**Copper catalyzed aryl amidation between Nα-Fmoc-protected amino acid azides and aryl boronic acids**

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**Experimental procedures**

**General information**

All chemicals were used as obtained from Sigma Aldrich Company, USA. All the solvents were dried and purified using recommended procedures in the literature whenever necessary. ESI mass spectra were recorded on a Micromass Q-TOF micromass spectrometer. 1H NMR and 13C NMR spectra were recorded on Bruker AV NMR 400 MHz and 100 MHz spectrometers, respectively, at the Indian Institute of Science, Bangalore. The RP-HPLC analysis of isomers was carried out by using an Agilent instrument at λ = 254 nm; flow rate: 0.5 mL/min; column: Phenomenex Lux Amylose-2, pore size-5 μm, diameter × length = 4.6 × 250 mm; method: gradient 0.1% TFA water-acetonitrile; Flow rate: 0.5 mL/min in 20 min. TLC experiments were performed using MERCK TLC aluminum sheets (silica gel 60 F254) and chromatograms were visualized by exposing in an iodine chamber or to a UV-lamp. Column chromatography was performed on silica gel (100–200 mesh) using ethyl acetate and hexane as the eluent.

**General procedure for the amidation reaction**

To a solution of Nα-Fmoc amino acid azide(1.0 mmol) in MeOH (10 ml), was added CuBr·S(Me)2 (5 mol %) and aryl boronic acid (1.5 mmol). The mixture was stirred at r.t. until the reaction was complete (TLC). The solution was filtered through a pad of Celite and washed with EtOAc (10 mL). The filterate was diluted with H2O (10 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed thrice with 10% Na2CO3 (3 × 10 mL), 1N HCl (3 × 10 mL) and H2O (3 × 10 mL) and dried over anhydrous Na2SO4. Evaporation of the solvent under *vacuo* followed by column chromatography on silica gel (mesh 100-200) using ethyl acetate and hexane as the eluents [Ethyl acetate : Hexane = 3:7], gave the product in good yields.

**Characterization data for compounds**

1. Fmoc-Ala-[CONH]-C6H5 [3a]: [1]

White solid, yield (92 %, 0.355g), m.p. = 190-192 °C (Lit. 191-193 °C). 1H NMR (400 MHz, CDCl3): *δ* 9.20 (s, 1H), 7.60-7.00 (m, 13H), 6.28 (d, *J* = 5.2 Hz, 1H), 4.95-4.82 (m, 1H), 4.35 (d, *J* = 5.2 Hz, 2H), 4.07 (t, *J* = 5.2 Hz, 1H), 1.3 (d, *J* = 5.6 Hz, 3H). 13C NMR (100 MHz, CDCl3): *δ* 171.0, 155.8, 143.5, 140.9, 138.1, 130.8, 128.5, 127.4, 126.8, 124.9, 123.7, 119.6, 66.4, 50.9, 46.8, 18.7. HRMS: m/z Calculated for C24H23N2O3 [M + H]+ 387.1709; found: 387.1706. Chromatography eluent [Ethyl acetate/Hexane = 2.5:7.5]

2. Fmoc-Gly-[CONH]-4-ClC6H4 [3b]:

White solid, yield (86 %, 0.349g), m.p. = 176-178 °C. 1H NMR (400 MHz, CDCl3): *δ* 9.34 (s, 1H), 7.75-7.03 (m, 12H), 6.35 (s, 1H), 4.33 (d, *J* = 6.0 Hz, 2H), 4.13 (t, *J* = 6.2 Hz, 1H), 3.91 (s, 2H). 13C NMR (100 MHz, CDCl3): *δ* 170.5, 156.3, 143.8, 140.8, 138.3, 135.5, 130.0, 127.7, 127.1, 125.1, 123.0, 120.0, 67.2, 46.9, 42.6. HRMS: m/z Calculated for C23H20ClN2O3 [M + H]+ 407.1162; found: 407.1182. Chromatography eluent [Ethyl acetate/Hexane = 2.5:7.5]

3. Fmoc-Ala-[CONH]-4-ClC6H4 [3c]:

White solid, yield (89 %, 0.374g), m.p. = 184-186 °C. 1H NMR (400 MHz, CDCl3): *δ* 9.44 (s, 1H), 7.63-7.00 (m, 12H), 6.28 (d, *J* = 6.0 Hz, 1H), 4.97-4.88 (m, 1H), 4.41 (d, *J* = 6.2 Hz, 2H), 4.11 (t, *J* = 6.0 Hz, 1H), 1.27 (d, *J* = 6.4 Hz, 3H). 13C NMR (100 MHz, CDCl3): *δ* 171.3, 155.8, 143.5, 140.9, 139.4, 133.8, 129.5, 127.4, 126.8, 124.8, 123.4, 119.6, 66.3, 50.9, 46.8, 18.6. HRMS: m/z Calculated for C24H21ClN2NaO3 [M + Na]+ 443.1138; found: 443.1133. Chromatography eluent [Ethyl acetate/Hexane = 2.5:7.5]

4. Fmoc-Pro-[CONH]-4-ClC6H4 [3d]:

White solid, yield (79 %, 0.353g), m.p. = 193-195 °C. 1H NMR (400 MHz, CDCl3): *δ* 9.11 (s, 1H), 7.82-7.00 (m, 12H), 4.75 (t, *J* = 6.0 Hz, 1H), 4.41 (d, *J* = 5.8 Hz, 2H), 4.21 (t, *J* = 5.4 Hz, 1H), 3.29 (t, *J* = 6.0 Hz, 2H), 2.05 (q, *J* = 6.0 Hz, 2H), 1.70-1.55 (m, 2H).13C NMR (100 MHz, CDCl3): *δ* 169.5, 156.6, 143.4, 141.1, 139.1, 134.2, 129.5, 127.7, 127.0, 124.8, 123.7, 119.9, 67.8, 60.8, 49.2, 47.0, 27.5, 24.5. HRMS: m/z Calculated for C26H24ClN2O3 [M + H]+ 447.1475; found: 447.1480. Chromatography eluent [Ethyl acetate/Hexane = 2.5:7.5]

5. Fmoc-Ile-[CONH]-4-BrC6H4 [3e]:

White solid, yield (83 %, 0.421g), m.p. = 156-158 °C. 1H NMR (400 MHz, CDCl3): *δ* 9.34 (s, 1H), 7.81-7.15 (m, 12H), 6.10 (s, 1H), 4.95 (t, *J* = 6.2 Hz, 1H), 4.71 (d, *J* = 6.0 Hz, 2H), 4.35 (t, *J* = 5.4 Hz, 1H), 2.11-1.96 (m, 1H), 1.62-1.53 (m, 2H), 1.26 (d, *J* = 5.4 Hz, 3H), 0.91 (t, *J* = 6.2 Hz, 3H). 13C NMR (100 MHz, CDCl3): *δ* 169.9, 155.6, 143.8, 141.3, 133.4, 131.3, 130.3, 127.7, 127.0, 125.0, 121.2, 120.0, 66.7, 64.3, 47.3, 37.9, 25.6, 14.1, 11.0. HRMS: m/z Calculated for C27H28BrN2O3 [M + H]+ 507.1283; found: 507.1282. Chromatography eluent [Ethyl acetate/Hexane = 2.5:7.5]

6. Fmoc-Val-[CONH]-4-OCH3C6H4 [3f]:

White solid, yield (84 %, 0.373g), m.p. = 206-208 °C. 1H NMR (400 MHz, CDCl3): *δ* 9.41 (s, 1H), 7.86-7.09 (m, 12H), 6.52 (s, 1H), 4.85 (t, *J* = 7.2 Hz, 1H), 4.50 (d, *J* = 6.8 Hz, 2H), 4.24 (t, *J* = 7.2 Hz, 1H), 3.66 (s, 3H), 2.77-2.68 (m, 1H), 0.97 (d, *J* = 7.2 Hz, 6H). 13C NMR (100 MHz, CDCl3): *δ* 170.0, 156.6, 153.2, 143.6, 141.1, 131.4, 129.1, 128.5, 127.5, 126.9, 124.8, 119.8, 66.7, 61.1, 53.0, 46.9, 30.2, 21.2. HRMS: m/z Calculated for C27H28N2NaO4 [M +Na]+ 467.1947; found: 467.1942. Chromatography eluent [Ethyl acetate/Hexane = 2.5:7.5]

7. Fmoc-Lys(Boc)-[CONH]-4-CH3C6H4 [3g]: [2]

White solid, yield (81 %, 0.428g), m.p. = 137-139 °C (Lit. 136-139 °C). 1H NMR (400 MHz, CDCl3): *δ* 9.31 (s, 1H), 7.92-7.28 (m, 12H), 6.74 (s, 1H), 6.53 (s, 1H), 4.93 (t, *J* = 6.0 Hz, 1H), 4.35-4.12 (m, 3H), 3.21 (q, *J* = 5.2 Hz, 2H), 2.32 (s, 3H), 1.91 (q, *J* = 4.8 Hz, 2H), 1.63-1.50 (m, 2H), 1.36 (s, 9H), 1.29-1.12 (m, 2H). 13C NMR (100 MHz, CDCl3): *δ* 171.5, 155.7, 155.3, 143.8, 142.6, 136.8, 135.4, 129.5, 127.3, 126.0, 124.6, 121.6, 120.2, 79.8, 67.3, 58.2, 47.3, 41.6, 31.9, 29.9, 28.5, 23.1, 21.9. HRMS: m/z Calculated for C33H39N3NaO5 [M + Na]+ 580.2787; found: 580.2783. Chromatography eluent [Ethyl acetate/Hexane = 3.5:6.5]

8. Fmoc-Tyr(OtBu)-[CONH]-3-CHOC6H4 [3h]:

White gummy solid, yield (77 %, 0.433g). 1H NMR (400 MHz, CDCl3): *δ* 9.51 (s, 1H), 9.30 (s, 1H), 7.81-6.89 (m, 16H), 6.41 (br s, 1H), 5.41-5.29 (m, 1H), 4.43 (d, *J* = 6.0 Hz, 2H), 4.22 (t, *J* = 6.2 Hz, 1H), 2.39-2.24 (m, 2H), 1.32 (s, 9H). 13C NMR (100 MHz, CDCl3): *δ* 194.5, 173.8, 155.7, 154.7, 143.8, 142.2, 140.8, 138.1, 133.4, 129.5, 128.0, 127.3, 126.6, 126.0, 125.3, 124.6, 123.9, 120.9, 119.6, 86.2, 67.6, 58.8, 47.3, 37.6, 27.8. HRMS: m/z Calculated for C35H34N2NaO5 [M + Na]+ 585.2365; found: 585.2369. Chromatography eluent [Ethyl acetate/Hexane = 3.5:6.5]

9. Fmoc-Glu(COOtBu)-[CONH]-C6H5 [3i]:

White solid, yield (78 %, 0.390g), m.p. = 142-144 °C. 1H NMR (400 MHz, CDCl3): *δ* 9.32 (s, 1H), 7.82-7.21 (m, 13H), 6.49 (s, 1H), 5.41-5.27 (m, 1H), 4.45 (d, *J* = 5.4 Hz, 2H), 4.22 (t, *J* = 5.8 Hz, 1H), 2.31 (t, *J* = 5.8 Hz, 2H), 2.10-1.98 (m, 2H), 1.43 (s, 9H). 13C NMR (100 MHz, CDCl3): *δ* 173.3, 172.2, 156.3, 143.8, 141.3, 138.5, 129.3, 128.6, 127.1, 126.3, 125.1, 122.0, 120.0, 82.4, 67.2, 58.5, 47.1, 31.2, 28.8, 27.1. HRMS: m/z Calculated for C30H33N2O5 [M + H]+ 501.2389; found: 501.2380. Chromatography eluent [Ethyl acetate/Hexane = 3.5:6.5]

10. Fmoc-Leu-[CONH]-Gly-[CONH]-4-CH3C6H4 [6a]:

Colourless gummy solid, yield (73 %, 0.364g). 1H NMR (400 MHz, CDCl3): *δ* 9.35 (s, 1H), 9.12 (s, 1H), 7.81-7.23 (m, 12H), 6.47 (br d, *J* = 6.4 Hz, 1H), 5.50-5.39 (m, 1H), 4.41 (d, *J* = 6.0 Hz, 2H), 4.21 (t, *J* = 6.0 Hz, 1H), 4.02 (s, 2H), 2.40 (s, 3H), 1.78 (q, *J* = 5.4 Hz, 2H), 1.44-1.36 (m, 1H), 0.94 (d, *J* = 5.4 Hz, 6H). 13C NMR (100 MHz, CDCl3): *δ* 172.5, 170.8, 155.9, 143.7, 141.4, 136.0, 135.3, 129.6, 128.6, 127.7, 125.0, 122.2, 120.1, 67.1, 56.7, 47.2, 44.2, 42.3, 24.0, 22.3, 20.9. HRMS: m/z Calculated for C30H34N3O4 [M + H]+ 500.2549; found: 500.2544. Chromatography eluent [Ethyl acetate/Hexane = 4:6]

11. Fmoc-Gly-[CONH]-Ala-[CONH]-C6H5 [6b]:

Colourless gummy solid, yield (75 %, 0.332g). 1H NMR (400 MHz, CDCl3): *δ* 9.32 (s, 1H), 9.11 (s, 1H), 7.81-7.23 (m, 13H), 6.73 (s, 1H), 5.53-5.41 (m, 1H), 4.43 (d, *J* = 6.4 Hz, 2H), 4.22 (t, *J* = 6.4 Hz, 1H), 3.93 (s, 2H), 1.52 (d, *J* = 6.0 Hz, 3H). 13C NMR (100 MHz, CDCl3): *δ* 173.3, 171.6, 156.4, 143.9, 142.5, 138.5, 129.2, 128.3, 126.7, 126.0, 125.7, 121.6, 120.6, 67.6, 53.1, 47.4, 44.3, 18.0. HRMS: m/z Calculated for C26H26N3O4 [M + H]+ 444.1923; found: 444.1927. Chromatography eluent [Ethyl acetate/Hexane = 4:6]

12. Fmoc-Leu-[CONH]-Gly-CON3 [5a]:

Gummy solid. 1H NMR (400 MHz, CDCl3): δ 9.49 (s, 1H), 7.82-7.21 (m, 8H), 6.75 (s, 1H), 4.73 (d, *J* = 4.8 Hz, 2H), 4.59 (t, *J* = 6.0 Hz, 1H), 4.46 (t, *J* = 6.0 Hz, 1H), 4.30 (s, 2H), 1.81 (t, *J* = 6.0 Hz, 2H), 1.59-1.38 (m, 1H), 0.94 (d, *J* = 6.0 Hz, 6H). 13C NMR (100 MHz, CDCl3): δ 178.7, 172.8, 156.1, 143.6, 141.3, 127.1, 126.3, 125.5, 120.0, 67.3, 57.1, 47.1, 45.4, 42.3, 25.0, 23.4. HRMS: m/z Calculated for C23H25N5NaO4 [M + Na]+ 458.1804; found: 458.1808. Chromatography eluent [Ethyl acetate/Hexane = 2:8]

13. Fmoc-Gly-[CONH]-Ala-CON3 [5b]:

Gummy solid. 1H NMR (400 MHz, CDCl3): δ 9.50 (s, 1H), 7.83-7.20 (m, 8H), 6.74 (s, 1H), 4.80-4.59 (m, 3H), 4.33 (t, *J* = 7.2 Hz, 1H), 3.88 (s, 2H), 1.46 (s, 3H). 13C NMR (100 MHz, CDCl3): δ 179.1, 172.6, 156.4, 143.7, 141.3, 127.1, 126.2, 125.1, 120.0, 67.1, 56.8, 47.1, 45.3, 18.1. HRMS: m/z Calculated for C20H19N5NaO4 [M + Na]+ 416.1335; found: 416.1336. Chromatography eluent [Ethyl acetate/Hexane = 2:8]

**References for reported compounds:**

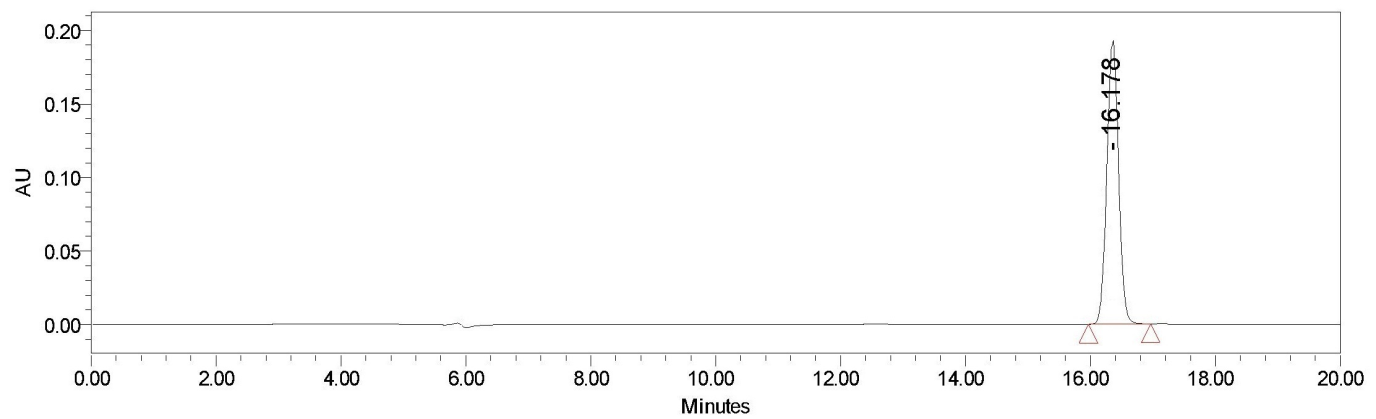
[1] Chilakapati, M.; Vishwanatha, T. M.; Sureshbabu, V. V. *Synthesis* **2013**, *45*, 19, 2727-2736.  
[2] Zhang, Z.; Zheng, D.; Wan, Y.; Zhang, G.; Bi, J.; Liu, Q.; Liu, T.; Shi. L. *J. Org. Chem*. **2018**, *83,* 3, 1369 - 1376.

**References for acid azide:**

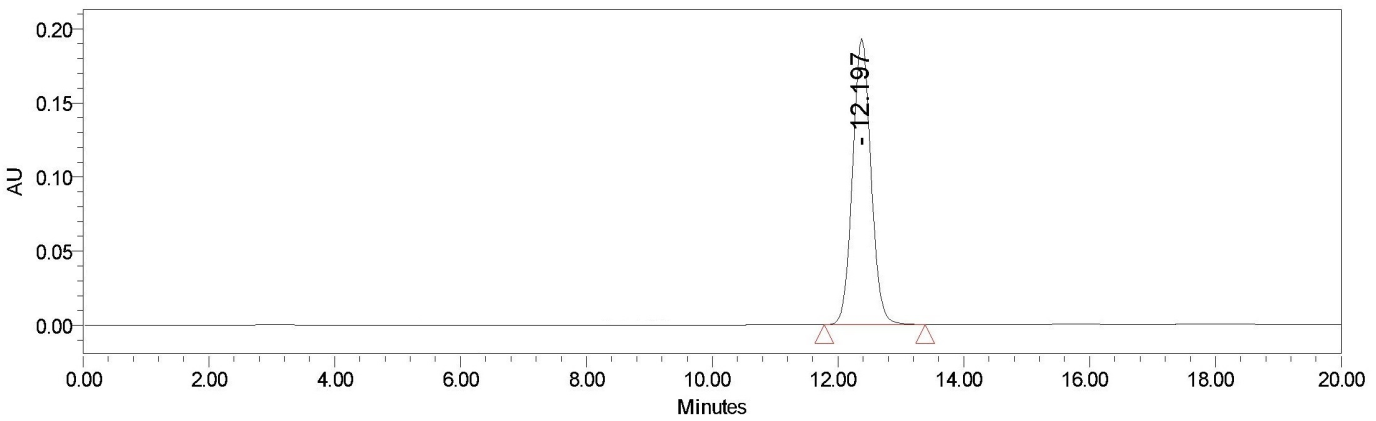
[1] Sureshbabu, V. V.; Ananda, K.; Vasanthakumar, G-R. *J. Chem. Soc*., *Perkin Trans.* **2000**, *1*, 4328 - 4331

[2] Patil, B. S.; Vasanthakumar, G-R.; Sureshbabu, V. V. *J. Org. Chem.* **2003**, *68*, 7274-7280.

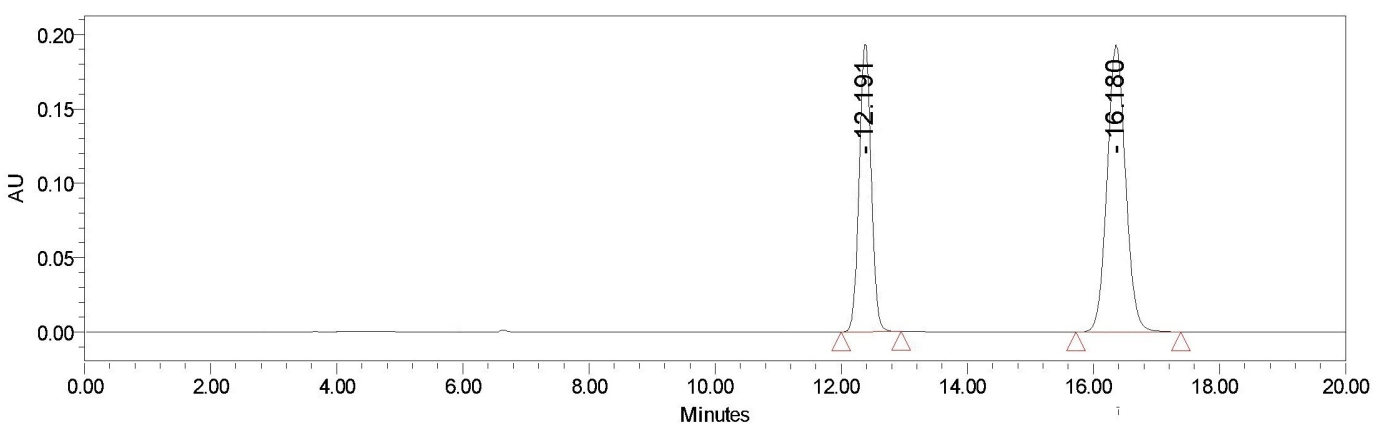
**SPECTRAL DATA**

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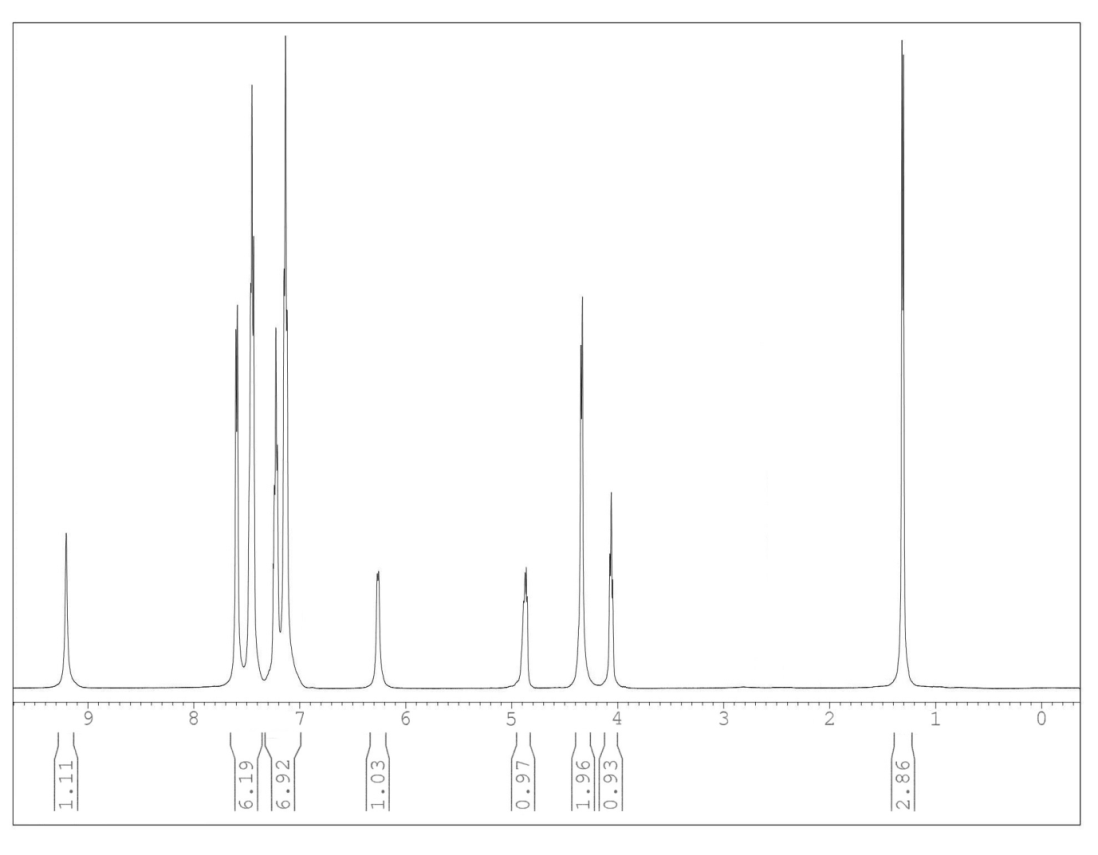
Racemization study of compound 3a [L-isomer]



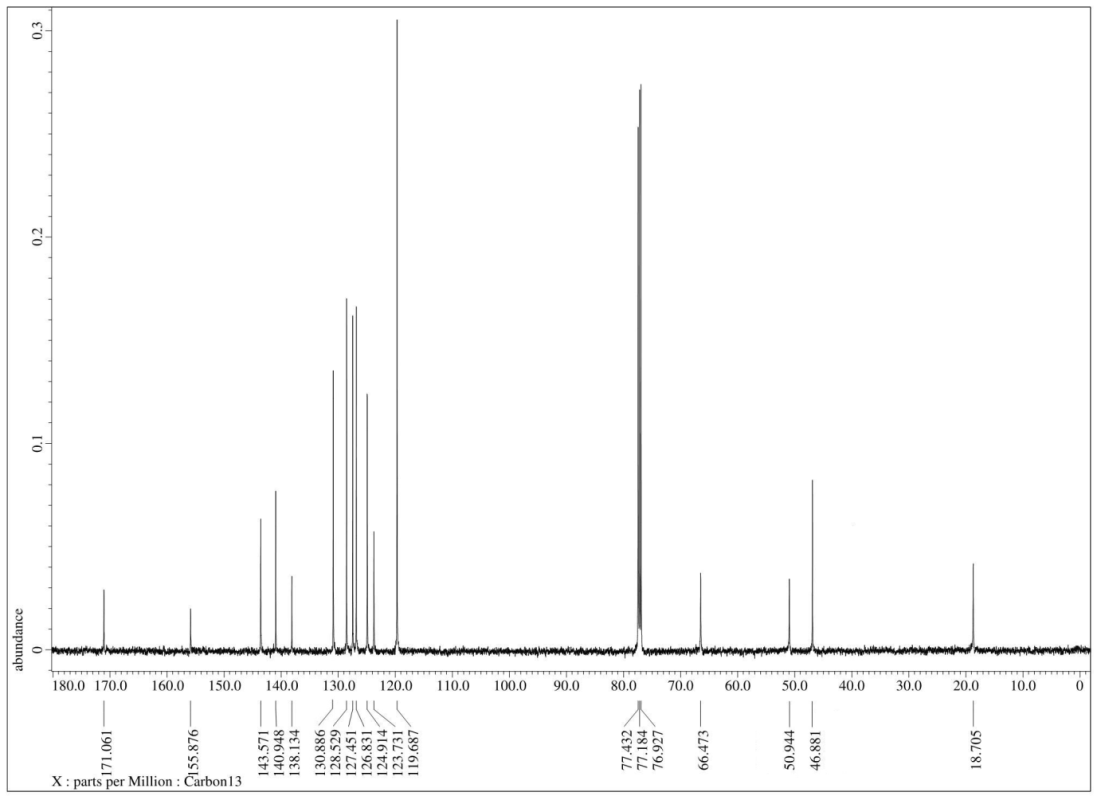
Racemization study of compound 3a\* [D-isomer]

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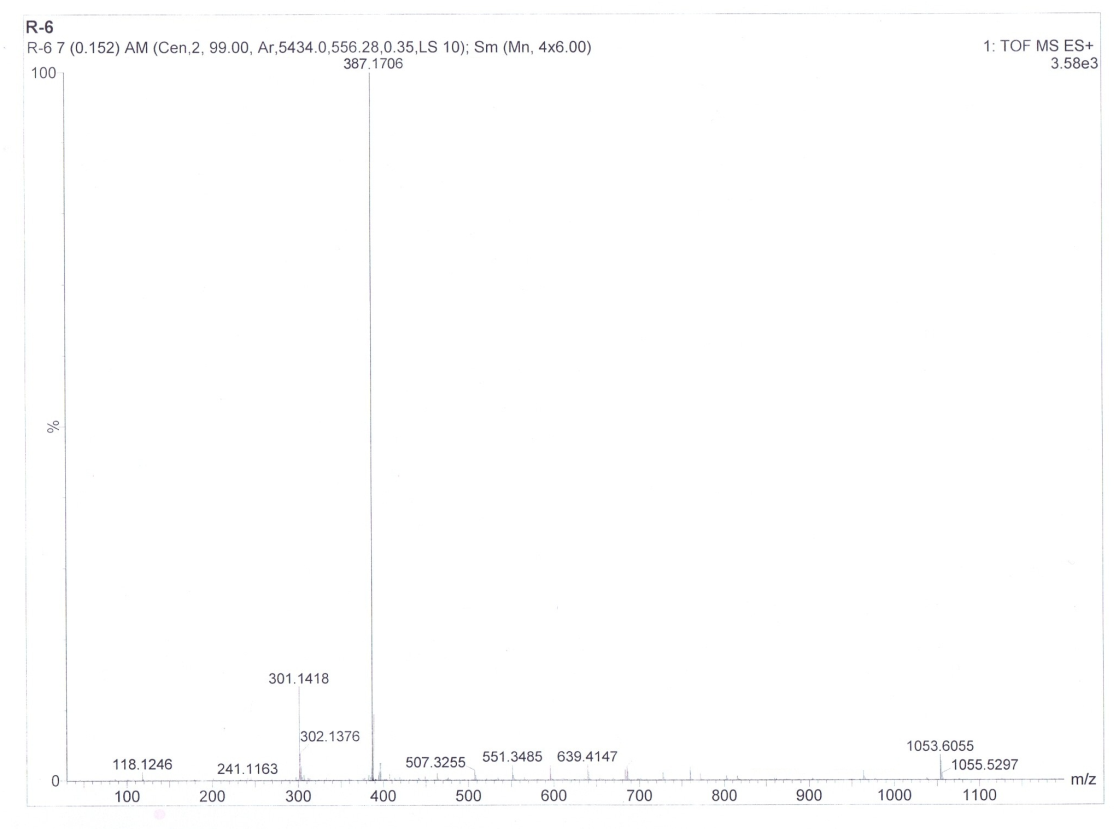
Racemization study of mixture of compound 3a & 3a\* [L- & D-isomer]



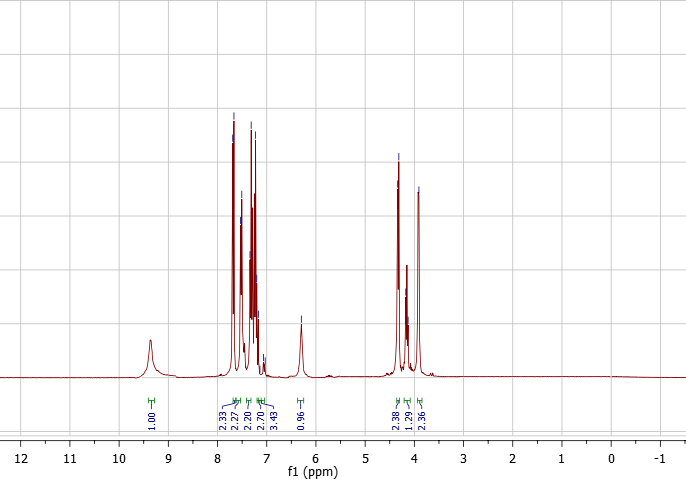
1H NMR Spectrum of Compound 3a



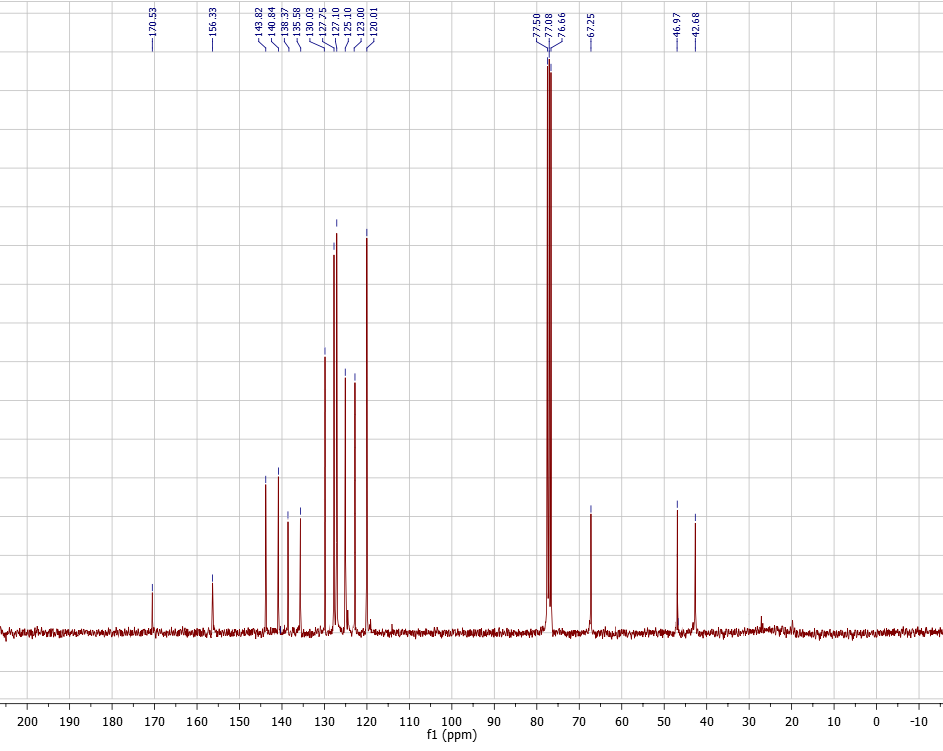
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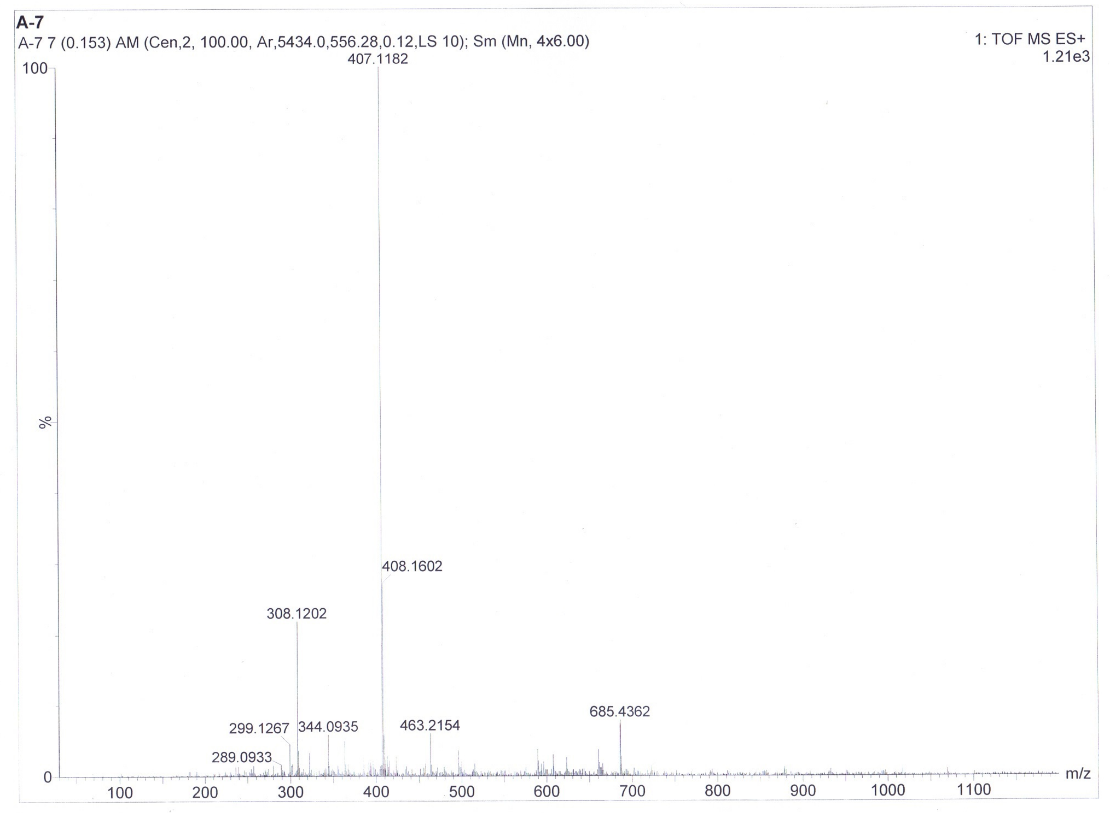
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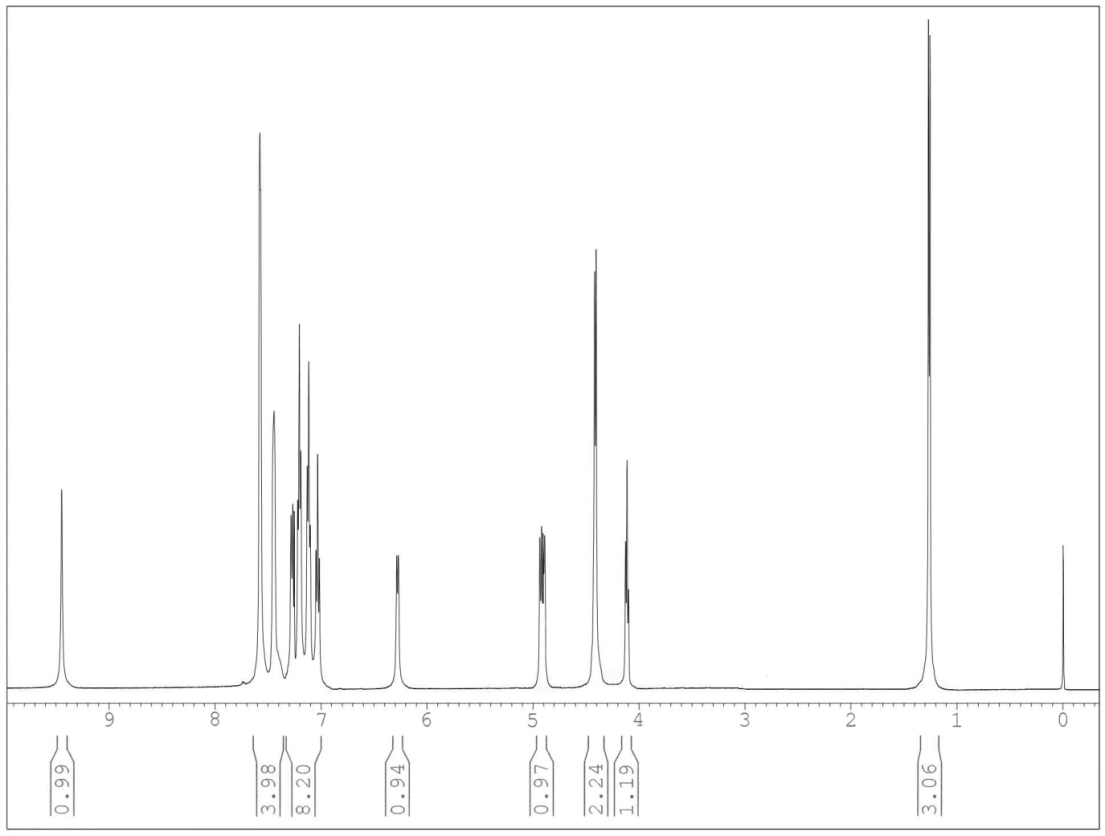
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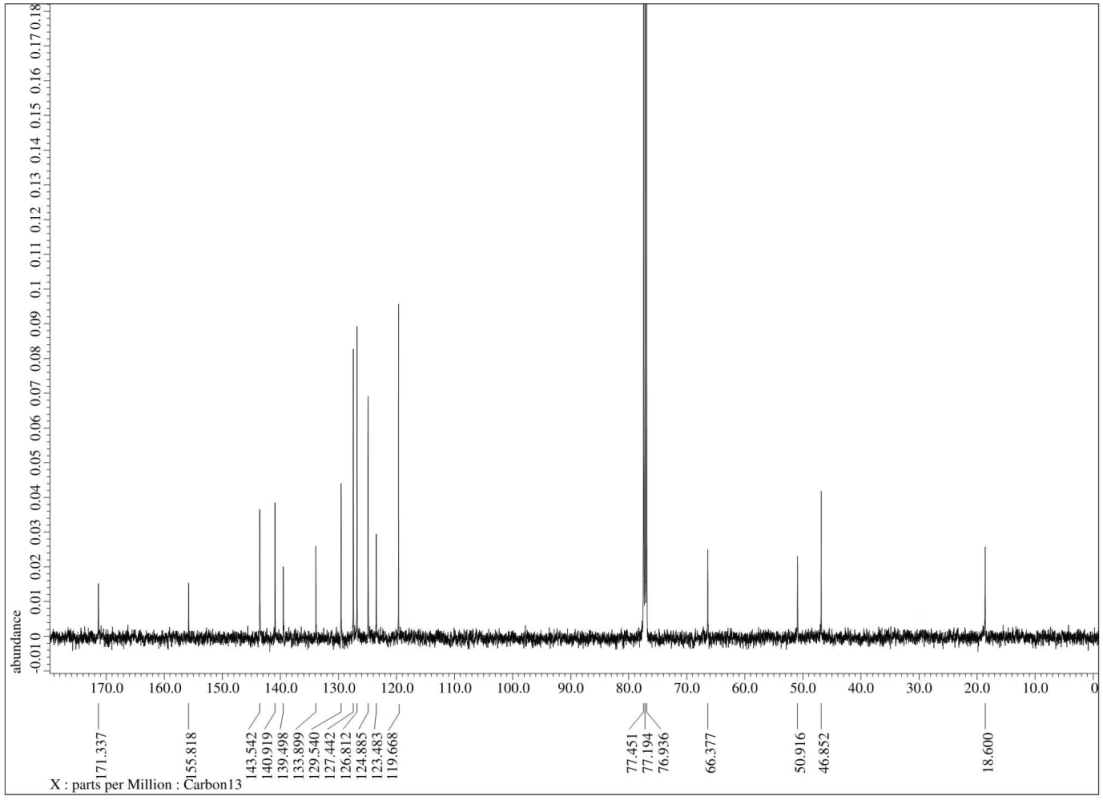
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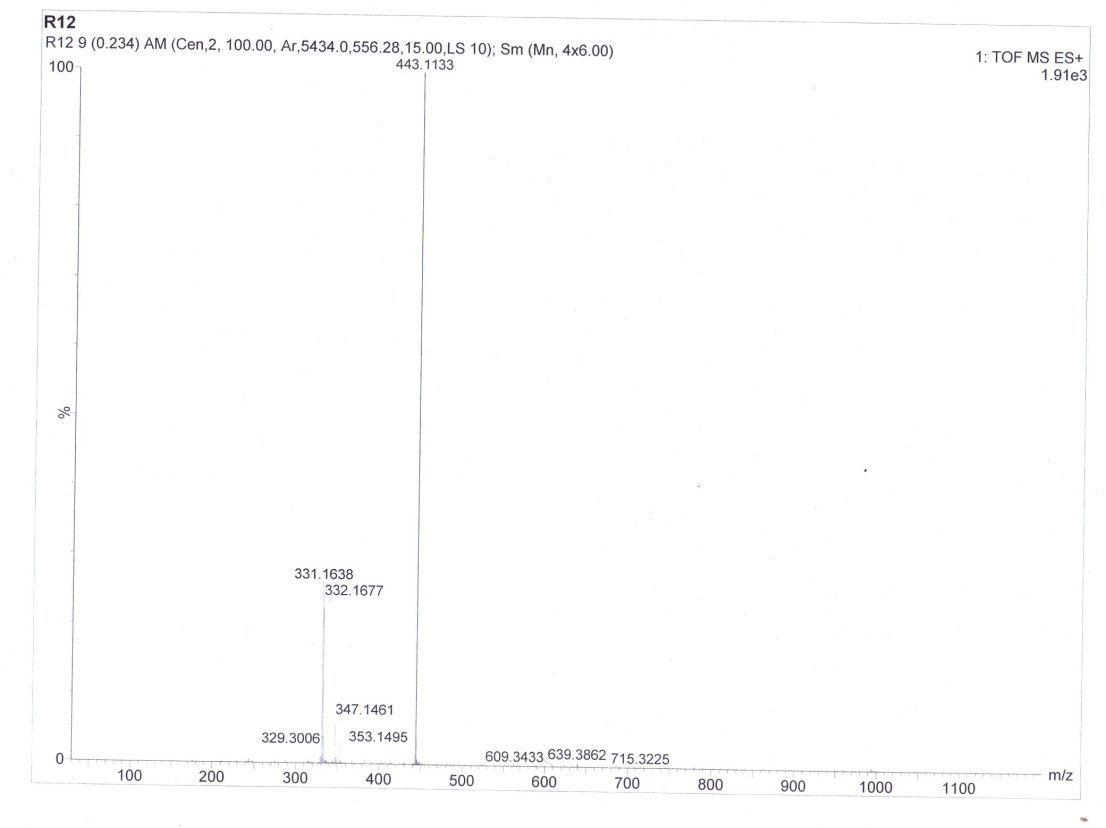
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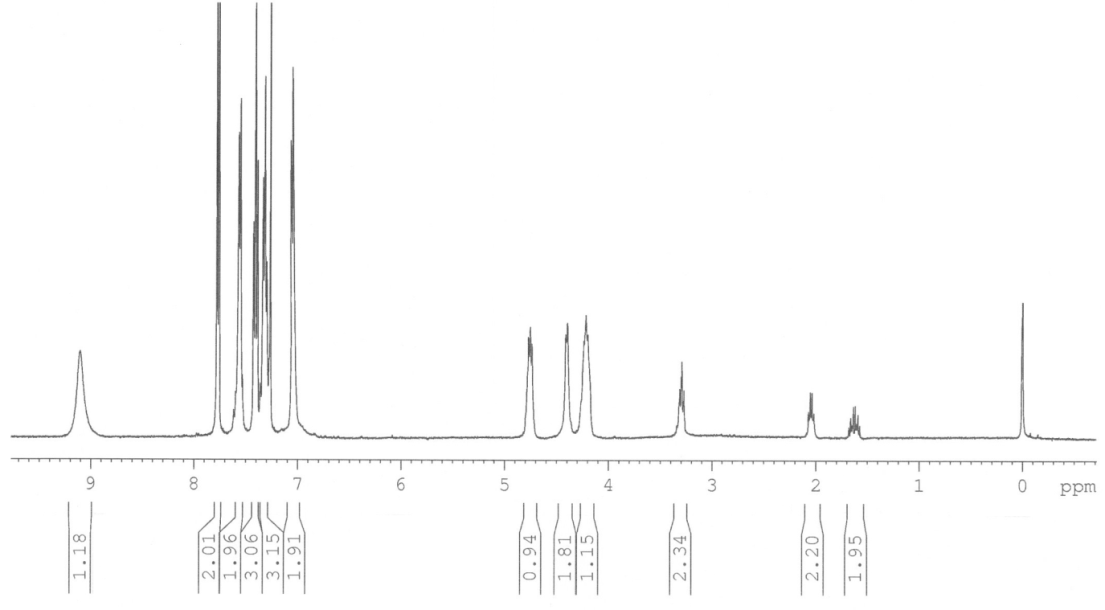
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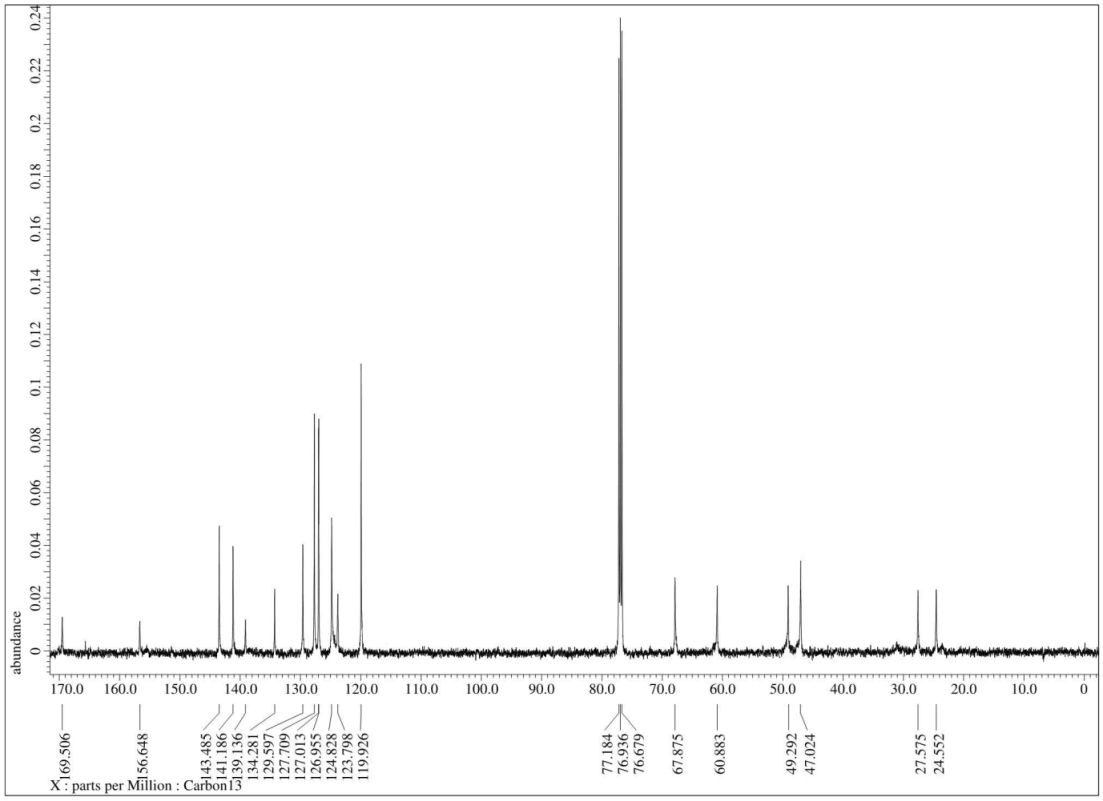
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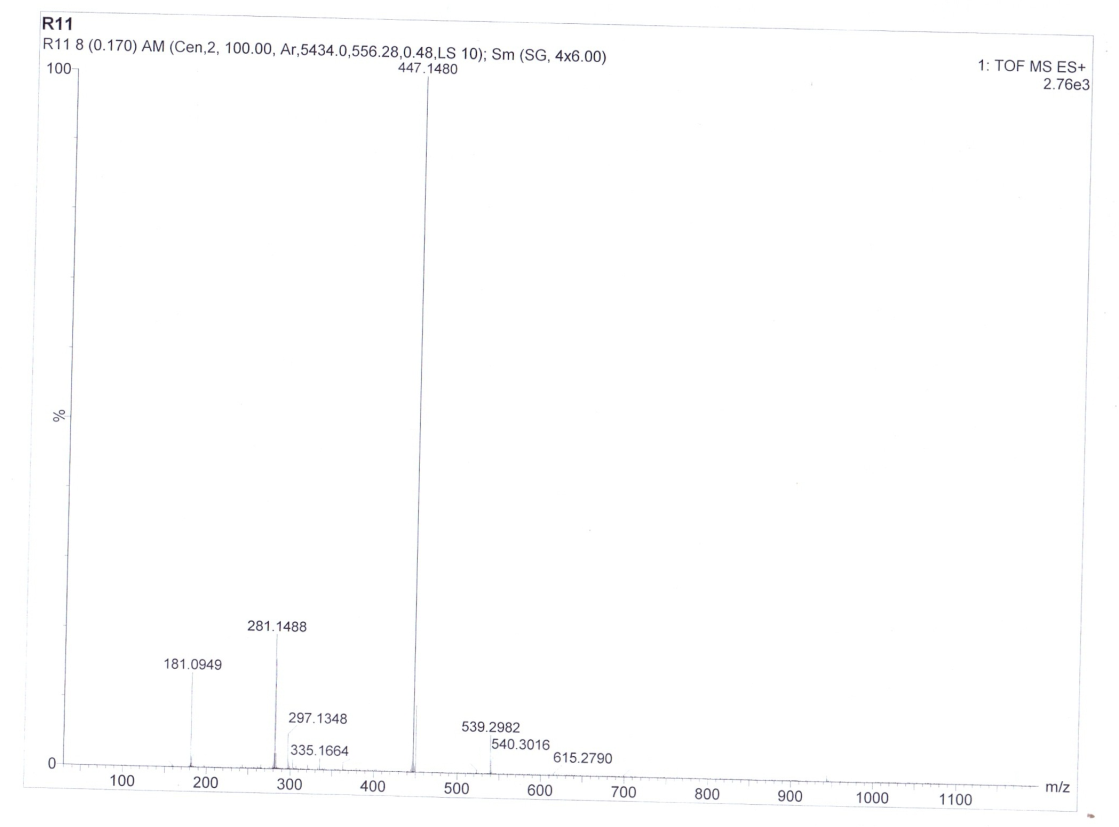
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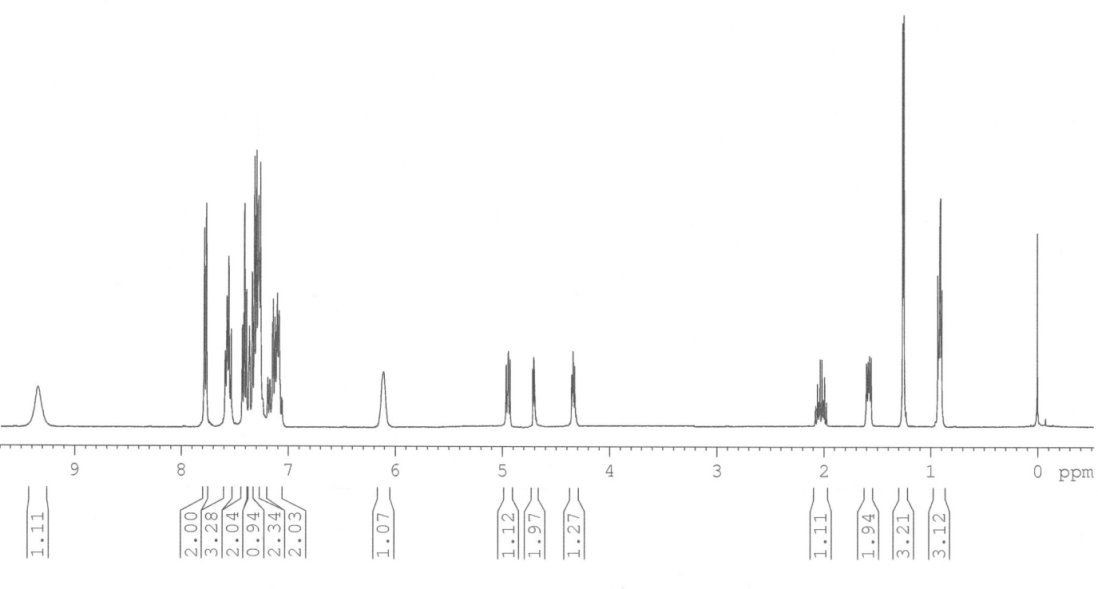
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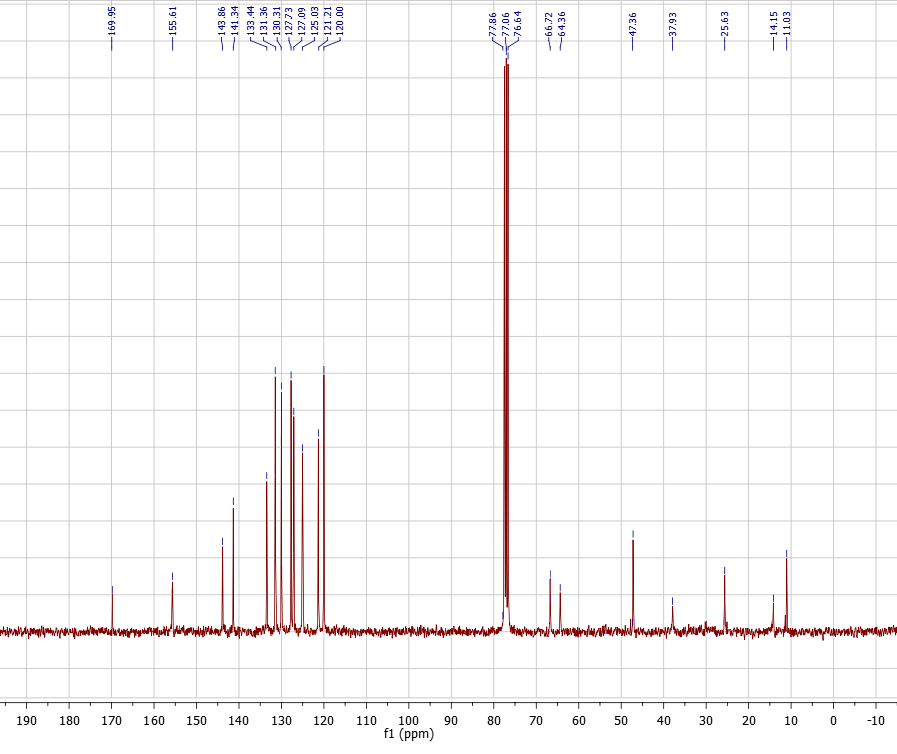
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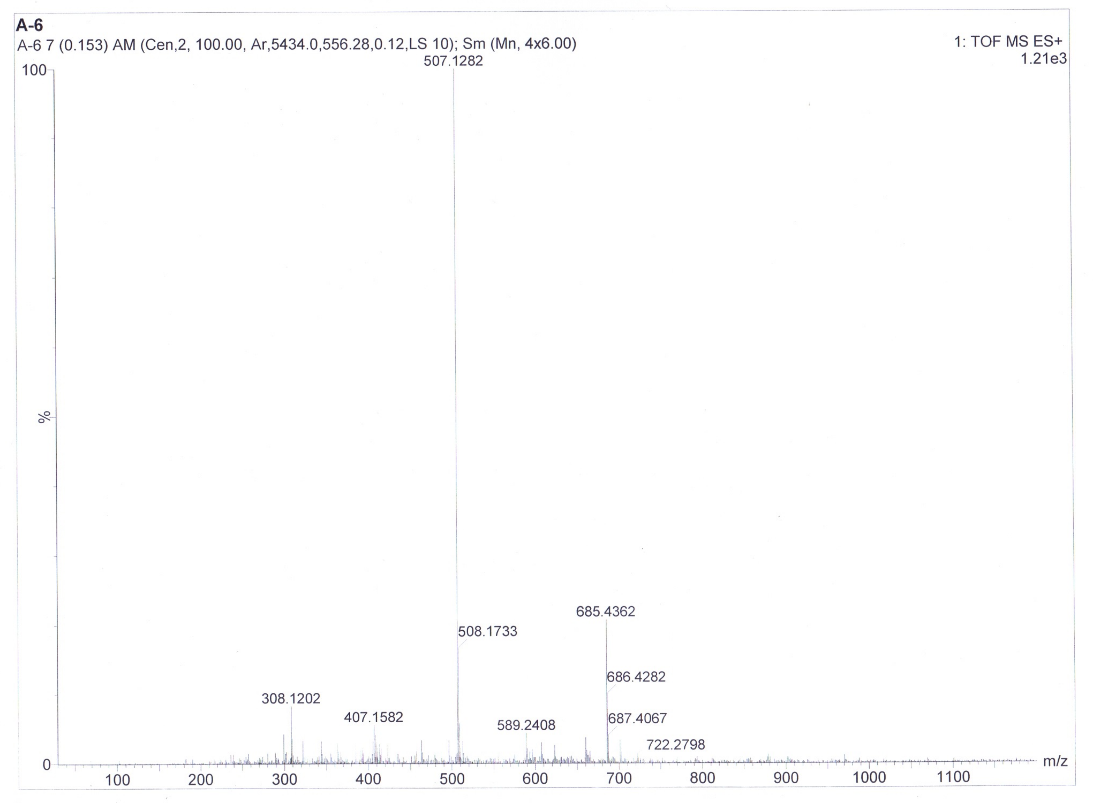
HRMS of Compound 3d



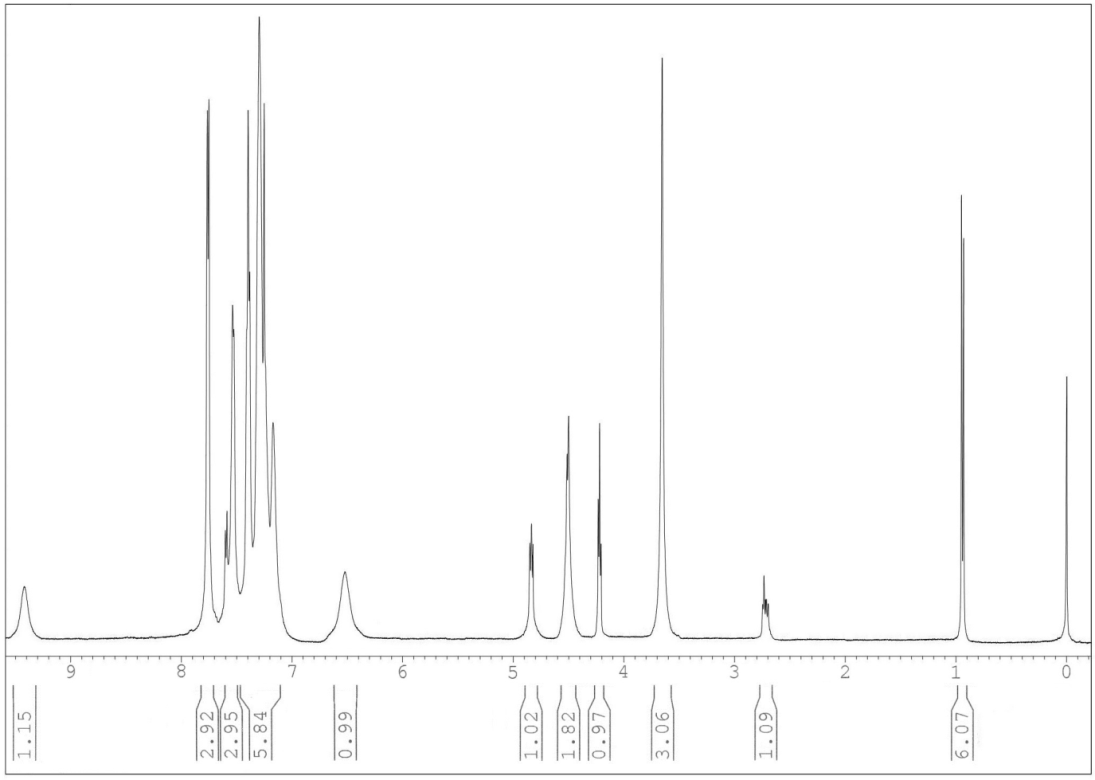
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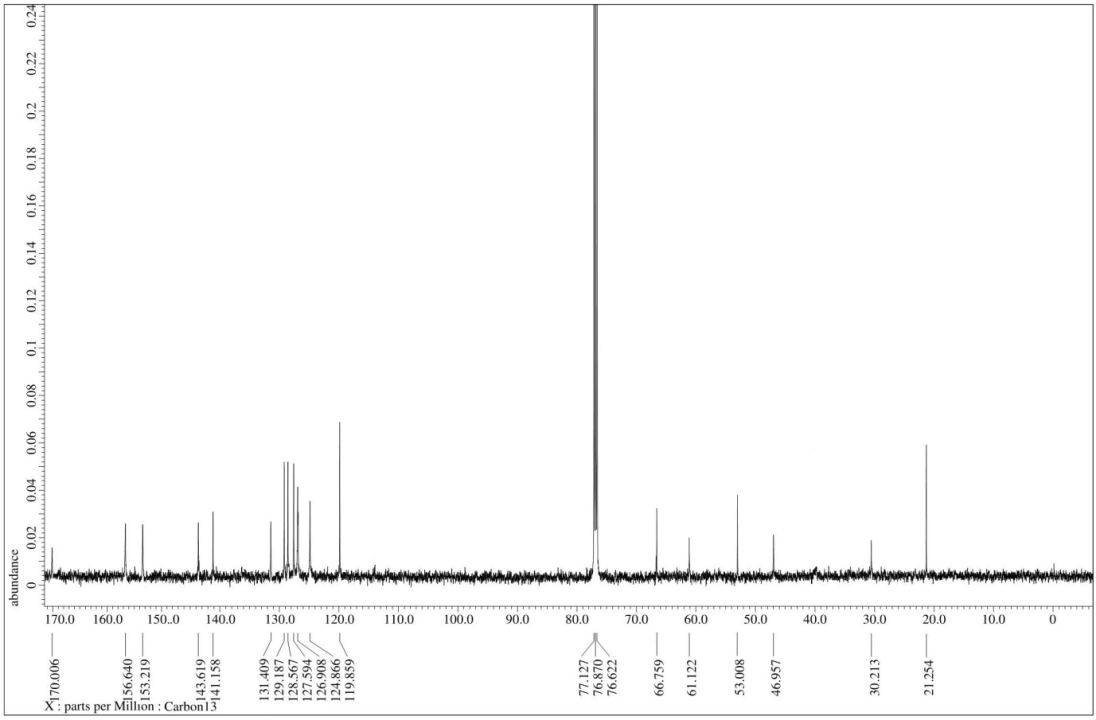
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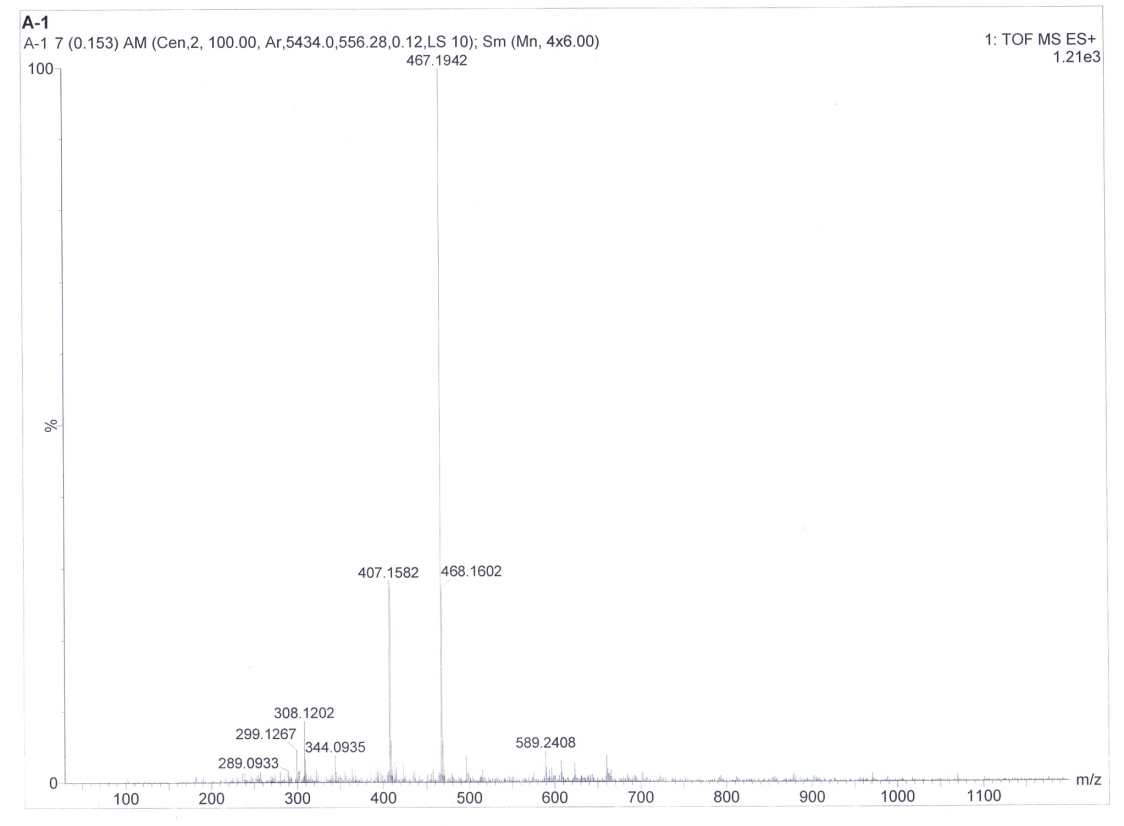
HRMS of compound 3e



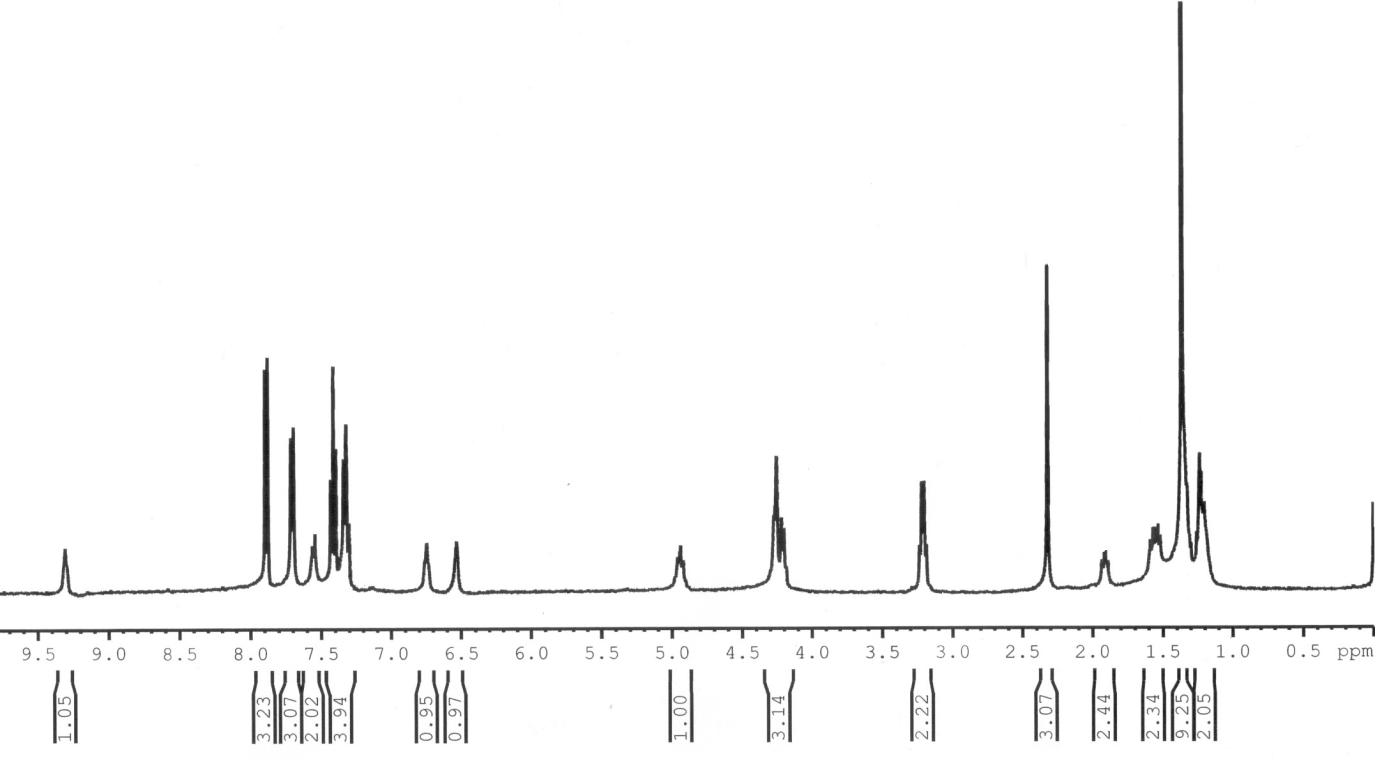
1H NMR Spectrum of Compound 3f



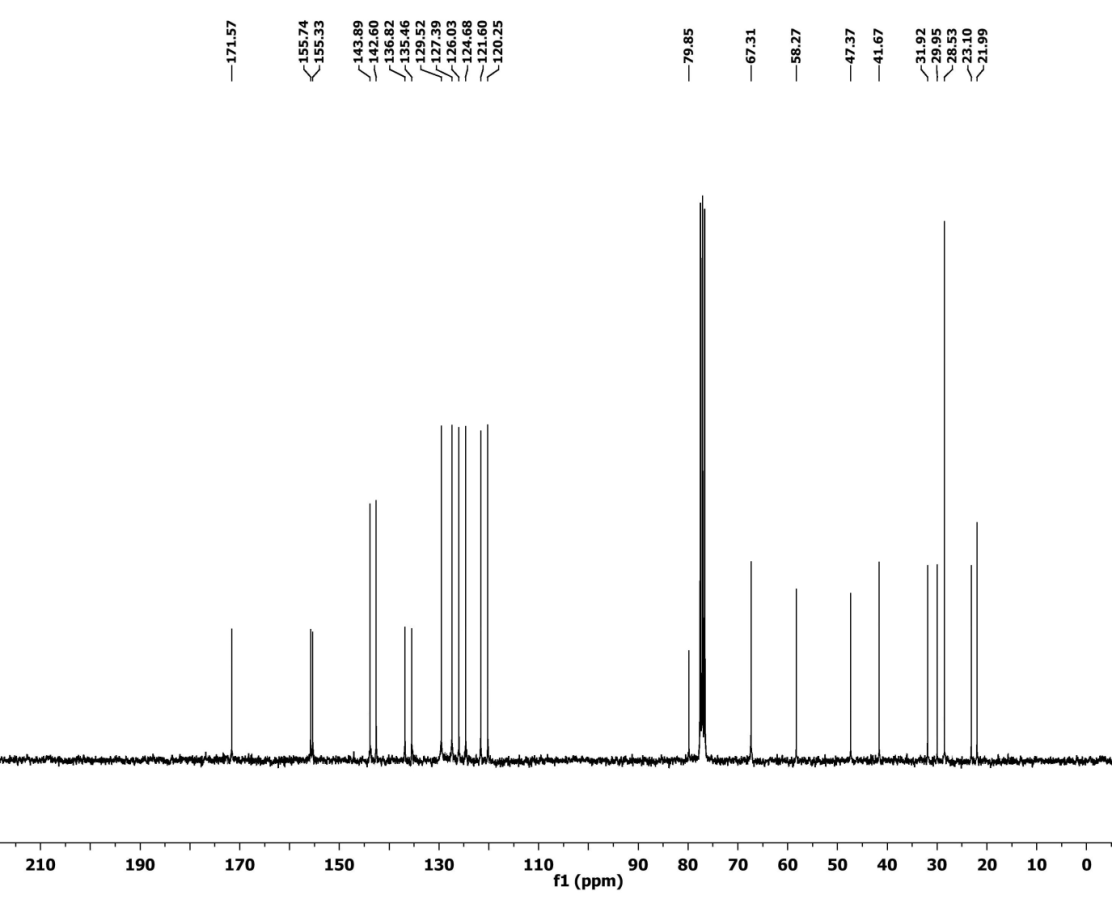
13C NMR Spectrum of Compound 3f



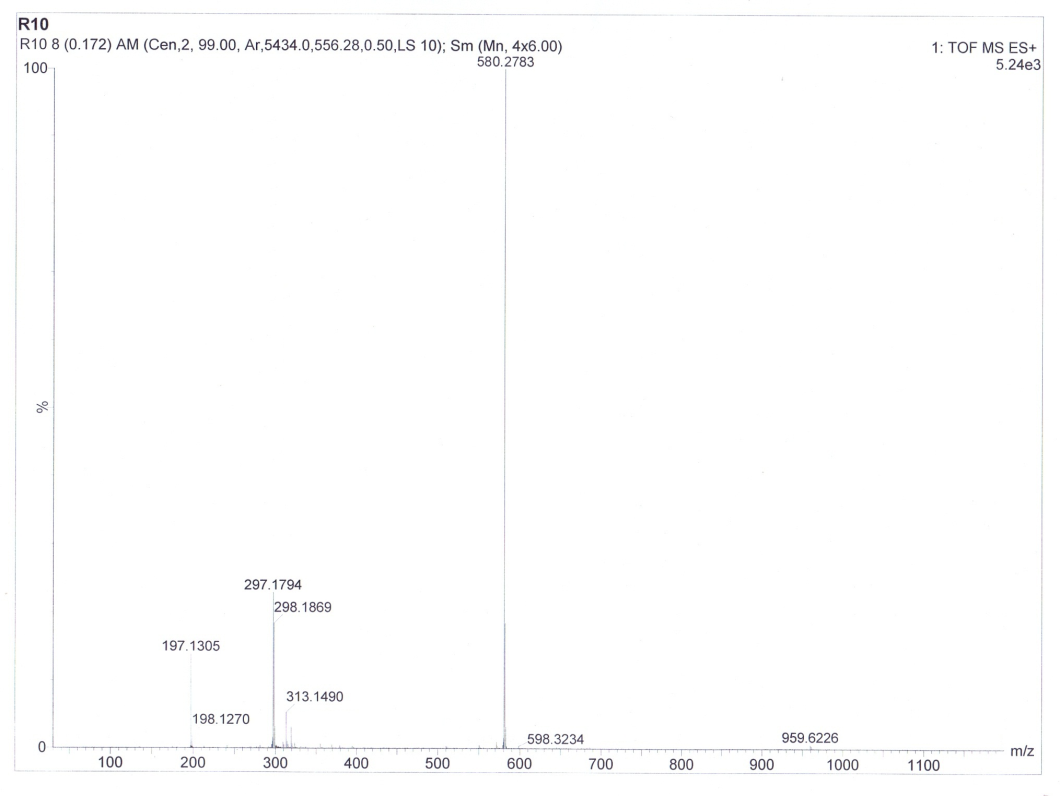
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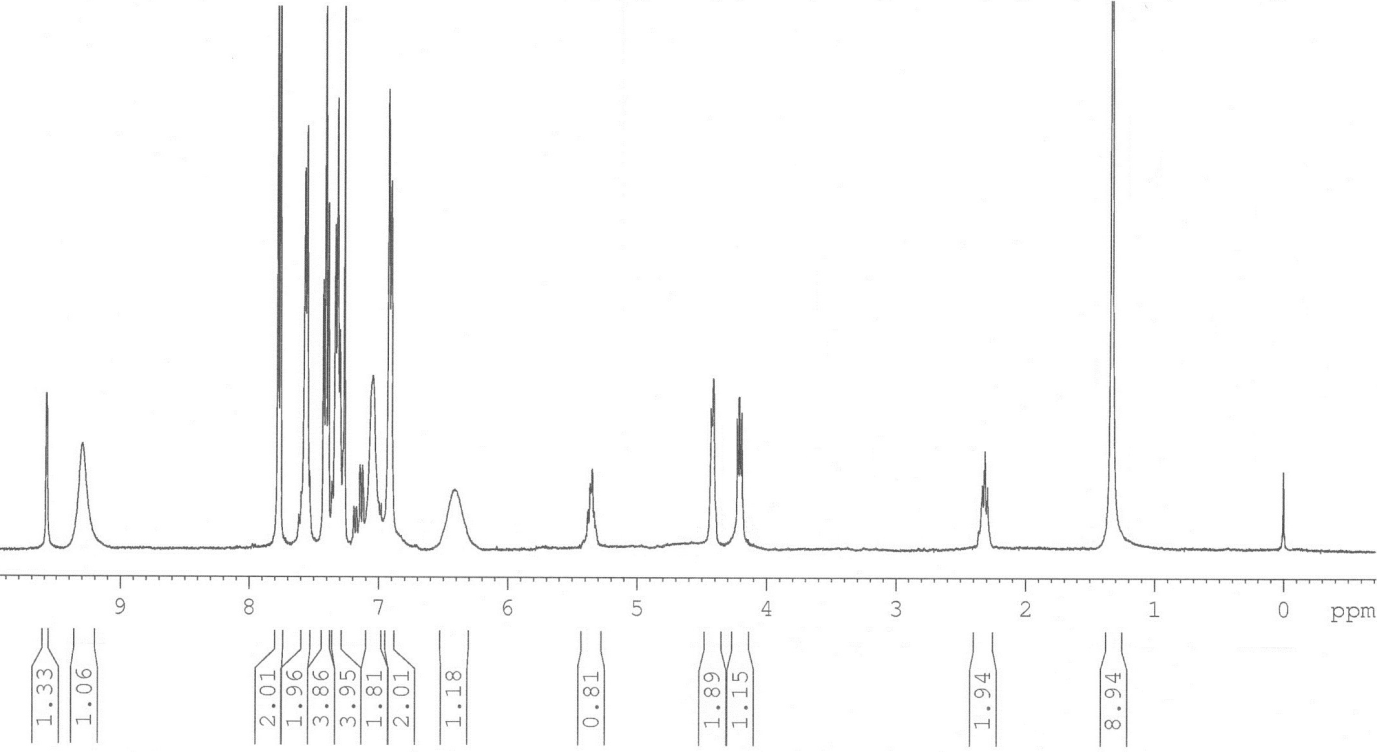
1H NMR Spectrum of Compound 3g



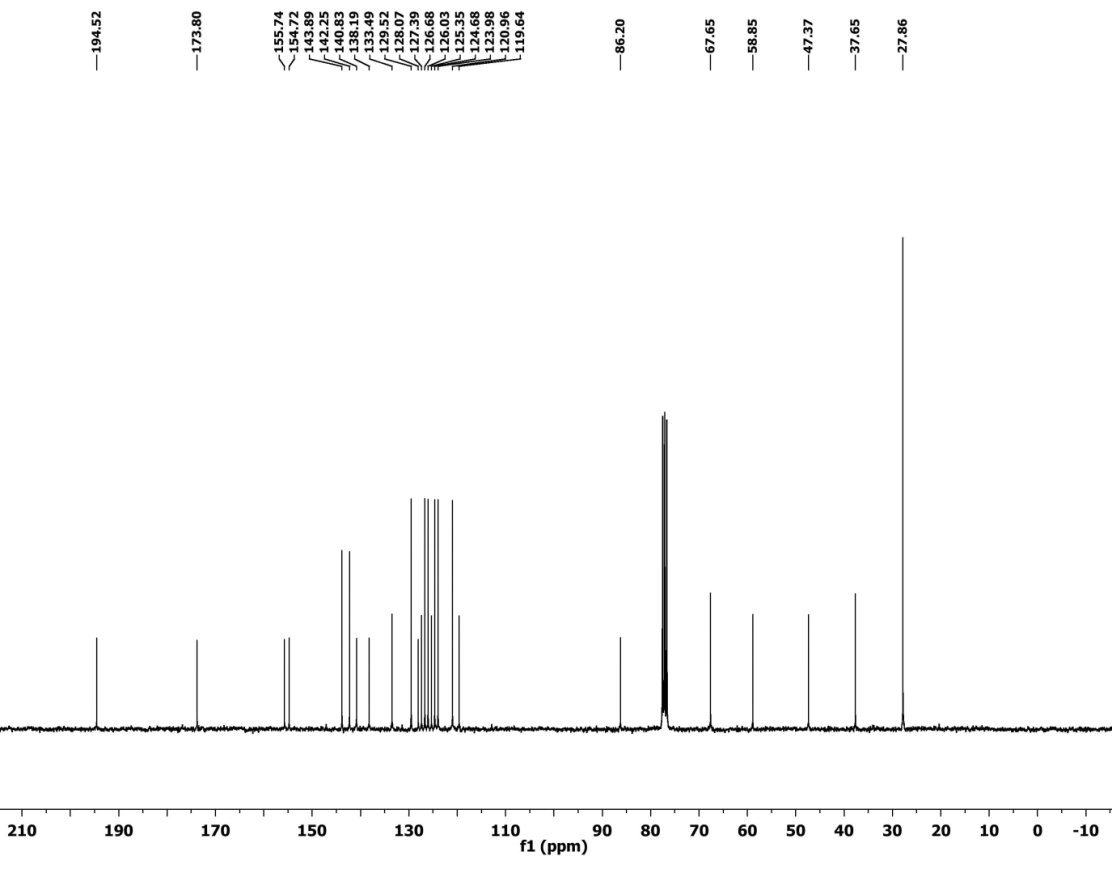
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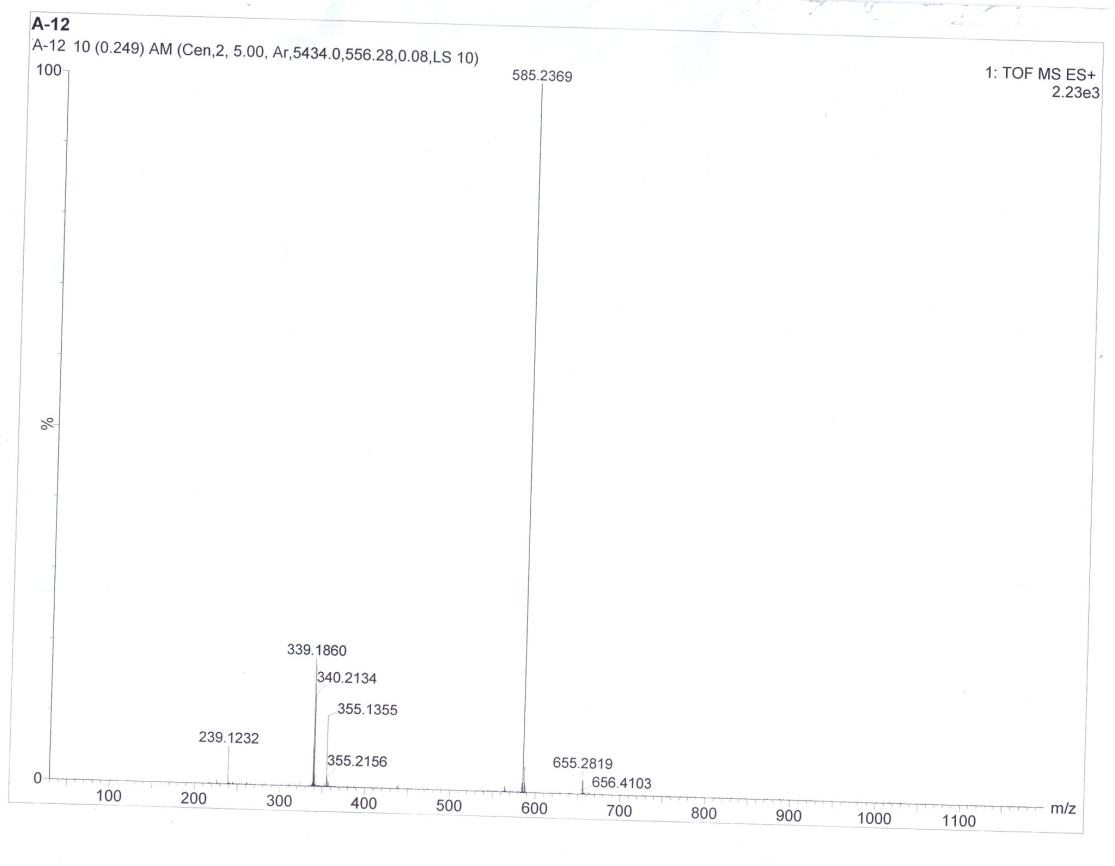
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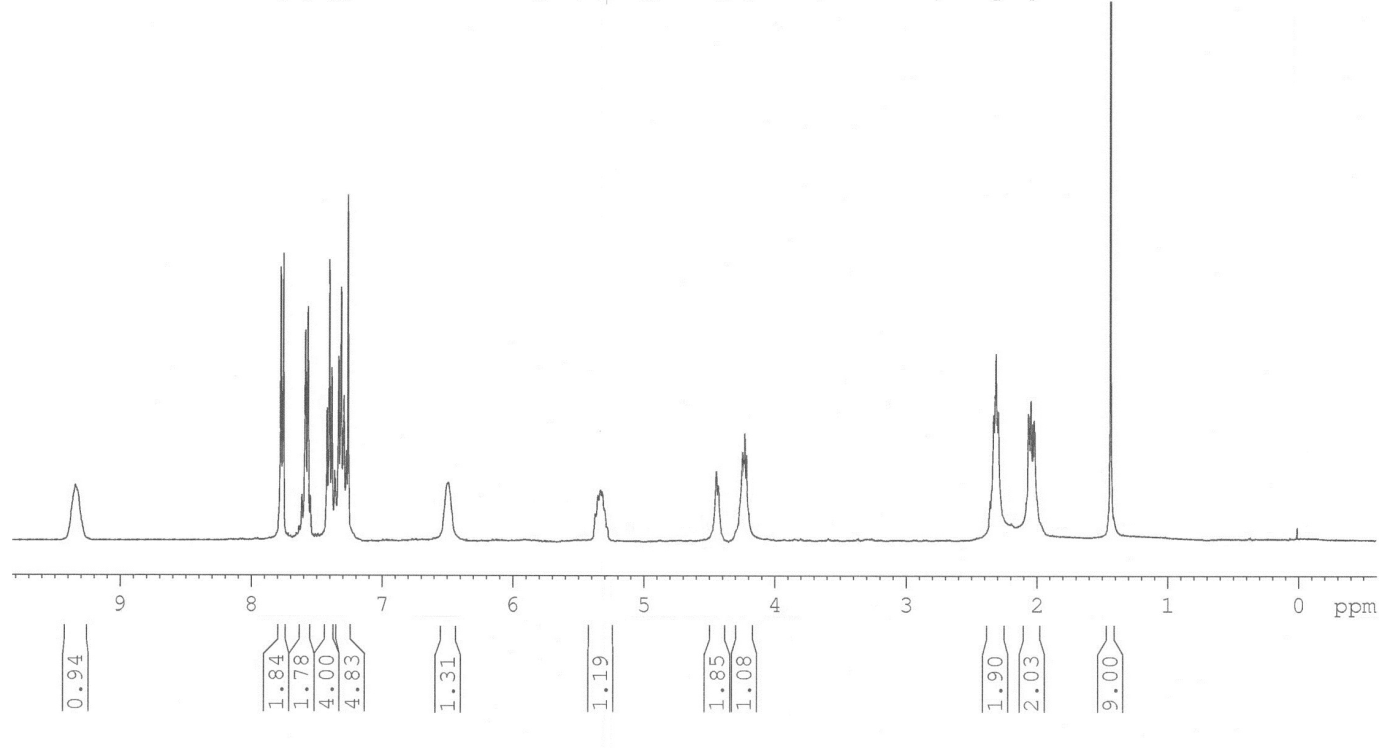
1H NMR Spectrum of Compound 3h



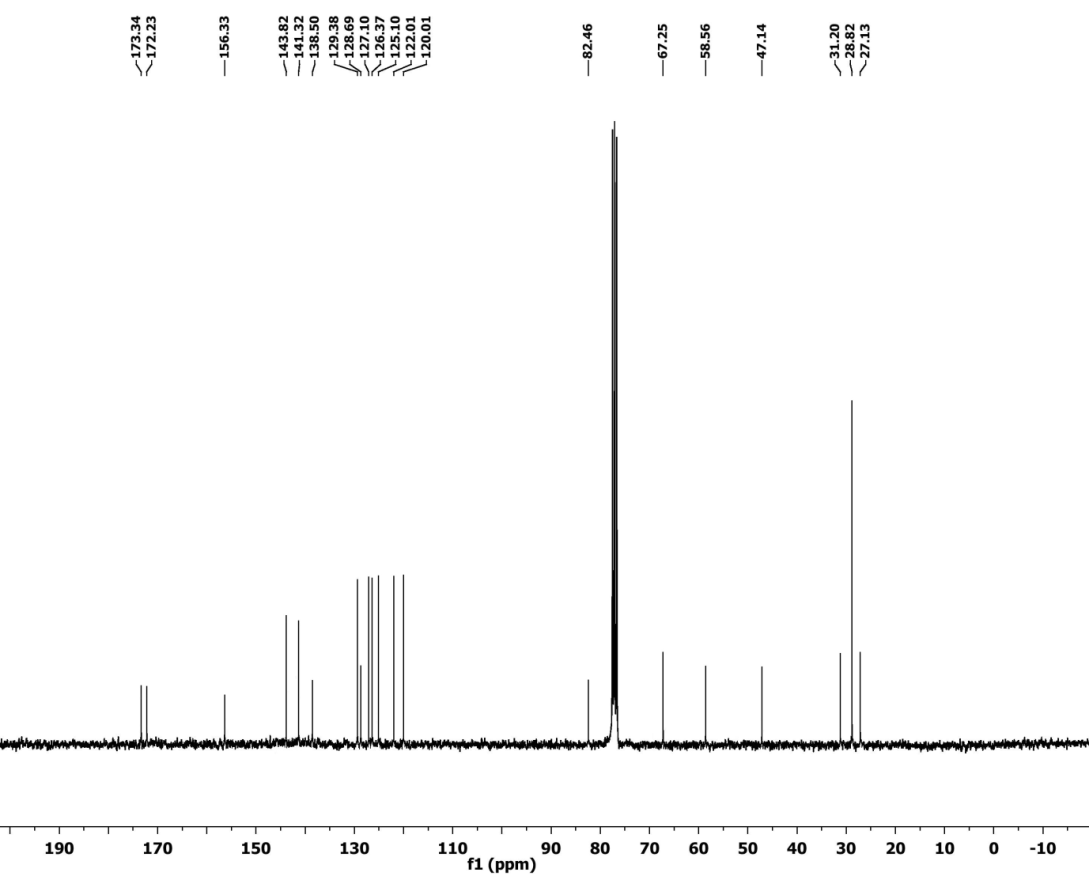
13C NMR Spectrum of Compound 3h



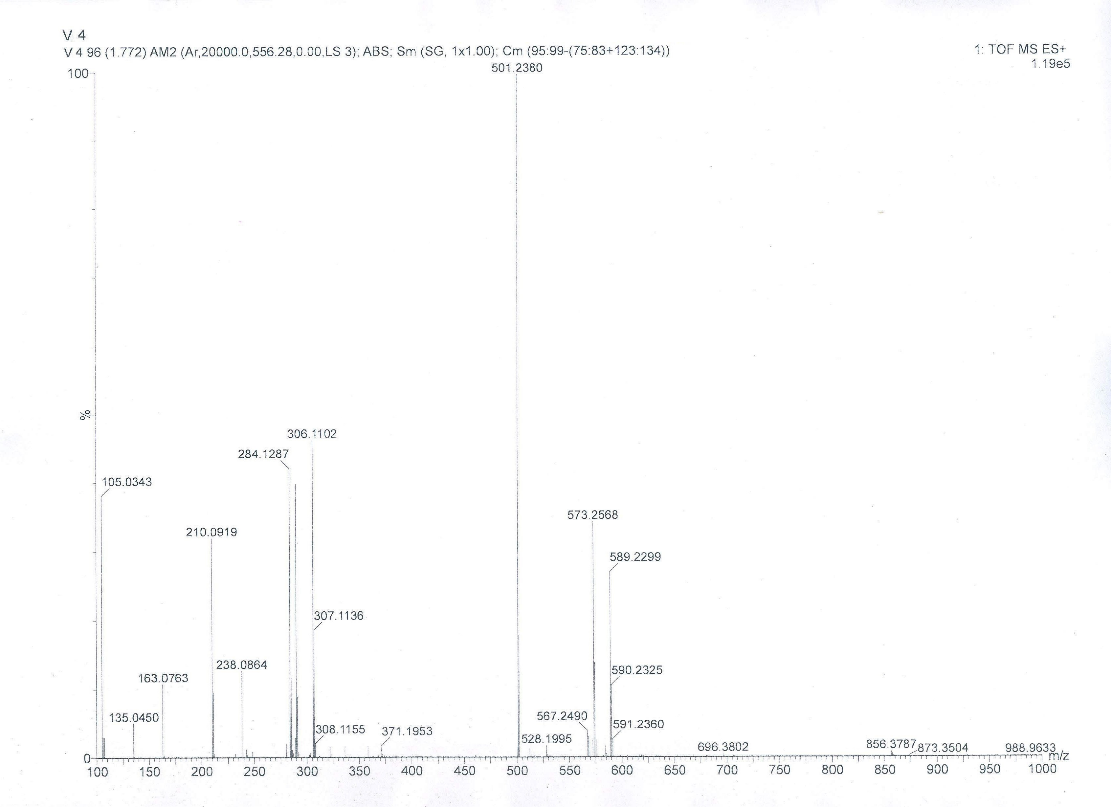
HRMS of compound 3h



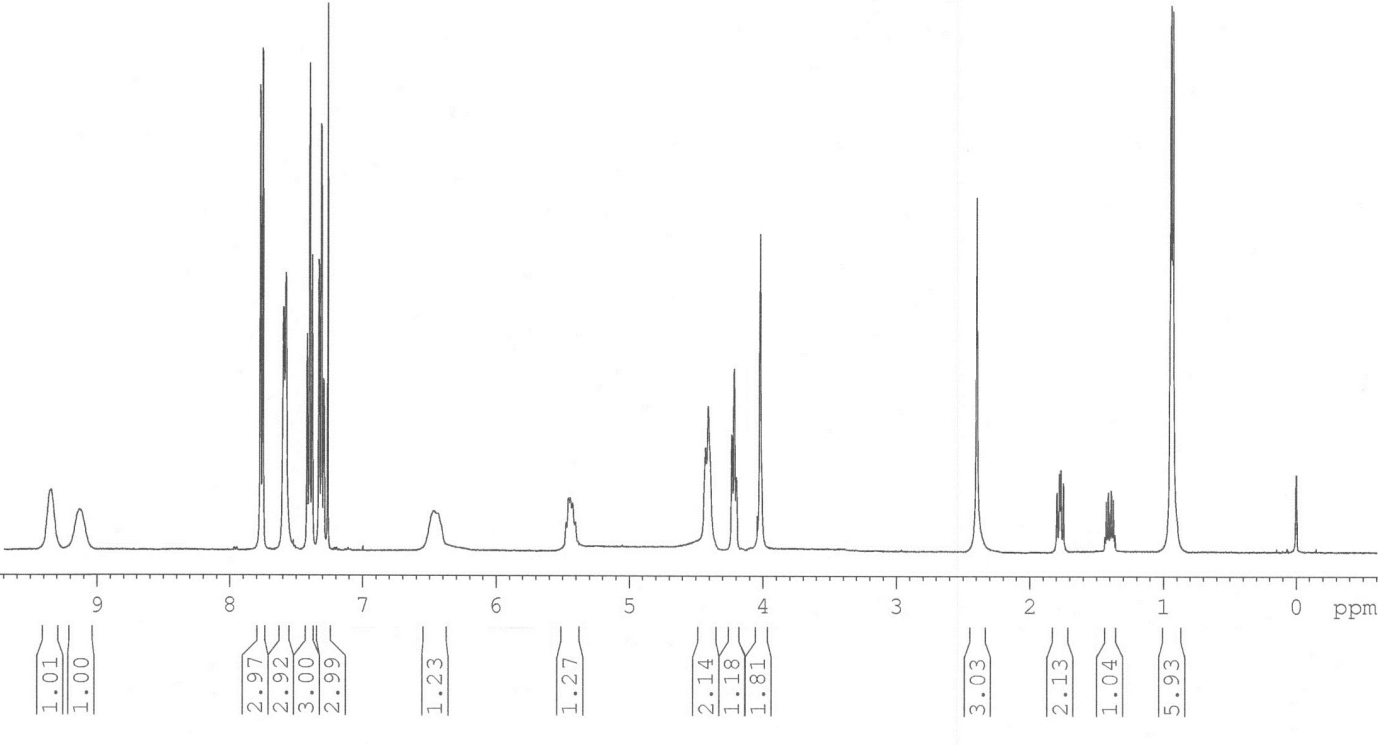
1H NMR Spectrum of Compound 3i



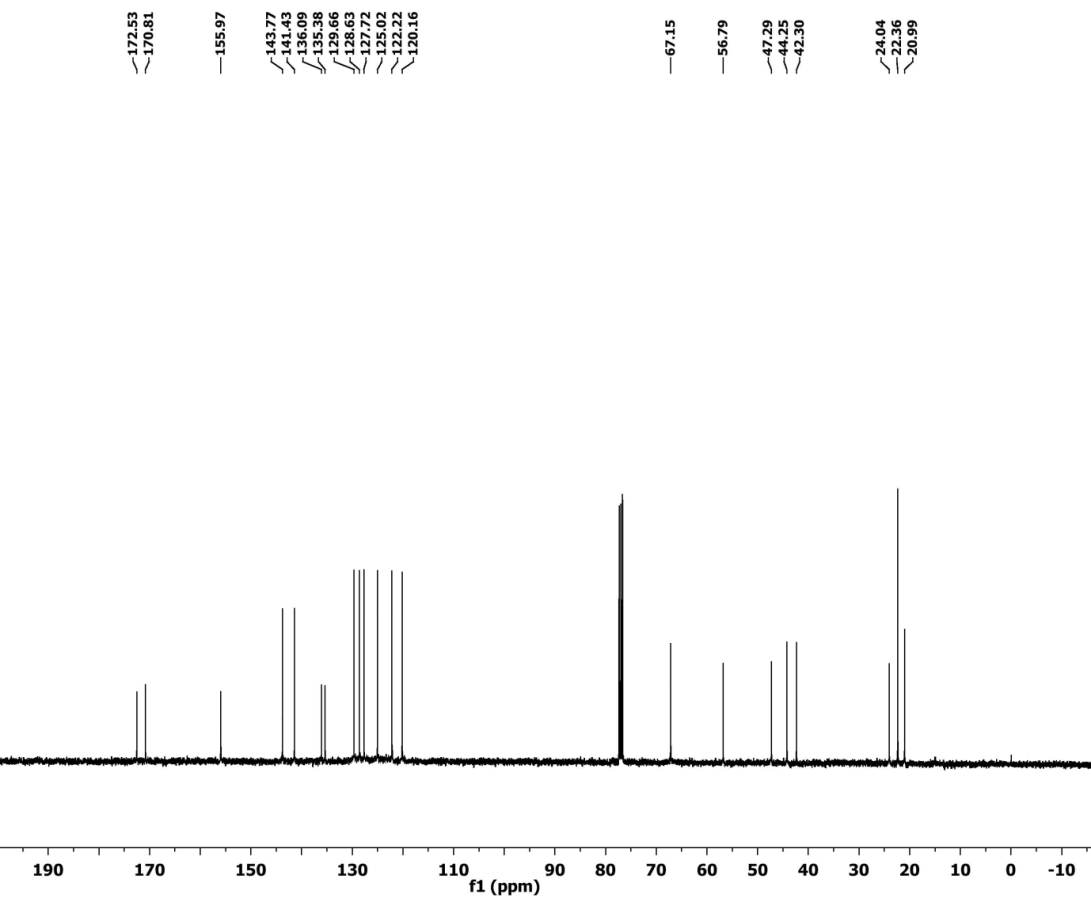
13C NMR Spectrum of Compound 3i



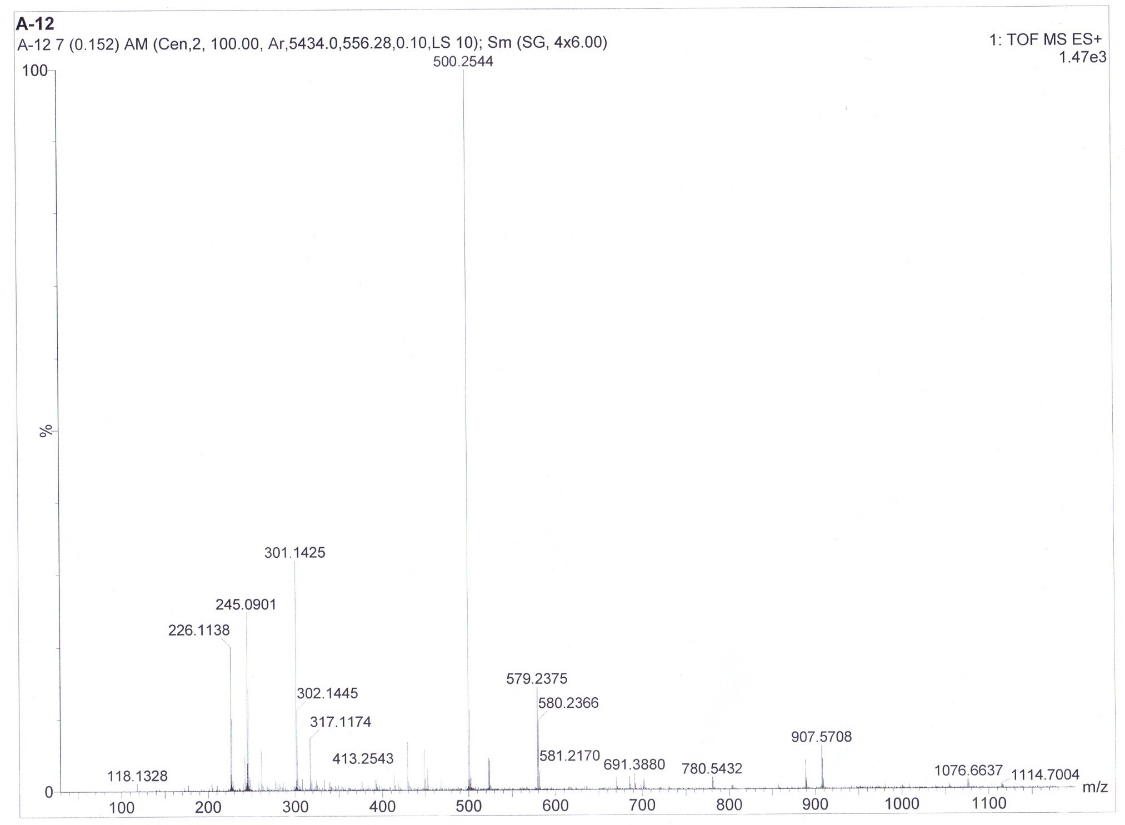
HRMS of compound 3i



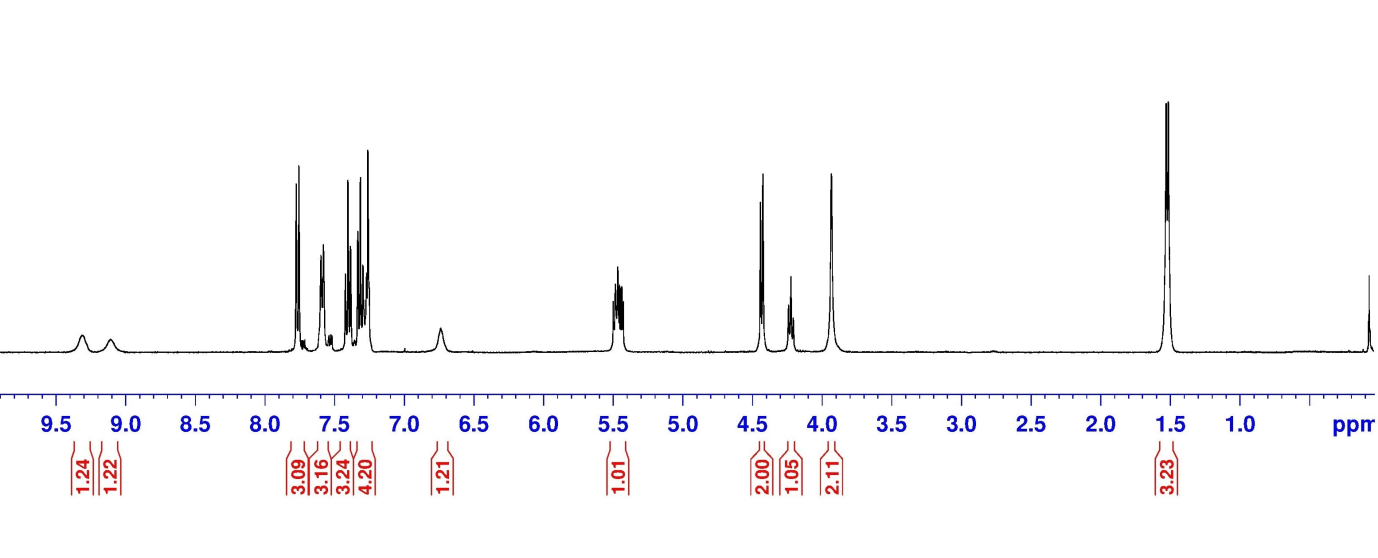
1H NMR Spectrum of Compound 6a



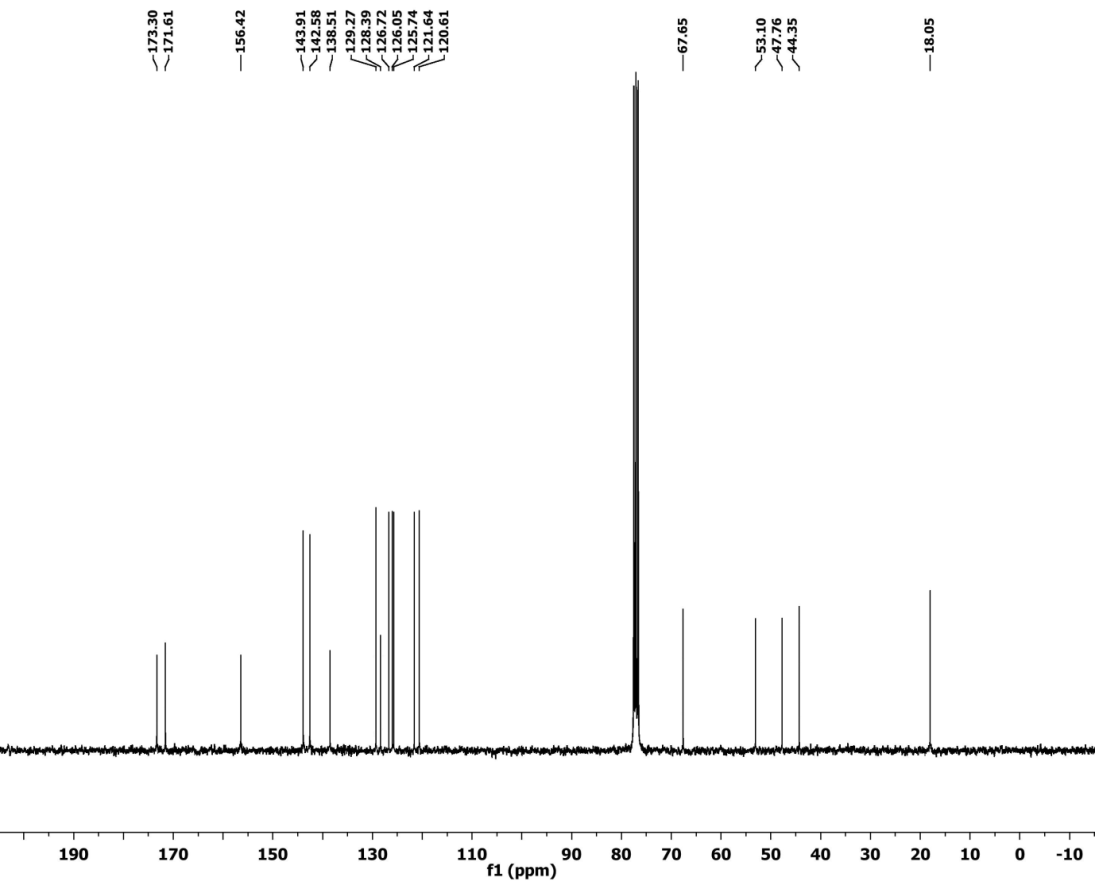
13C NMR Spectrum of Compound 6a



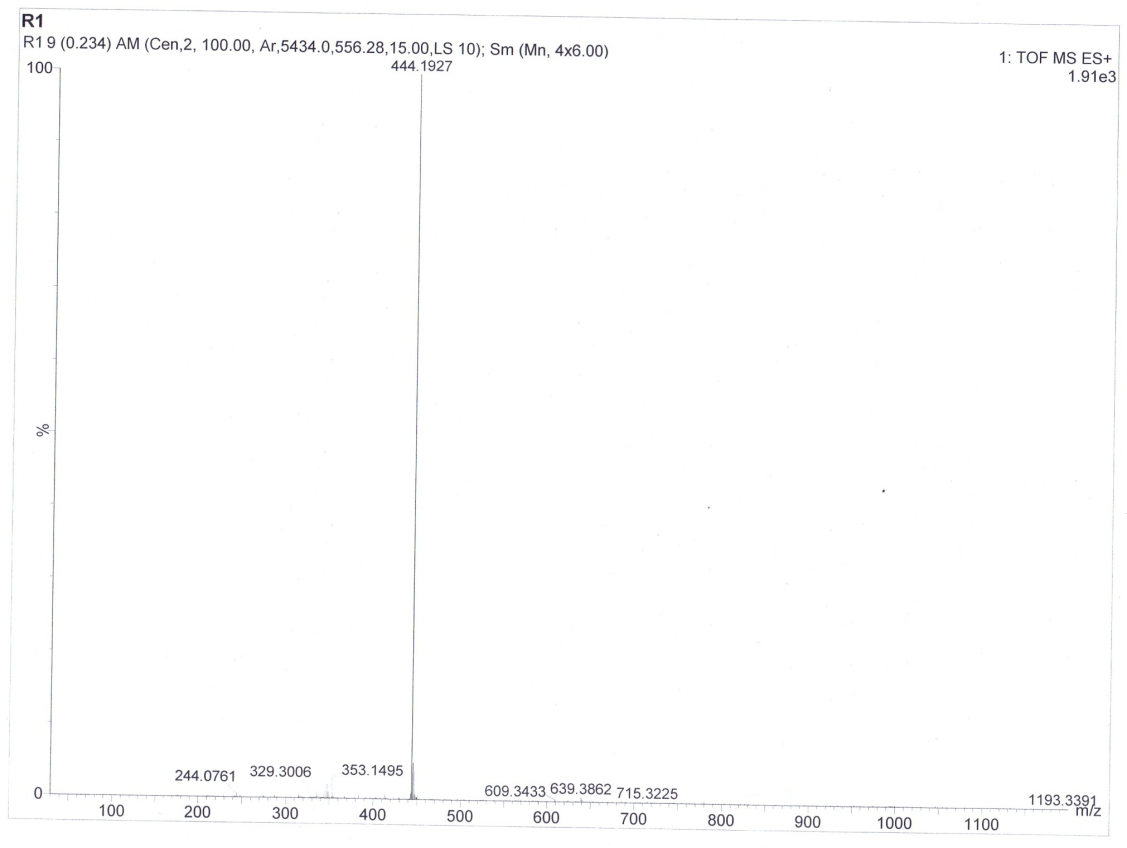
HRMS of compound 6a



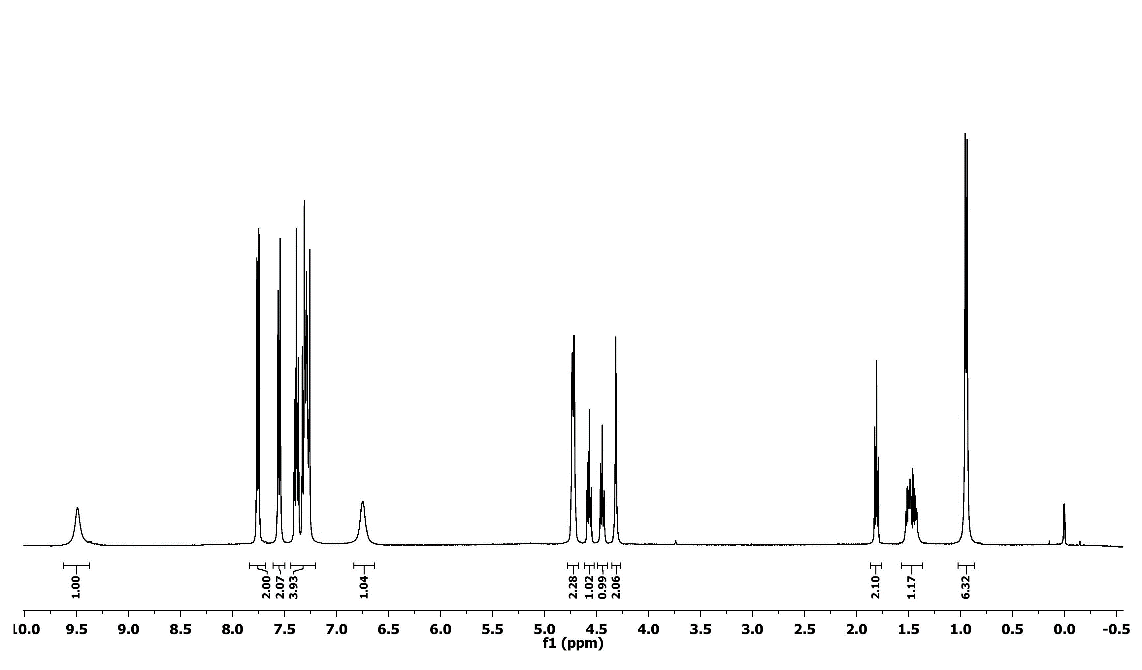
1H NMR Spectrum of Compound 6b



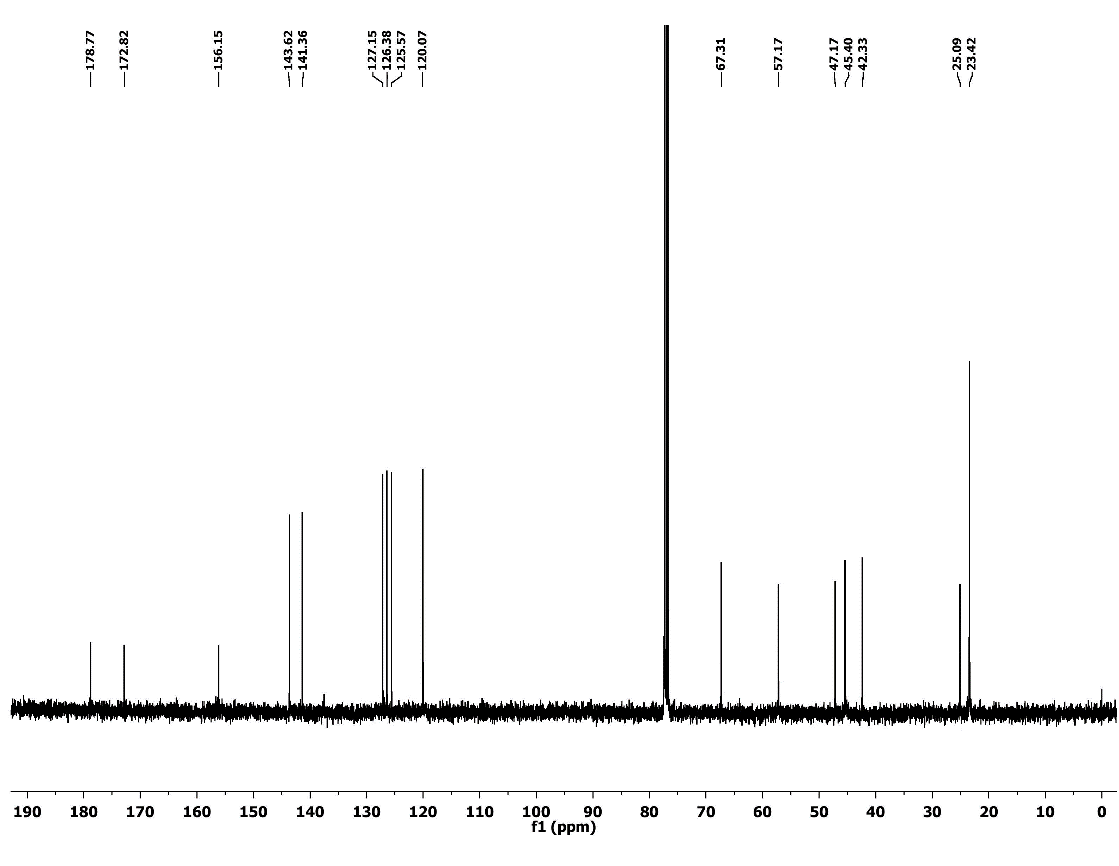
13C NMR Spectrum of Compound 6b



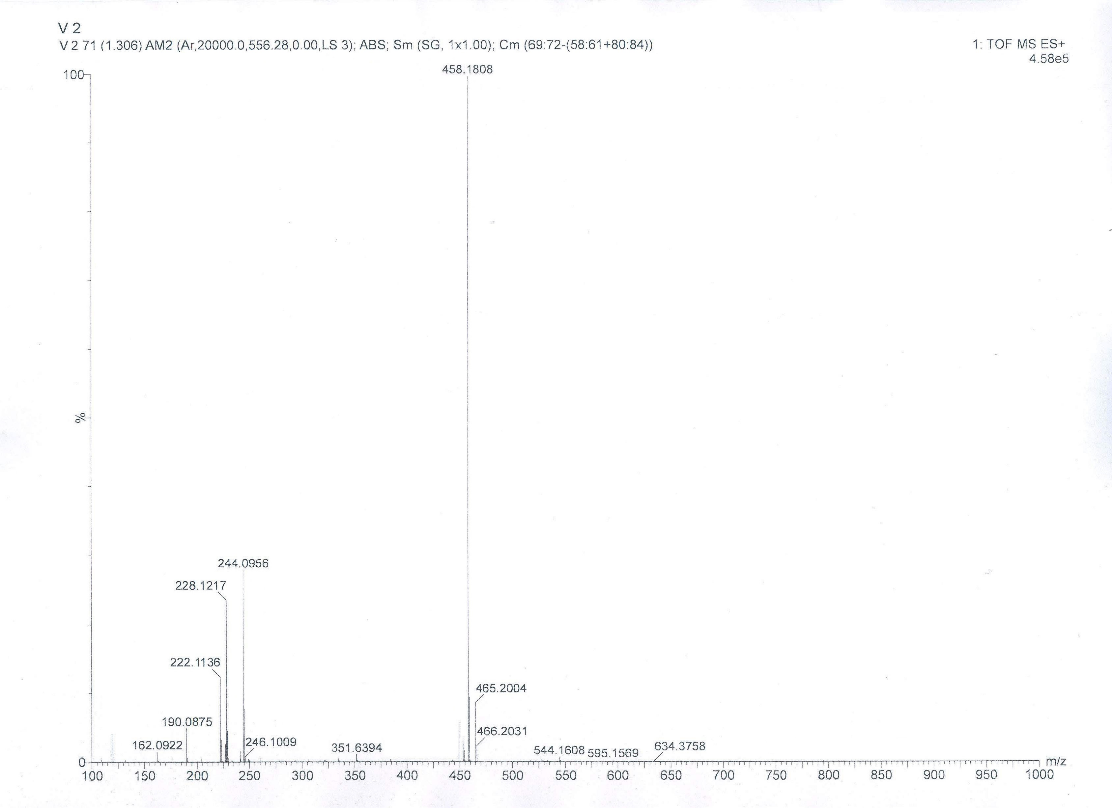
HRMS of compound 6b



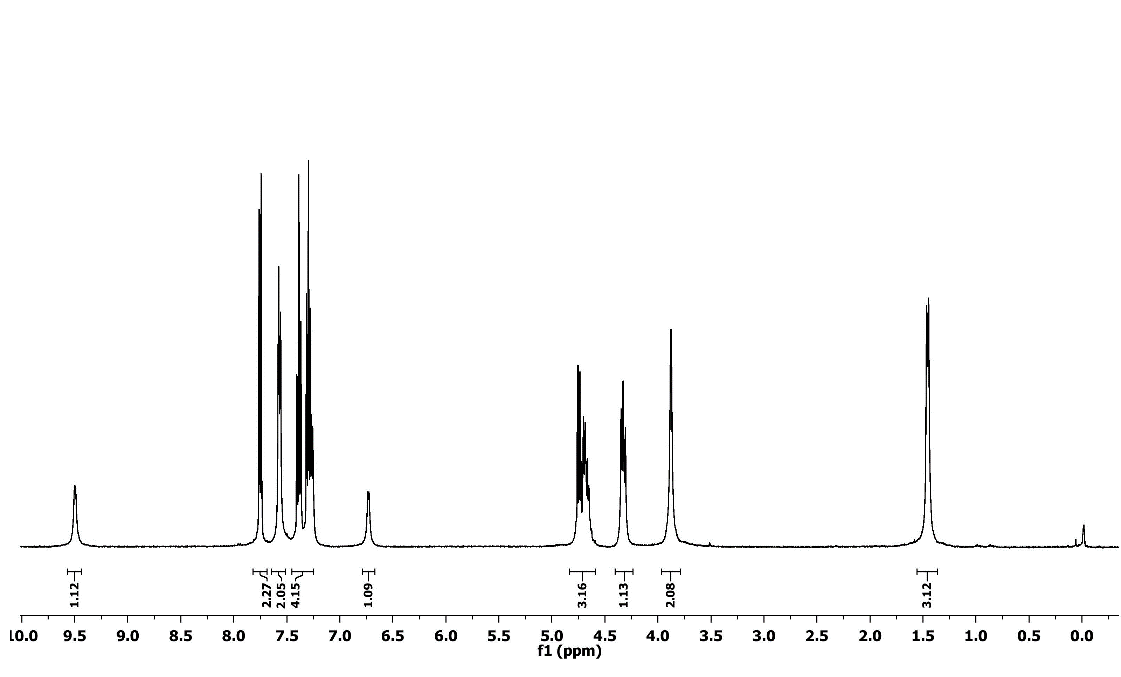
1H NMR Spectrum of Compound 5a



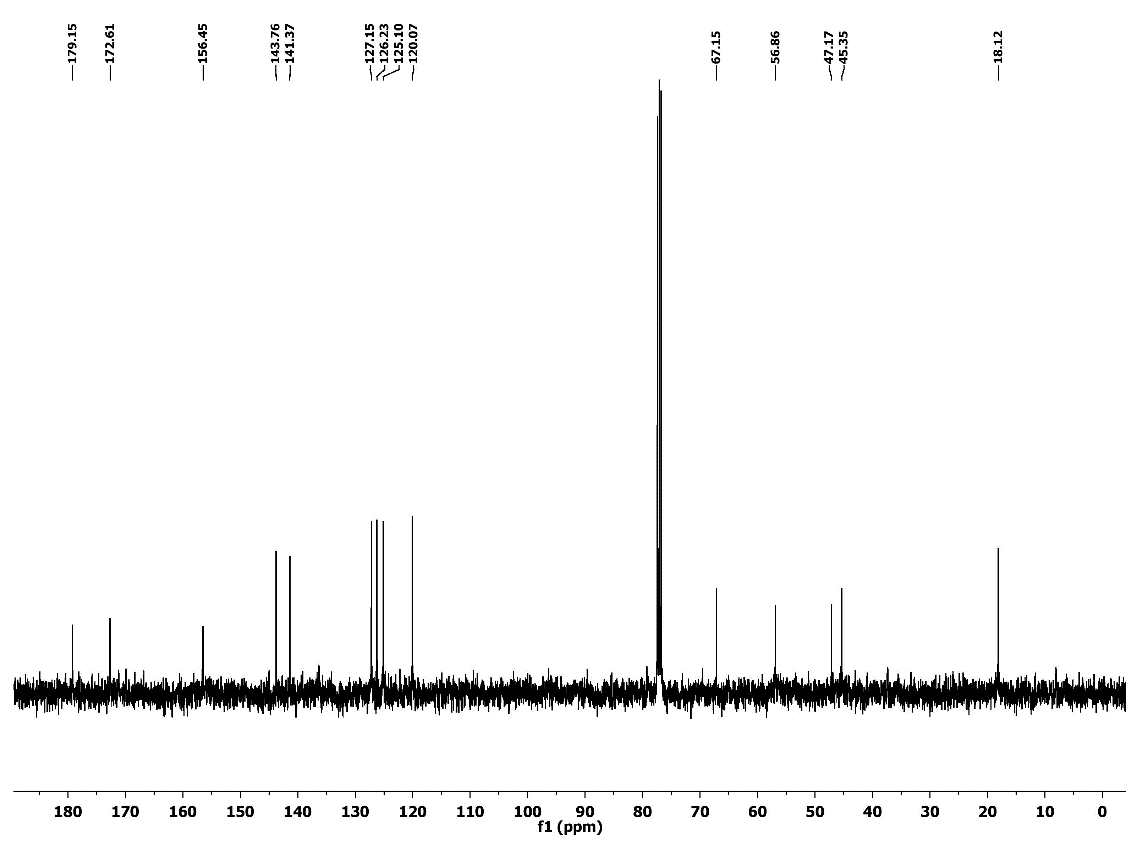
13C NMR Spectrum of Compound 5a



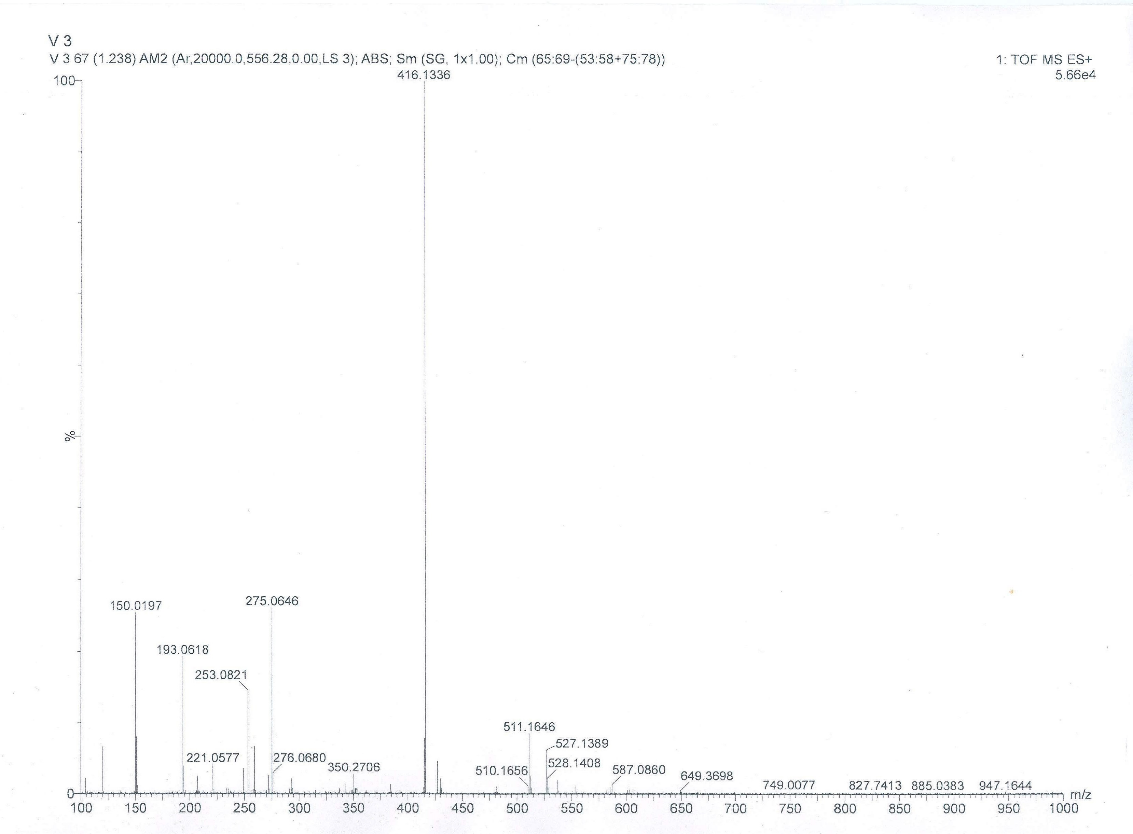
HRMS of compound 5a



1H NMR Spectrum of Compound 5b



13C NMR Spectrum of Compound 5b



HRMS of compound 5b