Pergamon

Bioorganic & Medicinal Chemistry, Vol. 2, No. 9, pp. 859-879, 1994

0968-0896/94 $7.00 + .00

0968-0896(94)00107-3

Synthesis, Antiviral Activity, and Bioavailability Studies of γ-Lactam Derived HIV Protease Inhibitors

Randall W. Hungate,* Jenny L. Chen, Ken E. Starbuck, Joseph P. Vacca, Stacey L. McDaniel, Rhonda B. Levin, Bruce D. Dorsey, James P. Guare, M. Katharine Holloway, Willie Whitter, Paul L. Darke, Joan A. Zugay, William A. Schleif, Emilio A. Emini, Julio C. Quintero, Juinn H. Lin, I-Wu Chen, Paul S. Anderson and Joel R. Huff

Merck Research Laboratories, West Point, PA 19486, U.S.A.

Abstract—Incorporation of a γ-lactam in hydroxyethylene isosteres results in modest inhibitors of HIV-1 protease. Additional structural activity studies have produced significantly more potent inhibitors with the introduction of the trisubstituted cyclopentane (see compound **20**) as the optimum substituent for the C-terminus. This new amino acid amide surrogate can be readily prepared in large scale from (*R*)-pulegone. Optimized compounds (**36**) and (**60**) are potent antiviral agents and are well absorbed (15–20 %) in a dog model after oral administration.

Introduction

The spread of Acquired Immunodeficiency Syndrome continues at an alarming rate, and new more effective therapeutic strategies are needed.[1] The causative agent of AIDS, human immunodeficiency virus type 1 (HIV-1), encodes a protease which cleaves viral *gag* and *gag–pol* polyproteins to produce infectious virions.[2] The identification of this proteolytic enzyme as an aspartyl protease further defined its mechanism of action.[3,4] Inactivation of the protease by site directed mutagenesis leads to non-infectious virions[5] and suggests that the protease is crucial in the life cycle of the virus. For this reason, HIV-1 protease is regarded as a crucial target for developing a chemotherapeutic agent for AIDS.

The screening of compounds prepared as inhibitors for the mechanistically related renin has led to the identification of potent HIV protease inhibitors.[6] In addition, novel strategies based on the symmetrical nature of the enzyme have also led to potent inhibitors.[7] Importantly, the effectiveness of protease inhibitors in preventing the spread of the virus in various cell types *in vitro* has been demonstrated, validating the potential utility of a protease inhibitor for the treatment of HIV infected individuals. Despite the success of these approaches, most compounds still lack the necessary pharmacokinetic behavior in animal models to be viable candidates for human clinical trials. For example, L-685,434 (Figure 1), was shown to be a potent inhibitor of HIV-1 protease and has *in vitro* activity against HIV infected H9 human T-lymphoid cells.[8] Unfortunately, oral administration of L-685,434 to dogs as a methocel suspension (10 mg/kg) indicated < 100nM peak levels of intact compound in the plasma.[9] This finding is typical of tetrapeptide analogs of this type, and the lack of significant drug concentrations in plasma has hampered the development of this class of inhibitors.[10]

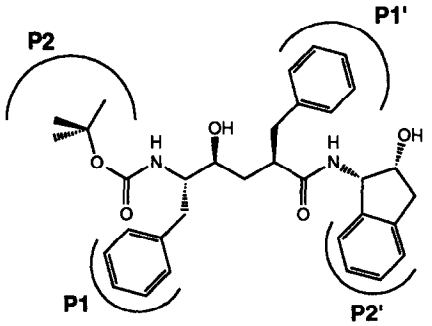


Figure 1.

We have continued in this area, and our effort to obtain compounds with improved oral absorption focused primarily on enhancing solubility and minimizing the number of amide bonds which might be cleaved *in vivo*. X-Ray crystallographic data of L-689,502, (Figure 2) a closely related analog of L-685,434, bound to HIV-1 protease has been studied in detail.[11] From the crystallographic data presented, it was apparent that the indan amide N–H and the C–H bond of the α-carbon were nearly eclipsed. This is best illustrated in the Newman projection shown in Figure 3 (**C1**). This finding suggested that incorporating a ring, Figure 3 (**C2**), would maintain the inhibitor in its bioactive conformation in this region of space and eliminate an amide bond which might be cleaved *in vivo*.

Previous work on the acyclic analogs L-687,965 (IC_{50} = 7 nM) and L-689,428 (IC_{50} = 136 nM) showed that N-methylation resulted in a decrease in binding affinity.[9] This result suggests that the amide N–H forms an important hydrogen bond to the floor of the enzyme. This was born out experimentally from the crystal structure of L-689,502 in the active site. It was observed that the amide N–H is within hydrogen bonding distance to glycine 27 (2.9 Å). In

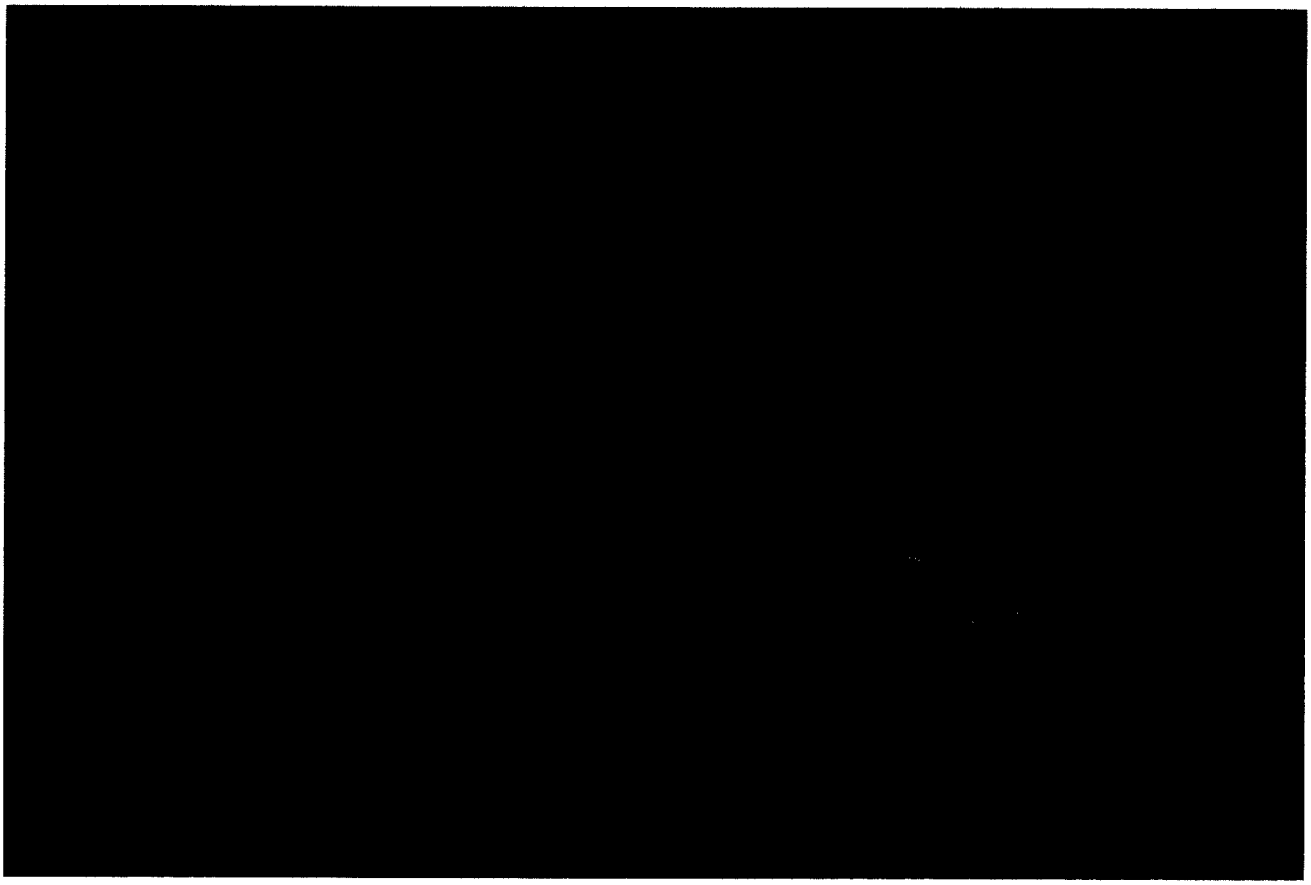


Figure 2. X-ray crystal structure of L-689,502 - HIV protease complex.[11] Stereoview illustrating the eclipsed conformation of indane N-H and δ C–H bond

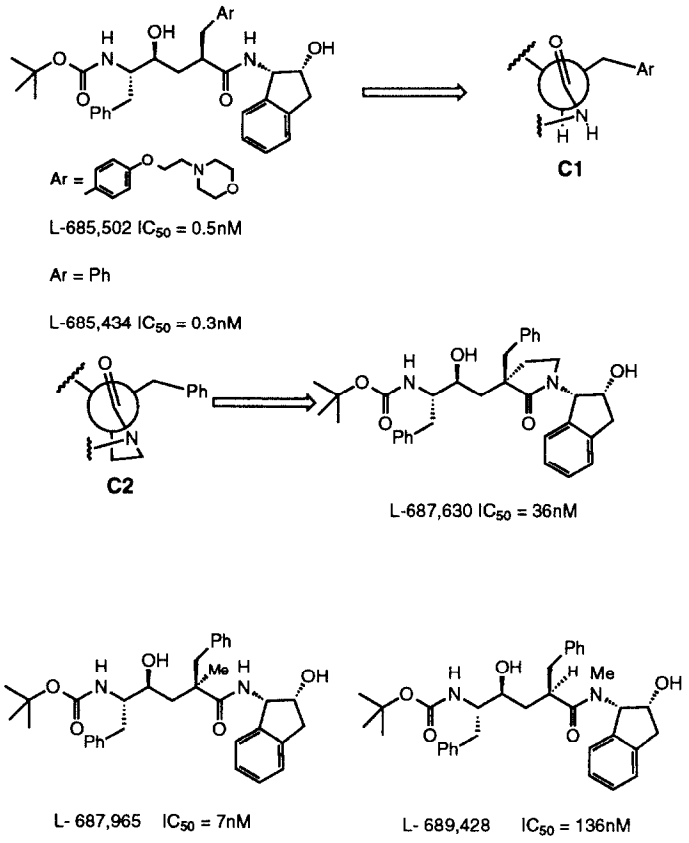


Figure 3.

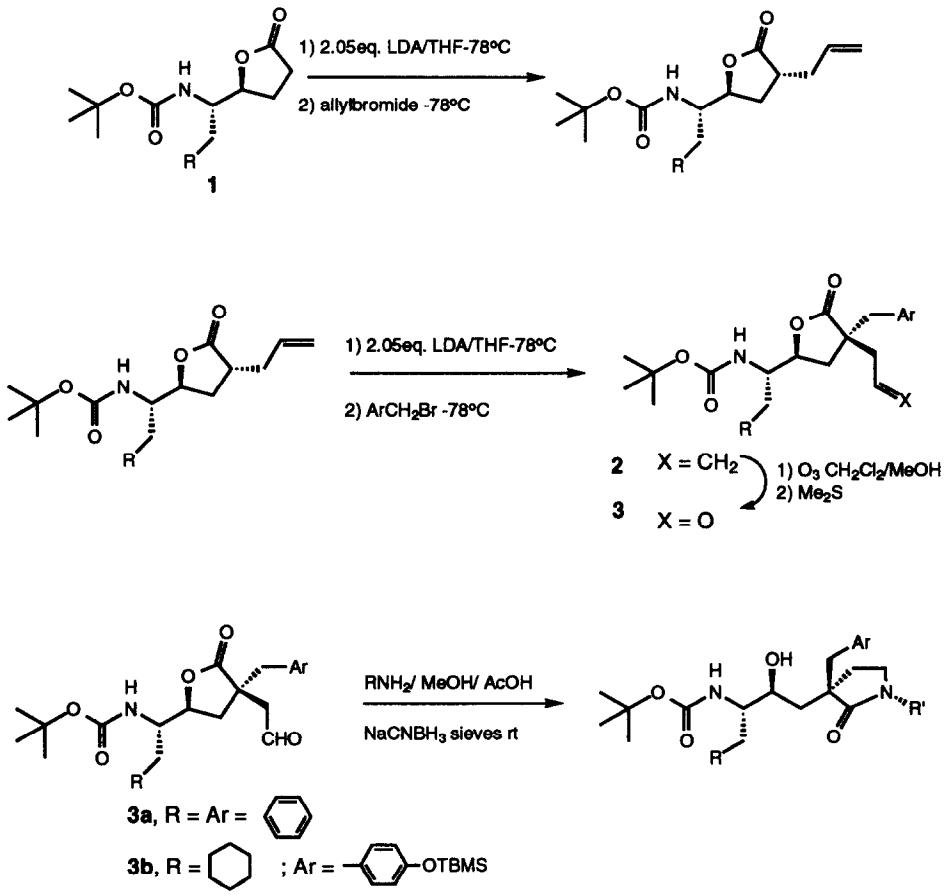
any event, formation of the γ lactam illustrated by **C2** (Figure 3) results in L-687,630 with an IC_{50} = 36 nM.[12] Additional structure–activity studies are the focus of this work with emphasis on improving the potency of this class of compounds and evaluating whether removal of this amide N–H leads to improved pharmacokinetic parameters. Although our data are far from complete, we have been able to significantly modify the physical properties of the inhibitors without sacrificing antiviral activity and make progress in obtaining orally bioavailable HIV protease inhibitors.

Results and Discussion

In this work we have focused primarily on the N and C termini while maintaining the residues that occupy the P_1 and P_1' binding pockets constant. We have also determined various physical properties of our more potent inhibitors, including solubility, partition coefficient (log P), and binding to serum proteins (protein binding). Although we have been unable to draw any definitive conclusions from these data, certain trends appear to be present and have aided in the design process.[13]

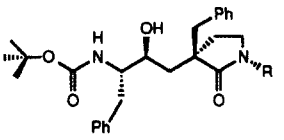
Synthesis

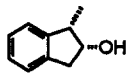
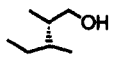
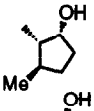
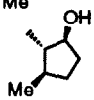
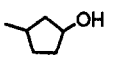
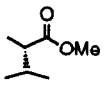
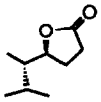
Synthesis of all compounds proceeded via the unsubstituted lactone **1** (Scheme I).[14] Dialkylation first with allylbromide followed by the appropriate benzyl halide provided the desired diastereomer (**2a** or **2b**) in excellent overall yield. Ozonolysis of the terminal olefin followed by dimethylsulfide workup produced aldehyde **3a** or **3b**. This material was coupled to a variety of primary amines using sodium cyanoborohydride ($NaCNBH_3$) in methanol containing 3 Å molecular sieves. In most cases these reaction conditions provided the desired γ lactams directly (Table 1). However, in the case of the indan and cyclopentane derivatives, compounds **16**, **20**, and **21**, the crude reaction mixture contained varying amounts of amino lactone and desired lactam. Conversion to the desired products were conveniently accomplished by simply warming the crude reaction mixture in toluene containing hydroxybenzotriazole as a transacylation catalyst.[15] Overall yields were good in most cases. Synthesis of the ethylmorpholine substituted tyrosine analogs found in Table 3 proceeded in an analogous fashion to aldehyde **3b**. Scheme II illustrates formation of the ethoxy morpholine derivatives from the *t*-butyldimethylsilyl protected phenol **4**. This route parallels the procedure previously reported from these laboratories.[11] However, in the present work overall yields were improved by using silyl protection in place of the benzyl group for the phenolic oxygen. Presumably, oxidation of the electron rich aromatic ring is reduced in the ozonolysis step. Modification of the P_2 site involved cleavage of the Boc group with anhydrous HCl followed by coupling the resultant amine with the appropriate acylating agent (Table 2, Table 3, Table 4). Additional modification with amino acid derivatives followed standard procedures via EDC/HOBT mediated coupling.



Scheme I.

Table 1.



Compound	R	IC_{50}	Formula[a]	HPLC[b]	Log P[c]
16		36nM	$C_{35}H_{42}N_2O_5 \cdot 0.25\ H_2O$	95%	5.2
17		78nM	$C_{29}H_{40}N_2O_5$	96%	
18		35nM	$C_{31}H_{44}N_2O_5$	97%	4.7
19		131nM	$C_{32}H_{46}N_2O_5\ 0.5\ H_2O$	96%	
20		12nM	$C_{32}H_{44}N_2O_5$	96%	4.8
21		228nM	$C_{32}H_{44}N_2O_5$	100%	
22		83nM[d]	$C_{31}H_{42}N_2O_5$	98%	
23		210nM	$C_{32}H_{43}N_2O_6$	97%	
24		17nM[e]	$C_{34}H_{46}N_2O_6 \cdot 0.45\ H_2O$	-	
25					
	a) R=H	82nM	$C_{30}H_{40}N_2O_5 \cdot 0.15\ H_2O$	100%	
	b) R=CH_3	73nM	$C_{31}H_{42}N_2O_5$	98%	4.8

[a]Elemental analysis within ± 0.4 % except where noted.
[b]Percent purity as determined by reverse-phase HPLC analysis at 215 nm, see experimental section for details.
[c]Determined by HPLC, see experimental section for details.
[d]Mixture of cis diastereomrs.
[e]Prepared as described in reference 14.

Amines used in the reductive amination step were commercially available except for entries **16**,[8] **20**, **21**, and **25**. The protected tetrahydrofuranyl amines **10a** and **10b** used for entries **25a** and **25b** were prepared from Z-aspartic acid as shown in Scheme III. Alkylation of lactone **8** following the procedure described by McGarvey, provided the *trans* isomer **9** as the major diastereomer.[16] Conversion of **8** and **9** to the Cbz protected amines **10a** and **10b** following the three step sequence of reduction, monotosylation and ring closure was straightforward. In a one step procedure the Cbz-protected compounds **10a** or **10b** and aldehyde **3a** were treated with 10 % Pd/C and H_2 which removed the benzyl carbamate and provided the desired lactam derivative directly. The tri-substituted cyclopentane derivatives, entries **20** and **21**, were prepared in excellent overall yield from (*R*)-pulegone as described previously.[17]

The heterocylic end groups used in Table 2 were commercially available except in the case of entries **38**, **39**, and **40**. These were prepared as shown in Scheme IV. The pyrazine ester **11** was prepared via literature procedure[18] and its conversion to acid **13** has recently been reported from these laboratories.[19] The nicotinic acid **14** and isonicotinic acid **15** derivatives were prepared following analogies found in the literature.[20] These heterocyclic carboxylic acids could be prepared without purification of intermediates.

In vitro *activity*

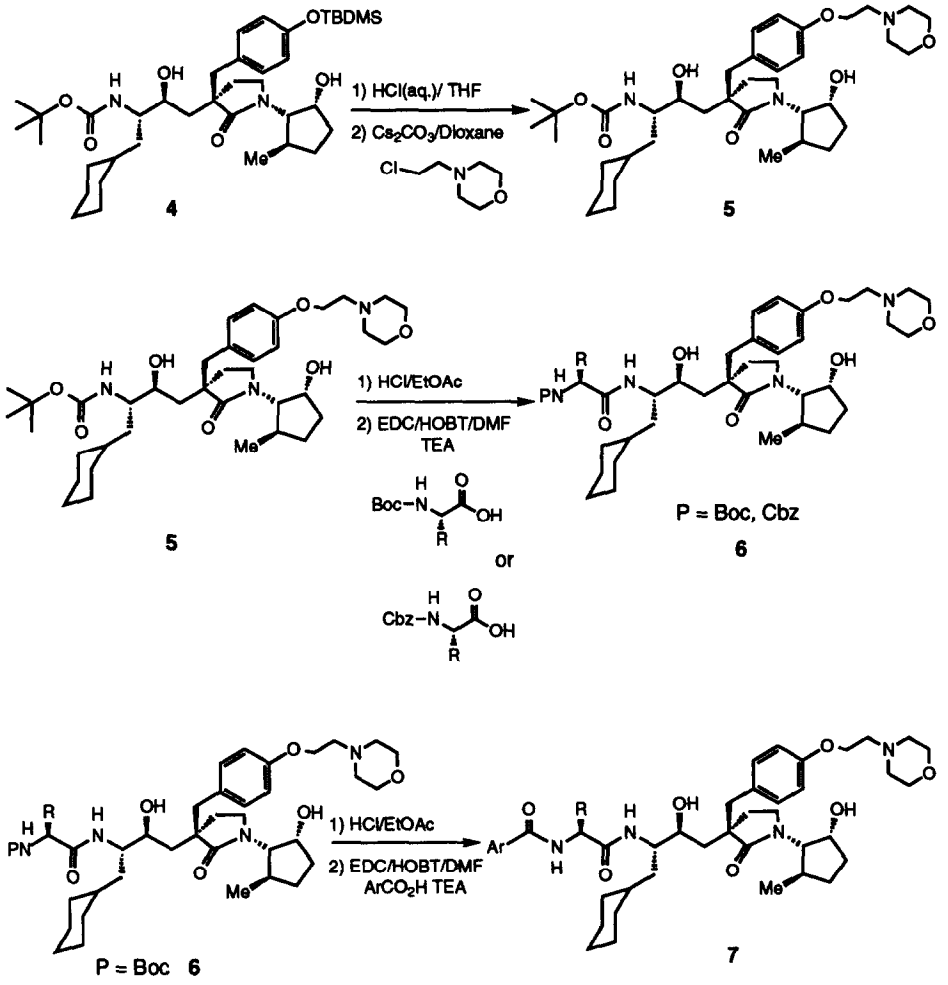
Evaluation of compounds for their ability to inhibit HIV-1 protease were determined from the extent of substrate cleavage as judged by HPLC.[21] The observed activity for the compounds tested is reported as the concentration to inhibit the reaction rate by 50 % (IC_{50}). In the acyclic compounds (Figure 4), the trisubstituted cyclopentane derivative L-694,702 was approximately 10–20 fold less

active than the corresponding indan analog L-692,048. However in the lactam series, the cyclopentane derivative was 3–4 times more potent (compounds **16**, **20** Table 1).

Interestingly, the valinol analog **18** is equipotent with the indan derivative as the C-terminal group despite the reduction of hydrophobic surface area. Modification of the N-terminus produced a large number of carbamates[22] and the key compounds (**26–30**) are shown in Table 2. These modifications did not significantly improve potency over the Boc derivatives. One exception was the tetrahydrofuranyl carbamate (**26** and **30**) which did give rise to a modest 3–4 fold increase in potency.[23] This was less than the 10–20 fold improvement that was observed in the acyclic series. We were interested in several issues in addition to improving potency. In general, Boc containing inhibitors were very insoluble and exhibited high partition coefficients (log P). The log P data serves to illustrate the effect the hydrophobic Boc group had on the inhibitor and how simple modifications in this region of the molecule affected log P values. For example, replacement of the hydrophobic *t*-butyl urethane **18** with the hydroxyethoxy carbamate **29** (Table 2), yielded an inhibitor of similar activity, and reduced log P by two units. Similarly, the tetrahydrofuranyl carbamate reduced log P approximately two units.

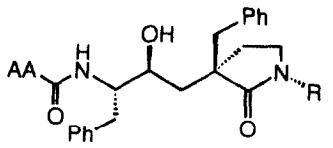
Simple amide replacements (data not shown) were much less active and were unsatisfactory as P_2 ligands. These results suggest that conformational and or the electronic nature of the urethane is critical when tetrapeptide inhibitors of this type are terminated with a carbamate. Ultimately, an adequate solution was obtained by substituting an acylated amino acid derivative for the *t*-butyl urethane (compounds **31–40**, Table 2 and **42–51**, Table 3). A brief survey of amino acids revealed that Asn and Val were comparable in activity and significantly more potent in the tyrosine based analogs (e.g. **42** and **43**, Table 3). However, in the series containing benzyl substituents in P_1 and P_1' sites, the valine residue was generally superior (**36** and **37**, Table 2).

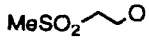
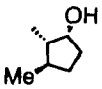
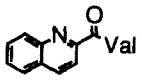
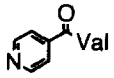
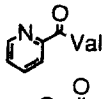
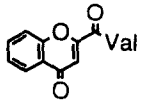
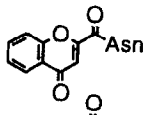
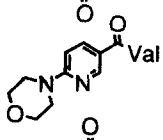
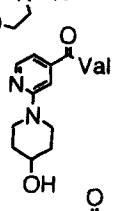
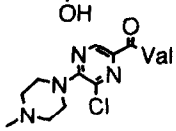
Table 4 highlights urea analogs that were prepared, and these results indicate the tolerance the P_3 binding pocket has for a variety of functional groups. The hydrophobic valine was the preferred residue for the P_2 pocket in this series as is illustrated by **60** and **61**. We were not, however, able to achieve the level of potency seen for the amides found in Table 2.



Scheme II.

Table 2.



Compound	AA	R	$IC_{50}(CIC_{95})$	Formula	HPLC	Log P
26			5.6nM (400nM)	$C_{31}H_{42}N_2O_6$ 1.05 H_2O	98%	3.0
27		"	57nM[a]	$C_{33}H_{44}N_2O_6S$ 0.45 $CHCl_3$[b]	98%	2.6
28		"	45nM	$C_{30}H_{42}N_2O_7$ 1.35 H_2O	99%	2.5
29		"	29nM	$C_{29}H_{40}N_2O_6$	99%	2.6
30			3nM (100nM)	$C_{32}H_{47}N_2O_6$ 0.8 H_2O	99%	3.4
31	CBZ-VAL	"	0.69nM (100nM)	$C_{40}H_{51}N_3O_6$ 0.6 H_2O	97%	-
32		"	0.72nM (100nM)	$C_{42}H_{50}N_4O_5$ 0.45 H_2O	96%	5.7
33		"	0.80nM (100nM)	$C_{38}H_{48}N_4O_5$ 0.75 H_2O	99%	3.6
34		"	2nM	$C_{38}H_{48}N_4O_5$ 0.75 H_2O	96%	3.6
35		"	4.6nM	$C_{38}H_{48}N_4O_5$ 0.60 H_2O	94%	4.3
36		"	0.10nM(10nM)	$C_{42}H_{49}N_{34}O_7$	100%	4.6
37		"	0.15nM (200nM)	$C_{41}H_{46}N_4O_8$ 0.50 H_2O	96%	-
38		"	0.86nM (25nM)	$C_{42}H_{55}N_5O_6$	99%	3.9
39		"	0.25nM (25nM)	$C_{43}H_{57}N_5O_6$	98%	-
40		"	0.07nM (<25nM)	$C_{42}H_{56}N_7O_5Cl$	100%	-

[a]mixture of diastereomers.
[b]C: calcd., 63.46; fournd, 58.93; H: calcd., 7.22; fournd, 6.73; N: calcd., 4.77; found, 4.22.

Viral spread activity

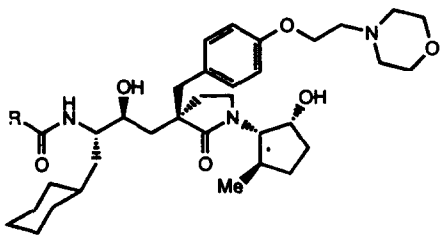
Selected lactam based inhibitors were tested for their ability to inhibit the spread of HIV-1 in H9 human T-lymphoid cells.[6a] Activities are expressed as cell IC_{95} (CIC_{95}) values, the concentration required to achieve 95 % inhibition of the spread of virus in the cell culture. Unfortunately, all compounds prepared that terminated

with the Boc group lacked sufficient antiviral activity in cells. In general, more potent inhibitors *in vitro* had a greater antiviral effect, with CIC_{95} values 50–100 times greater than IC_{50}, although a quantitative correlation between IC_{50} and CIC_{95} cannot be made. There were however several interesting results that warrant further comment. Despite their similar IC_{50} values, amides **36** and **37** (Table 2) differ significantly in their antiviral activity demonstrating the preference for valine over asparagine in this series. Ureas **60** and **61** (Table 4) further illustrate this point, and these results reveal how a small difference in enzyme inhibition (5 nM vs 16 nM) can produce significant differences in antiviral activity (200 nM vs > 3000 nM). The preference for valine in the lactam based inhibitors is in contrast to reported data from the hydroxyethylamine series of protease inhibitors, which shows a preference for asparagine in the P_2 pocket.[6f,g] Incorporation of hydrophobic aromatic heterocycles such as the chromanone **36**, substituted pyridines **38**, **39** and substituted pyrazine **40** analogs, results in potent antiviral agents with the chromanone carboxamide **36** being one of the more potent inhibitors produced from these laboratories.

In vivo *activity*

Depending on the residue that occupied the P_3 site, the overall physical properties and potency of the inhibitors could be modified. We then evaluated some of our more potent inhibitors *in vivo*. These compounds are listed in Table 5 and the compounds exhibit varying degrees of solubility, as well as a range of log P and protein binding values. *In vivo* properties of selected inhibitors were investigated in fasted dogs. Compound **36** despite its very low aqueous solubility (< 0.08 μg/mL, pH 7.4), achieves a C_{max} of 400 nM after 120 min when administered orally as

Table 3.



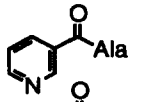
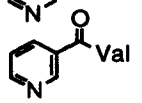
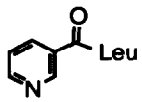
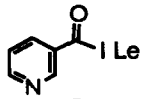
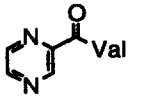
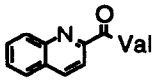
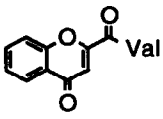
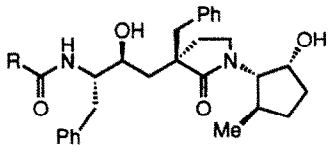
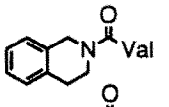
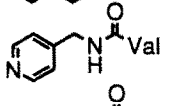
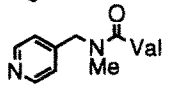
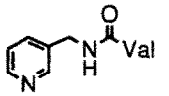
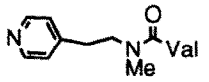
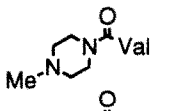
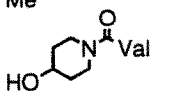
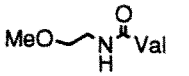
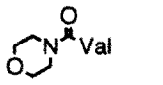
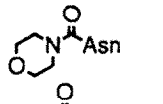
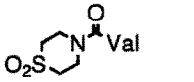
Compound	R	$IC_{50}(CIC_{95})$	Formula	HPLC	Log P
41		8.2nM (200nM)	$C_{38}H_{59}N_3O_8 \cdot 0.5\ H_2O$	99%	4.7
42	CBZ-Val	2nM	$C_{46}H_{68}N_4O_8$	98%	6.1
43	CBZ-Asn	2.2nM	$C_{45}H_{65}N_5O_9 \cdot 0.55\ H_2O$	97%	5.1
44	CBZ-Gln	75nM	$C_{46}H_{67}N_5O_9 \cdot 1.40\ H_2O$	97%	5.1
45		850nM	$C_{42}H_{61}N_5O_7 \cdot 0.75\ H_2O$	100%	4.1
46		2.9nM (75nM)	$C_{44}H_{63}N_5O_7 \cdot 0.65\ H_2O$	98%	4.1
47		186nM	$C_{45}H_{67}N_5O_7 \cdot 1.2\ H_2O$	96%	4.9
48		9.6nM	$C_{45}H_{67}N_5O_7$	98%	4.9
49		12nM (400nM)	$C_{43}H_{64}N_6O_7 \cdot 0.80\ H_2O$	95%	5.0
50		0.98nM	$C_{48}H_{67}N_5O_7 \cdot 0.75\ H_2O$	96%	6.6
51		0.19nM	$C_{48}H_{66}N_4O_9 \cdot 1.65\ H_2O$	98%	5.5

Table 4.

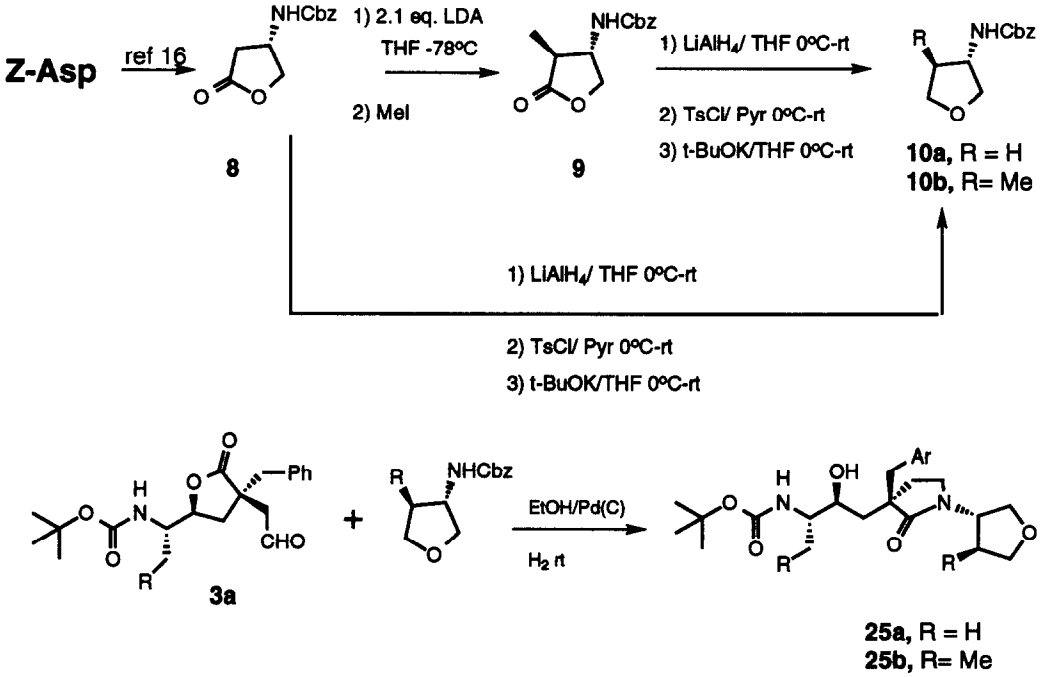


Compound	R	$IC_{50}(CIC_{95})$	Formula	HPLC	Log P
52		10nM (800nM)	$C_{42}H_{54}N_4O_5$ 0.5 H_2O	96%	5.3
53		1.7nM (200nM)	$C_{39}H_{51}N_5O_5$ 0.45 MeOH[a]	98%	-
54		1.79nM (100nM)	$C_{40}H_{53}N_5O_5$ 0.40 H_2O	98%	-
55		0.78nM	$C_{39}H_{51}N_5O_5$ 0.90 H_2O	98%	-
56		9.1nM (200nM)	$C_{41}H_{55}N_5O_5$	97%	-
57		19.5	$C_{38}H_{51}N_3O_5$ 0.60 H_2O	-	-
58		20nM	$C_{38}H_{54}N_4O_6$ 0.9 H_2O	95%	-
59		4.4nM (200nM)	$C_{36}H_{54}N_4O_6$ 0.20 CH_2Cl_2[b]	98%	-
60		5nM (200nM)	$C_{37}H_{52}N_4O_6$	99%	3.5
61		16nM (>3μM)	$C_{36}H_{49}N_5O_7 \cdot 1.05\ H_2O$	100%	-
62		4.2nM (400nM)	$C_{37}H_{52}N_4O_7S$	97%	-

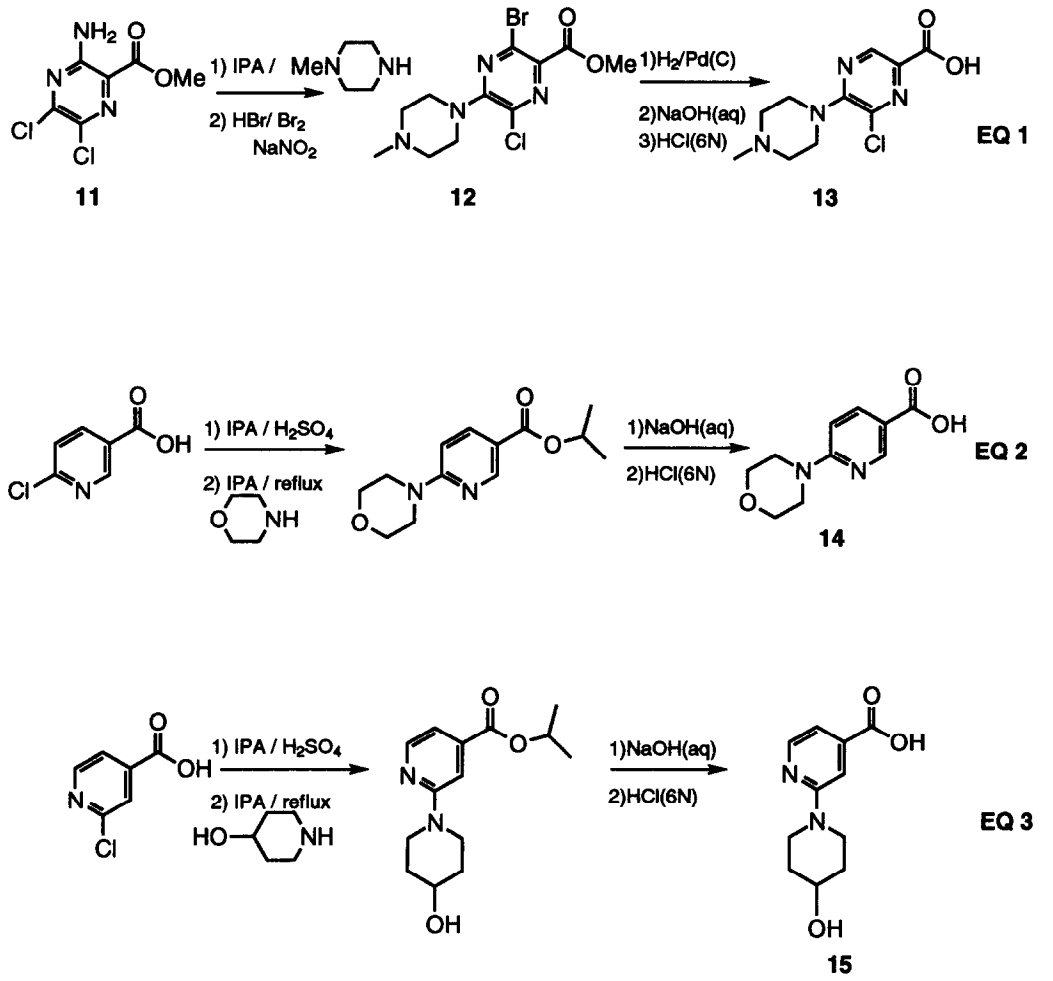
[a]N; C: calcd., 69.93; found, 69.22; H: calcd., 6.67; found, 7.58 HRMS: calcd 670.3908; found 670.3973 (M + 1).
[b]H, N; C: calcd., 67.79; found, 66.45 HRMS calcd 637.3965; found 637.3963 (M + 1)

a methocel suspension (10 mg/kg) (Figure 5). Importantly, even after 8 h, plasma levels of drug are 10 times CIC_{95} (CIC_{95} = 10nM). The bioavailability of this compound was about 15 %.[24] Compounds **40** and **46** which showed somewhat better aqueous solubility than **36**, achieved higher C_{max} levels but this did not increase the total area under the curve (AUC, Table 5). Presumably this is due to rapid biliary extraction of the compounds from plasma. Compound **60** is one of the more soluble inhibitors at pH 7.4 (Table 5) and was administered orally as crystalline material in a methocel suspension (10 mg/kg). Peak plasma levels in blood of greater than 2.5 μM were obtained. Unfortunately, this compound is cleared quite rapidly, and plasma levels are well below the CIC_{95} (200nM) after just 4 h (Figure 5). Despite this shortcoming, this inhibitor showed quite respectable bioavailability, calculated to be about 20 %.[23] Although we have only a limited data set at this time it is clear that increased aqueous solubility leads to greater amounts of compound being absorbed. What is not well understood at this time is precisely how the compounds are eliminated.[25]

In conclusion, we have described a series of potent HIV-1 protease inhibitors incorporating a γ-lactam. The homochiral 2(*S*)-amino-1(*R*)-hydroxy-3(*R*)-methylcyclopentane (see **20**, Table 1) prepared in large quantities from (*R*)-pulegone can be added to the list of amino acid amide surrogates binding well in the P_2' pocket and in certain instances is clearly superior to the amino indanol.[8] Selected compounds in this series are orally bioavailable (15–20 %) in a dog model. Interestingly, constraining the C-terminus in the form of a γ-lactam has been used successfully in the design of potent renin inhibitors, but this structural template in and of itself is not the sole source of the improved absorption for these compounds.[26] In that case no significant improvement in bioavailability was observed when the compounds were administered orally.



Scheme III.



Scheme IV.

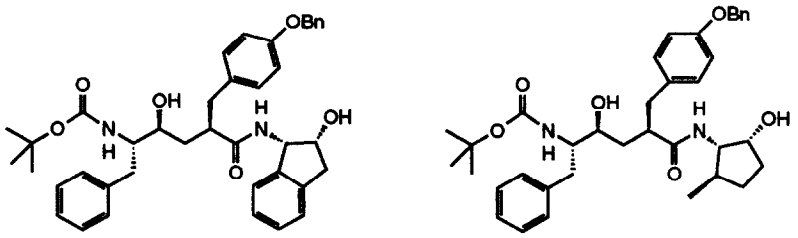
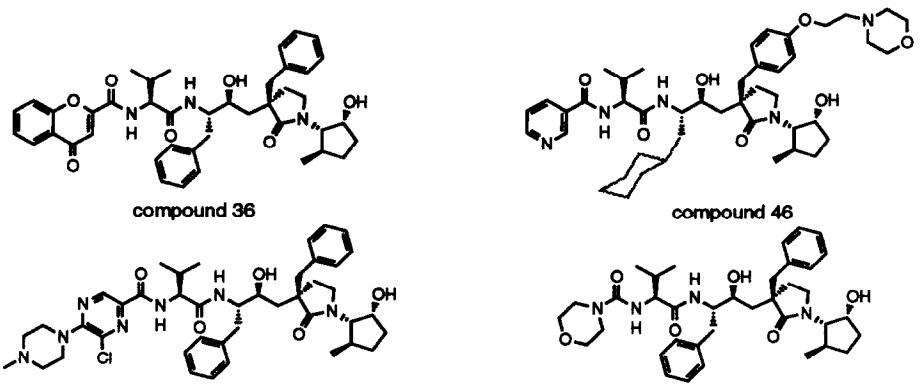


Figure 4.

Table 5.



Compound	IC_{50}	CIC_{95}	%bound[a]	Solubility (pH7.4)[b]	C_{max} (nM)[c]	T_{max} (min)	$t_{1/2}$ (min)[d]	AUC (mM/hr)[e]
36	0.07nM	10nM	95%	<0.08mg/mL	400	120	215	2.08
46	2.9nM	100nM	92%	0.2mg/mL	656	15	nt	0.54
40	0.07nM	<25nM	90%	0.03mg/mL	760	35	nt	1.10
60	5nM	200nM	80%	0.25mg/mL[f]	2670	15	130	3.25

[a]% bound in human plasma.
[b]Solubility of amorphous material except where noted.
[c]Cmax values represent maximum concentration observed after oral administration at 10 mg/kg (n = 2) in a methocel suspension (n = 2).
[d]t1/2 values represent terminal half-lives after oral administartion at 10 mg/kg (n =2, nt = not determined).
[e]AUC represents area under the curve after oral administration.
[f]Crystalline material.

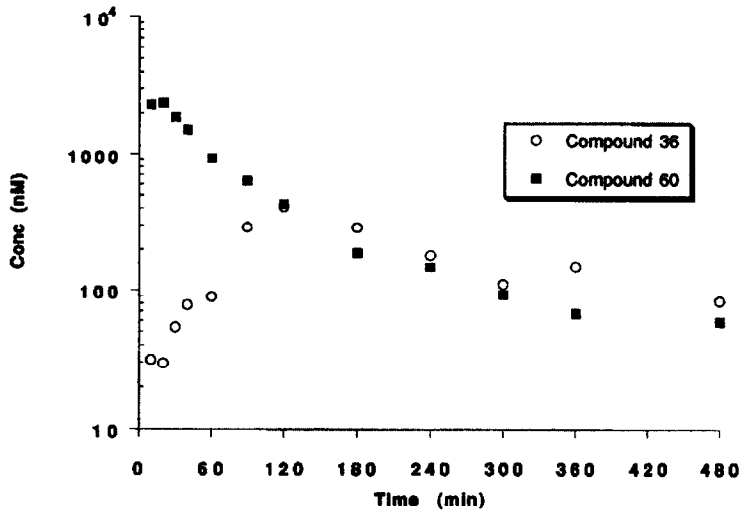


Figure 5. Compounds in dog 10 mpk 0.05 % methocel suspension

Experimental Section

All melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were obtained on either a Varian XL-300 (300 MHz) or a Varian VXR-400 (400 MHz) spectrometer using TMS as an internal standard. Flash chromatography was performed with E. Merck 240–400 mesh silica gel under low pressure (5–10 psi). Analytical HPLC data was obtained using a Specro-Physics instrument (SP8800 pump, SP8480 detector and SP4270 integrator) equipped with a Waters C_{18} reverse phase column (300 × 3.9 mm) at ambient temperature, a 95:5 to 5:95 A:B linear 30 min gradient, 3.00 mL/min flow rate (A = 0.1 % H_3PO_4 in H_2O, B = 0.1 % H_3PO_4 in CH_3CN), and detection at 215 nm. Thin layer chromatography was performed on E. Merck 60F-254 precoated silica gel plates (0.25 mm). Visualization was accomplished with UV light and/or phosphomolybdic acid stain. FAB mass spectra were obtained on a VG MM Zab-HF spectrometer at 8 keV. Analyses are within ± 4 % of theoretical value except where noted.

Allylation of lactone 1

(3R,5S,1'S)-3-Propen-3-yl-5- [1- (1,1-dimethylethoxycarbonylamino)-2-phenylethyl]-dihydrofuran-2-(3H)-one. In a flame dried 500 mL round bottom flask equipped with digital thermometer was added diisopropylamine (18.5 mL, 0.13 mol), and THF (135 mL). The flask was cooled to –78 °C and treated with *n*-BuLi (82.68 mL, 0.13 mol, 1.6 M in hexane). The temperature rose to –44 °C during the addition and was warmed further to10 °C and aged for 10 min. The LDA solution was cooled back to –78 °C and lactone **1** (19 g, 64.8 mmol) in THF was added dropwise via a double ended needle at a rate so that the internal temperature did not rise above –70 °C. The reaction was stirred for 1 h between –60 °C and –55 °C. The reaction was cooled back to –78 °C and allyl bromide (5.9 mL, 67.7 mmol) was added dropwise. The reaction was stirred at –78 °C for 30 min and –55 °C for 1 h at which point 10 % citric acid was added (100 mL) and Et_2O (200 mL). The layers were separated and the aqueous layer extracted further with Et_2O (2 × 200 mL). The organics were combined, washed with saturated NaCl and dried ($MgSO_4$). Flash chromatography 20 % EtOAc:hexane gave 17 g (80 %) of the desired material. ^{1}H NMR ($CDCl_3$) δ 7.24 (m, 5H), 5.71 (m, 1H), 5.07 (m, 2H), 4.60 (m, 2H), 3.99 (m, 1H), 2.88 (m, 2H), 2.74 (m, 1H), 2.50 (m, 1H), 2.25 (m, 2H), 1.98 (m, 1H), 1.38 (s, 9H).

(3R,5S,1'S)-3-Propen-3-yl-3-phenylmethyl-5- [1- (1,1-dimethylethoxycarbonylamino)-2-phenylethyl]-dihydrofuran-2-(3H)-one (2a). LDA was generated as described above and reaction performed similarly using benzyl bromide (1.25 eq.) as the electrophile. From 11.5 g of allylated lactone, 11.06 g (76 %) of the dialkylated lactone **2a** was obtained after flash chromatography (20 % EtOAc: hexane). ^{1}H NMR($CDCl_3$) δ 7.24 (m, 8H), 6.99 (m, 2H), 5.75 (m, 1H), 5.15 (m, 2H), 4.50 (d, *J* = 10 Hz, 1H), 3.72 (m, 1H), 3.18 (t, *J* = 8 Hz, 1H), 3.01 (d, *J* = 13 Hz, 1H), 2.35 (m, 1H), 2.05 (dd, *J* = 13.5 Hz, 8 Hz, 2H), 1.5–1.8 (m, 4H), 1.35 (s, 9H).

(3R,5S,1'S)-3-Ethanal-3-phenylmethyl-5-[1-(1,1-dimethylethoxycarbonylamino) -2-phenylethyl] -dihydrofuran -2-(3H)-one (3a). Lactone **2a** (2.9 g, 6.85 mmol) was dissolved MeOH/CH_2Cl_2 (4:1, 100 mL). The solution was cooled to –78 °C and ozone was bubbled into the solution until a deep blue color persisted (10 min). After purging the flask of excess ozone with argon, excess dimethyl sulfide (4 mL) was added. The reaction was allowed to warm to room temperature and stirred for 48 h. The solvents were evaporated, and the residue was chromatographed twice in 10 % acetone:$CHCl_3$ to give 1.95 g (65 % yield) of desired aldehyde **3a**. ^{1}H NMR($CDCl_3$) δ 9.7 (s, 1H), 7.2 (m, 10H), 5.05 (d, *J* = 9 Hz, 1H), 3.7 (m, 1H), 3.37 (m, 2H), 2.75 (m, 5H), 2.10 (d, *J* = 8 Hz, 2H), 1.38 (s, 9H).

Representative reductive amination using $NaCNBH_3$ (Procedure A)

N'-[2(S) -3-Methyl-l-butanol] -3(S) -[3(S) -(1,1-dimethylethoxycarbonylamino) -2(S) -hydroxy-4-phenylbutyl]-3(S)-phenylmethylpyrrolidin-2-one (18). (3*R*,5*S*,1'*S*)-3-Ethanal-3-phenylmethyl-5-[1-(1,1'-dimethylethoxycarbonylamino)-2-phenylethyl]-dihydrofuran-2-(3*H*)-one (**3a**) (0.97 g, 2.21 mmol) was dissolved in MeOH (10 mL). Activated 3 Å molecular sieves (powder), and *S*(+)-2-amino-3-methyl-l-butanol (0.30 g, 2.87 mmol) were added and the reaction stirred for 30 min at room temperature. $NaCNBH_3$ (0.19 g, 2.87 mmol) was then added to the flask, followed by several drops of glacial acetic acid. The reaction was allowed to proceed overnight under argon. Excess $NaCNBH_3$ was quenched by the addition of 10 % citric acid, and the resulting slurry was stirred for 2 h. The MeOH was evaporated, the residue that remained was taken up in EtOAc, washed with 10 % citric acid (30 mL) and brine (40 mL). The aqueous layer was extracted with EtOAc (6 × 10 mL). Organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography in 5 % MeOH/$CHCl_3$ to give 1.14 g (98 % yield); mp 165–167 °C; ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 8H), 7.00 (m, 2H), 6.04 (s, 1H), 5.2 (d, *J* = 10 Hz, 1H), 3.60 (m, 3H), 2.9 (m, 9H), 1.40 (s, 9H), 0.96 (d, *J* = 6 Hz, 3H), 0.83 (d, *J* = 6 Hz, 3H). Anal. $C_{31}H_{44}N_2O_5$ (524.7067) C, H, N; calcd, C: 70.96, H: 8.45, N: 5.34; found, C: 70.81, H: 8.40, N: 5.24.

Additional entries from Table 1 prepared by this method:

N'-[2(S) -2-Methyl-l-propanol] -3(S)-[3(S) -(1,1-dimethylethoxycarbonylamino) -2(S) -hydroxy-4-phenylbutyl]-3(S)-phenylmethylpyrrolidin-2-one (17). (42 %); ^{1}H NMR($CDCl_3$) δ 7.3 (m, 8H), 7.00 (m, 2H), 6.04 (s, 1H), 5.2 (d, *J* = 10 Hz, 1H), 4.07 (d, *J* = 10.5 Hz, 1H), 3.94 (m, 1H), 3.50 (m, 3H), 1.40 (s, 9H), 1.08 (d, *J* = 6 Hz, 3H). Anal. $C_{29}H_{40}N_2O_5$ (496.65) C, H, N; calcd, C: 70.13, H: 8.12, N: 5.64; found, C: 70.14, H: 8.33, N: 5.45.

N'- [2(S)- 3(R)- Methyl-l-pentanol]-3(S) -[3(S) -(1,1- dimethylethoxycarbonylamino)-2(S)-hydroxy-4-phenylbutyl]-3(S)-phenylmethylpyrrolidin-2-one (19). (55 %); mp 163–164 °C; ^{1}H NMR($CDCl_3$) δ 7.3 (m, 8H), 6.94 (m, 2H), 5.86 (s, 1H), 5.13 (d, *J* = 9.7 Hz, 1H), 4.12 (d, *J* = 12 Hz,

1H), 3.67 (m, 4H), 3.15 (m, 1H), 3.06 (d, J = 14 Hz, 1H), 2.95 (d, J = 7.8 Hz, 1H), 2.85 (m, 1H), 2.63 (d, J = 13 Hz, 1H), 2.12 (m, 1H), 1.75 (m, 3H), 1.42 (s, 9H), 0.93 (m, 6H). Anal. $C_{32}H_{46}N_2O_5 \cdot 0.5H_2O$ (547.74) C, H, N; calcd, C: 71.61, H: 8.26, N: 5.22; found, C: 71.92, H: 8.28, N: 5.20.

N'- *[3(RS)- Cyclopentan-1(RS)- ol]-3(S)- [3(S)- (1,1-dimethylethoxycarbonylamino)-2(S)-hydroxy-4-phenylbutyl]-3(S)-phenylmethylpyrrolidin-2-one (22).* (69 %); mp 53–55 °C; ^{1}H NMR($CDCl_3$) δ 7.3 (m, 8H), 6.94 (m, 2H), 6.33 (d, J = 7 Hz, 1H), 5.17 (d, J = 9.6 Hz, 1H), 4.22 (m, 2H), 4.03 (d, J = 10.6 Hz, 1H), 3.07 (m, 1H), 3.1 (m, 3H), 2.93 (d, J = 7.5 Hz, 1H), 2.47 (d, J = 13 Hz, 1H), 2.3 (m, 1H), 1.4–2.1 (m, 10H), 1.40 (s, 9H). Anal. $C_{31}H_{42}N_2O_5$ (522.68) C, H, N; calcd, C: 71.24, H: 8.10, N: 5.36; found, C: 71.04, H: 8.25, N: 5.18.

N'- *[(S)- Carbomethoxyvalinyl]-3(S)- [3(S)- (1,1-dimethylethoxycarbonylamino) -2(S)-hydroxy-4-phenylbutyl] -3(S)-phenylmethylpyrrolidin-2-one (23).* mp 140–141 °C; ^{1}H NMR($CDCl_3$) δ 7.34 (m, 3H), 7.10–7.25 (m, 5H), 6.83 (m, 2H), 5.10 (d, J = 12 Hz, 1H), 4.40 (d, J = 9.5 Hz, 1H), 4.10 (d, J = 11.4 Hz, 1H), 3.65 (s, 3H), 3.64 (m, 1H), 3.16 (m, 1H), 2.9 (m, 3H), 2.70 (m, 1H), 2.6 (d, J = 12 Hz, 1H), 1.70 (m, 2H), 1.4 (s, 9H), 0.94 (d, J = 6.6 Hz, 3H), 0.87 (d = 6.6 Hz, 3H). Anal. $C_{32}H_{43}N_2O_6$ (551.71) C, H, N; calcd, C: 69.67, H: 7.86, N: 5.08; found, C: 69.81 H: 7.60, N: 5.22.

N'- *[(5S,1'S)- 2- Methyl-ethyl-dihydrofuran -2- (3H)- one]-3(S)- [3(S)-(1,1-dimethylethoxycarbonylamino)-2(S)-hydroxy -4- phenylbutyl] -3(S)- phenylmethylpyrrolidin -2- one (24).* (17 %); ^{1}H NMR ($CDCl_3$) δ 6.8–7.4 (m, 10H), 4.9–5.2 (envelope, 3H), 4.72 (m, 1H), 3.5–3.8 (m, 4H), 3.3 (m, 2H), 3.08 (d, J = 12 Hz, 1H), 2.8 (m, 3H), 2.5–2.8 (m, 3H), 1.4–2.2 (envelope, 8H), 1.4 (s, 9H), 1.04 (d, J = 6 Hz, 3H), 0.88 (d, J = 6 Hz, 3H). Anal. $C_{24}H_{46}N_2O_6 \cdot 0.45H_2O$ (586.86) C, H, N; calcd, C: 69.58, H: 8.06, N: 4.77; found, C: 69.57, H: 8.06, N: 4.68.

Procedure B: hindered amines

N'- *[2(S)- Cyclopentyl-1(R)- hydroxy-3(R)- methyl]-3(S)-[3(S)-(1,1-dimethylethoxycarbonylamino)-2(S)-hydroxy-4-phenylbutyl]-3(S)-phenylmethylpyrrolidin-2-one (20).* Aldehyde (**3a**) (4.6 g, 10.6 mmol), 2(*S*)-amino-1(*R*)-hydroxy-3(*R*)-methylcyclopentane hydrochloride[17] (2 g, 13.8 mmol), and activated 3 Å molecular sieves (powder), were placed in a flame-dried round-bottom flask equipped with a stir bar. MeOH (60 mL) was added and the mixture stirred for 0.4 h. $NaCNBH_3$ (0.87 g, 13.8 mmol) was added to the mixture followed by glacial acetic acid (1 mL). The reaction was allowed to proceed overnight under an argon atmosphere. After 14 h, the solution was filtered through a celite pad and the filtrate adjusted to pH 2.5–3 with 10 % citric acid. The MeOH was removed and the residue diluted with equal volumes of CH_2Cl_2:$CHCl_3$ (150 mL total). The aqueous solution was made basic (pH 9.5) with 1 N NaOH and the layers separated. The aqueous layer was further extracted 1:1 $CHCl_3$:CH_2Cl_2 (5 × 80 mL). The organic layers were combined, washed with saturated NaCl, dried over $MgSO_4$, and concentrated to a foam (6 g). This was combined with another batch (5 g) prepared under identical conditions. The residue was dissolved in toluene (300 mL), HOBT (0.9 g) was added and the mixture was heated to 70 °C and stirred overnight. After concentrating, the oil was purified by flash chromatography using 70 % EtOAc:hexane to give 9.69 g of desired product (85 % yield based on 9.2 g of starting aldehyde); mp 146–148 °C; ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 10H), 5.12 (d, J = 9 Hz, 1H), 4.10 (m, 2H), 3.60 (m, 1H), 3.47 (dd, J = 11 Hz, 4.5 Hz, 1H), 3.17 (m, 2H), 2.95 (d, J = 7 Hz, 1H), 2.66 (m, 1H), 2.54 (d, J = 7 Hz, 1H), 1.8–2.2 (m, 6H), 1.40 (s, 9H), 0.91 (d, J = 6 Hz, 3H). Anal. $C_{32}H_{44}N_2O_5$ (536.71) C, H, N; calcd, C: 71.61, H: 8.26, N: 5.22; found, C: 71.91, H: 8.28, N: 5.20.

N'- *[2(S)- Cyclopentyl- 1(S)-hydroxy- 3(R)-methyl] -3(S)-[3(S)-(1,1-dimethylethoxycarbonylamino)-2(S)-hydroxy-4-phenylbutyl]-3(S)-phenylmethylpyrrolidin-2-one (21).* (72 %); mp 132–134; ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 8H), 7.04 (m, 2H), 5.13 (d, J = 9.6 Hz, 1H), 4.06 (d, J = 10.7 Hz, 1H), 3.8 (m, 1H), 3.78 (m, 2H), 3.17 (m, 2H), 3.05 (m, 2H), 2.93 (d, J = 8 Hz, 1H), 2.54 (d, J = 7 Hz, 1H), 2.40 (dd, J = 9.3 Hz, 8.1 Hz, 1H), 2.28 (m, 1H), 1.45–1.95 (m, 9H), 1.40 (s, 9H), 0.96 (d, J = 6 Hz, 3H). Anal. $C_{32}H_{44}N_2O_5$ (536.712) C, H, N; calcd, C: 71.61, H: 8.26, N: 5.22; found, C: 71.61, H: 8.16, N: 5.22.

3(R)- Methyl -4(S)- (benzyloxycarbonylamino)- dihydrofuran-2-(3H)-one. ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5H), 5.10 (s, 2H), 5.06 (brd, 1H), 4.51 (m, 1H), 4.15 (m, 1H), 3.95 (m, 1H), 2.5 (m, 1H), 1.33 (d, J = 7.2 Hz, 3H).

The lactone (1.25 g, 5.02 mmol) from above was dissolved in dry THF (15 mL), cooled to 0 °C and treated with solid $LiAlH_4$ (0.38 g, 10 mmol). The reaction was stirred at 0 °C for 1 h and room temperature for 30 min. It was then cooled back to 0 °C and carefully quenched with H_2O (0.4 mL), 1 N NaOH (0.4 mL), and finally H_2O (1.2 mL). The ice bath was removed and the heterogeneous reaction filtered with the aid of a celite pad. The filter cake was washed liberally with THF (2 × 50 mL) and the filtrate concentrated. The residue was taken up into EtOAc (150 mL) and washed with H_2O, NaCl and dried over Na_2SO_4. Flash chromatography (EtOAc) gave 925 mg of the desired product (73 %). ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 5H), 5.4 (brs, 1H), 5.09 (s, 2H), 3.84 (brs, 1H), 3.5–3.76 (m, 5H), 3.38 (m, 1H), 3.23 (brs, 2H), 1.95 (m, 1H), 0.84 (d, J = 7.1 Hz, 3H).

3(S)- (Benzyloxycarbonylamino)- 4 (R)- methyltetrahydrofuran. The diol from above (913 mg, 3.61 mmol) was dissolved in pyridine (5 mL), cooled to 0 °C and treated with *p*-toluenesulfonyl chloride (791 mg, 4.15 mmol). The reaction was stirred overnight with gradual warming to room temperature. After 14 h the pyridine was removed via rotoevaporator and the residue taken up in EtOAc (100 mL), washed with $NaHCO_3$, NaCl and dried with Na_2SO_4. After concentrating, the crude material was treated with K_2CO_3 (solid) in MeOH for 48 h. Workup and flash chromatography (hexane:EtOAc, 2:1). ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5H), 5.10 (s, 2H), 4.06 (m, 2H), 3.96 (m, 1H),

3.56 (m, 1H), 3.37 (dd, J = 6 Hz, 4 Hz, 1H), 2.1 (m, 1H), 1.10 (d, J = 7 Hz, 3H).

3(S)-(Benzyloxycarbonylamino)-tetrahydrofuran. mp 49–51 °C. ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 5H), 5.16 (s, 2H), 5.09 (s, 2H), 4.3 (brs, 1H), 3.8 (m, 3H), 3.14 (m, 1H), 2.4 (m, 1H), 1.8 (m, 1H).

Procedure C

The CBZ-protected tetrahydrofurans (**10a** and **10b**) were treated with 10 % Pd/C under an atmosphere of H_2 in MeOH and stirred for 48 h in the presence of aldehyde **3a**. Filtering off the catalyst and purification by flash chromatography produced the desired lactams.

N'- *[3(S)- Tetrahydrofuranyl]-[3(S)- (1,1-dimethylethoxy-carbonylamino)-2(S)-hydroxy-4-phenylbutyl]-3(S)-phenyl-methylpyrrolidin-2-one (25a).* (52 %); mp 125–126 °C; ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 8H), 7.02 (m, 2H), 5.13 (d, J = 10 Hz, 1H), 4.75 (m, 1H), 4.04 (d, J = 10 Hz, 1H), 3.85 (m, 1H), 3.68 (m, 3H), 3.50 (dd, J = 6 Hz, 3 Hz, 1H), 3 (m, 2H), 2.95 (m, 2H), 2.4 (d, J = 13 Hz, 1H), 2.2 (m, 2H), 1.9 (m, 1H), 1.7 (m, 1H), 1.40 (s, 9H). Anal. $C_{30}H_{40}N_2O_5$•0.15H_2O (511.36) C, H, N; calcd, C: 70.46, H: 7.94, N: 5.48; found, C: 70.40, H: 7.88, N: 5.61.

N'- *[3(S)- Tetrahydrofuranyl-4(R)- methyl]-[3(S)-(1,1-di-methylethoxycarbonylamino)-2(S)-hydroxy-4-phenylbutyl]-3(S)-phenylmethylpyrrolidin-2-one (25b).* (38 %); mp 141–143 °C; ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 8H), 7.02 (m, 2H), 5.12 (d, J = 10 Hz, 1H), 4.29 (m, 1H), 4.05 (d, J = 10 Hz, 1H), 3.98 (t, J = 8 Hz, 1H), 3.65 (m, 2H), 3.23 (t, J = 8.3 Hz, 1H), 3.1 (m, 2H), 2.92 (m, 3H), 2.47 (d, J = 7 Hz, 1H), 2.24 (m, 1H), 2.2 (m, 2H), 1.8 (m, 1H), 1.40 (s, 9H), 1.07 (d, J= 7 Hz, 3H). Anal. $C_{31}H_{42}N_2O_5$ (522.69) C, H, N; calcd, C: 71.24, H: 8.10, N: 5.36; found, C: 71.04, H: 8.02, N: 5.46.

Typical procedure for the formation of carbamates in Table 2 (compounds 26–30)

N'- *[2(S)-3- Methyl-l-butanol]- 3S)- [3(S)- (tetrahydro-furanyloxycarbonylamino) -2(S)- hydroxy-4-phenylbutyl]-3(S)-phenylmethylpyrrolidin-2-one (26).* Lactam (**18**) (88 mg, 0.16 mmol) was dissolved in CH_2Cl_2 and cooled to 0 °C. Trifluoroacetic acid was added and the reaction stirred for 45 min. The solvent was evaporated and the oily residue was redissolved in $CHCl_3$:toluene (1:20) and the solvents evaporated. The residue that remained was taken up into absolute EtOH (1 mL) and azeotroped with toluene and finally dried under vacuum. The TFA salt was dissolved in CH_2Cl_2 (3 mL) with 3(*S*)-tetrahydrofuranyl succinimidyl carbonate[19] (40.4 mg, 0.18 mmol) and cooled to 0 °C. Triethylamine (27 μL, 0.19 mmol) was added via syringe and the reaction stirred with warming to room temperature overnight. The volatile material was removed and the residue purified by flash chromatography (12 % acetone:$CHCl_3$) to 44 mg (51 %) of a white solid; mp 136–137 °C; ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 8H), 6.95 (m, 2H), 5.30 (d, J = 9.4 Hz, 1H), 5.16 (m, 1H), 4.14 (d, J = 11 Hz, 1H), 3.55–3.9 (m, 7H), 3.16 (m, 1H), 2.95 (m, 1H), 2.82 (AB, J = 13 Hz, 2H), 2.80 (m, 2H), 1.6–2.2 (m, 7H), 0.97 (d, J = 6 Hz, 3H), 0.84 (d, J = 6 Hz, 3H). Anal. $C_{31}H_{42}N_2O_6$•1.05H_2O (569.61) C, H, N; calcd, C: 66.74, H: 7.97, N: 5.02; found, C: 66.74, H: 7.72, N: 5.20.

N'-*[2(S)-3-Methyl-l-butanol] -3(S) -[3(S) -(tetrahydrothio-phenoxycarbonylaminodioxide)-2(S) -hydroxy-4-phenyl-butyl]-3(S)-phenylmethylpyrrolidin-2-one (27).* (88 %); mp 47–50 °C; ^{1}H NMR ($CDCl_3$) mixture of diastereomers δ 7.33 (m, 8H), 6.9 (m, 2H), 5.4 (m, 1H), 5.16 (m, 1H), 5.32 (m, 1H), 4.17 (d, J = 10 Hz, 1H), 3.6 (m, 3H), 2.8–3.3 (m, 9H), 2.63 (dd, J = 13 Hz, 5 Hz, 2H), 2.40 (m, 1H), 1.6–1.9 (m, 5H), 1.26 (t, J = 13 Hz, 1H), 0.96 (d, J = 6 Hz, 3H), 0.83 (apparent t, 3H). Anal. $C_{31}H_{42}N_2O_7S$•0.45$CHCl_3$ (640.48) C, H, N; calcd, C: 58.97, H: 6.68, N: 4.37; found, C: 58.93, H: 6.73, N: 4.22.

N'-*[2(S)-3-Methyl-l-butanol]-3(S)-[3(S)-(2-methylsulfonyl-ethoxycarbonylamino) -2(S)- hydroxy-4-phenylbutyl]-3(S)-phenylmethylpyrrolidin-2-one (28).* (88 %); ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 8H), 6.9 (m, 2H), 5.4 (m, 1H), 5.16 (m, 1H), 5.32 (m, 1H), 4.17 (d, J = 10 Hz, 1H), 3.6 (m, 3H), 2.8–3.3 (m, 9H), 2.63 (dd, J = 13 Hz, 5 Hz, 2H), 2.40 (m, 1H), 1.6–1.9 (m, 5H), 1.26 (t, J = 13 Hz, 1H), 0.96 (d, J = 6 Hz, 3H), 0.83 (apparent t, 3H). Anal. $C_{30}H_{42}N_2O_7S$•1.35H_2O (599.04) C, H, N; calcd, C: 60.14, H: 7.52, N: 4.68; found, C: 60.17, H: 7.24, N: 4.48.

N'- *[2(S)-3-Methyl-l-butanol]-3(S)- [3(S)- (hydroxyethoxy-carbonylamino)-2(S)-hydroxy-4-phenylbutyl]-3(S)-phenyl-methylpyrrolidin-2-one (29).* (73 %); mp 137.5–138.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 8H), 6.95 (m, 2H), 5.47 (d, J = 9.2 Hz, 1H), 4.2 (m, 3H), 3.78 (t, J = 4.8 Hz, 2H), 3.69 (d, J = 5.4 Hz, 2H), 3.62 (m, 1H), 3.54 (m, 1H), 3.2 (m, 1H), 2.95 (m, 2H), 2.86 (m, 1H), 2.85 (AB, J = 10.3 Hz, 2H), 2.15 (m, 1H), 1.7–1.95 (m, 3H), 1.48 (d, J = 15.6 Hz, 1H), 0.98 (d, J = 6 Hz, 3H), 0.85 (d, J = 6 Hz, 3H). Anal. $C_{29}H_{40}N_2O_6$ (512.65) C, H, N; calcd, C: 67.95, H: 7.86, N: 5.46; found, C: 68.02, H: 7.72, N: 5.60.

N'- *[2(S)- Cyclopentyl-1(R)- hydroxy-3(R)- methyl]-3(S)-[3(S)-(tetrahydrofuranyloxycarbonylamino)-2(S)-hydroxy-4-phenylbutyl]-3(S)-phenylmethylpyrrolidin-2-one (30).* (76 %); mp 126–127.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 10H), 5.33 (d, J = 9 Hz, 1H), 5.18 (m, 1H), 4.13 (m, 2H), 3.8 (m, 4H), 3.49 (dd, J = 11.4 Hz, 4.6 Hz, 2H), 3.18 (m, 2H), 2.97 (m, 2H), 2.7 (m, 1H), 2.57 (d, J = 13 Hz, 1H), 1.8–2.2 (m, 10H), 1.5 (m, 2H), 1.14 (m, 1H), 0.92 (d, J = 6.6 Hz, 3H). Anal. $C_{32}H_{47}N_2O_6$•0.8H_2O (569.41) C, H, N; calcd, C: 69.79, H: 7.69, N: 5.09; found, C: 70.08, H: 7.59, N: 4.91.

Representative procedure for amides found in Table 2 (compounds 31–40)

N'- *[2(S)- Cyclopentyl-1(R)- hydroxy-3(R)- methyl]-3(S)-[3(S)- [(1,1-dimethylethoxycarbonylamino)] -(L)- valinyl-2(S)-hydroxy-4-phenylbutyl]-3(S)-phenylmethylpyrrolidin-2-one.* Lactam (**20**) (9.69 g, 18.0 mmol) was dissolved in 80 mL CH_2Cl_2 and cooled to 0 °C. To this cold solution was added an ether solution saturated with HCl gas. The mixture was stirred for 2 h under argon until HPLC

showed no starting material. The solvents were evaporated, and the residue was dried under vacuum. A portion of the dried HCl salt (6.39 g, 13.5 mmol) was used. L-BOC-valine (3.82 g, 17.6 mmol), EDC (3.37 g, 17.6 mmol), and HOBT (2.38 g, 17.6 mmol) were added and dissolved in DMF (95 mL). The solution was cooled to 0 °C and triethylamine (3.96 mL, 28.4 mmol) was added via syringe and the reaction was stirred overnight with gradual warming to room temperature. After 16 h the DMF was concentrated under high vacuum. The resulting yellow oil was diluted with CH_2Cl_2:$CHCl_3$ (150 mL, 1:1), washed with 10 % citric acid (20 mL), H_2O (20 mL), saturated $NaHCO_3$ (20 mL), NaCl (20 mL), and dried over $MgSO_4$. Flash chromatography using 50 % EtOAc:hexane gave 7.08 g (83 % yield from HCl salt) of desired lactam; mp 159–160 °C; ^{1}H NMR ($CDCl_3$) δ 7.1–7.3 (m, 10H), 6.48 (d, J = 8.6 Hz, 1H), 4.93 (d, J = 7.6 Hz, 1H), 4.1 (m, 3H), 3.92 (m, 1H), 3.45 (m, 2H), 3.15 (m, 1H), 2.95 (m, 2H), 2.67 (m, 2H), 2.53 (d, J = 13 Hz, 2H), 1.7–2.2 (m, 10H), 1.45 (s, 9H), 1.1 (m, 1H), 0.92 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H). Anal. $C_{37}H_{53}N_3O_6$•0.25H_2O (640.85) C, H, N; calcd, C: 69.89, H: 8.4, N: 6.61; found, C: 69.39, H: 8.18, N: 6.60.

N'- *[2(S)- Cyclopentyl -1(R)- hydroxy-3(R)-methyl]-3(S)-[3 (S)- [(N- (4-oxo-4H-1-benzopyran-2-carbonyl)-L-valinyl)-amino]-2(S) -hydroxy-4-phenylbutyl]-3(S) -phenylmethyl-pyrrolidin-2-one (36).* Lactam from above (7.08 g, 11 mmol) was dissolved in CH_2Cl_2 (30 mL) and the t-butyl carbamate cleaved with HCl gas as described above. The HCl salt (2.0 g, 3.5 mmol), 4-oxo-4*H*-1-benzopyran-2-carboxylic acid (0.87 g, 4.55 mmol, Aldrich), EDC (0.87 g, 4.55 mmol), and HOBT (0.62 g, 4.55 mmol) were dissolved in 24 mL DMF and cooled to 0 °C. Triethylamine (1.02 mL, 7.35 mmol) was added and the reaction was allowed to gradually warm to room temperature and stirred overnight. Workup as described previously produced a brown oil that was purified by flash chromatography (70 % EtOAc:hexane), to give 1.09 g of an amorphous solid (56 %); mp 118–123 °C; ^{1}H NMR ($CDCl_3$) δ 8.24 (dd, J = 18 Hz, 1.7 Hz, 1H), 7.76 (dt, J = 8 Hz, 1.7 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.48 (dt, J = 7.6 Hz, 1 Hz, 1H), 7.38 (d, J = 9 Hz, 1H), 7.22 (m, 10H), 7.02 (t, J = 7 Hz, 1H), 6.58 (bs, 1H), 6.35 (d, J = 9.5 Hz, 1H), 4.37 (dd, J = 8.6 Hz, 6.7 Hz, 1H), 4.11 (m, 3H), 3.50 (dd, J = 13 Hz, 5 Hz, 1H), 3.24 (d, J = 13 Hz, 1H), 3.14 (dt, J = 10 Hz, 2.5 Hz, 1H), 2.96 (m, 2H), 2.67 (dd, J = 18.5 Hz, 8 Hz, 2H), 2.58 (d, J = 13 Hz, 1H), 1.68 (m, 12H), 0.99 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H), 0.87 (d, 3H, J = 6.6 Hz). High Resolution FAB-MS (M + 1) 708.366394; theoretical 708.364876; anal. $C_{42}H_{49}N_3O_7$ (707.885) C, H, N; calcd, C: 71.27, H: 6.98, N: 5.94; found, C: 71.04, H: 7.03, N: 6.04.

The hydrochloride salt from above was used to prepare the following examples shown in Table 2.

N'- *[2(S)- Cyclopentyl-1(R)- hydroxy-3(R)-methyl]-3(S)-[3 (S)-[(N-(isoquinolinyl-2-carbonyl)- L-valinyl)amino]-2(S)-hydroxy-4-phenylbutyl]-3(S)-phenylmethylpyrrolidin-2-one (32).* (82 %); mp 108–110 °C; ^{1}H NMR ($CDCl_3$) δ 8.78 (d, J = 6 Hz, 1H), 8.34 (m, 1H), 8.27 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.82 (dt, J = 6 Hz, 1.2 Hz, 1H), 7.61 (t, J = 7 Hz, 1H), 7.0 (m, 1H), 6.55 (d, J = 9 Hz, 1H), 4.44 (dd, J = 9 Hz, 5 Hz, 1H), 4.10 (m, 2H), 3.46 (dd, J = 12 Hz, 5.4 Hz, 1H), 3.20 (d, J = 13 Hz, 1H), 3.15 (m, 1H), 2.95 (m, 2H), 2.66 (dd, J = 15 Hz, 9 Hz, 1H), 2.56 (d, J = 13 Hz, 1H), 2.35 (m, 1H), 2.16 (m, 2H), 1.5–2.05 (m, 9H), 1.10 (m, 1H), 0.99 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H). Anal. $C_{42}H_{50}N_4O_5$•0.45H_2O (698.99) C, H, N; calcd, C: 72.16, H: 7.34, N: 8.02; found, C: 72.17, H: 7.13, N: 8.08.

N'-*[2(S)-Cyclopentyl-1(R)-hydroxy-3(R)- methyl]- 3(S)- [3 (S)- [(N- (pyridyl-3-carbonyl)-L-valinyl)amino]-2(S)-hydroxy -4- phenylbutyl]- 3(S)- phenylmethylpyrrolidin -2- one (33).* (60 %); mp 115–117 °C (dec); ^{1}H NMR ($CDCl_3$) major rotamer δ 9.56 (m, 1H), 8.9 (m, 2H), 8.0 (brs, 1H), 7.2 (m, 10H), 4.99 (m, 1H), 4.4 (m, 1H), 3.88 (dd, J = 12 Hz, 5 Hz, 1H), 3.1 (m, 1H), 2.96 (m, 2H), 2.60 (m, 2H), 1.6–2.2 (m, 10H), 1.04 (d, J = 6.8 Hz, 3H), 0.93 (m, 3H), 0.87 (d, J = 7.8 Hz, 3H). Anal. $C_{38}H_{48}N_4O_5$•0.75H_2O (654.34) C, H, N; calcd, C: 69.75, H: 7.63, N: 8.56; found, C: 69.75, H: 7.32, N: 8.60.

N'-*[2(S)-Cyclopentyl-1(R)-hydroxy-3(R)- methyl]- 3(S)- [3 (S)- [(N- (pyridyl-4-carbonyl)-L-valinyl)amino]-2(S)-hydroxy -4- phenylbutyl] -3(S)- phenylmethylpyrrolidin -2- one (34).* (58 %); mp 116–121 °C (dec); ^{1}H NMR ($CDCl_3$) major rotamer δ 8.87 (brs, 2H), 8.33 (brs, 2H), 7.25 (m, 10H), 4.4 (m, 1H), 4.12 (m, 3H), 3.45 (dd, J = 12 Hz, 5 Hz, 1H), 3.18 (m, 2H), 2.95 (m, 2H), 2.69 (m, 1H), 2.61 (d, J = 7 Hz, 1H), 1.5–2.3 (m, 10H), 1.01 (m, 1H), 1.0 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H). Anal. $C_{38}H_{48}N_4O_5$•0.75H_2O (654.37) C, H, N; calcd, C: 69.75, H: 7.63, N: 8.56; found, C: 69.71, H: 7.35, N: 8.53.

N'- *[2(S)- Cyclopentyl-1(R) hydroxy-3(R)-methyl]-3(S)- [3 (S)- [(N- (pyridyl-2-carbonyl)-L-valinyl)amino]-2(S)-hydroxy -4- phenylbutyl] -3(S)- phenylmethylpyrrolidin -2- one (35).* (94 %) mp 93–95 °C (dec); ^{1}H NMR ($CDCl_3$) major rotamer δ 8.63 (d, J = 4.4 Hz, 1H), 8.44 (d, J = 8.7 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 7.88 (m, 1H), 7.49 (m, 1H), 7.1–7.4 (m, 10H), 4.4 (m, 1H), 6.48 (d, J = 9.4 Hz, 1H), 4.43 (dd, J = 9 Hz, 6 Hz, 1H), 4.11 (m, 2H), 3.51 (dd, J = 12 Hz, 5 Hz, 1H), 3.20 (m, 2H), 2.96 (m, 2H), 2.69 (m, 1H), 2.59 (d, J = 13 Hz, 1H), 1.5–2.3 (m, 10H), 1.10 (m, 1H), 0.99 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.4 Hz, 3H), 0.92 (d, J = 6.4 Hz, 3H). Anal. $C_{38}H_{48}N_4O_5$•0.6H_2O (650.81) C, H, N; calcd, C: 70.04, H: 7.61, N: 8.60; found, C: 70.25, H: 7.52, N: 8.21.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)- [(N- (4-oxo-4H-1-benzopyran-2-carbonyl)-L-asparaginyl) amino] -2(S) -hydroxy-4-phenylbutyl] -3(S)- phenylmethylpyrrolidin-2-one (37).* (33 %); mp 136–138 °C; ^{1}H NMR ($CDCl_3$) δ 8.72 (d, J = 6 Hz, 1H), 8.24 (dd, J = 7 Hz, 1 Hz, 1H), 7.7 (m, 1H), 7.49 (m, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.48 (t, J = 6 Hz, 1H), 7.0–7.3 (m, 10H), 6.7 (m, 1H), 6.4 (m, 1H), 4.85 (m, 1H), 4.11 (m, 4H), 3.39 (dd, J = 11.5 Hz, 5 Hz, 1H), 3.18 (m, 1H), 2.95 (m, 2H), 2.5–2.7 (m, 3H), 1.8–2.2 (m, 7H), 1.5 (m, 2H), 1.1 (m, 1H), 0.93 (d, J = 6.4 Hz, 3H). Anal. $C_{41}H_{46}N_4O_8$•0.50H_2O (731.33)

C, H, N; calcd, C: 67.28, H: 6.47, N: 7.66; found, C: 67.24, H: 6.34, N: 7.85.

6-Morpholinyl nicotinic acid. 6-Chloro nicotinic acid (22.4 g) was gently refluxed for 16 h in isopropanol (400 mL) containing concentrated H_2SO_4 (9 mL, 1.2 eq.). The reaction was cooled to room temperature and carefully neutralized with $NaHCO_3$ (solid). Isopropanol was removed via rotoevaporator and the residue partitioned between Et_2O and saturated $NaHCO_3$. The layers were separated and the aqueous phase extracted further with Et_2O (2 × 100 mL). The organics were combined, washed with $NaHCO_3$, NaCl, and dried (Na_2SO_4). Volatiles were removed leaving an orange oil that was used without further purification. ^1H NMR ($CDCl_3$, crude) δ 8.99 (d, J = 2 Hz, 1H), 8.24 (dd, J = 6.6 Hz, 2 Hz, 1H), 7.41 (d, J = 9 Hz, 1H), 5.28 (m, 1H), 1.39 (d, J = 6 Hz, 6H). The chloroester (6 g, 30 mmol) was dissolved in isopropanol (60 mL) and treated with morpholine (13 mL, 150 mmol). The reaction was refluxed for 72 h, cooled to room temperature and the volatile material removed. The residue was partitioned between EtOAc:$NaHCO_3$. The layers were separated and the aqueous phase extracted with EtOAc (2 × 100 mL). The organics were combined, washed with $NaHCO_3$, NaCl, and dried over Na_2SO_4. The volatiles were removed to leave a yellow oil (7.8 g, 100 %) that solidified on standing; mp 110–112 °C; (Et_2O:hexanes) ^1H NMR ($CDCl_3$, crude) δ 8.8 (d, J = 2 Hz, 1H), 8.04 (dd, J = 6.6 Hz, 2 Hz, 1H), 6.57 (d, J = 9 Hz, 1H), 5.22 (m, 1H), 3.81 (m, 4H), 3.64 (m, 4H), 1.34 (d, J = 6 Hz, 6H). The ester from above (7.8 g) was treated with 1 N NaOH (40 mL, 31 mmol, 1.25 eq.) and stirred at 50 °C for 5 h and room temperature overnight. The reaction was carefully neutralized with concentrated HCl at 0 °C. The precipitated solid was filtered, washed with H_2O and air dried. The hydrochloride was made by simply dissolving the solid in MeOH containing a slight excess of concentrated HCl and precipitating with EtOAc (4.7 g, 66 %); mp 235–237 °C; ^1H NMR ($CDCl_3$) δ 8.47 (d, J = 2 Hz, 1H), 8.40 (dd, J = 6.6 Hz, 2 Hz, 1H), 7.47 (d, J = 9 Hz, 1H), 4.90 (brs, 2H), 3.83 (m, 8H).

N'- *[2(S)- Cyclopentyl-1(R)- hydroxy-3(R)-methyl]-3(S)-[3 (S)- [(N- (6- morpholinopyridyl -3- carbonyl) -L- valinyl)- amino] -2(S)- hydroxy-4-phenylbutyl] -3(S)- phenylmethyl- pyrrolidin-2-one (38).* (50 %); mp 130–132 °C; ^1H NMR ($CDCl_3$) δ 8.60 (d, J = 2.4 Hz, 1H), 7.81 (dd, J = 9 Hz, 6.6 Hz, 1H), 7.1–7.5 (m, 9H), 6.62 (d, J = 9 Hz, 1H), 6.48 (d, J = 9.4 Hz, 1H), 6.44 (s, 1H), 6.38 (d, J = 9 Hz, 1H), 4.42 (dd, J = 8 Hz, 6.3 Hz, 1H), 4.1 (m, 3H), 3.83 (m, 4H), 3.63 (m, 4H), 3.49 (dd, J = 7.6 Hz, 4.7 Hz, 1H), 3.21 (d, J = 14 Hz, 1H), 3.13 (m, 1H), 2.93 (m, 2H), 2.68 (m, 1H), 2.56 (d, J = 13 Hz, 1H), 1.45–2.2 (envelope, 9H), 0.95 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H). Anal. $C_{42}H_{55}N_5O_6$ (725.93) C, H, N; calcd, C: 68.98, H: 7.77, N: 9.81; found, C: 69.15, H: 7.65, N: 9.50.

2-(4-Hydroxypiperidinyl)isopropylisonicotinate. Starting from 2-chloro-isopropylisonicotinate this material was prepared as described for 6-morpholinylisopropylnicotinate (oil). ^1H NMR ($CDCl_3$) δ 8.25 (d, J = 4 Hz, 1H), 7.25 (brs, 1H), 7.08 (d, J = 4 Hz, 1H), 5.22 (m, 1H), 4.12 (m, 2H), 3.95 (m, 1H), 3.22 (m, 2H), 1.2 (m, 3H), 1.6 (m, 2H), 1.46 (d, J = 6 Hz, 6H).

2-(4-hydroxypiperidinyl)isonicotinic acid. ^1H NMR ($CDCl_3$) δ 8.10 (d, J = 6 Hz, 1H), 7.60 (s, 1H), 7.14 (d, J = 6 Hz, 1H), 4.05 (m, 2H), 3.82 (m, 1H), 3.53 (m, 2H), 1.85 (m, 2H), 1.50 (m, 2H).

N'- *[2(S)-Cyclopentyl-1(R)- hydroxy-3(R)-methyl]-3(S)-[3 (S)- [(N- (2- (4- hydroxypiperidyl)-pyridyl-4-carbonyl)-L- valinyl) amino] -2(S)-hydroxy-4-phenylbutyl]-3(S)-phenyl- methylpyrrolidin-2-one (39).* (40 %); mp 120–122 °C ^1H NMR ($CDCl_3$) major rotamer δ 8.18 (d, J = 4.4 Hz, 1H), 7.3 (m, 9H), 6.6 (m, 2H), 4.4 (m, 1H), 4.1 (m, 10H), 3.4 (m, 1H), 3.2 (m, 2H), 2.95 (m, 2H), 2.4 (m, 2H), 1.5–2.2 (m, 14H), 1.10 (m, 1H), 0.95 (d, J = 6.8 Hz, 6H), 0.85 (d, J = 6 Hz, 3H). Anal. $C_{43}H_{57}N_5O_6$ (739.96) C, H, N; calcd, C: 69.80, H: 7.76, N: 9.46; found, C: 69.88, H: 7.74, N: 9.70.

N'- *[2(S)- Cyclopentyl-1(R)- hydroxy-3(R)-methyl]-3(S)-[3 (S)- [(N- (2-N- methylpiperazinyl) -3- chloro-pyrazinyl -5- carbonyl) -L-valinyl)amino] -2(S)-hydroxy-4-phenylbutyl]- 3(S)-phenylmethylpyrrolidin-2-one (40).* (62 %); mp 127–128 °C; ^1H NMR ($CDCl_3$) δ 8.88 (s, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.2 (m, 10H), 6.46 (s, 1H), 6.39 (d, J = 9.4 Hz, 1H), 4.40 (dd, J = 6.4 Hz, 2.4 Hz, 1H), 4.3 (m, 1H), 3.9–4.1 (m, 5H), 3.5 (m, 2H), 2.8–3.2 (m, 4H), 2.68 (m, 1H), 2.57 (d, J = 13 Hz, 1H), 1.5–2.3 (m, 6H), 1.10 (m, 1H), 0.98 (d, J = 6 Hz, 3H), 0.85 (d, J = 6 Hz, 3H). High Resolution FAB-MS 774.410187; theoretical 774.410971; anal. $C_{42}H_{56}ClN_7O_5$ (774.41) C, H, N; calcd, C: 65.14, H: 7.29, N: 12.66; found, C: 65.07, H: 7.31, N: 12.33.

Preparation of inhibitors found in Table 3

(3R,5S,1'S) -3-Propen-3-yl-5- [1-(1,1-dimethylethoxycarb- onylamino) -2-cyclohexylethyl] -dihydrofuran-2-(3H) -one. (5*S*,1'*S*)-5- [1- (1,1-dimethylethoxycarbonylamino)-2-cyclo- hexylethyl]-dihydrofuran-2-(3*H*)-one (**1b**) (10 g, 32 mmol) was dissolved in dry THF (35 mL) and added to an LDA (0.82 eq.) solution prepared as described above over 30 min at –78 °C. The reaction mixture was stirred for 1 h at this temperature. Allyl bromide (2.9 mL, 34 mmol) was added to the flask at –78 °C and the reaction mixture was warmed to –50 °C and stirred for 1 h. Workup as described previously and flash chromatography using 85:15 hexane:EtOAc as eluent provided pure product as an oil (7 g, 75 %). ^1H NMR ($CDCl_3$) δ 5.7 (m, 1H), 5.13 (m, 2H), 4.46 (m, 1H), 4.34 (d, J = 9.7 Hz, 1H), 2.72 (m, 1H), 2.50 (m, 1H), 2.30 (m, 2H), 2.0 (m, 1H), 1.38 (s, 9H).

(3R,5S,1'S)-3-Propen-3-yl-3- (4- (t-butyldimethylsilyloxy)- phenylmethyl)-5-[1-(1,1-dimethylethoxycarbonylamino)-2- cyclohexylethyl]-dihydrofuran-2-(3H)-one (2b). LDA was generated as described and lactone from above (5.6 g, 15.9 mmol) was added via syringe in dry THF (30 mL) to the reaction mixture at –78 °C over 30 min. The reaction was allowed to proceed for 1 h at which point 4-*t*-butyldimethylsilyloxy benzyliodide (11.6 g, 33 mmol) was added dropwise in THF (10 mL). The reaction was brought

to −50 °C and aged for 1 h. Workup and flash chromatography using 90:10 hexane:EtOAc as the eluent provided the desired product as an oil (8.6 g, 95 %). ^{1}H NMR ($CDCl_3$) δ 7.05 (d, *J* = 8 Hz, 2H), 6.77 (d, *J* = 8 Hz, 2H), 5.74 (m, 1H), 5.15 (m, 2H), 4.28 (d, *J* = 10 Hz, 1H), 3.60 (m, 1H), 3.19 (apparent t, 1H), 2.78 (AB, *J* = 13 Hz, 2H), 2.40 (m, 2H), 2.05 (m, 2H), 1.65 (m, 4H), 1.41 (s, 9H), 0.96 (s, 9H), 0.19 (s, 6H).

*(3R,5S,1'S) -3- Ethanal -3- (4- (*t*- butyldimethylsilyloxy)-phenylmethyl) -5- [1- ((1,1-dimethylethoxycarbonylamino)-2-cyclohexylethyl)]-dihydrofuran-2-(3H)-one (**3b**).* The dialkylated lactone (**3b**) (3.73 g) was treated with ozone and excess dimethylsulfide (1 mL) as described previously. Workup and flash chromatography (3:1 hexane:EtOAc) provide the desired aldehyde (3.4 g, 92 %). ^{1}H NMR ($CDCl_3$) δ 9.92 (s, 1H), 7.07 (d, *J* = 8 Hz, 2H), 6.77 (d, *J* = 8 Hz, 2H), 4.63 (d, *J* = 10 Hz, 1H), 3.63 (m, 1H), 3.43 (m 1H), 2.85 (AB, *J* = 19 Hz, 2H), 2.82 (AB, *J* = 13 Hz, 2H), 2.15 (m, 2H), 1.62 (m, 5H), 1.41 (s, 9H), 1.18 (m, 4H), 0.96 (s, 9H), 0.19 (s, 6H).

Reductive amination using procedure B was used for entries found in Table 3.

*N'- [2(S)- Cyclopentyl-1(R)-hydroxy-3(R)- methyl]-3(S)-[3 (S)- (1,1'- dimethylethoxycarbonylamino)- 2(S)-hydroxy-4-cyclohexylbutyl] -3(S)- [(4-*t*-butyldimethylsilyloxy)-phenyl-methyl]-pyrrolidin-2-one (**4**).* The aldehyde **3b** from above (0.50 g, 0.87 mmol) and 2(*S*)-amino-1(*R*)-hydroxy-3(*R*)-methylcyclopentane HCl (0.17 g, 1.10 mmol) were treated with $NaCNBH_3$ as described to give the desired lactam (**4**) as a foam (300 mg, 51 %). Partial ^{1}H NMR ($CDCl_3$) δ 7.13 (d, *J* = 8 Hz, 2H), 6.75 (d, *J* = 8 Hz, 2H), 4.85 (d, *J* = 10 Hz, 1H), 4.14 (m, 1H), 4.01 (d, *J* = 9 Hz, 1H), 3.60 (m, 1H), 3.47 (dd, *J* = 11 Hz, 3 Hz, 1H), 3.19 (d, *J* = 13 Hz, 1H), 3.16 (m, 1H), 2.70 (m, 1H), 2.58 (d, *J* = 13 Hz, 1H), 2.18 (m, 2H), 1.9 (m, 3H), 1.4 (s, 9H), 0.96 (s, 9H), 0.89 (d, *J* = 6 Hz, 3H), 0.18 (s, 6H).

*N'- [2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)- (1,1'- dimethylethoxycarbonylamino)-2(S)- hydroxy-4-cyclohexylbutyl]- 3(S)- [4- (2- (4-morpholinyl) ethoxy)-phenylmethyl]-pyrrolidin-2-one (**5**).* In a separate experiment, the crude silylated lactam (**4**) (800 mg) obtained from the reductive amination was dissolved in THF:1 N HCl (4:1) and stirred for 72 h. The reaction was neutralized with solid $NaHCO_3$ (60 mg) and concentrated. The aqueous residue was extracted with EtOAc (3 × 40 mL). The organic layers were collected and dried ($MgSO_4$). The crude product was purified by flash chromatography (1:1 EtOAc:CH_2Cl_2) to give 540 mg (78 %) of the desired phenol; mp 52 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 7.13 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 4.88 (d, *J* = 10 Hz, 1H), 4.16 (m, 2H), 4.00 (d, *J* = 10 Hz, 1H), 3.6 (m, 1H), 3.48 (dd, *J* = 11.7 Hz, 4.6 Hz, 1H), 3.27 (d, *J* = 13 Hz, 1H), 3.16 (m, 1H), 2.68 (m, 1H), 2.58 (d, *J* = 13 Hz, 1H), 2.18 (m, 2H), 1.75–2.0 (m, 3H), 1.65 (m, 6H), 1.44 (s, 9H), 1.1–1.4 (m, 10H), 0.90 (d, *J* = 6.4 Hz, 3H). The phenol (0.35 g, 63 mmol), chloroethyl morpholine (0.47 g, 3.13 mmol) and Cs_2CO_3 (0.68 g, 2.09 mmol) were placed in a 50 mL round-bottom flask and dry dioxane (6 mL) was added. This mixture was stirred at 80 °C overnight under an argon atmosphere. After 14 h it was cooled to room temperature, diluted with $CHCl_3$ (20 mL) and filtered. The filtrate was concentrated and purified by flash chromatography 95:5 EtOAc:MeOH containing (5 %) concentrated NH_4OH to give 350 mg of product **5**. ^{1}H NMR ($CDCl_3$) δ 7.2 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.2 (brs, 1H), 4.85 (d, *J* = 10 Hz, 1H), 4.04 (m, 3H), 4.01 (d, *J* = 10 Hz, 1H), 3.76 (m, 4H), 3.60 (m, 1H), 3.48 (dd, *J* = 11.7 Hz, 4.6 Hz, 1H), 3.31 (d, *J* = 13 Hz, 1H), 3.15 (m, 1H), 2.85 (m, 1H), 2.46–2.74 (m, 6H), 2.08–2.25 (m, 2H), 1.05–2.05 (envelope, 30H), 0.90 (d, *J* = 6.4 Hz, 3H).

*N'- [2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)- (3(S)-tetrahydrofuranyloxycarbonylamino)-2(S)-hydroxy-4-cyclohexylbutyl]-3(S)-[4-(2-(4-morpholinyl)ethoxy)-phenylmethyl]-pyrrolidin-2-one (**41**).* The lactam **5** (0.31 g) was dissolved in 5 mL of CH_2Cl_2 and added to a saturated solution of HCl in EtOAc (20 mL). The reaction was stirred for 2 h at which time the reaction was judged complete by HPLC. The reaction was concentrated to give 350 mg of the HCl salt (crude weight). This salt was dissolved in 7 mL of CH_2Cl_2 and 3(*S*)-tetrahydrofuranyl succinimidyl carbonate (0.16 g, 0.68 mmol), followed by triethylamine (0.16 mL, 1.14 mmol) were added. The reaction was stirred for 2 h, concentrated and purified by flash chromatography 95:5 $CHCl_3$:MeOH containing (5 %) concentrated NH_4OH to give 246 mg (94 %) mp 52 °C (dec.); partial ^{1}H NMR ($CDCl_3$) δ 7.19 (d, *J* = 8 Hz, 2H), 6.83 (d, *J* = 8 Hz, 2H), 5.22 (m, 1H), 5.05 (d, *J* = 9 Hz, 1H), 4.85 (m, 16H), 1.68 (s, 9H), 0.89 (d, *J* = 6 Hz, 3H). Anal. $C_{38}H_{59}N_3O_8 \cdot 0.95H_2O$ (703.026) C, H, N; calcd, C: 64.92, H: 9.73, N: 5.98; found, C: 64.92, H: 8.36, N: 6.10.

*N'- [2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S) -[3 (S)- [N- (benzyloxycarbonylamino-L-valinyl)] -2(S)- hydroxy-4-cyclohexylbutyl]-3(S)-[4-(2-(4-morpholinyl)ethoxy)-phenylmethyl]-pyrrolidin-2-one (**42**).* The HCl salt prepared as described above (0.50 g, 0.78 mmol), HOBT (0.17 g, 1.24 mmol), EDC (0.24 g, 1.24 mmol), and CBZ-valine (0.24 g, 0.97 mmol) were combined in a 50 mL round-bottom flask and dissolved in DMF (10 mL). This solution was cooled to 0 °C and triethylamine (0.36 mL, 2.6 mmol) was added via syringe. The reaction was stirred overnight, gradually coming to room temperature. After 14 h the reaction was concentrated to dryness and the residue dissolved in EtOAc (50 mL), and washed with $NaHCO_3$ (2 × 20 mL). The organic layer was collected and dried ($MgSO_4$). The aqueous layer was re-extracted with EtOAc (75 mL) and combined with the first. The crude product (800 mg) was purified by flash chromatography 93:7 EtOAc:isopropanol containing 5 % concentrated NH_4OH to give 340 mg (55 %); mp 55–56 °C; partial ^{1}H NMR ($CDCl_3$) δ 7.35 (s, 5H), 7.19 (d, *J* = 8 Hz, 2H), 6.77 (d, *J* = 8 Hz, 2H), 6.5 (brs, 1H), 6.24 (d, *J* = 9 Hz, 1H), 5.3 (d, *J* = 7 Hz, 1H), 5.2 (s, 2H), 4.0 (m, 10H), 0.95 (d, *J* = 6 Hz, 3H), 0.90 (d, *J* = 6 Hz, 3H), 0.82 (d, *J* = 6 Hz, 3H). FAB-MS: m/z 805.6 (M + 1). Anal. $C_{46}H_{68}N_4O_8$ (804.5) C, H, N; calcd, C: 68.63, H: 8.51, N: 6.86; found, C: 68.24, H: 8.50, N: 6.94.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)- (N-(quinolinyl-2-carbonyl-L-valinyl))-2(S)-hydroxy-4-cyclohexylbutyl]- [4- (2- (4- morpholinyl) ethoxy) phenyl-methyl]-pyrrolidin-2-one (50).* Lactam (**42**), (0.13 g, 0.16 mmol) was dissolved in 5 mL of EtOH followed by the addition of 10 % Pd/C (100 mg). The flask was evacuated under house vacuum and backfilled with H_2 (balloon). This process was repeated three times. After 14 h the catalyst was filtered off and the solvent removed via rotoevaporator. The residue was azeotroped with toluene (2 × 4 mL) and the resulting amine was dissolved in DMF (5 mL). To this solution was added hydroxy benzotriazole (34 mg), EDC (49 mg) and quinaldic acid (35 mg, Aldrich). The solution was cooled to 0 °C and Et_3N (25 mL) was added via syringe. The solution was stirred overnight with gradual warming to room temperature. Workup and flash chromatography using EtOAc:MeOH (95:5) containing concentrated NH_4OH (5 %) gave the desired product (80 mg). Partial ^1H NMR ($CDCl_3$) δ 8.83 (d, J = 9 Hz, 1H), 8.71 (d, J = 9 Hz, 1H), 8.43 (s, 1H), 8.28 (d, J = 7 Hz, 2H), 8.21 (d, J = 7 Hz, 1H), 7.88 (m, 4H), 7.18 (d, J = 6 Hz, 2H), 6.98 (d, J = 6 Hz, 2H), 4.6 (m, 1H), 1.02 (apparent t, 6H), 0.98 (d, J = 6 Hz, 3H). Anal. $C_{48}H_{67}N_5O_7 \cdot 0.75H_2O$ (839.60) C, H, N; calcd, C: 68.66, H: 8.22, N: 8.34; found, C: 68.63, H: 8.00, N: 8.21.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)- [N- (benzyloxycarbonylamino-L-asparaginyl)] -2(S)-hydroxy-4-cyclohexylbutyl] -3(S)- [4- (2- (4- morpholinyl)-ethoxy)-phenylmethyl]-pyrrolidin-2-one (43).* (78 %); mp 88–90 °C; partial ^1H NMR ($CDCl_3$) δ 7.35 (s, 5H), 7.20 (d, J = 8 Hz, 2H), 6.80 (d, J = 8 Hz, 2H), 6.74 (d, J = 8 Hz, 1H), 6.3 (d, J = 6 Hz, 1H), 6.02 (brs, 1H), 5.87 (brs, 1H), 5.45 (brs, 1H), 5.1 (s, 2H), 4.5 (m, 1H), 3.9 (m, 9H), 0.85 (d, J = 6 Hz, 3H). FAB-MS m/z 820. Anal. $C_{45}H_{65}N_5O_9 \cdot 0.55H_2O$ (829.95) C, H, N; calcd, C: 65.12, H: 8.03, N: 8.44; found, C: 65.10, H: 7.88, N: 8.45.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)- [N- (benzyloxycarbonylamino-L-glutaminyl)] -2(S)-hydroxy-4-cyclohexylbutyl] -3(S)- [4- (2- (4-morpholinyl)-ethoxy)-phenylmethyl]-pyrrolidin-2-one (44).* mp 80–82 °C; partial ^1H NMR ($CDCl_3$) δ 7.35 (s, 5H), 7.18 (d, J = 8 Hz, 2H), 6.81 (d, J = 8 Hz, 2H), 6.62 (d, J = 9 Hz, 1H), 6.3 (brs, 1H), 6.10 (brs, 1H), 5.95 (d, J = 6 Hz, 1H), 5.45 (brs, 1H), 5.1 (s, 2H), 4.0 (m, 10H), 0.84 (d, J = 6 Hz, 3H). Anal. $C_{46}H_{67}N_5O_9 \cdot 1.4H_2O$ (859.29) C, H, N; calcd, C: 64.30, H: 8.19, N: 8.15; found, C: 64.29, H: 7.82, N: 8.38.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)-[N- ((pyridinyl-3-carbonyl)-L-alaninyl)]-2(S)-hydroxy-4-cyclohexylbutyl] -3(S)- [4- (2- (4- morpholinyl)ethoxy)-phenylmethyl]-pyrrolidin-2-one (45).* Partial ^1H NMR ($CDCl_3$) δ 9.05 (brs, 1H), 8.75 (brs, 1H), 8.12 (d, J = 9 Hz, 1H), 7.28 (d, J = 6 Hz, 1H), 6.84 (d, J = 6 Hz, 1H), 6.46 (brs, 1H), 6.18 (brs, 1H), 4.65 (m, 1H), 4.0–4.2 (m, 6H), 3.78 (brs, 4H), 3.48 (m, 1H), 3.32 (d, J = 13 Hz, 1H), 3.12 (m, 1H), 1.5 (d, J = 6 Hz, 3H), 0.86 and 0.84 (d, J = 6 Hz, 3H each diastereomeric CH_3). Anal. $C_{42}H_{61}N_5O_7 \cdot 0.75H_2O$ (761.50) C, H, N; calcd, C: 66.24, H: 8.27, N: 9.20; found, C: 66.24, H: 9.03, N: 9.14.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)-[N-((pyridinyl-3-carbonyl)-L-valinyl)]-2(S)-hydroxy-4-cyclohexylbutyl]-3(S)- [4- (2-(4-morpholinyl)ethoxy)-phenylmethyl]-pyrrolidin-2-one (46).* (72 %); partial ^1H NMR ($CDCl_3$) δ 9.05 (brs, 1H), 8.75 (brs, 1H), 8.12 (d, J = 9 Hz, 1H), 7.2 (d, J = 6 Hz, 2H), 6.84 (d, J = 8 Hz, 2H), 6.62 (d, J = 9 Hz, 1H), 6.3 (brs, 1H), 6.10 (brs, 1H), 5.95 (d, J = 6 Hz, 2H), 4.48 (m, 1H), 1.02 (d, J = 6 Hz, 6H), 0.83 (d, J = 6 Hz, 3H). Anal. $C_{44}H_{63}N_5O_7 \cdot 0.65H_2O$ (785.72) C, H, N; calcd, C: 67.25, H: 8.25, N: 8.91; found, C: 67.25, H: 8.34, N: 9.00.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)- [N- ((pyridinyl-3-carbonyl)-L-leucinyl)]-2(S)-hydroxy-4-cyclohexylbutyl] -3(S)- [4- (2- (4- morpholinyl)ethoxy)-phenylmethyl]-pyrrolidin-2-one (47).* (33 %); mp 60 °C (dec); partial ^1H NMR ($CDCl_3$) δ 9.1 (brs, 1H), 8.75 (d, J = 3 Hz, 1H), 8.1 (d, J = 7 Hz, 1H), 7.4 (m, 1H), 7.28 (d, J = 6 Hz, 2H), 6.84 (d, J = 8 Hz, 2H), 6.44 (brs, 1H), 6.27 (d, J = 9 Hz, 1H), 4.68 (m, 1H), 4.0 (m, 10H), 0.96 (appt, 6H), 0.85 (d, J = 6 Hz, 3H). FAB-MS: m/z 790.4. Anal. $C_{45}H_{67}N_5O_7 \cdot 1.2H_2O$ (811.68) C, H, N; calcd, C: 66.58, H: 8.25, N: 8.91; found, C: 66.44, H: 8.22, N: 8.52.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)- [N- ((pyridinyl-3-carbonyl)-L-isoleucinyl)]-2(S)- hydroxy-4-cyclohexylbutyl]-3(S)-[4-(2-(4-morpholinyl)ethoxy)-phenylmethyl]-pyrrolidin-2-one (48).* (49 %); mp 90 °C (dec.); partial ^1H NMR ($CDCl_3$) δ 9.04 (brs, 1H), 8.74 (d, J = 3 Hz, 1H), 8.1 (d, J = 7 Hz, 1H), 7.4 (dd, J = 6 Hz, 3 Hz, 1H), 7.18 (d, J = 6 Hz, 2H), 7.0 (d, J = 7 Hz, 1H), 6.84 (d, J = 8 Hz, 2H), 6.47 (brs, 1H), 6.22 (d, J = 10 Hz, 1H), 4.52 (m, 1H), 4.6 (m, 6H), 3.81 (brs, 3H), 0.98 (d, J = 6 Hz, 3H), 0.89 (t, J = 6 Hz, 3H), 0.81 (d, J = 6 Hz, 3H). FAB-MS: m/z 790.6. Anal. $C_{45}H_{67}N_5O_7$ (790.07) C, H, N; calcd, C: 68.41, H: 8.55, N: 8.86; found, C: 68.22, H: 8.57, N: 8.46.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)-[N-((pyrazinyl-2-carbonyl)-L-valinyl)]-3(S)-hydroxy-4-cyclohexylbutyl] -3(S)- [4-(2-(4-morpholinyl)ethoxy)-phenylmethyl]-pyrrolidin-2-one (49).* mp 95 °C (dec.); partial ^1H NMR ($CDCl_3$) δ 9.41 (s, 1H), 8.79 (d, J = 2 Hz, 1H), 8.6 (s, 1H), 8.30 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.5 (brs, 1H), 6.15 (d, J = 10 Hz, 1H), 4.43 (dd, J = 9 Hz, 6 Hz, 1H), 4.1 (m, 1H), 4.0 (m, 3H), 3.52 (m, 1H), 3.35 (d, J = 13.2 Hz, 1H), 3.1 (m, 1H), 2.57 (d, J = 13.2 Hz, 1H), 2.3 (m, 1H), 2.15 (m, 1H), 1.01 (d, J = 6.7 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H), 1.86 (d, J = 6.8 Hz, 3H). FAB-MS: m/z 777.026. Anal. $C_{43}H_{64}N_6O_7 \cdot 0.8H_2O$ (791.44) C, H, N; calcd, C: 65.25, H: 8.36, N: 10.62. found, C: 65.23, H: 8.21, N: 10.71.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)- [(N- (4-oxo-4H-1-benzopyran-2-carbonyl)-L-valinyl)-amino] -2(S)- hydroxy -4- phenylbutyl] -3(S)- [4- (2- (4-morpholinyl)ethoxy)-phenylmethyl]-pyrrolidin-2-one (51).* (26 %); partial ^1H NMR ($CDCl_3$) δ 8.24 (d, J = 8 Hz, 1H), 7.75 (t, J = 8 Hz, 1H), 7.60 (d, J = 9 Hz, 1H), 7.46 (t, J = 6 Hz, 1H), 7.18 (d, J = 6 Hz, 2H), 6.85 (d, J = 6 Hz, 2H), 6.55 (brs, 1H), 6.14 (d, J = 10 Hz, 1H), 4.45 (dd, J = 6 Hz, 3 Hz, 1H), 4.15 (m, 8H), 3.78 (m, 5H), 1.02 (d, J = 6 Hz,

6H), 0.95 (d, J = 6 Hz, 3H). Anal. $C_{48}H_{66}N_4O_9 \cdot 1.65H_2O$ (872.81) C, H, N; calcd, C: 66.05, H: 8.00, N: 6.42; found, C: 66.02, H: 7.65, N: 6.59.

Urea derivatives in Table 4.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)- [(N- (4-morpholinocarbonyl)-L-valinyl)amino] -2(S)- hydroxy-4-phenylbutyl]-3(S)-phenylmethylpyrrolidin-2-one (60).* The hydrochloride salt, (202 mg, 0.354 mmol) prepared from lactam **20** was dissolved in CH_2Cl_2 and cooled to 0 °C. Morpholine carbonyl chloride (0.4 mL, 0.53 mmol, Aldrich) was added, followed by dropwise addition of triethylamine (0.14 mL, 0.98 mmol). The reaction was allowed to warm to room temperature and stirred for 48 h under argon. The solvents were evaporated, and the oily residue was purified by flash column chromatography on silica gel with 8 % isopropanol:$CHCl_3$ as eluent to give 195 mg solid. Recrystallization of the solid using Et_2O gave 119 mg (52 %) of white crystals mp 163–164 °C. ^{1}H NMR ($CDCl_3$) δ 7.16 (m, 7H), 7.08 (m, 1H), 7.02 (m, 2H), 6.26 (d, J = 9 Hz, 1H), 4.93 (d, J = 8 Hz, 1H), 4.19 (dd, J = 7.8 Hz, 6 Hz, 1H), 4.11 (m, 3H), 4.03 (dd, J = 16 Hz, 8.8 Hz, 1H), 3.70 (t, J = 5 Hz, 4H), 3.48 (dd, J = 11.6 Hz, 5 Hz, 1H), 3.36 (m, 4H), 3.18 (d, J = 13 Hz, 1H), 3.12 (dt, J = 10 Hz, 2.8 Hz, 1H), 2.94 (m, 2H), 2.68 (dd, J = 18 Hz, 8.06 Hz, 1H), 2.54 (d, J = 13 Hz, 1H), 1.74 (m, 10H), 1.1 (m, 1H), 0.80 (d, J = 6.8 Hz, 3H), 0.75 (d, J = 6.4 Hz, 6H). High Resolution FAB-MS: m/z 649.3946; theoretical 649.3966 (M + 1). Anal. $C_{37}H_{52}N_4O_6$ (648.850) C, H, N; calcd, C: 68.49, H: 8.08, N: 8.63; found, C: 68.60, H: 8.04, N: 8.84.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)-[(N-(4-morpholinocarbonyl)-L-asparaginyl)amino]-2-(S)- hydroxy-4-phenylbutyl] -3(S)- phenylmethylpyrrolidin-2-one (61).* (35 %); mp 146–148 °C; ^{1}H NMR ($CDCl_3$) δ 7.14 (m, 12H), 5.88 (brs, 1H), 5.26 (brs, 1H), 4.62 (m, 1H), 4.12 (m, 3H), 3.72 (m, 4H), 3.40 (m, 4H), 3.18 (m, 2H), 2.9 (m, 4H), 2.7 (m, 1H), 2.57 (d, J = 13 Hz, 1H), 2.48 (m, 1H), 1.8–2.2 (m, 8H), 1.5 (m, 2H), 1.10 (m, 1H), 0.92 (d, J = 6 Hz, 3H). FAB-MS: m/z 664 (M + 1). Anal. $C_{36}H_{49}N_5O_7 \cdot 1.05H_2O$ (680.72) C, H, N; calcd, C: 63.40, H: 7.54, N: 10.28; found: C: 63.54, H: 7.33, N: 9.89.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)- [(N- (4-thiomorpholinedioxidecarbonyl) -L- valinyl)-amino]- 2(S)- hydroxy-4-phenylbutyl]- 3(S)- phenylmethyl-pyrrolidin-2-one (62). 4-Thiomorpholinyldioxidecarbonyl-amino-L-valine.* Valine benzyl ester:p-toluenesulfonate (1.47 g, 3.9 mmol, Bachem) was suspended in CH_2Cl_2 (8 mL) and cooled to 0 °C. Carbonyldiimidazole (627 mg, 3.9 mmol) and triethylamine (0.54 mL, 3.9 mmol), were added and the reaction stirred at 0 °C for 3 h. Thiomorpholine (1.1 eq.) was added and the reaction warmed to room temperature over 3 h. The reaction was diluted with CH_2Cl_2 (50 mL) and washed with 10 % citric acid, saturated NaCl and dried over Na_2SO_4. The volatiles were removed to leave a pale yellow oil (1.3 g, 97 %). This material was used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5H), 5.16 (AB, J = 12.2 Hz, 2H), 4.98 (d, J = 8.2 Hz, 1H), 4.52 (dd, J = 8.3 Hz, 4.5 Hz, 1H), 3.70 (t, J = 5 Hz, 4H), 2.59 (t, J = 5 Hz, 4H), 2.16 (m, 1H), 0.93 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H). The sulfide (1.3 g, 3.8 mmol) from above was dissolved in acetone:water (16 mL, 15:1) and treated sequentially with OsO_4 (1 mL, 2.5 % solution) and N-methylmorpholine N-oxide (1.36 g, 12 mmol). The reaction was stirred overnight and after 16 h quenched with excess sodium bisulfite (10 % solution). The volatiles were removed and the aqueous extracted with EtOAc (3 × 75 mL). The organics were combined, washed with sodium bisulfite solution (10 %), H_2O, NaCl, and dried over $MgSO_4$. Flash chromatography EtOAc:hexane (2:1) gave 1.2 g (84 %) of the desired sulfone. ^{1}H NMR ($CDCl_3$) δ 7.37 (m, 5H), 5.18 (AB, J = 12.2 Hz, 2H), 5.09 (d, J = 8 Hz, 1H), 4.48 (dd, J = 8.3 Hz, 4.5 Hz, 1H), 3.90 (m, 4H), 3.04 (m, 4H), 2.2 (m, 1H), 0.93 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H). The benzylester was cleaved using H_2 and Pd/C in EtOH. Acid mp 160–162 °C; ^{1}H NMR ($CDCl_3$) δ 6.78 (d, J = 8 Hz, 1H), 3.94 (t, J = 7 Hz, 1H), 3.68 (m, 4H), 3.04 (m, 4H), 2.04 (m, 1H), 0.90 (m, 6H). The acid was coupled in standard fashion. (88 %); mp 125–127 °C; ^{1}H NMR ($CDCl_3$) δ 7.1–7.35 (m, 10H), 6.4 (brs, 1H), 5.4 (brs, 1H), 4.0–4.2 (m, 4H), 3.89 (m, 4H), 3.48 (dd, J = 11 Hz, 5 Hz, 1H), 2.85–3.25 (m, 8H), 2.68 (m, 1H), 2.56 (d, J = 13 Hz, 1H), 1.85–2.25 (m, 5H), 1.75 (m, 2H), 1.1 (m, 1H), 0.80–0.95 (m, 9H). Anal. $C_{37}H_{52}N_4O_7S$ (696.91) C, H, N; calcd, C: 63.77, H: 7.52, N: 8.04; found, C: 63.48, H: 7.39, N: 7.96.

N-*(Tetrahydroisoquinolinylcarbonyl)-L-valine.* ^{1}H NMR ($CDCl_3$) δ 10.2 (brs, 1H), 7.41 (d, J = 8 Hz, 1H), 7.2 (m, 2H), 7.08 (m, 1H), 5.64 (d, J = 8 Hz, 1H), 4.75 (m, 2H), 4.43 (dd, J = 8.3 Hz, 5 Hz, 1H), 2.76 (t, J = 6.7 Hz, 2H), 2.02 (m, 1H), 1.0 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H).

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)- [(N- tetrahydroisoquinolinylcarbonyl) -L- valinyl)-amino] -2(S)- hydroxy-4-phenylbutyl] -3(S)- phenylmethyl-pyrrolidin-2-one (52).* ^{1}H NMR ($CDCl_3$) δ 7.1–7.4 (m, 10H), 5.6 (brs, 1H), 4.22 (dd, J = 8 Hz, 6 Hz, 1H), 4.18 (m, 3H), 3.8 (m, 1H), 3.64 (m, 1H), 3.47 (dd, J = 11.7 Hz, 4 Hz, 1H), 3.18 (m, 2H), 2.92 (m, 2H), 2.78 (t, J = 6 Hz, 1H), 2.65 (m, 1H), 2.54 (d, J = 13 Hz, 1H), 1.7–2.2 (envelope, 7H), 1.5 (m, 2H), 1.1 (m, 1H), 0.92 (d, J = 6.6 Hz, 3H) 0.88 (d, J = 6.6 Hz, 3H), 0.77 (d, J = 6.8 Hz, 3H). Anal. $C_{42}H_{54}N_4O_5 \cdot 0.5H_2O$ (703.93) C, H, N; calcd, C: 71.66, H: 7.88, N: 7.96; found, C: 71.64, H: 7.70, N: 8.17.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)-[(N-(4-aminomethylpyridylcarbonyl)-L-valinyl)amino]-2(S)-hydroxy-4-phenylbutyl]-3(S)-phenylmethylpyrrolidin-2-one (53).* (31 %); mp 199–202 °C; ^{1}H NMR (DMSO) δ 8.5 (m, 2H), 7.7 (d, J = 9 Hz, 1H), 7.4 (s, 1H), 7.2 (m, 8H), 6.95 (m, 2H), 6.65 (m, 1H), 3.8–4.4 (m, 6H), 3.05–3.70 (m, 8H), 2.75–2.90 (m, 2H), 2.55–2.70 (m, 2H), 2.5 (d, J = 13 Hz, 1H), 1.7–2.0 (m, 4H), 1.3–1.55 (m, 3H), 0.7–1.0 (m, 9H). High Resolution FAB-MS: m/z 670.3973; theoretical 670.3968 (M + 1). Anal. $C_{39}H_{51}N_5O_5 \cdot$ 0.45MeOH (684.29) C, H, N; calcd, C: 69.24, H: 7.78, N: 10.24; found, C: 69.22, H: 7.58, N: 10.19.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)- [(N- (N- methyl)-4-aminomethylpyridylcarbonyl) -L-valinyl) amino] -2(S)-hydroxy-4-phenylbutyl]-3(S)-phenyl-methylpyrrolidin-2-one (54).* mp 98–100 °C; ^{1}H NMR($CDCl_3$) δ 8.69 (d, *J* = 6 Hz, 2H), 7.75 (d, *J* = 5.5 Hz, 1H), 7.17–7.4 (m, 10H), 6.4 (d, *J* = 9 Hz, 1H), 5.32 (d, *J* = 9 Hz, 1H), 4.7 (d, *J* = 5.8 Hz, 1H), 4.10 (m, 3H), 3.44 (dd, *J* = 12 Hz, 4.7 Hz, 1H), 3.19 (d, *J* = 13 Hz, 1H), 3.10 (m, 1H), 3.03 (s, 3H), 2.95 (m, 2H), 2.68 (m, 1H), 2.57 (d, *J* = 13 Hz, 1H), 1.4–2.2 (m, 8H), 1.10 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6 Hz, 3H). Anal. $C_{40}H_{53}N_5O_5 \cdot 0.4H_2O$ (691.10) C, H, N; calcd, C: 69.51, H: 7.85, N: 10.13; found, C: 69.48, H: 7.81, N: 9.99.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)-[(N-(3-aminomethylpyridylcarbonyl)-L-valinyl)amino]-2(S)-hydroxy-4-phenylbutyl]-3(S)-phenylmethylpyrrolidin-2-one (55).* (60 %); ^{1}H NMR ($CDCl_3$) δ 9.02 (s, 1H), 8.52 (d, *J* = 5.7 Hz, 1H), 8.41 (d, *J* = 7.4 Hz, 1H), 7.86 (m, 1H), 7.5 (m, 1H), 7.26 (m, 10H), 4.80 (d, *J* = 15 Hz, 1H), 4.4 (d, *J* = 15 Hz, 1H), 4.1 (m, 3H), 3.95 (dd, *J* = 10.5 Hz, 1H), 3.31 (dd, *J* = 13 Hz, 5 Hz, 1H), 2.6–3.2 (m, 6H), 1.5–2.3 (m, 12H), 1.10 (m, 1H), 0.85 (m, 9H). Anal. $C_{39}H_{51}N_5O_5 \cdot 0.9H_2O$ (686.09) C, H, N; calcd, C: 68.27, H: 7.76, N: 10.21; found, C: 68.33, H: 7.57, N: 9.82.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)-[(N-(N-methyl)-(N-ethylpyridinyl)-2-carbonyl)-L-valinyl)amino]-2(S)-hydroxy-4-phenylbutyl]-3(S)-phenylmethylpyrrolidin-2-one (56).* (31 %); ^{1}H NMR ($CDCl_3$) δ 8.59 (s, 1H), 7.70 (brs, 1H), 7.24 (m, 11H), 5.50 (d, *J* = 9 Hz, 1H), 6.2 (s, 1H), 5.69 (brs, 1H), 4.10 (m, 4H), 3.6–3.82 (m, 2H), 3.48 (dd, *J* = 12 Hz, 4 Hz, 1H), 3.15 (m, 4H), 2.9 (m, 1H), 2.86 (s, 3H), 2.68 (m, 1H), 2.56 (d, *J* = 13 Hz, 1H), 1.4–2.2 (m, 8H), 1.4–1.6 (m, 2H), 1.10 (m, 1H), 0.80–1.0 (m, 9H). Anal. $C_{41}H_{55}N_5O_5$ (697.93) C, H, N; calcd, C: 70.56, H: 7.94, N: 10.03; found, C: 70.31, H: 7.80, N: 10.29.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)- [(N- (N-methylpiperazinylcarbonyl)-L-valinyl)amino]-2(S)-hydroxy-4-phenylbutyl]-3(S)-phenylmethylpyrrolidin-2-one (57).* mp 109–111 °C; ^{1}H NMR ($CDCl_3$) δ 7.14 (m, 12H), 5.88 (brs, 1H), 5.26 (brs, 1H), 4.62 (m, 1H), 4.12 (m, 3H), 3.72 (m, 4H), 3.40 (m, 4H), 3.18 (m, 2H), 2.9 (m, 4H), 2.7 (m, 1H), 2.57 (d, *J* = 13 Hz, 1H), 2.48 (m, 1H), 1.8–2.2 (m, 8H), 1.5 (m, 2H), 1.10 (m, 1H), 0.92 (d, *J* = 6 Hz, 3H). FAB-MS: m/z 662 (M + 1). Anal. $C_{38}H_{55}N_5O_5 \cdot 0.6H_2O$ (673.60) C, H, N; calcd, C: 67.76, H: 8.42, N: 10.40; found, C: 67.79, H: 8.20, N: 10.40.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)-[(N-(4-hydroxypiperadinylcarbonyl)-L-valinyl)amino]-2(S)-hydroxy-4-phenylbutyl]-3(S)-phenylmethylpyrrolidin-2-one (58).* (75 %); mp 240–242 °C; ^{1}H NMR ($CDCl_3$) δ 7.1–7.35 (m, 10H), 6.5 (d, *J* = 9 Hz, 1H), 6.45 (s, 1H), 4.0–4.2 (m, 5H), 3.35 (m, 5H), 3.14 (m, 2H), 2.80 (m, 2H), 2.68 (m, 1H), 2.55 (d, *J* = 13 Hz, 1H), 2.43 (m, 2H), 2.32 (s, 3H), 1.6–2.2 (m, 8H), 1.5 (m, 2H), 1.1 (m, 1H), 0.80–0.95 (m, 9H). FAB-MS: m/z 662 (M + 1). Anal. $C_{38}H_{55}N_4O_6 \cdot 0.9H_2O$ (692.63) C, H, N; calcd, C: 66.88, H: 8.09, N: 7.93; found, C: 66.96, H: 8.27, N: 8.21.

N'- *[2(S)- Cyclopentyl-1(R)-hydroxy-3(R)-methyl]-3(S)- [3 (S)- [(N- (2-methoxyethoxy)carbonyl)-L-valinyl)amino]-2-(S)- hydroxy-4-phenylbutyl] -3(S)- phenylmethylpyrrolidin-2-one (59).* (59 %); foam; ^{1}H NMR ($CDCl_3$) δ 6.95–7.45 (m, 12H), 3.95–4.15 (m, 4H), 3.4–3.7 (m, 3H), 3.15 (m, 2H), 2.85–3.20 (m, 2H), 2.65 (m, 1H), 2.55 (d, *J* = 13 Hz, 1H), 0.75–1.0 (m, 9H). High Resolution 637.3963; theoretical 637.3965 (M + 1). FAB-MS: m/z Anal. $C_{36}H_{54}N_4O_6 \cdot 0.2OCH_2Cl_2$ (655.84) C, H, N; calcd, C: 66.29, H: 8.36, N: 8.54; found, C: 66.49, H: 8.17, N: 8.42.

General procedure for estimating the octanol–buffer partition coefficient by HPLC

The isocratic HPLC conditions are a 65:35, methanol:buffer system with a flow rate of 1.7 mL/min and UV absorbance as the detection method. The standards selected and their Log P values are as reported in the literature.[27]

STANDARD	Log P
$NaNO_2$	void
volume	
Acetophenone	1.66
Toluene	2.74
Bromobenzene	2.99
Naphthalene	3.37
Phenanthrene	4.46

The chromatographic capacity factor k′ is defined as

$$k' = \frac{\text{retention time} - \text{void time}}{\text{void time}}$$

The linear standard curve fits the equation

$$\text{Log P} = m(\log k') + b$$

$$\text{Log P} = 2.93(\log k') + 1.54.$$

After injecting 5 μL of the standards onto the C-18 column, a curve is established from the retention times of the standards. A 500 μM solution of the test compounds is prepared in acetonitrile or methanol and the retention times are obtained for the test compound, with the same HPLC conditions used for the standard curve. The Log P values are calculated from the standard curve and the data are reported as the mean of two injections along with the standard error of the mean.

*General procedure for oral administration of compounds **36, 40, 46** and **60** to dogs*

Oral study. After an overnight fast, two male dogs (weighing 10–12 kg) received an oral dose of compound (10 mg/kg) as a suspension in 0.5 % methylcellulose.

Blood samples were taken from the jugular vein at 0, 10, 20, 30, 40, 60, 90, 120, 240, 300, 360, 420 and 480 min after dosing, and plasma was kept frozen (–20 °C) until assayed.

iv Study. The dogs used in the oral study also received an iv dose of 2 mg/kg of compound **36** and **60**. The drug was

prepared in DMSO at 2 mg/mL. Blood samples were collected at 0, 5, 15, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min. Plasma was obtained by immediate centrifugation and kept frozen (–20 °C) until assayed.

Pharmacokinetic analysis. Total plasma clearance of compound **36** and **60** was calculated as the dose divided by the total area under plasma concentration–time curve from zero to infinity ($[AUC]_0^\infty$). The apparent half-life was estimated from the slope of the terminal phase fitted to the log plasma concentration–time data by the method of least squares. The apparent volume of distribution (V_{dss}) of the drug was determined by the following equation:

$$V_{dss} = \frac{\text{Dose iv} \times \text{AUMC}_0^\infty}{(\text{AUC}_0^\infty)^2}$$

where AUM_0^∞ is the total area under the first moment of the drug concentration curve from zero to infinity.

Bioavailability was estimated by comparing the AUCs following oral and intravenous administration as follows:

$$\text{Bioavailability}(\%) = \frac{(\text{AUC}_0^\infty)\text{po}}{(\text{AUC}_0^\infty)\text{iv}} \times \frac{\text{Dose iv}}{\text{Dose po}}) \times 100$$

Plasma protein binding

Binding of compounds **36**, **44**, **40** and **60** to human plasma was determined by an ultrafiltration method. Compound was added to plasma to yield a final concentration range of 0.5 to 10 μg/mL. The drug solution was added in a volume equal to or less than 1 % of the plasma volume. Following incubation of plasma samples at 37 °C for 5 min, 0.8 mL of plasma was immediately transferred to a centrifree tube (Amicon, Co., Danvers, MA). The tube was then centrifuged at 1500 *g* for 15 min at 37 °C. The unbound fraction of the drug was estimated directly from the ratio of drug concentration in the ultrafiltrate to the total drug concentration in the original plasma samples before centrifugation. The drug concentration in filtrate and plasma was determined by HPLC.

Acknowledgements

The authors wish to thank Mr Matt M. Zrada for determining solubilities, Mr S. R. Michelson and Dr William C. Lumma for log P determinations, Dr H. Ramjit and Mr A. Coddington for running FAB mass spectra, and Ms. Jean Kaysen for manuscript preparation.

References and Notes:

1. *Morbidity and Mortality Weekly Report* **1991**, *40*, 357.

2. For recent reviews: (a) Tang, J.; Lin, Y.; Co, E.; Hartsuck, J. A.; Lin, X. *Scand. J. Clin. Lab. Invest.* **1992**, *52* (Suppl. 52), 127; (b) Huff, J. R. *J. Med. Chem.* **1991**, *34*, 2305; (c) Tomasselli, A. G.; Howe, W. J.; Sawyer, T. K.; Wlodawer, A.; Heinriksot, R. L. *Chimicaoggi* **1991**, 6.

3. (a) Hellen, C. U. T.; Wimmer, E. *Experientia* **1992**, *48*, 201; (b) Ross, E. K.; Fuerst, T. R.; Orenstein, J. M.; O'Neill, T.; Martin, M. A.; Venkatesan, S. *Aids Research and Human Retroviruses* **1991**, *7*, 475 and references therein.

4. (a) Navia, M. A.; Fitzgerald, P. M. D.; McKeever, B. M.; Leu, C.-T.; Heimbach, J. C.; Herber, W. K.; Sigal, I. S.; Darke, P. L.; Springer, J. P. *Nature* (Lond.) **1989**, *337*, 615; (b) Wlodawer, A.; Miller, M.; Jaskolski, M.; Sathyanarayana, B. K.; Baldwin, E.; Weber, I. T.; Selk, L. M.; Clawson, L.; Schneider, L.; Kent, S. B. H. *Science* **1989**, *245*, 616; (c) Labatto, R.; Blundell, T.; Hemmings, A.; Overington, J.; Wilderspin, A.; Wood, S.; Merson, J. R.; Whittle, D. J.; Banley, D. E.; Geophegan, K. F.; Hawrylik, S. J.; Lee, S. E.; Scheld, K. G.; Hobart, D. M. *Nature* (Lond.) **1989**, *342*, 299.

5. Kohl, N. E.; Emini, E. A.; Schleif, W. A.; Davis, L. J.; Heimbach, J. C.; Dixon, R. A. F.; Scolnick, E. M.; Sigal, I. S. *Proc. Natl Acad. Sci. U.S.A.* **1988**, *85*, 4686.

6. (a) Vacca, J. P.; Guare, J. P.; deSolms, S. J.; Sanders, W. M.; Giuliani, E. A.; Young, S. D.; Darke, P. L.; Zugay, J. A.; Sigal, I. S.; Schleif, W. A.; Quintero, J. C.; Emini, E. A.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1991**, *34*, 1225; (b) Young, S. D.; Payne, L. S.; Thompson, W. J.; Gaffin, N.; Lyle, T. A.; Britcher, S. F.; Graham, S. L.; Schultz, T. A.; Deana, A. A.; Darke, P. L.; Zugay, J. A.; Sigal, I. S.; Schleif, W. A.; Quintero, J. C.; Emini, E. A.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1992**, *35*, 1702; (c). deSolms, S. J.; Giuliani, E. A.; Guare, J. P.; Vacca, J. P.; Sanders, W. M.; Graham, S. L.; Wiggins, J. M.; Darke, P. L.; Zugay, J. A.; Sigal, I. S.; Schleif, W. A.; Quintero, J. C.; Emini, E. A.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1991**, *34*, 2852; (d) Humber, D. C.; Cammack, N.; Coates, J. A. V.; Cobley, K. N.; Orr, D. C.; Storer, R.; Weingarten, G. G.; Weir, M. P. *J. Med. Chem.* **1992**, *35*, 3080; (e) Dreyer, G. B.; Metcalf, B. W.; Tomaszek, Jr T. A. Carr, T. J.; Chandler, A. C.; Hyland, L.; Fakhoury, S. A.; Magnard, V. W.; Moore, M. L.; Strickler, J. E.; Debouck, C.; Meek, T. D. *Proc. Natl Acad. Sci. U.S.A.* **1989**, *86*, 9752; (f). Roberts, N. A.; Martin, J. A.; Kinchington, D.; Broadhurst, A. U.; Craig, J. C.; Duncan, I. B.; Galpin, S. A.; Handa, B. K.; Kay, J.; Krohn, A.; Lambert, R. W.; Merrett, J. H.; Mills, J. S.; Parkes, K. E. B.; Redshaw, S.; Ritchie, A. J.; Taylor, D. L.; Thomas, G. J.; Machin, P. J. *Science* **1990**, *248*, 358; (g) Getman, D. P.; DeCrescenzo, G. A.; Heintz, R. M.; Reed, K. L.; Talley, J. J.; Bryant, M. L.; Clare, M.; Houseman, K. A.; Marr, J. J.; Mueller, R. A.; Vazquez, M. L.; Shieh, H.-S.; Stallings, W. C.; Stegeman, R. A. *J. Med. Chem.* **1993**, *36*, 288.

7. (a) Kempf, D. J.; Norbeck, D. W.; Codacovi, L. M.; Wang, X. C.; Kohlbrenner, W. E.; Wideburg, N. E.; Paul, D. A.; Knigge, M. F.; Vasavanonda, S.; Craig-Kennard, A.; Saldivar, A.; Rossenbrook, Jr W.; Clement, J. J.; Plattner, J. J.; Erickson, J. *J. Med. Chem.* **1990**, *33*, 2687; (b) Erickson, J.; Neidhart, D. J.; Van Drie, J.; Kempf, D. J.; Wang, X. C.; Norbeck, D. W.; Plattner, J. J.; Rittenhouse, J. W.; Turan, M.; Wideburg, N. E.; Kohlbrenner, W. E.; Simmer, R.; Helfrich, R.; Paul, D. A.; Knigge, M. F. *Science* **1990**, *249*, 527; (c) Kempf, D. J.; Codacovi, L.; Wang, X. C.; Kohlbrenner, W. E.; Wideburg, N. E.; Saldivar, A.; Vasavanonda, S.; Marsh, K. C.; Bryant, P.; Sham, H. L.; Green, B. E.; Betebenner, D. A.; Erickson, J.; Norbeck, D. W. *J. Med. Chem.* **1993**, *36*, 320; (d) Babine, R. E.; Zhang, N.; Jurgens, A. R.; Schow, S. R.; Desai, P.R.; James, J. C.; Semmelhack, M. F. *BioMed. Chem. Lett.* **1992**, *2*, 541; (e) Bone, R.; Vacca, J. P.; Anderson, P. S.; Holloway, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 9382; (f) Wlodawer, A.; Erickson, J. W. *Ann. Rev. Biochem.* **1993**, *62*, 643.

8. Lyle, T. A.; Wiscount, C. M.; Guare, J. P.; Thompson, W. J.; Anderson, P. S; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif,

W. A.; Quintero, J. C.; Dixon, R. A. F.; Sigal, I. S.; Huff, J. R. *J. Med. Chem.* **1991**, *34*, 1228.

9. Lyle, T. A. unpublished results.

10. The Abbott group has recently reported encouraging results from their renin program: (a) Kleinert, H. D.; Rosenberg, S. H.; Baker, W. R.; Stein, H. H.; Klinghofer, V.; Barlow, J.; Spina, K.; Polakowski, J.; Kovar, P.; Cohen, J.; Dennisen, J. *Science* **1992**, *257*, 11490; (b) Rosenberg, S. H.; Spina, K.; Woods, K. W.; Polakowski, J.; Yao, Z.; Kovar, P.; Stein, H. H.; Cohen, J.; Barlow, J. L.; Egan, D. A.; Tricarico, K. A.; Baker, W. R.; Kleinert, H. D. *J. Med. Chem.* **1993**, *36*, 449; (c) Rosenberg, S. H.; Spina, K.; Condon, S. L.; Polakowski, J.; Martin, D. L.; Yao, Z.; Stein, H. H.; Cohen, J.; Barlow, J. L.; Klinghofer, V.; Egan, D. A.; Tricarico, K. A.; Perun, T. J.; Baker, W. R.; Kleinert, H. D. *J. Med. Chem.* **1993**, *36*, 460.

11. Thompson, W. J.; Fitzgerald, P. M. D.; Holloway, M. K.; Emini, E. A.; Darke, P. L.; McKeever, B. M.; Schleif, W. A.; Quintero, J. C.; Zugay, J. A.; Tucker, T. T.; Schwering, J. S.; Homnick, C. F.; Springer, J. P.; Huff, J. R. *J. Med. Chem.* **1992**, *35*, 1685.

12. Vacca, J. P.; Fitzgerald, P. M. D.; Holloway, M. K.; Hungate, R. W.; Starbuck, K. E.; Chen, L. J.; Darke, P. L.; Anderson, P. S.; Huff. J. R. *BioMed. Chem. Lett.* **1994**, *4*, 499.

13. (a) Goodman, L. S.; Gilman, A. G.; Gilman, A. In *The Pharmacological Basis of Therapeutics*, pp. 1–40, Mayer, S. E.; Melmon, K. L., Eds; MacMillan Inc.; New York, 1980; (b) Fichtl, B.; v. Nieciecki, A.; Walter, K. In *Advances in Drug Research, Tissue Binding versus Plasma Binding: General Principles and Pharmacokinetic Consequences*, Vol. 20, pp. 118–166, Testa, B., Ed.; Academic Press; New York 1991.

14. Decamp, A. E.; Kawaguchi, A. T.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1991**, *32*, 1867.

15. Zydowsky, T. M.; Dellaria, Jr J. F.; Nellans, H. N. *J. Org. Chem.* **1988**, *53*, 5607.

16. McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Oh, T. *J. Am. Chem. Soc.* **1986**, *108*, 4943.

17. Hungate, R. W.; Chen, J. L.; Starbuck, K. E. *Tetrahedron Lett.* **1991**, *32*, 6851.

18. (a) Cragoe, E. J.; Woltersdorf, O. W.; Bicking, J. B.; Kwong, S. F.; Jones, J. H. *J. Med. Chem.* **1967**, *10*, 66; (b) Jones, J. H.; Holtz, W. H.; Cragoe, E. J. *J. Med. Chem.* **1969**, *12*, 285.

19. Ghosh, A. K.; Thompson, W. J.; Holloway, M. K.; McKee, S. P.; Duong, T. T.; Lee, H. Y.; Munson, P. M.; Smith, A. M.; Wai, J. M.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 2300.

20. For related examples see: (a) Seydel, J. K.; Schaper, K.; Wempe, E.; Cordes, H. P. *J. Med. Chem.* **1976**, *19*, 483; (b) Campbell, A. D.; Chan, E.; Choi, S. Y.; Deady, L. W.: Shanks, R. A. *Aust. J. Chem.* **1971**, *24*, 377.

21. Heinbach, J. C.; Garsky, V. M.; Michelson, S. R.; Dixon, R. A. F.; Sigal, I. S.; Darke, P. L. *Biochem. Biophys. Res. Commun.* **1989**, *164*, 955.

22. Entries 1 through 5 represent the more potent carbamates that were prepared. A number of simple amides structurally related to the *t*-butyl urethane were also made, but showed a significant loss in activity compared to the Boc group.

23. Ghosh, A. K.; Thompson, W. J.; McKee, S. P.; Duong, T. T.; Lyle, T. A.; Chen, L. J.; Darke, P. L.; Zugay, J. A.; Schleif, W. A.; Emini, E. A.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1993**, *36*, 292.

24. % Bioavailability was calculated from $\frac{\text{AUC oral}}{\text{AUC iv}} \times \frac{\text{Dose iv}}{\text{Dose po}}$ over the period of 0–8 h as described in the Experimental Section.

25. In a separate series of experiments in cannulated rats, the compounds are well absorbed in this species despite the relatively large size of the inhibitors, but are metabolized after a short period of time (unpublished results from J. H. Lin).

26. Williams, P. D.; Perlow, D. S.; Payne, L. S.; Holloway, M. K.; Siegel, P. K. S.; Schorn, T. W.; Lynch, R. J.; Doyle, J. J.; Strouse, J. F.; Vlasuk, G. P.; Hoogsteen, K.; Springer, J. P.; Bush, B. L.; Halgren, T. A.; Richards, A. D.; Kay, J.; Veber, D. F. *J. Med. Chem.* **1991**, *34*, 887.

27. Haby, J. E.; Young, A. M. *J. Liquid Chromatogr.* **1984**, *7*, 675.

(*Received* 31 *May* 1994)