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Discovery of Non-peptidic P_2–P_3 Butanediamide Renin Inhibitors with High Oral Efficacy

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Abstract—A new series of non-peptidic renin inhibitors having a 2-substituted butanediamide moiety at the P_2 and P_3 positions has been identified. The optimized inhibitors have IC_{50} values of 0.8 to 1.4 nM and 2.5 to 7.6 nM in plasma renin assays at pH 6.0 and 7.4, respectively. When evaluated in the normotensive cynomolgus monkey model, two of the most potent inhibitors were orally active at a dose as low as 3 mg/kg. These potent renin inhibitors are characterized by oral bioavailabilities of 40 and 89% in the cynomolgus monkey. Inhibitor **3z** (BILA 2157 BS) was selected as candidate for pre-development.

Introduction

The renin–angiotensin system (RAS) plays an important role in the regulation of blood pressure and in the maintenance of fluid volume.[1] Renin, an aspartyl protease, is involved in the first and rate-limiting step of this enzymatic cascade. Renin cleaves the N-terminus of the circulating glycoprotein angiotensinogen to generate the decapeptide angiotensin I. Angiotensin-converting enzyme (ACE) next removes the carboxy terminal dipeptide of angiotensin I to give angiotensin II (AII), one of the most potent vasoconstrictors known. Inhibition of ACE proved to be an effective therapy for the treatment of hypertension and congestive heart failure.[2]

However, ACE is a non-specific enzyme that also cleaves bradykinin as well as other substrates and this lack of specificity may contribute to certain side-effects such as the persistent dry cough often observed during ACE inhibitor therapy.[3,4] Considering that renin has only one known natural substrate, angiotensinogen, it has been suggested that renin inhibitors could have an improved side-effect profile. A third site of intervention in the RAS, AII receptor antagonism has also been evaluated. The discovery of small and non-peptidic angiotensin II antagonists from high throughput screening led to the rapid identification of a series of candidates for development.[5] Although high levels of circulating AII resulting from receptor antagonism and the existence of receptor subtypes raised some concerns,[5] Losartan (Dup-753) was the first compound of this class to be approved for clinical use.[6] In contrast, no small molecule inhibitor of renin has been identified from screening. A rational design approach was therefore used to generate potent renin inhibitors.[7–9] As a result of the renin substrate requirements, these compounds have typically been quite large and peptidic. Most renin inhibitors have a high molecular weight since they usually cover the S_4–S_1' region of the enzyme in order to reach in vitro potency levels (low nM) required for reasonable in vivo efficacy. Both their peptidic character as well as their size have limited the oral bioavailability of these compounds. So far, a renin inhibitor has yet to be approved for use in humans. Nevertheless, potent renin inhibitors with improved oral bioavailability have been identified. For instance, good oral bioavailabilities have been reported in the cynomolgus monkey for A-72517 (8%),[10] FK906 (13%),[11] FK744 (30–50%)[12] and CP-108,671 (>27%)[13] as well as in the beagle dog for PD-134672 (CI-992, 18%)[7,14] and SC-53315 (30%)[15] which indicate significant progress in this area. Besides good bioavailability, a commercially

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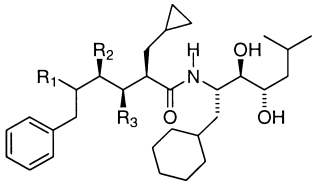
viable potent renin inhibitor would have to be produced economically in order to compete against several antihypertensive drugs already on the market including the newly introduced AII antagonists. To address these issues, much effort has been directed toward the reduction in size and peptidic character of renin inhibitors[9,16–20] and smaller inhibitors with good levels of potency have been recently reported.[15,21–24]

We recently described the identification of small and potent renin inhibitors **1** and **2** ($IC_{50} = 20$ nM).[25] Unfortunately, these inhibitors did not have the physico-chemical properties required for oral efficacy. Although these compounds were very small (MW 503), the reduction in size was achieved using synthetically complex molecules.



1 R_1 = (*S*)-OH, R_2 = OH, R_3 = H
2 R_1 = (*R*)-OH, R_2 = H, R_3 = OH

Returning to the drawing board using angiotensinogen as template, our objectives were to design small, synthetically less complex and potent renin inhibitors. The focus was put on the P_2–P_3–P_4 segment of the inhibitors while maintaining a known transition state analogue[26] at P_1–P_1'. The rationale behind the proposed P_2–P_3 butanediamide inhibitors **3** is outlined in Figure 1. A 2-substituted butanediamide could replace the P_2–P_3 dipeptide usually found in most renin inhibitors. The substituent at position 2 could play the role of the P_2 side chain. The P_2 amino acid amide NH, not involved in an important hydrogen bond, was simply replaced by a methylene. The carbonyl of the P_3 amino acid, which is involved in a critical hydrogen bond with the enzyme, was maintained via the carbonyl of the N^4,N^4-disubstituted amide moiety of the butanediamide. As a result, one group on the retro-amide could act as the P_3 side chain and the other as the P_4 side chain. The proposed replacement of the P_2–P_3 dipeptide by a readily accessible 2-substituted butanediamide eliminates one stereogenic center thereby contributing to the simplification of this portion of the molecule. Finally, the P_3–P_4 appendages were amenable to a simple P_3–P_4 amine moiety. The synthesis, structure–activity–relationship studies as well as biological properties of the novel butanediamide **3** are discussed.

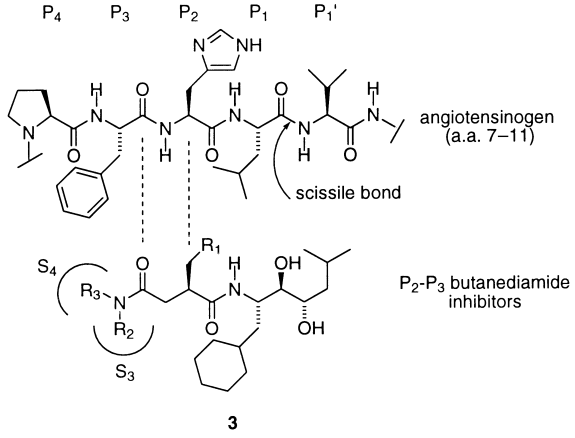
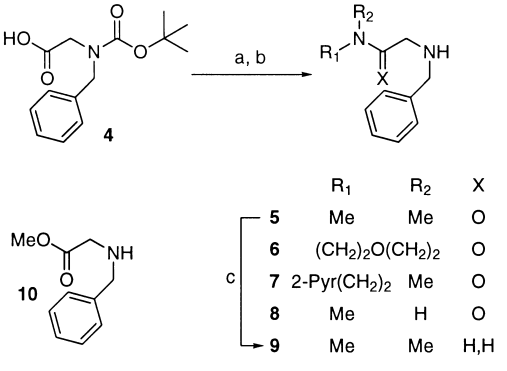


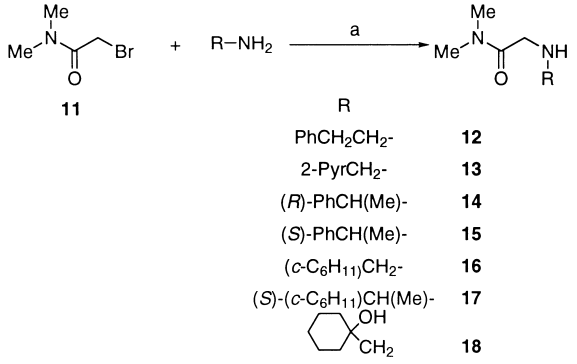
Figure 1. Proposed P_2–P_3 butanediamide inhibitors.

Chemistry

The inhibitors of general structure **3** were made starting in a convergent fashion from three synthons, the P_3–P_4 amine, the succinyl core and the transition state analogue, by formation of two amide bonds. The P_3–P_4 amines were either commercially available amines or easily accessible *N*-substituted glycine analogues. The 2-(benzylamino)acetamides **5–8** were prepared from Boc-*N*-benzylglycine (**4**)[27] in two steps: amide formation followed by the acidic cleavage of the Boc protective group (Scheme 1). Reduction of **5** with LAH gave the reduced analogue *N,N,N'*-trisubstituted 1,2-ethanediamine **9**. For the preparation of the P_3–P_4 amines that did not have an *N*-benzyl substituent, the direct alkylation of the P_3 amine with *N,N*-dimethyl 2-bromoacetamide (**11**) in the presence of triethylamine was used (Scheme 2). Although polyalkylation reduced the efficiency of the sequence, this method produced the desired secondary amines **12,13,16–18** in an expeditious fashion (26–43%). In the case of more hindered amines such as 1(*R*)- and 1(*S*)-phenylethylamine, the yield of secondary amines **14** and **15** increased to 70–76%. In the case of P_3–P_4 amines **27** and **29**, a very efficient but longer procedure was used in order to simplify the handling and purification of the intermediates and the polar amines (Scheme 3). The sequence started with the alkylation of the appropriate amine with ethyl 2-bromoacetate (**19**) in the presence of triethylamine. This occurred smoothly at room temperature to give the expected secondary amines **20** and **23**, respectively, in good yield. In these cases, only a trace (ca. 5%) of the corresponding tertiary amines was detected. The alkylation of cyclohexanemethylamine was significantly more efficient with 2-bromoacetate **19** (66%) than with 2-bromoacetamide **11** (30%). The secondary amines **20** and **23** were next converted into the corresponding Boc derivatives, **21** and **24**, and the



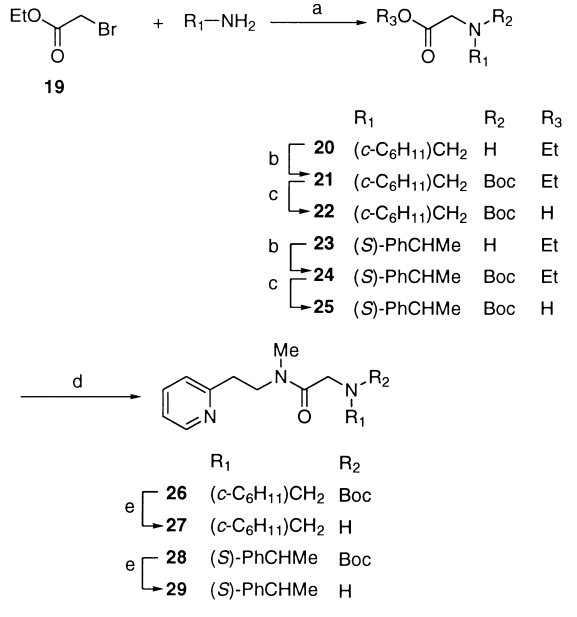
Scheme 1. Reagents and conditions: (a) R_1R_2NH, BOP·PF_6, *i*-Pr_2NEt, DMF, 25 °C; (b) 4 N HCl/dioxane, 25 °C, 76–86%; (c) LAH, THF, 65 °C, 100%.



Scheme 2. Reagents and conditions: (a) Et_3N, MeOH, 25 °C to reflux, 26–76%.

ester moiety was saponified to give the acids **22** and **25**. Finally, coupling with [2-(methylamino)ethyl]pyridine and subsequent cleavage of the BOC protective group gave the P_3–P_4 amines **27** and **29**.

The succinyl core portion of the inhibitors was prepared using Evans' alkylation method.[28] The required acids or acyl chlorides bearing the P_2 side chain (**30–34**) were readily available and were converted into the corresponding acyloxazolidinones **35–40** (Scheme 4). Alkylation of the lithium or sodium enolate of **36–40** with *tert*-butyl or benzyl 2-bromoacetate provided the succinyl intermediates **41–45** in good yields. These compounds were found to be quite versatile intermediates and could be utilized in two different routes. For the synthesis of the proposed inhibitors, the chiral auxiliary could first be removed to liberate the acid function (at C-1) and the transition state analogue portion could then be introduced via coupling. The ester (at C-4) could next be transformed into the acid and this acid converted into

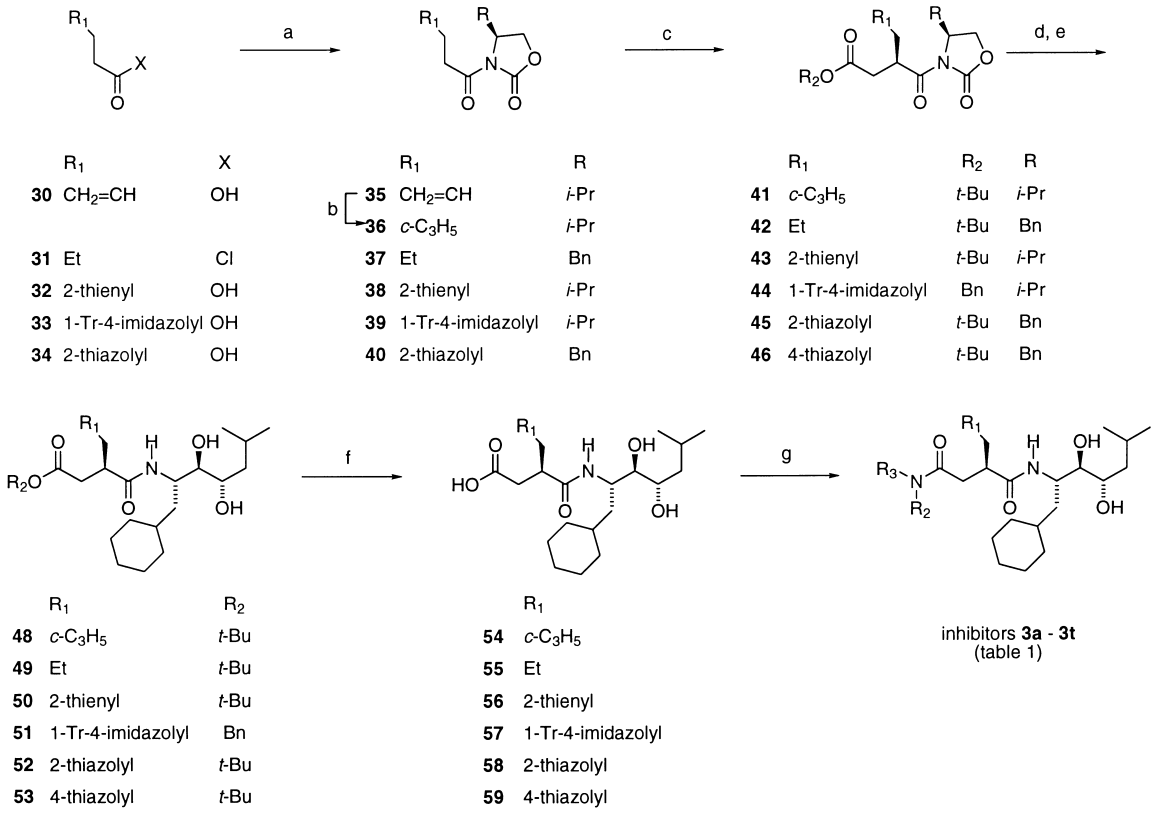


Scheme 3. Reagents and conditions: (a) Et_3N, THF, 25 °C, 62–66%; (b) $(Boc)_2O$, CH_2Cl_2, 25 °C, 98–100%; (c) aq NaOH, 25 °C, 96–99%; (d) 2-Pyr$(CH_2)_2$NHMe, BOP·PF_6, *i*-Pr_2NEt, DMF, 25 °C, 79–89%; (e) 4 N HCl/dioxane, 25 °C, 95–96%.

an amide using the P_3–P_4 amine. Alternatively, the ester (at C-4) of **41–46** could be first transformed into the amide, the chiral auxiliary removed, and the resulting acid coupled to the transition state analogue moiety to give the final inhibitors. The first approach gave rise to advanced intermediates for SAR studies at the P_3–P_4 positions. The second approach was useful for the SAR of the transition state analogue portion as well as for the synthesis of specific inhibitors since the more complex portion of the inhibitor is introduced at a later stage in the synthesis. Using the first approach strategy, the chiral auxiliary present in **41–46** was removed using LiOOH[29] to give the corresponding acids which were coupled with 2(*S*)-amino-1-cyclohexyl-6-methyl-3(*R*), 4(*S*)-heptanediol (**47**)[30,31] using BOP·PF_6 reagent to give amides **48–53**. Upon treatment of **48–50** and **52**, **53** with TFA in CH_2Cl_2 and selective hydrogenolysis of **51**, the corresponding acids **54–59** were obtained and used in the last amide bond formation reaction with the P_3–P_4 amines to generate inhibitors **3a–3t** generally in good yields. The observed yields, not optimized, were low (19 to 24%) for the 2- and 4-thiazolyl derivatives **52** and **53**. Because of even lower yields in the case of 2-amino-4-thiazolyl derivatives, the second approach was used instead. First, the key succinyl intermediates bearing a 4-thiazolylmethyl substituent at position 2 were prepared starting with the opening of succinic anhydride with the lithium salt of (1-methylethyl)-2-oxazolidinone which provided acid **60** (Scheme 5). This acid was transformed into bromomethylketone **61** in the usual way, via the reaction of the corresponding acyl chloride with CH_2N_2 and treatment of the resulting diazomethylketone with HBr. The elaboration of the heterocycle was achieved using Hantzsch synthesis conditions. Thus treatment of bromomethylketone **61** with thioformamide gave 4-thiazolyl analogue **62**. The reaction of **61** with thiourea afforded the 2-amino-4-thiazolyl analogue that was isolated as the 2,2,2-trichloroethyl carbamate derivative **63**. Alkylation of the sodium enolate of **62** and **63** with *tert*-butyl 2-bromoacetate gave, respectively, succinyl intermediates **46** and **64**. In the case of **64**, the *tert*-butyl ester was first cleaved with TFA to give the corresponding acid that was immediately coupled with the P_3–P_4 amines (**5**, **15**, **16**, **18**, **29**, or **27**) to afford amides **65–70** in good yields. The chiral auxiliary was next cleaved using either LiOOH (for **65–67**) or, in 2 steps, with $Mg(OMe)_2$[32] followed by aqueous NaOH saponification (for **68–70**) to deliver the corresponding acids. These acids were coupled to **47** in the usual manner to give butanediamides **71–76**. In the last coupling, a substantial amount (5–10%) of the epimeric 2(*S*)-substituted butanediamides was observed. The presence of this epimer made chromatographic separation and purification of the desired 2(*R*) derivatives rather difficult. Finally, the 2,2,2-trichloroethyl carbamate protective group was removed with zinc in aqueous HCl to afford inhibitors **3u–3z**.

Results and Discussion

The SAR studies were initiated at the P_3 and P_4 positions of the butanediamide inhibitor of general formula



	R_1	X
30	CH_2=CH	OH
31	Et	Cl
32	2-thienyl	OH
33	1-Tr-4-imidazolyl	OH
34	2-thiazolyl	OH

	R_1	R
35	CH_2=CH	*i*-Pr
36	*c*-C_3H_5	*i*-Pr
37	Et	Bn
38	2-thienyl	*i*-Pr
39	1-Tr-4-imidazolyl	*i*-Pr
40	2-thiazolyl	Bn

	R_1	R_2	R
41	*c*-C_3H_5	*t*-Bu	*i*-Pr
42	Et	*t*-Bu	Bn
43	2-thienyl	*t*-Bu	*i*-Pr
44	1-Tr-4-imidazolyl	Bn	*i*-Pr
45	2-thiazolyl	*t*-Bu	Bn
46	4-thiazolyl	*t*-Bu	Bn

	R_1	R_2
48	*c*-C_3H_5	*t*-Bu
49	Et	*t*-Bu
50	2-thienyl	*t*-Bu
51	1-Tr-4-imidazolyl	Bn
52	2-thiazolyl	*t*-Bu
53	4-thiazolyl	*t*-Bu

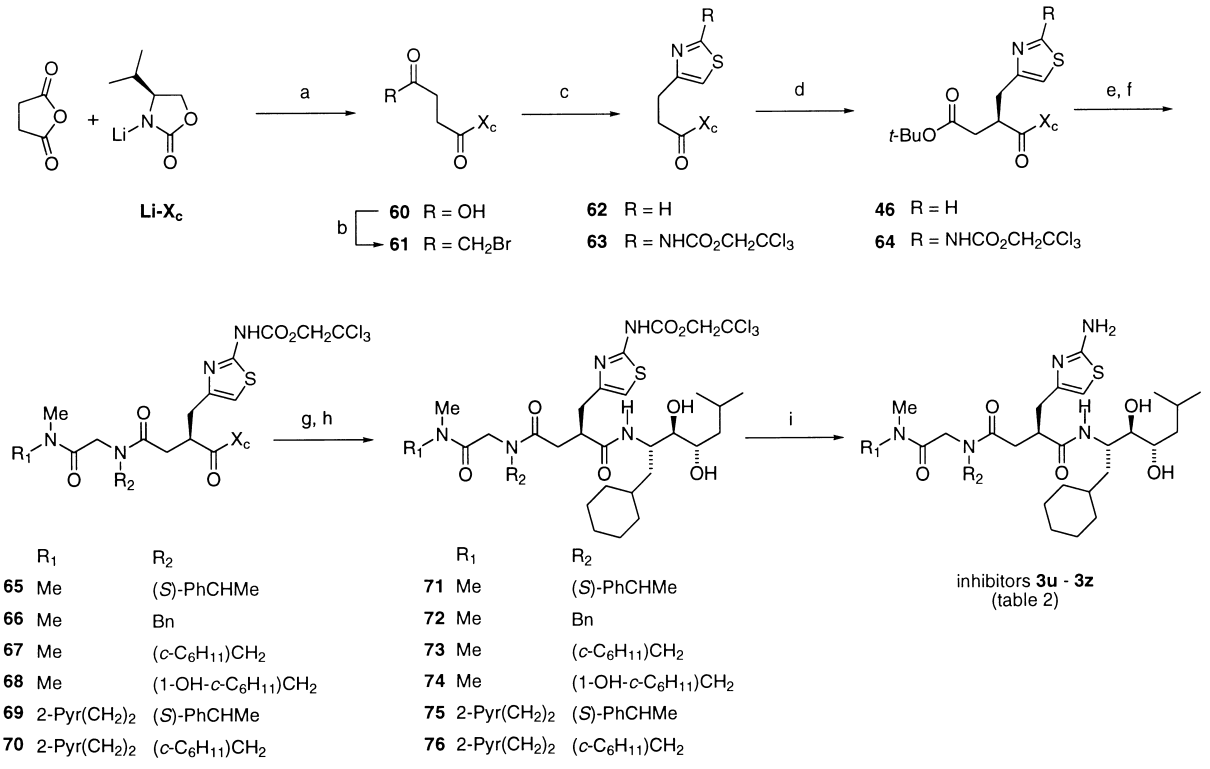
	R_1
54	*c*-C_3H_5
55	Et
56	2-thienyl
57	1-Tr-4-imidazolyl
58	2-thiazolyl
59	4-thiazolyl

Scheme 4. Reagents and conditions: (a) Me_3CCOCl, Et_3N, THF, −78 to 0 °C, then Li–X_c, −78 to 0 °C, 55–99%; for **31**, Li–X_c, −78 °C, 92%; (b) CH_2N_2, $Pd(OAc)_2$, Et_2O, 0 °C, 89% from **30**; (c) NaHMDS (LDA, DMPU for **36**), $BrCH_2CO_2R_2$, THF, −78 °C, 64–89%; (d) LiOOH, THF, H_2O, 0 to 25 °C; (e) **47**, BOP·PF_6, *i*-Pr_2NEt, DMF, 25 °C, 52–77%; (f) for R_2 = *t*-Bu: TFA, CH_2Cl_2, 0 to 25 °C, 46–100%; for R_2 = Bn: H_2 (1 atm), Pd/C, EtOAc, 25 °C, 99%; (g) $BnNH_2$, BnNHMe, **5–10** or **12–18**), BOP·PF_6, *i*-Pr_2NEt, DMF, 25 °C, 19–78%; and for **57** only, H_2 (1 atm), $Pd(OH)_2$/C, MeOH, 48%.

3, to determine the requirements at these positions. The exercise started with a 2(*R*)-(cyclopropylmethyl)butanediamide core. The cyclopropylmethyl substituent was selected as a starting point since it turned out to be a very good replacement for the histidine side chain in a previous series of inhibitors (e.g. **1** and **2**). The *N*-benzyl amide **3a** and the *N*-benzyl-*N*-methyl amide **3b** were the first members of this butanediamide series to be prepared. These small inhibitors demonstrated poor potency against renin with IC_{50} values of 640 and 455 nM, respectively (Table 1). They contain only one sizeable substituent that can occupy the S_3 or S_4 pockets considering the geometry of this terminal amide. In addition to the *N*-benzyl substituent, the introduction of a second substituent such as an *N,N*-disubstituted 2-acetamide group onto the nitrogen increased the potency of the resulting inhibitors by ca. tenfold which quickly demonstrated the potential of this new series of inhibitors. For instance, the *N,N*-dimethyl 2-acetamide analogue **3c** had an IC_{50} value of 56 nM. Other types of terminal tertiary amide such as morpholino (**3d**) or *N*-(2-pyridinyl)ethyl-*N*-methyl (**3e**) also afforded potent renin inhibitors having IC_{50} values of 65 and 33 nM, respectively. Note that the P_3–P_4 portion of inhibitors **3c–3e** constitutes a peptoid unit.[33]

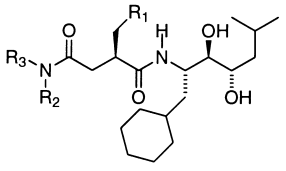
The carbonyl of the acetamide seems to match the one of the P_4 proline residue in the natural renin substrate. The presence of this extra carbonyl was therefore a requirement in order to generate very potent inhibitors. While the present work was well underway a patent application by Terumo[34] reporting a few renin inhibitors related to **3d** was published. However, the examples described were only restricted to N^4-(1-naphthylmethyl)butanediamide derivatives. To further probe the importance of the carbonyl at P_4, the corresponding tertiary amine **3f** of *N,N*-dimethyl amide **3c** was made and exhibited an IC_{50} value of 655 nM. Moreover, the tertiary amide was essential since the corresponding *N*-methyl amide **3g** as well as the methyl ester **3h** proved to be significantly less potent than **3c**. These findings are in complete agreement with observations made for other renin inhibitors having a N-terminal amide at the P_4 position.[7] Because of the presence of a non-symmetrical tertiary amide (N^4,N^4-disubstituted butanediamide), a mixture of rotamers was easily detected by ^{1}H NMR. So, the P_4 and P_3 side chains are defined as s-*cis* and s-*trans* respectively as drawn in **3** and are related to the nature and the requirements of the corresponding S_4 and S_3 pockets of the enzyme as well as the observed binding mode of these butanediamide inhibitors.[35]

Having defined the requirements of the P_4 position, we sought to optimize the P_3 position next. Since the P_3 side chain is linked to the nitrogen of an amide a variety of possibilities for the nature of this substituent were available. An N^4-phenylmethyl substituent on the butanediamide was first used, a substitution based on the



Scheme 5. Reagents and conditions: (a) THF, 0 °C, 67%; (b) (i) $(COCl)_2$,CH_2Cl_2, 0 °C; (ii) CH_2N_2, Et_2O, 0 °C then HBr/AcOH, 0 °C, 89%; (c) for **62**: $HCSNH_2$, *i*-PrOH, Δ, 55% from **61**; for **63**: (i) $(NH_2)_2CS$, *i*-PrOH, Δ (ii) $ClCO_2CH_2Cl_3$, *i*-Pr_2NEt, DMAP, CH_2Cl_2, 25 °C, 59% from **61**; (d) NaHMDS, THF, −78 °C, 59–86%; (e) TFA, CH_2Cl_2, 0 to 25 °C; (f) amine (**15**, **16**, **18**, **27**, **29**), BOP·PF_6, *i*-Pr_2NEt, DMF, 25 °C, 51–94%; (g) for **65–67**: LiOOH, THF, H_2O, 0 to 25 °C; for **68–70**: (i) $Mg(OMe)_2$, MeOH, 0 °C; (ii) aq NaOH; (h) **46**, BOP·PF6, *i*-Pr_2NEt, DMF, 25 °C, 24–48%; (i) Zn, 1 N aq HCl, dioxane, 10 °C, 50–85%.

Table 1. In vitro potency of P_2–P_3 butanediamide renin inhibitors



Compd no.	R_3	R_2	R_1	IC_{50} (nM)[a]
3a	$PhCH_2$	H	Cyclopropyl	640
3b	Me	$PhCH_2$	Cyclopropyl	455
3c	Me_2NCOCH_2	$PhCH_2$	Cyclopropyl	56
3d	$MorpholinoCOCH_2$	$PhCH_2$	Cyclopropyl	65
3e	$2\text{-}PyrCH_2CH_2NMeCOCH_2$	$PhCH_2$	Cyclopropyl	33
3f	$Me_2NCH_2CH_2$	$PhCH_2$	Cyclopropyl	655
3g	$MeNHCOCH_2$	$PhCH_2$	Cyclopropyl	350
3h	$MeOCOCH_2$	$PhCH_2$	Cyclopropyl	385
3i	Me_2NCOCH_2	$PhCH_2CH_2$	Cyclopropyl	52
3j	Me_2NCOCH_2	$2\text{-}PyrCH_2$	Cyclopropyl	145
3k	Me_2NCOCH_2	(*R*)-PhCHMe	Cyclopropyl	375
3l	Me_2NCOCH_2	(*S*)-PhCHMe	Cyclopropyl	43
3m	Me_2NCOCH_2	$CyclohexylCH_2$	Cyclopropyl	11
3n	Me_2NCOCH_2	(*S*)-CyclohexylCHMe	Cyclopropyl	12
3o	Me_2NCOCH_2	$(1\text{-}OH\text{-}Cyclohexyl)CH_2$	Cyclopropyl	16
3p	Me_2NCOCH_2	(*S*)-PhCHMe	Ethyl	35
3q	Me_2NCOCH_2	(*S*)-PhCHMe	2-Thienyl	11
3r	Me_2NCOCH_2	(*S*)-PhCHMe	1H-Imidazol-4-yl	7.3
3s	Me_2NCOCH_2	(*S*)-PhCHMe	2-Thiazolyl	3.7
3t	Me_2NCOCH_2	(*S*)-PhCHMe	4-Thiazolyl	2.9
3u	Me_2NCOCH_2	(*S*)-PhCHMe	2-Amino-4-thiazolyl	1.1

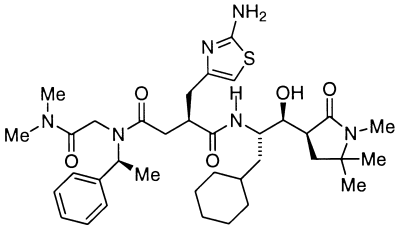
[a]Determined using a human plasma renin assay at pH 6.0.

observation of the side chain of phenylalanine being found at the P_3 position of most renin inhibitors. Replacement of the N^4-phenylmethyl by N^4-(2-phenylethyl) substituent provided inhibitor **3i**, which was equipotent to **3c**. As expected, a basic side chain such as 2-pyridinylmethyl was not well tolerated as inhibitor **3j** was three times less potent than **3c**. The introduction of a methyl group onto the benzylic position led to an equipotent inhibitor in the case of the *S* isomer (**3l**) whereas the *R* isomer (**3k**) was nine times less potent. The objective of the introduction of this stereogenic center was to probe for a possible beneficial orientation in the space of the P_3 side chain considering the planarity of the amide to which the benzyl is linked. Most likely, the benzylic hydrogen (C–H bond) would be in the same plane as the amide (allylic strain). So, the effect of the stereogenic center would be to orient the phenyl ring either on the bottom face (*S* configuration) or to the top face (*R* configuration) of the inhibitor related to the plane of the amide. Although the presence of the *S*-methyl showed no significant improvement in vitro, it proved to be very important in vivo (vide infra). It was found that the *S*-methyl group was projected into the solvent based on the X-ray analysis of a crystal structure of renin in complex with **3u**, an inhibitor similar to **3l**.[35] However, our observations contrast with findings reported for SC-51106[15], an (*S*)-β-methylhydrocinnamide (P_3) renin inhibitor lacking a P_4 residue. In that case, a sevenfold increase in potency was observed in comparison with the non-substituted hydrocinnamide derivative, while the *R*-epimer was inactive. A new binding site (S_3aux) was proposed to explain these results. The replacement of the N^4-phenylmethyl by a N^4-cyclohexylmethyl group provided the first significant improvement in potency leading to inhibitor **3m** which exhibited an IC_{50} value of 11 nM. Close analogues of **3m** such as the 1(*S*)-cyclohexylethyl and the (1-hydroxycyclohexyl)methyl derivatives **3n** and **3o** showed similar levels of potency.

Using inhibitor **3l** as a starting point, the P_2 side chain was next investigated (R_1). The inhibitor **3p** having an *n*-propyl side chain instead of a cyclopropylmethyl showed similar potency to **3l** with an IC_{50} value of 35 nM. It was quickly found that a five-membered ring heterocycle at this position was by far preferable for this series of butanediamide inhibitors. The 2-thienylmethyl analogue **3q** ($IC_{50} = 11$ nM) was four times more potent than the cyclopropylmethyl containing inhibitor **3l**. Inhibitor **3r**, which possesses the imidazolylmethyl side chain of the P_2 histidine present in the renin substrate, was even more potent with an IC_{50} value of 7.3 nM. At this point, a series of less basic imidazolyl surrogates were evaluated. The 2- and 4-thiazolylmethyl analogues **3s** and **3t** exhibited IC_{50} values of 3.7 and 2.9 nM, respectively. The (2-amino-4-thiazolyl)methyl analogue, inhibitor **3u**, proved to be the most potent inhibitor of this series with an IC_{50} of 1.1 nM. We believe that the 2-amino-4-thiazolyl heterocycle has stronger interactions with the enzyme than the imidazole ring. The crystal structure of renin-**3u** complex[35] showed that the amino group was hydrogen-bonded to the hydroxyl group of Ser222 and the carbonyl of Tyr220. The ring nitrogen of the thiazolyl was hydrogen bonded to the imidazole ring of His287 through a water molecule. The P_4 carbonyl and the amide of Tyr220 complete the tetrahedral coordination of the water molecule. The sulfur atom may also give rise to stronger van der Waals interactions with surrounding hydrophobic residues. By the sequential optimization of the P_4, P_3, and P_2 side chains, the potency of the inhibitors was quickly improved by 580-fold (cf. **3a** and **3u**), an enhancement attributed to the presence of: (a) an amide carbonyl at P_4; (b) N^4-cyclohexylmethyl or N^4-1(*S*)-phenylethyl substituents as the P_3 side chain and; (c) a 2-amino-4-thiazolylmethyl substituent as the P_2 side chain.

Having obtained highly potent inhibitors, we evaluated some in conscious sodium depleted cynomolgus monkeys. The renin inhibitors were given orally at a dose of 10 mg/kg (po). The mean arterial blood pressure (MABP) was monitored continuously for 3 h. Of the inhibitors (**3l**, **3p**, **3r**, **3s**, and **3u**) evaluated, only **3u** produced a statistically significant decrease in the MABP. The observed ca. 15% decrease of MABP was sustained at the end of the 3 h experiment. Plasma angiotensin II levels (−30% change) also decreased significantly. The nature of the P_2 side chain represents the sole structural difference among these inhibitors. For inhibitors **3l** and **3p** which were significantly less potent than **3u** (35-fold), the lack of oral efficacy could easily be explained based on the weak potency. However, since inhibitors **3r** and **3t** were only slightly less potent than **3u** (twofold to sixfold), their differences in absorption and/or hepatic extraction profile probably account for their poor oral efficacy. It was already reported that inhibitors with a basic histidine side chain at P_2 had poor oral efficacy due to rapid biliary elimination.[10,36] We had also noticed that inhibitors possessing thiazolylmethyl P_2 side chains were metabolized much faster by liver microsomes from cynomolgus monkeys than those compounds having a 2-amino-4-thiazolylmethyl side chain. These results clearly demonstrate that the 2-amino-4-thiazolylmethyl group at the P_2 side chain is critical for oral activity.

The next step was the optimization of **3u** based on in vivo activity. Using **3u** as our starting point, combined modifications at the P_4 and P_3 positions based on the previous exercise as well as other transition state mimics were investigated. So far, the cyclohexylamidodiol described by Abbott scientists[26] had been used at the P_1–P_1' portion of the inhibitors. Although other known transition state mimics were investigated, only the amidolactam,[37] shown in inhibitor **77**, produced a potent inhibitor with an IC_{50} value of 2.1 nM. Despite being equipotent to **3u**, **77** was found to be orally inactive when tested in the cynomolgus monkey model at 10 mg/kg.



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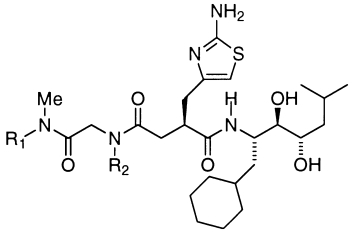
This result confirmed the choice of the transition state analogue unit for the P_2–P_3 butanediamide renin inhibitors. At the P_3 position, a simple N^4-benzyl substituent gave inhibitor **3v** (Table 2) that exhibited an IC_{50} value of 2.8 nM, slightly less potent than **3u** as expected (cf. **3c** and **3l**). To our surprise, inhibitor **3v** was inactive at 10 mg/kg po in the monkey model. The difference in potency was certainly an important element. In addition, the *S*-methyl substituent in **3u** could play a role in the metabolic stabilization of the N^4-benzyl position vis-à-vis oxidation/de-alkylation processes leading to the costly loss of the P_3 side chain. Inhibitor **3w**, possessing a cyclohexylmethyl substituent at the P_3 side chain, showed a profile similar to **3u**, in vitro and in vivo. A simple introduction of a hydroxyl group at position 1 of the cyclohexyl, giving **3x**, had again a significant impact in vivo. Inhibitor **3x** exhibited an IC_{50} value of 1.2 nM but was found to be orally inactive in the cynomolgus monkey model. Finally, a modification at the P_4 position brought the desired improvement in vivo. Replacement of the terminal *N,N*-dimethyl amide by an *N*-methyl-*N*-2-(2-pyridinyl)ethyl amide generated **3y** that was as potent as **3u** in the plasma renin assay but was orally active at a dose as low as 3 mg/kg in the cynomolgus monkey model. The corresponding analogue of **3w**, inhibitor **3z** had a profile very similar to **3y**. The effect of oral doses of 10, 3, and 1 mg/kg of inhibitor **3z** on MABP of cynomolgus monkeys are shown in Figure 2. Statistically significant decreases in MABP were observed for doses of 10 and 3 mg/kg in a dose-related fashion. Decreases in plasma angiotensin II levels were observed for doses of 10 and 3 mg/kg. Inhibitors **3y** and **3z** had oral efficacies comparable to that of one of the most potent renin inhibitors reported to date, A-72517.[10]

All the inhibitors generated in the optimization of **3u** exhibited IC_{50} values similar (0.8–2.8 nM) to that of **3u** ($IC_{50} = 1.1$ nM). In some cases, small chemical modifications had profound effects on the oral activity of the

Table 2. In vitro and in vivo potency of P_2–P_3 2-[(2-amino-4-thiazolyl)-methyl]butanediamide renin inhibitors



Compd no.	R_1	R_2	IC_{50} (nM)[a]	Oral activity[b] mg/kg po
3u	Me	(*S*)-PhCHMe	1.1	Active at 10
3v	Me	$PhCH_2$	2.8	Inactive at 10
3w	Me	CyclohexylCH_2	0.8	Active at 10
3x	Me	(1-OH-Cyclohexyl)CH_2	1.2	Inactive at 10
3y	2-PyrCH_2CH_2	(*S*)-PhCHMe	0.9	Active at 3
3z	2-PyrCH_2CH_2	CyclohexylCH_2	1.4	Active at 3

[a]Determined using a human plasma assay at pH 6.0.
[b]Determined using sodium depleted normotensive cynomolgus monkeys.

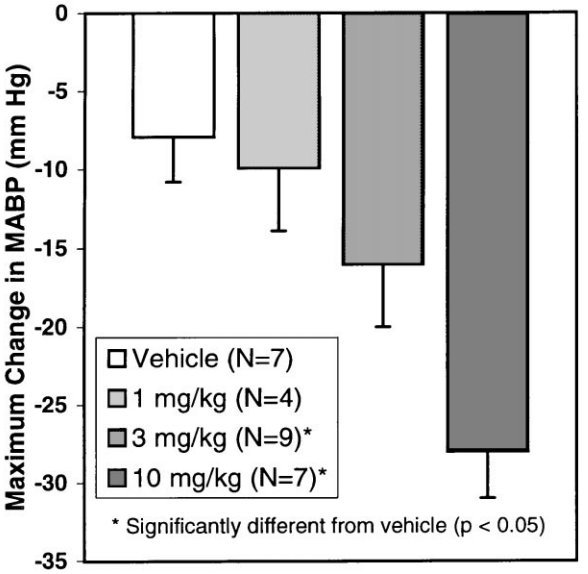


Figure 2. Maximum changes in mean arterial blood pressure (MABP) after oral administration of **3z** in conscious cynomolgus monkeys.

inhibitors. Obviously, these analogues possess different physicochemical properties that impact on their oral bioavailability profiles. The oral bioavailabilities in cynomolgus monkey (iv and oral doses of 1 and 10 mg/kg, respectively) for the orally active renin inhibitors **3u**, **3w**, **3y**, and **3z** were 17 ± 6%, 12 ± 8%, 89 ± 53%, and 40 ± 23%, respectively. After the oral dose, these compounds exhibited peak concentrations (C_{max}) of 168 ± 54, 131 ± 65, 865 ± 470, 710 ± 350 ng/mL, respectively, while their values for area under the curve (AUC) were 510 ± 191, 365 ± 260, 2330 ± 1570, 2500 ± 1650 ng h/mL, respectively. These compounds are among the most bioavailable renin inhibitors reported to date. It is interesting to note that the sole difference between **3u**, **3w**, and **3y**, **3z** is the addition of a 2-pyridinylmethyl moiety at the P_4 position. This heterocycle does not interact with the enzyme, the pyridine being exposed to the solvent.[35] The introduction of the 2-pyridinylmethyl substituent had obviously no impact on in vitro potency but had a beneficial contribution to absorption and oral bioavailability. Although the addition of this moiety increased the molecular weight of the inhibitors by 91 mass units (MW of 643 and 635 to 734 and 726), the oral bioavailability was significantly improved.

Although a human plasma assay at pH 6.0 (optimal pH for renin) was employed as the primary screen, in vitro potencies at physiological pH (7.4) were also considered during compound evaluation. It would be ideal to identify inhibitors with high potencies irrespective of pH. A comparison of IC_{50} values at pH 6.0 and 7.4 for a selection of inhibitors is shown in Table 3. Large shifts in the IC_{50} values were observed for inhibitors (**3l–3p**) possessing a cyclopropylmethyl or a *n*-propyl group at the P_2 position. For instance, since **3l** and **3p** have IC_{50} values of 760 and 300 nM at pH 7.4, it was not surprising to discover their lack of oral activity. Inhibitors having basic residues at the P_2 side chain shifted the

Table 3. In vitro potency of P_2–P_3 butanediamide inhibitors for renin at pH 6.0 and 7.4 and for cathepsin D

Compd no.	IC_{50} (nM) renin, plasma pH 6.0	IC_{50} (nM) renin, plasma pH 7.4	IC_{50} (nM) cathepsin D
3l	43	760	53
3m	11	110	30
3n	12	100	9
3o	16	94	50
3p	35	300	66
3r	7.3	11	0% inh. at 1 uM
3s	3.7	33	24
3t	2.9	24	57
3u	1.1	7.6	810
3v	2.8	18	600
3w	0.8	3.3	190
3x	1.2	5.4	595
3y	0.9	4.7	2650
3z	1.4	2.5	540

least and retained their potency against renin at pH 7.4. For inhibitor **3r**, the IC_{50} value did not change with pH. This inhibitor has an imidazolylmethyl P_2 side chain identical to the histidine side chain that is present in the renin substrate. Inhibitors **3s–3z** that possess basic surrogates of the imidazolyl ring, remain highly potent inhibitors at pH 7.4. For the most potent inhibitors, the ranking based on IC_{50} values remains more or less the same at both pH 6.0 and 7.4. All the orally active inhibitors were potent at both pHs. Potency at pH 7.4 seemed to be one of the requirements for oral activity.

The specificity of our inhibitors for renin was assessed using three other human aspartyl proteases: pepsin, gastricsin and cathepsin D. For pepsin and gastricsin, the activity observed was never a concern since it was only modest for all the inhibitors (a few % inhibition at 1 μM). In the case of cathepsin D, the situation was different. Inhibitors **3l–3p** had IC_{50} values very similar for cathepsin D and renin at pH 6.0 (Table 3). Others had only a small preference for renin (e.g. **3s**, **3t**). It is apparent that the nature of the P_2 side chain had a significant impact on the specificity of the inhibitors. The presence of the imidazolylmethyl substituent at P_2 (**3r**) eliminated completely the affinity of the compound for cathepsin D. Inhibitors possessing the 2-amino-4-thiazolylmethyl side chain (**3u–3z**) had a good window of selectivity, a good compromise between specificity, potency against renin at both pHs and in vivo properties. The nature of the P_3 side chain also had an impact on the specificity profile of this class of inhibitors. Cathepsin D seemed to prefer N^4-(cycloalkyl)alkyl over N^4-phenylalkyl side chains (cf. **3u** and **3w**, **3y** and **3z**). In general, bulkier and neutral lipophilic groups at P_2 and P_3 positions were preferred by cathepsin D as predicted by X-ray data.[38]

Conclusions

We have identified a new series of potent renin inhibitors having a 2-substituted butanediamide moiety at the P_2 and P_3 positions. The most potent inhibitors possess an N^4-2-(disubstituted-amino)-2-oxoethyl group at P_4 position and a (2-amino-4-thiazolyl)methyl substituent as the P_2 side chain. The orally active inhibitors (**3u**, **3w**, **3y**, **3z**) had IC_{50} values of 0.8 to 1.4 nM and 2.5 to 7.6 nM at pH 6.0 and 7.4, respectively. The presence of the 2-amino-4-thiazolyl heterocycle was critical for oral activity. From a synthetic standpoint, we believe that the introduction of the P_2–P_3 butanediamide segment contributed to the simplification of the P_2–P_3–P_4 portion of these renin inhibitors. Only one stereogenic center remains in this section of the molecule. This simplification had only a small impact on the level of potency obtained by the optimized inhibitors in comparison with more peptidic inhibitors. The P_2–P_3 butanediamide inhibitors contain no amino acid residue other than the N-terminal glycinamide. The optimized P_2–P_3 butanediamide inhibitors demonstrated good oral bioavailability in cynomolgus monkeys. The *N,N*-dimethyl amide derivatives **3u** and **3w** had oral bioavailabilities of 11.5 and 17%, molecular weights of 643 and 635, respectively, and were orally active at a dose of 10 mg/kg in the monkey model. Interestingly, the corresponding *N*-methyl *N*-2-(2-pyridinyl)ethyl derivatives **3y** and **3z** were orally active at 3 mg/kg in the monkey model, had oral bioavailabilities of 89 and 40%, respectively, values higher than **3u** and **3w** despite the fact that molecular weights were increased to 734 and 726. After further evaluation of the most potent orally active inhibitors **3y** and **3z** as well as close analogues, inhibitor **3z** (BILA 2157 BS) was selected as a candidate for pre-development.

Table 4. Yields and analytical properties of **3a–k**, **3m–o**, and **3v–3y**

Compd no.	Yield[a] (%)	MS FAB m/z $(MH)^+$	Elemental analysis[b] C, H, N ± 0.4%
3a	15	487	$C_{29}H_{46}N_2O_4$
3b	37	501	$C_{30}H_{48}N_2O_4$
3c	65	572	$C_{33}H_{53}N_3O_5$
3d	71	614	$C_{35}H_{55}N_3O_6$
3e	57	663	$C_{39}H_{58}N_4O_5 + 0.76\%\ H_2O$[c]
3f	14	558	$C_{33}H_{55}N_3O_4 + 0.74\%\ H_2O$[c]
3g	70	558	$C_{32}H_{51}N_3O_5$
3h	82	559	$C_{32}H_{50}N_2O_6$
3i	75	586	$C_{34}H_{55}N_3O_5$
3j	72	573	$C_{32}H_{52}N_4O_5 + 0.78\%\ H_2O$[c]
3k	66	586	$C_{34}H_{55}N_3O_6 + 0.99\%\ H_2O$
3m	59	578	$C_{33}H_{59}N_3O_5 + 0.74\%\ H_2O$
3n	70	592	$C_{34}H_{61}N_3O_6$
3o	77	594	$C_{33}H_{59}N_3O_6 + 1.92\%\ H_2O$
3v	10	630	$C_{33}H_{51}N_5O_5S + 1.03\%\ H_2O$
3w	22	636	$C_{33}H_{57}N_5O_5S + 1.86\%\ H_2O$
3x	19	652	$C_{33}H_{57}N_5O_6S + 2.00\%\ H_2O$
3y	26	735	$C_{40}H_{58}N_6O_5S$

[a]Compounds **3a–o** were prepared using the method described for **3l**. Compounds **3v**, **3w** and compounds **3x**, **3y** were synthesized from **64** according to the method described for **3u** and **3z**, respectively.
[b]The amount of H_2O (% w/w) was determined using the Karl Fisher method.
[c]Correct elemental analyses could not be obtained for these compounds. The homogeneity was determined to be >98% by RP-HPLC in two solvent systems.

Experimental

All reactions were performed under a nitrogen atmosphere. Reagents and anhydrous solvents were obtained

from commercial sources and were used without further purification or treatment. In order to remove traces of solvents, the inhibitors were dissolved in a mixture of water and acetonitrile, frozen and then lyophilized. Melting points were determined on an electrothermal Büchi 510 apparatus and are uncorrected. IR and FTIR spectra were recorded on a Perkin–Elmer 781 and ATI Mattson research series I, respectively. NMR spectra were recorded on a Bruker AMX400 spectrometer. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Electrospray ionization (ESI) mass spectra were determined on a Micromass Quattro II apparatus. Fast atom bombardment (FAB) mass spectra were determined on a VG AutoSpec-Q or Kratos M550 apparatus at the Université de Montréal. Microanalyses were performed on a Carlo Erba 1100 or Fisons EA 1108 instruments. The residual amount of water was quantified using the Karl Fisher method with a Metrohm 652 KF-Coulometer. RP-HPLC analyses were performed on a Waters 600-MS (A: Supelcosil® LC-ABZ; 10–80% MeCN + 0.10% TFA/H_2O + 0.10% TFA) and a Waters 625 system (B: Symmetry® C_8 column; 10–80% MeCN/50 mM NaH_2PO_4 pH 4.4) using a photodiode array detector.

Procedure for the preparation of amines 5–8. A solution of **4** (531 mg, 2.00 mmol), R_1R_2NH or $R_1R_2NH{\cdot}HCl$ (2.40–3.00 mmol), *i*-Pr_2NEt (776 mg, 6.00 mmol) and BOP·PF_6 (885 mg, 2.00 mmol) in DMF (8 mL) was stirred at 25 °C for 4–16 h. The reaction mixture was diluted with EtOAc and the resulting solution was successively washed with aqueous 1 N HCl (not for **7**), H_2O, saturated aqueous $NaHCO_3$ and brine, and then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude BOC derivative was treated with excess anhydrous 4 N HCl in dioxane at 25 °C for 1–2 h. The mixture was concentrated under reduced pressure and the residue partitioned between aqueous 5% Na_2CO_3 and EtOAc. The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the amines **5–8** that were used without any purification.

***N,N*-Dimethyl-2-[(phenylmethyl)amino]acetamide (5).** Colorless oil (77%): IR (film) ν_{max} 3520, 3330, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39–7.26 (m, 5H), 3.87 (s, 2H), 3.45 (s, 2H), 2.97 (s, 3H), 2.91 (s, 3H); MS (CI) *m/z* 193 $(MH)^+$.

4-[2-[(Phenylmethyl)amino]acetyl]morpholine (6). Yellowish oil (78%): IR (film) ν_{max} 3520, 3340, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.25 (m, 5H), 3.85 (s, 2H), 3.74–3.63 (m, 6H), 3.44 (s, 2H), 3.37–3.35 (m, 2H), 2.86 (broad s, 1H); MS (CI) *m/z* 235 $(MH)^+$.

***N*-Methyl-2-[(phenylmethyl)amino]-*N*-[2-(2-pyridinyl)-ethyl]acetamide (7).** Pale yellow oil (86%): IR (film) ν_{max} 3460, 3330, 1650 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.48, 8.44 (2d, *J* = 4.3 Hz, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.34–7.20 (m, 7H), 3.73, 3.64 (2s, 2H), 3.64, 3.59 (2t, *J* = 7.3 Hz, 2H), 3.40, 3.29 (2s, 2H), 2.95, 2.91 (2t, *J* = 7.3 Hz, 2H), 2.84 (s, 3H); MS (FAB) *m/z* 284 $(MH)^+$.

***N*-Methyl-2-[(phenylmethyl)amino]acetamide (8).** Pale yellow solid (77%): IR (film) ν_{max} 3300, 3220, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–7.27 (m, 5H), 7.21 (broad s, 1H), 3.80 (s, 2H), 3.34 (s, 2H), 2.83 (d, *J* = 5.1 Hz, 3H), 2.41 (broad s, 1H); MS (CI) *m/z* 179 $(MH)^+$.

***N,N*-Dimethyl-*N'*-(phenylmethyl)-1,2-ethanediamine (9).** The reduction of **5·HCl** with $LiAlH_4$ gave **9** (132 mg, ~100%) as a yellowish oil which was used without purification: IR (film) ν_{max} 3380, 3330, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.23 (m, 5H), 3.83 (s, 2H), 2.73 (t, *J* = 6.1 Hz, 2H), 2.47 (t, *J* = 6.1 Hz, 2H), 2.29 (broad s, 1H), 2.23 (s, 6H); MS (CI) *m/z* 179 $(MH)^+$.

Methyl 2-[(phenylmethyl)amino]acetate (10).[39]

Typical procedure for preparation of amines 12–18. A solution of **11** (500 mg, 3.01 mmol), a primary amine (1 equiv, 3.01 mmol) and Et_3N (610 mg, 6.02 mmol) in MeOH (6.0 mL) was stirred at 25 °C for 5 min then was heated to reflux for 30 min. The cooled mixture was diluted with EtOAc (100 mL) and the resulting solution was washed with saturated aqueous $NaHCO_3$ (30 mL), brine (30 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give the amines **12–18**.

***N,N*-Dimethyl-2-[(2-phenylethyl)amino]acetamide (12).** Using phenethylamine, **12** (36%) was obtained as a yellowish oil after purification by flash chromatography (EtOAc:MeOH, 3:1): IR (film) ν_{max} 3540, 3320, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–7.17 (m, 5H), 3.44 (s, 2H), 2.95 (s, 3H), 2.93 (s, 3H), 2.94–2.50 (m, 2H), 2.87–2.83 (m, 2H), 2.75 (broad s, 1H); MS (CI) *m/z* 207 $(MH)^+$.

***N,N*-Dimethyl-2-[(2-pyridinylmethyl)amino]acetamide dihydrochloride (13).** Using (2-aminomethyl)pyridine and the procedure described above, **13** could not be extracted from the $NaHCO_3$ solution (soluble). The aqueous layer was therefore concentrated under reduced pressure and the residue was treated with $(BOC)_2O$ (1 equiv) in CH_2Cl_2 (0.6 M) at 25 °C for 2 h. The BOC derivative was purified by flash chromatography ($CHCl_3$:EtOH, 15:1). Upon treatment of the BOC derivative with excess 5 M HCl/dioxane for 2 h, **13** (26%) was obtained as a yellow solid: FTIR (KBr) ν_{max} 3850–3540, 1652 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.43 (broad s, 1H), 8.65 (ddd, *J* = 5.1, 1.6, 1.0 Hz, 1H), 7.93 (~td, *J* = 7.9, 7.5, 1.6 Hz, 1H), 7.58 (broad d, *J* = 7.9 Hz, 1H), 7.47 (ddd, *J* = 7.5, 5.1, 1.0 Hz, 1H), 6.79 (broad s, 2H), 4.34 (s, 2H), 4.11 (s, 2H), 2.93 (s, 3H), 2.90 (s, 3H); MS (FAB) *m/z* 194 $(MH)^+$.

***N,N*-Dimethyl-2-[[1(*R*)-phenylethyl]amino]acetamide (14).** From 1(*R*)-phenylethylamine, **14** (76%) was obtained as a yellowish oil after purification by column chromatography (EtOAc:MeOH, 4:1): $[\alpha]_D^{25}$ +52.4° (*c* 1.28 MeOH); IR (film) ν_{max} 3320, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36–7.30 (m, 4H), 7.24 (broad t, *J* = 6.7 Hz, 1H), 3.81 (q, *J* = 6.3 Hz, 1H), 3.27 (s, 2H), 3.05 (broad s,

1H), 2.94 (s, 3H), 2.81 (s, 3H), 1.42 (d, $J = 6.3$ Hz, 3H); MS (CI) m/z 207 $(MH)^+$.

***N,N*-Dimethyl-2-[[1(*S*)-phenylethyl]amino]acetamide (15).** Using 1(*S*)-phenylethylamine, **15** (70%) was obtained as a yellowish oil: $[\alpha]_D^{25}$ −50.4° (*c* 0.98 MeOH); IR and ^{1}H NMR identical to enantiomer **14**; MS (CI) m/z 207 $(MH)^+$.

2-[(Cyclohexylmethyl)amino]-*N,N*-dimethylacetamide (16). From cyclohexanemethylamine, **16** (30%) was obtained as a yellowish solid after purification by flash chromatography ($CHCl_3$:EtOH, 9:1 to 6:1): IR (KBr) ν_{max} 3320, 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.43 (s, 2H), 2.97 (3H, s), 2.96 (s, 3H), 2.88 (broad s, 1H), 2.47 (d, $J = 6.7$ Hz, 2H), 1.73–1.63 (m, 5H), 1.54–1.47 (m, 1H), 1.30–1.12 (m, 3H), 0.99–0.90 (m, 2H); MS (CI) m/z 199 $(MH)^+$.

2-[[1(*S*)-Cyclohexylethyl]amino]-*N,N*-dimethylacetamide (17). From 1(*S*)-cyclohexylethylamine, **17** (42%) was obtained as a yellowish oil after purification by flash chromatography ($CHCl_3$:EtOH, 10:1): $[\alpha]_D^{25}$ +13.8° (*c* 0.98 MeOH); IR (film) ν_{max} 3320, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.53 (broad d, $J = 15.7$ Hz, 1H), 3.39 (broad d, $J = 15.7$ Hz, 1H), 2.97 (broad s, 6H), 2.54–2.45 (m, 1H), 1.81–1.61 (m, 5H), 1.46–1.34 (m, 1H), 1.31–1.00 (m, 8H); MS (CI) m/z 213 $(MH)^+$.

***N,N*-Dimethyl-2-[[(1-hydroxycyclohexyl)methyl]amino]-acetamide (18).** Using 1-(aminomethyl)cyclohexanol, **18** (43%) was obtained as a beige solid after purification by flash chromatography (CH_2Cl_2:EtOAc, 85:15 to 3:1): IR (KBr) ν_{max} 3410, 3370, 1655, 1630 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.02 (broad s, 1H), 3.35 (s, 2H), 2.91 (s, 3H), 2.83 (s, 3H), 2.42 (s, 2H), 2.34–2.22 (broad s, 1H), 1.60–1.29 (m, 9H), 1.27–1.16 (m, 1H); MS (EI) m/z 215 $(MH)^+$.

Ethyl 2-[(cyclohexylmethyl)amino]acetate (20). A solution of ethyl 2-bromoacetate (**19**) (500 mg, 3.00 mmol), cyclohexanemethylamine (340 mg, 3.00 mmol) and Et_3N (607 mg, 6.00 mmol) in THF (6.0 mL) was stirred at 25 °C for 1.5 h. The reaction mixture was diluted with EtOAc (100 mL) and the solution was washed with saturated aqueous $NaHCO_3$ (40 mL), brine (40 mL) and then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane:EtOAc, 4:1 to 2:1) to give **20** (394 mg, 66%) as a pale yellow oil: IR (film) ν_{max} 1736 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.08 (q, $J = 7.2$ Hz, 2H), 3.27 (s, 2H), 2.33 (d, $J = 6.7$ Hz, 2H), 2.04 (broad s, 1H), 1.72–1.60 (m, 5H), 1.38–1.28 (m, 1H), 1.24–1.07 (m, 3H), 1.19 (t, $J = 7.2$ Hz, 3H), 0.89–0.80 (m, 2H); MS (FAB) m/z 200 $(MH)^+$.

1,1-Dimethylethyl *N*-(cyclohexylmethyl)-*N*-(2-ethoxy-2-oxoethyl)carbamate (21). A solution of **20** (372 mg, 1.87 mmol) and $(Boc)_2O$ (396 mg, 1.81 mmol) in CH_2Cl_2 (3.7 mL) was stirred at 25 °C for 2.5 h. The reaction mixture was diluted with EtOAc (75 mL) and the resulting solution was washed with 1 N HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), brine (30 mL) and then was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **21** (533 mg, 98%): IR (film) ν_{max} 1746, 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (1:1 mixt. of rotamers) 4.12, 4.11 (2q, $J = 7.0$ Hz, 2H), 3.86, 3.77 (2s, 2H), 3.05, 3.02 (2d, $J = 7.3$ Hz, 2H), 1.69–1.55 (m, 5H), 1.48–1.40 (m, 1H), 1.40, 1.35 (2s, 9H), 1.21, 1.20 (2t, $J = 7.0$ Hz, 3H), ~1.23–1.07 (m, 3H), 0.90–0.78 (m, 2H); MS (FAB) m/z 300 $(MH)^+$.

1,1-Dimethylethyl *N*-(carboxymethyl)-*N*-(cyclohexylmethyl)carbamate (22). A heterogeneous solution of **21** (510 mg, 1.70 mmol) and 2 N NaOH (2.6 mL, 5.10 mmol) in MeOH (2.6 mL) was stirred at 25 °C for 16 h. The MeOH was removed under reduced pressure and the residual aqueous suspension was diluted with H_2O (70 mL). The resulting solution was washed with Et_2O (2×20 mL), rendered acidic (pH < 3) by addition of 1 N HCl and extracted with EtOAc (2×50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **22** (443 mg, 96%) as a colorless oil: IR (film) ν_{max} 1693 (broad) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.79, 3.77 (2s, 2H), 3.01 (broad d, $J = 7.3$ Hz, 2H), 1.67–1.45 (m, 6H), 1.38, 1.34 (2s, 9H), 1.28–1.09 (m, 3H), 0.90–0.82 (m, 2H); MS (FAB) m/z 272 $(MH)^+$.

Ethyl 2-[[1(*S*)-phenylethyl]amino]acetate (23). 1(*S*)-Phenylethylamine (3.03 g, 25.0 mmol) was converted into **23** using the procedure described for **20**. Purification by flash chromatography (hexane:EtOAc, 2:1) gave **23** as a colorless oil (3.20 g, 62%): ^{1}H NMR (DMSO-d_6) δ 7.33–7.29 (m, 4H), 7.24–7.20 (m, 1H), 4.06 (q, $J = 7.2$ Hz, 2H), 3.74 (q, $J = 6.6$ Hz, 1H), 3.17 (d, $J = 17.2$ Hz, 1H), 3.06 (d, $J = 17.2$ Hz, 1H), 2.35 (broad s, 1H), 1.25 (d, $J = 6.6$ Hz, 3H), 1.16 (t, $J = 7.2$ Hz, 3H); MS (ESI) m/z 208 $(MH)^+$.

1,1-Dimethylethyl *N*-(2-ethoxy-2-oxoethyl)-*N*-[1(*S*)-phenylethyl]carbamate (24). Using the procedure described for **21**, amine **23** (2.89 g, 13.9 mmol) and $(Boc)_2O$ (2.95 g, 13.5 mmol) gave carbamate **24** (4.14 g, 100%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ (1.7:1.0 mixt. of rotamers) 7.35–7.26 (m, 5H), 5.62, 5.33 (2q, $J = 6.6$ Hz, 1H), 4.11 (q, $J = 7.1$ Hz, 2H), 3.92, 3.70 (2d, $J = 17.0$, 17.6 Hz, 1H), 3.55, 3.44 (2d, $J = 17.0$, 17.6 Hz, 1H), 1.53–1.42 (m, 12H), 1.22 (t, $J = 7.1$ Hz, 3H); MS (FAB) m/z 308 $(MH)^+$.

1,1-Dimethylethyl *N*-(carboxymethyl)-*N*-[1(*S*)-phenylethyl]carbamate (25). Using the procedure described for **22**, **24** (3.07 g, 10.0 mmol) was transformed into acid **25** (2.45 g, 99%), isolated as a thick colorless oil: $[\alpha]_D^{23}$ −65.7° (*c* 0.63 MeOH); ^{1}H NMR (DMSO-d_6) δ (2:1 mixt. of rotamers) 7.36 (m, 5H), 5.36, 5.09 (2q, $J = 6.6$ Hz, 1H), 3.83, 3.67 (2d, $J = 17.3$ Hz, 1H), 3.67, 3.49 (2d, $J = 17.3$ Hz, 1H), 1.47, 1.43 (2d, $J = 6.6$ Hz, 3H), 1.38, 1.32 (2s, 9H); MS (FAB) m/z 280 $(MH)^+$. Anal. calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.42; H, 7.61; N, 4.97.

1,1-Dimethylethyl *N*-(cyclohexylmethyl)-*N*-[2-[methyl[2-(2-pyridinyl)ethyl]amino]-2-oxoethyl]carbamate (26). BOP·PF_6 (713 mg, 1.61 mmol) was added to a solution of **22** (417 mg, 1.53 mmol), 2-[2-(methylamino)ethyl]pyridine

(220 mg, 1.61 mmol) and *i*-Pr_2NEt (397 mg, 3.07 mmol) in DMF (6.0 mL) at 25 °C. The mixture was stirred at 25 °C for 3 h. The reaction mixture was diluted with EtOAc (100 mL) and the resulting solution was washed successively with saturated aqueous $NaHCO_3$ (30 mL), H_2O (2×20 mL) and brine (30 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc:MeOH, 20:1) to yield **26** (548 mg, 89%) as a colorless oil: IR (film) ν_{max} 3600–3260, 1675 (broad) cm^{-1}; ^1H NMR (DMSO-d_6) δ (~1:1:1:1 mixt. of rotamers) 8.52, 8.48 (2d, J = 4.4, 4.1 Hz, 1H), 7.75–7.67 (m, 1H), 7.31, 7.27–7.19 (d and m, J = 7.9 Hz, 2H), 3.92, 3.88, 3.79 (3s, 2H), 3.64–3.58 (m, 2H), 3.01–2.84 (m, 4H), 2.89, 2.82, 2.81 (3s, 3H), 1.70–1.43 (m, 6H), 1.38, 1.36, 1.31, 1.29 (4s, 9H), 1.19–1.09 (m, 3H), 0.90–0.76 (m, 2H); MS (FAB) m/z 390 $(MH)^+$.

2-[(Cyclohexylmethyl)amino]-*N*-methyl-*N*-[2-(2-pyridinyl)ethyl]acetamide (27). A solution of **26** (518 mg, 1.33 mmol) in 4 N anhydrous HCl in 1,4-dioxane (5.0 mL, 20 mmol) was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure. The residue was dissolved in H_2O and treated with aqueous 5% Na_2CO_3 before the resulting solution was extracted with EtOAc (5×50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **27** (365 mg, 95%) as a colorless oil: IR (film) ν_{max} 3500–3220, 1645 cm^{-1}; ^1H NMR (DMSO-d_6) δ (1:1 mixt. of rotamers) 8.50, 8.48 (2 broad d, J = 3.8, 4.8 Hz, 1H), 7.71, 7.69 (2td, J = 7.3, 1.6 Hz, J = 7.6, 1.9 Hz, 1H), 7.30–7.19 (m, 2H), 3.64–3.59 (m, 2H), 3.26, 3.11 (2s, 2H), 2.97, 2.89 (2t, J = 7.0, 7.0 Hz, 2H), 2.86, 2.82 (2s, 3H), 2.30, 2.16 (2d, J = 6.7, 6.7 Hz, 2H), 1.74–1.57 (m, 5H), 1.40–1.08 (m, 4H), 0.91–0.75 (m, 2H); MS (ESI) m/z 290 $(MH)^+$.

1,1-Dimethylethyl *N*-[2-[methyl[2-(2-pyridinyl)ethyl]amino]-2-oxoethyl]-*N*-[1(*S*)-phenylethyl]carbamate (28). Acid **25** (2.39 g, 8.56 mmol) was converted into **28** using the procedure described for **26**. Purification by flash chromatography (EtOAc:MeOH, 20:1) gave **28** (3.13 g, 79%) as a colorless oil: IR (film) ν_{max} 3615–3310, 1674 (broad) cm^{-1}; ^1H NMR (DMSO-d_6) δ (mixt. of rotamers) 8.48, 8.38 (d and broad s, J = 4.4 Hz, 1H), 7.72–7.66 (m, 1H), 7.36–7.09 (m, 7H), 5.29, 4.92 (2 broad s, 1H), 4.17–3.30 (m, 4H), 3.30–2.81 (m, 5H), 1.38–1.26 (m, 12H); MS (ESI) m/z 398 $(MH)^+$.

***N*-Methyl-2-[[1(*S*)-phenylethyl]amino]-*N*-[2-(2-pyridinyl)-ethyl]acetamide (29).** Using the procedure described for **27**, **28** (1.27 g, 3.19 mmol) was transformed into **29** (916 mg, 96%), isolated as a colorless oil: $[\alpha]_D^{23}$ −40.5° (*c* 1.61 MeOH); IR (film) ν_{max} 3550–3280, 1644 cm^{-1}; ^1H NMR (DMSO-d_6) δ (1:1 mixt. of rotamers) 8.47, 8.37 (2 broad d, J = 3.8, 4.1 Hz, 1H), 7.69, 7.65 (2td, J = 7.6, 1.9 Hz, J = 7.6, 1.6 Hz, 1H), 7.33–7.13 (m, 7H), 3.71–3.55 (m, 2H), 3.49, 2.88 (2t, J = 7.0, 7.3 Hz, 2H), 3.13, 3.01 (2s, 2H), 2.88–2.84 (m, 1H), 2.80, 2.73 (2s, 3H), 1.25, 1.21 (2d, J = 6.7, 6.7 Hz, 3H); MS (ESI) m/z 298 $(MH)^+$.

3-(3-Cyclopropyl-1-oxopropyl)-4(*S*)-(1-methylethyl)-2-oxazolidinone (36). Pivaloyl chloride (14.5 g, 120 mmol) was added (5 min) to an ice-cold solution of 4-pentenoic acid (12.0 g, 120 mmol) and *N*-methylmorpholine (14.2 g, 140 mmol) in THF (100 mL). The mixture was stirred at 0 °C for 30 min then was cooled to −78 °C. A cold (−78 °C) solution of the lithium salt of 4(*S*)-(1-methylethyl)-2-oxazolidinone (100 mmol) [prepared using 1.6 M *n*-BuLi/hexane (62.5 mL, 100 mmol)] in THF (150 mL) was added via cannula to the mixed anhydride and the reaction mixture was stirred at −78 °C for 30 min. Saturated aqueous NH_4Cl was then added, the mixture was allowed to warm to 25 °C and was poured into H_2O. The phases were separated and the aqueous layer extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **35**. Crude **35** was added to an ice-cold ether solution of CH_2N_2 (0.4 M, 175 mL) in a 4 L Erlenmeyer flask followed by the addition of $Pd(OAc)_2$ (112 mg, 0.5 mmol). After the vigorous reaction stopped, additional amounts of $Pd(OAc)_2$ (3×112 mg) and CH_2N_2 solution (3×175 mL) were added in sequence. The reaction mixture was filtered through a pad of Celite® and concentrated under reduced pressure. The residue was purified by distillation (bulb-to-bulb, 100 °C, 0.05 mm Hg) to yield **36** (22.4 g, 99%) as a colorless oil: IR (film) ν_{max} 1785, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.42–4.38 (m, 1H), 4.24 (~dd, J = 9.1, 8.3 Hz, 1H), 4.17 (dd, J = 9.1, 3.0 Hz, 1H), 3.05 (dt, J = 16.4, 7.4 Hz, 1H), 2.93 (dt, J = 16.4, 7.4 Hz, 1H), 2.34 (sept d, J = 7.0, 3.8 Hz, 1H), 1.53 (~q, J = 7.4 Hz, 2H), 0.88 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H), 0.76–0.67 (m, 1H), 0.41–0.38 (m, 2H), 0.06–0.02 (m, 2H); MS (CI) m/z 226 $(MH)^+$.

3-(1-Oxopentyl)-4(*S*)-(phenylmethyl)-2-oxazolidinone (37). Valeryl chloride (3.74 g, 31.0 mmol) was added (2 min) to a solution of the lithium salt of 4(*S*)-(phenylmethyl)-2-oxazolidinone (28.2 mmol) [prepared using 1.6 M *n*-BuLi/hexane (17.2 mL, 28.2 mmol) in THF at −78 °C. The mixture was stirred at −78 °C for 15 min, allowed to warm to 0 °C and stirred 2 h at this temperature. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with 5% aqueous Na_2CO_3 and brine, then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane:EtOAc, 4:1) to yield **37** (6.75 g, 92%) as a colorless oil: $[\alpha]_D^{25}$ +103.4° (*c* 2.05 MeOH); IR ν_{max} 1780, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–7.21 (m, 5H), 4.71–4.66 (m, 1H), 4.23–4.15 (m, 2H), 3.31 (dd, J = 13.3, 3.5 Hz, 1H), 3.03–2.87 (m, 2H), 2.78 (dd, J = 13.4, 9.9 Hz, 1H), 1.73–1.65 (m, 2H), 1.43 (sext, J = 7.3 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H); MS (CI) m/z 262 $(MH)^+$. Anal. calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.89; H, 7.39; N, 5.35.

4(*S*)-(1-Methylethyl)-3-(1-oxo-3-(2-thienyl)propyl)-2-oxazolidinone (38). Trimethylacetyl chloride (4.64 g, 38.5 mmol) was added dropwise to a cold (−78 °C) solution of **32**[40] (6.01 g, 38.5 mmol) and Et_3N (4.25 g, 42.0 mmol) in THF (155 mL). The mixture was allowed to warm to 0 °C, stirred at 0 °C for 30 min then cooled to −78 °C. A cold (−78 °C) solution of the lithium salt of 4(*S*)-(1-methylethyl)-2-oxazolidinone (35.0 mmol)

[prepared from *n*-BuLi/hexane (21.9 mL, 35.0 mmol)] in THF (140 mL) was added via cannula (10 min) to the reaction mixture. After stirring at −78 °C for 30 min and then at 0 °C for 45 min, saturated NH_4Cl (25 mL) was added. The mixture was poured into H_2O (600 mL) and the suspension was extracted with EtOAc (2×300 mL). The combined organic layers were washed with saturated $NaHCO_3$ (100 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane:EtOAc, 3:1) gave **38** (7.07 g, 69%) as a colorless oil: $[\alpha]_D^{25}$ +72.9° (*c* 2.19 MeOH); IR (film) ν_{max} 1780, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12 (dd, *J* = 5.1, 1.3 Hz, 1H), 6.9 (dd, *J* = 5.1, 3.2 Hz, 1H), 6.85 (dd, *J* = 3.2, 1.3 Hz, 1H), 4.45–4.41 (m, 1H), 4.26 (∼dd, *J* = 8.9, ∼8.3 > Hz, 1H), 4.20 (dd, *J* = 8.9, 3.2 Hz, 1H), 3.41–3.27 (m, 2H), 3.26–3.15 (m, 2H), 2.37 (sept d, *J* = 7.0, 4.1 Hz, 1H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H); MS (FAB) *m*/*z* 268 $(MH)^+$. Anal. calcd for $C_{13}H_{17}NO_3S$: C, 58.40; H, 6.41; N, 5.24. Found: C, 58.19; H, 6.40; N, 5.24.

3-[1-Oxo-3-(2-thiazolyl)propyl]-4(*S*)-(phenylmethyl)-2-oxazolidinone (40). Using the method described for **38**, acid **34**[40] (15.9 g, 89.9 mmol) gave, after purification by flash chromatography (hexane:EtOAc, 1.5:1), **40** (15.4, 55%) as a white solid: $[\alpha]_D^{25}$ +108.5° (*c* 1.055 MeOH); IR (film) ν_{max} 1781, 1694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (d, *J* = 3.2 Hz, 1H), 7.36–7.27 (m, 3H), 7.22–7.20 (m, 3H), 4.73–4.67 (m, 1H), 4.25–4.17 (m, 2H), 3.59–3.43 (m, 4H), 3.30 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.80 (dd, *J* = 13.4, 9.5 Hz, 1H); MS (CI) *m*/*z* 317 $(MH)^+$. Anal. calcd for $C_{16}H_{16}N_2O_3S$: C, 60.74; H, 5.10; N, 8.85. Found: C, 60.49; H, 5.00; N, 8.82.

3-[2(*R*)-(Cyclopropylmethyl)-4-(1,1-dimethylethoxy)-1,4-dioxobutyl]-4(*S*)-(1-methylethyl)-2-oxazolidinone (41). A solution of **36** (20.0 g, 88.8 mmol) in THF (40 mL) was added (45 min) to a solution of LDA [prepared from *i*-Pr_2NH (10.8 g, 106 mmol) and 1.4 M *n*-BuLi/hexane (70.0 mL, 96.0 mmol)] in THF (150 mL) cooled to −78 °C. The solution was stirred at −78 °C for 1 h. DMPU (25.0 g, 195 mmol) was added (5 min) followed by a solution of *tert*-butyl 2-bromoacetate (18.2 g, 93.2 mmol) (added over 10 min) in THF (20 mL). The reaction mixture was stirred at −78 °C for 1.5 h then saturated aqueous NH_4Cl was added and the mixture allowed to warm to 25 °C. The reaction mixture was diluted with EtOAc and the resulting solution was washed with 5% aqueous citric acid, saturated aqueous $NaHCO_3$, brine and then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The yellow oil obtained was purified by crystallization (EtOAc:hexane) at −20 °C to yield **41** (21.7 g, 72%) as white crystals: mp 104–105 °C; $[\alpha]_D^{25}$ +52.8° (*c* 1.02 $CHCl_3$); ^1H NMR (DMSO-d_6) δ 4.37–4.27 (m, 3H), 4.21–4.14 (m, 1H), 2.64 (dd, *J* = 16.5, 10.5 Hz, 1H), 2.54 (dd, *J* = 16.5, 4.4 Hz, 1H), 2.18 (sept d, *J* = 7.0, 3.2 Hz, 1H), 1.43 (dt, *J* = 13.8, 7.0 Hz, 1H), 1.36 (s, 9H), 1.29 (dt, *J* = 13.8, 7.0 Hz, 1H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.69–0.65 (m, 1H), 0.40–0.34 (m, 2H), 0.04–0.01 (m, 2H); MS (CI) *m*/*z* 340 $(MH)^+$. Anal. calcd for $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.13. Found: C, 63.67; H, 8.72; N, 4.10.

Procedure for the preparation of 42–46. A solution of 1 M NaHMDS in THF (1.1 equiv) was added (∼10 min) to a cold (−78 °C) solution of the acyl oxazolidinone in THF (0.2–0.25 M). The reaction mixture was stirred at −78 °C for 45 min. A solution of *tert*-butyl (or benzyl) 2-bromoacetate (2.0 equiv) in THF (1/1, v/v) was next added dropwise and the reaction mixture was stirred at the same temperature for 1.5–2 h. Saturated aqueous NH_4Cl was then added, the mixture was allowed to warm to 25 °C, poured into diluted aqueous NH_4Cl and extracted with EtOAc (3×). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure.

3-[2(*R*)-[2-(1,1-Dimethylethoxy)-2-oxoethyl]-1-oxopentyl]-4(*S*)-(phenylmethyl)-2-oxazolidinone (42). Starting with **37** (1.20 g, 4.60 mmol), **42** (1.35 g, 78%) was obtained as a white solid after purification by flash chromatography (hexane:EtOAc, 8:1): mp 90–92 °C; $[\alpha]_D^{25}$ +72.3° (*c* 1.06 MeOH); IR (film) ν_{max} 1749, 1717 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.34–7.23 (m, 5H), 4.67–4.61 (m, 1H), 4.33 (∼dd, *J* = 8.7, 8.3 Hz, 1H), 4.15 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.06–3.99 (m, 1H), 3.00 (dd, *J* = 13.5, 3.0 Hz, 1H), 2.86 (dd, *J* = 13.5, 7.8 Hz, 1H), 2.62 (dd, *J* = 16.5, 10.2 Hz, 1H), 2.48 (dd, *J* = 16.5, 4.8 Hz. 1H), 1.60–1.51 (m, 1H), 1.39 (s, 9H), 1.39–1.23 (m, 3H), 0.84 (t, *J* = 7.1 Hz, 3H); MS (FAB) *m*/*z* 376 $(MH)^+$. Anal. calcd for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.79; N, 3.73. Found: C, 67.19; H, 7.93; N, 3.65.

3-[4-(1,1-Dimethylethoxy)-1,4-dioxo-2(*S*)-(2-thienylmethyl)-butyl]-4(*S*)-(1-methylethyl)-2-oxazolidinone (43). Using **38** (4.00 g, 15.0 mmol), **43** (4.51 g, 79%) was obtained as a white solid after trituration of the crude residue with ether (75 mL): $[\alpha]_D^{25}$ +91.8° (*c* 0.51 $CHCl_3$); IR (KBr) ν_{max} 1785, 1730, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13 (dd, *J* = 5.1, 1.3 Hz, 1H), 6.91 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.86 (dd, *J*∼3.5, 1.3 Hz, 1H), 4.50–4.42 (m, 1H), 4.36–4.32 (m, 1H), 4.16 (dd, *J* = 8.9, 2.9 Hz, 1H), 4.12 (∼dd, *J* = 8.9, 8.3 Hz, 1H), 3.18 (dd, *J* = 14.3, 6.7 Hz, 1H), 2.91 (dd, *J* = 14.3, 7.9 Hz, 1H), 2.78 (dd, *J* = 16.5, 9.8 Hz, 1H), 2.44 (dd, *J* = 16.5, 4.8 Hz, 1H), 2.35 (sept d, *J* = 7.0, 4.1 Hz, 1H), 1.40 (s, 9H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H); MS (FAB) *m*/*z* 382 $(MH)^+$. Anal. calcd for $C_{19}H_{27}NO_5S$: C, 59.82; H, 7.13; N, 3.67. Found: C, 59.57; H, 7.18; N, 3.60.

3-[1,4-Dioxo-4-(phenylmethoxy)-2(*S*)-[(1-triphenylmethyl-1*H*-imidazol-4-yl)methyl]butyl]-4(*S*)-(1-methylethyl)-2-oxazolidinone (44). From **39**[25] (8.06 g, 16.3 mmol) and after purification by flash chromatography (EtOAc: hexane, 2:1), **44** (6.68 g, 64%) was obtained as a white solid: $[\alpha]_D^{25}$ +55.3° (*c* 0.45 MeOH); IR (KBr) ν_{max} 1785, 1735, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33–7.30 (m, 15H), 7.13–7.11 (m, 6H), 6.60 (broad s, 1H), 5.07 (s, 2H), 4.53–4.46 (m, 1H), 4.40–4.36 (m, 1H), 4.15–4.13 (m, 2H), 2.98 (dd, *J* = 16.8, 10.2 Hz, 1H), 2.89 (dd, *J* = 14.3, 6.4 Hz, 1H), 2.75 (dd, *J* = 14.3, 7.0 Hz, 1H), 2.60 (dd, *J* = 16.8, 4.4 Hz, 1H), 2.33 (sept d, *J* = 7.0, 3.8 Hz, 1H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H); MS (FAB) *m*/*z* 642 $(MH)^+$. Anal. calcd for $C_{40}H_{39}N_3O_5$: C, 74.86; H, 6.13; N, 6.55. Found: C, 74.98; H, 6.24; N, 6.56.

3-[4-(1,1-Dimethylethoxy)-1,4-dioxo-2(*S*)-(2-thiazolylmethyl)butyl]-4-(*S*)-(phenylmethyl)-2-oxazolidinone (45). The alkylation of **40** (6.25 g, 19.8 mmol) gave **45** (7.60 g, 89%) as a white solid after purification by flash chromatography (hexane:EtOAc, 2:1): $[\alpha]_D^{25}$ +102.2° (*c* 1.005 MeOH); IR (film) ν_{max} 1765, 1714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67 (d, *J* = 3.5 Hz, 1H), 7.36–7.26 (m, 5H), 7.23 (d, *J* = 3.5 Hz, 1H), 4.71–4.65 (m, 1H), 4.64–4.57 (m, 1H), 4.20–4.16 (m, 2H), 3.43 (dd, *J* = 14.7, 6.5 Hz, 1H), 3.36 (dd, *J* = 13.4, 3.2 Hz, 1H), 3.24 (dd, *J* = 14.7, 7.3 Hz, 1H), 2.92 (dd, *J* = 16.6, 9.5 Hz, 1H), 2.77 (dd, *J* = 13.4, 10.0 Hz, 1H), 2.59 (dd, *J* = 16.6, 4.9 Hz, 1H), 1.44 (s, 9H); MS (FAB) *m*/*z* 431 $(MH)^+$. Anal. calcd for $C_{22}H_{26}N_2O_5S$: C, 61.38; H, 6.09; N, 6.51. Found: C, 61.26; H, 6.10; N, 6.46.

3-[4-(1,1-Dimethylethoxy)-1,4-dioxo-2(*R*)-(4-thiazolylmethyl)butyl]-4-(*S*)-(1-methylethyl)-2-oxazolidinone (46). Starting with **62** (825 mg, 3.07 mmol) and after purification by flash chromatography (hexane:EtOAc, 2:1), **46** (1.02 g, 86%) was obtained as a white solid: $[\alpha]_D^{25}$ +144.0° (*c* 1.01 MeOH); IR (film) ν_{max} 1784, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.78 (d, *J* = 2.1 Hz, 1H), 7.16 (d, *J* = 2.1 Hz, 1H), 4.59–4.52 (m, 1H), 4.43 (dt, *J* = 8.3, ~3.5 Hz, 1H), 4.25 (~dd, *J* = 8.9, 8.3 Hz, 1H), 4.20 (dd, *J* = 8.9, 3.5 Hz, 1H), 3.19 (dd, *J* = 14.2, 6.2 Hz, 1H), 3.07 (dd, *J* = 14.2, 7.3 Hz, 1H), 2.83 (dd, *J* = 16.5, 9.9 Hz, 1H), 2.49 (dd, *J* = 16.5, 4.8 Hz, 1H), 2.37 (sept d, *J* = 7.0, 3.5 Hz, 1H), 1.41 (s, 9H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H); MS (CI) *m*/*z* 383 $(MH)^+$. Anal. calcd for $C_{18}H_{26}N_2O_5S$: C, 56.53; H, 6.85; N, 7.32. Found: C, 56.20; H, 6.84; N, 7.24.

Procedure for the preparation of 48–53. To an ice-cold solution of **41–46** in THF:H_2O (~3:1, 0.05–0.2 M) was added 30% (w/%) hydrogen peroxide (3–6 equiv) followed by $LiOH \cdot H_2O$ (1–3 equiv). The mixture was allowed to warm to 25 °C and was stirred at this temperature until disappearance (TLC) of the starting material (1.5–16 h). The mixture was cooled to 0 °C and the excess peroxide was destroyed by addition of 1.5 M aqueous Na_2SO_3. Most of the THF was removed under reduced pressure. The residual aqueous solution was diluted with H_2O and saturated aqueous $NaHCO_3$ and the resulting solution was washed with CH_2Cl_2 (3–4×). The aqueous layer was rendered acidic (pH 3) with 10% aqueous or solid citric acid and extracted with EtOAc (3×). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the corresponding acids. A solution of the acid, **47**·HCl (1.05 equiv), *i*-Pr_2NEt (3–4 equiv) and BOP·PF_6 (1.05 equiv) in DMF (0.2–0.4 M) was stirred at 25 °C for 1.5–6 h. The reaction mixture was diluted with EtOAc and washed successively with 10% aqueous citric acid or 1 N HCl, H_2O, saturated aqueous $NaHCO_3$ and brine, then was dried ($MgSO_4$), filtered and concentrated under reduced pressure.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-2(*R*)-(cyclopropylmethyl)-4-(1,1-dimethylethoxy)-4-oxobutanamide (48).** Starting with **41**, **48** (3.74 g, 76%) was obtained as a white solid after crystallization (EtOAc:hexane): mp 138–139 °C; ^1H NMR (DMSO-d_6) δ 7.66 (d, *J* = 9.2 Hz, 1H), 4.70 (d, *J* = 6.4 Hz, 1H), 4.60 (d, *J* = 3.8 Hz, 1H), 4.12–4.06 (m, 1H), 3.10–3.04 (m, 1H), 2.94–2.90 (m, 1H), 2.82–2.74 (m, 1H), 2.46 (dd, *J* = 16.2, 9.2 Hz, 1H), 2.31 (dd, *J* = 16.2, 5.7 Hz, 1H), 1.77–1.30 (m, 10H), 1.38 (s, 9H), 1.22–1.08 (m, 6H), 0.93–0.85 (m, 1H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.80–0.74 (m, 1H), 0.75 (d, *J* = 6.7 Hz, 3H), 0.68–0.63 (m, 1H), 0.40–0.35 (m, 2H), 0.05–0.00 (m, 2H); MS (CI) *m*/*z* 454 $(MH)^+$.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-2(*R*)-[2-(1,1-dimethylethoxy)-2-oxoethyl]pentanamide (49).** From **42**, **49** (0.80 g, 66%) was obtained as a white solid after purification by flash chromatography (hexane:EtOAc, 6:1): $[\alpha]_D^{25}$ −45.1° (*c* 1.0 MeOH); ^1H NMR (DMSO-d_6) δ 7.67 (d, *J* = 9.0 Hz, 1H), 4.71 (d, *J* = 6.3 Hz, 1H), 4.64 (d, *J* = 3.3 Hz, 1H), 4.11–4.05 (m, 1H), 3.10–3.04 (m, 1H), 2.93–2.90 (m, 1H), 2.72–2.67 (m, 1H), 2.41 (dd, *J* = 15.9, 8.8 Hz, 1H), 2.21 (dd, *J* = 15.9, 5.7 Hz, 1H), 1.80–1.41 (m, 9H), 1.38 (s, 9H), 0.93–0.74 (m, 2H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.83 (t, *J* = 7.0 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H); MS (FAB) *m*/*z* 442 $(MH)^+$.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-4-(1,1-dimethylethoxy)-4-oxo-2(*S*)-(2-thienylmethyl)-butanamide (50).** Using **43**, **50** (0.52 g, 73%) was obtained as a white solid after purification by flash chromatography (hexane:EtOAc, 3:1): $[\alpha]_D^{25}$ −27.3° (*c* 0.62 MeOH); IR (KBr) ν_{max} 3460, 3270, 1730, 1705, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18 (dd, *J* = 5.1, 1.3 Hz, 1H), 6.93 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.86 (~dd, *J* = 3.5, 1.3 Hz, 1H), 5.62 (d, *J* = 8.6 Hz, 1H), 4.23 (td, *J* = 8.6, 4.8 Hz, 1H) 3.27–3.16 (m, 1H), 3.08 (dd, *J* = 8.6, 1.3 Hz, 1H), 3.00 (dd, *J* = 8.9, 3.2 Hz, 1H), 2.98–2.90 (m, 2H), 2.70 (dd, *J* = 17.2, 9.2 Hz, 1H), 2.45 (dd, *J* = 17.2, 4.1 Hz, 1H), 1.92–1.82 (m, 1H), 1.75–1.59 (m, 6H), 1.51–1.10 (m, 9H), 1.46 (s, 9H), 0.95–0.79 (m, 2H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H); MS (FAB) *m*/*z* 496 $(MH)^+$. Anal. calcd for $C_{27}H_{45}NO_5S$: C, 65.42; H, 9.15; N, 2.82. Found: C, 65.27; H, 9.32; N, 2.76.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-4-oxo-4-(phenylmethoxy)-2(*R*)-[[(1-triphenylmethyl)-1*H*-imidazol-4yl]methyl]butanamide (51).** Starting with **44** and using the inseparable mixture of the acid and the chiral auxiliary in the coupling reaction, **51** (6.08 g, 77%) was obtained as a white solid after purification by flash chromatography (EtOAc then EtOAc:MeOH, 10:1): $[\alpha]_D^{25}$ −19.6° (*c* 0.70 MeOH); IR (KBr) ν_{max} 3380, 1735, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39–7.26 (m, 15H), 7.10–7.08 (m, 6H), 6.56 (s, 1H), 6.51 (d, *J* = 9.5 Hz, 1H), 5.09 (ABq, Δν = 16.8 Hz, *J* = 12.2 Hz, 2H), 4.43–4.37 (m, 1H), 4.46–4.17 (broad s, ~2H), 3.29 (t, *J* = 8.3 Hz, 1H), 3.15 (d, *J* = 8.6 Hz, 1H), 3.09–3.03 (m, 1H), 2.94 (dd, *J* = 16.5, 8.6 Hz, 1H), 2.86 (dd, *J* = 15.3, 7.6 Hz, 1H), 2.68 (dd, *J* = 15.3, 3.5 Hz, 1H), 2.38 (dd, *J* = 16.5, 5.7 Hz, 1H), 1.88–1.12 (m, 14H), 0.97–0.80 (m, 2H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.72 (d, *J* = 6.7 Hz, 3H); MS (FAB) *m*/*z* 756 $(MH)^+$.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-4-(1,1-dimethylethoxy)-4-oxo-2(*S*)-(2-thiazolylmethyl)butanamide (52).** Starting with **45**, **52** (9.20 g,

52%) was isolated as a white solid after purification by flash chromatography (hexane:EtOAc, 1.5:1): $[\alpha]_D^{25}$ −29.1° (*c* 1.0 MeOH); IR (film) ν_{max} 3462, 3263, 1703, 1634 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67 (d, *J* = 3.4 Hz, 1H), 7.24 (d, *J* = 3.4 Hz, 1H), 6.29 (broad s, 1H), 4.23 (∼td, *J* = 9.2, 5.1 Hz, 1H), 3.42 (dd, *J* = 15.4, 9.5 Hz, 1H), 3.33–3.24 (m, 1H), 3.14 (dd, *J* = 15.4, 2.5 Hz, 1H), 3.09 (d, *J* = 8.3 Hz, 1H), 2.98 (∼td, *J* = 10.2, 2.5 Hz, 1H), 2.70 (dd, *J* = 17.0, 8.6 Hz, 1H), 2.42 (dd, *J* = 17.0, 5.4 Hz, 1H), 1.79–1.47 (m, 8H), 1.39 (s, 9H), 1.39–1.05 (m, 6H), 0.92–0.70 (m, 2H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.69 (d, *J* = 6.4 Hz, 3H); MS (FAB) *m*/*z* 497 $(MH)^+$. Anal. calcd for $C_{26}H_{44}N_2O_5S$: C, 62.87; H, 8.93; N, 5.64. Found: C, 62.73; H, 9.16; N, 5.60.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-4-(1,1-dimethylethoxy)-4-oxo-2(*R*)-(4-thiazolylmethyl)butanamide (53).** Using **46**, **53** (365 mg, 72%) was isolated as a white solid after purification by flash chromatography (hexane:EtOAc, 1:1): $[\alpha]_D^{25}$ −26.9° (*c* 1.02 MeOH); ^1H NMR (DMSO-d_6) δ 9.00 (d, *J* = 1.7 Hz, 1H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.37 (d, *J* = 1.7 Hz, 1H), 4.71 (d, *J* = 6.7 Hz, 1H), 4.60 (d, *J* = 4.1 Hz, 1H), 4.08 (broad td, *J* = 8.9, 4.1 Hz, 1H), 3.17–3.10 (m, 1H), 3.03 (dd, *J* = 14.2, 6.5 Hz, 1H), 3.02–2.99 (m, 1H), 2.93–2.89 (m, 1H), 2.79 (dd, *J* = 14.2, 8.0 Hz, 1H), 2.46 (dd, *J* = 16.3, 9.2 Hz, 1H), 2.14 (dd, *J* = 16.3, 4.9 Hz, 1H), 1.77–1.50 (m, 7H), 1.47–1.35 (m, 2H), 1.25 (s, 9H), 1.20–1.07 (m, 5H), 0.92–0.75 (m, 2H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.74 (d, *J* = 6.7 Hz, 3H); MS (CI) *m*/*z* 497 $(MH)^+$, 423 $(M\text{-}OC(CH_3)_3)^+$. Anal. calcd for $C_{26}H_{44}N_2O_5S$: C, 62.87; H, 8.93; N, 5.64. Found: C, 62.61; H, 9.08; N, 5.58.

4-[[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]amino]-3-(*R*)-(cyclopropylmethyl)-4-oxobutanoic acid (54). A solution of **48** (2.00 g, 4.41 mmol) and TFA (7.0 mL) in CH_2Cl_2 (10 mL) was stirred at 0 °C for 7 h. The mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (25 mL) and the resulting suspension was filtered to give acid **54** (1.22 g, 70%) as a white solid: IR (KBr) ν_{max} 3400, 3290, 3140–2500, 1715, 1615, 1580 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.65 (d, *J* = 9.2 Hz, 1H), 4.68 (d, *J* = 6.4 Hz, 1H), 4.61 (d, *J* = 3.2 Hz, 1H), 4.10 (td, *J* = 9.2, 4.7 Hz, 1H), 3.10–3.05 (m, 1H), 2.92 (broad t, *J* = 7.8 Hz, 1H), 2.83–2.76 (m, 1H), 2.48 (dd, *J* = 16.5, 8.6 Hz, 1H), 2.33 (dd, *J* = 16.5, 5.7 Hz, 1H), 1.79–1.08 (m, 16H), 0.93–0.74 (m, 2H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.74 (d, *J* = 6.4 Hz, 3H), 0.70–0.63 (m, 1H), 0.40–0.35 (m, 2H), 0.08–0.01 (m, 2H); MS (FAB) *m*/*z* 398 $(MH)^+$.

Typical procedure for the preparation of inhibitors 3a–3o (0.1–0.38 mmol scale). N^1-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-2(*R*)-(cyclopropylmethyl)-N^4-[2-(dimethylamino)-2-oxoethyl]-N^4-[1(*S*)-phenylethyl]butanediamide (3l). BOP·PF_6 (1.53 g, 3.45 mmol) was added to an ice-cold solution of **54** (1.25 g, 3.14 mmol), **15** (811 mg, 3.93 mmol) and *i*-Pr_2NEt (691 mg, 5.34 mmol) in DMF (15.7 mL). The reaction mixture was stirred at 25 °C for 5.5 h. The mixture was diluted with EtOAc (400 mL) and the resulting solution was washed with 10% aqueous citric acid (100 mL), H_2O (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc) to give **3l** (1.43 g, 78%) as a white solid: $[\alpha]_D^{25}$ −59.0° (*c* 1.14 MeOH); IR (KBr) ν_{max} 3400, 1655, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ (1:1 mixt. of rotamers) 7.40–7.25 (m, 5H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.10, 5.23 (2q, *J* = 7.0, 6.7 Hz, 1H), 4.35, 3.81, 3.27 (d, AB_q and d, *J* = 16.2 Hz, Δν = 31.2 Hz and *J* = 17.8 Hz, *J* = 16.2 Hz, 2H), 3.41–3.32 (m, 1H), 3.21–3.18 (m, 1H), 2.96, 2.94, 2.92, 2.91 (4s, 6H), 2.96–2.86 (m, 2H), 2.60–2.56 (m, 1H), 1.95–1.10 (m, 16H), 1.62, 1.37 (2d, *J* = 7.0, 6.7 Hz, 3H), 0.98–0.85 (m, 2H), 0.94, 0.93, 0.86 (3d, *J* = 6.7, 6.7, 6.7 Hz, 6H), 0.73–0.70 (m, 1H), 0.49–0.45 (m, 2H), 0.14–0.09 (m, 2H); MS (FAB) *m*/*z* 586 $(MH)^+$. Anal. calcd for $C_{34}H_{55}N_3O_5 + 0.62\%$ (w/w) H_2O: C, 68.82; H, 9.59; N, 7.05. Found: C, 69.28; H, 9.49; N, 7.13.

***N*^{1}-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-*N*^{4}-[2-(dimethylamino)-2-oxoethyl]-*N*^{4}-[1(*S*)-phenylethyl]-2(*R*)-propylbutanediamide (3p).** TFA (3.4 mL) was added to an ice-cold solution of **49** (750 mg, 1.70 mmol) in CH_2Cl_2 (3.4 mL). The solution was stirred at 0 °C for 2 h, at 25 °C for 1 h then was concentrated under reduced pressure. The residue was coevaporated with Et_2O. The residue was triturated with hexane to give acid **55** (585 mg, 90%) as a white solid. BOP·PF_6 (2.34 g, 5.29 mmol) was added to a solution of **55** (1.70 g, 4.41 mmol), **15** (1.09 g, 5.29 mmol) and *i*-Pr_2NEt (1.14 g, 8.82 mmol) in DMF (22 mL) at 25 °C. After stirring for 5 h, the mixture was diluted with EtOAc (300 mL). The solution was washed with 1 N aqueous HCl, saturated aqueous $NaHCO_3$, H_2O and brine then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane:EtOAc:EtOH, 15:10:2) to give **3p** (1.77 g, 70%) as a white solid: IR (KBr) ν_{max} 3380, 1650 cm^{-1}; ^1H NMR (DMSO-d_6) δ (1.8:1.0 mixt. of rotamers) 7.64, 7.55 (2d, *J* = 9.0, 9.0 Hz, 1H), 7.54–7.24 (m, 5H), 5.78, 5.26 (2q, *J* = 6.9, 6.9 Hz, 1H), 4.71, 4.66 (2 broad s, 1H), 4.62, 4.58 (2d, *J* = 6.3, 6.3 Hz, 1H), 4.25, 4.20, 3.82, 3.46 (4d, *J* = 16.5, 18.1, 18.1, 16.5 Hz, 2H), 4.11–4.08 (m, 1H), 3.09 (broad q, *J* = 8.7 Hz, 1H), 2.92–2.76 (m, 2H), 2.88, 2.85, 2.79, 2.76 (4s, 6H), 2.58, 2.49, 2.36, 2.29 (4dd, *J* = 16.2, 8.1 Hz, *J* = 16.2, 6.0 Hz, *J* = 16.2, 7.0 Hz, *J* = 16.2, 6.6 Hz, 2H), 1.78–1.03 (m, 18H), 1.50, 1.32 (2d, *J* = 6.9, 6.9 Hz, 3H), 0.91–0.74 (m, 11H); MS (FAB) *m*/*z* 574 $(MH)^+$. Anal. calcd for $C_{33}H_{55}N_3O_5$: C, 69.07; H, 9.66; N, 7.32. Found: C, 68.68; H, 10.10; N, 7.12.

***N*^{1}-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-*N*^{4}-[2-(dimethylamino)-2-oxoethyl]-*N*^{4}-[1(*S*)-phenylethyl]-2(*S*)-(2-thienylmethyl)butanediamide (3q).** A solution of **50** (490 mg, 0.99 mmol) and TFA (2.0 mL) in CH_2Cl_2 (2.0 mL) was stirred at 0 °C for 75 min and at 25 °C for 75 min. The mixture was concentrated under reduced pressure. EtOAc (10 mL) was added and the acid was obtained by filtration. The filtrate was concentrated and the process repeated using EtOAc (2×) and ether (2×) to give **56** (369 mg, 86%). A solution of **56** (200 mg, 0.46 mmol), **15** (117 mg, 0.57 mmol), *i*-Pr_2NEt (100 mg, 0.77 mmol) and BOP·PF_6 (221 mg, 0.50 mmol) in DMF (2.3 mL) was stirred at 25 °C for

5.5 h. The reaction mixture was treated as described in the previous example. Purification by flash chromatography (EtOAc) yielded **3q** (222 mg, 78%) as a white solid: $[\alpha]_D^{25}$ −57.0° (*c* 0.99 MeOH); IR ν_{max} 3400, 3290, 1655, 1640 cm^{-1}; ^1H NMR (DMSO-d_6) δ (1.6:1.0 mixt. of rotamers) 7.77, 7.75 (2d, *J* = 8.6, ~8.6 Hz, 1H), 7.36–7.22 (m, 6H), 6.91, 6.89–6.86, 6.82 (dd, m and d, *J* = 5.1, 3.2 Hz, *J* = 3.2 Hz, 2H), 5.78, 5.18 (2q, *J* = 7.3, 7.0 Hz, 1H), 4.59 (broad s, 1H), 4.55 (d, *J* = 6.4 Hz, 1H), 4.24, 4.14, 3.80, 3.47 (4d, *J* = 16.0, 18.3, 18.3, 16.0 Hz, 2H), 4.11–4.03 (m, 1H), 3.18–2.62 (m, 6H), 2.88, 2.82, 2.78, 2.74 (4s, 6H), 2.43–2.32 (m, 1H), 1.79–1.01 (m, 14H), 1.47, 1.33 (2d, *J* = 7.0, 7.3 Hz, 3H), 0.92–0.69 (m, 2H), 0.86, 0.85 (2d, *J* = 6.6, 6.7 Hz, 3H), 0.76, 0.75 (2d, *J* = 6.3, 6.0 Hz, 3H); MS (FAB) *m*/*z* 628 $(MH)^+$; RP-HPLC, 100% (system A), 100% (system B).

N^1-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-N^4-[2-(dimethylamino)-2-oxoethyl]-2(*R*)-[(1*H*-imidazol-4-yl)methyl]-N^4-[1(*S*)-phenylethyl] butanediamide (3r). A solution of **51** (6.08 g, 8.04 mmol) in EtOH (80 mL) was stirred under an H_2 atmosphere (1 atm) in presence of Pd/C (600 mg) for 2.5 h. The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The residue was coevaporated with Et_2O (2×) to give the expected acid **57** (5.30 g, 99%) as a white solid. A solution of **57** (4.30 g, 6.46 mmol), **15** (1.66 g, 8.07 mmol, *i*-Pr_2NEt (1.42 g, 11.0 mmol) and BOP·PF_6 (3.00 g, 6.78 mmol) in DMF (32 mL) was stirred at 25 °C for 5 h. The reaction mixture was treated as described for **3p**. Purification by flash chromatography (EtOAc:MeOH, 10:1) yielded the corresponding amide (3.60 g, 65%) as a yellowish solid. The trityl protective group was removed by hydrogenolysis in a Parr shaker (50 psi) using $Pd(OH)_2$/C (1.44 g) in EtOH (42 mL) and AcOH (0.84 mL) for 41 h. The catalyst was removed by filtration through a pad of Celite®. The filtrate was concentrated under reduced pressure and the residue was dissolved in EtOAc (100 mL). The solution was washed with 5% aqueous Na_2CO_3 (25 mL) and brine (25 mL), then was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc:MeOH, 4:1) finally gave **3r** (1.24 g, 48%) as a white solid: $[\alpha]_D^{25}$ −59.1° (*c* 1.02 MeOH); IR ν_{max} 3380, 1650 (broad) cm^{-1}; ^1H NMR (DMSO-d_6) δ (1.4:1.0 mixt. of rotamers) 7.64, 7.54 (2d, *J* = 9.3, 9.3 Hz, 1H), 7.52, 7.48 (2 broad s, 1H), 7.36–7.23 (m, 5H), 6.82, 6.76 (2 broad s, 1H), 5.76, 5.15 (2q, *J* = 7.2, 6.7 Hz, 1H), 4.77–4.50 (m, 2H), 4.25, 4.09, 3.79, 3.42 (4d, *J* = 16.2, 18.2, 18.2, 16.2 Hz, 2H), 4.11–4.06 (m, 1H), 3.13–3.01 (m, 2H), 2.92–2.75 (m, 2H), 2.87, 2.82, 2.78, 2.75 (4s, 6H), 2.67–2.44 (m, 2H), 2.35 (broad d, *J* = 6.9 Hz, 1H), 1.78–1.04 (m, 14H), 1.46, 1.32 (2d, *J* = 6.7, 7.2 Hz, 3H), 0.92–0.70 (m, 2H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H); MS (FAB) *m*/*z* 612 $(MH)^+$; RP-HPLC, >99% (system A), 99.1% (system B).

N^1-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-N^4-[2-(dimethylamino)-2-oxoethyl]-N^4-[1(*S*)-phenylethyl]-2(*S*)-(2-thiazolylmethyl)butanediamide (3s). To an ice-cold solution of **52** (2.30 g, 4.63 mmol) in CH_2Cl_2 (15 mL) was added TFA (7.5 mL). The solution was allowed to warm to 25 °C and was stirred at 25 °C for 5 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography ($CHCl_3$:EtOH, 4:1) to afford **58** (940 mg, 46%) as a white solid. A solution of **58** (500 mg, 1.13 mmol), **15** (222 mg, 1.07 mmol), *i*-Pr_2NEt (439 mg, 3.40 mmol) and BOP·PF_6 (502 mg, 1.13 mmol) in DMF (6 mL) was stirred at 25 °C overnight. The mixture was diluted with EtOAc and the resulting solution was washed with H_2O, saturated aqueous $NaHCO_3$ (2×) and brine then was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane:EtOAc:EtOH, 5:5:1) to give **3s** (130 mg, 19%) as a white solid: $[\alpha]_D^{25}$ −66.6° (*c* 1.05 MeOH); IR ν_{max} 3420, 1650 (broad) cm^{-1}; ^1H NMR (DMSO-d_6) δ (1.6:1.0 mixt. of rotamers) 7.81, 7.77 (2d, *J* = 8.9, 8.9 Hz, 1H), 7.66, 7.63 (2d, *J* = 3.2, 3.4 Hz, 1H), 7.55, 7.53 (2d, *J* = 3.2, 3.4 Hz, 1H), 7.36–7.22 (m, 5H), 5.79, 5.21 (2q, *J* = 7.0, 7.0 Hz, 1H), 4.65–4.42 (m, 2H), 4.25, 4.21, 3.81, 3.49 (4d, *J* = 16.2, 18.0, 18.0, 16.2 Hz, 2H), 4.10–4.05 (m, 1H), 3.4–3.31 (hidden m, 1H), 3.28 (d, *J* = 14.8, 7.8 Hz, 1H), 3.11–2.95 (m, 2H), 2.88–2.57 (m, 2H), 2.88, 2.83, 2.78, 2.75 (4s, 6H), 2.46–2.39 (m, 1H), 1.76–1.00 (m, 14H), 1.48, 1.33 (2d, *J* = 7.0 Hz, 3H), 0.90–0.68 (m, 2H), 0.85 (broad d, *J* = 6.7 Hz, 3H), 0.75, 0.74 (2d, *J* = 6.4, 6.4 Hz, 3H); MS (FAB) *m*/*z* 629 $(MH)^+$; RP-HPLC, 98.8% (system A), 98.9% (system B).

N^1-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-N^4-[2-(dimethylamino)-2-oxoethyl]-N^4-[1(*S*)-phenylethyl]-2(*R*)-(4-thiazolylmethyl)butanediamide (3t). Using conditions identical to those described above for **3s**, **53** (3.70 g, 7.45 mmol) was first converted into acid **59** (100%). The coupling of acid **59** (2.00 g, 4.54 mmol) and amine **15** (1.21 g, 5.90 mmol) yielded **3t**. Purification of the crude residue by flash chromatography (hexane:EtOAc:EtOH, 5:5:1) gave **3t** (650 mg, 23%) as a white solid: $[\alpha]_D^{25}$ −55.9° (*c* 1.05 MeOH); IR ν_{max} 3400, 1650 (broad) cm^{-1}; ^1H NMR (DMSO-d_6) δ (1.6:1 mixt. of rotamers) 9.01, 8.98 (2s, 1H), 7.76, 7.67 (2d, *J* = 8.4, 9.0 Hz, 1H), 7.37–7.23 (m, 6H), 5.78, 5.18 (2q, *J* = 6.7, 7.0 Hz, 1H), 5.48–4.57 (m, 1H), 4.53 (d, *J* = 6.6 Hz, 1H), 4.25, 4.16, 3.81, 3.46 (4d, *J* = 16.3, 18.1, 18.1, 16.3 2H), 4.12–4.02 (m, 1H), 3.08–2.60 (m, 5H), 2.88, 2.84, 2.78, 2.75 (4s, 6H), 2.60–2.31 (m, 2H), 1.76–1.01 (m, 14H), 1.47, 1.33 (2d, *J* = 6.7, 7.0 Hz, 3H), 0.92–0.72 (m, 2H), 0.84, 0.73 (2d, *J* = 6.6, 6.3 Hz, 6H); MS (CI) *m*/*z* 629 $(MH)^+$. Anal. calcd for $C_{34}H_{52}N_4O_5S$ + 1.15% (w/w) H_2O: C, 64.19; H, 8.38; N, 8.81. Found: C, 64.14; H, 8.33; N, 8.77.

3-(3-Carboxy-1-oxopropyl)-4(*S*)-(1-methylethyl)-2-oxazolidinone (60). A solution of succinic anhydride (22.1 g, 220 mmol) in THF (400 mL) was added (30 min) to a cold (−78 °C) solution of the lithium salt of 4(*S*)-(1-methylethyl)-2-oxazolidinone (232 mmol) [prepared using 1.6 M *n*-BuLi/hexane (148 mL, 237 mmol)] in THF (460 mL). The reaction mixture was allowed to warm to 25 °C and was stirred at this temperature for 5 h. Ether (300 mL) and 1 N HCl (150 mL) were added and the phases were separated. The organic layer was extracted

with saturated aqueous $NaHCO_3$ (2×200 mL). The combined aqueous layers were rendered acidic (pH 3) by addition of solid citric acid and were extracted with ether (3×). The combined organic layers were washed with H_2O and brine then were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **60** (35.6 g, 67%) as a pale yellow oil: $[\alpha]_D^{25}$ +89.7° (*c* 1.01 MeOH); IR (film) ν_{max} 3540, 3180 (broad), 1785, 1745, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.44 (∼ddd, *J* = 8.3, 4.0, 3.2 Hz, 1H), 4.31 (∼dd, *J* = 9.2, 8.3 Hz, 1H), 4.23 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.29 (dt, *J* = 18.6, 6.4 Hz, 1H), 3.21 (dt, *J* = 18.6, 6.4 Hz, 1H), 2.73 (t, *J* = 6.4 Hz, 2H), 2.38 (sept d, *J* = 7.0, 4.0 Hz, 1H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H); MS (CI) *m*/*z* 230 $(MH)^+$.

3-(5-Bromo-1,4-dioxopentyl)-4(*S*)-(1-methylethyl)-2-oxazolidinone (61). $(COCl)_2$ (3.11 g, 24.5 mmol) was added to an ice-cold solution of **60** (4.68 g, 20.4 mmol) in CH_2Cl_2 (14 mL). The reaction mixture was stirred at 0 °C for 10 min, at 25 °C for 1.5 h then was heated to reflux for 30 min. The crude acyl chloride obtained by concentration was diluted with Et_2O (15 mL) and the solution was added (5 min) to an ice-cold solution of CH_2N_2 in Et_2O (∼0.6 M, 100 mL). The reaction mixture was stirred at 0 °C for 45 min then a solution of HBr in AcOH (45% w/v, 10 mL) was added (3 min). The mixture was stirred at 0 °C for 1 h then was poured into a saturated solution of $NaHCO_3$ (350 mL) containing also solid $NaHCO_3$ (42 g) and Et_2O (50 mL). The phases were separated. The aqueous layer was extracted with Et_2O (100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **61** (5.60 g, 89%) as a brown oil which solidified slowly: ^1H NMR ($CDCl_3$) δ 4.40–4.37 (m, 1H), 4.29 (∼dd, *J* = 9.1, 8.3 Hz, 1H), 4.21 (dd, *J* = 9.1, 3.0 Hz, 1H), 3.99 (s, 2H), 3.28–3.24 (m, 2H), 2.99–2.94 (m, 2H), 2.33 (sept d, *J* = 6.8, 3.8 Hz, 1H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H). The compound was used directly in the subsequent reaction.

3-[1-Oxo-3-(4-thiazolyl)propyl]-4(*S*)-(1-methylethyl)-2-oxazolidinone (62). A solution of **61** (12.5 g, 40.8 mmol) and freshly prepared thioformamide (5.00 g, 81.7 mmol) in THF (120 mL) was stirred at 25 °C overnight. The reaction mixture was diluted with EtOAc and the resulting solution was washed with saturated aqueous $NaHCO_3$ and brine then was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by distillation (bulb to bulb, ∼250 °C) under reduced pressure (∼1 mm Hg) to give **62** (6.00 g, 55%) as a pale yellow oil: $[\alpha]_D^{25}$ +77.1° (*c* 1.57 MeOH); IR (film) ν_{max} 1785, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.77 (d, *J* = 1.9 Hz, 1H), 7.06 (dt, *J* = 1.9, 0.9 Hz, 1H), 4.44 (∼ddd, *J* = 8.3, 3.8, 3.2 Hz, 1H), 4.28 (∼dd, *J* = 9.1, 8.3 Hz, 1H), 4.21 (dd, *J* = 9.1, 3.2 Hz, 1H), 3.49–3.33 (m, 2H), 3.23 (t, *J* = 7.5 Hz, 2H), 2.37 (sept d, *J* = 7.0, 3.8 Hz, 1H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H); MS (CI) *m*/*z* 269 $(MH)^+$.

4(*S*)-(1-Methylethyl)-3-[1-oxo-3-[2-[[(2,2,2-trichloroethoxy)-carbonyl]amino]-4-thiazolyl]propyl]-2-oxazolidinone (63). A solution of **61** (5.38 g, 17.6 mmol) and thiourea (1.34 g, 17.6 mmol) in *i*-PrOH (35 mL) was heated to reflux for 30 min. The resulting suspension was cooled to room temperature and poured into Et_2O (75 mL). The salt obtained by filtration was suspended in 5% aqueous Na_2CO_3 (100 mL) and extracted with EtOAc (2×150 mL). The combined organic layers were washed with brine (75 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the 2-amino-4-thiazolyl derivative (4.23 g). A solution of this derivative (4.23 g, ∼14.9 mmol), $ClCO_2CH_2CCl_3$ (4.74 g, 22.4 mmol), *i*-Pr_2NEt (2.12 g, 16.4 mmol) and DMAP (182 mg, 1.49 mmol) in CH_2Cl_2 (50 mL) was stirred at 0 °C for 45 min then at 25 °C for 16 h. The mixture was diluted with CH_2Cl_2 (150 mL) and the resulting solution was successively washed with saturated aqueous $NaHCO_3$ (100 mL), H_2O (100 mL) and brine (100 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane: EtOAc, 2:1) yielded **63** (4.90 g, 61%) as a white foam: $[\alpha]_D^{25}$ +46.0° (*c* 0.97 MeOH); IR (KBr) ν_{max} 1785, 1740, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.65 (s, 1H), 4.91 (Abq, δν = 6.4 Hz, *J* = 11.9 Hz, 2H), 4.45–4.41 (m, 1H), 4.28 (∼dd, *J* = 9.0, 8.6 Hz, 1H), 4.21 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.35–3.30 (m, 2H), 3.09 (t, *J* = 7.5 Hz, 2H), 2.36 (sept d, *J* = 7.0, 4.0 Hz, 1H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H); MS (FAB) *m*/*z* 458/460/462/464 $(MH)^+$. Anal. calcd for $C_{15}H_{18}N_3O_5SCl_3$: C, 39.27; H, 9.16; N, 3.95. Found: C, 38.77; H, 9.11; N, 3.83.

3-[4-(1,1-Dimethylethoxy)-1,4-dioxo-2(*R*)-[[2-[[(2,2,2-trichloroethoxy)carbonyl]amino]-4-thiazolyl]methyl]butyl]-4(*S*)-(1-methylethyl)-2-oxazolidinone (64). Starting with **63** and using the general procedure described for **42–46**, **64** (2.95 g, 59%) was obtained, after purification by flash chromatography (hexane:EtOAc, 3:1) and recrystallization, as white flakes: mp 98–101 °C; $[\alpha]_D^{25}$ +55.2° (*c* 0.99 MeOH); IR (KBr) ν_{max} 1775, 1745, 1730, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.71 (s, 1H), 4.95 (d, *J* = 12.1 Hz, 1H), 4.87 (d, *J* = 12.1 Hz, 1H), 4.53–4.48 (1H, m), 4.42 (∼ddd, *J* = 7.0, 4.1, 3.8 Hz, 1H), 4.23–4.17 (m, 2H), 3.04 (dd, *J* = 14.5, 6.0 Hz, 1H), 2.94 (dd, *J* = 14.5, 7.3 Hz, 1H), 2.78 (dd, *J* = 16.6, 9.7 Hz, 1H), 2.45 (dd, *J* = 16.6, 4.8 Hz, 1H), 2.34 (sept d, *J* = 7.0, 3.8 Hz, 1H), 1.41 (s, 9H), 1.33–1.25 (m, 3.5H), 0.92–0.87 (m, 9.5H); MS (FAB) *m*/*z* 572/574/576/578 $(MH)^+$. Anal. calcd for $C_{21}H_{28}N_3O_7SCl_3.0.5\ C_6H_{14}$: C, 46.80; H, 5.73; N, 6.82. Found: C, 46.27; H, 5.63; N, 6.78.

3-[4-[[2-(Dimethylamino)-2-oxoethyl][1(*S*)-phenylethyl]-amino]-1,4-dioxo-2(*R*)-[[2-[[(2,2,2-trichloroethoxy)carbonyl]amino]-4-thiazolyl]methyl]butyl]-4(*S*)-(1-methylethyl)-2-oxazolidinone (65). A solution of **64** (894 mg, 1.45 mmol) and TFA (2.9 mL) in CH_2Cl_2 (2.9 mL) was stirred at 0 °C for 30 min and at 25 °C for 3 h. The mixture was concentrated under reduced pressure. The residue was dissolved in C_6H_6 (3×25 mL) and the solution was concentrated under reduced pressure to give the corresponding acid. To a solution of the crude acid, **15** (359 mg, 1.74 mmol) and *i*-Pr_2NEt (319 mg, 2.47 mmol) in DMF (5.8 mL) was added BOP·PF_6 (705 mg, 1.60 mmol) at 25 °C. The solution was stirred at 25 °C for 25 h then was diluted with EtOAc (150 mL). The solution was successively washed with aqueous 10% citric acid (30 mL), H_2O (30 mL), saturated aqueous

$NaHCO_3$ (30 mL), brine (30 mL) and then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc: hexane, 3:1) to yield **65** (751 mg, 73%) as a white solid: $[\alpha]_D^{25}$ +13.7° (*c* 0.92 MeOH); IR (KBr) ν_{max} 1780, 1740, 1700, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ (1.7:1.0 mixt. of rotamers) 7.39–7.22 (m, 5H), 6.88, 6.79 (2s, 1H), 5.89, 5.22 (2q, *J* = 7.0, 6.7 Hz, 1H), 4.89–4.85 (m, 2H), 4.67–4.35 (m, 2H), 4.37, 3.81, 3.28 (d, AB_q and d, *J* = 16.2 Hz; Δν = 20.3 Hz, *J* = 17.6 Hz; *J* = 16.2 Hz, 2H), 4.31–4.24 (m, 1H), 4.21–4.16 (m, 1H), 3.16, 3.13 (2dd, *J* = 14.5, 5.1, *J* = 14.5, 5.1 Hz, 1H), 3.06 (dd, *J* = 16.4, 8.1 Hz, ~1H), 2.94–2.85 (m, 1H), 2.90, 2.78, 2.71 (3s, 6H), 2.78–2.69 (m, 1H), 2.43–2.32 (m, 1H), 1.60, 1.41 (2d, *J* = 6.7, 7.0 Hz, 3H), 0.95–0.87 (m, 6H); MS (FAB) *m*/*z* 704/706/708/710 $(MH)^+$.

3-[4-[(Cyclohexylmethyl)[2-[methyl[2-(2-pyridinyl)ethyl]-amino]-2-oxoethyl]amino]-1,4-dioxo-2(*R*)-[[2-[[(2,2,2-trichloroethoxy)carbonyl]amino]-4-thiazolyl]methyl]butyl]-4(*S*)-(1-methylethyl)-2-oxazolidinone (70). Using a procedure similar to the one described for **65**, **64** (14.0 g, 24.4 mmol) was first transformed into the corresponding acid. The coupling of the crude acid with amine **27** (28.1 mmol) followed by the purification by flash chromatography (EtOAc:MeOH, 40:1) of the residue gave **70** (16.96 g, 88%) as a white solid: $[\alpha]_D^{23}$ +40.9° (*c* 0.574 MeOH); IR (KBr) ν_{max} 1769, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ (2:2:1:1 mixt. of rotamers) 8.67, 8.59, 8.56, 8.51 (4d, *J* = 4.4, 4.4, 4.8, 5.1 Hz, 1H), 7.72–7.61 (m, 1H), 7.34–7.16 (m, 2H), 6.71, 6.68, 6.65 (3s, 1H), 4.89–4.80 (m, 2H), 4.49–4.57, 4.42–4.36 (2m, 2H), 4.26–4.18 (m, 3H), 3.94–3.57 (m, 3H), 3.33, 3.19–2.77, 2.71–2.60, 2.54–2.45 (dd, 3m, *J* = 13.8, 8.1 Hz, 8H), 2.93, 2.86 (2s, 3H), 2.40–2.32 (m, 1H), 1.77–1.42 (m, 6H), 1.26–1.13 (m, 3H), 0.91–0.82 (m, 8H); MS (ESI) *m*/*z* 787/789/801/803 $(MH)^+$.

***N*^{1}-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-*N*^{4}-[2-(dimethylamino)-2-oxoethyl]-*N*^{4}-[1(*S*)-phenylethyl]-2(*R*)-[[2-[[(2,2,2-trichloroethoxy)carbonyl]amino]-4-thiazolyl]methyl]butanediamide (71).** To an ice-cold solution of **65** (679 mg, 0.96 mmol) in THF:H_2O (3:1, 19 mL), was added 30% (w/%) H_2O_2 (0.55 mL, 4.81 mmol) followed by LiOH·H_2O (80.8 mg, 1.92 mmol). The reaction mixture was stirred at 0 °C for 1.5 h and at 25 °C for 3.5 h. The mixture was cooled to 0 °C, diluted with H_2O (20 mL) and aqueous 1.5 M Na_2SO_3 was added to decompose the excess of peroxide. The resulting mixture was diluted with H_2O (50 mL) and rendered acidic (pH 3) with aqueous citric acid. The mixture was extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a mixture of chiral auxiliary and the corresponding acid. To a solution of the crude acid, **47** (234 mg, 0.96 mmol) and *i*-Pr_2NEt (249 mg, 1.93 mmol) in DMF (4.8 mL) was added BOP·PF_6 (447 mg, 1.01 mmol). The solution was stirred at 25 °C for 3.5 h. The reaction mixture was diluted with EtOAc (125 mL) and the resulting solution was washed with saturated aqueous $NaHCO_3$ (30 mL), H_2O (2×30 mL), and brine (30 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Two successive purifications by flash chromatography ((a) hexane:*i*-PrOH, 5:1; (b) EtOAc) gave **71** (252 mg, 32%) as a white solid: $[\alpha]_D^{25}$ −47.3° (*c* 0.89 MeOH); IR (KBr) ν_{max} 3400 (broad), 1745, 1655, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ (1.2:1.0 mixt. of rotamers) 7.36–7.20 (m, 5H), 7.11, 6.88 (2d, *J* = 8.6, 8.9 Hz, 1H), 6.79 (s, 1H), 6.03, 5.16 (2q, *J* = 7.0, 7.0 Hz, 1H), 4.89–4.82 (m, 2H), 4.40, 3.97, 3.77, 3.24 (4d, *J* = 16.2, 17.6, 17.6, 16.2 Hz, 2H), 4.36–4.29, 4.28–4.21 (2m, 1H), 3.52–3.35, 3.30–3.16 (2m, ~4H), 2.97–2.66 (m, 4H), 2.94, 2.91, 2.86, 2.84 (4s, 6H), 2.55 (dd, *J* = 16.5, 6.7 Hz, 1H), 1.93–1.86 (m, 1H), 1.75–1.07 (m, 13H), 1.56, 1.38, (2d, *J* = 7.0, 7.0 Hz, 3H), 0.96–0.83 (m, 2H), 0.92, 0.87, 0.83 (3d, *J* = 6.4, 6.7, 6.7 Hz, 6H); MS (FAB) *m*/*z* 818/820/822/824 $(MH)^+$.

***N*^{4}-(Cyclohexylmethyl)-*N*^{1}-[1(*S*)-(cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-*N*^{4}-[2-[methyl[2-(2-pyridinyl)ethyl]amino]-2-oxoethyl]-2(*R*)-[[2-[[(2,2,2-trichloroethoxy)carbonyl]amino]-4-thiazolyl]methyl]butanediamide (76).** A solution of 0.8 M $Mg(OMe)_2$ in MeOH (122 mL, 97.4 mmol) was added (15 min) to an ice-cold solution of **70** (38.4 g, 48.7 mmol) in MeOH (500 mL). The reaction mixture was stirred at 0 °C for 1 h. Saturated aqueous NH_4Cl (500 mL) was then added and the resulting mixture was poured into H_2O (1 L). The solution was extracted with EtOAc (3×350 mL). The combined organic layers were washed with H_2O (2×500 mL), saturated aqueous $NaHCO_3$ (300 mL) and brine (300 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc:MeOH, 20:1) to give the corresponding methyl ester (30.3 g, 90%) as a white solid. A solution of this ester (28.7 g, 41.6 mmol) in THF:MeOH:H_2O (415 mL:40 mL:120 mL) was treated with aqueous 2 N NaOH (52 mL, 104 mmol) at 25 °C for 14 h. The reaction mixture was concentrated under reduced pressure and 1 N HCl (100 mL) and EtOAc (300 mL) were added. The phases were separated, and the aqueous layer was extracted with EtOAc (200 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the corresponding acid (27.9, 99%). A solution of this acid (25.7 g, 38.0 mmol), **47** (9.24 g, 38.0 mmol), *i*-Pr_2NEt (9.82 g, 76.0 mmol) and BOP·PF_6 (17.6 g, 38.0 mmol) in DMF (152 mL) was stirred at 25 °C for 3.5 h. The reaction mixture was poured into H_2O (1 L) and saturated aqueous $NaHCO_3$ (100 mL). The resulting solution was extracted with EtOAc (2×300 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (200 mL), a mixture of H_2O and brine (3:1, 2×300 mL), brine (250 mL), and then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography (EtOAc:MeOH, 50:1) gave a mixture of **76** and its epimer (92:8 mixture, 4.1 g 12%) and pure diastereomer **76** (18.4 g, 54%) as a white solid: $[\alpha]_D^{23}$ −16.8° (*c* 0.655 MeOH); IR (KBr) ν_{max} 3400–3150, 1738, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ (3:3:1:1 mixt. of rotamers) 10.31 (broad s, 1H), 8.64, 8.54, 8.51 (3d, *J* = 4.8, 4.1, 4.8 Hz, 1H), 7.67–7.58 (m, 1H), 7.23–7.11 (m, 2H), 6.76, 6.73, 6.71–6.69 (2d and m, *J* = 5.7, 5.7 Hz, 1H), 6.69, 6.61, 6.59 (3s, 1H), 4.90–4.79

(m, 2H), 4.50–4.36 , 4.26–4.13 (2m, 3H), 4.07, 3.94, 3.87, 3.80–3.61 (3d and m, J = 17.5, 17.5, 17.8 Hz, 3H), 3.44–2.82 (m, 9H), 2.92, 2.92 (2s, 3H), 2.67, 2.62–2.48, 2.37, 2.20, dd, m and 3 dd, J = 16.2, 7.3 Hz, J = 16.2, 5.7 Hz, J = 16.8, 5.7 Hz, 2H), 1.90–1.82 (m, 1H), 1.75–1.05 (m, 23H), 0.97–0.72 (m, 4H), 0.91, 0.84, 0.81 (3d, J = 6.7, 6.7, 6.4 Hz, 6H); MS (ESI) m/z 901/903/905/907 $(MH)^+$.

2(*R*)-[(2-Amino-4-thiazolyl)methyl]-*N*^{1}-[1(*S*)-(cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-*N*^{4}-[2-(dimethylamino)-2-oxoethyl]-*N*^{4}-[1(*S*)-phenylethyl]butanediamide (3u). To a solution of **71** (1.91 g, 2.34 mmol) in aqueous 1 N HCl (5.8 mL) and 1,4-dioxane (11.7 mL) was added Zn powder (19.0 g, 0.29 mol). The reaction mixture was stirred at 25 °C for 3 h. Saturated aqueous $NaHCO_3$ was added, the suspension was filtered and the aqueous phase extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ (2×), H_2O, brine (2×), and then was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was partially purified by flash chromatography (EtOAc: hexane:EtOH, 6:3:1) to give impure **3u** which was combined with another batch of the same material obtained from a similar reaction (starting with 4.14 g, 5.07 mmol of **71**). A second purification by flash chromatography ($CHCl_3$:MeOH:AcOH, 23:2:1) gave **3u** (2.40 g, 50%) as a white solid: $[\alpha]_D^{25}$ −58.8 (c 1.0 MeOH); IR (KBr) ν_{max} 3560–3100, 1635 (broad) cm^{-1}; ^1H NMR ($CDCl_3$) δ (1.5:1.0 mixt. of rotamers) 7.38–7.22 (m, 5H), 6.77, 6.64 (2d, J = 8.3, 10.2 Hz, 1H), 6.27, 6.23 (2s, 1H), 6.05, 5.18 (2q, J = 7.0, 6.7 Hz, 1H), 5.39–5.27 (m, 2H), 4.62–4.50 (m, 1H), 4.28–4.21 (m, 1H), 4.38, 3.79, 3.22 (d, ABq, d, J = 16.4 Hz, Δν = 16.7 Hz and J = 17.5 Hz, J = 16.4 Hz, 2H), 3.64–3.12 (m, 3H), 2.94, 2.91, 2.88, 2.82 (4s, 6H), 3.00, 2.95–2.50 (dd and m, J = 14.6, 7.0 Hz, 5H), 1.97–1.85 (m, 1H), 1.80–1.48 (m, 7H), 1.59, 1.38 (2d, J = 6.7, 7.0 Hz, 3H), 1.43–1.08 (m, 6H), 0.98–0.80 (m, 2H), 0.94, 0.90, 0.86 (3d, J = 6.7, 6.7, 6.7 Hz, 6H); MS (FAB) m/z 644 $(MH)^+$. Anal. calcd for $C_{34}H_{53}N_5O_5S$ + 2.58% (w/w) H_2O: C, 61.79; H, 8.39; N, 10.60. Found: C, 61.47; H, 8.31; N, 10.57.

2(*R*)-[(2-Amino-4-thiazolyl)methyl]-*N*^{4}-(cyclohexylmethyl)-*N*^{1}-[1(*S*)-(cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-*N*^{4}-[2-[methyl[2-(2-pyridinyl)ethyl]amino]-2-oxoethyl]butanediamide (3z). Zinc powder (36.0 g, 0.55 mol) was added in one portion to a cold solution (10 °C) of **76** (16.58 g, 18.37 mmol) in 1,4-dioxane (185 mL) and 1 N HCl (184 mL, 184 mmol). The mixture was stirred at 10 °C for 45 min. The mixture was cooled to 0 °C, saturated aqueous $NaHCO_3$ (350 mL) and EtOAc (1.3 L) were added and the heterogeneous mixture was stirred at 25 °C for 15 min. The salts were removed by filtration through a pad of Celite®. The phases were separated and the organic layer was washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc:MeOH, 10:1) to give **3z** (9.38 g, 70%) as a white solid: mp 93–96 °C; $[\alpha]_D^{25}$ −24.8° (c 1.0 MeOH); IR (KBr) ν_{max} 3350 (broad), 1645 (broad) cm^{-1}; ^1H NMR (DMSO-d_6) δ (~1:1:1:1 mixture of rotamers) 8.54–8.51, 8.48 (m and d, J = 4.8 Hz, 1H), 7.75–7.67 (m, 1H), 7.59, 7.56, 7.53 (3d, J = 9.0, 9.9, 9.6 Hz, 1H), 7.33–7.19 (m, 2H), 6.77, 6.73 (2s, 2H), 6.18, 6.17, 6.10, 6.06 (4s, 1H), 4.64–4.61, 4.59, 4.56 (m and 2d, J = 6.6, 6.6 Hz, 2H), 4.18, 4.17, 4.11, 4.09–4.01, 3.88, 3.85 (3d, m and 2d, J = 17.8, 16.2, 16.5, 17.8, 16.2 Hz, 3H), 3.69–3.51 (m, 2H), 3.10–2.80 (m, 7H), 2.90, 2.89, 2.83, 2.80 (4s, 3H), 2.74–2.62 (m, 1H), 2.51–2.32, 2.24, 2.14, 2.02 (m and 3dd, J = 15.8, 7.8 Hz, J = 16.1, 5.7 Hz, J = 15.8, 5.7 Hz, 3H), 1.78–1.05 (m, 23H), 0.90–0.69 (m, 4H), 0.86 (d, J = 6.9, 3H), 0.77 (d, J = 6.6 Hz, 3H); MS (FAB) m/z 727 $(MH)^+$. Anal. calcd for $C_{39}H_{62}N_6O_5S$: C, 64.42; H, 8.60; N, 11.56. Found: C, 64.15; H, 8.77; N, 11.49.

2(*R*)-[(2-Amino-4-thiazolyl)methyl]-*N*^{1}-[1(*S*)-(cyclohexylmethyl)-2(*S*)-hydroxy-2-(1,5,5-trimethyl-2-oxopyrrolidin-3(*S*)-yl)ethyl]-*N*^{4}-[2-(dimethylamino)-2-oxoethyl]-*N*^{4}-[1(*S*)-phenylethyl]butanediamide (77). Compound **77** was prepared using a method similar to the one described to prepare **3u** from **71**. The coupling of the acid (0.61 g, 1.05 mmol) obtained from **65** and the amine obtained via treatment of 1,1-dimethylethyl *N*-[1(*S*)-(cyclohexylmethyl)-2(*S*)-hydroxy-2-(1,5,5-trimethyl-2-oxopyrrolidin-3(*S*)-yl)ethyl]carbamate (0.40 g, 1.05 mmol) with TFA gave the corresponding amide (0.42 g, 47%) after purification by flash chromatography ($CHCl_3$:MeOH, 97:3 to 93:7). Upon treatment of this compound (0.53 g, 0.62 mmol) with Zn (0.40 g, 6.17 mmol) in 1,4-dioxane (10 mL) and 1 N HCl (6 mL) for 3 h as described for **3u**, **77** (0.20 g, 55%) was obtained as a white solid after purification by flash chromatography ($CHCl_3$:MeOH: AcOH, 10:2:1): ^1H NMR ($CDCl_3$) δ 7.40–7.29 (m, 5H), 6.17 (s, 1H), 6.03, 5.35 (2m, 1H), 5.64, 5.67 (2 broad s, 2H), 5.45 (m, 1H), 4.33, 3.79 (2d, J = 15.9, 15.9 Hz, 1H), 4.17–4.02 (m, 2H), 3.94–3.76 (m, 3H), 3.22–3.12 (m, 2H), 2.93–2.90 (2s, 6H), 2.87–2.76 (m, 2H), 2.74 (s, 3H), 2.70–2.61 (m, 3H), 2.28–2.18 (m, 1H), 2.10–1.70 (m, 6H), 1.64, 1.43 (2d, J = 6.7, 7.0 Hz, 3H), 1.32, 1.19 (2s, 6H), 1.35–1.05 (m, 4H), 1.00–0.82 (m, 1H), 0.82–0.68 (m, 1H); MS (FAB) m/z 683 $(MH)^+$; RP-HPLC, 95% (system A), 91.9% (system B).

Human plasma renin assay pH 6.0 and 7.4[41]

Human plasma (Biological Specialty Corporation, Lansdale, PA) was used as the source of both the enzyme, renin, and the substrate, angiotensinogen. Angiotensin I was quantified using a commercially available radioimmunoassay kit from NEN-Dupont (Cat. No. NEA-105). The assay (pH 6.0) was performed in 0.27 M MES (4-morpholineethanesulfonic acid), 1% HSA (human serum albumin), pH 5.85 containing 13 (μL/mL dimercaprol solution, 13 μL/mL 8-hydroxyquinoline sulfate solution and 1% DMSO. The dimercaprol and 8-hydroxyquinoline sulfate solutions were added just before use and were provided with the radioimmunoassay kit. For the pH 7.4 assay, the assay buffer was 0.15 M HEPES, 6 mM EDTA, 1% HSA, pH 7.4 containing 30 μL/mL 8-hydroxyquinoline sulfate solution and 1% DMSO. Each assay was carried out in a final volume of 100 μL in 1.0 mL polypropylene minitubes. To 50 μL of serial dilution of the test compounds in assay buffer or 50 μL of assay buffer only (37 °C and 4 °C controls) was added 50 μL of human plasma to initiate the reaction. After addition of the human

plasma, the assay mixture was incubated at 37 °C for 60 to 90 min (pH 6.0 assay) or 120 to 150 min (pH 7.4 assay) in order to achieve an angiotensin I generation of 2–3 ng/mL. In 37 °C controls, no inhibitor was added in order to determine the maximum angiotensin I level generated with the human plasma pool used. In 4 °C controls, no angiotensin I was generated, tubes being kept on ice-cold water during the incubation. These served to determine the background level of angiotensin I. When the incubation was completed, tubes were quickly returned to ice-cold water. The generation of angiotensin I was then quantified using the radioimmunoassay kit from NEN-Dupont according to the manufacturer instructions except that 2% PEG 8000 was added to the angiotensin I second antibody solution. IC_{50} values were generated from the inhibition curves using the SAS statistical software system (SAS Institute Inc., Cary, NC) and a non-linear curve fit using the Hill model.

Cathepsin D enzymatic assay

The enzyme activity was determined using the aspartyl protease specific chromophoric substrate H-Pro-Thr-Glu-Phe-Phe(NO_2)-Arg-Leu-OH.[42] Cathepsin D purified from human liver (Medor, Munchen, Germany) was dissolved at a concentration of 25 μg/mL in 100 mM HEPES, 300 mM KCl, 1 mM EDTA (pH adjusted to 7.5 with NaOH) and stored at −20 °C. The enzyme assay was conducted in a total of 520 μL. The assay volume consisted of 500 μL of 0.28 mM chromophoric substrate dissolved in 100 mM sodium formate buffer pH 3.0 (pH adjusted with NaOH), 10 μL of purified cathepsin D and 10 μL of DMSO in presence or absence of compound. The assay was initiated by addition of enzyme and incubation at 37 °C was carried out for 30 min. The degradation of the substrate was quantified by measuring the decrease in absorbance of the reaction mixture at 310 nm (Hewlett Packard diode array spectrophotometer, model HP 8452A). IC_{50} values were generated from the inhibition curve using the BMDP Statistical Software package for nonlinear regression (BMDP Statistical Software, Los Angeles, CA). For reference and comparison, pepstatin and A-72517 exhibited IC_{50} values of 3 and 575 nM, respectively, in this assay.

Conscious sodium depleted cynomolgus monkey model

The renin inhibitors were evaluated for their abilities to lower mean arterial blood pressure (MABP) in conscious, sodium and volume depleted primates. Cynomolgus primates (*Macacca fascicularis*, male, 4 to 8 kg) previously instrumented with a vascular access port (femoral artery) to facilitate the measurement of systemic blood pressure, were fed a low sodium diet (< 0.05%) for seven days prior to experimentation. In addition, the diuretic furosemide (Lasix®, 5 mg/kg, im) was administered at 40 h and 16 h prior to experimentation. Conscious animals were placed in primate restraining chairs. Following 30 min of equilibration, the inhibitor or phosphate buffer vehicle was administered orally by gavage. Finally, in some animals, blood samples were collected for the evaluation of plasma angiotensin II (AII, measured by HPLC followed by RIA).

Pharmacokinetic studies

Animal dosing and blood sampling were performed at TSI Mason Laboratories in Worcester, Massachusetts. Three male cynomolgus monkeys were fasted for 12 to 16 h prior to oral and intravenous administration of the compound. On the first day of the experiment, animals received the renin inhibitor (1.0 mg/kg) via intravenous injection. On the 15th day, the monkeys received the inhibitors (10 mg/kg) by gavage. Blood samples were obtained by peripheral venipuncture before the experiment and at 5 (iv treatment only), 15, 30, 45 min and 1, 1.5, 2, 3, 4, 6, 8, and 24 h after dosing. Plasma was recovered, frozen and stored at −20 °C until analysis. Plasma samples (0.5 mL) were alkalinized with 1.5 N NaOH (0.05 mL) and were shaken for 20 min with Et_2O (5 mL). The ether extracts were transferred to glass tubes (13×100 mm) and evaporated to dryness under N_2 at 40 °C. The residues were each dissolved in 50 mM KH_2PO_4: MeCN (40:60; 100 μL) and aliquots (75 μL) were analyzed by HPLC.

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