Electronic Supplementary Information

L-Proline catalyzed multi-component synthesis of *N*-pyridyl-tetrahydroisoquinolines and their α-C(sp3)-H oxygenation

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General information

All the commercially available reagents were used as received. Melting points were determined in open capillary tubes with a Buchi-540 micro melting point apparatus and were uncorrected. I.R. spectra were recorded on a Perkin-Elmer system 2000 FT-IR spectrometer. Mass spectra (ESI-HRMS) were recorded on Agilent Accurate-Mass Q-TOF LC/MS 6520. NMR spectra were recorded on a Bruker Avance DPX-400, -500 NMR spectrometer with TMS as the internal standard at room temperature. Chemical shifts (δ) are quoted in ppm and coupling constants (J) are measured in Hertz (Hz). All the experiments were monitored by thin layer chromatography (TLC) on pre-coated silica gel plates (Merck) and visualized under UV lamp at 254 nm for UV active materials. Further visualization was achieved by iodine vapor. Column chromatography was performed on silica gel (100-200 mesh, Merck) using ethyl acetate/hexane as eluent.

Representative procedure for the synthesis of 4a:

1,2,3,4-tetrahydroisoquinoline (1 mmol, 133 mg), malononitrile (2 mmol, 132 mg), benzaldehyde (1 mmol, 106 mg), and L-Proline (10 mol%, 11.5 mg) were taken in a round bottom flask under solvent-free conditions and heated at 120 ^{o}C in an oil bath for 6 hours. We monitored the progress of the reaction every hour by a TLC and found that the reaction was completed after 6 h. After the completion, the reaction mixture was cooled to room temperature, and 20 ml of water was added to it. It was then extracted with ethyl acetate (2 x 20 ml). The organic fraction was then dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated with the help of a rotary evaporator

under reduced pressure. The desired compound was then obtained by column chromatography using silica gel (100-200 mesh) and hexane/ethyl acetate as eluent.

Representative procedure for the synthesis of both 5a and 6a (Reaction-A):

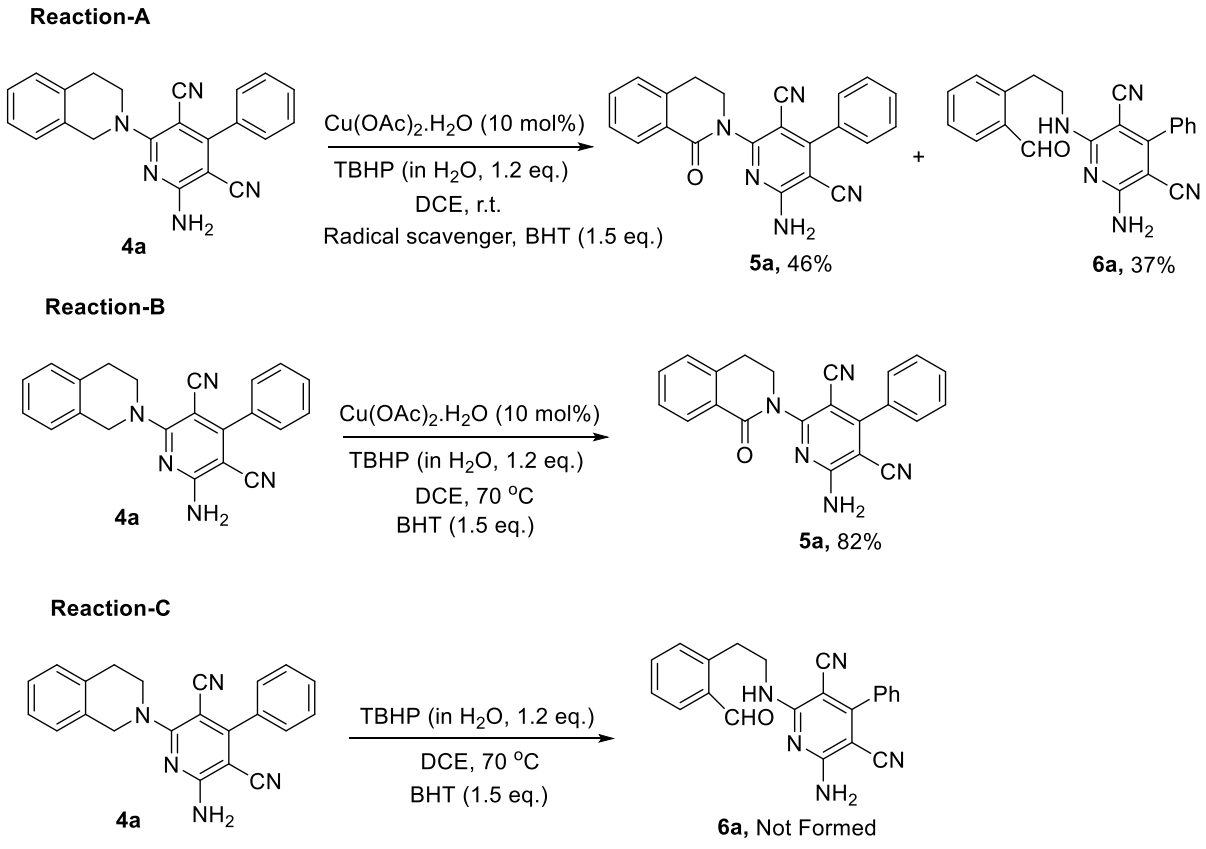
Compound **4** (0.5 mmol, 176 mg), TBHP (in H_2O, 1.2 eq., 77 mg), and $Cu(OAc)_2.H_2O$ (10 mol%, 10 mg) were taken in a round bottom flask and stirred at room temperature in DCE solvent (2 ml) for 6 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was extracted with ethyl acetate (30 ml) and water (20 ml). The organic fraction was then dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure in a rotary evaporator. The two products were isolated by column chromatography using silica gel (100-200 mesh), and hexane/ethyl acetate as eluent.

Representative procedure for the synthesis of 5a (Reaction-B):

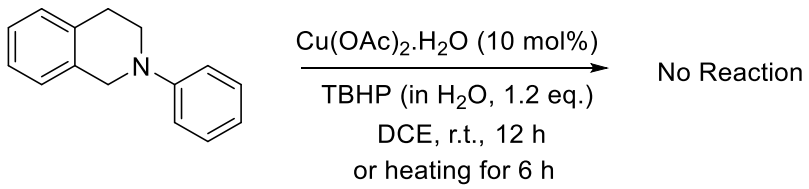
Compound **4** (0.5 mmol, 176 mg), TBHP (in H_2O, 1.2 eq., 77 mg), and $Cu(OAc)_2.H_2O$ (10 mol%, 10 mg) were taken in a round bottom flask in DCE (2 ml). The reaction mixture was then heated at 70 ^oC for 6 h. Progress of the reaction was monitored by TLC and observed the formation of only one product. After the reaction was finished, the mixture was extracted with ethyl acetate (30 ml) and water (20 ml), then dried the organic fraction over anhydrous Na_2SO_4. The organic solvent was then evaporated under reduced pressure in a rotary evaporator. The product was then isolated by column chromatography using silica gel (100-200 mesh), and hexane/ethyl acetate as eluent.

Representative procedure for the synthesis of 6a (Reaction-C):

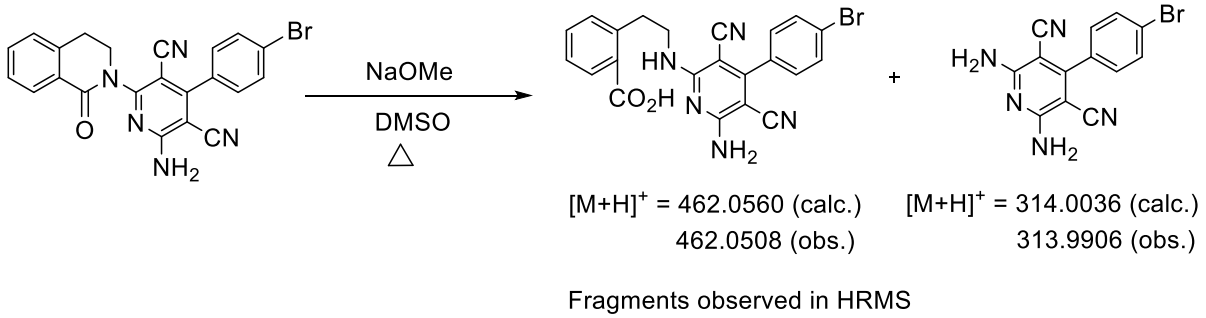
Compound **4** (0.5 mmol, 176 mg) and TBHP (in H_2O, 1.2 eq., 77 mg) were taken in a round bottom flask and heated the reaction mixture at 70 ^oC in DCE solvent (2 ml) for 12 h. Progress of the reaction was monitored by TLC and observed the formation of only less polar product. After the reaction was finished, the mixture was extracted with ethyl acetate (30 ml) and water (20 ml), then dried the organic fraction over anhydrous Na_2SO_4. The organic solvent was then removed under reduced pressure in a rotary evaporator. The product was then isolated by column chromatography using silica gel (100-200 mesh), and hexane/ethyl acetate as eluent.



Scheme S1. Radical scavenging reaction for the elucidation of the mechanism

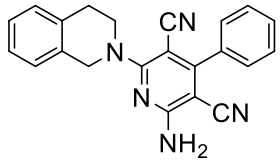
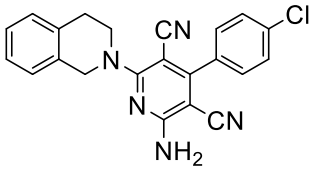
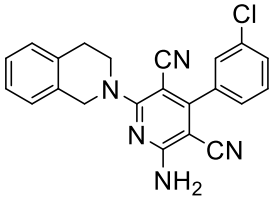
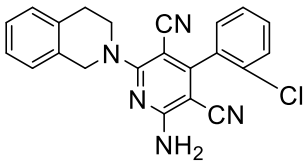


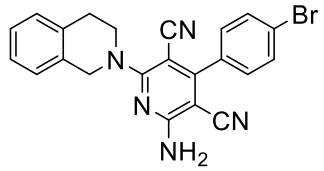
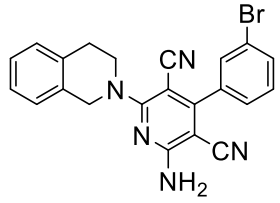
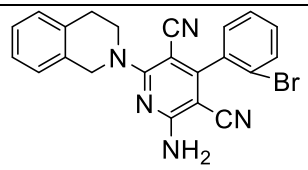
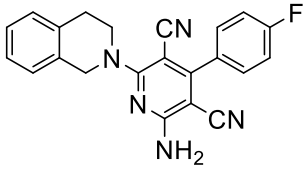
Scheme S2. Current reaction with N-phenylTHIQ

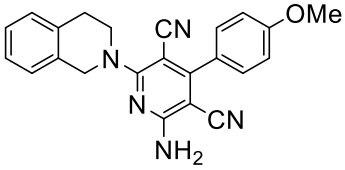
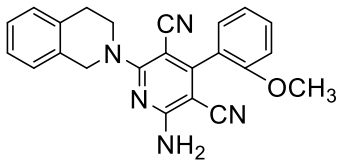
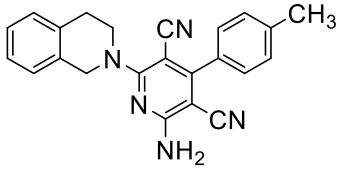
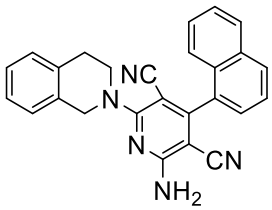


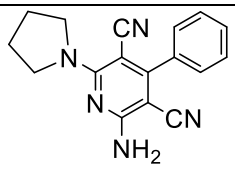
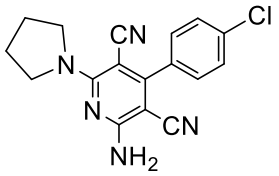
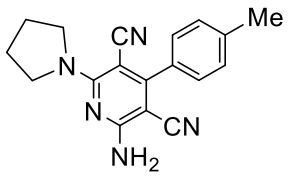
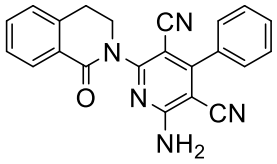
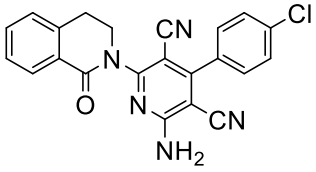
Scheme S3. Attempting deprotection of pyridyl moiety

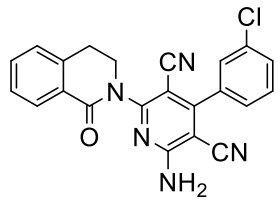
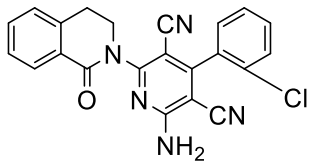
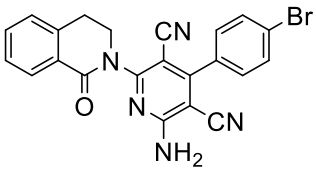
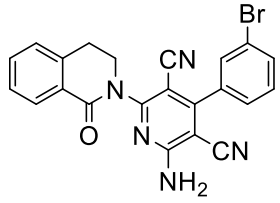
Characterization of the products

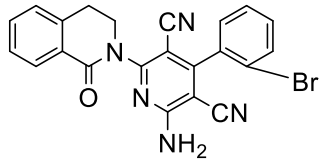
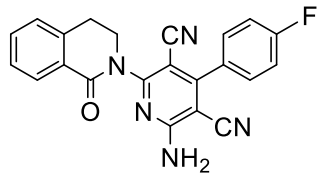
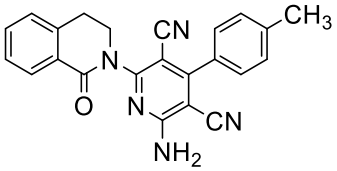
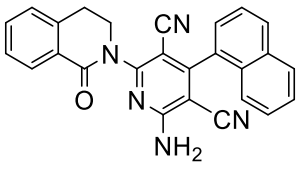
 **4a**	**2-Amino-6-(3,4-dihydroisoquinolin-2(1*H*)-yl)-4-phenylpyridine-3,5-dicarbonitrile (4a):** Yellow solid; Yield: 86%, 320 mg; M.p.: 224-226 ^{o}C; IR (KBr): 3432, 3343, 3057, 2925, 2203, 1610, 1364, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.49 (m, 4H), 7.23-7.14 (m, 5H), 5.45 (bs, 2H), 4.94 (s, 2H), 4.08 (t, *J* = 5.9 Hz, 2H), 3.05 (t, *J* = 5.9 Hz, 2H),; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3, 160.9, 159.3, 134.7, 133.1, 130.5, 129.0, 128.8, 128.6 (2C), 127.5, 126.9, 126.5, 126.4, 117.6, 116.4, 83.4, 82.1, 49.9, 46.3, 28.9; HRMS (ESI) exact mass calculated for $C_{22}H_{17}N_5$ $[M+H]^+$: 352.1557; found: 352.1564.
 **4b**	**2-Amino-4-(4-chlorophenyl)-6-(3,4-dihydroisoquinolin-2(1*H*)-yl)pyridine-3,5-dicarbonitrile (4b):** Orange solid; Yield: 80%, 309 mg; M.p.: 250-252 ^{o}C; IR (KBr): 3468, 3349, 3062, 3026, 2925, 2205, 1299, 1091, 744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.50 (m, 2H), 7.46-7.44 (m, 2H), 7.24-7.17 (m, 4H), 5.45 (bs, 2H), 4.94 (s, 2H), 4.08 (t, *J* = 5.8 Hz, 2H), 3.05 (t, *J* = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 160.7, 159.3, 136.8, 134.6, 133.0, 130.5, 130.1, 129.2, 129.0, 128.6, 127.0, 126.5, 126.4, 117.4, 116.2, 83.1, 81.9, 49.9, 46.2, 28.9; HRMS (ESI) exact mass calculated for $C_{22}H_{16}ClN_5$ $[M + H]^+$: 386.1167; found: 386.1172.
 **4c**	**2-Amino-4-(3-chlorophenyl)-6-(3,4-dihydroisoquinolin-2(1*H*)-yl)pyridine-3,5-dicarbonitrile (4c):** Yellow solid; Yield: 81%, 313 mg; M.p.: 233-235 ^{o}C; IR (KBr): 3441, 3346, 3061, 2935, 2210, 1276, 1093, 1001, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.46 (m, 2H), 7.38-7.35 (m, 1H), 7.23-7.17 (m, 5H), 5.46 (bs, 2H), 4.94 (s, 2H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.05 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 160.6, 159.2, 136.4, 134.8, 134.6, 133.0, 130.6, 130.2, 128.7, 128.6, 127.0, 126.8, 126.5, 126.4, 117.2, 115.9, 49.9, 46.3, 28.9; HRMS (ESI) exact mass calculated for $C_{22}H_{16}ClN_5$ $[M + H]^+$: 386.1167; found: 386.1171.
 **4d**	**2-Amino-4-(2-chlorophenyl)-6-(3,4-dihydroisoquinolin-2(1*H*)-yl)pyridine-3,5-dicarbonitrile (4d):** Yellow solid; Yield: 85%, 327 mg; M.p.: 199-201 ^{o}C; IR (KBr): 3435, 3349, 3058, 2929, 2209, 1356, 1245, 1093, 744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55-7.54 (m, 1H), 7.46-7.39 (m, 2H), 7.32-7.30 (m, 1H), 7.23-7.17 (m, 4H), 5.42 (bs, 2H), 4.94 (s, 2H), 4.14-4.04 (m, 2H), 3.04 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.0, 159.9, 159.0, 134.7, 134.0, 133.1, 132.2, 131.3, 130.3, 129.8, 128.5, 127.3, 127.0, 126.5, 126.4, 116.7, 115.5, 84.3, 82.9, 49.6, 46.1, 29.0; HRMS (ESI) exact mass calculated for $C_{22}H_{16}ClN_5$ $[M + H]^+$: 386.11267; found: 386.1174.
	2-Amino-4-(4-bromophenyl)-6-(3,4-dihydroisoquinolin-2(1*H*)-yl)pyridine-3,5-dicarbonitrile (4e): Yellow solid; Yield: 87%, 374 mg; M.p.: 261-262 ^{o}C; IR (KBr): 3427, 3365, 3055, 2942, 2206,

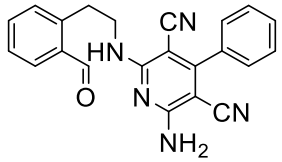
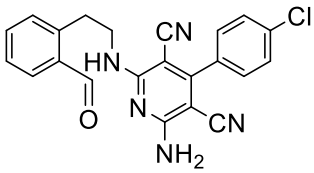
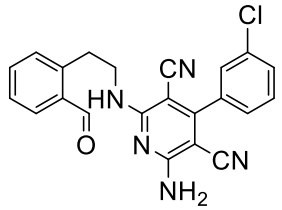
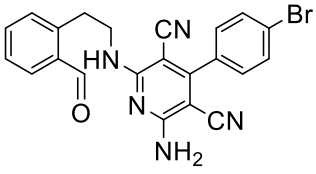
 **4e**	1617, 1289, 1098, 441 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.59-7.57 (m, 2H), 7.31-7.29 (m, 2H), 7.18-7.05 (m, 4H), 5.40 (bs, 2H), 4.85 (s, 2H), 4.00 (t, *J* = 5.8 Hz, 2H), 2.97 (t, *J* = 5.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.00, 160.7, 159.2, 134.6, 133.5, 133.0, 132.1, 132.0, 130.8, 130.3, 128.5, 127.0, 126.5, 126.3, 125.1, 117.4, 116.1, 82.9, 81.8, 49.8, 46.2, 28.8; HRMS (ESI) exact mass calculated for $C_{22}H_{16}BrN_5$ $[M + H]^+$: 430.0662; found: 430.0665.
 **4f**	**2-Amino-4-(3-bromophenyl)-6-(3,4-dihydroisoquinolin-2(1*H*)-yl)pyridine-3,5-dicarbonitrile (4f):** Yellow solid; Yield: 78%, 336 mg; M.p.: 241-243 °C; IR (KBr): 3436 (br), 2923, 2205, 1620, 1527, 1056, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.66-7.63 (m, 2H), 7.43-7.39 (m, 2H), 7.21-7.17 (m, 4H), 5.49 (bs, 2H), 4.93 (s, 2H), 4.07 (t, *J* = 5.6 Hz, 2H), 3.05 (t, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 160.5, 159.2, 136.5, 134.6, 133.5, 133.0, 131.5, 130.4, 128.5, 127.3, 127.0, 126.5, 126.3, 122.7, 117.2, 116.0, 83.0, 81.9, 49.8, 46.2, 28.8; HRMS (ESI) exact mass calculated for $C_{22}H_{16}BrN5$ $[M + H]^+$: 430.0662; found: 430.0668.
 **4g**	**2-Amino-4-(2-bromophenyl)-6-(3,4-dihydroisoquinolin-2(1*H*)-yl)pyridine-3,5-dicarbonitrile (4g):** Yellow solid; Yield: 83%, 357 mg; M.p.: 219-221 °C; IR (KBr): 3447, 3339, 3066, 2925, 2206, 1611, 1544, 1299, 1061, 747 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.74-7.72 (m, 1H), 7.48-7.45 (m, 1H), 7.38-7.35 (m, 1H), 7.31-7.29 (m, 1H), 7.24-7.17 (m, 4H), 5.43 (bs, 2H), 4.95 (s, 2H), 4.14-4.06 (m, 2H), 3.06-3.04 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.3, 159.9, 158.9, 136.0, 134.7, 133.4, 133.1, 131.4, 129.7, 128.5, 127.9, 127.0, 126.5, 126.4, 121.6, 116.7, 115.5, 84.2, 82.8, 49.6, 46.1, 28.9; HRMS (ESI) exact mass calculated for $C_{22}H_{16}BrN_5$ $[M + H]^+$: 430.0662; found: 430.0669.
 **4h**	**2-Amino-6-(3,4-dihydroisoquinolin-2(1*H*)-yl)-4-(4-fluorophenyl) pyridine-3,5-dicarbonitrile (4h):** Orange gummy; Yield: 81%, 299 mg; IR (neat): 3455, 3346, 3061, 2927, 2210, 1620, 1395, 1258, 1001, 946, 743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.51-7.49 (m, 2H), 7.23-7.17 (m, 6H), 5.45 (bs, 2H), 4.93 (s, 2H), 4.08 (t, *J* = 5.8 Hz, 2H), 3.05 (t, *J* = 5.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.0 (d, *J* = 250.9 Hz), 161.2, 160.8, 159.3, 134.6, 133.1, 130.9 (d, *J* = 8.7 Hz), 130.7 (d, *J* = 3.7 Hz), 128.6, 127.0, 126.5, 126.4, 117.5, 116.1 (d, *J* = 22.5 Hz), 83.3, 82.1, 49.9, 46.3, 28.9; HRMS (ESI) exact mass calculated for $C_{22}H_{16}FN_5$ $[M + H]^+$: 370.1463; found: 370.1462.

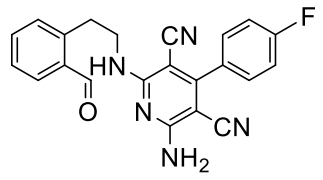
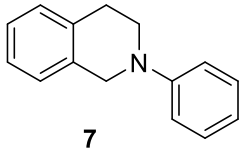
 **4i**	**2-Amino-6-(3,4-dihydroisoquinolin-2(1*H*)-yl)-4-(4-methoxyphenyl)pyridine-3,5-dicarbonitrile (4i):** Yellow solid; Yield: 79%, 301 mg; M.p.: 220-222 ^{o}C; IR (KBr): 3436, 3339, 3047, 2928, 2205, 1619, 1599, 1393, 1129, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.40 (m, 2H), 7.18-7.06 (m, 4H), 6.96-6.94 (m, 2H), 5.35 (bs, 2H), 4.85 (s, 2H), 3.99 (t, *J* = 5.8 Hz, 2H), 3.79 (s, 3H), 2.98 (t, *J* = 5.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.7, 161.1, 160.9, 159.2, 134.4, 132.9, 130.2, 129.9, 128.3, 126.6, 126.5, 126.2, 126.1, 117.7, 116.5, 114.0, 83.0, 81.7, 55.1, 49.7, 46.0, 28.6; HRMS (ESI) exact mass calculated for $C_{23}H_{19}N_5O$ $[M + H]^+$: 382.1663; found: 382.1660.
 **4j**	**2-Amino-6-(3,4-dihydroisoquinolin-2(1*H*)-yl)-4-(2-methoxyphenyl)pyridine-3,5-dicarbonitrile (4j):** Orange solid; Yield: 81%, 309 mg; M.p.: 209-211 ^{o}C; IR (KBr): 3444, 3336, 3215, 3018, 2936, 2206, 1612, 1543, 1387, 1294, 1010, 743 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.51-7.48 (m, 2H), 7.30-7.29 (m, 1H), 7.21-7.19 (m, 4H), 7.10-7.07 (m, 1H), 4.84 (bs, 2H), 4.69-4.56 (m, 2H), 4.00-3.91 (m, 2H), 3.80 (s, 3H), 3.02-2.95 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.4, 159.5, 155.9, 134.7, 133.6, 131.5, 130.9, 129.9, 128.5, 126.7, 126.3, 126.2, 124.2, 120.6, 117.5, 116.0, 112.0, 82.5, 82.4, 55.7, 49.0, 46.0, 28.3; HRMS (ESI) exact mass calculated for $C_{23}H_{19}N_5O$ $[M + H]^+$: 382.1663; found: 382.1667.
 **4k**	**2-Amino-6-(3,4-dihydroisoquinolin-2(1*H*)-yl)-4-(p-tolyl)pyridine-3,5-dicarbonitrile (4k):** Yellow gummy; Yield: 81%, 296 mg; IR (neat): 3432, 3336, 3065, 2925, 2210, 1627, 1544, 1396, 1288, 744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.39 (m, 2H), 7.32-7.30 (m, 2H), 7.22-7.16 (m, 4H), 5.44 (bs, 2H), 4.92 (s, 2H), 4.06 (t, *J* = 5.8 Hz, 2H), 3.04 (t, *J* = 5.8 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.4, 161.0, 159.4, 140.8, 134.7, 133.2, 131.7, 129.5, 128.6, 128.5, 126.9, 126.4, 126.3, 117.7, 116.5, 83.3, 82.1, 49.9, 46.3, 28.9, 21.4; HRMS (ESI) exact mass calculated for $C_{23}H_{19}N_5$ $[M + H]^+$: 366.1714; found: 366.1718.
 **4l**	**2-Amino-6-(3,4-dihydroisoquinolin-2(1*H*)-yl)-4-(naphthalen-1-yl)pyridine-3,5-dicarbonitrile (4l):** Reddish gummy; Yield: 79%, 324 mg; IR (KBr): 3442, 3331, 3065, 2922, 2206, 1610,1543, 1392, 1281, 744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99-7.92 (m, 2H), 7.60-7.57 (m, 2H), 7.54-7.49 (m, 2H), 7.46-7.45 (m, 1H), 7.23-7.17 (m, 4H), 5.45 (bs, 2H), 4.97 (s, 2H), 4.16-4.05 (m, 2H), 3.05 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.6, 160.2, 159.0, 134.7, 133.6, 133.1, 132.5, 130.5, 130.3, 128.8, 128.5, 127.2, 127.0, 126.5 (2C), 126.4 (2C), 125.2, 124.3, 116.9, 115.8, 85.0, 83.4, 49.7, 46.1, 28.9; HRMS (ESI) exact mass calculated for $C_{26}H_{19}N_5$ $[M + H]^+$: 402.1714; found: 402.1716.

 **4m**	**2-Amino-4-phenyl-6-(pyrrolidin-1-yl)pyridine-3,5-dicarbonitrile (4m):** Off white solid; Yield: 88%, 255 mg; M.p.: 188-190 ^{o}C; IR (KBr): 3475, 3321, 3057, 2926, 2210, 2198, 1584, 1299, 1230, 1001, 743 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.51-7.45 (m, 5H), 5.36 (bs, 2H), 3.80 (m, 4H), 1.98-1.96 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.1, 159.3, 157.5, 135.0, 130.2, 128.7, 128.4, 118.1, 116.7, 81.9, 81.0, 49.5, 24.1; HRMS (ESI) exact mass calculated for $C_{17}H_{15}N_5$ $[M + H]^+$: 290.1401; found: 290.1409.
 **4n**	**2-Amino-4-(4-chlorophenyl)-6-(pyrrolidine-1-yl)pyridine-3,5-dicarbonitrile (4n):** Off white solid, Yield: 82%, 265 mg; M.p.: 213-215 ^{o}C; IR (KBr): 3470, 3329, 3049, 2925, 2210, 2196, 1611, 1544, 1291, 1219, 981, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50-7.47 (m, 2H), 7.43-7.40 (m, 2H), 5.34 (bs, 2H), 3.81 (m, 4H), 2.00-1.97 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 159.2, 157.4, 136.5, 133.3, 130.5, 129.9, 129.1, 118.0, 116.5, 81.7, 80.8, 49.6, 24.1; HRMS (ESI) exact mass calculated for $C_{17}H_{14}ClN_5$ $[M+H]^+$: 324.1016; found: 324.1017.
 **4o**	**2-amino-6-(pyrrolidin-1-yl)-4-(p-tolyl)pyridine-3,5-dicarbonitrile (4o):** Off white solid; Yield: 80%, 242 mg; M.p.: 206-207 ^{o}C; IR (KBr): 3466, 3328, 3061, 2922, 2834, 2210, 2197, 1588, 1284, 1229, 1001, 744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.36 (m, 2H), 7.31-7.29 (m, 2H), 5.31 (bs, 2H), 3.81 (m, 4H), 2.41 (s, 3H), 1.99-1.96 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2, 159.3, 157.6, 140.4, 132.0, 129.4, 128.4, 118.4, 117.0, 81.9, 81.0, 49.6, 24.1, 21.5; HRMS (ESI) exact mass calculated for $C_{18}H_{17}N_5$ $[M+H]^+$: 304.1562; found: 304.1566.
 **5a**	**2-Amino-6-(1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-phenyl pyridine-3,5-dicarbonitrile (5a):** Off white solid; Yield: 85%, 311 mg; M.p.: 236-238 ^{o}C; IR (KBr): 3441, 3332, 3219, 2924, 2222, 1657, 1576, 1342, 1244, 1036, 744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24-8.23 (m, 1H), 7.62-7.60 (m, 2H), 7.55-7.50 (m, 4H), 7.40-7.37 (m, 1H), 7.27-7.26 (m, 1H), 5.75 (bs, 2H), 4.09 (t, *J* = 6.05 Hz, 2H), 3.18 (t, *J* = 6.05 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.3, 160.4, 159.8, 159.7, 139.2, 133.4, 133.3, 131.0, 129.6, 129.0, 128.8, 128.1, 127.4 (2C), 114.9, 97.6, 88.7, 47.6, 28.5, ; HRMS (ESI) exact mass calculated for $C_{22}H_{15}N_5O$ $[M + H]^+$: 366.1350; found: 366.1359.
 **5b**	**2-Amino-4-(4-chlorophenyl)-6-(1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)pyridine-3,5-dicarbonitrile (5b):** Off white solid; Yield: 83%, 332 mg; M.p.: 270-272 ^{o}C; IR (KBr): 3445, 3332, 2921, 2227, 1649, 1617, 1577, 1307, 1250, 744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18-8.16 (m, 1H), 7.51-7.44 (m, 5H), 7.35-7.31 (m, 1H), 7.22-7.19 (m, 1H), 5.67 (bs, 2H), 4.04 (t, *J* = 6.5 Hz, 2H), 3.12 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 160.3, 159.8, 158.4, 139.2, 137.5, 133.4, 131.7, 130.3, 129.6, 129.4, 127.9, 127.5, 127.4, 114.8, 97.4, 88.4, 47.7, 28.5; HRMS (ESI) exact mass

	calculated for $C_{22}H_{14}ClN_5O$ [M + H]$^+$: 400.0960; found: 400.0966.
 **5c**	**2-Amino-4-(3-chlorophenyl)-6-(1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)pyridine-3,5-dicarbonitrile (5c):** Yellow solid; Yield: 86%, 344 mg; M.p.: 260-262 ^{o}C; IR (KBr): 3417, 3331, 3060, 2925, 2222, 1656, 1575, 1468, 1100, 922, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24-8.22 (m, 1H), 7.58-7.48 (m, 5H), 7.41-7.38 (m, 1H), 7.28-7.26 (m, 1H), 5.85 (bs, 2H), 4.09 (t, *J* = 6.1 Hz, 2H), 3.18 (t, *J* = 5.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.4, 160.3, 159.7, 158.0, 139.2, 135.0, 133.4, 131.1, 130.4, 129.6, 128.7, 127.9, 127.4, 127.0, 114.6 (2C), 97.3, 88.5, 47.7, 28.4; HRMS (ESI) exact mass calculated for $C_{22}H_{14}ClN_5O$ [M + H]$^+$: 400.0960; found: 400.0963.
 **5d**	**2-Amino-4-(2-chlorophenyl)-6-(1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)pyridine-3,5-dicarbonitrile (5d):** Off white solid; Yield: 81%, 324 mg; M.p.: 206-208 ^{o}C; IR (KBr): 3444, 3332, 3230, 2925, 2224, 1654, 1572, 1377, 1311, 1246, 1033, 801, 699 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.20 (bs, 2H), 8.02-8.00 (m, 1H), 7.73-7.70 (m, 1H), 7.63-7.52 (m, 4H), 7.46-7.41 (m, 2H), 4.10-4.00 (m, 2H), 3.15 (t, *J* = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.5, 160.7, 159.1, 157.1, 139.9, 133.3 (2C), 132.0, 131.1, 130.3, 129.9, 128.4, 128.0, 127.9, 127.6, 127.2, 114.2, 95.2, 88.1, 47.2, 27.8; HRMS (ESI) exact mass calculated for $C_{22}H_{14}ClN_5O$ [M + H]$^+$: 400.0960; found: 400.0967.
 **5e**	**2-Amino-4-(4-bromophenyl)-6-(1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)pyridine-3,5-dicarbonitrile (5e):** Yellow solid; Yield: 88%, 391 mg; M.p.: 277-279 ^{o}C; IR (KBr): 3430, 3321, 2925, 2218, 1652, 1556, 1493, 1375, 1247, 1070, 750 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (bs, 2H), 8.03-8.02 (m, 1H), 7.84-7.82 (m, 2H), 7.62-7.59 (m, 1H), 7.55-7.53 (m, 2H), 7.46-7.41 (m, 2H), 4.04 (t, *J* = 6.8 Hz, 2H), 3.15 (t, *J* = 6.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.5, 161.0, 159.5, 158.1, 139.8, 133.3, 133.2, 131.9, 130.7, 128.3, 128.0, 127.7, 127.2, 124.2, 115.3, 114.8, 94.4, 87.5, 47.2, 27.8; HRMS (ESI) exact mass calculated for $C_{22}H_{14}BrN_5O$ [M + H]$^+$: 444.0455; found: 444.0458.
 **5f**	**2-Amino-4-(3-bromophenyl)-6-(1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)pyridine-3,5-dicarbonitrile (5f):** Yellow solid; Yield: 82%, 364 mg; M.p.: 248-250 ^{o}C; IR (KBr): 3440, 3331, 3224, 2931, 2851, 2221, 1658, 1624, 1541, 1394, 1022, 761 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.14 (bs, 2H), 8.04-8.00 (m, 1H), 7.81-7.80 (m, 2H), 7.63-7.56 (m, 3H), 7.46-7.42 (m, 2H), 4.03 (t, *J* = 5.5 Hz, 2H), 3.14 (t, *J* = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6, 161.0, 159.4, 157.6, 139.8, 136.3, 133.3 (2C), 131.1 (2C), 128.4, 128.0, 127.8, 127.7, 127.2, 121.8, 115.3, 114.8, 94.5, 87.7, 47.3, 27.8; HRMS (ESI) exact mass calculated for $C_{22}H_{14}BrN_5O$ [M + H]$^+$: 444.0455; found: 444.0460.

 **5g**	**2-Amino-4-(2-bromophenyl)-6-(1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)pyridine-3,5-dicarbonitrile (5g):** Off white solid; Yield: 82%, 364 mg; M.p.: 231-233 ^{o}C; IR (KBr): 3440, 3330, 3229, 2924, 2853, 2223, 1652, 1624, 1540, 1393, 1246, 1025, 764, 684 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.18 (bs, 2H), 8.02-8.00 (m, 1H), 7,87-7.85 (m, 1H), 7.61-7.59 (m, 2H), 7.52-7.50 (m, 2H), 7.46-7.42 (m, 2H), 4.08-4.01 (m, 2H), 3,15 (t, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.5, 160.6, 159.1, 158.7, 139.9, 135.4, 133.3, 133.0, 132.0, 130.2, 128.4, 128.3, 128.0, 127.6, 127.2, 120.9, 114.6, 114.2, 95.1, 88.1, 47.2, 27.8; HRMS (ESI) exact mass calculated for $C_{22}H_{14}BrN_5O$ $[M + H]^+$: 444.0455; found: 444.0459.
 **5h**	**2-Amino-4-(4-fluorophenyl)-6-(1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)pyridine-3,5-dicarbonitrile (5h):** Brownish solid; Yield: 81%, 311 mg; M.p.: 199-201 ^{o}C; IR (KBr): 3441, 3331, 3027, 2921, 2220, 1656, 1632, 1389, 1245, 743 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.11 (bs, 2H), 8.01-8.00 (m, 1H), 7.65-7.59 (m, 3H), 7.48-7.41 (m, 4H), 4.03 (t, *J* = 5.8 Hz, 2H), 3.14 (t, *J* = 5.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6, 163.3 (d, *J* = 248.1 Hz), 161.1, 159.6, 158.4, 139.9, 133.3, 131.3 (d, *J* = 9.2 Hz), 130.5 (d, *J* = 2.5 Hz), 128.4, 128.1, 127.7, 127.5, 127.3, 116.0 (d, *J* = 22.2 Hz), 115.5, 115.0, 94.8, 87.8, 47.3, 27.9; HRMS (ESI) exact mass calculated for $C_{22}H_{14}FN_5O$ $[M + H]^+$: 384.1256; found: 384.1259.
 **5k**	**2-Amino-6-(1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-(p-tolyl)pyridine-3,5-dicarbonitrile (5k):** Yellow solid; Yield: 80%, 304 mg; M.p.: 218-220 ^{o}C; IR (KBr): 3441, 3329, 3221, 2925, 2218, 1654, 1618, 1540, 1244, 1021, 754 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.08 (bs, 2H), 8.01-8.00 (m, 1H), 7.62-7.59 (m, 1H), 7.46-7.39 (m, 6H), 4.02 (t, *J* = 5.5 Hz, 2H), 3.14 (t, *J* = 5.5 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.5, 161.1, 159.6, 159.3, 140.4, 139.8, 133.2, 131.2, 129.3, 128.5, 128.3, 128.0, 127.7, 127.2, 115.6, 115.0, 94.7, 87.5, 47.2, 27.8, 21.0; HRMS (ESI) exact mass calculated for $C_{23}H_{17}N_5O$ $[M + H]^+$: 380.1506; found: 380.1505.
 **5l**	**2-Amino-4-(naphthalen-1-yl)-6-(1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)pyridine-3,5-dicarbonitrile (5l):** Yellow solid; Yield: 79%, 328 mg; M.p.: 290-292 ^{o}C; IR (KBr): 3438, 3328, 3058, 2925, 2222, 1655, 1624, 1393, 1314, 1166, 747 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.22 (bs, 2H, merged with other aromatic C-H), 8.16-8.14 (m, 1H), 8.10-8.08 (m, 1H), 8.02-8.00 (m, 1H), 7.72-7.69 (m, 1H), 7.65-7.59 (m, 5H), 7.45-7.41 (m, 2H), 4.12-4.08 (m, 2H), 3.16 (t, *J* = 5.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6, 160.9, 159.2, 158.5, 139.9, 133.3, 133.1, 131.9, 130.4, 129.7, 128.7, 128.4, 128.0, 127.7, 127.5, 127.2, 126.9, 126.7, 125.5, 124.3, 115.1, 114.6, 96.2, 89.0, 47.2, 27.8; HRMS (ESI) exact mass calculated for $C_{26}H_{17}N_5O$ $[M + H]^+$: 416.1506; found: 416.1510.

 **6a**	**2-Amino-6-((2-formylphenethyl)amino)-4-phenylpyridine-3,5-dicarbonitrile (6a):** Off white solid; Yield: 87%, 319 mg; M.p.: 176-178 ^{o}C; IR (KBr): 3452, 3347, 3235, 2925, 2842, 2203, 1697, 1641, 1557, 1585, 1472, 771 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.31 (s, 1H), 7.85-7.84 (m, 1H), 7.57-7.45 (m, 7H), 7.32-7.31 (m, 1H), 5.91 (bs, 1H), 5.54 (bs, 2H), 3.78-3.74 (m, 2H), 3.37 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.5, 161.0, 159.6, 159.2, 140.9, 134.4, 134.2, 134.0, 133.6, 131.7, 130.5, 128.9, 128.3, 127.5, 116.5, 116.2, 82.8, 80.6, 43.0, 32.6; HRMS (ESI) exact mass calculated for $C_{22}H_{17}N_5O$ [M + H]$^+$: 368.1506; found: 368.1503.
 **6b**	**2-Amino-4-(4-chlorophenyl)-6-((2-formylphenethyl)amino) pyridine-3,5-dicarbonitrile (6b):** Orange solid; Yield: 83%, 334 mg; M.p.: 188-190 ^{o}C; IR (KBr): 3450, 3345, 3241, 2957, 2853, 2203, 1699, 1584, 1485, 1301, 862 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.3 (s, 1H), 7.85-7.84 (m, 1H), 7.58-7.54 (m, 1H), 7.50-7.43 (m, 5H), 7.32-7.30 (m, 1H), 5.97 (t, *J* = 5.3 Hz, 1H), 5.59 (bs, 2H), 3.77-3.73 (m, 2H), 3.36 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6, 160.9, 159.5, 157.9, 140.8, 136.8, 134.3, 134.0, 133.7, 132.5, 131.7, 129.7, 129.2, 127.5, 116.3, 116.0, 82.5, 80.3, 43.0, 32.6; HRMS (ESI) exact mass calculated for $C_{22}H_{16}ClN_5O$ [M + H]$^+$: 402.1122; found: 402.1124.
 **6c**	**2-Amino-4-(3-chlorophenyl)-6-((2-formylphenethyl)amino) pyridine-3,5-dicarbonitrile (6c):** Orange solid; Yield: 82%, 330 mg; M.p.: 166-168 ^{o}C; IR (KBr): 3446, 3336, 3231, 2921, 2201, 1650, 1556, 1473, 1011, 744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.22 (s, 1H), 7.78-7.77 (m, 1H), 7.50-7.47 (m, 1H), 7.42-7.36 (m, 4H), 7.30-7.28 (m, 1H), 7.23-7.19 (s, 1H), 5.91 (t, *J* = 5.3 Hz, 1H), 5.52 (bs, 2H), 3.70-3.66 (m, 2H), 3.30-3.27 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6, 160.8, 159.4, 157.6, 140.8, 135.9, 134.8, 134.3, 134.0, 133.7, 131.7, 130.6, 130.2, 128.3, 127.5, 126.5, 116.1, 115.8, 82.6, 80.3, 43.0, 32.5; HRMS (ESI) exact mass calculated for $C_{22}H_{16}ClN_5O$ [M + H]$^+$: 402.1122; found: 402.1129.
 **6e**	**2-Amino-4-(4-bromophenyl)-6-((2-formylphenethyl)amino) pyridine-3,5-dicarbonitrile (6e):** Yellow solid; Yield: 89%, 397 mg; M.p.: 190-192 ^{o}C; IR (KBr): 3351 (br), 2925, 2203, 1630, 1582, 1555, 1487, 1011, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.22 (s, 1H), 7.79-7.76 (m, 1H), 7.59-7.57 (m, 2H), 7.51-7.47 (m, 1H), 7.42-7.38 (m, 1H), 7.31-7.29 (m, 2H), 7.25-7.23 (m, 1H), 5.88 (t, *J* = 5.6 Hz, 1H), 5.50 (bs, 2H), 3.70-3.65 (m, 2H), 3.29 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6, 160.9, 159.5, 157.9, 140.8, 139.3, 134.3, 134.0, 133.8, 133.0, 132.2, 131.7, 129.9, 127.6, 125.2, 116.0, 82.5, 80.2, 43.1, 32.6; HRMS (ESI) exact mass calculated for $C_{22}H_{16}BrN_5O$ [M + H]$^+$: 446.0611; found: 446.0618.
	2-Amino-4-(4-fluorophenyl)-6-((2-formylphenethyl)amino) pyridine-3,5-dicarbonitrile (6h): Yellow crystalline; Yield: 84%,

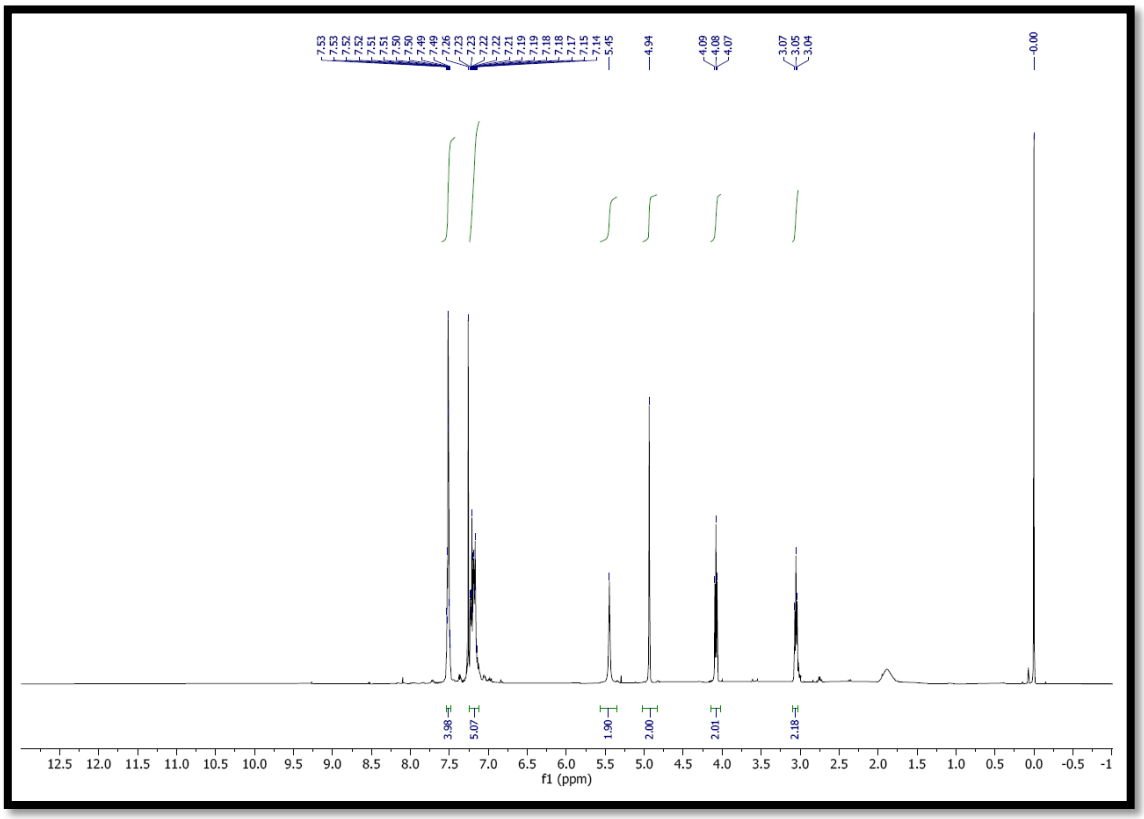
 **6h**	324 mg; M.p.: 159-161 ^{o}C; IR (KBr): 3446, 3345, 3240, 2925, 2855, 2205, 1688, 1585, 1445, 1299, 866, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.2 (s, 1H), 7.78-7.76 (m, 1H), 7.50-7.38 (m, 4H), 7.25-7.23 (m, 1H), 7.14-7.11 (m, 2H), 5.90 (t, *J* = 5.3 Hz, 1H), 5,51 (s, 2H), 3.69-3.65 (m, 2H), 3.28 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6, 163.9 (d, *J* = 251.4 Hz), 160.9, 159.5, 158.1, 140.8, 134.3, 134.0, 133.6, 131.7, 130.5 (d, *J* = 8.7 Hz), 130.2 (d, *J* = 3.2 Hz), 127.5, 116.4, 116.12 (d, *J* = 22.5 Hz), 116.14, 82.6, 80.4, 43.0, 32.5; HRMS (ESI) exact mass calculated for $C_{22}H_{16}FN_5O$ [M + H]$^{+}$: 386.1412; found: 386.1419.
 **7**	**2-Phenyl-1,2,3,4-tetrahydroisoquinoline (7)[1]:** Yellow liquid; Yield: 85%, 178 mg; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.27 (m, 2H), 7.17-7.16 (m, 4H), 6.99-6.97 (m, 2H), 6.84-6.81 (m, 1H), 4.40 (s, 2H), 5.57-3.54 (m, 2H), 2.99-2.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 134.8, 134.4, 129.2, 128.5, 126.5, 126.3, 126.0, 118.6, 115.1, 50.7, 46.5, 29.0.

REFERENCES:

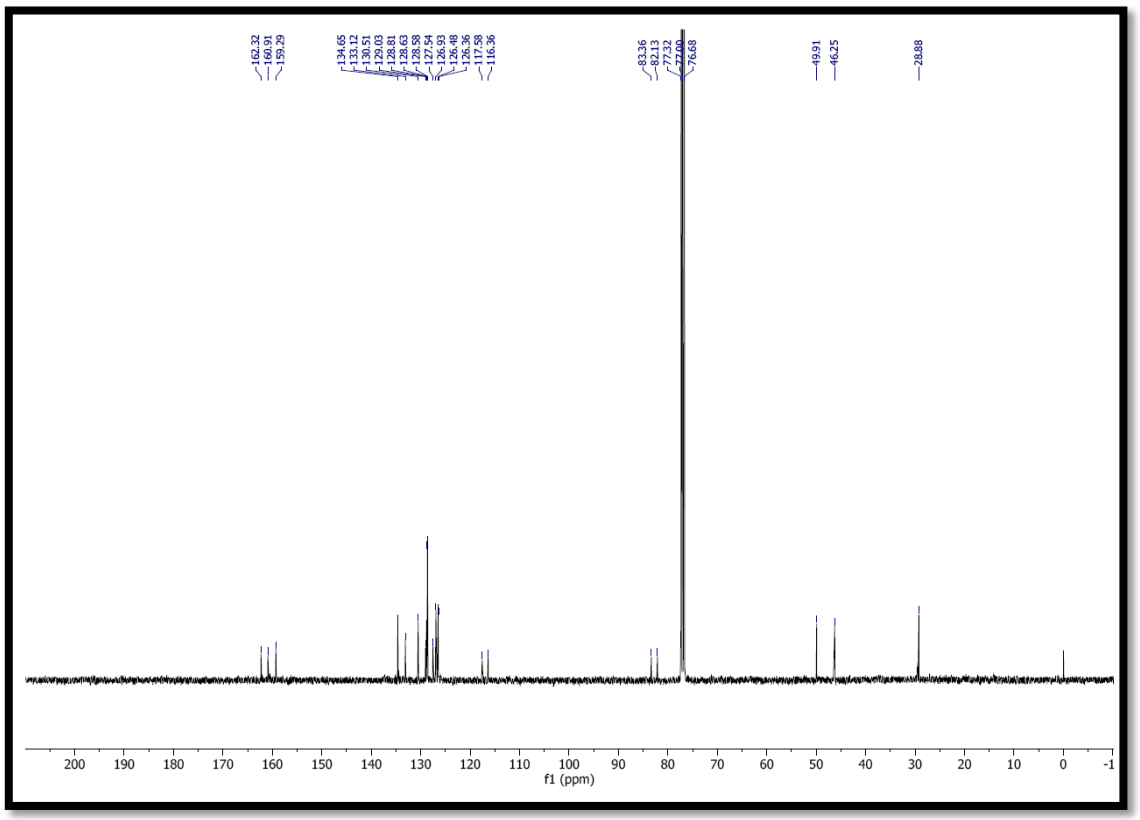
1. K. Sharma, A. Borah, K. Neog and P. Gogoi, CeO_2-Catalyzed C-H Functionalization of *N*-Aryltetrahydroisoquinolines: An Aerobic Cross-Dehydrogenative Coupling Reaction between Two sp^3 C-H Bonds, *ChemistrySelect*, 2016, **1**, 4620–4623.

NMR Spectra of the Products

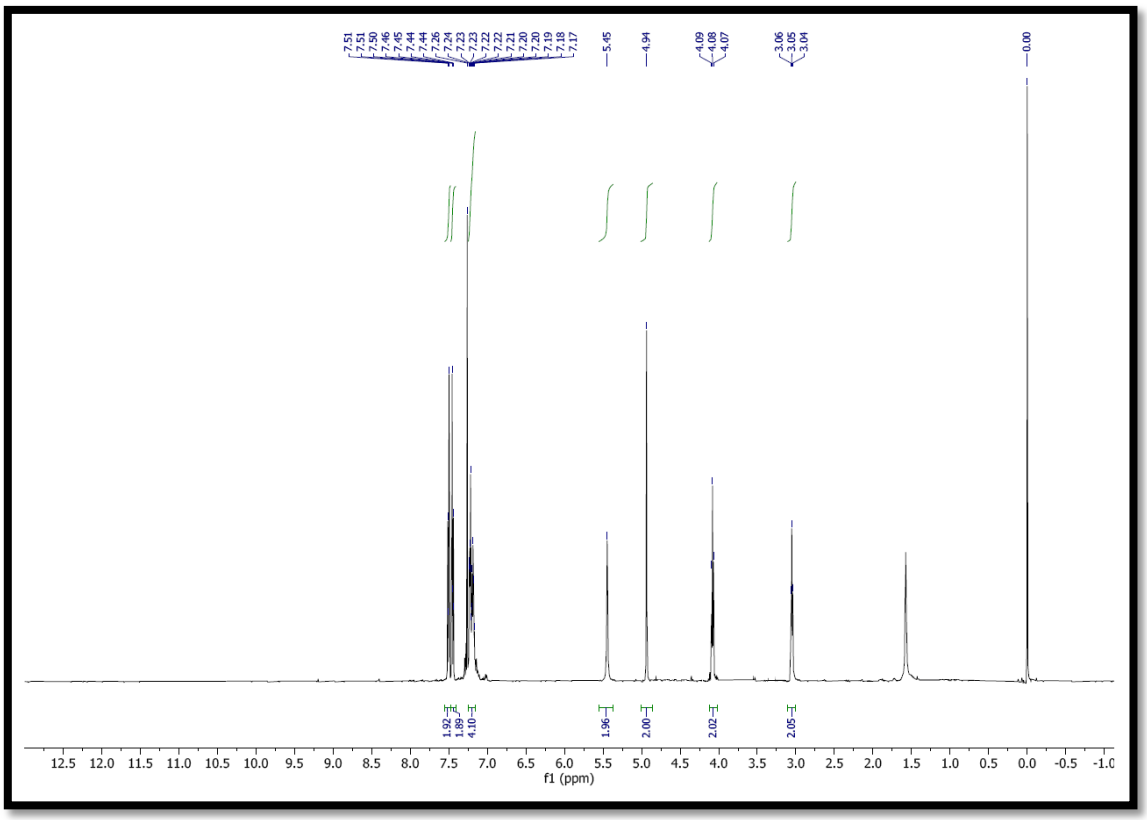
^{1}H NMR of compound 4a



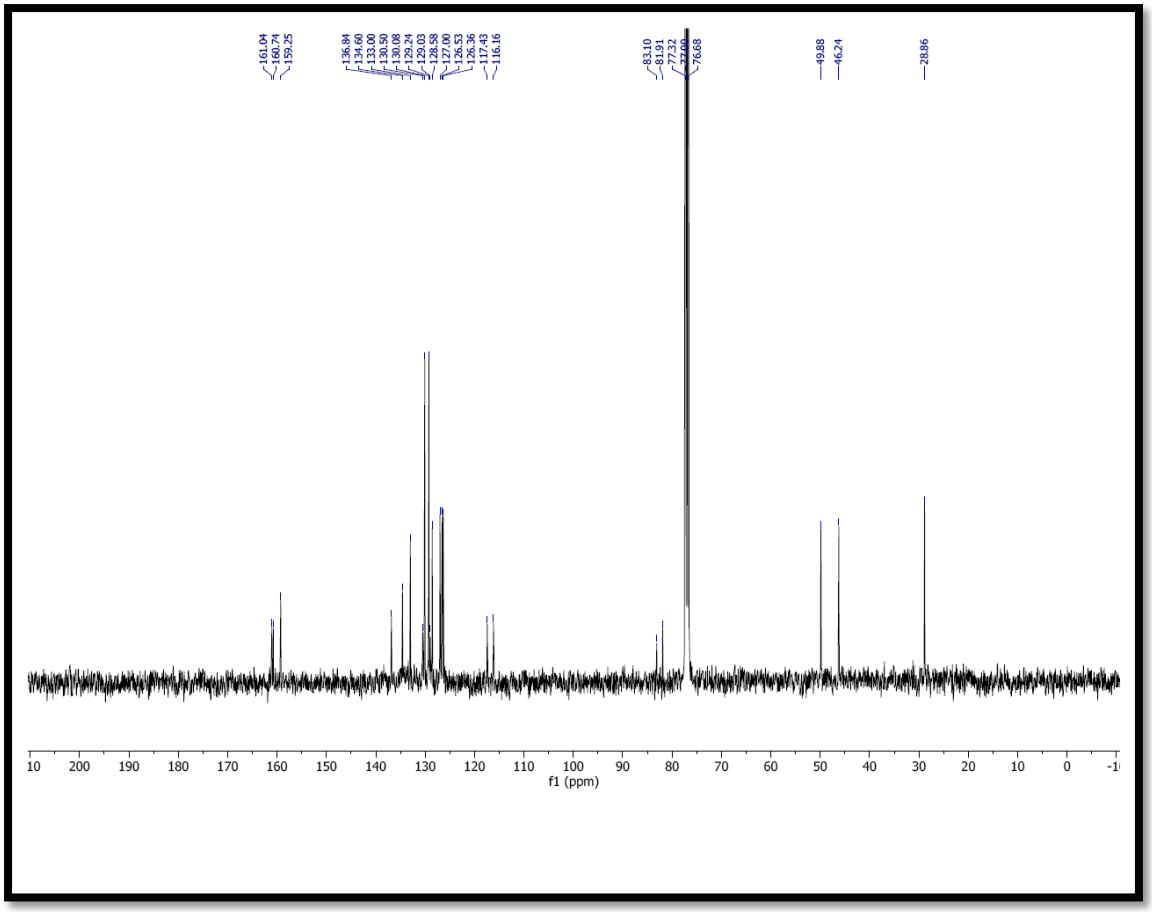
^{13}C NMR of compound 4a



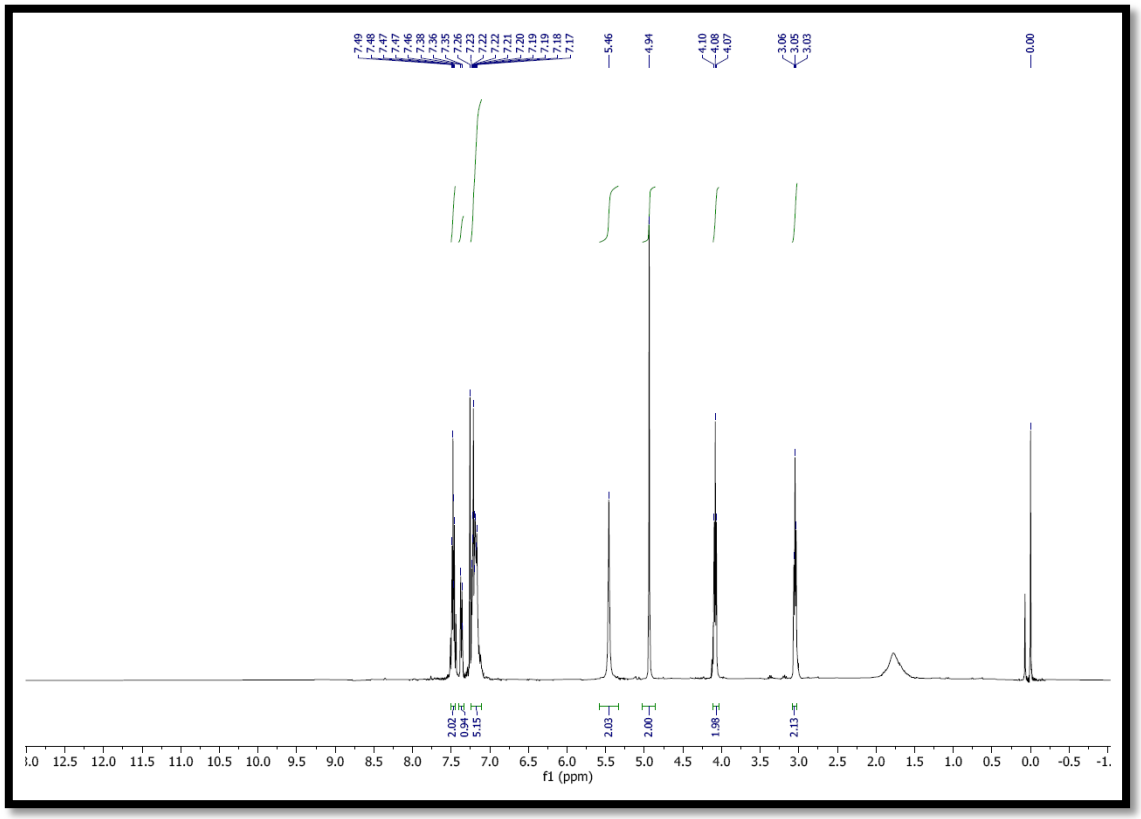
^{1}H NMR of compound 4b



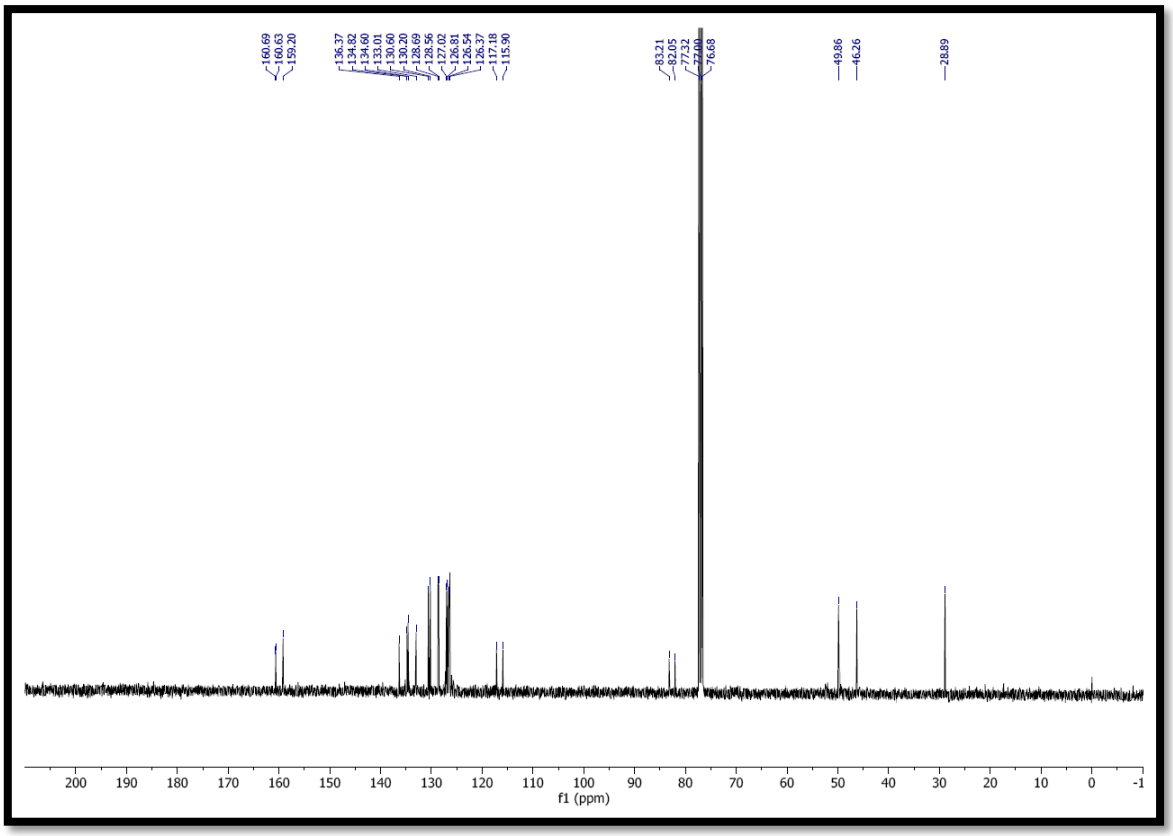
^{13}C NMR of compound 4b



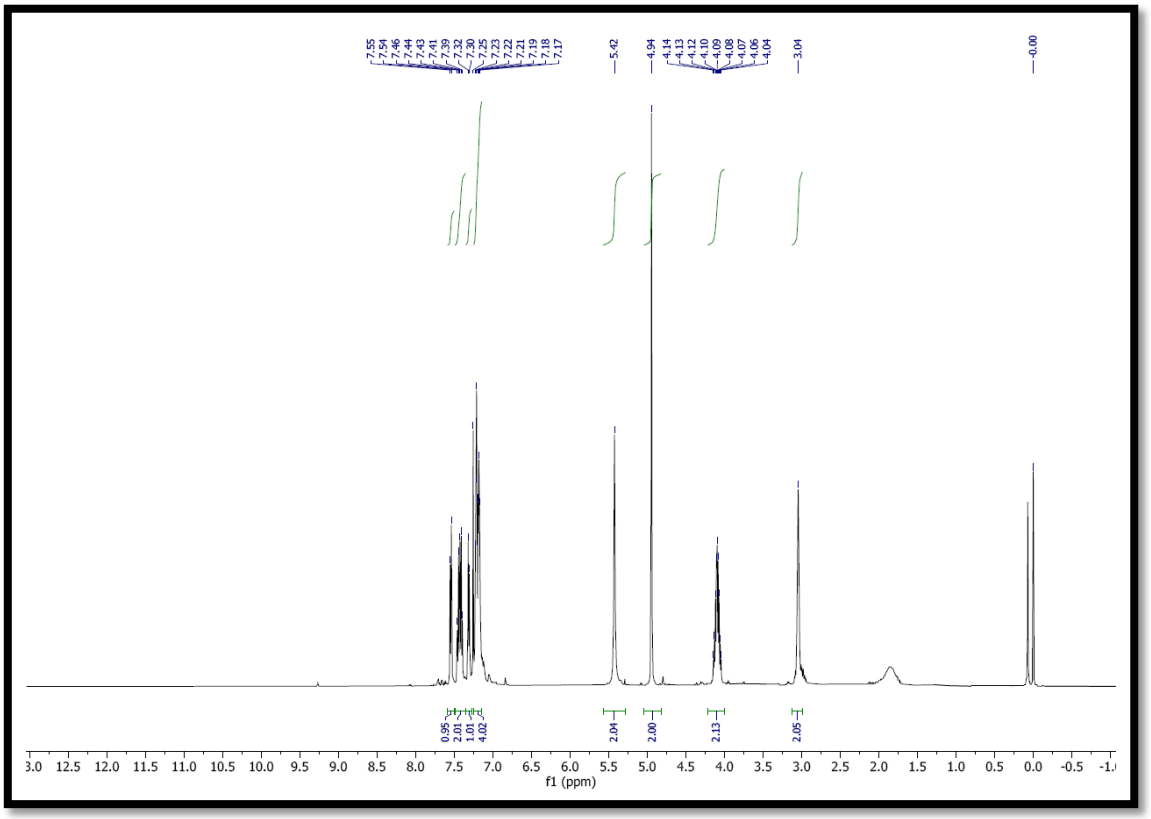
^{1}H NMR of compound 4c



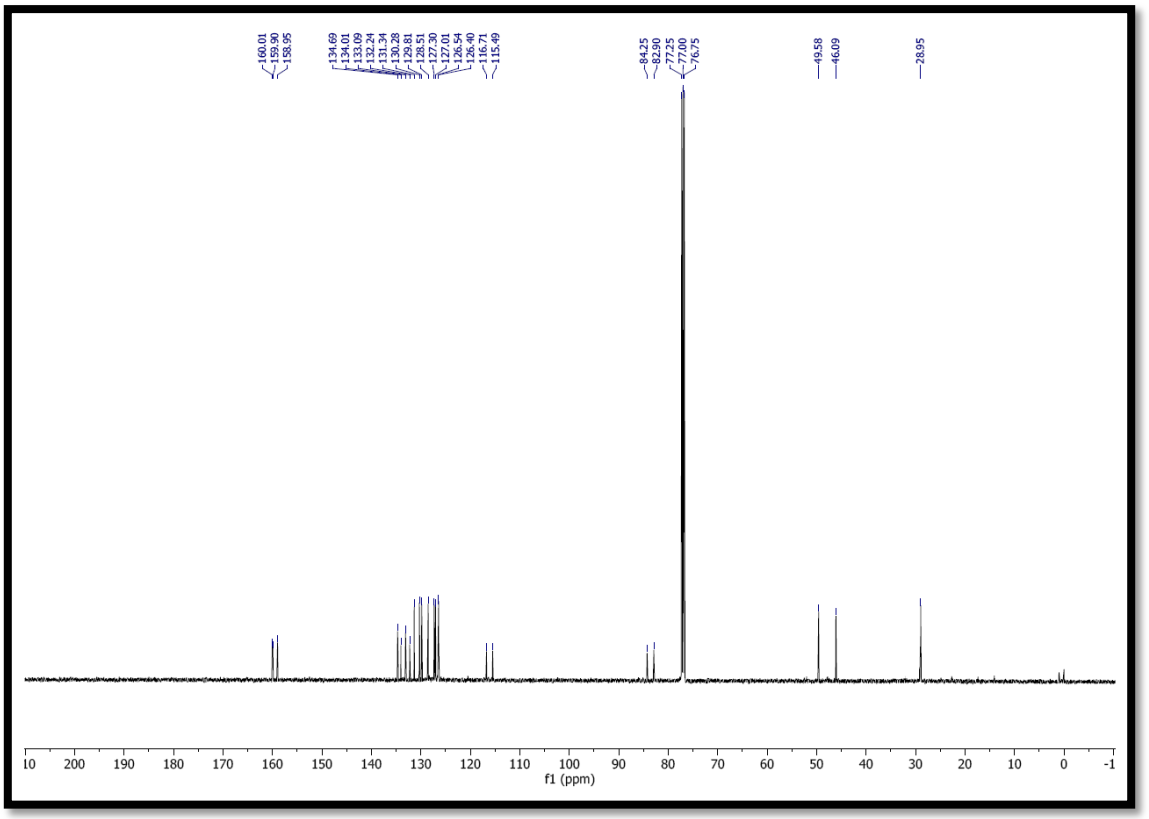
^{13}C NMR of compound 4c



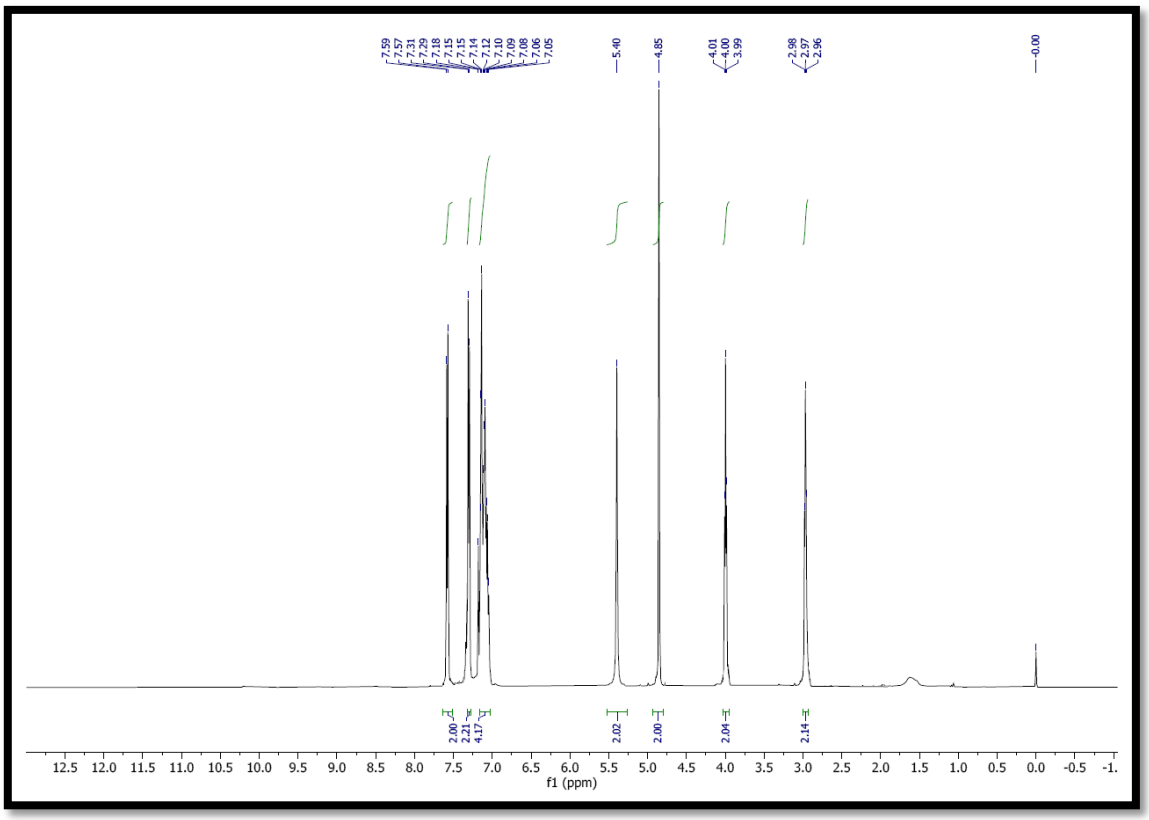
^{1}H NMR of compound 4d



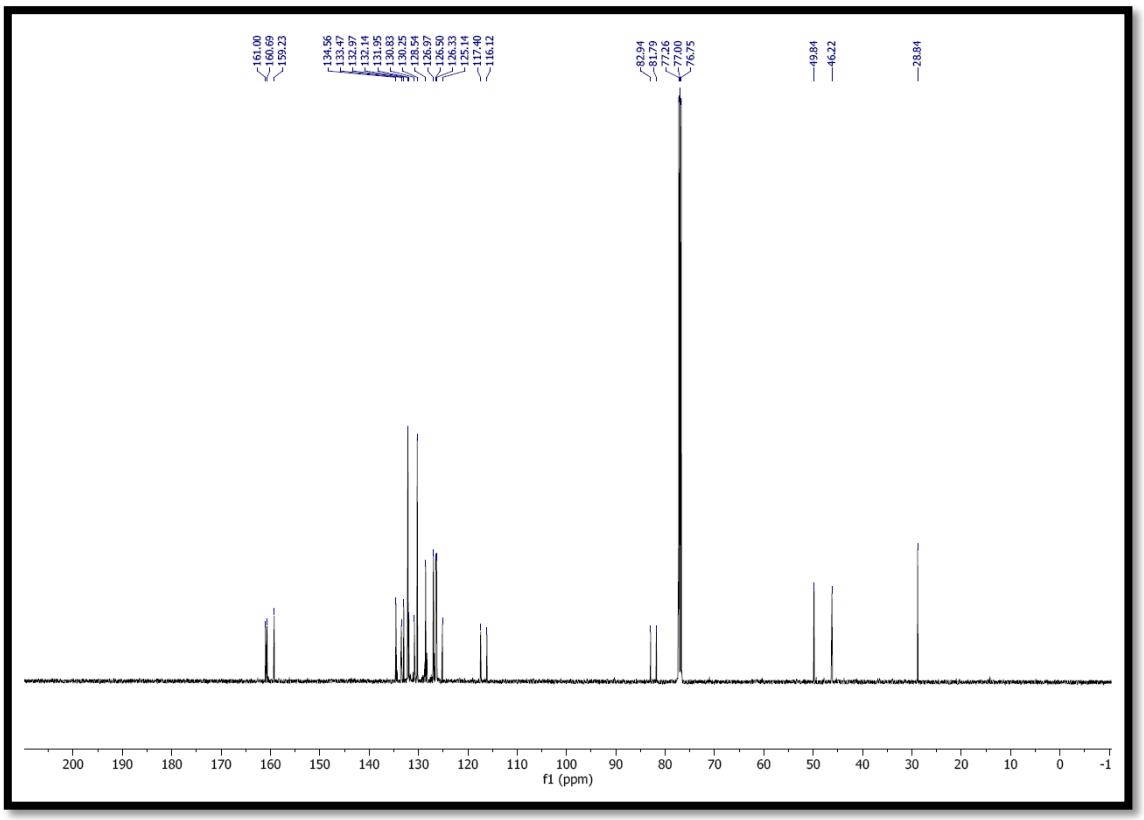
^{13}C NMR of compound 4d



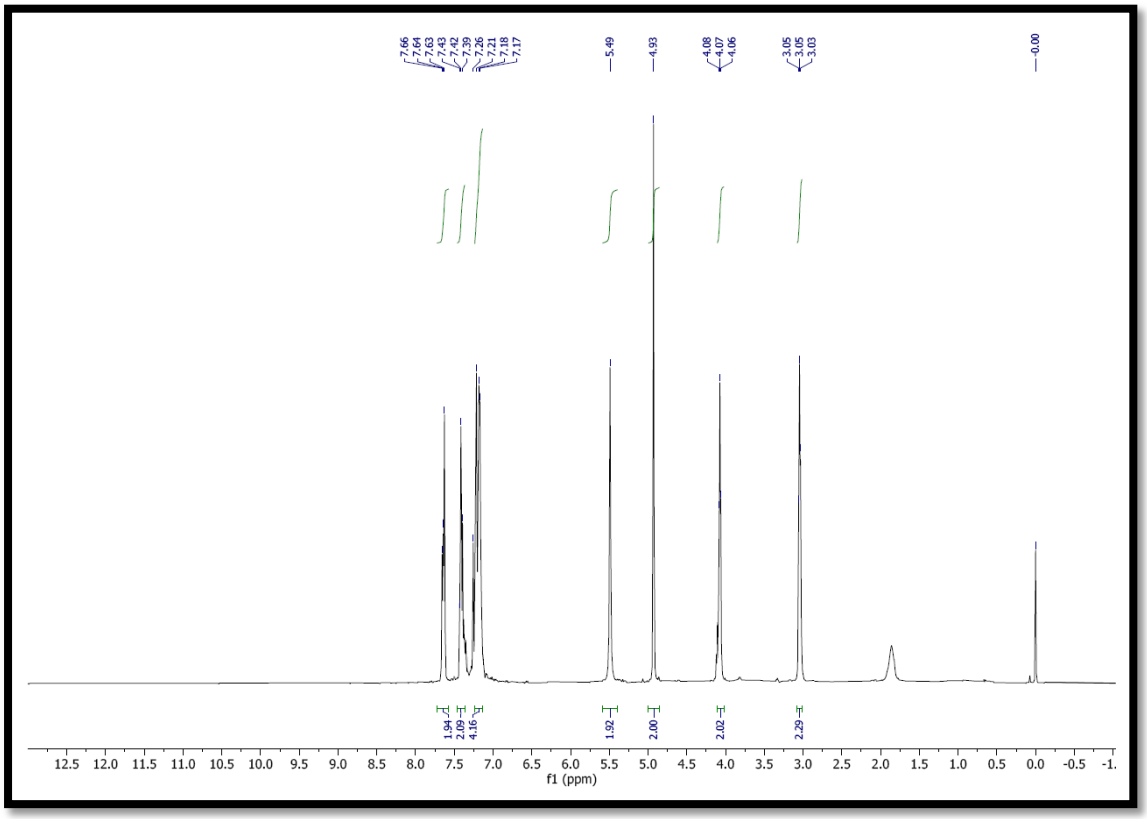
^{1}H NMR of compound 4e



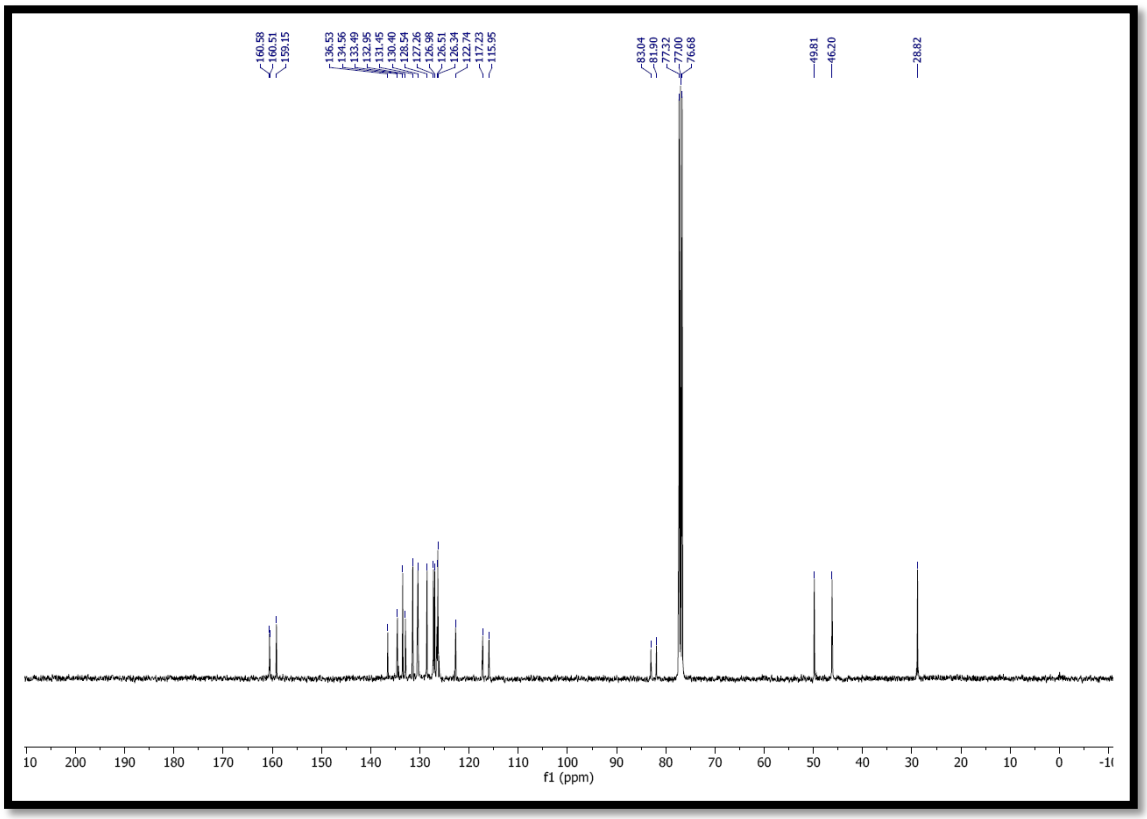
^{13}C NMR of compound 4e



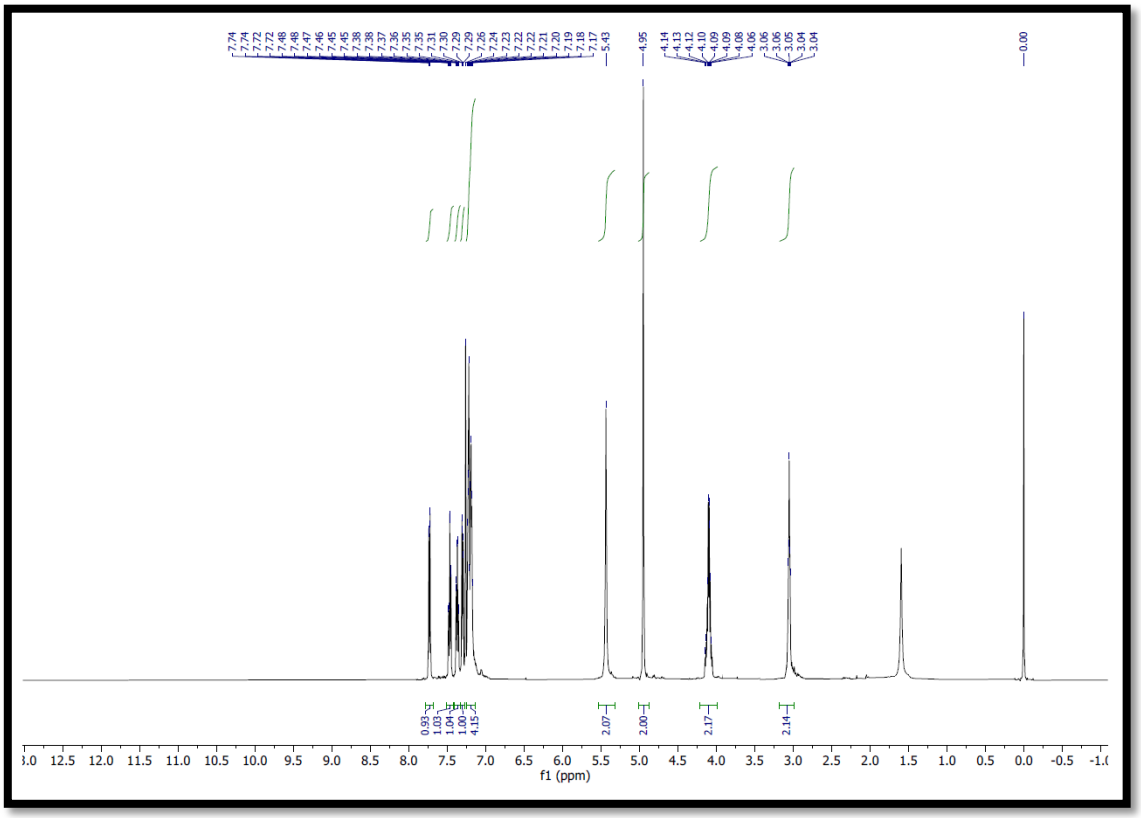
^{1}H NMR of compound 4f



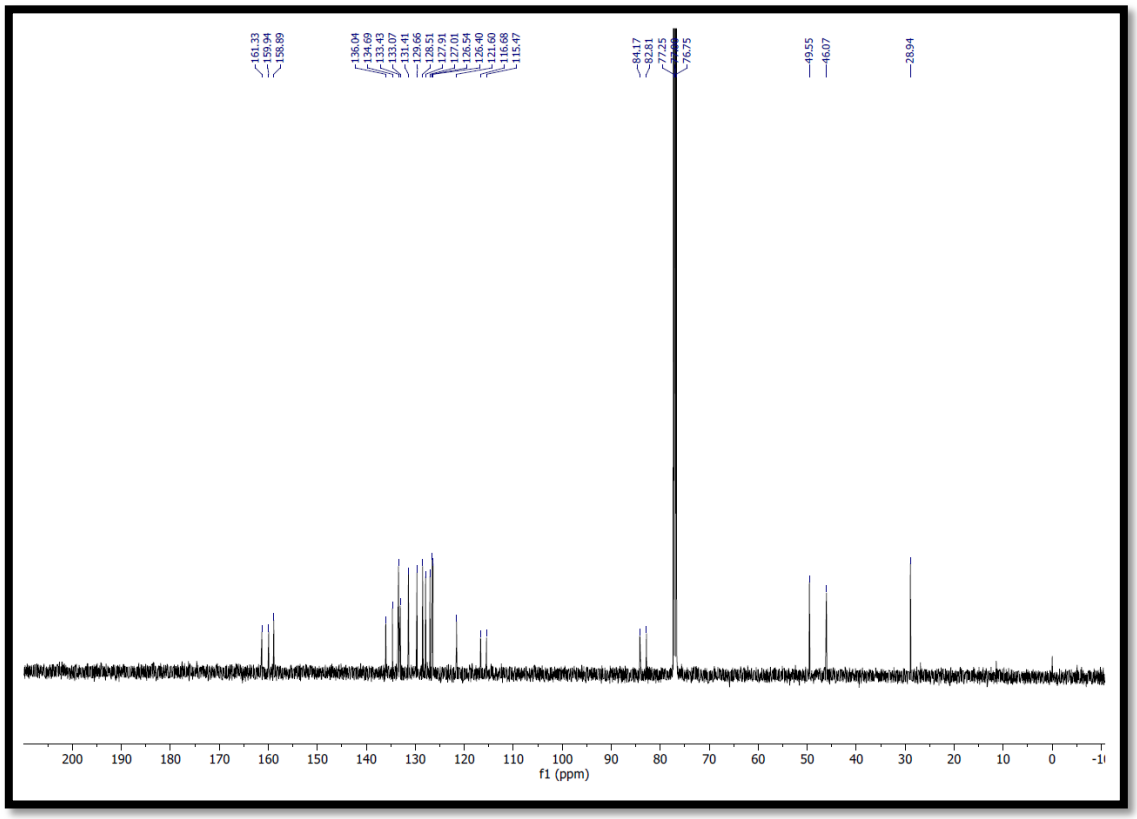
^{13}C NMR of compound 4f



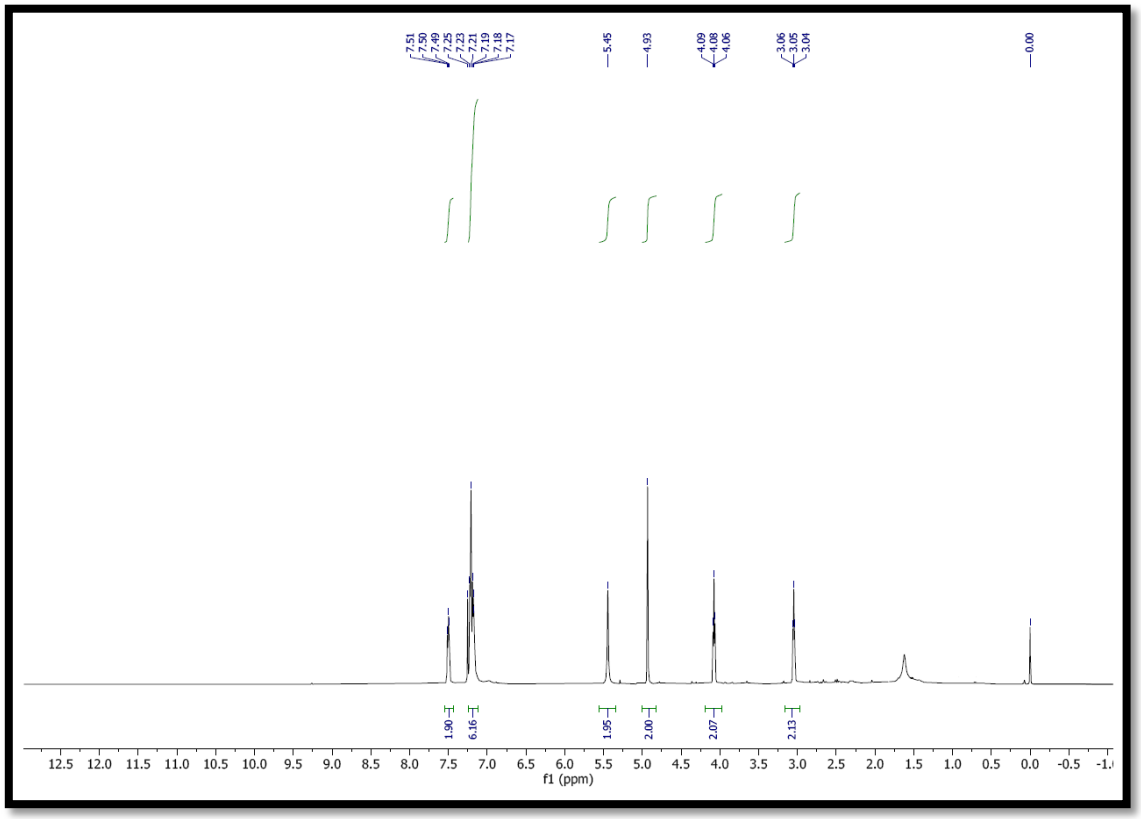
^{1}H NMR of compound 4g



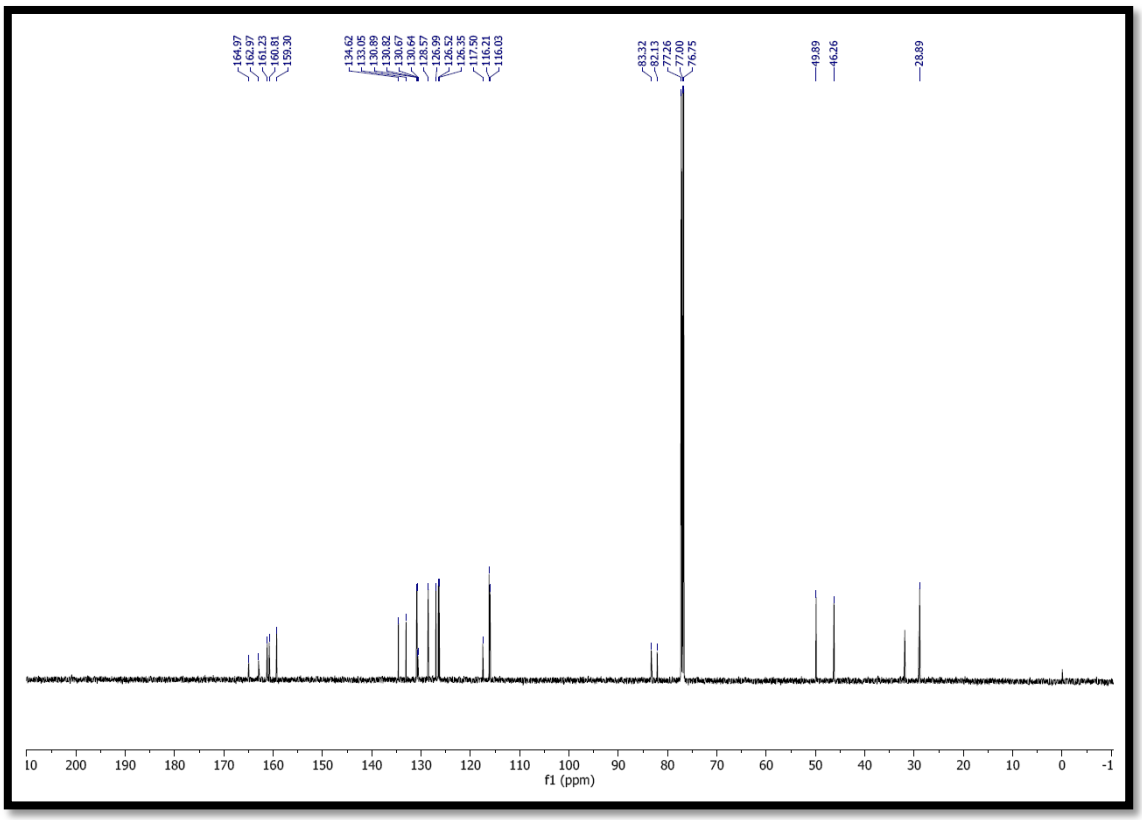
^{13}C NMR of compound 4g



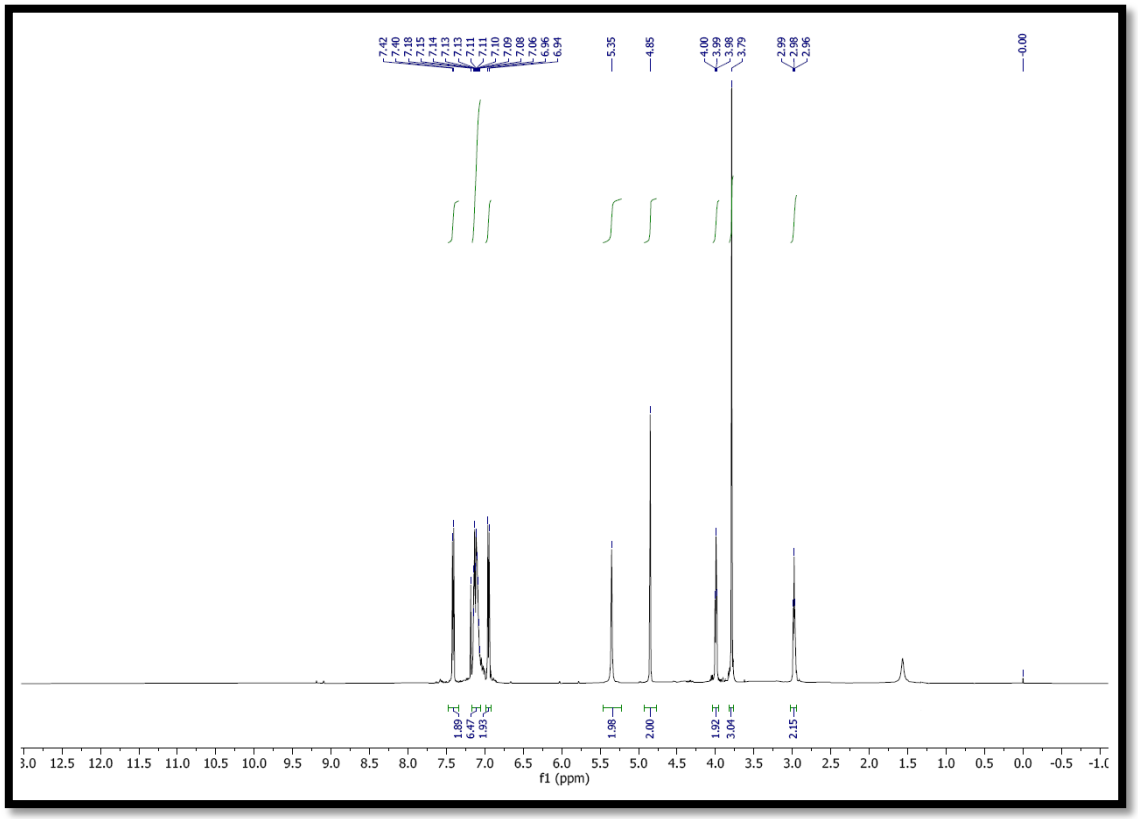
^{1}H NMR of compound 4h



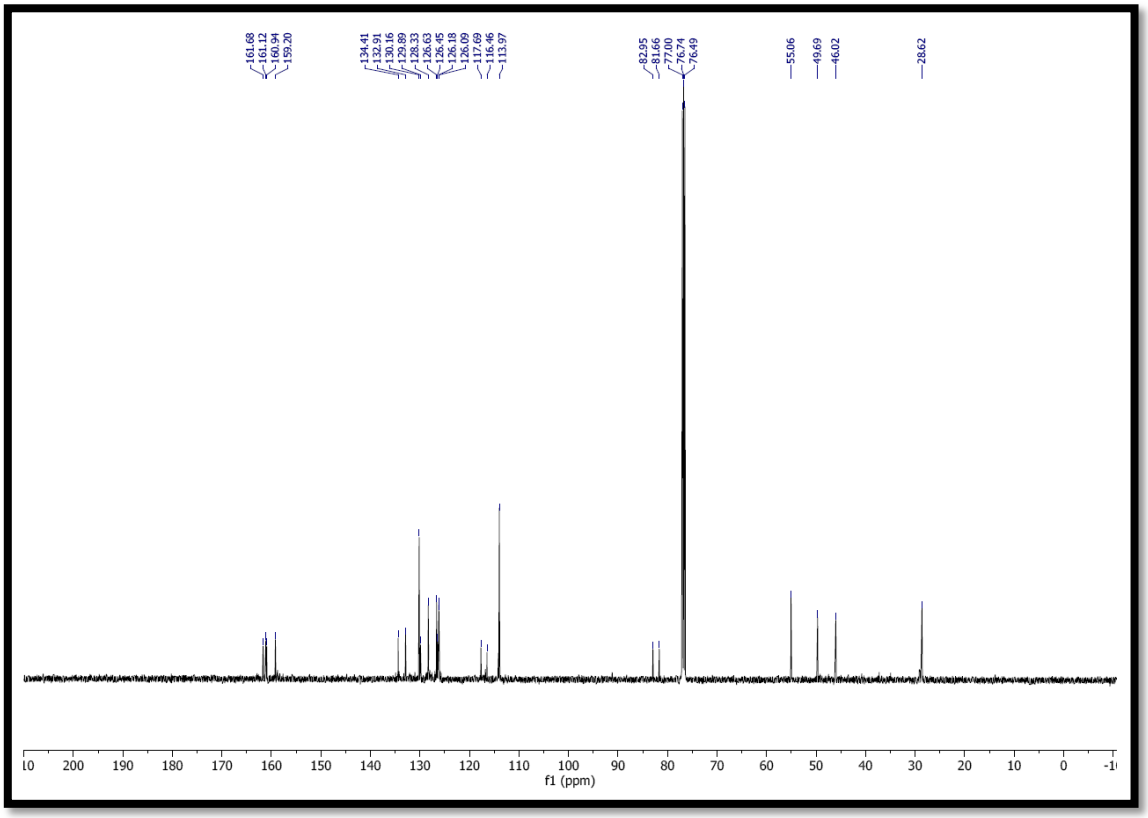
^{13}C NMR of compound 4h



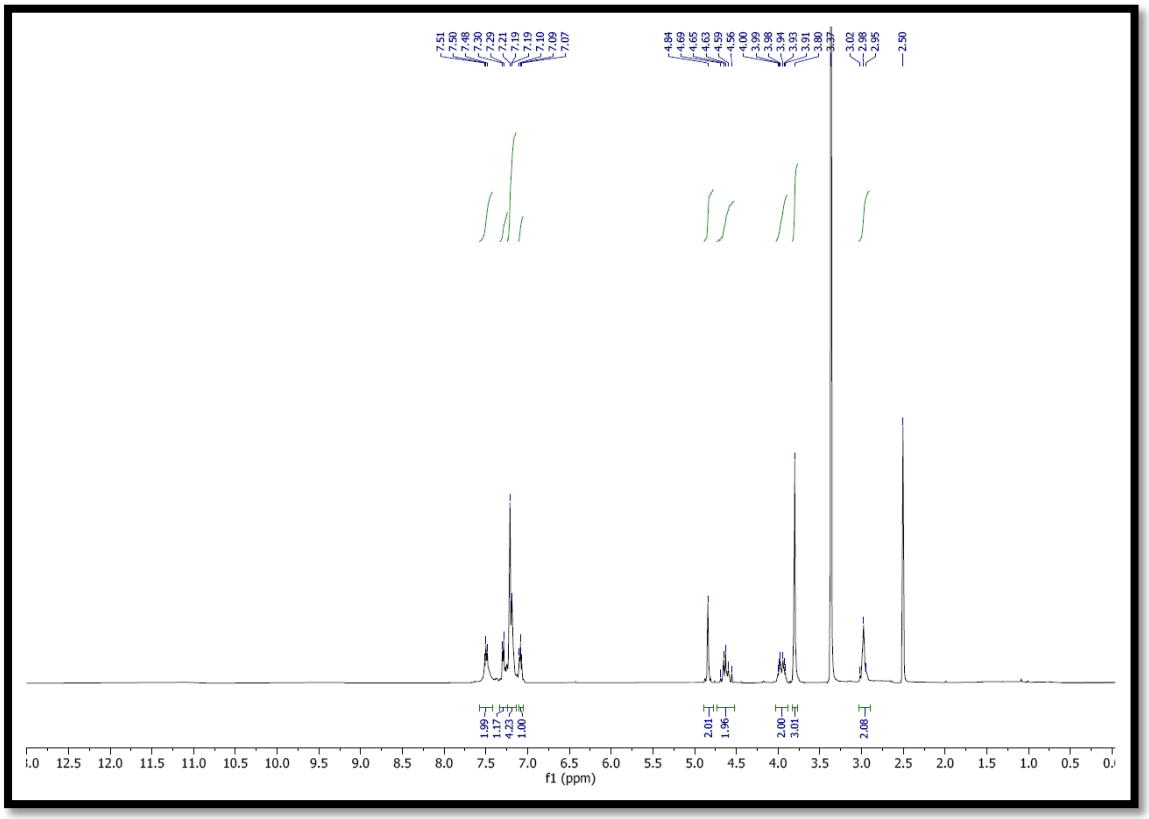
^{1}H NMR of compound 4i



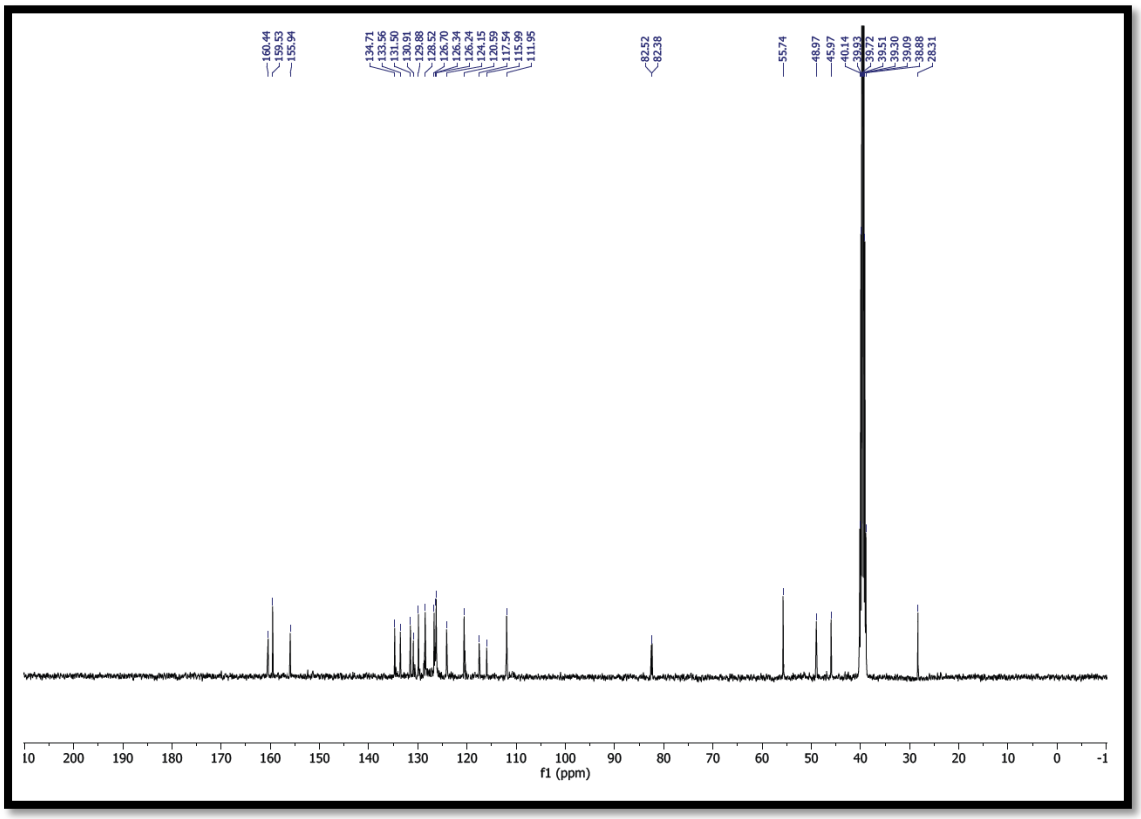
^{13}C NMR of compound 4i



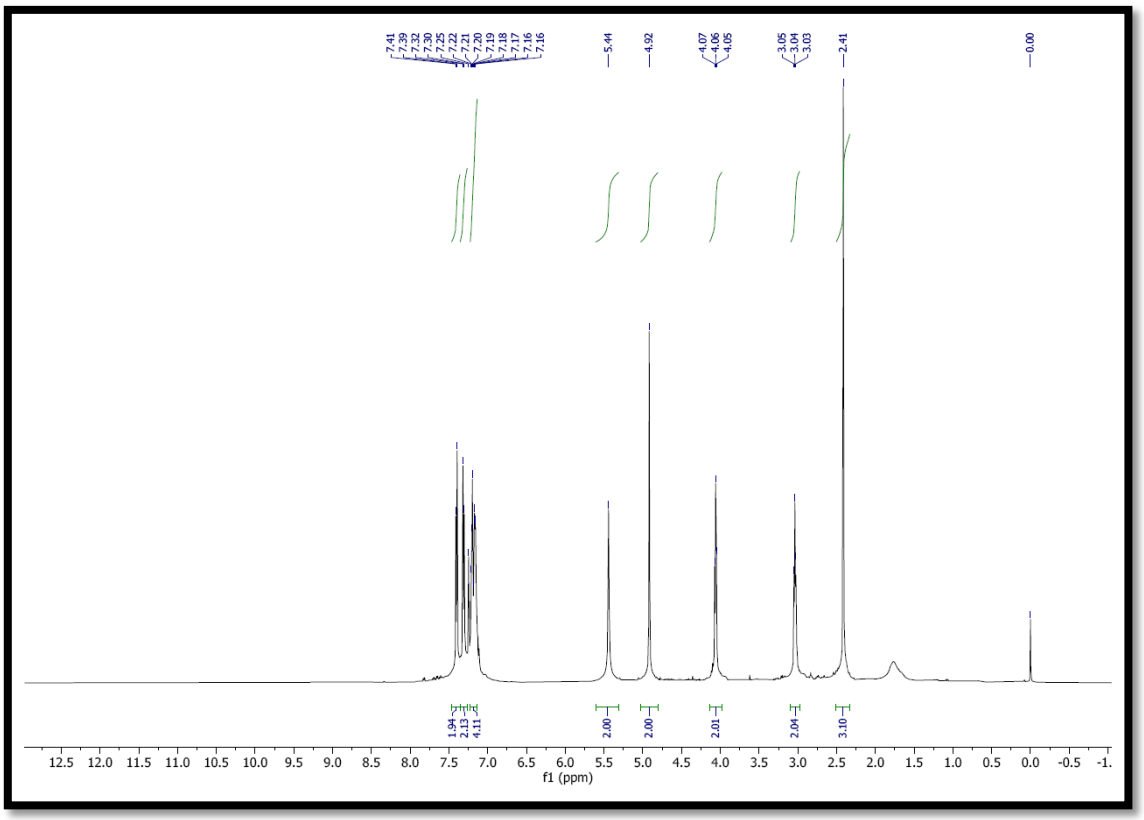
^{1}H NMR of compound 4j



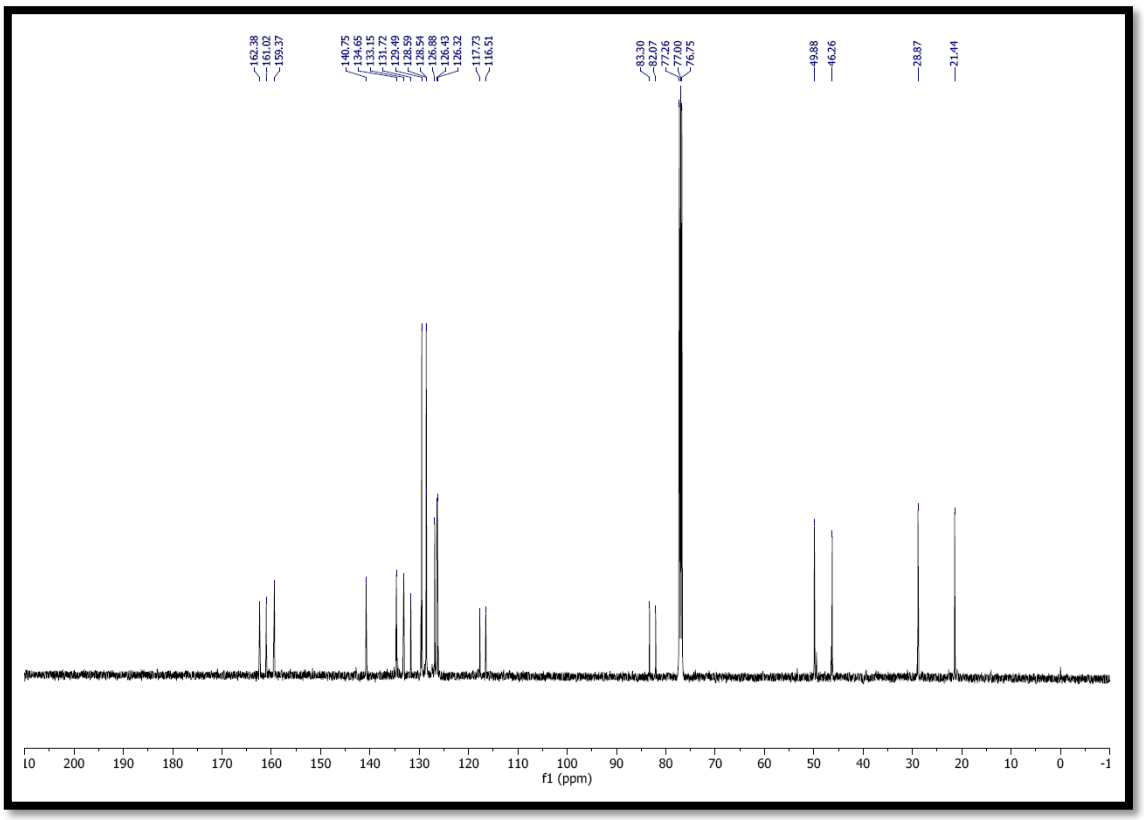
^{13}C NMR of compound 4j



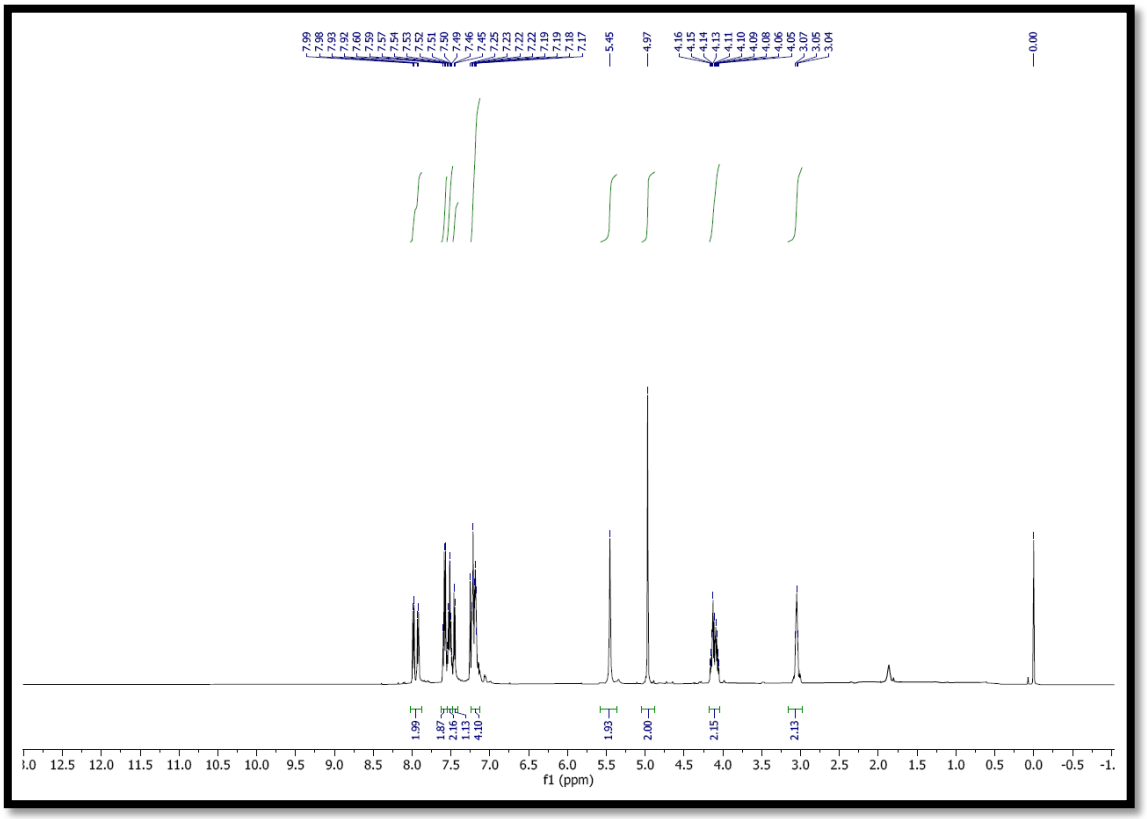
^{1}H NMR of compound 4k



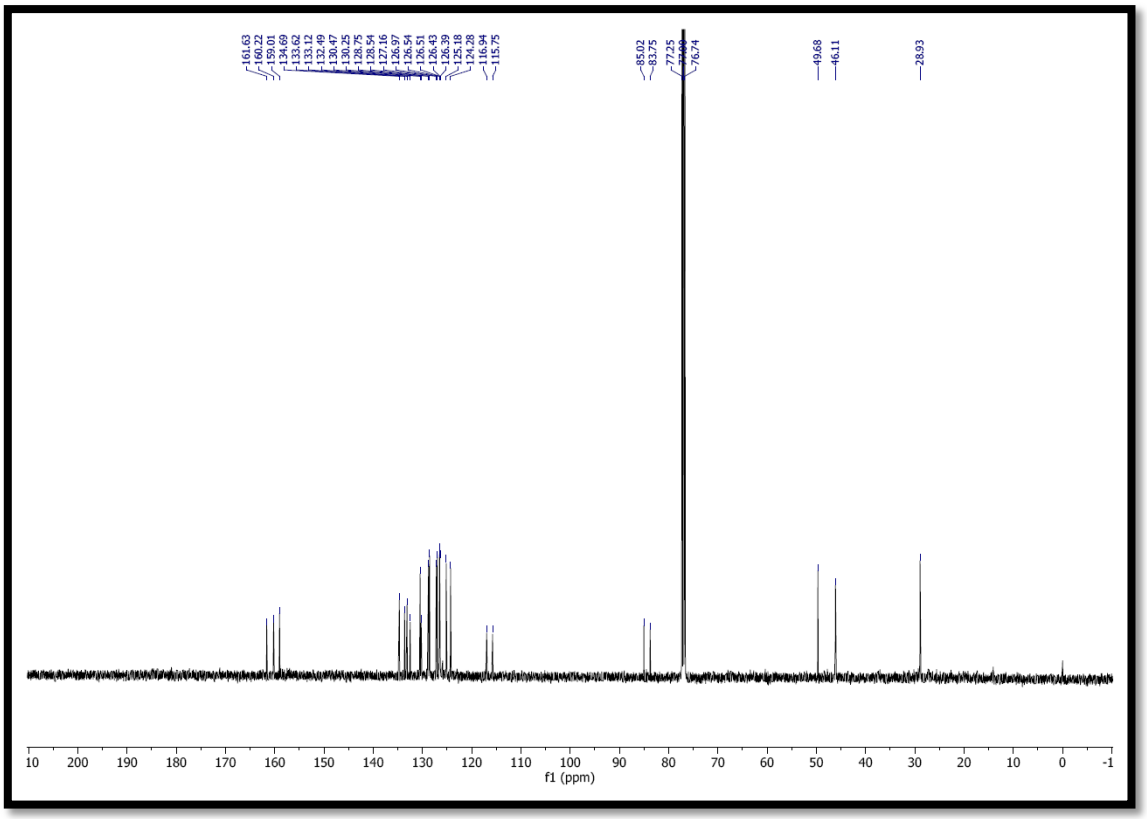
^{13}C NMR of compound 4k



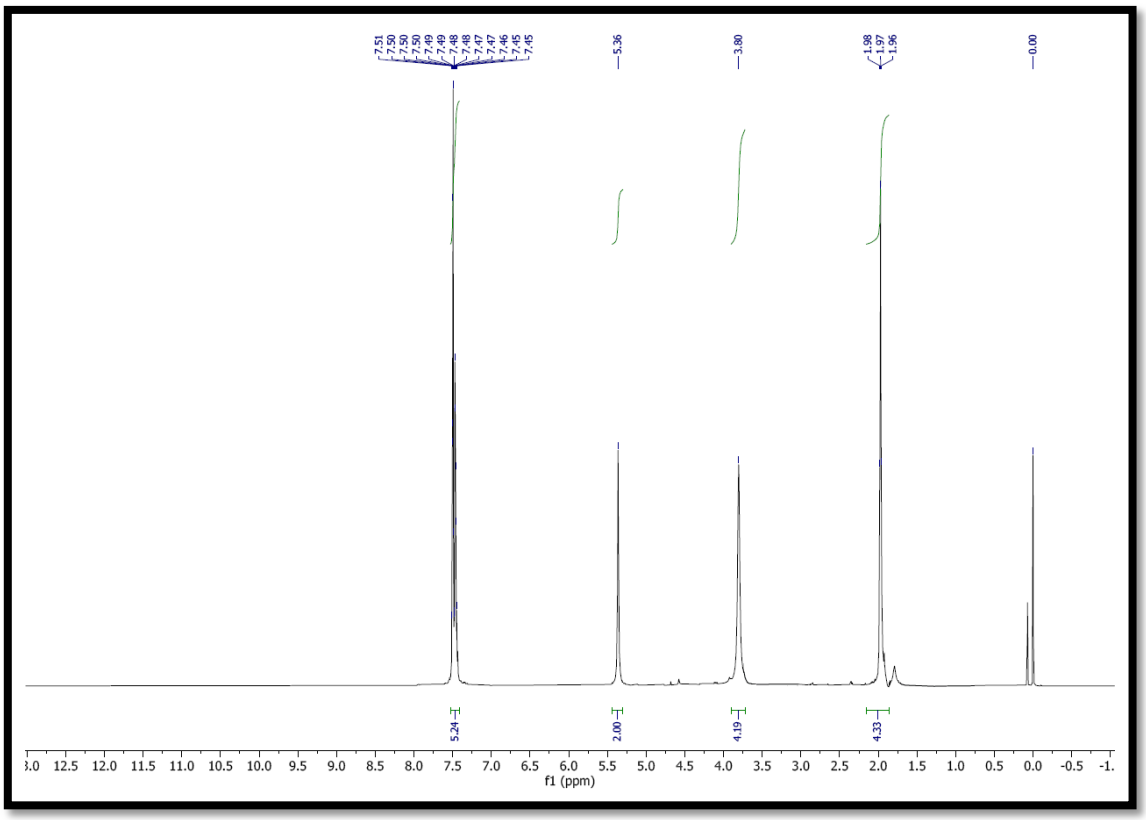
^{1}H NMR of compound 4l



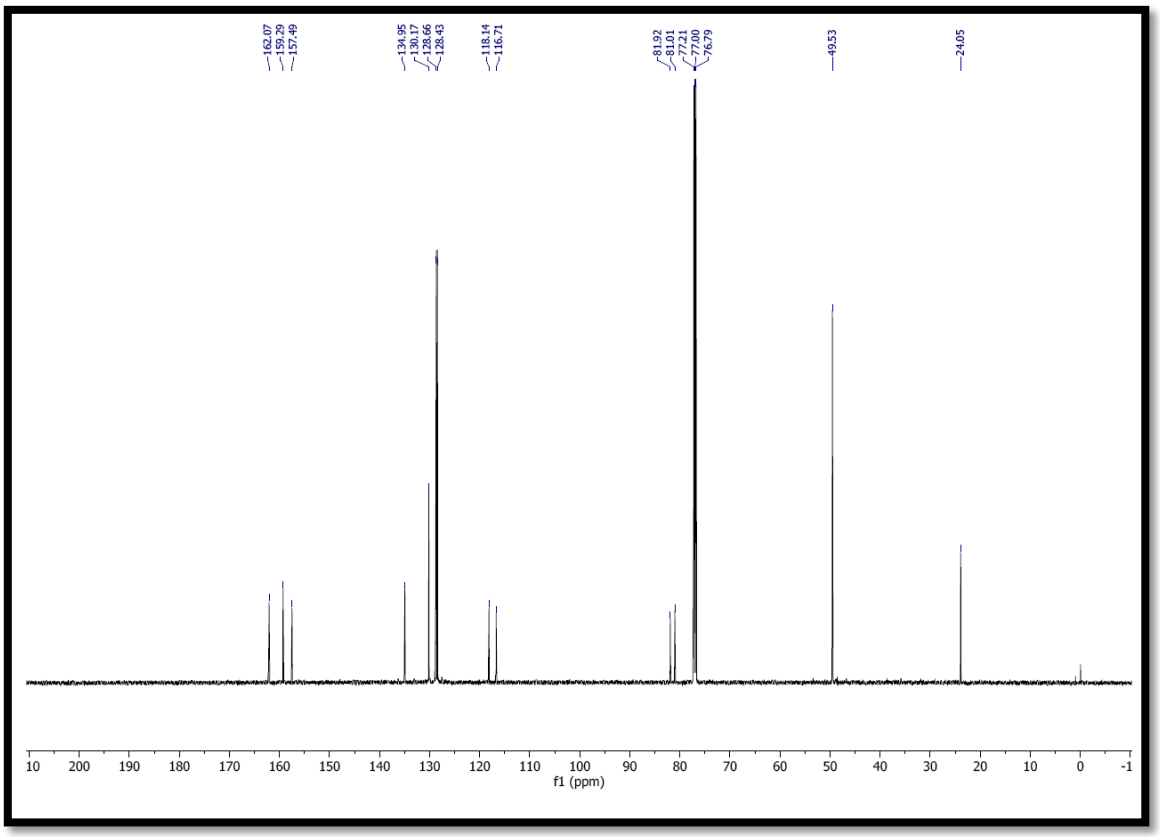
^{13}C NMR of compound 4l



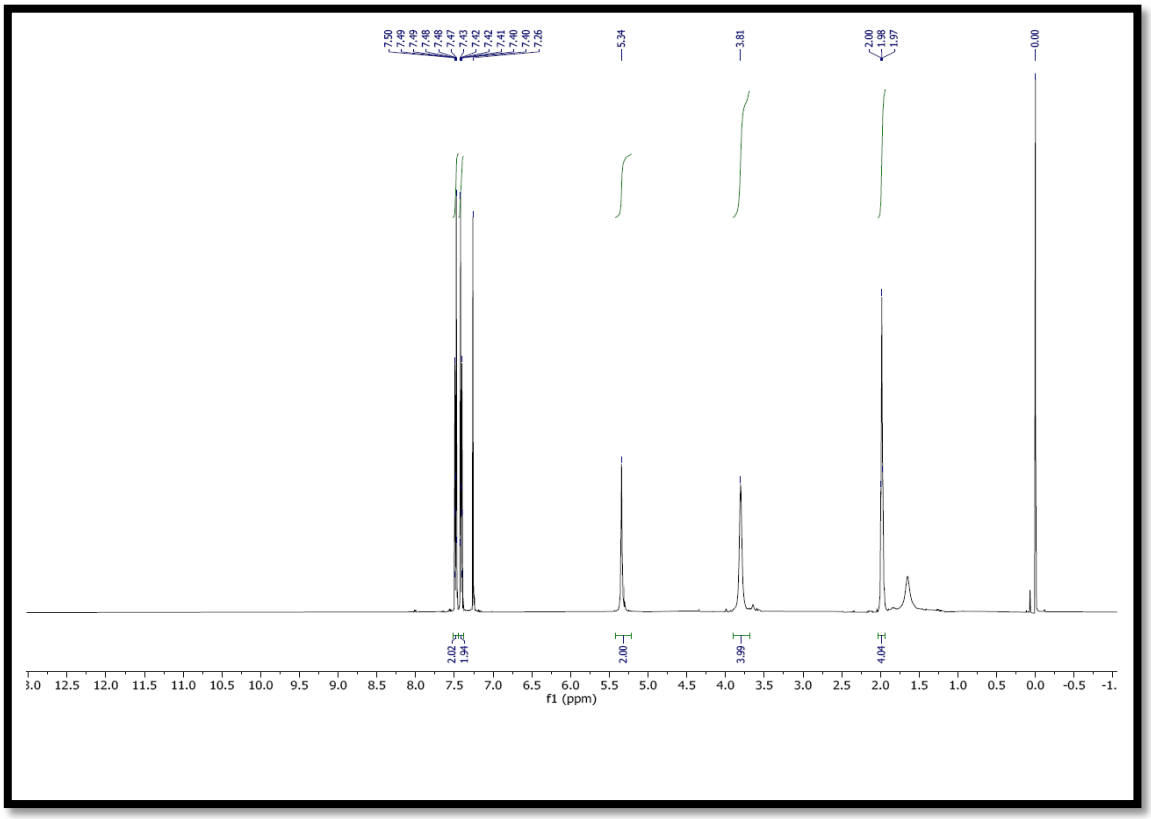
^{1}H NMR of compound 4m



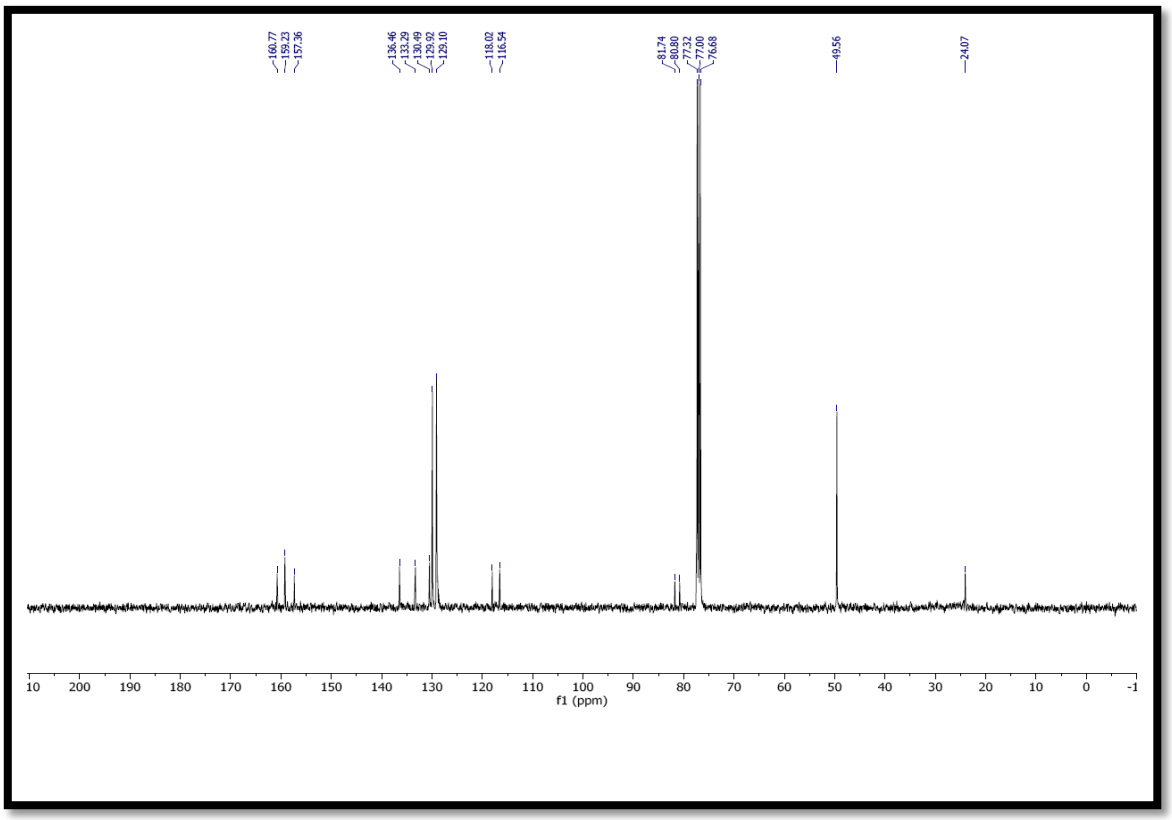
^{13}C NMR of compound 4m



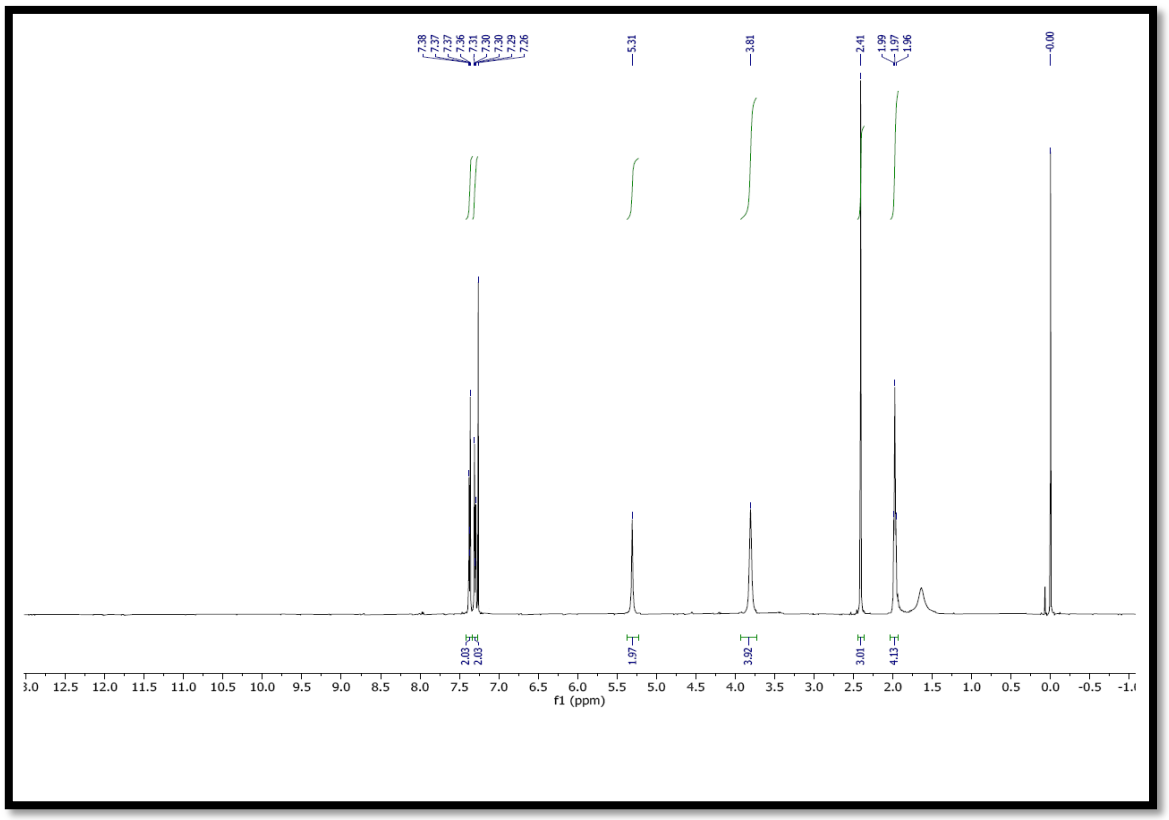
^{1}H NMR of compound 4n



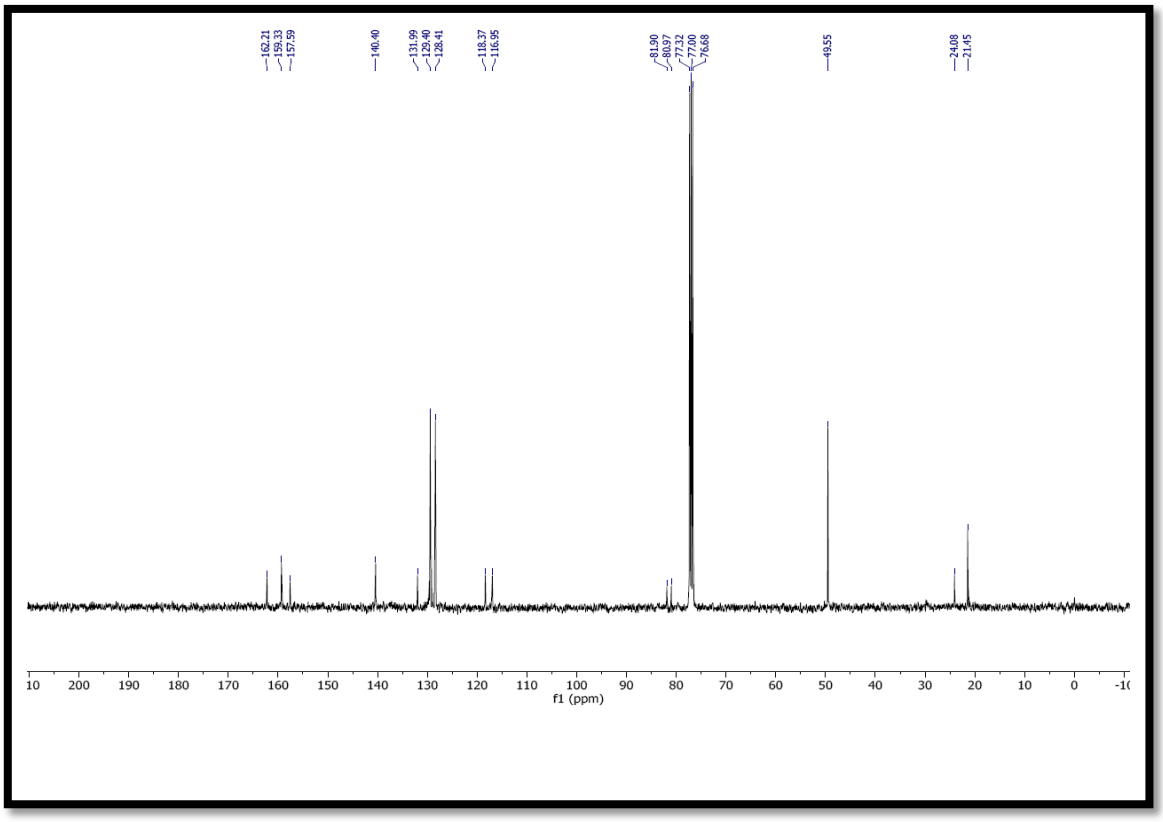
^{13}C NMR of compound 4n



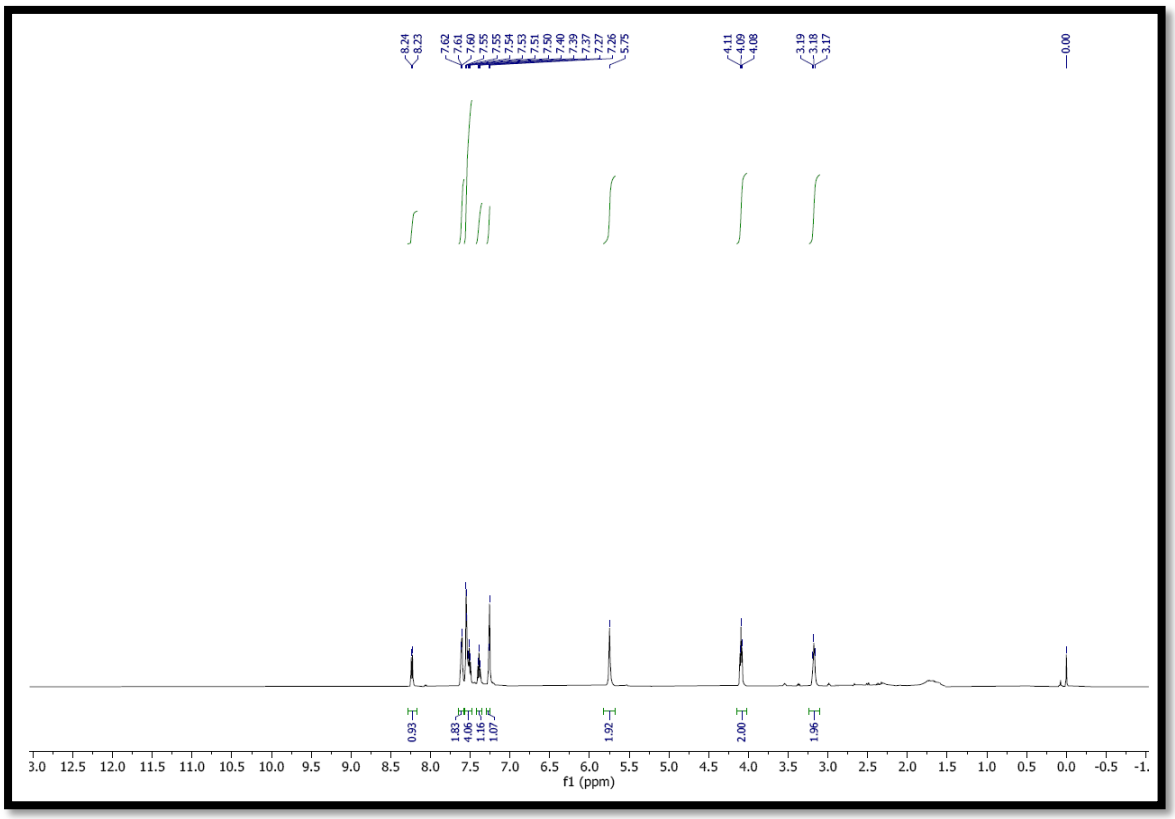
^{1}H NMR of compound 4o



^{13}C NMR of compound 4o



^{1}H NMR of compound 5a



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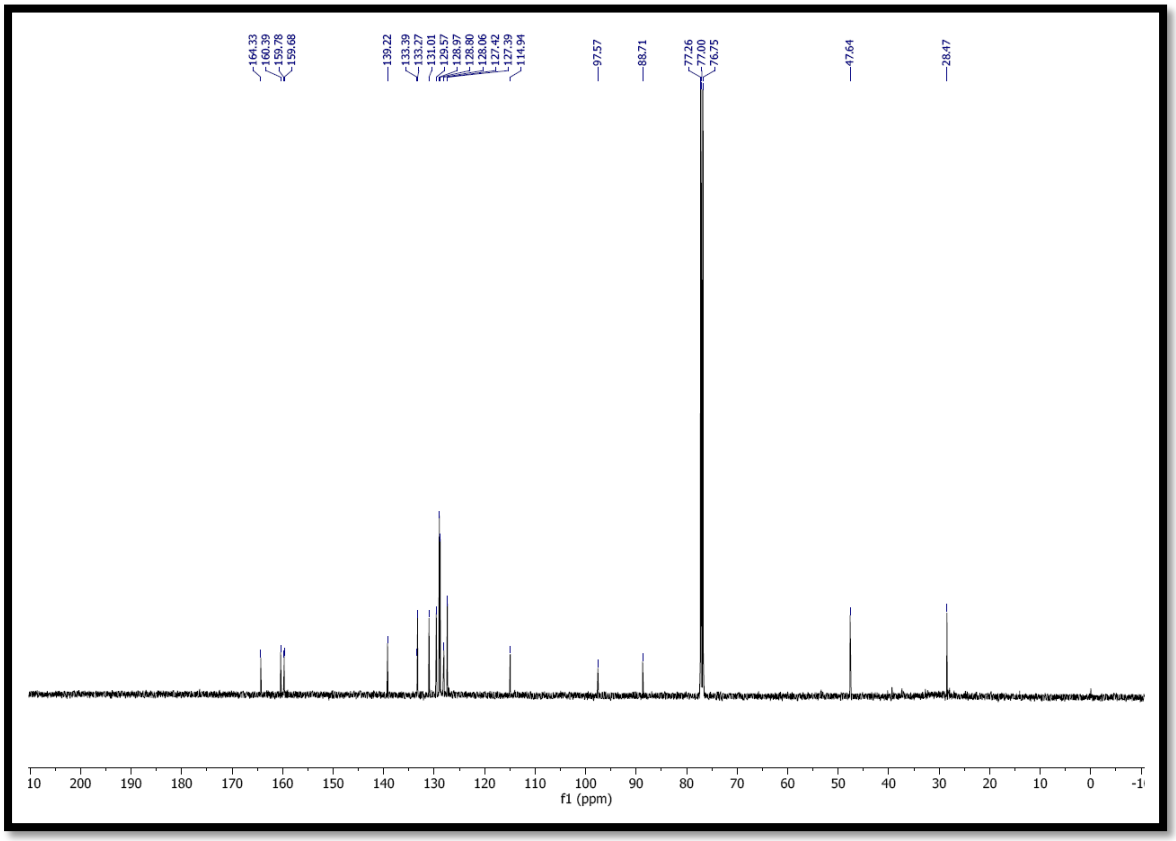
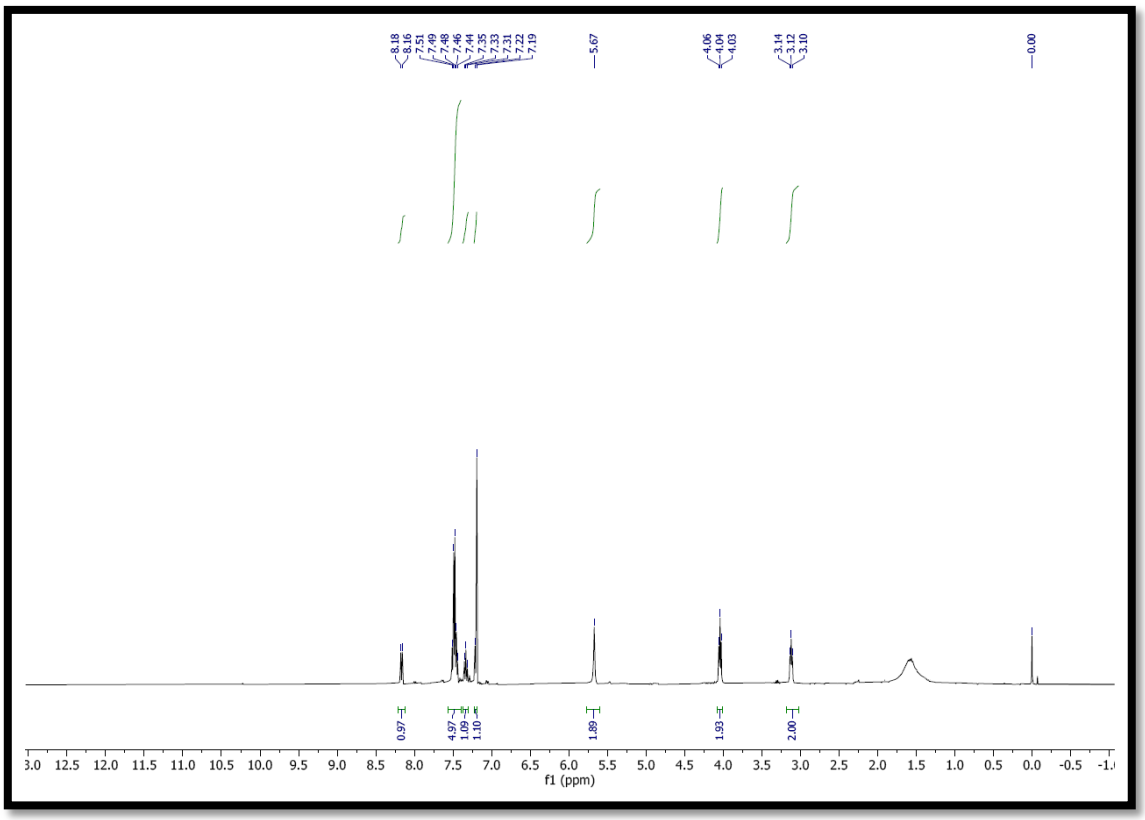


^{1}H NMR of compound 5b



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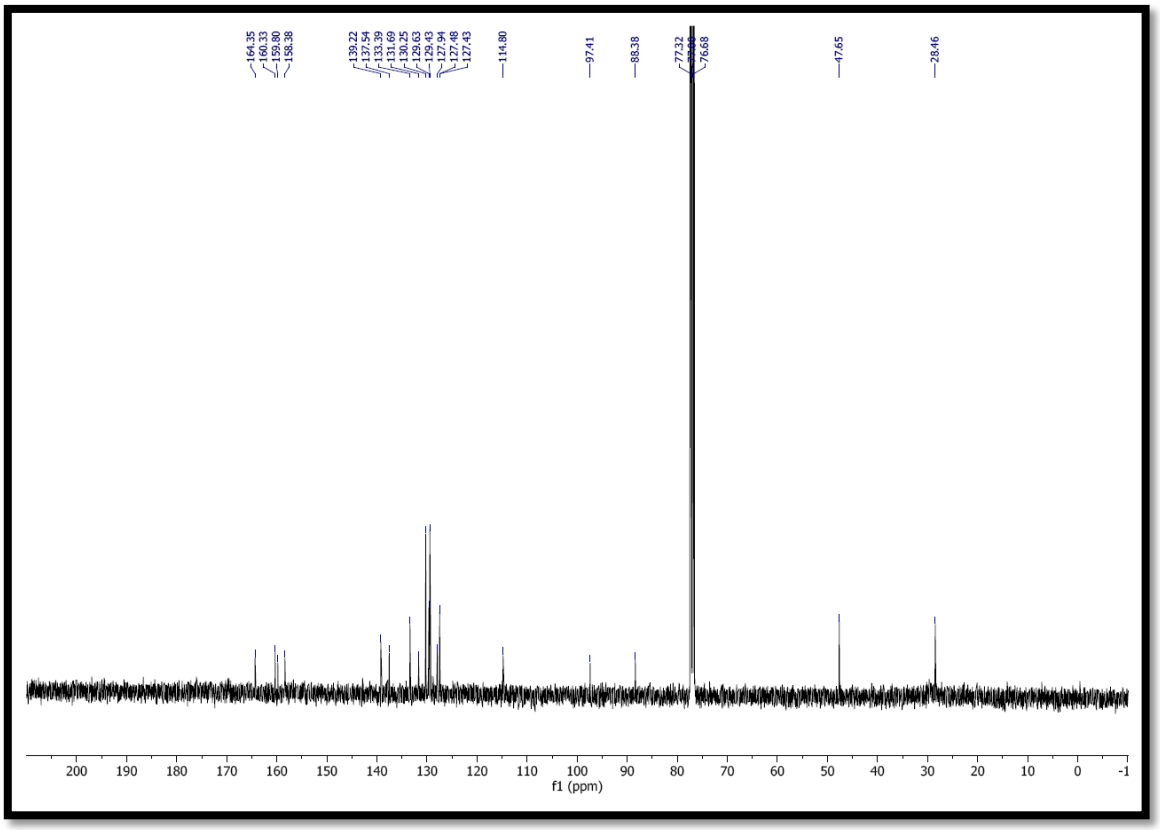
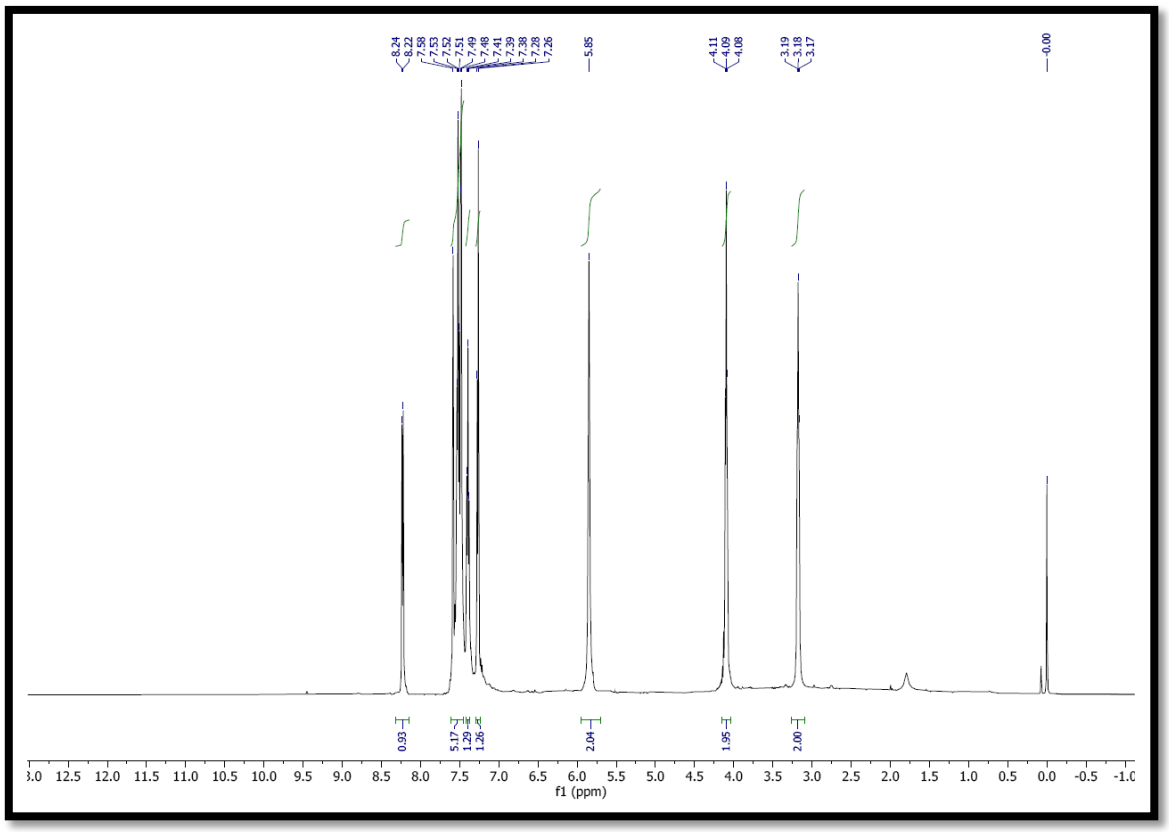
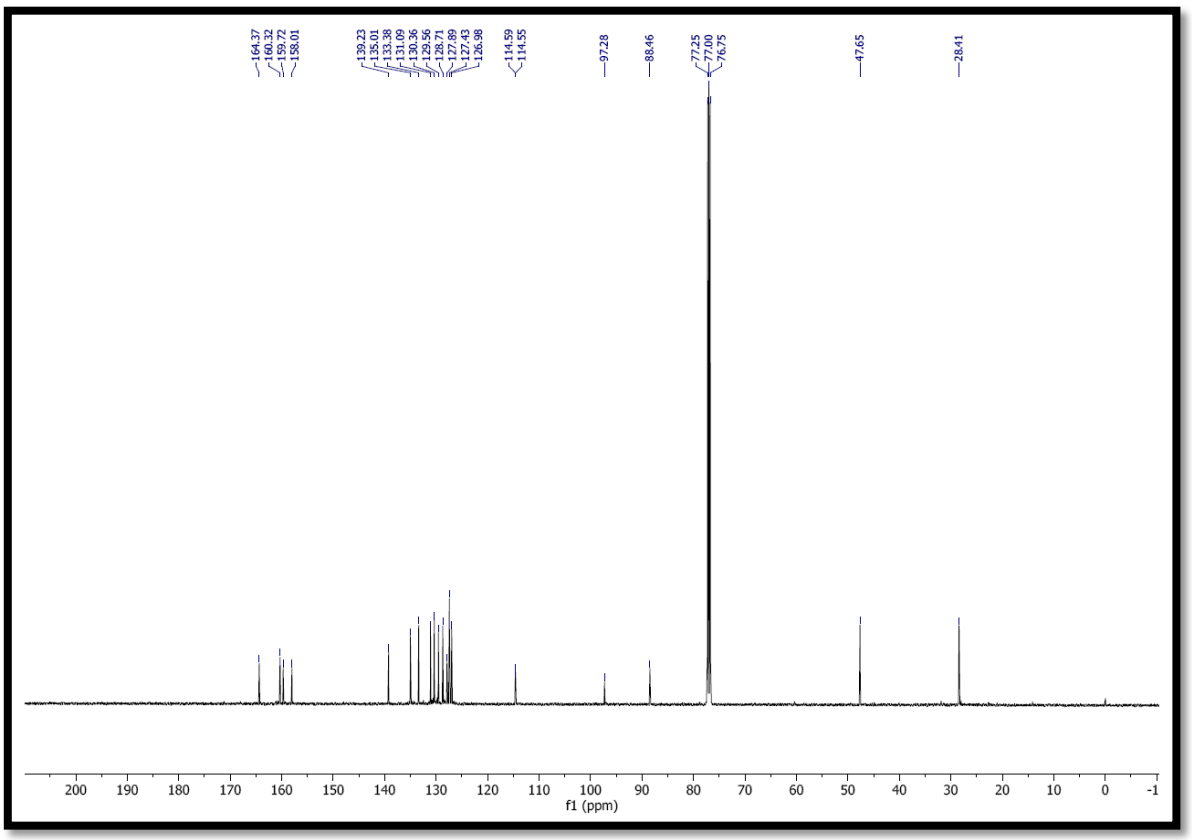


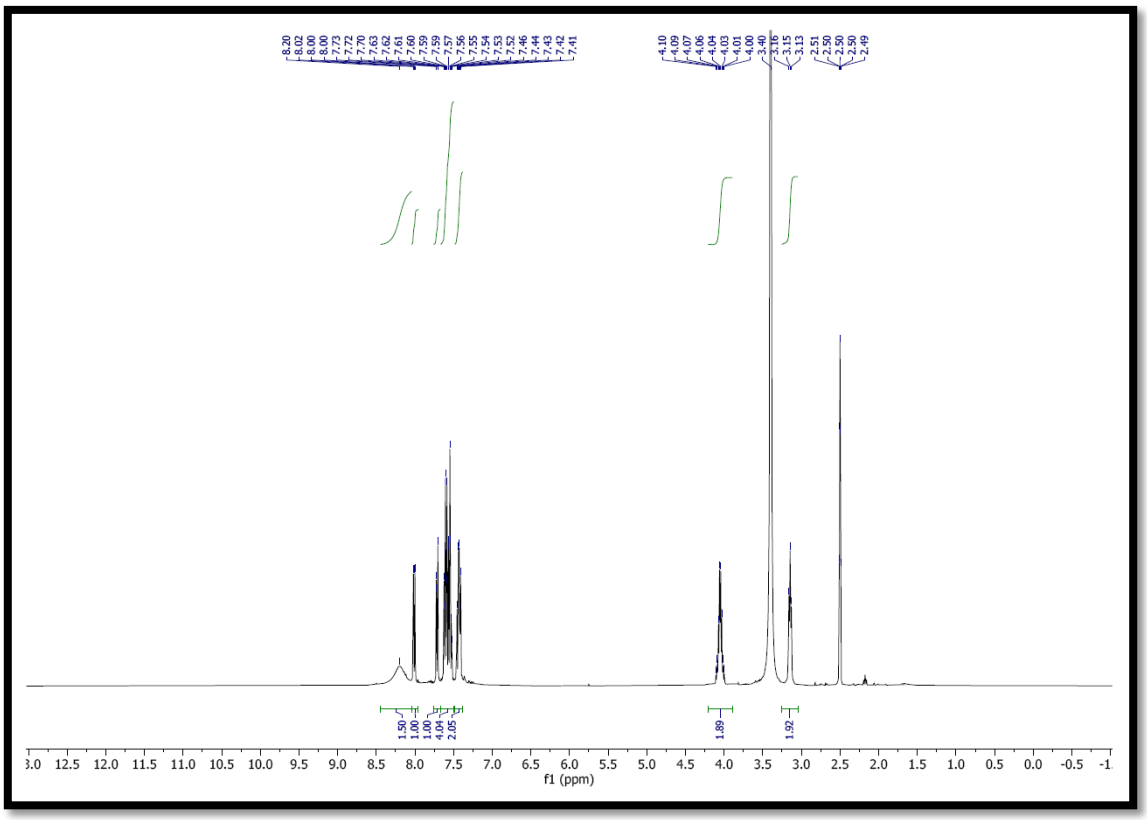
^{1}H NMR of compound 5c



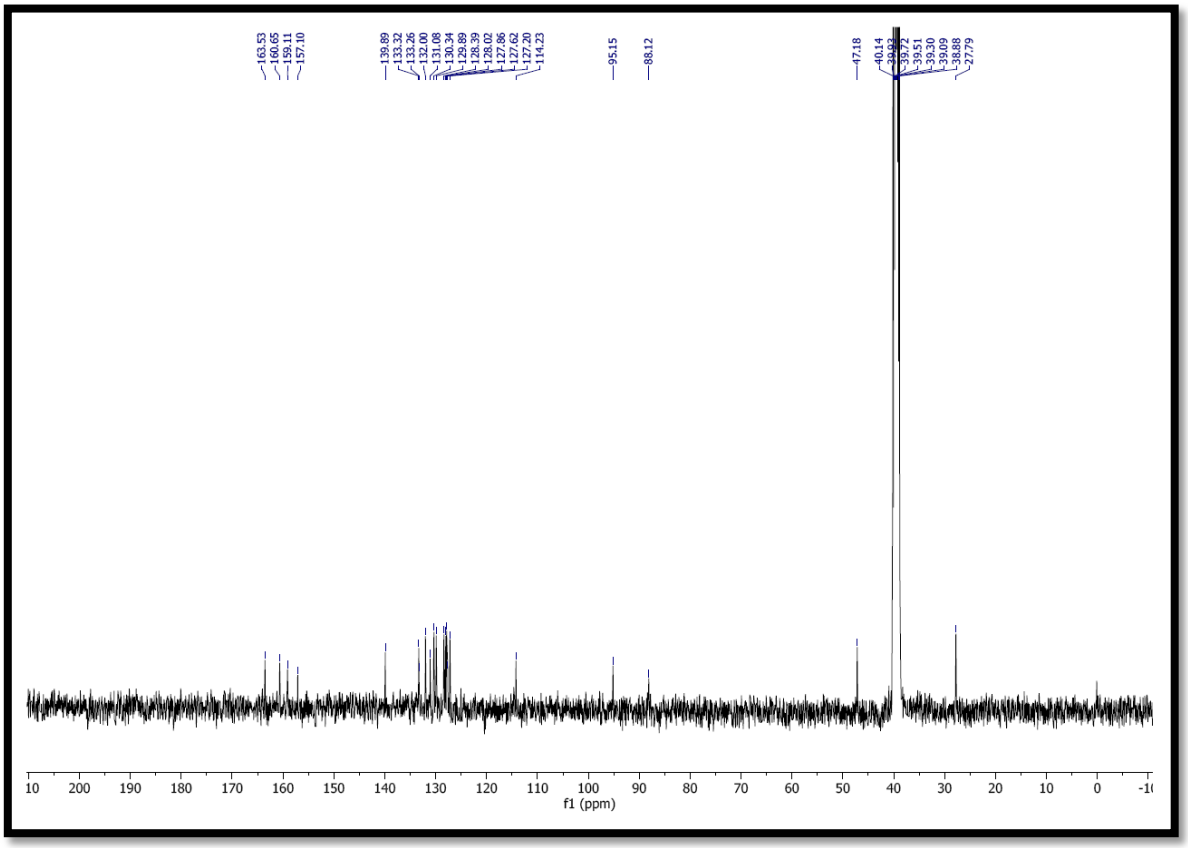
^{13}C NMR of compound 5c



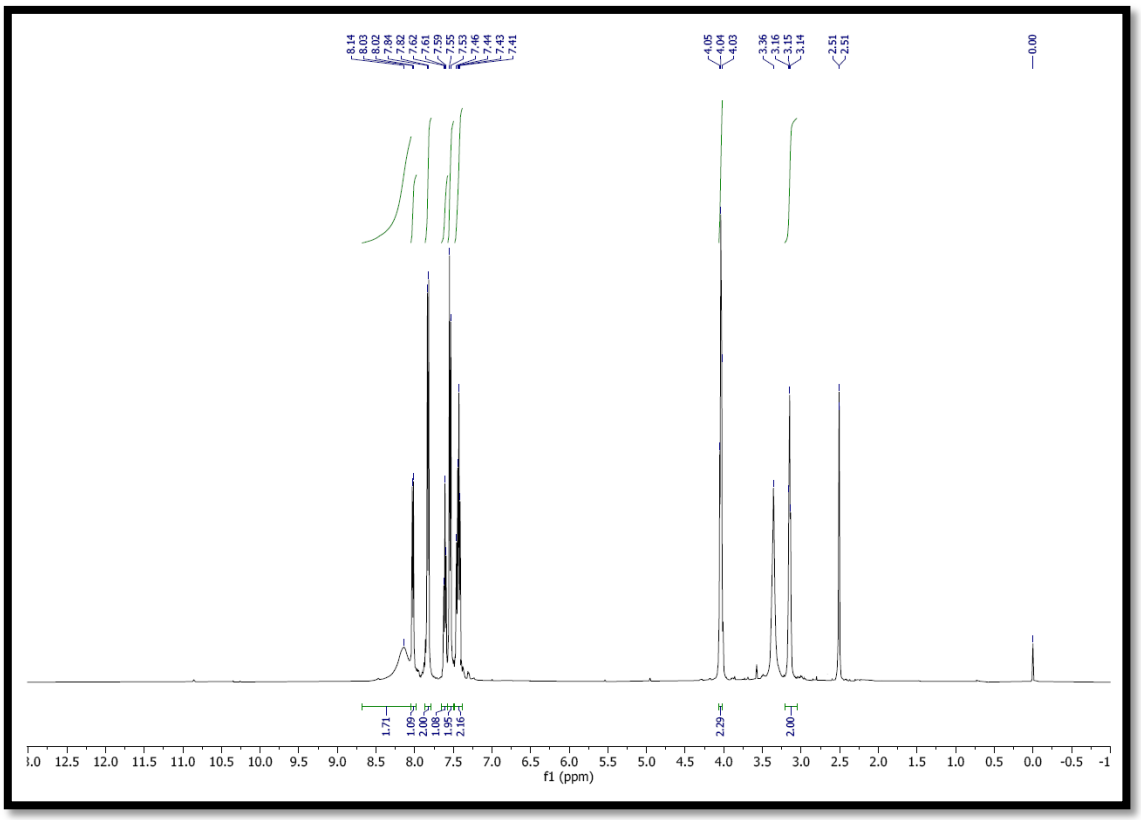
^{1}H NMR of compound 5d



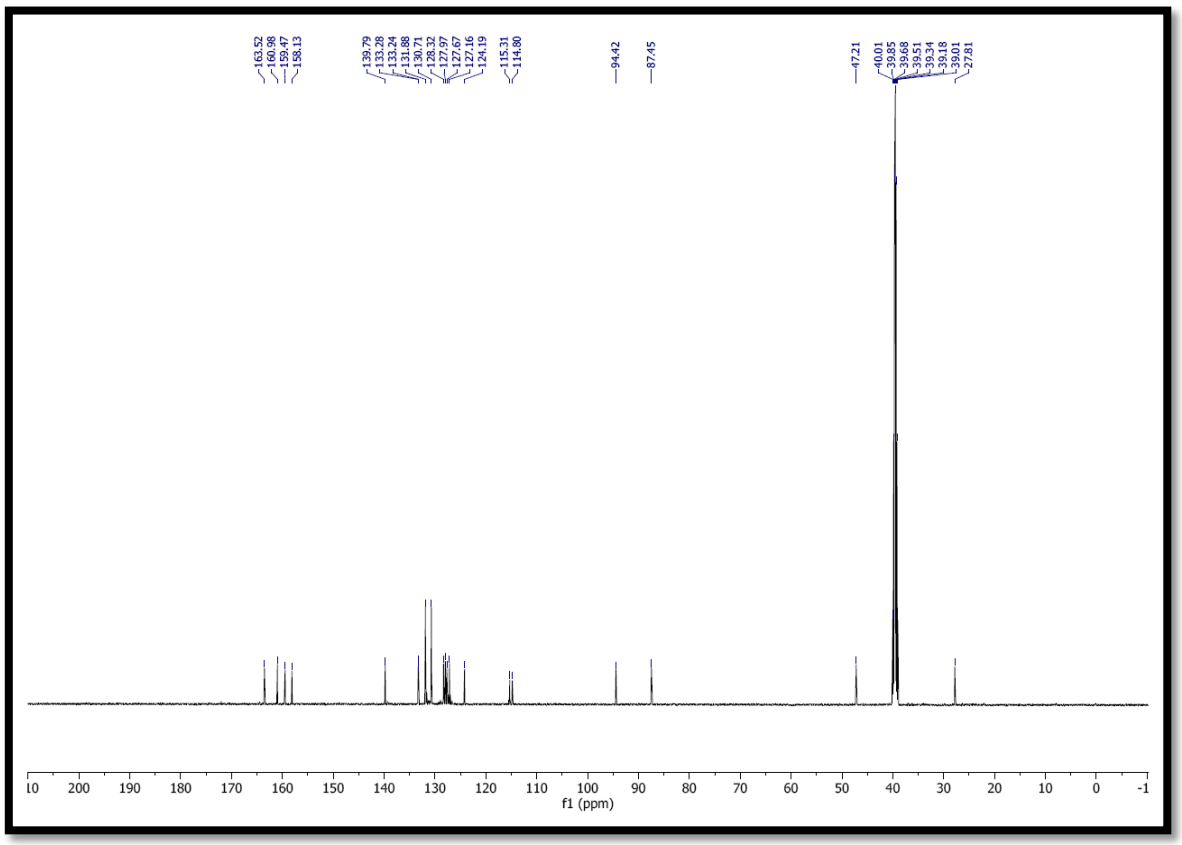
^{13}C NMR of compound 5d



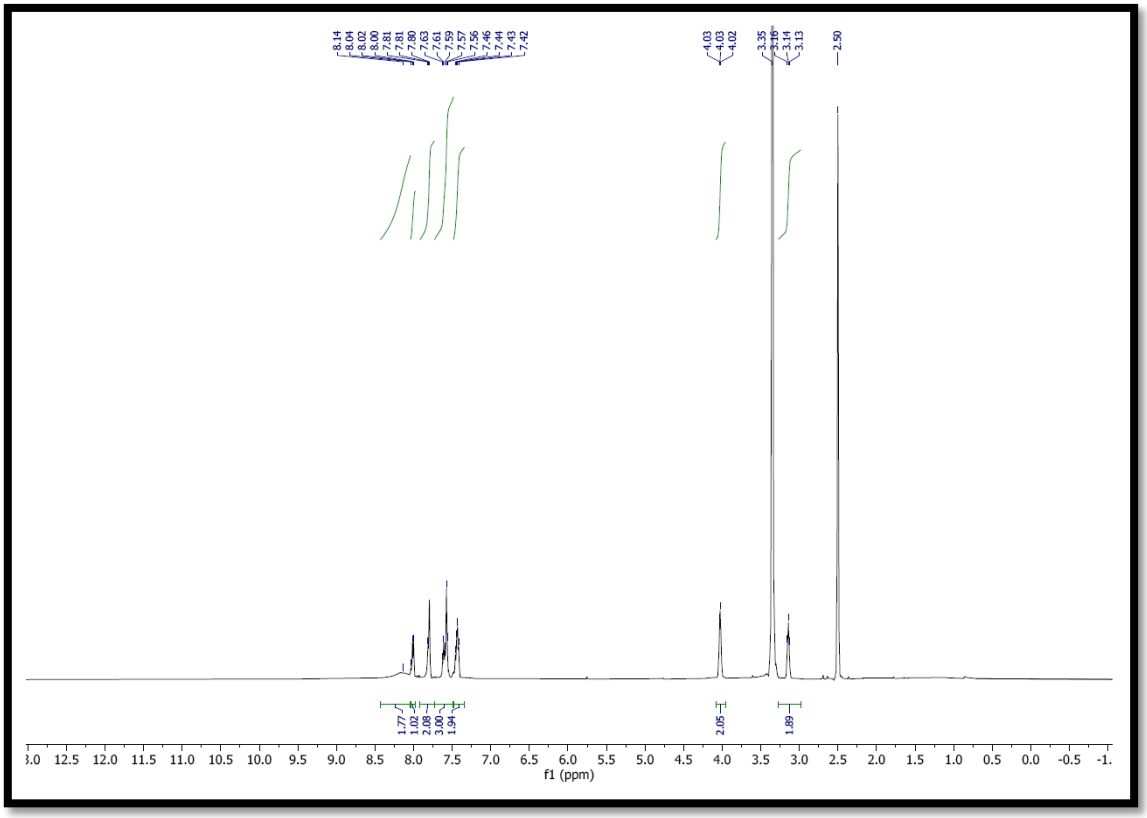
^{1}H NMR of compound 5e



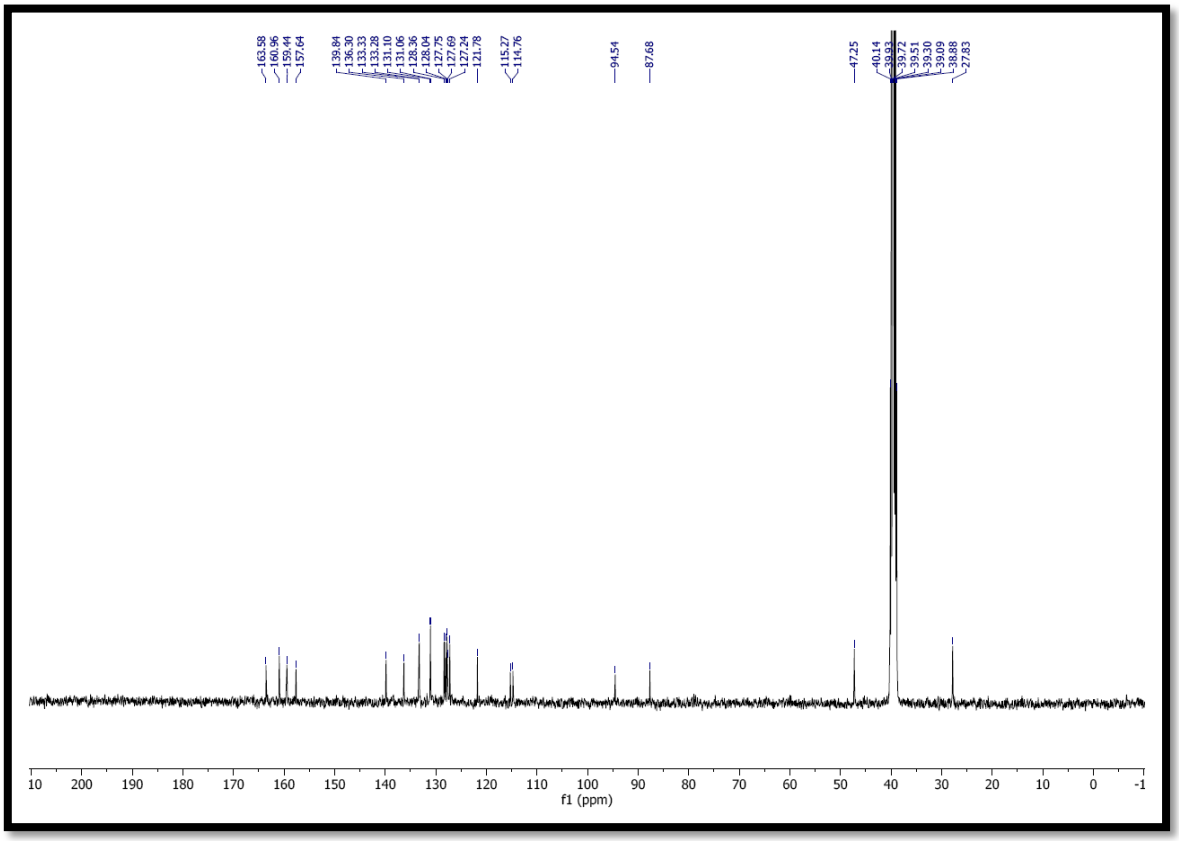
^{13}C NMR of compound 5e



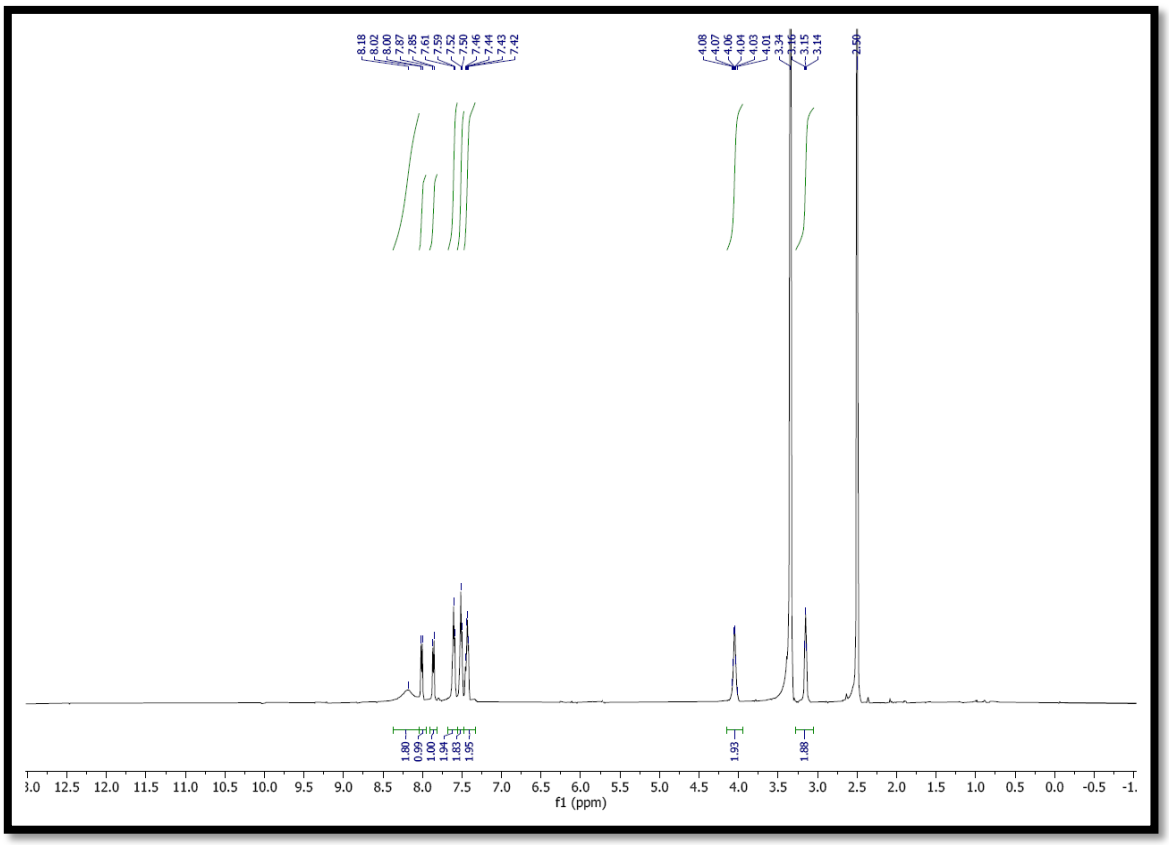
^{1}H NMR of compound 5f



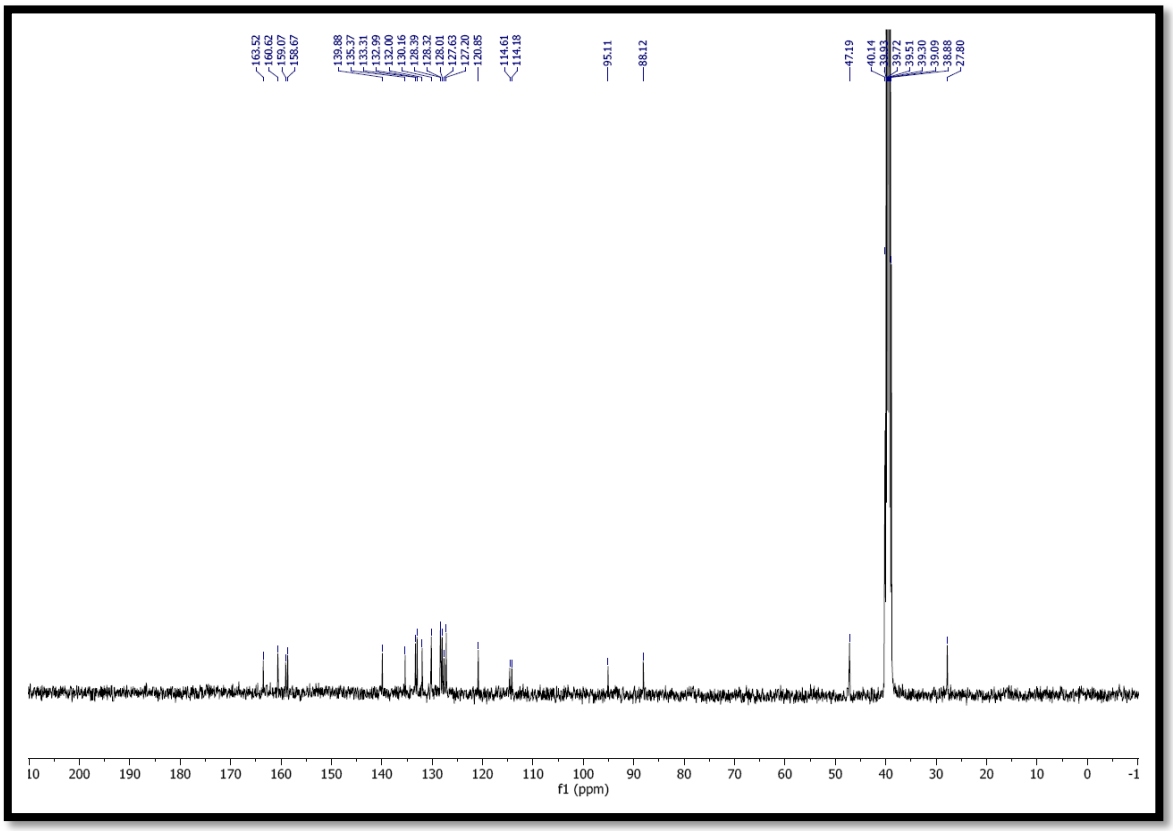
^{13}C NMR of compound 5f



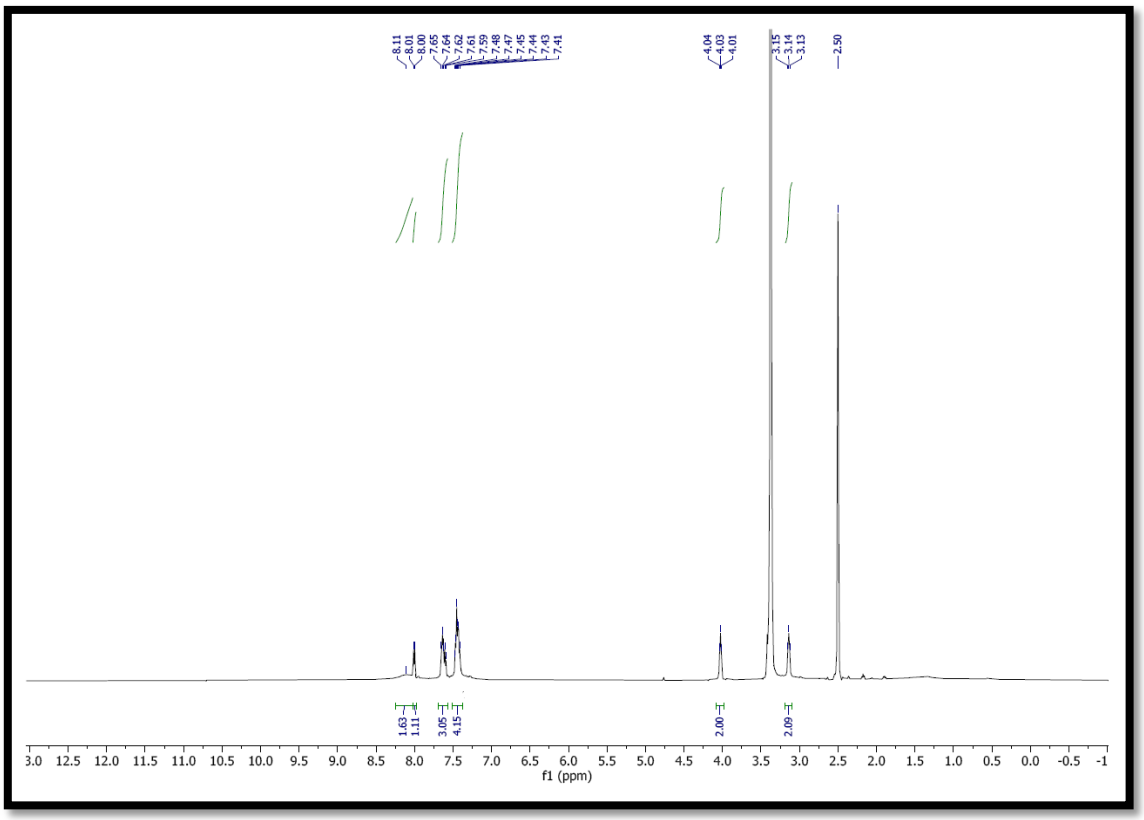
^{1}H NMR of compound 5g



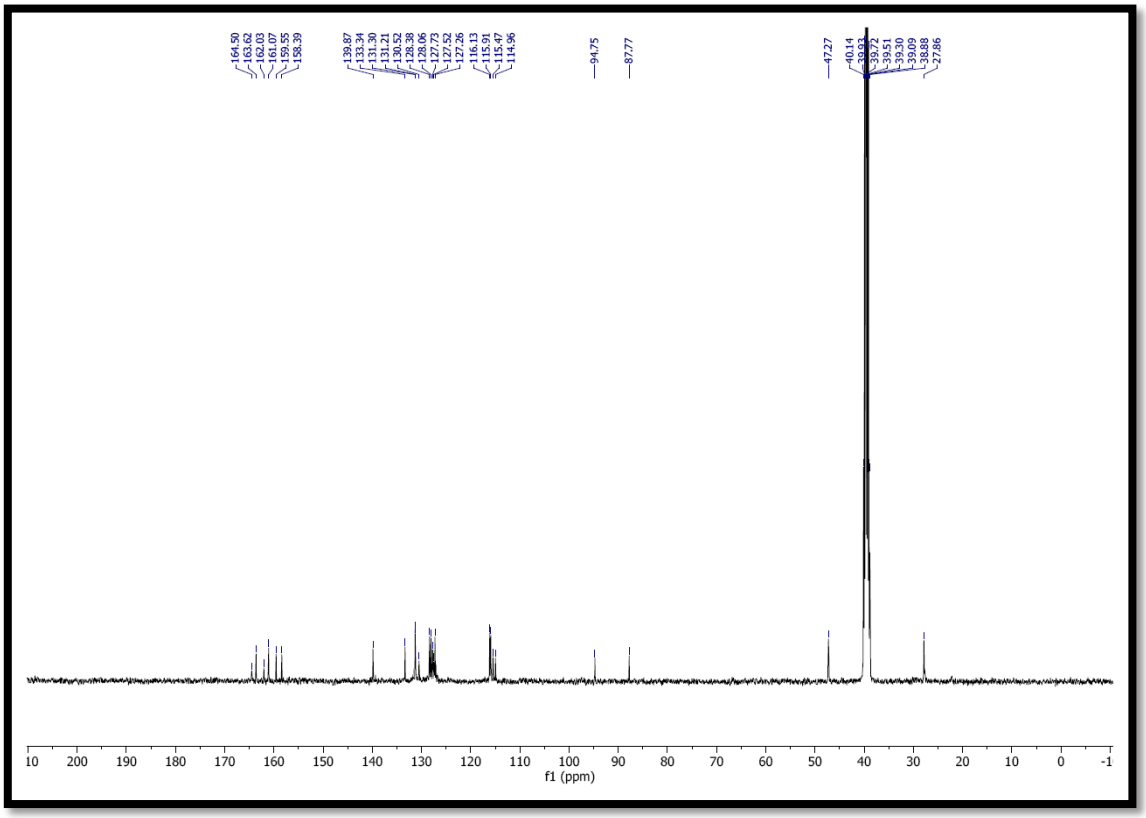
^{13}C NMR of compound 5g



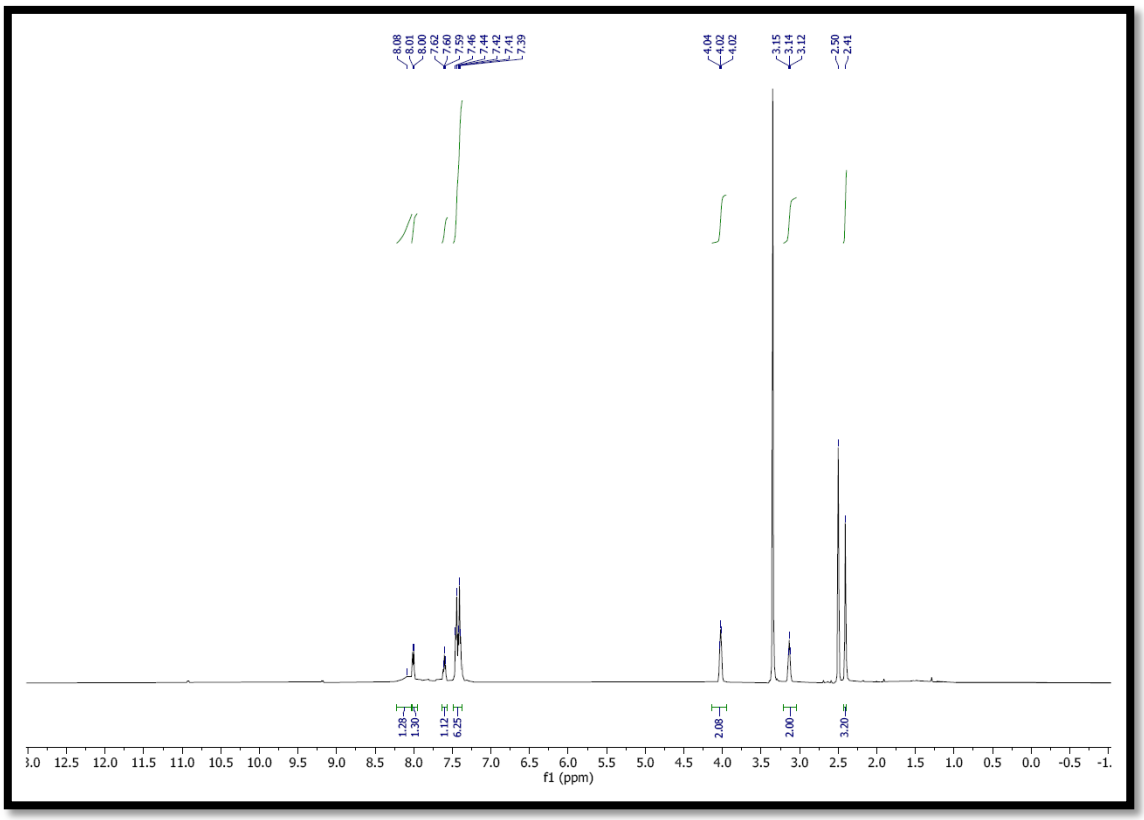
^{1}H NMR of compound 5h



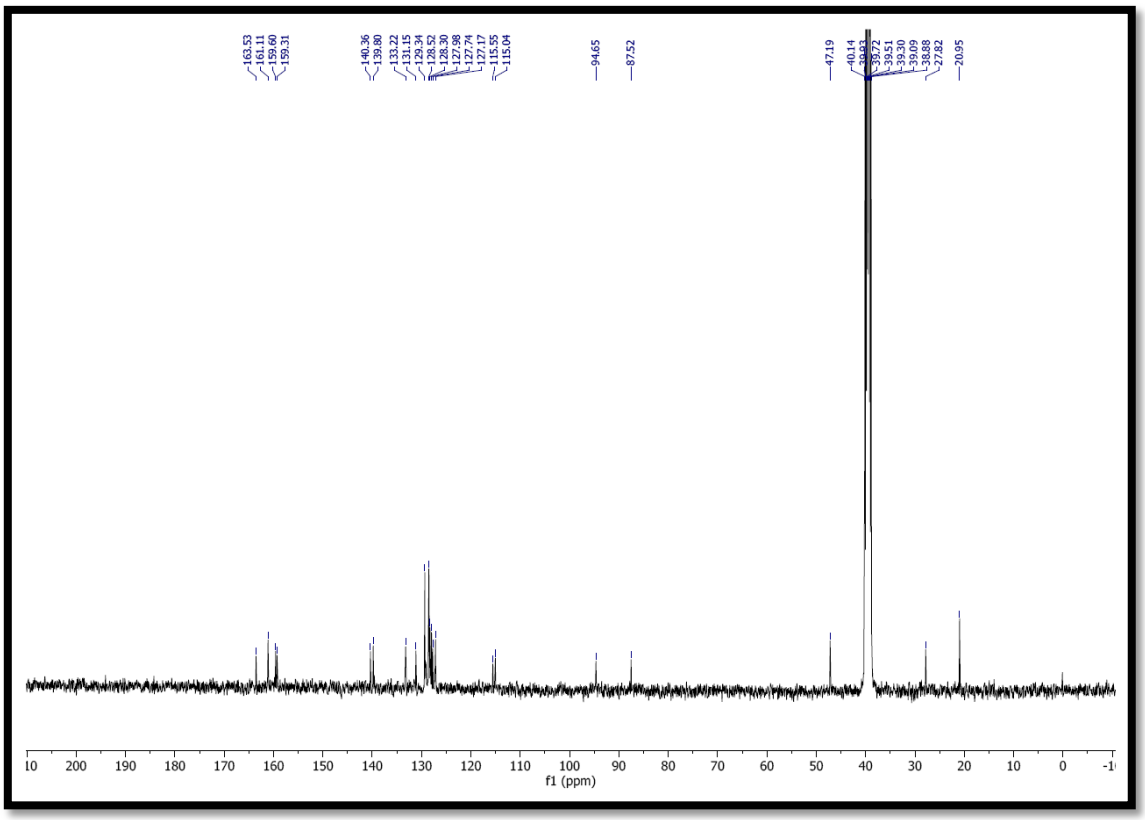
^{13}C NMR of compound 5h



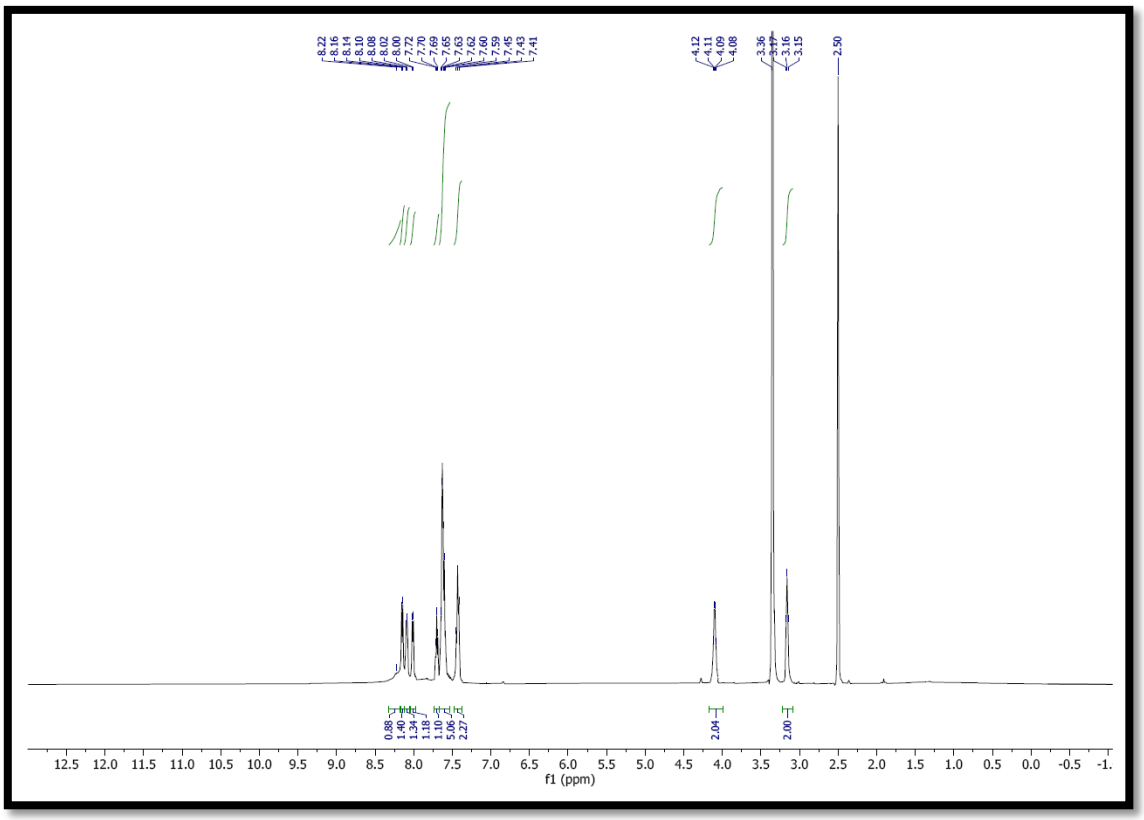
^{1}H NMR of compound 5k



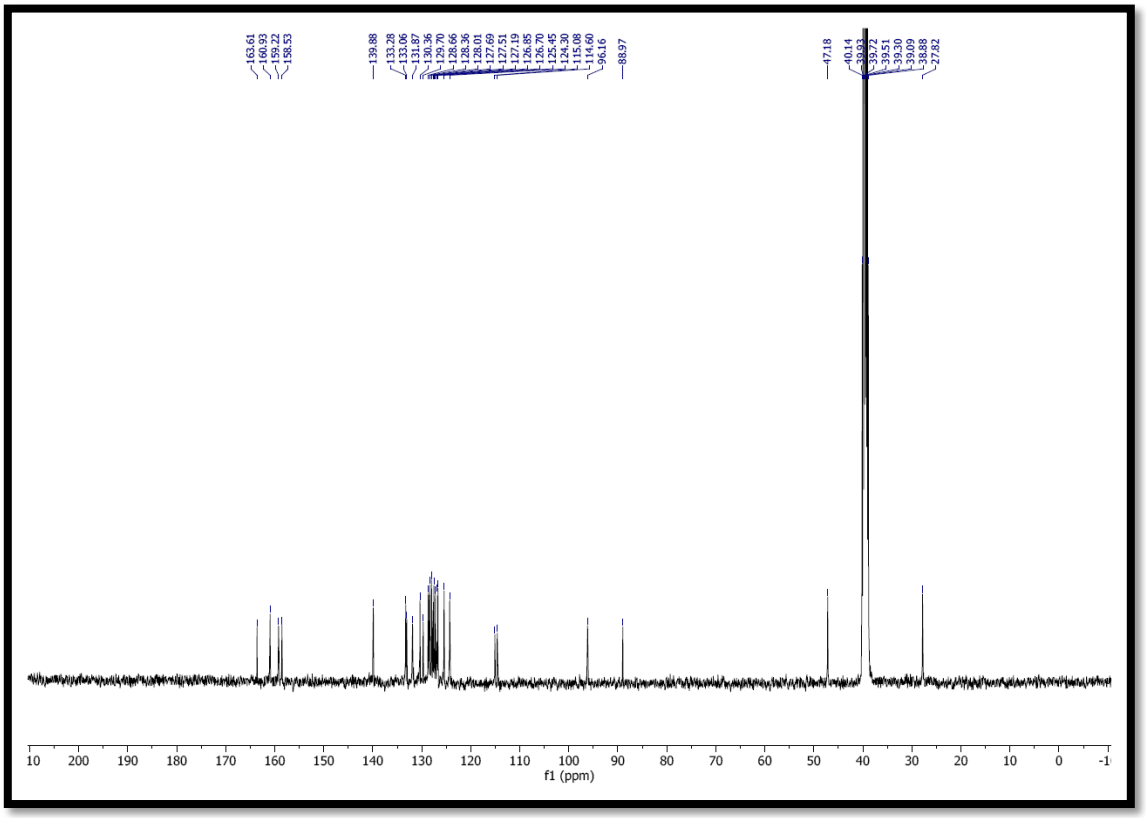
^{13}C NMR of compound 5k



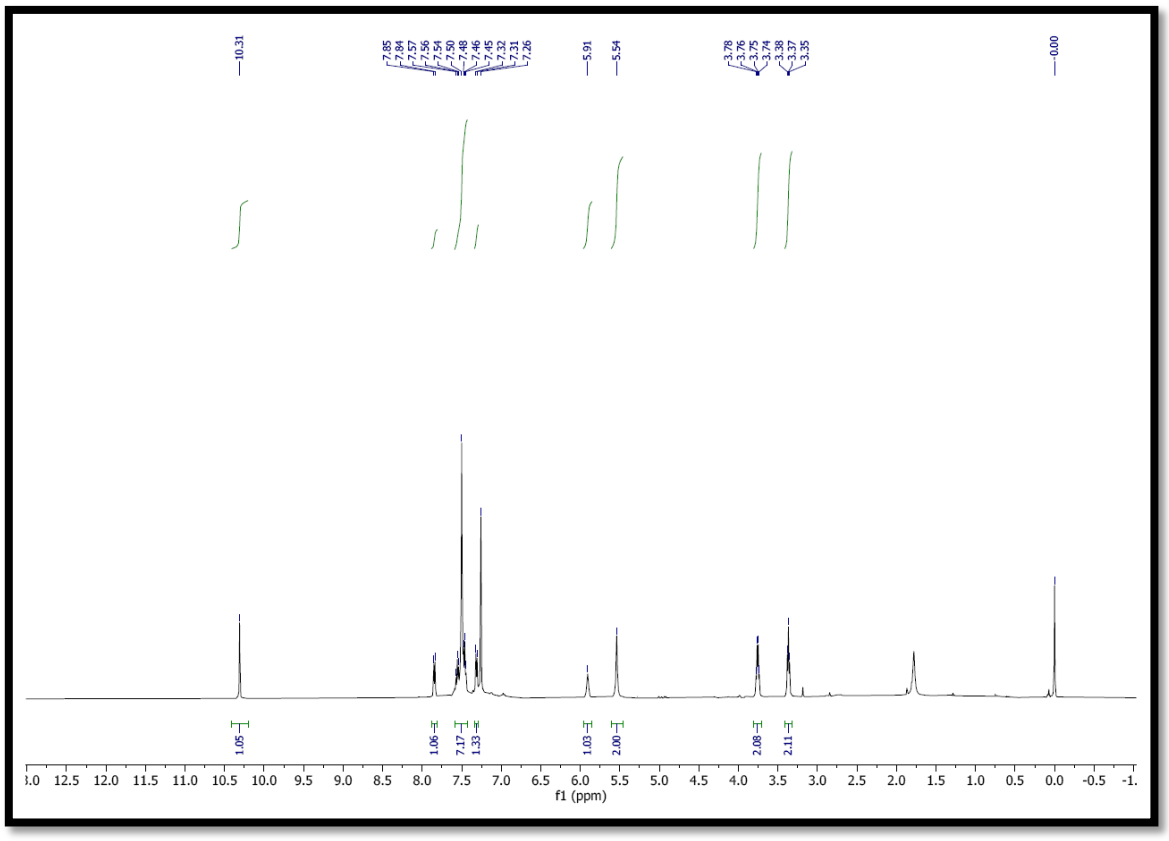
^{1}H NMR of compound 5l



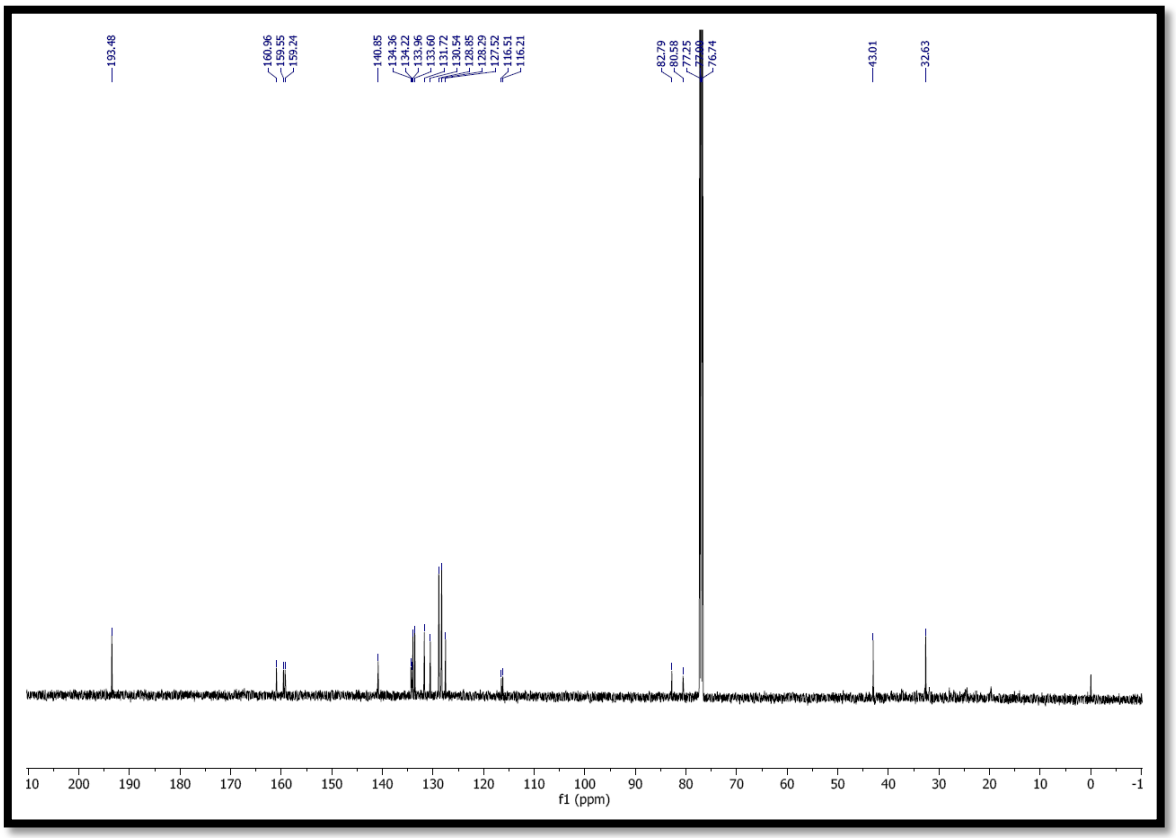
^{13}C NMR of compound 5l



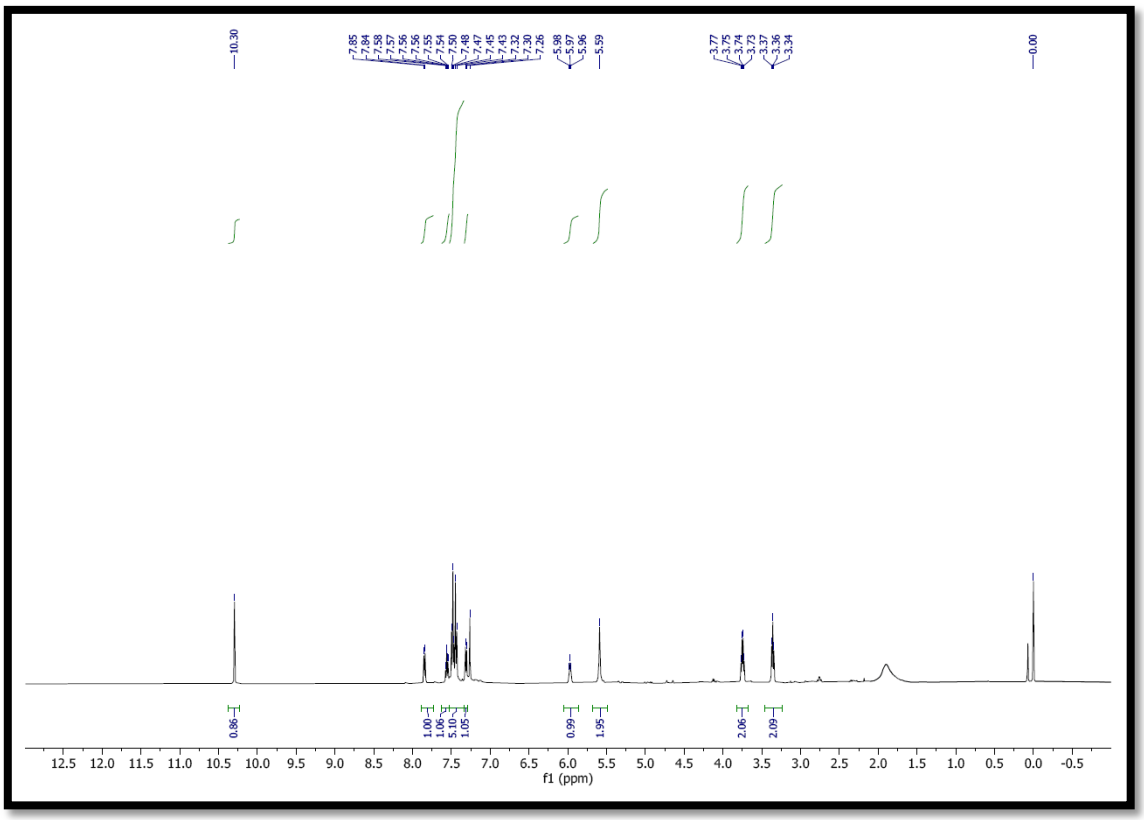
^{1}H NMR of compound 6a



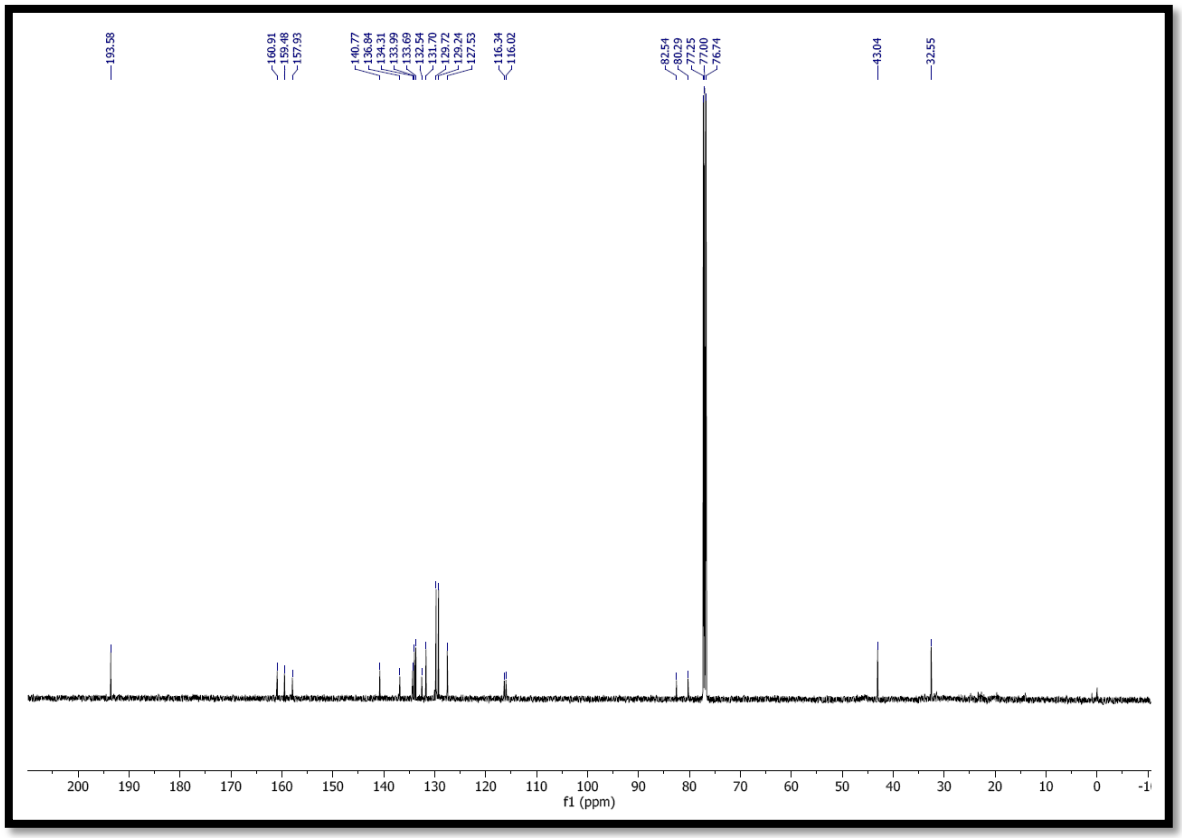
^{13}C NMR of compound 6a



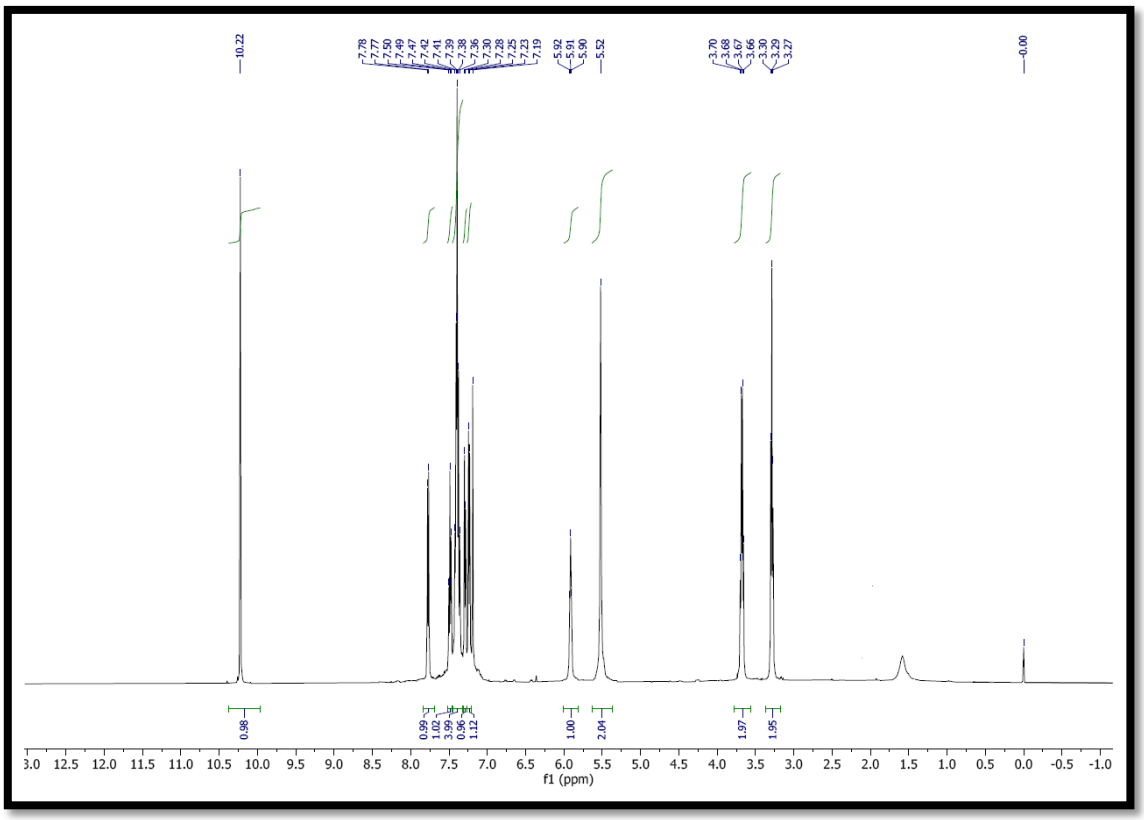
^{1}H NMR of compound 6b



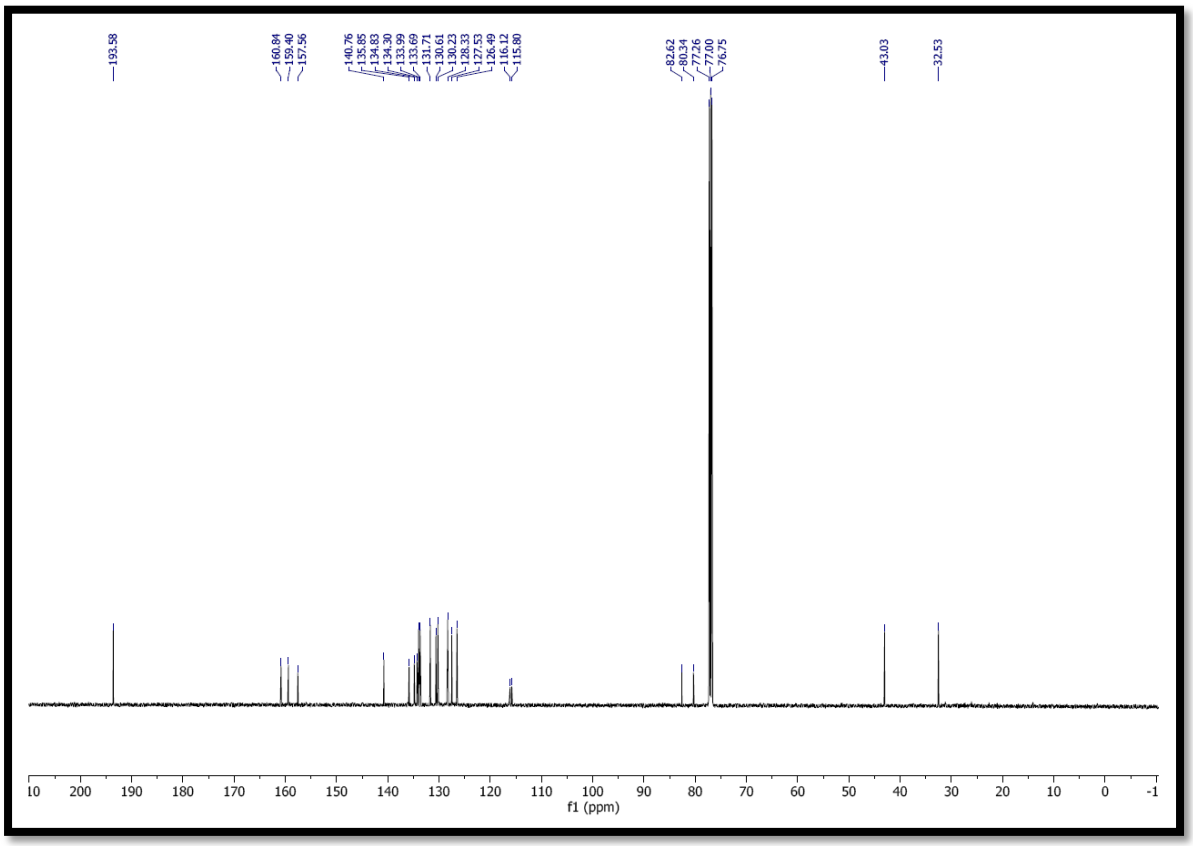
^{13}C NMR of compound 6b



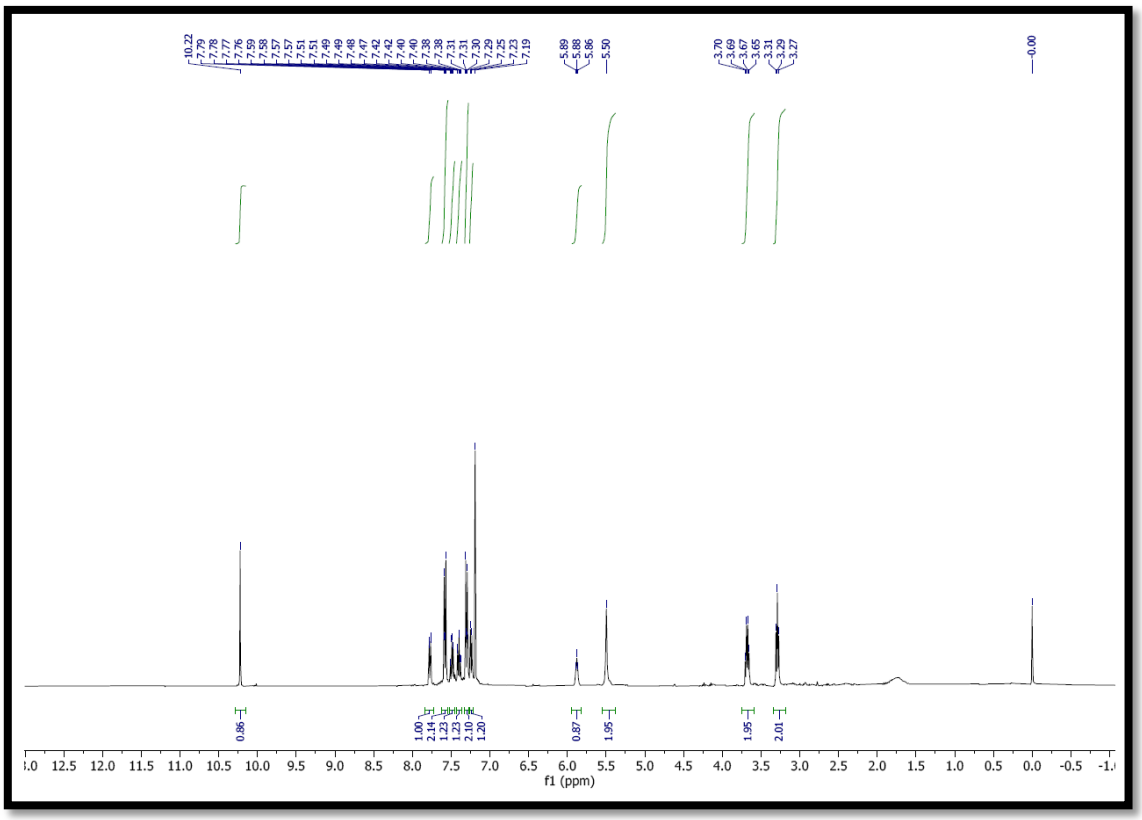
^{1}H NMR of compound 6c



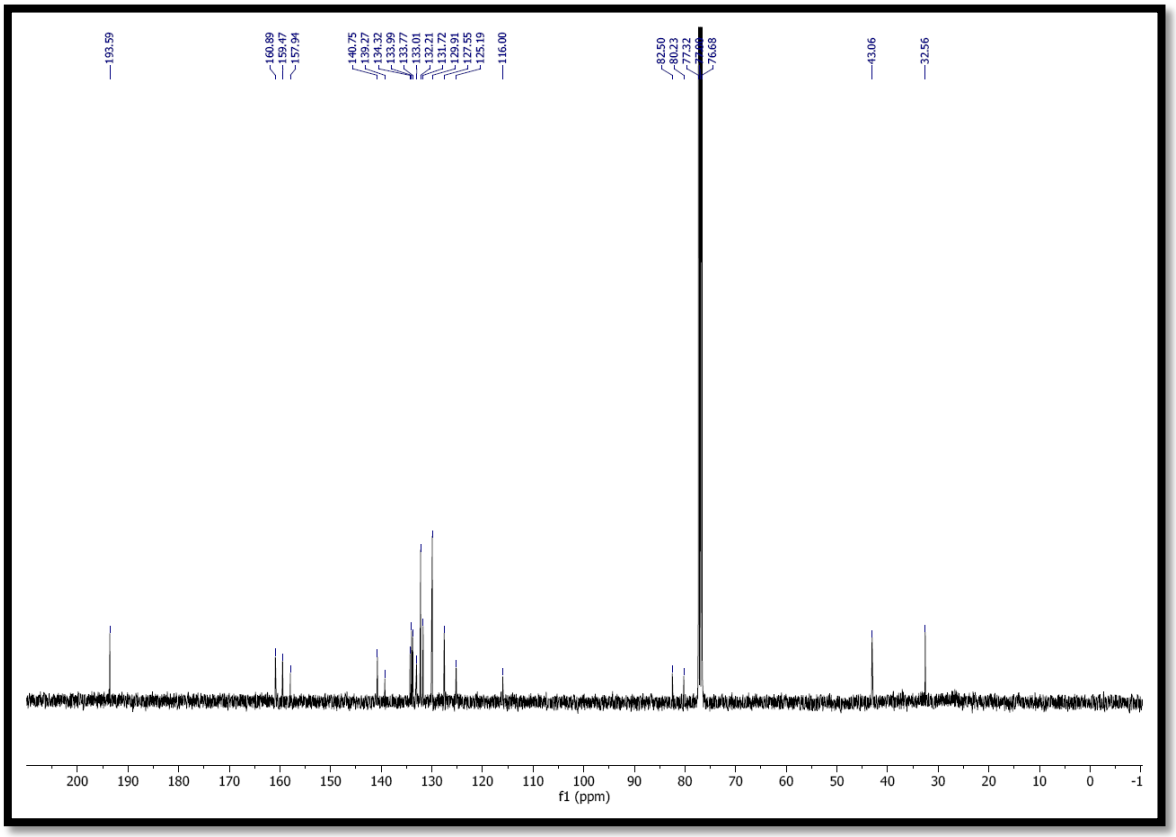
^{13}C NMR of compound 6c



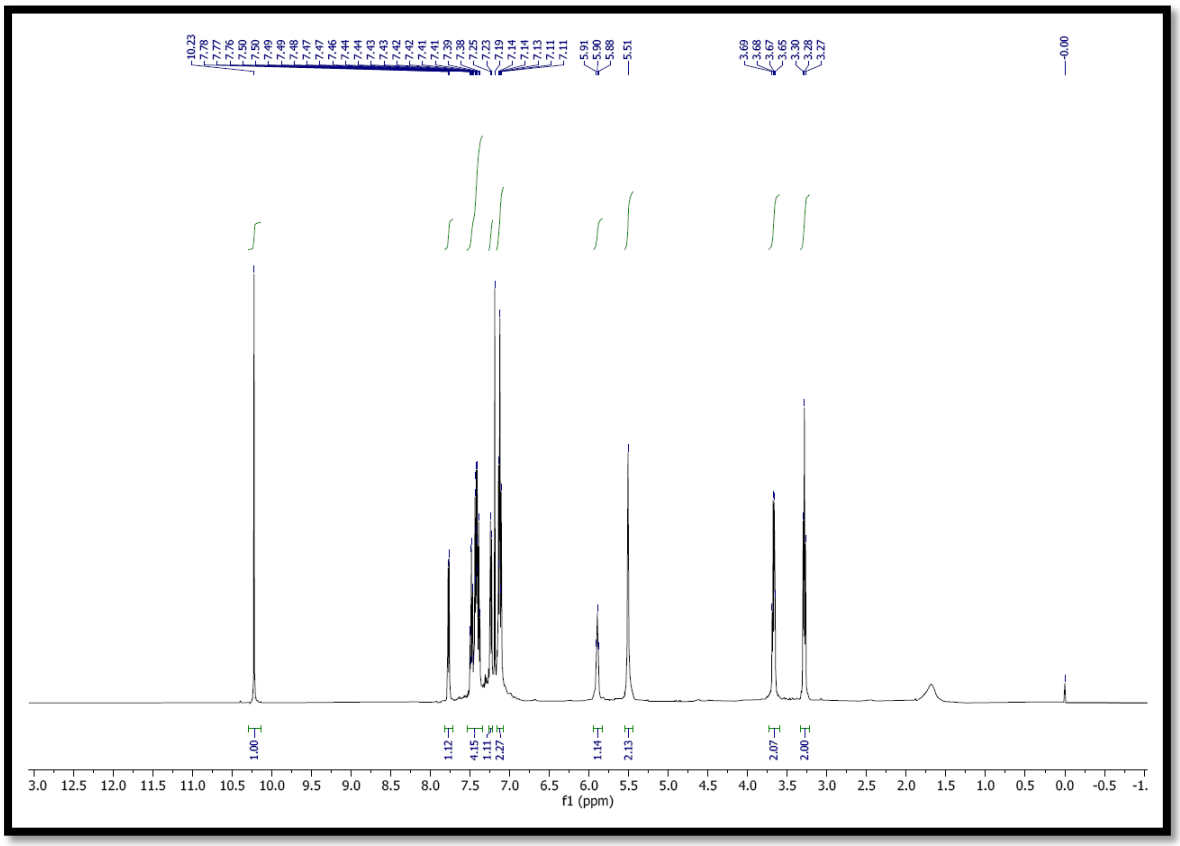
^{1}H NMR of compound 6e



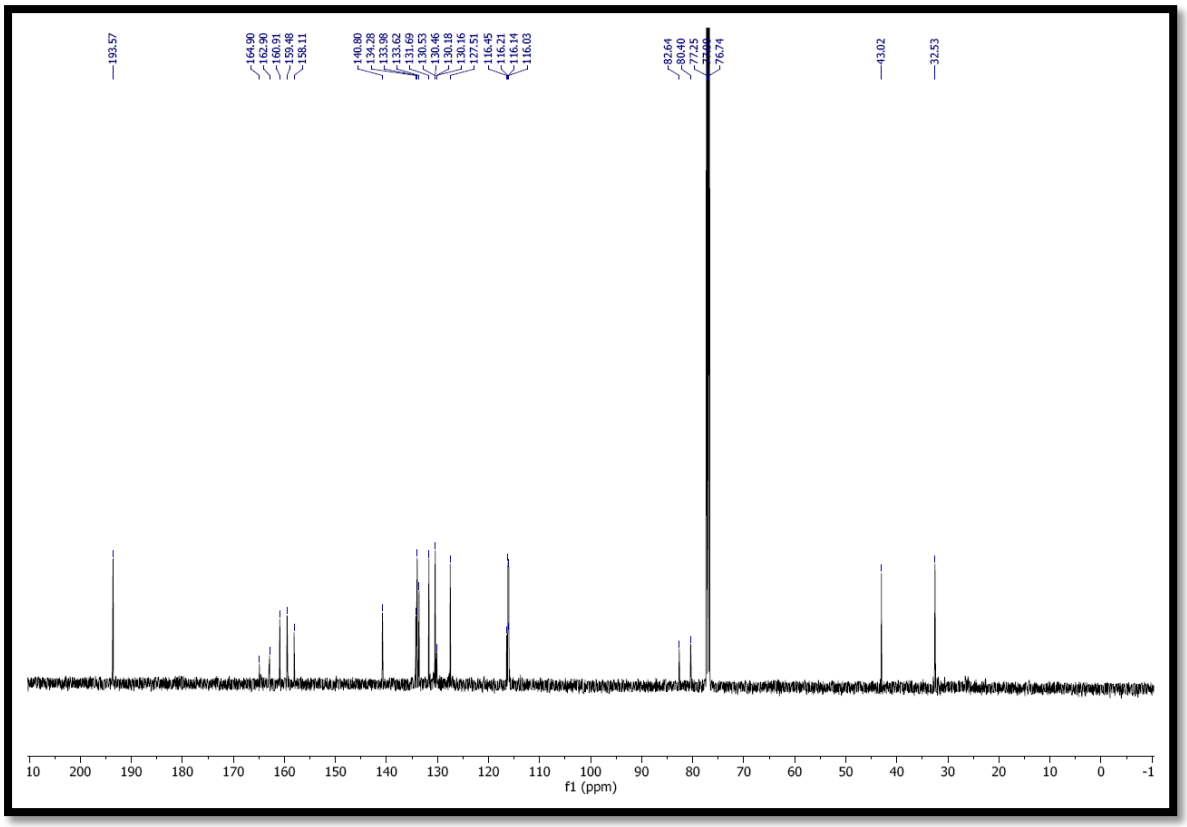
^{13}C NMR of compound 6e



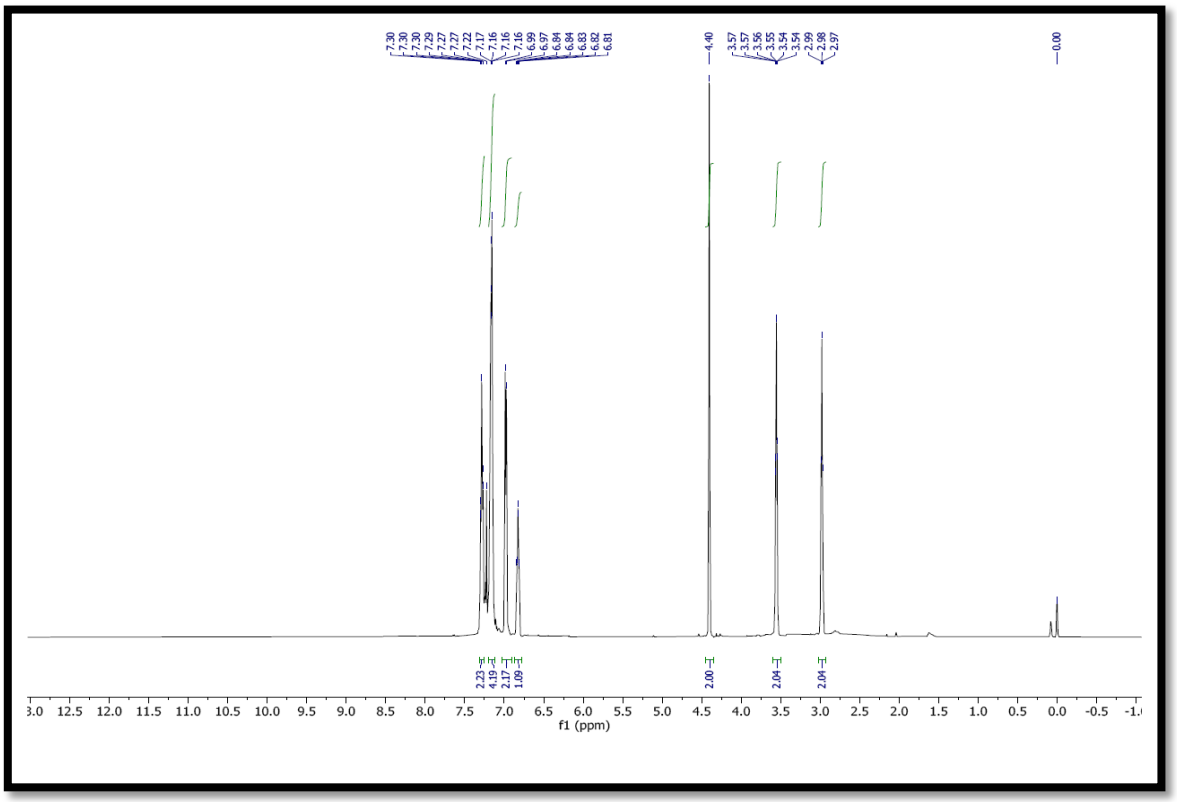
^{1}H NMR of compound 6h



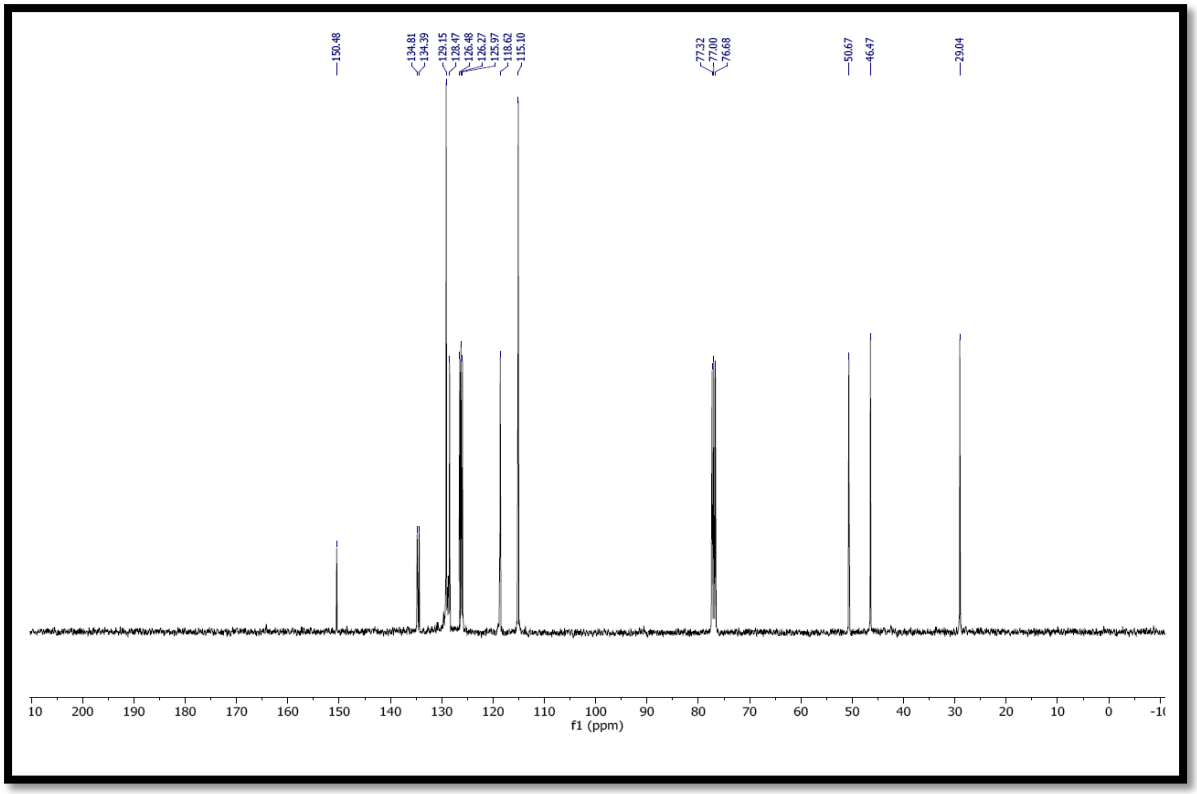
^{13}C NMR of compound 6h



^{1}H NMR of compound 7



^{13}C NMR of compound 7



HRMS of the failed deprotection reaction