Matrix Metalloproteinase Inhibitors: A Structure−Activity Study

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Modifications around the dipeptide-mimetic core of a hydroxamic acid based matrix metalloproteinase inhibitor were studied. These variations incorporated a variety of natural, unnatural, and synthetic amino acids in addition to modifications of the P1′ and P3′ substituents. The results of this study indicate the following structural requirements: (1) Two key hydrogen bonds must be present between the enzyme and potent substrates. (2) Potent inhibitors must possess strong zinc-binding functionalities. (3) The potential importance of the hydrophobic group at position R3 as illustrated by its ability to impart greater relative potency against stromelysin when larger hydrophobic groups are used. (4) Requirements surrounding the nature of the amino acid appear to be more restrictive for stromelysin than for neutrophil collagenase, 72 kDa gelatinase, and 92 kDa gelatinase. These requirements may involve planar fused-ring aryl systems and possibly hydrogen-bonding capabilities.

Introduction

An essential component of the inflammatory process is the recruitment of leukocytes by the immune system to a site of injury.[1] These cells carry a variety of enzymes essential for normal tissue defense and repair,[2−4] which include the matrix metalloproteinases (MMPs). This family of enzymes includes the collagenases, gelatinases, and stromelysins. MMPs are necessary for tissue remodeling and the healing cascade.[2,5] However, the overexpression of MMP activity or the presence of MMP activity in healthy and uninjured areas can contribute to the pathophysiology of a variety of disease states and conditions. For example, a wound possessing an excess of MMP activity will not heal normally and may become ulcerated.[6,7] MMP activity directed at healthy skin may be implicated in the development of psoriasis.[8,9] MMP-mediated degradation of myelin is postulated to be involved in the pathogenesis of multiple sclerosis.[10−12] Other MMP-mediated indications of current interest are rheumatoid arthritis,[13,14] resulting from loss of collagen from cartilage, and osteoporosis,[15,16] resulting from loss of collagen from bone.

In addition to tissue destruction and remodeling, MMPs are known to be essential for the growth of new blood vessels. This process of angiogenesis is essential for the vascularization and growth of tumors beyond the size of approximately 2 mm in diameter.[17] Consequently, MMP inhibitors (MMPIs) are currently under investigation for their utility in slowing or halting the progression of tumor growth and metastasis.[18] With all the indications potentially treatable by MMPIs, these compounds are actively being studied by numerous groups as potentially useful new medicines.[19]

The MMPs are a family of zinc-binding metalloendopeptidases capable of degrading extracellular matrix (ECM) components[20] including collagen, gelatin, myelin, laminin, fibronectin, and elastin. Recent X-ray crystallographic analyses of MMPs, with and without bound inhibitors, have helped to elucidate the nature of the interactions existing between small molecule MMPIs and the corresponding enzymes.[21−24]

Shown in Figure 1 is a representation of the fibroblast collagenase binding site with a bound inhibitor. The interactions shown are predicted from published X-ray data involving fibroblast collagenase and a related inhibitor.[20] Comparisons of available crystallographic information indicate significant sequence and structure homology from one MMP to the next. Thus, one may predict the illustrated hydrophobic and hydrogen-bonding interactions to qualitatively reflect analogous interactions throughout this family of enzymes.

Intense interest in this class of compounds has sparked a variety of studies designed to elucidate the structural requirements for enhanced potency and enzyme specificity.[25−27] Generally, these studies have focused on the effects surrounding modification of a single inhibitor residue or of a specific inhibitor class. We now report a systematic in vitro SAR study against four MMPs (neutrophil collagenase, 72 kDa gelatinase, 92 kDa gelatinase, stromelysin) involving the modification of six sites around a prototypical broad spectrum hydroxamate-based dipeptide mimetic MMPI, **6a**. Figure 2 illustrates the generic structure, based on the lead molecule, Galardin (compound **6a**),[28] which was utilized as the template for the present study.

Chemistry

The inhibitors of the present study[29] were prepared utilizing three general approaches. The first, presented in Schemes 1 and 2, represents the approach utilized for the majority of the compounds presented herein containing both natural[30] and unnatural[31,32] amino acids. As shown, a BOC-protected amino acid **1** was coupled to an amine utilizing CDI as an activating agent. The yields for this reaction ranged from 50% to 99%. Following the coupling reaction, the BOC group

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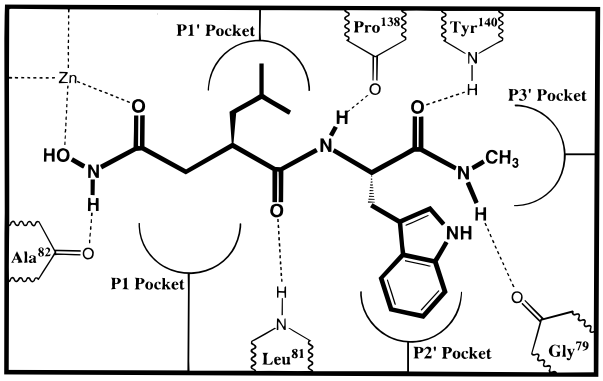


Figure 1. Compound **6a**/fibroblast collagenase predicted interactions.

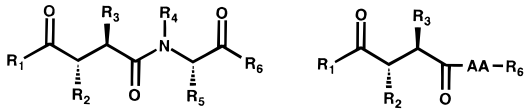
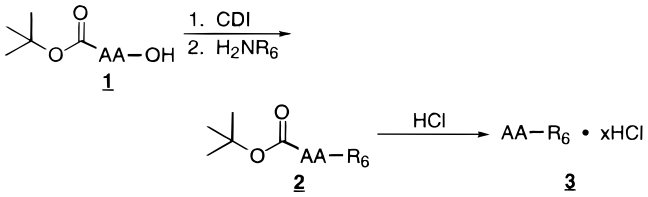


Figure 2. Generic MMPI SAR templates.

Scheme 1. Preparation of Amino Acid Amide Hydrochloride Salts



Scheme 2. Preparation of Hydroxamic Acids

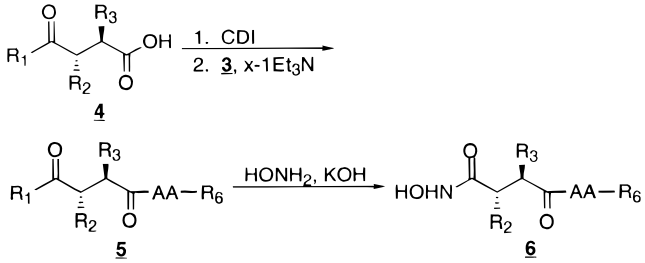
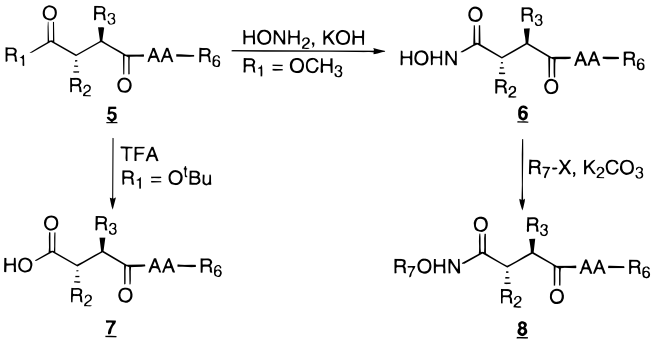


Table 1. BOC-Protected Amino Acids Utilized

compound	AA (abbreviation)	R6
1a	L-tryptophan (L-Trp)	OH
1b	D-tryptophan (D-Trp)	OH
1c	L-*N*-methyltryptophan (L-Trp(Me))	OH
1d	L-3-benzothienylalanine (L-3-Bal)	OH
1e	L-1-naphthylalanine (L-1-Nal)	OH
1f	L-2-naphthylalanine (L-2-Nal)	OH
1g	L-3-quinolylalanine (L-3-Qal)	OH
1h	L-8-quinolylalanine (L-8-Qal)	OH
1j	L-4,4′-biphenylalanine (L-4,4′-Bip)	OH
1k	L-phenylalanine (L-Phe)	OH
1l	L-3-pyridylalanine (L-3-Pal)	OH
1m	L-4-pyridylalanine (L-4-Pal)	OH
1n	L-*tert*-leucine (L-*tert*-Leu)	OH
1o	L-abrine (L-Abr)	OH

was removed under acidic conditions, giving a quantitative yield of an amine hydrochloride **3** which was then coupled to the substituted succinic acid monoester **4** in yields comparable to the first coupling step. It is important to note that when basic groups at R5 and/or R6 were present, the addition of triethylamine was essential in order to ensure progression of the coupling reaction. Once the methyl ester **5** was isolated, conversion to the corresponding hydroxamic acid **6** was accomplished by treatment with hydroxylamine under basic conditions with yields ranging from 30% to 60%. The specific intermediates and target compounds prepared according to Schemes 1 and 2 are shown in Tables 1−3.

Scheme 3. Preparation of Carboxylic Acids and Substituted Hydroxamates



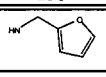
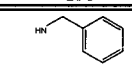
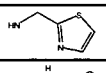
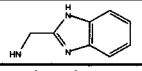
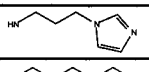
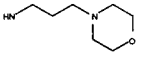
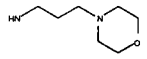
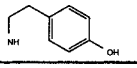
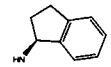
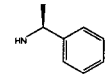
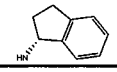
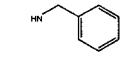
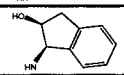
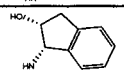
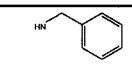
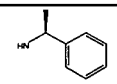
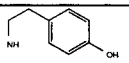
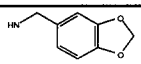
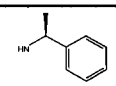
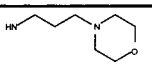
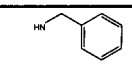
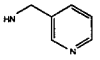
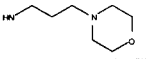
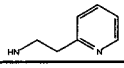
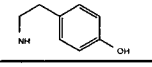
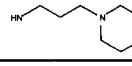
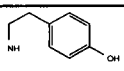
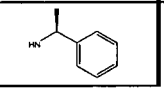
When carboxylic acids or modified hydroxamic acids were desired, the methods shown in Scheme 3 were applied. As illustrated, the methyl esters **5** were hydrolyzed under acidic conditions to carboxylic acids **7** in 40−70% yields. Alternately, the hydroxamic acids **6** were selectively alkylated on the hydroxamate oxygen, giving O-substituted hydroxamic acids **8**. The yields for this reaction ranged from 20% to 80%. The final products associated with Scheme 3 are shown in Table 4.

To prepare the compounds shown in Scheme 2, the common intermediate **4a** was required in large quantities. The synthesis of this compound was achieved as shown in Scheme 4. Maleic anhydride **9** was condensed with isobutylene, and the resulting ene adduct was reduced to **10**, utilizing catalytic hydrogenation. Subsequent methanolysis of the anhydride produced the mixture of regioisomers **11** and **12**. Separation and resolution of the desired regioisomer **12** with (*S*)-methylbenzylamine yielded the final product **4a**. The undesired regioisomer **11** was converted back to the anhydride **10** via hydrolysis to the diacid followed by dehydration with acetic anhydride. The isolated undesired stereoisomer **4b** was similarly utilized, as alluded to in Scheme 2, in subsequent structure activity studies.

Proof of the stereochemistry of intermediate **4a** was accomplished utilizing the asymmetric synthetic approach shown in Scheme 5. As illustrated, the acid chloride **13a** was coupled with a chiral auxiliary[33,34] to provide **14a** in near quantitative yields. **14a** was then treated with LDA and *tert*-butyl bromoacetate to give **15a** with high diastereomeric purity. The auxiliary was then removed on treatment with hydrogen peroxide and lithium hydroxide, giving the final product **4c**. As shown in Scheme 6, when **4c** was utilized in the synthesis of **5a**, the isolated product was chemically and physically identical with that obtained utilizing **4a**.

As indicated in Scheme 5 and Table 5, the isobutyl component of the core structure was replaced with alkyl groups of increasing chain length. However, if we consider that the stereochemical configuration of **4** is

Table 2. Intermediates and Products Associated with Schemes 1 and 2

Compound	Substitutions R3 = (R)-iBu		Compound	Substitutions R3 = (R)-iBu		Compound	Substitutions R3 = (R)-iBu	
2,3,5,6	AA	R6	2,3,5,6	AA	R6	2,3,5,6	AA	R6
a	L-Trp	$NHCH_3$	s	L-Trp		kk	L-2-Nal	
b	L-Trp	$NH(CH_2)_4CH_3$	t	L-Trp		ll	L-3-Qal	$NHCH_3$
c	L-Trp	$NH(CH_2)_2OH$	u	L-Trp		mm	L-8-Qal	$NHCH_3$
d	L-Trp	$NH(CH_2)_2NHCBZ$	v	L-Trp		oo	L-4,4'-Bip	$NHCH_3$
e	L-Trp		w	L-Trp		pp	L-4,4'-Bip	
f	L-Trp		x	L-Trp	$N(CH_3)_2$	qq	L-4,4'-Bip	
g	L-Trp		y	L-Trp		rr	L-4,4'-Bip	
h	L-Trp		z	L-Trp		ss	L-4,4'-Bip	
i	L-Trp		aa	L-Trp		tt	L-Phe	$NHCH_3$
j	L-Trp		bb	D-Trp	$NHCH_3$	uu	L-3-Pal	
k	L-Trp		cc	L-Trp(Me)	$NHCH_3$	vv	L-4-Pal	$NHCH_3$
l	L-Trp		dd	L-3-Bal	$NHCH_3$	xx	L-4-Pal	
m	L-Trp		ee	L-1-Nal	$NHCH_3$	yy	L-4-Pal	
n	L-Trp		ff	L-1-Nal		zz	L-4-Pal	
o	L-Trp		gg	L-2-Nal	$NHCH_3$	aaa	L-*tert*-Leu	$NHCH_3$
p	L-Trp		hh	L-2-Nal		bbb	L-Abr	$NHCH_3$
q	L-Trp		ii	L-2-Nal		ccc	L-Abr	
r	L-Trp		jj	L-2-Nal				

identical with that of D-malic acid **16**, then we can propose the synthesis of analogues bearing alkoxy groups as isobutyl replacements. As outlined in Scheme 7, D-malic acid was treated with 2,2-dimethoxypropane to yield the acetonide **17**. Conversion of **17** to the methyl ester **18** was accomplished on treatment with diazomethane. Following removal of the acetonide under acidic aqueous conditions, the acid **19** was converted to the benzyl ester **20** on treatment with benzyl bromide. The free hydroxyl group of **20** was then alkylated with a variety of groups utilizing silver oxide methodology, affording the ethers **21**. In the final step, catalytic hydrogenation of the ether analogues **21** yielded compounds **4g** and **4h** (Table 6). Use of these compounds according to Scheme 1 afforded the desired analogues bearing alkoxy surrogates for the parent isobutyl group (Table 3).

Where D-malic acid provides avenues into R3 alkoxy analogues, L-malic acid allows the formation of R2 hydroxy analogues.[35−37] As shown in Scheme 8, L-dimethyl malate **22** was treated with LDA followed by methallyl bromide yielding the alkylated compound **23**. Catalytic hydrogenation effected reduction of the olefin and subsequent hydrolysis of the diester provided the diacid **25**. Treatment of the diacid with 2,2-dimethoxypropane and PTSA yielded the acetonide **26**. This acetonide was then coupled with an amino acid amide to give compounds **27**. Following cleavage of the acetonides under acidic conditions, the resulting carboxylic acids **7** were converted to the methyl esters **5** utilizing

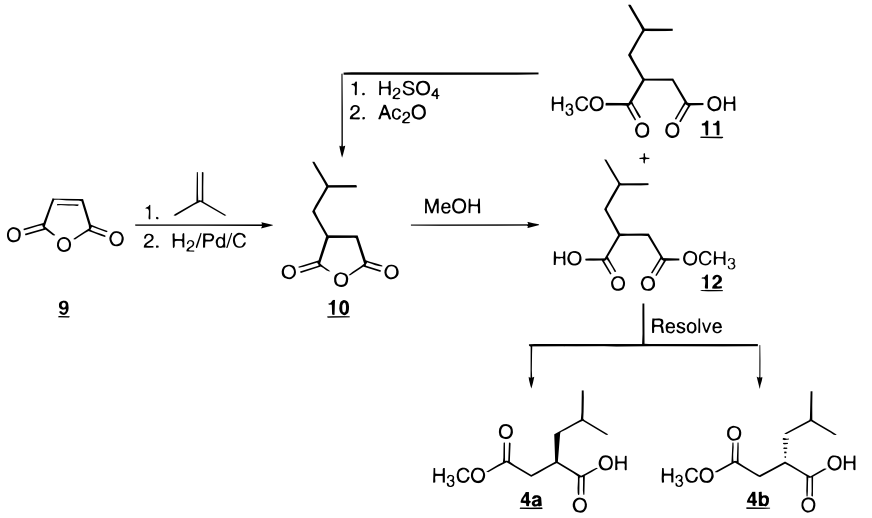
Table 3. Additional Intermediates and Products Associated with Scheme 2

compound		substitutions					
		R1 (**5**)	R1 (**6**)	R2	R3	AA	R6
5ddd	**6ddd**	MeO	NHOH	H	(*S*)iBu	l-Trp	$NHCH_3$
5eee		tBuO		H	(*R*)iBu	l-Trp	$NHCH_3$
5fff		tBuO		H	(*R*)Bu	l-Trp	$NHCH_3$
5ggg	**6eee**	MeO	NHOH	H	(*R*)Bu	l-Trp	$NHCH_3$
5hhh		tBuO		H	(*R*)Hex	l-Trp	$NHCH_3$
5iii	**6fff**	MeO	NHOH	H	(*R*)Hex	l-Trp	$NHCH_3$
5jjj		tBuO		H	(*R*)Oct	l-Trp	$NHCH_3$
5kkk	**6ggg**	MeO	NHOH	H	(*R*)Oct	l-Trp	$NHCH_3$
5lll	**6hhh**	MeO	NHOH	H	(*R*)O-iPr	l-Trp	$NHCH_3$
5mmm	**6iii**	MeO	NHOH	H	(*R*)O-Pen	l-Trp	$NHCH_3$
5nnn	**6jjj**	MeO	NHOH	(*S*)-OH	(*R*)iBu	l-Trp	$NHCH_3$
5ooo	**6kkk**	MeO	NHOH	(*S*)-OH	(*R*)iBu	l-*tert*-Leu	$NHCH_3$

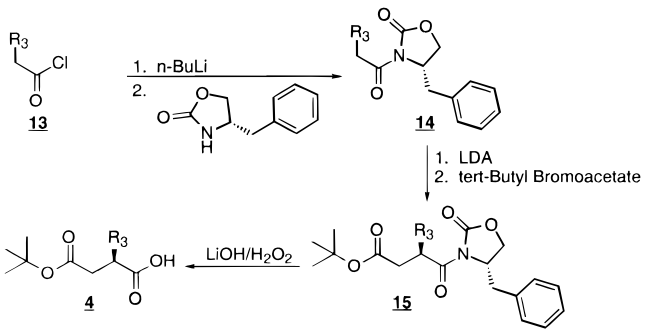
Table 4. Products Associated with Scheme 3

compound	R1/R7ONH	R2	R3	AA	R6
7a	OH	H	(*R*)-iBu	L-Trp	$NHCH_3$
7b	OH	H	(*R*)-Bu	L-Trp	$NHCH_3$
7c	OH	H	(*R*)-Hex	L-Trp	$NHCH_3$
7d	OH	H	(*R*)-Oct	L-Trp	$NHCH_3$
7e	OH	(*S*)-OH	(*R*)-iBu	L-Trp	$NHCH_3$
7f	OH	(*S*)-OH	(*R*)-iBu	L-*tert*-Leu	$NHCH_3$
8a	CH_3ONH	H	(*R*)-iBu	L-Trp	$NHCH_3$
8b	BnONH	H	(*R*)-iBu	L-Trp	$NHCH_3$
8c	CH_3OCOCH_2ONH	H	(*R*)-iBu	L-Trp	$NHCH_3$

Scheme 4. Preparation of Substituted Succinic Acid Monoesters



Scheme 5. Asymmetric Preparation of Succinic Acid Monoesters



diazomethane. Completion of the synthesis was achieved, as previously described, on treatment with hydroxylamine under basic conditions. The intermediates and products associated with Scheme 8 are shown in Table 7.

Table 5. Intermediates and Products Associated with Scheme 5

compound		substitution	
13, **14**, **15**	**4**	R1	R3
a	**c**	tBuO	(*R*)-iBu
b	**d**	tBuO	(*R*)-nBu
c	**e**	tBuO	(*R*)-nHex
d	**f**	tBuO	(*R*)-nOct

SAR Analysis. The compounds of the present study were assayed against MMPs, utilizing a fluorogenic substrate in a 96-well plate format. This assay was based on a published MMP assay utilizing a coumarin-labeled peptidic substrate.[38] All data are presented as K_i values (nM).

When comparing the activities of the compounds prepared for this study, several structure−activity relationships become apparent. Beginning with compound **6a**, we find that the stereochemistry of the amino

Scheme 6. Preparation of R_3 Alkyl Analogues

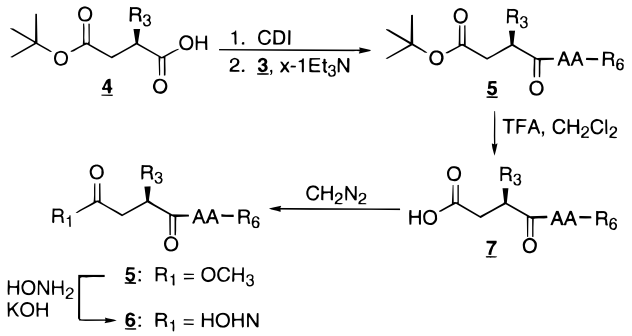


Table 6. Products Associated with Scheme 7

compound	R1	R3
4g	CH_3O	(*R*)-OiPr
4h	CH_3O	(*R*)-OPen

acid residue as well as the stereochemistry of the R3 substituent are essential for low nanomolar potency. This is illustrated when noting that compound **6bb** utilizes D-Trp and compound **6ddd** possesses the *S* configuration for the R3 substituent. As shown in Table 8, these compounds display substantially lower potencies compared to the parent compound. The stereochemical requirements established herein are further supported by the stereochemical configuration of the natural substrates of the MMPs.[37]

Having established the stereochemical requirements for optimal potency for this structural series, modifications of the parent compound, **6a**, were studied at six key sites. The first family of analogues was derived from the modification of the hydroxamic acid functionality. The results, shown in Table 9, illustrate the importance of the 1,4-bidentate nature of the zinc binding moiety as supported by the loss of potency noted for O-substituted hydroxamic acids (compounds **8a**, **8b**, and **8c**). The need for a potent zinc chelator is further demonstrated by the loss of 2 orders of magnitude in the potency when the hydroxamic acid was replaced by the carboxylic acid of compound **7a**.

The observations surrounding compound **7a** are consistent with reports for other carboxylate-containing inhibitors,[26] as well as those possessing phosphorus, and sulfur-based zinc-binding functionalities.[39,40] MMPIs with groups which bind more weakly to zinc usually require a substituent capable of interacting at the P1 pocket.[41,42] Though known to bind more weakly than hydroxamate-based inhibitors, some compounds possessing carboxylate functionalities as the zinc-binding component are reported to be orally bioavailable.[43] However, as hydroxamate-based analogues tend to bind zinc more strongly than analogues with other types of functionalities, inhibitors of this nature do not require additional appendages to achieve high levels of potency.

Recent reports describing the potency and pharmacokinetic properties of BB2516[37] (**6kkk**) prompted us to examine the importance of a hydroxyl group as the R2 substituent in this series. As **6kkk** was derived from L-*tert*-leucine, comparisons were made against the parent compound **6a**, the *tert*-leucine analogue **6aaa**, and the R2-hydroxylated analogue of **6a**, compound **6jjj**. The results, summarized in Table 10, show no significant change in the potencies against neutrophil collagenase, 92 kDa gelatinase, and 72 kDa gelatinase. However, the substitution of L-tryptophan with L-*tert*-leucine produced a 5-fold loss in potency against stromelysin. This will be discussed below in the context of amino acid modifications.

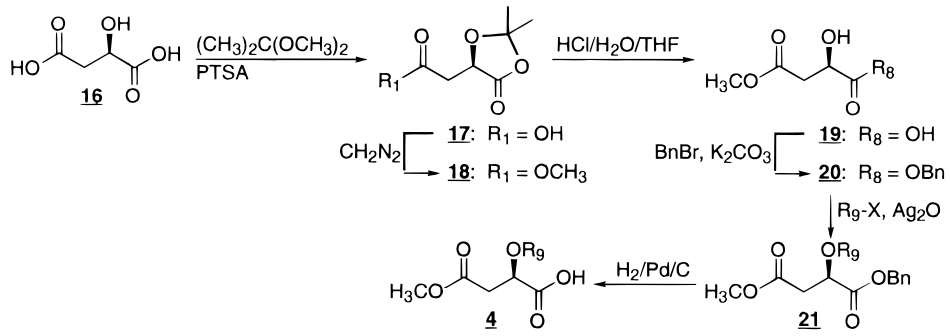
Structural modifications of the R3 substituent (isobutyl for compound **6a**) provided insight into the structural requirements of the P1′ binding site. The specific modifications were chosen based upon two criteria. First, the optimal size and shape of the R3 substituent was in question. Second, compound **4a**, and related starting materials, are expensive and tedious to prepare. If readily available chiral pool materials could be utilized in the synthesis of analogues or bioisosteres of **4a**, the preparation of inhibitors similar to those of the present study may become simpler and more economical.

As shown in Table 11, replacing an isobutyl group with other hydrophobic groups caused little change in the activities against neutrophil collagenase, 72 kDa gelatinase, and 92 kDa gelatinase. However, compounds **6fff** and **6ggg**, possessing hexyl and octyl groups, respectively, as the R3 substituents, appeared to have improved potency against stromelysin as compared to compound **6a**. This observation supports stromelysin possessing a substantially deeper P1′ binding pocket compared to the other three enzymes studied and is consistent with published SAR studies alluding to the nature of the P1′ substituent and the potencies of related inhibitors as tested against this enzyme.[26,44] Additionally, numerous reports focusing on the three-dimensional structure of stromelysin have elaborated upon the size and depth of this pocket as it appears to be unique to this enzyme.[45−47] With respect to the gelatinases, the IC_{50}s of matlystatin analogues were shown to gain 1−2 orders of magnitude when the P1′ group was extended to a nonyl group,[27] and in similar studies, substituted phenylpropyl substituents were reported to give low picomolar K_i's.[48] Although the compounds of the present study do not include aryl groups at the P1′ site, the trend differences noted between the matlystatins and compounds **6fff** and **6ggg** may be attributed to structural variations associated with the inhibitor backbones.

When an ether linkage was explored as a novel approach to join hydrophobic R3 groups to the inhibitor backbone (compounds **6hhh** and **6iii**), a significant loss in potency was observed. An explanation for this observation could involve a shift in the conformation of the inhibitor causing the need for a greater change in free energy in order for binding to occur. Alternately, the entrance to the P1′ binding pocket may possess residues not compatible with the presence of heteroatoms. Potencies of similar magnitudes against human fibroblast collagenase and human fibroblast stromelysin have been reported for MMPIs with heteroatoms located elsewhere on the P1′ substituent.[49]

Considering functionalization of the N-terminus of the amino acid component (R4 substituent), replacement of the hydrogen with a methyl group (**6bbb**) induced a 2 orders of magnitude reduction in potency compared to compound **6a**. Comparable results were noted with

Scheme 7. Preparation of R_3 Alkoxy Analogues



Scheme 8. Preparation of R_2 Hydroxy Analogues

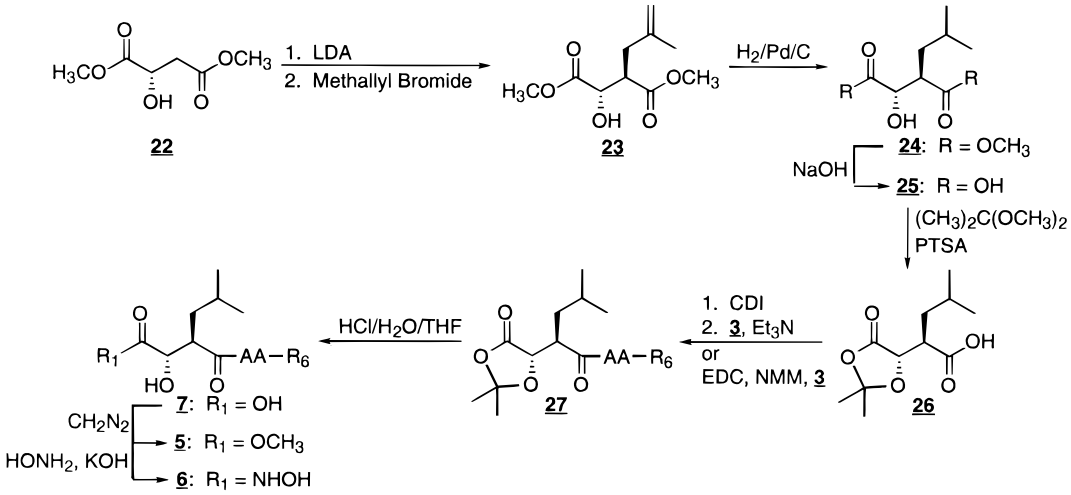


Table 7. Intermediates and Products Associated with Scheme 8

27	7	5	6	AA
a	**e**	**nnn**	**jjj**	L-Trp
b	**f**	**ooo**	**kkk**	L-*tert*-Leu

compound **6ccc**, the methylated version of compound **6w**. These data, shown in Table 12, support the importance of the hydrogen bonding interaction present between the internal amide proton and the enzyme backbone.[20,37]

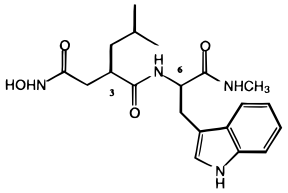
Among the most extensive modifications studied were substitutions involving the amino acid residue (R5 substituent) and the terminal amide residue (R6 substituent). The results of these studies are summarized in Tables 13 and 14.

As shown in Table 13, the nature of the amino acid residues studied in the present report caused little or no effect on the potency of the inhibitors against neutrophil collagenase, 72 kDa gelatinase, and 92 kDa gelatinase compared to compound **6a**. The most dramatic result in the neutrophil collagenase assay was observed when biphenylalanine was incorporated at R5 (compound **6oo**). This observation may imply a limit to the size of the residue acceptable to these enzymes. Finally, considering the stromelysin data, compounds **6oo**, **6tt**, and **6aaa** appear to have weaker potencies. This is interesting in view of the fact that the amino acids utilized in these analogues possess hydrophobic residues with no fused ring systems and no heteroatoms. This may indicate that optimal spatial occupation of the P2′ component of the stromelysin active site may require planar fused-ring aryl systems and possibly hydrogen-bonding capabilities.

The subtle importance of the P2′ substituent relative to potency and selectivity is further supported by a recent combinatorial approach to the synthesis of MMPIs which incorporated an analysis of the effect of varying the amino acid substituent.[50] Analogues possessing aromatic, heteroaromatic, and aliphatic side chains were tested against human collagenase. The results indicated weaker potencies associated with phenylalanine compared to leucine, tryptophan, 2-thienylalanine, and 3-pyridylalanine.

Considering the terminal amide (R6 substituent), some variability in the potencies was noted relative to compound **6a**. Hydrophobic amide residues (present on compounds **6b**, **6d**, **6e**, and **6f**) caused little effect on the relative potencies. The two exceptions involve the weaker inhibition noted for longer chain hydrophobic groups (compound **6b**) and the significantly improved stromelysin activity noted when a *N*-cyclopropylamide (compound **6e**) was incorporated in the inhibitor. As noted with compound **6c**, incorporation of a hydrophilic residue on the amide did not diminish potency. Of particular interest is the importance of the stereochemistry of the center bearing the amide nitrogen. As illustrated by compounds **6g**−**j**, a significant dependence linking potency to the stereochemical configuration exists. Of the remaining analogues prepared, the presence of aryl and heteroaryl amide residues was broadly tolerated. One outlier is the (aminomethyl)benzimidazolyl group present in compound **6u**. Finally, the incorporation of doubly substituted amides at the in-

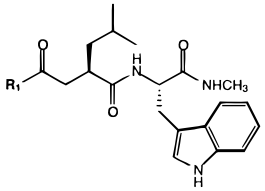
Table 8. Effect of Stereochemistry on Potency[a]



entry	3	6	neutrophil collagenase	92 kDa gelatinase	72 kDa gelatinase	stromelysin
6a	*R*	*S*	0.18 ± 0.09 (8)	0.57 ± 0.22 (7)	0.39 ± 0.20 (10)	26.0 ± 5.1 (8)
6bb	*R*	*R*	390	4500	1800	>1000
6ddd	*S*	*S*	54	270	300	>1000

[a] K_i (nM) values are reported against four MMPs.

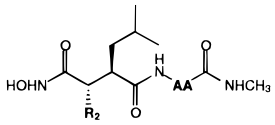
Table 9. Effect of Varying the R_1 Substituent[a]



entry	R_1	neutrophil collagenase	92 kDa gelatinase	72 kDa gelatinase	stromelysin
6a	HONH	0.18 ± 0.09 (8)	0.57 ± 0.22 (7)	0.39 ± 0.20 (10)	26.0 ± 5.1 (8)
7a	HO	17.0	100	170.0	39000
8a	CH_3ONH	7.70 ± 0.72 (2)	7.90	6.30	100
8b	BnONH	16.0 ± 5.8 (4)	13.0	11.0	480 ± 55 (2)
8c	CH_3OCOCH_2ONH	460	580	71000	46000

[a] K_i (nM) values are reported against four MMPs.

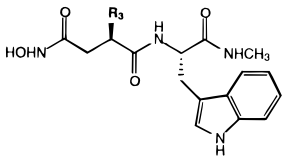
Table 10. Effect of Varying the R_2 Substituent[a]



entry	R_2	AA	neutrophil collagenase	92 kDa gelatinase	72 kDa gelatinase	stromelysin
6a	H	L-Trp	0.18 ± 0.09 (8)	0.57 ± 0.22 (7)	0.39 ± 0.20 (10)	26.0 ± 5.1 (8)
6jjj	OH	L-Trp	0.41	1.70 ± 0.83 (5)	0.89	20.0
6aaa	H	L-*tert*-Leu	0.65 ± 0.14 (2)	2.50 ± 0.75 (5)	1.10	130
6kkk	OH	L-*tert*-Leu	0.53	2.30 ± 0.70 (27)	0.47	13.0 ± 2.1 (3)

[a] K_i (nM) values are reported against four MMPs.

Table 11. Effect of Varying the R_3 Substituent[a]



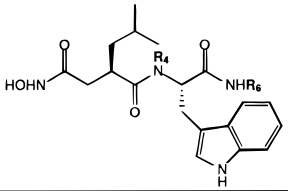
entry	R_3	neutrophil collagenase	92 kDa gelatinase	72 kDa gelatinase	stromelysin
6a	iBu	0.18 ± 0.09 (8)	0.57 ± 0.22 (7)	0.39 ± 0.20 (10)	26.0 ± 5.1 (8)
6eee	Bu	0.30	0.54 ± 0.25 (3)	0.57	41.0 ± 6.5 (2)
6fff	Hex	0.24 ± 0.14 (3)	0.41 ± 0.16 (6)	0.21 ± 0.03 (2)	8.3 ± 2.6 (2)
6ggg	Oct	1.6	0.63 ± 0.24 (4)	0.66	12.3 ± 0.2 (2)
6hhh	O-iPr	12.0	18.0 ± 7.3 (2)	42.0	830
6iii	O-Pen	7.8	26.0	43.0	700

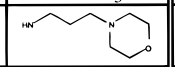
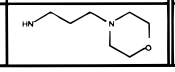
[a] K_i (nM) values are reported against four MMPs.

hibitor terminus (compounds **6x**−**z**,**aa**) caused a drop in potency. This result is consistent with the importance of an additional hydrogen bond between the terminal amide proton and the enzyme active sites.[20] A similar reduction in potency was reported with respect to matlystatin analogues.[27]

Presently, few reports are available addressing aspects of the R6 SAR.[26,27,51] However, the published analyses indicate that the P3′ residue provides little influence on the relative inhibitory activities. Of particular interest is the role the R6 substituent plays in affecting the degree of biliary excretion of hydroxamate-

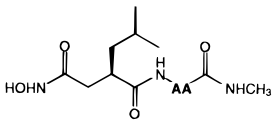
Table 12. Effect of Varying the R_4 Substituent[a]



Entry	R_4	R_6	Neutrophil Collagenase	92 kD Gelatinase	72 kD Gelatinase	Stromelysin
6a	H	$NHCH_3$	0.18 ± 0.09 (8)	0.57 ± 0.22 (7)	0.39 ± 0.20 (10)	26.0 ± 5.1 (8)
6bbb	CH_3	$NHCH_3$	21.0	42.0 ± 4.3 (3)	17.0	3,600 ± 130 (2)
6w	H		0.39 ± 0.23 (4)	1.9 ± 0.9 (36)	0.71 ± 0.33 (5)	30.0 ± 12.0 (4)
6ccc	CH_3		77.0	69.0 ± 11.0 (4)	55.0	3,000

[a] K_i (nM) values are reported against four MMPs.

Table 13. Effect of Varying the AA (R_5) Substituent[a]



entry	AA	neutrophil collagenase	92 kDa gelatinase	72 kDa gelatinase	stromelysin
6a	L-Trp	0.18 ± 0.09 (8)	0.57 ± 0.22 (7)	0.39 ± 0.20 (10)	26.0 ± 5.1 (8)
6cc	L-Trp(Me)	0.66	1.60 ± 0.59 (2)		31.0
6dd	L-3-Bal	0.45	0.83 ± 0.11 (5)	0.44	14.0
6ee	L-1-Nal	0.64	1.30 ± 0.71 (5)	0.42	46.0
6gg	L-2-Nal	1.3	0.99 ± 0.43 (3)	0.7	51.0
6ll	L-3-Qal	1.0	0.70 ± 0.16 (4)	1.0	66.0
6mm	L-8-Qal	0.54	1.50 ± 0.91 (5)	1.3	58.0
6oo	L-4,4¢-Bip	2.4	4.1 ± 1.5 (3)	4.0	140
6tt	L-Phe	0.82	0.96 ± 0.21 (3)	0.70	120
6vv	L-4-Pal	1.7 ± 1.4 (2)	2.8 ± 1.5 (21)	0.96 ± 0.17 (2)	85.0 ± 7.0 (2)
6aaa	L-*tert*-Leu	0.65 ± 0.14 (2)	2.50 ± 0.75 (5)	1.1	130

[a] K_i (nM) values are reported against four MMPs.

based MMPIs following iv administration to rats.[51] The present study demonstrates a dependence of stereochemistry of R6 substituents on the in vitro potency of hydroxamate-based inhibitors.

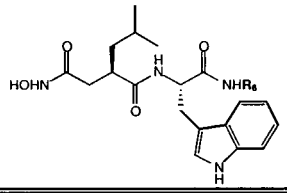
In the final phase of our study, we explored the modification of both the R5 and R6 sites. Interestingly, the relative potencies of this series compared to compound **6a** showed either no improvement or a loss of activity. These results, summarized in Table 15, failed to show any synergistic or additive effects between the most potent of the R5 and R6 analogues.

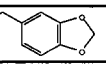
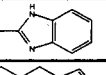
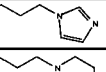
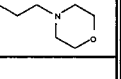
Although most reported SAR studies involve the systematic modification of individual sites on a given inhibitor backbone, few reports actually address the potential for synergy between the sites studied. One notable example, however, links the nucleophilic nitrogen present on the tryptophan residue to the terminal amide, thus providing a series of analogues modified simultaneously at the R5 and R6 positions.[52] The analogues of this study tended to show improved potency in their hydroxamic acid or carboxylic acid forms when compared to analogous materials bearing no tether between the R5 and R6 substituents.

Conclusions

The MMPI series of the present study illustrates many key points relevant to, and consistent with, the structural requirements for inhibitors of MMPs. First, the requirement for two key hydrogen bonds between the enzyme and potent test agents was supported by the drop in activity noted when tertiary amides were present as part of either the amino acid portion or the terminal amide. Second, the hydroxamic acid analogues were consistently more potent than the carboxylic acid analogues studied. This likely reflects the superior zinc binding interaction of the 1,4-bidentate hydroxamic acid ligand versus the 1,3-bidentate or monodentate interaction with carboxylic acids. Third, the potential importance of a hydrophobic group at position R3 is illustrated by the greater relative potency against stromelysin for analogues with larger hydrophobic groups. Other groups have seen increased potencies against gelatinases with compounds possessing large hydrophobic aryl substituents at R3 but, this was not observed for the alkyl substituents of the present study. The reduced potency of the R3 ether units could be related to the hydrophobicity requirements although it more likely reflects steric interactions resulting from torsional differences.

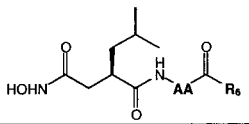
Table 14. Effect of Varying the R_6 Substituent[a]

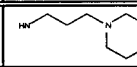
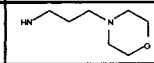
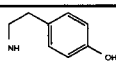
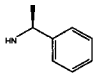
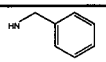
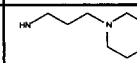
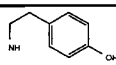
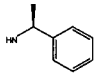
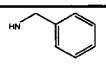
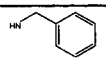
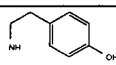
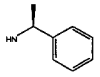
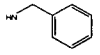


Entry	R_6	Neutrophil Collagenase	92 kD Gelatinase	72 kD Gelatinase	Stromelysin
6a	$NHCH_3$	0.18 ± 0.09 (8)	0.57 ± 0.22 (7)	0.39 ± 0.20 (10)	26.0 ± 5.1 (8)
6b	$NH(CH_2)_4CH_3$	6.5	7.1 ± 2.9 (6)	4.6	116
6c	$NH(CH_2)_2OH$	0.35 ± 0.35 (2)	0.76 ± 0.52 (2)	0.44 ± 0.24 (2)	37.0
6d	$NH(CH_2)_2NHCBZ$	0.94	1.10 ± 0.38 (4)		33.0
6e		0.34	1.20 ± 0.58 (3)	0.88	5.30
6f		1.6	3.0	2.6	42.0
6g		24.0	30.0 ± 17.0 (3)	19.0	93.0
6h		130 ± 130 (2)	100 ± 27 (2)	240	580 ± 66 (2)
6i		6.2	3.8	7.5	150
6j		73.0	74.0	46.0	270
6k		1.2	5.0 ± 4.4 (5)	2.0	11.0 ± 4.9 (3)
6l		0.75 ± 0.34 (4)	3.7 ± 1.4 (6)	0.64 ± 0.48 (4)	39.0 ± 5.9 (5)
6m		3.7	1.7	6.9	410
6n		0.29 ± 0.23 (2)	1.50 ± 0.29 (3)	0.6	39.0
6o		0.11	0.78 ± 0.52 (2)	0.52	29.0
6p		0.43	0.68 ± 0.32 (3)	0.54	57.0
6q		0.49	1.40 ± 0.74 (5)	0.73	42.0
6r		0.1	1.10 ± 0.39 (4)	0.52	11.0
6s		0.49	1.70 ± 0.93 (15)	0.92	20.0
6t		0.56	0.90 ± 0.14 (3)		31.0
6u		5.2 ± 5.4 (2)	3.0 ± 1.1 (5)	7.30 ± 0.61 (2)	26.0
6v		0.59	1.10 ± 0.08 (2)	1.3	12.0
6w		0.39 ± 0.23 (4)	1.9 ± 0.9 (36)	0.71 ± 0.33 (5)	30.0 ± 12.0 (4)
6x	$N(CH_3)_2$	8.5	22.0	19.0	280
6y		17.0	26.0	20.0	430
6z		27.0	13.0	19.0	200
6aa		6.9	8.70 ± 0.68 (3)	3.5	230

[a] K_i (nM) values are reported against four MMPs.

Table 15. Effects of Combined R_5/R_6 Modifications[a]



Entry	AA	R_6	Neutrophil Collagenase	92 kD Gelatinase	72 kD Gelatinase	Stromelysin
6ff	L-1-Nal		0.30	0.58 ± 0.10 (4)	0.59	12.0 ± 4.3 (2)
6hh	L-2-Nal		4.50	3.50 ± 0.63 (4)	3.0	56.0 ± 10.0 (2)
6ii	L-2-Nal		4.5	1.7 ± 1.5 (5)	8.1	1,900
6jj	L-2-Nal		14.0	6.9	13.0	160
6kk	L-2-Nal		7.7	5.3 ± 4.0 (3)	18.0	79.0
6pp	L-4,4'-Bip		6.8	3.6 ± 2.7 (6)	6.7	840
6qq	L-4,4'-Bip		13.0 ± 14.0 (2)	6.5 ± 5.5 (4)	8.1 ± 4.9 (2)	150 ± 160 (3)
6rr	L-4,4'-Bip		13.0	6.3	25.0	250
6ss	L-4,4'-Bip		3.6	3.0 ± 1.0 (4)		130
6uu	L-3-Pal		0.63	2.7 ± 1.4 (2)		130
6xx	L-4-Pal		0.33	1.70 ± 0.78 (3)	1.9	46.0
6yy	L-4-Pal		0.70	2.50 ± 0.59 (5)	1.9	120
6zz	L-4-Pal		0.96	1.50 ± 0.57 (3)		51.0

[a] K_i (nM) values are reported against four MMPs.

Finally, requirements surrounding the nature of the amino acid appear to be more restrictive for stromelysin that for the other three enzymes studied. These requirements may involve planar fused-ring aryl systems and possibly hydrogen bonding capabilities as illustrated by the weaker stromelysin activities noted for analogues possessing aliphatic hydrophobic residues and nonfused aryl residues.

None of the analogues incorporating two or more features from this study that independently improved potency provided any synergistic, or even additive, inhibition. However, the SAR results from this work, and SAR and structural work at other groups within various analogue series, all suggest that more potent and more selective MMPIs can be produced. Continued work on broad spectrum MMPIs such as those of the present study as well as those discussed elsewhere coupled with work on novel emerging inhibitors should provide new insights into the role of MMPs in disease and the therapeutic potential of MMPIs.

Experimental Section

General Procedure. Commercially available reagents and starting materials were obtained from Aldrich, Sigma, Fluka, Indofine, and Synthetech and were used with no additional purification. ^{1}H NMR spectra were recorded utilizing a Varian Gemini 300 MHz spectrometer or a Varian VXR 500S 500 MHz spectrometer. Optical rotations were determined utilizing a Perkin-Elmer 241 polarimeter. Chromatography generally refers to flash silica gel chromatography (J. T. Baker, 40 μM, flash chromatography silica gel) and TLC (Analtech precoated TLC plates, silica gel GHLF).

HPLC analyses were carried out on a VYDAC C18 analytical column (4.6 × 250 mm) utilizing the following methods. Solvent A = 10 mM H_3PO_4 in 5% CH_3CN/H_2O. Solvent B = 10 mM H_3PO_4 in 70% CH_3CN/H_2O. Solvent C = 10 mM H_3PO_4 in CH_3CN. HPLC method A = 90% solvent A/10% solvent B to 100% solvent B over 15 min with an additional 2 min at 100% solvent B. HPLC method B = 70% solvent A/30% solvent B to 100% solvent B over 16 min. HPLC method C = 80% solvent A/20% solvent B to 20% solvent A/80% solvent B over 28 min. HPLC method D = 80% solvent A/20% solvent B to 20% solvent A/80% solvent B over 30 min with an additional 3 min at 100% solvent B. HPLC method E = 80% solvent A/20% solvent B to 100% solvent B over 30 min. HPLC method F = 100% solvent A to 100% solvent B over 30 min. HPLC method G = 100% solvent A to 75% solvent A/25% solvent B over 2 min with an additional 30 min at 75% solvent A/25% solvent B. HPLC method H = 80% solvent A/20% solvent B for 30 min. HPLC method I = 60% solvent A/40% solvent B for 30 min. HPLC method J = 75% solvent A/25% solvent B for 30 min. HPLC method K = 50% solvent A/50% solvent B for 30 min. HPLC method L = 65% solvent A/35%

solvent B for 30 min. HPLC method M = 1% solvent A/99% H_2O to 50% solvent A/50% H_2O over 35 min. All flow rates were set at 1 mL/minute.

Human recombinant neutrophil collagenase was provided by Dr. Karen Hasty (University of Tennessee). Human 72 kDa gelatinase was provided by Dr. Henning Birkedal-Hansen (University of Alabama) and Dr. Eric Howard (University of Oklahoma). Human 92 kDa gelatinase/TIMP-1 complex was provided by Dr. Eric Howard (University of Oklahoma). Human recombinant stromelysin was provided by Dr. Hideaki Nagase (University of Kansas).

Isobutylsuccinic Anhydride (10). Maleic anhydride, **9** (750 g, 7.65 mol), was dissolved in hot toluene (500 mL), filtered, and allowed to cool, thus producing a finely divided crystalline precipitate. The resulting mixture was further cooled to 10 °C overnight. 2-Methylpropene was condensed into cold toluene (1 L). The cold maleic anhydride suspension was transferred, with the aid of additional toluene (300 mL), to the glass liner of a Parr 2 gallon stirred autoclave. The 2-methylpropene solution was then added followed by 4-*tert*-butylcatechol (2 g). The autoclave was sealed and heated, with stirring, to 170 °C over 45 min and maintained at that temperature for an additional 9.5 h. The reaction was then allowed to cool to 60 °C over 7 h after which the autoclave was vented. After an additional 1.5 h, the internal temperature had reached 45 °C and the autoclave was opened. The solvent was removed and the residue was distilled under aspirator pressure through a 10 in. vacuum-jacketed Vigreux column fitted with a partial take off head to give unreacted maleic anhydride (139.4 g, 18.6% yield) and β-methallylsuccinic anhydride (765.3 g, 79.8% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.7 (s, 3H), 2.3 (dd, 1H), 2.7 (m, 2H), 3.0 (dd, 1H), 3.25−3.35 (m, 1H), 4.75 (s, 1H), 4.9 (s, 1H).

β-Methallylsuccinic anhydride (539 g, 3.50 mol) was dissolved in toluene (800 mL) in a 1700 mL Parr stainless steel bottle fitted with a heating jacket. The 10% Pd/C (3.60 g) was added, and the bottle was connected to a Parr 2 L shaker fitted with two 4 L hydrogen tanks. After several evacuations and refilling with hydrogen, the shaker was started with the heater controlled for 60 °C. The initial pressure was 60 lbs. When the pressure fell to 10 lbs, the tanks were repressurized to 60 lbs. After 2 h, the controller was reset to 70 °C, and the reaction was continued for another 12 h. The heat was then turned off, and after another 5 h, the shaker was stopped. The reaction vessel was evacuated, and the reaction mixture was filtered and concentrated. Distillation of the residue through the Vigreux column described above (P = 9−10 mmHg, T = 180 °C) gave isobutylsuccinic anhydride (532.9 g, 97.6% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (dd, 6H), 1.5 (m, 1H), 1.65−1.8 (m, 1H), 1.8−1.9 (m, 1H), 2.65 (m, 1H), 3.05−3.2 (m, 2H).

D,L-2-Isobutyl-3-(methoxycarbonyl)propionic Acid (12). Isobutylsuccinic anhydride (501 g, 3.21 mol) was dissolved in anhydrous methanol (500 mL) and allowed to stand at room temperature for 5 days. The methanol was removed, and the residue was mixed with petroleum ether (500 mL) and refrigerated overnight. The solids were filtered, and the filtrate was cooled to 0 °C. After 3 days, the solids were filtered and the combined solids were recrystallized from petroleum ether to give D,L-2-isobutyl-3-(methoxycarbonyl)propionic acid (**12**, 337.5 g, 55.9% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.9 (dd, 6H), 1.3 (m, 1H), 1.55−1.7 (m, 2H), 2.45 (dd, 1H), 2.65 (dd, 1H), 2.9 (m, 1H), 3.7 (s, 3H).

Regeneration of Isobutylsuccinic Anhydride (10). After the combined petroleum ether filtrates from above were concentrated, 188 g (1 mol) of the crude material (mostly consisting of 3-(methoxycarbonyl)-5-methylhexanoic acid) was mixed with sodium hydroxide (120 g, 3 mol) and water (700 mL). The mixture was stirred on a steam bath for 14 h. The mixture was filtered and acidified with concentrated sulfuric acid (90 mL) and refrigerated. The suspension of sodium sulfate and the diacid was filtered, and the solids were thoroughly washed with ethyl acetate (500 mL). The aqueous solution was washed with ethyl acetate, and the combined ethyl acetate phases were concentrated and dried under vacuum to give the diacid (162.8 g, 93.6% yield). The diacid was heated with acetic anhydride (150 mL) under a 10 in.-vacuum jacketed Vigreux column. Acetic acid was removed over several hours at 118−120 °C. When the temperature began to fall, the pressure was gradually reduced to remove the excess acetic anhydride. Isobutylsuccinic anhydride (138 g, 88.5% yield) was collected by distillation (P = 10 mmHg, T = 144 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (dd, 6H), 1.5 (m, 1H), 1.65−1.8 (m, 1H), 1.8−1.9 (m, 1H), 2.65 (m, 1H), 3.05−3.2 (m, 2H).

***(R)*-2-Isobutyl-3-(methoxycarbonyl)propionic Acid (4a).** D,L-2-Isobutyl-3-(methoxycarbonyl)propionic acid (**12**, 17.55 g, 93.35 mmol) was dissolved in diethyl ether (85 mL), and (*S*)-methylbenzylamine (13.24 mL, 102.69 mmol) was added. The reaction mixture was stirred at room temperature for 24 h, and the solids were removed by filtration. Recrystallization of the solids from ethanol/diethyl ether provided white crystalline needles (9.24 g, 32% mass recovery, 64% yield) as a single diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.9 (dd, 6H), 1.25 (m, 1H), 1.5−1.65 (m, 5H), 2.4 (dd, 1H), 2.6 (dd, 1H), 2.8 (m, 1H), 3.625 (s, 3H), 4.3 (m, 1H), 7.25−7.45 (m, 5H).

The isolated crystalline needles (1.29 g, 4.18 mmol) were dissolved in $CHCl_3$ (100 mL) and washed with 1 N HCl (3 × 20 mL) and brine (20 mL). The organics were dried over anhydrous $MgSO_4$, filtered, and concentrated to give **4a** (0.77 g, 98% yield, $[\alpha]_D$ = +19.8) as a single enantiomer of greater than 97% optical purity. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (dd, 6H), 1.5 (m, 1H), 1.65−1.8 (m, 1H), 1.8−1.9 (m, 1H), 2.65 (m, 1H), 3.05−3.2 (m, 2H).

***(S)*-2-Isobutyl-3-(methoxycarbonyl)propionic Acid (4b).** The mother liquor from the isolation of **4a** was concentrated to dryness and dissolved in $CHCl_3$ (100 mL). The resulting solution was washed with 1 N HCl (3 × 20 mL) and brine (20 mL). The organics were dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was dissolved in diethyl ether, and (*R*)-methylbenzylamine (1.1 equiv) was added. The reaction mixture was stirred at room temperature for 24 h, and the solids were removed by filtration. Recrystallization of the solids from ethanol/diethyl ether provided white crystalline needles as a single diastereomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.9 (dd, 6H), 1.25 (m, 1H), 1.5−1.65 (m, 5H), 2.4 (dd, 1H), 2.6 (dd, 1H), 2.8 (m, 1H), 3.625 (s, 3H), 4.3 (m, 1H), 7.25−7.45 (m, 5H).

The isolated crystalline needles were dissolved in $CHCl_3$ (100 mL) and washed with 1 N HCl (3 × 20 mL) and brine (20 mL). The organics were dried over anhydrous $MgSO_4$, filtered, and concentrated to give **4b** (95% yield, $[\alpha]_D$ = −20.1) as a single enantiomer of greater than 96% optical purity. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (dd, 6H), 1.5 (m, 1H), 1.65−1.8 (m, 1H), 1.8−1.9 (m, 1H), 2.65 (m, 1H), 3.05−3.2 (m, 2H).

General Procedure A: Preparation of *N*-Acyloxazolidinones (14). (*S*)-4-Benzyl-2-oxazolidinone was dissolved in dry THF (10 mL/g) and cooled to −78 °C under argon. *n*-Butyllithium (1 equiv) was added over 10 min, and the resulting mixture was stirred for 1 h at −78 °C. An acid chloride (**13**, 1.1 equiv) was then added, the reaction mixture was stirred for 1 h at −78 °C and allowed to warm to room temperature over an additional 1 h. The reaction was quenched with saturated NH_4Cl (50% total reaction volume), the THF was removed under vacuum, and the aqueous phase was washed with CH_2Cl_2 (2×). The organic phase was then washed with 1 N NaOH (1×) and brine (1×), after which it was dried over anhydrous Na_2SO_4. The product was isolated following filtration and removal of the solvent under vacuum. No purification steps were required, and the isolated product was utilized in the next step.

General Procedure B: Preparation of Alkylated *N*-Acyl Oxazolidinones (15). Lithium hexamethyldisilazide (1 M in THF) was cooled to −78 °C under argon and a solution of an *N*-acyloxazolidinone (0.9 equiv) in dry THF (6 mL/g) was added while the internal reaction temperature was maintained below −65 °C. After 1 h of stirring at −78 °C, *tert*-butyl bromoacetate (2.5 equiv) was added while the internal reaction temperature was maintained below −70 °C. The resulting

mixture was stirred at −78 °C for 1 h and then allowed to warm to −40 °C over an additional 1 h. The reaction mixture was then warmed to 0 °C and the reaction quenched with saturated NH_4Cl (50% total reaction volume). The THF was removed under vacuum, and the aqueous phase was washed with EtOAc (2×). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified on silica gel (15% EtOAc/hexane), thus yielding the desired product.

General Procedure C: Preparation of Substituted Succinic Acid Monoesters 4. An alkylated *N*-acyloxazolidinone, **16**, was dissolved in THF/H_2O (4/1, 10 mL/g) and cooled to 0 °C. Hydrogen peroxide (30% in water, 0.62 mL/mmol) was added followed by a solution of LiOH in water (1.18 M, 1.34 equiv). The reaction mixture was stirred at 0 °C for 3 h, after which a solution of Na_2SO_3 in water (2.73 M, 1.34 equiv) was added over 10 min. The THF was then removed under vacuum, and the remaining aqueous phase was washed with CH_2Cl_2 (3×). The organic phase was then washed with 0.1 N NaOH (3×). The combined aqueous phases were acidified to pH = 2 with 2 N HCl and washed with EtOAc (3×). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated to give the desired product. No purification steps were required, and the isolated product was utilized in the next step.

General Procedure D: Preparation of BOC Amino Acid Amides 2. A BOC-protected amino acid, **1**, was dissolved in THF (7 mL/g) and followed by the addition of CDI (1 equiv). The resulting solution was stirred at room temperature for 2 h after which 1 equiv of a primary or secondary amine was added. After 24 h of stirring at room temperature, the reaction mixture was concentrated to dryness. The residue was diluted with ethyl acetate (100 mL) and washed with saturated $NaHCO_3$ (3 × 20 mL), water (3 × 20 mL), and brine (20 mL). After being dried over anhydrous $MgSO_4$, the organics were concentrated to dryness yielding the desired product. No purification steps were required, and the isolated product was utilized in the next step.

General Procedure E: Preparation of Amino Acid Amide Hydrochlorides 3. A BOC amino acid amide (**2**, 1 g) was dissolved in MeOH (10 mL), and 4 N HCl in dioxane (10 mL) was added. The reaction mixture was stirred at room temperature for 4 h. Concentration of the reaction mixture to dryness afforded the desired amine hydrochloride, **3**, in a quantitative yield. No purification steps were required, and the isolated product was utilized in the next step.

General Procedure F: Preparation of Amino Acid Amide−Succinic Acid Adducts 5. A substituted succinic acid monoester (**4**, **13**, **17**, or **22**) was dissolved in THF (10 mL/g). CDI (1 equiv) was added, and the reaction mixture was stirred at room temperature for 2 h. An amino acid amide hydrochloride (**3**, 1 equiv) was dissolved or suspended in THF (10 mL/g), and Et_3N (2 equiv) was added. The activated succinic acid monoester solution was then transferred to the amino acid amide hydrochloride via cannula. After 24−72 h of stirring, the reaction mixture was concentrated to dryness. The residue was diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ (3 × 20 mL), water (3 × 20 mL), and brine (20 mL). The organics were dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified on silica gel (50% EtOAc/hexane or $CHCl_3$/MeOH, 25/1).

General Procedure G: Formation of Hydroxamic Acids 6. [*Note:* concentrations and reagent ratios are critical to the success of this reaction.] Compound **5** (5 mmol) was dissolved in MeOH (10 mL). $HONH_2$·HCl (36 mmol) was dissolved in MeOH (24 mL). KOH (57 mmol) was dissolved in MeOH (16 mL). The KOH solution was poured into the $HONH_2$·HCl solution, and the resulting mixture was cooled to 0 °C for 1 h. The KOH/$HONH_2$ solution was then filtered into the solution of compound **5**, and the reaction mixture was stirred at room temperature until complete by TLC [TLC solvent = $CHCl_3$/MeOH/H_2O, 150/45/5, total reaction time is generally less than 15 min]. When TLC indicated total consumption of starting material, the reaction mixture was concentrated to dryness. The residue was then dissolved in H_2O (20 mL), acidified to pH = 5 with 6 N HCl, and neutralized with saturated $NaHCO_3$.

Workup procedures substantially varied from one compound to the next. The following is provided to guide workup procedures accordingly.

Typically, the product precipitated out and was collected by filtration. Alternately, extraction of the product into 15% MeOH/EtOAc may have been necessary. In cases of extreme water solubility, the mixture was lyophilized and the product was triturated from the salts with 2-propanol. Purification of the product was accomplished either by recrystallization from 2-propanol or by silica gel chromatography. If silica gel was used, MeOH/$CHCl_3$ mixtures may have been used for elution. Residual silica gel was then removed from the isolated product by trituration with 2-propanol. Final products were isolated as dry materials, hydrates, or 2-propanol (C_3H_8O) complexes.

General Procedure H: Formation of O-Substituted Hydroxamic Acids 8. Compound **6** was dissolved in MeOH (20 mL/g), and K_2CO_3 (1.1 equiv) was added followed by an alkyl halide (1.1 equiv). The reaction mixture was stirred at room temperature for 24 h, after which the solvent was removed under vacuum. The residue was partitioned between EtOAc and H_2O. The organic phase was washed with brine (3×), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by recrystallization or silica gel chromatography.

General Procedure I: Hydrolysis of *tert*-Butyl Esters to Acids 7. A *tert*-butyl ester was dissolved in CH_2Cl_2 (10 mL/g), and trifluoroacetic acid (4 mL/g) was added. The reaction mixture was stirred at room temperature for 30 min, after which it was concentrated to dryness. The residue was placed under vacuum for 2 h and dissolved in EtOAc (5 mL/g). The resulting solution was diluted with hexanes until the product precipitated. The solids were collected by filtration and dried under vacuum, giving the desired product. No purification step was necessary with this procedure.

General Procedure J: Formation of Methyl Esters 5. A carboxylic acid was dissolved in MeOH or Et_2O (10 mL/g), and a solution of CH_2N_2 in Et_2O was added until a persistent yellow color appeared. Acetic acid was then added dropwise until the yellow color disappeared. The resulting solution was concentrated to dryness, and the residue was dissolved in EtOAc (100 mL). The organic phase was washed with saturated $NaHCO_3$ (3 × 25 mL) and brine (25 mL). After being dried over anhydrous $MgSO_4$, the organic phase was filtered and concentrated to dryness, providing the desired product. No purification step was necessary with this procedure.

General Procedure K: Formation of BOC-Protected Amino Acids 1. An amino acid was dissolved in dry DMF (10 mL/g), and triethylamine (3 equiv) was added followed by di-*tert*-butyl dicarbonate (1.1 equiv). The reaction mixture was stirred at room temperature for 15 h, after which it was concentrated to dryness and the residue was dissolved in EtOAc (100 mL). The resulting mixture was washed with saturated $NaHCO_3$ (3 × 50 mL). The combined aqueous extracts were acidified to pH = 3 (pH paper) with 6 N HCl and washed with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated to give the desired product. No purification was necessary with this procedure.

***N*-BOC-L-[3-(1-methylindolyl)]alanine (1c).** Compound **1c** was prepared by subjecting *N*-methyltryptophan to general procedure K. Yield = 78%.

***N*-BOC-L-*tert*-leucine (1n).** Compound **1n** was prepared by subjecting L-*tert*-leucine to general procedure K. Yield = 64%. TLC: R_f = 0.56 ($CHCl_3$/MeOH/H_2O, 200/45/5).

***N*-BOC-L-abrine (1o).** Compound **1o** was prepared by subjecting L-abrine to general procedure K. Yield = 97%.

***N*-BOC-L-tryptophan *N*-Methylamide (2a).** Compound **2a** was prepared by coupling *N*-BOC-L-tryptophan, **1a**, with methylamine hydrochloride according to general procedure D. Yield = 97%.

***N*-BOC-L-tryptophan *N*-1-Pentylamide (2b).** Compound **2b** was prepared by coupling *N*-BOC-tryptophan, **1a**, with 1-aminopentane according to general procedure D. Yield = 92%.

***N*-BOC-L-tryptophan *N*-(Hydroxyethyl)amide (2c).** Compound **2c** was prepared by coupling *N*-BOC-tryptophan, **1a**, with ethanolamine according to general procedure D. Yield = 100%. TLC: $R_f = 0.71$ (10% MeOH/$CHCl_3$).

***N*-BOC-L-tryptophan *N*-[2-(Carbobenzyloxyamino)ethyl]amide (2d).** Compound **2d** was prepared by coupling *N*-BOC-tryptophan, **1a**, with mono(carboxybenzyloxy)ethylenediamine[53] according to general procedure D. Yield = 67%. TLC: $R_f = 0.50$ (70% EtOAc/hexane).

***N*-BOC-L-tryptophan *N*-Cyclopropylamide (2e).** Compound **2e** was prepared by coupling *N*-BOC-tryptophan, **1a**, with cyclopropylamine according to general procedure D. Yield = 92%.

***N*-BOC-L-tryptophan *N*-Cyclopentylamide (2f).** Compound **2f** was prepared by coupling *N*-BOC-tryptophan, **1a**, with cyclopentylamine according to general procedure D. Yield = 90%.

***N*-BOC-L-tryptophan *N*-[(*S*)-1-Indanyl]amide (2g).** Compound **2g** was prepared by coupling *N*-BOC-tryptophan, **1a**, with (*S*)-1-aminoindan according to general procedure D. Yield = 87%.

***N*-BOC-L-tryptophan *N*-[(*R*)-1-Indanyl]amide (2h).** Compound **2h** was prepared by coupling *N*-BOC-tryptophan, **1a**, with (*R*)-1-aminoindan according to general procedure D. Yield = 83%.

***N*-BOC-L-tryptophan [(1*R*,2*S*)-2-Hydroxy-1-indanyl]amide (2i).** Compound **2i** was prepared by coupling *N*-BOC-tryptophan, **1a**, with (1*R*,2*S*)-1-amino-2-indanol according to general procedure D. Yield = 78%.

***N*-BOC-L-tryptophan [(1*S*,2*R*)-2-Hydroxy-1-indanyl]amide (2j).** Compound **2j** was prepared by coupling *N*-BOC-tryptophan, **1a**, with (1*S*,2*R*)-1-amino-2-indanol according to general procedure D. Yield = 76%.

***N*-BOC-L-tryptophan *N*-Benzylamide (2k).** Compound **2k** was prepared by coupling *N*-BOC-tryptophan, **1a**, with benzylamine according to general procedure D. Yield = 98%.

***N*-BOC-L-tryptophan *N*-[(*S*)-Methylbenzyl]amide (2l).** Compound **2l** was prepared by coupling *N*-BOC-tryptophan, **1a**, with (*S*)-methylbenzylamine according to general procedure D. Yield = 98%.

***N*-BOC-L-tryptophan Piperonylamide (2m).** Compound **2m** was prepared by coupling *N*-BOC-tryptophan, **1a**, with piperonylamine according to general procedure D. Yield = 91%.

***N*-BOC-L-tryptophan *N*-(4-Pyridylmethyl)amide (2n).** Compound **2n** was prepared by coupling *N*-BOC-tryptophan, **1a**, with 4-(aminomethyl)pyridine according to general procedure D. Yield = 97%.

***N*-BOC-L-tryptophan *N*-(3-Pyridylmethyl)amide (2o).** Compound **2o** was prepared by coupling *N*-BOC-tryptophan, **1a**, with 3-(aminomethyl)pyridine according to general procedure D. Yield = 100%. TLC: $R_f = 0.22$ (EtOAc).

***N*-BOC-L-tryptophan *N*-(2-Pyridylmethyl)amide (2p).** Compound **2p** was prepared by coupling *N*-BOC-tryptophan, **1a**, with 2-(aminomethyl)pyridine according to general procedure D. Yield = 100%. TLC: $R_f = 0.33$ (EtOAc).

***N*-BOC-L-tryptophan *N*-[2-(2-Pyridyl)ethyl]amide (2q).** Compound **2q** was prepared by coupling *N*-BOC-tryptophan, **1a**, with 2-(aminoethyl)pyridine according to general procedure D. Yield = 98%. TLC: $R_f = 0.21$ (EtOAc).

***N*-BOC-L-tryptophan *N*-[2-(4-Hydroxyphenyl)ethyl]amide (2r).** Compound **2r** was prepared by coupling *N*-BOC-tryptophan, **1a**, with tyramine according to general procedure D. Yield = 100%. TLC: $R_f = 0.16$ (50% EtOAc/hexane).

***N*-BOC-L-tryptophan Furfurylamide (2s).** Compound **2s** was prepared by coupling *N*-BOC-tryptophan, **1a**, with furfurylamine according to general procedure D. Yield = 90%.

***N*-BOC-L-tryptophan *N*-(2-Thiazolylmethyl)amide (2t).** Compound **2t** was prepared by coupling *N*-BOC-tryptophan, **1a**, with 2-(aminomethyl)thiazole[54] according to general procedure D. Yield = 83%. TLC: $R_f = 0.15$ (50% EtOAc/hexane).

***N*-BOC-L-tryptophan *N*-(2-Benzimidazolylmethyl)amide (2u).** Compound **2u** was prepared by coupling *N*-BOC-tryptophan, **1a**, with 2-(aminomethyl)benzimidazole according to general procedure D. Yield = 70%.

***N*-BOC-L-tryptophan *N*-[3-(1-Imidazolylpropyl)]amide (2v).** Compound **2v** was prepared by coupling *N*-BOC-tryptophan, **1a**, with 1-(3-aminopropyl)imidazole according to general procedure D. Yield = 98%. TLC: $R_f = 0.10$ (5% MeOH/$CHCl_3$).

***N*-BOC-L-tryptophan *N*-[3-(4-Morpholinylpropyl)]amide (2w).** Compound **2w** was prepared by coupling *N*-BOC-tryptophan, **1a**, with 4-(3-aminopropyl)morpholine according to general procedure D. Yield = 96%. TLC: $R_f = 0.56$ (15% MeOH/$CHCl_3$).

***N*-BOC-L-tryptophan *N*,*N*-Dimethylamide (2x).** Compound **2x** was prepared by coupling *N*-BOC-tryptophan, **1a**, with dimethylamine hydrochloride according to general procedure D. Yield = 75%.

***N*-BOC-L-tryptophan Pyrolidinylamide (2y).** Compound **2y** was prepared by coupling *N*-BOC-tryptophan, **1a**, with pyrolidine according to general procedure D. Yield = 94%. TLC: $R_f = 0.14$ (50% EtOAc/hexane).

***N*-BOC-L-tryptophan Piperidinylamide (2z).** Compound **2z** was prepared by coupling *N*-BOC-tryptophan, **1a**, with piperidine according to general procedure D. Yield = 89%.

***N*-BOC-L-tryptophan Morpholinylamide (2aa).** Compound **2aa** was prepared by coupling *N*-BOC-tryptophan, **1a**, with morpholine according to general procedure D. Yield = 100%. TLC: $R_f = 0.42$ (EtOAc).

***N*-BOC-D-tryptophan *N*-Methylamide (2bb).** Compound **2bb** was prepared by coupling *N*-BOC-D-tryptophan, **1b**, with methylamine hydrochloride according to general procedure D. Yield = 97%.

***N*-BOC-L-[3-(1-methylindolyl)]alanine *N*-Methylamide (2cc).** Compound **2cc** was prepared by coupling *N*-BOC-1-methyltryptophan, **1c**, with methylamine hydrochloride according to general procedure D. Yield = 89%. TLC: $R_f = 0.85$ ($MeOH/CHCl_3$, 1/25).

***N*-BOC-L-(3-benzothienyl)alanine *N*-Methylamide (2dd).** Compound **2dd** was prepared by coupling *N*-BOC-benzothienylalanine, **1d**, with methylamine hydrochloride according to general procedure D. Yield = 97%. TLC: $R_f = 0.31$ (50% EtOAc/hexane).

***N*-BOC-L-(1-naphthyl)alanine *N*-Methylamide (2ee).** Compound **2ee** was prepared by coupling *N*-BOC-1-naphthylalanine, **1e**, with methylamine hydrochloride according to general procedure D. Yield = 95%. TLC: $R_f = 0.33$ (50% EtOAc/hexane).

***N*-BOC-L-(1-naphthyl)alanine *N*-[3-(4-Morpholinylpropyl)]amide (2ff).** Compound **2ff** was prepared by coupling *N*-BOC-1-naphthylalanine, **1e**, with 4-(3-aminopropyl)morpholine according to general procedure D. Yield = 90%. TLC: $R_f = 0.37$ (hexane/EtOAc/MeOH 3/3/1).

***N*-BOC-L-(2-naphthyl)alanine *N*-Methylamide (2gg).** Compound **2gg** was prepared by coupling *N*-BOC-2-naphthylalanine, **1f**, with methylamine hydrochloride according to general procedure D. Yield = 90%. TLC: $R_f = 0.60$ (10% MeOH/$CHCl_3$).

***N*-BOC-L-(2-naphthyl)alanine *N*-[3-(4-Morpholinylpropyl)]amide (2hh).** Compound **2hh** was prepared by coupling *N*-BOC-2-naphthylalanine, **1f**, with 4-(3-aminopropyl)morpholine according to general procedure D. Yield = 77%. TLC: $R_f = 0.61$ ($CHCl_3$/MeOH/H_2O, 30/9/1).

***N*-BOC-L-(2-naphthyl)alanine *N*-[2-(4-Hydroxyphenyl)ethyl]amide (2ii).** Compound **2ii** was prepared by coupling *N*-BOC-2-naphthylalanine, **1f**, with tyramine according to general procedure D. Yield = 95%. TLC: $R_f = 0.67$ ($CHCl_3$/MeOH/H_2O, 30/9/1).

***N*-BOC-L-(2-naphthyl)alanine *N*-[(*S*)-Methylbenzyl]amide (2jj).** Compound **2jj** was prepared by coupling *N*-BOC-2-naphthylalanine, **1f**, with (*S*)-methylbenzylamine according

to general procedure D. Yield = 89%. TLC: R_f = 0.89 ($CHCl_3$/MeOH/H_2O, 30/9/1).

***N*-BOC-L-(2-naphthyl)alanine *N*-Benzylamide (2kk).** Compound **2kk** was prepared by coupling *N*-BOC-2-naphthylalanine, **1f**, with benzylamine according to general procedure D. Yield = 94%. TLC: R_f = 0.83 ($CHCl_3$/MeOH/H_2O, 30/9/1).

***N*-BOC-L-(3-quinolyl)alanine *N*-Methylamide (2ll).** Compound **2ll** was prepared by coupling *N*-BOC-3-quinolylalanine, **1g**, with methylamine hydrochloride according to general procedure D. Yield = 88%. TLC: R_f = 0.81 (10% MeOH/$CHCl_3$).

***N*-BOC-L-(8-quinolyl)alanine Methylamide (2mm).** Compound **2mm** was prepared by coupling *N*-BOC-8-quinolylalanine, **1h**, with methylamine hydrochloride according to general procedure D. Yield = 69%. TLC: R_f = 0.80 (10% MeOH/$CHCl_3$).

***N*-BOC-L-(4,4′-biphenyl)alanine *N*-Methylamide (2oo).** Compound **2oo** was prepared by coupling *N*-BOC-4,4′-biphenylalanine, **1j**, with methylamine hydrochloride according to general procedure D. Yield = 83%. TLC: R_f = 0.0.77 (10% MeOH/$CHCl_3$).

***N*-BOC-L-(4,4′-biphenyl)alanine *N*-[3-(4-Morpholinylpropyl)]amide (2pp).** Compound **2pp** was prepared by coupling *N*-BOC-4,4′-biphenylalanine, **1j**, with (aminopropyl)-morpholine according to general procedure D. Yield = 72%. TLC: R_f = 0.65 ($CHCl_3$/MeOH/H_2O, 30/9/1).

***N*-BOC-L-(4,4′-biphenyl)alanine *N*-[2-(4-Hydroxyphenyl)ethyl]amide (2qq).** Compound **2qq** was prepared by coupling *N*-BOC-4,4′-biphenylalanine, **1j**, with tyramine according to general procedure D. Yield = 92%. TLC: R_f = 0.63 ($CHCl_3$/MeOH/H_2O, 30/9/1).

***N*-BOC-L-(4,4′-biphenyl)alanine *N*-[(*S*)-Methylbenzyl]amide (2rr).** Compound **2rr** was prepared by coupling *N*-BOC-4,4′-biphenylalanine, **1j**, with (*S*)-methylbenzylamine according to general procedure D. Yield = 78%. TLC: R_f = 0.90 ($CHCl_3$/MeOH/H_2O, 30/9/1).

***N*-BOC-L-(4,4′-biphenyl)alanine *N*-Benzylamide (2ss).** Compound **2ss** was prepared by coupling *N*-BOC-4,4′-biphenylalanine, **1j**, with benzylamine according to general procedure D. Yield = 84%. TLC: R_f = 0.90 ($CHCl_3$/MeOH/H_2O, 30/9/1).

***N*-BOC-L-phenylalanine *N*-Methylamide (2tt).** Compound **2tt** was prepared by coupling *N*-BOC-phenylalanine, **1k**, with methylamine hydrochloride according to general procedure D. Yield = 76%. TLC: R_f = 0.70 (10% MeOH/$CHCl_3$).

***N*-BOC-L-(3-pyridyl)alanine *N*-Benzylamide (2uu).** Compound **2uu** was prepared by coupling *N*-BOC-3-pyridylalanine, **1l**, with benzylamine according to general procedure D. Yield = 68%. TLC: R_f = 0.64 (10% MeOH/$CHCl_3$).

***N*-BOC-L-(4-pyridyl)alanine *N*-Methylamide (2vv).** Compound **2vv** was prepared by coupling *N*-BOC-4-pyridylalanine, **1m**, with methylamine hydrochloride according to general procedure D. Yield = 71%. TLC: R_f = 0.12 (EtOAc).

***N*-BOC-L-(4-pyridyl)alanine *N*-[2-(4-Hydroxyphenyl)-ethyl]amide (2xx).** Compound **2xx** was prepared by coupling *N*-BOC-4-pyridylalanine, **1m**, with tyramine according to general procedure D. Yield = 84%. TLC: R_f = 0.30 (10% MeOH/$CHCl_3$).

***N*-BOC-L-(4-pyridyl)alanine *N*-[(*S*)-Methylbenzyl]-amide (2yy).** Compound **2yy** was prepared by coupling *N*-BOC-4-pyridylalanine, **1m**, with (*S*)-methylbenzylamine according to general procedure D. Yield = 75%. TLC: R_f = 0.47 (10% MeOH/$CHCl_3$).

***N*-BOC-L-(4-pyridyl)alanine *N*-Benzylamide (2zz).** Compound **2zz** was prepared by coupling *N*-BOC-4-pyridylalanine, **1m**, with benzylamine according to general procedure D. Yield = 56%. TLC: R_f = 0.57 (10% MeOH/$CHCl_3$).

***N*-BOC-L-*tert*-leucine *N*-Methylamide (2aaa).** Compound **2aaa** was prepared by coupling *N*-BOC-*tert*-leucine, **1n**, with methylamine hydrochloride according to general procedure D. Yield = 60%. TLC: R_f = 0.42 (50% EtOAc/hexane).

***N*-BOC-L-abrine *N*-Methylamide (2bbb).** Compound **2bbb** was prepared by coupling *N*-BOC-L-abrine, **1o**, with methylamine hydrochloride according to general procedure D. Yield = 56%. TLC: R_f = 0.15 (50% EtOAc/hexane).

***N*-BOC-L-abrine *N*-[3-(4-Morpholinylpropyl)]amide (2ccc).** Compound **2ccc** was prepared by coupling *N*-BOC-abrine, **1o**, with 4-(3-aminopropyl)morpholine according to general procedure D. Yield = 50%. TLC: R_f = 0.23 (5% MeOH/$CHCl_3$).

L-Tryptophan *N*-Methylamide Hydrochloride Salt (3a). Compound **3a** was prepared by subjecting compound **2a** to general procedure E. Yield = 100%.

L-Tryptophan *N*-1-Pentylamide Hydrochloride Salt (3b). Compound **3b** was prepared by subjecting compound **2b** to general procedure E. Yield = 100%.

L-Tryptophan *N*-(Hydroxyethyl)amide Hydrochloride Salt (3c). Compound **3c** was prepared by subjecting compound **2c** to general procedure E. Yield = 100%.

L-Tryptophan *N*-[2-(Carbobenzyloxyamino)ethyl]-amide Hydrochloride Salt (3d). Compound **3d** was prepared by subjecting compound **2d** to general procedure E. Yield = 100%.

L-Tryptophan *N*-Cyclopropylamide Hydrochloride Salt (3e). Compound **3e** was prepared by subjecting compound **2e** to general procedure E. Yield = 100%.

L-Tryptophan *N*-Cyclopentylamide Hydrochloride Salt (3f). Compound **3f** was prepared by subjecting compound **2f** to general procedure E. Yield = 100%.

L-Tryptophan *N*-[(*S*)-1-Indanyl]amide Hydrochloride Salt (3g). Compound **3g** was prepared by subjecting compound **2g** to general procedure E. Yield = 100%.

L-Tryptophan *N*-[(*R*)-1-Indanyl]amide Hydrochloride Salt (3h). Compound **3h** was prepared by subjecting compound **2h** to general procedure E. Yield = 100%.

L-Tryptophan [(1*R*,2*S*)-2-Hydroxy-1-indanyl]amide Hydrochloride Salt (3i). Compound **3i** was prepared by subjecting compound **2i** to general procedure E. Yield = 100%.

L-Tryptophan [(1*S*,2*R*)-2-Hydroxy-1-indanyl]amide Hydrochloride Salt (3j). Compound **3j** was prepared by subjecting compound **2j** to general procedure E. Yield = 100%.

L-Tryptophan *N*-Benzylamide Hydrochloride Salt (3k). Compound **3k** was prepared by subjecting compound **2k** to general procedure E. Yield = 100%.

L-Tryptophan *N*-[(*S*)-Methylbenzyl]amide Hydrochloride Salt (3l). Compound **3l** was prepared by subjecting compound **2l** to general procedure E. Yield = 100%.

L-Tryptophan Piperonylamide Hydrochloride Salt (3m). Compound **3m** was prepared by subjecting compound **2m** to general procedure E. Yield = 100%.

L-Tryptophan *N*-(4-Pyridylmethyl)amide Hydrochloride Salt (3n). Compound **3n** was prepared by subjecting compound **2n** to general procedure E. Yield = 100%.

L-Tryptophan *N*-(3-Pyridylmethyl)amide Hydrochloride Salt (3o). Compound **3o** was prepared by subjecting compound **2o** to general procedure E. Yield = 100%.

L-Tryptophan *N*-(2-Pyridylmethyl)amide Hydrochloride Salt (3p). Compound **3p** was prepared by subjecting compound **2p** to general procedure E. Yield = 100%.

L-Tryptophan *N*-[2-(2-Pyridyl)ethyl]amide Hydrochloride Salt (3q). Compound **3q** was prepared by subjecting compound **2q** to general procedure E. Yield = 100%.

L-Tryptophan *N*-[2-(4-Hydroxyphenyl)ethyl]amide Hydrochloride Salt (3r). Compound **3r** was prepared by subjecting compound **2r** to general procedure E. Yield = 100%.

L-Tryptophan Furfurylamide Hydrochloride Salt (3s). Compound **3s** was prepared by subjecting compound **2s** to general procedure E. Yield = 100%.

L-Tryptophan *N*-(2-Thiazolylmethyl)amide Hydrochloride Salt (3t). Compound **3t** was prepared by subjecting compound **2t** to general procedure E. Yield = 100%.

L-Tryptophan *N*-(2-Benzimidazolylmethyl)amide Hydrochloride Salt (3u). Compound **3u** was prepared by subjecting compound **2u** to general procedure E. Yield = 100%.

L-Tryptophan *N*-[3-(1-Imidazolylpropyl)]amide Hydrochloride Salt (3v). Compound **3v** was prepared by subjecting compound **2v** to general procedure E. Yield = 100%.

L-Tryptophan *N*-[3-(4-Morpholinylpropyl)]amide Hydrochloride Salt (3w). Compound **3w** was prepared by subjecting compound **2w** to general procedure E. Yield = 100%.

L-Tryptophan *N,N*-Dimethylamide Hydrochloride Salt (3x). Compound **3x** was prepared by subjecting compound **2x** to general procedure E. Yield = 100%.

L-Tryptophan Pyrolidinylamide Hydrochloride Salt (3y). Compound **3y** was prepared by subjecting compound **2y** to general procedure E. Yield = 100%.

L-Tryptophan Piperidinylamide Hydrochloride Salt (3z). Compound **3z** was prepared by subjecting compound **2z** to general procedure E. Yield = 100%.

L-Tryptophan Morpholinylamide Hydrochloride Salt (3aa). Compound **3aa** was prepared by subjecting compound **2aa** to general procedure E. Yield = 100%.

D-Tryptophan *N*-Methylamide Hydrochloride Salt (3bb). Compound **3bb** was prepared by subjecting compound **2bb** to general procedure E. Yield = 100%.

L-[3-(1-Methylindolyl)]alanine *N*-Methylamide Hydrochloride Salt (3cc). Compound **3cc** was prepared by subjecting compound **2cc** to general procedure E. Yield = 100%.

L-(3-Benzothienyl)alanine *N*-Methylamide Hydrochloride Salt (3dd). Compound **3dd** was prepared by subjecting compound **2dd** to general procedure E. Yield = 100%.

L-(1-Naphthyl)alanine *N*-Methylamide Hydrochloride Salt (3ee). Compound **3ee** was prepared by subjecting compound **2ee** to general procedure E. Yield = 100%.

L-(1-Naphthyl)alanine *N*-[3-(4-Morpholinylpropyl)]-amide Hydrochloride Salt (3ff). Compound **3ff** was prepared by subjecting compound **2ff** to general procedure E. Yield = 100%.

L-(2-Naphthyl)alanine *N*-Methylamide Hydrochloride Salt (3gg). Compound **3gg** was prepared by subjecting compound **2gg** to general procedure E. Yield = 100%.

L-(2-Naphthyl)alanine *N*-[3-(4-Morpholinylpropyl)]-amide Hydrochloride Salt (3hh). Compound **3hh** was prepared by subjecting compound **2hh** to general procedure E. Yield = 100%. TLC: R_f = 0.63 ($CHCl_3$/MeOH/H_2O, 30/9/1).

L-(2-Naphthyl)alanine *N*-[2-(4-Hydroxyphenyl)ethyl]-amide Hydrochloride Salt (3ii). Compound **3ii** was prepared by subjecting compound **2ii** to general procedure E. Yield = 100%. TLC: R_f = 0.61 ($CHCl_3$/MeOH/H_2O, 30/9/1).

L-(2-Naphthyl)alanine *N*-[(*S*)-Methylbenzyl]amide Hydrochloride Salt (3jj). Compound **3jj** was prepared by subjecting compound **2jj** to general procedure E. Yield = 100%. TLC: R_f = 0.51 (10% MeOH/$CHCl_3$).

L-(2-Naphthyl)alanine *N*-Benzylamide Hydrochloride Salt (3kk). Compound **3kk** was prepared by subjecting compound **2kk** to general procedure E. Yield = 100%. TLC: R_f = 0.60 (10% MeOH/$CHCl_3$).

L-(3-Quinolyl)alanine *N*-Methylamide Hydrochloride Salt (3ll). Compound **3ll** was prepared by subjecting compound **2ll** to general procedure E. Yield = 100%. TLC: R_f = 0.40 (10% MeOH/$CHCl_3$).

L-(8-Quinolyl)alanine Methylamide Hydrochloride Salt (3mm). Compound **3mm** was prepared by subjecting compound **2mm** to general procedure E. Yield = 100%. TLC: R_f = 0.41 (10% MeOH/$CHCl_3$).

L-(4,4′-Biphenyl)alanine *N*-Methylamide Hydrochloride Salt (3oo). Compound **3oo** was prepared by subjecting compound **2oo** to general procedure E. Yield = 100%.

L-(4,4′-Biphenyl)alanine *N*-[3-(4-Morpholinylpropyl)]-amide Hydrochloride Salt (3pp). Compound **3pp** was prepared by subjecting compound **2pp** to general procedure E. Yield = 100%. TLC: R_f = 0.61 ($CHCl_3$/MeOH/H_2O, 30/9/1).

L-(4,4′-Biphenyl)alanine *N*-[2-(4-Hydroxyphenyl)ethyl]-amide Hydrochloride Salt (3qq). Compound **3qq** was prepared by subjecting compound **2qq** to general procedure E. Yield = 100%. TLC: R_f = 0.65 ($CHCl_3$/MeOH/H_2O, 30/9/1).

L-(4,4′-Biphenyl)alanine *N*-[(*S*)-Methylbenzyl]amide Hydrochloride Salt (3rr). Compound **3rr** was prepared by subjecting compound **2rr** to general procedure E. Yield = 100%. TLC: R_f = 0.65 ($CHCl_3$/MeOH/H_2O, 30/9/1).

L-(4,4′-Biphenyl)alanine *N*-Benzylamide Hydrochloride Salt (3ss). Compound **3ss** was prepared by subjecting compound **2ss** to general procedure E. Yield = 100%. TLC: R_f = 0.59 (10% MeOH/$CHCl_3$).

L-Phenylalanine *N*-Methylamide Hydrochloride Salt (3tt). Compound **3tt** was prepared by subjecting compound **2tt** to general procedure E. Yield = 100%. TLC: R_f = 0.38 (10% MeOH/$CHCl_3$).

L-(3-Pyridyl)alanine *N*-Benzylamide Hydrochloride Salt (3uu). Compound **3uu** was prepared by subjecting compound **2uu** to general procedure E. Yield = 100%. TLC: R_f = 0.24 (10% MeOH/$CHCl_3$).

L-(4-Pyridyl)alanine *N*-Methylamide Hydrochloride Salt (3vv). Compound **3vv** was prepared by subjecting compound **2vv** to general procedure E. Yield = 100%.

L-(4-Pyridyl)alanine *N*-[2-(4-Hydroxyphenyl)ethyl]-amide Hydrochloride Salt (3xx). Compound **3xx** was prepared by subjecting compound **2xx** to general procedure E. Yield = 100%.

L-(4-Pyridyl)alanine *N*-[(*S*)-Methylbenzyl]amide Hydrochloride Salt (3yy). Compound **3yy** was prepared by subjecting compound **2yy** to general procedure E. Yield = 100%.

L-(4-Pyridyl)alanine *N*-Benzylamide Hydrochloride Salt (3zz). Compound **3zz** was prepared by subjecting compound **2zz** to general procedure E. Yield = 100%. TLC: R_f = 0.44 ($CHCl_3$/MeOH/H_2O, 30/9/1).

L-*tert*-Leucine *N*-Methylamide Hydrochloride Salt (3aaa). Compound **3aaa** was prepared by subjecting compound **2aaa** to general procedure E. Yield = 100%.

L-Abrine *N*-Methylamide Hydrochloride Salt (3bbb). Compound **3bbb** was prepared by subjecting compound **2bbb** to general procedure E. Yield = 100%.

L-Abrine *N*-[3-(4-Morpholinylpropyl)]amide Hydrochloride Salt, 3ccc. Compound **3ccc** was prepared by subjecting compound **2ccc** to general procedure E. Yield (100)%.

(*R*)-2-(2-Methylpropyl)-3-(*tert*-butoxycarbonyl)propionic Acid (4c). Compound 4c was prepared by subjecting compound 15a to general procedure C. Yield = 68%.

(*R*)-2-Butyl-3-(*tert*-butoxycarbonyl)propionic Acid (4d). Compound **4d** was prepared by subjecting compound **15b** to general procedure C. Yield = 76%.

(*R*)-2-Hexyl-3-(*tert*-butoxycarbonyl)propionic Acid (4e). Compound **4e** was prepared by subjecting compound **15c** to general procedure C. Yield = 46%.

(*R*)-2-Octyl-3-(*tert*-butoxycarbonyl)propionic Acid (4f). Compound **4f** was prepared by subjecting compound **15d** to general procedure C. Yield = 76%.

(*R*)-2-(Isopropyloxy)-3-(methoxycarbonyl)propionic Acid (4g). 10% Pd/C (0.48 g) was placed under vacuum, and MeOH (5 mL) was added. Compound **21a** (1.92 g, 6.86 mmol) was dissolved in MeOH (10 mL) and added, via cannula, to the Pd/C. The mixture was degassed under vacuum and stirred under H_2 for 16 h. Filtration of the reaction through Celite and concentration under vacuum gave the desired product (1.30 g, 100%) which was used without further purification. TLC: R_f = 0.10 (15% EtOAc/hexane).

(*R*)-2-(Pentyloxy)-3-(methoxycarbonyl)propionic Acid (4h). 10% Pd/C (0.35 g) was placed under vacuum, and MeOH (10 mL) was added. The ether (1.40 g, 4.55 mmol) was dissolved in MeOH (5 mL) and added, via cannula, to the Pd/C. The mixture was degassed under vacuum and stirred under H_2 for 24 h. Filtration of the reaction through Celite and concentration under vacuum gave compound **4h** (0.98 g, 100%), which was used without further purification.

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-1-Pentylamide (5b). Compound **5b** was prepared by coupling compound **3b** with compound **4a** according to general procedure F. Yield = 67%.

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan (Hydroxyethyl)amide (5c). Compound **5c** was prepared by coupling compound **3c** with compound **4a** according to general procedure F. Yield = 14%. TLC: R_f = 0.58 (10% MeOH/$CHCl_3$).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-[2-(Carbobenzyloxyamino)ethyl]amide (5d). Compound **5d** was prepared by coupling compound **3d** with compound **4a** according to general procedure F. Yield = 40%. TLC: R_f = 0.67 (MeOH/$CHCl_3$, 1/25).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-Cyclopropylamide (5e). Compound **5e** was prepared by coupling compound **3e** with compound **4a** according to general procedure F. Yield = 79%.

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-Cyclopentylamide (5f). Compound **5f** was prepared by coupling compound **3f** with compound **4a** according to general procedure F. Yield = 58%.

3-(Methoxycarbonyl-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-[(*S*)-1-Indanyl]amide (5g). Compound **5g** was prepared by coupling compound **3g** with compound **4a** according to general procedure F. Yield = 48%.

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-[(*R*)-1-Indanyl]amide (5h). Compound **5h** was prepared by coupling compound **3h** with compound **4a** according to general procedure F. Yield = 44%.

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan [(1*R*,2*S*)-2-Hydroxy-1-indanyl]amide (5i). Compound **5i** was prepared by coupling compound **3i** with compound **4a** according to general procedure F. Yield = 56%.

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan [(1*S*,2*R*)-2-Hydroxy-1-indanyl]amide (5j). Compound **5j** was prepared by coupling compound **3j** with compound **4a** according to general procedure F. Yield = 72%.

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-Benzylamide (5k). Compound **5k** was prepared by coupling compound **3k** with compound **4a** according to general procedure F. Yield = 83%.

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-[(*S*)-Methylbenzyl]amide (5l). Compound **5l** was prepared by coupling compound **3l** with compound **4a** according to general procedure F. Yield = 50%.

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan Piperonylamide (5m). Compound **5m** was prepared by coupling compound **3m** with compound **4a** according to general procedure F. Yield = 77%.

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-(4-Pyridylmethyl)amide (5n). Compound **5n** was prepared by coupling compound **3n** with compound **4a** according to general procedure F. Yield = 44%. TLC: R_f = 0.15 (EtOAc).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-(3-Pyridylmethyl)amide (5o). Compound **5o** was prepared by coupling compound **3o** with compound **4a** according to general procedure F. Yield = 58%. TLC: R_f = 0.17 (EtOAc).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-(2-Pyridylmethyl)amide (5p). Compound **5p** was prepared by coupling compound **3p** with compound **4a** according to general procedure F. Yield = 70%.

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-[2-(2-Pyridyl)ethyl]amide (5q). Compound **5q** was prepared by coupling compound **3q** with compound **4a** according to general procedure F. Yield = 49%.

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-[2-(4-Hydroxyphenyl)ethyl]amide (5r). Compound **5r** was prepared by coupling compound **3r** with compound **4a** according to general procedure F. Yield = 40%. TLC: R_f = 0.11 (50% EtOAc/hexane).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan Furfurylamide (5s). Compound **5s** was prepared by coupling compound **3s** with compound **4a** according to general procedure F. Yield = 55%.

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-(2-Thiazolylmethyl)amide (5t). Compound **5t** was prepared by coupling compound **3t** with compound **4a** according to general procedure F. Yield = 45%. TLC: R_f = 0.36 (70% EtOAc/hexane).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-(2-Benzimidazolylmethyl)amide (5u). Compound **5u** was prepared by coupling compound **3u** with compound **4a** according to general procedure F. Yield = 71%.

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-[3-(1-Imidazolylpropyl)]amide (5v). Compound **5v** was prepared by coupling compound **3v** with compound **4a** according to general procedure F. Yield = 58%.

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-[3-(4-Morpholinylpropyl)]amide (5w). Compound **5w** was prepared by coupling compound **3w** with compound **4a** according to general procedure F. Yield = 50%. TLC: R_f = 0.55 (15% MeOH/$CHCl_3$).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*,*N*-Dimethylamide (5x). Compound **5x** was prepared by coupling compound **3x** with compound **4a** according to general procedure F. Yield = 69%.

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan Pyrolidinylamide (5y). Compound **5y** was prepared by coupling compound **3y** with compound **4a** according to general procedure F. Yield = 57%.

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan Piperidinylamide (5z). Compound **5z** was prepared by coupling compound **3z** with compound **4a** according to general procedure F. Yield = 85%.

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan Morpholinylamide (5aa). Compound **5aa** was prepared by coupling compound **3aa** with compound **4a** according to general procedure F. Yield = 78%. TLC: R_f = 0.41 (EtOAc).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-D-tryptophan Methylamide (5bb). Compound **5bb** was prepared by coupling compound **3bb** with compound **4a** according to general procedure F. Yield = 57%.

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-[3-(1-Methylindolyl)]alanine *N*-Methylamide (5cc). Compound **5cc** was prepared by coupling compound **3cc** with compound **4a** according to general procedure F. Separation of the diastereomers due to racemic **1c** was accomplished via column chromatography (silica gel, EtOAc/hexane, 2/1). Yield = 36%. TLC: R_f = 0.36 (EtOAc/hexane, 2/1).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(3-benzothienyl)alanine *N*-Methylamide (5dd). Compound **5dd** was prepared by coupling compound **3dd** with compound **4a** according to general procedure F. Yield = 84%. TLC: R_f = 0.20 (50% EtOAc/hexane).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(1-naphthyl)alanine *N*-Methylamide (5ee). Compound **5ee** was prepared by coupling compound **3ee** with compound **4a** according to general procedure F. Yield = 76%. TLC: R_f = 0.29 (50% EtOAc/hexane).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(1-naphthyl)alanine *N*-[3-(4-Morpholinylpropyl)]amide (5ff). Compound **5ff** was prepared by coupling compound **3ff** with compound **4a** according to general procedure F. Yield = 30%. TLC: R_f = 0.60 (10% MeOH/$CHCl_3$).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(2-naphthyl)alanine *N*-Methylamide (5gg). Compound **5gg** was prepared by coupling compound **3gg** with compound **4a** according to general procedure F. Yield = 66%. TLC: R_f = 0.75 (10% MeOH/$CHCl_3$).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(2-naphthyl)alanine *N*-[3-(4-Morpholinylpropyl)]amide (5hh). Compound **5hh** was prepared by coupling compound

3hh with compound **4a** according to general procedure F. Yield = 66%. TLC: R_f = 0.56 (20% MeOH/$CHCl_3$).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(2-naphthyl)alanine *N*-[2-(4-Hydroxyphenyl)ethyl]amide (5ii). Compound **5ii** was prepared by coupling compound **3ii** with compound **4a** according to general procedure F. Yield = 69%. TLC: R_f = 0.61 (10% MeOH/$CHCl_3$).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(2-naphthyl)alanine *N*-[(*S*)-Methylbenzyl]amide (5jj). Compound **5jj** was prepared by coupling compound **3jj** with compound **4a** according to general procedure F. Yield = 53%. TLC: R_f = 0.38 (EtOAc/hexane, 1/2).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(2-naphthyl)alanine *N*-Benzylamide (5kk). Compound **5kk** was prepared by coupling compound **3kk** with compound **4a** according to general procedure F. Yield = 85%. TLC: R_f = 0.50 (10% MeOH/$CHCl_3$).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(3-quinolyl)alanine *N*-Methylamide (5ll). Compound **5ll** was prepared by coupling compound **3ll** with compound **4a** according to general procedure F. Yield = 96%. TLC: R_f = 0.44 (MeOH/$CHCl_3$, 1/20).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(8-quinolyl)alanine Methylamide (5mm). Compound **5mm** was prepared by coupling compound **3mm** with compound **4a** according to general procedure F. Yield = 69%. TLC: R_f = 0.44 (10% MeOH/$CHCl_3$).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(4,4′-biphenyl)alanine *N*-Methylamide (5oo). Compound **5oo** was prepared by coupling compound **3oo** with compound **4a** according to general procedure F. Yield = 63%. TLC: R_f = 0.58 (MeOH/$CHCl_3$, 1/50).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(4,4′-biphenyl)alanine *N*-[3-(4-Morpholinylpropyl)]amide (5pp). Compound **5pp** was prepared by coupling compound **3pp** with compound **4a** according to general procedure F. Yield = 50%. TLC: R_f = 0.38 (MeOH/$CHCl_3$, 1/5).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(4,4′-biphenyl)alanine *N*-[2-(4-Hydroxyphenyl)ethyl]amide (5qq). Compound **5qq** was prepared by coupling compound **3qq** with compound **4a** according to general procedure F. Yield = 77%. TLC: R_f = 0.53 (20% MeOH/$CHCl_3$).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(4,4′-biphenyl)alanine *N*-[(*S*)-Methylbenzyl]amide (5rr). Compound **5rr** was prepared by coupling compound **3rr** with compound **4a** according to general procedure F. Yield = 51%. TLC: R_f = 0.50 (EtOAc/hexane, 2/1).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(4,4′-biphenyl)alanine *N*-Benzylamide (5ss). Compound **5ss** was prepared by coupling compound **3ss** with compound **4a** according to general procedure F. Yield = 54%. TLC: R_f = 0.36 (10% MeOH/$CHCl_3$).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-phenylalanine *N*-Methylamide (5tt). Compound **5tt** was prepared by coupling compound **3tt** with compound **4a** according to general procedure F. Yield = 65%. TLC: R_f = 0.71 (MeOH/$CHCl_3$, 1/5).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(3-pyridyl)alanine *N*-Benzylamide (5uu). Compound **5uu** was prepared by coupling compound **3uu** with compound **4a** according to general procedure F. Yield = 73%. TLC: R_f = 0.61 (MeOH/$CHCl_3$, 1/5).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(4-pyridyl)alanine *N*-Methylamide (5vv). Compound **5vv** was prepared by coupling compound **3vv** with compound **4a** according to general procedure F. Yield = 74%. TLC: R_f = 0.30 (5% MeOH/$CHCl_3$).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(4-pyridyl)alanine *N*-[2-(4-Hydroxyphenyl)ethyl]amide (5xx). Compound **5xx** was prepared by coupling compound **3xx** with compound **4a** according to general procedure F. Yield = 56%. TLC: R_f = 0.49 (10% MeOH/$CHCl_3$).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(4-pyridyl)alanine *N*-[(*S*)-Methylbenzyl]amide (5yy). Compound **5yy** was prepared by coupling compound **3yy** with compound **4a** according to general procedure F. Yield = 86%. TLC: R_f = 0.37 (MeOH/$CHCl_3$, 1/5).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-(4-pyridyl)alanine *N*-Benzylamide (5zz). Compound **5zz** was prepared by coupling compound **3zz** with compound **4a** according to general procedure F. Yield = 53%. TLC: R_f = 0.43 (MeOH/$CHCl_3$, 1/5).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-*tert*-leucine *N*-Methylamide (5aaa). Compound **5aaa** was prepared by coupling compound **3aaa** with compound **4a** according to general procedure F. Yield = 57%. TLC: R_f = 0.54 (EtOAc).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-abrine *N*-Methylamide (5bbb). Compound **4a** (0.46 g, 2.45 mmol) was dissolved in dry THF (5 mL), and oxalyl chloride (0.21 mL, 2.45 mmol) was added followed by the addition of DMF (1 drop). The reaction mixture was stirred for 20 min at room temperature, after which compound **3bbb** (0.65 g, 2.45 mmol) was added followed by triethylamine (1.19 mL, 8.56 mmol). The reaction mixture was stirred at room temperature for an additional 24 h and quenched with the addition of water (10 mL). The mixture was washed with EtOAc (30 mL), and the organic phase was sequentially washed with 1 N HCl (3 × 10 mL), saturated $NaHCO_3$ (3 × 10 mL), and brine (10 mL). After being dried over anhydrous $MgSO_4$, the organic phase was concentrated, and the residue was purified on silica gel (50% EtOAc/hexane), giving compound **5bbb** (0.84 g, 86%). TLC: R_f = 0.45 (EtOAc).

3-(Methoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-abrine *N*-[3-(4-Morpholinylpropyl)]amide (5ccc). Compound **5ccc** was prepared by coupling compound **3ccc** with compound **4a** according to the procedure utilized for the preparation of compound **5bbb**. Yield = 80%. TLC: R_f = 0.40 (10% MeOH/$CHCl_3$).

3-(Methoxycarbonyl)-2(*S*)-(isobutylpropionyl)-L-tryptophan *N*-Methylamide (5ddd). Compound **5ddd** was prepared by coupling compound **3a** with compound **4b** according to general procedure F. Yield = 53%.

3-(*tert*-Butoxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-Methylamide (5eee). Compound **5eee** was prepared by coupling compound **3a** with compound **4c** according to general procedure F. Yield = 48%.

3-(*tert*-Butoxycarbonyl)-2(*R*)-(butylpropionyl)-L-tryptophan *N*-Methylamide (5fff). Compound **5fff** was prepared by coupling compound **3a** with compound **4d** according to general procedure F. Yield = 47%. TLC: R_f = 0.15 (50% EtOAc/hexane).

3-(Methoxycarbonyl)-2(*R*)-(butylpropionyl)-L-tryptophan *N*-Methylamide (5ggg). Compound **5ggg** was prepared by subjecting compound **7eee** to general procedure J (solvent = MeOH). Yield = 92%. TLC: R_f = 0.40 (EtOAc).

3-(*tert*-Butoxycarbonyl)-2(*R*)-(hexylpropionyl)-L-tryptophan *N*-Methylamide (5hhh). Compound **5hhh** was prepared by coupling compound **3a** with compound **4e** according to general procedure F. Yield = 26%. TLC: R_f = 0.18 (50% EtOAc/hexane).

3-(Methoxycarbonyl)-2(*R*)-(hexylpropionyl)-L-tryptophan *N*-Methylamide (5iii). Compound **5iii** was prepared by subjecting compound **7fff** to general procedure J (solvent = MeOH). Yield = 95%. TLC: R_f = 0.45 (EtOAc).

3-(*tert*-Butoxycarbonyl)-2(*R*)-(octylpropionyl)-L-tryptophan *N*-Methylamide (5jjj). Compound **5jjj** was prepared by coupling compound **3a** with compound **4f** according to general procedure F. Yield = 38%. TLC: R_f = 0.20 (50% EtOAc/hexane).

3-(Methoxycarbonyl)-2(*R*)-(octylpropionyl)-L-tryptophan *N*-Methylamide (5kkk). Compound **5kkk** was prepared by subjecting compound **7ggg** to general procedure J (solvent = MeOH). Yield = 96%. TLC: R_f = 0.50 (EtOAc).

3-(Methoxycarbonyl)-2(*R*)-[(isopropyloxy)propionyl]-L-tryptophan Methylamide (5lll). Compound **5lll** was prepared by subjecting coupling compound **4g** with compound

3a according to general procedure F. Yield = 40%. TLC: R_f = 0.31 (EtOAc).

3-(Methoxycarbonyl)-2(*R*)-[(pentyloxy)propionyl]-L-tryptophan Methylamide (5mmm). Compound **5mmm** was prepared by coupling compound **4h** with compound **3a** according to general procedure F. Yield = 42%. TLC: R_f = 0.35 (EtOAc).

3-(Methoxycarbonyl)-3(*S*)-hydroxy-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-Methylamide (5nnn). Compound **5nnn** was prepared by subjecting compound **7e** to general procedure J (solvent = MeOH). Yield = 71%. TLC: R_f = 0.22 (EtOAc).

3-(Methoxycarbonyl)-3(*S*)-hydroxy-2(*R*)-(isobutylpropionyl)-L-*tert*-leucine *N*-Methylamide (5ooo). Compound **5ooo** was prepared by subjecting compound **7f** to general procedure J (solvent = MeOH). Yield = 93%. TLC: R_f = 0.39 (EtOAc).

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-(1-Pentyl)amide (6b). Compound **6b** was prepared by subjecting compound **5b** to general procedure G. Yield = 41%. Purity: >98% (HPLC method C). ^{1}H NMR (300 MHz, DMSO): δ 0.8 (t, 3H), 0.9 (dd, 6H), 1.1−1.4 (m, 9H), 1.9 (dd, 1H), 2.0 (dd, 1H), 2.7 (m, 1H), 3.0 (m, 3H), 3.1 (dd, 1H), 4.5 (m, 1H), 6.95 (t, 1H), 7.05 (t, 1H), 7.1 (s, 1H), 7.3 (d, 1H), 7.5 (d, 1H), 7.7 (t, 1H), 8.0 (d, 1H), 8.7 (s, 1H), 10.4 (s, 1H), 10.8 (s, 1H). Anal. ($C_{24}H_{36}N_4O_4$) H, N; C: calcd, 64.84; found, 65.25.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan (Hydroxyethyl)amide (6c). Compound **6c** was prepared by subjecting compound **5c** to general procedure G. Yield = 18%. TLC: R_f = 0.57 ($CHCl_3$/MeOH/H_2O, 45/9/1). Purity: >98% (HPLC method B). ^{1}H NMR (300 MHz, DMSO): δ 0.75 (dd, 6H), 0.95 (m, 1H), 1.35 (m, 2H), 1.9 (dd, 1H), 2.0 (dd, 1H), 2.65 (m, 1H), 2.95 (dd, 1H), 3.1 (m, 3H), 3.3 (m, 2H), 4.45 (m, 1H), 4.6 (t, 1H), 6.95 (t, 1H), 7.0 (t, 1H), 7.1 (s, 1H), 7.3 (d, 1H), 7.55 (d, 1H), 7.75 (m, 1H), 8.05 (d, 1H), 8.85 (s, 1H), 10.4 (s, 1H), 11.75 (s, 1H). Anal. ($C_{21}H_{30}N_4O_5$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-[2-(Carbobenzyloxyamino)ethyl]amide (6d). Compound **6d** was prepared by subjecting compound **5d** to general procedure G. Yield = 30%. TLC: R_f = 0.48 (MeOH/$CHCl_3$, 1/6). Purity: >92% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.75 (dd, 6H), 1.0 (m, 1H), 1.35 (m, 2H), 1.9 (dd, 1H), 2.05 (dd, 1H), 2.65 (m, 1H), 2.9−3.2 (m, 6H), 4.4 (m, 1H), 5.0 (s, 2H), 7.0 (t, 1H), 7.1 (t, 1H), 7.15 (s, 1H), 7.2 (m, 1H), 7.25−7.45 (m, 6H), 7.55 (d, 1H), 8.0 (m, 1H), 8.05 (d, 1H), 8.8 (bs, 1H), 10.4 (bs, 1H), 10.8 (s, 1H). Anal. ($C_{29}H_{37}N_5O_6$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-Cyclopropylamide (6e). Compound **6e** was prepared by subjecting compound **5e** to general procedure G. Yield = 11%. Purity: >95% (HPLC method E). ^{1}H NMR (300 MHz, DMSO): δ 0.3 (m, 2H), 0.55 (m, 2H), 0.8 (dd, 6H), 1.0 (m, 1H), 1.35 (m, 2H), 1.95 (dd, 1H), 2.05 (dd, 1H), 2.6 (m, 1H), 2.65 (m, 1H), 2.95 (dd, 1H), 3.1 (dd, 1H), 4.4 (m, 1H), 6.95 (t, 1H), 7.05 (t, 1H), 7.1 (s, 1H), 7.3 (d, 1H), 7.55 (d, 1H), 7.85 (d, 1H), 7.95 (d, 1H), 8.75 (s, 1H), 10.4 (s, 1H), 10.8 (s, 1H). Anal. ($C_{22}H_{30}N_4O_4$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-Cyclopentylamide (6f). Compound **6f** was prepared by subjecting compound **5f** to general procedure G. Yield = 22%. Purity: >95% (HPLC method E). ^{1}H NMR (300 MHz, DMSO): δ 0.75 (dd, 6H), 1.0 (m, 1H), 1.2−1.8 (m, 10H), 1.95 (dd, 1H), 2.05 (dd, 1H), 2.7 (m, 1H), 2.95 (dd, 1H), 3.05 (dd, 1H), 3.95 (m, 1H), 4.45 (m, 1H), 6.95 (t, 1H), 7.05 (t, 1H), 7.1 (s, 1H), 7.3 (d, 1H), 7.55 (d, 1H), 7.6 (d, 1H), 8.0 (d, 1H), 8.75 (bs, 1H), 10.4 (bs, 1H), 10.8 (s, 1H). Anal. ($C_{24}H_{34}N_4O_4$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-[(*S*)-1-Indanyl]amide (6g). Compound **6g** was prepared by subjecting compound **5g** to general procedure G. Yield = 21%. Purity: >94% (HPLC method E). ^{1}H NMR (300 MHz, DMSO): δ 0.75 (dd, 6H), 1.0 (m, 1H), 1.35 (m, 2H), 1.7 (m, 1H), 1.95 (m, 2H), 2.3 (m, 1H), 2.7−2.9 (m, 3H), 3.0 (dd, 1H), 3.15 (dd, 1H), 4.95 (m, 1H), 5.2 (m, 1H), 6.75 (d, 1H), 6.95 (t, 1H), 7.05 (t, 2H), 7.2 (m, 3H), 7.35 (d, 1H), 7.6 (d, 1H), 8.0 (d, 1H), 8.05 (d, 1H), 8.7 (s, 1H), 10.35 (s, 1H), 10.8 (s, 1H). Anal. ($C_{28}H_{34}N_4O_4$·0.25H_2O) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-[(*R*)-1-Indanyl]amide (6h). Compound **6h** was prepared by subjecting compound **5h** to general procedure G. Yield = 33%. Purity: >91% (HPLC method E). ^{1}H NMR (300 MHz, DMSO): δ 0.8 (dd, 6H), 1.0 (m, 1H), 1.4 (m, 2H), 1.65 (m, 1H), 1.95 (m, 2H), 2.25 (m, 1H), 2.7−2.9 (m, 3H), 3.0 (dd, 1H), 3.15 (dd, 1H), 4.55 (m, 1H), 5.25 (m, 1H), 6.95 (t, 1H), 7.0−7.15 (m, 3H), 7.15−7.25 (m, 3H), 7.3 (d, 1H), 7.6 (d, 1H), 8.1 (m, 2H), 8.7 (s, 1H), 10.35 (s, 1H), 10.8 (s, 1H). Anal. ($C_{28}H_{34}N_4O_4$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan-[(1*R*,2*S*)-2-Hydroxy-1-indanyl]amide (6i). Compound **6i** was prepared by subjecting compound **5i** to general procedure G. Yield = 14%. Purity: >98% (HPLC method E). ^{1}H NMR (300 MHz, DMSO): δ 0.75 (dd, 6H), 1.0 (m, 1H), 1.4 (m, 2H), 1.9 (m, 2H), 2.75 (m, 2H), 3.05 (m, 2H), 3.25 (dd, 1H), 4.4 (m, 1H), 4.65 (m, 1H), 4.85 (d, 1H), 5.15 (m, 1H), 6.8 (d, 1H), 7.0 (t, 1H), 7.1 (m, 2H), 7.2 (m, 3H), 7.35 (d, 1H), 7.65 (d, 1H), 7.7 (d, 1H), 8.3 (d, 1H), 8.7 (s, 1H), 10.35 (s, 1H), 10.8 (s, 1H). Anal. ($C_{28}H_{34}N_4O_5$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan-[(1*S*,2*R*)-2-Hydroxy-1-indanyl]amide (6j). Compound **6j** was prepared by subjecting compound **5j** to general procedure G. Yield = 20%. Purity: >98% (HPLC method C). ^{1}H NMR (300 MHz, DMSO): δ 0.8 (dd, 6H), 1.0 (m, 1H), 1.4 (m, 2H), 1.9 (m, 2H), 2.8 (m, 1H), 2.85 (dd, 1H), 3.0 (m, 2H), 3.3 (dd, 1H), 4.4 (m, 1H), 4.7 (m, 1H), 5.0 (d, 1H), 5.2 (m, 1H), 7.0 (t, 1H), 7.1−7.3 (m, 6H), 7.35 (d, 1H), 7.6 (dd, 2H), 8.4 (d, 1H), 8.7 (s, 1H), 10.4 (s, 1H), 10.8 (s, 1H). Anal. ($C_{28}H_{34}N_4O_5$·0.25H_2O) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-Benzylamide (6k). Compound **6k** was prepared by subjecting compound **5k** to general procedure G. Yield = 38%. Purity: >91% (HPLC method C). ^{1}H NMR (300 MHz, DMSO): δ 0.8 (dd, 6H), 1.0 (m, 1H), 1.4 (m, 2H), 1.95 (dd, 1H), 2.0 (dd, 1H), 2.7 (m, 1H), 3.0 (dd, 1H), 3.15 (dd, 1H), 4.25 (m, 2H), 4.6 (m, 1H), 6.95 (t, 1H), 7,0 (t, 1H), 7,1 (m, 3H), 7.2 (m, 4H), 7.3 (d, 1H), 8.1 (d, 1H), 8.3 (t, 1H), 8.75 (s, 1H), 10.5 (s, 1H), 11.0 (s, 1H). Anal. ($C_{26}H_{32}N_4O_4$·0.25H_2O) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-[(*S*)-Methylbenzyl]amide (6l). Compound **6l** was prepared by subjecting compound **5l** to general procedure G. Yield = 20%. Purity: >99% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.75 (dd, 6H), 1.0 (m, 1H), 1.3 (d, 3H), 1.3−1.45 (m, 2H), 1.9−2.1 (m, 2H), 2.7 (m, 1H), 2.95−3.15 (m, 2H), 4.45−4.55 (m, 1H), 4.8−5.0 (m, 1H), 6.95 (t, 1H), 7.05 (t, 1H), 7.1−7.3 (m, 6H), 7.45 (d, 1H), 7.55 (d, 1H), 8.1 (d, 1H), 8.2 (d, 1H), 8.6−10.6 (broad signals, 2H), 10.85 (s, 1H). Anal. ($C_{27}H_{34}N_4O_4$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan Piperonylamide (6m). Compound **6m** was prepared by subjecting compound **5m** to general procedure G. Yield = 10%. Purity: >95% (HPLC method E). ^{1}H NMR (300 MHz, DMSO): δ 0.75 (dd, 6H), 1.0 (m, 1H), 1.35 (m, 2H), 1.9 (dd, 1H), 2.05 (dd, 1H), 2.65 (m, 1H), 3.0 (dd, 1H), 3.15 (dd, 1H), 4.15 (m, 2H), 4.5 (m, 1H), 5.95 (s, 2H), 6.6 (d, 1H), 6.75 (t, 2H), 6.95 (t, 1H), 7.05 (t, 1H), 7.1 (s, 1H), 7.35 (d, 1H), 7.6 (d, 1H), 8.1 (d, 1H), 8.4 (t, 1H), 8.7−10.4 (broad signals, 2H), 10.8 (s, 1H). Anal. ($C_{27}H_{32}N_4O_6$·0.25H_2O) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-(4-Pyridylmethyl)amide (6n). Compound **6n** was prepared by subjecting compound **5n** to general procedure G. Yield = 45%. TLC: R_f = 0.60 ($CHCl_3$/MeOH/H_2O, 100/45/5). Purity: >90% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.8 (dd, 6H), 1.15 (m, 1H), 1.5 (m, 2H), 2.1 (dd, 1H), 2.25 (dd, 1H), 2.85 (m, 1H), 3.15 (dd, 1H), 3.3 (dd, 1H), 4.35 (d, 2H), 4.7 (m, 1H), 7.1 (t, 1H), 7.15 (m, 3H), 7.3 (s, 1H), 7.5 (d, 1H), 7.7 (d, 1H), 8.35 (d, 1H), 8.5 (d, 2H),

8.65 (t, 1H), 8.9 (s, 1H), 10.55 (s, 1H), 11.0 (s, 1H). Anal. ($C_{25}H_{31}N_5O_4 \cdot C_3H_8O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-(3-Pyridylmethyl)amide (6o). Compound **6o** was prepared by subjecting compound **5o** to general procedure G. Yield = 44%. TLC: R_f = 0.65 ($CHCl_3$/MeOH/H_2O, 100/45/5). Purity: >92% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.85 (dd, 6H), 1.15 (m, 1H), 1.45 (m, 2H), 2.05 (dd, 1H), 2.2 (dd, 1H), 2.85 (m, 1H), 3.15 (dd, 1H), 3.25 (dd, 1H), 4.3−4.5 (m, 2H), 4.65 (m, 1H), 7.05 (t, 1H), 7.15 (t, 1H), 7.25 (s, 1H), 7.4 (dd, 1H), 7.45 (d, 1H), 7.55 (d, 1H), 7.7 (d, 1H), 8.3 (d, 1H), 8.55 (s, 2H), 8.6 (t, 1H), 8.9 (s, 1H), 10.55 (s, 1H), 10.95 (s, 1H). Anal. ($C_{25}H_{31}N_5O_4$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-(2-Pyridylmethyl)amide (6p). Compound **6p** was prepared by subjecting compound **5p** to general procedure G. Yield = 15%. Purity: >98% (HPLC method D). ^{1}H NMR (300 MHz, DMSO): δ 0.8 (dd, 6H), 1.0 (m, 1H), 1.4 (m, 2H), 1.95 (dd, 1H), 2.05 (dd, 1H), 2.7 (m, 1H), 3.05 (dd, 1H), 3.2 (dd, 1H), 4.3 (d, 2H), 4.6 (m, 1H), 6.95−7.1 (m, 3H), 7.2 (s, 1H), 7.3 (m, 1H), 7.4 (d, 1H), 7.6 (m, 2H), 8.2 (d, 1H), 8.5 (m, 2H), 8.8 (s, 1H), 10.4 (s, 1H), 10.8 (s, 1H). Anal. ($C_{25}H_{31}N_5O_4 \cdot 0.25H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-[2-(2-Pyridyl)ethyl]amide (6q). Compound **6q** was prepared by subjecting compound **5q** to general procedure G. Yield = 12%. Purity: >97% (HPLC method D). ^{1}H NMR (300 MHz, DMSO): δ 0.85 (dd, 6H), 1.1 (m, 1H), 1.5 (m, 2H), 2.05 (dd, 1H), 2.15 (dd, 1H), 2.8 (m, 1H), 2.9 (t, 2H), 3.05 (dd, 1H), 3.15 (dd, 1H), 3.5 (m, 2H), 4.55 (m, 1H), 7.05 (t, 1H), 7.15 (t, 1H), 7.2 (d, 1H), 7.3 (m, 2H), 7.4 (d, 1H), 7.65 (d, 1H), 7.8 (dt, 1H), 8.05 (t, 1H), 8.15 (d, 1H), 8.6 (d, 1H), 8.9 (s, 1H), 10.5 (s, 1H), 10.9 (s, 1H). Anal. ($C_{26}H_{33}N_5O_4 \cdot 0.25H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-[2-(4-Hydroxyphenyl)ethyl]amide (6r). Compound **6r** was prepared by subjecting compound **5r** to general procedure G. Yield = 17%. TLC: R_f = 0.38 (15% MeOH/$CHCl_3$). Purity: >99% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.85 (dd, 6H), 1.15 (m, 1H), 1.5 (m, 2H), 2.05 (dd, 1H), 2.15 (dd, 1H), 2.6 (m, 2H), 2.8 (m, 1H), 3.05 (dd, 1H), 3.2 (dd, 1H), 3.2−3.35 (m, 2H), 4.55 (m, 1H), 6.75 (d, 2H), 7.05 (d, 2H), 7.05−7.2 (m, 2H), 7.25 (s, 1H), 7.45 (d, 1H), 7.7 (d, 1H), 8.0 (t, 1H), 8.15 (d, 1H), 8.9 (bs, 1H), 9.3 (bs, 1H), 10.5 (bs, 1H), 10.9 (bs, 1H). Anal. ($C_{27}H_{34}N_4O_5 \cdot 0.5H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan Furfurylamide (6s). Compound **6s** was prepared by subjecting compound **5s** to general procedure G. Yield = 18%. Purity: >96% (HPLC method E). ^{1}H NMR (300 MHz, DMSO): δ 0.75 (dd, 6H), 1.0 (m, 1H), 1.3 (m, 2H), 1.9 (dd, 1H), 2.05 (dd, 1H), 2.6 (m, 1H), 3.0 (dd, 1H), 3.15 (dd, 1H), 4.25 (m, 2H), 4.5 (m, 1H), 6.15 (s, 1H), 6.4 (s, 1H), 6.95 (t, 1H), 7.05 (t, 1H), 7.1 (s, 1H), 7.3 (d, 1H), 7.6 (m, 2H), 8.2 (d, 1H), 8.75 (bt, 1H), 8.8−10.4 (broad signals, 2H), 10.8 (bs, 1H). Anal. ($C_{24}H_{30}N_4O_5 \cdot 2.0H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-(2-Thiazolylmethyl)amide (6t). Compound **6t** was prepared by subjecting compound **5t** to general procedure G. Yield = 43%. TLC: R_f = 0.49 (MeOH/$CHCl_3$, 1/6). Purity: >98% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.85 (dd, 6H), 1.1 (m, 1H), 1.5 (m, 2H), 2.0−2.2 (m, 2H), 2.8 (m, 1H), 3.1 (dd, 1H), 3.25 (dd, 1H), 3.5 (m, 1H), 4.7 (m, 3H), 7.05−7.2 (m, 2H), 7.25 (s, 1H), 7.4 (d, 1H), 7.7 (m, 1H), 7.8 (s, 1H), 8.25 (d, 1H), 8.85 (s, 1H), 8.95 (t, 1H), 10.5 (s, 1H), 10.9 (s, 1H). Anal. ($C_{23}H_{29}N_5O_4S$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-(2-Benzimidazolylmethyl)amide (6u). Compound **6u** was prepared by subjecting compound **5u** to general procedure G. Yield = 22%. Purity: >99% (HPLC method E). ^{1}H NMR (300 MHz, DMSO): δ 0.7 (dd, 6H), 1.0 (m, 1H), 1.4 (m, 2H), 2.0 (dd, 1H), 2.1 (dd, 1H), 2.7 (m, 1H), 3.1 (dd, 1H), 3.25 (dd, 1H), 4.4−4.6 (m, 3H), 7.0 (t, 1H), 7.1 (t, 1H), 7.2 (m, 3H), 7.35 (d, 1H), 7.5 (m, 2H), 7.6 (d, 1H), 8.25 (d, 1H), 8.6 (t, 1H), 8.9 (s, 1H), 10.5 (s, 1H), 10.8 (s, 1H), 12.1 (s, 1H). Anal. ($C_{27}H_{32}N_6O_4 \cdot H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-[3-(1-Imidazolylpropyl)]amide (6v). Compound **6v** was prepared by subjecting compound **5v** to general procedure G. Yield = 19%. Purity: >95% (HPLC method E). ^{1}H NMR (300 MHz, DMSO): δ 0.7 (dd, 6H), 1.0 (m, 1H), 1.4 (m, 2H), 1.7 (m, 2H), 1.95 (dd, 1H), 2.15 (dd, 1H), 2.7 (m, 1H), 3.0 (m, 3H), 3.15 (dd, 1H), 3.8 (m, 2H), 4.45 (m, 1H), 6.9 (s, 1H), 7.0 (t, 1H), 7.05 (t, 1H), 7.1 (s, 1H), 7.15 (s, 1H), 7.3 (d, 1H), 7.6 (m, 2H), 7.95 (m, 1H), 8.1 (d, 1H), 8.8 (s, 1H), 10.4 (s, 1H), 10.8 (s, 1H). Anal. ($C_{25}H_{34}N_6O_4$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-[3-(4-Morpholinylpropyl)]amide (6w).[55] Compound **6w** was prepared by subjecting compound **5w** to general procedure G. Yield = 38%. Purity: >99% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.9 (dd, 6H), 1.15 (m, 1H), 1.4−1.6 (m, 4H), 2.05 (dd, 1H), 2.15 (dd, 1H), 2.25 (t, 2H), 2.3−2.4 (m, 4H), 2.8 (m, 1H), 3.0−3.25 (m, 4H), 3.65 (m, 4H), 4.55 (m, 1H), 7.05 (t, 1H), 7.15 (t, 1H), 7.25 (s, 1H), 7.45 (d, 1H), 7.7 (d, 1H), 7.9 (t, 1H), 8.15 (d, 1H), 8.95 (bs, 1H), 10.5 (s, 1H), 10.9 (s, 1H). Anal. ($C_{26}H_{39}N_5O_5 \cdot 0.5H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*,*N*-Dimethylamide (6x). Compound **6x** was prepared by subjecting compound **5x** to general procedure G. Yield = 28%. Purity: >96% (HPLC method E). ^{1}H NMR (300 MHz, DMSO): δ 0.8 (dd, 6H), 1.05 (m, 1H), 1.4 (m, 2H), 1.9−2.1 (m, 2H), 2.75 (s, 3H), 2.77 (s, 3H), 2.78 (m, 1H), 2.9 (dd, 1H), 3.05 (dd, 1H), 4.9 (m, 1H), 7.0 (t, 1H), 7.05 (t, 1H), 7.1 (s, 1H), 7.35 (d, 1H), 7.55 (d, 1H), 8.2 (d, 1H), 8.7 (s, 1H), 10.35 (s, 1H), 10.8 (s, 1H). Anal. ($C_{21}H_{30}N_4O_4$) C, H, N: calcd, 13.92; found, 13.15.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan Pyrolidinylamide (6y). Compound **6y** was prepared by subjecting compound **5y** to general procedure G. Yield = 18%. Purity: >90% (HPLC method E). ^{1}H NMR (300 MHz, DMSO): δ 0.8 (dd, 6H), 1.0 (m, 1H), 1.4 (m, 4H), 1.6 (m, 2H), 1.9−2.1 (m, 2H), 2.8 (m, 2H), 3.0 (dd, 1H), 3.05−3.2 (m, 4H), 4.7 (m, 1H), 7.0 (t, 1H), 7.05 (t, 1H), 7.15 (s, 1H), 7.25 (d, 1H), 7.5 (d, 1H), 8.2 (d, 1H), 8.7 (s, 1H), 10.4 (s, 1H), 10.8 (s, 1H). Anal. ($C_{23}H_{32}N_4O_4$) C, H, N: calcd, 13.07; found, 12.34.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan Piperidinylamide (6z). Compound **6z** was prepared by subjecting compound **5z** to general procedure G. Yield = 27%. Purity: >93% (HPLC method E). ^{1}H NMR (300 MHz, DMSO): δ 0.8 (dd, 6H), 1.0 (m, 1H), 1.2−1.6 (m, 8H), 1.9 (dd, 1H), 2.1 (dd, 1H), 2.8 (m, 1H), 2.9 (dd, 1H), 3.1 (dd, 1H), 3.2−3.4 (m, 4H), 5.0 (m, 1H), 6.95−7.1 (m, 3H), 7.3 (d, 1H), 7.6 (d, 1H), 8.3 (d, 1H), 8.7 (s, 1H), 10.5 (s, 1H), 10.8 (s, 1H). Anal. ($C_{24}H_{34}N_4O_4 \cdot 1.5H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan Morpholinylamide (6aa). Compound **6aa** was prepared by subjecting compound **5aa** to general procedure G. Yield = 32%. TLC: R_f = 0.71 ($CHCl_3$/MeOH/H_2O, 100/45/5). Purity: >99% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.95 (dd, 6H), 1.15 (m, 1H), 1.55 (m, 2H), 2.05 (dd, 1H), 2.20 (dd, 1H), 2.9 (m, 2H), 3.05 (dd, 1H), 3.2−3.3 (m, 3H), 3.3−3.5 (m, 5H), 5.05 (m, 1H), 7.05 (t, 1H), 7.15 (t, 1H), 7.25 (s, 1H), 7.45 (d, 1H), 7.7 (d, 1H), 8.5 (d, 1H), 8.85 (s, 1H), 10.5 (s, 1H), 10.95 (s, 1H). Anal. ($C_{23}H_{32}N_4O_5$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-D-tryptophan Methylamide (6bb). Compound **6bb** was prepared by subjecting compound **5bb** to general procedure G. Yield = 38%. Purity: >99% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.55 (d, 3H), 0.65 (d, 3H), 0.75−0.85 (m, 2H), 1.15 (m, 1H), 1.95 (dd, 1H), 2.15 (dd, 1H), 2.55−2.65 (m, 1H), 2.65 (d, 3H), 2.8 (dd, 1H), 3.3 (dd, 1H), 4.4 (m, 1H), 6.95 (t, 1H), 7.05 (t, 1H), 7.1 (s, 1H), 7.3 (d, 1H), 7.55 (d, 1H), 7.9 (m, 1H), 8.25 (d, 1H), 8.8 (s, 1H), 10.5 (s, 1H), 10.8 (s, 1H).

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-[3-(1-methylindolyl)]alanine *N*-Methylamide (6cc). Compound **6cc** was prepared by subjecting compound **5cc** to general procedure G. Yield = 42%. TLC: R_f = 0.48 (MeOH/

$CHCl_3$, 1/6). Purity: >99% (HPLC method A). ^1H NMR (300 MHz, DMSO): δ 0.85 (dd, 6H), 1.1 (m, 1H), 1.45 (m, 2H), 2.05 (dd, 1H), 2.2 (dd, 1H), 2.65 (d, 3H), 2.75 (m, 1H), 3.05 (dd, 1H), 3.2 (dd, 1H), 4.85 (s, 3H), 4.5 (m, 1H), 7.1 (t, 1H), 7.2 (m, 2H), 7.45 (d, 1H), 7.65 (d, 1H), 7.95 (m, 1H), 8.1 (d, 1H), 8.9 (s, 1H), 10.5 (s, 1H). Anal. ($C_{21}H_{30}N_4O_4$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(3-benzothienyl)alanine *N*-Methylamide (6dd). Compound **6dd** was prepared by subjecting compound **5dd** to general procedure G. Yield = 10%. TLC: R_f = 0.55 ($CHCl_3$/MeOH/H_2O, 150/45/5). Purity: >94% (HPLC method A). ^1H NMR (300 MHz, DMSO): δ 0.85 (dd, 6H), 1.1 (m, 1H), 1.3−1.5 (m, 2H), 2.05 (dd, 1H), 2.2 (dd, 1H), 2.7 (t, 3H), 2.75 (m, 1H), 3.25 (dd, 1H), 3.4 (dd, 1H), 4.65 (m, 1H), 7.45−7.55 (m, 3H), 8.0 (d, 1H), 8.05−8.15 (m, 2H), 8.3 (d, 1H), 8.9 (s, 1H), 10.55 (s, 1H). Anal. ($C_{20}H_{27}N_3O_4S$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(1-naphthyl)alanine *N*-Methylamide (6ee). Compound **6ee** was prepared by subjecting compound **5ee** to general procedure G. Yield = 25%. TLC: R_f = 0.79 ($CHCl_3$/MeOH/H_2O, 200/45/5). Purity: >93% (HPLC method L). ^1H NMR (300 MHz, DMSO): δ 0.85 (dd, 6H), 1.15 (m, 1H), 1.3−1.5 (m, 2H), 2.05 (dd, 1H), 2.2 (dd, 1H), 2.7 (m, 4H), 3.4 (dd, 1H), 3.7 (dd, 1H), 4.65 (m, 1H), 7.45−7.55 (m, 2H), 7.65−7.75 (m, 2H), 7.9 (d, 1H), 8.05 (d, 1H), 8.1 (m, 1H), 8.3−8.4 (m, 2H), 8.95 (s, 1H), 10.6 (bs, 1H). Anal. ($C_{22}H_{29}N_3O_4 \cdot 1.67H_2O$) C, N, H; calcd, 7.59; found, 6.93.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(1-naphthyl)alanine *N*-[3-(4-Morpholinylpropyl)]amide (6ff). Compound **6ff** was prepared by subjecting compound **5ff** to general procedure G. Yield = 41%. TLC: R_f = 0.55 ($CHCl_3$/MeOH/H_2O, 150/45/5). Purity: >93% (HPLC method A). ^1H NMR (300 MHz, DMSO): δ 0.9 (dd, 6H), 1.15 (m, 1H), 1.4−1.5 (m, 2H), 1.5−1.65 (m, 2H), 2.05 (dd, 1H), 2.2 (dd, 1H), 2.25 (m, 2H), 2.4 (m, 4H), 2.75 (m, 1H), 3.15 (m, 2H), 3.4 (m, 2H), 3.65 (m, 4H), 4.65 (m, 1H), 7.45−7.55 (m, 2H), 7.6−7.75 (m, 2H), 7.9 (m, 2H), 8.05 (d, 1H), 8.25 (d, 1H), 8.35 (d, 1H), 8.85 (bs, 1H), 10.5 (bs, 1H). Anal. ($C_{28}H_{40}N_4O_5$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(2-naphthyl)alanine *N*-Methylamide (6gg). Compound **6gg** was prepared by subjecting compound **5gg** to general procedure G. Yield = 54%. TLC: R_f = 0.60 ($CHCl_3$/MeOH/H_2O, 150/45/5). Purity: >99% (HPLC method A). ^1H NMR (300 MHz, DMSO): δ 0.75 (dd, 6H), 1.0 (m, 1H), 1.2−1.4 (m, 2H), 2.0 (dd, 1H), 2.15 (dd, 1H), 2.7 (m, 4H), 3.1 (dd, 1H), 3.35 (dd, 1H), 4.6 (m, 1H), 7.45−7.6 (m, 3H), 7.8 (s, 1H), 7.9−8.0 (m, 3H), 8.1 (m, 1H), 8.25 (d, 1H), 8.9 (s, 1H), 10.55 (s, 1H). Anal. ($C_{22}H_{29}N_3O_4$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(2-naphthyl)alanine *N*-[3-(4-Morpholinylpropyl)]amide (6hh). Compound **6hh** was prepared by subjecting compound **5hh** to general procedure G. Yield = 33%. TLC: R_f = 0.58 ($CHCl_3$/MeOH/H_2O, 150/45/5). Purity: >89% (HPLC method E). ^1H NMR (300 MHz, DMSO): δ 0.8 (dd, 6H), 1.05 (m, 1H), 1.45 (m, 2H). 1.55 (m, 2H), 2.0 (dd, 1H), 2.15 (dd, 1H), 2.25 (t, 2H), 2.35 (m, 4H), 2.75 (m, 1H), 3.05−3.2 (m, 3H), 3.3 (dd, 1H), 3.65 (m, 4H), 4.65 (m, 1H), 7.5−7.65 (m, 3H), 7.8 (s, 1H), 7.9−8.05 (m, 4H), 8.25 (d, 1H), 8.95 (bs, 1H), 10.5 (s, 1H). Anal. ($C_{28}H_{40}N_4O_5 \cdot 0.5H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(2-naphthyl)alanine *N*-[2-(4-Hydroxyphenyl)ethyl]amide (6ii). Compound **6ii** was prepared by subjecting compound **5ii** to general procedure G. Yield = 10%. TLC: R_f = 0.59 ($CHCl_3$/MeOH/H_2O, 150/45/5). Purity: >93% (HPLC method I). ^1H NMR (300 MHz, DMSO): δ 0.6 (d, 3H), 0.8 (d, 3H), 1.0 (m, 1H), 1.2 (m, 1H), 1.3 (m, 1H), 2.0 (dd, 1H), 2.2 (dd, 1H), 2.5−2.7 (m, 3H), 3.1 (dd, 1H), 3.2−3.5 (m, 3H), 4.6 (m, 1H), 6.8 (d, 2H), 7.1 (d, 2H), 7.5−7.65 (m, 3H), 7.8 (s, 1H), 7.9−8.0 (m, 3H), 8.4 (d, 1H), 8.7 (bs, 1H), 8.8−11 (broad signals, 3H). Anal. ($C_{29}H_{35}N_3O_5 \cdot 1.33H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(2-naphthyl)alanine *N*-[(*S*)-Methylbenzyl]amide (6jj). Compound **6jj** was prepared by subjecting compound **5jj** to general procedure G. Yield = 10%. TLC: R_f = 0.55 ($CHCl_3$/MeOH/H_2O, 200/45/5). Purity: >88% (HPLC method E). ^1H NMR (300 MHz, DMSO): δ 0.65 (dd, 6H), 0.95 (m, 1H), 1.2−1.35 (m, 2H), 1.4 (d, 3H), 1.9 (dd, 1H), 2.0 (dd, 1H), 2.6 (m, 1H), 3.0 (dd, 1H), 3.2 (dd, 1H), 4.6 (m, 1H), 4.9 (m, 1H), 7.15 (s, 5H), 7.35−7.5 (m, 3H), 7.7 (s, 1H), 7.75−7.85 (m, 3H), 8.2 (d, 1H), 8.45 (d, 1H), 8.8−10.5 (broad signals, 2H). Anal. ($C_{29}H_{35}N_3O_4 \cdot H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(2-naphthyl)alanine *N*-Benzylamide (6kk). Compound **6kk** was prepared by subjecting compound **5kk** to general procedure G. Yield = 11%. TLC: R_f = 0.67 ($CHCl_3$/MeOH/H_2O, 150/45/5). Purity: >98% (HPLC method E). ^1H NMR (300 MHz, DMSO): δ 0.8 (dd, 6H), 1.1 (m, 1H), 1.3−1.5 (m, 2H), 2.0 (dd, 1H), 2.15 (dd, 1H), 2.8 (m, 1H), 3.2 (dd, 1H), 3.35 (dd, 1H), 4.4 (d, 2H), 4.75 (m, 1H), 7.25 (m, 2H), 7.3 (m, 3H), 7.5−7.65 (m, 3H), 7.85 (s, 1H), 7.9−8.05 (m, 3H), 8.85 (d, 1H), 8.6 (t, 1H), 8.9 (s, 1H), 10.5 (s, 1H). Anal. ($C_{28}H_{33}N_3O_4 \cdot 0.33H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(3-quinolyl)alanine *N*-Methylamide (6ll). Compound **6ll** was prepared by subjecting compound **5ll** to general procedure G. Yield = 29%. TLC: R_f = 0.50 (MeOH/$CHCl_3$, 1/6). Purity: >95% (HPLC method F). ^1H NMR (300 MHz, DMSO): δ 0.65 (dd, 6H), 0.85−1.3 (m, 3H), 1.9 (dd, 1H), 2.05 (dd, 1H), 2.6 (m, 4H), 3.05 (dd, 1H), 3.25 (dd, 1H), 4.5 (m, 1H), 7.55 (t, 1H), 7.7 (m, 1H), 7.85−8.0 (m, 3H), 8.15 (s, 1H), 8.2 (m, 1H), 8.75 (s, 1H), 8.9 (s, 1H), 10.4 (s, 1H). Anal. ($C_{21}H_{28}N_4O_4 \cdot 0.67H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(8-quinolyl)alanine Methylamide (6mm). Compound **6mm** was prepared by subjecting compound **5mm** to general procedure G. Yield = 37%. TLC: R_f = 0.48 (MeOH/$CHCl_3$, 1/9). Purity: >88% (HPLC method A). ^1H NMR (300 MHz, DMSO): δ 0.65 (dd, 6H), 0.9 (m, 1H), 1.15 (m, 2H), 1.9 (dd, 1H), 2.0 (dd, 1H), 2.6 (d, 3H), 3.4 (m, 1H), 3.75 (dd, 1H), 4.65 (m, 1H), 7.45−7.6 (m, 4H), 7.8 (m, 2H), 8.1 (d, 1H), 8.35 (d, 1H), 8.8 (s, 1H), 8.95 (s, 1H), 10.45 (s, 1H). Anal. ($C_{21}H_{28}N_4O_4 \cdot 0.75H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(4,4′-biphenyl)alanine *N*-Methylamide (6oo). Compound **6oo** was prepared by subjecting compound **5oo** to general procedure G. Yield = 10%. TLC: R_f = 0.66 ($CHCl_3$/MeOH/H_2O, 150/45/5). Purity: >97% (HPLC method I). ^1H NMR (300 MHz, DMSO): δ 0.85 (dd, 6H), 1.1 (m, 1H), 1.3−1.5 (m, 2H), 2.05 (dd, 1H), 2.2 (dd, 1H), 2.7 (m, 4H), 3.0 (dd, 1H), 3.2 (dd, 1H), 4.55 (m, 1H), 7.4−7.5 (m, 3H), 7.55 (t, 2H), 7.65 (d, 2H), 7.75 (d, 2H), 8.05 (m, 1H), 8.2 (d, 1H), 8.9 (s, 1H), 10.55 (s, 1H). Anal. ($C_{24}H_{31}N_3O_4 \cdot 0.33H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(4,4′-biphenyl)alanine *N*-[3-(4-Morpholinylpropyl)]amide (6pp). Compound **6pp** was prepared by subjecting compound **5pp** to general procedure G. Yield = 13%. TLC: R_f = 0.62 ($CHCl_3$/MeOH/H_2O, 150/45/5). Purity: >96% (HPLC method I). ^1H NMR (300 MHz, DMSO): δ 0.85 (dd, 6H), 1.1 (m, 1H), 1.3−1.5 (m, 2H), 1.55−1.65 (m, 2H), 2.05 (dd, 1H), 2.15 (dd, 1H), 2.25−2.35 (t, 2H), 2.35−2.45 (m, 4H), 2.75 (m, 1H), 3.0 (dd, 1H), 3.1−3.25 (m, 3H), 3.6−3.7 (m, 4H), 4.55 (m, 1H), 7.4 (d, 2H), 7.45 (d, 1H), 7.55 (t, 2H), 7.7 (d, 2H), 7.75 (d, 2H), 8.0 (t, 1H), 8.25 (d, 1H), 8.95 (bs, 1H), 10.5 (s, 1H). Anal. ($C_{30}H_{42}N_4O_5 \cdot 0.5H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(4,4′-biphenyl)alanine *N*-[2-(4-Hydroxyphenyl)ethyl]amide (6qq). Compound **6qq was** prepared by subjecting compound **5qq** to general procedure G. Yield = 18%. TLC: R_f = 0.30 (MeOH/$CHCl_3$, 1/20). Purity: >97% (HPLC method E). ^1H NMR (300 MHz, DMSO): δ 0.65 (dd, 6H), 0.95 (m, 1H), 1.2 (m, 1H), 1.35 (m, 1H), 1.9 (dd, 1H), 2.15 (dd, 1H), 2.6 (m, 3H), 2.85 (m, 2H), 3.1−3.3 (m, 2H), 4.45 (m, 1H), 6.7 (d, 2H), 7.0 (d, 2H), 7.35 (m, 3H), 7.45 (m, 2H), 7.55 (d, 2H), 7.65 (d, 2H), 8.2 (m, 1H), 8.5 (bs, 1H), 8.8−9.8 (broad signals, 2H), 10.4 (broad signal, 1H). Anal. ($C_{31}H_{37}N_3O_5 \cdot H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(4,4′-biphenyl)alanine *N*-[(*S*)-Methylbenzyl]amide (6rr). Compound **6rr** was prepared by subjecting compound **5rr** to

general procedure G. Yield = 18%. TLC: R_f = 0.50 (MeOH/$CHCl_3$, 1/9). Purity: >92% (HPLC method F). ^{1}H NMR (300 MHz, DMSO): δ 0.75 (dd, 6H), 0.95 (m, 1H), 1.2−1.45 (m, 5H), 1.9 (dd, 1H), 2.05 (dd, 1H), 2.6 (m, 1H), 2.85 (dd, 1H), 3.05 (dd, 1H), 4.55 (m, 1H), 4.9 (m, 1H), 7.1−7.4 (m, 8H), 7.45 (t, 2H), 7.55 (d, 2H), 7.65 (m, 2H), 8.2 (d, 1H), 8.5−8.6 (m, 1H), 8.8−10.5 (broad signals, 2H). Anal. ($C_{31}H_{37}N_3O_4 \cdot 0.5H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(4,4′-biphenyl)alanine *N*-Benzylamide (6ss). Compound **6ss** was prepared by subjecting compound **5ss** to general procedure G. Yield = 10%. TLC: R_f = 0.35 (10% MeOH/$CHCl_3$). Purity: >99% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.85 (dd, 6H), 1.1 (m, 1H), 1.3−1.5 (m, 2H), 2.05 (dd, 1H), 2.15 (dd, 1H), 2.8 (m, 1H), 3.0 (dd, 1H), 3.2 (dd, 1H), 4.4 (m, 2H), 4.7 (m, 1H), 7.25−7.5 (m, 8H), 7.55 (t, 2H), 7.7 (d, 2H), 7.75 (d, 2H), 8.35 (d, 1H), 8.6 (t, 1H), 8.9 (s, 1H), 10.5 (bs, 1H). Anal. ($C_{30}H_{35}N_3O_4 \cdot 1.33H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-phenylalanine *N*-Methylamide (6tt). Compound **6tt** was prepared by subjecting compound **5tt** to general procedure G. Yield = 20%. TLC: R_f = 0.39 (MeOH/$CHCl_3$, 2/9). Purity: >85% (HPLC method E). ^{1}H NMR (300 MHz, DMSO): δ 0.8 (dd, 6H), 1.05 (m, 1H), 1.2 (m, 1H), 1.35 (m, 1H), 2.0 (dd, 1H), 2.25 (dd, 1H), 2.55 (m, 1H), 2.7 (d, 3H), 2.95 (dd, 1H), 3.25 (dd, 1H), 4.45 (m, 1H), 7.2−7.4 (m, 6H), 8.25 (d, 1H), 8.8 (bs, 1H), 10.4 (bs, 1H). Anal. ($C_{18}H_{27}N_3O_4$) C, H; N: calcd, 12.03; found, 11.54.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(3-pyridyl)alanine *N*-Benzylamide (6uu). Compound **6uu** was prepared by subjecting compound **5uu** to general procedure G. Yield = 15%. TLC: R_f = 0.45 (MeOH/$CHCl_3$, 1/6). Purity: >85% (HPLC method F). ^{1}H NMR (300 MHz, DMSO): δ 0.75 (dd, 6H), 0.95 (m, 1H), 1.2−1.45 (m, 2H), 1.8−2.0 (m, 2H), 2.15 (m, 1H), 2.85 (dd, 1H), 3.05 (dd, 1H), 4.25 (m, 2H), 4.5 (m, 1H), 7.1−7.3 (m, 5H), 7.65 (d, 1H), 8.25 (d, 1H), 8.35−8.55 (m, 4H), 8.85 (s, 1H), 10.35 (s, 1H). Anal. ($C_{23}H_{30}N_4O_4 \cdot H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(4-pyridyl)alanine *N*-Methylamide (6vv). Compound **6vv** was prepared by subjecting compound **5vv** to general procedure G. Yield = 28%. TLC: R_f = 0.40 ($CHCl_3$/MeOH/H_2O, 200/45/5). Purity: >99% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.85 (dd, 6H), 1.05 (m, 1H), 1.3 (m, 1H), 1.4 (m, 1H), 2.05 (dd, 1H), 2.15 (dd, 1H), 2.7 (m, 4H), 2.95 (dd, 1H), 3.2 (dd, 1H), 4.55 (m, 1H), 7.35 (d, 2H), 8.1 (m, 1H), 8.25 (d, 1H), 8.55 (d, 2H), 8.9 (s, 1H), 10.55 (s, 1H). Anal. ($C_{17}H_{26}N_4O_4$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(4-pyridyl)alanine *N*-[2-(4-Hydroxyphenyl)ethyl]amide (6xx). Compound **6xx** was prepared by subjecting compound **5xx** to general procedure G. Yield = 31%. TLC: R_f = 0.54 ($CHCl_3$/MeOH/H_2O, 150/45/5). Purity: >88% (HPLC method F). ^{1}H NMR (300 MHz, DMSO): δ 0.85 (dd, 6H), 1.05 (m, 1H), 1.3−1.5 (m, 2H), 1.95−2.15 (m, 2H), 2.6−2.8 (m, 3H), 2.95 (dd, 1H), 3.1 (dd, 1H), 3.25−3.4 (m, 2H), 4.6 (m, 1H), 6.8 (d, 2H), 7.1 (d, 2H), 7.35 (d, 2H), 8.15 (t, 1H), 8.25 (d, 1H), 8.55 (d, 2H), 8.9 (s, 1H), 9.3 (s, 1H), 10.5 (s, 1H). Anal. ($C_{24}H_{32}N_4O_5$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(4-pyridyl)alanine *N*-[(*S*)-Methylbenzyl]amide (6yy). Compound **6yy** was prepared by subjecting compound **5yy** to general procedure G. Yield = 25%. TLC: R_f = 0.52 ($CHCl_3$/MeOH/H_2O, 150/45/5). Purity: >94% (HPLC method E). ^{1}H NMR (300 MHz, DMSO): δ 0.85 (dd, 6H), 1.1 (m, 1H), 1.3−1.5 (m, 5H), 2.0−2.1 (m, 2H), 2.75 (m, 1H), 2.95 (dd, 1H), 3.15 (dd, 1H), 4.7 (m, 1H), 5.0 (m, 1H), 7.3−7.45 (m, 7H), 8.3 (d, 1H), 8.45 (d, 1H), 8.5 (d, 2H), 8.85 (s, 1H), 10.5 (s, 1H). Anal. ($C_{24}H_{32}N_4O_4$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-(4-pyridyl)alanine *N*-Benzylamide (6zz). Compound **6zz** was prepared by subjecting compound **5zz** to general procedure G. Yield = 10%. TLC: R_f = 0.55 (MeOH/$CHCl_3$, 1/3). Purity: >86% (HPLC method B). ^{1}H NMR (300 MHz, DMSO): δ 0.75 (dd, 6H), 0.9 (m, 1H), 1.1−1.4 (m, 2H), 1.8−2.0 (m, 2H), 2.6 (m, 1H), 2.85 (dd, 1H), 3.05 (dd, 1H), 4.25 (m, 2H), 4.55 (m, 1H), 7.1−7.4 (m, 7H), 8.2 (d, 1H), 8.4−8.6 (m, 3H), 8.75 (s, 1H), 10.35 (s, 1H). Anal. ($C_{23}H_{30}N_4O_4 \cdot 0.25H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-*tert*-leucine *N*-Methylamide (6aaa). Compound **6aaa** was prepared by subjecting compound **5aaa** to general procedure G. Yield = 23%. TLC: R_f = 0.54 ($CHCl_3$/MeOH/H_2O, 150/45/5). Purity: >96% (HPLC method G). ^{1}H NMR (300 MHz, DMSO): δ 0.9 (dd, 6H), 1.0 (s, 9H), 1.2 (m, 1H), 1.75 (m, 2H), 2.1 (dd, 1H), 2.25 (dd, 1H), 2.65 (d, 3H), 2.95 (m, 1H), 4.25 (d, 1H), 7.8 (d, 1H), 8.0 (m, 1H), 8.8 (bs, 1H), 10.45 (s, 1H). Anal. ($C_{15}H_{29}N_3O_4$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-abrine *N*-Methylamide (6bbb). Compound **6bbb** was prepared by subjecting compound **5bbb** to general procedure G. Yield = 23%. Purity: >85% (HPLC method M). ^{1}H NMR (300 MHz, DMSO): δ 0.0 (m, 0.5H), 0.3 (dd, 3H), 0.8 (m, 0.5H), 0.9 (d, 3H), 1.1−1.2 (m, 1H), 1.45−1.6 (m, 1H), 1.95−2.3 (m, 2H), 2.65 (d, 1.5H), 2.8 (d, 1.5H), 2.9 (s, 1.5H), 3.0−3.2 (m, 2.5H), 3.35−3.6 (m, 2H), 4.8−5.3 (m + m, 1H), 7.05−7.2 (m, 3H), 7.45 (m, 1H), 7.6−7.75 (m, 1H), 7.8−8.35 (m, 1H), 8.85−9.0 (s + s, 1H), 10.55−10.65 (s + s, 1H), 10.85−11.0 (s + s, 1H). Anal. ($C_{21}H_{30}N_4O_4$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-abrine *N*-[3-(4-Morpholinylpropyl)]amide (6cc). Compound **6ccc** was prepared by subjecting compound **5ccc** to general procedure G. Yield = 10%. TLC: R_f = 0.58 ($CHCl_3$/MeOH/H_2O, 150/45/5). Purity: >95% (HPLC method J). ^{1}H NMR (300 MHz, DMSO): δ 0.0 (m, 0.5H), 0.35 (dd, 3H), 0.8 (m, 0.5H), 0.9 (d, 3H), 1.1−1.25 (m, 1H), 1.5−1.65 (m, 2H), 1.7−1.8 (m, 1H), 1.95−2.5 (m, 9H), 2.9 (s, 1.5H), 3.0−3.1 (m, 1H), 3.1 (s, 1.5H), 3.15−3.25 (m, 2H), 3.3−3.45 (m, 1H), 3.6−3.7 (m, 4H), 4.75−5.25 (m + m, 1H), 7.05−7.2 (m, 3H), 7.45 (m, 1H), 7.7 (m, 1H), 7.85−8.35 (t + t, 1H), 8.9−9.15 (s + s, 1H), 10.55−10.65 (s + s, 1H), 10.9−11.05 (s + s, 1H). Anal. ($C_{27}H_{41}N_5O_5 \cdot 2H_2O$) C, N; H: calcd, 8.22; found, 7.67.

3-(*N*-Hydroxycarbamoyl)-2(*S*)-(isobutylpropionyl)-L-tryptophan Methylamide (6ddd). Compound **6ddd** was prepared by subjecting compound **5ddd** to general procedure G. Yield = 35%. Purity: >99% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.55 (d, 3H), 0.65 (d, 3H), 0.75−0.85 (m, 2H), 1.15 (m, 1H), 1.95 (dd, 1H), 2.15 (dd, 1H), 2.55−2.65 (m, 1H), 2.65 (d, 3H), 2.85 (dd, 1H), 3.3 (dd, 1H), 4.4 (m, 1H), 7.45 (t, 1H), 7.55 (t, 1H), 7.6 (s, 1H), 7.3 (d, 1H), 7.55 (d, 1H), 7.9 (m, 1H), 8.2 (d, 1H), 8.75 (s, 1H), 10.5 (s, 1H), 10.8 (s, 1H). Anal. ($C_{20}H_{28}N_4O_4 \cdot 0.25H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-Butylpropionyl-L-tryptophan Methylamide (6eee). Compound **6eee** was prepared by subjecting compound **5ggg** to general procedure G. Yield = 36%. TLC: R_f = 0.46 ($CHCl_3$/MeOH/H_2O, 150/45/5). Purity: >99% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.95 (t, 3H), 1.1−1.5 (m, 6H), 2.05 (dd, 1H), 2.2 (dd, 1H), 2.65 (m, 4H), 3.05 (dd, 1H), 3.2 (dd, 1H), 4.55 (m, 1H), 7.05 (t, 1H), 7.15 (t, 1H), 7.25 (s, 1H), 7.4 (d, 1H), 7.65 (d, 1H), 7.95 (m, 1H), 8.05 (d, 1H), 8.85 (bs, 1H), 10.5 (bs, 1H), 10.9 (s, 1H). Anal. ($C_{20}H_{28}N_4O_4$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-hexylpropionyl-L-tryptophan Methylamide (6fff). Compound **6fff** was prepared by subjecting compound **5iii** to general procedure G. Yield = 57%. TLC: R_f = 0.52 ($CHCl_3$/MeOH/H_2O, 150/45/5). Purity: >91% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.95 (t, 3H), 1.1−1.5 (m, 10H), 2.05 (dd, 1H), 2.2 (dd, 1H), 2.65 (m, 4H), 3.05 (dd, 1H), 3.2 (dd, 1H), 4.55 (m, 1H), 7.05 (t, 1H), 7.15 (t, 1H), 7.25 (s, 1H), 7.4 (d, 1H), 7.65 (d, 1H), 7.95 (m, 1H), 8.05 (d, 1H), 8.85 (bs, 1H), 10.5 (bs, 1H), 10.9 (s, 1H). Anal. ($C_{22}H_{32}N_4O_4 \cdot 0.33H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-octylpropionyl-L-tryptophan Methylamide (6ggg). Compound **6ggg** was prepared by subjecting compound **5kkk** to general procedure G. Yield = 56%. TLC: R_f = 0.60 ($CHCl_3$/MeOH/H_2O, 150/45/5). Purity: >92% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.95 (t, 3H), 1.1−1.5 (m, 14H), 2.05 (dd, 1H), 2.2

(dd, 1H), 2.65 (m, 4H), 3.05 (dd, 1H), 3.2 (dd, 1H), 4.55 (m, 1H), 7.05 (t, 1H), 7.15 (t, 1H), 7.25 (s, 1H), 7.4 (d, 1H), 7.65 (d, 1H), 7.95 (m, 1H), 8.05 (d, 1H), 8.85 (bs, 1H), 10.5 (bs, 1H), 10.9 (s, 1H). Anal. ($C_{24}H_{36}N_4O_4 \cdot 0.25H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-[(isopropyloxy)propionyl]-L-tryptophan Methylamide (6hhh). Compound **6hhh** was prepared by subjecting compound **5lll** to general procedure G. Yield = 39%. TLC: $R_f = 0.46$ ($CHCl_3$/MeOH/H_2O, 150/45/5). Purity: >98% (HPLC method H). ^{1}H NMR (300 MHz, DMSO): δ 1.0 (dd, 6H), 2.4 (m, 2H), 2.7 (d, 3H), 3.3 (d, 2H), 3.54 (m, 1H), 4.1 (m, 1H), 4.55 (m, 1H), 7.1 (t, 1H), 7.15 (t, 1H), 7.2 (d, 1H), 7.45 (t, 2H), 7.65 (d, 1H), 8.25 (m, 1H), 8.9 (s, 1H), 10.6 (s, 1H), 11.0 (s, 1H). Anal. ($C_{19}H_{26}N_4O_5$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-2(*R*)-[(pentyloxy)propionyl]-L-tryptophan Methylamide (6iii). Compound **6iii** was prepared by subjecting compound **5mmm** to general procedure G. Yield = 22%. TLC: $R_f = 0.51$ ($CHCl_3$/MeOH/H_2O, 150/45/5). Purity: >99% (HPLC method E). ^{1}H NMR (300 MHz, DMSO): δ 0.95 (t, 3H), 1.15−1.35 (m, 4H), 1.35−1.5 (m, 2H), 2.4 (m, 2H), 2.7 (d, 3H), 3.2−3.35 (m, 4H), 4.0 (m, 1H), 4.6 (m, 1H), 7.05 (t, 1H), 7.15 (t, 1H), 7.2 (d, 1H), 7.45 (d, 1H), 7.6 (d, 1H), 7.65 (d, 1H), 8.25 (m, 1H), 8.95 (s, 1H), 10.6 (s, 1H), 11.0 (s, 1H). Anal. ($C_{21}H_{30}N_4O_5$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-3(*S*)-hydroxy-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-Methylamide (6jjj). Compound **6jjj** was prepared by subjecting compound **5nnn** to general procedure G. Yield = 46%. TLC: $R_f = 0.32$ ($CHCl_3$/MeOH/H_2O, 150/45/5). Purity: >94% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.85 (dd, 6H), 1.1 (m, 1H), 1.35−1.6 (m, 2H), 2.65 (d, 3H), 2.7 (m, 1H), 3.1−3.3 (m, 2H), 3.95 (m, 1H), 4.55 (m, 1H), 5.65 (d, 1H), 7.05 (t, 1H), 7.15 (t, 1H), 7.25 (s, 1H), 7.45 (d, 1H), 7.65 (d, 1H), 7.85−7.95 (m, 2H), 8.95 (s, 1H), 10.7 (s, 1H), 10.85 (s, 1H). Anal. ($C_{20}H_{28}N_4O_5 \cdot 0.25H_2O$) C, H, N.

3-(*N*-Hydroxycarbamoyl)-3(*S*)-hydroxy-2(*R*)-(isobutylpropionyl)-L-*tert*-leucine *N*-Methylamide (6kkk). Compound **6kkk** was prepared by subjecting compound **5ooo** to general procedure G. Yield = 55%. TLC: $R_f = 0.56$ ($CHCl_3$/MeOH/H_2O, 150/45/5). Purity: >96% (HPLC method J). ^{1}H NMR (300 MHz, DMSO): δ 0.90 (dd, 6H), 0.95−1.05 (m, 1H), 1.00 (s, 9H), 1.40−1.60 (m, 2H), 2.70 (d, 3H), 2.75−2.85 (m, 1H), 3.80 (t, 1H), 4.30 (d, 1H), 5.50 (d, 1H) 7.60 (d, 1H), 8.00 (m, 1H), 9.00 (s, 1H), 10.70 (s, 1H). Anal. ($C_{15}H_{29}N_3O_5$) C, H, N.

3-(Hydroxycarbonyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-Methylamide (7a). Compound **7a** was prepared by subjecting compound **5eee** to general procedure I. Yield = 72%. Purity: >99% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.8 (dd, 6H), 1.1 (m, 1H), 1.35 (m, 2H), 2.15 (dd, 1H), 2.30 (dd, 1H), 2.55 (d, 3H), 2.7 (m, 1H), 2.95 (dd, 1H), 3.1 (dd, 1H), 4.45 (m, 1H), 6.95 (t, 1H), 7.05 (t, 1H), 7.1 (d, 1H), 7.3 (d, 1H), 7.55 (d, 1H), 7.75 (m, 1H), 8.0 (d, 1H), 10.8 (s, 1H). Anal. ($C_{20}H_{27}N_3O_4 \cdot 0.5H_2O$) C, H; N: calcd, 10.99; found, 10.52.

3-(Hydroxycarbonyl)-2(*R*)-(butylpropionyl)-L-tryptophan Methylamide (7b). Compound **7b** was prepared by subjecting compound **5fff** to general procedure I. Yield = 63%.

3-(Hydroxycarbonyl)-2(*R*)-(hexylpropionyl)-L-tryptophan Methylamide (7c). Compound **7c** was prepared by subjecting compound **5hhh** to general procedure I. Yield = 55%.

3-(Hydroxycarbonyl)-2(*R*)-(octylpropionyl)-L-tryptophan Methylamide (7d). Compound **7d** was prepared by subjecting compound **5jjj** to general procedure I. Yield = 76%.

3-(Hydroxycarbonyl)-3(*S*)-hydroxy-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-Methylamide (7e). Compound **27a** (2.19 g, 5.10 mmol) was dissolved in THF (20 mL) and diluted with H_2O (25 mL) and 6 N HCl (5 mL). The reaction mixture was stirred at room temperature for 5 h, after which it was concentrated to 50% its original volume. The resulting solution was lyophilized giving compound **7e** (2.00 g, 100%).

3-(Hydroxycarbonyl)-3(*S*)-hydroxy-2(*R*)-(isobutylpropionyl)-L-*tert*-leucine *N*-Methylamide (7f). Compound **27b** (4.17 g, 11.71 mmol) was dissolved in THF (50 mL), and 2 N HCl (50 mL) was added. The reaction mixture was stirred at room temperature for 4.5 h, after which it was concentrated to 50% its original volume. The resulting solution was lyophilized giving compound **7f** (3.69 g, 100%).

3-(*N*-Methoxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-Methylamide (8a). Compound **8a** was prepared by reacting compound **6a** with methyl iodide according to general procedure H. Yield = 20%. Purity: >92% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.9 (dd, 6H), 1.15 (m, 1H), 1.5 (m, 2H), 2.05 (dd, 1H), 2.15 (dd, 1H), 2.65 (d, 3H), 2.8 (m, 1H), 3.1 (dd, 1H), 3.2 (dd, 1H), 3.65 (s, 3H), 4.55 (m, 1H), 7.05 (t, 1H), 7.15 (t, 1H), 7.2 (s, 1H), 7.4 (d, 1H), 7.65 (d, 1H), 7.9 (m, 1H), 8.1 (d, 1H), 10.9 (s, 1H), 11.1 (s, 1H). Anal. ($C_{21}H_{30}N_4O_4$) C, H, N.

3-(*N*-Benzyloxycarbamoyl)-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-Methylamide (8b). Compound **8b** was prepared by reacting compound **6a** with benzyl bromide according to general procedure H. Yield = 32%. Purity: >90% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.75 (dd, 6H), 1.0 (m, 1H), 1.3−1.45 (m, 2H), 1.45 (dd, 1H), 2.1 (dd, 1H), 2.55 (d, 3H), 2.7 (m, 1H), 3.0 (dd, 1H), 3.15 (dd, 1H), 4.45 (m, 1H), 4.75 (m, 2H), 6.95 (t, 1H), 7.05 (t, 1H), 7.1 (s, 1H), 7.25−7.4 (m, 6H), 7.55 (d, 1H), 7.8 (m, 1H), 8.0 (d, 1H), 10.8 (s, 1H), 11.0 (s, 1H). Anal. ($C_{27}H_{34}N_4O_4 \cdot 0.25H_2O$) C, H, N.

3-[*N*-[(Methoxycarbonyl)methoxy]carbamoyl]-2(*R*)-(isobutylpropionyl)-L-tryptophan *N*-Methylamide (8c). Compound **8c** was prepared by reacting compound **6a** with methyl bromoacetate according to general procedure H. Yield = 35%. Purity: >90% (HPLC method A). ^{1}H NMR (300 MHz, DMSO): δ 0.75 (dd, 6H), 1.0 (m, 1H), 1.35 (m, 2H), 1.95−2.15 (m, 2H), 2.5 (bd, 3H), 2.7 (m, 1H), 2.95 (dd, 1H), 3.1 (dd, 1H), 3.7 (bs, 3H), 4.45 (m, 3H), 6.95−7.15 (m, 3H), 7.35 (d, 1H), 7.6 (d, 1H), 7.8 (d, 1H), 8.0 (d, 1H), 10.8 (s, 1H), 11.3 (s, 1H). Anal. ($C_{23}H_{32}N_4O_6$) C, H, N.

***N*-(4-Methylpentanoyl)−(*S*)-4-benzyl-2-oxazolidinone (14a).** Compound **14a** was prepared by coupling 4-methylpentanoyl chloride, **13a**, with (*S*)-4-benzyl-2-oxazolidinone according to general procedure A. Yield = 100%.

***N*-Hexanoyl-(*S*)-4-benzyl-2-oxazolidinone (14b).** Compound **14b** was prepared by coupling hexanoyl chloride, **13b**, with (*S*)-4-benzyl-2-oxazolidinone according to general procedure A. Yield = 97%. TLC: $R_f = 0.65$ (30% EtOAc/hexane).

***N*-Octanoyl-(*S*)-4-benzyl-2-oxazolidinone (14c).** Compound **14c** was prepared by coupling octanoyl chloride, **13c**, with (*S*)-4-benzyl-2-oxazolidinone according to general procedure A. Yield = 99%. TLC: $R_f = 0.70$ (30% EtOAc/hexane).

***N*-Decanoyl-(*S*)-4-benzyl-2-oxazolidinone (14d).** Compound **14d** was prepared by coupling decanoyl chloride, **13d**, with (*S*)-4-benzyl-2-oxazolidinone according to general procedure A. Yield = 95%. TLC: $R_f = 0.55$ (30% EtOAc/hexane).

***N*-[2(*R*)-(*tert*-Butylcarboxymethyl)-4-methylpentanoyl]-(*S*)-4-benzyl-2-oxazolidinone (15a).** Compound **15a** was prepared by subjecting compound **14a** to general procedure B. Yield = 89%.

***N*-[2(*R*)-(*tert*-Butylcarboxymethyl)hexanoyl]-(*S*)-4-benzyl-2-oxazolidinone (15b).** Compound **15b** was prepared by subjecting compound **14b** to general procedure B. Yield = 91%. de = 94%. TLC: $R_f = 0.5$ (10% EtOAc/hexane).

***N*-[2(*R*)-(*tert*-Butylcarboxymethyl)octanoyl]-(*S*)-4-benzyl-2-oxazolidinone (15c).** Compound **15c** was prepared by subjecting compound **14c** to general procedure B. Yield = 93%. de = 96%. TLC: $R_f = 0.5$ (10% EtOAc/hexane).

***N*-[2(*R*)-(*tert*-Butylcarboxymethyl)decanoyl]-(*S*)-4-benzyl-2-oxazolidinone (15d).** Compound **15d** was prepared by subjecting compound **14d** to general procedure B. Yield = 72%. de = 92%. TLC: $R_f = 0.5$ (10% EtOAc/hexane).

2,2-Dimethyl-4-oxo-5(*R*)-(carboxymethyl)-1,3-dioxolane (17). D-Malic acid (**16**, 24.97 g, 186.20 mmol) was suspended in CH_2Cl_2 (250 mL) and 2,2-dimethoxypropane (68.69 mL, 558.60 mmol). PTSA (0.35 g, 1.86 mmol) was added, and the reaction mixture was stirred at room temperature for 4 h. The resulting solution was filtered through silica gel (50% EtOAc/hexane) and concentrated to dryness giving the desired product (**17**, 29.04 g, 90%) as colorless crystals.

2,2-Dimethyl-4-oxo-5(*R*)-(methoxycarboxymethyl)-1,3-dioxalane (18). Compound **18** was prepared by subjecting compound **17** general procedure J (solvent = Et_2O). Yield = 94%. TLC: $R_f = 0.56$ (50% EtOAc/hexane).

***(R)*-2-Hydroxy-3-(methoxycarbonyl)propionic Acid (19).** Compound **18** (19.40 g, 103.19 mmol) was dissolved in THF (100 mL), and 1 N HCl (100 mL) was added. The reaction mixture was stirred at room temperature for 1 h, after which it was concentrated to 50% its original volume. After the resulting solution was saturated with NaCl, the product was extracted with EtOAc (12 × 50 mL). The combined organic extracts were dried over anhydrous MgSO4, filtered, and concentrated to provide compound **19** (14.62 g, 96%) as a light yellow oil.

(*R*)-2-Hydroxy-3-(methoxycarbonyl)propionic Acid Benzyl Ester (20). Compound **19** (3.40 g, 22.97 mmol) was dissolved in DMF (34 mL), and K_2CO_3 (6.35 g, 45.95 mmol) was added followed by benzyl bromide (3.00 mL, 25.27 mmol). The reaction mixture was stirred at room temperature for 1 h, after which it was diluted with EtOAc (150 mL). The resulting mixture was washed with H_2O (4 × 30 mL) and brine (30 mL). After being dried over anhydrous $MgSO_4$, the organic phase was filtered and concentrated to dryness. The residue was purified on silica gel (25% EtOAc/hexane), giving compound **20** (3.15 g, 58% yield) as a light yellow oil. TLC: R_f = 0.48 (50% EtOAc/hexane).

(*R*)-2-(Isopropyloxy)-3-(methoxycarbonyl)propionic Acid Benzyl Ester (21a). Compound **20** (3.15 g, 13.24 mmol) was dissolved in 2-bromopropane (15 mL), and Ag_2O (3.15 g) was added. The reaction was stirred at 50 °C for 48 h, after which it was filtered through Celite. The filtrate was concentrated to dryness, and the residue was purified on silica gel (50% EtOAc/hexane), giving compound **21a** (1.92 g, 52%) as a colorless oil. TLC: $R_f = 0.33$ (15% EtOAc/hexane).

(*R*)-2-(Pentyloxy)-3-(methoxycarbonyl)propionic Acid Benzyl Ester (21b). Compound **20** (3.05 g, 12.82 mmol) was dissolved in 1-iodopentane (13 mL), and Ag_2O (3.05 g) was added. The reaction was stirred at 80 °C for 48 h, after which it was filtered through Celite. The filtrate was concentrated to dryness, and the residue was purified on silica gel (5% EtOAc/hexane), giving compound **21b** (1.42 g, 36%) as a colorless oil. TLC: $R_f = 0.42$ (15% EtOAc/hexane).

(2*S*,3*R*)-3-Methallyl-2-hydroxysuccinic Acid Dimethyl Ester (23). Dimethyl L-mallate (**22**, 6.31 mL, 47.61 mmol) was dissolved in THF (150 mL) and cooled to −78 °C under argon. LDA (2 M solution, 47.61 mL, 95.21 mmol) was added over 5 min, and the reaction mixture was stirred from −78 to −20 °C over 2 h. After the mixture was cooled to −78 °C, methallyl bromide (6.00 mL, 59.51 mmol) was added. The reaction mixture was allowed to warm to −5 °C over 5 h, after which it was quenched with saturated NH_4Cl (100 mL). The resulting mixture was diluted with EtOAc (400 mL), and the layers were separated. The organic phase was washed with 1 N HCl (3 × 50 mL), saturated $NaHCO_3$ (3 × 50 mL), and brine (50 mL). After being dried over $MgSO_4$, the organics were filtered and concentrated to dryness. Purification of the residue on silica gel (30% EtOAc/hexanes) gave compound **23** (4.48 g, 44%). TLC: $R_f = 0.36$ (30% EtOAc/hexane).

(2*S*,3*R*)-3-Isobutyl-2-hydroxysuccinic Acid Dimethyl Ester (24). 10% Pd/C (1.96 g) was placed under vacuum, and MeOH (50 mL) was added. Compound **23** (6.99 g, 32.36 mmol) was dissolved in MeOH (50 mL) and added, via cannula, to the Pd/C. The mixture was degassed under vacuum and stirred under H_2 for 17 h. Filtration of the reaction through Celite and concentration under vacuum gave compound **24** (6.93 g, 98%), which was used without further purification. TLC: $R_f = 0.37$ (30% EtOAc/hexane).

(2*S*,3*R*)-3-Isobutyl-2-hydroxysuccinic Acid (25). Compound **24** (6.93 g, 31.79 mmol) was dissolved in MeOH (64 mL), and 2 N NaOH (64 mL) was added. The reaction mixture was stirred at room temperature for 9 h after which, the volume was reduced by 60% under vacuum. The residue was acidified to pH = 1 with 6 N HCl and saturated with NaCl. The product was extracted with EtOAc (6 × 50 mL). The organics were dried over $MgSO_4$, filtered, and concentrated to dryness, giving compound **25** (6.12 g, 100%). [Note: Crystals may precipitate at pH = 4−5. Do not isolate these crystals. They are probably succinic anhydride products and will not react in the next step. At pH = 1, all solids are dissolved and the only species should be the desired dicarboxylic acid.]

2(*R*)-[2,2-Dimethyl-4-oxo-1,3-5(*S*)-Dioxolanyl]-4-Methylpentanoic Acid (26). Compound **25** (6.12 g, 32.21 mmol) was dissolved in dimethoxypropane (60 mL), and TsOH (0.61 g, 3.22 mmol) was added. The reaction mixture was stirred at room temperature for 2.5 h, after which it was concentrated to dryness. The residue was diluted with EtOAc (100 mL) and washed with H_2O (3 × 20 mL) and brine (20 mL). The organics were dried over $MgSO_4$, filtered, and concentrated to dryness, giving compound **26** (6.14 g, 83%). [This reaction turns dark red. Some discoloration may be avoided by first filtering the reaction through a plug of silica gel and then concentrating the mixture as described. TLC: $R_f = 0.64$ ($CHCl_3$/MeOH/H_2O, 150/45/5).

2(*R*)-[2,2-Dimethyl-4-oxo-1,3-(5*S*)-dioxolanyl]-4-(methylpentanoyl)-L-tryptophan *N*-Methylamide (27a). Compound **26** (4.59 g, 19.96 mmol) was dissolved in CH_2Cl_2 (85 mL), and HOBT (2.97 g, 21.95 mmol), EDC (5.74 g, 29.93 mmol), and NMM (3.29 mL, 29.93 mmol) were sequentially added. The reaction mixture was stirred at room temperature for 15 min, after which compound **3a** (5.55 g, 21.95 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, after which it was concentrated to dryness. The residue was diluted with EtOAc (100 mL) and sequentially washed with 1 N HCl (3 × 20 mL), saturated $NaHCO_3$ (3 × 20 mL), and brine (20 mL). The organics were dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified on silica gel (50% EtOAc/hexane), giving compound **27a** (2.19 g, 26%) as a colorless solid. TLC: $R_f = 0.62$ (50% EtOAc/hexane).

2(*R*)-[2,2-Dimethyl-4-oxo-1,3-(5*S*)-dioxolanyl]-4-(methylpentanoyl)-L-*tert*-leucine *N*-Methylamide (27b). Compound **27b** was prepared by coupling compound **3bbb** with compound **26** according to general procedure F. Yield = 44%. TLC: $R_f = 0.34$ (50% EtOAc/hexane).

Enzyme Assays. Enzymes and Activation Conditions. A 96-well plate fluorogenic assay was used to measure the relative potency of a series of matrix metalloproteinase inhibitors (MMPIs) against a variety of matrix metalloproteinases MMPs. All enzymes were activated with a freshly prepared 10 mM stock of 4-aminophenyl mercuric acetate (APMA, Aldrich) in 20 mM NaOH. Optimal activation conditions for each of the MMPs were as follows: neutrophil collagenase and stromelysin required a 1.5 h incubation at 37 °C using 2.4 mM and 1 mM APMA, respectively; 72 kDa and 92 kDa gelatinases were incubated at 37 °C with 0.9 mM APMA for 1 and 2 h, respectively.

Substrate and Calibrating Standard. Stock solutions (10 mM) of the fluorogenic peptide MMP substrate (Mca-Pro-Leu-Gly-Leu-Dpa(Dnp)-Ala-Arg-NH_2) and the cleavage product (Mca-Pro-Leu-NH_2) (Bachem Bioscience, Inc.) were prepared in dimethylformamide. The cleavage product was used to convert arbitrary fluorescent units to a concentration (mmol/liter). For assay measurements, the MMP substrate was diluted to a final concentration of 10 μM with 50 mM Tris pH 7.5, 150 mM NaCl, and 20 mM $CaCl_2 \cdot 2H_2O$ (buffer A) in polystyrene tubes (Falcon no. 2017). Nonspecific binding of the substrate was observed if glass or other plastic tubes were substituted for polystyrene.

Equipment and Instrumentation. Assays were performed in white flat-bottomed 96-well plates (Dynatech) coated for 30 min with 1% BSA, 0.01% sodium azide in PBS to prevent adsorption of the MMPs which was observed with uncoated or siliconized plates (data not shown). Measurements were determined using a Titertek Fluoroskan II 96-well plate fluorometer (MTX Lab Systems, Inc.) equipped with 325 nm excitation and 460 nm emission filters. Data were collected and processed using the Delta Soft II ELISA analysis program (Bio Metallics, Inc.).

Enzyme Preparation. Each of the MMPs was added to a BSA-pretreated 15 mL conical tube just prior to use and diluted with buffer A to yield a rate in the absence of inhibitor of 0.77 (FlU/min)/mL.

Assay. The assay was initiated by adding 130 uL of diluted MMP to wells of the 96-well plate that contained 20 μL of MMPI (diluted from 5mM in DMSO with buffer A) ranging in concentration from 0 to 20 nM and 50 μL of a 40 μM dilution of MMP substrate. Kinetic rates were determined at constant dp/dt at room temperature and collected for 50 min. Using a Dixon plot (1/v versus [I]), relative K_i values for each of the MMPIs were determined using 10 μM substrate and 0−20 nM inhibitor. The K_i values were calculated as [−1(x intercept)], realizing that $(1 + S/K_m)$ would change the value by less than 2-fold for all enzymes tested (K_m for all enzymes tested was >10 μM).

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Supporting Information Available: ^{1}H NMR spectral data for intermediate compounds **1c**, **1n**, **1o**, **2b−ccc**, **3b−ccc**, **4c−h**, **5b-ooo**, **7b−f**, **14a−d**, **15b−d**, **17−20**, **21a,b**, **23−26**, **27a,b** (40 pages). Ordering information is given on any current masthead page.

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