Novel dithiocarbamates selectively inhibit 3CL protease of SARS-CoV-2 and other coronaviruses

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Table 1. The statistics for data collection and refinement

Protein	3CLp with compound 1	3CLp with compound 1x
PDB code	7NTQ	8AEB
Data collection statistics		
X-ray source	SOLEIL Proxima1	SOLEIL Proxima2a
Wavelength (Å)	0,978564	0,980104
Solvent content (%)	37,56	38,26
Space group	C 1 2 1	C 1 2 1
Unit cell dimensions (Å)	a=114.92 b=52.91 c=44.90	a=115.14 b=53.47 c=44.65
Unit cell angles (°)	α=90.00 β=102.88 γ=90.00	α=90.00 β=1021.30 γ=90.00
Resolution range (Å)*	47.62 - 1.49 (1.59 - 1.49)	48.37 - 1.83 (1.88 - 1.83)
N° observations	282693 (41311)	145658 (9493)
N° unique reflections	42066 (6311)	23313 (1587)
Rmeas	0.101 (1.406)	0.111 (1.464)
Completeness (%)	98.7 (91.9)	98.7 (89.8)
Mean I/σ(I)	9.77 (1.02)	9.9 (1.20)
Multiplicity	6.9 (7.0)	6.2 (6.0)
CC1/2[a]	0.998 (0.510)	0.997 (0.476)
Wilson B-factor (Å^2)	22,3	25,0
Refinement statistics		
Rwork / Rfree[b]	0.171 / 0.213	0.183 / 0.234
Average B, all atoms (Å^2)	25,0	34,0
Clashscore[c]	3	5
No. non-H atoms	2636	2505
Protein	2366	2355
Ligand/ion	54	22
Water	216	128
R.m.s. deviations		
Bond lengths (Å)	0,0107	0,0144
Bond angles (°)	1,675	2,067
Ramachandran		
favored	98,36	97,37
allowed	0,98	1,97
outliers	0,33	0,65

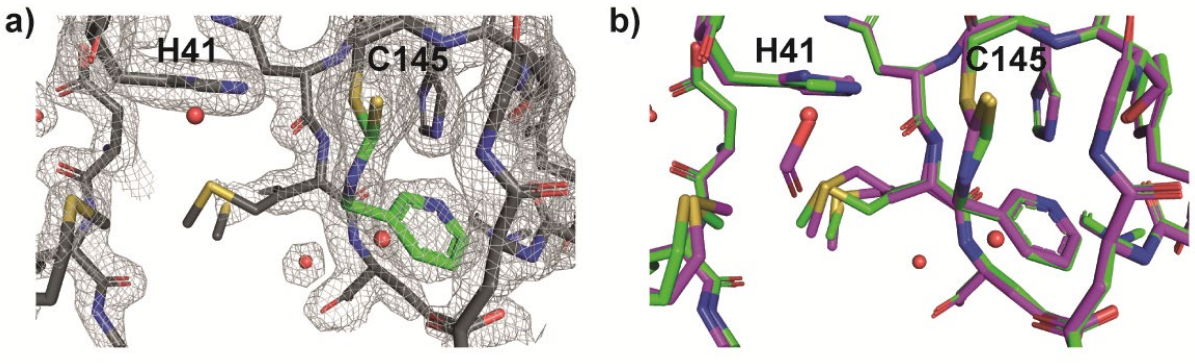
*Values in parentheses are for highest-resolution shell.

[a] percentage of correlation between intensities from random half-datasets. Karplus & Diederichs (2012), Science 336, 1030-33

[b] calculated for a test set of reflections (5%) omitted from the refinement.

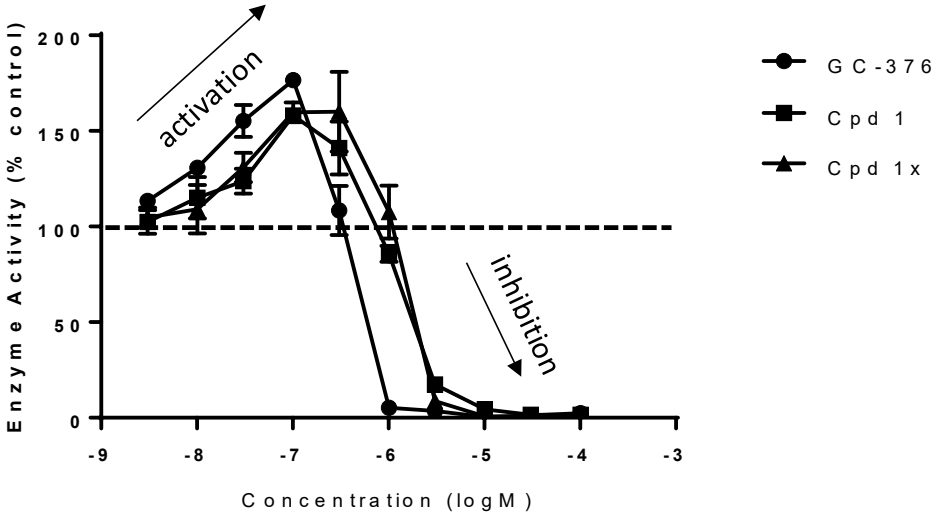
[c] defined as the number of clashes calculated for the model per 1000 atoms (includingH) of the model. Hydrogens were added by MolProbity (Chen et al., 2010)

Figure S1. Crystallographic structure of the SARS-CoV-2 3CL^{pro} after reaction with **1x**



(a) Crystallographic structure of the SARS-CoV-2 3CL^{pro} bound to the N-(pyridin-3-ylmethyl)thioformamide moiety (in green) from the compound **1x** (PDB ID: 8AEB). The 2*Fo-Fc* electron-density map, contoured at 1.5σ, is shown as light grey mesh. (b) Superimposition of the structures of the SARS-CoV-2 3CL^{pro} bound to the N-(pyridin-3-ylmethyl)thioformamide moiety coming either from the compound **1** (in magenta) or from the compound **1x** (in green).

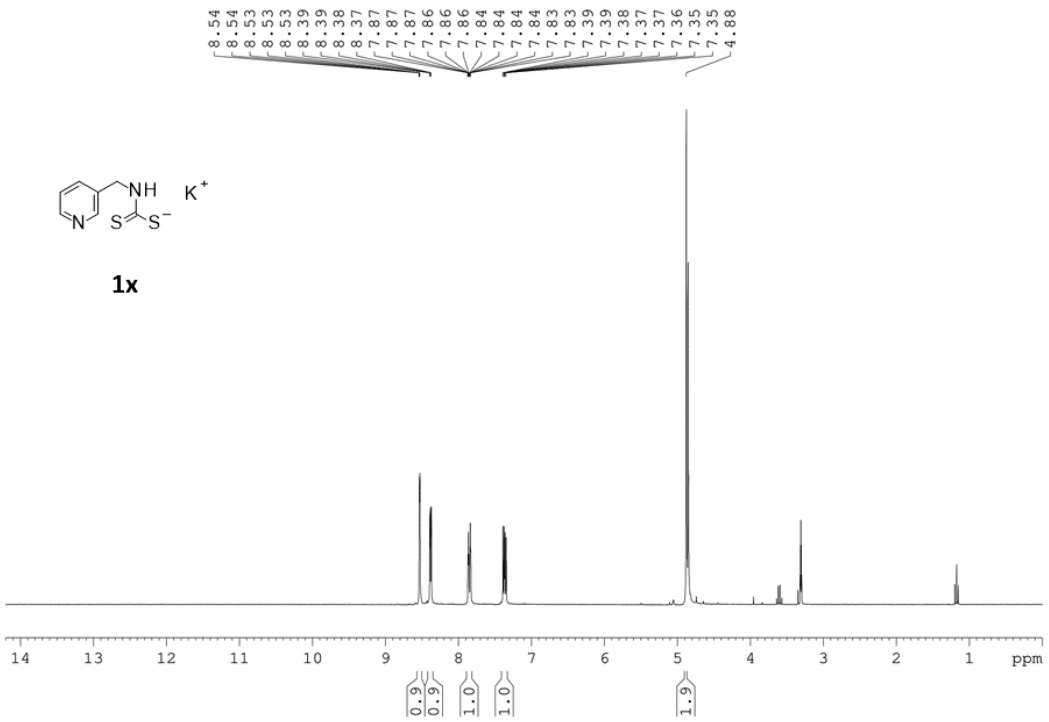
Figure S2. Activity of compounds against MERS-CoV 3CL^{pro}



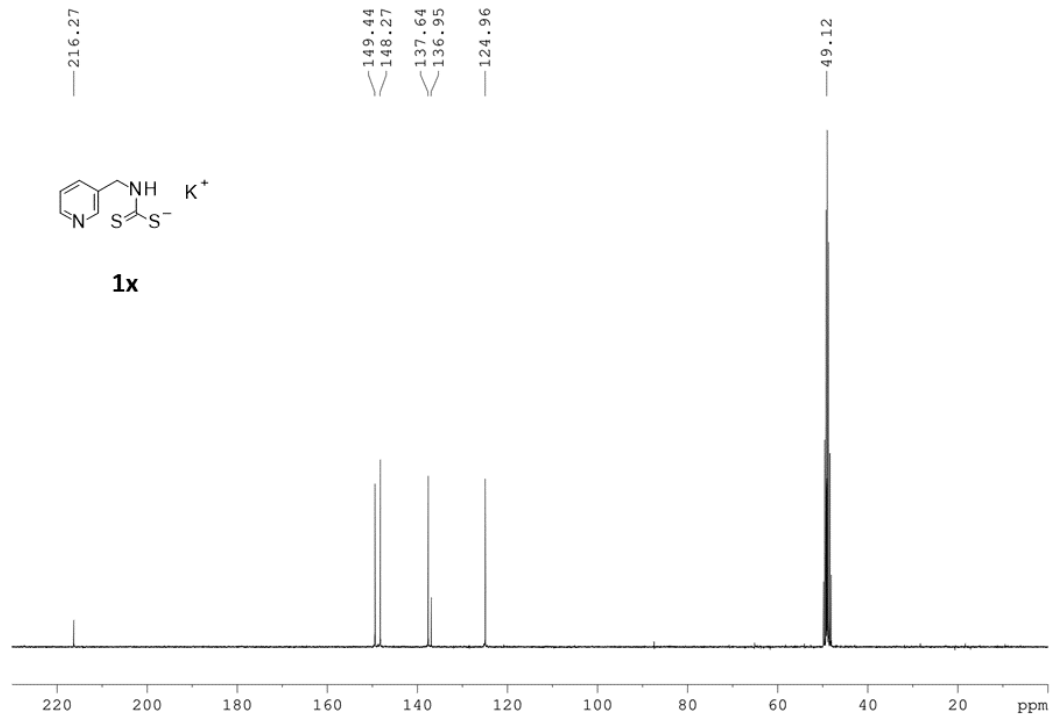
Enzymatic assays were performed without GSH in the buffer. The enzyme was pre-incubated for 1h with compound at increasing concentrations before starting the reaction with the substrate. Initial rates were expressed as percentage of control. Data are the mean of three separate experiments.

NMR spectra of representative compounds

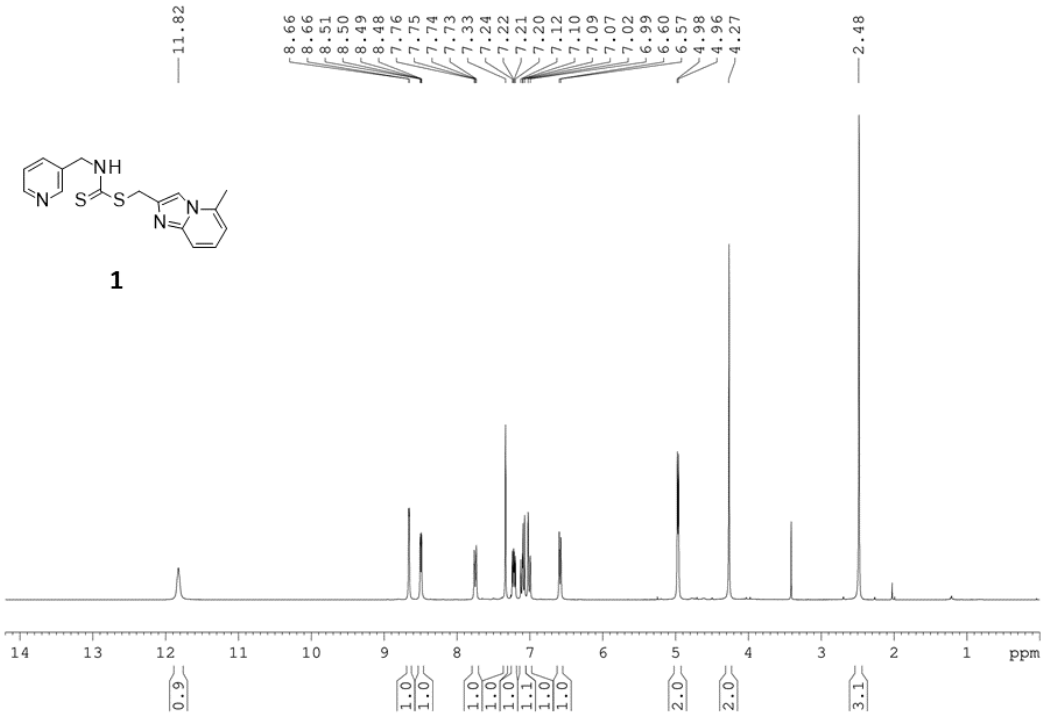
^{1}H NMR of compound **1x** (300 MHz, CD_3OD)



^{13}C NMR of compound **1x** (300 MHz, CD_3OD)

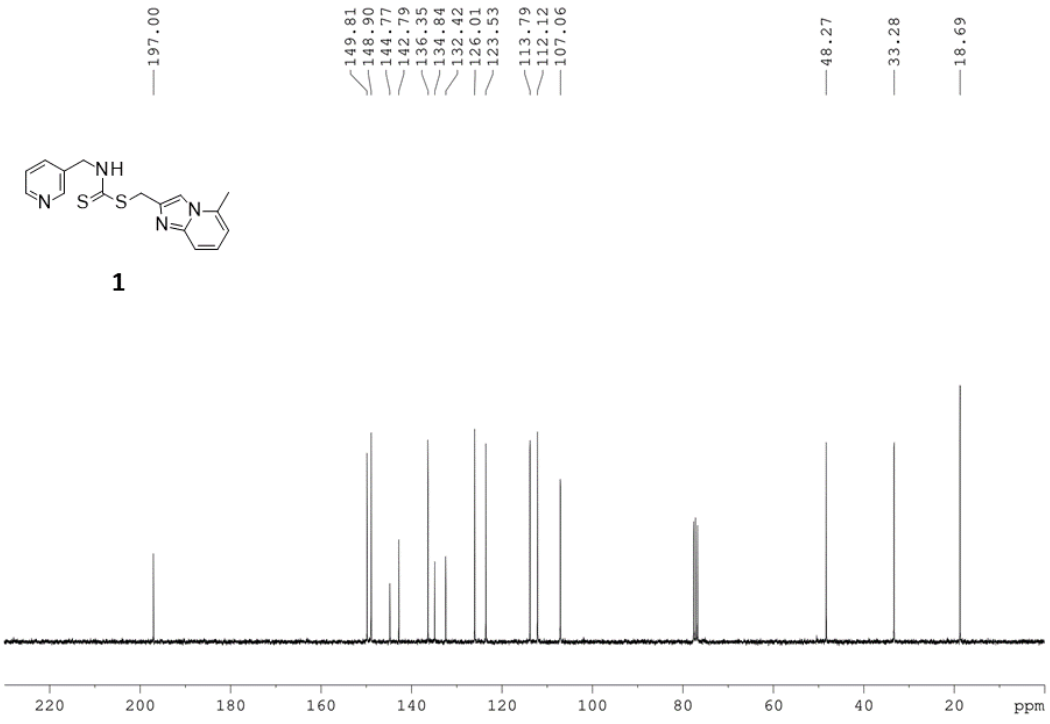


^{1}H NMR of compound **1** (300 MHz, $CDCl_3$)



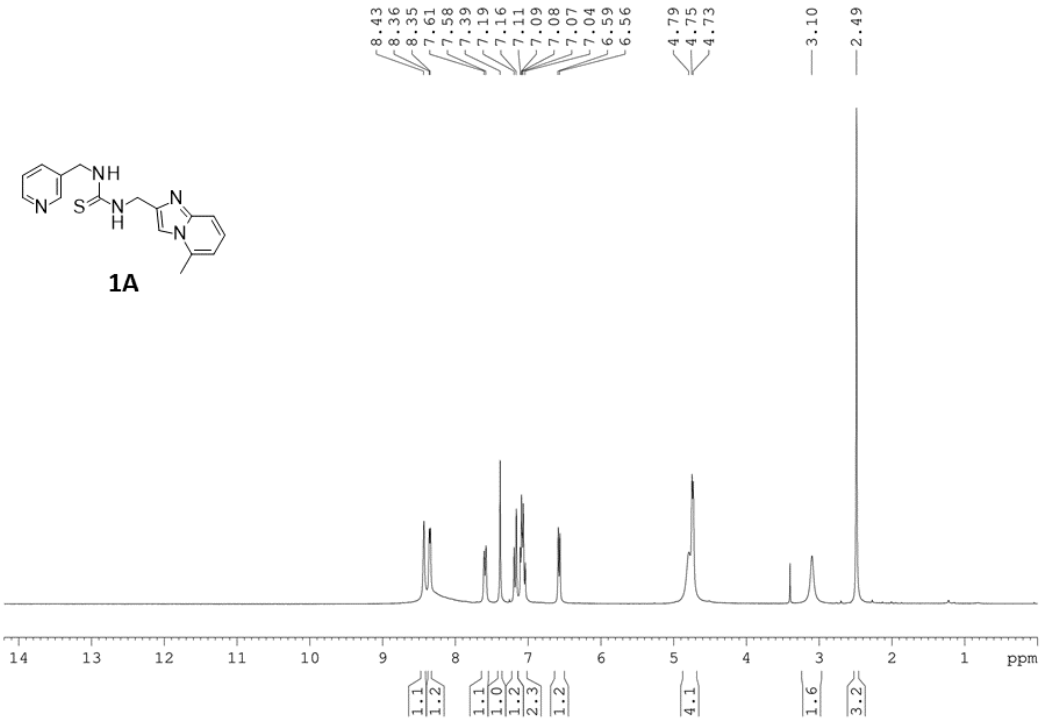
1

^{13}C NMR of compound **1** (300 MHz, $CDCl_3$)



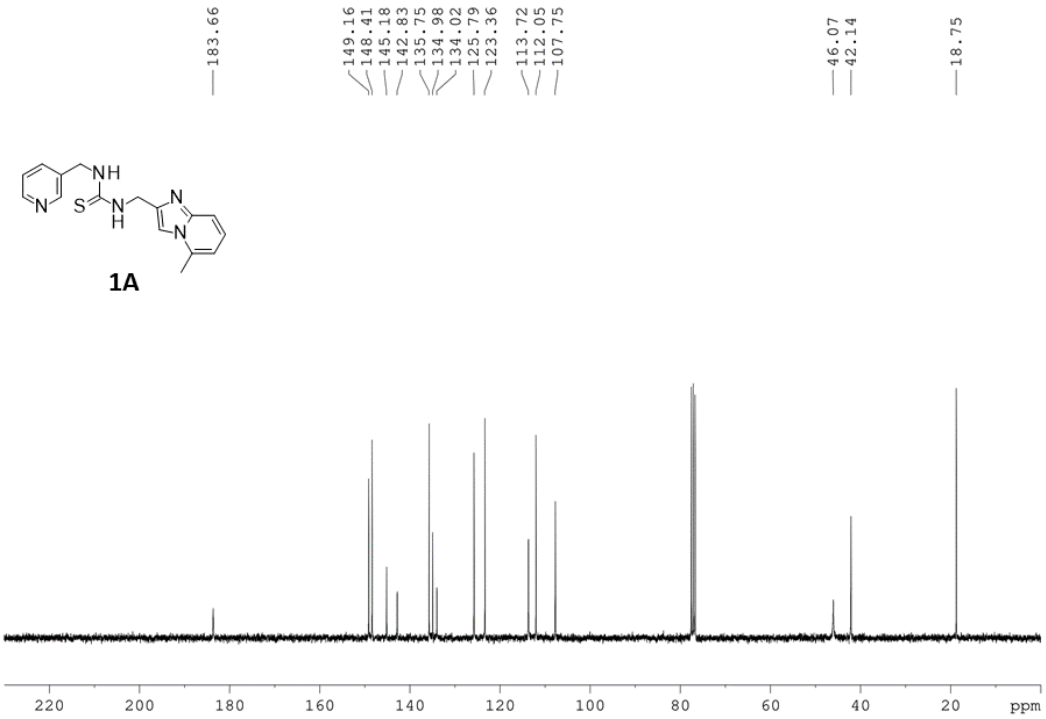
1

^{1}H NMR of compound **1A** (300 MHz, $CDCl_3$)



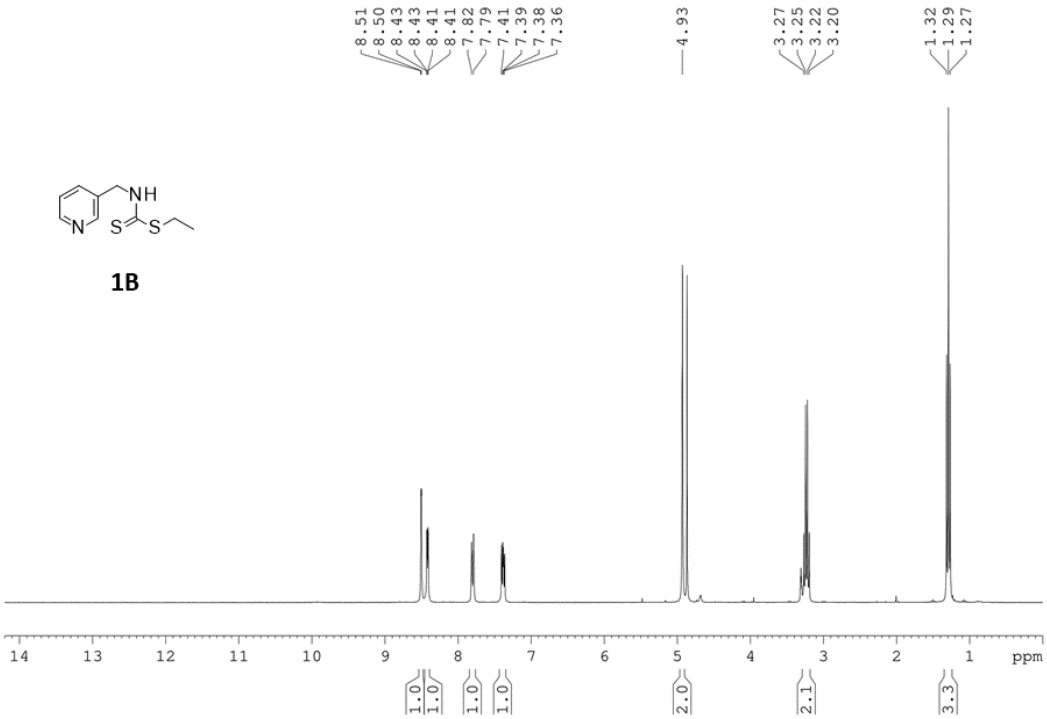
1A

^{13}C NMR of compound **1A** (300 MHz, $CDCl_3$)



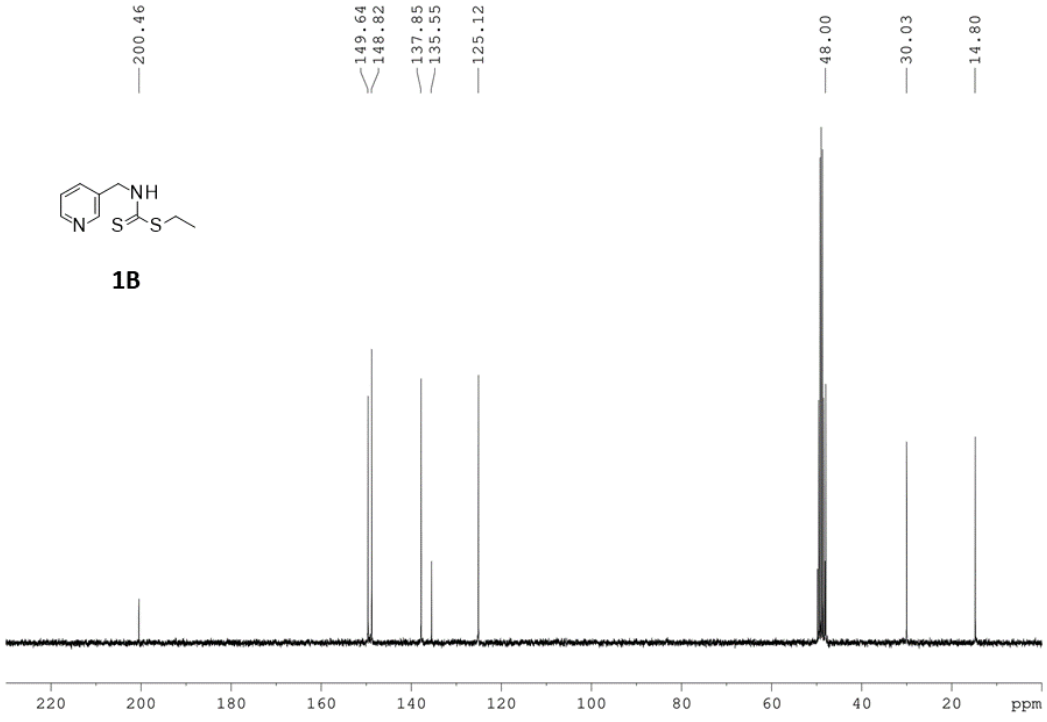
1A

^{1}H NMR of compound **1B** (300 MHz, CD_3OD)



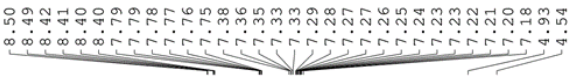
1B

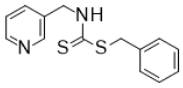
^{13}C NMR of compound **1B** (300 MHz, CD_3OD)



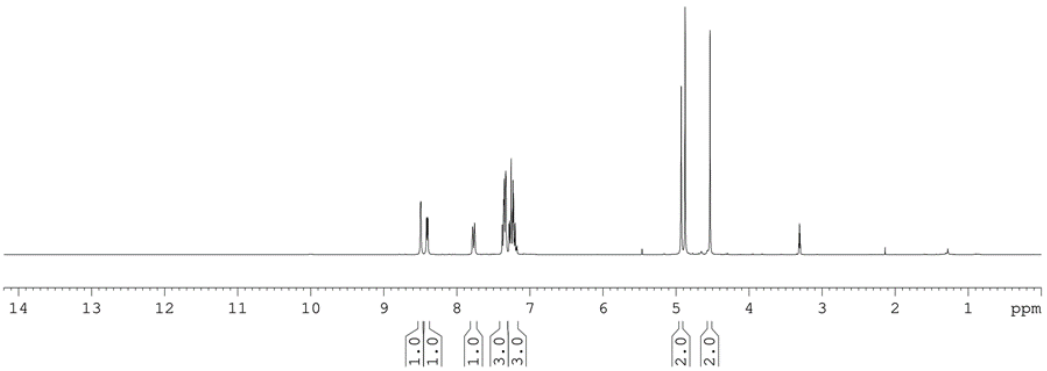
1B

^{1}H NMR of compound **1C** (300 MHz, CD_3OD)

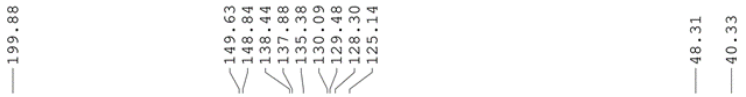


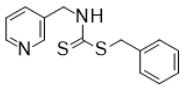


1C

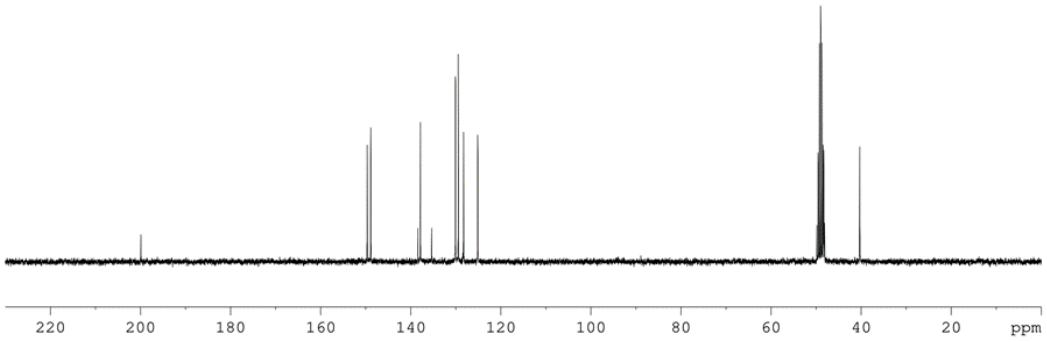


^{13}C NMR of compound **1C** (300 MHz, CD_3OD)

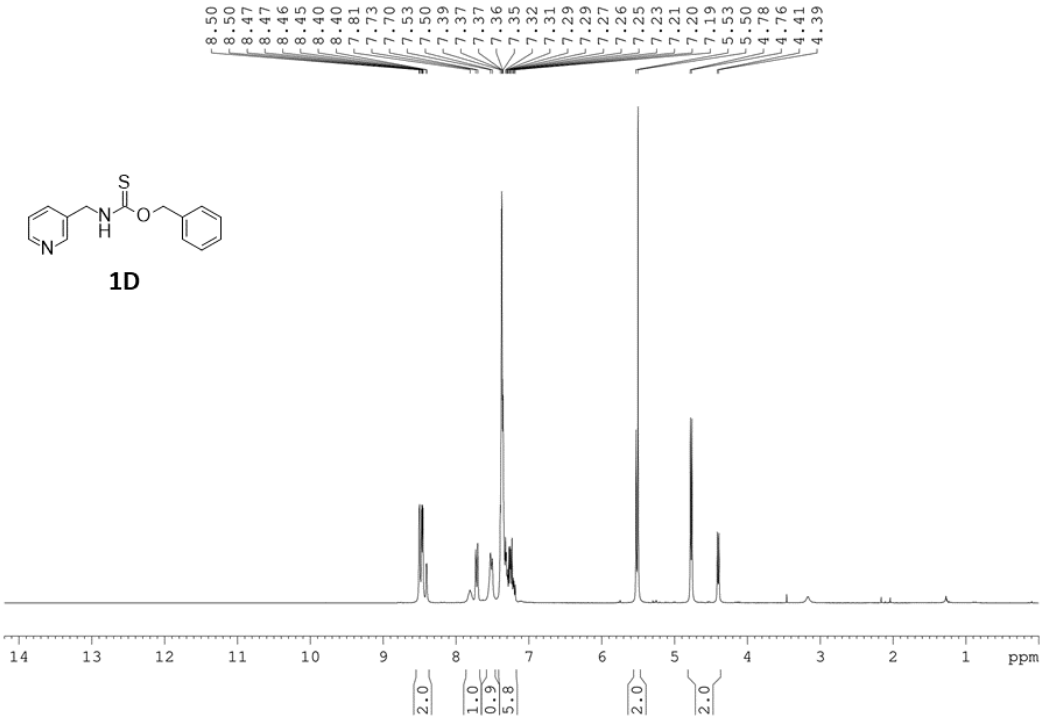




1C



^{1}H NMR of compound **1D** (300 MHz, $CDCl_3$)



^{13}C NMR of compound **1D** (300 MHz, $CDCl_3$)