Ketoamide-Based Inhibitors of Cysteine Protease, Cathepsin K: P3 Modifications

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Received May 26, 2004

Osteoporosis is a disease characterized by skeletal fragility. Cathepsin K, a lysosomal cysteine protease, has been implicated in the osteoclast mediated bone resorption. Inhibitors of this protease could potentially treat this skeletal disease. The present work describes exploration of the spatial requirements of the S3 subsite by the use of various sterically demanding P3 substituents. Sulfur and oxygen linked heterocycles as well as those without heteroatom linkers were found to provide potent inhibitors of cathepsin K. Representative examples from these series also afforded quite good selectivity ratios against most cathepsins tested. The tolerability of the S3 subsite for sterically demanding groups that provide potency and selectivity enhances the attractiveness of P3 changes to improve the physiochemical properties of inhibitors in the developments of compounds for the treatment of osteoporosis.

Introduction

Osteoporosis, a systemic skeletal disease, is characterized by low bone mass and microarchitectural deterioration of bone tissue. Osteoporosis results in an increase in bone fragility and susceptibility to fracture. Bone is a mechanically optimized connective tissue that is maintained in dynamic equilibrium via bone resorption by osteoclasts and bone formation by osteoblasts. A shift or uncoupling of this dynamic process favoring resorption results in osteoporosis. Cysteine proteases have been implicated in this osteoclast-mediated resorption of the bone matrix.[1] The expression of cathepsin K, a cysteine protease of the papain superfamily, is abundant and selective in osteoclasts suggesting that this enzyme is crucial for bone resorption.[2a,b] In addition, there are several reports implicating cathepsin K in bone resorption.[3−7] Recent work has shown that cathepsin K, and not cathepsin L, is the major protease responsible for human osteoclastic bone resorption.[6] Further, complex formation with glycosaminoglycans specifically enhances collagenase activity of cathepsin K in osteoclasts, while potently inhibiting collagenase activity of other cysteine proteases such as cathepsins L and S.[6c] These studies suggest that selective inhibition of cathepsin K could provide an effective therapy for the treatment of osteoporosis.

Cysteine proteases make up the vast majority of lysosomal proteases. There are currently 11 members of the human cathepsin cysteine protease family that are involved in protein degradation. Compared to cathepsin K, the physiological role and pathological implications of many cathepsins are less well understood. Various irreversible inhibitors such as epoxides, peptidyl vinyl sulfones, and acyloxymethyl ketones have been reported in the literature.[10] To avoid potential antigenicity due to covalent modification of proteins via irreversible inhibition, a selective reversible inhibitor was desired. Numerous warheads have been utilized in reversible cysteine protease inhibitors[12−16] There has also been a recent report on the use of noncovalent amides as cathepsin K inhibitors.[17,25b] This group was particularly interested in exploring α-ketoamides as reversible inhibitors of cathepsin K. The ketoamide class of inhibitors has been widely employed for inhibiting serine proteases.[16,18] Herein is described its application in the inhibition of the cysteine protease, cathepsin K.[19] Reports on the development of potent, selective, and orally bioavailable inhibitors were recently described from this laboratory.[19a,d] Those papers were primarily focused on modifications at the P′ and P2 regions of ketoamide-based inhibitors. The present report deals with exploring the spatial requirements of the S3 subsite keeping preferred hydrophobic P2 (cyclobutyl) and P′ (α-methylbenzyl) moieties constant (Figure 1). Exploration of the S3 region would allow for opportunities in improving upon the potency and physiochemical properties of these ketoamide-based inhibitors of cathepsin K.

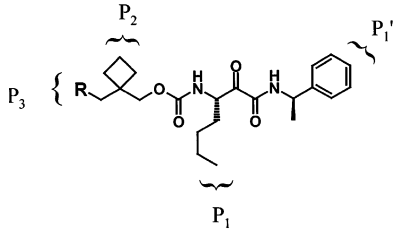

Figure 1.

Chemistry

The syntheses of the compounds **10a**, **13a**−**21a**, and **23a**−**31a** involved the formation of the key intermediate diol **2** that was formed by the reduction of diethylcyclobutane dicarboxylate with LAH. The sulfur-linked cyclobutyl analogues **10a**, **13a**−**18a** were formed using

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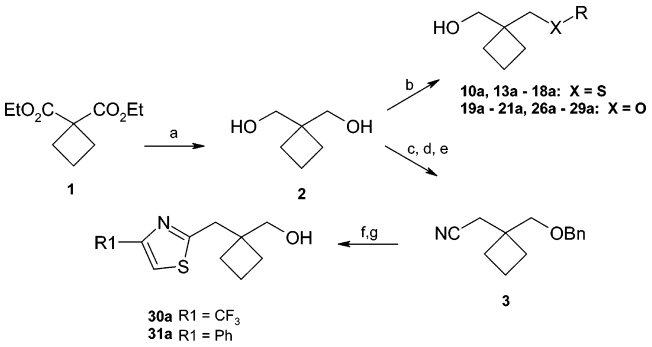
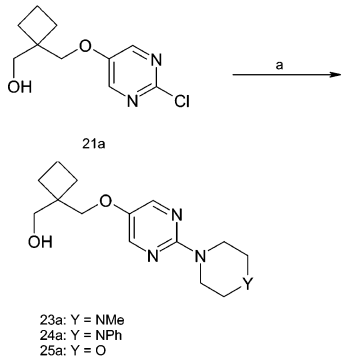
10.1021/jm040107n CCC: $27.50
Published on Web 09/08/2004

Scheme 1. Synthetic Route to Alcohols[a]



[a] (a) LAH, THF, reflux; (b) aryl thiol, PPh_3, $^tBuO_2CNNCO_2{}^tBu$, DCM (X = S); NaH, THF/DMF (1:1), aryl halide (X = O); (c) BnCl, NaH, THF/DMF; (d) $MeSO_2Cl$, DCM, Et_3N; (e) KCN, DMF, H_2O, 130 °C; (f) diethyldithiophosphate, THF, H_2O, reflux; (g) α-bromo ketone, CH_3CN; BBr_3, DCM.

Scheme 2. Synthetic Route to Alcohols[a]



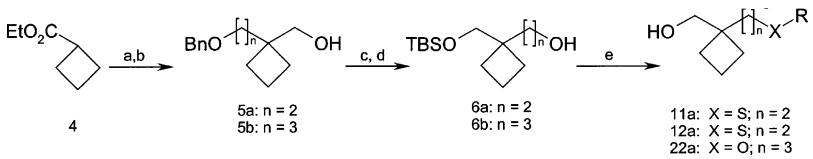
[a] *N*-Methylpiperazine (**23a**), *N*-phenylpiperazine (**24b**), morpholine (**25a**), DMF, 90 °C.

Mitsunobu conditions involving the treatment of the diol **2** with triphenylphosphine and di-*tert*-butyl azodicarboxylate followed by the subsequent addition of the thiol component (Scheme 1). The oxygen-linked cyclobutyl analogues **19a**−**21a**, **26a**−**29a**, containing one methylene spacer, were synthesized by monodeprotonation of the diol **2** with sodium hydride followed by displacement of the halide group (Scheme 1). Compound **21a**, obtained in Scheme 1, was used as an intermediate for the synthesis of analogues **23a**−**25a** involving the treatment with various secondary amines in DMF to displace the chloride moiety (Scheme 2). The thiazole analogues **30a**, **31a** were synthesized as shown in Scheme 1. The diol **2** was monobenzyl-protected followed by subsequent formation of the mesylate with methanesulfonyl chloride. The mesylate was treated with potassium cyanide to afford compound **3**. The cyanide functionality was then reacted with diethyldithiophosphate to afford the intermediate thioamide that was converted to the thiazoles by treatment with α-halo ketones. The compounds **11a**, **12a**, and **22a** (Scheme 3), possessing two or three methylene spacers, were synthesized by alkylation of ethyl cyclobutanecarboxylate with either benzyl 2-bromoethyl ether or benzyl 3-bromopropyl ether, followed by reduction of the ester with LAH to afford the alcohols **5a** and **5b**. The hydroxyl group was protected using *tert*-butyldimethylsilyl chloride followed by the subsequent deprotection of the benzyl ether with Pd/C under hydrogen to afford **6a** and **6b**. Compounds **11a**, **12a**, and **22a** were then synthesized from **6a** and **6b** using either Mitsunobu conditions or direct displacement of the halide as described in Scheme 1. The synthesis of the target compounds **10**−**31** is shown in Scheme 4. The acid **6** was converted to the mixed anhydride by treatment with isopropyl chloroformate followed by the reduction of the anhydride with sodium borohydride to afford the alcohol. Oxidation of the alcohol with sulfur trioxide pyridine complex followed by the treatment with (*R*)-α-methylbenzylisonitrile in the presence of benzoic acid using the Passerini conditions afforded the α-acyloxyamides **7**.[20] The ester and the carbamate groups were removed in a single step by treatment with sodium hydroxide to afford the *β*-amino-α-hydroxyamide **8**. Compound **8** was reacted with the appropriate chloroformates of the P2−P3 alcohols to afford **10b**−**31b**. Oxidation of the hydroxyl with Dess−Martin reagent gave the final products **10**−**31**.

Results and Discussion

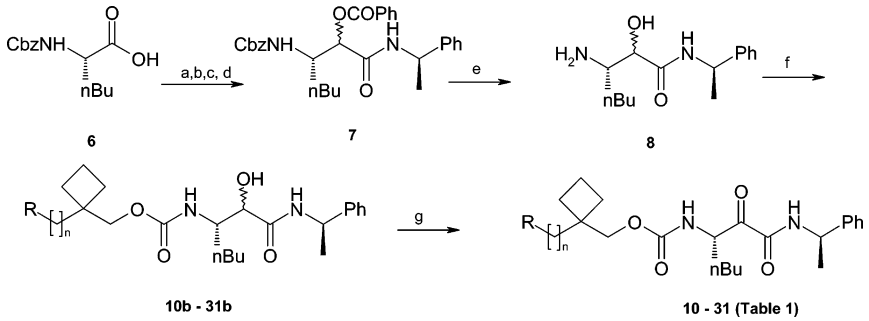
Modifications in the P′ and P2 regions were described in earlier reports,[19a,d] wherein it was found that the P′ substituent afforded potent and selective ketoamide-based inhibitors irrespective of the P2 substituent. In the current work, extension of the side chain on the P2 cyclobutyl moiety was explored with the hope of identifying a preferred P3 substituent that could potentially $\pi-\pi$ stack with ^{67}Tyr in the S3 subsite to enhance the potency, selectivity, and physiochemical properties of this class of inhibitors. A recent report describing the effects of P3 substitution on the potency and selectivity of nonpeptidic cathepsin K inhibitors was recently disclosed by others, indicating that P3 modifications could potentially provide selective cathepsin K inhibitors.[21] In the present work various heteroatom (sulfur, oxygen) as well as carbon-linked P3 substituents were studied (Table 1). The *N*-methylimidazole compound **10**, with one methylene spacer, was found to be a potent inhibitor of cathepsin K (IC_{50} = 61 nM). Increasing the conformational flexibility via extension of the carbon linker to reach deeper into the S3 subsite as in compounds **11** and **12** resulted in a loss in activity. The three-methylene spacer **12**, was reasonably more potent than the two-methylene spacer **11** (IC_{50} = 1900 nM). Addition of a *p*-chlorophenyl group as in compound **13** (IC_{50} = 230 nM) resulted in a 4-fold decrease in activity (**10** vs **13**). Movement of the phenyl substituent closer

Scheme 3. Synthetic Route to Alcohols[a]



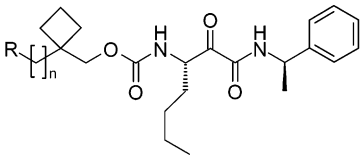
[a] (a) LDA, THF, benzyl 2-bromoethyl ether (**5a**); LDA, THF, benzyl 3-bromopropyl ether (**5b**); (b) LAH, THF, reflux; (c) TBSCl; (d) Pd/C, H_2; (e) PPh_3, $^tBuO_2CNNCO_2{}^tBu$, DCM (X = S); NaH, THF/DMF (1:1), aryl halide (X = O).

Scheme 4. Synthetic Route to Targets **10**−**31**[a]

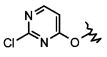
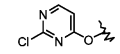
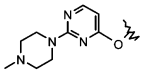
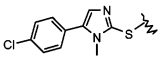
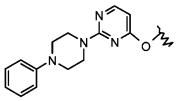
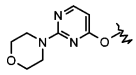
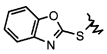
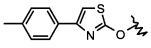
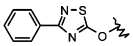
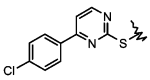
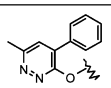
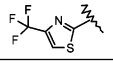
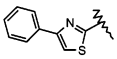


[a] (a) ^{i}PrOCOCl, Et_3N; (b) $NaBH_4$; (c) SO_3−Py; (d) (*R*)-α-methylbenzylisonitrile, PhCOOH; (e) NaOH, EtOH, reflux; (f) chloroformates, Hunig's base, DCM; (g) Dess−Martin, DCM or $(COCl)_2$, DMSO, DCM, −60 °C; NEt_3.

Table 1. Inhibitory Potencies (IC_{50}) vs Human Cathepsin K[a]



10 - 31

Cmpd	Structure (R)	n	K (IC_{50} nM)	Cmpd	Structure (R)	n	K (IC_{50} nM)
10		1	61	**21**		1	85
11		2	>12000	**22**		3	>12000
12		3	1900	**23**		1	54
13		1	230	**24**		1	31
14		1	87	**25**		1	54
15		1	17	**26**		1	98
16		1	51	**27**		1	150
17		1	11	**28**		1	50
18		1	9.5	**29**		1	57
19		1	37	**30**		1	7.9
20		1	260	**31**		1	5.5

[a] The IC_{50} values are the mean of two or three inhibition assays. Individual data points in each experiment were within 3-fold range of each other.

in space to the cyclobutyl P2 group in the hope of improving any putative ^{67}Tyr interaction in the S3 subsite gave compound **14** (IC_{50} = 87 nM) that had equivalent potency. Replacement of the *N*-methyl group with a sulfur as in compound **15** (IC_{50} = 17 nM) afforded a more potent inhibitor (**10** vs **15**). This increase in activity for **15** may result from a lower desolvation cost to remove associated water from the sulfur versus nitrogen analogue **10**. Alternatively, the loss of the methyl substituent may allow a more favorable binding

interaction. The ring-constrained analogue **16** was less active than the thiazole **15** but was an equipotent inhibitor of cathepsin K compared to the starting imidazole **10**. Incorporation of a six-membered heterocycle resulted in an increase in potency relative to the imidazole **10**. The pyrimidine analogue **17** (IC_{50} = 11 nM) was a very potent inhibitor of cathepsin K, supporting the earlier suggestion that the methyl substituent of the imidazole **10** impairs a more favorable binding interaction. Addition of a *p*-chlorophenyl substituent to the six-membered heterocycle also afforded a potent inhibitor **18** (IC_{50} = 9 nM). Interestingly, such a substitution in the five-membered heterocycle resulted in a loss in activity (**10** vs **13** and **17** vs **18**). Replacement of the sulfur linker with an oxygen atom projecting the substituents at an angle closer to a tetrahedral carbon was then studied (**19**−**29**). Although, there was no appreciable loss in activity in the oxygen-linked thiazole analogue **19** (IC_{50} = 37 nM) compared to the sulfur-coupled analogue **15** (IC_{50} = 17 nM), there was a significant drop of 23-fold in the activity for the six-membered pyrimidine analogue (**17** vs **20**). Movement of the oxygen from the 2- to the 4-position of the pyrimidine ring afforded compound **21** (IC_{50} = 85 nM). As before, the increase in conformational flexibility by addition of a three-methylene spacer as in analogue **22** (IC_{50} > 12 000) was found to have a detrimental effect on potency. A similar observation was encountered in the five-membered ring substitution (**10** vs **12**). In an effort to hopefully improve drug properties, the chlorine on the pyrimidine ring was substituted with water-solubilizing groups as in compounds **23**−**25**; these were found to be generally more or less equipotent. Interestingly, a larger group that could go deeper into the S3 subsite as in compound **24** (IC_{50} = 30 nM) was quite well accommodated. Constrained analogue **26** was also found to be quite potent. Movement of the phenyl substituent closer to the cyclobutyl P2 moiety as in compound **29** (IC_{50} = 57 nM) did not affect the potency of the inhibitor. A similar observation was also made for the five-membered heterocycle (**14** and **29**). Addition of a *p*-tolyl group to thiazole **19** gave compound **27** (IC_{50} = 150 nM) with a 4-fold drop in potency (**19** vs **27**). However, the thiadiazole analogue **28** (IC_{50} = 50 nM) resulted in a gain in potency versus **27**. Having gone through the heteroatom-linked P3 substituents, heterocyclic analogues having one methylene spacer were next studied (**30**, **31**). The trifluoromethyl thiazole analogue **30** (IC_{50} = 7.9 nM) was found to be a potent inhibitor of cathepsin K. Replacement of the trifluoromethyl with a phenyl group that would reach deeper in the S3 subsite afforded compound **31** (IC_{50} = 5.5 nM) that was apparently the most potent inhibitor in this P3 inhibitor series. These last two heteroaryl analogues have the P3 moiety one atom closer to the P2 substituent. Their excellent inhibitory potency may arise from reduced entropic cost resulting from decreased conformational flexibility.

Selectivity. Compounds **15** and **31** were chosen from Table 2 as representative examples for selectivity studies. From previous work in these laboratories,[19a] it was known that the P′ and P1 groups used in the present work did not confer complete selectivity over the other cathepsins. Further, various sterically demanding P2 groups were also found not to confer selectivity for the ketoamide-based inhibitors. Since P3 substitution was not explored in those studies,[19a,d] it was gratifying to find that compounds **15** and **31** were fairly selective. Addition of a P3 heterocyclic group as in **15** provided good selectivity over cathepsins B, H, L, and V. Incorporation of a larger P3 group as in **31**, in addition to B, H, and L, also provided some degree of selectivity over cathepsins S and V.

Table 2. Inhibitory Potencies (IC_{50}) vs Human Cathepsins K, L, S, V, H, and B

	IC_{50},[a] nM					
compd	K	L/K*	S/K*	V/K*	H/K*	B/K[b]
15	17	250	4.0	41	>720	390
31	5.5	220	22	20	>230	660

[a] The IC_{50} values are the mean of two or three inhibition assays. Individual data points in each experiment were within 3-fold range of each other. [b] Represents selectivity ratios over the other cathepsins (e.g., L/K = IC_{50}(cathepsin L)/IC_{50}(cathepsin K).

Conclusion

The present work was undertaken to study the spatial requirements of the P3 group desiring to enhance the potency and selectivity of the ketoamide-based inhibitors. Previous work from these laboratories described work on the P′ and P2 substituents that afforded potent and selective cathepsin K inhibitors. This work involved attaching substituents via heteroatoms such as sulfur and oxygen to the cyclobutyl P2 group previously studied. Both five- and six-membered heterocyclic replacements were explored. It was found that the S3 subsite could accommodate a variety of groups without significant loss in potency against cathepsin K. Further, direct attachment of a heterocyclic moiety without heteroatom linkers such as thiazoles also afforded quite potent inhibitors of cathepsin K. These P3 modifications provided inhibitors that were generally selective. The fact that various sterically demanding groups provide some degree of selectivity enhances the utility of these inhibitors for further development in the treatment of osteoporosis.

Experimental Section

Chemistry. General Methods. Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. Unless stated otherwise, reagents were obtained from commercial sources and were used directly. Reactions involving air- or moisture-sensitive reagents were carried out under a nitrogen atmosphere. If not specified, reactions were carried out at ambient temperature. Silica gel (EM Science, 230−400 mesh) was used for chromatographic purification unless otherwise indicated. Anhydrous solvents were obtained from Aldrich (Sure Seal). ^{1}H NMR spectra were recorded on a Varian spectrometer; chemical shifts are reported in parts per million (ppm) relative to TMS. The following abbreviations are used to describe peak patterns when appropriate: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High-performance liquid chromatography (HPLC) was performed on a Beckman 126 with a Beckman 166 UV detector (monitoring at 215 nm) with a Rainin Dynamax-60A column using a gradient consisting of 20/80 A/B to 10/90 A/B over 20 min, where A= 1% aqueous trifluoroacetic acid (TFA), B = 1% TFA in CH_3CN. Elemental analyses, performed by Atlantic Microlab, Inc., Norcross, GA, were within 0.4% of the theoretical values calculated for C, H, and N.

1-{[(1-Methyl-1*H*-imidazol-2-yl)sulfanyl]methyl}-cyclobutyl)methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]-

amino}acetyl)pentylcarbamate (10). [1-(Hydroxymethyl)-cyclobutyl]methanol (2). To a solution of diethyl 1,1-cyclobutanedicarboxylate, (10.0 g, 50.0 mmol) in diethyl ether (200 mL) cooled to 0 °C was added a 1.0 M solution of lithium aluminum hydride in THF (200 mL) over 15 min. The reaction mixture was then warmed to room temperature and left to stir for 3 h. A 20% sodium hydroxide solution (200 mL) was then added followed by addition of diethyl ether. The organic layer was isolated, dried with magnesium sulfate, and concentrated under vacuum to give a yellow oil, which was purified by silica gel chromatography using ethyl acetate as the eluent to afford 5.5 g (95%) of [1-(hydroxymethyl)cyclobutyl]methanol as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73 (s, 4H), 2.81 (br s, 2H), 2.02−1.89 (m, 4H), 1.78 (t, J = 8 Hz, 2H).

(1-{[(1-Methyl-1*H*-imidazol-2-yl)sulfanyl]methyl}-cyclobutyl)methanol (10a). To a solution of [1-(hydroxymethyl)cyclobutyl]methanol (1.0 g, 8.6 mmol) in dichloromethane (20 mL) was added triphenylphosphine (2.48 g, 9.48 mmol) and di-*tert*-butylazodicarboxylate (2.18 g, 9.48 mmol). After the mixture was stirred for 5 min, 1-methyl-2-mercaptoimidazole (1.03 g, 9.05 mmol) was added as a solid. After being stirred for 2 h, the reaction mixture was concentrated under vacuum and the residual was purified using silica gel chromatography, eluting with ethyl acetate/hexane (3:7) to afford 1.3 g (71%) of (1-{[(1-methyl-1*H*-imidazol-2-yl)sulfanyl]-methyl}cyclobutyl)methanol as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.87 (s, 1H), 6.54 (s br 1H), 3.62 (s, 2H), 3.56 (s, 3H), 3.43 (s, 2H), 1.98−1.75 (m, 6H).

(1-{[(1-Methyl-1*H*-imidazol-2-yl)sulfanyl]methyl}-cyclobutyl)methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate (10b). To a solution of (1-{[(1-methyl-1*H*-imidazol-2-yl)sulfanyl]methyl}-cyclobutyl)methanol (0.132 g, 0.625 mmol) in dichloromethane (2 mL) cooled to 0 °C was added a 1.0 M solution of phosgene in toluene (0.94 mL, 1.41 mmol), and the contents were stirred for 16 h. The reaction mixture was concentrated, and the residual was dissolved in THF (3 mL) and added to a 0 °C solution of (3*S*)-3-amino-2-hydroxy-*N*-[(1*R*)-1-phenylethyl]heptanamide (0.165 g, 0.63 mmol) and *N*,*N*-diisopropylethylamine (0.325 mL, 1.89 mmol) in THF (2 mL). After the mixture was stirred for 6 h, ethyl acetate (30 mL) and saturated sodium chloride (20 mL) were added. The organic phase was isolated, dried using magnesium sulfate, and concentrated under vacuum to afford the crude product, which was purified by silica gel chromatography using ethyl acetate (100%) as the eluent to afford 0.220 g (70%) of (1-{[(1-methyl-1*H*-imidazol-2-yl)sulfanyl]methyl}cyclobutyl)methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63−7.52 (m, 1H), 7.41 (m, 1H), 7.39−7.15 (m, 5H), 6.91, 6.98 (2s, 1H), 6.03 (s br, 1H), 5.69 (m, 1H), 5.19−5.11 (m, 1H), 4.18−3.95 (m, 4H), 3.61, 3.63 (2s, 2H), 3.28 (m, 2H), 2.21−1.61 (m, 10H), 1.60−1.16 (m, 5H), 0.90 (m, 3H). LC−MS *m*/*z* 503 (M + H).

(1-{[(1-Methyl-1*H*-imidazol-2-yl)sulfanyl]methyl}-cyclobutyl)methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]-amino}acetyl)pentylcarbamate (10). To a solution of (1-{[(1-methyl-1*H*-imidazol-2-yl)sulfanyl]methyl}cyclobutyl)-methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}-ethyl)pentylcarbamate (0.182 g, 0.364 mmol) in dichloromethane (3 mL) cooled to −60 °C was added oxalyl chloride (0.079 mL, 0.91 mmol) and DMSO (0.129 mL, 1.82 mmol), followed by triethylamine (0.204 mL, 1.45 mmol). After being stirred for 15 min, the reaction mixture was warmed to room temperature and applied directly to a silica gel column using ethyl acetate (100%) as the eluent to afford 0.052 g (29%) of (1-{[(1-methyl-1*H*-imidazol-2-yl)sulfanyl]methyl}cyclobutyl)-methyl (1*S*)-1-(oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentyl-carbamate as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.30 (m, 6H), 7.17 (d, J = 8.1 Hz, 1H), 6.98 (s, 1H), 5.41 (m, 1H), 5.23−5.11 (m, 2H), 4.16 (s, 2H), 3.58 (s, 3H), 3.36 (s, 2H), 2.07−1.89 (m, 6H), 1.48−1.16 (m, 6H), 1.56 (d, J = 6.9 Hz, 3H), 0.89 (t, J = 6.9 Hz, 3H). Anal. C, H, N

(1-{2-[(1-Methyl-1*H*-imidazol-2-yl)sulfanyl]ethyl}-cyclobutyl)methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]-amino}acetyl)pentylcarbamate (11). {1-[2-(Benzyloxy)-ethyl]cyclobutyl}methanol (5a). A solution of ethyl cyclobutanecarboxylate (3.0 g, 23 mmol) in THF (10 mL) was added to a −78 °C solution of LDA (25.74 mmol) in 45 mL of THF. The reaction mixture was warmed to 0 °C (15 min) and then cooled to −78 °C, followed by the addition of benzyl 2-bromoethyl ether (3.64 mL, 25.74 mmol) in THF (10 mL). The reaction mixture was gradually warmed to room temperature over 16 h, and then the reaction was quenched with saturated ammonium chloride (20 mL). The reaction mixture was concentrated, and ethyl acetate was added. The organic layer was isolated, dried with magnesium sulfate, and concentrated under vacuum to afford an oil, which was purified by silica gel chromatography using ethyl acetate/hexane (1:4) as the eluent to afford 4.3 g (70%) of ethyl 1-[2-(benzyloxy)-ethyl]cyclobutanecarboxylate as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.22 (m, 5H), 4.01 (q, J = 7.1 Hz, 2H), 4.40 (s, 2H), 2.4 (t, J = 6.7 Hz, 2H), 1.92−1.84 (m, 8H), 1.14 (t, J = 7.1 Hz, 3H). GC−MS *m*/*z* 263 (M + H).

To a solution of ethyl 1-[2-(benzyloxy)ethyl]cyclobutanecarboxylate (2.0 g, 7.63 mmol) obtained from the above procedure in diethyl ether (20 mL) at 0 °C was added a 1.0 M solution of lithium aluminum hydride in THF, 15.9 mL (15.9 mmol), and the contents were stirred for 2 h. The reaction was quenched with 20 mL of 20% sodium hydroxide solution. After filtration, the organic phase was isolated, dried with magnesium sulfate, and concentrated under vacuum to afford 1.6 g (95%) of {1-[2-(benzyloxy)ethyl]cyclobutyl}methanol as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.30 (m, 5H), 4.54 (s, 2H), 3.55 (t, J = 5.9 Hz, 2H), 2.03−1.83 (m, 10H).

2-[1-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)cyclobutyl]-ethanol (6a). To a solution of {1-[2-(benzyloxy)ethyl]cyclobutyl}-methanol (1.6 g, 7.27 mmol) in dichloromethane (16 mL) was added *tert*-butyldimethylsilyl chloride (1.20 g, 7.99 mmol) and imidazole (0.98 g, 14.54 mmol), and the contents were stirred for 16 h. Saturated ammonium chloride was added, and the layers were separated. The organic layer was dried with magnesium sulfate and concentrated under vacuum. To the crude silyl alcohol was added methanol (20 mL) and 10% palladium on carbon (0.24 g). The reaction mixture was stirred in an atmosphere of hydrogen for 16 h. The contents were filtered over Celite, and the filtrate was concentrated under vacuum to afford 2-[1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-cyclobutyl]ethanol as a colorless oil, 1.71 g (97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.57 (s, 2H), 3.55 (t, J = 5.7 Hz, 2H), 1.87−1.59 (m, 8H), 0.87 (s, 9H), 0.05 (s, 6H).

(1-{2-[(1-Methyl-1*H*-imidazol-2-yl)sulfanyl]ethyl}-cyclobutyl)methanol (11a). 1-Methyl-1*H*-imidazole-2-thiol were prepared using the same experimental procedure as in example **10a** to afford 2-({2-[1-({[*tert*-butyl(dimethyl)silyl]oxy}-methyl)cyclobutyl]ethyl}sulfanyl)-1-methyl-1*H*-imidazole. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (s, 1H), 7.01 (s, 1H), 3.58 (s, 3H), 3.43 (s, 2H), 1.85−1.73 (m, 6H), 2.91 (t, J = 5.7 Hz, 2H), 1.48 (s, 9H), 1.21 (t, J = 4.4 Hz, 2H), 0.04 (s, 6H). GC−MS *m*/*z* 341 (M + H).

To 2-({2-[1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)cyclobutyl]-ethyl}sulfanyl)-1-methyl-1*H*-imidazole (1.39 g, 4.1 mmol) in THF (10 mL) obtained in the above procedure was added a 1.0 M solution of TBAF in THF (4.92 mL, 5.33 mmol), and the contents were stirred for 16 h. The reaction mixture was concentrated, and the residual was poured directly onto a column of silica gel using ethyl acetate/hexane as the eluent to afford 0.57 g (62%) of (1-{2-[(1-methyl-1*H*-imidazol-2-yl)-sulfanyl]ethyl}cyclobutyl)methanol as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.82 (s, 1H), 5.30 (s br, 1H), 3.66 (s, 2H), 3.47 (s, 3H), 2.94 (m, 2H),1.99−1.64 (m, 8H).

(1-{2-[(1-Methyl-1*H*-imidazol-2-yl)sulfanyl]ethyl}-cyclobutyl)methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate (11b). The title compound was prepared using the same experimental procedure as in example **10b** from (1-{2-[(1-methyl-1*H*-imidazol-2-yl)sulfanyl]ethyl}cyclobutyl)methanol as the alcohol com-

ponent and (3*S*)-3-amino-2-hydroxy-*N*-[(1*R*)-1-phenylethyl]-heptanamide as the amino alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (m, 1H), 7.35−7.23 (m, 5H), 7.02 (s, 1H), 6.93, 6.90 (2s, 1H), 5.67 (m, 1H), 5.16 (m, 2H), 4.22−3.74 (m, 4H), 3.65 (s, 3H), 2.95 (m, 2H), 2.03−1.79 (m, 8H), 1.49 (d, J = 7.0 Hz, 3H), 1.36−1.27 (m, 6H), 0.91 (m, 3H). LC−MS *m*/*z* 517 (M + H).

(1-{2-[(1-Methyl-1*H*-imidazol-2-yl)sulfanyl]ethyl}-cyclobutyl)methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]-amino}acetyl)pentylcarbamate (11). To a solution of (1-{2-[(1-methyl-1*H*-imidazol-2-yl)sulfanyl]ethyl}cyclobutyl)-methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}-ethyl)pentylcarbamate **(11b)** (0.143 g, 0.27 mmol) in dichloromethane (2.0 mL) was added sodium bicarbonate (0.031 g, 0.375 mmol) followed by the addition of Dess−Martin periodinane (0.137 g, 0.32 mmol). The reaction mixture was stirred for 15 min and poured directly onto a silica gel column using ethyl acetate/hexane (3:7) as the eluent to afford 0.086 g (63%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.33 (m, 6H), 7.30 (s, 1H), 7.14 (s, 1H), 5.11 (d, J = 7.3 Hz, 1H), 5.09 (m, 2H), 4.07 (s, 2H), 3.76 (s, 3H), 3.02 (s, 2H), 2.03−1.85 (m, 10H), 1.56 (d, J = 6.8 Hz, 3H), 1.52−1.27 (m, 4H), 0.87 (t, J = 6.8 Hz, 3H). Anal. C, H, N

(1-{3-[(1-Methyl-1*H*-imidazol-2-yl)sulfanyl]propyl}-cyclobutyl)methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]-amino}acetyl)pentylcarbamate (12). Ethyl 1-[3-(Benzyl-oxy)propyl]cyclobutanecarboxylate (5b). The title compound was prepared using the same experimental procedure as in example **5a** using benzyl 3- bromopropyl ether as the electrophile. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.30 (m, 5H), 4.53 (s, 2H), 4.14 (t, J = 7.1 Hz, 2H), 3.48 (t, J = 6.4 Hz, 2H), 2.49−2.43 (m, 2H), 2.08−1.72 (m, 6H), 1.53 (m, 2H),1.27 (t, J = 7.1 Hz, 3H).

Preparation of 3-[1-({[*tert*-Butyl(dimethyl)silyl]oxy}-methyl)cyclobutyl]-1-propanol (6b). The title compound was prepared from ethyl 1-[3-(benzyloxy)propyl]cyclobutanecarboxylate using the same experimental procedure as in example **6a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (s, 2H), 3.46 (s, 2H), 1.84−1.41 (m, 11H), 0.88 (s, 9H), 0.03 (s, 6H).

Preparation of (1-{3-[(1-Methyl-1*H*-imidazol-2-yl)sulfanyl]propyl}cyclobutyl)methanol (12a). The title compound was prepared from 3-[1-({[*tert*-butyl(dimethyl)silyl]oxy}-methyl)cyclobutyl]-1-propanol using the same experimental procedure as in example **11a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 1H), 7.07 (s, 1H), 3.91 (s br, 1H), 3.69 (s, 3H), 3.55 (s, 2H), 2.91 (t, J = 6.6 Hz, 2H), 1.91−1.70 (m, 8H),1.58−1.46 (m, 2H).

Preparation of (1-{3-[(1-Methyl-1*H*-imidazol-2-yl)sulfanyl]propyl}cyclobutyl)methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate (12b). The title compound was prepared using the same experimental procedure as in example **11b** from (1-{3-[(1-methyl-1*H*-imidazol-2-yl)sulfanyl]propyl}cyclobutyl)-methanol as the alcohol component and (3*S*)-3-amino-2-hydroxy-*N*-[(1*R*)-1-phenylethyl]heptanamide as the amino alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.05 (m, 6H), 6.99 (s, 1H), 6.91 (s, 1H), 5.64 (m, 1H), 5.12 (m, 1H), 4.14, (m, 4H), 3.95 (m, 1H), 3.62, 3.64 (2s, 3H), 3.25 (m, 2H), 2.08−1.71 (m, 12H), 1.49 (d, J = 6.8 Hz, 3H), 1.41−1.32 (m, 4H), 1.29 (m, 3H). LC−MS *m*/*z* 531 (M + H).

Preparation of (1-{3-[(1-Methyl-1*H*-imidazol-2-yl)sulfanyl]propyl}cyclobutyl)methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcarbamate (12). The title compound was prepared using the same experimental procedure as in example **11** using (1-{3-[(1-methyl-1*H*-imidazol-2-yl)sulfanyl]propyl}cyclobutyl)methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate as the alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12−7.45 (m, 7H), 6.99 (s, 1H), 5.56−5.33 (m, 2H), 5.16 (m, 1H), 4.01 (s, 2H), 3.67 (s, 3H), 3.01 (s, 2H), 2.08−1.89 (m, 7H), 1.85−1.61 (m, 12H), 0.87 (m, 3H). Anal. C, H, N

[1-({[5-(4-Chlorophenyl)-1-methyl-1*H*-imidazol-2-yl]-sulfanyl}methyl)cyclobutyl]methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcarbamate (13). [1-({[5-(4-Chlorophenyl)-1-methyl-1*H*-imidazol-2-yl]sulfanyl}-methyl)cyclobutyl]methanol (13a). The title compound was prepared using the same experimental procedure as in example **10a** from [1-(hydroxymethyl)cyclobutyl]methanol and 5-(4-chlorophenyl)-1-methyl-1*H*-imidazole-2-thiol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.25 (m, 5H), 3.62 (s, 2H), 3.49 (s, 3H), 3.46 (s, 2H), 2.04−1.63 (m, 6H),

[1-({[5-(4-Chlorophenyl)-1-methyl-1*H*-imidazol-2-yl]-sulfanyl}methyl)cyclobutyl]methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate (13b). The title compound was prepared using the same experimental procedure as in example **10b** from [1-({[5-(4-chlorophenyl)-1-methyl-1*H*-imidazol-2-yl]sulfanyl}methyl)-cyclobutyl]methanol as the alcohol component and (3*S*)-3-amino-2-hydroxy-*N*-[(1*R*)-1-phenylethyl]heptanamide as the amino alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.20 (m, 10 H), 7.02 (s, 1H), 5.33 (d, J = 8.2 Hz, 1H), 5.12−5.05 (m, 2H), 4.30 (s, 1H), 4.17−4.04 (m, 3H), 3.89 (m, 2H), 3.55 (s, 2H), 3.32, 3.38 (2s, 2H), 2.03−1.88 (m, 6H), 1.55−1.22 (m, 9H), 0.82 (m, 3H). LC−MS *m*/*z* 613 (M + H).

[1-({[5-(4-Chlorophenyl)-1-methyl-1*H*-imidazol-2-yl]-sulfanyl}methyl)cyclobutyl]methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcarbamate (13). The title compound was prepared using the same experimental procedure as in example **11** from [1-({[5-(4-chlorophenyl)-1-methyl-1*H*-imidazol-2-yl]sulfanyl}methyl)cyclobutyl]methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentyl-carbamate as the alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.11 (m, 11H), 7.08 (s, 1H), 5.40 (m, 1H), 5.09 (m, 2H), 4.12 (s, 2H), 3.54 (s, 3H), 3.45 (s, 2H), 2.08−1.90 (m, 6H), 1.55−1.29 (m, 8H), 0.87 (t, J = 6.7 Hz, 3H). Anal. C, H, N

(1-{[(1-Phenyl-1*H*-imidazol-2-yl)sulfanyl]methyl}-cyclobutyl)methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]-amino}acetyl)pentylcarbamate (14). (1-{[(1-Phenyl-1*H*-imidazol-2-yl)sulfanyl]methyl}cyclobutyl)methanol (14a). The title compound was prepared using the same experimental procedure as in example **10a** using [1-(hydroxymethyl)cyclobutyl]methanol and 1-phenyl-1*H*-imidazole-2-thiol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.07 (m, 7H), 3.63 (s, 2H), 3.40 (s, 2H), 1.93−1.69 (m, 6H). GC−MS *m*/*z* 275 (M + H).

(1-{[(1-Phenyl-1*H*-imidazol-2-yl)sulfanyl]methyl}-cyclobutyl)methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate (14b). The title compound was prepared using the same experimental procedure as in example **20b** using (1-{[(1-phenyl-1*H*-imidazol-2-yl)sulfanyl]methyl}cyclobutyl)methanol as the alcohol component and (3*S*)-3-amino-2-hydroxy-*N*-[(1*R*)-1-phenylethyl]-heptanamide as the amino alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.06 (m, 13 H), 5.55 (s br, 1H), 5.20−5.09 (m, 2H), 4.10 (s br, 1H), 4.02−3.87 (m, 3H), 3.30 (s, 2H), 2.04−1.79 (m, 6H), 1.50−1.25 (m, 9H), 0.79 (m, 3H). LC−MS *m*/*z* 565 (M + H).

(1-{[(1-Phenyl-1*H*-imidazol-2-yl)sulfanyl]methyl}-cyclobutyl)methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]-amino}acetyl)pentylcarbamate (14). The title compound was prepared using the same experimental procedure as in example **11** using (1-{[(1-phenyl-1*H*-imidazol-2-yl)sulfanyl]-methyl}cyclobutyl)methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate as the starting alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.06 (m, 13 H), 5.46 (m, 1H), 5.15−5.05 (m, 2H), 4.0 (s, 2H), 3.47 (s, 2H), 2.08−1.65 (m, 6H), 1.52 (d, J = 6.7 Hz, 3H), 1.39−0.92 (m, 6H), 0.85 (t, J = 7.0 Hz, 3H). Anal. C, H, N

{1-[(1,3-Thiazol-2-ylthio)methyl]cyclobutyl}methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcarbamate (15). {1-[(1,3-Thiazol-2-ylthio)methyl]cyclobutyl}-methanol (15a). The title compound was prepared using the same experimental procedure as in example **10a** using [1-(hydroxymethyl)cyclobutyl]methanol and 1,3-thiazole-2-thiol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 3.3 Hz, 1H), 7.56 (d, J = 3.2 Hz, 1H), 3.39 (s, 2H), 3.34 (s, 2H), 1.60−1.41 (m, 6H). GC−MS *m*/*z* 216 (M + H).

{1-[(1,3-Thiazol-2-ylthio)methyl]cyclobutyl}methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)-pentylcarbamate (15b). The title compound was prepared using the same experimental procedure as in example **10b** using {1-[(1,3-thiazol-2-ylthio)methyl]cyclobutyl}methanol as the alcohol component and (3*S*)-3-amino-2-hydroxy-*N*-[(1*R*)-1-phenylethyl]heptanamide as the amino alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 3.3 Hz, 1H), 7.35−7.20 (m, 5H), 5.64 (m, 1H), 5.14−5.00 (m, 3H), 4.21−4.17 (m, 6H), 3.87 (m, 1H), 1.88 (m, 1H), 1.51 (d, J = 6.7 Hz, 3H), 1.41−1.1 (m, 11 H), 0.90 (m, 3H). LC−MS *m*/*z* 506 (M + H).

{1-[(1,3-Thiazol-2-ylthio)methyl]cyclobutyl}methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcarbamate (15). The title compound was prepared using the same experimental procedure as in example **11** using 1-[(1,3-thiazol-2-ylthio)methyl]cyclobutyl}methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate as the starting alcohol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.26 (m, 7H), 5.32−5.09 (m, 4H), 4.18 (s, 2H), 3.56 (s, 2H), 1.99−1.63 (m, 8H), 1.56 (d, J = 6.3 Hz, 3H), 1.34−1.22 (m, 4 H), 0.89 (s br, 3H). Anal. C, H, N.

{1-[(1,3-Benzoxazol-2-ylsulfanyl)methyl]cyclobutyl}-methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)-pentylcarbamate (16). {1-[(1,3-Benzoxazol-2-ylsulfanyl)-methyl]cyclobutyl}methanol (16a). The title compound was prepared using the same experimental procedure as in example **10a** using {1-[(1,3-benzoxazol-2-ylsulfanyl)methyl]-cyclobutyl}methanol as the thiol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.25 (m, 4H), 3.61 (s, 2H), 3.46 (s br, 1H), 3.35 (s, 2H), 1.54−1.31 (m, 6H). GC−MS *m*/*z* 250 (M + H).

{1-[(1,3-Benzoxazol-2-ylsulfanyl)methyl]cyclobutyl}-methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]-amino}ethyl)pentylcarbamate (16b). The title compound was prepared using the same experimental procedure as in example **10b** with {1-[(1,3-benzoxazol-2-ylsulfanyl)methyl]-cyclobutyl}methanol as the alcohol component and (3*S*)-3-amino-2-hydroxy-*N*-[(1*R*)-1-phenylethyl]heptanamide as the amino alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 7.3 Hz, 1H), 7.45 (d, J = 7.4 Hz, 1H), 7.44−7.24 (m, 7H), 7.16 (d, J = 7.8 Hz, 1H), 5.62 (m, 1H), 5.14 (m, 1H), 4.80 (s br, 1H), 4.36−4.09 (m, 3H), 3.87 (m, 1H), 3.63 (s, 2H), 2.02−1.68 (m, 8H), 1.63−1.26 (m, 7H), 0.92 (m, 3H). LC−MS *m*/*z* 540 (M + H).

Preparation of {1-[(1,3-Benzoxazol-2-ylsulfanyl)methyl]-cyclobutyl}methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]-amino}acetyl)pentylcarbamate (16). The title compound was prepared using the same experimental procedure as in example **11** with {1-[(1,3-benzoxazol-2-ylsulfanyl)methyl]-cyclobutyl}methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate as the starting alcohol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 7.3 Hz, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.31−7.07 (m, 7H), 5.26 (d, J = 7.5 Hz, 1H), 5.07−4.98 (m, 3H), 4.12 (s, 2H), 3.58 (s, 2H), 2.03−1.81 (m, 6H), 1.48 (d, J = 6.4 Hz, 3H), 1.42−1.23 (m, 6H), 0.80 (t, J = 6.3 Hz, 3H). Anal. C, H, N.

{1-[(2-Pyrimidinylsulfanyl)methyl]cyclobutyl}-methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)-pentylcarbamate (17). {1-[(2-Pyrimidinylsulfanyl)methyl]-cyclobutyl}methanol (17a). {1-[(2-Pyrimidinylsulfanyl)-methyl]cyclobutyl}methanol was prepared using the same experimental procedure as in example **10a** using 2-mercaptopyrimidine instead of 1-methyl-2-mercaptoimidazole as the thiol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 5 Hz, 2H), 7.01 (t, J = 4.9 Hz, 1H), 4.39 (t, J = 7.3 Hz, 1H), 3.55 (d, J = 7.1 Hz, 2H), 3.43 (s, 2H), 2.06−1.82 (m, 6H). GC−MS *m*/*z* 211 (M + H).

{1-[(2-Pyrimidinylsulfanyl)methyl]cyclobutyl}-methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]-amino}ethyl)pentylcarbamate (17b). The title compound was prepared using the same experimental procedure as in example **20b** with {1-[(2-pyrimidinylsulfanyl)methyl]cyclobutyl}-methanol as the alcohol component and (3*S*)-3-amino-2-hydroxy-*N*-[(1*R*)-1-phenylethyl]heptanamide as the amino alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 4.8 Hz, 2H), 7.37−7.25 (m 5H), 7.15 (d, J = 7.8 Hz, 1H), 6.95 (t, J = 4.8 Hz, 1H), 5.56 (d, J = 8.5 Hz, 1H), 5.09 (m, 1H), 4.96 (d, J = 5.5 Hz, 1H), 4.20−4.06 (m, 3H), 3.86 (m, 1H), 3.49 (s, 2H), 2.07−1.73 (m, 6H), 1.83−1.61 (m, 2H), 1.48 (d, J = 7 Hz, 3H), 1.37−1.26 (m, 4H), 0.92 (m, 3H). LC−MS *m*/*z* 501 (M + H).

{1-[(2-Pyrimidinylsulfanyl)methyl]cyclobutyl}-methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)-pentylcarbamate (17). The title compound was prepared using the same experimental procedure as in example **11** with {1-[(2-pyrimidinylsulfanyl)methyl]cyclobutyl}methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate as the starting alcohol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J = 4.6 Hz, 2H), 7.31−7.08 (m, 6H), 6.88 (t, J = 4.7 Hz, 1H), 5.25 (d, J = 7.2 Hz, 1H), 4.89−5.20 (m, 2H), 4.08 (s, 2H), 3.43 (s, 2H), 2.03−1.80 (m, 6H), 1.79−1.42 (m, 5H), 1.41−1.25 (m, 4H), 0.81 (s br, 3H). Anal. C, H, N

[1-({[4-(4-Chlorophenyl)-2-pyrimidinyl]sulfanyl}-methyl)cyclobutyl]methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenyl-ethyl]amino}acetyl)pentylcarbamate (18). [1-({[4-(4-Chlo-rophenyl)-2-pyrimidinyl]sulfanyl}methyl)cyclobutyl]-methanol (18a). The title compound was prepared using the same experimental procedure as in example **10a** from [1-(hydroxymethyl)cyclobutyl]methanol and 4-(4-chlorophenyl)-2-pyrimidinethiol. ^{1}H NMR (300 MHz, $CDCl_3$) 8.49 (d, J = 5.4 Hz, 1H), 7.95 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 5.5 Hz, 1H), 4.18 (t, J = 7.1 Hz, 1H), 3.54 (d, J = 7.0 Hz, 2H), 3.47 (s, 2H), 2.03−1.69 (m, 6H), GC−MS *m*/*z* 320 (M + H).

[1-({[4-(4-Chlorophenyl)-2-pyrimidinyl]sulfanyl}-methyl)cyclobutyl]methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate (18b). The title compound was prepared using the same experimental procedure as in example **10b** from [1-({[4-(4-chlorophenyl)-2-pyrimidinyl]sulfanyl}methyl) cyclobutyl] methanol as the alcohol component and (3S)-3-amino-2-hydroxy-N-[(1R)-1-phenylethyl] heptanamide as the amino alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) 8.50 (d, J = 5.0 Hz, 1H), 7.99 (d, J = 7.5 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.30−7.15 (m, 7H), 5.10−4.93 (m, 3H), 4.15 (m, 3H), 3.80 (m, 1H), 3.52 (s, 2H), 2.04−1.91 (m, 6H), 1.82−1.23 (m, 9H), 0.82 (m, 3H). LC−MS *m*/*z* 611 (M + H).

[1-({[4-(4-Chlorophenyl)-2-pyrimidinyl]sulfanyl}-methyl)cyclobutyl]methyl(1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]-amino}acetyl)pentylcarbamate (18). The title compound was prepared using the same experimental procedure as in example **23c** from [1-({[4-(4-chlorophenyl)-2-pyrimidinyl]-sulfanyl}methyl) cyclobutyl]methyl (1S)-1-(1-hydroxy-2-oxo-2-{[(1R)-1-phenylethyl]amino}ethyl) pentylcarbamate as the alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) 8.52 (d, J = 5.3 Hz, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.34−7.25 (m, 6H), 7.09 (d, J = 7.3 Hz, 1H), 5.24−5.04 (m, 3H), 4.17 (s, 2H), 3.55 (s, 2H), 2.03−1.95 (m, 6H), 1.56 (m, 2H), 1.52 (d, J = 6.6 Hz, 3H), 1.38−1.28 (m, 4H), 0.84 (t, J = 6.3 Hz, 3H). Anal. C, H, N

{1-[(1,3-Thiazol-2-yloxy)methyl]cyclobutyl}methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcar-bamate (19). {1-[(1,3-Thiazol-2-yloxy)methyl]cyclobutyl}-methanol (19a). To a solution of [1-(hydroxymethyl)cyclobutyl]methanol (0.5 g, 4.31 mmol) in DMF/THF (1:1) (15 mL) was added a 60% dispersion of sodium hydride in oil (0.165 g, 4.31 mmol). After the mixture was stirred for 15 min, 2-bromothiazole (0.71 g, 4.31 mmol) was added and the contents heated at reflux for 3 h. A saturated solution of sodium bicarbonate was added followed by ethyl acetate. The organic phase was isolated, dried with magnesium sulfate, and concentrated under vacuum. The crude product was purified by silica gel chromatography using ethyl acetate/hexane (2:3) as the eluent to afford 0.340 g (40%) of {1-[(1,3-thiazol-2-yloxy)-methyl]cyclobutyl}methanol as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, J = 3.8 Hz, 1H), 6.64 (d, J = 3.9 Hz, 1H), 4.51 (s, 2H), 3.59 (s, 2H), 2.03−1.72 (m, 6H). GC−MS *m*/*z* 200 (M + H).

{1-[(1,3-Thiazol-2-yloxy)methyl]cyclobutyl}methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)-pentylcarbamate (19b). The title compound was prepared using the same experimental procedure as in example **10b** using {1-[(1,3-thiazol-2-yloxy)methyl]cyclobutyl}methanol as the alcohol component and (3*S*)-3-amino-2-hydroxy-*N*-[(1*R*)-1-phenylethyl]heptanamide as the amino alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J = 5.8 Hz, 1H), 7.34−7.26 (m, 5H), 6.63 (d, J = 5.7 Hz, 1H), 5.44 (m, 1H), 5.07 (m, 1H), 4.94 (d, J = 7.6 Hz, 1H), 4.54 (d, J = 4.5 Hz, 1H), 4.37−4.18 (m, 5H), 3.74 (m, 1H), 1.47 (d, J = 6.9 Hz, 3H), 1.42−0.91 (m, 12 H), 0.81 (m, 3H). LC−MS *m*/*z* 490 (M + H).

{1-[(1,3-Thiazol-2-yloxy)methyl]cyclobutyl}methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcarbamate (19). The title compound was prepared using the same experimental procedure as in example **11** using {1-[(1,3-thiazol-2-yloxy)methyl]cyclobutyl}methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate as the starting alcohol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.26 (m, 6H), 7.11 (s, 1H), 6.67 (s, 1H), 5.27−5.08 (m, 3H), 4.40 (s, 2H), 4.18 (s, 2H), 1.98−1.81 (m, 6H), 1.65 (m, 2H), 1.53 (d, J = 6 Hz, 3H), 1.42−1.21 (m, 4 H), 0.85 (s br, 3H). Anal. C, H, N

{1-[(2-Pyrimidinyloxy)methyl]cyclobutyl}methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcarbamate (20). {1-[(2-Pyrimidinyloxy)methyl]cyclobutyl}-methanol (20a). The title compound was prepared using the same experimental procedure as in example **19a** from [1-(hydroxymethyl)cyclobutyl]methanol and 2-chloropyrimidine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50−8.47 (m, 2H), 6.95−6.89 (m, 1H), 4.48 (s, 2H), 3.63 (d, J = 5.9 Hz, 2H), 3.02 (t, J = 6.2 Hz, 1H), 2.01−1.78 (m, 6H). GC−MS *m*/*z* 195 (M + H).

{1-[(2-Pyrimidinyloxy)methyl]cyclobutyl}methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)-pentylcarbamate (20b). The title compound was prepared using the same experimental procedure as in example **10b** from {1-[(2-pyrimidinyloxy)methyl]cyclobutyl}methanol as the alcohol component and (3*S*)-3-amino-2-hydroxy-*N*-[(1*R*)-1-phenylethyl]heptanamide as the amino alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (m, 2H), 7.26 (m, 6H), 6.92−6.72 (m, 1H), 5.29 (m, 1H), 5.05 (m, 2H), 4.51 (s, 2H), 4.46−3.94 (m, 3H), 3.83 (m, 1H), 2.03−1.80 (m, 8H), 1.48−1.23 (m, 7H), 0.82 (m, 3H). LC−MS *m*/*z* 485 (M + H).

{1-[(2-Pyrimidinyloxy)methyl]cyclobutyl}methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcarbamate (20). The title compound was prepared using the same experimental procedure as in example **11** from {1-[(2-pyrimidinyloxy)methyl]cyclobutyl}methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate as the alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 4.8 Hz, 2H), 7.37 − 7.26 (m, 5H), 7.08 (d, J = 7.4 Hz, 1H), 6.91 (t, J = 4.8 Hz, 1H), 5.25 (d, J = 7.7 Hz, 1H), 5.11−5.04 (m, 2H), 4.35 (s, 2H), 4.24 (s, 2H), 2.0−1.94 (m, 6H), 1.52 (d, J = 6.9 Hz, 3H), 1.36−1.27 (m, 6H), 0.82 (t, J = 6.5 Hz, 3H). Anal. C, H, N

{1-{[(2-Chloro-4-pyrimidinyl)oxy]methyl}cyclobutyl)-methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)-pentylcarbamate (21). (1-{[(2-Chloro-4-pyrimidinyl)oxy]-methyl}cyclobutyl)methanol (21a). To a solution of [1-(hydroxymethyl)cyclobutyl]methanol (1.00 g, 8.62 mmol) in 20 mL THF/DMF (1:1) was added a 60% dispersion of sodium hydride in oil (0.413 g, 8.62 mmol). The reaction mixture was stirred for 15 min, and 2,4-dichloropyrimidine (1.28 g, 8.62 mmol) was added. After being stirred for 2 h, the reaction mixture was concentrated under vacuum and the residue was purified using silica gel chromatography and ethyl acetate/hexane (2:3) as eluent to afford 0.9 g (51%) of (1-{[(2-chloro-4-pyrimidinyl)oxy]methyl}cyclobutyl)methanol as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, J = 5.7 Hz, 1H), 6.69 (d, J = 7 Hz, 1H), 4.51 (s, 2H), 3.67 (s, 2H), 2.35 (s br, 1H), 2.05−1.87 (m, 6H).

(1-{[(2-Chloro-4-pyrimidinyl)oxy]methyl}cyclobutyl)-methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]-amino}ethyl)pentylcarbamate (21b). The title compound was prepared using the same experimental procedure as in example **10b** from (1-{[(2-chloro-4-pyrimidinyl)oxy]methyl}-cyclobutyl)methanol as the alcohol component and (3*S*)-3-amino-2-hydroxy-*N*-[(1*R*)-1-phenylethyl] heptanamide as the amino alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, J = 5.6 Hz, 1H), 7.32−7.10 (m, 6H), 6.67 (d, J = 5.7 Hz, 1H), 5.61−5.53 (m, 1H), 5.13−5.08 (m, 1H), 4.79, 4.89 (2d, J = 5, 5.6 Hz, 1H), 4.36, 4.39 (2s, 2H), 4.38−4.18 (m, 3H), 3.84 (m, 1H), 2.07−1.50 (m, 10 H), 1.47−1.26 (m, 5H), 0.88 (m, 3H). LC−MS *m*/*z* 519 (M + H).

(1-{[(2-Chloro-4-pyrimidinyl)oxy]methyl}cyclobutyl)-methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)-pentylcarbamate (21). The title compound was prepared using the same experimental procedure as in example **11** from (1-{[(2-chloro-4-pyrimidinyl)oxy]methyl}cyclobutyl)methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)-pentylcarbamate as the alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (m, 5.7 Hz, 1H), 7.41−7.29 (m, 5H), 7.13 (d, J = 7.1 Hz, 1H), 6.69 (d, J = 5.6 Hz, 1H), 5.29 (d, J = 7.5 Hz, 1H), 5.18−5.08 (m, 2H), 4.41 (s, 2H), 4.20 (s, 2H), 2.07−1.71 (m, 7H), 1.56 (d, J = 6.8 Hz, 3H), 1.26−1.32 (m, 5H), 0.88 (t, J = 6.5 Hz, 3H). Anal. C, H, N

(1-{3-[(2-Chloro-4-pyrimidinyl)oxy]propyl}cyclobutyl)-methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)-pentylcarbamate (22). (1-{3-[(2-Chloro-4-pyrimidinyl)-oxy]propyl}cyclobutyl)methanol (22a). 3-[1-({[*tert*-Butyl-(dimethyl)silyl]oxy}methyl)cyclobutyl]-1-propanol (**6b**) and 2,4-dichloropyrimidine were reacted using the same experimental procedure as in example **19a** to afford the intermediate 4-{3-[1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)cyclobutyl]propyloxy}-2-chloropyrimidine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J = 5.7 Hz, 1H), 6.59 (d, J = 5.7 Hz, 1H), 4.33 (t, J = 6.4 Hz, 2H), 3.44 (s, 2H), 1.81−1.51 (m, 8H), 1.21 (m, 2H), 0.84 (s, 9H), −0.002 (s, 6H). GC−MS *m*/*z* 371 (M + H).

The above compound was desilylated using the same experimental procedure as in example **11a** to afford (1-{3-[(2-chloro-4-pyrimidinyl)oxy]propyl}cyclobutyl)methanol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, J = 5.6 Hz, 1H), 6.69 (d, J = 5.7 Hz, 1H), 4.43 (t, J = 6.3 Hz, 2H), 3.61 (s, 2H), 1.98−1.46 (m, 10H).

(1-{3-[(2-Chloro-4-pyrimidinyl)oxy]propyl}cyclobutyl)-methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]-amino}ethyl)pentylcarbamate (22b). The title compound was prepared using the same experimental procedure as in example **10b** from (1-{3-[(2-chloro-4-pyrimidinyl)oxy]propyl}-cyclobutyl)methanol as the alcohol component and (3*S*)-3-amino-2-hydroxy-*N*-[(1*R*)-1-phenylethyl]heptanamide as the amino alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 5.6 Hz, 1H), 7.38−7.17 (m, 6H), 6.69 (d, J = 5.7 Hz, 1H), 5.62 (d, J = 8.8 Hz, 1H), 5.33 (m, 1H), 4.98 (d, J = 5.6 Hz, 1H), 4.40 (m, 2H), 4.15−3.86 (m, 3H), 1.89−1.58 (m, 14H), 1.52 (d, J = 7.0 Hz, 3H), 1.39 (m, 2H), 0.92 (m, 3H). LC−MS *m*/*z* 547 (M + H).

(1-{3-[(2-Chloro-4-pyrimidinyl)oxy]propyl}cyclobutyl)-methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)-pentylcarbamate (22). The title compound was prepared using the same experimental procedure as in example **11** using (1-{3-[(2-chloro-4-pyrimidinyl)oxy]propyl}cyclobutyl)methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)-pentylcarbamate as the alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, J = 5.7 Hz, 1H), 7.41−7.29 (m, 5H), 7.17 (d, J = 7.9 Hz, 1H), 6.70 (d, J = 5.7 Hz, 1H), 5.32 (d, J = 8.2 Hz, 1H), 5.19 (m, 2H), 4.42 (t, J = 6.2 Hz, 1H), 4.08 (s, 2H), 1.94−1.61 (m, 15H), 1.59 (d, J = 7.1 Hz, 3H), 1.37 (m, 2H), 0.92 (t, J = 6.7 Hz, 3H). Anal. C, H, N

[1-({[2-(4-Methyl-1-piperazinyl)-4-pyrimidinyl]oxy}-methyl)cyclobutyl]methyl (1S)-1-(Oxo{[(1*R*)-1-phenyl-ethyl]amino}acetyl)pentylcarbamate (23). [1-({[2-(4-Meth-yl-1-piperazinyl)-4-pyrimidinyl]oxy}methyl)cyclobutyl]-methanol (23a). To a solution of (1-{[(2-chloro-4-pyrimidinyl)-oxy]methyl}cyclobutyl)methanol (**21a**) (0.5 g, 2.19 mmol) in DMF (5.0 mL) was added *N*-methylpiperidine (0.36 mL, 3.28 mmol), and the contents heated at 90 °C for 3 h. The reaction mixture was concentrated under vacuum and taken directly

to the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 5.6 Hz, 1H), 5.97 (d, J = 5.5 Hz, 1H), 4.41 (s, 2H), 3.81 (t, J = 5.1 Hz, 4H), 3.63 (s, 2H), 2.45 (t, J = 5.1 Hz, 4H), 2.35 (s, 3H), 1.97−1.91 (m, 6H).

[1-({[2-(4-Methyl-1-piperazinyl)-4-pyrimidinyl]oxy}methyl)cyclobutyl]methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate (23b). The title compound was prepared using the same experimental procedure as in example **10b** starting with [1-({[2-(4-methyl-1-piperazinyl)-4-pyrimidinyl]oxy}methyl)cyclobutyl]methanol as the alcohol component and (3*S*)-3-amino-2-hydroxy-*N*-[(1*R*)-1-phenylethyl]heptanamide as the amino alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 5.6 Hz, 1H), 7.34−7.20 (m, 5H), 5.97 (d, J = 5.6 Hz, 1H), 5.63 (d, J = 8.0 Hz, 1H), 5.06 (m, 1H), 4.26 (s, 2H), 4.21−4.07 (m, 3H), 3.83 (m, 4H), 2.49 (m, 4H), 2.35 (s, 3H), 2.06−1.94 (m, 6H), 1.70−1.22 (m, 12 H), 0.89 (m, 3H). LC−MS m/z 599 (M + H).

[1-({[2-(4-Methyl-1-piperazinyl)-4-pyrimidinyl]oxy}methyl)cyclobutyl]methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcarbamate (23). The title compound was prepared using the same experimental procedure as in example **11** using [1-({2-(4-methyl-1-piperazinyl)-4-pyrimidinyl]oxy}methyl)cyclobutyl]methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate as the starting material. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (m, 1H), 8.10 (m, 1H), 7.36−7.33 (m, 5H), 7.26 (d, J = 7.2 Hz, 1H), 6.07 (d, J = 4.6 Hz, 1H), 5.01 (m, 1H), 4.20 (m, 1H), 4.07 (m, 1H), 3.76 (m, 4H), 2.43 (m, 4H), 2.28 (s, 3H), 2.15−1.90 (m, 6H), 1.49 (d, J = 8.1 Hz, 3H), 1.38−1.11 (m, 9H), 0.84 (t, J = 6.8 Hz, 3H). Anal. C, H, N.

[1-({[2-(4-Phenyl-1-piperazinyl)-4-pyrimidinyl]oxy}methyl)cyclobutyl]methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcarbamate (24). [1-({[2-(4-Phenyl-1-piperazinyl)-4-pyrimidinyl]oxy}methyl)cyclobutyl]methanol (24a). The title compound was prepared from (1-{[(2-chloro-4-pyrimidinyl)oxy]methyl}cyclobutyl)methanol using the same experimental procedure as in example **23a** using 1-phenylpiperazine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 5.6 Hz, 1H), 7.21 (m, 2H), 6.92−6.82 (m, 3H), 5.93 (d, J = 5.6 Hz, 1H), 4.37 (s, 2H), 3.90 (m, 4H), 3.58 (s, 2H), 3.18 (m, 4H), 2.54 (s br, 1H), 1.91−1.61 (m, 6H).

[1-({[2-(4-Phenyl-1-piperazinyl)-4-pyrimidinyl]oxy}methyl)cyclobutyl]methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate (24b). The title compound was prepared using the same experimental procedure as in example **10b** using [1-({[2-(4-phenyl-1-piperazinyl)-4-pyrimidinyl]oxy}methyl)cyclobutyl]methanol as the alcohol component and (3*S*)-3-amino-2-hydroxy-*N*-[(1*R*)-1-phenylethyl]heptanamide as the amino alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 5.7 Hz, 1H), 7.35−6.90 (m, 11H), 6.03 (d, J = 5.5 Hz, 1H), 5.15−5.06 (m, 2H), 4.98 (s br, 1H), 4.46−4.12 (m, 5H), 4.01 (m, 4H), 3.98 (m, 1H), 3.28 (m, 4H), 2.08−1.61 (m, 8H), 1.51 (d, J = 7.0 Hz, 3H), 1.32−1.27 (m, 4H), 0.88 (m, 3H), LC−MS m/z 645 (M + H).

[1-({[2-(4-Phenyl-1-piperazinyl)-4-pyrimidinyl]oxy}methyl)cyclobutyl]methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcarbamate (24). The title compound was prepared using the same experimental procedure as in example **11** using [1-({[2-(4-phenyl-1-piperazinyl)-4-pyrimidinyl]oxy}methyl)cyclobutyl]methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate as the alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 5.7 Hz, 1H), 7.41−7.30 (m, 8H), 7.14−6.90 (m, 3H), 6.04 (d, J = 5.7 Hz, 1H), 5.32−5.08 (m, 3H), 4.33 (s, 2H), 4.22 (s, 2H), 4.0 (t, J = 5.1 Hz, 4H), 3.28 (t, J = 4.9 Hz, 4H), 2.12−1.98 (m, 7H), 1.96 (m, 4H), 1.33−1.27 (m, 4H), 0.89 (t, J = 6.2 Hz, 3H). Anal. C, H, N.

[1-({[2-(4-Morpholinyl)-4-pyrimidinyl]oxy}methyl)cyclobutyl]methyl (1S)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcarbamate (25). [1-({[2-(4-Morpholinyl)-4-pyrimidinyl]oxy}methyl)cyclobutyl]methanol (25a). [1-({[2-(4-Morpholinyl)-4-pyrimidinyl]oxy}methyl)cyclobutyl]methanol was prepared using the same experimental procedure as in example **23a** using *N*-methylmorpholine instead of *N*-methylpiperidine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 5.7 Hz, 1H), 5.99 (d, J = 5.7 Hz, 1H), 4.38 (s, 2H), 3.75 (m, 4H), 3.62 (s, 2H), 2.15 (m, 4H), 1.95−1.89 (m, 6H).

[1-({[2-(4-Morpholinyl)-4-pyrimidinyl]oxy}methyl)cyclobutyl]methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate (25b). The title compound was prepared using the same experimental procedure as in example **10b** using [1-({[2-(4-morpholinyl)-4-pyrimidinyl]oxy}methyl)cyclobutyl]methanol as the alcohol component and (3*S*)-3-amino-2-hydroxy-*N*-[(1*R*)-1-phenylethyl]-heptanamide as the amino alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 5.6 Hz, 1H), 7.37−7.25 (m, 5H), 7.13 (d, J = 7.8 Hz, 1H), 6.01 (d, J = 5.7 Hz, 1H), 5.56 (d, J = 8.8 Hz, 1H), 5.12−5.07 (m, 1H), 4.91 (d, J = 4.4 Hz, 1H), 4.32−4.09 (m, 5H), 3.79 (m, 5H), 2.07−1.49 (m, 12H), 1.46 (d, J = 6.9 Hz, 3H), 1.36−1.27 (m, 4H), 0.91 (m, 3H). LC−MS m/z 570 (M + H).

[1-({[2-(4-Morpholinyl)-4-pyrimidinyl]oxy}methyl)cyclobutyl]methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcarbamate (25). The title compound was prepared using the same experimental procedure as in example **11** using [1-({[2-(4-morpholinyl)-4-pyrimidinyl]oxy}methyl)cyclobutyl]methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate as the starting material. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 5.7 Hz, 1H), 7.38−7.29 (m, 5H), 7.12 (d, J = 8.1 Hz, 1H), 6.03 (d, J = 5.5 Hz, 1H), 5.08−5.33 (m, 3H), 4.29 (s, 2H), 4.20 (s, 2H), 3.81 (m, 8H), 2.11−1.96 (m, 8H), 1.56 (d, J = 6.6 Hz, 3H), 1.31−1.26 (m, 4H), 0.88 (s br, 3H). Anal. C, H, N.

{1-[(Thieno[3,2-*d*]pyrimidin-4-yloxy)methyl]cyclobutyl}methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcarbamate (26). {1-[(Thieno[3,2-*d*]pyrimidin-4-yloxy)methyl]cyclobutyl}methanol (26a). The title compound was prepared using the same experimental procedure as in example **19a** using [1-(hydroxymethyl)cyclobutyl]methanol and 4-chlorothieno[3,2-d]pyrimidine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.87 (d, J = 5.3 Hz, 1H), 7.49 (d, J = 5.4 Hz, 1H), 4.69 (s, 2H), 3.61 (d, J = 5.8 Hz, 2H), 3.36 (t, J = 6.4 Hz, 1H), 2.01−1.82 (m, 6H). GC−MS m/z 251 (M + H).

{1-[(Thieno[3,2-*d*]pyrimidin-4-yloxy)methyl]cyclobutyl}methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate (26b). The title compound was prepared using the same experimental procedure as in example **10b** using {1-[(thieno[3,2-d]pyrimidin-4-yloxy)methyl]-cyclobutyl}methanol as the alcohol component and (3*S*)-3-amino-2-hydroxy-*N*-[(1*R*)-1-phenylethyl]heptanamide as the amino alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.82 (m, 1H), 7.52−7.09 (m, 7H), 5.11−5.04 (m, 2H), 4.83 (m, 1H), 4.54 (s, 2H), 4.36−4.10 (m, 3H), 3.79 (m, 1H), 2.03−1.88 (m, 6H), 1.83−1.23 (m, 9H), 0.82 (m, 3H). LC−MS m/z 541 (M + H).

{1-[(Thieno[3,2-*d*]pyrimidin-4-yloxy)methyl]cyclobutyl}methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcarbamate (26). The title compound was prepared using the same experimental procedure as in example **11** using {1-[(thieno[3,2-d]pyrimidin-4-yloxy)methyl]cyclobutyl}methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)-pentylcarbamate as the starting alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.83 (d, J = 5.6 Hz, 1H), 7.51 (d, J = 5.3 Hz, 1H), 7.41−7.12 (m, 6H), 5.29 (d, J = 8.1 Hz, 1H), 5.14−5.03 (m, 2H), 4.59 (s, 2H), 4.23 (s, 2H), 2.08−1.68 (m, 6H), 1.65−1.51 (m, 5H), 1.39−1.27 (m, 4H), 0.83 (t, J = 6.4 Hz, 3H). Anal. C, H, N.

[1-({[4-(4-Methylphenyl)-1,3-thiazol-2-yl]oxy}methyl)cyclobutyl]methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcarbamate (27). [1-({[4-(4-Methylphenyl)-1,3-thiazol-2-yl]oxy}methyl)cyclobutyl]methanol (27a). The title compound was prepared using the same experimental procedure as in example **19a** from [1-(hydroxymethyl)cyclobutyl]methanol and 2-chloro-4-(4-methylphenyl)-1,3-thiazole. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 6.78 (s, 1H), 4.62 (s, 2H), 3.77 (t, J = 6.8 Hz, 1H), 3.60 (d, J = 6.7 Hz, 2H), 2.35 (s, 3H), 2.04−1.90 (m, 6H). GC−MS m/z 290 (M + H).

[1-({[4-(4-Methylphenyl)-1,3-thiazol-2-yl]oxy}methyl)-cyclobutyl]methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate (27b). The title compound was prepared using the same experimental procedure as in example **10b** from [1-({[4-(4-methylphenyl)-1,3-thiazol-2-yl]oxy}methyl)cyclobutyl]methanol as the alcohol component and (3*S*)-3-amino-2-hydroxy-*N*-[(1*R*)-1-phenylethyl]-heptanamide as the amino alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (m, 2H), 7.33−7.01 (m, 7H), 6.79 (m, 2H), 5.06−4.99 (m, 3H), 4.44 (m, 2H), 4.21−4.12 (m, 3H), 3.81 (m, 1H), 2.37 (s, 3H), 2.05−1.73 (m, 6H), 1.68−1.24 (m, 9H), 0.83 (m, 3H). LC−MS *m*/*z* 580 (M + H).

[1-({[4-(4-Methylphenyl)-1,3-thiazol-2-yl]oxy}methyl)-cyclobutyl]methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]-amino}acetyl)pentylcarbamate (27). The title compound was prepared using the same experimental procedure as in example **11** from [1-({[4-(4-methylphenyl)-1,3-thiazol-2-yl]oxy}-methyl)cyclobutyl]methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate as the alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 7.9 Hz, 2H), 7.34−7.18 (m, 7H), 7.08 (d, J = 7.0 Hz, 1H), 6.79 (s, 1H), 5.26 (d, J = 7.5 Hz, 1H), 5.16 − 5.40 (m, 2H), 4.49 (s, 2H), 4.21 (s, 2H), 2.36 (s, 3H), 2.03−1.93 (m, 6H), 1.37−1.29 (m, 4H), 1.52 (m, 5H), 0.84 (t, J = 6.2 Hz, 3H). Anal. C, H, N.

(1-{[(3-Phenyl-1,2,4-thiadiazol-5-yl)oxy]methyl}-cyclobutyl)methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]-amino}acetyl)pentylcarbamate (28). (1-{[(3-Phenyl-1,2,4-thiadiazol-5-yl)oxy]methyl}cyclobutyl)methanol (28a). The title compound was prepared using the same experimental procedure as in example **19a** from [1-(hydroxymethyl)cyclobutyl]methanol and 5-chloro-3-phenyl-1,2,4-thiadiazole. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (m, 2H), 7.39 (m, 3H), 4.63 (s, 2H), 3.62 (d, J = 6.4 Hz, 2H), 2.71 (t, J = 6.4 Hz, 1H), 1.88−1.97 (m, 6H). GC−MS *m*/*z* 277 (M + H).

(1-{[(3-Phenyl-1,2,4-thiadiazol-5-yl)oxy]methyl}-cyclobutyl)methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate (28b). The title compound was prepared using the same experimental procedure as in example **10b** using (1-{[(3-phenyl-1,2,4-thiadiazol-5-yl)oxy]methyl}cyclobutyl)methanol as the alcohol component and (3*S*)-3-amino-2-hydroxy-*N*-[(1*R*)-1-phenylethyl]-heptanamide as the amino alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (m, 2H), 7.48−7.26 (m, 8H), 7.13 (d, J = 7.9 Hz, 1H), 5.63 (m, 1H), 5.07 (m, 1H), 4.78 (d, J = 5.5 Hz, 1H), 4.57 (s, 2H), 4.27−4.10 (m, 3H), 3.85 (m, 1H), 2.09−1.80 (m, 6H), 1.47 (d, J = 6.8 Hz, 3H), 1.32−1.25 (m, 6H), 0.94 (m, 3H). LC−MS *m*/*z* 567 (M + H).

(1-{[(3-Phenyl-1,2,4-thiadiazol-5-yl)oxy]methyl}-cyclobutyl)methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]-amino}acetyl)pentylcarbamate (28). The title compound was prepared using the same experimental procedure as in example **11** using (1-{[(3-phenyl-1,2,4-thiadiazol-5-yl)oxy]-methyl}cyclobutyl)methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate as the starting alcohol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (m, 2H), 7.49−7.29 (m, 8H), 7.12 (d, J = 7.8 Hz, 1H), 5.34−5.10 (m, 3H), 4.60 (s, 2H), 4.26 (s, 2H), 2.08−1.99 (m, 6H), 1.55 (d, J = 6.5 Hz, 3H), 1.34−1.24 (m, 6H), 0.88 (s br, 3H). Anal. C, H, N.

(1-{[(6-Methyl-4-phenylpyridazin-3-yl)oxy]methyl}-cyclobutyl)methyl (1*R*)-1-(Oxo{[(1*R*)-1-phenylethyl]-amino}acetyl)pentylcarbamate (29). (1-{[(6-Methyl-4-phenyl-3-pyridazinyl)oxy]methyl}cyclobutyl)methanol (29a). The title compound was prepared using the same experimental procedure as in example **19a** from [1-(hydroxy-methyl)cyclobutyl]methanol and 3-chloro-6-methyl-4-phenylpyridazine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.25 (m, 6H), 4.64 (s, 2H), 3.59 (d, J = 6.2 Hz, 2H), 3.05 (t, J = 6.6 Hz, 1H), 2.63 (s, 3H), 2.0−1.73 (m, 6H). GC−MS *m*/*z* 285 (M + H).

(1-{[(6-Methyl-4-phenylpyridazin-3-yl)oxy]methyl}-cyclobutyl)methyl (1*R*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate (29b). The title compound was prepared using the same experimental procedure as in example **10b** from (1-{[(6-methyl-4-phenyl-3-pyridazinyl)oxy]methyl}cyclobutyl)methanol as the alcohol component and (3*S*)-3-amino-2-hydroxy-*N*-[(1*R*)-1-phenylethyl]-heptanamide as the amino alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.22 (m, 12H), 6.12 (m, 1H), 5.22−4.99 (m, 2H), 4.54 (m, 1H), 4.23−3.89 (m, 4H), 2.84 (s br, 1H), 2.59 (m, 3H), 2.04−1.90 (m, 6H), 1.50−1.23 (m, 9H), 0.79 (m, 3H). LC−MS *m*/*z* 575 (M + H).

(1-{[(6-Methyl-4-phenylpyridazin-3-yl)oxy]methyl}-cyclobutyl)methyl (1*R*)-1-(Oxo{[(1*R*)-1-phenylethyl]-amino}acetyl)pentylcarbamate (29). The title compound was prepared using the same experimental procedure as in example **11** from (1-{[(6-methyl-4-phenyl-3-pyridazinyl)oxy]-methyl}cyclobutyl)methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate as the alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.14 (m, 12H), 5.19−5.06 (m, 3H), 4.53 (s, 2H), 4.12 (s, 2H), 2.65 (s, 3H), 2.03−1.92 (m, 6H), 1.53 (m, 2H), 1.52 (d, J = 6.9 Hz, 3H), 1.41−1.28 (m, 4H), 0.83 (s br, 3H). Anal. C, H, N.

{1-[(4-Methyl-1,3-thiazol-2-yl)methyl]cyclobutyl}-methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)-pentylcarbamate (30). {1-[(Benzyloxy)methyl]cyclobutyl}-acetonitrile (3). To a solution of [1-(hydroxymethyl)cyclobutyl]methanol (**2**) (8.0 g, 69 mmol) in 120 mL of THF/DMF (1:1) was added a 60% dispersion of sodium hydride in oil (3.30 g, 69 mmol), and the contents were stirred for 30 min. Benzyl bromide (8.6 mL, 72.4 mmol) was then added, and the contents were stirred for 2 h. The reaction was quenched with aqueous ammonium chloride followed by the addition of diethyl ether. The organic phase was isolated, dried using magnesium sulfate, and concentrated under vacuum to afford the crude product, which was purified by silica gel chromatography using ethyl acetate/hexane (3:7) as the eluent to afford 12.0 g (86%) of the intermediate {1-[(benzyloxy)methyl]cyclobutyl}methanol as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.25 (m, 5H), 4.49 (s, 2H), 3.66 (d, J = 6 Hz, 2H), 3.52 (s, 2H), 2.53 (t, J = 6 Hz, 1H), 1.91−1.73 (m, 6H). GC−MS *m*/*z* 207 (M + H).

To a solution of {1-[(benzyloxy)methyl]cyclobutyl}methanol (12.0 g, 59.0 mmol) in dichloromethane (180 mL) was added TEA (9.93 mL, 70.8 mmol) at 0 °C followed by the addition of methanesulfonyl chloride (5.02 mL, 64.9 mmol). After the mixture was stirred for 2 h, saturated sodium chloride solution was added. The organic phase was isolated, dried using magnesium sulfate, and concentrated under vacuum to afford the crude product, which was used directly in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.32 (m, 5H), 4.57 (s, 2H), 4.30 (s, 2H), 3.52 (s, 2H), 2.98 (s, 3H), 1.95 (m, 6H).

To a solution of the crude {1-[(benzyloxy)methyl]cyclobutyl}-methyl methanesulfonate (16.75 g, 59.0 mmol), obtained from the above procedure, in DMF (150 mL) and water (15 mL) was added KCN (4.97 g, 88.5 mmol), and the contents were heated at 130 °C for 5 h. The reaction mixture was cooled and diluted with ether and water, and the layers were separated. The organic phase was dried using magnesium sulfate and concentrated under vacuum to afford the crude product, which was purified by silica gel chromatography using ethyl acetate/hexane (1:3) as the eluent to afford 8.0 g (88%) of {1-[(benzyloxy)methyl]cyclobutyl}acetonitrile as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 − 7.29 (m, 5H), 4.59 (s, 2H), 3.5 (s, 2H), 2.6 (s, 2H), 2.08−1.92 (m, 6H).

{1-[(4-Trifluoromethyl-1,3-thiazol-2-yl)methyl]cyclobutyl}methanol (30a). To a solution of {1-[(benzyloxy)-methyl]cyclobutyl}acetonitrile (**3**) (9.7 g, 45 mmol) in THF (100 mL) and water (10 mL) was added diethyldithiophosphate (15.13 mL, 90.2 mmol), and the contents were heated at reflux for 16 h. Ethyl acetate and water were added, and the layers were separated. The organic phase was dried using magnesium sulfate and concentrated under vacuum to afford the crude product, which was purified by silica gel chromatography using ethyl acetate/hexane (1:4) as the eluent to afford 8.0 g (71%) of 2-{1-[(benzyloxy)methyl]cyclobutyl}ethanethioamide as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.0 (s br 2H), 7.39−7.30 (m, 5H), 4.59 (s, 2H), 3.58 (s, 2H), 3.09 (s, 2H), 2.14−1.87 (m, 6H).

To a solution of 2-{1-[(benzyloxy)methyl]cyclobutyl}ethanethioamide (0.5 g, 2.01 mmol), obtained in the above procedure,

in acetonitrile (10 mL) was added 1-bromo-4,4,4-trifluoro-2-butanone (0.383 g, 2.01 mmol), and the contents were stirred at room temperature for 3 h. The mixture was concentrated under vacuum and the residual was purified by silica gel chromatography using ethyl acetate/hexane (1:4) as the eluent to afford 0.417 g (83%) of the intermediate benzyloxy compound as a colorless oil. To a solution of this intermediate (0.750 g, 2.2 mmol) in dichloromethane (15 mL) was added a 1.0 M solution of boron tribromide (2.2 mL, 2.2 mmol), and the contents were stirred at room temperature for 16 h. After the reaction was quenched with methanol (10 mL), the contents were concentrated under vacuum and the residual was purified by silica gel chromatography using ethyl acetate/hexane (1:9) as the eluent to afford 0.16 g (29%) of the title compound as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (s, 1H), 3.35 (s, 2H), 2.82 (s, br 2H), 2.02−1.91 (m, 6H).

{1-[(4-Trifluoromethyl-1,3-thiazol-2-yl)methyl]cyclobutyl}methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate (30b). The title compound was prepared using the same experimental procedure as in example **10b** from (1-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]methyl}cyclobutyl)methanol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.13 (m, 6H), 5.16−5.09 (m, 1H), 4.84 (m, 1H), 4.24−4.12 (m, 2H), 3.82 (m, 1H), 3.60 (m, 1H), 3.34 (s, 2H), 2.82 (s, 2H), 2.02−1.92 (m, 6H), 1.65 (m, 2H), 1.49 (d, J = 6.7 Hz, 3H), 1.47−1.27 (m, 4H), 0.85 (m, 3H). LC−MS m/z 542 (M + H).

{1-[(4-Trifluoromethyl-1,3-thiazol-2-yl)methyl]cyclobutyl}methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcarbamate (30). The title compound was prepared using the same experimental procedure as in example **11** from (1-{[4-(trifluoromethyl)-1,3-thiazol-2yl]methyl}cyclobutyl)methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate as the alcohol component. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.11 (m, 7H), 5.33 (m, 1H), 5.12−5.05 (m, 2H), 4.15 (s, 2H), 2.82 (s, 2H), 2.04−1.92 (m, 6H), 1.61 (m, 2H), 1.53 (d, J = 6.6 Hz, 3H), 1.42−1.31 (m, 4H), 0.86 (s br, 3H). Anal. C, H, N.

{1-[(4-Phenyl-1,3-thiazol-2-yl)methyl]cyclobutyl}methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcarbamate (31). **{1-[(4-Phenyl-1,3-thiazol-2-yl)methyl]cyclobutyl}methanol (31a).** 2-{1-[(Benzyloxy)methyl]cyclobutyl}ethanethioamide and phenacyl bromide were reacted using the same experimental procedure as in example **30a** to provide the intermediate 2-({1-[(benzyloxy)methyl]cyclobutyl}methyl)-4-phenyl-1,3-thiazole. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.96−7.25 (m, 10H), 4.60 (s, 2H), 3.50 (s, 2H), 3.35 (s, 2H), 2.13−1.95 (m, 6H).

2-({1-[(Benzyloxy)methyl]cyclobutyl}methyl)-4-phenyl-1,3-thiazole (0.7 g, 2.0 mmol) obtained in the above procedure was deprotected using boron tribromide following the same procedure as in example **30a** to afford the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.92−7.29 (m, 5H), 4.13 (t, J = 6.7 Hz, 1H), 3.66 (d, J = 6 Hz, 2H), 3.3 (s, 2H), 2.08−1.94 (m, 6H). GC−MS m/z 260 (M + H).

{1-[(4-Phenyl-1,3-thiazol-2-yl)methyl]cyclobutyl}methyl (1*S*)-1-(1-Hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate (31b). The title compound was prepared using the same experimental procedure as in example **10b** from {1-[(4-phenyl-1,3-thiazol-2-yl)methyl]cyclobutyl}methanol **(31a)** to afford a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90, 7.92 (2s, 1H), 7.46−7.18 (m, 10 H), 5.61 (d, J = 8.8 Hz, 1H), 5.14−5.01 (m, 2H), 4.19−4.06 (m, 4H), 3.88 (m, 1H), 3.23 (s, 2H), 2.21−1.50 (m, 10 H), 1.46 (d, J = 7 Hz, 3H), 1.37−1.27 (m, 2H), 0.94 (m, 3H). LC−MS m/z 550 (M + H).

{1-[(4-Phenyl-1,3-thiazol-2-yl)methyl]cyclobutyl}methyl (1*S*)-1-(Oxo{[(1*R*)-1-phenylethyl]amino}acetyl)pentylcarbamate (31). To a solution of {1-[(4-phenyl-1,3-thiazol-2-yl)methyl]cyclobutyl}methyl (1*S*)-1-(1-hydroxy-2-oxo-2-{[(1*R*)-1-phenylethyl]amino}ethyl)pentylcarbamate (0.2 g, 0.364 mmol) in dichloromethane (3 mL) cooled to −60 °C was added oxalyl chloride (0.079 mL, 0.91 mmol) and DMSO (0.129 mL, 1.82 mmol), followed by the addition of triethylamine (0.204 mL, 1.45 mmol). After being stirred for 15 min, the reaction mixture was warmed to room temperature and applied directly to a silica gel column using ethyl acetate/hexane (3:7) as the eluent to afford 0.19 g (96%) of {1-[(4-phenyl-1,3-thiazol-2-yl)methyl]-cyclobutyl}methyl (1*S*)-1-(oxo{[(1*R*)-1-phenylethyl]amino}-acetyl)pentylcarbamate as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.21 (d, J = 8.4 Hz, 1H), 7.98 (m, 3H), 7.64 (d, J = 7.6 Hz, 1H), 7.25−7.23 (m, 8 H), 4.96−5.01 (m, 1H), 4.80 (m, 1H), 4.01 (s, 2H), 3.30 (s, 2H), 2.12−1.64 (m, 10 H), 1.42 (d, J = 7 Hz, 3H), 1.29−1.21 (m, 2H), 0.822 (t, J = 7 Hz, 3H). Anal. C, H, N.

Biological Data. Protocols used for the enzyme assays were described in a previous paper (ref 19a).

Acknowledgment. The authors thank Randy Rutkowski, Robert Johnson, and Peter Kitrinos for analytical support.

Supporting Information Available: Results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM040107N