

## **Supplementary Information 1:**

# **Design, Synthesis and Antiproliferative Evaluation of Glucose 6''-OH Modified Open-Chain Analogues of Ipomoeassin F**

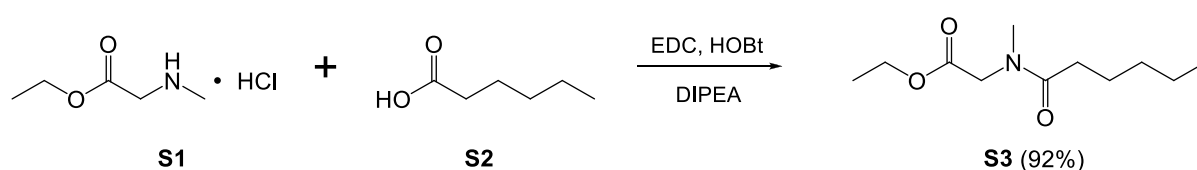
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Wei Q. Shi

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## Part I: Synthesis of carboxylic acid **9**

**General methods:** Reactions were carried out in oven-dried glassware. Unless otherwise stated, all commercially obtained reagents were used without further purification and all reactions were conducted under argon/nitrogen atmosphere. Reaction progress was monitored by TLC using silica gel F254 glass back plates with detection under UV lamp (254 nm) or charring with 5 % (v/v) H<sub>2</sub>SO<sub>4</sub> (sulfuric acid) in EtOH (ethanol). Column chromatographic purifications were performed using silica gel (70 – 230 mesh) with a ratio that spanned from 100 to 50: 1 (w/w) between the silica gel and crude products. All <sup>1</sup>H NMR spectra were obtained in deuterated chloroform (CDCl<sub>3</sub>), using chloroform (CHCl<sub>3</sub>,  $\delta$  = 7.26) or tetramethylsilane (TMS,  $\delta$  = 0) as an internal reference. All <sup>13</sup>C NMR spectra were proton decoupled and obtained in CDCl<sub>3</sub> with CHCl<sub>3</sub> ( $\delta$  = 77.16) as internal references. NMR data are reported in the form: chemical shifts ( $\delta$ ) in ppm, multiplicity, coupling constants (*J*) in Hz, and integrations. <sup>1</sup>H data are reported as though they were first order. Other 1D and 2D NMR spectra like <sup>135</sup>DEPT, COSY, HMQC, and HMBC were collected in addition to <sup>1</sup>H and <sup>13</sup>C for new compounds. High resolution mass spectrometry (HRMS) data were acquired by the Mass Spectrometry Lab at the University of Illinois Urbana-Champaign. Purity was analyzed using a Shimadzu HPLC with a dual wavelength UV detector set at 254 nm and 280 nm, a RESTEK Ultra reverse phase column (C18, 5  $\mu$ m, 4.6x200 mm) and an isocratic mobile phase of acetonitrile in water.

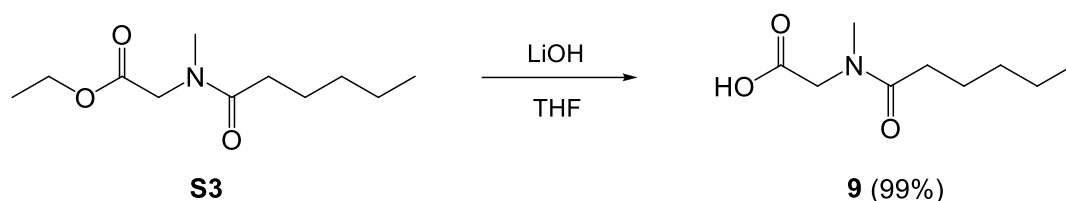


**Synthesis of ethyl *N*-hexanoyl-*N*-methylglycinate **S3** [1]:** To an ice-cold solution of hexanoic acid **S2** (272.0 mg, 2.34 mmol, 1.2 equiv) in DCM (6 ml) was added EDC (561.0 mg, 2.93 mmol, 1.5 equiv) and HOBt (449.0 mg, 2.93 mmol, 1.5 equiv). After 10 minutes, sarcosine ethyl ester hydrochloride **S1** (300 mg, 1.95 mmol) was added, followed by addition of DIPEA (757 mg, 5.86 mmol, 3 equiv) dropwise. The mixture was stirred overnight while warming up to room temperature. At this point, TLC (Hex: EtOAc 3:1) showed the reaction was complete. The reaction was then quenched by NaHCO<sub>3</sub> and extracted by DCM three times. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. After the solvents were removed under reduced pressure, the resulting

residue was purified by column chromatography (15:1→3:1, hexanes–EtOAc) to afford the product **S3** as a colorless oil (387.0 mg, 92%). The ratio of the two rotamers (~3.75:1) was estimated from the  $^1\text{H}$  NMR spectrum.

Major rotamer:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.19 (q,  $J = 7.0$  Hz, 2H), 4.12 (s, 2H), 3.08 (s, 3H), 2.38 (t,  $J = 7.6$  Hz, 2H), 1.57–1.74 (m, 2H), 1.22–1.40 (m, 7H), 0.83–0.97 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  174.0 (C=O), 169.6 (C=O), 61.2 ( $\text{OCH}_2$ ), 49.5 ( $\text{CH}_2$ ), 36.6 ( $\text{CH}_3$ ), 33.2 ( $\text{CH}_2$ ), 31.6 ( $\text{CH}_2$ ), 24.7 ( $\text{CH}_2$ ), 22.6 ( $\text{CH}_2$ ), 14.2 ( $\text{CH}_3$ ), 14.0 ( $\text{CH}_3$ ).

Minor rotamer:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.23 (q,  $J = 7.0$  Hz, 2H), 4.04 (s, 2H), 2.98 (s, 3H), 2.23 (t,  $J = 7.7$  Hz, 2H), 1.57–1.74 (m, 2H), 1.22–1.40 (m, 7H), 0.83–0.97 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.7 (C=O), 169.2 (C=O), 61.7 ( $\text{OCH}_2$ ), 51.8 ( $\text{CH}_2$ ), 34.9 ( $\text{CH}_3$ ), 33.0 ( $\text{CH}_2$ ), 31.6 ( $\text{CH}_2$ ), 24.8 ( $\text{CH}_2$ ), 22.5 ( $\text{CH}_2$ ), 14.2 ( $\text{CH}_3$ ), 14.0 ( $\text{CH}_3$ ).



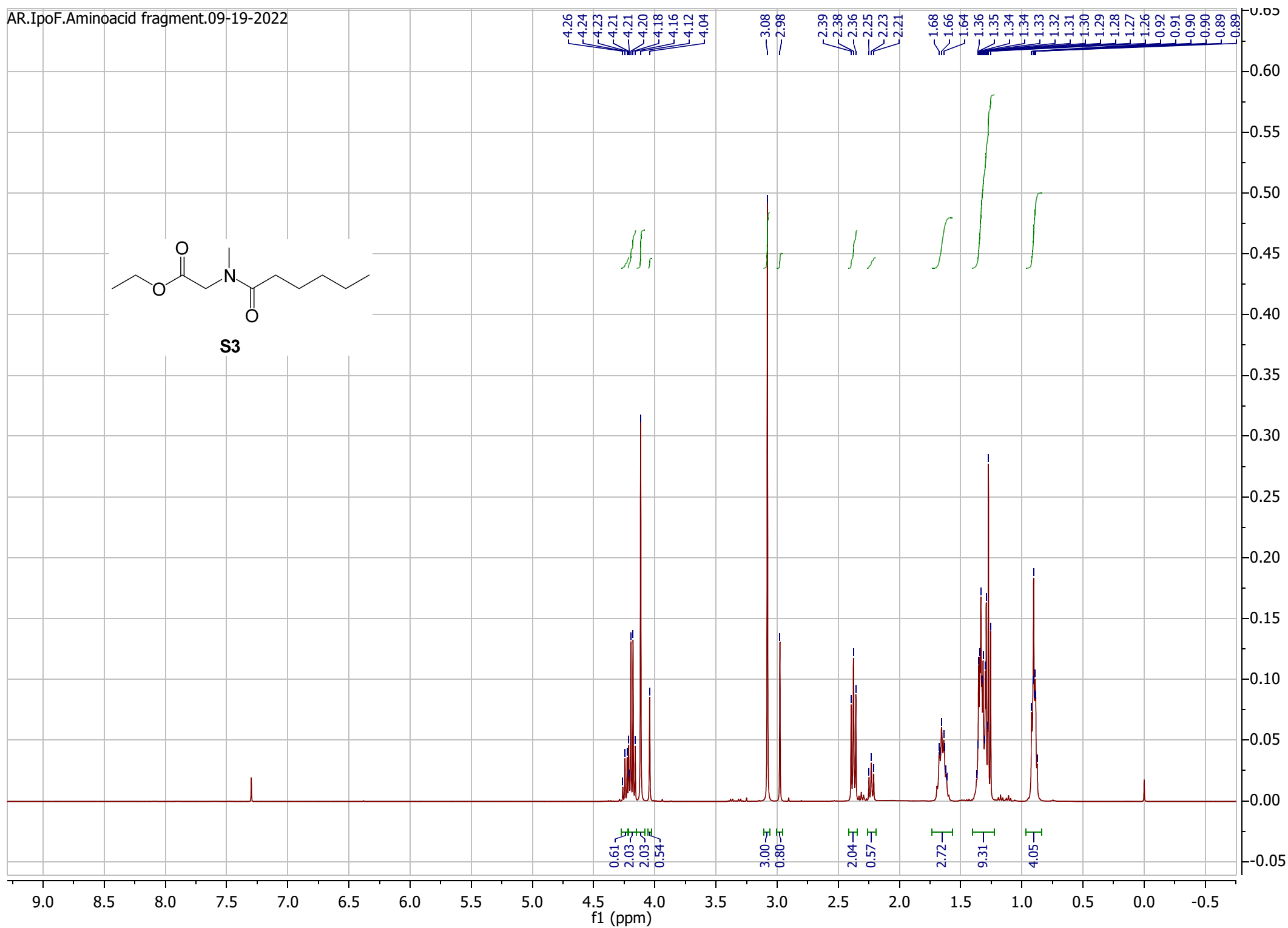
**Synthesis of *N*-hexanoyl-*N*-methylglycine **9** [1]:** To a solution of ethyl *N*-hexanoyl-*N*-methylglycinate **S3** (387.0 mg, 1.8 mmol) in THF (12 ml) was added an aqueous solution of LiOH (0.2 M, 12 ml, 2.4 mmol, 1.33 equiv). The reaction mixture was stirred at room temperature for 1 hour. TLC (Hex: EtOAc 3:1) showed the reaction was complete. The mixture was acidified by 1N HCl at 0 °C and extracted with DCM. The aqueous layer was extracted with DCM twice and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ . After filtration, the solvents were evaporated under reduced pressure to afford the product as a colorless oil (333.0 mg, 99%). The ratio of the two rotamers (~3.5:1) was estimated from the  $^1\text{H}$  NMR spectrum.

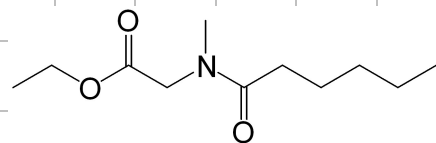
Major rotamer:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.57 (br s, 1H), 4.15 (s, 2H), 3.10 (s, 3H), 2.40 (t,  $J = 7.7$  Hz, 2H), 1.53–1.66 (m, 2H), 1.22–1.41 (m, 4H), 0.82–0.98 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.2 (C=O), 172.8 (C=O), 49.6 ( $\text{CH}_2$ ), 36.9 ( $\text{CH}_3$ ), 33.2 ( $\text{CH}_2$ ), 31.5 ( $\text{CH}_2$ ), 24.7 ( $\text{CH}_2$ ), 22.5 ( $\text{CH}_2$ ), 14.0 ( $\text{CH}_3$ ).

Minor rotamer:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.57 (br s, 1H), 4.02 (s, 2H), 2.99 (s, 3H), 2.27 (t,  $J = 7.7$  Hz, 2H), 1.53–1.66 (m, 2H), 1.22–1.41 (m, 4H), 0.82–0.98 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  174.8 (C=O), 171.9 (C=O), 51.7 ( $\text{CH}_2$ ), 35.2 ( $\text{CH}_3$ ), 33.0 ( $\text{CH}_2$ ), 31.5 ( $\text{CH}_2$ ), 24.9 ( $\text{CH}_2$ ), 22.5 ( $\text{CH}_2$ ), 14.0 ( $\text{CH}_3$ ).

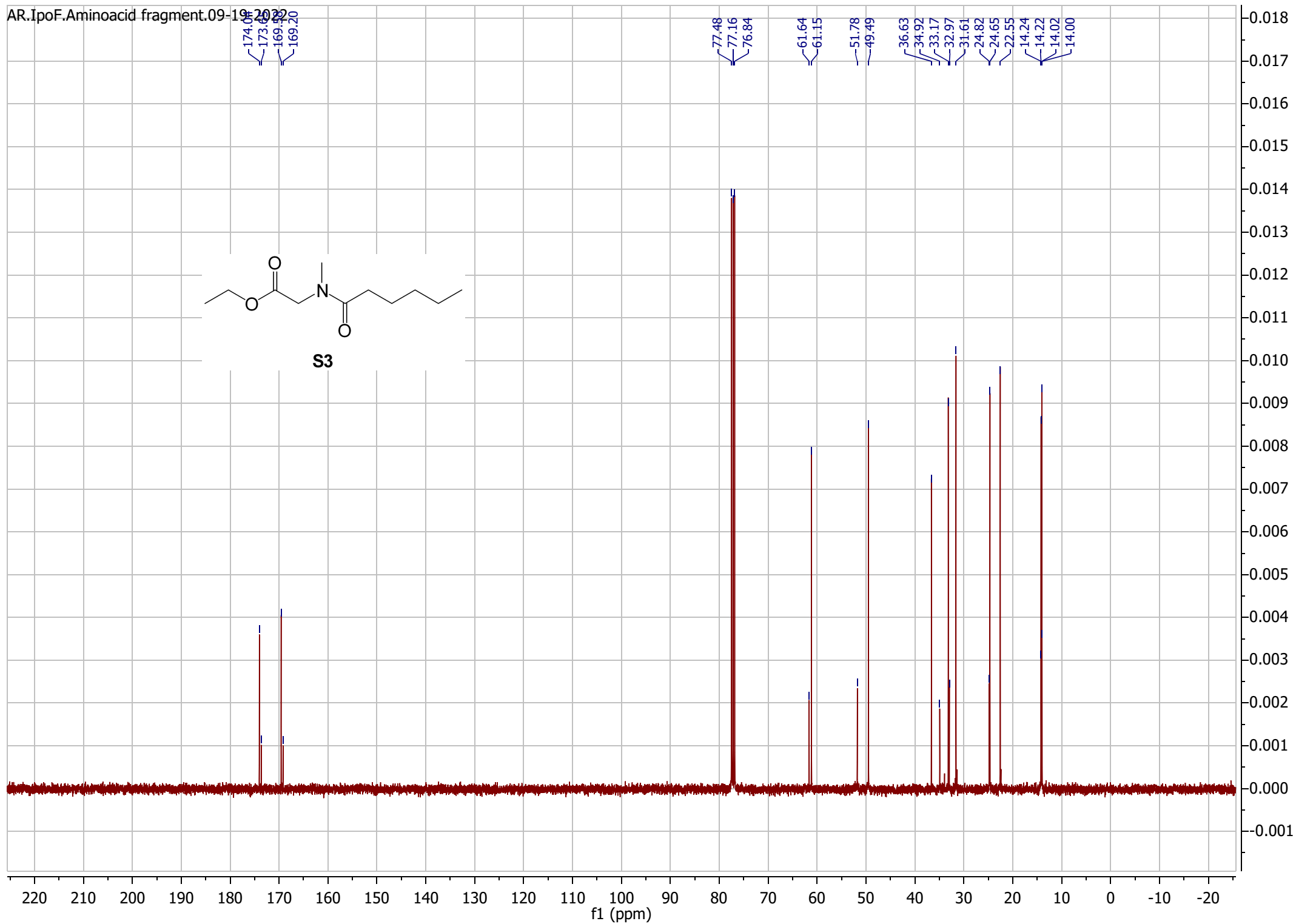
## References

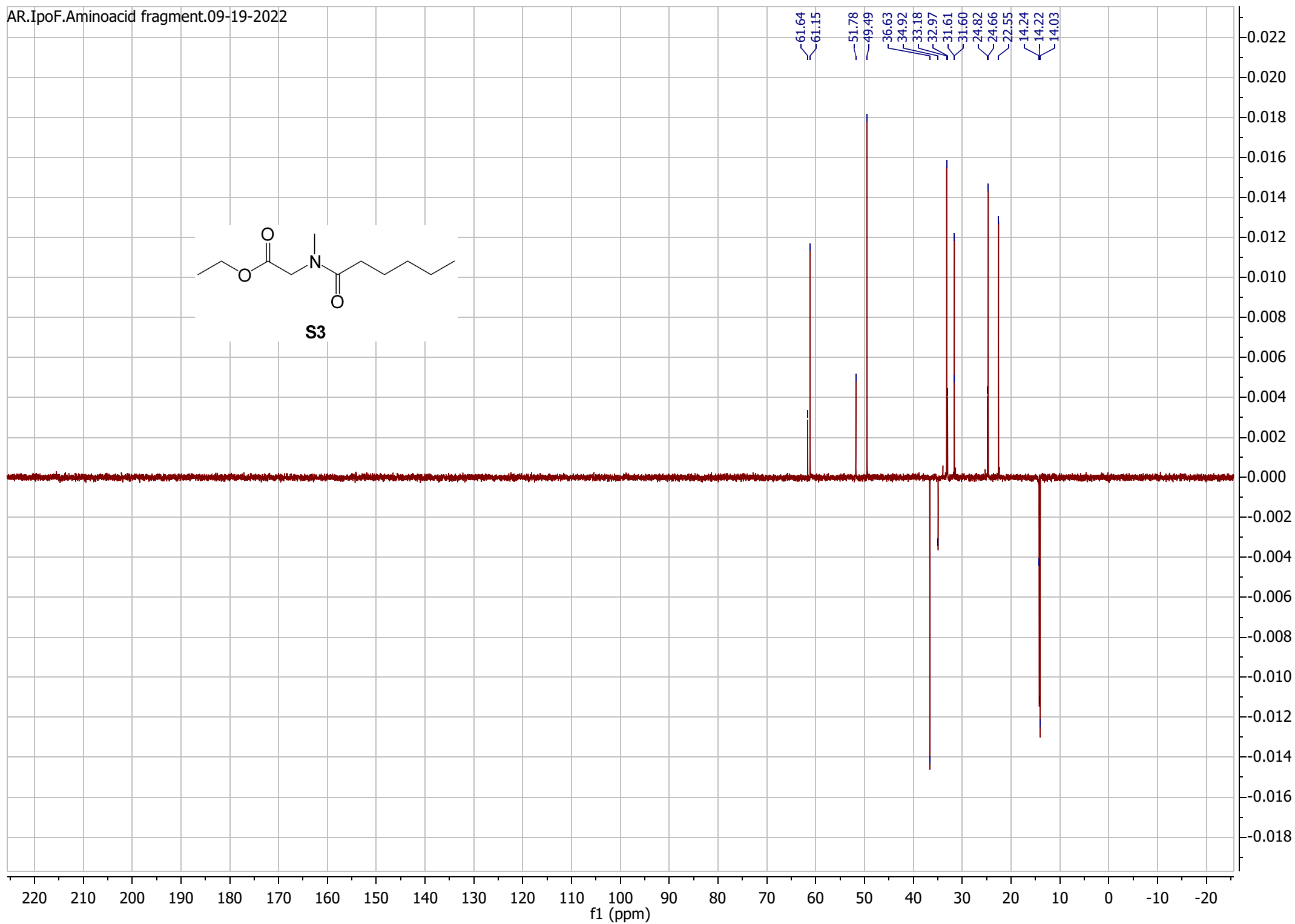
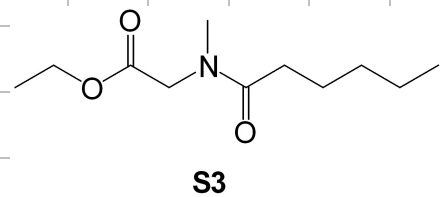
1. Steinmetz, H.; Li, J.; Fu, C.; Zaburannyi, N.; Kunze, B.; Harmrolfs, K.; Schmitt, V.; Herrmann, J.; Reichenbach, H.; Höfle, G.; et al. Isolation, Structure Elucidation, and (Bio)Synthesis of Haprolid, a Cell-Type-Specific Myxobacterial Cytotoxin. *Angew. Chem. Int. Ed.* **2016**, *55*, 10113-10117, doi:10.1002/anie.201603288.



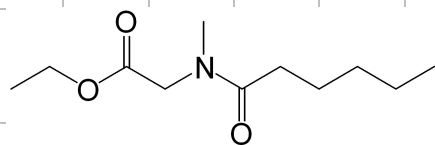


S3





AR.IpoF.Aminoacid fragment.09-19-2022

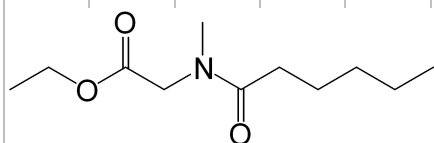


S3

f1 (ppm)

f2 (ppm)

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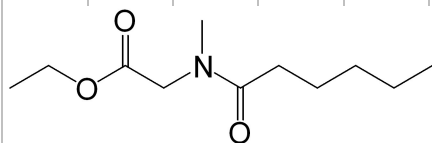


S3

f1 (ppm)

f2 (ppm)

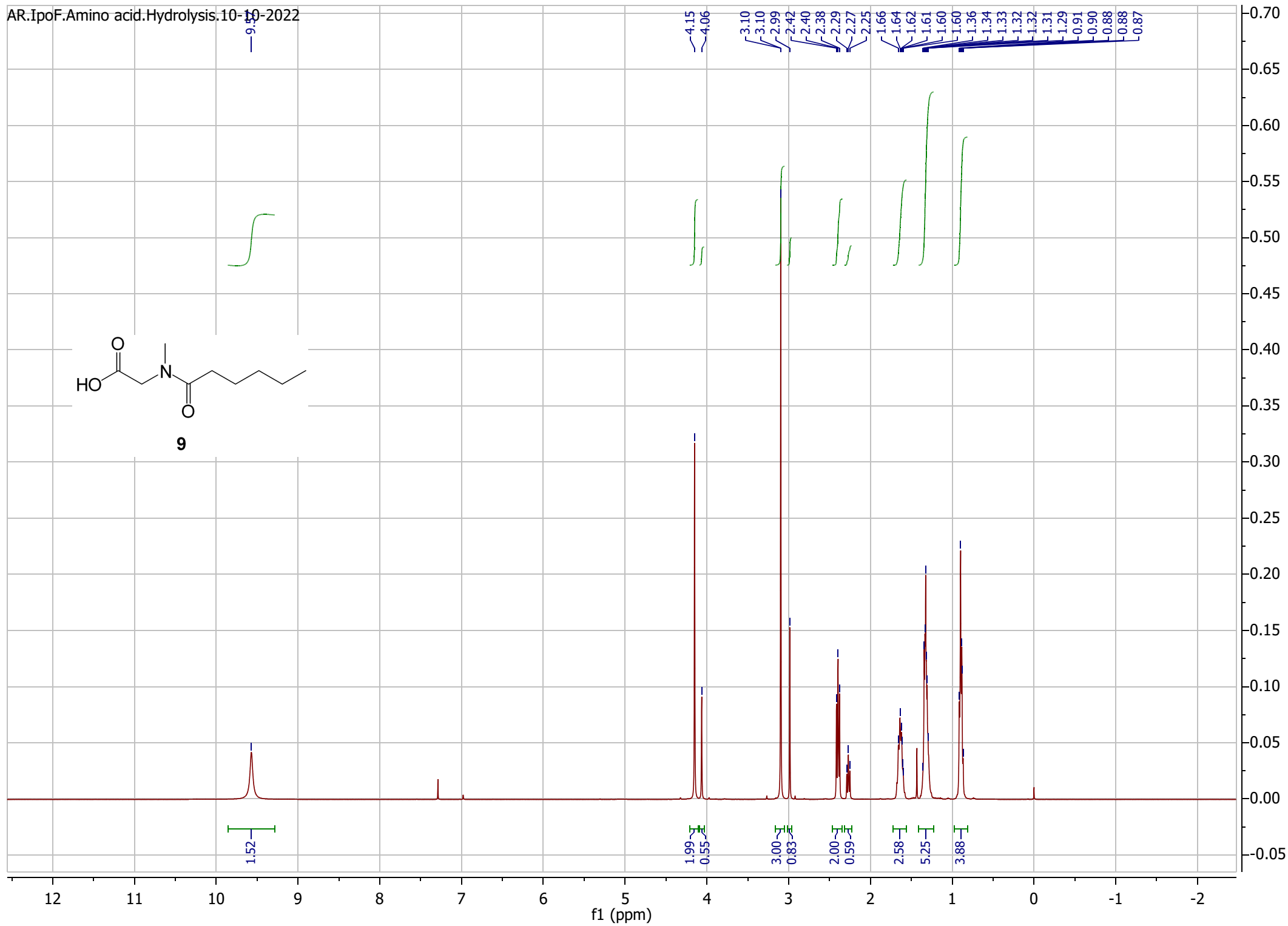
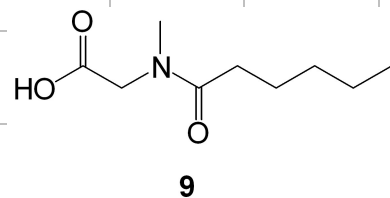
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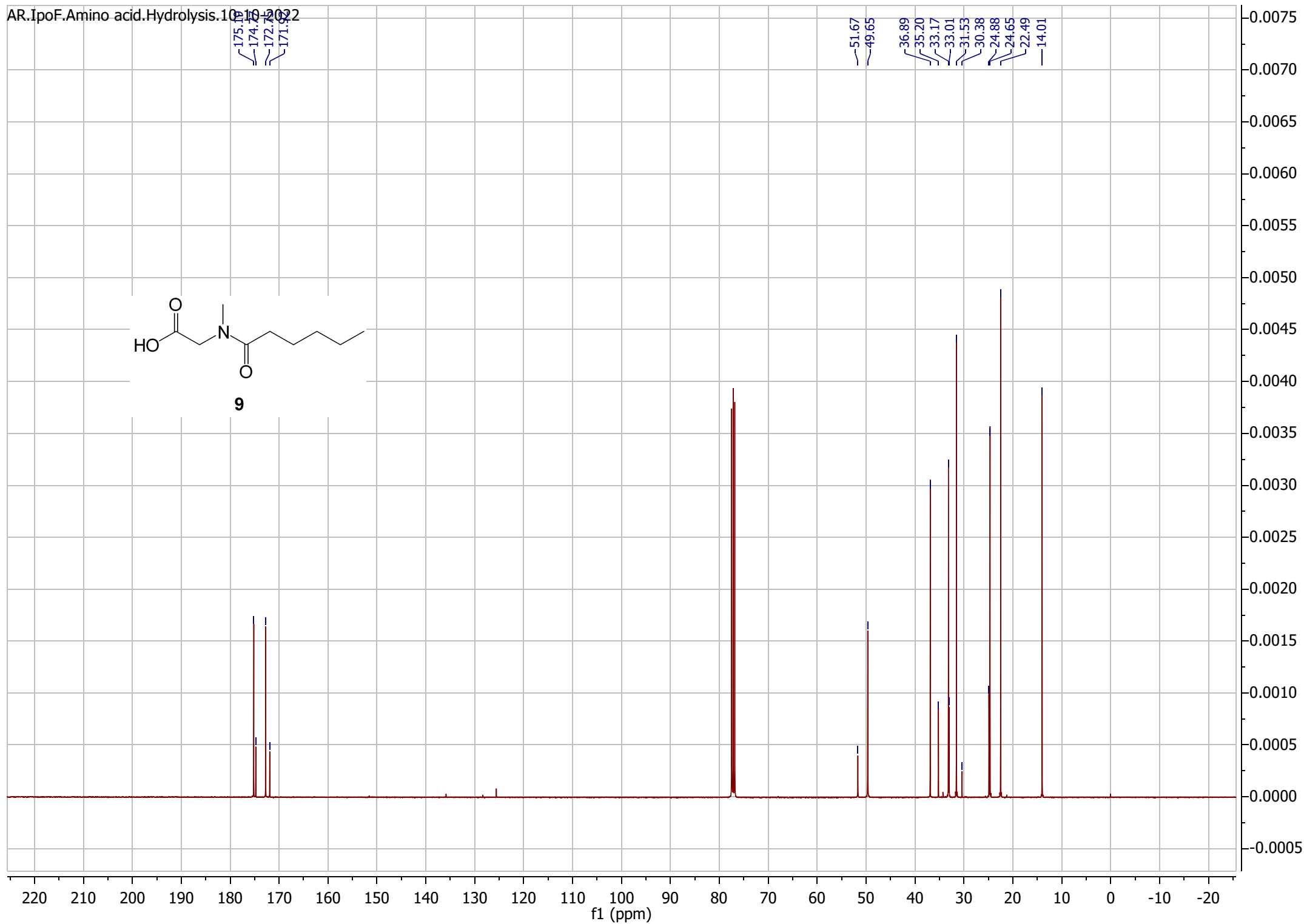
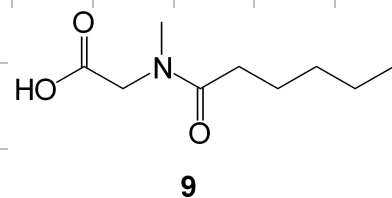


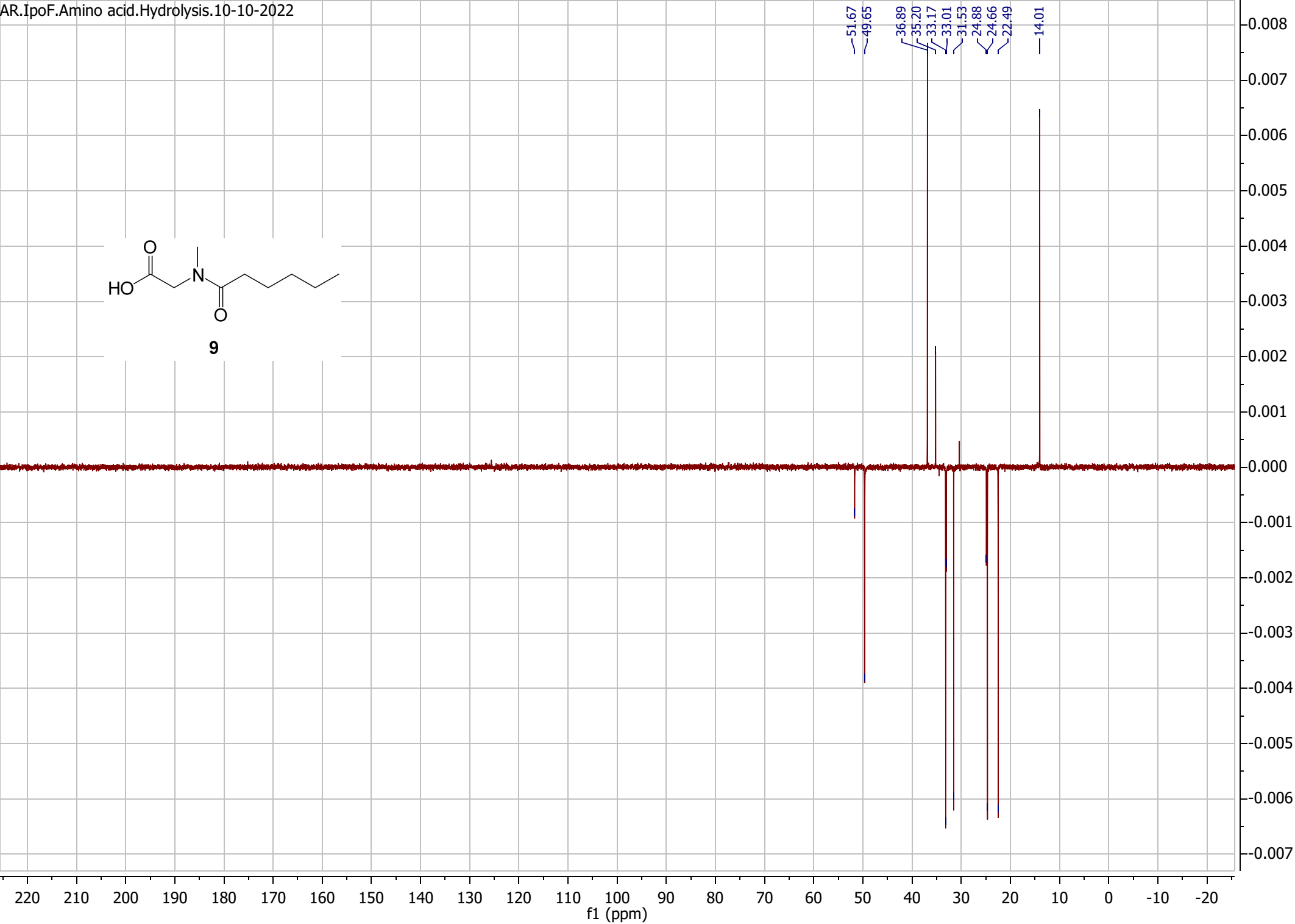
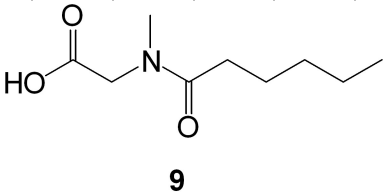
S3

f1 (ppm)

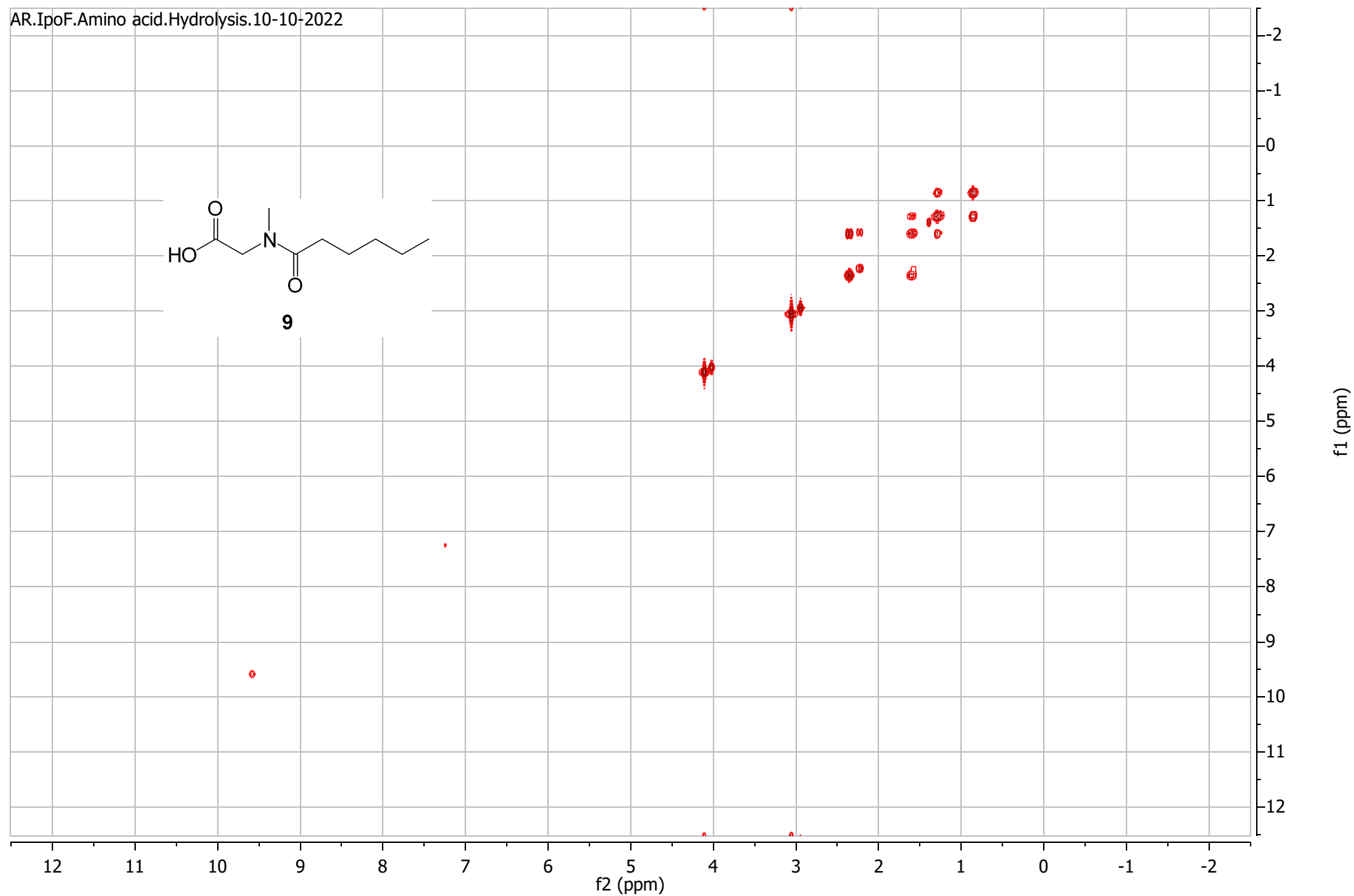
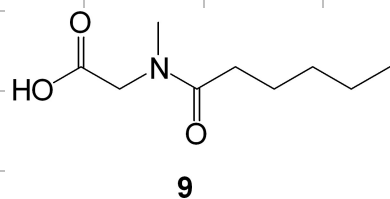
f2 (ppm)

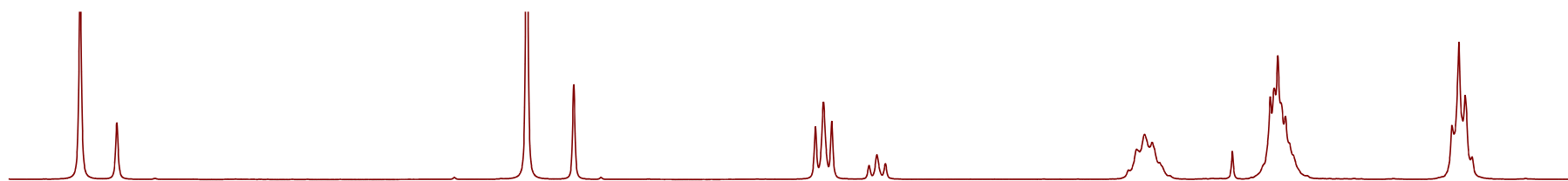




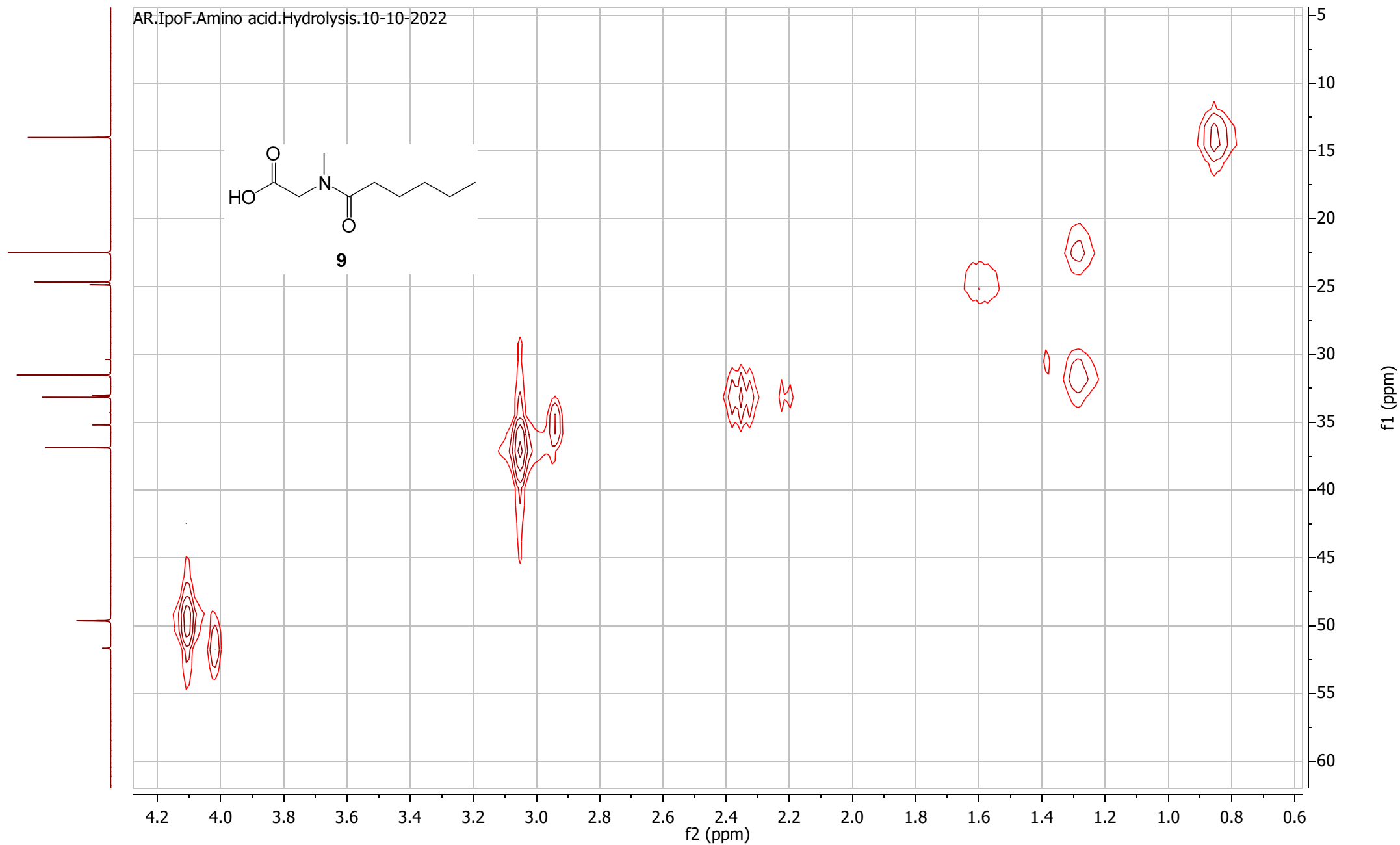
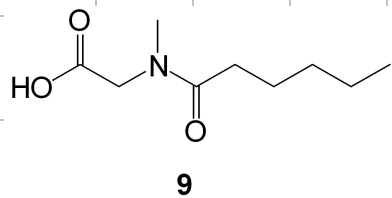


AR.IpoF.Amino acid.Hydrolysis.10-10-2022





AR.IpoF.Amino acid.Hydrolysis.10-10-2022



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