Identification of a Dual Inhibitor of Secreted Phospholipase A_2 (GIIA $sPLA_2$) and SARS-CoV-2 Main Protease

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SUPPLEMENTARY MATERIALS

Contents

Table S1. Structural details of structures 1-7 concerning the configuration of 2-carbon and the dihedral angle $C\beta_{C145}$-S_{C145}-C2-O2 related to the covalent bond formatted between Cys145 and 2-oxoamide moiety. Molecular Dynamics RMSDs for the protein and the ligand along with MM-GBSA Binding Energy.

Structure	Configuration of 2-carbon	MM-GBSA Binding Energy (kcal/mol)	Average Protein RMSD ±StDev	Average Ligand RMSD ±StDev	Major Interactions	Dihedral Angle Cβ-S-C2-O2
1	*R*	-58.69	2.84±0.48	3.36±0.95	S144	-73.68
2	*R*	-56.37	1.77±0.24	4.63±0.70	E166	-175.218
3	*S*	-54.51	1.73±0.28	7.36±3.73	-	86.525
4	*S*	-47.03	2.29±0.35	5.53±0.89	T26, T24	-45.037
5	*R*	-46.41	2.00±0.32	3.97±1.10	H41, E166	-50.033
6	*S*	-45.17	1.95±0.31	5.05±0.95	H41, N142, H164	134.808
7	*S*	-43.26	1.79±0.26	3.22±0.79	T26, H41, N142	-55.195

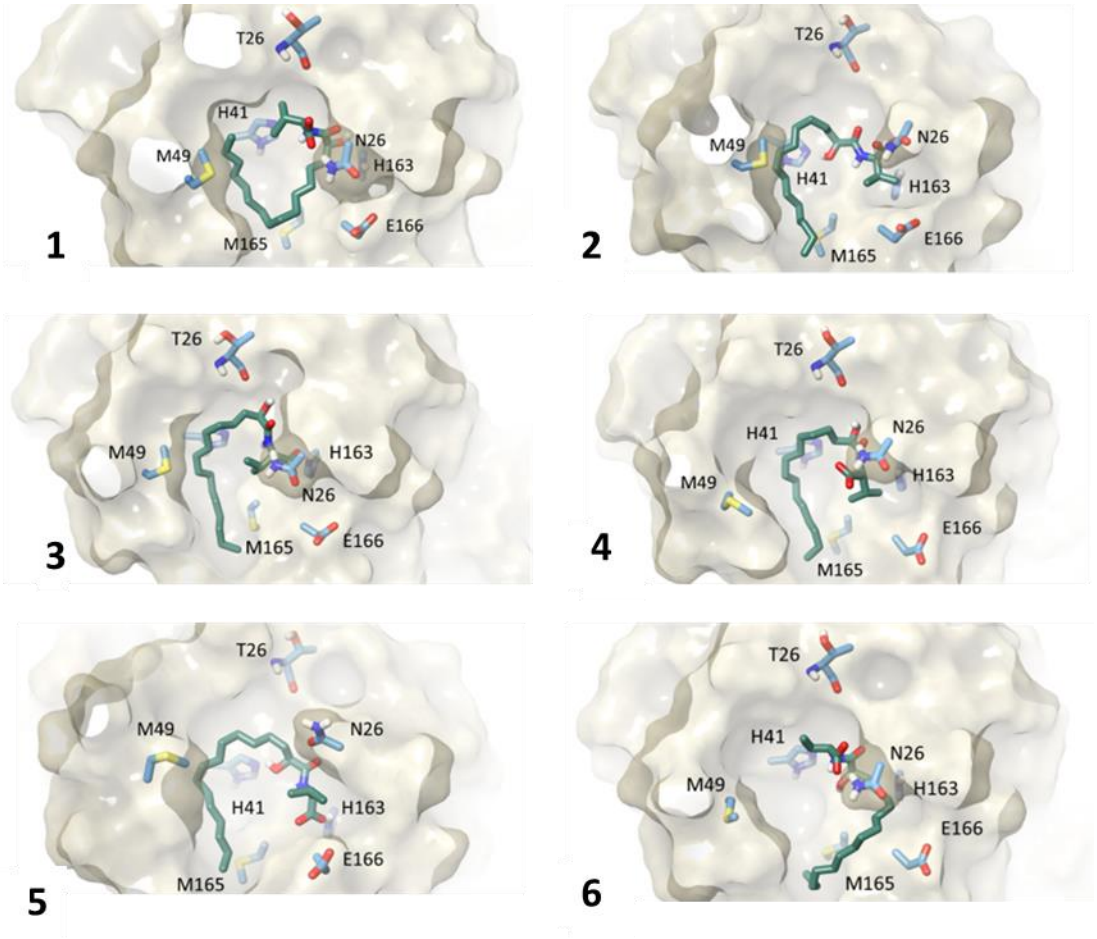


Figure S1. Structural details for the M^{pro}-GK241 interactions in structures 1-6 resulted by covalent docking calculations.

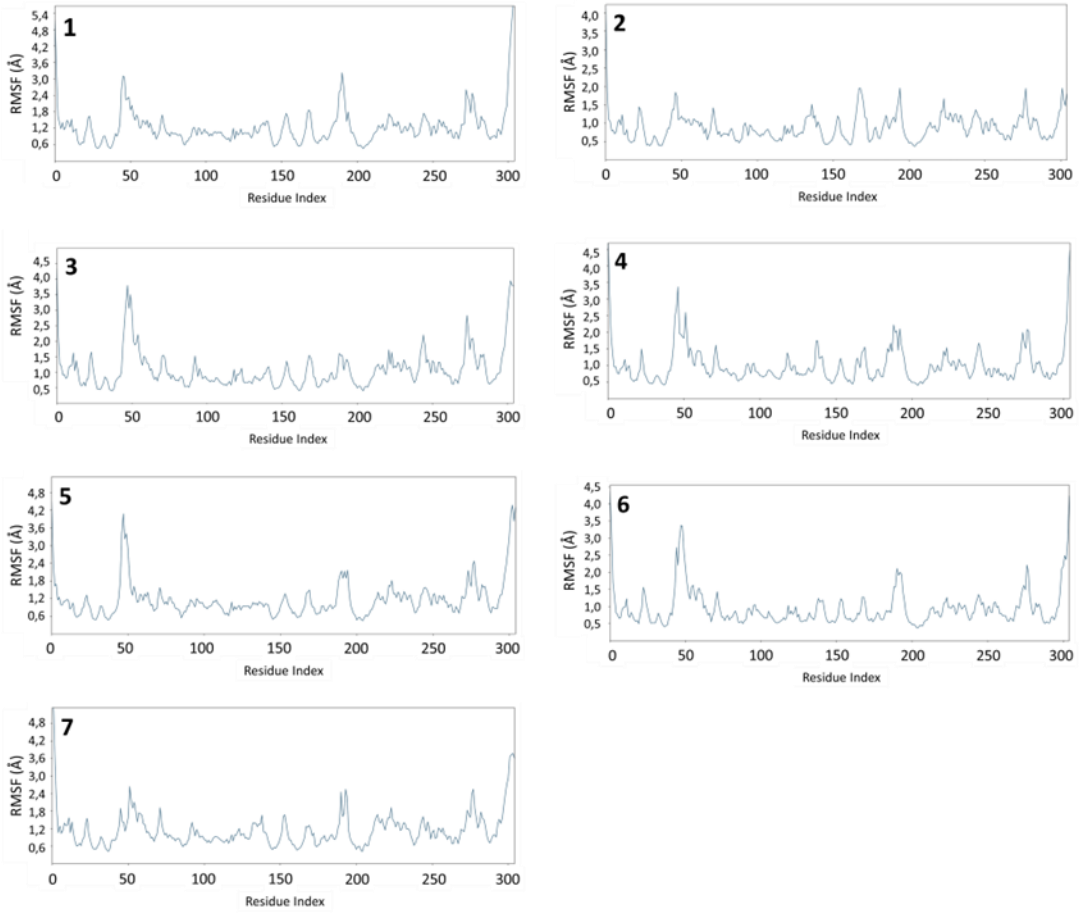


Figure S2. Protein residues Root Mean Square Fluctuation during the 50 nsec MD simulation showing local changes among the protein chain.

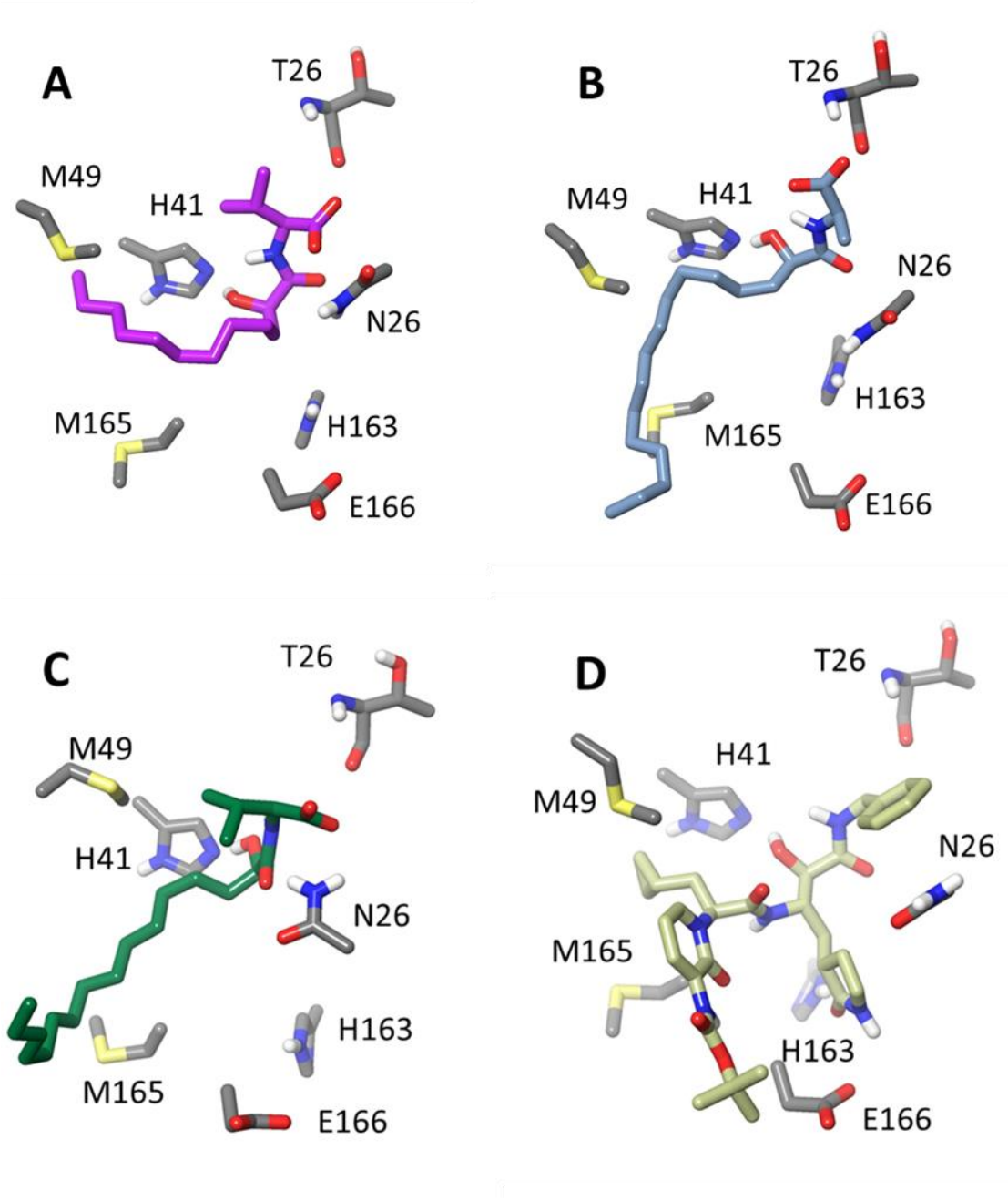
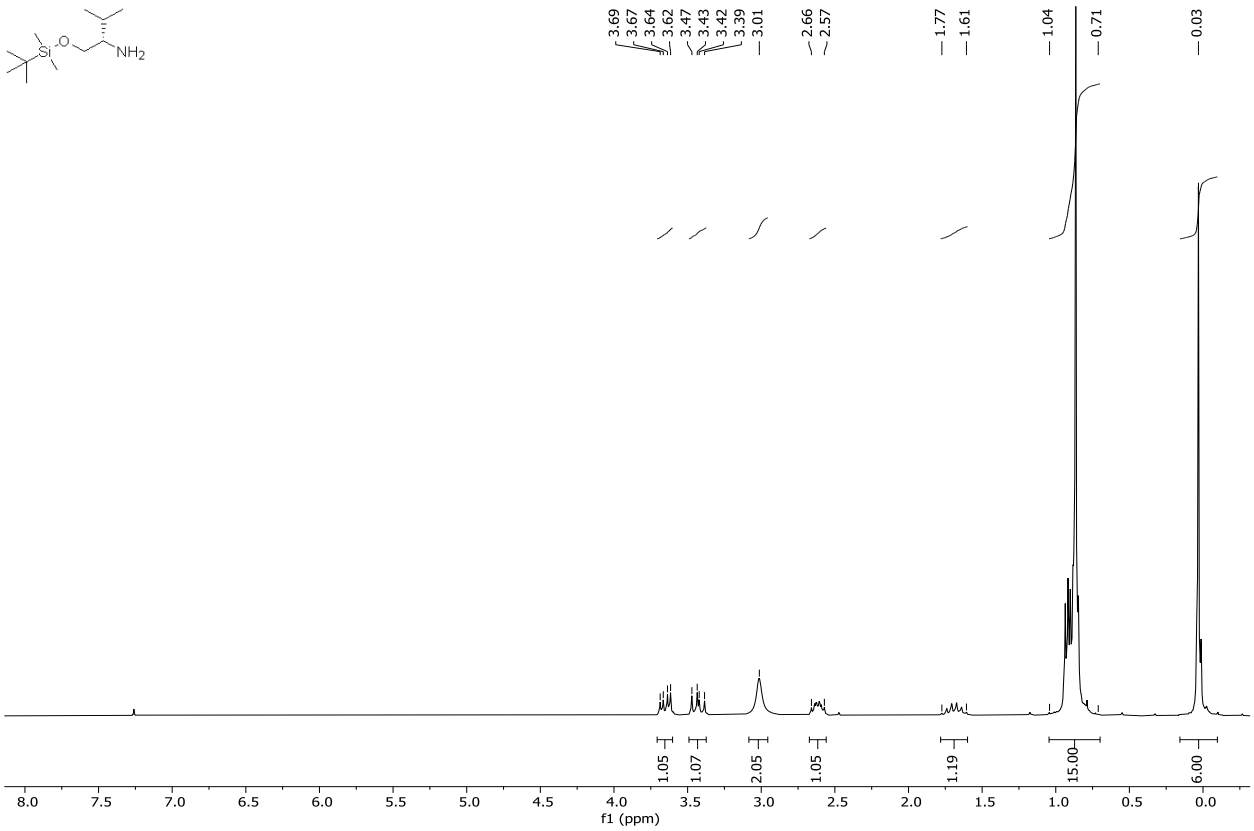
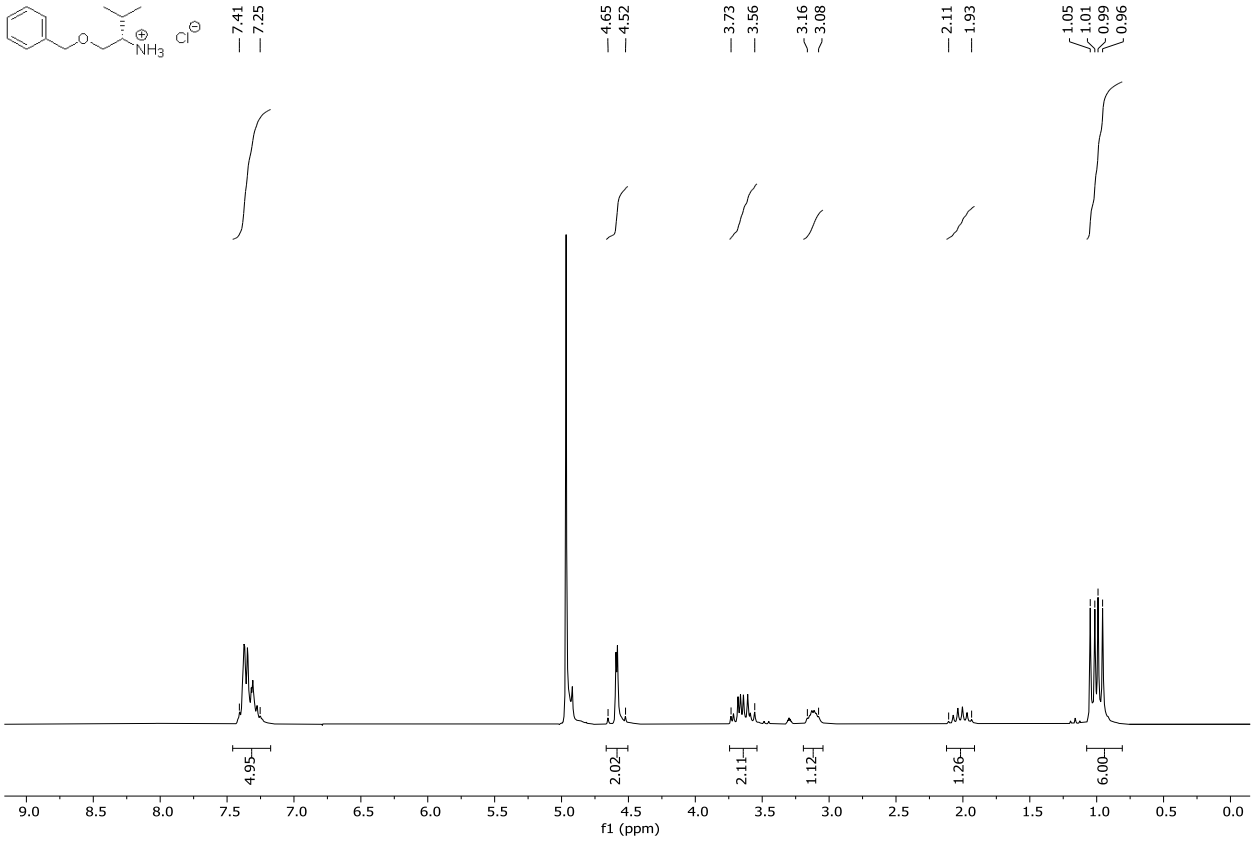


Figure S3. Structures of **8d** (**A**) in magenta and **8a** (**B**) in blue bound to M^{pro} in comparison with GK241 (**C**) in green and crystal structure PDB 6Y2F (**D**) in chaki. The side chain in derivative **8d** adopts a curved conformation exploring part of S1 and S2 protease cavities. Derivative **8a** aliphatic chain adopts a very similar structural arrangement to GK241, however the alanine moiety appears to interact weakly with N142 and T26.

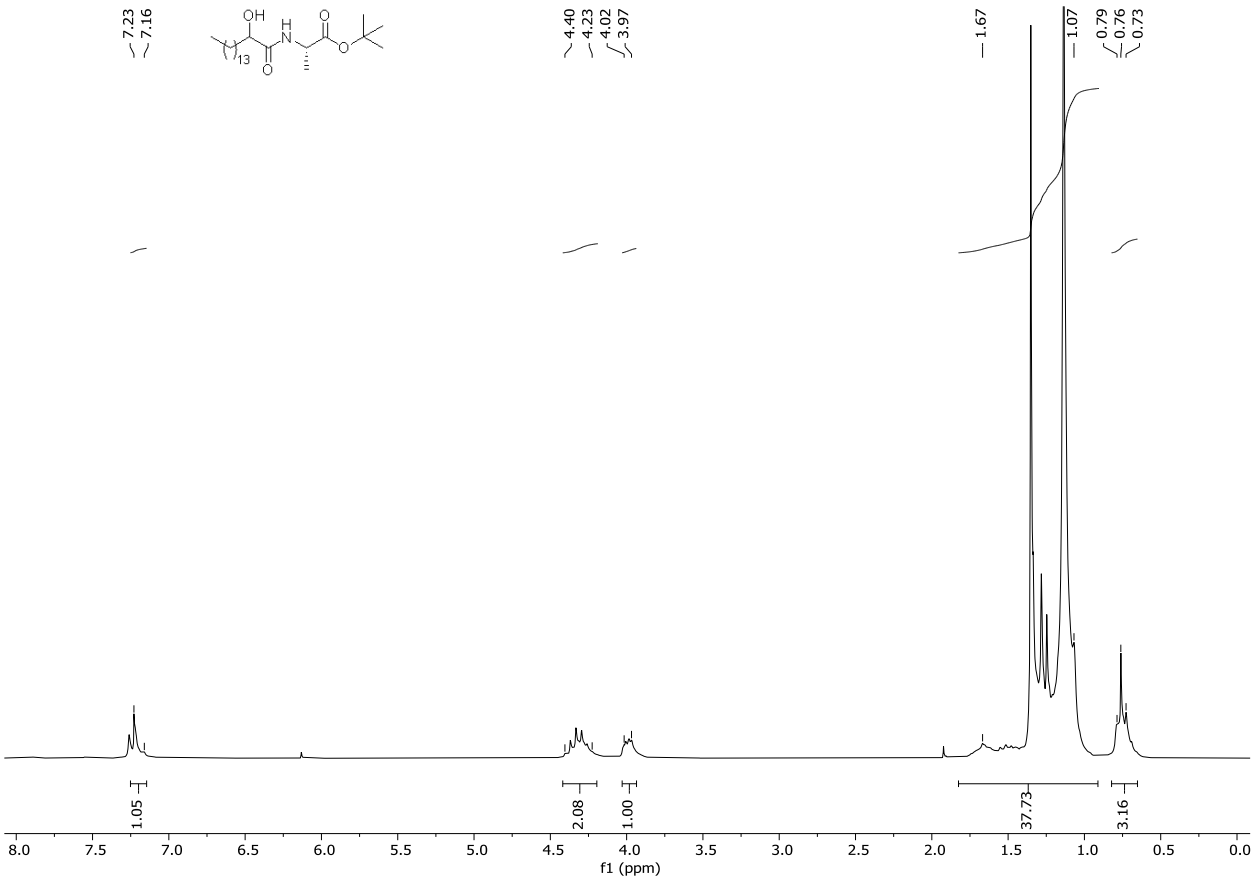
NMR Spectra



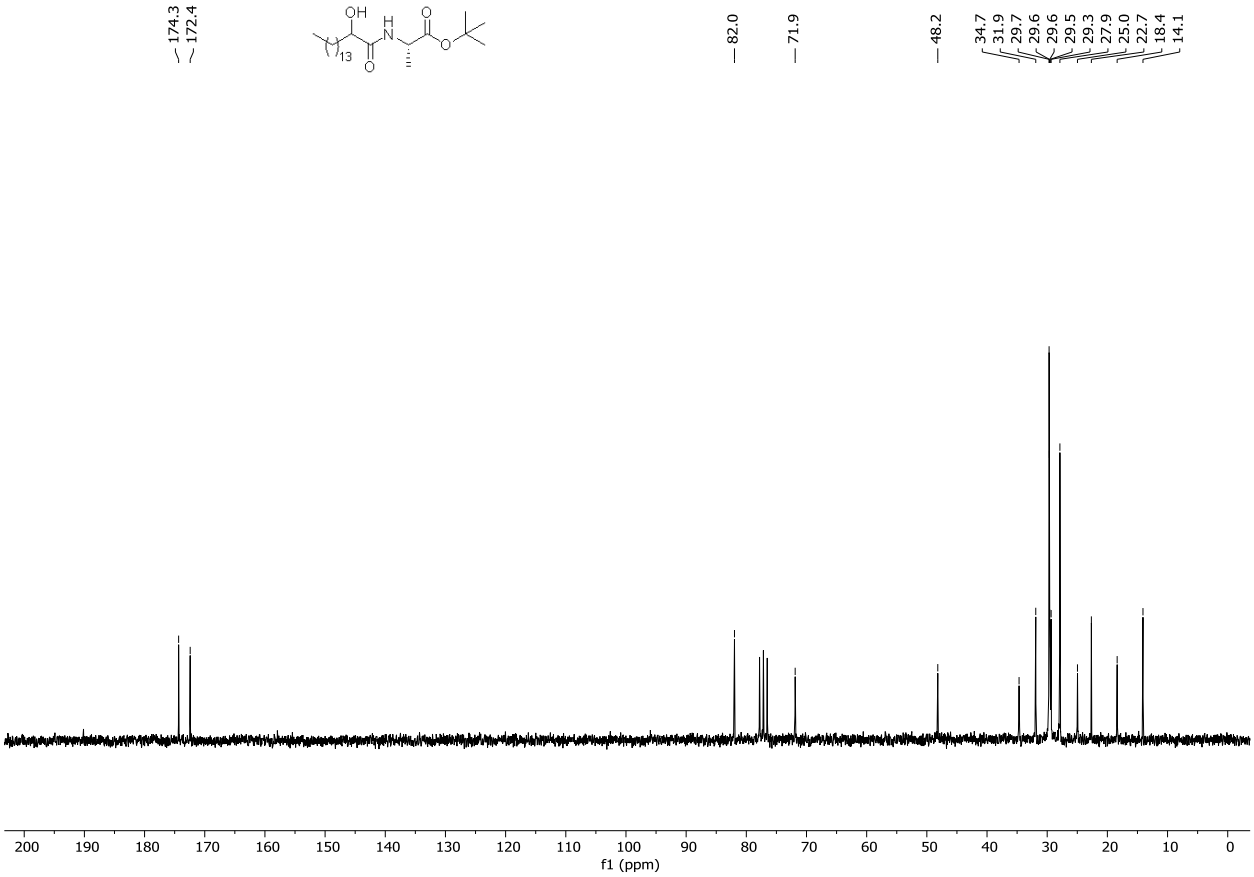
^{1}H NMR spectrum of **5b**.



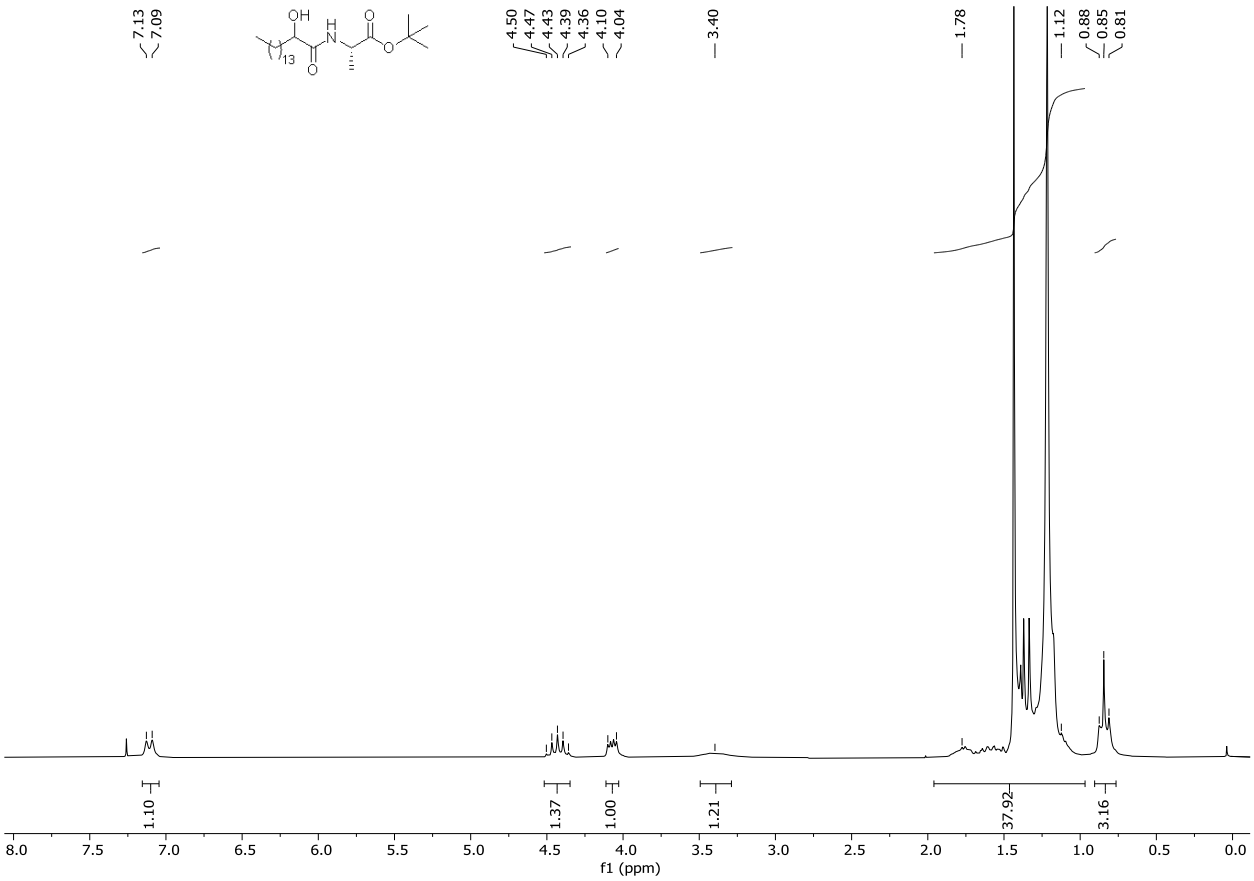
^{1}H NMR spectrum of **5c**.



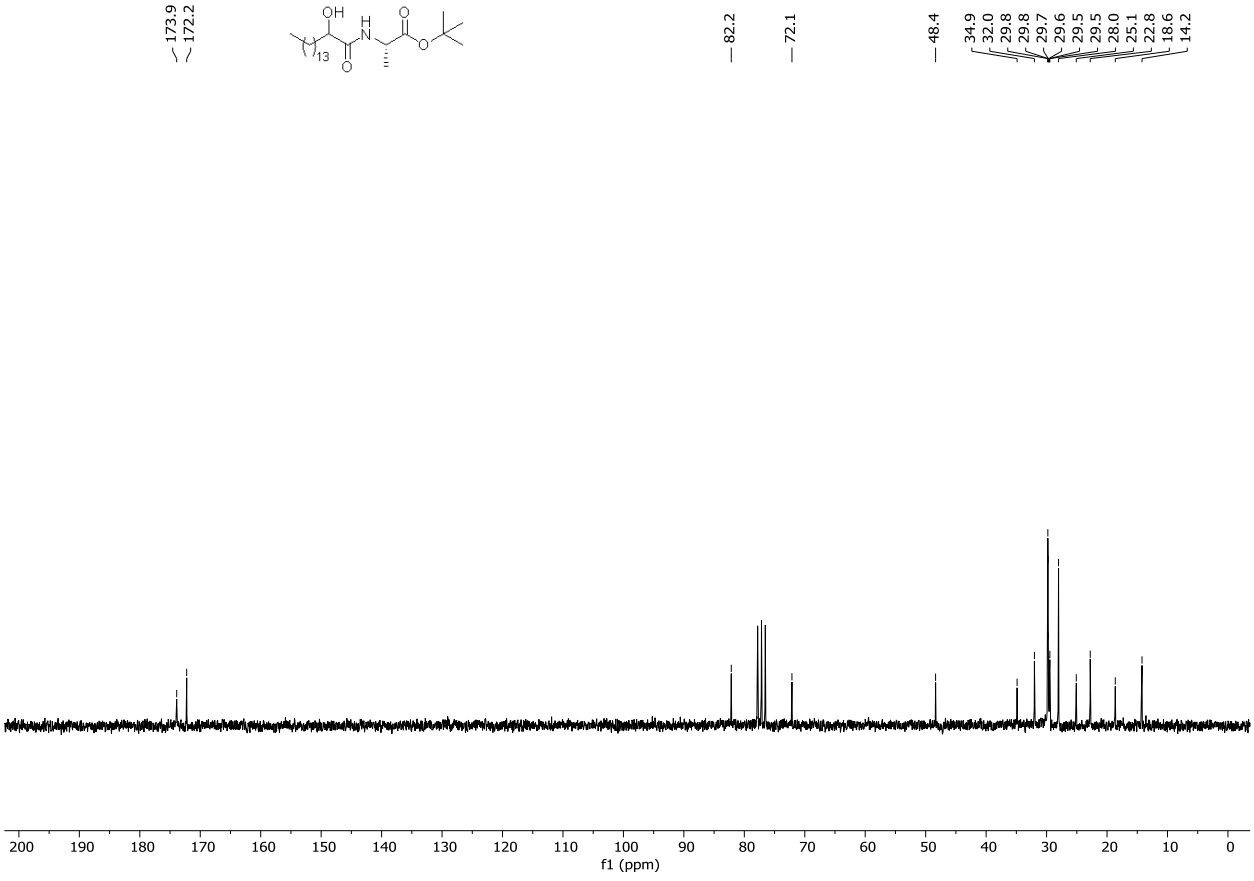
^{1}H NMR spectrum of **6a**, Diastereoisomer 1.



^{13}C NMR spectrum of **6a**, Diastereoisomer 1.



^{1}H NMR spectrum of **6a**, Diastereoisomer 2.



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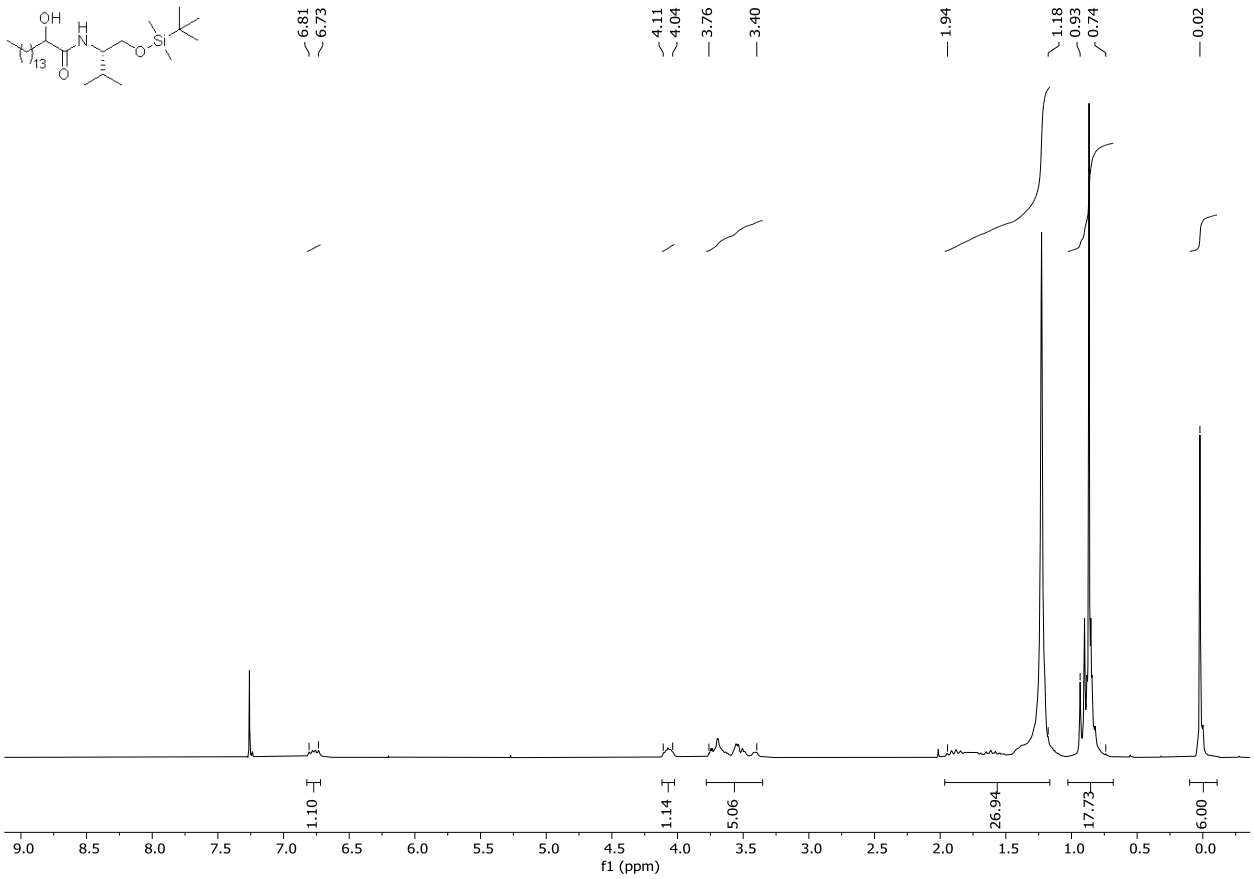
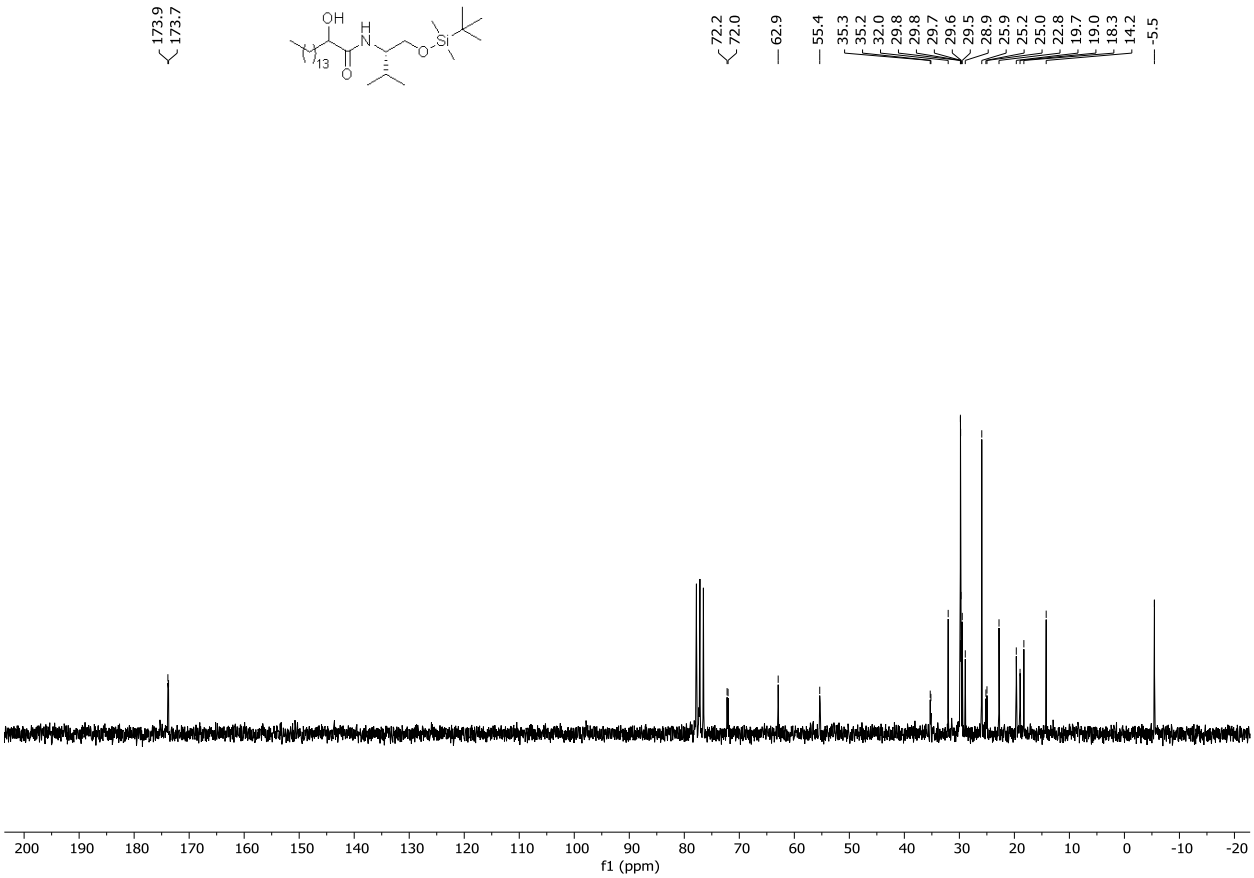


^{1}H NMR spectrum of **6b**.



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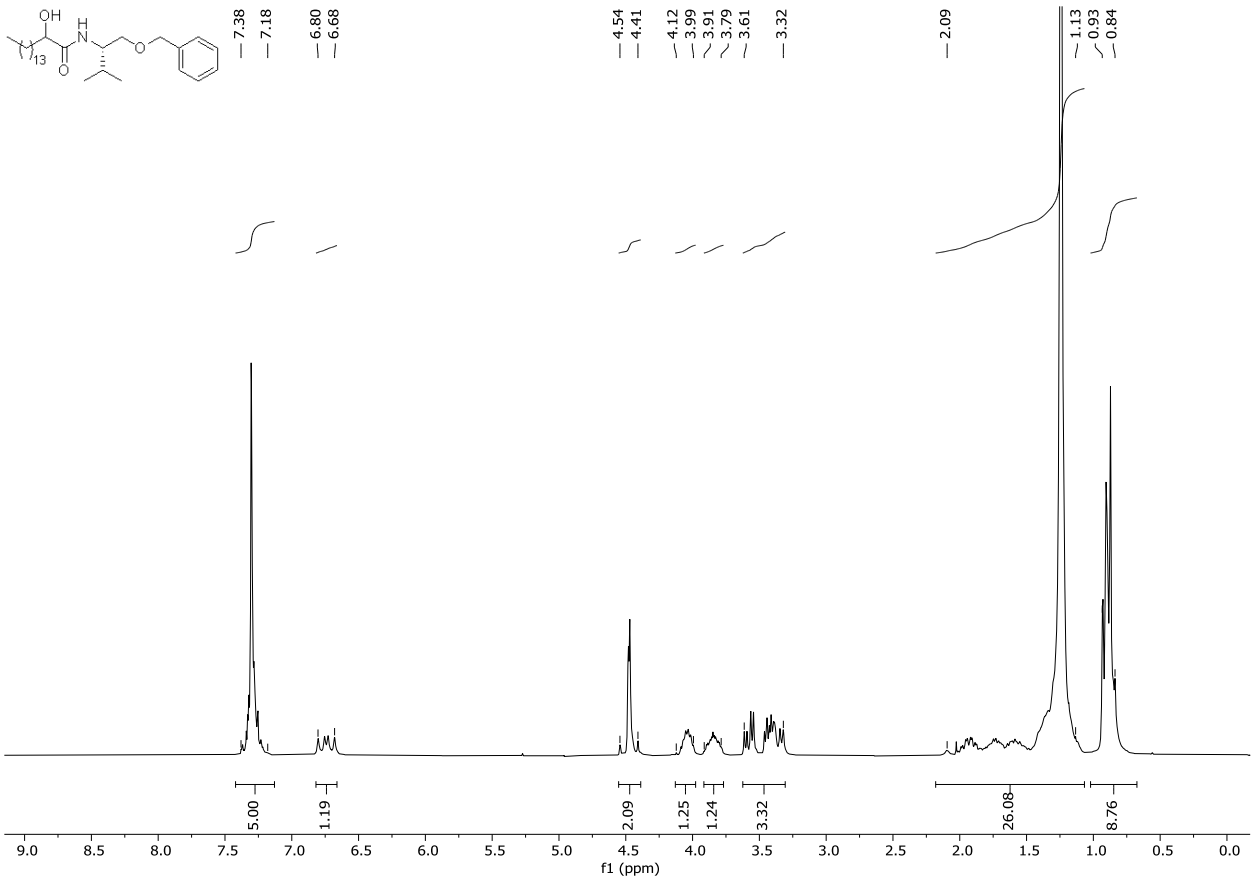
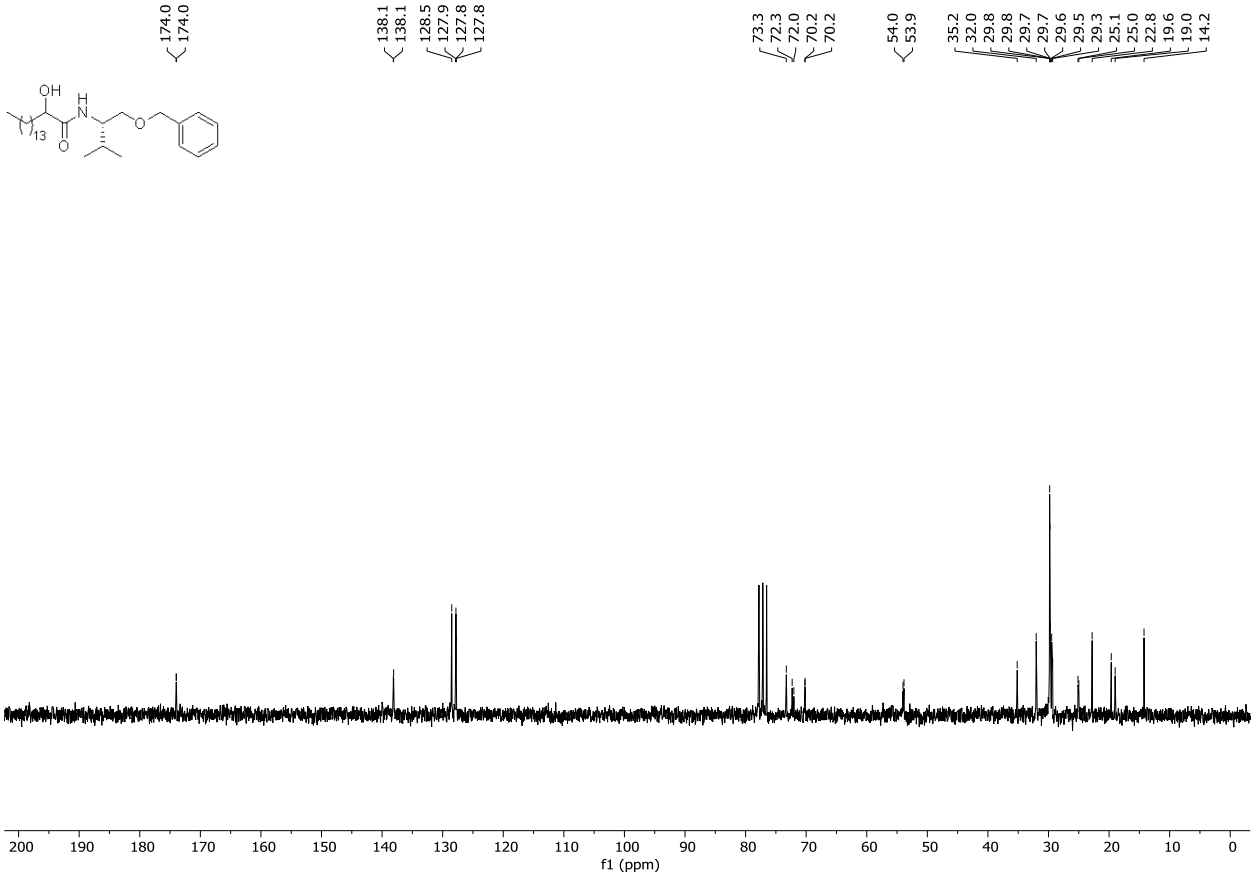


^{1}H NMR spectrum of **6c**.



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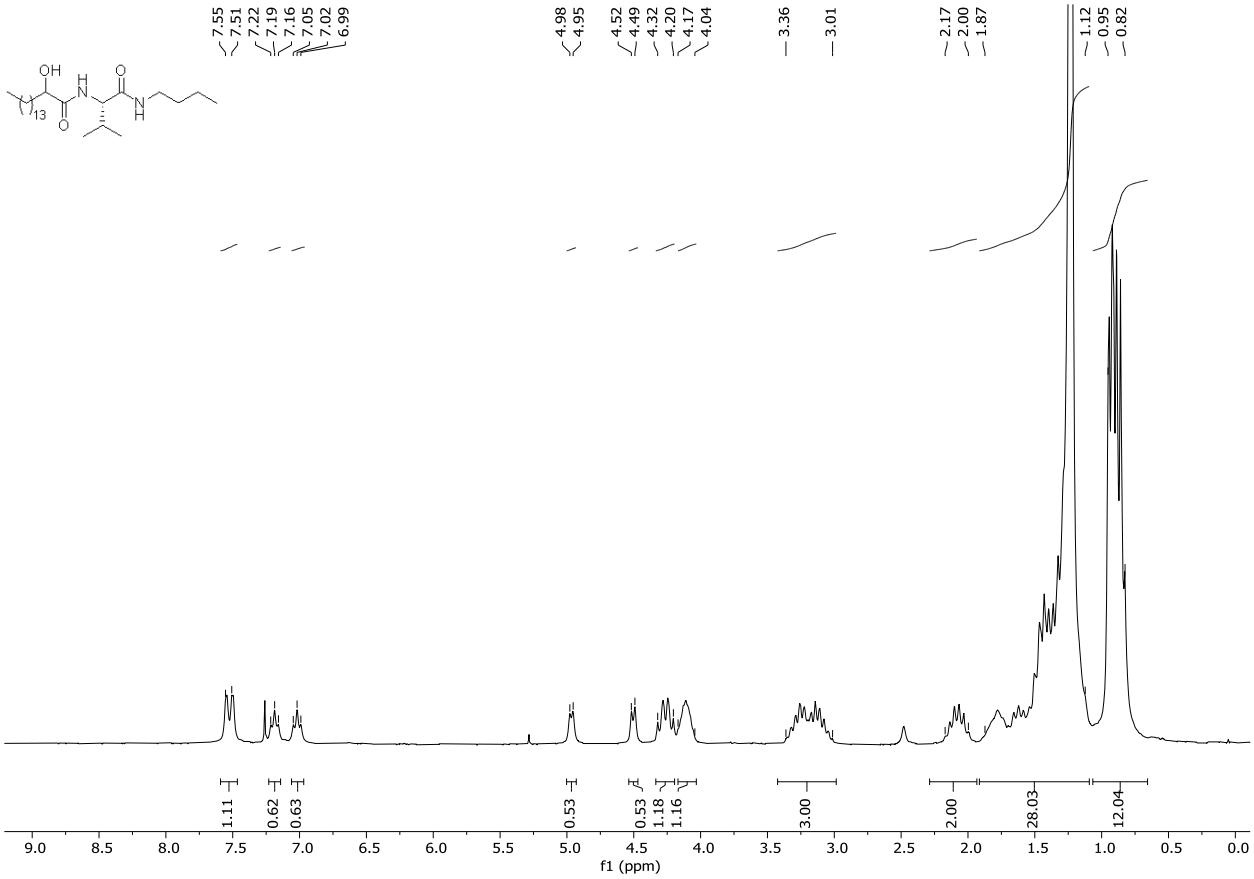

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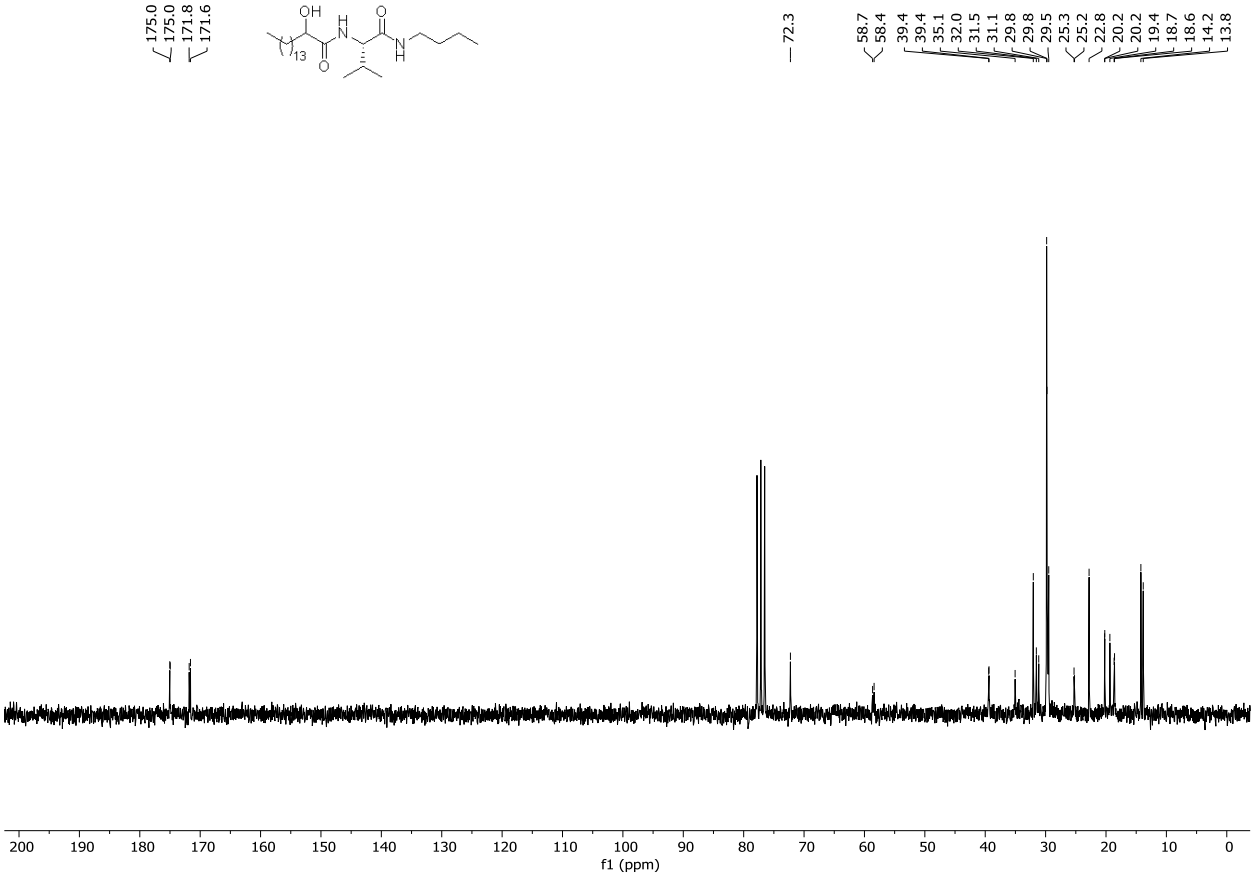

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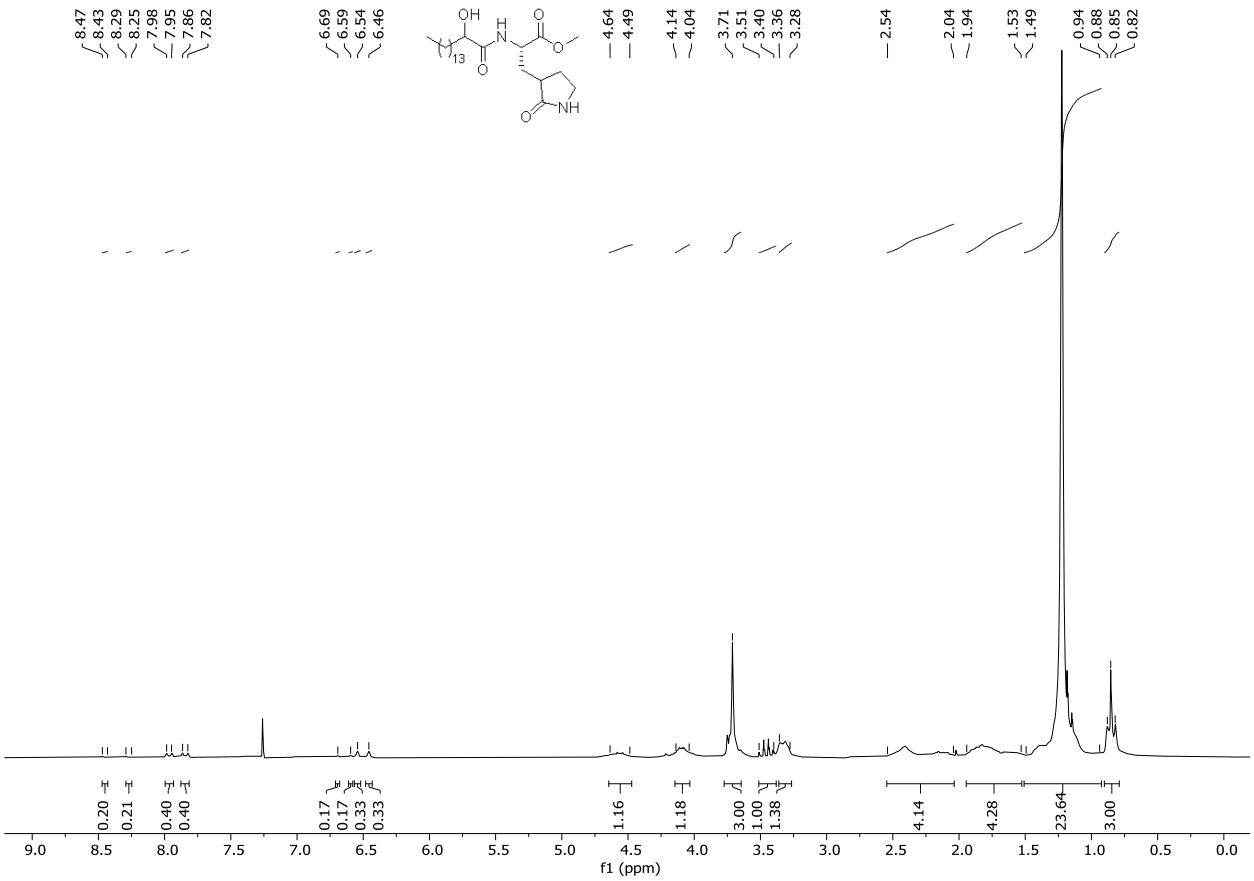

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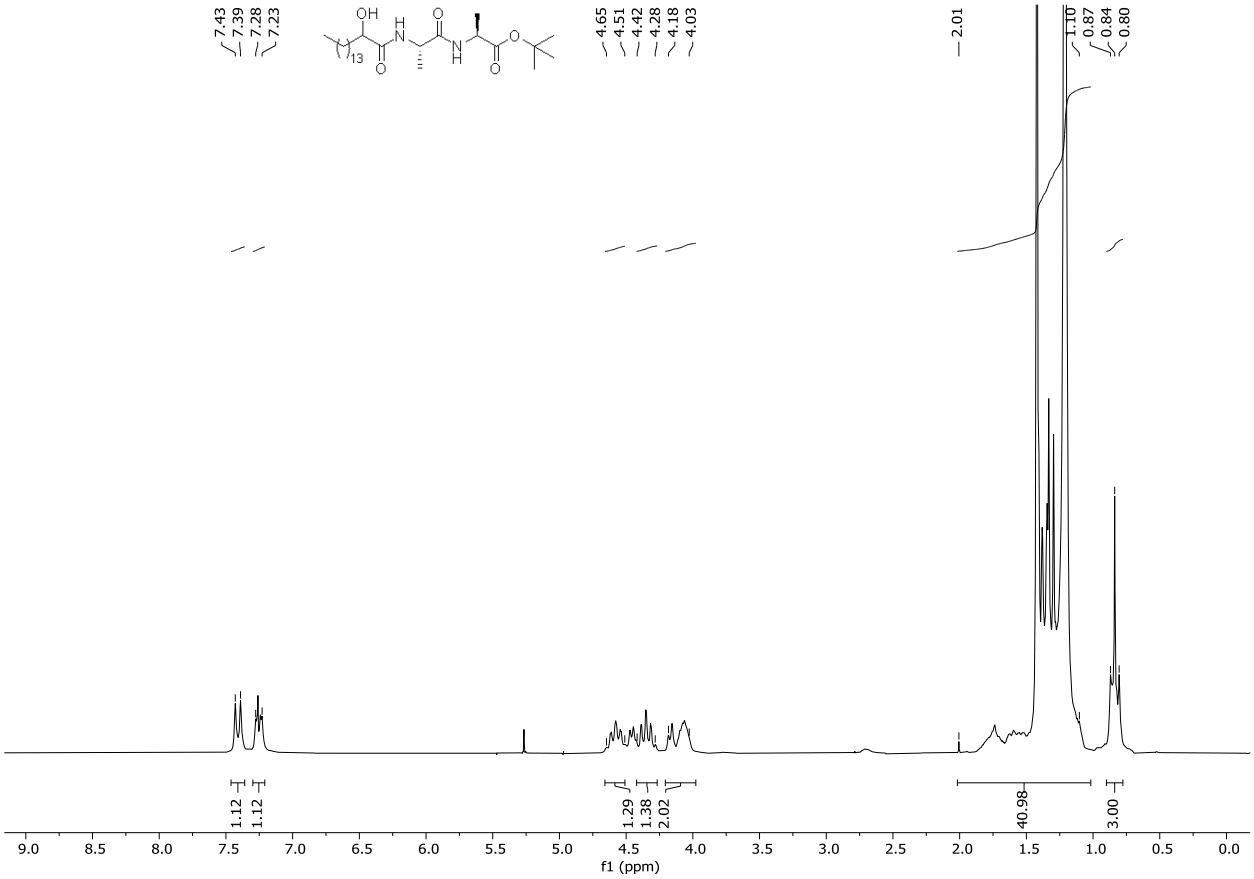
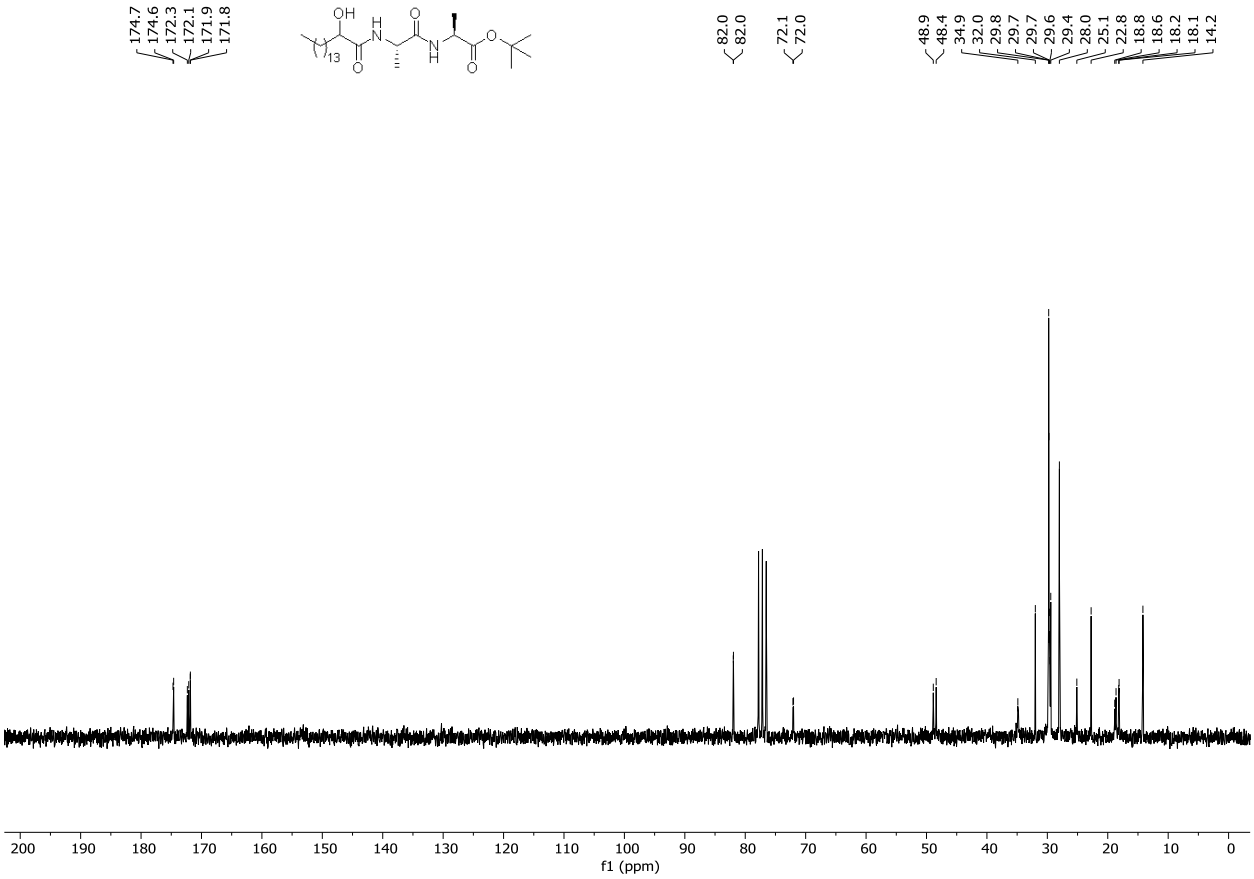


^{1}H NMR spectrum of **6f**.



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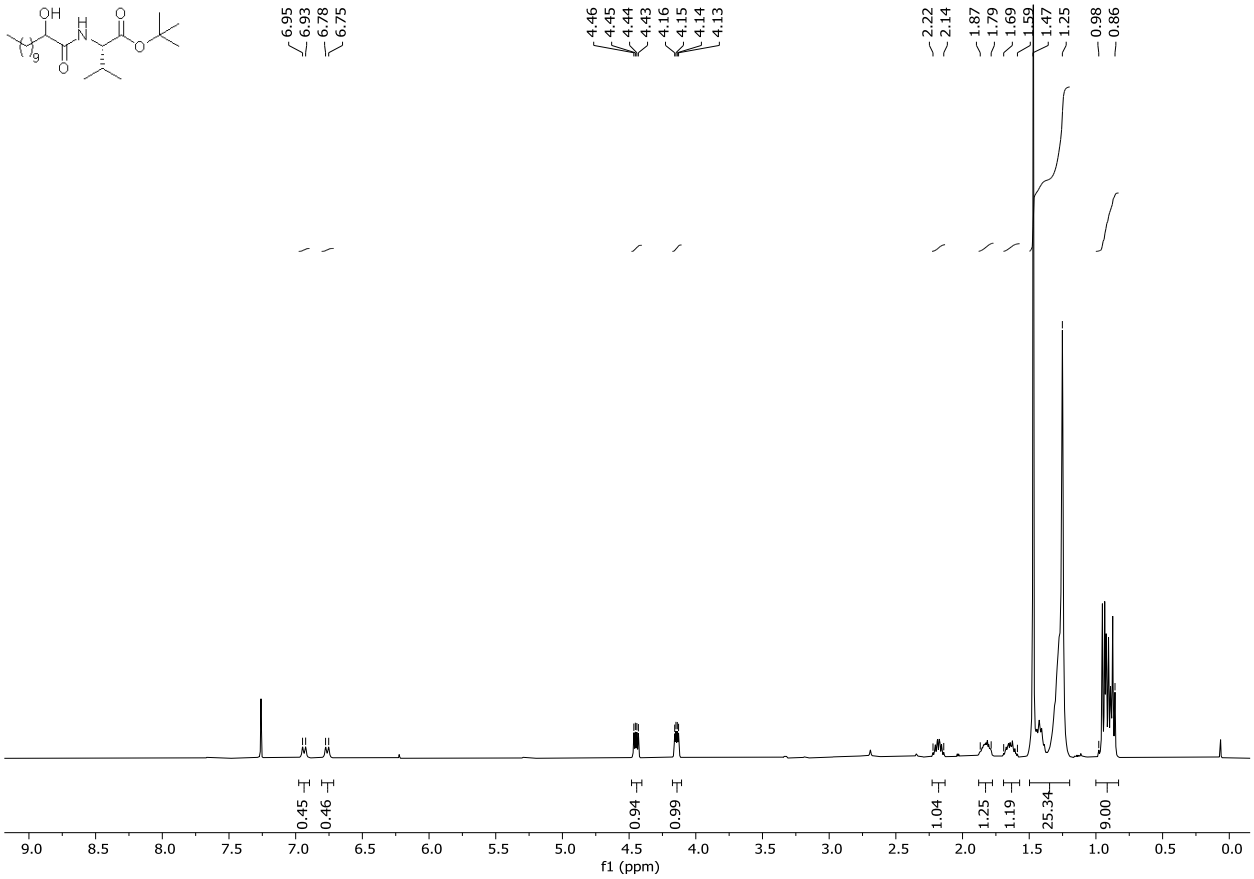

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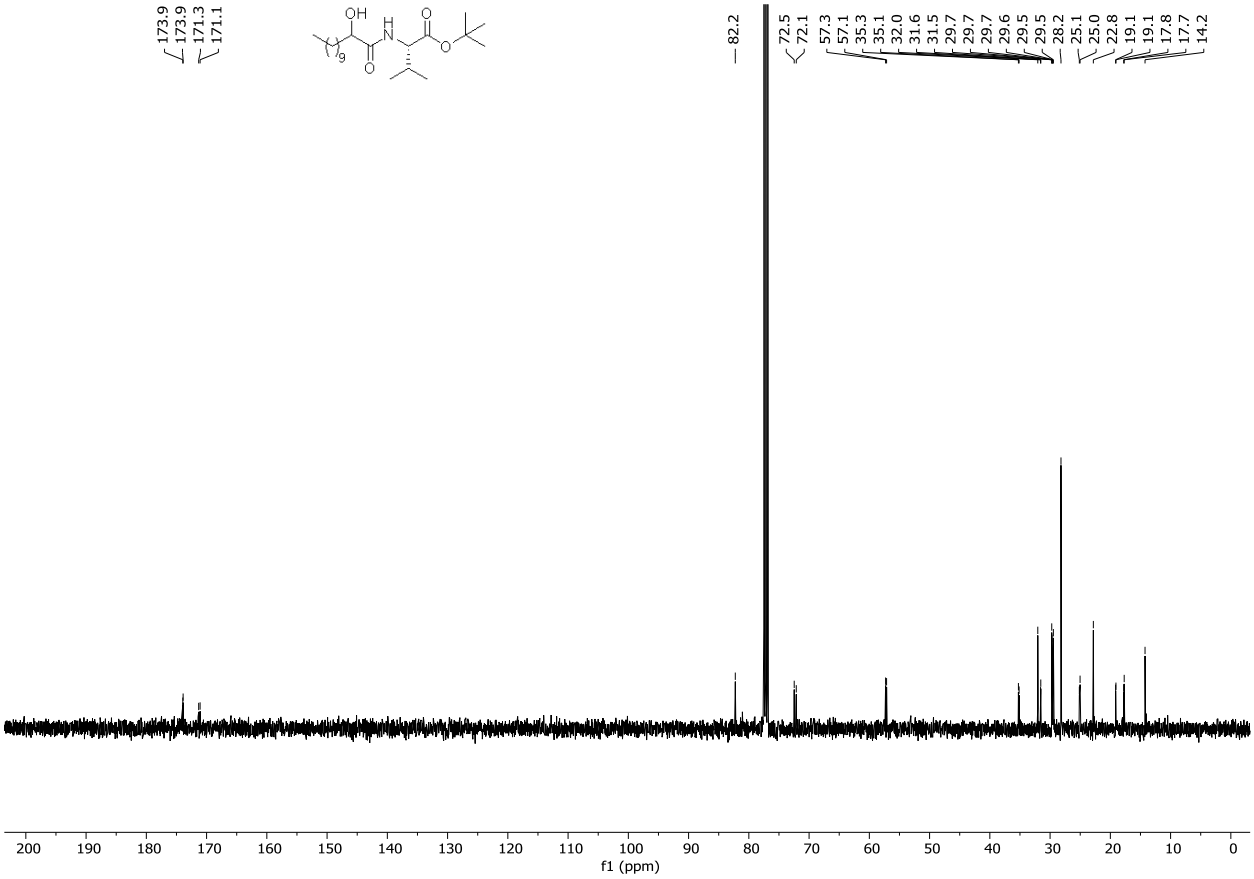

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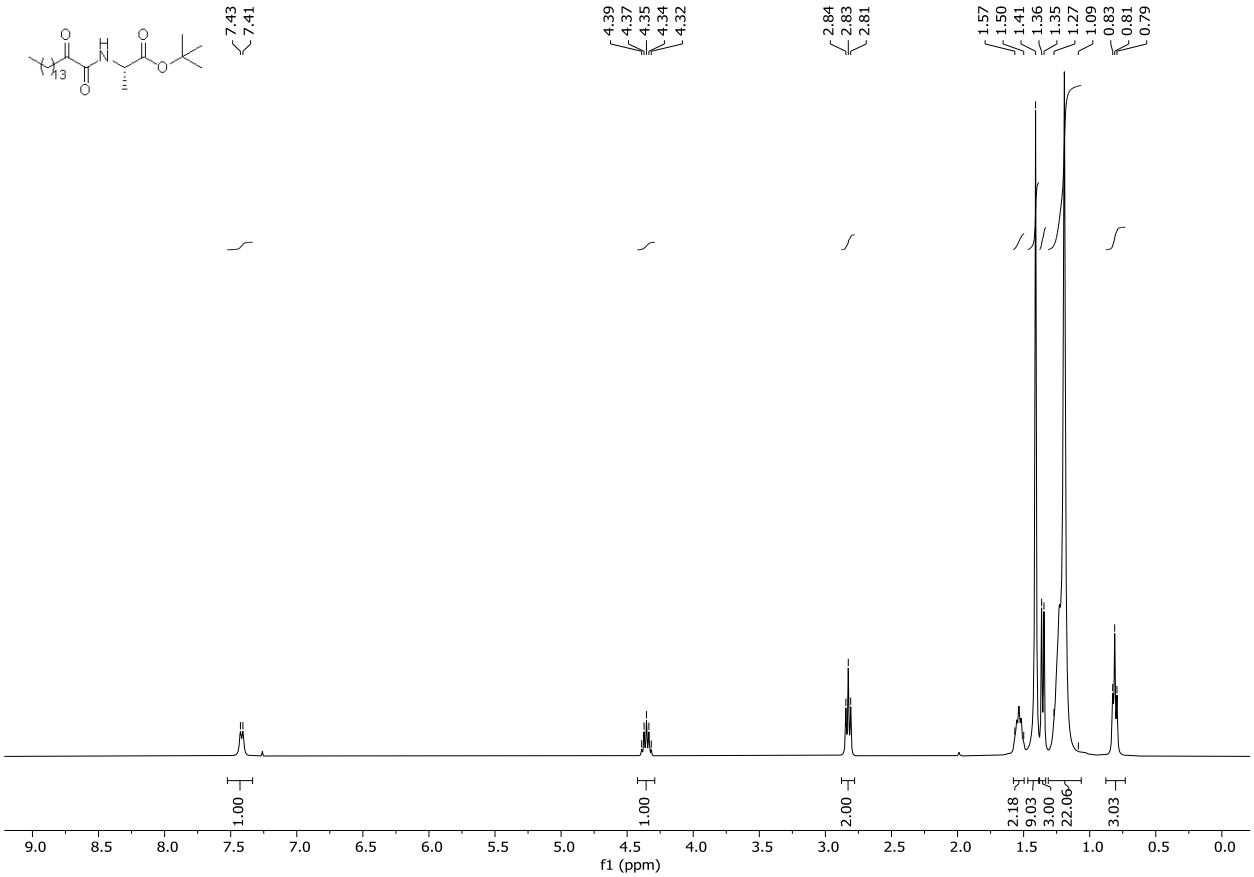

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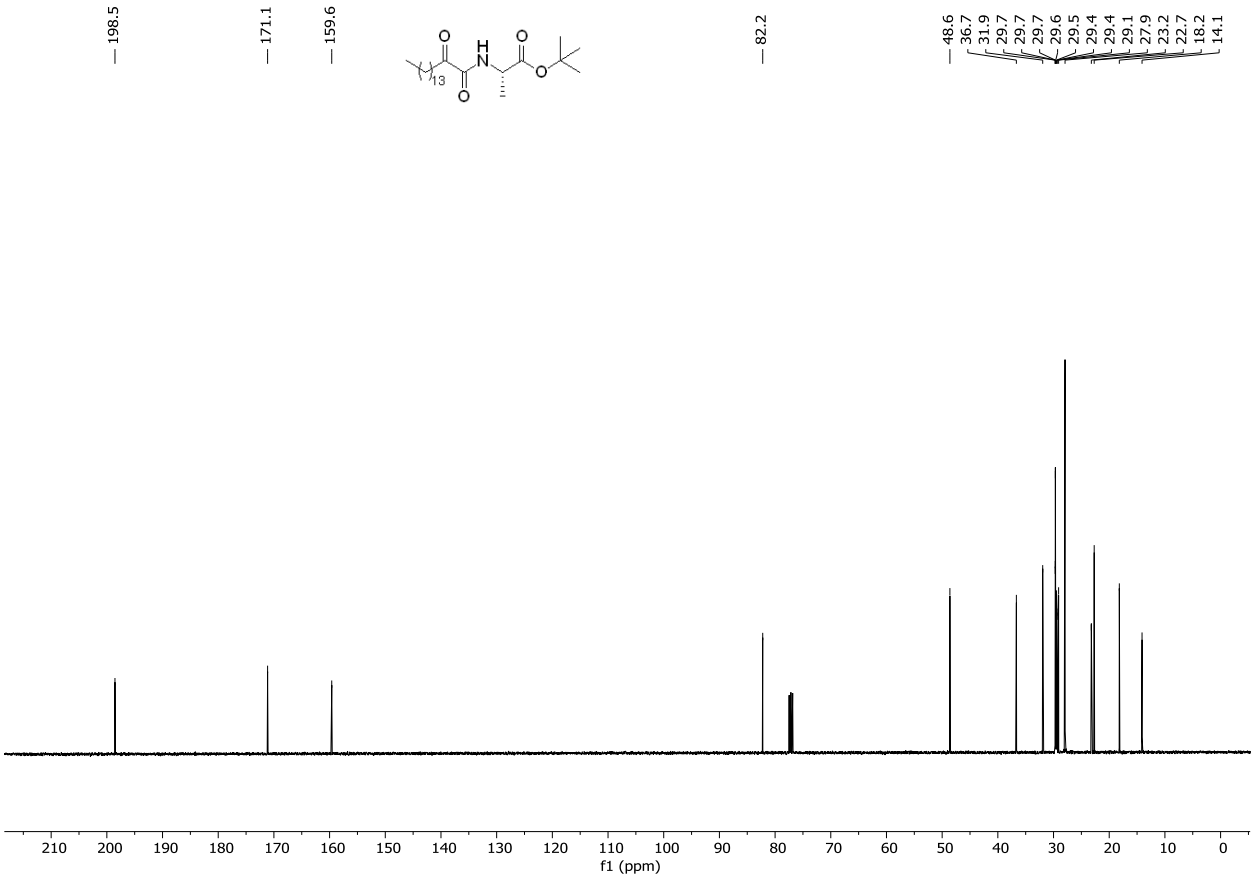

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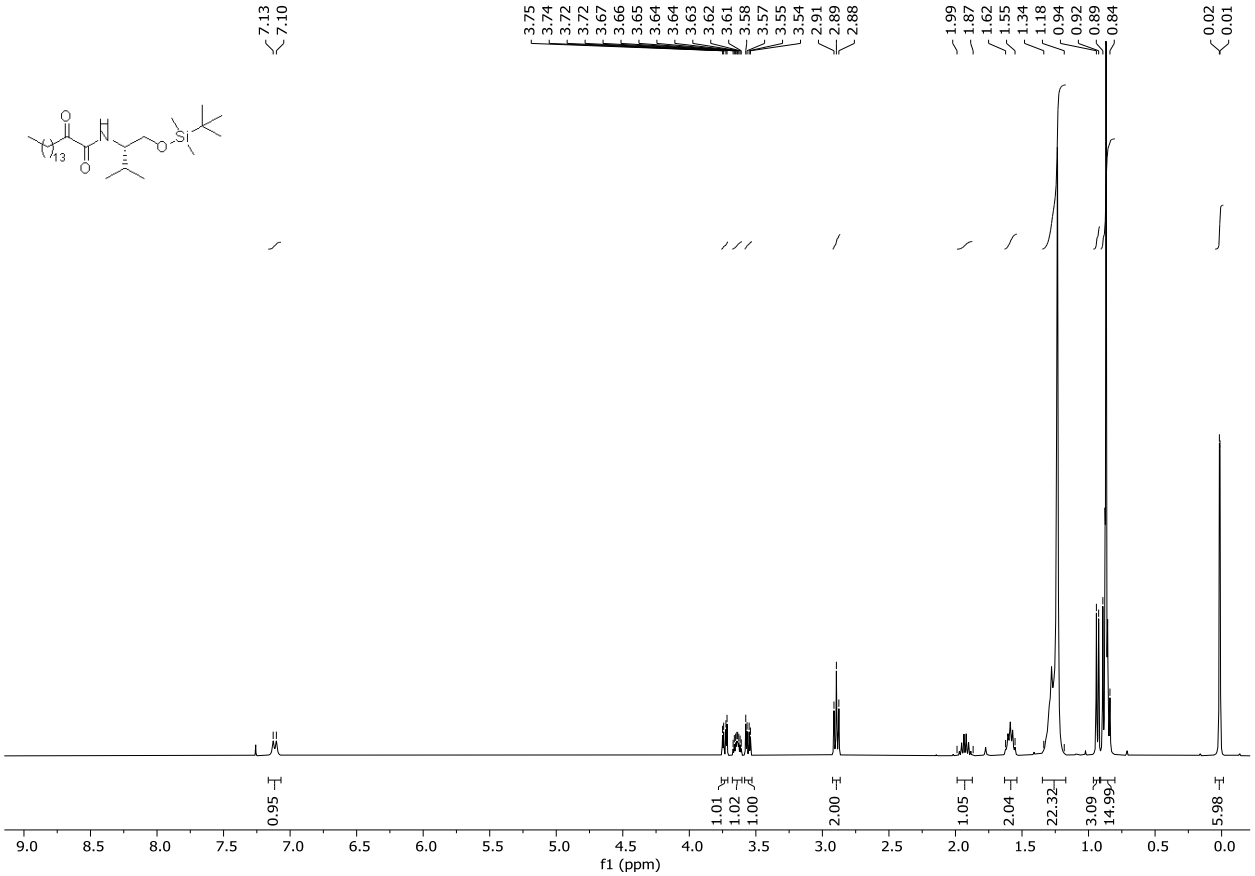

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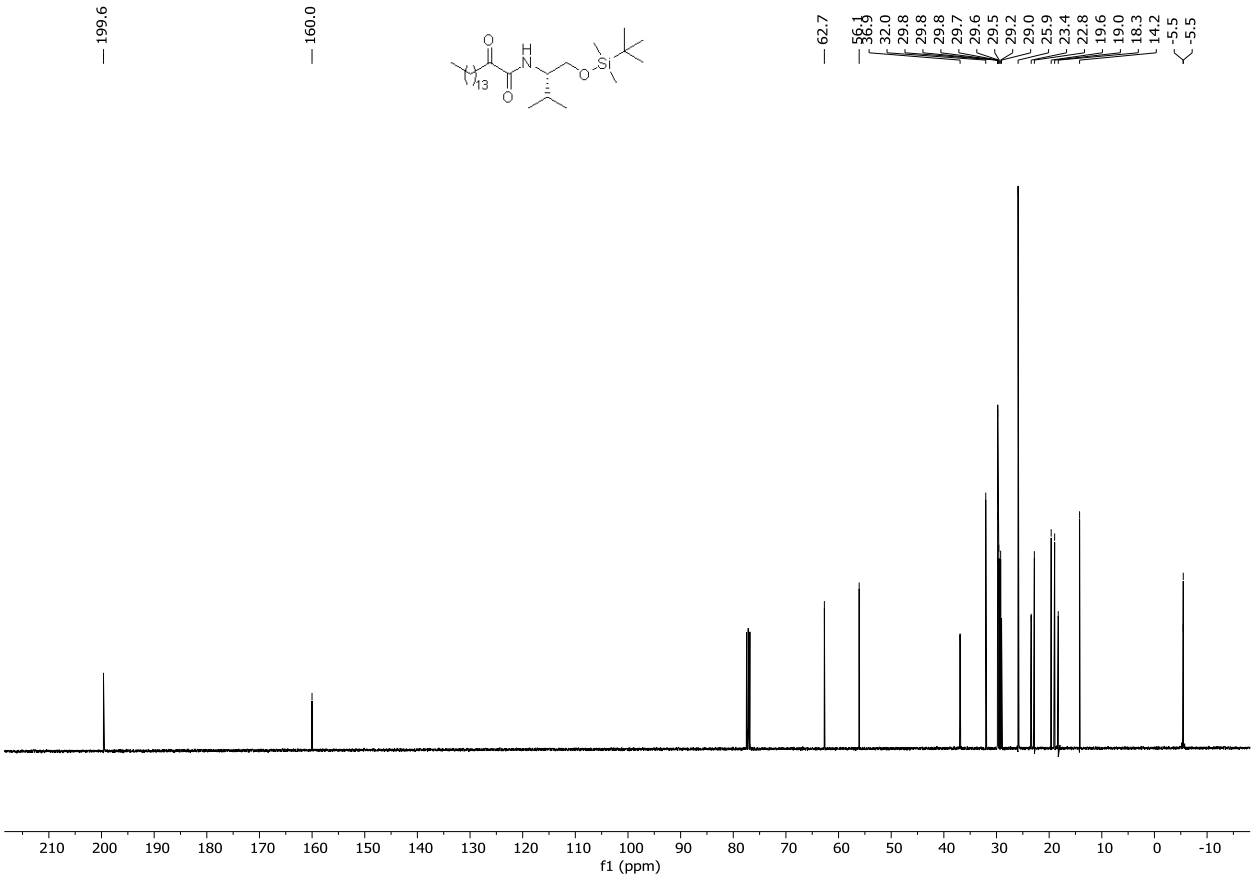

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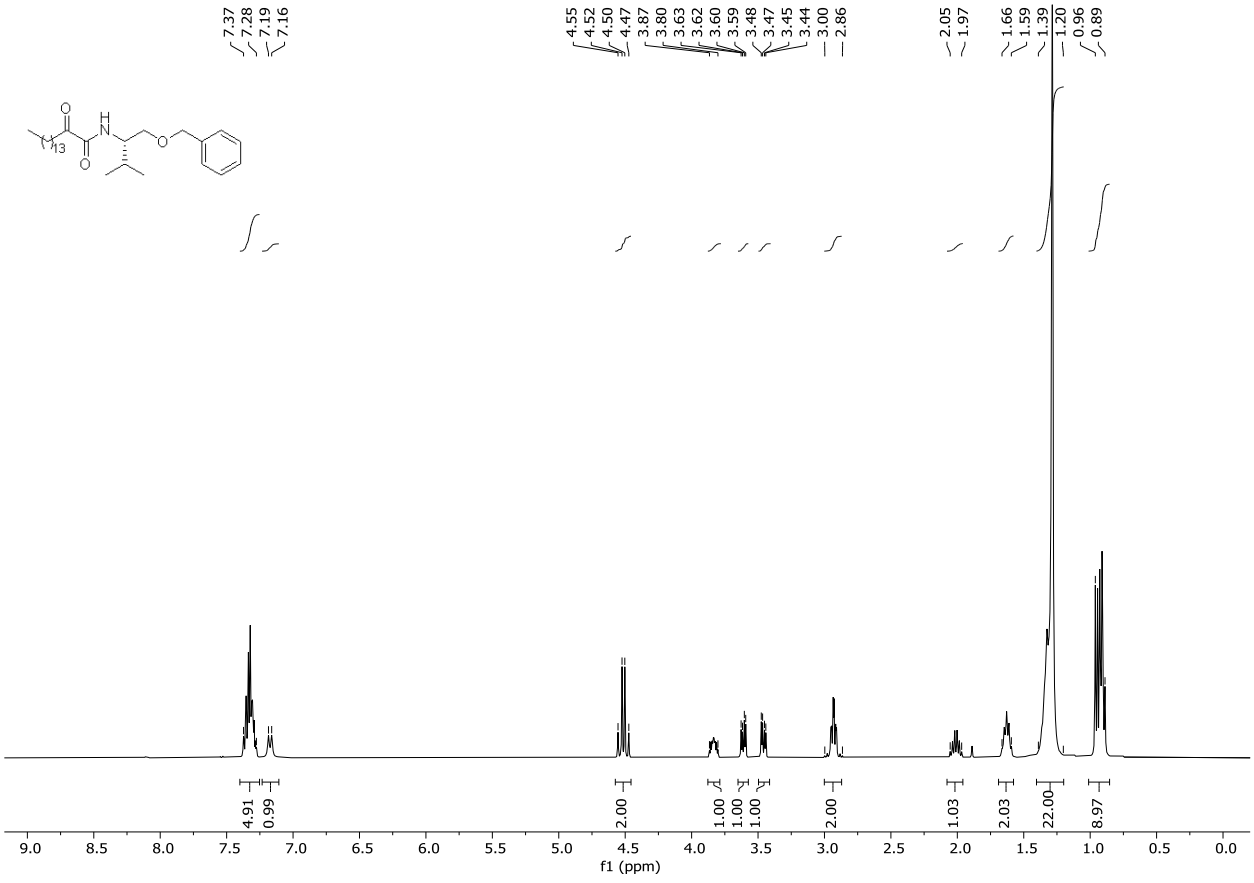

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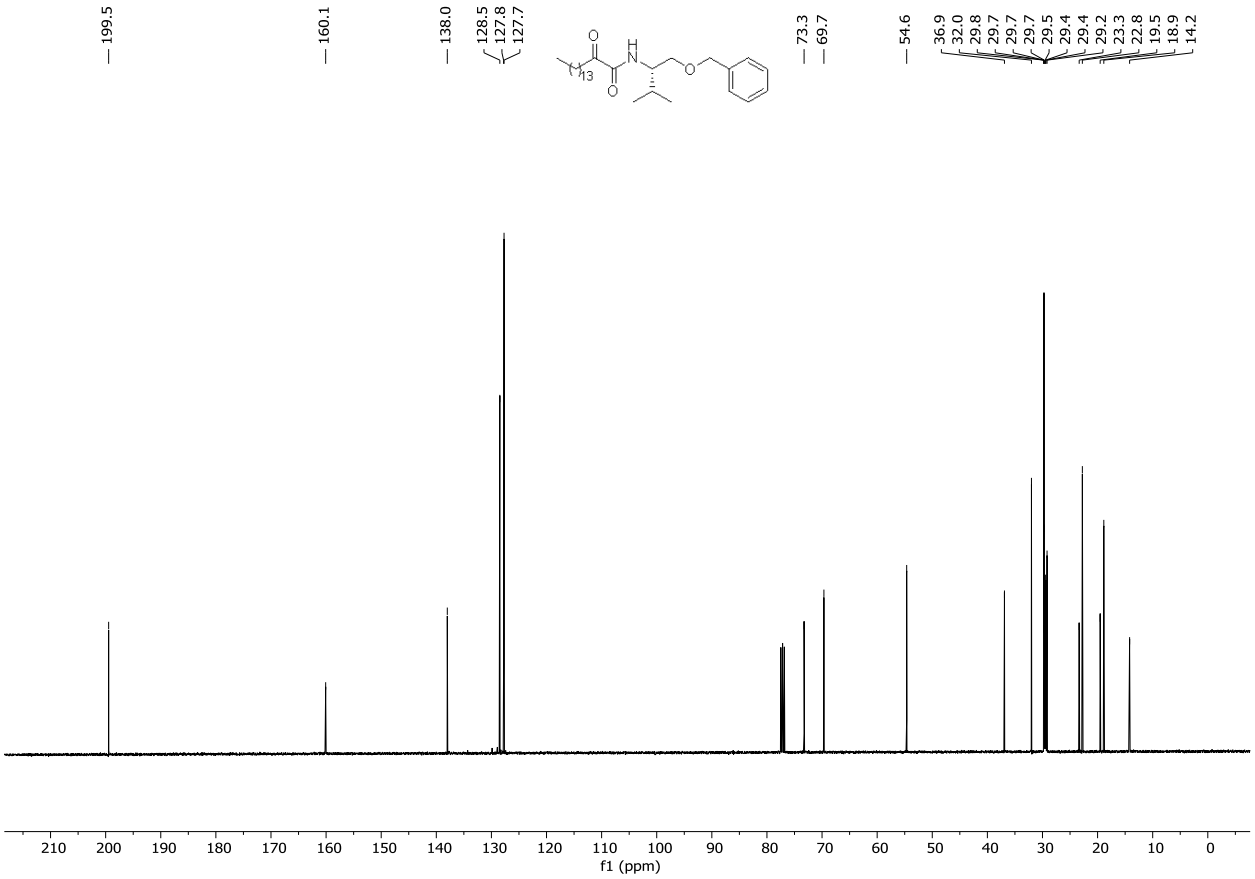

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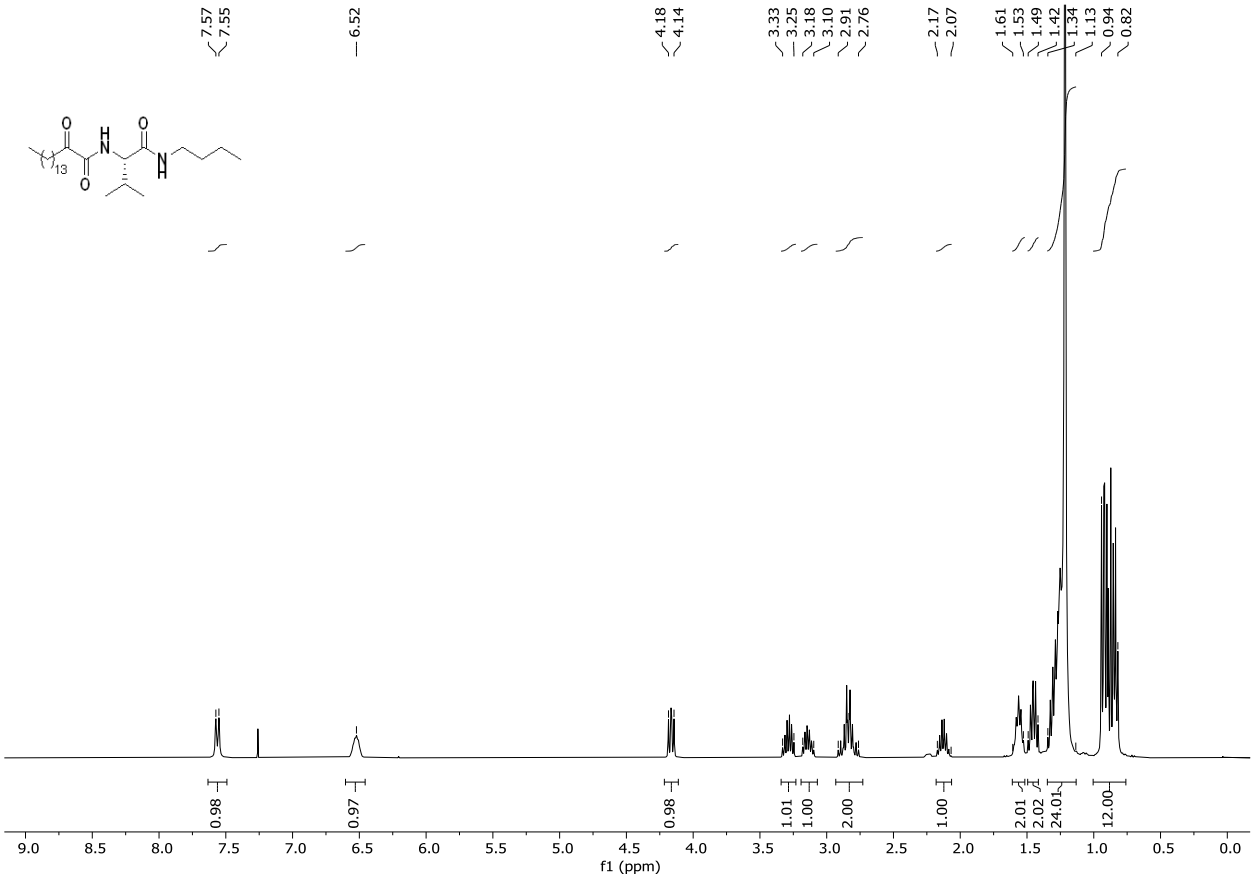

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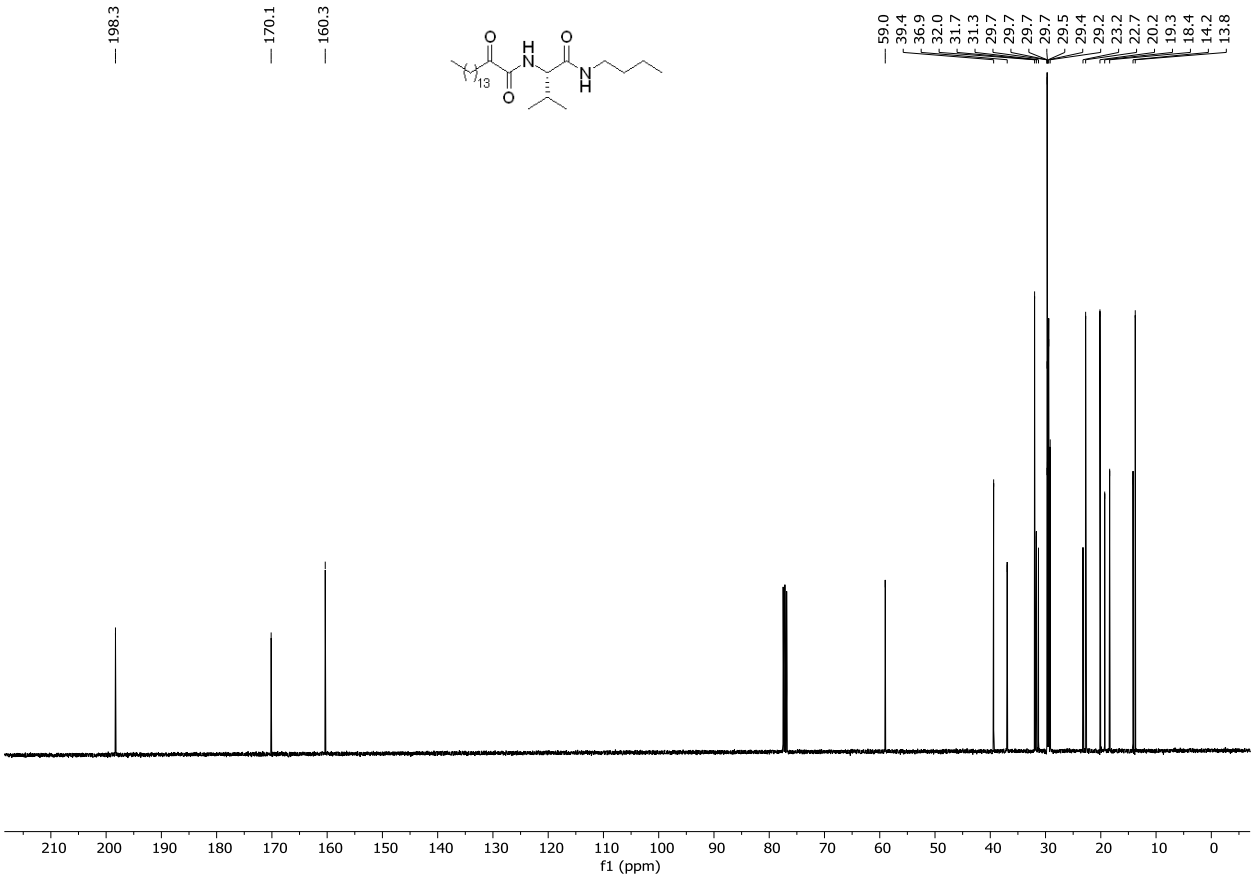

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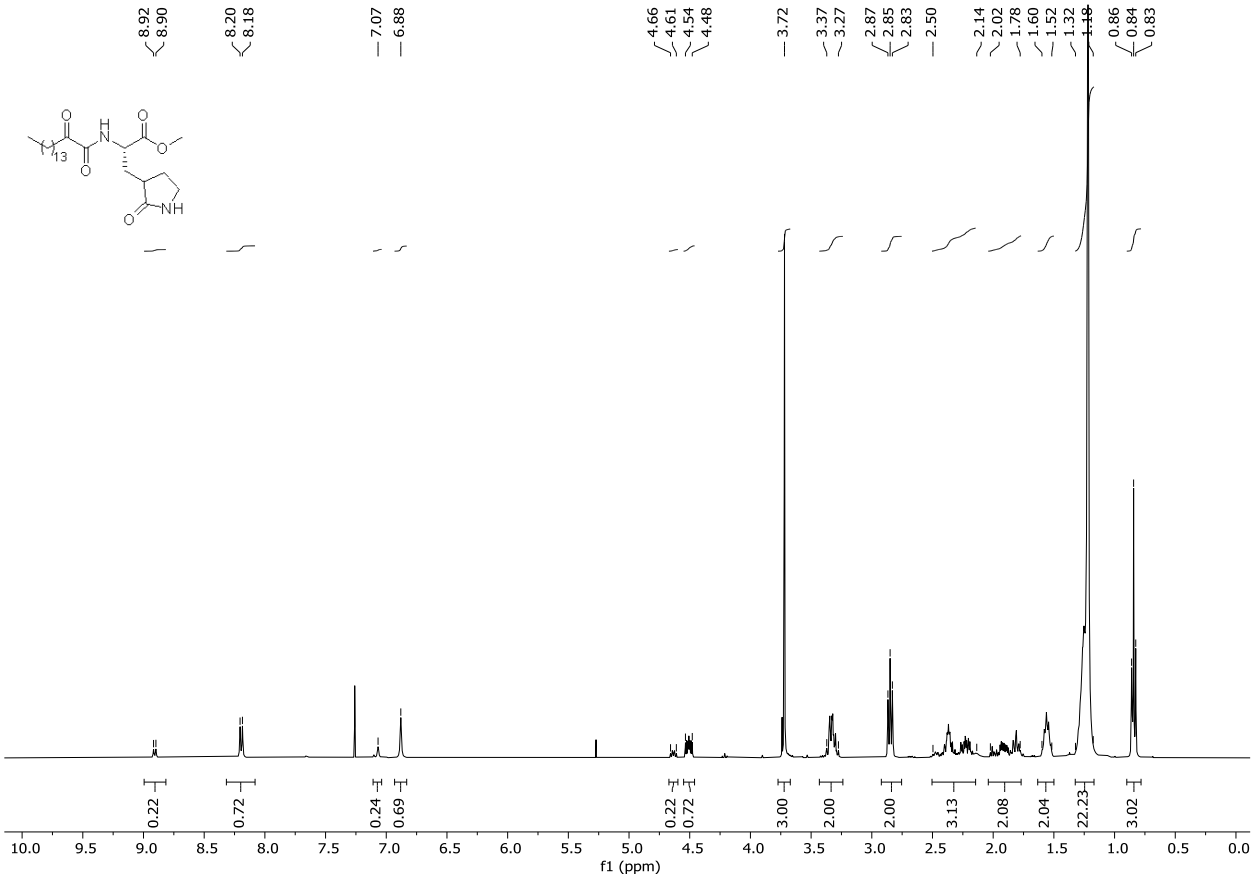

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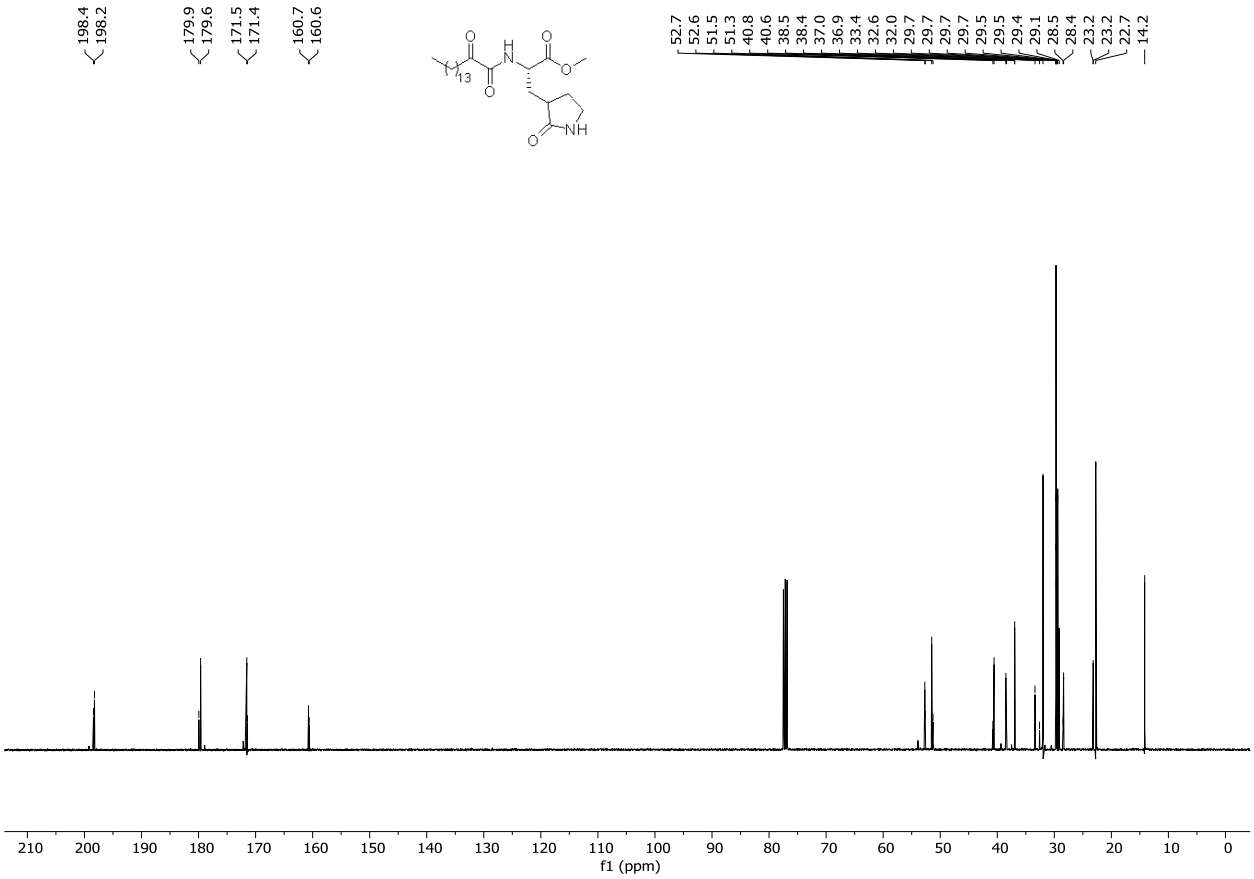

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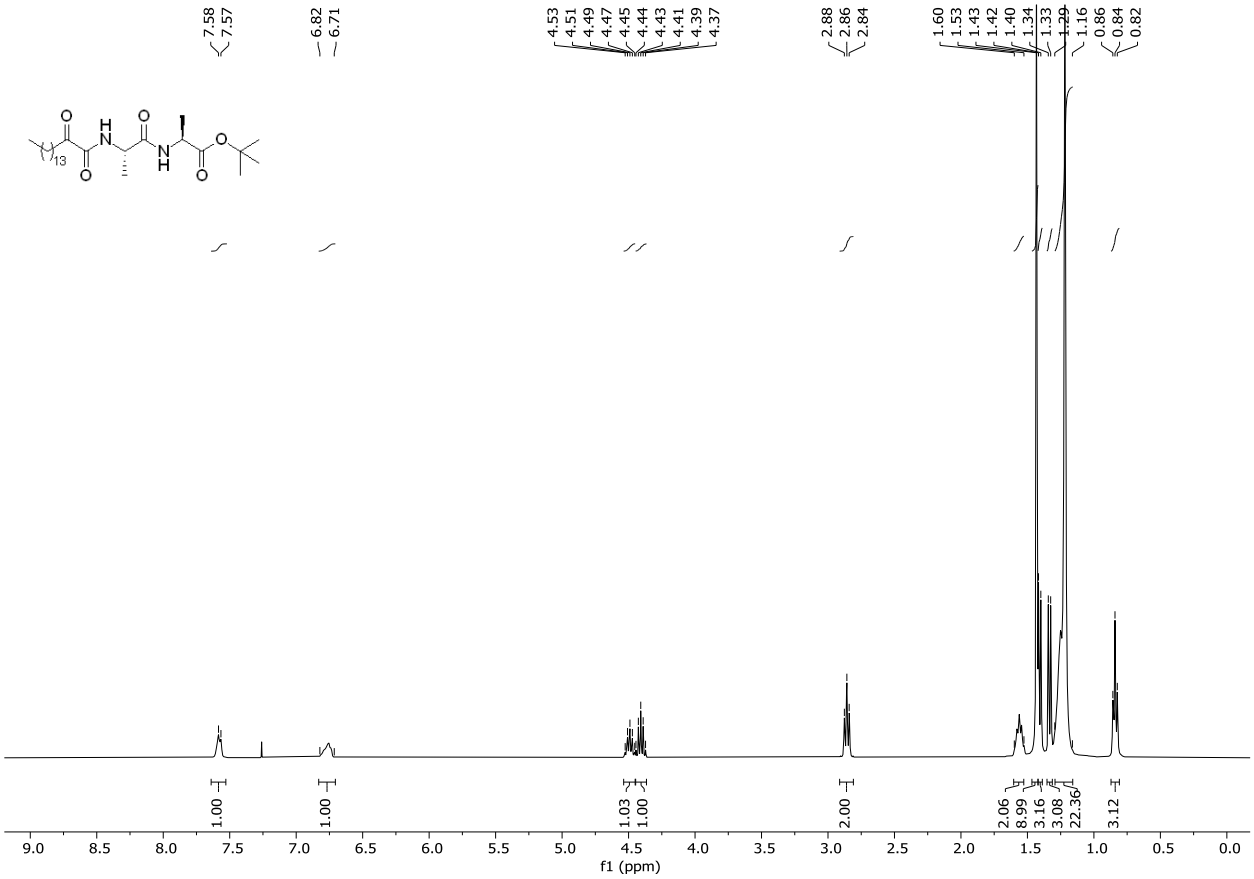

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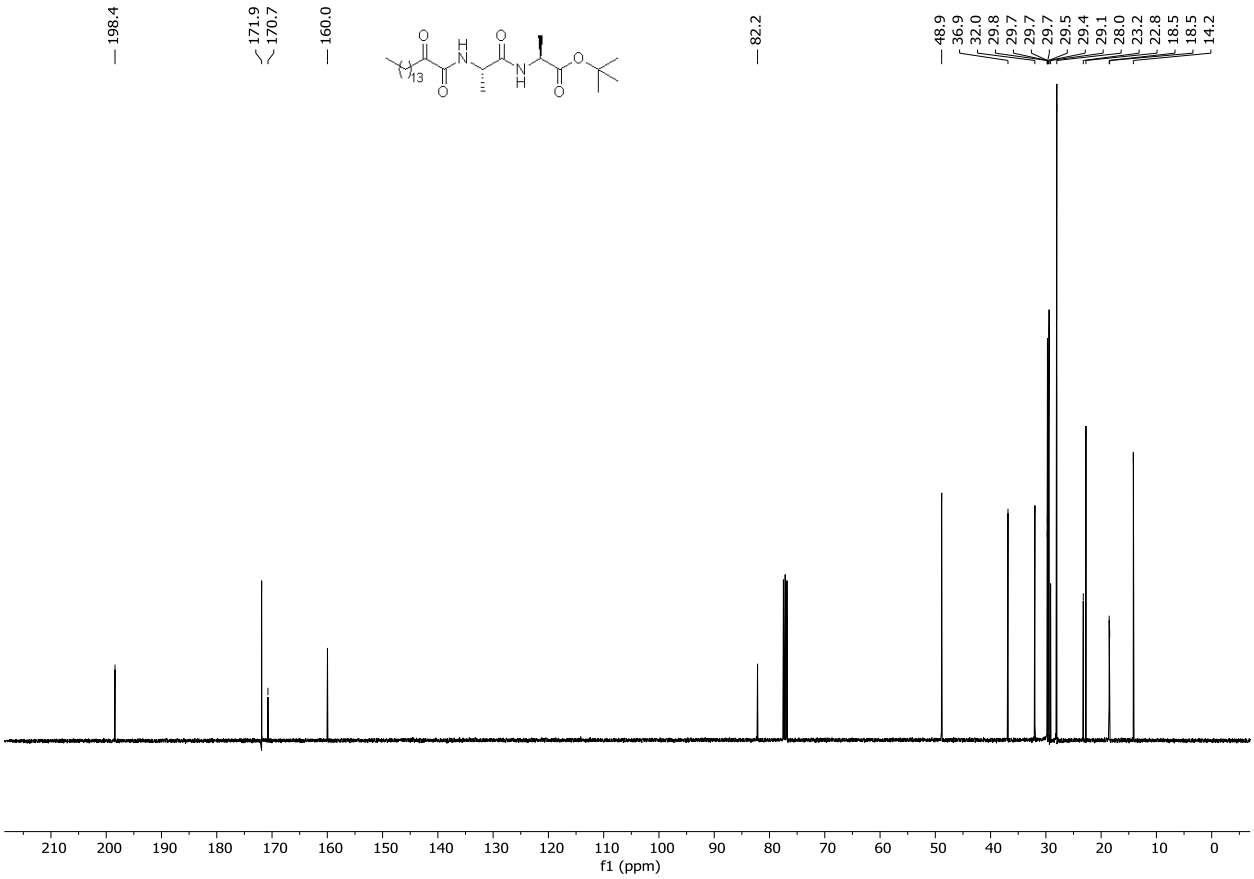

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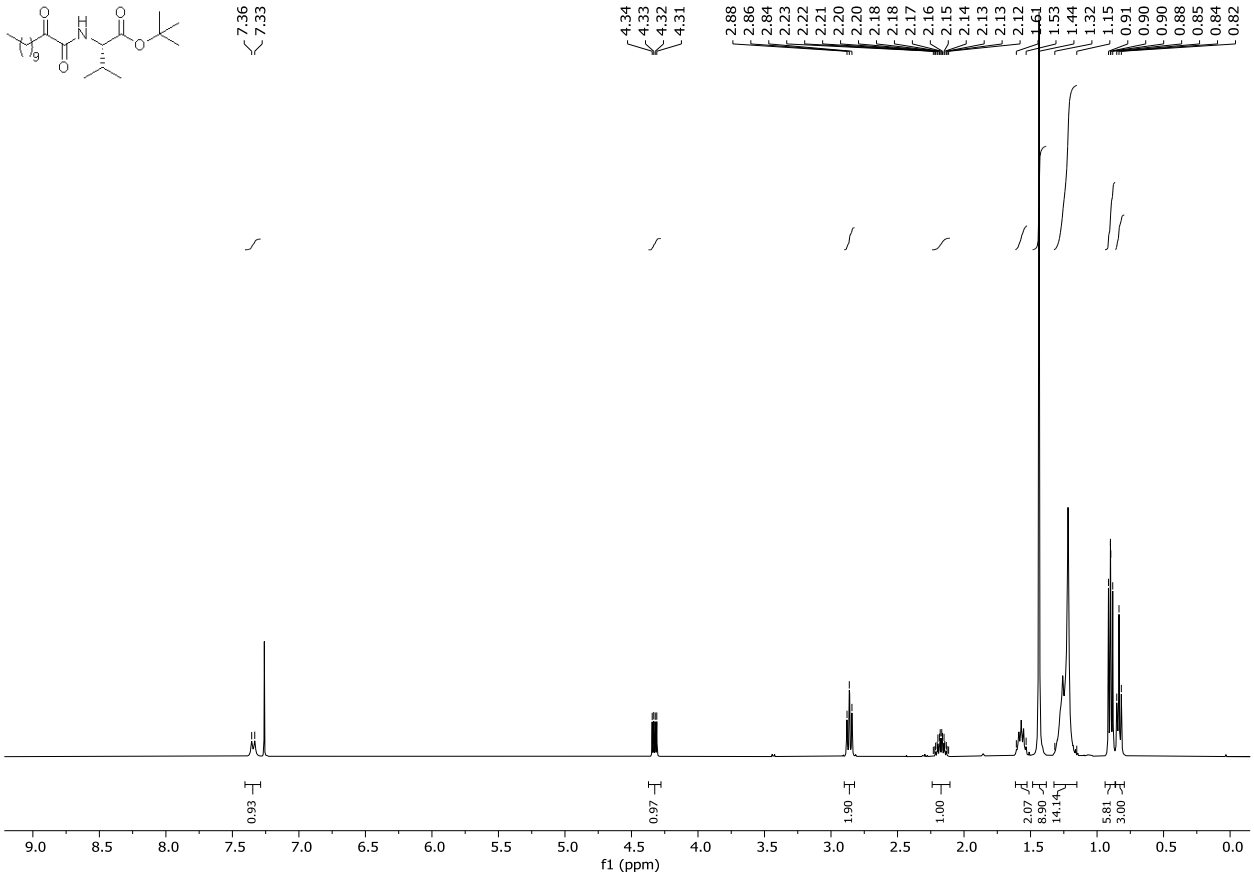

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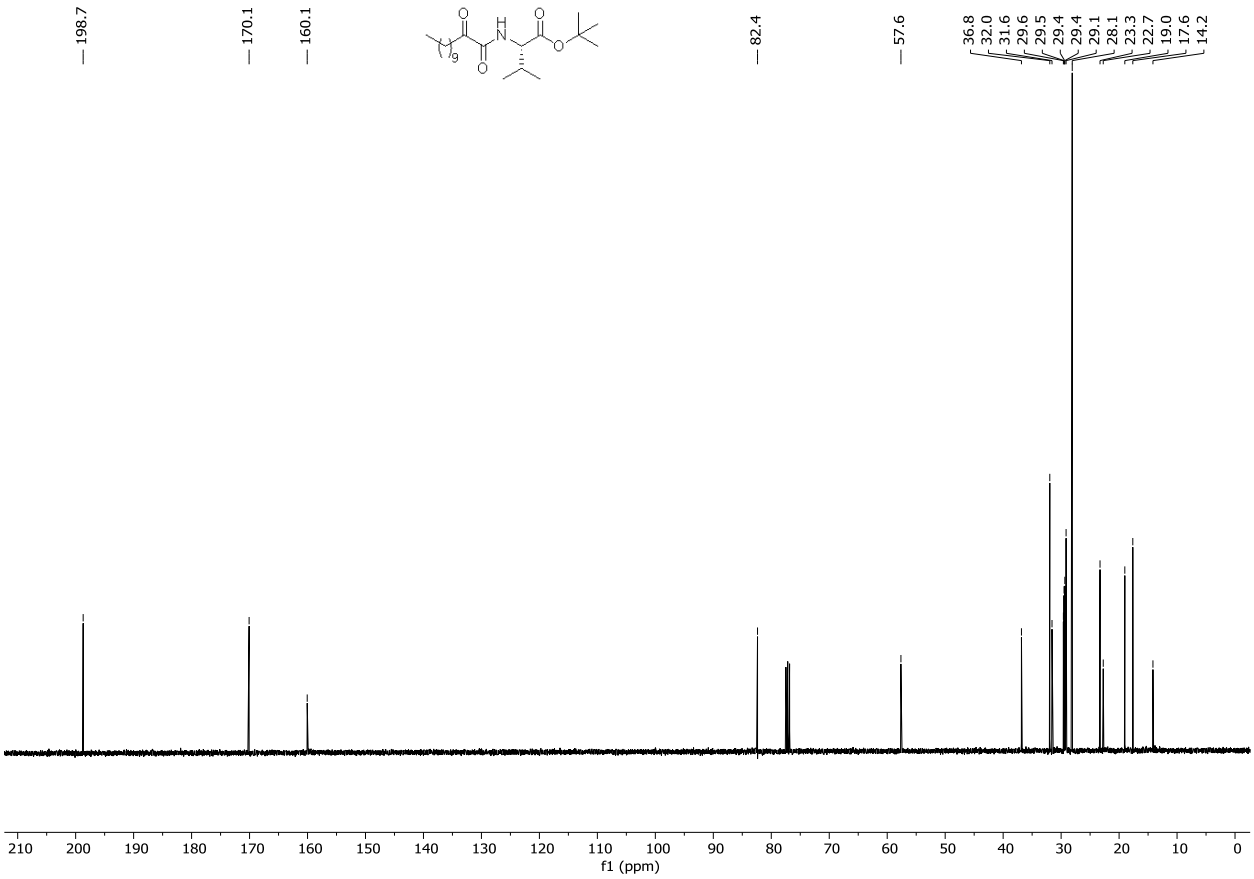

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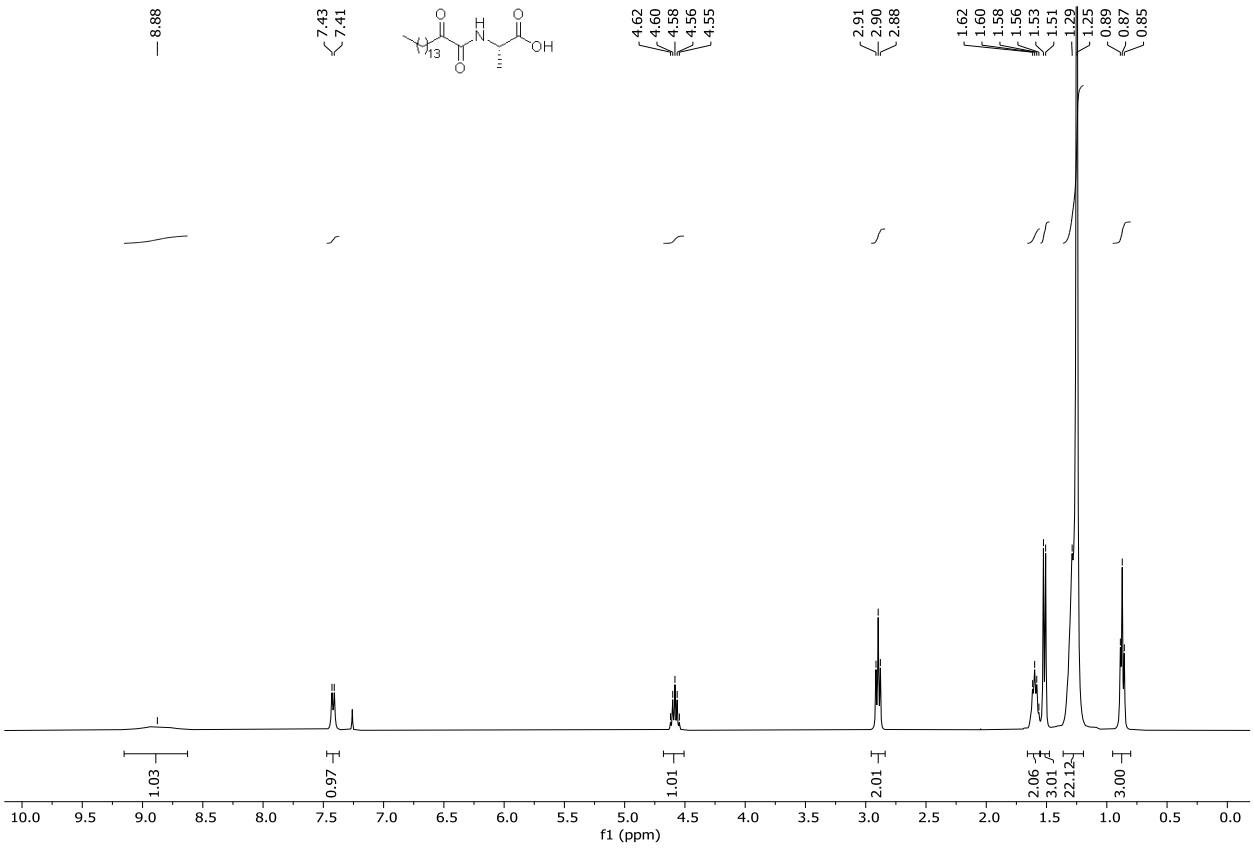

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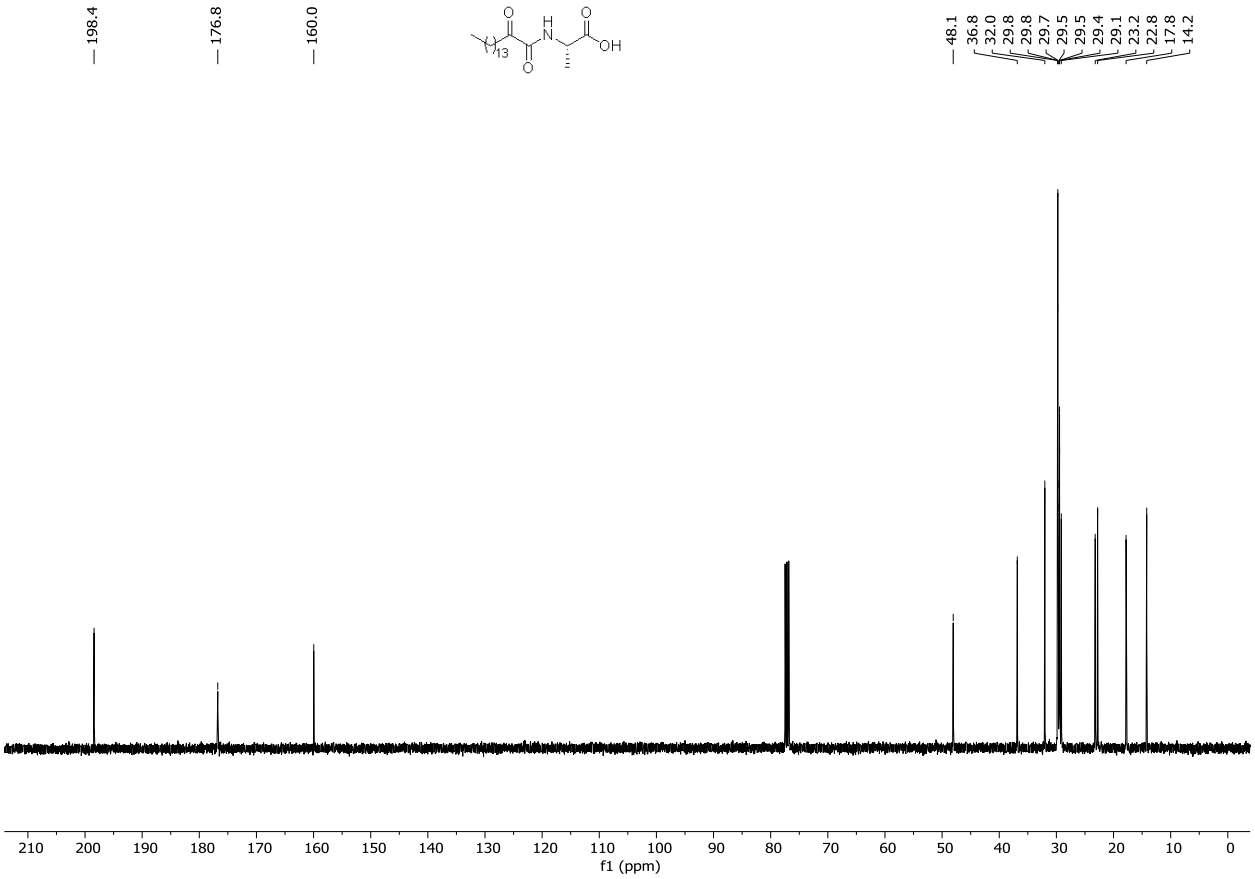

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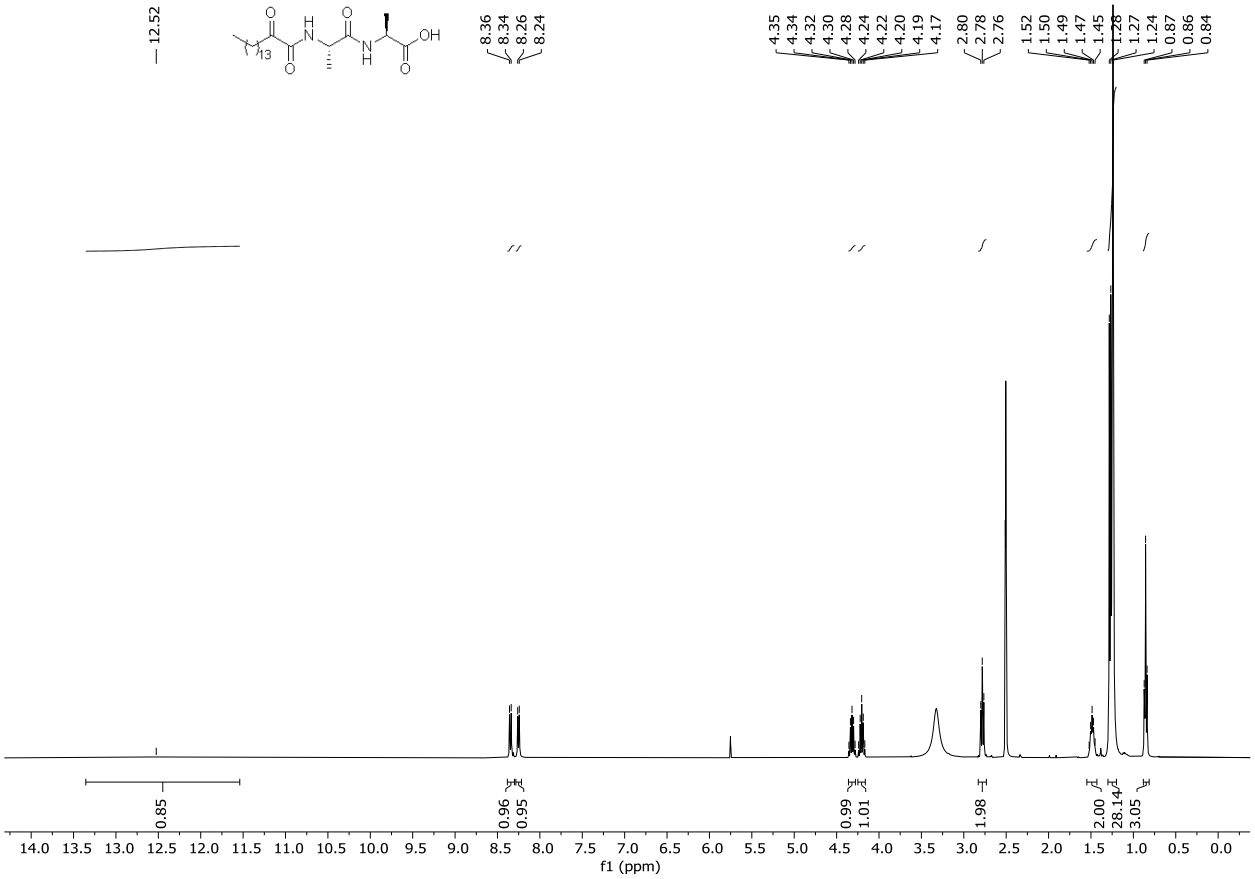

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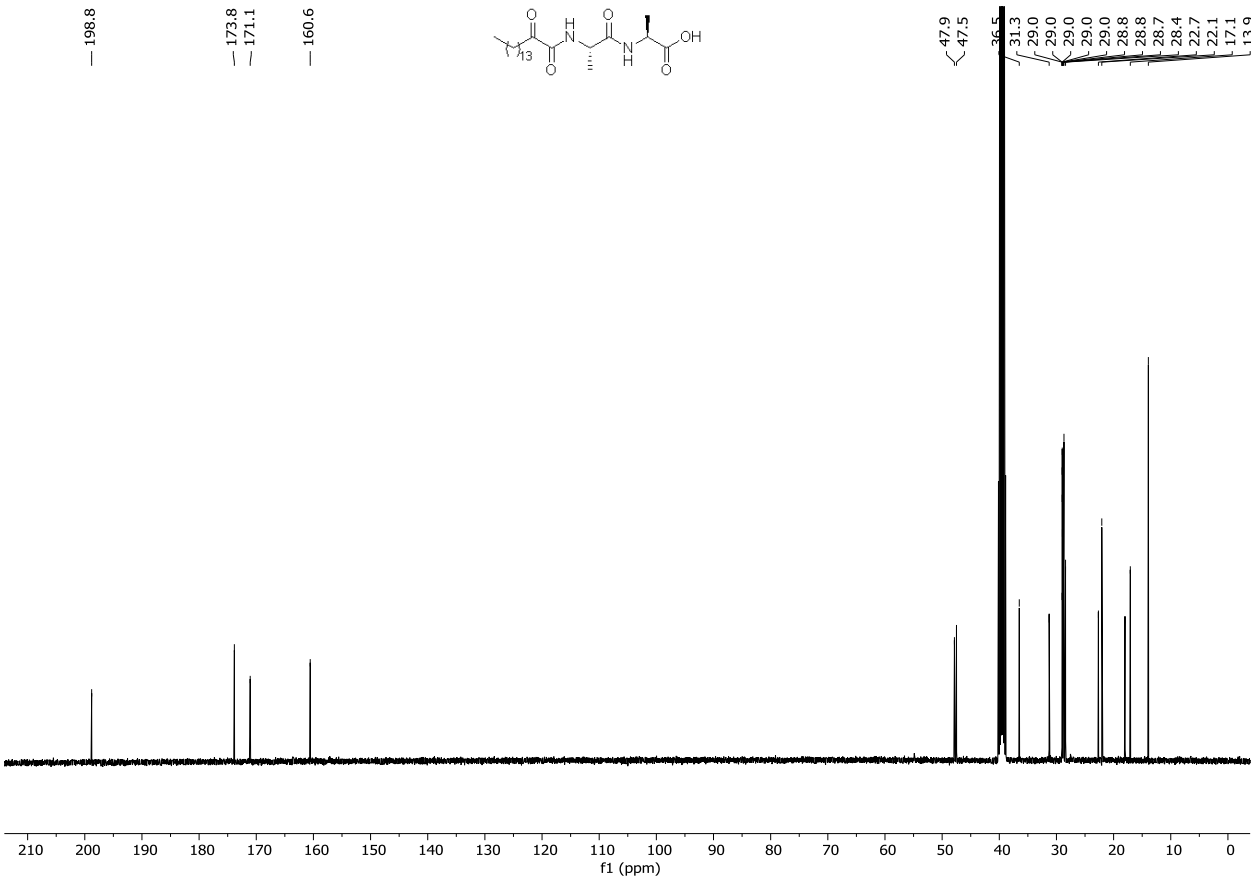

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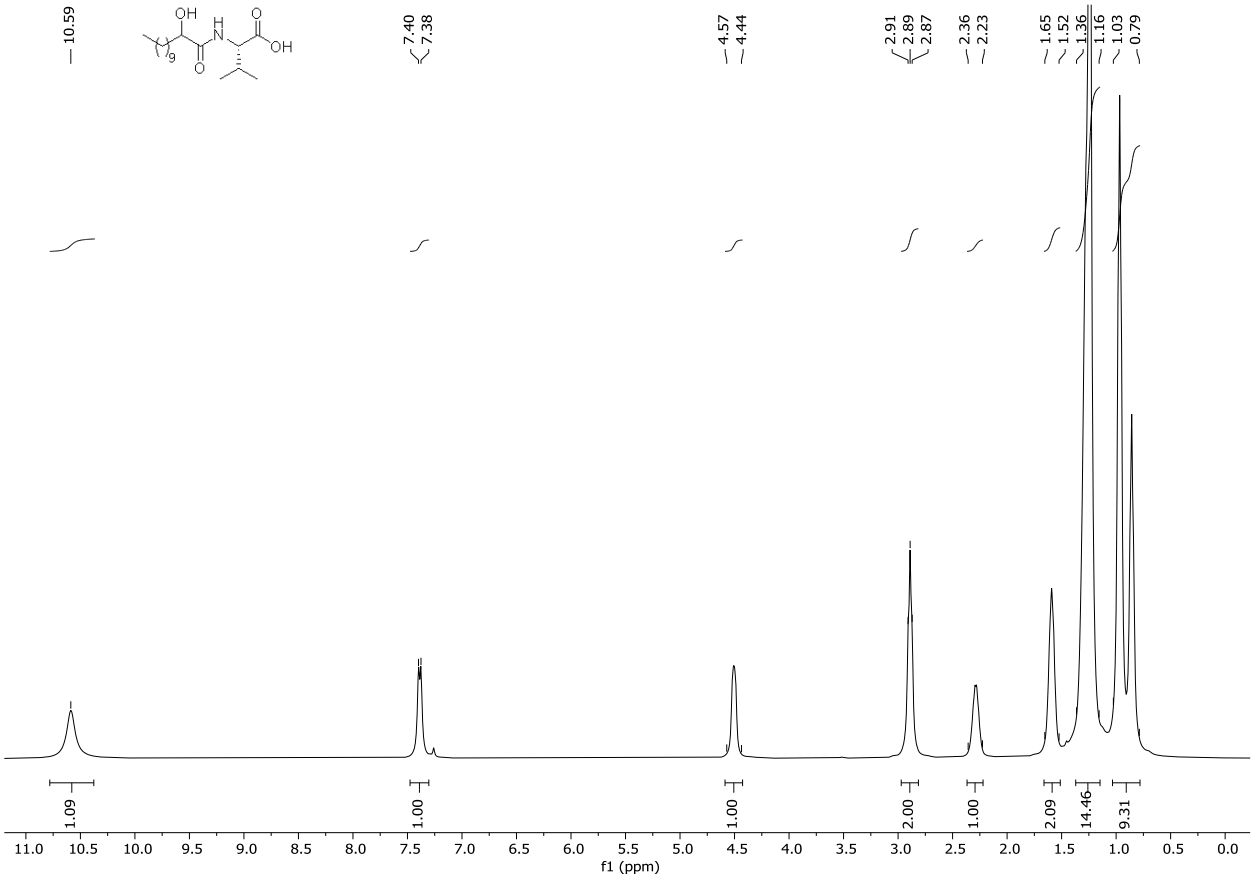

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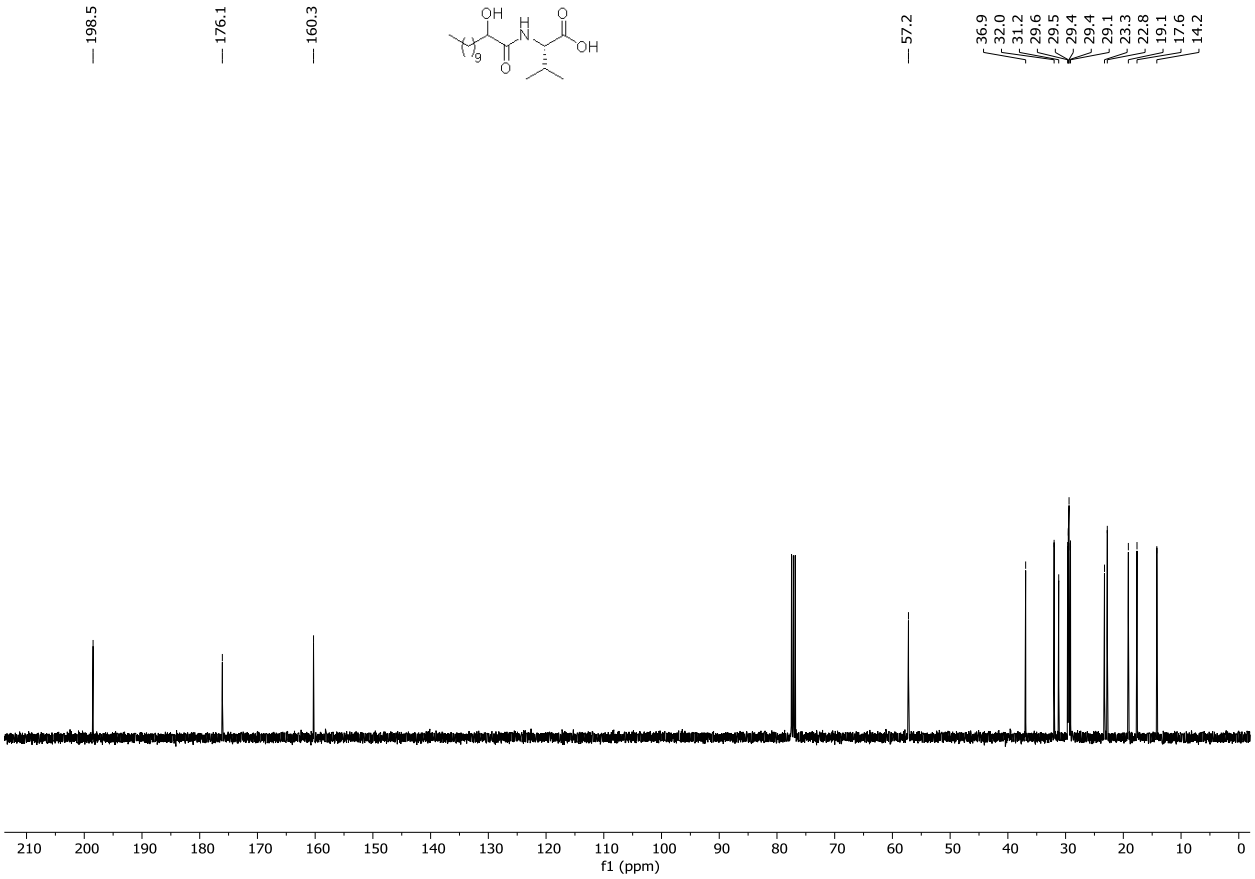

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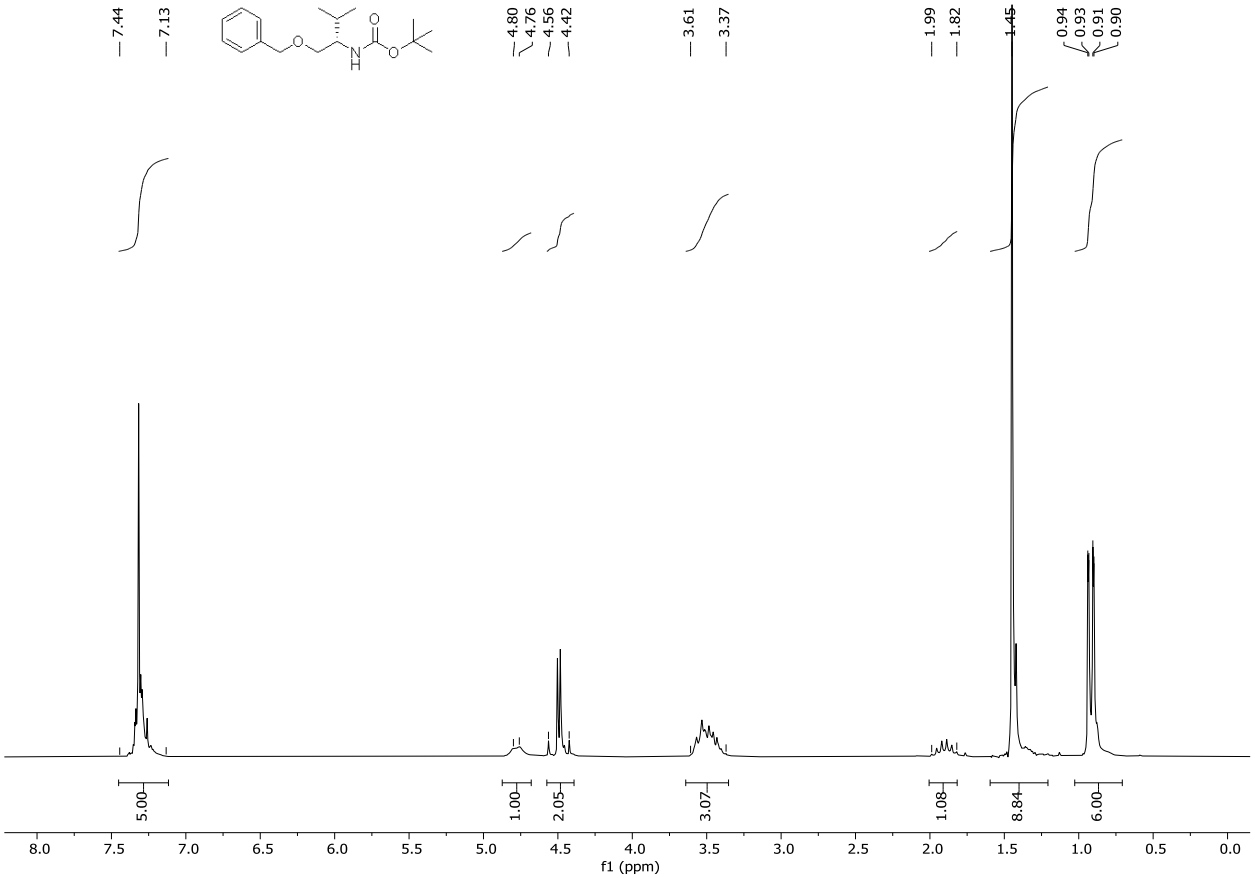

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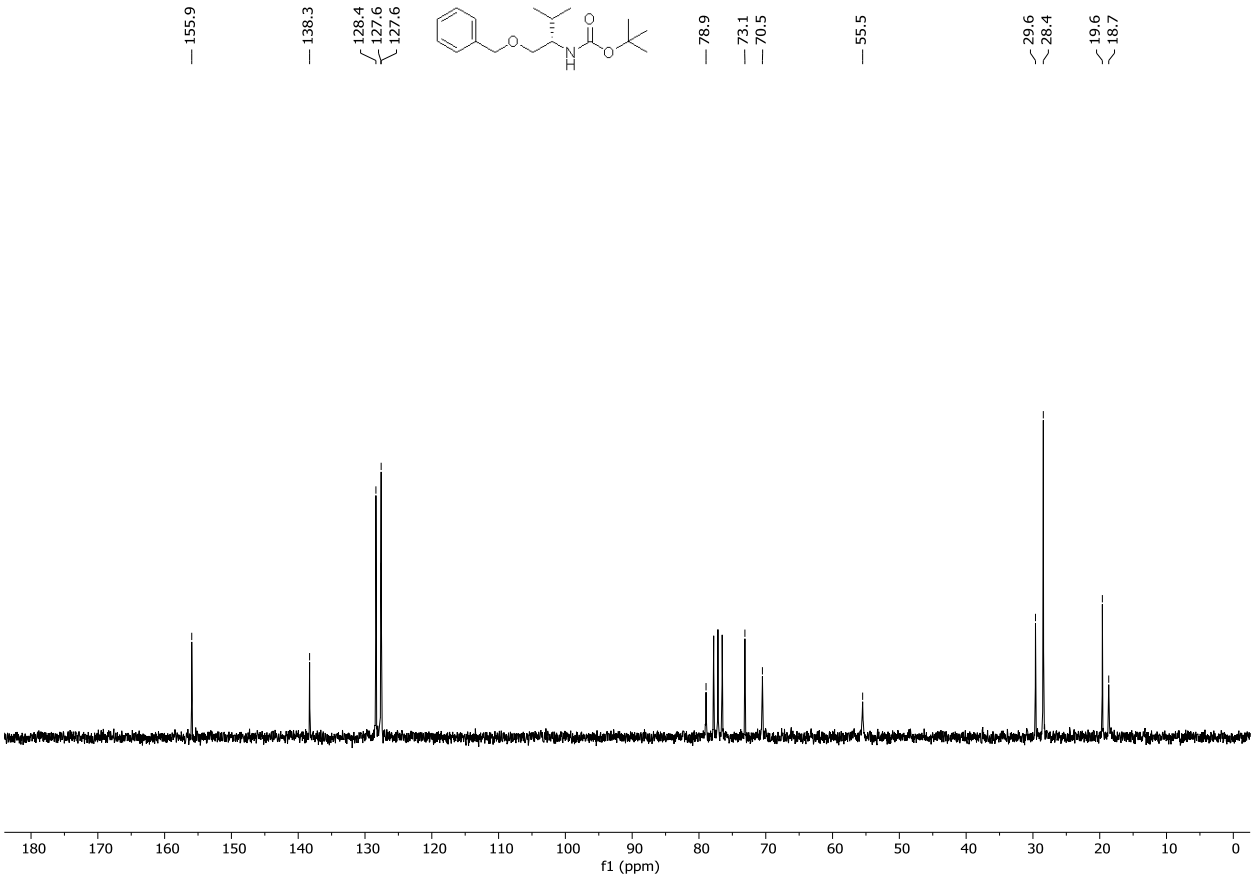

^{13}C NMR spectrum of **10**.