

Synthesis of *N*-urethane protected amino alkyl (*S*-methyl)- isothiuronium compounds and carbodiimide tethered peptidomimetics: An application to guanidino and substituted guanidino peptidomimetics synthesis

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Supporting information

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General methods

All solvents were freshly distilled before use. Amino acids were used as received from Sigma-Aldrich Company, USA. All the amino acids used, except glycine, are of L-configuration unless otherwise specified. IR spectra were recorded on Shimadzu model FT-IR spectrophotometer (KBr pellets, 3 cm^{-1} resolution). High resolution mass spectra were recorded on a Micromass Q-TOF micro mass spectrometer and PE-SCIEX 150 EX LCMS using electron spray ionization mode, elemental analyses were carried out using Carlo Erba 1106 CHN analyzer, ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX spectrometer using TMS as an internal standard. The ultrasound bath (Elma, T 310/H) was German made and operated at 35 kHz. The RP-HPLC experiments were carried out in Agilent 1100 series instrument having G1311A VWD at $\lambda = 254\text{ nm}$ for Fmoc, 230 nm for Z and 211 nm for Boc compounds, flow 0.5 mL/min, column: Agilent Eclipse XDB-C18, pore size- $5\mu\text{m}$, diameter x length = $4.6 \times 150\text{ mm}$; method: gradient 0.1% TFA, water-acetonitrile system in 30 min. Chiral HPLC analysis was recorded on phenominex made Lux, pore size- 5μ , cellusole-1, diameter x length = $250 \times 4.6\text{ mm}$. TLC experiments were done using MERCK TLC aluminium sheets (silica gel 60 F₂₅₄) and chromatograms were visualized by exposing in iodine chamber, UV-lamp or spraying with KMnO_4 and heating. Column chromatography was performed on neutral alumina and silica gel (100-200 mesh) using ethyl acetate and hexane mixtures as eluent.

Experimental

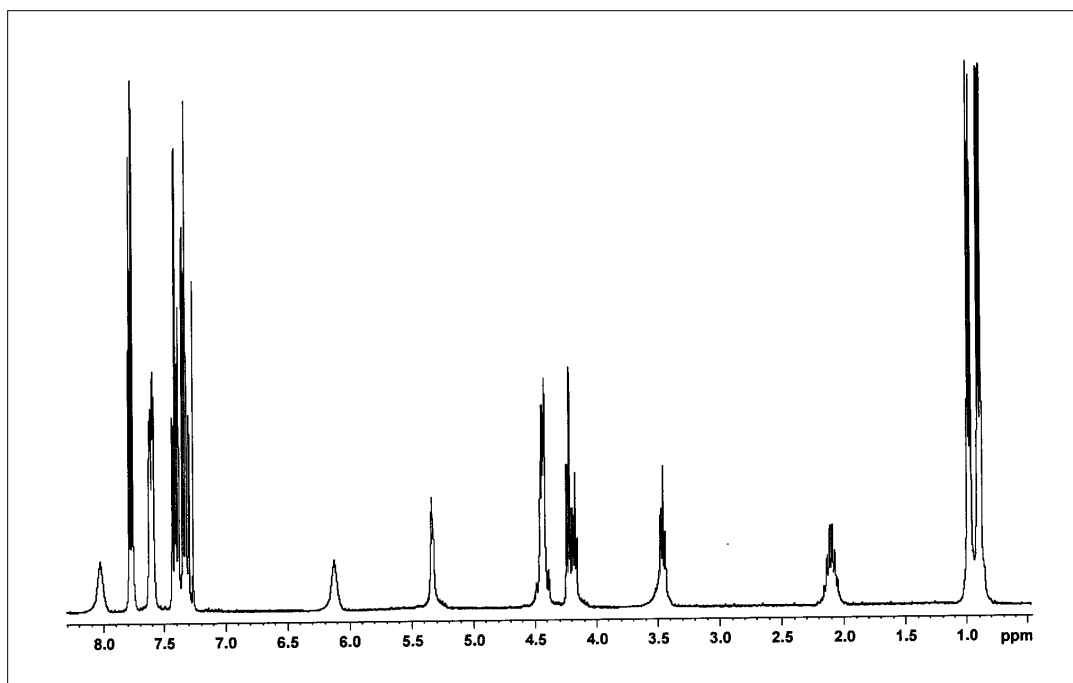
General procedure for the synthesis of *N*^α-protected amino alkyl thioureas 2a-h: To a stirred solution of *N*^α-protected amino alkyl isothiocyanate (1.0 mmol) in THF (5.0 mL) was added 3.0 eq of ammonium bicarbonate in 3.0 mL of water. The reaction mixture was cooled to 0 °C and stirred further for 3 h. After completion of the reaction as monitored through TLC, the reaction mixture was concentrated and diluted with EtOAc. The organic layer was washed with water (10 mL) and brine (5 mL) and dried over anhydrous sodium sulfate. The organic layer was evaporated *in vacuo* to afford the product **2** in quantitative yield.

General procedure for the synthesis of *N*^α-protected amino alkyl isothiuronium derivatives 3a-h: To a solution of *N*^α-protected amino alkyl thiourea **2** (1.0 mmol) in acetone (8.0 mL) was added methyl iodide (1.5 mmol) and the reaction mixture was heated at reflux. The reaction was completed in 1-2 h as judged by TLC. Then the solvent was evaporated *in vacuo* and the resultant product **3** was obtained in excellent yield.

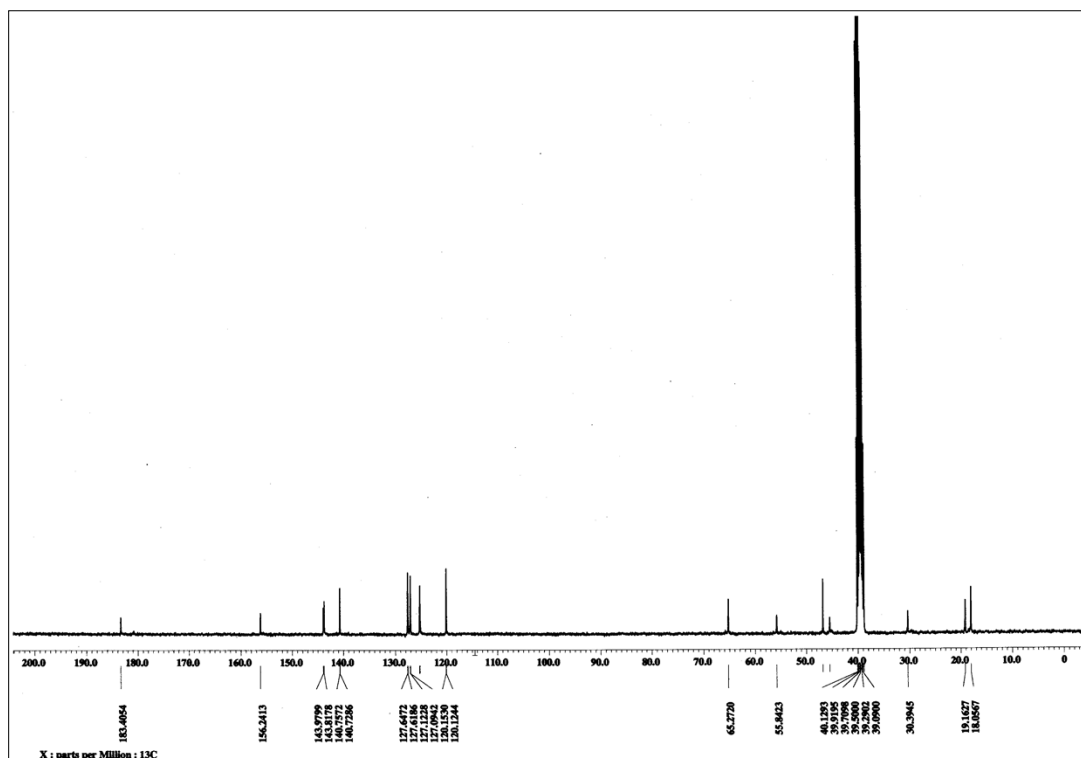
General procedure for the synthesis of guanidine tethered peptidomimetics 4a-c, 4e, 4g-h: To a neutralized solution of isothiuronium derivative **3** (1.0 mmol) in acetonitrile (6.0 mL) was added amino acid ester (1.3 mmol). The resultant mixture was heated at 60 °C till the completion of the reaction as monitored through TLC. After completion of the reaction, solvent was evaporated *in vacuo* and the obtained crude product **4** was then purified through column chromatography. [*Caution:* reaction has to be carried out in a fume hood as it involves the expulsion of toxic methyl mercaptan (CH₃SH) as byproduct].

General procedure for the synthesis of carbodiimide 5 and guanidine tethered peptidomimetics 4i-m: To a solution of *N*-protected amino alkyl azide in dry CH₂Cl₂ at 0 °C was added triphenylphosphine (1.2 mmol). The reaction mixture was stirred for 10-15 min. then isothiocyanato ester (1.3 mmol) was added and the mixture was stirred for about 2-3 h at same temperature till the completion of the reaction. The progress of the reaction was monitored through IR, where it showed a strong absorption band in the region 2116-2130 cm⁻¹ characteristic of carbodiimide 5. The solvent was evaporated under reduced pressure and the product was purified through neutral alumina. To the solution of carbodiimide 5, in CH₃CN was added NH₄Cl (2.0 mmol). The reaction mixture was heated at 60 °C till the completion of the reaction as monitored through TLC. The organic layer was then evaporated *in vacuo* to afford the crude product 4 in quantitative yield. The product was then purified through column chromatography.

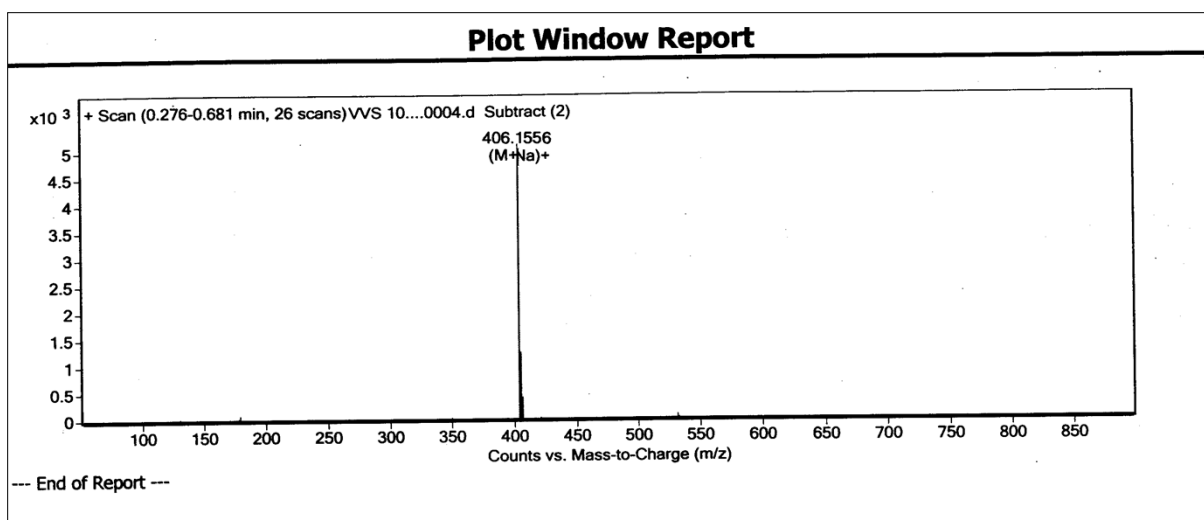
General procedure for the synthesis of *N*-hydroxyguanidine (6a-cb, aminoguanidine (7a-b) and cyanoguanidines (8a-b) and trisubstituted guanidine mimetics (9a-c): To a stirred solution of carbodiimide 5 in acetonitrile (8.0 mL) was added neutralized solution of hydroxylamine hydrochloride or hydrazine hydrate or sodium cyanamide or amine (1.5 mmol). The resulting mixture was heated at 60 °C till the completion of the reaction as monitored by TLC. Then the organic layer was evaporated *in vacuo* to afford the crude product (6, 7, 8 and 9) in quantitative yield. The product was then purified through column chromatography.



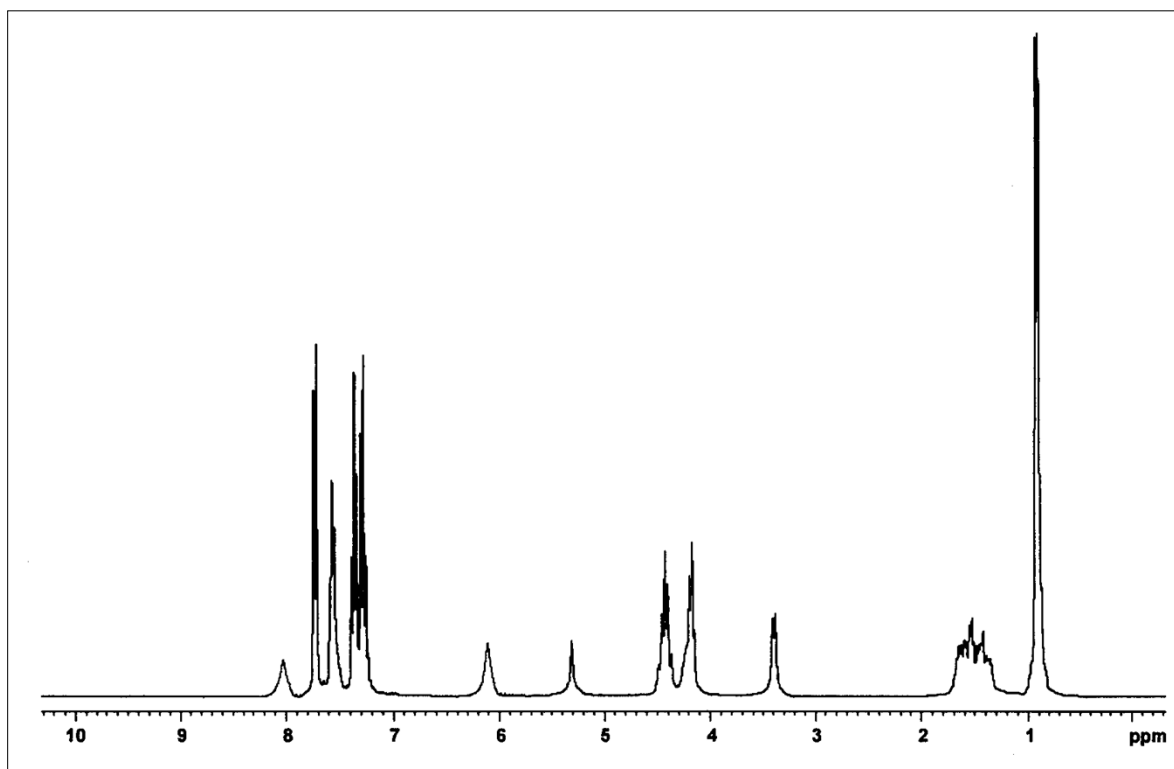
^1H NMR spectrum of compound **2a**



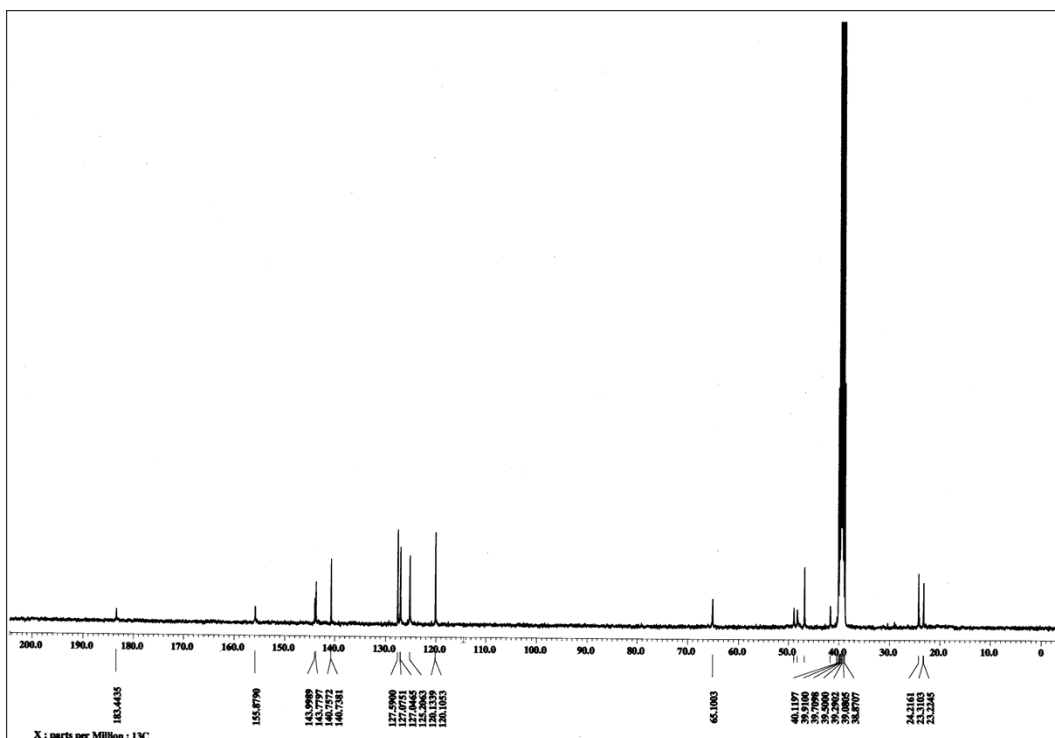
^{13}C NMR spectrum of compound **2a**



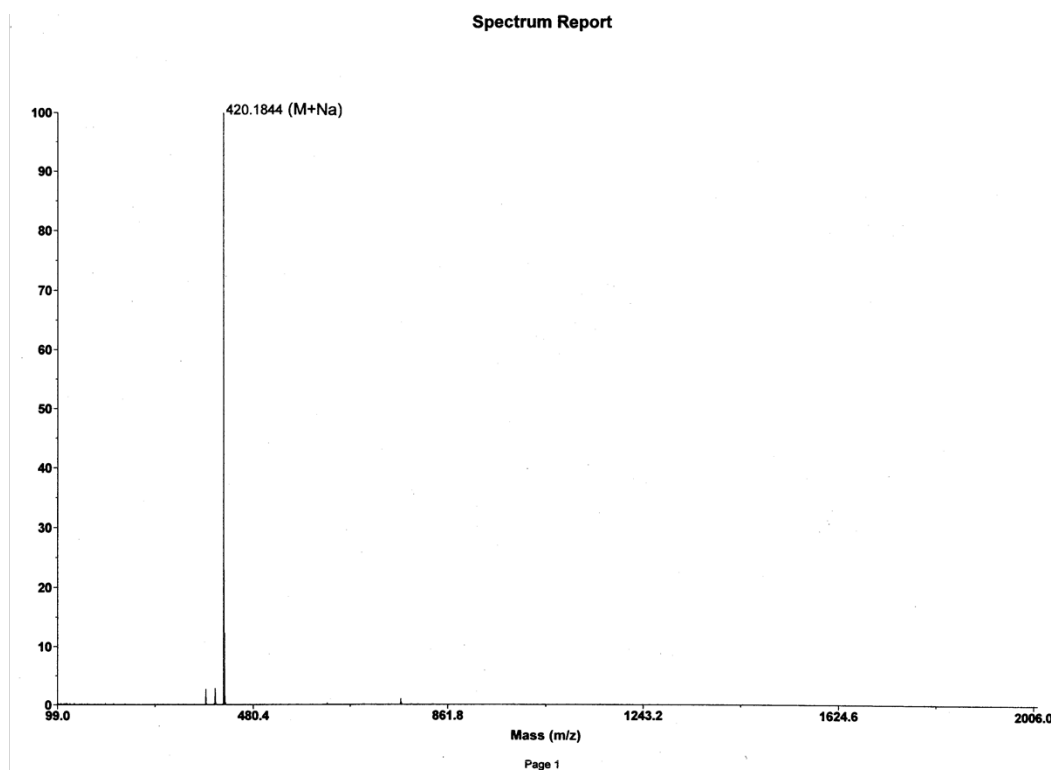
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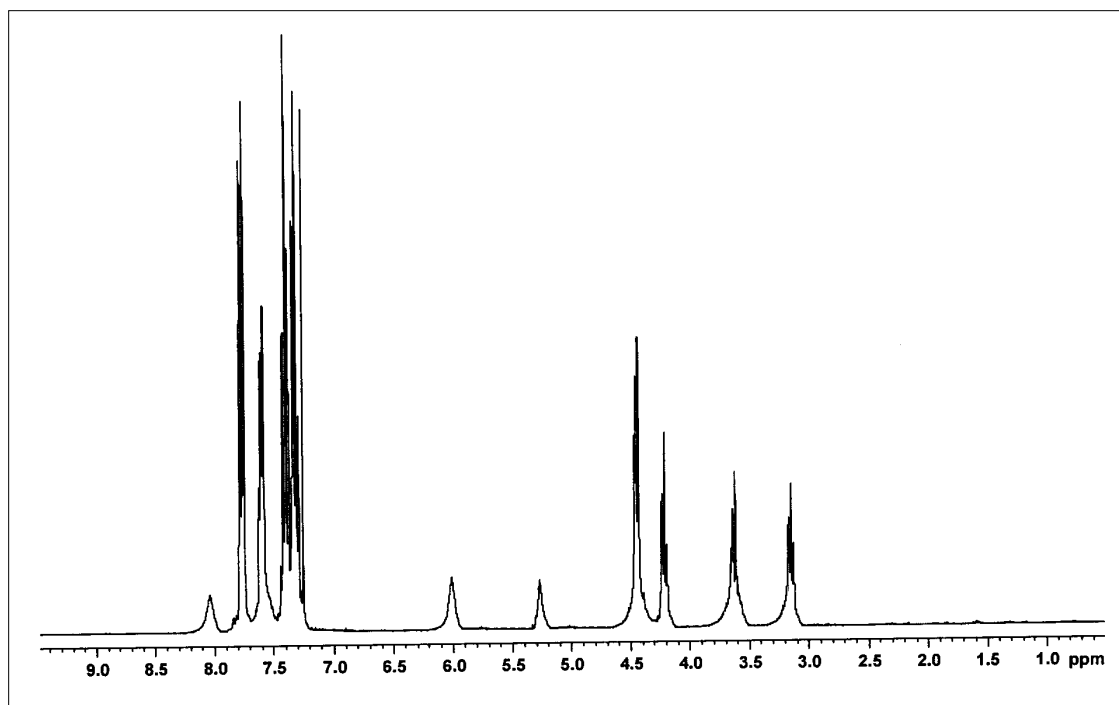
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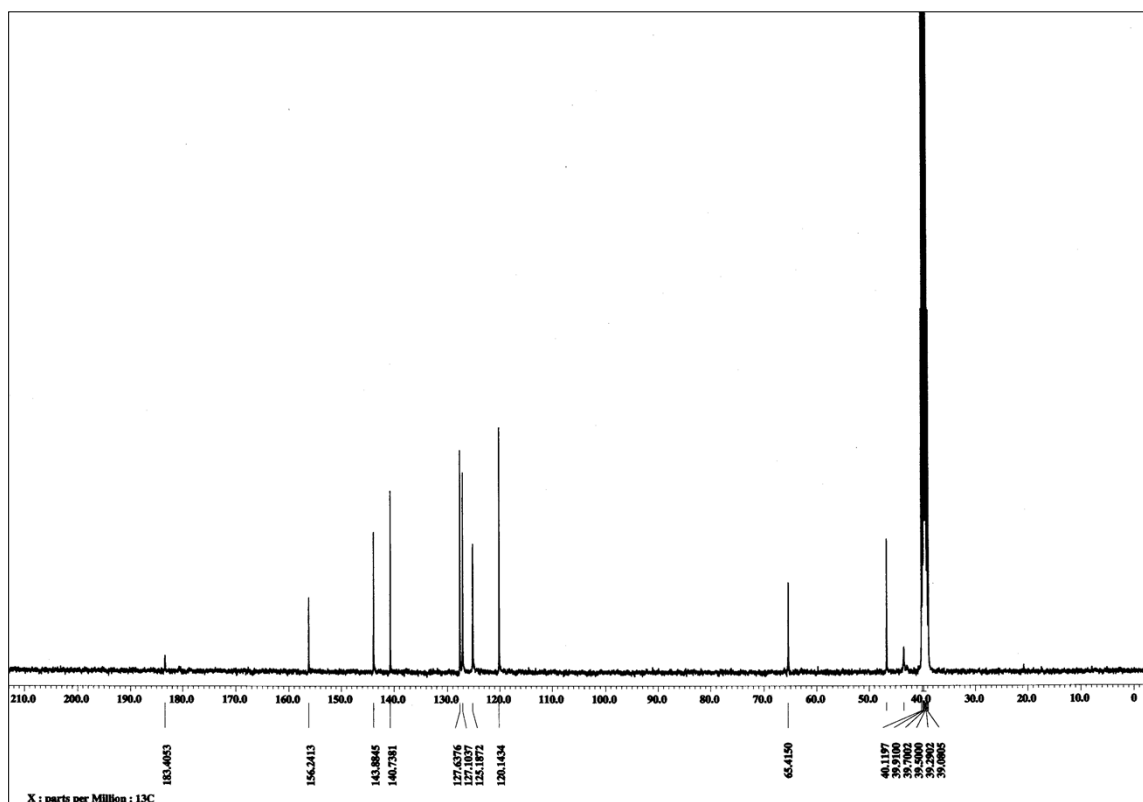
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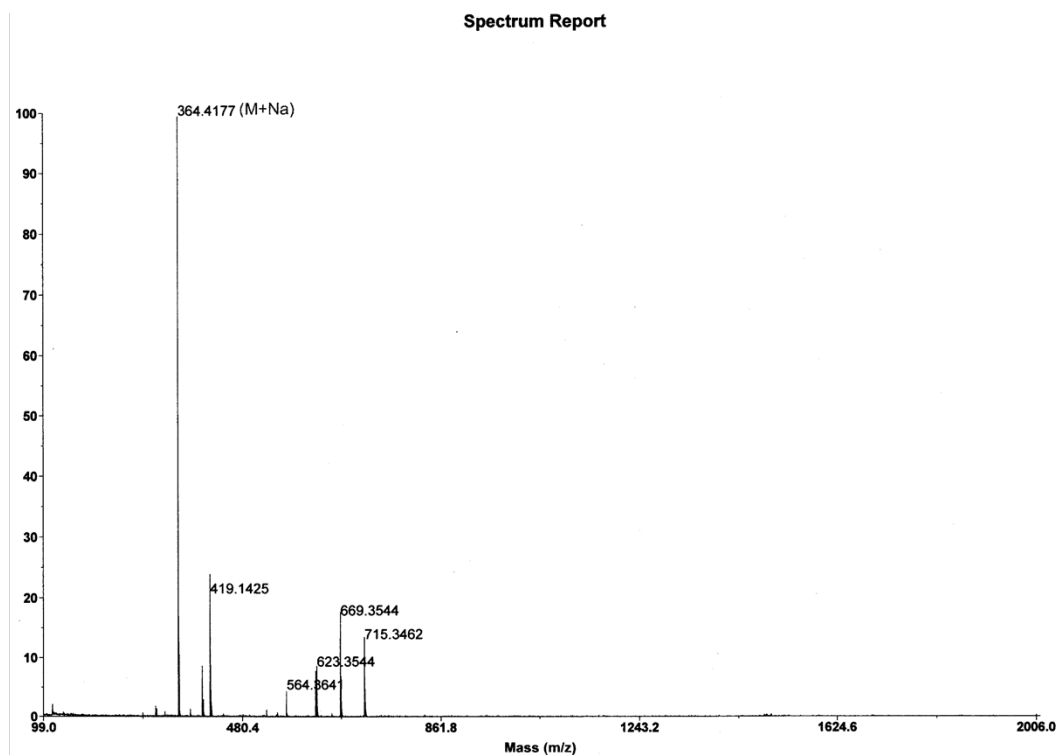
HRMS spectrum of compound **2b**



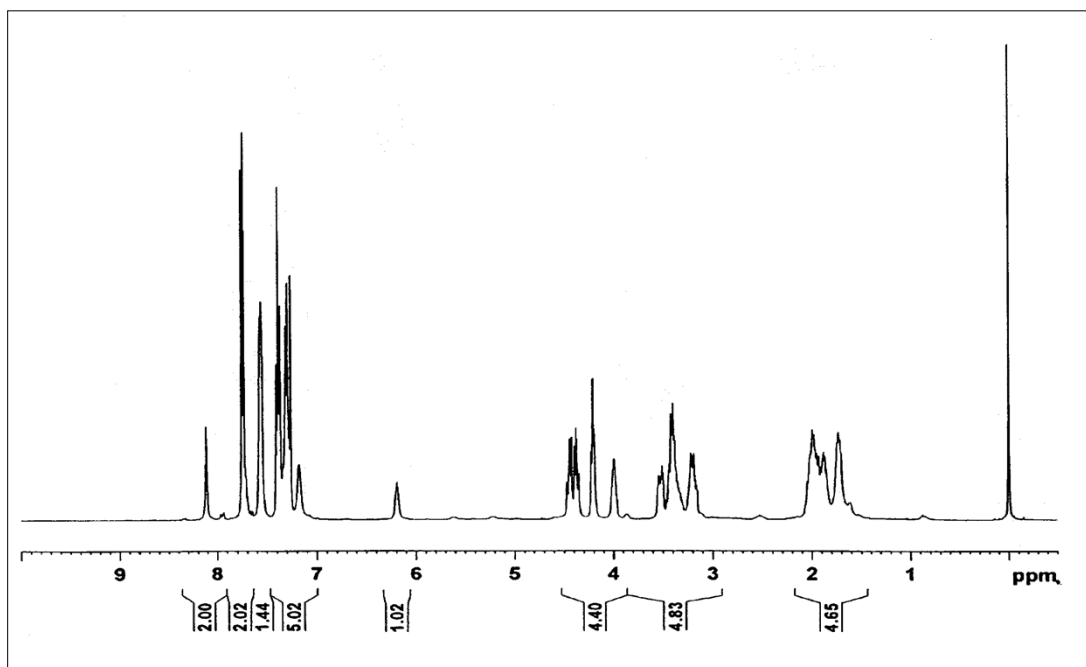
^1H NMR spectrum of compound **2c**



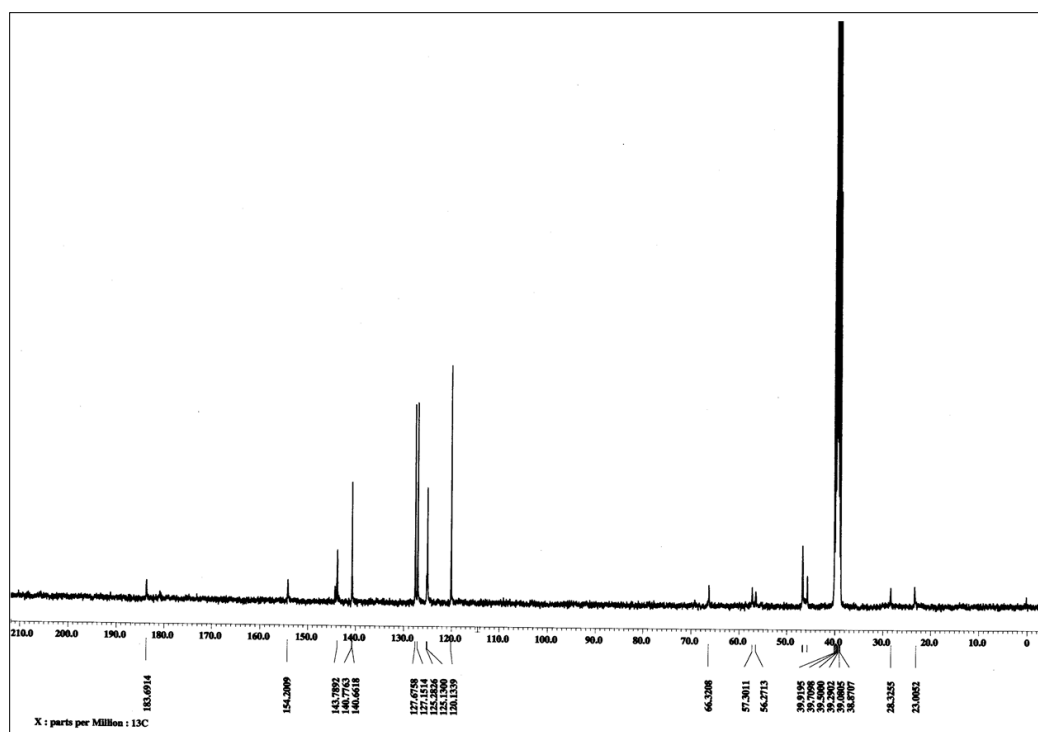
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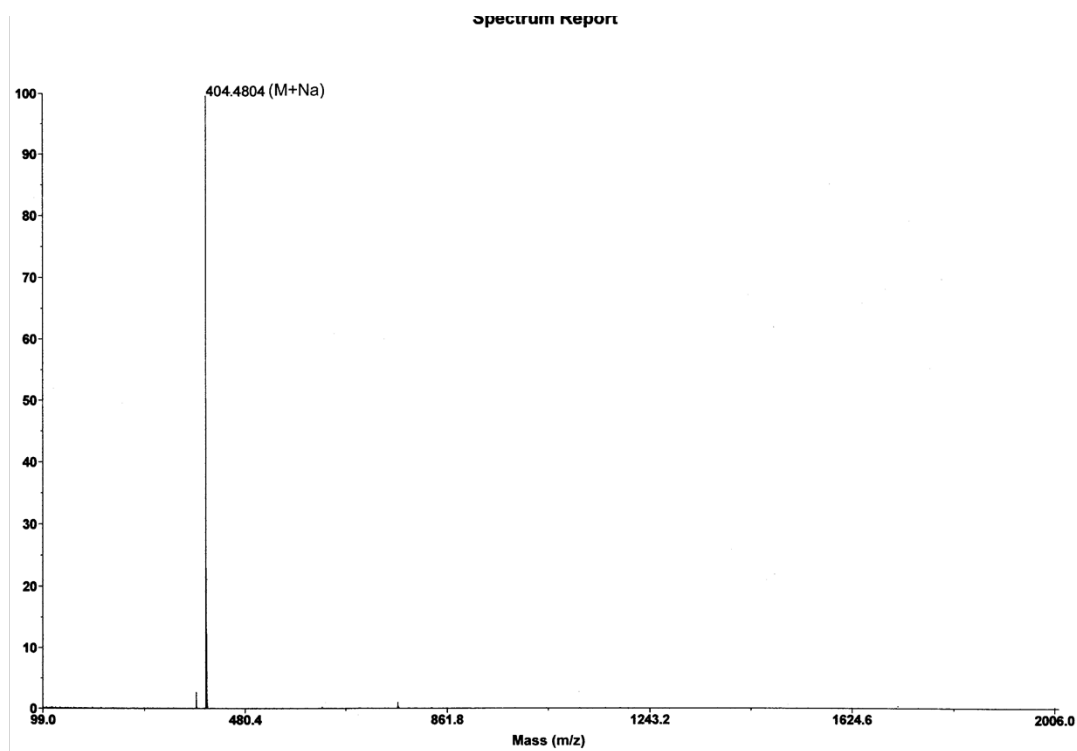
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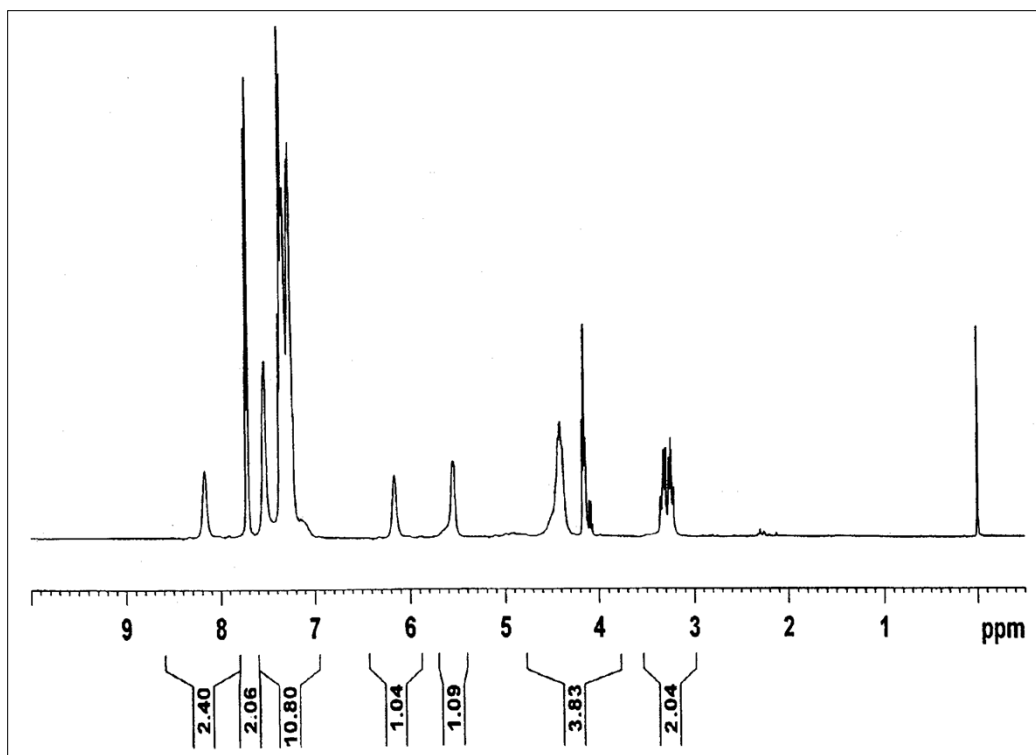
¹H NMR spectrum of compound **2d**



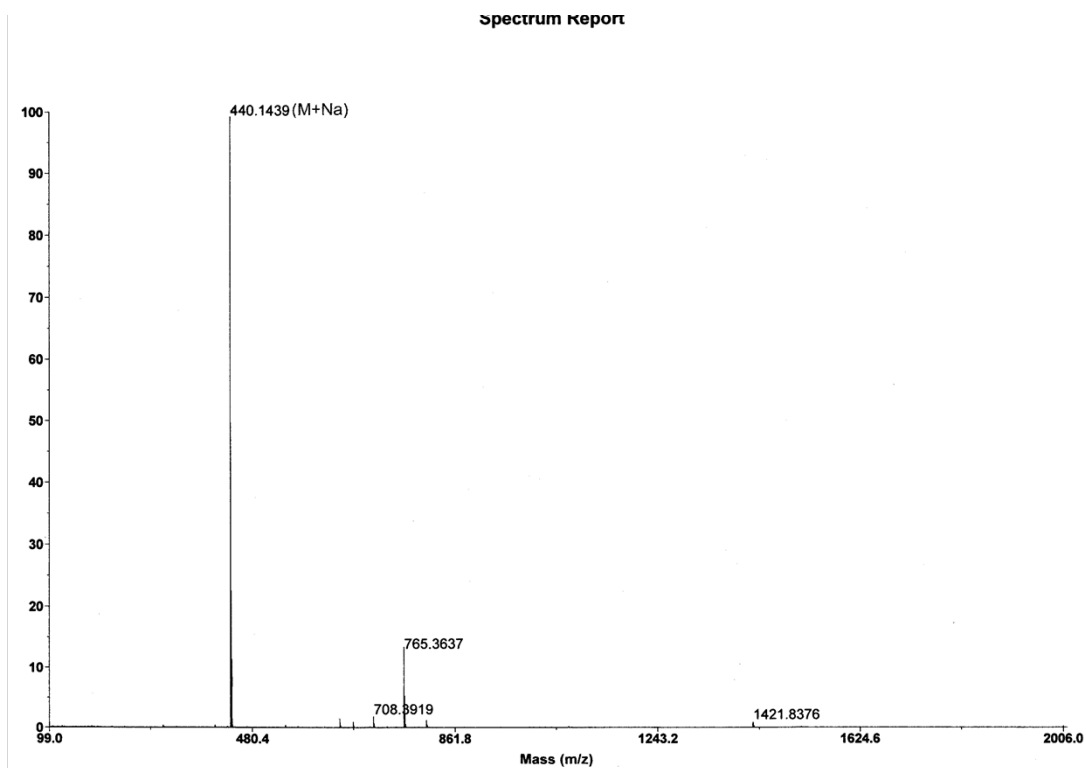
¹³C NMR spectrum of compound **2d**



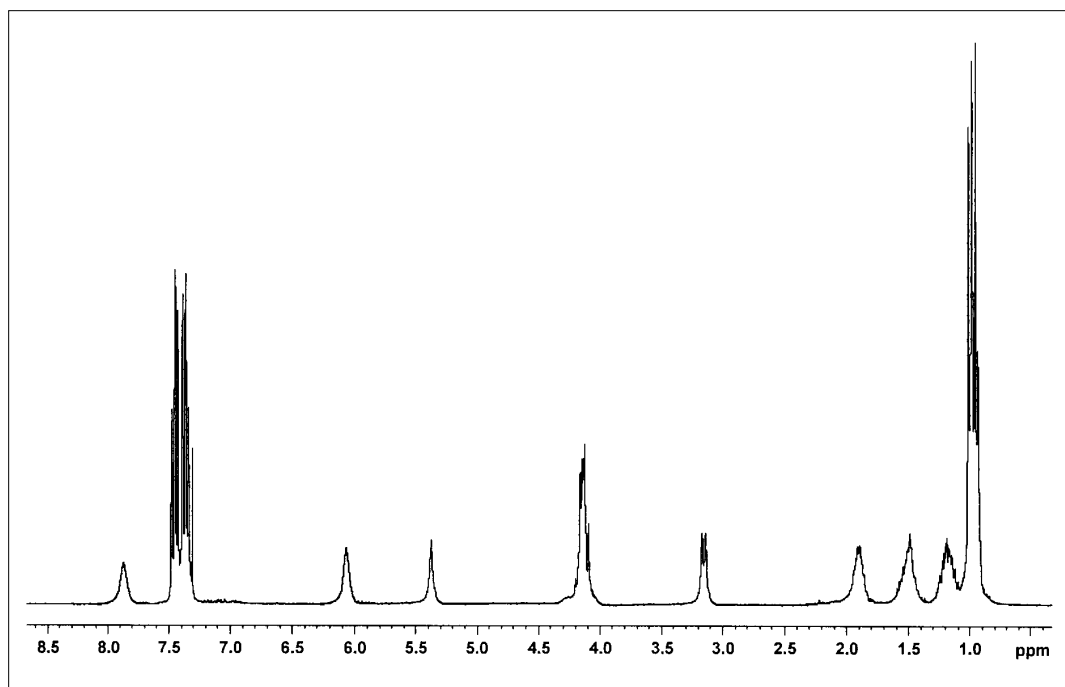
HRMS spectrum of compound **2d**



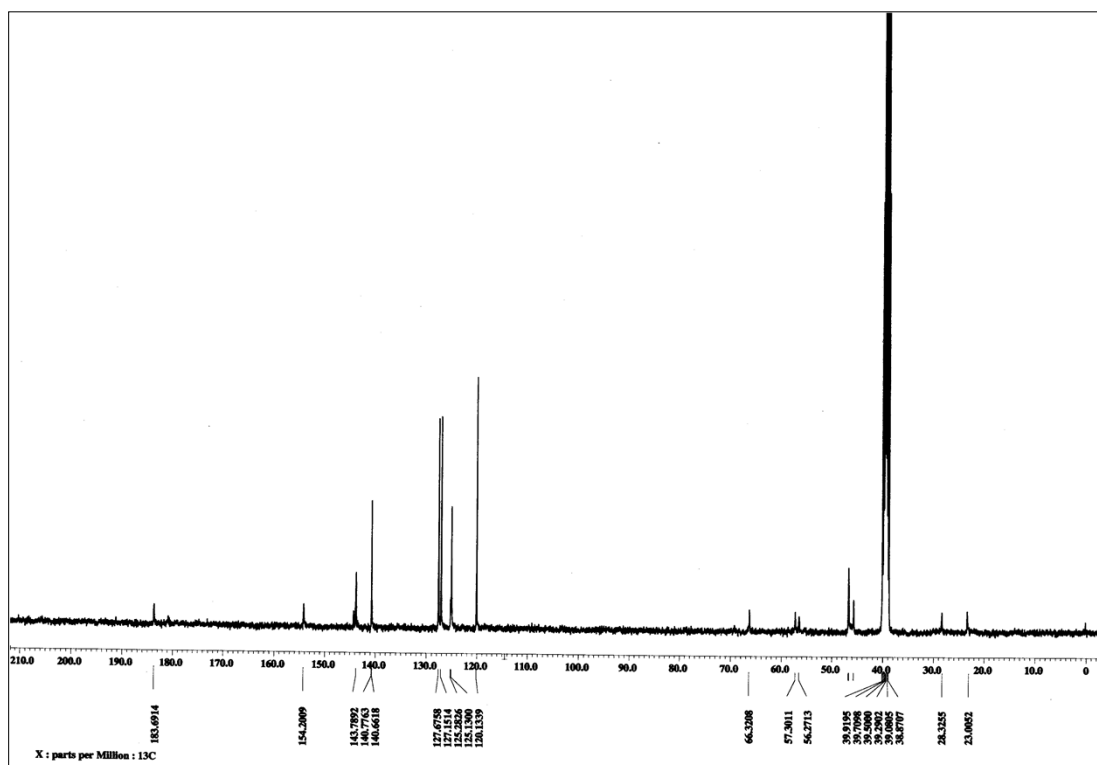
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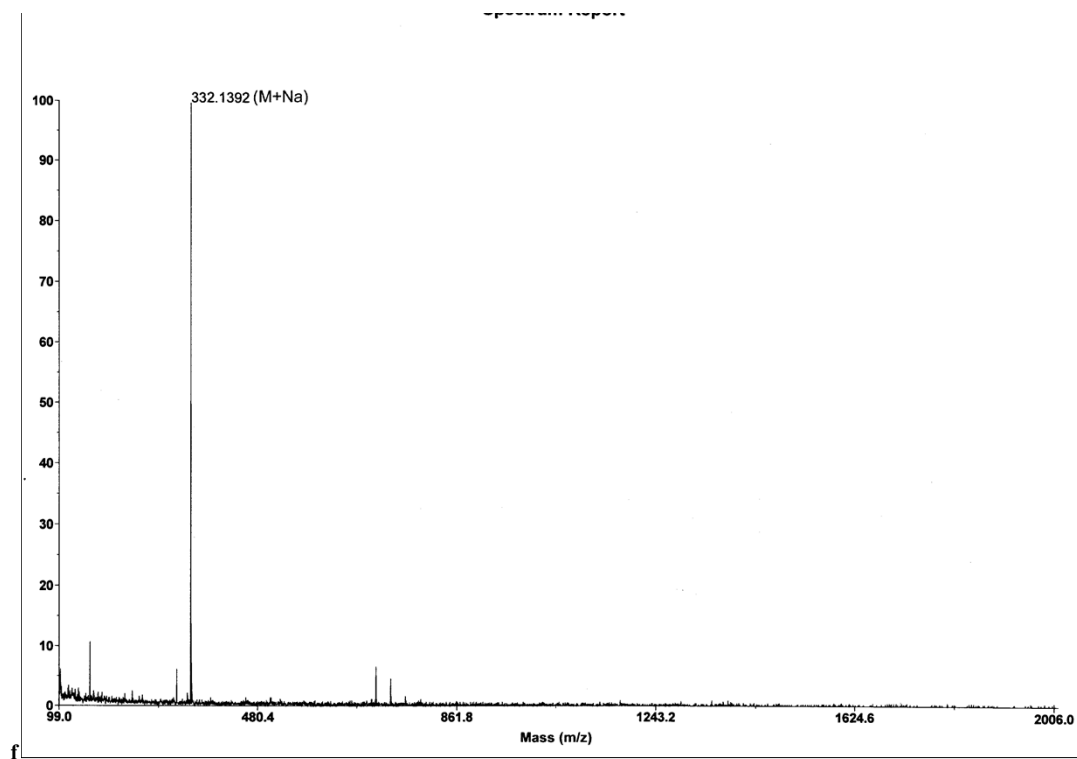
HRMS spectrum of compound **2e**



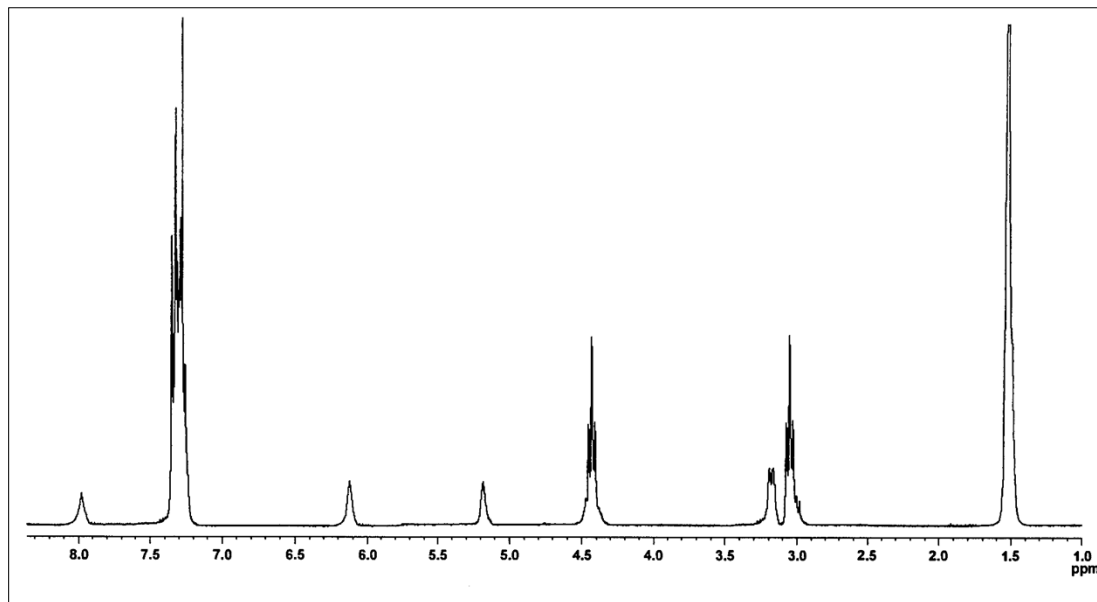
^1H NMR spectrum of compound **2f**



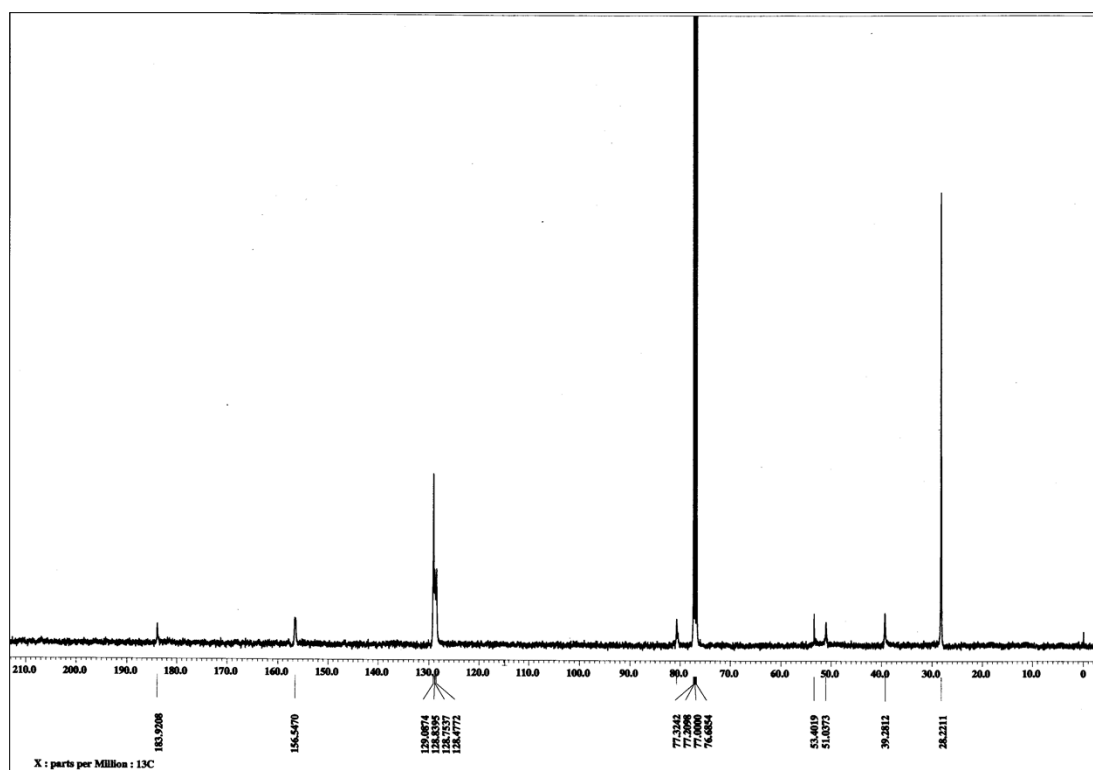
^{13}C NMR spectrum of compound **2f**



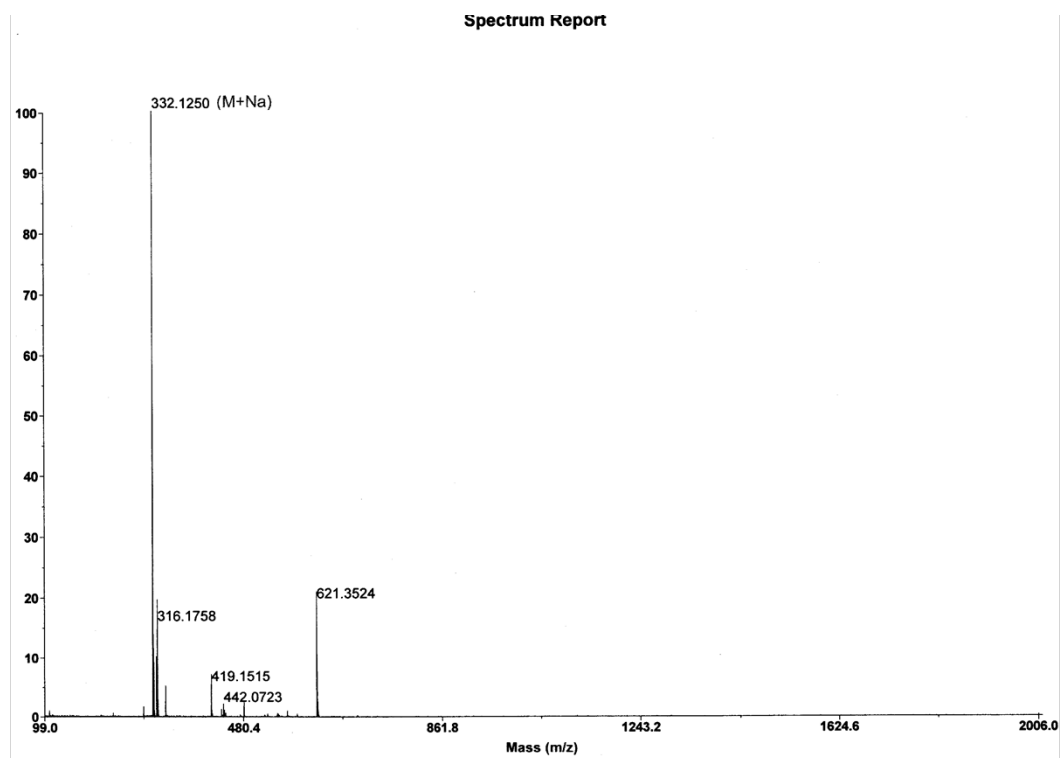
HRMS spectrum of compound **2f**



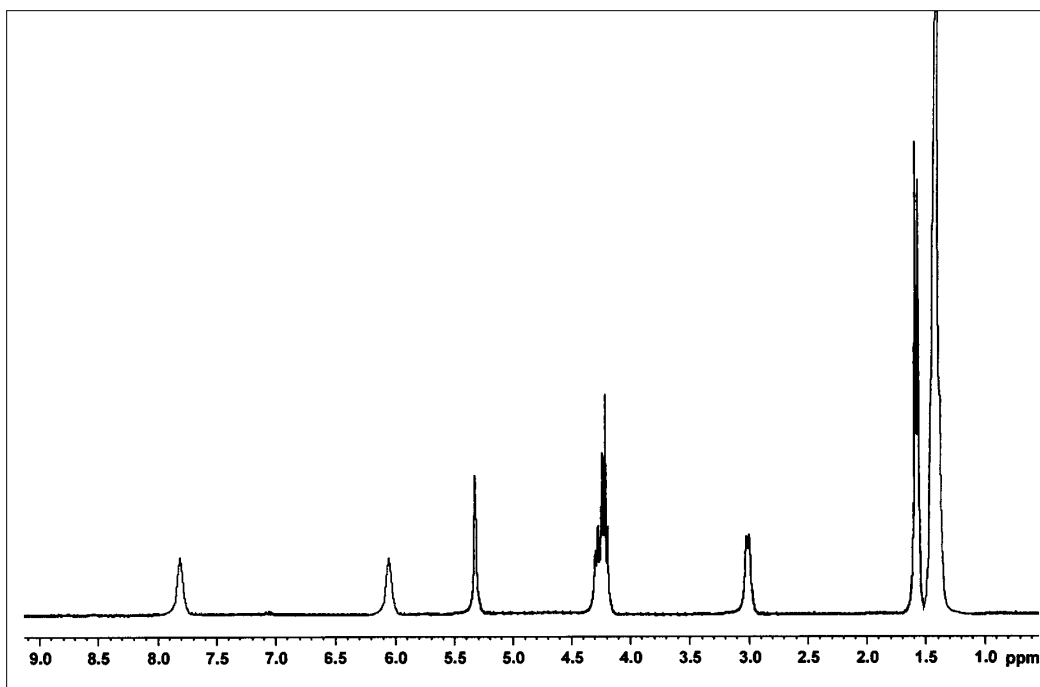
1H NMR spectrum of compound **2g**



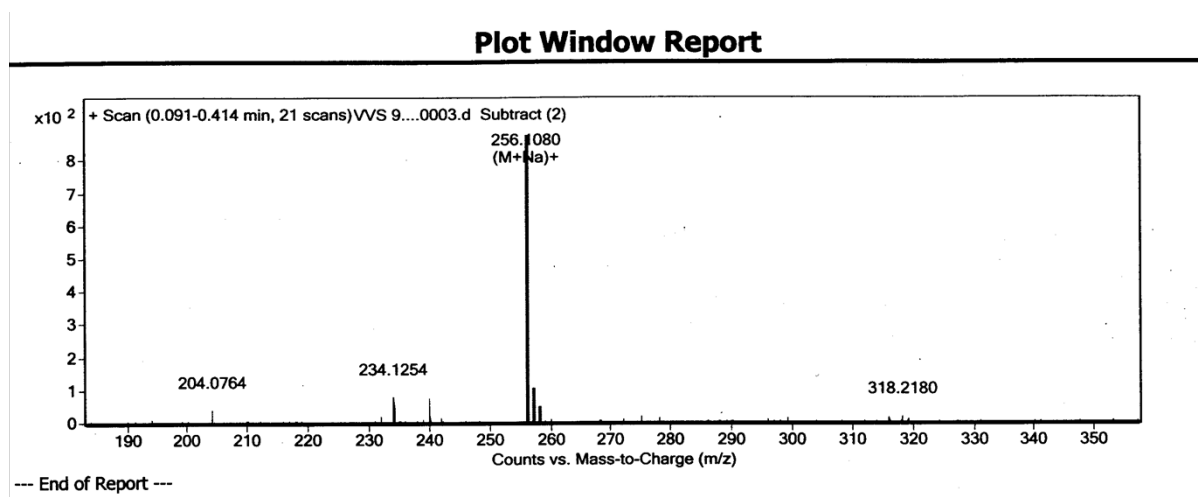
¹³C NMR spectrum of compound 2g



HRMS spectrum of compound 2g



^1H NMR spectrum of compound **2h**



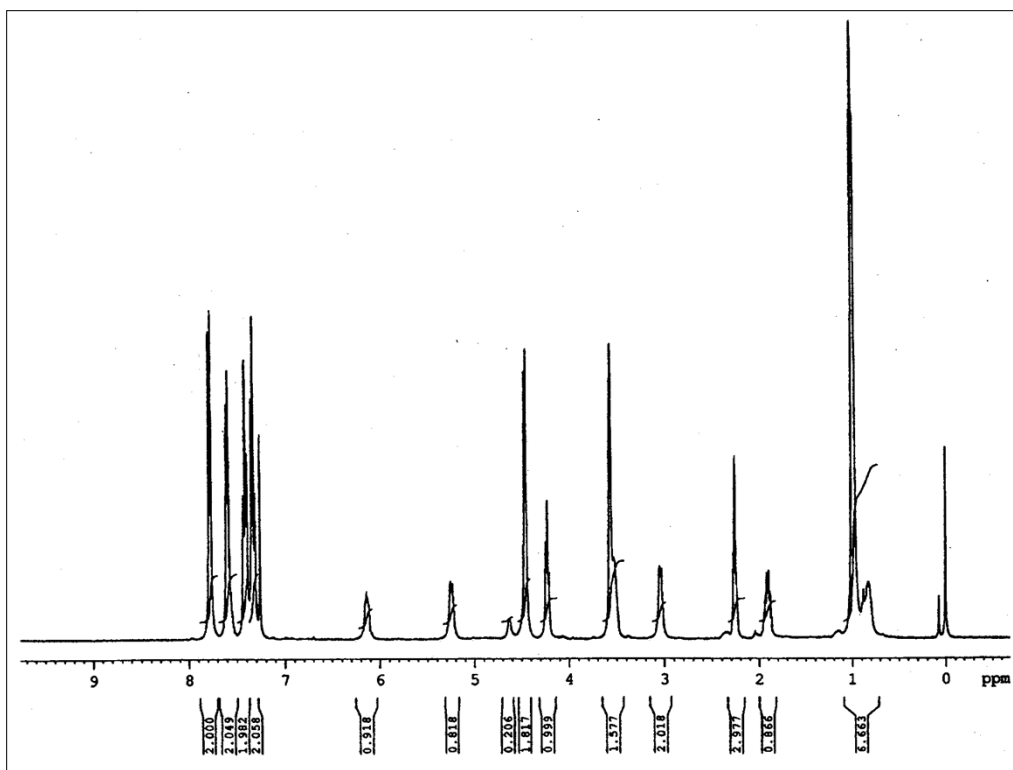
HRMS spectrum of compound **2h**

Chiral HPLC chromatogram of compound **2e**

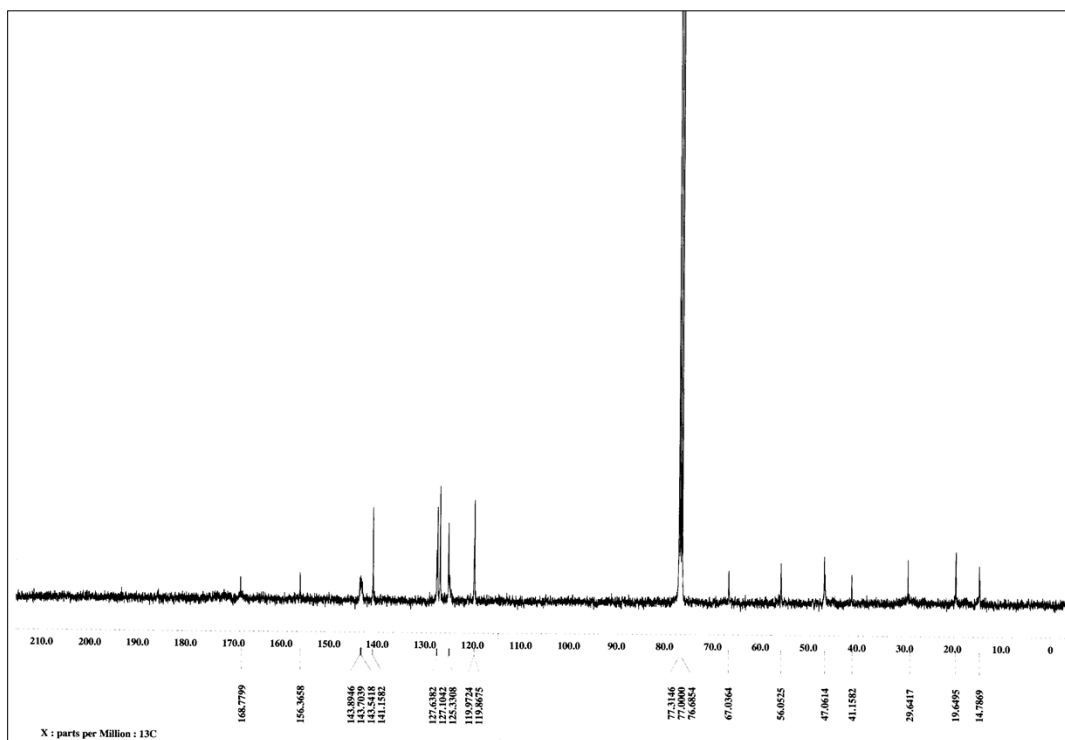
Chiral HPLC chromatogram of compound **2e'**

Chiral HPLC chromatogram of mixture **2e** and **2e'**

(Method: $\lambda = 254$ nm, flow: 1.0 mL/min, column: phenominex made Lux, pore size-5 μ , cellusole-1, diameter x length = 250 x 4.6 mm; 80:20 *n*-hexane/isopropanol in isocratic mode in 40 min.)

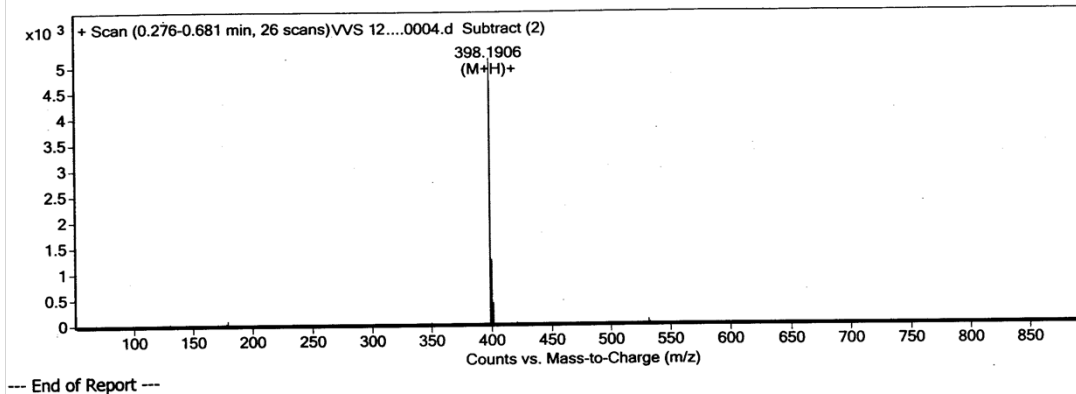


¹H NMR spectrum of compound **3a**

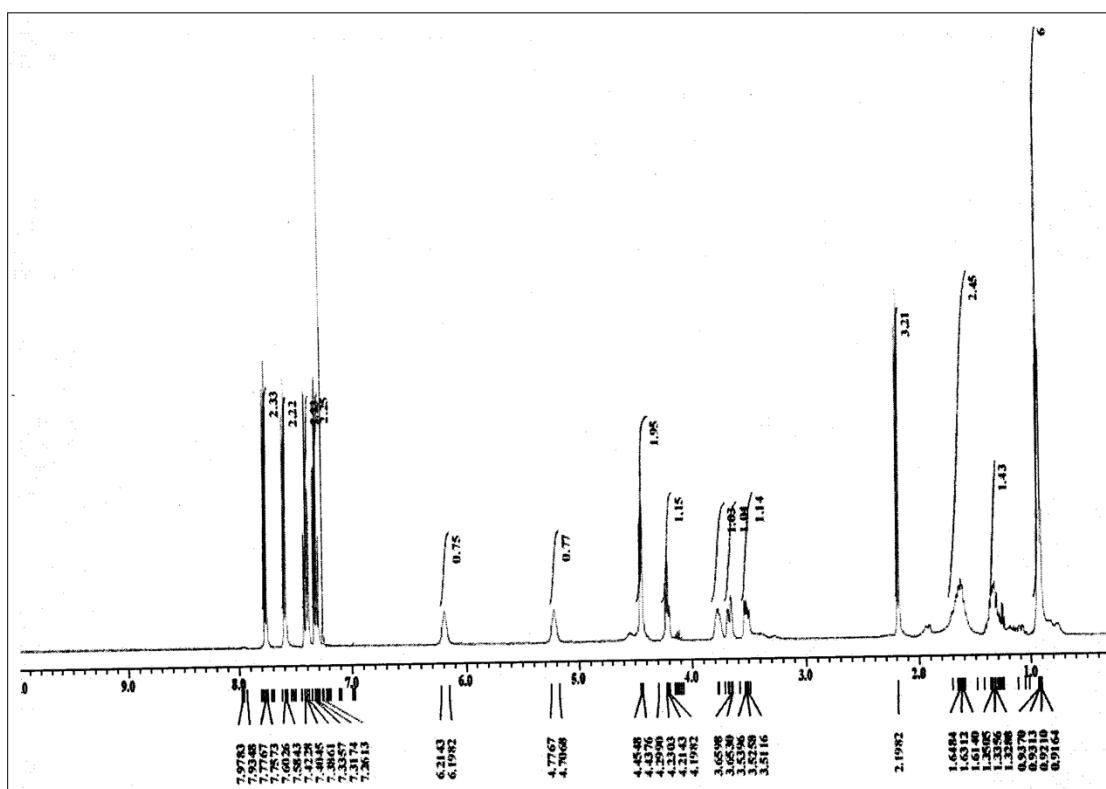


¹³C NMR spectrum of compound **3a**

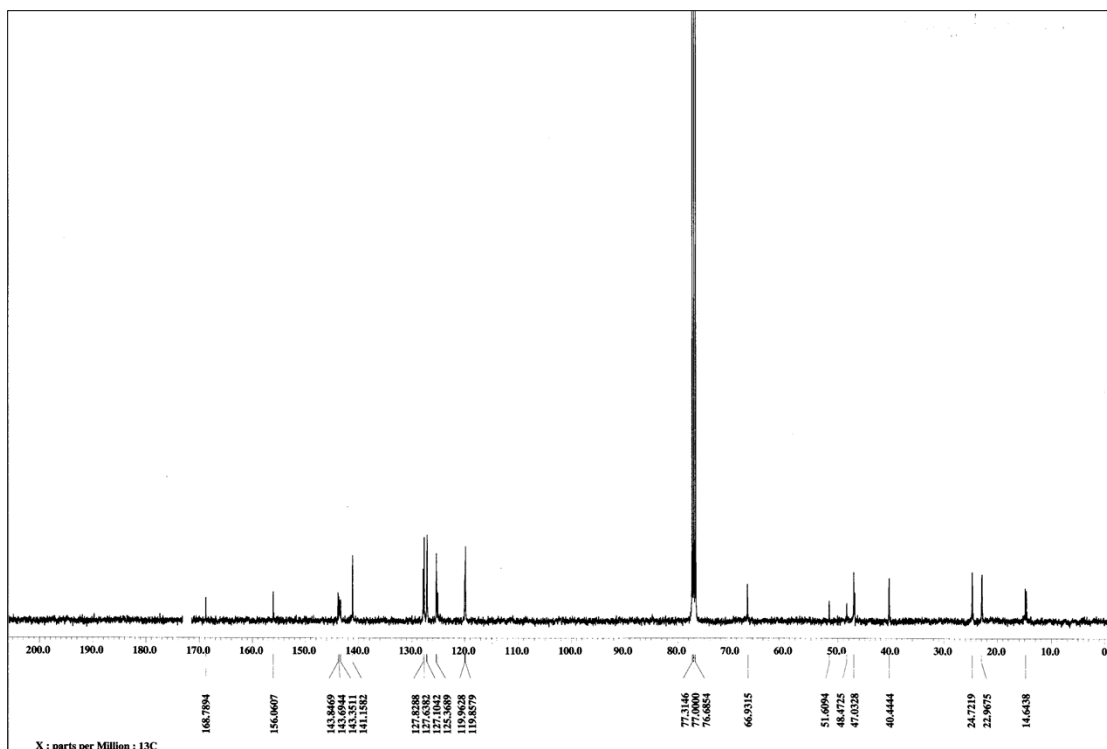
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HRMS spectrum of compound **3a**

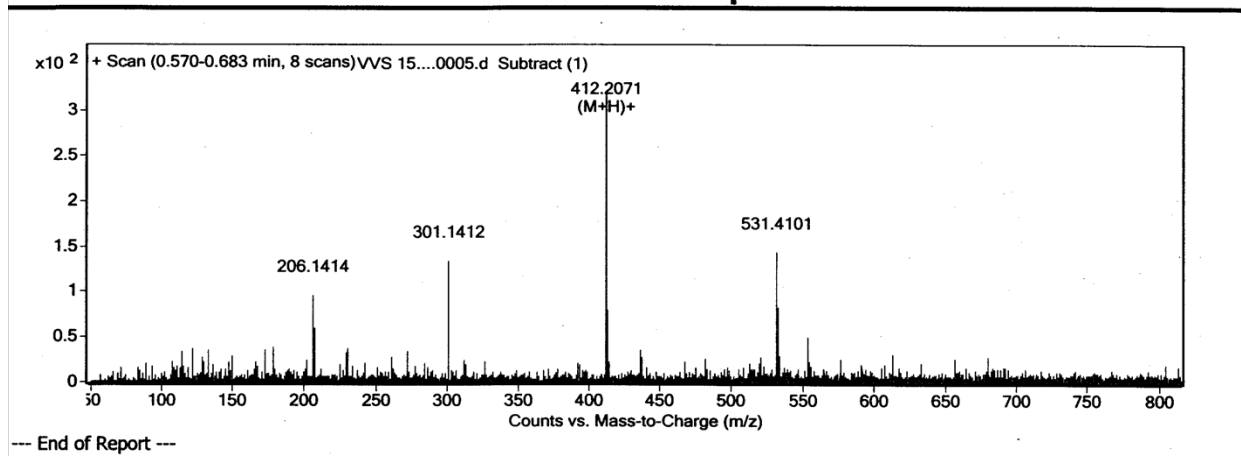


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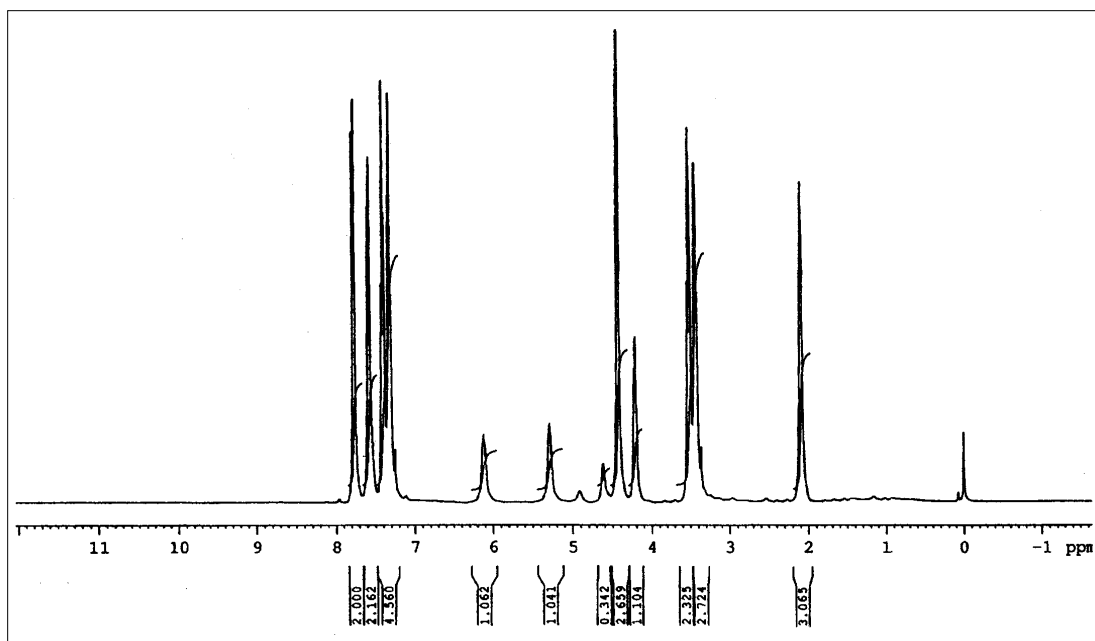


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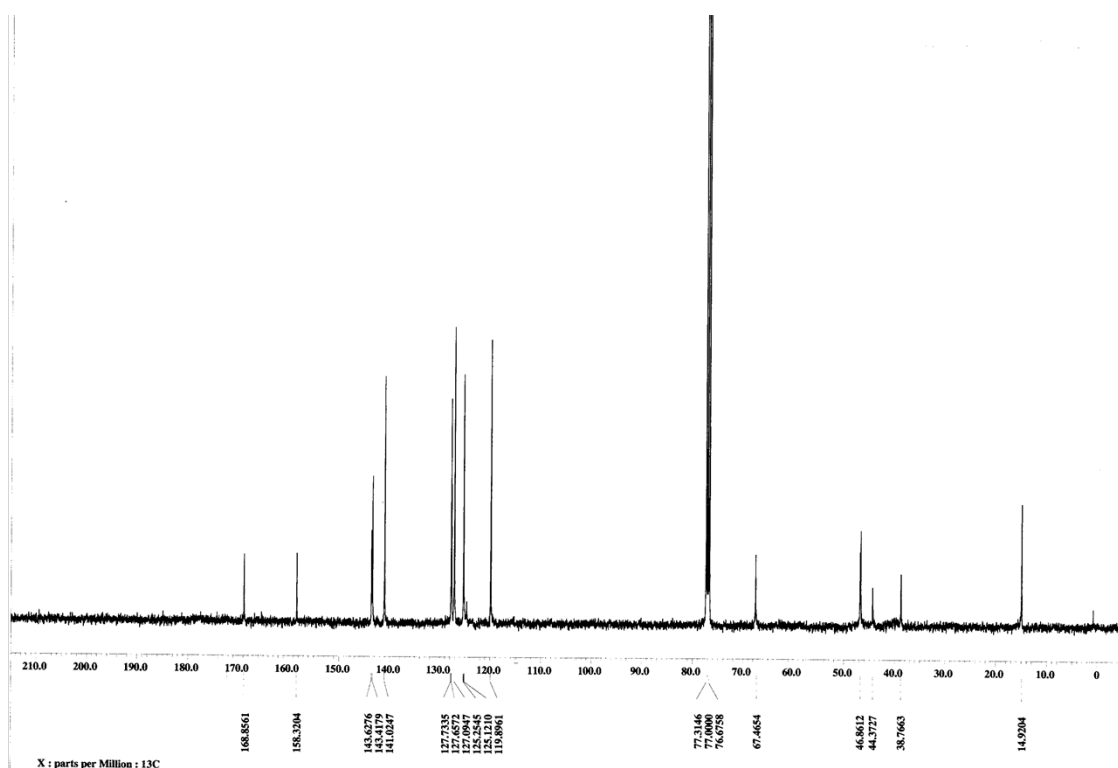
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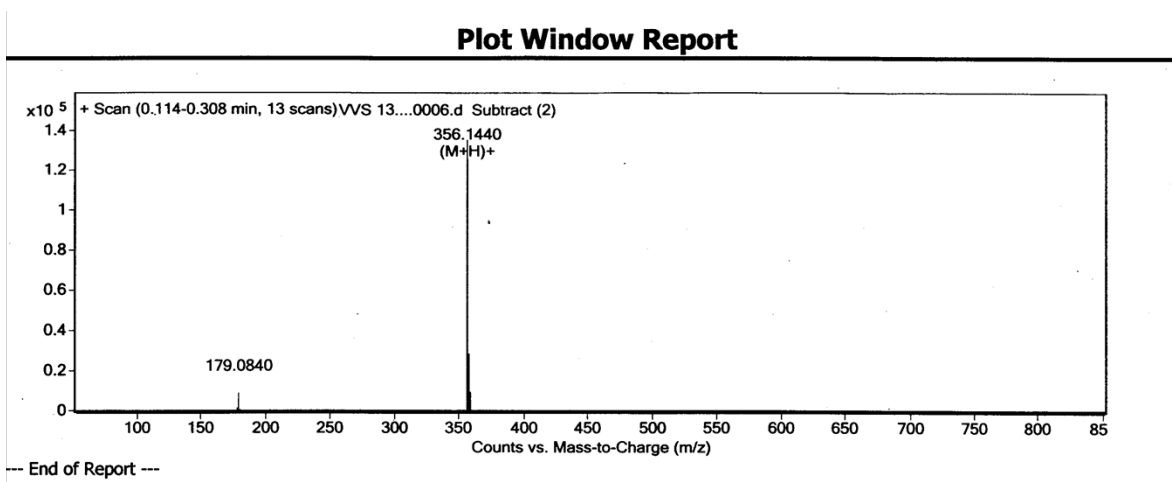
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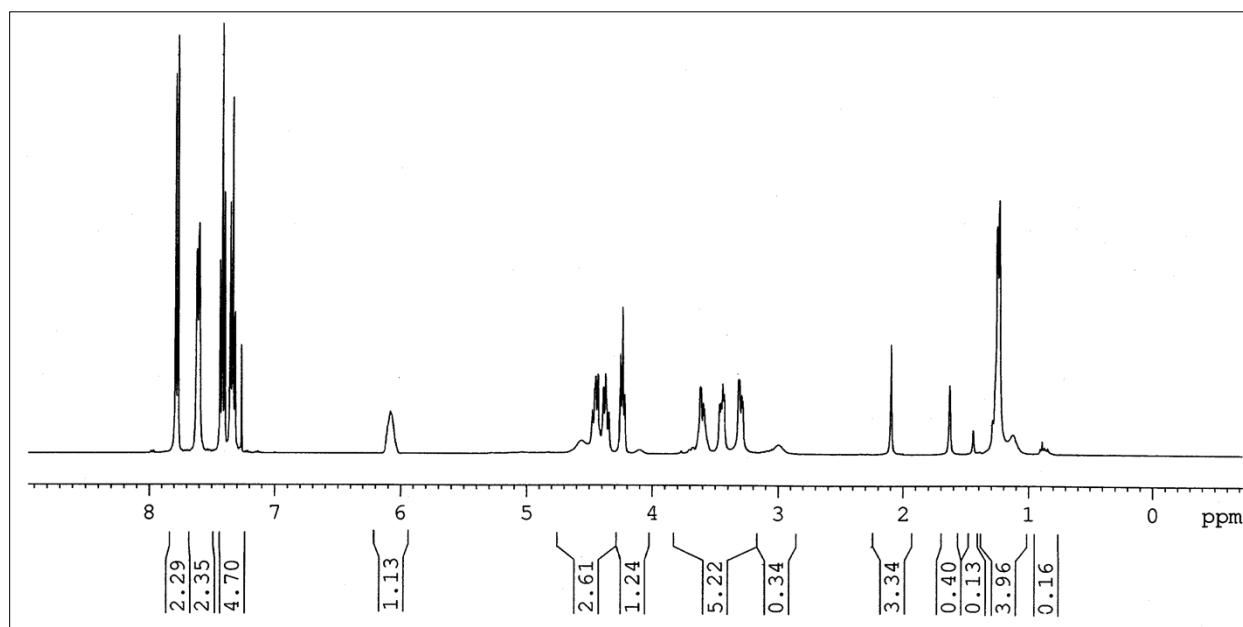
¹H NMR spectrum of compound **3c**



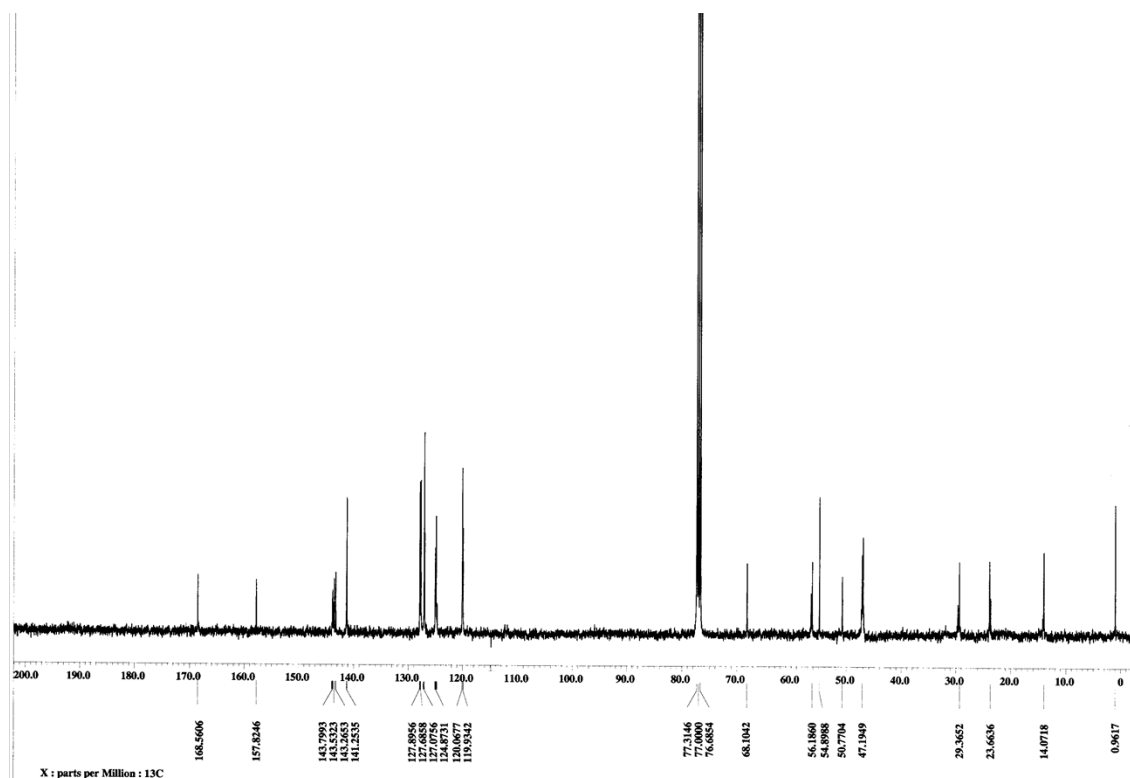
¹³C NMR spectrum of compound **3c**



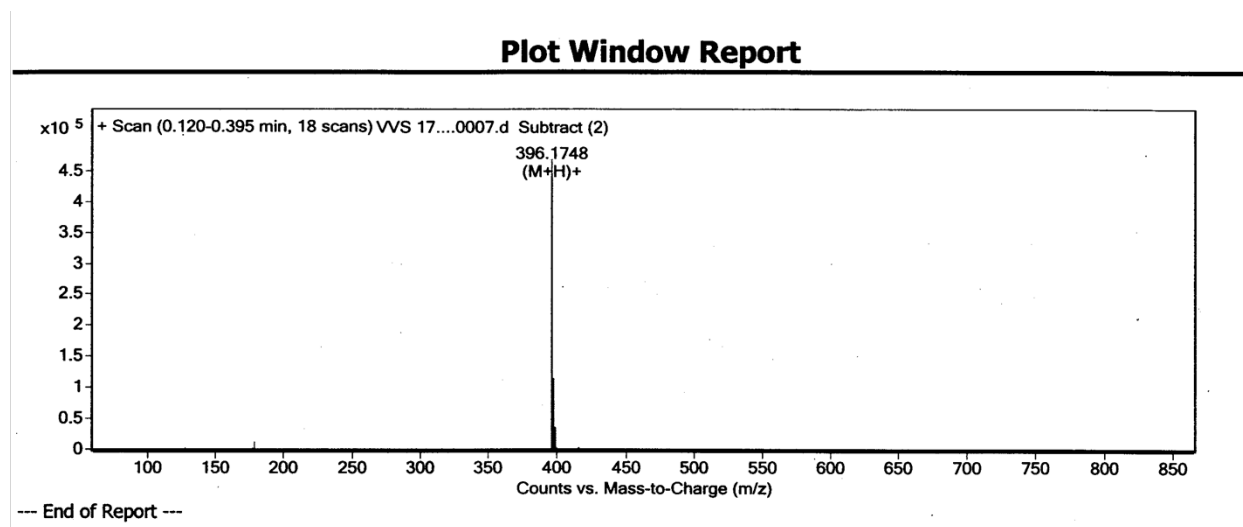
HRMS spectrum of compound **3c**



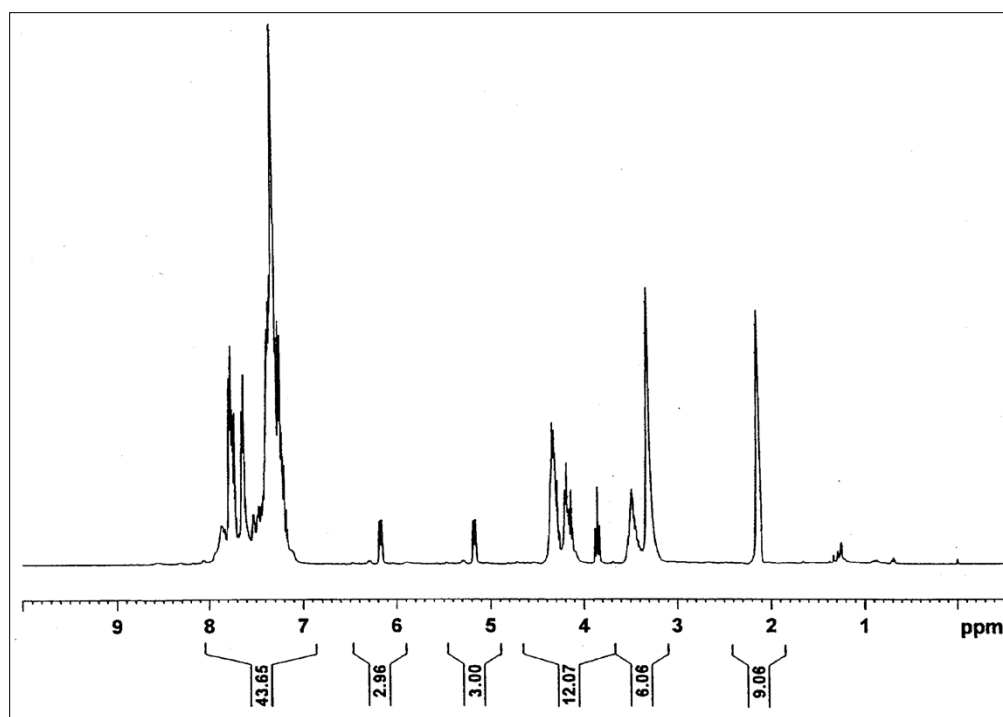
^1H NMR spectrum of compound **3d**



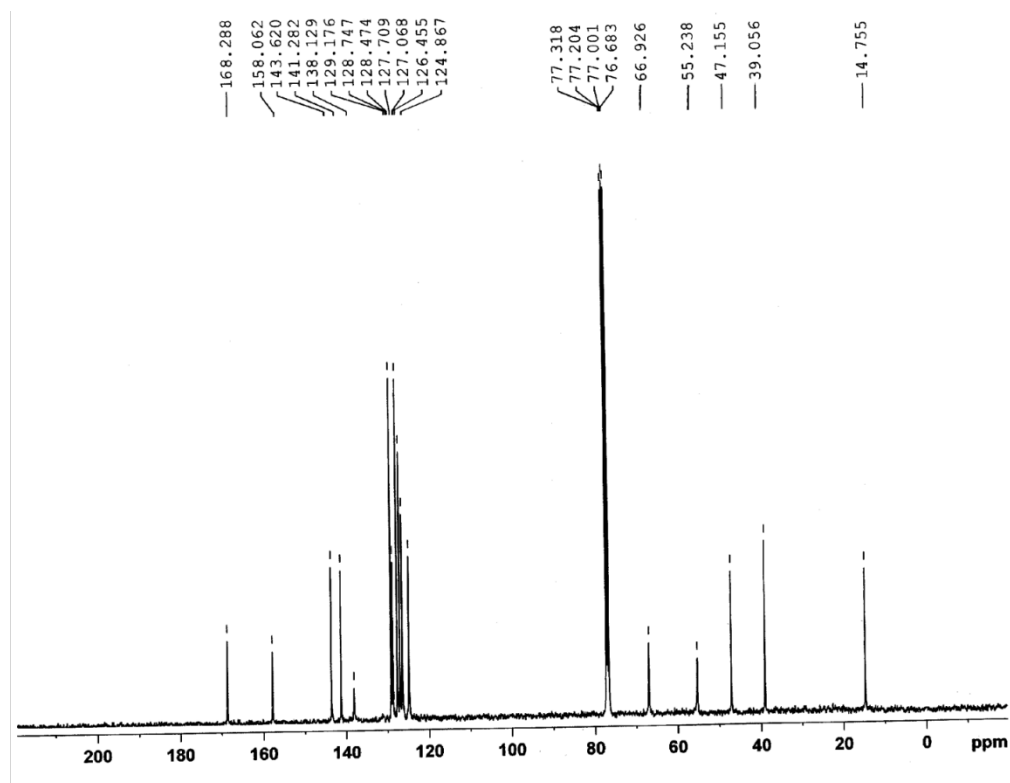
^{13}C NMR spectrum of compound **3d**



HRMS spectrum of compound **3d**

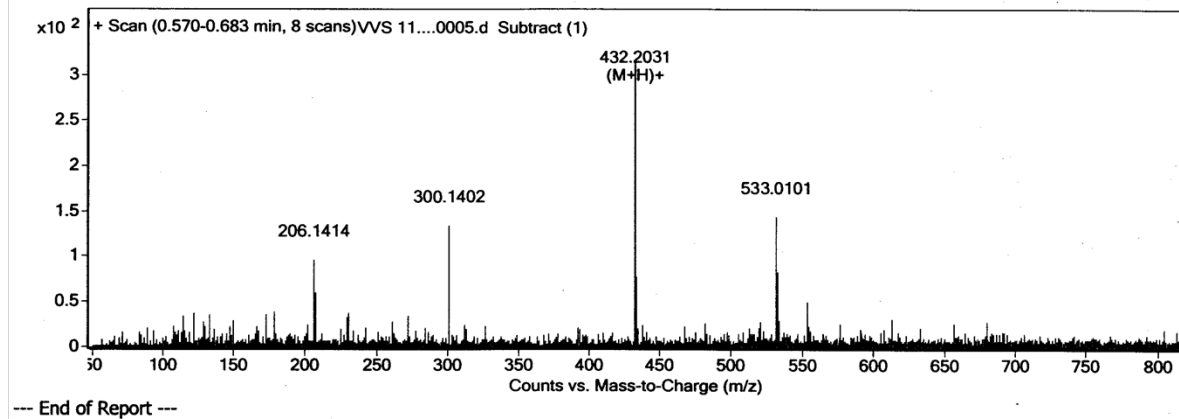


^1H NMR spectrum of compound **3e**

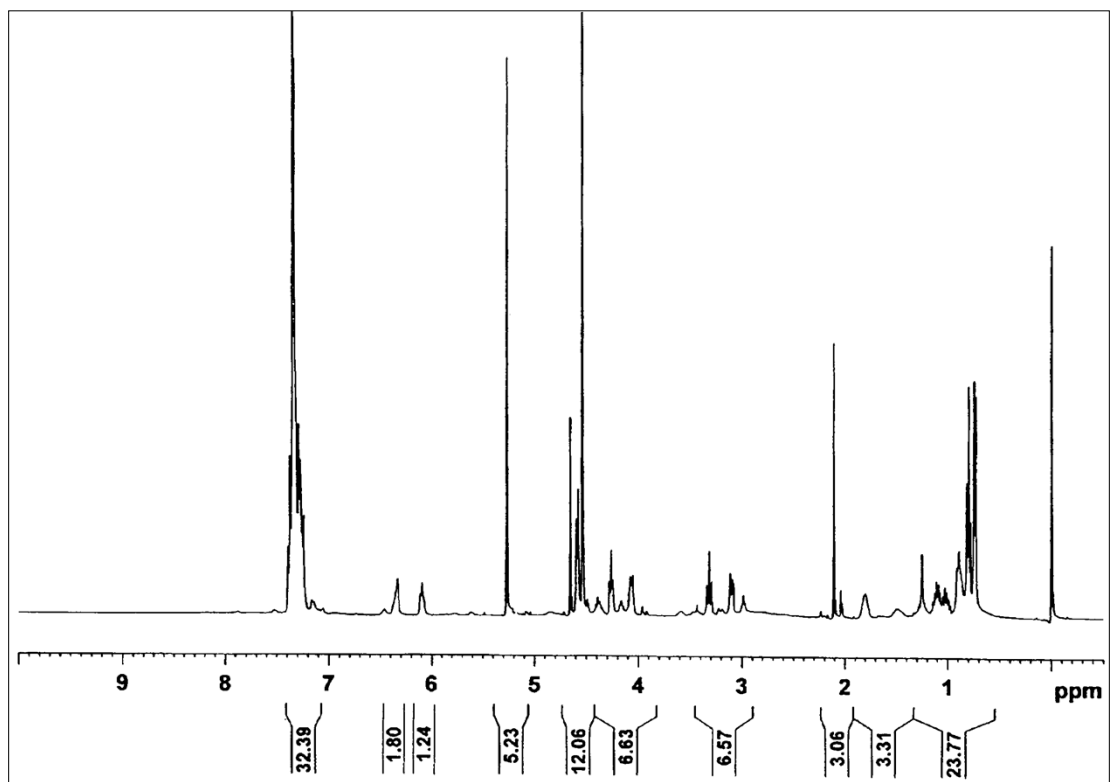


^{13}C NMR spectrum of compound **3e**

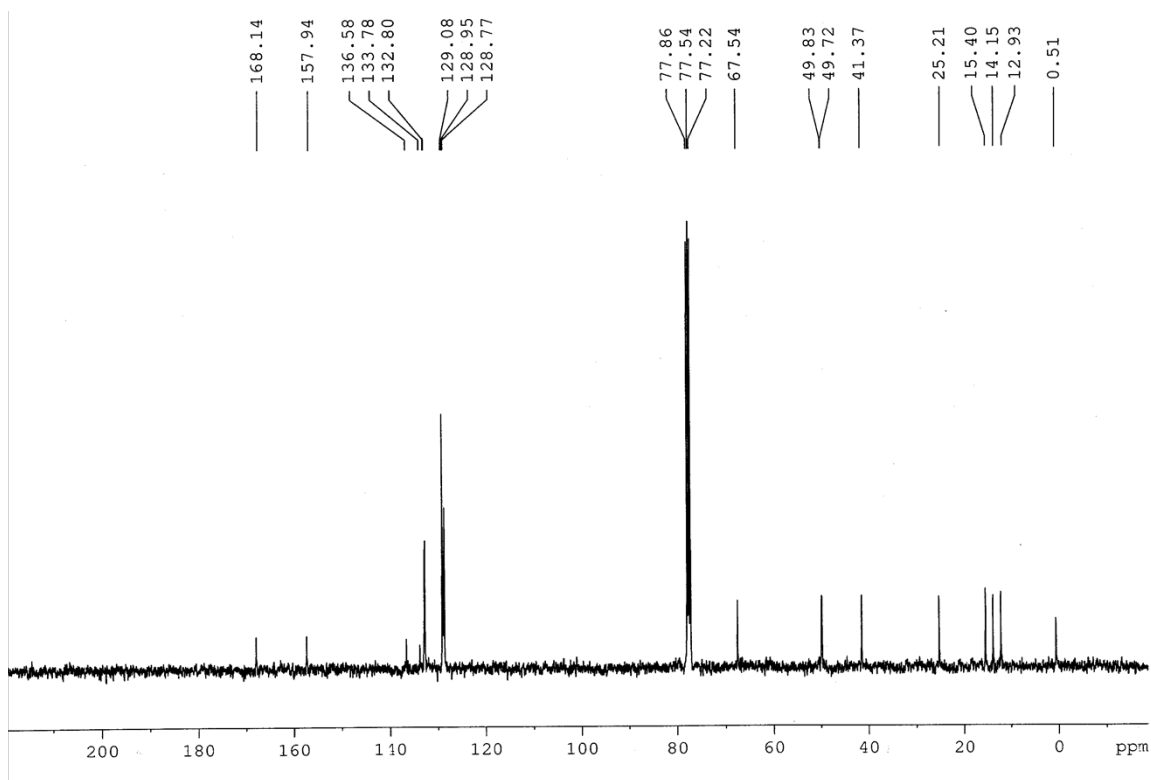
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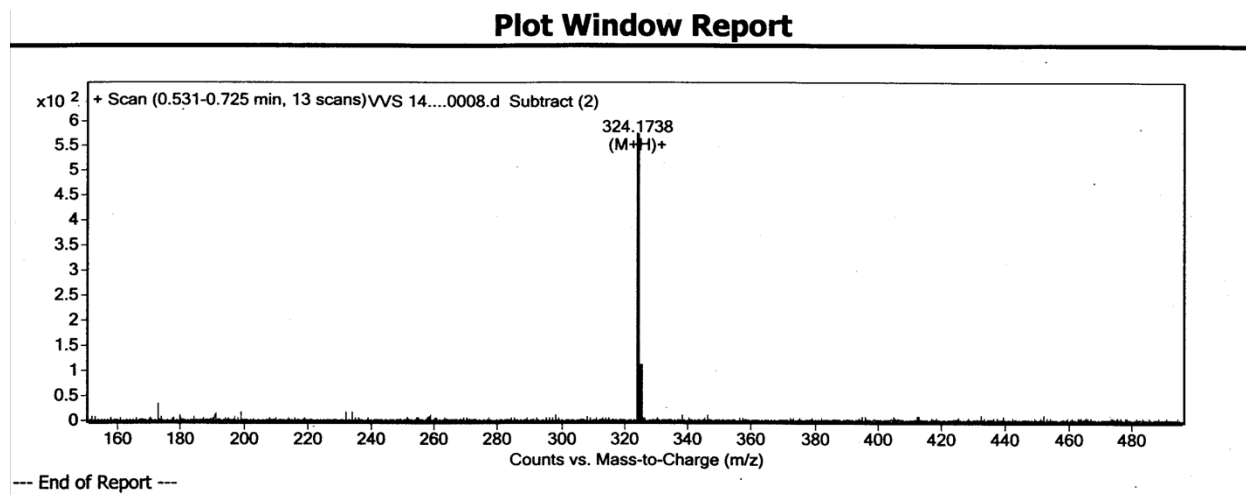
HRMS spectrum of compound **3e**



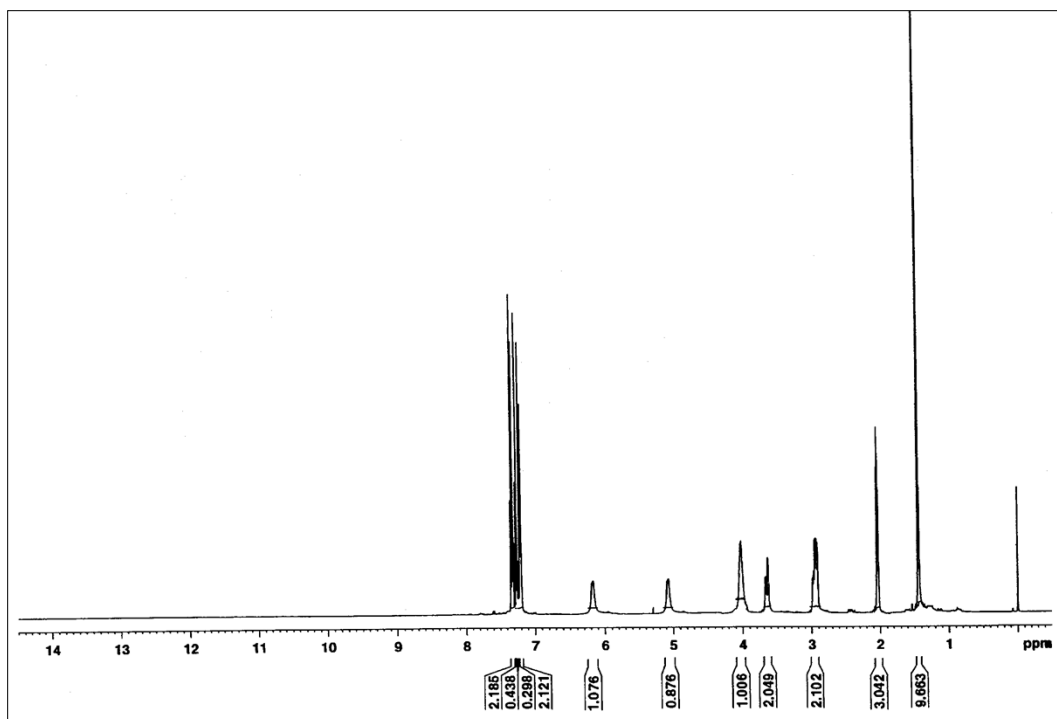
^1H NMR spectrum of compound **3f**



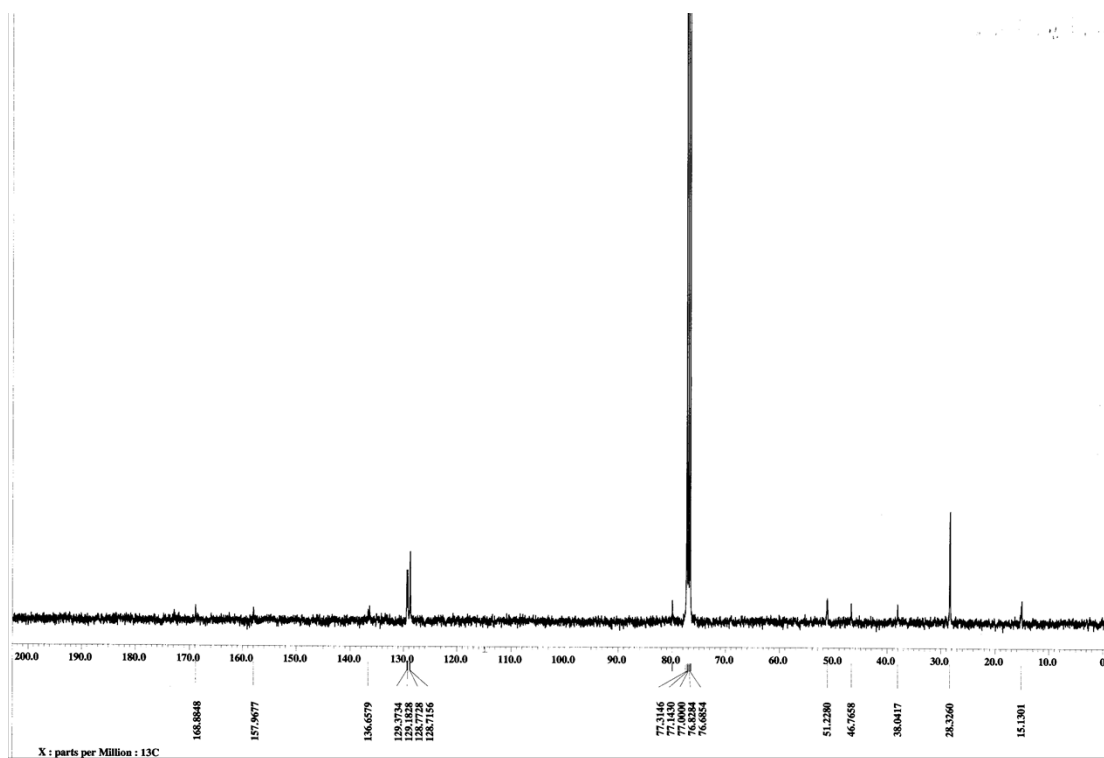
¹³C NMR spectrum of compound **3f**



HRMS spectrum of compound **3f**

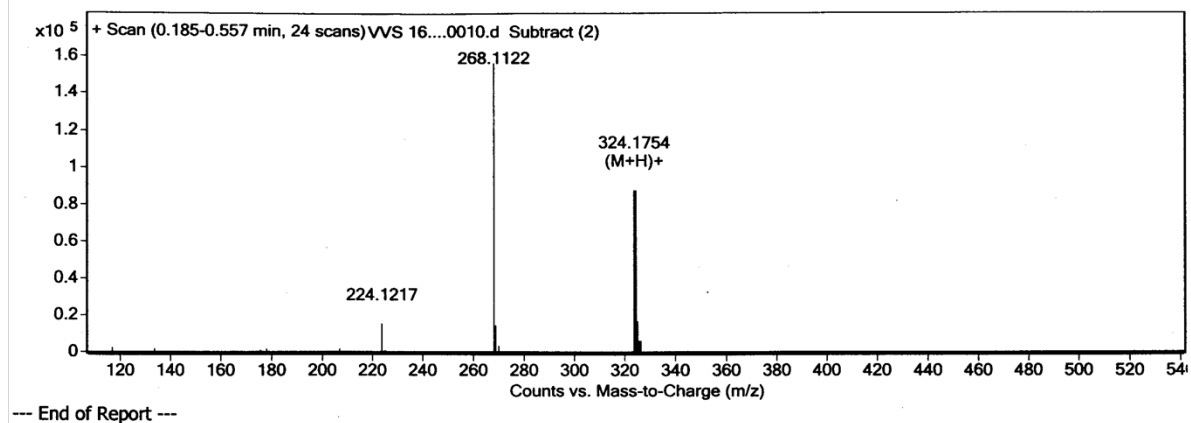


^1H NMR spectrum of compound **3g**

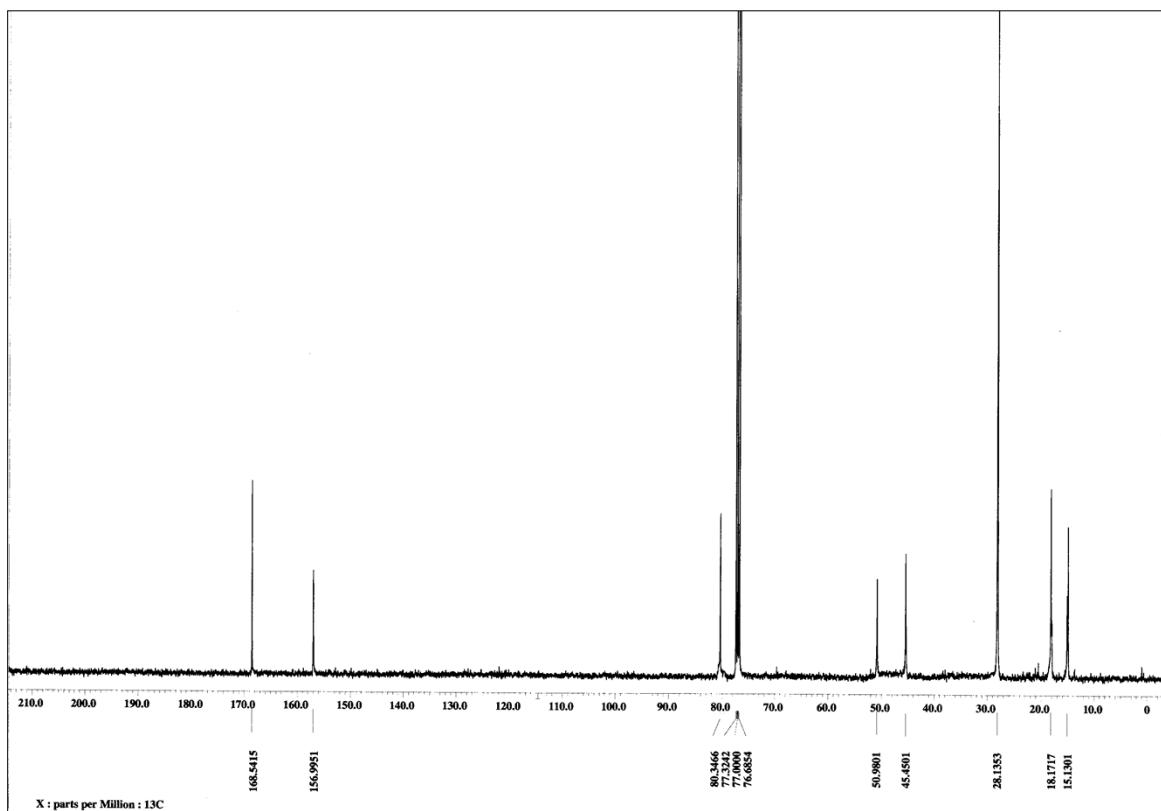


^{13}C NMR spectrum of compound **3g**

Plot Window Report

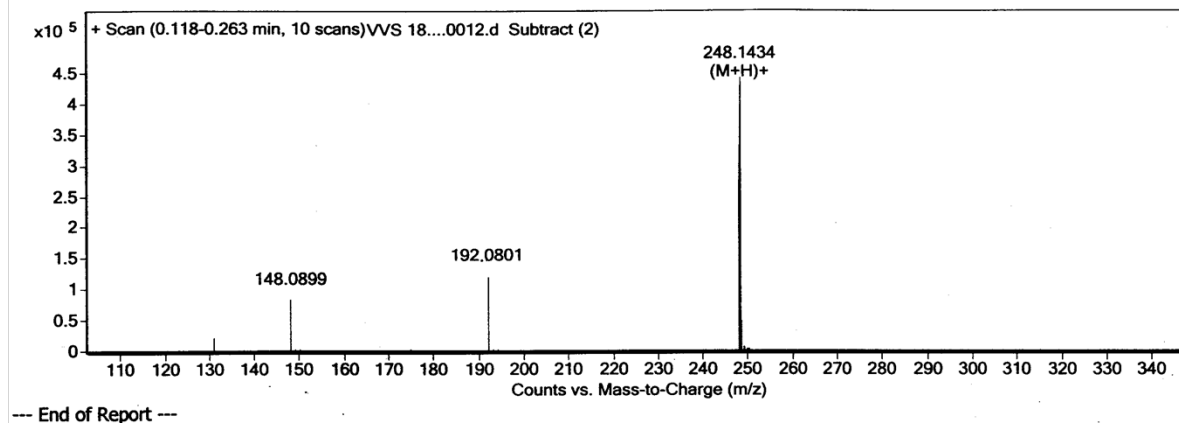


HRMS spectrum of compound **3g**

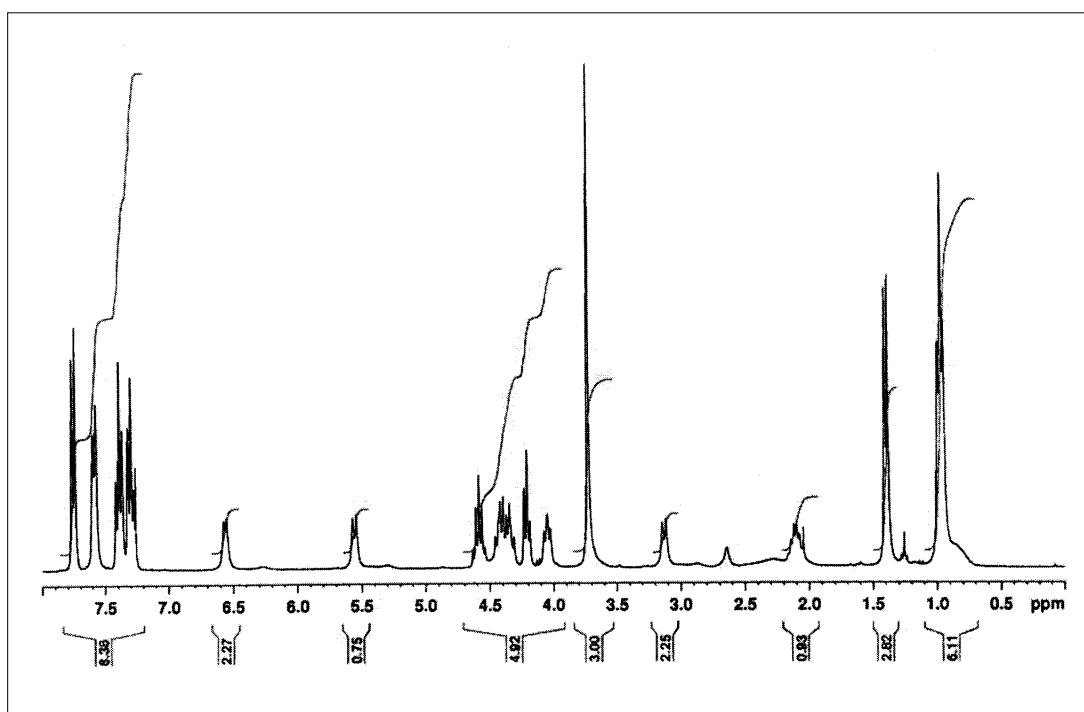


¹³C NMR spectrum of compound **3h**

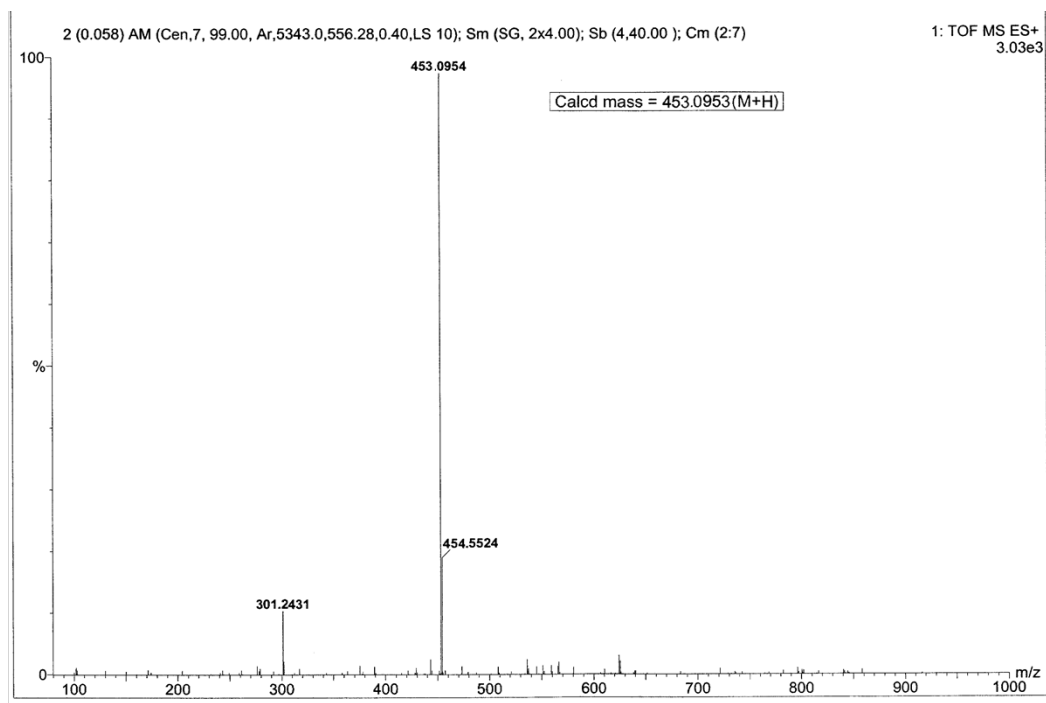
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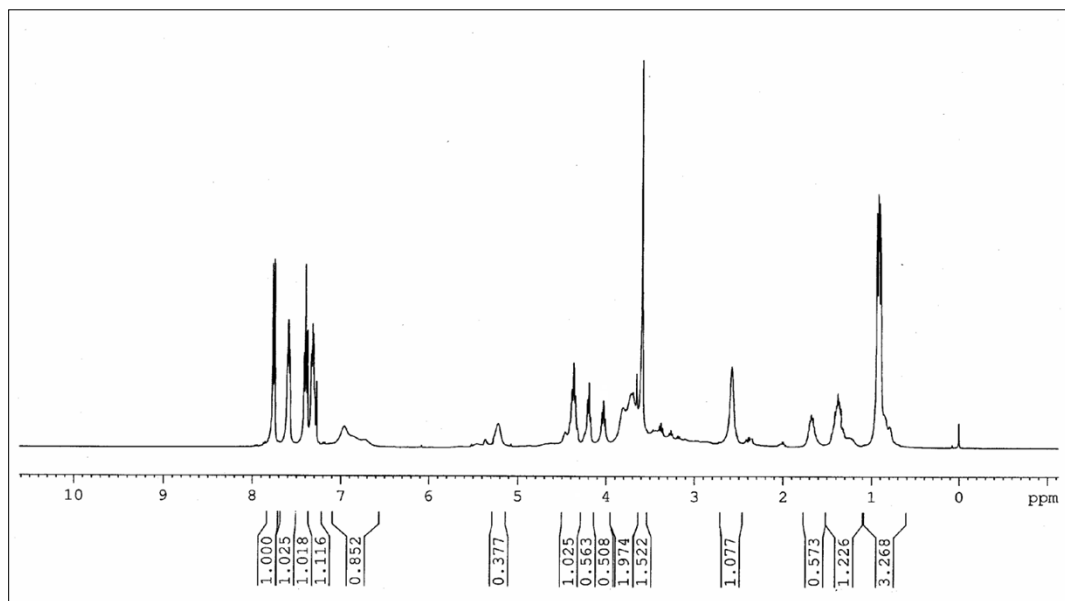
HRMS spectrum of compound **3h**



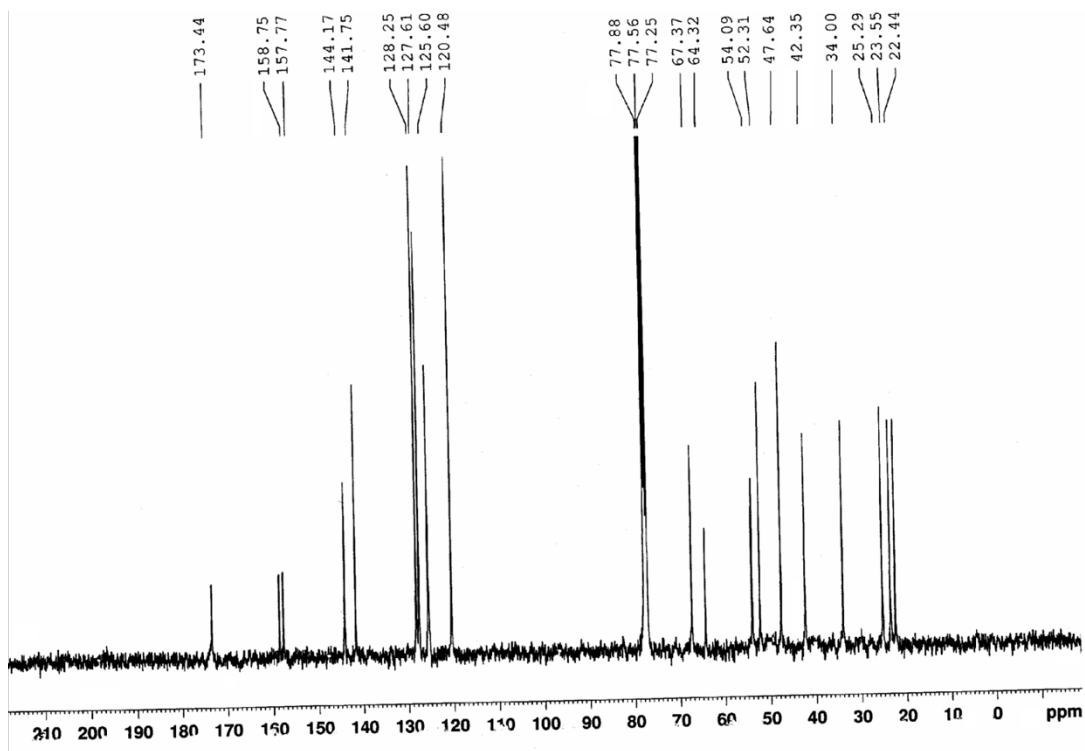
¹H NMR spectrum of compound **4a**



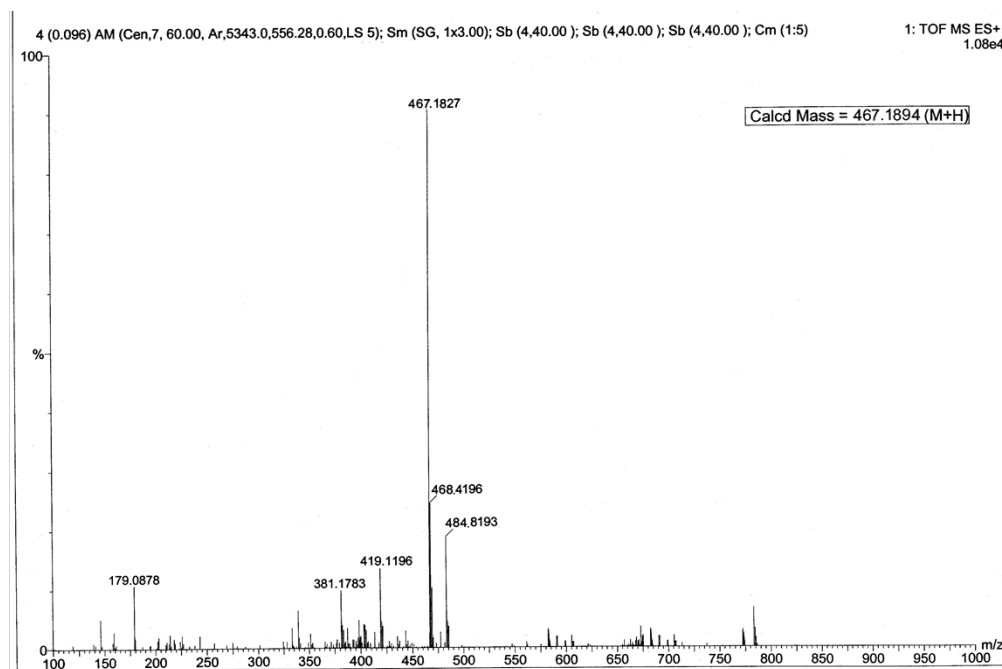
HRMS spectrum of compound **4a**



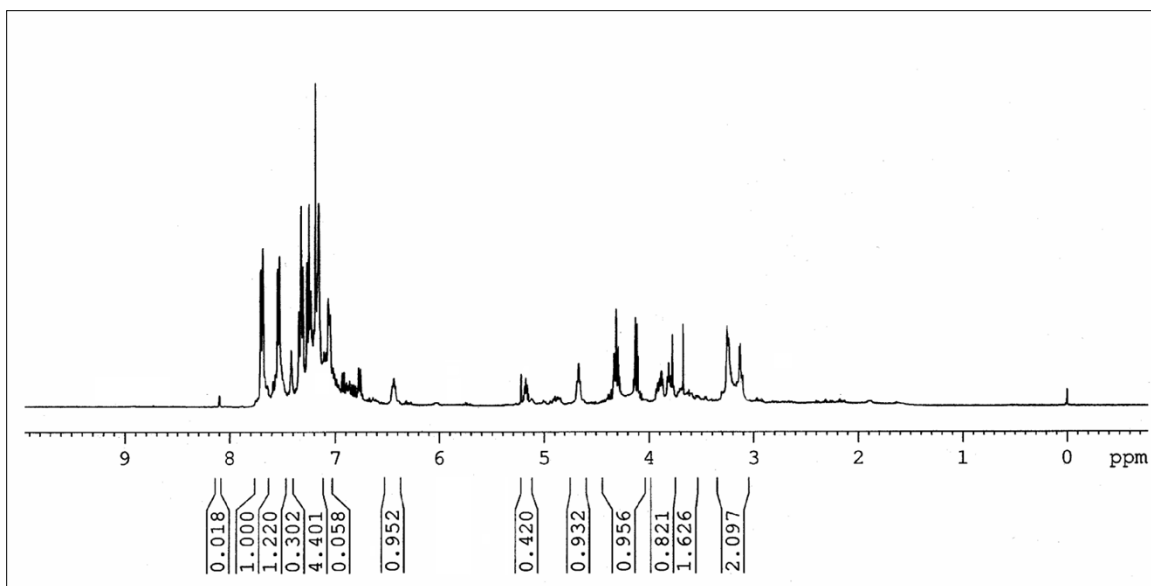
^1H NMR spectrum of compound **4b**



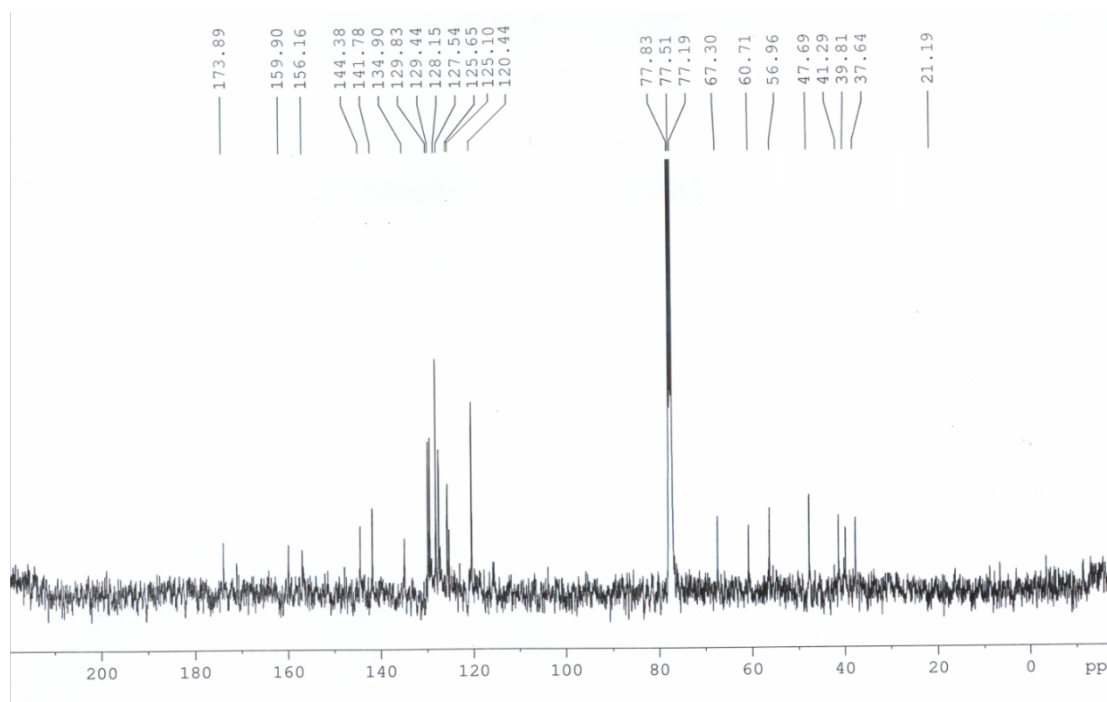
^{13}C NMR spectrum of compound **4b**



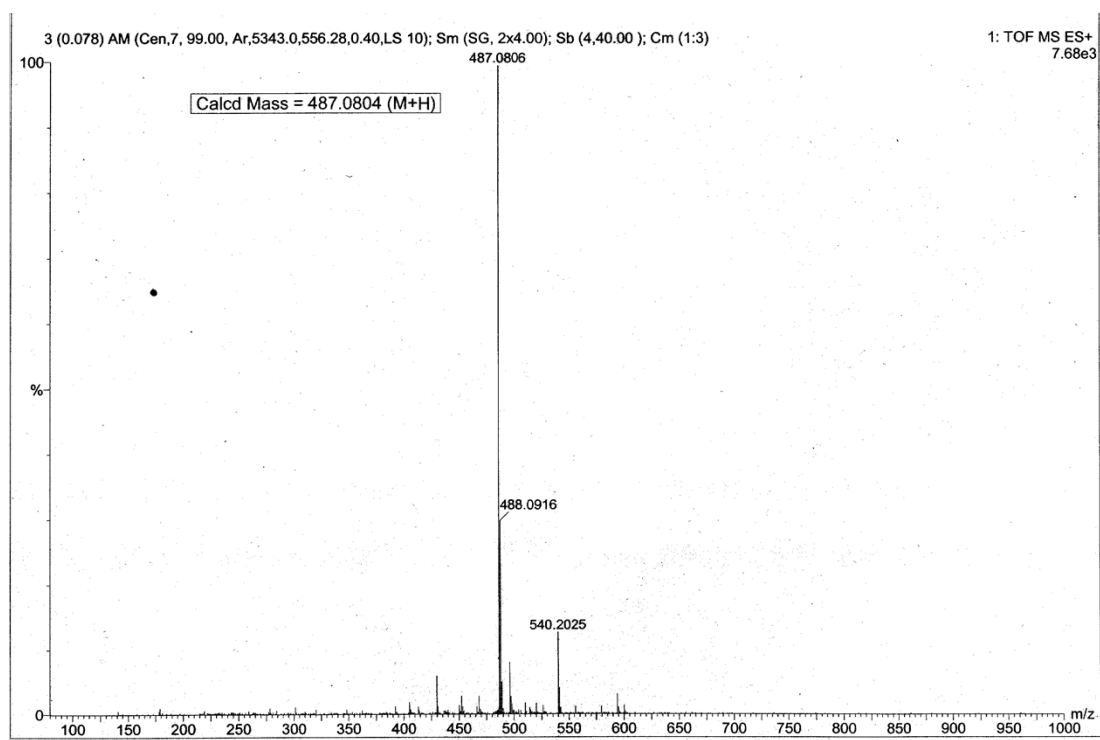
HRMS spectrum of compound **4b**



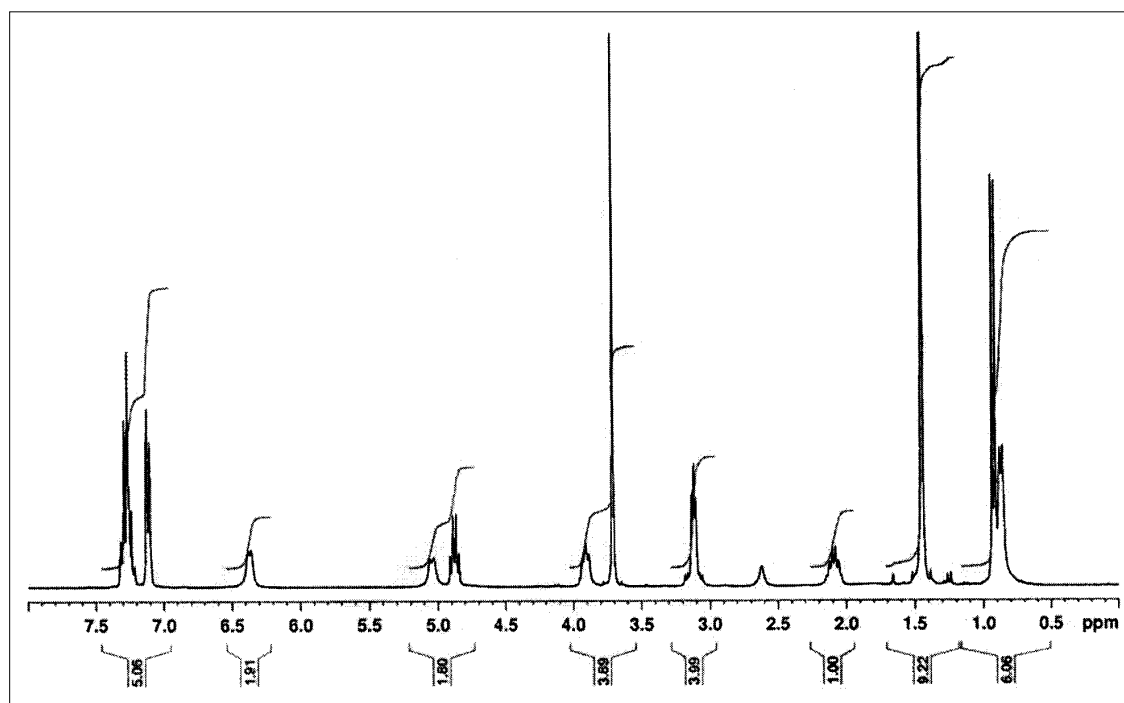
^1H NMR spectrum of compound **4c**



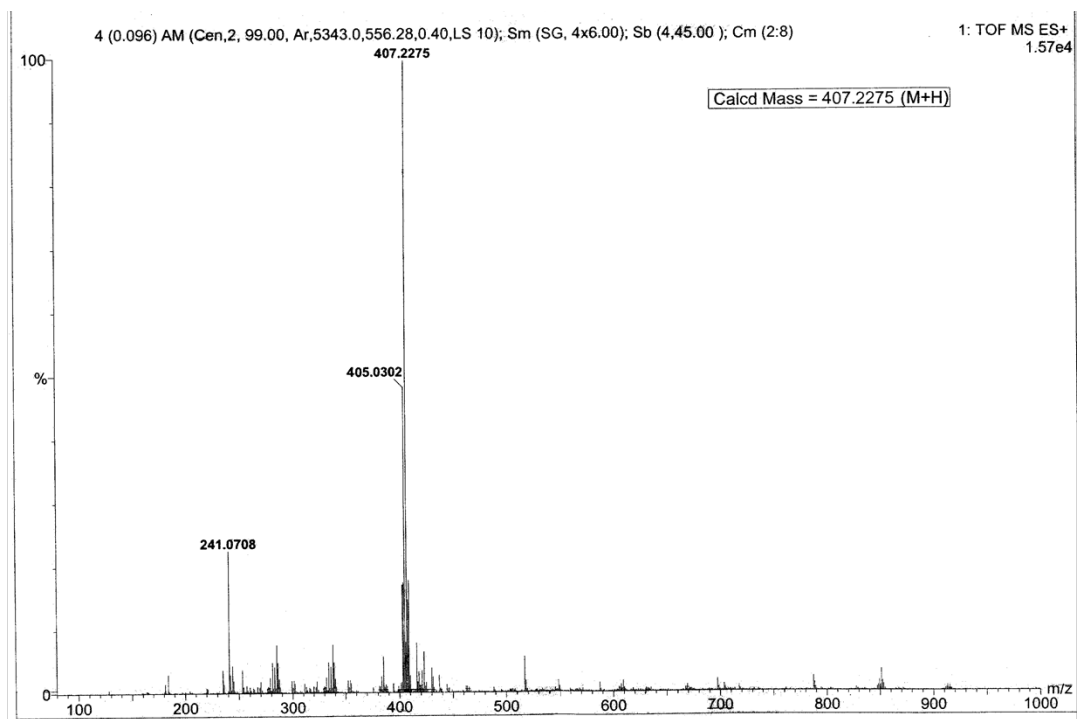
^{13}C NMR spectrum of compound **4c**



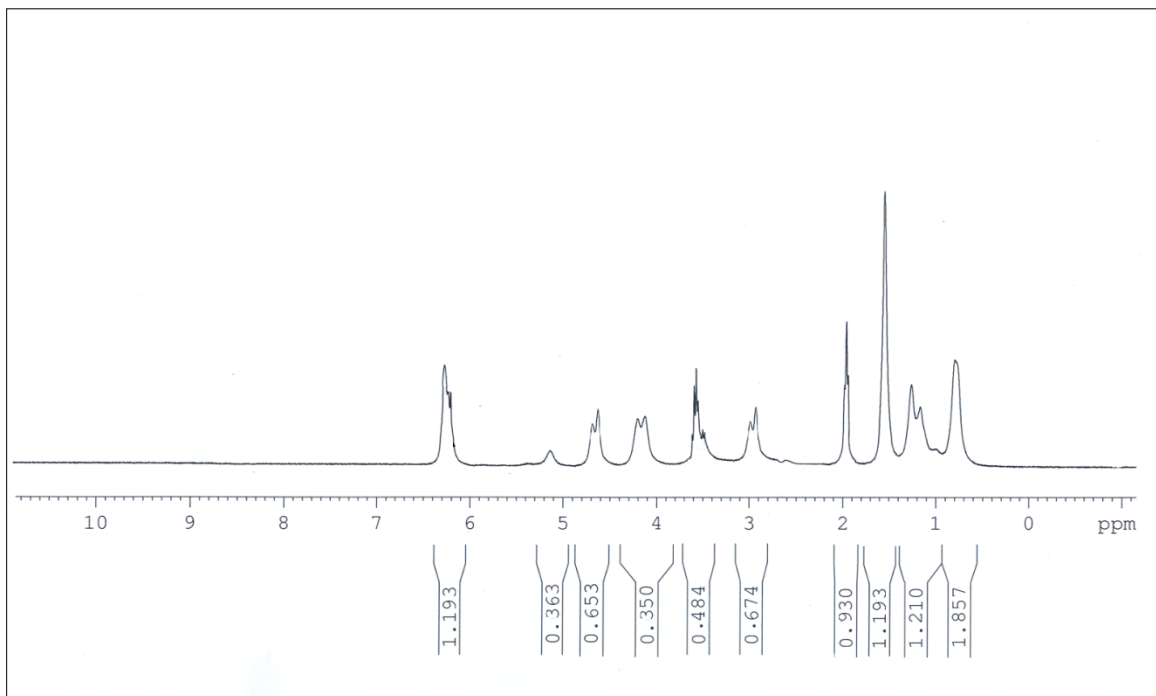
HRMS spectrum of compound **4c**



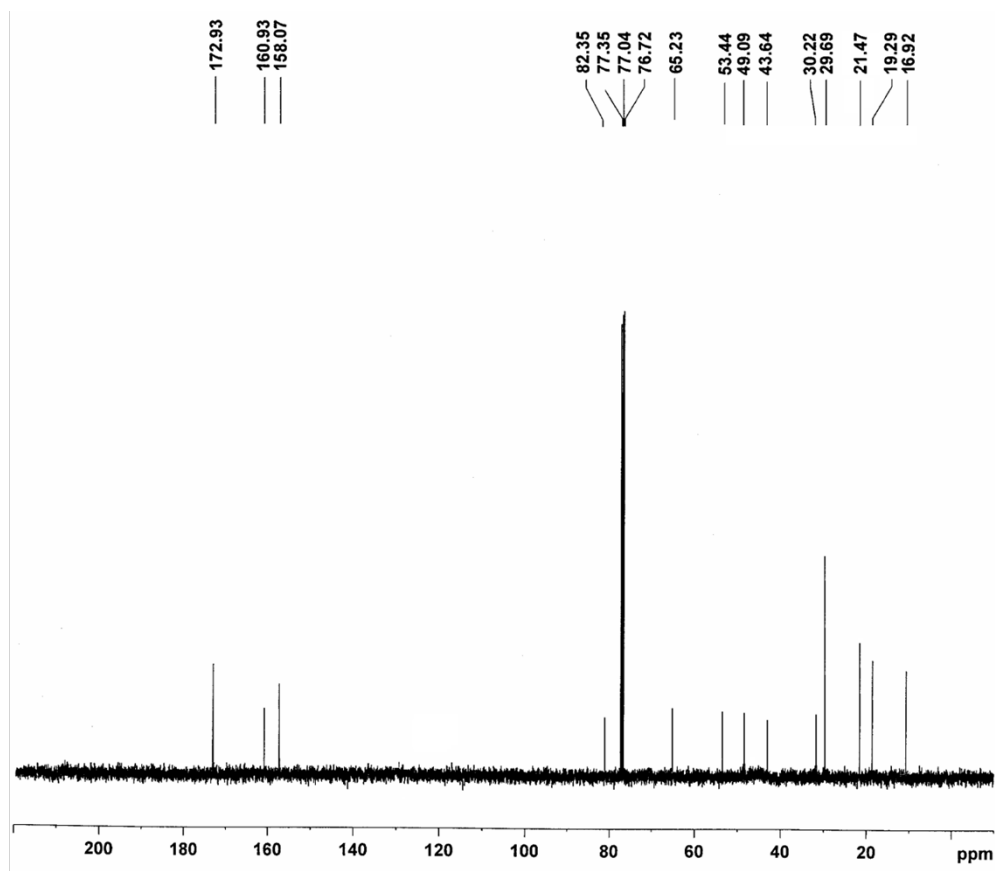
¹H NMR spectrum of compound **4g**



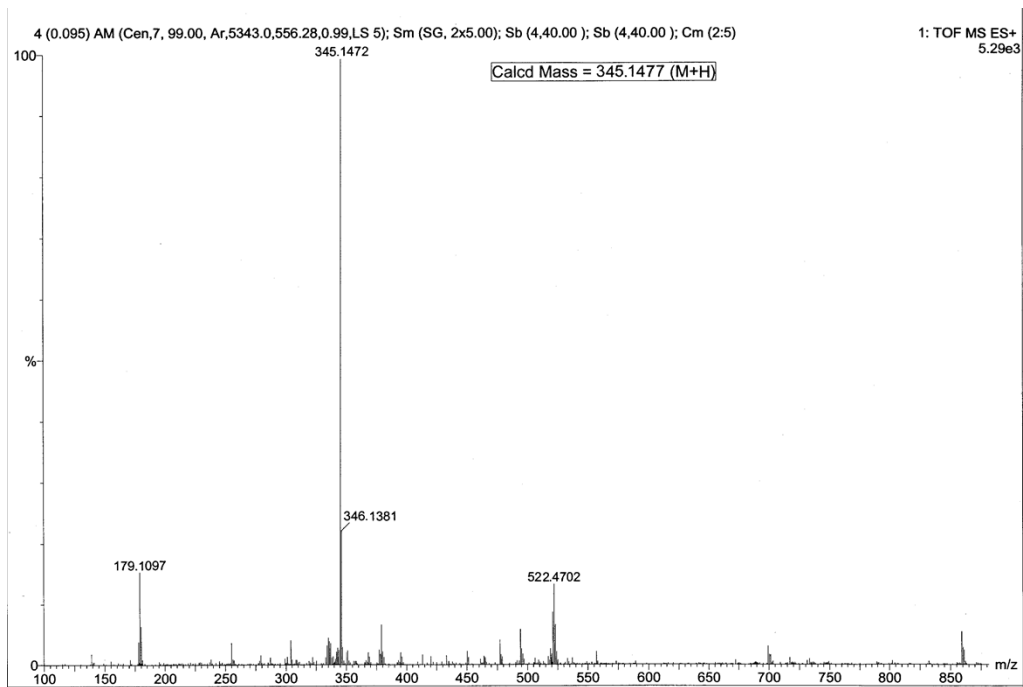
HRMS spectrum of compound **4g**



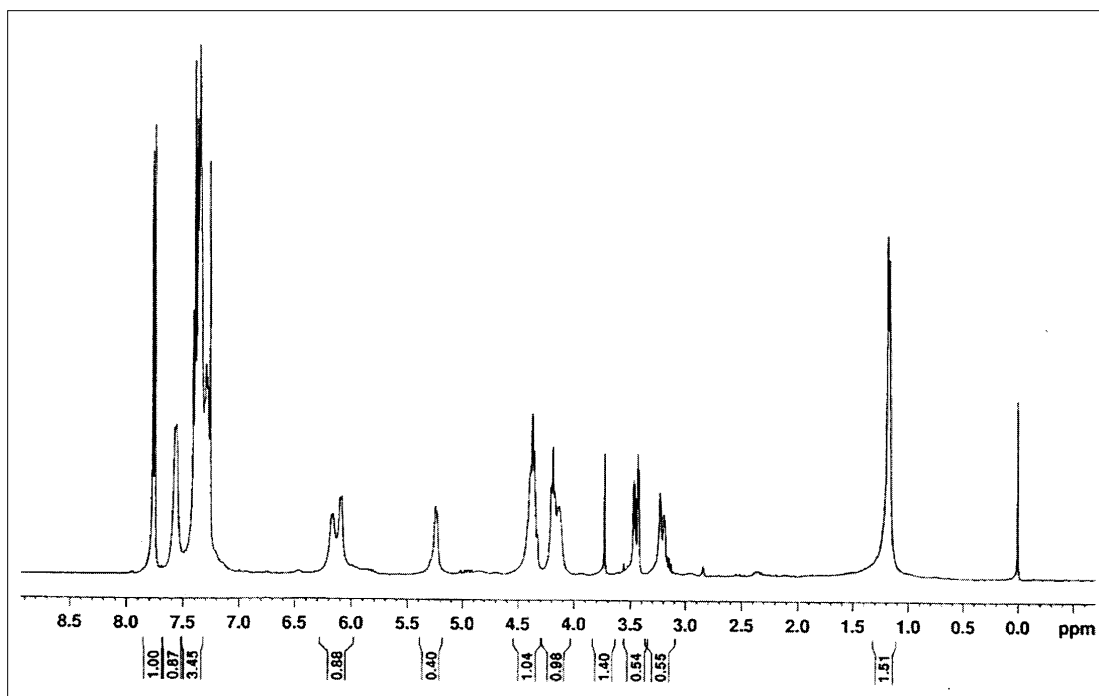
^1H NMR spectrum of compound **4h**



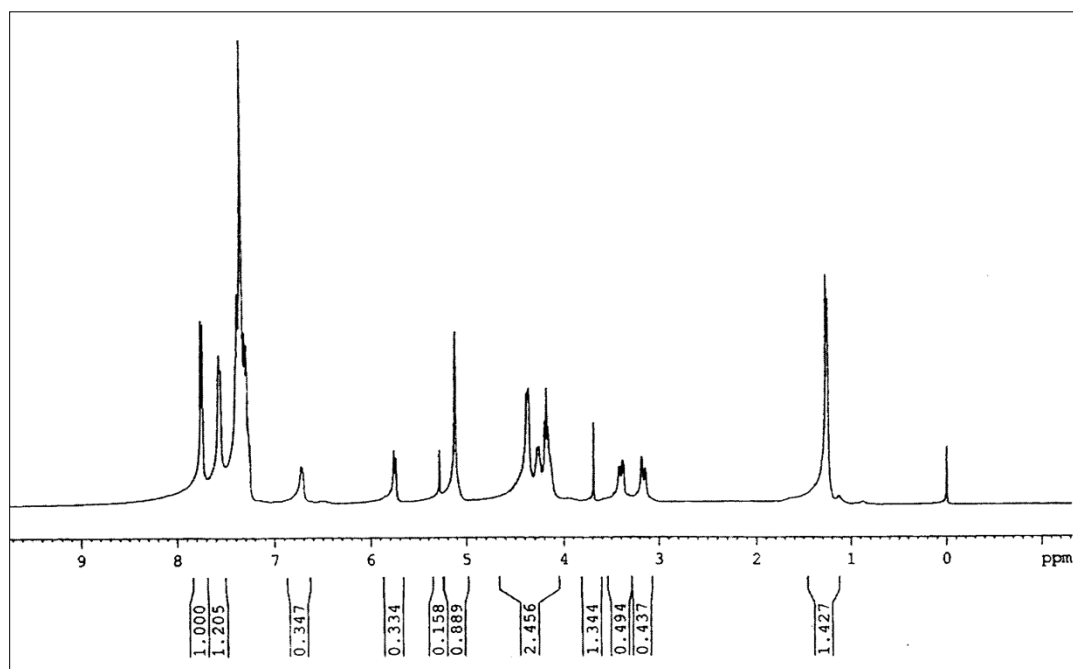
^{13}C NMR spectrum of compound **4h**



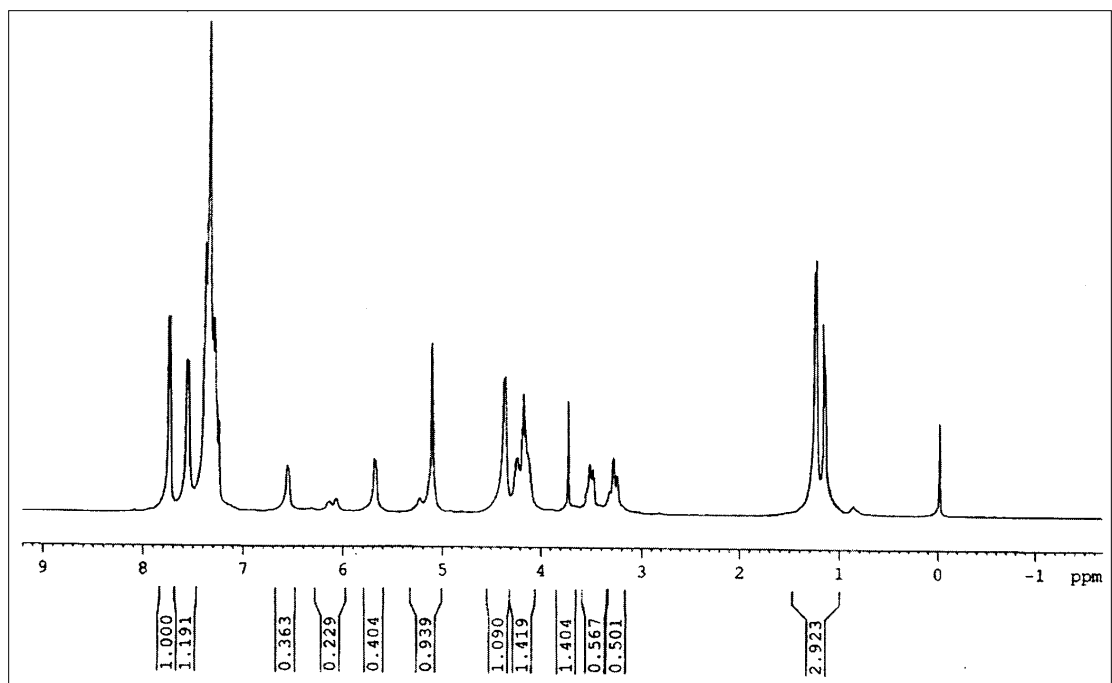
HRMS spectrum of compound **4h**



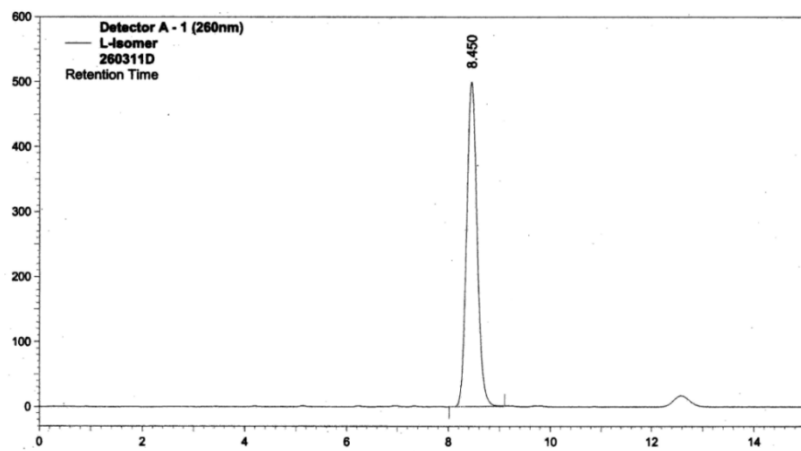
^1H NMR spectrum of compound **4e**



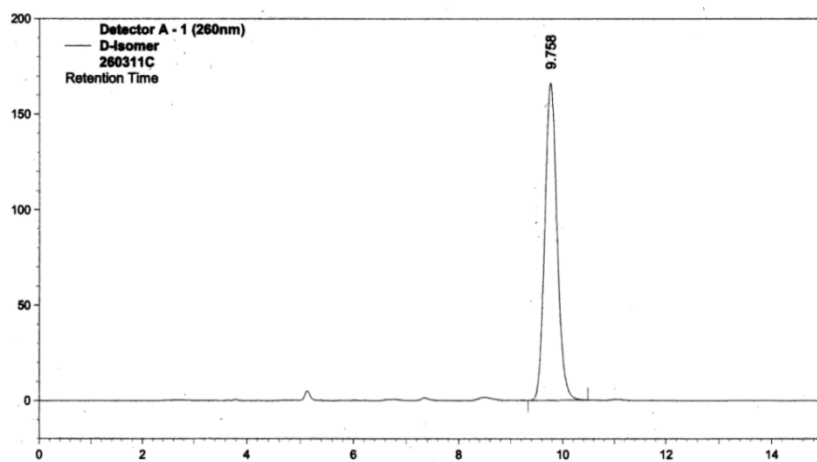
^1H NMR spectrum of compound **4e'**



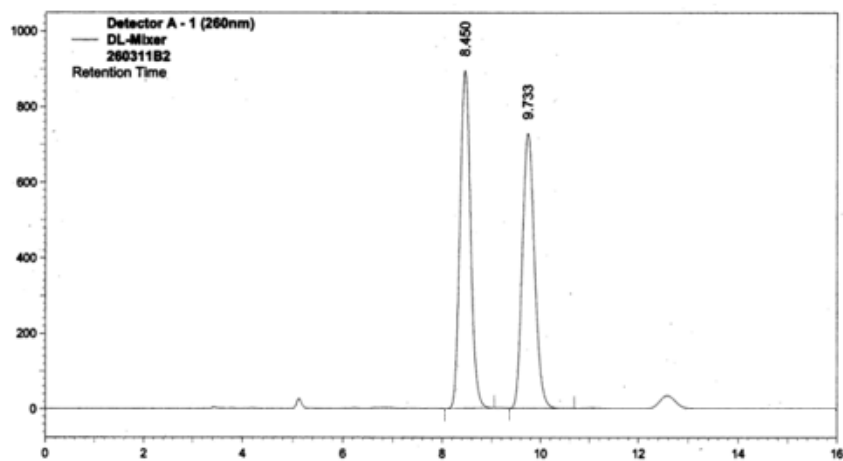
^1H NMR spectrum of mixture of **4e** and **4e'**



Chiral HPLC chromatogram of compound **4e**

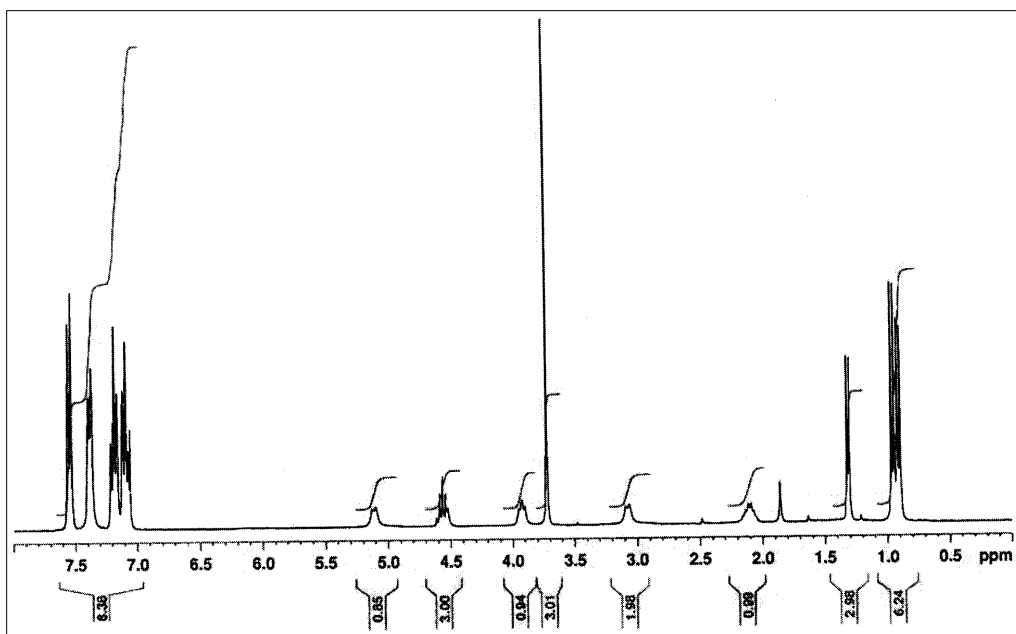


Chiral HPLC chromatogram of compound **4e'**

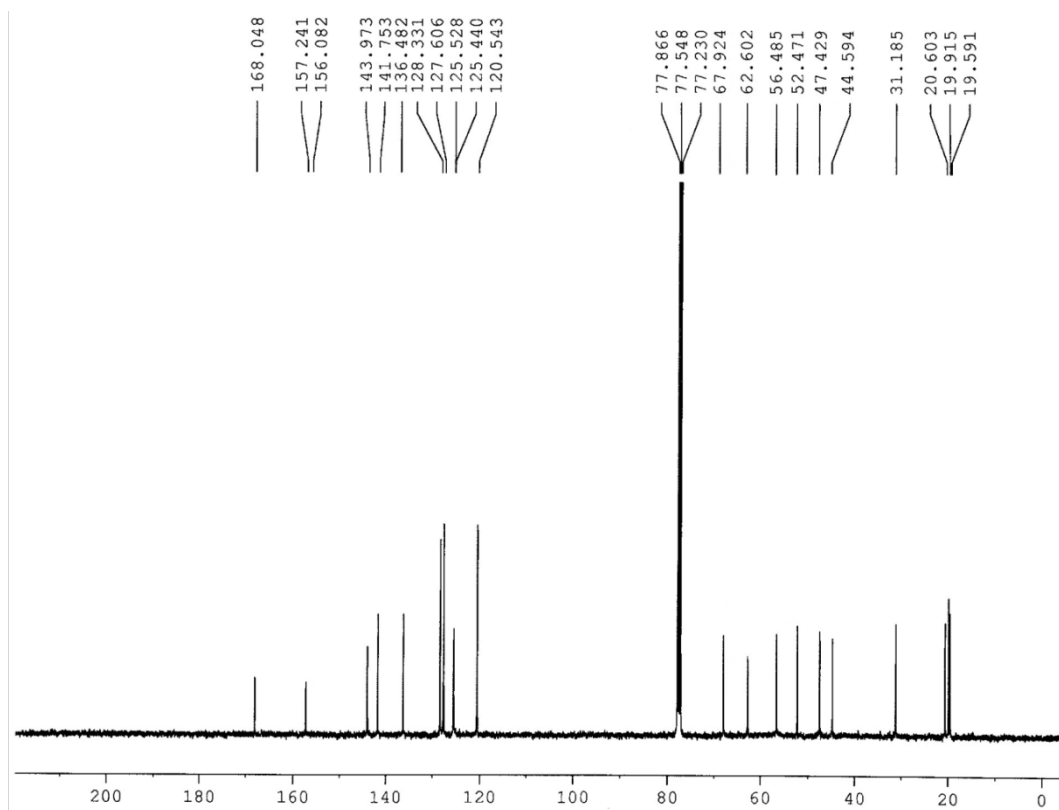


Chiral HPLC chromatogram of mixture of **4e** and **4e'**

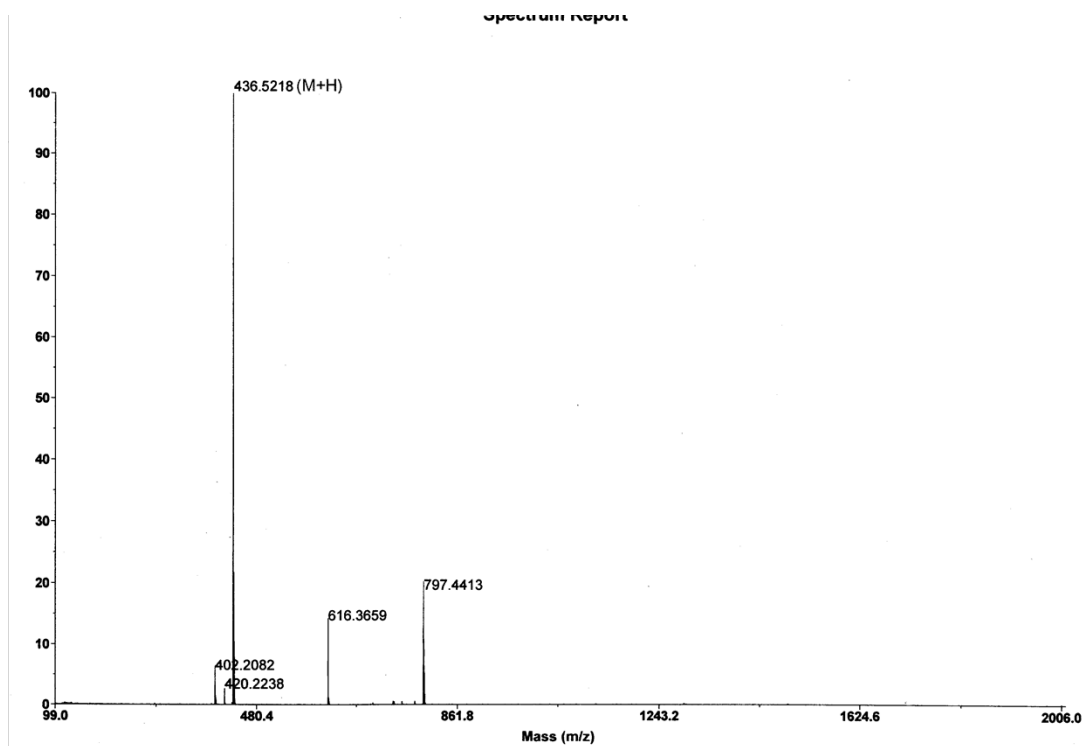
(Method: $\lambda=254$ nm; flow rate: 1.0 mL/min; chiralpak IA, 250 x 4.6 mm; 5 μ L; isocratic: hexane: EtOH; 9:1.)



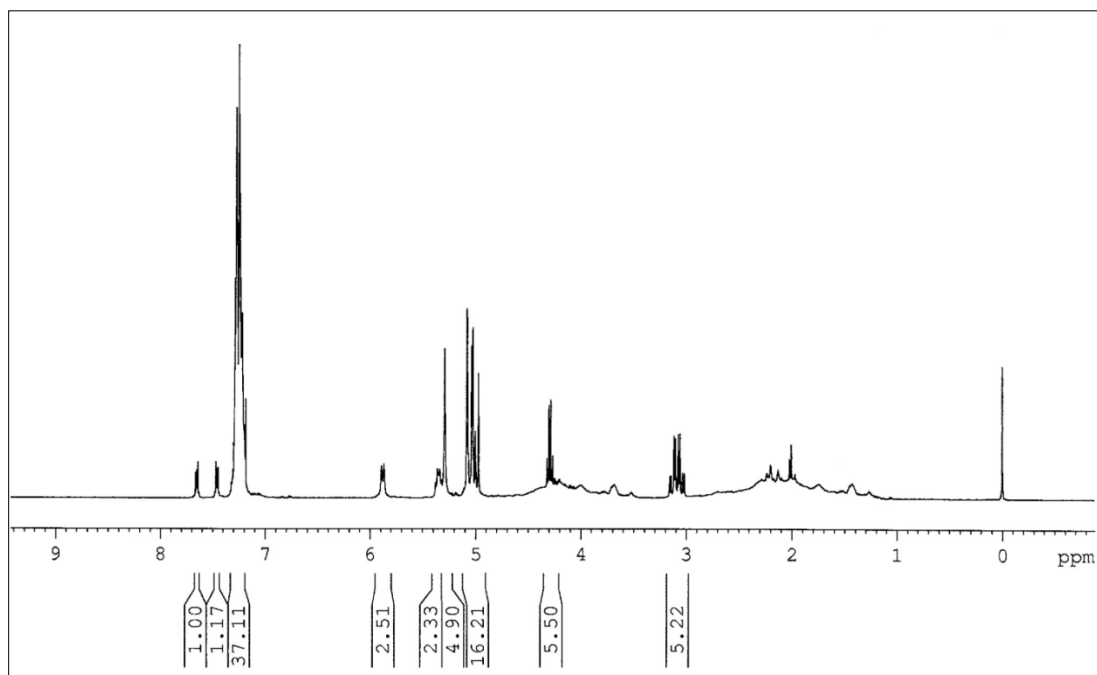
^1H NMR spectrum of compound **5a**



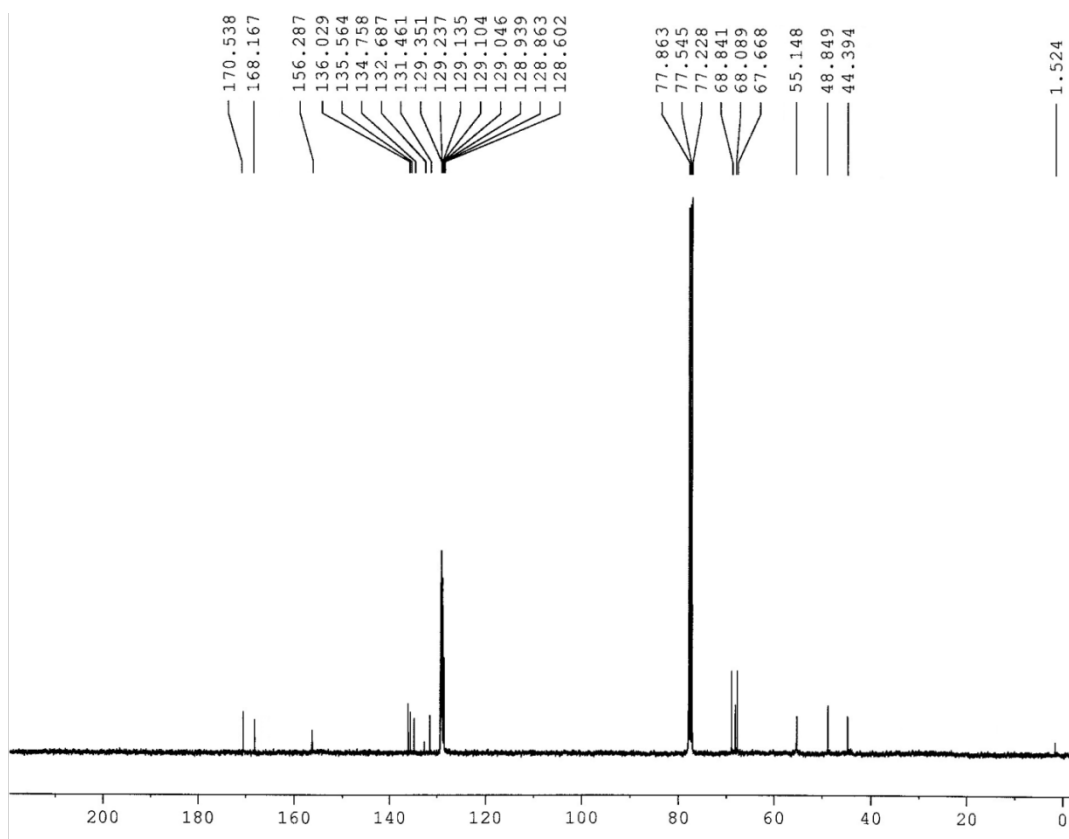
^{13}C NMR spectrum of compound **5a**



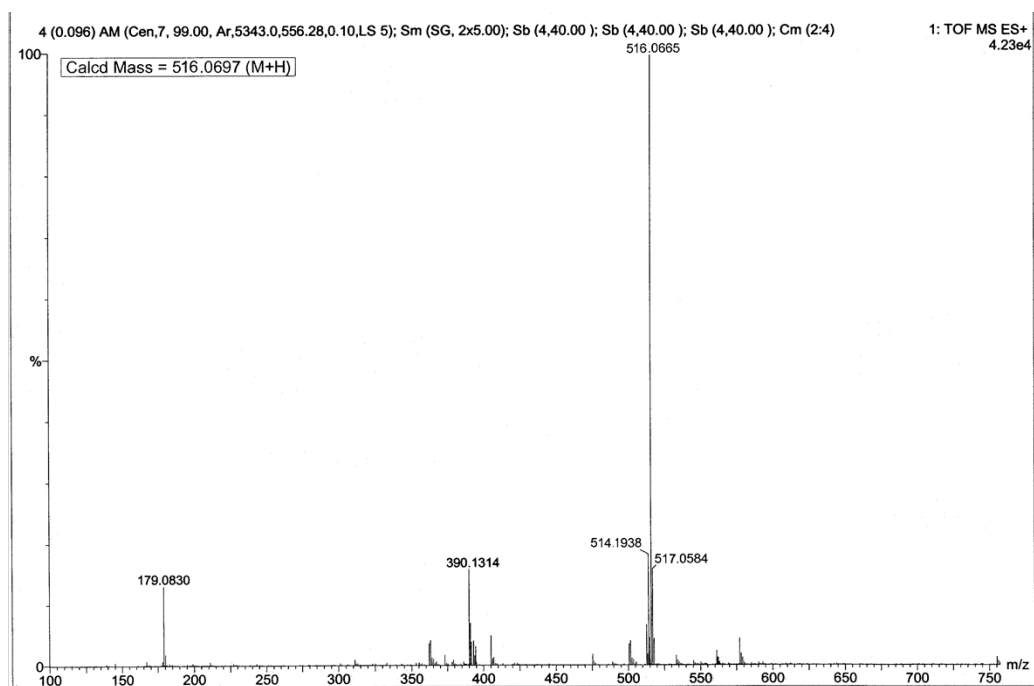
HRMS spectrum of compound **5a**



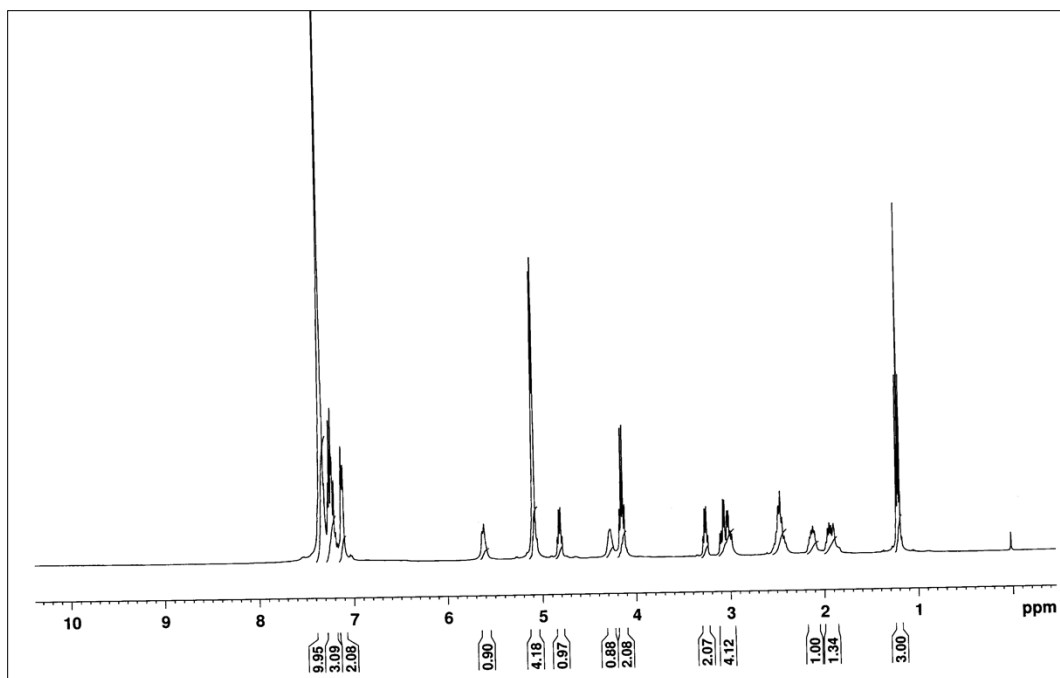
^1H NMR spectrum of compound **5b**



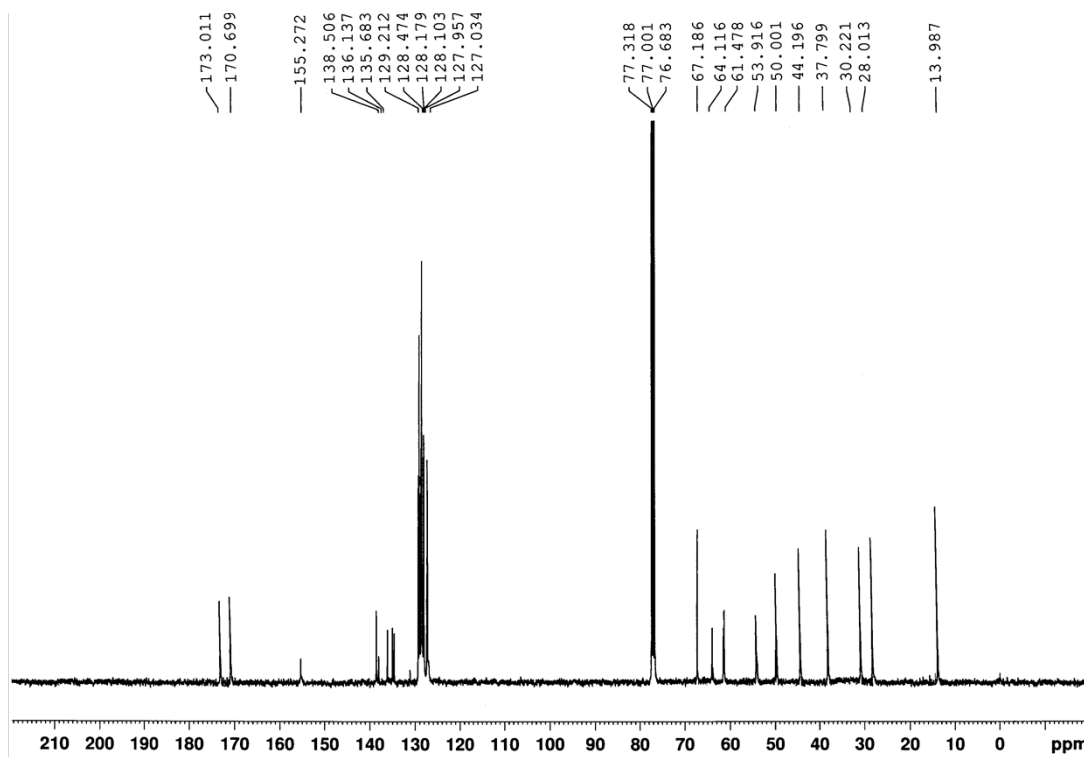
^1H NMR spectrum of compound **5b**



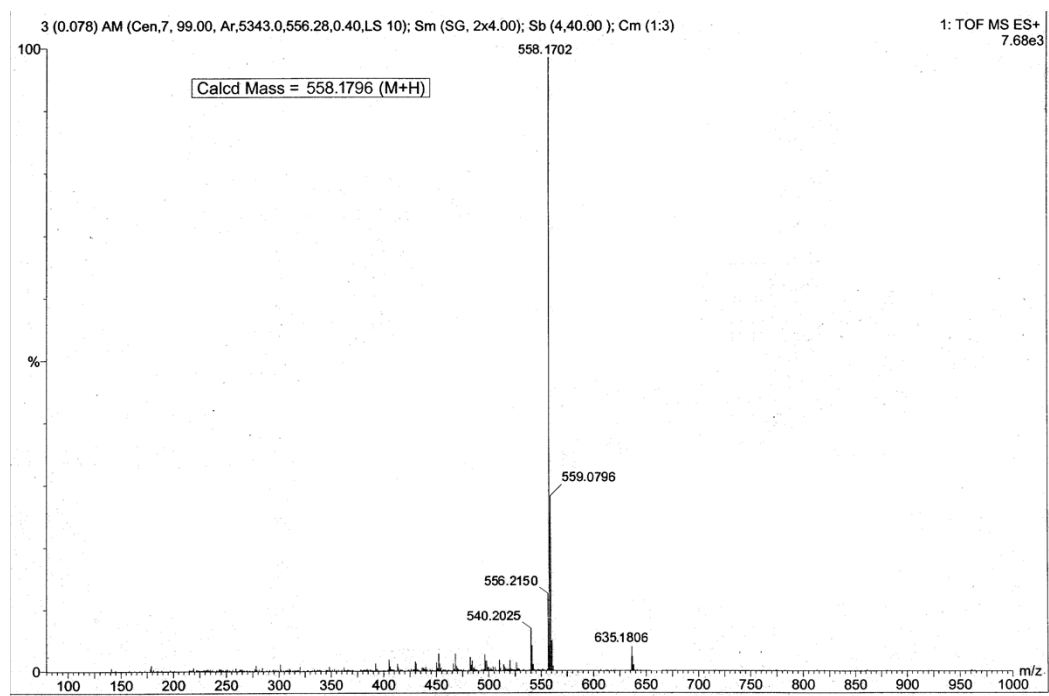
HRMS spectrum of compound **5b**



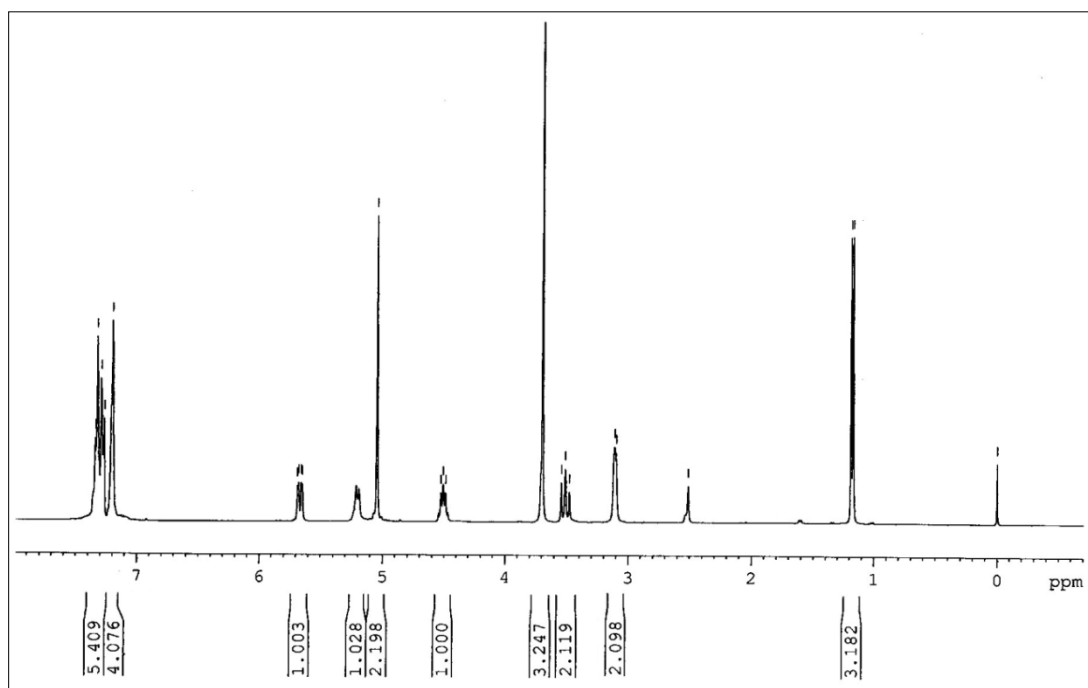
¹H NMR spectrum of compound **5c**



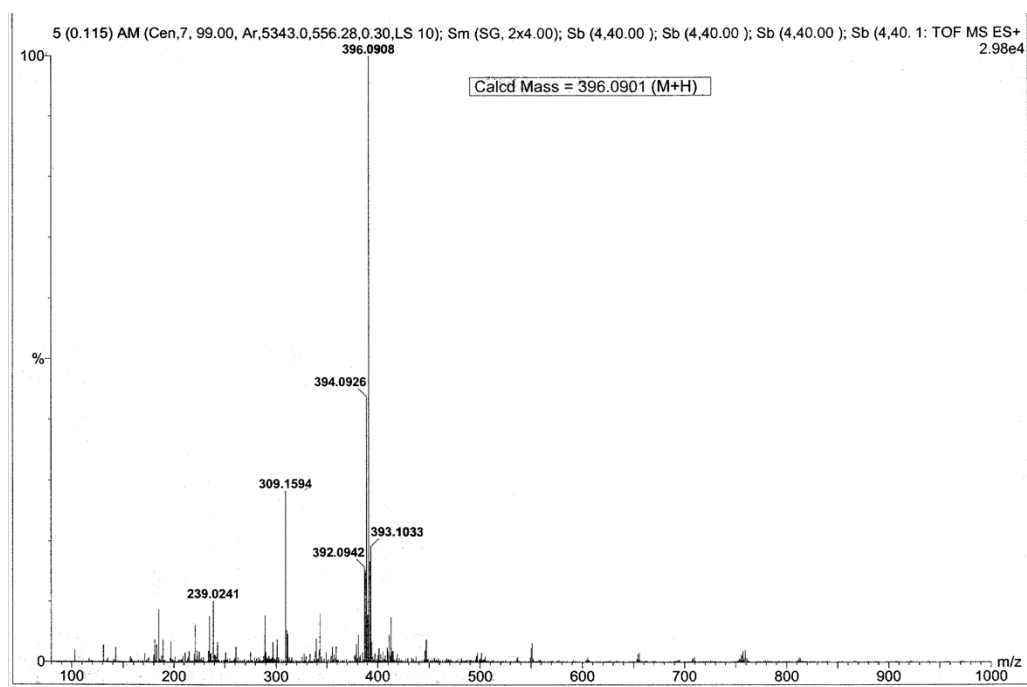
¹³C NMR spectrum of compound **5c**



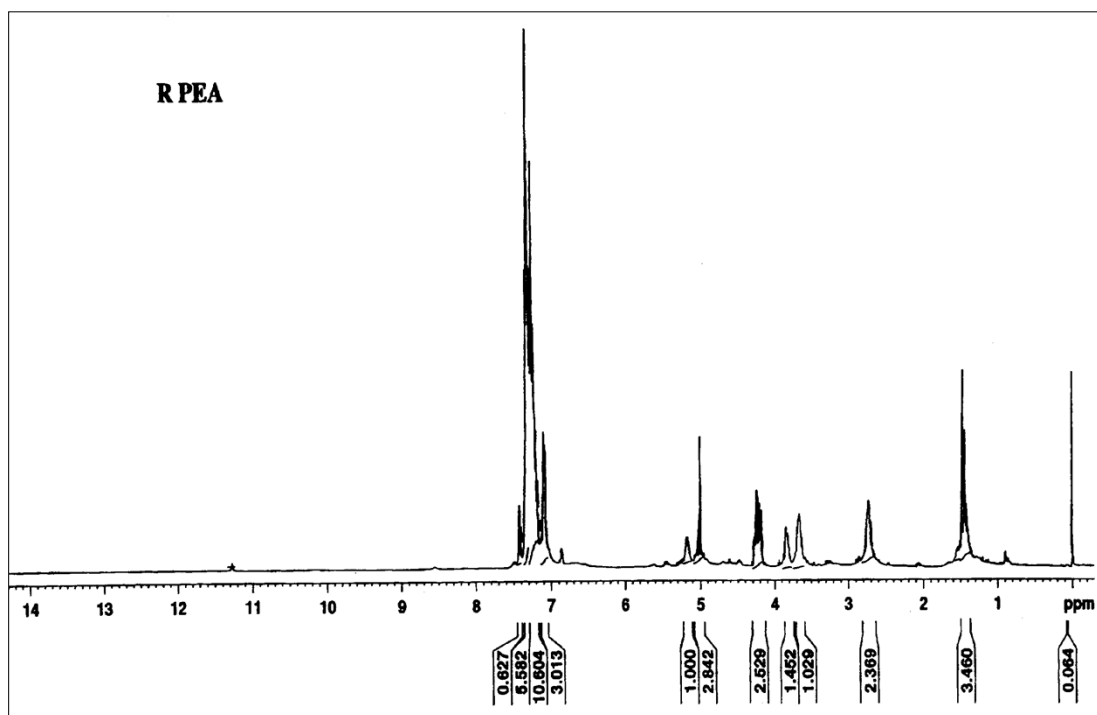
HRMS spectrum of compound **5c**



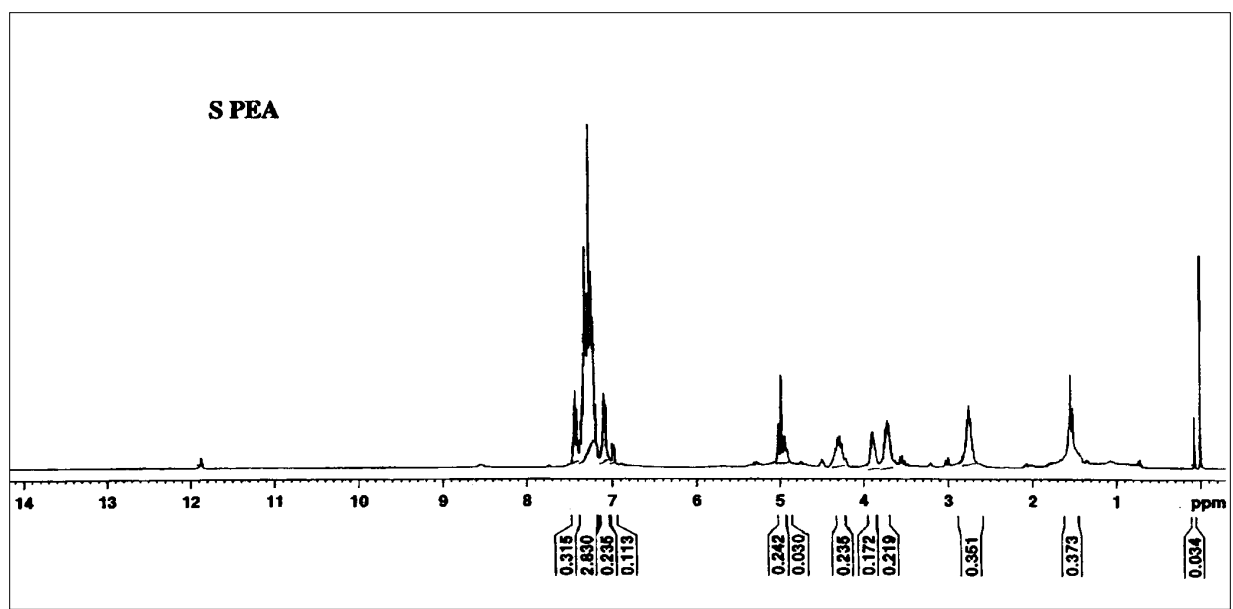
^1H NMR spectrum of compound **5d**



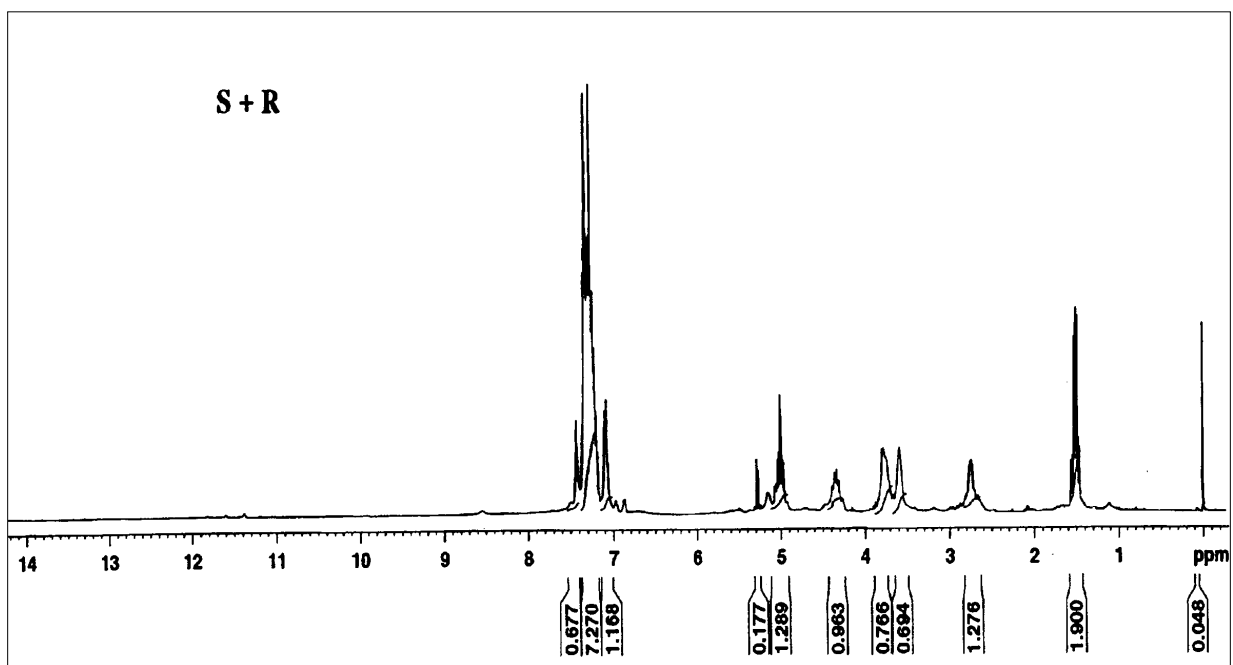
HRMS spectrum of compound **5d**



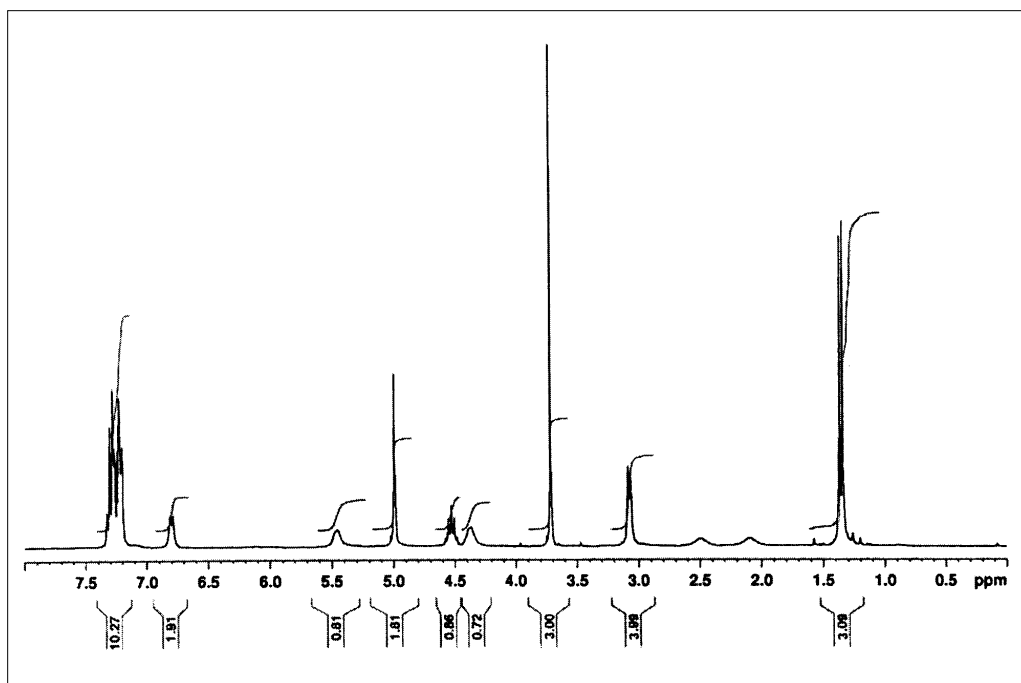
¹H NMR spectrum of compound **5e**



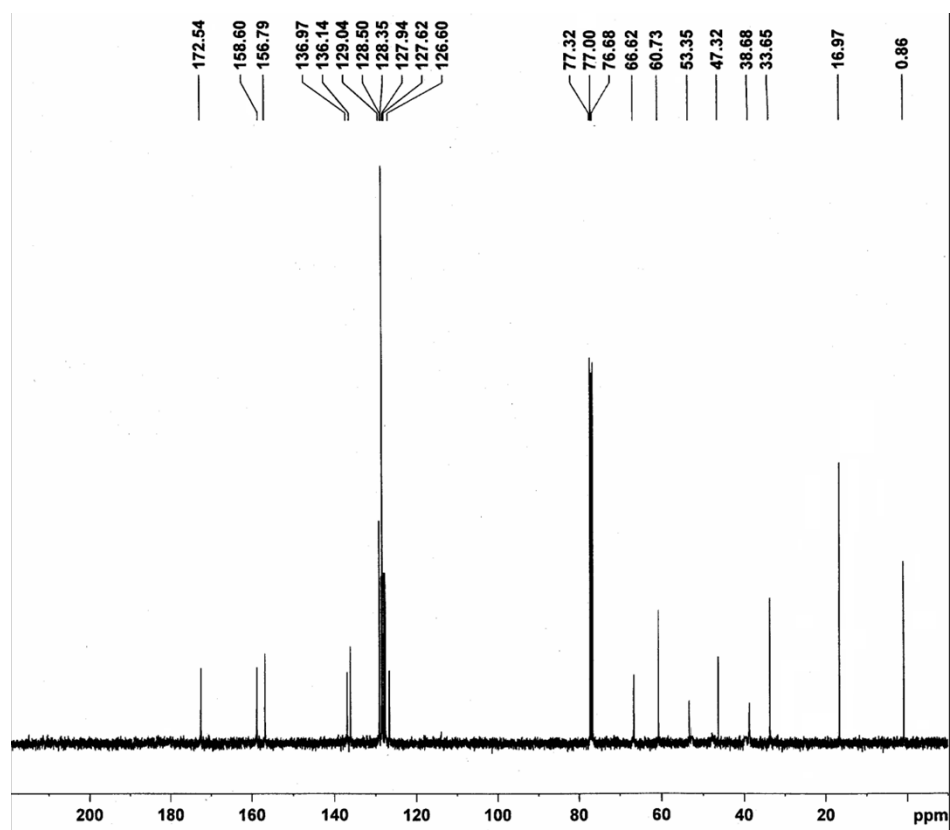
^1H NMR spectrum of compound **5f**



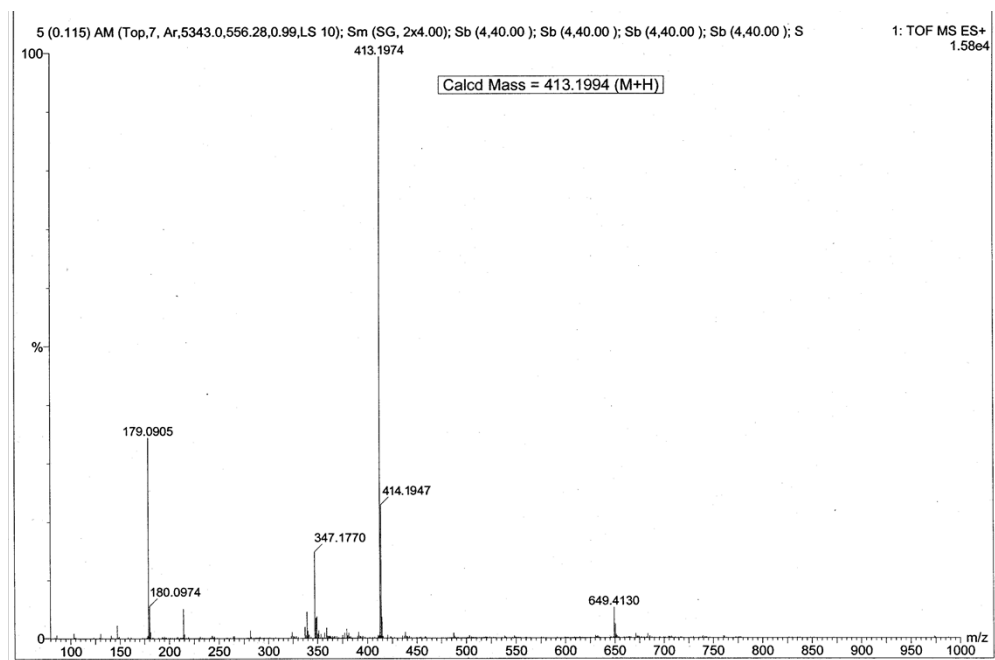
^1H NMR spectrum of mixture of **5e** and **5f**



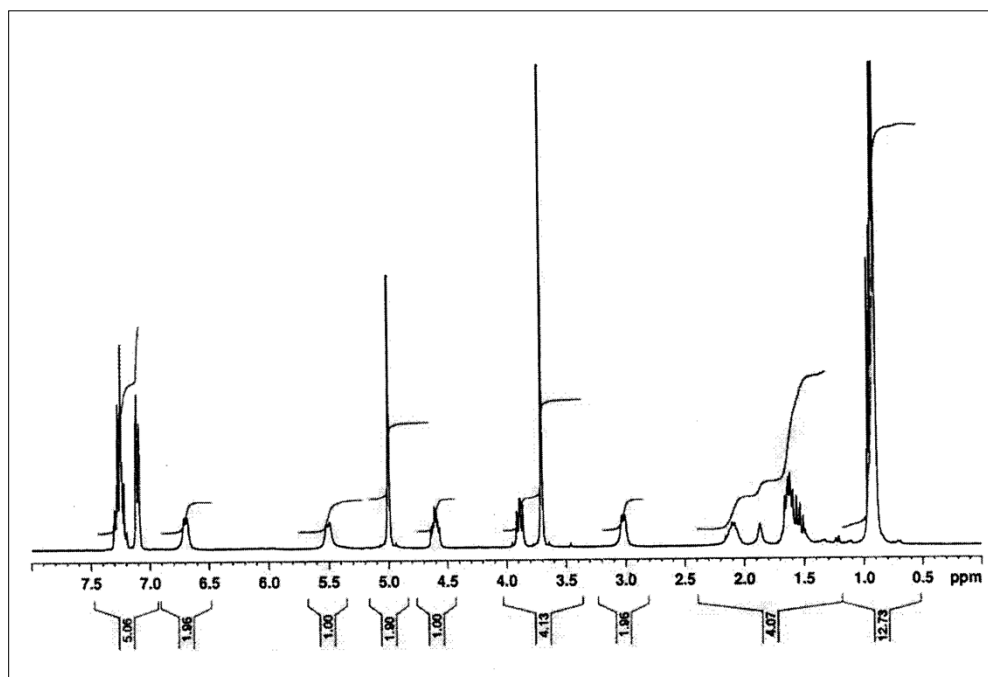
¹H NMR spectrum of compound **6a**



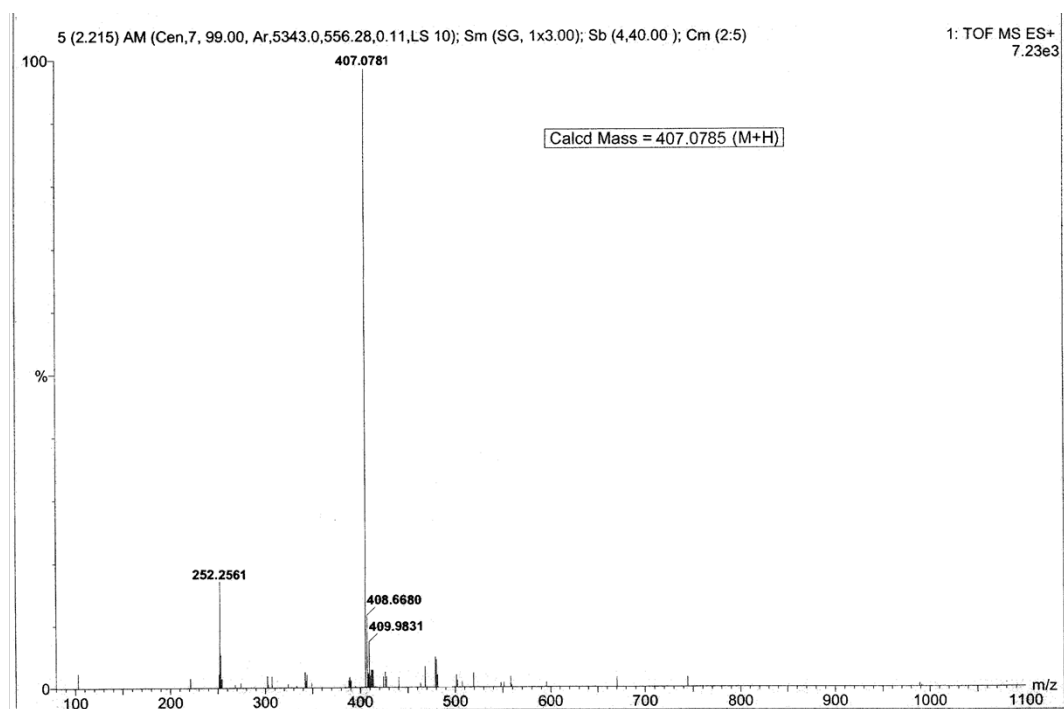
¹³C NMR spectrum of compound **6a**



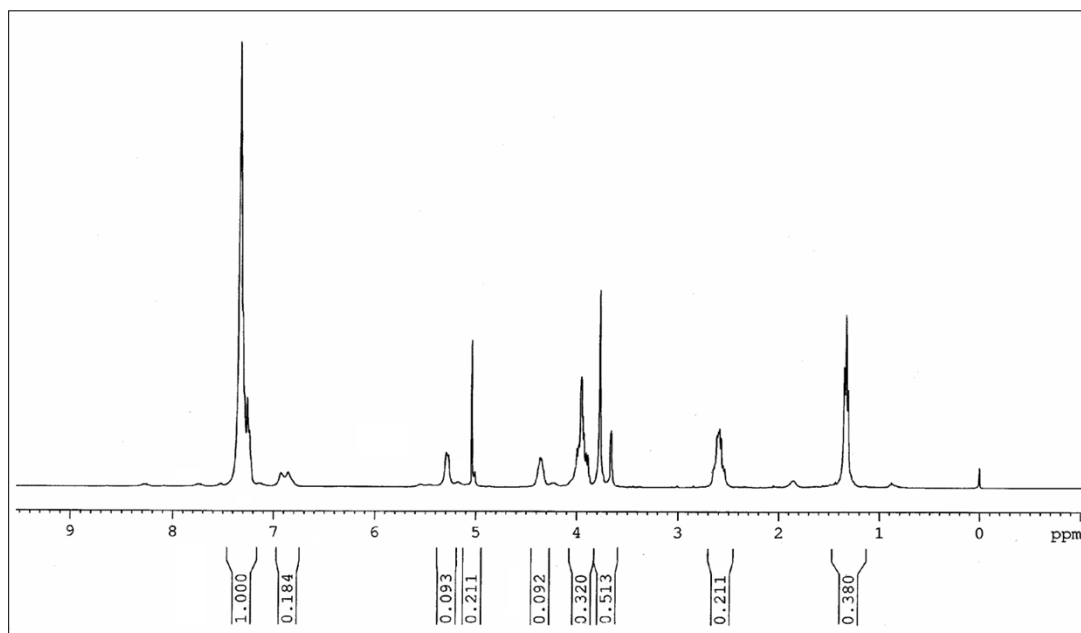
HRMS spectrum of compound **6a**



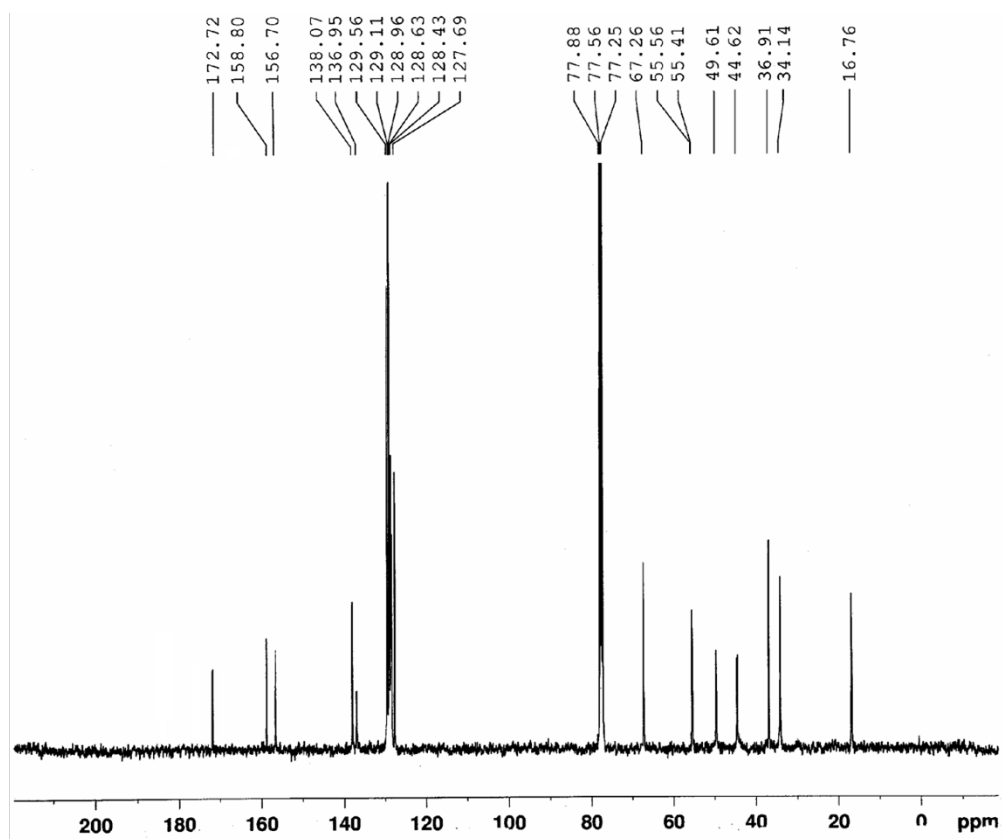
^1H NMR spectrum of compound **6b**



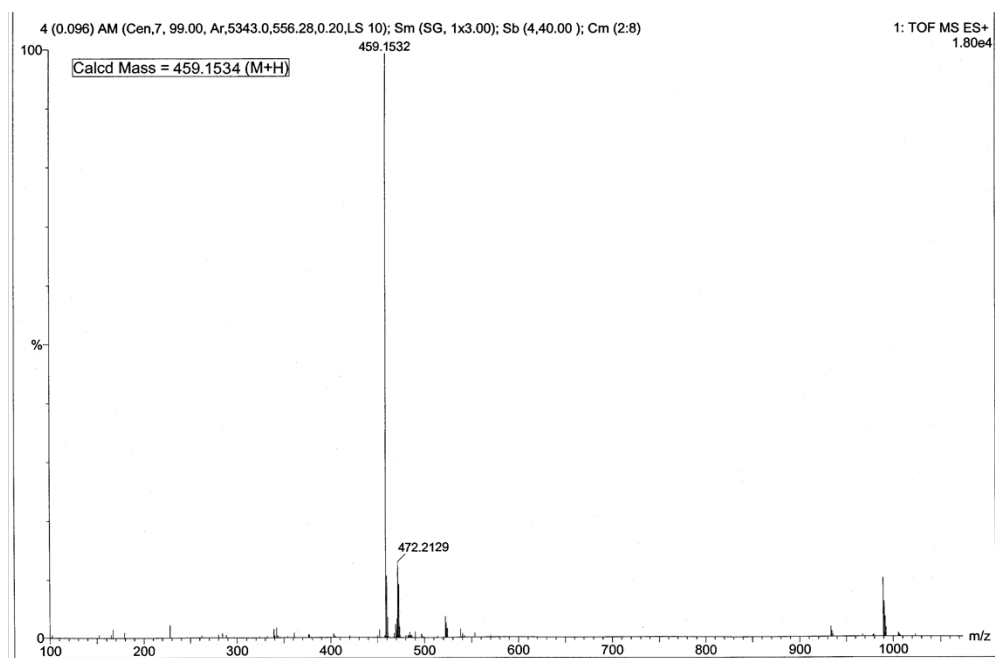
HRMS spectrum of compound **6b**



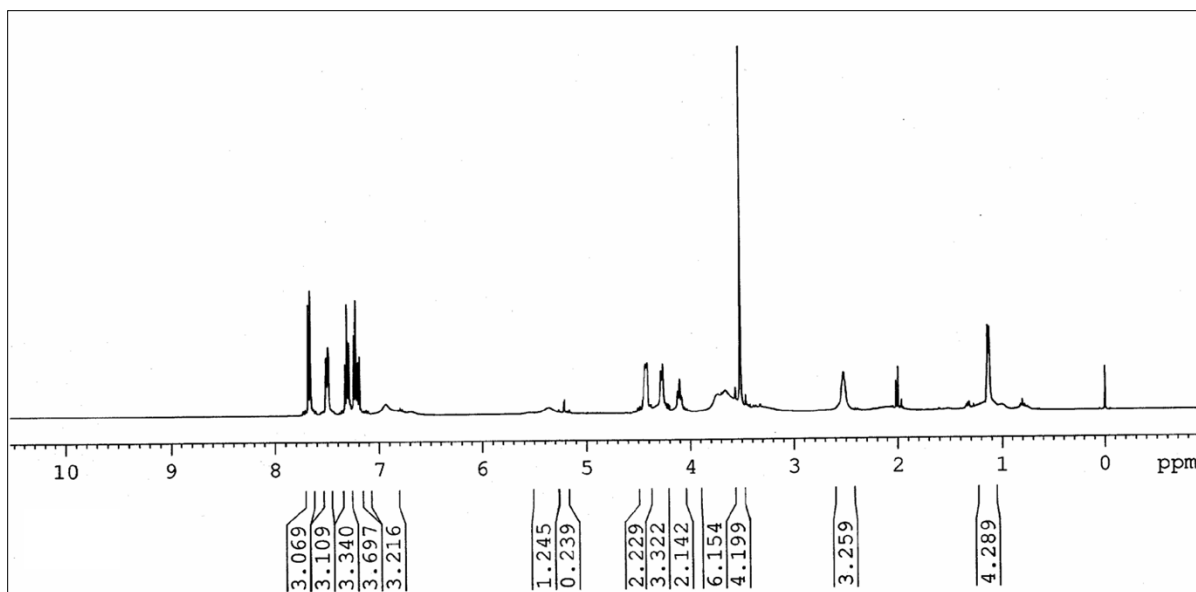
^1H NMR spectrum of compound **6c**



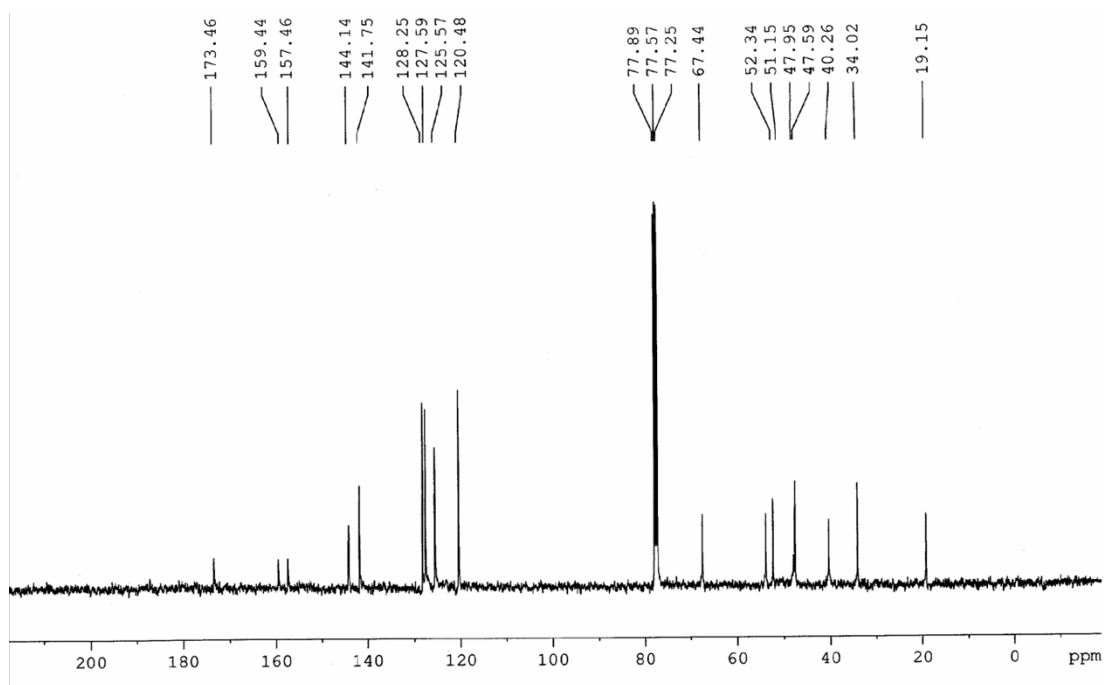
^{13}C NMR spectrum of compound **6c**



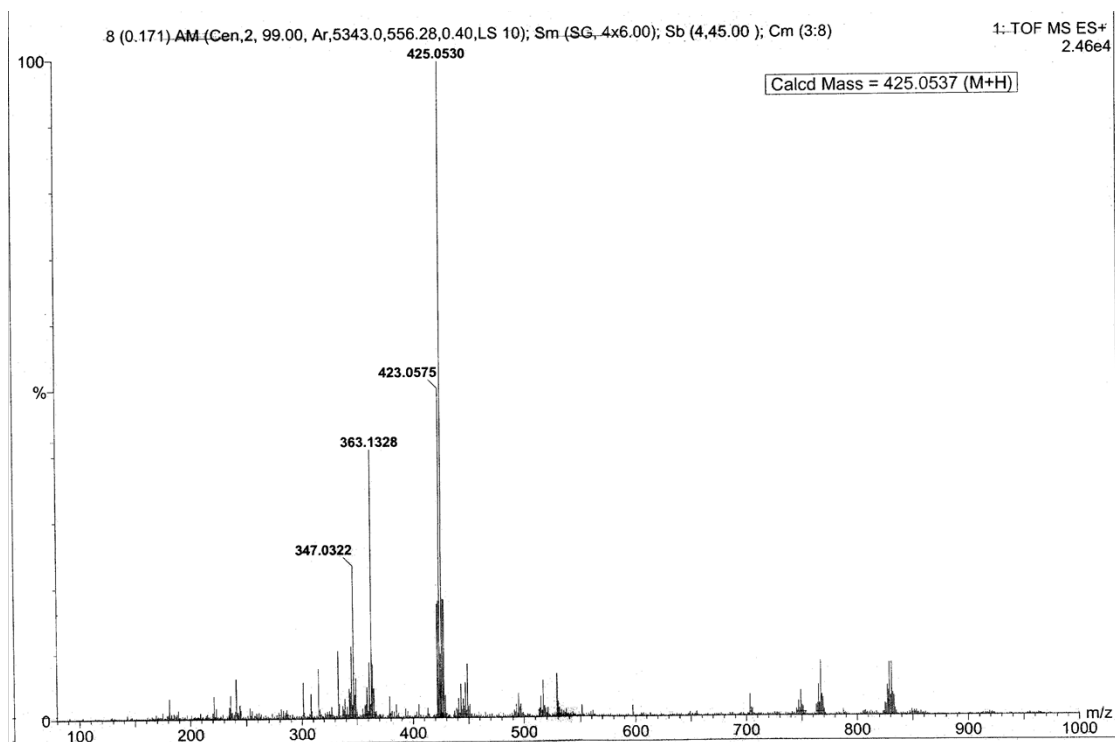
HRMS spectrum of compound **6c**



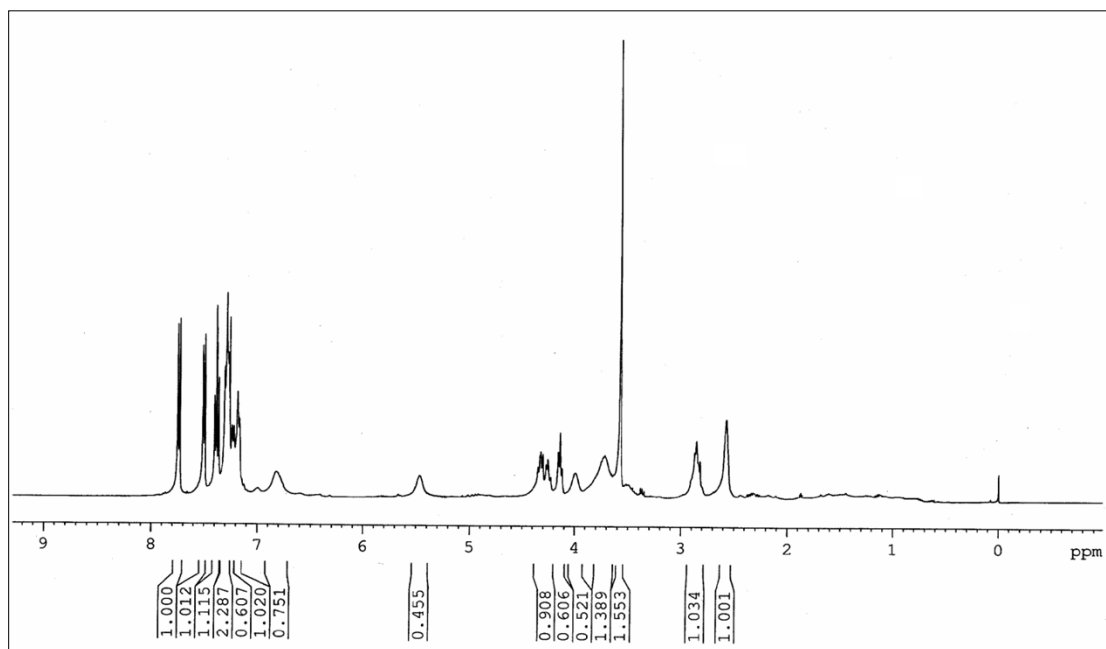
^1H NMR spectrum of compound **6d**



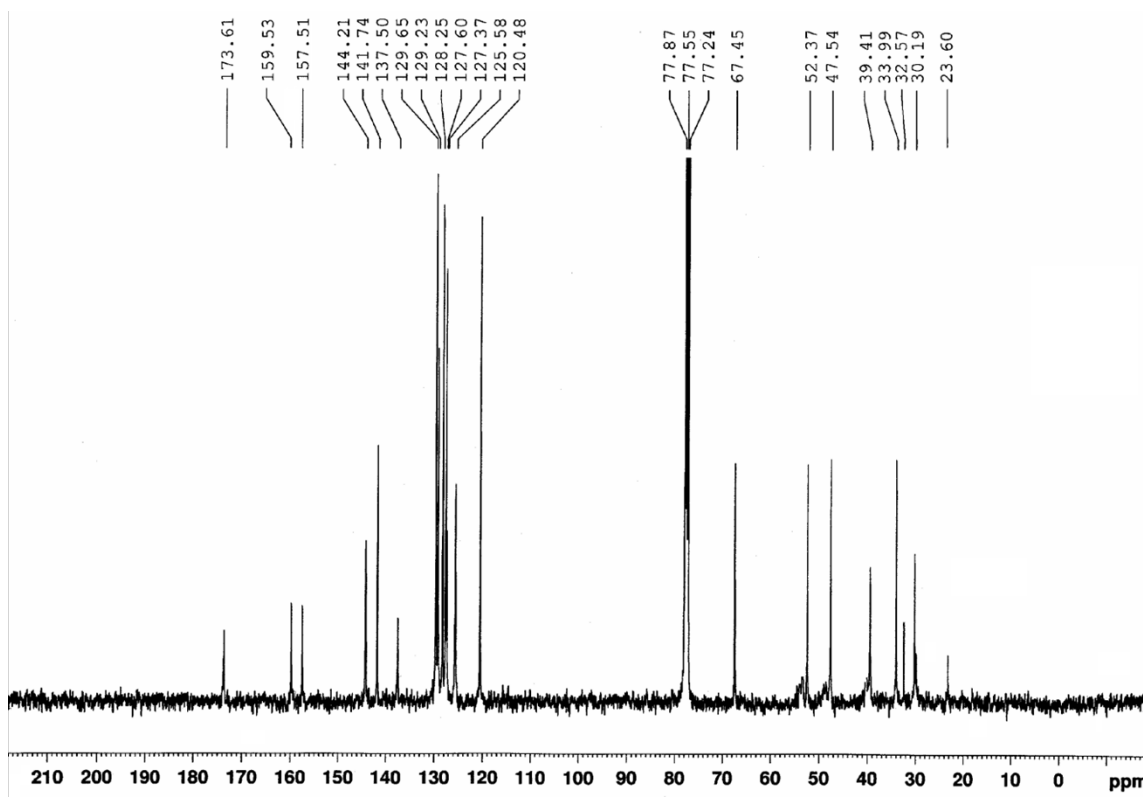
^{13}C NMR spectrum of compound **6d**



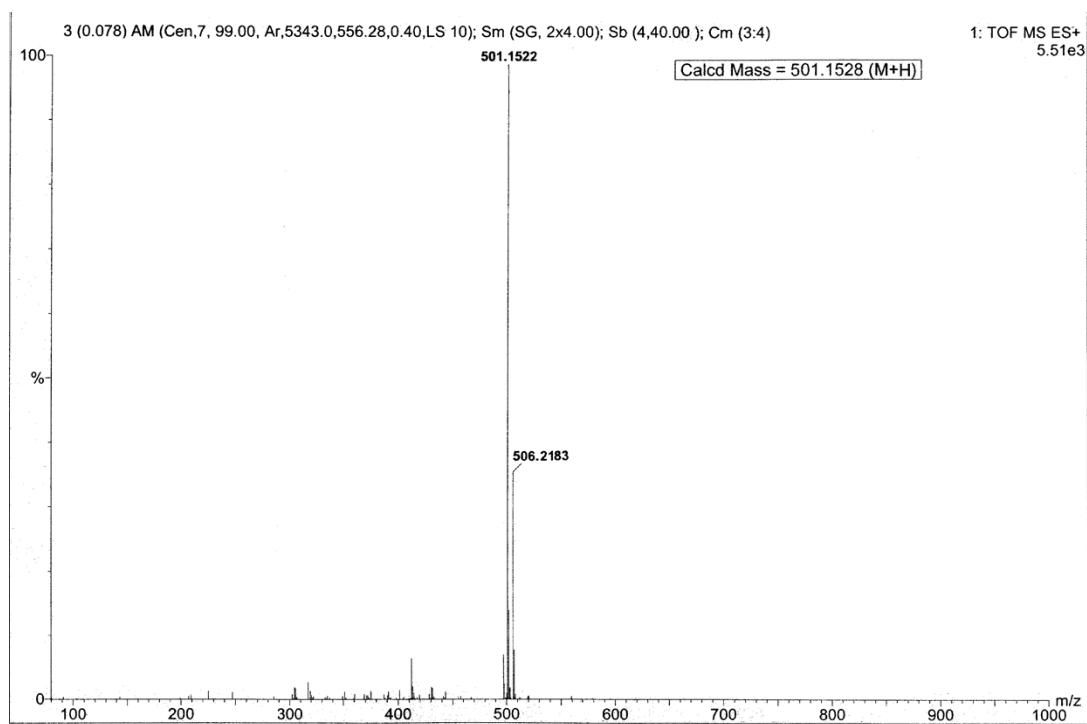
HRMS spectrum of compound **6d**



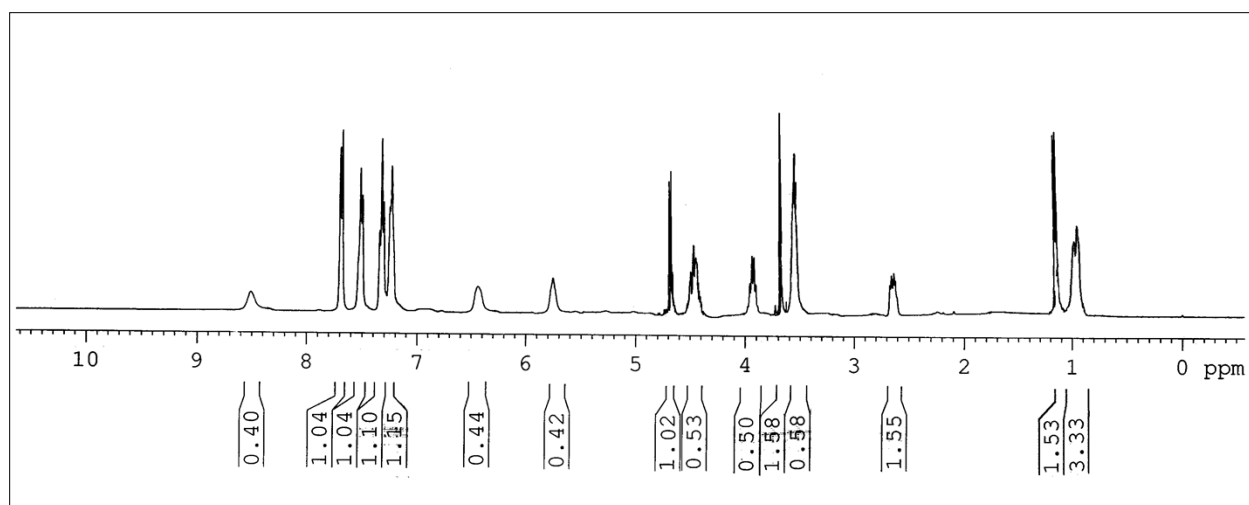
^1H NMR spectrum of compound **6e**



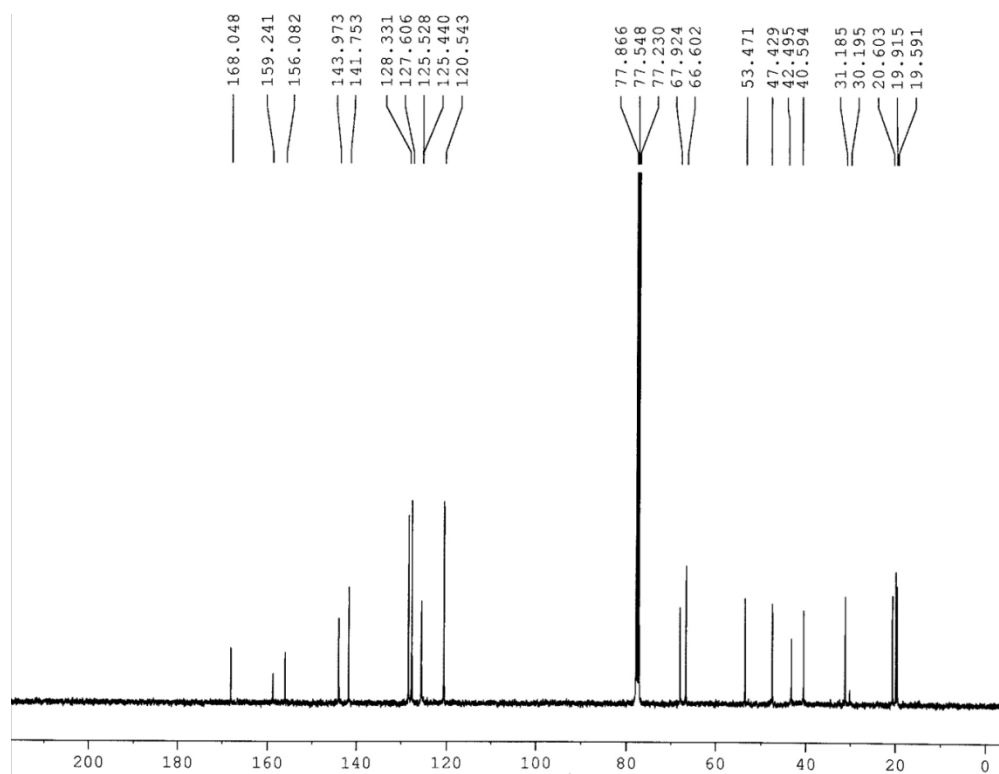
^{13}C NMR spectrum of compound **6e**



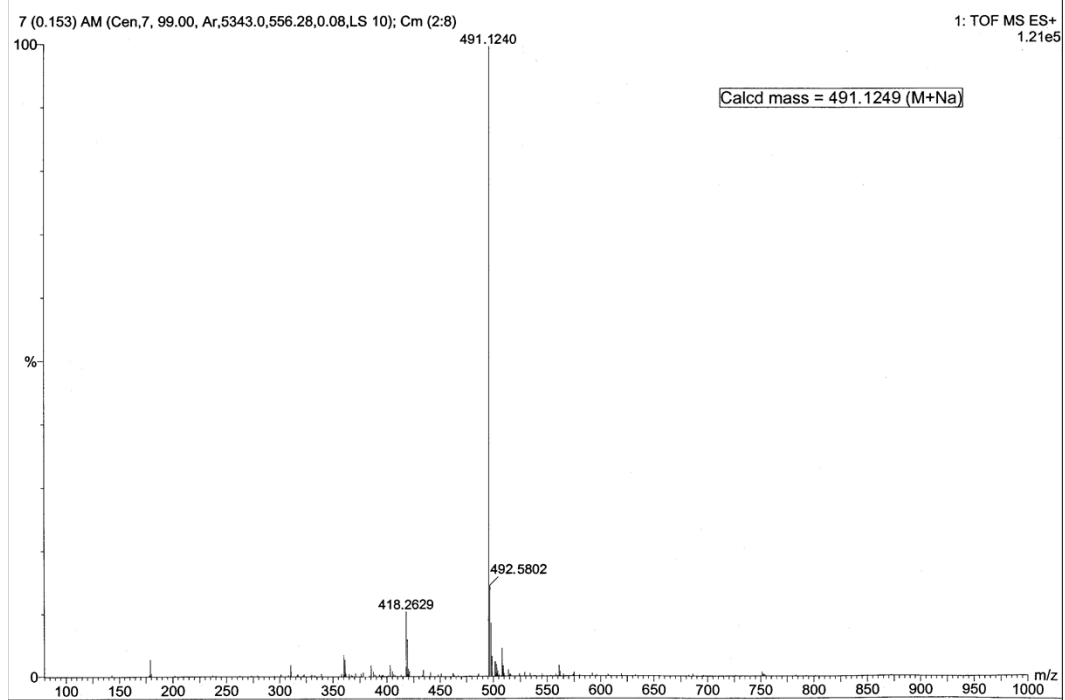
HRMS spectrum of compound **6e**



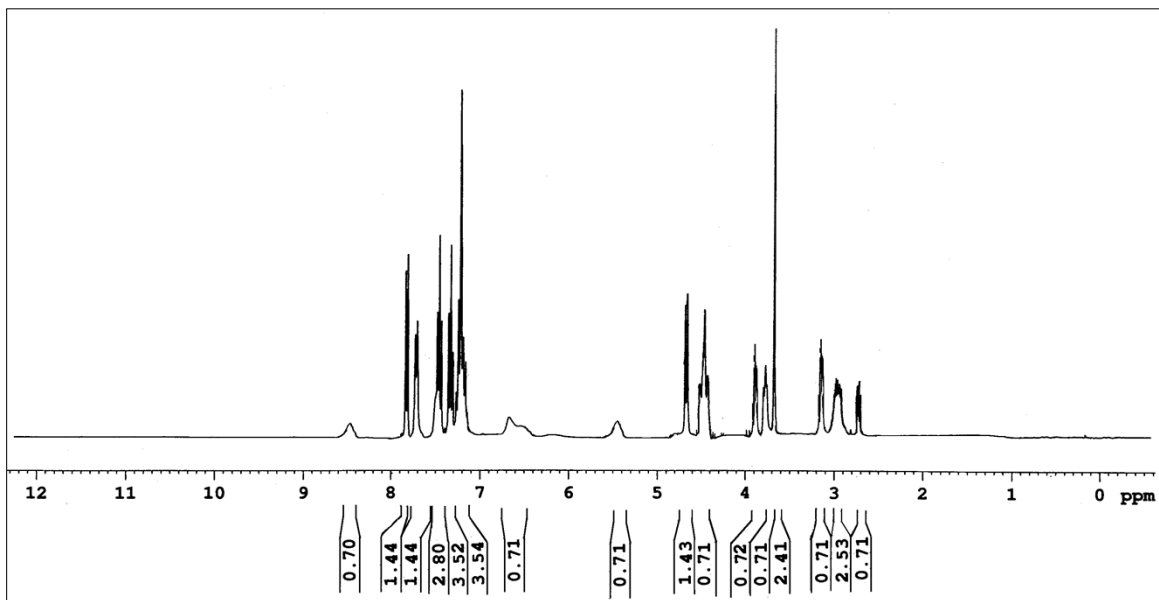
¹H NMR spectrum of compound **7a**



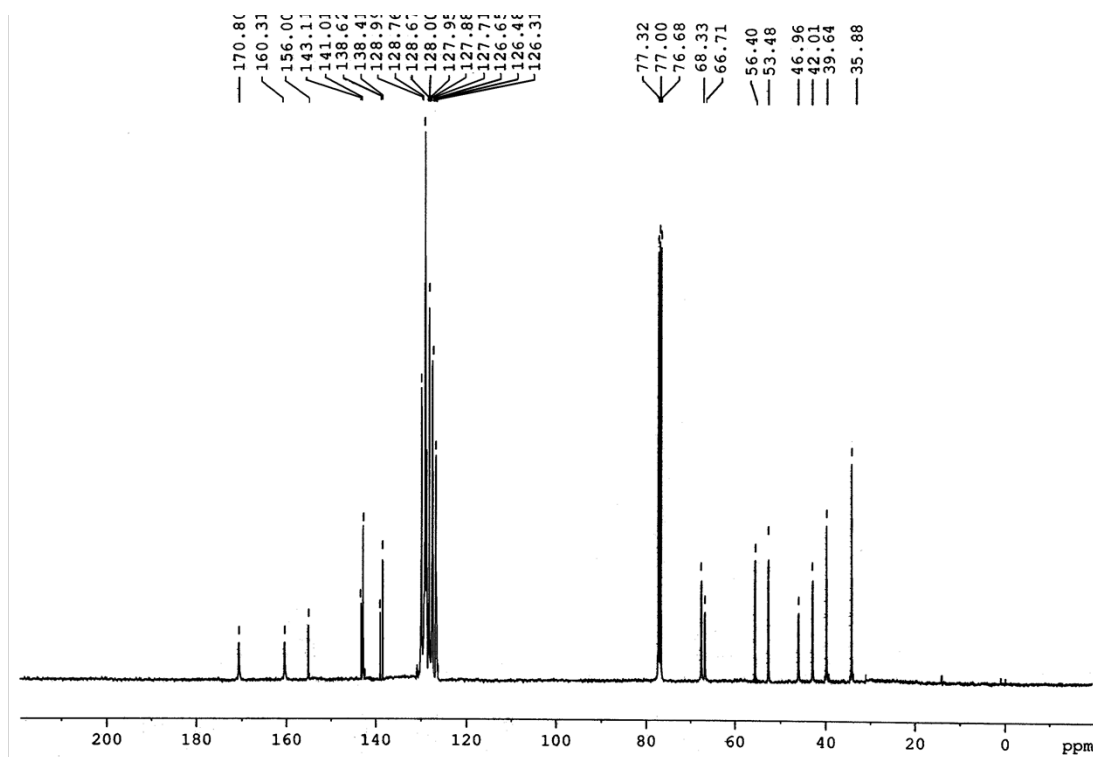
¹³C NMR spectrum of compound **7a**



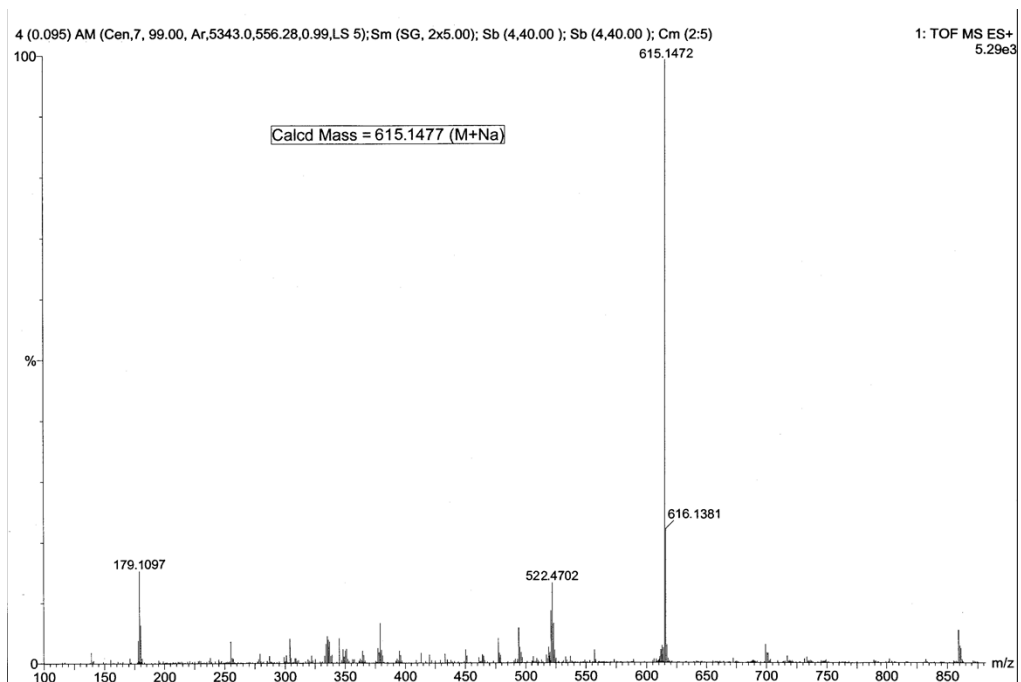
HRMS spectrum of compound **7a**



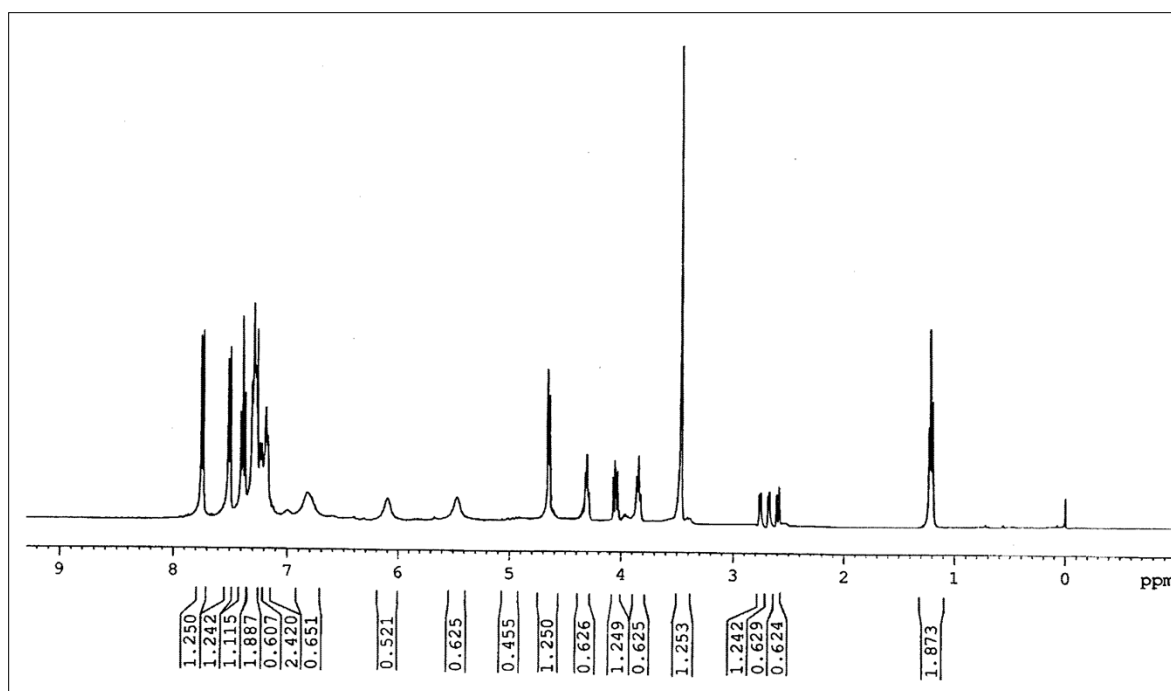
^1H NMR spectrum of compound **7b**



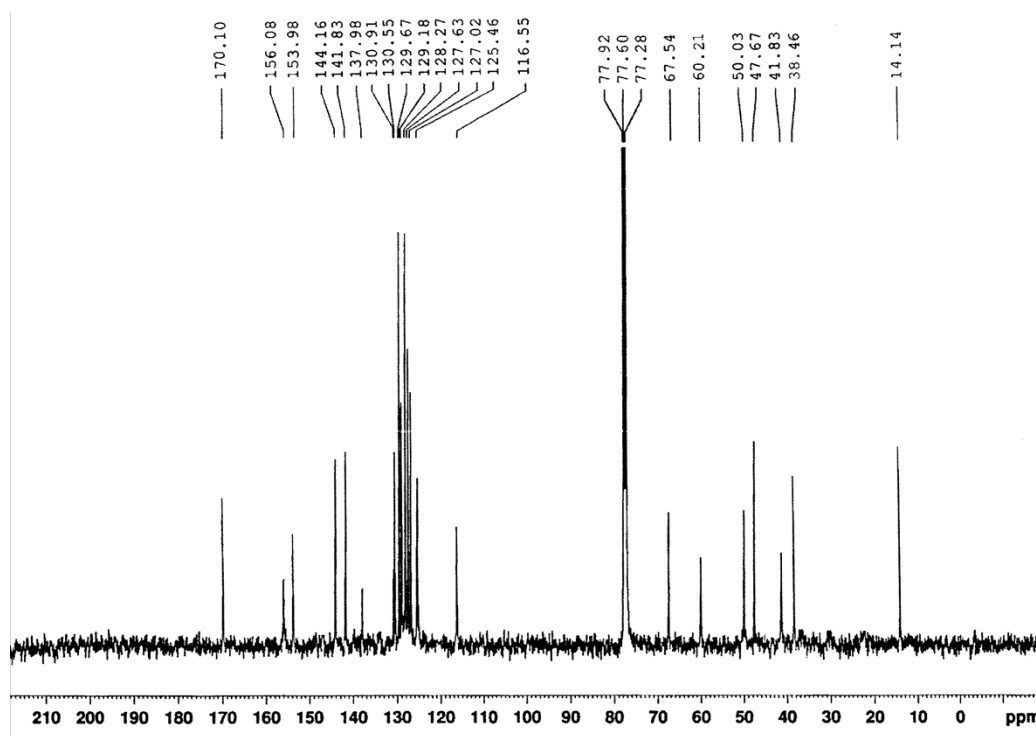
^{13}C NMR spectrum of compound **7b**



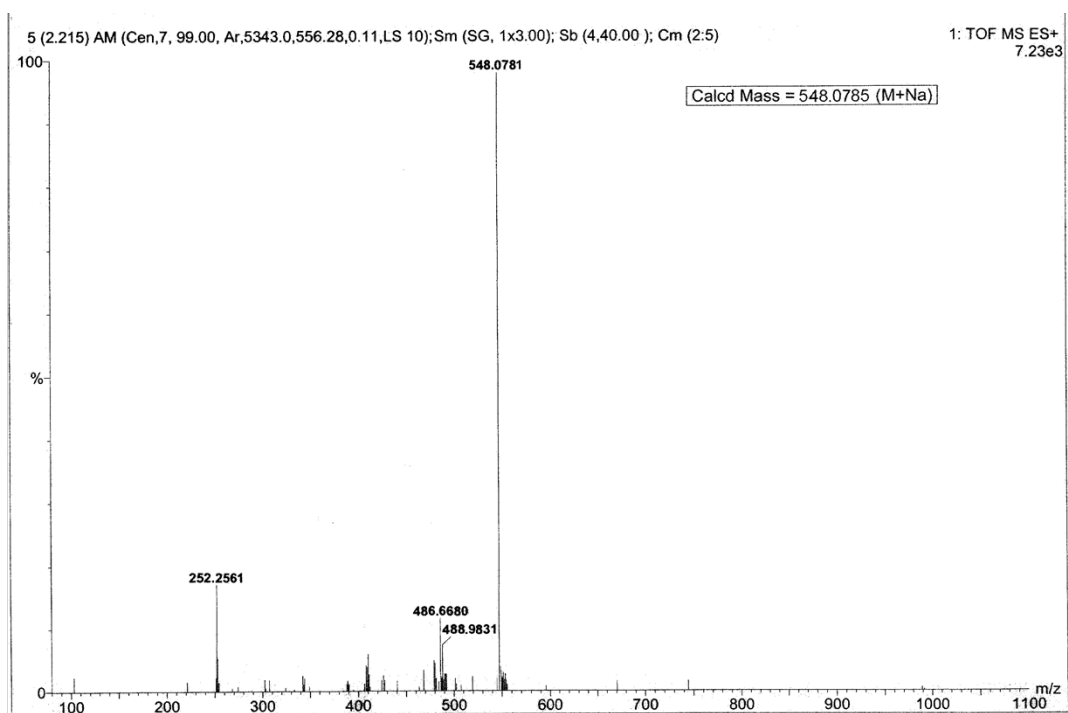
HRMS spectrum of compound **7b**



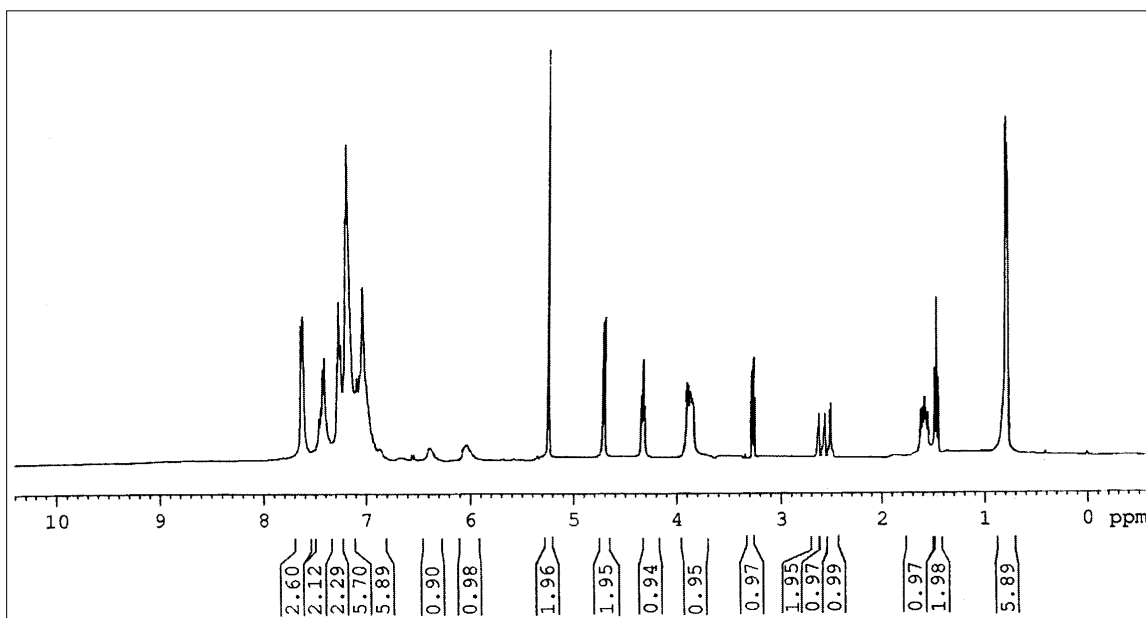
¹H NMR spectrum of compound **8a**



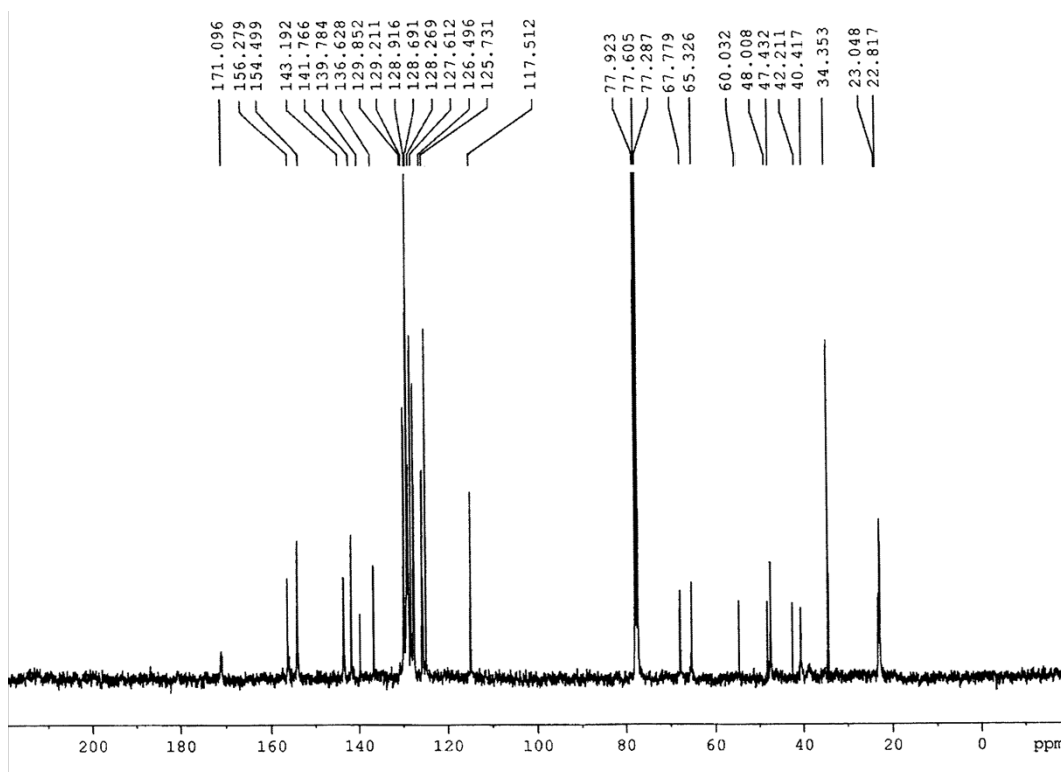
¹³C NMR spectrum of compound **8a**



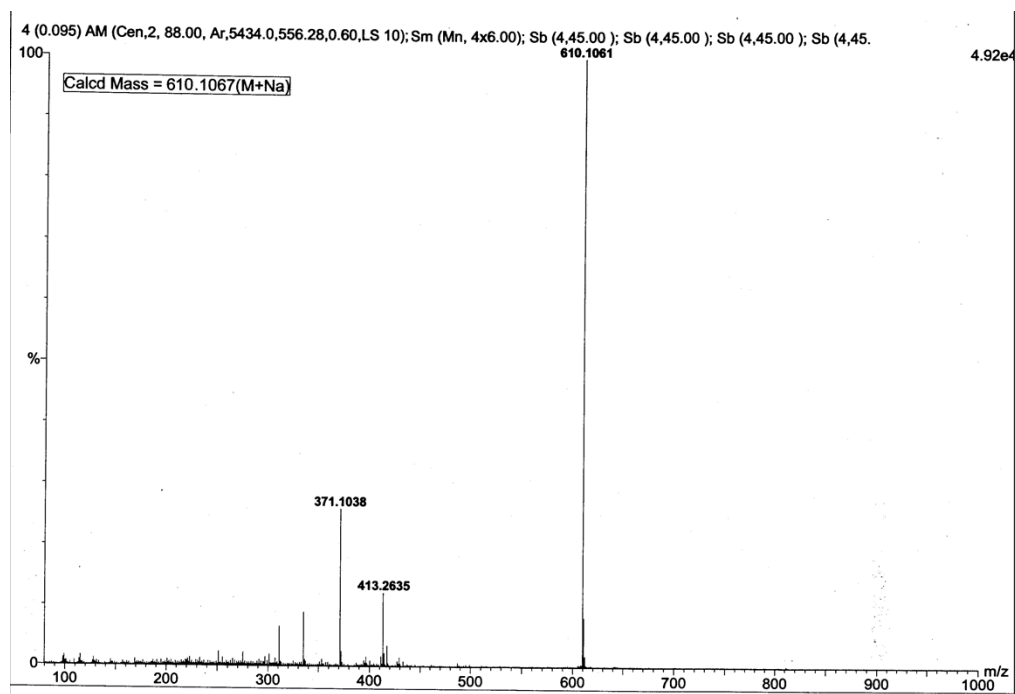
HRMS spectrum of compound **8a**



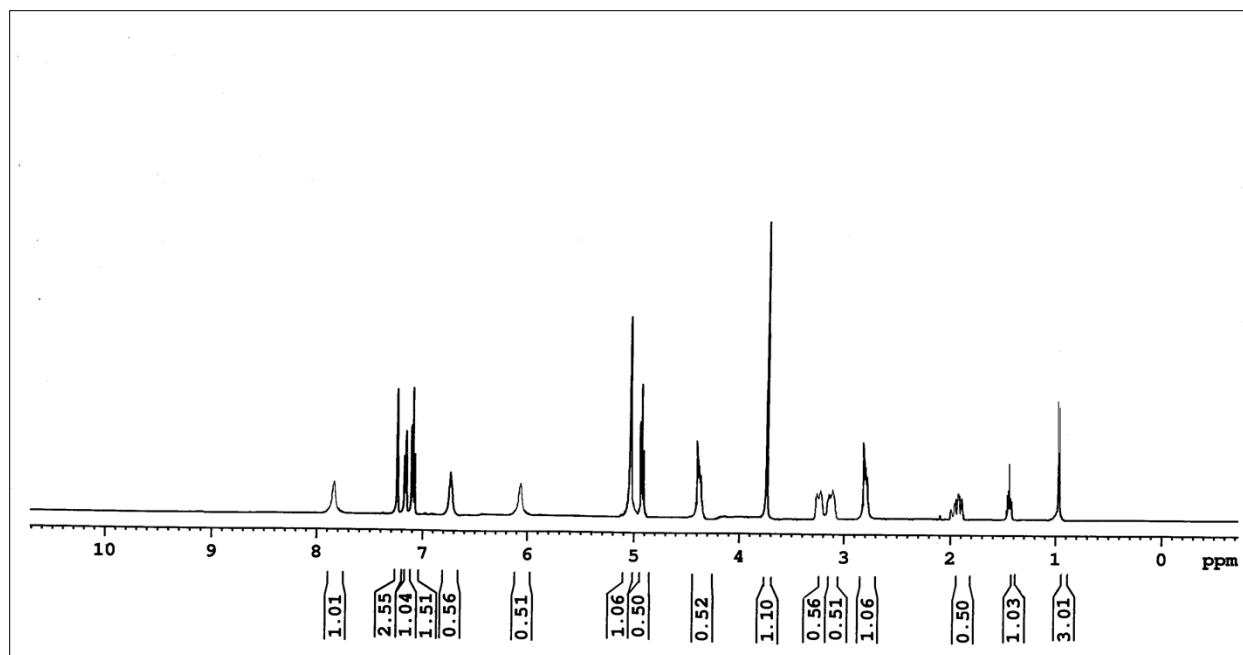
^1H NMR spectrum of compound **8b**



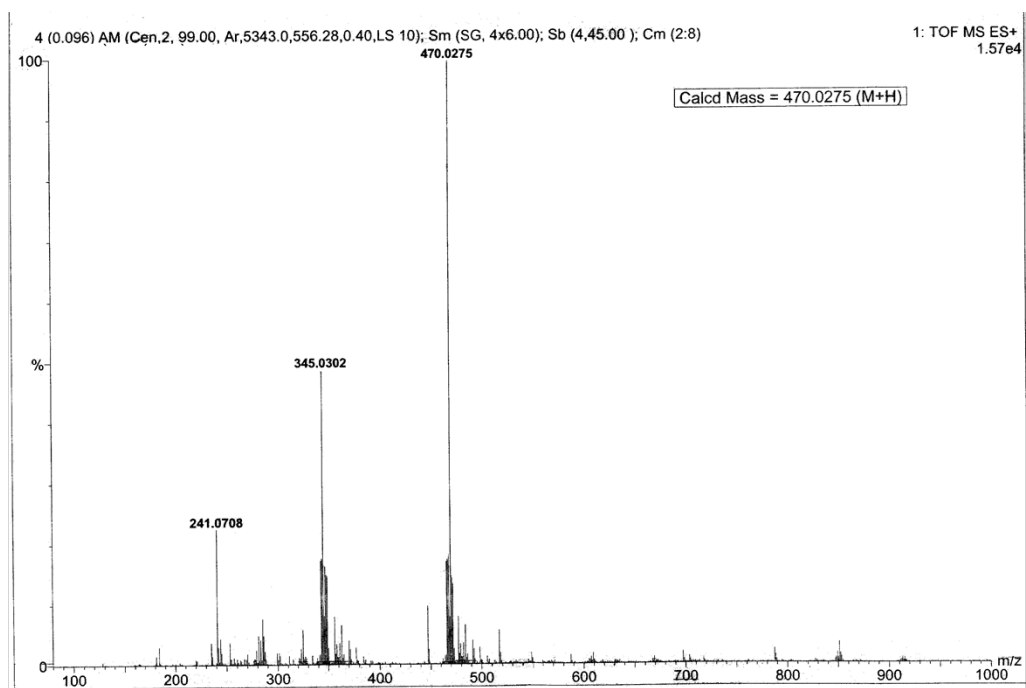
^{13}C NMR spectrum of compound **8b**



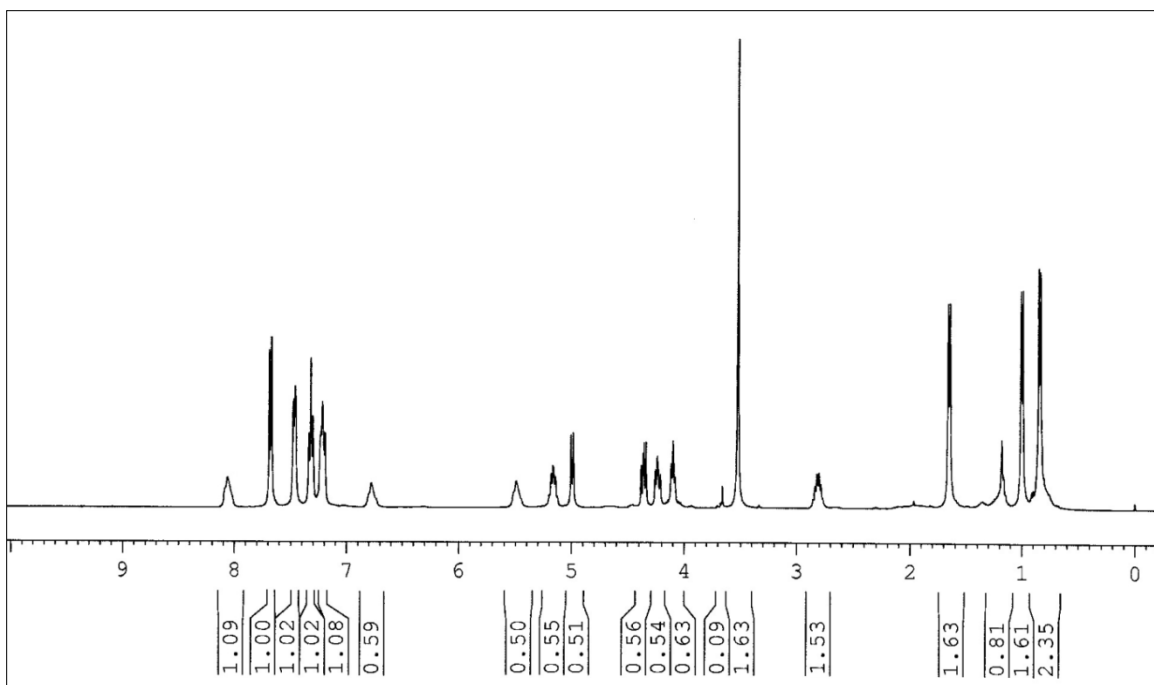
HRMS spectrum of compound **8b**



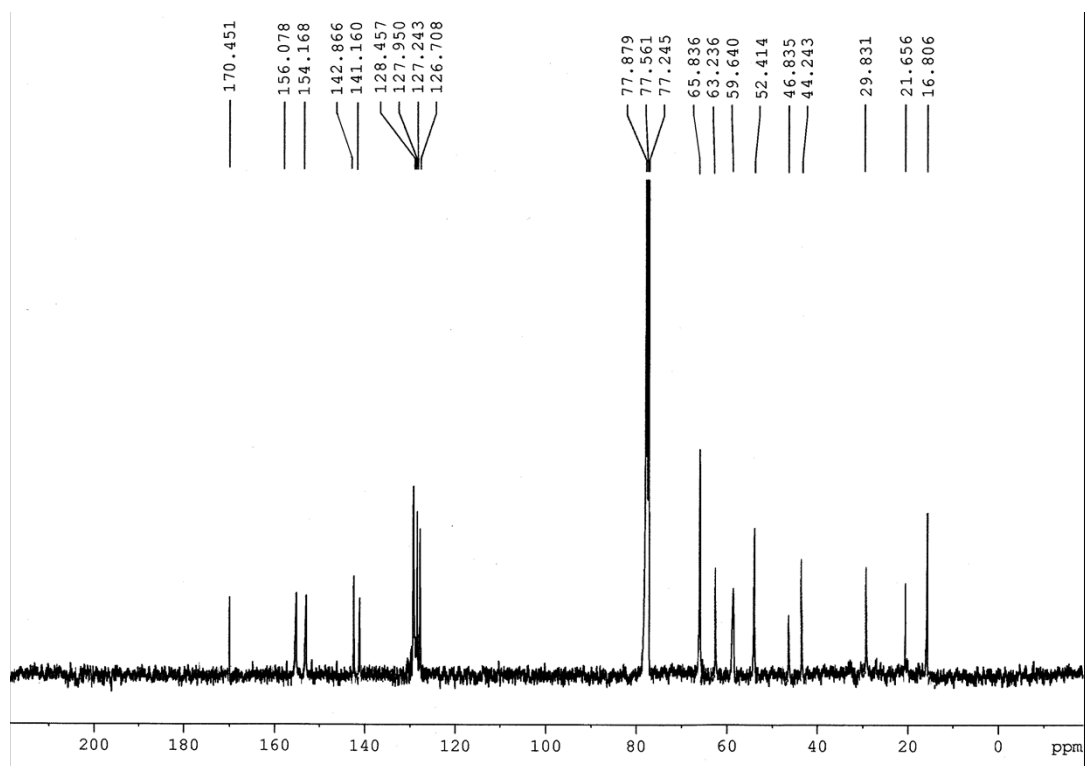
^1H NMR spectrum of compound **9a**



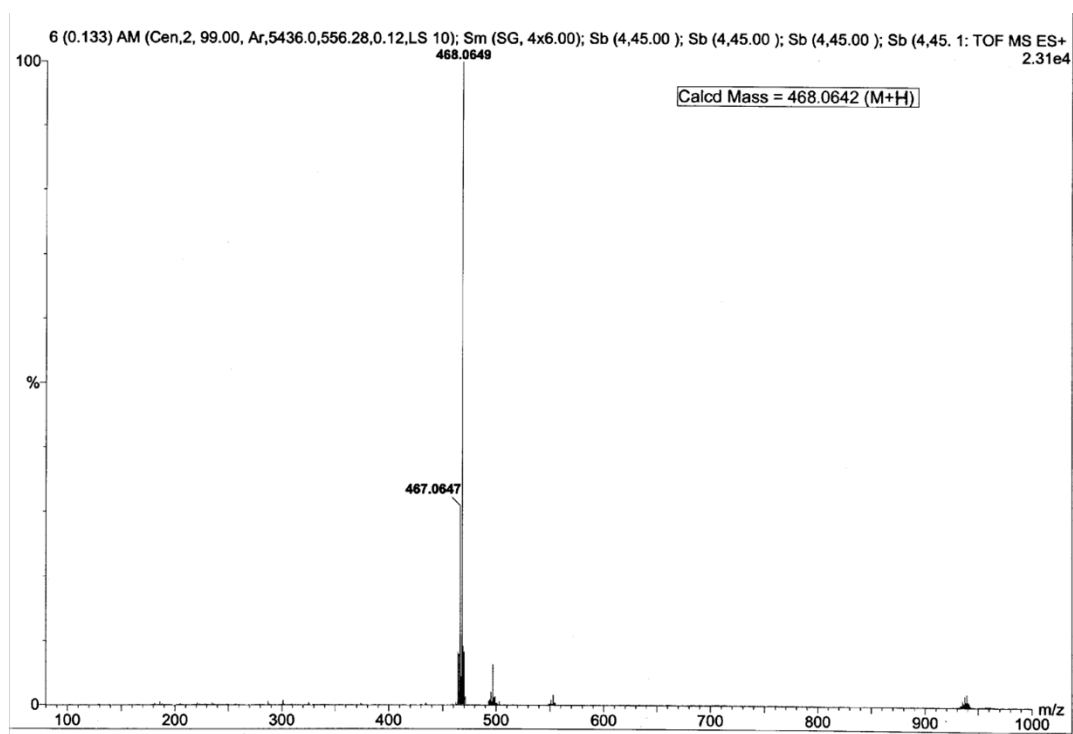
HRMS spectrum of compound **9a**



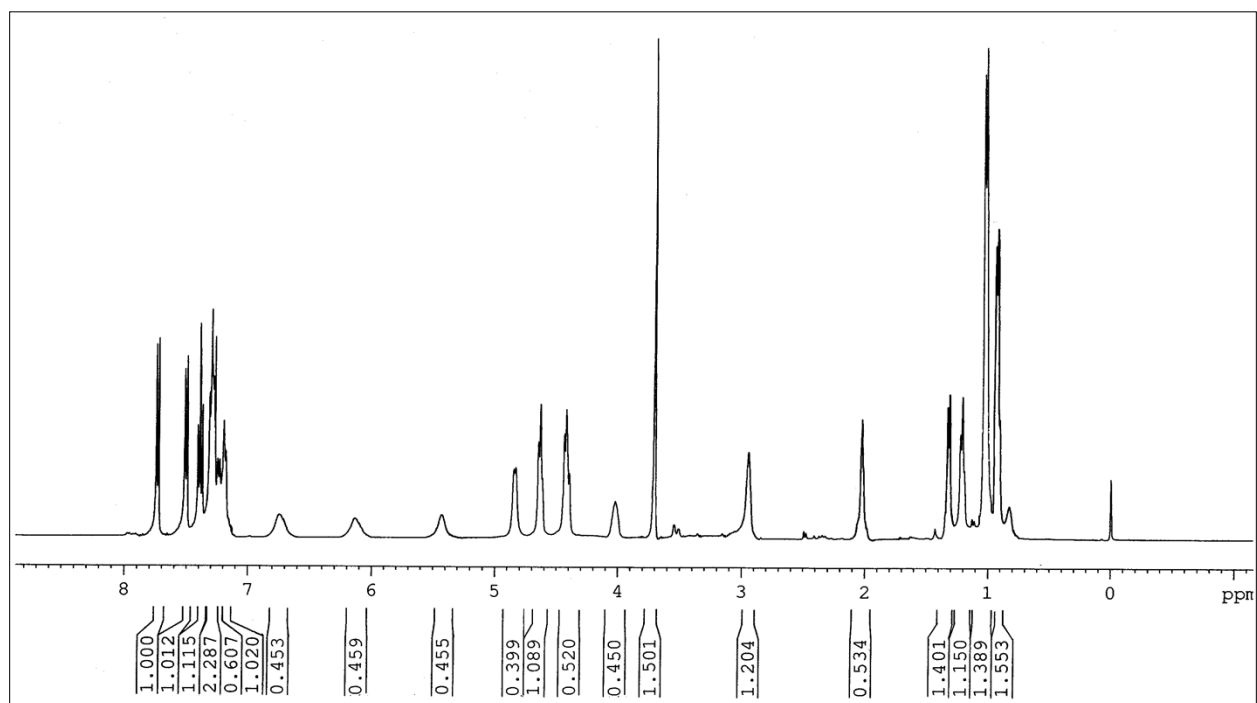
¹H NMR spectrum of compound **9b**



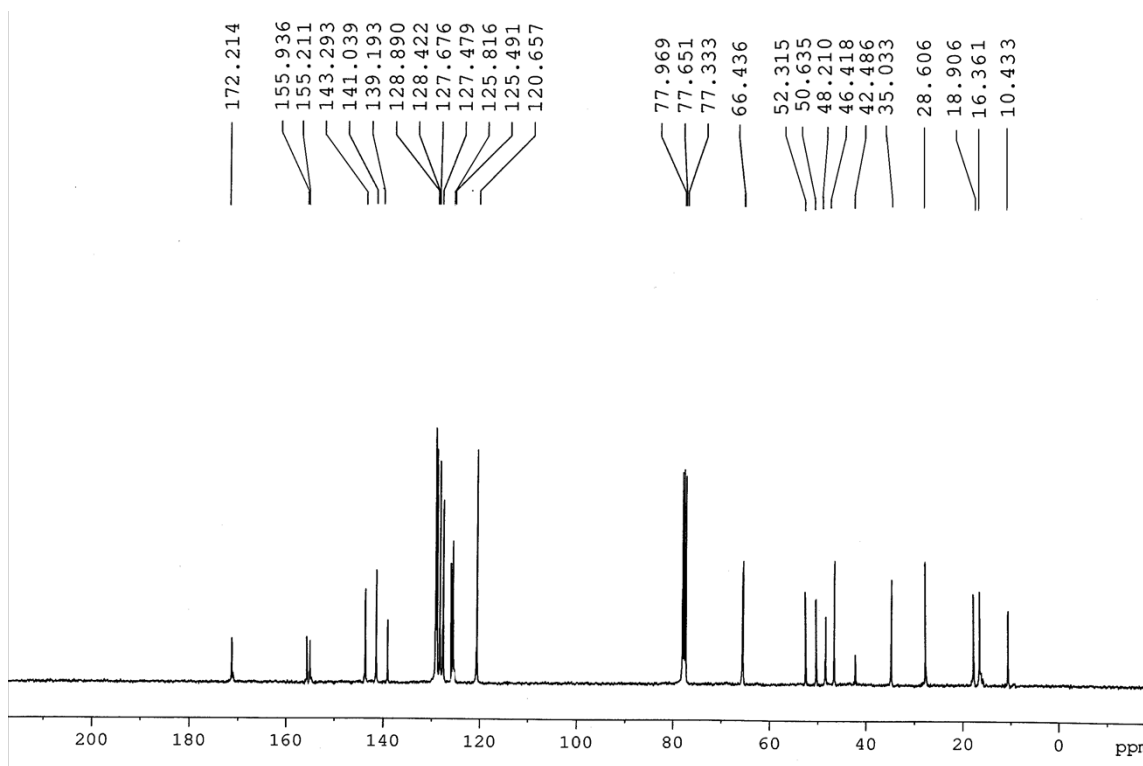
¹³C NMR spectrum of compound **9b**



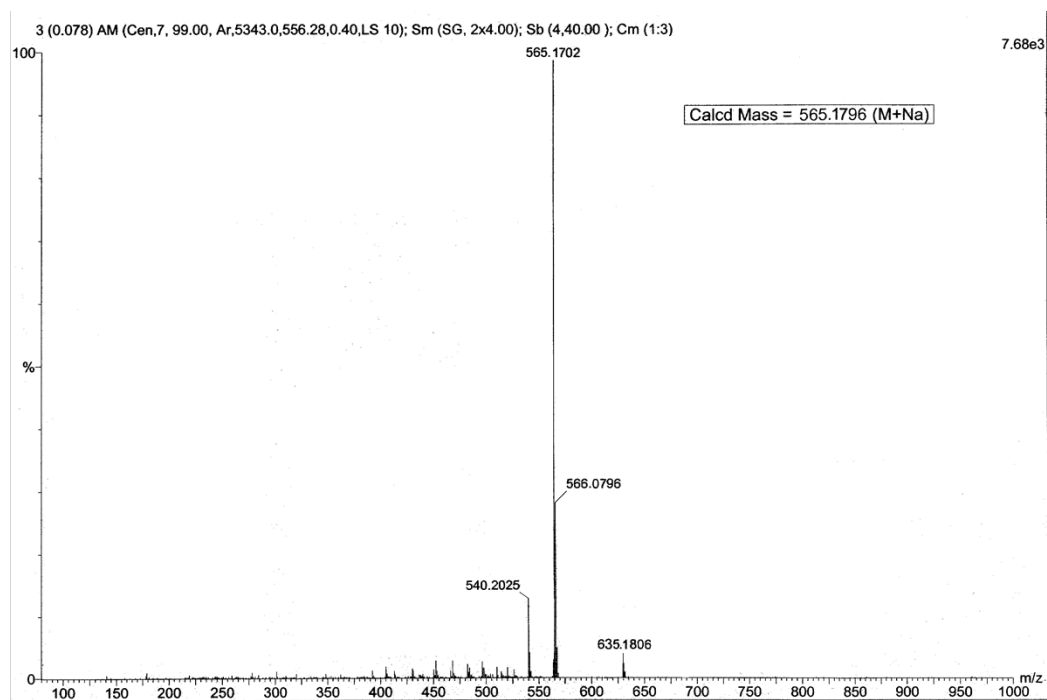
HRMS spectrum of compound **9b**



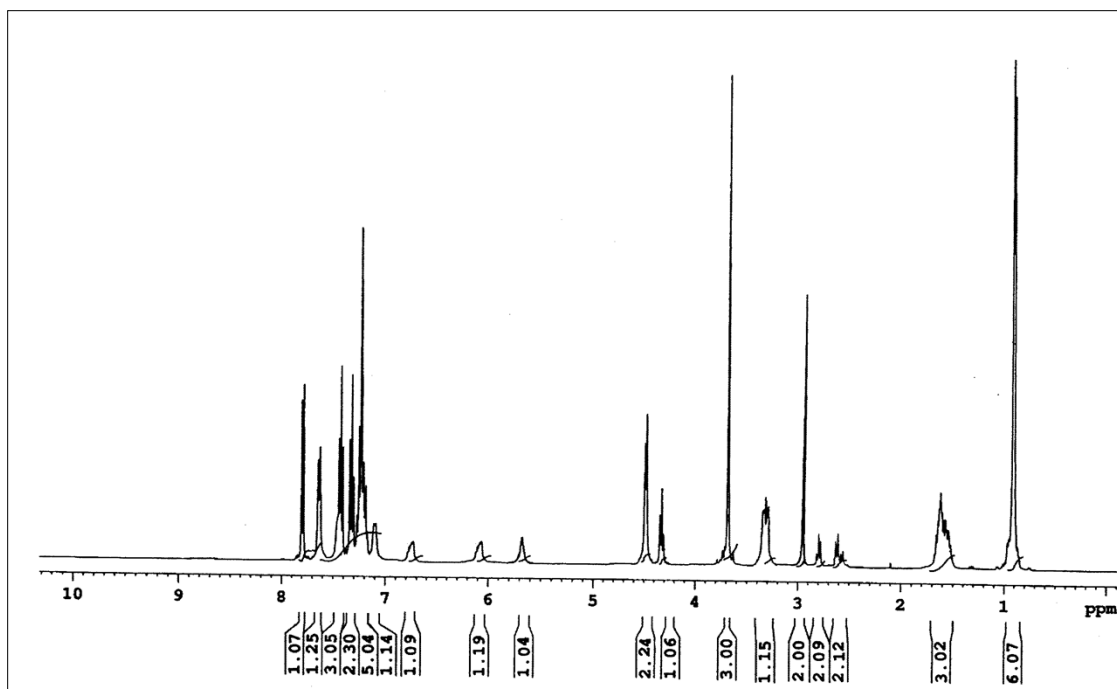
^1H NMR spectrum of compound **10a**



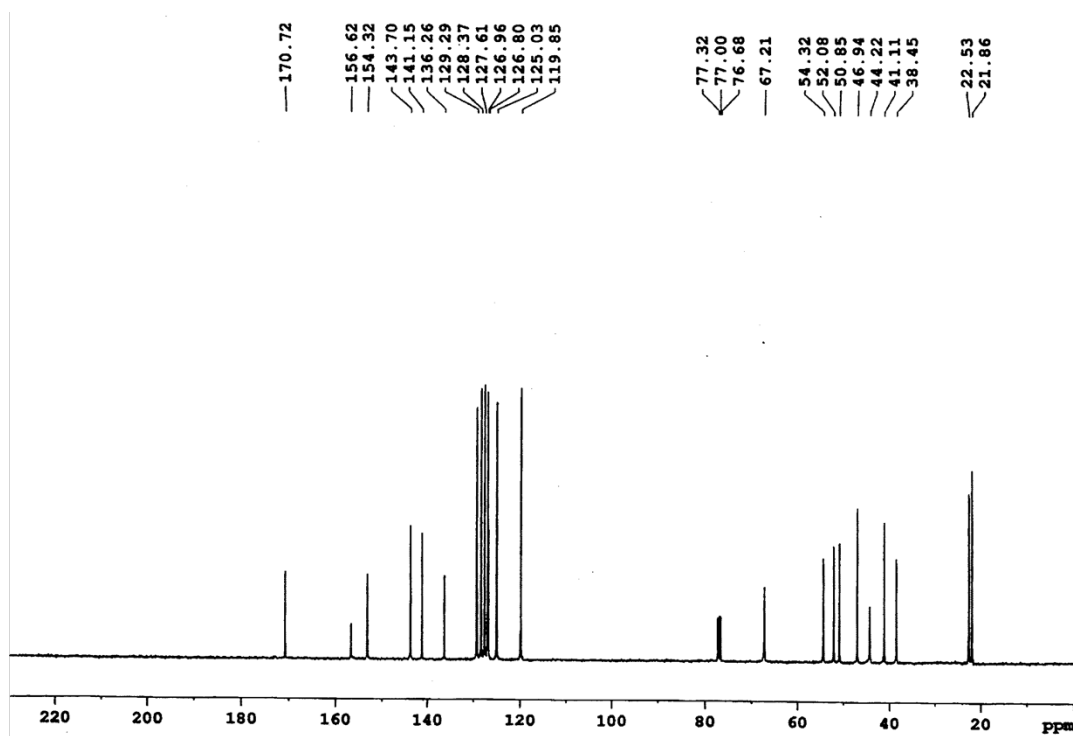
^{13}C NMR spectrum of compound **10a**



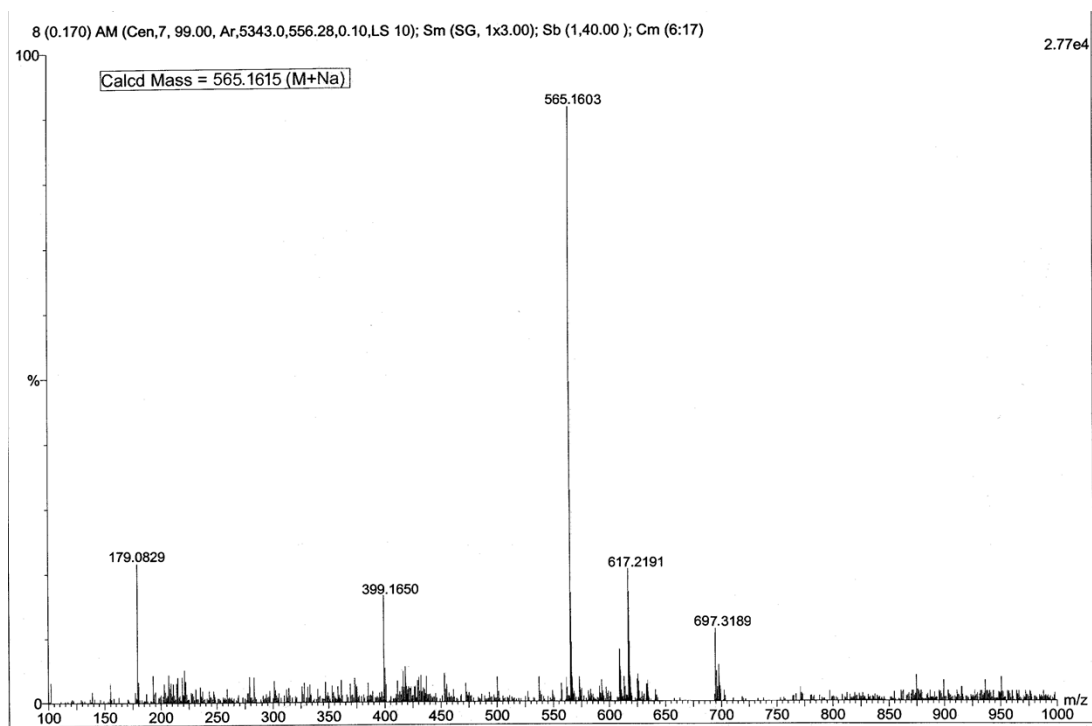
HRMS spectrum of compound **10a**



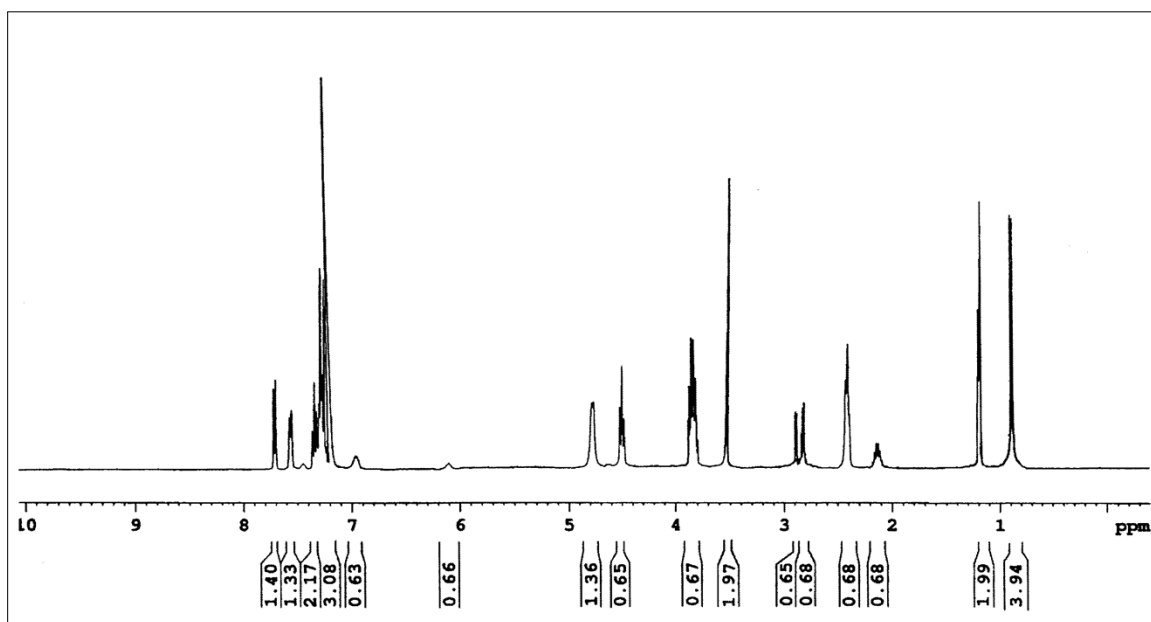
¹H NMR spectrum of compound **10b**



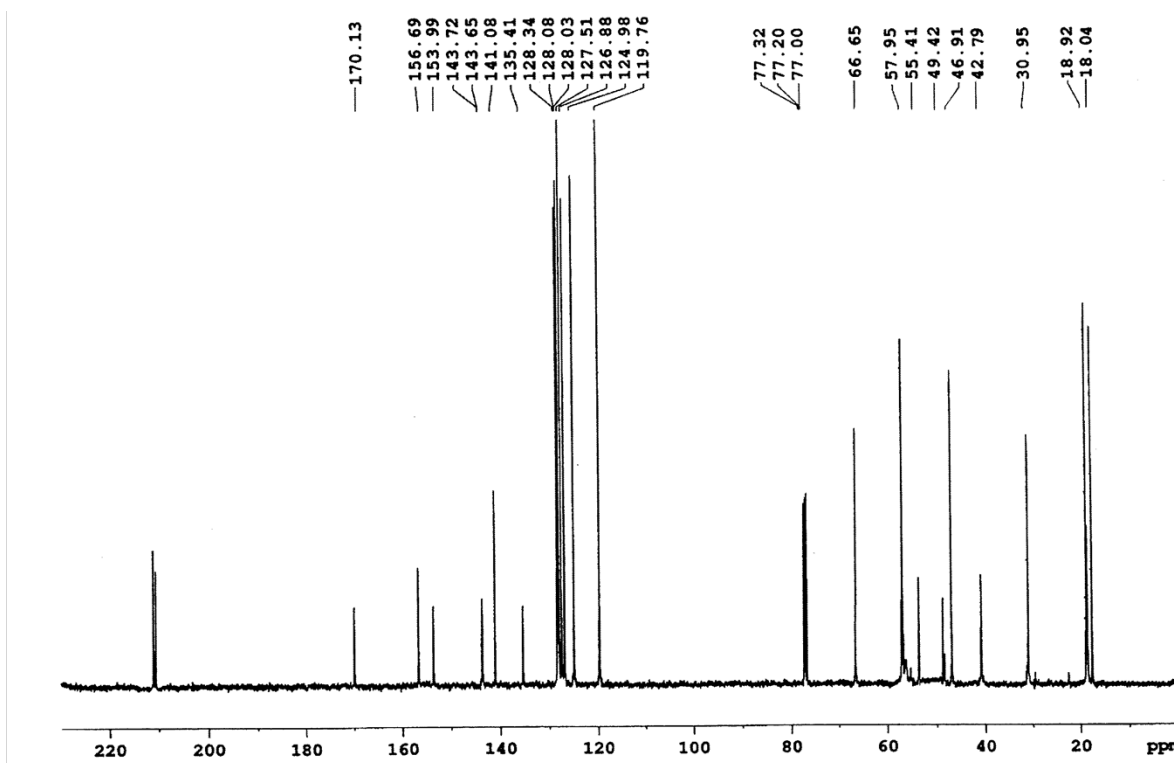
¹³C NMR spectrum of compound **10b**



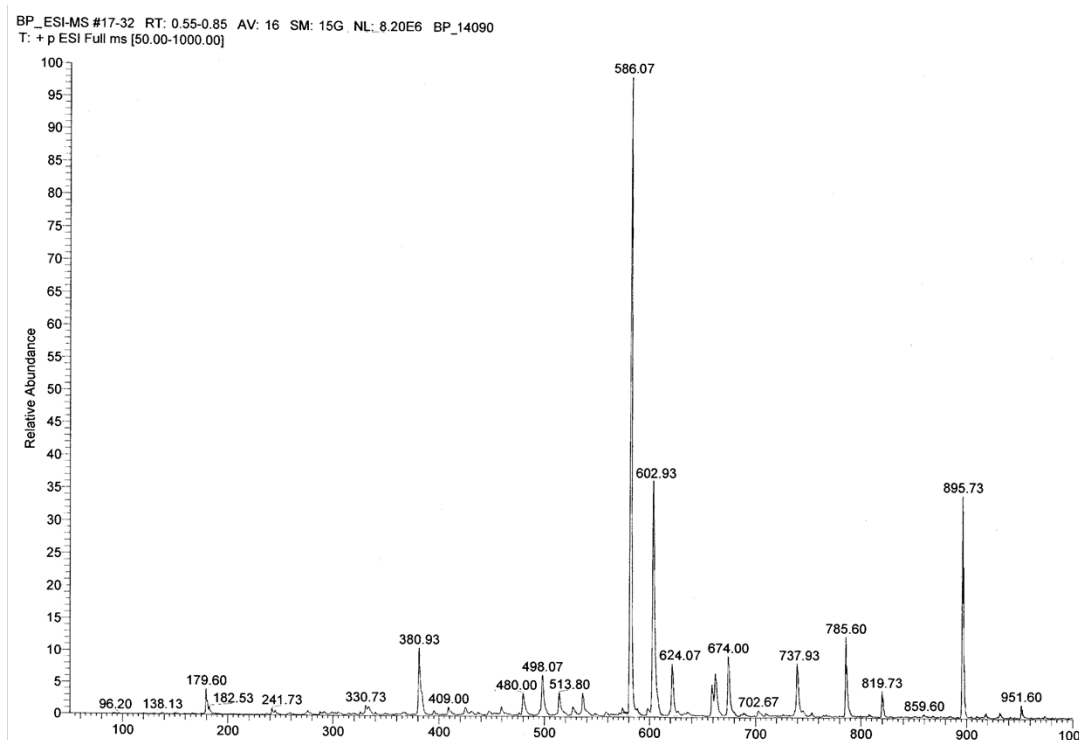
HRMS spectrum of compound **10b**



^1H NMR spectrum of compound **10c**



^{13}C NMR spectrum of compound **10c**



ESMS spectrum of compound **10c**