Electronic Supplementary Information

Developing Flow Photo-Thiol-Ene Functionalizations of Cinchona Alkaloids with an Autonomous Self-Optimizing Flow Reactor

Kouakou Eric Konan,[a,b] Elvina Barré,[a] Ehu Camille Aka,[a,b] Abollé Dieurègne Abollé,[b] Vincent Coeffard,[a] and François-Xavier Felpin[a,*]

[a] Université de Nantes, CNRS, CEISAM UMR 6230, 2 rue de la Houssinière, 44322 Nantes, France.

[b] Université Nangui Abrogoua, Laboratoire de Thermodynamique et de Physico-Chimie du Milieu, 02 BP 801 Abidjan 02, Côte d'Ivoire

* Corresponding author. Tel.: +33-025-112-5422; e-mail: fx.felpin@univ-nantes.fr; ORCID: 0000-0002-8851-246X; Website: http://felpin.univ-nantes.fr/

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1. General information

All reagents, starting materials and solvents were obtained from commercial suppliers and used as such without further purification, unless otherwise noted. High-field ^{1}H and ^{13}C NMR spectra were recorded at 300 or 400 and 75 or 100 MHz, respectively. ^{1}H and ^{13}C NMR spectra were referenced to the internal deuterated solvent ($CDCl_3$) at 7.26 and 77.16 ppm, respectively and Coupling constants were measured in Hertz. All chemical shifts were quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. FT-IR spectra were recorded in the ATR mode. Wavelengths of maximum absorbance (ν_{max}) are shown in wave numbers (cm^{-1}). High resolution mass spectrometry (HRMS) was recorded on a microTOF spectrometer equipped with orthogonal electrospray interface (ESI). Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254), and visualization was accomplished with UV light at 254 nm. Flash column chromatography was performed using silica gel 60 (40−63 μm).

2. Optimization algorithm

The optimization algorithm here used has been described in our previous reports.[1, 2]

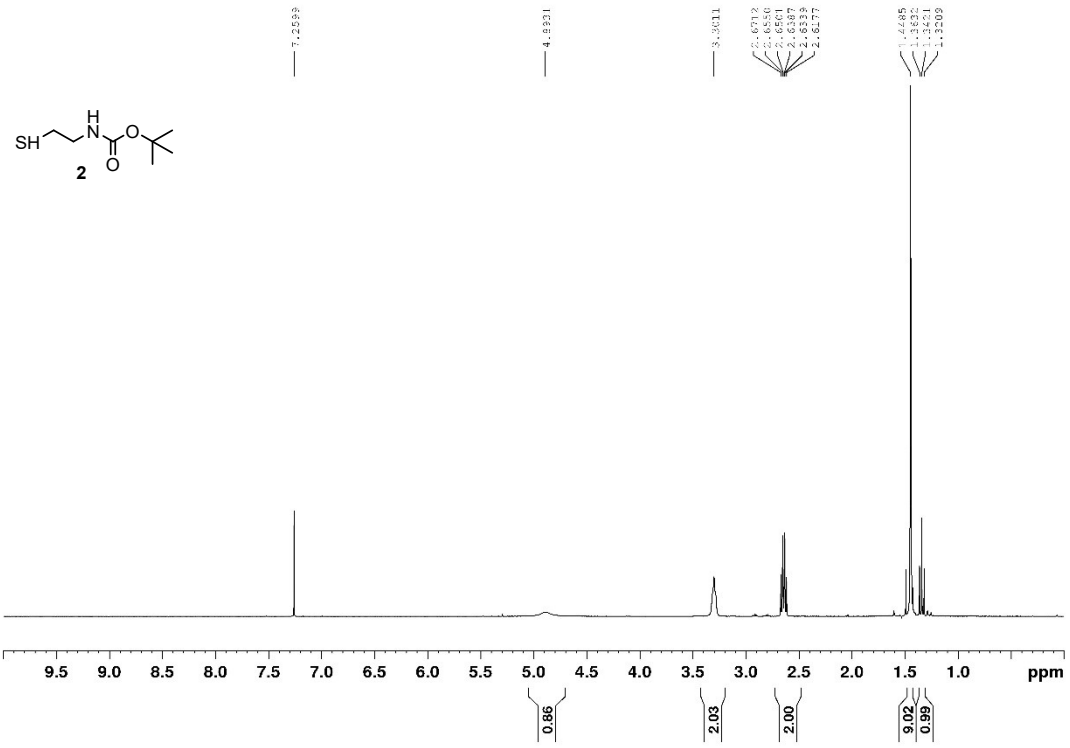
3. Details of the experimental setup. HPLC pumps (JASCO PU2080) equipped with a RS-232 port were employed to flow the solution through the system. A sampler handler (JASCO AS 2055) equipped with a RS-232 port was used to inject reagent in the line. The reactor coil was heated with a heating plate (Heidolph, MR Hei-Connect) equipped with a RS-232 port. A 2-way 6-port valve (VICI, Cheminert C2-3006D) equipped with a RS-232 port was used to inject an aliquot of the crude mixture within the on-line HPLC unit. The HPLC column outlet was connected to a UV detector (JASCO, UV 2075) equipped with a RS-232 port. The flow outlet was connected to a programmable fraction collector (Advantec, CHF 1225C). All units equipped with a RS-232 port were autonomously controlled with MATLAB® through the use of communication protocols provided by the manufacturers.

4. Optimization studies thiol-ene reaction

Table S1. Maximization of the yield of quinine derivative **3a**

Experiment	DMPA (equiv.)	Thiol (equiv.)	Residence time (min)	Yield (%)
1	1.0	1.0	10.0	13
2	1.3	1.0	10.0	19
3	1.0	2.0	10.0	32
4	1.0	1.0	20.0	68
5	1.2	1.7	16.7	81
6	1.3	2.0	20.0	94
7	0.9	2.3	23.3	94
8	1.1	1.6	32.2	91
9	**1.2**	**2.9**	**30.0**	**99**

5. NMR Spectra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H
N
O
O
2
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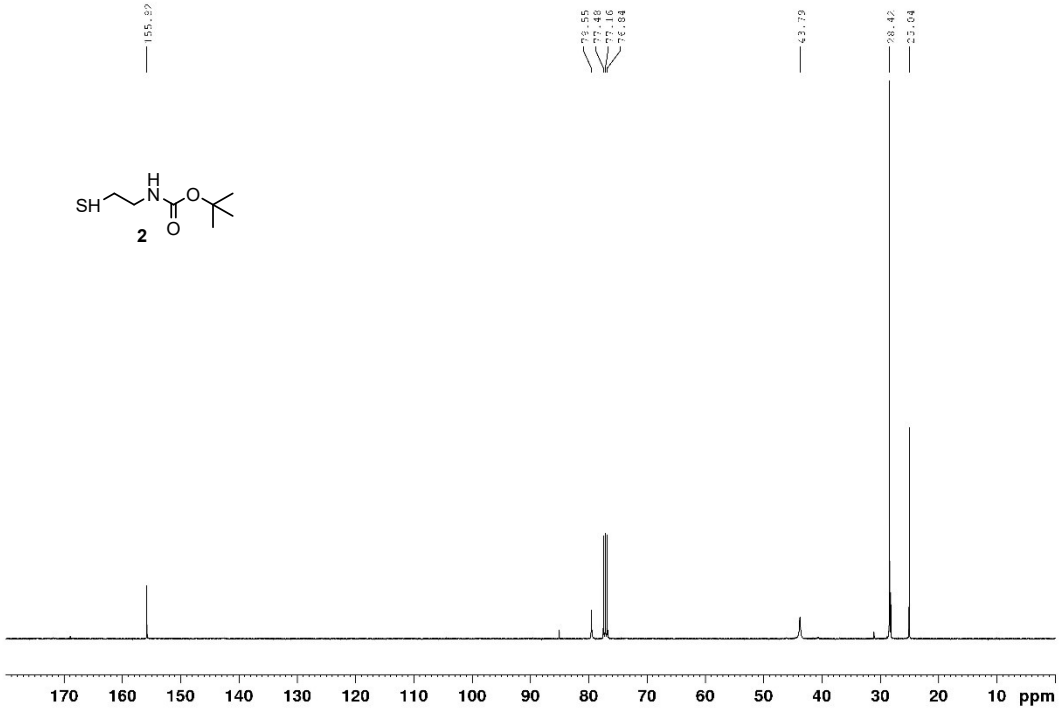
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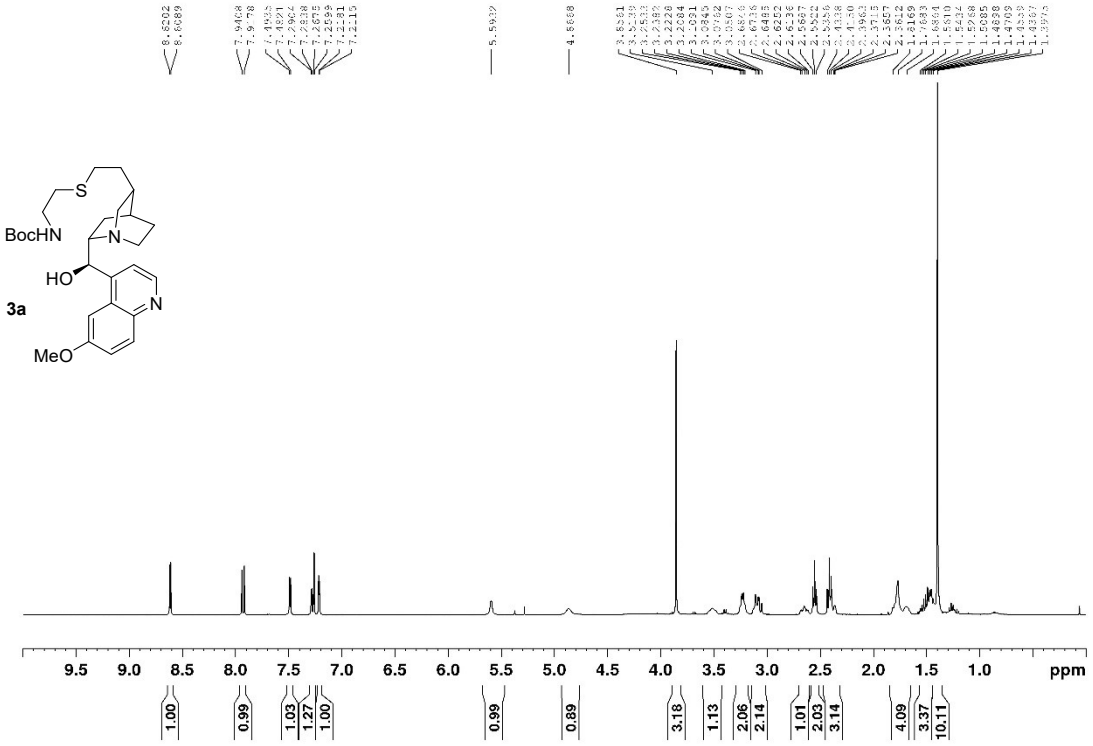
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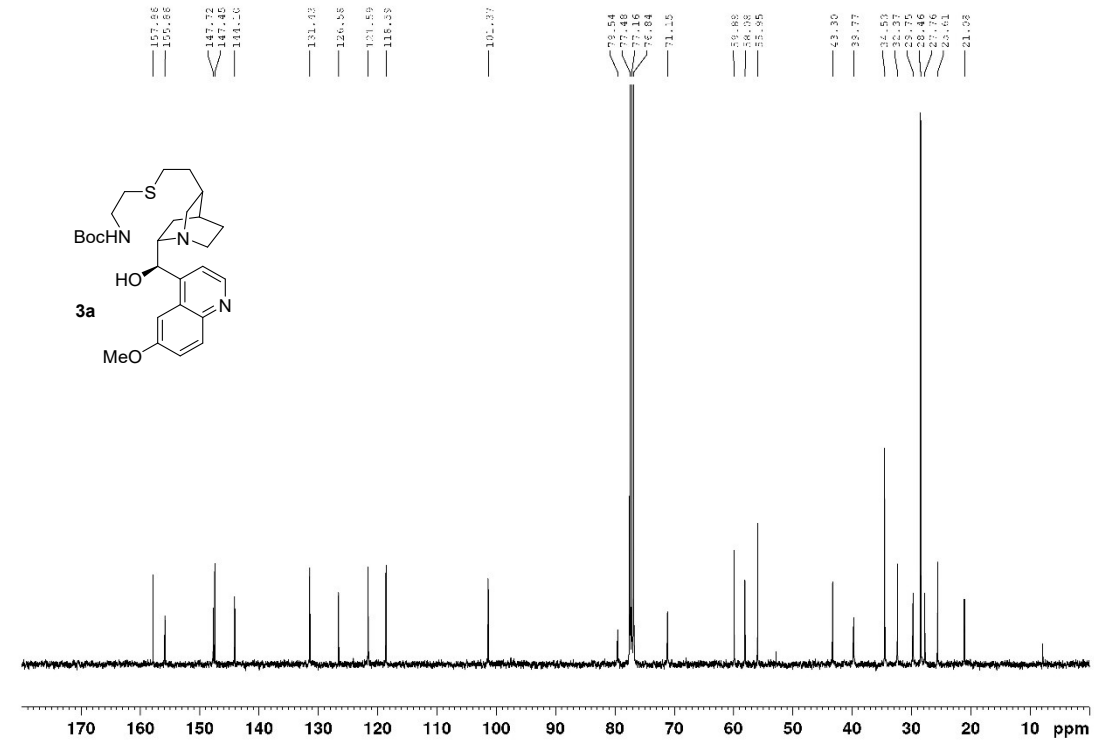
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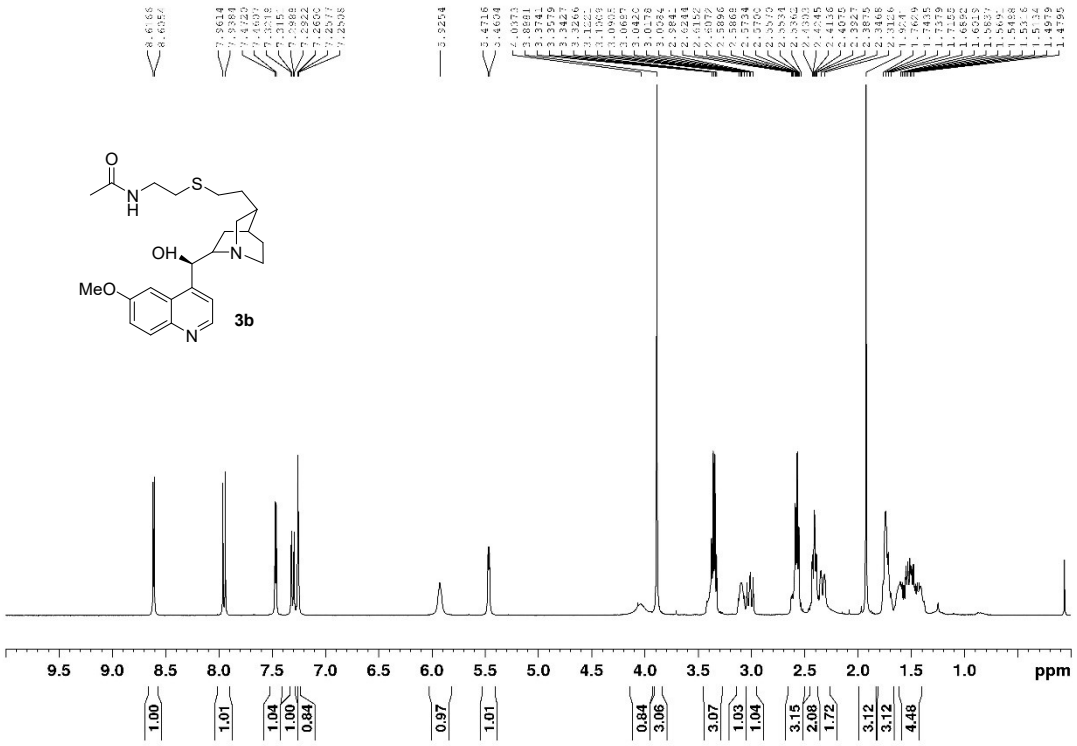
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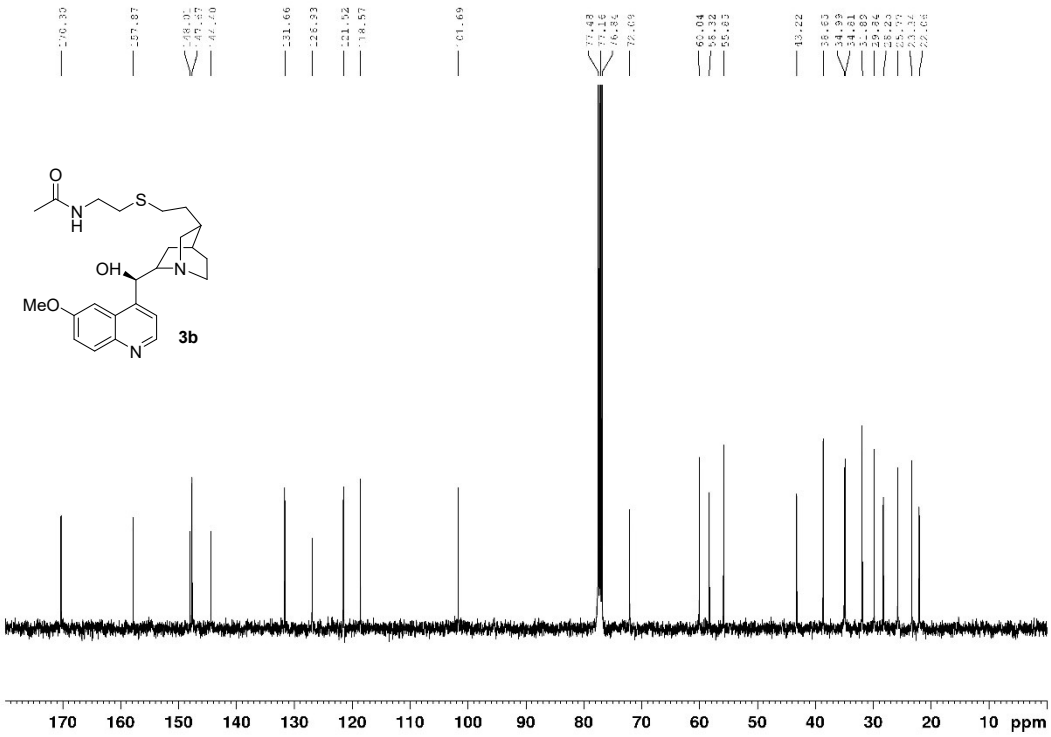
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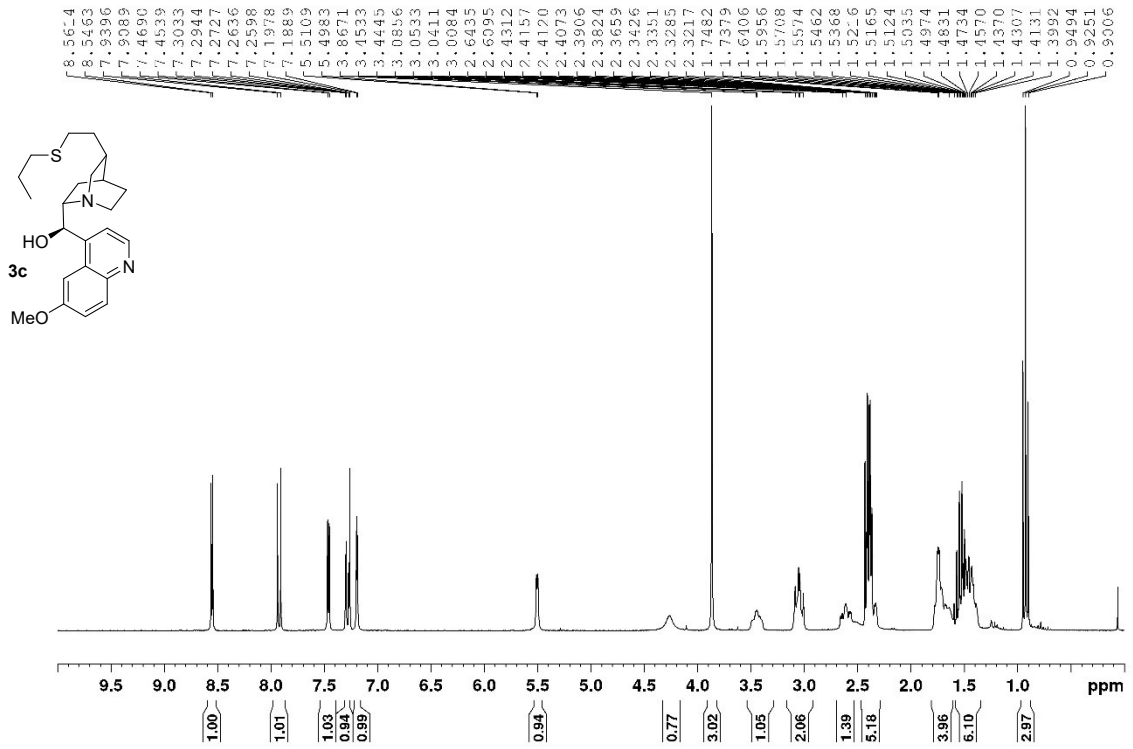
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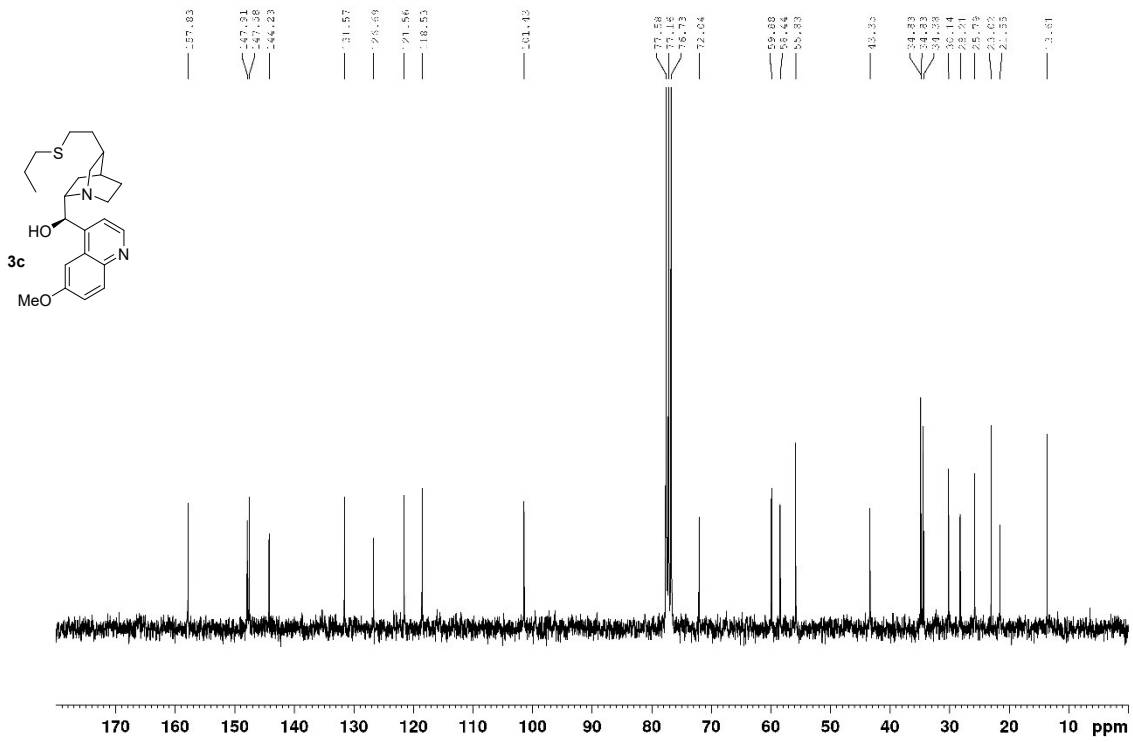
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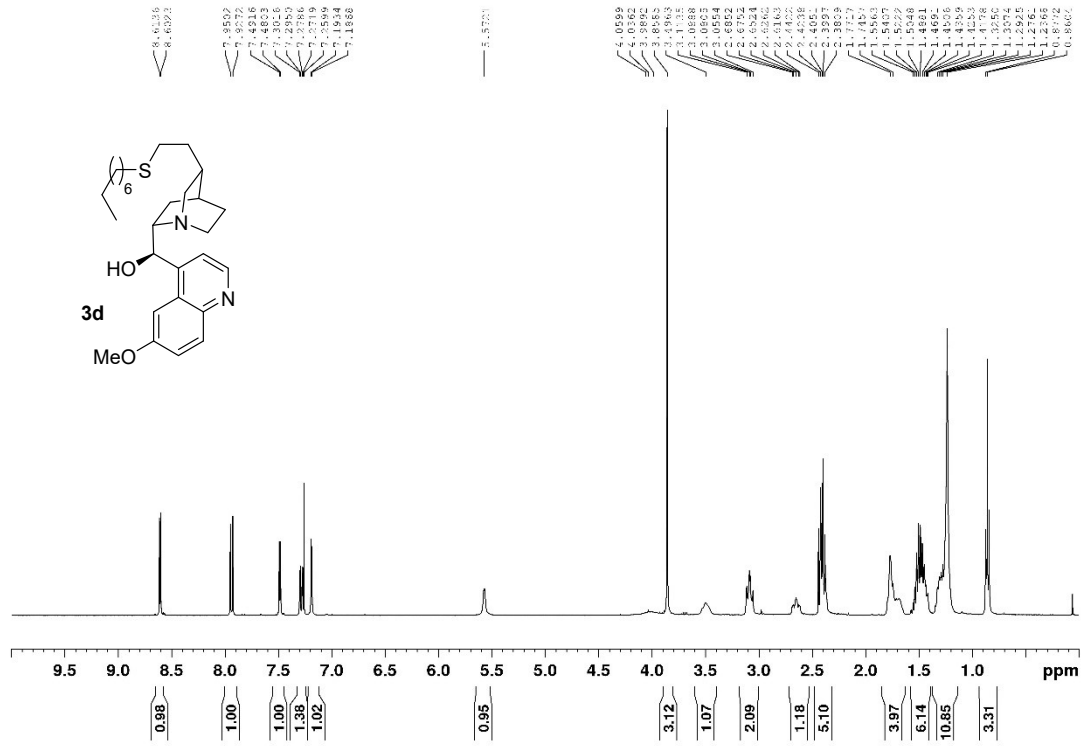
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N
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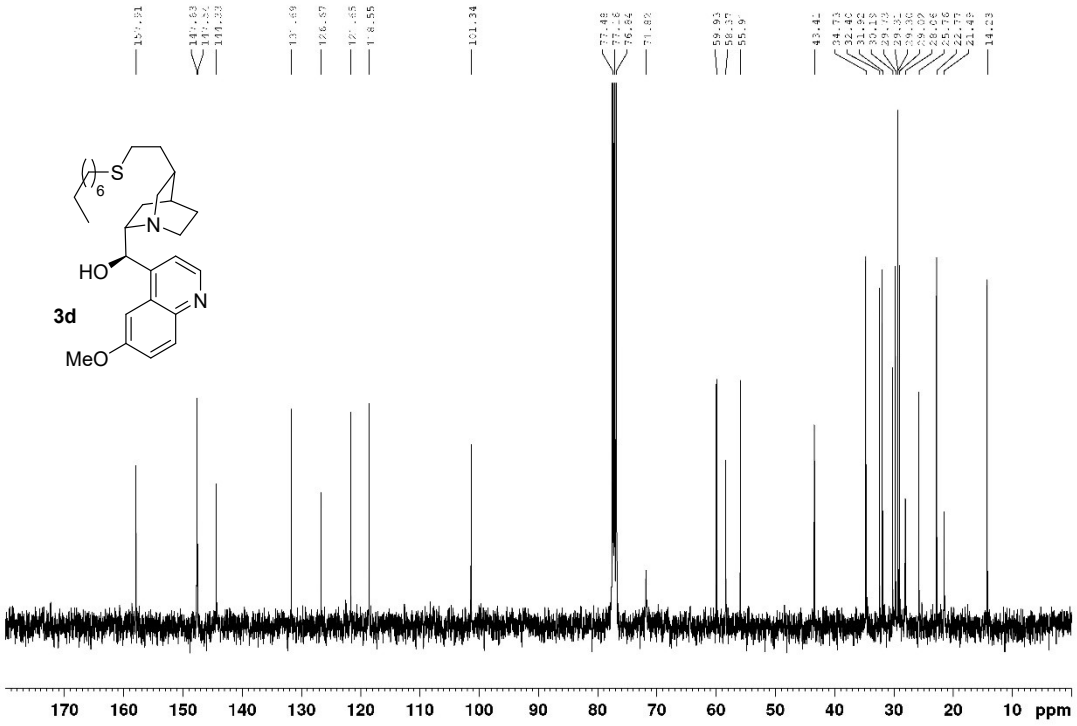
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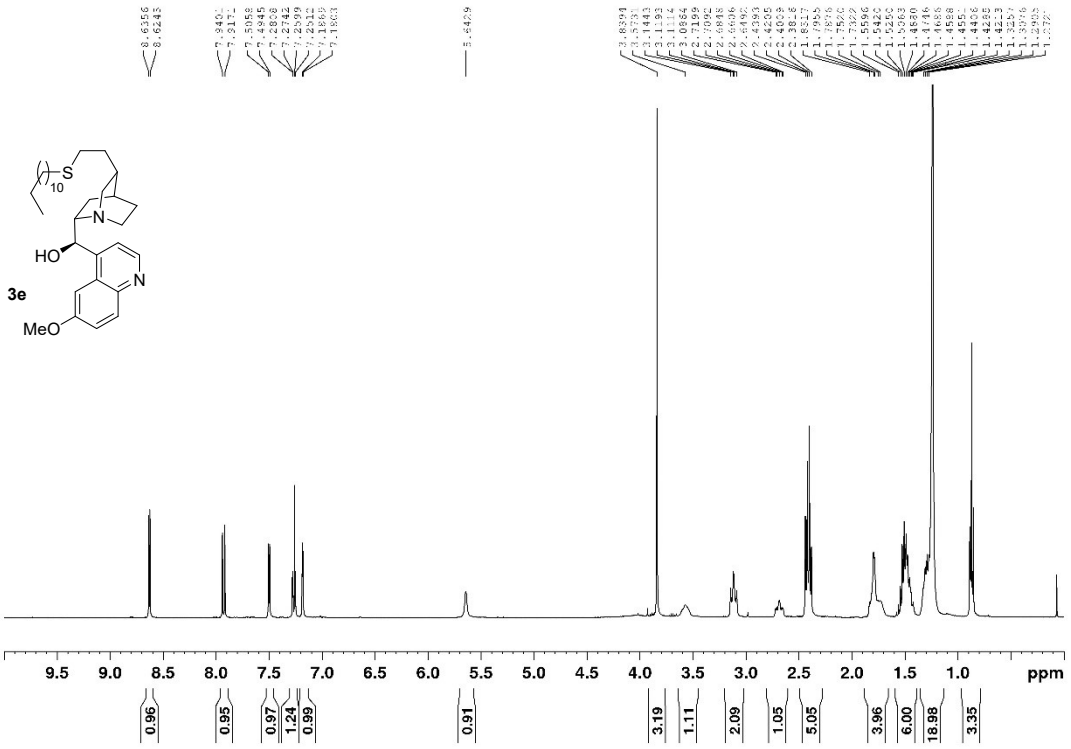
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S
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0.96
0.95
0.97
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2.09
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5.05
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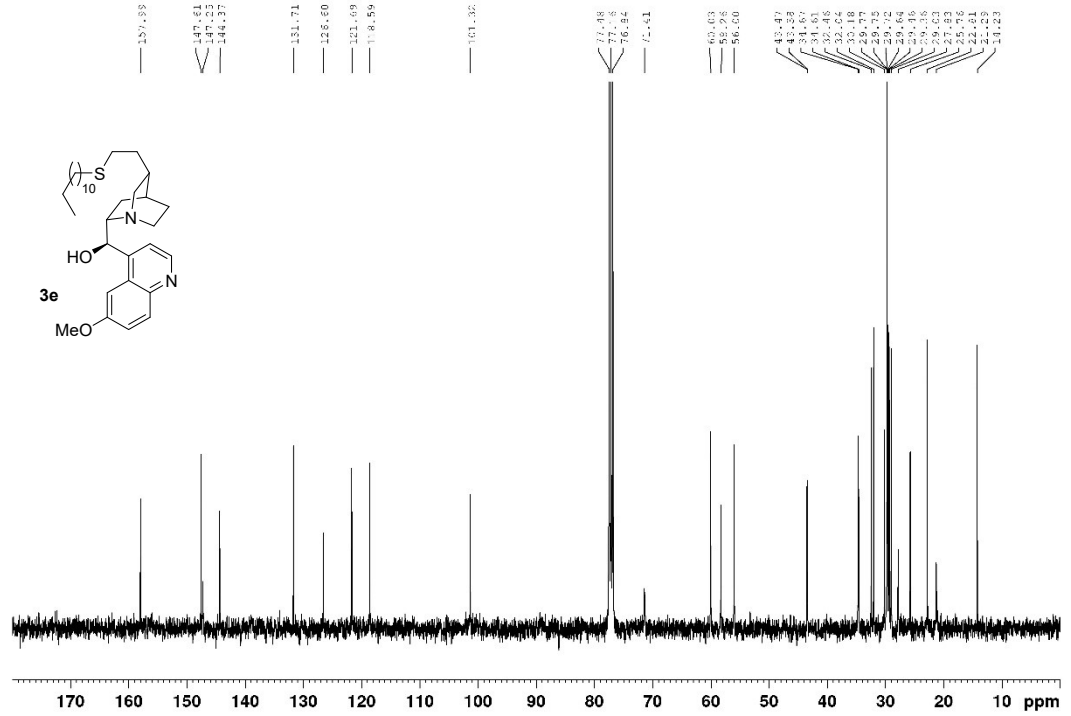
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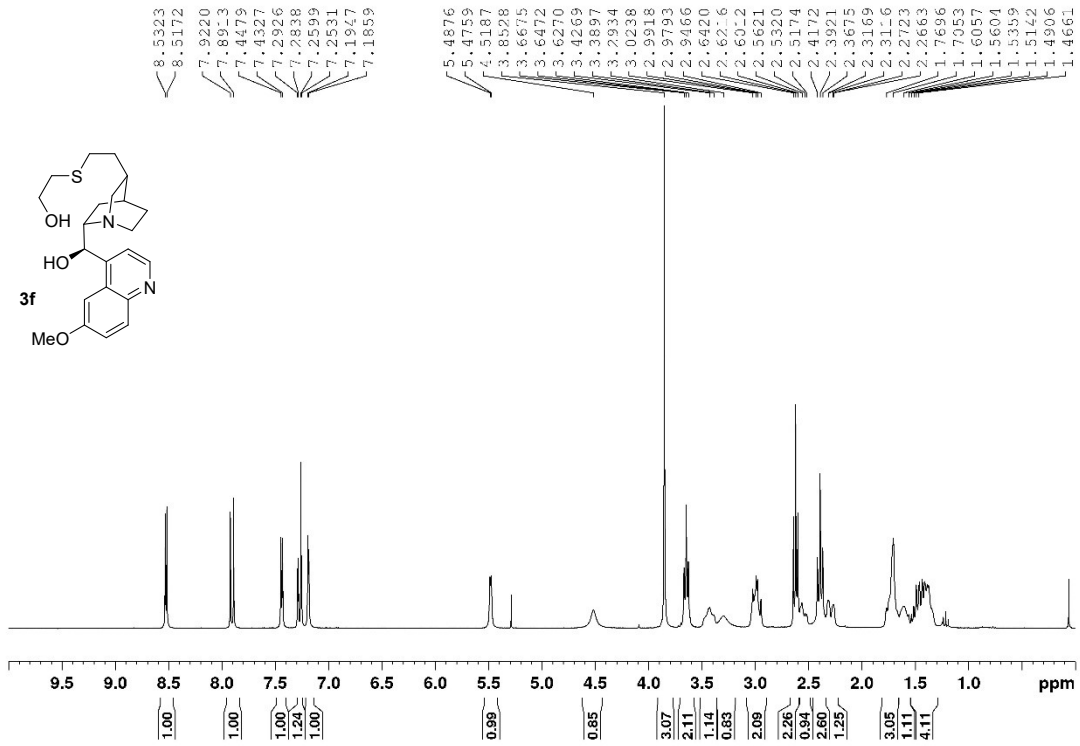
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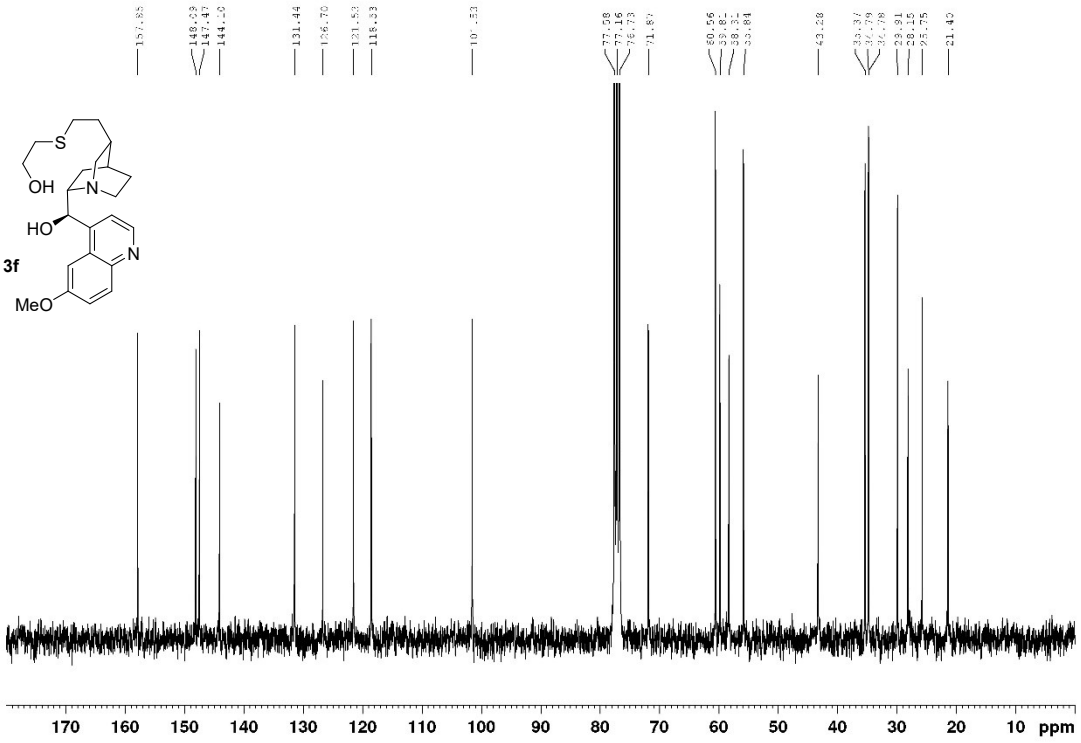
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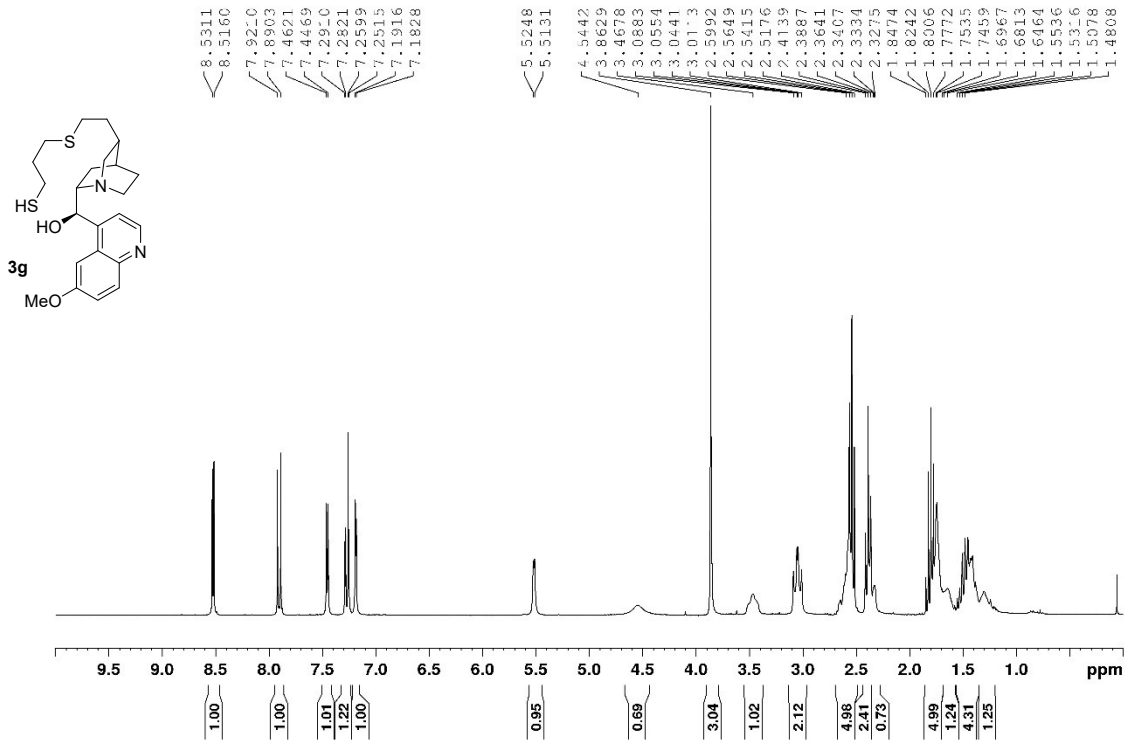
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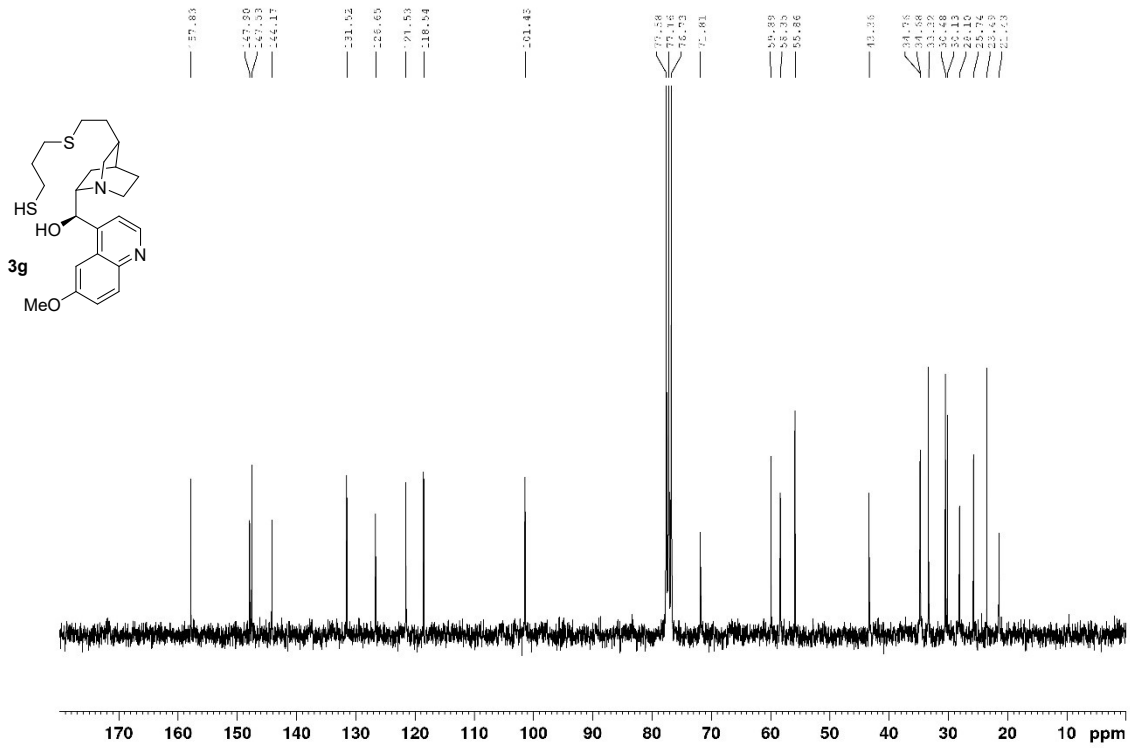
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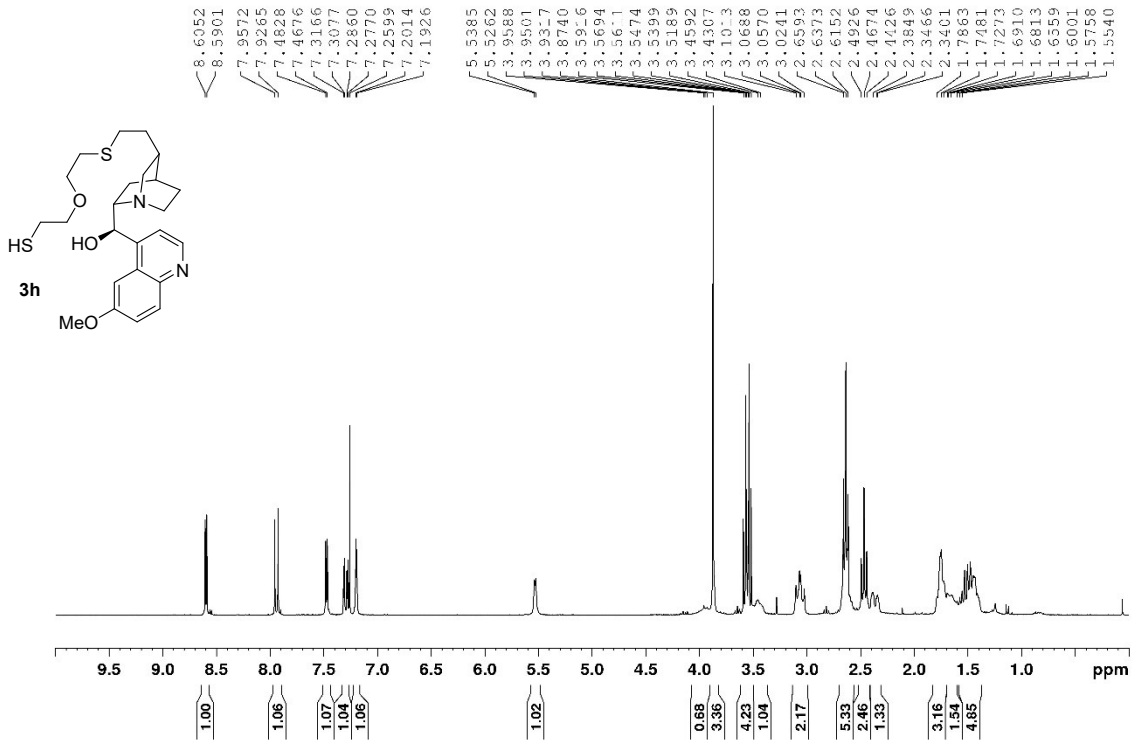
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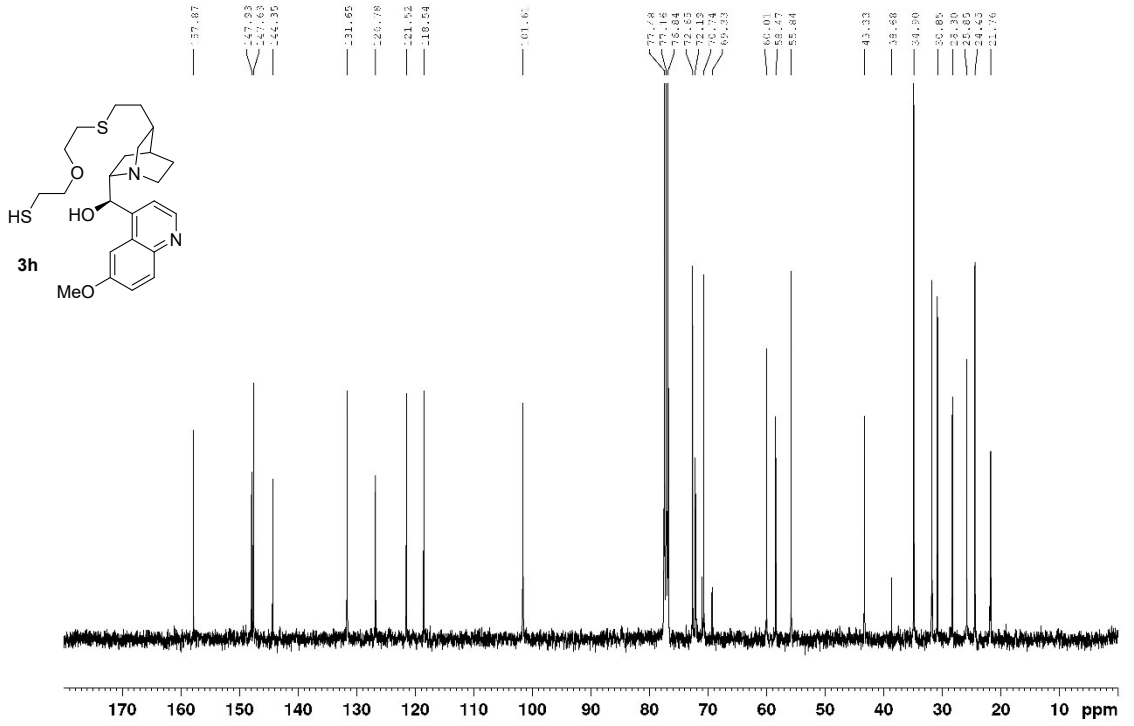
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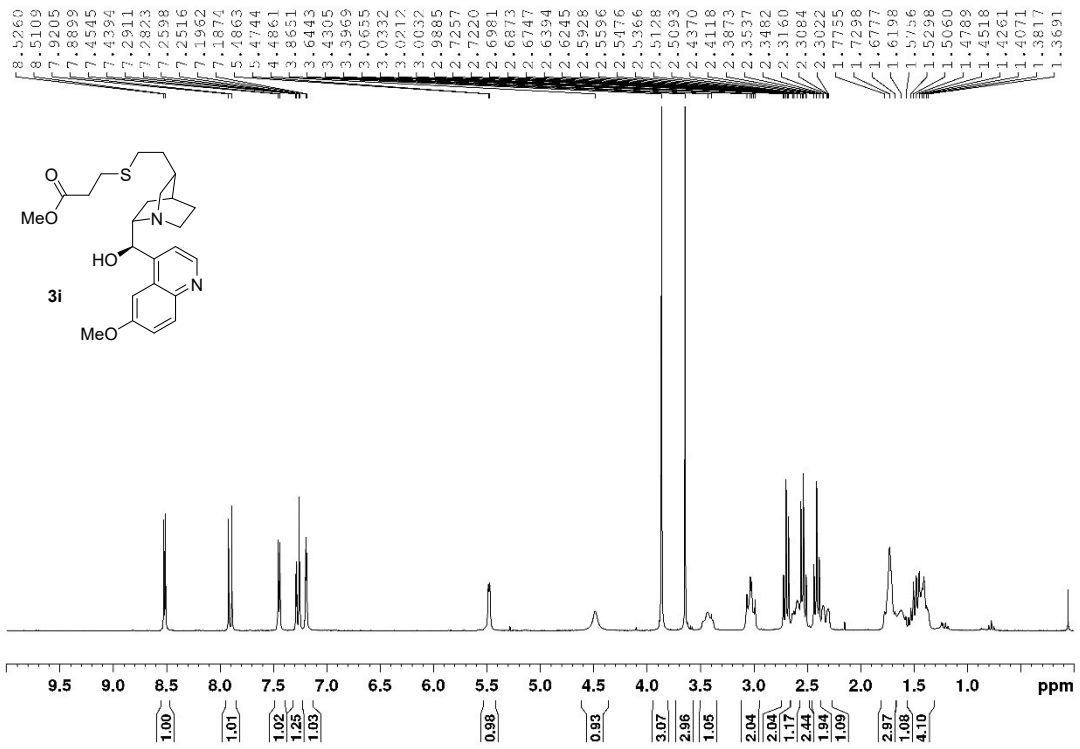
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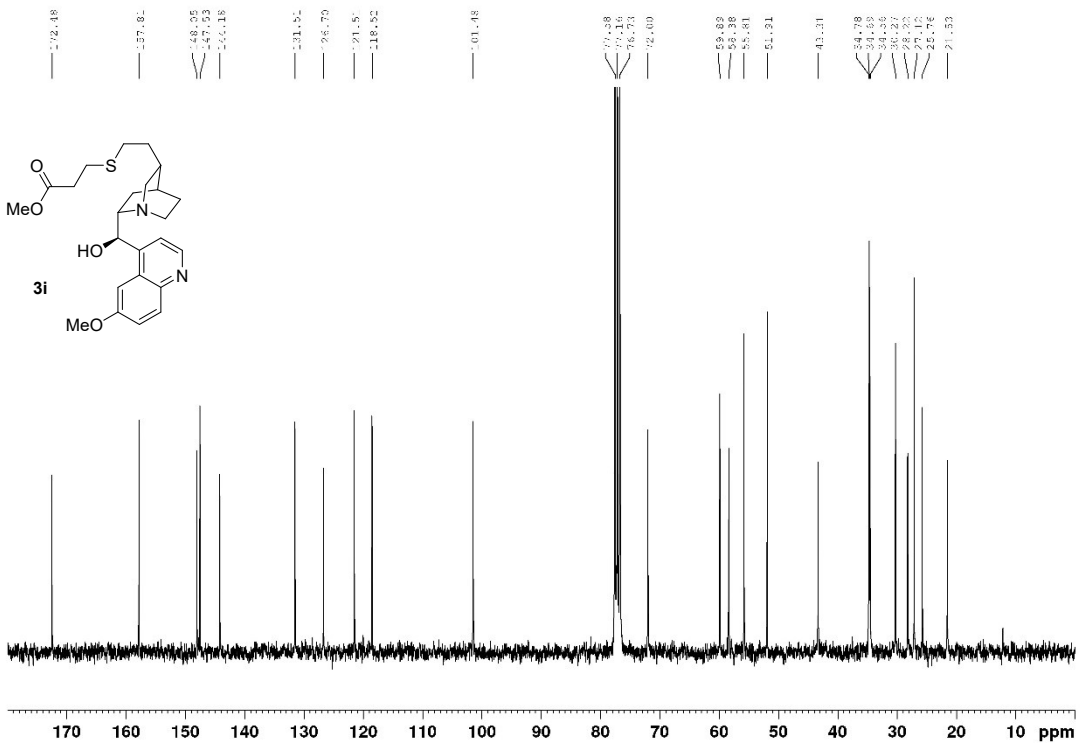
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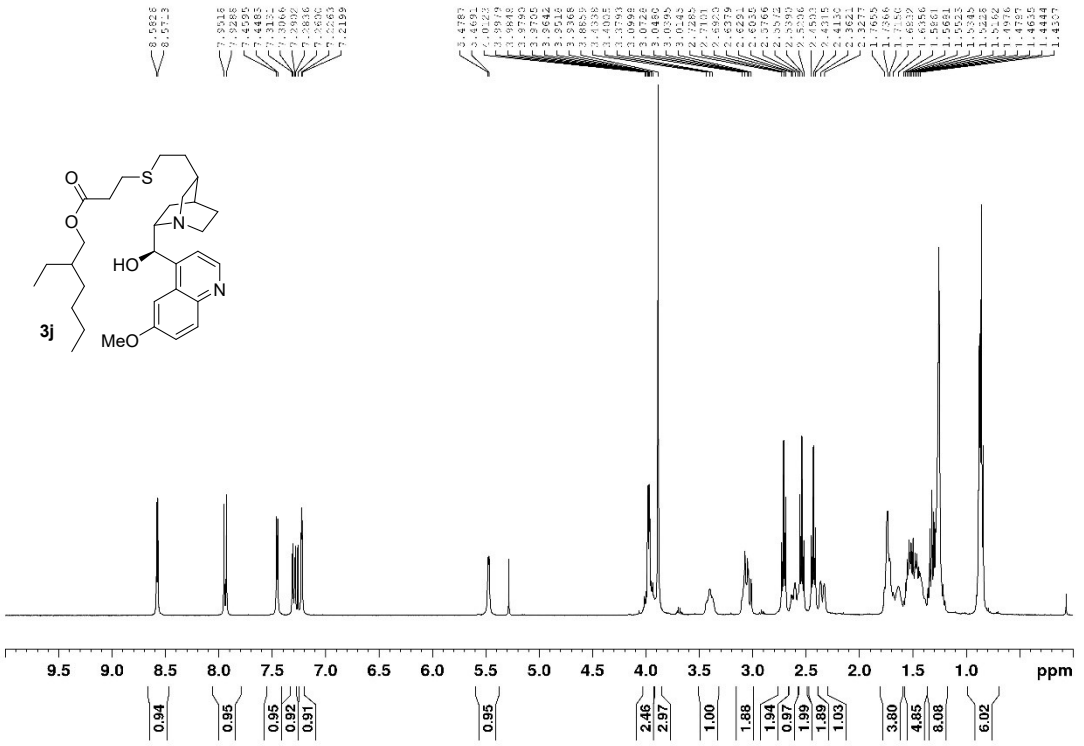
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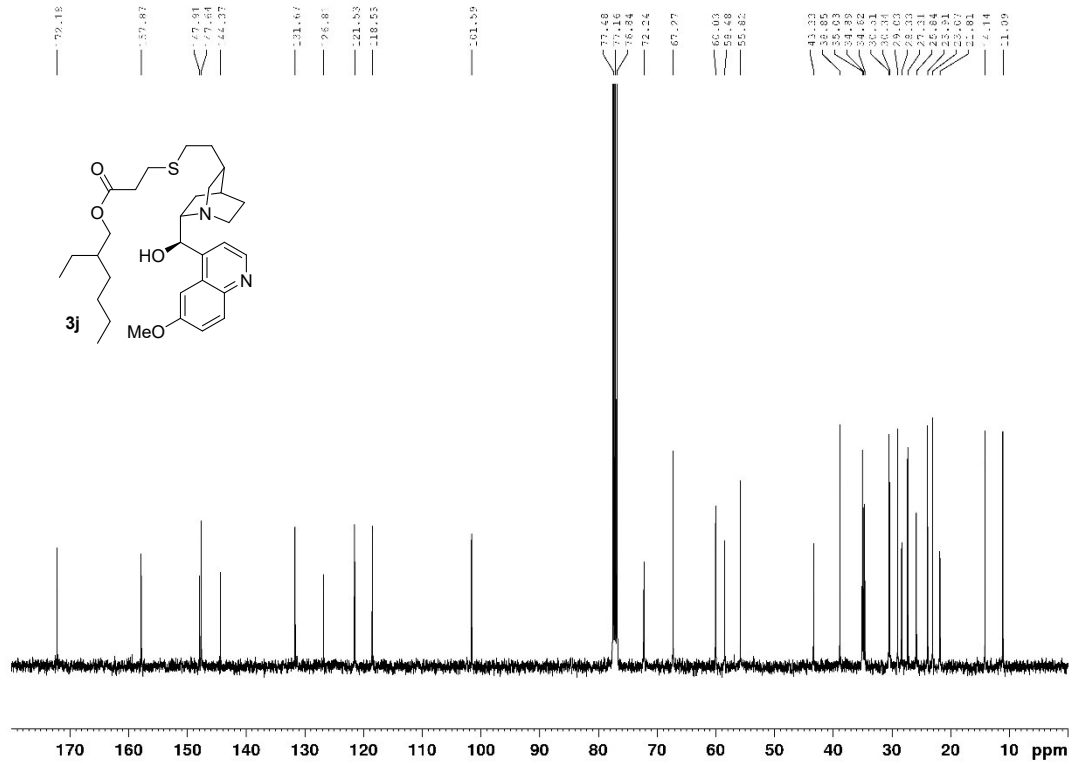
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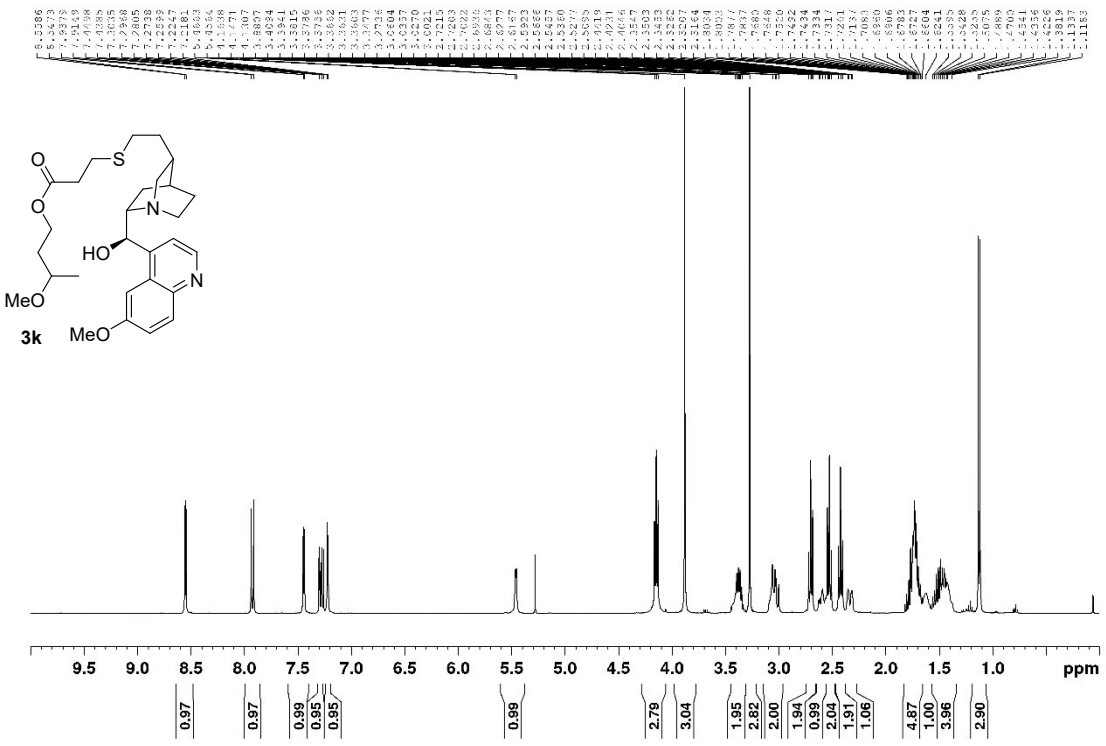
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MeO
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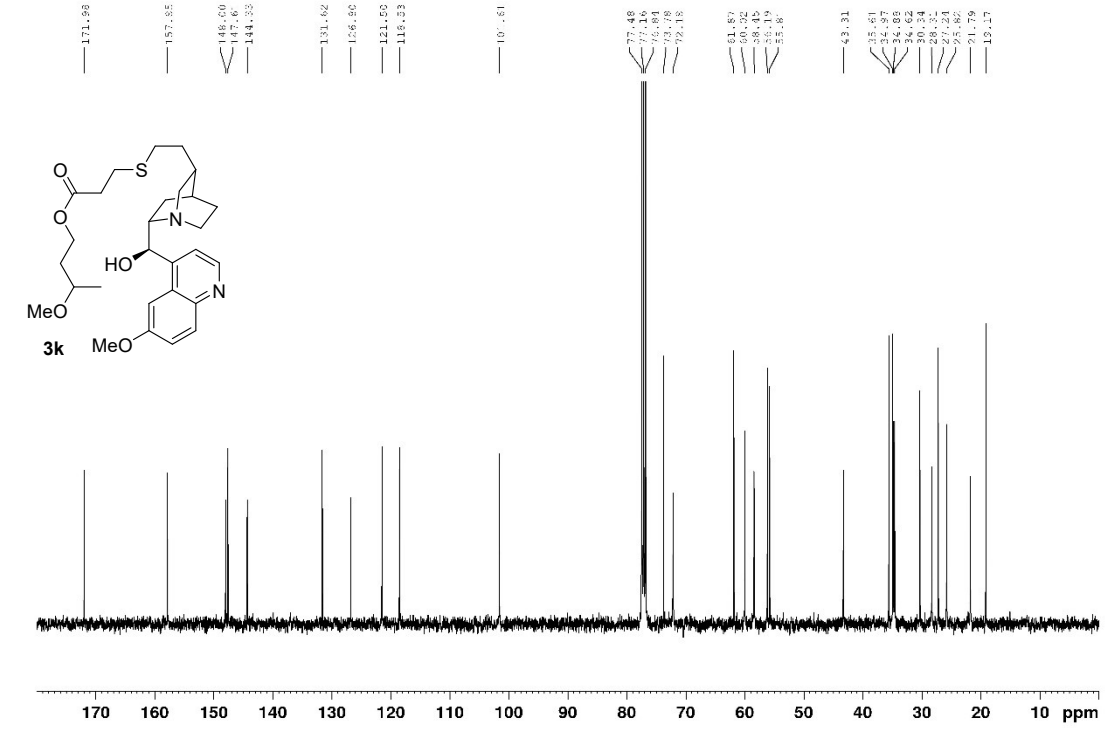
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35.61
34.97
34.89
34.62
30.34
28.31
27.41
25.82
21.79
13.17
O
O
S
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HO
N
MeO
MeO
3k
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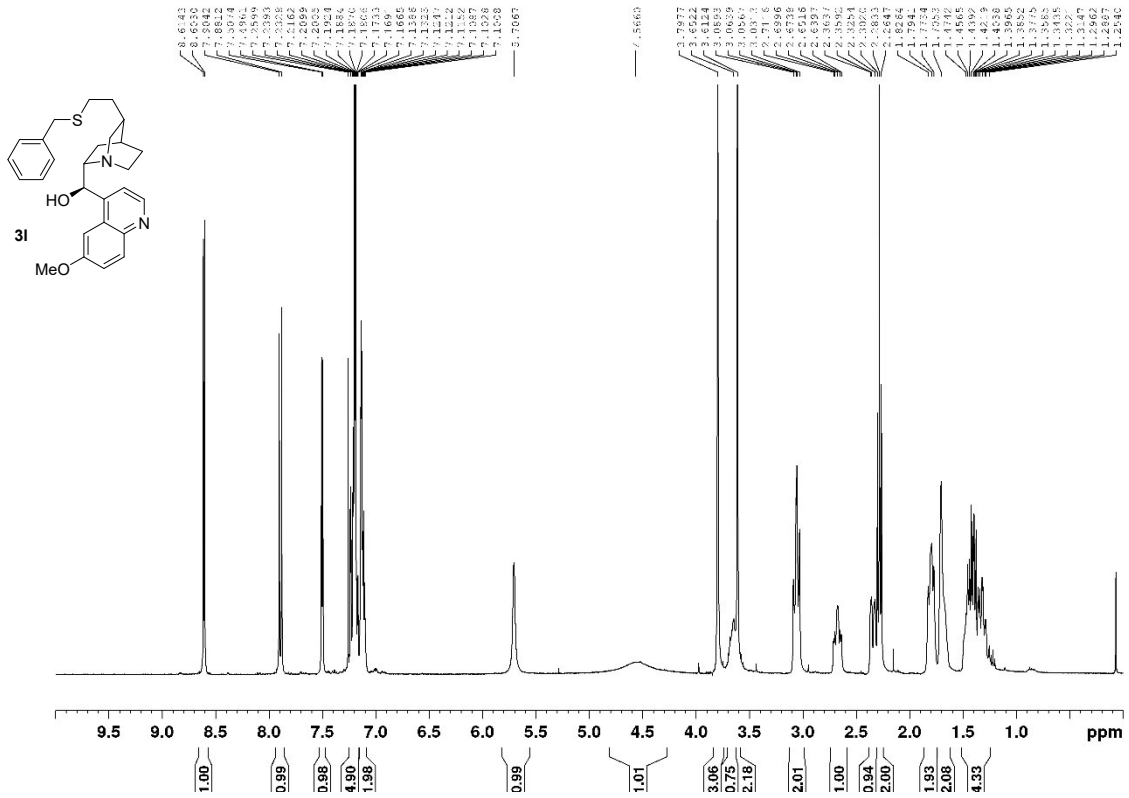
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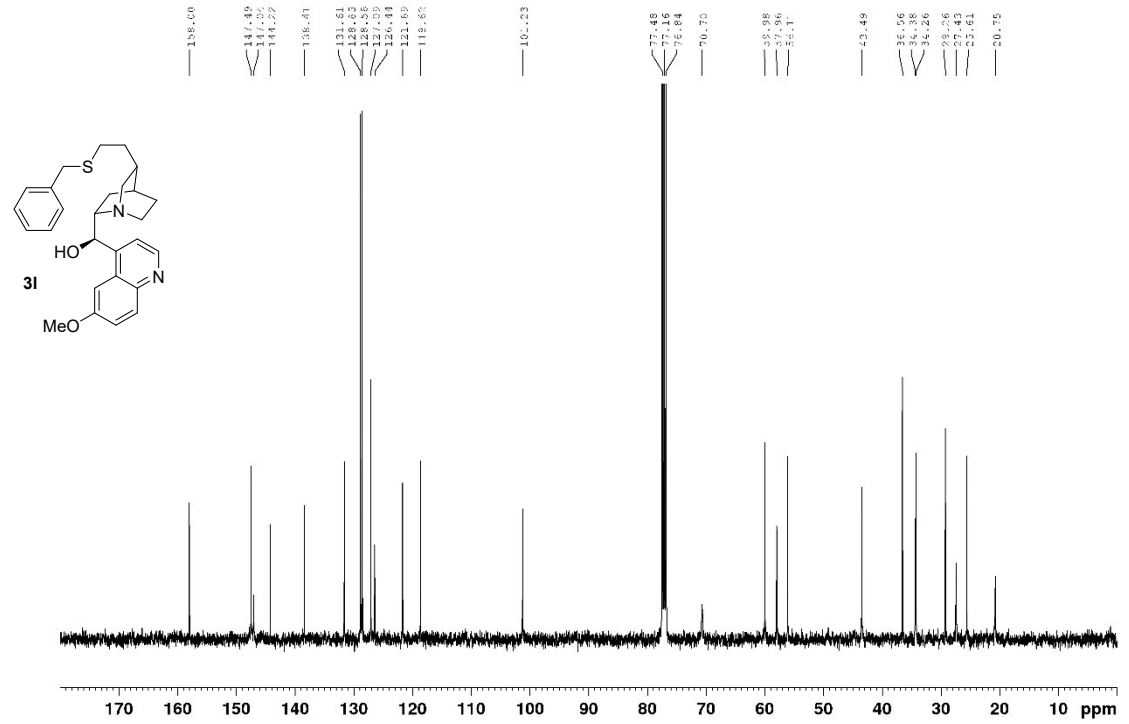
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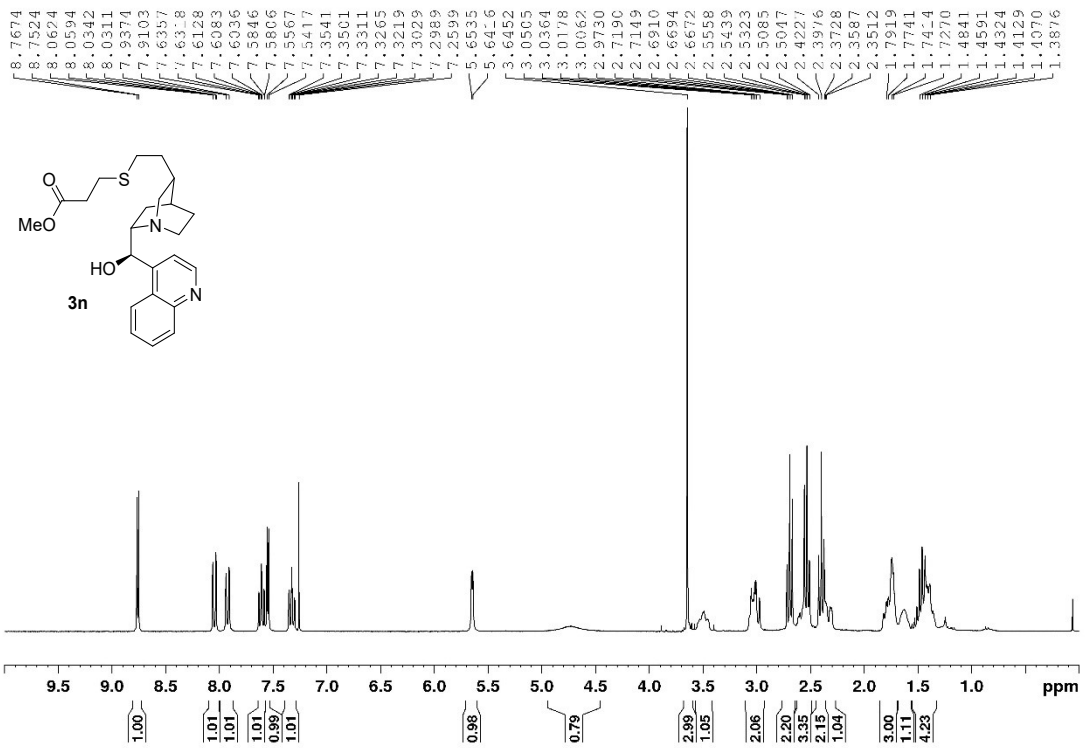
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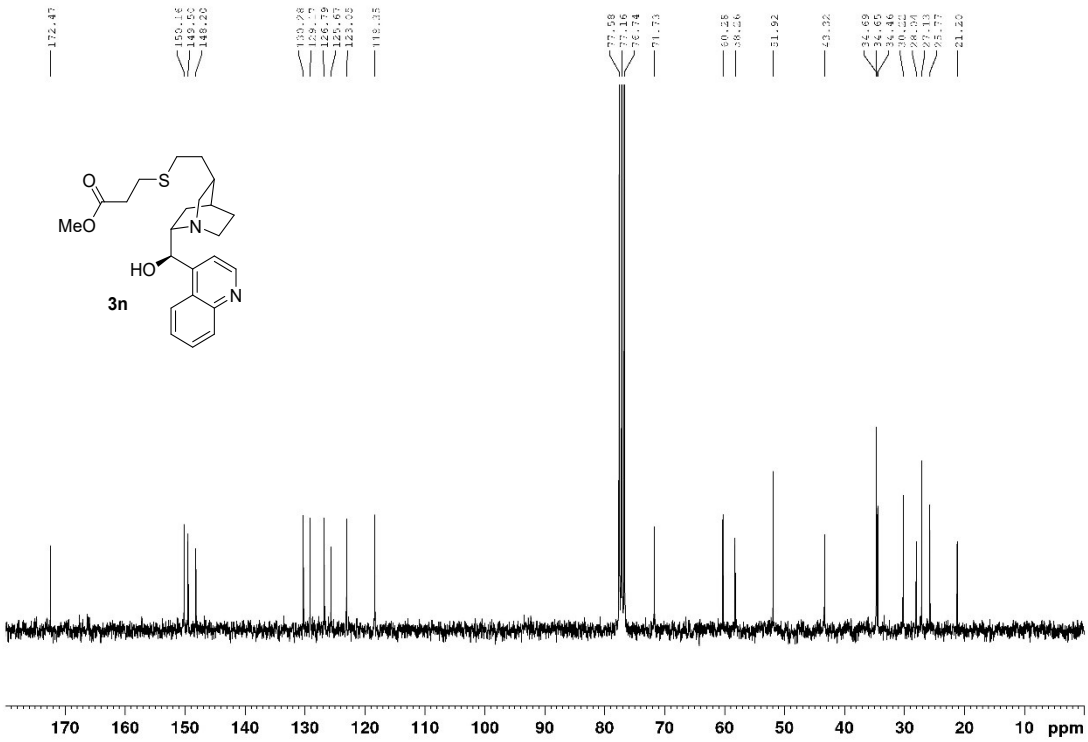
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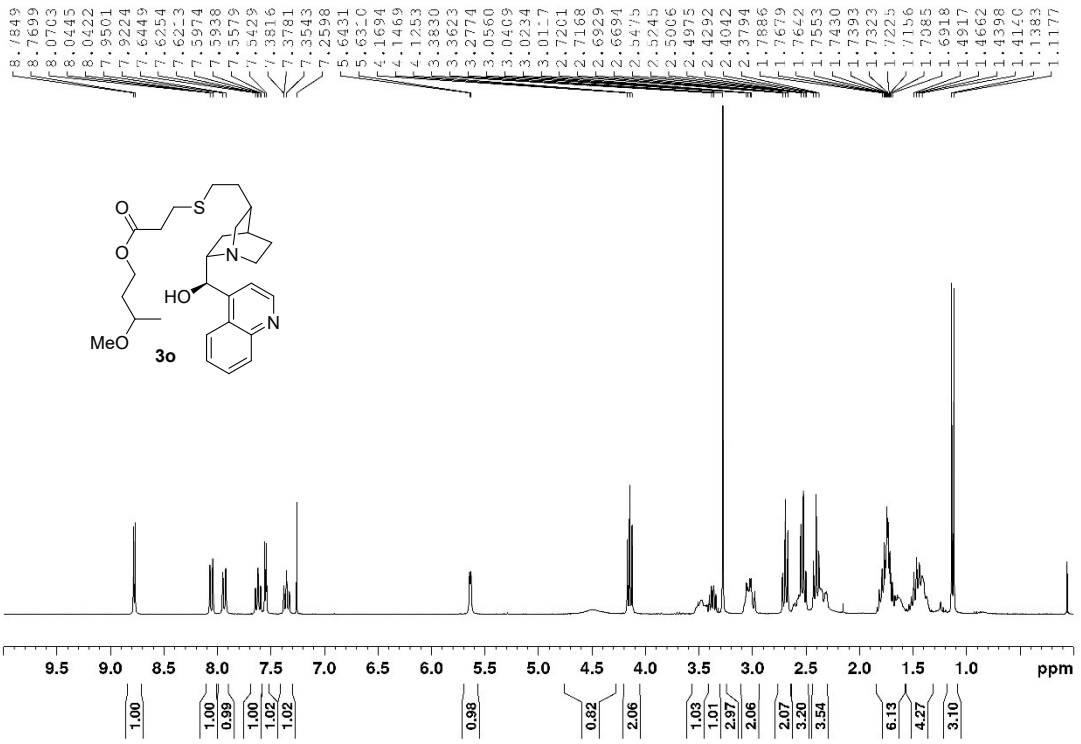
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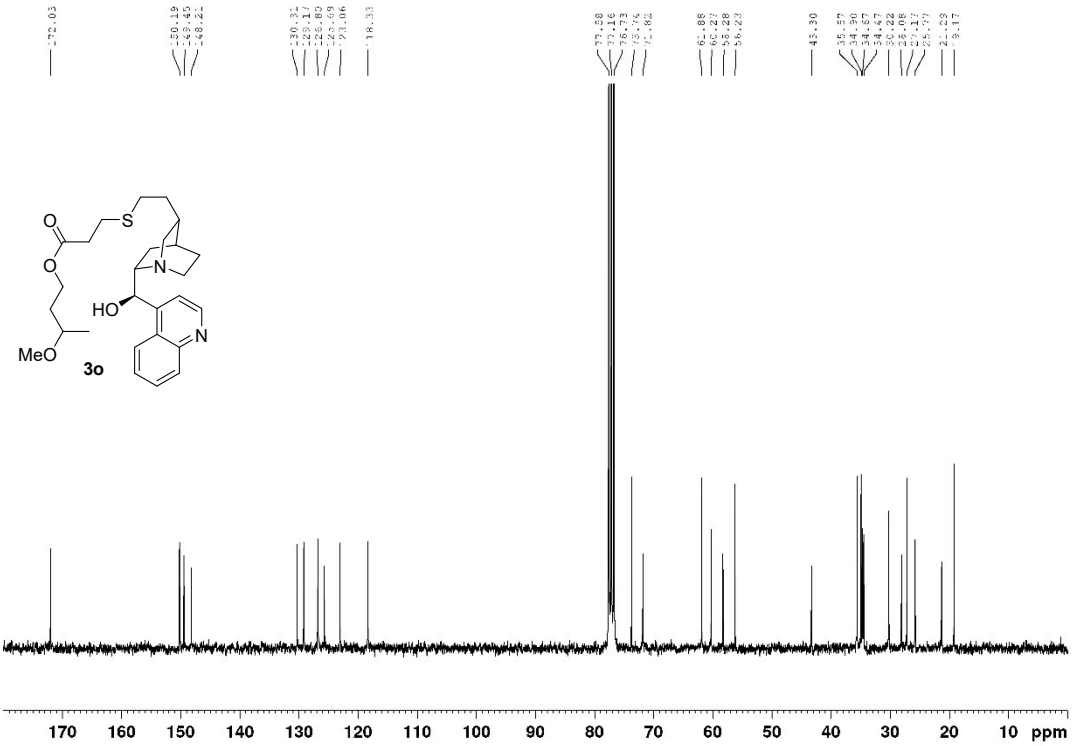
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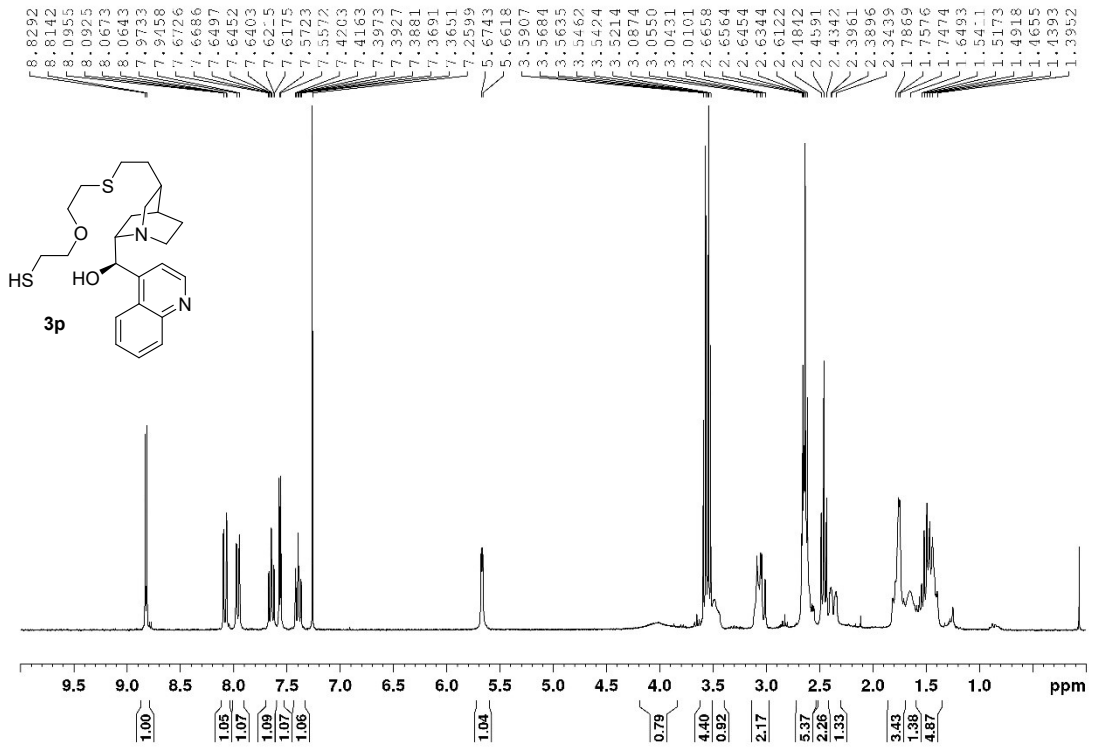
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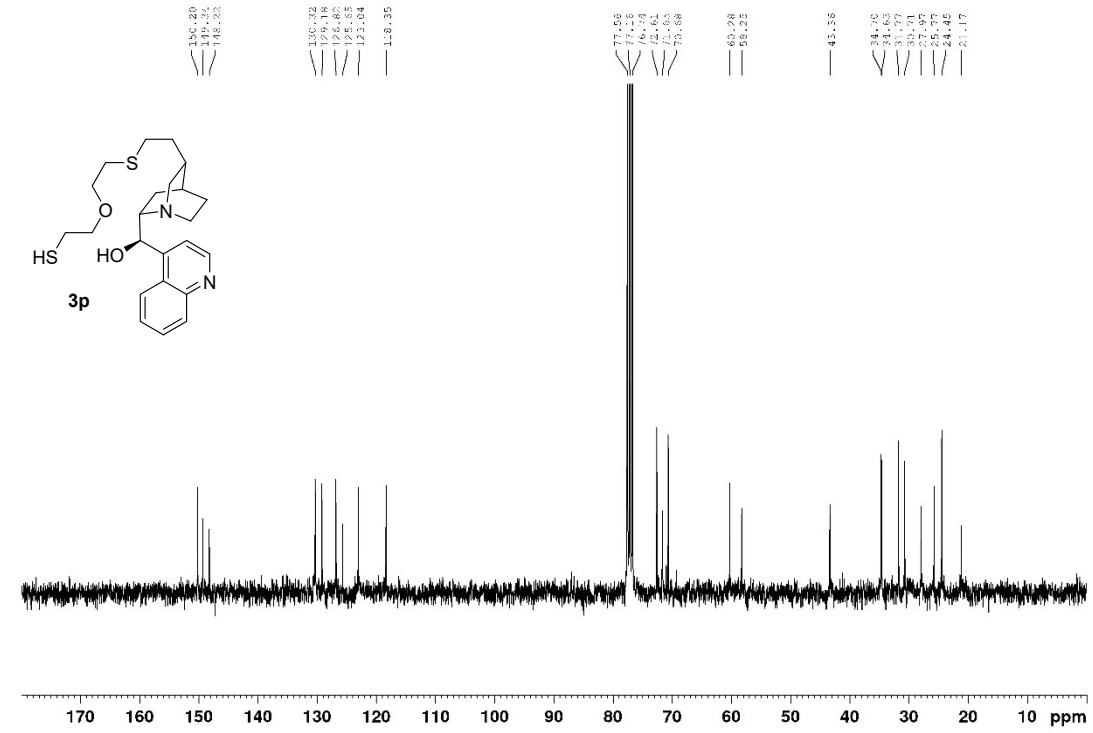
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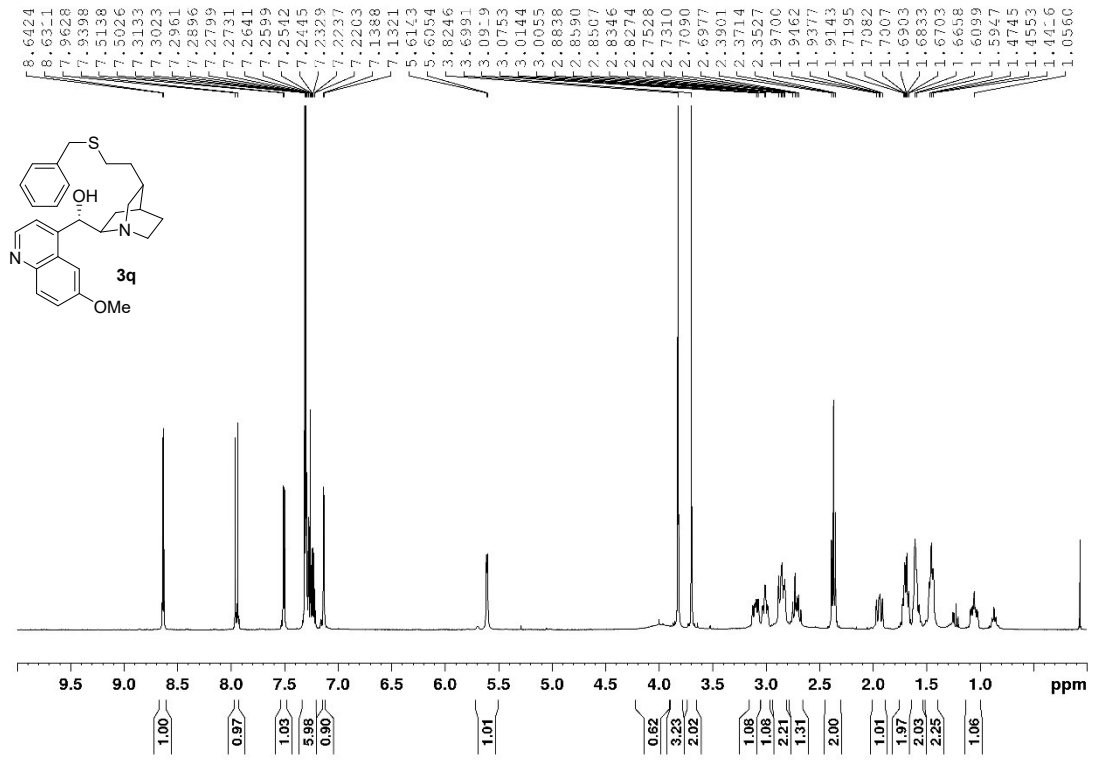
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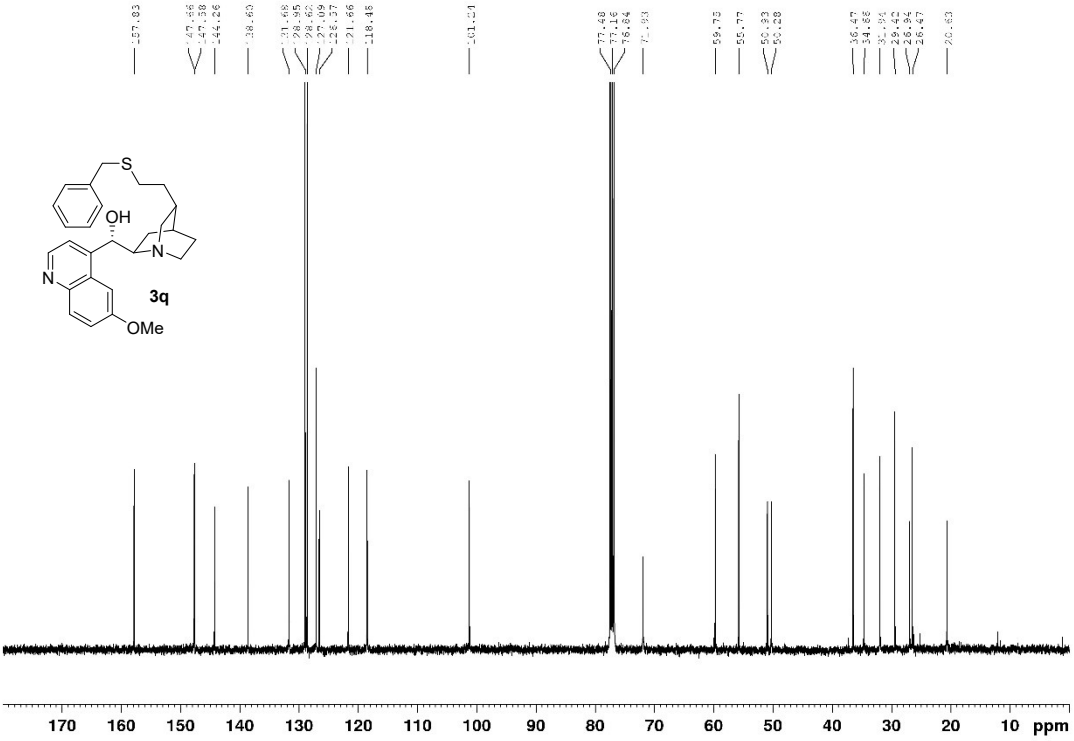
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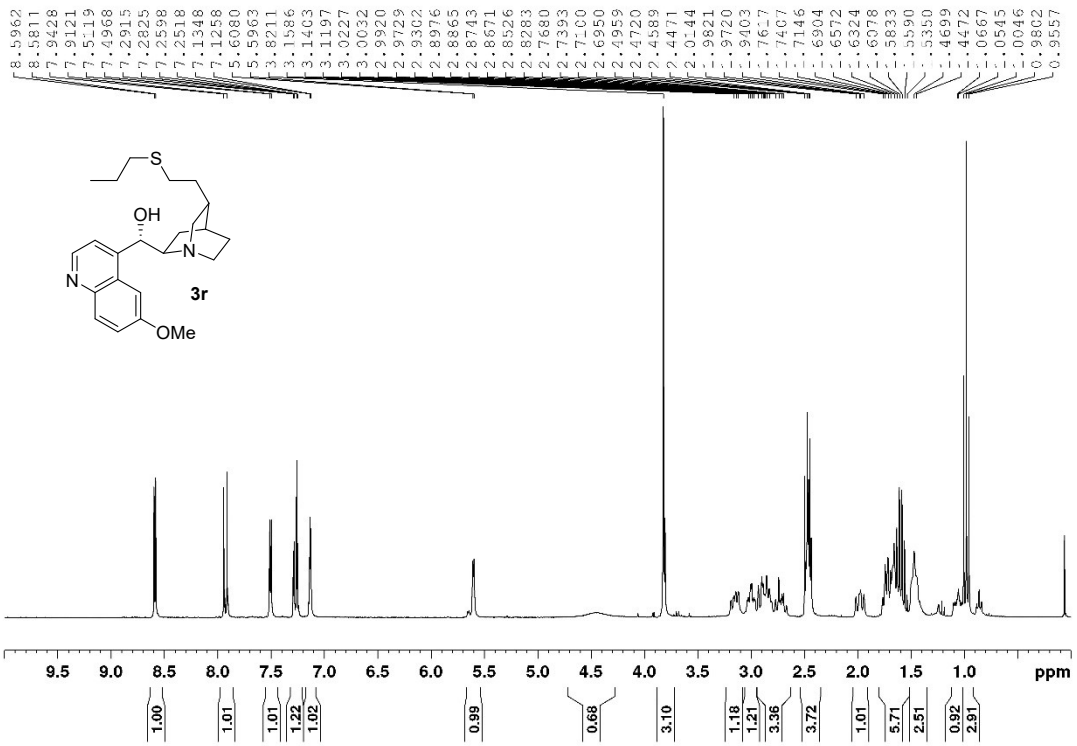
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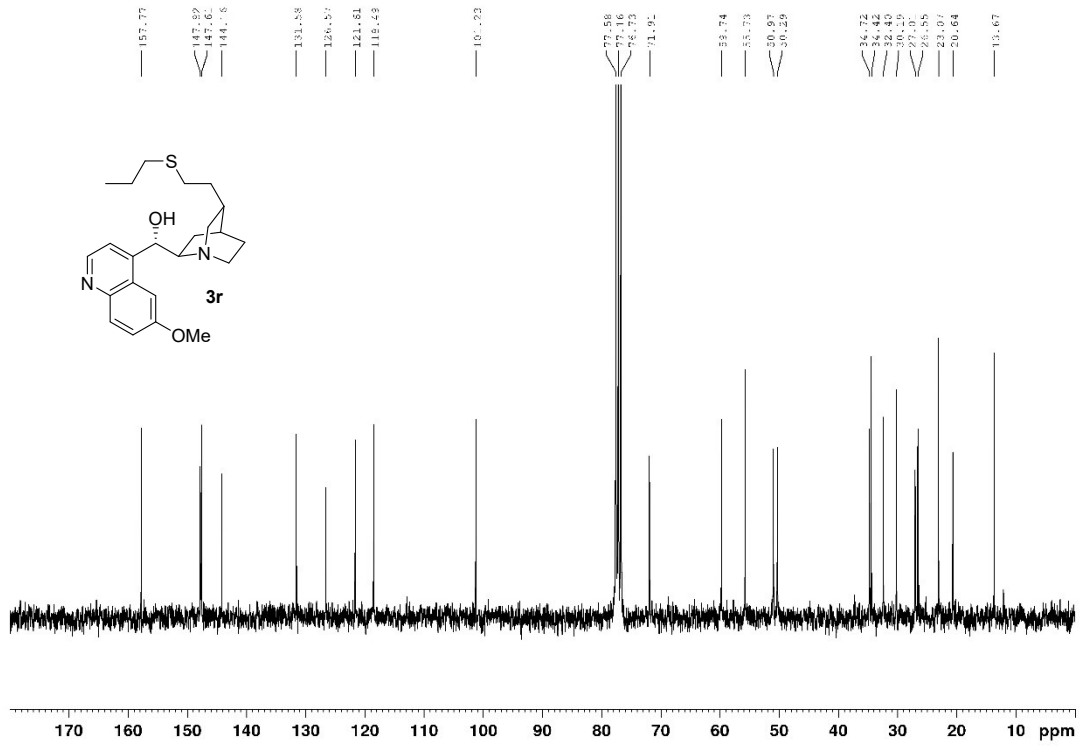
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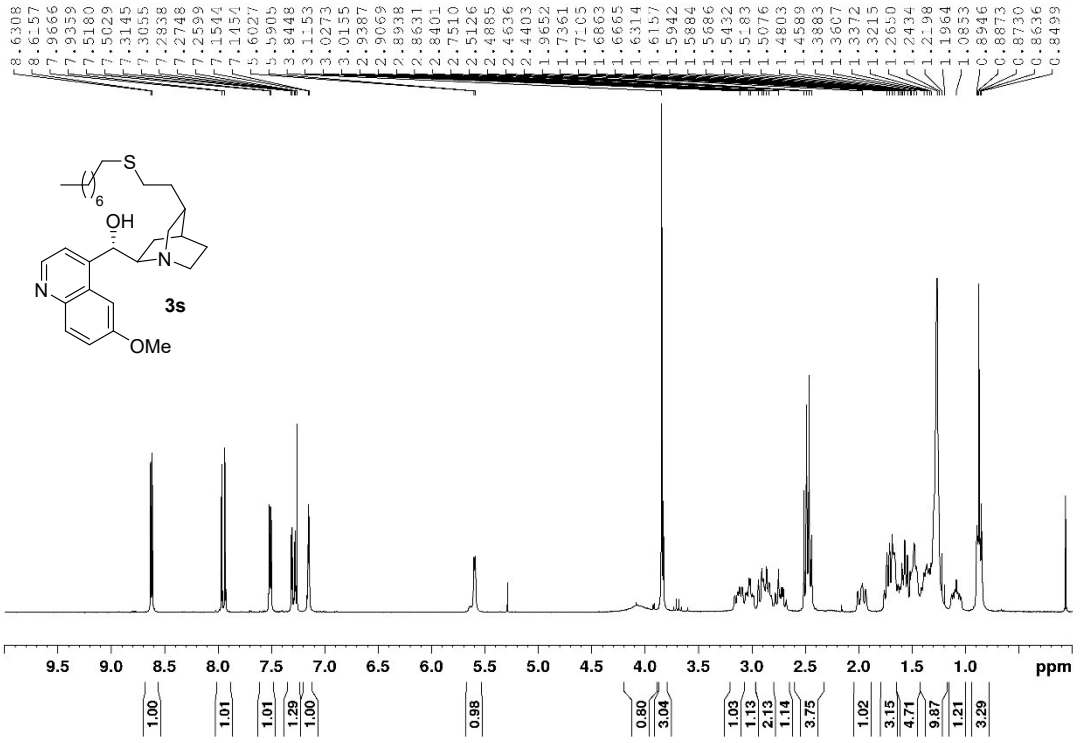
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OMe
OH
N
S
6
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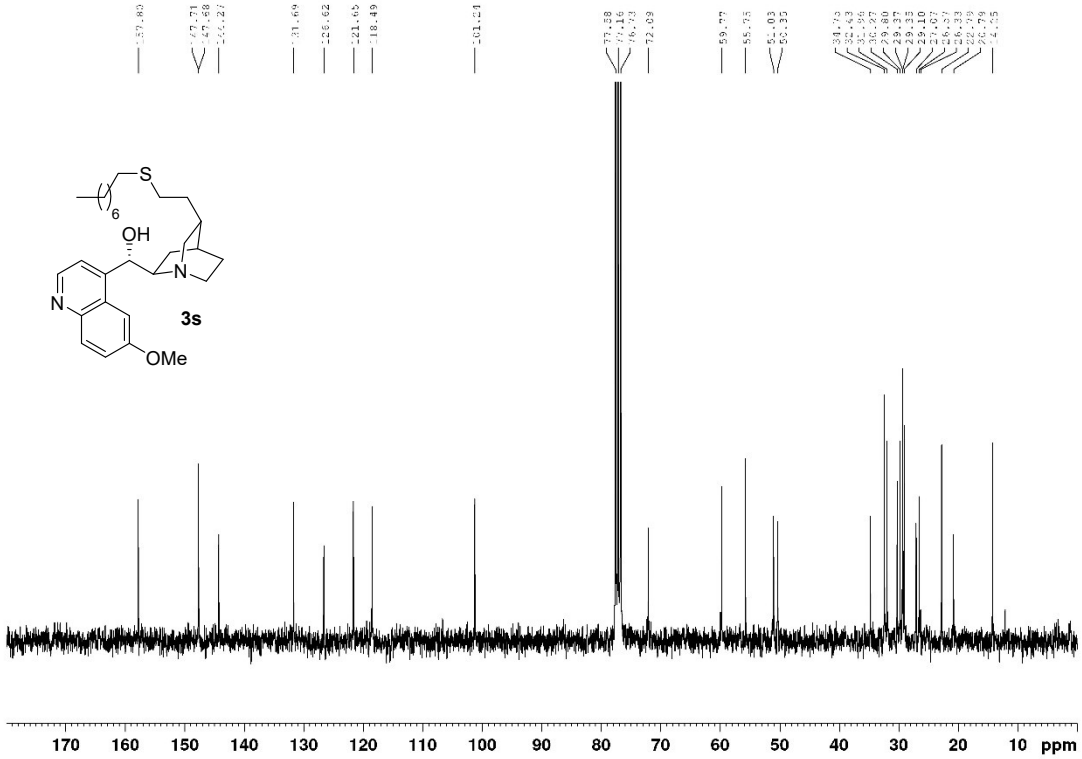
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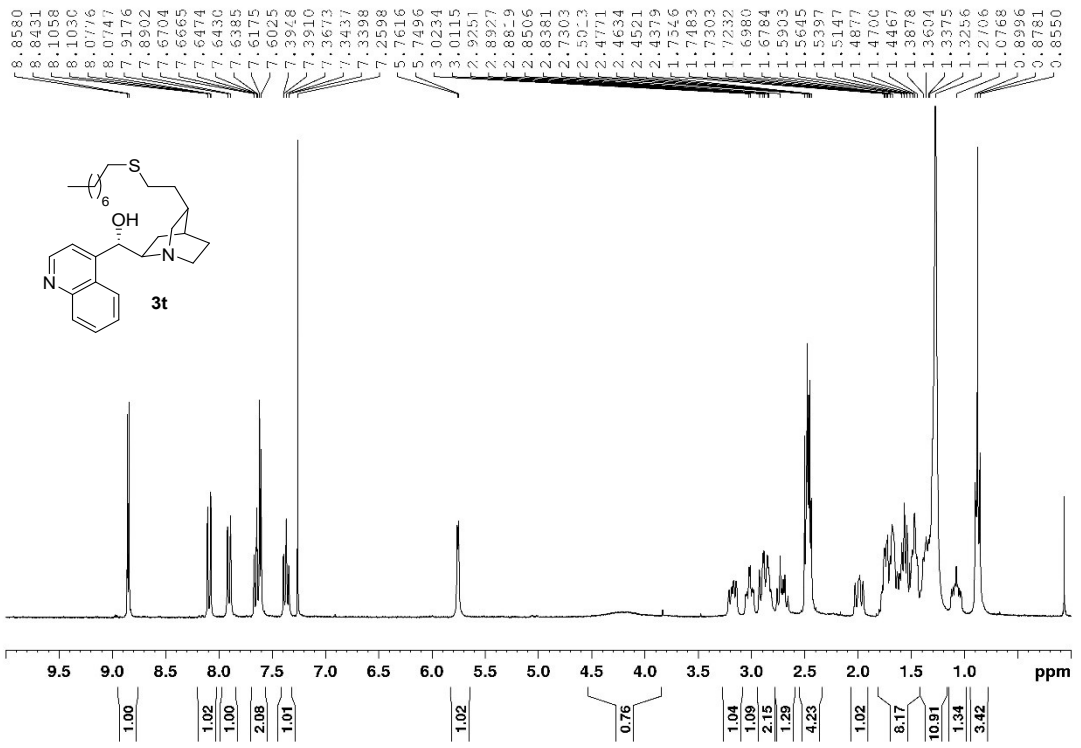
OMe
OH
N
S
6
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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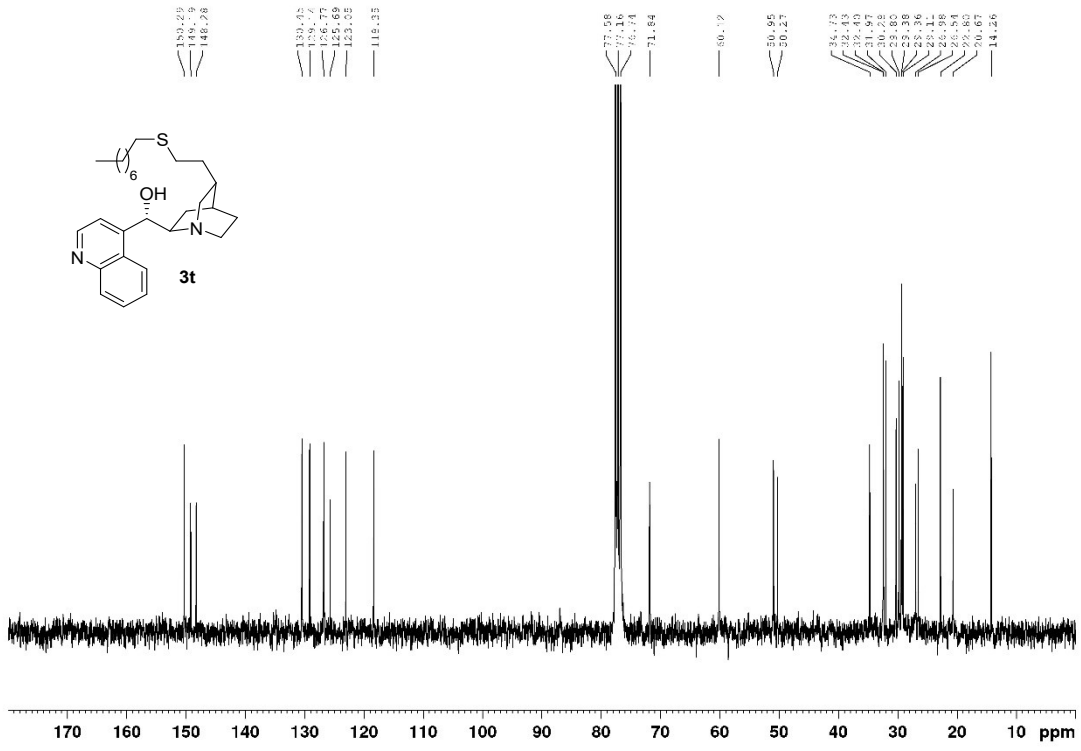
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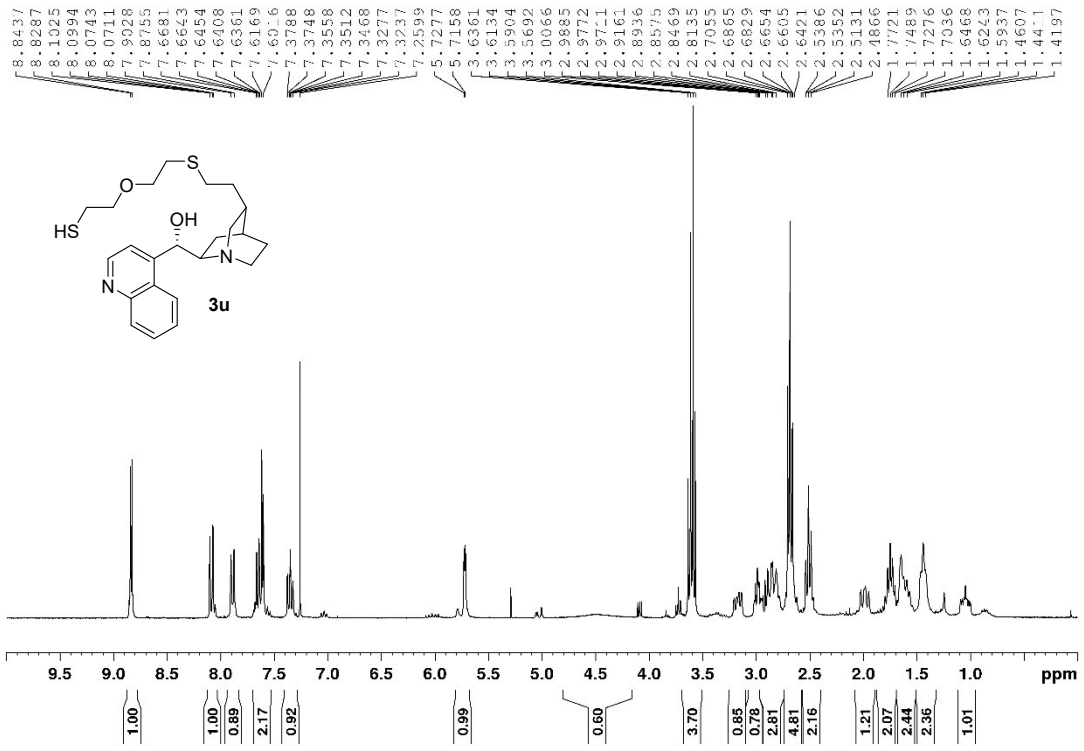
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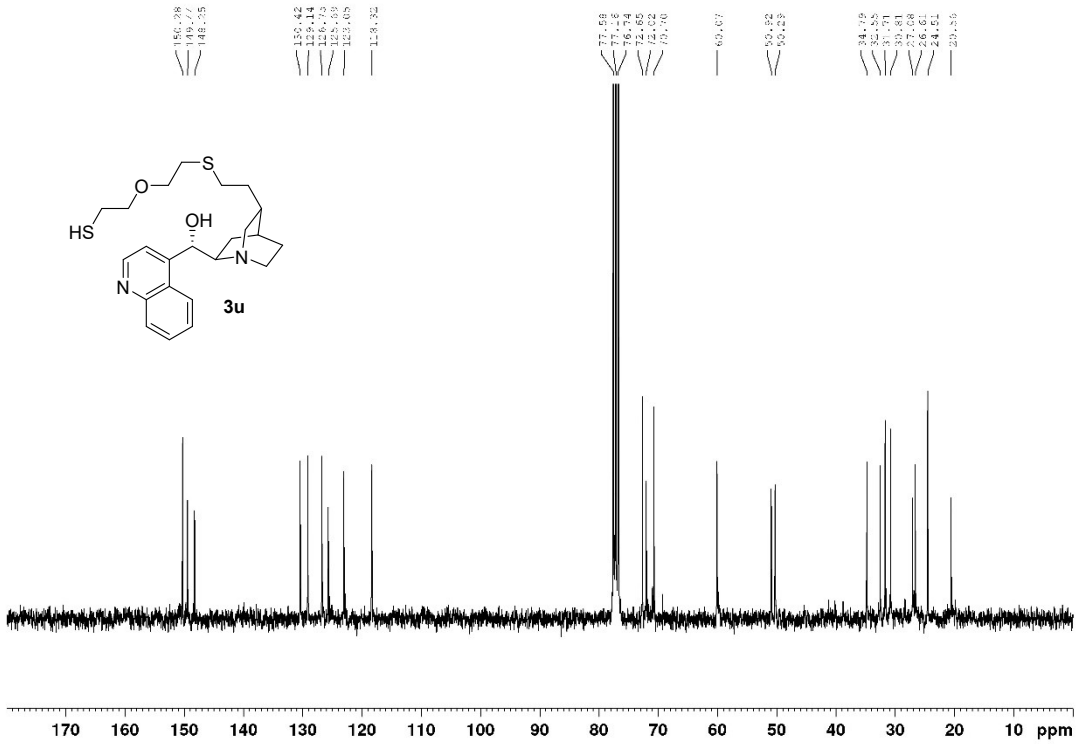
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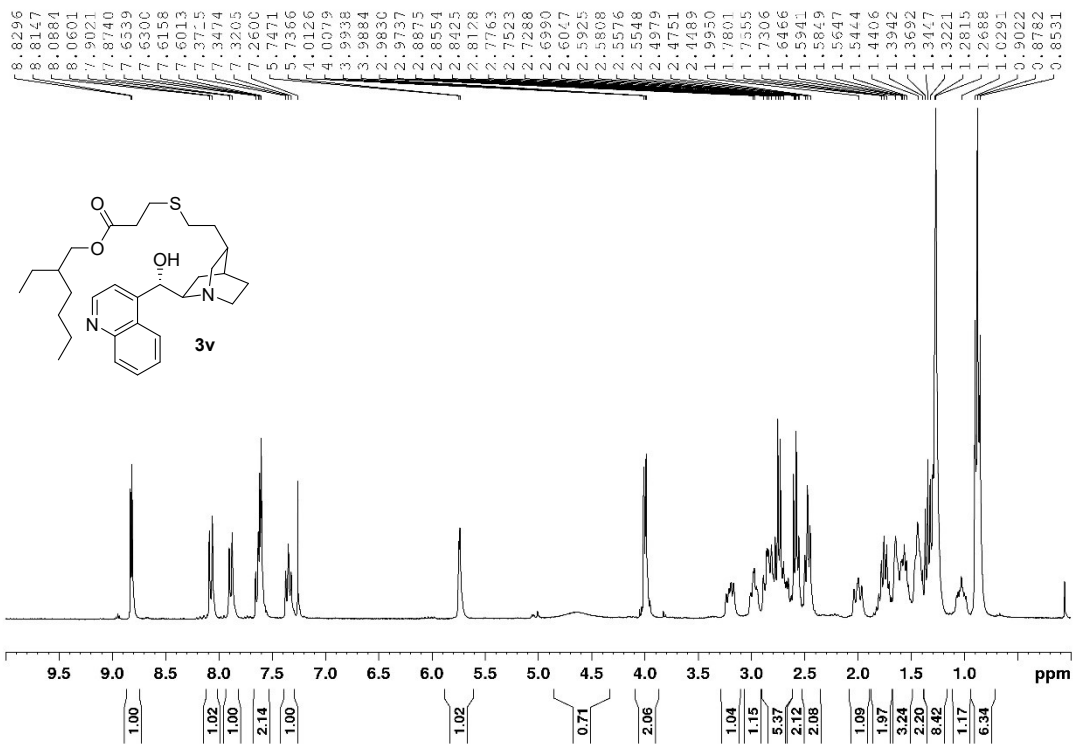
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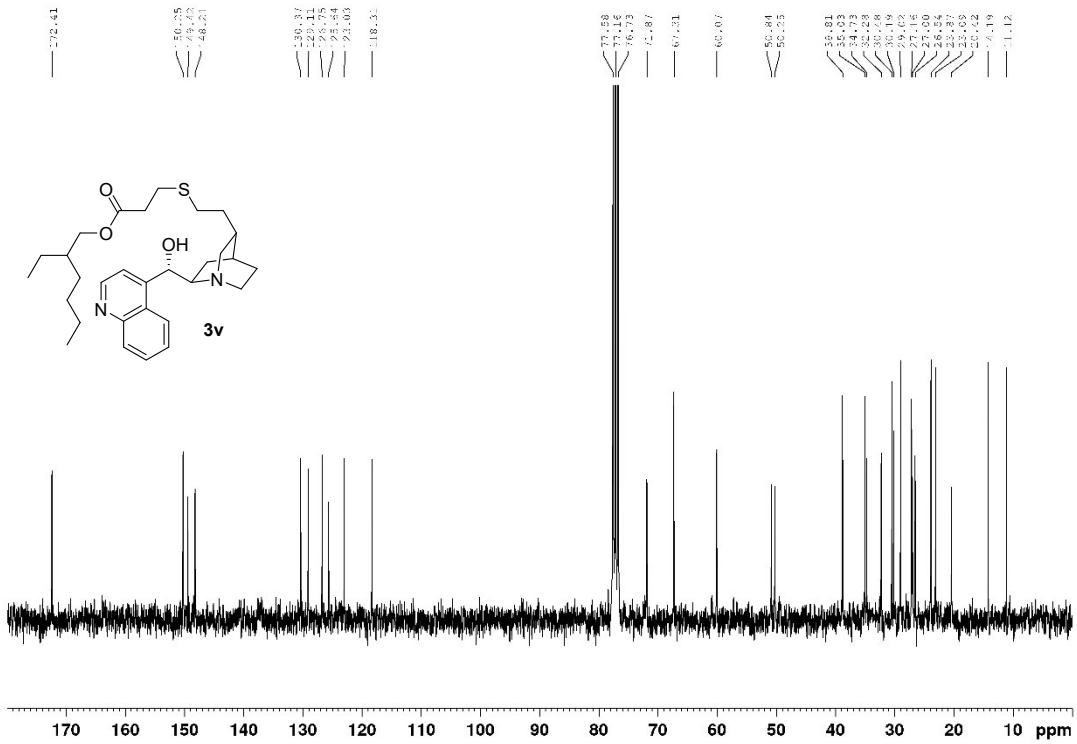
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6. References

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