Electronic Supplementary Information

Copper catalysed dehydrogenative self-coupling/cyclization of 5-aminopyrazoles: Synthesis and photophysical study of pyridazines

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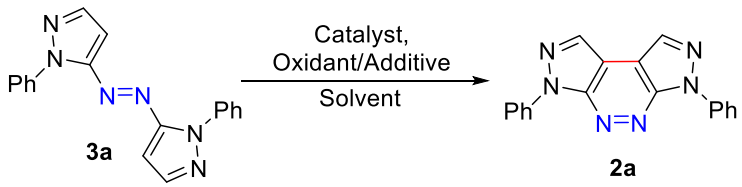
General information

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. IR spectra were recorded on a Perkin-Elmer system 2000 FT-IR spectrometer. HRMS data were recorded by electrospray ionization with a Q-TOF mass analyzer (Waters). NMR spectra were recorded on Bruker–500 (125) MHz and Jeol-400 (100) MHz NMR spectrometer with tetramethylsilane (TMS) as the internal standard. 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 vapour. Column chromatography was performed on silica gel (100-200 mesh, Merck) using ethyl acetate/hexane as eluent. Crystal data were recorded using Single Crystal X-ray Diffractometer [model: Single source supernova E (Mo Source); make Agilent]. Photophysical properties of all the samples were evaluated on HITACHI (U-3900) UV-Visible spectrophotometer and Horiba (Fluorlolog-3) fluorescence spectrophotometer.

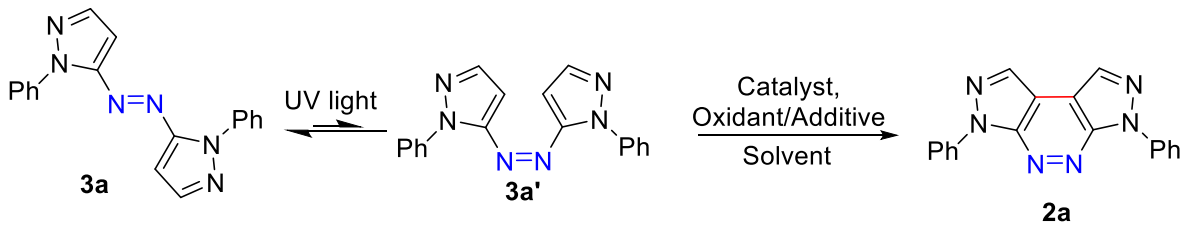
Table S1



Sl. No.	Catalyst (mol%)	Oxidants/ Additives (eq.)	Time (h)	Solvent	Temp (°C)	Yields (%)
1	$Cu(OAc)_2.H_2O$ (10)	-	6	Toluene	120	ND
2	CuBr (10)	-	6	Toluene	120	ND
3	$Cu(OAc)_2.H_2O$ (10)	TBHP (1)	6	Toluene	120	ND
4	$Cu(OAc)_2.H_2O$ (10)	H_2O_2(1)	6	Toluene	120	ND
5	$Cu(OAc)_2.H_2O$ (10)	Ag_2CO_3 (1)	6	Toluene	120	ND
6	$Pd(OAc)_2$ (10)	TBHP (1)	6	Toluene	120	ND
7	CuBr (10)	$PhCO_2H$ (1)	6	Toluene	120	ND
8	CuBr (10)	$PhCO_2H$ (1)	6	*p*-Xylene	130	ND
9	CuBr (10)	$PhCO_2H$ (1)	6	DMSO	130	ND

ND – not detected

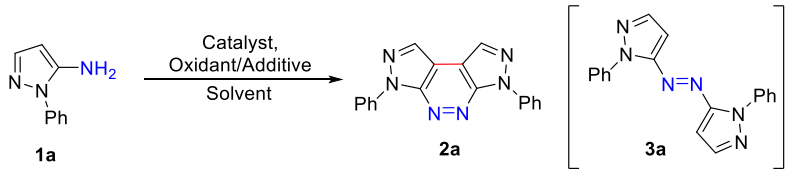
Table S2



Sl. No.	Catalyst (mol%)	Oxidants/ Additives (eq.)	Time (h)	Solvent	Temp (°C)	Yields (%)
1	$Cu(OAc)_2.H_2O$ (10)	-	6	Toluene	120	ND
2	CuBr (10)	-	6	Toluene	120	ND
3	$Cu(OAc)_2.H_2O$ (10)	TBHP (1)	6	Toluene	120	ND
4	$Cu(OAc)_2.H_2O$ (10)	H_2O_2(1)	6	Toluene	120	ND
5	$Cu(OAc)_2.H_2O$ (10)	Ag_2CO_3 (1)	6	Toluene	120	ND
6	$Pd(OAc)_2$ (10)	TBHP (1)	6	Toluene	120	ND
7	CuBr (10)	$PhCO_2H$ (1)	6	Toluene	120	ND
8	CuBr (10)	$PhCO_2H$ (1)	6	p-Xylene	130	ND
9	CuBr (10)	$PhCO_2H$ (1)	6	DMSO	130	ND

All the reactions were carried out in the presence of UV light (11 W)

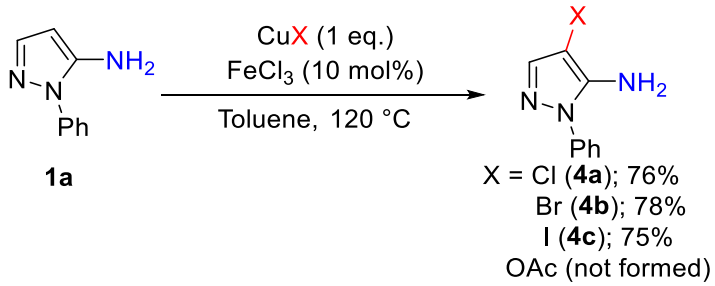
Table S3 Optimization of the reaction[a]



Sl. No.	Catalyst (mol%)	Oxidants/ Additives (eq.)	Time (h)	Solvent	Temp (°C)	Yields (%)[b]	
						2a	3a
1	$Cu(OAc)_2.H_2O$ (10)	TBHP (1)	6	Toluene	120	--	62
2	$Cu(OAc)_2.H_2O$ (10)	H_2O_2(1)	6	Toluene	120	--	50
3	$Cu(OAc)_2.H_2O$ (10)	AgOAc (1)	6	Toluene	120	--	56
4	$Cu(OAc)_2.H_2O$ (10)	SC (1)	6	Toluene	120	--	57
5	$Pd(OAc)_2$ (10)	TBHP (1)	6	Toluene	120	--	--
6	$FeCl_3$ (10)	TBHP (1)	6	Toluene	120	--	--
7[c]	$FeCl_3$ (10)	CuBr (1)	6	Toluene	120	--	--
8	CuBr (10)	--	6	Toluene	120	--	66
9	CuBr (10)	SC (1)	6	Toluene	120	--	65
10	CuBr (10)	SC(1)+BA(1)	6	Toluene	120	60	--
11	CuBr (10)	SC(1)+BA(1)	6	Toluene	130	66	--
12[d]	**CuBr (10)**	SC(1)+BA(1)	**6**	**Toluene**	**130**	**78**	**--**
13	$CuBr_2$ (10)	SC(1)+BA(1)	6	Toluene	130	25	--
14	$Cu(OAc)_2.H_2O$ (10)	SC(1)+BA(1)	6	Toluene	130	17	--
15	CuBr (10)	SC(1)+PNBA (1)	6	Toluene	130	33	-
16	CuBr (10)	SC(1)+AcOH (1)	6	Toluene	130	--	--
17	CuBr (10)	SC(1)+HCO_2H(1)	6	Toluene	130	--	--
18	CuBr (10)	SC(1)+BA(1)	6	*p*-Xylene	130	36	--
19	CuBr (10)	SC(1)+BA(1)	6	DMSO	130	28	10
20	CuBr (5)	SC(1)+BA(1)	6	Toluene	130	74	--
21	CuBr (15)	SC(1)+BA(1)	6	Toluene	130	68	--
22	CuBr (10)	SC(1)+BA(0.5)	6	Toluene	130	41	--
23	CuBr (10)	SC(0.5)+BA(1)	6	Toluene	130	35	--
24	CuBr (10)	SC(1.5)+BA (1.5)	6	Toluene	130	75	--
25	CuBr (10)	SC(1)+BA(1)	6	Toluene	140	78	--
26	CuBr (10)	SC(1)+BA(1)	7	Toluene	130	72	--

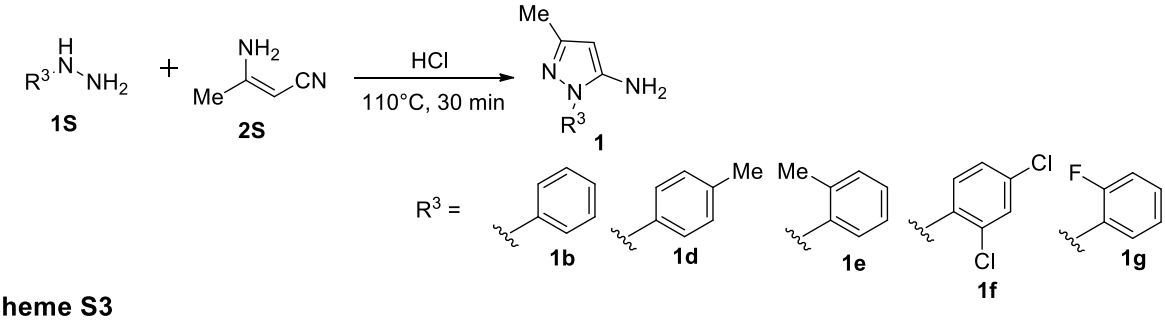
[a]All the reactions were performed using 0.5 mmol of **1a**. Unless mentioned 3 mL of solvent was used in each case. [b]Yields are for isolated products. [c]Isolated 4-bromo substituted 1-phenyl-1*H*-pyrazol-5-amine product (Scheme SI-1). [d]Reaction was performed in pressure tube and all the subsequent reactions were performed similarly. PNBA is 4-nitrobenzoic acid, SC is silver carbonate and BA is benzoic acid.

Scheme S1. Synthesis of 4-halo substituted 5-aminopyrazole

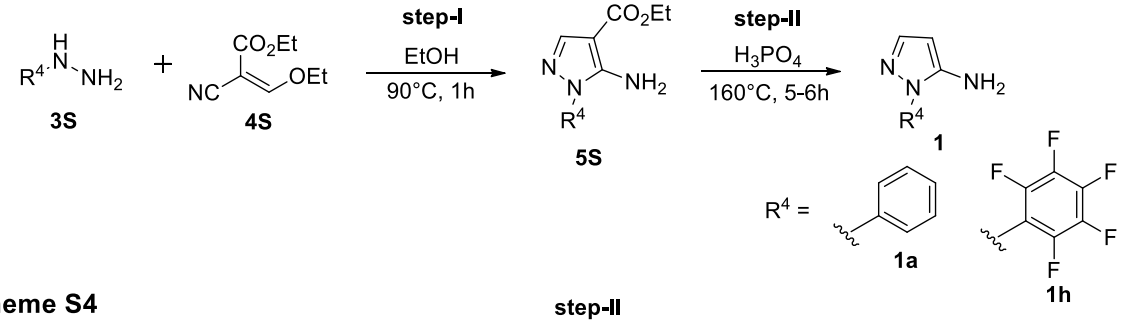


Schemes for synthesis of 1a-h

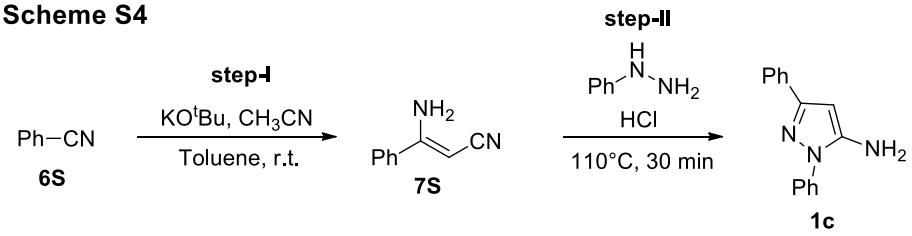
Scheme S2



Scheme S3



Scheme S4



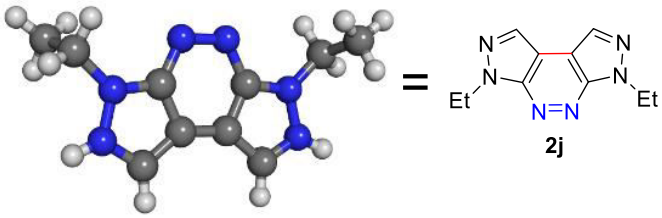


Fig. S1. Single crystal structure of **2j** (CCDC number- 2262732)

Measurement of fluorescent quantum yields (Φ_F)

Fluorescence quantum yield (Φ_F) of all synthesized compounds was calculated according to the equation 1. In this calculation quinine sulfate (0.5 M H_2SO_4 solution) is taken as internal standard.

$$\emptyset_{sample} = \emptyset_{ref}\left(\frac{A_{sample}}{A_{ref}}\right) \times \left(\frac{OD_{ref}}{OD_{sample}}\right) \times \left(\frac{n_{ref}}{n_{sample}}\right) \qquad \text{Equation 1}$$

$\emptyset_{sample}$ = *Quantum yield of the sample*

$\emptyset_{ref}$ = *Quantum yield of the reference*

A_{sample}= *area under the emission spectra of the sample*

A_{ref}= *area under the emission spectra of the reference*

OD_{ref}= *absorbance of the reference*

OD_{sample}= *absorbance of the sample*

n_{ref}= *refractive index of the sample*

n_{sample}= *refractive index of the reference*

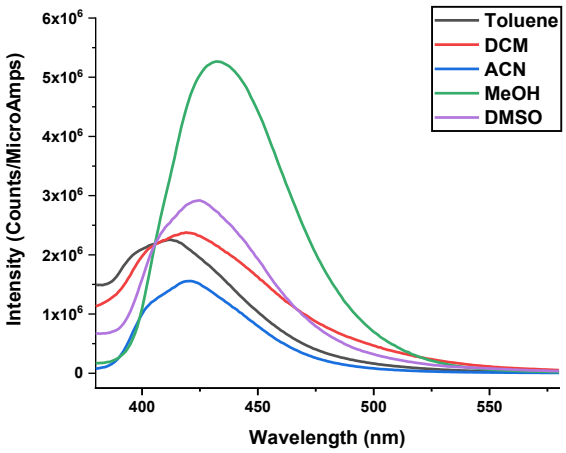


Fig. S2. Fluorescence spectra of compound **2j** in different solvents

Representative procedure for the synthesis of 1b, 1d-1g

Mixture of compound **2S** (5 mmol) and 2.5 N HCl (12.5 mmol) was heated to 50 °C. Compound **1S** (5.5 mmol) was added followed by 12N HCl (60 mmol) and heated the mixture at 110 °C for 30 min. After cooling the reaction mixture, 14N NH_4OH (aq.) was added until the solution became basic. Extracted the organic fraction with EtOAc (100 mL), washed with water (100 mL) and brine (100 mL) respectively. The organic fraction was dried with anhydrous Na_2SO_4 and then filtered. Removed the solvent in rotavapor under reduced pressure and the crude product was then purified by column chromatography using silica gel 100-200 mesh and hexane/ethyl acetate as eluent.

Representative procedure for the synthesis of 1a and 1h

Step I

Compound **3S** (5 mmol) was dissolved in 5 mL EtOH and refluxed for 1h. Then solution of compound **4S** (5 mmol**)** in 10 mL EtOH was slowly added with the help of dropping funnel and the obtained mixture was refluxed for 30 min. After cooling, the reaction mixture was poured into ice cold water. The precipitate was collected and washed with ice cold water (100 mL). Dried crude was used as it is for the next step.

Step II

A mixture of crude product obtained in step I and 10 mL of 85% phosphoric acid was heated for 6h at 170 °C. After completion of reaction as monitored by TLC, crushed ice was added. Reaction mixture was basified by adding 6M NaOH, extracted with EtOAc (100 mL) washed with water (100 mL) and brine (100 mL) respectively. The organic fraction was dried with anhydrous Na_2SO_4 and then filtered. Removed the solvent in rotavapor under reduced pressure and the crude product was then purified by column chromatography using silica gel 100-200 mesh and hexane/ethyl acetate as eluent.

Representative procedure for the synthesis of 1c

Step I

Compound **6S** (10 mmol) was dissolved in anhydrous toluene (20 mL). Anhydrous acetonitrile (20 mmol) was added followed by potassium *tert*-butoxide (40 mmol). Reaction mixture was stirred for 30 h under nitrogen atmosphere. After completion of reaction as monitored by TLC, 2% $NaHCO_3$ solution (100 mL) was added. Then extracted the organic fraction with EtOAc (100 mL), washed with water (100 mL) and brine (100 mL) respectively. The organic fraction was dried with anhydrous Na_2SO_4 and then filtered. Dried crude was used as it is for the next step.

Step II

Crude product obtained in step-I, **7S** and 2.5 N HCl (12.5 mmol) was heated to 50 °C. Compound **1S** (5.5 mmol) was added followed by 12N HCl (60 mmol) and heated the mixture at 110 °C for 30 min. After cooling the reaction mixture, 14N NH_4OH (aq.) was

added until the solution became basic. Extracted the organic fraction with EtOAc (100 mL), washed with water (100 mL) and brine (100 mL) respectively. The organic fraction was dried with anhydrous Na_2SO_4 and then filtered. Removed the solvent in rotavapor and the crude product was then purified by column chromatography using silica gel 100-200 mesh and hexane/ethyl acetate as eluent.

Representative procedure for the synthesis of compound 2

5-Aminopyrazole (0.5 mmol), CuBr (10 mol%), silver carbonate (1 eq.), benzoic acid (1 eq.) and toluene (3 mL) were added sequentially in an oven dried 15 mL pressure tube equipped with magnetic stir bar (10mm x 5mm). The reaction vessel was carefully tightened with 'O' ring and PTFE threaded plug. The reaction mixture was heated at 130°C for 6 h. After cooling the reaction mixture was filtered over celite bed, saturated solution of $NaHCO_3$ (20 mL) was added and organic portion extracted with ethyl acetate (2 x 20 mL). Organic layer was separated and washed with water (2 x 50 mL) and brine (50 mL) respectively. The organic fraction was dried with anhydrous Na_2SO_4 and then filtered. The Solvent was evaporated under reduced pressure and the residue was then purified by column chromatography using silica gel 100-200 mesh and hexane/ethyl acetate as eluent.

*Use fume hood and blast shield for all the pressure tube reactions. High pressure is generated in seal tube and therefore, one must not fill more than half of total volume of seal tube.

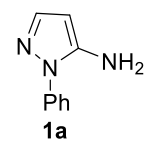
Representative procedure for the synthesis of compound 3

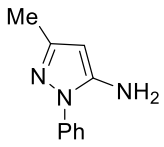
5-Aminopyrazole (0.5 mmol), $Cu(OAc)_2$ or CuBr (10 mol%) and toluene (5 mL) were added sequentially in an oven dried 50 mL round bottom flask. The reaction mixture was refluxed at 120°C for 6 h. After cooling water (50mL) was added and organic portion extracted with ethyl acetate (2 x 50 mL). Organic layer was separated and washed with water (2 x 50 mL) and brine (50 mL) respectively. The organic fraction was dried with anhydrous Na_2SO_4 and then filtered. The Solvent was evaporated under reduced pressure and the residue was then purified by column chromatography using silica gel 100-200 mesh and hexane/ethyl acetate as eluent.

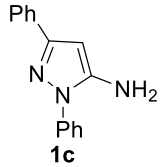
Representative procedure for the synthesis of compound 4

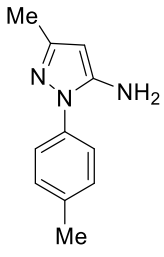
5-Aminopyrazole (0.5 mmol), CuX (0.5 mmol), $FeCl_3$ (10 mol%) and toluene (5 mL) were added sequentially in an oven dried 50 mL round bottom flask. The reaction mixture was refluxed at 120°C for 6 h. After cooling water (50mL) was added and organic portion extracted with ethyl acetate (2 x 50 mL). Organic layer was separated and washed with water (2 x 50 mL) and brine (50 mL) respectively. The organic fraction was dried with anhydrous Na_2SO_4 and then filtered. The Solvent was evaporated under reduced pressure and the residue was then purified by column chromatography using silica gel 100-200 mesh and hexane/ethyl acetate as eluent.

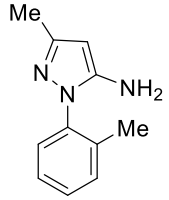
Characterization of the Products

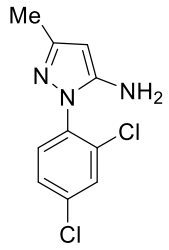
 **1a**	**1-Phenyl-1*H*-pyrazol-5-amine (1a):**[1] Brown liquid; R_f = 0.3 (hexane/EtOAc,1:1), Yield 58 %, 465 mg; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.52 (m, 2H), 7.47-7.43 (m, 2H), 7.40-7.39 (m, 1H), 7.35-7.31 (m, 1H), 5.58-5.57 (m, 1H), 3.89 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8, 140.2, 138.5, 129.3, 127.3, 123.8, 90.5; HRMS (ESI) exact mass calculated for $C_9H_9N_3$ $[M + H]^+$: 160.0875; found: 160.0874.

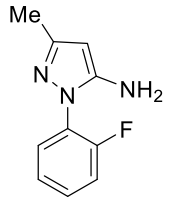
 **1b**	**3-Methyl-1-phenyl-1*H*-pyrazol-5-amine (1b):**[2] Yellow solid; M. P. 115-116 °C; R_f = 0.45 (hexane/EtOAc, 1:1), Yield 96 %, 830 mg; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.52 (m, 2H), 7.47-7.43 (m, 2H), 7.33-7.29 (m, 1H), 5.44 (s, 1H), 3.79 (bs, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4, 145.2, 138.6, 129.4, 127.0, 123.8, 90.7, 13.9; HRMS (ESI) exact mass calculated for $C_{10}H_{11}N_3$ $[M + H]^+$: 174.1031; found: 174.1028.

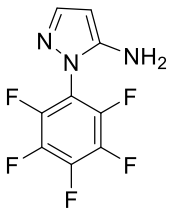
 **1c**	**1,3-Diphenyl-1*H*-pyrazol-5-amine (1c):**[3] Light brown solid; M. P. 129-130 °C; R_f = 0.40 (hexane/EtOAc, 1:1), Yield 46 %, 1.08 g; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83-7.81 (m, 2H), 7.63-7.60 (m, 2H), 7.50-7.45 (m, 2H), 7.40-7.35 (m, 3H), 7.32-7.38 (m, 1H), 5.93 (s, 1H), 3.85 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 145.8, 138.6, 133.4, 129.5, 128.5, 127.8, 127.4, 125.6, 124.1, 88.1; HRMS (ESI) exact mass calculated for $C_{15}H_{13}N_3$ $[M + H]^+$: 236.1188; found: 236.1187.

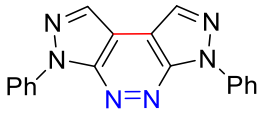
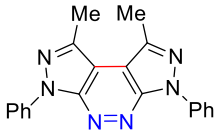
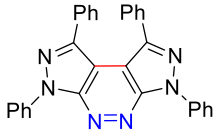
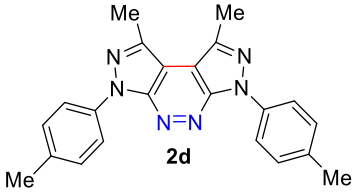
 **1d**	**3-Methyl-1-(*p*-tolyl)-1*H*-pyrazol-5-amine (1d):**[2] Yellow solid; M. P. 208-209 °C; R_f = 0.35 (hexane/EtOAc, 1:1), Yield 95 %, 900 mg; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.37 (m, 2H), 7.24-7.21 (m, 2H), 5.39 (s, 1H), 3.78 (bs, 2H), 2.37 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9, 145.2, 136.8, 135.9, 129.8, 123.7, 90.2, 20.9, 13.7; HRMS (ESI) exact mass calculated for $C_{11}H_{13}N_3$ $[M + H]^+$: 188.1188; found: 188.1185.

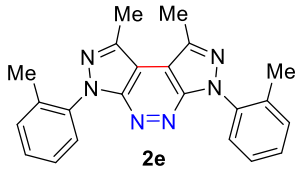
 **1e**	**3-Methyl-1-(*o*-tolyl)-1*H*-pyrazol-5-amine (1e):**[2] Yellow liquid; R_f = 0.45 (hexane/EtOAc, 1:1), Yield 92 %, 860 mg; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.23 (m, 4H), 5.37 (s, 1H), 3.56 (bs, 2H), 2.21 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 145.9, 136.7, 136.6, 131.0, 129.0, 128.0, 126.6, 88.7, 17.3, 13.9; HRMS (ESI) exact mass calculated for $C_{11}H_{13}N_3$ $[M + H]^+$: 188.1188; found: 188.1186.

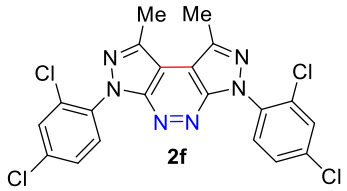
 **1f**	**1-(2,4-Dichlorophenyl)-3-methyl-1*H*-pyrazole (1f):**[2] Yellow solid; M. P. 114-115 °C; R_f = 0.40 (hexane/EtOAc, 1:1), Yield 94 %, 1.14 g; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.54 (m, 1H), 7.42-7.35 (m, 2H), 5.46 (s, 1H), 3.60 (bs, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4, 146.6, 135.4, 134.6, 132.9, 131.0, 130.1, 128.1, 90.3, 13.9; HRMS (ESI) exact mass calculated for $C_{10}H_9Cl_2N_3$ $[M + H]^+$: 242.0252; found: 242.0251.

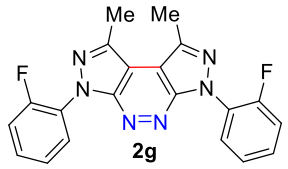
 **1g**	**1-(2-Fluorophenyl)-3-methyl-1*H*-pyrazol-5-amine (1g):**[2] Brown liquid; R_f = 0.45 (hexane/EtOAc, 1:1), Yield 96 %, 920 mg; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.49 (m, 1H), 7.39-7.34 (m, 1H), 7.27-7.19 (m, 2H), 5.46 (s, 1H), 3.73 (bs, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3 (d, J_{C-F} = 250.5 Hz), 150.4, 146.5, 129.7 (d, J_{C-F} = 7.7 Hz), 128.9, 126.2 (d, J_{C-F} = 11.6 Hz), 125.0 (d, J_{C-F} = 3.9 Hz), 116.5 (d, J_{C-F} = 19.3 Hz), 90.8, 13.9; HRMS (ESI) exact mass calculated for $C_{10}H_{10}FN_3$ $[M + H]^+$: 192.0937; found: 192.0933.

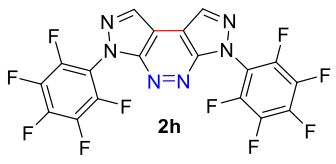
 **1h**	**1-(Perfluorophenyl)-1*H*-pyrazol-5-amine (1h):** Dark brown liquid; R_f = 0.35 (hexane/EtOAc, 1:1), Yield 50 %, 625 mg; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 1.8 Hz, 1H), 5.69 (d, J = 1.8 Hz, 1H), 3.76 (bs, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.9, 145.0 (m), 142.94, 142.9 (m), 140.8 (m), 138.9 (m), 136.9 (m), 113.6 (m), 91.7; HRMS (ESI) exact mass calculated for $C_9H_4F_5N_3$ $[M + H]^+$: 250.0404; found: 250.0405.

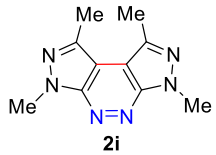
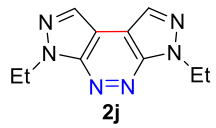
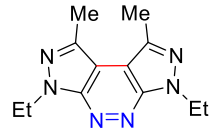
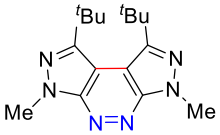
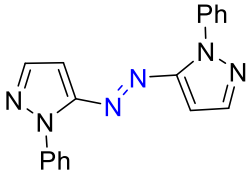
 **2a**	**3,6-Diphenyl-3,6-dihydrodipyrazolo[3,4-*c*:4',3'-*e*]pyridazine (2a):** Yellow; M. P. 240-241 °C: R_f = 0.65 (hexane/EtOAc, 9.5:0.5), Yield 78 %, 61 mg; IR (KBr): 2960, 1596, 1527, 1501, 1416, 1186, 1112, 945, 681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (s, 2H), 8.48-8.45 (m, 4H), 7.63-7.58 (m, 4H), 7.45-7.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.9, 139.1, 131.3, 129.3, 127.2, 121.9, 109.5; HRMS (ESI) exact mass calculated for $C_{18}H_{12}N_6$ $[M + H]^+$: 313.1202; found: 313.1200.
 **2b**	**1,8-Dimethyl-3,6-diphenyl-3,6-dihydrodipyrazolo[3,4-*c*:4',3'-*e*]pyridazine (2b):** Yellow solid; M. P. 241-242 °C; R_f = 0.68 (hexane/EtOAc, 9.5:0.5), Yield 71 %, 60 mg; IR (KBr): 1592, 1499, 1426, 1148, 1104, 756, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.44-8.42 (m, 4H), 7.59-7.55 (m, 4H), 7.40-7.35 (m, 2H), 3.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 140.3, 139.2, 129.2, 126.6, 121.6, 109.7, 15.4; HRMS (ESI) exact mass calculated for $C_{20}H_{16}N_6$ $[M + H]^+$: 341.1515; found: 341.1513.
 **2c**	**1,3,6,8-Tetraphenyl-3,6-dihydrodipyrazolo[3,4-*c*:4',3'-*e*]pyridazine (2c):** Light yellow solid; M. P. 215-216 °C; R_f = 0.78 (hexane/EtOAc, 9.5:0.5), Yield 64 %, 74 mg; IR (KBr): 3380, 1597, 1499, 1154, 1080, 949 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.53-8.50 (m, 4H), 7.63-7.60 (m, 4H), 7.45-7.42 (m, 2H), 7.39-7.37 (m, 4H), 7.23-7.20 (m, 2H), 7.05-7.02 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.1, 144.7, 139.1, 132.3, 129.3, 128.6, 128.5, 127.8, 127.2, 122.3, 108.2; HRMS (ESI) exact mass calculated for $C_{30}H_{20}N_6$ $[M + H]^+$: 465.1828; found: 465.1824.
 **2d**	**1,8-Dimethyl-3,6-di-*p*-tolyl-3,6-dihydrodipyrazolo[3,4-*c*:4',3'-*e*]pyridazine (2d):** Yellow solid; M. P. 271-272 °C R_f = 0.60 (hexane/EtOAc, 9.5:0.5), Yield 81 %, 75 mg; IR (KBr): 2916, 1509, 1432, 1151, 917, 814 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.28-8.26 (m, 4H), 7.37-7.35 (m, 2H), 2.98 (s, 6H), 2.44 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.4, 139.9, 136.8, 136.4, 129.8, 121.5, 109.4, 21.1, 15.4; HRMS (ESI) exact mass calculated for $C_{22}H_{20}N_6$ $[M + H]^+$: 369.1828; found: 369.1833.

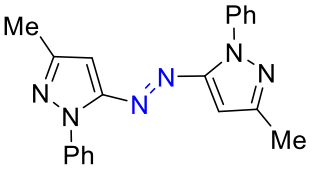
	**1,8-Dimethyl-3,6-di-*o*-tolyl-3,6-dihydrodipyrazolo[3,4-*c*:4',3'-*e*]pyridazine (2e):** Light yellow solid; M. P. 220-221 °C; R_f = 0.68 (hexane/EtOAc, 9.5:0.5), Yield 80 %, 74 mg; IR (KBr): 2920, 1537, 1501, 1450, 1311, 1221, 1086, 842, 750, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50-7.36 (m, 8H), 2.74 (s, 6H), 2.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 142.6, 137.2, 135.5, 133.2, 131.3, 128.7, 127.7, 126.7, 18.7, 11.7; HRMS (ESI) exact mass calculated for $C_{22}H_{20}N_6$ $[M + H]^+$: 369.1828; found: 369.1826.

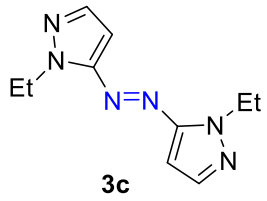
	**3,6-Bis(2,4-dichlorophenyl)-1,8-dimethyl-3,6-dihydrodipyrazolo[3,4-c:4',3'-e]pyridazine (2f):** Light yellow solid; M. P. 198-199 °C; R_f = 0.68 (hexane/EtOAc, 9.5:0.5), Yield 68 %, 81 mg; IR (KBr): 2926, 1543, 1495, 1439, 1381, 1194, 1101, 1012, 924, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 1.8 Hz, 2H), 7.60 (s, 1H), 7.58 (s, 1H), 7.47 (d, J = 2.5 Hz, 1H), 7.45 (d, J = 2.5 Hz, 1H), 3.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4, 141.5, 135.8, 134.3, 133.0, 130.6, 130.5, 127.9, 108.7, 15.4; HRMS (ESI) exact mass calculated for $C_{20}H_{12}C_{l4}N_6$ $[M + H]^+$: 476.9956; found: 476.9954.

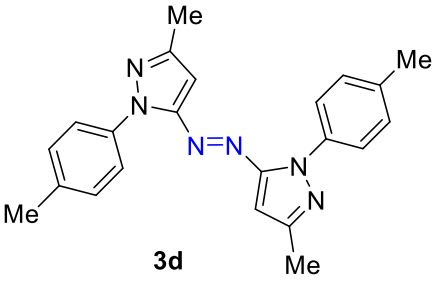
	**3,6-Bis(2-fluorophenyl)-1,8-dimethyl-3,6-dihydrodipyrazolo[3,4-*c*:4',3'-*e*]pyridazine (2g):** Light yellow solid; M. P. 229-230 °C; R_f = 0.64 (hexane/EtOAc, 9.5:0.5), Yield 56 %, 53 mg; IR (KBr): 2923, 1515, 1463, 1312, 1252, 1140, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.76-7.72 (m, 2H), 7.51-7.45 (m, 2H), 7.39-7.33 (m, 4H), 2.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7 (d, J_{C-F} = 254.3 Hz), 143.9, 143.4, 133.6, 129.6 (d, J_{C-F} = 7.7 Hz), 128.0, 126.1 (d, J_{C-F} = 11.6 Hz), 124.7 (d, J_{C-F} = 3.9 Hz), 117.1 (d, J_{C-F} = 19.3 Hz), 11.7; HRMS (ESI) exact mass calculated for $C_{20}H_{14}F_2N_6$ $[M + H]^+$: 377.1326; found: 377.1325.

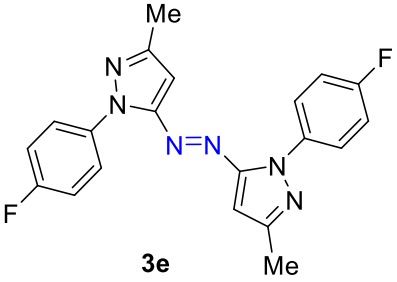
	**3,6-Bis(perfluorophenyl)-3,6-dihydrodipyrazolo[3,4-*c*:4',3'-*e*]pyridazine (2h):** Brown liquid; R_f = 0.68 (hexane/EtOAc, 9.5:0.5), Yield 55 %, 68 mg; IR (KBr): 2963, 1535, 1519, 1403, 1328, 1261, 1213, 1191, 1100, 998, 884, 810, 760, 703, 687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.74 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.2, 145.3-145.1 (m), 143.7-143.0 (m), 141.9-141.5 (m), 139.2-139.0 (m), 137.3-137.0 (m), 134.5, 113.2-112.9 (m), 109.2; ^{19}F NMR (470.6 MHz, $CDCl_3$) δ -143.9 (dd, 2F, ortho), -150.1 (t, 1F, para), -160.2 (dt, 2F, meta); HRMS (ESI) exact mass calculated for $C_{18}H_2F_{10}N_6$ $[M + H]^+$: 493.0260; found: 493.0257.

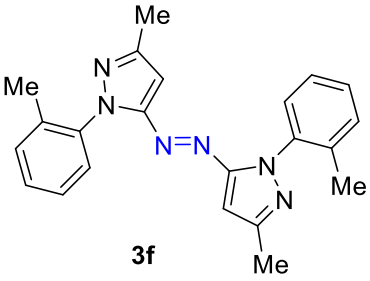
 **2i**	**1,3,6,8-Tetramethyl-3,6-dihydrodipyrazolo[3,4-*c*:4',3'-*e*]pyridazine (2i):** Light yellow solid; M. P. 104-105 °C: R_f = 0.65 (hexane/EtOAc, 9.5:0.5), Yield 84 %, 45 mg; IR (KBr): 2919, 1532, 1494, 1446, 1379, 1213, 1281, 1089, 772, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.41 (s, 6H), 2.85 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 138.0, 107.5, 35.1, 14.9; HRMS (ESI) exact mass calculated for $C_{10}H_{12}N_6$ $[M + H]^+$: 217.1202; found: 217.1200.
 **2j**	**3,6-Diethyl-3,6-dihydrodipyrazolo[3,4-*c*:4',3'-*e*]pyridazine (2j):** Light yellow solid; M. P. 105-106 °C R_f = 0.65 (hexane/EtOAc, 9.5:0.5), Yield 86 %, 46 mg; IR (KBr): 2983, 1524, 1459, 1266, 1205, 1086, 855, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 2H), 4.95 (q, *J* = 7.3 Hz, 4H), 1.68 (*t*, *J* = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3, 129.2, 107.8, 44.0, 15.2; HRMS (ESI) exact mass calculated for $C_{10}H_{12}N_6$ $[M + H]^+$: 217.1202; found: 217.1201.
 **2k**	**3,6-Diethyl-1,8-dimethyl-3,6-dihydrodipyrazolo[3,4-*c*:4',3'-*e*] pyridazine (2k):** Brown solid; M. P. 95-97 °C R_f = 0.55 (hexane/EtOAc, 9:1), Yield 83 %, 42 mg; IR (KBr): 2922, 1735, 1534, 1481, 1445, 1379, 1208, 1007 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.86 (q, *J* = 7.2 Hz, 4H), 2.86 (s, 6H), 1.62 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0, 137.9, 107.6, 43.5, 15.3, 15.0; HRMS (ESI) exact mass calculated for $C_{12}H_{16}N_6$ $[M + H]^+$: 245.1515; found: 245.1514.
 **2l**	**1,8-Di-tert-butyl-3,6-dimethyl-3,6-dihydrodipyrazolo[3,4-*c*:4',3'-*e*]pyridazine (2l):** Light yellow solid; M. P. 156-158 °C R_f = 0.75 (hexane/EtOAc, 9.5:0.5), Yield 85 %, 53 mg; IR (KBr): 2921, 1721, 1543, 1434, 1400, 1268, 1158, 966 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.15 (s, 6H), 1.62 (s, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 142.7, 131.0, 33.9, 33.8, 29.3; HRMS (ESI) exact mass calculated for $C_{16}H_{24}N_6$ $[M + H]^+$: 301.2141; found: 301.2138.
 **3a**	**(*E*)-1,2-Bis(1-phenyl-1*H*-pyrazol-5-yl)diazene (3a):** Yellow solid; M. P. 115-116 °C; R_f = 0.75 (hexane/EtOAc, 9.5:0.5), Yield 66 %, 52 mg; IR (KBr): 3409, 1596, 1499, 1395, 1320, 1214, 1131, 1071, 761, 676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.74-7.72 (m, 6H), 7.54-7.50 (m, 4H), 7.45-7.41 (m, 2H), 6.63 (d, *J* = 1.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 140.6, 138.9, 128.8, 127.9, 125.0, 95.3; HRMS (ESI) exact mass calculated for $C_{18}H_{14}N_6$ $[M + H]^+$: 315.1358; found: 315.1355.

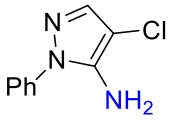
 **3b**	**(*E*)-1,2-Bis(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)diazene (3b):**[4] Yellow solid; M. P. 197-198 °C; R_f = 0.70 (hexane/EtOAc, 9.5:0.5), Yield 72 %, 62 mg; IR (KBr): cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.71-7.68 (m, 4H), 7.52-7.48 (m, 4H), 7.42-7.38 (m, 2H), 6.40 (s, 2H), 2.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 149.9, 139.0, 128.8, 127.5, 124.8, 94.6, 14.0; HRMS (ESI) exact mass calculated for $C_{20}H_{18}N_6$ $[M + H]^+$: 343.1671; found: 343.1667.

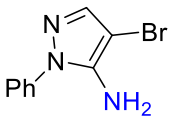
 **3c**	**(*E*)-1,2-Bis(1-ethyl-1*H*-pyrazol-5-yl)diazene (3c):** Yellow solid; M. P. 83-84 °C; R_f = 0.75 (hexane/EtOAc, 9.5:0.5), Yield 70 %, 38 mg; IR (KBr): 3115, 1501, 1465, 1318, 1244, 1199, 1056, 925, 818, 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 2.5 Hz, 2H), 6.55 (d, *J* = 1.8 Hz, 2H), 4.60 (q, *J* = 7.3 Hz, 4H), 1.54 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8, 139.2, 93.8, 44.2, 15.8; HRMS (ESI) exact mass calculated for $C_{10}H_{14}N_6$ $[M + H]^+$: 219.1358; found: 219.1355.

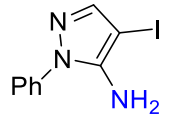
 **3d**	**(*E*)-1,2-Bis(3-methyl-1-(*p*-tolyl)-1*H*-pyrazol-5-yl)diazene (3d):** Yellow solid; M. P. 177-178 °C; R_f = 0.70 (hexane/EtOAc, 9.5:0.5), Yield 63 %, 58 mg; IR (KBr): 2920, 1515, 1438, 1347, 1175, 1137, 821, 793 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.57-7.55 (m, 4H), 7.30-7.28 (m, 4H), 6.37 (s, 2H), 2.43 (s, 6H), 2.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 149.7, 137.4, 136.6, 129.3, 124.7, 94.4, 21.1, 14.0; HRMS (ESI) exact mass calculated for $C_{22}H_{22}N_6$ $[M + H]^+$: 371.1984; found: 371.1981.

 **3e**	**(*E*)-1,2-Bis(1-(4-fluorophenyl)-3-methyl-1*H*-pyrazol-5-yl)diazene (3e):** Yellow solid; M. P. 227-228 °C; R_f = 0.75 (hexane/EtOAc, 9.5:0.5), Yield 61 %, 58 mg; IR (KBr): 1512, 1447, 1225, 1181, 830, 793 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68-7.64 (m, 4H), 7.21-7.17 (m, 4H), 6.37 (s, 2H), 2.38 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8 (d, *J* = 247.6 Hz), 154.1, 150.1, 135.1 (d, *J* = 2.9 Hz), 126.5 (d, *J* = 8.2 Hz), 116.7 (d, *J* = 22.6 Hz), 94.6, 14.0; HRMS (ESI) exact mass calculated for $C_{20}H_{16}N_6F_2$ $[M + H]^+$: 379.1483; found: 379.1484.

 **3f**	**(*E*)-1,2-Bis(3-methyl-1-(*o*-tolyl)-1*H*-pyrazol-5-yl)diazene (3f):** Light yellow solid; M. P. 156-157 °C, R_f = 0.70 (hexane/EtOAc, 9.5:0.5), Yield 65 %, 60 mg; IR (KBr): 2926, 1526, 1498, 1463, 1176, 1135, 1030, 778, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.34 (m, 2H), 7.31-7.26 (m, 6H), 6.22 (s, 2H), 2.32 (s, 6H), 2.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 149.6, 137.9, 135.4, 130.7, 128.9, 128.0, 126.1, 93.7, 17.9, 13.9; HRMS (ESI) exact mass calculated for $C_{22}H_{22}N_6$ $[M + H]^+$: 371.1984; found: 371.1980.

 **4a**	**4-Chloro-1-phenyl-1*H*-pyrazol-5-amine (4a):** White solid; M. P. 107-108 °C R_f = 0.40 (hexane/EtOAc, 5:1), Yield 76 %, 74 mg; IR (KBr): 3399, 1616, 1489, 1454, 1219, 843, 770, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.56-7.54 (m, 2H), 7.51-7.47 (m, 2H), 7.43-7.42 (m, 1H), 7.39-7.36 (m, 1H), 3.91 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.0, 138.6, 137.8, 129.6, 127.8, 123.4, 93.4; HRMS (ESI) exact mass calculated for $C_9H_8ClN_3$ $[M + H]^+$: 194.0485; found: 194.0481.

 **4b**	**4-Bromo-1-phenyl-1*H*-pyrazol-5-amine (4b):** White solid; M. P. 118-119 °C; R_f = 0.40 (hexane/EtOAc, 5:1), Yield 78 %, 93 mg; IR (KBr): 3396, 1615, 1454, 1407, 843, 762, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.57-7.54 (m, 2H), 7.52-7.49 (m, 2H), 7.45-7.44 (m, 1H), 7.40-7.36 (m, 1H), 3.94 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 138.6, 137.9, 129.6, 127.9, 123.5, 77.5; HRMS (ESI) exact mass calculated for $C_9H_8BrN_3$ $[M + H]^+$: 237.9980; found: 237.9979.

 **4c**	**4-Iodo-1-phenyl-1*H*-pyrazol-5-amine (4c):** White solid; M. P. 124-125 °C; R_f = 0.42 (hexane/EtOAc, 5:1), Yield 75 %, 107 mg; IR (KBr): 3392, 1612, 1556, 1453, 1404, 1284, 844, 760, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52-7.46 (m, 4H), 7.42 (m, 1H), 7.38-7.35 (m, 1H), 3.99 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.2, 143.4, 138.5, 129.5, 127.8, 123.6, 41.8; HRMS (ESI) exact mass calculated for $C_9H_8IN_3$ $[M + H]^+$: 285.9841; found: 285.9837.

References

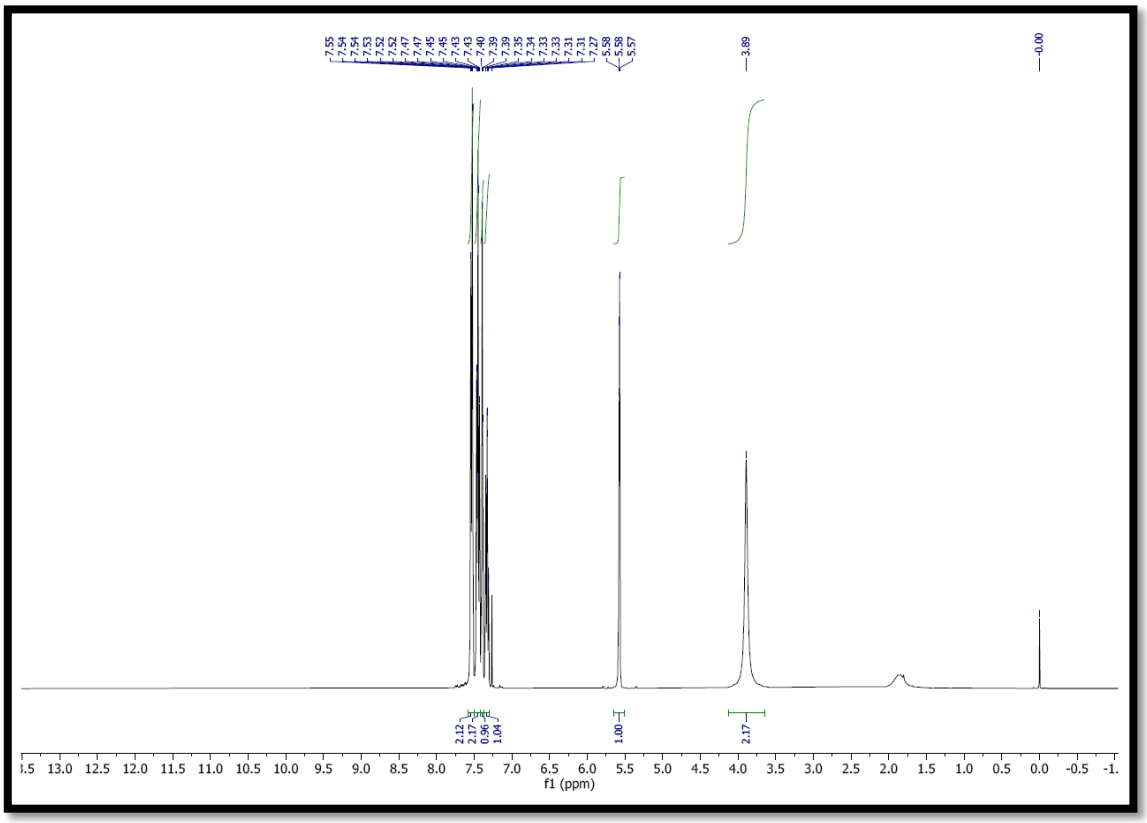
1. T. B. Silva, A. M. R. Bernardino, M. de L. G. Ferreira, K. R. Rogerio, L. J. M. Carvalho, N. Boechat and L. C. S. Pinheiro, *Bioorganic & Medicinal Chemistry*, 2016, **24**, 4492 - 4498.

2. Y. Li, X. Huang, J. He, S. Peng, J. Wang, M. Lang, *Adv. Synth. Catal.*, 2023, **365**, 490 - 495.

3. M-F Zou, J. Cao, A. L. Rodriguez, P. J. Conn and A. H. Newman, *Bioorganic & Medicinal Chemistry Letters*, 2011**, 21**, 2650 - 2654.

4. I. Rahman, B. Deka, R. Thakuria, M. L. Deb and P. K. Baruah, *Org. Biomol. Chem.*, 2020, **18**, 6514 - 6518.

^{1}H NMR 1a



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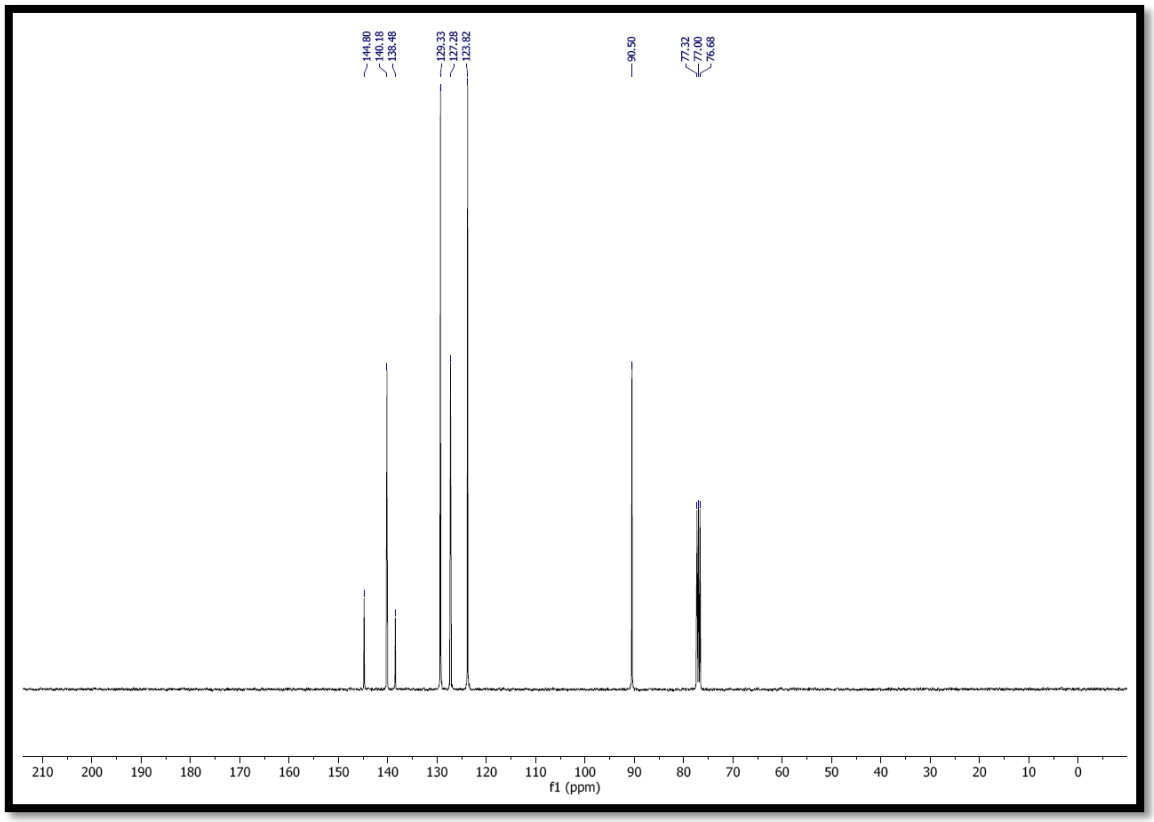

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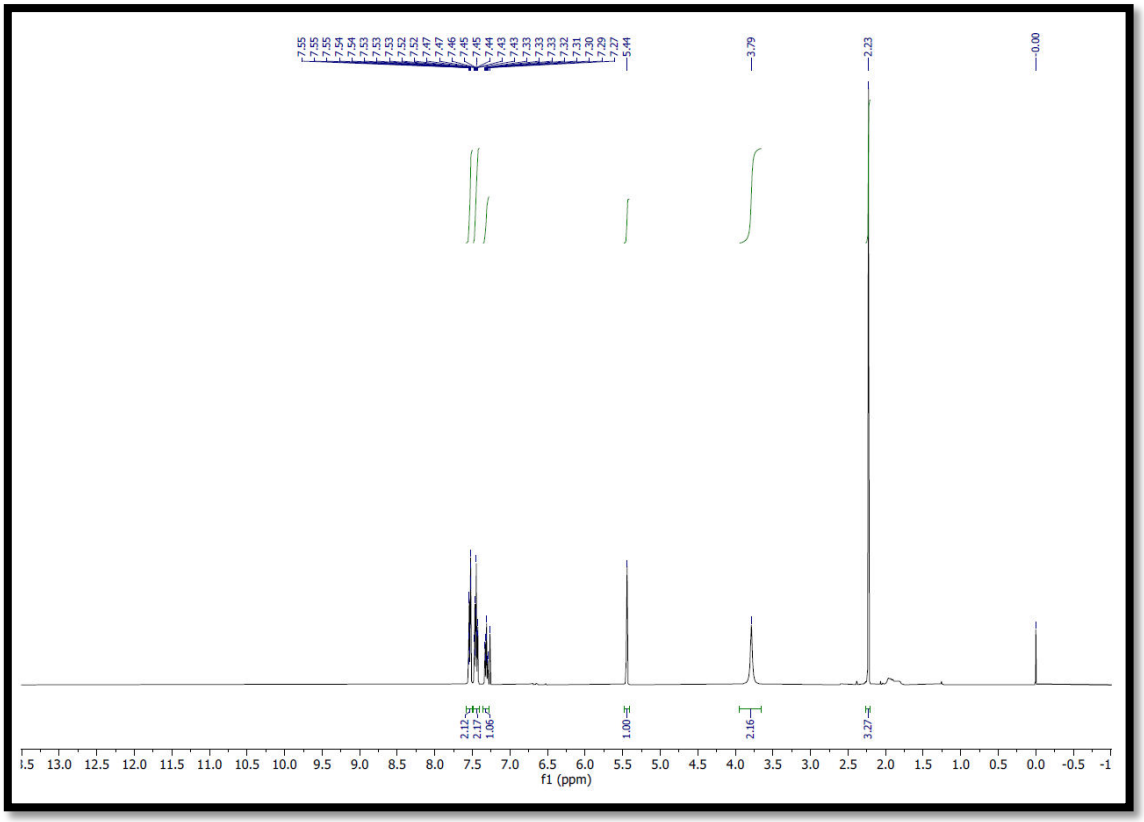

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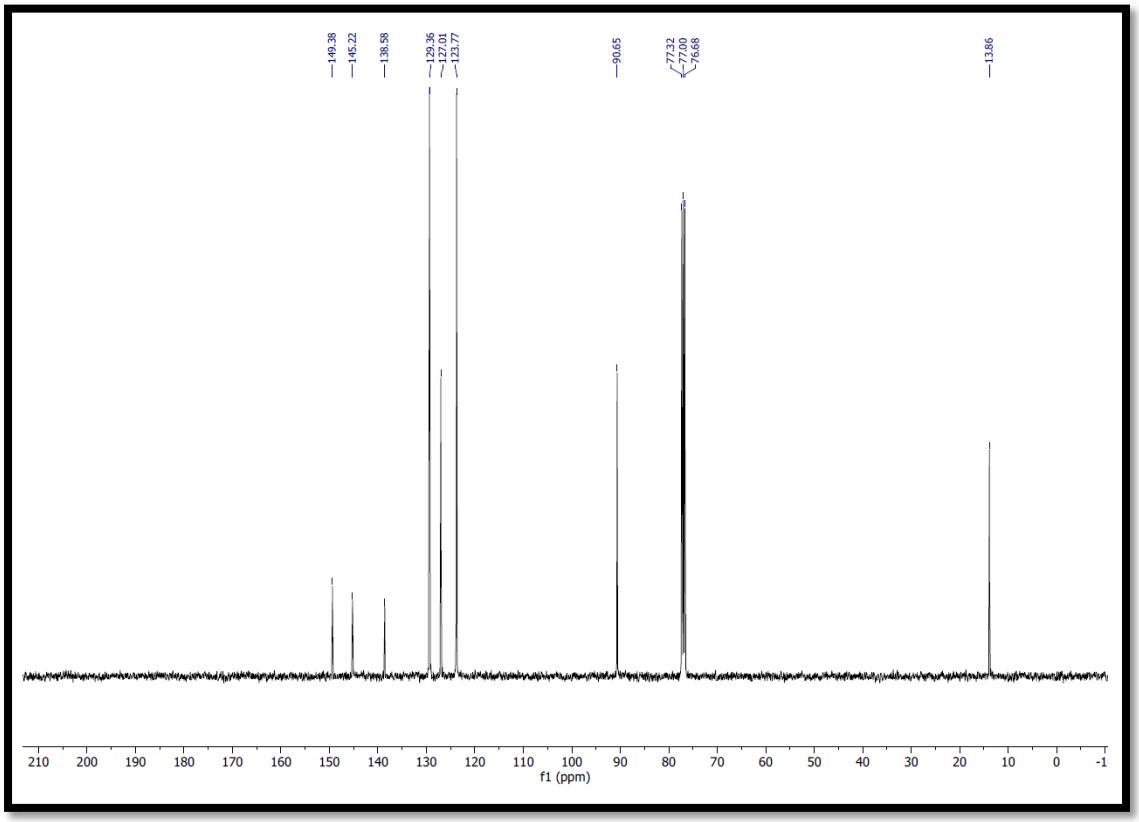

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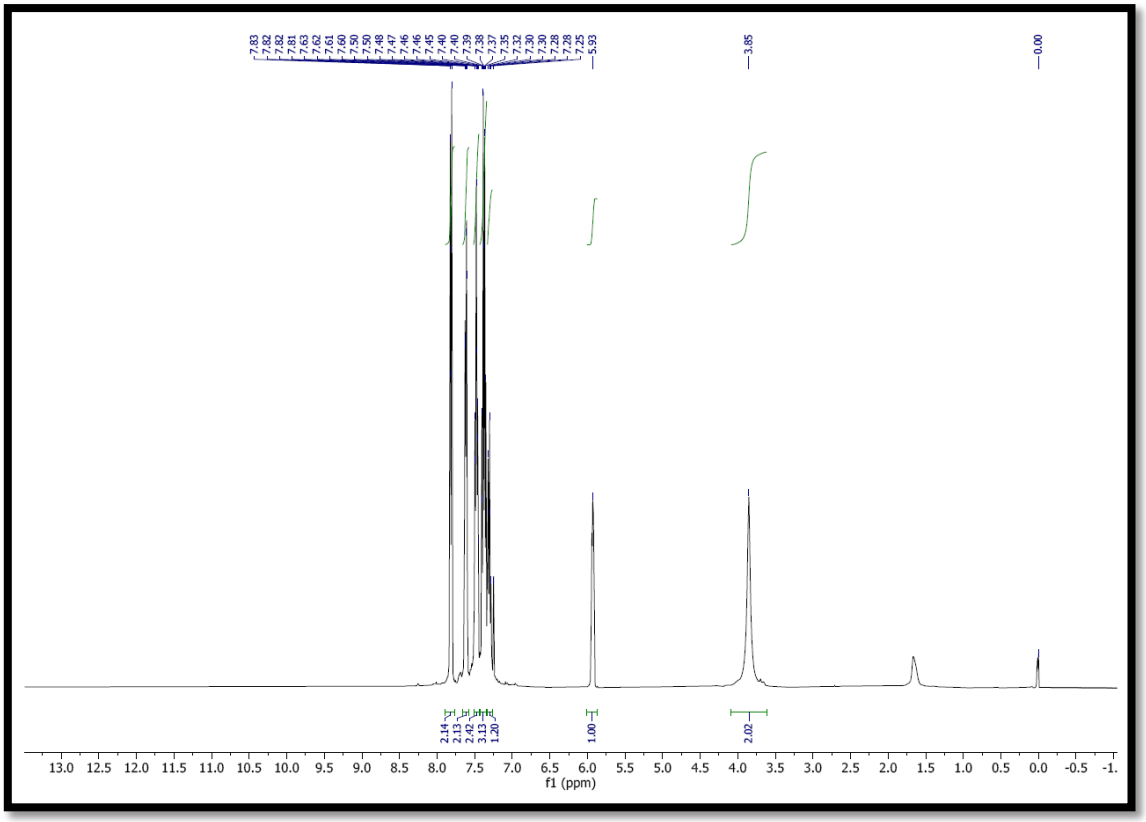

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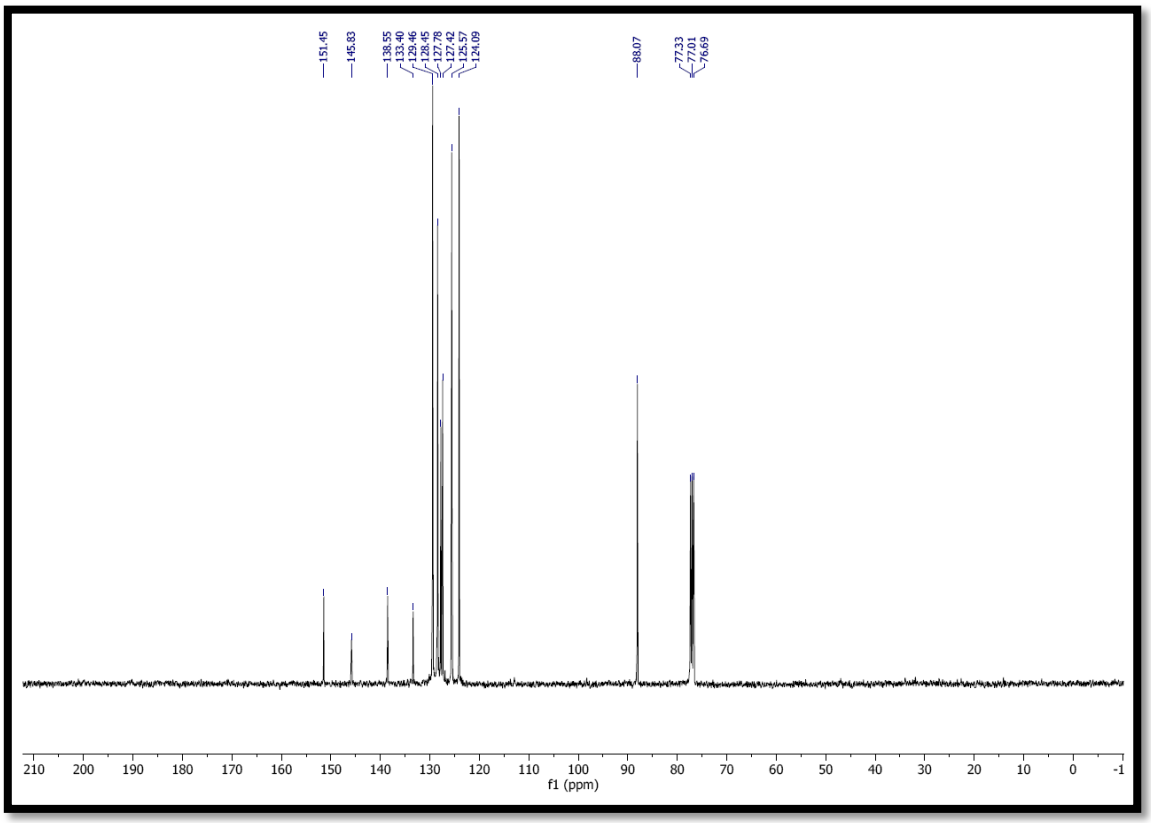

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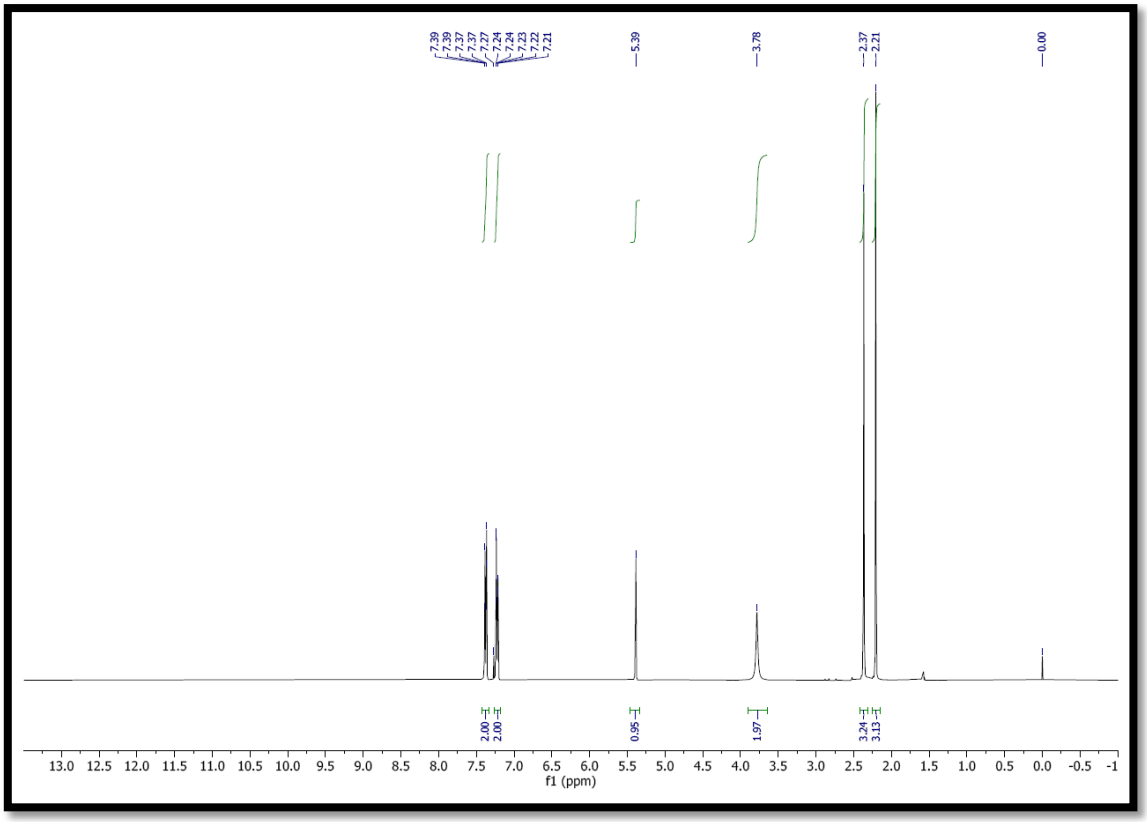

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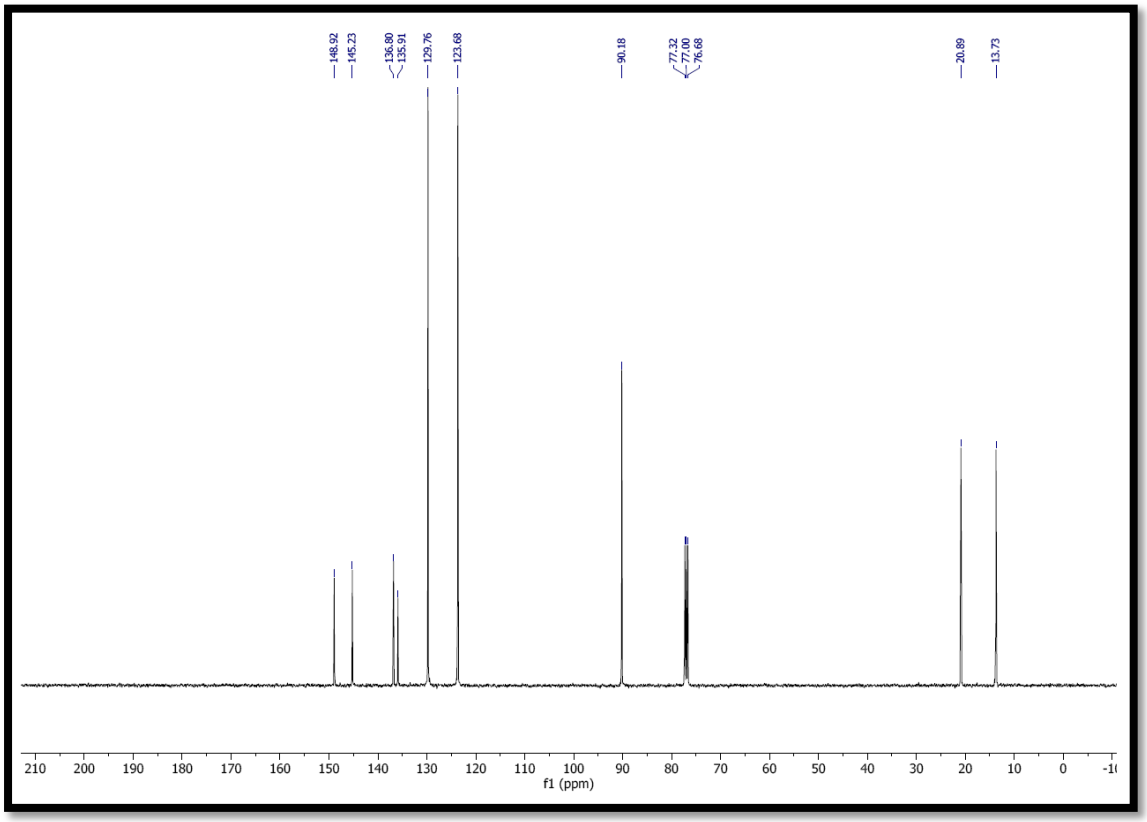

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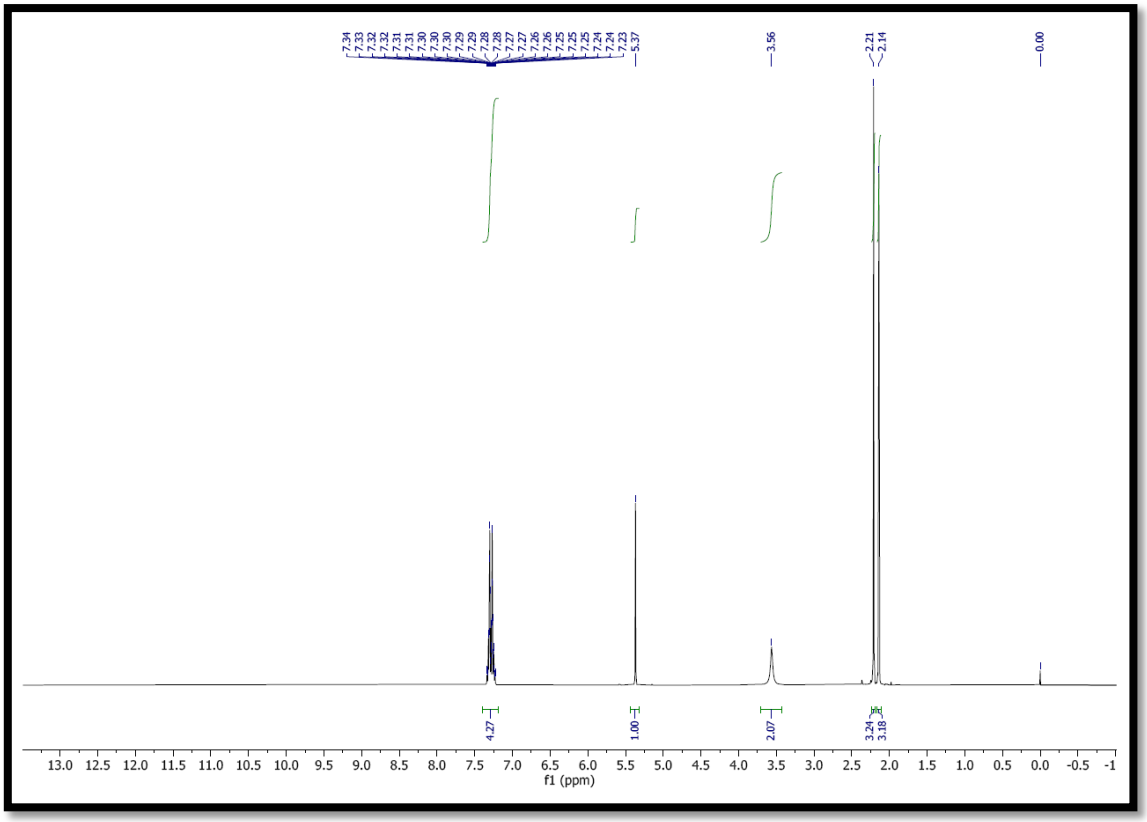

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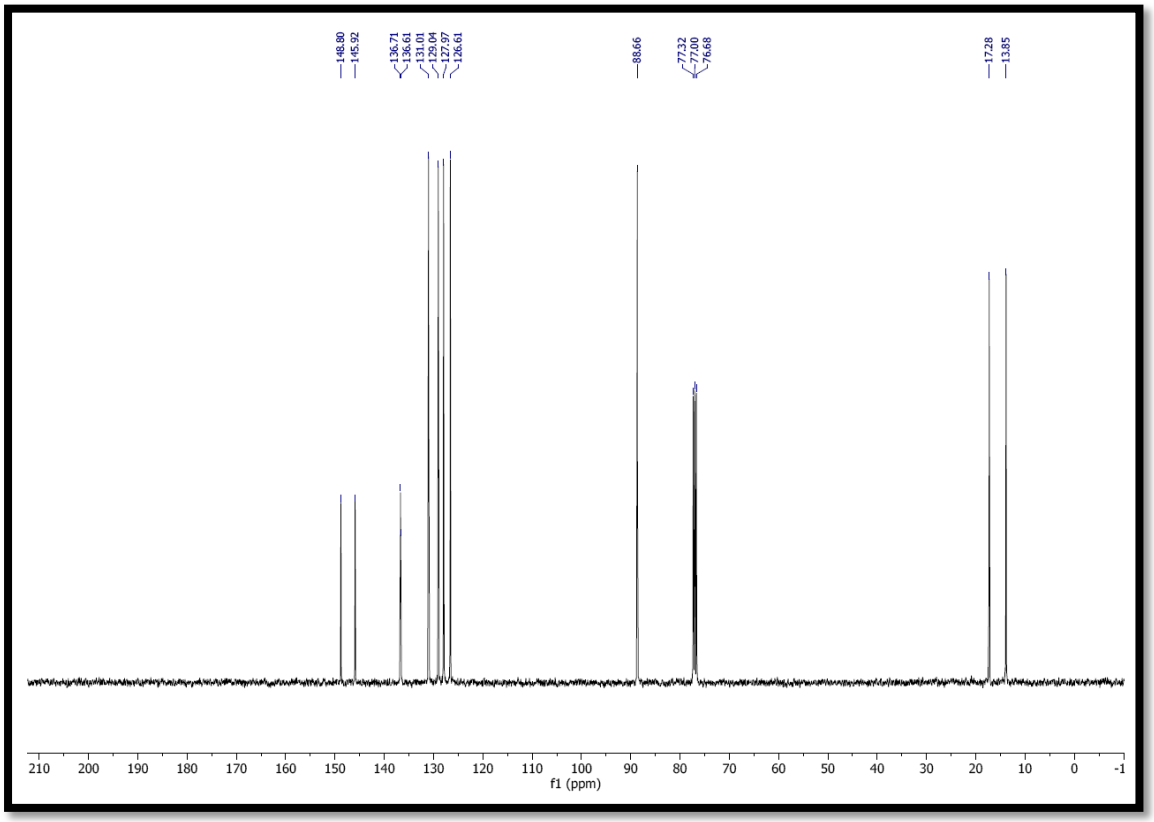

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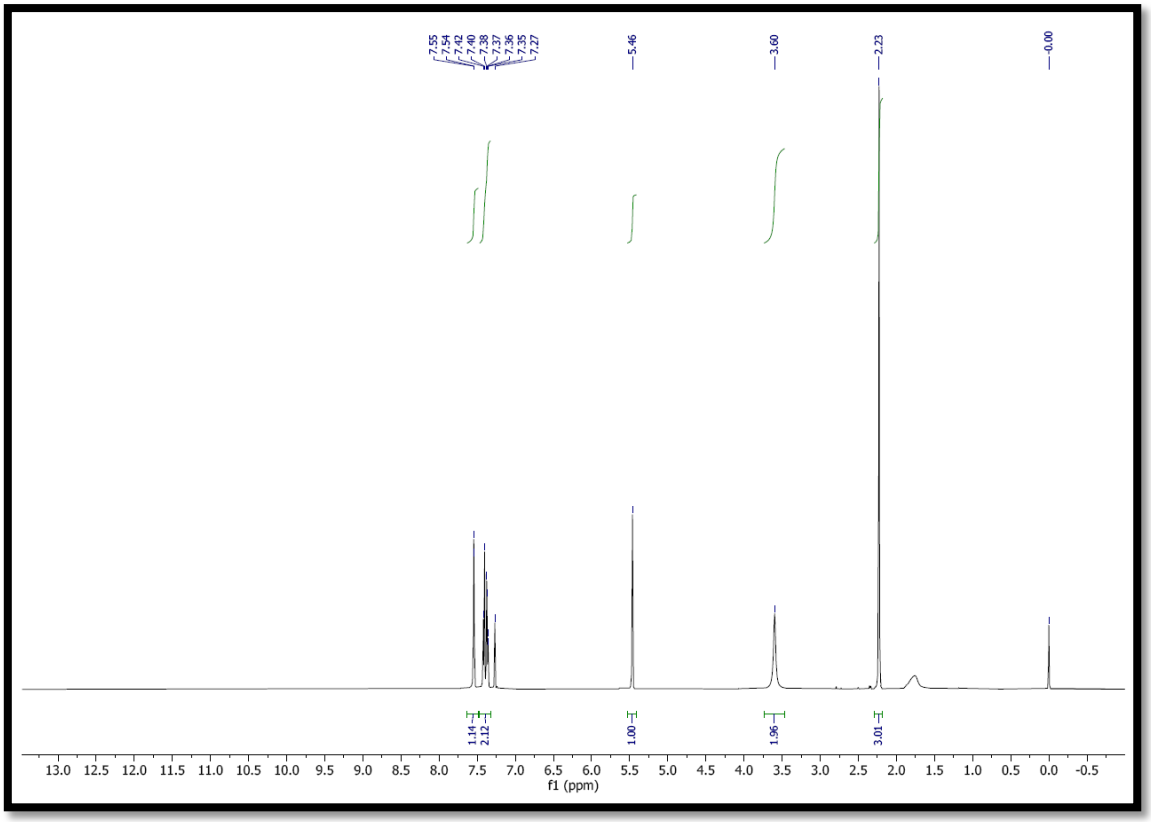

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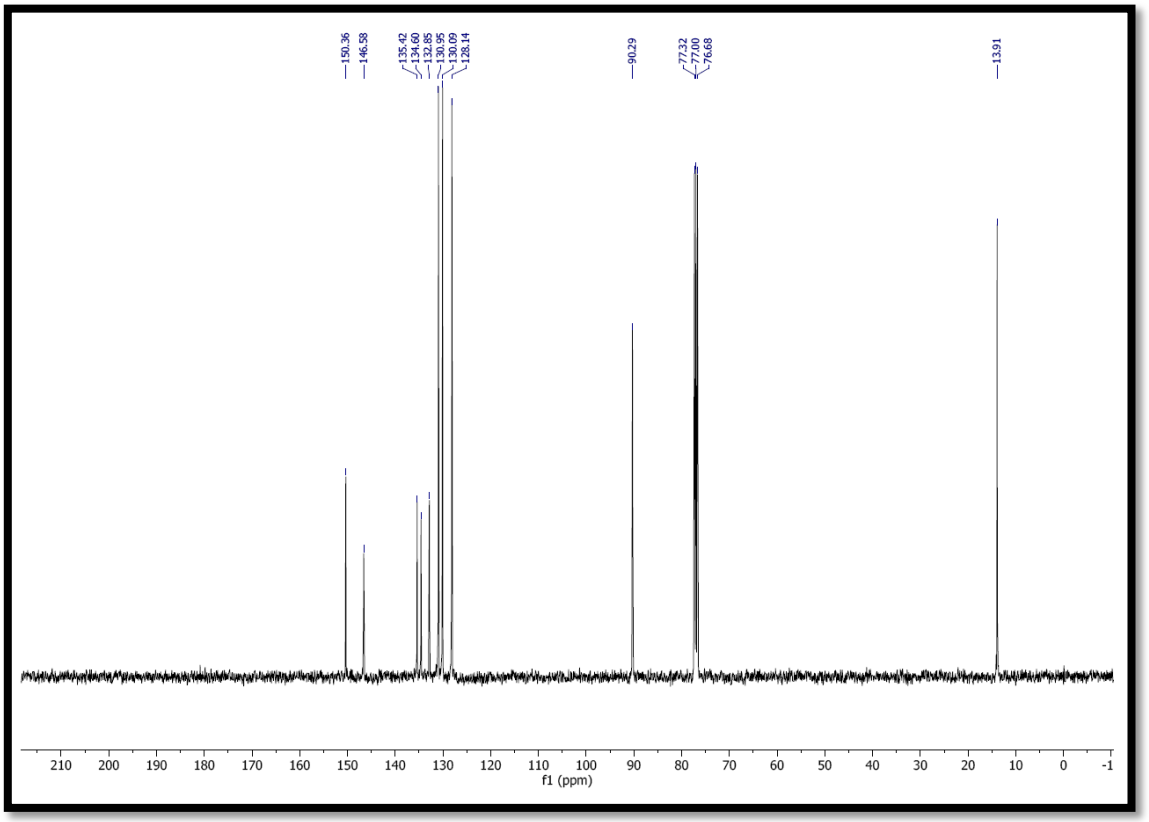

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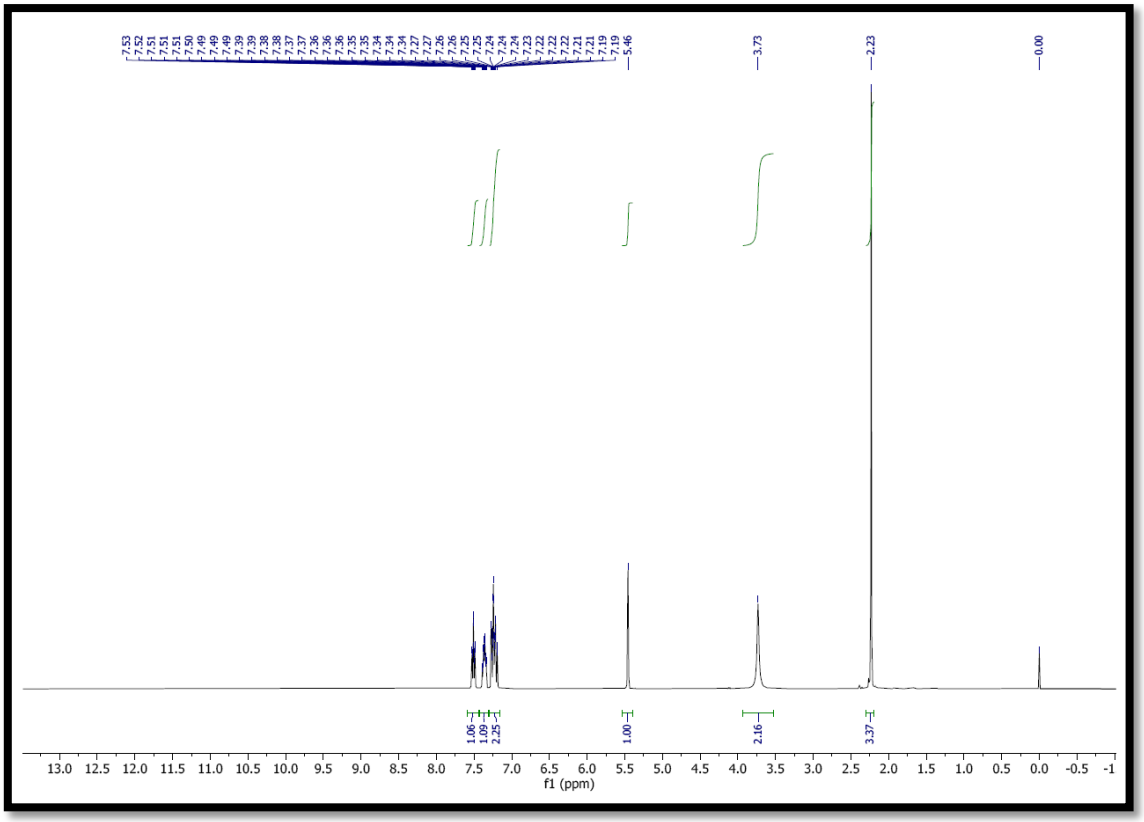

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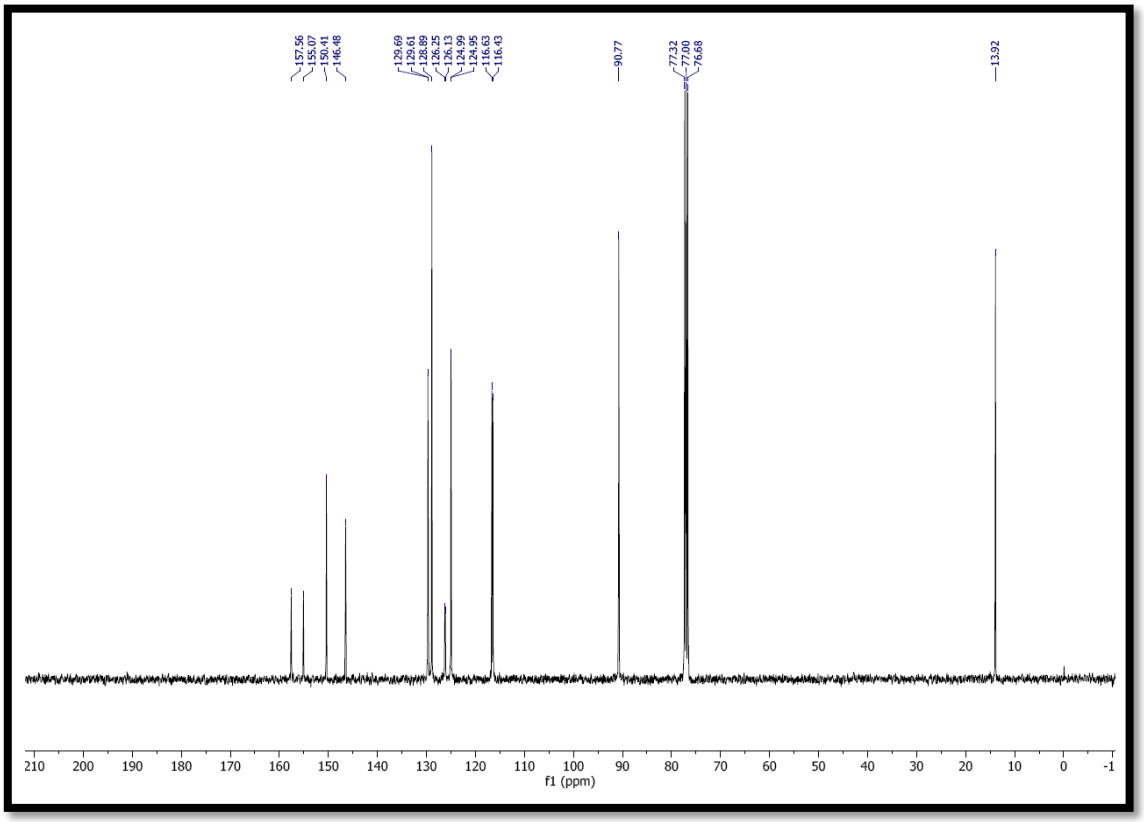

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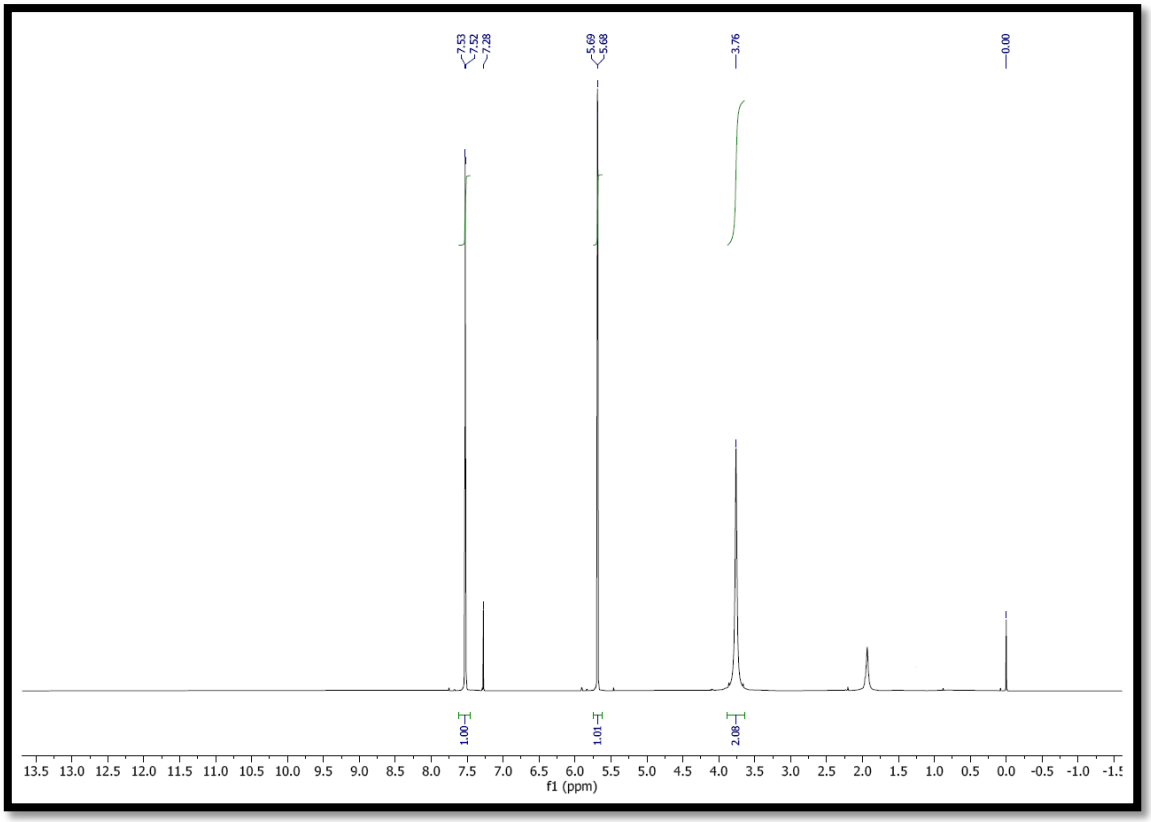

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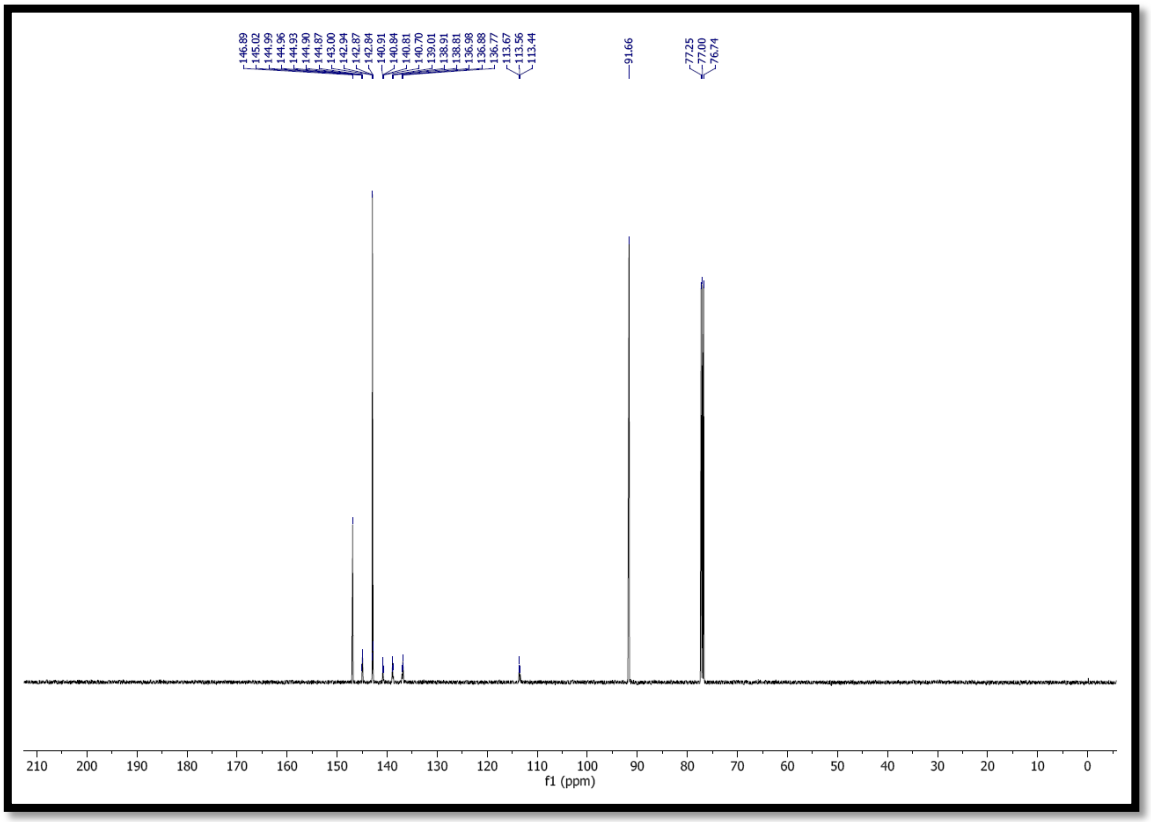

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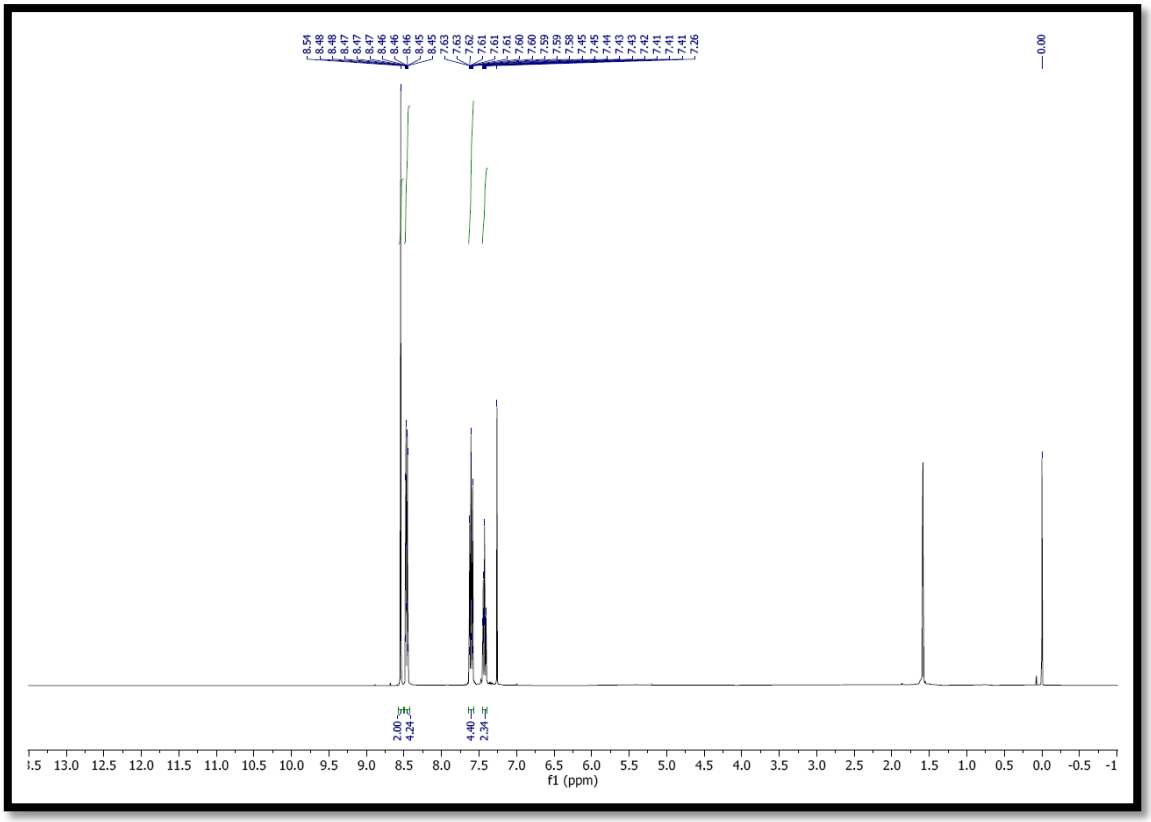

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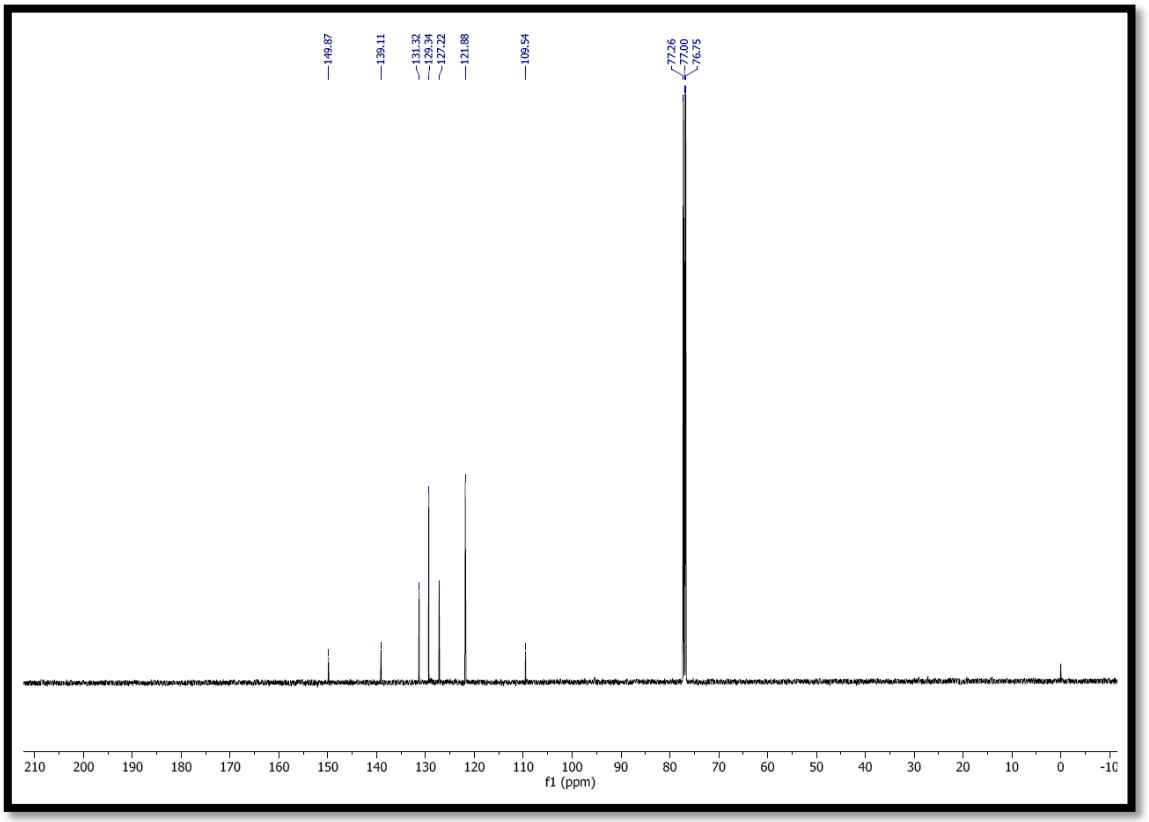

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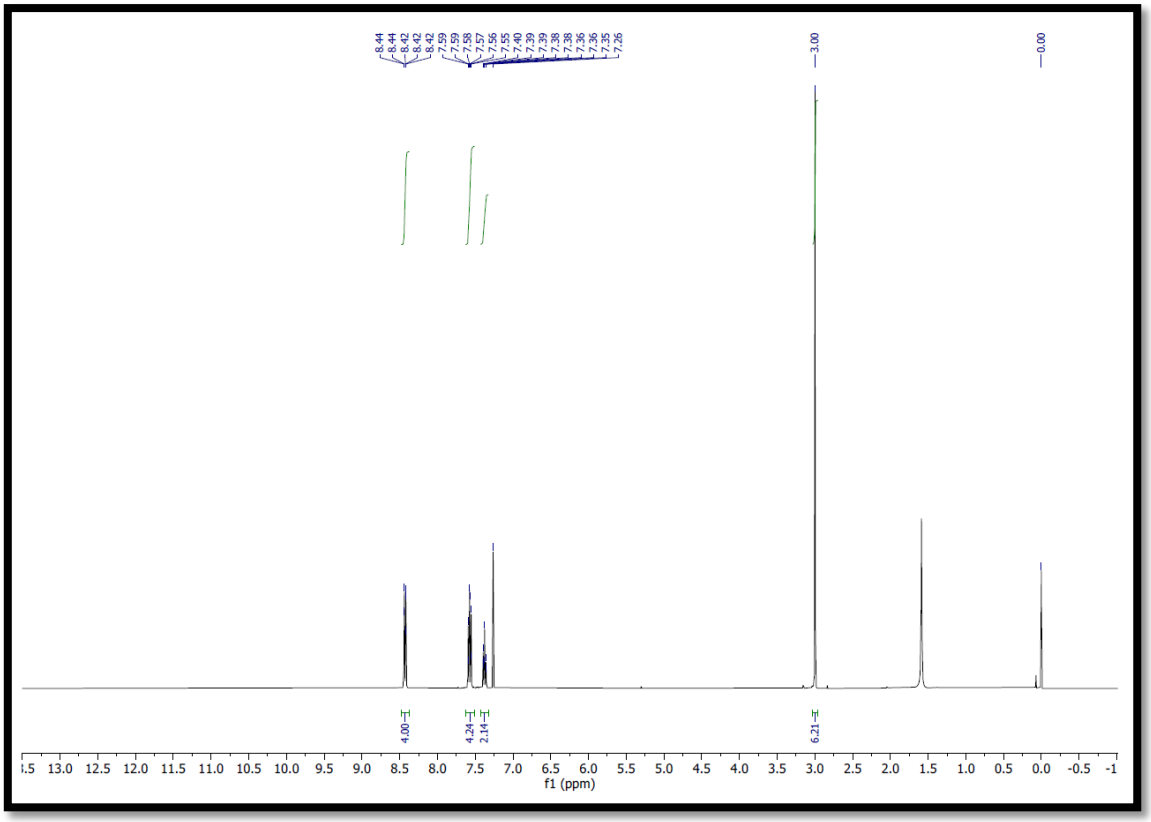

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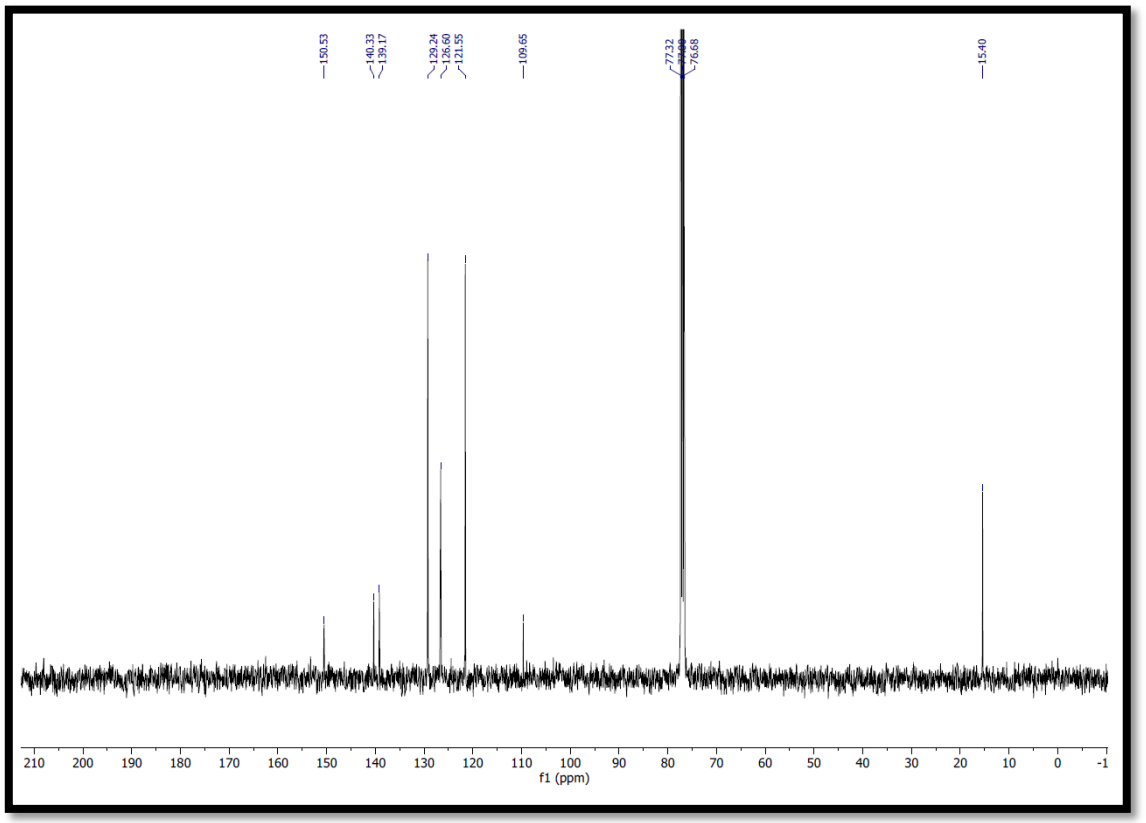

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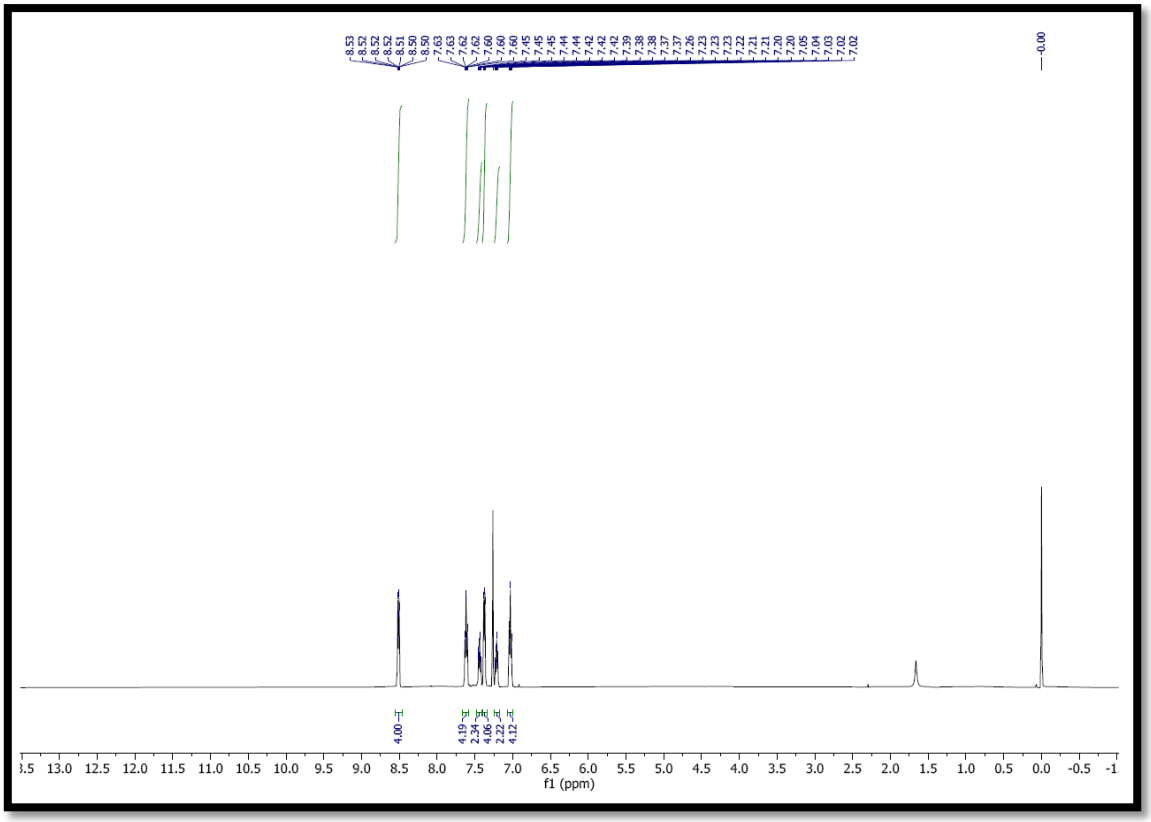

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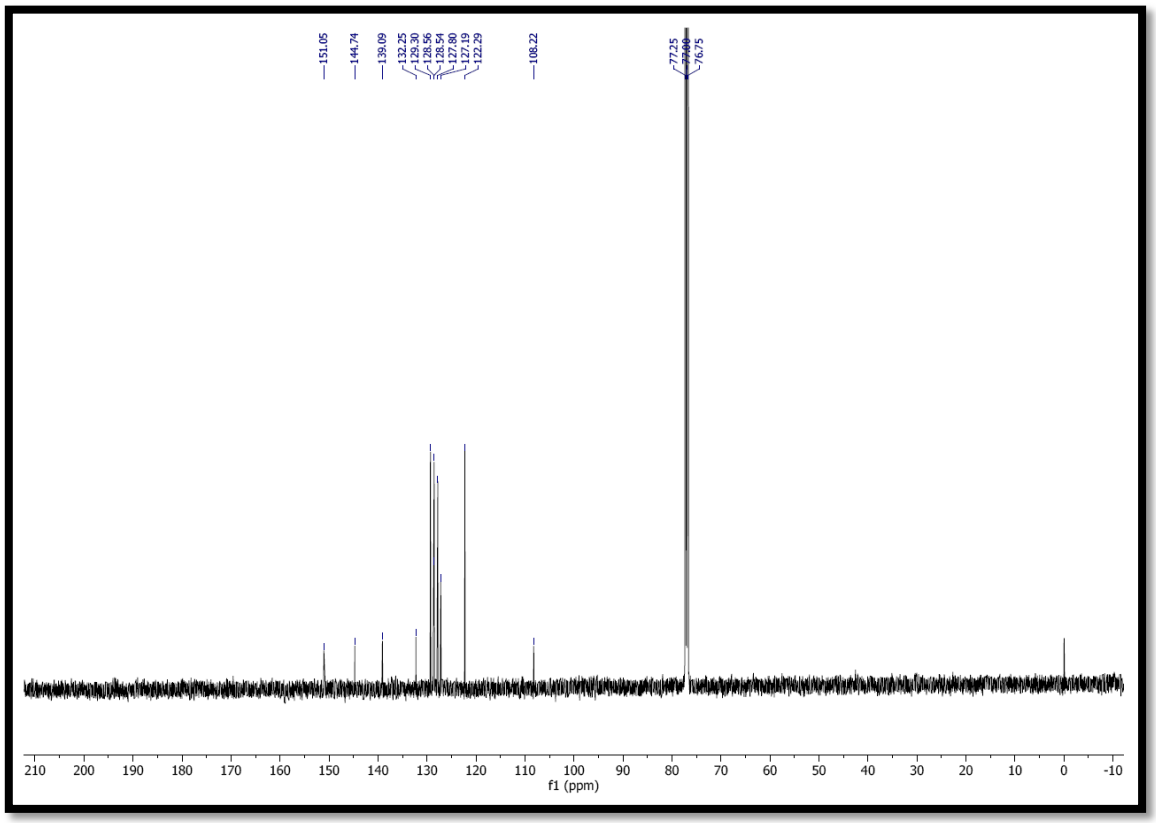

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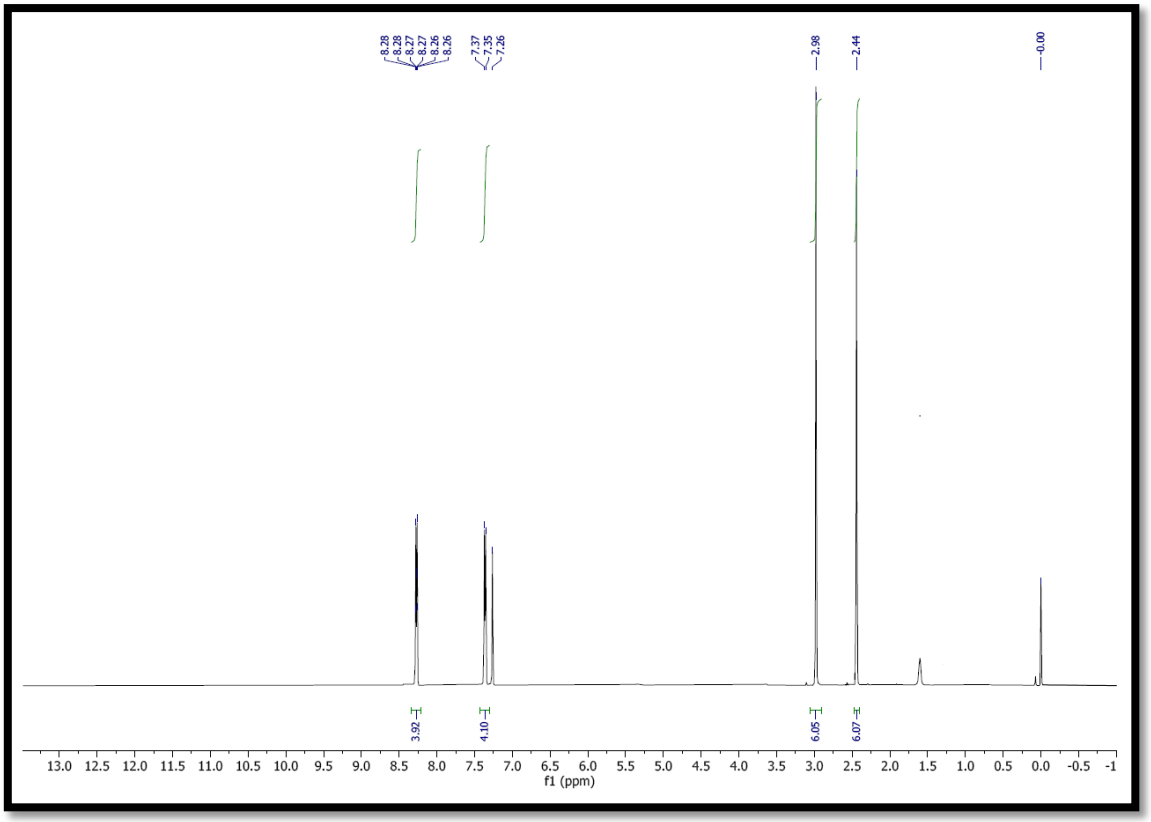

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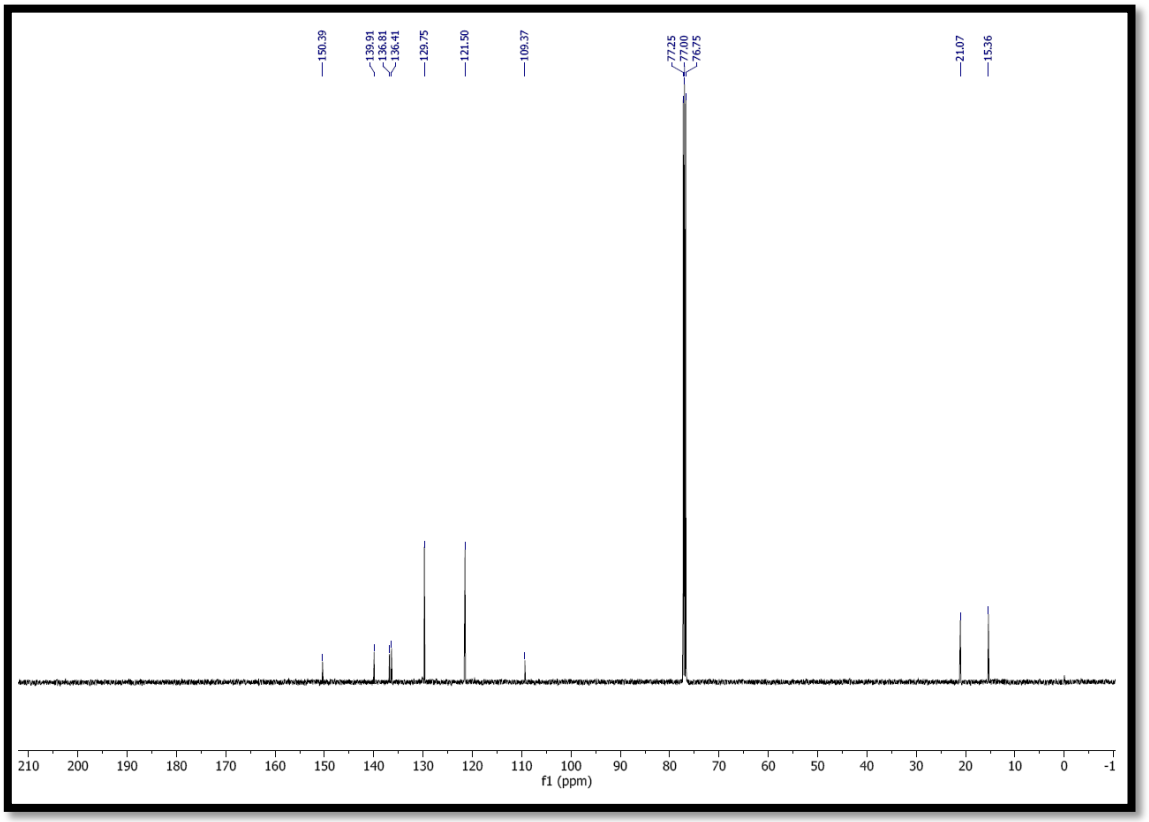

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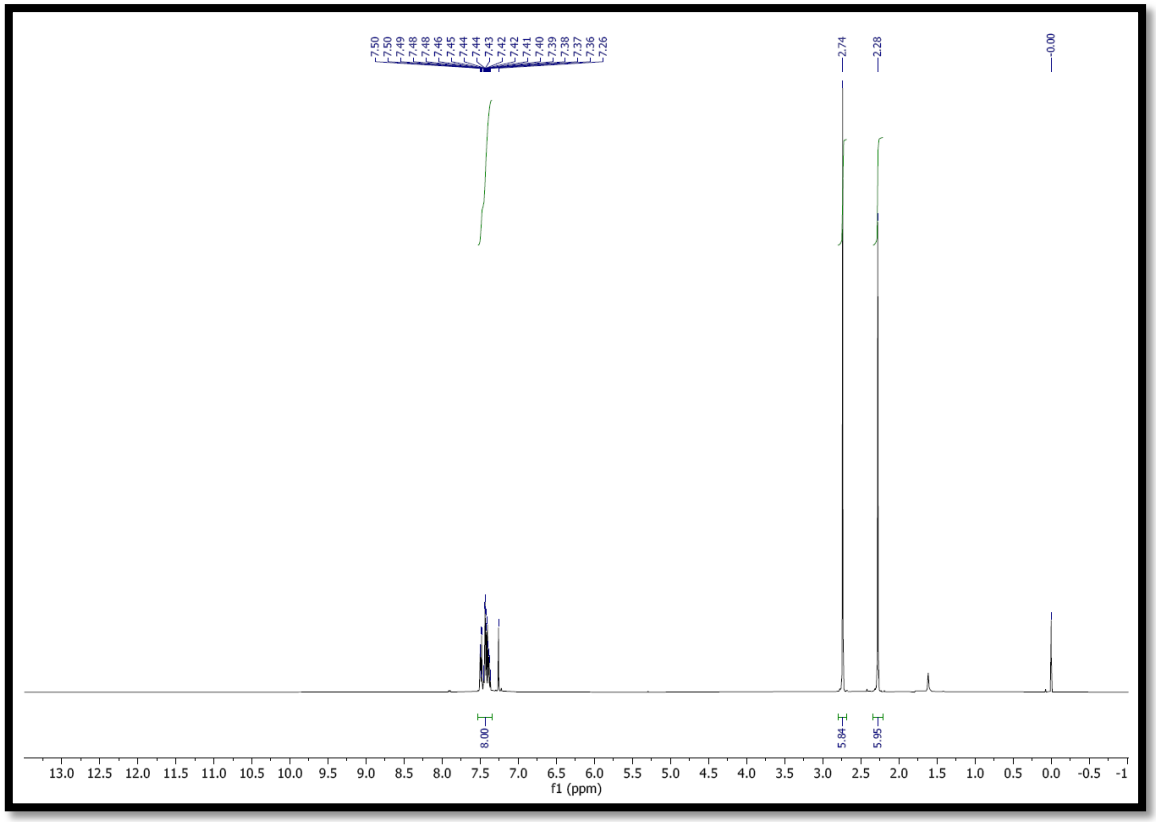

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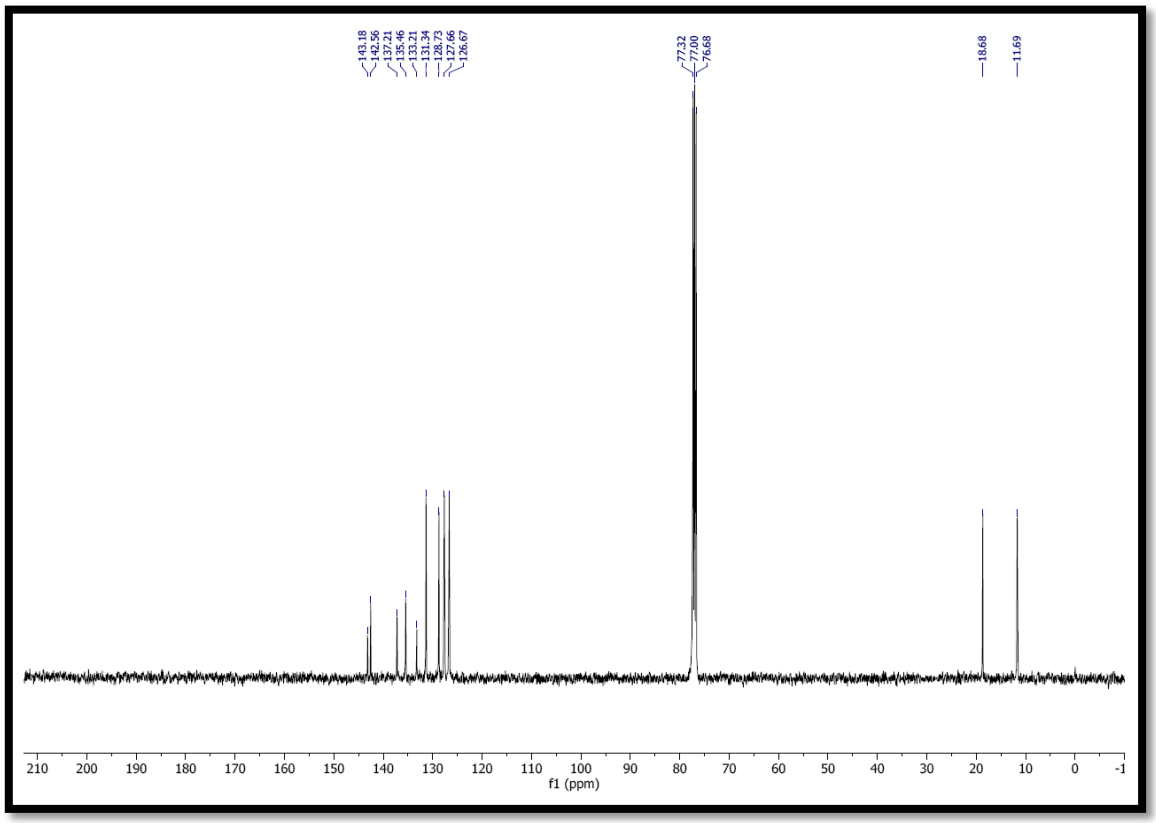

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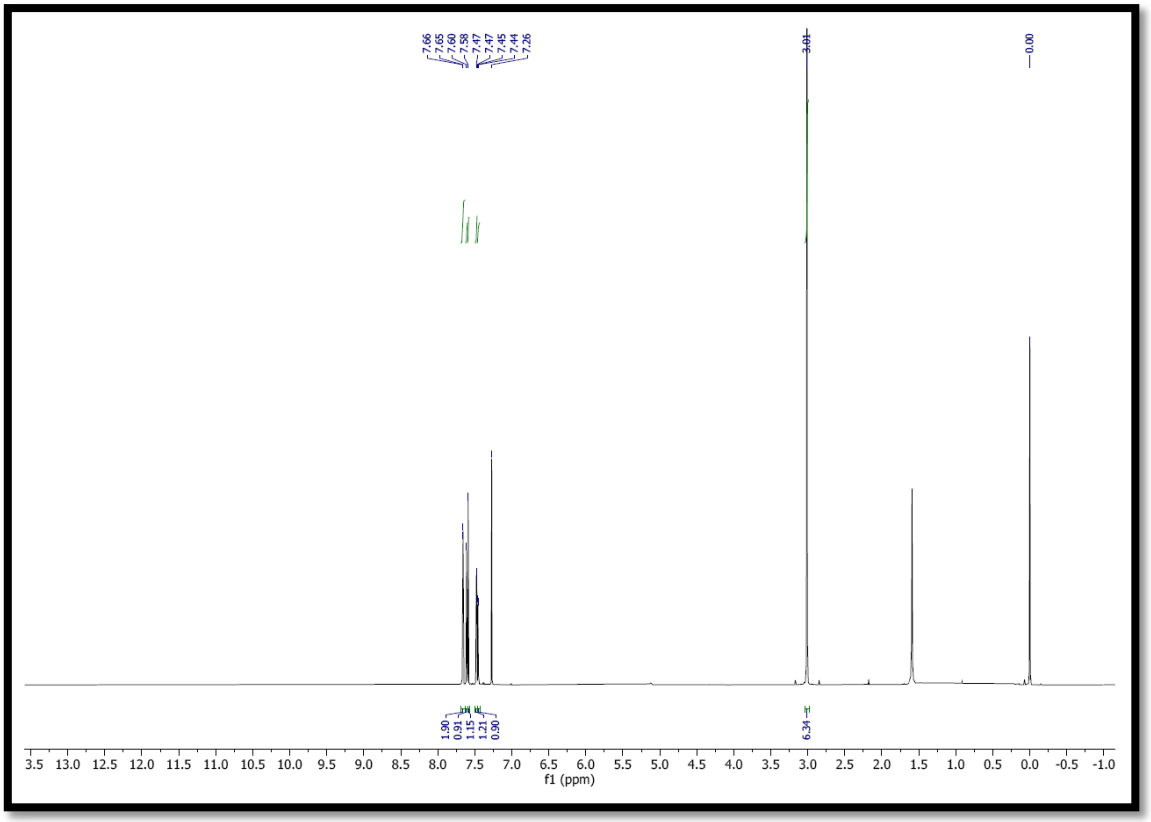

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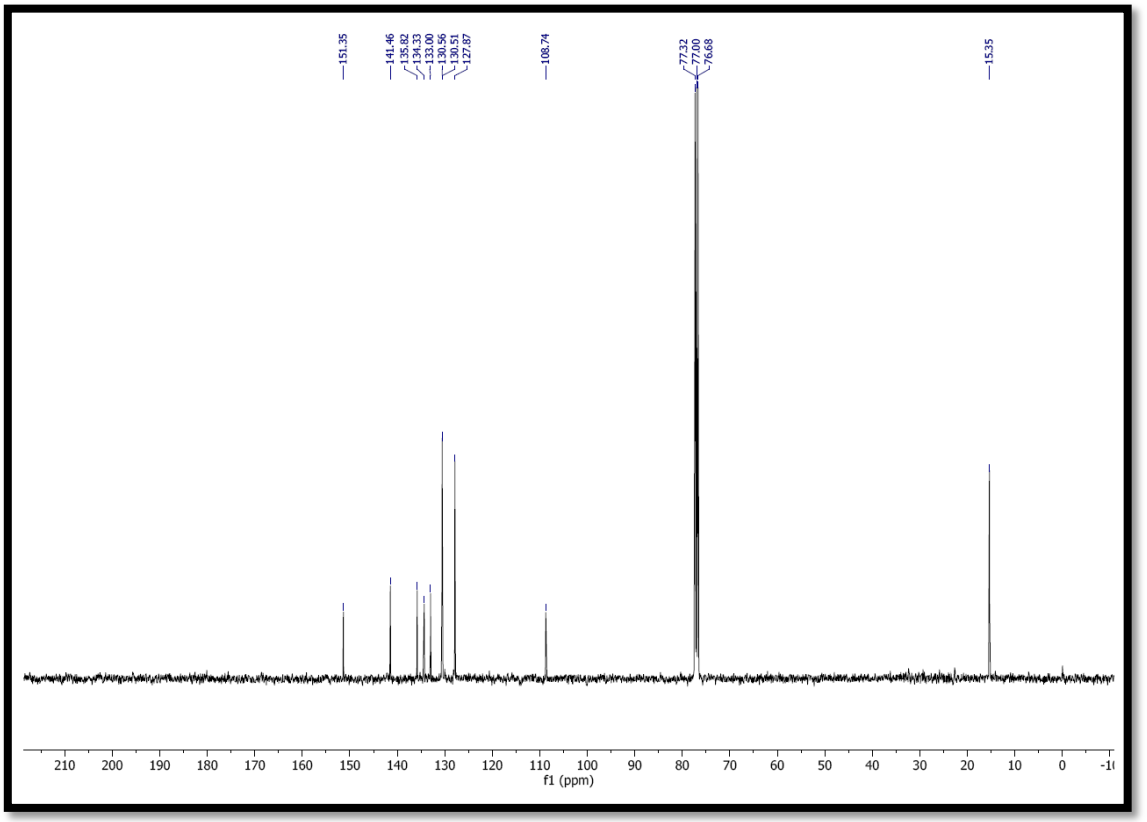

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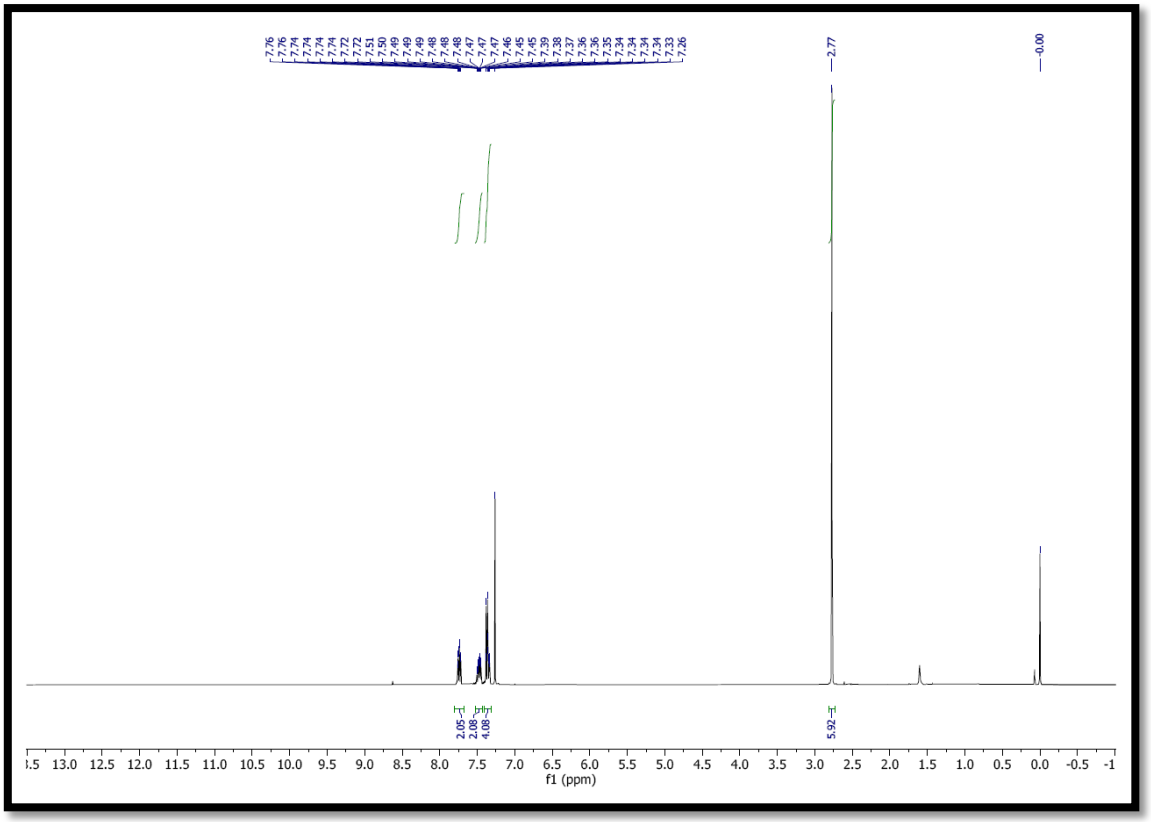

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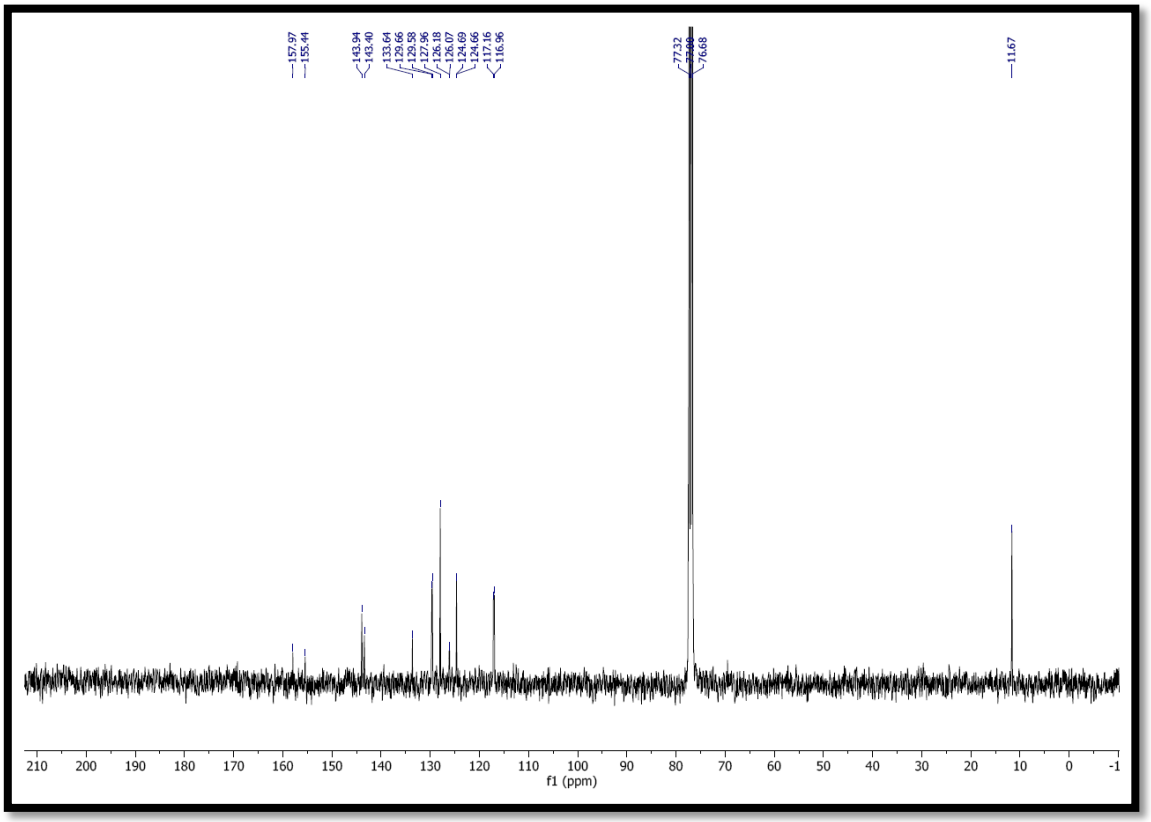

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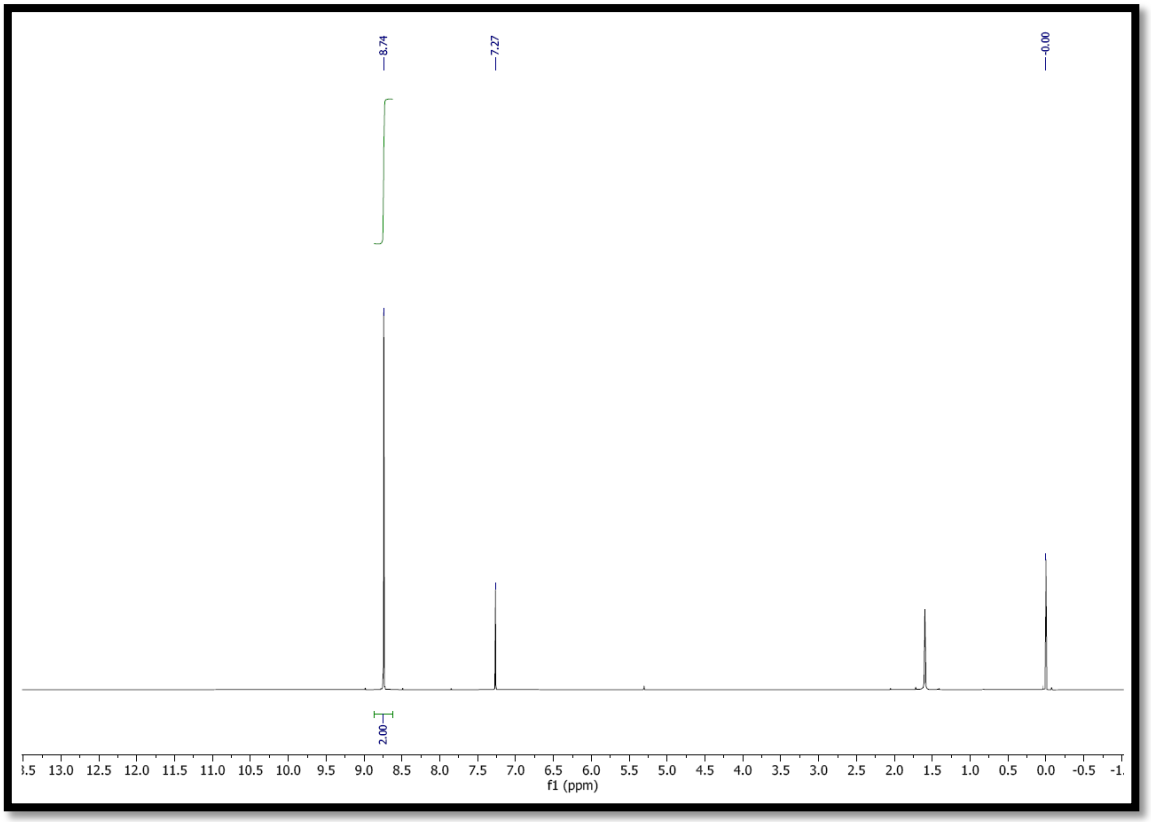

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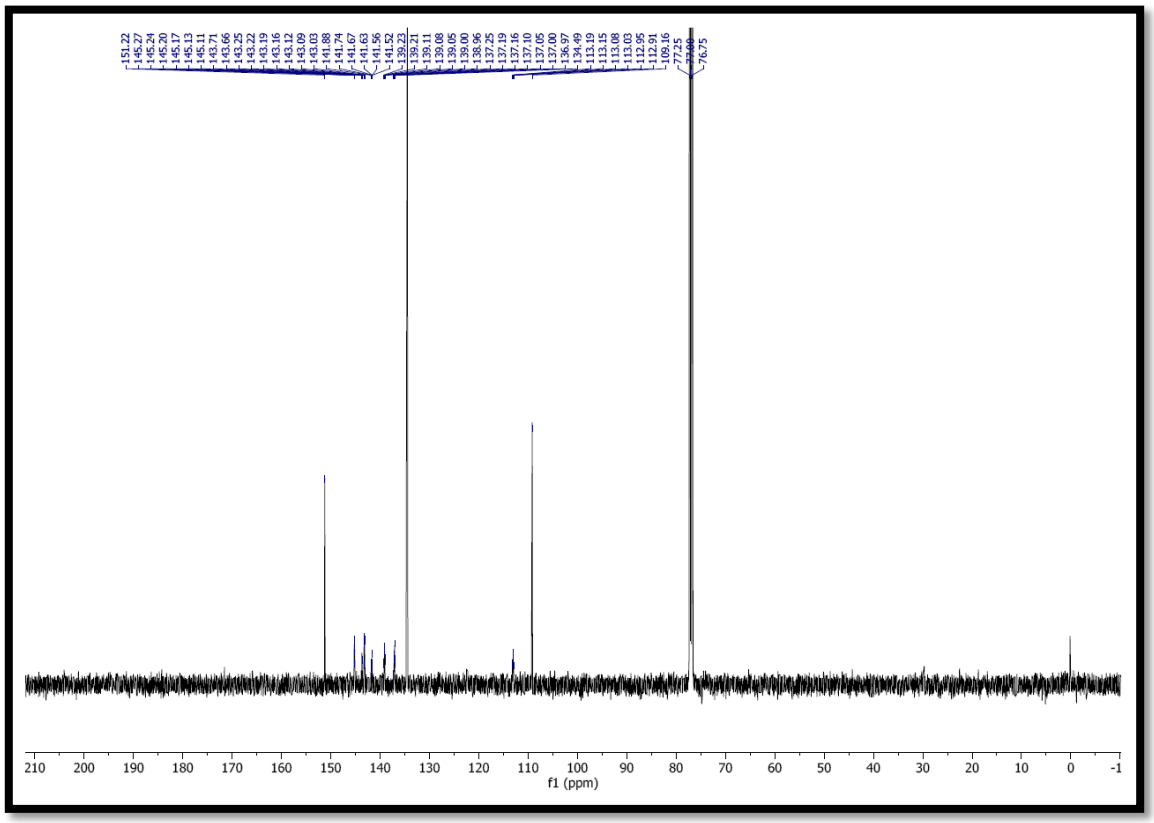

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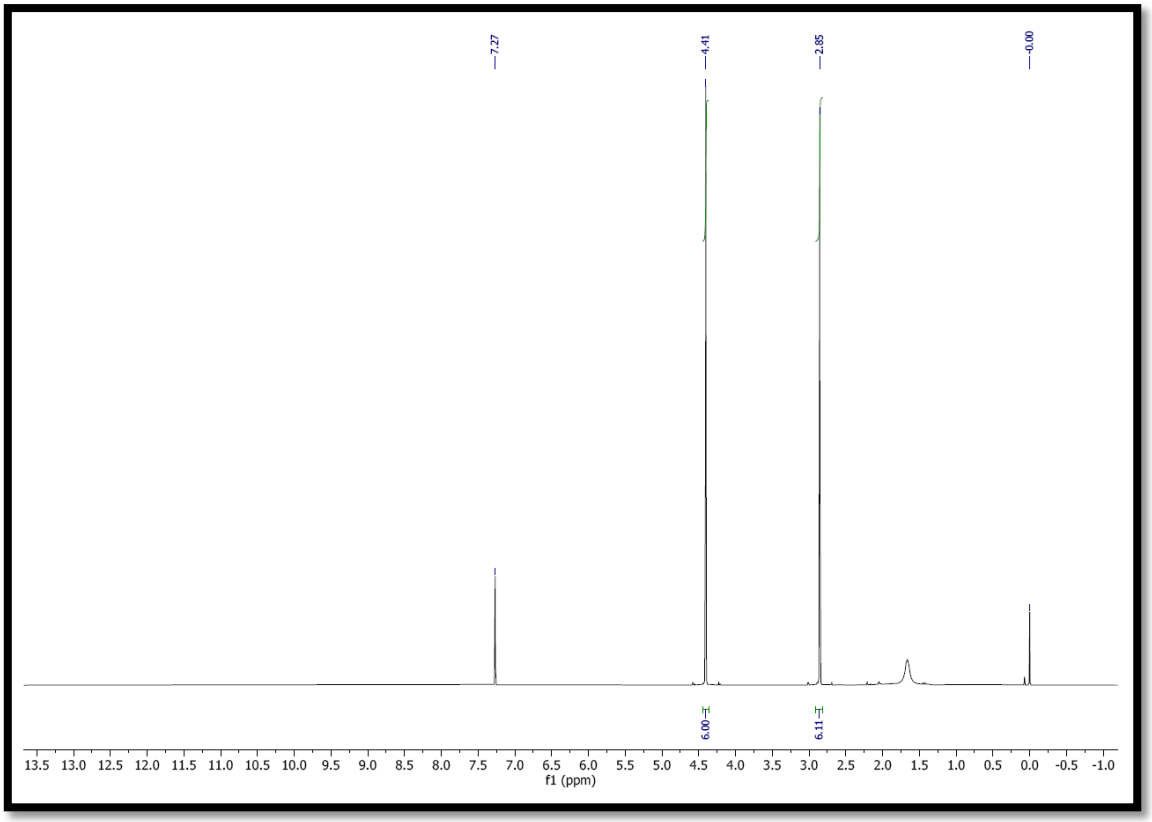

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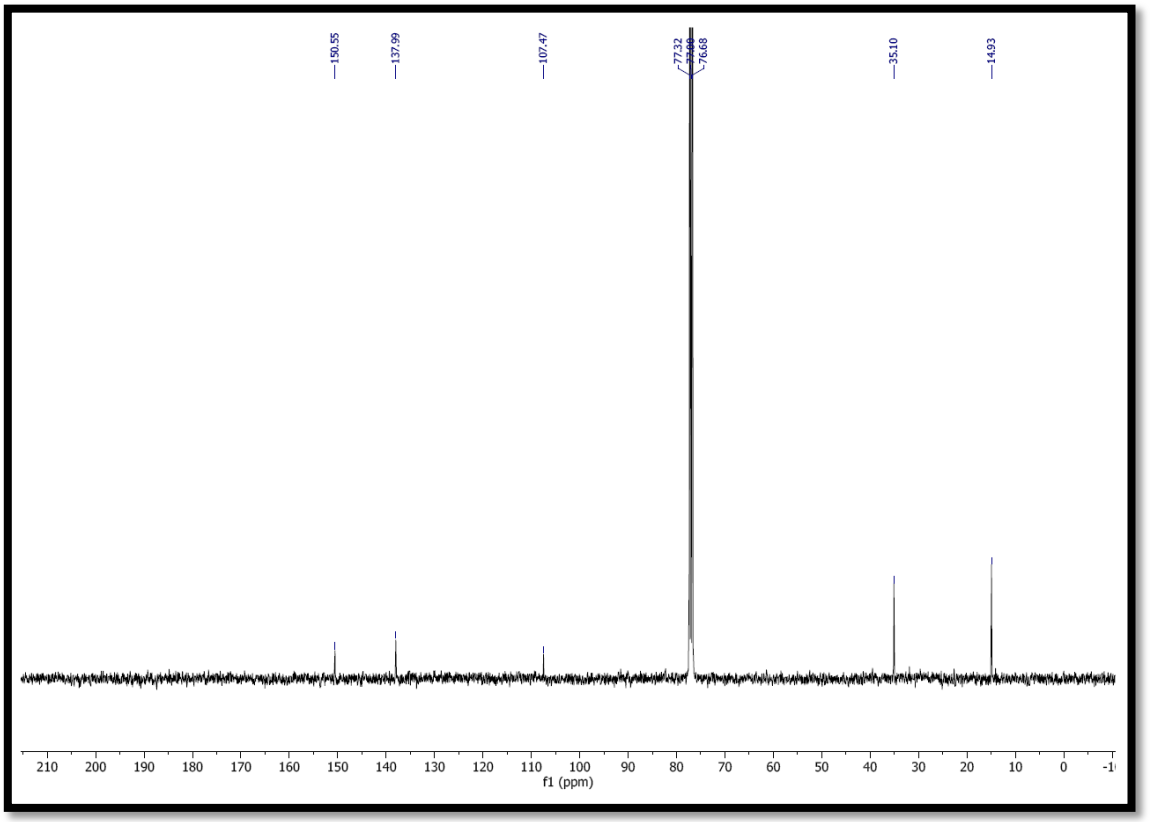

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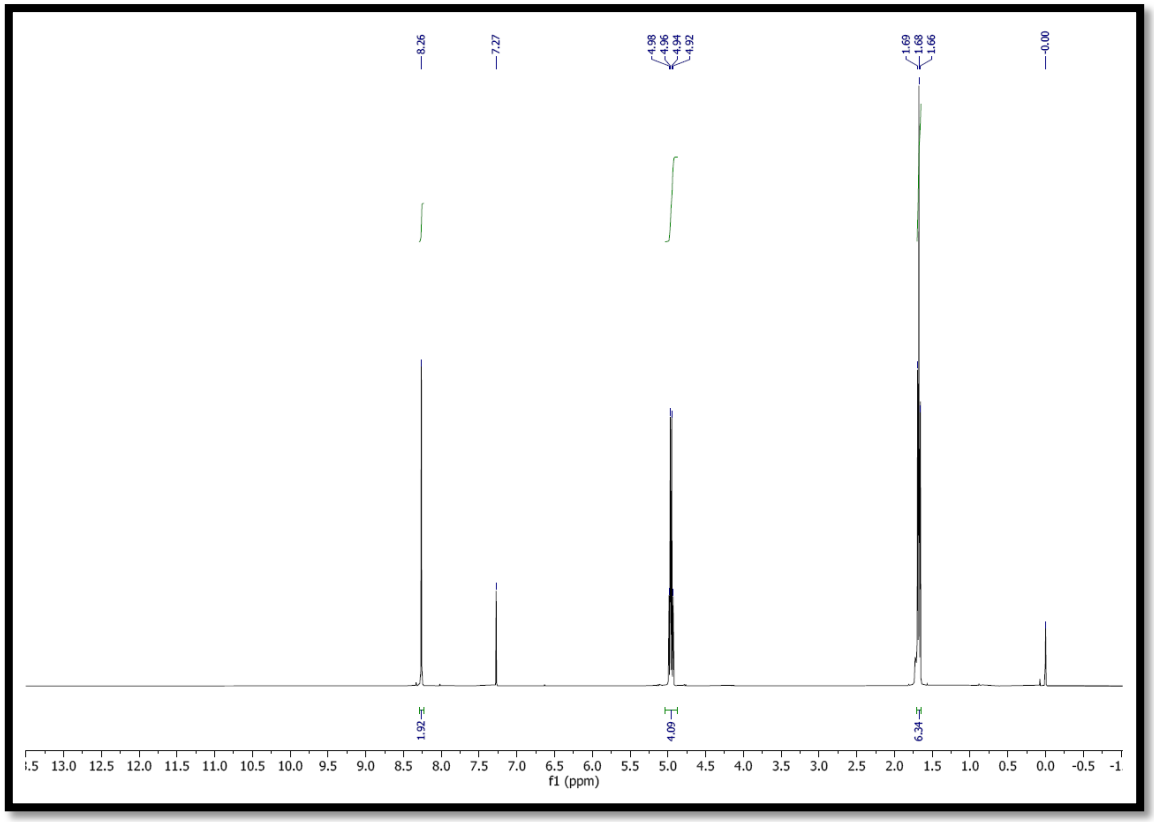
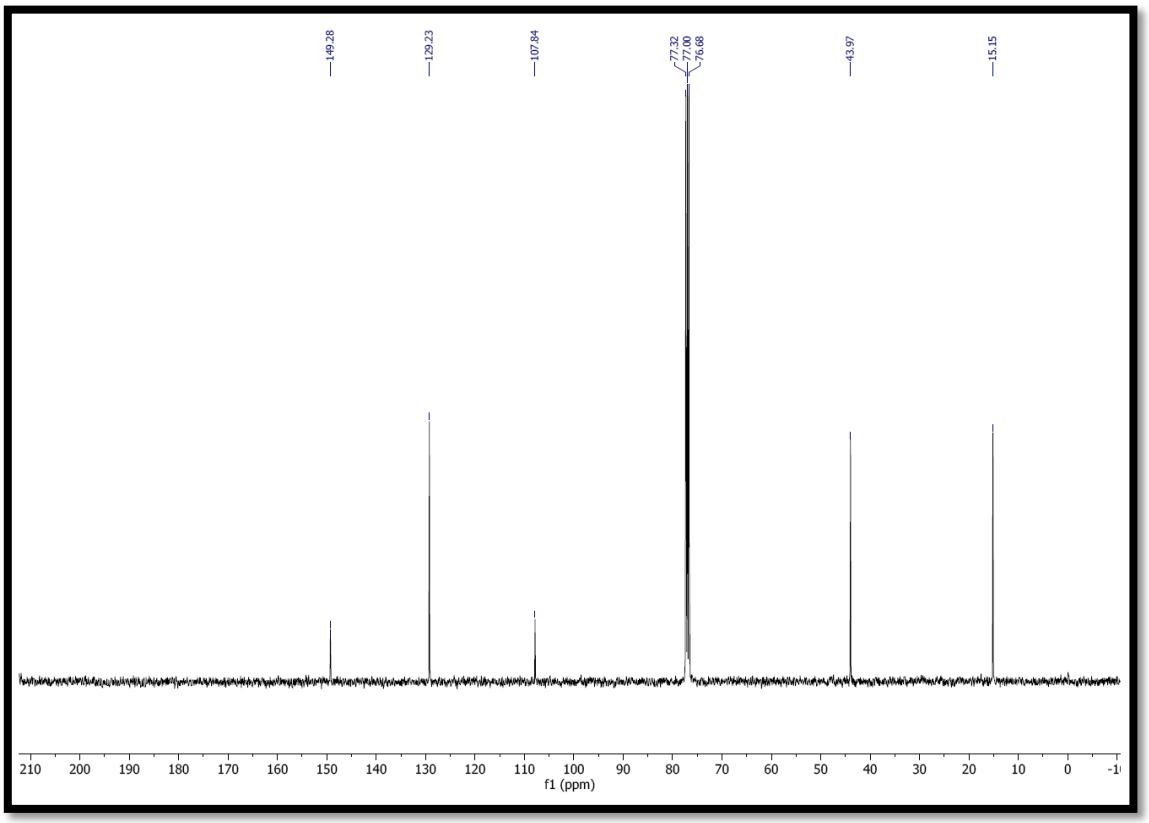
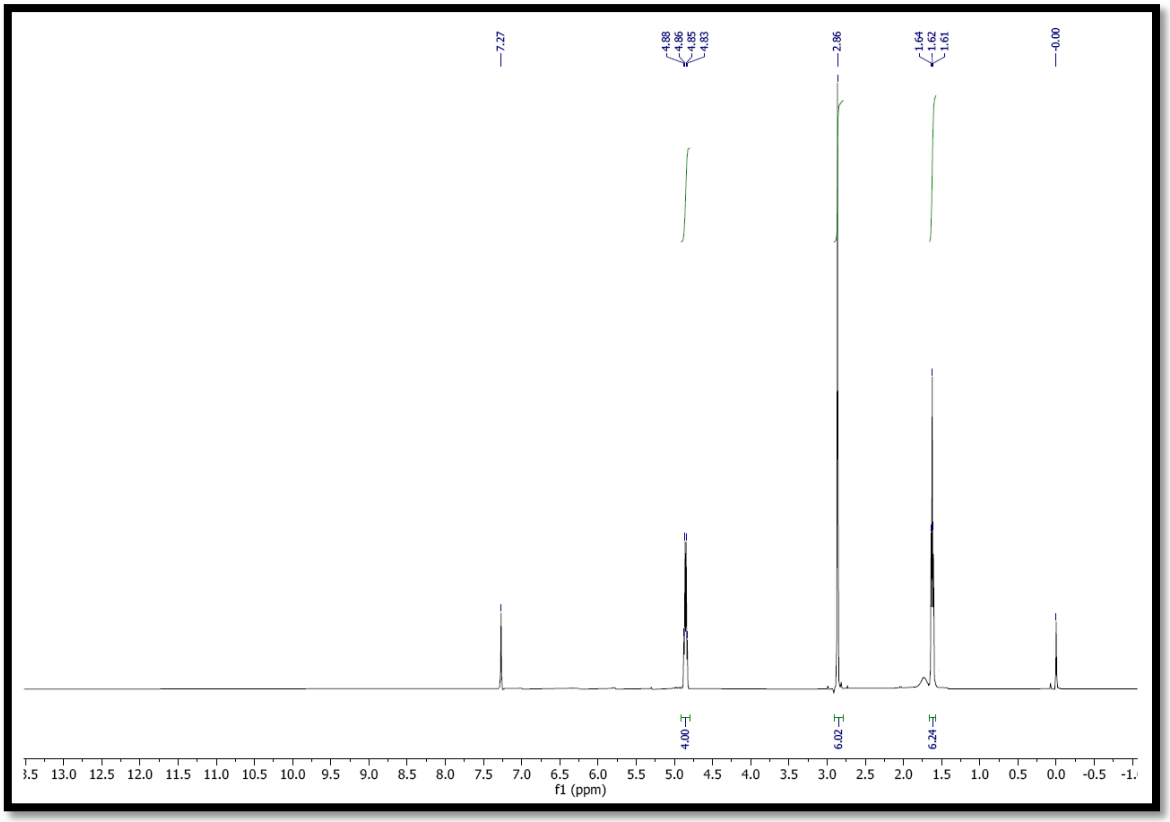


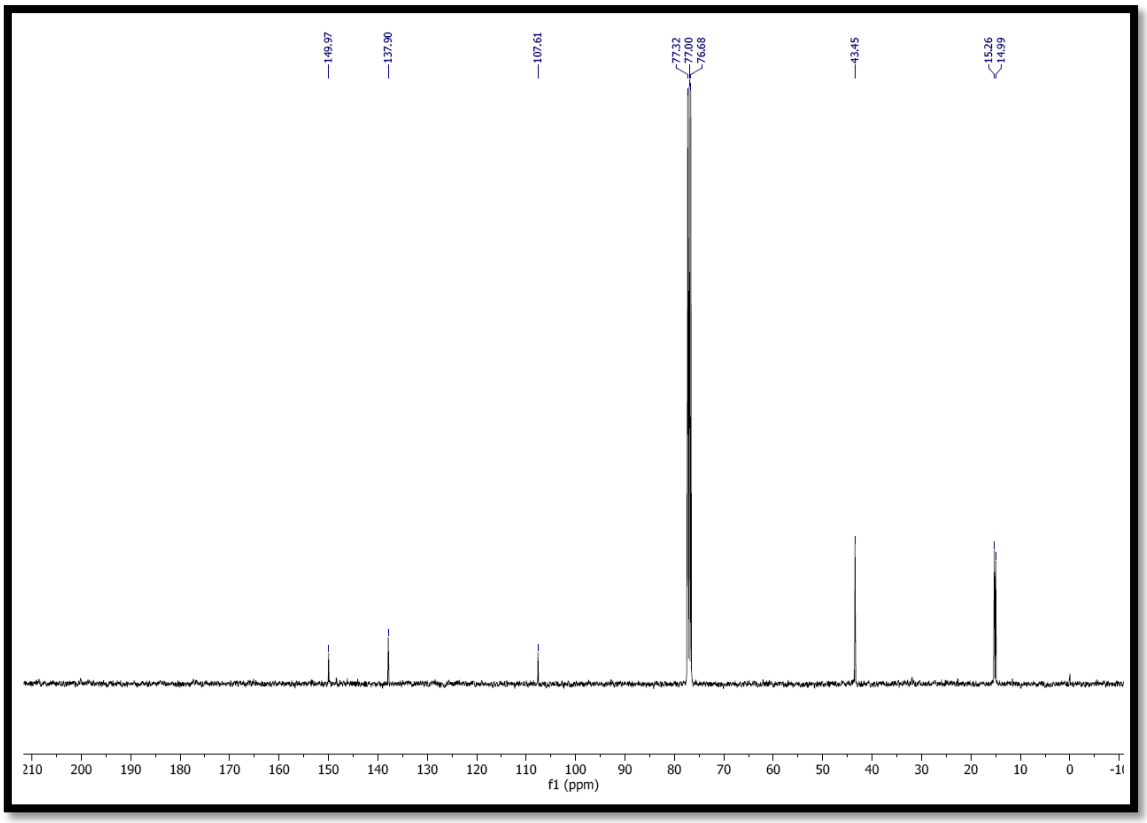
^{13}C NMR 2j



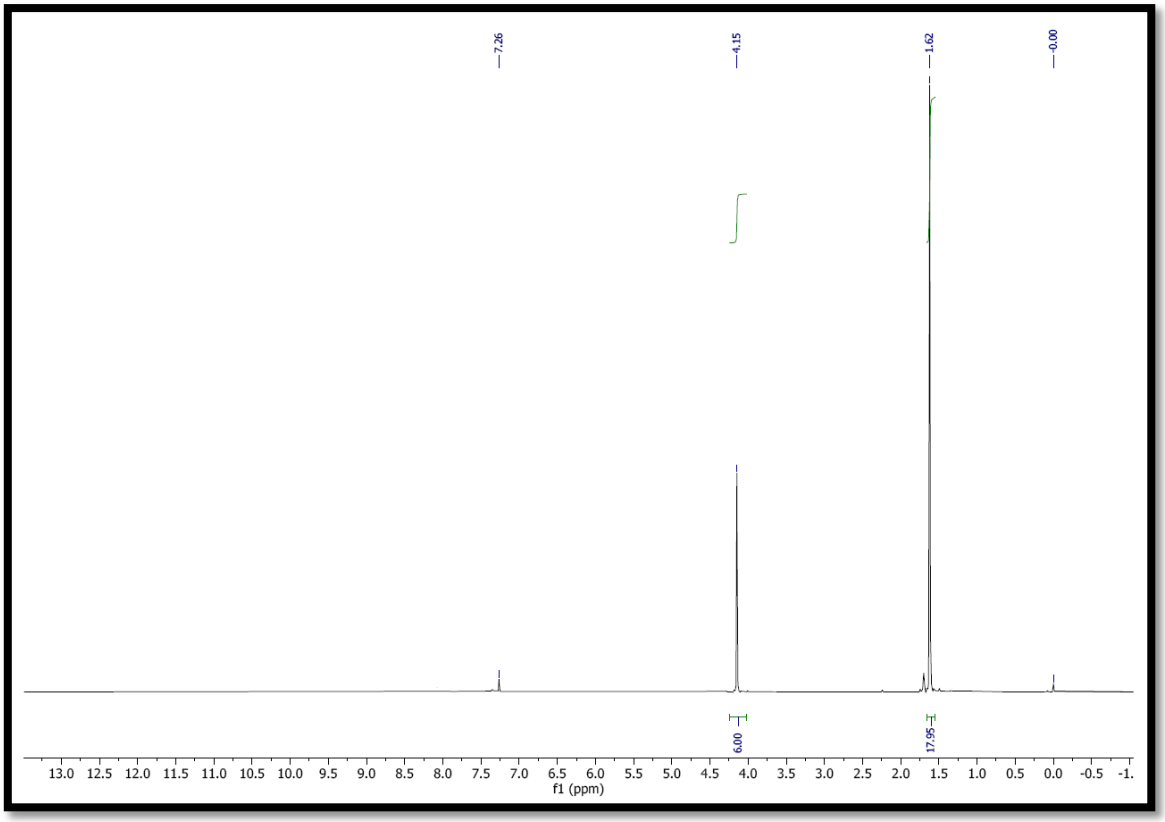
^{1}H NMR 2k



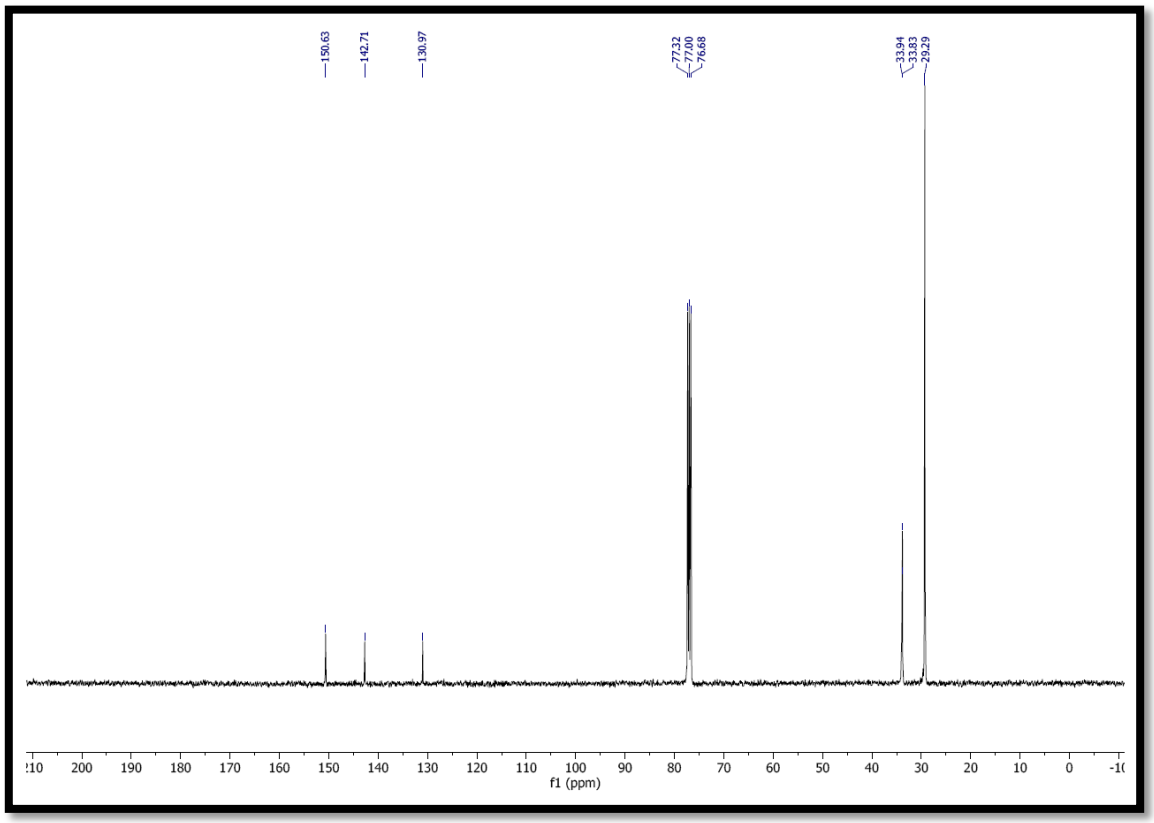
^{13}C NMR 2k



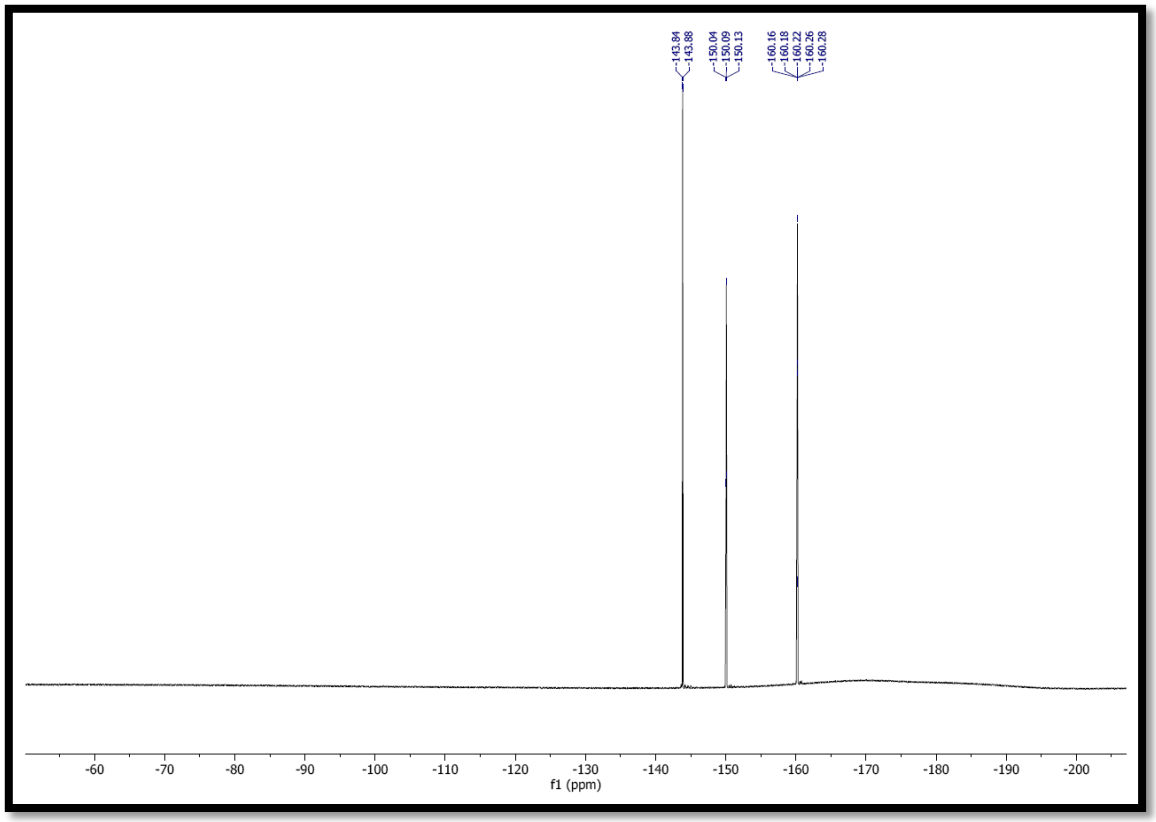
^{1}H NMR 2l



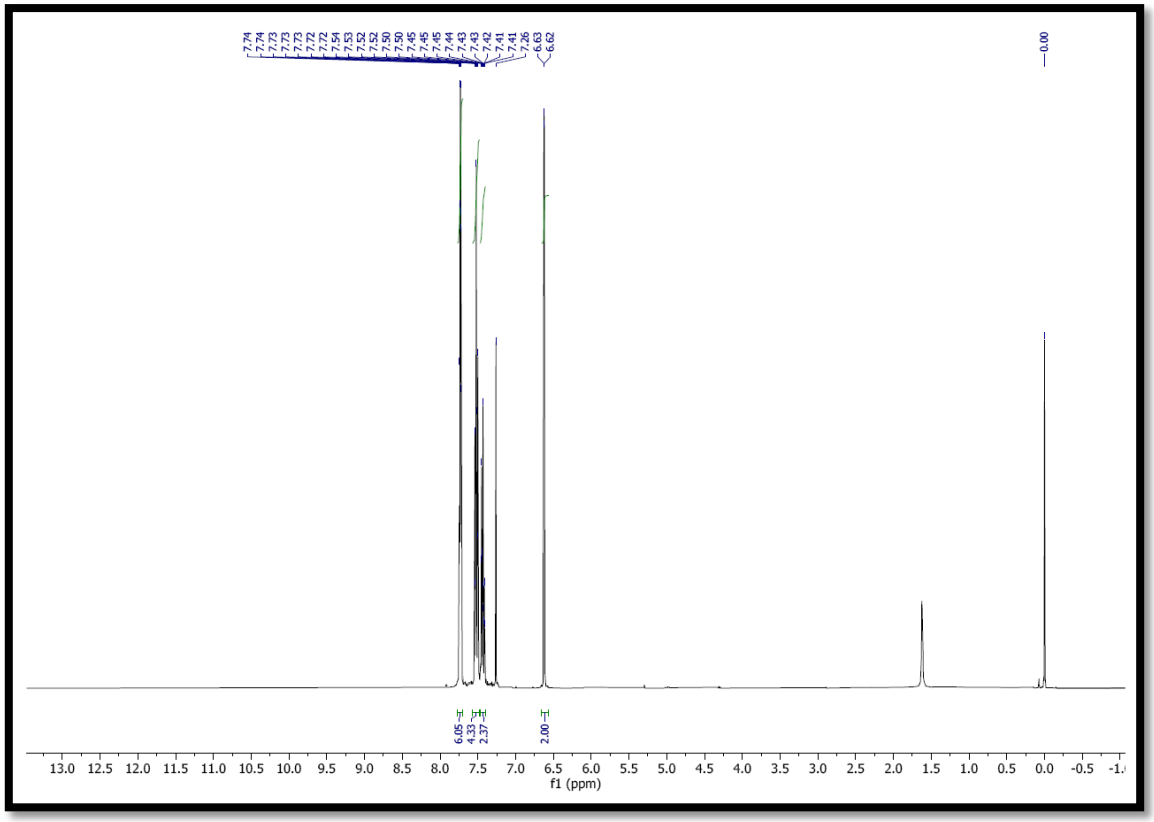
^{13}C NMR 2l



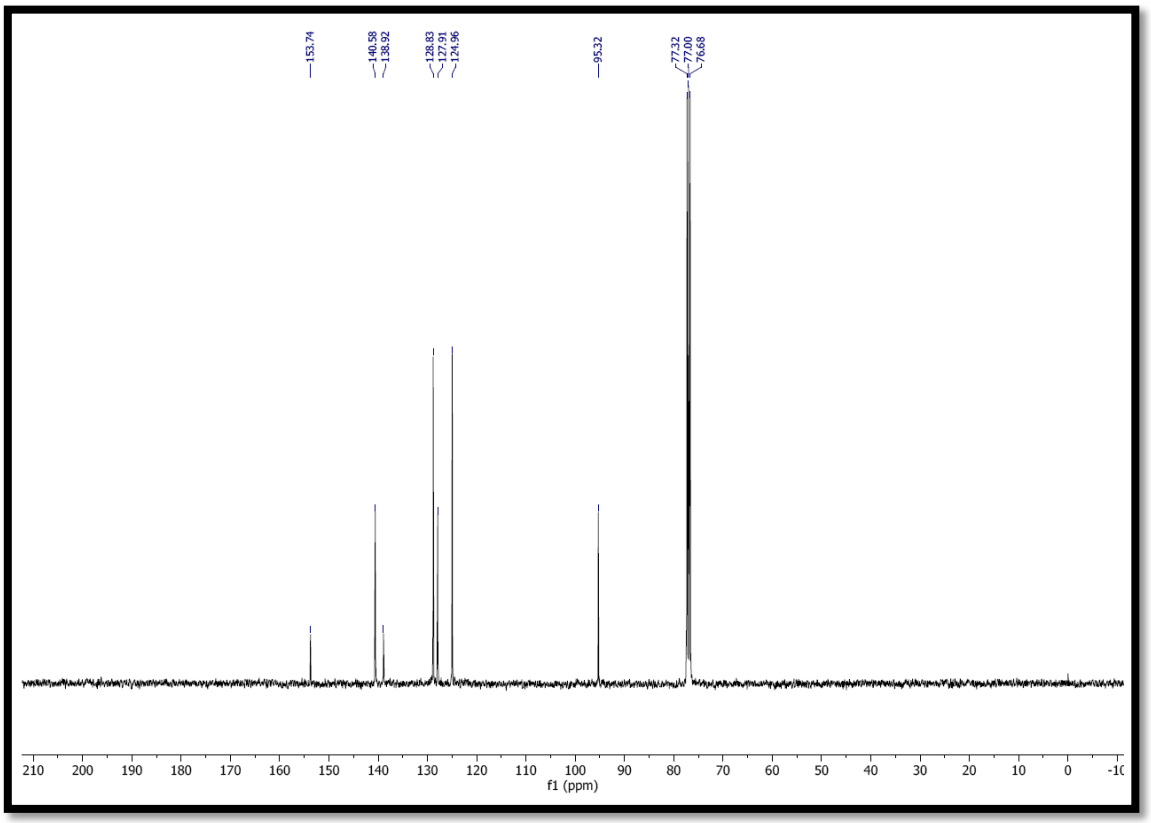
^{19}F NMR of 2h


-143.84
-143.88
-150.04
-150.09
-150.13
-160.16
-160.18
-160.22
-160.26
-160.28
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

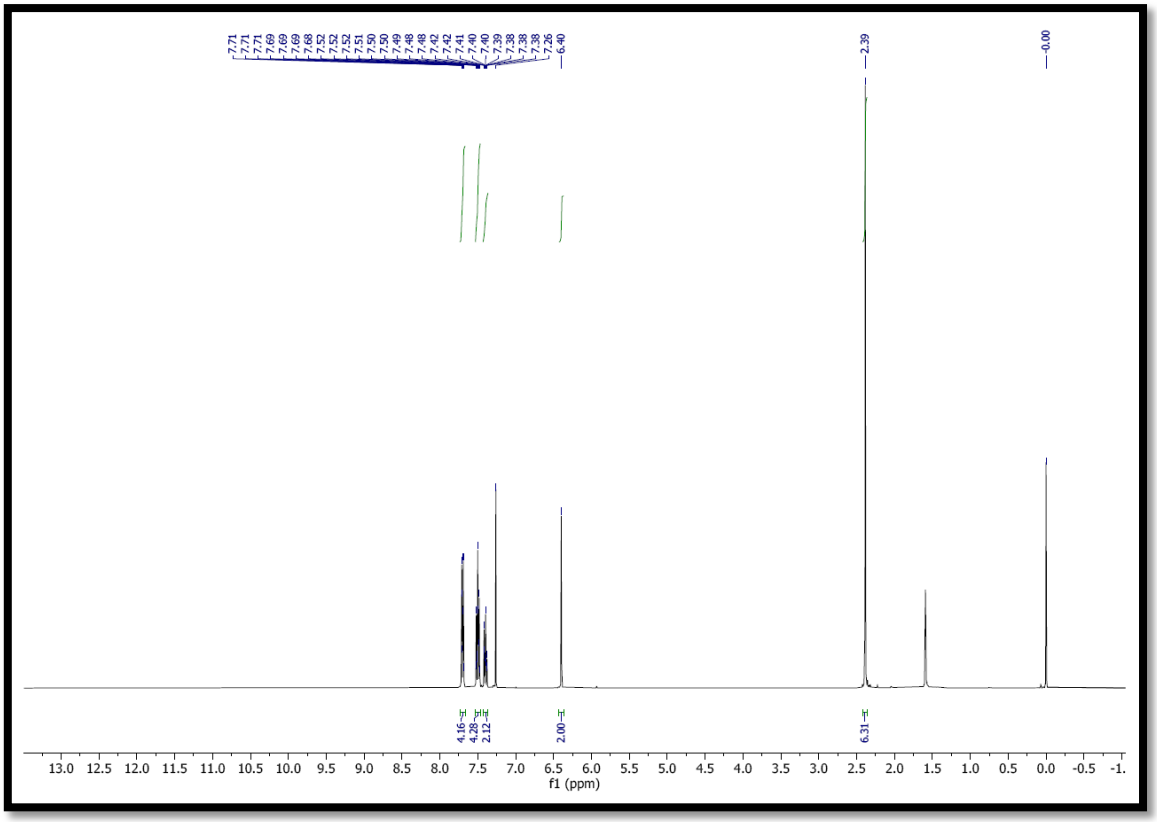
^{1}H NMR 3a



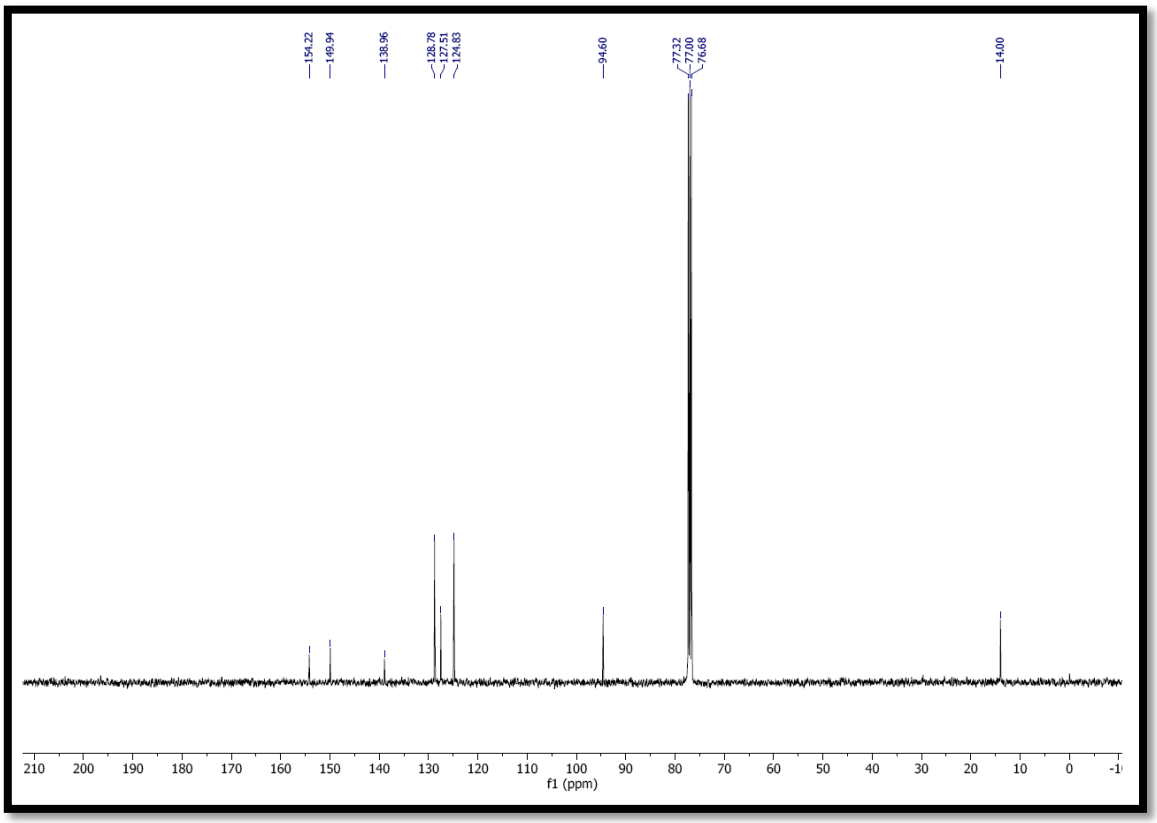
^{13}C NMR 3a



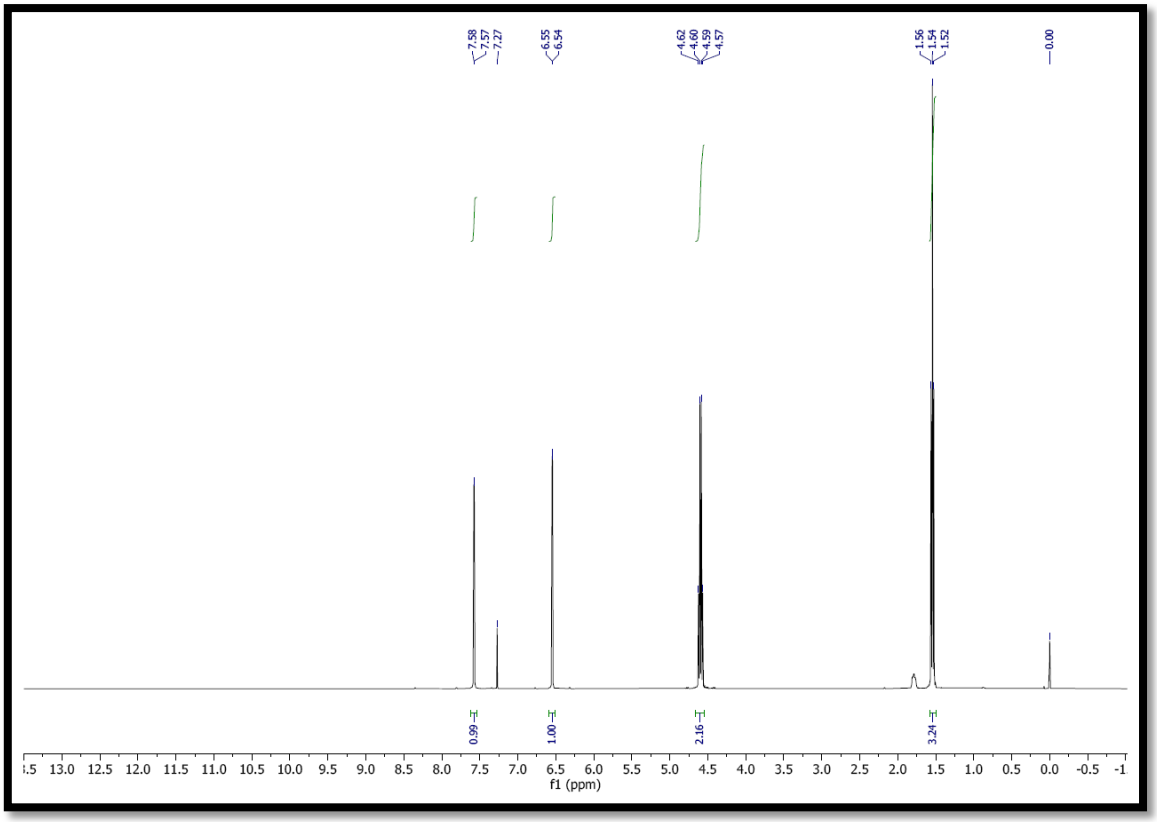
^{1}H NMR 3b



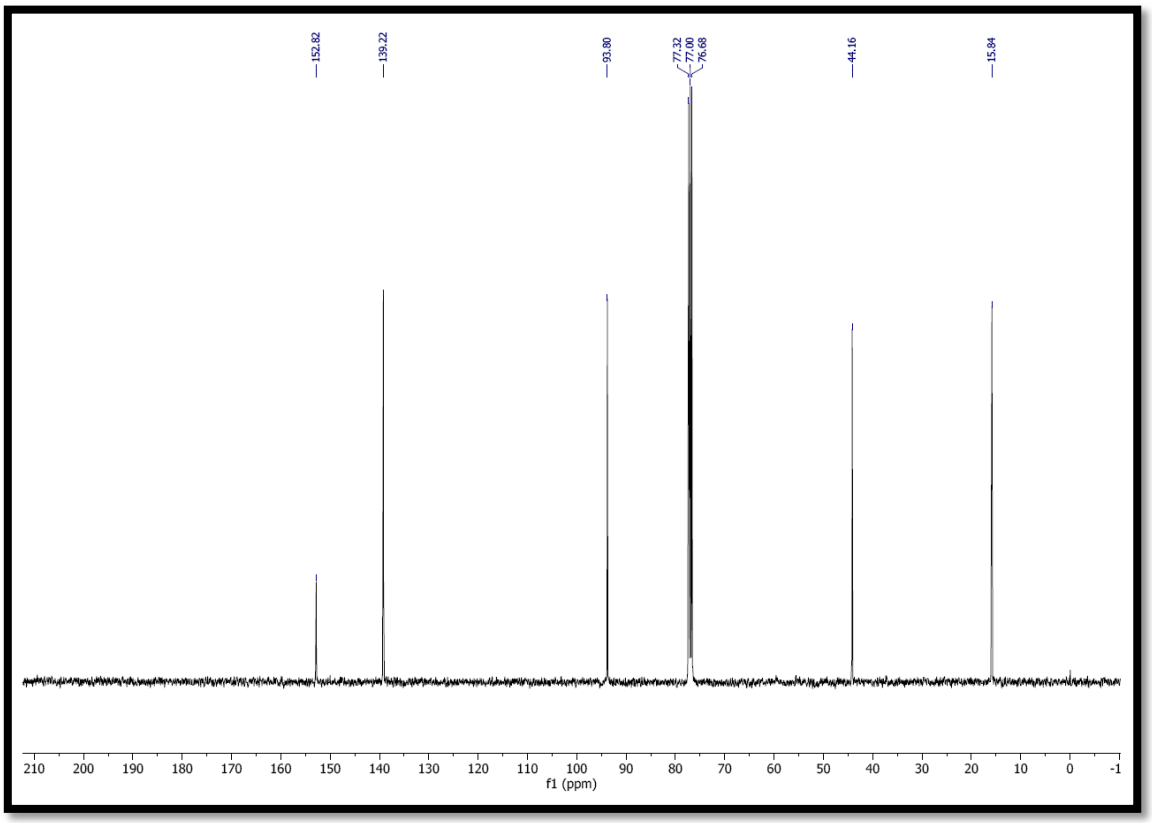
^{13}C NMR 3b



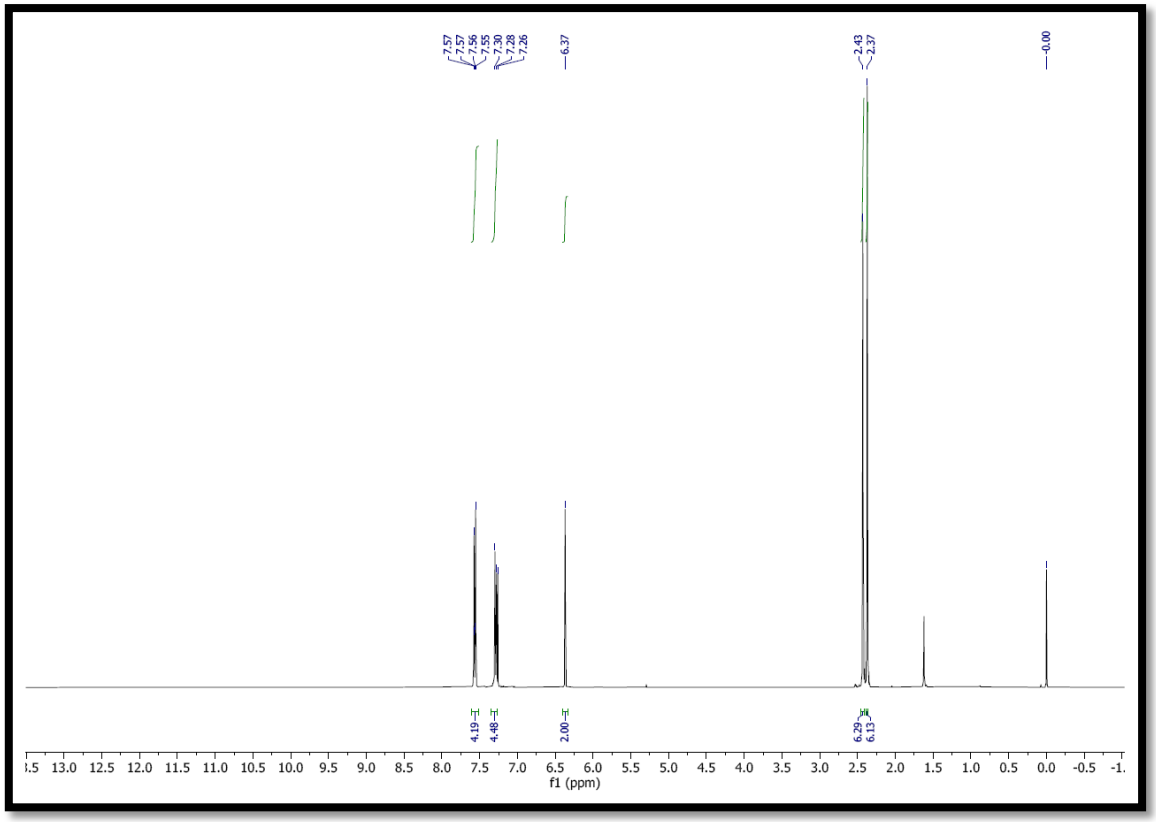
^{1}H NMR 3c



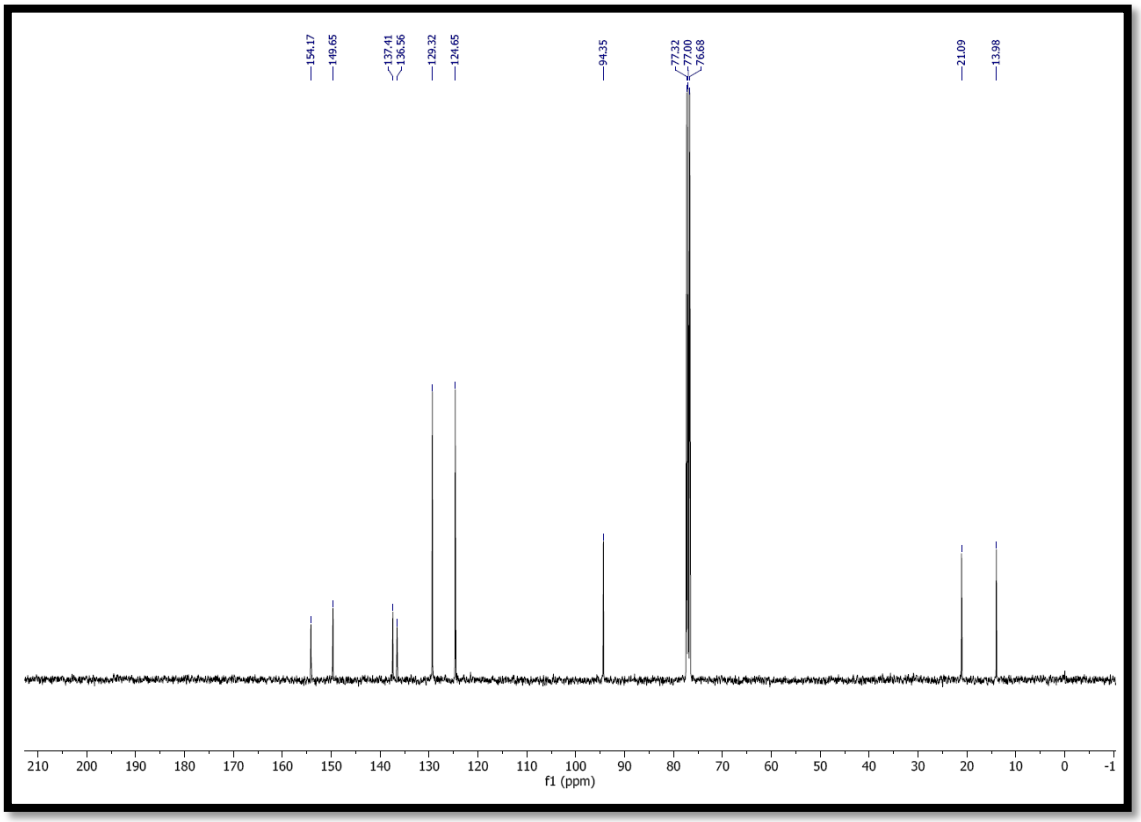
^{13}C NMR 3c



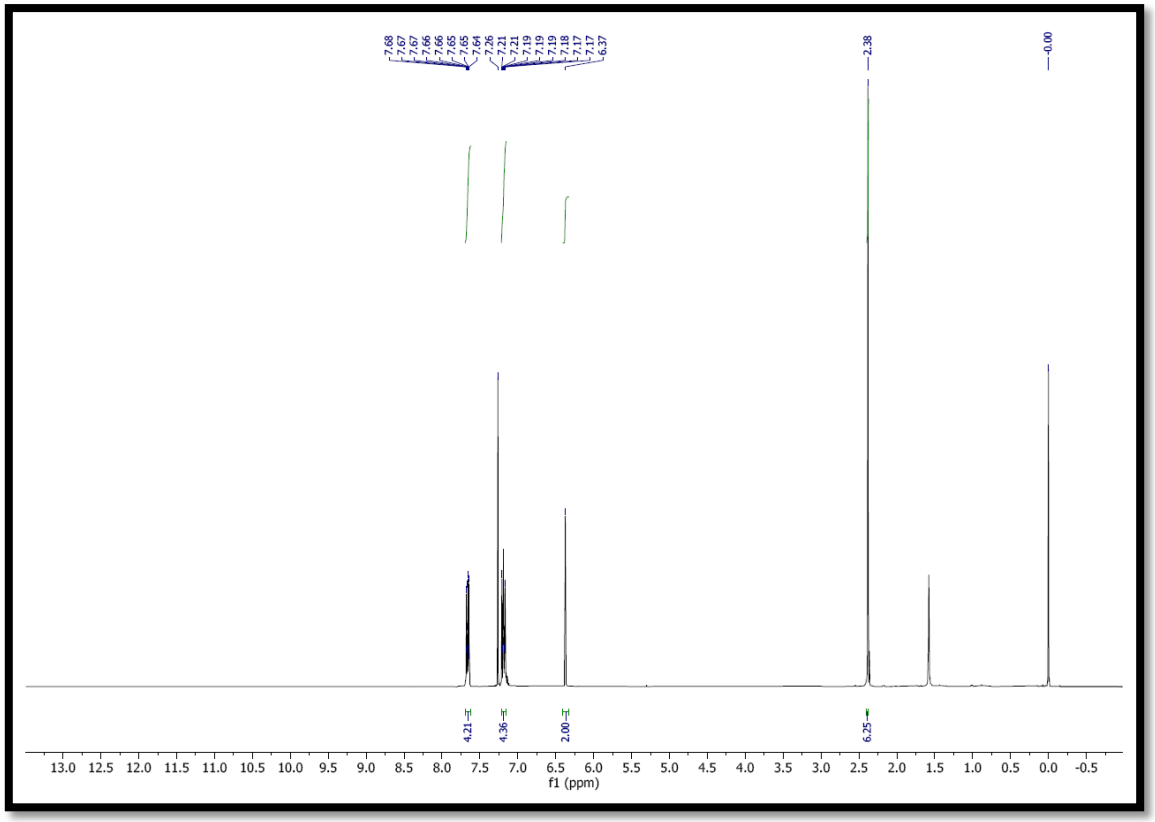
^{1}H NMR 3d



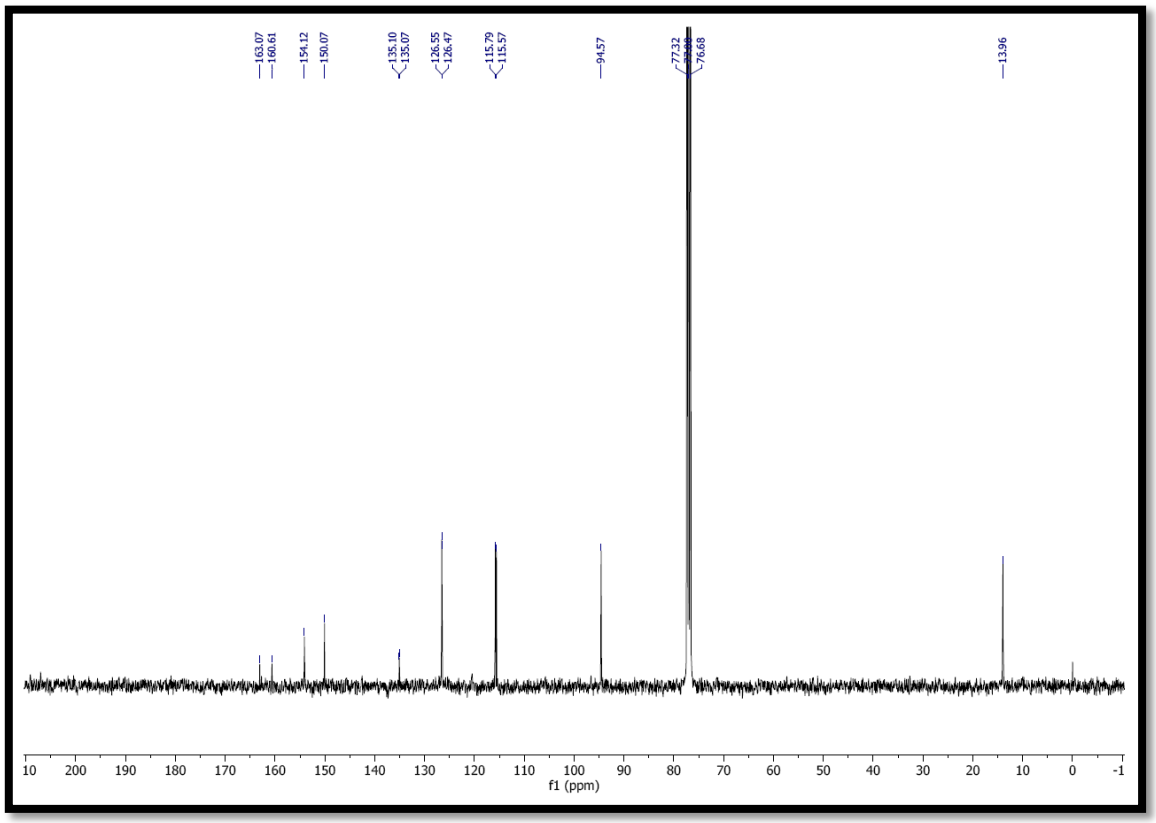
^{13}C NMR 3d



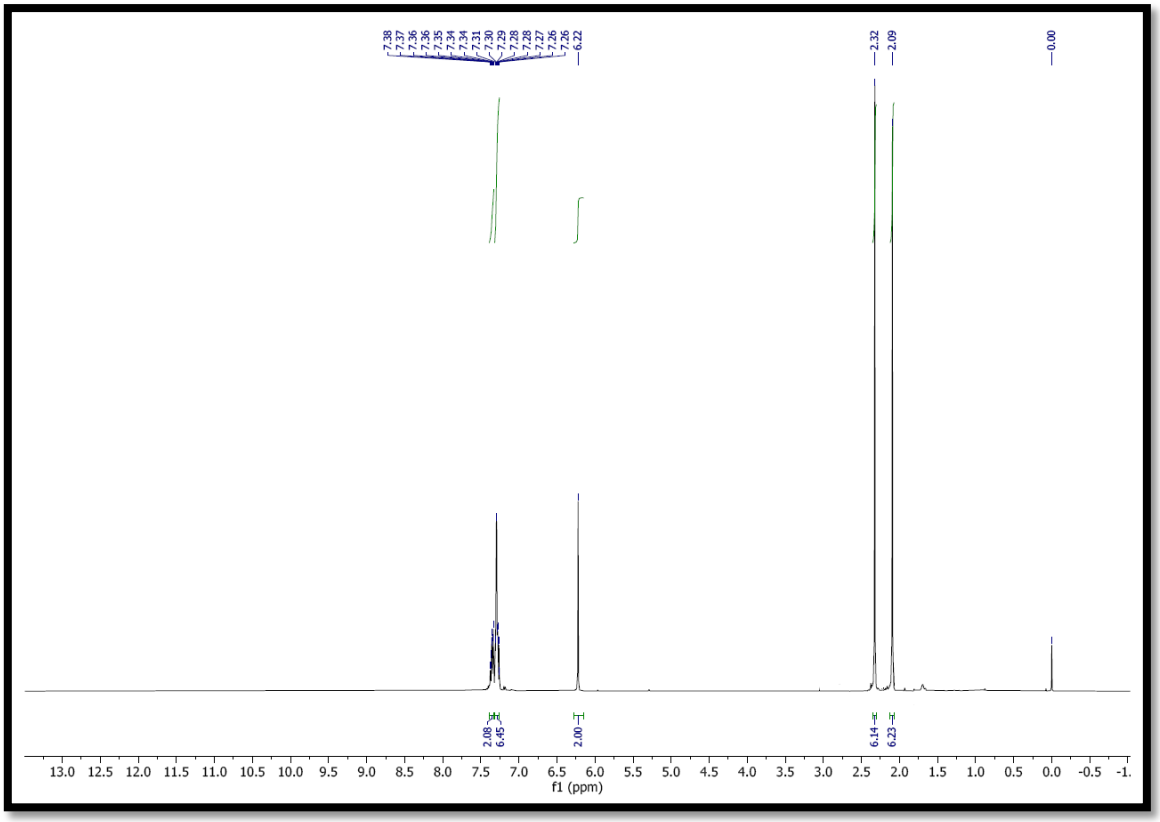
^{1}H NMR 3e



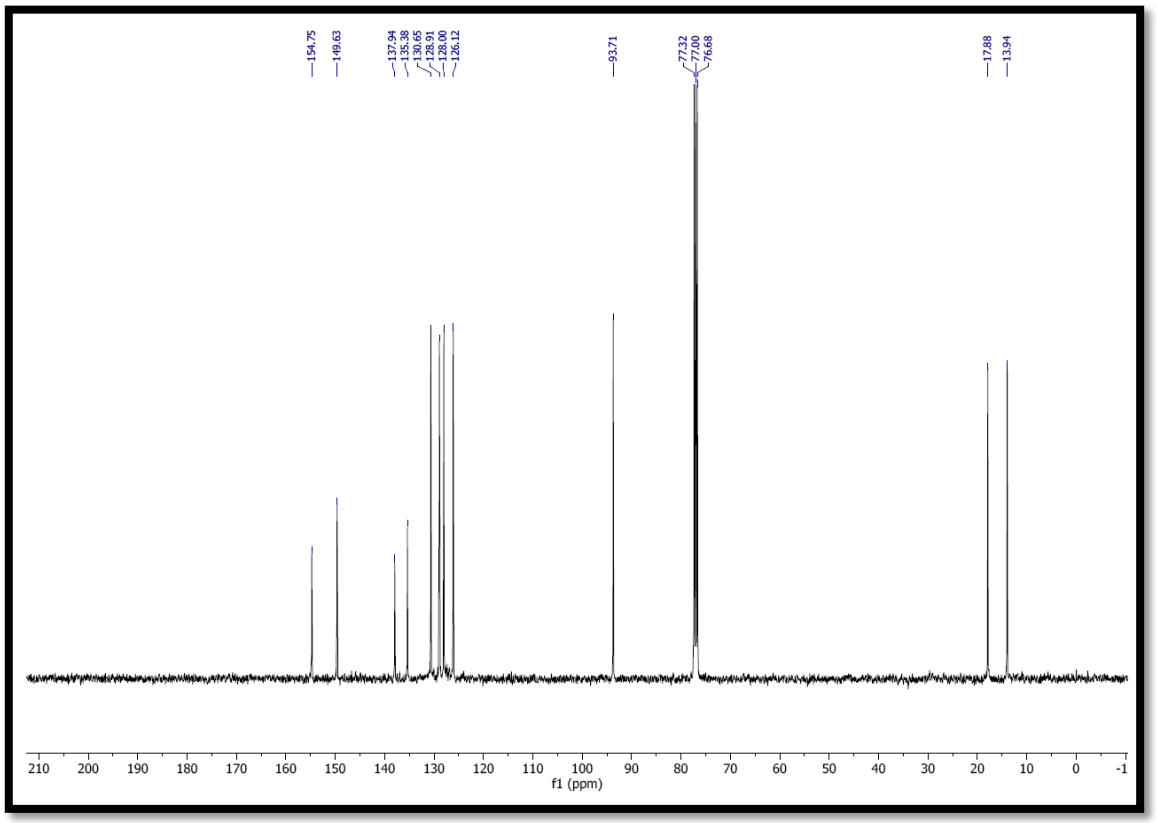
^{13}C NMR 3e



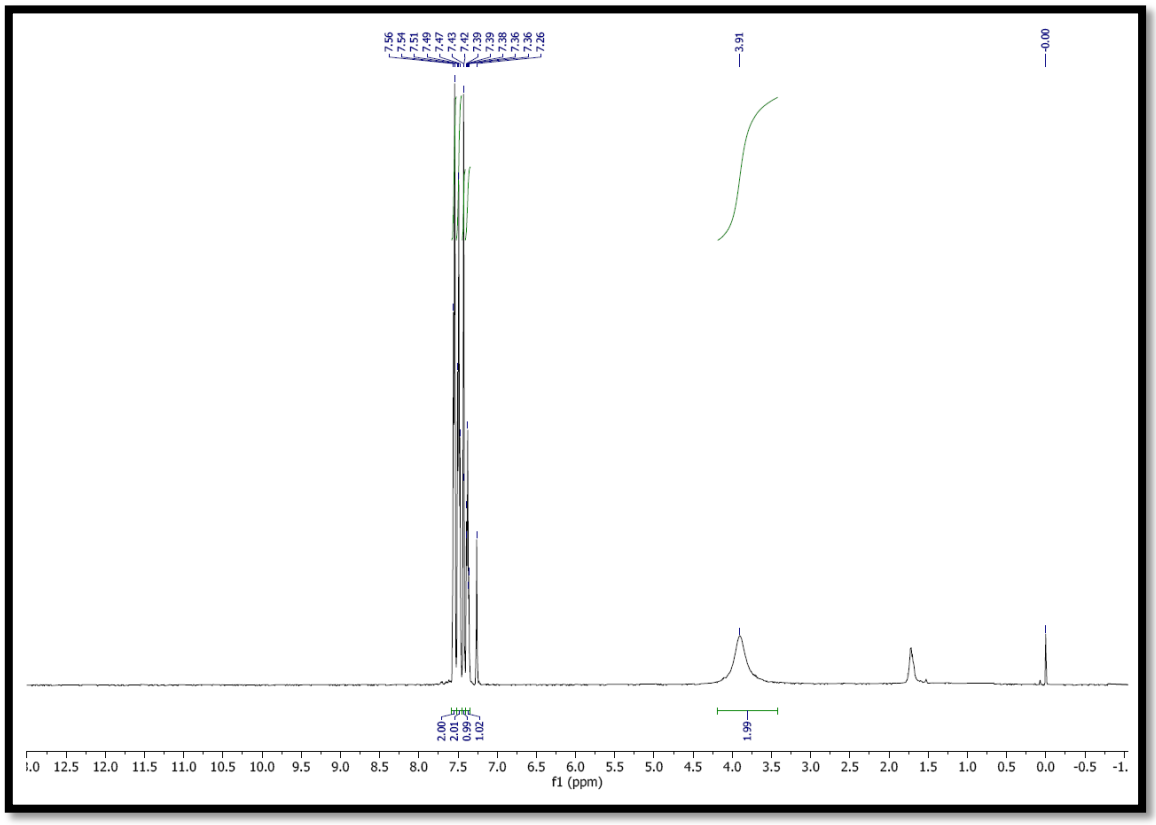
^{1}H NMR 3f



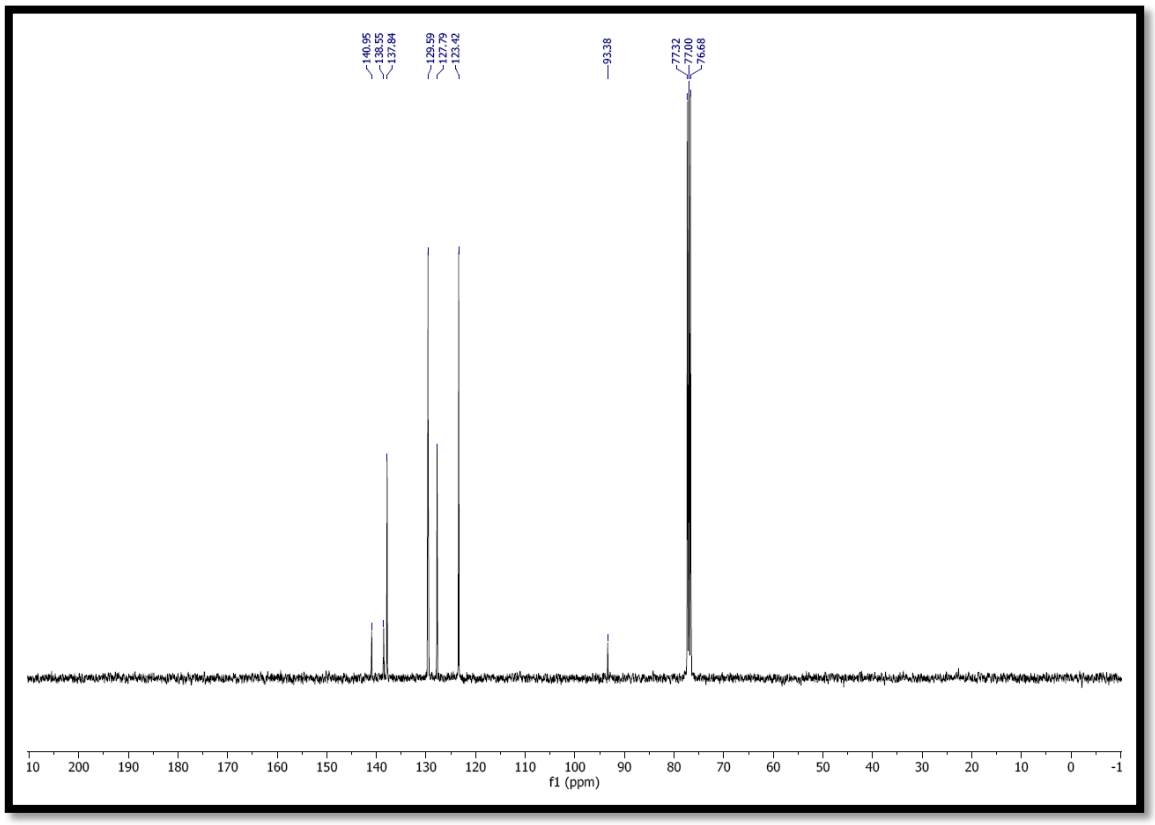
^{13}C NMR 3f



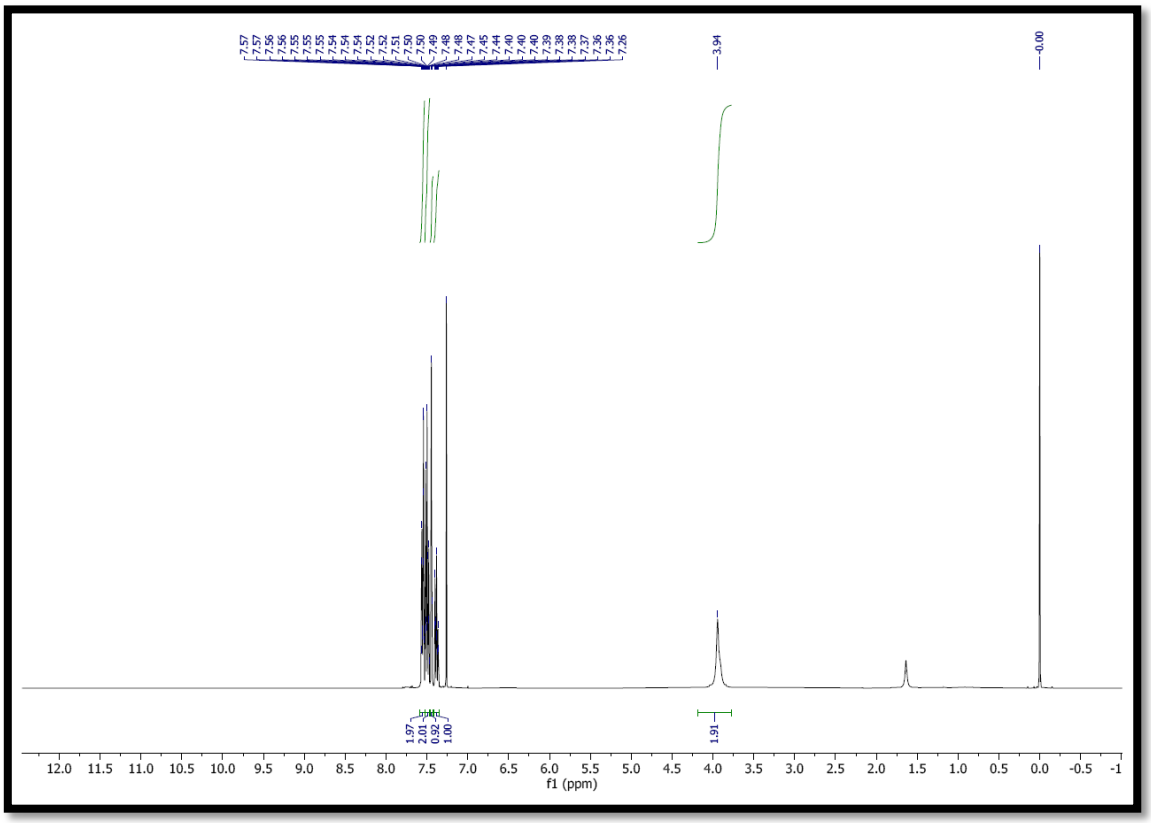
^{1}H NMR4a



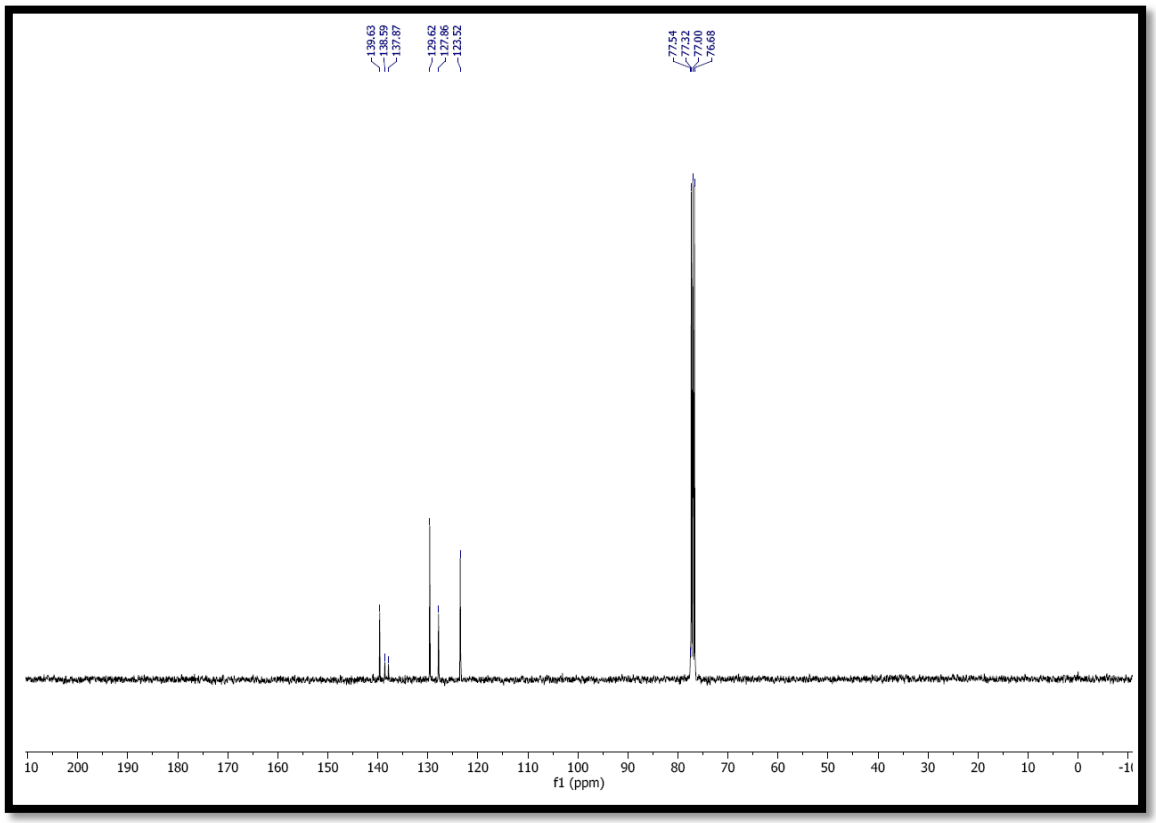
^{13}C NMR 4a



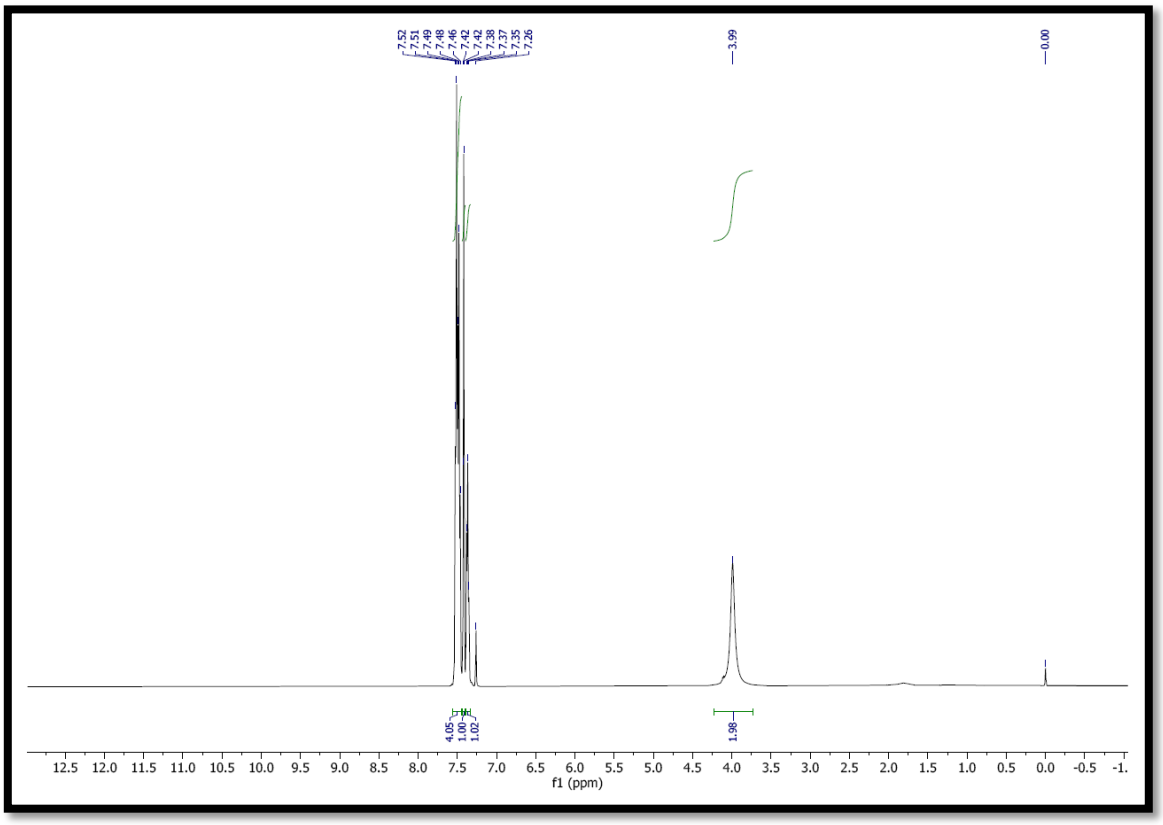
^{1}H NMR 4b



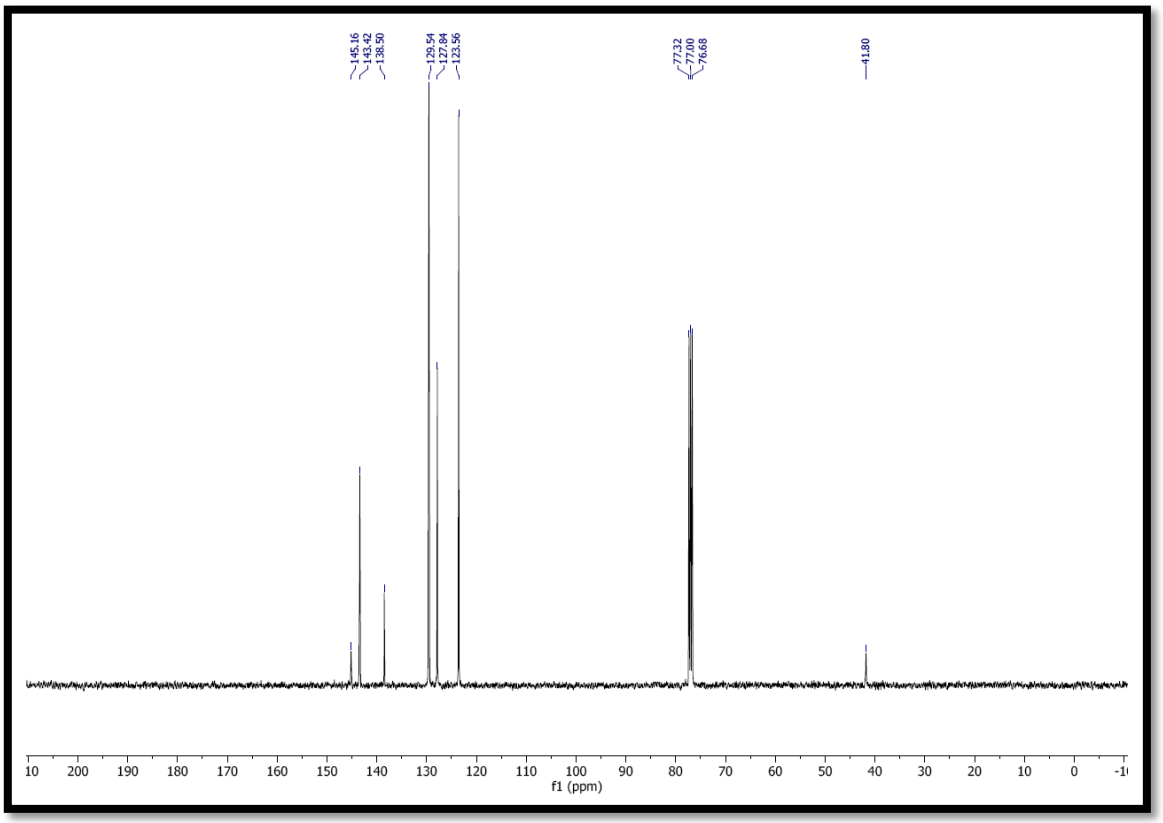
^{13}C NMR 4b



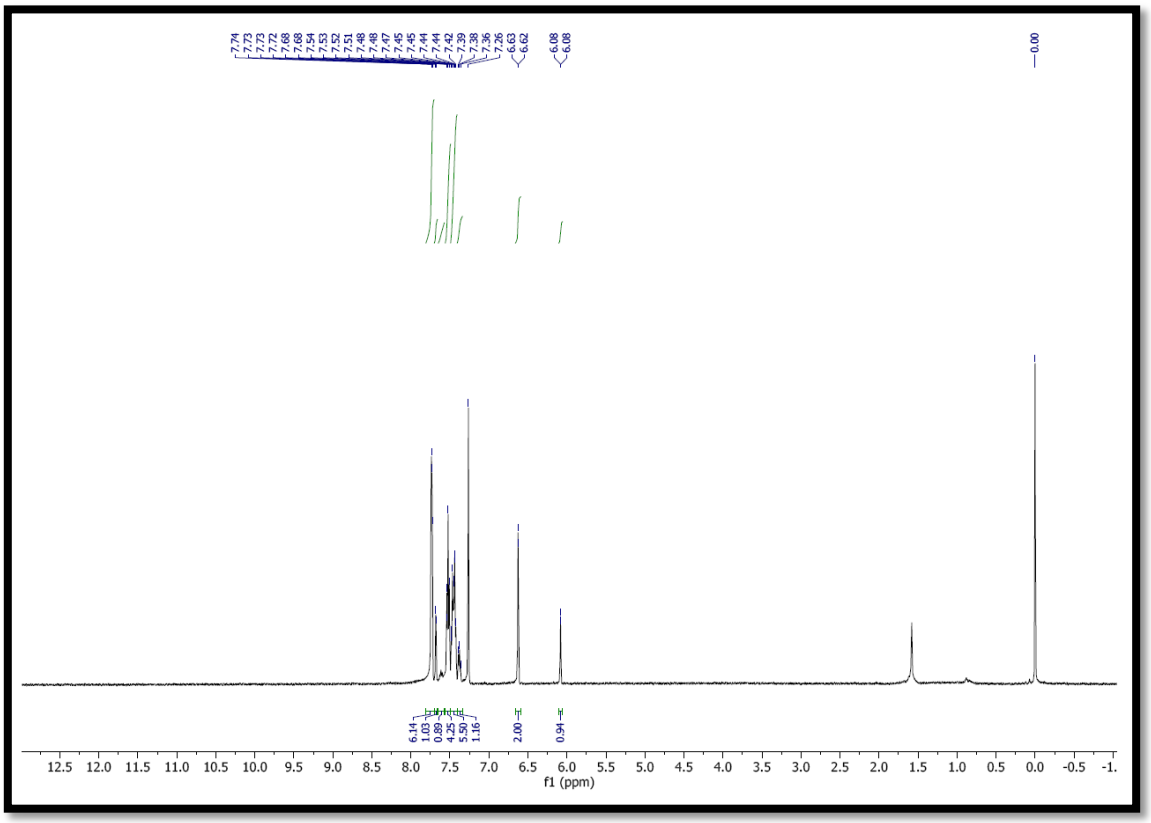
^{1}H NMR4c



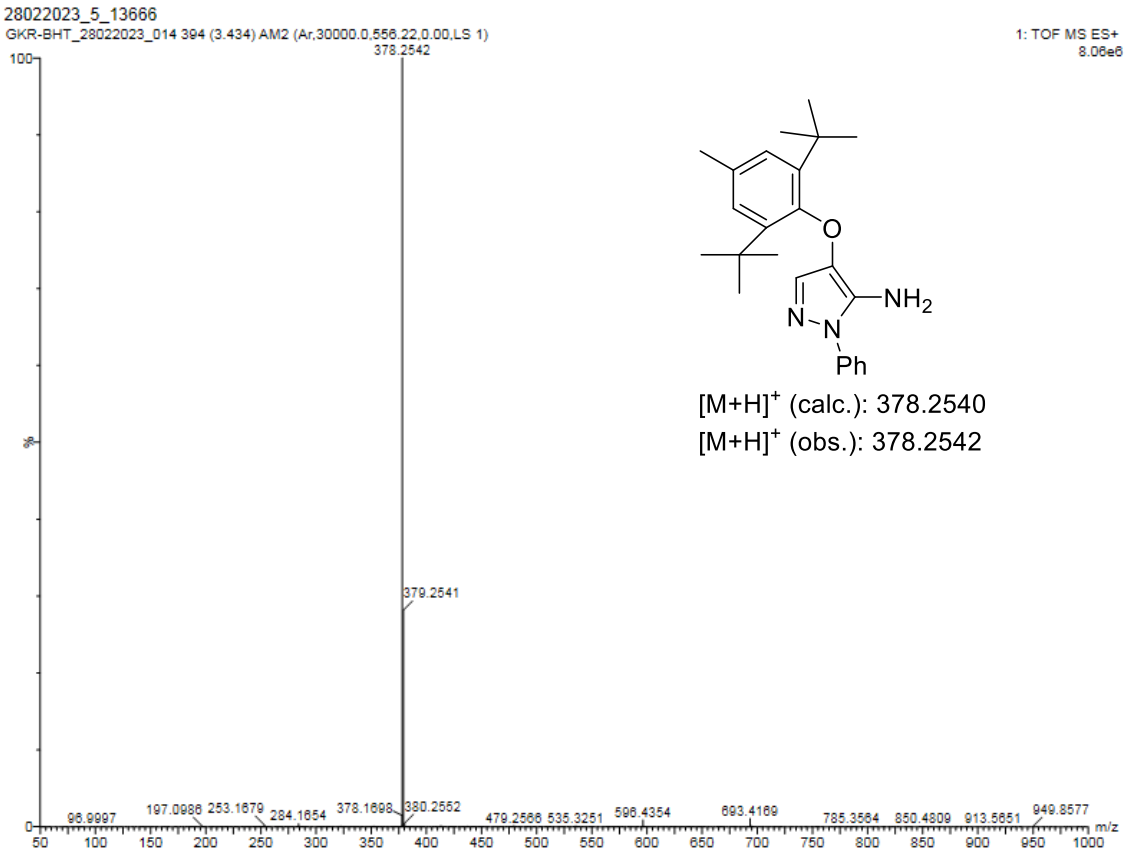
^{13}C NMR 4c



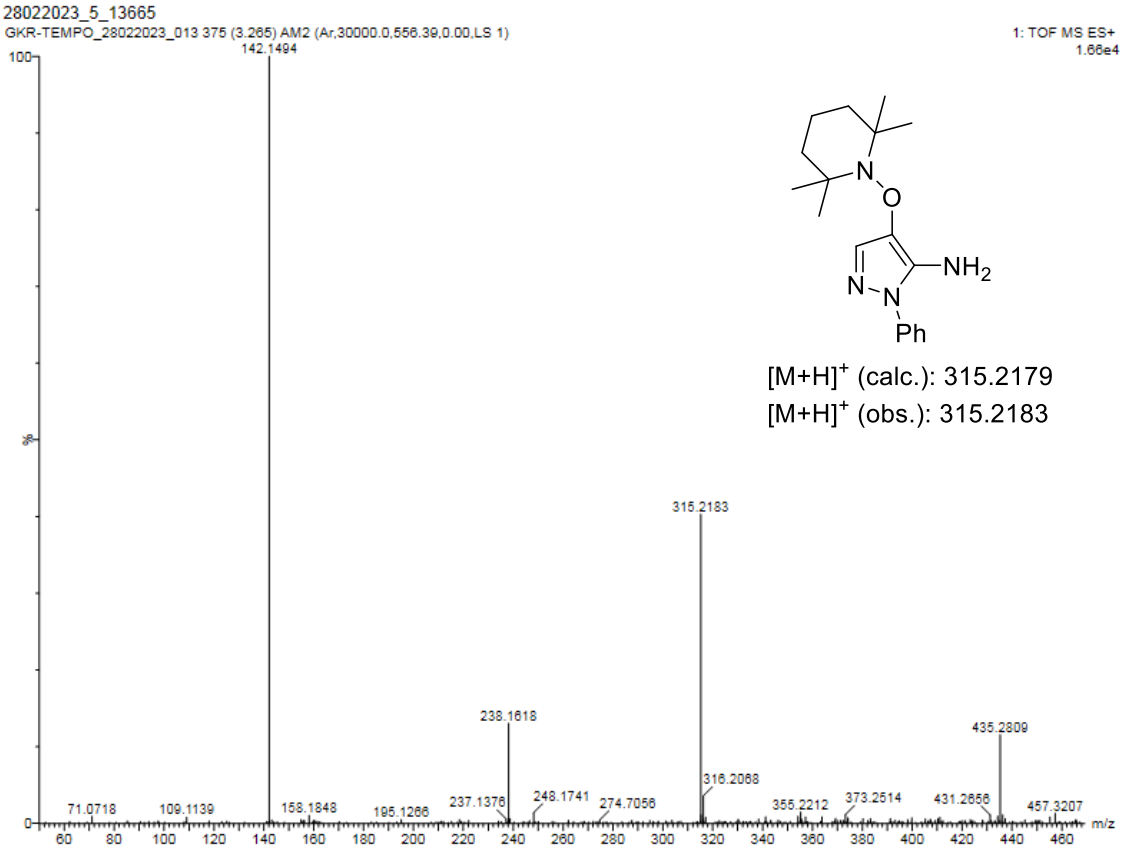
^{1}H NMR of 3a showing Cis and Trans mixture



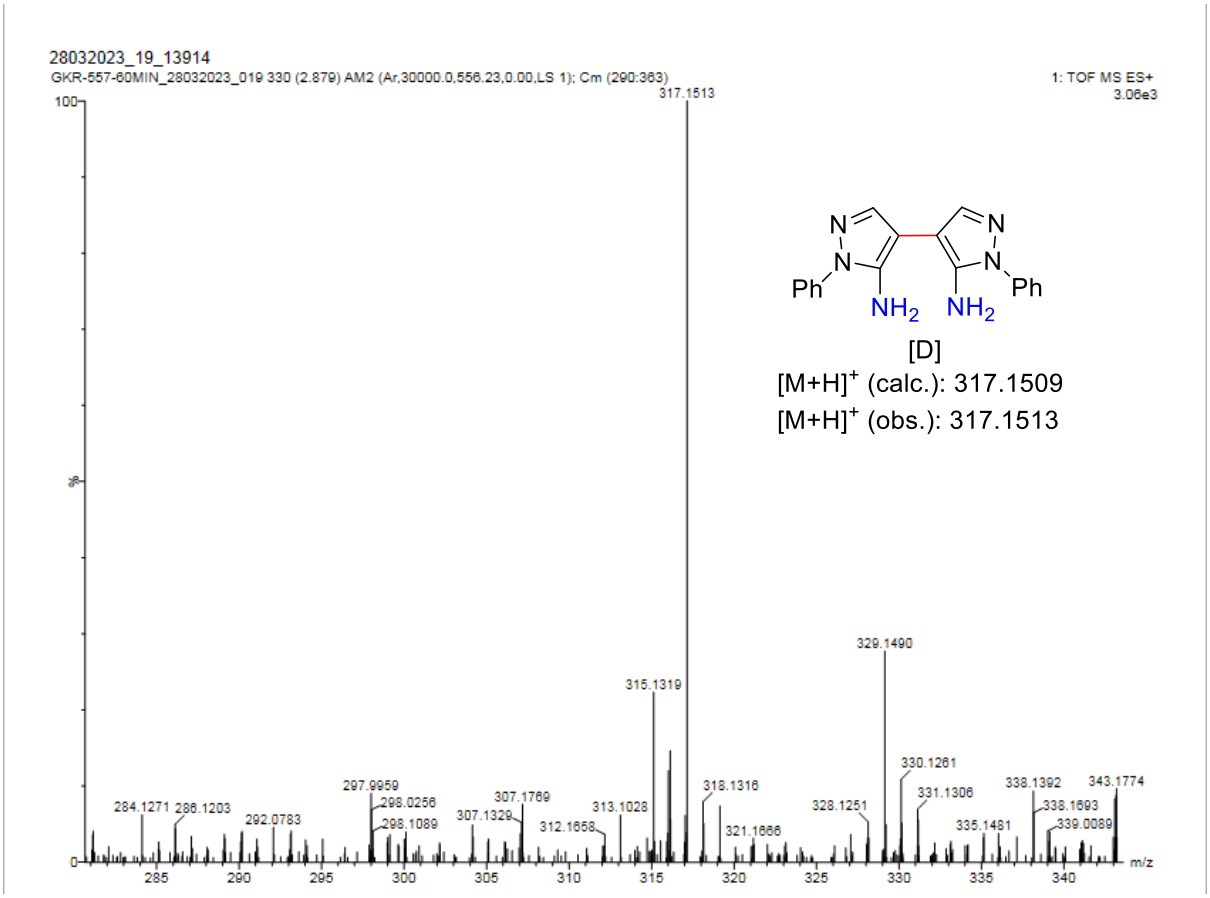
HRMS of reaction mixture with BHT



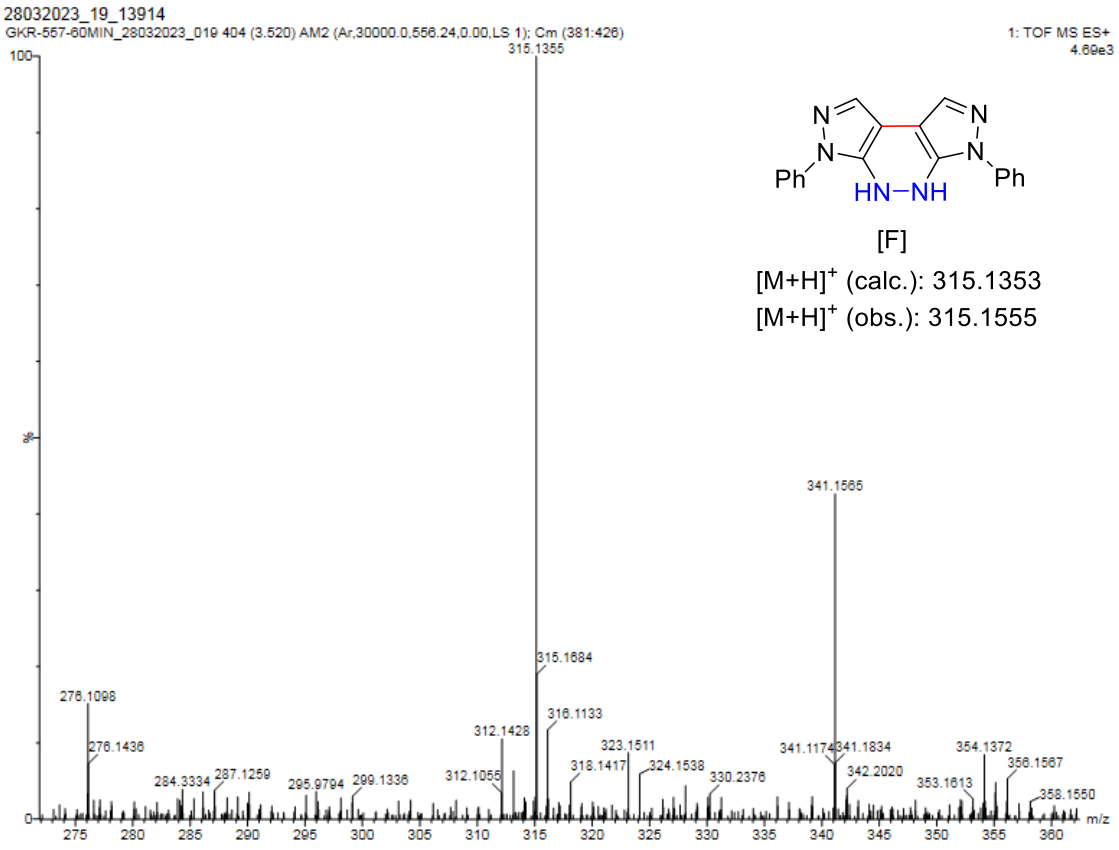
HRMS of reaction mixture with TEMPO



HRMS crude reaction mixture: intermediate (D)



HRMS of crude reaction mixture: intermediate (F)

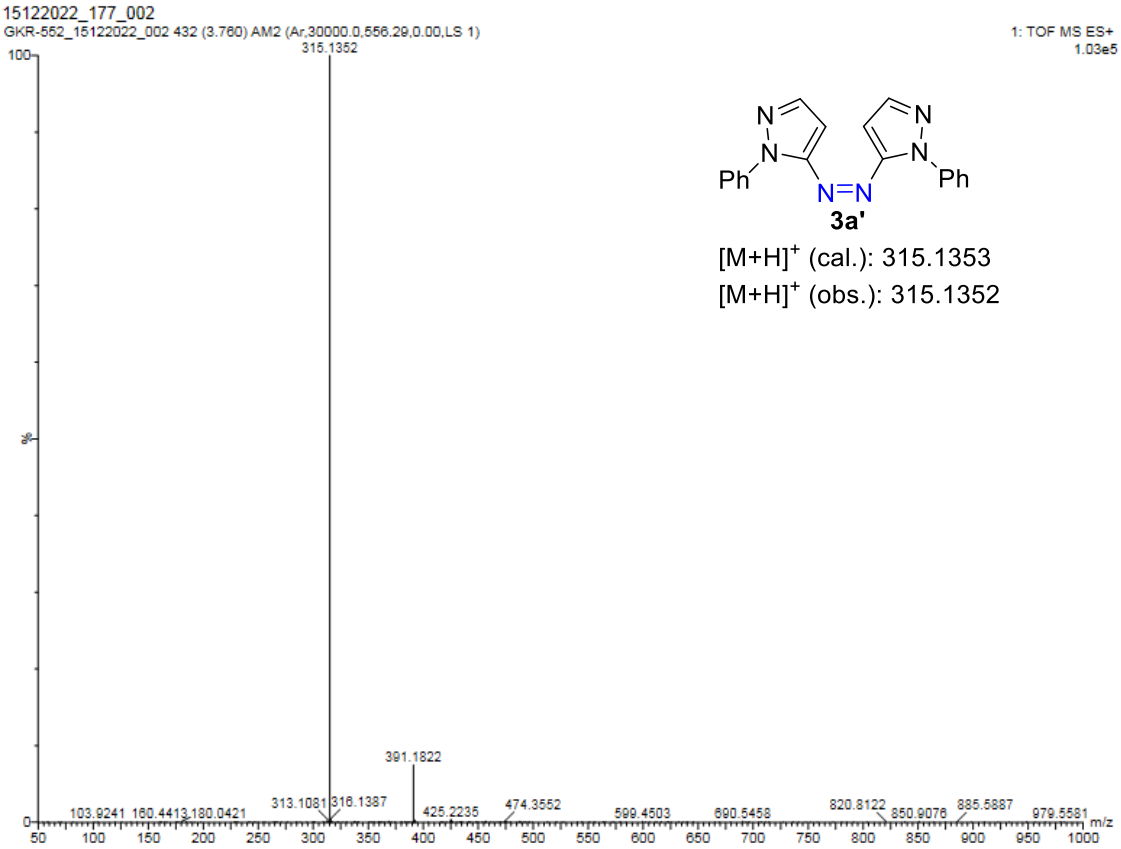


[F]

$[M+H]^+$ (calc.): 315.1353

$[M+H]^+$ (obs.): 315.1555

HRMS of *Z*-isomer (3a')



3a'

$[M+H]^+$ (cal.): 315.1353

$[M+H]^+$ (obs.): 315.1352