Supporting Information

Liquid-assisted mechanochemical synthesis of thioamide building blocks with Lawesson reagent. Ex-situ monitoring and detection of intermediate polymorphs.

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Contenido

General Information

^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz Jeol spectrometer operating at 500 MHz for ^{1}H and at 126 MHz for ^{13}C nuclei in $CDCl_3$ or DMSO-d_6 solvent, and using TMS as an internal reference. The recorded spectra were analyzed using the MestReNova software and documented in the following order: chemical displacements (δ) are expressed in parts per million (ppm), multiplicities are expressed with standard abbreviations such as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublets of doublets), etc. The coupling constants (*J*) are expressed in Hertz (Hz).

X-Ray Powder Diffraction analysis was carried out in Bragg-Bentano mode on a BRUKER D8-ADVANCE eco diffractometer equipped with a LynxEye detector (λCu-Kα1+2 = 1.541874 Å). Data were collected at room temperature in the range of 2θ = 5-45° (step of 0.02, step time 0.5 s).

The photographs included below were taken with a 64 MP camera from a Zeiss Standard 25 trinocular Biological Microscope. Includes: Binocular phototube 35°/20 with sliding prism 100 obs /100 doc with 10x eyepieces. Mechanical stage 75x30 R with ceramic-coated stage surface and specimen holder.

Melting points were recorded on a Buchi B-540 melting point apparatus.

Low-resolution mass spectra were obtained using an Agilent Technologies simple quadruple equipment provided with electrospray ionization, while the high-resolution mass spectra were obtained by electrospray ionization time-of-flight mass spectrometry (ESI-TOF). HPLC was performed using a Thermo Scientific Dionex Ultimate 3000 with a diode array detector with a chiral stationary phase with CHIRALPACK AS-H columns.

The grinding experiments were carried out in a RETSCH MM200 and MM400 mixing mills using various milling jars: acrylic with a capacity of 7.5 mL, Teflon with a capacity of 8 mL, stainless steel with a capacity of 7 mL, and agate with a capacity of 5 mL. Balls made of different materials were used: copper (11 mm, 5.6 g), Teflon (10 mm, 1.7 g), stainless steel (12 mm, 6.8 g) and agate (15 mm, 4.8 g). All reactions were controlled by thin layer chromatography (TLC); The products were purified by silica gel column chromatography (400 mesh size silica gel) using combinations of ethyl acetate and hexane as the eluent.

Preparation of substrates

The procedures reported in the literature for the preparation of the amides were followed.

Preparation of benzamide.

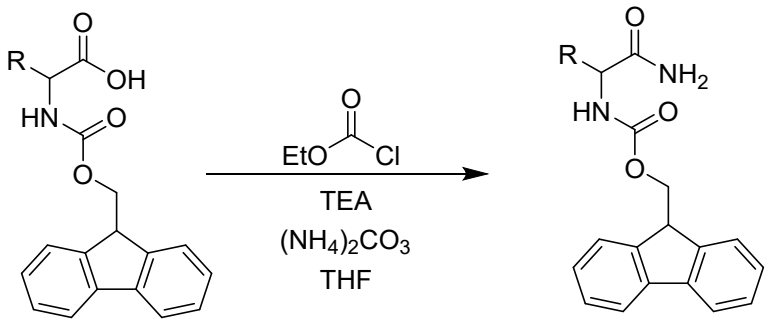
The procedure reported[1] was followed with minor modifications. Thionyl chloride (8.92 mL, 123 mmol, 1.5 equiv.) was added dropwise to a stirring solution of benzoic acid (10.0 g, 82 mmol, 1.0 equiv.) in dry CH_2Cl_2 (240 mL) and dry DMF (6 drops) at 0 °C. The solution was allowed to stir at room temperature for 6 hours and the resulting solution was evaporated to dryness and redissolved in CH_2Cl_2 (10 mL) before dropwise addition to a flask containing KOH (9.2 g, 164 mmol, 2.0 equiv.) and NH_4Cl (5.2 g, 98 mmol, 1.2 eq.) in H_2O/MeCN (1:5, 340 mL) at 0 °C. The resulting biphasic mixture was heated overnight before addition of methanol (80 mL) and concentration to dryness. The crude product was then purified through a pad of silica gel (eluent CH_2Cl_2: MeOH, 8:2) to obtain benzamide in yield 95% (9.4g).

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.95 (br. s, 1H); 7.36 (br. s, 1H), 7.89–7.84 (m, 2H), 7.53–7.48 (m, 1H), 7.46–7.41 (m, 2H), ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.43, 134.79, 131.74, 128.71, 127.96.

Preparation of amino acid amides

For the preparation of amino acid amides, the procedures reported in the literature were followed[2,3] with commercial amino acids of Gly, Ala, Val, Phe, Pro, Tpr protected with Fmoc (fluorenylmethoxycarbonyl).

The N-Fmoc protected amino acid (1.0 mmol) was dissolved in THF, before addition of NMM (1.5 mmol) and $ClCO_2Et$ (1.5 mmol) at −15 °C, followed by the addition of $(NH_4)_2CO_3$ (1.5 mmol). The reaction mixture was stirred until the reaction was complete (the progress of the reaction was verified by TLC). Following removal of THF solvent, the product was extracted in ethyl acetate (15 mL) and the organic layer was washed with dilute HCl solution (10 mL), then with aqueous Na_2CO_3 solution (twice with 15 mL), water (15 mL), and brine (15 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The spectra of NMR of amino acid amides were correlated with those reported in the literature.



Entry	Primary Amide	Yield (%)[a]
1	Fmoc-L-Gly-NH_2	96.1
2	Fmoc-L-Ala-NH_2	92.5
3	Fmoc-L-Val-NH_2	90.3
4	Fmoc-L-Phe-NH_2	92.3
5	Fmoc-L-Pro-NH_2	86.1

[a]Isolated yield.

Fmoc Gly-NH_2

^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.89 (d, *J* = 7.5 Hz, 2H), 7.72 (d, *J* = 7.4 Hz, 2H), 7.42 (m, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.26 (br. s, 1H), 6.98 (br. s, 1H), , 4.29 (d, *J* = 7.1 Hz, 2H), , 4.23 (m, 1H), 3.56 (d, *J* = 6.15, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.62, 156.99, 144.41, 141.26, 128.16, 127.61, 125.80, 120.64, 66.20, 47.20, 43.78.

Fmoc- L-AlaNH_2

^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.89 (d, *J* = 8.5 Hz, 2H), 7.74 (d, *J* = 6.7 Hz, 2H), 7.41 (m, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.29 (br. s, 1H), 6.95 (br. s, 1H), 4.27 (d, *J* = 7.7 Hz, 2H), 4.22 (m, 1H), 3.98 (m, 1H), 1.32 (d, *J*=7 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 209.71, 155.69, 144.50, 141.33, 128.12, 127.56, 125.70, 120.51, 66.48, 56.68, 47.47, 21.73.

Fmoc- L-ValNH_2

^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.86 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 1.96 (ddd, *J* = 6.8, 7.0, 8.2 Hz), 3.80 (dd, *J* = 7.6, 8.2 Hz, 1H), 4.22–4.29 (m, 3H), 7.04 (br. s, 1H), 7.29–7.44, 7.75, 7.90 (m, d, d, *J* = 5.9, 7.5 Hz, 6H.

^{13}C NMR (126 MHz, DMSO-d_6) δ: 173.1, 156.0, 143.8, 143.7, 140.6, 127.5, 127.0, 125.3, 120.0, 65.6, 60.0, 46.6, 30.1, 19.2, 18.0.

Fmoc- L-PheNH$_2$

^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.16–7.43, 7.54, 7.64, 7.88 (m, d, t, d, J = 8.8, 8.2, 7.6 Hz, 9H, 1H, 2H, 2H, NHCH, C6H5, Fmoc), 7.45 (br. s, 1H), 7.08 (br. s, 1H), 4.11–4.20 (m, 4H), 3.0 (dd, *J* = 4.2, 13.6 Hz, 1H), 2.78 (dd,*J* = 10.6, 13.6 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 173.4, 155.8, 143.8,. 140.7, 138.3, 129.2, 128.0, 127.6, 127.0, 126.2, 125.4, 125.3, 120.1, 65.6, 46.6, 56.1, 37.5.

Fmoc-Pro-L-NH$_2$

^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.89 (t, *J* = 6.7 Hz, 2H), 7.67 (t, J = 6.7 Hz, 2H), 7.52 (1H, br. s, NH), 7.42 (t, *J* = 7.3 Hz, 2H), 7.37–7.30 (m, 3H), 7.10 (br. s, 1H), 6.92 (br. s, 1H), 4.31–4.24 (m, 1H), 4.27 (s, 2H), 4.29–4.11 (m, 1H), 4.11–4.05 (m, 1H) 3.51–3.30 (m, 2H) 2.26– 2.15 (m, 1H), 2.13–2.01 (m, 1H), 1.95–1.86 (m, 1H,), 1.87–1.76 (m, 1H), 1.88–1.76 (, m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 174.2, 173.9, 154.1, 144.0, 143.8, 143.8, 143.7, 140.8, 140.6, 127.7, 127.2, 127.2, 125.5, 125.2, 120.1, 67.0, 66.5, 59.8, 59.5, 47.1, 46.7, 46.4, 31.4, 30.1, 23.9 , 23.0.

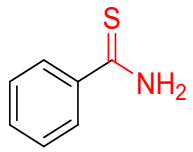
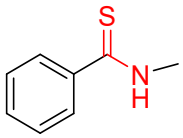
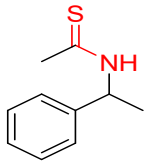
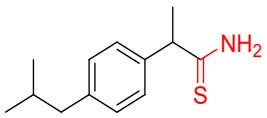
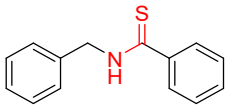
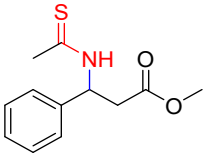
Tables

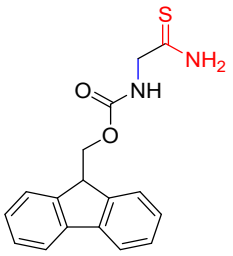
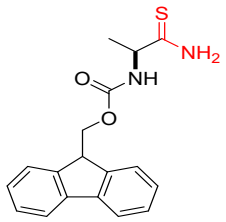
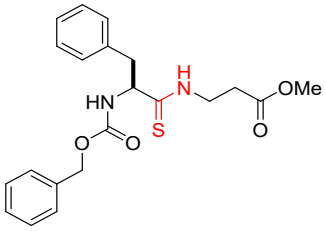
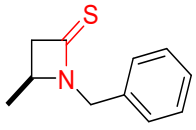
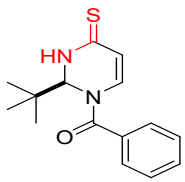
Table S1. Yields of the thioamides obtained thionation of the corresponding amides with Lawesson's reagent under mechanochemical activation (see Figure 1 in the main text).

Thioamide	Assay[a]o	Yield (%)[b]
1	1	95.2
	2	96.5
2	1	89.1
	2	93.3
3	1	91.4
	2	89.0
4	1	88.2
	2	89.2
5	1	88.4
	2	87.6
6	1	83.4
	2	81.3
7	1	80.0
	2	78.5
8	1	71.2
	2	69.1
9	1	86.6
	2	89.2
10	1	84.3
	2	86.1
11	1	89.4
	2	87.5

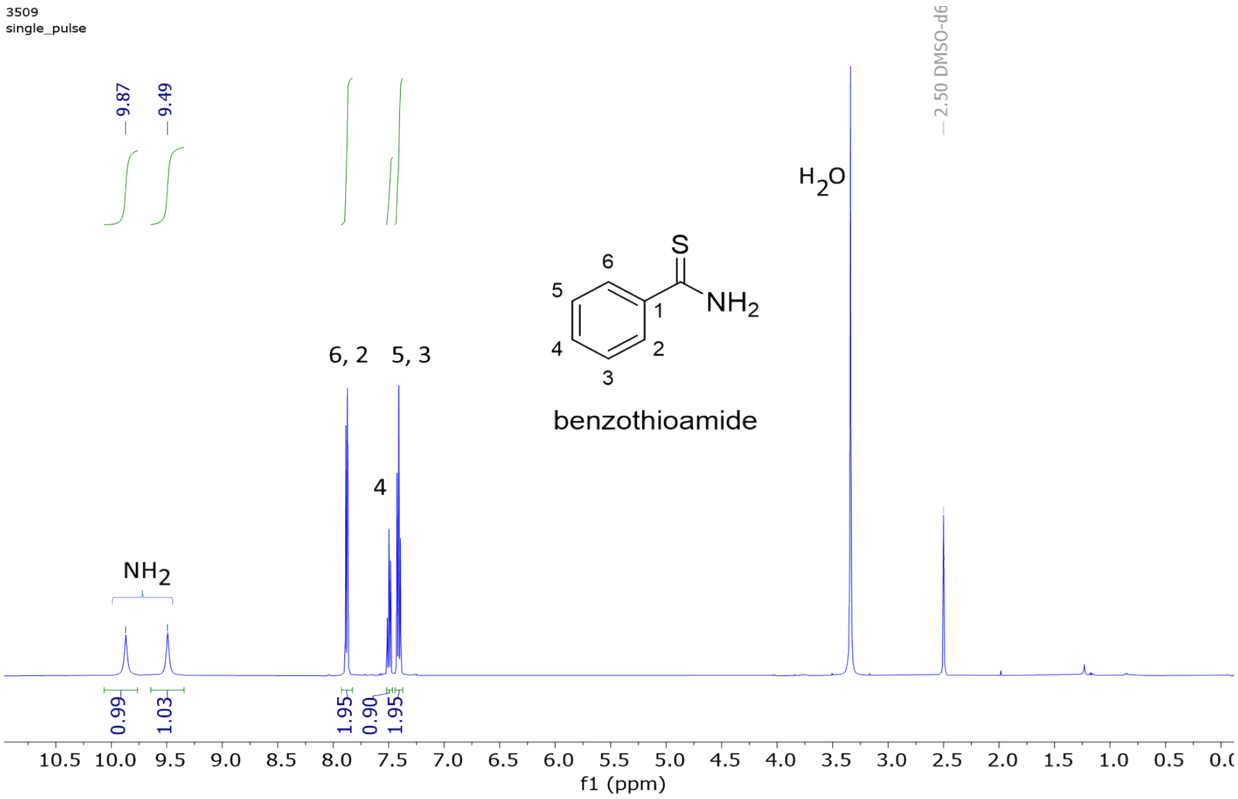
[a]Each of the reactions was carried out in duplicate, [b]Isolated yield.

Table S2. Characterization of thioamides obtained by the thionation method with the Lawesson´s reagent under mechanochemical activation.

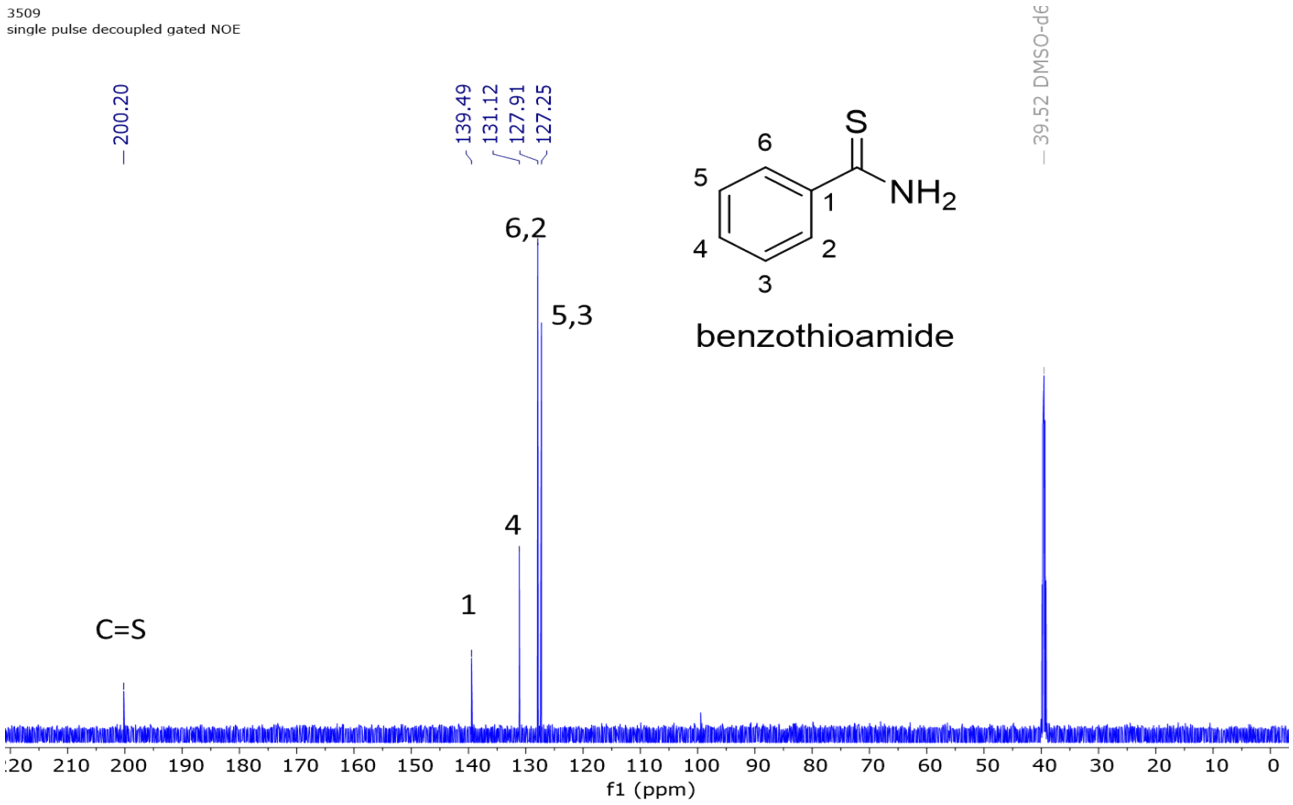
 Benzothioamide (**1**)	Pale yellow solid purified by silica gel column chromatography using *n*-hexane:ethyl acetate (3:1 v/v) as eluent; R_f = 0.23. mp 116.2-116.9 °C. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 9.87 (br. s, 1H), 9.5 (br. s, 1H), 7.88-7.90 (m, 2H), 7.54-7.47 (m, 1H), 7.45-7.38 (m, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 200.20, 139.49, 131.12, 127.91, 127.25. Calculated m/z for C_7H_7NS + 1, 138.03 (100.0%), found 138.1.
 *N*-methylbenzothioamide (**2**)	Pale yellow solid purified by silica gel column chromatography using *n*-hexane:ethyl acetate (3:1 v/v) as eluent; R_f = 0.3. mp 75-76 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.84 (br. s, 1H), 7.71-7.69 (m, 2H), 7.45-7.41 (m, 1H), 7.37-7.32 ((m, 2H), 3.29 (d, *J* = 4.9 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 200.19, 141.68, 131.14, 128.57, 126.70, 33.80. Calculated m/z for C_8H_9NS + 1, 152.05 (100.0%), found 152.1.
 *N*-(1-Phenylethyl)ethanethioamide (**3**)	Pale yellow solid purified by silica gel column chromatography using *n*-hexane:ethyl acetate (3:1 v/v) as eluent; R_f = 0.28. mp 58-59.5 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.62 (br. s, 1H, NH), 7.36-7.31 (m, 4H), 7.28(m, 1H), 5.71 (m, 1H), 2.50 (s, 3H), 1.6 (d, *J* = 6.9 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 199.58, 141.24, 128.86, 127.92, 126.65, 54.89, 34.45, 20.03. Calculated m/z for $C_{10}H_{13}NS$ + 1, 180.08 (100.0%), found 180.1.
 2-(4-Isobutylphenyl)propanethioamide (**4**)	Light yellow solid purified by silica gel column chromatography using *n*-hexane:ethyl acetate (3:1 v/v) as eluent; R_f = 0.28). mp 85-86.5 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.64 (br. s, 1H), 7.65 (br s, 1H), 7.25-7.21 (m, 2H), 7.15-7.11 (m, 2H), 4.0 (q, *J* = 7.2 Hz, 1H), 2.45 (d, *J* = 7.1 Hz, 2H), 1.83 (dq, *J* = 7, 7.2, 13.8 H), 1.66 (d, *J* = 7.24 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 213.39, 141.52, 138.06, 129.96, 127.39, 53.49, 45.10, 30.29, 22.50, 21.48. Calculated m/z for $C_{13}H_{19}NS$ + 1, 222.12 (100.0%), found 222.2.
 N-Benzylbenzothioamide (**5**)	Pale yellow solid purified by silica gel column chromatography using *n*-hexane:ethyl acetate (3:1 v/v) as eluent; R_f = 0.10). mp 84-85 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.76-7.72 (m, 3H), 7.47-7.33 (m, 8H, NH), 4.93 (d, *J* = 5.2 Hz, 2H,). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 199.28, 141.80, 136.29, 131.31, 129.17, 128.67, 128.51, 128.37, 126.83, 51.18. Calculated m/z for $C_{14}H_{13}NS$ + 1, 228.08 (100.0%), found 228.1.
 Methyl 3-ethanethioamido-3-phenylpropanoate (**6**)	Pale yellow semisolid purified by silica gel column chromatography using *n*-hexane:ethyl acetate (3:1 v/v) as eluent; R_f = 0.10). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.48 (br. s, 1H), 6.35-6.25 (m, 5H), 6.02 (dt, *J* = 5.5, 8.5 Hz, 1H), 3.60 (s, 3H) 3.08 (dd, *J* = 5, 16.2 Hz, 1H), 2.94 (dd, *J* = 5, 16.2 Hz, 1H), 2.56 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 200.59, 171.96, 138.68, 128.91, 128.08, 126.54, 55.24, 52.10, 37.97, 34.40. Calculated m/z for $C_{12}H_{15}NO_2S$ + 1, 238.08 (100.0%), found 238.1.

 (9H-Fluoren-9-yl)methyl (2-amino-2-thioxoethyl)carbamate (**7**)	Pale yellow solid purified by silica gel column chromatography using *n*-hexane:ethyl acetate (3:1 v/v) as eluent; R_f = 0.23). mp 188.2-190 °C. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.71 (br. s, 1H), 9.08 (br. s, 1H), 7.89 (d, *J* = 7.6 Hz, 2H), 7.73 (d, *J* = 7.6 Hz, 2H), 7.7 (m, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 4.29 (d, *J* = 6.5 Hz, 2H), 4.23 (t, *J* = 6.9 Hz), 3.88 (d, *J* = 6.14, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 204.25, 156.85, 144.38, 141.25, 128.18, 127.62, 125.86, 120.66, 66.33, 51.19, 47.17. Calculated m/z for $C_{17}H_{16}N_2O_2S$ + 1, 313.09 (100.0%), found 313.1.
 (9H-Fluoren-9-yl)methyl (*S*)-(1-amino-1-thioxopropan-2-yl)carbamate (**8**)	Pale yellow solid purified by silica gel column chromatography using *n*-hexane:ethyl acetate (3:1 v/v) as eluent; R_f = 0.25. mp 190.2-191.3 °C. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.34 (br. s, 1H, S=CNH), 8.91 (br. s, 1H), 7.86 (d, *J* = 7.6 Hz, 2H), 7.69 (t, *J* = 7.7 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.02 (br. s, 1H), 4.41 (m, 1H), 4.30 (m, 2H), 4.23 (t, *J* = 7 Hz, 1H), 1.34 (d, *J* = 7 Hz, 3H). ^{13}C-NMR (126 MHz, DMSO-d_6) δ 209.71, 155.69, 144.50, 141.33, 128.12, 127.56, 125.70, 120.51, 66.48, 56.68, 47.47, 21.73. Calculated m/z for $C_{18}H_{18}N_2O_2S$ +1, 327.11 (100.0%), found 327.1.
 Methyl (*S*)-3-(2-(((benzyloxy)carbonyl)amino)-3-phenylpropanethioamido)propanoate (**9**)	Pale yellow semisolid purified by silica gel column chromatography using *n*-hexane:ethyl acetate (3:1 v/v) as eluent; R_f = 0.28). mp 65.2-66.1°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.17 (br. s, 1H), 7.37-7.28 (m, 5H, cbz), 7.25-7.12 (m, 5H) 5.85 (br. s, 1H), 5.05 (m, 2H), 4.63 (m, 1H), 3.87 (dtd, *J* = 5, 6.6, 6.6, 13.42 Hz, 1H), 3.62 (m, 1H), 3.60 (s, 3H), 3.12 (m, 2H), 2.47 (m, 1H), 2.32 (m, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 202.62, 172.26, 155.89, 136.48, 136.22, 128.32, 128.06, 67.17, 62.85, 52.01, 42.64, 40.48, 31.66. Calculated m/z for $C_{21}H_{24}N_2O_4S$ + 1, 401.15 (100.0%), found 401.2.
 (*S*)-1-benzyl-4-methylazetidine-2-thione (**10**)	Brown liquid purified by silica gel column chromatography using *n*-hexane:ethyl acetate (3:1 v/v) as eluent; R_f = 0.3). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.94 (d, *J* = 14.8, 1H), 4.34 (d, *J* = 14.8, 1H), 4.07 (m, 1H), 3.12 (dd, *J* = 4.4, 15.6 Hz, 1H), 2.66 (dd, J = 3.3, 15.1 Hz, 1H), 1.24 (d, *J* = 6.35 Hz, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 199.98, 134.61, 128.99, 128.70, 128.19, 56.50, 47.64, 47.45, 17.95. Calculated m/z for $C_{11}H_{13}NS$ + 1, 192.08 (100.0%), found HRMS (ESI-TOF) 192.0841.
 (*S*)-(2-(*tert*-Butyl)-4-thioxo-3,4-dihydropyrimidin-1(2H)-yl)(phenyl)methanone (**11**)	Pale yellow solid purified by silica gel column chromatography using *n*-hexane:ethyl acetate (3:1 v/v) as eluent; R_f= 0.23. mp 166.2-166.9 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.53 (br. s, 1H), 7.55-7.43 (m, 5H), 6.92 (d, *J* = 7.9 Hz, 1H), 5.79 (m, 1H), 5.77 (d, *J* = 7.9 Hz, 1H), 1.04 (s, 9H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ 188.74, 169.70, 132.95, 131.73, 131.69, 129.07, 128.14, 112.45, 70.48, 41.52, 25.74. Calculated m/z for $C_{15}H_{18}N_2OS$ + 1, 275.11 (100.0%), found HRMS (ESI-TOF) 275.1220.

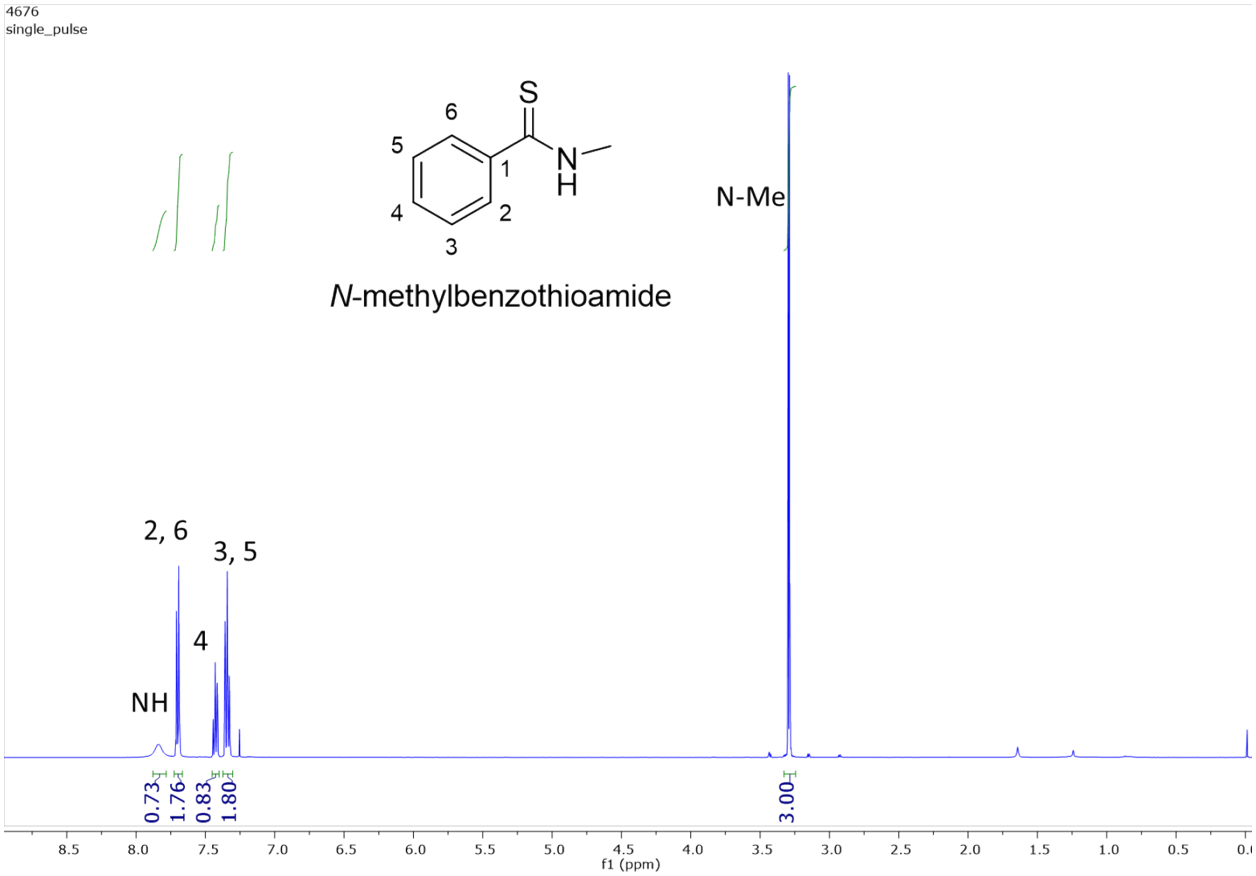
NMR spectra



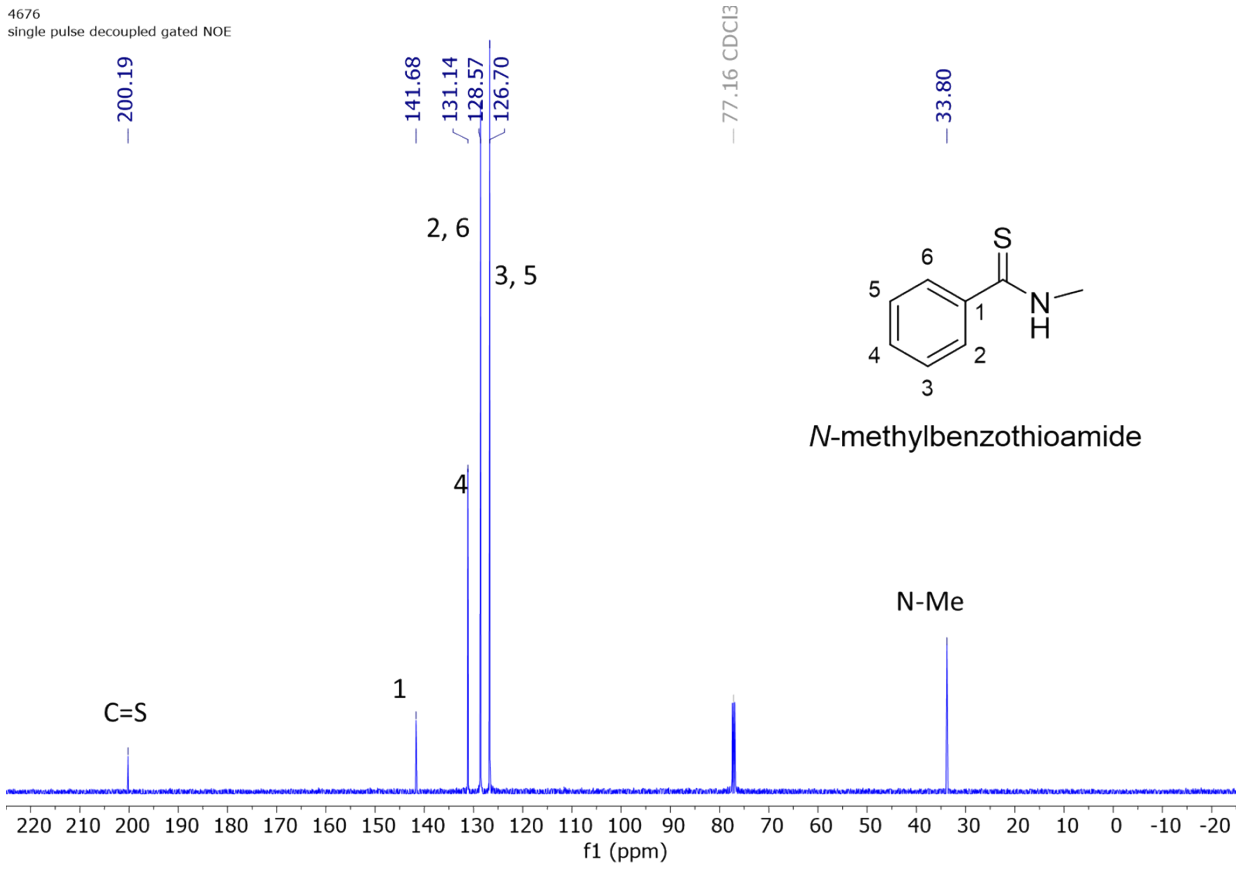
^{1}H-NMR spectrum of benzothioamide (**1**) (500 MHz, DMSO-d_6).



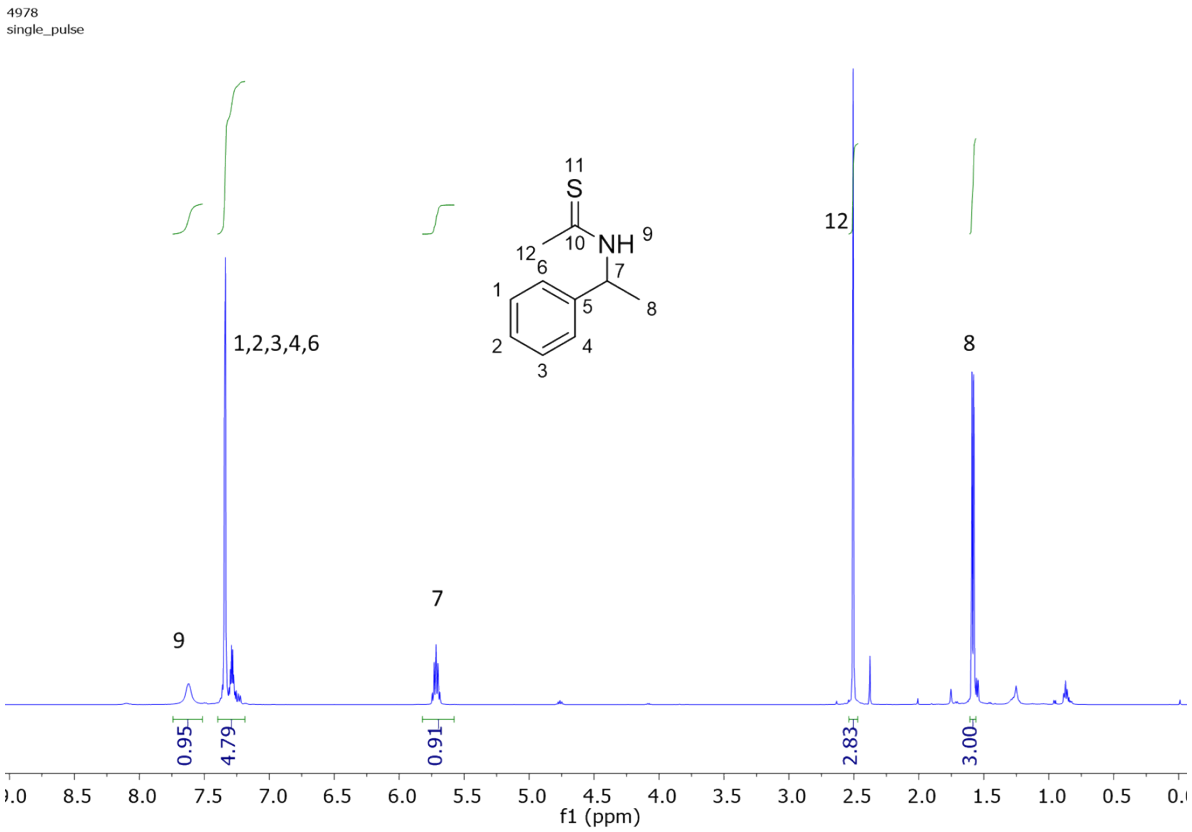
^{13}C NMR spectrum of benzothioamide (**1**) (126 MHz, DMSO-d_6).



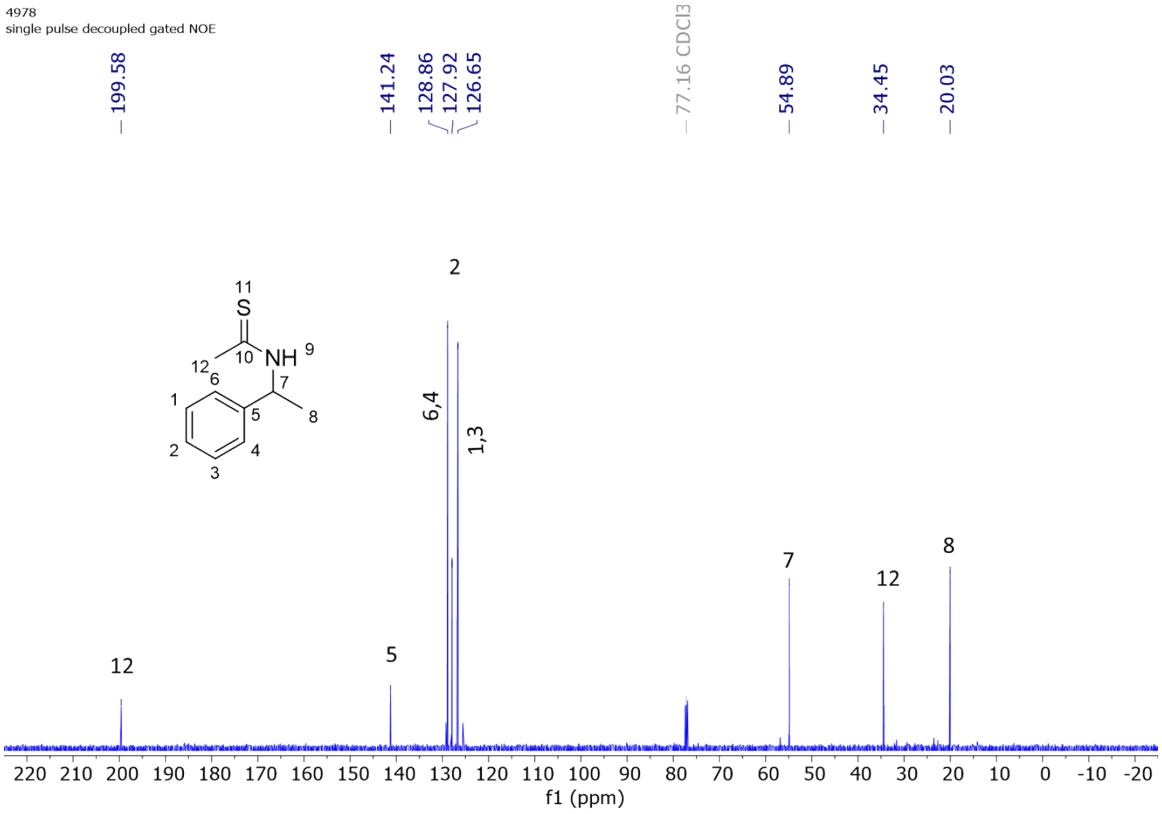
^{1}H-NMR spectrum of *N*-methylbenzothioamide (**2**) (500 MHz, $CDCl_3$).



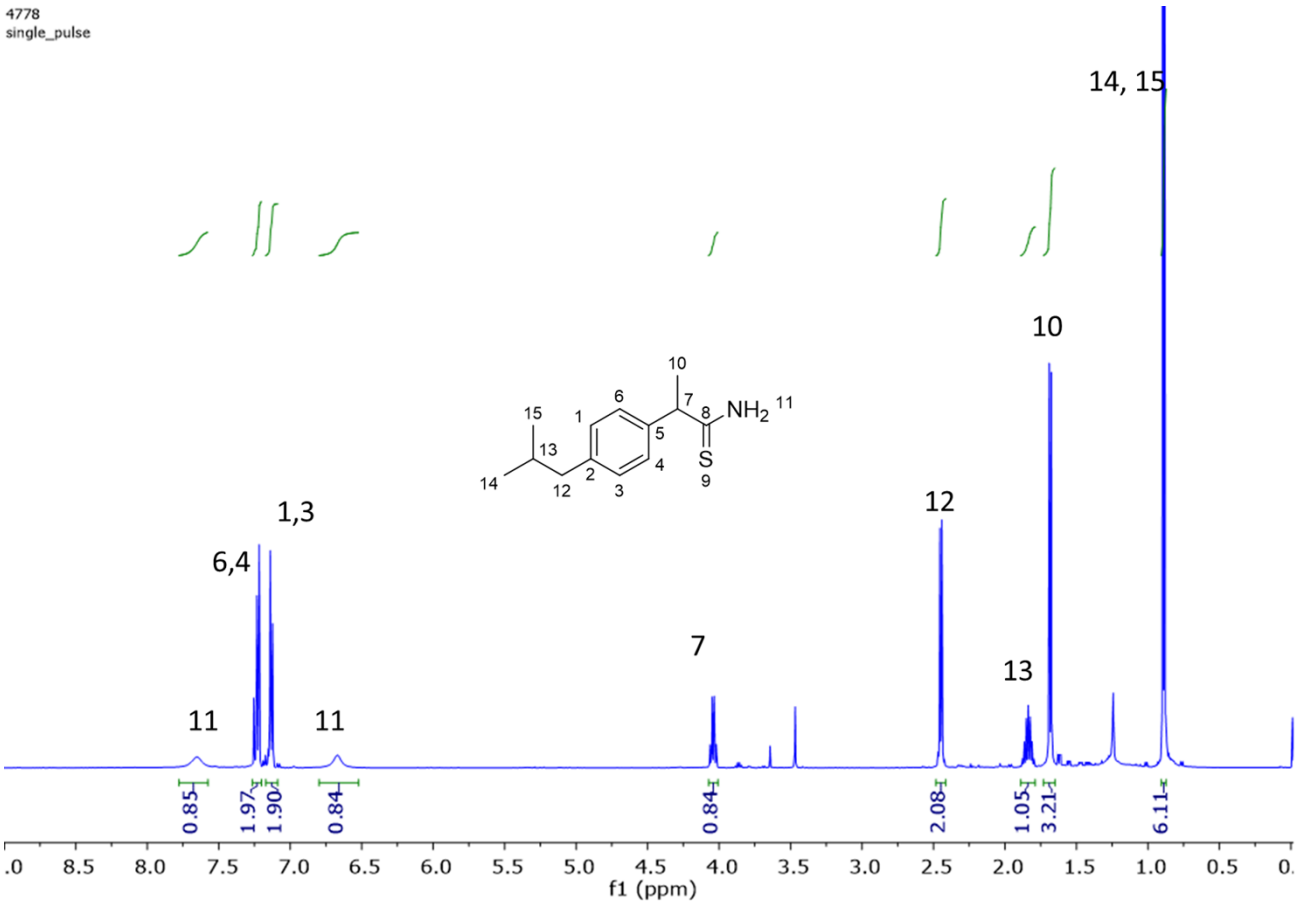
^{13}C-NMR spectrum of *N*-methylbenzothioamide (**2**) (126 MHz, $CDCl_3$).



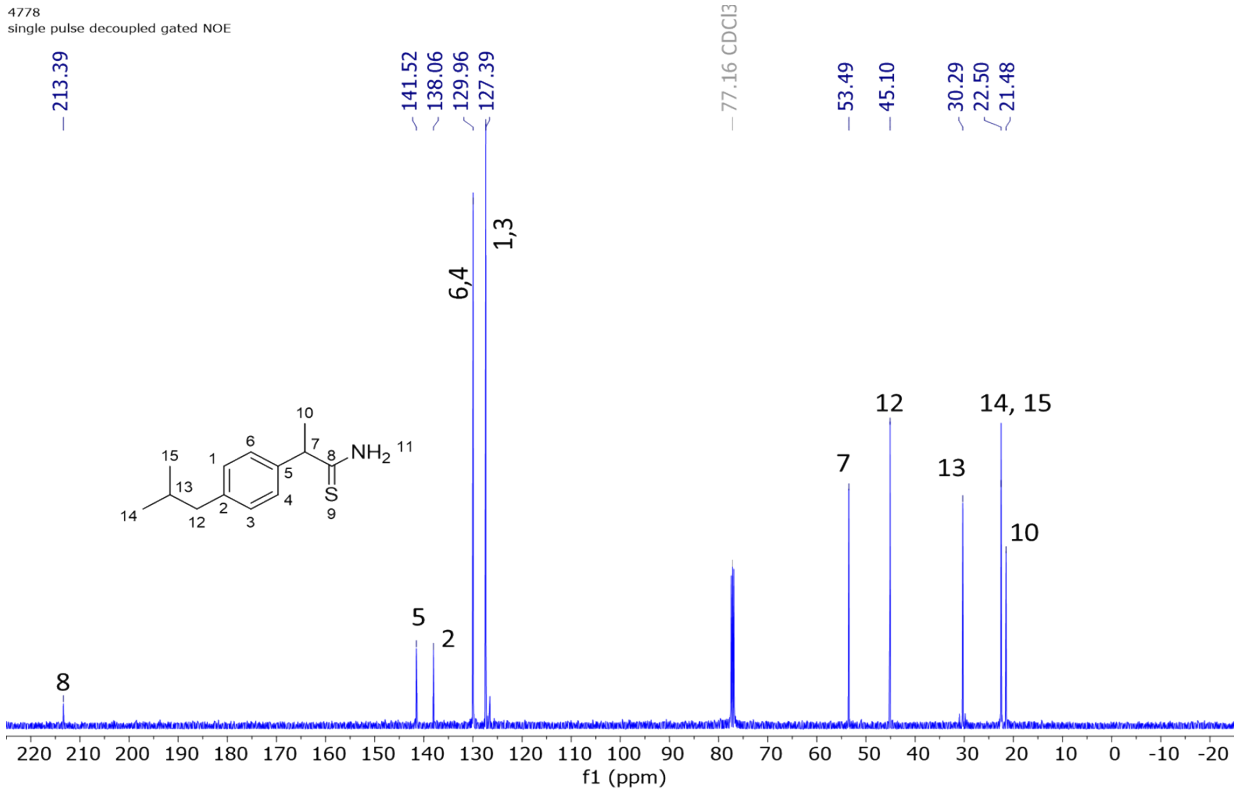
^{1}H-NMR spectrum of *N*-(1-phenylethyl)ethanethioamide (**3**) (500 MHz, $CDCl_3$).



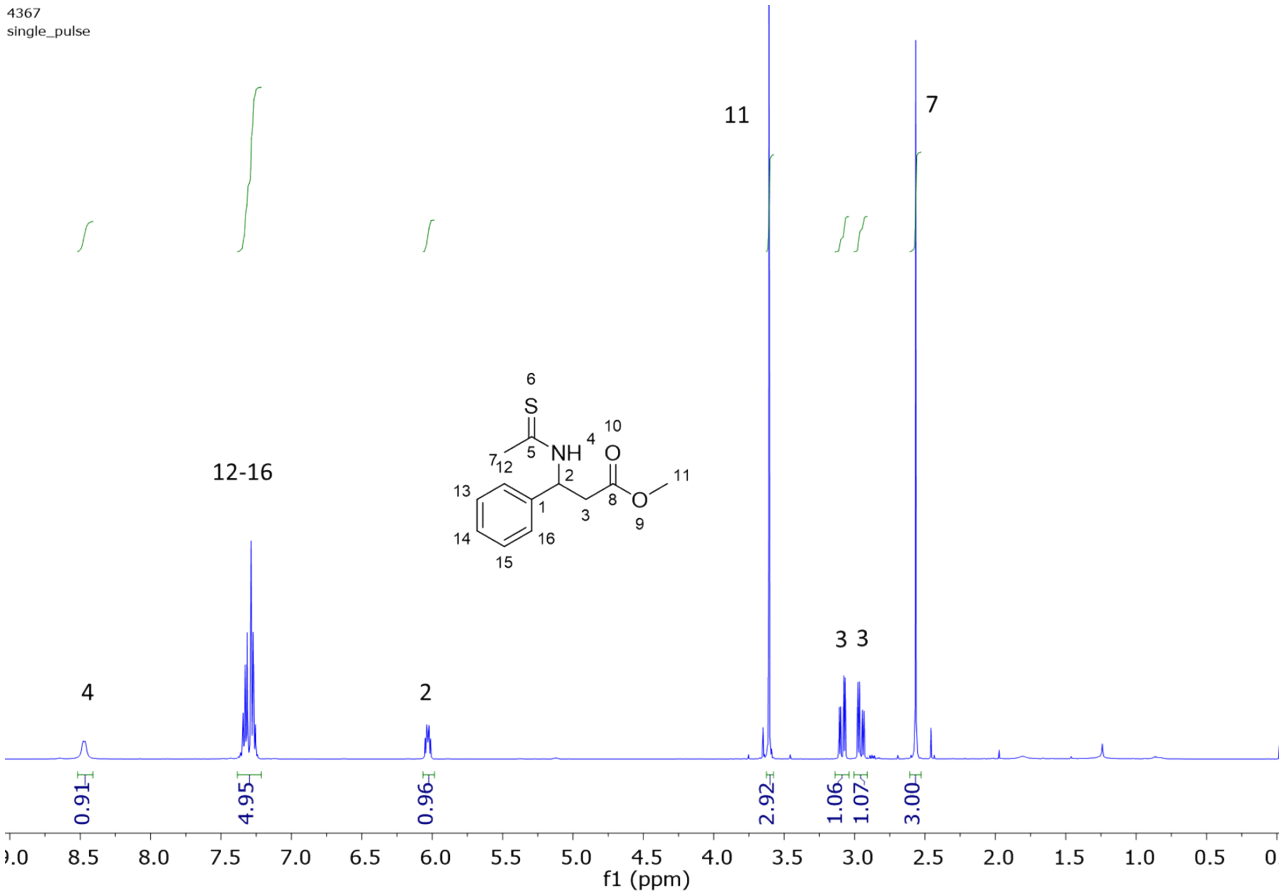
^{13}C-NMR spectrum of *N*-(1-phenylethyl)ethanethioamide (**3**) (126 MHz, $CDCl_3$).



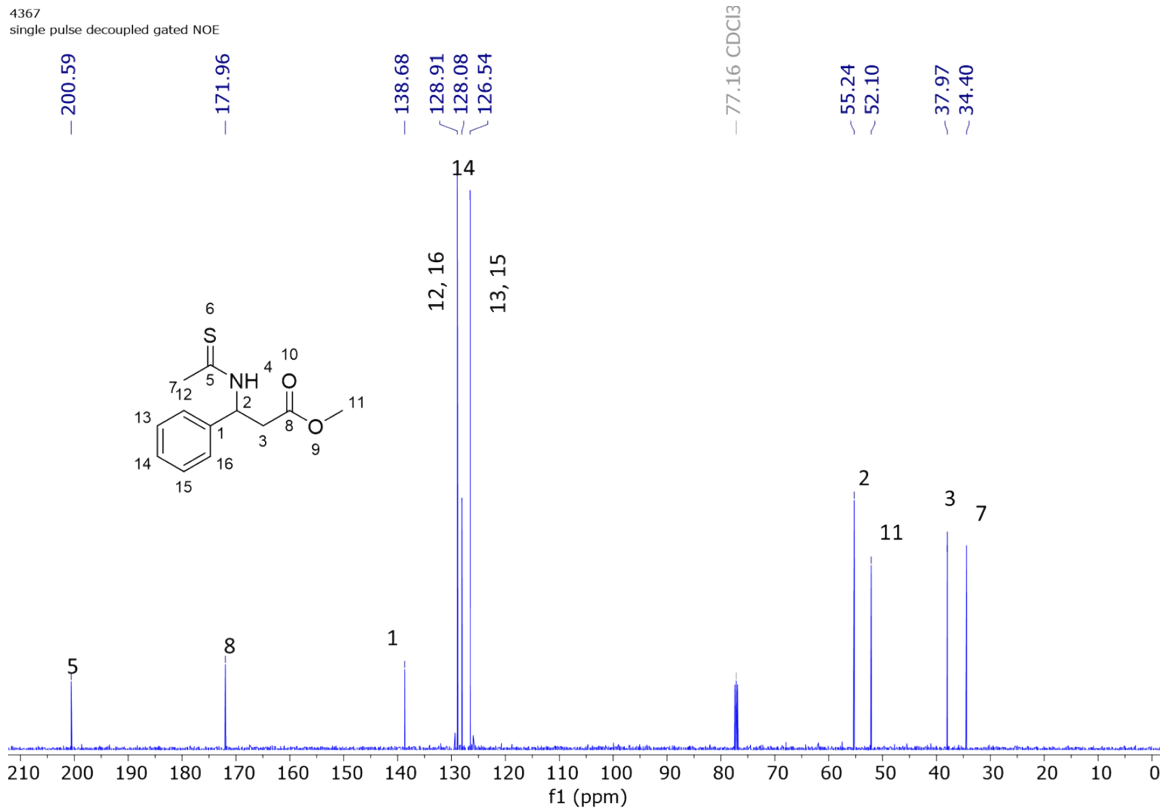
^{1}H-NMR spectrum of 2-(4-isobutylphenyl)propanethioamide (**4**) (500 MHz, $CDCl_3$).



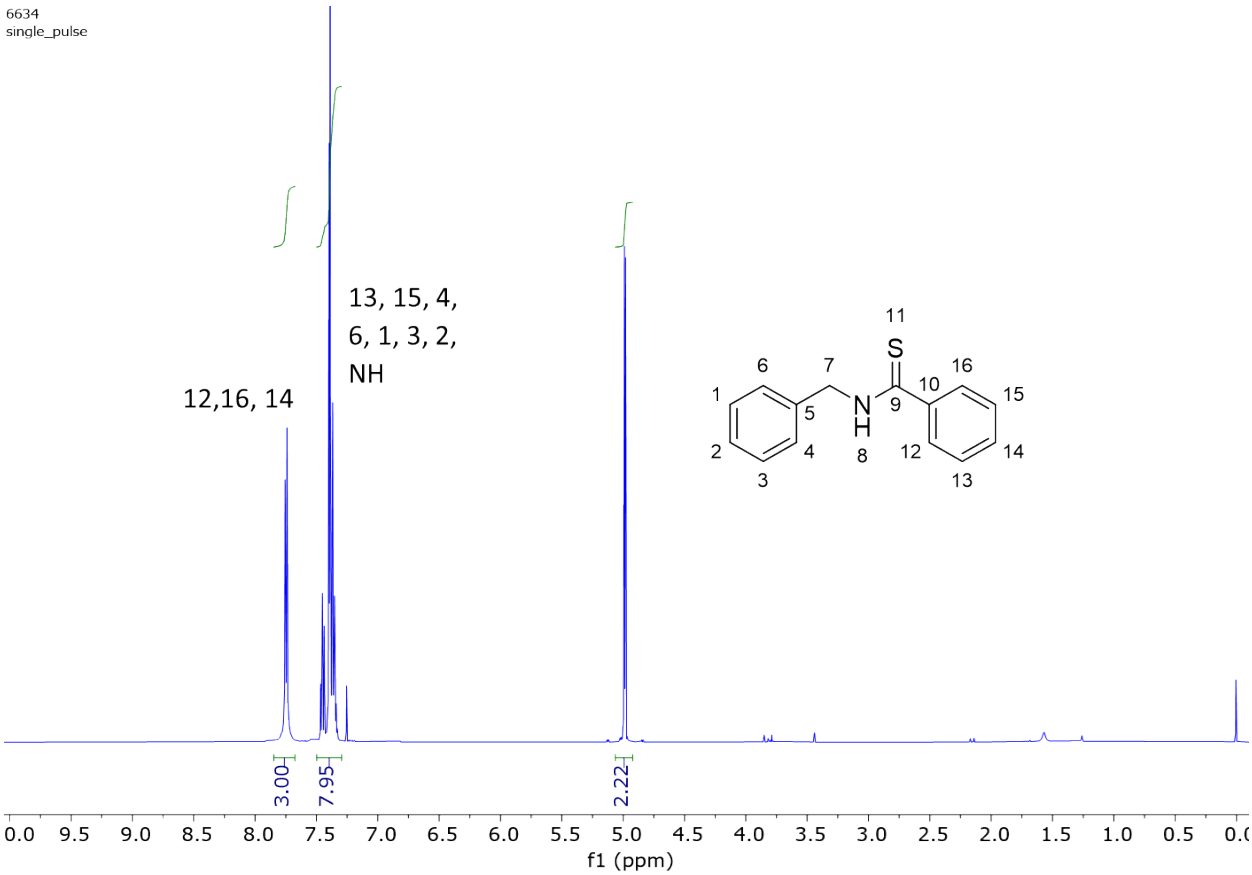
^{13}C-NMR spectrum of 2-(4-isobutylphenyl)propanethioamide (**4**) (126 MHz, $CDCl_3$).



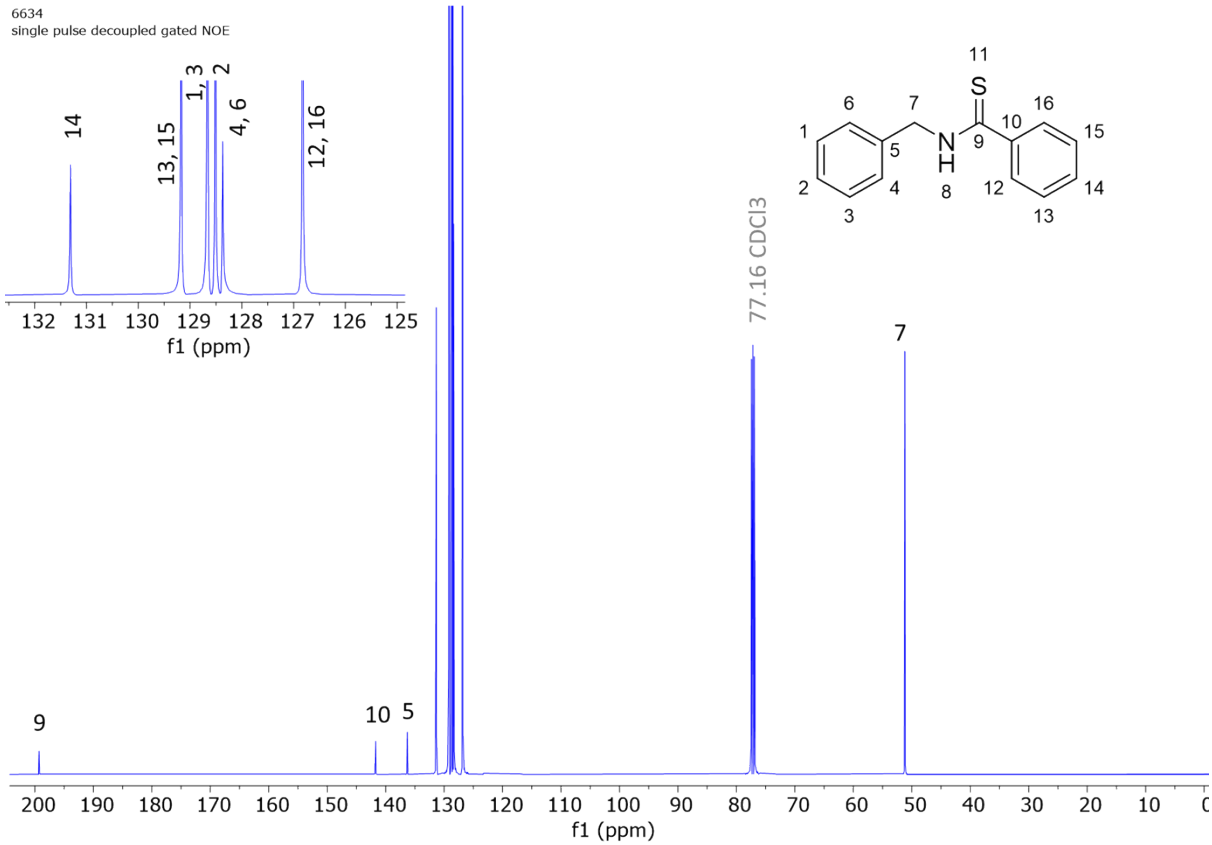
^{1}H-NMR spectrum of methyl 3-ethanethioamido-3-phenylpropanoate (**5**) (500 MHz, $CDCl_3$).



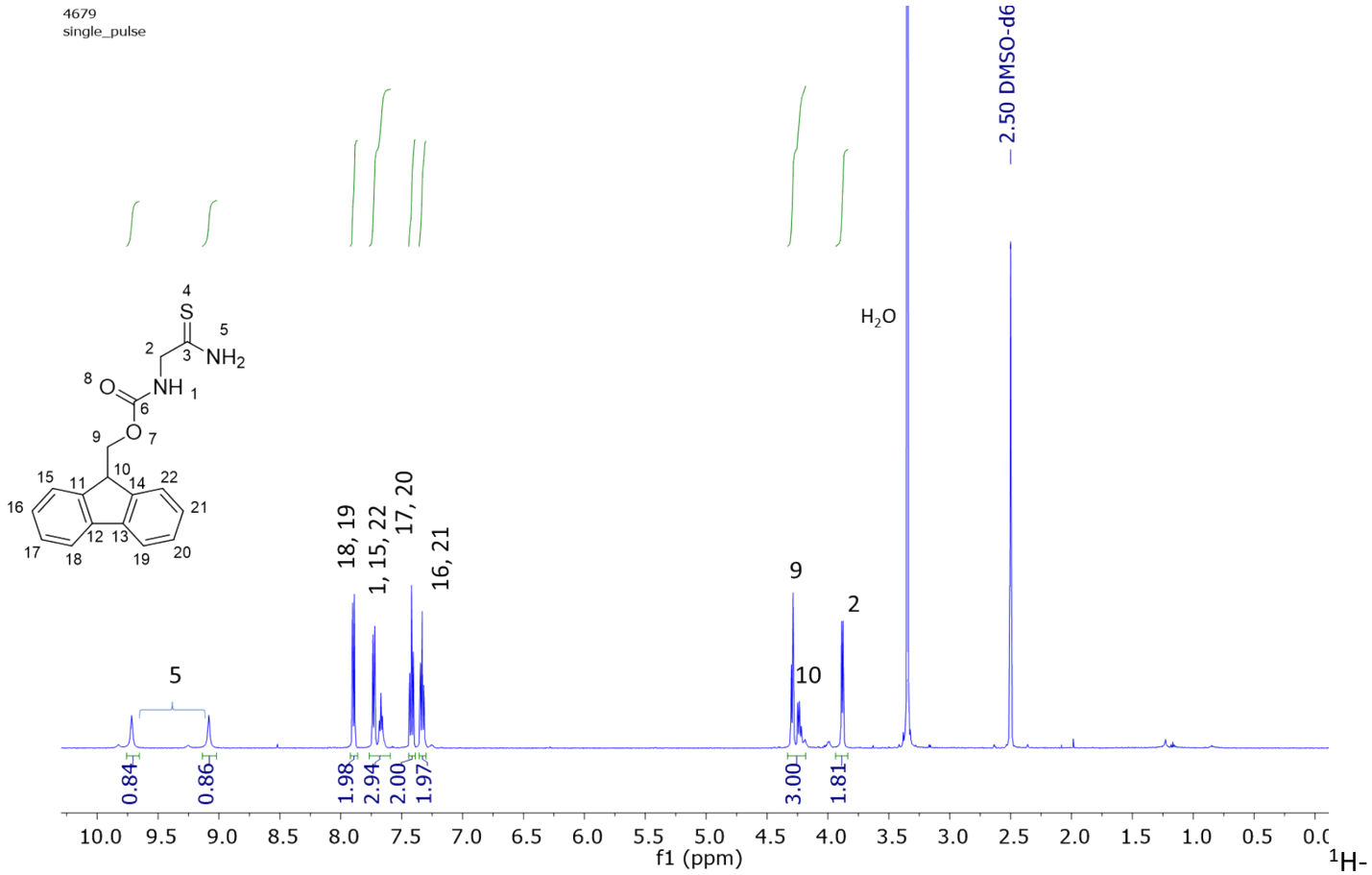
^{13}C-NMR spectrum of methyl 3-ethanethioamido-3-phenylpropanoate (**5**) (126 MHz, $CDCl_3$).



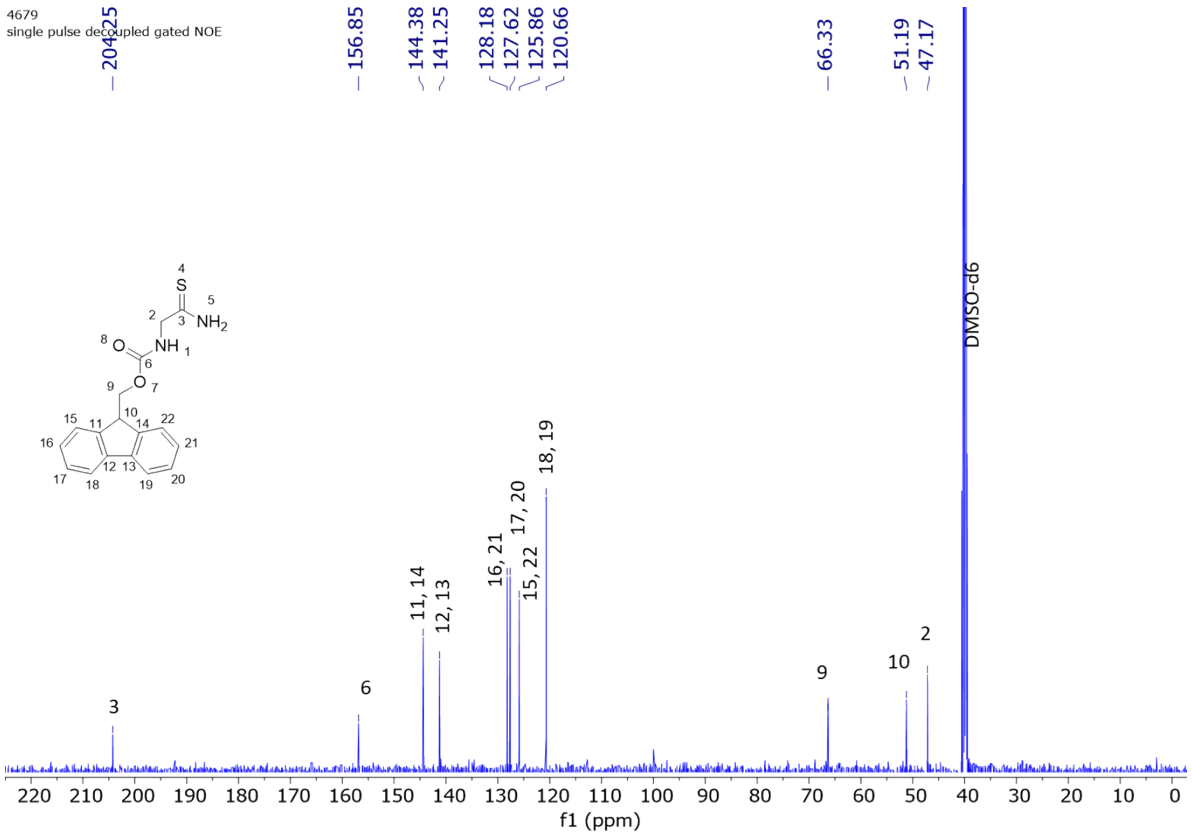
^{1}H-NMR spectrum of *N*-benzylbenzothioamide (**6**) (500 MHz, $CDCl_3$).



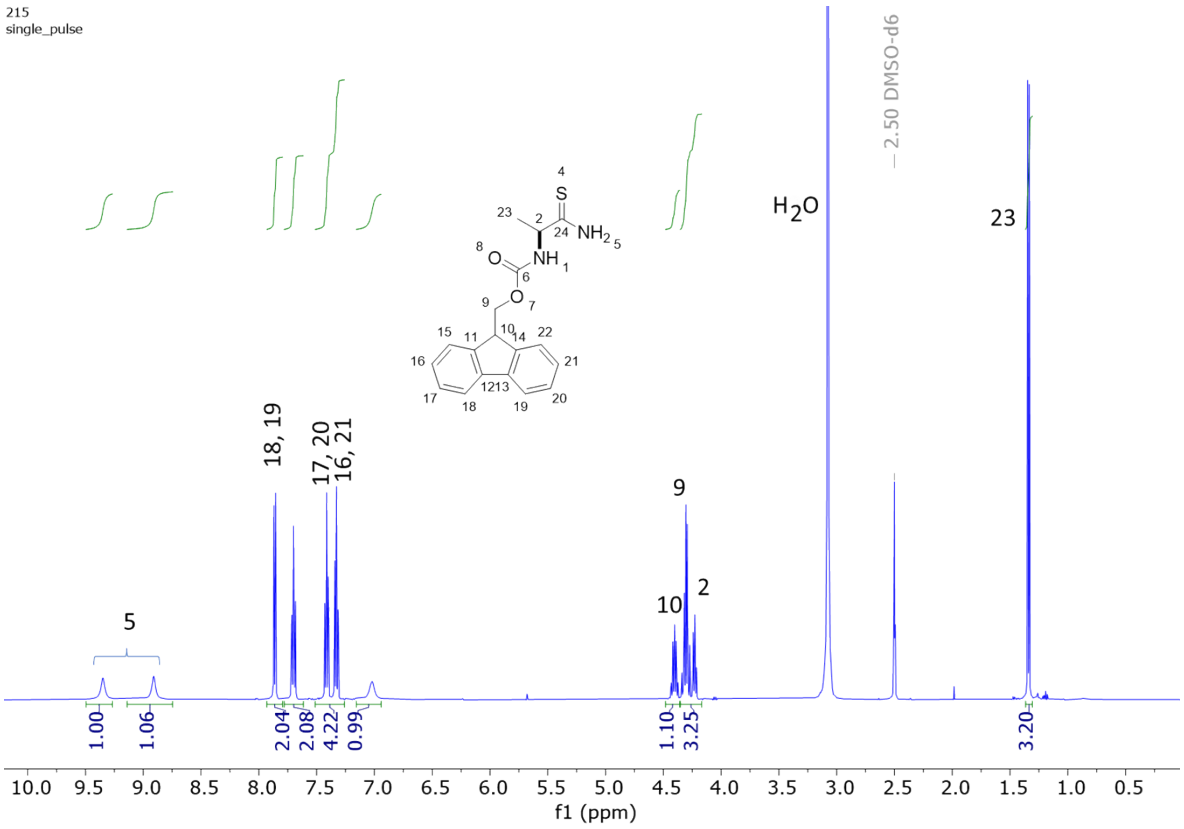
^{13}C-NMR spectrum of *N*-benzylbenzothioamide (**6**) (126 MHz, $CDCl_3$).



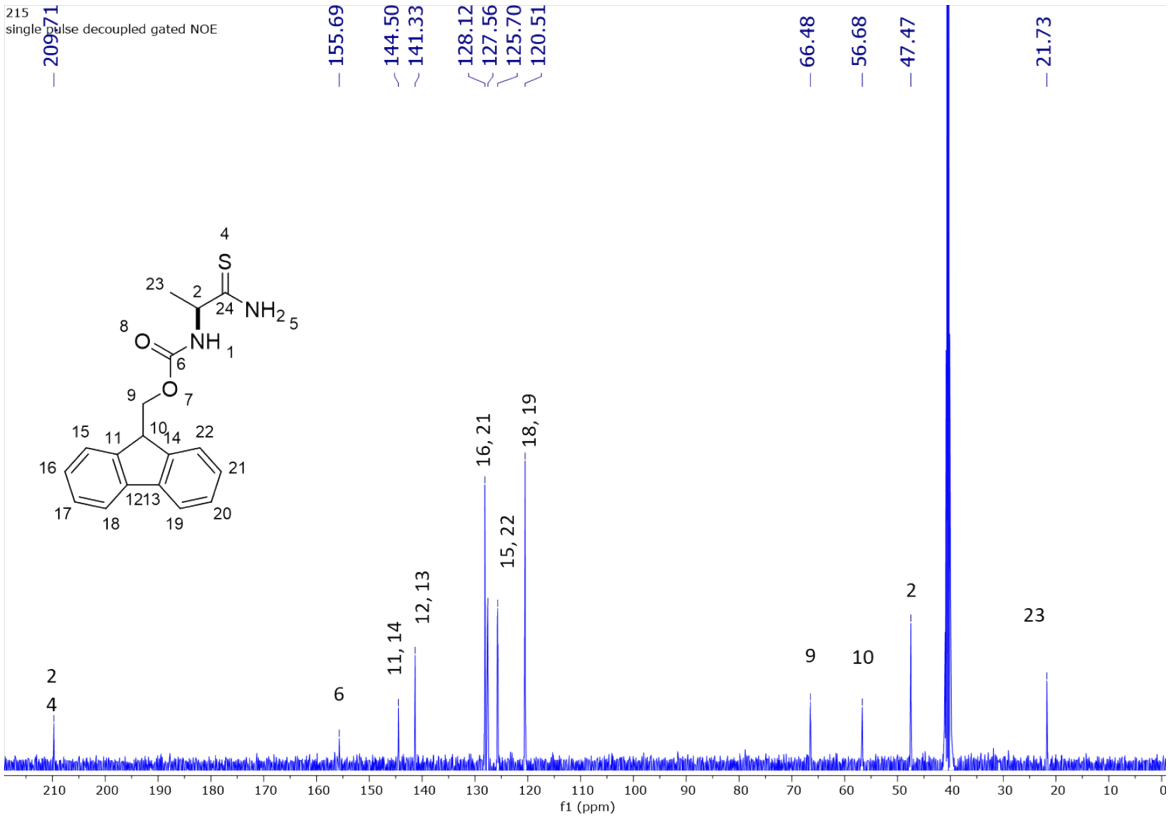
^{1}H-NMR spectrum of (9H-fluoren-9-yl)methyl (2-amino-2-thioxoethyl)carbamate (**7**) (500 MHz, DMSO-d_6).



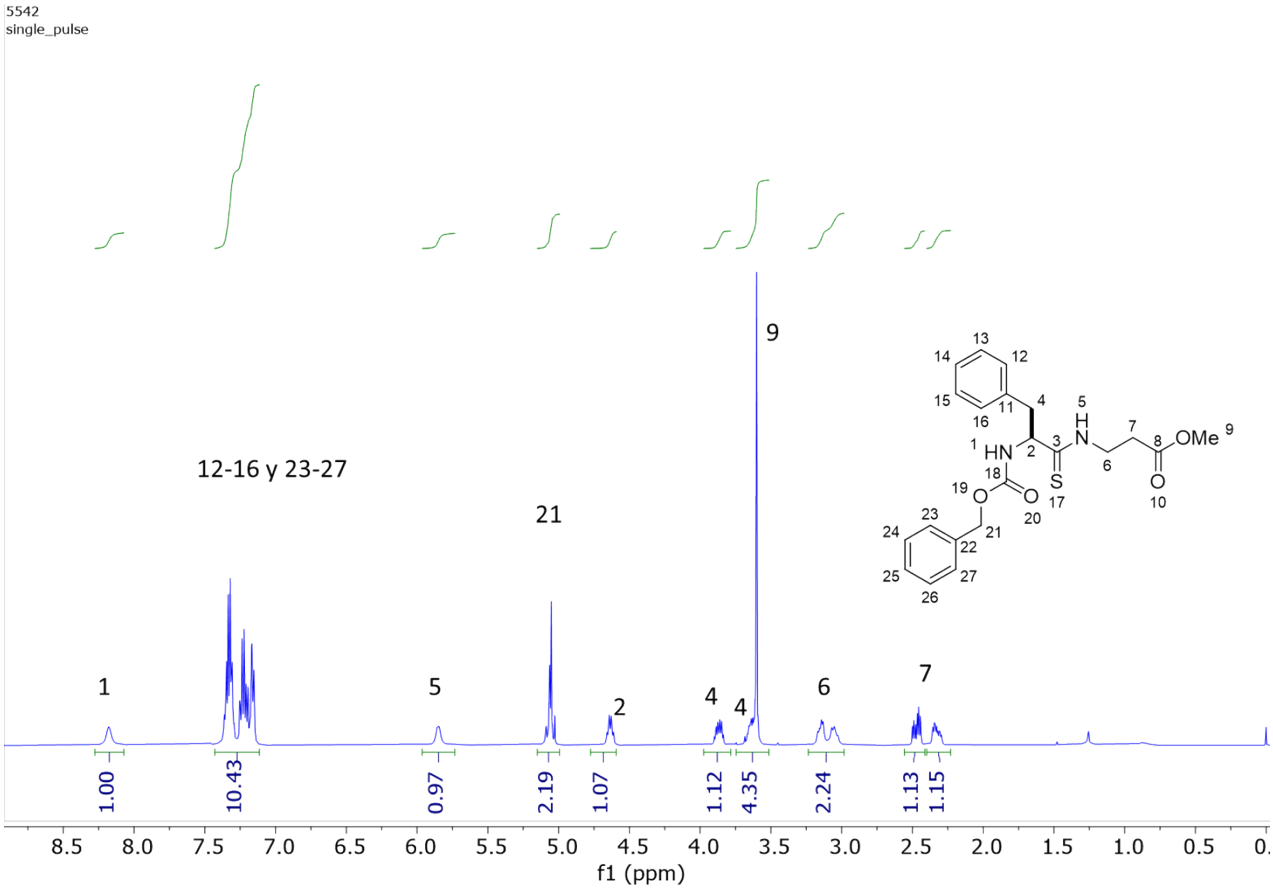
^{13}C-NMR spectrum of (9H-fluoren-9-yl)methyl (2-amino-2-thioxoethyl)carbamate (**7**) (126 MHz, DMSO-d_6).



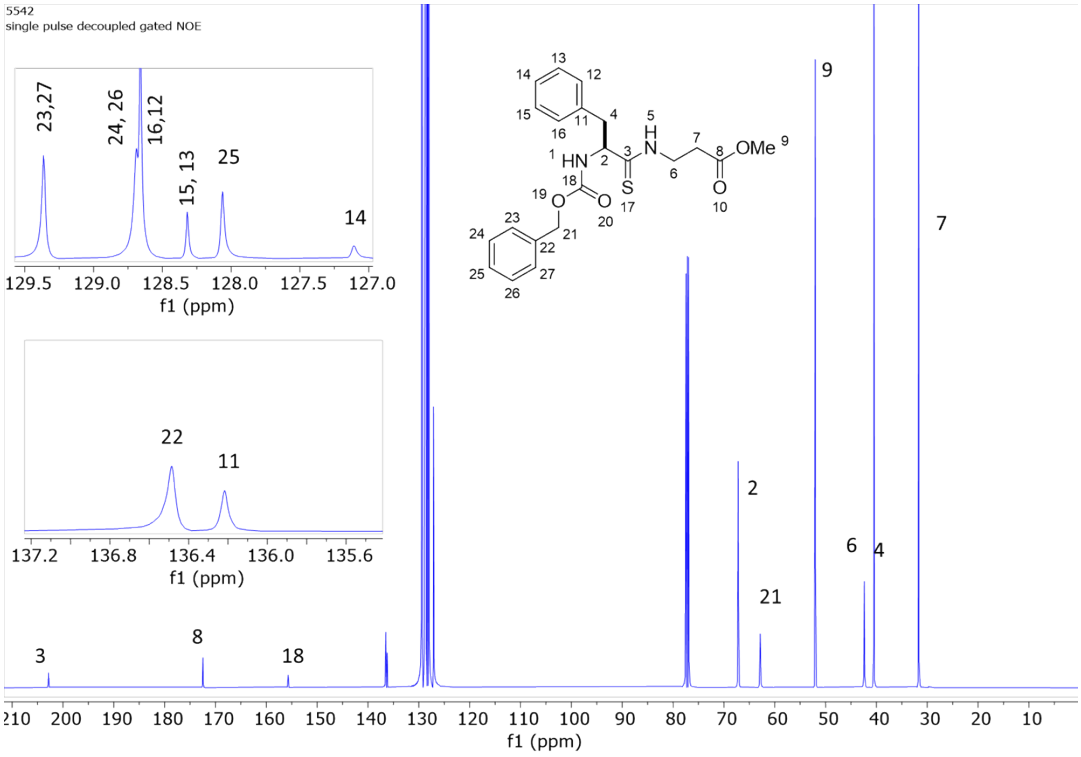
^{1}H-NMR spectrum of (9H-fluoren-9-yl)methyl (S)-(1-amino-1-thioxopropan-2-yl)carbamate (**8**) (500 MHz, DMSO-D_6).



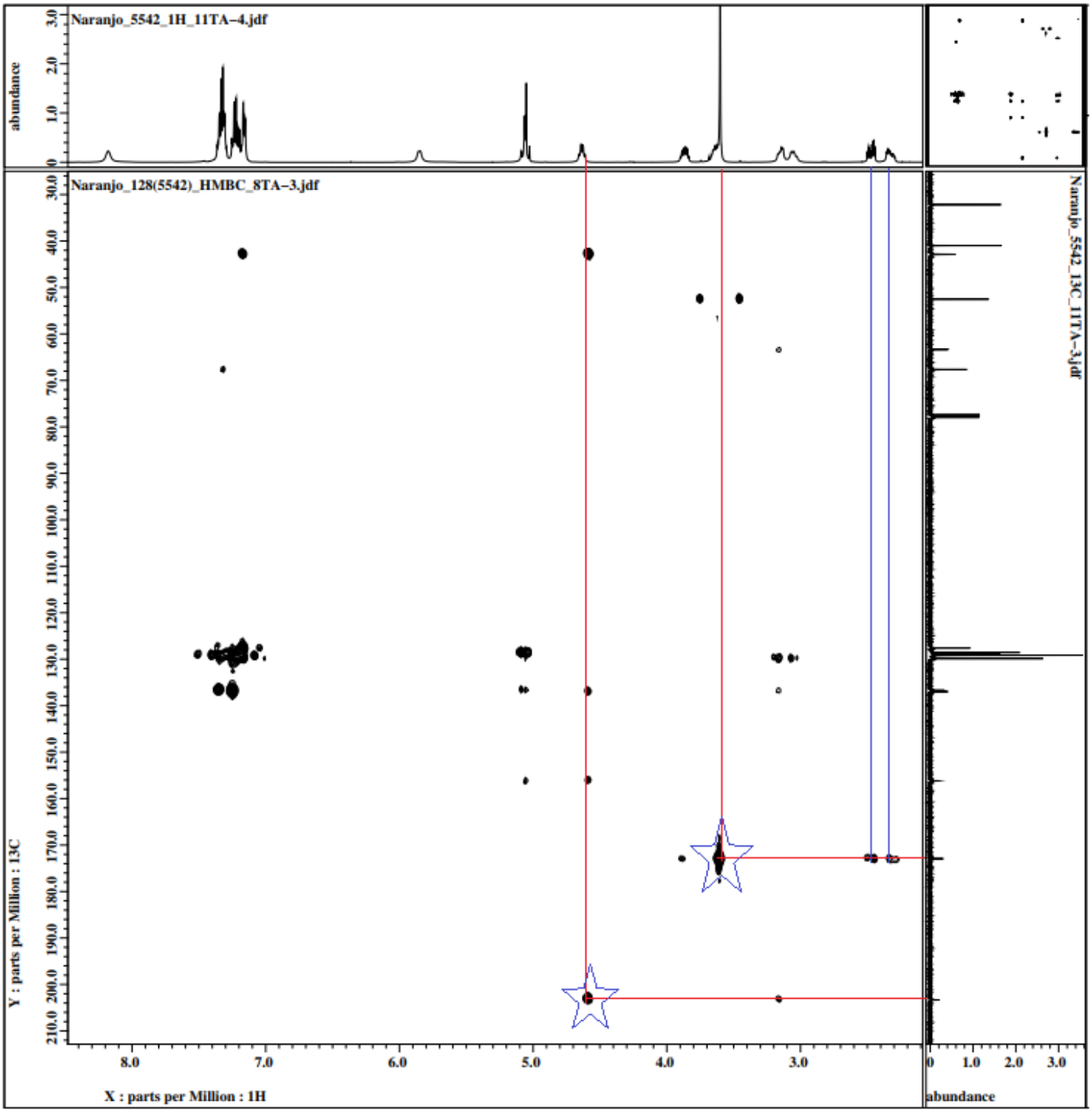
^{13}C-NMR spectrum of (9H-fluoren-9-yl)methyl (S)-(1-amino-1-thioxopropan-2-yl)carbamate (**8**) (126 MHz, DMSO-d_6).



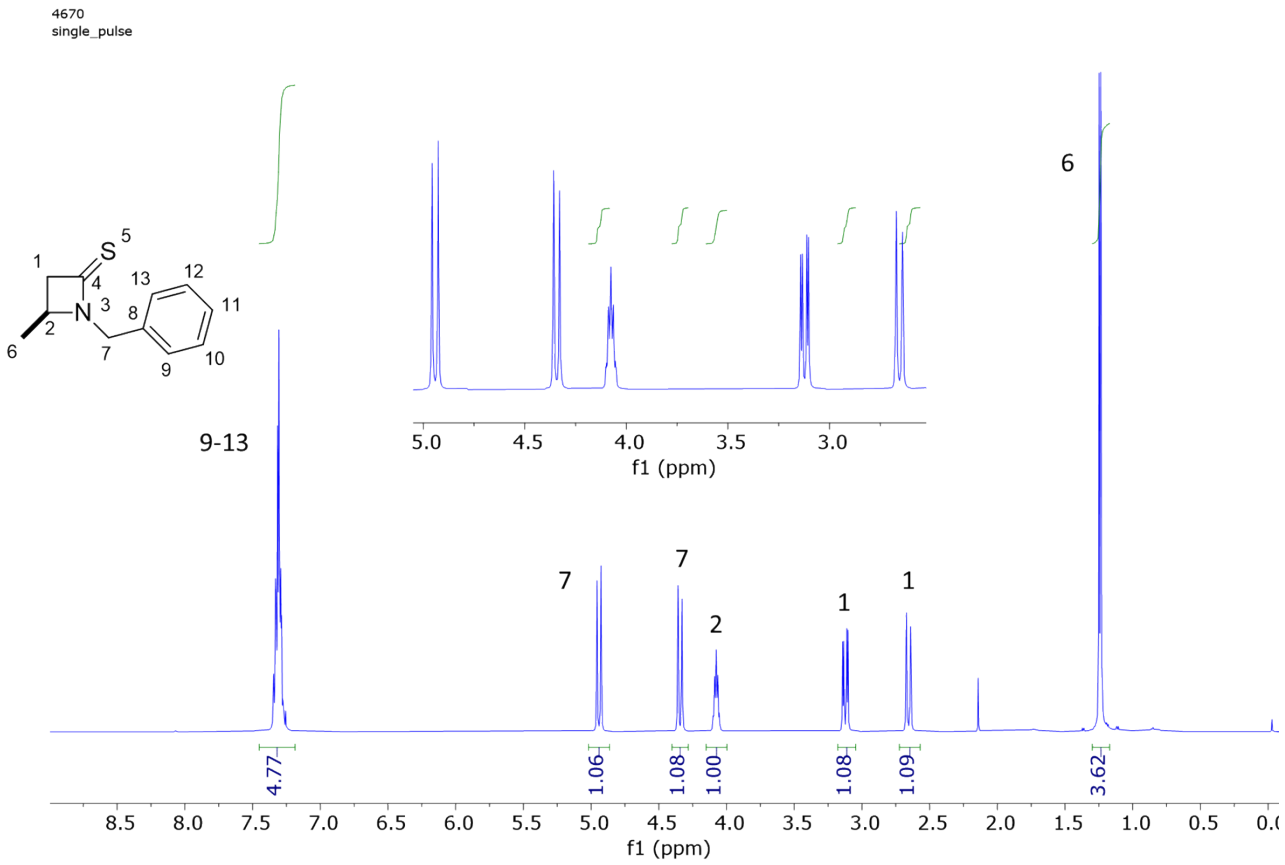
^{1}H-NMR spectrum of methyl (S)-3-(2-(((benzyloxy)carbonyl)amino)-3-phenylpropanethioamido)propanoate (**9**) (500 MHz, $CDCl_3$).



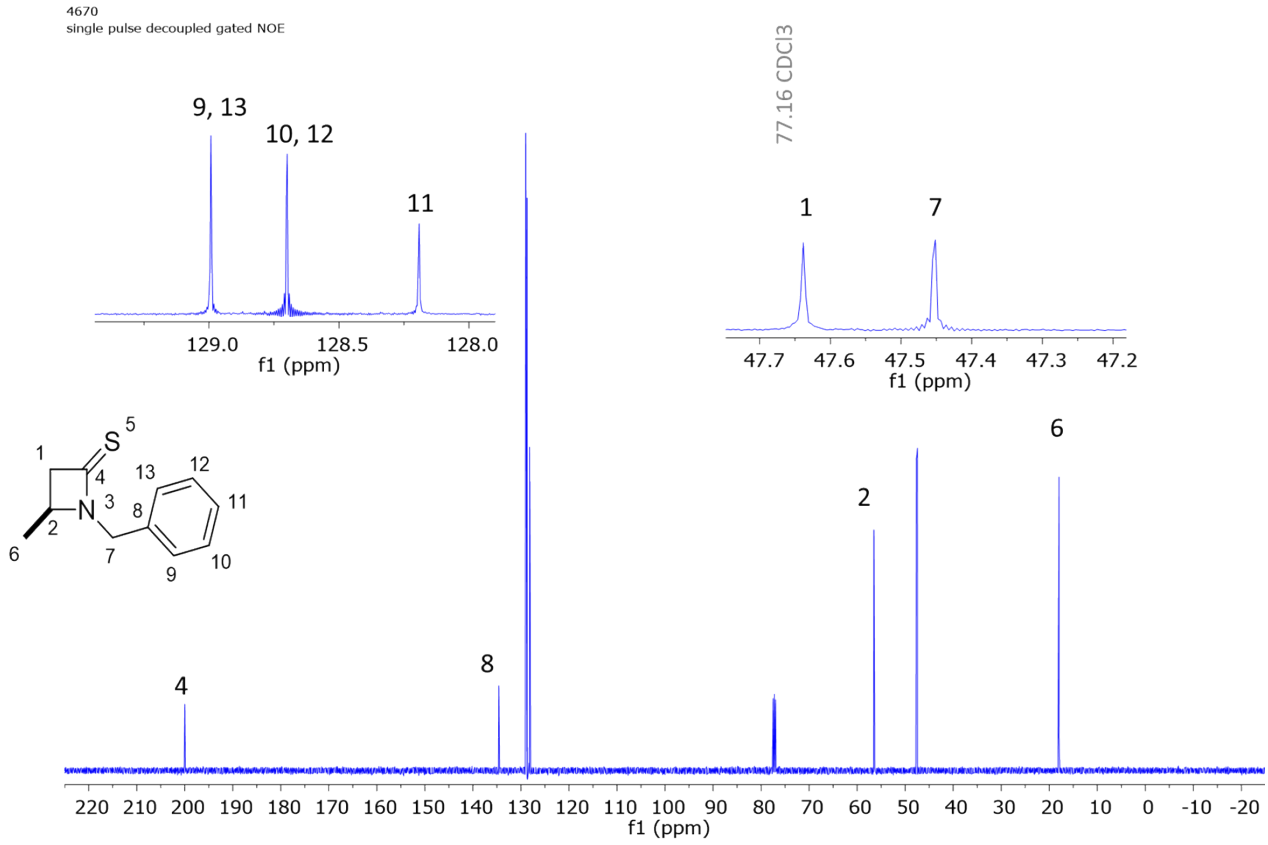
^{13}C-NMR spectrum of methyl (S)-3-(2-(((benzyloxy)carbonyl)amino)-3-phenylpropanethioamido)propanoate (**9**) (126 MHz, $CDCl_3$).



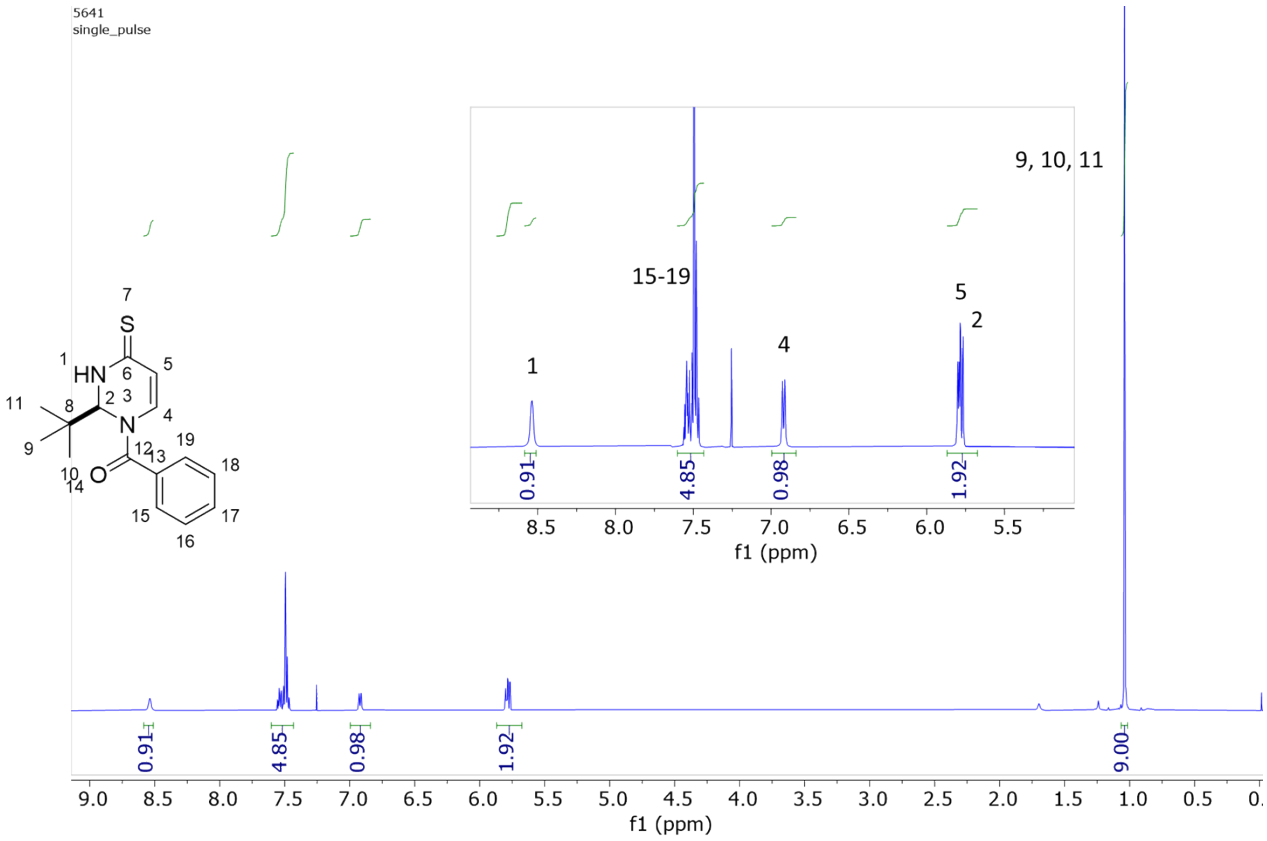
2D NMR-HMBC of methyl (*S*)-3-(2-(((benzyloxy)carbonyl)amino)-3-phenylpropanethioamido)propanoate (**9**) (500 MHz, $CDCl_3$).



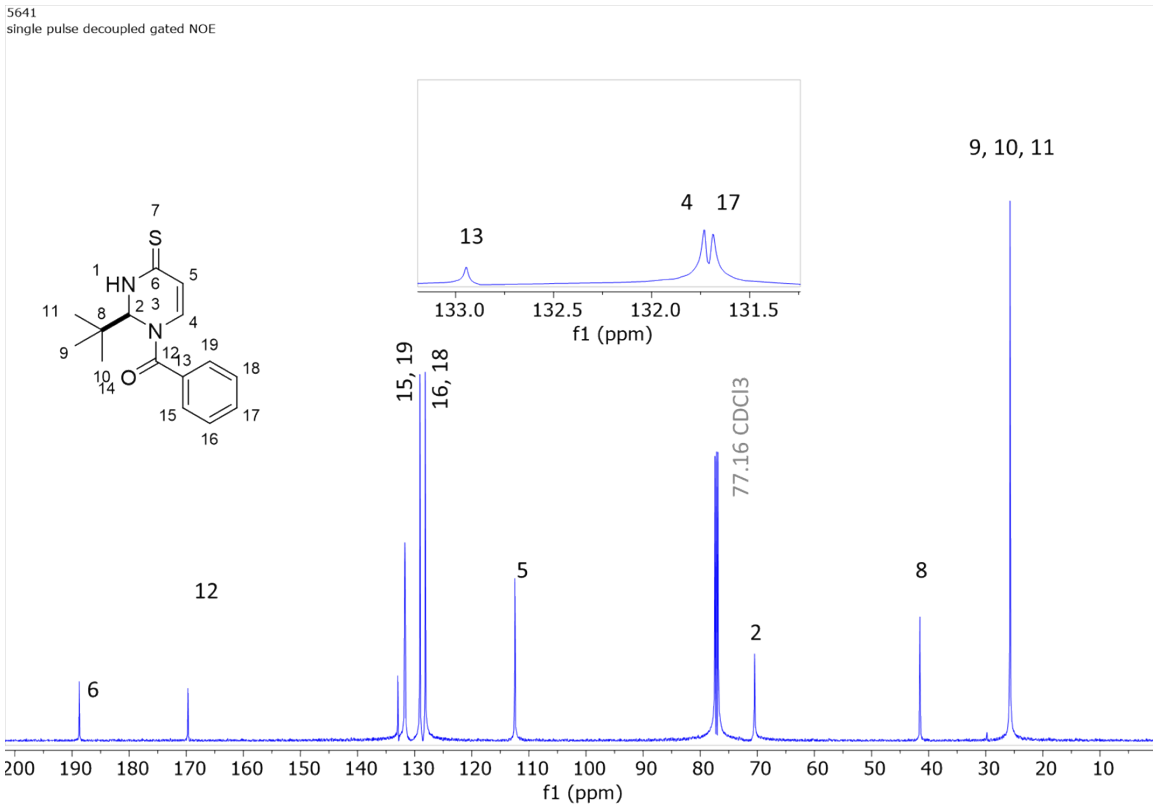
^{1}H-NMR spectrum of (*S*)-1-benzyl-4-methylazetidine-2-thione (**10**) (500 MHz, $CDCl_3$).



^{13}C-NMR spectrum of (*S*)-1-benzyl-4-methylazetidine-2-thione (**10**) (126 MHz, $CDCl_3$).



^{1}H-NMR spectrum of (*S*)-(2-(tert-butyl)-4-thioxo-3,4-dihydropyrimidin-1(2H)-yl)(phenyl)methanone (**11**) (500 MHz, $CDCl_3$).



^{13}C-NMR spectrum of (*S*)-(2-(*tert*-butyl)-4-thioxo-3,4-dihydropyrimidin-1(2H)-yl)(phenyl)methanone (**11**) (126 MHz, $CDCl_3$).

Mass spectra

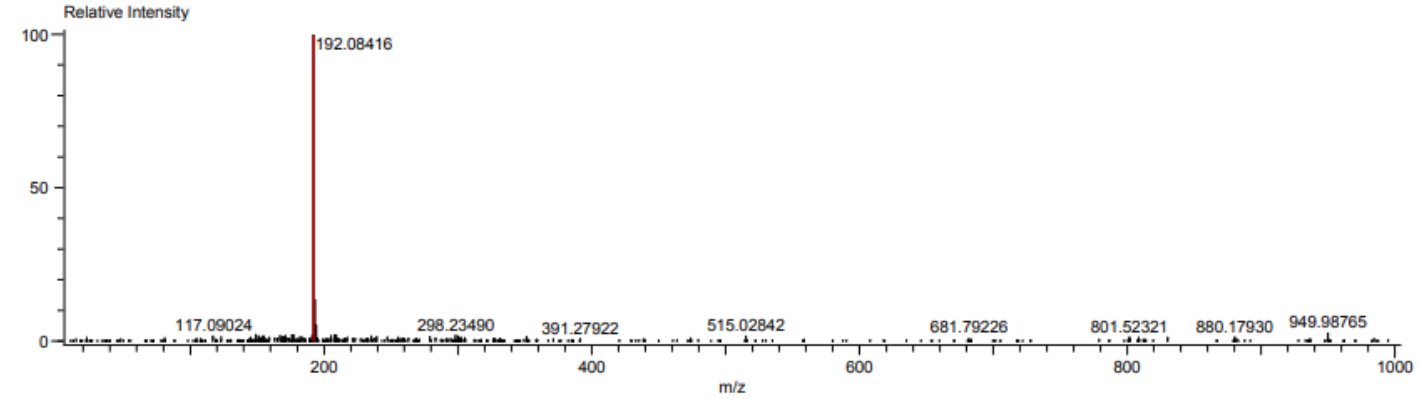
Data:U-169 10TA
Sample Name:Dr. Miranda / Diego Aleman
Description:
Ionization Mode:ESI+
History:Determine m/z[Peak Detect[Centroid,30,Area];Correct Base[];Smooth[5]];Correct Base[5.0%];Average(MS[...

Acquired:2/9/2024 12:04:42 PM
Operator:AccuTOF
Mass Calibration data:Cal_PEG_600
Created:2/9/2024 12:31:55 PM
Created by:AccuTOF

Charge number:1
Element:^{12}C:0 .. 11, ^{1}H:0 .. 14, ^{14}N:0 .. 1, ^{32}S:0 .. 1

Tolerance:3.00(ppm), 5.00 .. 15.00(mmu)

Unsaturation Number:-1.0 .. 20.0 (Fraction:Both)



Mass	Intensity	Calc. Mass	Mass Difference (mmu)	Mass Difference (ppm)	Possible Formula	Unsaturation Number
192.08416	13900.24	192.08469	-0.54	-2.79	$^{12}C_{11}{}^{1}H_{14}{}^{14}N_{1}{}^{32}S_{1}$	6.5

HRMS (ESI-TOF) of (*S*)-1-benzyl-4-methylazetidine-2-thione (**10**)

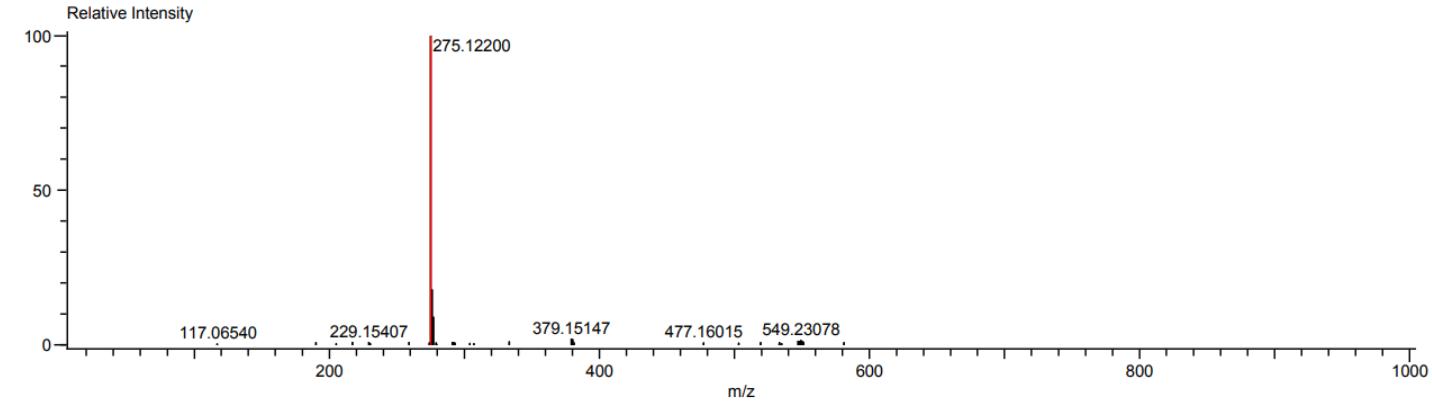
Data:U-170 11TA
Sample Name:Dr. Miranda / Diego Aleman
Description:
Ionization Mode:ESI+
History:Determine m/z[Peak Detect[Centroid,30,Area];Correct Base[];Smooth[5]];Correct Base[5.0%];Average(MS[...

Acquired:2/9/2024 12:09:13 PM
Operator:AccuTOF
Mass Calibration data:Cal_PEG_600
Created:2/9/2024 12:38:07 PM
Created by:AccuTOF

Charge number:1
Element:^{12}C:0 .. 15, ^{1}H:0 .. 19, ^{14}N:0 .. 2, ^{16}O:0 .. 1, ^{32}S:0 .. 1

Tolerance:3.00(ppm), 5.00 .. 15.00(mmu)

Unsaturation Number:-1.0 .. 20.0 (Fraction:Both)



Mass	Intensity	Calc. Mass	Mass Difference (mmu)	Mass Difference (ppm)	Possible Formula	Unsaturation Number
275.12200	305769.57	275.12181	0.19	0.70	$^{12}C_{15}{}^{1}H_{19}{}^{14}N_{2}{}^{16}O_{1}{}^{32}S_{1}$	8.5

HRMS (ESI-TOF) of (*S*)-(2-(*tert*-butyl)-4-thioxo-3,4-dihydropyrimidin-1(2H)-yl)(phenyl)methanone (**11**)

HPLC Chromatograms

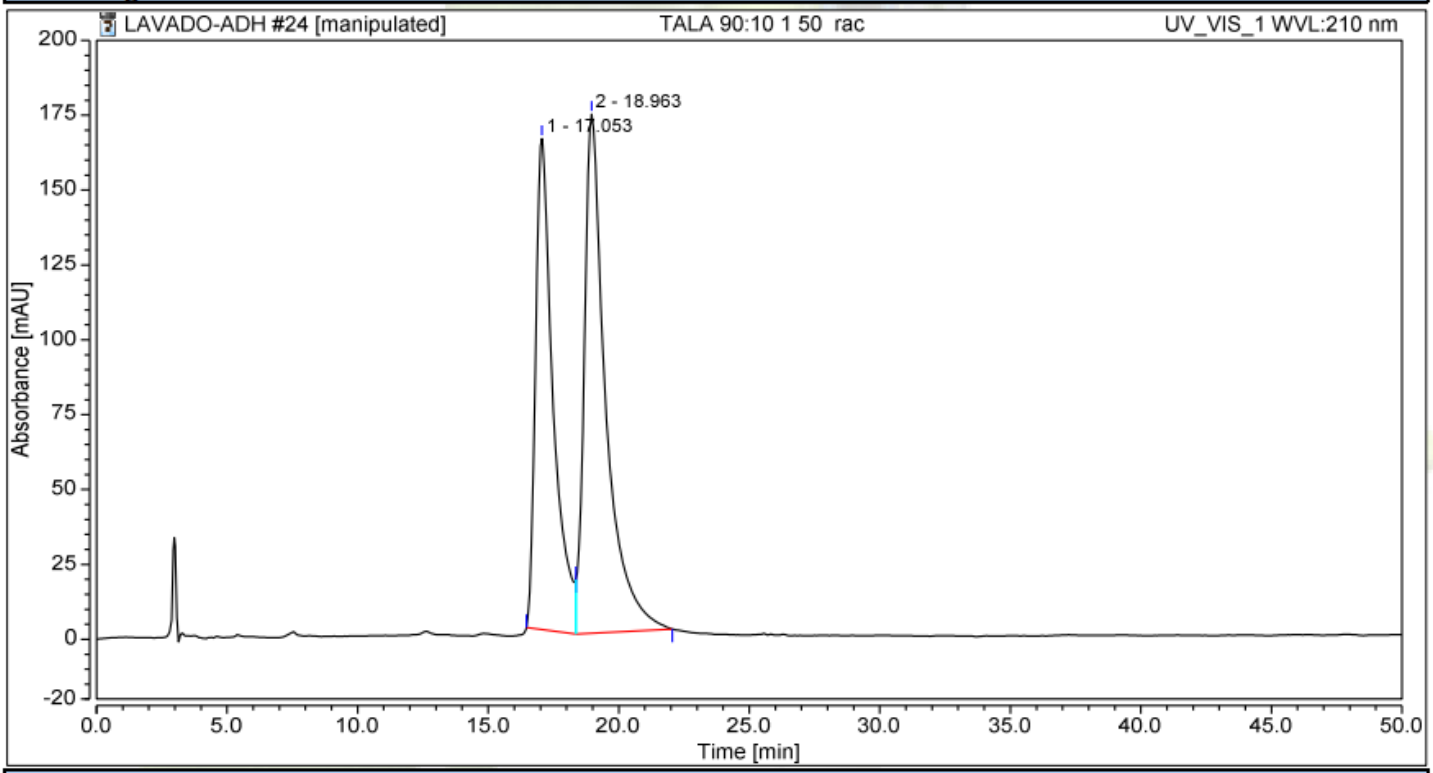
Studies for Determining Racemization of 6g (9H-fluoren-9-yl)methyl-(1-amino-1-thioxopropan-2-yl)carbamate (**8**)

Chromatogram and Results

Injection Details

Injection Name:	**TALA 90:10 1 50**	*Run Time (min):*	**50.00**
Vial Number:	**BA5**	*Injection Volume:*	**20.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_1**
Calibration Level:		*Wavelength:*	**210.0**
Instrument Method:	**ASH 9010 HEXIPA 1 50**	*Bandwidth:*	**4**
Processing Method:	**EMP_aldolica**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**23/ene/24 18:14**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		17.053	128.482	163.994	43.72	48.61	n.a.
2		18.963	165.401	173.377	56.28	51.39	n.a.
Total:			**293.883**	**337.371**	**100.00**	**100.00**	

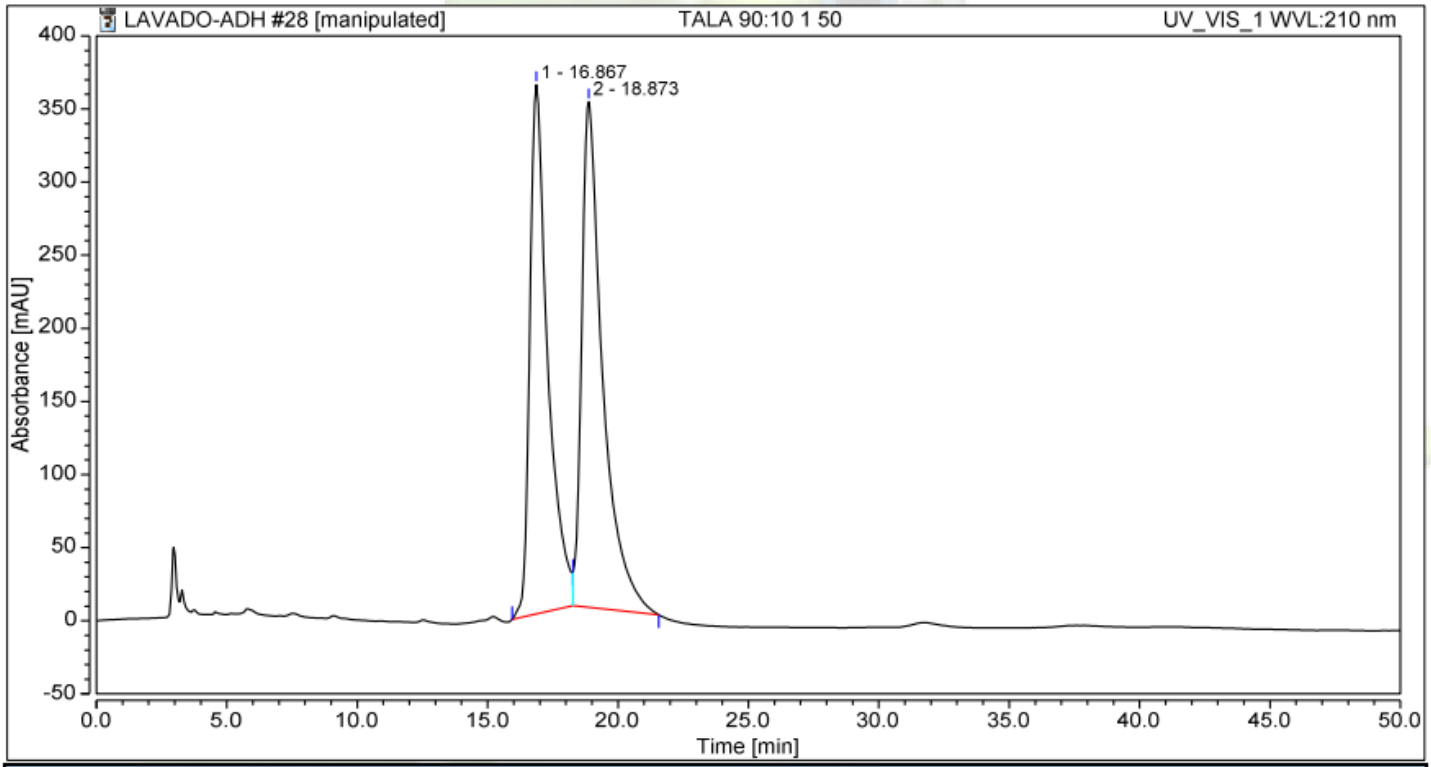
Racemic HPLC condition: Chiralpak® AS-H 150 x 2.1 mm column; hexanes (solvent A): isopropanol (solvent B); isocratic 10% solvent B in 50 min; flow rate = 1.0 mL/min; detection wavelength = 210 nm

Chromatogram and Results

Injection Details

Injection Name:	**TALA 90:10 1 50**	*Run Time (min):*	**50.00**
Vial Number:	**BA7**	*Injection Volume:*	**20.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_1**
Calibration Level:		*Wavelength:*	**210.0**
Instrument Method:	**ASH 9010 HEXIPA 1 50**	*Bandwidth:*	**4**
Processing Method:	**EMP_aldolica**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**24/ene/24 09:59**	*Sample Weight:*	**1.0000**

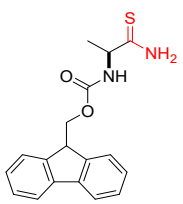
Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		16.867	289.707	362.018	47.25	51.15	n.a.
2		18.873	323.405	345.695	52.75	48.85	n.a.
Total:			**613.112**	**707.714**	**100.00**	**100.00**	

HPLC condition: Chiralpak® AS-H 150 x 2.1 mm column; hexanes (solvent A): isopropanol (solvent B); isocratic 10% solvent B in 50 min; flow rate = 1.0 mL/min; detection wavelength = 210 nm



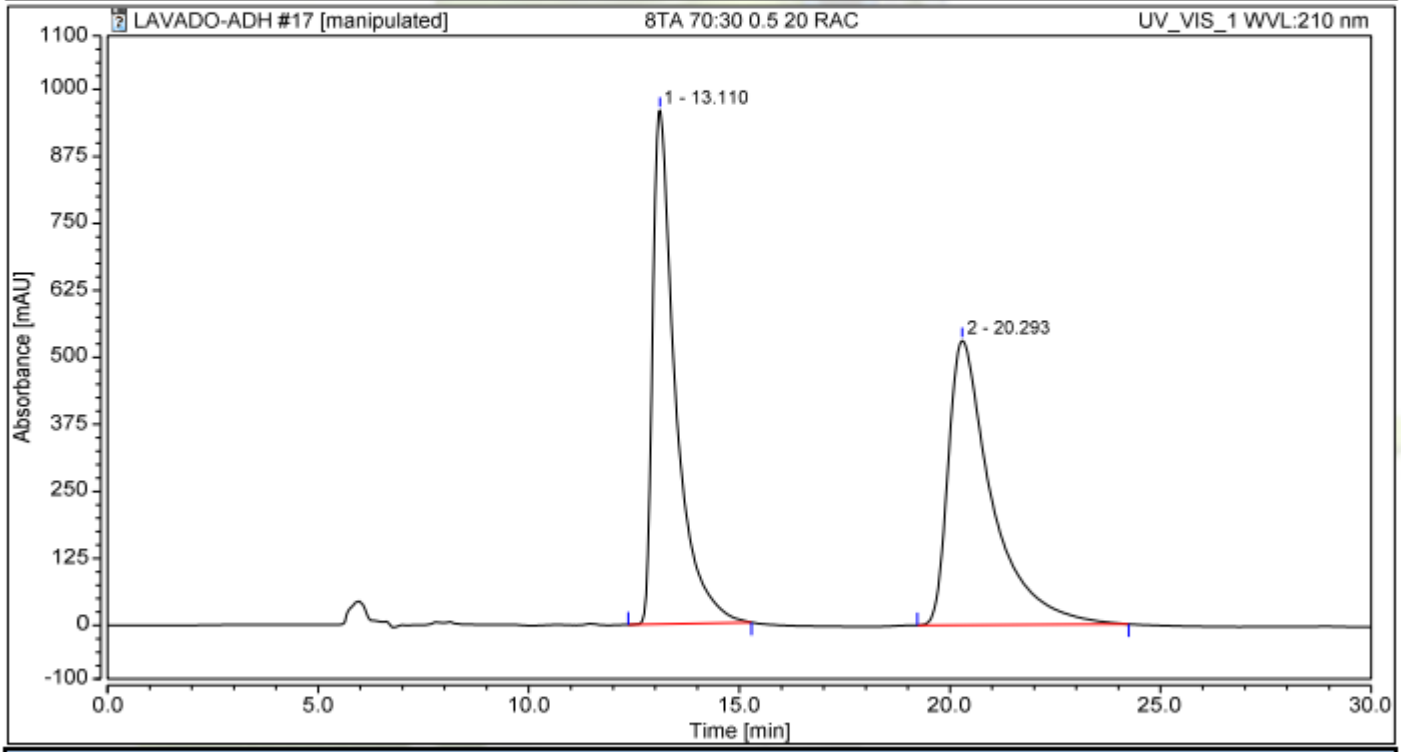
Studies for Determining Racemization of 6g of methyl (*S*)-3-(2-(((benzyloxy)carbonyl)amino)-3-phenylpropanethioamido)propanoate (**9**)

Chromatogram and Results

Injection Details

Injection Name:	**8TA 70:30 0.5 20 RAC**	*Run Time (min):*	**30.00**
Vial Number:	**BA2**	*Injection Volume:*	**20.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_1**
Calibration Level:		*Wavelength:*	**210.0**
Instrument Method:	**ASH 7030 HEXIPA 1 30**	*Bandwidth:*	**4**
Processing Method:	**EMP_aldolica**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**19/ene/24 11:35**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		13.110	603.982	959.256	48.76	64.37	n.a.
2		20.293	634.695	531.036	51.24	35.63	n.a.
Total:			**1238.677**	**1490.292**	**100.00**	**100.00**	

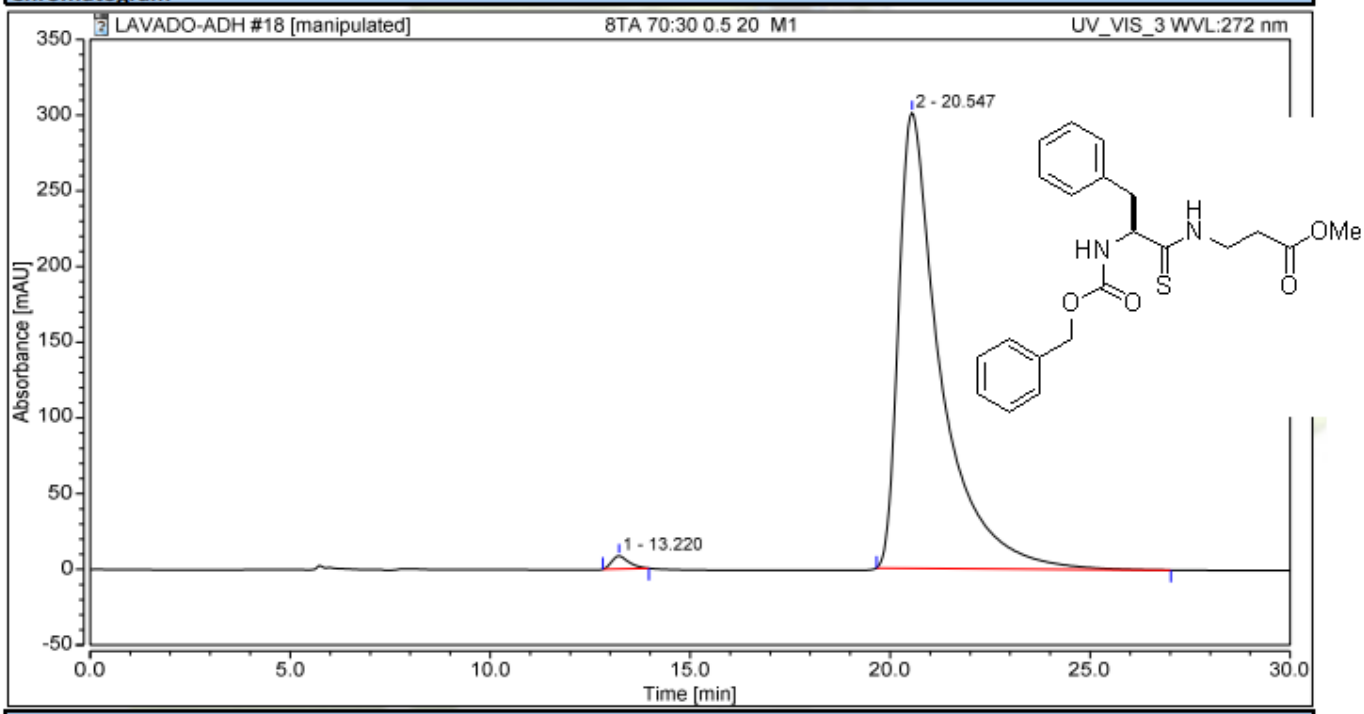
Racemic, HPLC condition: Chiralpak® AS-H 150 x 2.1 mm column; hexanes (solvent A): isopropanol (solvent B); isocratic 30% solvent B in 30 min; flow rate = 1.0 mL/min; detection wavelength = 210 nm

Chromatogram and Results

Injection Details

Injection Name:	**8TA 70:30 0.5 20 M1**	*Run Time (min):*	**30.00**
Vial Number:	**BA3**	*Injection Volume:*	**20.00**
Injection Type:	**Unknown**	*Channel:*	**UV_VIS_3**
Calibration Level:		*Wavelength:*	**210.0**
Instrument Method:	**ASH 7030 HEXIPA 1 30**	*Bandwidth:*	**4**
Processing Method:	**EMP_aldolica**	*Dilution Factor:*	**1.0000**
Injection Date/Time:	**19/ene/24 12:24**	*Sample Weight:*	**1.0000**

Chromatogram



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		13.220	4.246	8.566	1.15	2.77	n.a.
2		20.547	365.888	300.776	98.85	97.23	n.a.
Total:			**370.134**	**309.342**	**100.00**	**100.00**	

HPLC condition: Chiralpak® AS-H 150 x 2.1 mm column; hexanes (solvent A): isopropanol (solvent B); isocratic 30% solvent B in 30 min; flow rate = 1.0 mL/min; detection wavelength = 210 nm. 1.5% corresponds to the Purity of the starting amino acid.

X-Ray Powder Diffraction Analysis

Before performing the monitoring studies of the thionation reactions, we confirmed the crystallographic purity of the starting materials by XRPD experiments. The powder pattern of the purified solid samples was examined and compared with those obtained from the Cambridge Crystallographic Data Centre (CCDC).[4]

Visual comparison of the XRPD patterns after data normalization established a relationship between the crystalline samples and their calculated patterns (Figures S1 and S2). Sharp peaks indicate the absence of additional peaks and rule out the presence of other crystalline phases or solvents in the sample.

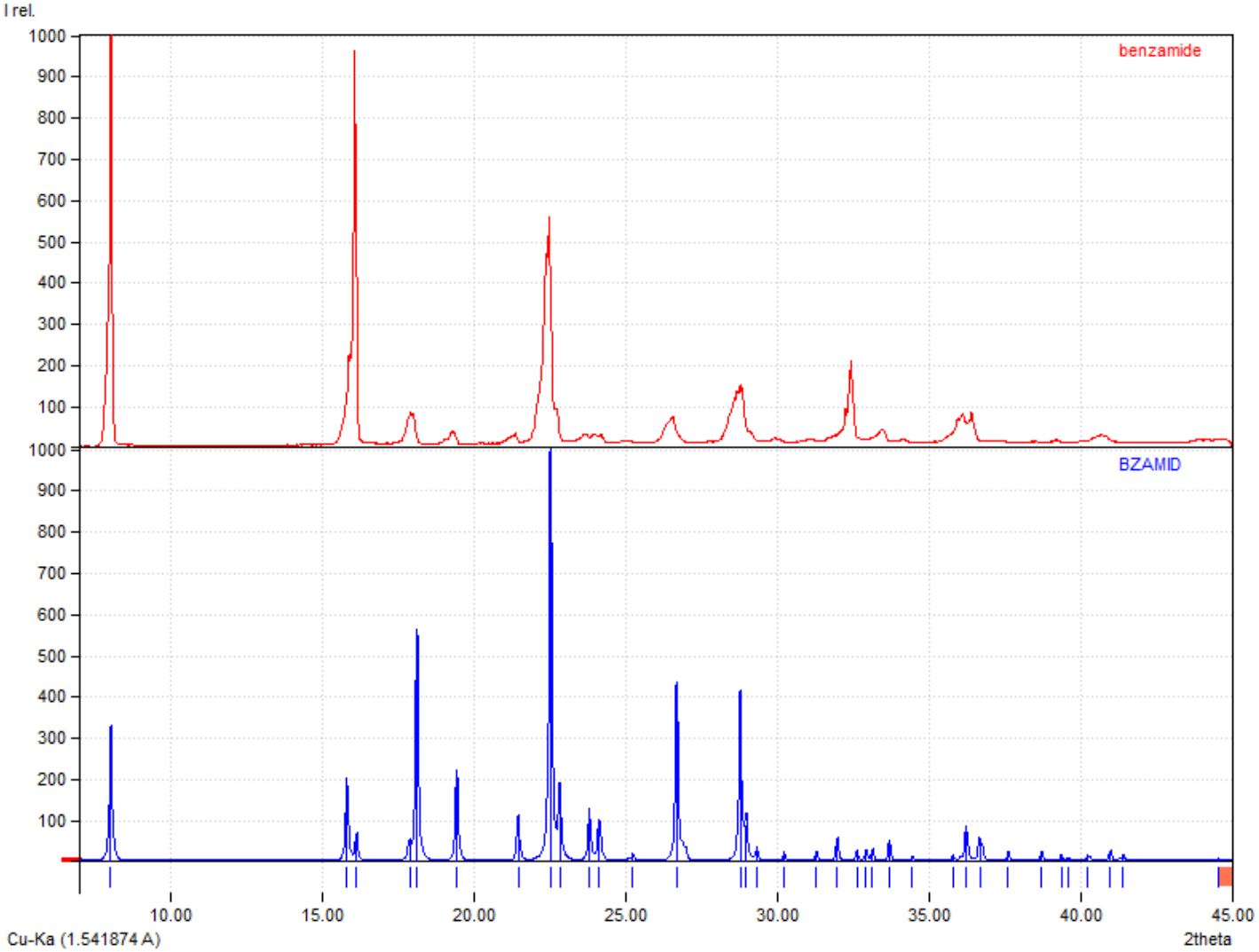


Figure S1. XRPD patterns of benzamide: red diffractogram of benzamide obtained benzamide sample (Sigma-Aldrich®), blue diffractogram of benzamide calculated.

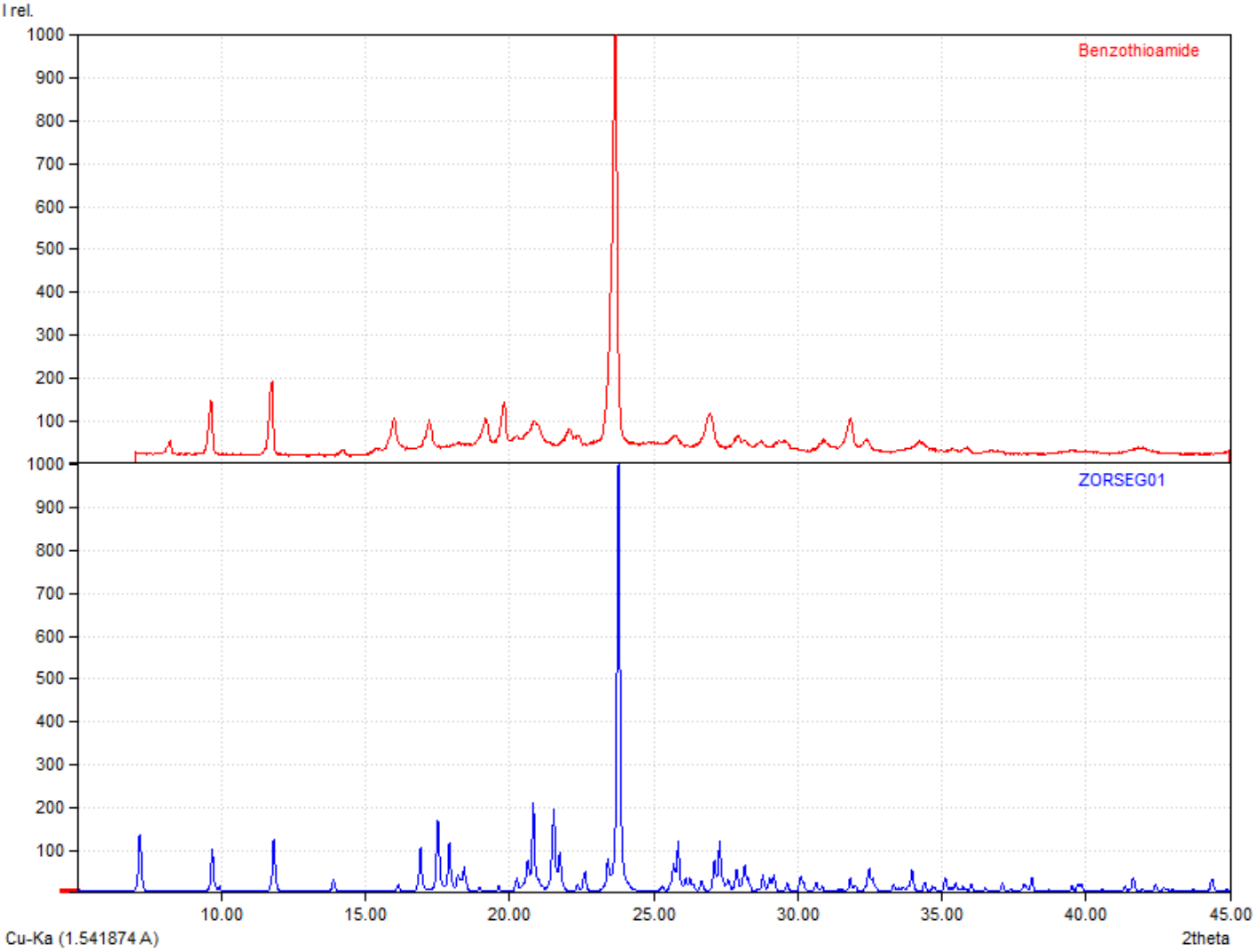


Figure S2. PXRD patterns of thiobenzamide: red diffractogram obtained after grinding in a Teflon jar milling; blue diffractogram calculated.

D, *DOC*, *AC* parameters were obtained with the Match! program version DEMO 4.0 Build 306.[5] Match! estimates the crystallite size *D* (average, in Å) in the sample using the Scherrer formula. Additionally, an instrumental standard of LaB6 was included.

In some cases, the files were plotted with the *Origin* program, Academic Version 2020.

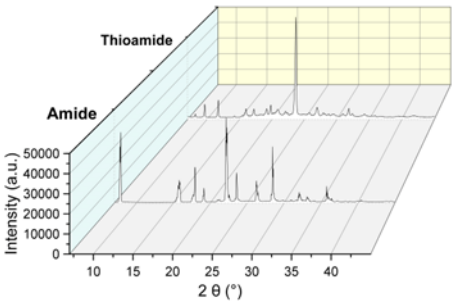
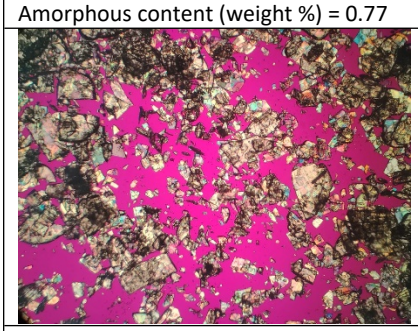
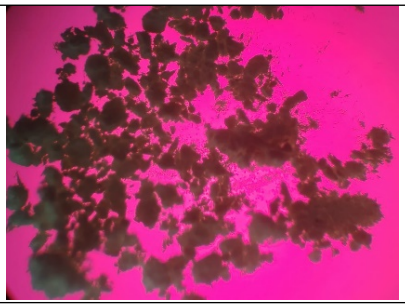
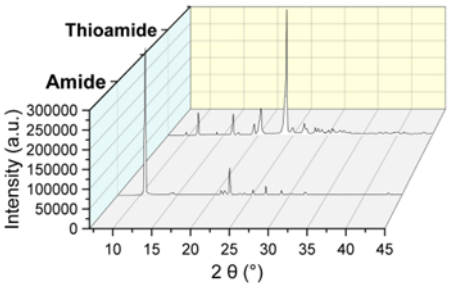
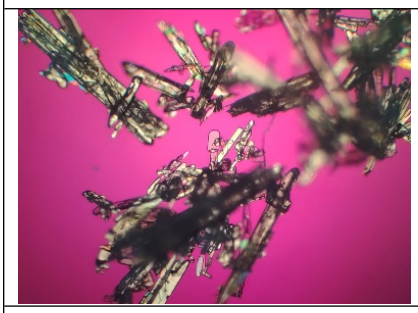
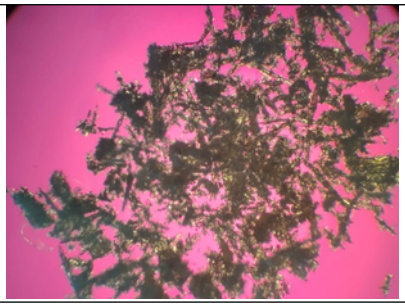
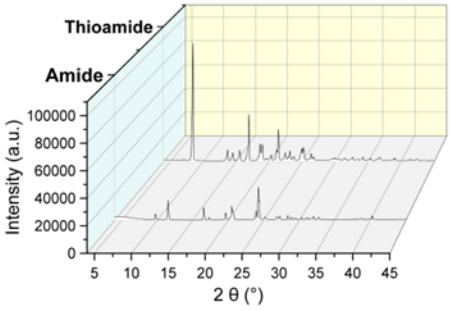
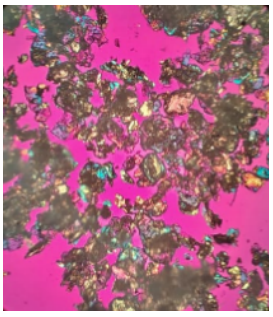
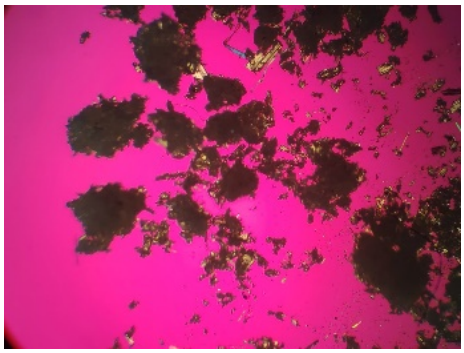
D = average crystallite size (nm)

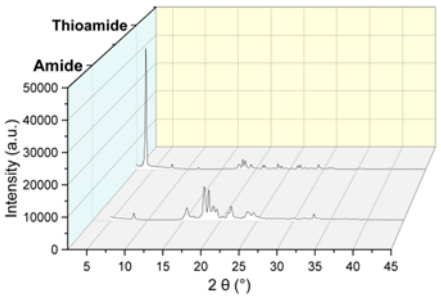
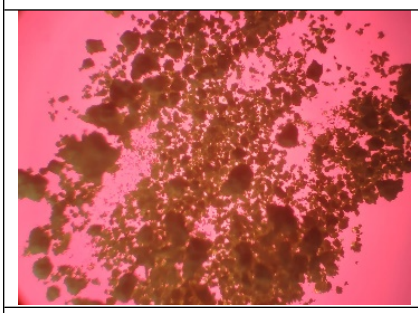
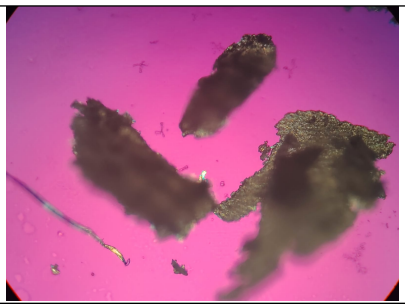
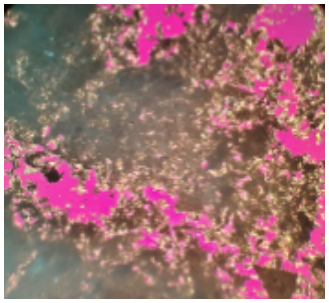
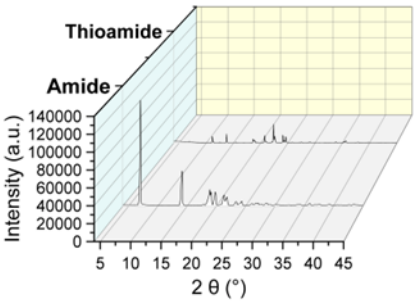
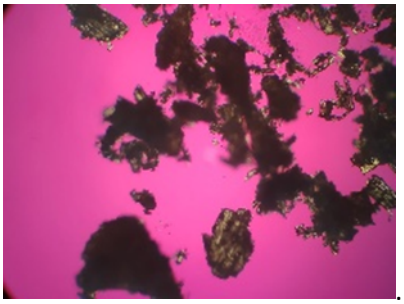
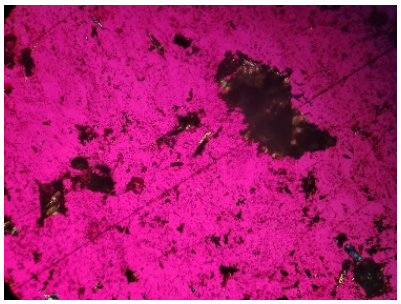
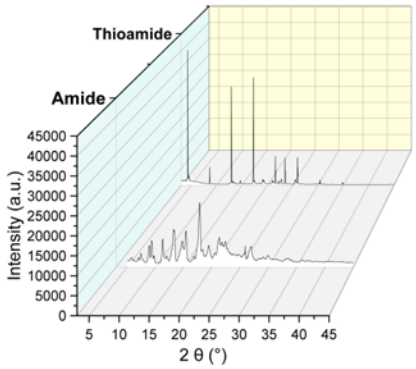
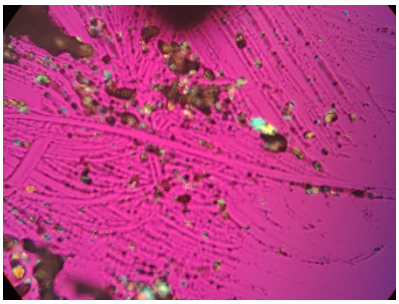
DOC = Diffraction peaks = Degree of crystallinity

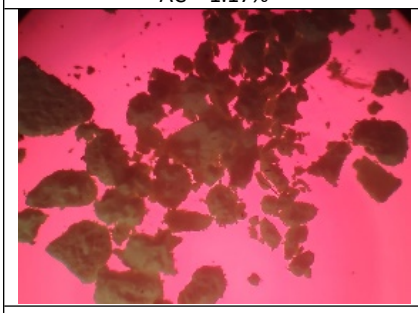
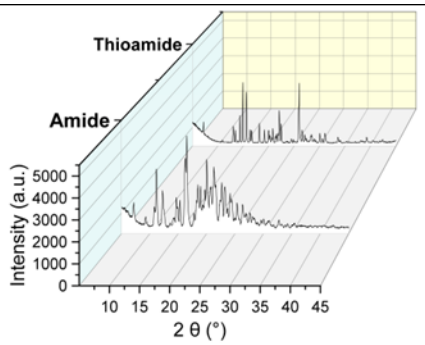
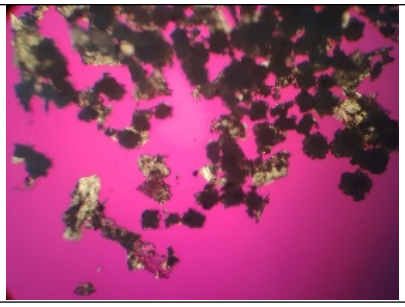
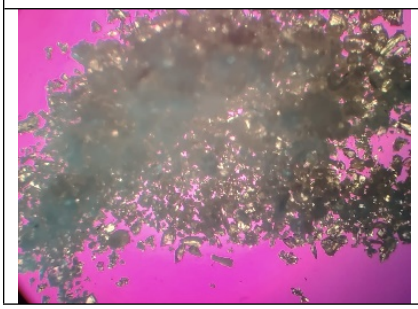
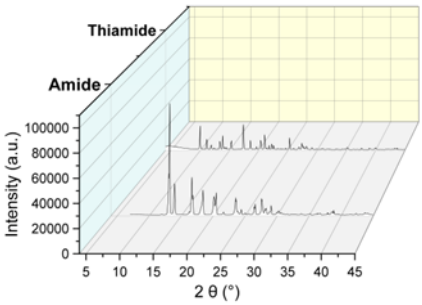
AC = Amorphous pashes (Amorphous content weight %)

For the analysis of the degree of crystallinity, in addition to the sample diffraction pattern, the diffraction pattern of the empty sample holder was used under the same experimental conditions. The results are presented in Tables S3.

Table S3. Characterization of amides and thioamides from the optimized reaction in Teflon milling jars.

Amide Crystallite	**X-Ray diffraction patterns (difractograms) of amide and thioamide**	**Thioamide Crystallite**
Benzamide Sigma-Aldrich® *D* = average crystallite size (nm) = 710.59 nm Degree of crystallinity (DOC) = 99.23% Amorphous content (weight %) = 0.77		Benzothioamide (**1**) *D* = 457.66 nm DOC = 49.0% AC = 51.0%
		
N-methylbenzamide *D* = 72.06 nm DOC = 67.01% AC = = 32.99		*N*-methylbenzothioamide (**2**) *D* = 105.89 nm DOC = 62.99% AC = %) = 37.01%
		
N-(1-phenylethyl)acetamide *D* = 114.8 nm DOC = 100% AC= ---		*N*-(1-Phenylethyl)ethanethioamide (**3**) *D* = 782.33 nm DOC = 56.94% AC = 43.06%
		
2-(4-isobutylphenyl)propanamide		Isobutylphenyl)propanethioamide (**4**)

D = 23.5 nm DOC = 52.90% AC = 47.10%		D = 225.2 nm DOC = 43.30% AC = 53.70%
		
N-benzylbenzamide *D* = 29.84 nm DOC = 62.01% AC = 37.99%		N-Benzylbenzothioamide (**5**) *D* = 539.85 nm DOC = 99.81% AC = 0.19%
		 .19
(9H-fluoren-9-yl)methyl (2-amino-2-oxoethyl)carbamate *D* = 34.81 nm DOC = 48.33% AC= 51.67%		(9H-Fluoren-9-yl)methyl (2-amino-2-thioxoethyl)carbamate (**7**) *D* = 215.8 nm DOC = 44.99% AC= 55.01%
		
(9H-fluoren-9-yl)methyl (1-amino-1-oxopropan-2-		(9H-Fluoren-9-yl)methyl (*S*)-(1-amino-1-thioxopropan-2-yl)carbamate (**8**) *D* = 77.18 nm

yl)carbamate *D* = 35.18 nm DOC = 48.83% AC = 1.17% 		DOC = 30.74% AC = 69.26% 
(*S*)-1-benzoyl-2-(tert-butyl)-2,3-dihydropyrimidin-4(1H)-one *D* = 97.42 nm DOC = 62.77% AC = 7.23% 		(*S*)-(2-(*tert*-Butyl)-4-thioxo-3,4-dihydropyrimidin-1(2H)-yl)(phenyl)methanone (**11**) *D* = 408.4 nm DOC = 42.20% AC = 57.80% 

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