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A facile one-pot synthesis of 2-amino-1, 3, 4-oxadiazole tethered peptidomimetics by molecular-iodine-mediated cyclodeselenization

L. Santhosh, C. Srinivasulu, S. Durgamma, Girish Prabhu and Vommina. V. Sureshbabu*

Room No. 109, Peptide Research Laboratory, Department of Chemistry, Central College Campus, Dr. B. R. AmbedkarVeedhi, Bangalore University, Bangalore 560 001, India.
E-mail: sureshbabuvommina@rediffmail.com, hariccb@gmail.com, hariccb@hotmail.com.

Supporting information

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Experimental section

All chemicals were used as obtained from Sigma Aldrich Company, USA. All the solvents were dried and purified using recommended procedures in the literature whenever necessary. High resolution mass spectra were recorded on a Micromass Q-TOF micromass spectrometer using electron spray ionization mode. 1H NMR and 13C NMR spectra were recorded on a Bruker AMX 400 MHz and 100 MHz spectrometer, respectively. Melting points were determined in an open capillary and are uncorrected. TLC experiments were done using MERCK TLC aluminum sheets (silica gel 60 F254) and chromatograms were visualized by exposing in iodine chamber and in UV-lamp. Column chromatography was performed on silica gel (100-200 mesh) using ethyl acetate and hexane mixture as eluent.

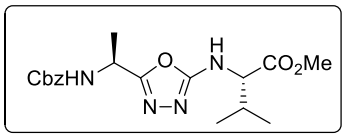
General procedure

Synthesis of 2-amino-1, 3, 4-oxadiazole peptidomimetics *(4)*

To a solution of N^{α}-protected amino acid hydrazide**1** (1.0 mmol) in THF (8 mL) was added a solution of isoselenocyanato ester **2** (1.0 mmol) and the reaction mixture was stirred for 1-2 h at room temperature till the complete conversion of starting materials (TLC analysis). Then the mixture is cooled to 0 ^{O}C and then TEA (2.0 mmol) was added followed by addition of iodine (1.0 mmol) portion-wise over 5 min. Stirring was continued for 15 min and during the reaction precipitation of reddish brown selenium powder was observed. After the reaction was completed (monitored by TLC), the selenium powder was filtered off and washed with THF (10 mL). The combined filtrate was concentrated under vacuum and the residue was diluted with EtOAc and washed with Sat.$Na_2S_2O_3$, 10% citric acid, 5% Na_2CO_3, brine solution and finally dried over Na_2SO_4, and solvent was evaporated under reduced pressure, the resulting crude product was purified by column chromatography on silica gel (n-hexane-EtOAc = 7:3).

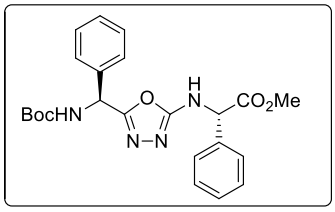
Characterization data:

(S)-methyl-2-((5-((S)-1-(((benzyloxy)carbonyl)amino)ethyl)-1,3,4-oxadiazol-2-yl)amino)-3-methylbutanoate (4a)



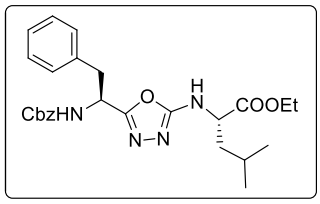
White solid; yield: 92%; mp132-133 °C; $[\alpha]^{26}_{D}$ (c 1.0, MeOH) -16.3; IR (ν cm^{-1}): 1029, 1233, 1643, 1689, 1742, 2914, 2966, 3011, 3221, 3358; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.80-0.88 (m, 6H), 1.25 (d, *J* = 6.8 Hz, 3H), 2.37-2.46 (m, 1H), 3.28 (d, *J* = 6.4 Hz, 1H), 3.53 (s, 3H), 4.86-4.92 (m, 1H), 5.15 (s, 2H), 6.08 (br s, 1H), 6.45 (br s, 1H), 7.30-7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.3, 20.7, 29.8, 48.1, 50.1, 62.3, 68.1, 127.9, 128.3, 128.4, 138.4, 156.4, 159.3, 160.5, 171.7; HRMS (ESI): *m/z* calcd for $C_{18}H_{24}N_4O_5Na$ $[M + Na]^+$ 399.1644, found: 399.1638.

(S)-methyl-2-((5-((S)-((tert-butoxycarbonyl)amino)(phenyl)methyl)-1,3,4-oxadiazol-2-yl)amino)-2-phenylacetate (4b)



White solid; Yield: 94%; mp: 123-124 °C; $[\alpha]^{26}_{D}$ (c 1.0, MeOH) -2.3; IR (ν cm^{-1}): 1167, 1245, 1365, 1630, 1692, 1749, 2952, 2977, 3033, 3063, 3275, 3369; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.41 (s, 9H), 3.72 (s, 3H), 5.35 (s, 1H), 5.65 (d, *J* = 7.2 Hz, 1H), 5.92 (br s, 1H), 6.14 (s, 1H), 7.25-7.38 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ**:** 28.2, 53.1, 59.6, 63.6, 81.5, 126.9, 127.0, 127.2, 128.5, 128.8, 128.9 (2C), 135.7, 137.1, 154.9, 159.9, 162.2, 170.8; HRMS (ESI): *m/z* calcd for $C_{23}H_{26}N_4O_5Na$ $[M + Na]^+$ 461.1801, found 461.1801.

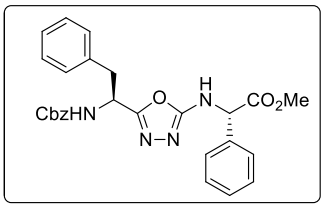
(S)-ethyl-2-((5-((S)-1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)-1,3,4-oxadiazol-2-yl)amino)-4-methylpentanoate (4c)



White solid; Yield: 89%; mp: 141-143 °C; $[\alpha]^{26}_{D}$ (c 1.0, MeOH) -23.6; IR (ν cm^{-1}): 1023, 1247, 1286, 1622, 1694, 1724, 2869, 2929, 2956, 3032, 3063, 3245, 3332; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.95 (d, *J* = 6 Hz, 6H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.62-1.74 (m, 3H), 3.10-3.20 (m, 1H), 3.21-3.31 (m, 1H), 4.18-4.23 (m, 2H), 4.32-4.40 (m, 1H), 5.09 (dd, *J* = 15.6 Hz, *J* = 12 Hz, 2H), 5.13-5.23 (m, 2H), 5.31 (br s, 1H), 7.10-7.15 (m, 2H), 7.21-7.38 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 21.9, 22.8, 24.8, 39.2, 41.5, 48.7, 54.8, 61.7, 67.1, 127.1,

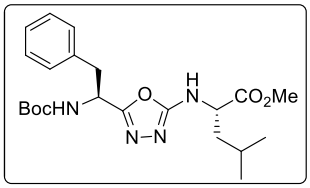
128.0, 128.2, 128.5, 128.6, 129.4, 129.5, 135.7, 136.2, 155.6, 159.9, 163.1, 173.1; HRMS (ESI): *m/z* calcd for $C_{26}H_{32}N_4O_5Na$ $[M + Na]^+$ 503.2270, found 503.2270.

(S)-methyl-2-((5-((S)-1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)-1,3,4-oxadiazol-2-yl)amino)-2-phenylacetate (4d)



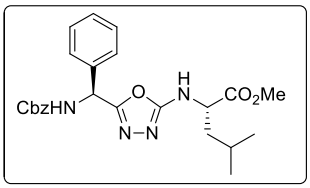
White solid; Yield: 92%; mp: 140-142 °C; $[\alpha]^{26}_D$ (c 1.0, MeOH) -28.7; IR (ν cm^{-1}): 1027, 1246, 1636, 1692, 1734, 2924, 2953, 3030, 3063, 3086, 3229, 3312; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.02-3.25 (m, 2H), 3.75 (s, 3H), 5.07 (dd, *J* = 18.8 Hz, *J* = 12 Hz, 2H), 5.16 (s, 1H), 5.21-5.29 (m, 1H), 5.35 (s, 1H), 5.9 (s, 1H), 6.98-7.45 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.2, 53.1, 59.6, 67.1, 127.1, 127.2 (2C), 128.0, 128.1, 128.4, 128.5, 128.9 (2C), 129.0, 129.3, 135.2, 135.4, 135.7, 155.4, 160.1, 162.0, 170.8; HRMS (ESI): *m/z* calcd for $C_{27}H_{26}N_4O_5Na$ $[M + Na]^+$ 509.1801, found 509.1802.

(S)-methyl-2-((5-((S)-1-((tert-butoxycarbonyl)amino)-2-phenylethyl)-1,3,4-oxadiazol-2-yl)amino)-4-methylpentanoate (4e)



White solid; Yield: 93%; mp: 137-139^{0}C; $[\alpha]^{26}_D$ (c 1.0, MeOH) -25.1; IR (ν cm^{-1}): 1021, 1153, 1247, 1366, 1627, 1693, 1753, 2871, 2955, 3033, 3231, 3370; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.94 (d, *J* = 6 Hz, 6H), 1.38 (s, 9H), 1.60-1.75 (m, 3H), 3.07-3.15 (m, 1H), 3.19-3.27 (m, 1H), 3.75 (s, 3H), 4.37-4.40 (m, 1H), 5.0-5.27 (m, 3H), 7.10-7.17 (m, 2H), 7.19-7.31 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.9, 22.8, 24.8, 28.3, 39.6, 41.5, 48.1, 52.6, 54.8, 80.2, 127.0, 128.6, 129.5, 135.9, 154.9, 160.2, 163.0, 173.5; HRMS (ESI): *m/z* calcd for $C_{22}H_{32}N_4O_5Na$ $[M + Na]^+$ 455.2270, found 455.2270.

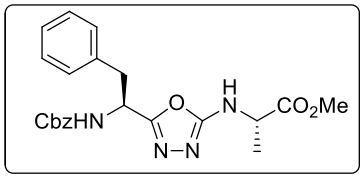
(S)-methyl-2-((5-((S)-(((benzyloxy)carbonyl)amino)(phenyl)methyl)-1,3,4-oxadiazol-2-yl)amino)-4-methylpentanoate (4f)



White solid; Yield: 91%; mp: 121-123 ^{0}C; $[\alpha]^{26}_D$ (c 1.0, MeOH) -6.7; IR (ν cm^{-1}): 1040, 1153, 1249, 1624, 1688, 1746, 2870, 2955, 3033, 3230, 3299; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (d, *J* = 6 Hz, 6H), 1.57-1.78 (m, 3H), 3.70 (s, 3H), 4.30-4.41 (m, 1H), 5.10 (s, 2H), 5.39

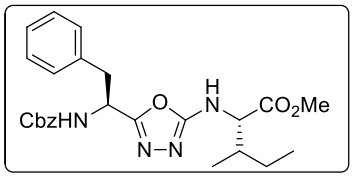
(br s, 1H), 6.0-6.12 (m, 2H), 7.21-7.40 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.8, 22.6, 24.6, 41.6, 51.7, 52.5, 54.7, 67.3, 127.0, 128.1 (2C), 128.4, 128.6, 128.7, 128.9, 129.0, 135.9, 136.8, 155.3, 159.3, 163.2, 173.2; HRMS (ESI): *m/z* calcd for $C_{24}H_{28}N_4O_5Na$ $[M + Na]^+$ 475.1957, found 475.1956.

(S)-methyl-2-((5-((S)-1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)-1,3,4-oxadiazol-2-yl)amino)propanoate (4g)



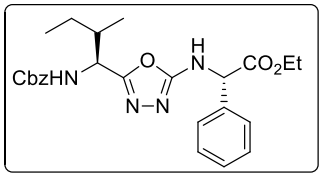
White solid; yield: 90%; mp 171-172 °C; $[\alpha]^{26}_D$ (c 1.0, MeOH) -21.3; IR (ν cm^{-1}): 1043, 1288, 1635, 1698, 1744, 2933, 2972, 2988, 3028, 3042, 3266, 3318; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (d, *J* = 7.2 Hz, 3H), 3.09 (d, *J* = 7 Hz, 1H), 3.21 (d, *J* = 7 Hz, 1H), 3.73 (s, 3H), 3.96-4.01 (m, 1H), 5.07 (s, 2H), 5.32-5.37 (m, 1H), 5.85 (br s, 1H), 6.05 (br s, 1H), 7.25-7.42 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.2, 38.6, 52.1, 54.2, 58.4, 64.2, 127.1, 127.8, 128.2, 128.6, 129.4, 129.7, 137.2, 138.2, 156.3, 158.6, 163.8, 171.9; ESI-MS: *m/z* calcd for $C_{22}H_{24}N_4O_5Na$ $[M + Na]^+$ 447.1644, found: 447.1642.

(2S,3R)-methyl-2-((5-((S)-1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)-1,3,4-oxadiazol-2-yl)amino)-3-methylpentanoate (4h)



White solid; Yield: 91%; mp: 116-118 °C; $[\alpha]^{26}_D$ (c 1.0, MeOH) -10.3; IR (ν cm^{-1}): 1024, 1244, 1284, 1621, 1688, 1737, 2877, 2923, 2962, 3032, 3061, 3246, 3326; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88-0.97 (m, 6H), 1.16-1.31 (m, 2H), 1.94-2.04 (m, 1H), 3.11-3.19 (m, 1H), 3.23-3.28 (m, 1H), 3.76 (s, 3H), 5.08 (dd, *J* = 20.8 Hz, *J* = 12.8 Hz, 2H), 5.15-5.22 (m, 1H), 5.26-5.41 (m, 3H), 7.11-7.36 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.6, 14.2, 26.1, 37.6, 48.5, 52.4, 59.6, 60.6, 67.1, 127.0, 128.0, 128.1, 128.5, 128.6, 129.3, 135.4, 135.5, 155.4, 159.8, 163.4, 172.6; HRMS (ESI): *m/z* calcd for $C_{25}H_{30}N_4O_5Na$ $[M + Na]^+$ 489.2114, found 489.2112.

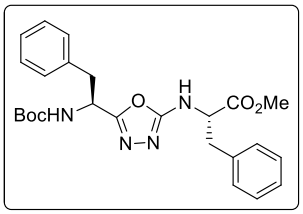
(S)-ethyl-2-((5-((1S,2S)-1-(((benzyloxy)carbonyl)amino)-2-methylbutyl)-1,3,4-oxadiazol-2-yl)amino)-2-phenylacetate (4i)



White solid; Yield: 92%; mp: 143-144 °C; $[\alpha]^{26}_D$ (c 1.0, MeOH) -35.1; IR (ν cm^{-1}): 1026, 1152, 1249, 1625, 1693, 1750, 2871, 2956,

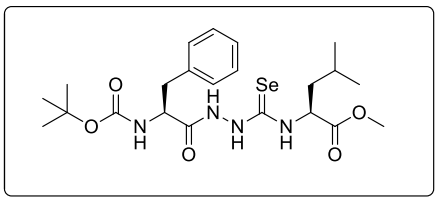
3033, 3233, 3307; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.83-0.90 (m, 6H), 1.03-1.18 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.35-1.48 (m, 1H), 4.20-4.27 (m, 2H), 4.51 (br s, 1H), 4.68 (s, 1H), 5.10 (dd, *J* = 15.3 Hz, *J* = 12.1 Hz, 2H), 5.35 (d, *J* = 6.8 Hz, 1H), 6.07 (br s, 1H), 7.27-7.44 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.3, 13.9, 15.0, 24.8, 38.4, 51.9, 59.7, 62.3, 67.1, 127.1, 128.1 (2C), 128.4, 128.7 (2C), 128.8, 128.9, 136.0, 155.7, 159.9, 161.9, 170.4; HRMS (ESI): *m/z* calcd for $C_{25}H_{30}N_4O_5Na$ $[M + Na]^+$ 489.2114, found 489.2113.

(S)-methyl-2-((5-((S)-1-((tert-butoxycarbonyl)amino)-2-phenylethyl)-1,3,4-oxadiazol-2-yl)amino)-3-phenylpropanoate (4j)

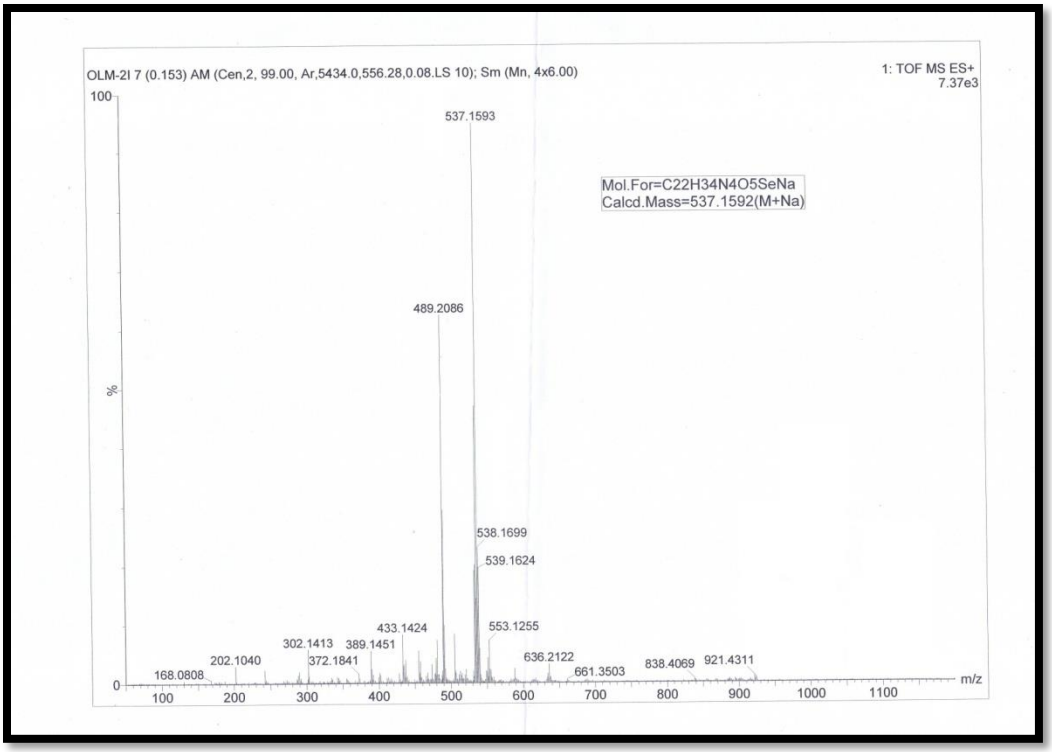


White solid; yield: 94%; mp: 146-148 °C; $[\alpha]^{26}_D$ (c 1.0, MeOH) -17.1; IR (ν cm^{-1}): 1112, 1266, 1645, 1698, 1745, 2958, 2966, 3033, 3068, 3075, 3258, 3383; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.39 (s, 9H), 3.08-3.31 (m, 4H), 3.75 (s, 3H), 4.66 (d, *J* = 6.4 Hz, 1H), 5.09 (br d, *J* = 6.8 Hz, 1H), 5.19 (br s, 1H), 6.51 (br s, 1H), 7.05-7.30 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.3, 37.7, 39.6, 48.1, 52.7, 56.8, 80.8, 127.1, 127.4, 128.6, 128.7, 129.4, 129.5, 135.3, 135.8, 154.9, 160.4, 162.3, 171.6; HRMS (ESI): *m/z* calcd for $C_{25}H_{30}N_4O_5Na$ $[M + Na]^+$ 489.2114, found: 489.2114.

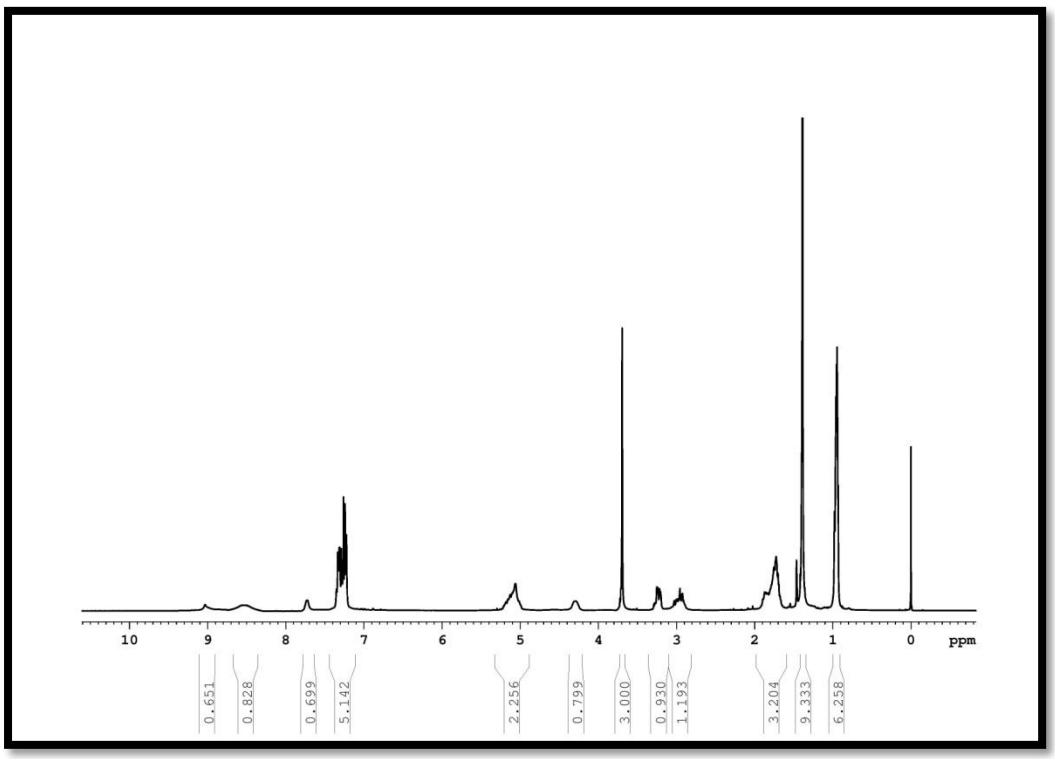
(2S, 8S)-methyl-8-benzyl-2-isobutyl-12,12-dimethyl-7,10-dioxo-4-selenoxo-11-oxa-3,5,6,9-tetraazatridecan-1-oate (3e)



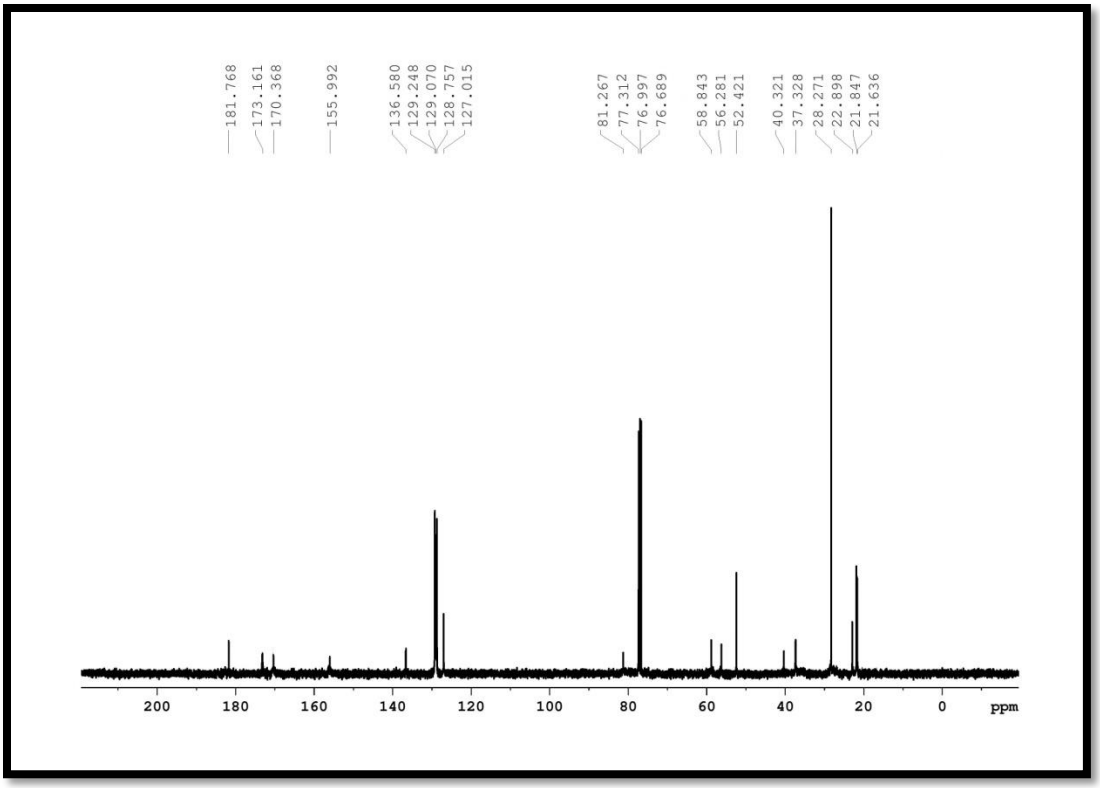
^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93-0.96 (m, 6H), 1.40 (s, 9H), 1.66-1.90 (m, 3H), 2.92-3.02 (m, 1H), 3.20-3.26 (m, 1H), 3.69 (s, 3H), 4.29 (br s, 1H), 5.01-5.19 (m, 2H), 7.21-7.35 (m, 5H), 7.73 (br s, 1H), 8.54 (br s, 1H), 9.04 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 21.8, 22.8, 28.2, 37.3, 40.3, 52.4, 56.2, 58.8, 81.2, 127.0, 128.7, 129.0, 129.2, 136.5, 155.9, 170.3, 173.1, 181.7; HRMS (ESI): *m/z* calcd for $C_{22}H_{34}N_4O_5SeNa$ $[M + Na]^+$ 537.1592, found: 537.1593.



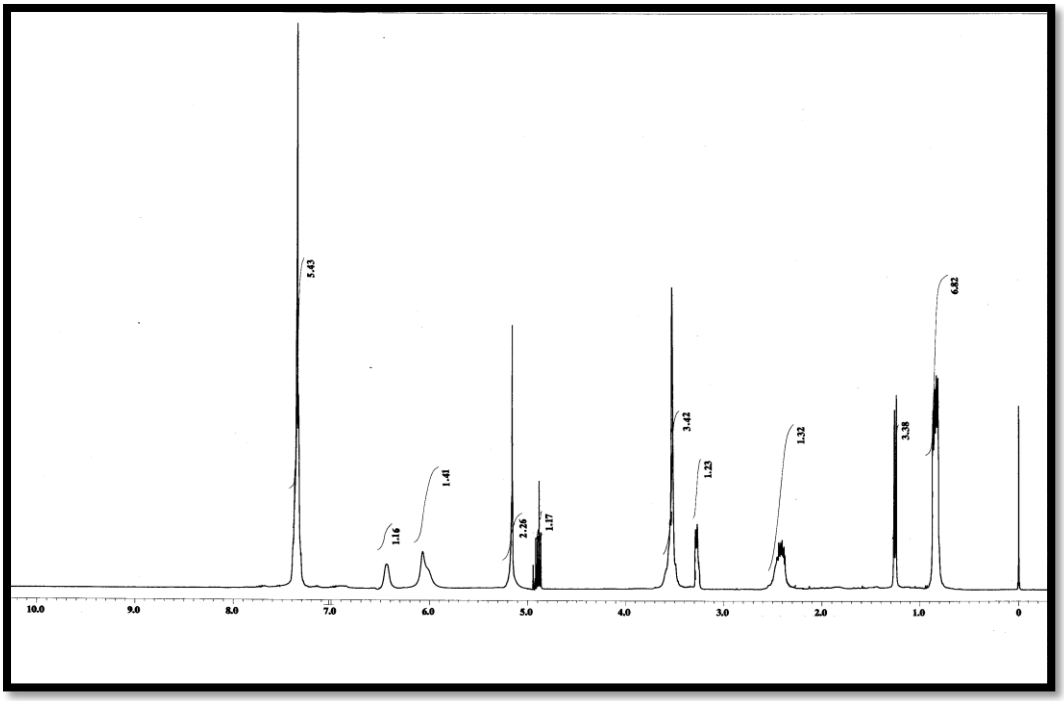
HRMS Spectrum of **3e**



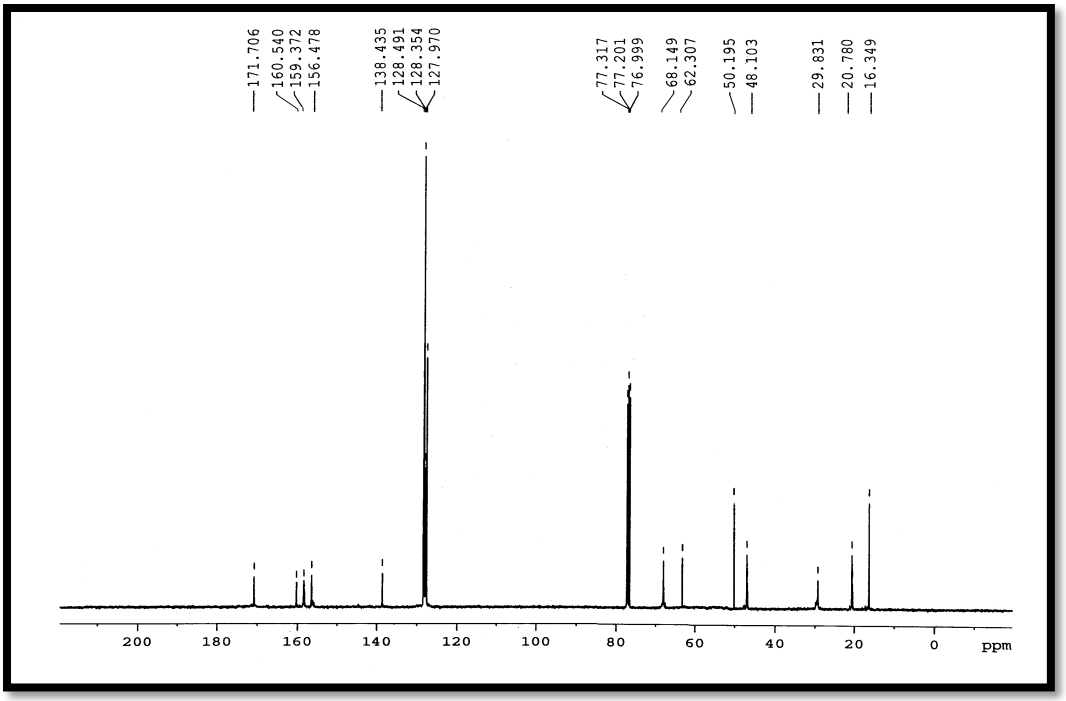
^{1}H NMR spectrum of **3e**



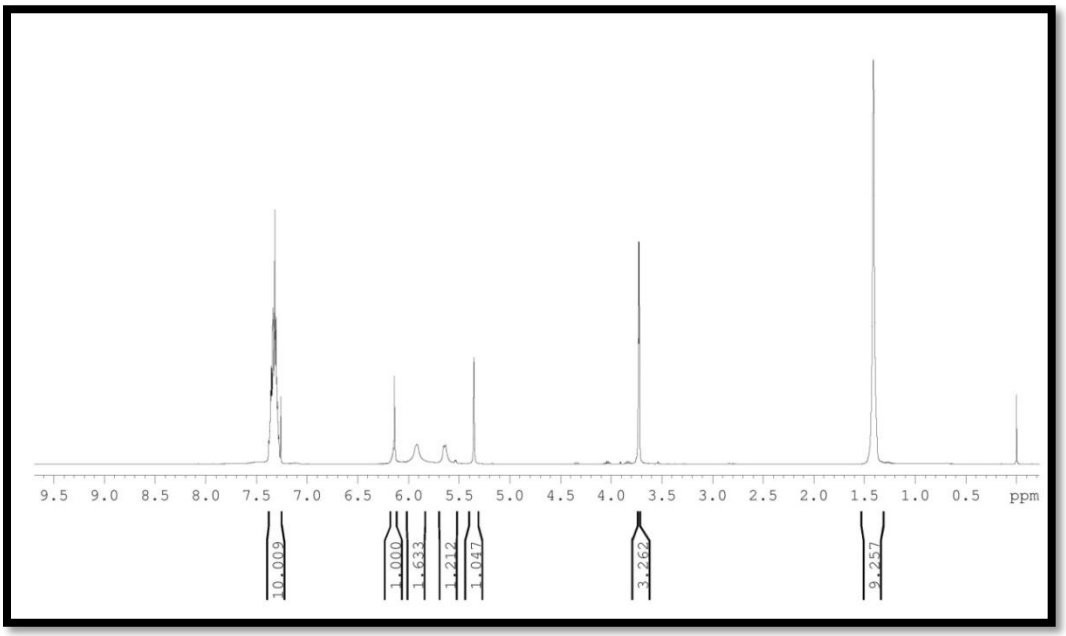
^{13}C NMR spectrum of **3e**



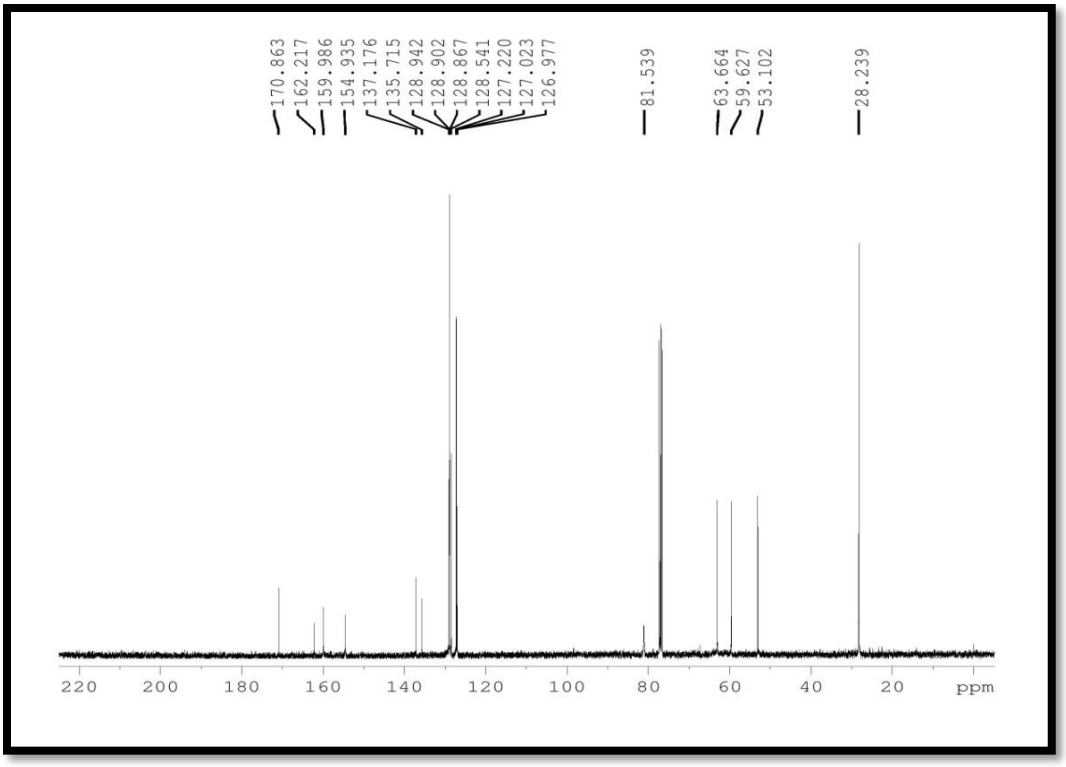
^{1}H NMR spectrum of **4a**



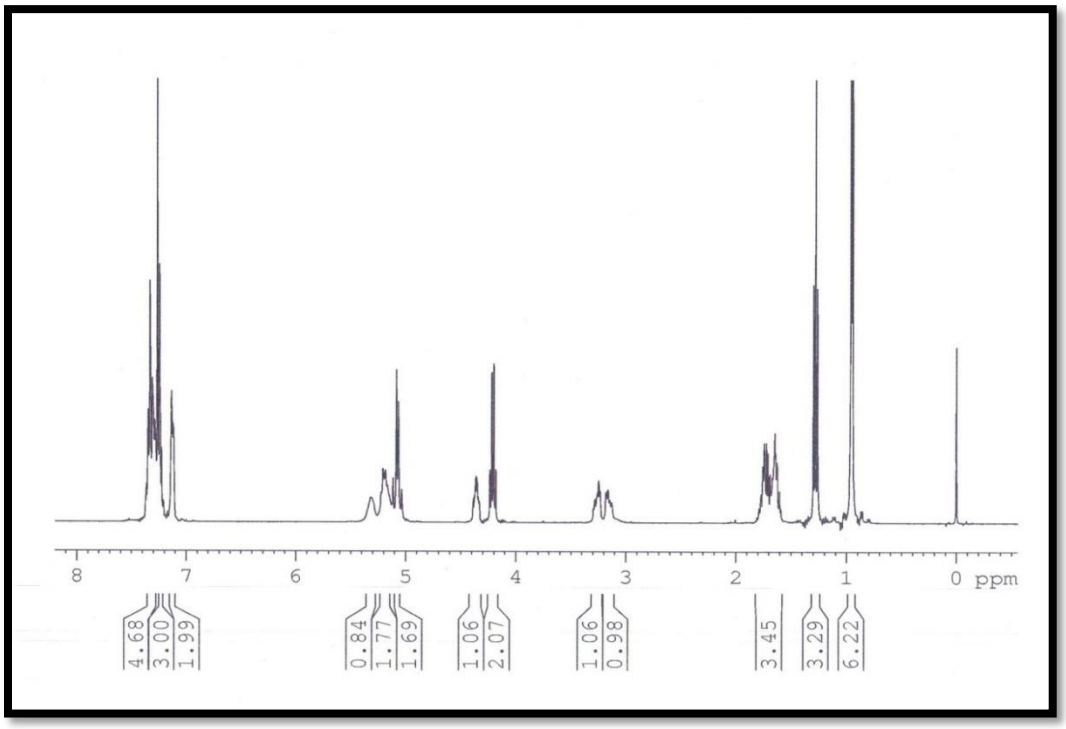
^{13}C NMR spectrum of **4a**



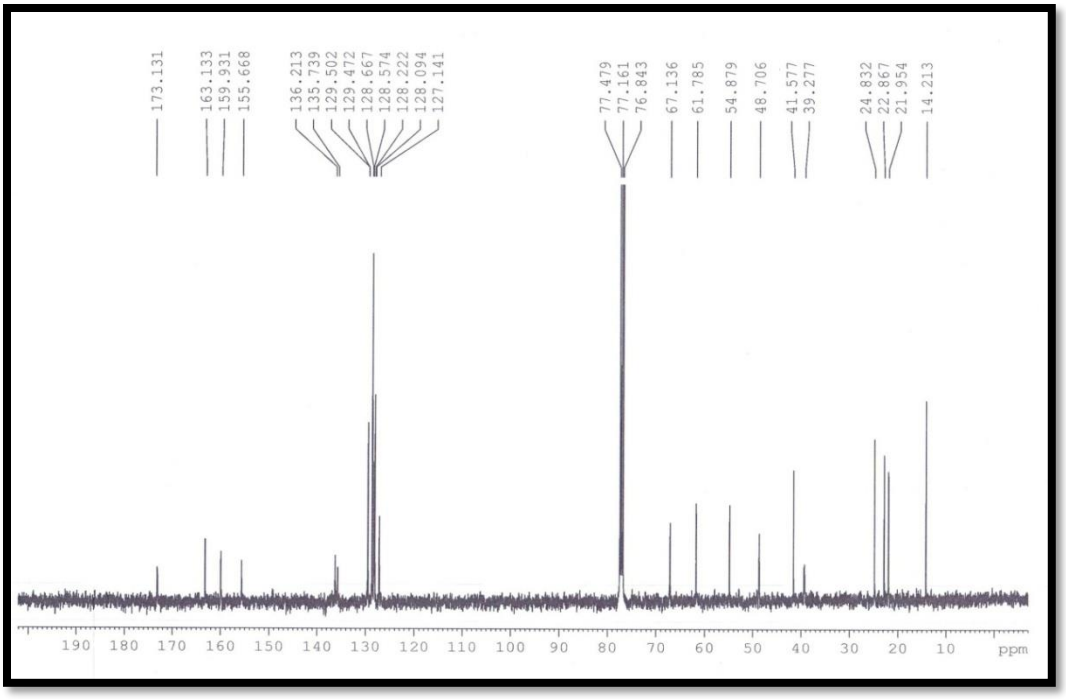
^{1}H NMR spectrum of **4b**



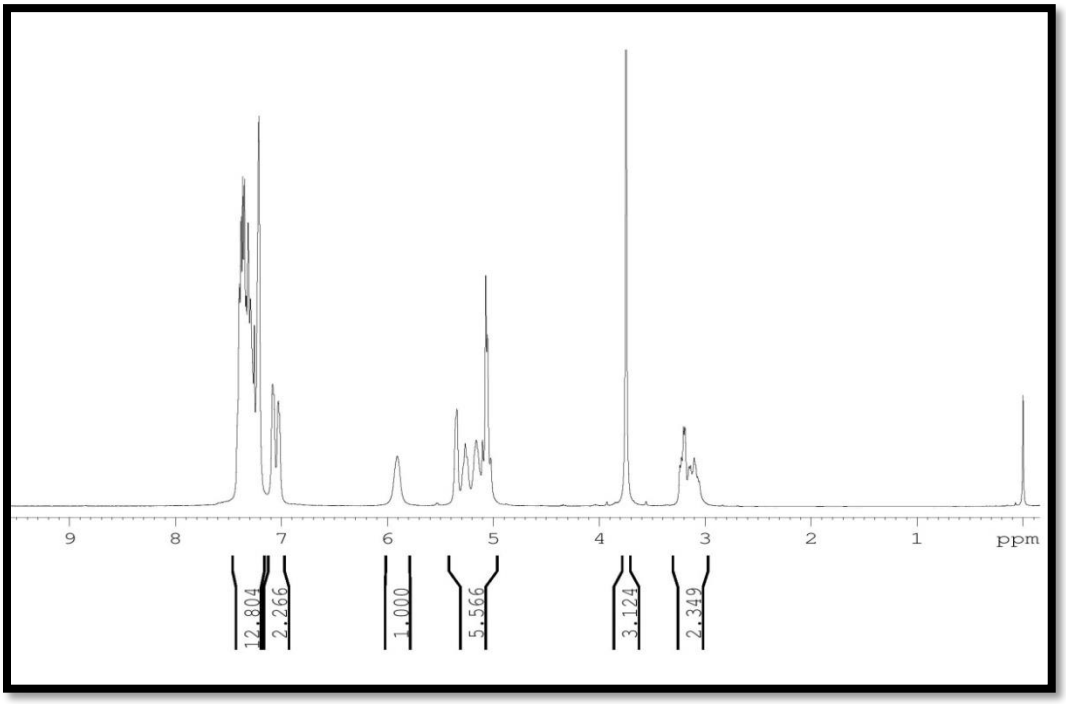
^{13}C NMR spectrum of **4b**



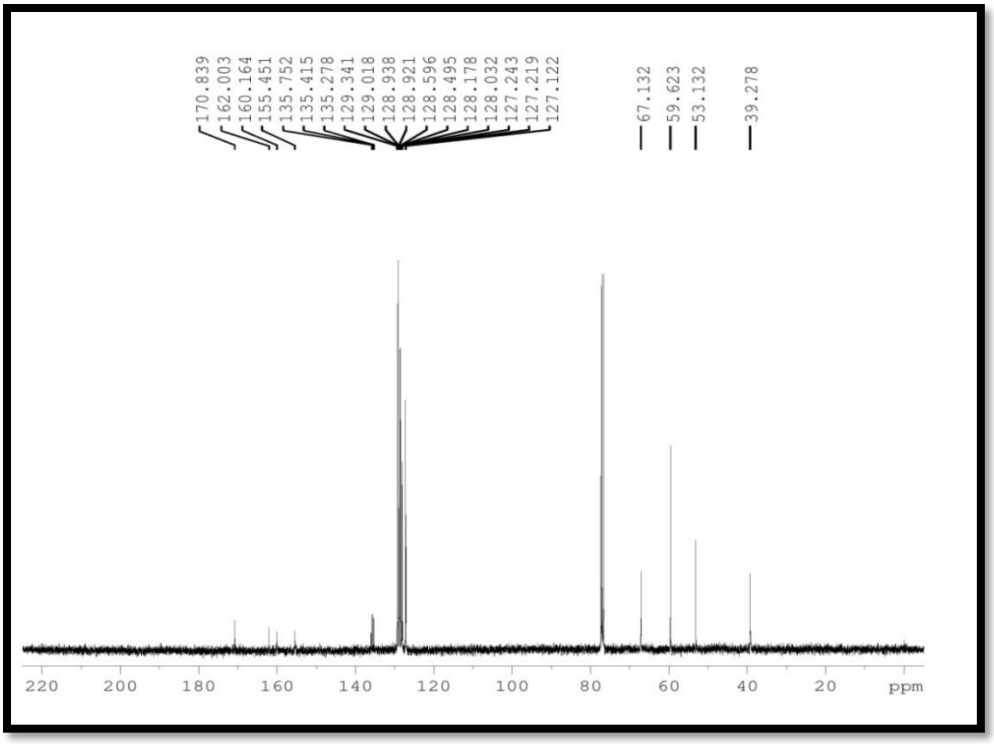
^{1}H NMR spectrum of **4c**



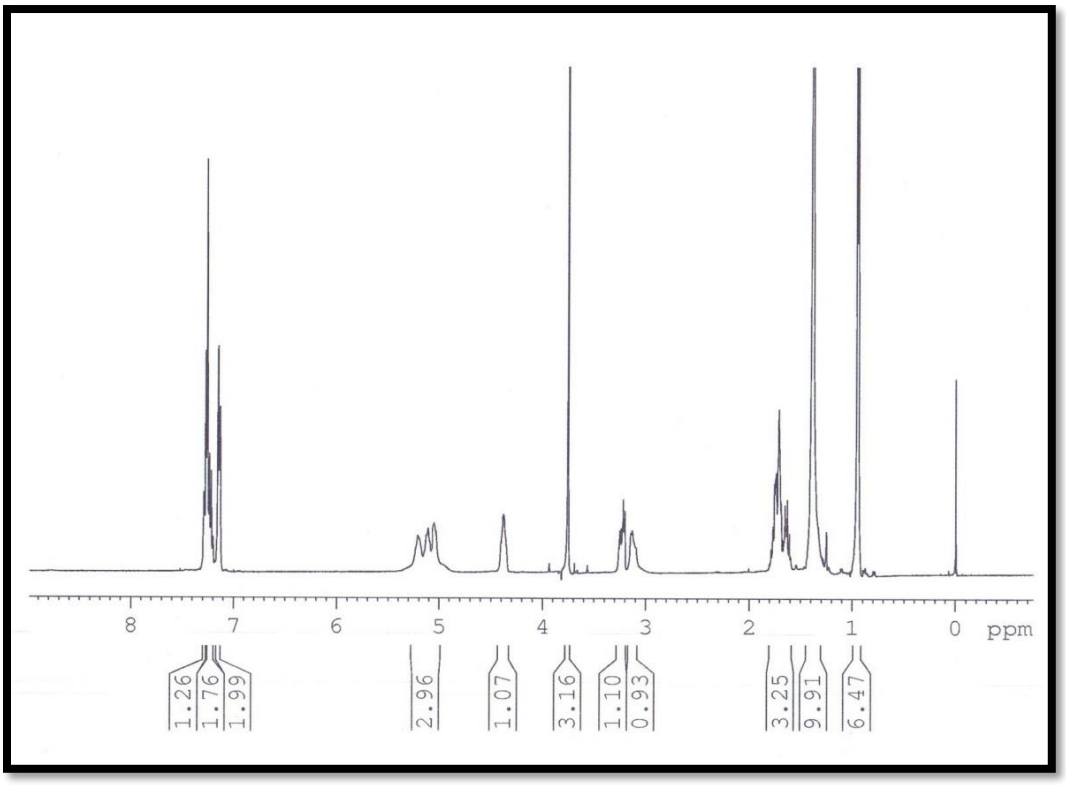
^{13}C NMR spectrum of **4c**



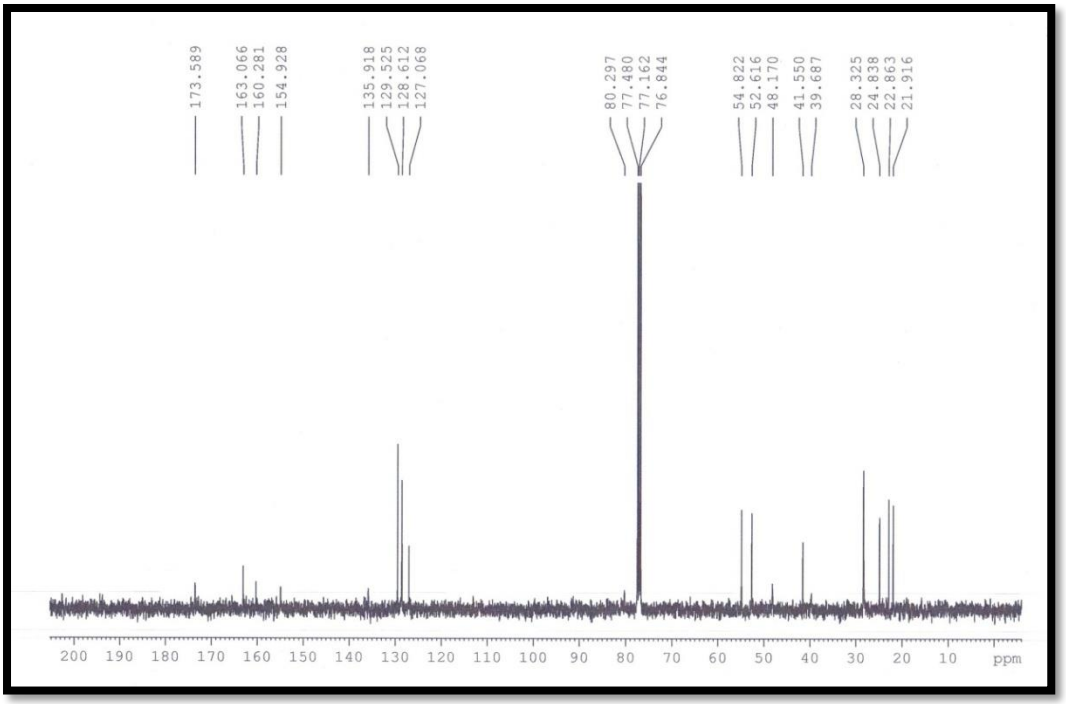
^{1}H NMR spectrum of **4d**



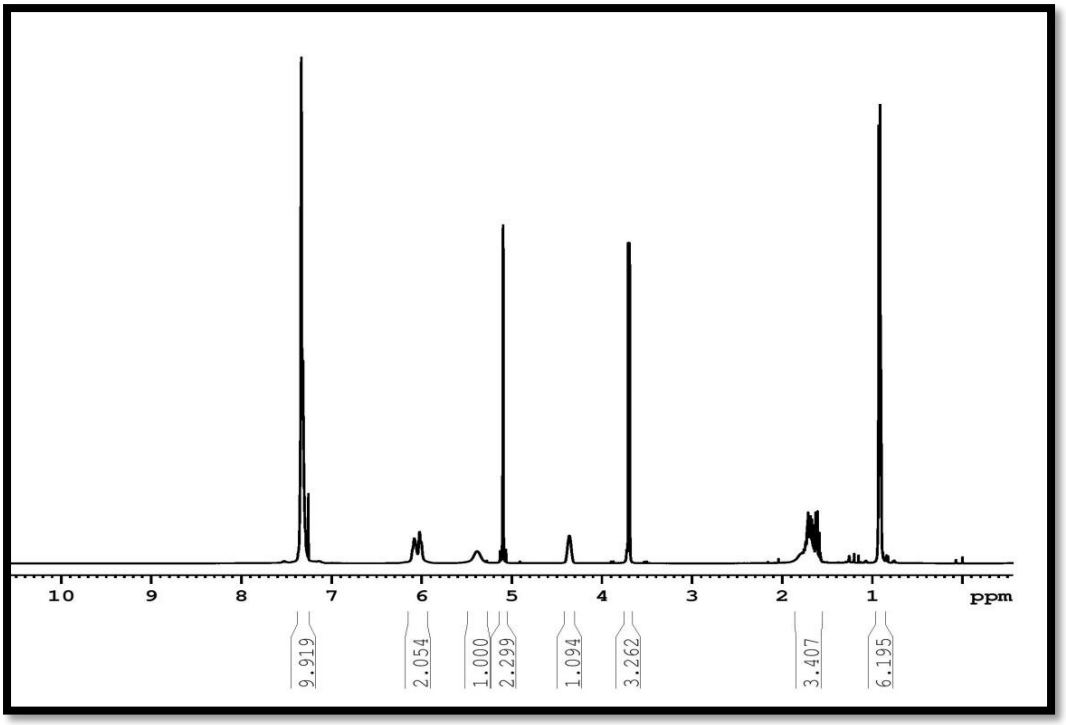
^{13}C NMR spectrum of **4d**



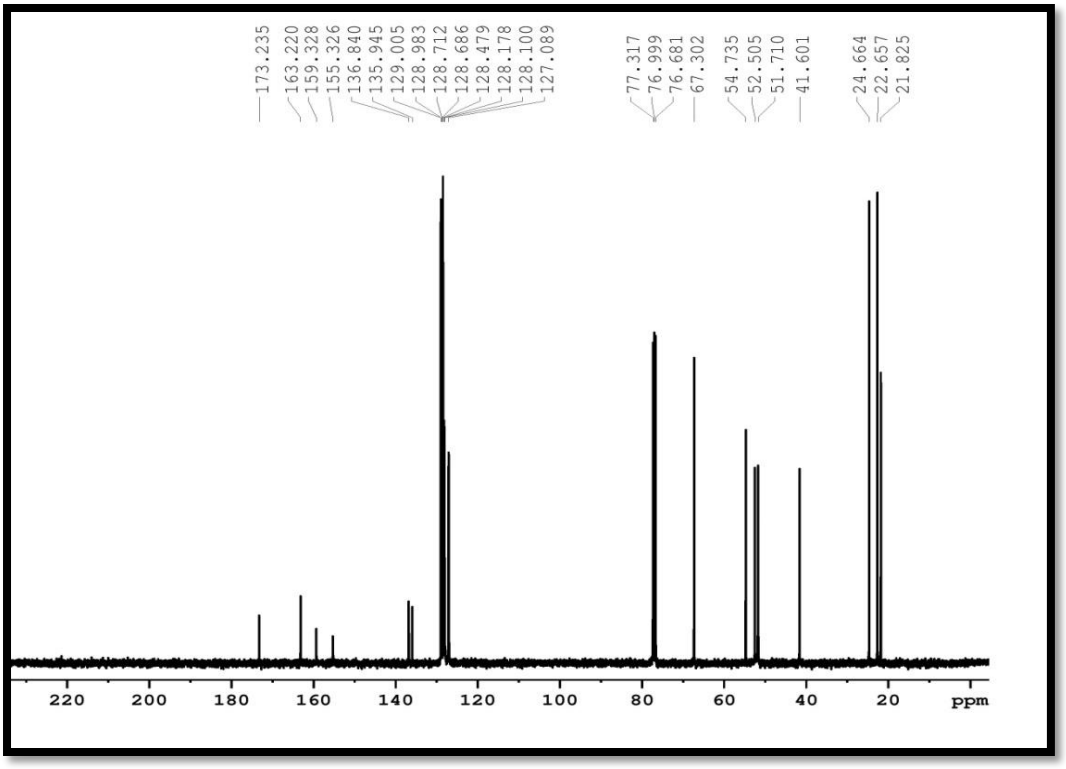
^{1}H NMR spectrum of **4e**



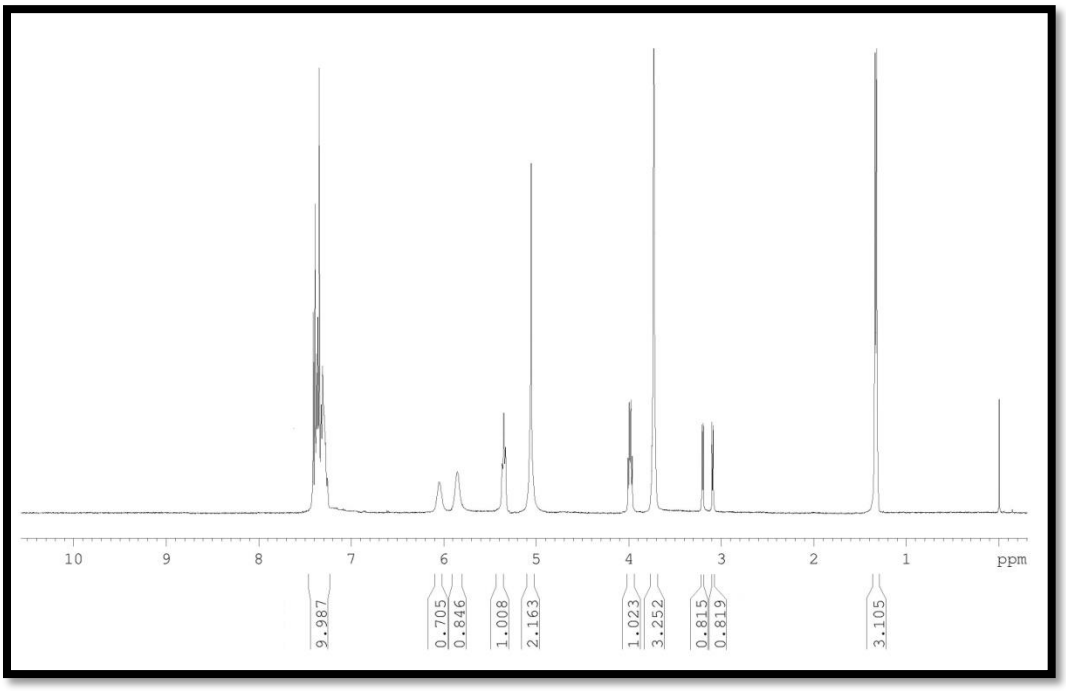
^{13}C NMR spectrum of **4e**



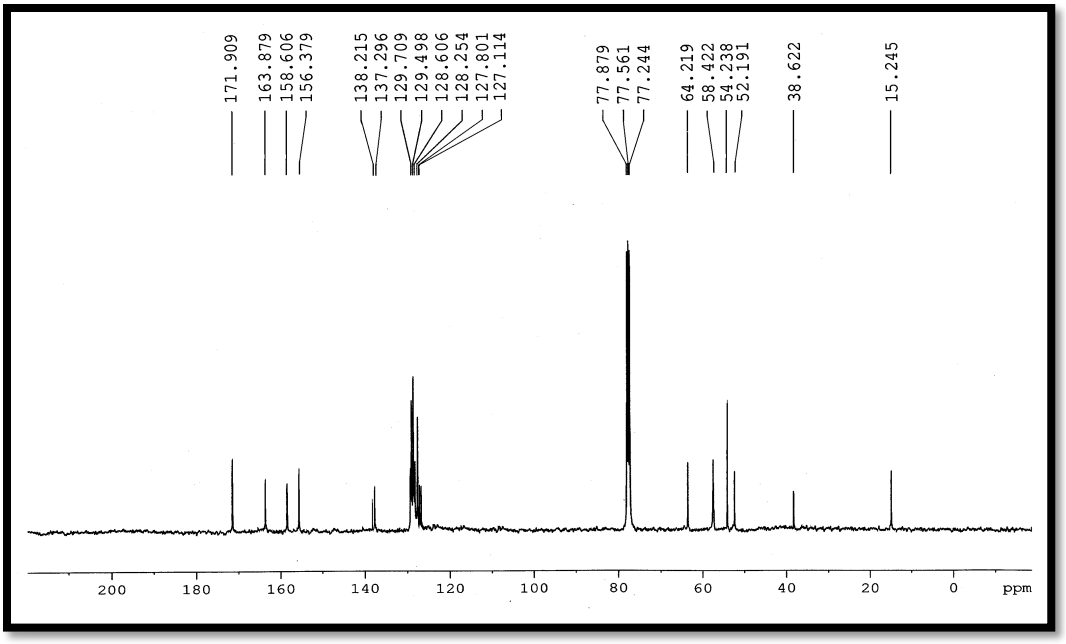
^{1}H NMR spectrum of **4f**



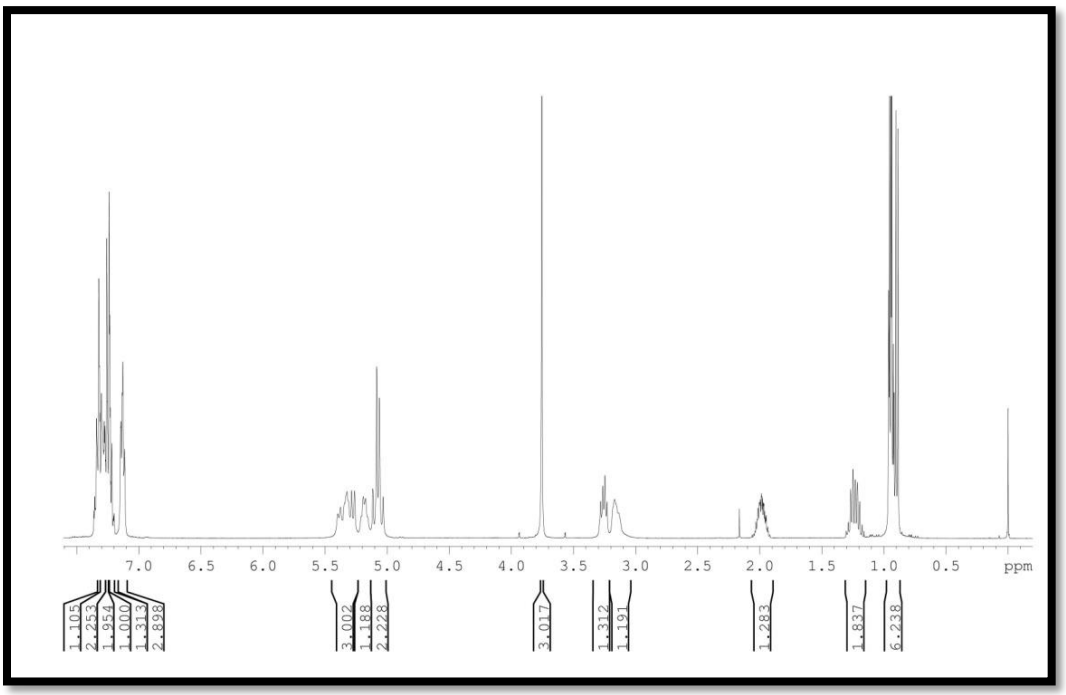
^{13}C NMR spectrum of **4f**



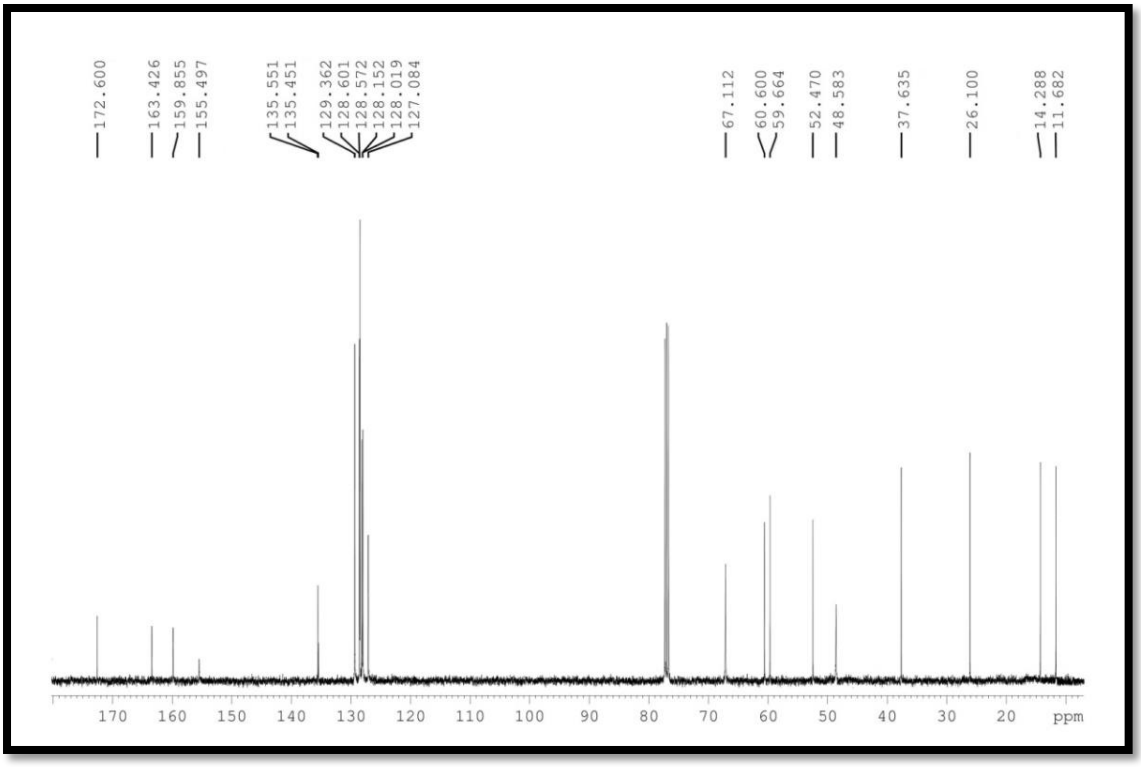
^{1}H NMR spectrum of **4g**



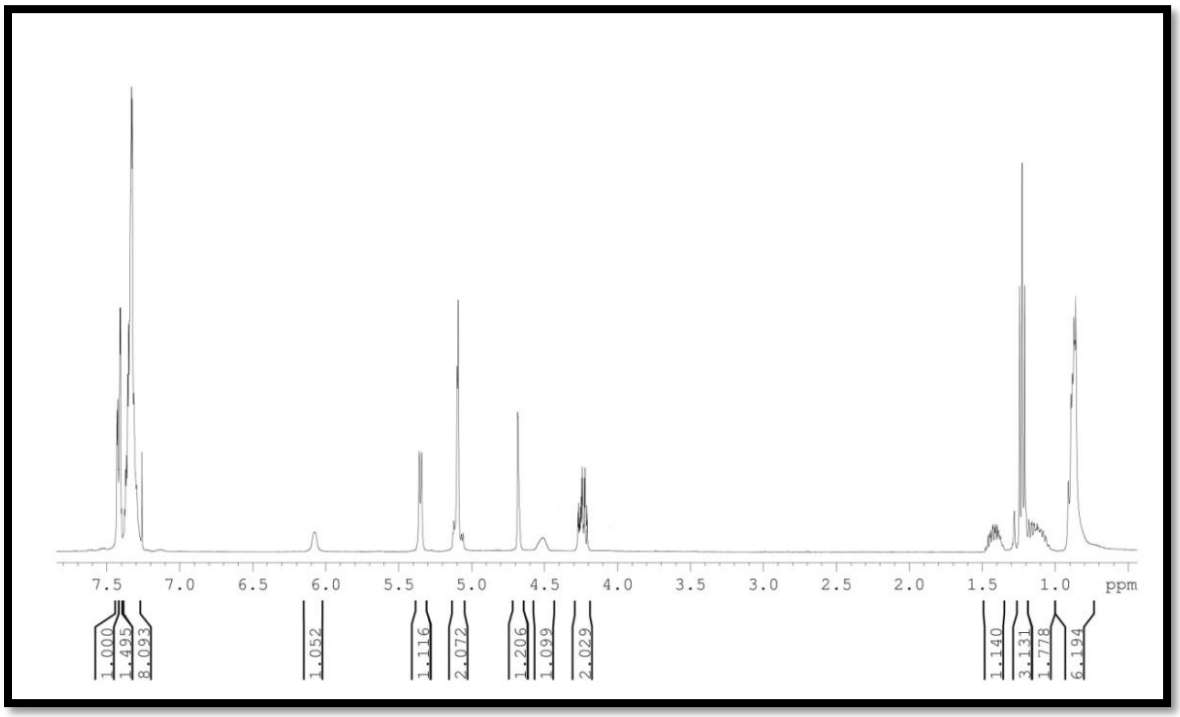
^{13}C NMR spectrum of **4g**



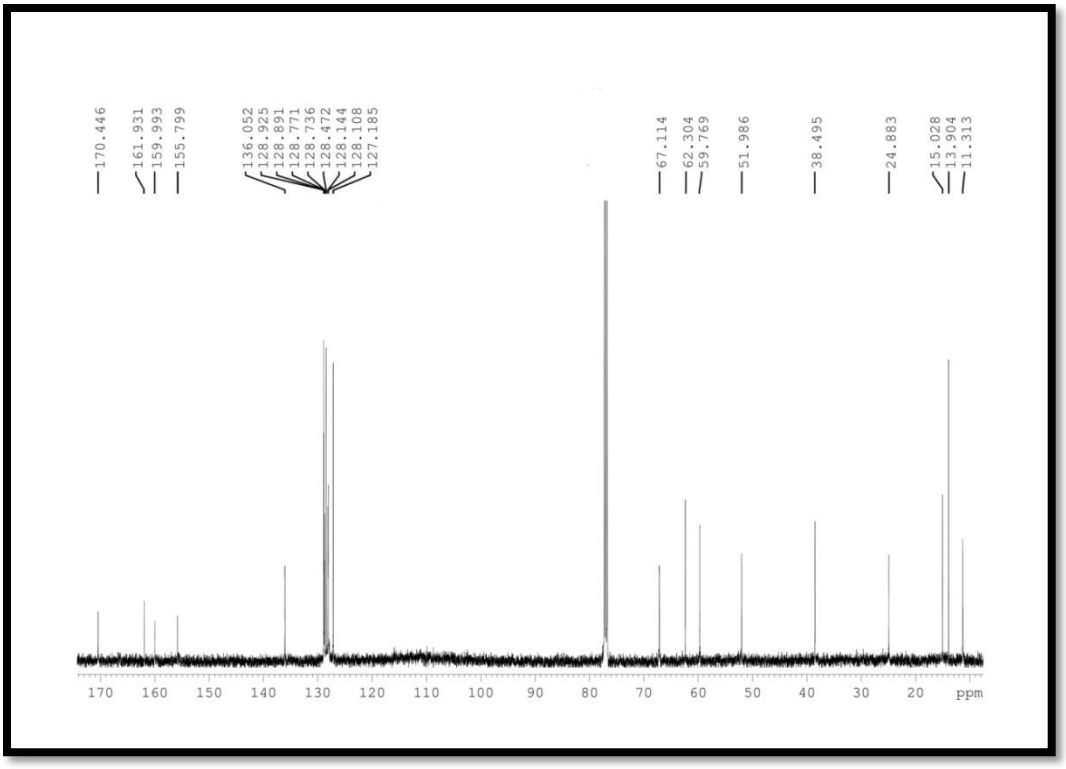
^{1}H NMR spectrum of **4h**



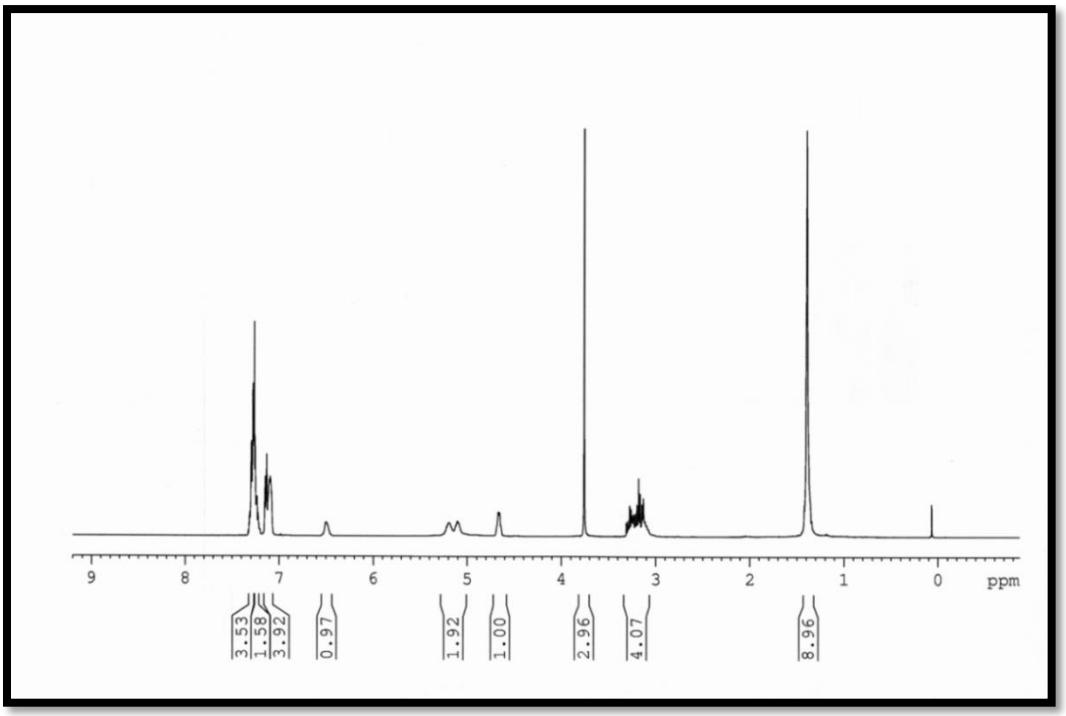
^{13}C NMR spectrum of **4h**



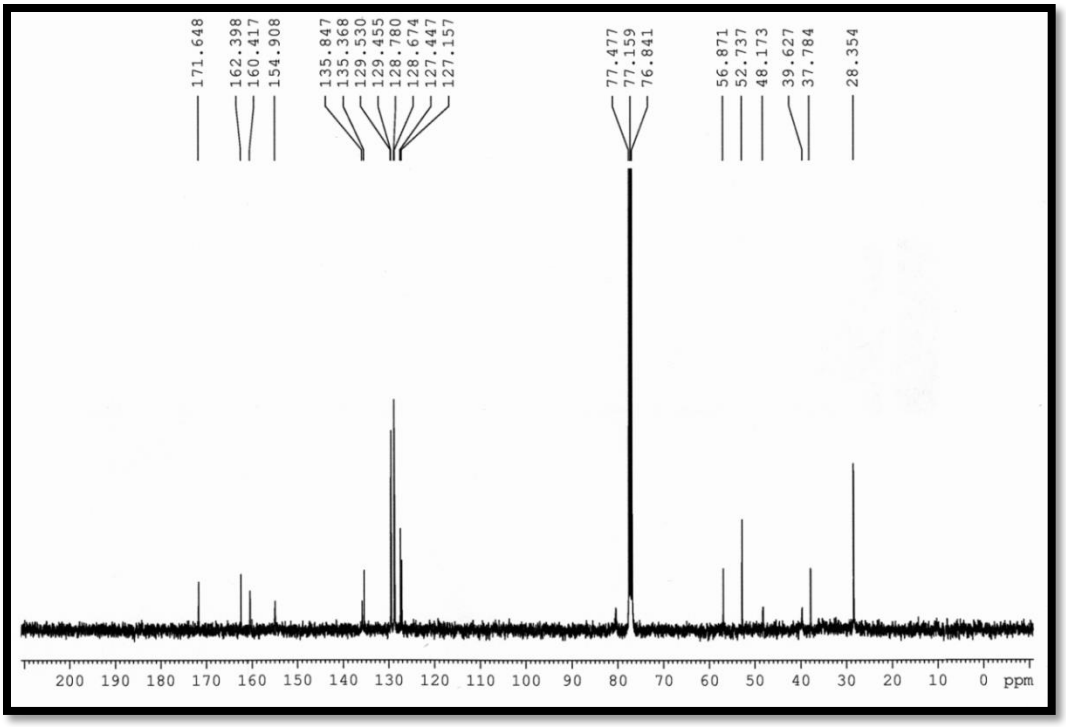
^{1}H NMR spectrum of **4i**



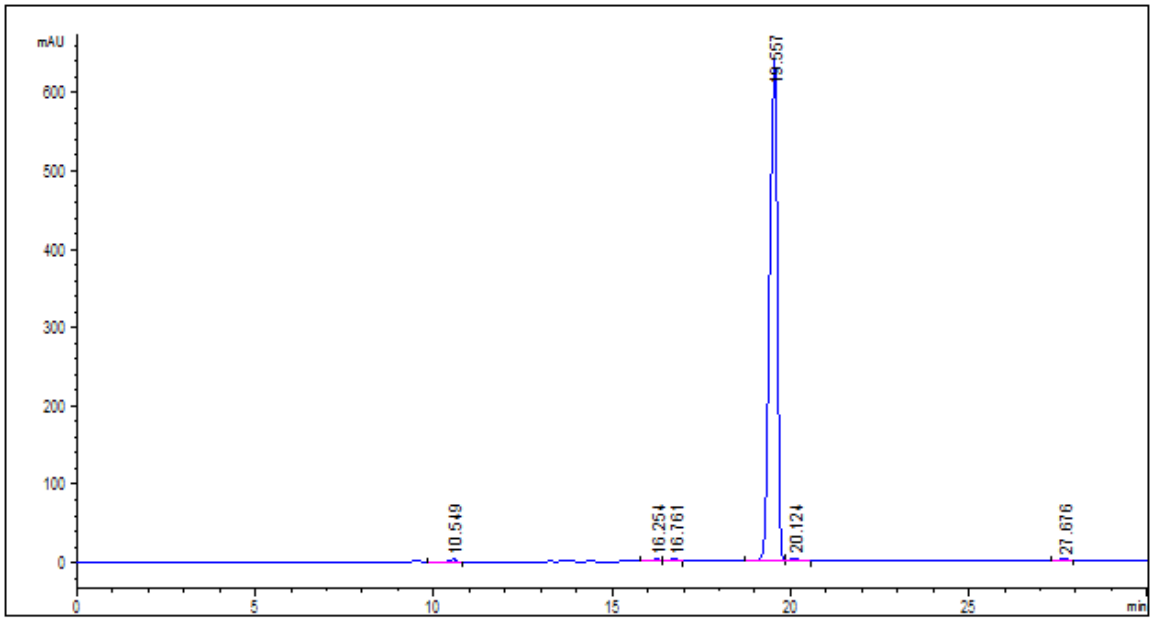
^{13}C NMR spectrum of **4i**



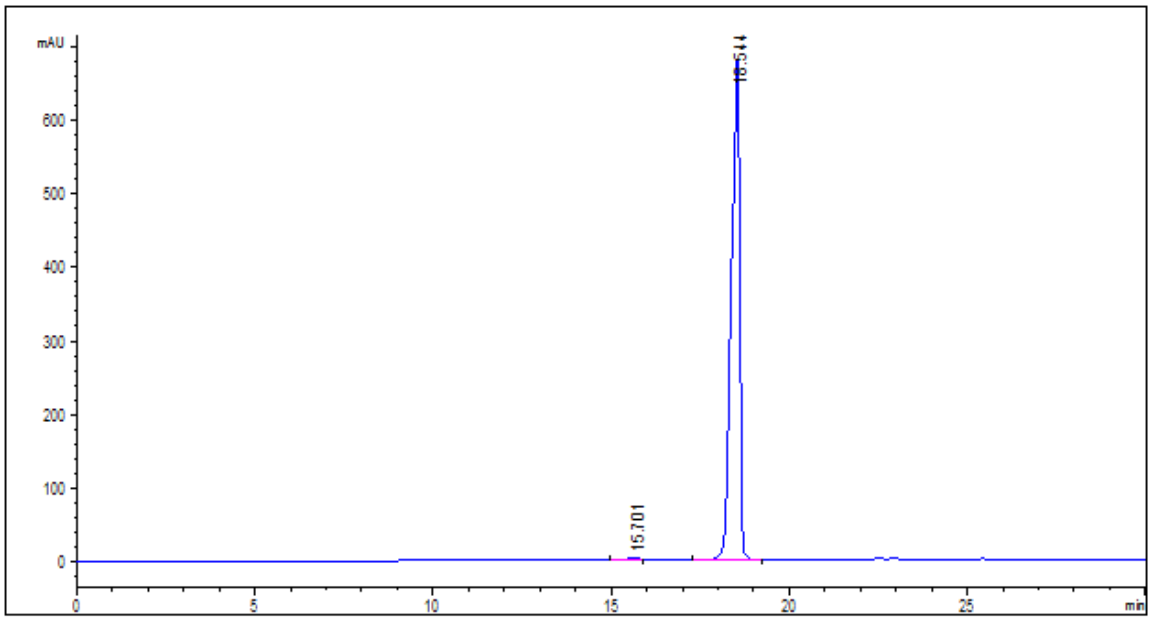
^{1}H NMR spectrum of **4j**



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



Cbz-Phe-ψ-[C_2N_2O]-NH-L-Ala-OMe **4g**



Cbz-Phe-ψ-[C_2N_2O]-NH-D-Ala-OMe **4g***

RP-HPLC profiles of Cbz-Phe-ψ-[C_2N_2O]-NH-L-Ala-OMe (**4g**) and Cbz-Phe-ψ-[C_2N_2O]-NH-D-Ala-OMe (**4g***) (method: gradient 0.1% TFA water-acetonitrile; acetonitrile 30-100% in 30 min; VWD at λ = 254 nm; flow rate: 0.5 mL/min; column: Agilent Eclipse, XDB-C18, pore size-5 µm, diameter x length = 4.6 x 150 nm).