Inhibition of Human Neutrophil Elastase with Peptidyl Electrophilic Ketones.[†] 2. Orally Active P_G-Val-Pro-Val Pentafluoroethyl Ketones

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Valylprolylvalyl pentafluoroethyl ketones with different N-protecting groups were evaluated *in vitro* and *in vivo* as inhibitors of human neutrophil elastase (HNE). Several of these compounds were found to be orally active in HNE-induced rat and hamster lung hemorrhage models. The compound with 4-(4-morpholinylcarbonyl)benzoyl as the protecting group, **7l** (MDL 101,146), was studied in greater detail. Hydration and epimerization studies were performed on **7l** and related compounds in various media, including human blood serum. High-performance liquid chromatography studies on a reversed-phase system as a measure of the lipophilicity of **7l** and related compounds revealed a small range of relative retention times wherein the orally active compounds fell. The K_i value determined for **7l** vs HNE was 25 nM.

Introduction

The inhibition of human neutrophil elastase (HNE) (EC 3.4.21.37) is an attractive therapeutic target since this enzyme is implicated in tissue destruction in several disease states. The glycosylated, basic serine proteinase, which is found in human polymorphonuclear leukocytes (PMN), is released by inflammatory stimuli and is thought to contribute to the pathogenesis of emphysema,[1] rheumatoid arthritis,[2] chronic bronchitis,[3] cystic fibrosis,[4] adult respiratory distress syndrome,[5] and glomerulonephritis.[6] Thus, there exists a number of therapeutic areas that would benefit from the development of HNE inhibitors.

Our research has focused on tetrapeptide[7,8] and tripeptide[9a,10,11] recognition sequences for elastase inhibition and has used α-diketone,[9a,12,13] α-keto ester,[7,9a,12–14] and trifluoromethyl ketone[7] electrophilic functionalities at the scissile bond carbonyl site for interaction with the catalytic center Ser195 hydroxyl group.[9b] The important features of the tripeptide inhibitors are categorized into five components as shown in Figure 1. Recently, we[10,11] and others[15–17] have described the use of pentafluoroethyl ketones as proteinase inhibitors. Our synthetic approach to pentafluoroethyl ketones employs the versatile Weinreb amides which are treated with *in situ* generated pentafluoroethyl lithium, which makes them very accessible. Moreover, we have found another striking advantage of the pentafluoroethyl ketone activator. *When attached as part of the tripeptide recognition sequence, in combination with certain N-protecting groups, the pentafluoroethyl ketone moiety confers oral bioavailability to the elastase inhibitor.* This report describes the preparation of a series of orally active elastase inhibitors, their inhibition constants for HNE, and the investigation of physical parameters which may contribute to their oral bioavailability.

P$_G$ P$_3$ P$_2$ P$_1$ A$_G$
N-protecting group — recognition sequence — carbonyl activating group

Figure 1. General structure of tripeptidyl elastase inhibitors (P_G-P_3-P_2-P_1-A_G).

Chemistry

Boc-L-valine (**1**) and *N,O*-dimethylhydroxylamine hydrochloride were coupled using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) in the presence of 4-(dimethylamino)pyridine (DMAP) to generate Weinreb amide **2**[18,19] as shown in Scheme 1. Reaction of pentafluoroethyl lithium[20] with **2** gave pentafluoroethyl ketone **3**.[10] Removal of the protecting group with hydrogen chloride in ethyl acetate gave the amine hydrochloride **4**, which was coupled to Boc-Val-Pro-OH using the mixed anhydride method to give protected tripeptide pentafluoroethyl ketone **5**. Deprotection using hydrogen chloride in ethyl acetate gave the amine hydrochloride salt **6**.

The syntheses of the pentafluoroethyl ketone elastase inhibitors are summarized in Table 1. Compounds were prepared by one of the following four methods from HCl·H-Val-Pro-Val-CF_2CF_3 (**6**): method A, isobutyl chloroformate (IBCF) coupling of **6** with a carboxylic acid in methylene chloride in the presence of *N*-methylmorpholine (NMM); method B, acylation of **6** with an acid chloride generated from a carboxylic acid and oxalyl chloride in dimethylformamide (DMF) and methylene chloride; method C, acylation of **6** with an acid chloride generated from a carboxylic acid and thionyl chloride in dichloroethane in the presence of benzyltriethylammonium chloride; and method D, acylation of **6** with a commercially available acid chloride. Exceptions were compounds **7j,r** whose syntheses are presented in Scheme 2. Thus, *tert*-butyl ester **7k** was converted to **7j** with hydrogen chloride in ethyl acetate. The acid chloride of **7j** was prepared with oxalyl chloride and used to acylate 4-[2-(methylamino)ethyl]morpholine to give **7r**.

[†] For part 1 in this series, see ref 7.
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Scheme 1

Table 1. Preparation of Tripeptidyl Pentafluoroethyl Ketones

Methods
A. RCO_2H/IBCF/NMM;
B. $RCO_2H/(COCl)_2/DMF/CH_2Cl_2$
C. $RCO_2H/SOCl_2/BnEt_3NCl/ClCH_2CH_2Cl$; OR
D. commercially available RCOCl

HCl-H-Val-Pro-Val-CF_2CF_3 → R-C(O)-Val-Pro-Val-C_2F_5

Cpd No.	R	Method	Yield(%)	Cpd No.	R	Method	Yield(%)
7a	$(H_3C)_2N$–	D	48	7j	HO_2C–C6H4–	–[a]	–
7b	O(CH2CH2)2N–	D	63	7k	t-BuO_2C–C6H4–	A	55
7c	O(CH2CH2)2CH–	B	79	7l	O(CH2CH2)2NC(O)–C6H4–	C	86
7d	2-furyl	D	95	7m	O(CH2CH2)2NC(O)–pyridyl–	C	70
7e	HCl·O(CH2CH2)2NCH2–	B	96	7n	O(CH2CH2)2NS(O)2–C6H4–	C	50
7f	O(CH2CH2)2NC(O)CH2–	B	75	7p	O(CH2CH2)2NC(O)NH–C6H4–	B	82
7g	O(CH2CH2)2NC(O)CH(CH(CH3)2)–	A	63	7q	Cl–C6H4–S(O)2NHC(O)–C6H4–	B	51
7h	pyridyl–CH2CH2–	A	74	7r	O(CH2CH2)2NCH2CH2CH(CH3)C(O)–C6H4–	–[a]	–
7i	C6H5–	D	87	7s	O(CH2CH2)2NC(O)N(CH2CH2)2NC(O)–C6H4–	B	74

[a] Prepared as described in Scheme 4.

Preparation of the protecting groups required for the synthesis of compounds **7c,e–g,l,m,p,s** (Table 1) is shown in Schemes 3–8. Tetrahydropyran-4-one (**8**) was treated with (methoxymethylene)triphenylphosphorane to give enol ether **9**,[21] which was hydrolyzed and treated with Jones reagent to give 4-carboxytetrahydropyran **10** (Scheme 3), which was used to prepare **7c**. Alkylation of morpholine (**11**) with *tert*-butyl bromoacetate, as shown in Scheme 4, gave amino ester **12**, which was treated with trifluoroacetic acid to give amino acid **13**, which was used to prepare **7e**. Also shown in Scheme 4 are the preparations of carboxy amides **15** and **17**, used in the syntheses of compounds **7f,g**, respectively. Acylation of morpholine (**11**) with methyl malonyl chloride gave ester **14**, which was hydrolyzed with lithium hydroxide in aqueous methanol to give **15**.

Scheme 2

RO—C(=O)—C6H4—C(=O)—Val-Pro-Val—CF_2CF_3 (7k R = $C(CH_3)_3$; HCl(g)/EtOAc → 7j R = H) —(1) $(COCl)_2$/DMF/CH_2Cl_2; (2) morpholine-$NCH_2CH_2NHCH_3$→ morpholine-$NCH_2CH_2N(CH_3)$—C(=O)—C6H4—C(=O)—Val-Pro-Val—CF_2CF_3

7r

Scheme 3

8 (tetrahydropyran-4-one) —$(Ph)_3P{=}CHOCH_3$→ 9 (=$CHOCH_3$) —(1) HCl/H_2O acetone; (2) Jones oxdn→ 10 (tetrahydropyran-4-carboxylic acid, COOH)

Alkylation of ester **14** with isopropyl iodide gave ester **16** which was hydrolyzed in the same manner as **14** to give **17**.

In Scheme 5 is shown the preparation of 4-(4-morpholinylcarbonyl)benzoic acid (**20**) from terephthalic acid monomethyl ester (**18**). The acid chloride of **18** was prepared using oxalyl chloride and treated with morpholine to give ester **19**. Hydrolysis of **19** with lithium hydroxide in aqueous methanol gave **20**, which was used in the preparation of **7l**. The pyridine analog of **20** (**24**) was prepared as shown in Scheme 6. 2-Carbomethoxypyridine-5-carboxylic acid (**21**)[22] was treated with 2-*tert*-butyl-1,3-dicyclohexylisourea[23] to afford the differentiated diester **22**. Treatment of **22** with morpholine cleanly gave amide **23** which was then converted to **24** with hydrogen chloride in nitromethane. Acid **24** was used in the preparation of **7m**.

4-Carboethoxyphenyl isocyanate (**25**) was treated with morpholine to give amide **26**, which was hydrolyzed with lithium hydroxide in aqueous ethanol to provide **27** (Scheme 7). Acid **27** was used to prepare **7p**.

4-Morpholinecarbonyl chloride (**28**) was treated with *tert*-butyl carbamate **29** to afford urea **30** as shown in Scheme 8. Removal of the amine protecting group with trifluoroacetic acid gave amine salt **31**, which was treated with the acid chloride of **18** in the presence of *N*-methylmorpholine to give **32**. Hydrolysis of ester **32** with lithium hydroxide in aqueous ethanol gave acid **33**, which was used in the preparation of **7s**.

Preparation of the three tripeptidyl trifluoromethyl ketones which were used for comparison in oral studies with the corresponding pentafluoroethyl ketones is shown in Scheme 9. 1,1,1-Trifluoro-3-amino-4-methyl-2-pentanol hydrochloride (**34**) was coupled to Boc-Val-Pro-OH using the mixed anhydride method to give trifluoromethyl alcohol **35**, which was oxidized using the Swern procedure[24] to give trifluoromethyl ketone **36**. Removal of the protecting group with hydrogen chloride in ethyl acetate gave the amine hydrochloride **37** which was used to make the N-protected tripeptidyl trifluoromethyl ketones **38–40**.[25] Thus, treatment of **37** with 4-(4-morpholinylcarbonyl)benzoyl chloride gave **38**; treatment of **37** with 4-morpholinecarbonyl chloride gave **39**; and treatment of **37** with 4-[[[(4-chlorophenyl)sulfonyl]amino]carbonyl]benzoyl chloride gave **40**.

Pharmacological Evaluation

The ability of compounds to inhibit HNE-induced pulmonary hemorrhage when administered orally was examined in rats or hamsters. The screening protocol for rats involved oral (po) administration of test compound 45 min prior to intratracheal (it) instillation of 100 μg of HNE and determination of the lung hemorrhage in the bronchoaveolar (BAL) lavage fluid after 1 h.[26] The screening protocol for hamsters involved oral administration of test compound 30 min prior to it instillation of 10 or 20 μg of HNE and determination of the lung hemorrhage after 1 h. The amount of pulmonary hemorrhage was determined by lavaging the lungs with saline, and the amount of hemoglobin (Hgb) in the BAL was calculated by comparison to a Hgb standard curve at a spectrophotometric range of 536–546 nm using standard clinical lab procedures.[27] Statistical evaluation included a one-way analysis of variance (ANOVA) followed by a Dunnett's multiple comparison test to evaluate if compound-treated groups were different from vehicle-treated groups ($p \leq 0.05$ was the criterion for statistical significance).

High-Performance Liquid Chromatographic (HPLC) Studies. The HPLC system used was a Waters 600E HPLC equipped with a Waters WISP 712

Scheme 4

11 (morpholine, NH) —$BrCH_2CO_2C(CH_3)_3$, THF→ 12 (morpholine-NCH_2—C(=O)—$OC(CH_3)_3$) —CF_3CO_2H→ 13 (morpholine-NCH_2—C(=O)—OH•CF_3CO_2H)

11 —$CH_3O_2CCH_2COCl$, CH_2Cl_2→ 14 (morpholine-N—C(=O)—CH_2—C(=O)—OCH_3) —LiOH, CH_3OH/H_2O→ 15 (morpholine-N—C(=O)—CH_2—C(=O)—OH)

14 —(1) NaH/THF; (2) $(CH_3)_2CHI$→ 16 (morpholine-N—C(=O)—CH($CH(CH_3)_3$)—C(=O)—OCH_3) —LiOH, CH_3OH/H_2O→ 17 (morpholine-N—C(=O)—CH($CH(CH_3)_3$)—C(=O)—OH)

Scheme 5

HO–C(=O)–C6H4–C(=O)–OCH3 (18) → (1) (COCl)2, DMF/CH2Cl2; (2) morpholine → morpholine–C(=O)–C6H4–C(=O)–OR; LiOH, CH3OH/H2O: 19 R = CH3 → 20 R = H

Scheme 6

H3CO–C(=O)–pyridine–C(=O)–OH (21) → CH2Cl2 → H3CO–C(=O)–pyridine–C(=O)–OC(CH3)3 (22) → morpholine, THF → morpholine–C(=O)–pyridine–C(=O)–OR; HCl(g), CH3NO2: 23 R = C(CH3)3 → 24 R = H

Scheme 7

OCN–C6H4–C(=O)–OCH2CH3 (25) → morpholine, toluene → morpholine–C(=O)–NH–C6H4–C(=O)–OR; LiOH, CH3CH2OH/H2O: 26 R = CH2CH3 → 27 R = H

autosampler and an Applied Biosystems 757 absorbance detector (240 nm). Data were acquired and analyzed by a computer automated laboratory system (CALS) supplied by Beckman. Isolation of the individual diasteromers of **71** was performed on a Waters μPorasil column (300 × 7.8 mm) with a mobile phase of hexane/2-propanol (55/45) and a flow rate of 3 mL/min. The retention time comparison of **71** and related compounds was performed on a Zorbax R_x column (150 × 4.6 mm) with a mobile phase of acetonitrile/water (55/45) and a flow rate of 1 mL/min. Relative retention times for all inhibitors were expressed relative to **71**, whose retention time was designated as 1.00.

^{19}F NMR Ketone/Hydrate and Epimerization Studies. ^{19}F NMR spectra were obtained using Varian VXR 300, Unity 300, and Unity 400 NMR spectrometers. Chemical shifts are reported versus external $CFCl_3$. All spectra were obtained at 25 °C except as noted. Typically, 0.5–2 mg of sample was dissolved in the appropriate deuterated solvent, and an initial spectrum was immediately obtained. Additional spectra were obtained at later time points, and any changes were noted. The buffered saline was purchased from Sigma Diagnostics (St. Louis, MO; Cat. No. 1000-3) and prepared as per label except that D_2O was used instead of H_2O. The nominal concentrations of the resulting solution were 120 mM NaCl, and 10 mM phosphate buffer (pH = 7.4). The methanol experiments were run with nondeuterated methanol and water. For the methanol, blood serum, and blood plasma experiments, a sealed D_2O capillary tube was inserted into the 5 mm NMR tube for "lock". The blood samples were obtained from four associates (three male, one female) by the Toxicology Department and used fresh. Two surfactants, obtained from BioRad Laboratories (Richmond, CA), were used to mimic possible surface interactions which can occur with proteins or other macromolecules in blood. Surfactants examined were BigCHAP, which has a hydrophobic bile acid skeleton with a glucamide head group [critical micellization concentration (CMC) is 3.4 nM], and Tween 20 (CMC = 0.06 mM), a poly(oxyethylene)-based surfactant. Samples were prepared in buffered saline with added surfactants at the concentrations reported.

Results and Discussion

Most of the compounds in Table 2 displayed K_i values in the low nanomolar range, with the exception of the tripeptide hydrochloride salt **6**, suggesting that differential binding of the inhibitors to the enzyme is a function of the N-protecting group. We assume that differences in affinity are due to interaction of the protecting group with the outer surface of the enzyme, on the basis of the crystal structure of the enzyme which was cocrystallized with a related inhibitor.[28] The decrease in enzyme affinity for ureas **7a,b** may stem from changes in the binding energy between the enzyme and the protecting group (P_G) carbonyl, due to electronic differences of the urea functionality relative to the amide functionality.

The double-reciprocal plot for the inhibition of HNE by **71**, which is a mixture of two diastereomers epimeric at the P_1 valine, illustrates that the compound is a competitive inhibitor of the enzyme. The K_i value obtained from the plot is 25 nM (2.5×10^{-8} M). No time dependence due to "slow-binding" or mechanism-based inactivation was observed (e.g., the binding equilibrium was rapidly established within the assay time course), indicating that the compound is a reversible inhibitor.

The K_i values for the individual diastereomers of **71** were as follows: MDL 103,139 (the L-L-D diastereomer), 74 nM; and MDL 103,542 (the L-L-L diastereomer), 17 nM. Thus, there is a modest stereochemical preference by the enzyme for the L-L-L diastereomer. Apparently, the catalytic center is flexible enough to accommodate recognition units of both L and D stereochemistries at P_1.

Table 3 shows the results of a specificity study of proteinase inhibition by **71**. One of each known class of proteinases was chosen. Cathepsin B is a cysteine proteinase, enkephalinase is a zinc metalloproteinase, cathepsin G is a serine proteinase with a preference for a bulky hydrophobic residue at P_1, thrombin is a serine proteinase with a preference for a basic residue at P_1, and pepsin is an aspartic proteinase. Cathepsin G was marginally inhibited (15%) at a 0.5 mM concentration of **71**, and pepsin was 40% inhibited at 0.2 mM **71**. Therefore, **71** is a specific inhibitor of human neutrophil elastase, as shown by this limited study. This specificity is expected, given the structure of the inhibitor (the peptide recognition sequence) and the probable mecha-

Scheme 8

Scheme 9

nism of inhibition, which involves covalent 1,2-addition of the active site serine hydroxyl group across the activated carbonyl group.[28]

The *in vivo* activity of the inhibitors was evaluated using rodent models of HNE-induced lung damage[29-31] as shown in Table 2. Lung damage was assessed by measuring the amount of hemoglobin in the BAL of rodents 1 h after they recieved an it instillation of HNE. The majority of the compounds were evaluated by administration of a single oral dose at a number of time points prior to the instillation of HNE, and the percent inhibition was calculated by comparing the hemorrhage in the compound-treated group with the positive control vehicle-treated group. Compounds **7b**,**l** have been examined in detail for their bioavailability and other pharmacokinetic properties and will be the subject of a separate publication. The data presented in Table 2 are shown for a single time point for simplicity (the other time points tested are included in the supplementary material). The compounds shown in Table 2 were designated as orally active when the value for percent inhibition of rat or hamster lung hemorrhage was statistically significant, as determined by an ANOVA followed by a Dunnett's multiple comparison test.

Compounds **7l**,**b** demonstrated comparable *in vivo* activity in the HNE-induced hemorrhage models. Compound **7l** was chosen for additional studies because its lower K_i value made it potentially more versatile for administration by a number of different routes and its duration of action was longer (supplementary material, Table 1). Compound **7l** has been shown to be a potent inhibitor of HNE-induced hemorrhage when administered it and iv.[31] Oral (po) administration of **7l** to rats at 50 mg/kg, 45 min before it instillation of HNE,

Table 2. *In Vitro* and *in Vivo* HNE Inhibitory Activity of Selected RCO-Val-Pro-Val-CF_2CF_3 Derivatives

		hemorrhage activity[a]			
		rat lung		hamster lung	
compd no.	K_i (nM)[b]	dose (mg/kg)	% inhibitn (n)[c]	dose (mg/kg)	% inhibitn (n)[c]
6	1200	NT		NT	
7a	261	50	70 ± 12* (6)	NT	
7b	170	50	69 ± 20* (7)	25	69 ± 6* (8)
7c	59	50	71 ± 10* (7)	NT	
7d	190	45	44 ± 13 (6)	NT	
7e	60	50	77 ± 6* (6)	NT	
7f	70	25	41 ± 16 (5)	NT	
7g	44	NT		25	70 ± 6* (7)
7h	29	NT		25	67 ± 6* (19)
7i	70	NT		NT	
7j	39	NT		25	−3 ± 16 (6)
7k	21	NT		NT	
7l	25	50	69 ± 6* (10)	25	74 ± 7* (14)
7m	28	NT		25	61 ± 19* (7)[d]
7n	2	NT		25	30 ± 22 (7)
7p	43	50	26 ± 18 (6)	NT	
7q	7	100	−30 ± 22 (6)	NT	
7r	19	NT		25	17 ± 15 (6)
7s	24	NT		25	31 ± 9 (7)

[a] See Pharmacological Evaluation section for methodology. The compounds were administered at the given dose (po) 45 min for rats or 30 min for hamsters prior to administration of HNE it (100 μg in rats and 20 μg in hamsters except 10 μg for **7b,l**). [b] The K_i value for **7l** was determined from a double-reciprocal plot, and the other values were determined using the abbreviated method. [c] Percent inhibition of lung hemorrhage is presented as the mean ± SEM of BAL Hgb from 5 to 10 rats and 6 to 19 hamsters (*, $p \leq 0.05$ is the criterion for statistical significance). [d] Given 15 min prior to administration of HNE it. NT = not tested.

Table 3. Inhibition of Proteinases by **7l** at 0.5 mM Concentration[a]

enzyme	% inhibition
human neutrophil cathepsin G	15
bovine thrombin	<5
rat kidney enkephalinase	<5
bovine liver cathepsin B	<5
pepsin	40[b]

[a] This concentration is 2×10^4 times greater than its K_i value for HNE. [b] At 0.2 mM concentration of **7l**.

inhibited lung hemorrhage by 69%. In hamsters, when **7l** was administered po at 25 mg/kg, HNE-induced pulmonary hemorrhage was inhibited by 74%.

Oral activity of the pentafluoroethyl ketones in Table 2 is an interesting contrast to closely related compounds which do not display oral activity. In Table 4 are shown three pairs of homologous trifluoromethyl ketone and pentafluoroethyl ketone elastase inhibitors. The K_i values for the three pairs of homologous trifluoromethyl ketone and pentafluoroethyl ketone inhibitors are quite similar. However, we feel that the striking differences in the oral activities in the first two sets of compounds are largely due to the structurally subtle but intrinsically different properties of the trifluoromethyl and pentafluoroethyl ketones. The combination of the pentafluoroethyl group on the C-terminus and the 4-morpholinylcarbonyl group on the N-terminus, which has previously been used in the design of orally active renin inhibitors,[32,33] appears to be important in imparting oral activity. Pentafluoroethyl ketones **7l,b** are orally active, whereas the corresponding trifluoromethyl ketones **38** and **39** are not. A possible explanation for this difference is the degree of hydration of the two electrophilic ketones. As shown in Figure 2, ^{19}F NMR spectra of **7b**

Table 4. Structurally Related HNE Inhibitors with and without Oral Activity

Compound	Ki (nM)	Oral Activity[a]
7l	25	active
38	12	inactive
7b	170	active
39	195	inactive
7q	7	inactive
40	3	inactive[b]

[a] A compound was considered to be orally active if, when administered 30 or 45 min before enzyme at a dose of 50 mg/kg, it affected a statistically significant inhibition of HNE-induced pulmonary hemorrhage. [b] See: Williams, J. C.; et al. *Am. Rev. Respir. Dis.* **1991**, *144*, 875–883.

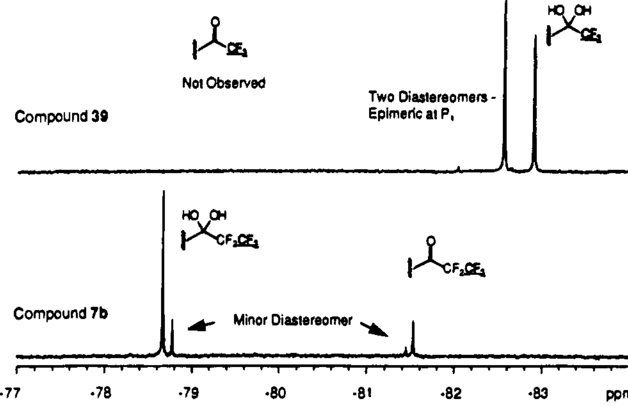

Figure 2. ^{19}F NMR spectra (CF_3 region only) of **7b** and **39** in buffered saline.

and **39** show that, in buffered saline, trifluoromethyl ketone **39** is completely hydrated whereas pentafluoromethyl ketone **7b** is only ca. 80% hydrated. These ketone/hydrated ketone ratios were a function only of the carbonyl activating group (pentafluoroethyl vs trifluoromethyl), as approximately 20% ketone was also observed for **7b,q** while no ketone was observed for the trifluoromethyl analogs **39** and **40**. The extent of ketone hydration does not relate to the ability of the inhibitor to inhibit the enzyme, since both trifluoromethyl and pentafluoroethyl ketones are potent inhibitors of HNE. It may be that only the ketone form of the fluorinated

Table 5. Effect of Solvent on Ketone/Hydrated Ketone Equilibria for **7l** and Corresponding Trifluoromethyl Ketone **38**

compd no.	substituent	solvent	temperature (°C)	% ketone[a]
7l	$-CF_2CF_3$	$CDCl_3$	25	100
38	$-CF_3$	$CDCl_3$	25	100
7l	$-CF_2CF_3$	buffered saline	25	20
38	$-CF_3$	buffered saline	25	NO[b]
7l	$-CF_2CF_3$	methanol	25	80
7l	$-CF_2CF_3$	methanol/water (80/20)	25	58
7l	$-CF_2CF_3$	blood serum	25	20
7l	$-CF_2CF_3$	blood serum	37	40
7l	$-CF_2CF_3$	BigCHAP (6 mM)	25	20
7l	$-CF_2CF_3$	BigCHAP (33 mM)	25	26
7l	$-CF_2CF_3$	Tween 20 (81 mM)	25	49
38	$-CF_3$	Tween 20 (81 mM)	25	3

[a] This measurement was performed using ^{19}F NMR. [b] NO = not observed.

ketones is readily absorbed or that the hydrated ketone is very rapidly absorbed and eliminated. The importance of the N-terminal group to oral bioavailability is evident from compounds **7q** and **40** in Table 4. Compounds **7q** and **40** are potent inhibitors of HNE *in vitro* and when administered *in vivo* by a parenteral route;[34,35] however, both of these compounds are inactive when administered orally, indicating that the ketone, by itself, is insufficient to impart oral activity.

To further study the hydration phenomenon, the amount of parent ketone and hydrated ketone present at equilibrium in a variety of media was measured for **7l** and its corresponding trifluoromethyl ketone, **38**, as shown in Table 5. These measurements were performed using ^{19}F NMR spectroscopy; fluorine signals are separated for these two species and can easily be detected, differentiated, and measured (Figure 2). In chloroform solution, both **7l** and **38** existed solely in their ketone forms. As previously mentioned, in buffered saline the ketone form of **38** was not observed whereas the ketone form of **7l** was still present to the extent of 20%. The ketone/hydrate equilibrium for **7l** was reached quickly as no differences were observed between the initial spectrum and those obtained after 24 or 48 h. As expected, the amount of water in the medium also affected the ketone percentage. In methanol, the ketone percentage of **7l** was 80, the rest being the hydrate from incipient water and the hemiketal adduct formed with methanol. In 80/20 methanol/water, the ketone percentage fell to 58. Blood serum, at 25 °C, proved to be similar to buffered saline, where 20% ketone was observed for **7l**. When the serum temperature was elevated to 37 °C, the physiological temperature for man, the percentage of ketone increased to 40, whereas only hydrated ketone was observed for an analogous trifluoromethyl ketone under these conditions (data not shown). Surfactants had a measurable enhancing effect on ketone percentage. As can be seen from Table 5, the addition of surfactants to the buffered saline solution led to increased amounts of ketone for both **7l** and **38**, suggesting that surface interactions in physiological media may play a role in determining the solution structure of these compounds.

HPLC analyses of compounds which were evaluated for oral activity were performed to see whether any relationship could be drawn between lipophilicity parameters and oral activity. Since lipophilicity correlates with cell membrane permeability, passage of compound through the gut wall into the blood stream should reflect the lipophilic character of the compound. The relationship between retention time, as determined by reversed-phase HPLC, and lipophilicity is now well-documented.[36] Table 6 lists the reversed-phase relative retention times for compounds contained in Table 1 and its respective oral activity in the hamster or rat model. An approximate window of relative retention time of ca 0.8–1.0 seemed to correlate with oral activity. Since lipophilicity is only one component of bioavailability, we believe this window represents a necessary but not sufficient condition for oral activity (see **7p,r,s**).

Table 6. Comparison of Retention Time by Reversed-Phase HPLC

compd no.	rel t_R (vs **7l**[a])	oral activity[b]
7k	6.27	NT[c]
7i	2.04	NT[c]
7n	1.97	no
7d	1.55	no
7g	1.02	yes
7l	1.00	yes
7h	0.98	yes
7p	0.98	no
7a	0.94	yes
7c	0.90	yes
7e	0.90[d]	yes
7r	0.90	no
7b	0.85	yes
7s	0.83	no
7m	0.80	no
7j	0.51	no
7q	0.45	no

[a] The absolute retention time for **7l** on this reversed-phase HPLC system was 5.2 min. HPLC conditions: Zorbax R_x column (150 × 4.6 mm), water/acetonitrile (45/55), flow = 1 mL/min. [b] A compound was considered to be orally active if it was sufficiently bioavailable at the dose administered to affect a statistically significant inhibition of HNE-induced pulmonary hemorrhage.[c] NT = not tested. [d] Value is for the corresponding free amine, which is present under the HPLC conditions.

The propensity of the pentafluoroethyl ketone inhibitors to epimerize at the chiral center α to the ketone carbonyl was noted during synthesis. Since preparation of an equilibrated mixture of diastereomers would simplify synthetic considerations and render a consistent drug entity composition, we endeavored to determine whether the epimerization was as facile in biological media as in organic solvents. We first chose to study the epimerization of the L-L-L isomer of **7l** in human serum, using ^{19}F NMR spectroscopy to watch the L-L-L isomer epimerize to a mixture of P_1 diastereomers. Indeed, the epimerization was rapid in serum samples from three different individuals, as shown in Table 7. At 37 °C, the half-life was ca. 30 min. A marked temperature effect was observed; at 25 °C, the half-life was extended to 3.6 h. Similar epimerization rates were observed for both the L-L-L- and L-L-D diastereomers of **7l** in human plasma. Similar rates were also recorded with an analog of **7l** in heat denatured serum, which indicated that the epimerization process was not enzyme-catalyzed. Interestingly, the epimerization in serum and plasma was significantly faster than in buffered saline even though the percent of ketone, and presumably enol,[37] present in both serum and buffered saline is identical (see Table 5). These differences led us to postulate that surface interactions with lipids or macromolecules in the blood samples may be contributing to the rapid epimerization observed. To mimic these potential interactions, the epimerization of the L-L-L isomer of **7l** was studied in buffered saline with

Table 7. Summary of Epimerization Data for the Diastereomers of **7l**

solvent	temperature (°C)	half-life[a]
L-L-L Diastereomer		
human blood serum 1	37	30 min
human blood serum 2	37	30 min
human blood serum 3	37	30 min
human blood serum 1	25	3.6 h
human blood plasma	37	30 min
buffered saline	25	>200 h[b]
Tween 20 (81 mM)	25	70 min
BigCHAP (33 mM)	25	c
L-L-D Diastereomer		
human blood plasma	37	30 min

[a] Half-lives were determined from ^{19}F NMR spectra. [b] Based on initial and 46 h time points. [c] Epimerization not observed after 3 h.

added surfactants. In 81 mM Tween 20 at 25 °C, epimerization with a half-life of 70 min was observed. By contrast, in 33 mM BigCHAP no epimerization was observed after 3 h. These experiments indicate that certain detergents above the CMC can interact in solution to cause epimerization of the P_1 valine, which suggests a possible explanation for the enhanced epimerization observed in human blood serum and plasma. On the basis of the rapid epimerization of the individual diastereomers of **7l** in biological media, we have chosen to develop **7l** as an equilibrated mixture of diastereomers (ca. 1:1).

Summary

Tripeptidyl pentafluoroethyl ketones with selected N-protecting groups were shown to be potent inhibitors of HNE *in vitro* and orally active *in vivo* in HNE-induced acute hemorrhagic assays in the rat and hamster. An attempt was made to correlate oral activity with reversed-phase HPLC retention times and degree of ketone hydration in this series of inhibitors. The compound selected for further investigation from this group was *N*-[4-(4-morpholinylcarbonyl)benzoyl]-L-valyl-*N*-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide (**7l**). Future reports from our laboratory will describe modifications at each amino acid center of the tripeptide portion (e.g., P_1, P_2, and P_3) of this set of inhibitors, changes in the carbonyl activating group (A_G), and the pharmacology of **7l** in detail.

General Methods and Materials

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. TLC analyses were performed with Merck DC-F254 or Analtech GHLF silica gel plates, with visualization by I_2, alkaline permanganate, or UV irradiation. Flash chromatography was performed with Merck silica gel 60 (0.040−0.063 mm). NMR spectra were recorded on Varian VXR-300, Unity 300, Unity 400, or Gemini-300 spectrometers in $CDCl_3$, unless otherwise stated. ^{1}H and ^{13}C NMR signals are reported in ppm from tetramethylsilane, ^{19}F NMR signals are reported in ppm from $CFCl_3$, and coupling constants are reported in hertz (Hz). IR spectra were recorded on a Perkin-Elmer Model 1800 or Mattson Galaxy 5020 FT-IR spectrophotometer. MS data were collected at 70 eV on a Finnigan MAT 4600, MAT TSQ-700, or VG Analytical Limited ZAB2-SE mass spectrophotometer, and computerized peak matching with perfluorokerosene as the reference was utilized for HRMS. Combustion analysis performed using a Perkin-Elmer Model 2400 elemental analyzer fell within ±0.4% of the calculated values. All reactions were run under an inert atmosphere. The organic extracts were dried over anhydrous $MgSO_4$ or Na_2SO_4 prior to solvent removal on a rotary evaporator. Starting materials and solvents were purchased from Aldrich Chemical Co. with the following exceptions: Boc-L-Val-L-Pro-OH was purchased from Bachem Bioscience Inc. and Advanced ChemTech, Boc-L-Val-OH was purchased from Sigma Chemical Co., and hydrogen chloride gas from AGA Burdox. Several lots of pentafluoroethyl iodide were purchased from Aldrich Chemical Co. and successfully used in the synthesis of **3**, but following the receipt of a substandard lot[38] (Lot #15521AF; GC purity 76%), we changed sources to Pfaltz and Bauer Chemical Co., Strem Chemical Co., or Richmond Chemical Co. The following compounds were prepared by literature methods: 3-(3-pyridyl)propanoic acid,[39] 4-[2-(methylamino)ethyl]morpholine,[40] hydrogen *tert*-butyl phthalate,[41] 4-(4-morpholinylsulfonyl)-benzoic acid,[42] 4-[[[(4-chlorophenyl)sulfonyl]amino]carbonyl]-benzoic acid,[25] 2-carbomethoxypyridine-5-carboxylic acid,[22] and 2-*tert*-butyl-1,3-dicyclohexylisourea.[23]

Enzyme Inhibition. Partially purified HNE from human purulent sputum was assayed as described previously[9a] using MeO-Suc-Ala-Ala-Pro-Val-(*p*-nitroanilide) as the substrate. Compound **7l** was dissolved in dimethyl sulfoxide to make a stock solution of 5 or 10 mM. A stock solution of the substrate was also made in dimethyl sulfoxide. Portions of the inhibitor and substrate stock solutions and dimethyl sulfoxide were used in the assay such that the assay mixture contained a total of 10%, v/v, of dimethyl sulfoxide. A double-reciprocal plot of $1/v$ vs 1/[S] at four substrate and three inhibitor concentrations for **7l** (MDL 101,146), generated with the kinetics software of the Hewlett Packard HP8452A spectrophotometer, was indicative of competitive inhibition. A K_i value was also obtained from this plot. The other compounds were assumed to be competitive inhibitors and were assayed at three concentrations at a fixed substrate concentration of 0.2 mM, which was approximately equivalent to the K_m value. K_i values were calculated numerically from $v_o/v_i = 1 + ([I]/K_{i,app})$ and $K_i = K_{i,app}/[1 + ([S]/K_m)]$, where v_o is the control initial rate and v_i is the initial rate in the presence of inhibitor at concentration [I]. K_i values obtained at three inhibitor concentrations for a given inhibitor generally agreed within 10%. All inhibitors were tested at concentrations ranging from 5 to 100-fold higher than the enzyme concentration (calculated for 100% purity of the protein). No correction was made to these apparent K_i values to take into account the extent of hydration of the compounds. Since the concentration of the inhibitory species, the keto form, is about 30% of the total concentration, the reported K_i values for two compounds (**7n,q**) that were tested at the low range of concentrations may be taken as upper limits for the true K_i values. Other compounds were tested at sufficiently high concentrations that even with a reduction of the effective inhibitor concentration to 30% of the total, the inhibitor concentration would still be in large excess over the concentration of the enzyme.

(*S*)-[1-[(Methoxymethylamino)carbonyl]-2-methylpropyl]carbamic Acid, 1,1-Dimethylethyl Ester (2). To a solution of *N*-(*tert*-butoxycarbonyl)-L-valine (11.3 g, 52.2 mmol) in CH_2Cl_2 (200 mL) was added DMAP (6.37 g, 52.2 mmol), *N,O*-dimethylhydroxylamine hydrochloride (5.09 g, 52.2 mmol), NMM (5.27 g, 52.2 mmol, 5.73 mL), and EDCI (10.0 g, 52.2 mmol), and the solution was stirred at room temperature for 20 h. The solution was washed with 10% HCl (4 × 150 mL), saturated $NaHCO_3$ (3 × 150 mL), and brine (1 × 150 mL), and the solvent was removed *in vacuo* to give 12.6 g (93%) of **2**[19] as a clear, colorless oil.

(*S*)-[3,3,4,4,4-Pentafluoro-1-(1-methylethyl)-2-oxobutyl]-carbamic Acid, 1,1-Dimethylethyl Ester (3). To a −78 °C solution of **2** (10.0 g, 38.4 mmol) in Et_2O (1 L) was added condensed pentafluoroethyl iodide[38] (28.98 g, 118.29 mmol). To the mixture was added methyllithium−lithium bromide complex (78 mL, 117.0 mmol) at a rate which maintained an internal reaction temperature below −65 °C. The reaction mixture was stirred at −65 to −78 °C for 1.5 h, the cold bath removed, and stirring continued for 15 min during which time the internal temperature rose to −40 °C. The mixture was poured into H_2O (1 L), and the aqueous phase was acidified with potassium hydrogen sulfate. The aqueous phase was extracted with additional Et_2O (500 mL), and the combined

organic extracts were washed with saturated $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the crude product was loaded onto silica gel (225 g) and eluted with hexane/EtOAc (25:1) to give **3**[43,44] (10.4 g, 85%) as a white solid. ^{1}H NMR: δ 4.98 (br d, 1H, NH), 4.80 (dd , 1H, CH), 2.29 (m, 1H, β-CH), 1.44 (s, 9H, *t*-Bu), 1.07 (d, J = 6.6 Hz, 3H, CH_3), 0.85 (d, J = 6.6 Hz, 3H, CH_3). ^{13}C NMR: δ 194.89 (t, J = 27.1 Hz), 177.65, 117.84 (qt, J = 288.6, 34.1 Hz), 107.05 (tq, J = 269.5, 38.1 Hz), 80.59, 60.60, 28.97, 27.85, 19.57, 15.90. ^{19}F NMR: δ −82.3 (s, CF_3), −121.7 and −123.0 (AB quartet, J = 296 Hz, CF_2). HRMS ($C_{12}H_{19}F_5NO_3$) (MH^+): calcd, 320.1285; obsd, 320.1310.

(*S*)-4-Amino-1,1,1,2,2-pentafluoro-5-methyl-3-hexanone, Hydrochloride Salt (4). Into a stirred solution of **3** (14.2 g, 44.4 mmol) in EtOAc (300 mL) cooled in an ice−water bath was bubbled HCl gas for 7 min. Bubbling was ceased, and the reaction mixture was capped with a drying tube. After 1 h, the solution was allowed to warm to room temperature. The solution was concentrated, 300 mL of Et_2O/hexane (1:1) was added to the gelatinous residue, and the mixture was concentrated to give an off-white solid. The solid was triturated with Et_2O (300 mL), crushed, and filtered to give **4** (10.7 g, 96%) as a white solid. ^{1}H NMR: δ 9.07 (br s, 3H, NH_3), 4.73 (d, 1H, CH), 2.70−2.53 (m, 1H, CH), 1.35 (d, 3H, CH_3), 1.07 (d, 3H, CH_3). ^{19}F NMR: δ −82.16 (s, CF_3), −120.59 and −122.69 (AB quartet, J = 300 Hz, CF_2). MS (DCI/CH_4): m/z (rel intensity) 439 (dimer MH^+, 22), 220 (MH^+, 100), 200 (23), 178 (50), 72 (33). HRMS ($C_7H_{11}F_5NO$) (MH^+): calcd, 220.0761; obsd, 220.0759.

***N*-[(1,1-Dimethylethoxy)carbonyl]-L-valyl-*N*-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide (5).** To a solution of *N*-(*tert*-butoxycarbonyl)-L-valyl-L-proline (6.15 g, 19.6 mmol) and NMM (1.98 g, 19.6 mmol, 2.15 mL) in CH_2Cl_2 (300 mL) at −20 °C was added IBCF (2.67 g, 19.6 mmol, 2.54 mL) at an internal temperature of −18 °C. After stirring for 20 min, an additional equivalent of NMM (1.98 g, 19.6 mmol, 2.15 mL) was added followed by the addition of **4** (5.00 g, 19.6 mmol) in several portions at an internal temperature of −17 °C. Stirring was continued at −20 °C for 1 h. Cooling was discontinued, and upon reaching room temperature, the solution was diluted with CH_2Cl_2 (250 mL) and washed with 1 N HCl (4 × 200 mL), saturated $NaHCO_3$ (2 × 200 mL), and brine (1 × 200 mL). Solvent removal *in vacuo* gave 8.89 g of an off-white foam. Flash chromatography (10 × 25 cm silica gel column eluting with a gradient of 25−50% EtOAc in hexane) gave 8.05 g (80%; 97:3 L-L-L:L-L-D by ^{1}H NMR)[45] of **5**[43] as a white solid foam. TLC: R_f 0.56 (1:1 hexane:EtOAc). ^{1}H NMR: δ 7.57 (br d, J = 7.6 Hz, 1H, NH), 5.22 (br d, J = 9.3 Hz, 1H, NH), 4.94 (dd, J = 7.6, 4.4 Hz, 1H, CH of Val), 4.63 (dd, J = 8.1, 2.8 Hz, 1H, CH of Pro), 4.28 (dd, J = 9.3, 6.5 Hz, 1H, CH of Val), 3.81−3.69 and 3.64−3.54 (pr m, 2H, CH_2N), 2.44−1.81 (series of m, 6H, 2 × β-CH of Val, CH_2CH_2), 1.44 (s, 9H, *t*-Bu), 1.02 (d, J = 6.8 Hz, 3H, CH_3), 0.98 (d, J = 6.8 Hz, 3H, CH_3), 0.95 (d, J = 6.8 Hz, 3H, CH_3), 0.88 (d, J = 6.8 Hz, 3H, CH_3). ^{19}F NMR: δ −82.15 (s, CF_3), −121.70 and −122.70 (AB quartet, J = 296 Hz, CF_2). MS (DCI/CH_4): m/z (rel intensity) 556 (M + $C_3H_5^+$, 5), 544 (M + $C_2H_5^+$, 19), 516 (MH^+, 52), 496 (4), 460 (MH − $C_4H_8^+$, 100), 440 (11), 416 (26), 396 (6). Anal. ($C_{22}H_{34}F_5N_3O_5$): C, H, N.

***N*-L-Valyl-*N*-[3,3,4,4,4-pentafluoro-1-(methylethyl)-2-oxobutyl]-L-prolinamide, Hydrochloride Salt (6).** Into a stirred solution of **5** (7.88 g, 15.3 mmol) in EtOAc (250 mL) cooled in an ice−water bath was bubbled HCl gas for 9 min. The bubbling was ceased, and the reaction mixture was capped with a drying tube. After 1 h, the reaction mixture was allowed to warm to room temperature and concentrated. EtOAc (100 mL) and hexane (100 mL) were added to the residue, and the mixture was concentrated again. The residue was dissolved in the minimum amount of hot EtOAc (ca. 15 ml) and added slowly to rapidly stirred hexane (750 mL). Filtration and drying under vacuum over KOH pellets gave **6** (6.32 g, 91%; greater than 97% L-L by ^{19}F NMR) as a white solid. ^{1}H NMR: δ 8.48−8.13 (m, 3H, NH_3), 7.75 (br d, 1H, NH), 4.95 (dd, 1H, CH), 4.83−4.70 (m, 1H, CH), 4.07−3.92 (m, 1H, CH), 3.92−3.78 and 3.64−3.51 (pr m, 2H, CH_2N), 2.43−1.96 (m, 6H, 2 × CH and CH_2CH_2), 1.12 (overlapping pr d, 6H, 2 × CH_3), 1.02 (d, 3H, CH_3), 0.92 (d, 3H, CH_3). ^{1}F NMR: δ −82.31 (s, CF_3), −122.44 (s, CF_2). MS (DCI/CH_4): m/z (rel intensity) 416 (MH^+, 100), 396 (10), 317 (22), 197 (8), 169 (8), 72 (10). Anal. ($C_{17}H_{26}F_5N_3O_3{\cdot}HCl{\cdot}0.75H_2O$): C, H, N.

Method A. *N*-[3-Methyl-2-(4-morpholinylcarbonyl)-1-oxobutyl]-L-valyl-*N*-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide (7g). To a suspension of **17** (0.304 g, 1.33 mmol) in CH_2Cl_2 (8.9 mL) was added NMM (0.446 g, 4.43 mmol, 0.489 mL), and the resulting clear, colorless solution was cooled to −22 °C. IBCF (0.182 g, 1.33 mmol, 0.173 mL) was added and the reaction mixture stirred for 20 min, followed by addition of **6** in one portion. After being stirred at −22 °C for 4 h, the reaction mixture was diluted with additional CH_2Cl_2 (35 mL) and washed successively with 1 N HCl (3 × 20 mL), saturated $NaHCO_3$ (2 × 20 mL), and brine (1 × 20 mL). Drying and concentration followed by purification by flash chromatography (20:80 acetone:EtOAc) gave 0.343 g (63%) of **7g** (mixture of four diasteromers; L:D 4:1 at P_1 residue, L:D 1:1 at P_4 residue)[45] as a white foam. R_f 0.49 (3:7 acetone:EtOAc). ^{1}H NMR: δ 7.95 (br d, J = 7.5 Hz, 0.2H, P_1-NH), 7.65 (br d, J = 8.5 Hz, 0.5H, P_4-NH), 7.59 (br d, 7.5 Hz, 0.8H, P_1-NH), 7.17 (br d, J = 8.5 Hz, 0.5H, P_4-NH), 4.95−4.87 (m, 1H, α-CH of Val), 4.71 (dm, J = 8.0 Hz, 0.2H, α-CH of Pro), 4.53−4.42 (m, 1H, α-CH of Val), 3.91−3.47 (m, 10H, NCH_2 of Pro and 2 × OCH_2CH_2N), 3.17 (d, J = 9.7 Hz, 0.5H, α-CH of P_4), 3.15 (d, J = 10.3 Hz, 0.5H, α-CH of P_4), 2.54−1.69 (m, 7H, β-CH of P_4, 2 × β-CH of Val and CH_2CH_2 of Pro), 1.11−0.84 (m, 18H, 6 × CH_3). ^{19}F NMR: δ −82.13 (s, CF_3, major), −82.18 (s, CF_3, minor), −121.56 and −122.52 (AB quartet, J = 293 Hz, CF_2, major), −121.56 and −122.62 (AB quartet, J = 293 Hz, CF_2, minor). IR (film): 3304, 2968, 2936, 1753, 1641, 1528, 1439 cm^{-1}. MS (DCI/CH_4): m/z (rel intensity) 613 (MH^+, 53), 317 (89), 297 (100), 269 (31). Anal. ($C_{27}H_{41}F_5N_4O_6{\cdot}0.25H_2O$): C, H, N.

Method B. *N*-[(Tetrahydro-2*H*-pyran-4-yl)carbonyl]-L-valyl-*N*-[3,3,4,4,4-pentafluoro-1-methylethyl)-2-oxobutyl]-L-prolinamide (7c). To a mixture of **10** (146 mg, 1.12 mmol) and DMF (0.2 mL) in CH_2Cl_2 (10 mL) was added oxalyl chloride (142 mg, 1.12 mmol, 0.1 mL). The mixture was stirred at room temperature for 0.5 h, followed by the addition of NMM (287 mg, 2.84 mmol, 0.32 mL) and **6** (270 mg, 0.60 mmol). The mixture was stirred for 2.5 h, poured into H_2O, and extracted with ethyl acetate. The combined extracts were dried and concentrated, and the residue was purified by recrystallization (hexane/ethyl acetate) to yield 252 mg (79%) of **7c** (L-L-L)[44] as a white solid. ^{1}H NMR: δ 7.44 (d, J = 7.9 Hz, 1H, NH), 6.18 (d, J = 8.7 Hz, 1H, NH), 4.98 (ddd, J = 7.9, 4.3, 1.0 Hz, 1H, α-CH of Val), 4.62 (m, 2H, α-CH of Val and α-CH of Pro), 4.02 (m, 2H, CH_2OCH_2), 3.80 (m, 1H, NCH_2), 3.62 (m, 1H, NCH_2), 3.41 (m, 2H, CH_2OCH_2), 2.45−1.7 (series of m, 11H, CHCON, 2 × β-CH of Val, CH_2CH_2, and CH_2CCH_2) 1.03 (d, J = 6.6 Hz, 3H, CH_3), 0.99 (d, J = 6.6 Hz, 3H, CH_3), 0.94 (d, J = 6.6 Hz, 3H, CH_3), 0.88 (d, J = 6.6 Hz, 3H, CH_3). ^{19}F NMR: δ −82.15 (s, CF_3), −121.61 and −122.66 (AB quartet, J = 296 Hz, CF_2). IR (KBr): 3303, 3274, 2871, 1751, 1673, 1657, 1639, 1200 cm^{-1}. MS (DCI/CH_4): m/z (rel intensity) 528 (MH^+, 80), 317 (100). HRMS ($C_{23}H_{34}F_5N_3O_5$) (M^+): calcd, 527.2418; obsd, 527.2419.

Method C. *N*-[4-(4-Morpholinylcarbonyl)benzoyl]-L-valyl-*N*-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide (7l). To a stirred suspension of 4-(4-morpholinylcarbonyl)benzoic acid (11.2 g, 47.8 mmol) and benzyltriethylammonium chloride[46] (9 mg, 0.04 mmol) in 1,2-dichloroethane (90 mL) was added thionyl chloride (3.49 mL, 47.8 mmol), and the reaction mixture was heated at reflux. After 19 h, the solution was allowed to cool to room temperature and concentrated to give the acid chloride as a light-orange liquid, which was used without further purification. In a separate flask, a stirred solution of **6** (18.0 g, 39.8 mmol) in CH_2Cl_2 (450 mL) was cooled to −20 °C. NMM (17.52 mL, 0.16 mmol) was added and immediately followed by the addition of a solution of the acid chloride in CH_2Cl_2 (50 mL) at such a rate as to maintain the internal reaction temperature at −13 °C or less. After the addition was complete, the reaction mixture was allowed to warm to room temperature.

After an additional 2 h, the reaction mixture was diluted with CH_2Cl_2 (500 mL) and washed with 0.5 N HCl (2 × 500 mL), saturated $NaHCO_3$ (2 × 500 mL), and brine (250 mL). Drying and concentration gave crude **7l** (28.5 g). Recrystallization from EtOAc/hexane followed by flash chromatography (10 × 20 cm silica gel column) eluting with acetone/EtOAc (1:9) gave **7l** (19.9 g; 88:12 L-L-L:L-L-D by HPLC)[45,47] as a white solid. Chromatography of the filtrate (6 × 13 cm silica gel column) eluting with a gradient (0–10%) of acetone/EtOAc gave additional **7l** (1.77 g, 86% total; 3:2 L-L-L:L-L-D by HPLC)[45,47] as a white solid. The 21.7 g of **7l** was pooled with other batches and subjected to epimerization (see below).

Epimerization. A solution of **7l** (55.7 g, 88.0 mmol) and NMM (8.90 g, 88.0 mmol, 9.68 mL) in CH_2Cl_2 (880 mL) was stirred at room temperature for 23 h. The solution was diluted to 1.5 L with additional CH_2Cl_2 and washed with 0.5 N HCl (5 × 400 mL), saturated $NaHCO_3$ (3 × 400 mL), and brine (400 mL). The organics were concentrated and dried over P_2O_5 to give 53.8 g (97%; 49.9:50.1 L-L-L:L-L-D by HPLC)[45,47] of **7l** as a white solid foam. TLC: R_f 0.24 (30:70 acetone:EtOAc). ^{1}H NMR: δ 7.92–7.79 and 7.52–7.40 (pr m, 5H, aryl and NH), 6.88 (d, J = 9.0 Hz, 1H, NH), 5.02–4.95 (m, 1H, α-CH of Val), 4.85 (dd, J = 8.6, 7.0 Hz, 1H, α-CH of Val), 4.71 (dd, J = 7.9, 1.9 Hz, 0.5H, CH of Pro), 4.61 (dd, J = 7.9, 2.8 Hz, 0.5H, CH of Pro), 3.96–3.27 (m, 10H, 2 × NCH_2CH_2O and NCH_2 of Pro), 2.56–1.75 (series of m, 6H, 2 × β-CH of Val and CH_2CH_2), 1.17–0.82 (m, 12H, 4 × CH_3). ^{19}F NMR: δ −83.12 (s, CF_3, isomer I) and −82.17 (s, CF_3, isomer II), −121.52 and −122.74 (AB quartet, J = 271 Hz, CF_2), −121.58 and −122.62 (AB quartet, J = 301 Hz, CF_2, isomer II). IR (KBr pellet): 3435, 3317, 1630 cm^{-1}. MS (DCI/CH_4): m/z (rel intensity) 633 (MH$^+$, 13), 317 (100). Anal. ($C_{29}H_{37}F_5N_4O_6$·0.4H_2O): C, H, N.

Method D. N-[(Dimethylamino)carbonyl]-L-valyl-N-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide, Hydrochloride Salt (7a). To a solution of **6** (290 mg, 0.64 mmol) in CH_2Cl_2 (20 mL) were added dimethylcarbamyl chloride (274 mg, 2.56 mmol, 0.24 mL) and NMM (130 mg, 1.29 mmol, 0.14 mL). The mixture was stirred for 2.5 h, the solvent concentrated, and the residue purified by flash chromatography (1:3 acetone:EtOAc) to yield 149 mg (48%) of **7a** (3:1 L-L-L:L-L-D)[45] as a white solid. ^{1}H NMR: δ 7.96 (d, J = 7.6 Hz, 0.3H, NH), 7.62 (d, J = 7.7 Hz, 0.7 H, NH), 4.99 d, J = 8.0 Hz, 1H, NH), 4.97–4.90 (m, 1H, α-CH of Val), 4.71 (dd, J = 8.0, 2.5 Hz, 0.3H, α-CH of Pro), 4.62 (dd, J = 8.0, 2.5 Hz, 0.7H, α-CH of Pro), 4.46 (dd, J = 8.7, 7.3 Hz, 1H, α-CH of Val), 3.87 (m, 1H, NCH_2), 3.61 (m, 1H, NCH_2), 2.94 [s, 6H, $N(CH_3)_2$], 2.50–1.75 (series of m, 6H, 2 × β-CH of Val and CH_2CH_2), 1.00 (m, 9H, 3 × CH_3), 0.88 (d, J = 6.9 Hz, 2.1H, CH_3), 0.89 (d, J = 6.9 Hz, 0.9H, CH_3). ^{19}F NMR: δ −82.16 (s, CF_3, major isomer) and −82.21 (s, CF_3, minor isomer), −121.61 and −122.61 (AB quartet, J = 296 Hz, CF_2, major isomer), −121.66 and −122.68 (AB quartet, J = 293 Hz, CF_2, minor isomer). IR (KBr pellet): 3428, 2969, 1693, 1632, 1526, 1221, 1200 cm^{-1}. MS (DCI/CH_4): m/z (rel intensity) 487 (MH$^+$, 45), 345 (10), 317 (15), 171 (100). HRMS ($C_{20}H_{31}F_5N_4O_4$) (M$^+$): calcd, 486.2265; obsd, 486.2256.

N-(4-Morpholinylcarbonyl)-L-valyl-N-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide (7b). A solution of **6** (1.06 g, 2.35 mmol) was reacted with 4-morpholinecarbonyl chloride (1.09 mL, 9.38 mmol) and NMM (0.52 mL, 4.69 mmol) as described in method D. Purification by flash chromatography (3:7 acetone:EtOAc) gave 0.78 g (63%) of **7b** (7:1 L-L-L:L-L-D)[45] as a white solid. TLC: R_f 0.33 (35:65 acetone:EtOAc). ^{1}H NMR: δ 7.90 (br d, J = 7.7 Hz, 1/8H, NH), 7.53 (br d, J = 7.7 Hz, 7/8H, NH), 5.10 (br d, J = 8.7 Hz, 1H, NH), 4.99–4.92 (m, 1H, α-CH of Val), 4.71 (dd, J = 7.9, 1.9 Hz, 1/8H, NH of Pro), 4.61 (dd, J = 8.0, 2.7 Hz, 7/8H, NH of Pro), 4.49 (dd, J = 8.7, 7.0 Hz, 1H, α-CH of Val), 4.95–4.76 and 3.68–3.57 (pr m, 2H, CH_2N), 3.69 (t, J = 5.1 Hz, 4H, CH_2OCH_2), 3.47–3.24 (m, 4H, CH_2NCH_2), 2.53–2.25 and 2.19–1.81 (pr m, 6H, 2 × β-CH and CH_2CH_2), 1.12–0.83 (m, 12H, 4 × CH_3). ^{19}F NMR: δ −82.25 (s, CF_3, major isomer), −82.30 (s, CF_3, minor isomer), −121.70 and −122.72 (AB quartet, J = 296 Hz, CF_2, major isomer), −121.64 and −122.82 (AB quartet, J = 296 Hz, CF_2, minor isomer). MS (DCI/CH_4): m/z (rel intensity) 529 (MH$^+$, 57), 345 (18), 317 (60), 214 (18), 213 (100), 185 (32). Anal. ($C_{22}H_{33}F_5N_4O_5$): C, H, N.

N-(2-Furoyl)-L-valyl-N-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide (7d). 2-Furoyl chloride (143 mg, 1.11 mmol) was coupled with **6** (250 mg, 0.55 mmol) in the presence of NMM (112 mg, 1.11 mmol), as described in method D. Purification by flash chromatography (3:1 EtOAc:hexane) gave 270 mg (95%) of **7d** (L-L-L)[45] as a white solid. ^{1}H NMR: δ 7.50 (d, J = 7.7 Hz, 1H, NH), 7.47 (dd, J = 1.7, 0.8 Hz, 1H, pyranyl), 7.12 (dd, J = 3.5, 0.8 Hz, 1H, pyranyl), 6.96 (d, J = 9.42 Hz, 1H, NH), 6.50 (dd, J = 3.6, 1.8 Hz, 1H, pyranyl), 4.96 (ddd, J = 7.8, 4.2, 1.1 Hz, 1H, α-CH of Val), 4.76 (dd, J = 9.1, 7.3 Hz, 1H, α-CH of Val), 4.61 (dd, J = 8.0, 2.7 Hz, 1H, CH of Pro), 3.86 (m, 1H, NCH_2), 3.67 (m, 1H, NCH_2), 2.45–1.75 (series of m, 6H, 2 × β-CH of Val and CH_2CH_2), 1.04 (m, 9H, 3 × CH_3), 0.90 (d, J = 6.9 Hz, 3H, CH_3). ^{19}F NMR: δ −82.08 (s, CF_3), −121.50 and −122.55 (AB quartet, J = 293 Hz, CF_2). IR (KBr pellet): 3421, 3305, 2939, 1754, 1635, 1593, 1224, 1200 cm^{-1}. MS (DCI/CH_4): m/z (rel intensity) 510 (MH$^+$, 40), 317 (100). HRMS ($C_{22}H_{29}F_5N_3O_5$) (MH$^+$): calcd, 510.2027; obsd, 510.2025.

N-[2-(4-Morpholinyl)ethanoyl]-L-valyl-N-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide, Hydrochloride Salt (7e). The acid **13** (260 mg, 1.0 mmol) was activated with oxalyl chloride (120 mg, 1.0 mmol) and coupled with **6** (220 mg, 0.5 mmol) in the presence of NMM (300 mg, 3.0 mmol), as described in method B. Purification by flash chromatograpny (1:3 acetone:EtOAc) gave 189 mg (96%) of **7e** (3:2 L-L-L:L-L-D)[45] as a white solid. ^{1}H NMR: δ 12.63 (br s, 1H, HCl), 8.92 (m, 1.3H, NH), 8.71 (d, J = 8.7 Hz, 0.7H, NH), 8.20 (d, J = 6.9 Hz, 1H, NH), 5.15 (m, 0.75H), 5.04 (m, 1.25H), 4.79 (m, 1H), 4.50 (m, 2H), 1.14–0.90 (m, 12H, 4 × CH_3). ^{19}F NMR: δ −81.98 (s, CF_3, minor isomer), −82.16 (s, CF_3, major isomer), −120.49 and −123.29 (AB quartet, J = 299 Hz, CF_2, minor isomer), −121.90 and −122.78 (AB quartet, J = 296 Hz, CF_2, major isomer). IR (KBr pellet): 3430, 3280, 2971, 1754, 1685, 1629, 1449, 1224, 1200 cm^{-1}. MS (DCI/CH_4): m/z (rel intensity) 543 (MH$^+$, 100), 317 (10), 226 (10). Anal. ($C_{23}H_{35}F_5N_4O_5$·HCl·0.8H_2O): C, H, N.

N-[3-(4-Morpholinyl)-1,3-dioxopropyl]-L-valyl-N-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide (7f). The acid **15** (561 mg, 3.24 mmol) was activated with oxalyl chloride (400 mg, 3.17 mmol) and coupled with **6** (500 mg, 3.17 mmol) in the presence of NMM (980 mg, 9.70 mmol), as described in method B. Purification by flash chromatography (1:3 acetone:EtOAc) gave 475 mg (75%) of **7f** (2:1 L-L-L:L-L-D)[45] as a white solid. ^{1}H NMR: δ 8.03 (m, 1H, NH), 7.97 (d, J = 7.6 Hz, 0.33H, NH), 7.62 (d, J = 7.7 Hz, 0.67H, NH), 4.93 (m, 1H, α-CH of Val), 4.72 (dd, J = 8.0, 2.0 Hz, 0.33H, CH of Pro), 4.63 (dd, J = 8.0, 2.7 Hz, 0.67H, α-CH of Pro), 4.58 (dd, J = 8.3, 7.2 Hz, 1H, CH of Val), 3.86–3.42 (m, 10H, 2 × NCH_2CH_2O and NCH_2 of Pro), 3.36 (s, 2H, CH_2), 2.54–1.75 (series of m, 6H, 2 × β-CH of Val and CH_2CH_2), 1.09–0.87 (m, 12H, 4 × CH_3). ^{19}F NMR: δ −82.17 (s, CF_3, major isomer), −82.21 (s, CF_3, minor isomer), −121.64 and −122.61 (AB quartet, J = 298 Hz, CF_2, major isomer), −121.59 and −122.72 (AB quartet, J = 293 Hz, CF_2, minor isomer). IR (KBr pellet): 3301, 2969, 1753, 1628, 1531, 1444, 1224, 1199, 1116 cm^{-1}. MS (DCI/CH_4): m/z (rel intensity) 571 (MH$^+$, 100), 317 (75), 255 (20), 228 (18). HRMS ($C_{24}H_{35}F_5N_4O_6$) (MH$^+$): calcd, 570.2476; obsd, 570.2455.

N-[3-(3-Pyridyl)propanoyl]-L-valyl-N-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide (7h). 3-(3-Pyridyl)propionic acid[39] (174 mg, 1.15 mmol) was activated with NMM (0.38 mL, 3.45 mmol), Et_3N (0.32 mL, 2.30 mmol), and IBCF (0.15 mL, 1.15 mmol) and coupled with **6** (520 mg, 1.15 mmol) using NMM (0.13 mL, 1.15 mmol), as described in method A. Purification by flash chromatography (75:25 acetone:EtOAc) gave 470 mg (74%) of **7h** (3:1 L-L-L:L-L-D)[45] as a white solid foam. TLC: R_f 0.42 (3:1 acetone:EtOAc). ^{1}H NMR: δ 8.49 (br s, 1H, aryl), 8.45 (br d, J = 4.2 Hz, 1H, aryl), 7.84 (br d, J = 7.7 Hz, 1/4H, NH), 7.53 (dt, J = 7.8, 1.7 Hz, 1H, aryl), 7.50 (br d, 3/4H, NH), 7.21 (dd, J = 7.7, 4.8 Hz, 1H, aryl), 6.31 (br d, J = 8.9 Hz, 3/4H, NH), 6.24 (br d, J = 8.9 Hz, 1/4H, NH), 5.02–4.92 (m, 1H, CH), 4.67 (dd, J = 8.1, 2.1 Hz, 1/4H, α-CH of Pro), 4.63–4.55 (m, 1 3/4H, α-CH of Pro and

α-CH of Val), 3.87–3.72 and 3.70–3.55 (pr m, 2H, CH_2N), 3.07–2.87 and 2.63–2.50 (pr m, 4H, aryl CH_2CH_2CO) 2.50–1.80 (m, 6H, 2 × β-CH and CH_2CH_2), 1.12–0.79 (series of d, 12H, 4 × CH_3). ^{19}F NMR: δ −82.13 (s, CF_3, major isomer), −82.17 (s, CF_3, minor isomer), −121.53 and −122.71 (AB quartet, J = 295 Hz, CF_2, minor isomer), −121.59 and −122.61 (AB quartet, J = 295 Hz, CF_2, major isomer). MS (EI): m/z (rel intensity) 548 (M^+, 4), 401 (6), 233 (65), 205 (100), 134 (45), 106 (35), 70 (77). Anal. ($C_{25}H_{33}F_5N_4O_4$·$0.3H_2O$): C, H, N.

***N*-Benzoyl-L-valyl-*N*-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide (7i).** Benzoyl chloride (140 mg, 1.0 mmol) was coupled with **6** (200 mg, 0.44 mmol) in the presence of NMM (89 mg, 0.89 mmol), as described in method D. Purification by flash chromatography (6:4 EtOAc: hexane) gave 200 mg (87%) of **7i** (L-L-L)[45] as a white solid. ^1H NMR: δ 7.81 (m, 2H, CH aryl), 7.48 (m, 3H, CH aryl), 6.90 (d, J = 8.7 Hz, 1H, NH), 4.99 (dd, J = 7.8, 4.4 Hz, 1H, α-CH of Val), 4.84 (dd, J = 8.5, 7.1 Hz, 1H, α-CH of Val), 4.63 (dd, J = 8.1, 2.9 Hz, 1H, CH of Pro), 3.90 (m, 1H, CH_2 of Pro), 3.70 (m, 1H, CH_2 of Pro), 2.41–1.8 (series of m, 6H, 2 × β-CH of Val and CH_2CH_2), 1.04 (m, 9H, 3 × CH_3), 0.89 (d, J = 6.8 Hz, 3H, CH_3). ^{19}F NMR: δ −82.12 (s, CF_3), −121.43 and −122.89 (AB quartet, J = 295 Hz, CF_2). IR (KBr pellet): 3425, 3315, 2939, 1753, 1691, 1631, 1222, 1201 cm^{-1}. MS (DCI/CH_4): m/z (rel intensity) 520 (MH^+, 8), 317 (100). HRMS ($C_{24}H_{30}F_5N_3O_4$) (M^+): calcd, 519.2156; obsd, 519.2162.

***N*-(4-Carboxybenzoyl)-L-valyl-*N*-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide (7j).** A solution of **7k** (750 mg, 1.21 mmol) in ethyl acetate (300 mL) was cooled to −5 °C and treated with HCl (gas) until saturation. The mixture was stirred at −5 °C for 3 h, the solvent was removed *in vacuo*, and the crude residue was redissolved in EtOAc. The organic phase was extracted with dilute $NaHCO_3$. The $NaHCO_3$ extract was acidified with $KHSO_4$, and the product was extracted with diethyl ether. Removal of solvent gave 400 mg (64%) of **7j** (3:2 L-L-L:L-L-D)[45] as a white solid. ^1H NMR: δ 8.09 (d, J = 8.6 Hz, 0.5H, NH), 8.03 (d, J = 8.6 Hz, 0.5H, NH), 7.98 (d, J = 8.1 Hz, 2H, CH aryl), 7.89 (d, J = 8.1 Hz, 2H, CH aryl), 7.64 (d, J = 7.8 Hz, 0.5H, NH), 7.06 (d, J = 7.2 Hz, 0.5H, NH), 5.02 (m, 1H, α-CH of Val), 4.77 (m, 1.5H, α-CH of Val and 0.5 of CH of Pro), 4.63 (m, 0.5H, CH of Pro), 4.12 (m, 1H, CH_2 of Pro), 3.77 (m, 1H, CH_2 of Pro), 2.52–1.88 (series of m, 6H, 2 × β-CH of Val and CH_2CH_2), 1.11 (m, 9H, 3 × CH_3), 0.89 (m, 3H, CH_3). ^{19}F NMR: δ −82.11 (s, CF_3, major isomer), −82.14 (s, CF_3, minor isomer), −121.54 and −122.57 (AB quartet, J = 293 Hz, CF_2, major isomer), −121.43 and −122.80 (AB quartet, J = 296 Hz, CF_2, minor isomer). IR (KBr pellet): 3425, 3313, 2941, 1753, 1697, 1631, 1529, 1224 cm^{-1}. MS (DCI/CH_4): m/z (rel intensity) 564 (MH^+, 45), 317 (100). HRMS ($C_{23}H_{31}F_5N_3O_6$) (MH^+): calcd, 564.2133; obsd, 564.2125.

***N*-[4-[(1,1-Dimethylethoxy)carbonyl]benzoyl]-L-valyl-*N*-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide (7k).** Hydrogen *tert*-butyl pthalate[41] was activated with IBCF (0.41 g, 3.0 mmol) and NMM (0.91 g, 3.0 mmol) and coupled with **6** (1.2 g, 2.6 mmol), as described in method A. Purification by flash chromatography (1:3 EtOAc: hexane) gave 1.10 g (55%) of **7k** (1:1 L-L-L:L-L-D)[45] as a white solid. ^1H NMR: δ 8.05 (d, J = 2.5 Hz, 1H, 0.5 of 2CH aryl), 8.02 (d, J = 2.5, 1H, 0.5 of 2CH aryl), 7.85 (d, J = 5.4 Hz, 1H, 0.5 of 2CH aryl), 7.84 (overlapped, 0.5H, NH), 7.82 (d, J = 5.4 Hz, 1H, CH of aryl), 7.47 (d, J = 7.8 Hz, 0.5H, NH), 6.95 (m, 1H, NH), 4.99 (m, 1H, α-CH of Val), 4.84 (m, 1H, α-CH of Val), 4.75 (dd, J = 8.0, 2.1 Hz, 0.5H, CH of Pro), 4.63 (dd, J = 8.0, 2.9 Hz, 0.5H, CH of Pro), 3.89 (m, 1H, NCH_2), 3.70 (m, 1H, NCH_2), 2.51–1.85 (series of m, 6H, 2 × β-CH of Val and CH_2CH_2), 1.66 [s, 4.5H, 0.5 of $C(CH_3)_3$], 1.63 [s, 4.5H, 0.5 of $C(CH_3)_3$], 1.06 (m, 9H, 3 × CH_3), 0.88 (d, J = 6.9 Hz, 3H, CH_3). ^{19}F NMR: δ −82.13 (s, CF_3, isomer I), −82.17 (s, CF_3, isomer II), −121.54 and −122.63 (AB quartet, J = 296 Hz, CF_2, isomer I), −121.57 and −122.66 (AB quartet, J = 287 Hz, CF_2, isomer II). IR (KBr pellet): 3425, 3325, 2974, 1755, 1715, 1695, 1631, 1529, 1224, 1199 cm^{-1}. MS (DCI/CH_4): m/z (rel intensity) 620 (MH^+, 78), 564 (24), 544 (20), 516 (99), 317 (100). HRMS ($C_{29}H_{38}F_5N_3O_6$) (M^+): calcd, 619.2681; obsd, 619.2667.

***N*-[[6-(4-Morpholinylcarbonyl)pyrid-3-yl]carbonyl]-L-valyl-*N*-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide (7m).** The acid **24** (0.200 g, 0.847 mmol) was activated with thionyl chloride (0.101 g, 0.847 mmol, 61.5 μL) and benzyltriethylammonium chloride (trace) in dichloroethane (1.6 mL) and coupled with **6** (0.383 g, 0.847 mmol) in the presence of NMM (0.343 g, 3.39 mmol, 0.372 mL) in CH_2Cl_2 (10 mL), as described in method C. Purification by flash chromatography (1:9 acetone:EtOAc) gave 0.375 g (70%) of **7m** (1.5:1 L-L-L:L-L-D)[45] as a white foam. TLC: R_f 0.40 (3:7 acetone:EtOAc). ^1H NMR: δ 9.05 (d, J = 1.8 Hz, 1H, aryl), 8.21 (dd, J = 8.1, 1.0 Hz, 1H, aryl), 7.88 (d, J = 7.8 Hz, 0.4H, NH), 7.74 (dd, J = 8.0, 2.3 Hz, 1H, aryl), 7.46 (d, J = 8.0 Hz, 0.6H, NH), 7.29 (d, J = 8.9 Hz, 0.6H, NH), 7.25 (d, J = 8.8 Hz, 0.4H, NH), 5.03–4.96 (m, 1H, α-CH of Val), 4.82 (dd, J = 8.6, 7.3 Hz, 1H, α-CH of Val), 4.65 (dd, J = 7.9, 2.3 Hz, 0.4H, α-CH of Pro), 4.56 (dd, J = 7.8, 3.0 Hz, 0.6H, α-CH of Pro), 3.97–3.57 (series of m, 10H, 2 × OCH_2CH_2N and CH_2N of Pro), 2.49–1.84 (m, 6H, CH_2CH_2 of Pro and 2 × β-CH of Val), 1.12–0.85 (m, 12H, 4 × CH_3). ^{19}F NMR: δ −82.12 (s, CF_3, major), −82.15 (s, CF_3, minor), −121.46 and −122.78 (AB quartet, J = 296 Hz, CF_2, minor), −121.82 and −122.58 (AB quartet, J = 296 Hz, CF_2, major). MS (DCI/CH_4): m/z (rel intensity) 634 (MH^+, 27), 317 (100). Anal. ($C_{28}H_{36}F_5N_5O_6$·$0.3H_2O$): C, H, N.

***N*-[4-(4-Morpholinylsulfonyl)benzoyl]-L-valyl-*N*-[3,3,-4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide (7n).** 4-(4-Morpholinylsulfonyl)benzoic acid[42] (0.240 g, 0.885 mmol) was activated with IBCF (0.121 g, 0.885 mmol, 0.115 mL) and NMM (0.446 g, 4.43 mmol, 0.489 mL) in CH_2Cl_2 (9 mL) and coupled with **6** (0.400 g, 0.885 mmol), as described in method A. Purification by flash chromatography (1:3 hexane:EtOAc) gave 0.295 g (50%) of **7n** (3:1 L-L-L:L-L-D)[45] as a white foam. TLC: R_f 0.49 (EtOAc). ^1H NMR: δ 8.02–7.93 (m, 2H, aryl), 7.85–7.77 (m, 2.25H, aryl and NH), 7.70 (d, J = 7.3 Hz, 0.75H, NH), 6.93 (d, J = 9.0 Hz, 1H, NH), 5.04–4.96 (m, 1H, α-CH of Val), 4.86 (dd, J = 8.7, 6.7 Hz, 1H, α-CH of Val), 4.71 (dd, J = 8.1, 2.0 Hz, 0.25H, α-CH of Pro), 4.61 (dd, J = 8.1, 3.0 Hz, 0.75H, α-CH of Pro), 3.92–3.64 (m, 6H, CH_2OCH_2 and CH_2N of Pro), 3.07–2.96 (m, 4H, CH_2NCH_2), 2.55–1.82 (series of m, 6H, 2 × β-CH of Val, CH_2CH_2 of Pro), 1.12–0.85 (m, 12H, 4 × CH_3). ^{19}F NMR: δ −82.12 (s, CF_3, major), −82.16 (s, CF_3, minor), −121.50 and −122.74 (AB quartet, J = 296 Hz, CF_2, minor), −121.56 and −122.60 (AB quartet, J = 299 Hz, CF_2, major). MS (DCI/CH_4): m/z (rel intensity) 669 (MH^+, 55), 317 (100). Anal. ($C_{28}H_{37}F_5N_4O_7S$·$0.33H_2O$): C, H; N: calcd, 8.30; found, 7.82.

***N*-[4-[(4-Morpholinylcarbonyl)amino]benzoyl]-L-valyl-*N*-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide (7p).** The acid **27** (400 mg, 1.60 mmol) was activated with oxalyl chloride (201 mg, 1.60 mmol) and coupled with **6** (250 mg, 0.55 mmol) in the presence of NMM (380 mg, 3.75 mmol), as described in method B. Purification by flash chromatography (3:7 EtOAc:hexane) gave 295 mg (82%) of **7p** (4:1 L-L-L:L-L-D)[45] as a white solid. ^1H NMR: δ 7.91 (d, J = 7.9 Hz, 0.2H, NH), 7.74 (d, J = 8.7 Hz, 0.2H, NH), 7.72 (d, J = 8.7 Hz, 2H, aryl), 7.54 (d, J = 8.0 Hz, 0.8H, NH), 7.43 (d, J = 8.7 Hz, 2H, aryl), 6.88 (d, J = 8.7 Hz, 0.8H, NH), 6.82 (s, 1H, NH), 4.97 (dd, J = 7.8, 4.8 Hz, 1H, α-CH of Val), 4.80 (dd, J = 8.7, 7.0 Hz, 1H, α-CH of Val), 4.70 (dd, J = 7.8, 2.8 Hz, 0.2H, α-CH of Pro), 4.61 (dd, J = 7.8, 2.8 Hz, 0.8H, CH of Pro), 3.86 (m, 1H, NCH_2 of Pro), 3.73 (m, 4H, CH_2OCH_2), 3.67 (m, 1H, NCH_2 of Pro), 3.50 (m, 4H, CH_2NCH_2), 2.51–1.75 (series of m, 6H, 2 × β-CH of Val and CH_2CH_2), 1.11–1.00 (m, 9H, 3 × CH_3), 0.87 (d, J = 6.9 Hz, 3H, CH_3). ^{19}F NMR: δ −82.16 (s, CF_3, major isomer), −82.19 (s, CF_3, minor isomer), −121.72 and −122.59 (AB quartet, J = 293 Hz, CF_2, major isomer), −121.75 and −122.26 (AB quartet, J = 293 Hz, CF_2, minor isomer). IR (KBr pellet): 3328, 2969, 1753, 1635, 1522, 1442, 1312, 1240, 1198 cm^{-1}. MS (DCI/CH_4): m/z (rel intensity) 648 (MH^+, 30), 589 (38), 561 (90), 317 (100). HRMS ($C_{29}H_{39}F_5N_5O_3$) (MH^+): calcd, 648.2820; obsd, 648.2812.

***N*-[4-[[[(4-Chlorophenyl)sulfonyl]amino]carbonyl]-benzoyl]-L-valyl-*N*-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide (7q).** 4-[[[(4-Chlorophenyl)sulfonyl]amino]carbonyl]benzoic acid[25] (450 mg, 1.32 mmol) was

activated with oxalyl chloride (168 mg, 1.32 mmol) and coupled with **6** (590 mg, 1.31 mmol), as described in method B. Purification by flash chromatography (70:30:1 EtOAc:hexane: acetic acid) gave 490 mg (51%) of **7q** (3:2 L-L-L:L-L-D)[45] as a white solid. ^{1}H NMR: δ 10.60 (br s, 1H, SO_2NH), 8.07 (d, J = 8.8 Hz, 2H, CH aryl), 7.76 (d, J = 8.1 Hz, 2H, CH aryl), 7.62 (d, J = 8.4 Hz, 1H, CH aryl), 7.61 (d, J = 8.4 Hz, 1H, CH aryl), 7.51 (d, J = 8.1 Hz, 2H, CH aryl), 7.22 (m, 2H, NH), 5.00 (m, 1H, α-CH of Val), 4.93 (m, 1H, α-CH of Val), 4.67 (dd, J = 7.9, 2.7 Hz, 0.4H, CH of Pro, minor isomer), 4.57 (dd, J = 7.9, 3.6 Hz, 0.6H, CH of Pro, major isomer), 3.93 (m, 1H, NCH_2), 3.70 (m, 1H, NCH_2), 2.44–1.87 (series of m, 6H, 2 × β-CH of Val and CH_2CH_2), 1.12–0.99 (m, 9H, 3 × CH_3), 0.85 (d, J = 7.0 Hz, 1.2H, CH_3), 0.84 (d, J = 7.0 Hz, 1.8H, CH_3). ^{19}F NMR: δ −82.14 (s, CF_3), −121.46 and −122.77 (AB quartet, J = 295 Hz, CF_2, minor isomer), −121.67 and −122.59 (AB quartet, J = 296 Hz, CF_2, major isomer). IR (KBr pellet): 3423, 2971, 1754, 1695, 1670, 1632, 1525, 1441, 1225, 1201, 1170 cm^{-1}. MS (DCI/CH_4): m/z (rel intensity) 737 (MH^+, 54), 546 (25), 518 (38), 490 (30), 317 (100). HRMS ($C_{31}H_{35}ClF_5N_4O_7S$) (MH^+): calcd, 737.1835; obsd, 737.1816.

***N*-[4-[[Methyl[2-(4-morpholinyl)ethyl]amino]carbonyl]-benzoyl]-L-valyl-*N*-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide (7r).** The acid **7j** (0.36 g, 0.64 mmol) was activated with oxalyl chloride (0.07 mL, 0.83 mmol) and DMF (3 drops) and coupled with 4-[2-(methylamino)ethyl]-morpholine[40] (92 mg, 0.64 mmol) using NMM (0.14 mL, 1.28 mmol), as described in method B. Purification by flash chromatography (75:25 acetone:EtOAc) gave 0.25 g (57%) of **7r** (7:1 L-L-L:L-L-D)[45] as an off-white foam. TLC: R_f 0.19 (3:1 acetone:EtOAc). ^{1}H NMR (partial): δ 7.88–7.82 and 7.52–7.46 (pr m, 4H, aryl), 7.42 (br d, J = 7.6 Hz, 1H, NH), 6.84 (br d, J = 8.8 Hz, 1H, NH), 5.02–4.96 (m, 1H, CH), 4.85 (dd, J = 8.6, 7.0 Hz, 1H, CH), 4.72 (dd, J = 8.0, 2.0 Hz, $^1/_8$H, CH of Pro), 4.61 (dd, J = 8.1, 2.9 Hz, $^7/_8$H, CH of Pro), 1.14–0.82 (m, 12H, 4 × CH_3). ^{19}F NMR: δ −82.12 (s, CF_3, major isomer), −82.15 (s, CF_3, minor isomer), −121.52 and −122.70 (AB quartet, J = 294 Hz, CF_2, minor isomer), −121.54 and −122.58 (AB quartet, J = 294 Hz, CF_2, major isomer). MS (DCI/CH_4): m/z (rel intensity) 691 (26), 690 (MH^+, 100), 374 (62), 317 (18), 113 (22), 100 (43), 84 (36), 83 (23). HRMS ($C_{32}H_{45}F_5N_5O_6$) (MH^+): calcd, 690.3290; obsd, 690.3274.

***N*-[4-[[4-(4-Morpholinylcarbonyl)-1-piperazinyl]carbonyl]benzoyl]-L-valyl-*N*-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide (7s).** The acid **33** (230 mg, 0.66 mmol) was activated with oxalyl chloride (64 μL, 0.73 mmol) and DMF (2 drops) and coupled with **6** (299 mg, 0.66 mmol) using NMM (0.22 mL, 1.99 mmol), as described in method B. Purification by flash chromatography (45:55 acetone:EtOAc) gave 366 mg (74%) of **7s** (9:1 L-L-L:L-L-D)[45] as a white solid. TLC: R_f 0.33 (1:1 acetone:EtOAc). ^{1}H NMR: δ 7.87 and 7.48 (pr br d, J = 7.3 Hz, 4H, aryl), 7.39 (br d, J = 7.8 Hz, 1H, NH), 6.89 (br d, J = 8.5 Hz, 1H, NH), 4.99 (dd, J = 7.6, 4.2 Hz, 1H, α-CH), 4.85 (t, J = 7.5 Hz, 1H, α-CH of Val), 4.71 (d, J = 7.3 Hz, 0.1H, CH of Pro), 4.61 (dd, J = 7.7, 2.4 Hz, 0.9H, CH of Pro), 3.98–3.59 and 3.59–3.15 (pr m, 18H), 2.56–1.84 (m, 6H, 2 × β-CH of Val and CH_2CH_2), 1.14–0.82 (m, 12H, 4 × CH_3). ^{19}F NMR: δ −82.11 (s, CF_3, major isomer), −82.15 (s, CF_3, minor isomer), −121.50 and −122.70 (AB quartet, J = 297 Hz, CF_2, minor isomer), −121.54 and −122.58 (AB quartet, J = 297 Hz, CF_2, major isomer). MS (DCI/CH_4): m/z (rel intensity) 745 (MH^+, 100), 547 (15), 317 (55), 169 (16). Anal. ($C_{34}H_{45}F_5N_6O_7$): C, H, N.

Tetrahydro-4-(methoxymethylene)-2*H*-pyran (9). To a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (24.82 g, 72.41 mmol) in THF (250 mL) cooled in an ice–water bath was added *n*-BuLi (24.76 mL of 2.42 M solution in hexane, 59.93 mmol). The reaction mixture was allowed to warm to room temperature for 1 h and then recooled in an ice–water bath and a solution of tetrahydro-4*H*-pyran-4-one (5.00 g, 49.94 mmol) in THF (10 mL) added. After 20 min the reaction mixture was concentrated to an oily residue, the residue was triturated with Et_2O (150 mL), and the supernatant was decanted. This process was repeated (6 × 75 mL), and the combined supernatants were concentrated to give crude **9** (7.3 g) as an orange oil. Flash chromatography (10 × 18 cm) eluting with a gradient (5–10%) of EtOAc/hexane gave **9**[21] (2.25 g, 35%) as a volatile, colorless oil. TLC: R_f 0.13 (5:95 EtOAc:hexane). ^{1}H NMR: δ 5.85 (s, 1H, vinyl), 3.69–3.61 (m, 4H, CH_2OCH_2), 3.56 (s, 3H, OCH_3), 2.32 and 2.06 (pr t, 4H, 2 × CH_2).

Tetrahydro-2*H*-pyran-4-carboxylic Acid (10). To a stirred solution of **9** (2.24 g, 17.48 mmol) in acetone (35 mL) was added 1.0 N HCl (1 mL). After 3 h, TLC indicated that **9** had been consumed and a new, lower R_f material (presumably aldehyde) had been formed. The solution was diluted with additional acetone (65 mL) and treated with Jones reagent until a brown color persisted in the supernatant. The reaction mixture was concentrated to ca. 4 mL and flash chromatographed (6 × 16 cm column) eluting with a gradient (75–100%) of EtOAc/hexane to give **10** (1.11 g, 49%) as a white solid. Mp: 86–88 °C (lit.[48] mp 87 °C). ^{1}H NMR: δ 10.84 (br s, 1H, CO_2H), 3.99 (dt, J = 11.6, 3.6 Hz, 2H, $^1/_2CH_2OCH_2$), 3.46 (ddd, J = 13.7, 10.6, 3.0 Hz, 2H, $^1/_2CH_2OCH_2$), 2.59 (tt, J = 10.5, 4.5 Hz, 1H, CH), 1.98–1.74 (m, 4H, 2 × CH_2). ^{13}C NMR: δ 180.4, 66.9, 39.8, 28.3. MS (DCI/CH_4): m/z (rel intensity) 131 (MH^+, 38), 114 (17), 113 (100), 86 (22), 85 (99). Anal. ($C_6H_{10}O_3$): C, H.

(4-Morpholinyl)acetic Acid, 1,1-Dimethylethyl Ester (12). To a stirred solution of *tert*-butyl bromoacetate (1.61 mL, 10.0 mmol) in THF (25 mL) was added morpholine (1.74 mL, 20.0 mmol); the resultant suspension was stirred for 1.5 h and then concentrated. The residue was dissolved in CH_2Cl_2 (50 mL)/saturated Na_2CO_3 (75 mL), the layers were separated, and the aqueous layer was extracted with additional CH_2Cl_2 (2 × 25 mL). The combined organics were washed with saturated Na_2CO_3 (20 mL) and brine (30 mL), dried, and concentrated to give crude **12**. Tituration with EtOAc (15 mL), filtration, and concentration of the filtrate gave **12** (2.01 g, 100%) as a colorless oil. TLC: R_f 0.45 (EtOAc). ^{1}H NMR: δ 3.79–3.73 (m, 4H, CH_2OCH_2), 3.11 (s, 2H, CH_2), 2.61–2.55 (m, 4H, CH_2NCH_2), 1.46 (s, 9H, *t*-Bu). MS (DCI/CH_4): m/z (rel intensity) 202 (MH^+, 15) 201 (8), 200 (13), 174 (20), 146 (100), 100 (23). HRMS ($C_{10}H_{19}NO_3$) (M^+): calcd, 201.1365; obsd, 201.1371.

(4-Morpholinyl)acetic Acid, Trifluoroacetic Acid Salt (13). Trifluoroacetic acid (15 mL) was added to **12** (1.00 g, 4.97 mmol); the solution was stirred for 5 h and concentrated to give a yellow oil. Trituration with Et_2O (25 mL) gave **13** (1.06 g, 82%) as an off-white solid. Mp: 118–121 °C. ^{1}H NMR (DMSO-d_6): δ 4.06 (s, 2H, CH_2), 3.88–3.74 (m, 4H, CH_2OCH_2), 3.30–3.16 (m, 4H, CH_2NCH_2). ^{19}F NMR (DMSO-d_6): δ −73.3 (s, CF_3). MS (DCI, CH_4): m/z (rel intensity) 146 (MH^+, 100), 115 (45), 100 (30). Anal. ($C_6H_{11}NO_3{\cdot}CF_3CO_2H$): C, H, N.

2-(4-Morpholinylcarbonyl)ethanoic Acid, Methyl Ester (14). To a solution of methyl malonyl chloride (10.0 g, 73.2 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added rapidly dropwise a solution of morpholine (16.0 g, 0.183 mmol, 16.0 mL) in CH_2Cl_2 (50 mL), and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was filtered, the filtrate was diluted with additional CH_2Cl_2 (200 mL) and then washed successively with 1 N HCl, saturated $NaHCO_3$, and brine. The organics were concentrated to give a yellow oil which was purified by flash chromatography (EtOAc) to give 9.70 g (71%) of the desired amide, **14**, as a pale yellow oil. R_f 0.28 (EtOAc). ^{1}H NMR: δ 3.76 (s, 3H), 3.72–3.62 (m, 6H), 3.49–3.43 (m, 4H). ^{13}C NMR: δ 167.81, 164.33, 66.61, 66.42, 52.46, 46.74, 42.22, 40.75. IR (neat): 1742, 1647, 1441. MS (EI): m/z (rel intensity) 187 (M^+, 28), 156 (M^+ − OCH_3, 20), 144 (37), 114 (52), 101 (39), 86 (100). HRMS ($C_8H_{13}NO_4$) (MH^+): calcd, 188.0923; obsd, 188.0918.

2-(4-Morpholinylcarbonyl)ethanoic Acid (15). To a solution of **14** (1.70 g, 9.08 mmol) in MeOH (45 mL) was added 1 N LiOH (10 mL, 9.99 mmol), and the reaction mixture was stirred at room temperature for 2.5 h. The pH was adjusted to 3 with 1 N HCl and the solvent removed *in vacuo*. Recrystallization from CH_3CN gave 0.216 g (14%) of **15** as a white solid. ^{1}H NMR: δ 13.17–12.32 (very br s, 1H), 3.61–3.51 (m, 4H), 3.50–3.36 (m, 4H), 3.45 (s, 2H). ^{13}C NMR: δ 169.14, 165.09, 65.96, 46.15, 41.62, 40.62. MS (EI): m/z (rel intensity) 173 (M^+, 18), 129 (M^+ − CO_2, 53), 86 (77), 57 (100). HRMS ($C_7H_{11}NO_4$) (MH^+): calcd, 174.0766; obsd, 174.0765.

3-Methyl-2-(4-morpholinylcarbonyl)butanoic Acid, Methyl Ester (16). To a solution of **14** (9.70 g, 51.8 mmol) in THF at 0 °C was added NaH (1.71 g, 57.0 mmol, 80% dispersion in mineral oil) in three portions. After gas evolution subsided, the reaction mixture was allowed to warm to room temperature, isopropyl iodide (13.2 g, 77.7 mmol, 7.77 mL) added, and the reaction mixture heated at 60 °C for 8 h followed by 64 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and then washed with H_2O and brine and dried. The organics were concentrated to give a brown oil which was purified by flash chromatography to yield 7.70 g (65%) of **16** as an orange oil. TLC: R_f 0.53 (EtOAc). ^{1}H NMR: δ 3.73 (s, 3H, CO_2CH_3), 3.80–3.52 (m, 8H, 2 × OCH_2CH_2N), 3.26 (d, J = 9.7 Hz, 1H, α-CH), 2.55 (d of hept, J = 9.7, 6.7 Hz, 1H, β-CH), 0.99 (d, J = 6.7 Hz, 3H, CH_3), 0.95 (d, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR: δ 169.7, 166.4, 66.9, 66.6, 56.5, 52.3, 46.4, 42.6, 28.8, 21.0, 20.4. IR (film): 1747, 1647 cm^{-1}. MS (EI): m/z (rel intensity) 230 (MH^+, 38), 229 (M^+, 16), 198 (M^+ − OMe, 28), 187 (M^+ − C_3H_6, 93), 170 (M^+ − CO_2Me, 82), 114 (70), 86 (100). HRMS ($C_{11}H_{19}NO_4$) (MH^+): calcd, 230.1392; obsd, 230.1399.

3-Methyl-2-(4-morpholinylcarbonyl)butanoic Acid (17). To a solution of **16** (7.70 g, 33.6 mmol) in MeOH (150 mL) was added LiOH (37 mL, 1 N in H_2O), and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was acidified with concentrated HCl and the solvent removed *in vacuo*. The residue was triturated with hexane, collected on a fritted funnel, washed with several portions of hexane, and dried *in vacuo* over P2O5 to give 5.82 g (81%) of **17** as a white solid. ^{1}H NMR (DMSO-d_6): δ 3.63–3.44 (m, 8H, 4 × CH_2), 3.39 (d, J = 9.4 Hz, 1H, α-CH), 2.24 (d of sept, J = 9.3, 6.7 Hz, 1H, β-CH), 0.94 (d, J = 6.7 Hz, 3H, CH_3), 0.85 (d, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 170.59, 166.99, 66.14, 55.09, 46.05, 41.99, 28.16, 20.42, 20.22. IR (KBr pellet): 3420, 2969, 2872, 1732, 1626, 1462, 1451 cm^{-1}. MS (EI): m/z (rel intensity) 216 (MH^+, 10), 215 (M^+, 4), 173 (M^+ − C_3H_6, 36), 171 (M^+ − CO_2, 35), 129 (67), 86 (56), 57 (100). HRMS ($C_{10}H_{17}NO_4$) (MH^+): calcd, 216.1236; obsd, 216.1236.

4-(4-Morpholinylcarbonyl)benzoic Acid, Methyl Ester (19). To a stirred suspension of monomethyl terephthalate (25.0 g, 0.14 mmol) in CH_2Cl_2 (500 mL) and DMF (4 mL) was added, dropwise, oxalyl chloride (12.1 mL, 0.14 mol). NOTE: VIGOROUS GAS EVOLUTION. After the cessation of gas evolution, the reaction mixture was stirred for 45 min and then cooled in an ice–water bath. Morpholine (48.4 mL, 0.56 mol) was then added. NOTE: EXOTHERMIC. After the addition was completed, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was washed with 0.5 N HCl (2 × 500 mL), half-saturated $NaHCO_3$ (2 × 500 mL), H_2O (2 × 500 mL), and brine (300 mL). Drying and concentration gave **19** (33.8 g, 98%) as a white solid. Mp: 74–76 °C. TLC: R_f 0.59 (35:65 acetone:EtOAc). ^{1}H NMR: δ 8.13–8.06 and 7.52–7.44 (pr m, 4H, aryl), 3.93 (s, 3H, OCH_3), 3.89–3.55 and 3.49–3.32 (pr m, 8H, 2 × OCH_2CH_2N). MS (DCI/CH_4): m/z (rel intensity) 251 (15), 250 (MH^+, 100). MS (EI): m/z (rel intensity) 249 (M^+, 35), 248 (43), 234 (22), 218 (20), 163 (100), 135 (20), 86 (30), 56 (23). Anal. ($C_{13}H_{15}NO_4$): C, H, N.

4-(4-Morpholinylcarbonyl)benzoic Acid (20). To a stirred solution of **19** (50.1 g, 0.20 mol) in CH_3OH (800 mL) was added 1 N LiOH (241 mL, 0.24 mol) followed by H_2O (160 mL). After 7 h at room temperature, additional H_2O (100 mL) was added. After 24 h, the solution was concentrated to remove CH_3OH and the alkaline aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL) followed by Et_2O (200 mL). The aqueous layer was chilled in an ice–water bath and acidified to pH 1 with 12 N HCl (ca. 20 mL). Filtration gave crude **20** as a white solid. A suspension of the crude material in CH_2Cl_2 (2 L) was heated to reflux and cooled to room temperature, $MgSO_4$ was added, and the suspension was filtered. The filtrate was concentrated to give **20** (42.2 g, 89%) as a white solid. Mp: 194–196 °C. ^{1}H NMR: δ 8.20–8.13 and 7.56–7.49 (pr m, 4H, aryl), 3.95–3.53 and 3.53–3.31 (pr m, 8H, 2 × OCH_2CH_2N). MS (EI): m/z (rel intensity) 235 (M^+, 40), 234 (52), 220 (18), 149 (100), 121 (18), 86 (201), 65 (18), 56 (19). Anal. ($C_{12}H_{13}NO_4$): C, H, N.

Pyridine -2,5-dicarboxylic Acid, 5-*tert*-Butyl Ester, 2-Methyl Ester (22). To a solution of 2-*tert*-butyl-1,3-dicyclohexyl isourea[23] (5.63 g, 20.1 mmol) in CH_2Cl_2 (20 mL) at 5 °C was added **21**[22] (1.49 g, 8.24 mmol) in several portions. After 15 min, the cooling bath was removed. As the reaction mixture began to warm, a precipitate formed and the reaction temperature rose above 25 °C. The reaction mixture was cooled to room temperature and CH_2Cl_2 (5 mL) added to aid stirring. After stirring overnight, the mixture was diluted with CH_2Cl_2 (30 mL) and filtered and the pale blue-green solid washed with CH_2Cl_2. The combined filtrates were diluted with ether, washed with dilute $NaHCO_3$, and concentrated. The residue was purified by flash chromatography (55:45 cyclohexane: EtOAc) to give 1.01 g (52%) of **22** as a white solid. A portion of the material was recrystallized (ether/pentane) to give an analytically pure sample. Mp: 111–112 °C. ^{1}H NMR: δ 9.26 (d, J = 2.1 Hz, 1H), 8.39 (dd, J = 8.1, 2.1 Hz, 1H), 8.19 (dd, J = 8.1, 0.7 Hz, 1H), 4.04 (s, 3H), 1.63 (s, 9H). IR (KBr): 3420, 2984, 1711, 1379, 1310, 1290, 1246, 1134, 1126, 746 cm^{-1}. MS (EI): m/z (rel intensity) 238 (M + 1), 237 (M^+), 182, 179, 164, 57 (100). Anal. ($C_{12}H_{15}NO_4$): C, H, N.

6-(4-Morpholinylcarbonyl)nicotinic Acid, *tert*-Butyl Ester (23). A solution of **22** (0.935 g, 3.94 mmol) and morpholine (3.96 g, 46.0 mmol, 3.98 mL) in THF (6 mL) was refluxed for 3 days. The reaction mixture was concentrated; the residue was dissolved in EtOAc, washed with H_2O (2×), and concentrated to give 1.01 g of a light-yellow solid. Recrystallization (ether/pentane, 2×) gave 0.542 g (47%) of **23** as a pale cream solid. Mp: 91–93 °C. ^{1}H NMR: δ 9.13 (dd, J = 2.1, 1.0 Hz, 1H), 8.36 (dd, J = 8.1, 2.1 Hz, 1H), 7.75 (dd, J = 8.1, 0.9 Hz, 1H), 3.83 (s, 4H), 3.73–3.55 (m, 4H), 1.62 (s, 9H). IR (KBr): 2984, 2965, 1707, 1634, 1370, 1317, 1287, 1169, 1132, 117 cm^{-1}. MS (DCI/CH_4): m/z (rel intensity) 293 (MH^+), 292, 123, 86 (100). Anal. ($C_{15}H_{20}N_2O_4$): C, H, N.

6-(4-Morpholinylcarbonyl)nicotinic Acid (24). Into a solution of **23** (0.606 g, 2.07 mmol) in CH_3NO_2 (5 mL) was bubbled HCl(g) for 20 min. After standing for 20 min, the solvent was removed *in vacuo* to give a pale yellow solid. Recrystallization (acetone) gave 0.335 g (68%) of **24** as a white solid. Mp: 181–183 °C. ^{1}H NMR (CD_3OD): δ 9.26 (d, J = 1.1 Hz, 1H), 8.78 (dd, J = 8.1, 2.0 Hz, 1H), 8.00 (d, J = 8.1 Hz, 1H), 3.80 (s, 4H), 3.67 (m, 2H), 3.51 (m, 2H). IR (KBr): 2928, 2872, 1717, 1601, 1285, 1262, 1111 cm^{-1}. MS (DCI/CH_4): m/z (rel intensity) 277 (M + $C_3H_7^+$), 265 (M + $C_2H_5^+$), 238, 237 (MH^+, 100). Anal. ($C_{11}H_{12}N_2O_4$): C, H, N.

4-[(4-Morpholinylcarbonyl)amino]benzoic Acid, Ethyl Ester (26). To a solution of morpholine (0.684 g, 7.85 mmol, 0.687 mL) in toluene (8 mL) was added dropwise ethyl 4-isocyanatobenzoate (1.50 g, 7.85 mmol) in toluene (8 mL). After stirring for 18 h at room temperature, the precipitate was filtered, washed with cold toluene, and dried under vacuum to give 2.00 g (91%) of **26** as a white solid. ^{1}H NMR: δ 7.96 (d, J = 8.8 Hz, 2H, aryl), 7.45 (d, J = 8.8 Hz, 2H, aryl), 6.80 (br s, 1H, NH), 4.35 (q, J = 7.1 Hz, 2H, CO_2CH_2), 3.75–3.70 (m, 4H, CH_2OCH_2), 3.53–3.47 (m, 4H, CH_2NCH_2), 1.38 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR: δ 166.3, 154.4, 143.2, 130.7, 124.7, 118.5, 66.4, 60.8, 44.3, 14.3. IR (KBr): 3328, 1716, 1645, 1592, 1526, 1423, 1308, 1279, 1247 cm^{-1}. MS (DCI/CH_4): m/z (rel intensity) 307 (M + $C_2H_5^+$, 39), 279 (MH^+, 100). Anal. ($C_{14}H_{18}N_2O_4$): C, H, N.

4-[(4-Morpholinylcarbonyl)amino]benzoic Acid (27). To a solution of **26** (0.823 g, 2.96 mmol) in MeOH (15 mL) was added 1 N LiOH (3.25 mL, 3.25 mmol), and the reaction mixture was stirred at room temperature for 18 h. The MeOH was removed *in vacuo* and the aqueous residue acidified with concentrated HCl. After 1 h at 0 °C, the precipitate was collected, washed with H_2O, and dried under vacuum over KOH to give 0.281 g (38%) of **27** as a fluffy white powder. ^{1}H NMR: δ 13.51–11.37 (very br s, 1H, CO_2H), 8.88 (s, 1H, NH), 7.86–7.80 (m, 2H, aryl), 7.62–7.56 (m, 2H, aryl), 3.64–3.59 (m, 4H, CH_2OCH_2), 3.48–3.43 (m, 4H, CH_2NCH_2). ^{13}C NMR: δ 167.13, 154.66, 144.79, 130.05, 123.63, 118.25, 65.96, 44.22. MS (DCI/CH_4): m/z (rel intensity) 250 (M^+, 31), 114 (100), 70 (77). HRMS ($C_{12}H_{14}N_2O_4$) (MH^+): calcd, 251.1032; obsd, 251.1039.

4-(4-Morpholinylcarbonyl)-1-piperazinecarboxylic Acid, 1,1-Dimethylethyl Ester (30). To a stirred solution of *tert*-butyl 1-piperazinecarboxylate (2.50 g, 13.42 mmol) in CH_2Cl_2 (75 mL) cooled in an ice–water bath was added 4-morpholinecarbonyl chloride (1.57 mL, 13.42 mmol) followed by Et_3N (3.74 mL, 26.84 mmol), and the reaction mixture was allowed to warm to room temperature. After 15 h, the reaction mixture was washed with 1.0 N HCl (50 mL), saturated $NaHCO_3$ (75 mL), and brine (50 mL), dried, and concentrated to give **30** (3.80 g, 95%) as a white solid. Mp: 171–173 °C. ^{1}H NMR: δ 3.69 (t, J = 4.9 Hz, 4H, CH_2OCH_2), 3.46–3.40 (m, 4H, CH_2NCH_2), 3.28 (t, J = 4.9 Hz, 4H, CH_2NCH_2), 3.25–3.20 (m, 4H, CH_2CH_2), 1.47 (s, 9H, *t*-Bu). MS (DCI/CH_4): *m/z* (rel intensity) 300 (MH^+, 73), 272 (28), 244 (100), 200 (73). Anal. ($C_{14}H_{25}N_3O_4$): C, H, N.

4-(1-Piperazinylcarbonyl)morpholine, Bis(trifluoroacetic acid salt) (31). Trifluoroacetic acid (10 mL) was added to **30** (1.50 g, 5.01 mmol); the solution was stirred for 30 min and then concentrated to give an oil. Trituration with Et_2O (15 mL) and filtration gave **31** (2.02 g, 94%) as a white solid. ^{1}H NMR (DMSO-d_6): δ 8.91 (br s, 2H), 8.20 (br s, 1H), 3.53 (t, J = 4 Hz, 4H, CH_2OCH_2), 3.29 (t, J = 5.5 Hz, 4H, CH_2NCH_2), 3.15 (t, J = 4 Hz, 4H, CH_2NCH_2), 3.12–3.02 (m, 4H, CH_2NCH_2). MS (DCI/CH_4): *m/z* (rel intensity) 201 (26), 200 (MH^+, 100), 199 (32), 198 (33), 115 (90), 113 (44). HRMS ($C_7H_{18}N_3O_2$) (MH^+ free amine): calcd, 200.1399; obsd, 200.1410.

4-[[4(4-Morpholinylcarbonyl)-1-piperazinyl]carbonyl]benzoic Acid, Methyl Ester (32). To a stirred suspension of monomethyl terephthalate (0.40 g, 2.20 mmol) in CH_2Cl_2 (10 mL) and DMF (0.2 mL) was added oxalyl chloride (0.19 mL, 2.20 mmol) dropwise. NOTE: VIGOROUS GAS EVOLUTION. After cessation of gas evolution, the reaction mixture was stirred for 45 min and then concentrated to give the corresponding acid chloride as a white solid. The acid chloride, without further purification, was dissolved in CH_2Cl_2 (15 mL) and a solution of **31** (0.94 g, 2.20 mmol) and NMM (0.97 mL, 8.80 mmol) in CH_2Cl_2 (5 mL) added. After 2.5 h, the reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with 1.0 N HCl (2 × 35 mL), saturated $NaHCO_3$ (2 × 25 mL), and brine (25 mL). Drying and concentration gave crude **32**. Flash chromatography (4 × 12 cm) eluting with acetone/EtOAc (15:85) gave **32** (0.53 g, 66%) as a white solid. TLC: R_f 0.20 (3:7 acetone:EtOAc). ^{1}H NMR (DMSO-d_6): δ 8.04–7.97 and 7.57–7.51 (pr m, 4H, aryl), 3.87 (s, 3H, OCH_3), 3.67–3.57 (m, 2H, CH_2N), 3.54 (t, J = 4 Hz, 4H, CH_2OCH_2), 3.32–3.19 and 3.17–3.10 (pr m, 6H, 3 × CH_2N), 3.13 (t, J = 4 Hz, 4H, CH_2NCH_2). MS (EI): *m/z* (rel intensity) 361 (M^+, 12), 330 (8), 231 (22), 163 (100), 114 (71), 70 (41). HRMS ($C_{18}H_{24}N_3O_5$) (MH^+): calcd, 362.1716; obsd, 362.1707.

4-[[4-(4-Morpholinylcarbonyl)-1-piperazinyl]carbonyl]benzoic Acid (33). To a stirred solution of **32** (0.52 g, 1.44 mmol) in CH_3OH (10 mL) and CH_3CN (8 mL) were added 1.0 N LiOH (1.7 mL, 1.7 mmol) and water (4 mL). After 18 h, the reaction mixture was concentrated to remove CH_3OH and CH_3CN, and the alkaline aqueous solution was adjusted to pH 3 using 1.0 N HCl. After the solution was cooled, a white solid (0.43 g), crude **33**, was collected by filtration. The solid was stirred with CH_2Cl_2 (40 mL) for 20 min, Na_2SO_4 was added, and the mixture was filtered. Addition of hexane to the filtrate and concentration gave **33** (0.29 g, 58%) as a white solid. Mp: 203–205 °C. ^{1}H NMR: δ 8.20–8.13 and 7.54–7.47 (pr m, 4H, aryl), 3.90–3.74 (m, 2H, CH_2N), 3.70 (t, J = 4.4 Hz, 4H, CH_2OCH_2), 3.52–3.18 (m, 6H, 3 × CH_2N), 3.32 (t, J = 4.4 Hz, 4H, CH_2NCH_2). MS (DCI, CH_4): *m/z* (rel intensity) 349 (20), 348 (MH^+, 100), 217 (15). HRMS ($C_{17}H_{22}N_3O_5$) (MH^+): calcd, 348.1559; obsd, 348.1548.

***N*-[(1,1-Dimethylethoxy)carbonyl]-L-valyl-*N*-[3,3,3-trifluoro-2-hydroxy-1-(1-methylethyl)propyl]-L-prolinamide (35).** Boc-L-Val-L-Pro-OH (2.00 g, 6.36 mmol) in CH_3CN (85 mL) was activated with NMM (0.70 mL, 6.36 mmol) and IBCF (0.83 mL, 6.36 mmol) and coupled to **34**[7] (a single pair of enantiomers; 1.78 g, 6.36 mmol) using NMM (0.70 mL, 6.36 mmol), as described in method A. Trituration with Et_2O/hexane and filtration gave 2.41 g (81%) of **35** (mixture of two diastereomers, ratio ≃ 1:1) as an off-white solid. ^{1}H NMR (DMSO-d_6): δ 7.70 (br d, 0.5H, NH), 7.39 (br d, 0.5H, NH), 6.77 (br d, 0.5H, NH), 6.71 (br d, 0.5H, NH), 6.39 (d, 0.5H, OH), 6.36 (d, 0.5H, OH), 4.40–4.26 (m, 1H, α-CH), 4.09–3.94 (m, 2H), 3.94–3.46 (m, 3H), 2.20–1.60 (m, 6H), 1.37 (s, 9H, *t*-Bu), 0.98–0.72 (m, 12H, 4 × CH_3). ^{19}F NMR: δ −74.04 (d, J = 6.8 Hz, CF_3, diastereomer A), −74.14 (d, J = 6.8 Hz, CF_3, diastereomer B). MS (DCI, CH_4): *m/z* (rel intensity) 468 (MH^+, 40), 412 (92), 368 (100). Anal. ($C_{21}H_{36}F_3N_3O_5$): C, H, N.

***N*-[(1,1-Dimethylethoxy)carbonyl]-L-valyl-*N*-[3,3,3-trifluoro-1-(1-methylethyl)-2-oxopropyl]-L-prolinamide (36).** To a stirred solution of oxalyl chloride (0.31 mL, 3.56 mmol) in CH_2Cl_2 (30 mL) cooled to −60 °C was added DMSO (0.51 mL, 7.12 mmol) dropwise. After 6 min, a solution of **35** (1.11 g, 2.37 mmol) in a mixture of CH_2Cl_2 (5 mL) and DMSO (3 mL) was slowly added, and 20 min later, Et_3N (1.99 mL, 14.25 mmol) was added. The reaction mixture was allowed to warm to room temperature, diluted with CH_2Cl_2 (100 mL), and washed with 0.5 N HCl (2 × 150 mL) and half-saturated $NaHCO_3$ (2 × 100 mL) followed by brine (75 mL). Drying and concentration gave **36** (1.06 g, 96%; mixture of two diastereomers, ratio ≃ 1:1) as a white foam. ^{1}H NMR: δ 7.98 (br d, 0.5H, NH), 7.61 (br d, 0.5H, NH), 5.23 (d, 1H, NH), 4.87–4.79 (m, 1H, α-CH), 4.74 (dd, 0.5H, α-CH), 4.64 (dd, 0.5H, α-CH), 4.36–4.24 (m, 1H, α-CH), 3.82–3.68 and 3.65–3.54 (pr m, 2H, CH_2N), 2.57–1.76 (m, 6H, CH_2CH_2 and 2 × CH), 1.42 (s, 9H, *t*-Bu), 1.10–0.87 (m, 12H, 4 × CH_3). ^{19}F NMR: δ −76.94 (s, CF_3, diastereomer A), −77.00 (s, CF_3, diastereomer B). MS (DCI/CH_4): *m/z* (rel intensity) 466 (MH^+, 58), 410 (100), 390 (17), 366 (17). HRMS ($C_{21}H_{35}F_3N_3O_5$) (MH^+): calcd, 466.2529; obsd, 466.2507.

***N*-L-Valyl-*N*-[3,3,3-trifluoro-1-(1-methylethyl)-2-oxopropyl]-L-prolinamide, Hydrochloride Salt (37).** A stirred solution of **36** (1.19 g, 2.56 mmol) was cooled to 0 °C and treated with HCl (gas) until saturation. The mixture was stirred at 0 °C for 30 min, and the solvent was removed *in vacuo* to give **37** (1.0 g, 97%; mixture of two diastereomers of ketone form and two diastereomers of hydrate form, 3:1 ratio of diastereomers and 4:1 ratio of hydrate to ketone) as a white solid. ^{1}H NMR (DMSO-d_6): δ 8.80 (d, J = 7.15 Hz, 0.1H, NH), 8.73 (d, J = 7.15 Hz, 0.2H, NH), 8.14 (br s, 3H), 7.69 (d, J = 10.2 Hz, 0.7H, NH), 7.52 (d, J = 10.2 Hz, 0.1H, NH), 6.93 (s, 0.2H, OH), 6.90 (s, 0.6H, NH), 6.84 (s, 0.6H, NH), 6.79 (s, 0.2H, NH), 4.75 (series of m, 1H), 4.04–3.91 (series of m, 2H), 3.73 (m, 1H), 3.47 (m, 1H), 2.34–1.66 (series of m, 6H, 2 × β-CH of Val and CH_2CH_2), 1.06–0.77 (m, 12 H, 4 × CH_3). ^{19}F NMR (DMSO-d_6): δ −74.84 (s, $COCF_3$), −74.98 (s, $COCF_3$), −80.88 [s, $C(OH)_2CF_3$], −81.10 [s, $C(OH)_2CF_3$]. IR (KBr pellet): 3431, 2970, 1647, 1595, 1506, 1471, 1172 cm^{-1}; MS (DCI/CH_4): *m/z* (rel intensity) 366 (MH^+, 100), 267 (48), 197 (20), 169 (25). HRMS ($C_{16}H_{27}F_3N_3O_3$) (MH^+ free amine): calcd, 366.2005; obsd, 366.1995.

***N*-[4-(4-Morpholinylcarbonyl)benzoyl]-L-valyl-*N*-[3,3,3-trifluoro-1-(1-methylethyl)-2-oxopropyl]-L-prolinamide (38).** The acid **20** (1.10 g, 4.68 mmol, 0.35 mL) was activated with thionyl chloride (0.57 g, 4.80 mmol, 0.35 mL) and benzyltriethylammonium chloride (5 mg) in dichloroethane (10 mL) and coupled with **37** (1.00 g, 2.49 mmol) using NMM (2 mL) in CH_2Cl_2 (20 mL), as described in method C. Purification by flash chromatography (1:19 acetone:EtOAc) gave 1.20 g (82%) of **38** (2:1 L-L-L:L-L-D) as a white foam. ^{1}H NMR: δ 7.85 (d, J = 8.0 Hz, 2H, aryl), 7.76 (d, J = 7.0 Hz, 0.5H, NH), 7.47 (d, J = 8.0 Hz, 2H, aryl), 7.34 (d, J = 7.5 Hz, 0.75H, NH), 6.80 (d, J = 8.6 Hz, 1H, NH), 4.86 (m, 2H), 4.70 (dd, J = 8.0, 2.13 Hz, 0.33H, CH of Pro), 4.61 (dd, J = 8.3, 3.1 Hz, 0.66H, CH of Pro), 3.91–3.35 (m, 10H), 2.53–1.80 (series of m, 6H, 2 × β-CH of Val and CH_2CH_2), 1.12–0.88 (m, 12H, 4 × CH_3). ^{19}F NMR: δ −76.89 (s, CF_3), −76.96 (s, CF_3). MS (DCI/CH_4): *m/z* (rel intensity) 583 (MH^+, 20), 317 (10), 267 (100). HRMS ($C_{28}H_{38}F_3N_4O_6$) (MH^+): calcd, 583.2793; obsd, 583.2765.

***N*-(4-Morpholinylcarbonyl)-L-valyl-*N*-[3,3,3-trifluoro-1-(1-methylethyl)-2-oxopropyl]-L-prolinamide (39).** A solution of **37** (430 mg, 1.07 mmol) in CH_2Cl_2 (35 mL) was reacted with 4-morpholinecarbonyl chloride (0.50 mL, 4.28 mmol) and NMM (0.24 mL, 2.14 mmol), as described in method D. Purification by flash chromatography (20:80 acetone:EtOAc) followed by trituration with Et_2O/hexane gave 240 mg (47%)

of **39** (mixture of two diastereomers of ketone form and two diastereomers of hydrate form, ratio ≃ 9:9:1:1, respectively) as a white solid. ^{19}F NMR: δ −76.94 (s, $COCF_3$), −77.01 (s, $COCF_3$), −82.51 [s, $C(OH)_2CF_3$], −83.04 [s, $C(OH)_2CF_3$]. MS (DCI/CH_4): *m/z* (rel intensity) 479 (MH^+, 62), 267 (43), 213 (100), 185 (22). Anal. ($C_{21}H_{33}F_3N_4O_5$·1.25 H_2O·0.15C_6H_{14}): C, H, N.

***N*-[4-[[[(4-Chlorophenyl)sulfonyl]amino]carbonyl]-benzoyl]-L-valyl-*N*-[3,3,3-trifluoro-1-(1-methylethyl)-2-oxopropyl]-L-prolinamide (40).** 4-[[[(4-Chlorophenyl)sulfonyl]-amino]carbonyl]benzoic acid[25] (0.68 g, 2.02 mmol) was activated with oxalyl chloride (0.18 mL, 2.02 mmol) and DMF (2 mL) in CH_2Cl_2 (18 mL) and coupled with **37** (0.81 g, 2.02 mmol) using NMM (1.00 mL, 9.07 mmol), as described in method B. Purification by flash chromatography [gradient (54−74%) of EtOAc in hexane containing 1% acetic acid] gave 0.96 g (70%) of **40**[25] (1:1 L-L-L:L-L-D)[45] as a white solid foam. ^{1}H NMR: δ 10.40 (br s, 1H, SO_2NH), 8.11−8.03 and 7.79−7.71 and 7.68−7.60 and 7.56−7.49 (4 m, 8H, 2 × Ar), 7.28−7.13 (m, 2H, 2 × NH), 4.97−4.84 (m, 2H, 2 × CH), 4.67 (dd, 0.5H, α-CH), 4.59 (dd, 0.5H, α-CH), 3.99−3.86 and 3.77−3.61 (pr m, 2H, CH_2N), 2.47−1.83 (m, 6H), 1.14−0.81 (m, 12H, 4 × CH_3). ^{19}F NMR: −76.89 (s, CF_3, diastereomer A), −76.97 (s, CF_3, diastereomer B). MS (DCI/CH_4): *m/z* (rel intensity) 687 (MH^+, 38), 267 (100), 249 (45), 247 (58). Anal. ($C_{30}H_{34}ClF_3N_4O_7S$): C, H, N.

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Supplementary Material Available: Table 1 (Inhibition of HNE Data in Rats), Table 2 (Inhibition of HNE Data in Hamsters), and Table 3 (Physical Properties) (4 pages). Ordering information is given on any current masthead page.

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(45) The shorthand L-L-L refers to a tripeptide (P_3-P_2-P_1) having the L configuration at the P_1, P_2, and P_3 residues, whereas L-L-D refers to a tripeptide (P_3-P_2-P_1) having the L configuration at the P_3 and P_2 residues and the D configuration at the P_1 residue.

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