

## **An efficient, green approach for the synthesis of 2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylates using Bi<sub>2</sub>O<sub>3</sub>/ZrO<sub>2</sub> as a reusable catalyst**

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### **Catalyst instrumentation details**

Employing a Bruker D8 Advance instrument (Cu K radiation source with a wavelength of 1.5406 Å), the X-ray diffraction data related the structural phases of the catalyst were acquired. Using a Jeol JEM-1010 electron microscope and JEOL JSM-6100 microscope, the TEM and SEM analysis data was recorded. iTEM software was used analyze the TEM data and images. Employing the X-ray analyzer (energy-dispersive), EDX-analysis on the SEM images was conducted.

### **Experimental Section:**

All chemicals and reagents required for the reaction were of analytical grade and were used without any further purification. Bruker AMX 400 MHz NMR spectrometer was used to record the  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and  $^{15}\text{N}$  NMR spectral values. High-resolution mass data were obtained using a Bruker micro TOF-Q II ESI instrument operating at ambient temperature. The DMSO- $d_6$  solution was utilized for this while TMS served as the internal standard. TMS was further used as an internal standard for reporting the all chemical shifts in  $\delta$  (ppm). Purity of all the reaction products was confirmed by TLC using aluminum plates coated with silica gel (Merck Kieselgel 60 F254).

Ethyl 6-amino-5-cyano-4-(2-methoxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5a):

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 1.01 (t,  $J$  = 7.12 Hz, 3H, CH<sub>3</sub>), 3.69 (s, 3H, OCH<sub>3</sub>), 4.01-4.06 (m, 2H, CH<sub>2</sub>), 5.05 (s, 1H, CH), 6.82 (d,  $J$  = 8.56 Hz, 2H, ArH), 6.85 (s, 2H, NH<sub>2</sub>), 6.89 (dd,  $J$  = 1.56 Hz,  $J$  = 1.56 Hz, 1H, ArH), 6.94 (d,  $J$  = 8.04, 1H, ArH), 7.15-7.22 (m, 1H, ArH), 13.57 (s, 1H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ): 13.57, 31.62, 55.43, 56.00, 60.62, 103.58, 111.33, 120.21, 127.87, 128.59, 132.41, 136.46, 156.25, 156.60, 158.25, 160.56;  $^{15}\text{N}$  NMR (40.55 MHz, DMSO- $d_6$ )  $\delta$  = 6.85 (s, 2H, NH<sub>2</sub>), 13.57 (s, 1H, NH). HRMS of [C<sub>17</sub>H<sub>16</sub>N<sub>4</sub>O<sub>4</sub>-H<sup>+</sup>] (m/z): 339.1082; Calcd.: 339.0992.

Ethyl 6-amino-5-cyano-4-(4-methoxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5b):

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 1.08 (t,  $J$  = 7.08 Hz, 3H, CH<sub>3</sub>), 3.70 (s, 3H, OCH<sub>3</sub>), 4.07-4.12 (m, 2H, CH<sub>2</sub>), 4.69 (s, 1H, CH), 6.83 (d,  $J$  = 8.56 Hz, 2H, ArH), 6.97 (s, 2H, NH<sub>2</sub>), 7.00 (d,  $J$  = 8.6 Hz, 2H, ArH), 13.69 (s, 1H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ): 13.77, 36.16, 54.95, 58.16, 60.79, 113.53, 115.16, 120.31, 124.08, 128.31, 133.32, 137.07, 157.87, 158.12, 159.87.  $^{15}\text{N}$  NMR (40.55 MHz, DMSO- $d_6$ )  $\delta$  = 6.97 (s, 2H, NH<sub>2</sub>), 13.69 (s, 1H, NH). HRMS of [C<sub>17</sub>H<sub>16</sub>N<sub>4</sub>O<sub>4</sub>-H<sup>+</sup>] (m/z): 339.1082; Calcd.: 339.1093.

Ethyl 6-amino-5-cyano-4-(2,3-dimethoxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5c):

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 1.06 (t,  $J$  = 7.04 Hz, 3H, CH<sub>3</sub>), 3.54 (s, 3H, OCH<sub>3</sub>), 3.76 (s, 3H, OCH<sub>3</sub>), 4.07-4.09 (m, 2H, CH<sub>2</sub>), 4.91 (s, 1H, CH), 6.60 (d,  $J$  = 7.13 Hz, 2H, ArH), 6.89 (d,  $J$  = 8.28 Hz, 1H, ArH), 6.91 (s, 2H, NH<sub>2</sub>), 6.95 (d,  $J$  = 7.92 Hz, 1H, ArH), 13.55 (s, 1H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ): 13.72, 32.79, 55.48, 56.90, 59.69, 60.67, 103.87, 111.46, 120.56, 121.37, 123.18, 128.68, 137.21, 146.42, 152.26, 155.91, 158.19, 160.48;  $^{15}\text{N}$  NMR (40.55 MHz, DMSO- $d_6$ )  $\delta$  = 6.91 (s, 2H, NH<sub>2</sub>), 13.55 (s, 1H, NH). HRMS of [C<sub>18</sub>H<sub>18</sub>N<sub>4</sub>O<sub>5</sub>+Na<sup>+</sup>] (m/z): 393.1188; Calcd.: 393.1175.

Ethyl 6-amino-5-cyano-4-(3,4-dimethoxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5d):

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 1.08 (t,  $J$  = 7.12 Hz, 3H, CH<sub>3</sub>), 3.68 (d,  $J$  = 5.72 Hz, 6H, OCH<sub>3</sub>), 4.08-4.13 (m, 2H, CH<sub>2</sub>), 4.70 (s, 1H, CH), 6.56 (dd,  $J$  = 1.84 Hz,  $J$  = 1.84 Hz, 1H, ArH), 6.71 (d,  $J$  = 1.84 Hz, 1H, ArH), 6.55 (d,  $J$  = 8.32 Hz, 1H, ArH), 6.96 (s, 2H, NH<sub>2</sub>), 13.55 (s, 1H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ): 13.76, 36.46, 55.44, 58.04, 60.79, 103.84, 111.73, 119.22, 127.24, 128.93, 137.55, 148.25, 154.42, 155.48, 158.15, 159.93, 160.59;  $^{15}\text{N}$  NMR (40.55 MHz, DMSO- $d_6$ )  $\delta$  = 6.96 (s, 2H, NH<sub>2</sub>), 13.55 (s, 1H, NH). HRMS of [C<sub>18</sub>H<sub>19</sub>N<sub>4</sub>O<sub>5</sub>+H<sup>+</sup>] (m/z): 371.0389; Calcd.: 371.0395.

Ethyl 6-amino-5-cyano-4-(2,5-dimethoxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5e):

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 1.04 (t,  $J$  = 7.12 Hz, 3H, CH<sub>3</sub>), 3.61 (d,  $J$  = 6.61 Hz, 6H, OCH<sub>3</sub>), 4.03-4.09 (m, 2H, CH<sub>2</sub>), 4.97 (s, 1H, CH), 6.46 (d,  $J$  = 2.66 Hz, 1H, ArH), 6.74 (dd,  $J$  = 3 Hz,  $J$  = 3.04 Hz, 1H, ArH), 6.85 (s, 1H, ArH), 6.87 (s, 2H, NH<sub>2</sub>), 13.58 (s, 1H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ): 13.58, 32.12, 55.18, 56.05, 56.57, 60.69, 103.39, 111.52, 112.60, 115.48, 120.33, 128.61, 133.54, 150.99, 152.82, 156.18, 158.25, 160.62;  $^{15}\text{N}$  NMR (40.55 MHz, DMSO- $d_6$ )  $\delta$  = 6.87 (s, 2H, NH<sub>2</sub>), 13.58 (s, 1H, NH).

Ethyl 6-amino-5-cyano-4-(2,4,6-trimethoxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5f):

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 1.06 (t,  $J$  = 7.09 Hz, 3H, CH<sub>3</sub>), 3.73 (s, 3H, OCH<sub>3</sub>), 3.89 (d,  $J$  = 7.96 Hz, 6H, OCH<sub>3</sub>), 4.02-4.11 (m, 2H, CH<sub>2</sub>), 5.27 (s, 1H, CH), 6.33 (s, 2H, ArH), 6.88 (s, 2H, NH<sub>2</sub>), 13.25 (s, 1H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ): 13.78, 25.41, 55.04, 55.79, 56.11, 60.38, 103.69, 104.51, 112.39, 113.84, 116.38, 120.70, 156.67, 158.59, 159.55, 167.37;  $^{15}\text{N}$  NMR (40.55 MHz, DMSO- $d_6$ )  $\delta$  = 6.88 (s, 2H, NH<sub>2</sub>), 13.25 (s, 1H, NH). HRMS of [C<sub>19</sub>H<sub>20</sub>N<sub>4</sub>O<sub>6</sub>+Na<sup>+</sup>] (m/z): 423.1297; Calcd.: 423.1281.

Ethyl 6-amino-5-cyano-4-(3-hydroxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5g):

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 1.07 (t,  $J$  = 7.08 Hz, 3H, CH<sub>3</sub>), 4.08-4.13 (m, 2H, CH<sub>2</sub>), 4.63 (s, 1H, CH), 6.40 (s, 1H, ArH), 6.51-6.58 (m, 2H, ArH), 6.99 (s, 2H, NH<sub>2</sub>), 7.05 (t,  $J$  = 7.79 Hz, 1H, ArH), 9.27 (s, 1H, OH), 13.71 (s, 1H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ): 13.74, 36.85, 55.98, 60.80, 103.74, 113.59, 114.06, 117.99, 120.26, 128.95, 129.07, 146.30, 155.56, 157.16, 158.16, 160.02;  $^{15}\text{N}$  NMR (40.55 MHz, DMSO- $d_6$ )  $\delta$  = 6.99 (s, 2H, NH<sub>2</sub>), 13.71 (s, 1H, NH).

Ethyl 6-amino-5-cyano-4-(3,4-dihydroxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5h):

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 1.12 (t,  $J$  = 7.12 Hz, 3H, CH<sub>3</sub>), 4.10-4.15 (m, 2H, CH<sub>2</sub>), 4.54 (s, 1H, CH), 6.37-6.42 (m, 2H, ArH), 6.60 (d,  $J$  = 8.04 Hz, 1H, ArH), 6.93 (s, 2H, NH<sub>2</sub>), 8.67 (s, 1H, OH), 8.79 (s, 1H, OH), 13.65 (s, 1H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ): 13.82, 36.34, 58.42, 60.80, 104.41, 114.50, 115.04, 118.12, 120.41, 128.81, 136.05, 143.91, 144.55, 155.47, 158.23, 159.83;  $^{15}\text{N}$  NMR (40.55 MHz, DMSO- $d_6$ )  $\delta$  = 6.93 (s, 2H, NH<sub>2</sub>), 13.65 (s, 1H, NH). HRMS of [C<sub>16</sub>H<sub>14</sub>N<sub>4</sub>O<sub>5</sub>-H<sup>+</sup>] (m/z): 341.0886; Calcd.: 341.0886.

Ethyl 6-amino-5-cyano-4-(2-nitrophenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5i):

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  = 0.92 (t,  $J$  = 7.08 Hz, 3H, CH<sub>3</sub>), 3.96-4.05 (m, 2H, CH<sub>2</sub>), 5.57 (s, 1H, CH), 7.14 (s, 2H, NH<sub>2</sub>), 7.22 (dd,  $J$  = 1.08,  $J$  = 1.08 Hz, 1H, ArH), 7.44-7.48 (m,

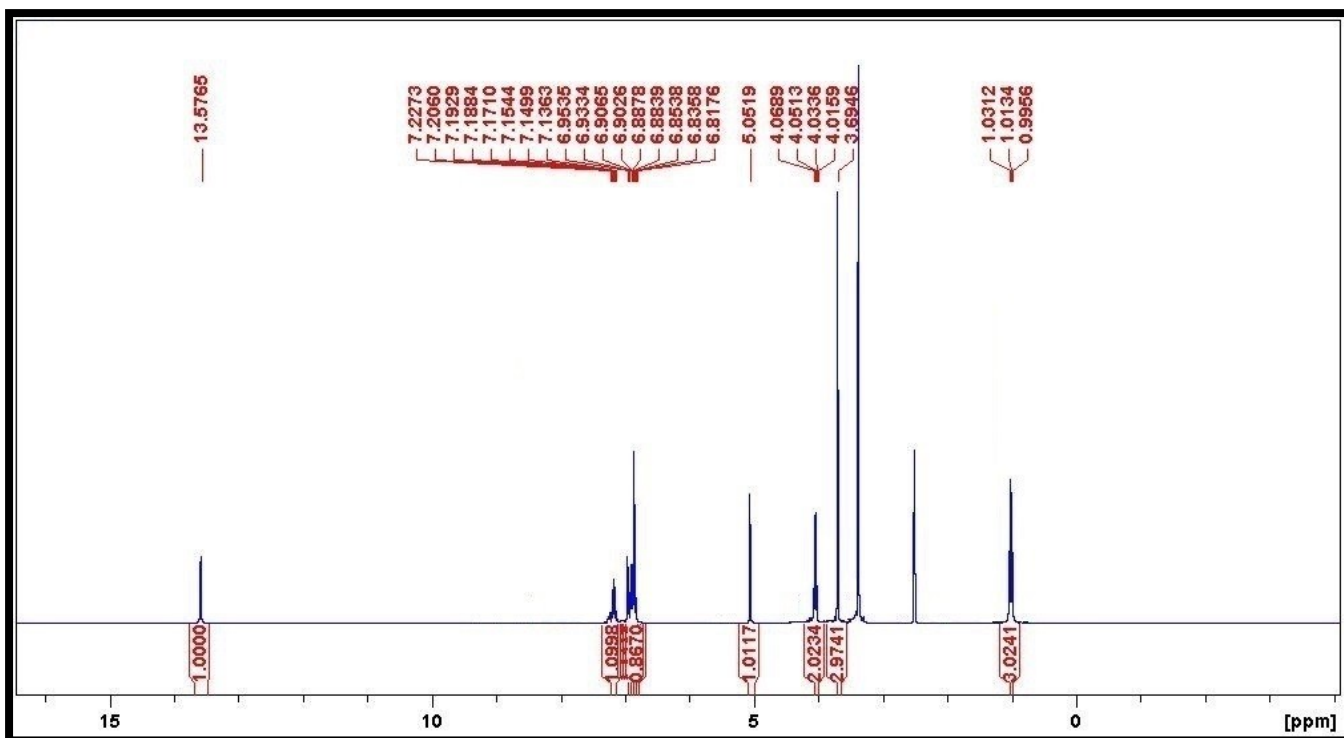
1H, ArH), 7.61-7.65 (m, 1H, ArH), 7.92 (dd,  $J = 1.12$  Hz,  $J = 1.12$  Hz, ArH), 13.79 (s, 1H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ): 13.63, 31.49, 56.12, 60.85, 102.33, 119.60, 128.02, 128.99, 131.07, 133.64, 138.89, 148.20, 155.58, 157.73, 160.55;  $^{15}\text{N}$  NMR (40.55 MHz, DMSO- $d_6$ )  $\delta = 7.14$  (s, 2H, NH<sub>2</sub>), 13.79 (s, 1H, NH). HRMS of [ $\text{C}_{16}\text{H}_{13}\text{N}_5\text{O}_5\text{—H}^+$ ] (m/z): 354.0850; Calcd.: 354.0838.

Ethyl 6-amino-4-(4-bromophenyl)-5-cyano-2,4-dihydropyran[2,3-c]pyrazole-3-carboxylate (5j):

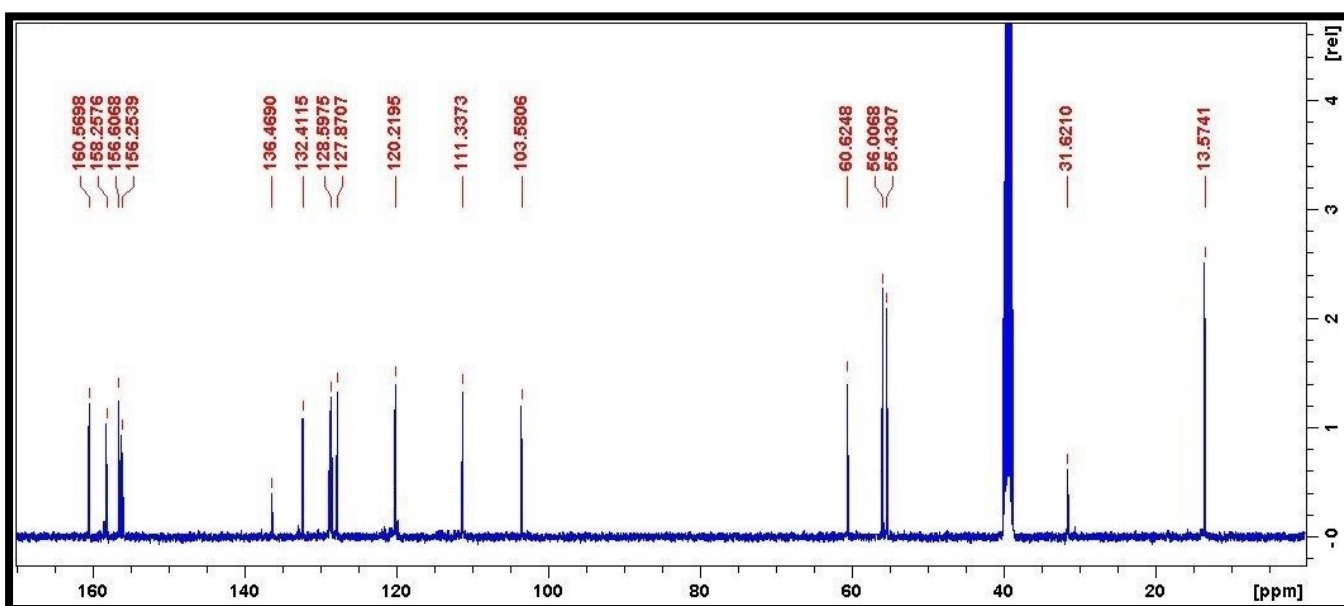
$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta = 1.05$  (t,  $J = 3.56$  Hz, 3H, CH<sub>3</sub>), 4.06-4.12 (m, 2H, CH<sub>2</sub>), 4.76 (s, 1H, CH), 7.05 (s, 2H, ArH), 7.07 (s, 2H, NH<sub>2</sub>), 7.47 (d,  $J = 8.32$ , 2H, ArH), 13.77 (s, 1H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ): 13.76, 36.37, 57.27, 60.85, 102.99, 119.59, 120.09, 129.06, 129.62, 131.11, 144.26, 155.45, 157.97, 160.00;  $^{15}\text{N}$  NMR (40.55 MHz, DMSO- $d_6$ )  $\delta = 7.07$  (s, 2H, NH<sub>2</sub>), 13.77 (s, 1H, NH). HRMS of [ $\text{C}_{16}\text{H}_{13}\text{BrN}_4\text{O}_3\text{—H}^+$ ] (m/z): 387.0106; Calcd.: 387.0093.

Ethyl 6-amino-5-cyano-4-(4-ethylphenyl)-2,4-dihydropyran[2,3-c]pyrazole-3-carboxylate (5k):

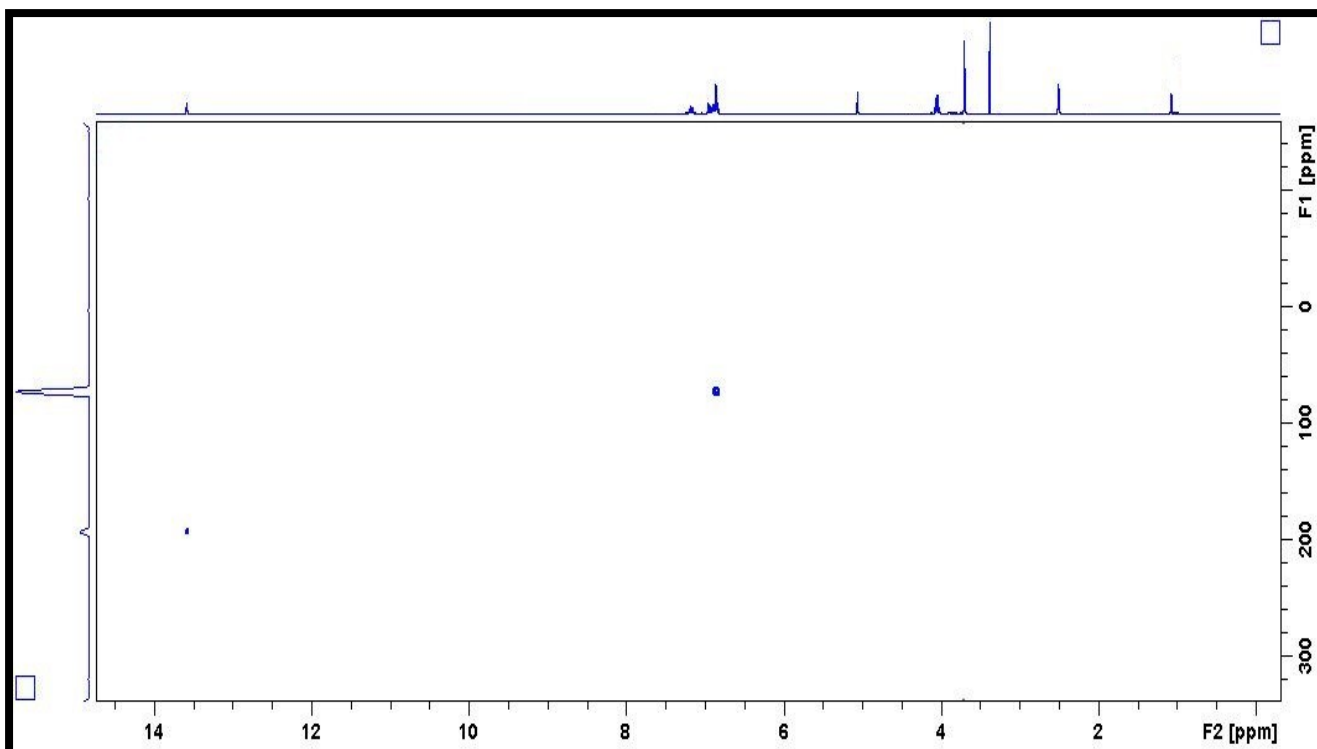
$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta = 1.06$  (d,  $J = 6.44$  Hz, 3H, CH<sub>3</sub>), 1.15 (d,  $J = 6.44$  Hz, 3H, CH<sub>3</sub>), 2.54 (d,  $J = 7.04$  Hz, 2H, CH<sub>2</sub>), 4.09 (d,  $J = 5.56$  Hz, 2H, CH<sub>2</sub>), 4.70 (s, 1H, CH), 6.99 (s, 2H, NH<sub>2</sub>), 7.11 (d,  $J = 6.60$  Hz, 4H, ArH), 13.70 (s, 1H, NH);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ): 13.71, 15.49, 27.70, 36.55, 57.95, 60.76, 103.83, 120.31, 127.17, 127.55, 128.91, 141.93, 142.23, 155.54, 158.12, 159.97;  $^{15}\text{N}$  NMR (40.55 MHz, DMSO- $d_6$ )  $\delta = 6.99$  (s, 2H, NH<sub>2</sub>), 13.70 (s, 1H, NH). HRMS of [ $\text{C}_{18}\text{H}_{18}\text{N}_4\text{O}_3\text{—H}^+$ ] (m/z): 337.1310; Calcd.: 337.1301.



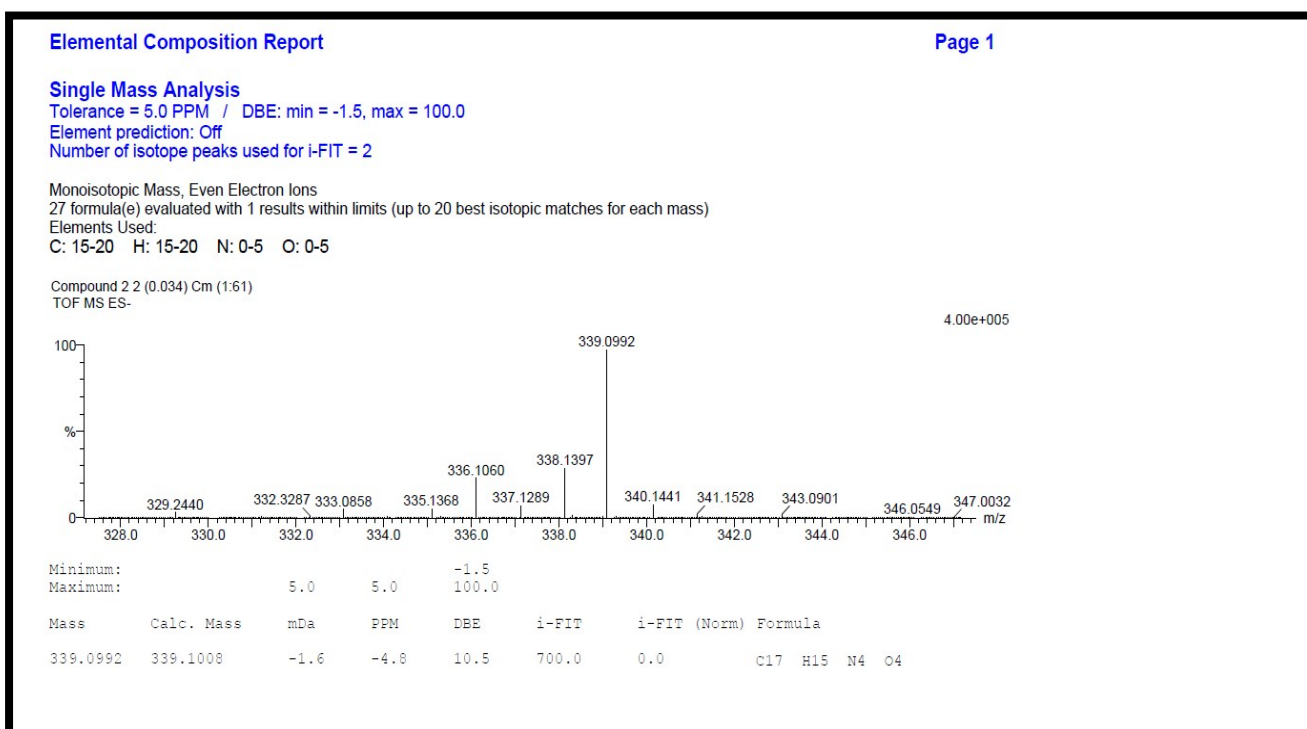
<sup>1</sup>H NMR spectra of compound 5a



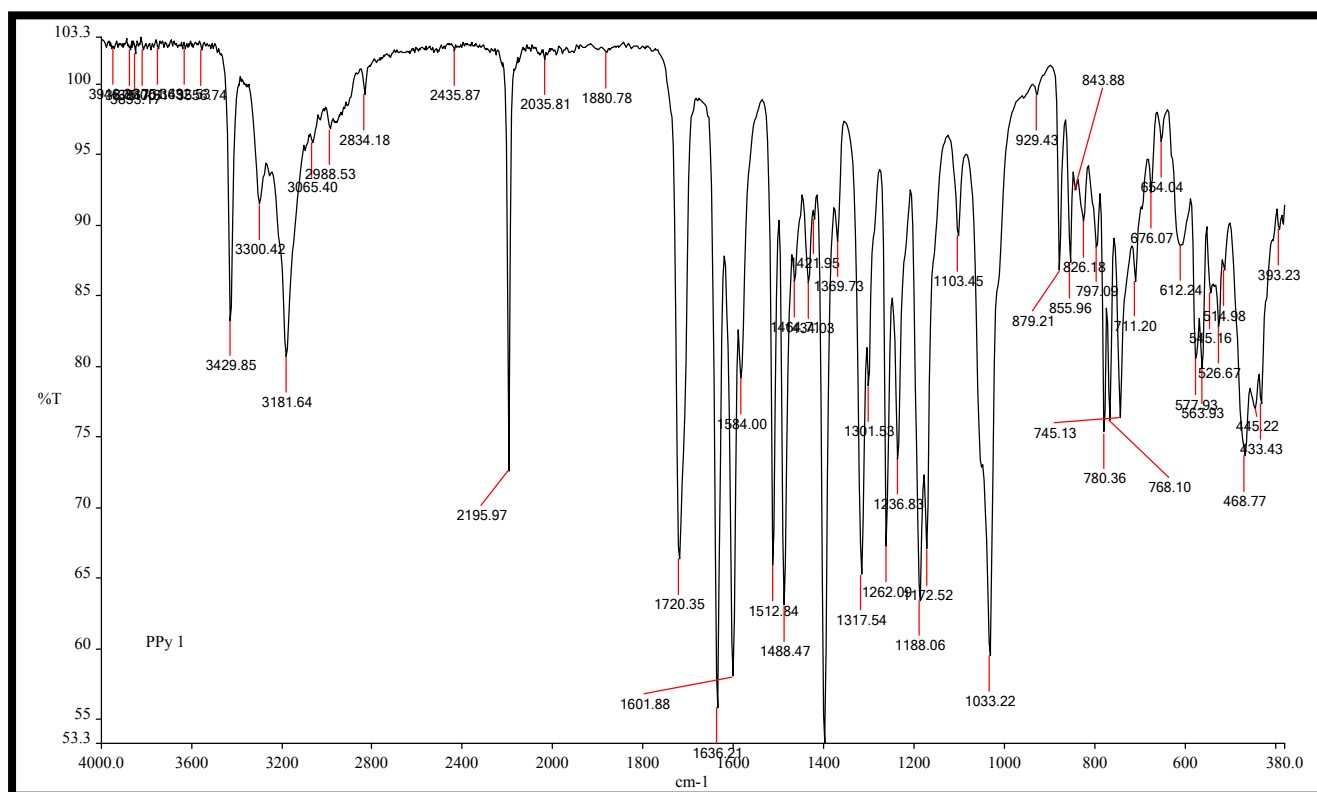
<sup>13</sup>C NMR spectra of compound 5a



<sup>15</sup>N NMR spectra of compound **5a**

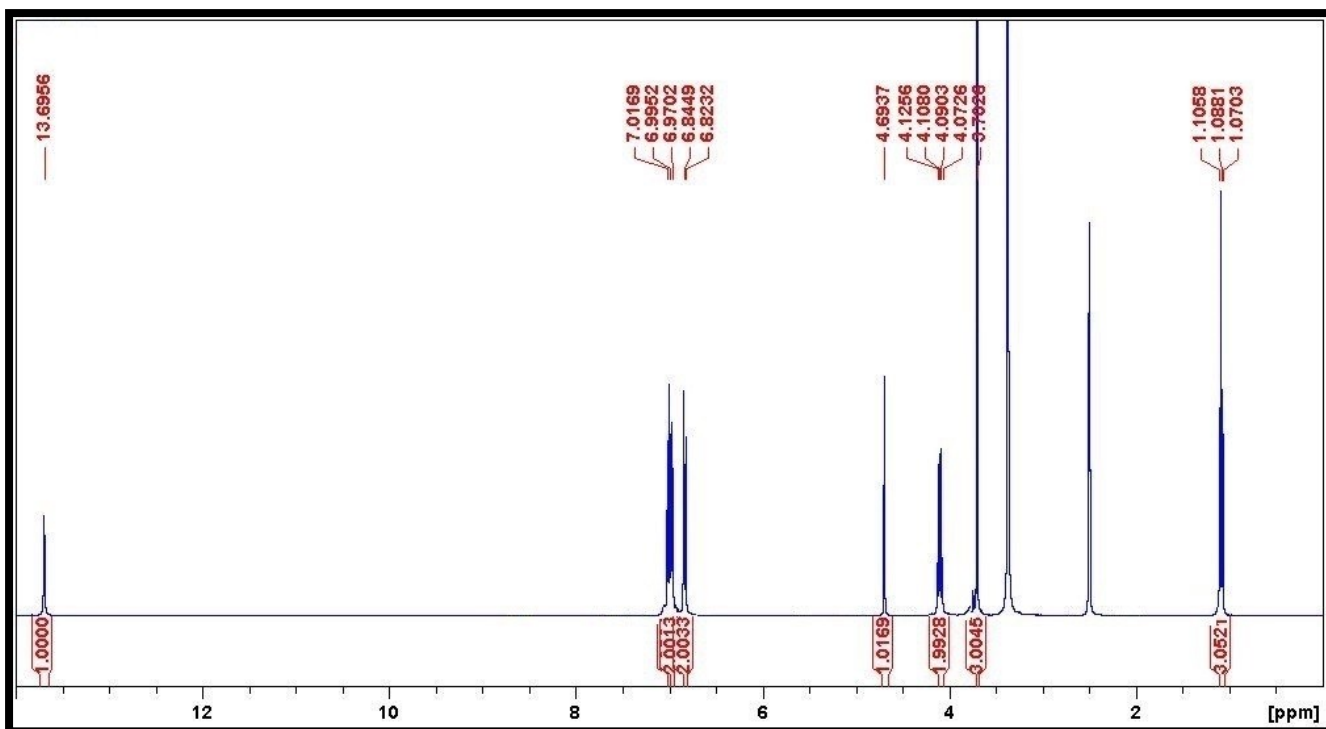


HRMS spectra of compound **5a**

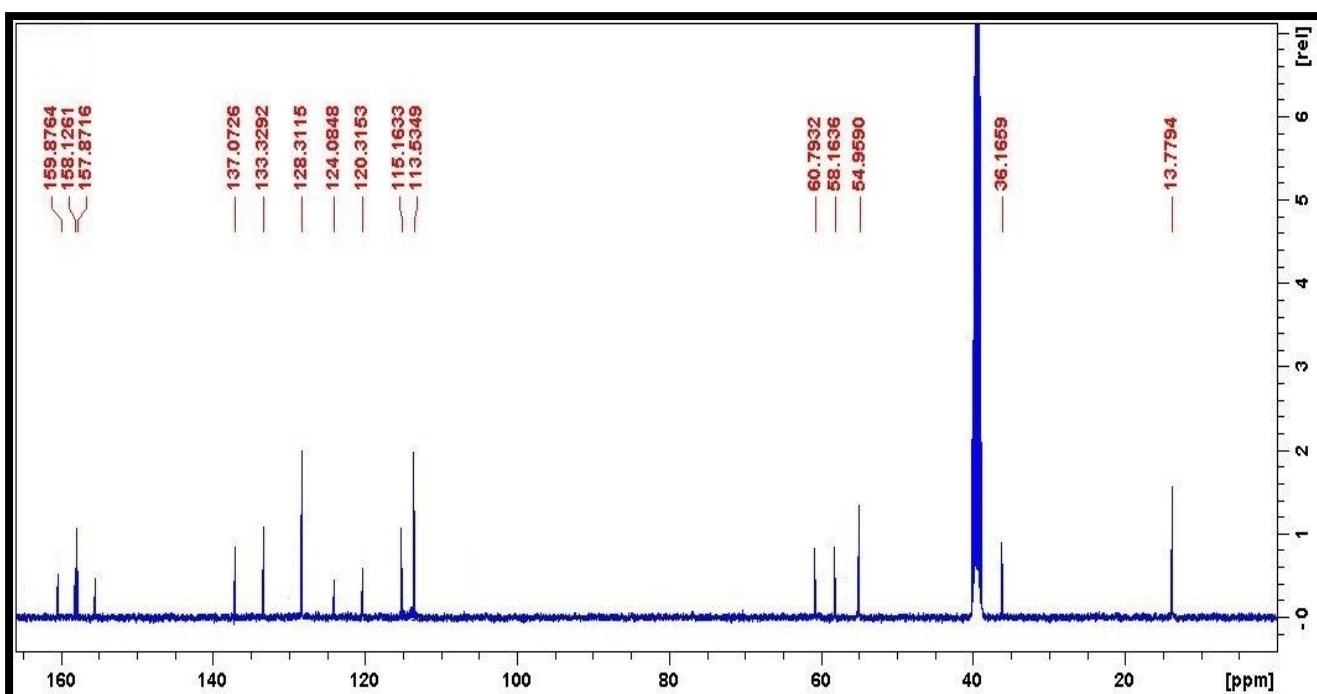


FT-IR spectra of compound 5a

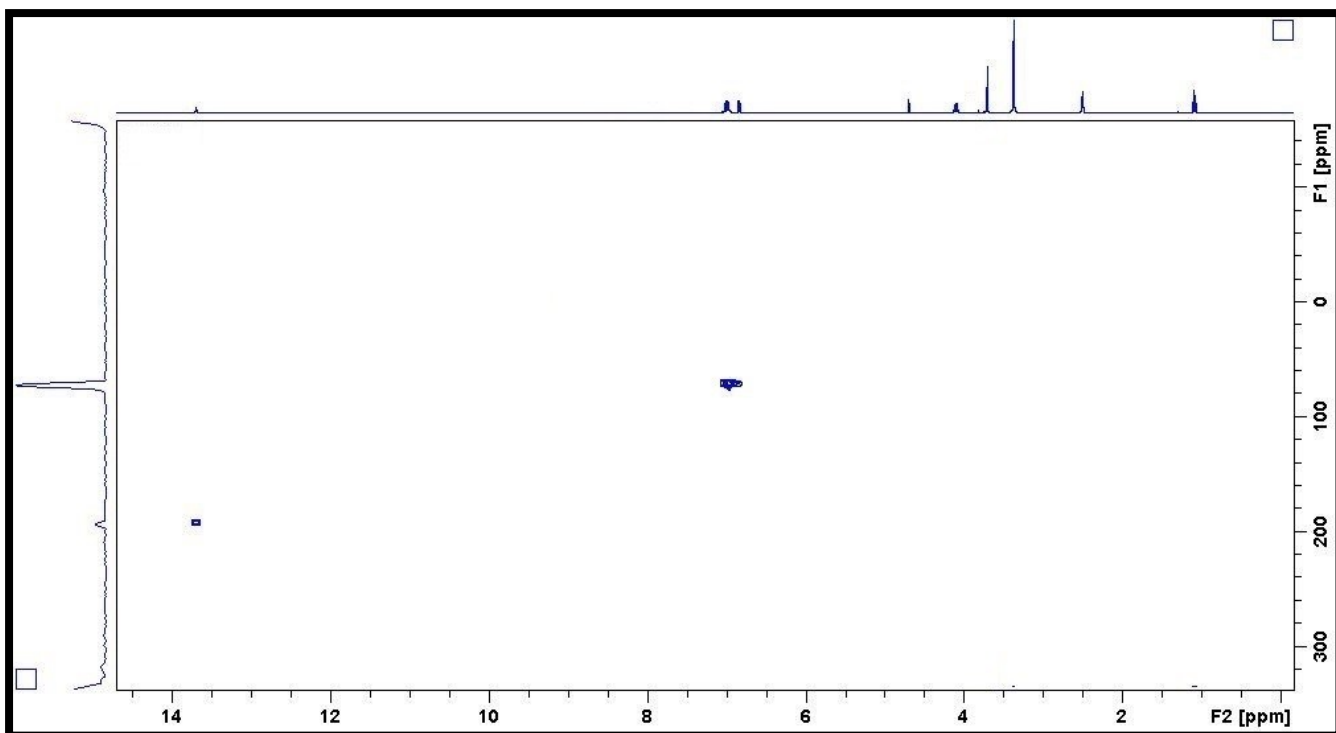




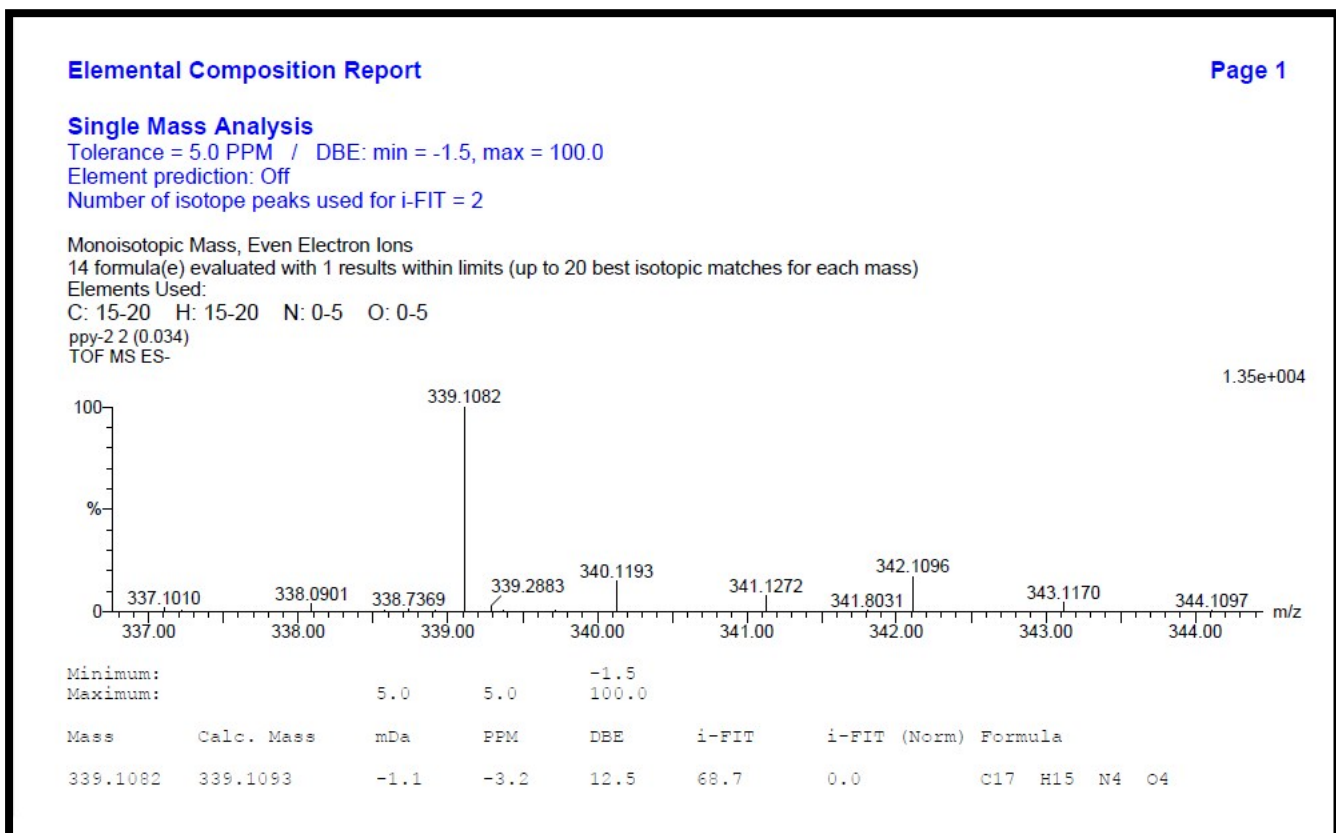
<sup>1</sup>H NMR spectra of compound **5b**



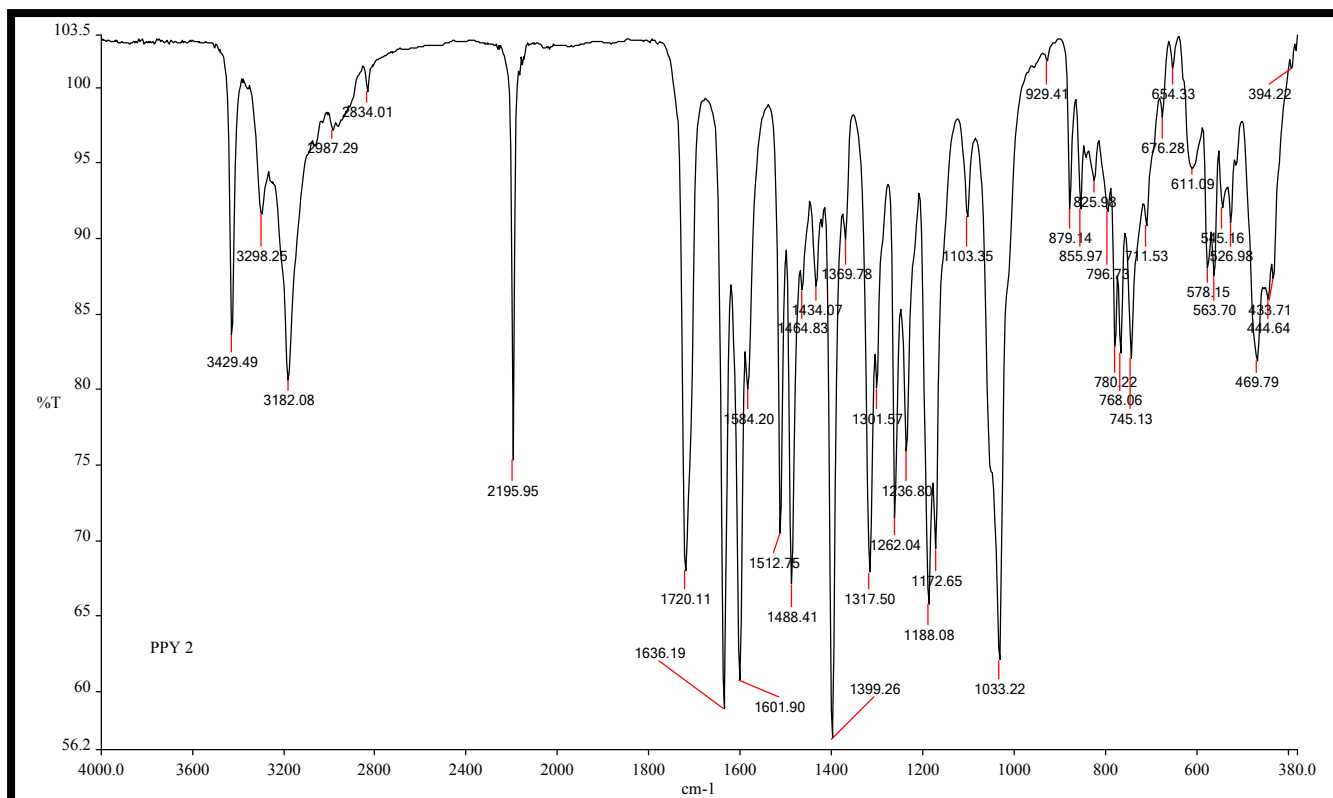
<sup>13</sup>C NMR spectra of compound **5b**



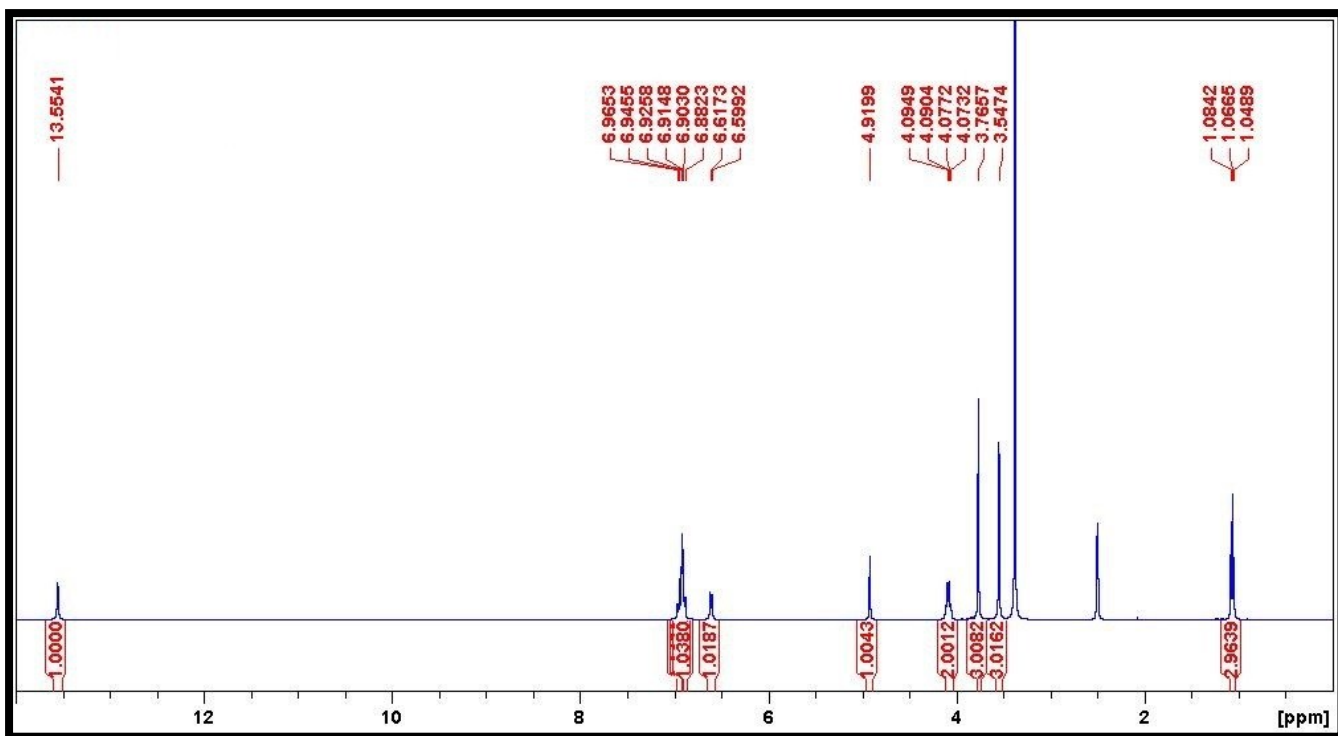
<sup>15</sup>N NMR spectra of compound **5b**



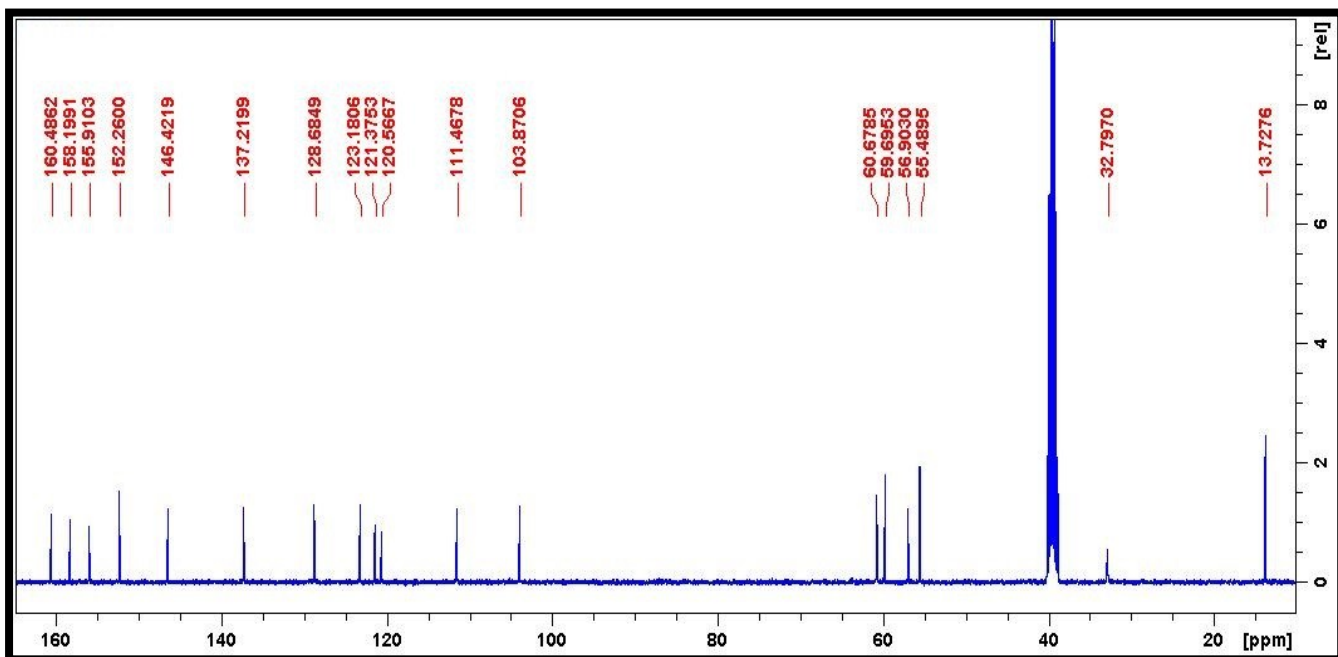
HRMS spectra of compound **5b**



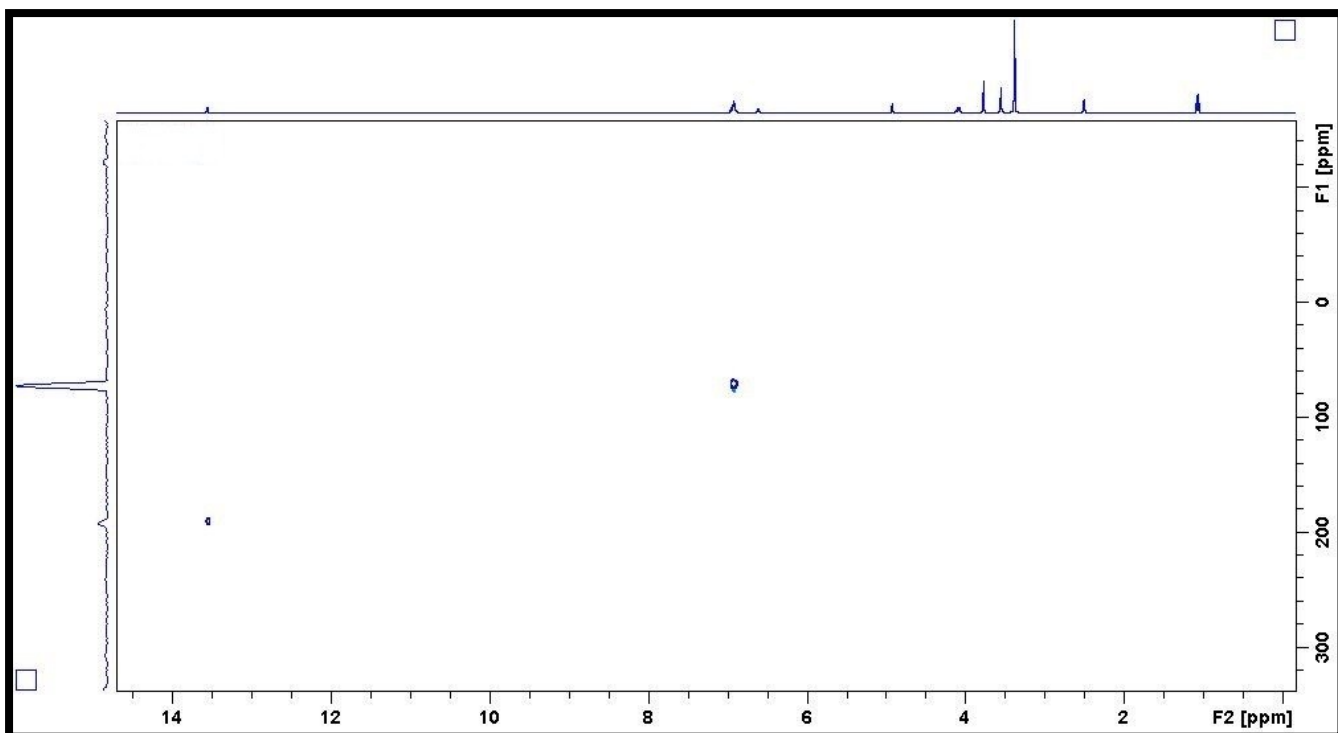
FT-IR spectra of compound **5b**



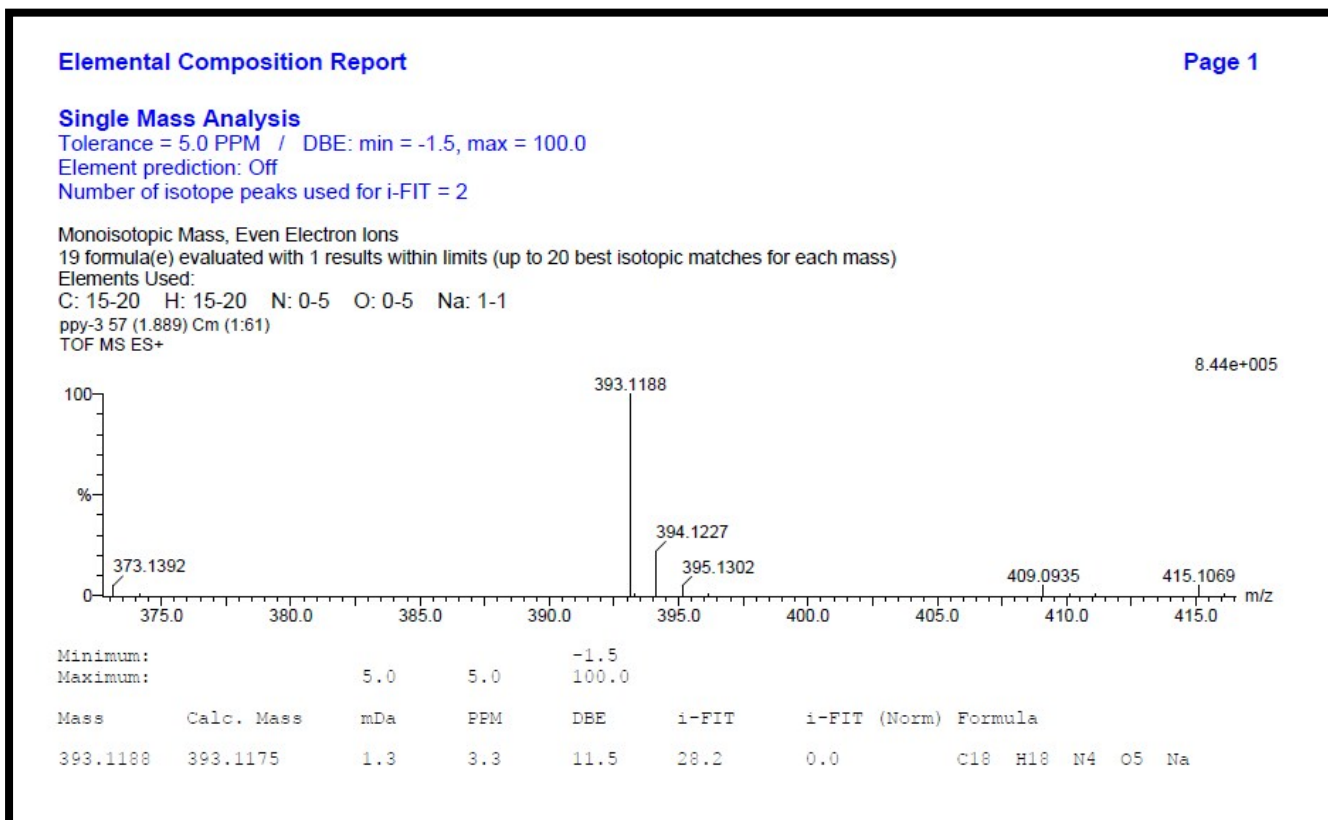
$^1\text{H}$  NMR spectra of compound **5c**



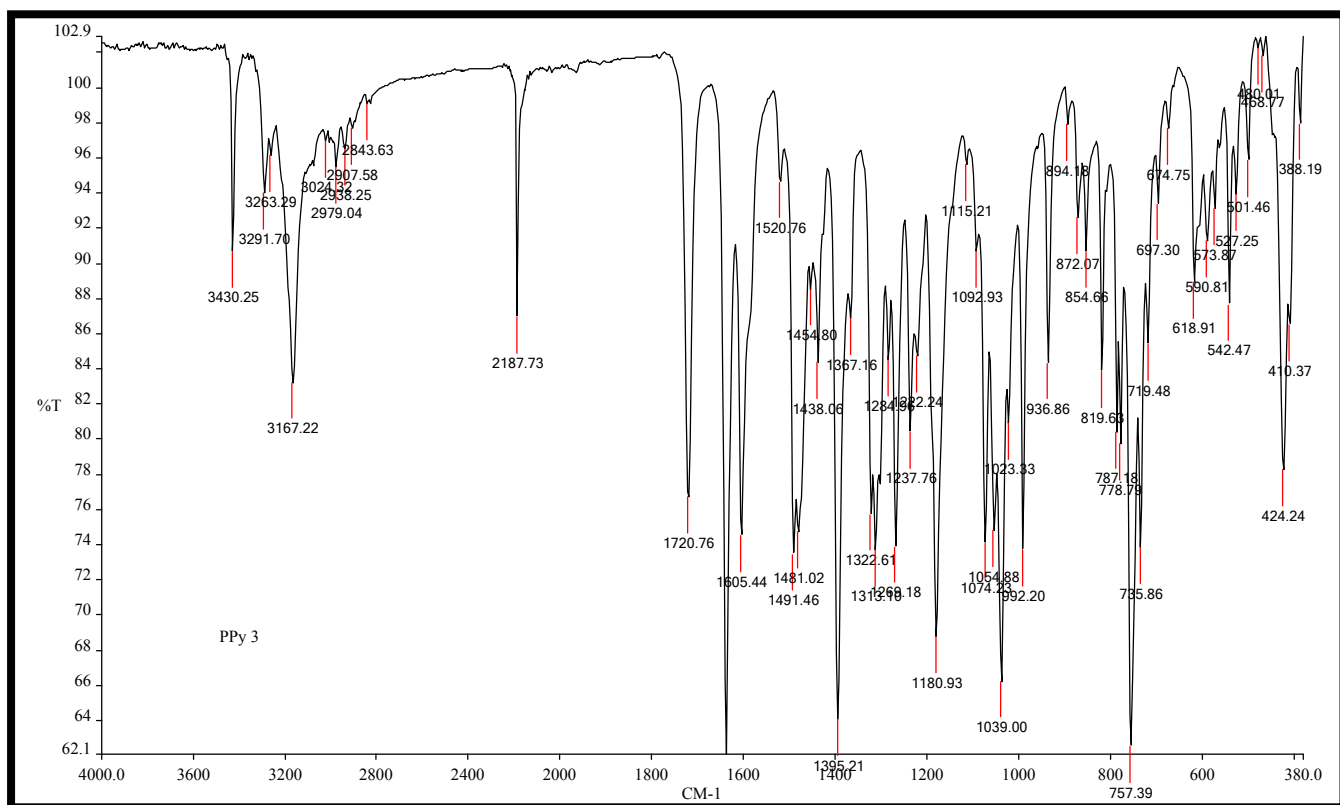
$^{13}\text{C}$  NMR spectra of compound **5c**



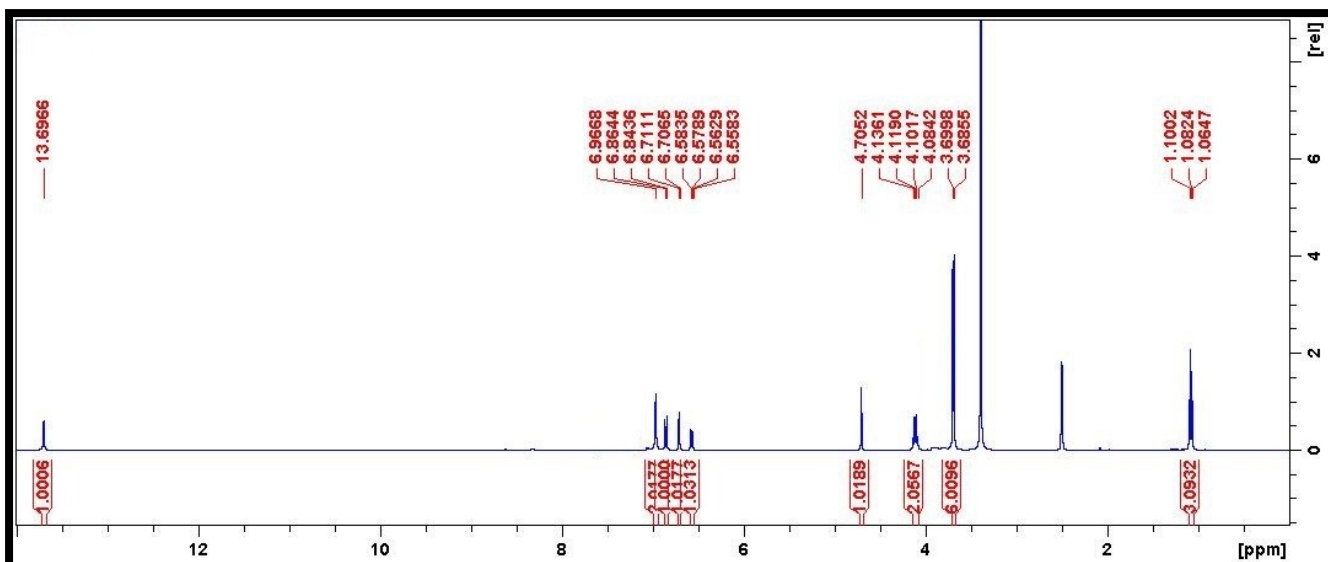
<sup>15</sup>N NMR spectra of compound **5c**



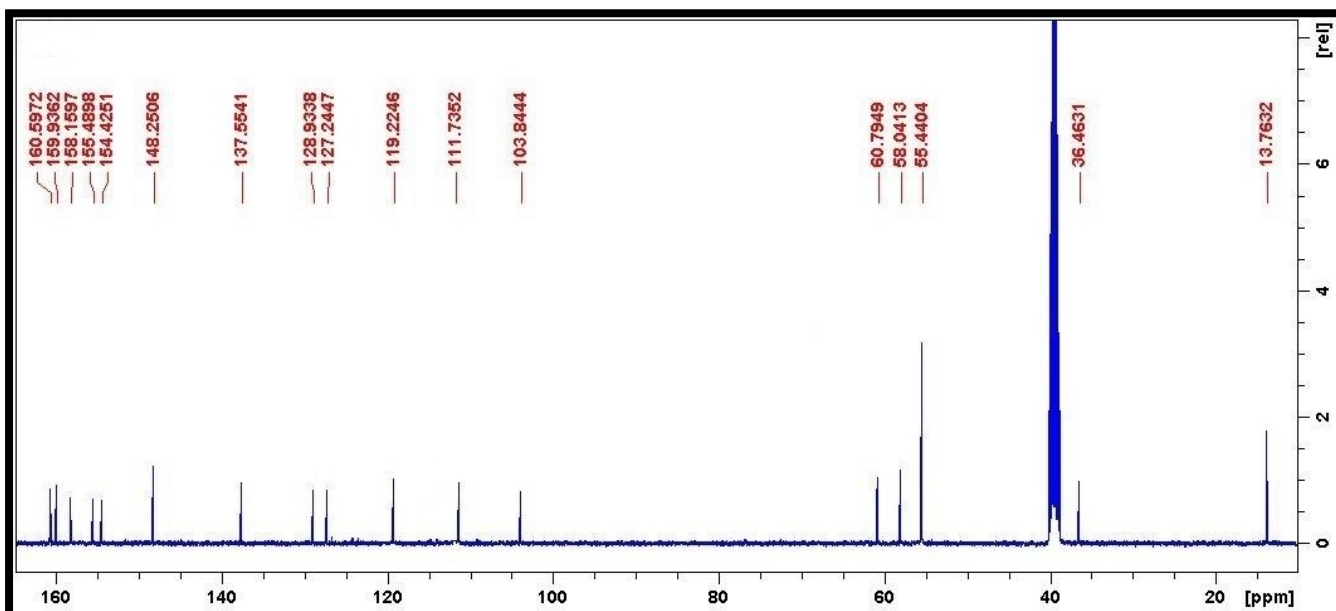
HRMS spectra of compound **5c**



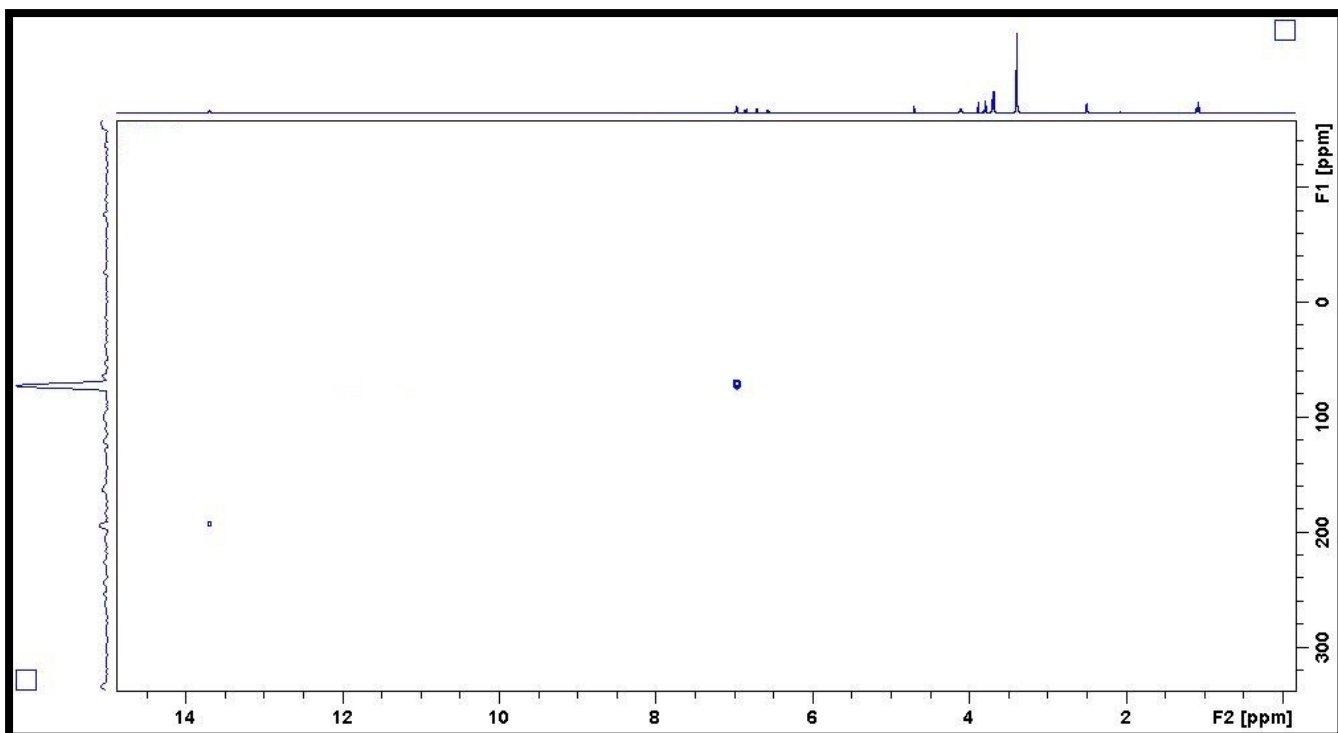
FT-IR spectra of compound 5c



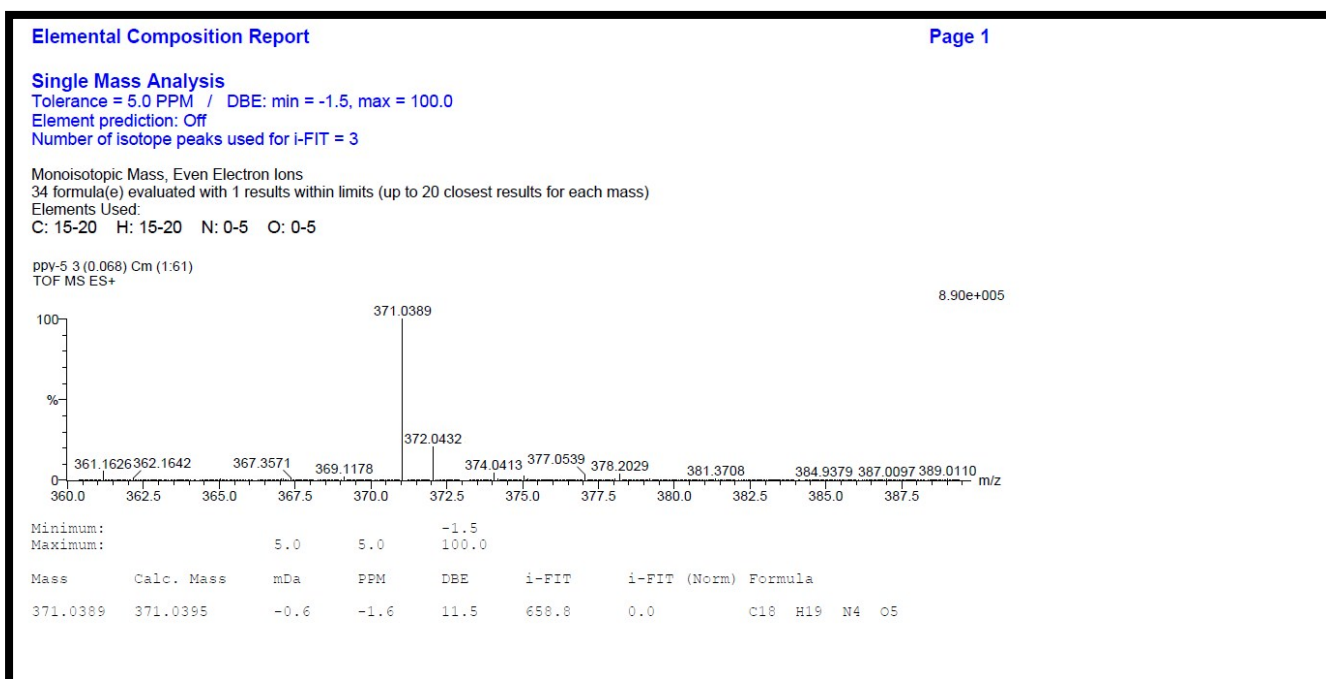
<sup>1</sup>H NMR spectra of compound **5d**



<sup>13</sup>C NMR spectra of compound **5d**

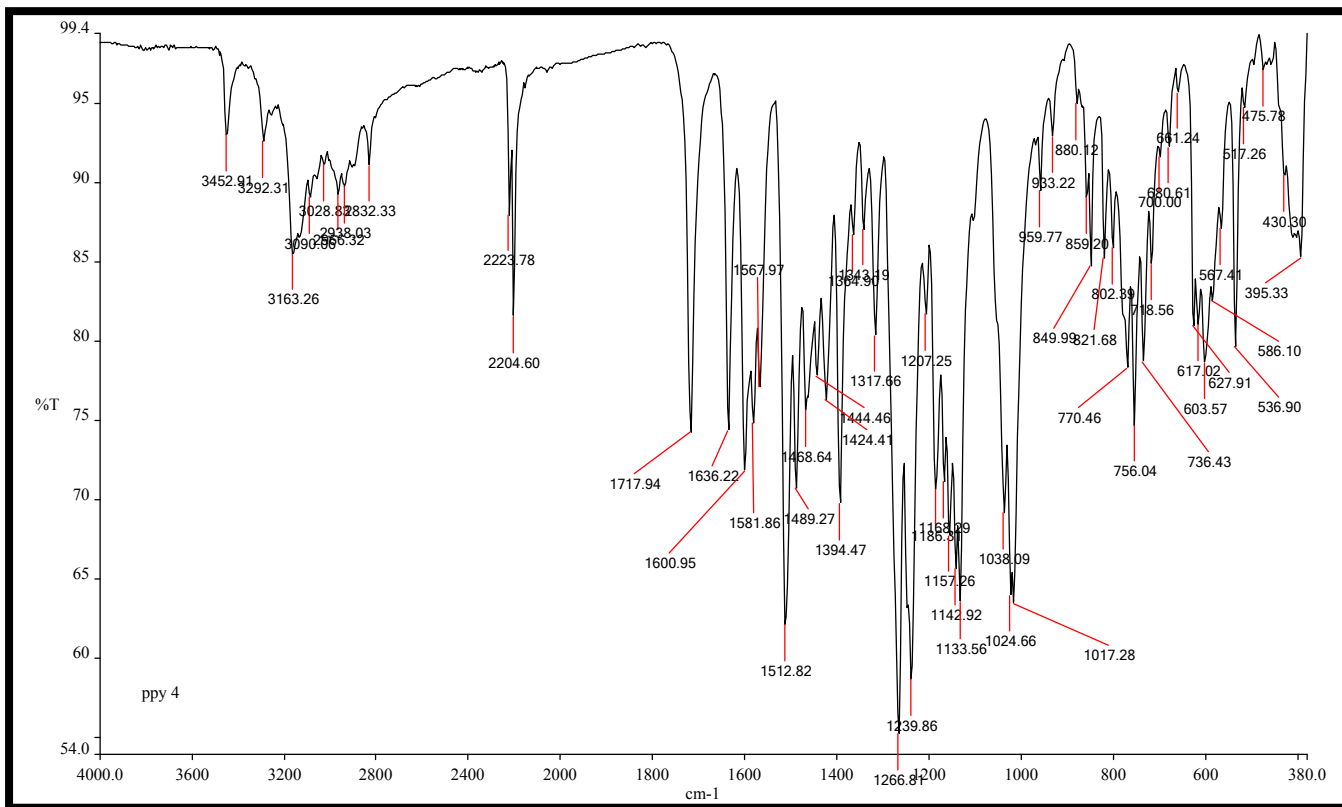


<sup>15</sup>N NMR spectra of compound **5d**

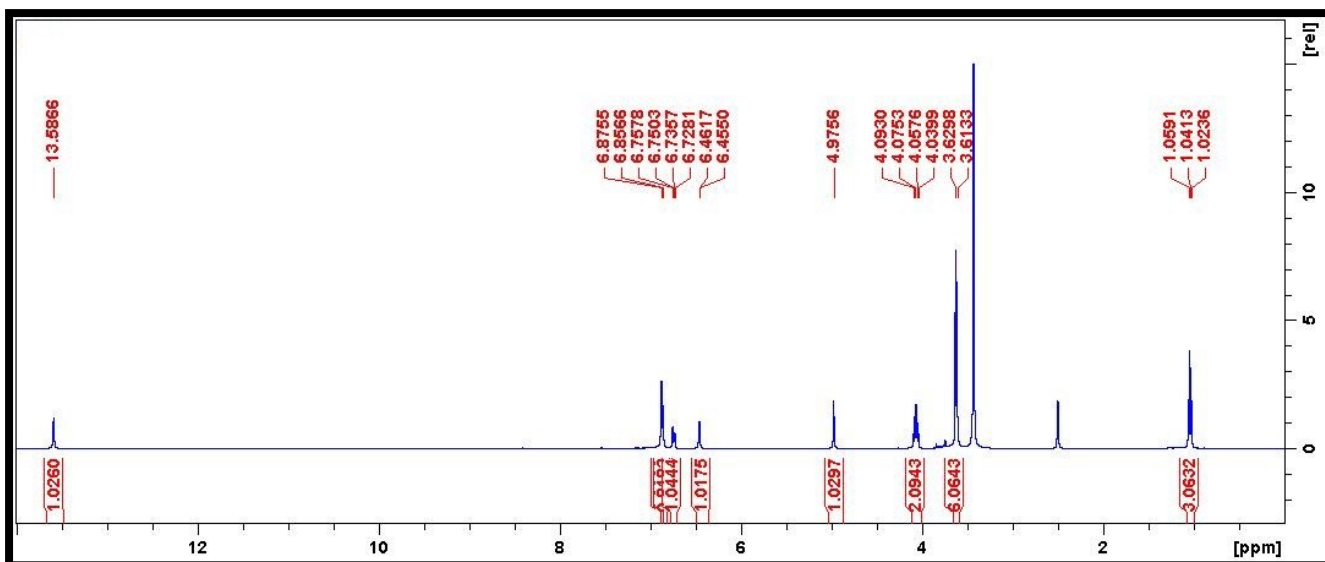


HRMS spectra of compound **5d**

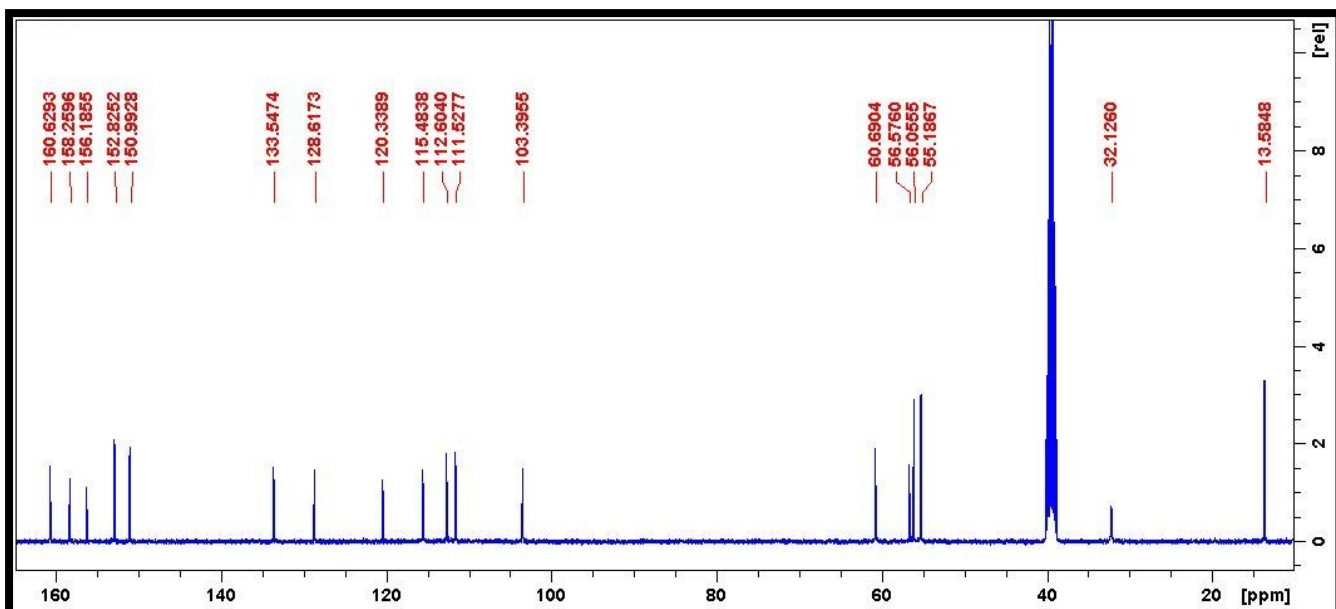




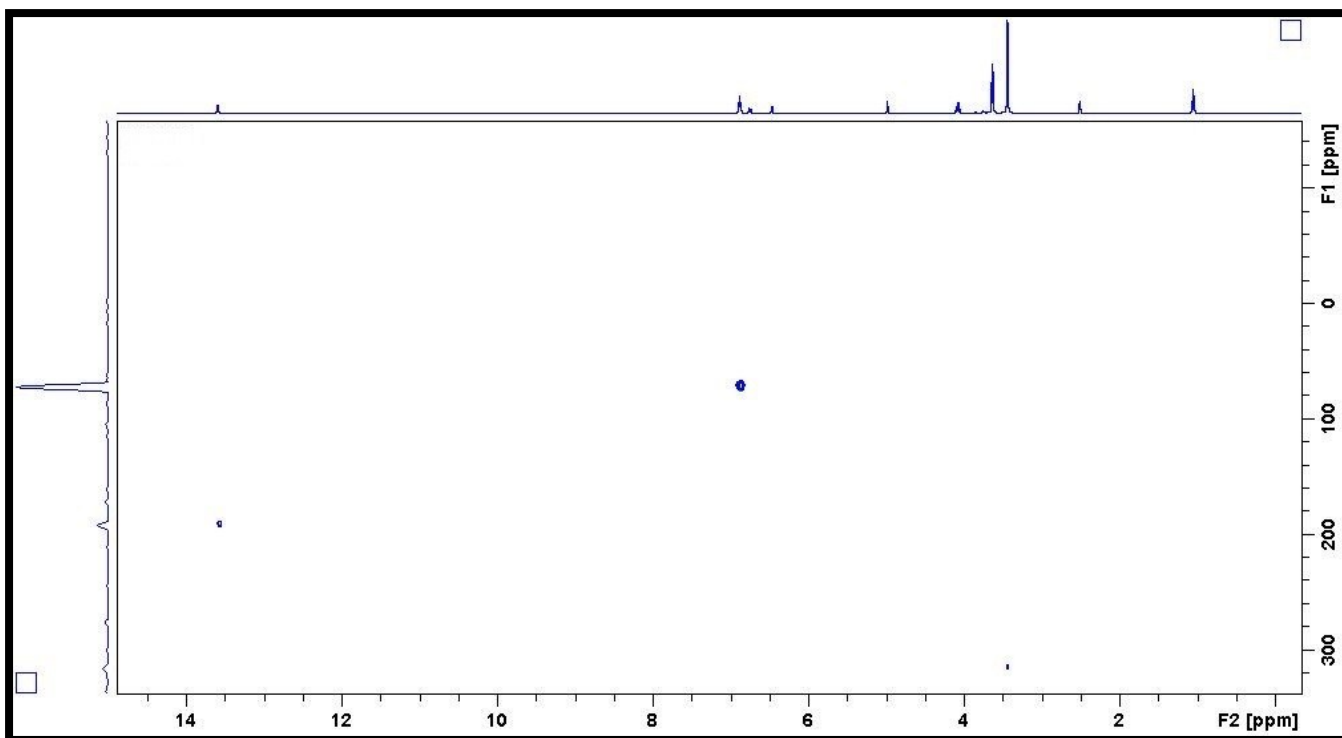
FT-IR spectra of compound 5d



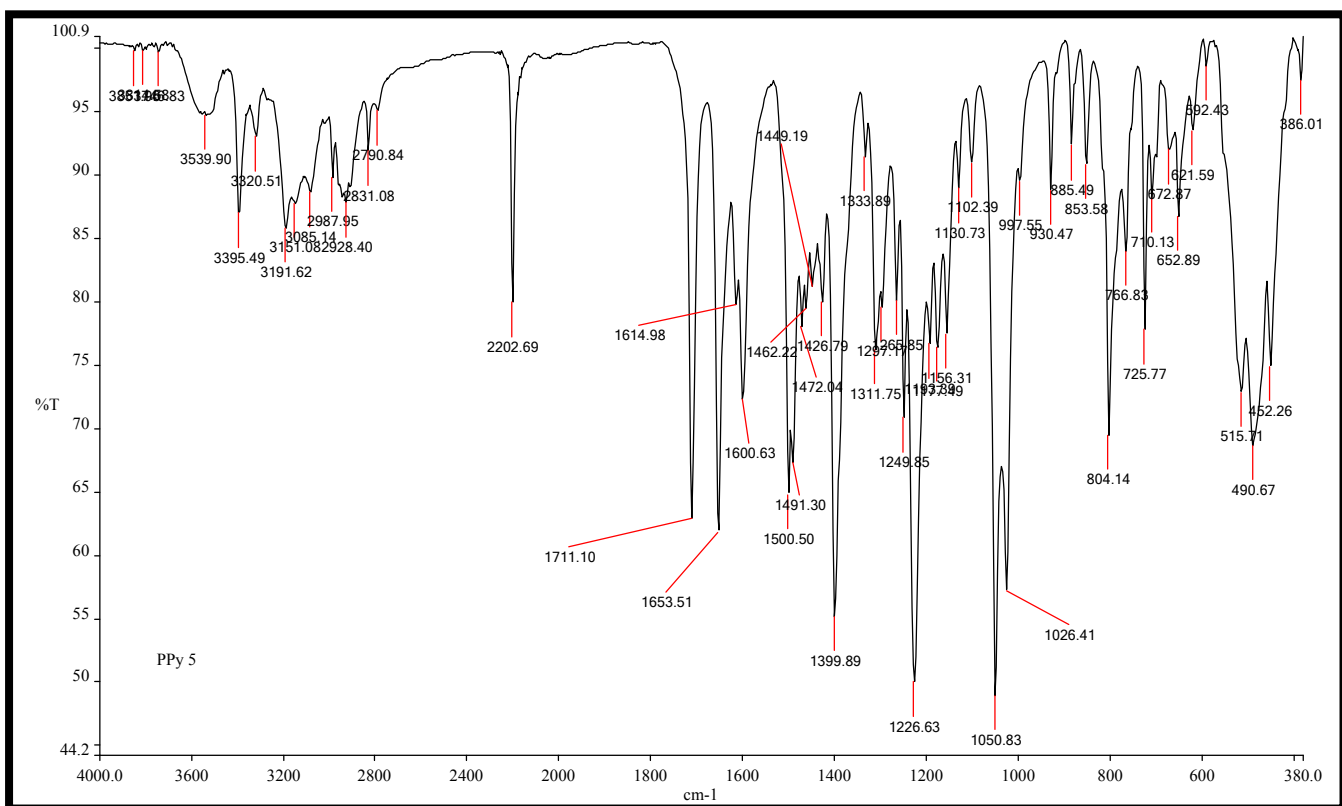
<sup>1</sup>H NMR spectra of compound 5e



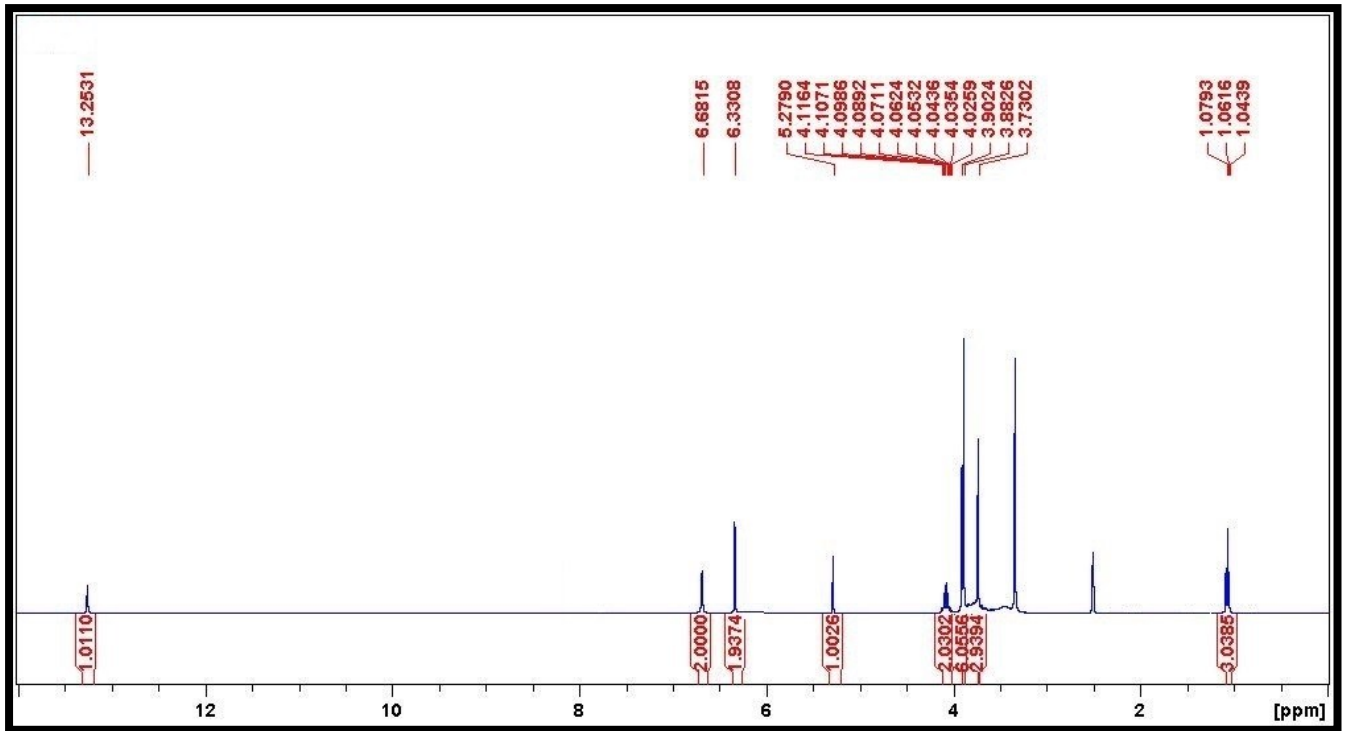
<sup>13</sup>C NMR spectra of compound 5e



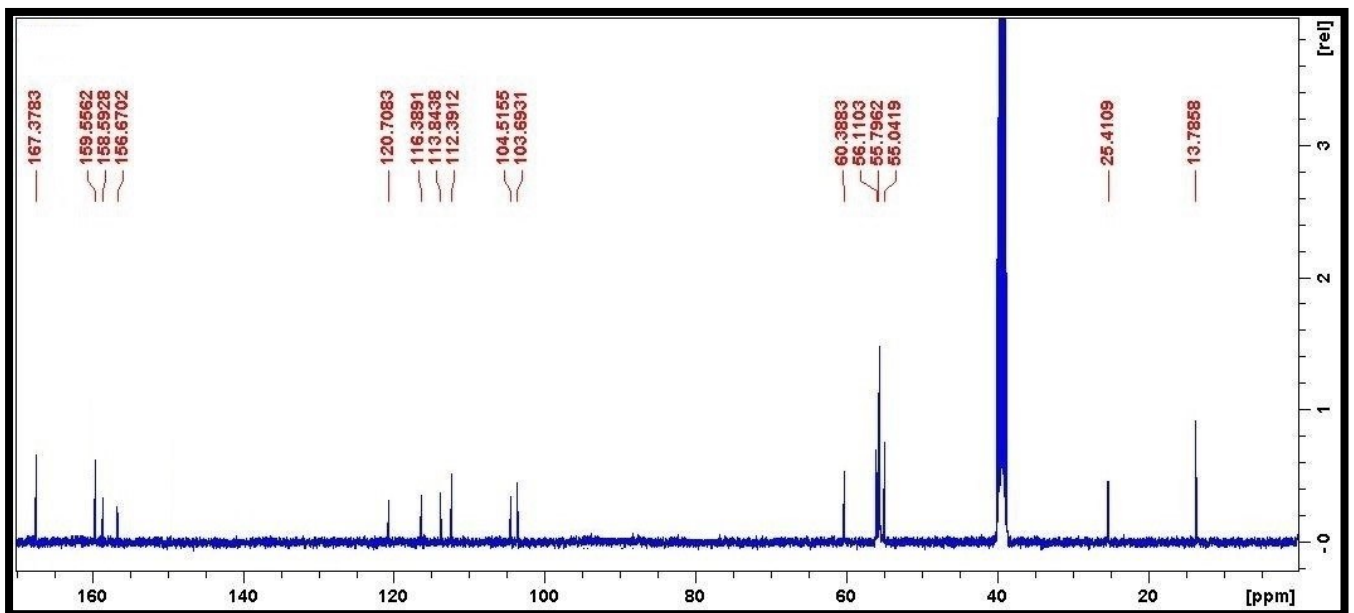
$^{15}\text{N}$  NMR spectra of compound **5e**



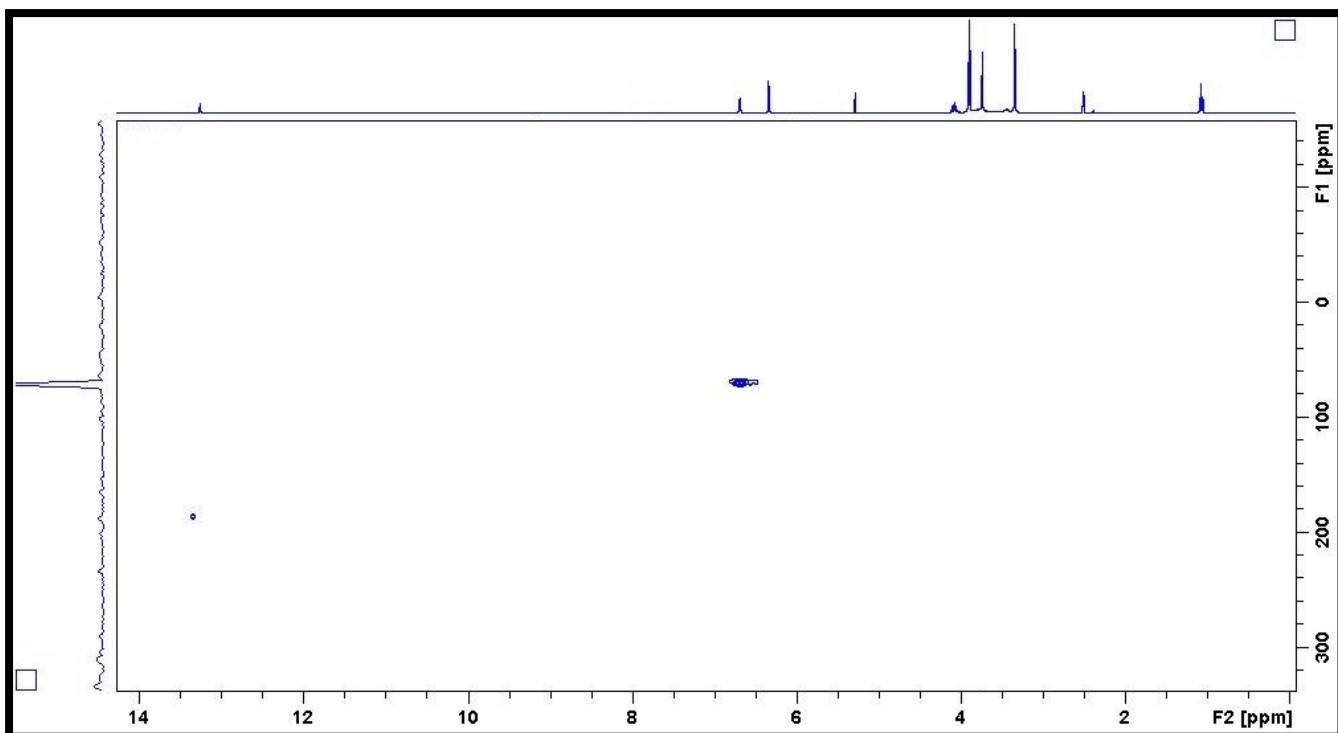
FT-IR spectra of compound **5e**



<sup>1</sup>H NMR spectra of compound **5f**



<sup>13</sup>C NMR spectra of compound **5f**



<sup>15</sup>N NMR spectra of compound **5f**

**Elemental Composition Report**

**Single Mass Analysis**

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

15 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass)

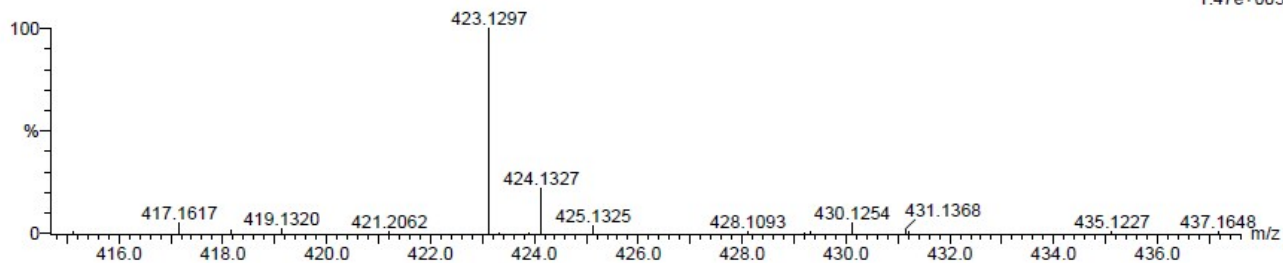
Elements Used:

C: 15-20 H: 15-20 N: 0-5 O: 5-10 Na: 1-1

ppy-6 3 (0.068) Cm (1:61)

TOF MS ES+

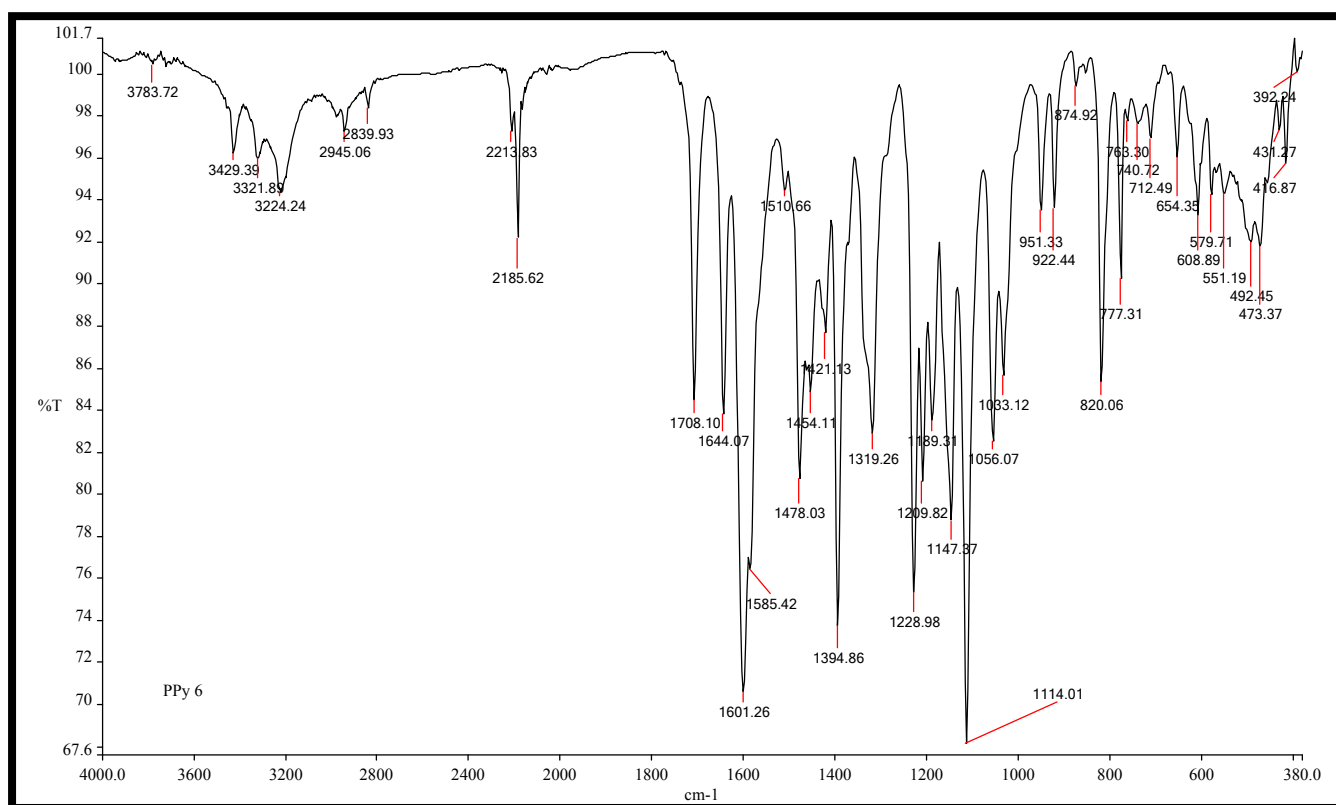
1.47e+005



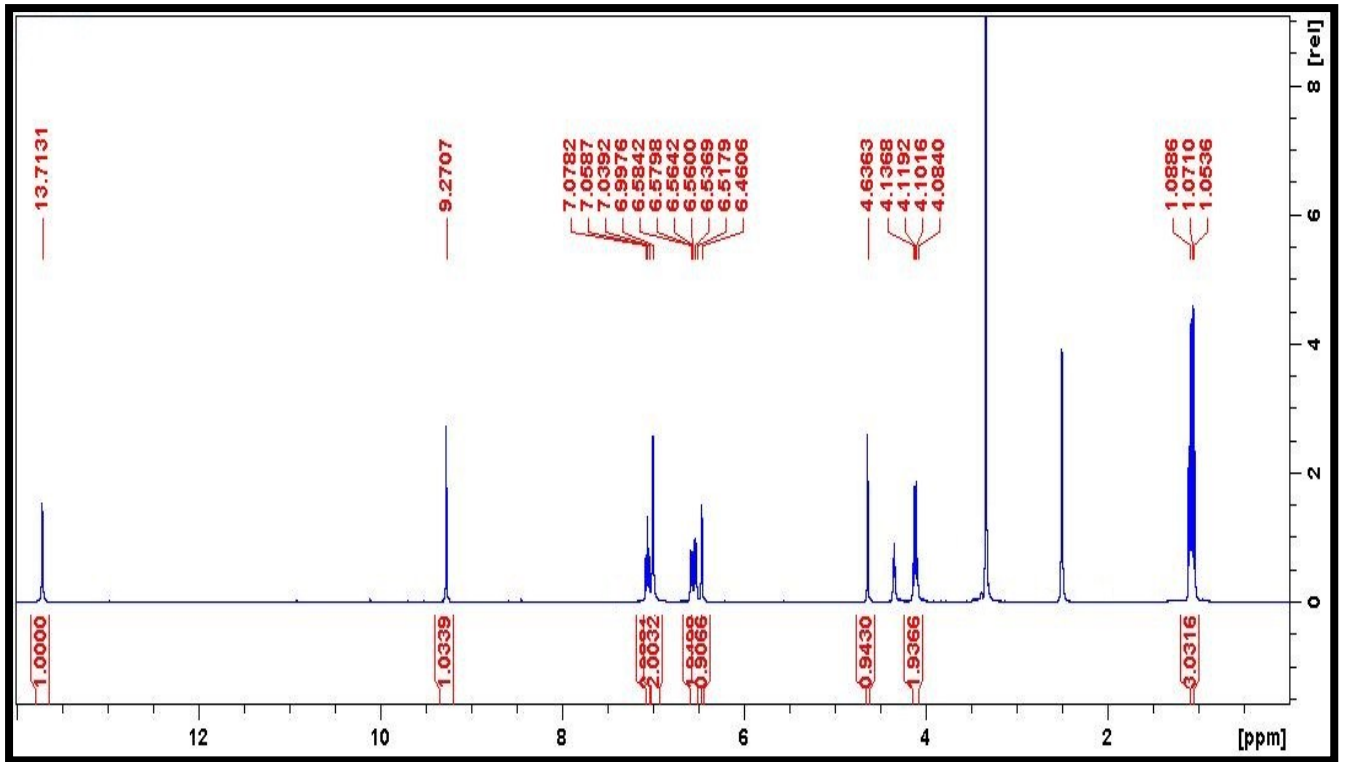
Minimum: -1.5  
Maximum: 5.0 5.0 100.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
423.1297	423.1281	1.6	3.8	11.5	39.8	0.0	C19 H20 N4 O6 Na

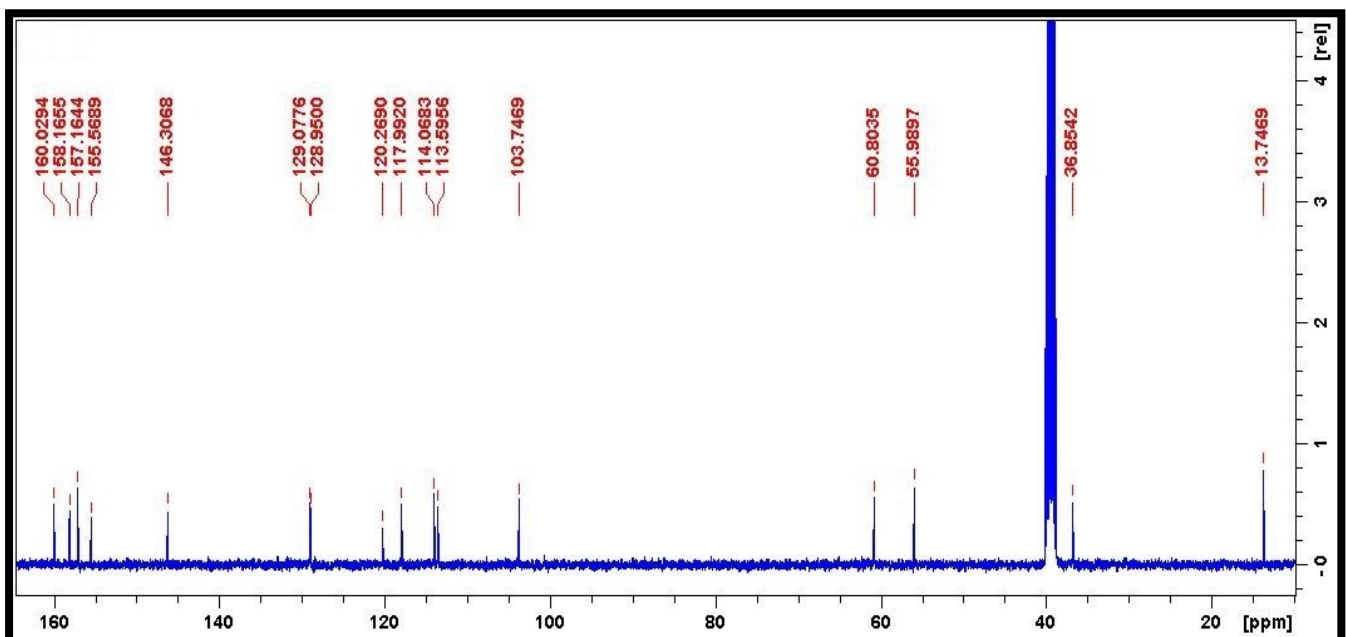
HRMS spectra of compound **5f**



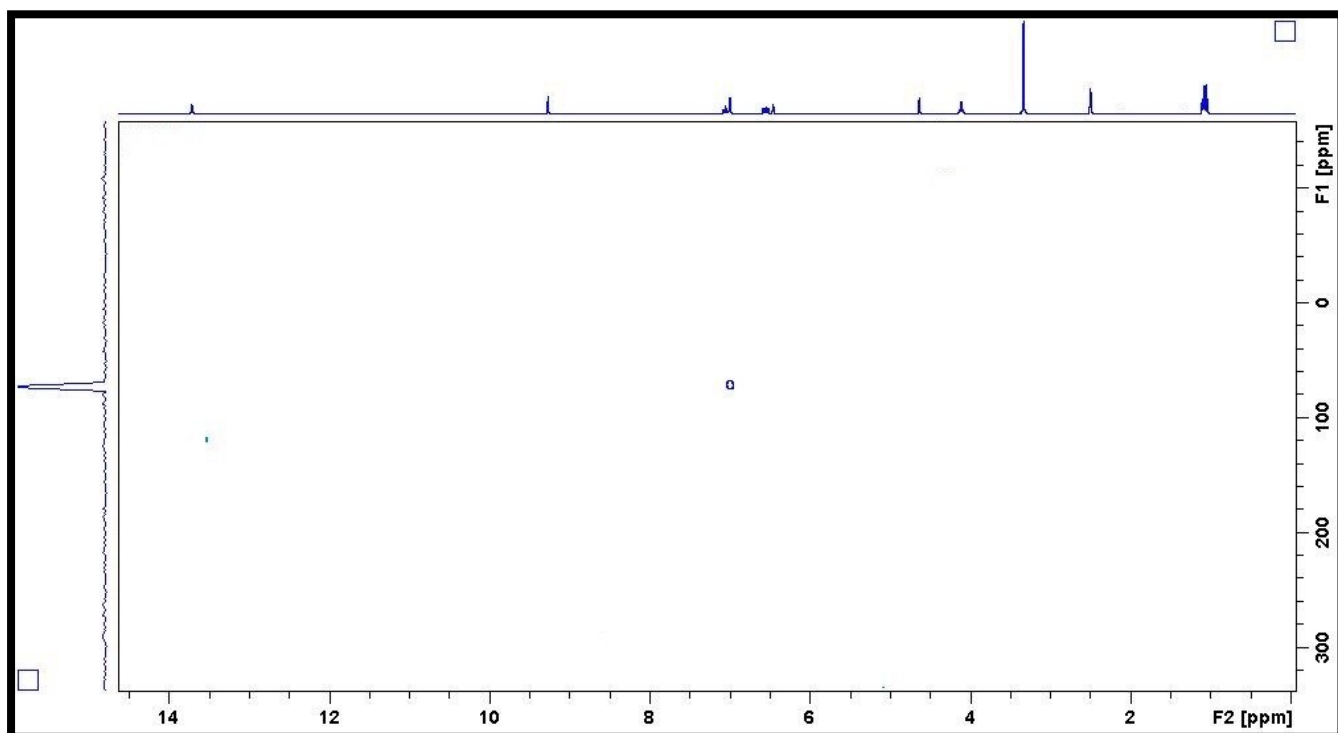
FT-IR spectra of compound **5f**



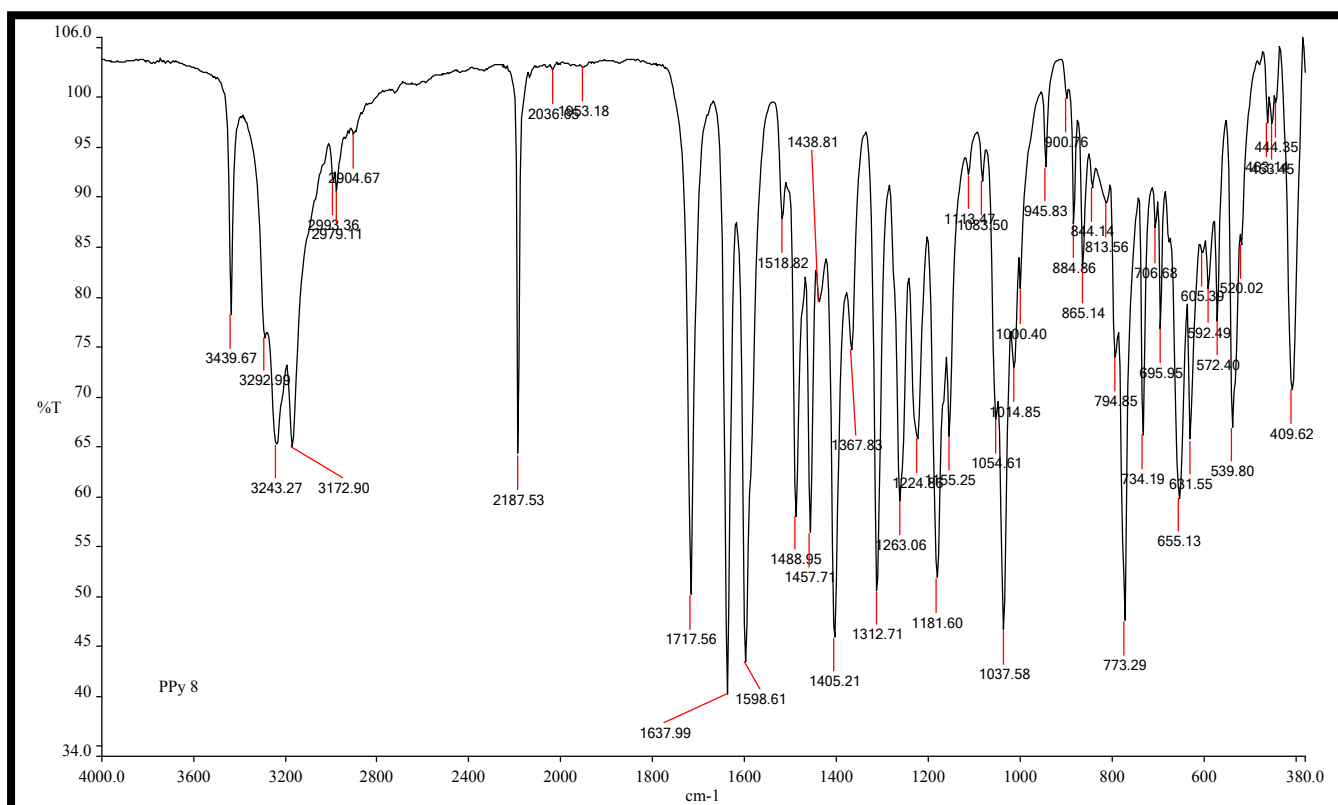
<sup>1</sup>H NMR spectra of compound 5g



$^{13}\text{C}$  NMR spectra of compound **5g**

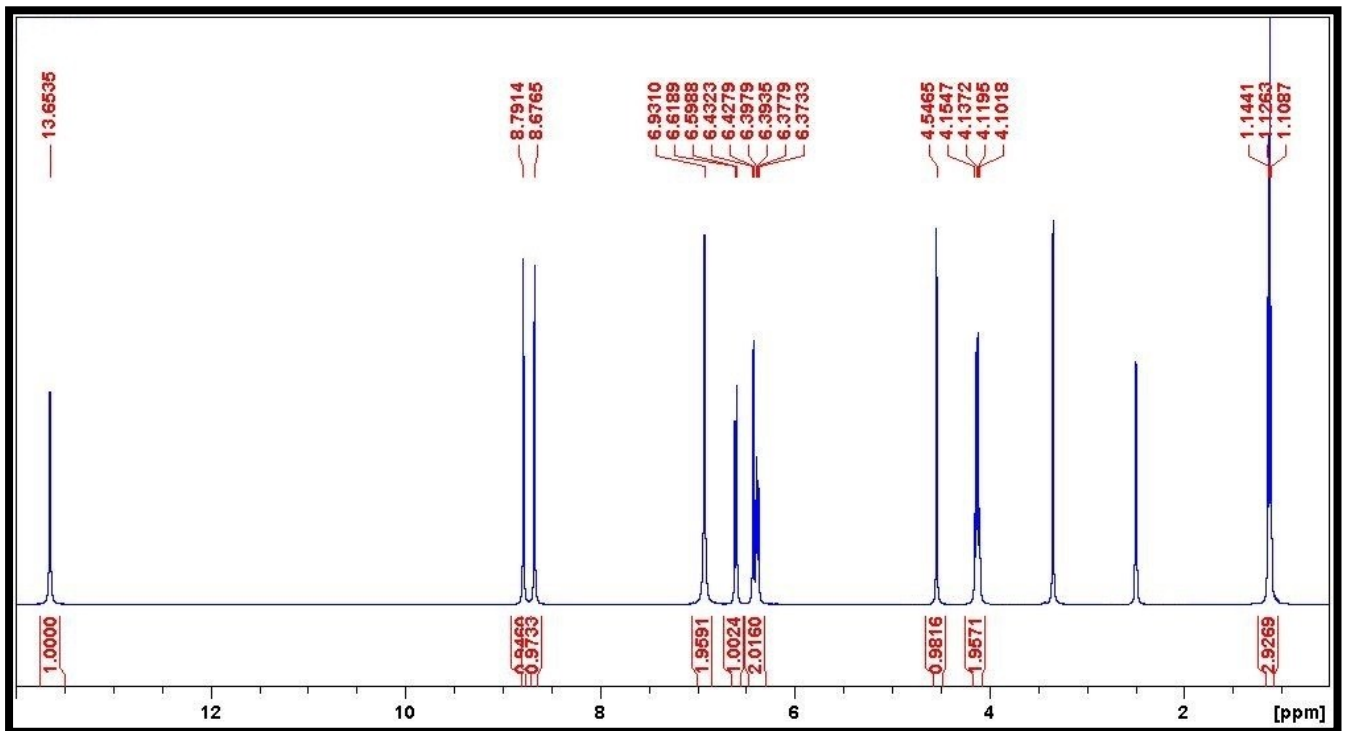


$^{15}\text{N}$  NMR spectra of compound **5g**

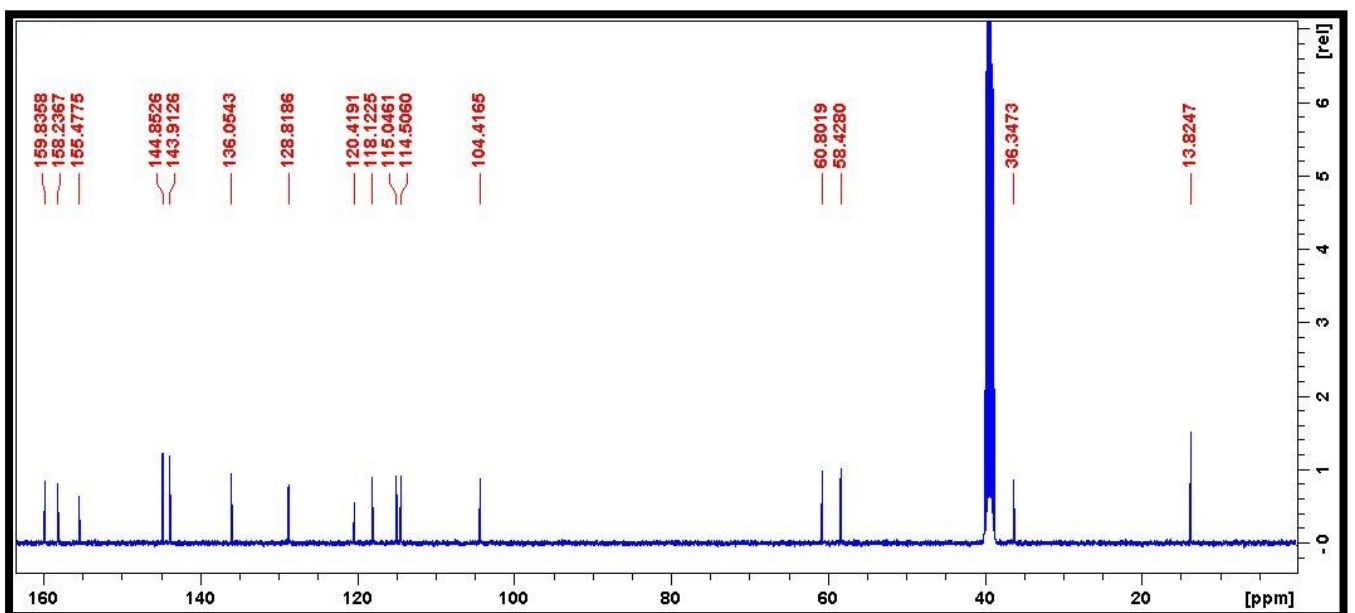




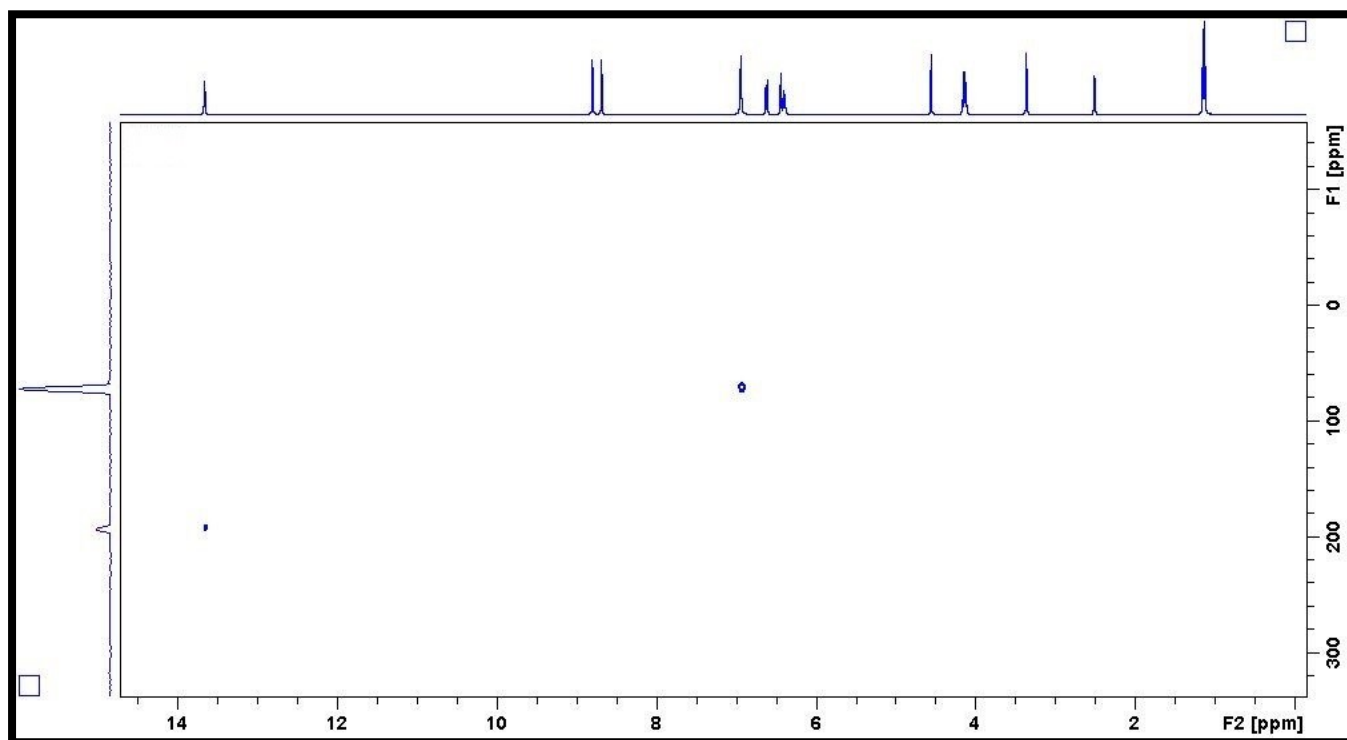
FT-IR spectra of compound 5g



<sup>1</sup>H NMR spectra of compound 5h



<sup>13</sup>C NMR spectra of compound **5h**



<sup>15</sup>N NMR spectra of compound **5h**

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

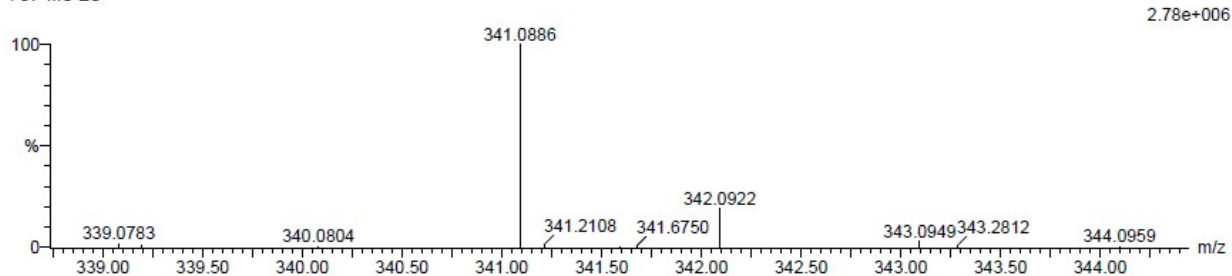
15 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass)

Elements Used:

C: 15-20 H: 10-15 N: 0-5 O: 0-5

ppy-9 61 (2.024) Cm (1:61)

TOF MS ES-

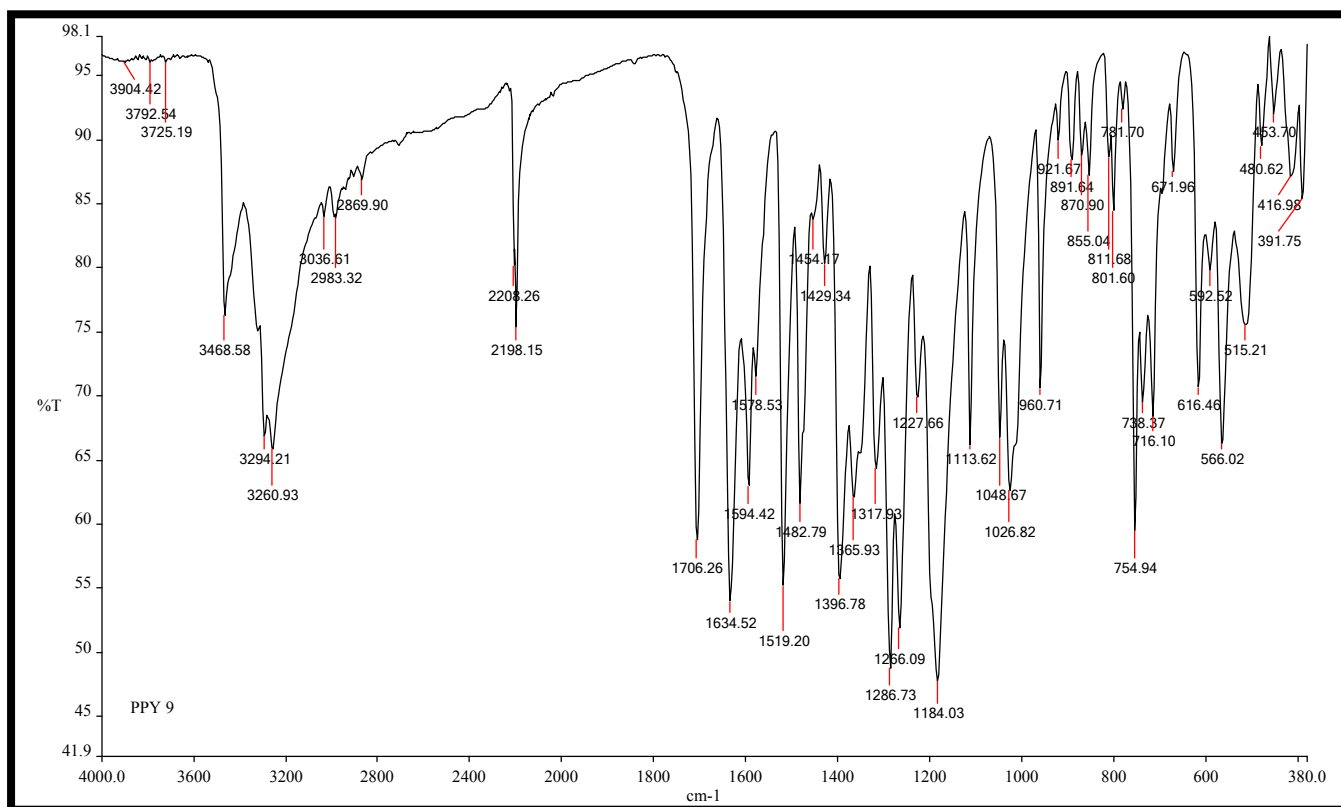


Minimum:

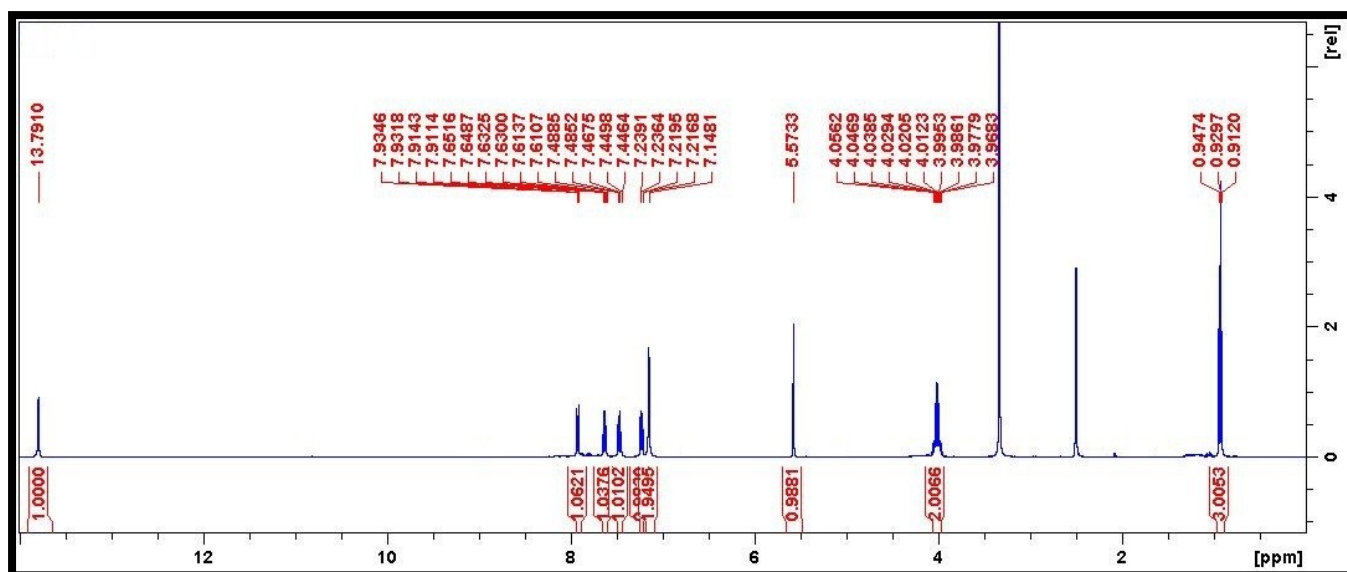
Maximum: 5.0 5.0 -1.5 100.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
341.0886	341.0886	0.0	0.0	12.5	74.2	0.0	C16 H13 N4 O5

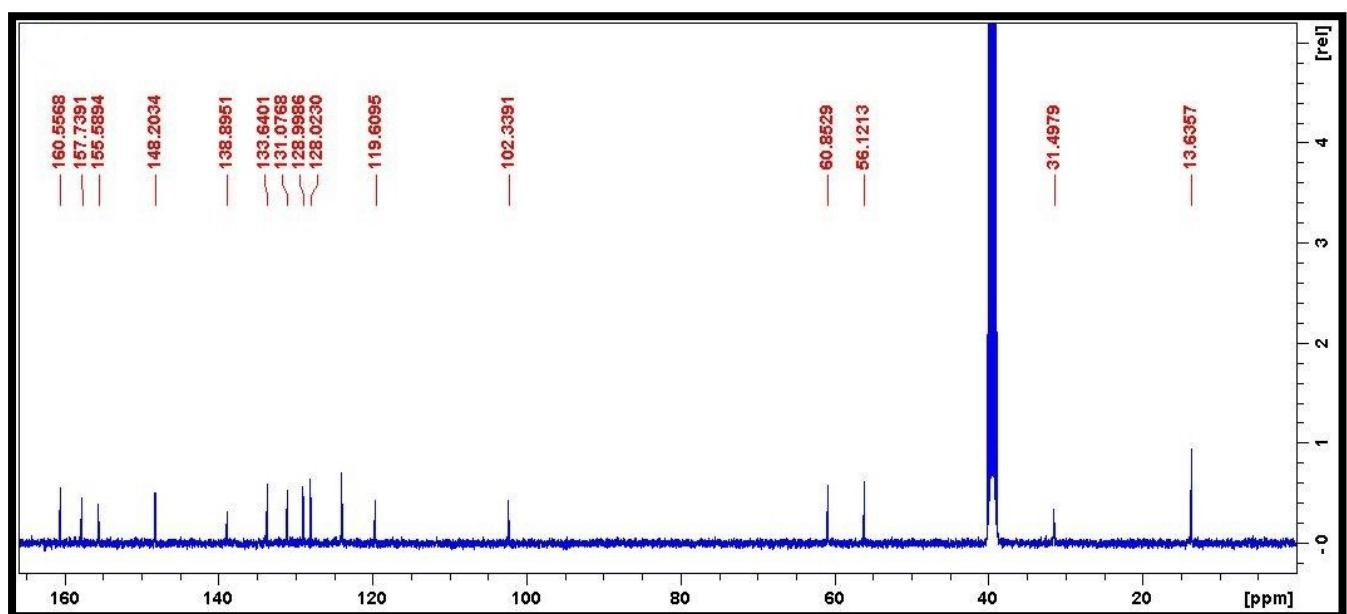
### HRMS spectra of compound **5h**



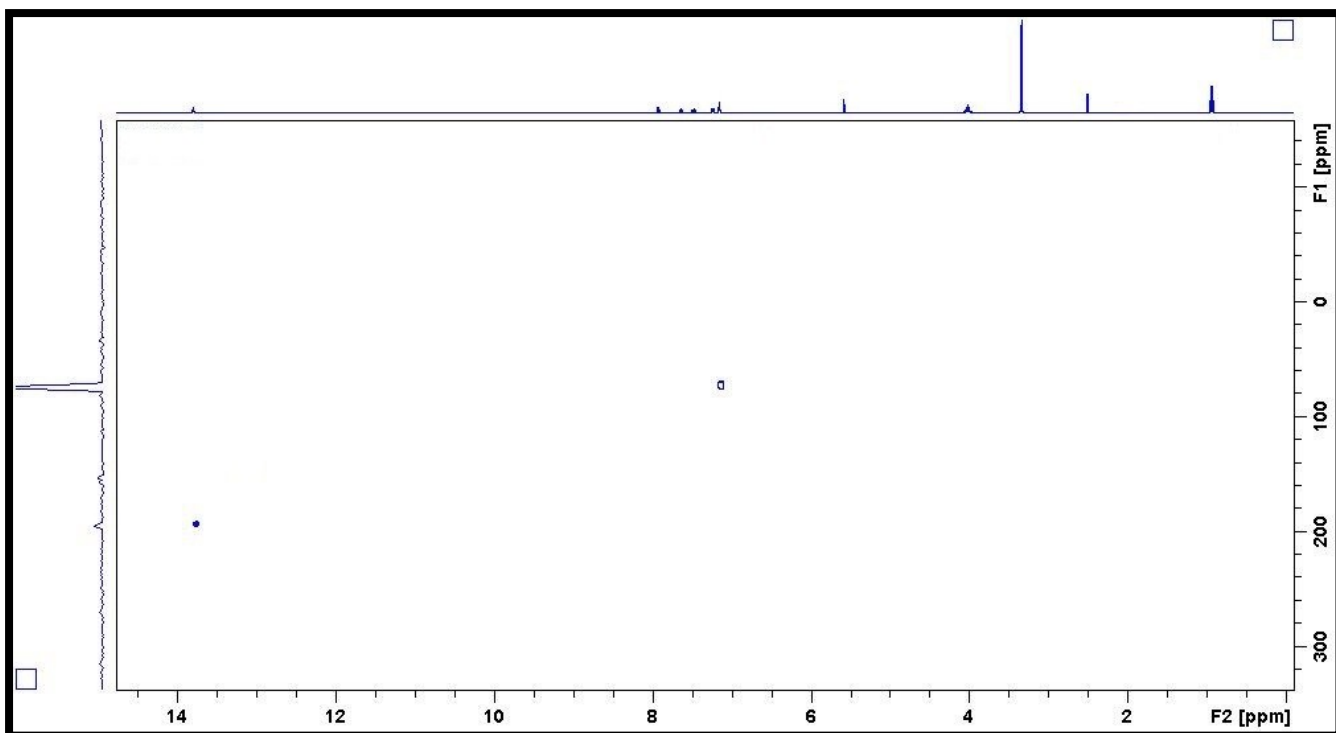
### FT-IR spectra of compound **5h**



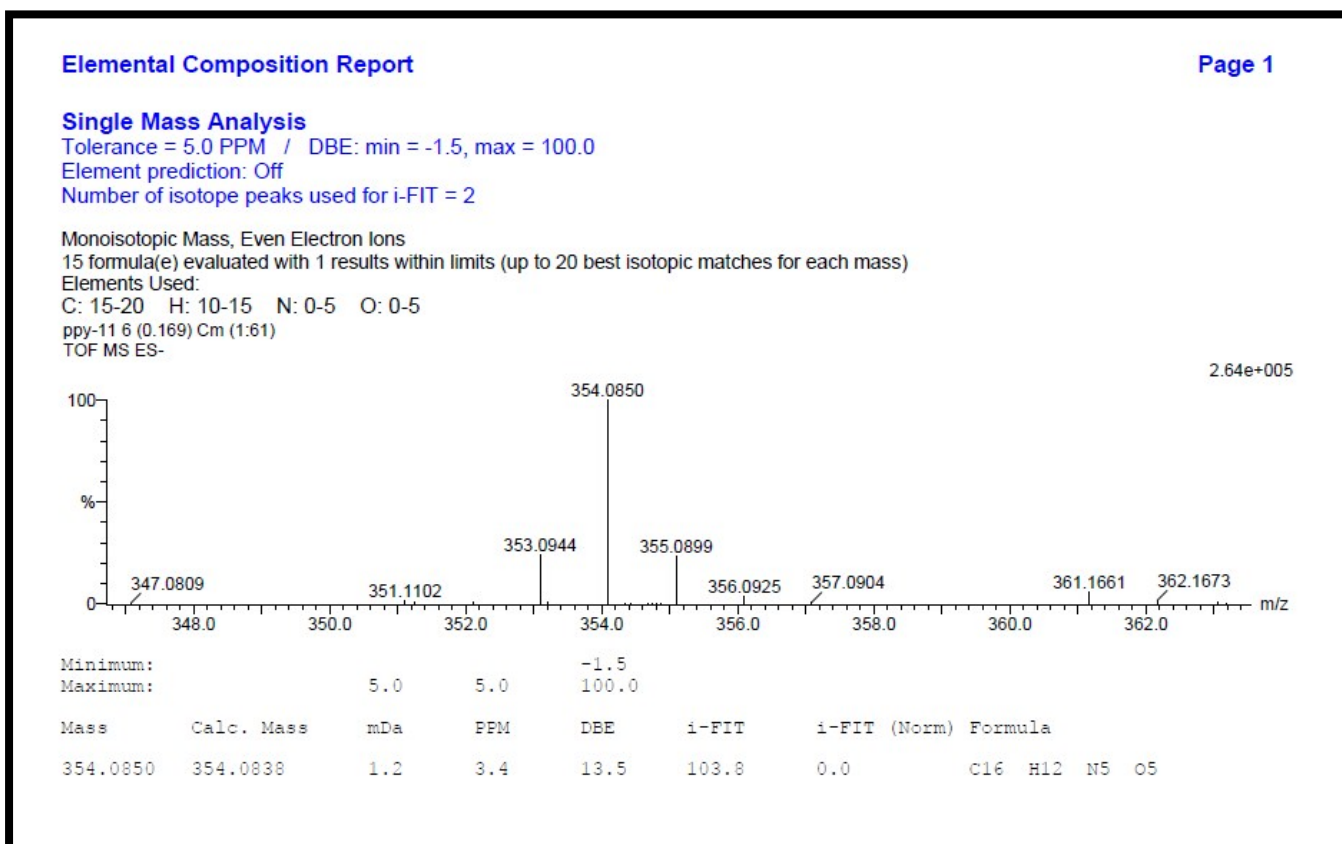
<sup>1</sup>H NMR spectra of compound 5i



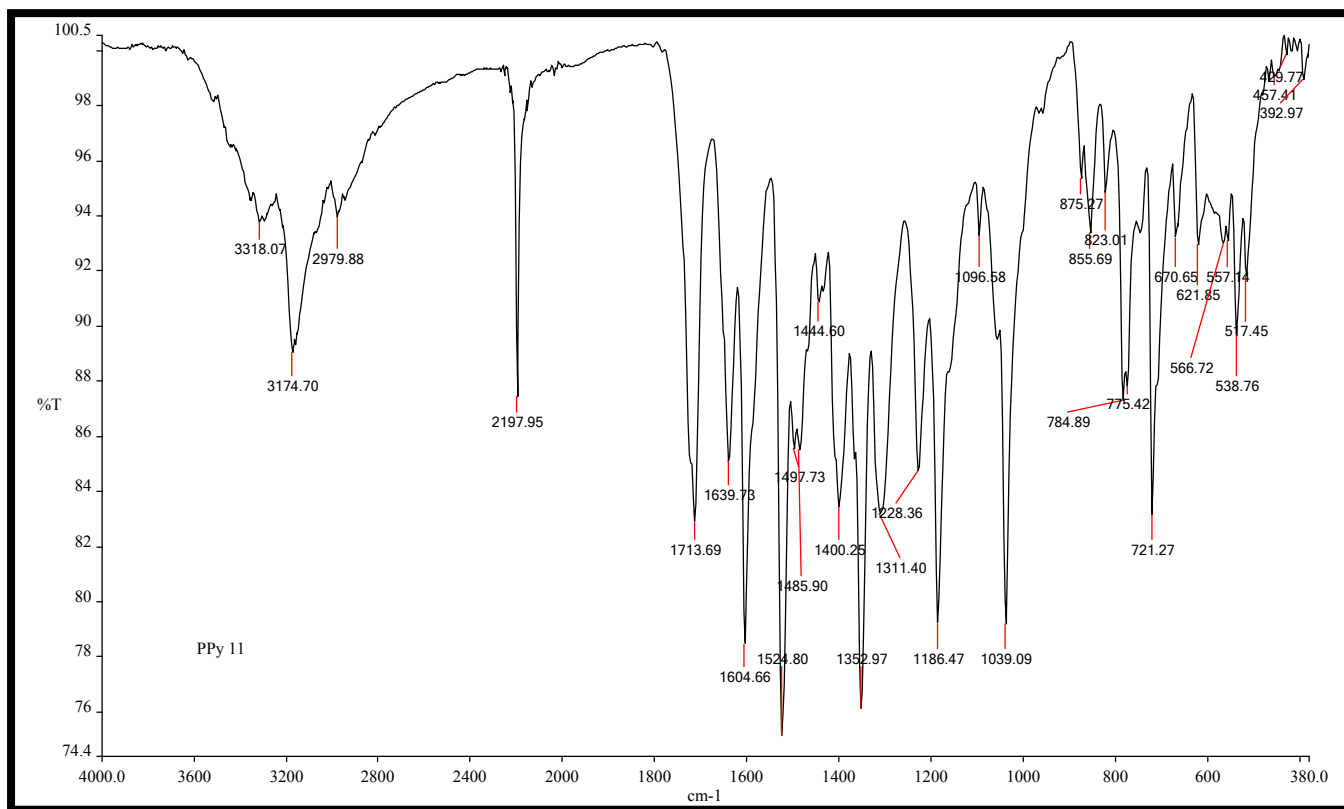
<sup>13</sup>C NMR spectra of compound 5i



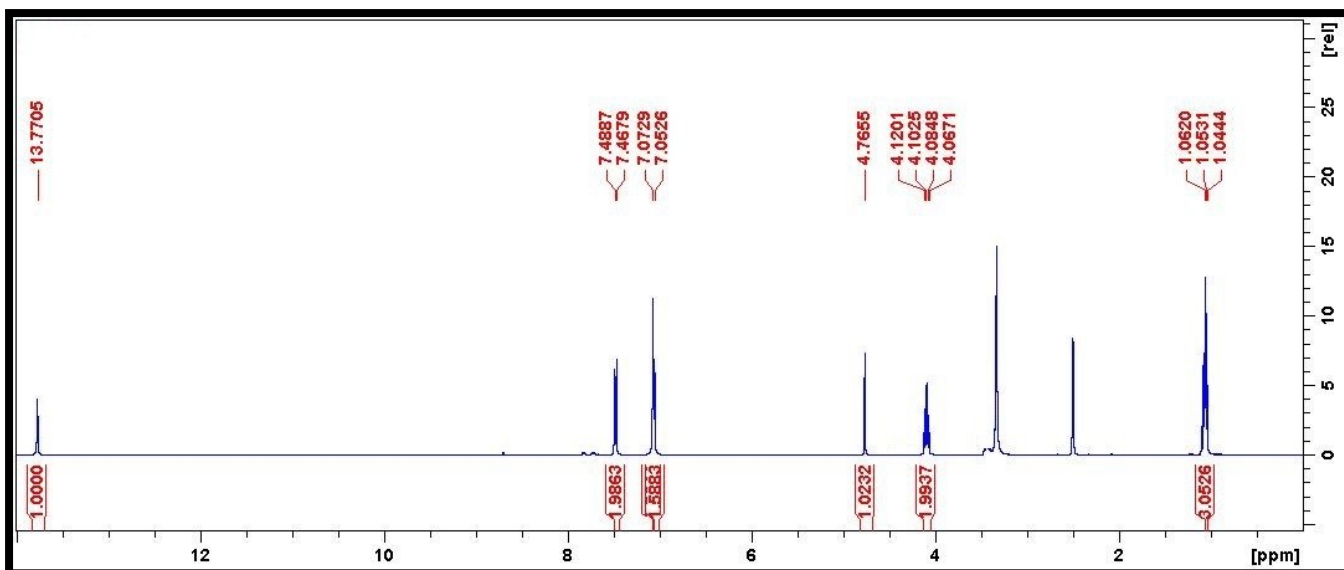
<sup>15</sup>N NMR spectra of compound **5i**



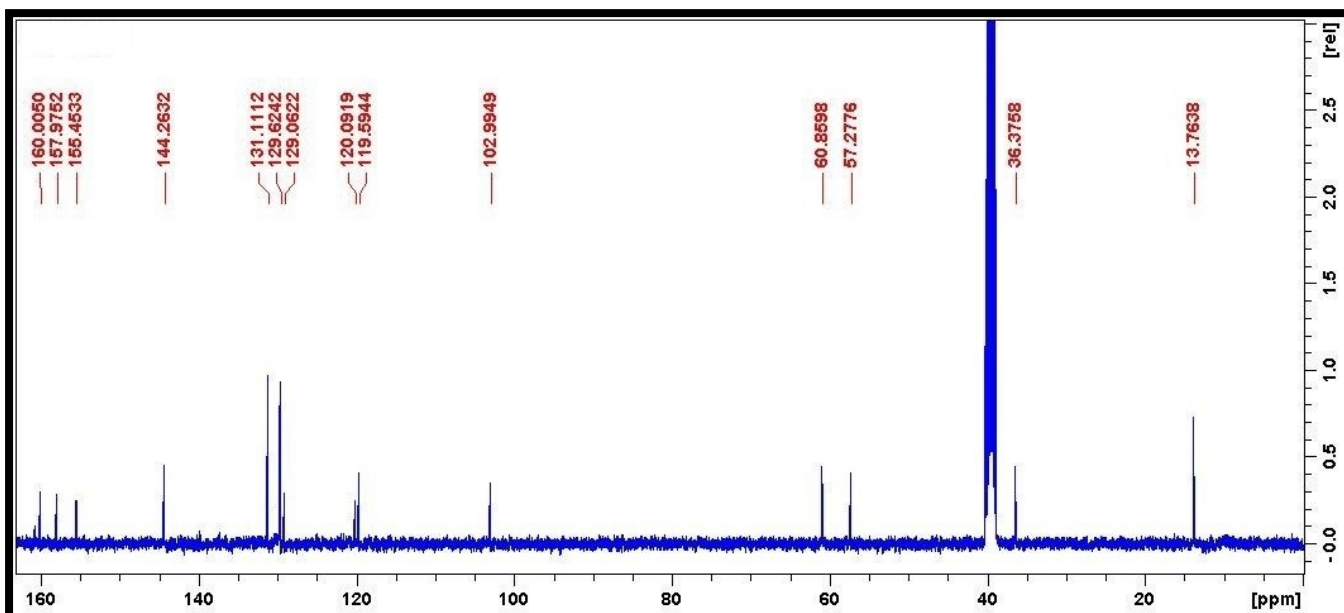
HRMS spectra of compound **5i**



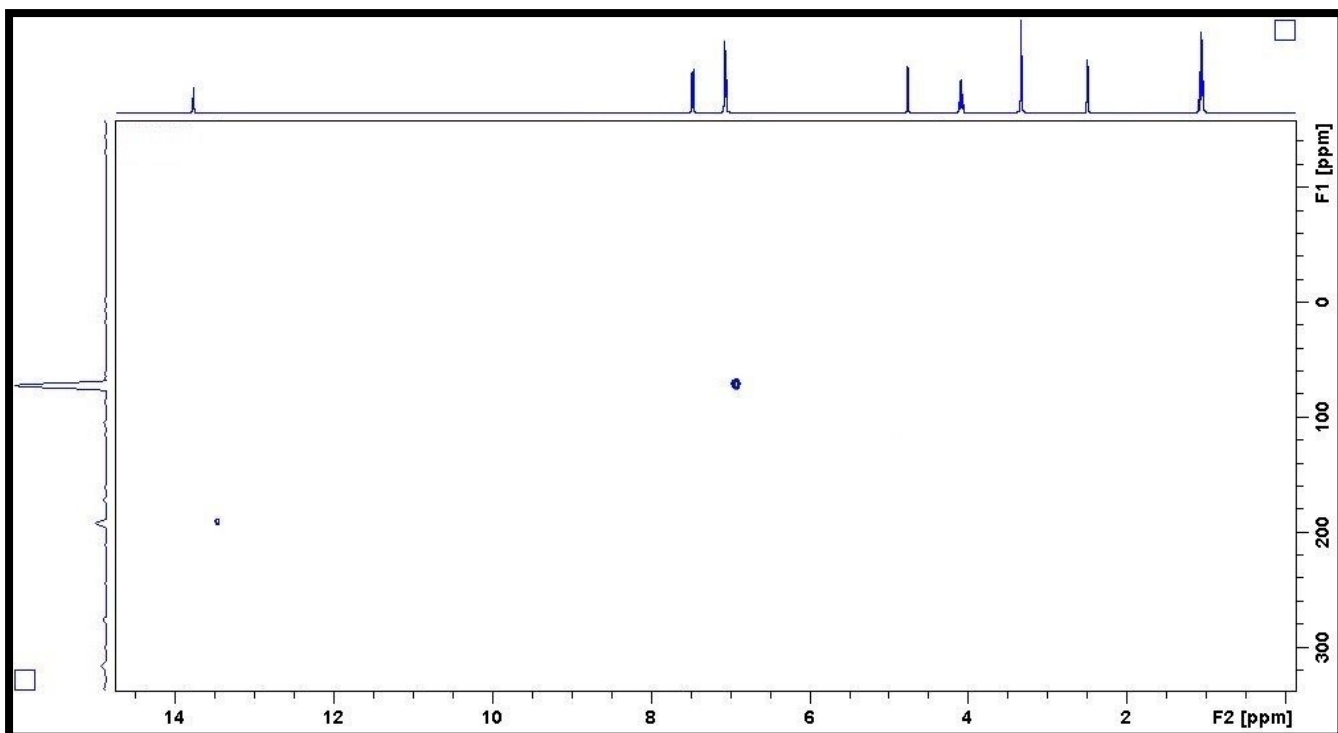
FT-IR spectra of compound **5i**



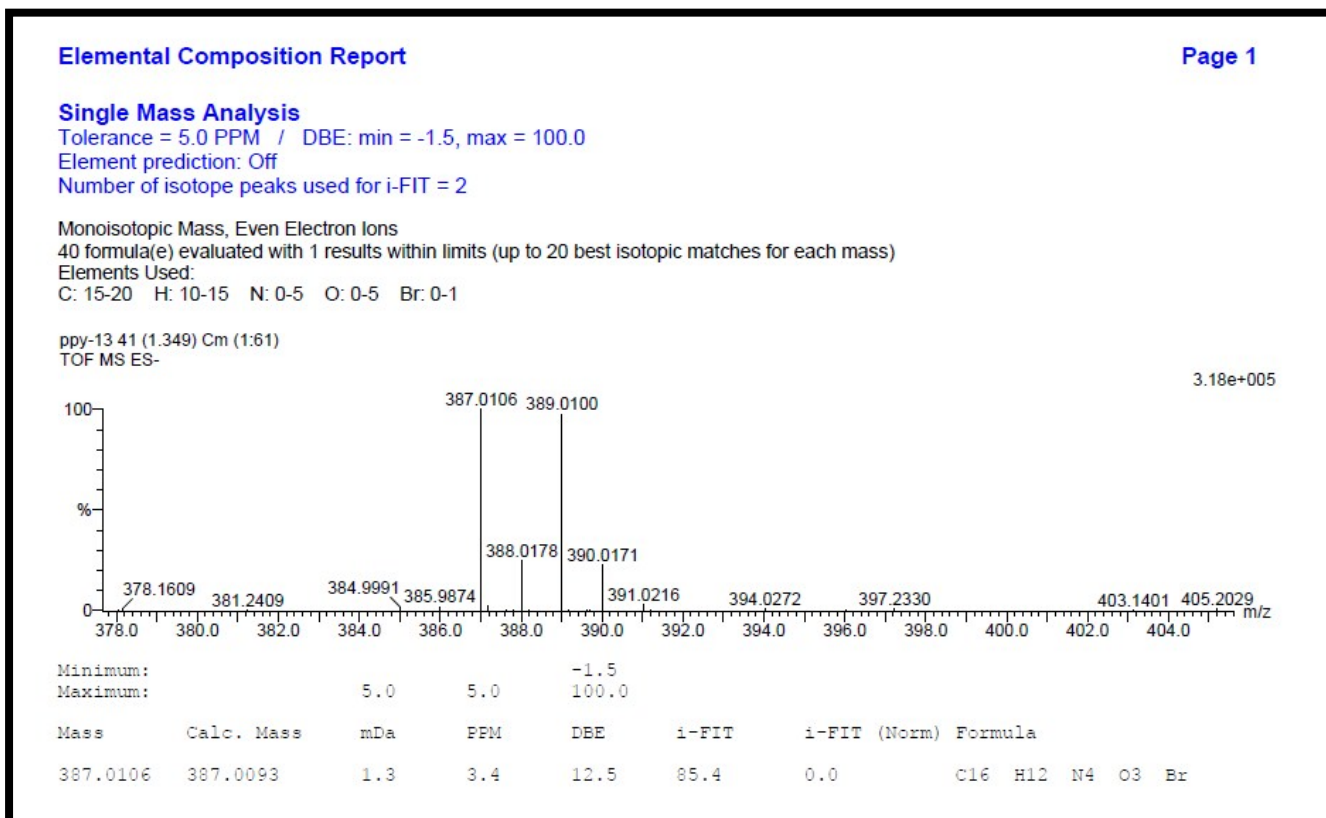
<sup>1</sup>H NMR spectra of compound **5j**



<sup>13</sup>C NMR spectra of compound **5j**

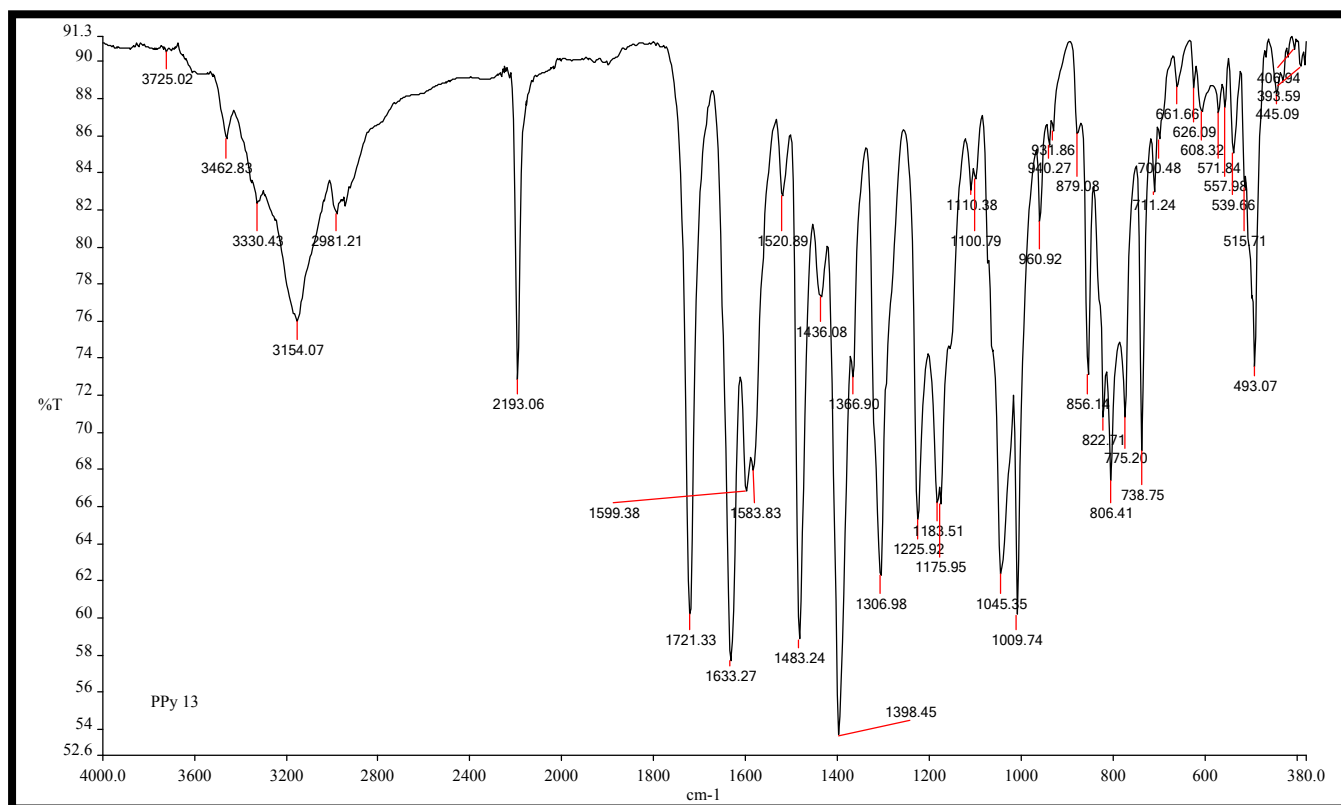


<sup>15</sup>N NMR spectra of compound **5j**

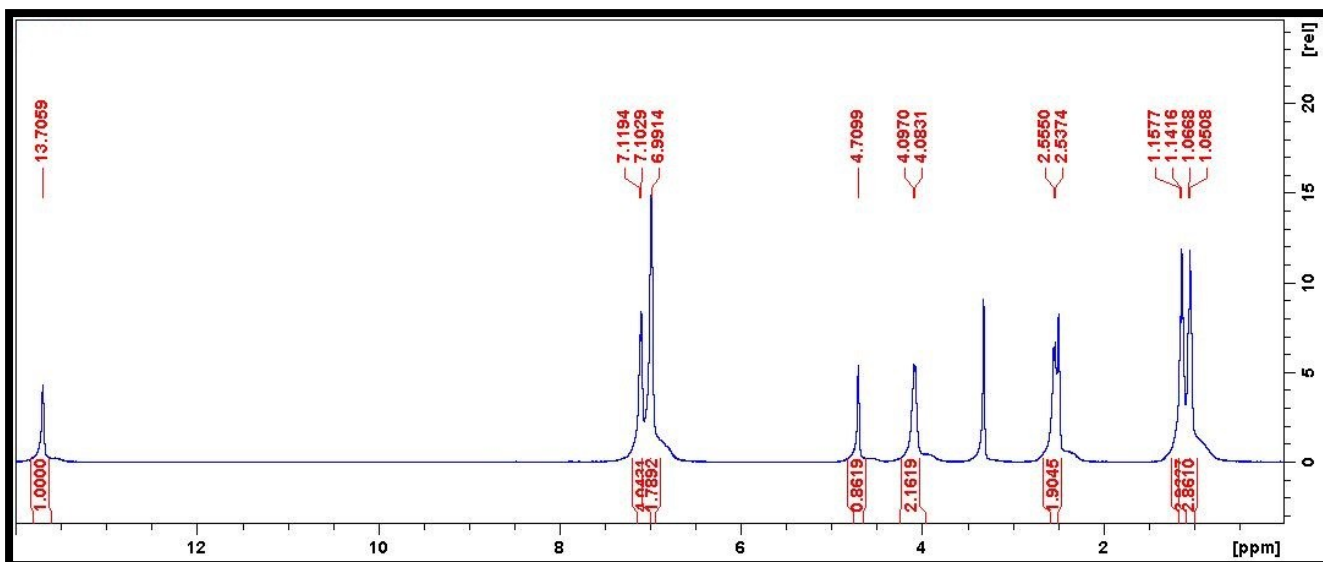


HRMS spectra of compound **5j**

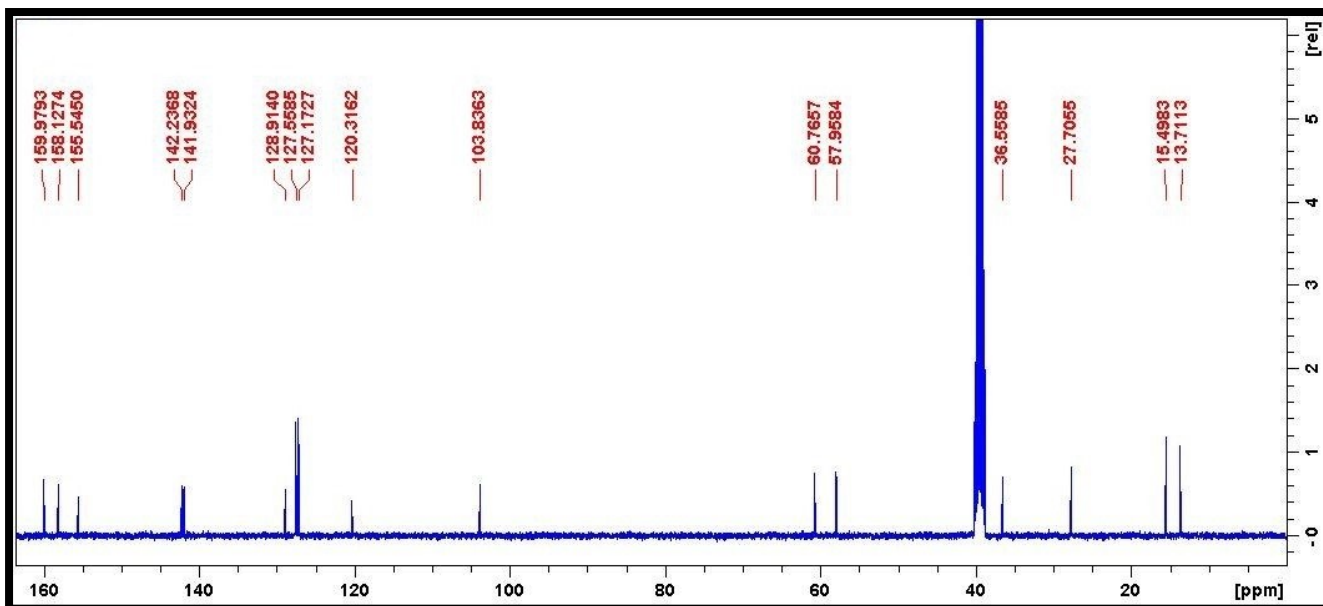




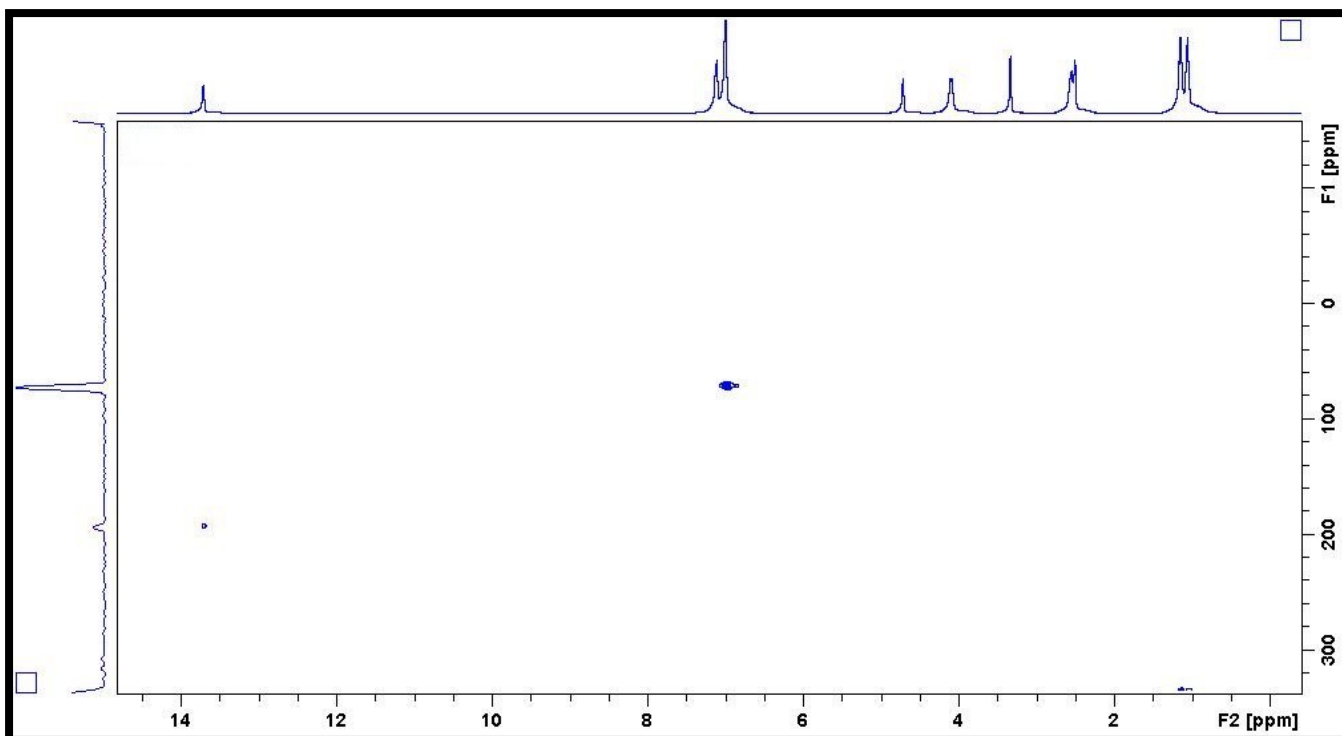
$^1\text{H}$  NMR spectra of compound **5j**



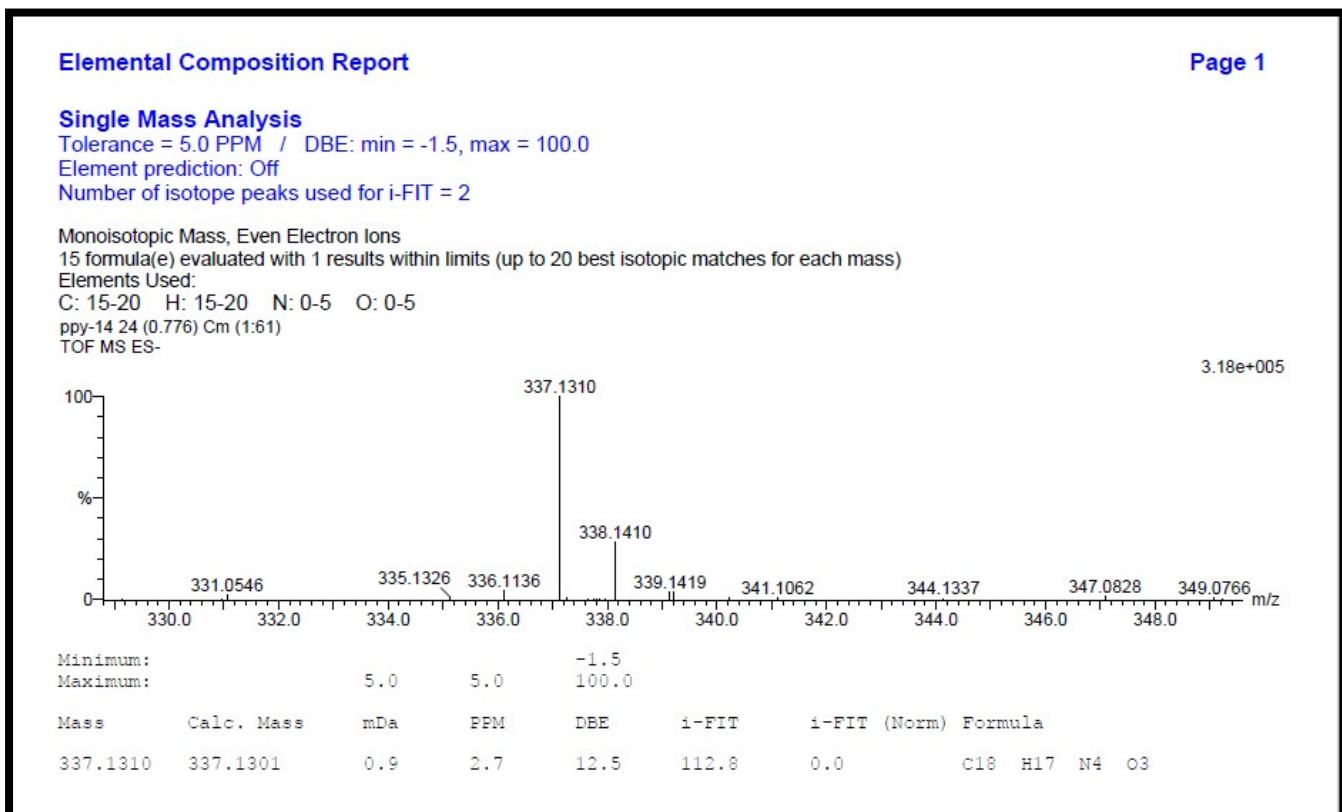
<sup>1</sup>H NMR spectra of compound **5k**



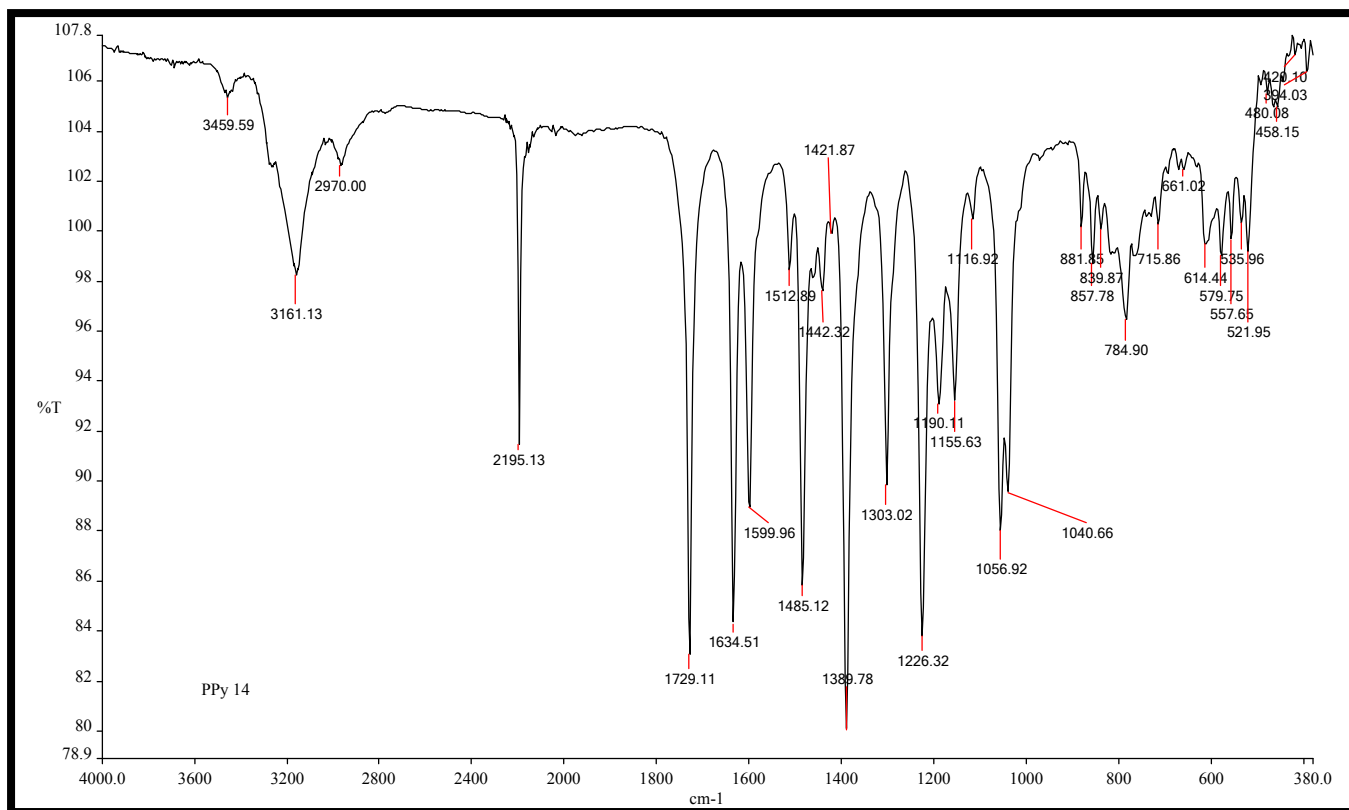
<sup>13</sup>C NMR spectra of compound **5k**



<sup>15</sup>N NMR spectra of compound **5k**



HRMS spectra of compound **5k**



FT-IR spectra of compound 5k

