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Effects of Thionation and Fluorination on Cis−Trans Isomerization in Tertiary Amides: An Investigation of *N*-Alkylglycine (Peptoid) Rotamers

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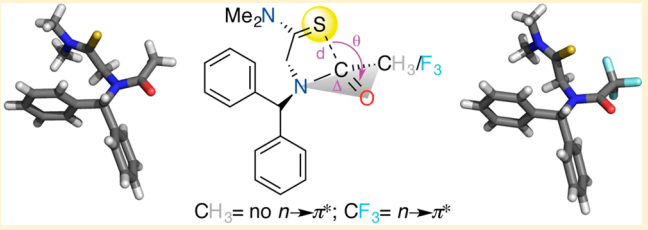
Supporting Information

ABSTRACT: Peptoids constitute a class of peptidomimetics with potential as protease resistant, biologically active ligands. To harness the full potential of such compounds, however, detailed predictive insight into their propensity to adopt well-defined secondary structures is highly desirable. In this work we present an investigation of the effects of thioamides and/or fluorides in peptoid monomer model systems using chemical synthesis, NMR spectroscopy, and X-ray crystallography. We find that the steric environment surrounding the tertiary amide bonds is the key promoter of conformational preference, and X-ray crystallographic interrogation of our model systems did not suggest the presence of stabilizing $n \rightarrow \pi^*$ interactions unless the carbonyls were altered electronically by α-halogenation or thioamide formation. In addition to the function as an investigative tool, these two types of modification may thus be utilized as stabilizers of secondary structure in future oligomer designs, such as the *cis*-amide-based polypeptoid helices that resemble the polyproline type-I helix.

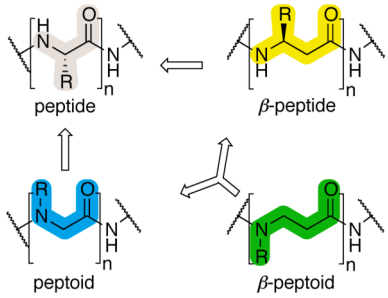


INTRODUCTION

Development of biopharmaceutical drugs and their approval by governing agencies such as the Food and Drug Administration in the United States has flourished immensely in recent years.[1] Monoclonal antibodies, proteins, and naturally occurring peptides often exhibit highly potent and selective activities with possible therapeutic benefit, but they are inherently susceptible to proteolytic degradation, which causes a reduction in half-life and efficacy and hence increases the required dosage. For these reasons, the ability to mimic or modify natural peptide-based compounds has become highly desirable, and one of the many approaches pursued in the area of peptidomimetics entails modification of the peptide backbone architecture to achieve resistance to proteases.[2] Two prominent examples of abiotic designs that exhibit high stability are the β-peptides[3] and peptoids[4] (Chart 1), and both of these have received considerable attention during the last two decades. Both designs have been investigated as homooligomeric constructs as well as in hybrid backbones containing canonical α-amino acids or other residues,[2c−e] and recently β-amino acids have been site-specifically incorporated in a therapeutic polypeptide to increase pharmacokinetic properties in vivo, demonstrating improvement of biopharmaceuticals through backbone modification.[5]

Access to structurally diverse peptoids through chemical synthesis is inexpensive and highly efficient,[6] and since the first report in 1992,[7] these compounds have been studied in numerous contexts including antimicrobials,[8] antifouling agents,[9] nanomaterials,[10] and ligands for protein−protein interactions.[11] Still, limited success has been achieved in design and characterization of secondary structures by high-resolution X-ray diffraction structure determination[12,13] or NMR spectroscopy,[14,15] except for macrocyclic constructs in which the inherently flexible peptoid backbones are locked into well-

Chart 1. Generic Structures of the Backbone Architectures of Peptides, Peptoids (α-peptoids), β^3-Peptides (β^2- and disubstituted β-peptides are not shown), and β-Peptoids



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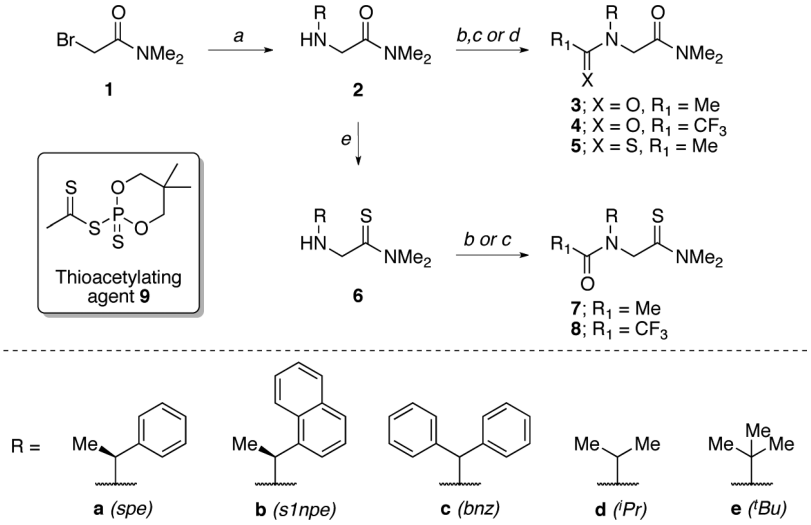
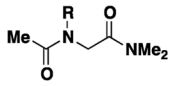
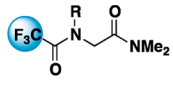
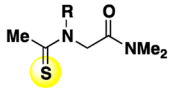
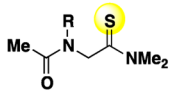
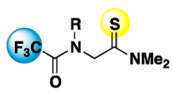
Scheme 1. Synthesis of Peptoid Model Compounds Under Investigation[a]



[a]Reagents and conditions: (*a*) For aromatic side chains H_2N–R (2 equiv), Et_3N (2 equiv), THF, 16 h and for aliphatic side chains H_2N–R (3 equiv), Et_3N (2 equiv), EtOAc, 0 °C → rt, 16 h; (*b*) Ac_2O (2 equiv) or AcCl (2 equiv), Et_3N (2 equiv), CH_2Cl_2, 0 °C → rt, 16 h; (*c*) trifluoroacetic anhydride (2 equiv), pyridine (2 equiv), DMF, 0 °C → rt, 2–16 h; (*d*) 5,5-dimethyl-2-sulfido-1,3,2-dioxaphosphinan-2-yl ethanedithioate (**9**; 1.1 equiv), pyridine (1.1 equiv) CH_2Cl_2, rt, 1 h; (*e*) Lawesson's reagent (1.5 equiv), THF, reflux, 2 h. Nonstandard abbreviations for *N*-alkyl side chains are used as follows: *spe* = (*S*)-1-phenylethyl,[14] *s1npe* = (*S*)-1-(1-naphthyl)ethyl,[18] *bnz* = benzhydryl.

Table 1. Rotamer Equilibrium Constants ($K_{cis/trans}$)[a] in Selected Solvents and Associated Differences in Free Energy (ΔG, in kcal mol^{-1})[b]

			D_2O		CD_3OD		CD_3CN		$CDCl_3$	
scaffold	compd	R	$K_{cis/trans}$	ΔG	$K_{cis/trans}$	ΔG	$K_{cis/trans}$	ΔG	$K_{cis/trans}$	ΔG
	**3a**	*spe*	0.9	0.06	1.1	−0.06	1.8	−0.35	0.6	0.30
	3b	*s1npe*	2.8	−0.61	4.1	−0.83	7.2	−1.16	2.7	−0.59
	3c	*bnz*	1.5	−0.24	1.6	−0.28	3.2	−0.69	0.7	0.21
	3d	^{i}Pr	0.5	0.41	0.6	0.30	0.9	0.06	0.3	0.71
	3e	^{t}Bu	all *cis*	–	all *cis*	–	all *cis*	–	all *cis*	–
	**4a**	*spe*	0.5	0.41	0.5	0.41	0.6	0.30	0.3	0.71
	4b	*s1npe*	n.s.[c]	–	7.1	−1.16	8.2	−1.24	5.0	−0.95
	4c	*bnz*	1.5[d]	−0.24	1.5	−0.24	2.3	−0.49	0.9	0.06
	4d	^{i}Pr	0.3	0.71	0.3	0.71	0.3	0.71	0.2	0.95
	4e	^{t}Bu	all *cis*	–	all *cis*	–	all *cis*	–	all *cis*	–
	**5a**	*spe*	0.6	0.30	0.9	0.06	1.8	−0.35	0.4	0.54
	5b	*s1npe*	n.s.	–	4.5	−0.89	7.5	−1.19	2.1	−0.44
	5c	*bnz*	n.s.	–	1.2	−0.11	3.1	−0.67	0.6	0.30
	5d	^{i}Pr	0.5	0.41	0.4	0.54	0.9	0.06	0.4	0.54
	5e[e]	^{t}Bu	–	–	–	–	–	–	–	–
	**7a**	*spe*	1.1	−0.06	1.8	−0.35	2.0	−0.41	0.5	0.41
	7b	*s1npe*	2.8[d]	−0.61	3.9	−0.80	4.8	−0.93	1.7	−0.31
	7c	*bnz*	n.s.	–	2.7	−0.59	3.9	−0.80	0.6	0.30
	7d	^{i}Pr	0.6	0.30	1.3	−0.15	1.3	−0.15	0.3	0.71
	7e	^{t}Bu	–	–	–	–	all *cis*	–	all *cis*	–
	**8a**	*spe*	n.s.	–	0.6	0.30	0.7	0.21	0.2	0.95
	8b	*s1npe*	n.s.	–	5.0	−0.95	5.1	−0.96	3.1	−0.67
	8c	*bnz*	n.s.	–	2.6	−0.56	3.3	−0.70	0.9	0.06
	8d	^{i}Pr	0.2[d]	0.95	0.3	0.71	0.3	0.71	0.1	1.36
	8e	^{t}Bu	all *cis*	–	all *cis*	–	all *cis*	–	all *cis*	–

[a]Determined by integration of ^{1}H NMR spectra of 12 mM compound solutions at ambient temperature. [b]$\Delta G = -RT \times \ln (K_{cis/trans})$. [c]Not soluble. [d]Low solubility resulting in <12 mM NMR sample concentration. [e]Synthesis of the thioacetylated version of the hindered *tert*-butyl-containing compound was not successful in our hands and was left out of the study.

defined conformations.[16] Compared to peptides and *β*-peptides, peptoids lack the ability to stabilize folding through intramolecular hydrogen-bond networks and are also endowed with an additional degree of flexibility due to the low energy barrier between cis and trans amide conformations of tertiary amide bonds (Chart 1), as observed for proline residues in native proteins.

Control of the cis–trans isomerization in peptoids has been demonstrated by introduction of certain *N*-alkyl side chains that direct this equilibrium toward either the cis or the trans conformation.[17−19] Due to interest in a backbone design called *β*-peptoids[20] (Chart 1), we reported a similar study of the effect of side chain structure in this system and furthermore included thioamide and trifluoroacetyl modifications[21] inspired by model studies[22,23] of proline behavior.[24] Thionation and fluorination permutations may report on the nature of putative stereoelectronic interactions and may also stabilize desired cis–trans equilibria of tertiary amide bonds. A recent study provided

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detailed insight into the effect of thioacetylation in a range of structurally diverse tertiary amides containing peptoid-derived side chains,[25] and the effect on rotamer preference of tertiary amides has been investigated by altering the acyl moiety as well, including halogenation of the α-position of the acyl group.[26] However, C-terminal amide groups were not included in these studies, which prohibited interrogation of putative carbonyl−carbonyl interactions. In the present work, we thus disclose the first systematic investigation of the effects of thioamidation and/or haloacetylation on cis−trans isomerism in α-peptoid model systems by using NMR spectroscopy and X-ray crystallography.

RESULTS

Design and Synthesis. An initial compound collection was designed to mimic the environment of a single peptoid residue within an oligomer in a minimalistic manner. The C-termini were therefore chosen to be dimethylamides, and the amide bonds to be probed for cis−trans isomerism were based on acetyl (**3**), trifluoroacetyl (**4**), or thioacetyl (**5** prepared using reagent **9**[27]) as outlined in Scheme 1. To examine putative carbonyl−carbonyl interactions in both N → C and C → N directions, we also included thioamides in the C-termini (**7** and **8**). These series were prepared from common intermediates **2a**−**e** by thionation using Lawesson's reagent[28] to give **6a**−**e**, which were subsequently acylated (Scheme 1). Previous studies of rotamer isomerism in proline model systems have primarily focused on identifying the nature of trans carbonyl−carbonyl interactions in the N → C direction ($C{=}O_i{\cdots}C{=}O_{i+1}$)[22,23] due to the stabilizing effect on protein folding.[29] However, since the two available X-ray crystal structures of oligomeric peptoids revealed helical arrangements similar to the all-cis polyproline type-I helix,[12,13] we found it relevant to include strongly cis-directing side chains such as (*S*)-1-(1-naphthyl)-ethyl (*s1npe*; **b**) and *tert*-butyl (**e**) in our series. The full matrix of compounds was prepared according to Scheme 1, except compound **5e**, for which several strategies failed to deliver the target compound, presumably due to steric congestion.

Cis−Trans Equilibrium Constants Determined by ^{1}H NMR Spectroscopy. Measuring the cis−trans amide equilibrium constants by NMR spectroscopy is straightforward as integration of peaks from each conformation report quantitatively on their relative concentrations. Because previous evaluation of thioamide-containing peptoids revealed significant solvent effects on cis−trans equilibria,[21] it was decided to record NMR spectra in four different deuterated solvents of varying polarities (Table 1). Rotating frame Overhauser effect spectroscopy (ROESY) and ^{1}H−^{19}F heteronuclear Overhauser effect spectroscopy (HOESY) experiments were performed in order to assign the signals to the correct conformations (Figure 1).

First, compound **3a** containing the (*S*)-1-phenylethyl (*spe*) side chain, a well-studied moiety with respect to the folding behavior of peptoids,[14,30] showed data that were fully in agreement with previously published studies.[18] Furthermore, the more sterically demanding *s1npe*-containing side chain in compound **3b** showed trends that were in accordance with previously reported data obtained for similar compounds based on both peptoids[18] and β-peptoids.[21] There was a significant preference for the cis conformation in all four solvents, increasing in the order $CDCl_3$ < D_2O < CD_3OD < CD_3CN.

Increasing the bulk of the *N*-alkyl side chain relative to *spe* by introduction of a benzhydryl (*bnz*) group (**3c**) also led to an

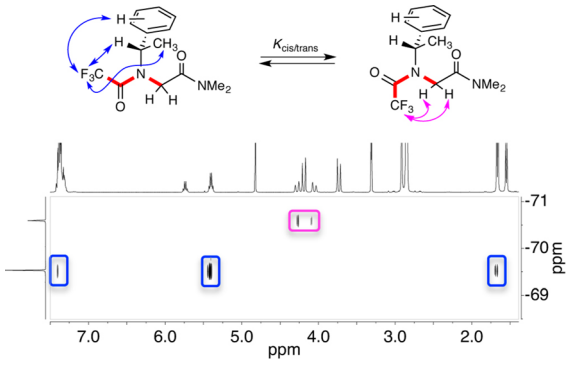

Figure 1. Example of a HOESY spectrum recorded in CD_3OD (compound **4a**) applied for signal assignment. Highlighted signals correspond to correlations involving the fluorine atoms. In blue boxes are shown the correlations with the side chain methine, methyl, and aromatic protons in the trans conformation. In magenta, correlation to the backbone methylene protons confirms the cis conformation.

increase in $K_{cis/trans}$ in all solvents, albeit to a lesser extent. Interestingly, when comparing *spe* and *bnz* groups in β-peptoid model systems, similar $K_{cis/trans}$ values were observed.[21] This indicates that the increased population of the cis conformation in *bnz*-containing α-peptoids is due to steric rather than electronic effects. Moreover, when we replaced the phenyl groups of **3c** with methyl groups (**3d**) we observed a change of preference to the trans rotamer, which supports the notion that the main driving force is of a steric nature. Finally, introduction of the bulky *tert*-butyl *N*-alkyl group (**3e**) gave exclusively the cis conformation ($K_{cis/trans}$ > 20) at our level of detection, which is also in agreement with previously published data.[19]

Introduction of a trifluoroacetyl group should make the carbonyl carbon more electron deficient due to the inductive effect of the fluorines. It is furthermore known that the fluorine lone pairs can donate electron density into the π^* orbital of the adjacent carbonyl group if ideally positioned.[31] On the other hand, the trifluoromethyl group resembles an isobutyl group in size,[23] giving rise to simultaneous steric and electronic effects that may complicate the interpretation of the driving forces behind the conformational changes. Since compound **4b** showed an increase in $K_{cis/trans}$ value compared to **3b**, while compounds **4a**, **4c**, and **4d** showed a decrease, we indeed suspect that there are differential forces at play depending on the specific structures of the model systems.

Raines and co-workers studied carbonyl−carbonyl interactions in proline model systems by substituting oxygen atoms with sulfur to increase the nucleophilicity of the putative carbonyl donor.[22] Inspired by these studies, we investigated both N- and C-terminal thioamide-containing model systems individually. The thioacetylated compounds **5a**−**e** displayed roughly the same trends as their acetylated counterparts (**3a**−**e**). This indicates that there are negligible contributions from the $n \rightarrow \pi^*$ interaction in the N → C direction in this series.

The C-terminal thioamide series (**7a**−**e**), on the other hand, displayed slightly higher $K_{cis/trans}$ values compared to the C-terminal oxoamide series as well as the (*O*,*O*)-series (**3**), except for the *s1npe*-containing compounds **5b** and **7b**, where the trend was opposite (Table 1). The latter would agree with a stabilizing effect between the sulfur and a C(sp^2)−H on the naphthyl ring in **5b** as previously indicated for β-peptoids.[21] The difference in ^{1}H NMR chemical shifts of the aromatic hydrogen atom in proximity to the carbonyl in the **3b**−**8b**

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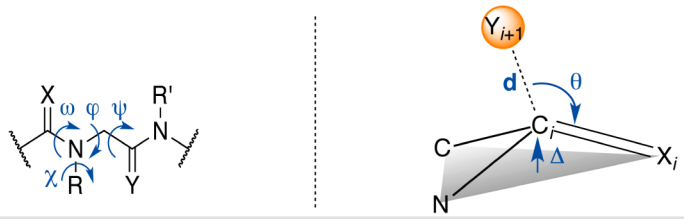
Table 2. Torsion Angles and Distances in Crystal Structures



compd	dihedral angles				trajectory	distance	pyramidalization
	ϕ (deg)	ψ (deg)	ω (deg)	χ (deg)[a]	θ (deg)	d (Å)	Δ (Å)
3b	–79.4	–150.5	–11.7	–10.1	126.4	3.09	0.019
5b	–76.8	–156.3	–13.7	–13.7	122.4	2.98	0.014
7b	–83.2	–156.8	–10.2	–11.7	121.5	3.34	0.022
3c	77.3	159.1	8.4	–2.1	127.2	3.10	0.007
4c	74.8	170.4	24.7	–46.2	117.1	2.97	0.050
5c	–77.4	174.4	–173.5	44.7	87.2	3.38	0.0011[b]
					90.2	3.08	0.0023[c,d]
7c	–89.5	–152.4	–11.5	48.1	117.4	3.38	0.010
8c	–77.0	–164.6	27.4	50.1	111.6	3.18	0.065
4a	–71.3	170.9	174.9	2.1	84.4	3.00	0.015[d]
8a	–84.8	–160.3	171.6	3.0	86.4	3.29	0.003[d]
Helix[e]	68–86	142–177	0.1–3.5		128–135	3.0–3.2	

[a]Measured from the methine proton in the *N*-alkyl side chains. [b]C═S···C═O direction. [c]C═O···C═S direction. [d]Pyramidalization away from donor carbonyl. [e]Measurements from the X-ray diffraction crystal structure of a peptoid pentamer reported by Barron and co-workers.[12] The sign of χ-angles in achiral compounds **3c**–**8c** were assigned according to the crystallized form of the compounds.

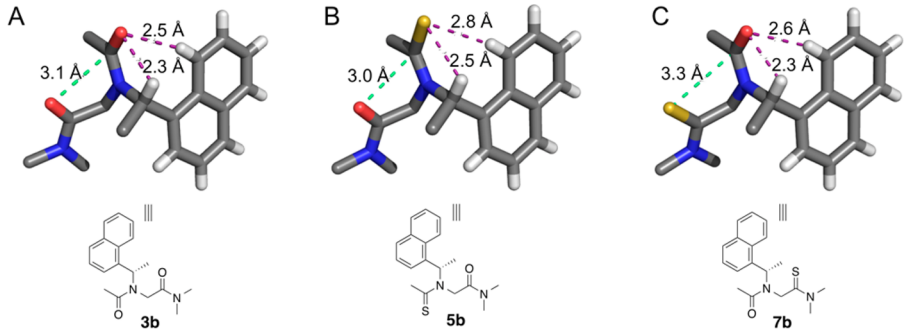


Figure 2. X-ray diffraction crystal structures of *s1npe*-containing compounds **3b** (A), **5b** (B), and **7b** (C). Stick representations showing the C═O/S_{i+1}···C_i═O/S distance in green and distances between N-terminal carbonyls and their two closest hydrogen atoms in magenta. Atom-coloring scheme: gray, carbon; white, hydrogen; red, oxygen; blue, nitrogen; and yellow, sulfur. Hydrogen atoms in methyl and methylene groups have been removed for clarity.

series supports the existence of such an interaction (Supporting Information Figure S1).

The attenuated hydrogen-bond acceptor capability of the trifluoroacetyl group correlates with an upfield shift of this proton (Supporting Information Figure S1). On the other hand, the thioacetyl group gave rise to a slight downfield shift as previously rationalized by NBO calculations of similar *β*-peptoids to arise from increased orbital overlap.[21] Furthermore, $K_{cis/trans}$ values of **3a**–**e** determined in $CDCl_3$ were generally higher than those of both **5a**–**e** and **7a**–**e** and were lower or similar when recorded in CD_3OD and CD_3CN, except for **7b** in CD_3CN. Overall, the extent of solvent effects between compound series results in difficulty in deriving truly general trends regarding the $K_{cis/trans}$ values across all compounds in all solvents (Table 1). Fortunately, however, a number of model compounds were crystallized in X-ray diffraction quality, which provided further insight into the various features affecting conformational preference (vide infra).

Finally, the series containing a combination of N-terminal trifluoroacetylation and C-terminal thionation (**8a**–**e**) exhibited similar $K_{cis/trans}$ values as found for trifluoroacetylated compounds (**4a**–**e**), thus, exhibiting lower overall resemblance to the other C-terminal thioamide series (**7a**–**e**), which qualitatively may indicate a stronger cis-directing effect of the sterically demanding trifluoroacetyl group compared to the effect of the thioamide donor capability in a C → N terminal carbonyl–carbonyl interaction.

X-ray Crystallography. A number of the model compounds were obtained in diffraction quality crystal forms, and their high-resolution solid-state structures were solved by single-crystal X-ray diffraction structure determination. Crystal structures can provide useful, atomic resolution information about potential interactions that may stabilize certain cis–trans

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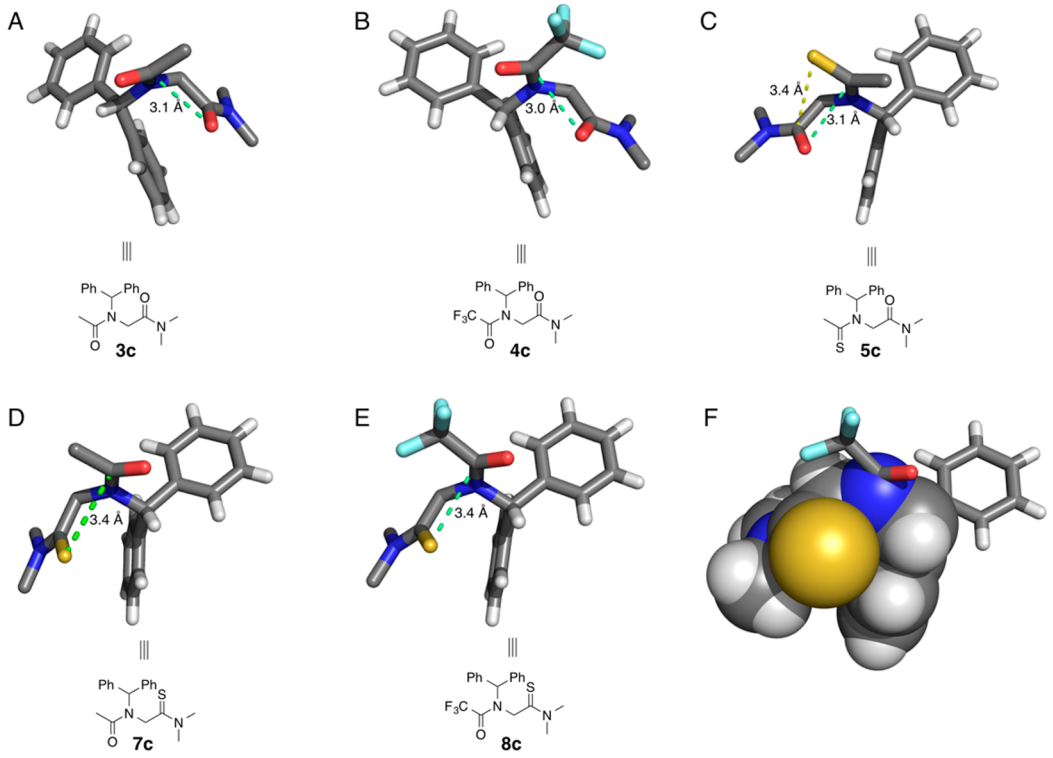

Figure 3. X-ray diffraction crystal structures of *bnz*-containing compounds (A) **3c**, (B) **4c**, (C) **5c**, (D) **7c**, and (E) **8c**, as well as compound **8c** shown in partial space-filling representation (F). Stick representations showing the C═O/S$_{i+1}$···C$_i$═O/S distances in green and the C═S$_i$···C$_{i+1}$═O distance in yellow. Atom-coloring scheme: gray, carbon; white, hydrogen; red, oxygen; blue, nitrogen; cyan, fluorine; and yellow, sulfur. Hydrogen atoms in methyl and methylene groups have been removed for clarity.

amide bond conformations; in particular, the angle between interacting carbonyls as well as the acceptor carbonyl pyramidalization can report on the probability of possible $n \rightarrow \pi^*$ interactions.[32]

Three X-ray diffraction structures of *s1npe*-containing compounds were solved, and all showed a cis amide conformation consistent with the obtained $K_{cis/trans}$ values in solution (Figure 1).

The distances between the C-terminal carbonyl heteroatoms and the carbon of the N-terminal carbonyls were consistent with an orbital overlap in all cases, but the angles were 14−19° higher than the optimal Bürgi−Dunitz trajectory of 107°, and the degree of pyramidalization (Δ) was relatively low (Table 2) compared to values found in proline model systems.[32] In agreement with our previous studies,[21] the distance between the hydrogen atom in the 8 position of the naphthyl group and the thiocarbonyl in compound **5b** (Figure 2B) was consistent with an aromatic C−H···S$_{amide}$ interaction. This potential interaction is also observed in the two other compounds (Figure 2A and 2C). Notably, the longer interaction distances of the sulfur of 0.2−0.3 Å compared to oxygen is in agreement with the larger van der Waals radius (1.80 and 1.52 Å, respectively). The close proximity of the side chain methine hydrogen and the carbonyl in the crystal structures are also consistent with the chemical shifts in ^{1}H NMR discussed above.

Gratifyingly, we were also able to obtain X-ray diffraction quality crystals of the entire *bnz* series, **3c**−**8c** (Figure 3A−E). Compounds **3c**, **4c**, **7c**, and **8c** crystallized in the cis conformation, while the X-ray diffraction crystal structure of **5c** was in the trans conformation. Comparing the acetylated compounds (**3c** and **7c**) with their trifluoroacetylated analogues (**4c** and **8c**), the trifluoroacetylated compounds displayed trajectory angles closer to the Bürgi−Dunitz angle and also showed significantly increased pyramidalization (Table 2).

This correlates with an improved acceptor character of the trifluoroacetyl group compared to acetyl. Interestingly, ω angles of the trifluoroacetylated model compounds deviated significantly from planarity compared to their acetylated analogues, which indicates a steric influence of the trifluoromethyl group in the cis conformation as well. Thus, common for the four crystal structures that exhibit cis conformation (Figure 3A, B, D, and E) is packing of the backbone with one of the phenyl rings of the *bnz* group, which reduces its flexibility and ability to point away from the bulk of the trifluoromethyl group in compounds **4c** and **8c** (see, Figure 3F for example). Furthermore, the distribution of steric bulk across the two side chains in *bnz* results in altered χ angles in all examples where increased bulk (fluorination and/or thionation) is introduced into the backbone (Table 2). Finally, in agreement with the presence of $n \rightarrow \pi^*$ interactions with C → N directionality, the C-terminal thioamide-containing compounds exhibited angles closer to 107° and stronger pyramidalization than their C-terminal oxoamide analogues (Table 2).

The trans amide conformation of compound **5c** showed distances indicating possible carbonyl−carbonyl interactions in both N → C and C → N directions, which could help explain its preferred crystallization in this conformation. However, inspection of the geometry in this crystal structure revealed trajectory angles and pyramidalization in poor agreement with $n \rightarrow \pi^*$ interactions (Table 2). Nevertheless, since **5c** was crystallized by vapor diffusion from chloroform it could be reasoned that the trans conformation in the crystal is due to its conformational preference in this solvent as indicated by the NMR analyses above (Table 1).

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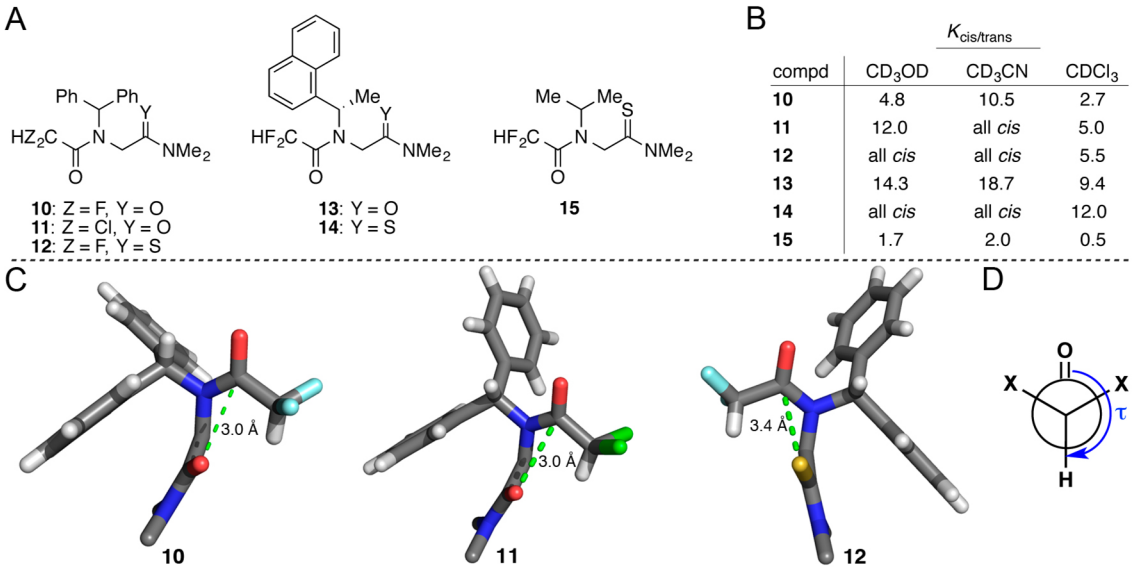

Figure 4. (A) Chemical structures of dihaloacetylated monomers. (B) $K_{cis/trans}$ values determined by ^{1}H NMR. "All cis" refers to ratios above 20. (C) X-ray diffraction crystal structures of compounds **10**, **11**, and **12**. (D) Newman projection showing the τ angle. Atom-coloring scheme: gray, carbon; white, hydrogen; red, oxygen; blue, nitrogen; cyan, fluorine; green, chlorine; and yellow, sulfur. Hydrogen atoms in methyl and methylene groups have been removed for clarity.

Table 3. Torsion Angles and Distances in Crystal Structures of Compounds 10−14

	torsion angles							
compd	ϕ	ψ	ω	χ^a	τ	trajectory, θ	distance, d (Å)	pyramidalization, Δ (Å)
10	74.5°	151.2°	4.8°	−7.0°	−176.1°	132.4°	2.99	0.010
11	75.3°	152.9°	10.2°	−34.8°	−152.5°	128.5°	2.95	0.024
12	−80.3°	−156.9°	−18.2°	47.9°	133.9°	115.9°	3.21	0.033
13	83.7°	144.2°	−5.4°	−24.8°	−139.8°	133.3°	3.11	0.030
14	−84.5°	−142.9°	−13.6°	−12.6°	140.9°	122.5°	3.29	0.033

[a]Measured from the methine proton in the *N*-alkyl side chains. The sign of the χ angle of achiral compounds **10**−**12** was assigned according to the single-crystal X-ray diffraction structures.

We also acquired two crystal structures with the *spe* side chain (**4a** and **8a**), which both crystallized in the trans conformation as would be expected based on their $K_{cis/trans}$ values. Notably, even though compound **8a** contains the donor−acceptor pair identified above to be most likely to engage in an $n \rightarrow \pi^*$ interaction, the trajectory angle and pyramidalization do not indicate the presence of a particularly strong interaction (Table 2; please consult the Supporting Information Figure S2 for ORTEP illustrations of these structures).

Dihalogenated Acyl Compounds (10−15). To further investigate stereoelectronic versus steric effects in haloacetylated compounds, we prepared a selection of dihaloacetylated peptoid model compounds shown in Figure 4A. In a study by Raines and co-workers,[23,33] the donor capability of the carbonyl in mono-, di-, and trifluoroacetyl groups was investigated, whereas the acceptor capacity is under scrutiny here. We chose benzhydryl (**10**−**12**) and *s1npe* (**13** and **14**) as side chains and also included compound **15** with an isopropyl side chain to test if these backbone modifications would be able to shift the preference from trans to cis conformation.

Interestingly, the difluoroacetylated compounds (**10** and **12**−**15**) all showed higher $K_{cis/trans}$ values than their trifluoroacetylated counterparts (Figure 4B). When introducing the dichloroacetyl group, preference for the cis conformation was even more pronounced than difluoro- or trifluoroacetyl (**11** vs **4c** and **10**). This strongly suggests a predominant steric effect of the two chlorine atoms since the inductive potency should be lower than that of fluorine and should therefore give rise to lower $K_{cis/trans}$.

The steric effect is further supported by the X-ray diffraction crystal structure of **11** where the CH of the dichloromethyl group is close to antiperiplanar in relation to the carbonyl (τ angle in Table 3), pointing the chlorines away from the backbone (Figure 4C). This will also disfavor the donation of chlorine lone pairs into the π^* orbital of the adjacent carbonyl to attenuate its acceptor capacity for possible carbonyl−carbonyl $n \rightarrow \pi^*$ interactions.[31,33,34] The same was observed in both crystal structures of difluoroacetylated compounds **10** and **12** (Figure 4C and Table 3). Compound **12** exhibited the highest degree of pyramidalization as well as a trajectory angle that was closer to 107° than the other two compounds, thus adhering to the same trend as observed for **4c** vs **8c**.

Compounds **13** and **14** also exhibited increased $K_{cis/trans}$ values in all solvents compared to their trifluoroacetylated homologues **3b** and **7b**, respectively (Figure 4B). Although the backbone would not be as rotationally restricted as in the benzhydryl case discussed above, this observation correlates with favorable accommodation of the difluoromethyl group compared to the trifluoromethyl group toward the backbone face. Interestingly, however, the ϕ and ψ angles of compound **13** showed opposite signs compared to all other *s1npe*-

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containing compounds, thus giving rise to a packing of the backbone similar to that observed in the benzhydryl-containing compounds (Figure 5A). Furthermore, compound **14** contains

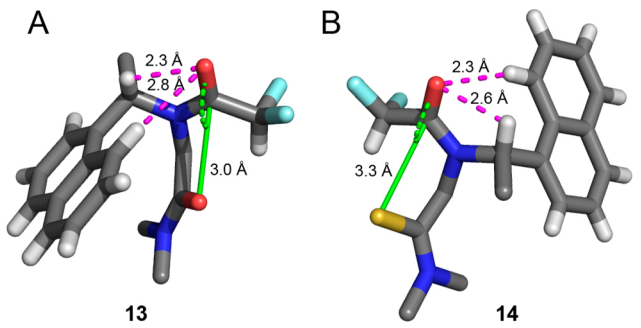

Figure 5. X-ray diffraction crystal structures of difluoroacetylated compounds **13** and **14**. Stick representations showing the C═O/S_{i+1}···C_i═O distance in green and distances between N-terminal carbonyls and their two closest hydrogen atoms in magenta. Atom-coloring scheme: gray, carbon; white, hydrogen; red, oxygen; blue, nitrogen; cyan, fluorine; green, chlorine; and yellow, sulfur. Hydrogen atoms in methyl and methylene groups have been removed for clarity.

both haloacetylation and C-terminal thioamide, which is indicated above to promote a carbonyl−carbonyl $n \rightarrow \pi^*$ interaction in the C → N direction. The increase in $K_{cis/trans}$ observed for **14** compared to **13** is also in agreement with such an interaction. The X-ray diffraction crystal structures revealed carbonyl−carbonyl distances in agreement with orbital overlap and pyramidalization indicative of $n \rightarrow \pi^*$ interaction in the C → N direction in both cases. However, the angles in compound **13** and **14** differed by 26° and 15° from the ideal Bürgi−Dunitz trajectory, respectively.

Finally, compound **15** revealed an increased fraction of cis conformation in comparison to the entire ^{i}Pr series (**3d**−**8d**). Trifluoroacetylation (**4d** and **8d**) resulted in a slight decrease in $K_{cis/trans}$ values, while difluoroacetylation furnished an increase in $K_{cis/trans}$, which again is in agreement with favorable accommodation of the less hindered difluoromethyl group toward the backbone in the cis conformation. Moreover, a carbonyl−carbonyl interaction as observed for compound **12** may add to the stabilization of this conformation, but we do not have X-ray diffraction data to support this.

DISCUSSION

Overall, the observed changes in $K_{cis/trans}$ values in response to structural changes in our model system series demonstrate that a complex combination of interactions work in concert to determine conformational preference of the molecules. In general, the steric demand of the side chain appears to be the prime determinant of conformational preference. Not surprisingly, the bulky *s1npe* side chain repels the sterically demanding methyl or halomethyl groups, giving rise to high $K_{cis/trans}$ values, albeit with subtle effects of altering carbonyls by thioamide substitution. However, the less bulky *bnz* side chain, which more readily adopts both conformations in a solvent-dependent manner, allowed for a more detailed inspection of the effect of the electronic properties of the carbonyl groups (**3c**−**8c** and **10**−**12**). In particular, the X-ray diffraction structures of the N-terminally haloacetylated model systems with a C-terminal thioamide, which should provide a strong acceptor−donor pair, showed pyramidalization and trajectory angles in agreement with $n \rightarrow \pi^*$ interactions. The X-ray diffraction crystal structures of trifluoroacetylated compounds (**4c** and **8c**) obtained in the cis conformation showed clear evidence of steric effects as the amides were twisted out of the planarity preferred for amide bonds. In addition, the data obtained for dihaloacetylated model systems (**10**, **11**, and **12**) support the argument of steric congestion between the backbone and the haloacetyl group by displaying higher $K_{cis/trans}$ values. This could be explained by conformations where the single hydrogen of the dihalomethyl groups faces the backbone, which is indeed the case in the crystal structures of **10**−**12** where the dihaloacetyl groups adopt near antiperiplanar conformations. The data thus suggest that when the steric environment allows for it, carbonyl−carbonyl interactions can be optimized to affect conformational space.

The steric effect of the side chain in response to trifluoroacetylation becomes less prominent in the *spe* and ^{i}Pr series, where the cis−trans equilibrium is significantly shifted toward the trans conformation. Interestingly, the difluoroacetylated compound **15** displays opposite conformational preference than its trifluoroacetylated analog (**8d**) in MeOH and MeCN. Since there is no steric argument for a cis preference of **15**, this also supports that, when sterically allowed, stereoelectronic effects in the form of the carbonyl−carbonyl interactions may affect conformational preference in peptoids.

On the basis of the qualitative relationship between the strength of a potential $n \rightarrow \pi^*$ interaction and the degree of pyramidalization of the carbonyl acceptor, the crystal structures of the *bnz* series provide insight into the stereoelectronic effects of our various modifications. Improving the carbonyl acceptor by trifluorination (**4c**) significantly enhances the character of a putative $n \rightarrow \pi^*$ interaction, while enhanced carbonyl donor capacity in a thioamide (**7c**) results in an improved trajectory angle but modest pyramidalization. Combination of the two modifications (**8c**), however, gives rise to a trajectory close to the Bürgi−Dunitz angle as well as the highest degree of acceptor pyramidalization observed in all our X-ray diffraction crystal structures.

In summary, we systematically investigated the conformational preference in an array of structurally diverse α-peptoid (*N*-alkylglycine) model systems using NMR spectroscopy as well as X-ray crystallography of more than a dozen of the model compounds. Collectively, our data show no evidence for a general stabilizing effect of trans amide bonds by $n \rightarrow \pi^*$ interactions in peptoids, which, compared to proline systems,[22,23,29] may arise from the increased flexibility of the acyclic peptoids under investigation herein. Nevertheless, we see strong evidence for the ability to promote such interactions in the C → N direction in cis-configured peptoids by altering the electronic properties of the donor and acceptor carbonyls, respectively. Whereas compelling evidence for an $n \rightarrow \pi^*_{aryl}$ interaction between a carbonyl lone pair and a positively charged triazolium side chain has been reported for peptoids,[19] the present work provides the first demonstration of subtle backbone modifications (α-fluorination and thioamidation) that may stabilize certain peptoid conformations. On the basis of the complete body of data, we therefore propose a model for the factors affecting conformational space in peptoids that is first and foremost dependent on sterics but may include stabilizing effects of carbonyl−carbonyl interactions in electronically altered systems.

Thioamide substitution has been shown to affect the equilibrium between α- and 3_{10}-helices in peptides,[35] and we thus envision that the insights provided herein may be utilized

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for stabilization of peptoid secondary structures, such as those resembling polyproline type-I helix.

EXPERIMENTAL SECTION

General. All chemicals were analytical grade and used without further purification. All reactions were performed in dry solvents and under argon atmosphere. Dichloromethane, *N,N*-dimethylformamide (DMF), tetrahydrofuran (THF), and toluene were retrieved from a solvent purification system, and EtOAc was dried over molecular sieves (4 Å). Vacuum liquid chromatography (VLC) purification was performed on silica gel 60 (particle size 0.015−0.040 μm). UPLC−MS analyses were performed using an ultra-high-performance liquid chromatography system. A gradient with eluent I (0.1% HCOOH in water) and eluent II (0.1% HCOOH in MeCN) rising linearly from 0% to 95% of II during t = 0.00−2.50 min was applied at a flow rate of 0.6 mL/min (gradient A) or during t = 0.00−5.20 min (gradient B). Compounds, which were not obtained in sufficient purity by VLC, were purified by preparative HPLC performed on a 250 mm × 20 mm, C18 column (5 μm, 100 Å) using a diode array UV detector. A gradient C with eluent III [95:5:0.1, water−MeCN−trifluoroacetic acid (TFA)] and eluent IV (0.1% TFA in MeCN) rising linearly from 0% to 95% of IV during t = 5−45 min was applied at a flow rate of 20 mL/min. All final compounds were determined by analytical HPLC analysis to be >95% pure on a 150 mm × 4.6 mm, C18 column (3 μm) using a multiwavelength UV detector. The gradient consisted of eluent III (95:5:0.1, water−MeCN−TFA) and eluent IV (0.1% TFA in MeCN) rising linearly from 0% to 95% of IV during t = 2−20 min at a flow rate of 1 mL/min (gradient D; data not shown). NMR chemical shifts are reported in ppm relative to deuterated solvent peaks as internal standards (δH, D_2O 4.79 ppm; δH, CD_3OD 3.31 ppm; δH, CD_3CN 1.94 ppm; δH, $CDCl_3$ 7.26 ppm; δC, $CDCl_3$ 77.16 ppm). Coupling constants (J) are given in hertz (Hz). Multiplicities of NMR signals are reported as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; sept, septet; m, multiplet. Signals in the NMR data marked with an asterisk correspond to peaks assigned to the minor rotamer conformation and (*) denotes peaks where both rotamers overlap. The HRMS spectra were recorded using either matrix-assisted laser desorption/ionization (MALDI) or electrospray ionization (ESI) as indicated for each compound with Fourier transform ion cyclotron resonance (FT-ICR) as mass analyzer.

2-Bromo-*N,N*-dimethylacetamide (1). Bromoacetyl bromide (7.32 mL, 84 mmol) was dissolved in CH_2Cl_2 (80 mL), and dimethylammonium chloride (5.7 g, 70 mmol) was added. The suspension was cooled to 0 °C, and a solution of triethylamine (Et_3N) (22.3 mL, 160 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 15 min. The reaction was stirred overnight, where the temperature reached room temperature (rt). The mixture was washed with 10% w/v aq. citric acid (100 mL) and saturated aqueous $NaHCO_3$ (100 mL), and the organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by VLC (60% EtOAc in hexane) to give **1** as a yellow oil (5.09 g, 44%).

General Procedure for Synthesis of Compounds 2a−c. 2-Bromo-*N,N*-dimethylacetamide (1 equiv) was dissolved in THF to give a 0.4 M solution, and the desired primary amine (2 equiv) was added at 0 °C. Then, Et_3N (2 equiv, 1 M in THF) was added by syringe, and the reaction was stirred at rt overnight. The formed precipitate was filtered off, and the organic solvent was removed in vacuo. The resulting crude products were purified by VLC.

*(S)-N,N-Dimethyl-2-((1-phenylethyl)amino)acetamide (**2a**).* Yield: 1.74 g (79%) as oil. VLC eluent: 5% EtOH in EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (m, 4H), 7.25−7.17 (m, 1H), 3.76 (q, J = 6.4 Hz, 1H), 3.23 (s, 2H), 2.92 (s, 3H), 2.79 (s, 3H), 2.55 (s, 1H), 1.38 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 145.2, 128.5, 127.1, 126.9, 58.4, 48.4, 36.0, 35.6, 24.8. UPLC-MS gradient B, t_R = 0.75 min, m/z 207.2 ([M + H]$^+$, $C_{12}H_{19}N_2O^+$ calcd 207.2). $[\alpha]_{589.3}$: −73° (c = 0.11, 293 K, MeOH).

*(S)-N,N-Dimethyl-2-((1-(naphthalen-1-yl)ethyl)amino)acetamide (**2b**).* Yield: 1.26 g (82%) as oil. VLC eluent: 1−5% EtOH in EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 7.5 Hz, 1H), 7.88−7.82 (m, 1H), 7.74 (d, J = 7.5 Hz, 2H), 7.53−7.40 (m, 3H), 4.65 (q, J = 6.5 Hz, 1H), 3.35 (d, J = 16.1 Hz, 1H), 3.24 (d, J = 16.1 Hz, 1H), 2.93 (s, 3H), 2.69 (s, 3H), 2.62 (s, 1H), 1.53 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 140.7, 134.0, 131.4, 128.9, 127.2, 125.8, 125.8, 125.3, 123.0, 53.8, 48.6, 35.8, 35.5, 24.2. UPLC-MS gradient B, t_R = 1.08 min, m/z 257.2 ([M + H]$^+$, $C_{16}H_{21}N_2O^+$ calcd 257.2). $[\alpha]_{589.3}$: −11° (c = 0.14, 293 K, MeOH).

*2-(Benzhydrylamino)-N,N-dimethylacetamide (**2c**).* Yield: 1.05 g (66%) as amorphous substance. VLC eluent: hexane−EtOAc−EtOH (70:28:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.41 (m, 4H), 7.32−7.28 (m, 4H), 7.24−7.18 (m, 2H), 4.89 (s, 1H), 3.39 (s, 2H), 3.08 (s, 1H), 2.96 (s, 3H), 2.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 143.3, 128.7, 127.6, 127.3, 67.3, 48.7, 36.1, 35.7. UPLC-MS gradient B, t_R = 1.05 min, m/z 269.2 ([M + H]$^+$, $C_{17}H_{21}N_2O^+$ calcd 269.2).

General Procedure for Synthesis of Compounds 2d−e. 2-Bromo-*N,N*-dimethylacetamide (1 equiv) was dissolved in EtOAc to give a 0.5 M solution, and Et_3N (2 equiv) was added. The solution was cooled to 0 °C before addition of the desired primary amine (4 equiv, 1.5 M in EtOAc). The reaction mixture was allowed to reach rt and stirred overnight. The solvent was removed in vacuo, and the crude material was taken up in CH_2Cl_2−water (1:1). The aqueous phase was extracted with CH_2Cl_2 (3×), and the combined organic layers were washed with water (2×) and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The products were elaborated without further purification.

*2-(Isopropylamino)-N,N-dimethylacetamide (**2d**).* Yield: 612 mg (47%) as oil, which solidified upon storage at −18 °C.

*2-(tert-Butylamino)-N,N-dimethylacetamide (**2e**).* Yield: 1.44 g (76%) as oil, which solidified upon storage at −18 °C.

General Procedure for Synthesis of Compounds 6a−e. Lawesson's reagent (1.5 equiv) was suspended in THF (0.15 M) and heated to reflux. Then, **2a−e** in THF (2 M) was added, and stirring was continued under reflux for 1 h. The reaction mixture was cooled to rt, and the solvent was removed in vacuo. Most thionation byproducts were removed by VLC to give the crude product, which was used without further purification.

*(S)-N,N-Dimethyl-2-((1-phenylethyl)amino)ethanethioamide (**6a**).* Crude amount: 402 mg as oil. VLC eluent: CH_2Cl_2−MeOH−NH_4OH_{aq} (100:0:0−95:4.5:0.5). UPLC-MS gradient B, t_R = 1.05 min, m/z 223.1 ([M + H]$^+$, $C_{17}H_{21}N_2S^+$ calcd 223.1).

*(S)-N,N-Dimethyl-2-((1-(naphthalen-1-yl)ethyl)amino)-ethanethioamide (**6b**).* Crude amount: 363 mg as oil. VLC eluent: CH_2Cl_2−MeOH−NH_4OH_{aq} (98:1.8:0.2). UPLC-MS gradient B, t_R = 1.22 min, m/z 273.2 ([M + H]$^+$, $C_{16}H_{21}N_2S^+$ calcd 273.1).

*2-(Benzhydrylamino)-N,N-dimethylethanethioamide (**6c**).* Crude amount: 114 mg as oil. VLC eluent: hexane−EtOAc−EtOH (90:9:1−60:36:4). UPLC-MS gradient B, t_R = 1.30 min, m/z 285.2 ([M + H]$^+$, $C_{17}H_{21}N_2S^+$ calcd 285.1).

*2-(Isopropylamino)-N,N-dimethylethanethioamide (**6d**).* Crude amount: 580 mg as amorphous substance. VLC eluent: CH_2Cl_2−MeOH−NH_4OH_{aq} (100:0:0−90:9:1). UPLC-MS gradient B, t_R = 0.40 min, m/z 161.1 ([M + H]$^+$, $C_7H_{17}N_2S^+$ calcd 161.1).

*2-(tert-Butylamino)-N,N-dimethylethanethioamide (**6e**).* Crude amount: 240 mg as amorphous substance. VLC eluent: CH_2Cl_2−MeOH−NH_4OH_{aq} (100:0:0−90:9:1). UPLC-MS gradient B, t_R = 0.26 min, m/z 175.1 ([M + H]$^+$, $C_7H_{17}N_2S^+$ calcd 175.1).

General Procedure for Acetylation. Acetic anhydride or acetyl chloride (3 equiv) was added dropwise at 0 °C to a solution of secondary amine (**2** or **6**; 1 equiv) and pyridine (2 equiv) in CH_2Cl_2 to give a 0.4 M solution with respect to the amine. The reaction mixture was then stirred at rt for 16 h, after which it was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc (3×). The combined organic phases were dried ($NaSO_4$), filtered, and concentrated in vacuo. The crude products were purified by VLC.

*(S)-N,N-Dimethyl-2-(N-(1-phenylethyl)acetamido)acetamide (**3a**).* Crude amount: 91 mg (60%) as oil. VLC eluent: 0−1.75% MeOH in CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.28 (m, 5H, Ar-*H*), 6.11*/5.19 (2 × q, J = 7.1 Hz, 1H, NC*H*CH_3), 4.39/3.35 (2 × d, J = 16.0 Hz, 2H, COCH_2), 3.84*/3.65* (2 × d, J = 17.7 Hz, 2H,

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$COCH_2$), 2.96/2.94/2.90*/2.86* (4 × s, 6H, $N(CH_3)_2$), 2.26/2.08* (2 × s, 3H, $COCH_3$), 1.66/1.44* (2 × d, J = 7.1 Hz, 3H, $NCHCH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9*, 171.1, 168.1, 168.0*, 141.2, 140.9*, 128.9, 128.5*, 127.8, 127.7*, 127.5*, 126.6, 56.5, 51.0*, 45.3*, 43.9, 36.6, 36.3*, 36.1*, 36.0, 22.2*, 21.8, 18.4, 16.1*. UPLC-MS gradient B, t_R = 1.44 min, m/z 249.2 ($[M + H]^+$, $C_{14}H_{20}N_2O_2^+$ calcd 249.2). $[\alpha]_{589.3}$: −29° (c = 0.13, 293 K, $CHCl_3$). HRMS (MALDI) m/z calcd for $[M + Na]^+$, $C_{14}H_{20}N_2NaO_2^+$ 271.1417; found 271.1422.

*(S)-N,N-Dimethyl-2-(N-(1-(naphthalen-1-yl)ethyl)acetamido)-acetamide (**3b**).* Yield: 143 mg (70%) as colorless solid. Mp: 153−155 °C. VLC eluent: 0−1% MeOH in CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−7.43 (m, 7H, Ar-H), 6.70/5.79* (2 × q, J = 6.9 Hz, 1H, $NCHCH_3$), 4.46*/3.35* (2 × d, J = 16.0 Hz, 2H, $COCH_2$), 3.65/3.52 (2 × d, J = 17.8 Hz, 2H, $COCH_2$), 2.91*/2.87*/2.82/2.67 (4 × s, 6H, $N(CH_3)_2$), 2.32*/2.05 (2 × s, 3H, $COCH_3$), 1.80*/1.58 (2 × d, J = 7.0 Hz, 3H, $NCHCH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 171.4*, 168.5*, 168.0, 137.0*, 136.5, 134.1*, 134.0, 132.2, 131.1*, 129.3*, 129.0, 128.9*, 128.6, 127.0*, 127.0, 126.2, 126.1*, 125.5*, 124.9, 124.8, 124.4, 124.2*, 122.7*, 54.1*, 48.4, 44.8, 44.1*, 36.7*, 36.3, 36.0, 22.3, 21.8*, 19.6*, 16.7. UPLC-MS gradient B, t_R = 1.65 min, m/z 299.2 ($[M + H]^+$, $C_{18}H_{24}N_2O_2^+$ calcd 299.2). $[\alpha]_{589.3}$: −88° (c = 0.16, 293 K, $CHCl_3$). HRMS (MALDI) m/z calcd for $[M + Na]^+$, $C_{18}H_{22}N_2NaO_2^+$ 321.1573; found 321.1578.

*2-(N-Benzhydrylacetamido)-N,N-dimethylacetamide (**3c**).* Yield: 182 mg (90%) as oil. VLC eluent: 0−1.5% MeOH in CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.18 (m, 10H, Ar-H), 7.09*/6.30 (2 × s, 1H, $NCH(C_6H_5)_2$), 4.07/4.04* (2 × s, 2H, $COCH_2$), 2.74/2.73/2.61*/2.57* (4 × s, 6H, $N(CH_3)_2$), 2.21*/2.12 (2 × s, 3H, $COCH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4*, 172.3, 167.3, 167.1*, 139.4(*), 129.2(*), 129.0(*), 128.6(*), 128.3(*), 128.0, 127.5*, 66.4, 61.4*, 46.8*, 45.6, 36.2, 35.7*, 22.5(*). UPLC-MS gradient B, t_R = 1.82 min, m/z 311.2 ($[M + H]^+$, $C_{19}H_{23}N_2O_2^+$ calcd 311.2). HRMS (MALDI) m/z calcd for $[M + Na]^+$, $C_{19}H_{22}N_2NaO_2^+$ m/z 333.1573; found 333.1579.

*2-(N-Isopropylacetamido)-N,N-dimethylacetamide (**3d**).* Yield: 118 mg (57%) as oil. VLC eluent: 0−2.25% MeOH in CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85*/4.09 (2 × sept, J = 6.8 Hz, 1H, $NCH(CH_3)_2$), 3.93/3.91* (2 × s, 2H, $COCH_2$), 3.04(*)/2.97*/2.93 (4 × s, 6H, $N(CH_3)_2$), 2.15/1.95* (2 × s, 3H, $COCH_3$), 1.17/1.03* (2 × d, J = 6.8 Hz, 6H, $NCH(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3*, 170.3, 168.4, 168.2*, 49.3, 44.6*, 44.2*, 41.6, 36.6, 36.4*, 36.2*, 36.0, 22.3*, 21.6, 21.2, 20.1*. HRMS (ESI) m/z calcd for $[M + Na]^+$, $C_9H_{18}N_2NaO_2^+$ 209.1260; found 209.1261.

*2-(N-(tert-Butyl)acetamido)-N,N-dimethylacetamide (**3e**).* Yield: 99 mg (49%) as oil. VLC eluent: 0−1.25% MeOH in CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (s, 2H, $COCH_2$), 3.01/2.97 (2 × s, 6H, $N(CH_3)_2$), 1.98 (s, 3H, $COCH_3$), 1.41 (s, 9H, $NC(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 169.0, 57.2, 47.8, 36.4, 36.1, 28.7, 25.2. UPLC-MS gradient B, t_R = 1.09 min, m/z 201.1 ($[M + H]^+$, $C_{10}H_{21}N_2O_2S^+$ calcd 201.2). HRMS (ESI) m/z calcd for $[M + Na]^+$, $C_{10}H_{20}N_2NaO_2^+$ 223.1417; found 223.1421.

*(S)-N-(2-(Dimethylamino)-2-thioxoethyl)-N-(1-phenylethyl)-acetamide (**7a**).* Yield: 82 mg (78%) as oil, obtained over two steps from **2a**. VLC eluent: 20−80% EtOAc in hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.16 (m, 5H, Ar-H), 6.01*/5.23 (2 × q, J = 6.9 Hz, 1H, $CHCH_3$), 4.74/3.84 (2 × d, J = 16.1 Hz, 2H, $CSCH_2$), 4.06*/3.91*(2 × d, J = 16.1 Hz, 2H, $CSCH_2$), 3.43(*)/3.28/3.12* (4 × s, 6H, $N(CH_3)_2$), 2.16(*) (2 × s, 3H, $COCH_3$), 1.72/1.50* (2 × d, J = 7.0 Hz, 3H, $NCHCH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.0, 198.6*, 172.6*, 171.8, 142.1, 141.3*, 128.9, 128.5*, 127.8*, 127.6, 126.3, 57.0, 52.4*, 52.3*, 51.4, 45.5*, 45.4, 41.2, 40.6*, 23.2*, 22.5, 19.6, 17.09*. UPLC-MS gradient B, t_R = 1.57 min, m/z 265.2 ($[M + H]^+$, $C_{14}H_{21}N_2OS^+$ calcd 265.1). $[\alpha]_{589.3}$: −11° (c = 0.14, 293 K, $CHCl_3$). HRMS (ESI) m/z calcd for $[M + Na]^+$, $C_{14}H_{20}N_2NaOS^+$ 287.1189; found 287.1190.

*(S)-N-(2-(Dimethylamino)-2-thioxoethyl)-N-(1-(naphthylen-1-yl)-ethyl)acetamide (**7b**).* Yield: 222 mg (64%) as colorless solid, obtained over two steps from **2b**. Mp: 123−125 °C. VLC eluent: 0−75% EtOAc in hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−7.39 (m, 7H, Ar-H), 6.72/5.91* (2 × q, J = 7.0 Hz, 1H, $NCHCH_3$), 4.97*/3.93* (2 × d, J = 16.2 Hz, 2H, $CSCH_2$), 3.84/3.78 (2 × d, 2H, $COCH_2$), 3.45*/3.39/3.29*/2.93 (4 × s, 6H, $N(CH_3)_2$), 2.15/2.12* (2 × s, 3H, $COCH_3$), 1.84*/1.66 (2 × d, J = 7.0 Hz, 3H, $NCHCH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7*, 198.9, 172.4*, 172.2, 139.1*, 136.8, 134.0, 134.0*, 132.1, 130.4*, 129.3*, 129.0, 128.7, 128.5*, 127.0, 126.9*, 126.2, 126.1*, 125.7*, 124.9, 124.8, 124.3, 123.4*, 122.3*, 54.5*, 51.9, 51.3*, 49.1, 45.5(*), 41.1*, 40.4, 23.3, 22.4*, 20.8*, 17.8. UPLC-MS gradient B, t_R = 1.89 min, m/z 315.1 ($[M + H]^+$, $C_{18}H_{23}N_2OS^+$ calcd 315.2). $[\alpha]_{589.3}$: −69° (c = 0.17, 293 K, $CHCl_3$). HRMS (ESI) m/z calcd for $[M + Na]^+$, $C_{18}H_{22}N_2NaOS^+$ 337.1345; found 337.1346.

*N-Benzhydryl-N-(2-(dimethylamino)-2-thioxoethyl)acetamide (**7c**).* Yield: 44 mg (43%) as colorless solid, obtained over two steps from **2c**. Mp: 174−176 °C. VLC eluent: 0−1.25% MeOH in CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.18 (m, 10H, Ar-H), 6.87*/6.42 (2 × s, 1H, $NCH(C_6H_5)_2$), 4.48/4.32* (2 × s, 2H, $CSCH_2$), 3.25/3.14*/3.03/2.84* (4 × s, 6H, $N(CH_3)_2$), 2.31*/2.03 (2 × s, 3H, $COCH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2, 197.7*, 172.9, 172.8*, 139.8*, 139.7, 129.5*, 129.2, 128.6, 128.2*, 128.0, 127.4*, 66.6, 62.6*, 53.2*, 52.6, 45.1(*), 40.8, 40.2*, 23.8*, 23.5. UPLC-MS gradient B, t_R = 1.90 min, m/z 327.2 ($[M + H]^+$, $C_{19}H_{23}N_2OS^+$ calcd 327.2). HRMS (ESI) m/z calcd for $[M + Na]^+$, $C_{19}H_{22}N_2NaOS^+$ 349.1345; found 349.1346.

*N-(2-(Dimethylamino)-2-thioxoethyl)-N-isopropylacetamide (**7d**).* Yield: 43 mg (23%) as oil, obtained over two steps from **2d.** VLC eluent: 0−2% MeOH in CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72*/4.12 (2 × sept, J = 6.8 Hz, 1H, $NCH(CH_3)_2$), 4.26/4.09* (2 × s, 2H, $CSCH_2$), 3.49*/3.44/3.34*/3.32 (4 × s, 6H, $N(CH_3)_2$), 2.16/2.01* (2 × s, 3H, $COCH_3$), 1.24/1.08* (2 × d, J = 6.8 Hz, 6H, $NCH(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.4, 199.0*, 172.0*, 170.6, 51.4*, 49.9, 49.2, 45.9*, 45.6*, 45.4, 41.3, 40.6*, 23.3*, 22.0, 21.4, 20.4*. UPLC-MS gradient B, t_R = 1.13 min, m/z 203.1 ($[M + H]^+$, $C_9H_{19}N_2OS^+$ calcd 203.1). HRMS (ESI) m/z calcd for $[M + Na]^+$, $C_9H_{18}N_2NaOS^+$ 225.1032; found 225.1035.

*N-(tert-Butyl)-N-(2-(dimethylamino)-2-thioxoethyl)acetamide (**7e**).* Yield: 9 mg (2%) as oil, obtained over two steps from **2e**. VLC eluent: 0−40% EtOAc in hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (s, 2H, $CSCH_2$), 3.53/3.34 (2 × s, 6H, $N(CH_3)_2$), 2.07 (s, 3H, $COCH_3$), 1.47 (s, 9H, $NC(CH_3)_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.2, 172.4, 57.8, 54.3, 45.7, 40.5, 29.0, 25.7. UPLC-MS gradient B, t_R = 1.39 min, m/z 217.2 ($[M + H]^+$, $C_{10}H_{21}N_2OS^+$ calcd 217.1). HRMS (ESI) m/z calcd for $[M + Na]^+$, $C_{10}H_{20}N_2NaOS^+$ 239.1189; found 239.1191.

General Procedure for Di- and Trifluoroacetylation. Di- or trifluoroacetic anhydride (3 equiv) was added dropwise to a solution of secondary amine (**2** or **6**; 1 equiv) and Et_3N (3 equiv) in CH_2Cl_2 (to give a 0.4 M solution with respect to the amine) at 0 °C. The reaction mixture was then stirred for 2−18 h (monitored by TLC) at rt, poured into saturated aqueous $NaHCO_3$, and extracted with EtOAc (3×). The combined organic phases were dried ($NaSO_4$), filtered, and concentrated in vacuo. The crude products were purified by VLC.

*(S)-N-(2-(Dimethylamino)-2-oxoethyl)-2,2,2-trifluoro-N-(1-phenylethyl)acetamide (**4a**).* Yield: 162 mg (79%) as oil. VLC eluent: 0−2% MeOH in CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.31 (m, 5H, Ar-H), 5.84*/5.40 (2 × q, J = 6.9 Hz, 1H, $NCHCH_3$), 4.13/3.36 (2 × d, J = 16.0 Hz, 2H, $COCH_2$), 4.05*/3.72* (2 × d, J = 18.0 Hz, 2H, $COCH_2$), 2.92(*)/2.89/2.80* (4 × s, 6H, $N(CH_3)_2$), 1.68/1.57* (2 × d, J = 7.0 Hz, 3H, $NCHCH_3$).^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0*, 165.9, 157.3 (q, J = 36.4 Hz), 139.0*, 138.6, 129.0, 128.9*, 128.4, 128.3*, 127.9*, 127.3, 116.9 (q, J = 288.2 Hz), 55.5 (q, J = 3.0 Hz), 55.0*, 45.2*, 44.6, 36.6, 36.2 (2C)*, 36.0, 17.3, 16.1*. UPLC-MS gradient B, t_R = 1.81 min, m/z 303.2 ($[M + H]^+$, $C_{14}H_{18}F_3N_2O_2^+$ calcd 303.1). $[\alpha]_{589.3}$: −38° (c = 0.16, 293 K, $CHCl_3$). HRMS (ESI) m/z calcd for $[M + Na]^+$, $C_{14}H_{17}F_3N_2NaO_2^+$ 325.1134; found 325.1137.

*(S)-N-(2-(Dimethylamino)-2-oxoethyl)-2,2,2-trifluoro-N-(1-(naphthalen-1-yl)ethyl)acetamide (**4b**).* Yield: 77 mg (75%) as colorless solid. Mp: 113−115 °C. VLC eluent: 0−40% EtOAc in hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90−7.47 (m, 7H, Ar-H), 6.52/6.04* (2 × q, J = 6.7 Hz, 1H, $NCHCH_3$), 4.19*/3.41* (2 × d, J = 16.0 Hz, 2H, $COCH_2$), 3.89/3.52 (2 × d, J = 18.0 Hz, 2H, $COCH_2$), 2.90*/2.88/

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2.80*/2.64 (4 × s, 6H, N(CH_3)$_2$), 1.90*/1.72 (2 × d, J = 6.8 Hz, 3H, NCHCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1$^{(*)}$, 158.5 (q, J = 36.4 Hz), 134.2, 134.1*, 131.9*, 131.3*, 129.8, 129.3*, 129.0, 127.4, 127.3*, 126.5, 126.3*, 125.7, 125.3*, 125.2*, 125.0, 123.3, 116.7 (q, J = 289.9 Hz), 53.7*, 51.8, 45.3*, 44.7 (q, J = 3.4 Hz), 36.6*, 36.2, 19.7*, 16.4. UPLC-MS gradient B, t_R = 2.12 min, m/z 353.2 ([M + H]$^+$, $C_{18}H_{20}F_3N_2O_2^+$ calcd 353.1). $[\alpha]_{589.3}$: −47° (c = 0.19, 293 K, $CHCl_3$). HRMS (ESI) m/z calcd for [M + Na]$^+$, $C_{18}H_{19}F_3N_2NaO_2^+$ 375.1291; found 375.1292.

*N-Benzhydryl-N-(2-(dimethylamino)-2-oxoethyl)-2,2,2-trifluoroacetamide (**4c**).* Yield: 76 mg (75%) as colorless solid. Mp: 137−139 °C. VLC eluent: 0−30% EtOAc in hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.22 (m, 10H, Ar-H), 6.78*/6.58 (2 × s, 1H, NCH(C_6H_5)$_2$), 4.18*/4.14 (2 × s, 2H, COCH_2), 2.73*/2.66/2.56* (3 × s, 6H, N(CH_3)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2*, 164.5, 158.5 (q, J = 38.4 Hz), 137.9*, 137.7, 134.7, 129.7, 129.7*, 129.2, 128.9, 128.7, 128.5*, 128.4*, 128.2*, 128.1$^{(*)}$, 116.8* (q, J = 288.9 Hz), 116.6 (q, J = 289.9 Hz), 67.5*, 64.5, 46.7*, 45.9, 36.4*, 36.1*, 35.8, 35.8. UPLC-MS gradient B, t_R = 2.09 min, m/z 365.2 ([M + H]$^+$, $C_{19}H_{20}F_3N_2O_2^+$ calcd 365.1). HRMS (ESI) m/z calcd for [M + Na]$^+$, $C_{19}H_{19}F_3N_2NaO_2^+$ 387.1291; found 387.1299.

*N-(2-(Dimethylamino)-2-oxoethyl)-2,2,2-trifluoro-N-isopropylacetamide (**4d**).* Yield: 58 mg (54%) as oil. VLC eluent: 0−2.25% MeOH in CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49*/4.33 (2 × sept, J = 6.6 Hz, 1H, NCH(CH_3)$_2$), 4.08*/4.00 (2 × s, 2H, COCH_2), 3.06/3.02*/2.98*/2.97 (4 × s, 6H, N(CH_3)$_2$), 1.23/1.21* (2 × d, J = 6.8 Hz, 6H, NCH(CH_3)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1*, 166.1, 157.0 (q, J = 36.0 Hz), 116.7 (q, J = 287.9 Hz), 49.8*, 48.9 (q, J = 3.7 Hz), 44.8*(q, J = 3.7 Hz), 42.6, 36.6, 36.3*, 36.2*, 36.1, 21.0, 19.4*. HRMS (ESI) m/z calcd for [M + Na]$^+$, $C_9H_{15}F_3N_2NaO_2^+$ 263.0978; found 263.0983.

*N-(tert-Butyl)-N-(2-(dimethylamino)-2-oxoethyl)-2,2,2-trifluoroacetamide (**4e**).* Yield: 24 mg (23%) as oil. VLC eluent: 0−40% EtOAc in hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (s, 2H, COCH_2), 3.00/2.98 (2 × s, 6H, N(CH_3)$_2$), 1.48 (s, 9H, NC(CH_3)$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 157.2 (q, J = 34.3 Hz), 116.5 (q, J = 291.2 Hz), 60.3, 46.1 (q, J = 3.7 Hz), 36.4, 36.2, 27.6. UPLC-MS gradient B, t_R = 1.53 min, m/z 255.2 ([M + H]$^+$, $C_{10}H_{18}F_3N_2O_2^+$ calcd 255.1). HRMS (ESI) m/z calcd for [M + Na]$^+$, $C_{10}H_{17}F_3N_2NaO_2^+$ 277.1134; found 277.1139.

*(S)-N-(2-(Dimethylamino)-2-thioxoethyl)-2,2,2-trifluoro-N-(1-phenylethyl)acetamide (**8a**).* Yield: 35 mg (28%) as oil, obtained over two steps from **2a**. VLC eluent: 0−30% EtOAc in hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.30 (m, 5H, Ar-H), 5.61*/5.44 (2 × q, J = 6.5 Hz, 1H, NCHCH$_3$), 4.36/3.55 (2 × d, J = 16.2 Hz, 2H, CSCH_2), 4.26*/4.20* (2 × d, J = 16.2 Hz, 2H, CSCH_2), 3.43$^{(*)}$/3.19/3.11* (4 × s, 6H, N(CH_3)$_2$), 1.79/1.67* (2 × d, J = 6.9 Hz, 3H, NCHCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 157.7 (q, J = 36.4 Hz), 138.9, 129.0, 128.8*, 128.4, 128.2*, 127.8*, 127.3, 116.9 (q, J = 287.3 Hz), 57.2*, 56.0 (q, J = 3.0 Hz), 52.5*, 51.2, 45.6*, 45.4, 41.0, 40.5*, 17.8$^{(*)}$. UPLC-MS gradient B, t_R = 2.12 min, m/z 341.1 ([M + Na]$^+$, $C_{14}H_{17}F_3N_2NaOS^+$ calcd 341.1). $[\alpha]_{589.3}$: −8° (c = 0.17, 293 K, $CHCl_3$). HRMS (ESI) m/z calcd for [M + Na] $^+$, $C_{14}H_{17}F_3N_2NaOS^+$ 341.0906; found 341.0908.

*(S)-N-(2-(Dimethylamino)-2-thioxoethyl)-2,2,2-trifluoro-N-(1-(naphthalen-1-yl)ethyl)acetamide (**8b**).* Yield: 54 mg (40%) as colorless solid, obtained over two steps from **2b**. Mp: 50−61 °C. VLC eluent: 0−25% EtOAc in hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90−7.46 (m, 7H, Ar-H), 6.47/6.11* (2 × q, J = 6.7 Hz, 1H, NCHCH$_3$), 4.50*/3.77* (2 × d, J = 16.1 Hz, 2H, CSCH_2), 4.07/3.88 (2 × d, J = 18.2 Hz, 2H, CSCH_2), 3.42$^{(*)}$/3.15/2.94 (4× s, 6H, N(CH_3)$_2$), 1.99*/1.78 (2 × d, J = 6.9 HZ, 3H, NCHCH_3).^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 196.2*, 159.3 (q, J = 35.7 Hz), 135.7*, 135.1, 134.1, 131.8*, 130.9*, 129.6, 129.3*, 129.0, 127.3, 127.3*, 126.5, 126.3*, 125.3, 125.2*, 125.0, 124.8*, 123.4, 122.5*, 116.7 (q, J = 289.5 Hz) 54.1*, 52.9, 52.0*, 51.6, 45.7, 45.5*, 41.1*, 40.4, 20.3*, 17.5. UPLC-MS gradient B, t_R = 2.36 min, m/z 369.3 ([M + H]$^+$, $C_{18}H_{20}F_3N_2OS^+$ calcd 369.1). $[\alpha]_{589.3}$: −39° (c = 0.20, 293 K, $CHCl_3$). HRMS (ESI) m/z calcd for [M + Na]$^+$, $C_{18}H_{19}F_3N_2NaOS^+$ 391.1062; found 391.1064.

*N-Benzhydryl-N-(2-(dimethylamino)-2-thioxoethyl)acetamide (**8c**).* Yield: 66 mg (49%) as colorless solid, obtained over two steps from **2c**. Mp: 194−196 °C. VLC eluent: 0−25% EtOAc in hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.20 (m, 10H, Ar-H), 6.64*/6.57 (2 × s, 1H, NCH(C_6H_5)$_2$), 4.47*/4.40 (2 × s, 2H, CSCH_2), 3.21/3.17*/3.05*2.76 (4 × s, 6H, N(CH_3)$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.0, 193.9*, 159.3 (q, J = 35.7 Hz), 158.5* (q, J = 34.3 Hz), 138.4, 137.8*, 129.3*, 129.3, 128.7*, 128.5, 128.5, 128.4*, 128.0, 116.7* (q, J = 288.9 Hz), 116.5 (q, J = 289.5 Hz), 65.5, 65.0* (q, J = 3.0 Hz), 52.9 (q, J = 3.0 Hz), 51.5*, 45.3, 45.0*, 40.5*, 40.2. UPLC-MS gradient B, t_R = 2.32 min, m/z 381.1 ([M + H]$^+$, $C_{19}H_{20}F_3N_2OS^+$ calcd 381.1). HRMS (ESI) m/z calcd for [M + Na]$^+$, $C_{19}H_{19}F_3N_2NaOS^+$ 403.1062; found 403.1064.

*N-(2-(Dimethylamino)-2-thioxoethyl)-2,2,2-trifluoro-N-isopropylacetamide (**8d**).* Yield: 65 mg (14%) as oil, obtained over two steps from **2d**. VLC eluent: 0−30% EtOAc in hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37/3.39* (2 × sept, J = 6.6 Hz, 1H, NCH(CH_3)$_2$), 4.27*/4.23 (2 × s, 2H, CSCH_2), 3.49*/3.37 (2 × s, 6H, N(CH_3)$_2$), 1.30$^{(*)}$ (d, J = 6.6 Hz, 6H, NCH(CH_3)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.2$^{(*)}$, 157.2 (q, J = 36.0 Hz), 116.7 (q, J = 288.2 Hz), 52.4*, 49.5 (q, J = 3.7 Hz), 49.2, 45.5, 41.2, 40.6*, 21.3, 19.7*. UPLC-MS gradient B, t_R = 1.76 min, m/z 257.1 ([M + H]$^+$, $C_9H_{16}F_3N_2OS^+$ calcd 257.1). HRMS (ESI) m/z calcd for [M + Na]$^+$, $C_9H_{15}F_3N_2NaOS^+$ 279.0749; found 279.0751.

*N-(tert-Butyl)-N-(2-(dimethylamino)-2-thioxoethyl)-2,2,2-trifluoroacetamide (**8e**).* Yield: 29 mg (5%) as oil, obtained over two steps from **2e**. VLC eluent: 0−45% EtOAc in hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (s, 2H, CSCH_2), 3.51/3.32 (2 × s, 6H, N(CH_3)$_2$), 1.52 (s, 9H, NC(CH_3)$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.8, 157.5 (q, J = 34.3 Hz), 116.4 (q, J = 291.6 Hz), 61.1, 52.3 (q, J = 3.7 Hz), 45.6, 40.6, 27.9. UPLC-MS gradient B, t_R = 1.92 min, m/z 271.2 ([M + H]$^+$, $C_{10}H_{18}F_3N_2OS^+$ calcd 271.1). HRMS (ESI) m/z calcd for [M + Na]$^+$, $C_{10}H_{17}F_3N_2NaOS^+$ 293.0906; found 293.0907.

*N-Benzhydryl-N-(2-(dimethylamino)-2-oxoethyl)-2,2-difluoroacetamide (**10**).* Yield: 46 mg (36%) as colorless solid. Mp: 159−161 °C. VLC eluent: 0−100% of EtOAc in hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.18 (m, 6H, Ar−H), 7.04/6.59* (2 × s, 1H, NCH(C_6H_5)$_2$), 6.32/6.09* (2 × t, J = 53.5 Hz, 1H, COCF_2H), 4.16/4.11* (2 × s, 2H, COCH_2), 2.77*/2.73*/2.62/2.52 (4 × s, 6H, N(CH_3)$_2$). ^{13}C (101 MHz, $CDCl_3$) δ 166.8, 165.6*, 164.2 (t, J = 24.4 Hz), 137.9*, 137.8, 129.0, 128.9*, 128.7*, 128.5, 128.3*, 128.0, 109.3/108.3* (2 × t, J = 246.5 Hz), 64.2*, 62.2, 45.7*, 44.7, 44.1, 37.7*, 36.4*, 36.2, 36.1*, 35.7. UPLC-MS gradient B, t_R = 1.93 min, m/z 347.2 ([M + H]$^+$, $C_{19}H_{21}F_2N_2O_2^+$ calcd 347.2). HRMS (ESI) m/z calcd for [M + Na]$^+$, $C_{19}H_{20}F_2N_2NaO_2^+$ 369.1385; found 369.1387.

*N-Benzhydryl-N-(2-(dimethylamino)-2-thioxoethyl)-2,2-difluoroacetamide (**12**).* Yield: 57 mg (89%) as colorless solid. Mp: 192−194 °C. VLC eluent: 0−0.5% MeOH in CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.19 (m, 10H, Ar-H), 6.84/6.67* (2 × s, 1H, NCH(C_6H_5)$_2$), 6.56/5.87* (2 × t, J = 53.7 Hz, 1H, COCHF_2), 4.45*/4.38 (2 × s, 2H, CSCH_2), 3.25*/3.14/3.09*/2.77 (4 × s, 6H, N(CH_3)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.8*, 196.7, 164.6 (q, J = 26.6 Hz), 138.2, 138.1*, 129.4, 129.3*, 128.7*, 128.4$^{(*)}$, 128.0, 108.5 (t, J = 246.4 Hz), 65.2*, 63.1, 52.5*, 50.5, 45.3, 40.3. UPLC-MS gradient B, t_R = 2.13 min, m/z 363.2 ([M + H]$^+$, $C_{19}H_{21}F_2N_2OS^+$ calcd 363.1). HRMS (ESI) m/z calcd for [M + Na]$^+$, $C_{19}H_{20}F_2N_2NaOS^+$ 385.1157; found 385.1162.

*(S)-N-(2-(Dimethylamino)-2-oxoethyl)-2,2-difluoro-N-(1-(naphthalen-1-yl)ethyl)acetamide (**13**).* Yield: 75 mg (60%) as colorless solid. Mp: 123−125 °C. VLC eluent: 0−1% MeOH in CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95−7.46 (m, 7H, Ar-H), 6.61 (q, J = 6.9 Hz, 1H, NCHCH$_3$), 6.19 (t, J = 53.8 Hz, 1H, COCHF_2), 3.83/3.64 (2 × d, J = 18.0 Hz, 2H, COCH_2), 2.73/2.62 (2 × s, 6H, N(CH_3)$_2$), 1.63 (d, J = 6.9 Hz, 3H, CHCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 163.5 (t, J = 24.7 Hz), 134.6, 134.0, 132.0, 129.6, 128.6, 127.3, 126.6, 125.2, 124.8, 124.0, 108.6 (t, J = 248.0 Hz), 50.1, 42.8 (t, J = 3.0 Hz), 36.3, 36.0, 16.3. UPLC-MS gradient B, t_R = 1.87 min, m/z 335.2 ([M + H]$^+$, $C_{18}H_{21}F_2N_2O_2^+$ calcd 335.2). $[\alpha]_{589.3}$: −118° (c = 0.18, 293 K, $CHCl_3$). HRMS (ESI) m/z calcd for [M + Na]$^+$, $C_{18}H_{20}F_2N_2NaO_2^+$ 357.1385; found 357.1387.

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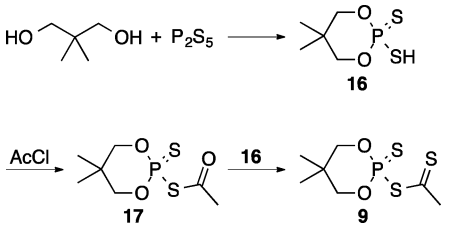
*(S)-N-(2-(Dimethylamino)-2-thioxoethyl)-2,2-difluoro-N-(1-(naphthalen-1-yl)ethyl)acetamide (**14**).* Yield: 46 mg (79%) as colorless solid. Mp: 127−129 °C. VLC eluent: 0−0.5% MeOH in CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96−7.45 (m, 7H, Ar-*H*), 6.62 (q, *J* = 6.9 Hz, 1H, NC*H*CH$_3$), 6.41 (t, *J* = 53.8 Hz, 1H, COC*H*F$_2$), 3.92 (d, *J* = 4.2 Hz, 2H, CSC*H*$_2$), 3.35/2.94 (2 × s, 6H, N(C*H*$_3$)$_2$), 1.66 (d, *J* = 7.0 Hz, 3H, CHC*H*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5, 164.0 (t, *J* = 25.8 Hz), 135.0, 134.1, 132.0, 129.6, 128.7, 127.3, 126.6, 125.1, 124.7, 124.0, 108.1 (t, *J* = 246.9 Hz), 50.5, 49.3, 49.2, 45.7, 40.6, 17.0. UPLC-MS gradient B, t_R = 2.11 min, *m*/*z* 351.2 ([M + H]$^+$, $C_{18}H_{21}F_2N_2OS^+$ calcd 351.1). $[\alpha]_{589.3}$: −147° (*c* = 0.19, 293 K, $CHCl_3$). HRMS (ESI) *m*/*z* calcd for [M + Na]$^+$, $C_{18}H_{20}F_2N_2NaOS^+$ 373.1157; found 373.1160.

*N-(2-(Dimethylamino)-2-thioxoethyl)-2,2-difluoro-N-isopropylacetamide (**15**).* Yield: 45 mg (16%) as oil. VLC eluent: 0−30% EtOAc in heptane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21*/6.18 (2 × t, *J* = 54 Hz, 1H, COCF$_2$*H*), 4.64*/4.40 (2 × sept, *J* = 6.7 Hz, 1H, NC*H*(CH$_3$)$_2$), 4.27/4.24* (2 × s, 2H, COC*H*$_2$), 3.52*/3.49/3.38*/3.36 (4 × s, 6H, N(C*H*$_3$)$_2$), 1.31/1.16* (2 × d, *J* = 6.6 Hz, 6H, NCH(C*H*$_3$)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.8*, 197.0, 162.2 (t, *J* = 25.3 Hz), 110.3/108.2* (2 × t, *J* = 251.0 Hz), 49.1*, 49.1, 48.6 (t, *J* = 4.0 Hz), 47.7*, 45.7*, 45.4, 41.1, 40.6*, 21.3, 19.8*. UPLC-MS gradient B, t_R = 1.36 min, *m*/*z* 239.1 ([M + H]$^+$, $C_9H_{17}F_2N_2OS^+$ calcd 239.3). HRMS (ESI) *m*/*z* calcd for [M + Na]$^+$, $C_9H_{16}F_2N_2NaOS^+$ 261.0844; found 261.0848.

*N-Benzhydryl-2,2-dichloro-N-(2-(dimethylamino)-2-oxoethyl)-acetamide (**11**).* Dichloroacetyl chloride (3 equiv) was added to a solution of **2c** (1 equiv) and Et$_3$N (3 equiv) in CH_2Cl_2 (20 mL) at 0 °C. The reaction was stirred for 2 h. The reaction mixture was poured into satd aq $NaHCO_3$ (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The product was isolated as a colorless solid, after preparative HPLC (gradient C). Yield: 12 mg (9%). Mp: 122−134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.18 (m, 10H, Ar−*H*), 7.06/6.53* (2 × s, 1H, NC*H*(C$_6$H$_5$)$_2$), 6.42/6.17* (2 × s, 1H, COCCl$_2$*H*), 4.12/4.07* (2 × s, 2H, COC*H*$_2$), 2.77*/2.74*/2.62/2.48 (4 × s, 6H, N(C*H*$_3$)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.62, 165.47, 138.01, 128.9, 128.8*, 128.4, 128.0*, 127.9, 127.3, 66.4, 62.5, 45.4, 36.2, 35.7. UPLC-MS gradient B, t_R = 2.06 min, *m*/*z* 379.1 ([M + H]$^+$, $C_{19}H_{21}Cl_2N_2O_2^+$ calcd 379.1). HRMS (ESI) *m*/*z* calcd for [M + Na]$^+$, $C_{19}H_{20}Cl_2N_2NaO_2^+$ *m*/*z* 401.0794; found 401.0798.

Procedure for Synthesis of Thioacetylation Reagent 9. The synthesis was adapted from the reported procedure by Doszczak and Rachon.[27] P_2S_5 (11.2 g, 25 mmol) was suspended in toluene (70 mL), 2,2-dimethylpropane-1,3-diol (10.4 g, 100 mmol) was added, and the mixture was heated to 80 °C overnight. The reaction was cooled to rt and filtered. The filtrate was concentrated, and the crude was recrystallized from CCl_4 (25 mL). After letting the compound precipitate in the freezer (−18 °C) for 6 h, the solvent was removed by filtration and the colorless crystals were dried in vacuo to give **16** (13.0 g, 66%). Compound **16** (1.98 g, 10 mmol) was dissolved in CH_2Cl_2 (30 mL), and acetyl chloride (710 μL, 10 mmol) was added at rt. The mixture was cooled to 0 °C, and Et$_3$N (1.4 mL, 10 mmol) was added dropwise. The reaction was stirred at 0 °C for 15 min followed by 15 min at rt. The mixture was then filtered through a pad of silica gel, and the filtrate was concentrated in vacuo to give **17** (1.75 g, 73%). Compounds **16** (2.78 g, 14 mmol) and **17** (1.7 g, 7 mmol) were then dissolved in toluene (50 mL) and heated to 90 °C for 2.5 h, at which point the solution turned red. The solution was allowed to cool to rt, and the solvent was removed in vacuo. The crude was dissolved in CH_2Cl_2 (50 mL), washed with satd aq $NaHCO_3$ and water. The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo to give **9** (1.52 g, 85%), which was used without further purification.

General Procedure for Thioacetylation. A solution of **2a−e** (1 equiv) and pyridine (1 equiv) in CH_2Cl_2 (0.7 M) was added dropwise to thioacetylation reagent **9** (0.9 equiv) in CH_2Cl_2 (0.2 M) at rt. After stirring for 1 h the reaction mixture was washed with satd aq $NaHCO_3$ and water. The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by VLC.



*(S)-N,N-Dimethyl-2-(N-(1-phenylethyl)ethanethioamido)-acetamide (**5a**).* Yield: 87 mg (22%) as oil. VLC eluent: 0−80% EtOAc in hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.22 (m, 5H, Ar-*H*), 7.30*/5.63 (2 × q, *J* = 6.9 Hz, 1H, NC*H*CH$_3$), 5.02/3.70 (2 × d, *J* = 15.6 Hz, 2H COC*H*$_2$), 4.13*/3.90* (2 × d, *J* = 15.6 Hz, 2H COC*H*$_2$), 3.00/2.95/2.88*/2.81* (4 × s, 6H, N(C*H*$_3$)$_2$), 2.86/2.64* (2 × s, 3H, CSC*H*$_3$), 1.76/1.53* (2 × d, *J* = 7.0 Hz, 3H, NCHC*H*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.2*, 201.0, 166.3, 166.0*, 139.5, 139.3*, 129.2, 128.7*, 128.2, 128.1*, 127.8*, 126.6, 60.6, 59.0*, 50.7, 48.1*, 36.9, 36.5*, 36.1, 35.0*, 33.2*, 32.4, 17.8, 14.8*. UPLC-MS gradient B, t_R = 1.58 min, *m*/*z* 287.1 ([M + Na]$^+$, $C_{14}H_{20}N_2NaOS$ calcd 287.1). $[\alpha]_{589.3}$: −48° (*c* = 0.14, 293 K, $CHCl_3$). HRMS (ESI) *m*/*z* calcd for [M + Na]$^+$, $C_{14}H_{20}N_2NaOS^+$ 287.1189; found 287.1191.

*(S)-N,N-Dimethyl-2-(N-(1-(naphthalen-1-yl)ethyl)ethanethioamido)acetamide (**5b**).* Yield: 75 mg (38%) as amorphous substance. VLC eluent: 0−50% EtOAc in hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−7.43 (m, 7H, Ar-*H*), 7.55/6.12* (2 × q, *J* = 6.9 Hz, 1H, NC*H*CH$_3$), 5.05*/3.75* (2 × d, *J* = 15.5 Hz, 2H, COC*H*$_2$), 3.96/3.79 (2 × d, *J* = 15.5 Hz, 2H, COC*H*$_2$), 2.96*/2.60 (2 × s, 3H, CSC*H*$_3$), 2.94*/2.91*/2.75/2.62 (4 × s, 6H, N(C*H*$_3$)$_2$), 1.93*/1.70 (2 × d, *J* = 6.9 Hz, 3H, NCHC*H*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.0, 201.2*, 166.7*, 165.8, 135.8, 135.6*, 134.1*, 133.9, 132.4, 131.1*, 129.5, 129.5*, 129.4*, 128.5, 127.5*, 127.3, 126.5, 126.3*, 125.6*, 125.4, 125.0, 124.9, 124.5*, 122.3*, 58.5*, 57.2, 51.0*, 47.9, 36.9*, 36.3*, 36.1, 36.0, 33.2, 32.2*, 19.0*, 14.8. UPLC-MS gradient B, t_R = 1.93 min, *m*/*z* 315.2 ([M + H]$^+$, $C_{18}H_{23}N_2OS^+$ calcd 315.2). $[\alpha]_{589.3}$: −189° (*c* = 0.17, 293 K, $CHCl_3$). HRMS (ESI) *m*/*z* calcd for [M + Na]$^+$, $C_{18}H_{22}N_2NaOS^+$: 337.1345; found 337.1347.

*2-(N-Benzhydrylethanethioamido)-N,N-dimethylacetamide (**5c**).* Yield: 75 mg (15%) as amorphous substance. VLC eluent: 0−0.8% MeOH in CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24*/6.66 (2 × s, 1H, NC*H*(C$_6$H$_5$)$_2$), 7.38−7.18 (m, 10H, Ar-*H*), 4.72/4.34* (2 × s, 2H, COC*H*$_2$), 2.79*/2.71 (2 × s, 3H, CSC*H*$_3$), 2.78/2.74/2.57(*) (4 × s, 6H, N(C*H*$_3$)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.5*, 203.6, 165.3, 165.1*, 138.3, 137.8*, 129.4*, 129.2, 128.9, 128.5, 128.4*, 128.0*, 70.4, 68.7*, 52.8, 49.8*, 36.5*, 36.3, 35.8*, 35.6, 33.6*, 33.4. UPLC-MS gradient B, t_R = 1.92 min, *m*/*z* 327.2 ([M + H]$^+$, $C_{19}H_{23}N_2OS^+$ calcd 327.2). HRMS (ESI) *m*/*z* calcd for [M + Na]$^+$, $C_{19}H_{22}N_2NaOS^+$: 349.1351; found 349.1346.

*2-(N-Isopropylethanethioamido)-N,N-dimethylacetamide (**5d**).* Yield: 30 mg (6%) as oil. VLC eluent: 0−1% MeOH in CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96*/4.56 (2 × sept, *J* = 6.8 Hz, 1H, NC*H*(CH$_3$)$_2$), 4.51/4.19* (2 × s, 2H, COC*H*$_2$), 3.12/3.07*/3.01*/2.98 (4 × s, 6H, N(C*H*$_3$)$_2$), 2.75/2.55* (2 × s, 3H, CSC*H*$_3$), 1.29/1.15* (2 × d, *J* = 6.7 Hz, 6H, NCH(C*H*$_3$)$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 166.4, 53.7, 48.4, 36.9, 36.7*, 36.3*, 36.1, 31.9, 20.8, 19.3*. UPLC-MS gradient B, t_R = 1.05 min, *m*/*z* 225.2 ([M + Na]$^+$, $C_9H_{19}N_2NaOS^+$ calcd 225.1). HRMS (ESI) *m*/*z* calcd for [M + Na]$^+$, $C_9H_{18}N_2NaOS^+$: 225.1032; found 225.1033.

NMR Spectroscopy. 1D and 2D NMR spectra were recorded at 298 K. Spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C. The correlation spectroscopy (COSY) spectra were recorded with a relaxation delay of 1.5 s before each scan, a spectral width of 3 k × 3 k, collecting 4 FIDs and 1 k × 128 data points. The heteronuclear single quantum coherence (HSQC) spectra were recorded with a relaxation delay of 1.5 s before each scan, a spectral width of 4.8 k × 16.6 k, collecting 4 FIDs and 1 k × 256 data points. Heteronuclear multiple-bond correlation (HMBC) spectra were recorded with a relaxation delay of 1.34 s before each scan, a spectral width of 3.5 k × 22.3 k, collecting 32 FIDs and 2k × 256 data points. Rotating frame Overhauser effect (ROESY) spectra were recorded with a relaxation

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delay of 2 s before each scan, a spectral width of 3.5 k × 3.5 k, collecting 8 FIDs at 295 K, 1 k × 256 data points, and a mixing time of 100 ms. Heteronuclear Overhauser effect (HOESY) spectra[36] were recorded with a relaxation delay of 1.5 s before each scan, a spectral width of 5 × 19 kHz, collecting 64 FIDs at 300 K, 2 k × 256 data points, and a mixing time of 50 ms. The gradient augmented pulse sequence was 'hoesyetgp.2'.

X-ray Crystallography. All final compounds were subjected to vapor diffusion crystallization with chloroform as solvent and pentane as precipitant. Compounds unsuccessful to this method were attempted crystallized by slow evaporation from solubility compatible solvents (e.g., chloroform, EtOAc, CH_2Cl_2, or acetone). Compounds **7c** and **10** were crystallized by slow evaporation from acetone and **12** by slow evaporation from chloroform. X-ray diffraction profile data from ω scans were collected on using Cu Kα radiation. Data was processed and scaled using the *CrysAlisPro* software [Version 1.171.36.28 (released Jan 02, 2013 CrysAlis171.NET)]. Details of the data collection are found in the supplementary CIF files. All crystal structures were solved using SHELXS and refined using SHELXL[37,38] in the OLEX2 interface.[38] Hydrogen atoms were observed and included on ideal positions using riding coordinates.

Crystal Data from Single-Crystal Diffraction Studies for Compound ***3b***. $C_{22}H_{22}N_2O_2$, M_r = 298.38, orthorhombic, space group $P2_12_12_1$, colorless, a = 9.37265(13) Å, b = 9.64096(14) Å, c = 17.45640(2) Å, T = 120 K, Z = 4, R_{int} = 0.0222, GOF = 1.052, R1[$F_0 > 4s(F_0)$] = 0.0337, wR2[all data] = 0.0876.

Crystal Data from Single-Crystal Diffraction Studies for Compound ***3c***. $C_{19}H_{22}N_2O_2$, M_r = 310.39, orthorhombic, space group $Pna2_1$, colorless, a = 10.88660(16) Å, b = 14.8755(2) Å, c = 10.23202(14) Å, T = 120 K, Z = 4, R_{int} = 0.0264, GOF = 1.024, R1[$F_0 > 4s(F_0)$] = 0.0323, wR2[all data] = 0.0865.

Crystal Data from Single-Crystal Diffraction Studies for Compound ***4a***. $C_{14}H_{17}F_3N_2O_2$, M_r = 302.30, hexagonal, space group $P6_1$, colorless, a = 15.74885(18) Å, c = 11.05787(17) Å, T = 120 K, Z = 6, R_{int} = 0.0453, GOF = 1.090, R1[$F_0 > 4s(F_0)$] = 0.0756, wR2[all data] = 0.2306.

Crystal Data from Single-Crystal Diffraction Studies for Compound ***4c***. $C_{19}H_{19}F_3N_2O_2$, M_r = 364.36, orthorhombic, space group $P2_12_12_1$, colorless, a = 9.46505(10) Å, b = 10.52840(11) Å, c = 18.0621(2) Å, T = 120 K, Z = 4, R_{int} = 0.0235, GOF = 1.096, R1[$F_0 > 4s(F_0)$] = 0.0368, wR2[all data] = 0.0941.

Crystal Data from Single-Crystal Diffraction Studies for Compound ***5b***. $C_{18}H_{22}N_2OS$, M_r = 314.44, orthorhombic, space group $P2_12_12_1$, colorless, a = 9.42849(13) Å, b = 10.19836(14) Å, c = 17.3158(3) Å, T = 120 K, Z = 4, R_{int} = 0.0287, GOF = 1.053, R1[$F_0 > 4s(F_0)$] = 0.0339, wR2[all data] = 0.0908.

Crystal Data from Single-Crystal Diffraction Studies for Compound ***5c***. $C_{19}H_{22}N_2OS$, M_r = 326.45, triclinic, space group $P\bar{1}$, colorless, a = 8.6606(3) Å, b = 8.8909(2) Å, c = 11.7871(4) Å, T = 120 K, Z = 4, R_{int} = 0.0275, GOF = 1.087, R1[$F_0 > 4s(F_0)$] = 0.0391, wR2[all data] = 0.1072.

Crystal Data from Single-Crystal Diffraction Studies for Compound ***7b***. $C_{18}H_{22}N_2OS$, M_r = 314.44, orthorhombic, space group $P2_12_12_1$, colorless, a = 9.53269(13) Å, b = 9.99519(13) Å, c = 17.7400(3) Å, T = 120 K, Z = 4, R_{int} = 0.0267, GOF = 1.042, R1[$F_0 > 4s(F_0)$] = 0.0318, wR2[all data] = 0.0824.

Crystal Data from Single-Crystal Diffraction Studies for Compound ***7c***. $C_{19}H_{22}N_2OS$, M_r = 326.45, monoclinic, space group $P2_1/c$, colorless, a = 14.2453(4) Å, b = 6.3820(2) Å, c = 19.0726(6) Å, T = 120 K, Z = 4, R_{int} = 0.0515, GOF = 1.292, R1[$F_0 > 4s(F_0)$] = 0.1146, wR2[all data] = 0.2848.

Crystal Data from Single-Crystal Diffraction Studies for Compound ***8a***. $C_{14}H_{17}F_3N_2OS$, M_r = 318.36, orthorhombic, space group $P2_12_12_1$, colorless, a = 5.78072(13) Å, b = 9.29719(17) Å, c = 27.6640(5) Å, T = 120 K, Z = 4, R_{int} = 0.0656, GOF = 1.059, R1[$F_0 > 4s(F_0)$] = 0.0464, wR2[all data] = 0.1257.

Crystal Data from Single-Crystal Diffraction Studies for Compound ***8c***. $C_{19}H_{19}F_3N_2OS$, M_r = 380.42, orthorhombic, space group $P2_12_12_1$, colorless, a = 9.42268(11) Å, b = 10.66811(13) Å, c = 18.2399(2) Å, T = 120 K, Z = 4, R_{int} = 0.0253, GOF = 1.025, R1[$F_0 > 4s(F_0)$] = 0.0297, wR2[all data] = 0.0794.

Crystal Data from Single-Crystal Diffraction Studies for Compound ***10***. $C_{19}H_{20}F_2N_2O_2$, M_r = 346.37, orthorhombic, space group $Pna2_1$, colorless, a = 11.35582(11) Å, b = 15.33727(14) Å, c = 9.60241(9) Å, T = 120 K, Z = 4, R_{int} = 0.0255, GOF = 1.033, R1[$F_0 > 4s(F_0)$] = 0.0301, wR2[all data] = 0.0799.

Crystal Data from Single-Crystal Diffraction Studies for Compound ***11***. $C_{19}H_{20}Cl_2N_2O_2$, M_r = 379.27, orthorhombic, space group $Pbca$, colorless, a = 17.97160(18) Å, b = 10.96238(11) Å, c = 19.1950(2) Å, T = 120 K, Z = 8, R_{int} = 0.0362, GOF = 1.053, R1[$F_0 > 4s(F_0)$] = 0.0452, wR2[all data] = 0.1269.

Crystal Data from Single-Crystal Diffraction Studies for Compound ***12***. $C_{19}H_{20}F_2N_2OS$, M_r = 362.43, orthorhombic, space group $P2_12_12_1$, colorless, a = 9.31801(6) Å, b = 10.65613(7) Å, c = 18.11473(12) Å, T = 120 K, Z = 4, R_{int} = 0.0392, GOF = 1.088, R1[$F_0 > 4s(F_0)$] = 0.0240, wR2[all data] = 0.0635.

Crystal Data from Single-Crystal Diffraction Studies for Compound ***13***. $C_{18}H_{20}F_2N_2O_2$, M_r = 334.36, triclinic, space group P_1, colorless, a = 7.3111(4) Å, b = 8.9012(5) Å, c = 14.1362(8) Å, T= 120 K, Z = 2, R_{int} = 0.0279, GOF = 1.011, R1[$F_0 > 4s(F_0)$] = 0.0522, wR2[all data] = 0.1508.

Crystal Data from Single-Crystal Diffraction Studies for Compound ***14***. $C_{18}H_{20}F_2N_2OS$, $CHCl_3$, M_r = 469.79, orthorhombic, space group $P2_12_12_1$, colorless, a = 8.1156(6) Å, b = 19.8520(12) Å, c = 12.9765(9) Å, T= 120 K, Z = 4, R_{int} = 0.0343, GOF = 1.101, R1[$F_0 > 4s(F_0)$] = 0.0609, wR2[all data] = 0.1851.

CIF files for the X-ray diffraction crystal structures have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under accession codes 1041654−1041666.

■ ASSOCIATED CONTENT

Supporting Information

Supplementary figures and tables and copies of ^{1}H and ^{13}C NMR spectra; X-ray crystallographic data files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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