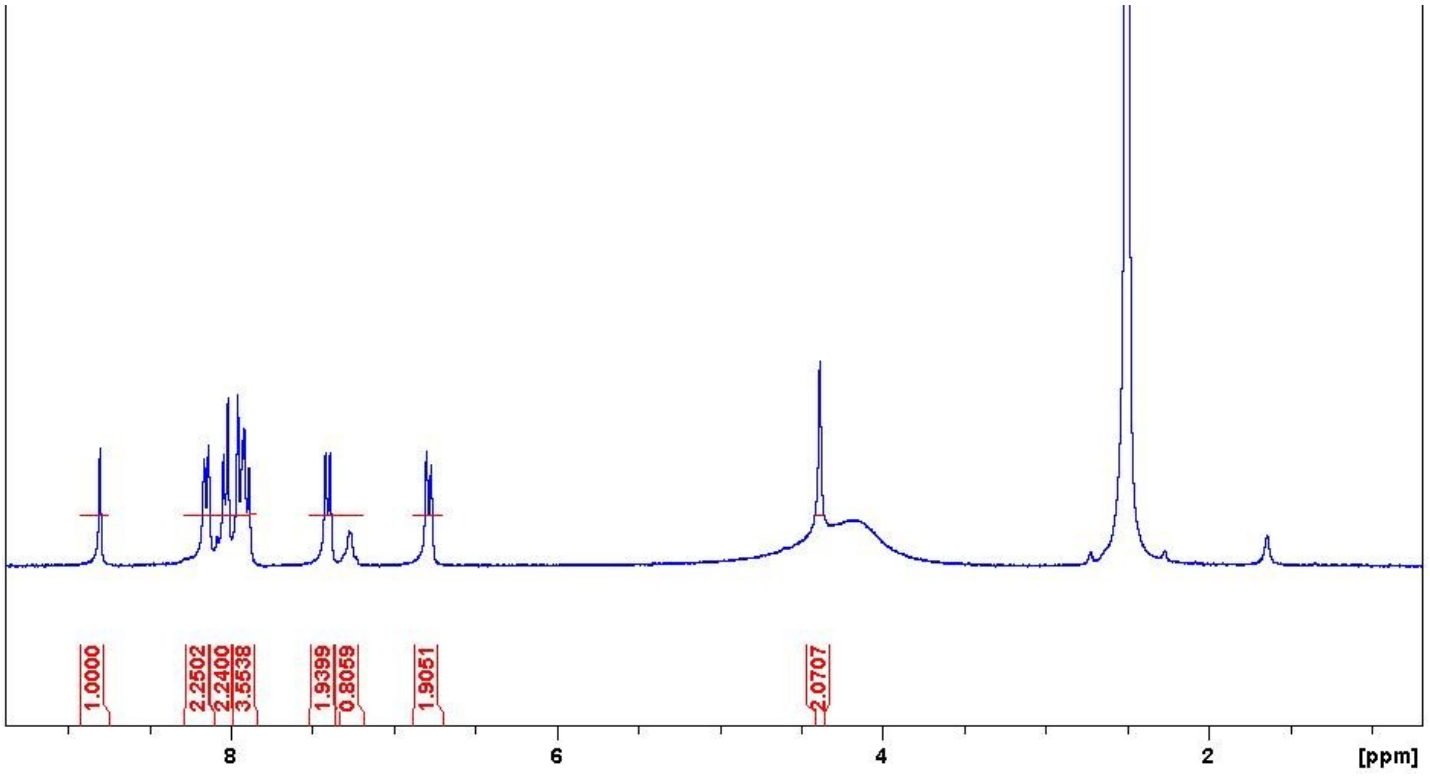
^{1}H NMR spectrum of compound **12**



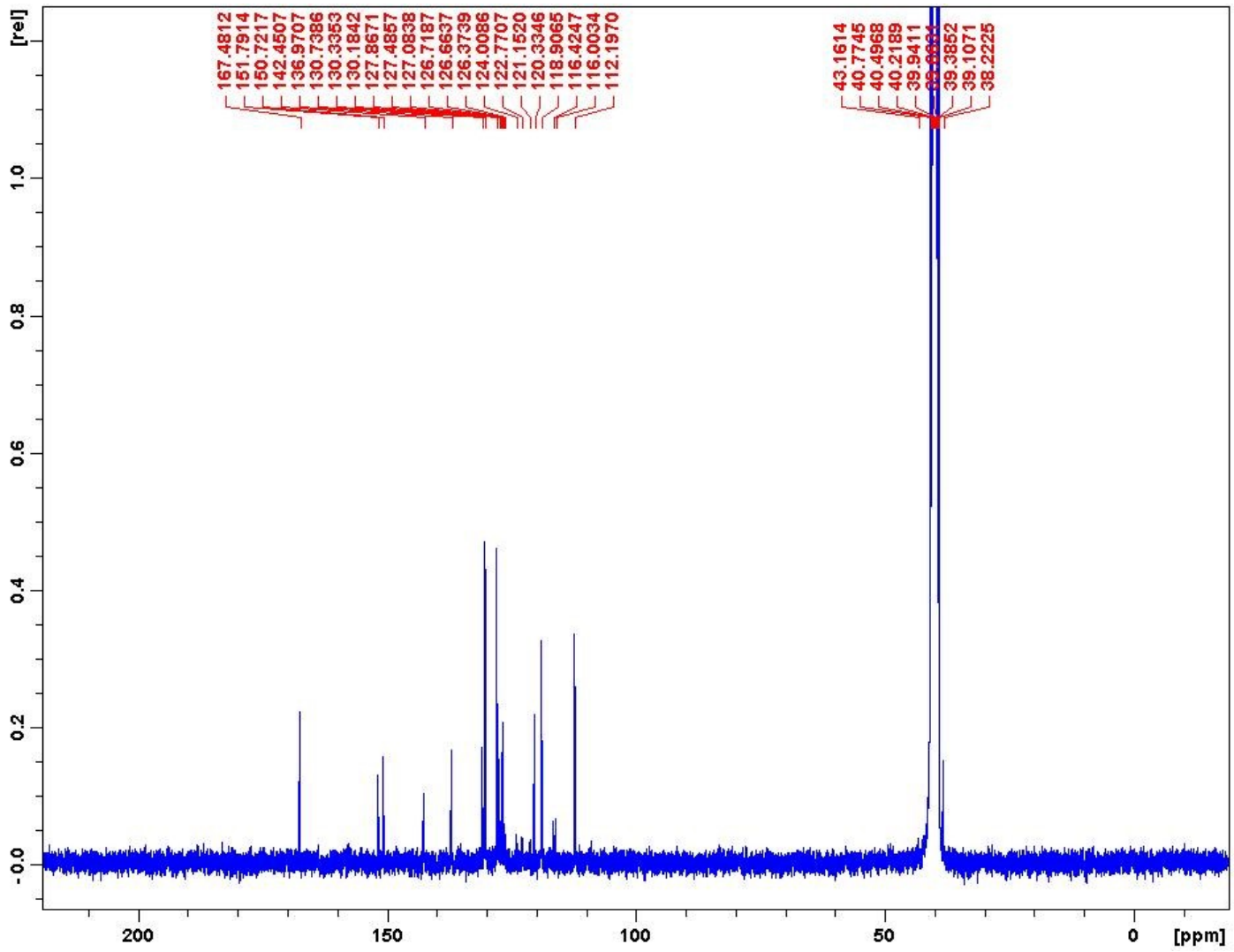
^{13}C NMR spectrum of compound **12**



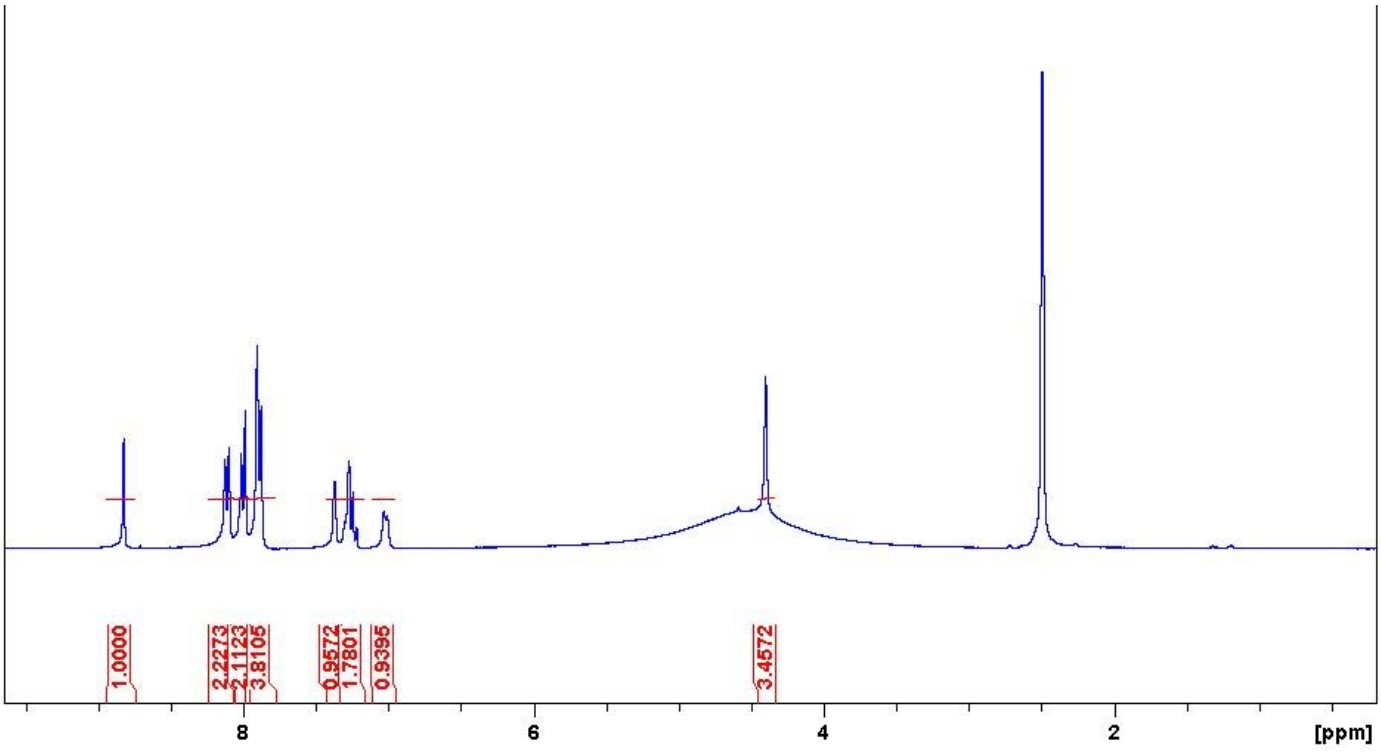
^{1}H NMR spectrum of compound **13**



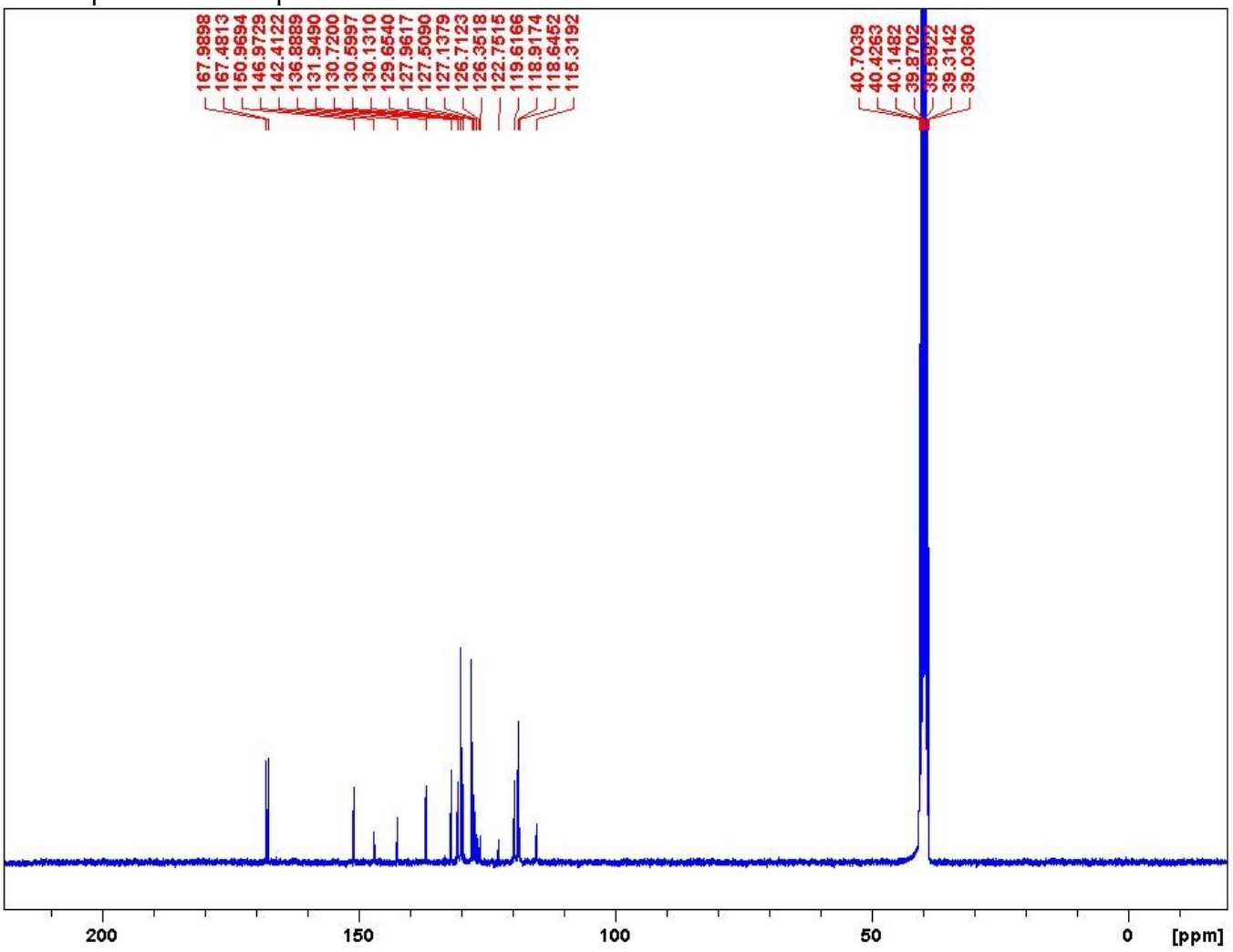
^{13}C NMR spectrum of compound **13**



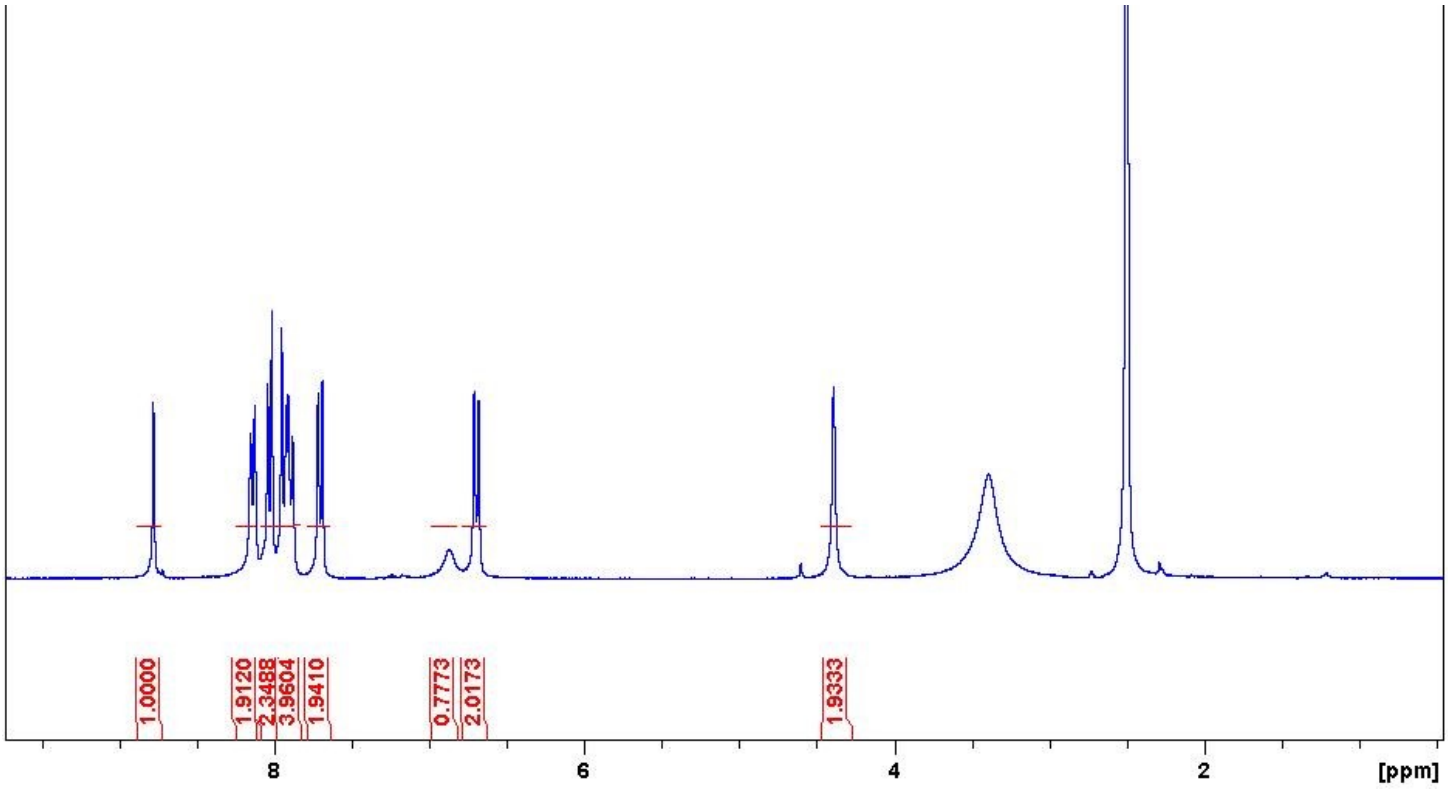
^{1}H NMR spectrum of compound **14**



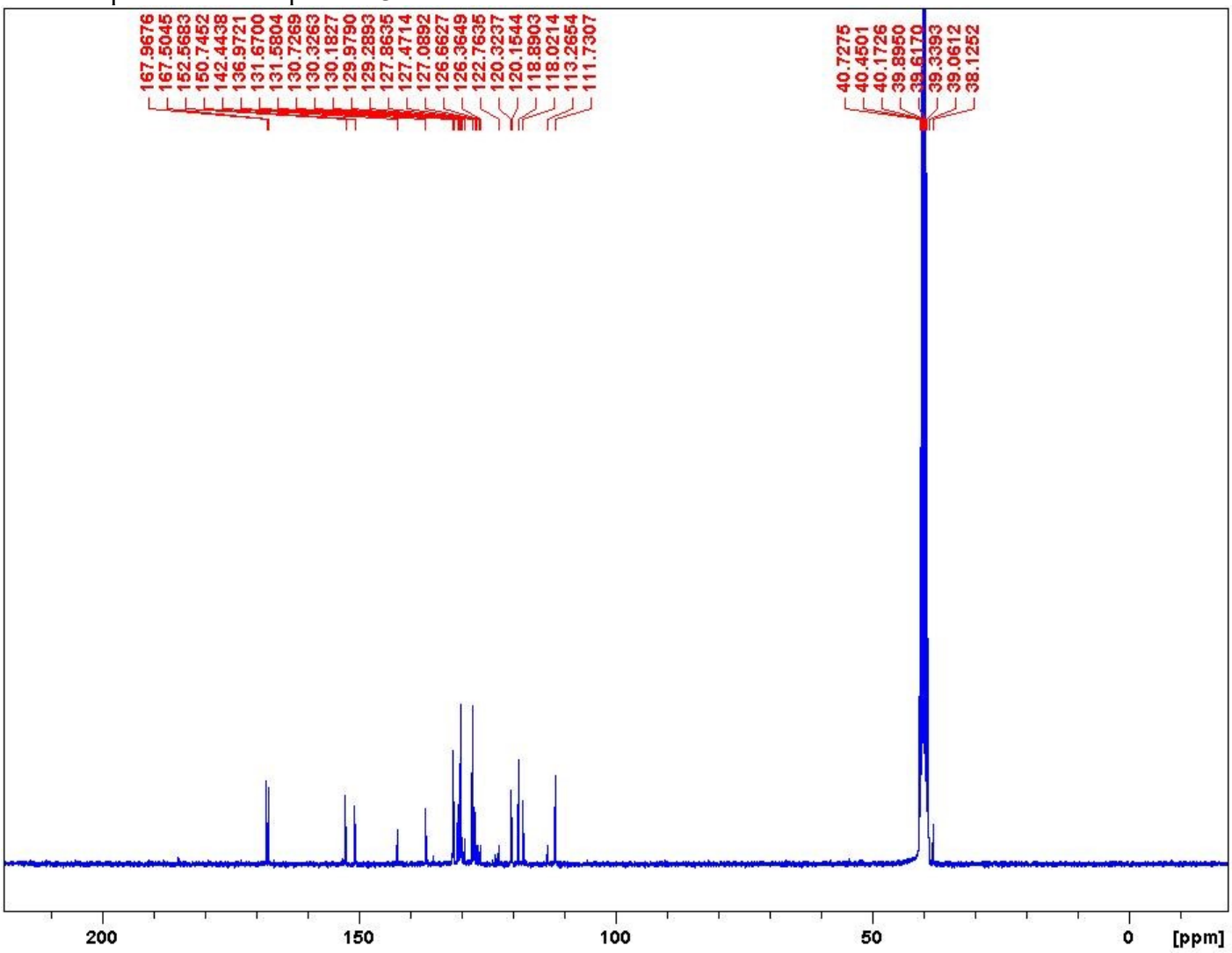
^{13}C NMR spectrum of compound **14**



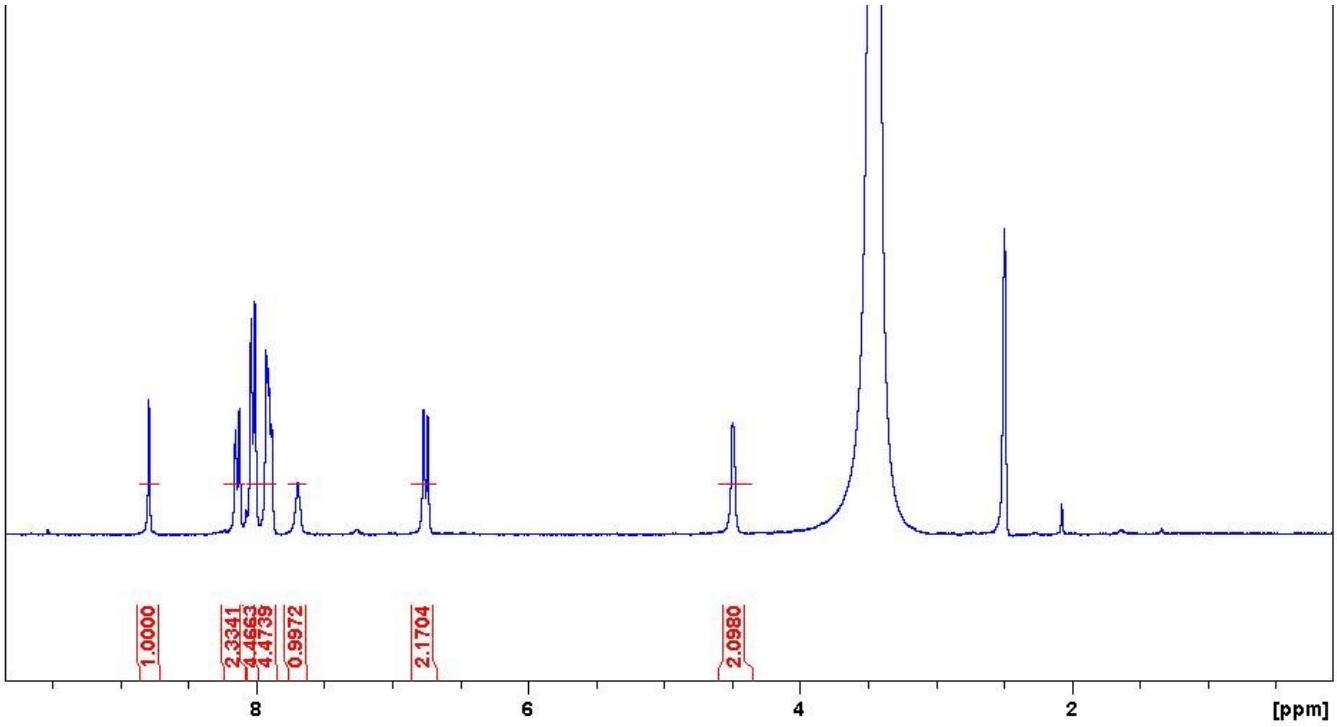
^{1}H NMR spectrum of compound **15**



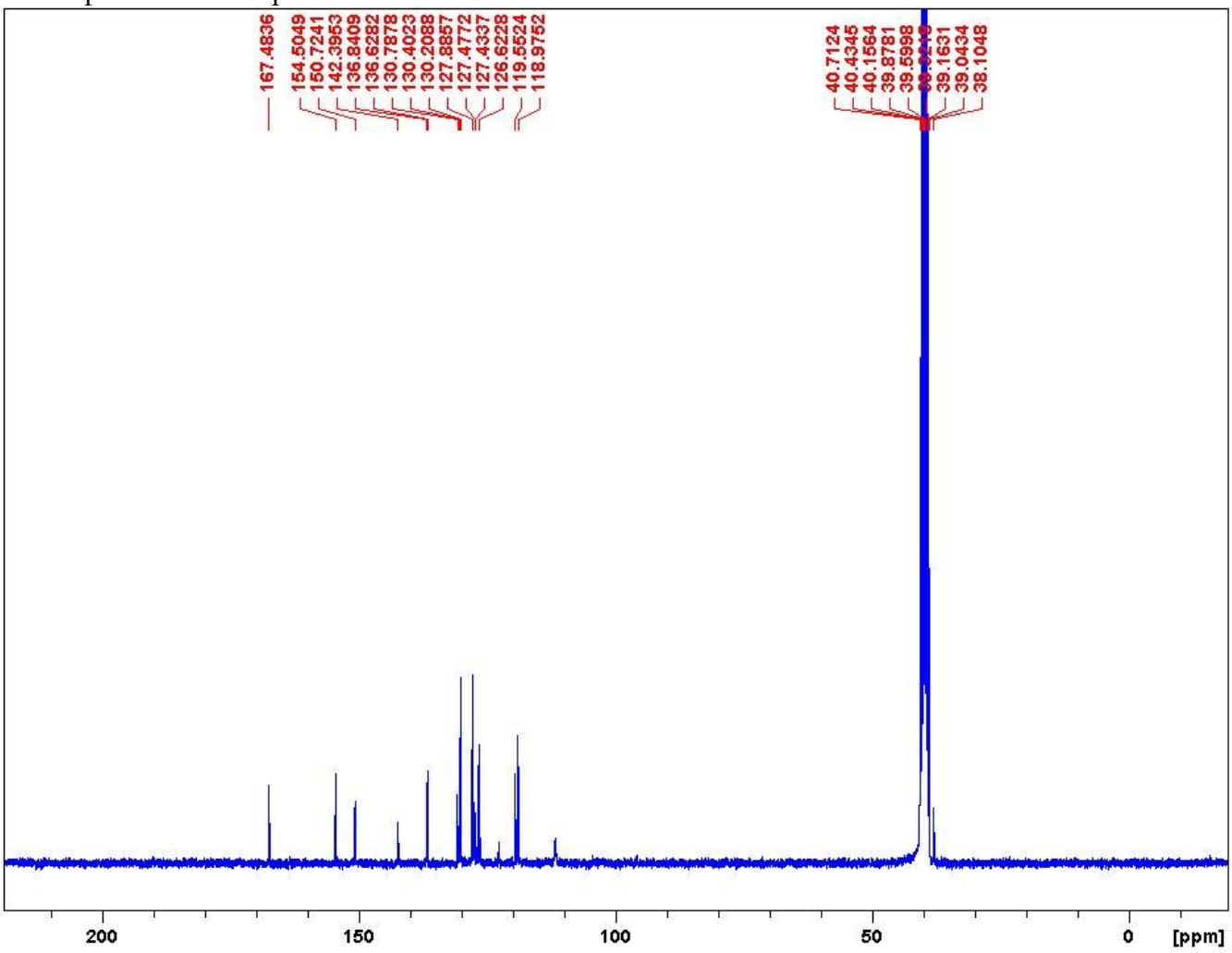
^{13}C NMR spectrum of compound **15**



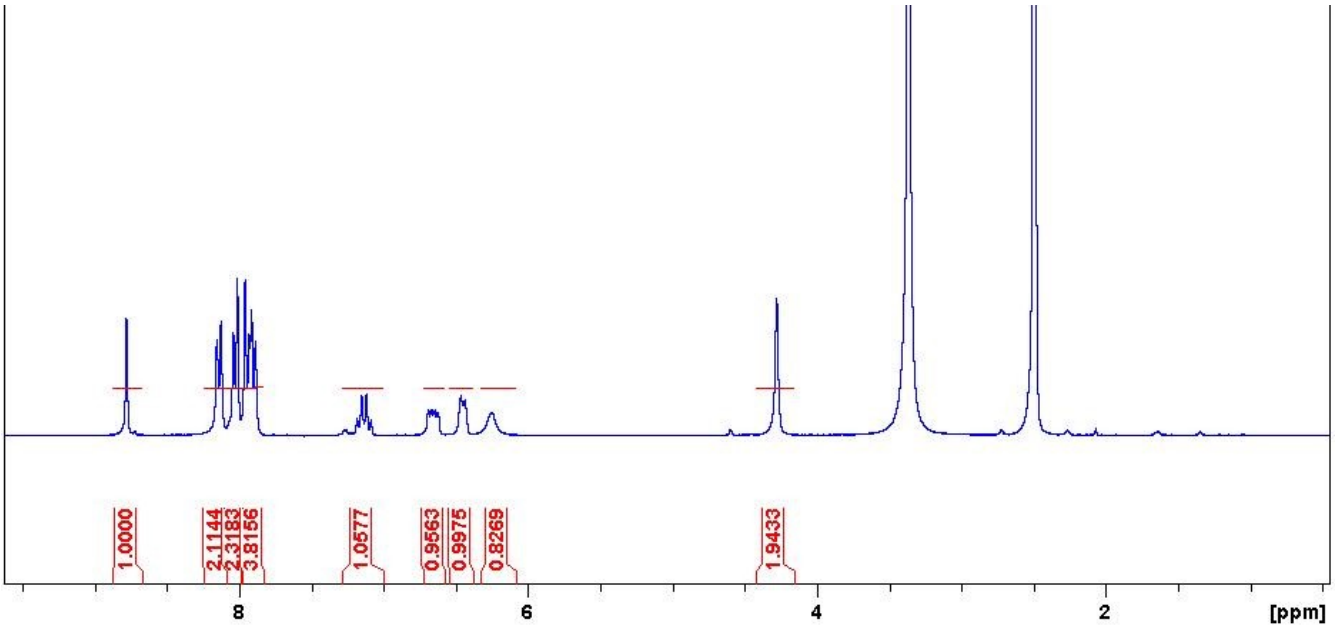
^{1}H NMR spectrum of compound **16**



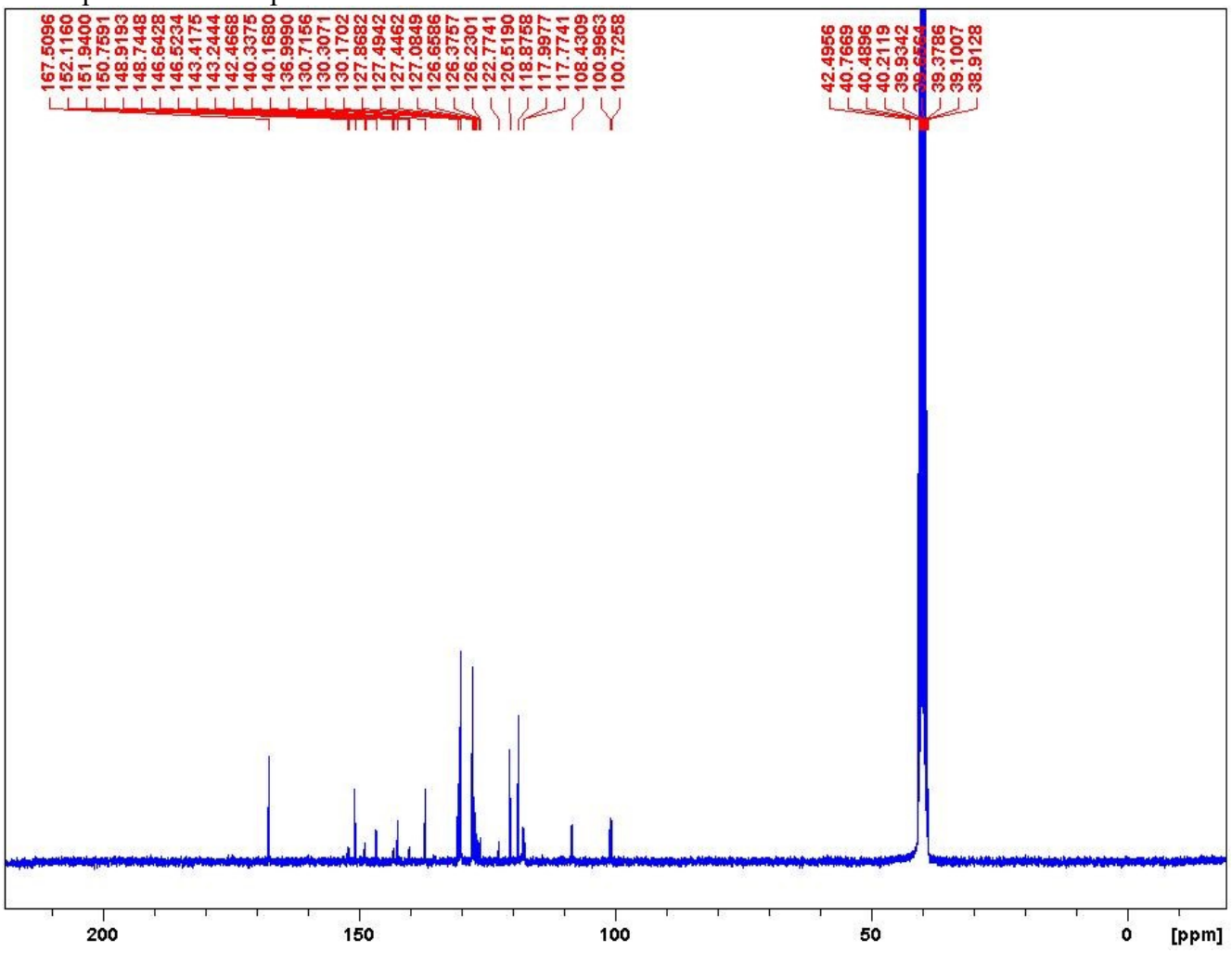
^{13}C NMR spectrum of compound **16**



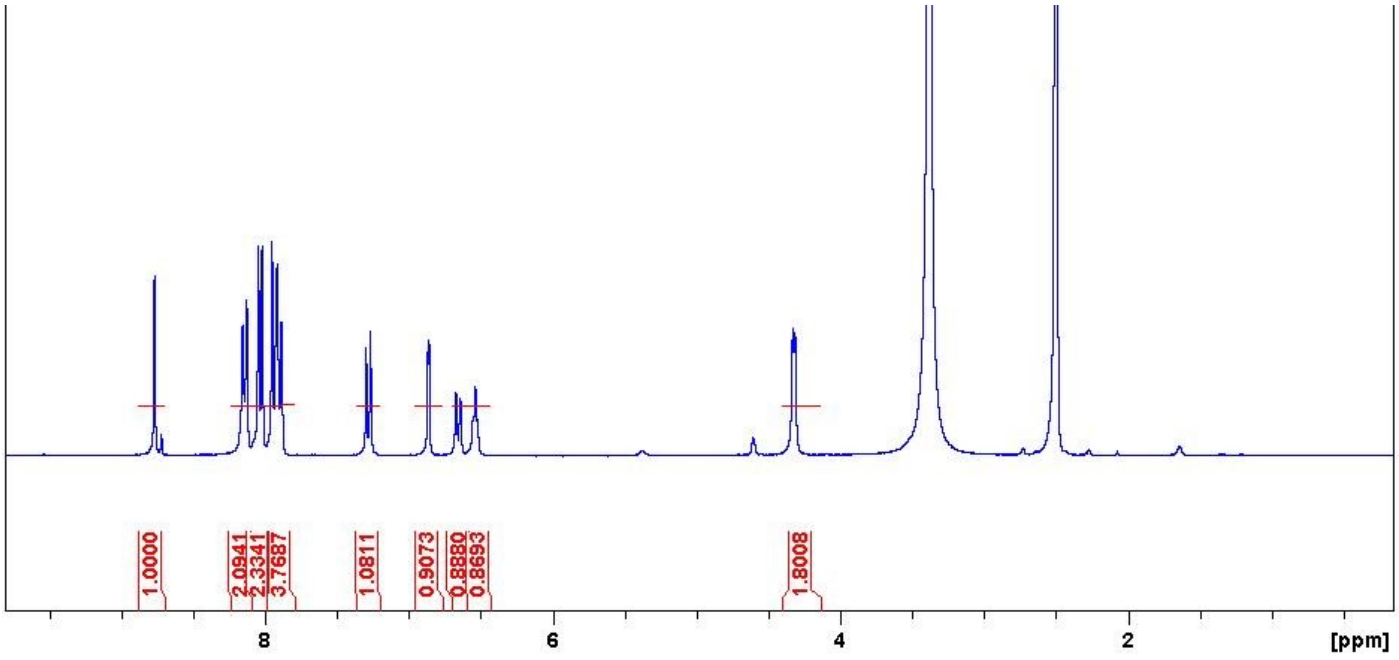
^{1}H NMR spectrum of compound **17**



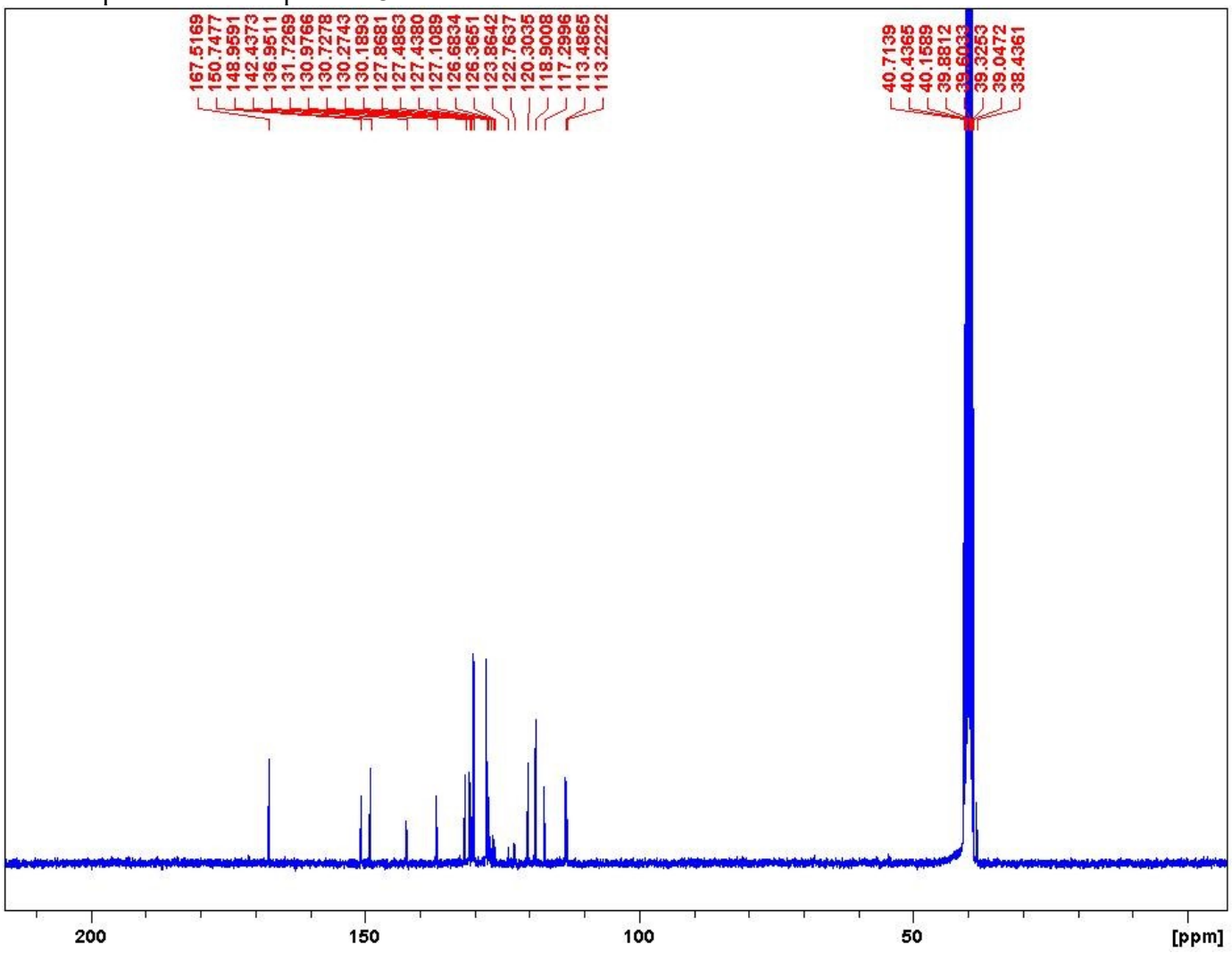
^{13}C NMR spectrum of compound **17**



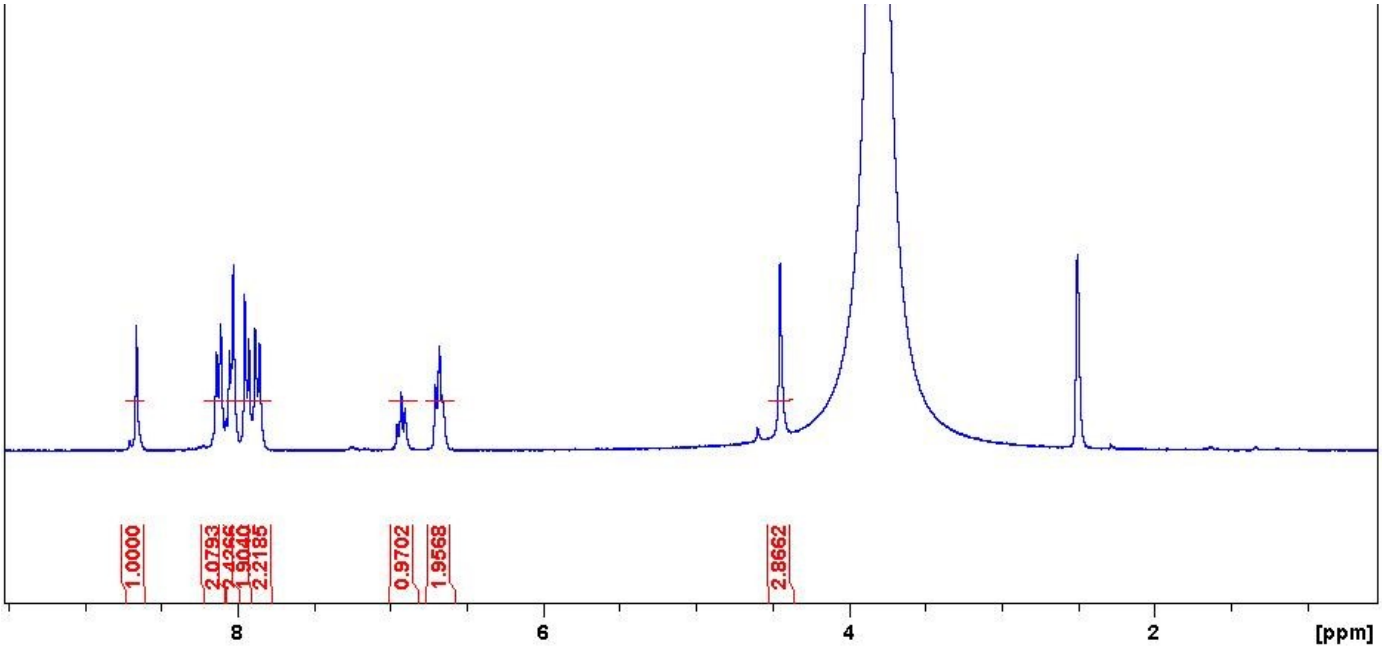
^{1}H NMR spectrum of compound **18**



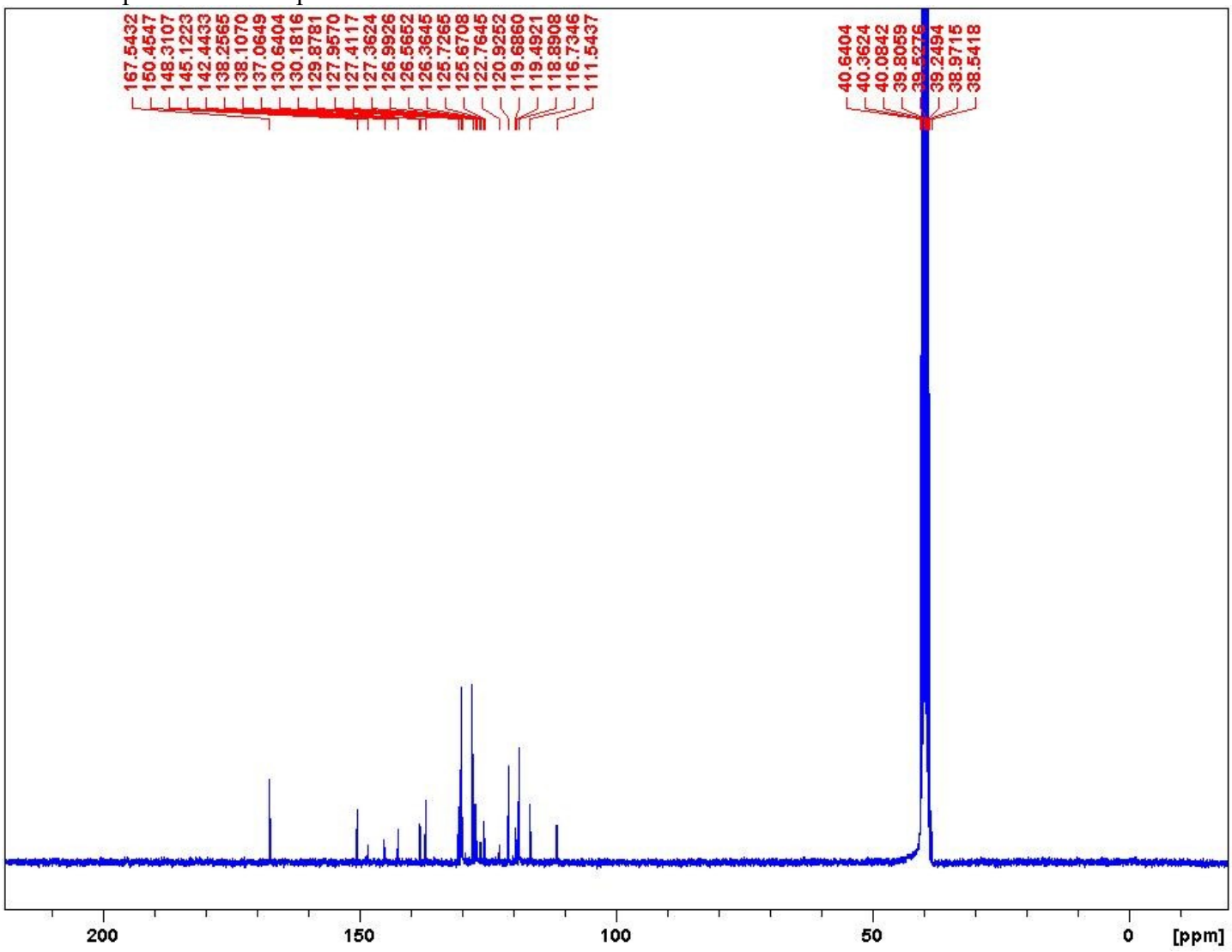
^{13}C NMR spectrum of compound **18**



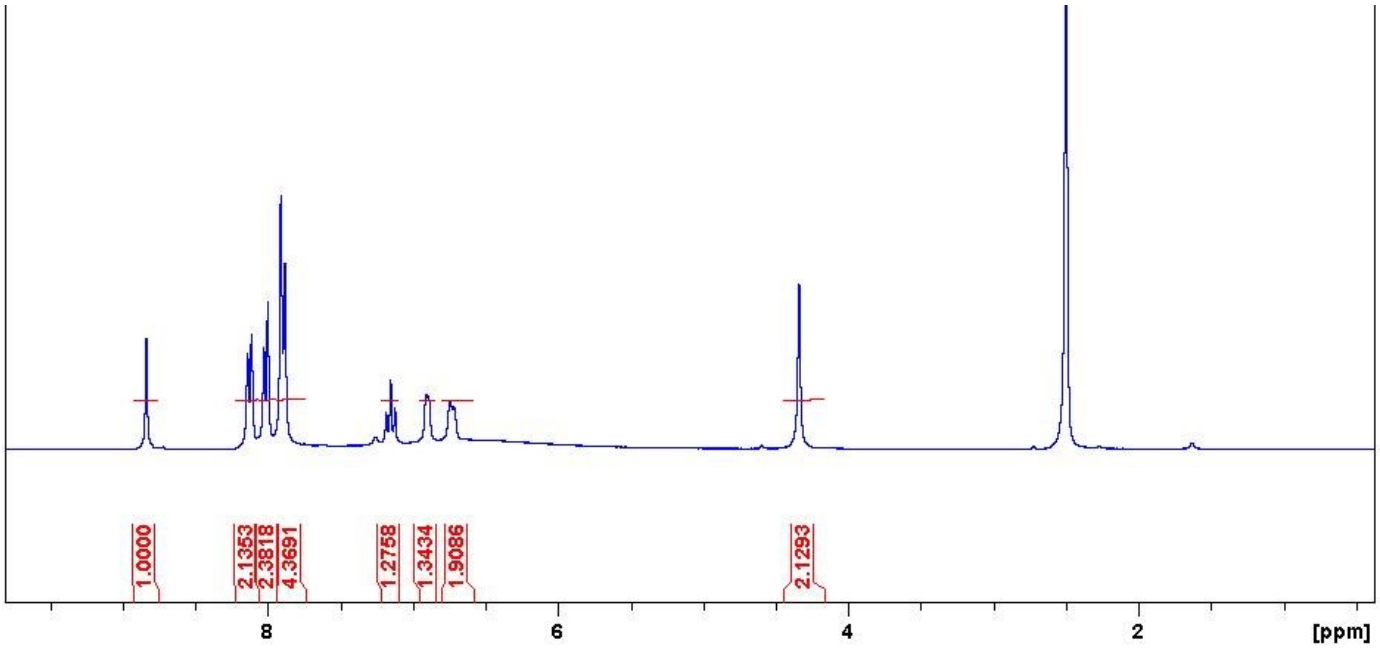
^{1}H NMR spectrum of compound **19**



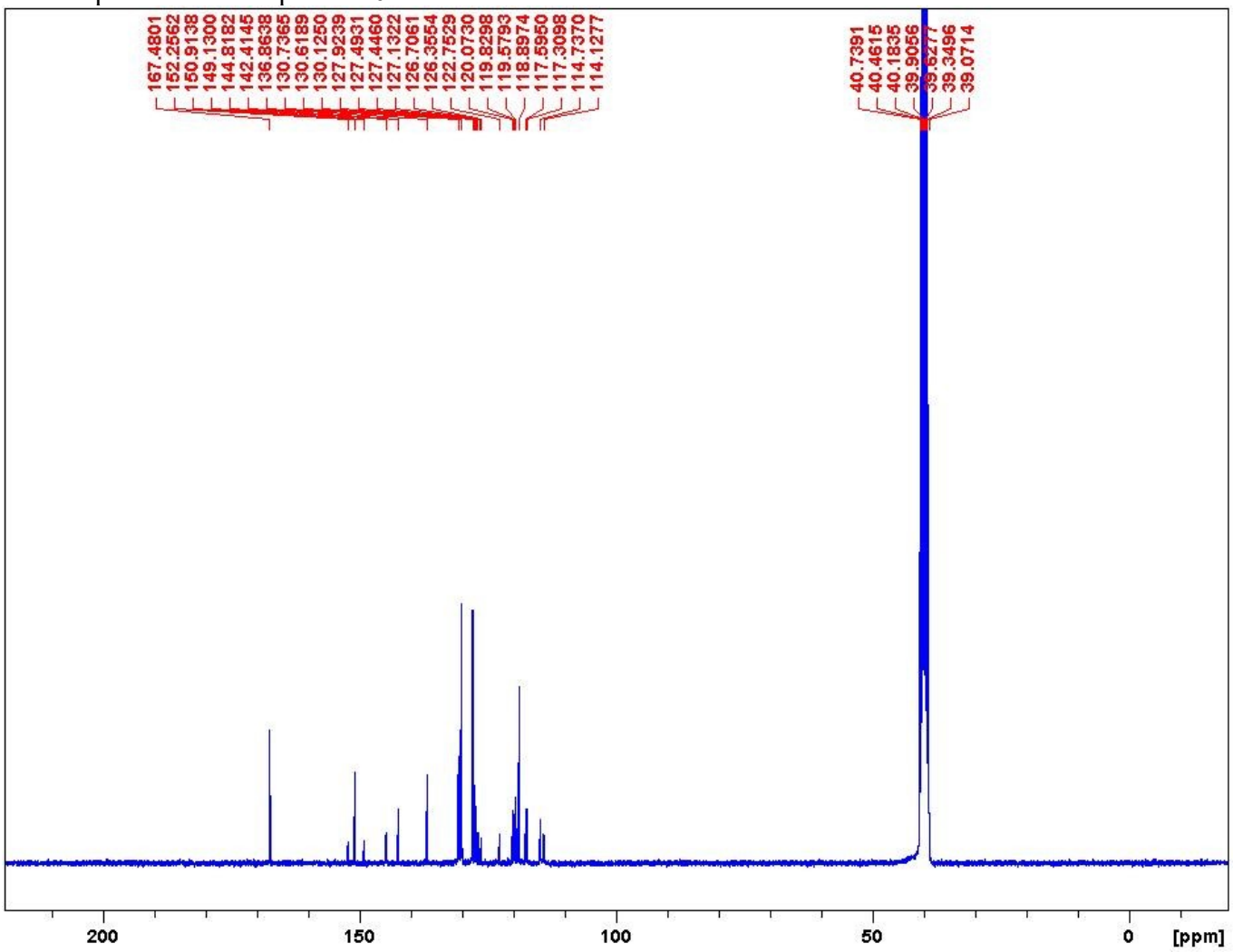
^{13}C NMR spectrum of compound **19**



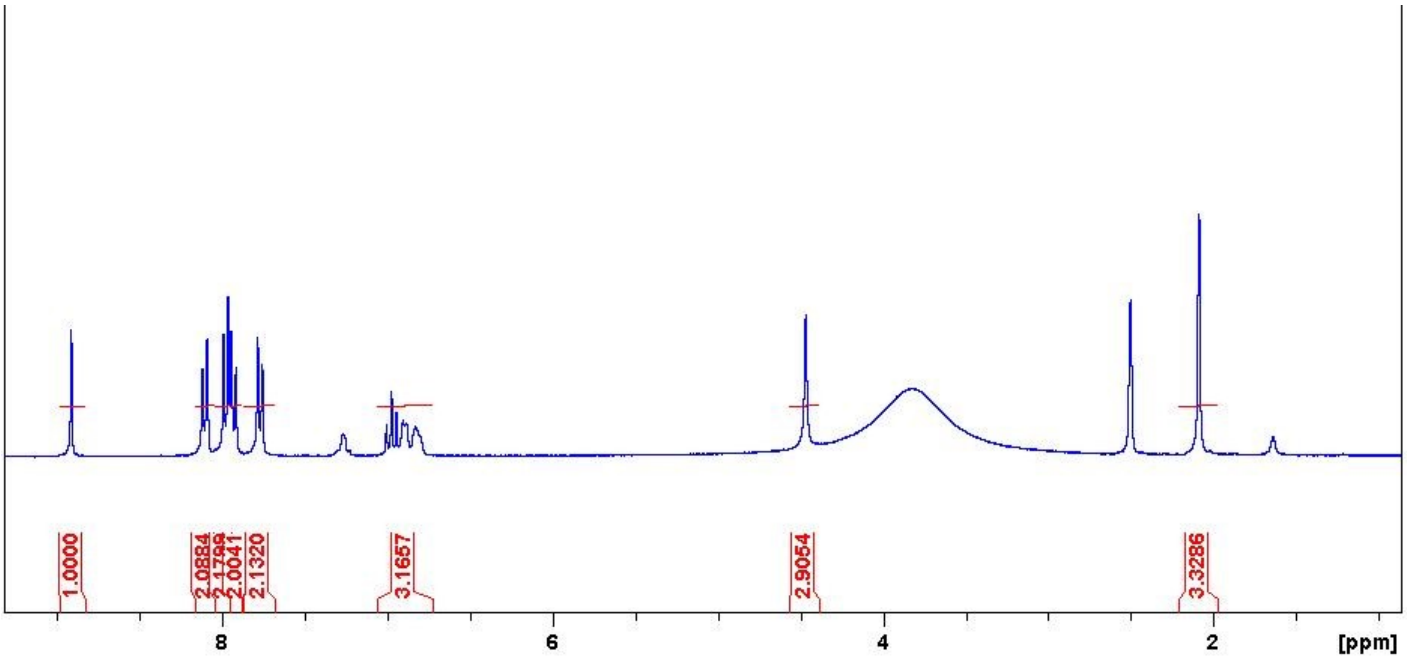
^{1}H NMR spectrum of compound **20**



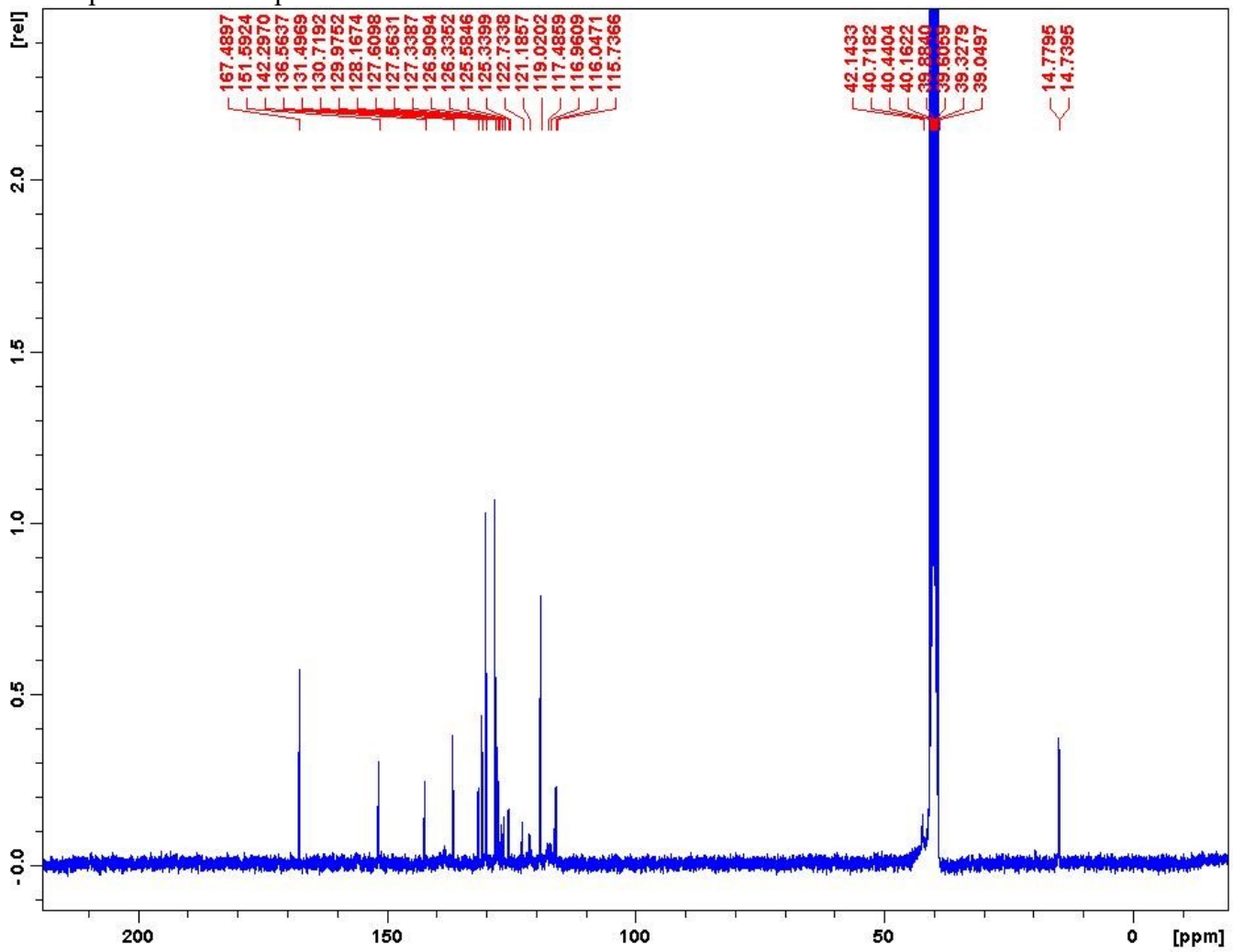
^{13}C NMR spectrum of compound **20**



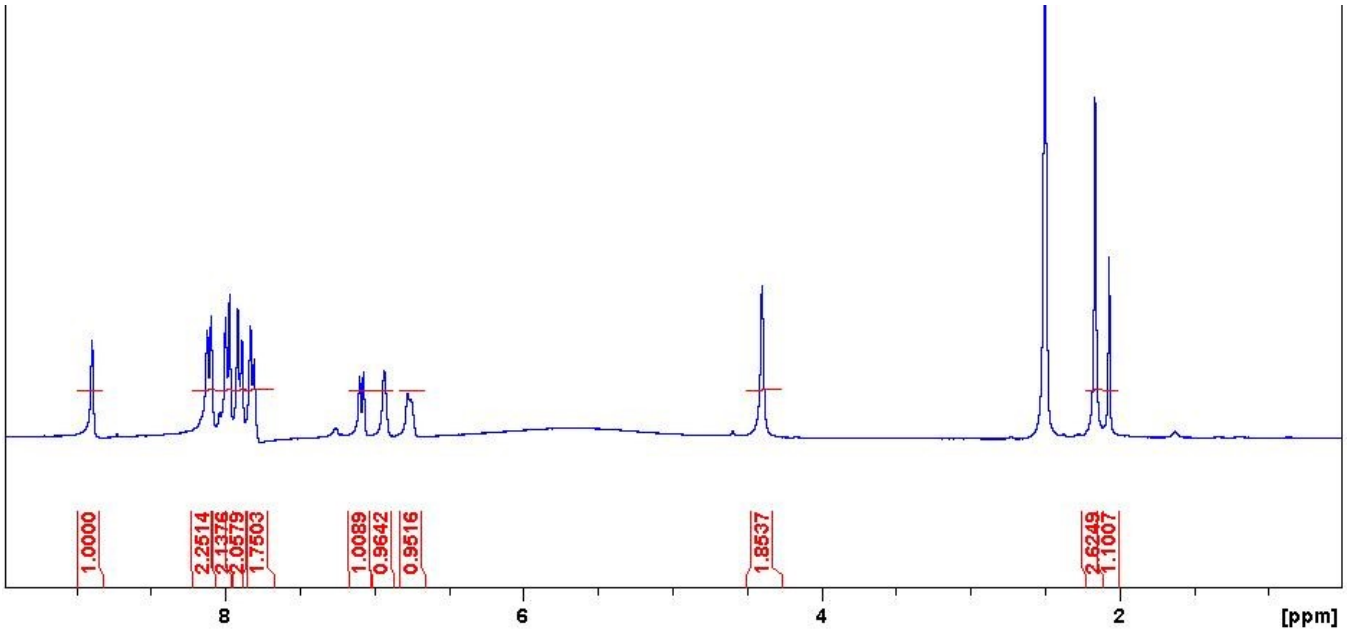
^{1}H NMR spectrum of compound **21**



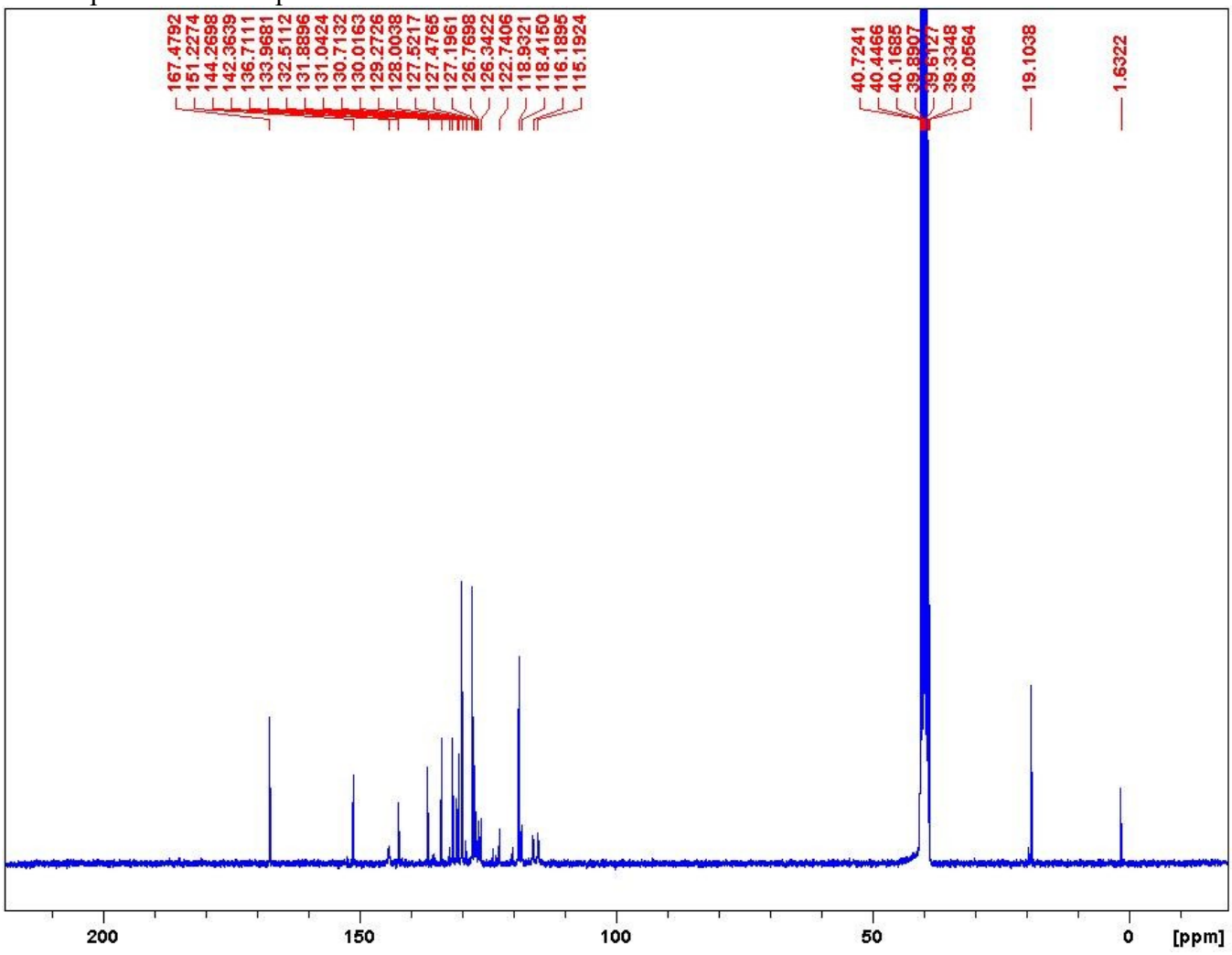
^{13}C NMR spectrum of compound **21**



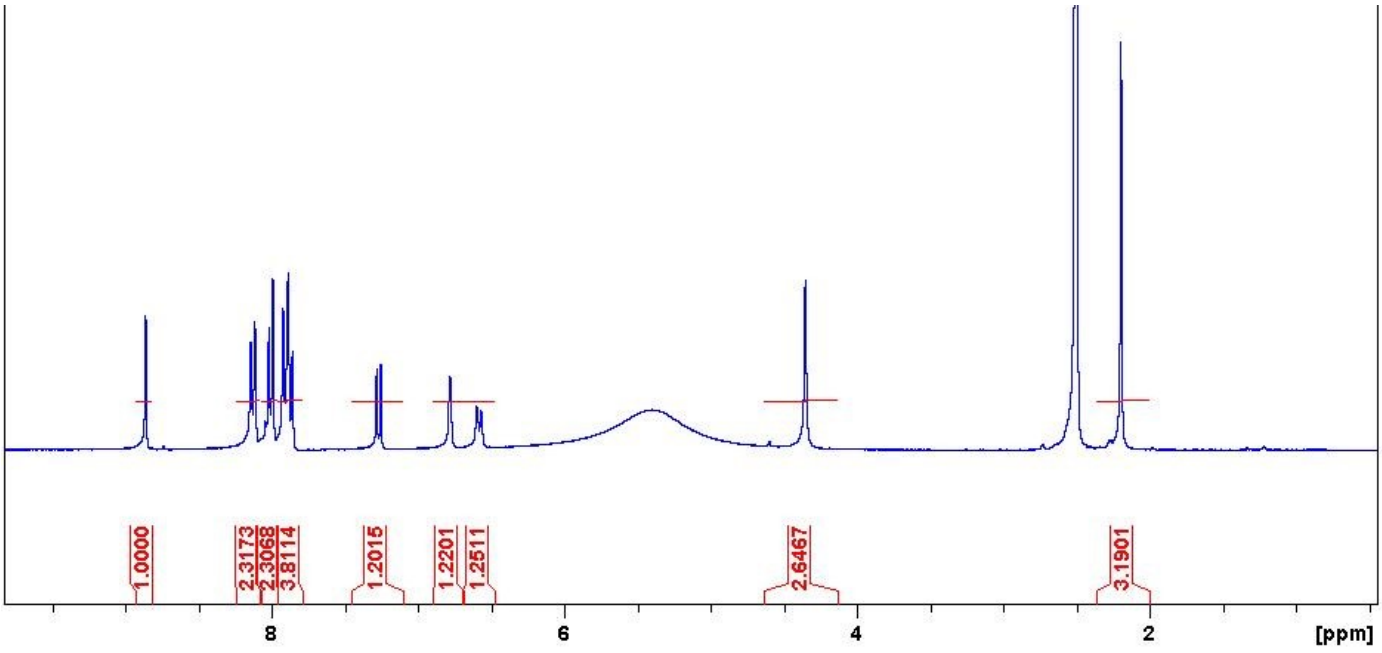
^{1}H NMR spectrum of compound **22**



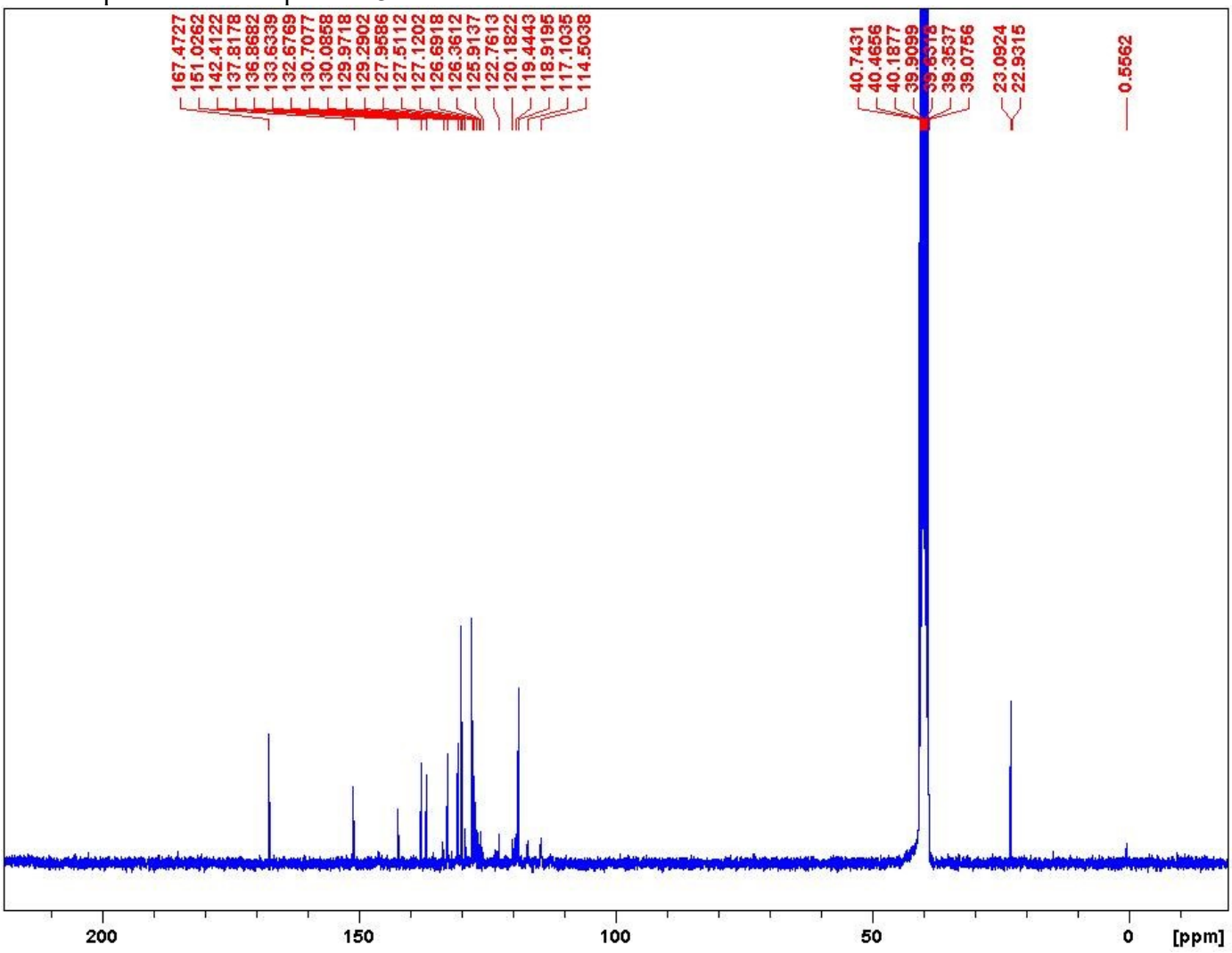
^{13}C NMR spectrum of compound **22**



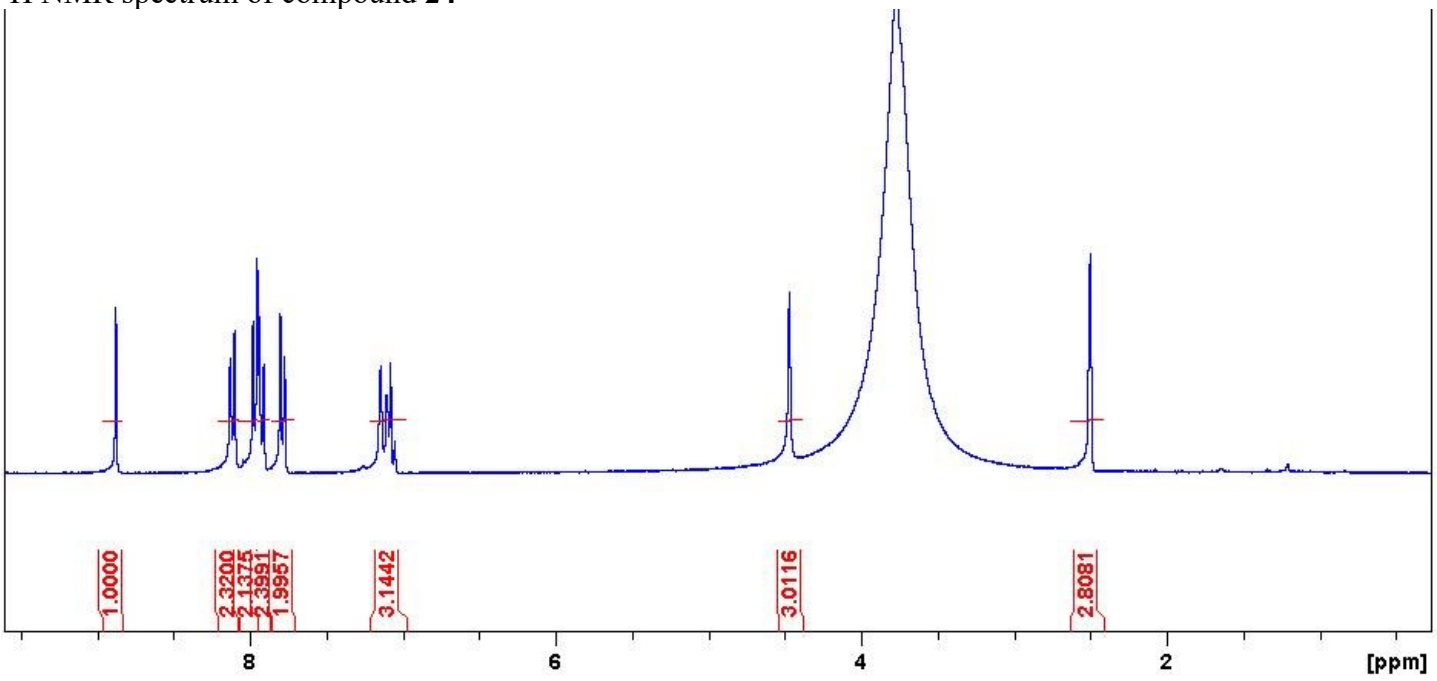
^{1}H NMR spectrum of compound **23**



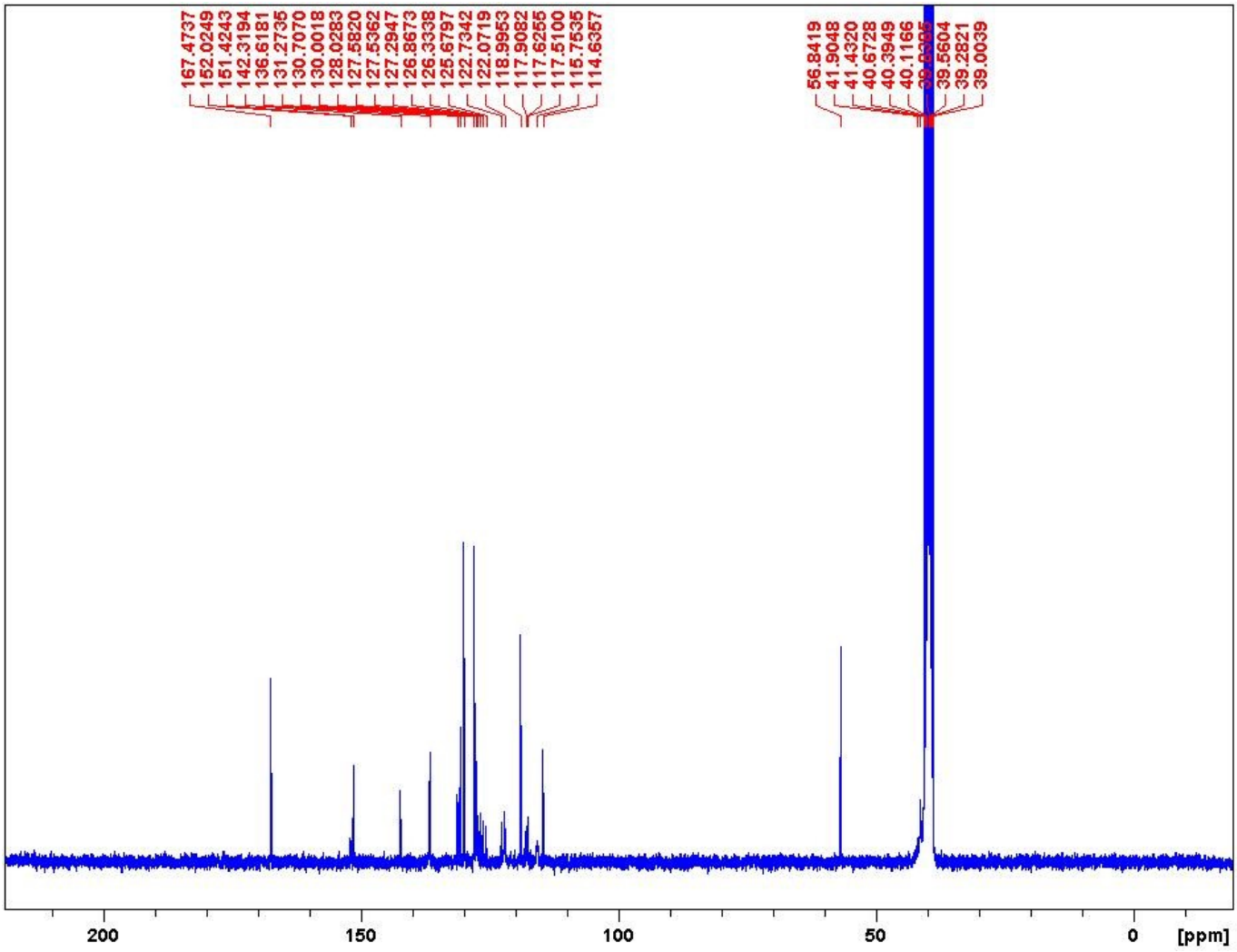
^{13}C NMR spectrum of compound **23**



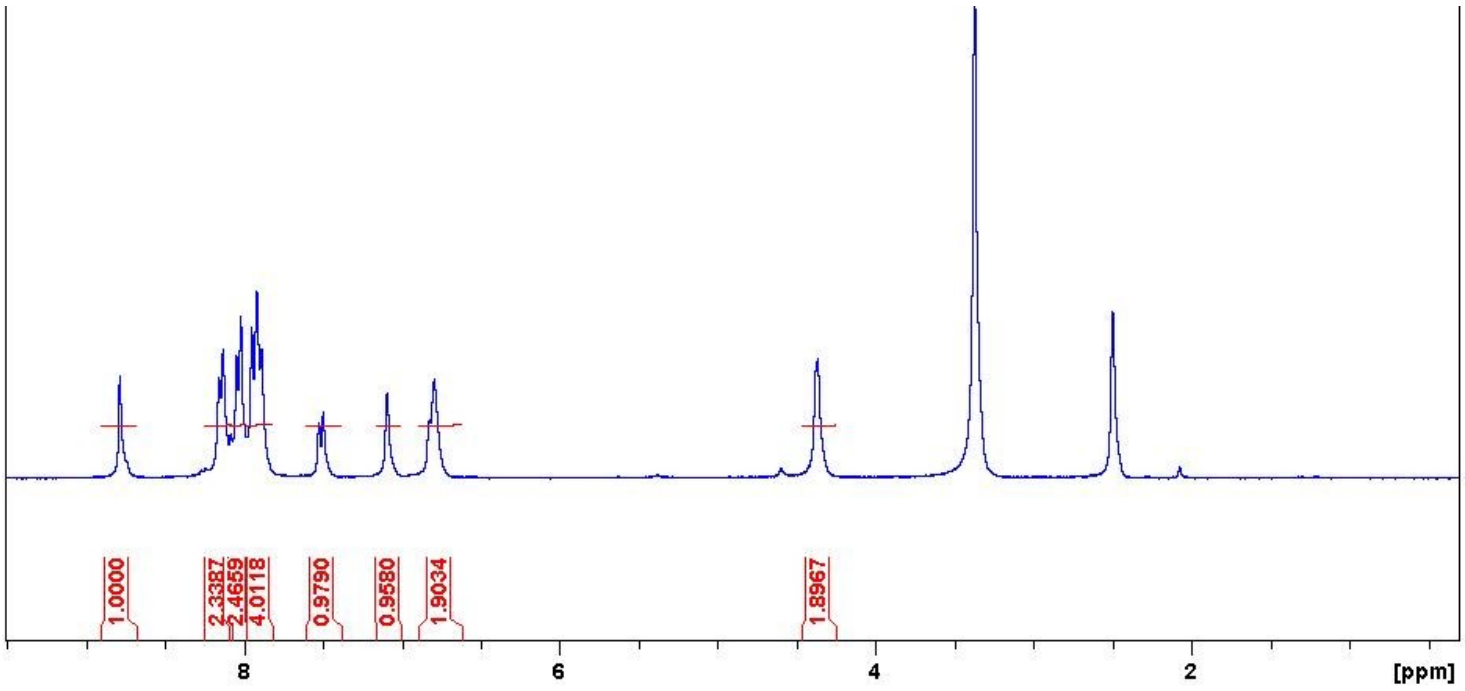
^{1}H NMR spectrum of compound **24**



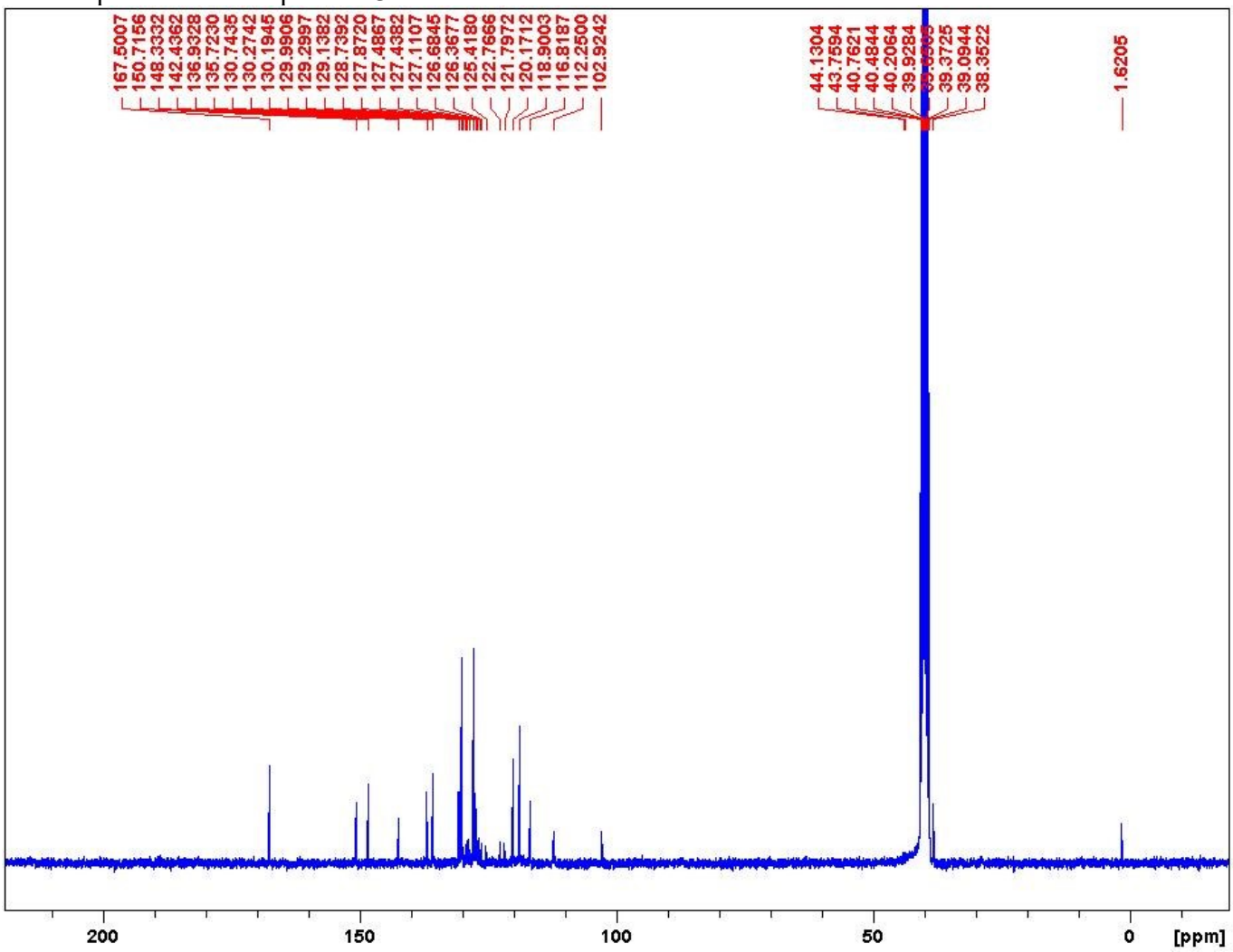
^{13}C NMR spectrum of compound **24**



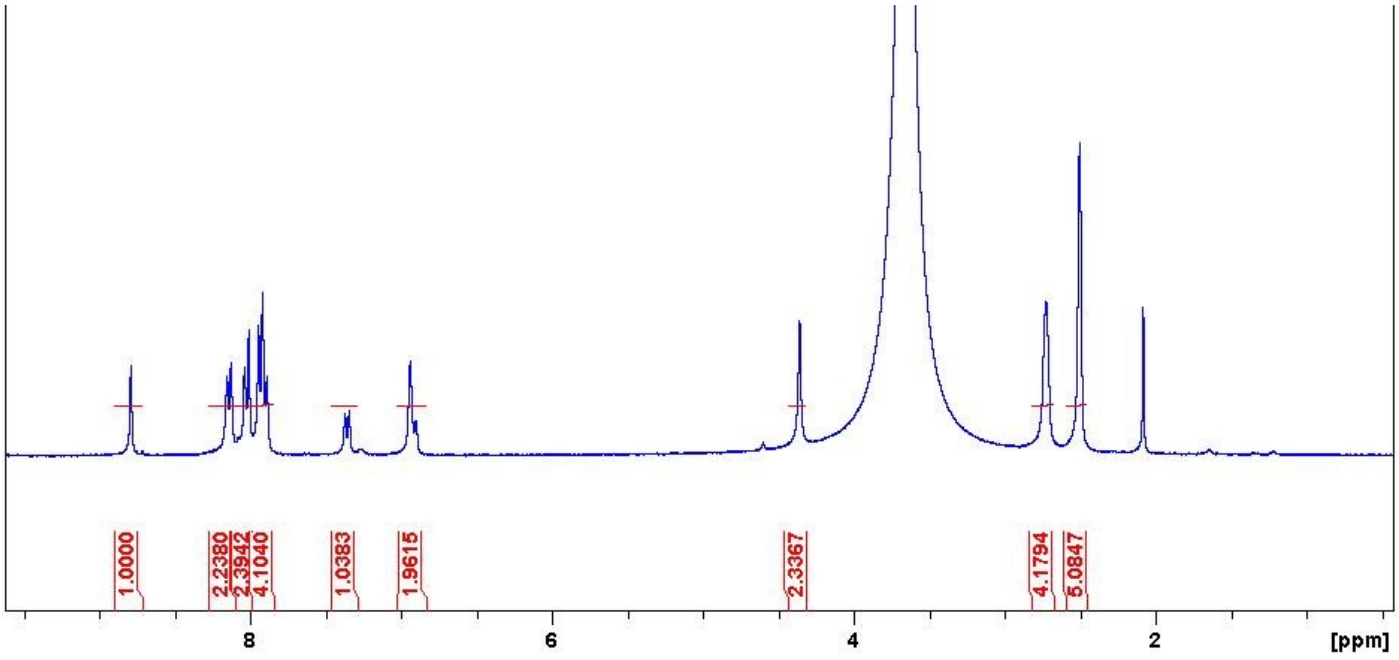
^{1}H NMR spectrum of compound **25**



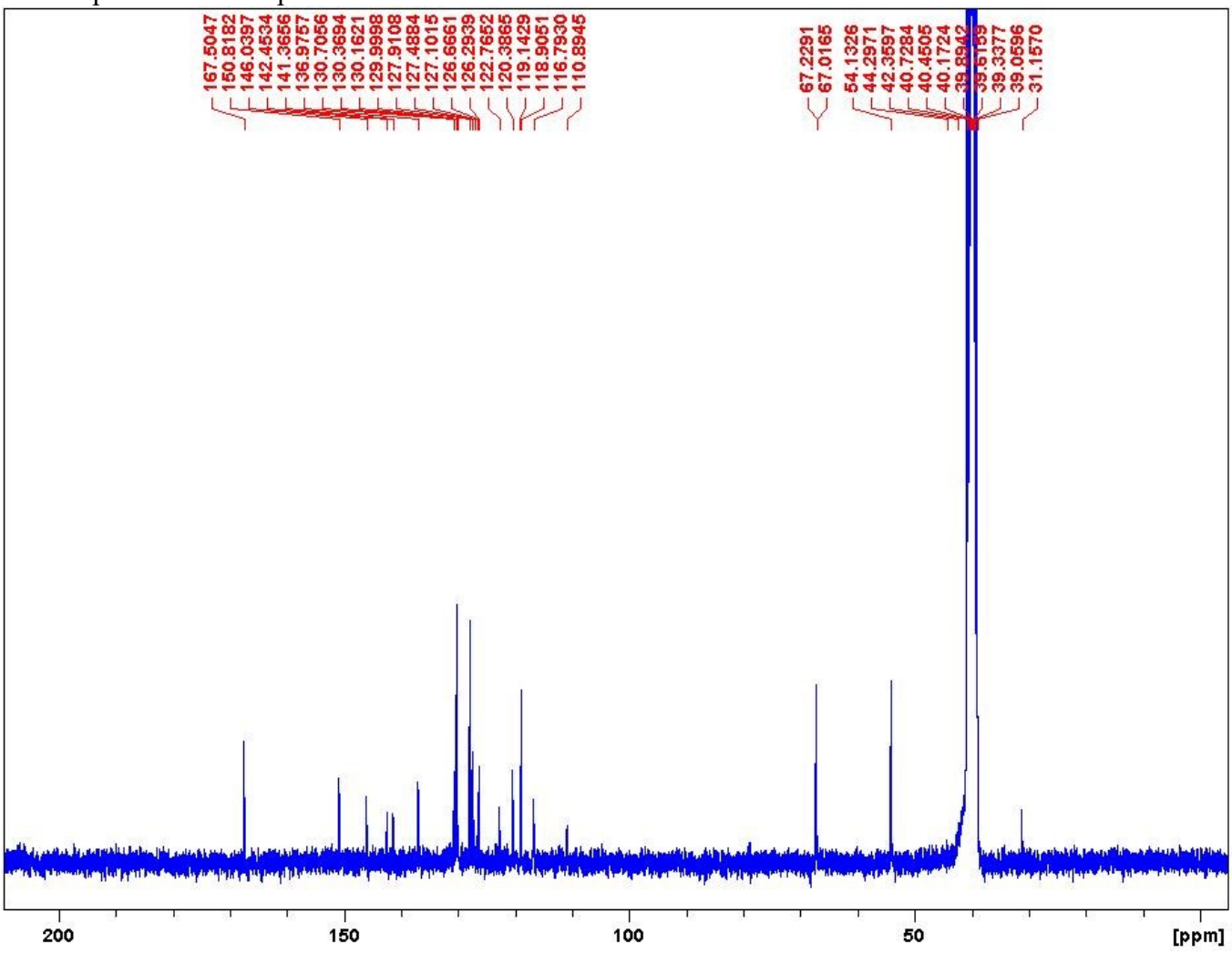
^{13}C NMR spectrum of compound **25**



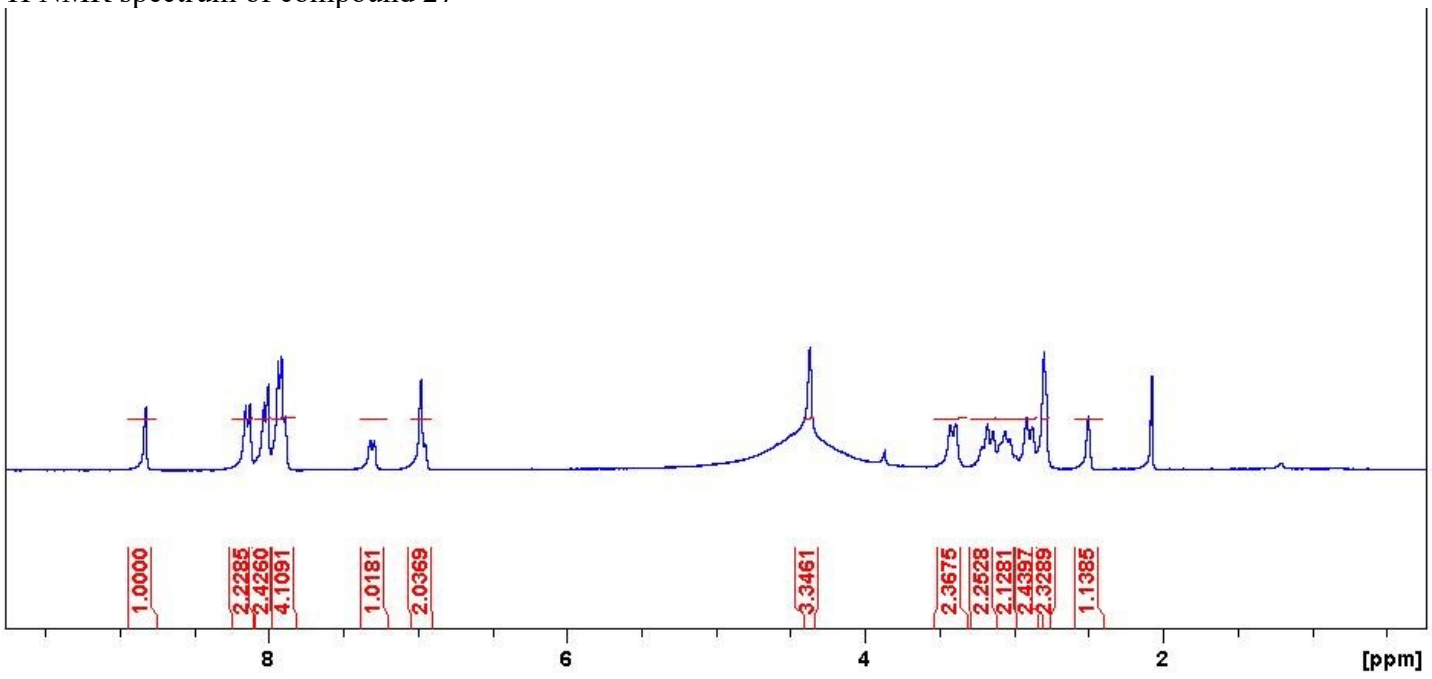
^{1}H NMR spectrum of compound **26**



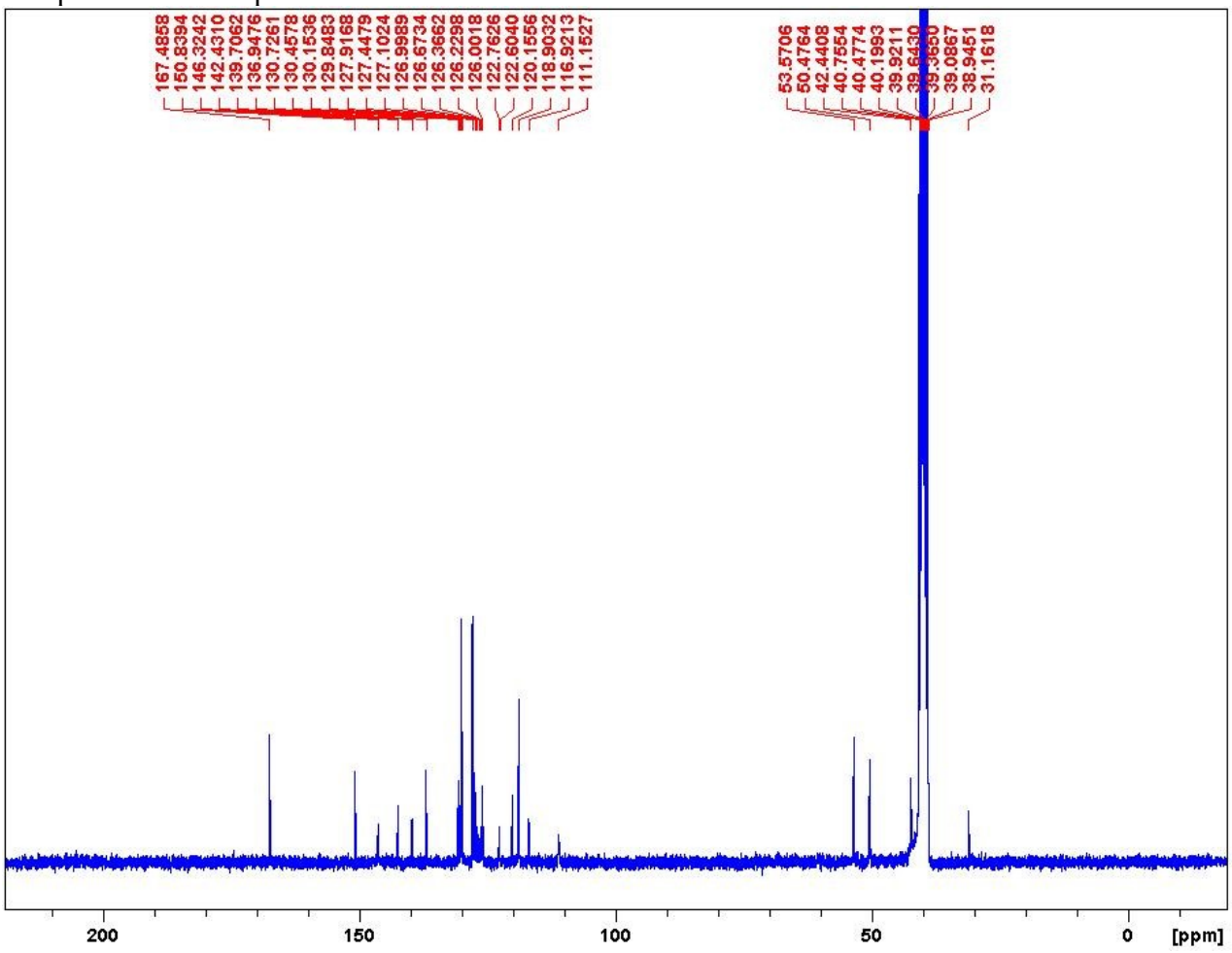
^{13}C NMR spectrum of compound **26**



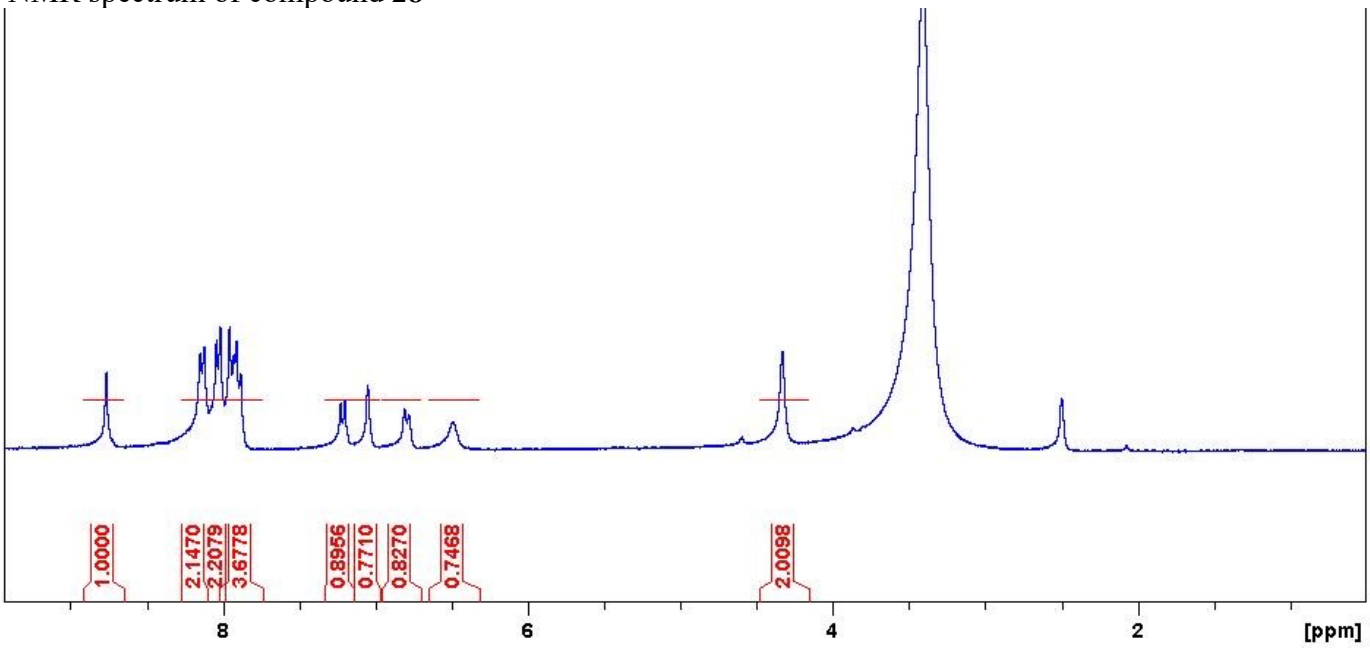
^{1}H NMR spectrum of compound **27**



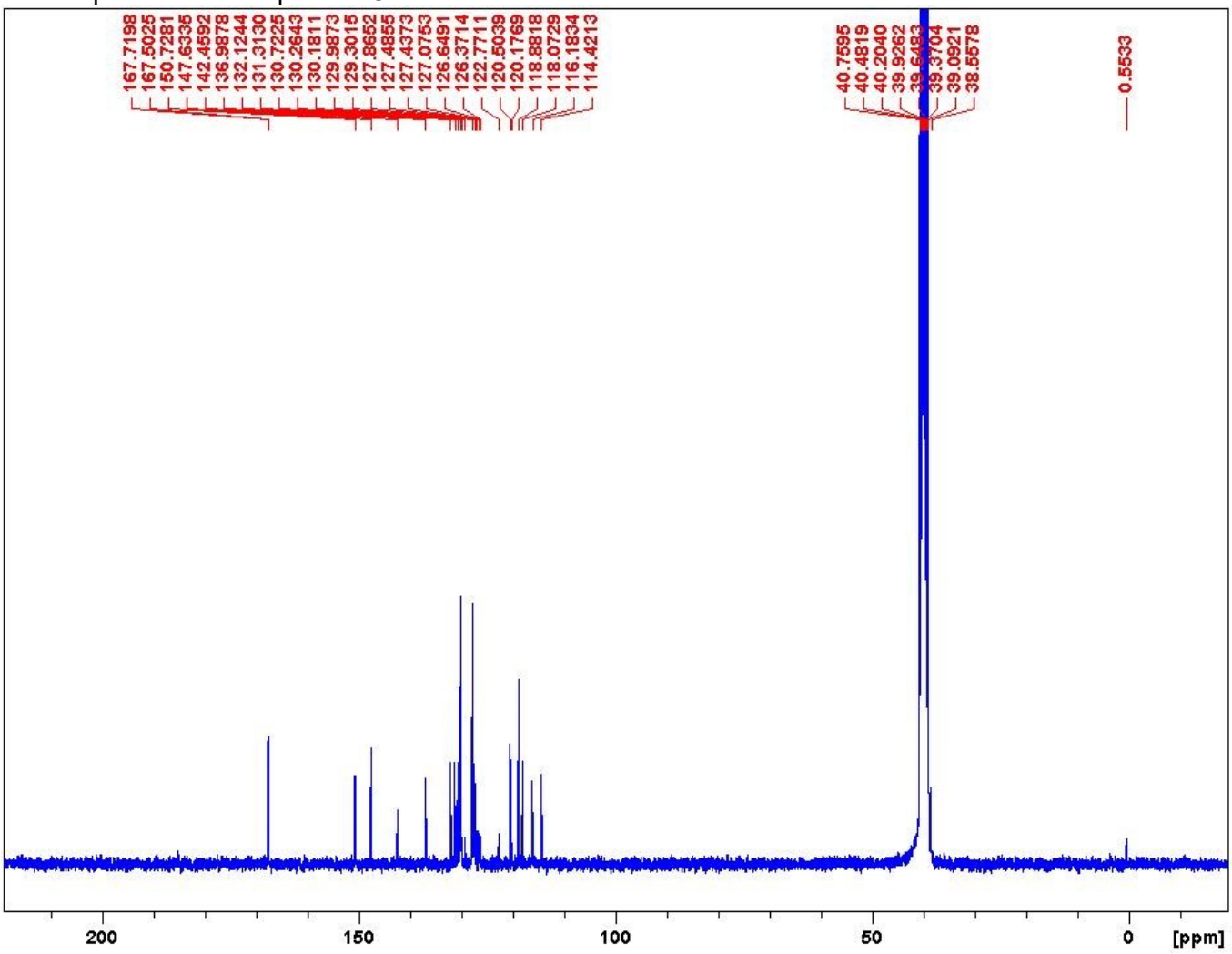
^{13}C NMR spectrum of compound **27**



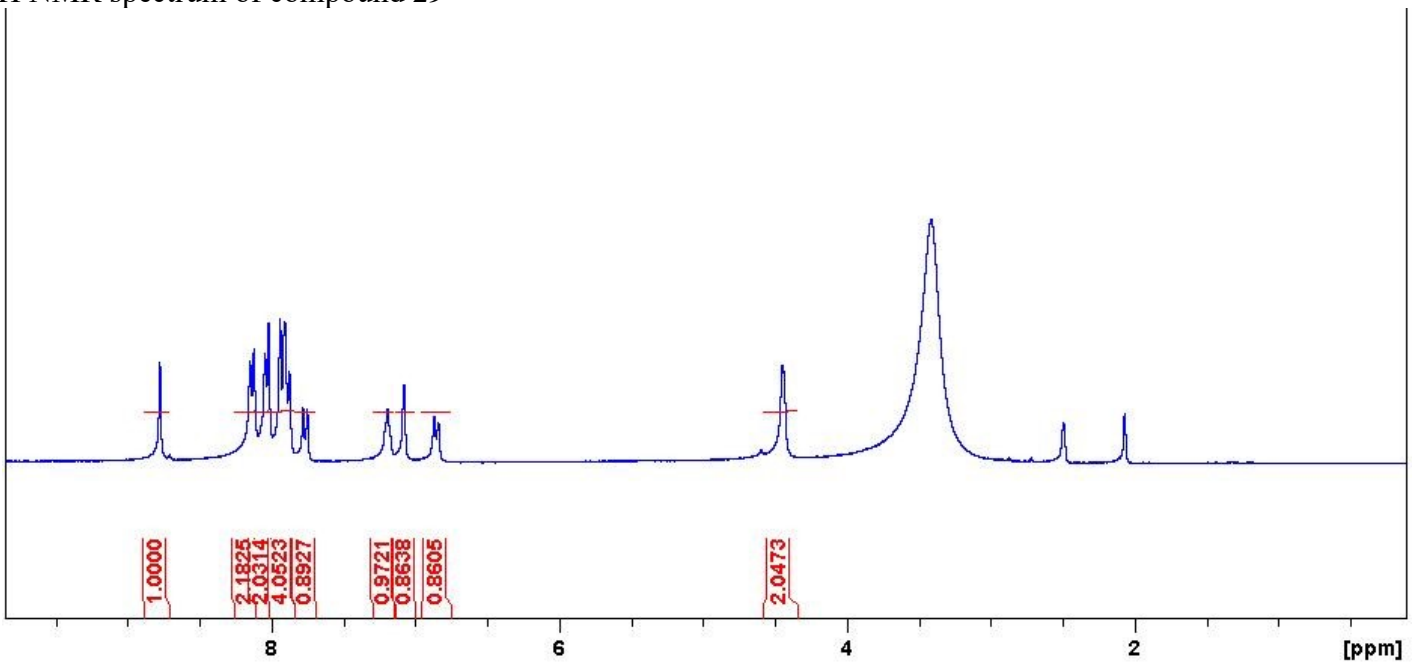
^{1}H NMR spectrum of compound **28**



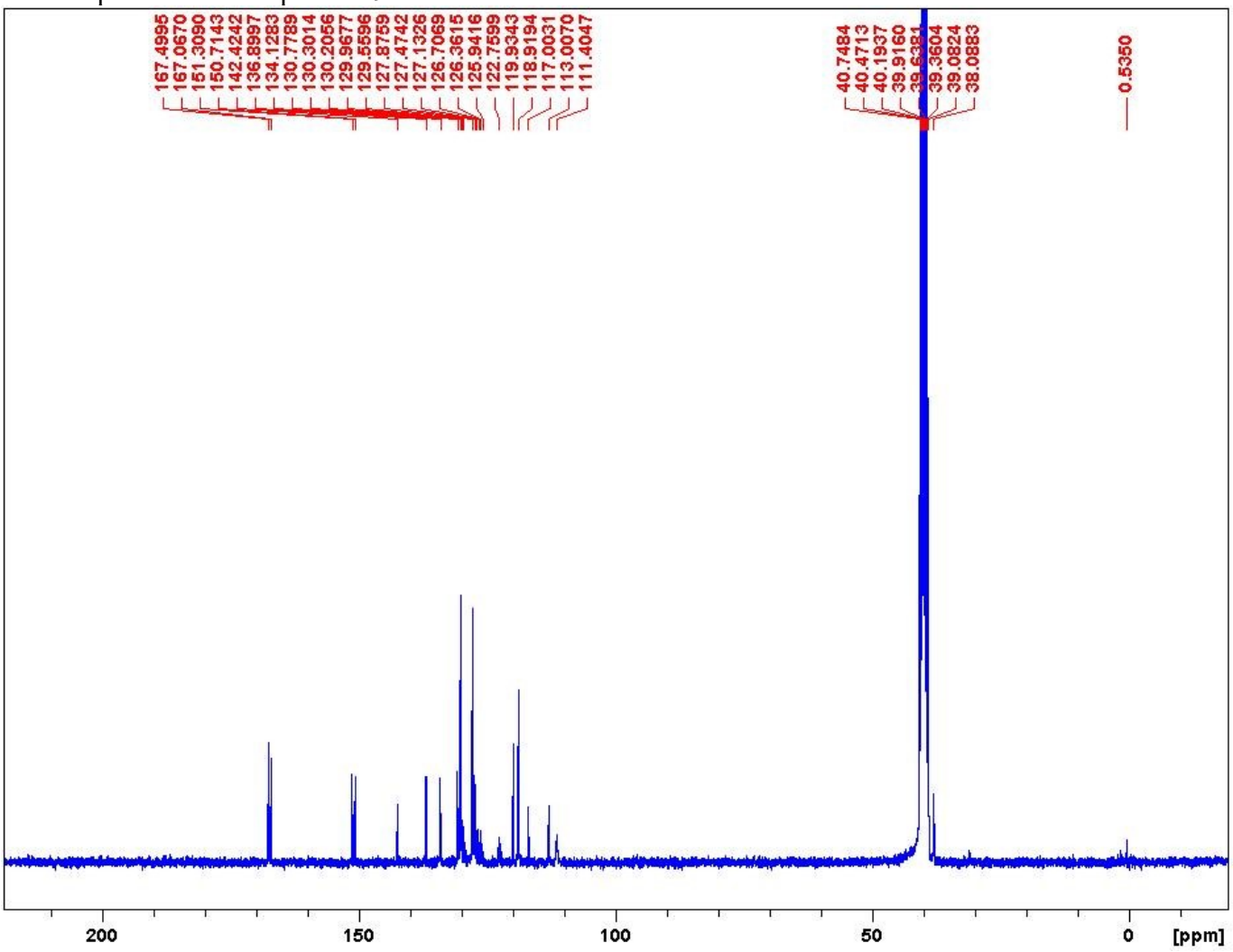
^{13}C NMR spectrum of compound **28**



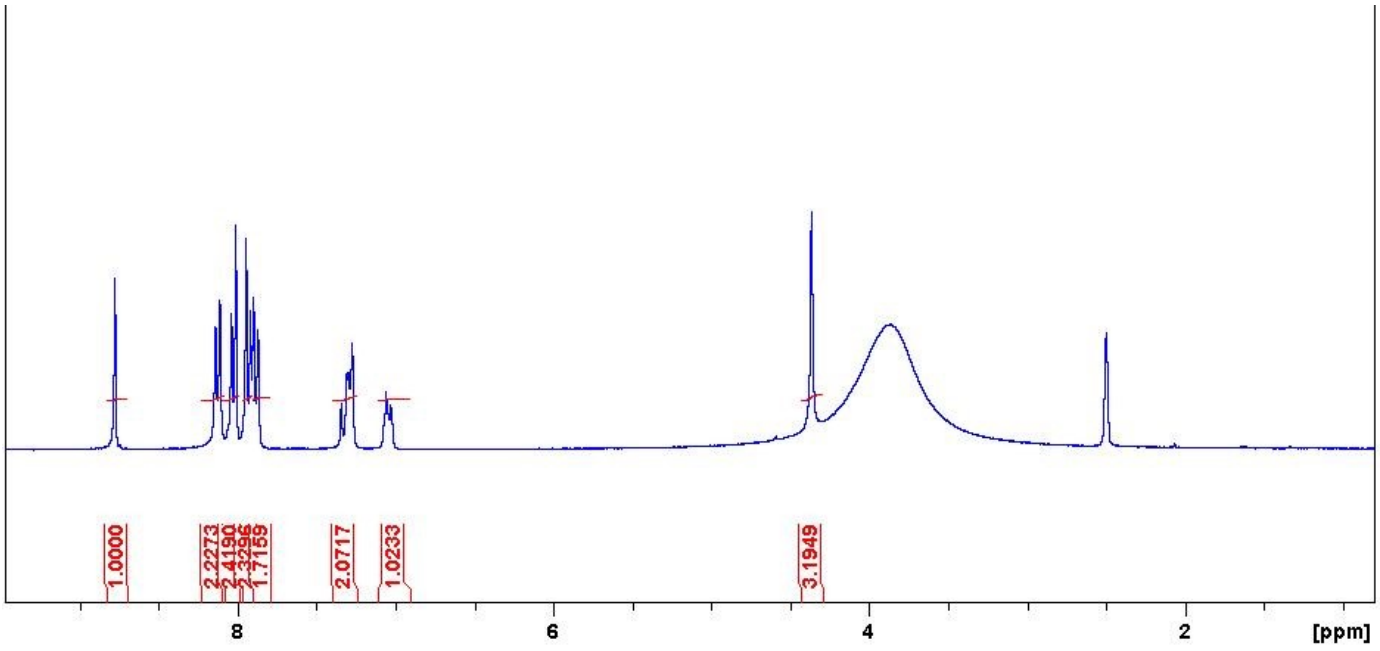
^{1}H NMR spectrum of compound **29**



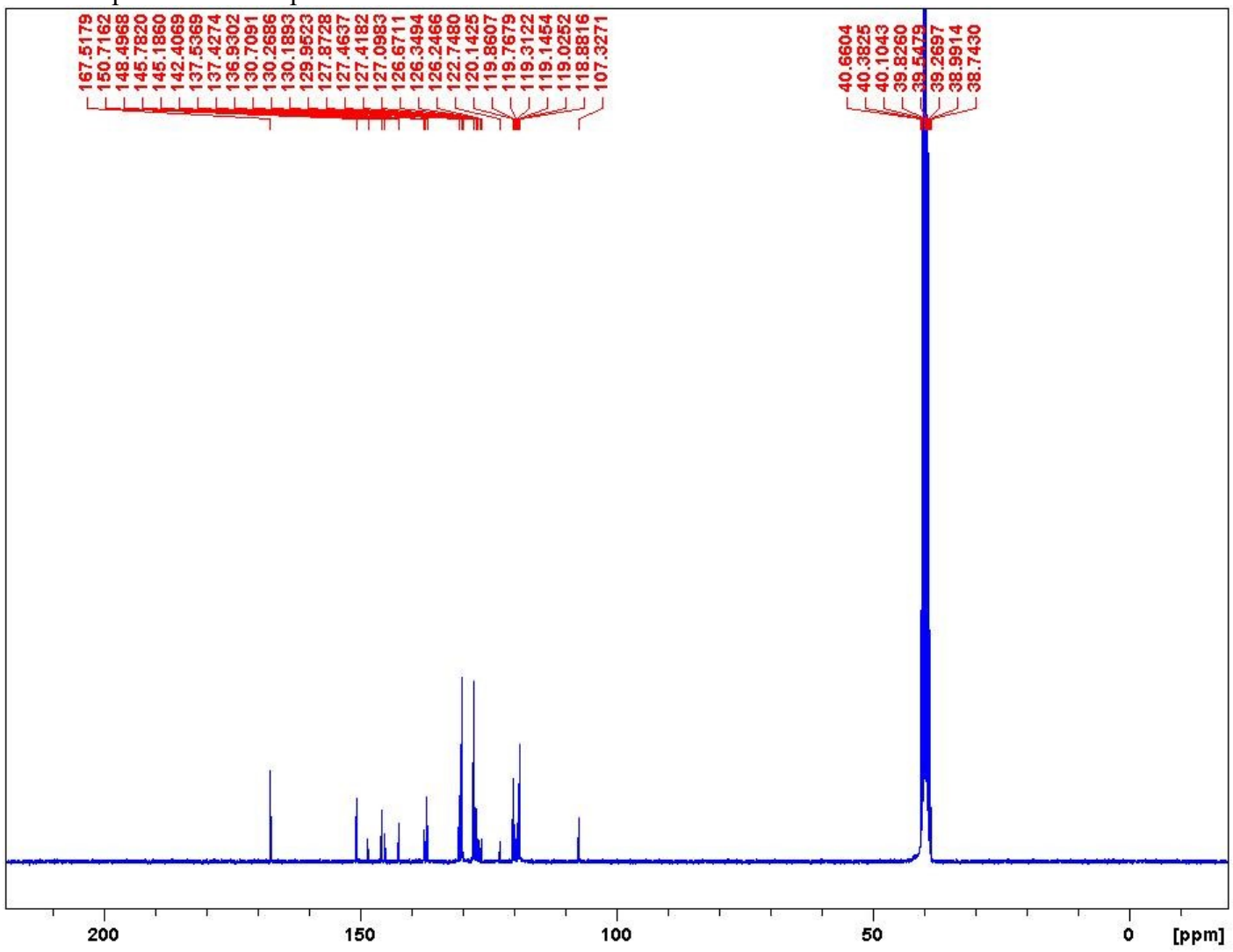
^{13}C NMR spectrum of compound **29**



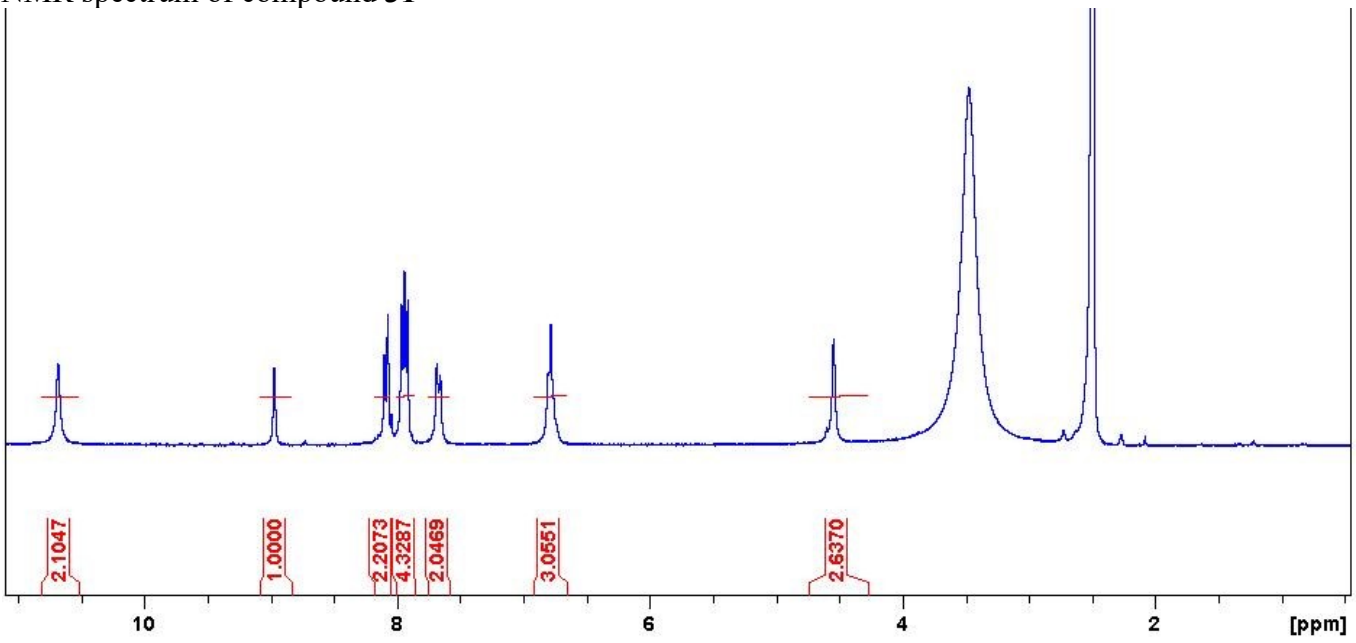
^{1}H NMR spectrum of compound **30**



^{13}C NMR spectrum of compound **30**



^{1}H NMR spectrum of compound **31**



^{13}C NMR spectrum of compound **31**