Electronic Supplementary Material (ESI) for RSC Advances.

Supporting Information

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

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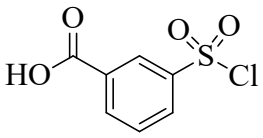
General considerations

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_{254} plates having 0.2 nm 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 μm. 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 μL 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 (^{1}H NMR) and 75 MHz (^{13}C NMR). Chemical shifts are mentioned in delta (δ) units while coupling constants (*J*) values are in Hertz unit (Hz).

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

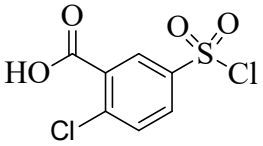
The chlorosulfonation was carried out using the reported procedure. [1] In a 250 mL round bottom flask, 2-substituted benzoic acid (0.1mol, 100 mol%) was added in small portions to the cooled chlorosulfonic acid (40 mL, 0.6 mol, 600 mol%). The resulting mixture was heated at 95 ºC for 12 h. After completion of the reaction, the reaction mixture was allowed to come to room temperature and poured into ice. The 5-(chlorosulphonyl)-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 ºC (lit. 128 ºC); R_f: 0.5 (chloroform: methanol:: 9.5: 0.5).

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

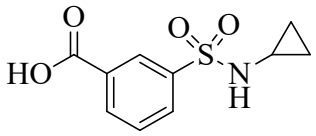


Yield: 76 %; light brown; m.p. : 145-147 ºC (lit. 146 ºC); R_f: 0.4 (chloroform: methanol :: 9.5: 0.5)

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 *p*H 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 ºC; R_f: 0.4 (chloroform: methanol :: 9.5: 0.5).

^{1}H NMR (300 MHz, DMSO-d_6): **δ** (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}C NMR (75 MHz, DMSO-d_6): **δ** (ppm) 166.6, 141.2, 133.5, 132.2, 131.3, 130.3, 127.9, 24.6, 5.5 (2C).

ESI-HRMS- (m/z): $[M+H]^+$ calc'd for $C_{10}H_{12}NO_4S^+$, 242.0482; found, 242.0486.

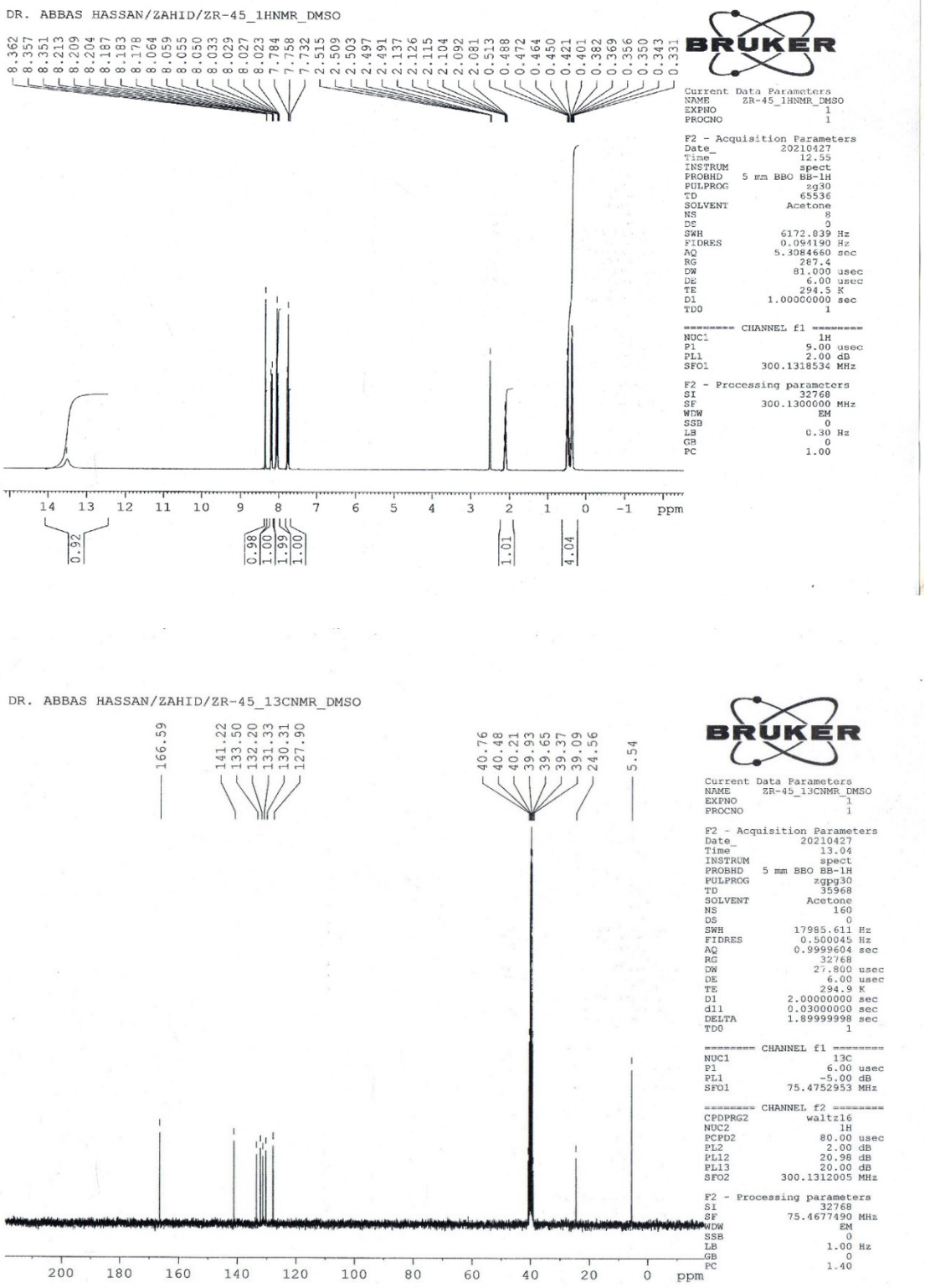
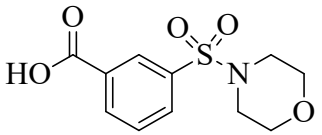


Fig. S-1: ^{1}H and ^{13}C NMR spectra for compound **2a.**

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

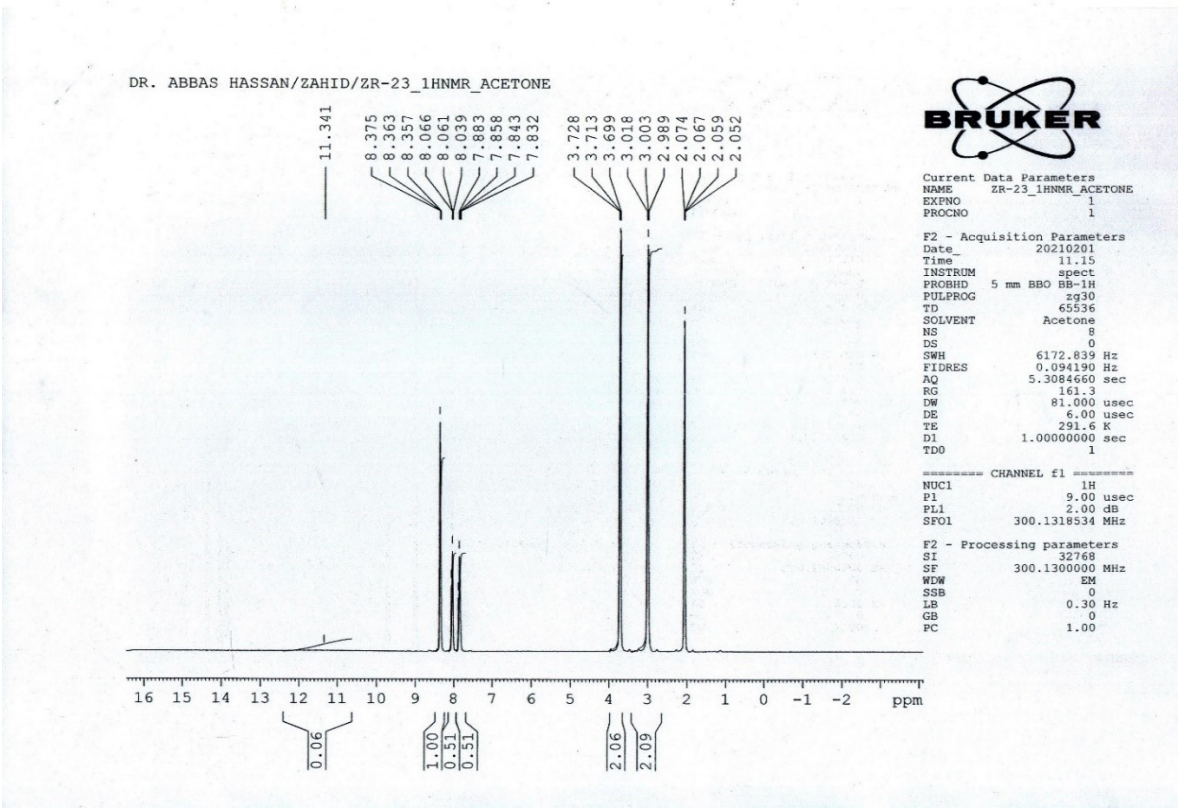


Yield: 89 %; white solid; m.p. : 192-195 ºC; R_f: 0.3 (chloroform: methanol :: 9.5: 0.5).

^{1}H NMR (300 MHz, Acetone-d_6): **δ** (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}C NMR (75 MHz, Acetone-d_6): **δ** (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): $[M+H]^+$ calc'd for $C_{11}H_{15}NO_5S^+$, 273.0666; found, 273.0668.



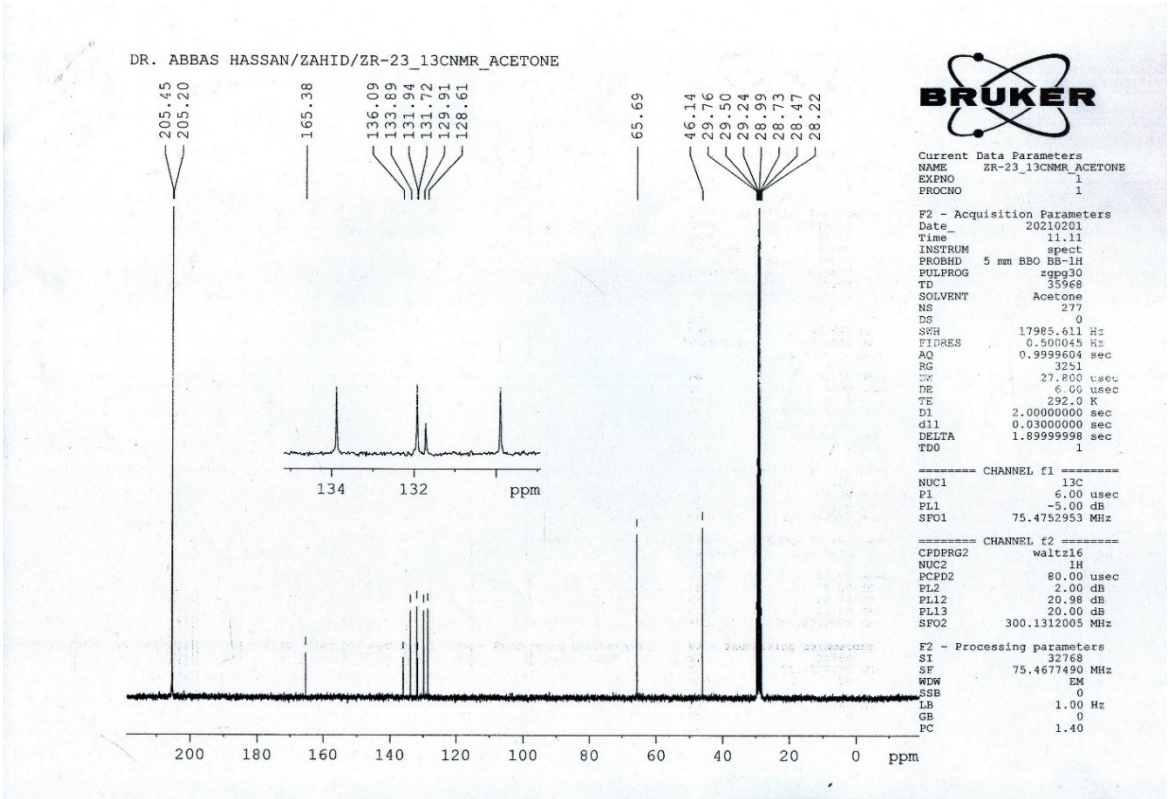
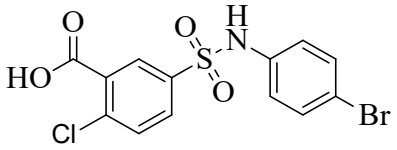


Fig. S-2: ^{1}H and ^{13}C NMR spectra for compound **2b.**

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



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

^{1}H NMR (300 MHz, Acetone-d_6): **δ** (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}C NMR (75 MHz, Acetone-d_6): **δ** (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 $C_{13}H_{10}NO_4S^+$, 389.9197; found, 389.9199.

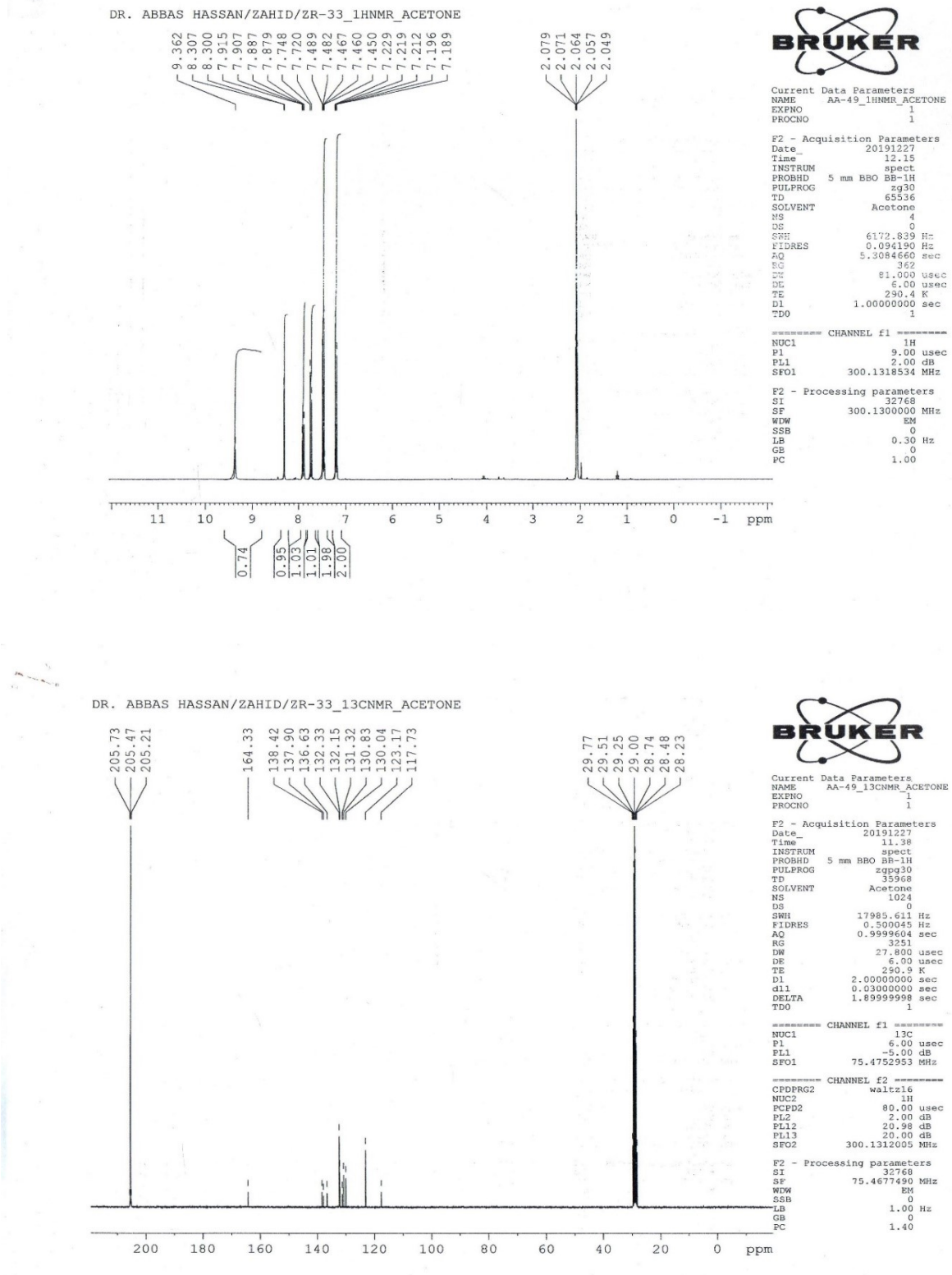
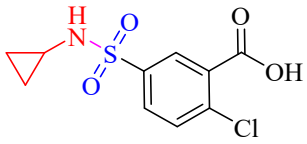


Fig. S-3: ^{1}H and ^{13}C NMR spectra for compound **2c.**

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



Yield: 76% **m.p.:**195-197 °C. white solid **R_f:** 0.29 (chloroform : methanol :: 8 : 2).

^{1}H NMR (300 MHz, DMSO-d_6): 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).

^{13}C NMR (75 MHz, DMSO-d_6): 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): $[M+H]^+$ calc'd for $C_{10}H_{11}NO_4S^+$, 276.0092; found, 276.0097.

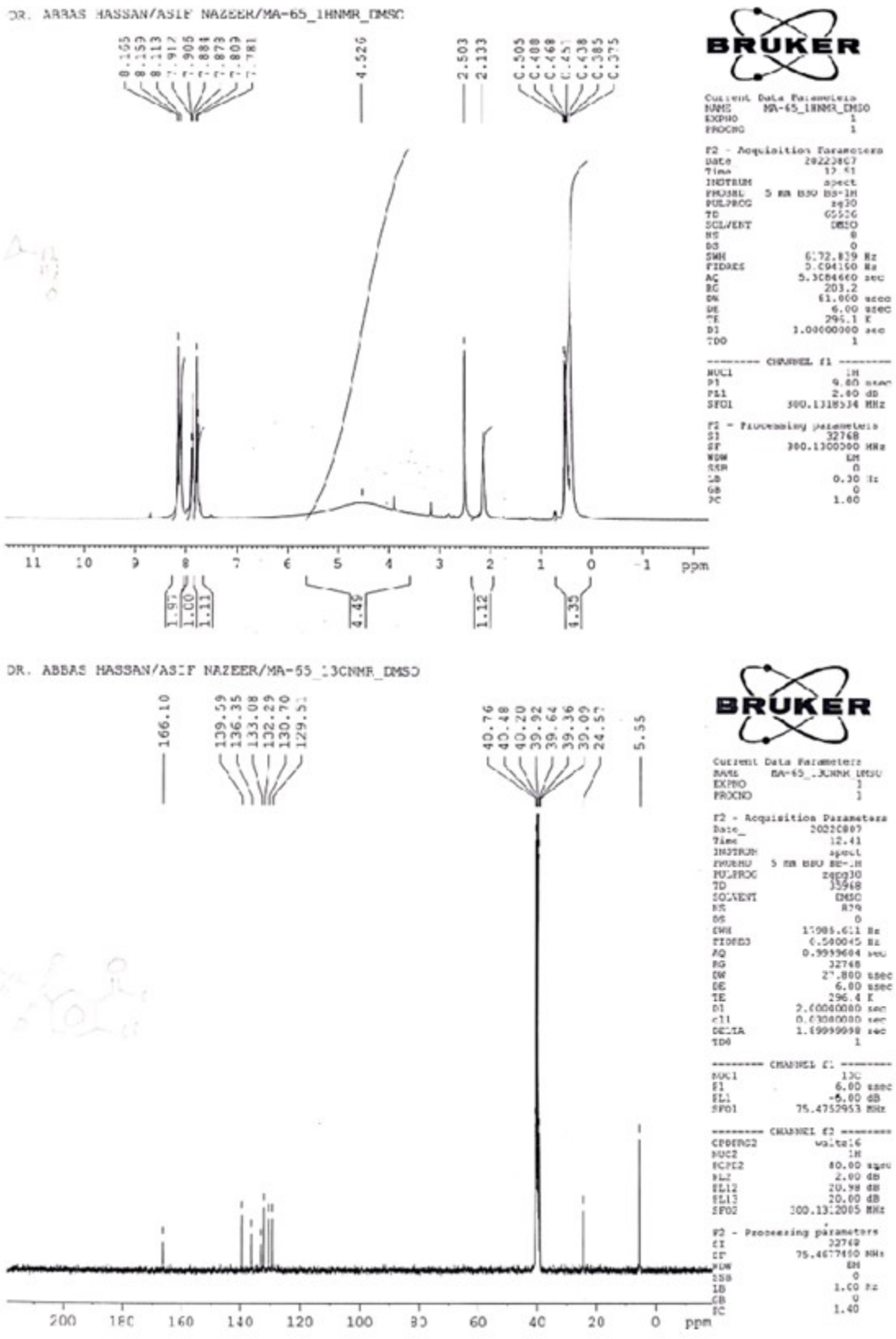
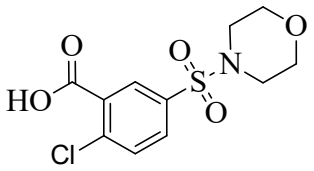


Fig. S-4: ^{1}H and ^{13}C NMR spectra for compound **2d.**

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



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

^{1}H NMR (300 MHz, Acetone-d_6): **δ** (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}C NMR (75 MHz, Acetone-d_6): **δ** (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): $[M+H]^+$ calc'd for $C_{11}H_{13}NO_5S^+$, 306.0197; found, 306.0201.

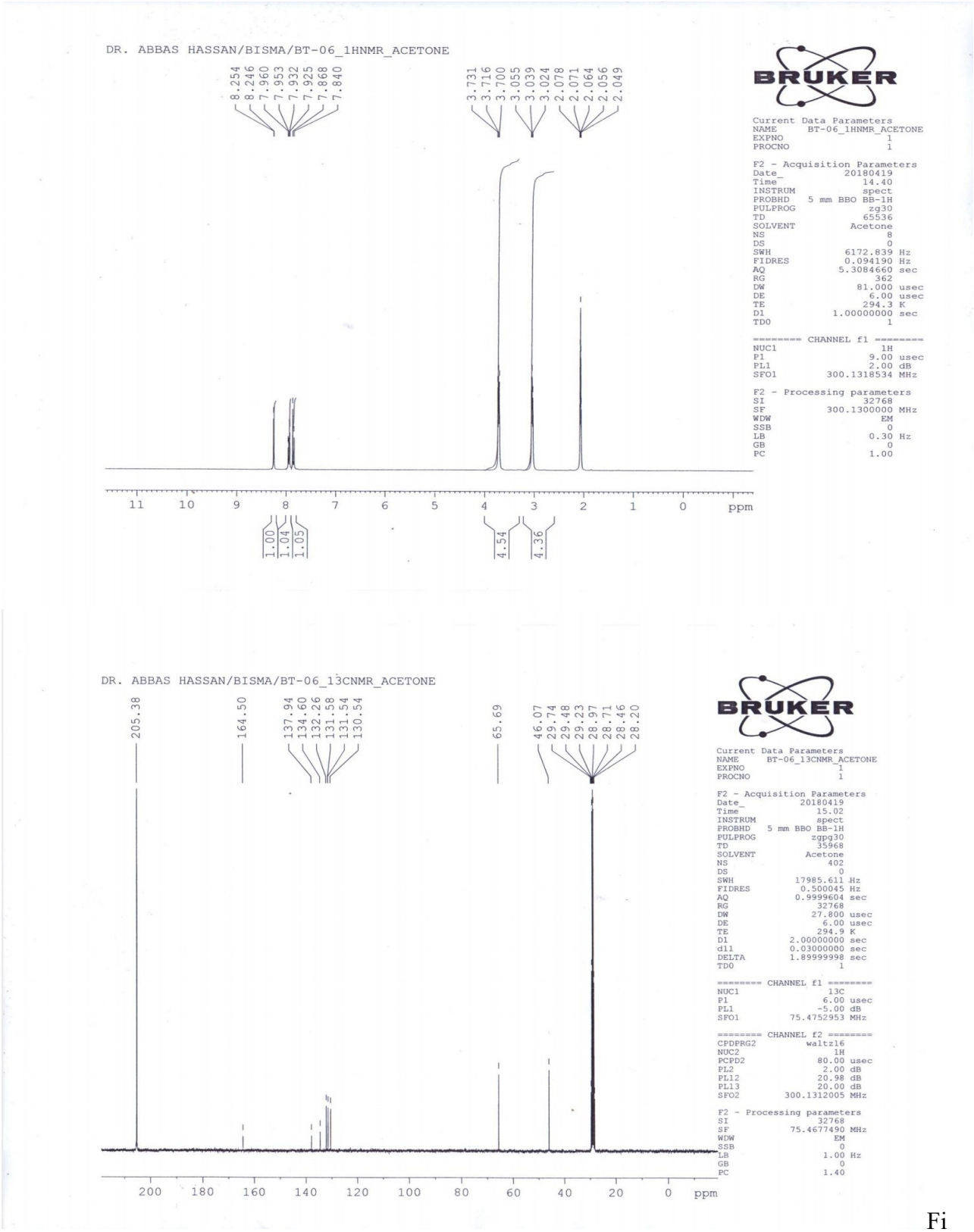
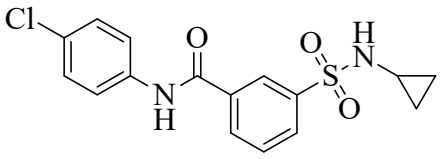


Fig. S-5: ^{1}H and ^{13}C NMR spectra for compound **2e.**

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 ºC; R_f: 0.6 (*n*-hexane: ethyl acetate :: 7:3).

^{1}H NMR (300 MHz, DMSO-d_6): **δ** (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}C NMR (75 MHz, DMSO-d_6): **δ** (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): $[M+H]^+$ calc'd for $C_{16}H_{16}ClN_2O_3S^+$, 351.0565; found, 351.0564.

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

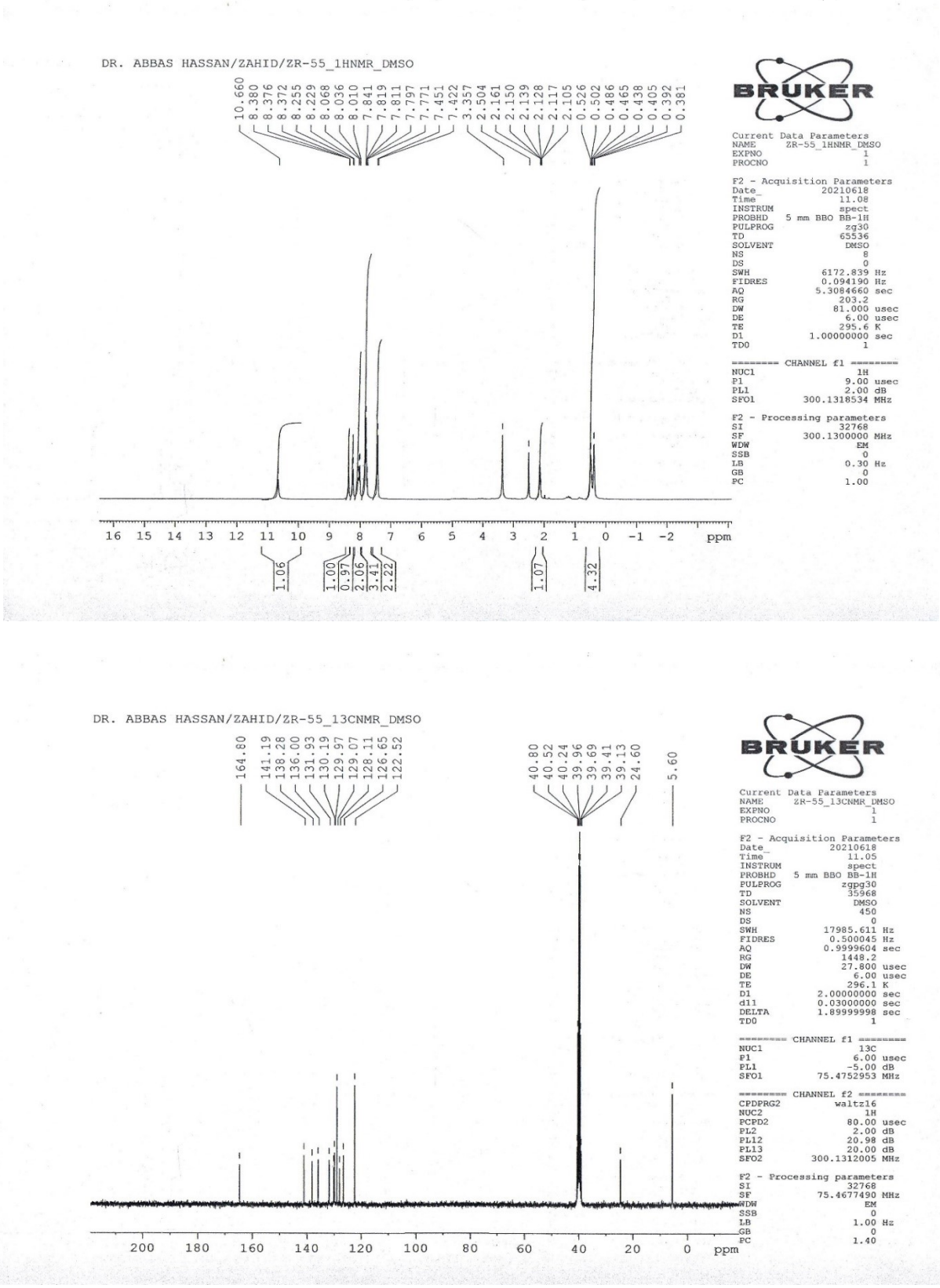


Fig. S-6: ^{1}H and ^{13}C NMR spectra for compound **3a.**

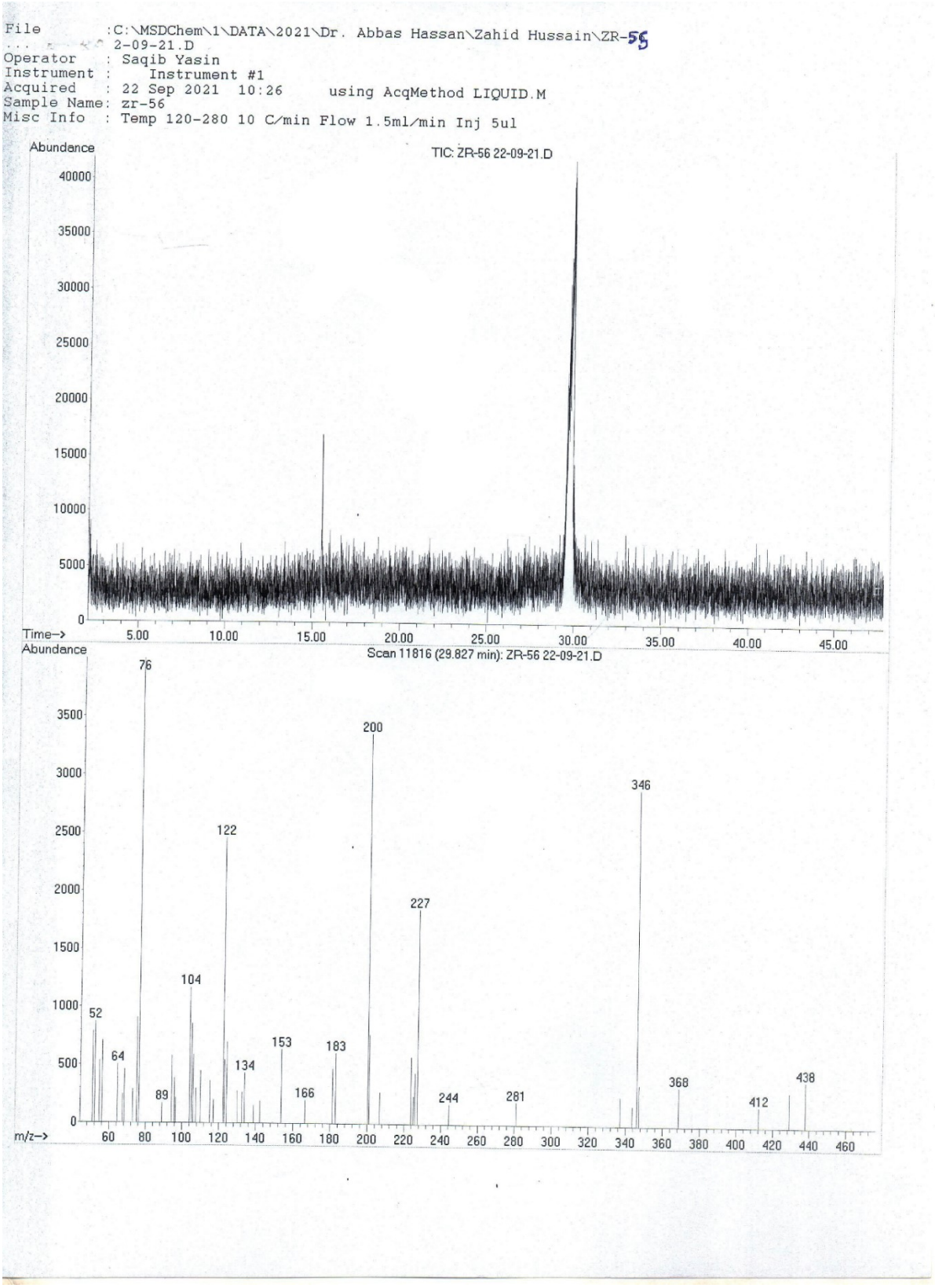
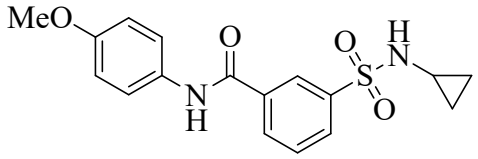


Fig. S-7: GCMS spectrum for compound **3a.**

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



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

^{1}H NMR (300 MHz, DMSO-d_6): **δ** (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}C NMR (75 MHz, DMSO-d_6): **δ** (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): $[M+H]^+$ calc'd for $C_{17}H_{19}N_2O_4S^+$, 347.1060; found, 347.1064.

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

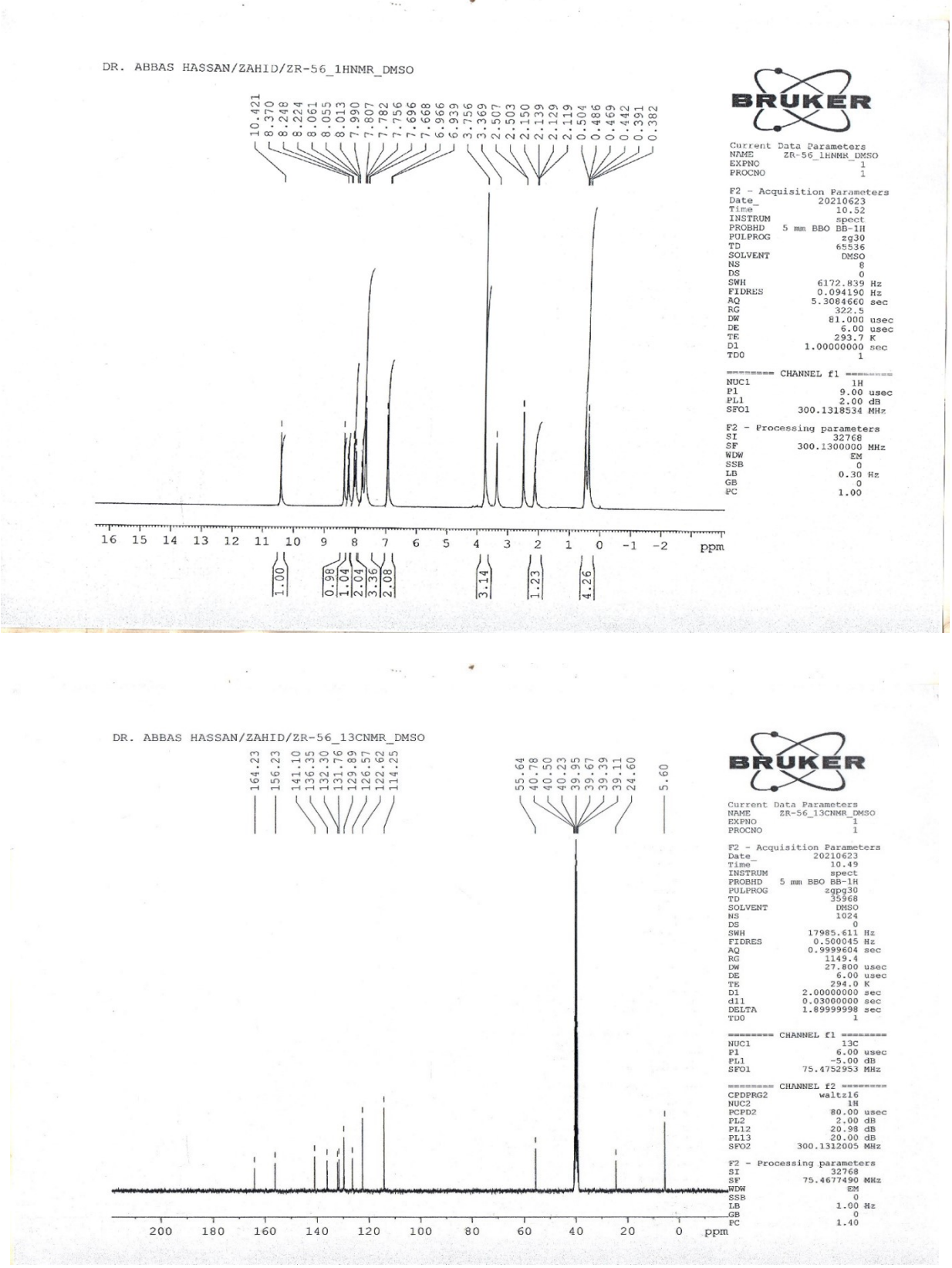


Fig. S-8: ^{1}H and ^{13}C NMR spectra for compound **3b.**

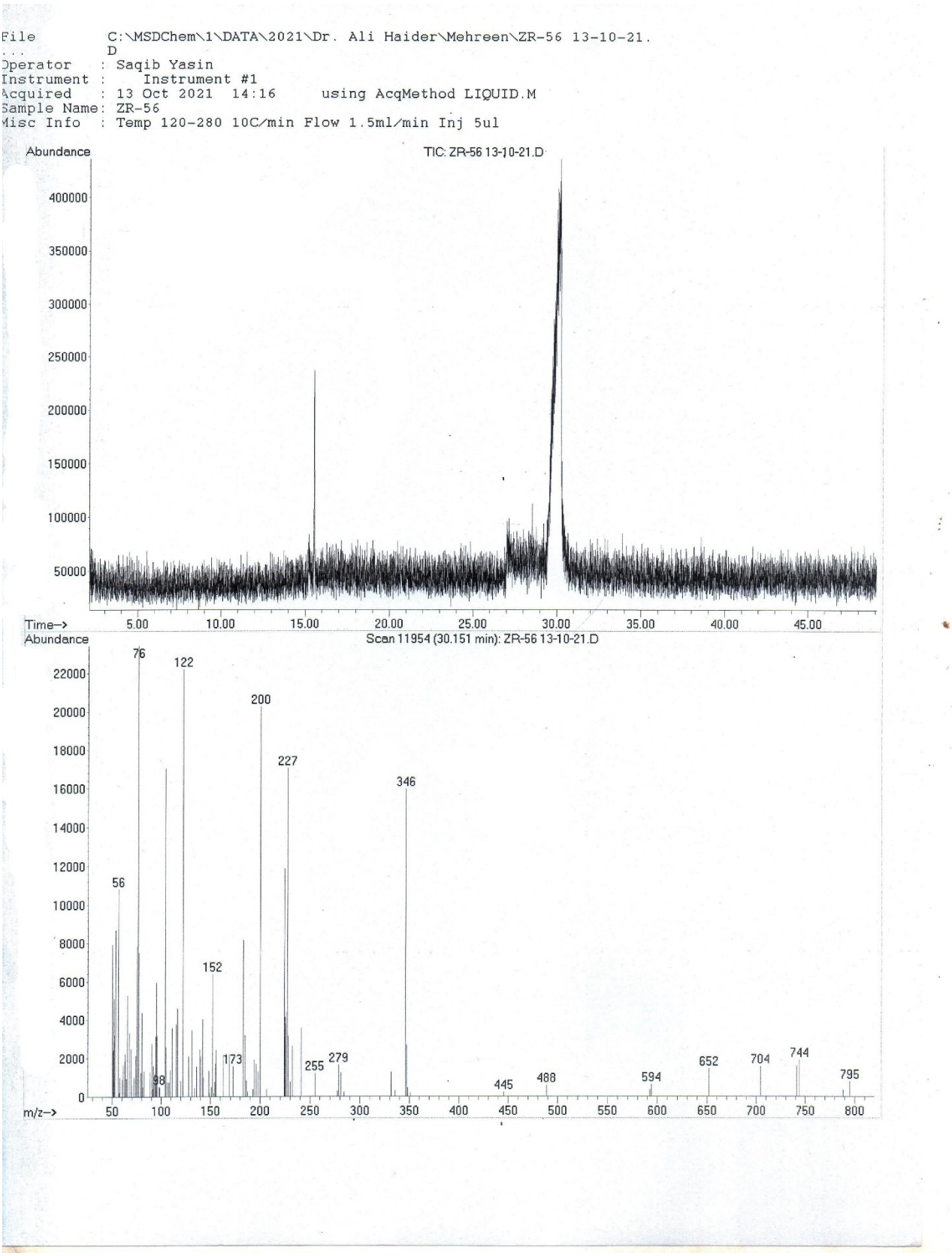
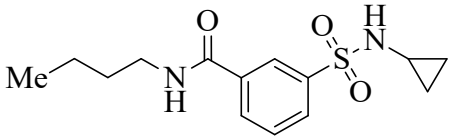


Fig. S-9: GCMS spectrum for compound **3b.**

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



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

^{1}H NMR (300 MHz, DMSO-d_6): **δ** (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}C NMR (75 MHz, DMSO-d_6): **δ** (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): $[M+H]^+$ calc'd for $C_{14}H_{21}N_2O_3S^+$, 297.1267; found, 297.1269.

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

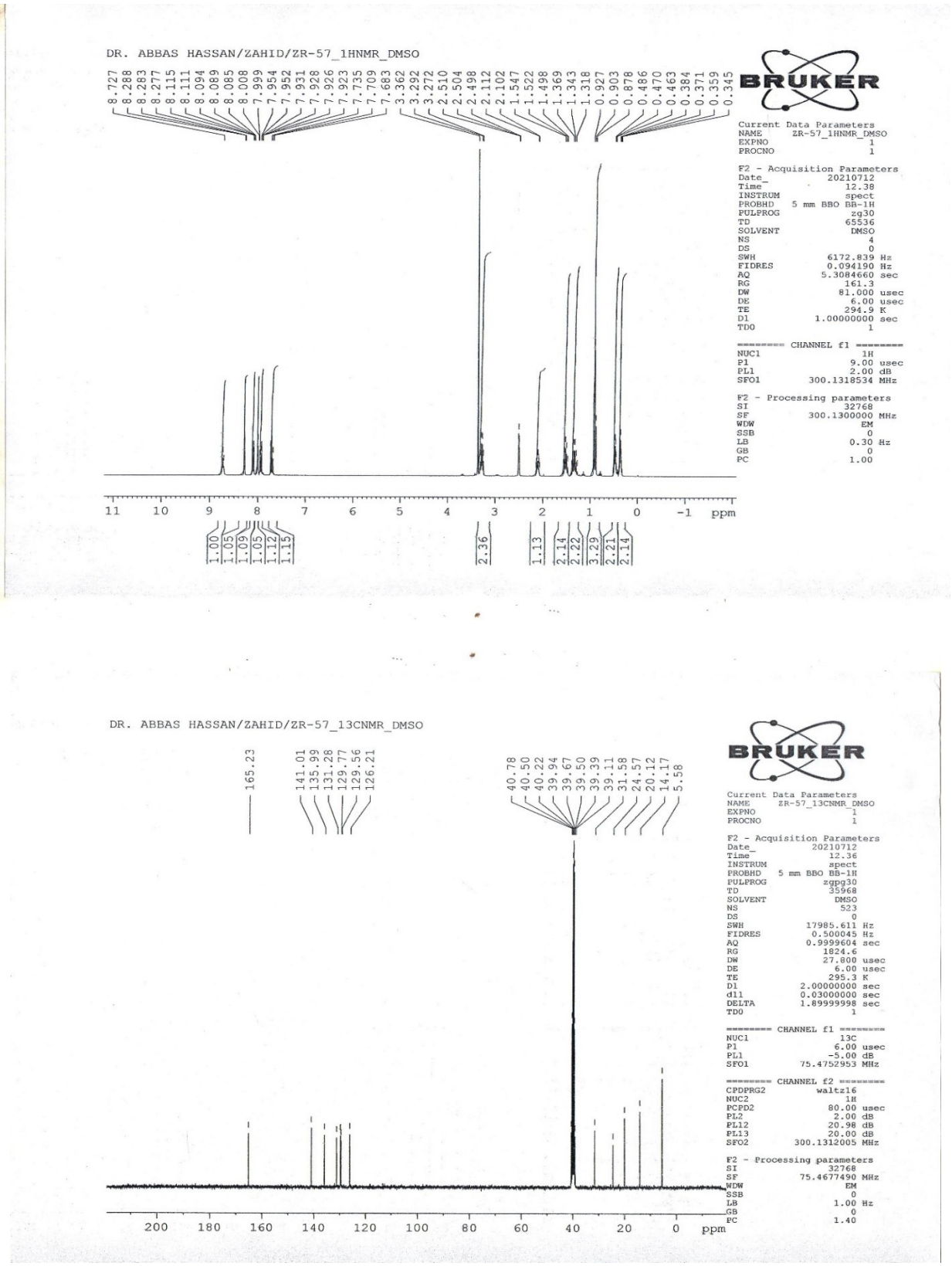


Fig. S-10: ^{1}H and ^{13}C NMR spectra for compound **3c.**

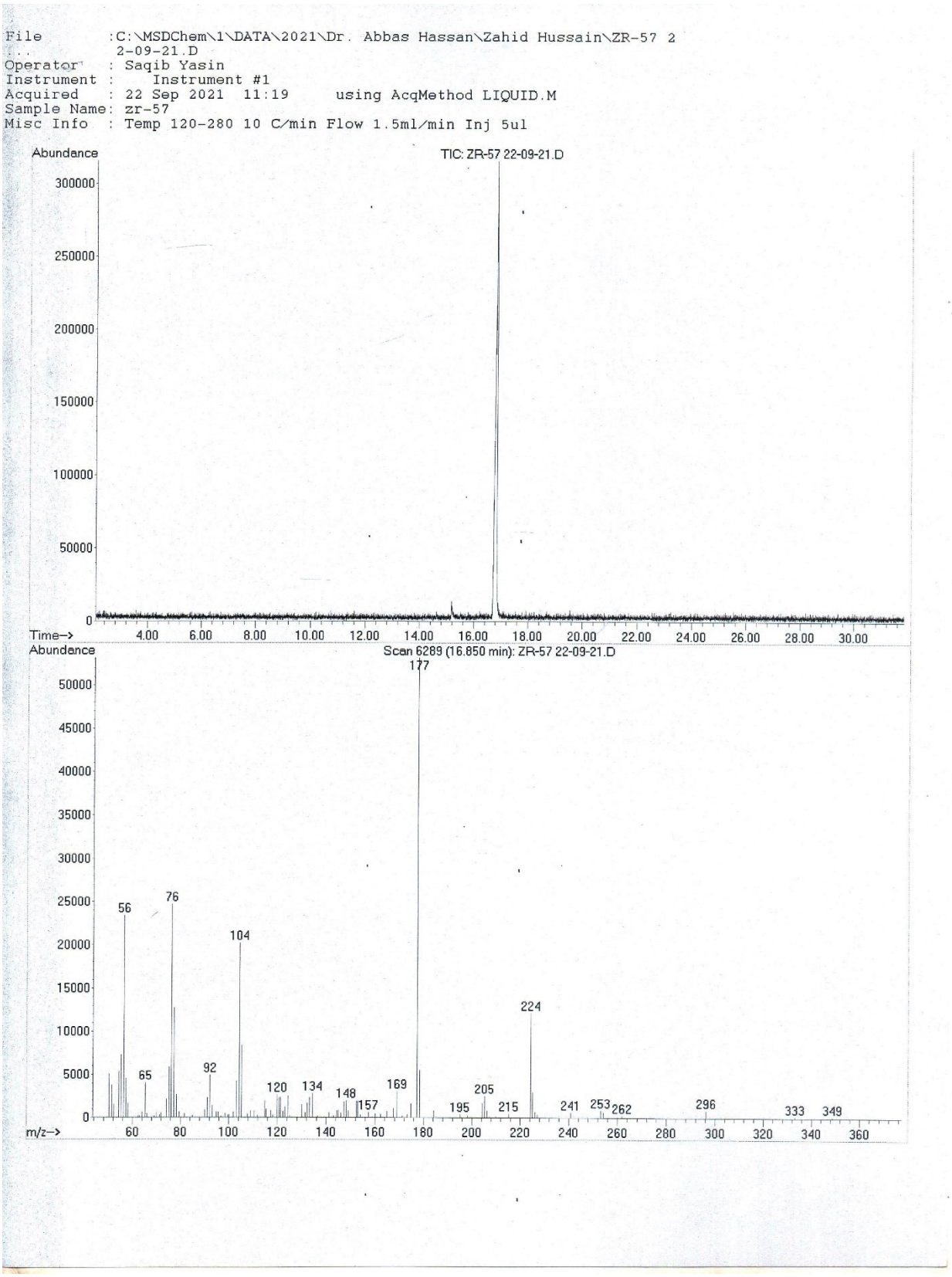
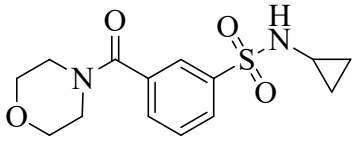


Fig. S-11: GCMS spectrum for compound **3c.**

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

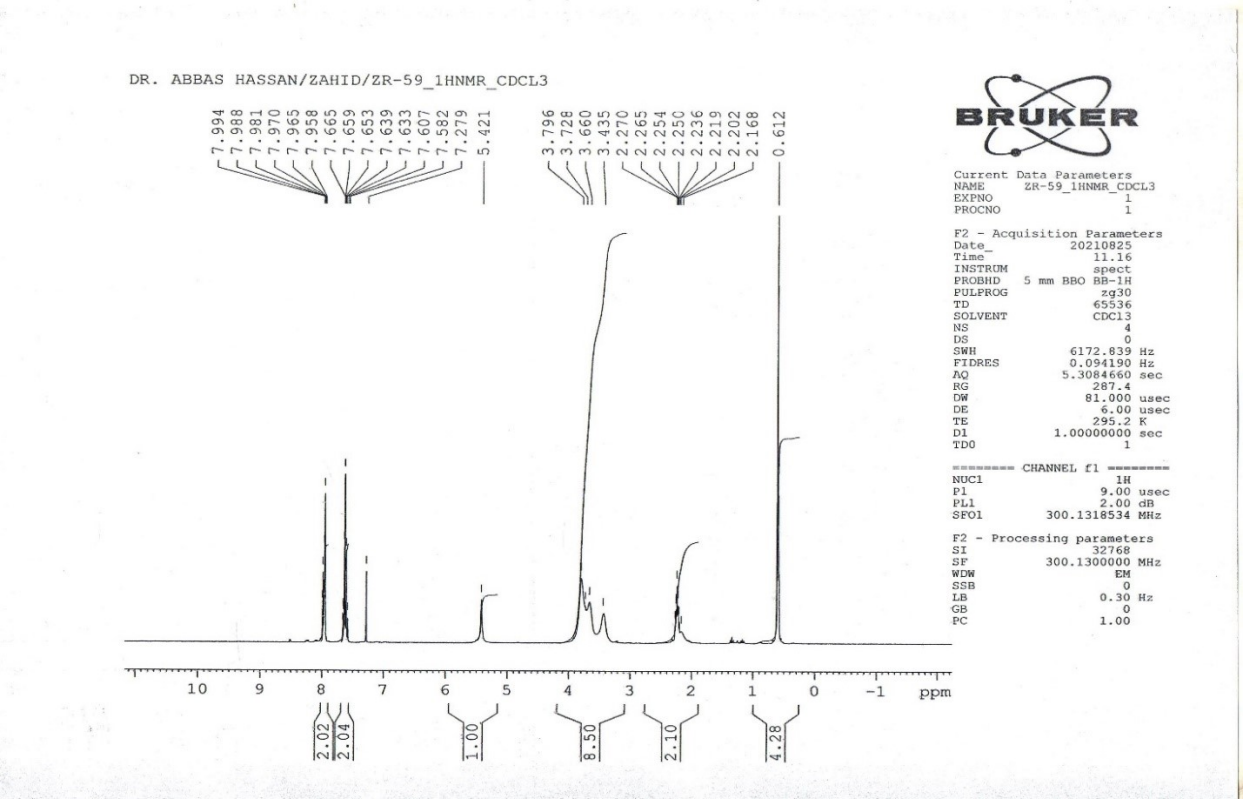


Yield: 69 %; white solid; m.p. : 187-189 ºC; R_f: 0.3 (*n*-hexane: ethyl acetate :: 7:3).

^{1}H NMR (300 MHz, $CDCl_3$): **δ** (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}C NMR (75 MHz, $CDCl_3$): **δ** (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): $[M+H]^+$ calc'd for $C_{14}H_{19}N_2O_4S^+$, 311.1060; found, 311.3759.



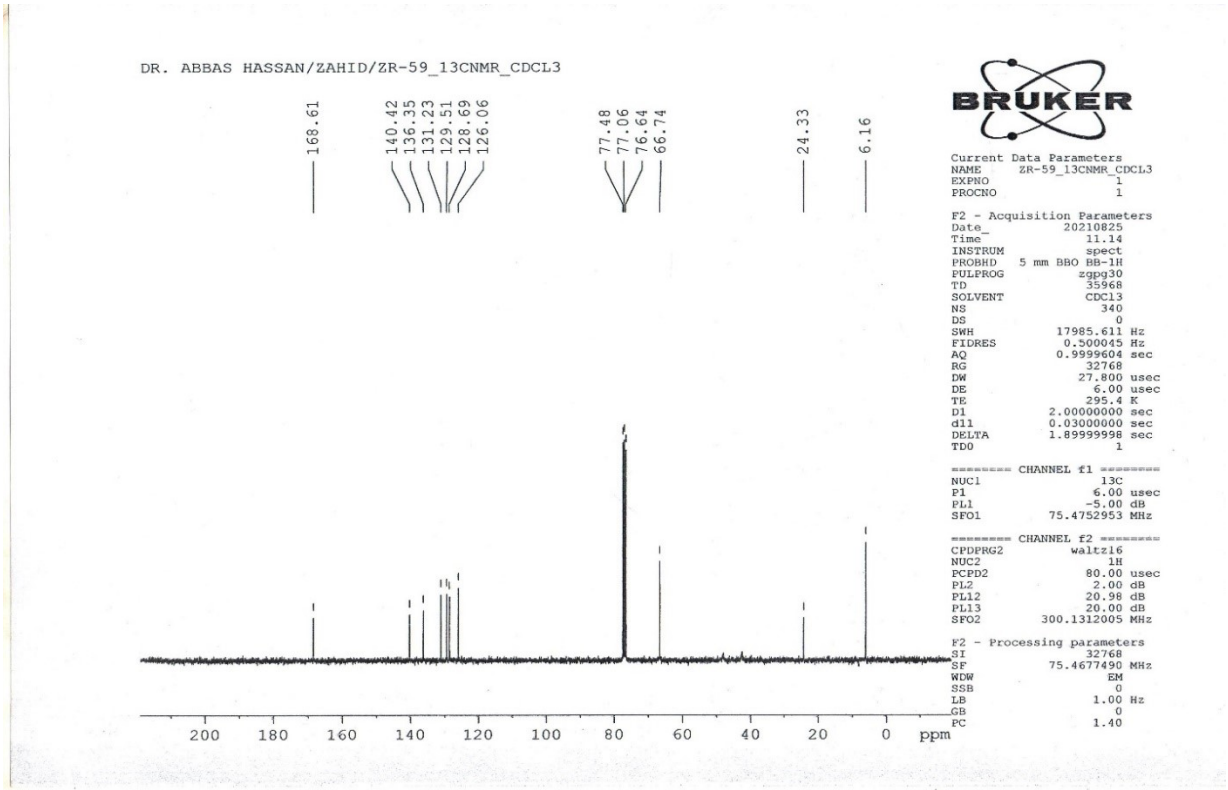
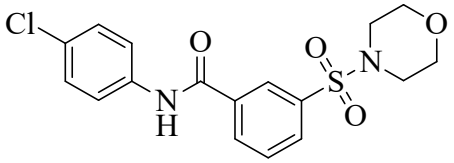


Fig. S-12: ^{1}H and ^{13}C NMR spectra for compound **3d.**

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



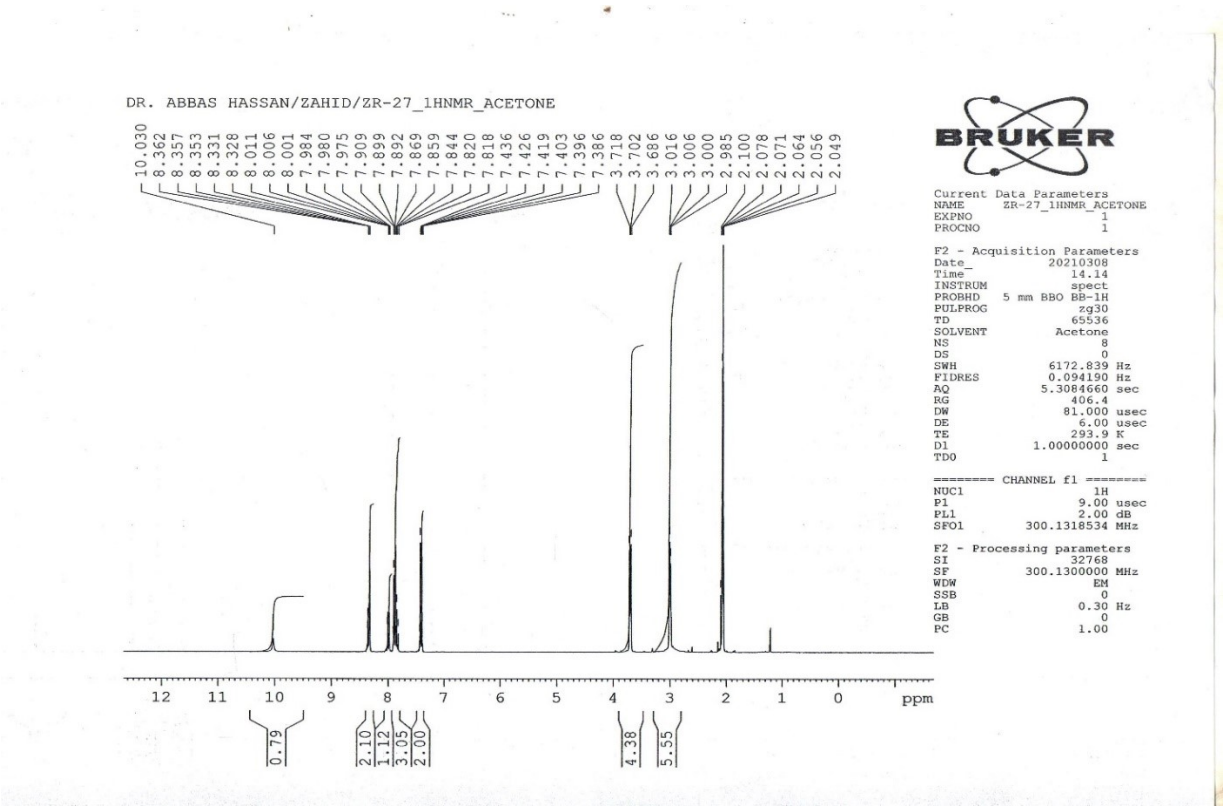
Yield: 71 %; white solid; m.p. : 179-182 ºC; R_f: 0.3 (*n*-hexane: ethyl acetate :: 7:3).

^{1}H NMR (300 MHz, Acetone-d_6): **δ** (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}C NMR (75 MHz, Acetone-d_6): **δ** (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): $[M+H]^+$ calc'd for $C_{17}H_{18}ClN_2O_4S^+$, 381.0670; found, 381.0674.

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



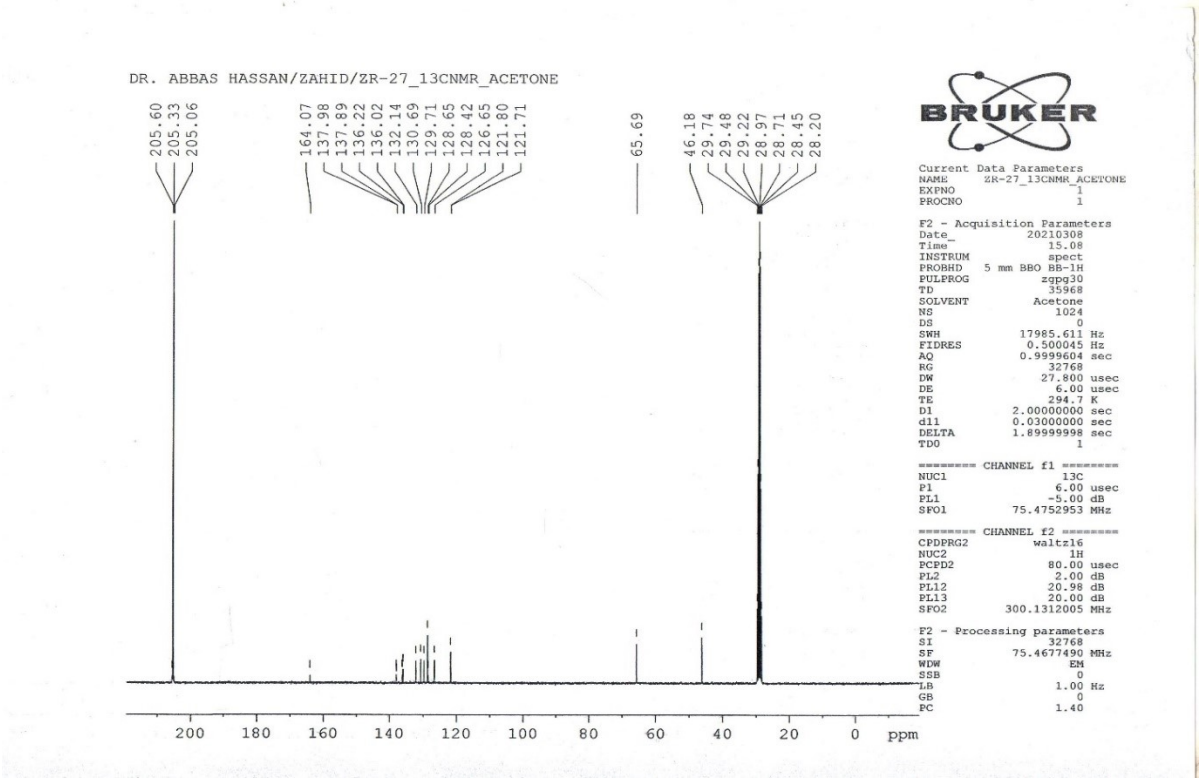


Fig. S-13: ^{1}H and ^{13}C NMR spectra for compound **3e.**

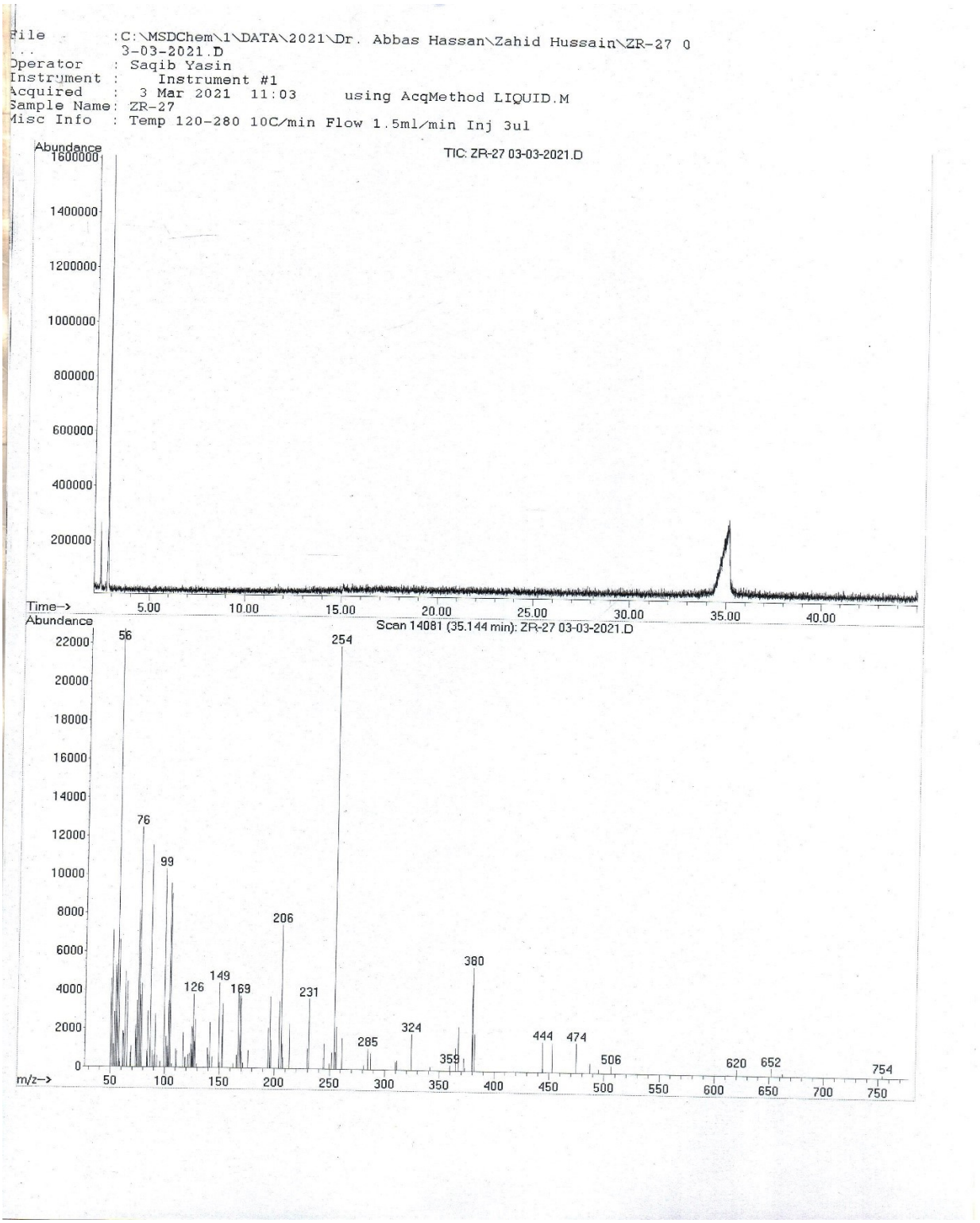
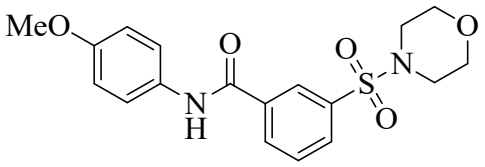


Fig. S-14: GCMS spectrum for compound **3e.**

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



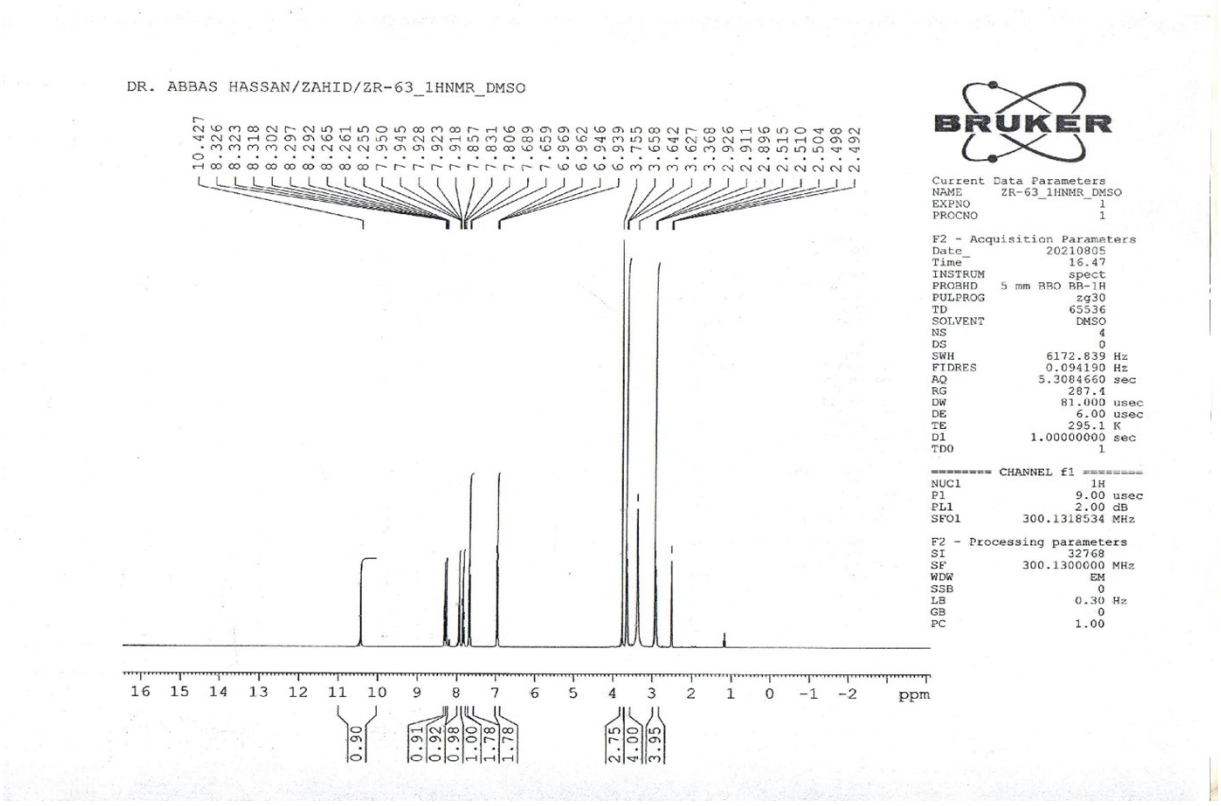
Yield: 69 %; white solid; m.p. : 182-185 ºC; R_f: 0.4 (*n*-hexane: ethyl acetate :: 7:3).

^{1}H NMR (300 MHz, DMSO-d_6): **δ** (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}C NMR (75 MHz, DMSO-d_6): **δ** (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): $[M+H]^+$ calc'd for $C_{18}H_{21}N_2O_5S^+$, 377.1166; found, 377.1171.

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



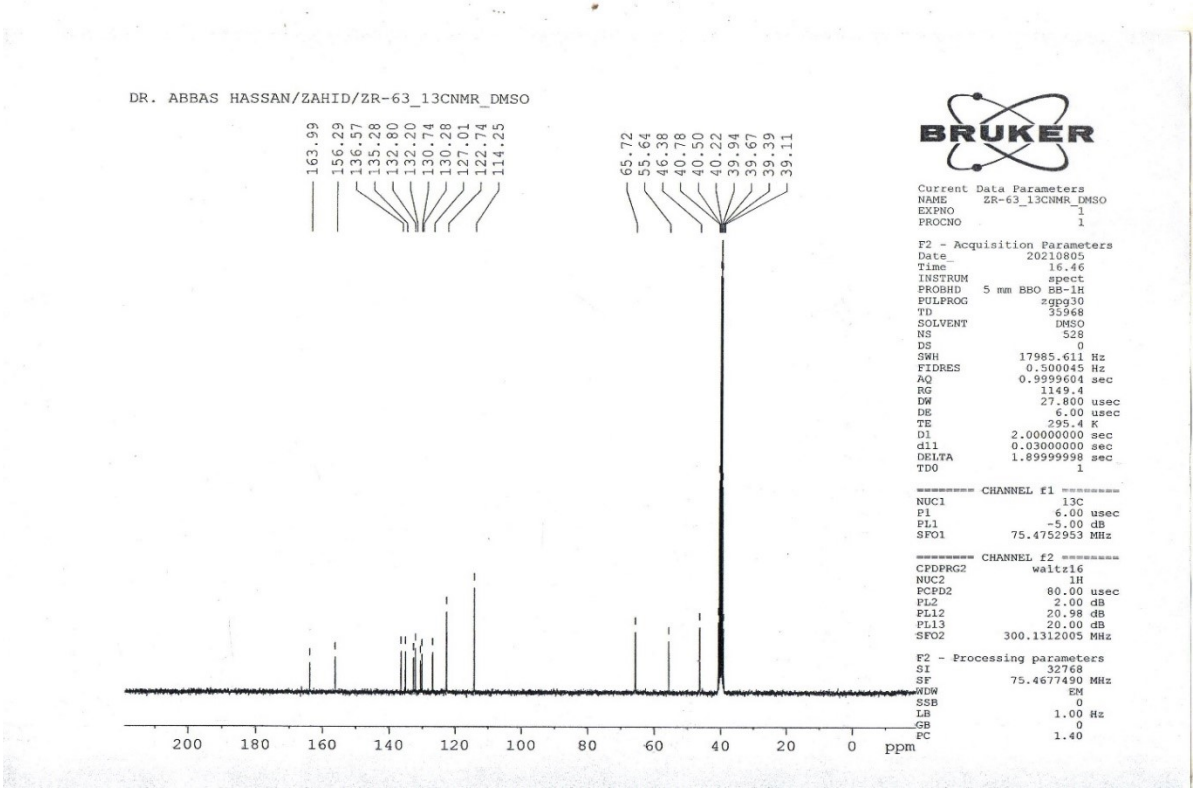


Fig. S-15: ^{1}H and ^{13}C NMR spectra for compound **3f.**

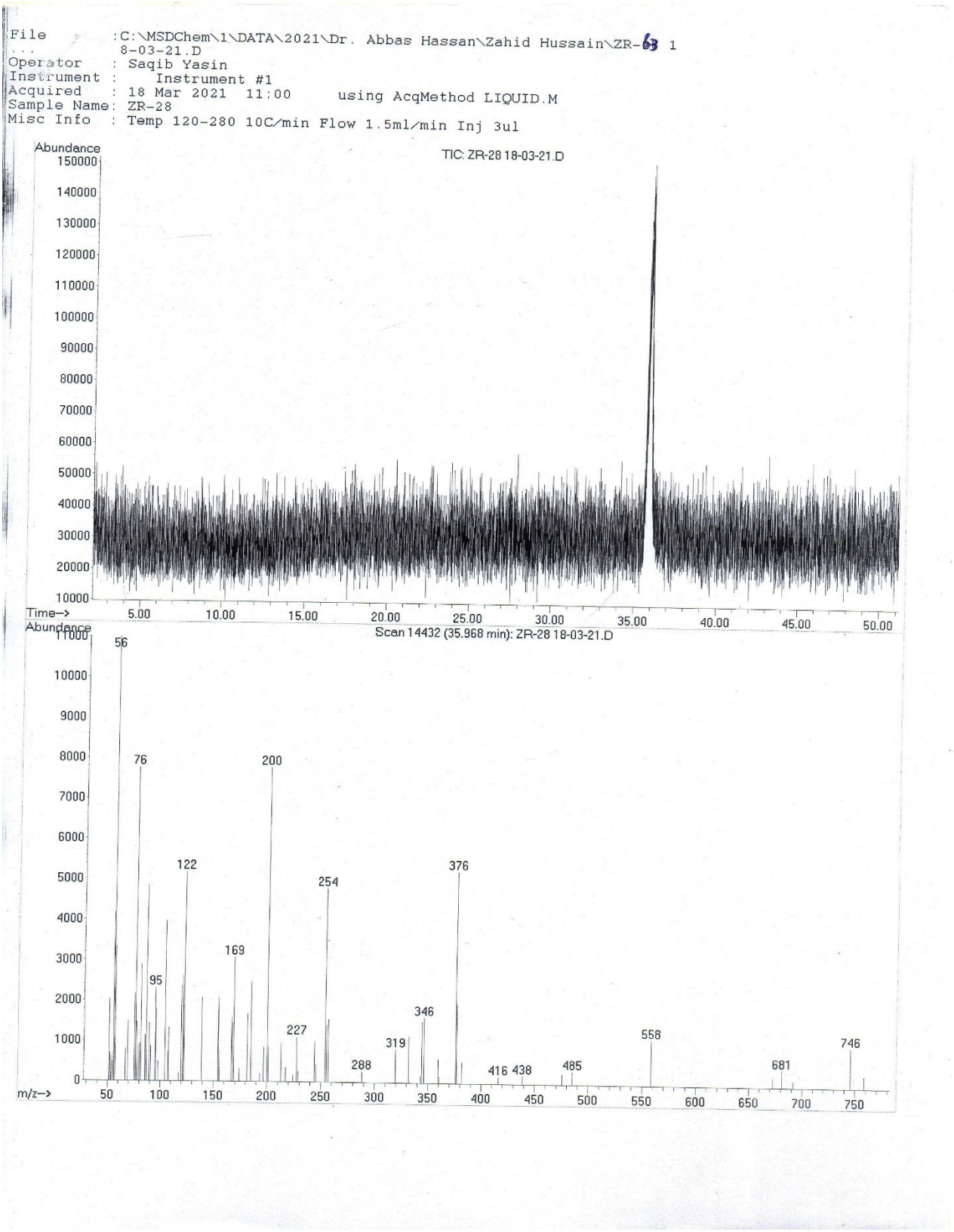
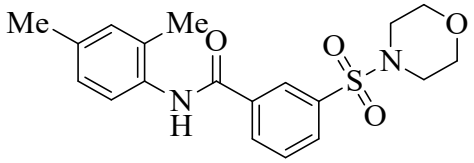


Fig. S-16: GCMS spectrum for compound **3f.**

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



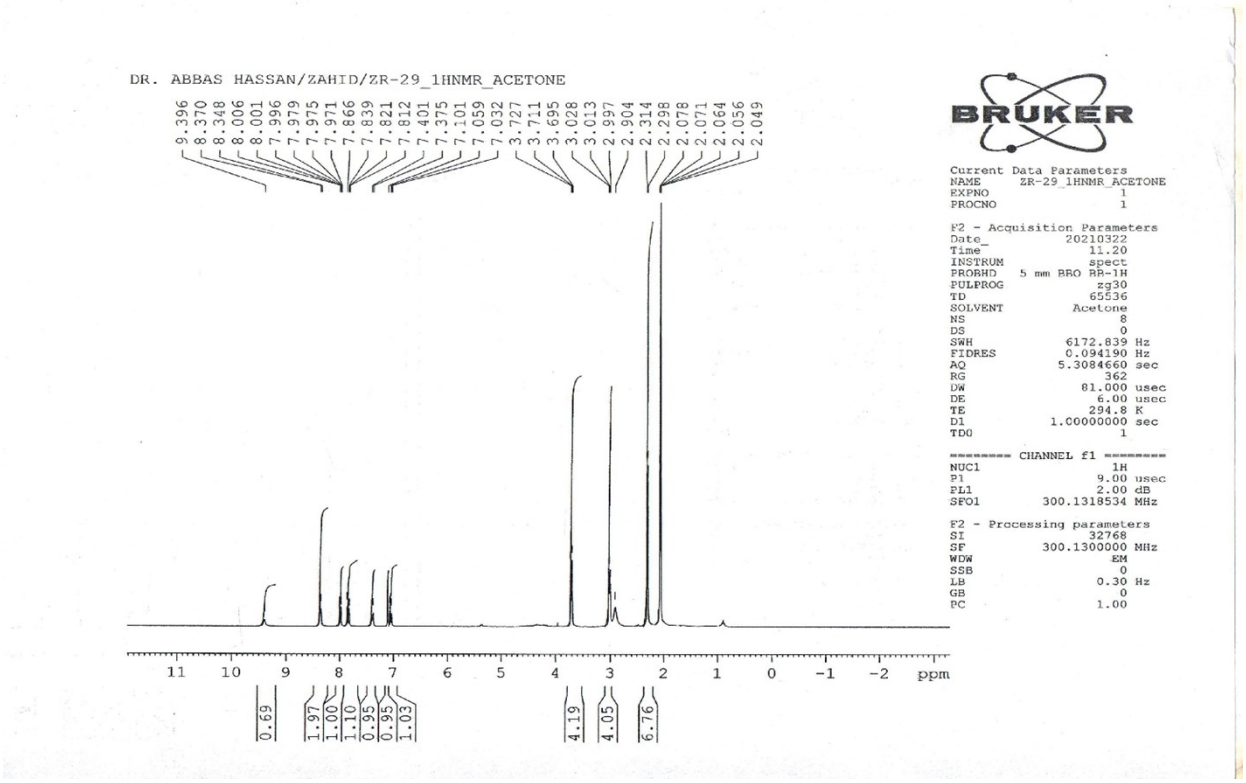
Yield: 47 %; white solid; m.p. : 172-175 ºC; R_f: 0.5 (*n*-hexane: ethyl acetate :: 7:3).

^{1}H NMR (300 MHz, Acetone-d_6): **δ** (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}C NMR (75 MHz, Acetone-d_6): **δ** (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): $[M+H]^+$ calc'd for $C_{19}H_{23}N_2O_4S^+$, 375.1373; found, 375.1377.

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



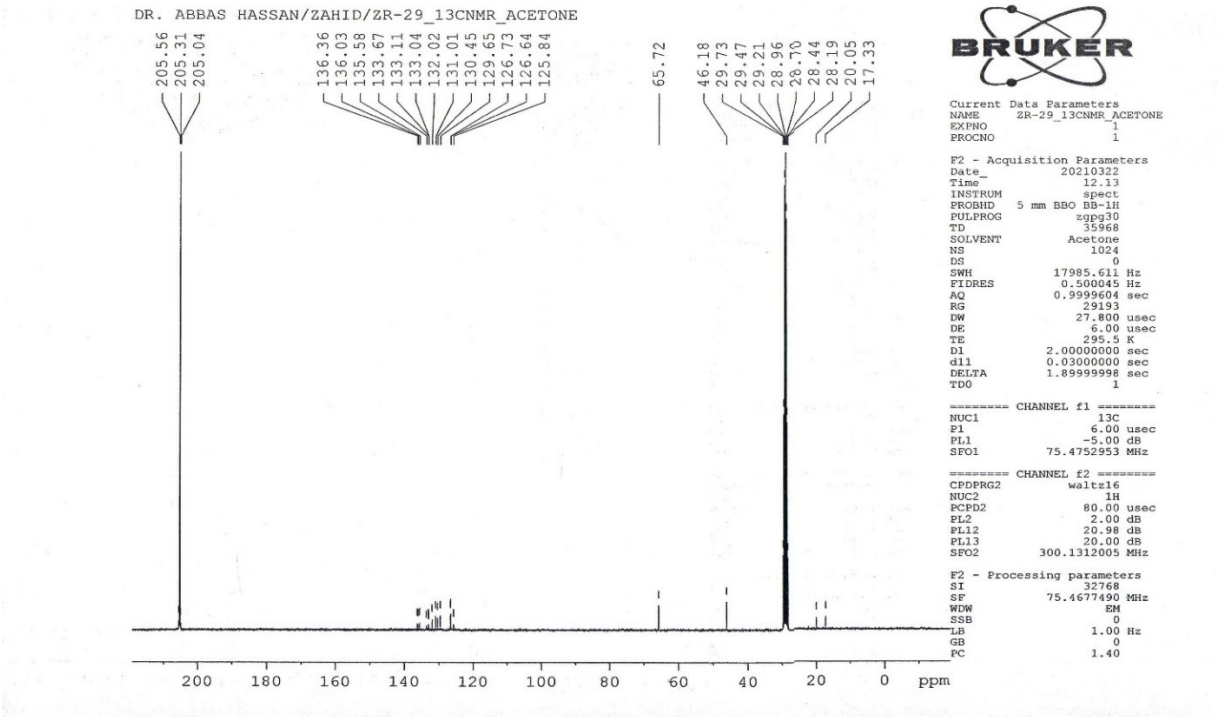


Fig. S-17: ^{1}H and ^{13}C NMR spectra for compound **3g.**

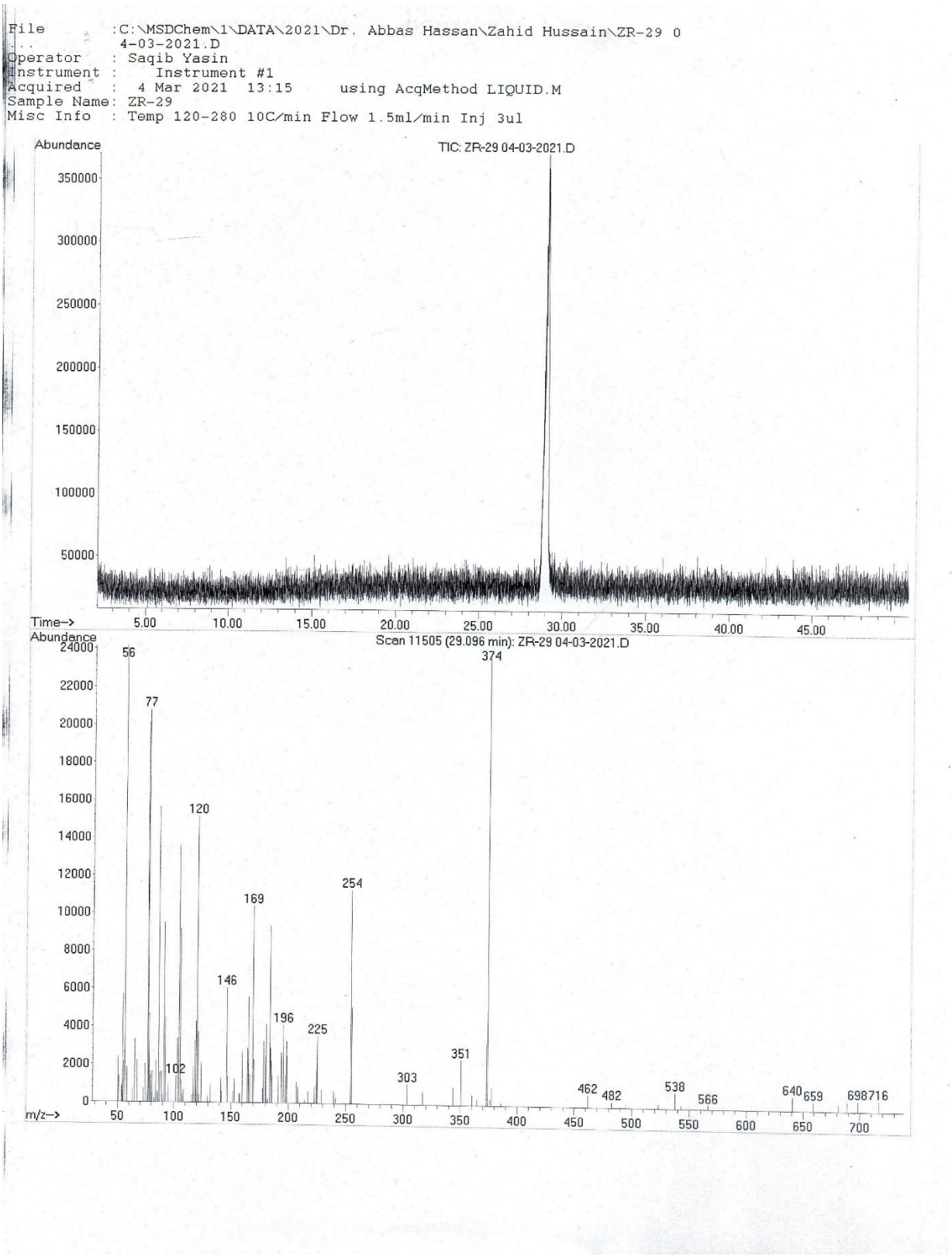
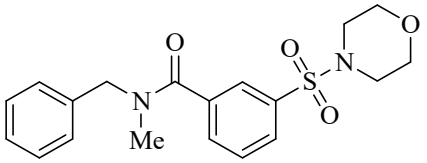


Fig. S-18: GCMS spectrum for compound **3g.**

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



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

^{1}H NMR (300 MHz, $CDCl_3$): **δ** (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}C NMR (75 MHz, $CDCl_3$): **δ** (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): $[M+H]^+$ calc'd for $C_{19}H_{23}N_2O_4S^+$, 375.1373; found, 375.1378.

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

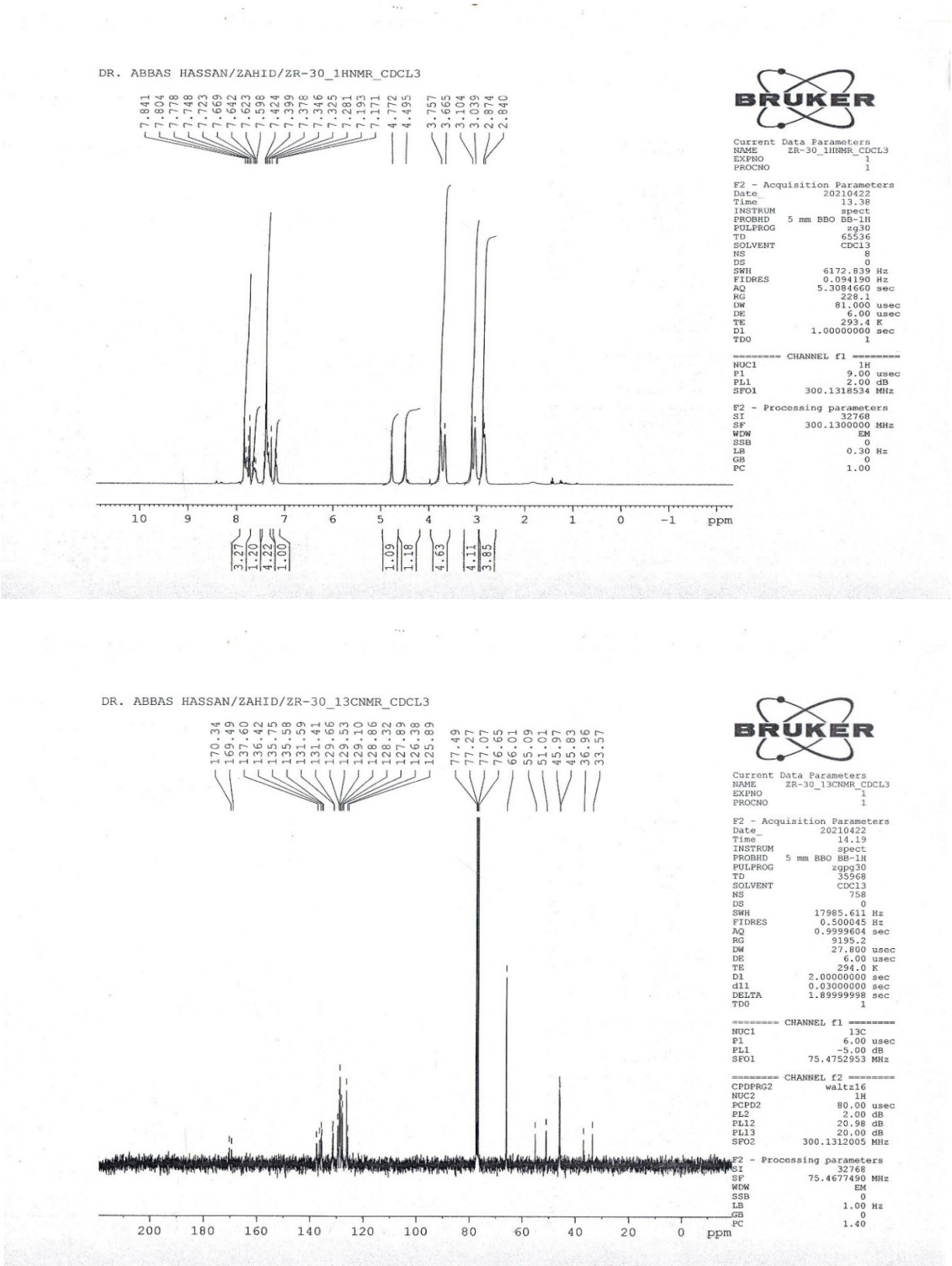


Fig. S-19: ^{1}H and ^{13}C NMR spectra for compound **3h.**

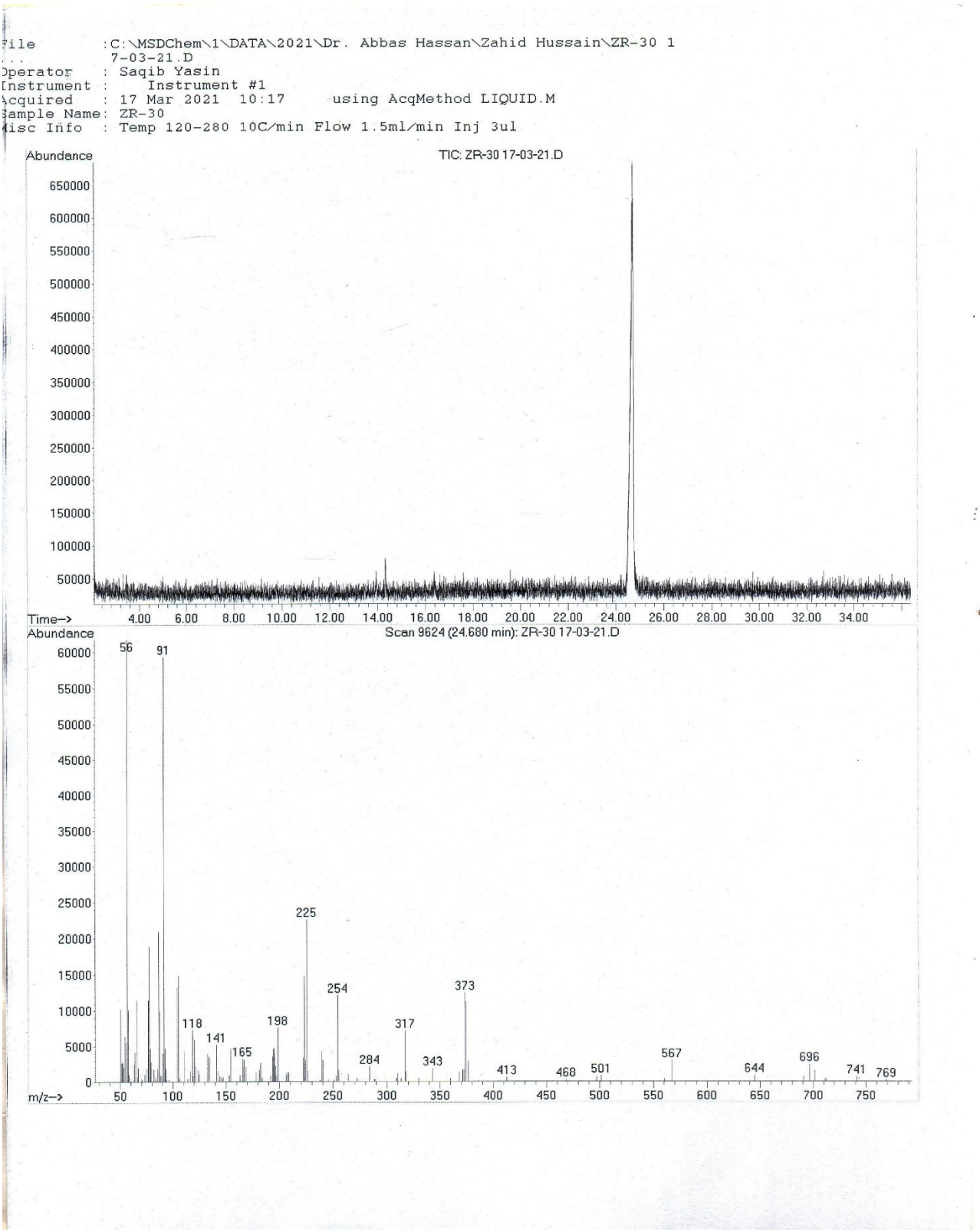
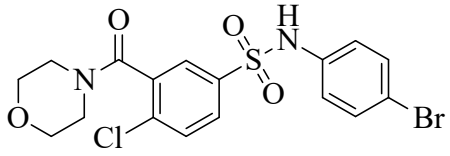


Fig. S-20: GCMS spectrum for compound **3h.**

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



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

^{1}H NMR (300 MHz, $CDCl_3$): **δ** (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}C NMR (75 MHz, $CDCl_3$): **δ** (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): $[M+H]^+$ calc'd for $C_{17}H_{17}BrClN_2O_4S^+$, 458.9775; found, 458.9782.

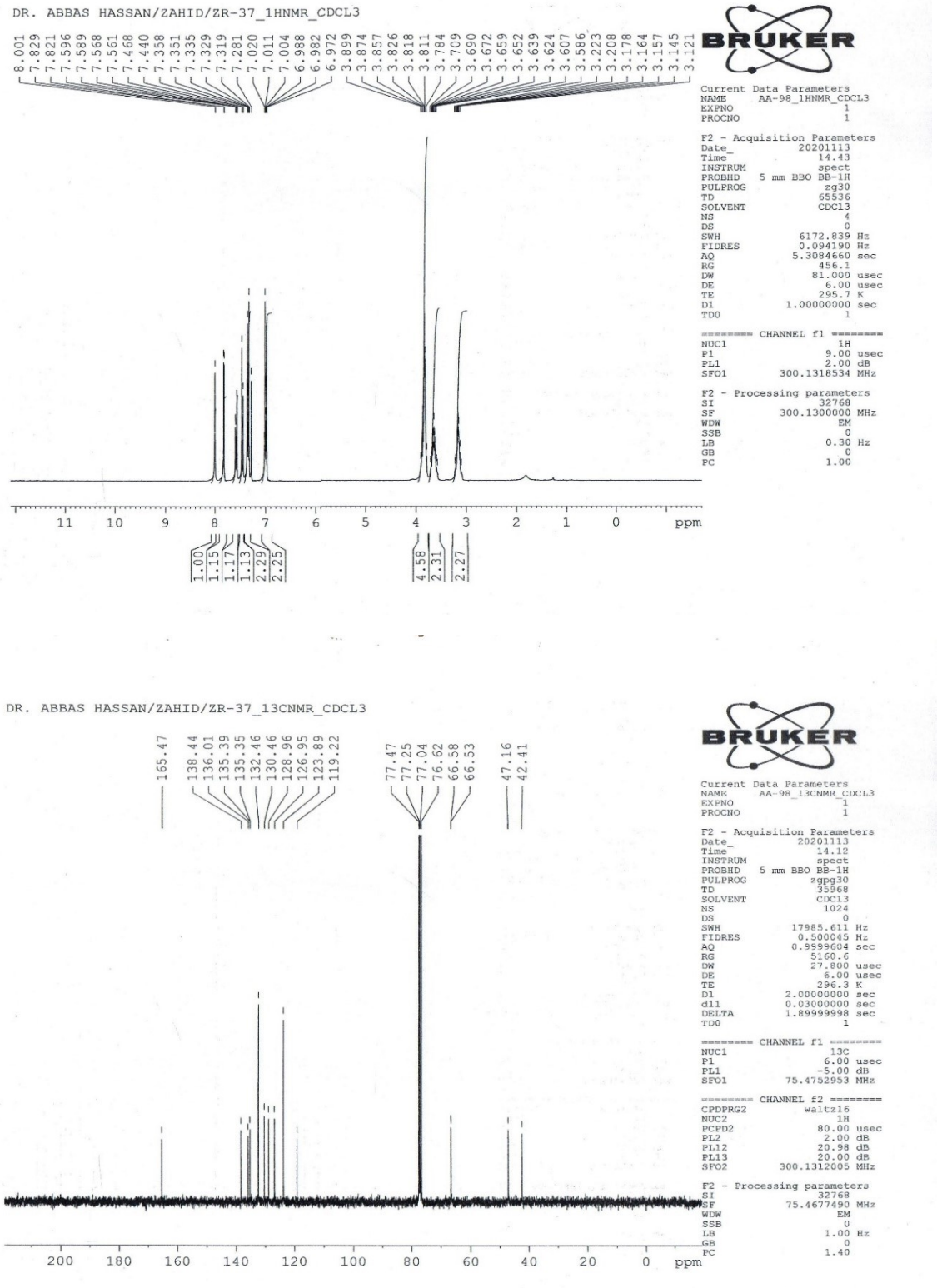
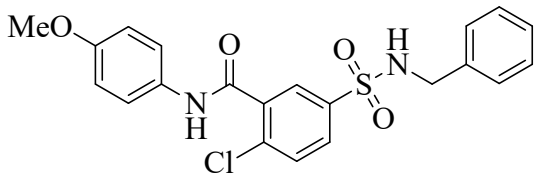


Fig. S-21: ^{1}H and ^{13}C NMR spectra for compound **3i.**

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



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

^{1}H NMR (300 MHz, Acetone-d_6): **δ** (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}C NMR (75 MHz, Acetone-d_6): **δ** (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): $[M+H]^+$ calc'd for $C_{21}H_{20}ClN_2O_4S^+$, 431.0827; found, 431.0830.

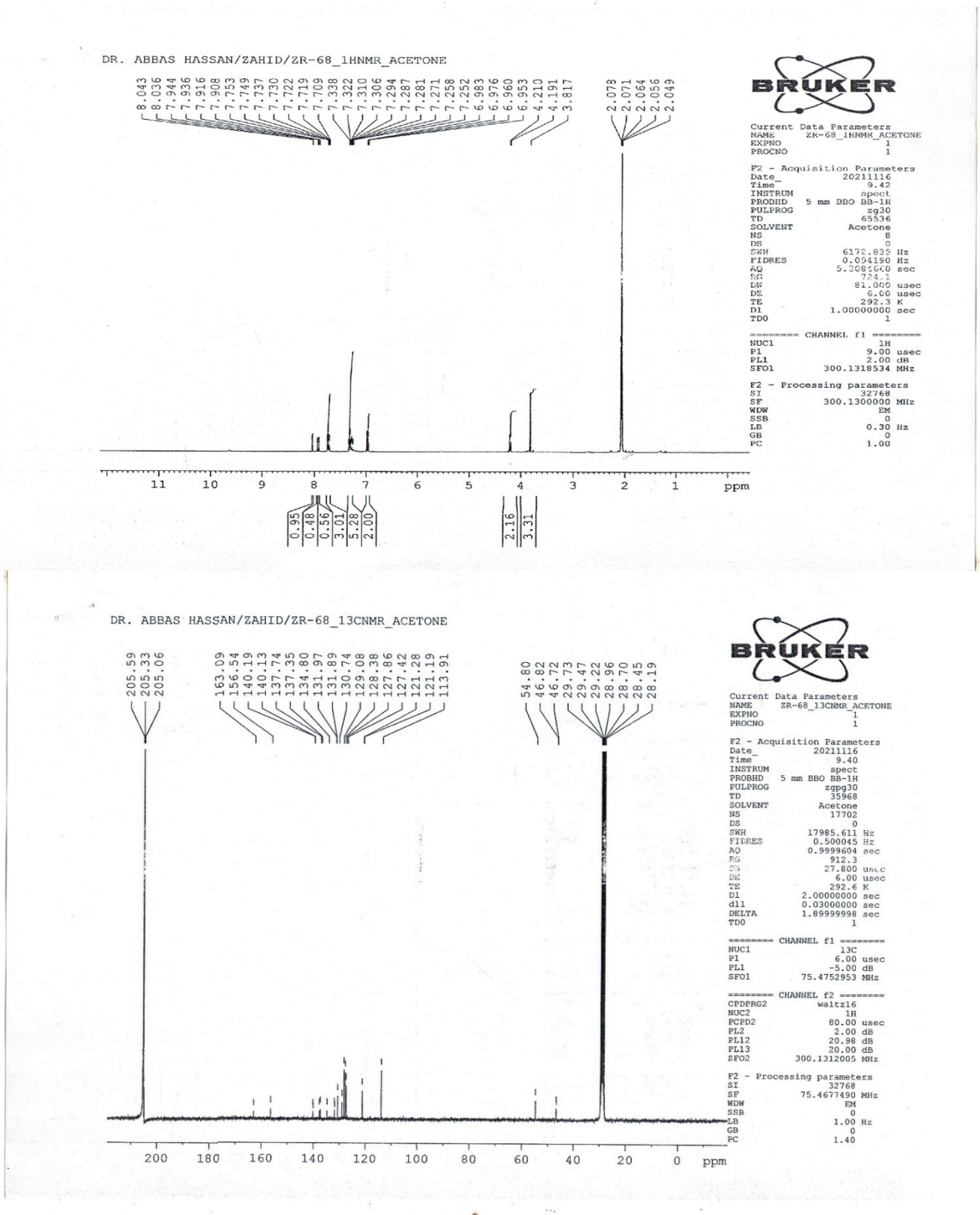
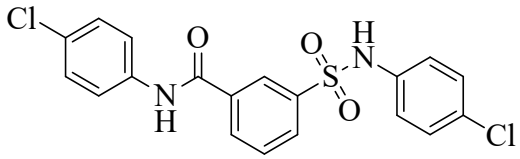


Fig. S-22: ^{1}H and ^{13}C NMR spectra for compound **3j.**

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 ºC for 12 h. The mixture was cooled up to 0 ºC 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 *p*H 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 ºC; R_f: 0.5 (*n*-hexane: ethyl acetate :: 7:3).

^{1}H NMR (300 MHz, Acetone-d_6): **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).

^{13}C NMR (75 MHz, Acetone-d_6): **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): $[M+H]^+$ calc'd for $C_{19}H_{15}Cl_2N_2O_3S^+$, 421.0175; found, 421.0181.

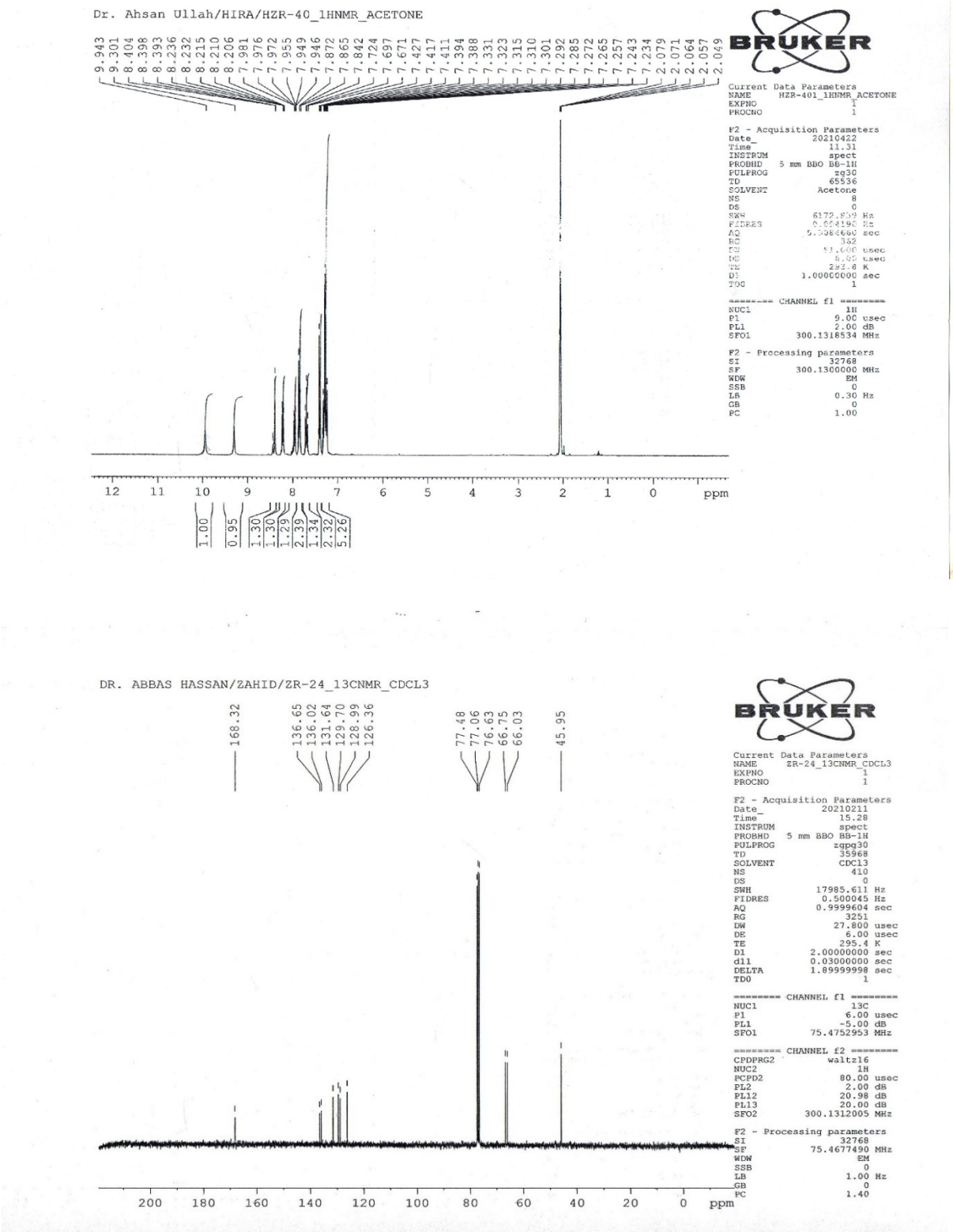
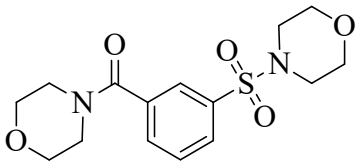


Fig. S-23: ^{1}H and ^{13}C NMR spectra for compound **4a.**

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



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

^{1}H NMR (300 MHz, $CDCl_3$): δ (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}C NMR (75 MHz, CDCl3): δ (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): $[M+H]^+$ calc'd for $C_{15}H_{21}N_2O_5S^+$, 341.1166; found, 341.1168.

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

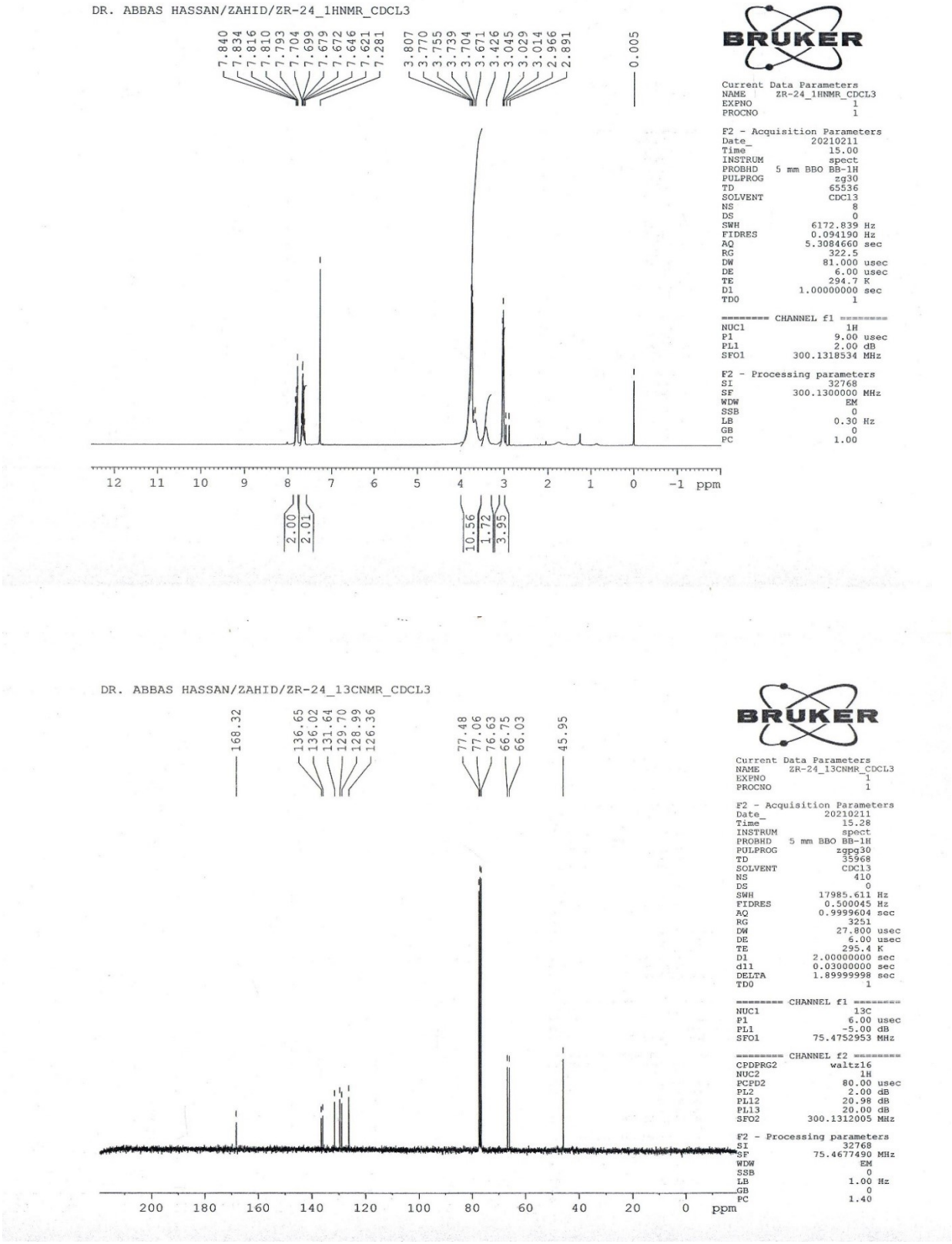


Fig. S-24: ^{1}H and ^{13}C NMR spectra for compound **4b.**

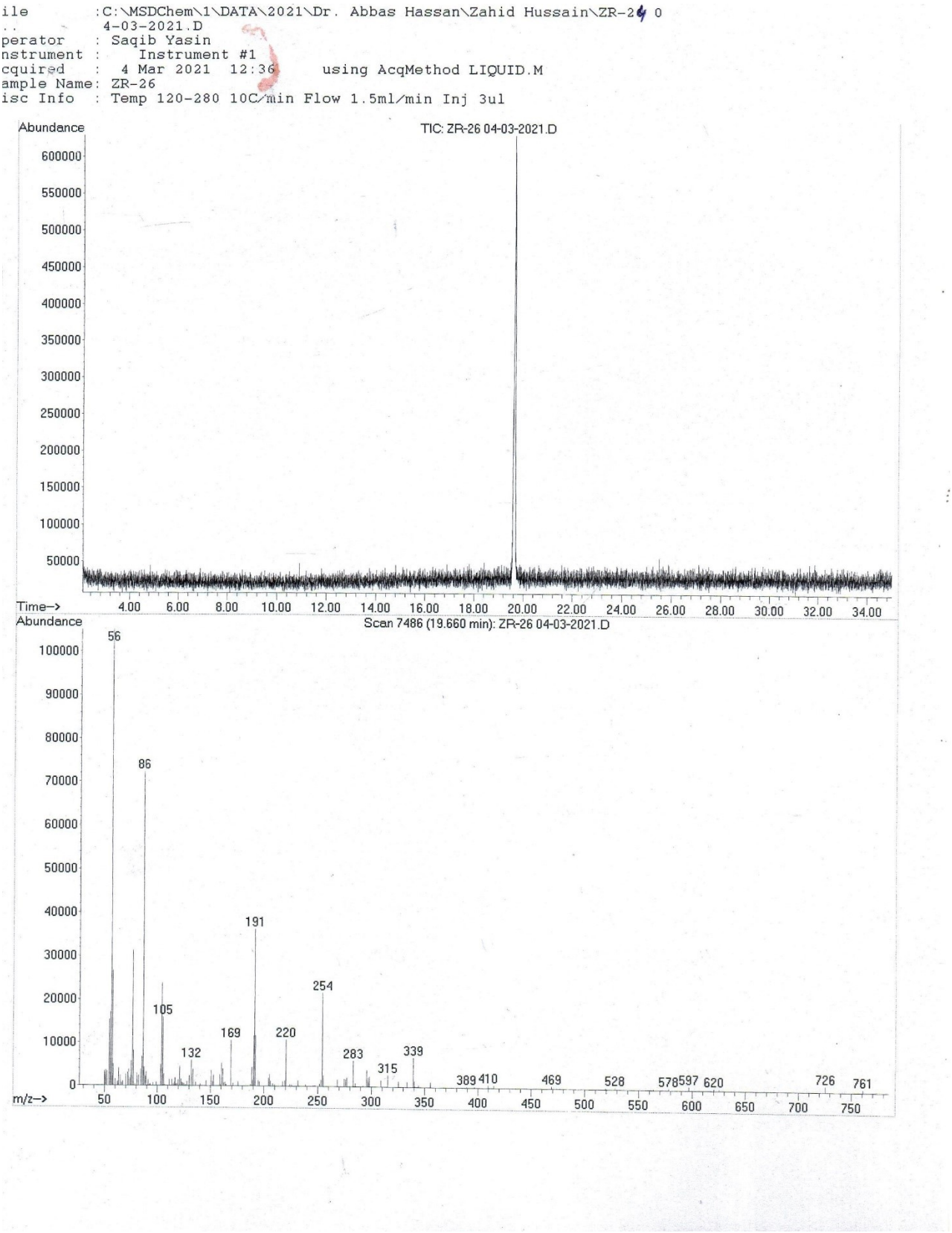
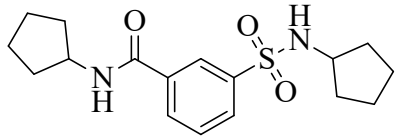


Fig. S-25: GCMS spectrum for compound **4b.**

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



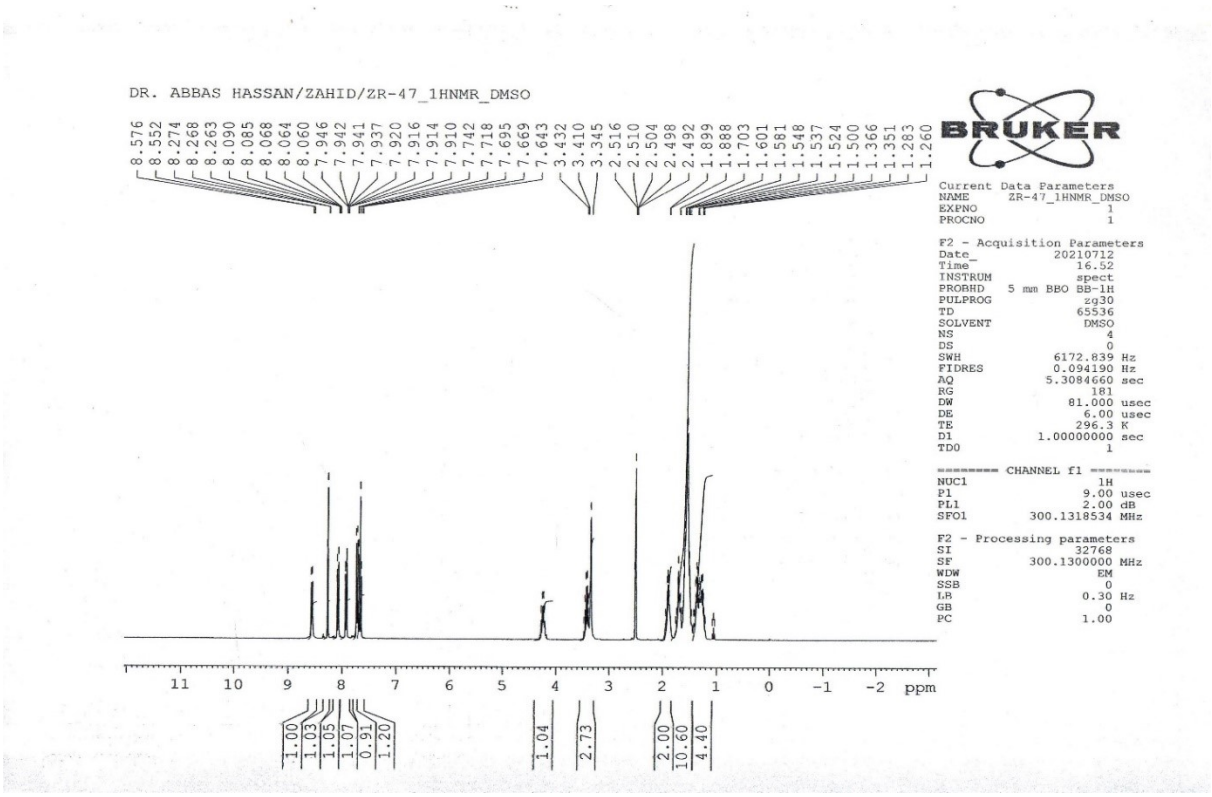
Yield: 70 %; white solid; m.p. : 169-172 ºC; R_f: 0.7 (*n*-hexane: ethyl acetate :: 7:3).

^{1}H NMR (300 MHz, DMSO-d_6): **δ** (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}C NMR (75 MHz, DMSO-d_6): **δ** (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): $[M+H]^+$ calc'd for $C_{17}H_{25}N_2O_3S^+$, 337.4575; found, 341.1168.

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



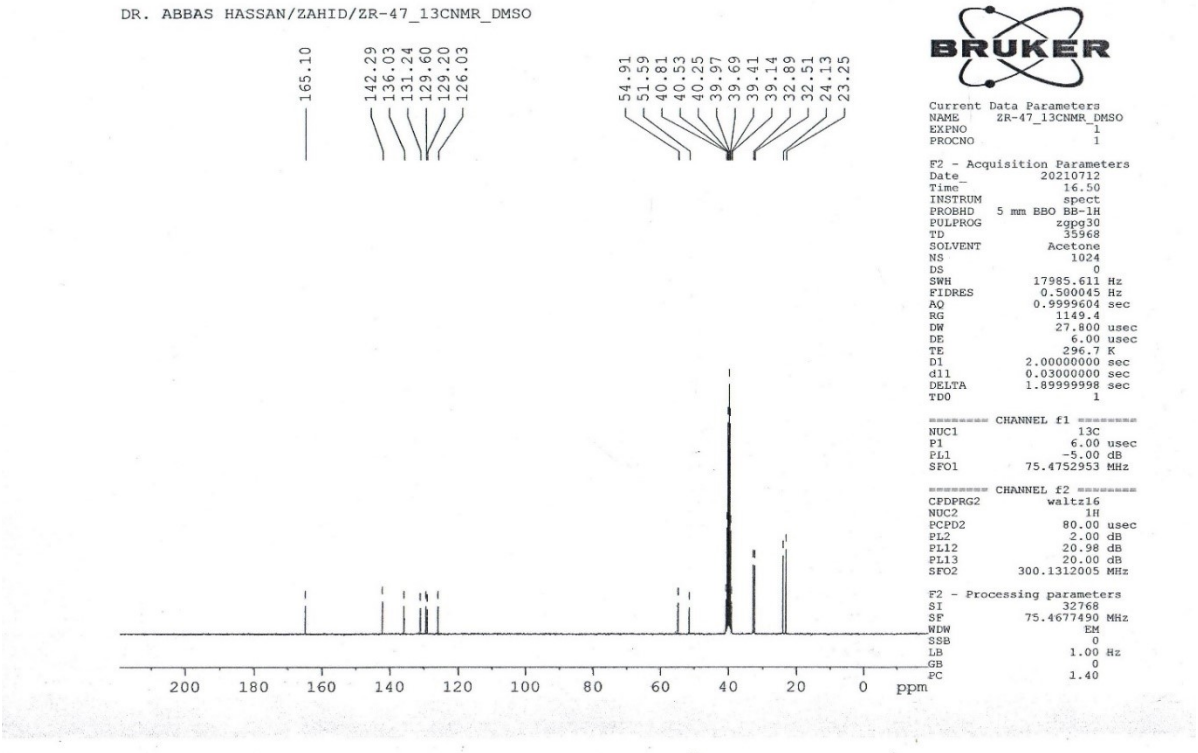


Fig. S-26: ^{1}H and ^{13}C NMR spectra for compound **4c.**

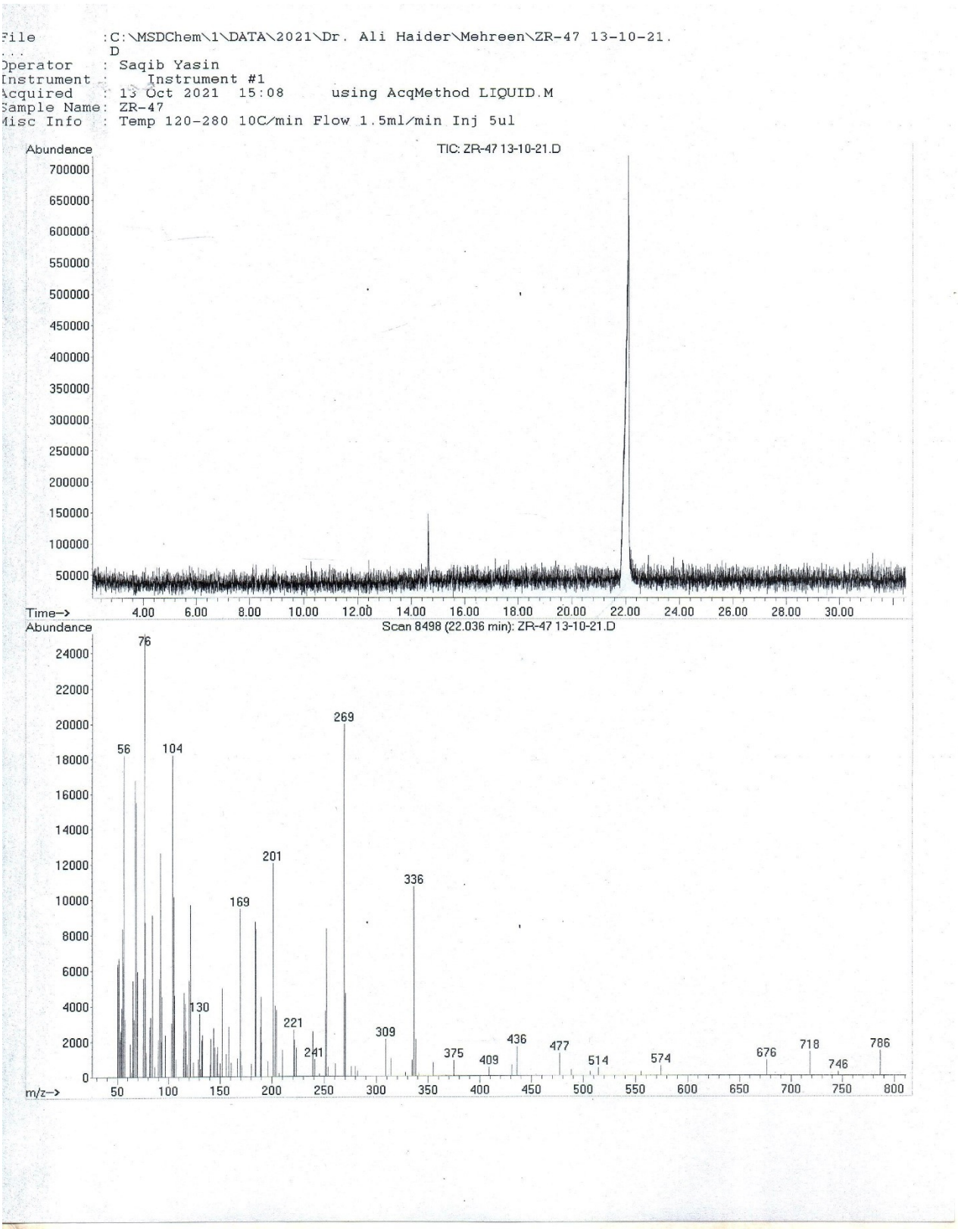
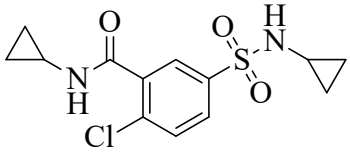


Fig. S-27: ^{1}H and ^{13}C NMR spectra for compound **4c.**

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



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

^{1}H NMR (300 MHz, Acetone-d_6): **δ** (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}C NMR (75 MHz, Acetone-d_6): **δ** (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): $[M+H]^+$ calc'd for $C_{13}H_{16}ClN_2O_3S^+$, 315.0565; found, 315.0569.

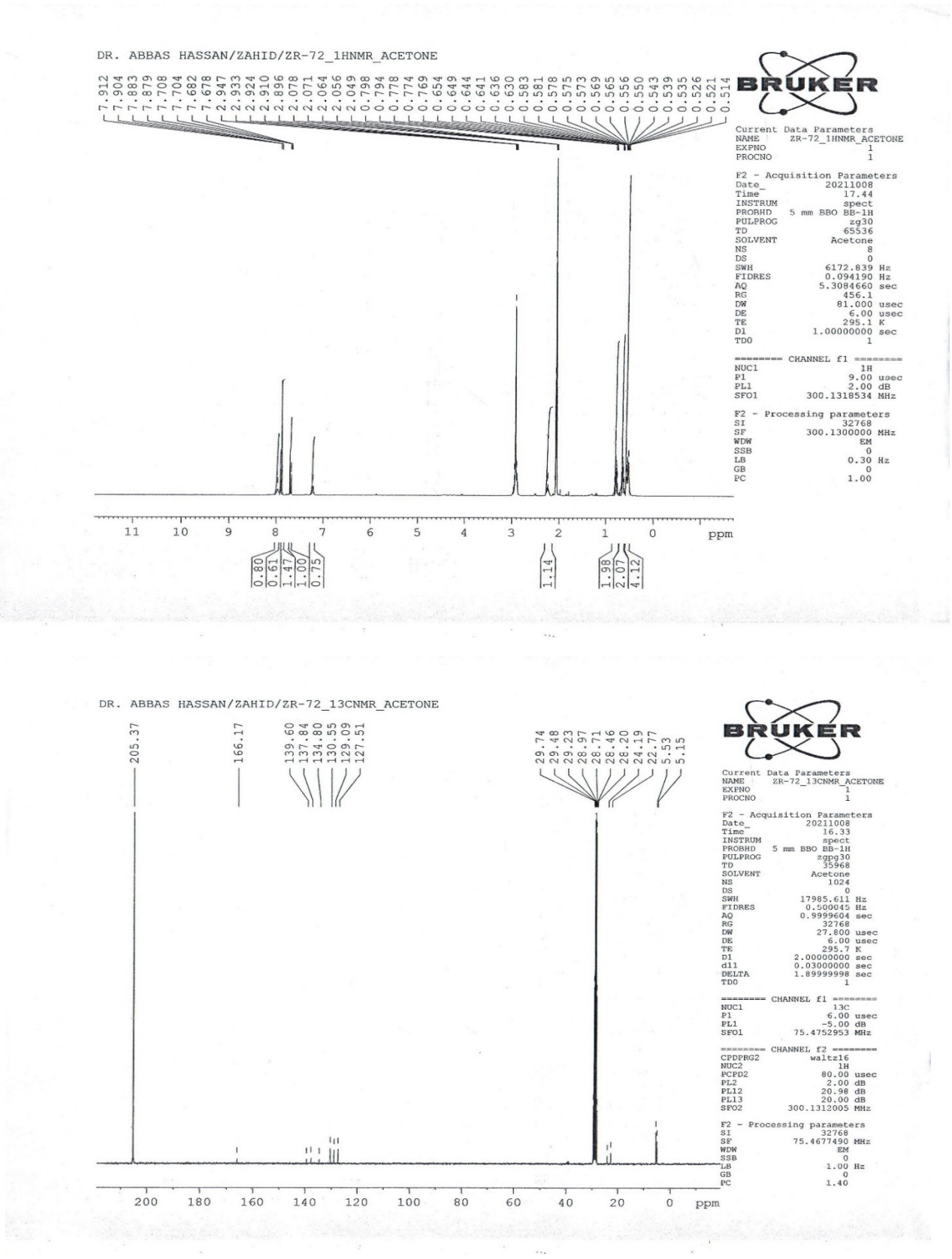
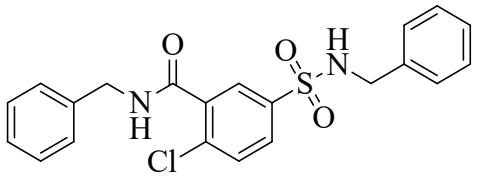


Fig. S-28: ^{1}H and ^{13}C NMR spectra for compound **4d.**

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



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

^{1}H NMR (300 MHz, DMSO-d_6): **δ** (ppm(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}C NMR (75 MHz, DMSO-d_6): **δ** (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): $[M+H]^+$ calc'd for $C_{21}H_{20}ClN_2O_3S^+$, 415.0878; found, 415.0883.

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

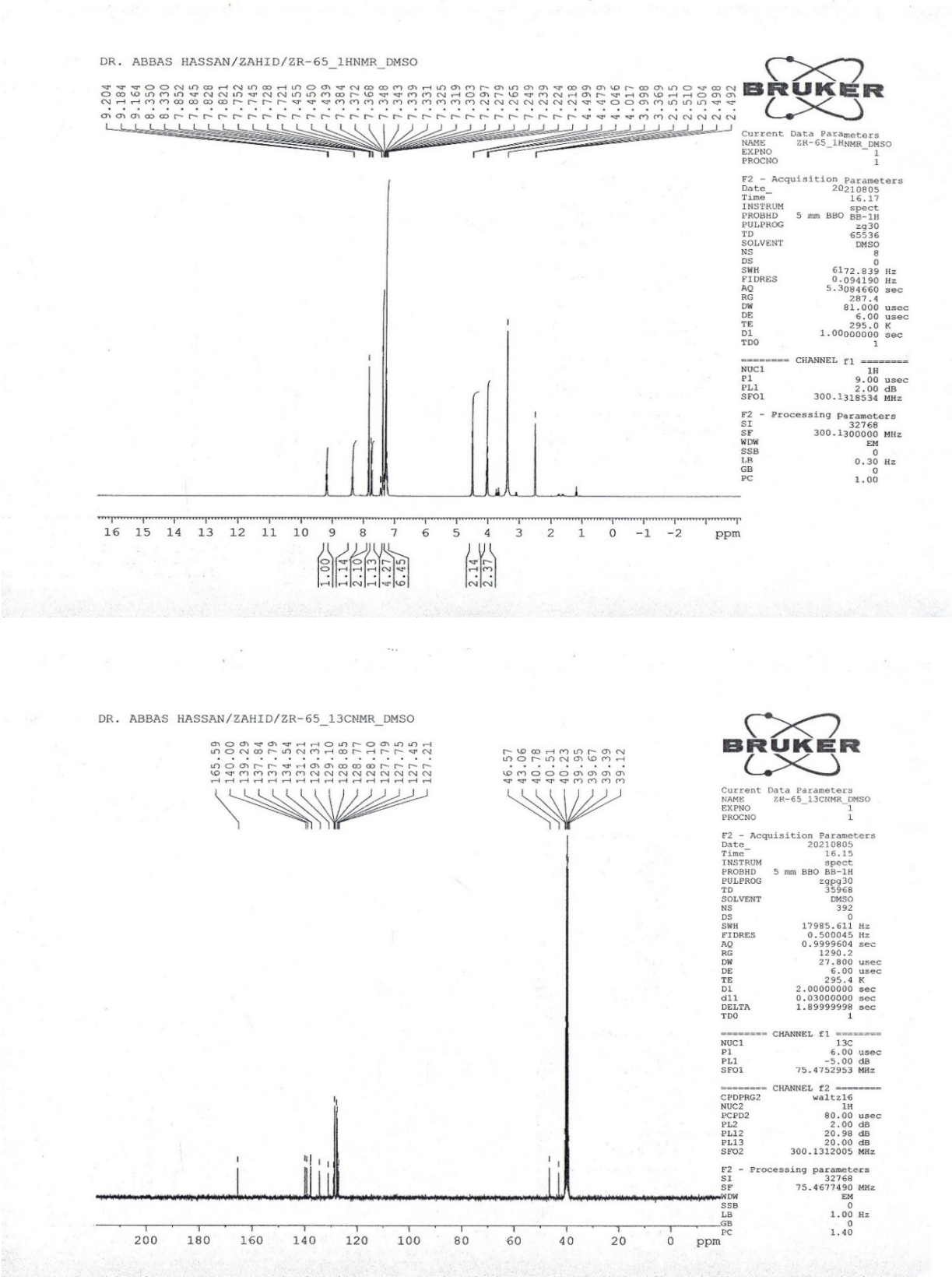


Fig. S-29: ^{1}H and ^{13}C NMR spectra for compound **4e.**

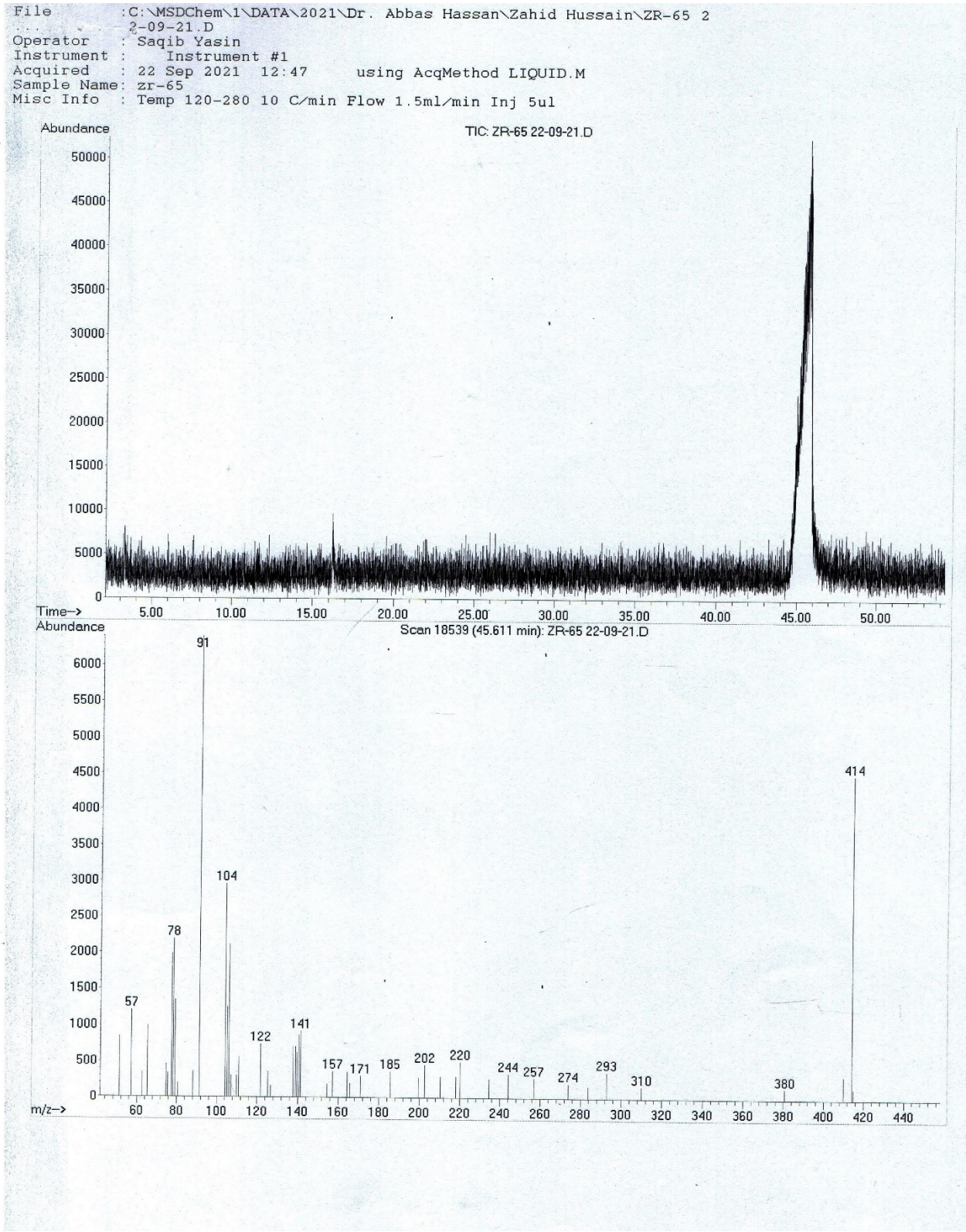


Fig. S-30: GCMS spectrum for compound **4e.**

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.
2. Khanfar, M.A., et al., *Development and characterization of 3-(benzylsulfonamido)benzamides as potent and selective SIRT2 inhibitors.* European Journal of Medicinal Chemistry, 2014. **76**: p. 414-426.
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 avilable 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.
6. Dhimitruka, I.S., *Investigation of the Yamaguchi esterification mechanism. Synthesis of a Lux-S enzyme inhibitor using an improved esterification method. Organic lett.*, 2006. **8**(1): p. 47-50.