Electronic Supplementary Information (ESI)

Mild and convenient one-pot synthesis of 2-amino-1,3,4-thiadiazoles using trimethylsilyl isothiocyanate (TMSNCS)

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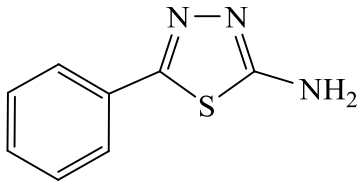
1. General Information

Melting points were determined in open capillaries on a Stuart apparatus and are uncorrected. Reagents and solvents were obtained in the highest available purity and used without further purification unless indicated. The purity of the compounds was checked by TLC (silica gel, ethyl acetate/hexane (1:3)). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX 400 NMR spectrometer in DMSO. Mass spectra were recorded on a low-resolution (Agilent Technologies GC/MS: 6890N, 5973N mass selective detector) EI mass spectrometer. All products **2** were known compounds.

2. Experimental Section

Typical experimental procedure for synthesis of 2-amino-5-substituted-1,3,4-thiadiazole(2a-m): A mixture of acid hydrazide (1.0 mmol) and trimethylsilyl isothiocyanate (1.0 mmol) and ethanol (10 ml) were refluxed for 2-4 h, and then and then reaction mixture was concentrated. After adding 10.0 mL of con. H_2SO_4 the solution was stirred at r.t for 1-2h. It was then cooled and poured into crushed ice. Resultant solid was filtered on a Buchner funnel and dried. Recrystallization of the solid from ethanol afforded pure products **2a-m**.

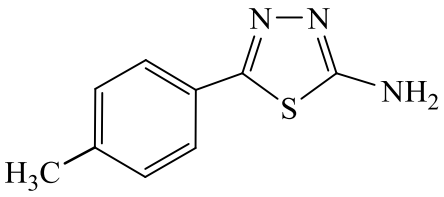
2-Amino-5-phenyl-1,3,4-thiadiazole (2a) [S1]



2a

Compound **2a,** Yield: 87%; White solid; M.p. 222-224 °C. ^{1}H NMR (400 MHz, DMSO): δ = 7.43 (bs, 2H, NH_2) 7.66-7.72 (m, 5H, Ph-H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 126.24, 126.74, 131.44, 149.44 (Aromatic carbons), 156.41 (C-5), 169.09 (C-2) ppm. GC/MS: m/z (%), 177 (M^+, 100), 135 (10), 121 (26), 103 (72), 74 (46), 51 (9).

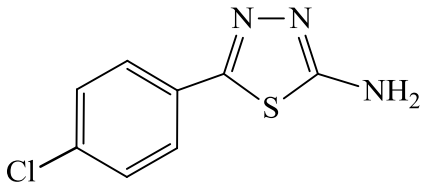
2-Amino-5-(*p*-methylphenyl)-1,3,4-thiadiazole (2b) [S2]



2b

Compound **2b,** Yield: 83%; White solid; M.p. 214-216 °C. ^{1}H NMR (400 MHz, DMSO): δ = 2.38 (s, 3H, Ph-CH_3), 6.94 (bs, 2H, NH_2), 7.28 (d, 2H, Ph-H), 7.72 (d, 2H, Ph-H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 21.28 (CH_3), 121.02, 125.81, 128.91, 139.21 (Aromatic carbons), 158.21 (C-5), 168.23 (C-2) ppm.

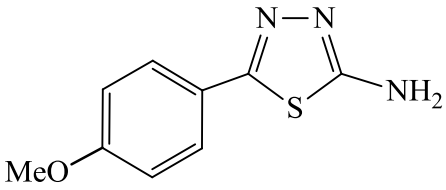
2-Amino-5-(*p*-chlorophenyl)-1,3,4-thiadiazole (2c)[S2]



2c

Compound **2c,** Yield: 85%; White solid; M.p. 233-235 °C. ^{1}H NMR (400 MHz, DMSO): δ = 7.29 (bs, 2H, NH_2), 7.51 (d, 2H, Ph-H), 7.78 (d, 2H, Ph-H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 128.62, 128.86, 129.77, 131.40 (Aromatic carbons), 155.18 (C-5), 169.82 (C-2) ppm. GC/MS: m/z (%), 211 (M^+, 100), 155 (29), 138 (25), 111 (14), 74 (78), 60 (9).

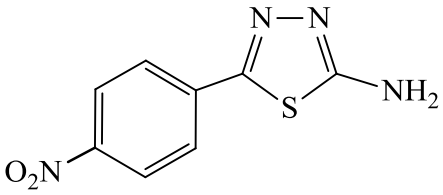
2-Amino-5-(*p*-methoxyphenyl)-1,3,4-thiadiazole (2d) [S2]



2d

Compound **2d,** Yield: 83%; Brown solid; M.p. 210-212 °C. ^{1}H NMR (400 MHz, DMSO): δ = 3.84 (s, 3H, OCH_3) 7.13 (d, 2H, Ph-H), 7.72 (d, 2H, Ph-H), 8.91 (bs, 2H, NH_2) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 56.21 (OCH_3), 114.13, 118.33, 128.25, 149.23 (Aromatic carbons), 160.58 (C-5), 167.24 (C-2) ppm.

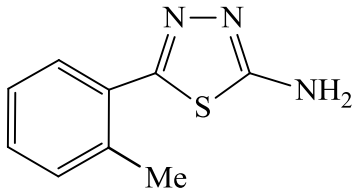
2-Amino-5-(*p*-nitrophenyl)-1,3,4-thiadiazole (2e) [S2]



2e

Compound **2e,** Yield 80%; Yellow solid; M.p. 227-228 °C. ^{1}H NMR (400 MHz, DMSO): δ = 8.04 (d, 2H, Ph-H), 8.30 (d, 2H, Ph-H), 8.65 (bs, 2H, NH_2) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 124.91, 128.08, 135.60, 148.61 (Aromatic carbons), 154.41 (C-5), 170.49 (C-2) ppm.

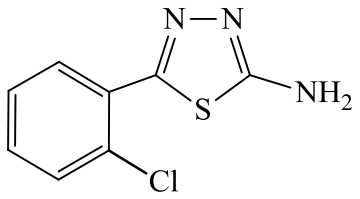
2-Amino-5-(*o*-methylphenyl)-1,3,4-thiadiazole (2f) [S2]



2f

Compound **2f,** Yield: 76%; White solid; M.p. 208-209 °C. ^{1}H NMR (400 MHz, DMSO): δ = 2.31 (s, 3H, Ph-CH_3), 6.78 (bs, 2H, NH_2), 7.28-7.41 (m, 4H, Ph-H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 20.91 (CH_3), 123.42, 124.92, 128.38, 130.91, 132.43, 136.34 (Aromatic carbons), 156.21 (C-5), 168.93 (C-2) ppm.

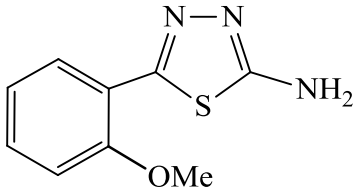
2-Amino-5- (*o*-chlorophenyl)-1,3,4-thiadiazole (2g)[S2]



2g

Compound **2g,** Yield: 78%; White solid; M.p. 202-204 °C. ^{1}H NMR (400 MHz, DMSO): δ = 5.82 (bs, 2H, NH_2), 7.48-7.56 (m, 2H, Ph-H), 7.64 (d, 1H, Ph-H), 7.98 (d, 1H, Ph-H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 128.11, 128.40, 130.78, 130.95, 131.45, 132.30 (Aromatic carbons), 152.32 (C-5), 170.34 (C-2) ppm.

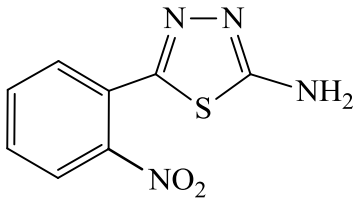
2-Amino-5-(*o*-methoxyphenyl)-1,3,4-thiadiazole (2h) [S3]



2h

Compound **2h,** Yield: 74%; White solid; M.p. 204-206 °C. ^{1}H NMR (400 MHz, DMSO): δ = 4.00 (s, 3H, OCH_3), 7.26 (d, 1H, Ph-H), 7.77 (d, 1H, Ph-H), 7.79 (d, 1H, Ph-H), 8.29 (d, 1H, Ph-H), 9.35 (bs, 2H, NH_2) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 57.20 (OCH_3), 112.59, 116.01, 124.57, 130.91, 141.99, 150.91 (Aromatic carbons), 156.24 (C-2), 169.83 (C-2) ppm.

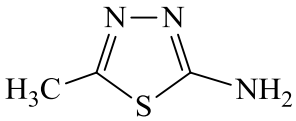
2-Amino-5-(*o*-nitrophenyl)- 1,3,4-thiadiazole (2i)[S4]



2i

Compound **2i,** Yield: 72%; Pale yellow solid; M.p. 230-232 °C. ^{1}H NMR (400 MHz, DMSO): δ = 7.11 (bs, 2H, NH_2), 7.32-7.46 (m, 4H, Ph-H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 122.31, 126.08, 128.93, 131.14, 133.16, 144.73 (Aromatic carbons), 158.63 (C-5), 166.83 (C-2) ppm.

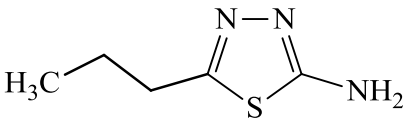
2-Amino-5-methyl -1,3,4-thiadiazole (2j)[S5]



2j

Compound **2j,** Yield: 74%; White solid; M.p. 206-208 °C. ^{1}H NMR (400 MHz, DMSO): δ = 2.49 (s, 3H, CH_3). 7.08 (bs, 2H, NH_2) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 14.81 (CH_3), 148.37 (C-5), 161.93 (C-2) ppm.

2-Amino-5-propyl-1,3,4-thiadiazole (2k)[S6]

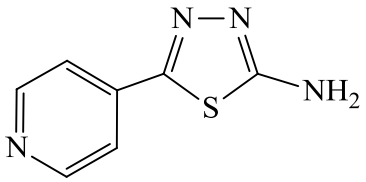


2k

Compound **2k,** Yield: 72%; White solid; M.p. 203-205°C. ^{1}H NMR (400 MHz, DMSO): δ = 0.94 (t, 3H, CH_3), 1.48-1.56 (q, 2H, CH_2) 2.38 (t, 2H, CH_2), 6.94 (bs, 2H, NH_2) ppm. ^{13}C NMR

(100 MHz, DMSO): δ = 12.43 (CH_3), 19.34 (CH_2), 25.96 (CH_2), 152.38 (C-5), 170.42 (C-2) ppm.

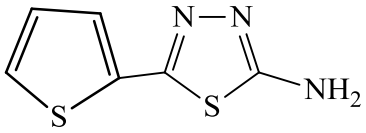
2-Amino-5-(pyridin-4-yl)-1,3,4-thiadiazole (2l) [S7]



2l

Compound **2l,** Yield: 83%; Pale yellow solid; M.p. 240-242°C. ^{1}H NMR (400 MHz, DMSO): δ = 7.24 (bs, 2H, NH_2), 7.85 (d, 2H, Py-H), 8.44 (s, 2H, Py-H). ^{13}C NMR (100 MHz, DMSO): δ = 119.28, 129.46, 144.34 (Pyridine carbons), 158.42 (C-5), 169.21 (C-2) ppm.

2-Amino-5-(thiophen-2-yl)- 1,3,4-thiadiazole (2m)[S8]



2m

Compound **2m,** Yield: 85%; Brown solid; M.p. 202-203°C. ^{1}H NMR (400 MHz, DMSO): δ = 6.65 (bs, 2H, NH_2), 7.11 (t, 1H, Th-H), 7.66 (d, 1H, Th-H), 7.76 (d, 1H, Th-H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 125.54, 127.09, 127.78, 128.93 (Thiophene carbons), 156.89 (C-5), 170.22 (C-2) ppm. GC/MS: m/z (%), 183 (M^+, 100), 127 (25), 110 (20), 74 (31), 69 (15), 60 (7).

References

S1 G. Peng, Feng'e Sun, H. Xuben , W. Feng, Y. Fan, X. Wenfang and F. Hao, *Bioorg. Med. Chem.*, 2012, **20**, 3865.

S2 P. Mullick, S. A. Khan, S. Verma, and O. Alam, *Bull. Korean Chem. Soc.* 2011, **32**, 1011.

S3 X. C. Wang, X. M. Ding, S. Q. Wang, X. F. Chen and Z. J. Quan, *Chinese Chem. Lett.* 2010, **21** 301.

S4 A. G. Shankar and A. R. Kallanagouda, *Med. Chem. Res.* 2012, **21**, 816.

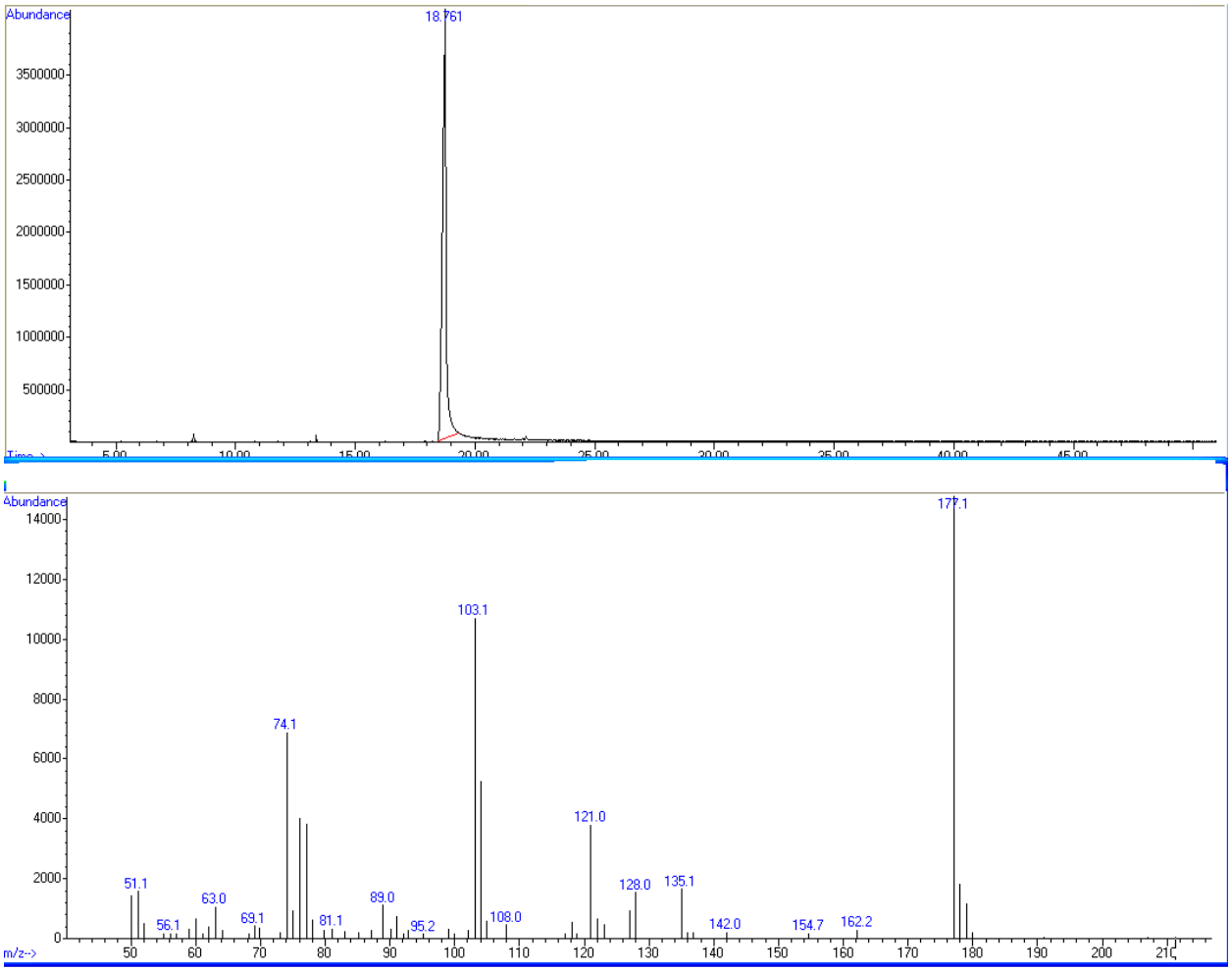
S5 S. Ferrari, F. Morandi, D. Motiejunas, E. Nerini, S. H, R Luciani, A. Venturelli, S. Lazzari, S. Calo, S.Gupta, V. Hannaert, P. A. M. Michels, R. C. Wade and M. P. Costi, *J. Med. Chem.* 2011, **54**, 211.

S6 M. Palomar-Pardavé, M. Romero-Romo, H. Herrera-Hernández, M. A. Abreu-Quijano, N. V. Likhanova, J. Uruchurtu and J. M. Juárez-García, *Corrosion Sci.* 2012, **54**, 231.

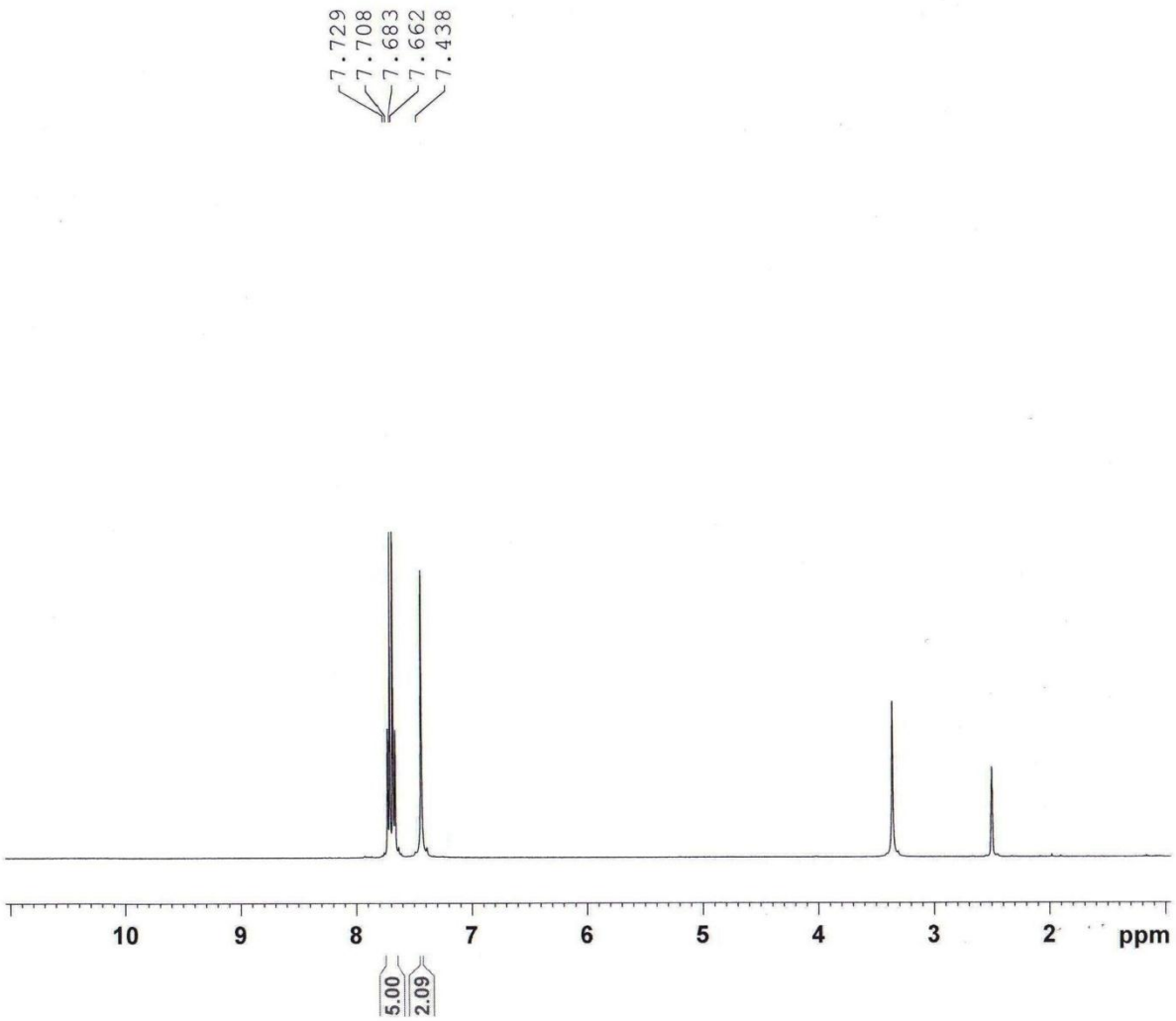
S7 B. P. Manishkumar, R. M. Nishith, P. R. Jignesh and K. M. Shobhana, *Org. Biomol. Chem*., 2012, **10**, 1785.

S8 N. S. Begum, D. E. Vasundhara, C. R. Girija, G. D. Kolavi, V. S. Hegde and I. M. Khazi, *J. Chem. Crystallogr*, 2007, **37**, 561.

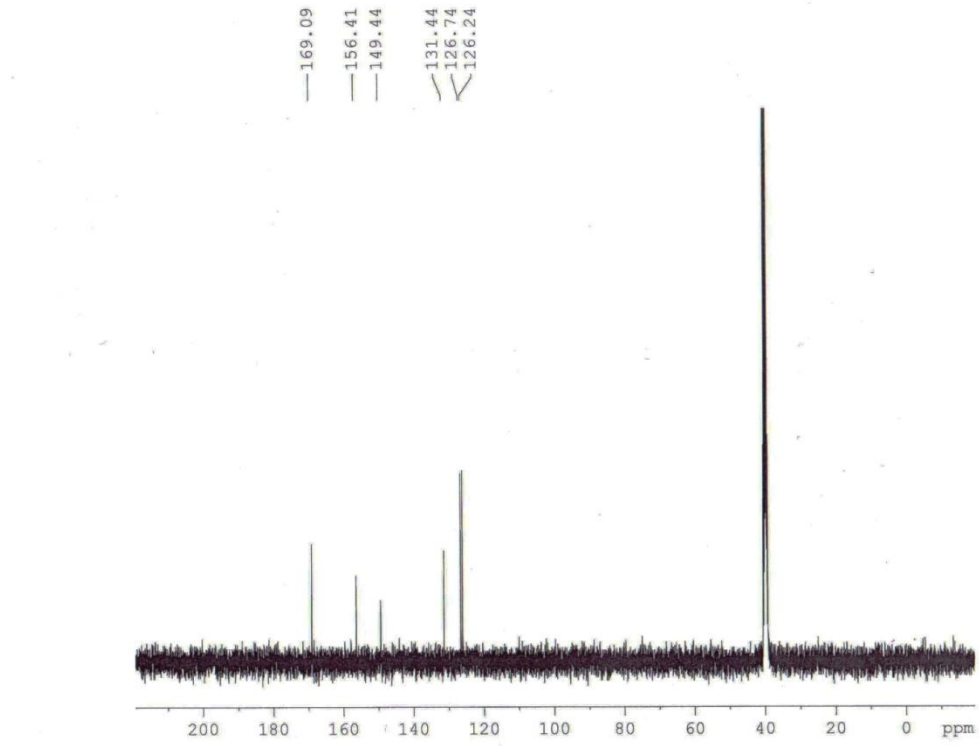
Spectra of Compound 2a-m



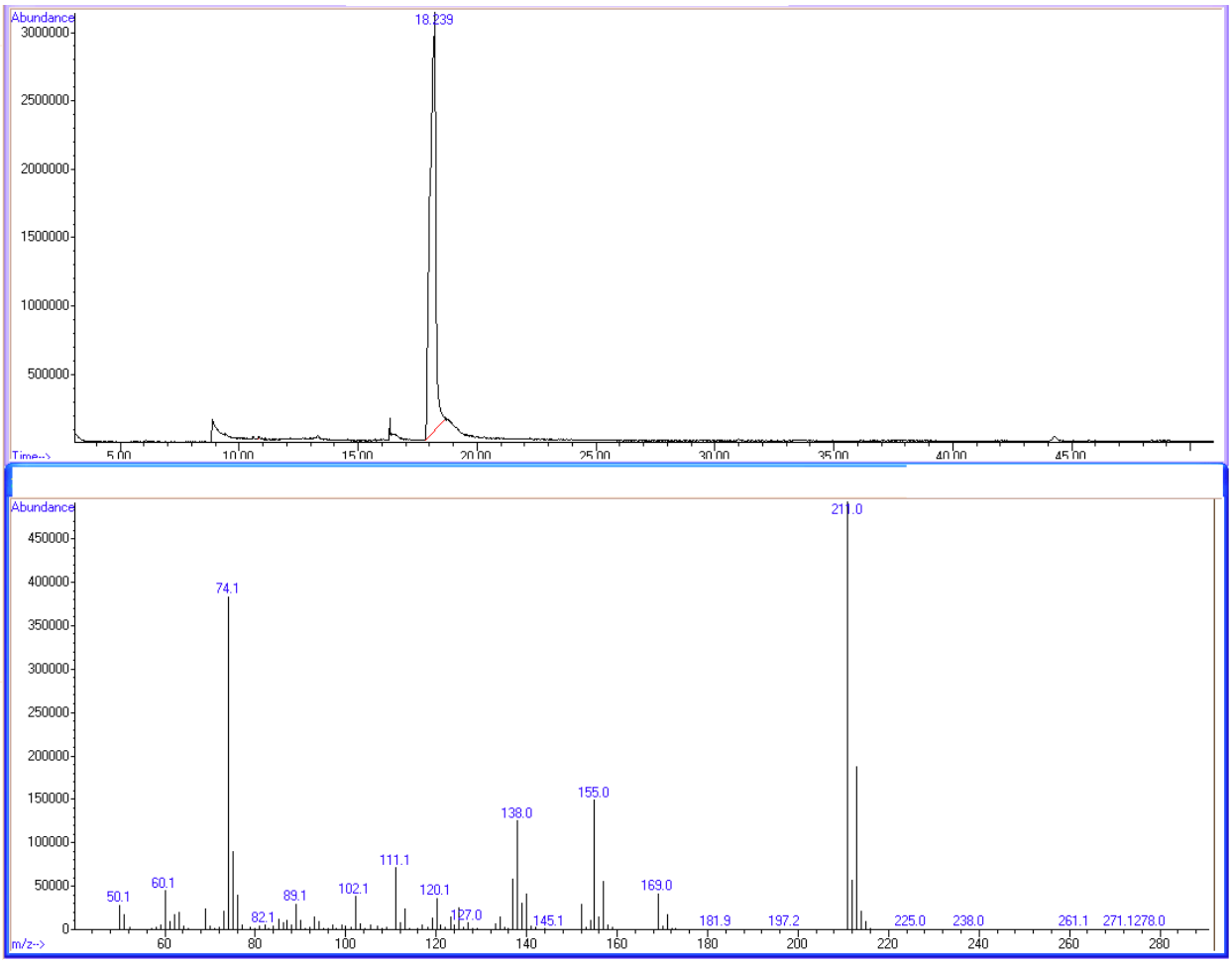
GC / MS of **2a**



^{1}H NMR of **2a**



^{13}C NMR of **2a**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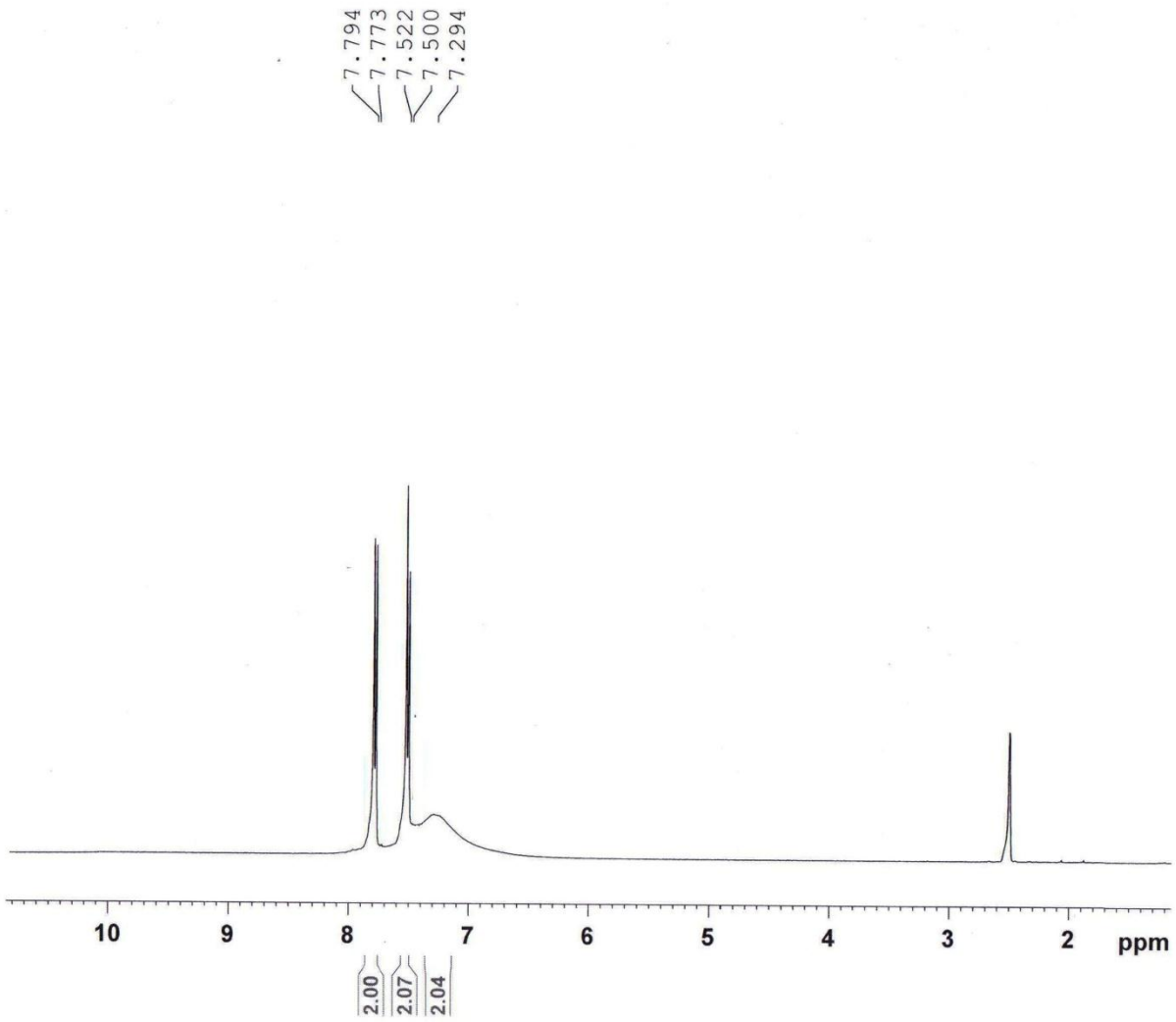
m/z-->

GC-MS of **2c**



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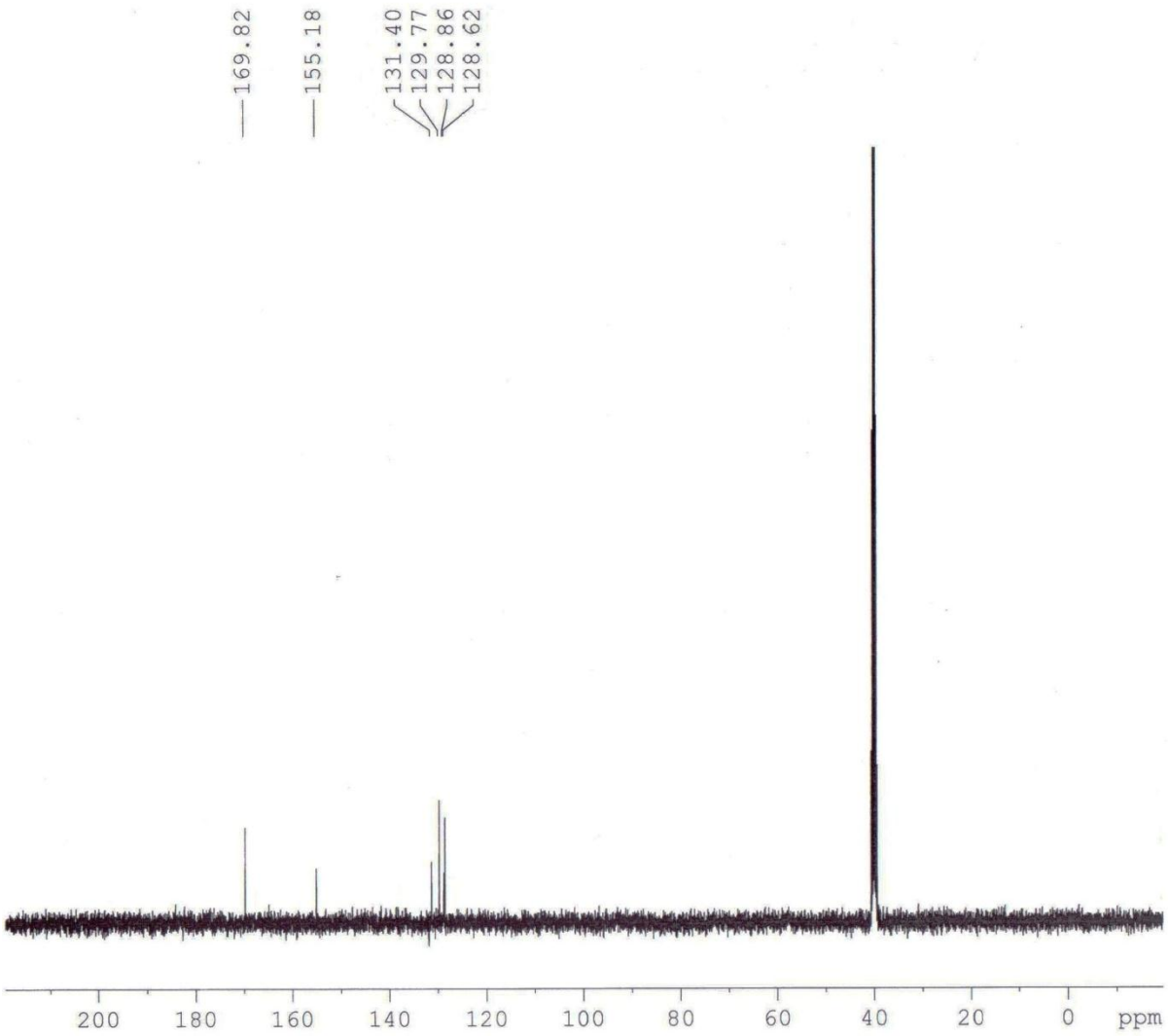
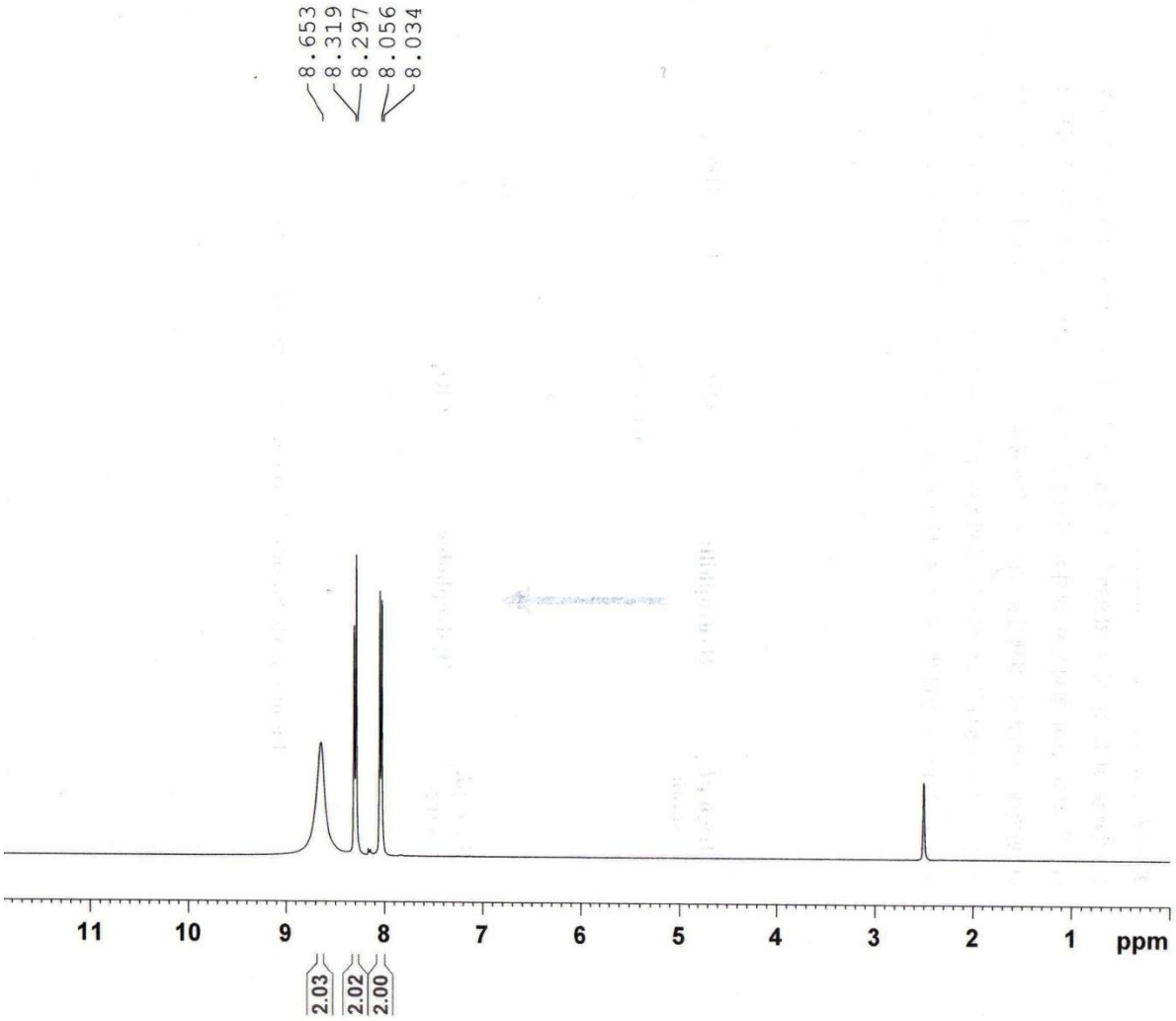


^{13}C NMR of **2c**



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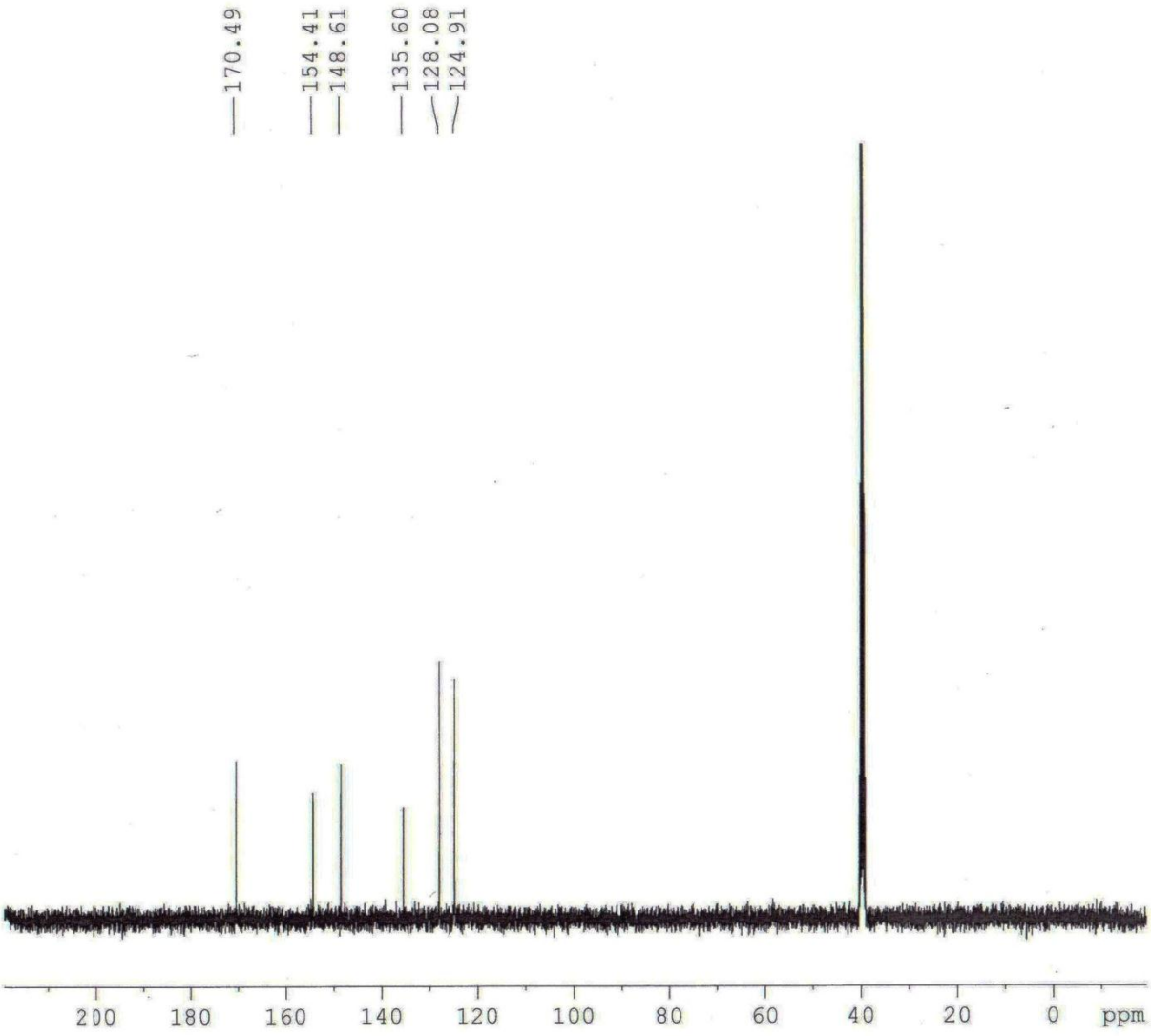

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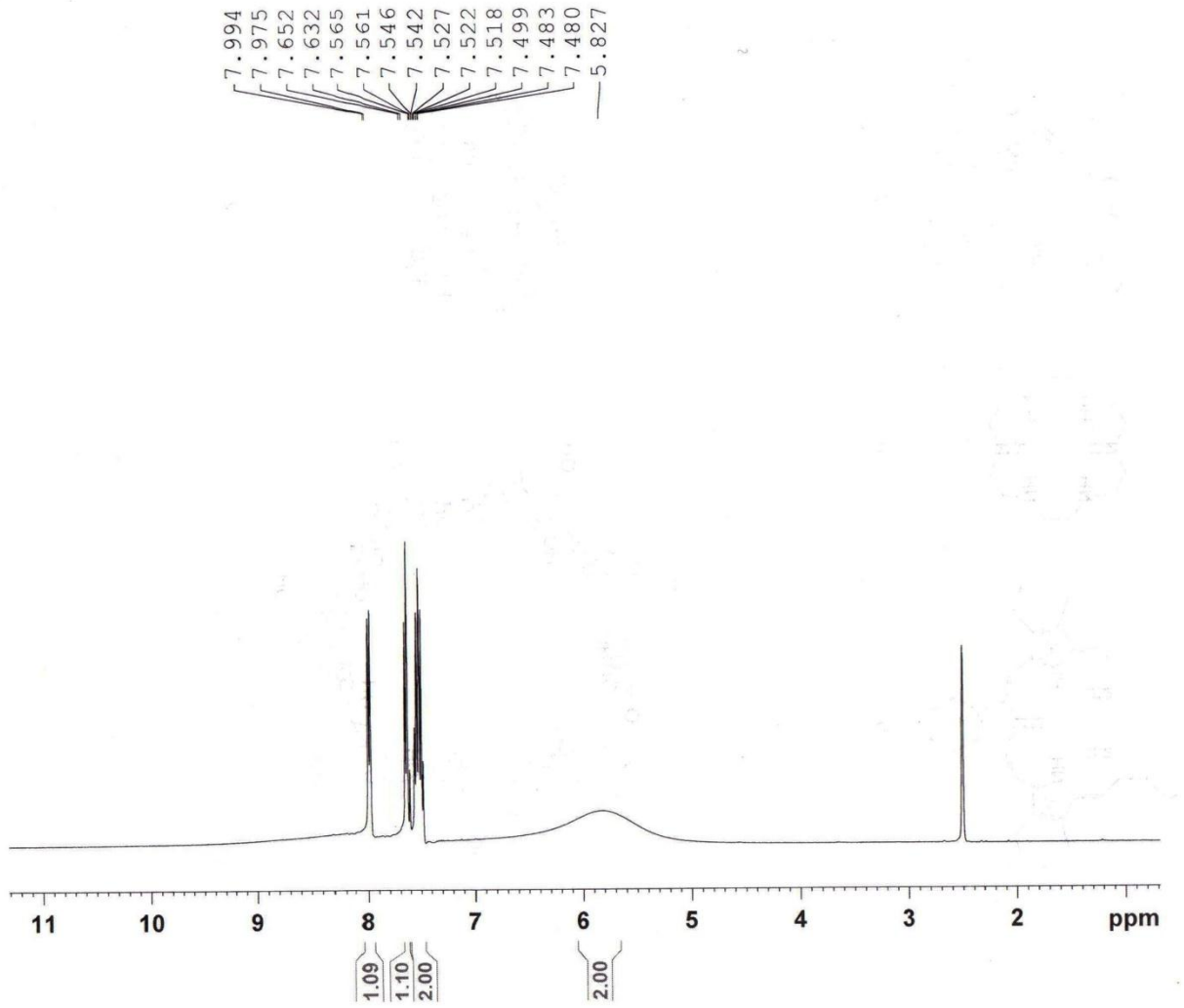
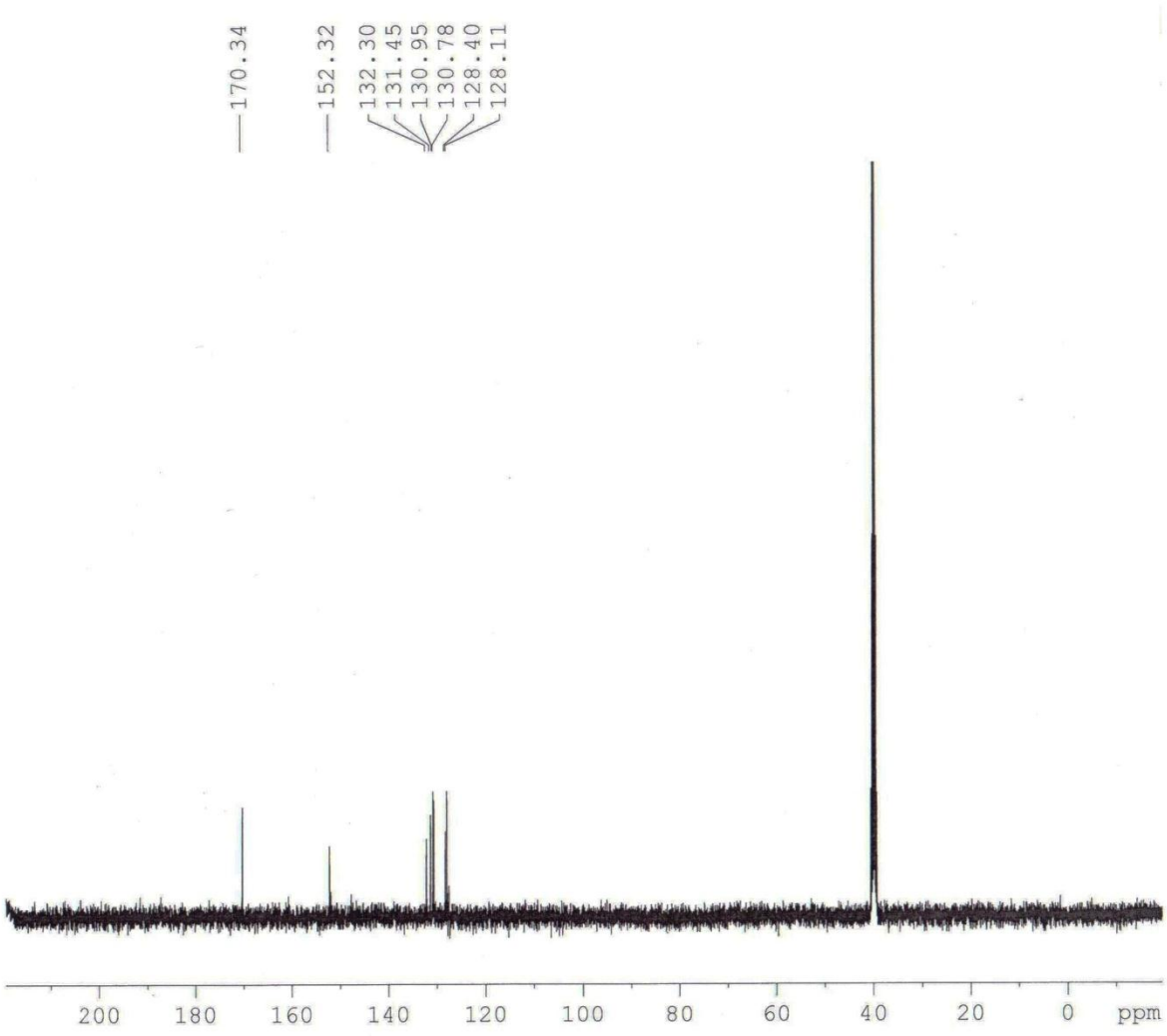


^{1}H NMR of **2g**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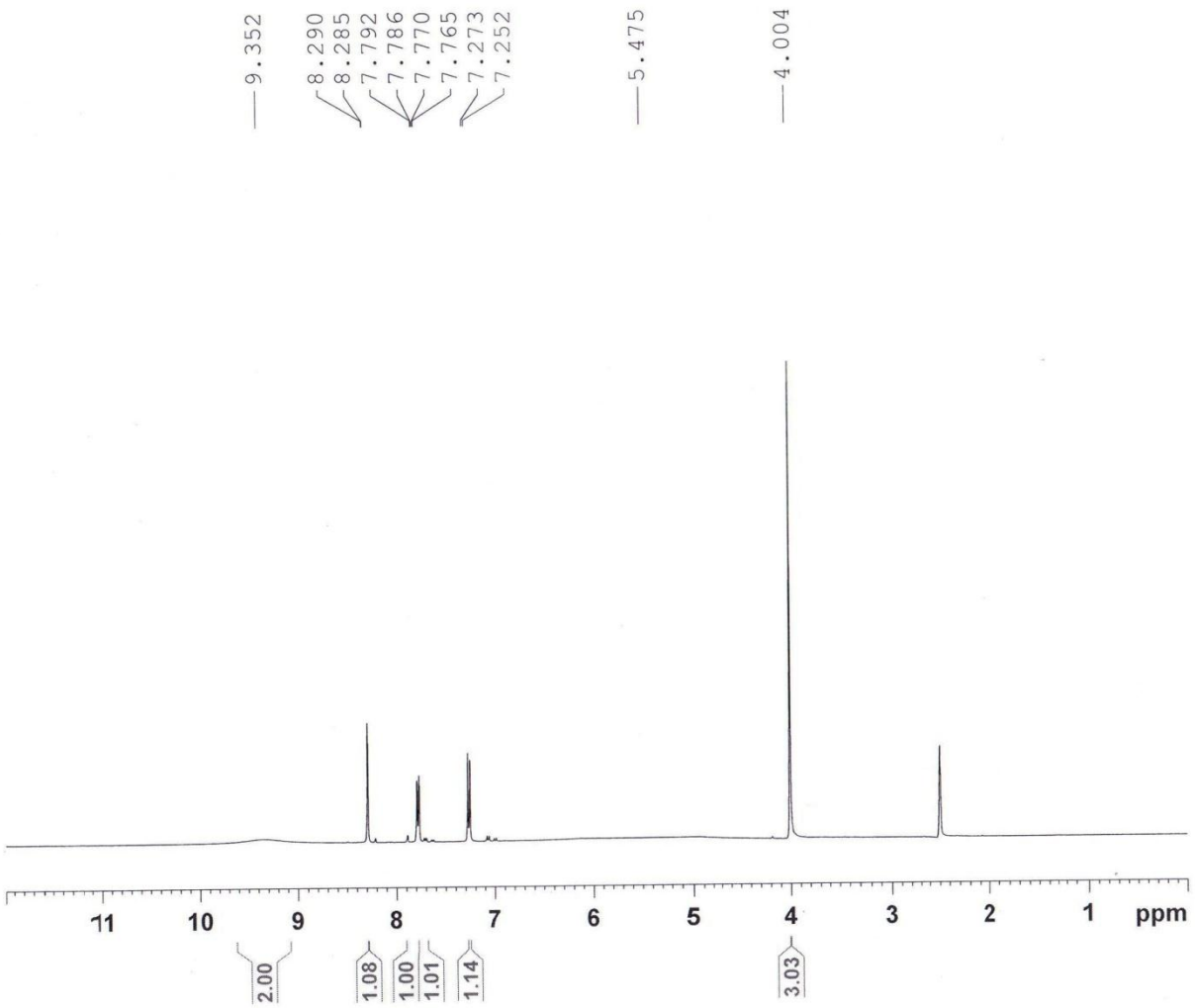
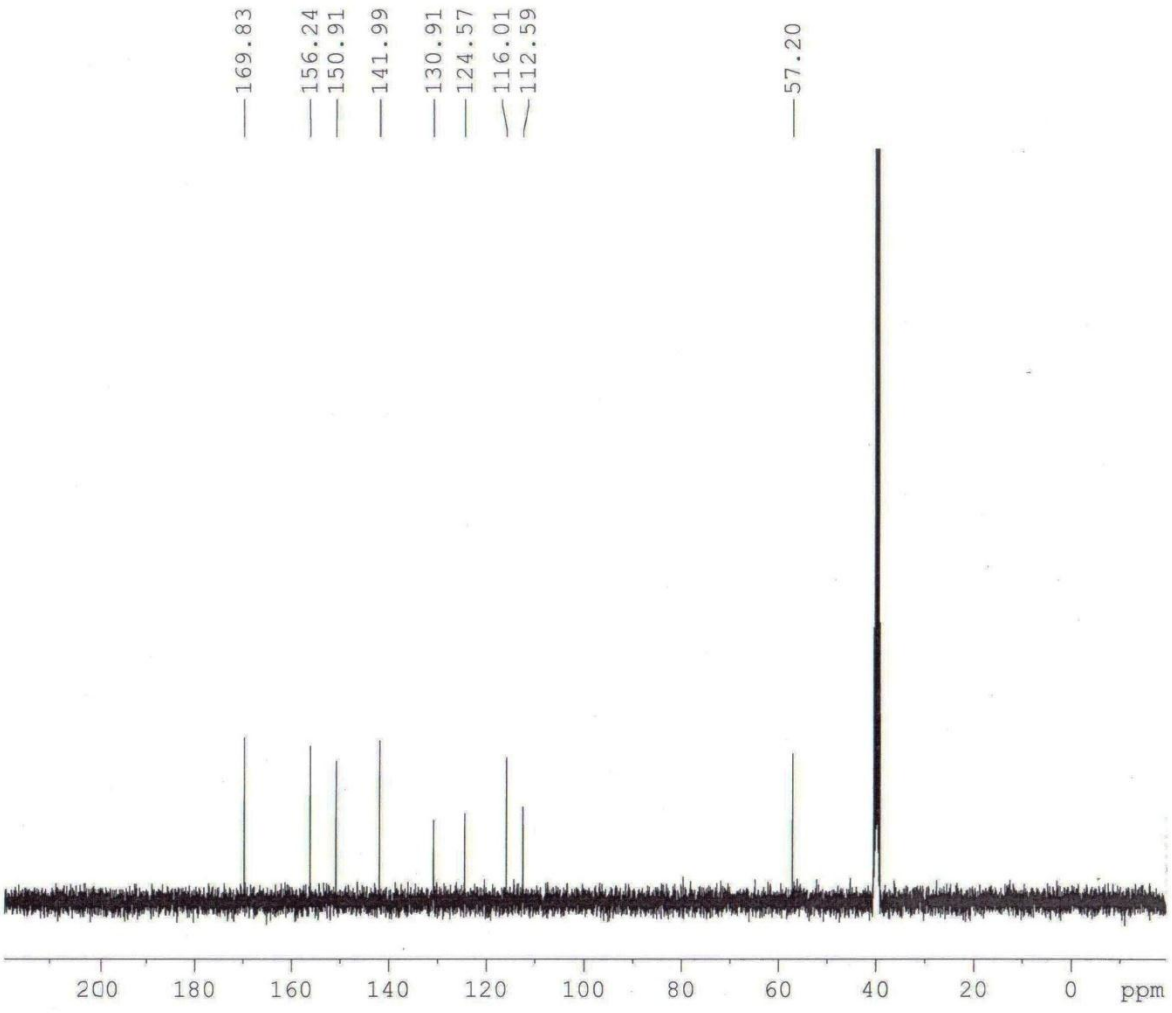
ppm

^{13}C NMR of **2g**



^{1}H NMR of **2h**



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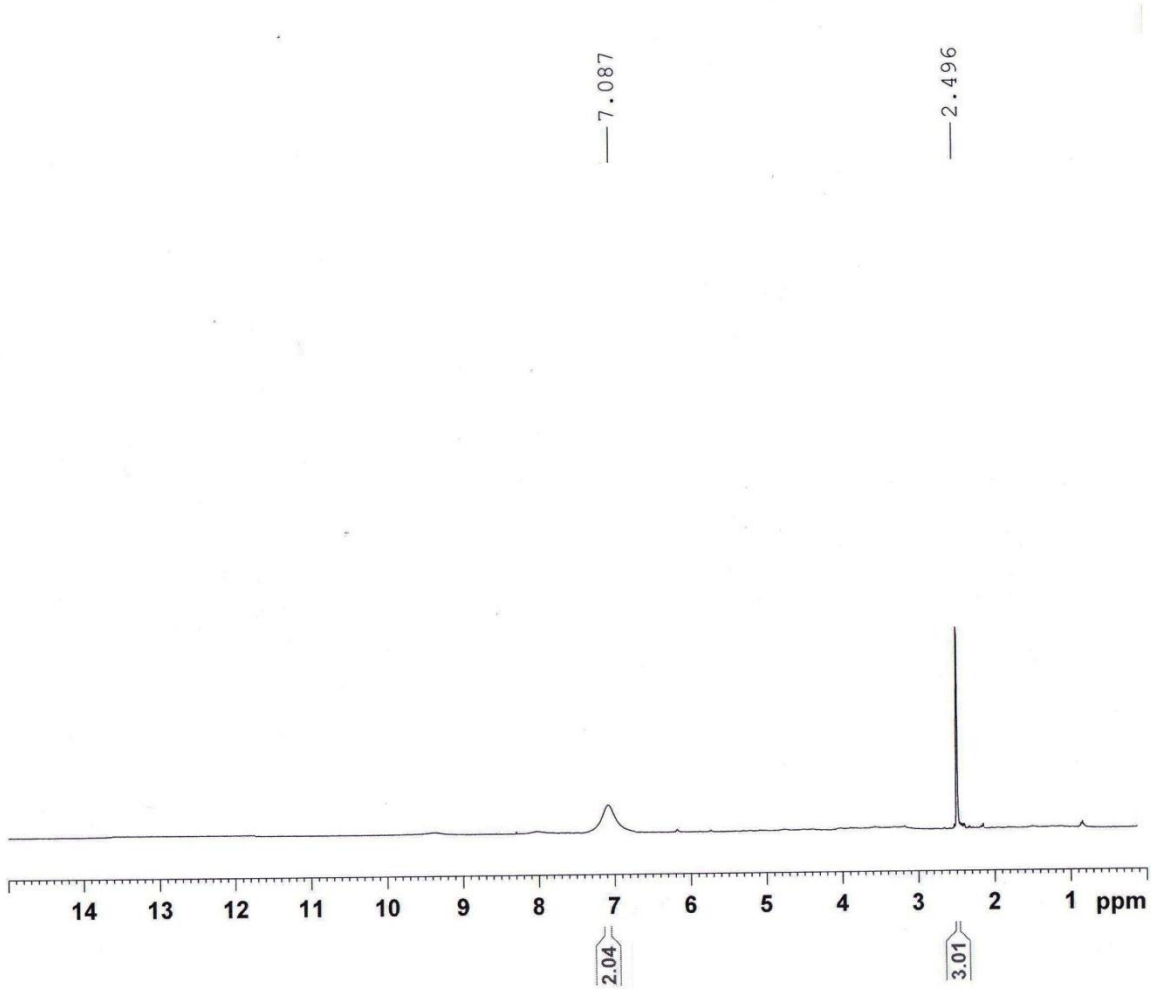
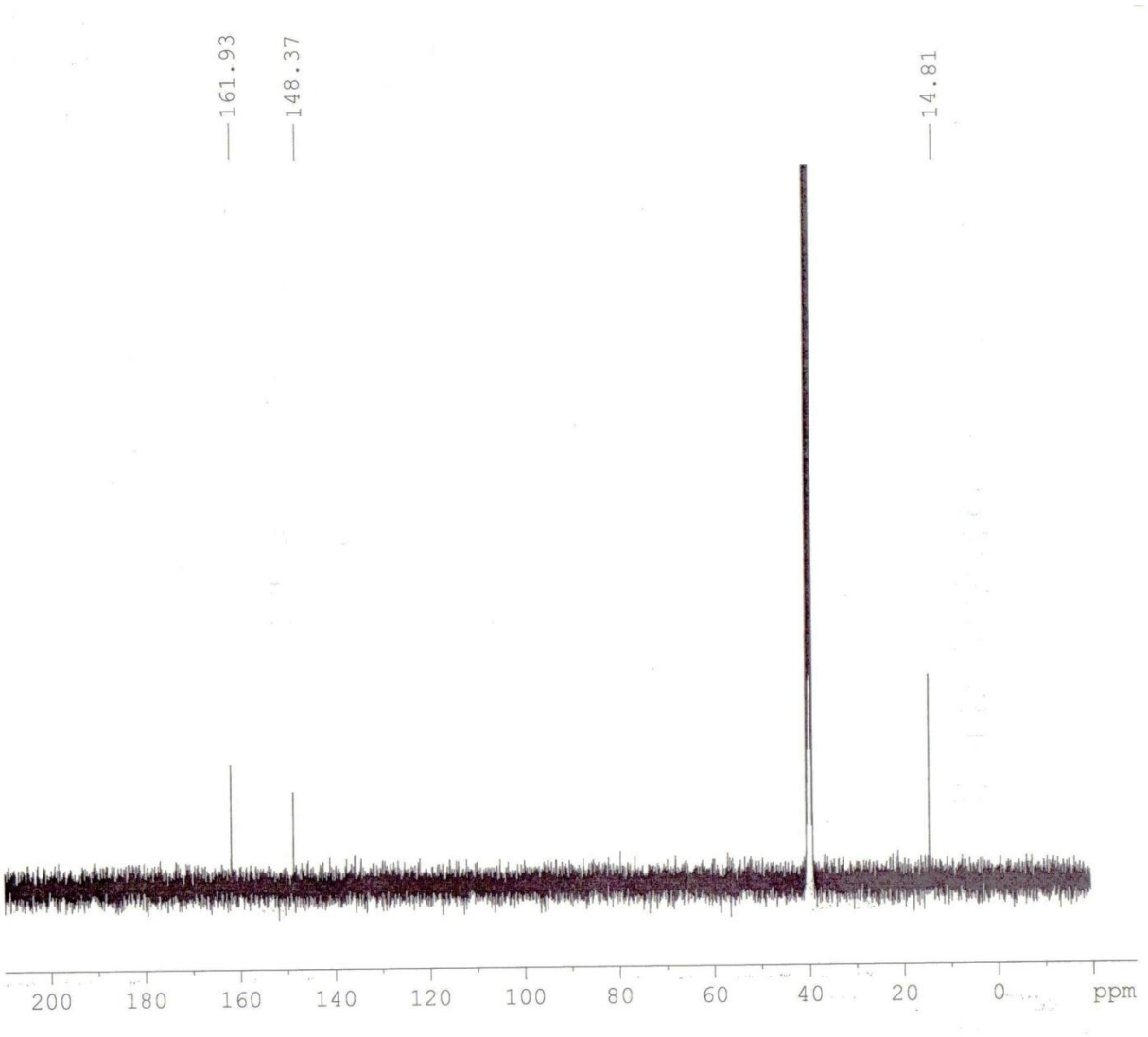


^{1}H NMR of **2j**



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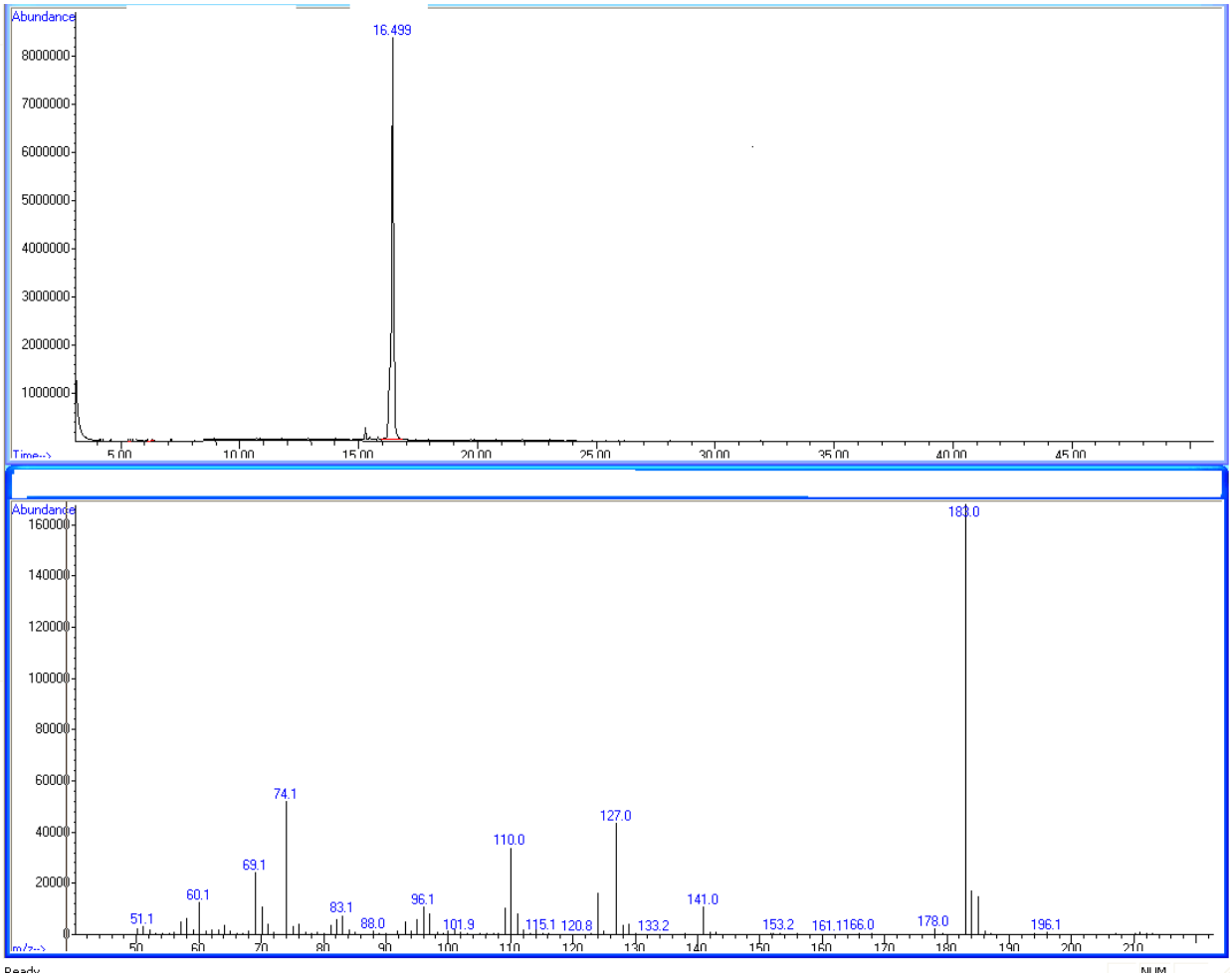
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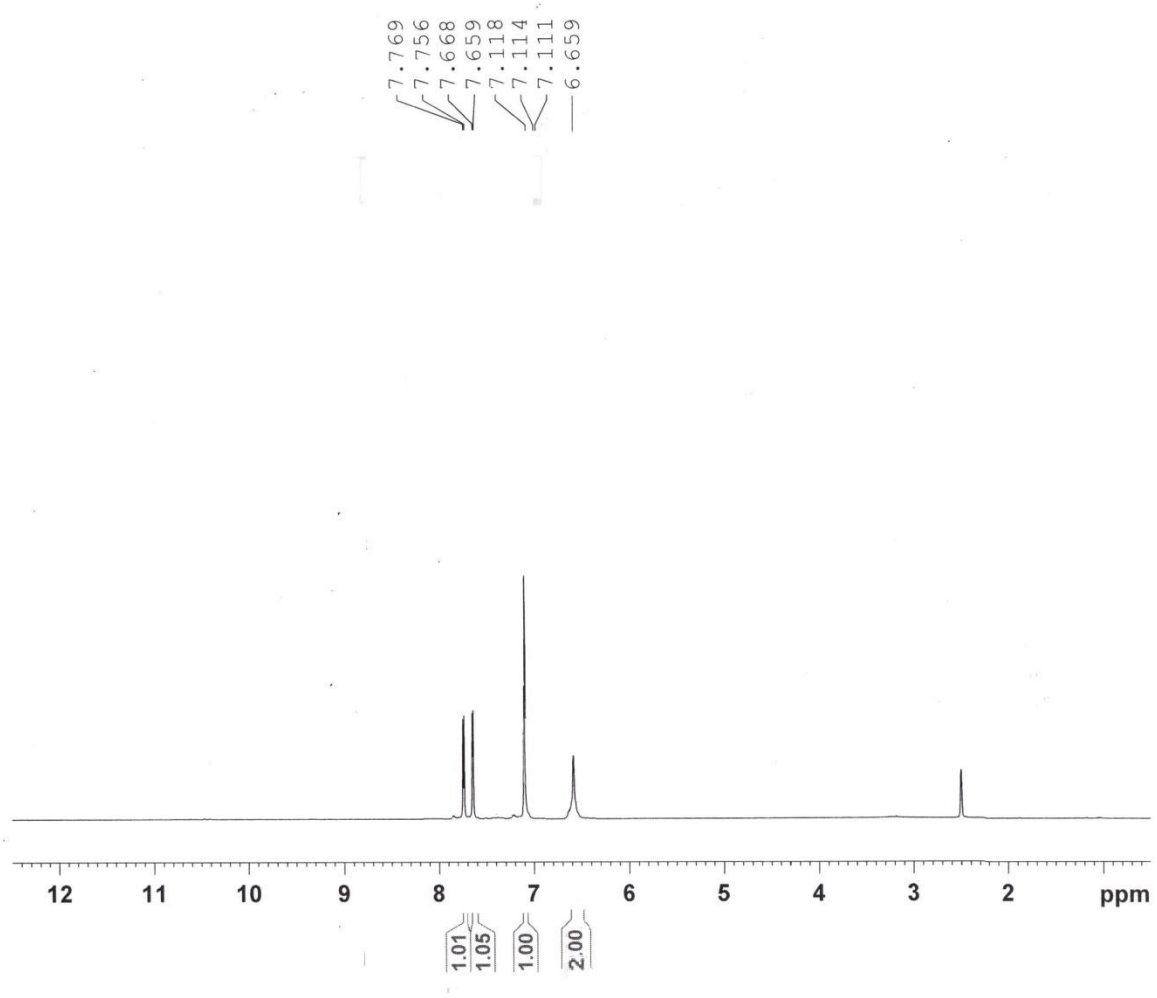
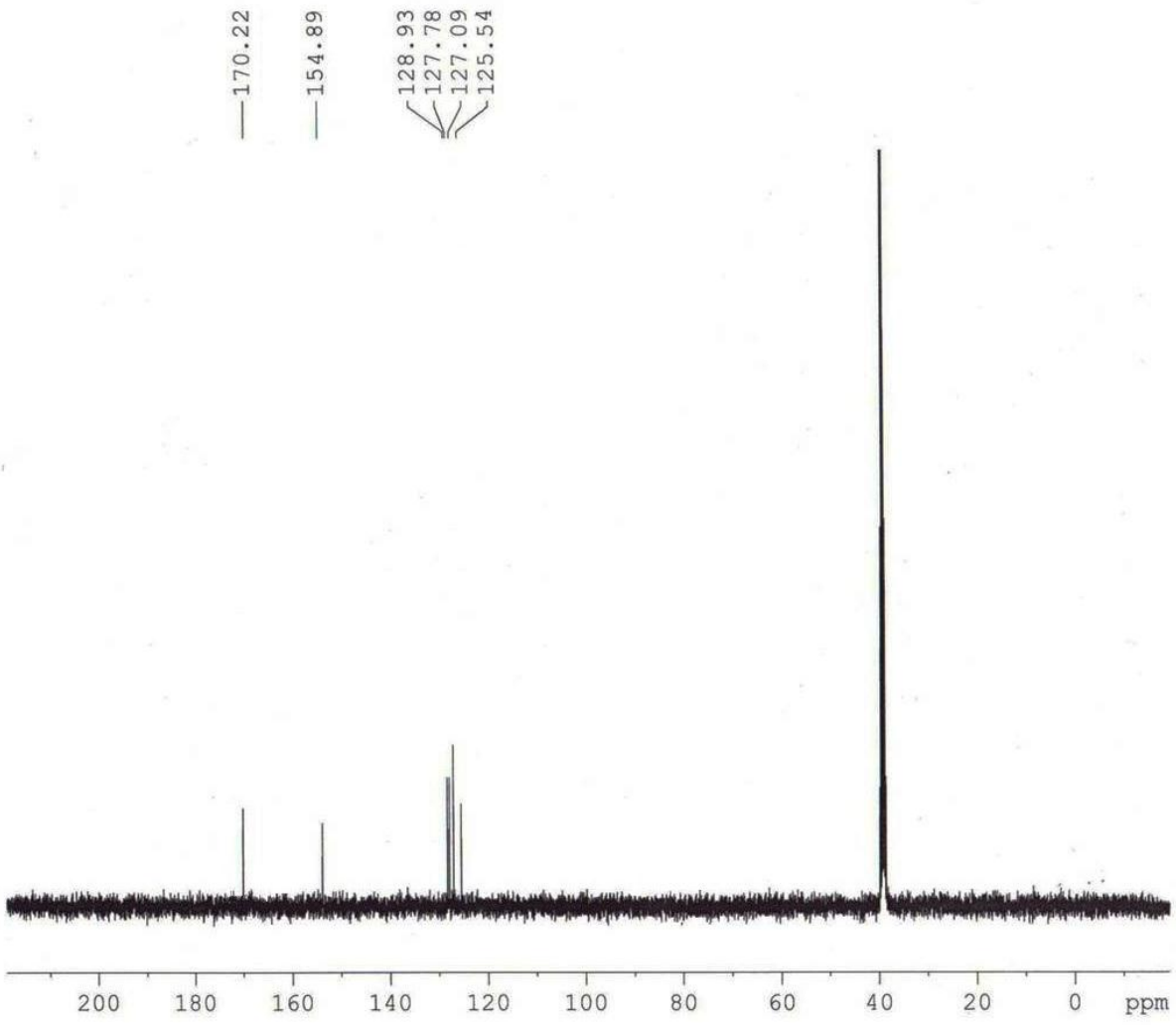
GC-MS of **2m**



^{1}H NMR of 2m



^{13}C NMR of 2m