

## Supporting Information

### Synthesis and Biological Evaluation of Sulfamoyl Benzamide Derivatives as Selective Inhibitors for *h*-NTPDases

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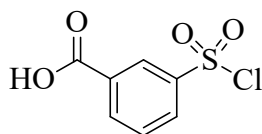
## General considerations

All the experiments were performed in washed, rinsed, and dried apparatus. Before configuring the reactions, the solvents were dried and distilled. Chemicals were purchased from Sigma-Aldrich and Merck chemical companies. The progress of the reaction was monitored by thin-layer chromatography. TLC plates were purchased from Merck (Germany). Pre-coated silica gel-60 F<sub>254</sub> plates having 0.2 mm thickness were used for chromatographic analysis. UV-active compounds were visualized under a UV lamp at 254 nm wavelength while UV-inactive compounds were spotted by using different spraying reagents such as anisaldehyde and ninhydrin. The purification of sulfamoyl-benzamide was accomplished by flash column chromatography using 200-300 mesh-sized silica gel as a stationary phase. GCMS of the volatile compounds was performed using Agilent Technologies instrument, model 5975 MS with 6890 GC, with column specification of DB-5MS 30 m, 0.25 mm, 0.25  $\mu$ m. The method utilized for GCMS was at a temperature of 120-280 °C with a ramp of 10 °C/min, a flow rate of 1.5ml/min, an injection volume of 5  $\mu$ L and the inlet temperature was set at 250 °C. Mass spectrometric (HRMS) experiments were carried out on Finnigan MAT-311A (Germany) mass spectrometer with (ESI) ionization techniques. NMR spectra were obtained using a Bruker 300 NMR MHz spectrometer in deuterated solvents using TMS as an internal reference, at 300 MHz (<sup>1</sup>H NMR) and 75 MHz (<sup>13</sup>C NMR). Chemical shifts are mentioned in delta ( $\delta$ ) units while coupling constants (*J*) values are in Hertz unit (Hz).

### General procedure for the synthesis of 5-(chlorosulfonyl)-2-substituted benzoic acids (ZR-22 & 32)

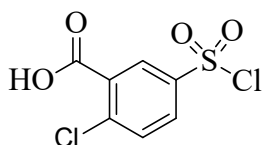
The chlorosulfonation was carried out using the reported procedure. [1] In a 250 mL round bottom flask, 2-substituted benzoic acid (0.1mol, 100 mol%) was added in small portions to the cooled chlorosulfonic acid (40 mL, 0.6 mol, 600 mol%). The resulting mixture was heated at 95 °C for 12 h. After completion of the reaction, the reaction mixture was allowed to come to room temperature and poured into ice. The 5-(chlorosulfonyl)-2-substituted benzoic acid precipitates were collected through vacuum filtration and washed with cold water. The compounds were used in the next step without purification.

#### 3-(Chlorosulfonyl)benzoic acid (ZR-22) [2]



Yield: 80 %; light yellow; m.p.: 127-129 °C (lit. 128 °C);  $R_f$ : 0.5 (chloroform: methanol:: 9.5: 0.5).

#### 2-Chloro-5-(chlorosulfonyl)benzoic acid (ZR-32) [3] [4]



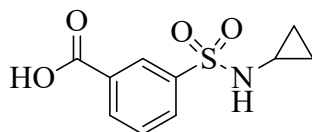
Yield: 76 %; light brown; m.p. : 145-147 °C (lit. 146 °C);  $R_f$ : 0.4 (chloroform: methanol :: 9.5: 0.5)



### General procedure for the synthesis of 5-(substituted sulfamoyl)-2-substituted benzoic acid (ZR-23, 33, 45 & 61)

The sulfonamide were synthesized following a slightly modified reported procedure. [5] The reaction of 5-(chlorosulphonyl)-2-substitutedbenzoic acid (3.0 mmol, 100 mol%) with the corresponding amine (3.0 mmol, 100 mol%) was carried out in the presence of water (15 mL, 0.2 M) as a solvent. The reaction was stirred at room temperature and the progress is monitored through TLC. After completion of the reaction, conc. HCl was slowly added to adjust the pH to 3. The aqueous layer was partitioned with ethyl acetate (20 mL) and the organic layer was separated. The aqueous layer was further extracted with ethyl acetate (15 mL x 2). The combined organic layer was dried and concentrated under *vacuo* to obtain the desired product as white solid. The products were further purified through recrystallization from ethanol.

### 3-(*N*-Cyclopropylsulfamoyl)benzoic acid 2a (ZR-45)



Yield: 92 %; white solid; m.p.: 223-225 °C;  $R_f$ : 0.4 (chloroform: methanol :: 9.5: 0.5).

$^1\text{H NMR}$  (300 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  (ppm) 13.60 (*s*, 1H), 8.36 (*d*,  $J = 1.5$  Hz, 1H), 8.18-8.21 (*t*,  $J = 1.8$  Hz, 1H), 8.02-8.06 (*m*, 2H), 7.75 (*t*,  $J = 7.8$  Hz, 1H), 2.08-2.14 (*m*, 1H), 0.33-0.51 (*m*, 4H).

$^{13}\text{C NMR}$  (75 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  (ppm) 166.6, 141.2, 133.5, 132.2, 131.3, 130.3, 127.9, 24.6, 5.5 (2C).

ESI-HRMS- ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calc'd for  $\text{C}_{10}\text{H}_{12}\text{NO}_4\text{S}^+$ , 242.0482; found, 242.0486.

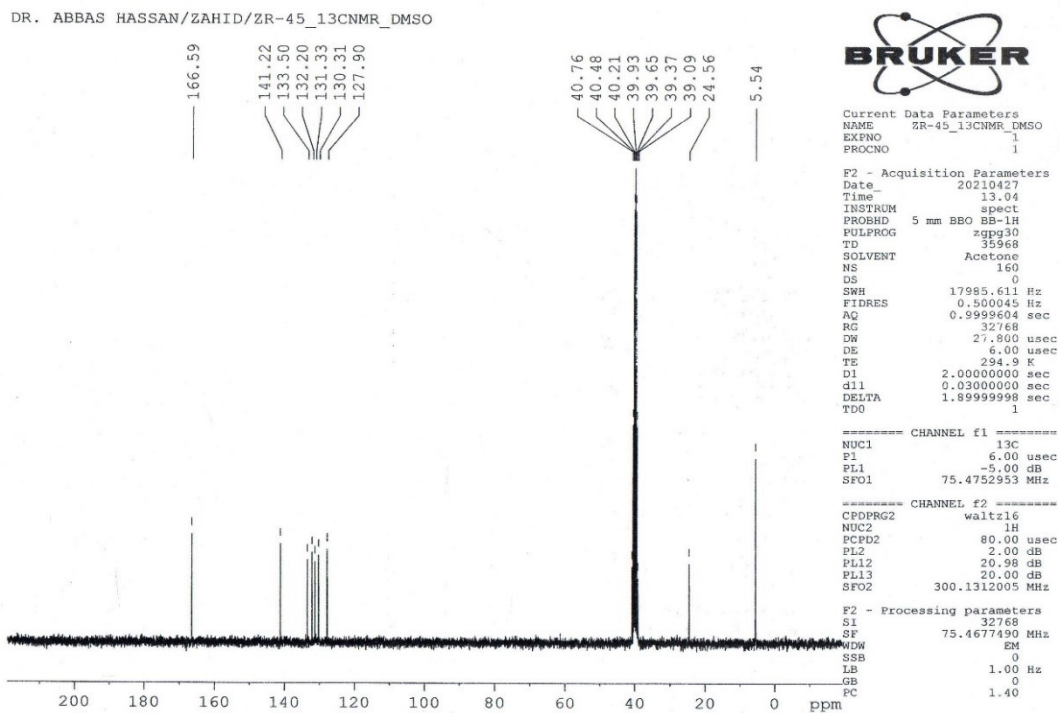
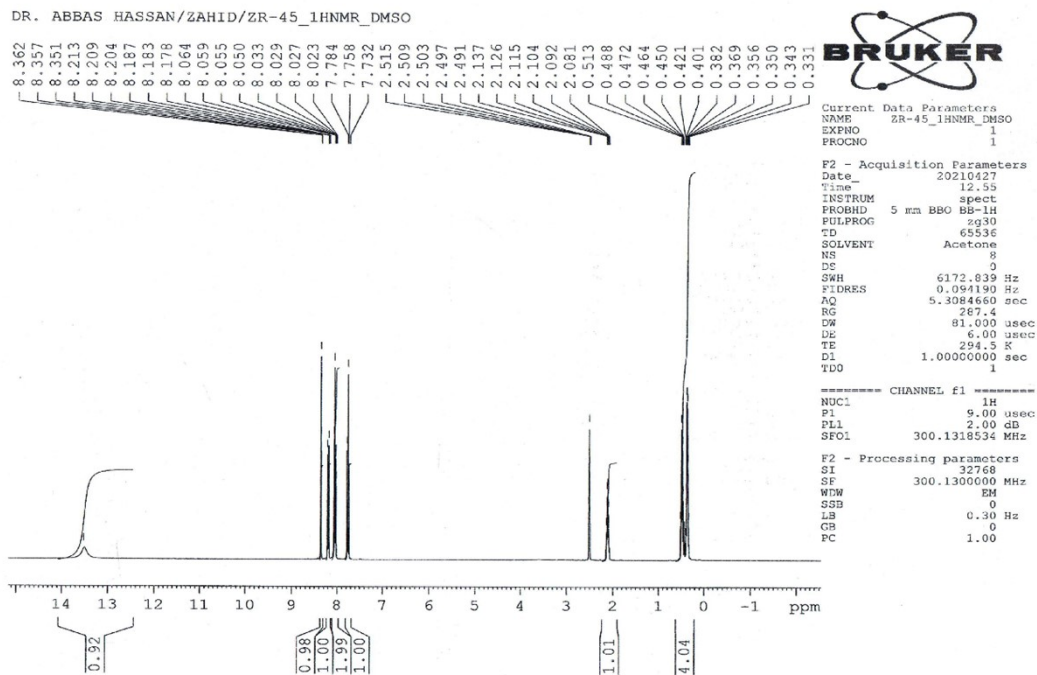
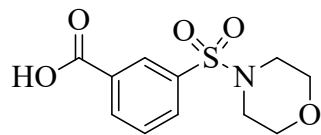


Fig. S-1:  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compound **2a**.

**3-(Morpholinosulfonyl)benzoic acid 2b (ZR-23)**



Yield: 89 %; white solid; m.p. : 192-195 °C;  $R_f$ : 0.3 (chloroform: methanol :: 9.5: 0.5).

$^1\text{H NMR}$  (300 MHz, Acetone- $d_6$ ):  $\delta$  (ppm) 11.34 (*s*, 1H), 8.38 (*s*, 1H), 8.35-8.36 (*m*, 1H), 8.03-8.06 (*m*, 1H), 7.83-7.88 (*m*, 1H), 3.69-3.72 (*m*, 4H), 2.98-3.01 (*m*, 4H).

$^{13}\text{C NMR}$  (75 MHz, Acetone- $d_6$ ):  $\delta$  (ppm) 165.4, 136.1, 133.9, 131.9, 131.7, 129.9, 128.6, 65.7 (2C), 46.1 (2C).

**ESI-HRMS-** ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calc'd for  $\text{C}_{11}\text{H}_{15}\text{NO}_5\text{S}^+$ , 273.0666; found, 273.0668.

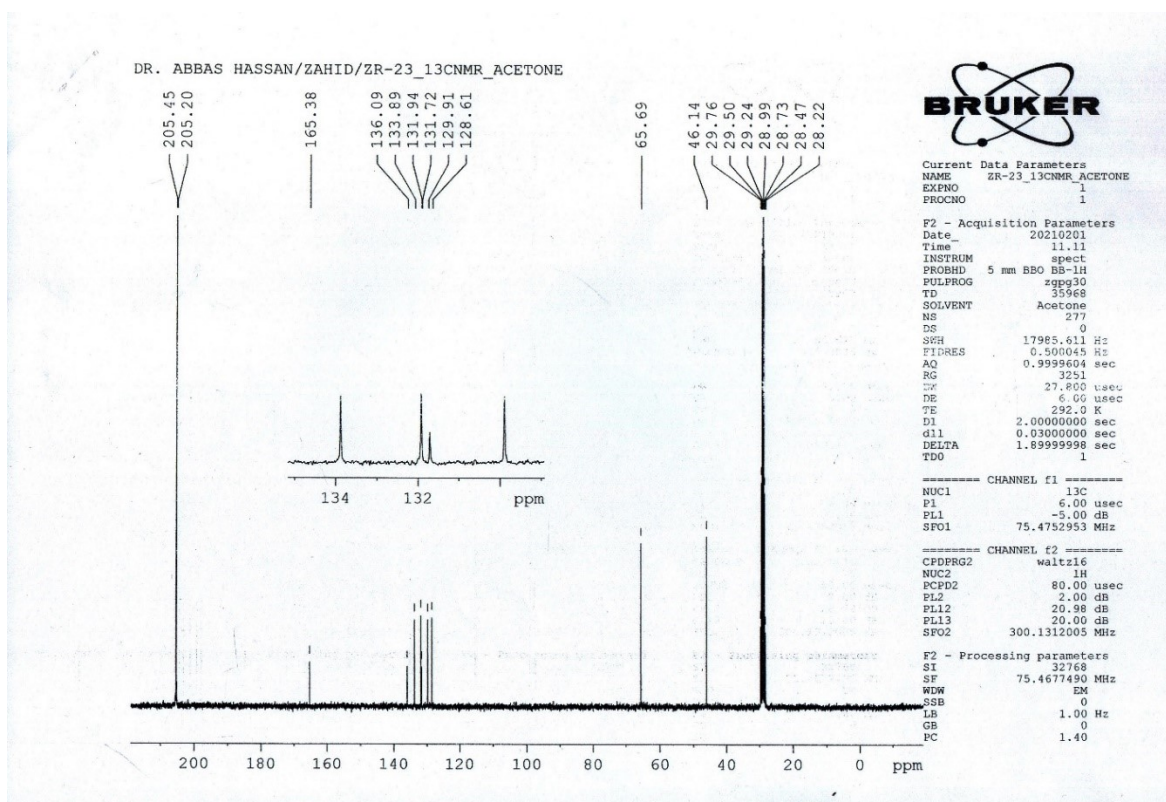
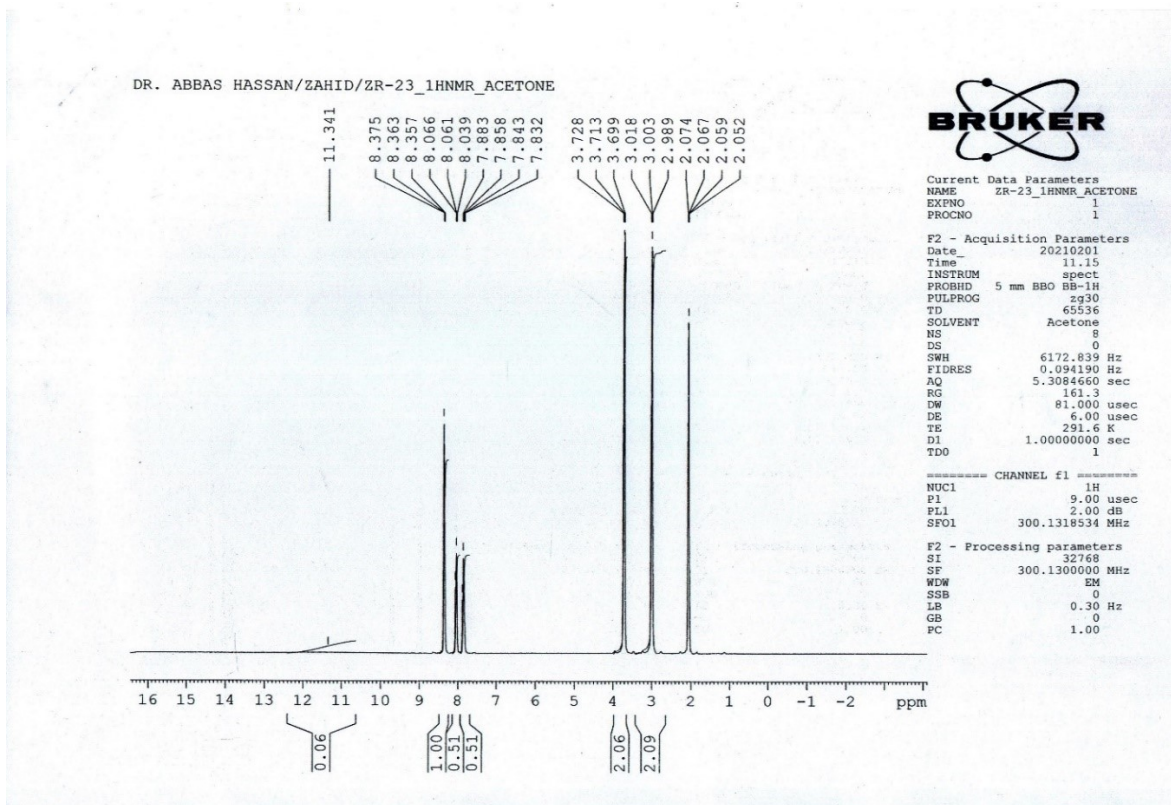
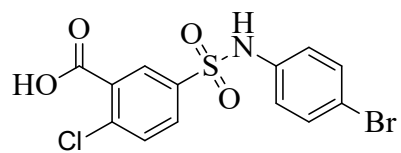


Fig. S-2:  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compound **2b**.

**5-(*N*-(4-Bromophenyl)sulfamoyl)-2-chlorobenzoic acid 2c (ZR-33)**



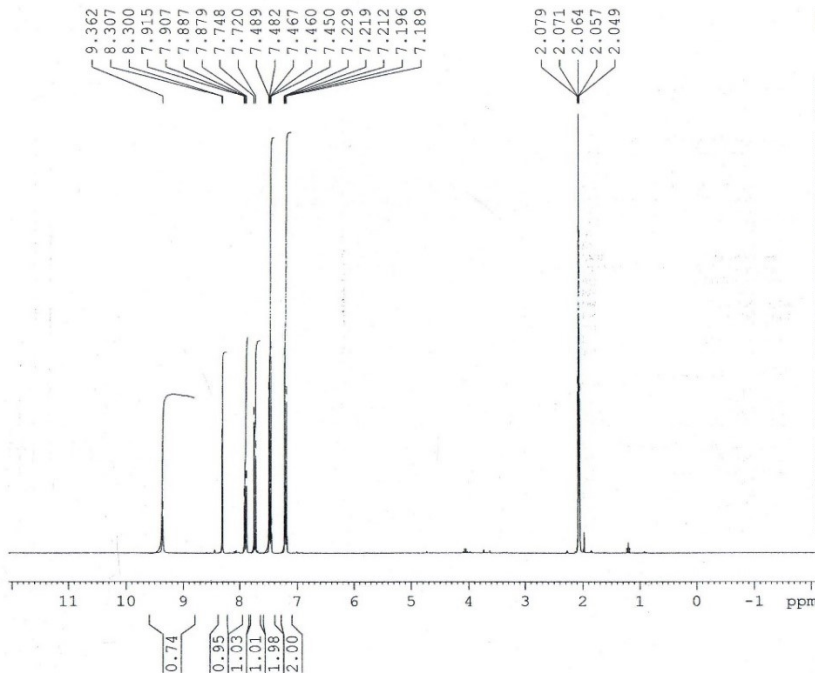
Yield: 83 %; white solid; m.p. : 225-228 °C;  $R_f$ : 0.6 (chloroform: methanol :: 9.5: 0.5).

$^1\text{H NMR}$  (300 MHz, Acetone- $d_6$ ):  $\delta$  (ppm) 9.36 (*s*, 1H), 8.30 (*d*,  $J = 1.9$  Hz, 1H), 7.88-7.91 (*m*, 1H), 7.73 (*d*,  $J = 6.7$  Hz, 1H), 7.45-7.49 (*m*, 2H), 7.19-7.23 (*m*, 2H).

$^{13}\text{C NMR}$  (75 MHz, Acetone- $d_6$ ):  $\delta$  (ppm) 164.3, 138.4, 137.9, 136.6, 132.3, 132.2 (2C), 131.3, 130.8, 130.0, 123.2 (2C), 117.7.

**ESI-HRMS-** ( $m/z$ ):  $[M+H]^+$  calc'd for  $\text{C}_{13}\text{H}_{10}\text{NO}_4\text{S}^+$ , 389.9197; found, 389.9199.

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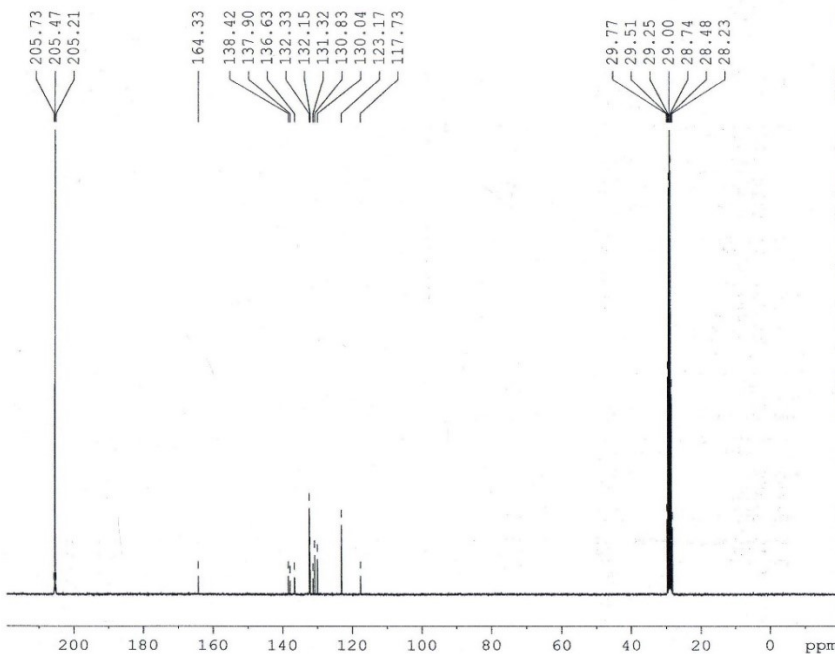
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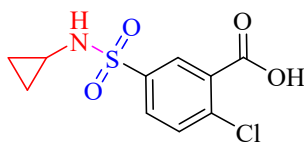
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Fig. S-3: <sup>1</sup>H and <sup>13</sup>C NMR spectra for compound 2c.

**5-(N-Cyclopropylsulfamoyl)-2-chlorobenzoic acid 2d (MA-65)**



**Yield:** 76%    **m.p.:** 195-197 °C.    white solid    **R<sub>f</sub>:** 0.29 (chloroform : methanol :: 8 : 2).

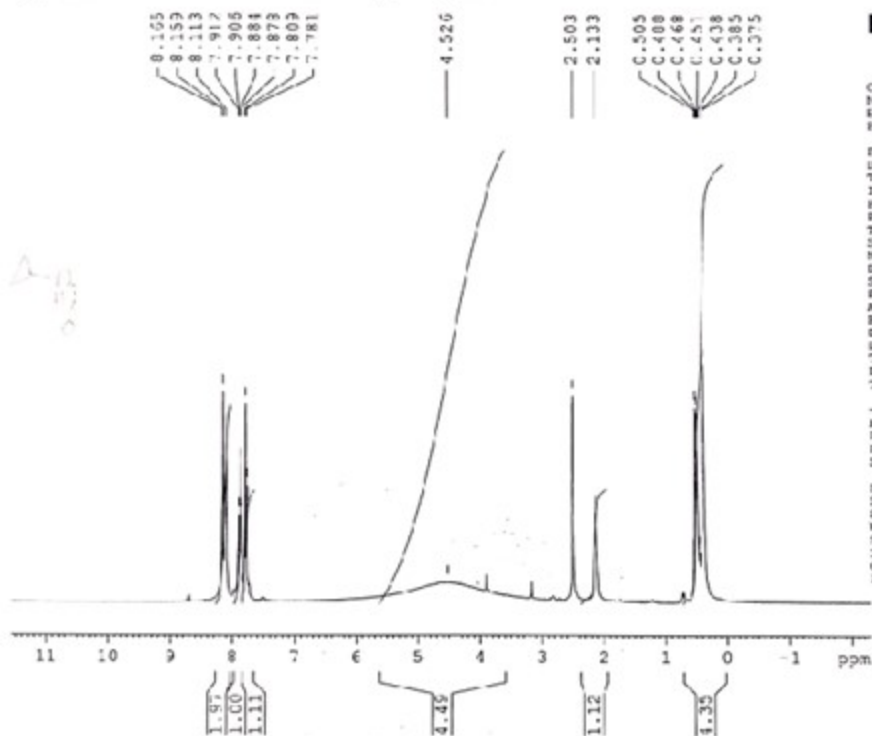
**<sup>1</sup>H NMR** (300 MHz, DMSO-d<sub>6</sub>): δ (ppm) 13.89 (s, H-1a), 8.11-8.16 (m, H-3 and H-4), 7.88-7.91 (dd, H-6), 7.78-7.81 (d, H-2a), 2.13 (ap. s, H-8), 0.38-0.50 (m, H-9 and H-10).

**<sup>13</sup>C NMR** (75 MHz, DMSO-d<sub>6</sub>): δ (ppm) 166.1 (C-7), 139.6 (C-2), 136.4 (C-6), 133.1 (C-1), 132.3 (C-5), 130.7 (C-4), 129.5 (C-3), 24.5 (C-8), 5.5 (C-9 and C-10).

**ESI-HRMS-** (m/z): [M+H]<sup>+</sup> calc'd for C<sub>10</sub>H<sub>11</sub>NO<sub>4</sub>S<sup>+</sup>, 276.0092; found, 276.0097.



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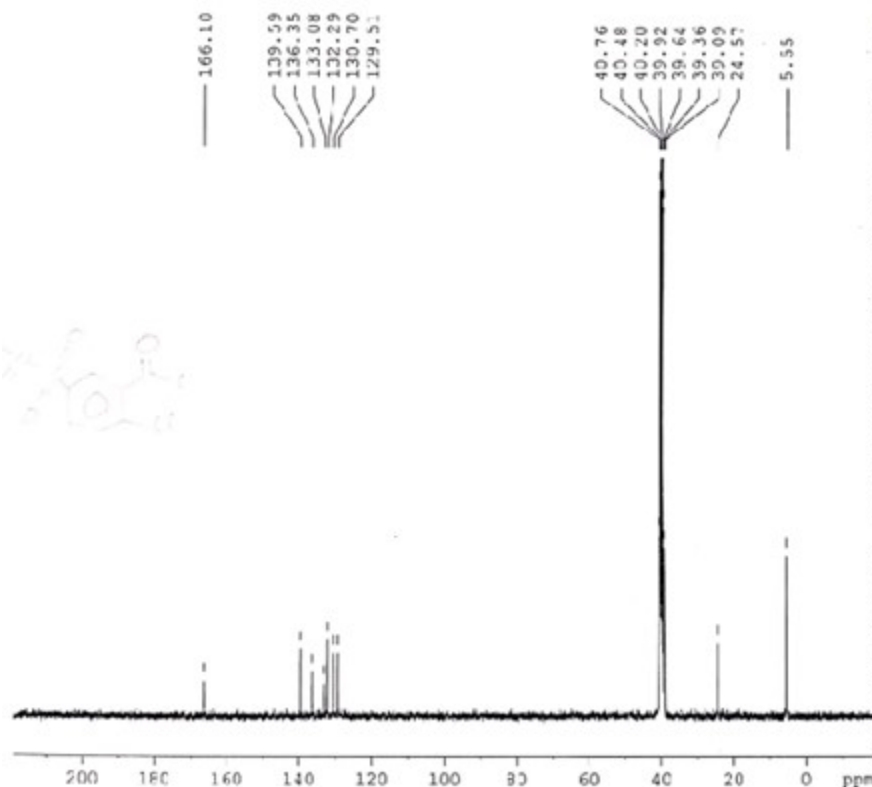
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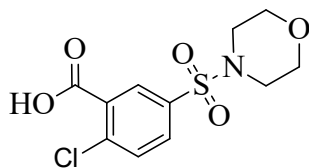
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Fig. S-4: <sup>1</sup>H and <sup>13</sup>C NMR spectra for compound 2d.



**2-Chloro-5-(morpholinosulfonyl)benzoic acid 2e (BT-06)**



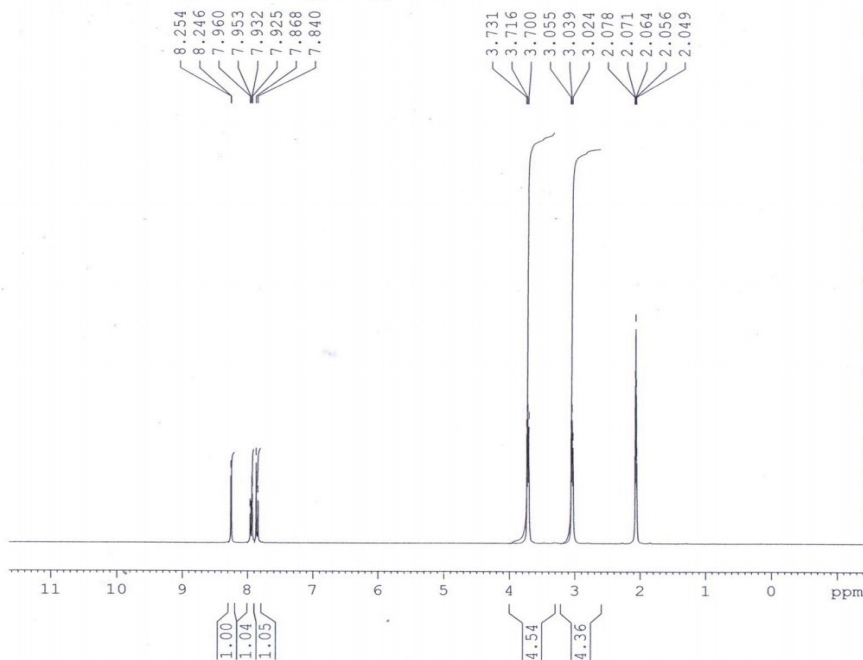
Yield: 76 %; white solid; m.p. : 219-222 °C;  $R_f$ : 0.3 (chloroform: methanol :: 9.5: 0.5).

$^1\text{H NMR}$  (300 MHz, Acetone- $d_6$ ):  $\delta$  (ppm) 8.25 (*d*,  $J = 2.4$  Hz, 1H), 7.92-7.96 (*m*, 1H), 7.85 (*d*,  $J = 8.4$  Hz, 1H), 3.70-3.73 (*m*, 4H), 3.02-3.06 (*m*, 4H).

$^{13}\text{C NMR}$  (75 MHz, Acetone- $d_6$ ):  $\delta$  (ppm) 164.5, 137.9, 134.6, 132.5, 131.6, 131.5, 130.5, 65.7 (2C), 46.1 (2C).

**ESI-HRMS-** ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calc'd for  $\text{C}_{11}\text{H}_{13}\text{NO}_5\text{S}^+$ , 306.0197; found, 306.0201.

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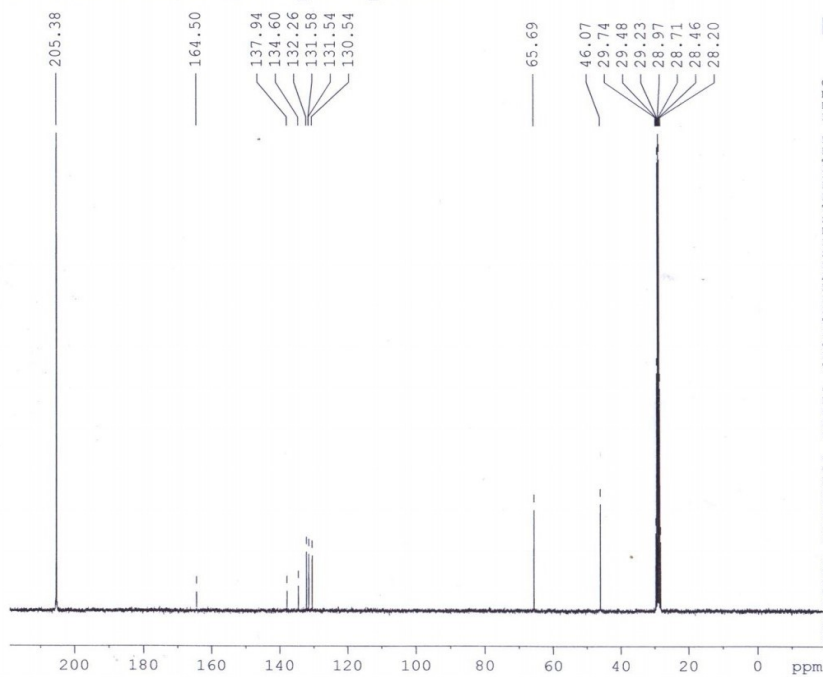
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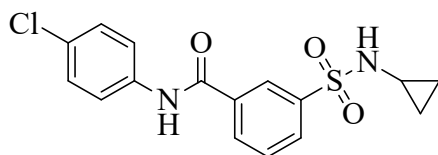
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g. S-5:  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compound **2e**.

**General procedure for the synthesis of *N*-substituted-5-(*N*-substituted sulfamoyl)-2-substituted benzamide *via* sequential synthesis (ZR-55, 56, 57, 59, 27, 63, 29, 30 & 37)**

5-(Substituted sulfamoyl)-2-substitutedbenzoic acid (0.5 mmol, 100 mol%) was dissolved in mixture of DCM (3.3 mL, 0.15 M) and DMF (0.33 mL, 1.5 M) in a 25 mL round bottom flask. DMAP (12.2 mg, 0.1 mmol, 20 mol%), the corresponding amine (0.5 mmol, 100 mol%) and EDC.HCl (144.0 mg, 0.75 mmol, 150 mol%) were added to the reaction mixture and allowed to stir overnight at room temperature. After the completion of the reaction as evident by TLC, the volatiles were removed under reduced pressure and aqueous HCl (10 mL, 0.1 M) was added to the residue and stirred for 10 min. The residue is partitioned with ethyl acetate (20 mL) and the organic layer is separated. The organic layer is further washed with water (10 mL x 2) and concentrated under *vacuo*. The crude carboxamide products were purified by flash column chromatography using silica gel as stationary phase and *n*-hexane and ethyl acetate as mobile phase.

***N*-(4-Chlorophenyl)-3-(*N*-cyclopropylsulfamoyl)benzamide 3a (ZR-55)**



Yield: 68 %; white solid; m.p. : 171-174 °C;  $R_f$ : 0.6 (*n*-hexane: ethyl acetate :: 7:3).

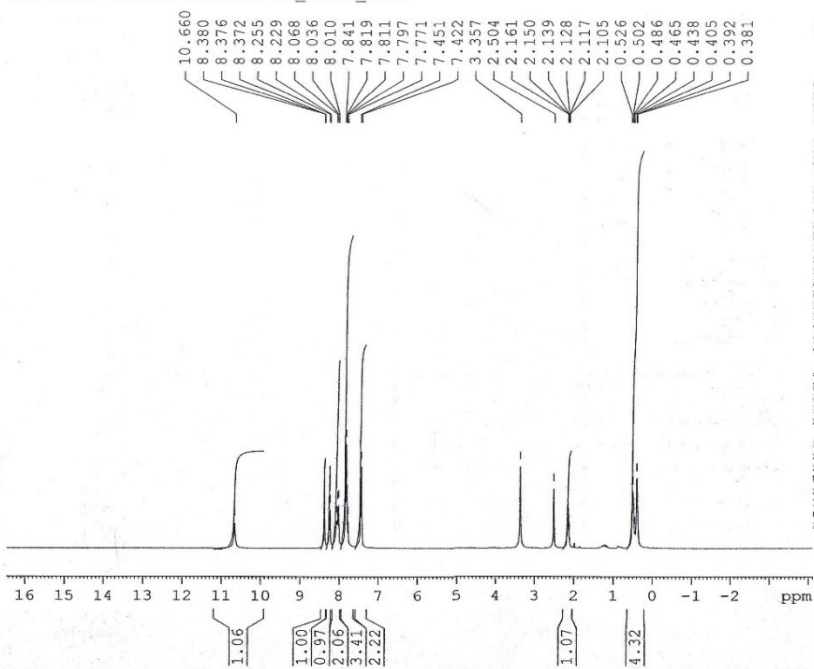
$^1\text{H NMR}$  (300 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) 10.66 (*s*, 1H), 8.38 (*t*,  $J = 1.2$  Hz, 1H), 8.24 (*d*,  $J = 7.8$  Hz, 1H), 8.01-8.07 (*m*, 2H), 7.77-7.84 (*m*, 3H), 7.44 (*d*,  $J = 8.7$  Hz, 2H), 2.10-2.16 (*m*, 1H), 0.38-0.53 (*m*, 4H).

$^{13}\text{C NMR}$  (75 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) 164.8, 141.2, 138.3, 136.3, 131.9, 130.2, 130.0, 129.1 (2C), 128.1, 126.6, 122.5 (2C), 24.6, 5.6 (2C).

**ESI-HRMS-** ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calc'd for  $\text{C}_{16}\text{H}_{16}\text{ClN}_2\text{O}_3\text{S}^+$ , 351.0565; found, 351.0564.

**GC-EIMS** ( $m/z$ ): 346, 227, 200, 122, 104, 76.

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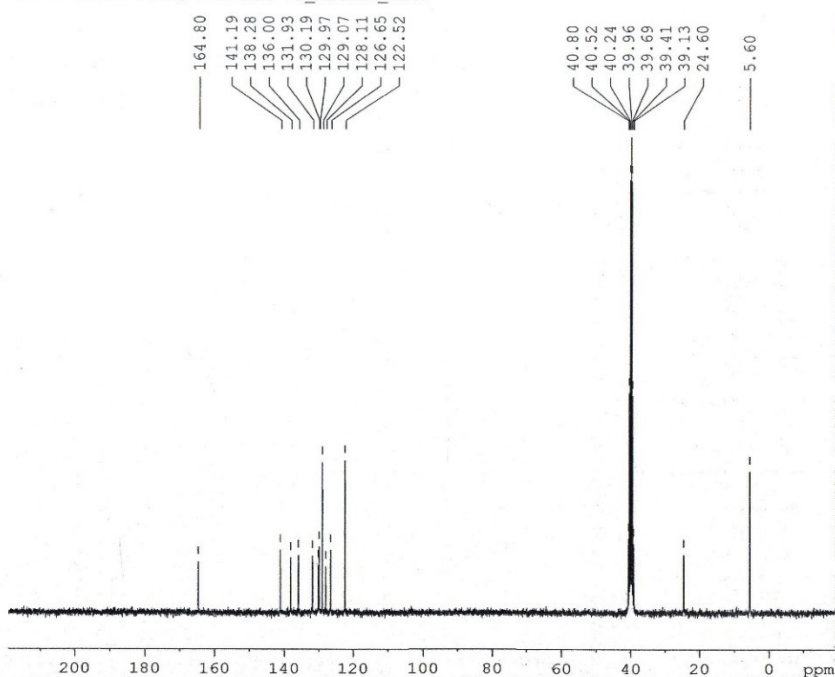
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PROBHD 5 mm BBO BB-1H  
PULPROG zg30  
TD 65536  
SOLVENT DMSO  
NS 8  
DS 0  
SWH 6172.839 Hz  
FIDRES 0.094190 Hz  
AQ 5.3084660 sec  
RG 203.2  
DW 81.000 usec  
DE 6.00 usec  
TE 295.6 K  
D1 1.0000000 sec  
TD0 1

----- CHANNEL f1 -----  
NUC1 1H  
P1 9.00 usec  
PL1 2.00 dB  
SFO1 300.1318534 MHz

F2 - Processing parameters  
SI 32768  
SF 300.1300000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

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Current Data Parameters  
NAME ZR-55\_13CNMR\_DMSO  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
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Time 11.05  
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PULPROG zgpg30  
TD 35968  
SOLVENT DMSO  
NS 450  
DS 0  
SWH 17985.611 Hz  
FIDRES 0.500045 Hz  
AQ 0.9999604 sec  
RG 1448.2  
DW 27.800 usec  
DE 6.00 usec  
TE 295.1 K  
D1 2.0000000 sec  
d11 0.0300000 sec  
DELTA 1.8999999 sec  
TD0 1

----- CHANNEL f1 -----  
NUC1 13C  
P1 6.00 usec  
PL1 -5.00 dB  
SFO1 75.4752953 MHz

----- CHANNEL f2 -----  
CPDPRG2 waltz16  
NUC2 1H  
FPCPD2 80.00 usec  
PL2 2.00 dB  
PL12 20.98 dB  
PL13 20.00 dB  
SFO2 300.1312005 MHz

F2 - Processing parameters  
SI 32768  
SF 75.4677490 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

Fig. S-6:  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compound **3a**.

File : C:\MSDCHEM\1\DATA\2021\Dr. Abbas Hassan\Zahid Hussain\ZR-56  
... 2-09-21.D  
Operator : Saqib Yasin  
Instrument : Instrument #1  
Acquired : 22 Sep 2021 10:26 using AcqMethod LIQUID.M  
Sample Name : zr-56  
Misc Info : Temp 120-280 10 C/min Flow 1.5ml/min Inj 5ul

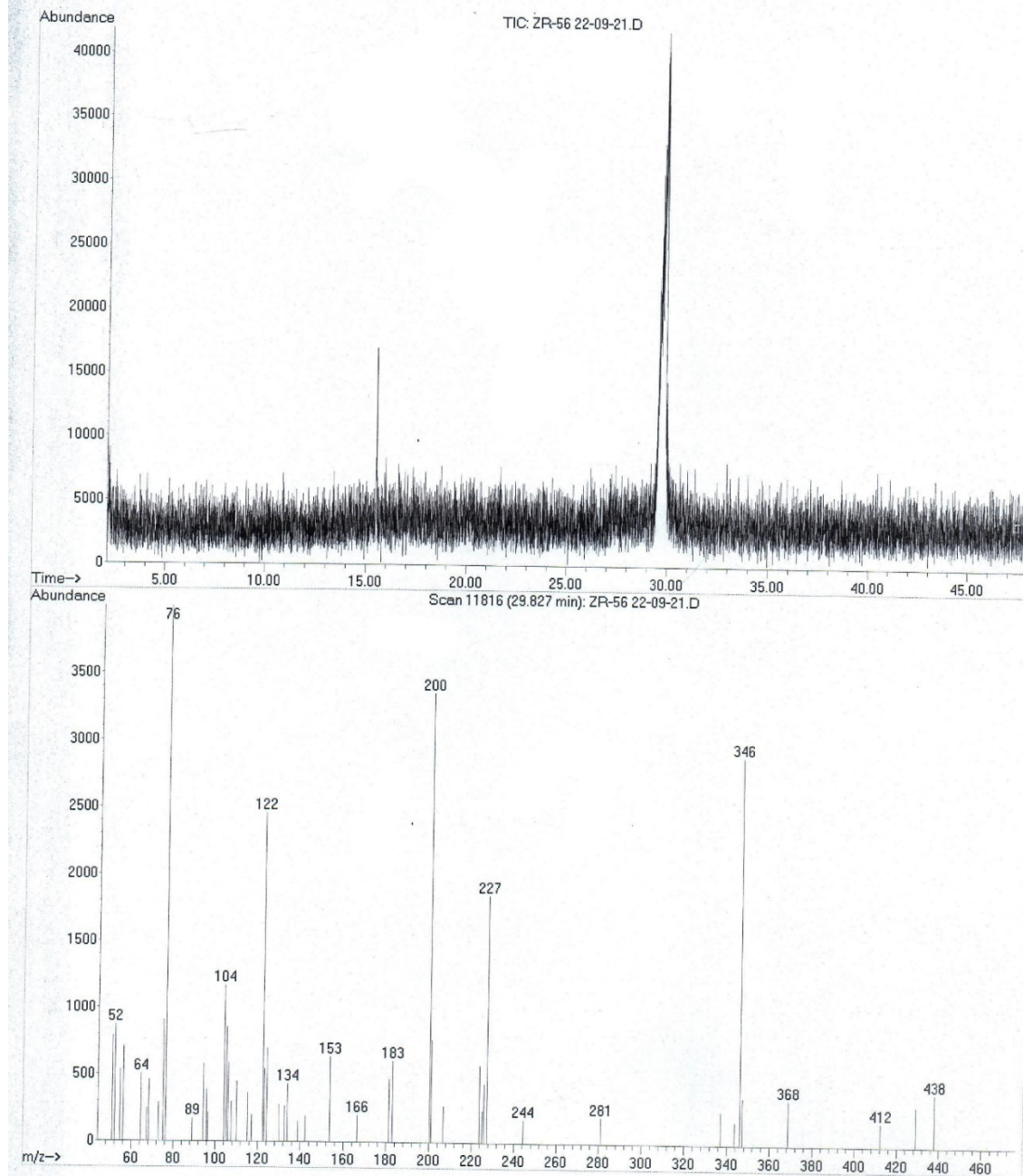
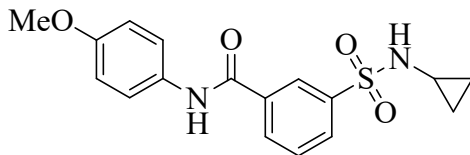


Fig. S-7: GCMS spectrum for compound 3a.

**3-(N-Cyclopropylsulfamoyl)-N-(4-methoxyphenyl)benzamide 3b (ZR-56)**



Yield: 72 %; white solid; m.p. : 173-176 °C;  $R_f$ : 0.5 (*n*-hexane: ethyl acetate :: 7:3).

**$^1\text{H}$  NMR** (300 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) 10.42 (s, 1H), 8.37 (s, 1H), 8.23 (d,  $J = 7.2$  Hz, 1H), 7.99-8.06 (m, 2H), 7.67-7.80 (m, 3H), 6.95 (d,  $J = 8.1$  Hz, 2H), 3.75 (s, 3H), 2.12-2.15 (m, 1H), 0.38-0.50 (m, 4H).

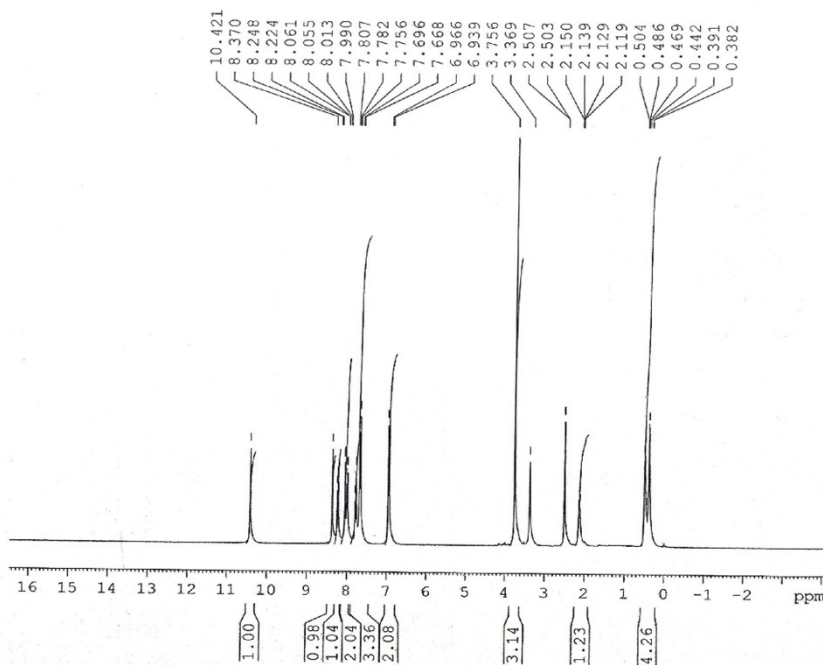
**$^{13}\text{C}$  NMR** (75 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) 164.2, 156.2, 141.1, 136.4, 132.3, 131.8, 129.9 (2C), 126.6, 122.6 (2C), 114.2 (2C), 55.6, 24.6, 5.6 (2C).

**ESI-HRMS-** (m/z):  $[\text{M}+\text{H}]^+$  calc'd for  $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}_4\text{S}^+$ , 347.1060; found, 347.1064.

**GC-EIMS** (m/z): 346 ( $\text{M}^+$ ), 227, 200, 122, 104, 76, 56.



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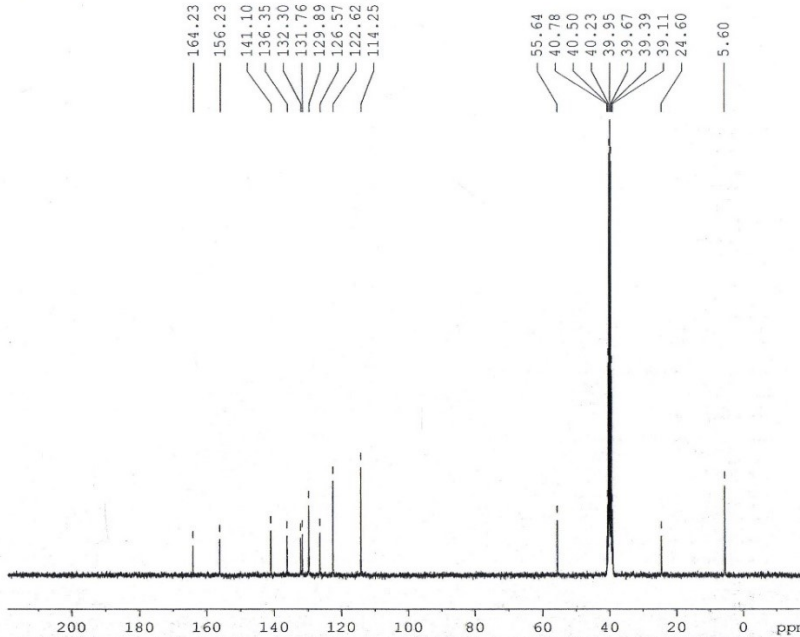
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EXPNO 1  
PROCNO 1

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PULPROG zg30  
TD 65536  
SOLVENT DMSO  
NS 8  
DS 0  
SWH 6172.839 Hz  
FIDRES 0.094150 Hz  
AQ 5.3084660 sec  
RG 322.5  
DW 81.000 usec  
DE 6.00 usec  
TE 293.7 K  
D1 1.00000000 sec  
TD0 1

==== CHANNEL f1 =====  
NUC1 1H  
P1 9.00 usec  
PL1 2.00 dB  
SFO1 300.1318534 MHz

F2 - Processing parameters  
SI 32768  
SF 300.1300000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

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Current Data Parameters  
NAME ZR-56\_13CNMR\_DMSO  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date 20210623  
Time 10.49  
INSTRUM spect  
PROBHD 5 mm BBO BB-1H  
PULPROG zgpg30  
TD 35968  
SOLVENT DMSO  
NS 1024  
DS 0  
SWH 17985.611 Hz  
FIDRES 0.500045 Hz  
AQ 0.9999604 sec  
RG 1149.4  
DW 27.800 usec  
DE 6.00 usec  
TE 294.0 K  
D1 2.00000000 sec  
d11 0.03000000 sec  
DELTA 1.89999998 sec  
TD0 1

==== CHANNEL f1 =====  
NUC1 13C  
P1 6.00 usec  
PL1 -5.00 dB  
SFO1 75.4752953 MHz

==== CHANNEL f2 =====  
CDDPRG2 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
PL2 2.00 dB  
PL12 20.98 dB  
PL13 20.00 dB  
SPO2 300.1312005 MHz

F2 - Processing parameters  
SI 32768  
SF 75.4677490 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

Fig. S-8:  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compound **3b**.

File C:\MSDCHEM\1\DATA\2021\Dr. Ali Haider\Mehreen\ZR-56 13-10-21.D  
Operator : Saqib Yasin  
Instrument : Instrument #1  
Acquired : 13 Oct 2021 14:16 using AcqMethod LIQUID.M  
Sample Name: ZR-56  
Misc Info : Temp 120-280 10C/min Flow 1.5ml/min Inj 5ul

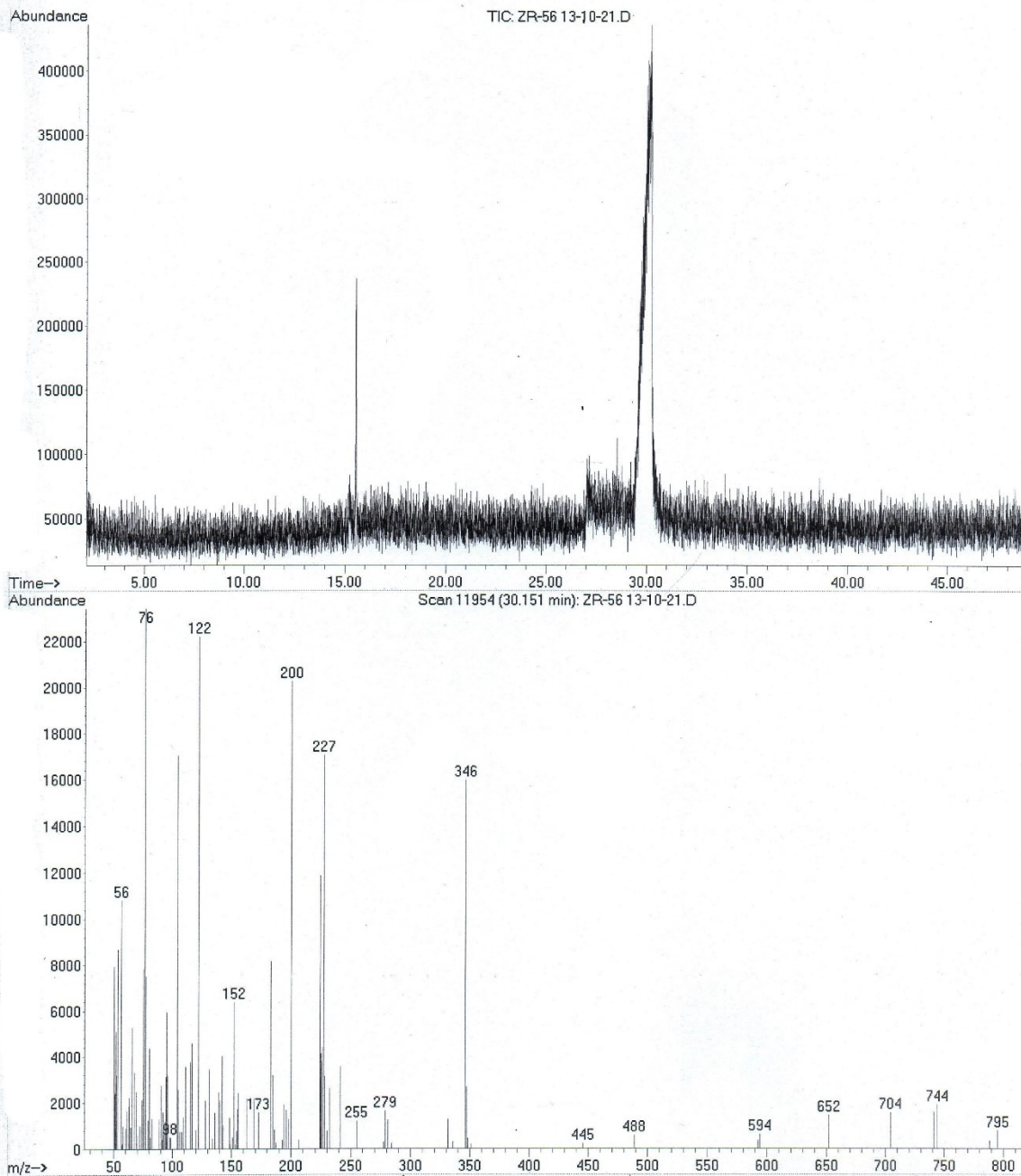
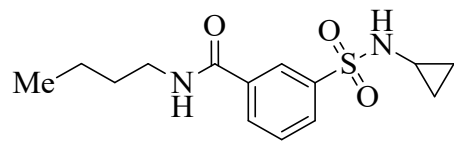


Fig. S-9: GCMS spectrum for compound **3b**.



***N*-Butyl-3-(*N*-cyclopropylsulfamoyl)benzamide 3c (ZR-57)**



Yield: 73 %; white solid; m.p. : 169-172 °C;  $R_f$ : 0.7 (*n*-hexane: ethyl acetate :: 7:3).

**$^1\text{H}$  NMR** (300 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) 8.72. (*t*,  $J = 5.4$  Hz, 1H), 8.27-8.28 (*m*, 1H), 8.08-8.12 (*m*, 1H), 8.00 (*d*,  $J = 2.7$  Hz, 1H), 7.92-7.96 (*m*, 1H), 7.70 (*t*,  $J = 7.8$  Hz, 1H), 3.28 (*q*,  $J = 6.9$  Hz, 2H), 2.07-2.15 (*m*, 1H), 1.52 (*quint*,  $J = 6.6$  Hz, 2H), 1.33 (*sext*,  $J = 6.6$  Hz, 2H), 0.90 (*t*,  $J = 6.8$  Hz, 3H), 0.45-0.49 (*m*, 2H), 0.34-0.38 (*m*, 2H).

**$^{13}\text{C}$  NMR** (75 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) 165.2, 141.0, 136.0, 131.3, 129.7, 129.6, 126.2, 31.6, 24.6, 20.1, 14.6 (2C), 5.6 (2C).

**ESI-HRMS-** ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calc'd for  $\text{C}_{14}\text{H}_{21}\text{N}_2\text{O}_3\text{S}^+$ , 297.1267; found, 297.1269.

**GC-EIMS** ( $m/z$ ): 296 ( $\text{M}^+$ ), 224, 177, 104, 76, 56.

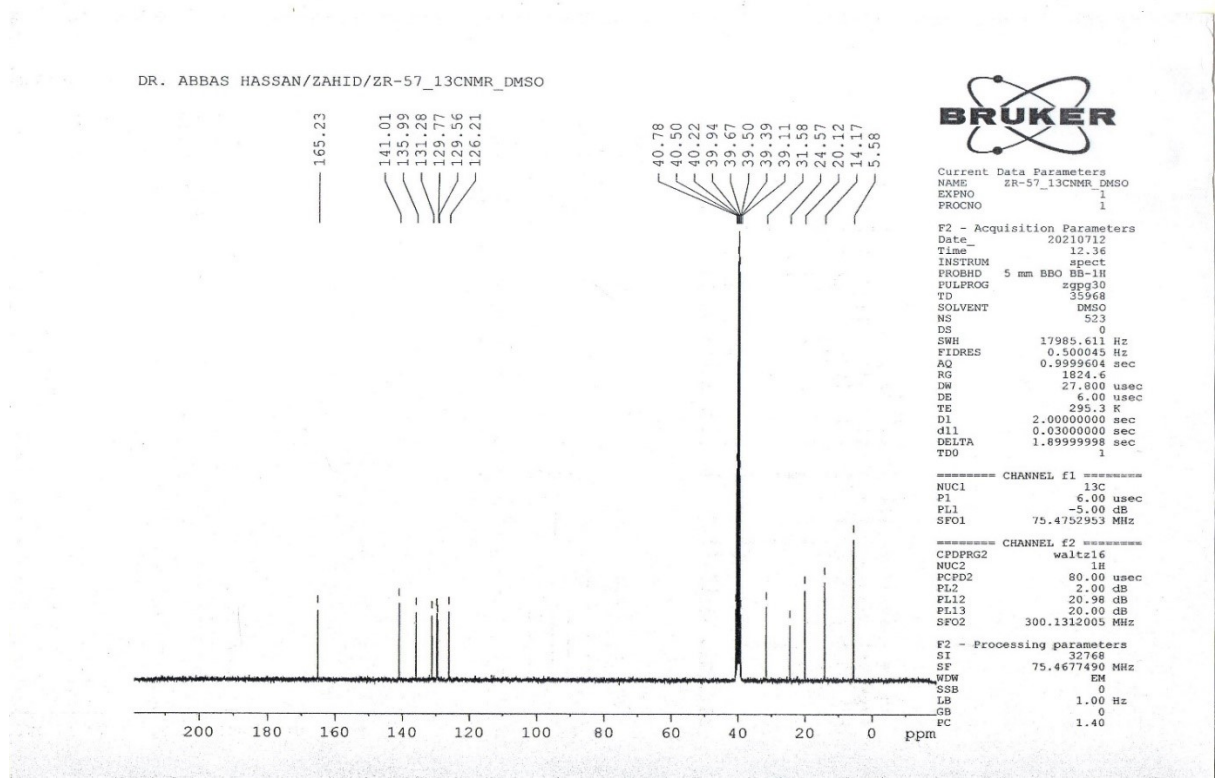
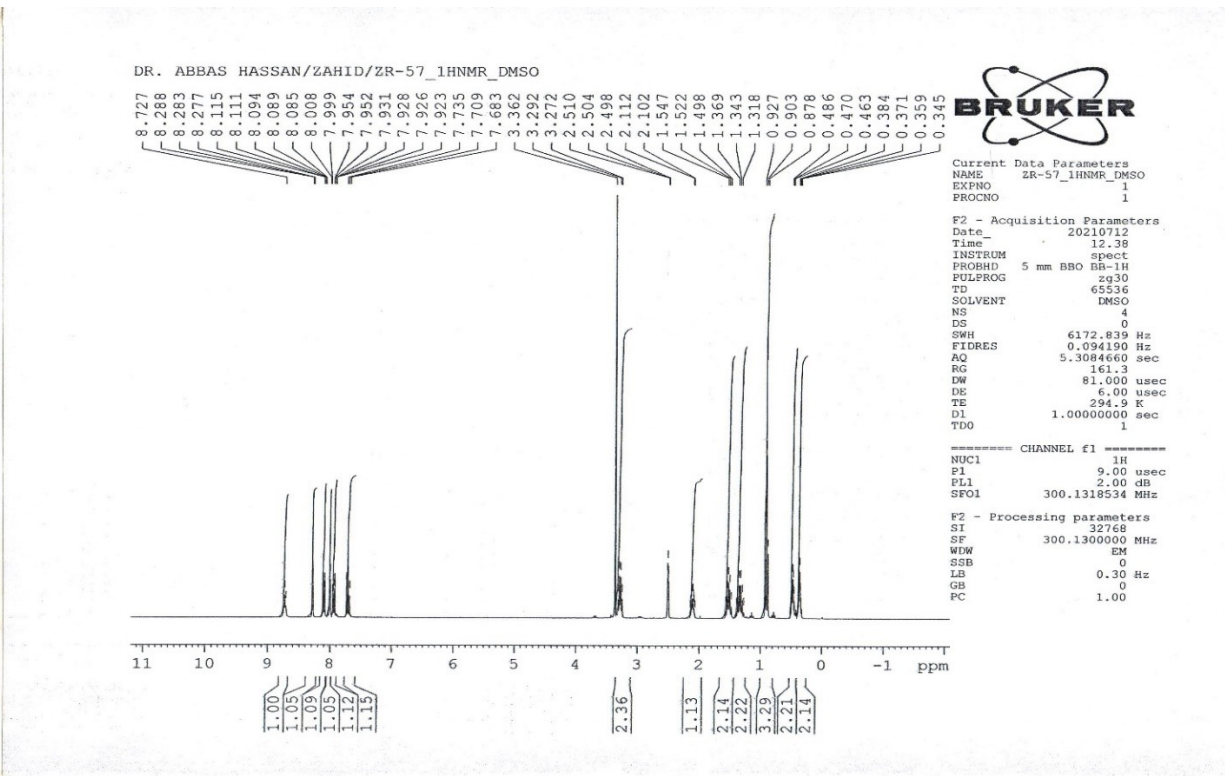


Fig. S-10: <sup>1</sup>H and <sup>13</sup>C NMR spectra for compound **3c**.

File : C:\MSDCHEM\1\DATA\2021\Dr. Abbas Hassan\Zahid Hussain\ZR-57 2  
2-09-21.D  
Operator : Saqib Yasin  
Instrument : Instrument #1  
Acquired : 22 Sep 2021 11:19 using AcqMethod LIQUID.M  
Sample Name : ZR-57  
Misc Info : Temp 120-280 10 C/min Flow 1.5ml/min Inj 5ul

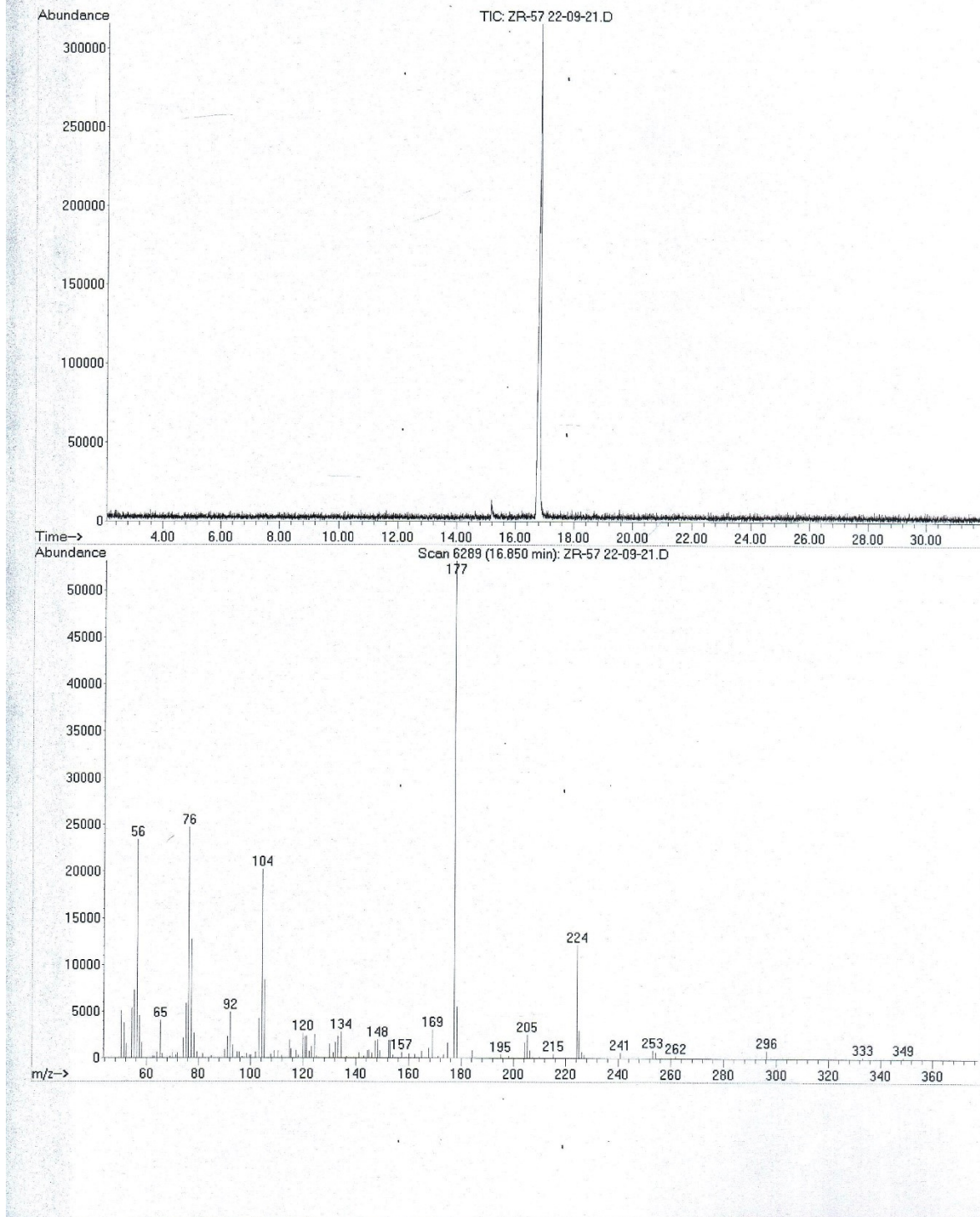
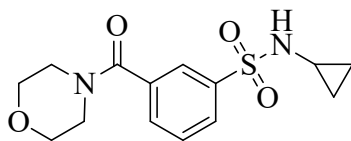


Fig. S-11: GCMS spectrum for compound 3c.

***N*-Cyclopropyl-3-(morpholine-4-carbonyl)benzene sulfonamide 3d (ZR-59)**



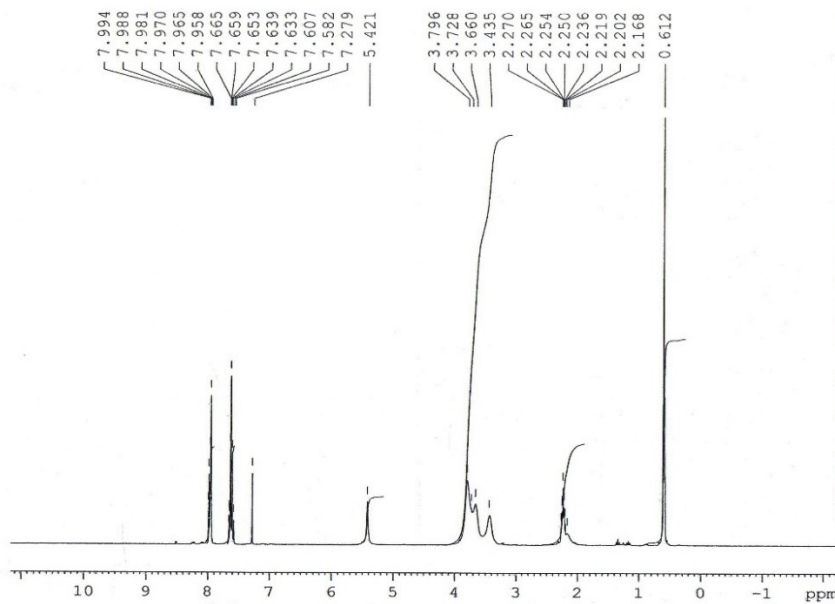
Yield: 69 %; white solid; m.p. : 187-189 °C;  $R_f$ : 0.3 (*n*-hexane: ethyl acetate :: 7:3).

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 7.97-7.99 (*m*, 2H), 7.58-7.66 (*m*, 2H), 5.42 (*s*, 1H), 3.44-3.79 (*m*, 8H), 2.17-2.27 (*m*, 1H), 0.61 (*s*, 4H).

$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 164.6, 140.4, 136.4, 131.2, 129.5, 128.7, 126.0, 66.7 (4C), 24.3, 6.2 (2C).

**ESI-HRMS** (*m/z*):  $[\text{M}+\text{H}]^+$  calc'd for  $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_4\text{S}^+$ , 311.1060; found, 311.3759.

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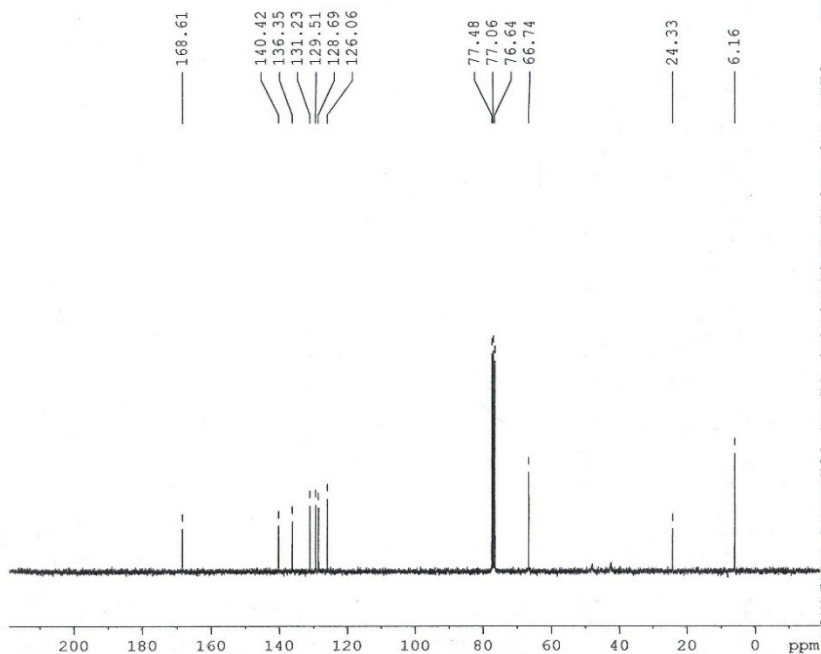
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PROCNO 1

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PULPROG zg30  
TD 65536  
SOLVENT CDCL3  
NS 4  
DS 0  
SWH 6172.839 Hz  
FIDRES 0.094190 Hz  
AQ 5.3084660 sec  
RG 287.4  
DW 81.0000 usec  
DE 6.00 usec  
TE 295.2 K  
D1 1.00000000 sec  
TDO 1

----- CHANNEL f1 -----  
NUC1 1H  
P1 9.00 usec  
PL1 2.00 dB  
SFO1 300.1318534 MHz

F2 - Processing parameters  
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SF 300.1300000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

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Current Data Parameters  
NAME ZR-59\_13CNMR\_CDCL3  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
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Time 11.14  
INSTRUM spect  
PROBHD 5 mm BBO BB-1H  
PULPROG zgpg30  
TD 35968  
SOLVENT CDCL3  
NS 340  
DS 0  
SWH 17985.611 Hz  
FIDRES 0.300045 Hz  
AQ 0.9999604 sec  
RG 32768  
DW 27.800 usec  
DE 6.00 usec  
TE 295.4 K  
D1 2.00000000 sec  
d11 0.03000000 sec  
DELTA 1.89999998 sec  
TDO 1

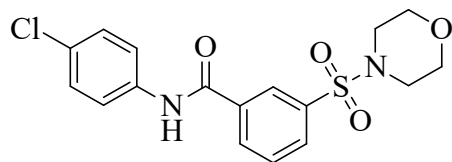
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P1 6.00 usec  
PL1 -5.00 dB  
SFO1 75.4752953 MHz

----- CHANNEL f2 -----  
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NUC2 1H  
PCPD2 80.00 usec  
PL2 2.00 dB  
PL12 20.98 dB  
PL13 20.00 dB  
SFO2 300.1312005 MHz

F2 - Processing parameters  
SI 32768  
SF 75.4677490 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

Fig. S-12:  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compound **3d**.

***N*-(4-Chlorophenyl)-3-(morpholinylsulfonyl)benzamide 3e (ZR-27)**



Yield: 71 %; white solid; m.p. : 179-182 °C;  $R_f$ : 0.3 (*n*-hexane: ethyl acetate :: 7:3).

**$^1\text{H NMR}$**  (300 MHz, Acetone- $d_6$ ):  $\delta$  (ppm) 10.03 (*s*, 1H), 8.33-8.36 (*m*, 2H), 7.98-8.01 (*m*, 1H), 7.82-7.91 (*m*, 3H), 7.39-7.44 (*m*, 2H), 3.70 (*t*,  $J = 4.8$  Hz, 4H), 2.98-3.02 (*m*, 4H).

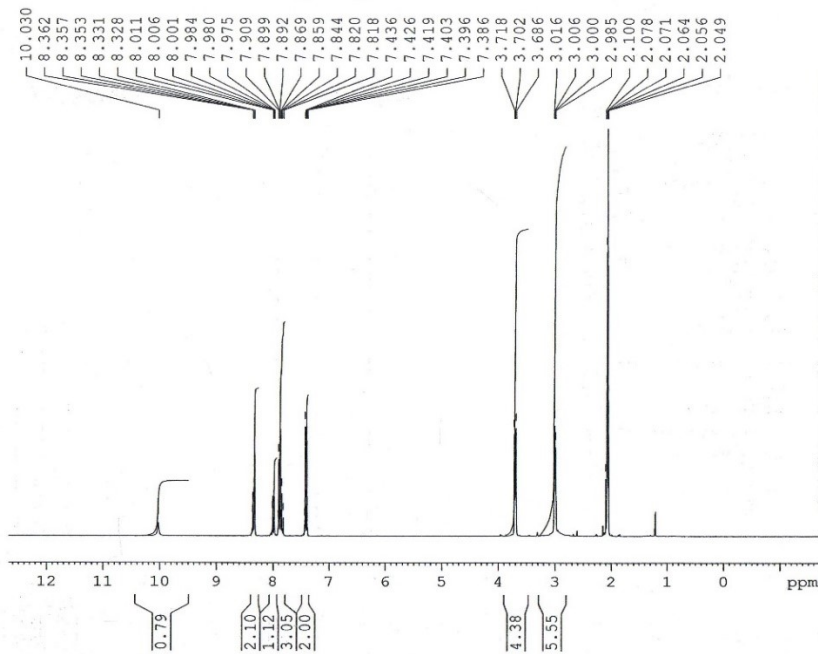
**$^{13}\text{C NMR}$**  (75 MHz, Acetone- $d_6$ ):  $\delta$  (ppm) 164.1, 138.0, 137.9, 136.2, 136.0, 132.1, 130.7, 129.7, 128.7, 128.4, 126.7, 121.8, 121.7, 65.7 (2C), 46.2 (2C).

**ESI-HRMS** ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calc'd for  $\text{C}_{17}\text{H}_{18}\text{ClN}_2\text{O}_4\text{S}^+$ , 381.0670; found, 381.0674.

**GC-EIMS** ( $m/z$ ): 380 ( $\text{M}^+$ ), 254, 206, 99, 76, 56.



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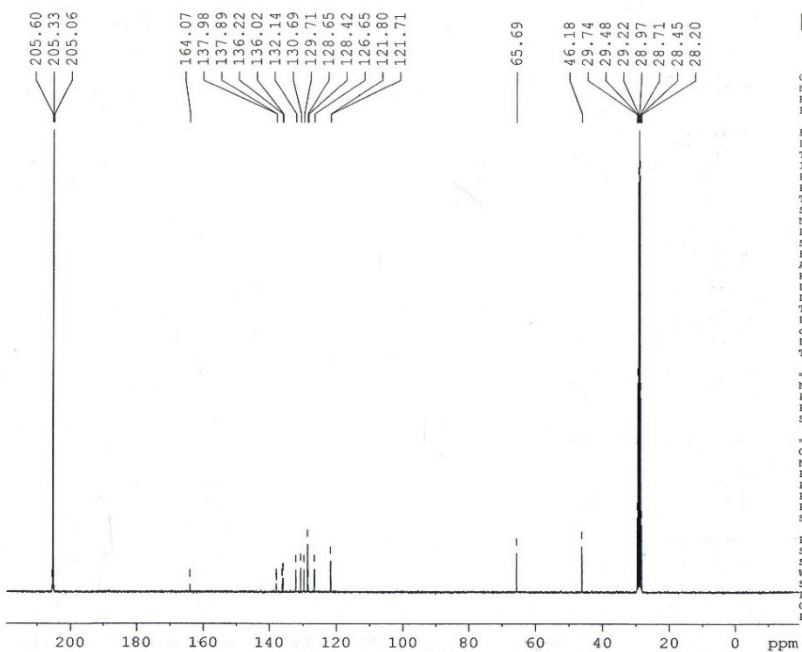
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 PROCNO 1

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 PULPROG zg30  
 TD 65536  
 SOLVENT Acetone  
 NS 8  
 DS 0  
 SWH 6172.839 Hz  
 FIDRES 0.094190 Hz  
 AQ 5.3084660 sec  
 RG 406.4  
 DW 81.000 usec  
 DE 6.00 usec  
 TE 293.9 K  
 D1 1.00000000 sec  
 TDO 1

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 P1 9.00 usec  
 PL1 2.00 dB  
 SF01 300.1318534 MHz

F2 - Processing parameters  
 SI 32768  
 SF 300.1300000 MHz  
 WDW EM  
 SSB 0  
 LB 0.30 Hz  
 GB 0  
 PC 1.00

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Current Data Parameters  
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 EXPNO 1  
 PROCNO 1

F2 - Acquisition Parameters  
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 INSTRUM spect  
 PROBHD 5 mm BBO BB-1H  
 PULPROG zgpg30  
 TD 35968  
 SOLVENT Acetone  
 NS 1024  
 DS 0  
 SWH 17985.611 Hz  
 FIDRES 0.500045 Hz  
 AQ 0.9999604 sec  
 RG 32768  
 DW 27.800 usec  
 DE 6.00 usec  
 TE 294.7 K  
 D1 2.00000000 sec  
 d11 0.03000000 sec  
 DELTA 1.69999998 sec  
 TDO 1

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 P1 6.00 usec  
 PL1 -5.00 dB  
 SF01 75.4752953 MHz

===== CHANNEL f2 =====  
 CPDPRG2 waltz16  
 NUC2 1H  
 FCFD2 80.00 usec  
 PL2 2.00 dB  
 PL12 20.98 dB  
 PL13 20.00 dB  
 SF02 300.1312005 MHz

F2 - Processing parameters  
 SI 32768  
 SF 75.4677490 MHz  
 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.40

Fig. S-13:  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compound **3e**.

File : C:\MSDCHEM\1\DATA\2021\Dr. Abbas Hassan\Zahid Hussain\ZR-27 0  
3-03-2021.D  
Operator : Saqib Yasin  
Instrument : Instrument #1  
Acquired : 3 Mar 2021 11:03 using AcqMethod LIQUID.M  
Sample Name : ZR-27  
Misc Info : Temp 120-280 10C/min Flow 1.5ml/min Inj 3ul

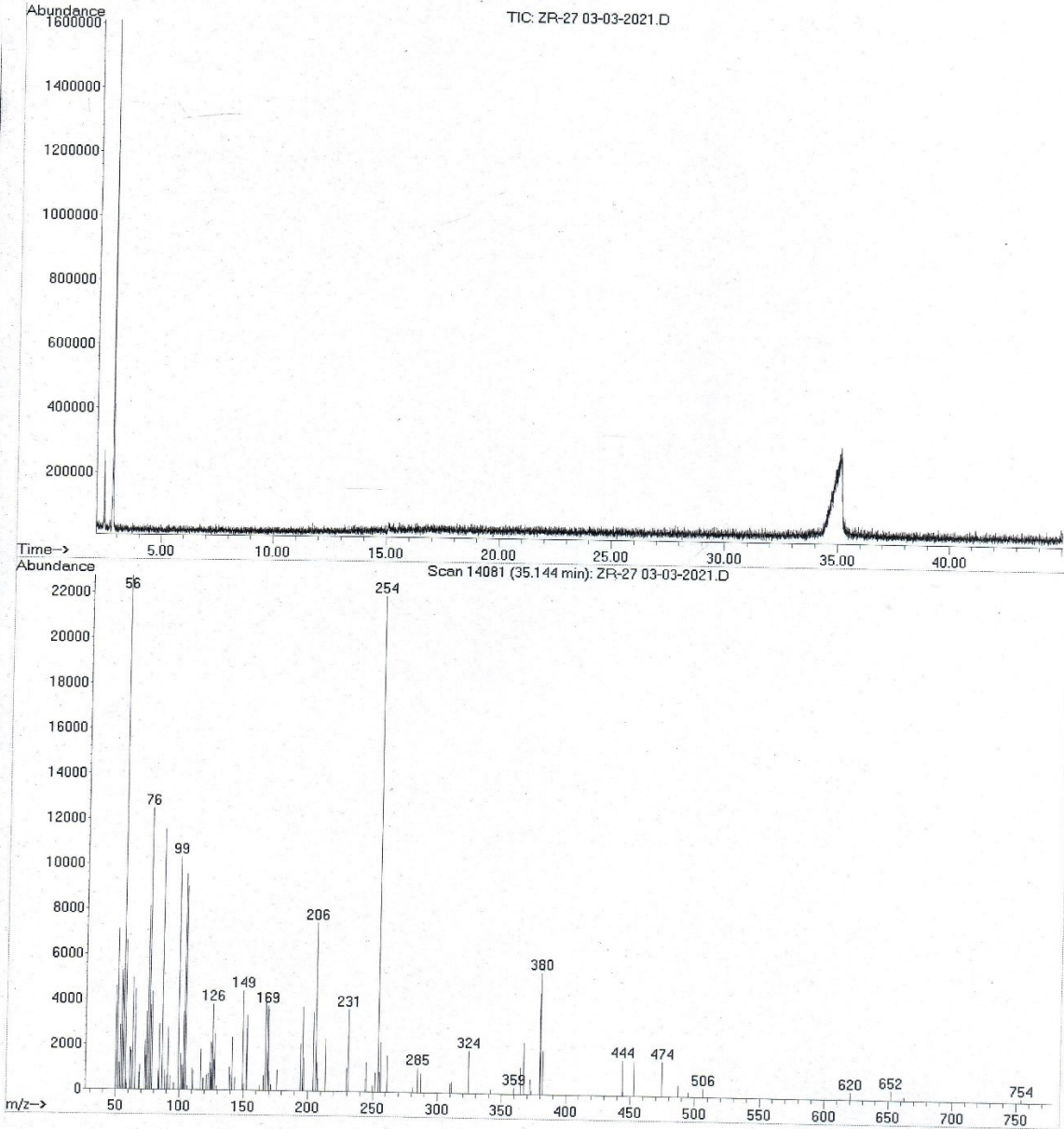
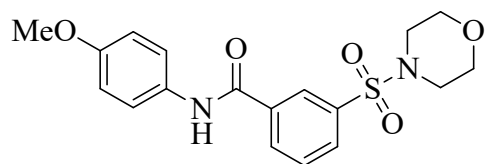


Fig. S-14: GCMS spectrum for compound 3e.



***N*-(4-Methoxyphenyl)-3-(morpholinosulfonyl)benzamide 3f (ZR-63)**



Yield: 69 %; white solid; m.p. : 182-185 °C;  $R_f$ : 0.4 (*n*-hexane: ethyl acetate :: 7:3).

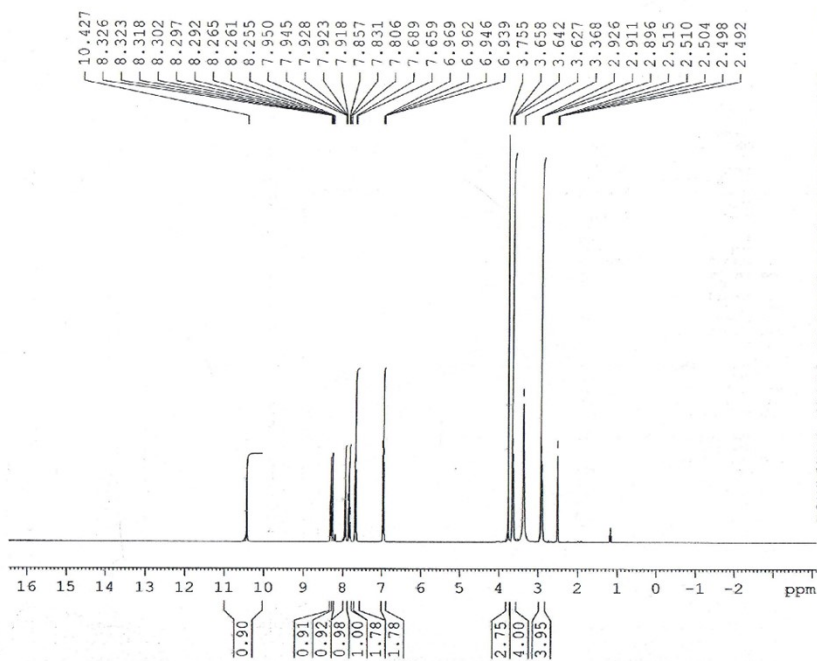
**$^1\text{H}$  NMR** (300 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) 10.42 (*s*, 1H), 8.29-8.32 (*m*, 1H), 8.26 (*t*, 1H), 7.92-7.95 (*m*, 1H), 7.83 (*t*,  $J = 7.5$  Hz, 1H), 7.67 (*d*,  $J = 9.0$  Hz, 2H), 6.95 (*dd*,  $J = 4.8$  & 2.1, 2H), 3.75 (*s*, 3H), 3.64 (*t*,  $J = 4.8$  Hz, 4H), 2.91 (*t*,  $J = 4.5$  Hz, 4H).

**$^{13}\text{C}$  NMR** (75 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) 164.0, 156.3, 136.6, 135.3, 132.8, 132.2, 130.7, 130.3, 127.0, 122.7 (2C), 114.2 (2C), 65.7 (2C), 55.6, 46.4 (2C).

**ESI-HRMS** ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calc'd for  $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_5\text{S}^+$ , 377.1166; found, 377.1171.

**GC-EIMS** ( $m/z$ ): 376 ( $\text{M}^+$ ), 200, 169, 122, 105, 76, 56.

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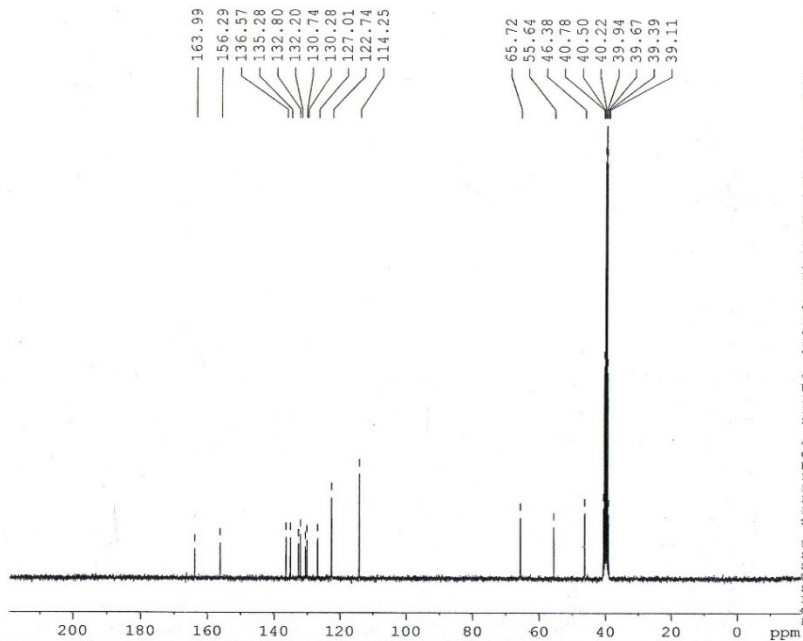
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PROCNO 1

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PULPROG zg30  
TD 65536  
SOLVENT DMSO  
NS 4  
DS 0  
SWH 6172.839 Hz  
FIDRES 0.094190 Hz  
AQ 5.3084660 sec  
RG 287.4  
DW 81.000 usec  
DE 6.00 usec  
TE 295.1 K  
D1 1.00000000 sec  
TDO 1

==== CHANNEL f1 =====  
NUC1 1H  
P1 9.00 usec  
PL1 2.00 dB  
SFO1 300.1318534 MHz

F2 - Processing parameters  
SI 32768  
SF 300.1300000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

DR. ABBAS HASSAN/ZAHID/ZR-63\_13CNMR\_DMSO



Current Data Parameters  
NAME ZR-63\_13CNMR\_DMSO  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20210805  
Time 16.46  
INSTRUM spect  
PROBHD 5 mm BBO BB-1H  
PULPROG zgpg30  
TD 35968  
SOLVENT DMSO  
NS 528  
DS 0  
SWH 17985.611 Hz  
FIDRES 0.500045 Hz  
AQ 0.9999604 sec  
RG 1149.4  
DW 27.800 usec  
DE 6.00 usec  
TE 295.4 K  
D1 2.00000000 sec  
d11 0.03000000 sec  
DELTA 1.89999998 sec  
TDO 1

==== CHANNEL f1 =====  
NUC1 13C  
P1 6.00 usec  
PL1 -5.00 dB  
SFO1 75.4752953 MHz

==== CHANNEL f2 =====  
CFPPRG2 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
PL2 2.00 dB  
PL12 20.00 dB  
PL13 20.00 dB  
SFO2 300.1312005 MHz

F2 - Processing parameters  
SI 32768  
SF 75.4677490 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

Fig. S-15:  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compound **3f**.

File : C:\MSDCHEM\1\DATA\2021\Dr. Abbas Hassan\Zahid Hussain\ZR-63 1  
8-03-21.D  
Operator : Saqib Yasin  
Instrument : Instrument #1  
Acquired : 18 Mar 2021 11:00 using AcqMethod LIQUID.M  
Sample Name: ZR-28  
Misc Info : Temp 120-280 10C/min Flow 1.5ml/min Inj 3ul

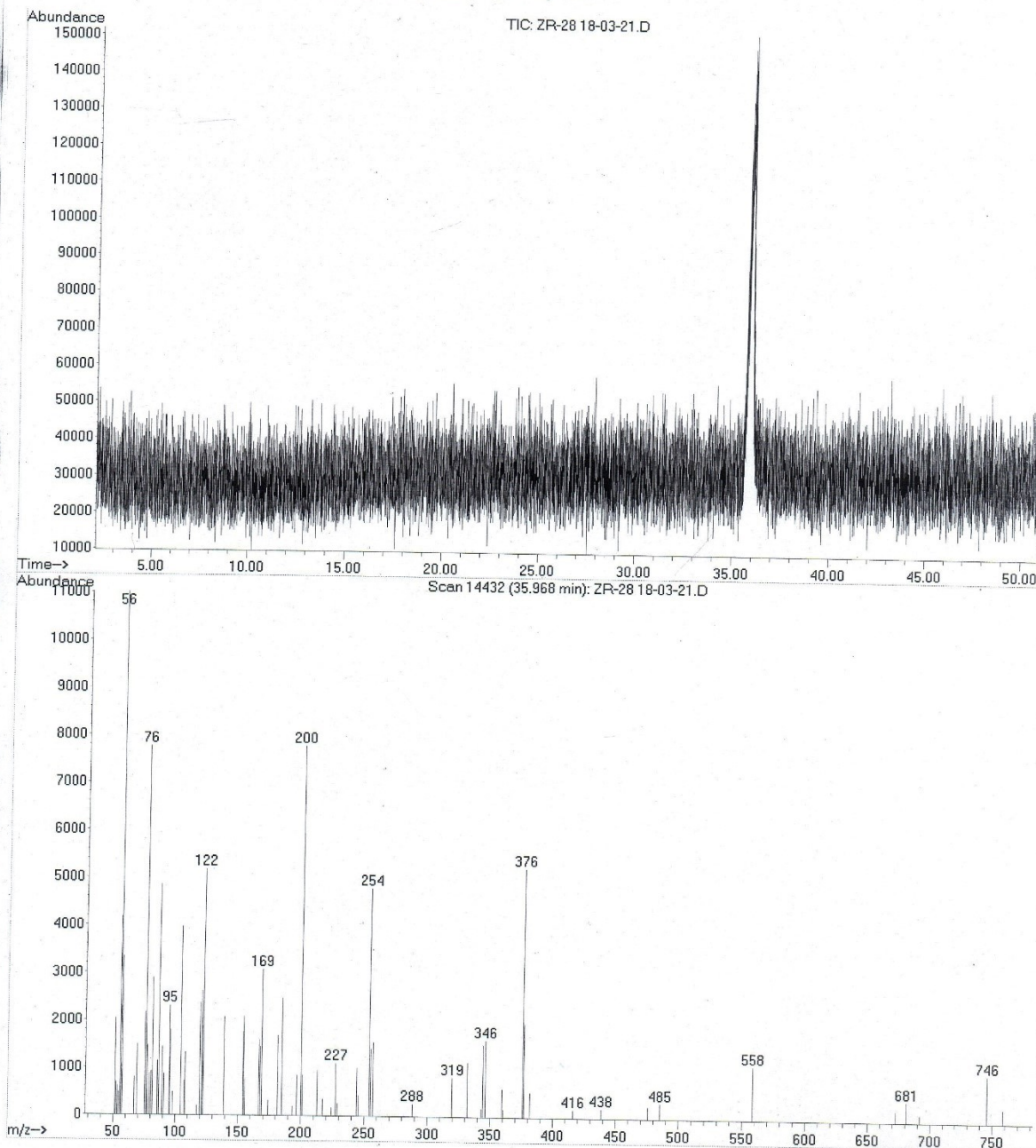
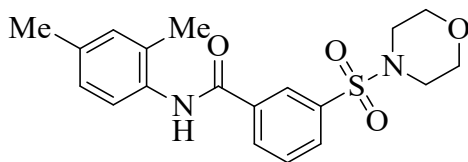


Fig. S-16: GCMS spectrum for compound 3f.

***N*-(2,4-Dimethylphenyl)-3-(morpholinosulfonyl)benzamide 3g (ZR-29)**



Yield: 47 %; white solid; m.p. : 172-175 °C;  $R_f$ : 0.5 (*n*-hexane: ethyl acetate :: 7:3).

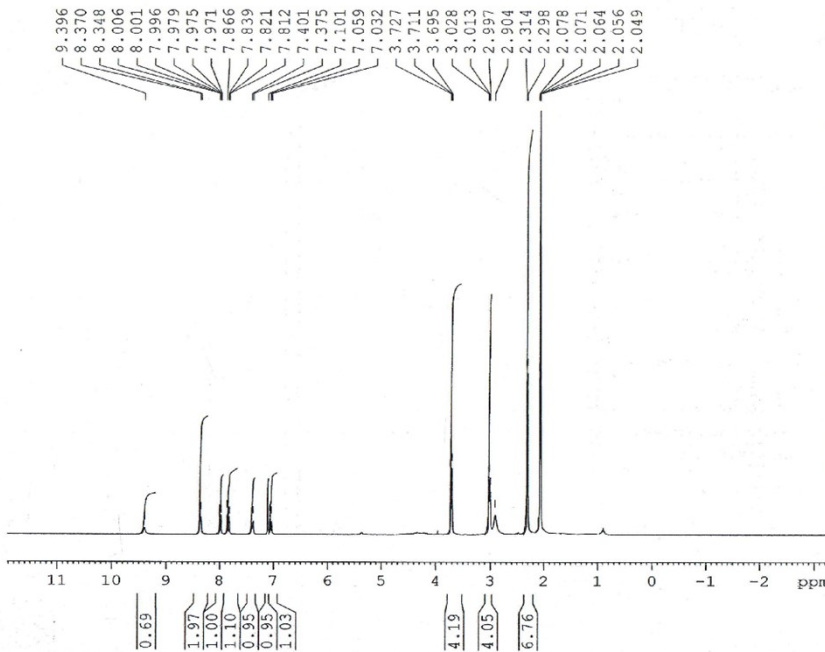
**$^1\text{H NMR}$**  (300 MHz, Acetone- $d_6$ ):  $\delta$  (ppm) 9.39 (*s*, 1H), 8.36 (*d*,  $J = 1.7$  Hz, 1H), 7.98 (*dt*,  $J = 7.8$  & 2.1 Hz, 1H), 7.83 (*t*,  $J = 8.1$  Hz, 1H), 7.39 (*d*,  $J = 7.4$  Hz, 1H), 7.10 (*s*, 1H), 7.04 (*d*,  $J = 7.1$  Hz, 1H), 3.71 (*t*,  $J = 4.8$  Hz, 4H), 3.01 (*t*,  $J = 7.8$  Hz, 4H), 2.31 (*s*, 3H), 2.30 (*s*, 3H).

**$^{13}\text{C NMR}$**  (75 MHz, Acetone- $d_6$ ):  $\delta$  (ppm) 163.1, 136.4, 136.0, 135.5, 132.4, 131.4, 131.4, 130.6, 130.3, 129.9, 127.5, 126.4, 123.9, 66.0 (2C), 46.0 (2C), 21.0, 18.0.

**ESI-HRMS** ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calc'd for  $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_4\text{S}^+$ , 375.1373; found, 375.1377.

**MS** ( $m/z$ ): 374 ( $\text{M}^+$ ), 254, 169, 120, 77, 56.

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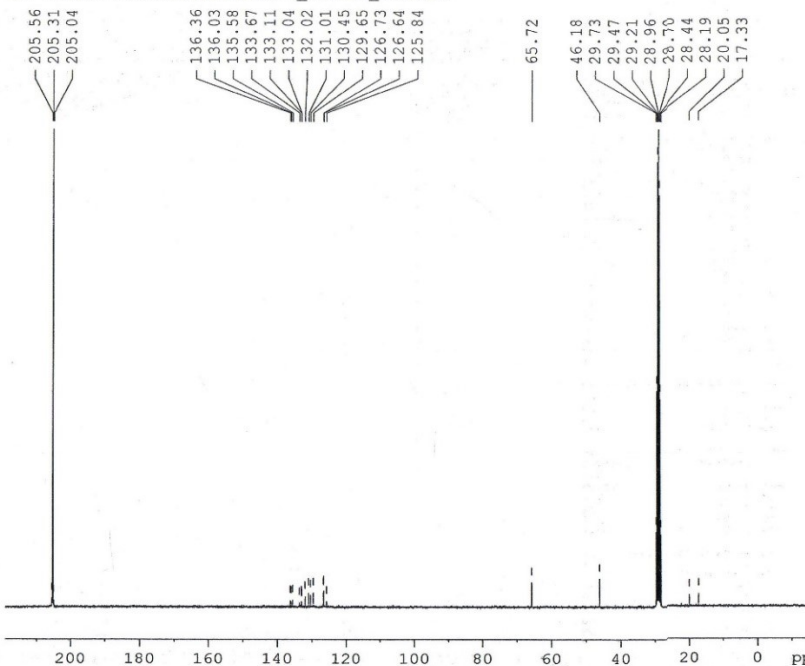
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 PROCNO 1

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 PULPROG zg30  
 TD 65536  
 SOLVENT Acetone  
 NS 8  
 DS 0  
 SWH 6172.839 Hz  
 FIDRES 0.094190 Hz  
 AQ 5.3084660 sec  
 RG 362  
 DW 81.000 usec  
 DE 6.00 usec  
 TE 294.8 K  
 D1 1.00000000 sec  
 TDO 1

----- CHANNEL f1 -----  
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 P1 9.00 usec  
 PL1 2.00 dB  
 SFO1 300.1318534 MHz

F2 - Processing parameters  
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 SF 300.1300000 MHz  
 WW 4  
 SSB 0  
 LB 0.30 Hz  
 GB 0  
 PC 1.00

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Current Data Parameters  
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 PROCNO 1

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 PULPROG zgpg30  
 TD 35868  
 SOLVENT Acetone  
 NS 1024  
 DS 0  
 SWH 17985.611 Hz  
 FIDRES 0.500045 Hz  
 AQ 0.9999604 sec  
 RG 29193  
 DW 27.800 usec  
 DE 6.00 usec  
 TE 295.5 K  
 D1 2.00000000 sec  
 d11 0.03000000 sec  
 DELTA 1.89999998 sec  
 TDO 1

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 P1 6.00 usec  
 PL1 -5.00 dB  
 SFO1 75.4752953 MHz

----- CHANNEL f2 -----  
 CPDPRG2 waltz16  
 NUC2 1H  
 PCPD2 80.00 usec  
 PL2 2.00 dB  
 PL12 20.98 dB  
 PL13 20.00 dB  
 SFO2 300.1312005 MHz

F2 - Processing parameters  
 SI 32768  
 SF 75.4677490 MHz  
 WW 4  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.40

Fig. S-17:  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compound **3g**.



File : C:\MSDCHEM\1\DATA\2021\Dr. Abbas Hassan\Zahid Hussain\ZR-29 0  
4-03-2021.D  
Operator : Saqib Yasin  
Instrument : Instrument #1  
Acquired : 4 Mar 2021 13:15 using AcqMethod LIQUID.M  
Sample Name: ZR-29  
Misc Info : Temp 120-280 10C/min Flow 1.5ml/min Inj 3ul

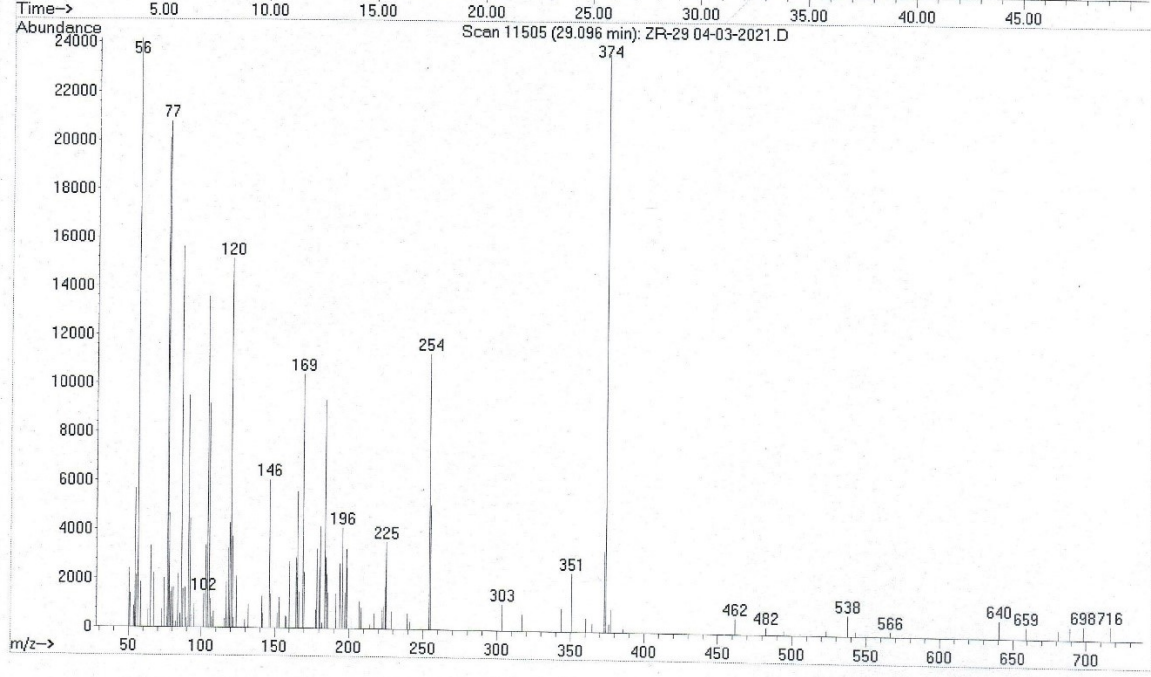
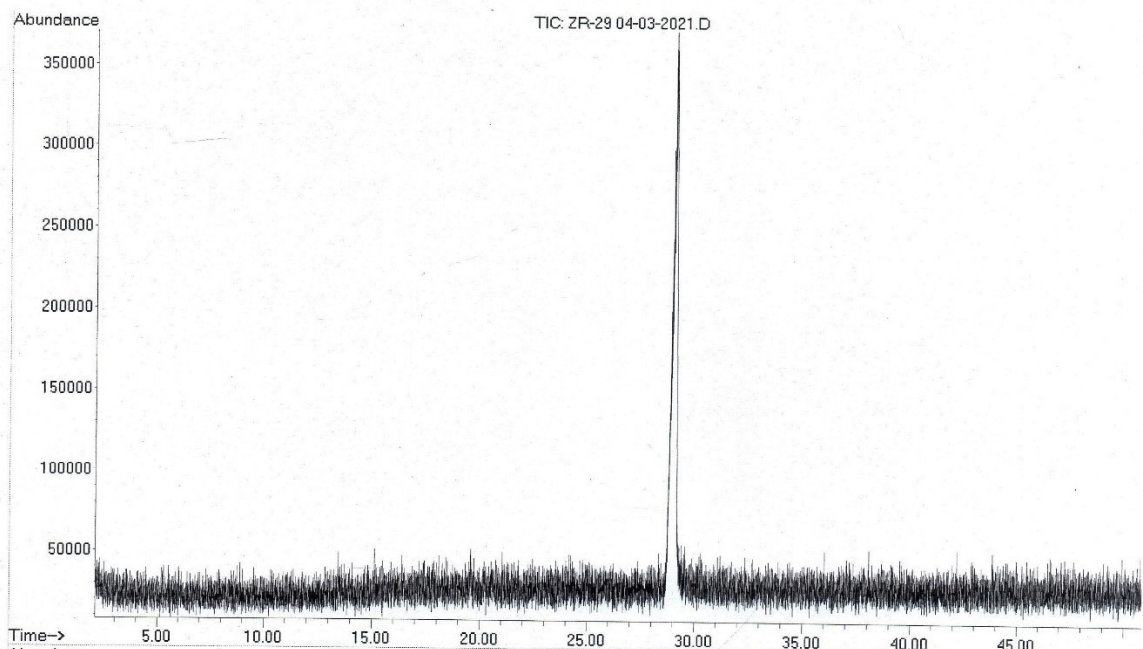
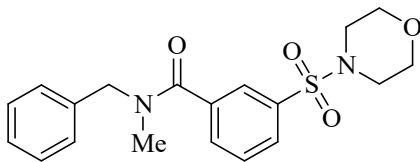


Fig. S-18: GCMS spectrum for compound **3g**.

***N*-Benzyl-*N*-methyl-3-(morpholinosulfonyl)benzamide 3h (ZR-30)**



Yield: 55 %; white solid; m.p. : 174-177 °C;  $R_f$ : 0.5 (*n*-hexane: ethyl acetate :: 7:3).

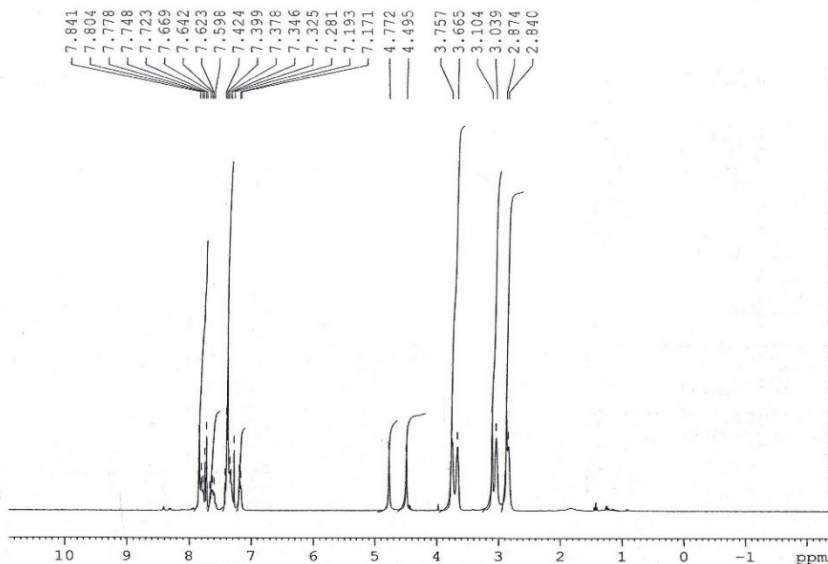
**$^1\text{H NMR}$**  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 7.72-7.84 (*m*, 3H), 7.60-7.67 (*m*, 1H), 7.28-7.42 (*m*, 4H), 7.18 (*d*,  $J = 6.6$  Hz, 1H), 4.77 (*s*, 1H), 4.49 (*s*, 1H), 3.66-3.75 (*m*, 4H), 3.03-3.10 (*m*, 4H), 2.87 (*s*, 3H).

**$^{13}\text{C NMR}$**  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 170.3, 169.5, 137.7, 136.4, 135.8, 135.6, 135.6, 131.6, 131.4, 129.7, 129.5, 129.1, 128.9, 128.3, 127.9, 126.6, 125.9, 66.0, 55.0, 51.0, 46.0, 45.8, 37.0, 33.6.

**ESI-HRMS** ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calc'd for  $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_4\text{S}^+$ , 375.1373; found, 375.1378.

**MS** ( $m/z$ ): 373, 254, 225, 104, 91, 76, 56.

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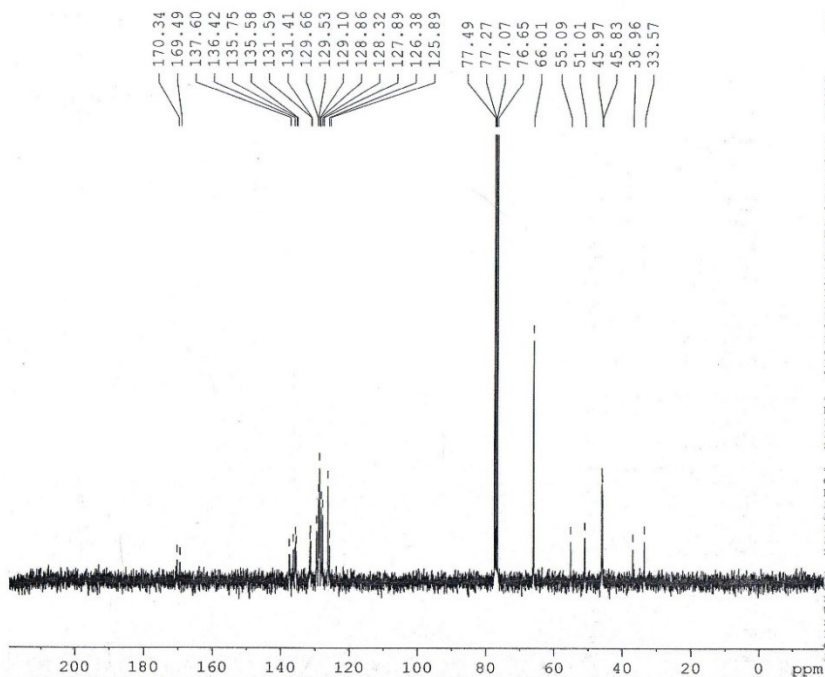


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PROCNO 1

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SOLVENT CDCL3  
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DS 0  
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FIDRES 0.094190 Hz  
AQ 5.308460 sec  
RG 228.1  
DW 81.000 usec  
DE 6.00 usec  
TE 293.4 K  
D1 1.00000000 sec  
TDO 1

CHANNEL f1  
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P1 9.00 usec  
PL1 2.00 dB  
SFO1 300.1318534 MHz  
F2 - Processing parameters  
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SF 300.1300000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

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Current Data Parameters  
NAME ZR-30\_13CNMR\_CDCL3  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
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Time 14.19  
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PULPROG zgpg30  
TD 35968  
SOLVENT CDCL3  
NS 758  
DS 0  
SWH 17985.611 Hz  
FIDRES 0.500045 Hz  
AQ 0.9999604 sec  
RG 9195.2  
DW 27.800 usec  
DE 6.00 usec  
TE 294.0 K  
D1 2.00000000 sec  
d11 0.03000000 sec  
DELTA 1.89999998 sec  
TDO 1

CHANNEL f1  
NUC1 13C  
P1 6.00 usec  
PL1 -5.00 dB  
SFO1 75.4752953 MHz

CHANNEL f2  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
EL2 2.00 dB  
FL12 20.98 dB  
FL13 20.00 dB  
SFO2 300.1312005 MHz

F2 - Processing parameters  
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SF 75.4677490 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

Fig. S-19:  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compound **3h**.



File : C:\MSDCHEM\1\DATA\2021\Dr. Abbas Hassan\Zahid Hussain\ZR-30 1  
7-03-21.D  
Operator : Saqib Yasin  
Instrument : Instrument #1  
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Sample Name: ZR-30  
Disc Info : Temp 120-280 10C/min Flow 1.5ml/min Inj 3ul

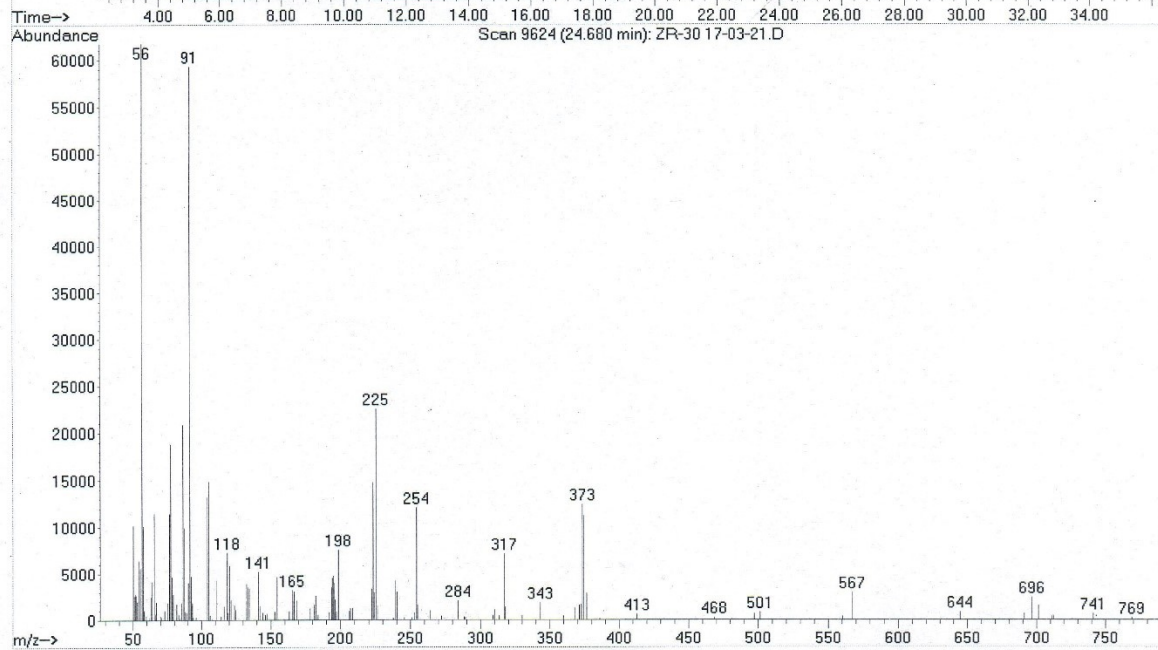
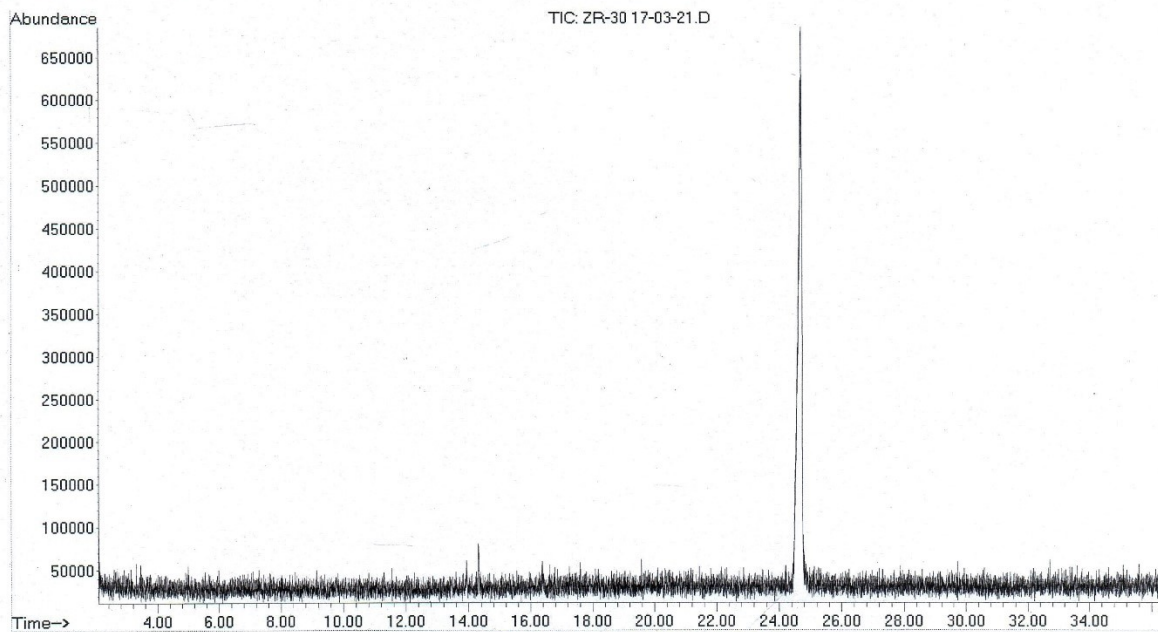
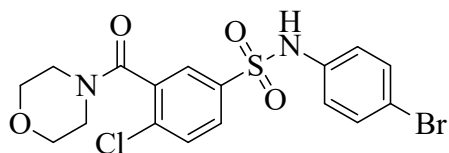


Fig. S-20: GCMS spectrum for compound **3h**.

***N*-(4-bromophenyl)-4-chloro-3-(morpholine-4-carbonyl)benzenesulfonamide 3i (ZR-37)**



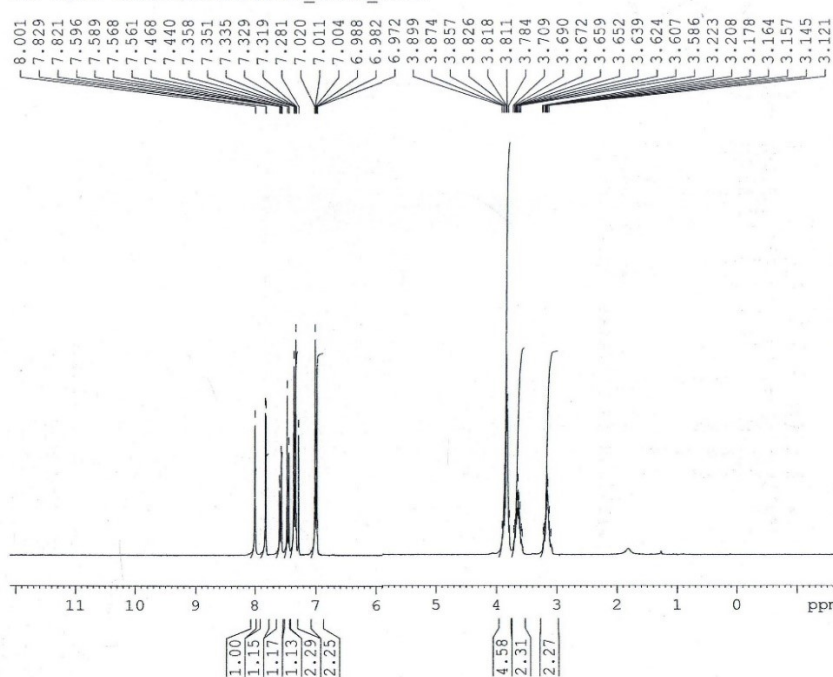
Yield: 65 %; white solid; m.p. : 169-172 °C;  $R_f$ : 0.7 (*n*-hexane: ethyl acetate :: 7:3).

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 8.00 (*s*, 1H), 7.82 (*d*,  $J = 1.9$  Hz, 1H), 7.57 (*dd*,  $J = 9.4$  & 2.1 Hz, 1H), 7.45 (*d*,  $J = 7.4$  Hz, 1H), 7.28-7.35 (*m*, 2H), 6.97-7.02 (*m*, 2H), 3.78-3.89 (*m*, 4H), 3.57-3.71 (*m*, 2H), 3.09-3.22 (*m*, 2H).

$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 165.4, 138.4, 136.0, 135.4, 135.3, 132.5 (2C), 130.5, 129.0, 127.0, 123.9 (2C), 119.2, 66.6, 66.5, 47.7, 42.4.

**ESI-HRMS** ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calc'd for  $\text{C}_{17}\text{H}_{17}\text{BrClN}_2\text{O}_4\text{S}^+$ , 458.9775; found, 458.9782.

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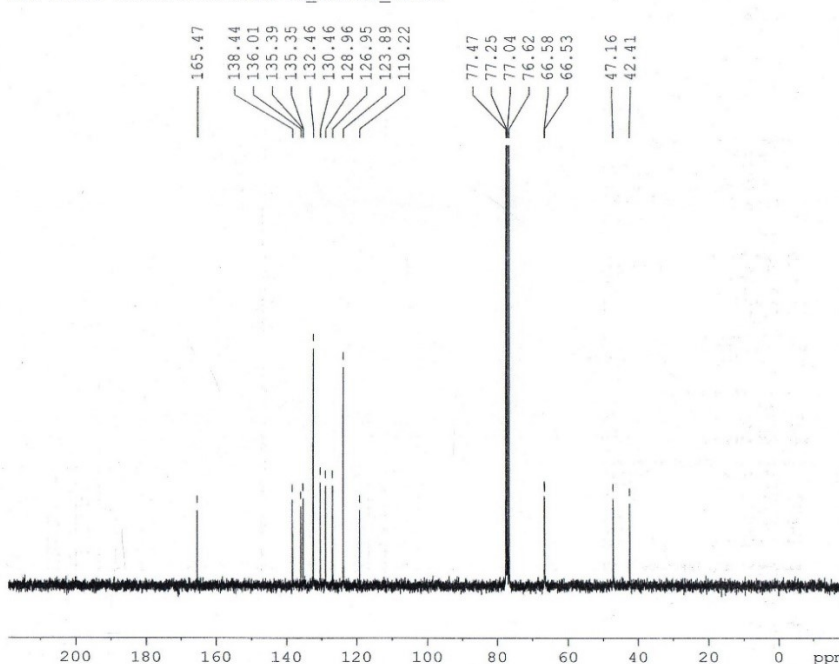
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SOLVENT CDCL3  
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DS 0  
SWH 6172.839 Hz  
FIDRES 0.094190 Hz  
AQ 5.3084660 sec  
RG 456.1  
DW 81.000 usec  
DE 6.00 usec  
TE 295.7 K  
D1 1.00000000 sec  
TD0 1

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P1 9.00 usec  
PL1 2.00 dB  
SFO1 300.1318534 MHz

F2 - Processing parameters  
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SF 300.1300000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

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Current Data Parameters  
NAME AA-98\_13CNMR\_CDCL3  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
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Time 14.12  
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PROBHD 5 mm BBO BB-1H  
PULPROG zgpg30  
TD 35968  
SOLVENT CDCL3  
NS 1024  
DS 0  
SWH 17985.611 Hz  
FIDRES 0.500045 Hz  
AQ 0.9999604 sec  
RG 5160.6  
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DELTA 1.89999998 sec  
TD0 1

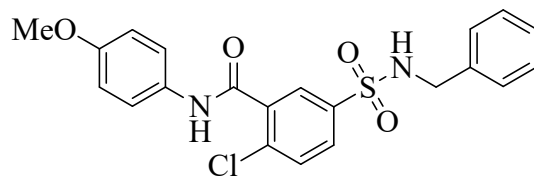
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SFO1 75.4752953 MHz

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NUC2 1H  
PCPD2 80.00 usec  
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PL13 20.00 dB  
SFO2 300.1312005 MHz

F2 - Processing parameters  
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SF 75.4677490 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

Fig. S-21:  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compound **3i**.

**5-(*N*-Benzylsulfamoyl)-2-chloro-*N*-(4-methoxyphenyl)benzamide 3j (ZR 68)**



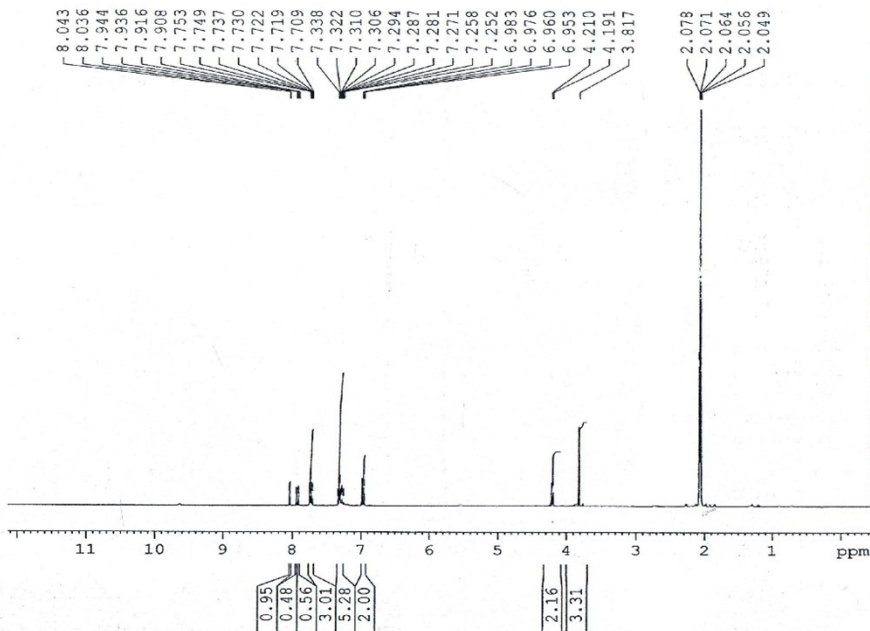
Yield: 68 %; white solid; m.p. : 172-174 °C;  $R_f$ : 0.7 (*n*-hexane: ethyl acetate :: 7:3).

$^1\text{H NMR}$  (300 MHz, Acetone- $d_6$ ):  $\delta$  (ppm) 8.04 (*d*,  $J = 2.1$  Hz, 1H), 7.94 (*d*,  $J = 2.4$  Hz, 1H), 7.91 (*d*,  $J = 2.4$  Hz, 1H), 7.71-7.75 (*m*, 3H), 7.25-7.34 (*m*, 5H), 6.97 (*dd*,  $J = 6.9$  & 2.1 Hz, 2H), 4.20 (*d*,  $J = 5.7$  Hz, 2H), 3.81 (*s*, 3H).

$^{13}\text{C NMR}$  (75 MHz, Acetone- $d_6$ ):  $\delta$  (ppm) 163.1, 156.5, 140.2, 140.1, 137.7, 137.4, 134.8, 132.0, 131.9, 130.7, 129.1, 128.4, 127.9, 127.4, 121.3, 121.2, 113.9 (2C), 54.8, 46.8, 46.7.

**ESI-HRMS** ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calc'd for  $\text{C}_{21}\text{H}_{20}\text{ClN}_2\text{O}_4\text{S}^+$ , 431.0827; found, 431.0830.

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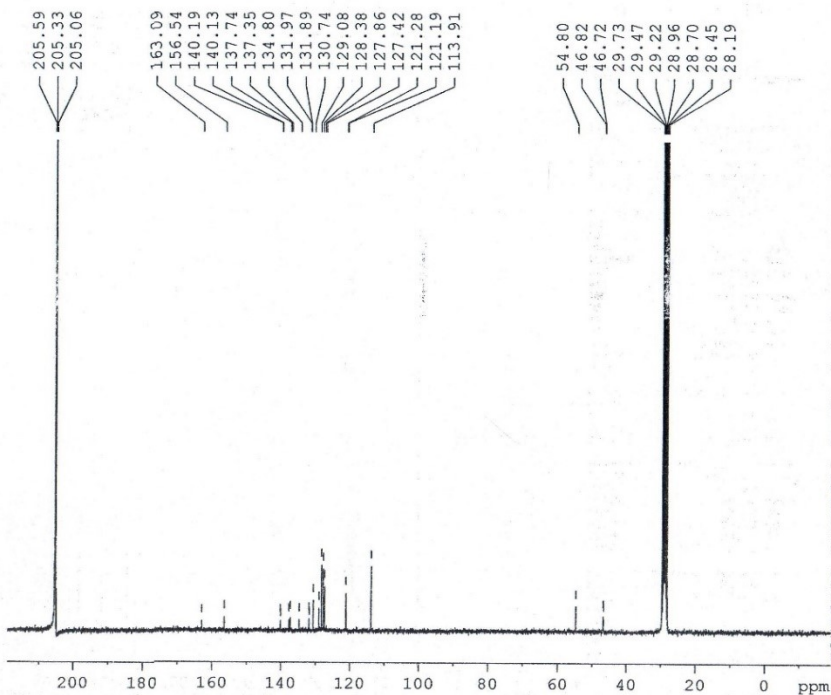
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PULPROG zg30  
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SOLVENT Acetone  
NS 8  
DS 0  
SWH 6172.832 Hz  
FIDRES 0.094150 Hz  
AQ 5.308160 sec  
RG 724.1  
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DE 6.00 usec  
TE 292.3 K  
D1 1.00000000 sec  
TDO 1

CHANNEL f1  
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P1 9.00 usec  
PL1 2.00 dB  
SFO1 300.1318534 MHz

F2 - Processing parameters  
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SF 300.1300000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

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Current Data Parameters  
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PROCNO 1

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TD 35968  
SOLVENT Acetone  
NS 17702  
DS 0  
SWH 17985.611 Hz  
FIDRES 0.500045 Hz  
AQ 0.9999604 sec  
RG 912.3  
DQ 27.600 usec  
DE 6.00 usec  
TE 292.6 K  
D1 2.00000000 sec  
d11 0.03000000 sec  
DELTA 1.89999998 sec  
TDO 1

CHANNEL f1  
NUC1 13C  
P1 6.00 usec  
PL1 -5.00 dB  
SFO1 75.4752953 MHz

CHANNEL f2  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
PL2 2.00 dB  
PL12 20.98 dB  
PL13 20.00 dB  
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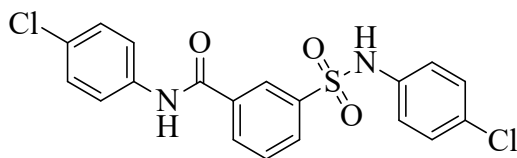
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LB 1.00 Hz  
GB 0  
PC 1.40

Fig. S-22:  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compound **3j**.

**General procedure for synthesis of benzene sulphonamide carboxamide *via* one pot synthesis (ZR-40, 26, 47, 72 & 65)**

To a 25 mL round bottom flask was added chlorosulphonic acid (0.8 mL, 12 mmol, 600 mol%) and the temperature was lower with ice-bath. 2-Substitutedbenzoic acid (2 mmol, 100 mol%) was added in portion to chlorosulfonic acid. The resulting mixture was heated at 95 °C for 12 h. The mixture was cooled up to 0 °C and THF (2 mL) and DMF (0.2 mL) was added as solvent, followed by triethylamine (1.1 mL, 8 mmol, 400 mol%), DMAP (49 mg, 0.4 mmol, 20 mol%) and the corresponding amine (8 mmol, 400 mol%) in this order. The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was quenched with water and the solvent is evaporated under *vacuo*. Conc. HCl was slowly added to adjust the *pH* to 4 and the mixture was extracted with ethyl acetate (10 mL x 3). The combined organic layer was dried with anhydrous sodium sulfate and concentrated under *vacuo*. The crude product was further purified by flash column chromatography using silica gel as stationary phase and *n*-hexane: ethyl acetate as mobile phase. [6]

***N*-(4-Chlorophenyl)-3-(*N*-(4-chlorophenyl)sulfamoyl)benzamide 4a (ZR-40)**



Yield: 67 %; white solid; m.p. : 178-182 °C; *R<sub>f</sub>*: 0.5 (*n*-hexane: ethyl acetate :: 7:3).

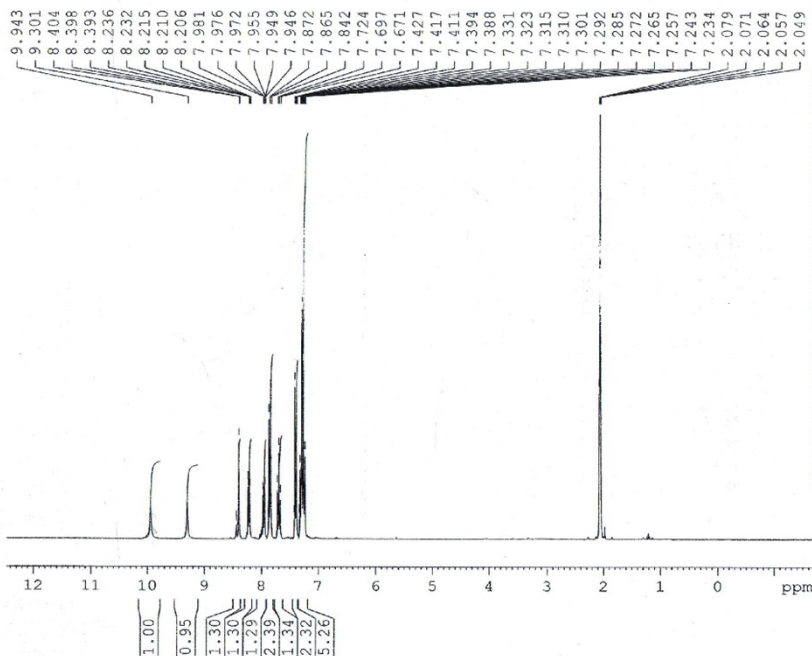
**<sup>1</sup>H NMR** (300 MHz, Acetone-*d*<sub>6</sub>): δ (ppm) 9.94 (*s*, 1H), 9.30 (*s*, 1H), 8.44-8.40 (*m*, 1H), 8.20-8.23 (*m*, 1H), 7.94-7.98 (*m*, 1H), 7.84-7.88 (*m*, 2H), 7.67-7.72 (*m*, 1H), 7.38-7.42 (*m*, 2H), 7.23-7.33 (*m*, 4H).

**<sup>13</sup>C NMR** (75 MHz, Acetone-*d*<sub>6</sub>): δ (ppm) 163.9, 140.2, 137.9, 136.4, 136.1, 131.8, 129.9, 129.8, 129.5, 129.2 (2C), 128.7 (2C), 128.5, 128.0, 126.3, 122.7, 122.5, 121.8.

**ESI-HRMS** (*m/z*): [M+H]<sup>+</sup> calc'd for C<sub>19</sub>H<sub>15</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub>S<sup>+</sup>, 421.0175; found, 421.0181.



Dr. Ahsan Ullah/HIRA/HZR-40\_1HNMN ACETONE



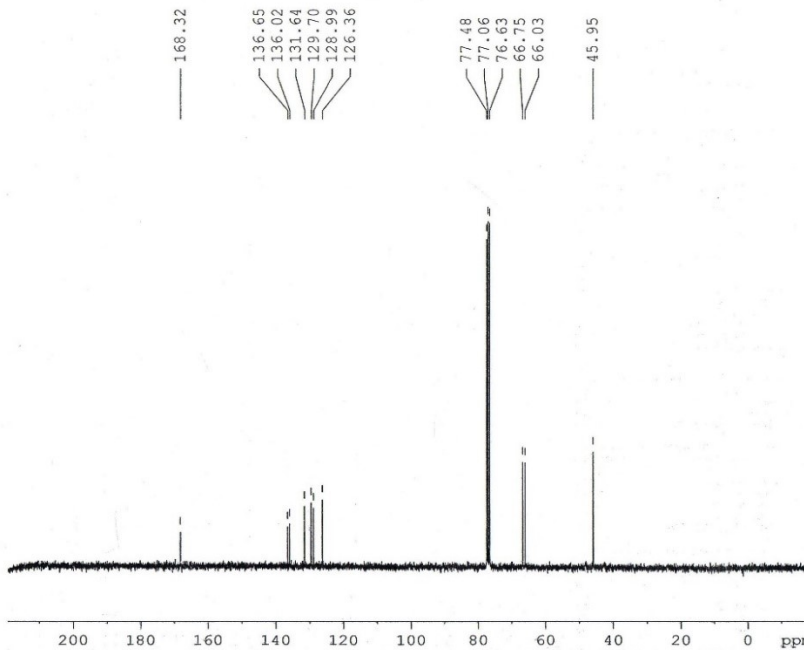
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 SOLVENT Acetone  
 NS 8  
 DS 0  
 SWH 6172.809 Hz  
 FIDRES 0.004190 Hz  
 AQ 5.0088660 sec  
 RG 342  
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 DC 6.50 usec  
 TE 292.8 K  
 D1 1.00000000 sec  
 TDO 1

CHANNEL f1  
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 P1 9.00 usec  
 PL1 2.00 dB  
 SFO1 300.1318534 MHz

F2 - Processing parameters  
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 SSB 0  
 LB 0.30 Hz  
 GB 0  
 PC 1.00

DR. ABBAS HASSAN/ZAHD/ZR-24\_13CNMR\_CDCL3



Current Data Parameters  
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 PROCNO 1

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 PULPROG zgpg30  
 TD 35968  
 SOLVENT CDCl3  
 NS 410  
 DS 0  
 SWH 17985.611 Hz  
 FIDRES 0.500045 Hz  
 AQ 0.9999604 sec  
 RG 3251  
 DW 27.800 usec  
 DE 6.00 usec  
 TE 295.4 K  
 D1 2.00000000 sec  
 d11 0.03000000 sec  
 DELTA 1.89999998 sec  
 TDO 1

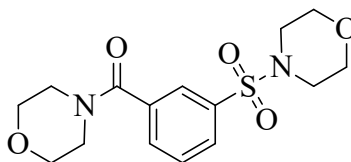
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 SFO1 75.4752953 MHz

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F2 - Processing parameters  
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 WDW EM  
 SSB 0  
 LB 1.00 Hz  
 GB 0  
 PC 1.40

Fig. S-23: <sup>1</sup>H and <sup>13</sup>C NMR spectra for compound 4a.

**Morpholino(3-(morpholinosulfonyl)phenyl)methanone 4b (ZR-26)**



Yield: 68 %; white solid; m.p. : 186-189 °C;  $R_f$ : 0.2 (*n*-hexane: ethyl acetate :: 7:3).

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 7.79-7.84 (*m*, 2H), 7.62-7.70 (*m*, 2H), 3.73-3.80 (*m*, 10H), 3.67-3.70 (2H), 2.89-3.04 (*m*, 4H).

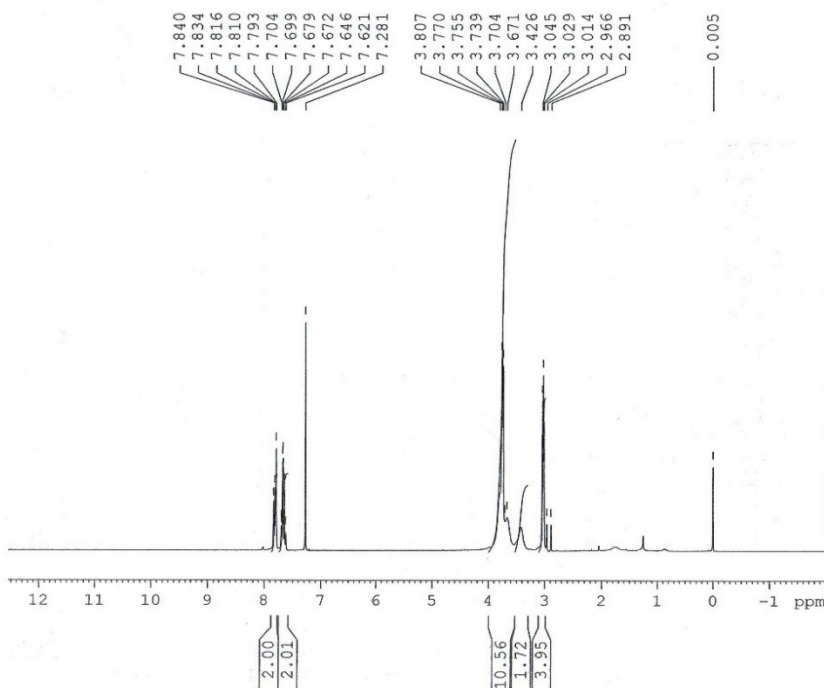
$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 168.3, 136.6, 136.0, 131.6, 129.7, 129.0, 126.4, 66.8 (2C), 66.0 (2C), 45.6 (4C).

**ESI-HRMS** ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calc'd for  $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_5\text{S}^+$ , 341.1166; found, 341.1168.

**GC-EIMS** ( $m/z$ ): 339, 254, 191, 86, 56.



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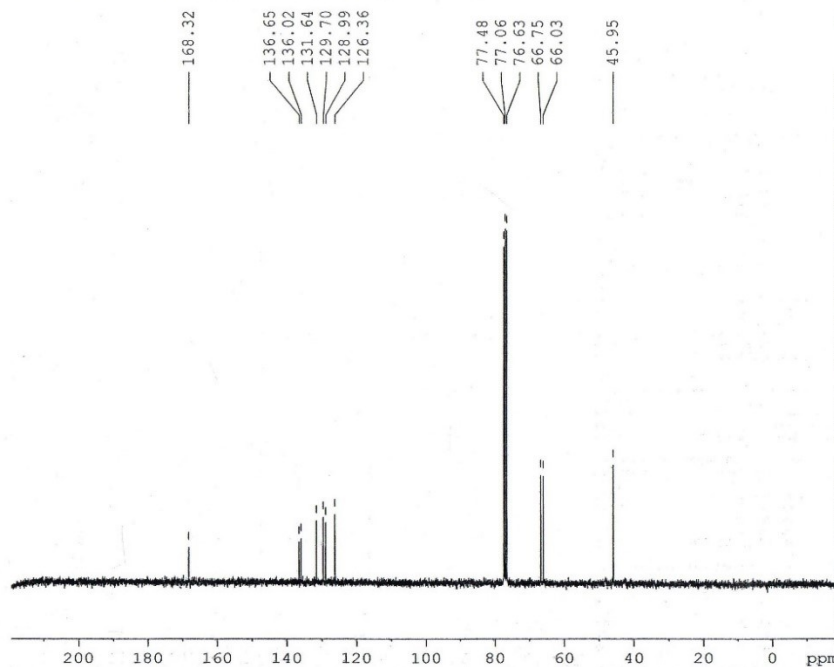
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PROCNO 1

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Time 15.00  
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SOLVENT CDCL3  
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DS 0  
SWH 6172.839 Hz  
FIDRES 0.094190 Hz  
AQ 5.3084660 sec  
RG 322.5  
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DE 6.00 usec  
TE 294.7 K  
D1 1.0000000 sec  
TD0 1

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P1 9.00 usec  
PL1 2.00 dB  
SFO1 300.1318534 MHz

F2 - Processing parameters  
SI 32768  
SF 300.1300000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

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Current Data Parameters  
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EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
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DS 0  
SWH 17985.611 Hz  
FIDRES 0.500045 Hz  
AQ 0.9999604 sec  
RG 3251  
DW 27.800 usec  
DE 6.00 usec  
TE 295.4 K  
D1 2.0000000 sec  
d11 0.0300000 sec  
DELTA 1.89999998 sec  
TD0 1

CHANNEL f1  
NUC1 13C  
P1 6.00 usec  
PL1 -5.00 dB  
SFO1 75.4752953 MHz

CHANNEL f2  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
PL2 2.00 dB  
PL12 20.98 dB  
PL13 20.00 dB  
SFO2 300.1312005 MHz

F2 - Processing parameters  
SI 32768  
SF 75.4677490 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

Fig. S-24:  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compound **4b**.

file : C:\MSDCHEM\1\DATA\2021\Dr. Abbas Hassan\Zahid Hussain\ZR-26 0  
4-03-2021.D  
operator : Saqib Yasin  
instrument : Instrument #1  
acquired : 4 Mar 2021 12:36 using AcqMethod LIQUID.M  
sample Name: ZR-26  
disc Info : Temp 120-280 10C/min Flow 1.5ml/min Inj 3ul

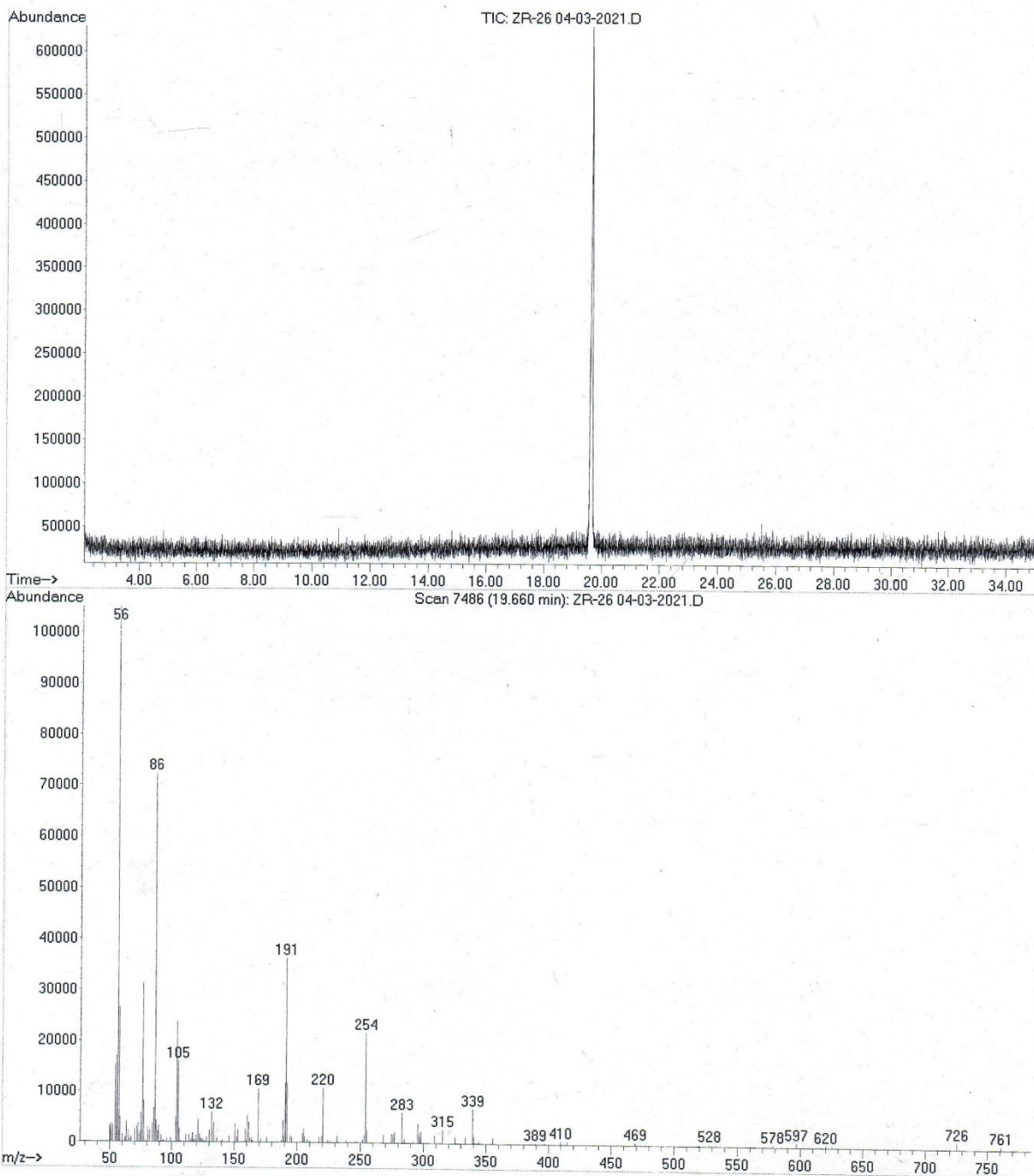
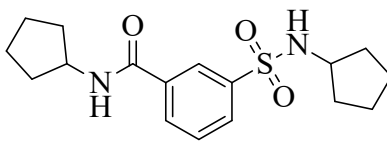


Fig. S-25: GCMS spectrum for compound **4b**.

***N*-Cyclopentyl-3-(*N*-cyclopentylsulfamoyl)benzamide 4c (ZR-47)**



Yield: 70 %; white solid; m.p. : 169-172 °C;  $R_f$ : 0.7 (*n*-hexane: ethyl acetate :: 7:3).

**$^1\text{H}$  NMR** (300 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) 8.56 (*d*,  $J = 1.9$  Hz, 1H), 8.27 (*t*,  $J = 1.8$  Hz), 8.06-8.09 (*m*, 1H), 7.91-7.94 (*m*, 1H), 7.64-7.69 (*m*, 1H), 3.34-3.43 (*m*, 2H), 1.70-1.90 (*m*, 2H), 1.50-1.60 (*m*, 10H), 1.26-1.37 (*m*, 4H).

**$^{13}\text{C}$  NMR** (75 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) 165.1, 142.3, 136.0, 131.2, 129.6, 129.2, 126.0, 54.9, 51.6, 32.9 (2C), 32.5 (2C), 24.1 (2C), 23.2 (2C).

**ESI-HRMS** ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calc'd for  $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_3\text{S}^+$ , 337.4575; found, 341.1168.

**GC-EIMS** ( $m/z$ ): 336 ( $\text{M}^+$ ), 269, 201, 169, 104, 76, 56.

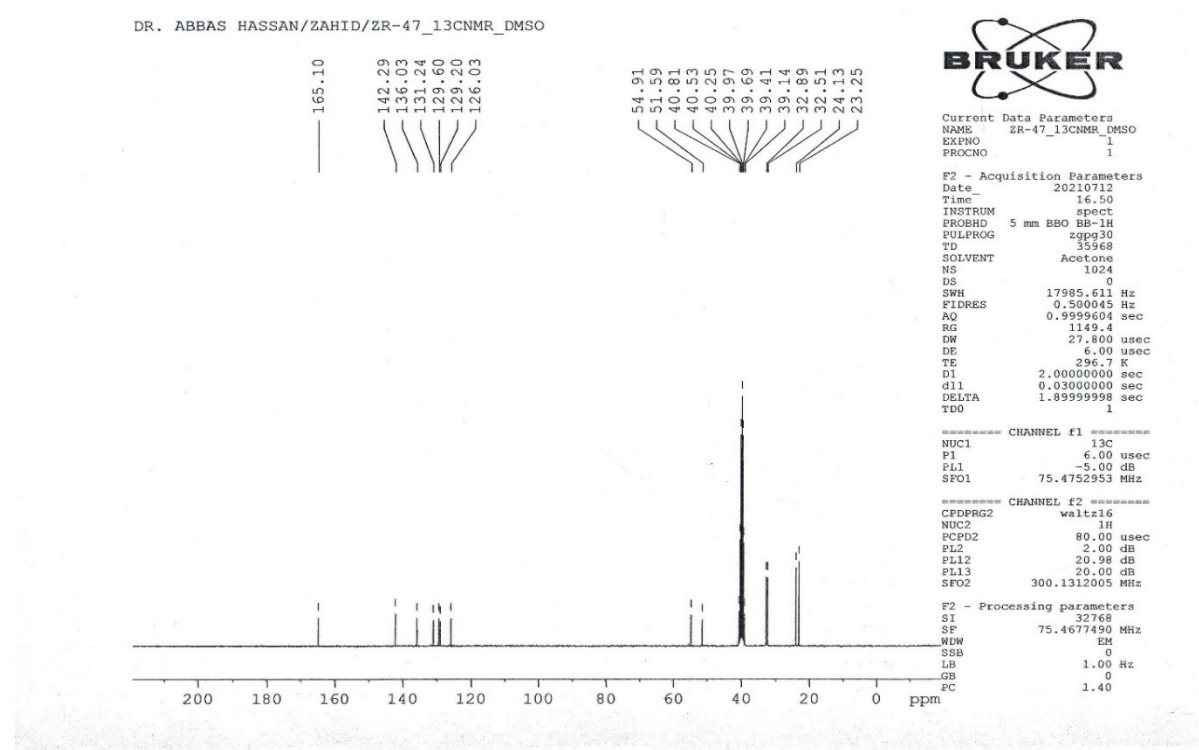
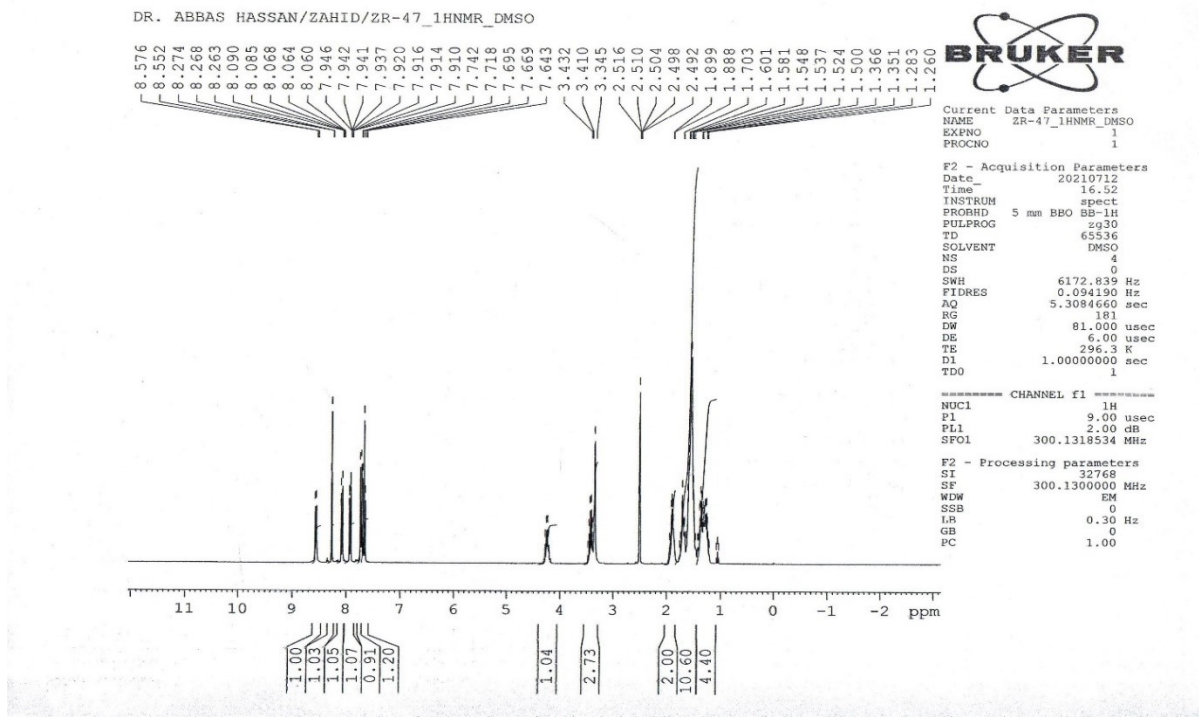


Fig. S-26: <sup>1</sup>H and <sup>13</sup>C NMR spectra for compound **4c**.

File : C:\MSDCHEM\1\DATA\2021\Dr. Ali Haider\Mehreen\ZR-47 13-10-21.D  
Operator : Saqib Yasin  
Instrument : Instrument #1  
Acquired : 13 Oct 2021 15:08 using AcqMethod LIQUID.M  
Sample Name : ZR-47  
Misc Info : Temp 120-280 10C/min Flow 1.5ml/min Inj 5ul

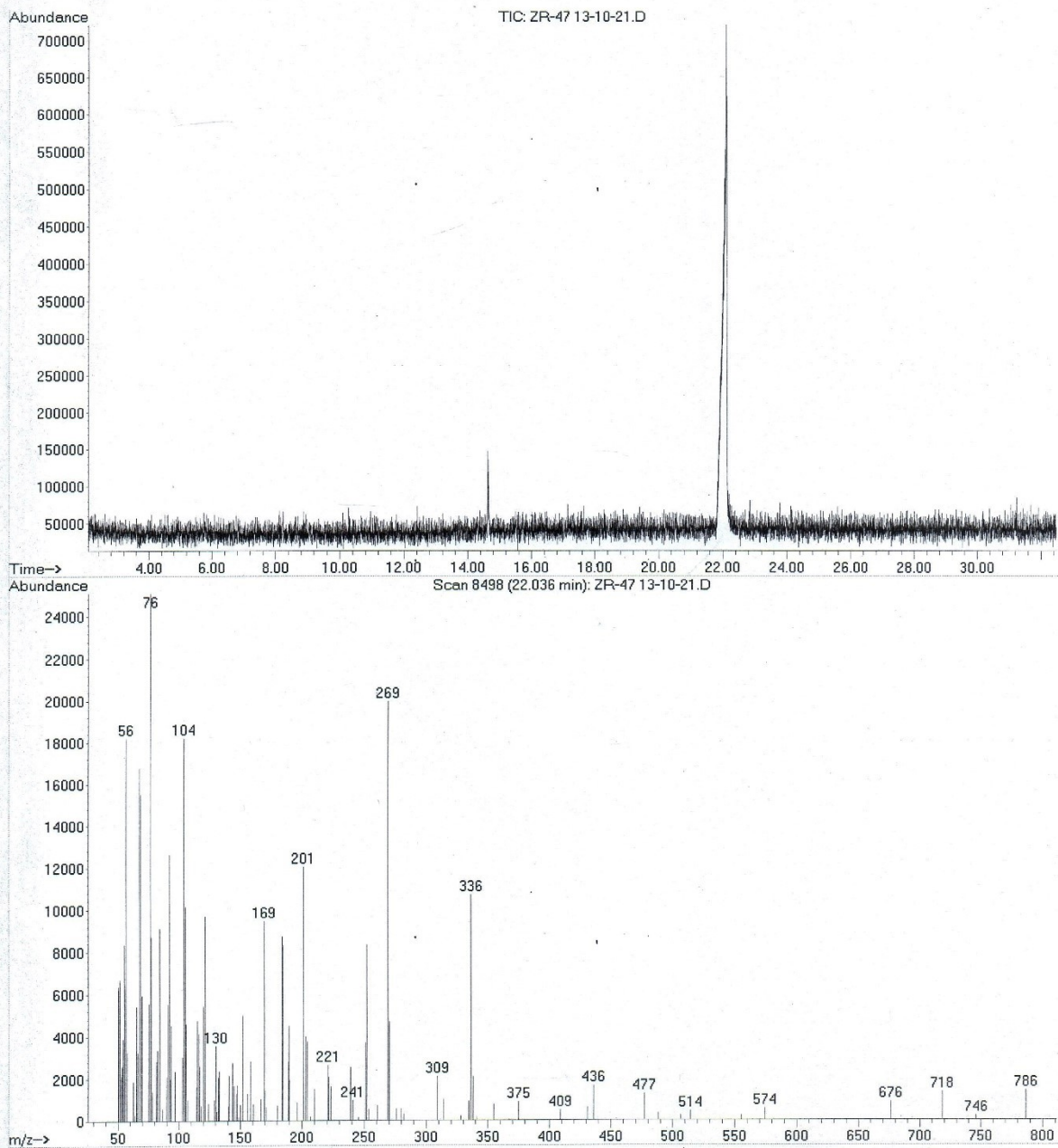
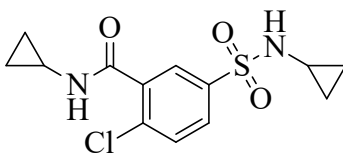


Fig. S-27:  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compound **4c**.

**2-Chloro-*N*-cyclopropyl-5-(*N*-cyclopropylsulfamoyl)benzamide 4d (ZR-72)**



Yield: 66 %; white solid; m.p. : 183-186 °C;  $R_f$ : 0.4 (*n*-hexane: ethyl acetate :: 7:3).

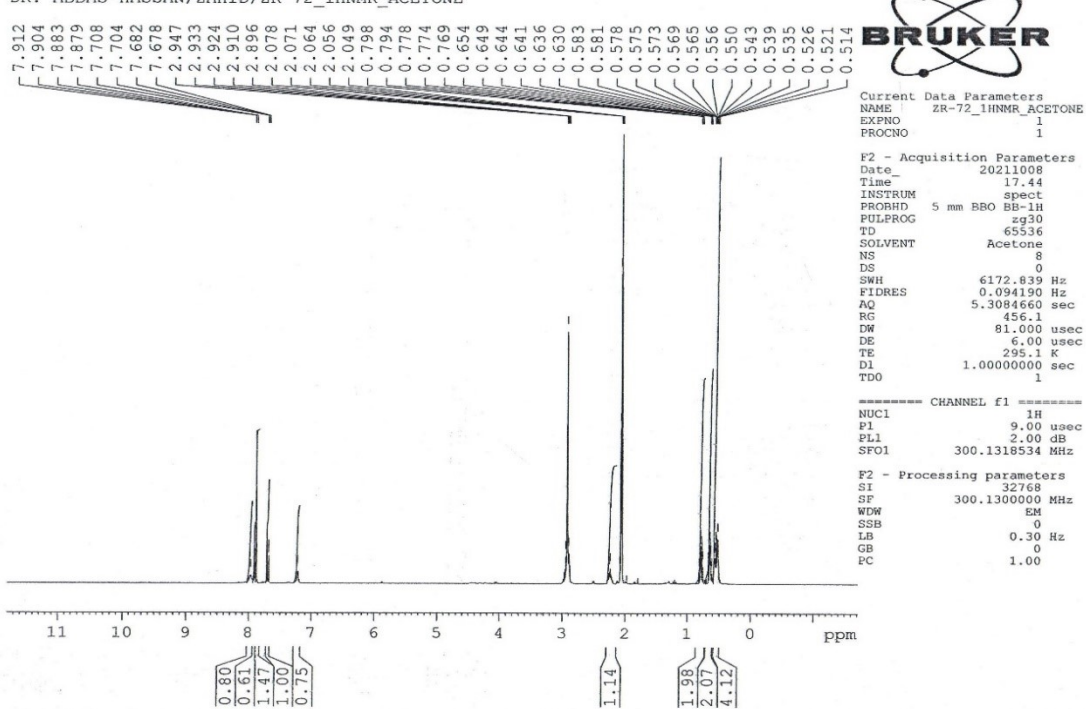
$^1\text{H NMR}$  (300 MHz, Acetone- $d_6$ ):  $\delta$  (ppm) 7.90 (*d*,  $J = 2.4$  Hz, 1H), 7.88 (*d*,  $J = 1.2$  Hz, 1H), 7.71 (*s*, 1H), 7.70 (*s*, 1H), 7.68 (*s*, 1H), 7.67 (*s*, 1H), 2.05-2.95 (*m*, 2H), 0.77-0.80 (*m*, 2H), 0.58-0.65 (*m*, 2H), 0.57-0.51 (*m*, 4H).

$^{13}\text{C NMR}$  (75 MHz, Acetone- $d_6$ ):  $\delta$  (ppm) 166.8, 139.6, 137.8, 134.8, 130.6, 129.1, 127.5, 24.2, 22.8, 5.5 (2C), 5.2 (2C).

**ESI-HRMS** ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calc'd for  $\text{C}_{13}\text{H}_{16}\text{ClN}_2\text{O}_3\text{S}^+$ , 315.0565; found, 315.0569.



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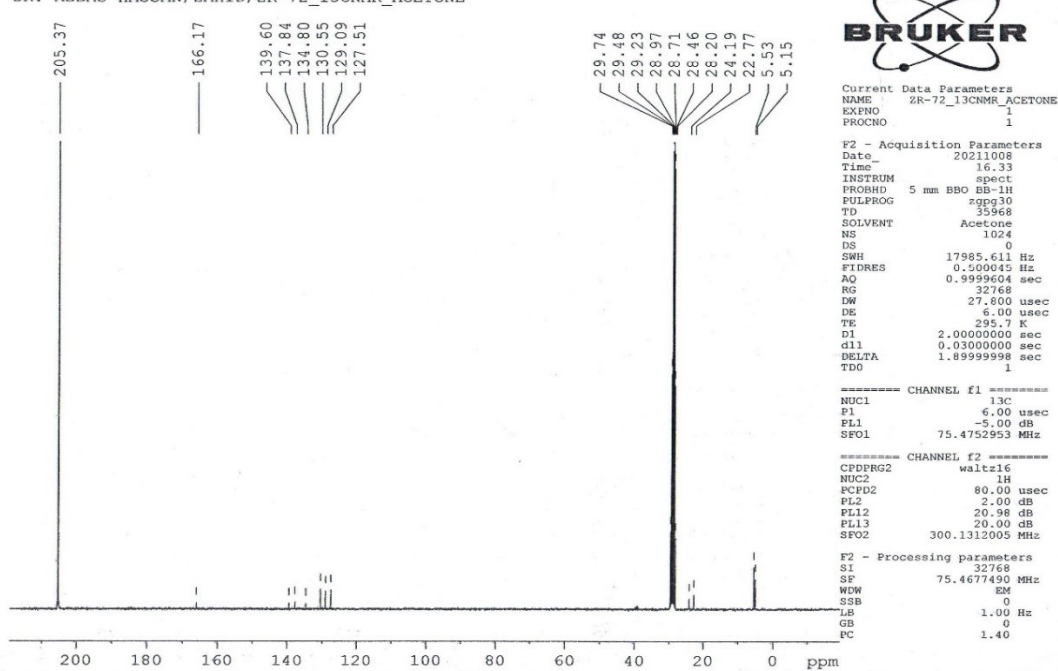
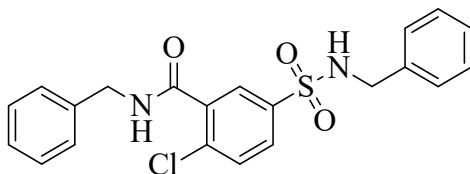


Fig. S-28:  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compound **4d**.



***N*-Benzyl-5-(*N*-benzylsulfamoyl)-2-chlorobenzamide 4e (ZR-65)**



Yield: 72 %; white solid; m.p. : 171-174 °C;  $R_f$ : 0.6 (*n*-hexane: ethyl acetate :: 7:3).

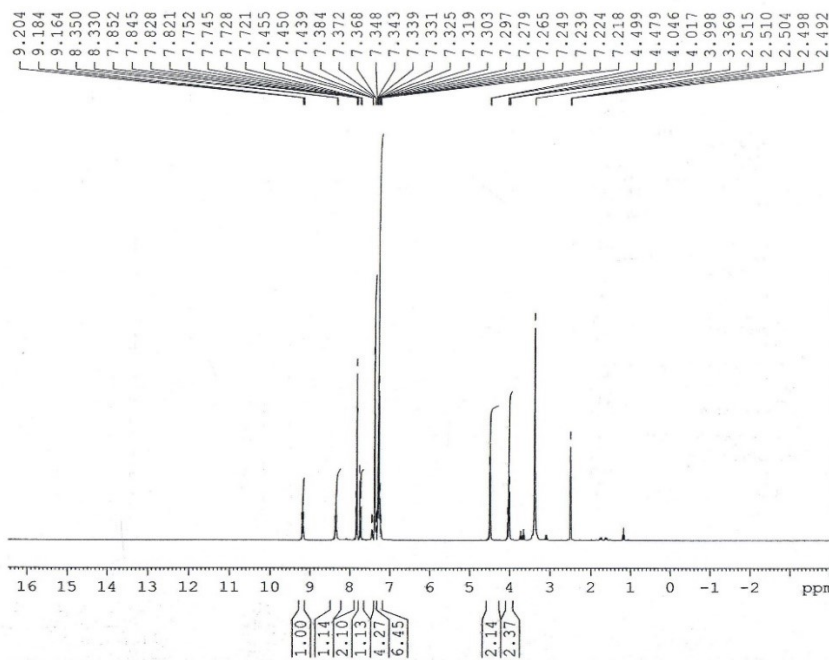
**$^1\text{H}$  NMR** (300 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) 9.18 (*t*,  $J = 6.0$  Hz, 1H), 8.34 (*d*,  $J = 6.0$  Hz, 1H), 7.82-7.86 (*m*, 2H), 7.82 (*d*,  $J = 2.1$  Hz, 1H), 7.35-7.45 (*m*, 4H), 7.21-7.32 (*m*, 6H), 4.48 (*d*,  $J = 6.0$  Hz, 2H), 4.01 (*t*,  $J = 5.7$  Hz, 2H).

**$^{13}\text{C}$  NMR** (75 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) 165.6, 140.6, 139.3, 137.8, 137.8, 134.5, 131.2, 129.3, 129.1, 128.9 (2C), 128.8 (2C), 128.1 (2C), 127.8 (2C), 127.7, 127.4, 46.8, 43.0.

**ESI-HRMS** ( $m/z$ ):  $[\text{M}+\text{H}]^+$  calc'd for  $\text{C}_{21}\text{H}_{20}\text{ClN}_2\text{O}_3\text{S}^+$ , 415.0878; found, 415.0883.

**GC-EIMS** ( $m/z$ ): 414 ( $\text{M}^+$ ), 141, 104, 91, 78.

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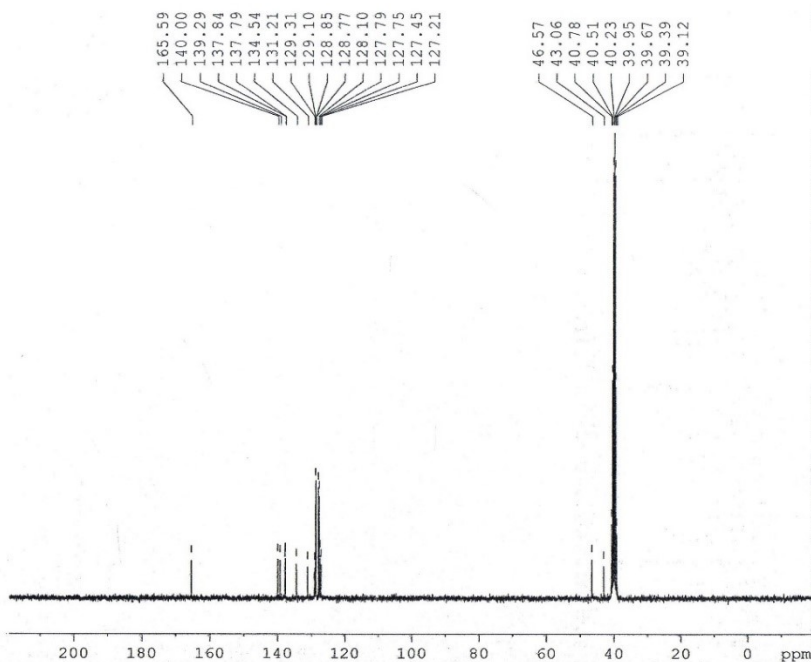
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SWH 6172.839 Hz  
FIDRES 0.094190 Hz  
AQ 5.3084660 sec  
RG 287.4  
DW 81.000 usec  
DE 6.00 usec  
TE 295.0 K  
D1 1.0000000 sec  
TDO 1

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PL1 2.00 dB  
SFO1 300.1318534 MHz

F2 - Processing Parameters  
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WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

DR. ABBAS HASSAN/ZAHID/ZR-65\_13CNMR\_DMSO



Current Data Parameters  
NAME ZR-65\_13CNMR\_DMSO  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
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INSTRUM spect  
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TD 35968  
SOLVENT DMSO  
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DS 0  
SWH 17985.611 Hz  
FIDRES 0.500045 Hz  
AQ 0.9999604 sec  
RG 1290.2  
DW 27.800 usec  
DE 6.00 usec  
TE 295.4 K  
D1 2.0000000 sec  
d11 0.0300000 sec  
DELTA 1.89999998 sec  
TDO 1

===== CHANNEL f1 =====  
NUC1 13C  
P1 6.00 usec  
PL1 -5.00 dB  
SFO1 75.4752953 MHz

===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 80.00 usec  
PL2 2.00 dB  
PL12 20.98 dB  
PL13 20.00 dB  
SFO2 300.1312005 MHz

F2 - Processing parameters  
SI 32768  
SF 75.4677490 MHz  
NDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

Fig. S-29:  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compound **4e**.

File : C:\MSDCHEM\1\DATA\2021\Dr. Abbas Hassan\Zahid Hussain\ZR-65 2  
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Operator : Saqib Yasin  
Instrument : Instrument #1  
Acquired : 22 Sep 2021 12:47 using AcqMethod LIQUID.M  
Sample Name : zr-65  
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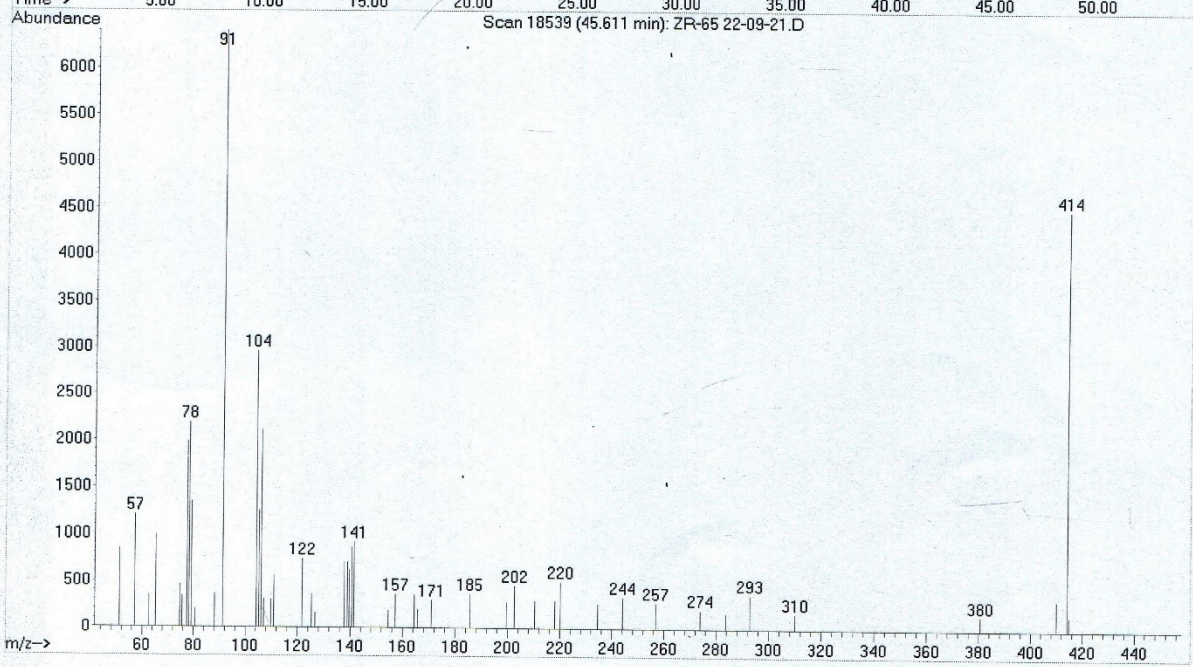
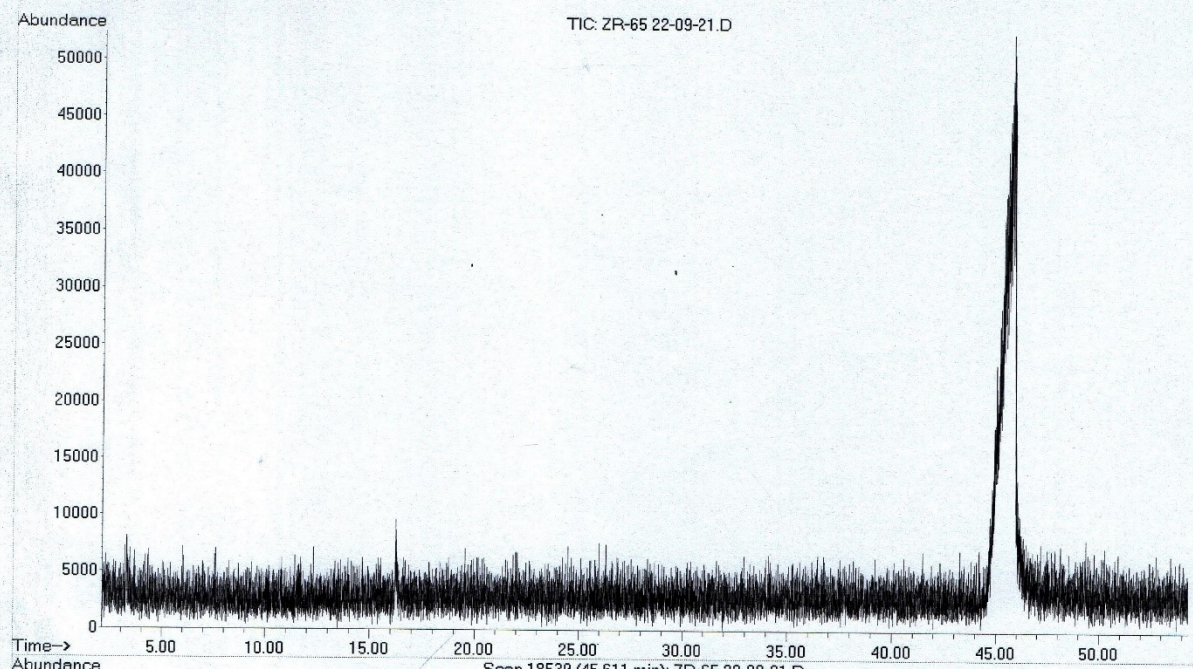


Fig. S-30: GCMS spectrum for compound **4e**.



## References

1. Cremlyn, R.J., F.J. Swinbourne, and L. Goodman, *A NOVEL REACTION OF BENZALACETONE WITH CHLOROSULFONIC ACID*. Phosphorus and Sulfur and the Related Elements, 1986. **28**(3): p. 395-398.
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3. Bradley, D. M.; Branch, C. L.; Brown, B. J.; Chan, W. N.; Coulton, S.; et al. WO2006094840A1·2006-09-14.
4. The chlorosulfonylbenzoic acid is also commercially available from the following source; <https://www.chemblink.com/products/137-64-4.htm>
5. Deng, X.M., Neelakandha., *A facile, environmentally benign sulfonamide synthesis in water*. Green Chem., 2006. **8**(9): p. 835-838.
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