Electronic Supplementary Material (ESI) for RSC Advances.

Supporting Information

An operational transformation of 3-carboxy-4-quinolones into 3-nitro-4-quinolones via ipso-nitration using polysaccharide supported copper nanoparticles: synthesis of 3-tetrazolyl bioisosteres of 3-carboxy-4-quinolones as antibacterial

Chandra S Azad and Anudeep K Narula*

"Hygeia" Centre of Excellence in Pharamceutical Sciences (CEPS), GGS Indraprastha Univeristy, Sec. 16-C, Dwarka, New Delhi, India, E-mail: medchemlab58@gmail.com

General Information

Reagent grade solvents were used for the extraction and flash chromatography. All the reagents and chemicals were purchased from Sigma Aldrich Chemical Co., Merck and were used directly without further purification. The progress of reactions was checked by analytical thin-layer chromatography (TLC, Merck silica gel 60F-254 plates). The plates were visualized by UV illumination. Column chromatography was performed using silica gel (60-120 mesh). The solvent compositions reported for all chromatographic separations are on a volume/volume (v/v) basis. All glassware's were dried oven before use in connection with an inert atmosphere. Solvents were evaporated under reduced pressure. Tetramethylsilane (0.0 ppm) was used as an internal standard in ^{1}H NMR and $CDCl_3$ (77.0 ppm) was used in ^{13}C NMR. The abbreviations used to indicate the peak multiplicity were; s, singlet; bs, broad singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; Hz, Hertz. FAB MS was recorded on Jeol (Japan)/SX-102. Infrared spectrum was taken with ATR on Shimadzu IR-affinity-1s. Melting points were determined on a Buchi 565 digital melting point apparatus and were uncorrected..

Experimental procedure:

Synthesis of Polysac-Cu-NP

For the preparation of Plysac-Cu-NP cellulose and starch used as such but chitosan grind to very fine powder in mortar and pastel prior to use. The polysaccharide (1gm) were suspended in de-ionised water and sonicated at 40 kHz for 20 min. To polysaccharide suspension copper sulphate (250 mg) was added. The reaction mixture was stirred for 15 min under nitrogen atmosphere at room temperature and then cooled to $0^{o}C$ by ice bath. The polysaccharide cupper suspension carefully reduced by sodium borohydride (100 mg) in small portion with short interwal of time. The black reaction mixture was again stirred for 1 hr till the temperature reached to rt. The black suspension again sonicated for about 15 min before filtration. The solid black mass washed with de-ionised water, vacuumed dried and stored under nitrogen atmosphere.

ED-XRF report of chit-cu-NP synthesized

12/9/2015 4:09:00 PM
AIRF-JNU
Auto Quantify -

Sample Id.: CEPS-01
Date / Time: 12/9/2015 4:00:33 PM
Type: Routine - 1/1
Initial weight (g): 1.16
Total weight (g): 1.27

Compound	Corr. (cps/mA)	Conc.	Unit	Result Status
C		90.472	%	
Al2O3	0.371	0.115	%	Calibrated
SiO2	2.555	0.438	%	Calibrated
S	0.596	251.065	ppm	Calibrated
Cl	3.797	592.215	ppm	Calibrated
K2O	7.244	312.649	ppm	Calibrated
CaO	12.834	410.358	ppm	Calibrated
TiO2	1.883	77.566	ppm	Calibrated
Fe2O3	34.126	258.232	ppm	Calibrated
Cu	18181.180	8.682	%	Calibrated
ZnO	69.927	281.003	ppm	Calibrated
Yb	10.298	690.471	ppm	Calibrated
W	6.242	60.409	ppm	Calibrated
Sum		100.000	%	

ED-XRF report of chit-cu-NP after fifth cycle

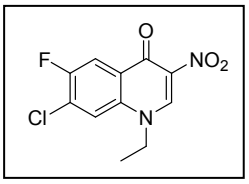
12/9/2015 3:50:00 PM
AIRF-JNU
Auto Quantify -

Sample Id.: CEPS-02
Date / Time: 12/9/2015 3:33:51 PM
Type: Routine - 1/1
Initial weight (g): 1.56
Total weight (g): 1.78

Compound	Corr. (cps/mA)	Conc.	Unit	Result Status
CH2		92.057	%	
Al2O3	0.389	1971.364	ppm	Calibrated
SiO2	2.335	0.667	%	Calibrated
S	0.632	230.896	ppm	Calibrated
Cl	3.710	501.802	ppm	Calibrated
K2O	7.121	266.161	ppm	Calibrated
CaO	12.400	343.187	ppm	Calibrated
TiO2	1.362	48.612	ppm	Calibrated
Fe2O3	32.772	214.970	ppm	Calibrated
Cu	17819.500	6.865	%	Calibrated
ZnO	91.815	329.780	ppm	Calibrated
Rb	0.000	0.000	ppm	Calibrated
W	24.219	208.989	ppm	Calibrated
Sum		100.000	%	

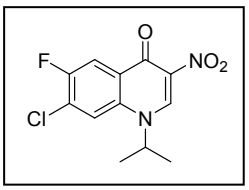
Typical experimental procedure for the synthesis of 3-nitro-4-quinolone: In a typical experiment, the quinolone acid (**7**) (1 mmol)[1], Chit-Cu-NP (37 mg, 5 mol %) and nitronium tetrafluoroborate (1.2 mmol) were taken in 50 ml round-bottom flask containing DMF (10 mL) and the reaction mixture was refluxed, till the completion of the reaction (monitored by TLC). After completion the reaction mixture was vacuum and extracted with ethyl acetate (25 ml x3) after addition of de-ionised water (50 ml), the collected EtOAc dried over sodium sulphate and evaporated under vacuum to give crude product (**7**). Crude was purified by silica gel (60-120 mesh) column chromatography to afford the corresponding product.

7-chloro-1-ethyl-6-fluoro-3-nitroquinolin-4(1H)-one (7a)



Yield: 92 %; pale yellow solid; mp 270-272^{o}C (uncorrected). IR (ν_{max}, ATR, cm-1): 3444, 3278, 1660, 1434, 1309, 1249, 839, 456, 180. ^{1}H NMR (300 MHz,) δ 9.71 (s, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 5.9 Hz, 1H), 4.50 (q, *J* = 6.9 Hz, 2H), 1.56 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSOd_6) δ 162.94 (d, *J* = 6.5 Hz), 157.95 (s), 152.75 (s), 146.18 (s), 135.61 (d, *J* = 8.5 Hz), 131.89 (s), 126.12 (*m*), 117.85 (d, *J* = 11 Hz), 113.22, 112.82, 48.66 (s), 13.64 (s). ES-MS (M+H): 271.0 m/z.

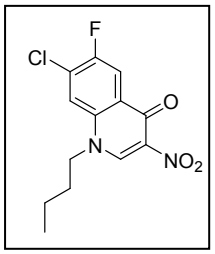
7-chloro-6-fluoro-1-isopropyl-3-nitroquinolin-4(1H)-one (7b)



Yield 85%; pale yellow solid; mp 263-256^{o}C (uncorrected). IR (ν_{max}, ATR, cm^{-1}): 3432, 3258, 1655, 1480, 1320, 1232, 842, 460; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H), 8.11 (m, 1H), 7.70 (dd, *J* = 3.4, 2.5 Hz, 1H), 4.74 (m, 1H), 1.56 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSOd_6) δ 162.88 (d, *J* = 8.7 Hz), 157.98 (s), 152.78 (s), 147.24 (s), 137.47 (d, *J* = 8.5 Hz), 132.12(s), 127.80 (d, *J* = 10 Hz), 126.19, 125.82, 118.89 (d, *J* = 13 Hz), 113.08, 112.69, 54.41 (s), 19.83 (s). ES-MS (M+H): 285.0 m/z.

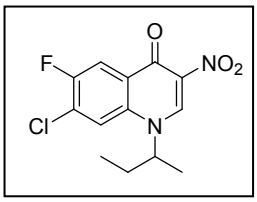
1-butyl-7-chloro-6-fluoro-3-nitroquinolin-4(1H)-one (7c)

1. Note: All the precursors were synthesized according to the published literature. (Koga, H.; Itoh A.; Murayama, S.; Suzue S. and Irikura T., *J. Med. Chem.*; 1980, **23**, 1358)
2. Raghavan, K.; Lang, S. A. and Marshall M. S., *J. Heterocycl. Chem*, 1986, **23**, 1801.



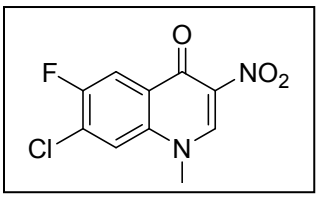
Yield: 82%; pale yellow solid; mp 275-278°C (uncorrected). IR (ν_{max}, ATR, cm^{-1}): 3465, 3262, 1652, 1474, 1322, 1232, 1211, 851. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.13 (m, 1H), 7.79 (d, *J* = 5.7 Hz, 1H), 4.10 (t, *J* = 7.6 Hz, 2H), 1.81 (m, 2H), 1.59 (m, 2H), 1.10 (dd, *J* = 8.8, 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO*d*$_6$) δ 162.83 (d, *J* = 6.5 Hz), 157.90 (s), 152.70 (s), 145.21 (s), 135.4 (d, *J* = 6.5 Hz), 131.70 (s), 126.37, 125.9943, 124.60 (d, *J* = 11 Hz), 116.31 (d, *J* = 11 Hz), 113.26, 112.88, 48.21 (s), 29.21 (s), 18.99 (s), 13.28 (s). Anal. calcd for $C_{13}H_{12}ClFN_2O_3$: C, 52.27; H, 4.05; N, 9.38; Found C, 52.21; H, 4.12; N, 9.21. ES-MS (M+H): 299.1 m/z.

1-(sec-butyl)-7-chloro-6-fluoro-3-nitroquinolin-4(1H)-one (7d)



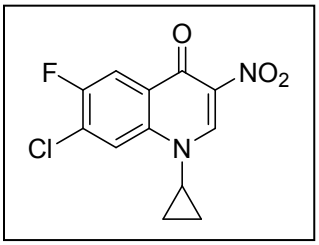
Yield 85%; pale yellow solid; mp 265-270°C (uncorrected). IR (ν_{max}, ATR, cm^{-1}): 3421, 3269, 1644, 1452, 1325, 1238, 867, 380, 190. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 8.11 (m, 1H), 7.75 (d, *J* = 5.6 Hz, 1H), 4.78 (m, 1H), 1.48 (m, 2H), 1.17 (d, *J* = 6.1 Hz, 3H), 0.92 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO*d*$_6$) δ 162.88 (d, *J* = 9 Hz), 157.63 (s), 152.43 (s), 145.59 (s), 137.97 (d, *J* = 9 Hz), 132.26 (s), 127.44 (d, *J* = 12 Hz), 126.25 (s), 125.88 (s), 118.92 (d, *J* = 11 Hz), 113.14 (s), 112.75 (s), 50.46 (s), 26.77 (s), 19.91 (s), 8.00 (s). Elemental Analysis calculated for $C_{13}H_{12}ClFN_2O_3$: C, 52.27; H, 4.05; N, 9.38; Found C, 52.11; H, 4.10; N, 9.29. ES-MS (M+H): 299.1 m/z.

7-chloro-6-fluoro-1-methyl-3-nitroquinolin-4(1H)-one (7e)



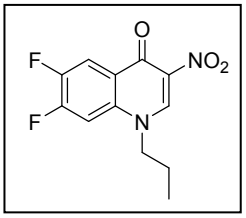
Yield 79%; yellow solid; m.p. 198-200°C, IR (νmax, ATR, cm-1): 3412, 1610, 1511, 1302, 1121, 1062, 541; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.67 (d *J*=0.5 Hz, 1H), 8.15 (m,1H), 7.87 (d *J*=5.5 Hz, 1H), 3.5 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO *d6*): δ 168.34 (d, *J* = 2.53 Hz), 156.97 , 153.89, 151.37, 141.28 (d, *J* = 3 Hz), 127.48 (t, *J* = 20 Hz), 121.99 (d, *J* = 8.34 Hz), 115.0 (t, *J* = 7.64 Hz), 110.61 (d, *J* = 19.88 Hz), 38.23 ; ES-MS (M+H): 257.04 m/z.

7-chloro-1-cyclopropyl-6-fluoro-3-nitroquinolin-4(1H)-one (7f)



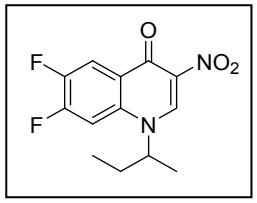
Yield 76%; yellow solid; m.p. 210-212°C. IR (νmax, ATR, cm-1): 3310, 1643, 1555, 1363, 1122, 1069, 581; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.69 (s, 1H), 8.14 (d *J*= 7.95 Hz, 1H), 7.73 (d J= 5.64 Hz, 1H), 3.75 (m, 1H), 1.04 (d *J*=4.83 Hz, 2H), 0.84 (d *J*= 2.43 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO *d6*): δ 13C NMR (100 MHz, Common NMR Solvents) δ 168.35 (d, *J* = 2.93 Hz), 158.32, 158.67 ,157.99, 155.47, 140.22 (d, J = 2.84 Hz), 127.97 (d, *J* = 19.76 Hz), 120.20 (d, *J* = 8.34 Hz), 119.34, 114.05 (d, *J* = 7.66 Hz, H), 113.01 (d, *J* = 1.73 Hz), 113.0, 40.13, 10.78 ; ES-MS (M+H): 283.12 m/z.

6,7-difluoro-3-nitro-1-propylquinolin-4(1H)-one (7g)



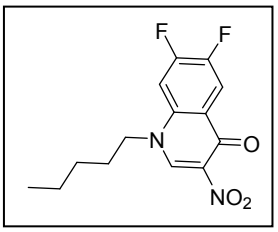
Yield 86% pale yellow solid; mp 262-263°C (uncorrected). IR (ν_{max}, ATR, cm^{-1}): 3286, 3050, 1644, 1534, 1454, 1311, 1211, 831. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (m, 1H), 8.30 (t, *J* = 9.5 Hz, 1H), 7.42 (dd, *J* = 11.0, 6.5 Hz, 1H), 3.59 (t, *J* = 7.4 Hz, 2H), 1.55 (m, 2H), 1.04 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSOd_6) δ 161.32 (d, *J* = 9 Hz), 155.71 (s), 154.93(s), 150.49 (d, *J* = 1.2 Hz), 150.11 (d, *J* = 2 Hz), 149.73 (s), 145.28 (s), 144.90 (m), 136.04 (m), 132.00 (s), 123.84 (m), 112.90 (d, *J* = 11 Hz), 112.52 (d, *J* = 11.5 Hz) 114.20 (d, *J* = 13 Hz) 104.01 (d, *J* = 13 Hz), 50.83 (s), 21.73 (s), 9.96 (s). ES-MS (M+H): 269.8 m/z.

1-(sec-butyl)-6,7-difluoro-3-nitroquinolin-4(1H)-one (7h)



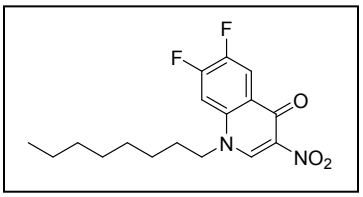
Yield 88 %; yellow solid; mp 265-266°C (uncorrected). IR (ν_{max}, ATR, cm^{-1}): 3276, 3105, 1631, 1510, 1432, 1331, 1232, 852. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.31 (t, *J* = 9.4 Hz, 1H), 7.43 (m, 1H), 4.79 (m, 1H), 1.49 (m, 2H), 1.17 (d, *J* = 6.0 Hz, 3H), 0.94 (dd, *J* = 9.4, 5.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSOd_6) δ 161.23 (d, *J* = 6.5 Hz), 154.96 (s), 154.57 (s), 150.48 (s), 150.11 (s), 149.74 (s), 147.40 (d, *J* = 0.6 Hz), 145.43 (s), 145.1 (d, *J* = 0.5 Hz), 144.90 (d, *J* = 1 Hz), 136.68 (m), 132.20 (s), 124.36 (m), 122.75 (d, *J* = 11 Hz), 12.37 (d, *J* = 13 Hz), 105.05 (d, *J* = 14 Hz) 104.67 (d, *J* = 11.5 Hz), 50.29 (s), 27.38 (s), 19.73 (s), 8.00 (s). ES-MS (M+H): 283.0 m/z.

6,7-difluoro-3-nitro-1-pentylquinolin-4(1H)-one (7i) Yiled 91%; pale yellow solid; mp 269-271°C (uncorrected). IR (ν_{max}, ATR, cm^{-1}): 3406, 3209, 3109, 1648, 1551, 1469, 1325, 1212, 867. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 1H), 8.31 (t, *J* = 9.5 Hz, 1H), 7.58 (dd, *J* = 11.0, 6.4 Hz, 1H), 4.03 (t, *J* = 7.5 Hz,



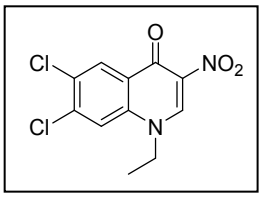
2H), 1.30 (m, 6H), 0.87 (dd, J = 8.5, 4.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSOd_6) δ 161.21 (d, J = 9 Hz), 155.29 (s), 154.91 (s), 150.77 (s), 150.40 (s), 150.08 (s), 149.71 (d, J = 0.75 Hz), 145.58 (s), 145.33 (s), 145.19 (s), 135.35 (m), 131.63 (s), 122.01 (m), 122.85 (d, J = 11 Hz), 122.49 (d, J = 11 Hz), 102.55 (d, J = 11 Hz), 102.16 (d, J = 13 Hz), 48.55 (s), 30.54 (s), 27.94 (s), 21.15 (s), 12.30 (s). ES-MS (M+H): 297.1 m/z.

6,7-difluoro-3-nitro-1-octylquinolin-4(1H)-one (7j)



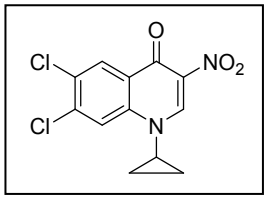
Yield 82% pale yellow solid; mp 276-279°C (uncorrected). IR (ν_{max}, ATR, cm^{-1}): 3434, 3221, 3089, 1659, 1532, 1473, 1362, 1239, 856. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 1H), 8.31 (t, J = 9.5 Hz, 1H), 7.59 (dd, J = 11.0, 6.4 Hz, 1H), 4.04 (dd, J = 11.5, 4.1 Hz, 2H), 1.42 (m, 2H), 1.22 (m, 10H), 0.84 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSOd_6) δ 161.19 (d, J = 9 Hz), 155.26 (s), 154.88 (s), 150.76 (s), 150.39 (s), 150.07 (s), 149.68 (s), 145.95 (s), 145.56 (s), 145.18 (s), 135.36 (m), 131.62 (s), 122.02 (m), 112.85 (d, J = 13 Hz), 112.48 (d, J = 13 Hz), 102.52 (d, J = 11 Hz), 102.14 (d, J = 11 Hz), 49.77 (s), 30.40 (s), 28.68 (s), 28.59 (s), 27.71 (s), 26.67 (s), 21.91 (s), 13.37 (s); ES-MS (M+H): 339.1 m/z.

6,7-dichloro-1-ethyl-3-nitroquinolin-4(1H)-one (7k)



Yield 79%; pale yellow solid; mp 266-267°C (uncorrected). IR (ν_{max}, ATR, cm^{-1}): 3421, 3211, 3090, 1651, 1512, 1485, 1352, 1231, 856, 660; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.49 (s, 1H), 7.97 (s, 1H), 4.53 (q, J = 6.7 Hz, 2H), 1.56 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSOd_6) δ 163.41, 146.26, 136.80, 136.45, 132.07, 129.76, 128.04, 126.82, 117.46, 48.05, 13. 65. ES-MS (M+H): 286.9 m/z.

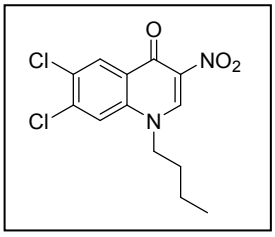
6,7-dichloro-1-cyclopropyl-3-nitroquinolin-4(1H)-one (7l)



Yield 75% pale yellow solid; mp 271-271°C (uncorrected). IR (ν_{max}, ATR, cm^{-1}): 3440, 3321, 3101, 1644, 1521, 1467, 1331, 1242, 866, 649. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.47 (s, 1H), 7.89 (s, 1H), 3.67 (dd, J =

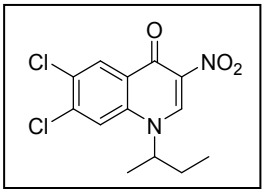
2.9, 1.9 Hz, 1H), 1.02 (m, 2H), 0.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSOd_6) δ 163.01, 147.23, 136.17, 135.26, 132.60, 129.79, 127.79, 127.75, 118.75, 33.42, 10.32. ES-MS (M+H): 298.9 m/z.

1-butyl-6,7-dichloro-3-nitroquinolin-4(1H)-one (7m)



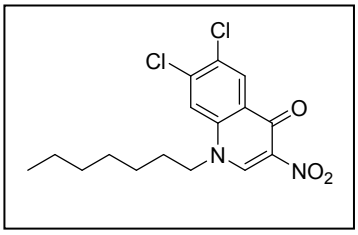
Yield 79%; yellow solid; 268-270°C (uncorrected). IR (ν_{max}, ATR, cm^{-1}): 3412, 3287, 3089, 1639, 1532, 1471, 1328, 1220, 869, 598. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.49 (s, 1H), 7.95 (s, 1H), 4.13 (t, *J* = 7.6 Hz, 2H), 1.81 (m, 2H), 1.60 (m, 2H), 1.09 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSOd_6) δ 163.27, 145.26, 137.15, 136.48, 131.86, 129.70, 128.05, 125.14, 115.71, 47.60, 29.21, 18.96, 13.27. ES-MS (M+H): 315.02 m/z.

1-(sec-butyl)-6,7-dichloro-3-nitroquinolin-4(1H)-one (7n)



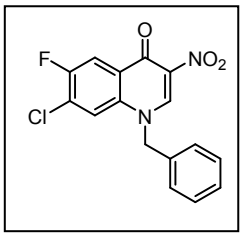
Yield 79%; pale yellow solid; mp 265-266°C (uncorrected). IR (ν_{max}, ATR, cm^{-1}): 3367, 3298, 3083, 1661, 1541, 1469, 1373, 1249, 841, 582, 421. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.45 (s, 1H), 7.97 (s, 1H), 4.79 (m, 1H), 1.49 (m, 2H), 1.16 (d, *J* = 6.1 Hz, 3H), 0.91 (dd, *J* = 9.6, 5.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSOd_6) δ 163.30, 145.65, 137.82, 136.37, 132.45, 129.43, 128.00, 127.96, 118.37, 49.83, 26.76, 19.90, 8.01; ES-MS (M+H): 315.02 m/z.

6,7-dichloro-1-heptyl-3-nitroquinolin-4(1*H*)-one (7o)



Yield 89%; pale yellow solid; mp 280-282°C (uncorrected). IR (ν_{max}, ATR, cm^{-1}): 3421, 3321, 3211, 3108, 1659, 1488, 1392, 1241, 860, 637, 487. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (m, 1H), 8.48 (s, 1H), 7.95 (s, 1H), 4.10 (td, *J* = 7.5, 0.6 Hz, 2H), 1.45 (m, 4H), 1.21 (m, 6H), 0.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSOd_6) δ 163.25, 146.18, 137.11, 136.47, 131.86, 129.69, 128.05, 125.13, 115.70, 48.26, 30.99, 27.78, 27.32, 26.65, 21.98, 13.37. ES-MS (M+H): 357.07 m/z.

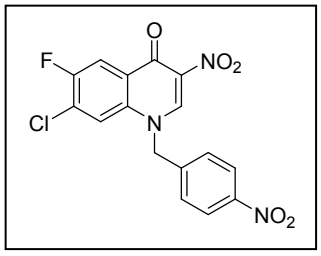
1-benzyl-7-chloro-6-fluoro-3-nitroquinolin-4(1H)-one (10a)



Yield 52%; orange yellow; mp 244-246°C (uncorrected);). IR (νmax, ATR, cm-1): 3461, 3311, 3286, 3124, 1599, 1488, 1342. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (s,1H), 8.15 (d *J*=7.74 Hz, 1H), 7.58-7.43 (m, 1H), 7.41-7.16 (m, 2H),

7.16-6.90 (m, 1H), 5.58 (s, 2H) ^{13}C NMR (100 MHz, $CDCl_3$ + DMSOd_6) δ 168.34 (d, *J* = 2.93 Hz), 155.90, 155.39, 152.86, 138.78 (d, *J* = 3 Hz), 136.46, 127.76 (d, J=27.45 Hz), 127.32 (d, *J* = 16.84 Hz), 120.02 (d, *J* = 8.11 Hz), 116.97 (d, *J* = 7.6 Hz), 112.04, 110.45 (d, *J* = 21.08 Hz), 53.56. ES-MS (M+H): 333.62 m/z.

7-chloro-6-fluoro-3-nitro-1-(4-nitrobenzyl)quinolin-4(1H)-one (10b)

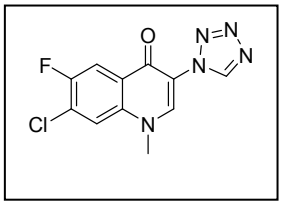


Yield 22%; canary yellow; mp 256-285°c; ^{1}H NMR (300 MHz, CDCl3) δ 9.7 (s, 1H), 8.36-8.03 (m, 3H), 7.71-7.46 (m, 3H), 5.67 (s, 2H); ^{13}C NMR (100 MHz, CDCl3 + DMSOd6) δ 168.35 (d, *J* = 2.93 Hz), 155.91, 155.40, 152.87, 144.87, 144.23, 138.79 (d, *J* = 3 Hz), 127.66 (d, *J* = 6.78 Hz), 127.42, 122.92, 122.88, 120.03 (d, J = 8.11 Hz), 116.98 (d, *J* = 7.61 Hz), 112.05, 110.46 (d, *J* = 19.69 Hz, H), 53.57. ES-MS (M+H): 378.07 m/z.

General method for the preparation of 7-chloro-6-fluoro-1-methyl-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one

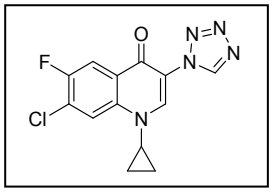
To a pre-cooled solution of 8 (4 mmol) in conc. HCl (25 ml) was added portion wise anhydrous $SnCl_4$ (3.5 equivalent) with vigorous stirring. The resulting mixture was then allowed to rt, and stirring was continued for additional 4 h. Afterward, the reaction mixture was diluted with cold water (25ml), basified with 40 % cold aq. NaOH solution to pH ~ 12-14. The precipitated solid product was collected by suction filtration, washed with cold water, dried and recrystallized from ethanol to give 3-amine derivative, which was further purified by column chromatography using eluent 5% $CH_3OH/CHCl_3$. 10 mmole of 3-amine derivative was dissolved in 25 ml of glacial acetic acid and to that 11mmol of NaN_3 and 12 mmole of triethyl orthoformate were added and the resultant reaction mixture was heated to 100-110°C for 7-8 h. The flow of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured into crushed ice (100gm) and the solid was filtered, washed with water and dried under vacuum to yield 12 in good yield.

7-chloro-6-fluoro-1-methyl-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one (14a)



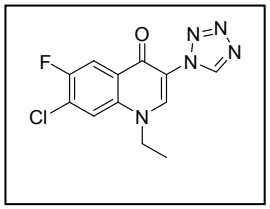
Yield 82%; yellow solid; m.p. 252-253°C, IR (νmax, ATR, cm-1): 3417, 1608, 1534, 1300, 1122, 1012, 563; NMR (300 MHz, $CDCl_3$): δ 4.57 (s,

3H), 8.16 (d *J*=8Hz, 1H), 7.22 (d *J*=6 Hz), 8.19 (d, *J*=8Hz), 9.55 (s, 1H), 9.64 (s, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 43.83, 111.69, 114.38, 114.74, 117.53, 117.65, 125.34, 125.46, 126.9, 127.29, 129.43, 138.01, 140.39, 140.47, 153.51, 158.71, 175.69, 175.77; ES-MS (M+H): 280.04 m/z.



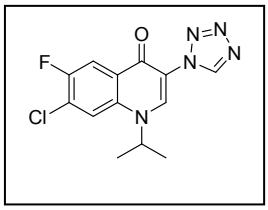
7-chloro-1-cyclopropyl-6-fluoro-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one (14b)

Yield 82%; yellow solid; m.p. 268-270^{o}C, IR (νmax, ATR, cm-1): 3409, 1605, 1532, 1304, 1115, 1043, 564; NMR (300 MHz, $CDCl_3$): δ 1.97–1.88 (m, 4H), 4.10-4.11 (m, 1H), 7.22 (d *J*=6 Hz), 8.20 (d, *J*=8Hz), 9.55 (s, 1H), 9.64 (s, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.43, 35.44, 112.46, 113.96, 114.33, 120.06, 120.18, 126.49, 126.86, 127.54, 127.69, 136.01, 136.09, 137.81, 153.57, 158.74, 175.22, 175.3; ES-MS (M+H): 306.05 m/z.



7-chloro-1-ethyl-6-fluoro-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one (14c)

Yield 82%; yellow solid; m.p. 277-278^{o}C, IR (νmax, ATR, cm-1): 3410, 1605, 1580, 1318, 1122, 1022, 582; NMR (300 MHz, $CDCl_3$): δ 1.42 (t, 3H), 4.48 (d, *J*=6.8 Hz), 7.25 (d, *J*=6 Hz), 8.19 (d, *J*=8Hz), 9.55 (s, 1H), 9.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.7, 49.22, 111.92, 114.24, 114.61, 118.59, 118.69, 126.22, 126.35, 126.77, 127.14, 128.6, 136.63, 136.7, 137.32, 153.53, 158.74, 175.62, 175.7; ES-MS (M+H): 294.8 m/z.

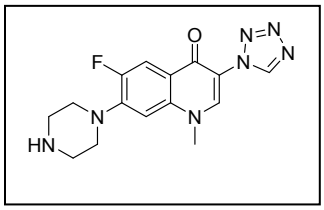


7-chloro-6-fluoro-1-isopropyl-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one (14d)

Yield 82%; yellow solid; m.p. 273-274^{o}C, IR (νmax, ATR, cm-1): 3410, 1608, 1484, 1322, 1119, 1025, 566; NMR (300 MHz, $CDCl_3$): δ 1.55 (6H), 4.93 (s, 1H), 7.25 (d, *J*=6 Hz), 8.19 (d, *J*=8Hz), 9.55 (s, 1H), 9.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.87, 56.12, 112.14, 114.1, 114.48, 119.61, 119.73, 126.62, 127.01, 127.08, 127.2, 127.77, 137.96, 138.13, 138.2, 153.56, 158.76, 175.54, 175.61; ES-MS (M+H): 308.8 m/z.

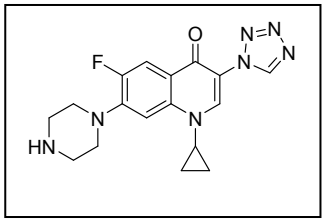
General method for the preparation of 6-fluoro-1-alkyl-7-(piperazin-1-yl)-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one

4 mmol of **8** was taken in a round bottom flask having 20 mm of DMSO in which 6 mmol of piperazine was added and reaction mixture was allowed to stirrer at 120-130^{o}C for about 9-10h. After completion of reaction as evidenced by TLC, DMSO was removed in vacuum and reaction mixture partitioned in between DCM and water. DCM layer was succesveily wased with 0.5 N HCl (20 ml), water (20ml X 3) and finally with brine. The DCM layer on vaccume evaporation yield crude **11** which was further purified by column chromatography using eluent 40% EtOAc/Hexane. After getting **11** same method was applied as used for the synthesis of 12a-d to yield 11a-d in good yield.



6-fluoro-1-methyl-7-(piperazin-1-yl)-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one (13a)

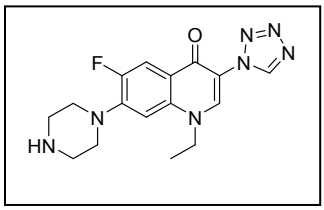
Yield 82%; light brown solid; m.p. 326-3227^{o}C, IR (νmax, ATR, cm-1): 3412, 1603, 1484, 1322, 1122, 1023, 756, 583; NMR (300 MHz, $CDCl_3$+DMSO-d6): δ 3.14 (m, 4H), 3.50 (m, 4H), 4.02 (bs, NH), 4.52 (s, 3H), 6.60 (d, J=6.73 Hz, 1H), 7.83 (d, J=12.6 Hz, 1H), 9.50 (s, 1H), 9.59 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d6): δ 43.99, 45.1, 49.9, 49.99, 102.85, 102.98, 107.47, 112.48, 112.87, 121.33, 121.46, 129.36, 138.02, 141, 141.08, 144.59, 144.96, 150.06, 155.25, 175.06, 175.14; ES-MS (M+H): 330.2 m/z.



1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one (13b)

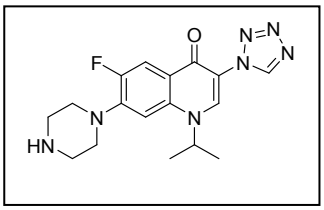
Yield 82%; light brown solid; m.p. 333-334^{o}C, IR (νmax, ATR, cm-1): 3414, 1599, 1481, 1319, 1119, 1033, 777, 576; NMR (300 MHz, $CDCl_3$+DMSO-d6): δ 0.98 (m, 2H), 1.13 (m, 2H), 3.10 (m, 4H), 3.44 (m, 4H), 4.05 (bs, NH), 7.57 (s, 1H), 7.84 (d, J=6.5 Hz), 9.51 (s, 1H), 9.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d6): δ 6.78, 33.55, 45.1, 49.9, 49.98, 106.56, 106.68, 108.24, 112.06, 112.44, 122.68, 122.81, 127.64, 137.82, 138.76, 138.83, 143.18, 143.56, 150.1, 155.28, 174.6, 174.68; ES-MS (M+H): 356.3 m/z.

1-ethyl-6-fluoro-7-(piperazin-1-yl)-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one (13c)

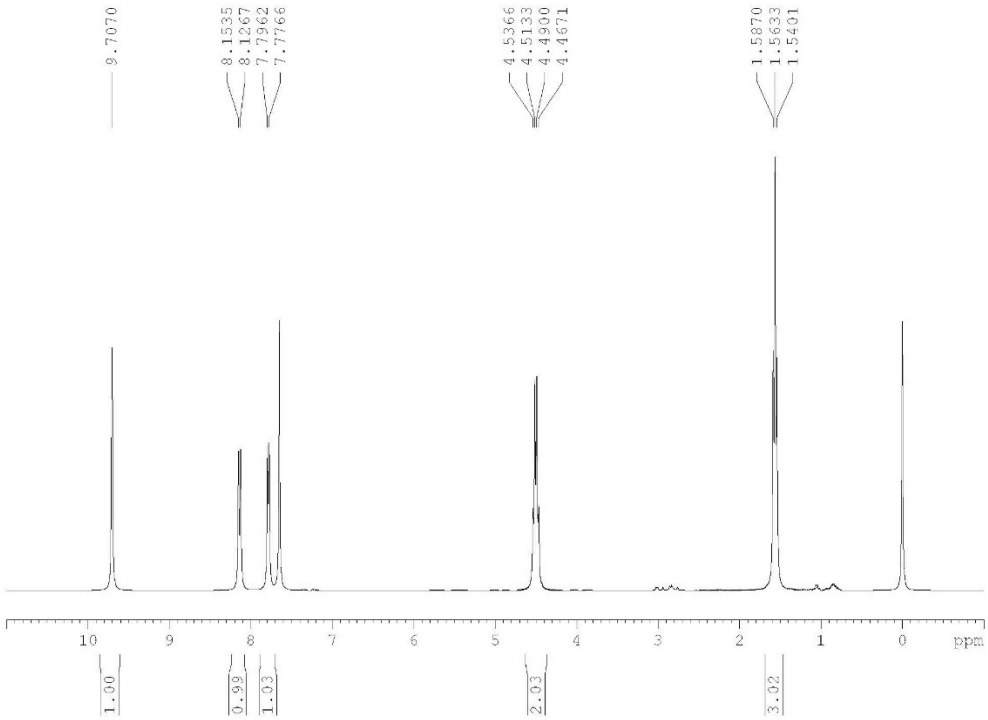


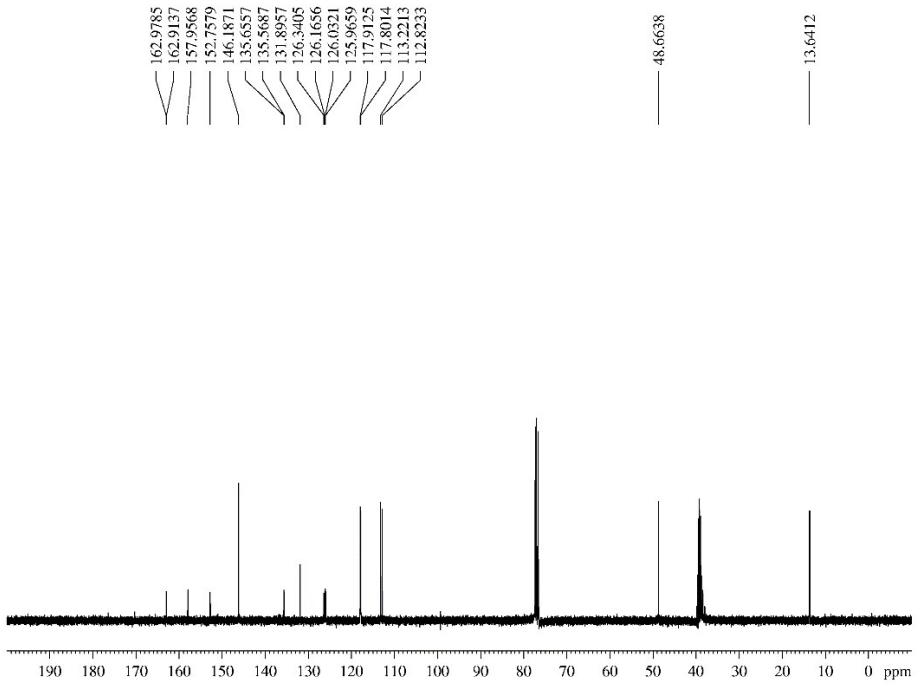
Yield 82%; light brown solid; m.p. 356°C, IR (νmax, ATR, cm-1): 3408, 1402, 1321, 1131, 1028, 802, 566; NMR (300 MHz, $CDCl_3$+DMSO-d6): δ 1.44 (t, 2H), 3.15 (m, 4H), 3.51 (m, 4H), 4.08 (bs, NH), 4.50 (dd, 2H), 7.02 (d, J=6Hz, 1H), 7.88 (d, J=12.5Hz, 1H), 9.56 (s, 1H), 9.67 (s,1H); ^{13}C NMR (75 MHz, CDCl3+DMSO-d6): δ 10.93, 45.1, 48.79, 49.9, 49.97, 104.18, 104.28, 107.7, 112.34, 112.74, 121.79, 121.91, 128.52, 137.32, 138.73, 138.8, 144.97, 145.36, 150.08, 155.27, 174.99, 175.06; ES-MS (M+H): 344.3 m/z.

6-fluoro-1-isopropyl-7-(piperazin-1-yl)-3-(1H-tetrazol-1-yl)quinolin-4(1H)-one (13d)

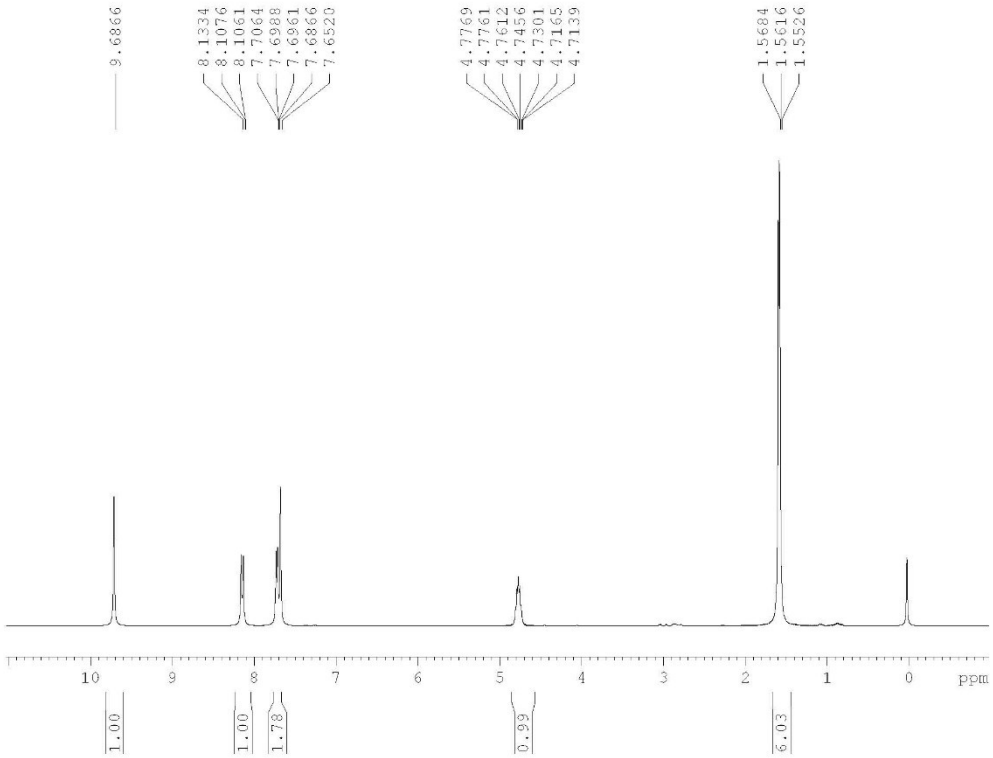


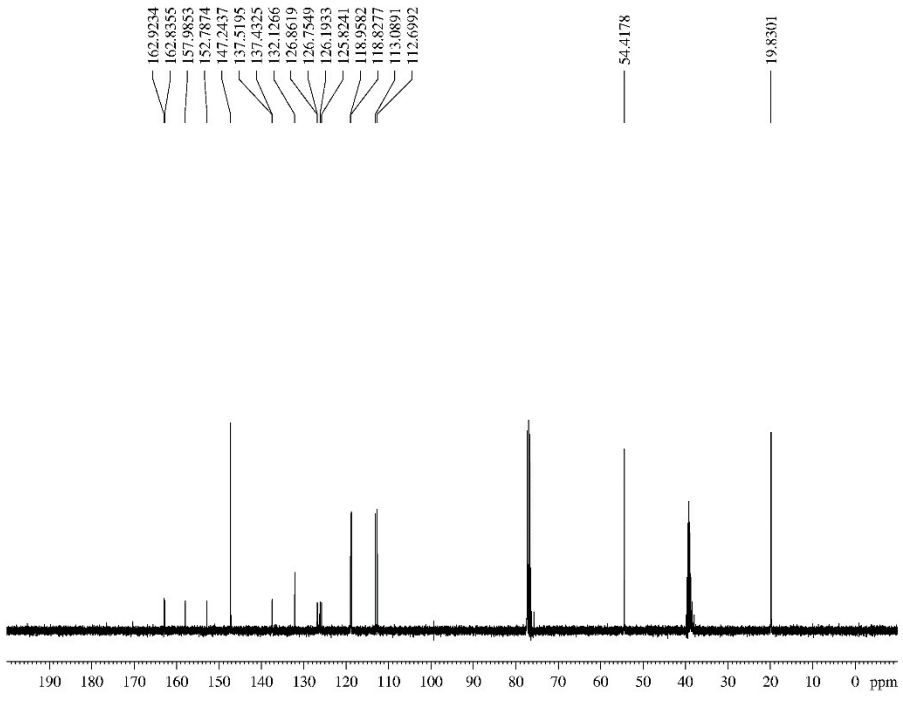
Yield 82%; light brown solid; m.p. 348-349°C, IR (νmax, ATR, cm-1): 3422, 1610, 1490, 1304, 1132, 1042, 768, 595; NMR (300 MHz, $CDCl_3$): δ 1.47 (m, 6H), 3.05 (m, 4H), 3.43 (m, 4H), 3.98 (bs, NH(, 4.85 (m, 1H), 7.52 (s, 1H), 7.76 (m, 1H), 9.46 (s, 1H), 9.55 (s, 1H); ^{13}C NMR (75 MHz, CDCl3+DMSO-d6): δ 17.1, 45.11, 49.89, 49.98, 55.88, 106.11, 106.23, 107.92, 112.22, 112.6, 122.22, 122.34, 127.71, 137.98, 141.69, 141.76, 143.33, 143.71, 150.1, 155.3, 174.91, 175; ES-MS (M+H): 358.2.2 m/z.



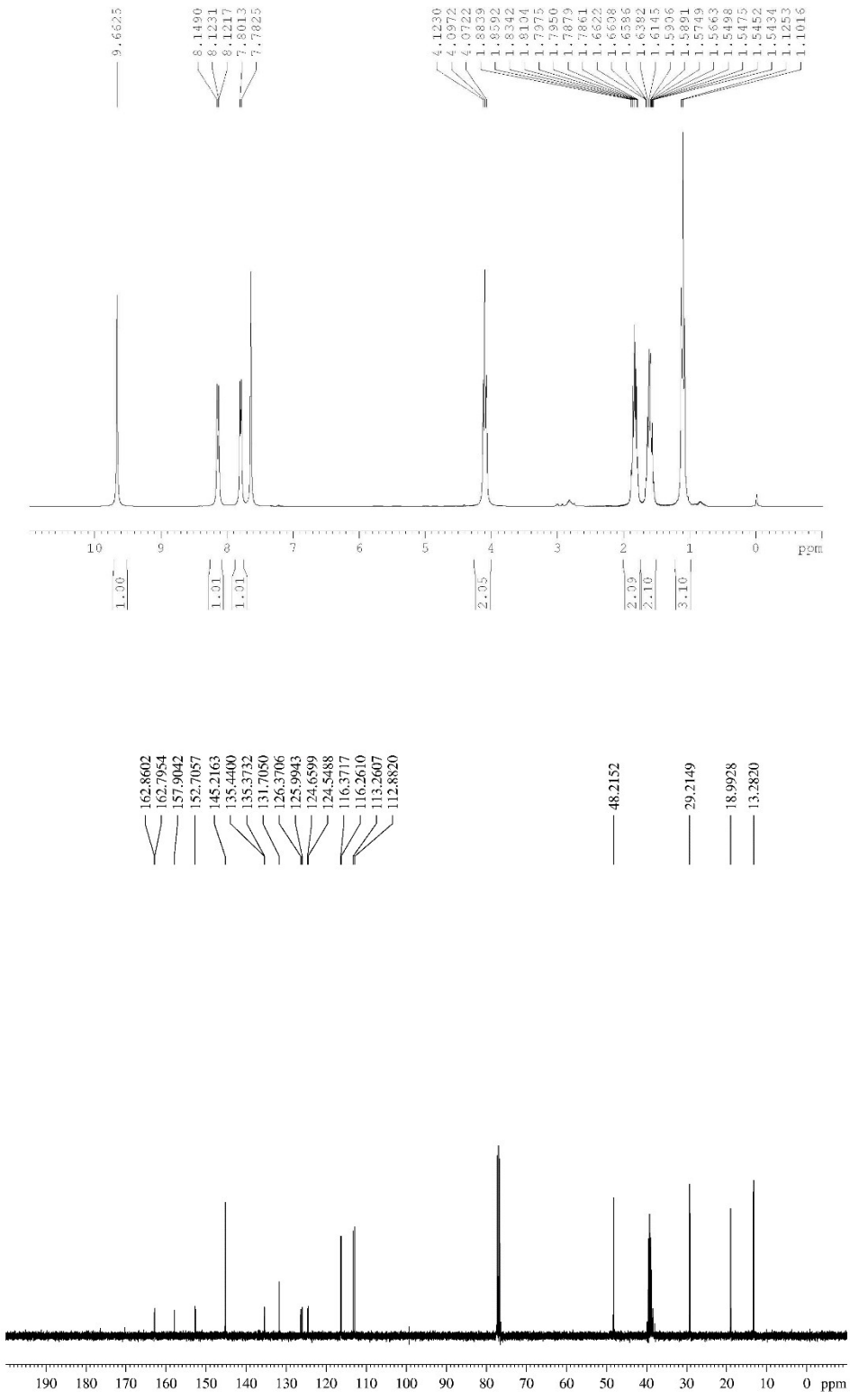


^{1}H and **^{13}C** NMR Spectra of compound **7a**

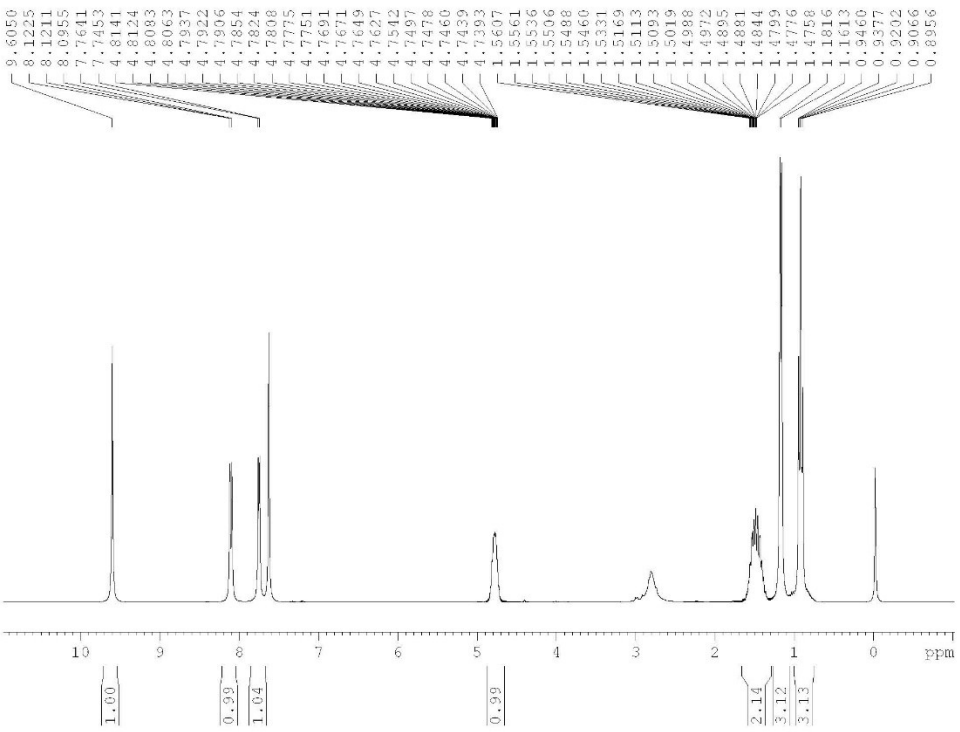


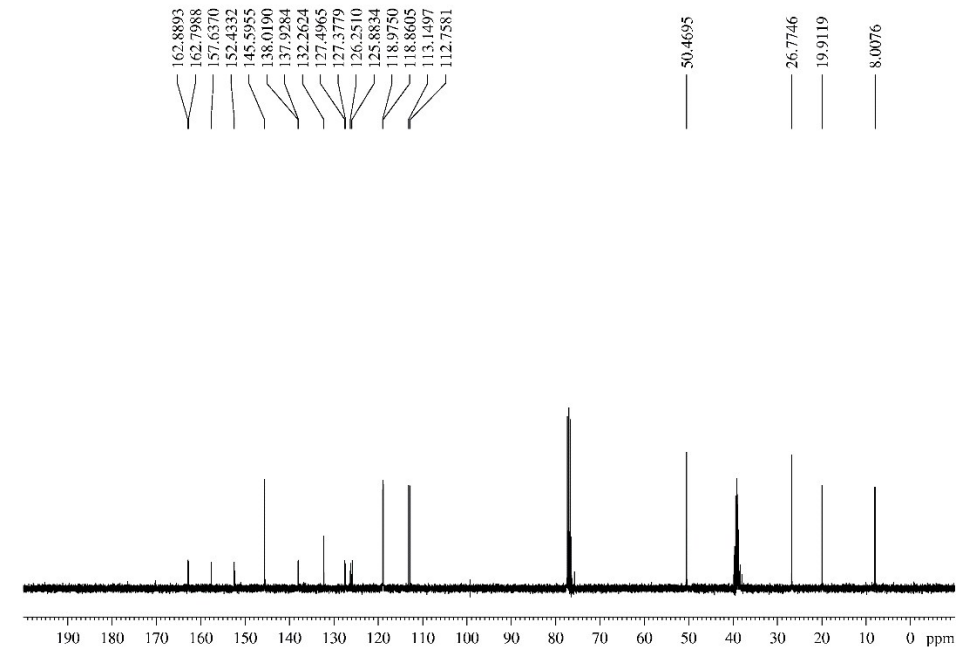


[1]H and **[13]C** NMR Spectra of compound **7b**

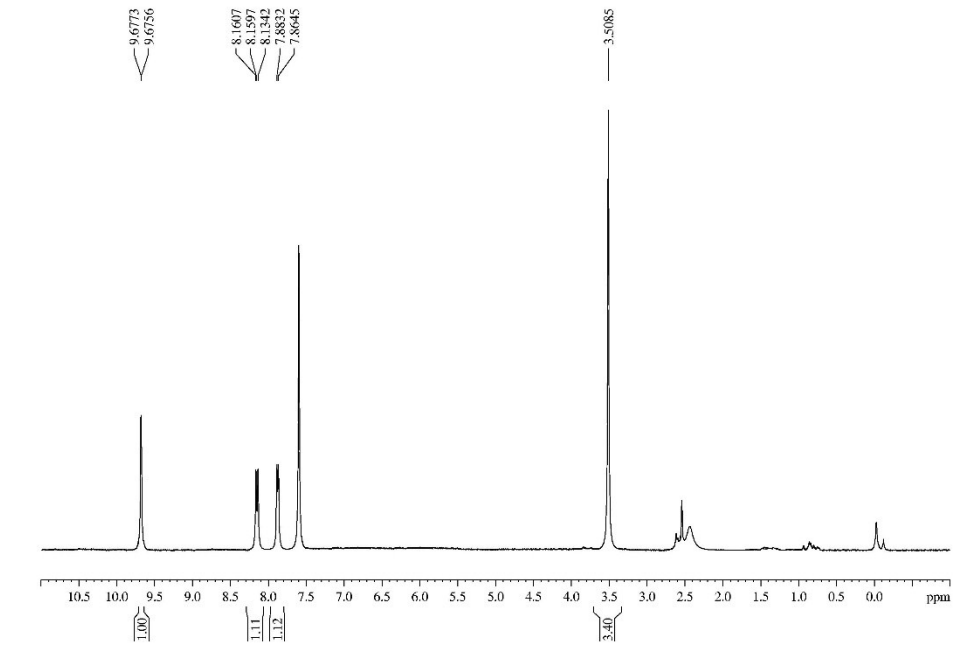


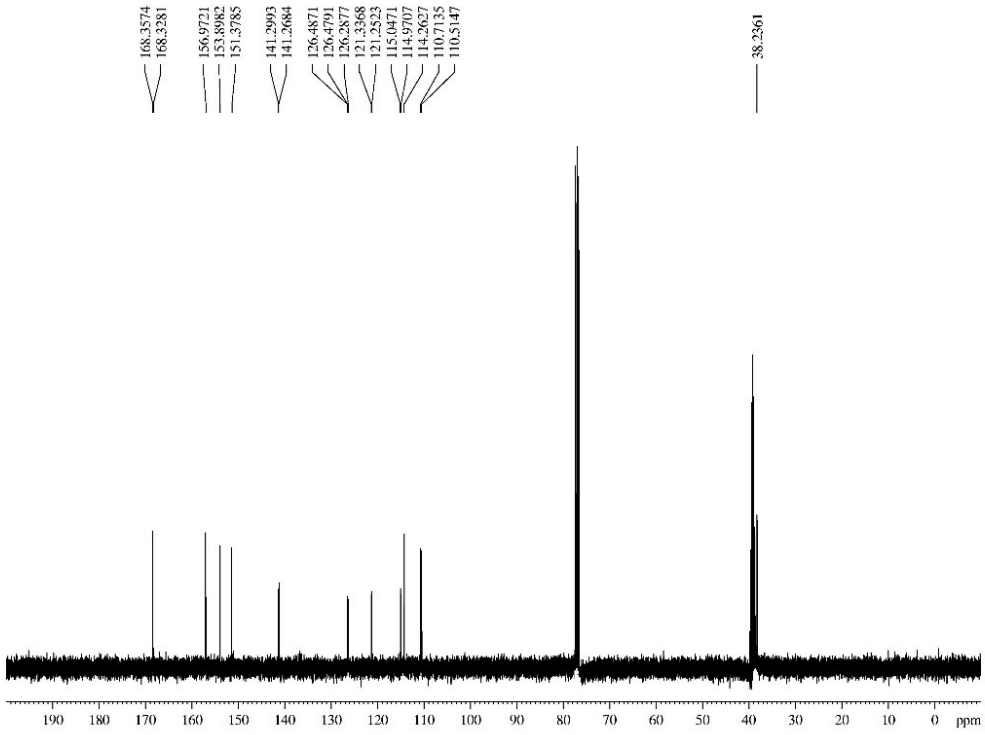
^{1}H and **^{13}C** NMR Spectra of compound **7c**



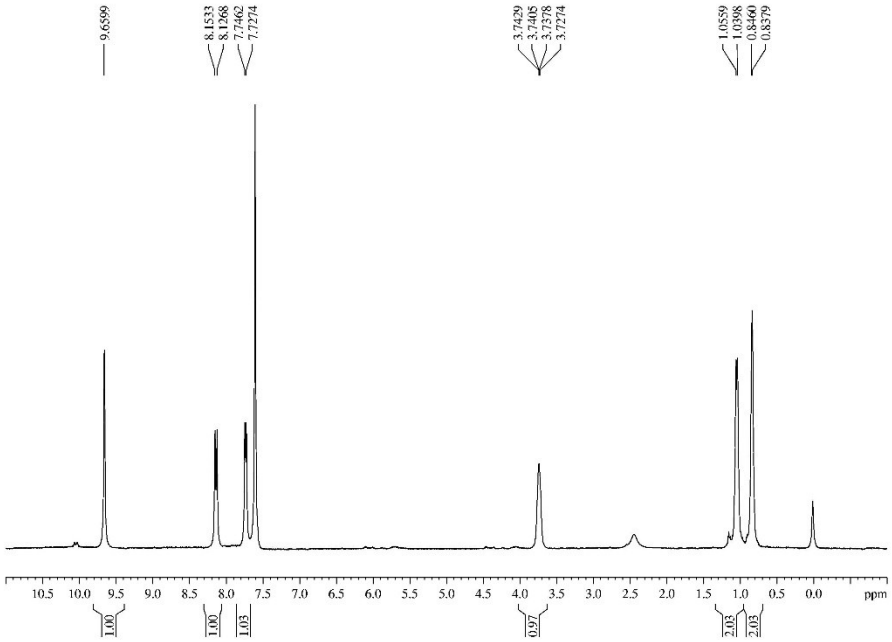


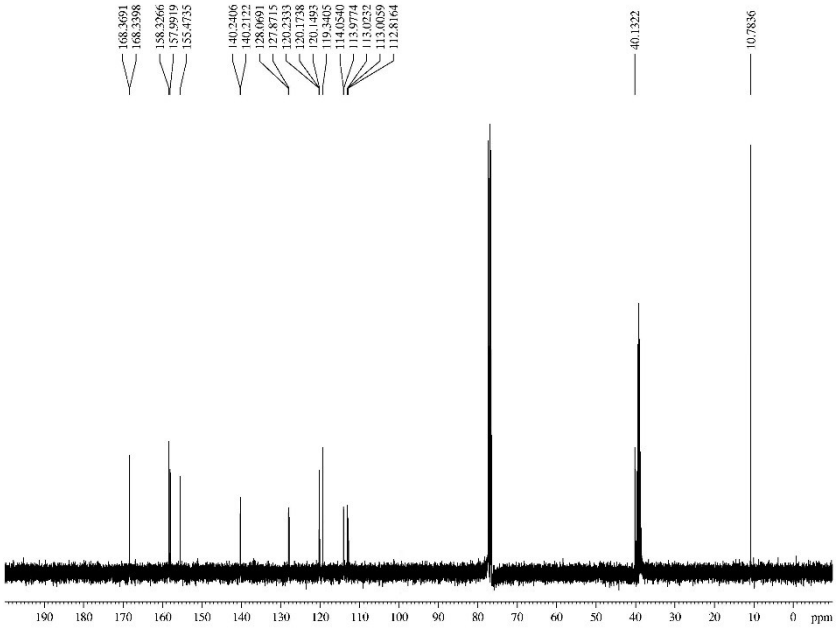
[1]H and **[13]C** NMR Spectra of compound **7d**



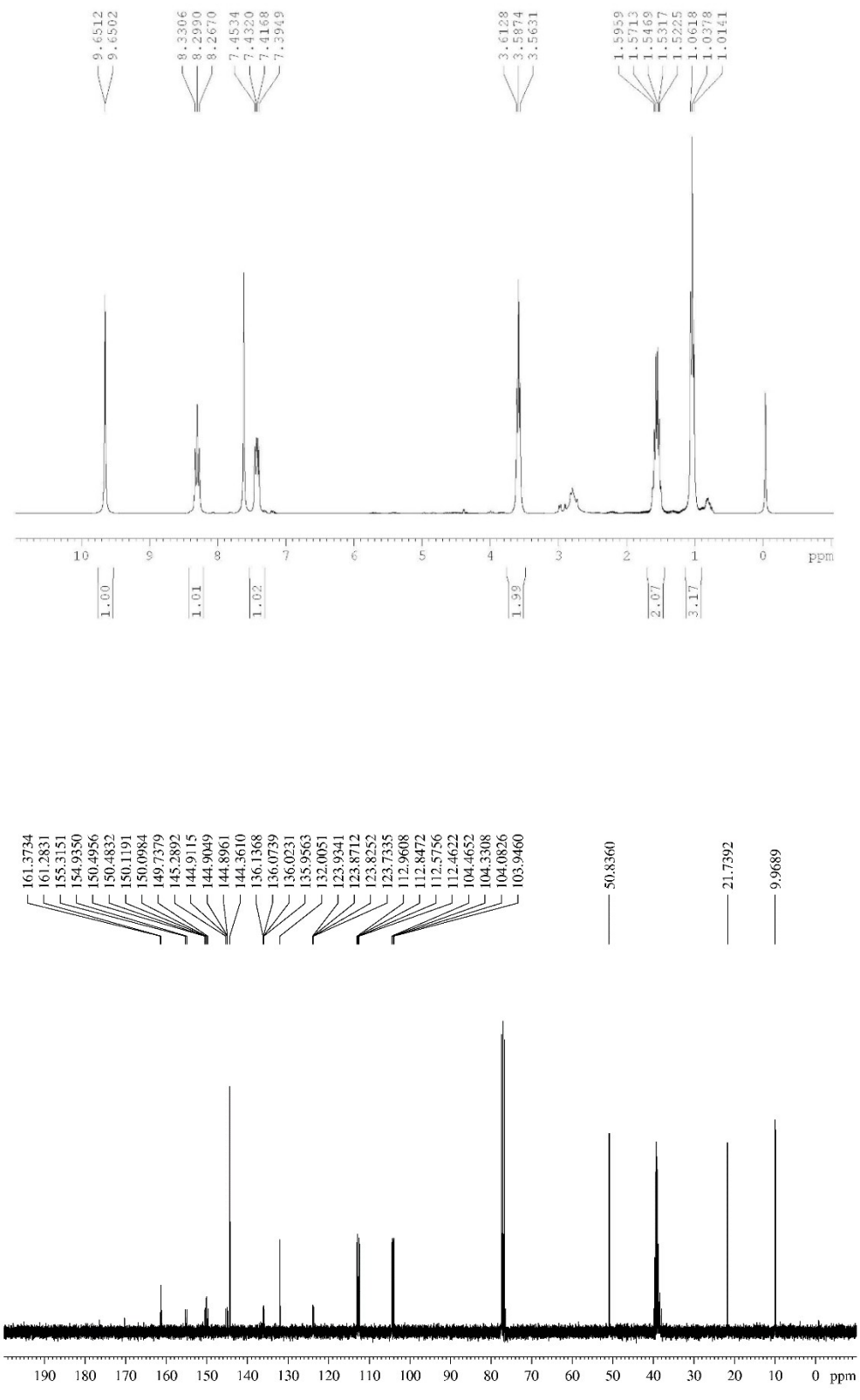


^{1}H and **^{13}C** NMR Spectra of compound **7e**

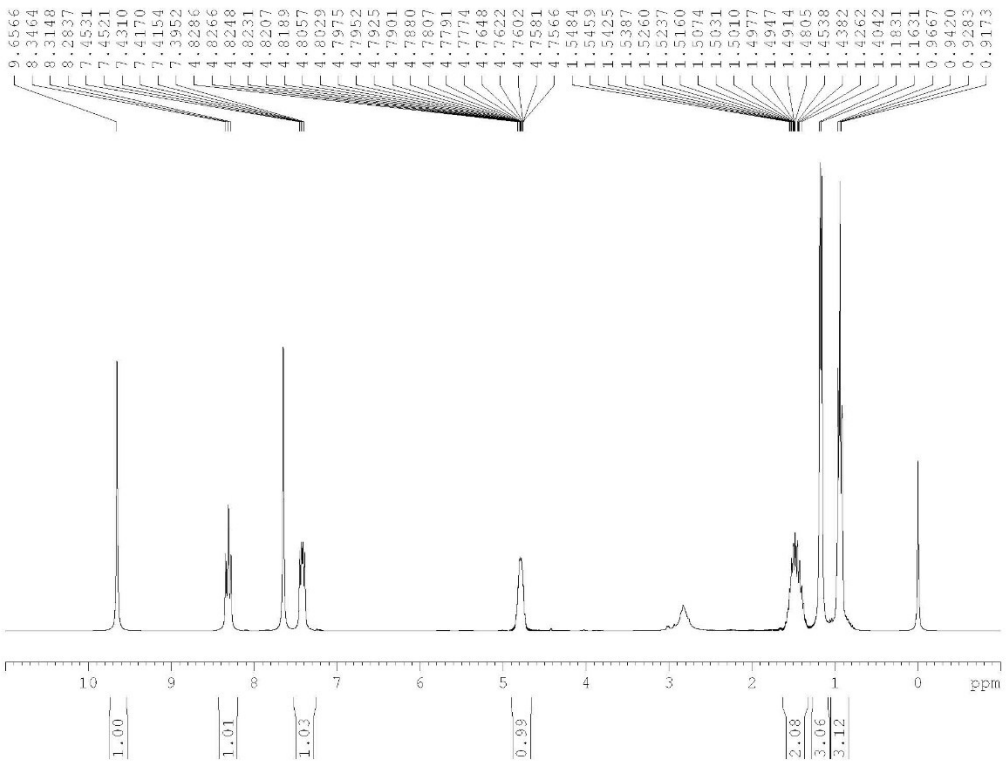


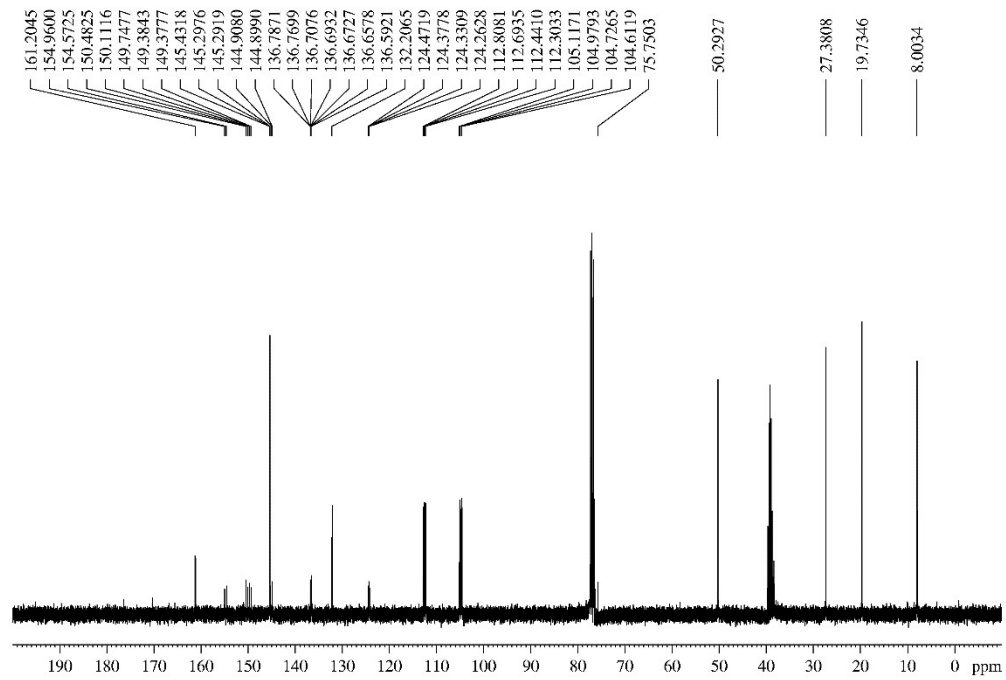


^{1}H and **^{13}C** NMR Spectra of compound **7f**

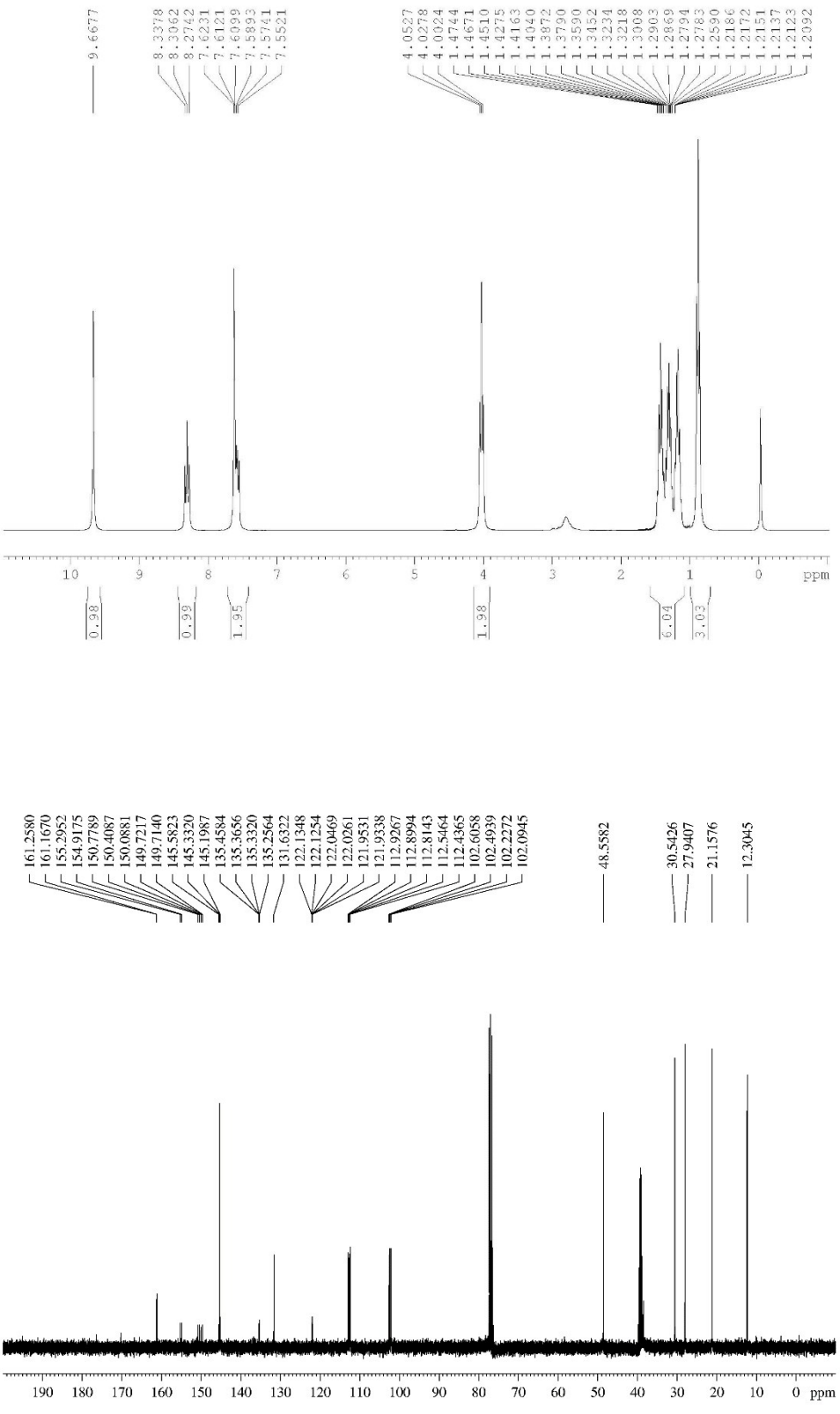


^{1}H and **^{13}C** NMR Spectra of compound **7g**

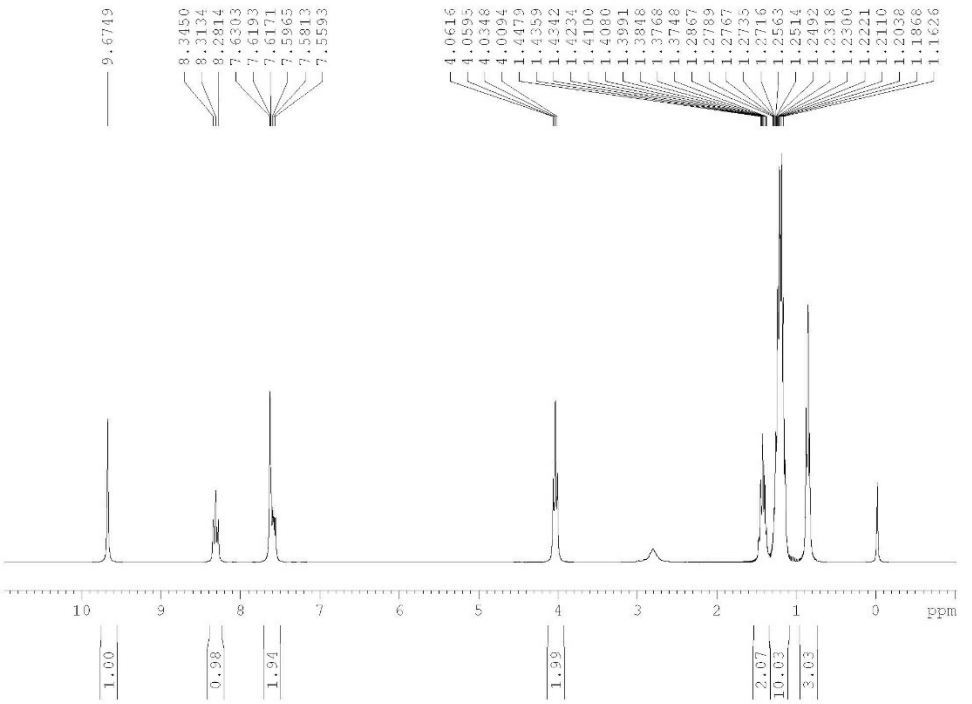


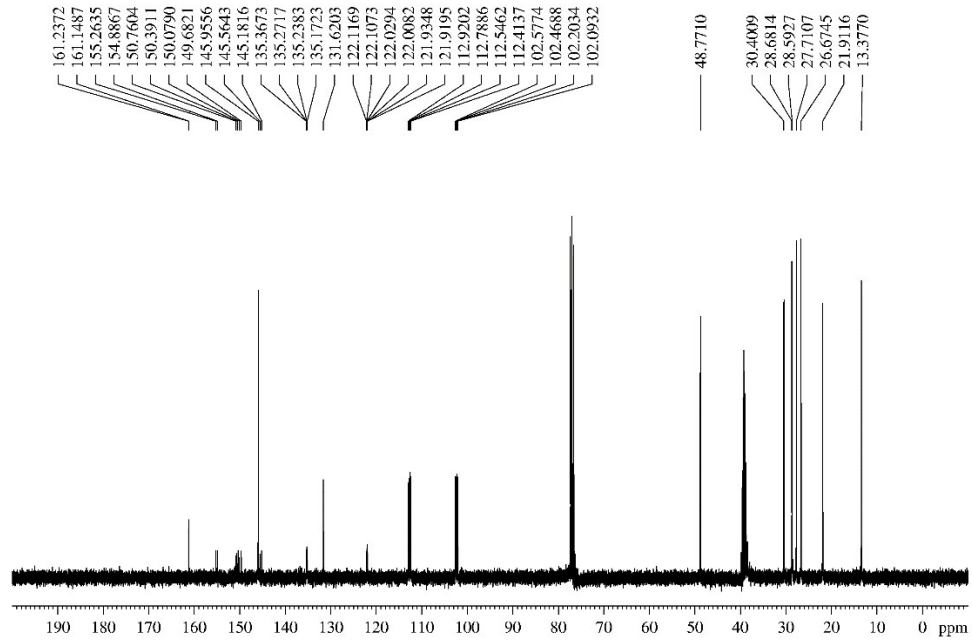


[1]H and **[13]C** NMR Spectra of compound **7h**

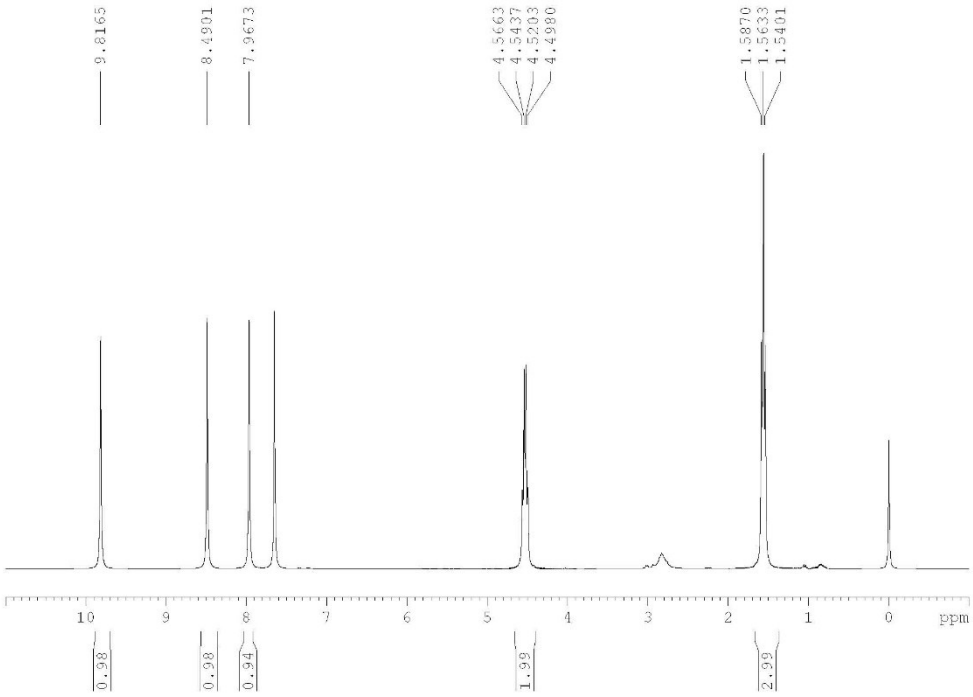


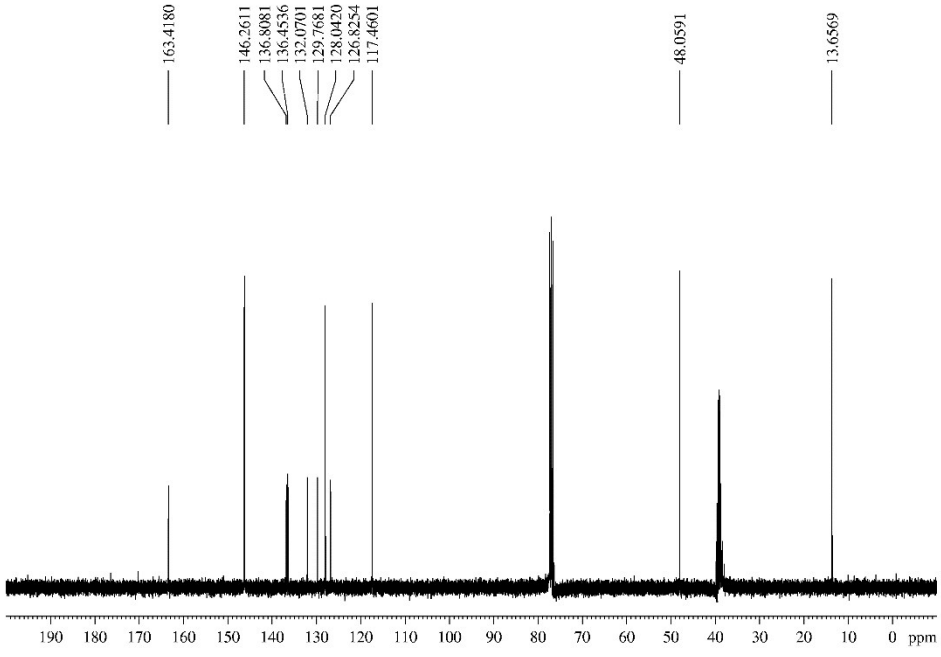
^{1}H and **^{13}C** NMR Spectra of compound **7i**



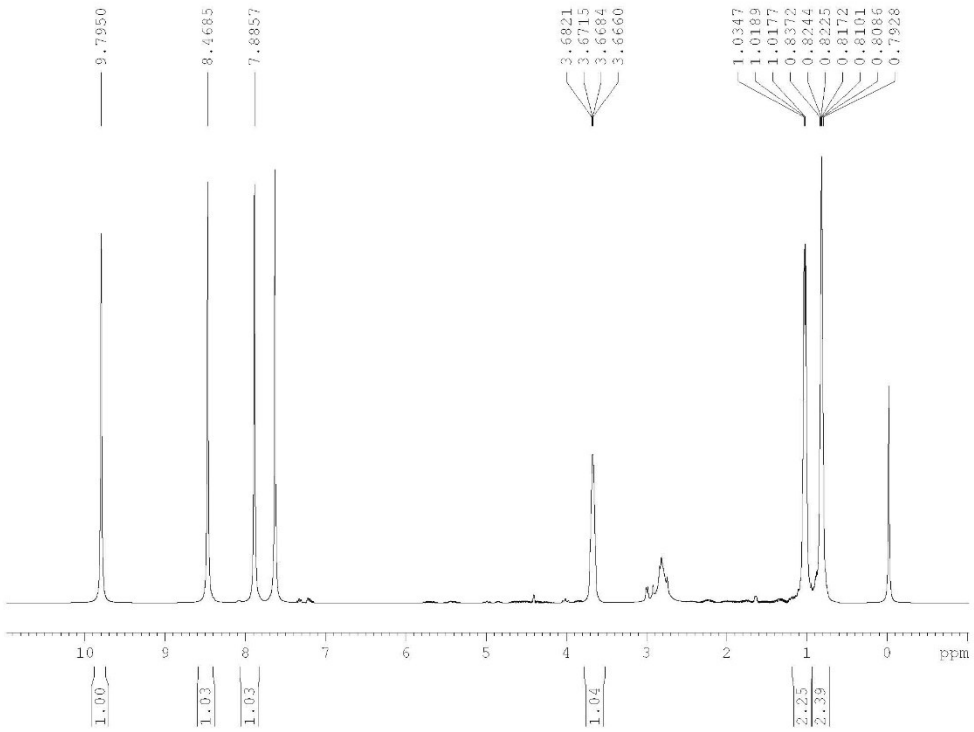


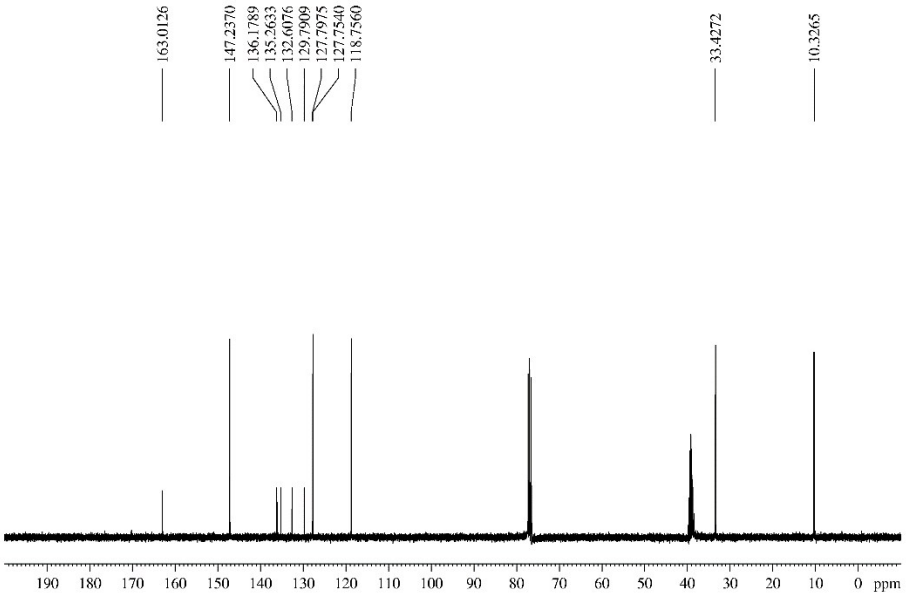
^{1}H and **^{13}C** NMR Spectra of compound **7j**



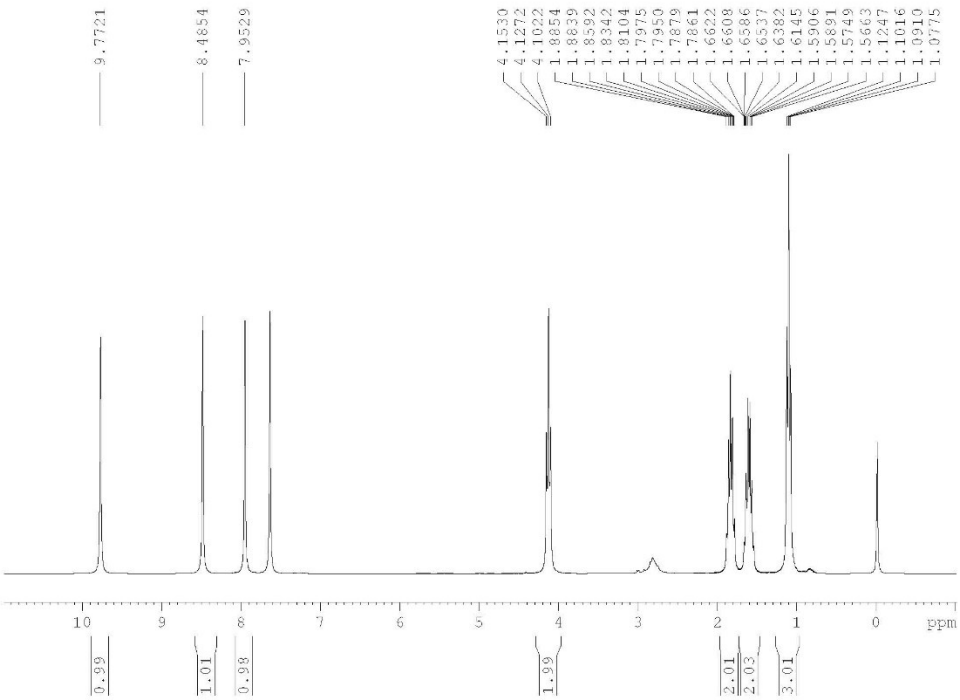


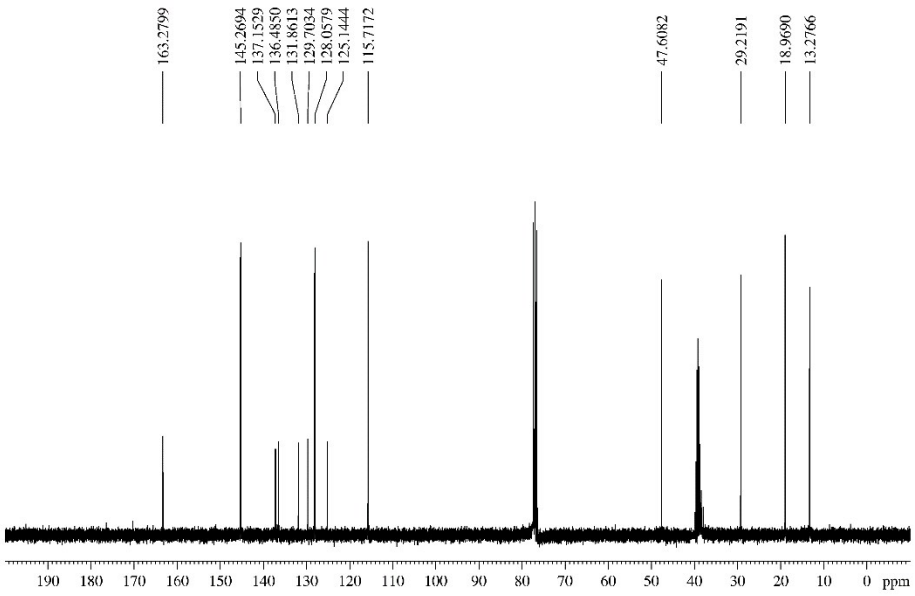
^{1}H and **^{13}C** NMR Spectra of compound **7k**



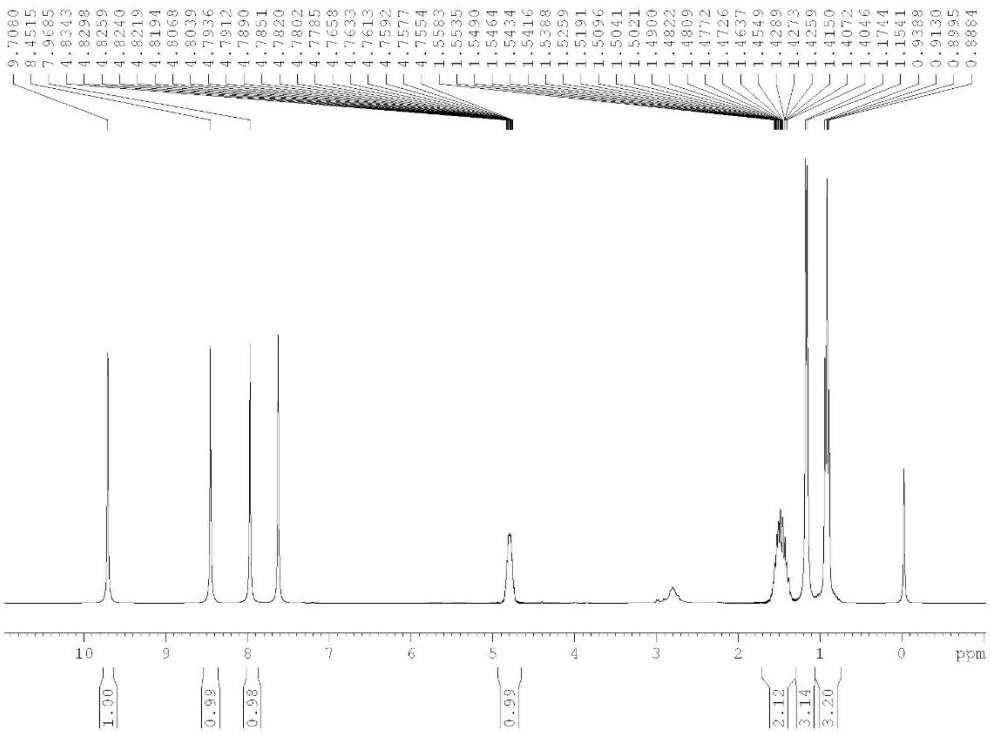


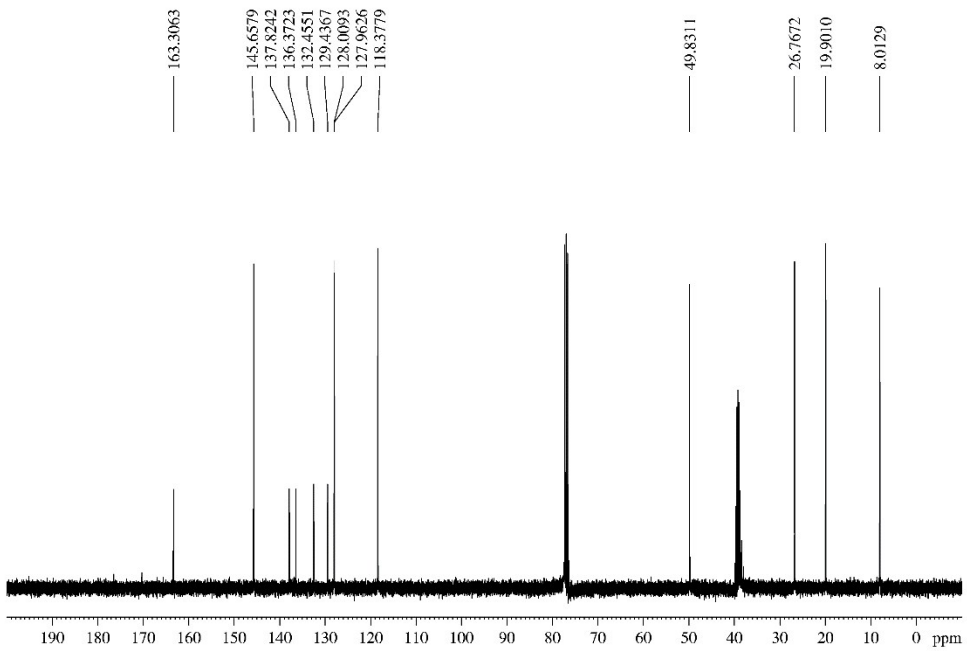
^{1}H and **^{13}C** NMR Spectra of compound **7l**



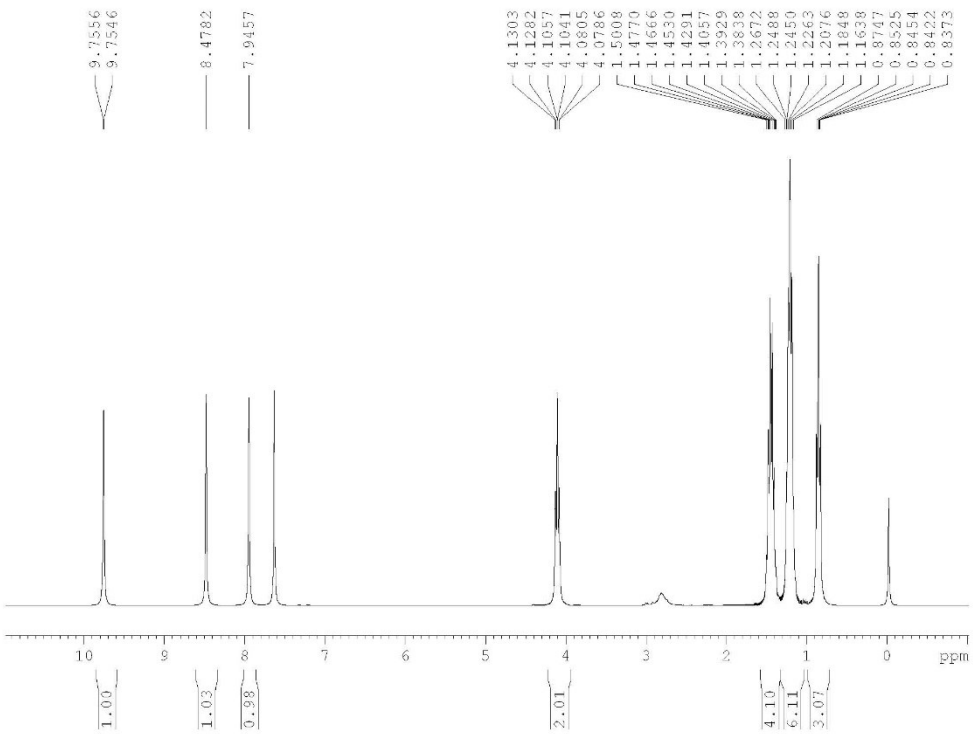


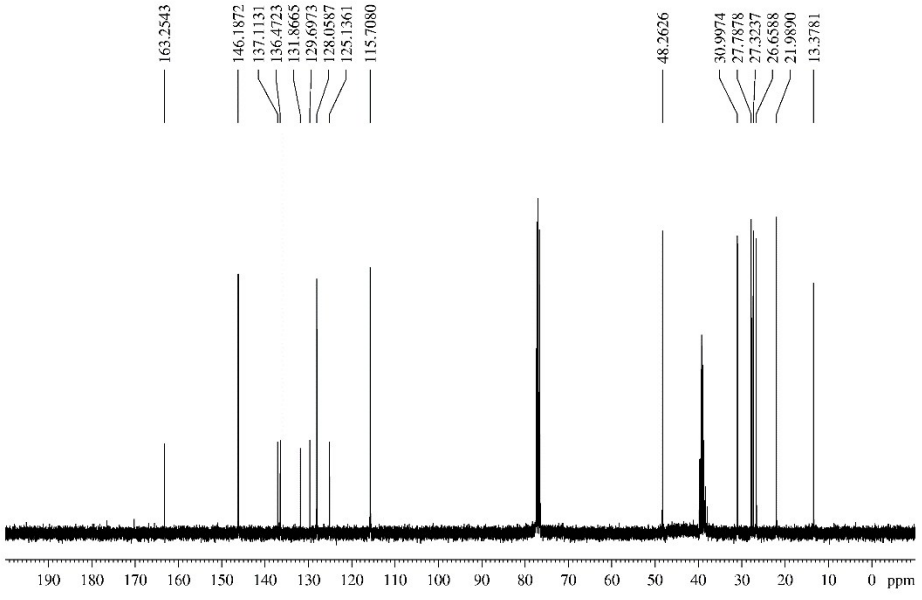
^{1}H and **^{13}C** NMR Spectra of compound **7m**



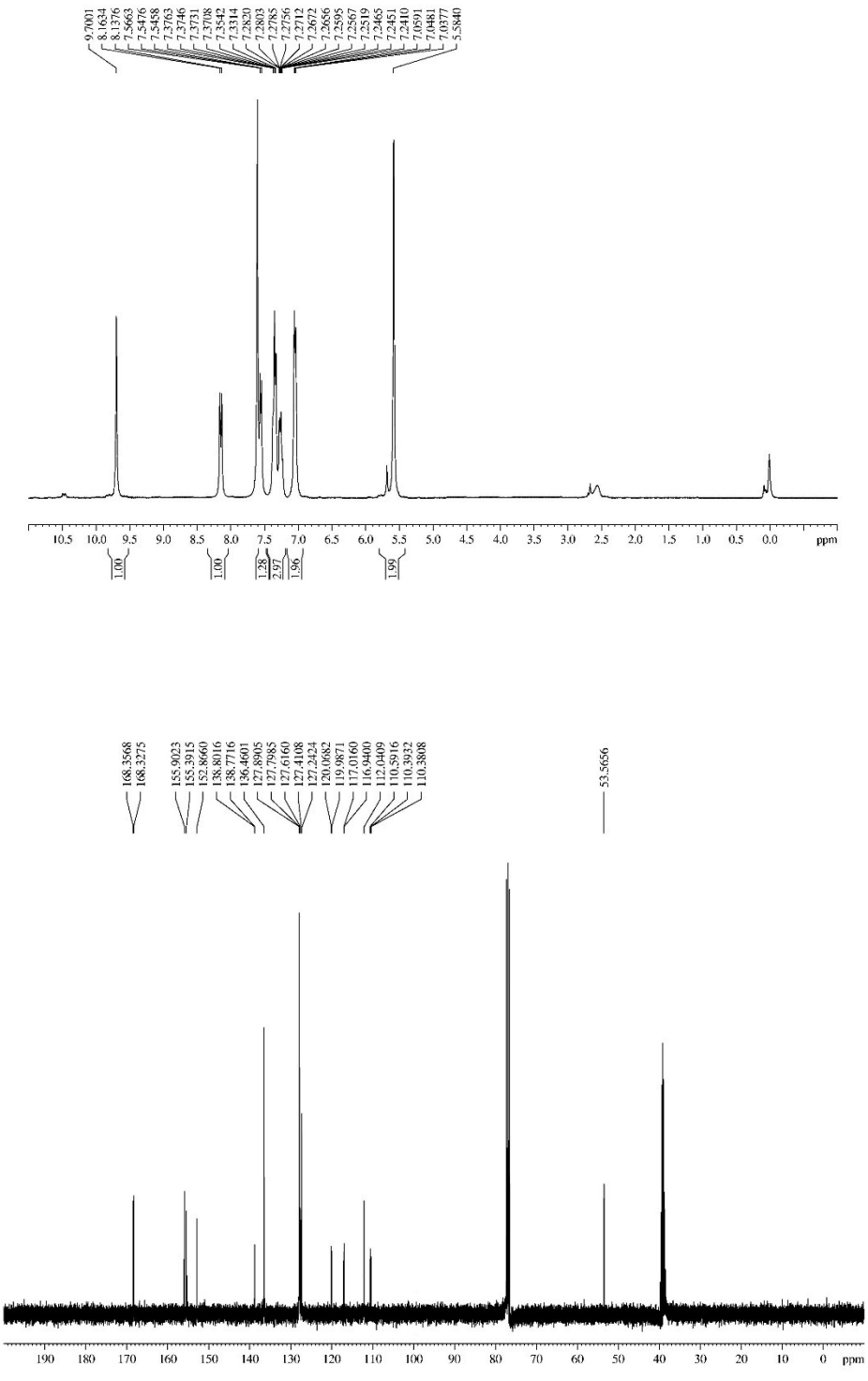


^{1}H and **^{13}C** NMR Spectra of compound **7n**

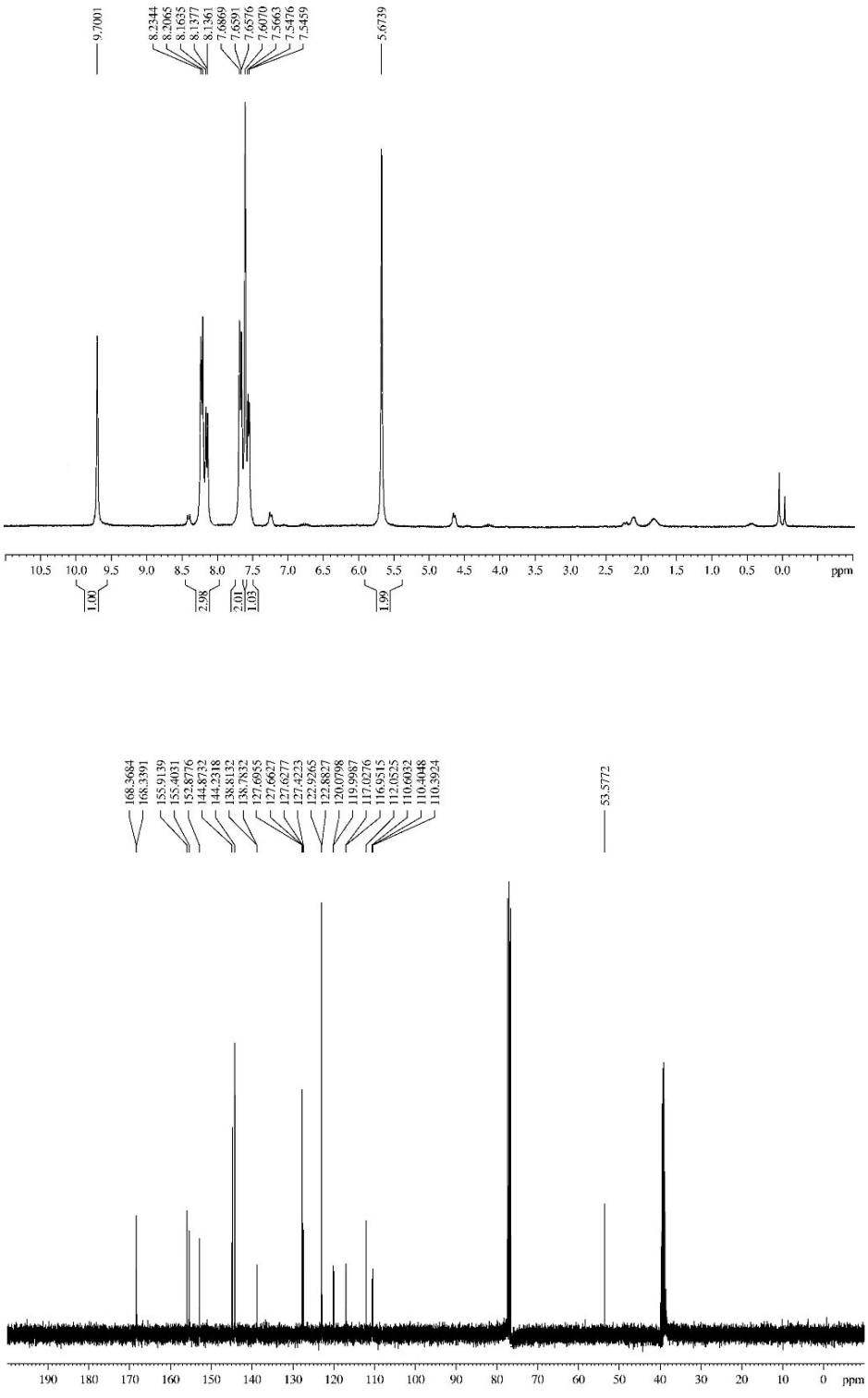




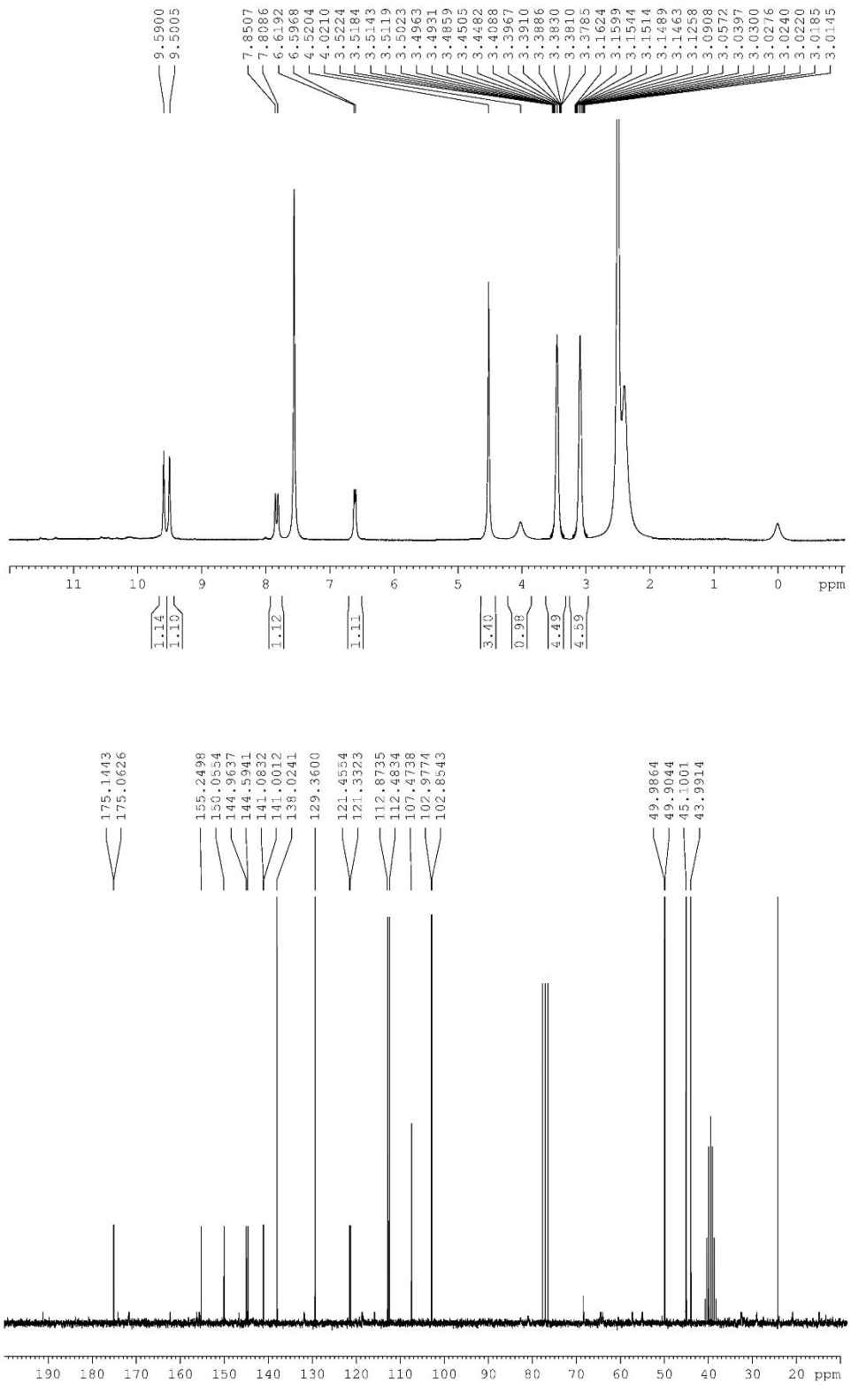
^{1}H and **^{13}C** NMR Spectra of compound **7o**



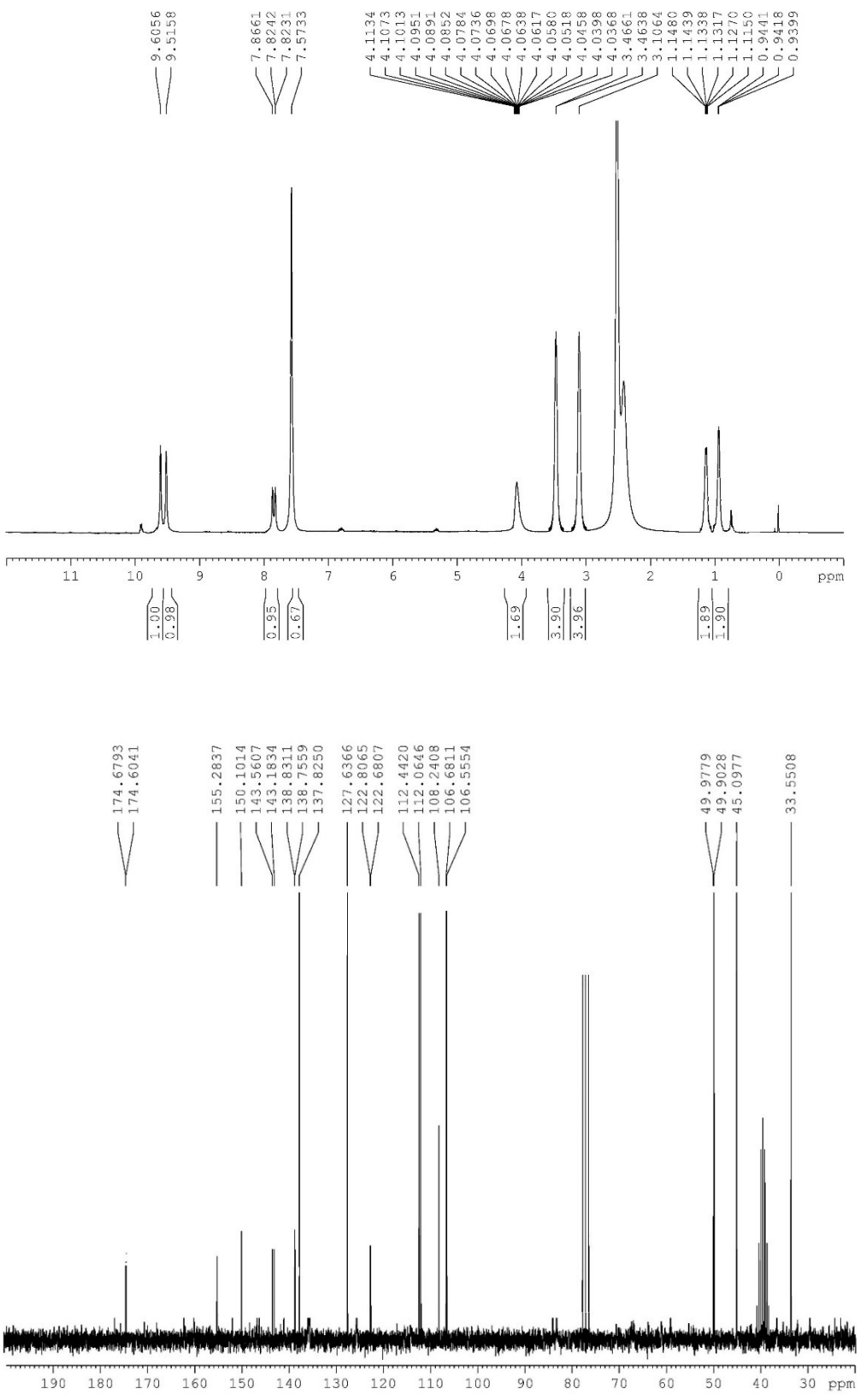
^{1}H and **^{13}C** NMR Spectra of compound **10a**



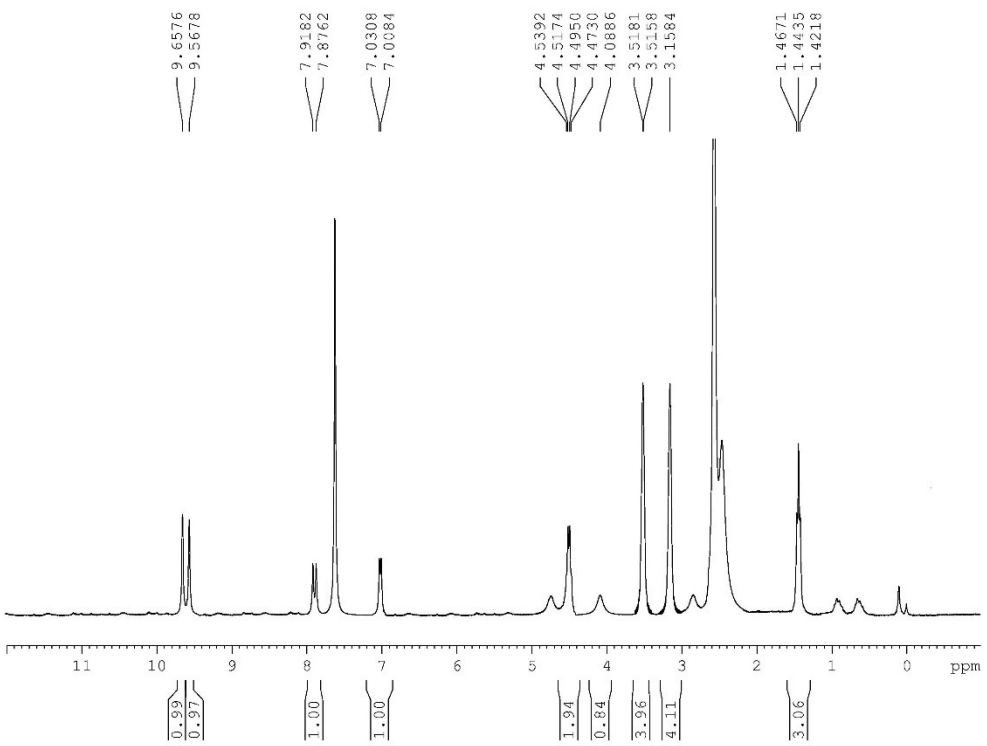
^{1}H and **^{13}C** NMR Spectra of compound **10b**

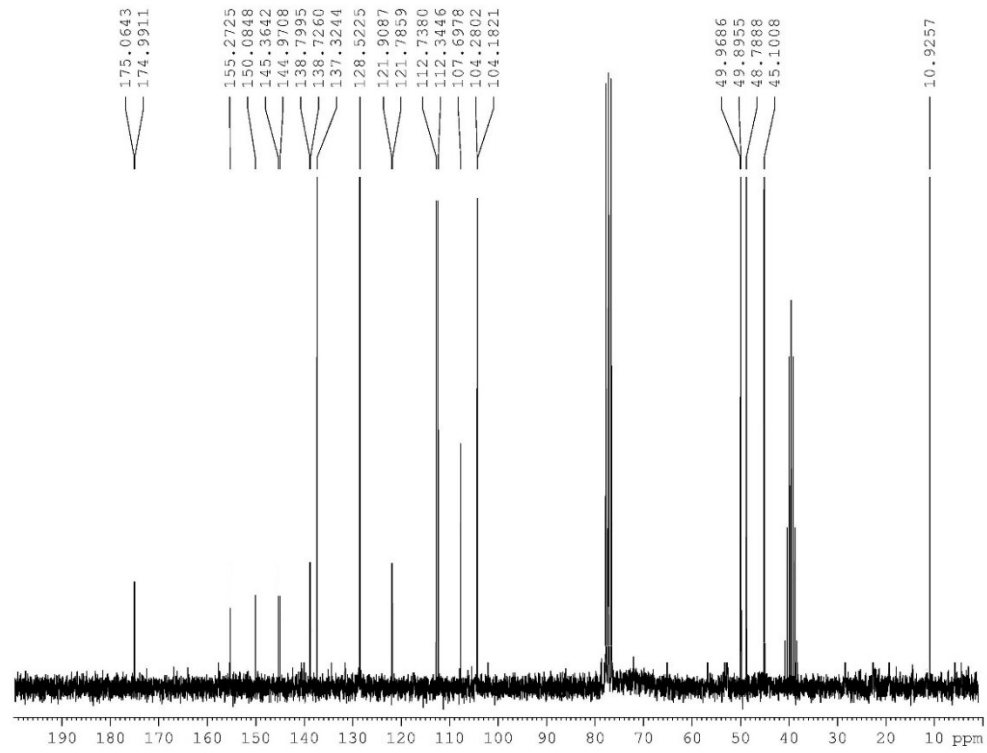


^{1}H and **^{13}C** NMR Spectra of compound **13a**

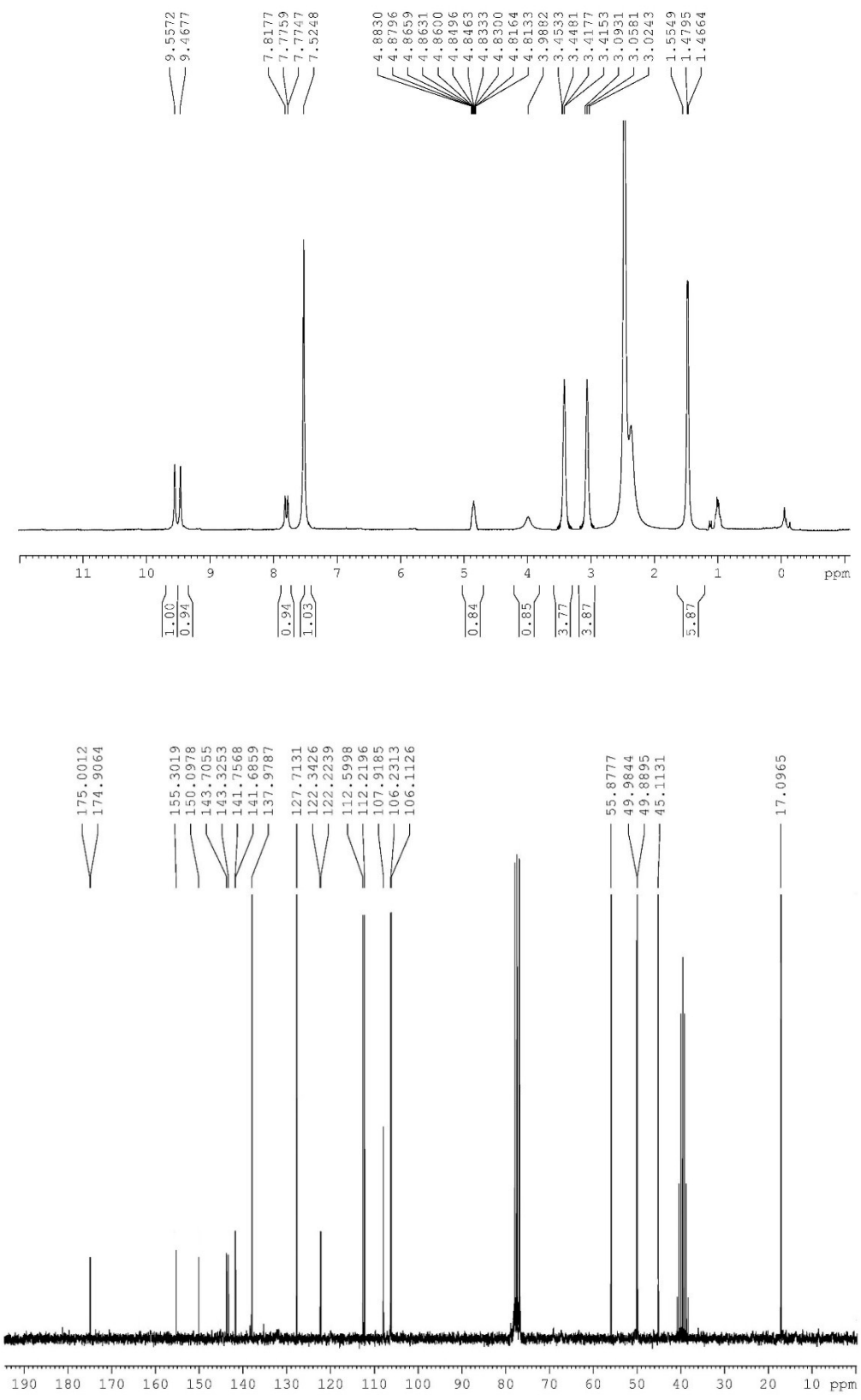


[1]H and **[13]C** NMR Spectra of compound **13b**

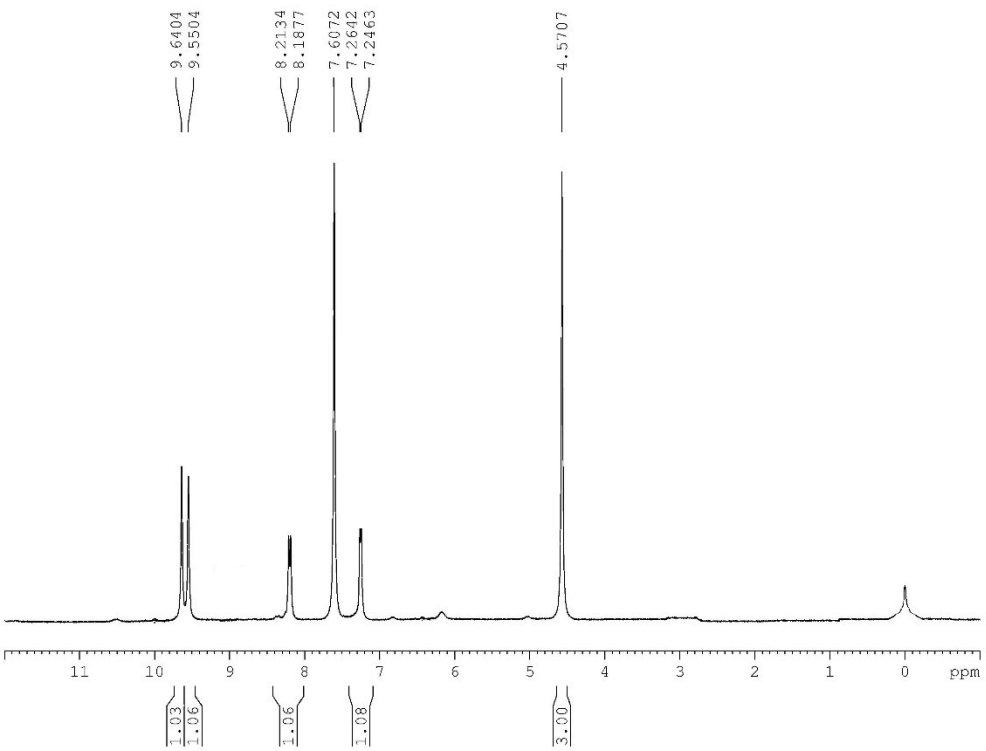


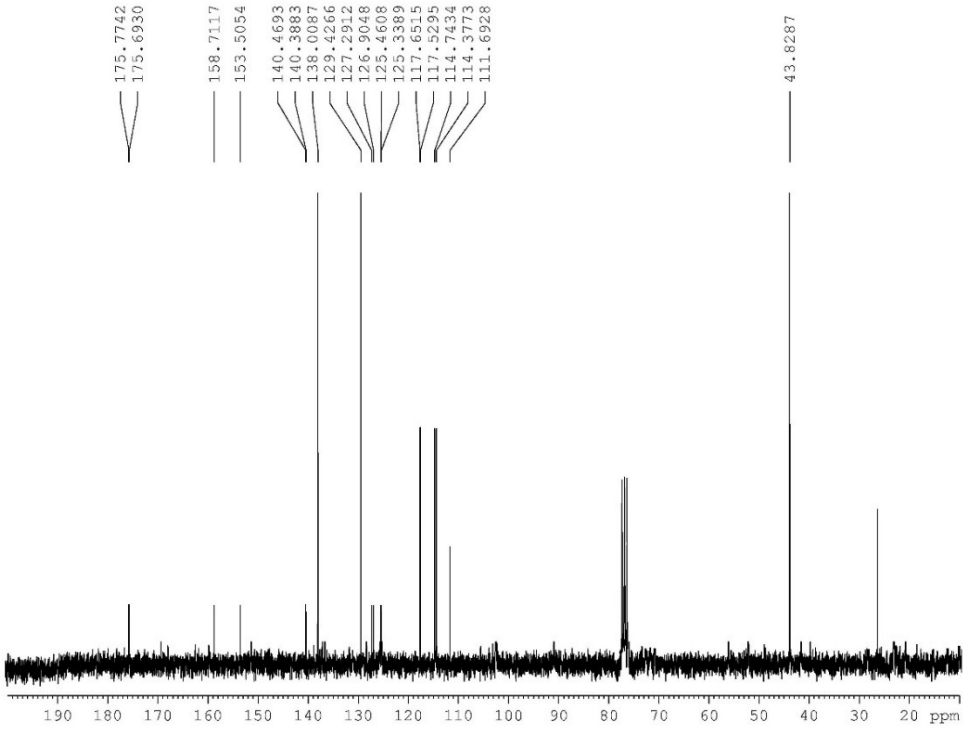


^{1}H and **^{13}C** NMR Spectra of compound **13c**

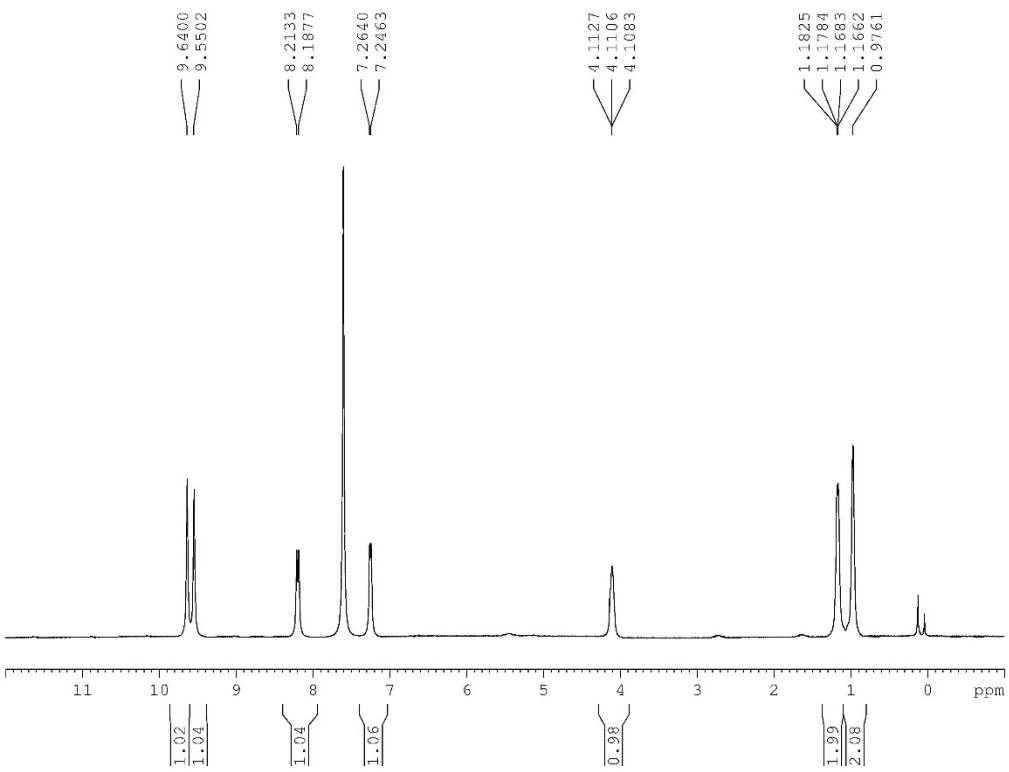


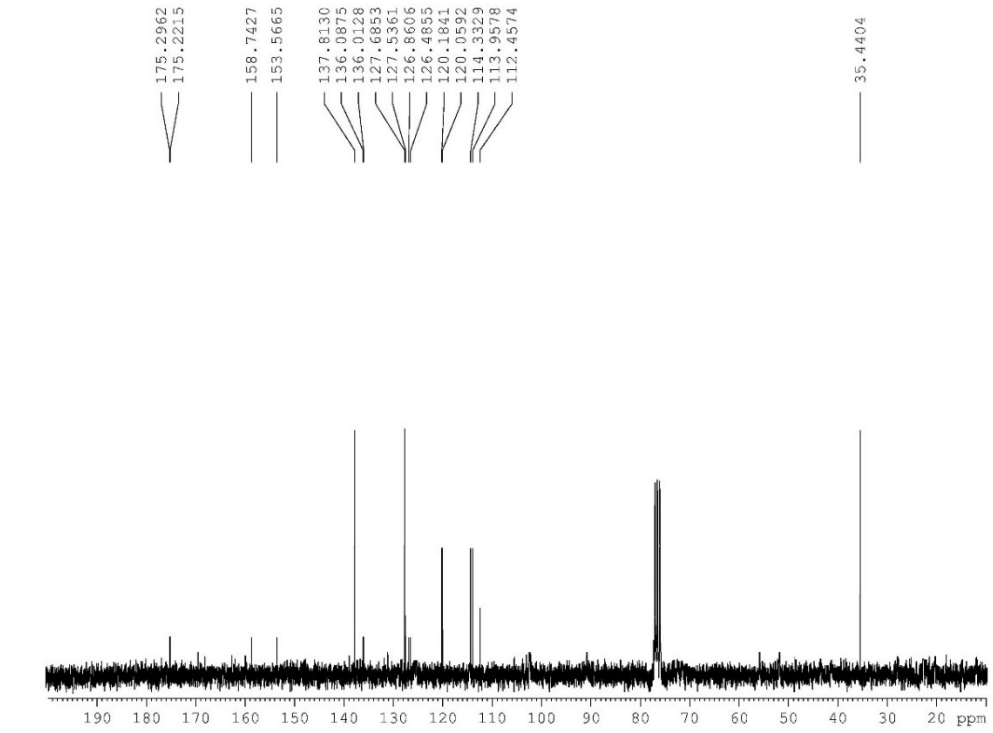
[1]H and **[13]C** NMR Spectra of compound **13d**



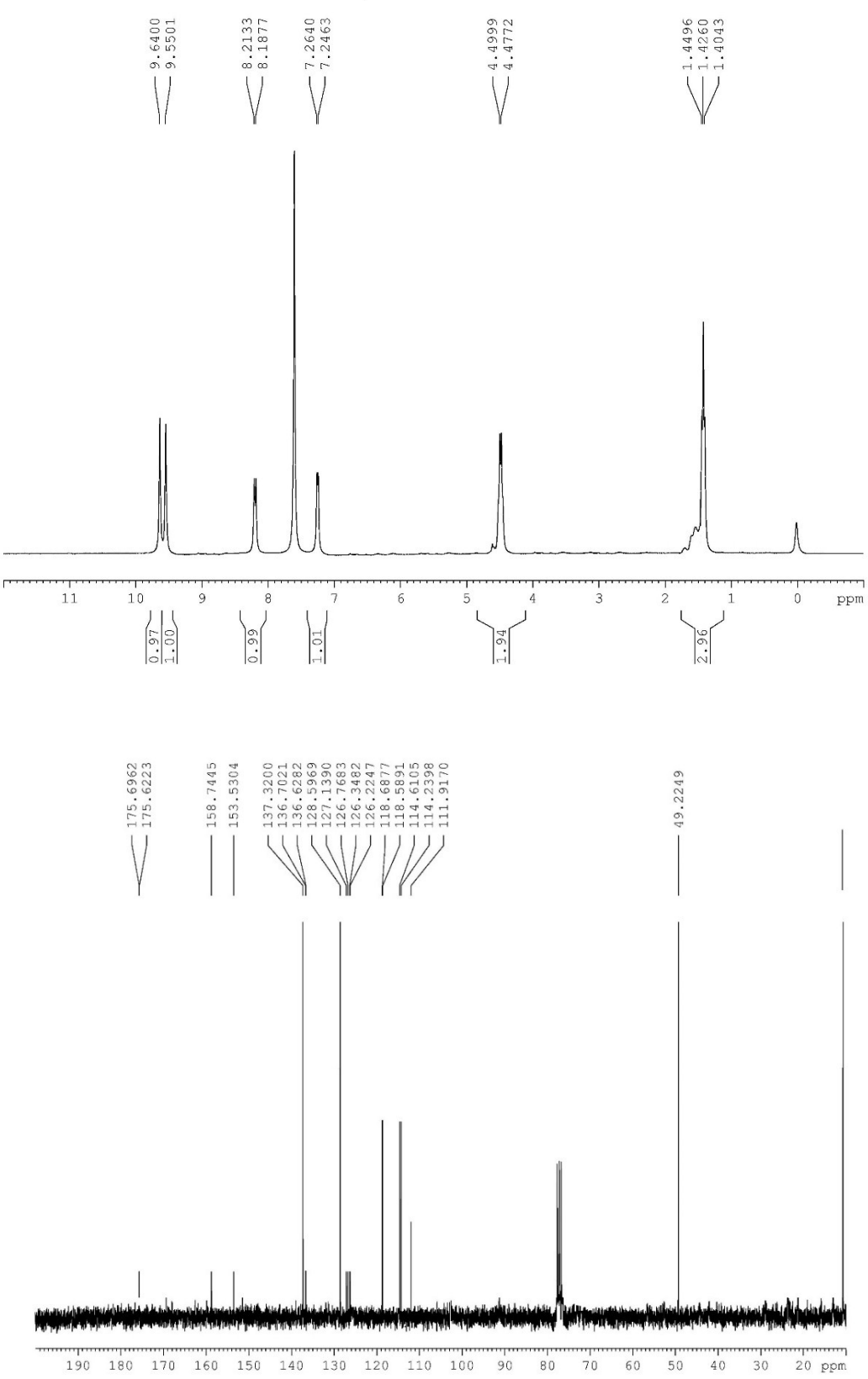


^{1}H and **^{13}C** NMR Spectra of compound **14a**

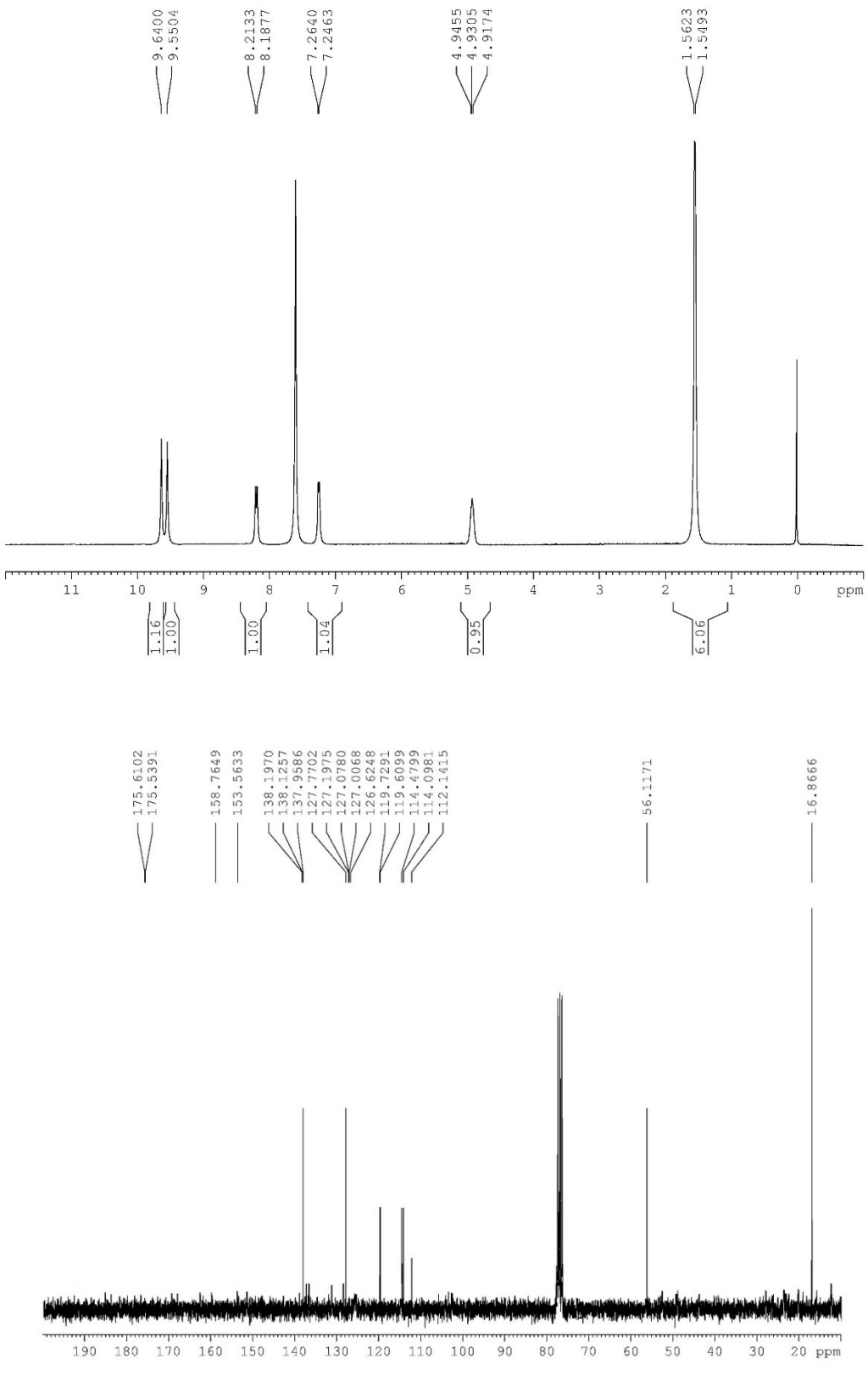




^{1}H and **^{13}C** NMR Spectra of compound **14b**



^{1}H and **^{13}C** NMR Spectra of compound **14c**



^{1}H and **^{13}C** NMR Spectra of compound **14d**

Method for biological evaluation

Solvent Used: DMSO

Standard Antibiotic used: Ciprofloxacin

Concentrations screened: 6.25, 12.5, 25, 50 and 100 µM

Stock Sample Concentration: 1 mM

Name of the analysis method: Mirco-dilution method

Bacteria analyzed: *Staphylococcus aureus, Staphylococcus aureus (MRSA), Escherichia coli, Salmonella typhii* and *Vibrio cholerae*

Description:

Media Used (Muller Hinton broth): Beef extract 2g; Casein hydrolysate 17.5g; Starch 1.5g in 1000 ml of distilled water. Initially, the stock cultures of bacteria were revived by inoculating in broth media and grown at 37ºC for 18 hrs. A 0.5ml culture was centrifuged and resuspended in 250µl volume of above sterile medium to obtain a 5x109 CFU/ml which was diluted to 5x105 CFU/ml. Ciprofloxacin was used as a standard and compounds (CSA001- CSA004) were added at the concentrations mentioned above. The bacterial solution (4x107 CFU/ml) was mixed well and this suspension was added to each well of microtitre plate so that the final volume of compounds and media reaches to 200 µl. The microtitre plate was incubated at 37ºC for 24 h and bacterial growth was observed. The visual MIC was reached by comparing the turbidity with that of uninoculated broth. The complete visual similarity of test wells with that of uninoculated broth is considered as MIC.

Reference:

Methods for dilution anti-microbial susceptibility tests for bacteria that grow aerobically, January, 2012, Clinical and Laboratory Standards Institute (CLSI), M07-A9, Vol 32 (2), pp 17-18.

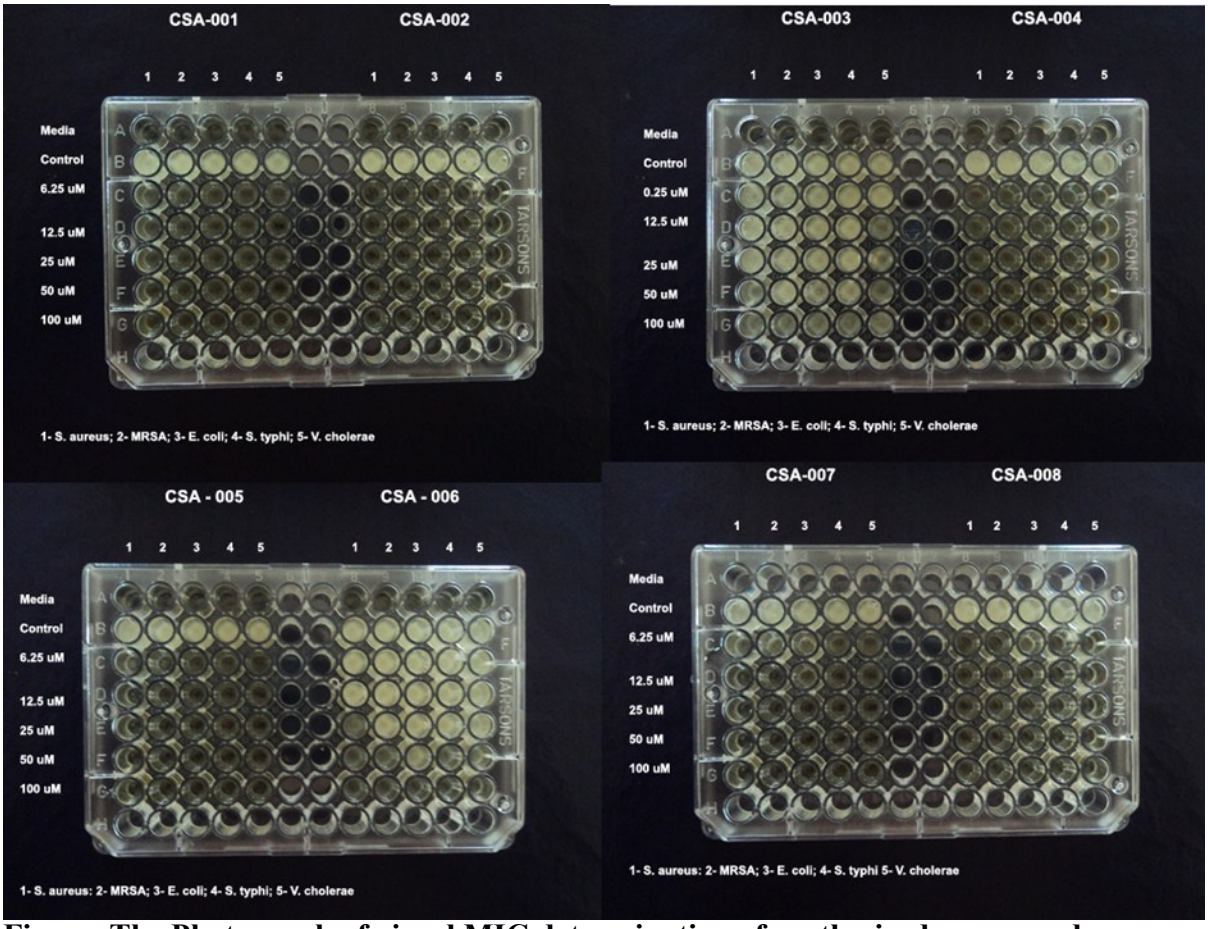


Figure. The Photograph of visual MIC determination of synthesized compounds.

Method for docking studies

The molecular modelling study was performed with Molegro Virtual Docker (MVD) v 4.0.0 (www.molegro.com) along with Graphical User Interface (GUI), MVD tools was used to generate grid, calculate dock score and evaluate conformers. The scoring function used by MolDock is derived from the Piecewise Linear Potential (PLP) scoring functions. The active binding site was considered as a rigid molecule, whereas the ligands were treated as being flexible, that is, all non-

ring torsions were allowed. The structures of title compounds (13 and 14) were subjected to energy minimization using molecular mechanics (MM2). The minimization was performed until the root mean square (RMS) gradient value reached a value smaller than 0.001 kcal/mol. Finally the protein target (2XCT) was prepared for molecular docking simulation in such a way that all heteroatoms (i.e., non-receptor atoms such as water, ions, etc) were removed. The active binding site region was defined as a spherical region which encompasses all protein within 15.0 Å of bound crystallographic ligand atom. The docking protocol includes the grid resolution of 0.30, for grid generation and 15 A radius from the template as the binding site. MolDock SE was used as a search algorithm and the number of runs was set to 10 Å population size of 50 and maximum interactions of 1500 were used for parameter settings. The maximum number of poses generated was 10. Since MVD works by an evolutionary algorithm, successive docking runs do not give precisely the same pose and interactions. To address this inherent randomness, three consecutive runs were done and the best three poses were used to visualize the interactions of all inhibitors.