Discovery of a Series of Cyclohexylethylamine-Containing Protein Farnesyltransferase Inhibitors Exhibiting Potent Cellular Activity

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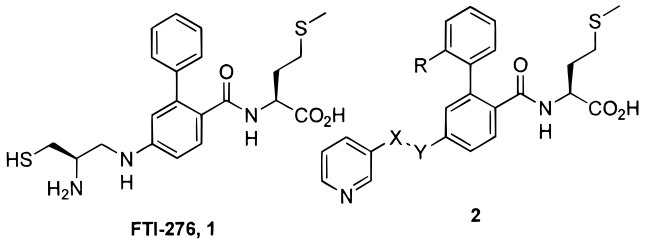
Synthesis of a library of secondary benzylic amines based on the Sebti−Hamilton type peptidomimetic farnesyltransferase (FTase) inhibitor FTI-276 (**1**) led to the identification of **6** as a potent enzyme inhibitor (IC_{50} of 8 nM) which lacked the problematic thiol residue which had been a common theme in many of the more important FTase inhibitors reported to date. It has previously been disclosed that addition of *o*-tolyl substitution to FTase inhibitors of the general description **2** had a salutary effect on both FTase inhibition and inhibition of Ras prenylation in whole cells. Combination of these two observations led us to synthesize **7**, a potent FTase inhibitor which displayed an IC_{50} of 0.16 nM for in vitro inhibition of FTase and an EC_{50} of 190 nM for inhibition of whole cell Ras prenylation. Modification of **7** by classical medicinal chemistry led to the discovery of a series of potent FTase inhibitors, culminating in the identification of **25** which exhibited an IC_{50} of 0.20 nM and an EC_{50} of 4.4 nM. In vivo tests in a nude mouse xenograft model of human pancreatic cancer (MiaPaCa cells) showed that oral dosing of **25** gave rise to impressive attenuation of the growth of this aggressive tumor cell line.

Introduction

Ras p21 is a GTPase which acts as a molecular switch and plays a central role in the transduction of extracellular mitogenic signals to the nucleus.[1,2] Ras mutants which are stuck in the "on" state have been found in a high percentage of several important human tumors, including pancreatic, colon, and lung,[2] and certain types of ovarian cancers.[3] Several posttranslational modifications normally occur before Ras can take part in the signaling cascade,[4−9] but the only critical modification is prenylation by protein farnesyltransferase (FTase) of the cysteine of a conserved carboxyl-terminal CA_1A_2X motif, which is followed by localization to the inner surface of the cellular membrane. This observation has led several groups to examine inhibitors of FTase as potential anticancer agents.[10−26] There is now significant evidence that Ras may not be the only substrate of FTase germane to the issue of oncogenesis,[27] but FTase inhibitors have been demonstrated to slow the growth of Ras-dependent tumors in nude mice.[12,23,25]

In 1995, Sebti and Hamilton disclosed the structure of FTI-276 (**1**; Chart 1), which was conceived as a nonpeptide CA_1A_2M mimic in which the lipophilic amino acid units (A_1A_2) were replaced with a rigid biphenyl spacer. It exhibited a potent in vitro IC_{50} (0.5 nM inhibition of farnesylation of an H-ras ligand) and slowed the growth of human lung tumor cells in nude mice.[22−25] Recently, Augeri et al. disclosed that compounds of the general description **2** (either anilines or benzylic amines), in which the cysteinamine portion of

Chart 1



FTI-276 was replaced with a pyridyl ring, could dramatically and unexpectedly be improved in their ability to act as FTase inhibitors by including an *o*-methyl substituent on the flanking phenyl ring of the biphenyl unit (i.e. **2**, R = Me).[26a]

Chemistry

Drawing on some of the more promising aspects of the aforementioned work, a focused combinatorial library of benzylic amines was constructed to explore replacements for the 3-pyridyl moiety in structure **2**. The requisite acid−aldehyde was prepared from commercially available dimethyl iodoterephthalate in five steps and coupled to L-methionine Wang resin (Scheme 1).[28] The coupling was attempted under several standard conditions (Table 1), and use of HATU[29] was determined to be superior based on analysis of the acid recovered from TFA cleavage from the polymer support.[30] The polymer-bound aldehyde was used as the starting point for the synthesis of a small library of secondary amines by reductive amination with sodium cyanoborohydride followed by TFA-mediated cleavage from the resin. Reductive amination with cyclohex-

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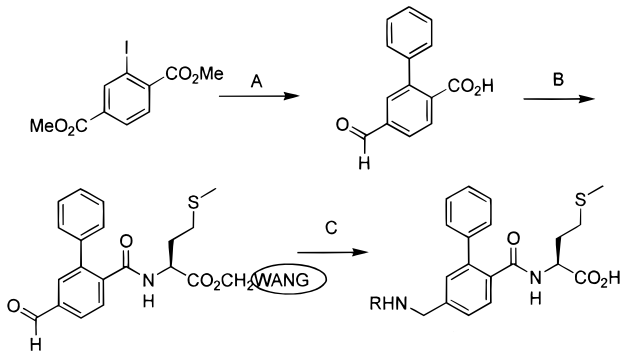
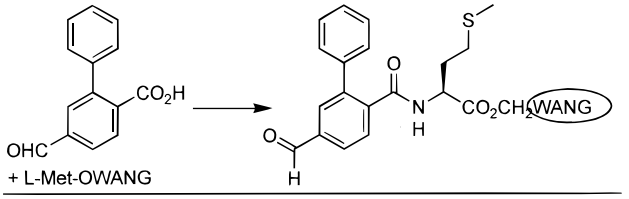
Scheme 1[a]



[a] (A) i. $PhB(OH)_2$, $Pd(OAc)_2$, Ph_3P, Na_2CO_3, H_2O−PhMe reflux, 98%, ii. KOH, H_2O/MeOH/THF, rt, 70%, iii. BH_3−THF, 98%, iv. Swern, quant., v. KOH, H_2O/MeOH/THF; (B) see Table 1; (C) i. RNH_2, $NaBH_3CN$, DMA, ii. TFA−H_2O.

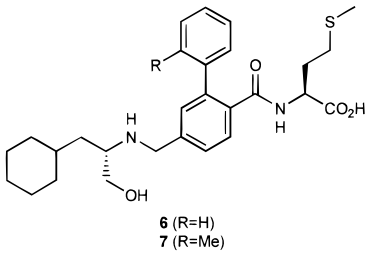
Table 1. Conditions for Coupling of Biphenyl Core Acid to Methionine Residue on Wang Resin[a]



Coupling conditions	Result
DIC(5 equiv); HOOBT(5 equiv) DIEA(1 equiv), NMP	38% coupled
DIC(5 equiv); HOAT(5equiv) DIEA(1 equiv), NMP	35% coupled
PyBrOP(5 equiv); DIEA(15 equiv) NMP	98% coupled (Ninhydrin assay) 66% pure (HPLC)
HATU(5 equiv); DIEA(15 equiv) NMP	99% coupled (Ninhydrin assay) 75% pure (HPLC)

[a] Reactions performed with 5 equiv of biphenyl acid.

Chart 2

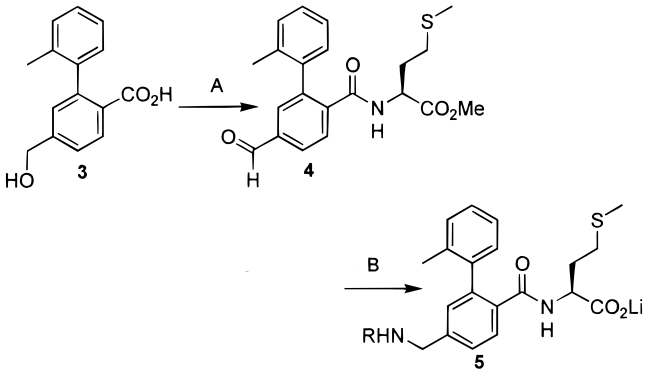


6 (R=H)
7 (R=Me)

ylalanol gave rise to **6** (Chart 2), which after preliminary screening and HPLC purification was identified as a nanomolar inhibitor of FTase (vide infra).

This initial lead was optimized using standard solution-phase medicinal chemistry. The chemistry essentially followed the reductive amination strategy outlined above on solid phase. The hydroxy acid core (**3**) was prepared by the method previously reported,[26a] replacing phenylboronic acid with *o*-methylphenylboronic acid. Coupling of the acid to L-methionine methyl or ethyl ester followed by Swern oxidation[31] gave **4**, which was a common intermediate for reductive amination with a wide variety of mono- or disubstituted amines using sodium triacetoxyborohydride in dichloroethane.[32] In most cases, the requisite amine partner for the reductive

Scheme 2[a]



[a] (A) i. L-Met(OMe), EDCI, HOBt, NMM, ii. Swern; (B) i. RNH_2, $NaBH(OAc)_3$, ii. LiOH, MeOH, H_2O.

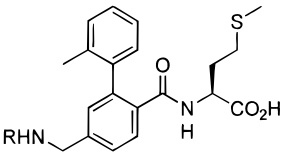
amination procedure was obtained by saturating the corresponding aryl derivative under catalytic reduction conditions or by modification of commercially available cyclohexylalanol by way of the corresponding *N*-Boc-*O*-mesylate. In a few instances, the final compound was prepared by modification of the reductive amination product (e.g. acylation or alkylation) before saponification of the methionine ester. In a limited number of instances we examined the properties of compounds where the methionine residue was replaced by methionine sulfone. Those compounds were prepared according to Scheme 2, substituting methionine sulfone for methionine. After reductive amination, the methionine esters were saponified, and the final compounds were isolated in the appropriate salt form.

Results and Discussion

First, the biphenyl core of **6** (IC_{50} = 8.0 nM) was appended to contain an *o*-methyl substituent giving structure **7**. Whereas previous examples of this type of modification resulted in 10−40-fold enhancement in IC_{50}, we observed a 50-fold increase in activity resulting in an IC_{50} of 0.16 nM. In an effort to explore what modifications were tolerable on the amine portion, several similar structures were prepared, varying the sense of chirality and the length of the alkyl chain and testing the requirement for the cyclohexyl group (Table 2). Each of these changes resulted in loss of greater than 1 order of magnitude of activity. On the basis of this information, we chose to limit further studies to compounds with an *o*-tolylbiphenyl core, which conserve a benzylic cyclohexylethylamine unit with a chiral center adjacent to the amine possessing the *S* configuration (as in **7**).

We next examined the requirements for the branched portion of the amine (Table 3). Etherification of the hydroxyl group to give **12** was explored, in addition to replacement of the oxygen with a variety of lipophilic chains, and all such modifications resulted in subnanomolar FTase inhibitors. It was also discovered that the hydroxyl group, and even the entire hydroxymethyl group, could be omitted without sacrificing in vitro activity (**14**, **13**). Nitrogen substitution on **13**, the simplest member of this series (Table 4), retained subnanomolar activity only in a limited number of cases. It is curious that, in this limited number of compounds, the side chains with the most disparate properties (BOC − **20** and methyl − **24**) had the best IC_{50} and EC_{50} data,

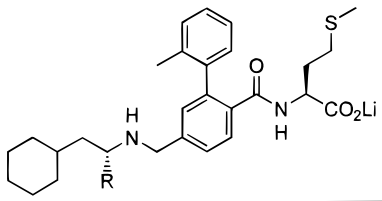
Table 2. Initial SAR of Cyclohexylethyl Region of Lead Structure **7**[a]



compd	R	IC_{50} (nM)	EC_{50} (nM)
7	*c*-C_6H_{11}	0.16	190
8	*c*-C_6H_{11}	12	ND
9		4.6	ND
10	*c*-C_6H_{11}	4.0	ND
11	*c*-C_6H_{11}	10.	ND

[a] All compounds were assayed once. The reliability of the in vitro assay is ±50%. The reliability of the cellular assay is ±50−100%. Compounds differing by 3-fold should be considered statistically different.

Table 3. SAR of Substitution on Cyclohexylethylamine[a]



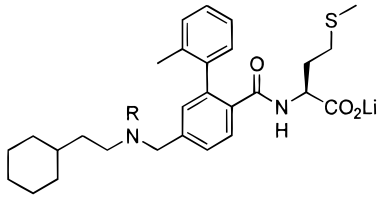
compd	R	IC_{50} (nM)	EC_{50} (nM)
12	MeOCH2	0.66	47%@300nM
13	H	0.17[b]	200
14	Me	0.70	>1000
15	Et	0.70	>1000
16	n-Bu	0.46[c]	4.3
17	4-methylpentyl	0.28	52
18	4-methylpent-1-enyl	0.22	ND
19	cyclohexylmethyl	0.25	75%@1000nM

[a] Unless otherwise indicated, all compounds were assayed once. The reliability of the in vitro assay is ±50%. The reliability of the cellular assay is ±50−100%. Compounds differing by 3-fold should be considered statistically different. [b] $n = 2$. [c] $n = 4$.

while intermediate members of the series were relatively poor.

Despite the fact that compounds of this general description (i.e. benzylic cyclohexylethylamines) tended to have very good in vitro activity against FTase, their cellular activity varied considerably. This is not unexpected since by nature the readout from a cell-based

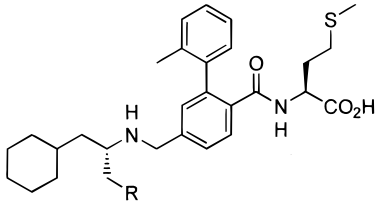
Table 4. SAR of Nitrogen Substitution[a]



compd	R	IC_{50} (nM)	EC_{50} (nM)
20	*t*-BuOCO	0.17	160
21	CH_3CO	2.9	>1000
22	PhCO	1.1	>1000
23	$PhCH_2$	3.5	>1000
24	Me	0.87[b]	12

[a] Unless otherwise indicated, all compounds were assayed once. The reliability of the in vitro assay is ±50%. The reliability of the cellular assay is ±50−100%. Compounds differing by 3-fold should be considered statistically different. [b] $n = 2$.

Table 5. Chalcogen Substitution of Cyclohexylalanol Fragment[a]



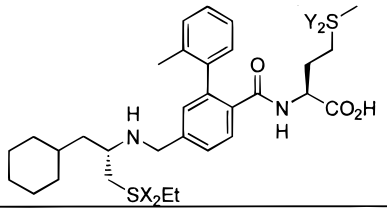
compd	R	IC_{50} (nM)	EC_{50} (nM)
12	OMe	0.66	47%@300nM
25	SEt	0.20[b]	4.4[c]
26	S-*t*-Bu	0.60	2.8
27	SPh	0.20	12
28	S-*o*-tolyl	0.42	77%@1000nM
29	S-*cyclo*-C_6H_{11}	0.41	80%@1000nM

[a] Unless otherwise indicated, all compounds were assayed once. The reliability of the in vitro assay is ±50%. The reliability of the cellular assay is ±50−100%. Compounds differing by 3-fold should be considered statistically different. [b] $IC_{50} = 0.20 \pm 0.003$ nM ($n = 8$). [c] $EC_{50} = 4.4 \pm 1.4$ nM ($n = 8$).

assay is a higher-order phenomenon and depends on a number of different factors such as cellular transport and intracellular distribution in addition to enzyme inhibition. We have learned that, in general, only compounds exhibiting subnanomolar FTase activity are likely to express good cellular potency, but that even some compounds with exceptional IC_{50}'s may have very poor cellular activity. Compound **16** is particularly noteworthy since it had very good activity in the FTase assay and displayed a remarkable EC_{50} of 4.3 nM in our whole cell Ras processing assay.

Despite our success with compounds containing relatively few heteroatoms on the "left" portion, we were intrigued by the presence of a zinc atom in the active site of FTase[33] and chose to explore a series of compounds which might have a higher propensity to interact with a nearby metal atom (Table 5). The aforementioned methyl ether **12** fits this paradigm and indeed exhibits a good level of enzyme inhibition. We prepared a series of thioethers (**25**−**29**), in which the sulfur atom is situated in the same manner relative to the biphenyl core as the sulfhydryl group in FTI-276 (**1**). All members of this series exhibited exceptional FTase inhibition, and most had very good cellular activity. We then chose to survey analogues of **25** in higher oxidation states (Table

Table 6. Sulfone Permutations of Compound **25**



compd	X	Y	IC_{50} (nM)	EC_{50} (nM)
30	O	:	0.14	59%@50nM
31	:	O	1.0	34%@300nM
32	O	O	1.2(b)	63%@1000nM

[a] Unless otherwise indicated, all compounds were assayed once. The reliability of the in vitro assay is ±50%. The reliability of the cellular assay is ±50−100%. Compounds differing by 3-fold should be considered statistically different. [b] $n = 2$.

6) to assess the relative importance of the two sulfur atoms for FTase inhibition. Oxidation of the left-side thioether of **25** to the sulfone had no effect on in vitro potency but resulted in slightly reduced cellular potency. Oxidation of the methionine sulfur or the combination of both oxidation events was not well-tolerated. Although there is no direct evidence that indicates how this type of molecule interacts with the enzyme, these data do not support the idea that the sulfur on the "left" portion of the inhibitors interacts with a metal atom. On the other hand, the difficulty which we and others have experienced finding useful replacements for the methionine portion of the inhibitor does suggest a vital role for the methionine atom.[26,34] It should also be considered that the requisite cyclohexylethyl portion of the compounds described in this paper might occupy the farnesylpyrophosphate binding site of FTase, but the kinetic experiments required to explore this issue have not yet been undertaken. It is interesting that compound **30** ($IC_{50} = 0.14$ nM) contains all the structural elements of a transition-state analogue for the alkylation of CAAX with farnesylpyrophosphate.

It was hoped that the high cellular potency of many of these compounds would allow for a clear demonstration of efficacy in an animal model of cancer. In preliminary efficacy studies, compound **25** did in fact exhibit exciting properties. When nude mice were inoculated subcutaneously with MiaPaCa-2 cells, oral dosing of compound **25** at 100 mpk, qd effected a 54% reduction in tumor size relative to untreated control on day 13 (mean tumor size of control, 669 mg). In a similar experiment, compound **24** also demonstrated measurable in vivo efficacy. Oral dosing of **24** at 100 mpk, qd effected a 23% reduction in tumor size on day 16, and dosing of **24** at 6.25 mpk, qd, ip gave a 40% reduction in tumor size on day 16 (mean tumor size for untreated control on day 16, 980 mg). Although the exact magnitude of the efficacy of FTase inhibitors has been difficult to reproducibly quantify, these results clearly demonstrate a measurable level of in vivo efficacy against human pancreatic cancer cells. Further in vivo efficacy studies with this type of FTase inhibitor will be reported in due course.[26d]

Experimental Section

General. Proton magnetic resonance spectra were obtained on a Nicolet QE-300 (300 MHz) or General Electric GN-300 (300 MHz) instrument. Chemical shifts are reported as δ values (ppm) downfield relative to tetramethylsilane as an internal standard. Mass spectra were obtained with a Hewlett-Packard HP5965 spectrometer; CI/NH_3 indicates chemical ionization mode in the presence of ammonia, and APCI indicates atmospheric pressure chemical ionization mode. Combustion analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ. Purification was performed by flash column chromatography using silica gel 60 (230−400 mesh) from E. Merck. Compounds synthesized by combinatorial techniques which displayed biological activity were resynthesized by solution-phase techniques in order to obtain authenticated samples for biological assay. All compounds synthesized by solution-phase methods were determined to be >95% pure by analytical reverse-phase HPLC.

General Procedure: Coupling of 4-Formyl-2-phenylbenzoic Acid to L-Methionine-Wang-Polystyrene Resin. A 100-mL manual peptide synthesis flask was charged with 7.70 g of L-Met-Wang-polystyrene resin (Novabiochem; 0.47 mmol/g, 3.62 mmol). The resin was suspended in *N*-methylpyrrolidinone (NMP). The flask was then placed on a manual 120° shaker and was gently rocked for 5 min. The flask was then drained and the resin was washed with additional NMP (2 × 5 min). The resin was resuspended in a minimal volume of NMP followed by addition of diisopropylethylamine (9.5 mL, 54.4 mmol, 15 equiv), 4-formyl-2-phenylbenzoic acid as a solution in NMP (4.10 g, 18.1 mmol, 5 equiv), and *O*−(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU)[29] (6.90 g, 18.1 mmol, 5 equiv). The resin-slurry was then shaken for 16 h at ambient temperature. The reaction vessel was drained and washed as follows: acetone (1 × 2 min), dimethylformamide (DMF) (5 × 5 min), 2-propanol (5 × 5 min), DMF (3 × 5 min), methanol (2 × 5 min), and diethyl ether (2 × 5 min). The resin was dried in vacuo overnight at ambient temperature. Quantitative ninhydrin analysis[30] of a portion of the resin indicated 98% completion for this coupling reaction.

General Procedure: Solid-Phase Synthesis of Secondary Amine-type FTase Inhibitors by Reductive Amination. All reactions were performed either in a manual solid-phase synthesis flask using a 120° rotary shaker or on an Advanced ChemTech model 396 multiple peptide synthesizer (Advanced ChemTech Inc., Louisville, KY) at ambient temperature. Resin (80 mg, substitution of 0.40 mmol/g) containing 4-formyl-2-phenylbenzamide-L-methionine-Wang-polystyrene resin was swollen with dimethylacetamide (DMA; 1.0 mL, 3 min). The solvent was drained and the resin was washed with additional DMA (2 × 1.0 mL, 3 min). The resin was suspended in DMA (0.20 mL) followed by addition of the desired primary amine (0.48 mmol, 10 equiv) as a 1.0-mL solution in 3:1 DMA/acetic acid. The resin was shaken for 2 h and treated with sodium cyanoborohydride (0.25 mL of a 2.4 mM solution in DMA, 10 equiv). The resin-slurry was shaken for an additional 2 h. The solvents were drained and the resin was washed with DMA (6 × 1.0 mL, 3 min), DMF (6 × 1.0 mL, 3 min), IPA (6 × 1.0 mL, 3 min), DMF (6 × 1.0 mL, 3 min), MeOH (6 × 1.0 mL, 3 min), and diethyl ether (6 × 1.0 mL, 3 min). The resin was air-dried and subjected to subsequent cleavage.

General Procedure: Cleavage of FTase Inhibitors from the Resin. Air-dried resin (80−90 mg) containing the desired secondary amine was treated with a 1.50-mL solution of 95/5 trifluoroacetic acid/water for 1.5 h at ambient temperature. The spent resin was removed by filtration and the resulting cleavage solution was poured into pretared storage vials. An aliquot of the solution (0.150−0.250 mL) was removed and evaporated in vacuo into a separate vial for analysis. The remaining bulk solution was evaporated in vacuo and saved for biological screening. In most cases, 5−20 mg of the crude compound was obtained. Those compounds that contained the desired product as determined by electrospray mass spectroscopy and which had an HPLC purity of 40−90% were screened for FTase inhibition.

***N*-[4-(3-Cyclohexyl-1-hydroxypropan-2-ylaminomethyl)-2-phenylbenzoyl]-L-methionine (6):** HPLC purity 65%; MS

ESI(+) 499 $(MH)^+$; resynthesized by the general procedure described below; ^{1}H NMR (DMSO-d_6) δ 0.78−0.88 (m, 3H), 1.10−1.40 (m, 10H), 1.64−1.73 (m, 6H), 2.10−2.18 (m, 1H), 2.72 (m, 1H), 3.43 (m, 1H), 3.87−3.99 (m, 2H), 4.10−4.17 (m, 2H), 7.05−7.25 (m, 5H), 7.43 (d, J = 7 Hz, 1H), 7.46 (d, J = 7 Hz, 1H), 7.90 (m, 1H); MS (CI/NH_3) m/z 499 $(MH)^+$. Anal. ($C_{28}H_{38}N_2O_4S\cdot 2.0\ H_2O$) C, H, N.

General Procedure: Reductive Amination of Ethyl *N*-[4-formyl-2-(2-methylphenyl)benzoyl]-L-methionine (4) with an Amine. Ethyl *N*-[4-(2(*S*)-3-cyclohexyl-1-hydroxypropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine. To a solution of cyclohexylalanol (33 mg, 0.21 mmol) and **4** (84 mg, 0.21 mmol) in dichloroethane (0.7 mL) was added sodium triacetoxyborohydride (62 mg, 0.29 mmol). The reaction was stirred at ambient temperature for 3 h, at which time it was judged to be complete by TLC. The reaction was quenched by addition of 15% NaOH (1 mL), and the mixture was extracted twice with ethyl acetate (5 mL). The organic solution was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel chromatography eluting with 5% methanol/chloroform to afford the ethyl ester of **7** as a clear oil (56 mg, 49%): ^{1}H NMR ($CDCl_3$) δ 0.83−0.95 (m, 2H), 1.10−1.73 (m, 17H), 1.85 (m, 1H), 2.01−2.11 (m, 6H), 2.77 (m, 1H), 3.27 (dd, J = 6, 11 Hz, 1H), 3.64 (dd, J = 4, 11 Hz, 1H), 3.82 (d, J = 14 Hz, 1H), 3.90 (d, J = 14 Hz, 1H), 4.11 (q, J = 7 Hz, 2H), 4.60 (m, 1H), 5.91 (d, J = 7.5 Hz, 1H), 7.16 (s, 1H), 7.25−7.33 (m, 3H), 7.41 (dd, J = 2, 8 Hz, 1H), 7.92 (dd, J = 8, 15 Hz, 1H); MS (CI/NH_3) m/z 541 $(MH)^+$.

General Procedure: Saponification of Methionine Esters. *N*-[4-(2(*S*)-3-Cyclohexyl-1-hydroxypropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine (7). To a solution of ethyl *N*-[4-(3-cyclohexyl-1-hydroxypropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine (86.0 mg, 0.159 mmol) in THF (0.53 mL) was added a 1 M aqueous solution of lithium hydroxide (175 μL, 1.1 equiv), and the solution was stirred at ambient temperature until judged to be complete by TLC analysis (ca. 5 h). The solvent was removed under reduced pressure, and the residue was dissolved in water (2 mL). The solution was neutralized with a 1 M aqueous solution of sodium bisulfate, and the product was extracted into chloroform. The chloroform solution was dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. If the salt-free compound was desired, the residue was dissolved in aqueous acetonitrile and lyophilized to give a white powder (65 mg, 80%): ^{1}H NMR (DMSO-d_6) δ 0.77−0.89 (m, 3H), 1.08−1.38 (m, 10H), 1.55−1.85 (m, 6H), 2.00−2.18 (m, 4H), 2.65 (m, 1H), 3.45 (m, 1H), 3.84−3.92 (m, 2H), 4.12−4.18 (m, 2H), 7.05−7.23 (m, 4H), 7.42 (d, J = 7 Hz, 1H), 7.49 (d, J = 7 Hz, 1H), 7.85 (m, 1H); MS (CI/NH_3) m/z 513 $(MH)^+$. Anal. ($C_{29}H_{40}N_2O_4S\cdot 1.5H_2O$) C, H, N.

In other compounds, it was determined on a case-by-case basis that the lithium carboxylate or the ammonium trifluoroacetate salts gave well-behaved powders with superior solubility properties. If the lithium carboxylate or the ammonium trifluoroacetate salts were desired, the residue from the chloroform extraction was dissolved in aqueous acetonitrile (1−2 mL) followed by addition of lithium hydroxide monohydrate (1 equiv) or dilute aqueous trifluoroacetic acid and lyophilization.

***N*-[4-(2(*R*)-3-Cyclohexyl-1-hydroxypropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine trifluoroacetate salt (8):** ^{1}H NMR (DMSO-d_6) δ 0.77−0.89 (m, 3H), 1.08−1.38 (m, 10H), 1.55−1.85 (m, 6H), 2.00−2.18 (m, 4H), 2.65 (m, 1H), 3.45 (m, 1H), 3.84−3.92 (m, 2H), 4.12−4.18 (m, 2H), 7.05−7.23 (m, 4H), 7.42 (d, J = 7 Hz, 1H), 7.49 (d, J = 7 Hz, 1H), 7.85 (m, 1H); MS (CI/NH_3) m/z 513 $(MH)^+$. Anal. ($C_{29}H_{40}N_2O_4S\cdot C_2HF_3O_2\cdot 1.5H_2O$) C, H, N.

***N*-[4-(2(*S*)-3-Phenyl-1-hydroxypropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine (9):** ^{1}H NMR (DMSO-d_6) δ 1.50−1.76 (m, 2H), 1.76−2.04 (m, 5H), 1.91 (s, 3H), 2.15 (brs, 1H), 2.60−2.74 (m, 2H), 3.25 (m, 1H), 3.70 (m, 1H), 3.80 (m, 2H), 4.14 (brs, 1H), 4.55 (brs, 1H), 6.87 (m, 2H), 7.07−7.22 (m, 10H), 7.29 (d, J = 8 Hz, 1H), 7.44 (d, J = 8 Hz, 1H); MS (ESI(+)) m/e 507 $(MH)^+$. Anal. ($C_{29}H_{33}N_2O_4SLi\cdot 1.8H_2O$) C, H, N.

***N*-[4-(1(*S*)-1-Cyclohexyl-2-hydroxyeth-1-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine lithium salt (10):** ^{1}H NMR (DMSO−d_6) δ 0.93−1.19 (m, 6H), 1.35−1.77 (m, 4H), 1.77−2.06 (m, 7H), 1.91 (s, 3H), 2.18 (brs, 1H), 2.26 (m, 3H), 3.40−3.48 (m, 1H), 3.59−3.70 (m, 1H), 3.73 (d, J = 14.2 Hz, 1H), 3.81 (d, J = 13.9 Hz, 1H), 4.36 (brs, 1H), 6.87−7.00 (m, 1H), 7.11−7.27 (m, 5H), 7.36 (d, J = 8 Hz, 1H), 7.47 (d, J = 8 Hz, 1H); MS (ESI(+)) m/e 499 $(MH)^+$. Anal. ($C_{28}H_{37}N_2O_4SLi\cdot 0.75H_2O$) C, H, N.

***N*-[4-(1(*R*)-1-Cyclohexyl-2-hydroxyeth-1-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine lithium salt (11):** ^{1}H NMR (DMSO-d_6) δ 0.92−1.18 (m, 5H), 1.37−1.77 (m, 8H), 1.80−2.02 (m, 7H), 2.12−2.28 (m, 2H), 3.31 (m, 1H), 3.46 (m, 1H), 3.65−3.82 (m, 3H), 4.40 (t, J = 5 Hz, 1H), 6.90 (m, 1H), 7.08−7.20 (m, 4H), 7.37 (dd, J = 8, 1 Hz, 1H), 7.48 (d, J = 8 Hz, 1H); MS (ESI(+)) m/e 499 $(MH)^+$. Anal. ($C_{28}H_{37}N_2O_4SLi\cdot 1.5H_2O$) C, H, N.

***N*-[4-(2(*S*)-3-Cyclohexyl-1-methoxypropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine lithium salt (12):** ^{1}H NMR (DMSO-d_6) δ 0.65−0.88 (m, 2H), 1.00−1.88 (m, 15H), 1.91 (s, 3H), 1.95−2.19 (m, 3H), 2.61−2.68 (m, 1H), 3.20 (s, 3H), 3.20−3.26 (m, 2H), 3.62−3.84 (m, 3H), 6.85−7.00 (m, 2H), 7.09−7.24 (m, 5H), 7.36 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H); MS (APCI(−)) m/e 525 $(M - H)^-$. Anal. ($C_{30}H_{41}N_2O_4SLi\cdot 0.60H_2O$) C, H, N.

***N*-[4-(2-Cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine trifluoroacetate salt (13):** ^{1}H NMR (DMSO-d_6) δ 0.72−0.87 (m, 2H), 1.00−1.26 (m, 4H), 1.37−1.45 (m, 2H), 1.47−1.78 (m, 7H), 1.86 (s, 3H), 1.90−2.11 (m, 5H), 2.80−2.87 (m, 2H), 4.11 (s, 2H), 4.14 (m, 1H), 6.98−7.16 (m, 3H), 7.26 (m, 1H), 7.42−7.49 (m, 2H), 8.09 (m, 1H); MS (CI/NH_3) m/z 483 $(MH)^+$. Anal. ($C_{28}H_{38}N_2O_3S\cdot C_2HF_3O_2\cdot 1.5H_2O$) C, H, N.

***N*-[4-(2(*R*)-1-Cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine (14):** ^{1}H NMR (DMSO-d_6) δ 0.77−0.90 (m, 2H), 1.02−1.50 (m, 9H), 1.52−1.84 (m, 7H), 1.94 (s, 3H), 1.94−2.17 (m, 5H), 2.85 (m, 1H), 3.89 (d, J = 14 Hz, 1H), 3.97 (d, J = 14 Hz, 1H), 4.06 (m, 1H), 7.04−7.25 (m, 4H), 7.43−7.52 (m, 2H), 7.63 (m, 1H); MS (CI/NH_3) m/z 497 $(MH)^+$. Anal. ($C_{29}H_{40}N_2O_3S\cdot 1.45H_2O$) C, H, N.

***N*-[4-(2(*R*)-1-Cyclohexylbut-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine (15):** ^{1}H NMR (DMSO-d_6) δ 0.70−0.90 (m, 2H), 0.79 (t, J = 7 Hz, 3H), 1.06−1.41 (m, 8H), 1.50−2.20 (m, 15H), 2.42 (m, 1H), 3.65−3.80 (m, 3H), 6.88 (m, 1H), 7.09−7.25 (m, 4H), 7.36 (d, J = 6 Hz, 1H), 7.48 (d, J = 8 Hz, 1H); MS (CI/NH_3) m/z 511 $(MH)^+$. Anal. ($C_{30}H_{41}N_2O_3SLi\cdot 1.25H_2O$) C, H, N.

***N*-[4-(2(*R*)-1-Cyclohexylhex-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine (16):** ^{1}H NMR (DMSO-d_6) δ 0.75−0.88 (m, 5H), 1.07−1.40 (m, 12H), 1.50−2.18 (m, 15H), 2.45 (m, 1H), 3.62−3.75 (m, 3H), 6.90 (m, 1H), 7.07−7.24 (m, 4H), 7.36 (dd, J = 8, 1 Hz, 1H), 7.47 (d, J = 8 Hz, 1H); MS (CI/NH_3) m/z 537 $(M - H)^-$. Anal. ($C_{32}H_{45}N_2O_3SLi\cdot 1.0H_2O$) C, H, N.

***N*-[4-(2(*R*)-1-Cyclohexyl-6-methylhept-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine (17):** ^{1}H NMR (DMSO-d_6) δ 0.80 (d, J = 5 Hz, 3H), 0.82 (d, J = 5 Hz, 3H), 1.02−1.40 (m, 12H), 1.40−1.65 (m, 12H), 1.75−1.83 (m, 1H), 1.92 (s, 3H), 1.99 (m, 1H), 2.16 (m, 1H), 2.43 (m, 1H), 3.60−3.77 (m, 3H), 6.86−6.95 (m, 1H), 7.08−7.22 (m, 5H), 7.35 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H); MS (APCI(+)) m/e 567 $(MH)^+$. Anal. ($C_{34}H_{49}N_2O_3SLi\cdot 2.0H_2O$) C, H, N.

***N*-[4-(2(*R*)-(*Z*)-1-Cyclohexyl-6-methylhept-3-en-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine lithium salt (18):** ^{1}H NMR (DMSO-d_6) δ 0.86−1.74 (m, 7H), 1.02−1.19 (m, 4H), 1.27−1.38 (m, 2H), 1.46−1.87 (m, 14H), 1.93 (s, 3H), 1.99 (s, 3H), 2.17 (m, 1H), 3.51−3.82 (m, 3H), 5.11 (m, 1H), 5.43 (m, 1H), 6.83−6.96 (m, 1H), 7.00−7.24 (m, 5H), 7.24−7.36 (m, 1H), 7.47 (d, J = 7 Hz, 1H); MS (APCI(+)) m/e 565 $(MH)^+$. Anal. ($C_{34}H_{47}N_2O_3SLi\cdot 2.0H_2O$) C, H, N.

***N*-[4-(1,3-Dicyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine lithium salt (19):** ^{1}H NMR (DMSO-d_6) δ 0.70−0.88 (m, 4H), 1.01−1.17 (m, 8H), 1.20−1.38 (m, 4H), 1.46−1.64 (m, 12H), 1.64−1.75 (m, 2H),

1.92 (s, 3H), 1.94−2.02 (m, 2H), 2.13−2.18 (m, 2H), 3.60−3.76 (m, 3H), 6.84−6.97 (m, 1H), 7.04−7.24 (m, 5H), 7.36 (dd, J = 8, 1 Hz, 1H), 7.45 (d, J = 8 Hz, 1H); MS (ESI(+)) m/e 579 $(MH)^+$. Anal. ($C_{35}H_{49}N_2O_3SLi\cdot0.75H_2O$) C, H, N.

***N*-[4-(*N*-*tert*-Butoxycarbonyl-2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine Lithium Salt (20).** To a solution of methyl *N*-[4-(2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine (methyl ester of **13**, 89 mg, 0.18 mmol) in THF (0.6 mL) was added di-*tert*-butyl dicarbonate (47 mg, 0.21 mmol), and the reaction was stirred at ambient temperature for 1 h. The reaction was partitioned between saturated sodium bicarbonate and ethyl acetate (5 mL each), and the organic phase was collected, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 20% ethyl acetate in hexanes to afford methyl *N*-[4-(*N*-*tert*-butoxycarbonyl-2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine (92 mg, 91%): ^{1}H NMR ($CDCl_3$) δ 0.82−0.93 (m, 2H), 1.10−1.70 (m, 23H), 1.95 (m, 1H), 2.01−2.08 (m, 6H), 3.14−3.25 (m, 2H), 3.65 (s, 3H), 4.42−4.50 (m, 2H), 4.62 (m, 1H), 5.86 (m, 1H), 7.04 (s, 1H), 7.20−7.34 (m, 4H), 7.92 (m, 1H). The methyl ester was saponified according to the general procedure to provide the title compound **20**: ^{1}H NMR (DMSO-d_6) δ 0.75−0.88 (m, 2H), 1.05−1.45 (m, 16H), 1.51−1.66 (m, 8H), 1.91 (s, 3H), 1.91−2.02 (m, 2H), 2.14 (m, 1H), 3.13−3.25 (m, 2H), 3.61−3.69 (m, 1H), 4.41 (s, 2H), 6.93−7.31 (m, 6H), 7.51 (m, 1H); MS (APCI(−)) m/z 581 $(M - H)^-$. Anal. ($C_{33}H_{45}N_2O_5SLi\cdot1.5H_2O$) C, H, N.

***N*-[4-(*N*-Acetyl-2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine Lithium Salt (21).** To a solution of ethyl *N*-[4-(2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine (ethyl ester of **13**, 102 mg, 0.20 mmol) in THF (0.67 mL) were added acetyl chloride (20 μL, 0.30 mmol) and diisopropylethylamine (70 μL, 0.40 mmol). After stirring 1 h at ambient temperature the reaction was quenched by addition of saturated aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate, and the organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 50% ethyl acetate in hexanes to afford ethyl *N*-[4-(*N*-acetyl-2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine (111 mg, 100%) as an amber oil: ^{1}H NMR ($CDCl_3$) δ 0.85−1.00 (m, 2H), 1.10−1.73 (m, 17H), 1.95 (m, 1H), 2.00−2.19 (m, 8H), 3.19−3.42 (m, 2H), 4.07−4.17 (m, 2H), 4.56−4.66 (m, 4H), 5.88 (m, 1H), 7.00 minor conformer 7.05 major conformer (s, 1H), 7.14−7.36 (m, 4H), 7.90 major conformer 7.95 minor conformer (dd, J = 8, 14 Hz, 1H). The ethyl ester was saponified according to the general procedure to provide the title compound **21**: ^{1}H NMR (DMSO-d_6) δ 0.83−0.95 (m, 2H), 1.07−1.25 (m, 4H), 1.30−1.44 (m, 3H), 1.56−1.77 (m, 7H), 1.85−2.21 (m, 10H), 3.25−3.33 (m, 2H), 3.80 (m, 1H), 4.57 major conformer 4.63 minor conformer (s, 2H), 6.96−7.07 (m, 2H), 7.14−7.25 (m, 3H), 7.31 (d, J = 8 Hz, 1H), 7.53 major conformer 7.59 minor conformer (d, J = 8 Hz, 1H); MS (APCI(−)) m/z 523 $(M - H)^-$. Anal. ($C_{30}H_{39}N_2O_4SLi\cdot1.5H_2O$) C, H, N.

***N*-[4-(*N*-Benzoyl-2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine Lithium Salt (22).** To a solution of methyl *N*-[4-(2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine (methyl ester of **13**, 88 mg, 0.18 mmol) in THF (0.6 mL) were added benzoyl chloride (31 μL, 0.27 mmol) and diisopropylethylamine (63 μL, 0.36 mmol). After stirring 1 h at ambient temperature the reaction was quenched by addition of saturated aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate, and the organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 33% ethyl acetate in hexanes to afford methyl *N*-[4-(*N*-benzoyl-2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine as a clear viscous oil (82 mg, 76%): ^{1}H NMR ($CDCl_3$) δ 0.70−1.23 (m, 9H), 1.53−1.85 (m, 6H), 1.87 (m, 1H), 2.00−2.10 (m, 6H), 2.18 (m, 1H), 3.18 (m, 1H), 3.48 (m, 1H), 3.66 (s, 3H), 4.50−4.67 (m, 2H), 4.80 (m, 1H), 5.88 (d, J = 8 Hz, 1H), 7.18 (m, 1H), 7.27−7.40 (m, 9H), 7.91 (dd, J = 8, 16 Hz, 1H). The methyl ester was saponified according to the general procedure to afford 74 mg of the lithium carboxylate as a white powder: ^{1}H NMR (DMSO-d_6) δ 0.55−0.68 (m, 2H), 1.15−1.70 (m, 14H), 1.94−2.17 (m, 7H), 3.10−3.18 (m, 2H), 3.61−3.67 (m, 1H), 4.68−4.73 (m, 2H), 6.94 (m, 1H), 7.08−7.25 (m, 4H), 7.32−7.45 (m, 6H), 7.53 (m, 1H); MS (APCI(−)) m/z 585 $(M - H)^-$. Anal. ($C_{35}H_{41}N_2O_4SLi\cdot1.8H_2O$) C, H, N.

***N*-[4-(*N*-Benzyl-2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine Lithium Salt (23).** *N*−Benzylcyclohexylethylamine was prepared by reductive amination of cyclohexylethylamine (330 mg, 2.6 mmol) and benzaldehyde (240 μL, 2.3 mmol) with sodium triacetoxyborohydride according to the general procedure to afford the secondary amine (110 mg, 22%) after silica gel purification with 5% methanol/chloroform: ^{1}H NMR ($CDCl_3$) δ 0.83−0.95 (m, 2H), 1.12−1.35 (m, 4H), 1.40−1.47 (m, 2H), 1.60−1.73 (m, 5H), 2.66 (d, J = 8 Hz, 2H), 3.80 (s, 2H), 7.22−7.34 (m, 5H). This amine was employed in a reductive amination with **4** according to the general procedure to provide ethyl *N*-[4-(*N*-benzyl-2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine: ^{1}H NMR ($CDCl_3$) δ 0.74−0.86 (m, 2H), 1.05−1.42 (m, 9H), 1.47−1.66 (m, 8H), 1.84 (m, 1H), 2.00−2.08 (m, 6H), 2.43 (t, J = 7 Hz, 2H), 3.56 (s, 2H), 3.58 (s, 2H), 4.11 (q, J = 7 Hz, 2H), 4.60 (m, 1H), 5.87 (m, 1H), 7.18−7.33 (m, 9H), 7.44 (d, J = 8 Hz, 1H), 7.89 (dd, J = 8, 14 Hz, 1H). The ethyl ester was saponified according to the general procedure to provide **23**: ^{1}H NMR (DMSO-d_6) δ 0.68−0.81 (m, 2H), 1.02−1.38 (m, 7H), 1.42−1.58 (m, 7H), 1.91 (s, 3H), 1.95−2.15 (m, 4H), 2.38 (t, J = 7 Hz, 2H), 3.53 (s, 2H), 3.56 (s, 2H), 3.69 (m, 1H), 6.92 (d, J = 6 Hz, 1H), 7.12−7.38 (m, 10H), 7.50 (d, J = 8 Hz, 1H); MS (APCI(−)) m/z 571 $(M - H)^-$. Anal. ($C_{35}H_{43}N_2O_3Sli\cdot1.75H_2O$) C, H, N.

***N*-[4-(*N*-2-Cyclohexylethyl-*N*-methylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine lithium salt (24):** ^{1}H NMR (DMSO-d_6) δ 0.76−0.90 (m, 2H), 1.05−1.35 (m, 7H), 1.50−1.74 (m, 7H), 1.92 (s, 3H), 1.80−2.06 (m, 3H), 2.12 (s, 3H), 2.15 (m, 1H), 2.32 (t, J = 7 Hz, 2H), 3.49 (s, 2H), 3.64−3.73 (m, 1H), 6.93 (d, J = 6 Hz, 1H), 7.06−7.25 (m, 4H), 7.32 (dd, J = 8, 1 Hz, 1H), 7.49 (d, J = 8 Hz, 1H); MS (CI/NH_3) m/z 497 $(MH)^+$. Anal. ($C_{29}H_{39}N_2O_3SLi\cdot1.0H_2O$) C, H, N.

General Procedure: Displacement of Cyclohexylalanine *N*-Boc-*O*-mesylate with Thiolates. (2*S*)-Amino-3-cyclohexyl-1-propanol hydrochloride (1.9 g, 10.0 mmol), diisopropylethylamine (1.9 mL, 11.0 mmol), and di-*tert*-butyl dicarbonate (2.7 g, 12.5 mmol) were combined in a (1:1) mixture of 1,4-dioxane:water (20 mL) and allowed to stir for 18 h at ambient temperature. The reaction mixture was partitioned between a solution of aqueous 2 N hydrochloric acid/ethyl acetate and the phases were separated. The ethyl acetate phase was washed with saturated potassium carbonate solution, dried ($MgSO_4$), and concentrated to afford a clear oil: ^{1}H NMR ($CDCl_3$) δ 0.90−1.00 (m, 2H), 1.14−1.35 (m, 5H), 1.45 (s, 9H), 1.55−1.86 (m, 6H), 3.50 (m, 1H), 3.63−3.80 (m, 2H); MS (CI/NH_3) m/z 258 $(MH)^+$.

Methanesulfonyl chloride (820 μL, 10.5 mmol) was added dropwise to a solution of the crude product from the above step and triethylamine (1.5 mL, 10.5 mmol) in THF (40 mL) at 0 °C. The mixture was allowed to stir for 30 min and then a solution of saturated $NaHCO_3$ was added. The reaction mixture was then extracted with ethyl acetate and the organic phase was washed with 2 N hydrochloric acid, dried ($MgSO_4$), and concentrated. The residue was chromatographed (silica gel; hexane/ethyl acetate, 80:20) to afford a clear oil (2.3 g, 67%): ^{1}H NMR ($CDCl_3$) δ 0.90−1.02 (m, 2H), 1.16−1.40 (m, 5H), 1.45 (s, 9H), 1.61−1.82 (m, 6H), 3.95 (m, 1H), 4.14 (dd, J = 4, 10 Hz, 1H), 4.27 (m, 1H); MS (CI/NH_3) m/z 336 $(MH)^+$. Ethanethiol (1.0 mL, 13.5 mmol) was added to a slurry of sodium hydride (425 mg of an 80% dispersion, 13.9 mmol) in THF (40 mL). After 15 min, a solution of the *N*−Boc-*O*-mesylate of cyclohexylalanine in THF (1.5 g, 4.5 mmol, in 5 mL) was added dropwise. The reaction was warmed to reflux for 1 h and cooled. The reaction was quenched by addition of saturated aqueous sodium bicarbonate. The mixture was

extracted with ethyl acetate, and the organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford crude 2(*S*)-*N*-*tert*-butoxycarbonyl-3-cyclohexyl-1-ethylthio-2-propylamine. The residue was dissolved in methylene chloride (15 mL) followed by addition of trifluoroacetic acid (15 mL). After 30 min of stirring, solvent was removed and the residue redissolved in methylene chloride, washed with a solution of saturated potassium carbonate, dried ($MgSO_4$), and concentrated. The crude product was chromatographed (silica gel; chloroform/methanol, 90:10) to afford 2(*S*)-3-cyclohexyl-1-ethylthio-2-propylamine as a clear oil (810 mg, 75%): ^{1}H NMR ($CDCl_3$) δ 0.90−1.00 (m, 2H), 1.26 (t, J = 7.5 Hz, 3H), 1.10−1.50 (m, 6H), 1.61−1.80 (m, 5H), 2.34 (dd, J = 13, 8.5 Hz, 1H), 2.55 (q, J = 7.5 Hz, 2H), 2.68 (dd, J = 13, 4 Hz, 1H), 2.97 (m, 1H); MS (CI/NH_3) m/z 202 $(MH)^+$.

***N*-[4-(2(*S*)-1-Cyclohexyl-3-ethylthioprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine (25).** The title compound was prepared from 2(*S*)-3-cyclohexyl-1-ethylthio-2-propylamine and **4** according to the general procedure for reductive amination: ^{1}H NMR (DMSO-d_6) δ 0.70−0.90 (m, 2H), 1.12 (t, J = 7.5 Hz, 3H), 1.02−1.21 (m, 3H), 1.25−1.45 (m, 4H), 1.50−1.88 (m, 7H), 1.95−2.22 (m, 5H), 2.44 (q, J = 7.5 Hz, 2H), 2.51 (s, 3H), 2.60−2.74 (m, 2H), 3.78−3.88 (m, 2H), 4.21 (m, 1H), 7.05−7.22 (m, 4H), 7.38−7.50 (m, 2H), 8.02 (m, 1H); MS (CI/NH_3) m/z 557 $(MH)^+$. Anal. ($C_{31}H_{44}N_2O_3S_2$·1.0H_2O) C, H, N.

***N*-[4-(2(*S*)-1-Cyclohexyl-3-*tert*-butylthioprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine Lithium Salt (26).** 2(*S*)-3-Cyclohexyl-1-*tert*-butylthio-2-propylamine was prepared from *tert*-butylmercaptan according to the general procedure: ^{1}H NMR ($CDCl_3$) δ 0.82−0.95 (m, 2H), 1.06−1.40 (m, 15H), 1.62−1.83 (m, 5H), 2.40 (dd, J = 8, 12 Hz, 1H), 2.67 (dd, J = 4, 12 Hz, 1H), 2.97 (m, 1H). The title compound was then prepared according to the general procedures for reductive amination with **4** and saponification: ^{1}H NMR (DMSO-d_6) δ 0.68−0.91 (m, 2H), 1.00−1.74 (m, 24 H), 1.77−2.18 (m, 8H), 2.63 (m, 1H), 3.65 (m, 1H), 3.72−3.87 (m, 2H), 6.97 (m, 1H), 7.13−7.23 (m, 4H), 7.37 (dd, J = 8, 1 Hz, 1H), 7.47 (d, J = 8 Hz, 1H); MS (CI/NH_3) m/z 584 $(MH)^+$. Anal. ($C_{33}H_{47}N_2O_3S_2Li$·4.0H_2O) C, N; H: calcd, 8.38; found, 7.43.

***N*-[4-(2(*S*)-1-Cyclohexyl-3-phenylthioprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine Lithium Salt (27).** 2(*S*)-3-Cyclohexyl-1-phenylthio-2-propylamine was prepared from thiophenol according to the general procedure procedures for reductive amination with **4** and saponification: ^{1}H NMR ($CDCl_3$) δ 0.79−1.00 (m, 2H), 1.08−1.75 (m, 11H), 2.74 (dd, J = 8, 13 Hz, 1H), 3.02 (m, 1H), 3.09 (dd, J = 4, 13 Hz, 1H), 7.18 (m, 1H), 7.25−7.33 (m, 2H), 7.35−7.40 (m, 2H). The title compound was then prepared according to the general procedure for reductive amination with **4**: ^{1}H NMR (DMSO-d_6) δ 0.60−2.17 (m, 23H), 2.67 (m, 1H), 2.87 (m, 1H), 3.11 (dd, J = 13, 5 Hz, 1H), 3.65−3.86 (m, 3H), 6.85−7.34 (m, 11H), 7.46 (d, J = 8 Hz, 1H); MS (CI/NH_3) m/z 605 $(MH)^+$. Anal. ($C_{35}H_{43}N_2O_3S_2Li$·1.20H_2O) C, H, N.

***N*-[4-(2(*S*)-1-Cyclohexyl-3-(2-methylphenyl)thioprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine Lithium Salt (28).** 2(*S*)-3-Cyclohexyl-1-(2-methylphenyl)thio-2-propylamine was prepared from 2-methylthiophenol according to the general procedure. The title compound was then prepared according to the general procedure for reductive amination with **4**: ^{1}H NMR (DMSO-d_6) δ 0.63−0.90 (m, 2H), 0.98−1.85 (m, 14H), 1.90−1.97 (m, 2H), 1.92 (s, 3H), 2.08−2.16 (m, 2H), 2.23 (s, 3H), 2.62−2.74 (m, 1H), 2.78−2.88 (m, 1H), 3.06 (dd, J = 12.5, 4.4 Hz, 1H), 3.64−3.82 (m, 3H), 6.85−7.32 (m, 10H), 7.45 (d, J = 7.8 Hz, 1H); MS (CI/NH_3) m/z 617 $(M - H)^-$. Anal. ($C_{36}H_{45}N_2O_3S_2Li$·1.0H_2O) C, H, N.

***N*-[4-(2(*S*)-1-Cyclohexyl-3-cyclohexylthioprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine Lithium Salt (29).** 2(*S*)-3-Cyclohexyl-1-cyclohexylthio-2-propylamine was prepared from cyclohexylmercaptan according to the general procedure. The title compound was then prepared according to the general procedure for reductive amination with **4**: ^{1}H NMR (DMSO-d_6) δ 0.75−0.87 (m, 2H), 1.02−1.87 (m, 26H), 1.90 (s, 3H), 1.90−2.15 (m, 4H), 2.54−2.64 (m, 2H), 3.66−3.83 (m, 3H), 6.88−6.96 (m, 1H), 7.06−7.21 (m, 4H), 7.34 (m, 1H), 7.48 (d, J = 7.7 Hz, 1H); MS (CI/NH_3) m/z 609 $(M - H)^-$. Anal. ($C_{35}H_{49}N_2O_3S_2Li$·1.05H_2O·1.60$C_2HF_3O_2$) C, H, N.

***N*-[4-(2(*S*)-1-Cyclohexyl-3-ethylsulfonylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-L-methionine Lithium Salt (30).** 2(*S*)-*N*-*tert*-Butoxycarbonyl-3-cyclohexyl-1-ethylthio-2-propylamine (vide supra, 565 mg, 1.87 mmol) was dissolved in methylene chloride (7.5 mL), followed by addition of mCPBA (1.3 g, 7.5 mmol), and the heterogeneous mixture was stirred overnight at ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate. The mixture was extracted with methylene chloride, and the organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 20% ethyl acetate in hexanes to afford the sulfone (480 mg, 77%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.83−1.06 (m, 2H), 1.16−1.47 (m, 17H), 1.57−1.85 (m, 6H), 3.03−3.11 (m, 3H), 3.30 (m, 1H), 4.10 (m, 1H). This compound was dissolved in methylene chloride (5 mL) followed by addition of trifluoroacetic acid (5 mL). After 1 h, the reaction was concentrated under reduced pressure. The residue was redissolved in methylene chloride and extracted to neutrality with aqueous potassium carbonate. The organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 2(*S*)-3-cyclohexyl-1-ethanesulfonyl-2-propylamine as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.84−1.04 (m, 2H), 1.08−1.23 (m, 9H), 1.60−1.81 (m, 5H), 2.89 (dd, J = 9, 14 Hz, 1H), 2.98 (dd, J = 3, 14 Hz, 1H), 3.00 (q, J = 7 Hz, 2H), 3.58 (m, 1H). The title compound was prepared from 2(*S*)-3-cyclohexyl-1-ethanesulfonyl-2-propylamine according to the general procedure for reductive amination with **4** and for saponification of the methionine ester: ^{1}H NMR (DMSO-d_6) δ 0.75−0.92 (m, 2H), 1.08−1.78 (m, 16H), 1.81−2.28 (m, 8H), 2.97 (dd, J = 14, 5 Hz, 1H), 3.07−3.20 (m, 3H), 3.33 (m, 1H), 3.68−3.83 (m, 3H), 6.97 (m, 1H), 7.10−7.27 (m, 4H), 7.38 (dd, J = 8, 1 Hz, 1H), 7.52 (d, J = 8 Hz, 1H); MS (CI/NH_3) m/z $(MH)^+$ 589. Anal. ($C_{31}H_{43}N_2O_5S_2$-Li·1.5H_2O·1.9LiOH) C, H, N.

***N*-[4-(2(*S*)-1-Cyclohexyl-3-ethylthioprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-2(*S*)-2-amino-4-methylsulfonylbutanoate Lithium Salt (31).** A solution of methyl 4-hydroxymethyl-2-(2-methylphenyl)benzoate (1.0 g, 4.1 mmol) in methanol (12 mL) was combined with a solution of saturated lithium hydroxide (4.0 mL) and heated at reflux for 3.5 h. The mixture was allowed to cool to ambient temperature and then extracted with diethyl ether. The phases were separated followed by addition of concentrated hydrochloric acid to the aqueous phase which was extracted with ethyl acetate (2×). The organic solution was dried ($MgSO_4$) and concentrated to dryness to afford the 4-hydroxymethyl-2-(2-methylphenyl)benzoic acid as a white solid: MS (CI/NH_3) m/z 243 $(MH)^+$. A solution of crude acid, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI; 940 mg, 4.5 mmol), *N*-hydroxybenzotriazole (1.1 g, 8.2 mmol), L-methionine sulfone methyl ester hydrochloride (1.0 mg, 4.5 mmol), and diisopropylethylamine (2.1 mL, 12.3 mmol) in dimethylformamide (15 mL) was stirred at ambient temperature for 16 h. The reaction was diluted with ethyl acetate (100 mL) and washed with 2 M HCl, saturated sodium bicarbonate, and brine. The organic solution was dried ($MgSO_4$) and concentrated to dryness. The crude residue was chromatographed (silica gel; methanol/chloroform, 5:95) to afford methyl *N*-[4-hydroxymethyl-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfonylbutanoate (963 mg, 56%). Dimethyl sulfoxide (325 μL, 4.6 mmol) was added to a solution of oxalyl chloride (200 μL, 2,5 mmol) at −78 °C. After stirring for 5 min, methyl *N*-[4-hydroxymethyl-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfonylbutanoate (955 mg, 2.3 mmol) in methylene chloride (2.5 mL) was added to the reaction vessel. After 15 min, triethylamine (950 μL, 6.8 mL) was added and the cold bath was removed. After stirring for 30 min, a solution of 2 N

hydrochloric acid was added to the mixture and the phases were separated. The organic phase was dried ($MgSO_4$) and concentrated. The residue was chromatographed (silica gel; methanol/chloroform, 2:98) to afford methyl *N*-[4-formyl-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfonylbutanoate as a clear oil (866 mg, 91%): ^{1}H NMR ($CDCl_3$) δ 1.88 (m, 1H), 2.11−2.30 (m, 4H), 2.47−2.73 (m, 2H), 2.71 (s, 3H), 3.71 (s, 3H), 4.65 (m, 1H), 6.12 (t, J = 8 Hz, 1H), 7.20 (d, J = 7 Hz, 1H), 7.27−7.41 (m, 2H), 7.76 (s, 1H), 7.95−8.06 (m, 2H), 10.10 (s, 1H); MS (CI/NH_3) m/z 418 $(MH)^+$. To a solution of methyl *N*-[4-formyl-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfonylbutanoate (285 mg, 1.4 mmol) and 2(*S*)-3-cyclohexyl-1-ethylthio-2-propylamine (618 mg, 1.5 mmol) in ethylene chloride (6 mL) was added sodium triacetoxyborohydride (415 mg, 2.0 mmol) at ambient temperature, and the mixture was allowed to stir for 18 h. A solution of saturated sodium bicarbonate was added and the mixture was extracted with ethyl acetate (2×). The organic solutions were combined, dried ($MgSO_4$), and concentrated. The residue was chromatographed (silica gel; MeOH/$CHCl_3$, 2:98) to afford methyl *N*-[4-(*N*-3-cyclohexyl-1-ethylthioprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfonylbutanoate as a clear oil (753 mg, 89%): MS (CI/NH_3) m/z 418 $(MH)^+$. The methyl ester was saponified according to the general procedure to give the title compound **31** as a white powder: ^{1}H NMR (DMSO-d_6) δ 0.70−0.91 (m, 2H), 1.12−1.65 (m, 14H), 1.75−2.20 (m, 5H), 2.35−2.67 (m, 7H), 2.82 (s, 3H), 3.66−3.86 (m, 3H), 6.95 (m, 1H), 7.10−7.25 (m, 4H), 7.38 (d, J = 8 Hz, 1H), 7.53 (d, J = 8 Hz, 1H); MS (APCI(−)) m/z 587 $(M - H)^-$. Anal. ($C_{31}H_{43}N_2O_5S_2Li\cdot1.90H_2O$) C, H, N.

***N*-[4-(2(*S*)-1-Cyclohexyl-3-ethylsulfonylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-2(*S*)-2-amino-4-methylsulfonylbutanoate Lithium Salt (32).** The title compound was prepared from methyl *N*-[4-formyl-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfonylbutanoate and 2(*S*)-3-cyclohexyl-1-ethanesulfonyl-2-propylamine (vide supra) according to the general procedures for reductive amination and saponification: ^{1}H NMR (DMSO-d_6) δ 0.84−0.92 (m, 2H), 1.07−2.28 (m, 21H), 2.80 (s, 3H), 2.91−3.21 (m, 4H), 3.25 (m, 1H), 3.65−3.78 (m, 3H), 6.97 (m, 1H), 7.09−7.25 (m, 4H), 7.37 (d, J = 8 Hz, 1H), 7.53 (d, J = 8 Hz, 1H); MS (ESI(+)) m/z 621 $(MH)^+$. Anal. ($C_{31}H_{43}N_2O_7S_2Li\cdot1.0H_2O$) C, H, N.

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