Synthesis M. C. Mollo et al. Paper

Microwave-Assisted Synthesis of 2-Substituted 2-Thiazolines and 5,6-Dihydro-4*H*-1,3-thiazines

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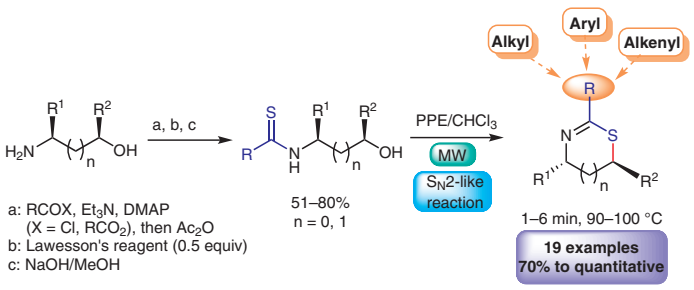

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Abstract An efficient and general method for the synthesis of 2-substituted thiazolines and 5,6-dihydro-4*H*-1,3-thiazines is developed via microwave-assisted ring closure of ω-thioamidoalcohols promoted by ethyl polyphosphate (PPE). The cyclization reaction involves an S_N2-type mechanism and features the advantages of very short reaction times, high yields and a predictable stereochemical outcome. The acyclic precursors are prepared in high overall yields by an improved diacylation–thionation–saponification sequence from commercially available ω-aminoalcohols. The whole process is metal-free and operationally simple.

Key words cyclic iminothioethers, thiazolines, dihydrothiazines, PPE, microwaves, thioamidoalcohols

2-Thiazolines (4,5-dihydrothiazoles) (TZs) are interesting heterocycles, frequently found in Nature as a result of post-translational modification of cysteine residues in peptidic compounds.[1] TZs have been reported to possess a wide spectrum of bioactivities such as anti HIV-1,[2] antitumor,[3,4] antiparasitic and antifungal,[5] siderophore,[6] and analgesic, among others.[7] Their higher homologues (5,6-dihydro-4*H*-1,3-thiazines) (DHTZs) are also interesting compounds, behaving as anthelmintics,[8] antivirals[9] and fungicides.[10] TZs and DHTZs also find many applications in organic synthesis as protecting groups,[11] synthetic intermediates,[12–14] and as chiral ligands,[15–18] being an extremely important field in modern synthetic chemistry where the difference between oxygen- and sulfur-chelating behavior toward metal ions causes TZs to sometimes behave differently from the better known oxazolines in various metal-catalyzed reactions.[19]

As a result of its numerous applications, many methods have been developed for the synthesis of 2-thiazolines, among which some have been successfully extrapolated to dihydrothiazines. The synthetic approaches to these compounds can be classified with respect to their inter or intramolecular character, the source of the C-2 atom (almost invariably a carboxylic acid or a derivative thereof) and whether an aminomercaptan or an aminoalcohol is used, the latter being more versatile due to the relative scarcity of commercial aminothiols.

Among the intermolecular strategies, carboxylic acids have been converted into TZs by employing aminothiols and condensing agents such as Ph_3P/CCl_4/tertiary amine,[20] and *m*-nitrophenylboronic acid.[21] Aminoethanols afford the corresponding thiazolines using Lawesson's reagent (LR), which acts as both a sulfurizing and condensing agent under microwave (MW) irradiation.[22] Condensation of nitriles and aminothiols in the presence of acid (trichloroisocyanuric acid,[23] Dowex-50W,[24] $H_3PW_{12}O_{40}$,[25] $ZnCl_2$[15]) or under basic conditions (NaOH[26]) also leads to TZs. In addition, esters have been condensed with aminomercaptans in the presence of Al(*i*-Bu)$_3$,[27] as have amides as the *N*-acylbenzotriazoles[28] or as imidoyl triflates.[29] Thioamides, via tandem alkylation–cyclization with haloalkylamines,[30] and aldehydes, via hemiaminal–thioether oxidation with $Ru(Ph_3P)_3Cl_2$/TBHP,[31] have also been used as a source of the C-2 atom.

Intramolecular synthetic strategies are well suited for the preparation of TZs, and some of them are also efficient for the preparation of DHTZs. Thus, *N*-2-thioethylamides have been cyclized in the presence of 1,1,3,3-tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoromethanesulfonate)[32] and P_2S_5,[33] respectively. LR has been used to bring about cyclization of ω-hydroxy and ω-halo ethylene and propylene-amides,[34,35] whilst *N*-2-hydroxyethylthioamides have been cyclized to give the corresponding TZs by using DAST,[36] Mitsunobu's reagent,[37,38] Deoxo-Fluor®,[39] MsCl/Et$_3$N,[40] and perfluoroalkane sulfonylfluorides.[41] Most of these reagents are either quite specialized, unstable, hazardous, or generate large amounts of waste products. On the other hand, the polyphosphoric acid (PPA) esters PPE and PPSE (ethyl and

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trimethylsilyl polyphosphate, respectively) are irreversible dehydrating agents of the Lewis acid type that also activate nitrogen and oxygen functional groups toward nucleophilic attack. These reagents find many applications in organic synthesis,[42] among which heterocycle synthesis is of special relevance. PPA esters, due to their aprotic nature, are mild reagents with wide functional group tolerance. They have practical advantages compared to other cyclodehydrating reagents, as they are easily prepared from inexpensive starting materials, are soluble in many common organic solvents and are environmentally safe. They are also compatible with microwave irradiation, a feature that has widened their scope and has enabled cyclization reactions of low reactivity substrates, which have previously demonstrated low efficiency or were completely unreactive when using alternative systems.[43]

As part of our ongoing interest on the synthesis of nitrogen heterocycles by ring-closure reactions promoted by PPA esters under microwave irradiation,[44] we have developed a method for the preparation of 2-oxazolines and 5,6-dihydro-4*H*-1,3-oxazines by ring closure of the corresponding ω-amidoalcohols.[44f] In connection with this, we recently reported preliminary data on the synthesis of 4,5,6,7-tetrahydro-1,3-thiazepines using the PPA ester/MW protocol.[45]

In view of the relevance of thiazolines and dihydrothiazines, and on the basis of our previous research, we report herein a simple, efficient and expeditious method for their synthesis by MW-assisted ring closure of ω-thioamidoalcohols promoted by PPE. The synthesis of the acyclic precursors from ω-aminoalcohols by an improved protection–thionation–deprotection sequence is also presented.

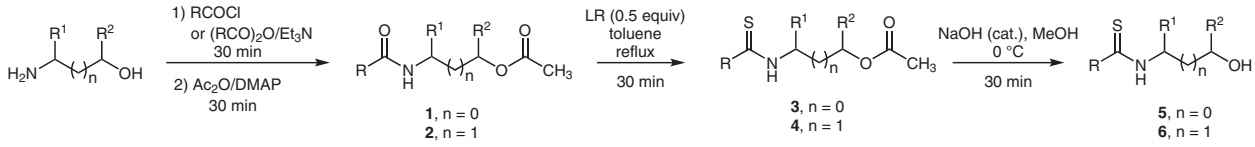
In principle, 2-thiazolines and dihydrothiazines can be synthesized by ring closure of two different monosulfurized precursors, namely ω-amidothiols and ω-thioamidoalcohols. The preparation of both necessarily involves a selective thionation step, for which the relative reactivities follow the order OH ≈ amide >> ester.[46] However, the reactions of ω-amidoalcohols with LR, the most common reagent for such purposes, are not efficient and lead to mixtures of the desired and several collateral products.[47] Another disadvantage of this approach is that amidothiols are prone to spontaneous oxidation leading to the corresponding disulfides.[32] Therefore, as a starting point, we chose a diacylation–thionation–saponification sequence,[36] which had been optimized to achieve high overall yields of *N*-thioacylaminobutanols.[45] The yields were lower for substrates containing sterically hindered substituents such as *i*-Pr or *t*-Bu on the thioamide group, which required more drastic reaction conditions and significantly longer reaction times both in the diacylation and deprotection steps. Thus, 2-aminoethanol and 1-aminopropan-2-ol were subjected to the diacylation–thionation–saponification sequence. The first step was carried out with the corresponding aroyl chloride as the acylating agent, triethylamine as the solvent and DMAP as the catalyst, affording the corresponding diacyl derivatives in 95% and 92% yields, respectively. Both diacylated compounds reacted smoothly with stoichiometric amounts of LR in toluene at reflux, generating the corresponding thioamidoesters in high yields (90% for both) after 30 minutes. The saponification step, however, was not successful under the previously employed reaction conditions,[45] leading to a mixture of the desired *N*-thioacyl aminoalcohol **5a** (41%) and the corresponding 2-oxazoline (35%), when starting from the 2-aminoethanol derivative. Furthermore, the oxazoline (76%) was the only product obtained from saponification of the branched derivative.[48]

To suppress this side reaction and to avoid problems associated with the different reactivity during the introduction and removal of the protecting groups, and in order to develop a robust and general protocol, we decided to switch to the more reactive, readily available, affordable and atom-economic acetyl moiety as the OH protecting group. Thus, 2-aminoethanol was converted quantitatively into the corresponding *N*-monobenzoyl derivative by treatment with benzoyl chloride (1:1 molar ratio). The product was then *O*-acetylated in a one-pot, two-step procedure, affording compound **1a** quantitatively after purification (Table 1). The resulting amidoester was reacted with LR using the previously described conditions, and the resulting thioamidoester **3a** was then smoothly hydrolyzed to give the desired thioamidoalcohol **5a** in almost quantitative yield using catalytic NaOH/methanol. The whole sequence afforded precursor **5a** in 80% overall yield from 2-aminoethanol (Table 1). In the same way, linear and branched β-aminoalcohols, as well as 3-aminopropanol, were expeditiously converted into the corresponding thioamidoalcohols via their ω-thioamidoalkyl acetates. The results are summarized in Table 1.

The yields of the whole sequence (Table 1, final column) were in general excellent and compared favorably with the previously reported literature examples on analogous compounds.[36] The improved protocol was efficient even for the sterically hindered derivatives **3j** and **4h**,**i**.

For the ring-closure reaction, a mixture of compound **5a** and a chloroform solution of PPE were irradiated in a closed vessel microwave reactor at 90 °C, affording 2-phenyl-2-thiazoline (**7a**) as the only product in 90% yield after 1 minute (Table 2). Using the same procedure, we synthesized several 2-thiazolines and dihydrothiazines (Table 2). The irradiation temperatures and times were adjusted according to the reactivity of each substrate by monitoring its disappearance by TLC. Five- and six-membered thioimidates with 2-aryl substituents were prepared in high to quantitative yields in very short reaction times. The reaction was also efficient for 2-benzyl, styryl and alkyl derivatives. Sterically hindered substrates **6h**,**i** required slightly higher temperatures and longer reaction times. As previously mentioned, 2-styryl-dihydrothiazines are bioactive as anthelmintics, antifungals and antivirals. Such compounds are generally prepared in modest yields by condensation of 2-methyl-5,6-dihydro-4*H*-1,3-thiazine with aldehydes.[8–10] Our method,

Table 1 Synthesis of ω-Thioamidoalcohols

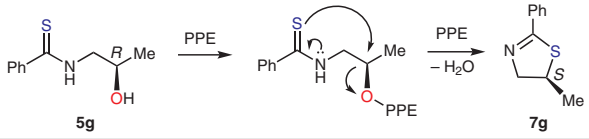


Product	R	n	R^1	R^2	Yield of **1**/**2** (%)	Yield of **3**/**4** (%)	Yield of **5**/**6** (%)	Overall yield (%)[a]
5a	C_6H_5	0	H	H	quant.[b]	86	93	80
5b	4-ClC_6H_4	0	H	H	84[b]	86	quant.	72
5c	4-$MeOC_6H_4$	0	H	H	95[b]	75	97	70
5d	4-$O_2NC_6H_4$	0	H	H	82[b]	77	81	51
5e	2-MeC_6H_4	0	H	H	91[b]	71	97	62
5f	C_6H_5	0	Me	H	96[b]	83	90	71
5g	C_6H_5	0	H	Me	96[b]	86	92	76
5h	$CH{=}CHC_6H_5$	0	H	H	90[b]	69	88	54
5i	$C_6H_5CH_2$	0	H	H	quant.[b]	90	77	62
5j	*i*-C_3H_7	0	H	H	93[c]	80	82	61
6a	C_6H_5	1	H	H	96[b]	85	90	73
6b	4-ClC_6H_4	1	H	H	84[b]	90	92	70
6c	4-MeC_6H_4	1	H	H	83[b]	85	quant.	71
6d	4-$O_2NC_6H_4$	1	H	H	83[b]	76	quant.	63
6e	2-MeC_6H_4	1	H	H	91[b]	85	95	74
6f	$CH{=}CHC_6H_5$	1	H	H	90[b]	85	97	74
6g	$CH_2C_6H_5$	1	H	H	75[b]	quant.	97	73
6h	*i*-C_3H_7	1	H	H	93[c]	82	quant.	76
6i	*t*-C_4H_9	1	H	H	85[c]	88	quant.	75

[a] Yield of pure product.
[b] Reaction performed with the acid chloride.
[c] Reaction performed with the acid anhydride.

therefore, represents a simple and high yielding alternative synthetic approach for the preparation of such compounds. The procedure was also reliable and efficient for the cyclization of chiral substrates **5f**,**g**.

Unlike with oxazolines and their homologues, where the heterocyclic oxygen can, in principle, come from either of the oxygenated functions present in the precursor, ring closure of ω-thioamidoalcohols to yield the thia-heterocycles would take place by nucleophilic attack of the thioamide sulfur on the ω-carbon with expulsion of the OH group previously activated by the cyclization agent. In the ring closure leading to chiral oxazolines, the ability of PPA esters to promote this type of reactivity has been demonstrated.[44f] Taking all this into account, it can be assumed that the reaction proceeds through an S_N2-like mechanism after activation of the OH group by PPE. This hypothesis was further confirmed in the cyclization of chiral derivative **5g**, which resulted in inversion of the configuration at the carbinol stereocenter (Scheme 1).

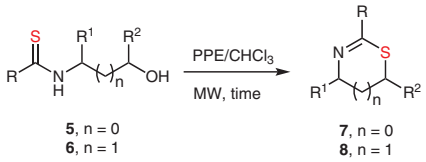


Scheme 1 A plausible reaction path for the PPE/MW cyclization of **5g**

One enantiomer of 5-methyl-2-phenyl-2-thiazoline (**7g**) is mentioned in the literature,[49] but its configuration was not reported. Direct assignment by X-ray crystallography is unfeasible because the compound is a viscous oil, therefore its absolute stereochemistry was determined by chiro-optical techniques such as electronic and vibrational circular dichroism (ECD and VCD) in combination with time-dependent density functional theory (TD-DFT) and density functional theory (DFT) calculations.

The calculated ECD spectrum for the *S* absolute configuration, using four different functionals and the 6-311++G(2d,p) basis set (see details in the Supporting

Table 2 Synthesis of 2-Triazolines **7** and 5,6-Dihydro-4*H*-1,3-thiazines **8**



5, n = 0
6, n = 1

7, n = 0
8, n = 1

Product	R	R^1	R^2	Temp (°C)	Time (min)	Yield (%)[a]
7a	C_6H_5	H	H	90	1	90
7b	4-ClC_6H_4	H	H	90	1	90
7c	4-MeC_6H_4	H	H	90	3	86
7d	4-$O_2NC_6H_4$	H	H	90	1	71
7e	2-MeC_6H_4	H	H	90	1	89
7f	C_6H_5	Me	H	90	1	83
7g	C_6H_5	H	Me	90	1	87
7h	CH=CHC_6H_5	H	H	90	1	83
7i	$CH_2C_6H_5$	H	H	90	1	70
7j	*i*-C_3H_7	H	H	90	2	70
8a	C_6H_5	H	H	90	1	80
8b	4-ClC_6H_4	H	H	90	1	97
8c	4-MeC_6H_4	H	H	90	1	90
8d	4-$O_2NC_6H_4$	H	H	90	2	99
8e	2-MeC_6H_4	H	H	90	1	96
8f	CH=CHC_6H_5	H	H	90	1	94
8g	$CH_2C_6H_5$	H	H	90	1	81
8h	*i*-C_3H_7	H	H	100	6	quant.
8i	*t*-C_4H_9	H	H	100	6	90

[a] Yield of pure product.

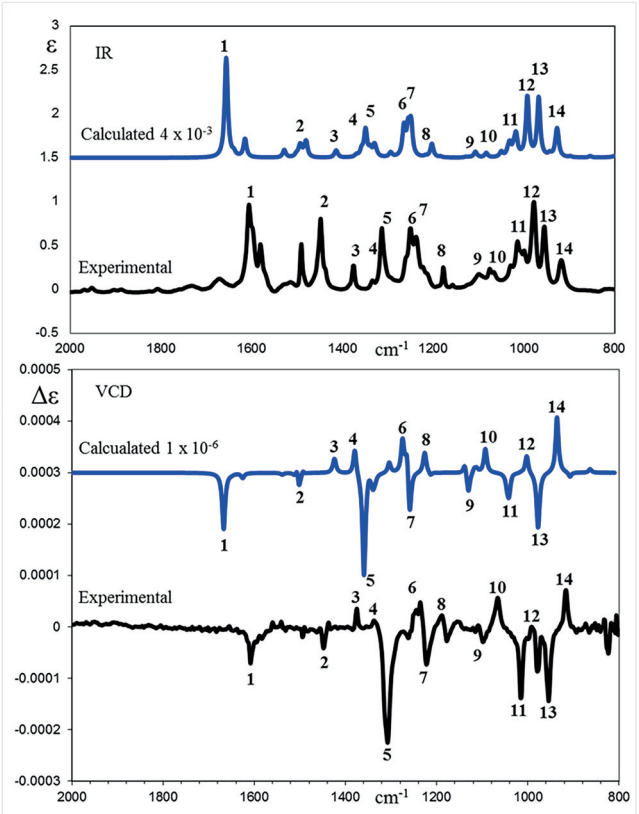


Figure 1 Calculated (blue) and experimental (black) IR (top) and VCD spectra (bottom) of compound **7g**

Information), was in a fair agreement with the experimental spectrum. However, the weak experimental ECD spectrum (see Figure S1) did not allow a good interpretation of the bands. Therefore the absolute configuration was independently determined by means of VCD (see details in the Supporting Information).[50] The experimental IR and VCD spectra were compared with those calculated by DFT at the B3LYP/6-311+g(2d,p) level (see Figures S5 and S6). The experimental spectra are well reproduced by the simulation obtained assuming the *S* absolute configuration (Figure 1).

In summary, we have developed a simple and efficient protocol for the synthesis of 2-substituted 2-thiazolines and dihydro-4*H*-1,3-thiazines from the corresponding aminoalcohols. The whole sequence is metal-free, involves readily available starting materials and reagents and is operationally simple. The required acyclic precursors were prepared in high to excellent overall yields by an improved diacylation–thionation–saponification sequence. The MW-assisted cyclization promoted by PPE led to the target heterocycles as the only products in good to high yields in only a few minutes. The reaction mechanism involves PPE activation of the OH followed by intramolecular S_N2 attack. This assumption was further confirmed by the stereochemical outcome of the reaction in a chiral derivative, the absolute configuration of which was determined by circular dichroism. Taken together with our preliminary results on tetrahydro-1,3-thiazepines, the MW-assisted ring closure of ω-thioamidoalcohols promoted by PPA esters is, to our knowledge, the first general method for the preparation of five- to seven-membered heterocyclic iminothioethers.

Reagents, solvents and starting materials were purchased from standard suppliers and purified according to literature procedures. Chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). Thin-layer chromatography was performed on silica gel plates with visualization under UV light. Melting points were determined with a Büchi capillary apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker BioSpin Avance III 600 MHz spectrometer, using deuteriochloroform as the solvent. The ^1H and ^{13}C NMR chemical shifts (ppm) are referenced to the $CHCl_3$ (7.26 ppm in $CDCl_3$) and deuterated solvent (77.0 ppm in $CDCl_3$) signals. Splitting multiplicities are reported as singlet (s), broad signal (br s), doublet

(d), doublet of doublets (dd), triplet (t), quartet (q), septet (sept) and multiplet (m). HRMS (ESI) were recorded with a Bruker MicroTOF-Q II spectrometer.

Attempted Synthesis of *N*-(2-hydroxyethyl)benzothioamide (5a) and (*R*)-4-Chloro-*N*-(2-hydroxypropyl)benzothioamide

2-Benzamidoethyl Benzoate and (*R*)-1-(4-Chlorobenzamido)propan-2-yl 4-Chlorobenzoate

A solution of the acyl chloride (5 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise to a mixture of the aminoalcohol (2.5 mmol), DMAP (0.10 mmol) and triethylamine (0.7 mL). The reaction mixture was stirred at room temperature until the disappearance of the acid chloride. After the reaction was complete, the solvent was evaporated in vacuo. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 3:2 → 1:1).

2-Benzamidoethyl Benzoate[51]

[CAS Reg. No. 16180-99-7]

White solid; yield: 640 mg (95%); mp 87–90 °C; R_f = 0.60 (CH_2Cl_2/EtOAc, 1:1).

(*R*)-1-(4-Chlorobenzamido)propan-2-yl 4-Chlorobenzoate

White solid; yield: 810 mg (92%); mp 119–120 °C; R_f = 0.67 (CH_2Cl_2/EtOAc, 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.45 (d, *J* = 5.4 Hz, 3 H, -CH_3), 3.69 (ddd, *J* = 4.5, 8.0, 5.7 Hz, 1 H, -NC*H*H), 3.76 (ddd, *J* = 14.5, 5.5, 3.4 Hz, 1 H, -NCH*H*), 5.32–5.38 (m, 1 H, -CH-), 6.68 (br s, 1 H, NH), 7.38 (d, *J* = 8.7 Hz, 2 H, arom), 7.41 (d, *J* = 8.7 Hz, 2 H, arom), 7.67 (d, *J* = 8.7 Hz, 2 H, arom), 7.97 (d, *J* = 8.7 Hz, 2 H, arom).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 18.0, 45.2, 71.2, 128.3, 128.8, 128.8, 131.0, 132.5, 137.8, 139.8, 166.1, 166.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}Cl_2NO_3$: 352.0502; found: 352.0495.

2-Phenylthioamidoethyl Benzoate and (*R*)-1-(4-Chlorophenylthioamido)propan-2-yl 4-Chlorobenzoate

To a solution of 2-benzamidoethyl benzoate or (*R*)-1-(4-chlorobenzamido)propan-2-yl 4-chlorobenzoate (2 mmol) in toluene (20 mL) was added Lawesson's reagent (LR) (1 mmol). The mixture was heated at reflux for 30 min, after which the solvent was evaporated in vacuo. The residue was purified by column chromatography (silica gel, CH_2Cl_2).

2-Phenylthioamidoethyl Benzoate

White solid; yield: 514 mg (90%); mp 120–122 °C; R_f = 0.56 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.22 (q, *J* = 5.0 Hz, 2 H, N-CH_2), 4.71 (t, *J* = 5.0 Hz, 2 H, O-CH_2), 7.37–7.41 (m, 2 H, arom), 7.44–7.48 (m, 2 H, arom), 7.58–7.61 (m, 2 H, arom), 7.80 (dd, *J* = 8.4, 1.3 Hz , 2 H, arom), 8.06 (dd, *J* = 8.4, 1.3 Hz, 2 H, arom), 8.38 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 46.9, 62.7, 126.7, 128.50, 128.51, 129.3, 129.8, 131.2, 133.5, 141.2, 167.5, 199.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}NO_2S$: 286.0896; found: 286.0902.

(*R*)-1-(4-Chlorophenylthioamido)propan-2-yl 4-Chlorobenzoate

Yellow oil; yield: 663 mg (90%); R_f = 0.56 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.55 (d, *J* = 6.4 Hz, 3 H, -CH_3), 4.01 (ddd, *J* = 15.3, 9.0, 4.6 Hz, 1 H, -NC*H*H), 4.15 (ddd, *J* = 15.3, 5.0, 2.4 Hz, 1 H, -NCH*H*), 5.49–5.55 (m, 1 H, -OCH), 7.36 (d, *J* = 8.7 Hz, 2 H, arom), 7.44 (d, *J* = 8.7 Hz, 2 H, arom), 7.72 (d, *J* = 8.7 Hz, 2 H, arom), 7.99 (d, *J* = 8.7 Hz, 2H, arom), 8.47 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 18.5, 52.8, 70.7, 127.9, 128.0, 128.7, 128.9, 131.2, 137.5, 139.3, 140.2, 166.9, 197.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}Cl_2NO_2S$: 368.0273; found: 368.0280.

Saponification of 2-Phenylthioamidoethyl Benzoate and (*R*)-1-(4-Chlorophenylthioamido)propan-2-yl 4-Chlorobenzoate

A mixture of the thioamidoester (1.5 mmol) and a solution of K_2CO_3 in water/methanol (1:1) was stirred at 70 °C for 30 min. After completion of the reaction as indicated by TLC, the solvent was evaporated in vacuo. The residue was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 1:1 → 2:3).

Saponification of 2-phenylthioamidoethyl benzoate led to a mixture of compound *N*-(2-hydroxyethyl)benzothioamide (**5a**) (41%) and 2-phenyl-4,5-dihydrooxazole (35%).

2-Phenyl-4,5-dihydrooxazole[52]

[CAS Reg. No.7127-19-7]

Colorless oil; yield: 77 mg (35%).

Saponification of (*R*)-1-(4-chlorophenylthioamido)propan-2-yl 4-chlorobenzoate led to (*R*)-5-methyl-2-phenyl-4,5-dihydrooxazole.

(*R*)-2-(4-Chlorophenyl)-5-methyl-4,5-dihydrooxazole

Colorless oil; yield: 223 mg (76%); R_f = 0.64 (CH_2Cl_2/EtOAc, 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.42 (d, *J* = 6.6 Hz, 3 H, -CH_3), 3.60 (dd, *J* = 14.5, 7.5 Hz, 1 H, NC*H*H), 4.13 (dd, *J* = 14.5, 9.3 Hz, 1 H, NCH*H*), 4.79–4.91 (m, 1 H, -OCH), 7.37 (d, *J* = 8.7 Hz, 2 H, arom), 7.87 (t, *J* = 7.4 Hz, 2 H, arom).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 21.1, 61.5, 76.5, 126.5, 128.6, 129.5, 137.3, 163.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{11}ClNO$: 196.0524; found: 196.0520.

Amidoethyl Acetates 1 and 3-Amidopropyl Acetates 2; General Procedure

A solution of the acyl chloride or acid anhydride (2.5 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise to a mixture of the aminoalcohol (2.5 mmol) and triethylamine (0.7 mL). The reaction mixture was stirred at 0 °C until disappearance of the acid chloride was confirmed by TLC (30 min), after which acetic anhydride (2.5 mmol) and DMAP (0.10 mmol) were added. After completion of the reaction (30 min), the solvent was evaporated in vacuo and the crude residue was purified by column chromatography (silica gel, hexane/EtOAc, 3:2 → 1:1).

2-Benzamidoethyl Acetate (1a)[53]

[CAS Reg. No. 92367-87-8]

White solid; yield: 518 mg (100%); mp 49–52 °C; R_f = 0.67 (CH_2Cl_2/EtOAc, 1:1).

2-(4-Chlorobenzamido)ethyl Acetate (1b)

White solid; yield: 508 mg (84%); mp 105–107 °C; R_f = 0.67 (CH_2Cl_2/EtOAc, 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.09 (s, 3 H, CH_3CO), 3.71 (q, *J* = 5.4 Hz, 2 H, N-CH_2), 4.29 (t, *J* = 5.3 Hz, 2 H, O-CH_2), 6.60 (br s, 1 H, NH), 7.41 (d, *J* = 8.5 Hz, 2 H, H-3′), 7.71 (d, *J* = 8.5 Hz, 2 H, H-2′).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.9, 39.8, 63.2, 126.9, 128.4, 128.9, 132.5, 137.9, 166.5, 171.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{13}ClNO_3$: 242.0578; found: 242.0587.

2-(4-Methoxybenzamido)ethyl Acetate (1c)

White solid; yield: 563 mg (95%); mp 59–61 °C; R_f = 0.60 (CH_2Cl_2/EtOAc, 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.08 (s, 3 H, CH_3CO), 3.69 (q, *J* = 5.4 Hz, 2 H, N-CH_2), 3.84 (s, 3 H, -OCH_3), 4.27 (t, *J* = 5.3 Hz, 2 H, O-CH_2), 6.54 (br s, 1 H, NH), 6.92 (d, *J* = 8.8 Hz, 2 H, arom), 7.74 (d, *J* = 8.8 Hz, 2 H, arom).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.9, 39.5, 55.4, 63.4, 113.8, 126.5, 128.8, 162.3, 167.1, 171.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NO_4$: 238.1074; found: 238.1066.

2-(4-Nitrobenzamido)ethyl Acetate (1d)[54]

[CAS Reg. No. 418787-99-2]

White solid; yield: 517 mg (82%); mp 109–111 °C; R_f = 0.60 (CH_2Cl_2/EtOAc, 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.11 (s, 3 H, CH_3CO), 3.76 (q, *J* = 5.2 Hz, 2 H, N-CH_2), 4.33 (t, *J* = 5.2 Hz, 2 H, O-CH_2), 6.75 (br s, 1 H, NH), 7.95 (d, *J* = 8.8 Hz, 2 H, H-2′), 8.31 (d, *J* = 8.8 Hz, 2 H, H-3′).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.9, 40.2, 63.1, 123.9, 128.2, 139.7, 149.7, 165.4, 171.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{13}N_2O_5$: 253.0819; found: 253.0811.

2-(2-Methylbenzamido)ethyl Acetate (1e)

White solid; yield: 503 mg (91%); mp 50–53 °C; R_f = 0.58 (CH_2Cl_2/EtOAc, 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.06 (s, 3 H, CH_3CO), 2.42 (s, 3 H, CH_3), 3.69 (q, *J* = 5.5 Hz, 2 H, N-CH_2), 4.25 (t, *J* = 5.3 Hz, 2 H, O-CH_2), 6.18 (br s, 1 H, NH), 7.18–7.21 (m, 2 H, arom), 7.29–7.34 (m, 2 H, arom).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 19.7, 20.8, 39.0, 63.3, 125.7, 126.6, 130.0, 131.0, 136.0, 136.1, 170.2, 171.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NO_3^+$: 222.1125; found: 222.1119.

(*S*)-2-Benzamidopropyl Acetate (1f)[55]

[CAS Reg. No. 157774-54-4]

Colorless oil; yield: 531 mg (96%); $[\alpha]_D^{25}$ –14.7 (*c* 2.12, $CHCl_3$); R_f = 0.64 (CH_2Cl_2/EtOAc, 1:1).

(*R*)-1-Benzamidopropan-2-yl Acetate (1g)

Colorless oil; yield: 531 mg (96%); $[\alpha]_D^{25}$ +5.8 (*c* 2.5, $CHCl_3$); R_f = 0.64 (CH_2Cl_2/EtOAc, 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.31 (d, *J* = 6.4 Hz, 3 H, -CH_3), 2.06 (s, 3 H, CH_3CO), 3.57 (ddd, *J* = 14.2, 7.8, 6.0 Hz, 1 H, -NC*H*H), 3.64 (ddd, *J* = 14.2, 5.5, 3.3 Hz, 1 H, -NCH*H*), 5.09–5.14 (m, 1 H, OCH-), 6.62 (br s, 1 H, NH), 7.43 (t, *J* = 7.5 Hz, 2 H, H-3′), 7.49 (t, *J* = 7.5 Hz, 1 H, H-4′), 7.76 (d, *J* = 7.5 Hz, 2 H, H-2′).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 17.8, 21.2, 44.9, 70.2, 126.9, 128.6, 131.5, 134.2, 167.5, 171.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NO_3$: 222.1125; found: 222.1126.

(*E*)-2-Cinnamamidoethyl Acetate (1h)

White solid; yield: 525 mg (90%); mp 78–80 °C; R_f = 0.57 (CH_2Cl_2/EtOAc, 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.09 (s, 3 H, CH_3CO), 3.67 (q, *J* = 5.5 Hz, 2 H, N-CH_2), 4.24 (t, *J* = 5.3 Hz, 2 H, O-CH_2), 6.04 (br s, 1 H, NH), 6.41 (d, *J* = 15.6 Hz, 1 H, =C*H*CO), 7.33–7.38 (m, 3 H, arom), 7.49–7.51 (m, 2 H, arom), 7.64 (d, *J* = 15.6 Hz, 1 H, Ar*H*C=).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.9, 39.0, 63.3, 120.2, 127.8, 128.8, 129.8, 134.7, 141.5, 166.0, 171.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{16}NO_3$: 234.1125; found: 234.1131.

2-(2-Phenylacetamido)ethyl Acetate (1i)[56]

[CAS Reg. No. 861058-36-8]

White solid; yield: 542 mg (98%); R_f = 0.66 (CH_2Cl_2/EtOAc, 1:1).

2-Isobutyramidoethyl Acetate (1j)

Colorless oil; yield: 403 mg (93%); R_f = 0.62 (CH_2Cl_2/EtOAc, 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 6.9 Hz, 6 H, -CH_3), 2.05 (s, 3 H, CH_3CO), 2.31–2.37 (m, 1 H, -CH-), 3.50 (q, *J* = 6.4 Hz, 2 H, N-CH_2), 4.15 (t, *J* = 6.1 Hz, 2 H, O-CH_2), 5.88 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 19.5, 20.8, 35.5, 38.6, 63.3, 171.2, 177.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{16}NO_3$: 174.1125; found: 174.1130.

3-Benzamidopropyl Acetate (2a)[57]

[CAS Reg. No. 129348-90-9]

Yellowish oil; yield: 531 mg (96%); R_f = 0.74 (CH_2Cl_2/EtOAc, 1:1).

3-(4-Chlorobenzamido)propyl Acetate (2b)

White solid; yield: 537 mg (84%); mp 65–67 °C; R_f = 0.62 (CH_2Cl_2/EtOAc, 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.93–1.98 (m, 2 H, -CH_2-), 2.09 (s, 3 H, CH_3CO), 3.51 (q, *J* = 6.3 Hz, 2 H, N-CH_2), 4.23 (t, *J* = 6.0 Hz, 2 H, O-CH_2), 6.57 (br s, 1 H, NH), 7.42 (d, *J* = 8.5 Hz, 2 H, H-3′), 7.73 (d, *J* = 8.5 Hz, 2 H, H-2′).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 21.0, 28.7, 36.6, 61.9, 128.3, 128.8, 132.8, 137.7, 166.3, 171.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}ClNO_3$: 256.0735; found: 256.0726.

3-(4-Methoxybenzamido)propyl Acetate (2c)[58]

[CAS Reg. No. 2378751-11-0]

White solid; yield: 521 mg (83%); mp 74–76 °C; R_f = 0.58 (CH_2Cl_2/EtOAc, 1:1).

3-(4-Nitrobenzamido)propyl Acetate (2d)

White solid; yield: 552 mg (83%); mp 94–96 °C; R_f = 0.61 (CH_2Cl_2/EtOAc, 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.93–1.98 (m, 2 H, -CH_2-), 2.08 (s, 3 H, CH_3CO), 3.53 (q, *J* = 6.3 Hz, 2 H, N-CH_2), 4.23 (t, *J* = 6.0 Hz, 2 H, O-CH_2), 6.88 (br s, 1 H, NH), 7.96 (d, *J* = 8.8 Hz, 2 H, H-2′), 8.27 (d, *J* = 8.8 Hz, 2 H, H-3′).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.9, 28.6, 36.7, 61.7, 123.8, 128.1, 140.0, 149.6, 165.3, 171.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}N_2O_5$: 267.0975; found: 267.0973.

3-(2-Methylbenzamido)propyl Acetate (2e)

Yellowish oil; yield: 535 mg (91%); R_f = 0.59 (CH_2Cl_2/EtOAc, 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.94–1.99 (m, 2 H, -CH_2-), 2.10 (s, 3 H, CH_3CO), 2.46 (s, 3 H, -CH_3), 3.48 (q, *J* = 6.4 Hz, 2 H, N-CH_2), 4.20 (t, *J* = 6.3 Hz, 2 H, O-CH_2), 6.92 (br s, 1 H, NH), 7.21–7.26 (m, 2 H, arom), 7.34–7.37 (m, 2 H, arom).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 19.3, 20.5, 28.3, 36.2, 61.8, 125.3, 126.4, 129.4, 130.5, 135.4, 136.2, 170.1, 170.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{18}NO_3$: 236.1281; found: 236.1276.

(*E*)-3-Cinnamamidopropyl Acetate (2f)

White solid; yield: 556 mg (90%); mp 112–113 °C; R_f = 0.60 (CH_2Cl_2/EtOAc, 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.88–1.92 (m, 2 H, -CH_2-), 2.05 (s, 3 H, CH_3CO), 3.44 (q, *J* = 6.4 Hz, 2 H, N-CH_2), 4.16 (t, *J* = 6.0 Hz, 2 H, O-CH_2), 6.24 (br s, 1 H, NH), 6.42 (d, *J* = 15.6 Hz, 1 H, =*CH*CO), 7.29–7.33 (m, 3 H, arom), 7.47–7.48 (m, 2 H, arom), 7.61 (d, *J* = 15.6 Hz, 1 H, Ar*HC*=).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.9, 28.7, 36.4, 61.8, 120.6, 127.7, 128.7, 129.6, 134.7, 140.9, 166.0, 171.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}NO_3$: 248.1281; found: 248.1281.

3-(2-Phenylacetamido)propyl Acetate (2g)[59]

[CAS Reg. No. 2170181-02-7]

White solid; yield: 441 mg (75%); mp 51–53 °C; R_f = 0.61 (CH_2Cl_2/EtOAc, 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.87–1.91 (m, 2 H, -CH_2-), 2.10 (s, 3 H, CH_3CO), 3.40 (q, *J* = 6.3 Hz, 2 H, N-CH_2), 3.69 (s, 2 H, -CH_2CO), 4.15 (t, *J* = 5.8 Hz, 2 H, O-CH_2), 5.78 (br s, 1 H, NH), 7.38 (d, *J* = 7.4 Hz, 2 H, H-2′), 7.41 (m, 1 H, H-4′), 7.47 (m, 2 H, H-3′).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.8, 28.6, 36.5, 43.8, 61.9, 127.3, 129.0, 129.4, 134.9, 171.0, 171.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{18}NO_3$: 236.1281; found: 236.1277.

3-Isobutyramidopropyl Acetate (2h)

Colorless oil; yield: 435 mg (93%); R_f = 0.58 (CH_2Cl_2/EtOAc, 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 6.9 Hz, 6 H, -CH_3), 1.80–1.84 (m, 2 H, -CH_2-), 2.05 (s, 3 H, CH_3CO), 2.33 (sept, *J* = 6.9 Hz, 1 H, -CH-), 3.30 (q, *J* = 6.4 Hz, 2 H, N-CH_2), 4.12 (t, *J* = 6.1 Hz, 2 H, O-CH_2), 5.84 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 19.6, 20.9, 28.7, 35.6, 36.0, 61.9, 171.3, 177.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{18}NO_3$: 188.1281; found: 188.1275.

3-Pivalamidopropyl Acetate (2i)

Colorless oil; yield: 428 mg (85%); R_f = 0.57 (CH_2Cl_2/EtOAc, 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.18 (s, 9 H, -CH_3), 1.79–1.82 (m, 2 H, -CH_2-), 2.05 (s, 3 H, CH_3CO), 3.29 (q, *J* = 6.3 Hz, 2 H, N-CH_2), 4.12 (t, *J* = 6.1 Hz, 2 H, O-CH_2), 6.03 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.9, 27.5, 28.6, 36.3, 38.6, 62.0, 171.3, 178.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{20}NO_3^+$: 202.1438; found: 202.1433.

Thioamidoethyl Acetates 3 and Thioamidopropyl Acetates 4; General Procedure

LR (0.75 mmol) was added to a solution of the amidoester **1** or **2** (2 mmol) in toluene (20 mL) and the resulting mixture was heated at reflux for 30 min. After the reaction was complete, the solvent was evaporated in vacuo and the residue was purified by column chromatography (silica gel, CH_2Cl_2).

2-Phenylthioamidoethyl Acetate (3a)

Yellow solid; yield: 384 mg (86%); mp 42–44 °C; R_f = 0.56 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.14 (s, 3 H, CH_3CO), 4.12 (q, *J* = 5.0 Hz, 2 H, N-CH_2), 4.47 (t, *J* = 5.0 Hz, 2 H, O-CH_2), 7.42 (t, *J* = 7.9 Hz, 2 H, H-3′), 7.50 (t, *J* = 6.9 Hz, 1 H, H-4′), 7.81 (d, *J* = 8.0 Hz, 2 H, H-2′), 8.22 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.9, 46.7, 62.2, 126.7, 128.5, 131.2, 141.2, 172.0, 199.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}NO_2S$: 224.0740; found: 224.0731.

2-(4-Chlorophenylthioamido)ethyl Acetate (3b)

Yellow solid; yield: 443 mg (86%); mp 102–104 °C; R_f = 0.56 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.12 (s, 3 H, CH_3CO), 4.06 (q, *J* = 5.0 Hz, 2 H, N-CH_2), 4.44 (t, *J* = 5.0 Hz, 2 H, O-CH_2), 7.36 (d, *J* = 8.6 Hz, 2 H, H-3′), 7.73 (d, *J* = 8.6 Hz, 2 H, H-2′), 8.25 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.9, 47.0, 62.2, 128.0, 128.7, 137.5, 139.4, 172.2, 197.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{13}ClNO_2S$: 258.0350; found: 258.0347.

2-(4-Methoxyphenylthioamido)ethyl Acetate (3c)

Yellow solid; yield: 380 mg (75%); mp 56–59 °C; R_f = 0.58 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.11 (s, 3 H, CH_3CO), 3.84 (s, 3 H, -OCH_3), 4.08 (q, *J* = 5.0 Hz, 2 H, N-CH_2), 4.44 (t, *J* = 5.0 Hz, 2 H, O-CH_2), 6.89 (d, *J* = 8.8 Hz, 2 H, H-3′), 7.80 (d, *J* = 8.8 Hz, 2 H, H-2′), 8.13 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.9, 46.7, 55.5, 62.3, 113.6, 128.5, 133.5, 162.3, 172.1, 198.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NO_3S$: 254.0845; found: 254.0848.

2-(4-Nitrophenylthioamido)ethyl Acetate (3d)

Yellow solid; yield: 413 mg (77%); mp 77–79 °C; R_f = 0.54 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.13 (s, 3 H, CH_3CO), 4.07 (q, *J* = 4.9 Hz, 2 H, N-CH_2), 4.47 (t, *J* = 4.9 Hz, 2 H, O-CH_2), 7.90 (d, *J* = 8.8 Hz, 2 H, arom), 8.23 (d, *J* = 8.8 Hz, 2 H, arom), 8.45 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.9, 47.3, 62.2, 123.7, 127.7, 146.1, 149.0, 172.5, 196.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{13}N_2O_4S$: 269.0591; found: 269.0587.

2-(2-Methylphenylthioamido)ethyl Acetate (3e)

Yellow oil; yield: 337 mg (71%); R_f = 0.50 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.97 (s, 3 H, -CH_3), 2.27 (s, 3 H, CH_3CO), 3.90–3.93 (m, 2 H, N-CH_2), 4.22–4.24 (m, 2 H, O-CH_2), 7.11–7.20 (m, 4 H, arom), 8.01 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 18.9, 20.5, 44.6, 61.4, 125.6, 126.4, 128.7, 130.4, 132.5, 143.4, 171.0, 201.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NO_2S$: 238.0896; found: 238.0892.

(*S*)-2-Phenylthioamidopropyl Acetate (3f)

Yellow oil; yield: 394 mg (83%); $[\alpha]_D^{25}$ –44.6 (*c* 2.00, $CHCl_3$); R_f = 0.56 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.8 Hz, 3 H, -CH_3), 2.11 (s, 3 H, CH_3CO), 4.27 (dd, *J* = 11.7, 5.9 Hz, 1 H, -NCH), 4.38 (dd, *J* = 11.7, 5.9 Hz, 1 H, C*H*HCO), 5.03–5.09 (m, 1 H, CH*H*CO), 7.39 (t, *J* = 7.5 Hz, 2 H, H-3′), 7.46 (t, *J* = 7.5 Hz, 1 H, H-4′), 7.74 (d, *J* = 7.5 Hz, 2 H, H-2′), 7.87 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 15.8, 20.8, 51.2, 66.3, 126.6, 128.5, 131.1, 141.7, 171.6, 198.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NO_2S^+$: 238.0896; found: 238.0901.

(*R*)-1-Phenylthioamidopropan-2-yl Acetate (3g)

Yellow oil; yield: 408 mg (86%); $[\alpha]_D^{25}$ +16.3 (*c* 1.00, $CHCl_3$); R_f = 0.56 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 6.5 Hz, 3 H, -CH_3), 2.10 (s, 3 H, CH_3CO), 3.90 (ddd, *J* = 13.5, 8.5, 5.0 Hz, 1 H, -NC*H*H), 4.03 (ddd, *J* = 15.0, 5.0, 2.5 Hz, 1 H, -NCH*H*), 5.24–5.29 (m, 1 H, -OCH), 7.39 (t, *J* = 8.0 Hz, 2 H, H-3′), 7.46 (t, *J* = 8.0 Hz, 1 H, H-4′), 7.77 (d, *J* = 8.0 Hz, 2 H, H-2′), 8.30 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 18.2, 21.2, 52.3, 69.6, 126.6, 128.5, 131.2, 141.2, 172.0, 199.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NO_2S$: 238.0896; found: 238.0900.

(*E*)-2-(3-Phenylprop-2-enethioamido)ethyl Acetate (3h)

Yellow solid; yield: 344 mg (69%); mp 94–96 °C; R_f = 0.50 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.12 (s, 3 H, CH_3CO), 4.08 (q, *J* = 5.1 Hz, 2 H, N-CH_2), 4.40 (t, *J* = 5.1 Hz, 2 H, O-CH_2), 6.84 (d, *J* = 15.4 Hz, 1 H, =*CH*CS), 7.34–7.38 (m, 3 H, arom), 7.53–7.54 (m, 2 H, arom), 7.80 (d, *J* = 15.4 Hz, 1 H, Ar*H*C=), 7.84 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.9, 45.7, 62.2, 127.4, 128.0, 128.9, 129.9, 134.8, 141.9, 171.8, 195.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{16}NO_2S$: 250.0896; found: 250.0893.

2-(2-Phenylethanethioamido)ethyl Acetate (3i)

Yellow oil; yield: 427 mg (90%); R_f = 0.57 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.95 (s, 3 H, CH_3CO), 3.88 (q, *J* = 5.2 Hz, 2 H, N-CH_2), 4.14 (s, 2 H, -CH_2-), 4.22 (t, *J* = 5.3 Hz, 2 H, O-CH_2), 7.27–7.40 (m, 5 H, arom).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.6, 45.3, 53.2, 61.5, 127.9, 129.2, 129.6, 134.8, 171.1, 203.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NO_2S$: 238.0896; found: 238.0900.

2-(2-Methylpropanethioamido)ethyl Acetate (3j)

Yellow oil; yield: 303 mg (80%); R_f = 0.55 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 6.7 Hz, 6 H,-CH_3), 2.11 (s, 3 H, CH_3CO), 2.80–2.85 (m, 1 H, -CH-), 3.94 (q, *J* = 5.1 Hz, 2 H, N-CH_2), 4.35 (t, *J* = 5.1 Hz, 2 H, O-CH_2), 7.70 (br s,1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.9, 22.5, 44.6, 45.6, 62.1, 171.9, 212.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{16}NO_2S$: 190.0896; found: 190.0898.

3-Phenylthioamidopropyl Acetate (4a)

Yellow oil; yield: 403 mg (85%); R_f = 0.50 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.07–2.10 (m, 5 H, -CH_2-, -CH_3)*, 3.87–3.90 (m, 2 H, N-CH_2), 4.20–4.22 (m, 2 H, O-CH_2), 7.38 (t, *J* = 8.0 Hz, 2 H, arom), 7.45 (t, *J* = 8.0 Hz, 1 H, arom), 7.76 (d, *J* = 8.0 Hz, 2 H, arom), 8.16 (br s, 1 H, NH); * overlapping signals.

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.9, 27.0, 43.4, 62.2, 126.6, 128.4, 131.1, 141.6, 171.5, 199.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NO_2S$: 238.0896; found: 238.0891.

3-(4-Chlorophenylthioamido)propyl Acetate (4b)

Yellow oil; yield: 489 mg (90%); R_f = 0.60 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.06–2.11 (m, 5 H, -CH_2-, CH_3CO)*, 3.89 (q, *J* = 6.2 Hz, 2 H, N-CH_2), 4.22 (t, *J* = 5.9 Hz, 2 H, O-CH_2), 7.35 (d, *J* = 8.6 Hz, 2 H, H-3′), 7.73 (d, *J* = 8.6 Hz, 2 H, H-2′), 8.17 (br s, 1 H, NH); * overlapping signals.

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.9, 27.1, 43.3, 62.1, 128.0, 128.6, 137.4, 139.8, 171.7, 197.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}ClNO_2S$: 272.0507; found: 272.0512.

3-(4-Methoxyphenylthioamido)propyl Acetate (4c)

Yellow oil; yield: 454 mg (85%); R_f = 0.56 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.06–2.10 (m, 5 H, -CH_2-, CH_3CO)*, 3.83 (s, 3 H, OCH_3), 3.90 (q, *J* = 6.2 Hz, 2 H, N-CH_2), 4.22 (t, *J* = 5.9 Hz, 2 H, O-CH_2), 6.87 (d, *J* = 8.8 Hz, 2 H, H-3′), 7.80 (d, *J* = 8.8 Hz, 2 H, H-2′), 8.07 (br s, 1 H, NH); * overlapping signals.

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.9, 27.2, 43.2, 55.4, 62.2, 113.6, 128.4, 133.8, 162.2, 171.6, 197.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{18}NO_3S$: 268.1002; found: 268.0996.

3-(4-Nitrophenylthioamido)propyl Acetate (4d)

Yellow oil; yield: 429 mg (76%); R_f = 0.48 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.09–2.13 (m, 5 H, -CH_2-, CH_3CO)*, 3.91 (q, *J* = 6.2 Hz, 2 H, N-CH_2), 4.25 (t, *J* = 5.8 Hz, 2 H, O-CH_2), 7.92 (d, *J* = 8.6 Hz, 2 H, arom), 8.24 (d, *J* = 8.6 Hz, 2 H, arom), 8.33 (br s, 1 H, NH); * overlapping signals.

^{13}C NMR (151 MHz, $CDCl_3$): δ = 21.0, 27.0, 43.3, 61.9, 123.7, 127.6, 146.6, 149.0, 171.9, 196.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}N_2O_4S$: 283.0747; found: 283.0751.

3-(2-Methylphenylthioamido)propyl Acetate (4e)

Yellow oil; yield: 427 mg (85%); R_f = 0.48 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.03 (s, 3 H, CH_3CO), 2.05–2.09 (m, 2 H, -CH_2-), 2.36 (s, 3 H, CH_3), 3.88 (q, *J* = 6.4 Hz, 2 H, N-CH_2), 4.18 (t, *J* = 6.0 Hz, 2 H, O-CH_2), 7.16–7.18 (m, 2 H, arom), 7.22–7.25 (m, 2 H, arom), 7.70 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 19.3, 20.8, 27.1, 42.7, 62.0, 125.9, 126.4, 128.9, 130.7, 132.8, 143.9, 171.3, 201.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{18}NO_2S$: 252.1053; found: 252.1055.

(*E*)-3-(3-Phenylprop-2-enethioamido)propyl Acetate (4f)

Yellow solid; yield: 448 mg (85%); mp 62–65 °C; R_f = 0.43 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.04–2.08 (m, 2 H, -CH_2-), 2.10 (s, 3 H, CH_3CO), 3.88 (q, *J* = 6.4 Hz, 2 H, N-CH_2), 4.21 (t, *J* = 6.0 Hz, 2 H, O-CH_2), 6.84 (d, *J* = 15.4 Hz, 1 H, =*CH*CS), 7.35–7.38 (m, 3 H, arom), 7.51–7.53 (m, 2 H, arom), 7.80 (d, *J* = 15.4 Hz, 1 H, Ar*H*C=), 7.80 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 21.0, 27.3, 42.4, 62.0, 127.7, 128.0, 128.9, 129.8, 134.8, 141.4, 171.6, 194.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}NO_2S$: 264.1053; found: 264.1057.

3-(2-Phenylethanethioamido)propyl Acetate (4g)

Yellow oil; yield: 503 mg (100%); R_f = 0.41 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.88–1.92 (m, 2 H, -CH_2-), 1.98 (s, 3 H, CH_3CO), 3.71 (q, *J* = 6.3 Hz, 2 H, N-CH_2), 4.02 (t, *J* = 6.0 Hz, 2 H, O-CH_2), 4.12 (s, 2 H, -CH_2CO), 7.27 (d, *J* = 7.4 Hz, 2 H, H-2′), 7.32 (t, *J* = 7.4 Hz, 1 H, H-4′), 7.36–7.39 (m, 3 H, H-3′, NH)*; * overlapping signals.

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.8, 26.9, 42.8, 53.2, 61.8, 127.8, 129.2, 129.4, 134.9, 171.2, 202.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{18}NO_2S$: 252.1053; found: 252.1056.

3-(2-Methylpropanethioamido)propyl Acetate (4h)

Colorless oil; yield: 333 mg (82%); R_f = 0.7 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.7 Hz, 6 H, -CH_3), 1.97–2.01 (m, 2 H, -CH_2-), 2.08 (s, 3 H, CH_3CO), 2.82 (sept, *J* = 6.7 Hz, 1 H, -CH-), 3.73 (q, *J* = 6.4 Hz, 2 H, N-CH_2), 4.16 (t, *J* = 6.0 Hz, 2 H, O-CH_2), 7.69 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.9, 22.4, 22.5, 27.0, 42.3, 44.6, 62.0, 171.5, 211.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{18}NO_2S$: 204.1053; found: 204.1046.

3-(2,2-Dimethylpropanethioamido)propyl Acetate (4i)

Colorless oil; yield: 382 mg (88%); R_f = 0.65 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.35 (s, 9 H, -CH_3), 1.97–2.00 (m, 2 H, -CH_2-), 2.09 (s, 3 H, CH_3CO), 3.74 (q, *J* = 5.9 Hz, 2 H, N-CH_2), 4.17 (t, *J* = 5.6 Hz, 2 H, O-CH_2), 7.89 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.9, 26.9, 30.0, 43.0, 44.5, 62.2, 171.6, 213.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{20}NO_2S$: 218.1209; found: 218.1208.

***N*-(2-Hydroxyethyl)thioamides 5 and *N*-(3-Hydroxypropyl)thioamides 6; General Procedure**

Thioamidoester **3** or **4** (1.5 mmol) was placed in a round-bottomed flask and a solution of 10% NaOH/methanol was added. The mixture was stirred for 30 minutes at 0 °C. After completion of the reaction (30 min), as indicated by TLC, the solvent was evaporated in vacuo and the residue was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 1:1 → 2:3).

***N*-(2-Hydroxyethyl)benzothioamide (5a)**[41]

[CAS Reg. No. 36926-15-5]

Yellow solid; yield: 253 mg (93%); mp 91–93 °C; R_f = 0.35 (hexane/EtOAc, 3:2).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 48.5, 60.5, 126.7, 128.5, 131.2, 141.6, 199.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{12}NOS$: 182.0634; found: 182.0640.

4-Chloro-*N*-(2-hydroxyethyl)benzothioamide (5b)

[CAS Reg. No. 36926-21-3]

Yellow solid; yield: 323 mg (100%); mp 91–93 °C; R_f = 0.35 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.88 (br s, 1 H, OH), 3.96 (t, *J* = 4.9 Hz, 2 H, O-CH_2), 4.01 (q, *J* = 4.9 Hz, 2 H, N-CH_2), 7.35 (d, *J* = 8.6 Hz, 2 H, H-3′), 7.71 (d, *J* = 8.6 Hz, 2 H, H-2′), 8.08 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 48.6, 60.4, 128.1, 128.6, 137.4, 139.8, 198.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{11}ClNOS$: 216.0244; found: 216.0246.

***N*-(2-Hydroxyethyl)-4-methoxybenzothioamide (5c)**[60]

[CAS Reg. No. 96316-04-0]

Pale yellow oil; yield: 307 mg (97%); R_f = 0.37 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.93 (br s, 1 H, OH), 3.85 (s, 3 H, OCH_3), 3.95–3.99 (m, 2 H, O-CH_2), 4.05 (q, *J* = 5.0 Hz, 2 H, N-CH_2), 6.89 (d, *J* = 8.7 Hz, 2 H, H-3′), 7.80 (d, *J* = 8.7 Hz, 2 H, H-2′), 7.94 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 48.4, 55.5, 60.8, 113.6, 128.6, 133.9, 162.3, 198.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{14}NO_2S$: 212.0740; found: 212.0732.

***N*-(2-Hydroxyethyl)-4-nitrobenzothioamide (5d)**

[CAS Reg. No. 957755-55-4]

Yellow solid; yield: 275 mg (81%); mp 151–153 °C; R_f = 0.40 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.78 (br s, 1 H, OH), 4.01–4.07 (m, 4 H, N-CH_2, O-CH_2)*, 7.91 (d, *J* = 8.8 Hz, 2 H, arom), 8.08 (br s, 1 H, NH), 8.26 (d, *J* = 8.8 Hz, 2 H, arom); * overlapping signals.

^{13}C NMR (151 MHz, $CDCl_3$): δ = 48.5, 60.2, 123.8, 127.7, 146.8, 149.1, 197.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{11}N_2O_3S$: 227.0485; found: 227.0487.

N-(2-Hydroxyethyl)-2-methylbenzothioamide (5e)

White solid; yield: 284 mg (97%); mp 103–105 °C; R_f = 0.45 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.15 (br s, 1 H, OH), 2.37 (s, 3 H, -CH_3), 3.88–3.91 (m, 2 H, O-CH_2), 3.95–3.98 (m, 2 H, N-CH_2), 7.16–7.19 (m, 2 H, arom), 7.22–7.25 (m, 1 H, arom), 7.26–7.28 (m, 1 H, arom), 7.80 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 21.0, 47.8, 60.4, 125.9, 126.6, 129.0, 130.7, 132.9, 143.8, 202.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{14}NOS$: 196.0791; found: 196.0786.

(*S*)-*N*-(1-Hydroxypropan-2-yl)benzothioamide (5f)[41]

Yellow oil; yield: 264 mg (90%); $[\alpha]_D^{25}$ +40.2 (*c* 2.3, $CHCl_3$); R_f = 0.35 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.8 Hz, 3 H, -CH_3), 2.27 (br s, 1 H, OH), 3.74 (dd, *J* = 11.0, 4.2 Hz, 1 H, -NCH), 3.92 (dd, *J* = 11.0, 3.2 Hz, 1 H, CH*H*O), 4.86–4.92 (m, 1 H, C*H*HO), 7.37 (t, *J* = 7.7 Hz, 2 H, H-3′), 7.45 (t, *J* = 7.4 Hz, 1 H, H-4′), 7.73 (d, *J* = 7.7 Hz, 2 H, H-2′), 7.83 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 15.9, 53.0, 65.2, 126.7, 128.4, 131.1, 141.9, 198.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{14}NOS$: 196.0791; found: 196.0788.

(*R*)-*N*-(2-Hydroxypropyl)benzothioamide (5g)[41]

[CAS Reg. No. 861058-58-4]

Pale yellow oil; yield: 269 mg (92%); $[\alpha]_D^{28}$ –36.3 (*c* 0.46, $CHCl_3$); R_f = 0.35 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 6.2 Hz, 3 H, -CH_3), 2.27 (br s, 1 H, OH), 3.58 (ddd, *J* = 13.9, 8.3, 4.6 Hz, 1 H, NC*H*H), 4.12 (ddd, *J* = 14.0, 6.3, 3.2 Hz, 1 H, NCH*H*), 4.15–4.20 (m, 1 H, -*H*CO), 7.36 (t, *J* = 8.0 Hz, 2 H, H-3′), 7.45 (t, *J* = 7.4 Hz, 1 H, H-4′), 7.76 (d, *J* = 7.4 Hz, 2 H, H-2′), 8.10 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 21.4, 53.2, 66.3, 126.7, 128.5, 131.1, 141.6, 199.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{14}NOS$: 196.0791; found: 196.0795.

(*E*)-*N*-(2-Hydroxyethyl)-3-phenylprop-2-enethioamide (5h)

Yellow solid; yield: 274 mg (88%); mp 65–67 °C; R_f = 0.35 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.92 (br s, 1 H, OH), 3.96 (t, *J* = 5.1 Hz, 2 H, O-CH_2), 4.04 (q, *J* = 5.2 Hz, 2 H, N-CH_2), 6.85 (d, *J* = 15.3 Hz, 1 H, =*CH*CS), 7.35–7.40 (m, 3 H, arom), 7.53–7.55 (m, 2 H, arom), 7.71 (br s, 1 H, NH), 7.83 (d, *J* = 15.3 Hz, 1 H, Ar*HC*=).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 47.7, 60.8, 127.5, 128.0, 128.9, 129.9, 134.8, 142.0, 195.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}NOS$: 208.0791; found: 208.0785.

N-(2-Hydroxyethyl)-2-phenylethanethioamide (5i)[61]

[CAS Reg. No. 861058-58-4]

Yellow solid; yield: 226 mg (77%); mp 115–117 °C; R_f = 0.30 (hexane/EtOAc, 3:2).

N-(2-Hydroxyethyl)-2-methylpropanethioamide (5j)

Yellow oil; yield: 181 mg (82%); R_f = 0.30 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.8 Hz, 6 H, -CH_3), 2.56 (br s, 1 H, -OH), 2.80–2.86 (m, 1 H, -CH-), 3.83–3.87 (m, 4 H, N-CH_2, O-CH_2), 7.84 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 22.5, 44.4, 47.5, 60.4, 212.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_6H_{14}NOS$: 148.0791; found: 148.0794.

N-(3-Hydroxypropyl)benzothioamide (6a)[62]

[CAS Reg. No. 36926-17-7]

Yellow oil; yield: 264 mg (90%); R_f = 0.25 (EtOAc/hexane, 3:2).

4-Chloro-*N*-(3-hydroxypropyl)benzothioamide (6b)

Yellow solid; yield: 317 mg (92%); mp 97–100 °C; R_f = 0.15 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.96–2.00 (m, 2 H, -CH_2-), 3.89 (t, *J* = 5.3 Hz, 2 H, O-CH_2), 3.98 (q, *J* = 5.5 Hz, 2 H, N-CH_2), 7.35 (d, *J* = 8.5 Hz, 2 H, H-3′), 7.73 (d, *J* = 8.5 Hz, 2 H, H-2′), 8.62 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 30.0, 46.1, 62.0, 128.0, 128.6, 137.3, 139.8, 197.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{13}ClNOS$: 230.0401; found: 230.0395.

N-(3-Hydroxypropyl)-4-methoxybenzothioamide (6c)

Yellow oil; yield: 338 mg (100%); R_f = 0.14 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.91–1.94 (m, 2 H, -CH_2-), 3.81 (t, *J* = 5.5 Hz, 2 H, O-CH_2), 3.82 (s, 3 H, OCH_3), 3.97 (q, *J* = 5.6 Hz, 2 H, N-CH_2), 6.85 (d, *J* = 8.8 Hz, 2 H, H-3′), 7.77 (d, *J* = 8.8 Hz, 2 H, H-2′), 8.53 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 30.4, 45.3, 55.4, 61.2, 113.5, 128.5, 133.6, 162.1, 197.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{16}NO_2S$: 226.0896; found: 226.0903.

N-(3-Hydroxypropyl)-4-nitrobenzothioamide (6d)

Yellow solid; yield: 360 mg (100%); mp 69–71 °C; R_f = 0.15 (hexane/EtOAc, 5:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.95 (br s, 1 H, OH), 2.01–2.05 (m, 2 H, -CH_2-), 3.94–3.97 (m, 2 H, O-CH_2), 4.01 (q, *J* = 5.5 Hz, 2 H, N-CH_2), 7.92 (d, *J* = 8.8 Hz, 2 H, arom), 8.23 (d, *J* = 8.8 Hz, 2 H, arom), 8.85 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 29.5, 46.8, 62.7, 123.7, 127.7, 146.7, 149.4, 195.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{13}N_2O_3S$: 241.0641; found: 241.0647.

N-(3-Hydroxypropyl)-2-methylbenzothioamide (6e)

Yellow solid; yield: 298 mg (95%); mp 54–56 °C; R_f = 0.15 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.84–1.88 (m, 2 H, -CH_2-), 2.35 (s, 3 H, CH_3), 2.59 (br s, 1 H, OH), 3.73 (t, *J* = 5.5 Hz, 2 H, O-CH_2), 3.93 (q, *J* = 6.0 Hz, 2 H, N-CH_2), 7.14–7.17 (m, 2 H, arom), 7.21–7.26 (m, 2 H, arom), 8.10 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 19.3, 30.5, 44.0, 60.5, 125.9, 126.6, 128.9, 130.7, 132.8, 143.7, 201.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{16}NOS$: 210.0947; found: 210.0942.

(*E*)-*N*-(3-Hydroxypropyl)-3-phenylprop-2-enethioamide (6f)

Yellow oil; yield: 322 mg (97%); R_f = 0.15 (hexane/EtOAc, 3:2).

This compound was obtained as an inseparable mixture of *E*/*Z* diastereoisomers. Only data for the major isomer is reported.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.91–1.95 (m, 2 H, -CH_2-), 2.39 (br s, 1 H, OH), 3.82 (t, *J* = 5.9 Hz, 2 H, O-CH_2), 4.01 (q, *J* = 5.4 Hz, 2 H, N-CH_2), 6.81 (d, *J* = 15.4 Hz, 1 H, =*CH*CS), 7.36–7.38 (m, 3 H, arom), 7.52–7.53 (m, 2 H, arom), 7.80 (d, *J* = 15.4 Hz, 1 H, Ar*H*C=), 8.06 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 30.6, 44.3, 61.1, 127.7, 128.0, 128.9, 129.8, 134.9, 141.6, 194.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}NOS$: 222.0947; found: 222.0950.

N-(3-Hydroxypropyl)-2-phenylethanethioamide (6g)

Yellow solid; yield: 305 mg (97%); mp 72–74 °C; R_f = 0.15 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.71–1.75 (m, 2 H, -CH_2-), 2.24 (br s, 1 H, OH), 3.62 (t, *J* = 5.4 Hz, 2 H, O-CH_2), 3.79 (q, *J* = 5.9 Hz, 2 H, O-CH_2), 4.12 (s, 2 H, -CH_2CO), 7.24–7.26 (m, 2 H, arom), 7.29–7.32 (m, 1 H, arom), 7.35–7.37 (m, 2 H, arom), 7.80 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 30.2, 44.3, 53.1, 60.5, 127.8, 129.1, 129.6, 134.8, 202.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{16}NOS$: 210.0947; found: 210.0950.

N-(3-Hydroxypropyl)-2-methylpropanethioamide (6h)

Yellow oil; yield: 242 mg (100%); R_f = 0.14 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.8 Hz, 6 H, -CH_3), 1.83–1.87 (m, 2 H, -CH_2-), 2.82 (sept, *J* = 6.7 Hz, 1 H, -CH), 3.75 (t, *J* = 5.4 Hz, 2 H, O-CH_2), 3.85 (q, *J* = 5.9 Hz, 2 H, N-CH_2), 8.06 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 22.4, 30.4, 43.9, 44.6, 60.7, 211.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_7H_{16}NOS$: 162.0947; found: 162.0947.

N-(3-Hydroxypropyl)-2,2-dimethylpropanethioamide (6i)

Yellow oil; yield: 263 mg (100%); R_f = 0.27 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.34 (s, 9 H, -CH_3), 1.85–1.89 (m, 2 H, -CH_2-), 2.56 (br s, 1 H, OH), 3.79 (t, *J* = 5.3 Hz, 2 H, O-CH_2), 3.85 (q, *J* = 5.3 Hz, 2 H, N-CH_2), 8.35 (br s, 1 H, NH).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 30.0, 30.1, 44.5, 45.2, 61.3, 76.8, 77.2, 213.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{18}NOS$: 176.1104; found: 176.1096.

2-Thiazolines 7 and 5,6-Dihydro-4*H*-1,3-thiazines 8; General Procedure

A mixture of the corresponding compound **5** or **6** (1 mmol) and a chloroform solution of PPE (1.7 M, 2 mL) was reacted in a microwave reactor (Monowave 300, Anton Paar) at the indicated temperature and time (see Table 2). After reaching room temperature, the resulting oil was treated with EtOAc (25 mL) and 10% aqueous NaOH (10 mL). The aqueous phase was extracted with EtOAc (2 × 25 mL). The organic phases were combined, washed with water (5 mL), dried over Na_2SO_4, filtered and the solvent removed in vacuo. The crude residue was purified by column chromatography (silica gel, hexane/EtOAc, 3:2).

2-Phenyl-4,5-dihydrothiazole (7a)[35]

[CAS Reg. No. 2722-34-1]

Pale yellow oil; yield: 147 mg (90%); R_f = 0.65 (hexane/EtOAc, 3:2).

2-(4-Chlorophenyl)-4,5-dihydrothiazole (7b)[35]

[CAS Reg. No. 13084-29-2]

Yellow solid; yield: 178 mg (90%); mp 50–52 °C; R_f = 0.60 (hexane/EtOAc, 3:2).

2-(4-Methoxyphenyl)-4,5-dihydrothiazole (7c)[63]

[CAS Reg. No. 2519-93-9]

Yellow solid; yield: 166 mg (86%); mp 54–56 °C; R_f = 0.60 (hexane/EtOAc, 3:2).

2-(4-Nitrophenyl)-4,5-dihydrothiazole (7d)[64]

[CAS Reg. No. 2518-13-0]

Orange solid; yield: 148 mg (71%); mp 150–152 °C; R_f = 0.60 (hexane/EtOAc, 3:2).

2-(2-Methylphenyl)-4,5-dihydrothiazole (7e)

Yellow oil; yield: 158 mg (89%); R_f = 0.74 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, -CH_3), 3.39 (t, *J* = 8.5 Hz, 2 H, S-CH_2), 4.49 (t, *J* = 8.5 Hz, 2 H, N-CH_2), 7.20–7.24 (m, 2 H, arom), 7.28–7.30 (m, 1 H, arom), 7.55 (m, 1 H, arom).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 20.7, 33.8, 65.8, 125.5, 129.5, 129.6, 130.9, 133.0, 136.8, 168.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{12}NS$: 178.0685; found: 178.0681.

(*S*)-4-Methyl-2-phenyl-4,5-dihydrothiazole (7f)[65]

[CAS Reg. No. 22906-50-9]

Yellow oil; yield: 147 mg (83%); $[\alpha]_D^{25}$ +61.0 (*c* 0.60, $CHCl_3$); R_f = 0.70 (hexane/EtOAc, 3:2).

(*S*)-5-Methyl-2-phenyl-4,5-dihydrothiazole (7g)

Yellow oil; yield: 154 mg (87%); $[\alpha]_D^{25}$ +80.0 (*c* 0.9 $CHCl_3$); R_f = 0.79 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.43 (d, *J* = 6.9 Hz, 3 H, -CH_3), 4.02–4.07 (m, 1 H, S-CH), 4.22 (dd, *J* = 15.6, 4.4 Hz, 1 H, -NC*H*H), 4.42 (dd, *J* = 15.6, 7.9 Hz, 1 H, -NCH*H*), 7.41–7.44 (m, 2 H, arom), 7.46–7.49 (m, 1 H, arom), 7.85–7.86 (m, 2 H, arom).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 22.1, 45.9, 72.2, 128.2, 128.4, 131.0, 133.5, 167.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{12}NS$: 178.0685; found: 178.0688.

(*E*)-2-Styryl-4,5-dihydrothiazole (7h)[8]

[CAS Reg. No. 25468-93-3]

Yellow solid; yield: 157 mg (83%); mp 101–103 °C; R_f = 0.70 (hexane/EtOAc, 3:2).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 33.0, 64.8, 122.7, 127.4, 128.8, 129.4, 135.3, 141.1, 167.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}NS$: 190.0685; found: 190.0687.

2-Benzyl-4,5-dihydrothiazole (7i)[35]

[CAS Reg. No. 18732-64-4]

Yellow oil; yield: 124 mg (70%); R_f = 0.75 (hexane/EtOAc, 3:2).

2-Isopropyl-4,5-dihydrothiazole (7j)

Yellow oil; yield: 90 mg (70%); R_f = 0.65 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 6.9 Hz, 6 H, -CH_3), 2.73–2.80 (m, 1 H, -CH-), 3.21 (t, *J* = 8.4 Hz, 2 H, S-CH_2), 4.18 (t, *J* = 8.4 Hz, 2 H, N-CH_2).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 21.0, 33.1, 33.8, 64.3, 177.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_6H_{12}NS$: 130.0685; found: 130.0680.

2-Phenyl-5,6-dihydro-4*H*-1,3-thiazine (8a)[35]

[CAS Reg. No. 6638-35-3]

Pale yellow oil; yield: 142 mg (80%); R_f = 0.60 (hexane/EtOAc, 3:2).

2-(4-Chlorophenyl)-5,6-dihydro-4*H*-1,3-thiazine (8b)[35]

[CAS Reg. No. 830356-07-5]

Pale yellow oil; yield: 205 mg (97%); R_f = 0.60 (hexane/EtOAc, 3:2).

2-(4-Methoxyphenyl)-5,6-dihydro-4*H*-1,3-thiazine (8c)

Yellow solid; yield: 186 mg (90%); mp 80–82 °C; R_f = 0.50 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.88–1.92 (m, 2 H, -CH_2-), 3.14 (t, *J* = 5.5 Hz, 2 H, S-CH_2), 3.82 (s, 3 H, -OCH_3), 3.88 (t, *J* = 6.1 Hz, 2 H, N-CH_2), 6.88 (d, *J* = 8.8 Hz, 2 H, H-3′), 7.73 (d, *J* = 8.9 Hz, 2 H, H-2′).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 19.3, 26.6, 47.9, 55.3, 113.5, 127.7, 132.3, 157.3, 161.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}NOS$: 208.0791; found: 208.0784.

2-(4-Nitrophenyl)-5,6-dihydro-4*H*-1,3-thiazine (8d)[66]

[CAS Reg. No. 21977-88-8]

Yellow solid; yield: 220 mg (99%); mp 121–124 °C; R_f = 0.60 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.93–1.96 (m, 2 H, -CH_2-), 3.20 (t, *J* = 6.0 Hz, 2 H, S-CH_2), 3.96 (t, *J* = 5.5 Hz, 2 H, N-CH_2), 7.94 (d, *J* = 8.9 Hz, 2 H, H-2′), 8.23 (d, *J* = 8.9 Hz, 2 H, H-3′).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 18.9, 26.5, 48.3, 123.5, 127.2, 144.9, 148.8, 156.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{11}N_2O_2S$: 223.0536; found: 223.0540.

2-(2-Methylphenyl)-5,6-dihydro-4*H*-1,3-thiazine (8e)

Pale yellow oil; yield: 184 mg (96%); R_f = 0.65 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.93–1.97 (m, 2 H, -CH_2-), 2.40 (s, 3 H, CH_3), 3.16 (t, *J* = 6.0 Hz, 2 H, S-CH_2), 3.88 (t, *J* = 5.5 Hz, 2 H, N-CH_2), 7.16–7.19 (m, 2 H, arom), 7.22–7.25 (m, 1 H, arom), 7.28–7.29 (m, 1 H, arom).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 19.0, 19.2, 27.4, 47.7, 125.5, 127.7, 128.9, 130.6, 135.2, 139.8, 159.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}NS$: 192.0841; found: 192.0833.

(*E*)-2-Styryl-5,6-dihydro-4*H*-1,3-thiazine (8f)[9]

[CAS Reg. No. 33587-28-9]

Yellow solid; yield: 191 mg (94%); mp 60–61 °C; R_f = 0.60 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.88–1.92 (m, 2 H, -CH_2-), 3.11 (t, *J* = 6.1 Hz, 2 H, S-CH_2), 3.86 (t, *J* = 5.5 Hz, 2 H, N-CH_2), 6.69 (d, *J* = 16.4 Hz, 1 H, -CH=), 7.22 (d, *J* = 16.4 Hz, 1 H, -CH=), 7.28–7.31 (m, 2 H, arom), 7.33–7.36 (m, 2 H, arom), 7.46–7.48 (m, 1 H, arom).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 19.6, 26.0, 48.1, 127.3, 128.7, 128.8, 129.5, 134.5, 135.7, 156.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}NS$: 204.0841; found: 204.0844.

2-Benzyl-5,6-dihydro-4*H*-1,3-thiazine (8g)[8]

[CAS Reg. No. 2547-53-9]

Yellow oil; yield: 155 mg (81%); R_f = 0.50 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.79–1.83 (m, 2 H, -CH_2-), 2.99 (t, *J* = 6.1 Hz, 2 H, S-CH_2), 3.66 (s, 2 H, -CH_2-Ph), 3.72 (t, *J* = 5.5 Hz, 2 H, N-CH_2), 7.26–7.30 (m, 1 H, arom), 7.32–7.35 (m, 4 H, arom).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 18.9, 26.4, 47.3, 48.4, 126.7, 128.3, 129.1, 136.7, 160.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}NS$: 192.0841; found: 192.0837.

2-Isopropyl-5,6-dihydro-4*H*-1,3-thiazine (8h)

Yellow oil; yield: 143 mg (100%); R_f = 0.70 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 6.9 Hz, 6 H, -CH_3), 1.76–1.80 (m, 2 H, -CH_2-), 2.46 (sept, *J* = 6.8 Hz, 1 H , -CH), 2.99 (t, *J* = 6.1 Hz, 2 H, S-CH_2), 3.63 (t, *J* = 4.7 Hz, 2 H, N-CH_2).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 19.4, 20.8, 26.2, 40.4, 47.2, 166.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_7H_{14}NS^+$: 144.0841; found: 144.0839.

2-(*tert*-Butyl)-5,6-dihydro-4*H*-1,3-thiazine (8i)

Yellow oil; yield: 142 mg (90%); R_f = 0.70 (hexane/EtOAc, 3:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.08 (s, 9 H, -CH_3), 1.62–1.66 (m, 2 H, -CH_2), 2.88 (t, *J* = 6.2 Hz, 2 H, S-CH_2), 3.55 (t, *J* = 5.5 Hz, 2 H, N-CH_2).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 19.1, 25.7, 28.5, 41.9, 47.3, 168.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{16}NS$: 158.0998; found: 158.1005.

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Supporting Information

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