Design, Synthesis, and Structure−Activity Relationships of Macrocyclic Hydroxamic Acids That Inhibit Tumor Necrosis Factor α Release in Vitro and in Vivo

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Received March 21, 2001

To search for TNF-α (tumor necrosis factor α) converting enzyme (TACE) inhibitors, we designed a new class of macrocyclic hydroxamic acids by linking the P1 and P2′ residues of acyclic *anti*-succinate-based hydroxamic acids. A variety of residues including amide, carbamate, alkyl, sulfonamido, Boc-amino, and amino were found to be suitable P1−P2′ linkers. With an *N*-methylamide at P3′, the 13−16-membered macrocycles prepared exhibited low micromolar activities in the inhibition of TNF-α release from LPS-stimulated human whole blood. Further elaboration in the P3′−P4′ area using the cyclophane and cyclic carbamate templates led to the identification of a number of potent analogues with IC_{50} values of ≤0.2 μM in whole blood assay (WBA). Although the P3′ area can accommodate a broad array of structurally diversified functional groups including polar residues, hydrophobic residues, and amino and carboxylic acid moieties, in both the cyclophane series and the cyclic carbamate series, a glycine residue at P3′ was identified as a critical structural component to achieve both good in vitro potency and good oral activity. With a glycine residue at P3′, an *N*-methylamide at P4′ provided the best cyclophane analogue, SL422 (WBA IC_{50} = 0.22 μM, LPS-mouse ED_{50} = 15 mg/kg, po), whereas a morpholinylamide at P4′ afforded the most potent and most orally active cyclic carbamate analogue, SP057 (WBA IC_{50} = 0.067 μM, LPS-mouse ED_{50} = 2.3 mg/kg, po). Further profiling for SL422 and SP057 showed that these macrocyclic compounds are potent TACE inhibitors, with K_i values of 12 and 4.2 nM in the porcine TACE assay, and are broad-spectrum MMP inhibitors. Pharmacokinetic studies in beagle dogs revealed that SL422 and SP057 are orally bioavailable, with oral bioavailabilities of 11% and 23%, respectively.

Introduction

Tumor necrosis factor α (TNF-α),[1] a critical proinflammatory cytokine produced primarily by activated monocytes/macrophages in response to a variety of stimuli, is a key mediator of the biological response to bacterial infection and inflammation and an inducer of other proinflammatory cytokines such as IL-1β, IL-6, and IL-8.[2−4] During normal host defense, low levels of serum TNF-α confer protection against infectious agents, tumors, and tissue damage, and have an important role in the development of the humoral immune response.[5] However, overproduction of TNF-α can lead to a variety of infectious, autoimmune, and inflammatory disorders including rheumatoid arthritis (RA), septic shock, multiple sclerosis, cachexia, congestive heart failure, periodontal disease, and Crohn's disease.[6−9] For example, elevated TNF-α concentrations have been demonstrated in a variety of human inflammatory diseases such as RA[10] and Crohn's disease.[11,12]

TNF-α is synthesized as a membrane-bound proform comprising 233 amino acids, with a molecular mass of 26 kDa. The pro-TNF-α is then processed by TNF-α converting enzyme (TACE)[13,14] to yield a monomeric soluble form of 17 kDa comprising 157 nonglycosylated amino acids. Under physiological conditions, the soluble TNF-α forms a noncovalently bound homotrimer.[15] Although the biological function of pro-TNF-α has yet to be understood clearly,[16] the mature TNF-α exerts its multiple biological effects via interaction with two structurally and functionally distinct high-affinity receptors: TNFR1 (p55) and TNFR2 (p75). Binding of TNF-α to these receptors results in the activation of several signal transduction pathways.

Given the essential role of this cytokine in inflammatory diseases, inhibition of TNF-α production or reduction of TNF-α levels should be beneficial in treating these pathological conditions. This has now been proved by anti-TNF-α drugs currently available on the market. For instance, the disease-modifying anti-TNF-α drugs such as the PDE-4 inhibitor pentoxifylline[17] and thalidomide[18] are TNF-α synthesis blockers. They act through interference with transcription, translation, or mRNA half-life, although their effects are broad and have been associated with considerable toxicity. Perhaps

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10.1021/jm010127e CCC: $20.00
Published on Web 07/10/2001

the benefit in treating autoimmune diseases by inhibition of TNF-α production has been most clearly demonstrated by the monoclonal TNF-α antibody Remicade (infliximab)[19−21] and the soluble TNF p75 receptor fusion protein (TNFRp75:Fc) Enbrel (etanercept).[22,23] These recently approved biologics have proven to be effective anti-TNF-α drugs. Remicade was approved for the treatment of Crohn's disease in 1998, and in conjunction with methotrexate was later approved for the treatment of RA.[24] Enbrel received approval for the treatment of RA in 1998.[25] Both drugs eliminate TNF-α effects by neutralizing excess TNF-α in the body. As proteins, however, these drugs are expensive and inconvenient to patients. Given the drawbacks of the current anti-TNF-α biologics, small-molecule anti-TNF-α agents are currently being exploited through multiple approaches.[7] One very promising small-molecule approach is the inhibition of TNF-α processing through the inhibition of TACE.

TACE (ADAM 17), described independently by two groups,[13,14] is a membrane-anchored multidomain enzyme containing extracellular disintegrin and protease regions. It is a member of the adamalysin/ADAM subfamily of the metzincin superfamily that also includes the astacins, serralysins, and MMPs. It has been shown that TACE is the primary enzyme responsible for the shedding of the biologically active TNF-α from its membrane-bound proform and inhibition of TACE blocks TNF-α release.[26] This evidence strongly implicates the therapeutic potential of TACE inhibitors for the treatment of TNF-α-mediated pathologies. As a result, TACE has recently emerged as a vigorously pursued therapeutic target.[27] The high wave of interest in TACE inhibitors is attributed not only to their potential therapeutic application but also to the observation that MMP inhibitors inhibit TNF-α release in vitro and in vivo,[28,29] implying that the target is approachable using MMP leads. Small-molecule MMP inhibitors have been an extensively explored area.[30−32] The large number of MMP inhibitors prepared by many groups of researchers provide in-house libraries for screening. Structure−activity relationship (SAR) data on MMP inhibitors have been extensively reported in the literature and provide useful information for the design of TACE inhibitors.

As part of our efforts to search for TACE inhibitors, we have designed a new class of macrocyclic hydroxamic acids based on *anti*-succinate-based hydroxamic acids.[33,34] Our extensive investigations on the cyclic linkage and further systematic SAR studies in the P3′−P4′ area have led to the identification of a number of macrocycles that are potent inhibitors of TNF-α release from cells. In our previous paper, we disclosed the two test molecules SC903 and SE205.[33] This paper will provide a comprehensive account of the rational design, synthesis, and systematic SAR studies of these macrocyclic inhibitors.

Design

Succinate-based hydroxamic acids represent an extensively studied class of potent MMP inhibitors[30] possessing modest cellular activity in the inhibition of TNF-α release.[27] The structural requirements of this class of inhibitor for MMP activity and anti-TNF-α activity include a hydroxamic acid as zinc chelator, a P1 residue, a P1′ residue (typically an isobutyl group), a P2′ residue, and a P3′ residue (typically an *N*-methylamide). Conformational analysis using molecular modeling reveals that the preferred backbone conformation of this type of inhibitor is an extended conformation, with the two carboxylates of the succinate moiety assuming an antiperiplanar arrangement, placing the P1 residue and the P2′ residue on the same side with a close relationship spatially. X-ray crystallographic studies of inhibitor/enzyme complexes provided a clearer understanding of the inhibitor binding interaction at the active site. This includes chelation of the hydroxamic acid to the active site Zn and hydrogen-bonding of both the P1′−P2′ amide bond and the P2′−P3′ amide bond with the enzyme. In addition, while the P1′ isobutyl binds in the S1′ pocket, the P1 and P2′ residues have little interaction with the enzyme and are directed away from the active site into the solvent. The close proximity of the P1 and P2′ residues and their exposure to solvent prompted us to consider a linkage to hold these two residues to form a macrocycle. Besides novelty, macrocycles are known to impart improved physical properties such as solubility, metabolic stability, and permeability due to ring rigidity.[35] The prerequisite for this is that the macrocycle should be able to hold all of the structural elements critical to binding in positions analogous to those in the corresponding acyclic molecule. Molecular modeling suggested that the smallest macrocycle ring should be a 13-membered ring to maintain the active extended conformation of the acyclic molecules required for optimal enzyme−inhibitor interaction. We first chose marimastat as the template to test our design hypothesis. Replacement of the P2′ L-*tert*-leucine residue in marimastat with an L-lysine residue, alkylation at the hydroxyl group α to the hydroxamic acid with bromoacetate, and amide bond formation between the acetate and the lysine side chain amine provided the first test molecule, SC903, a 13-membered lactam (Figure 1). Based on BB-16, another test molecule, SE205, a 14-membered cyclophane, was constructed by tying up the methyl group at P1 and the methoxy group at P2′ in BB-16 with a methylene residue (Figure 1).

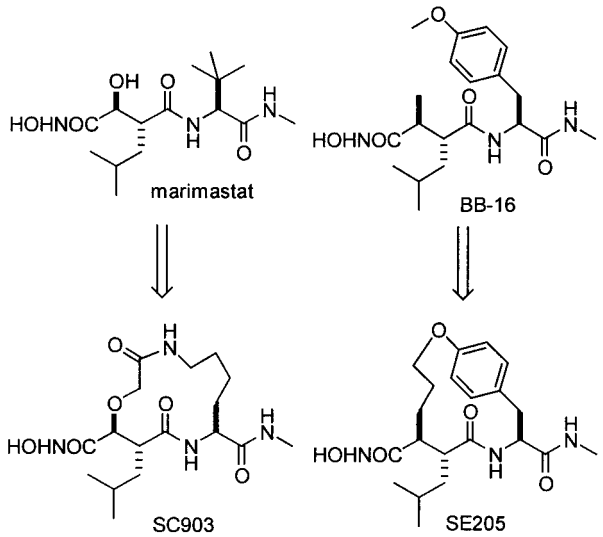
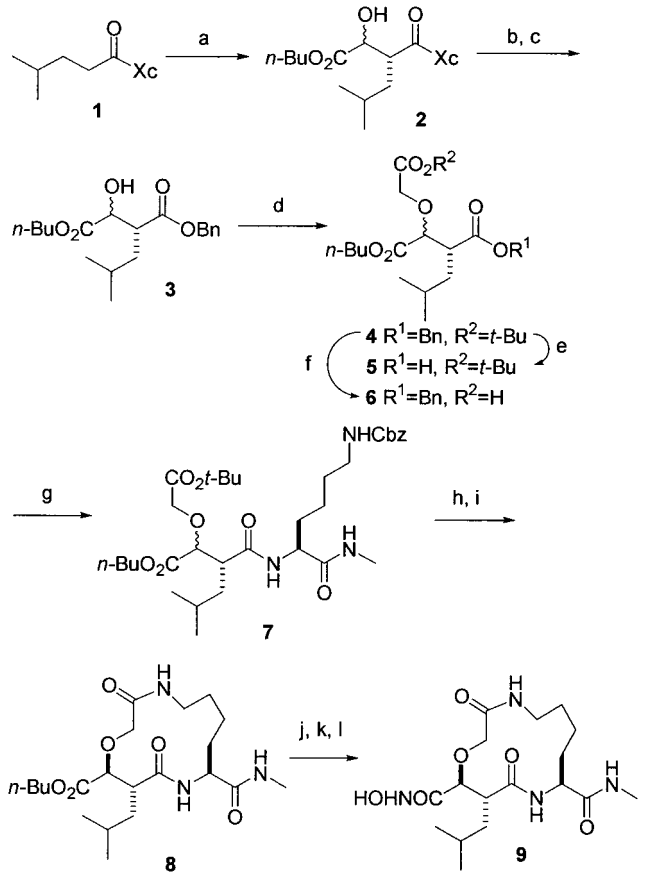


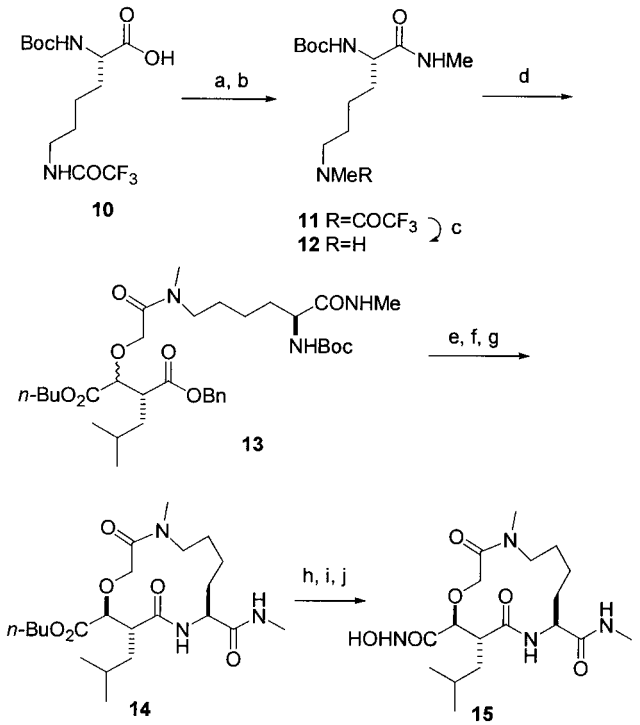
Figure 1. Design of SC903 and SE205 based on marimastat and BB-16.

Scheme 1[a]



[a] Conditions: (a) *n*-BuO_2CCHO, LDA/THF, 36%; (b) LiOH, H_2O_2, 74%; (c) BnBr, DBU, benzene, 79%; (d) NaH, $BrCH_2CO_2$-*t*-Bu, THF, 71%; (e) H_2, Pd−C, MeOH, 99%; (f) TFA, CH_2Cl_2; (g) L-Lys(Cbz)NHMe, BOP, DIEA, DMF, 75%; (h) H_2, Pd−C, followed by 4 N HCl/dioxane; (i) BOP, DIEA, DMF/$CHCl_3$, 50%; (j) 1 N LiOH, THF, 73%; (k) $BnONH_2$·HCl, BOP, DIEA, DMF, 35%; (l) H_2, Pd−C, MeOH, 62%.

Scheme 2[a]



[a] Conditions: (a) NH_2CH_3·HCl, BOP, DIEA, DMF, 94%; (b) CH_3I, K_2CO_3, DMF, 100 °C, 43%; (c) LiOH, THF, 100%; (d) **6**, BOP, DIEA, DMF, 93%; (e) 4 N HCl/dioxane; (f) H_2, Pd−C, 2-propanol; (g) BOP, DIEA, DMF, 38% for three steps; (h) LiOH, THF, 85%; (i) $BnONH_2$·HCl, BOP, DIEA, DMF, 79%; (j) H_2, Pd−C, MeOH.

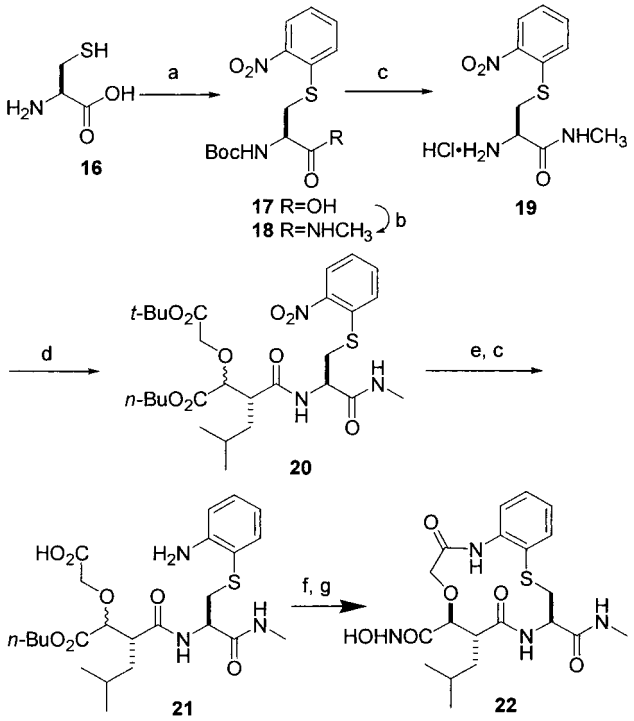
Chemistry

The first macrocyclic compound, **9** (SC903), with an ether−amide linkage, was prepared using the sequence depicted in Scheme 1. Evan's aldol condensation[36] of **1** [Xc = (*S*)-4-benzyl-2-oxazolidinone] with *n*-butyl glyoxylate provided 2-hydroxy-3(*R*)-isobutylsuccinate **2** as a 3:1 mixture of two diastereomers, with the major diastereomer the desired *anti* isomer.[37] The mixture was inseparable by silica gel chromatography and was carried all the way through macrocyclization. Removal of the chiral auxiliary group in **2** using $LiOH/H_2O_2$ followed by benzyl esterification provided the benzyl ester **3**, which was subjected to an alkylation at the hydroxyl group with *tert*-butyl bromoacetate to give compound **4**. Hydrogenolytic removal of the benzyl group and acidolytic removal of the *tert*-butyl group in **4** afforded the two carboxylic acids **5** and **6**, respectively. Coupling of **5** with N^{ϵ}-Cbz-L-lysine *N*-methylamide afforded the amide **7**. Following removal of the *tert*-butyl group using acid and of the Cbz group by hydrogenolysis, an intramolecular cyclization was performed using BOP to afford the macrocycle as a mixture of two diastereomers. Separation of the two diastereomers by silica gel chromatography furnished the major diastereomer **8**. The hydroxamic acid **9** was then obtained by sequential hydrolysis of the *n*-butyl ester, coupling of the resulting carboxylic acid with *O*-benzylhydroxylamine, and hydrogenolytic removal of the benzyl group.

Unlike the synthesis of **9**, the synthesis of its *N*-methyl analogue **15** involved an intramolecular cyclization at the backbone amide bond as shown in Scheme 2. The N^{ϵ}-methyl-L-lysine derivative **12** was obtained by subjecting the commercially available N^{α}-Boc-N^{ϵ}-(CF_3CO)-L-Lys (**10**) to a coupling with methylamine using BOP and subsequently to a methylation with CH_3I/K_2CO_3 at an elevated temperature followed by a hydrolysis using LiOH to remove the trifluoroacetyl group. Coupling of **12** with the acid intermediate **6** afforded the amide **13** as a 3:1 mixture of two diastereomers. Intramolecular cyclization was accomplished using BOP following hydrogenolytic removal of the Cbz group and acidolytic removal of the Boc group in **13**. The optically pure ester **14**, obtained by silica gel chromatography after cyclization, was then converted to the hydroxamic acid **15** in a manner similar to that described for the preparation of **9** in Scheme 1.

The macrocycle **22** was prepared using the protocol outlined in Scheme 3. The L-cysteine derivative **17** was obtained by treatment of L-cysteine (**16**) with *o*-chloronitrobenzene followed by Boc protection. After conversion of the carboxylic acid to an *N*-methylamide (**18**), the Boc group was removed using acid. The resulting amine **19** was coupled with the acid intermediate **5** to give amide **20**. The nitro group in **20** was reduced to an amine using zinc, and the *tert*-butyl group was cleaved with acid. Following intramolecular cyclization using BOP, we did not try to convert the *n*-butyl ester to a hydroxamic acid using the normal procedures described in Scheme 1 due to the presence of the thioether in the

Scheme 3[a]



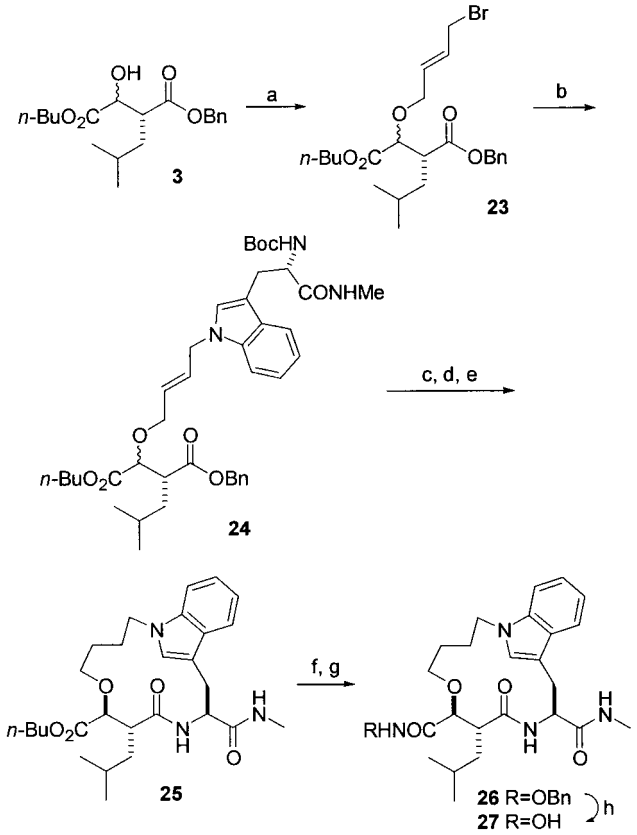
[a] Conditions: (a) (1) *o*-chloronitrobenzene, K_2CO_3, DMF, 60 °C, (2) $(Boc)_2O$, 48%; (b) NH_2CH_3·HCl, BOP, DIEA, DMF, 82%; (c) 4 N HCl/dioxane; (d) **5**, BOP, DIEA, DMF, 83%; (e) Zn, AcOH, H_2O; (f) BOP, DIEA, DMF, 71%; (g) NH_2OH·HCl, DIEA, MeOH, 60 °C, 40%.

molecule. Instead, the hydroxamic acid **22** was obtained by treatment of the *n*-butyl ester with hydroxylamine in MeOH at 60 °C, although the yield was low (40%).

The macrocycle **27** was synthesized starting from the intermediate **3** (Scheme 4). Alkylation of **3** with 1,4-dibromo-2-butene using NaH gave the ether derivative **23**. Following a second alkylation with N^{α}-Boc-L-tryptophan *N*-methylamide on **23** using NaH, the resulting intermediate **24** was subjected to a hydrogenolysis to remove the benzyl group and reduce the olefin and subsequently to an acid treatment to remove the Boc group. Macrocyclization using BOP followed by silica gel chromatography afforded the desired *anti* diastereomer **25**. Conversion of the ester **25** to the hydroxamic acid **27** was accomplished by employing conditions similar to those used for the preparation of **9** in Scheme 1.

Scheme 5 illustrates the synthesis of two common key intermediates (**31a,b**) and subsequent conversion of **31a** to **38**. LDA-promoted alkylation of **28a** (R = isobutyl) and **28b** (R = *n*-hexyl)[38] with allyl bromide provided the corresponding succinate derivatives as a 10:1 (*syn*:*anti*) mixture of two diastereomers. Epimerization by enolization using LDA followed by addition of Et_2AlCl prior to quenching with methanol altered the ratio of the two diastereomers to 1:8 (*syn*:*anti*). Without the use of Et_2-AlCl, the two diastereomers were obtained in a 1:1 ratio. The desired *anti* diastereomer was isolated by silica gel chromatography following conversion of the carboxylic acids **29a,b** to benzyl esters **30a,b**. Hydroboration of the olefin in **30a,b** using 9-BBN provided alcohols **31a,b**. Hydrogenation of **31a** produced the carboxylic acid **32**, which was subsequently used for the synthesis of the macrocycle **38**. This involved coupling of **32** with N^{ϵ}-Cbz-L-Lys-NHMe using BOP, oxidation of the alcohol

Scheme 4[a]



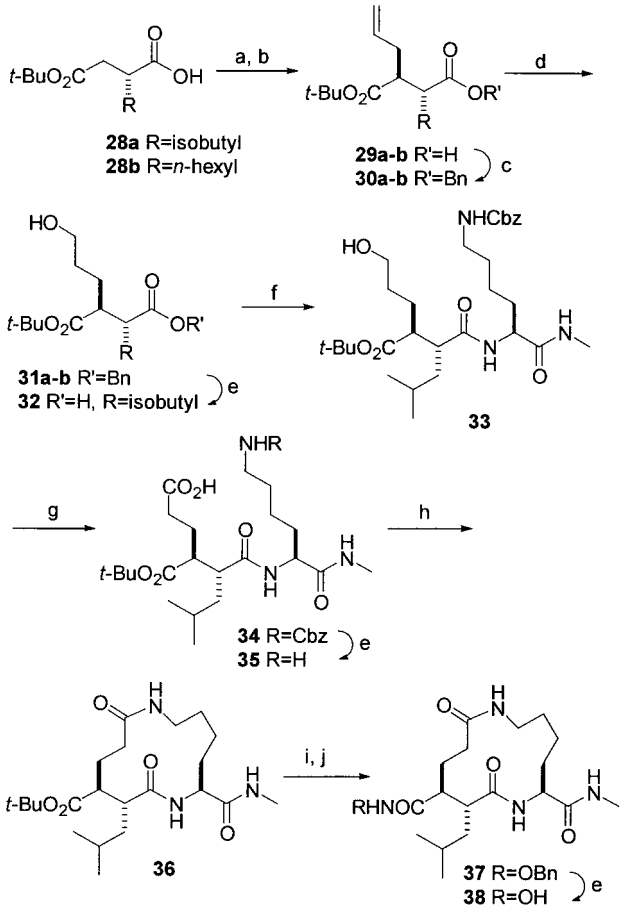
[a] Conditions: (a) 1,4-dibromo-2-butene, NaH, DMF, 0 °C, 65%; (b) N^{α}-Boc-L-TrpNHMe, NaH, DMF, 0 °C, 62%; (c) H_2, Pd−C, 2-propanol, 91%; (d) 4 N HCl/dioxane; (e) BOP, DIEA, DMF, $CHCl_3$, 45%; (f) LiOH, THF; (g) $BnONH_2$·HCl, BOP, DIEA, DMF, 65%; (h) H_2, Pd−C, MeOH, 86%.

in **33** to a carboxylic acid using $RuCl_3/H_5IO_6$, hydrogenolytic removal of the Cbz group in **34**, and macrocyclization of **35** using BOP to give the 13-membered lactam **36**. Cleavage of the *tert*-butyl ester in **36** with acid followed by coupling with *O*-benzylhydroxylamine using BOP furnished the *O*-benzyl hydroxamate **37**, from which the hydroxamic acid **38** was obtained by catalytic hydrogenation.

Starting from the intermediate **32**, three macrocycles (**41**, **43**, and **44**) were prepared as shown in Scheme 6. Coupling of **32** with an L-lysine derivative provided the amides **39a,b**, which were subjected to an intramolecular Mitsunobu reaction to furnish the cyclic sulfonamides **40a,b**. The phenylsulfonamide intermediate **40a** was then converted to a hydroxamic acid (**41**) using procedures analogous to those described for **38**. Removal of the mesitylsulfonyl group in **40b** using HBr/AcOH followed by Boc protection provided the carboxylic acid **42**, which was converted to a hydroxamic acid (**43**) by coupling with *O*-benzylhydroxylamine followed by catalytic hydrogenolysis. Removal of the Boc group in **43** using acid afforded target compound **44**.

The enantiopure amino acid derivative **48**, which was used for the synthesis of the cyclophane **57**, was prepared using Meyers' methodology[39] as illustrated in Scheme 7. The alcohol **45** was treated with methanesulfonyl chloride, and the resulting mesylate was converted to iodide **46**. LDA alkylation of pseudoephedrine glycinamide with **46** provided the amide **47**, which was subsequently hydrolyzed and esterified to give **48**.

Scheme 5[a]

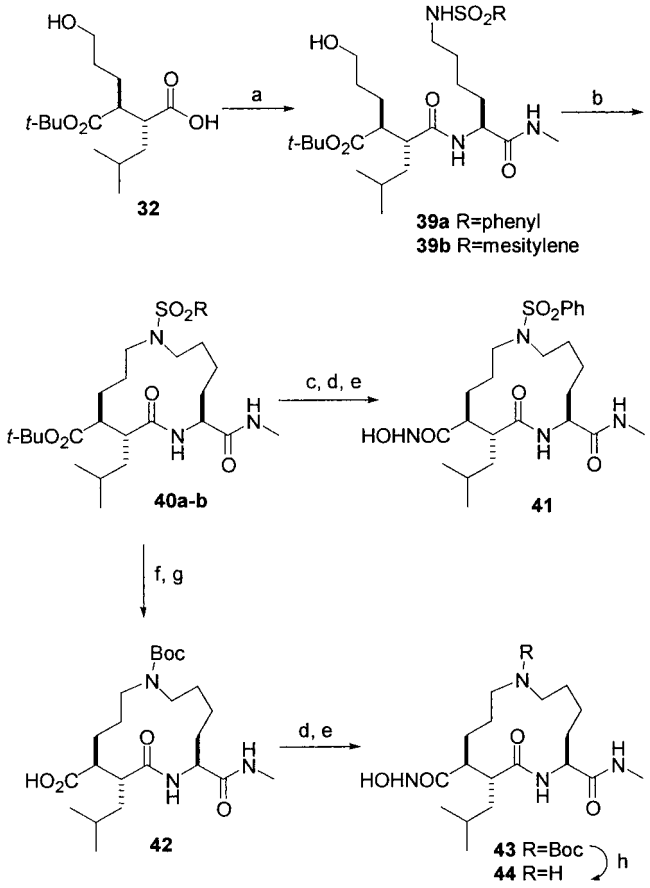


[a] Conditions: (a) LDA, allyl bromide, THF; (b) (1) LDA, THF, −78 °C to rt, (2) −78 °C, Et_2AlCl, −78 °C to rt, (3) −78 °C, MeOH; (c) BnBr, DBU, benzene; (d) 9-BBN, H_2O_2, NaOAc, THF; (e) H_2, Pd−C, MeOH; (f) L-Lys(Cbz)NHMe, BOP, DIEA, DMF, 77%; (g) $RuCl_3$, H_5IO_6, 60%; (h) BOP, DIEA, DMF, 70%; (i) TFA, CH_2Cl_2; (j) $BnONH_2$·HCl, BOP, DIEA, DMF, 61%.

Several series of cyclophanes were prepared starting from the intermediates **31a** and **31b** (Scheme 8). The alcohol in **31a,b** was converted to a bromide, and the benzyl group was subsequently removed by hydrogenation. Coupling of **49a,b** with an L-tyrosine derivative, an L-homotyrosine derivative, or **48** gave the cyclization precursors **50a**−**d**. Cyclization was carried out using Cs_2CO_3 in a mixed solvent system of DMF/DMSO at an elevated temperature to provide the cyclophanes **51a**−**d** in high yields. Removal of the *tert*-butyl group using TFA followed by coupling with *O*-benzylhydroxylamine provided the benzyl-protected hydroxamates **52a**−**d**. Hydrogenation of **52b** afforded compound **53**. Saponification of the methyl ester in **52a**−**d**, subsequent coupling of the carboxylic acid with an amino residue, and hydrogenolysis furnished compounds **54a**−**v** (R = isobutyl, n = 1), **55a**−**g** (R = n-hexyl, n = 1), **56** (R = isobutyl, n = 2), and **57** (R = isobutyl, n = 3). Removal of the Boc group at the lysine side chain in **54v** and **55g** afforded compounds **58** and **59**.

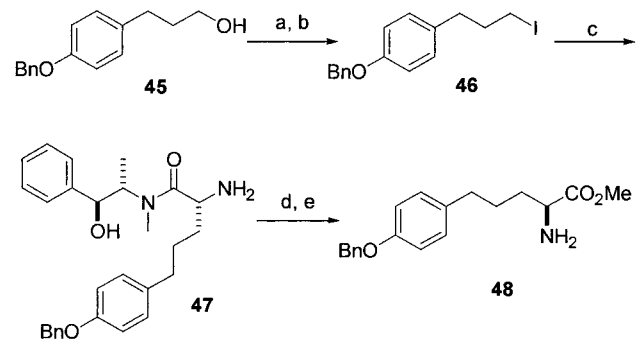
The side chain *N*-methyl derivative of L-lysine (**63**), which was used for the synthesis of a series of cyclic *N*-methylcarbamate analogues, was prepared according to Scheme 9. Reaction of the commercially available N^{α}-Cbz-L-Lys (**60**) with ethyl trifluoroacetate gave N^{α}-Cbz-L-Lys-(CF_3CO)OH (**61**) in high yield. Methylation of **61**

Scheme 6[a]



[a] Conditions: (a) L-Lys(RSO_2)NHMe, BOP, DIEA, DMF; (b) DIAD, PPh_3, THF; (c) TFA, CH_2Cl_2, (d) $BnONH_2$·HCl, BOP, DIEA, DMF; (e) H_2, Pd−C, MeOH; (f) HBr, AcOH; (g) $(Boc)_2O$, DIEA, DMF; (h) 4 N HCl/dioxane.

Scheme 7[a]

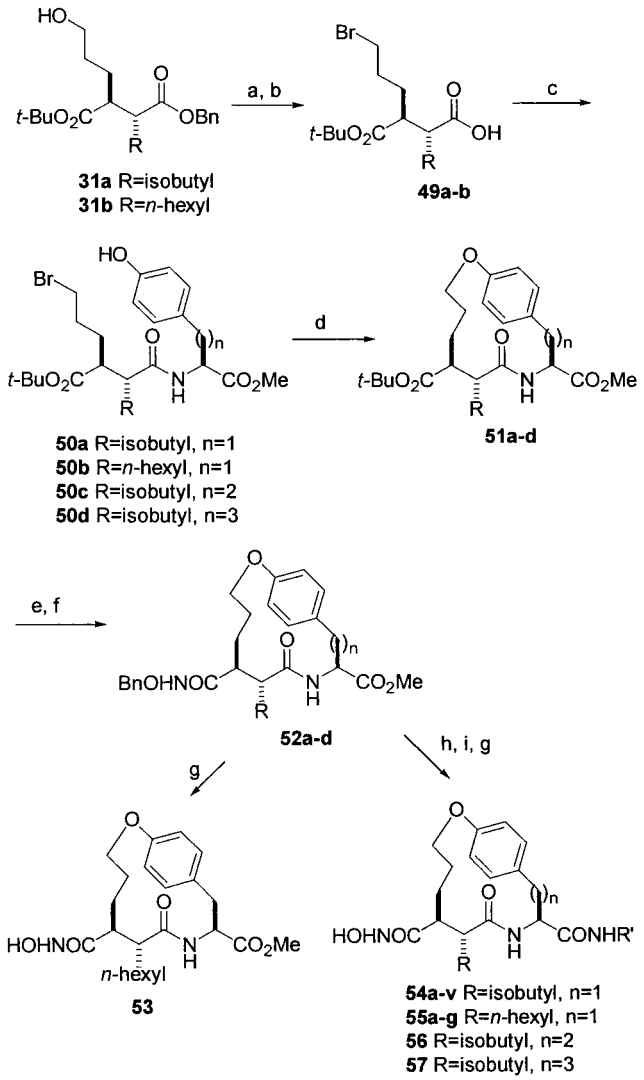


[a] Conditions: (a) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 100%; (b) NaI, acetone, reflux, 96%; (c) (1*S*,2*S*)-pseudoephedrine glycinamide, LDA, LiCl, THF, 47%; (d) NaOH, MeOH, reflux; (e) MeOH, HCl, reflux, 99%.

with iodomethane using K_2CO_3 in DMF at 110 °C produced the dimethylated product **62**, which was then subjected to treatment with LiOH in THF to hydrolyze the trifluoroacetyl group. The methyl ester was also hydrolyzed under these conditions. Subsequent reesterification using 4 N HCl in dioxane/MeOH afforded the lysine methyl ester **63**.

The synthesis of two series of cyclic carbamate analogues started with the intermediate **31a** (Scheme 10). Reaction of the alcohol **31a** with 4-nitrophenyl chloroformate gave the activated carbonate **64**, which was converted to a carbamate (**65a**, R^1 = H; **65b**, R^1 =

Scheme 8[a]

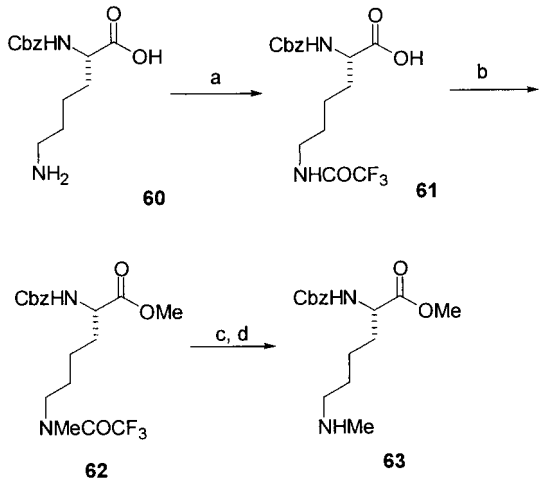


[a] Conditions: (a) CBr_4, PPh_3, DIEA, THF; (b) H_2, Pd−C, MeOH; (c) L-TyrOMe, TBTU, DIEA, DMF; (d) Cs_2CO_3, DMF, DMSO, 60 °C; (e) TFA, CH_2Cl_2; (f) $BnONH_2$·HCl, TBTU, DIEA, DMF, 80 °C; (g) H_2, Pd−$BaSO_4$, MeOH; (h) LiOH, THF; (i) R′NH_2, TBTU, DIEA, DMF.

Me) by treatment with N^{α}-Cbz-L-Lys-OMe or **63**. After hydrogenolytic removal of the Cbz and the benzyl groups, the carboxylic acid and the amine generated were coupled together to form a macrocyclic carbamate (**66a**, R^1 = H; **66b**, R^1 = Me). The *tert*-butyl ester was then converted to a benzyl-protected hydroxamate using the standard procedures. The final target compounds **68a**−**z** and **68aa**−**kk** (R^1 = H) and **69a**−**h** (R^1 = Me) were obtained by hydrolysis of the methyl ester, coupling of the generated carboxylic acid with an amine, and hydrogenation to remove the benzyl group. Removal of the Boc group at the lysine side chain in compound **68w** furnished compound **70**.

The macrocyclic carbamate compounds **75** and **76** (R^1 = H) and **74a**−**f** (R^1 = Me) containing an *N*-thiazolylamide residue or an *N*-pyridylamide residue were prepared using a sequence different from that described in Scheme 10. This sequence involves the introduction of an aminopyridine or aminothiazole group at P3′−P4′ before conversion of the *tert*-butyl ester to a hydroxamate (Scheme 11). Hydrolysis of the methyl ester in **66a,b**

Scheme 9[a]



[a] Conditions: (a) CF_3CO_2Et, K_2CO_3, MeOH, H_2O, 100%; (b) CH_3I, K_2CO_3, DMF, 110 °C, 90%; (c) LiOH, THF; (d) 4 N HCl/dioxane, MeOH.

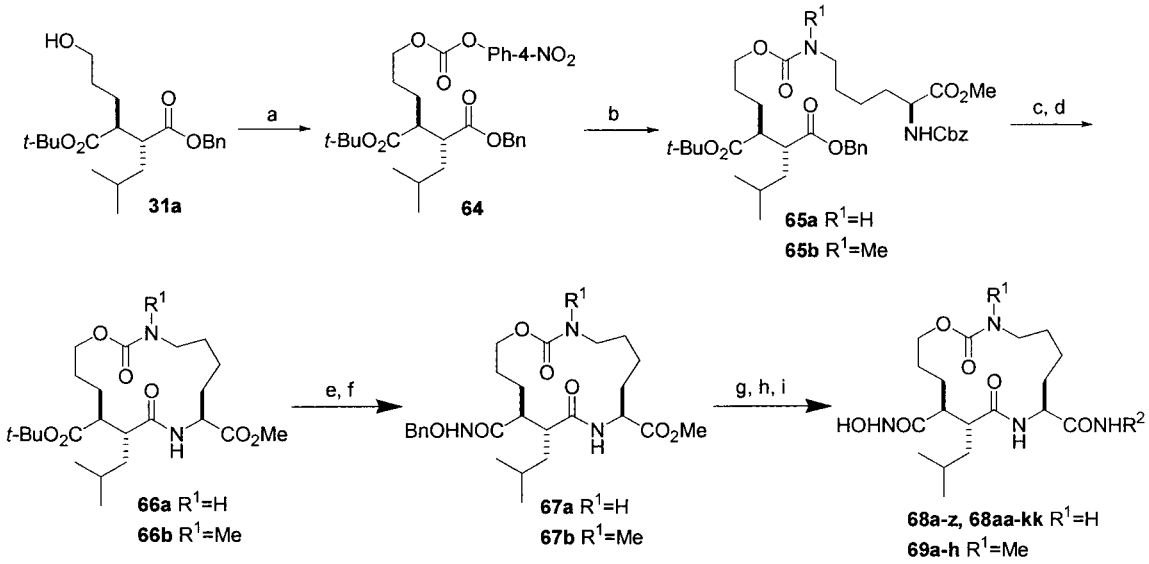
followed by coupling with an aminopyridine or aminothiazole derivative produced the intermediates **71** (R^1 = H) and **72a**−**f** (R^1 = Me), which were subjected to an acidolytic removal of the *tert*-butyl group and subsequently to a coupling with hydroxylamine hydrochloride to afford hydroxamic acids **73** (R^1 = H) and **74a**−**f** (R^1 = Me). Hydrolysis of the methyl ester in **73** (R^2 = 4-(2-methoxy-2-oxoethyl)thiazol-2-yl) using LiOH afforded compound **75**. The carboxylic acid in **75** was then coupled with morpholine using BOP to provide compound **76**. In this reaction, an excess amount of morpholine (5 equiv) was used to avoid coupling of the carboxylic acid with the hydroxamic acid in **75**.

Results and Discussion

A cellular assay was used to determine the activity in the inhibition of TNF-α release from LPS-stimulated human whole blood.[40] Since whole blood activities are determined and contributed to by many factors including serum protein binding and cell penetration, we also counterscreened with MMP (1, 3, and 9) enzyme assays in the early stage of study to aid in our design. On the basis of the assumption that TACE has a high level of homology with MMPs in the active site, MMP activities could provide us with a better understanding of the effect of a linkage on the backbone conformation that is critical to binding. Compounds that were potent in whole blood assay (WBA) were selected for further studies in the LPS-mouse model to assess their oral activity.

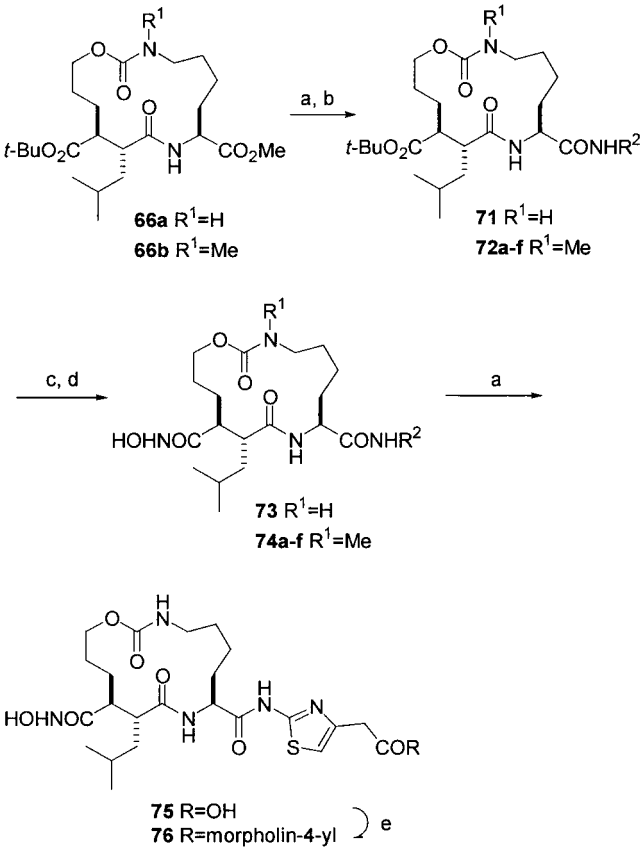
SARs of the P1−P2′ Linkage. Based on marimastat, we designed and synthesized the first test molecule, **9** (SC903), a 13-membered lactam with an ether−amide linkage. As illustrated in Table 1, SC903 was potent against MMP-1, MMP-2, and MMP-9 and had an IC_{50} of 6 μM in WBA, which is slightly less active than marimastat (IC_{50} = 4.1 μM). An X-ray crystallographic study of SC903 bound to MMP-3 reveals that this macrocycle effectively maintains the extended conformation with a binding mode very similar to that of the linear inhibitors,[33] confirming our design hypothesis. Encouraged by these results, several modifications were made to improve the anti-TNF-α activity. One of the

Scheme 10[a]



[a] Conditions: (a) *p*-nitrophenyl chloroformate, DIEA, THF, 91%; (b) N^{α}-Cbz-L-Lys(R^1)OMe, K_2CO_3, DMF; (c) H_2, Pd−C, MeOH; (d) BOP, DIEA, DMF, $CHCl_3$; (e) TFA, CH_2Cl_2; (f) $BnONH_2$·HCl, BOP, DIEA, DMF; (g) LiOH, THF; (h) R^2NH_2, BOP, DIEA, DMF; (i) H_2, Pd−$BaSO_4$, MeOH.

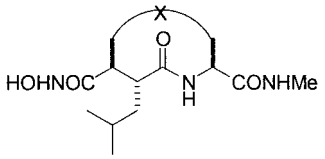
Scheme 11[a]



[a] Conditions: (a) LiOH, THF; (b) R^2NH_2, BOP, DIEA, DMF; (c) TFA, CH_2Cl_2; (d) $HONH_2$·HCl, DIEA, BOP, DMF; (e) morpholine, BOP, DIEA, DMF.

physical properties observed for SC903 is its high polarity, presumably due to too many amide bonds in the molecule. This observation prompted us to make an *N*-methyl substitution at the linker amide bond, which was accompanied by significantly improved MMP-1 and MMP-3 activity and slightly improved whole blood activity (**15**, WBA $IC_{50} = 3.8\ \mu M$). The speculation that

Table 1. Cyclic Inhibitors with a Variety of Linkers



compd	X	WBA[a] IC_{50}, μM	K_i, nM[b] MMP-1	MMP-3	MMP-9
marimastat		4.1	<1	2.4	<1
BB-16		1.8	<1	1.93	<1
9 (SC903)	-$OCH_2CONH(CH_2)_4$-	6.5	2.8	24.1	2.6
15	-$OCH_2CON(Me)(CH_2)_4$-	3.8	<1	3	3.9
22	-$OCH_2CONHPh$-2-SCH_2-	8.0	<1	22.3	NT[c]
27	-$O(CH_2)_4$(1-indol-3-yl)CH_2-	3.7	<1	2.88	NT
38	-$(CH_2)_2CONH(CH_2)_4$-	1.6	1.4	NT	3.6
44	-$(CH_2)_3NH(CH_2)_4$-	2.7	<1	NT	12.8
41	-$(CH_2)_3N(PhSO_2)(CH_2)_4$-	1.3	<1	3.4	<1
43	-$(CH_2)_3N(Boc)(CH_2)_4$-	1.4	<1	3	<1
68a	-$(CH_2)_3OCONH(CH_2)_4$-	1.0	<1	NT	1.1
69a	-$(CH_2)_3OCONMe(CH_2)_4$-	2.3	<1	NT	<1
54a(SE205)	-$(CH_2)_3OPh$-4-CH_2-	1.2	1.2	32.7	1.8
56	-$(CH_2)_3OPh$-4-$(CH_2)_2$-	1.0	5.3	48.0	2.1
57	-$(CH_2)_3OPh$-4-$(CH_2)_3$-	2.4	1.8	16.2	3.3

[a] Inhibition of TNF-α release in human WBA was determined in three donors. [b] K_i values are from a single determination. [c] NT = not tested.

the better WBA potency of BB-16 ($IC_{50} = 1.8\ \mu M$) than that of marimastat ($IC_{50} = 4.1\ \mu M$) might be ascribed to the more hydrophobic 4-methoxybenzyl P2′ group in BB-16 led us to prepare two analogues with a hydrophobic aromatic ring at P2′. Thus, replacement of the P2′ L-lysine residue in SC903 with an *S*-(2-aminophenyl)-L-cysteine residue afforded the 13-membered lactam **22**, which was more potent against MMP-1 and equipotent against MMP-3 but slightly less potent in WBA ($IC_{50} = 8.0\ \mu M$) relative to SC903. The P2′ L-tryptophan analogue **27**, a 15-membered macrocycle with an alkyl linkage, was equipotent to inhibitor **15** in the inhibition of MMP-1, MMP-3, and TNF-α release ($IC_{50} = 3.7\ \mu M$).

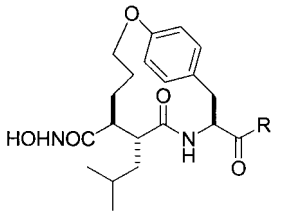
We next replaced the oxygen α to the hydroxamate in SC903 with a methylene, affording the 13-membered

lactam **38**. Interestingly, while this replacement resulted in similar MMP-1 and MMP-9 activities, the WBA potency was improved by approximately 4-fold (IC_{50} = 1.6 μM), suggesting that a less polar group α to the hydroxamate is beneficial to whole blood activity. Several analogues were synthesized by variation at the linkage in **38** while the P2′ lysine residue was kept constant. Replacement of the carbonyl of the linker amide in **38** with a methylene furnished the secondary amino analogue **44**, which showed better MMP-1 activity but reduced MMP-9 activity and slightly diminished whole blood activity (IC_{50} = 2.7 μM) relative to **38**. *N*-Substitution at the amino in **44** with a phenylsulfonyl (**41**) or a Boc (**43**) led to a 2-fold improvement in WBA potency and a marked improvement in MMP-9 activity over **44**, suggesting that a lipophilic group is preferred at this position. Insertion of an oxycarbonyl into the secondary amino linkage in **44** afforded the 15-membered macrocyclic carbamate **68a**, which demonstrated better WBA (IC_{50} = 1.0 μM) and MMP-9 activities compared with **44**. *N*-Methyl substitution at the carbamate residue in **68a** resulted in a 2-fold drop in the inhibition of TNF-α release (**69a**, WBA IC_{50} = 2.3 μM). This result is in contrast to that observed for SC903 in which *N*-methyl substitution resulted in slightly improved whole blood activity.

Based on BB-16, we designed and synthesized the second test molecule, **54a** (SE205), a 14-membered cyclophane. While SE205 was less active in the inhibition of MMPs than BB-16, it was equipotent to BB-16 in the inhibition of TNF-α release (WBA IC_{50} = 1.2 μM).[41] The crystal structure of SE205 bound to MMP-3 reveals that the 14-membered cyclophane ring holds all the structural elements (hydroxamate, P1′ isobutyl, and two amide bonds) in positions analogous to those in BB-16.[34] More importantly, SE205 was found to exhibit much better water solubility (13 mg/mL) compared with BB-16 (0.3 mg/mL) and good oral activity in the LPS-mouse model, with an ED_{50} of 17 mg/kg, making this molecule an attractive prototype for further modification. To explore the effect of ring size, two more cyclophanes with larger rings were prepared by replacing the L-tyrosine in SE205 with L-homotyrosine (**56**) and L-homo-homotyrosine (**57**). While the 15-membered cyclophane **56** maintained the WBA potency (IC_{50} = 1.0 μM), the 16-membered cyclophane **57** showed a 2-fold loss in the inhibition of TNF-α release (IC_{50} = 2.4 μM).

Beginning with the design of the first two test molecules, SC903 and SE205, we have conducted extensive investigations into the macrocyclic framework using a variety of linkages or by changing the ring size, leading to the identification of several inhibitors with IC_{50} values of 1−2 μM in the inhibition of TNF-α release. However, the similar whole blood activities among the majority of inhibitors illustrated in Table 1 suggest that changing the linkage has little effect on the cellular anti-TNF-α activity. This observation prompted us to shift our efforts to the P3′−P4′ area for further SAR exploration. On the basis of low molecular weight, whole blood potency, and water solubility, the cyclophane template SE205 and the cyclic carbamate template **68a** were selected for further structure refinement and potency optimization in the P3′−P4′ area, with emphasis on improving WBA potency and oral anti-TNF-α activity in the LPS-mouse model.

Table 2. Cyclophanes with Isobutyl at P1′ [a]



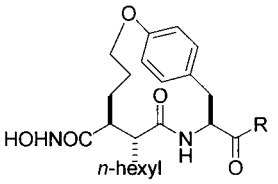
compd	R	WBA IC_{50}, μM	LPS-mouse (po) % inhib or ED_{50} (mg/kg)
54a (SE205)	NHMe	1.2	ED_{50} = 17
54b	$NHCH_2CF_3$	0.68	NT
54c	$NHCH(CH_3)_2$	0.70	34% at 10 mg/kg
54d	$NH(CH_2)_2Ph(4\text{-}SO_2NH_2)$	1.0	NT
54e (SL422)	Gly-NHMe	0.22	ED_{50} = 15
54f	Gly-$NHCH_2CF_3$	0.24	NT
54g	Gly-NH-cyclobutyl	0.20	31% at 30 mg/kg
54h	Gly-NH-*t*-Bu	0.20	21% at 30 mg/kg
54i	Gly-NHPh	0.20	0% at 10 mg/kg
54j	Gly-NH(2,4-difluoroPh)	0.70	NT
54k	Gly-NH-fluoren-1-yl	0.93	NT
54l	Gly-NMe_2	0.40	45% at 30 mg/kg
54m	Gly(piperidin-1-yl)	0.14	49% at 10 mg/kg
54n	Gly(4-hydroxypiperidin-1-yl)	0.20	ED_{50} = 21
54o	Gly(3,5-dimethylpiperidin-1-yl)	0.27	15% at 10 mg/kg
54p	Gly(3,3-dimethylpiperidin-1-yl)	0.46	NT
54q	L-Ala-NHMe	0.70	ED_{50} > 30
54r	D-Ala-NHMe	4.49	NT
54s	L-Tyr(OMe)NHMe	0.85	NT
54t	L-Ser(O-*t*-Bu)NHMe	0.95	NT
58	L-Lys-NHMe	0.83	NT
54u	L-Val-NHMe	1.51	NT

[a] See footnotes *a* and *c* in Table 1.

Cyclophane Series. As shown in Table 2, replacement of the P3′ *N*-methyl group in SE205 with a longer alkyl (**54b**, trifluoroethyl; **54c**, isopropyl) or arylalkyl (**54d**, 4-(aminosulfonyl)phenethyl) led to a relatively minor improvement in WBA potency. A more remarkable enhancement in potency in the inhibition of TNF-α release was achieved when a glycine *N*-methylamide residue was incorporated into the P3′ position, as observed with **54e** (SL422; IC_{50} = 0.22 μM). Despite its 5-fold improvement in whole blood activity over SE205, SL422 was found to be equipotent to SE205 in the LPS-mouse model. Larger, more hydrophobic groups than methyl at P4′ such as trifluoroethyl (**54f**), cyclobutyl (**54g**), *tert*-butyl (**54h**), and phenyl (**54i**) maintained the WBA potency but reduced the oral activity. Further increasing the lipophilicity at P4′ was found to be detrimental to whole blood activity as seen in the 2,4-difluorophenyl analogue **54j** and the fluoren-1-yl analogue **54k**, possibly due to higher protein binding of these groups. While *N*-methyl substitution at the P4′ *N*-methylamide moiety in SL422 led to a drop in in vitro and in vivo potencies (**54l**), the P4′ piperidine amide analogue **54m** showed WBA and oral activities comparable to those of SL422. Substitution with a polar hydroxyl group on the piperidine ring (**54n**) basically retained the in vitro and in vivo potencies, whereas hydrophobic substituents on the piperidine ring (**54o** and **54p**) reduced the WBA and oral activities.

By keeping the P4′ *N*-methylamide constant, we next investigated the SAR at the P3′ position by replacing the glycine residue in SL422 with several other amino acid residues. In general, increasing the size of the P3′

Table 3. Cyclophanes with *n*-Hexyl at P1′ [a]



compd	R	WBA IC_{50}, μM	LPS-mouse (po) inhib at 30 mg/kg
53	OMe	>50	NT
55a	NHMe	2.5	26% at 100 mg/kg
55b	NHBn	2.2	NT
55c	$NH(CH_2)_2Ph(4\text{-}SO_2NH_2)$	0.48	26%
55d	$NH(CH_2)_3$(imidazol-1-yl)	0.82	30%
55e	Gly-NHMe	0.55	NT
59	L-Lys-NH_2	0.76	36%
55f	L-Ser(O-*t*-Bu)NHMe	0.30	18%

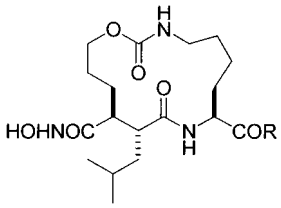
[a] See footnotes in Tables 1 and 2.

residue diminished the WBA potency as indicated by comparison of **54q, 54s,t**, and **58** with SL422 (Table 2). The similar whole blood activities among **54q, 54s,t**, and **58** suggest that the TACE S3′ pocket can accommodate a variety of structurally diversified groups including an amino residue (**58**). However, a sterically congested group such as an isopropyl (**54u**, $IC_{50} = 1.51$ μM) at the α-position of the glycine residue is less tolerated. The over 6-fold difference in WBA potency between the D-alanine analogue **54r** and the L-alanine analogue **54q** indicates that the stereochemistry at this position is important to anti-TNF-α activity.

In an SAR study parallel to that of the SE205 series, we investigated the P3′−P4′ area of the cyclophane template bearing a longer P1′ alkyl group (*n*-hexyl) that replaces the P1′ isobutyl group in the SE205 series. This study was initiated on the basis of the rationale that a longer, more hydrophobic P1′ group might confer better binding to TACE in the S1′ pocket as has been observed with some MMPs.[42] A comparison of the WBA data in Table 3 with those in Table 2 reveals that there is no clear trend as to whether the *n*-hexyl offers any advantage over the isobutyl in the in vitro anti-TNF-α activity. While the P3′ *N*-methylamide analogue **55a**[41] and the P3′ glycine *N*-methylamide analogue **55e** are about 2-fold less active than their isobutyl counterparts SE205 and SL422, analogues **55c** and **55f** are 2-fold and 3-fold more active than their isobutyl counterparts **54d** and **54t**, respectively, in WBA. However, the dramatic loss in oral activity in the LPS-mouse model when the isobutyl in SE205 was replaced with *n*-hexyl (**55a**) clearly indicates that a longer, hydrophobic P1′ group results in lower oral activity. Of particular note is the result from the replacement of the P3′ *N*-methylamide in **55a** with a methyl ester (**53**). The complete loss in whole blood activity in **53** suggests the importance of the amide NH for binding (as a hydrogen bond donor) at this position.

Cyclic Carbamate Series. The SAR data of the cyclic carbamate series are shown in Table 4. While replacement of the P3′ methyl group in **68a** with a trifluoroethyl group (**68b**) resulted in a 2-fold loss in WBA, a phenyl at this position (**68c**) enhanced the activity by over 3-fold. To improve the water solubility of **68c**, a polar morpholinyl group was introduced at the *para* position of the phenyl group (**68d**) or the phenyl

Table 4. Cyclic Carbamate Analogues[a]



compd	R	WBA IC_{50}, μM	LPS-mouse (po) inhib at 10 mg/kg or ED_{50} (mg/kg)
68a	NHMe	1.0	NT
68b	$NHCH_2CF_3$	2.0	NT
68c	NHPh	0.28	NT
68d	NHPh(morpholin-4-yl)	0.19	31%
75	NH(4-carboxymethylthiazol-2-yl)	0.083	44%
76	NH{[4-(morpholin-4-yl)carbonyl-methyl]thiazol-2-yl}	0.12	24%
68e	NHBn	0.74	NT
68f	NH(2-picolyl)	0.70	NT
68g	NH(3-picolyl)	0.50	NT
68h	NH(4-picolyl)	0.49	NT
68i	NH[2-(2-pyridyl)ethyl]	0.39	NT
68j	NH[2-(6-methoxyindol-3-yl)ethyl]	0.094	0%
68k	NH[2-(5-methoxyindol-3-yl)ethyl]	0.49	4%
68l	NH[2-(5-fluoroindol-3-yl)ethyl]	0.13	39%
68m	NH[2-(5-methylindol-3-yl)ethyl]	1.17	NT
68n	NH(2-hydroxy-2-phenylethyl)	0.085	21%
68o	NH(1-ethoxycarbonyl-piperidin-4-yl)	0.13	33%
68p	NH(2(*R*)-hydroxy-1(*S*)-indane)	0.11	27%
68q	NH(2(*S*)-hydroxy-1(*R*)-indane)	0.40	NT
68r	$NHCH_2$(2(*S*)-tetrahydrofuranyl)	0.26	NT
68s	$NHCH_2$(2(*R*)-tetrahydrofuranyl)	0.98	NT
68t	Gly-NHMe	0.12	45%
68u	L-Ala-NHMe	0.27	NT
68v	L-Leu-NHMe	0.10	0%
68w	L-Lys(Boc)NHMe	0.21	0%
70	L-Lys-NHMe	0.69	NT
68x	L-*tert*-Leu-NHMe	1.2	NT
68y (SP057)	Gly(morpholin-4-yl)	0.067	$ED_{50} = 2.6$
68z	Gly(2,6-dimethylmorpholin-4-yl)	0.15	43%
68aa	Gly(4-methyl-piperazin-1-yl)	0.16	37%
68bb	Gly(4-phenylpiperazin-1-yl)	0.070	29%
68cc	Gly[4-(2-pyridinyl)piperazin-1-yl]	0.070	$ED_{50} = 8.7$
68dd	Gly(4-ethoxycarbonyl-piperazin-1-yl)	0.13	$ED_{50} = 7$
68ee	Gly(4-hydroxypiperidin-1-yl)	0.28	$ED_{50} = 3.6$
68ff	Gly[4-(piperidin-1-yl)-piperidin-1-yl]	0.18	$ED_{50} = 8.1$
68gg	Gly(4-carboxypiperidin-1-yl)	0.22	NT
68hh	Gly(3-carboxypiperidin-1-yl)	0.58	NT
68ii	L-Ala(morpholin-4-yl)	0.15	$ED_{50} > 10$
68jj	L-Ser(morpholin-4-yl)	0.10	$ED_{50} > 10$
68kk	b-Ala(morpholin-4-yl)	0.17	0%

[a] See footnotes in Tables 1 and 2.

was replaced with a thiazole bearing a polar substituent at the 4-position (**75** and **76**). These modifications resulted in some improvement in WBA potency over that of **68c**. Unfortunately, these potent analogues exhibited low oral activity in the LPS-mouse model. The similar in vitro potencies between **75** and **76** suggest that a carboxylic acid at this position is tolerated for whole blood activity.

Several aryl or heteroaryl groups connected to the P2′−P3′ amide through 1−2 methylene unit(s) were examined at the P3′ position. Insertion of a methylene between the amide bond and the phenyl group in **68c** led to a slight loss in WBA as observed with **68e**. Replacement of the phenyl in **68e** with more polar pyridyl residues (**68f**−**h**) did not significantly improve the WBA potency. One carbon longer between the P2′−P3′ amide bond and the pyridyl in **68f** led to a relatively

minor enhancement in WBA (**68i**). The in vitro activity of the four indolyl analogues **68j**−**m** is dependent on the nature and position of the substituent on the indole ring, with the 6-methoxyindolyl analogue **68j** exhibiting the best WBA potency (IC_{50} = 0.094 μM) but a lack of oral activity. A 2-hydroxy-2-phenylethyl group at P3′ provided another potent analogue (**68n**) in WBA (IC_{50} = 0.085 μM), which was inactive when administered orally in the LPS-mouse model.

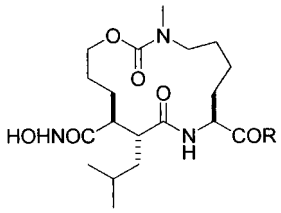
Nonaromatic carbocycles or heterocycles appended to the P2′−P3′ amide through 0−1 methylene spacer were also examined. The 1-ethoxycarbonylpiperidin-4-yl analogue **68o**, 2(*R*)-hydroxy-1(*S*)-indane analogue **68p**, and 2(*S*)-tetrahydrofuran analogue **68r** all were potent in whole blood but lacked oral activity. The almost 4-fold difference in WBA potency between **68p** and **68q** and between **68r** and **68s** provides further evidence that the stereochemistry at this position is important to anti-TNF-α activity.

Our next phase of the SAR investigations at P3′−P4′ was to incorporate an amino acid residue at P3′ with an *N*-methylamide at P4′. The glycine *N*-methylamide analogue **68t** demonstrated good WBA potency with weak oral activity in the LPS-mouse model. In contrast to the SAR in the SE205 series (vide supra), increasing the size of P3′ had a lesser effect on the in vitro anti-TNF activity as revealed by comparison of **68u**, **68v**, and **68w** with **68t**. Despite the good in vitro potency, however, the L-leucine analogue and the L-lysine analogue showed no in vivo activity when dosed orally to mice. In parallel to the SAR seen in the SE205 series, a sterically hindered group such as a *tert*-butyl at P3′ is detrimental to whole blood activity (**68x**, IC_{50} = 1.2 μM). The 3-fold loss in WBA (**70**) by removing the lysine side chain Boc in **68w** suggests that a charge at P3′ is less preferred in this series.

Keeping the P3′ glycine residue constant, we next examined a variety of heterocycles including morpholine, piperazine, and piperidine that form a tertiary amide bond with the glycine residue at P4′. With a glycine residue at P3′, a morpholino residue at P4′ afforded one of the most potent inhibitors, **68y** (SP057), with an IC_{50} of 67 nM in WBA. More importantly, SP057 was highly potent in the inhibition of TNF-α release when administered orally to mice, with an ED_{50} of 2.6 mg/kg. Dimethyl substitution at the 2,6-positions on the morpholine (**68z**) decreased the in vitro and in vivo potencies. Replacement of the morpholine in SP057 with a piperazine or piperidine derivative (**68aa**−**hh**) resulted in similar or less WBA potency. Although the *N*-phenylpiperazino analogue **68bb** and the *N*-2-pyridylpiperazino analogue **68cc** were equipotent to SP057 in WBA, they were less active orally. However, despite the 4-fold drop in WBA potency when the morpholine in SP057 was replaced with 4-hydroxypiperidine, the resulting analogue **68ee** exhibited oral activity (ED_{50} = 3.6 mg/kg) comparable to that of SP057. The similar WBA potencies between the 4-carboxypiperidine analogue **68gg** and the neutral piperidine analogue **68ee** or the basic piperidine analogue **68ff** suggest that a carboxylic acid at P4′ is tolerated for whole blood activity.

To further assess the importance of the P3′ glycine residue to in vitro and in vivo activity, three more analogues bearing a morpholino at P4′ were prepared. Surprisingly, replacing the glycine residue in SP057 with an L-alanine residue (**68ii**), an L-serine residue (**68jj**), or a β-alanine residue (**68kk**) resulted only in a minor loss in WBA potency but in a dramatic loss in oral activity. These results, taken together with those from the previous studies in this series and the cyclophane series (vide supra), provide convincing evidence that a glycine residue at P3′ is a critical structural component to achieve both good in vitro activity and good oral activity.

Table 5. Cyclic *N*-Methylcarbamate Analogues[a]



compd	R	WBA IC_{50}, μM	LPS-mouse (po) ED_{50}, mg/kg
69a	NHMe	2.3	NT
69b	Gly(morpholin-4-yl)	0.20	4.9
69c	Gly(4-hydroxypiperidin-1-yl)	0.30	2.7
69d	Gly(4-methylpiperazin-1-yl)	0.12	11.4
69e	Gly(4-ethoxycarbonylpiperazin-1-yl)	0.60	>30
69f	Gly-N(Me)$_2$	0.30	6.3
69g	Gly(pyrrolidin-1-yl)	0.40	>30
69h	Gly-NHMe	0.42	>30
74a	Gly-NH(pyridin-2-yl)	0.20	28
74b	Gly-NH(4-methylthiazol-2-yl)	0.30	>30
74c	NH(pyridin-2-yl)	0.20	>30
74d	NH(pyridin-3-yl)	0.50	>30
74e	NH(pyridin-4-yl)	0.50	>30
74f	NH(4-methylthiazol-2-yl)	0.30	>30

[a] See footnotes in Tables 1 and 2.

To understand whether *N*-methylation at the carbamate moiety can offer any advantage in whole blood activity and/or oral potency, we also conducted SAR studies at the P3′−P4′ area using the *N*-methylcarbamate template **69a** (Table 5). In general, this series of analogues were less active in WBA as compared with their NH-carbamate counterparts. For example, the morpholino analogue **69b**, the 4-(ethoxycarbonyl)piperazino analogue **69e**, and the glycine *N*-methylamide analogue **69h** were 3-fold, over 4-fold, and over 3-fold less active than their NH-carbamate counterparts SP057, **68dd**, and **68t**, respectively, in in vitro anti-TNF-α activity. More polar residues at P4′ appeared to maintain the WBA and oral activities as revealed by comparison of **69c** and **69d** with their counterparts **68ee** and **68aa**, respectively. Of particular note in this series is the dramatic enhanced oral activity of the P4′ *N*,*N*-dimethyl analogue **69f** (ED_{50} = 6.3 mg/kg) versus the P4′ *N*-methyl analogue **69h**. This oral activity was completely lost when the dimethylamino in **69f** was replaced with a pyrrolidino moiety (**69g**). Analogues with a pyridine or thiazole directly connected to the P2′−P3′ amide or through a glycine residue (**74a**−**f**) showed good WBA potency but lacked oral activity. These results further confirm our previous observations that arylamide- or heteroarylamide-containing analogues have low oral anti-TNF-α activity.

TACE Activity and Selectivity Profile of SL422 and SP057. SL422 and SP057, representing the cyclophane series and the cyclic carbamate series, respec-

Table 6. Inhibitory Profiles for SL422 and SP057

	K_i, nM[a]										
compd	pTAC E	MMP-1	MMP-2	MMP-3	MMP-7	MMP-8	MMP-9	MMP-13	MMP-14	MMP-15	MMP-16
SL422	12	3.0	1.1	14	0.8	0.5	0.9	0.45	94	20	35
SP057	4.2	13	1.1	7.8	1.5	1.1	1.2	2.3	140	71	107

[a] K_i values are from five determinations for TACE and three determinations for MMPs.

Table 7. Pharmacokinetics of SL422 and SP057 in Beagle Dogs

compd	dose, mg/kg	$T_{1/2}$, h	Cl, L/h/kg	V_{ss}, L/kg	C_{max}, ng/mL	T_{max}, h	AUC, ng·h/mL	F, %
SL422	0.74 (iv)	0.81	0.42	0.70	121	0.88	2613	11
	0.863 (po)	1.29					342	
SP057	0.5 (iv)	1.0	0.29	0.33	667	1.25	2080	23
	2.0 (po)	2.2					1910	

tively, were tested in the porcine TACE assay. As seen in Table 6, SP057 and SL422 are potent against TACE, with K_i values of 4.2 and 12 nM, respectively. The 3-fold better TACE potency of SP057 versus SL422 is consistent with what we have observed with these two compounds in WBA, where SP057 is about 3-fold more potent than SL422. To gain insight into the selectivity of TACE over MMPs, SL422 and SP057 were screened against a panel of 10 MMPs. As shown in Table 6, these two inhibitors exhibited high potency against MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, and MMP-13 and lesser potency against MMP-14, MMP-15, and MMP-16. These results indicate that SL422 and SP057 are nonselective TACE inhibitors. Since excessive TNF-α production has been noted in several disease conditions that are also characterized by MMP-mediated tissue degradation, it is likely that these nonselective inhibitors that inhibit both TACE and MMPs may provide some advantage in the treatment of diseases where both mechanisms are involved.

Pharmacokinetics of SL422 and SP057 in Beagle Dogs. SL422 and SP057 were selected for pharmacokinetic studies in beagle dogs (Table 7). Both compounds showed a short half-life following iv or oral dosing, with $T_{1/2}$ values of 0.81 h (iv) and 1.29 h (po) for SL422 and 1.0 h (iv) and 2.2 h (po) for SP057. After oral dosing, both compounds were rapidly absorbed, with T_{max} values of 0.88 and 1.25 h for SL422 and SP057, respectively. The oral bioavailability (F) was 11% and 23% for SL422 and SP057, respectively. The low bioavailability of both compounds may reflect an incomplete oral absorption rather than presystematic metabolism as indicated by their low clearances.

Conclusion

We designed a new class of macrocyclic hydroxamic acids by linking the P1 and P2′ residues of acyclic *anti*-succinate-based hydroxamic acids. A variety of residues including amide, carbamate, alkyl, sulfonamido, Boc-amino, and amino were found to be suitable P1−P2′ linkers. With an *N*-methylamide at P3′, the 13−16-membered macrocycles exhibited moderate inhibition of TNF-α release in WBA ($IC_{50} > 1$ μM). The similar whole blood potencies observed among the majority of the cyclic templates prepared suggest that, like MMPs, the TACE P1−P2′ area might be a solvent-exposed area.

To further improve the whole blood activity, we selected the cyclophane and cyclic carbamate templates for refinement and optimization in the P3′−P4′ area. Our SAR studies revealed that the P3′−P4′ area can accommodate a broad array of functional groups including polar residues, hydrophobic residues, and amino and carboxylic acid moieties, suggesting that, like the P1−P2′ area, the TACE P3′−P4′ area might also be a solvent-exposed area. While a number of structurally diversified residues at P3′ are able to confer good in vitro potency in WBA, in both series, a glycine residue at P3′ was identified as a critical structural component to achieve both good in vitro potency and good oral activity. With a glycine residue at P3′, an *N*-methylamide at P4′ provided the best cyclophane analogue, SL422 (WBA $IC_{50} = 0.22$ μM, LPS-mouse $ED_{50} = 15$ mg/kg, po), whereas a morpholinylamide at P4′ afforded the most potent and most orally active cyclic carbamate analogue, SP057 (WBA $IC_{50} = 0.067$ μM, LPS-mouse $ED_{50} = 2.3$ mg/kg, po). Although replacement of the P1′ isobutyl in the cyclophane series with a longer alkyl (*n*-hexyl) had positive and negative effects on WBA potency depending on the P3′−P4′ residues, it was clearly demonstrated that a longer, hydrophobic group at P1′ resulted in lower oral activity. *N*-Methyl substitution at the carbamate moiety in the cyclic carbamate series offered no advantage in WBA and oral activities.

Further profiling for SL422 and SP057 showed that these macrocyclic compounds are potent TACE inhibitors, with K_i values of 12 and 4.2 nM in the porcine TACE assay, and are broad-spectrum MMP inhibitors. Pharmacokinetic studies in beagle dogs revealed that SL422 and SP057 are orally bioavailable, with $F = 11\%$ and 23%, respectively. The antiarthritic efficacy of these two compounds has been studied in animal models, and the results will be published in due course.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Analytical HPLC was run on a Vydac C18 column (4.6 × 250 mm) operated at room temperature, eluting at 1 mL/min using a linear gradient of water (0.05% TFA)/acetonitrile (0.05% TFA) from 90:10 to 20:80 over 30 min. Preparative HPLC was performed on a Vydac C18 column (22 × 250 mm) operated at room temperature, eluting at 8 mL/min with a linear gradient of water (0.1% TFA)/acetonitrile (0.1% TFA) from 100:0 to 0:100 over 80 min. UV detection was at 220 nm. ^{1}H NMR data were obtained at 300 MHz using a Varian VXR400 spectrometer and were referenced to TMS. Mass spectral data were obtained on either a VG 70-VSE (FAB, high-resolution FAB, high-resolution DCI) or a Finnigan MAT 8230 (DCI) mass spectrometer. Combustion analyses were performed by Quantitative Technologies, Inc., Bound Brook, NJ. Solvents and reagents were used as purchased from commercial suppliers unless otherwise indicated. Yields quoted herein are isolated yields.

(4*S*)-4-Benzyl-3-(4-methylpentanoyl)-1,3-oxazolidin-2-one (1). To a stirred solution of 4(*S*)-(phenylmethyl)-2-oxazolidinone (48.3 g, 272 mmol) in THF (500 mL) cooled to −78 °C was added 2.5 M *n*-butyllithium (131 mL, 327 mmol) in hexane over 20 min, and stirring was continued at −78 °C for 45 min. To it was added 4-methylpentanoyl chloride (44 g, 327 mmol). The solution was allowed to warm to room temperature, and stirring was continued for 2.5 h. The volatiles were removed under reduced pressure, and EtOAc (500 mL) was added. The resulting solution was washed with 10% citric acid, brine, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Purification by flash chromatography on silica eluting with 10% EtOAc/hexanes yielded the desired product (68.53 g, 91.5%) as an oil: MS *m*/*z* 276.3 $(M + H)^+$. Anal. ($C_{16}H_{21}NO_3$) C, H, N.

Butyl (3*R*)-3-{[(4*S*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]-carbonyl}-2-hydroxy-5-methylhexanoate (2). To a stirred solution of diisopropylamine (3.25 mL, 23.25 mmol) in THF (20 mL) cooled to −78 °C was added 2.5 M *n*-butyllithium (9.3 mL, 23.25 mmol) in hexane. The solution was allowed to stir at 0 °C for 30 min and then cooled back to −78 °C. To it was added a solution of **1** (5.82 g, 21.13 mmol) in THF (50 mL) cooled at −78 °C. After the resulting solution was stirred at −78 °C for 1 h, a solution of *n*-butyl glyoxalate (4.12 g, 31.69 mmol) in THF (10 mL) was added. The mixture was stirred at −78 °C for 3 h, and the reaction was quenched with ice water. Ethyl acetate was added followed by 10% citric acid solution. The organic layer was separated, washed with water, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Purification on silica gel eluting gradually with 5% EtOAc/hexanes, 10% EtOAc/hexanes, and 20% EtOAc/hexanes provided compound **2** (3.1 g, 36%) as a mixture of two diastereomers (3:1): MS *m*/*z* 406.2 $(M + H)^+$. Anal. ($C_{22}H_{31}NO_6$) C, H, N.

4-Benzyl 1-Butyl (3*R*)-2-Hydroxy-3-isobutylbutanedioate (3). To a solution of **2** (5.1 g, 12.57 mmol) in THF/H_2O (250 mL, 4:1) cooled in an ice bath was added hydrogen peroxide (7.84 mL, 50.3 mmol) followed by a solution of LiOH (791 mg, 18.85 mmol) in water (8 mL). After the resulting solution was stirred for 1 h, the reaction was quenched with a solution of Na_2SO_3 (6.33 g, 50.28 mmol) in water. THF was removed under reduced pressure, and the solution was extracted with ethyl acetate twice. The water layer was acidified with cold concentrated HCl to pH 3 and extracted with CH_2Cl_2 three times. The combined CH_2Cl_2 layer was washed with water and brine, dried ($MgSO_4$), and concentrated. Silica gel chromatography eluting gradually with $CHCl_3$, 5% MeOH/$CHCl_3$, and 10% MeOH/$CHCl_3$ provided the carboxylic acid (2.29 g, 74%) as a mixture of two diastereomers (3:1): MS (NH_3, CI) *m*/*z* 264.0 $(M + NH_4)^+$.

A mixture of the above carboxylic acid (8.33 g, 33.82 mmol), benzyl bromide (7.0 g, 37.2 mmol), and DBU (6.07 mL, 40.58 mmol) in benzene (100 mL) was stirred at 50 °C for 3 h. Benzene was removed under reduced pressure. The residue was taken up in EtOAc. The solution was washed with brine 3×, dried ($MgSO_4$), and concentrated. Flash chromatography on a silica gel column eluting with 10% EtOAc/hexanes provided **3** (9 g, 79%) as a mixture of two diastereomers (ratio 3:1): MS (ESI) *m*/*z* 337.3 $(M + H)^+$. Anal. ($C_{19}H_{28}O_5$) C, H, N.

4-Benzyl 1-Butyl (3*R*)-2-(2-*tert*-Butoxy-2-oxoethoxy)-3-isobutylbutanedioate (4). To a solution of **3** (8.95 g, 26.64 mmol) and *tert*-butyl bromoacetate (4.33 mL, 29.3 mmol) in THF (50 mL) cooled in an ice bath was added NaH (1.5 g, 60% oil dispersion, 32 mmol) in batches. The mixture was stirred in the ice bath for 30 min and at room temperature for 2 h. The reaction was terminated by quenching with 10% citric acid solution. EtOAc was added, and the solution was washed with 10% citric acid and brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on a silica gel column to give **4** (8.6 g, 71%) as a mixture of two diastereomers (3:1): MS (ESI) *m*/*z* 451.4 $(M + H)^+$. Anal. ($C_{25}H_{38}O_7$) C, H, N.

(2*R*)-2-[2-Butoxy-1-(2-*tert*-butoxy-2-oxoethoxy)-2-oxoethyl]-4-methylpentanoic Acid (5). To a solution of **4** (5 g, 11.11 mmol) in MeOH (50 mL) was added 10% Pd/C (0.5 g). The mixture was stirred under H_2 (balloon) for 3 h. The catalyst was filtered off, and the solution was concentrated to give **5** (3.96 g, 99%) as a mixture of two diastereomers (3:1): MS (ESI) *m*/*z* 361.4 $(M + H)^+$.

{[(2*R*)-2-[(Benzyloxy)carbonyl]-1-(butoxycarbonyl)-4-methylpentyl]oxy}acetic Acid (6). To a solution of **4** (2.5 g, 5.55 mmol) in CH_2Cl_2 (25 mL) was added TFA (25 mL). The solution was stirred at room temperature for 4 h and concentrated to give **6** (2.45 g) as a mixture of two diastereomers (3:1): MS (ESI) *m*/*z* 395.3 $(M + H)^+$.

***tert*-Butyl (9*S*,12*R*)-13-(Butoxycarbonyl)-12-isobutyl-9-[(methylamino)carbonyl]-3,11-dioxo-1-phenyl-2,14-dioxa-4,10-diazahexadecan-16-oate (7)**. To a solution of N^{α}-(*tert*-butoxycarbonyl)-N^{ϵ}-[(benzyloxy)carbonyl]-L-lysine (12.39 g, 32 mmol) and methylamine hydrochloride (4.4 g, 65 mmol) in DMF (30 mL) cooled in an ice bath was added BOP (14.16 g, 32 mmol) followed by DIEA (25 mL, 128 mmol). The solution was allowed to stir at room temperature overnight. EtOAc (250 mL) was added, and the solution was washed with 10% citric acid, brine, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Purification on a silica gel column eluting with 80% EtOAc/hexanes yielded the *N*-methylamide (12.92 g, 95%) as a solid: MS (ESI) *m*/*z* 394.4 $(M + H)^+$.

The above *N*-methylamide (6 g, 15.26 mmol) was dissolved in 4 N HCl/dioxane (50 mL). After being stirred at room temperature for 1 h, the solution was concentrated under reduced pressure. The residue was triturated with ether to give the Boc-deprotected product (5.2 g, 100%) as a solid: MS (ESI) *m*/*z* 294.3 $(M + H)^+$.

Compound **5** (1.76 g, 4.88 mmol) and the above lysine *N*-methylamide (1.61 g, 4.88 mmol) were dissolved in DMF (10 mL), and the solution was cooled in an ice bath. To it was added BOP (2.16 g, 4.88 mmol) followed by DIEA (3.42 mL, 10.58 mmol). The mixture was allowed to stir at room temperature for 4 h. EtOAc was added, and the solution was washed with 10% citric acid, brine, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Flash chromatography on a silica gel column eluting with 10% MeOH/$CHCl_3$ provided **7** (2.32 g, 75%) as a mixture of two diastereomers (3:1): MS (ESI) *m*/*z* 636.6 $(M + H)^+$.

Butyl (9*S*,12*R*,13*S*)-12-Isobutyl-9-[(methylamino)carbonyl]-3,11-dioxo-1-oxa-4,10-diazacyclotridecane-13-carboxylate (8). To a solution of **7** (2.21 g, 3.47 mmol) in 2-propanol (30 mL) and 4 N HCl/dioxane (1 mL) was added 10% Pd/C (0.35 g). The mixture was stirred under H_2 (balloon) for 2 h. The catalyst was filtered off, and the solution was concentrated under reduced pressure to give a solid. The solid was dissolved in 4 N HCl/dioxane (30 mL). The solution was stirred for 2 h and concentrated under reduced pressure. The residue was taken up in DMF (5 mL). This solution was slowly added to a solution of BOP (1.64 g, 3.7 mmol) and DIEA (2.6 mL, 14.6 mmol) in $CHCl_3$ (100 mL) cooled in an ice bath over a period of 2 h. The solution was allowed to stir at room temperature overnight and concentrated. The residue was taken up in EtOAc, and the solution was washed with 10% citric acid, brine, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated to give the crude product as a mixture of two diastereomers. The two diastereomers were separated by flash chromatography on a silica gel column eluting with 15% MeOH/CH_2Cl_2 to give the major diastereomer **8** (0.8 g, 50%) as a solid: MS (ESI) *m*/*z* 428.3 $(M + H)^+$.

(9*S*,12*R*,13*S*)-N^{13}-Hydroxy-12-isobutyl-N^9-methyl-3,11-dioxo-1-oxa-4,10-diazacyclotridecane-9,13-dicarboxamide (9). To a solution of **8** (0.77 g, 1.8 mmol) in THF (10 mL) was added 1 N LiOH (4 mL). The solution was stirred at room temperature for 2 h and acidified with 4 N HCl/dioxane to pH 3. The volatiles were removed under reduced pressure, and *tert*-butyl alcohol was added. The organic phase was separated, washed with brine 3×, dried ($MgSO_4$), and concentrated to give the carboxylic acid (0.49 g, 73%) as a powder: MS (ESI) *m*/*z* 372.2 $(M + H)^+$.

To a solution of the above carboxylic acid (0.47 g, 1.27 mmol) and *O*-benzylhydroxylamine hydrochloride (0.2 g, 1.27 mmol) in DMF (5 mL) cooled in an ice bath was added BOP (0.56 g, 1.27 mmol) followed by DIEA (1.0 mL, 5.2 mmol). The solution

was allowed to stir at room temperature overnight. EtOAc was added, and the solution was washed with 10% citric acid, brine, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Purification on a silica gel column eluting with 5% MeOH/CH_2Cl_2 provided the *O*-benzylhydroxamate (0.21 g, 35%) as a solid: MS (ESI) *m*/*z* 477.3 $(M + H)^+$.

The *O*-benzylhydroxamate (100 mg, 0.21 mmol) was dissolved in MeOH (10 mL), and 10% Pd/C (15 mg) was added. The mixture was stirred under H_2 (balloon) for 2 h. The catalyst was filtered off, and the solution was concentrated. The residue was purified by reversed-phase HPLC to give **9** (50 mg, 62%) as a powder: ^{1}H NMR (DMSO-d_6) δ 10.95 (s, 1H), 9.20 (br, 1H), 8.31 (d, 1H), 7.84 (q, 1H), 6.96 (t, 1H), 4.25 (m, 1H), 3.92 (d, 1H), 3.85 (d, 1H), 3.60 (d, 1H), 2.95 (m, 2H), 2.62 (d, 3H), 2.48 (m, 1H), 1.8−1.2 (m, 9H), 0.92 (d, 3H), 0.84 (d, 3H); MS (ESI) *m*/*z* 387.3 $(M + H)^+$. Anal. ($C_{17}H_{30}N_4O_6$) C, H, N.

tert*-Butyl (1*S*)-1-[(Methylamino)carbonyl]-5-[methyl-(trifluoroacetyl)amino]pentylcarbamate *(11). To a solution of N^{α}-[(*tert*-butyloxy)carbonyl]-N^{ϵ}-(trifluoroacetyl)-L-lysine (**10**) (10.27 g, 30 mmol) and methylamine hydrochloride (4.05 g, 60 mmol) in DMF (30 mL) cooled in an ice bath was added BOP (13.27 g, 30 mmol) followed by DIEA (23.5 mL, 135 mmol). The mixture was stirred at room temperature overnight. EtOAc (500 mL) was added. The solution was washed with 10% citric acid, brine, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated to give a solid. Recrystallization from EtOAc/Et_2O provided the *N*-methylamide (10.1 g, 94%) as a crystal: mp 95−98 °C; MS (ESI) *m*/*z* 356.3 $(M + H)^+$.

A mixture of the above *N*-methylamide (9.9 g, 27.88 mmol), iodomethane (13.88 mL, 223 mmol), and K_2CO_3 (7.7 g, 55.8 mmol) in DMF (50 mL) was stirred at 100 °C for 24 h. After the mixture was cooled to room temperature, insoluble materials were filtered off. The filtrate was diluted with EtOAc (500 mL). The resulting solution was washed with brine 3×, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica eluting with 5% MeOH/CH_2Cl_2 to give **11** (4.45 g, 43%) as a solid: MS (ESI) *m*/*z* 370.2 $(M + H)^+$. Anal. ($C_{15}H_{26}N_3O_4F_3$) C, H, N.

***tert*-Butyl (1*S*)-1-[(Methylamino)carbonyl]-5-(methylamino)pentylcarbamate (12)**. To a solution of **11** (4.35 g, 11.78 mmol) in MeOH (20 mL) was added 1 N LiOH (14.5 mL). The solution was stirred at room temperature for 30 min and concentrated. The residue was taken up in $CHCl_3$, and insoluble materials were filtered off. The filtrate was dried ($MgSO_4$) and concentrated to give **12** (3.65 g, 100%) as an oil: MS (ESI) *m*/*z* 274.5 $(M + H)^+$.

4-Benzyl 1-Butyl (3*R*)-2-{2-[[(5*S*)-5-[(*tert*-butoxycarbonyl)amino]-6-(methylamino)-6-oxohexyl]methylamino]-2-oxoethoxy}-3-isobutylbutanedioate (13). To a solution of **6** (3.06 g, 7.77 mmol) and **12** (2.4 g, 7.77 mmol) in DMF (15 mL) cooled in an ice bath was added BOP (3.44 g, 7.77 mmol) followed by DIEA (4.74 mL, 27 mmol). The mixture was stirred at room temperature overnight. EtOAc was added, and the solution was washed with citric acid, brine, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Flash chromatography on a silica gel column eluting with 5% MeOH/CH_2Cl_2 provided **13** (4.46 g, 93%) as a mixture of two diastereomers (3:1): MS (ESI) *m*/*z* 650.7 $(M + H)^+$. Anal. ($C_{34}H_{55}N_3O_9$) C, H, N.

Butyl (9*S*,12*R*,13*S*)-12-Isobutyl-4-methyl-9-[(methylamino)carbonyl]-3,11-dioxo-1-oxa-4,10-diazacyclotridecane-13-carboxylate (14). Compound **13** (4.31 g, 6.98 mmol) was dissolved in 4 N HCl in dioxane (50 mL). After being stirred for 1 h, the solution was concentrated. The residue was taken up in 2-propanol (60 mL), and 10% Pd−C (0.5 g) was added. The mixture was stirred under H_2 (balloon) for 2 h. The catalyst was filtered off, and the solvent was removed under reduced pressure to give a solid. The solid was dissolved in $CHCl_3$ (20 mL). This solution was slowly added to a solution of BOP (2.68 g, 6.05 mmol) and DIEA (3.69 mL, 21.2 mmol) in $CHCl_3$ (200 mL) cooled in an ice bath over 1 h. The mixture was stirred at room temperature overnight. The volatiles were removed under reduced pressure. The residue was taken up in EtOAc, and the solution was washed with citric acid, brine, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated to give the crude product as a mixture of two diastereomers which were separated by flash chromatography on silica gel eluting with 5% MeOH/CH_2Cl_2, affording the major diastereomer **14** (1 g, 38%) as a solid: MS (ESI) *m*/*z* 442.5 $(M + H)^+$.

(9*S*,12*R*,13*S*)-N^{13}-Hydroxy-12-isobutyl-N^9,4-dimethyl-3,11-dioxo-1-oxa-4,10-diazacyclotridecane-9,13-dicarboxamide (15). To a solution of **14** (0.25 g, 0.566 mmol) in THF (5 mL) was added 1 N LiOH (0.7 mL). The solution was stirred at room temperature for 1 h, acidified with 1 N HCl solution, and concentrated. Purification by reversed-phase HPLC provided the carboxylic acid (180 mg, 85%) as a powder: MS (ESI) *m*/*z* 386.3 $(M + H)^+$.

To a solution of the above carboxylic acid (0.17 g, 0.48 mmol) and *O*-benzylhydroxylamine hydrochloride (91 mg, 0.576 mmol) in DMSO (2 mL) cooled in an ice bath was added BOP (254 mg, 0.576 mmol) followed by DIEA (0.33 mL, 1.92 mmol). The solution was stirred at room temperature for 1 h. Purification by reversed-phase HPLC provided *O*-benzylhydroxamate (170 mg, 79%) as a powder: MS (ESI) *m*/*z* 491.6 $(M + H)^+$.

The above *O*-benzylhydroxamate was hydrogenated following the procedure described for **9** to provide the hydroxamic acid **15**: ^{1}H NMR (DMSO-d_6) δ 10.90 (s, 1H), 8.08 (d, 1H), 7.68 (q, 1H), 4.50 (m, 1H), 4.40 (m, 1H), 3.80 (dd, 2H), 3.60 (m, 2H), 3.00 (m, 1H), 2.70 (s, 3H), 2.58 (d, 3H), 1.65 (m, 2H), 1.5−1.2 (m, 7H), 0.85−75 (m, 6H); MS (ESI) *m*/*z* 401.6 $(M + H)^+$. Anal. ($C_{18}H_{32}N_4O_6 \cdot 0.5H_2O \cdot 0.3CF_3CO_2H$) C, H, N.

(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-[(2-nitrophenyl)sulfanyl]propanoic Acid (17). A suspension of 2-chloronitrobenzene (7.88 g, 50 mmol), L-cysteine (6.66 g, 55 mmol), and potassium carbonate (7.6 g, 55 mmol) in DMF (30 mL) was stirred at 80 °C for 4 h. After the suspension was cooled to room temperature, water (20 mL) was added and the solution was cooled in an ice bath. To it was added di-*tert*-butyl dicarbonate (10.9 g, 50 mmol). The solution was stirred for 2 h, and water (100 mL) was added. The resulting solution was extracted with ether 3×. The water layer was acidified with 1 N HCl at 0 °C and extracted with ethyl acetate 3×. The combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated to give **17** (8.21 g, 48%) as a solid: MS (ESI) *m*/*z* 343.2 $(M + H)^+$.

(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-*N*-methyl-3-[(2-nitrophenyl)sulfanyl]propanamide (18). To a solution of **17** (8.1 g, 23.66 mmol) and methylamine hydrochloride (2.03 g, 30 mmol) cooled in an ice bath was added DIEA (16.5 mL, 95 mmol) followed by BOP (10.47 g, 23.66 mmol). After the resulting solution was stirred for 2 h at room temperature, EtOAc was added and the solution was washed with citric acid, brine, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Purification on a silica gel column eluting with 5% MeOH/CH_2Cl_2 provided **18** (6.24 g, 82%) as a solid: MS (ESI) *m*/*z* 356.3 $(M + H)^+$.

(2*S*)-2-Amino-*N*-methyl-3-[(2-nitrophenyl)sulfanyl]propanamide (19). Compound **18** (6.0 g, 17 mmol) was dissolved in 4 N HCl in dioxane (50 mL). After being stirred for 1 h, the solution was concentrated. The residue was triturated with ether to give **19** (3.88 g, 71%) as a solid: MS (ESI) *m*/*z* 256.1 $(M + H)^+$.

Butyl (3*R*)-2-(2-*tert*-Butoxy-2-oxoethoxy)-5-methyl-3-{[((1*S*)-2-(methylamino)-1-{[(2-nitrophenyl)sulfanyl]methyl}-2-oxoethyl)amino]carbonyl}hexanoate (20). To a solution of **5** (2.36 g, 6.5 mmol) and **19** (1.91 g, 6.5 mmol) in $CHCl_3$ (15 mL) cooled in an ice bath was added DIEA (4.53 mL, 26 mmol) followed by BOP (2.88 g, 6.5 mmol). The solution was stirred at room temperature overnight and concentrated. The residue was taken up in EtOAc, and the solution was washed with citric acid, brine, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Flash chromatography on a silica gel column eluting with 3% MeOH/25% EtOAc/72% CH_2Cl_2 provided **20** (3.21 g, 83%) as a mixture of two diastereomers (3:1): MS (ESI) *m*/*z* 598.6 $(M + H)^+$.

{[(2*R*)-2-({[(1*S*)-1-{[(2-Aminophenyl)sulfanyl]methyl}-2-(methylamino)-2-oxoethyl]amino}carbonyl)-1-(butoxycarbonyl)-4-methylpentyl]oxy}acetic Acid (21). To a so-

lution of **20** (3.05 g, 5.1 mmol) in acetic acid (15 mL) and water (0.5 mL) was added zinc (3 g). The mixture was stirred at room temperature for 30 min. Methanol was added, and insoluble materials were filtered off. The filtrate was concentrated under reduced pressure. The residue was taken up in EtOAc. The solution was washed with $NaHCO_3$ 3×, dried ($MgSO_4$), and concentrated. The residue was taken up in 4 N HCl in dioxane (30 mL) in the presence of 0.5 mL of water. After the solution was stirred for 1 h, the solvent was removed under reduced pressure to give **21** as a mixture of two diastereomers (3:1): MS (ESI) *m*/*z* 512.5 $(M + H)^+$.

(5*S*,6*R*,9*S*)-*N*^{5}-Hydroxy-6-isobutyl-*N*^{9}-methyl-2,7-dioxo-2,3,5,6,7,8,9,10-octahydro-1*H*-4,11,1,8-benzoxathiadiazacyclotridecine-5,9-dicarboxamide (22). To a solution of BOP (1.81 g, 4.1 mmol) in $CHCl_3$ (50 mL) cooled in an ice bath was added a solution of **21** (2.1 g, 4.1 mmol) and DIEA (2.86 mL, 16.4 mmol) in $CHCl_3$ (20 mL) over a period of 2 h. The solution was allowed to stir at room temperature overnight. The solvent was removed under reduced pressure. EtOAc was added, and the solution was washed with citric acid, brine, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Flash chromatography on a silica gel column eluting with 1% 2-propanol/10% EtOAc/89% CH_2Cl_2 provided the cyclized product (1.45 g, 71%) as a mixture of two diastereomers: MS (ESI) *m*/*z* 494.4 $(M + H)^+$.

A portion of the above cyclized product (0.76 g, 1.53 mmol) was dissolved in MeOH (10 mL). To it were added $HONH_2$·HCl (0.43 g, 6.19 mmol) and DIEA (2 mL, 11.5 mmol). The mixture was stirred at 50 °C overnight and the solvent removed under reduced pressure. The residue was purified by reversed-phase HPLC to provide the major diastereomer **22** (276 mg, 40%) as a powder: ^{1}H NMR (DMSO-d_6) δ 10.90 (s, 1H), 9.47 (s, 1H), 8.75 (d, 1H), 8.28 (d, 1H), 7.70 (q, 1H), 7.66 (d, 1H), 7.35 (t, 1H), 7.10 (t, 1H), 4.10 (d, 1H), 3.85 (m, 1H), 3.68 (dd, 2H), 3.00 (m, 3H), 2.45 (d, 3H), 1.35 (m, 2H), 1.20 (m, 1H), 0.80 (d, 3H), 0.70 (d, 3H); MS (ESI) *m*/*z* 453.4 $(M + H)^+$. Anal. ($C_{20}H_{28}N_4O_6S$·CH_3CN·2.8H_2O) C, H, N.

4-Benzyl 1-Butyl (3*R*)-2-{[(2*E*)-4-Bromo-2-butenyl]oxy}-3-isobutylbutanedioate (23). To a solution of **3** (4.03 g, 12 mmol) in DMF (24 mL) cooled in an ice bath was added NaH (691 mg, 60% dispersion in oil, 14.4 mmol). The mixture was stirred for 15 min, at which time 1,4-dibromo-2-butene (10.2 g, 48 mmol) was added. After the resulting mixture was stirred in the ice bath for 20 min, EtOAc (200 mL) was added. The solution was washed with brine 3×, dried ($MgSO_4$), and concentrated. Flash chromatography on a silica gel column eluting with 10% EtOAc/hexanes provided **23** (3.64 g, 65%) as a mixture of two diastereomers (3:1): MS (ESI) *m*/*z* 471.2 $(M + H)^+$. Anal. ($C_{23}H_{33}O_5Br$) C, H, N.

4-Benzyl 1-Butyl (3*R*)-2-[((2*E*)-4-{3-[(1*S*)-1-[(*tert*-Butoxycarbonyl)amino]-2-(methylamino)-2-oxoethyl]-1*H*-indol-1-yl}-2-butenyl)oxy]-3-isobutylbutanedioate (24). To a solution of *N*$^\alpha$-Boc-L-tryptophan *N*-methylamide (1.96 g, 6.2 mmol) in DMF (14 mL) cooled in an ice bath was added NaH (446 mg, 9.3 mmol) with vigorous stirring. After the resulting solution was stirred for 15 min, compound **23** (2.9 g, 6.2 mmol) was added. The mixture was allowed to stir in the ice bath for 1 h. EtOAc (200 mL) was added. The solution was washed with citric acid and brine, dried ($MgSO_4$), and concentrated. Purification on a silica gel column eluting with 5% MeOH/CH_2Cl_2 provided **24** (2.7 g, 62%) as a mixture of two diastereomers (3:1): MS (ESI) *m*/*z* 706.4 $(M + H)^+$. Anal. ($C_{40}H_{55}N_3O_8$) C, H, N.

Butyl (7*S*,8*R*,11*S*)-8-Isobutyl-11-[(methylamino)carbonyl]-9-oxo-6-oxa-1,10-diazatricyclo[11.6.1.0^{14,19}]icosa-13-(20),14,16,18-tetraene-7-carboxylate (25). To a solution of **24** (2.65 g, 3.75 mmol) in 2-propanol (40 mL) was added 10% Pd on carbon (265 mg). The mixture was stirred under H_2 (balloon) for 4 h. The catalyst was filtered off, and the solvent was removed under reduced pressure to give the carboxylic acid (2.1 g, 91%) as a solid. The solid was dissolved in 4 N HCl in dioxane (20 mL). The solution was stirred for 1.5 h and concentrated. The residue was taken up in $CHCl_3$ (15 mL). The resulting solution was added dropwise to a solution of BOP (1.65 g, 3.75 mmol) and DIEA (2.1 mL, 12 mmol) in $CHCl_3$ (50 mL) cooled in an ice bath. The mixture was allowed to stir at room temperature for 2 h. The solvent was removed under reduced pressure and the residue taken up in EtOAc. The EtOAc solution was washed with brine 3×, dried ($MgSO_4$), and concentrated. Flash chromatography on silica eluting with 3% MeOH/CH_2Cl_2 provided the major diastereomer **25** (843 mg, 45%) as a solid: mp 225 °C; MS (ESI) *m*/*z* 500.4 $(M + H)^+$.

(7*S*,8*R*,11*S*)-*N*^{7}-(Benzyloxy)-8-isobutyl-*N*^{11}-methyl-9-oxo-6-oxa-1,10-diazatricyclo[11.6.1.0^{14,19}]icosa-13(20),14,-16,18-tetraene-7,11-dicarboxamide (26). To a solution of **25** (450 mg, 1.05 mmol) in THF (10 mL) was added 1 N LiOH (2 mL). The solution was stirred for 30 min and acidified with 1 N HCl. EtOAc was added. The solution was washed with brine 3×, dried ($MgSO_4$), and concentrated. The residue was taken up in DMF (5 mL), and the solution was cooled in an ice bath. To it were added *O*-benzylhydroxamine (207 mg, 1.3 mmol), BOP (575 mg, 1.3 mmol), and DIEA (0.95 mL, 5.2 mmol). The mixture was stirred in the ice bath for 1 h. EtOAc (100 mL) was added. The resulting solution was washed with citric acid, brine, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Purification by reversed-phase HPLC provided **26** (360 mg, 65%) as a solid: MS (ESI) *m*/*z* 549.4 $(M + H)^+$.

(7*S*,8*R*,11*S*)-*N*^{7}-Hydroxy-8-isobutyl-*N*^{11}-methyl-9-oxo-6-oxa-1,10-diazatricyclo[11.6.1.0^{14,19}]icosa-13(20),14,16,18-tetraene-7,11-dicarboxamide (27). To a solution of **26** (260 mg, 0.474 mmol) in MeOH (20 mL) was added 10% Pd on carbon (50 mg). The mixture was stirred under H_2 (balloon) for 1.5 h. The catalyst was filtered off, and the solvent was removed under reduced pressure. Purification by reversed-phase HPLC provided the hydroxamic acid **27** (188 mg, 86%) as a powder: ^{1}H NMR (DMSO-d_6) δ 10.80 (s, 1H), 8.20 (d, 1H), 7.65 (q, 1H), 7.58 (d, 1H), 7.40 (d, 1H), 7.30 (s, 1H), 7.10 (t, 1H), 7.00 (t, 1H), 4.45 (m, 1H), 4.05 (m, 2H), 3.42 (d, 1H), 3.15 (m, 1H), 2.98 (m, 2H), 2.83 (m, 1H), 2.70 (m, 1H), 2.62 (d, 3H), 2.00 (m, 1H), 1.75 (m, 1H), 1.40 (m, 2H), 1.00 (m, 1H), 0.80 (m, 8H); MS (ESI) *m*/*z* 459.4 $(M + H)^+$. Anal. ($C_{24}H_{34}N_4O_5$) C, H, N.

(2*R*,3*S*)-3-(*tert*-Butoxycarbonyl)-2-isobutyl-5-hexenoic Acid (29a). To a stirred solution of (2*S*)-2-(2-*tert*-butoxy-2-oxoethyl)-4-methylpentanoic acid (**28a**) (20 g, 87 mmol) in anhydrous THF (400 mL) cooled at −78 °C was added 1 M LDA in THF (180 mL) over 20 min. After the resulting solution was stirred for 1 h, 8.3 mL (96 mmol) of allyl bromide was added dropwise. The mixture was allowed to slowly warm to ambient temperature and stirred overnight. The reaction was quenched with 10% aqueous citric acid followed by removal of the volatiles under reduced pressure. The remaining material was taken into EtOAc and the solution washed with water. The aqueous phase was extracted 3× with EtOAc, and the combined organic phase was washed with 10% citric acid, saturated $NaHCO_3$ (2×), H_2O (2×), and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure, affording 23.3 g (99%) of the acid that was carried on without purification. Proton NMR indicated a 1:10 ratio of two diastereomers (*anti*/*syn*): MS (ESI) *m*/*z* 293 $(M + Na)^+$.

To a stirred solution of the above acid (2 g, 7.4 mmol) in anhydrous THF (25 mL) cooled at −78 °C was added LDA (16.3 mmol) over 15 min. The reaction was stirred at −78 °C for 15 min and in a water bath (24 °C) for 15 min. After the reaction was cooled back to −78 °C, a solution of 1 M diethylaluminum chloride in hexane (25.6 mL) was added. The reaction was stirred for 10 min at −78 °C and for 15 min in an ambient temperature water bath. After being cooled back to −78 °C, the reaction was quenched with the rapid addition of methanol. The mixture was concentrated to ∼1/4 its original volume under reduced pressure, and the resulting material was dissolved in EtOAc (200 mL). The EtOAc solution was washed with 1 N HCl (70 mL) containing 100 g of ice. The aqueous phase was extracted 2× with EtOAc. The combined organic phase was washed with a solution of KF (3.5 g) in water (100 mL) containing 1 N HCl (15 mL), and with brine and dried over $MgSO_4$, and the volatiles were removed under reduced

pressure, affording 1.84 g (92%) of **29a**. ^{1}H NMR indicated an 8:1 ratio of two diastereomers (*anti*:*syn*): MS (ESI) *m*/*z* 293 $(M + Na)^+$.

4-Benzyl 1-*tert*-Butyl (2*S*,3*R*)-2-Allyl-3-isobutylbutanedioate (30a). To a stirred solution of **29a** (20.6 g, 76 mmol) in benzene (75 mL) cooled in an ice bath was added DBU (11.4 mL, 76 mmol) followed by benzyl bromide (9.98 g, 84 mmol). After 10 min the mixture was heated to reflux for 4 h. The reaction was then cooled and diluted to 3× its original volume with EtOAc. This was washed 3× with 10% aqueous citric acid. The combined aqueous phase was extracted 3× with EtOAc. The combined organic phase was then washed with brine and dried over $MgSO_4$, and the volatiles were removed under reduced pressure. The resulting material was chromatographed on silica gel eluting with 2.2% EtOAc/hexanes, affording 16.9 g (62%) of the benzyl ester **30a**: MS (CI, NH_3) *m*/*z* 378 $(M + NH_4)^+$.

4-Benzyl 1-*tert*-Butyl (2*S*,3*R*)-2-(3-Hydroxypropyl)-3-isobutylbutanedioate (31a). To a stirred solution of **30a** (5.2 g, 14.4 mmol) in anhydrous THF (100 mL) at 0 °C was added 0.5 M 9-BBN in THF (72.2 mL) over 1 h. The reaction was allowed to warm to room temperature over 12 h. After the reaction was cooled to 0 °C, H_2O (2.9 mL) was added (caution foaming) dropwise over 5 min, and after the reaction was stirred for an additional 20 min, H_2O (8 mL) containing NaOAc (3.21 g) was added simultaneously with 30% H_2O_2 (8 mL) over 5 min. The mixture was stirred for 20 min, followed by removal of the volatiles under reduced pressure. The remaining material was dissolved in EtOAc and the solution washed with brine. The aqueous layer was extracted twice with EtOAc. The combined organic phase was washed with water and brine and then dried over $MgSO_4$. The volatiles were removed under reduced pressure following filtration. The resulting material was chromatographed on silica gel eluting gradually with 1:20, 1:10, and 1:5 EtOAc/hexanes, affording 3.5 g (64%) of the alcohol **31a**: MS (ESI) *m*/*z* 379 $(M + H)^+$; HRMS *m*/*z* 379.250194 [$(M + H)^+$, calcd for $C_{22}H_{35}O_5$ 379.248450].

(2*R*,3*S*)-3-(*tert*-Butoxycarbonyl)-6-hydroxy-2-isobutylhexanoic Acid (32). Compound **31a** was subjected to a hydrogenation following the procedure described for **5**: MS (ESI) *m*/*z* 289.2 $(M + H)^+$.

***tert*-Butyl (2*S*,3*R*)-3-[({(1*S*)-5-{[(Benzyloxy)carbonyl]amino}-1-[(methylamino)carbonyl]pentyl}amino)carbonyl]-2-(3-hydroxypropyl)-5-methylhexanoate (33)**. To a solution of the acid **32** (170 mg, 0.6 mmol) and *N*-[(benzyloxy)carbonyl]-L-lysine *N*-methylamide (224.6 mg, 0.8 mol) in DMF (6 mL) were added DIEA (0.26 mL, 1.5 mmol) and BOP (286.9 mg, 0.6 mmol). After the resulting solution was stirred overnight, EtOAc was added and the solution was washed with 10% citric acid, saturated $NaHCO_3$ solution, and brine. The EtOAc layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by silica gel chromatography to yield the amide **33** (255 mg, 77%) as a white foam: MS (ESI) *m*/*z* 564.4 $(M + H)^+$.

(4*S*,5*R*)-5-[({(1*S*)-5-{[(Benzyloxy)carbonyl]amino}-1-[(methylamino)carbonyl]pentyl}amino)carbonyl]-4-(*tert*-butoxycarbonyl)-7-methyloctanoic Acid (34). To a solution of **33** (813 mg, 1.4 mmol) in a mixed solvent of CH_3CN (3 mL), CCl_4 (3 mL), and H_2O (4.5 mL) at room temperature were added H_5IO_6 (1.3 g, 5.9 mmol) and $RuCl_3 \cdot H_2O$ (6 mg, 0.03 mmol). After the resulting solution was stirred for 1.5 h, 10% citric acid was added and the layers were separated. The organic layer was dried and concentrated. The resulting residue was purified by silica gel chromatography to yield the acid **34** (504 mg, 60%) as a white foam: MS (ESI) *m*/*z* 578.5 $(M + H)^+$.

(4*S*,5*R*)-5-[({(1*S*)-5-Amino-1-[(methylamino)carbonyl]pentyl}amino)carbonyl]-4-(*tert*-butoxycarbonyl)-7-methyloctanoic Acid (35). The *N*-Cbz amine **34** (45 mg, 0.08 mmol) was hydrogenated in MeOH (5 mL) with 5% Pd/C-Degussa (15 mg) under a hydrogen atmosphere (50 psi). After the solution was stirred overnight, the catalyst was filtered off and the solution was concentrated to yield the amino acid **35** (32 mg, 90%) as a white foam: MS (ESI) *m*/*z* 444.4 $(M + H)^+$.

***tert*-Butyl *(6S,9R,10S)*-9-Isobutyl-6-[(methylamino)carbonyl]-8,13-dioxo-1,7-diazacyclotridecane-10-carboxylate (36).** To a solution of HBTU (769 mg, 2.0 mmol) and NMM (0.15 mL, 6.0 mmol) in DMF (10 mL) at 60 °C was added a solution of **35** (200.0 mg, 0.4 mmol) in DMF (10 mL) dropwise. After the addition was complete, the mixture was stirred for an additional 30 min. The solution was concentrated, and silica gel chromatography afforded the lactam **36** (135 mg, 70%) as a light yellow solid: MS (ESI) *m*/*z* 426.2 $(M + H)^+$.

(2*S*,11*S*,12*R*)-N^{11}-(Benzyloxy)-12-isobutyl-N^2-methyl-8,-13-dioxo-1,7-diazacyclotridecane-2,11-dicarboxamide (37). The lactam **36** (85 mg, 0.2 mmol) was dissolved in CH_2Cl_2 (2 mL) and TFA (2 mL). After being stirred overnight, the solution was concentrated to afford the crude acid. This material was dissolved in DMF (1.5 mL) along with *O*-benzylhydroxylamine (78.8 mg, 0.6 mmol), DIEA (0.07 mL, 0.4 mmol), and BOP (97.3 mg, 0.2 mmol). After the resulting solution was stirred overnight, the solid product was filtered from the solution to give the *O*-benzylhydroxamate **37** (58 mg, 61%): MS (ESI) *m*/*z* 497.3 $(M + Na)^+$.

(2*S*,11*S*,12*R*)-N^{11}-Hydroxy-12-isobutyl-N^2-methyl-8,13-dioxo-1,7-diazacyclotridecane-2,11-dicarboxamide (38). The *O*-benzylhydroxamate **37** (50 mg, 0.1 mmol) was hydrogenated in a MeOH/$CHCl_3$ mixture (3:1, 40 mL) with 10% Pd/C (20 mg) under a hydrogen atmosphere (balloon). After the solution was stirred for 6 h, the catalyst was filtered off and the solution was concentrated to yield the title hydroxamate **38** (38 mg, 93%) as a white foam: ^{1}H NMR (DMSO-d_6) δ 10.51 (s, 1H), 8.71 (s, 1H), 7.95 (d, 1H), 7.70 (m, 1H), 7.51 (t, 1H), 4.33 (m, 1H), 3.21 (m, 1H), 2.78 (m, 1H), 2.57 (d, 3H), 2.26 (m, 2H), 1.80−1.08 (m, 12H), 0.88 (m, 1H), 0.82 (d, 3H), 0.75 (d, 3H); MS (ESI) *m*/*z* 407.3 $(M + Na)^+$; HRMS *m*/*z* 385.246983 [$(M + H)^+$ calcd for $C_{18}H_{33}N_4O_5$ 385.245096].

***tert*-Butyl (2*S*,3*R*)-2-(3-Hydroxypropyl)-5-methyl-3-[({-(1*S*)-1-[(methylamino)carbonyl]-5-[(phenylsulfonyl)amino]-pentyl}amino)carbonyl]hexanoate (39a).** To a solution of the acid **32** (460.0 mg, 1.6 mmol), N^{ϵ}-(phenylsulfonyl)-L-lysine *N*-methylamide (696.5 mg, 2.1 mmol), and DIEA (0.84 mL, 4.8 mmol) in DMF (5 mL) was added BOP (849.6 mg, 1.9 mmol). After the resulting solution was stirred overnight, EtOAc was added and the solution was washed with 10% citric acid, saturated $NaHCO_3$ solution, and brine. The ethyl acetate layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by silica gel chromatography to yield the amide **39a** (833 mg, 90%) as a white foam: MS (ESI) *m*/*z* 570.3 $(M + H)^+$.

***tert*-Butyl (6*S*,9*R*,10*S*)-9-Isobutyl-6-[(methylamino)carbonyl]-8-oxo-1-(phenylsulfonyl)-1,7-diazacyclotridecane-10-carboxylate (40a).** The amide **39a** (875.0 mg, 1.5 mmol) was dissolved in THF (27 mL) prior to the addition of PPh_3 (1.21 g, 4.5 mmol) followed by DIAD (0.88 mL, 4.5 mmol) dropwise. After being stirred overnight, the solution was concentrated, and the residue was purified by silica gel chromatography to yield the sultam **40a** (470 mg, 55%) as a white solid: MS (ESI) *m*/*z* 552.4 $(M + H)^+$.

(2*S*,11*S*,12*R*)-N^{11}-Hydroxy-12-isobutyl-N^2-methyl-13-oxo-7-(phenylsulfonyl)-1,7-diazacyclotridecane-2,11-dicarboxamide (41). The sultam **40a** (473.0 mg, 0.86 mmol) was dissolved in CH_2Cl_2 (6 mL) and TFA (5 mL). After being stirred overnight, the solution was concentrated to afford the crude acid. A portion of this acid (260.0 mg, 0.52 mmol) was dissolved in DMF prior to the addition of *O*-benzylhydroxylamine (192.0 mg, 1.6 mmol), DIEA (0.18 mL, 1.0 mmol), and BOP (278.0 mg, 0.63 mmol). After the resulting solution was stirred overnight, the solid product was filtered from the solution to give the crude *O*-benzylhydroxamate (172 mg, 57%). A portion of this *O*-benzylhydroxamate (150.0 mg, 0.25 mmol) was hydrogenated in a MeOH/$CHCl_3$ mixture (3:1, 50 mL) with 5% Pd/$BaSO_4$ (300 mg) under a hydrogen atmosphere (50 psi). After the resulting solution was stirred for 3 h, the catalyst was filtered off and the solution was concentrated to yield the

hydroxamate **41** (52 mg, 41%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 10.44 (s, 1H), 8.78 (br, 1H), 8.26 (d, 1H), 7.72 (d, 2H), 7.67−7.48 (m, 4H), 4.22 (m, 1H), 3.15−2.95 (m, 2H), 2.78−2.56 (m, 4H), 2.54 (d, 3H), 1.95 (m, 1H), 1.8−1.2 (m, 10H), 0.86 (m, 1H), 0.83 (d, 3H), 0.73 (d, 3H); MS (ESI) *m*/*z* 511.3 (M + H)$^+$; HRMS *m*/*z* 511.261183 [(M + H)$^+$ calcd for $C_{24}H_{39}N_4O_6$ 511.259032].

***tert*-Butyl (6*S*,9*R*,10*S*)-9-Isobutyl-6-[(methylamino)carbonyl]-8-oxo-1-(mesitylsulfonyl)-1,7-diazacyclotridecane-10-carboxylate (40b).** To a solution of the acid **32** (990 mg, 3.4 mmol) and N^e-(mesitylsulfonyl)-L-lycine *N*-methylamide hydrochloride (1.7 g, 4.5 mmol) in DMF were added DIEA (1.8 mL, 10.2 mmol) and BOP (1.8 g, 4.1 mmol). After the resulting solution was stirred overnight, DMF was removed under reduced pressure and CH_2Cl_2 was added. The solution was washed with 10% citric acid, saturated $NaHCO_3$ solution, and brine. The CH_2Cl_2 layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by silica gel chromatography to yield the crude amide (2 g), which was dissolved in THF (158 mL). To the THF solution was added PPh_3 (2.8 g, 10.6 mmol) followed by DIAD (2 mL, 10.1 mmol) in THF. After being stirred overnight, the solution was concentrated, and the residue was purified by silica gel chromatography to yield the sultam **40b** (680 mg, 30%) as a yellow solid: MS (ESI) *m*/*z* 594.5 (M + H)$^+$.

(6*S*,9*R*,10*S*)-1-(*tert*-Butoxycarbonyl)-9-isobutyl-6-[(methylamino)carbonyl]- 8-oxo-1,7-diazacyclotridecane-10-carboxylic Acid (42). The sultam **40b** (300 mg, 0.5 mmol) was dissolved in 33% HBr/AcOH (6.8 mL) containing phenol (63 mg, 0.67 mmol). After being stirred for 5 h, the solution was concentrated, and the solid was filtered off with CH_2Cl_2/Et_2O. This provided the crude amino acid salt (500 mg, quantitative). A portion of this amino acid (140 mg, 0.32 mmol) was dissolved in THF (4 mL)/H_2O (0.6 mL). To it was added Et_3N (0.38 mL, 2.6 mmol) followed by $(Boc)_2O$ (452 mg, 206 mmol) at room temperature. After the resulting solution was stirred overnight, the solvent was removed and CH_2Cl_2 was added. The CH_2Cl_2 solution was washed with 10% HCl, dried ($MgSO_4$), and concentrated. The resulting residue was purified by silica gel chromatography to yield the *N*-Boc acid **42** (130 mg) as a solid: MS (ESI) *m*/*z* 456.5 (M + H)$^+$.

***tert*-Butyl (6*S*,9*R*,10*S*)-10-[(Hydroxyamino)carbonyl]-9-isobutyl-6-[(methylamino)carbonyl]-8-oxo-1,7-diazacyclotridecane-1-carboxylate (43).** The *N*-Boc acid **42** (130 mg) was dissolved in DMF (5 mL) prior to the addition of *O*-benzylhydroxylamine (108 mg, 0.87 mmol), DIEA (0.15 mL, 0.82 mmol), and BOP (214 mg, 0.48 mmol). After the solution was stirred overnight, the solid product was filtered off with CH_2Cl_2 to give *O*-benzylhydroxamate (120 mg, 67%). The *O*-benzylhydroxamate (160 mg, 0.29 mmol) was hydrogenated in MeOH (40 mL) with 5% Pd/$BaSO_4$ (240 mg) under a hydrogen atmosphere (50 psi). After the resulting solution was stirred for 3 h, the catalyst was filtered off and the solution was concentrated to yield the hydroxamate **43** (140 mg quantitative) as a pale yellow solid: ^{1}H NMR (CD_3OD) δ 4.40 (m, 1H), 3.2−2.9 (m, 4H), 2.70 (s, 3H), 2.45 (m, 1H), 2.02 (m, 1H), 1.44 (s, 9H), 1.8−1.2 (m, 12H), 0.99 (m, 1H), 0.91 (d, 3H), 0.83 (d, 3H): MS (ESI) *m*/*z* 471.5 (M + H)$^+$; HRMS *m*/*z* 471.319240 [(M + H)$^+$ calcd for $C_{23}H_{43}N_4O_6$ 471.318261].

(2*S*,11*S*,12*R*)-N^{11}-Hydroxy-12-isobutyl-N^2-methyl-13-oxo-1,7-diazacyclotridecane-2,11-dicarboxamide (44). The *N*-Boc hydroxamate **43** (56 mg, 0.12 mmol) was dissolved in 4 N HCl in dioxane (2 mL) at room temperature. After the solution was stirred for 3 h, the solvent was removed under reduced pressure to yield the desired hydroxamate **44** (45 mg, quantitative): ^{1}H NMR (CD_3OD) δ 4.19 (m, 1H), 2.99 (m, 4H), 2.72 (s, 3H), 2.15 (m, 1H), 1.88 (m, 1H), 1.78−1.24 (m, 12H), 1.03 (m, 1H), 0.93 (d, 3H), 0.84 (d, 3H); MS (ESI) *m*/*z* 371.4 (M + H)$^+$; HRMS *m*/*z* 471.267256 [(M + H)$^+$ calcd for $C_{18}H_{35}N_4O_4$ 471.265831].

1-(Benzyloxy)-4-(3-iodopropyl)benzene (46). To a stirred solution of 3-[4-(benzyloxy)phenyl]-1-propanol (**45**) (5.0 g, 20.6 mmol) in THF (100 mL) cooled in an ice bath was added triethylamine (4.3 mL, 31 mmol) followed by methanesulfonyl chloride (1.76 mL, 22.7 mmol). After being stirred for 1 h, the solution was poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted 2× with CH_2Cl_2. The organic phase was washed with H_2O, 10% aqueous citric acid, H_2O, and brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure, affording a quantitative yield of the mesylate as a white solid: MS (ESI) *m*/*z* 338 (M + H)$^+$.

To the above mesylate in acetone (100 mL) was added NaI (3.9 g). After the solution was stirred overnight at ambient temperature, an additional 3.9 g of NaI was added and the reaction was refluxed for 1 h. The mixture was filtered, and the volatiles were removed under reduced pressure. The solid, which immediately started turning yellow, was dissolved in hexane, washed with H_2O, 5% aqueous sodium thiosulfate, H_2O, and brine, and dried over $MgSO_4$, and the volatiles were removed under reduced pressure, affording 6.79 g (96%) of **46**: MS (ESI) *m*/*z* 370 (M + H)$^+$.

(2*S*)-2-Amino-5-[4-(benzyloxy)phenyl]-*N*-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*-methylpentanamide (47). To a stirred slurry of 1.15 g of LiCl (previously flame-dried in flask under vacuum) and 2-amino-*N*-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*-methylacetamide[39] (0.99 g, 4.48 mmol) in THF (30 mL) cooled to −78 °C was added a solution of 1 M LDA in THF/hexane (8.7 mL) over 10 min. The mixture was stirred for 20 min at −78 °C and 30 min at 0 °C, at which time a solution of **46** (1.57 g, 4.25 mmol) in THF (10 mL) was added dropwise over 10 min. The mixture was allowed to slowly warm to room temperature while being stirred overnight. The reaction was quenched with 10% aqueous citric acid, and the volatiles were removed under reduced pressure. The remaining material was dissolved in EtOAc. The resulting solution was washed with H_2O, 5% aqueous sodium thiosulfate, H_2O, saturated aqueous $NaHCO_3$, H_2O, and brine and dried over $MgSO_4$, and the volatiles were removed under reduced pressure. The residue was chromatographed on silica gel eluting with MeOH/$CHCl_3$ (4:100), affording 0.9 g (47%) of **47**: MS (ESI) *m*/*z* 447 (M + H)$^+$.

Methyl (2*S*)-2-Amino-5-[4-(benzyloxy)phenyl]pentanoate (48). To a solution of **47** (3.5 g, 7.8 mmol) in H_2O (40 mL) and MeOH (25 mL) was added 1 N aqueous NaOH (15.7 mL). The reaction was refluxed for 1 h, at which time more MeOH (25 mL) was added. The reaction was refluxed for an additional 3 h, and the volatiles were removed under reduced pressure. The solid was triturated with CH_2Cl_2 and filtered, affording a mixture of NaOH and the sodium salt of the product (5.5 g). The CH_2Cl_2 filtrate was evaporated, and the solid was triturated with Et_2O, affording an additional 1.1 g of the sodium salt of the product: MS (ESI) *m*/*z* 298 (M + H)$^+$.

To the above mixture of sodium salt and NaOH in MeOH (150 mL) was added concentrated HCl (3 mL). The solution was refluxed overnight, and the volatiles were removed under reduced pressure. The resulting material was taken into EtOAc, the solution was washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$, and the volatiles were removed under reduced pressure, affording 2.4 g (99%) of **48**: MS (ESI) *m*/*z* 314 (M + H)$^+$.

(2*R*,3*S*)-6-Bromo-3-(*tert*-butoxycarbonyl)-2-isobutylhexanoic Acid (49a). To a stirred solution of PPh_3 (8.32 g, 31.7 mmol), imidazole (2.15 g 31.6 mmol), and CBr_4 (10.54 g, 31.8 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added dropwise over 15 min a solution of **31a** (8.0 g, 21.2 mmol) in CH_2Cl_2 (60 mL). The reaction was stirred at 0 °C for 30 min followed by a second addition of PPh_3 (4.15 g, 15.8 mmol), imidazole (1.55 g, 22.8 mmol), and CBr_4 (5.25 g, 15.8 mmol) in CH_2Cl_2 (30 mL) in one portion. The reaction was stirred for an additional 2.5 h at 0 °C and then for 20 min at ambient temperature, followed by dilution with hexanes (320 mL), filtration through a short silica gel plug, and rinsing with 25% EtOAc/hexanes. The volatiles were removed under reduced pressure, and the resulting material was chromatographed on silica gel eluting with a 1−10% EtOAc/hexanes gradient, affording 6.1 g (65%) of the bromide: MS (ESI) *m*/*z* 441 (M + H)$^+$.

To the above benzyl ester (10.5 g, 23.9 mmol) in MeOH (250 mL) was added 10% Pd−C (1 g). The mixture was stirred

under H_2 (balloon) for 3 h. The catalyst was removed by filtration through a 0.45 μM PTFE disposable filter, and the volatiles were evaporated under reduced pressure, affording 8.3 g (99%) of the acid **49a**: MS (ESI) *m/z* 349 $(M - H)^-$.

***tert*-Butyl (2*R*,3*S*)-2-(3-Bromopropyl)-3-({[(1*R*)-1-(4-hydroxybenzyl)-2-methoxy-2-oxoethyl]amino}carbonyl)-5-methylhexanoate (50a)**. To a solution of **49a** (8.4 g, 24 mmol), L-tyrosine methyl ester hydrochloride (5.5 g, 24 mmol), and NMM (9.1 mL, 65 mmol) in DMF (200 mL) was added a solution of TBTU (9.52 g, 29.6 mmol) in DMF (120 mL) over 30 min. The reaction was stirred for 2 h at ambient temperature followed by removal of the volatiles under reduced pressure. The resulting material was dissolved in EtOAc. The solution was washed with cold 1 N HCl. The aqueous phase was extracted 3× with EtOAc. The combined organic phase was washed with H_2O, saturated $NaHCO_3$, H_2O, and brine and dried over $MgSO_4$, and the volatiles were removed under reduced pressure. The residue was chromatographed on silica gel eluting with a gradient of 25−33% EtOAc/hexanes, affording 9.5 g (75%) of the amide product **50a**: MS (ESI) *m/z* 529 $(M + H)^+$.

6-*tert*-Butyl 10-Methyl (6*S*,7*R*,10*S*)-7-Isobutyl-8-oxo-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxylate (51a). To a stirred suspension of Cs_2CO_3 (5.2 g, 16 mmol) in DMF (130 mL) and DMSO (32.5 mL) at 60 °C was added a solution of **50a** (2.35 g, 4.45 mmol) in DMF (25 mL) over 15 min. The reaction was heated at 80 °C for 30 min, cooled in an ice bath, and quenched with 10% citric acid. The volatiles were removed under reduced pressure, and the resulting material was partitioned in EtOAc/H_2O. The aqueous layer was extracted 4× with EtOAc, the combined organic extracts were washed 4× with H_2O and once with brine and dried over $MgSO_4$, and the volatiles were removed under reduced pressure. The residue was chromatographed on silica gel eluting with 1.5% MeOH/CH_2Cl_2, affording 2.0 g (74%) of the macrocycle **51a**: MS (ESI) *m/z* 448 $(M + H)^+$.

Methyl (6*S*,7*R*,10*S*)-6-{[(Benzyloxy)amino]carbonyl}-7-isobutyl-8-oxo-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-triene-10-carboxylate (52a). Compound **51a** (0.77 g, 1.7 mmol) was dissolved in TFA (25 mL). The solution was stirred for 1 h at ambient temperature. The volatiles were removed under reduced pressure, affording 0.67 g (99%) of the acid: MS (ESI) *m/z* 392 $(M + H)^+$.

To a solution of the above acid (2.4 g, 6.1 mmol) in DMF (75 mL) were added NMM (3.37 mL, 24 mmol), HATU (5.24 g, 13.7 mmol), and *O*-benzylhydroxylamine hydrochloride (3.77 g, 23.6 mmol). After being stirred overnight at ambient temperature, the reaction was heated to 60 °C for 30 min. After the reaction was cooled to room temperature, the volatiles were removed under reduced pressure and the resulting material was dissolved in EtOAc. The solution was washed with 10% citric acid. The aqueous layer was extracted 3× with EtOAc. The combined organic phase was washed 3× with H_2O and brine and dried over $MgSO_4$, and the volatiles were removed under reduced pressure. The residue was triturated 4× with a mixture of 1:1:2 EtOAc/hexane/ether to afford 1.4 g of product. The mother liquor was concentrated and chromatographed on silica gel eluting with a gradient of 25−90% EtOAc/hexanes, affording an additional 1.05 g of **52a** (combined yield 81%).

(6*S*,7*R*,10*S*)-N^6-Hydroxy-7-isobutyl-N^{10}-[2-(methylamino)-2-oxoethyl]-8-oxo-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54e). To a solution of **52a** (0.7 g, 1.4 mmol) in THF (65 mL) and H_2O (15 mL) was added saturated aqueous LiOH (2.23 mL). The reaction was stirred for 2 h at ambient temperature and quenched with the addition of 1 N HCl (10 mL). The majority of the volatiles were removed under reduced pressure. The remaining material was diluted with EtOAc and washed with H_2O and 1 N HCl. The combined aqueous phase was extracted 4× with EtOAc. The combined organic phase was washed with H_2O and brine and dried over $MgSO_4$, and the volatiles were removed under reduced pressure, affording 0.67 g (99%) of the acid: ^{1}H NMR ($CDCl_3$) δ 9.53 (s, 1H), 7.20 (m, 5H), 7.00 (m, 1H), 6.85 (m, 2H), 6.73 (m, 1H), 6.29 (d, J = 9.9 Hz, 1H), 4.92 (m, 1H), 4.70 (s, 2H), 3.92 (m, 2H), 3.40 (m, 1H), 2.45 (m, 1H), 2.05 (m, 2H), 1.72 (m, 1H), 1.02−1.28 (m, 5H), 0.72 (m, 1H), 0.62 (d, J = 6.6 Hz, 3H), 0.56 (d, J = 6.6 Hz, 3H), −0.60 (m, 1H); MS (ESI) *m/z* 483 $(M + H)^+$.

To a solution of the acid (30 mg) in DMF (2 mL) were added NMM (0.030 mL), glycine-*N*-methylamide hydrochloride (15 mg), and TBTU (26 mg). After being stirred for 18 h at ambient temperature, the reaction was heated to 80 °C for 15 min. The volatiles were removed under reduced pressure, and the resulting material was purified by preparative TLC (1 mm with 0.25 mm concentration zone) eluting with 5% MeOH/$CHCl_3$, affording 30 mg of the intermediate. This was dissolved in MeOH (10 mL), and to this was added 5% Pd/$BaSO_4$ (35 mg). The mixture was shaken under H_2 (50 psi) for 6 h and filtered, and the volatiles were removed under reduced pressure, affording 20 mg (70%) of **54e**: ^{1}H NMR (CD_3OD) δ 7.21 (m, 1H), 7.10 (m, 2H), 6.86 (m, 1H), 4.92 (m, 1H), 4.12 (m, 2H), 3.82 (m, 2H), 3.35 (m, 1H), 2.73 (s, 3H), 2.68 (m, 1H), 2.14 (m, 1H), 1.68 (m, 1H), 1.30 (m, 5H), 0.85 (m, 1H), 0.81 (d, J = 6.6 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H), −0.55 (m, 1H); MS (ESI) *m/z* 463.2 $(M + H)^+$. Anal. ($C_{23}H_{34}N_4O_6$) C, H, N.

The following compounds were prepared in a manner analogous to that for **54e**.

(6*S*,7*R*,10*S*)-N^6-Hydroxy-7-isobutyl-N^{10}-methyl-8-oxo-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54a): mp 350−352 °C; IR ν 574, 642, 672, 1002, 1054, 1172, 1184, 1194, 1222, 1258, 1298, 1366, 1406, 1442, 1516, 1636, 2928, 3314 cm^{-1}; ^{1}H NMR (CD_3OD) δ 8.20 (d, 1H), 7.85 (m, 1H), 7.18 (m, 1H), 7.11 (m, 1H), 7.04 (m, 1H), 6.85 (m, 1H), 4.90 (m, 1H), 4.10 (m, 2H), 3.23 (m, 1H), 2.74 (m, 1H), 2.70 (s, 3H), 2.14 (m, 1H), 1.66 (m, 1H), 1.26−1.37 (m, 5H), 0.88 (m, 1H), 0.78 (m, 6H), −0.55 (m, 1H); MS (ESI) *m/z* 404.2 $(M - H)^-$; HRMS *m/z* 406.234761 [$(M + H)^+$ calcd for $C_{21}H_{32}N_3O_5$ 406.234197]. Anal. ($C_{21}H_{31}N_3O_5$) C, H, N.

(6*S*,7*R*,10*S*)-N^6-Hydroxy-7-isobutyl-8-oxo-2-oxa-N^{10}-(2,2,2-trifluoroethyl)-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54b): ^{1}H NMR (CD_3OD) δ 8.30 (d, 1H), 7.20 (d, 1H), 7.10 (d, 1H), 7.02 (d, 1H), 6.85 (d, 1H), 4.80 (m, 1H), 4.10 (m, 2H), 3.95 (m, 2H), 2.86 (t, J = 13.2 Hz, 2H), 2.10 (m, 2H), 1.65 (m, 2H), 1.4−1.2 (m, 4H), 0.90 (m, 1H), 0.79 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 6.6 Hz, 3H), −0.55 (m, 1H); MS (ESI) *m/z* 474.2. Anal. ($C_{22}H_{30}F_3N_3O_5 \cdot 0.5H_2O$) C, H, N.

(6*S*,7*R*,10*S*)-N^6-Hydroxy-7-isobutyl-N^{10}-isopropyl-8-oxo-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54c): ^{1}H NMR (CD_3OD) δ 7.88 (s, 1H), 7.25−7.00 (m, 3H), 6.85 (d, 1H), 4.60 (m, 1H), 4.10 (m, 2H), 3.30 (m, 1H), 2.80 (m, 2H), 2.10 (m, 2H), 1.60 (m, 2H), 1.4−0.9 (m, 10H), 0.82 (d, J = 6.2 Hz, 3H), 0.74 (d, J = 5.9 Hz, 3H), −0.60 (m, 1H); MS (ESI) *m/z* 434.2. Anal. ($C_{23}H_{35}N_3O_5 \cdot 0.2CF_3CO_2H$) C, H, N.

(6*S*,7*R*,10*S*)-N^{10}-{2-[4-(Aminosulfonyl)phenyl]ethyl}-N^6-hydroxy-7-isobutyl -8-oxo-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54d): ^{1}H NMR (CD_3OD) δ 8.21 (d, J = 9.5 Hz, 1H), 8.10 (m, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.10 (m, 3H), 6.84 (m, 1H), 4.80 (m, 1H), 4.10 (m, 2H), 3.45 (m, 2H), 3.18 (m, 1H), 2.88 (m, 2H), 2.60 (m, 1H), 2.12 (m, 1H), 1.65 (m, 1H), 1.30 (m, 5H), 0.86 (m, 1H), 0.81 (d, J = 6.4 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H), −0.55 (m, 1H); MS (ESI) *m/z* 573.2 $(M - H)^-$. Anal. ($C_{28}H_{38}N_4O_7S \cdot 0.5H_2O$) C, H, N.

(6*S*,7*R*,10*S*)-N^6-Hydroxy-7-isobutyl-8-oxo-N^{10}-{2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl}-2-oxa-9-azabicyclo-[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54f): ^{1}H NMR (CD_3OD) δ 8.28 (d, J = 9.5 Hz, 1H), 7.22 (m, 1H), 7.08 (m, 2H), 6.86 (m, 1H), 4.86 (m, 1H), 4.10 (m, 2H), 3.80 (m, 4H), 3.38 (m, 1H), 2.66 (m, 1H), 2.14 (m, 1H), 1.68 (m, 1H), 1.22−1.39 (m, 5H), 0.86 (m, 1H), 0.80 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 6.6 Hz, 3H), −0.56 (m, 1H); MS (ESI) *m/z* 529.1 $(M - H)^-$. Anal. ($C_{24}H_{33}F_3N_4O_6 \cdot 0.2CF_3CO_2H$) C, H, N.

(6*S*,7*R*,10*S*)-N^{10}-[2-(Cyclobutylamino)-2-oxoethyl]-N^6-hydroxy-7-isobutyl-8-oxo-2-oxa-9-azabicyclo[10.2.2]-hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54g): ^{1}H

NMR (CD_3OD) δ 8.30 (d, J = 9.9 Hz, 1H), 7.21 (m, 1H), 7.10 (m, 2H), 6.80 (m, 1H), 4.90 (m, 1H), 4.28 (m, 1H), 4.12 (m, 2H), 3.80 (m, 2H), 3.36 (m, 1H), 2.66 (m, 1H), 2.12 (m, 3H), 1.92 (m, 2H), 1.70 (m, 3H), 1.20−1.39 (m, 5H), 0.86 (m, 1H), 0.80 (d, J = 6.2 Hz, 3H), 0.74 (d, J = 6.6 Hz, 3H), −0.55 (m, 1H); MS (ESI) m/z 503 $(M + H)^+$. Anal. ($C_{26}H_{38}N_4O_6 \cdot 0.7H_2O$) C, H, N.

(6*S*,7*R*,10*S*)-*N*^{10}-[2-(*tert*-Butylamino)-2-oxoethyl]-*N*^{6}-hydroxy-7-isobutyl-8-oxo-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54h): ^{1}H NMR (CD_3OD) δ 8.27 (d, J = 9.9 Hz, 1H), 7.47 (s, 1H), 7.22 (m, 1H), 7.08 (m, 2H), 6.86 (m, 1H), 4.92 (m, 1H), 4.10 (m, 2H), 3.80 (m, 2H), 3.38 (m, 1H), 2.65 (m, 1H), 2.15 (m, 1H), 1.68 (m, 1H), 1.25−1.39 (m, 5H), 1.31 (s, 9H), 0.86 (m, 1H), 0.82 (d, J = 6.6 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H), −0.55 (m, 1H). Anal. ($C_{26}H_{40}N_4O_6 \cdot H_2O$) C, H, N.

(6*S*,7*R*,10*S*)-*N*^{10}-(2-Anilino-2-oxoethyl)-*N*^{6}-hydroxy-7-isobutyl-8-oxo-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),-12,15-triene-6,10-dicarboxamide (54i): ^{1}H NMR (CD_3OD) δ 8.33 (d, J = 9.9 Hz, 1H), 7.54 (d, J = 7.7 Hz, 2H), 7.26 (m, 3H), 7.08 (m, 3H), 6.86 (m, 1H), 4.98 (m, 1H), 4.08 (m, 4H), 3.40 (m, 1H), 2.71 (m, 1H), 2.18 (m, 1H), 1.68 (m, 1H), 1.23−1.40 (m, 5H), 0.86 (m, 1H), 0.80 (d, J = 6.6 Hz, 3H), 0.73 (d, J = 6.2 Hz, 3H), −0.55 (m, 1H); MS (ESI) m/z 523.2 $(M - H)^-$. Anal. ($C_{28}H_{36}N_4O_6 \cdot 0.95H_2O$) C, H, N.

(6*S*,7*R*,10*S*)-*N*^{10}-{2-[(2,4-Difluorobenzyl)amino]-2-oxoethyl}-*N*^{6}-hydroxy-7-isobutyl-8-oxo-2-oxa-9-azabicyclo-[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54j): ^{1}H NMR (CD_3OD) δ 7.36 (m, 1H), 7.21 (m, 1H), 7.08 (m, 2H), 6.89 (m, 3H), 4.92 (m, 1H), 4.39 (s, 2H), 4.10 (m, 2H), 3.90 (m, 2H), 3.37 (m, 1H), 2.66 (m, 1H), 2.14, (m, 1H), 1.66 (m, 1H), 1.18−1.38 (m, 5H), 0.86 (m, 1H), 0.79 (d, J = 6.6 Hz, 3H), 0.71 (d, J = 6.2 Hz, 3H), −0.55 (m, 1H); MS (ESI) m/z 573.1 $(M - H)^-$. Anal. ($C_{29}H_{36}F_2N_4O_6 \cdot 0.5H_2O$) C, H, N.

(6*S*,7*R*,10*S*)-*N*^{10}-[2-(9*H*-Fluoren-9-ylamino)-2-oxoethyl]-*N*^{6}-hydroxy-7-isobutyl-8-oxo-2-oxa-9-azabicyclo[10.2.2]-hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54k): ^{1}H NMR (CD_3OD) δ 8.30 (d, J = 9.5 Hz, 1H), 7.74 (d, J = 7.3 Hz, 2H), 7.52 (d, J = 7.3 Hz, 2H), 7.38 (t, J = 7.3 Hz, 2H), 7.3−7.0 (m, 5H), 6.86 (m, 1H), 6.09 (s, 1H), 4.95 (m, 1H), 4.10 (m, 2H), 3.90 (m, 2H), 3.38 (m, 1H), 2.68 (m, 1H), 2.14 (m, 1H), 1.68 (m, 1H), 1.23−1.38 (m, 5H), 0.86 (m, 1H), 0.82 (d, J = 6.6 Hz, 3H), 0.73 (d, J = 6.2 Hz, 3H), −0.55 (m, 1H); MS (ESI) m/z 611.2 $(M - H)^-$. Anal. ($C_{35}H_{40}N_4O_6 \cdot 1.1H_2O$) C, H, N.

(6*S*,7*R*,10*S*)-*N*^{10}-[2-(Dimethylamino)-2-oxoethyl]-*N*^{6}-hydroxy-7-isobutyl-8-oxo-2-oxa-9-azabicyclo[10.2.2]-hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54l): ^{1}H NMR (CD_3OD) δ 8.28 (d, J = 9.9 Hz), 7.23 (m, 1H), 7.10 (m, 2H), 6.86 (m, 1H), 4.95 (m, 1H), 4.10 (m, 4H), 3.40 (m, 1H), 3.02 (s, 3H), 2.94 (s, 3H), 2.65 (m, 1H), 2.14 (m, 1H), 1.68 (m, 1H), 1.23−1.39 (m, 5H), 0.86 (m, 1H), 0.82 (d, J = 6.6 Hz, 3H), 0.75 (d, J = 6.2 Hz, 3H), −0.56 (m, 1H). Anal. ($C_{24}H_{36}N_4O_6 \cdot H_2O$) C, H, N.

(6*S*,7*R*,10*S*)-*N*^{6}-Hydroxy-7-isobutyl-8-oxo-*N*^{10}-[2-oxo-2-(1-piperidinyl)ethyl]-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54m): ^{1}H NMR (CD_3OD) δ 8.28 (d, J = 9.5 Hz, 1H), 7.23 (m, 1H), 7.10 (m, 2H), 6.86 (m, 1H), 4.95 (m, 1H), 4.10 (m, 4H), 3.53 (m, 2H), 3.40 (m, 3H), 2.65 (m, 1H), 2.14 (m, 1H), 1.50−1.69 (m, 7H), 1.23−1.39 (m, 5H), 0.86 (m, 1H), 0.82 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 6.2 Hz, 3H), −0.57 (m, 1H); MS (ESI) m/z 515.2 $(M - H)^-$. Anal. ($C_{27}H_{40}N_4O_6 \cdot H_2O$) C, H, N.

(6*S*,7*R*,10*S*)-*N*^{6}-Hydroxy-*N*^{10}-[2-(4-hydroxy-1-piperidinyl)-2-oxoethyl]-7-isobutyl-8-oxo-2-oxa-9-azabicyclo[10.2.2]-hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54n): ^{1}H NMR (CD_3OD) δ 8.29 (d, J = 9.5 Hz, 1H), 7.94 (m, 1H), 7.22 (m, 1H), 7.10 (m, 2H), 6.86 (m, 1H), 4.95 (m, 1H), 4.10 (m, 5H), 3.82 (m, 1H), 3.68 (m, 1H), 3.41 (m, 1H), 3.20 (m, 2H), 2.65 (m, 1H), 2.14 (m, 1H), 1.85 (m, 2H), 1.66 (m, 1H), 1.22−1.55 (m, 7H), 0.86 (m, 1H), 0.82 (d, J = 6.2 Hz, 3H), 0.75 (d, J = 6.2 Hz, 3H), −0.56 (m, 1H). Anal. ($C_{27}H_{40}N_4O_7 \cdot 0.2C_6H_6$) C, H, N.

(6*S*,7*R*,10*S*)-*N*^{10}-[2-(3,5-Dimethyl-1-piperidinyl)-2-oxoethyl]-*N*^{6}-hydroxy-7-isobutyl-8-oxo-2-oxa-9-azabicyclo-[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54o): ^{1}H NMR (CD_3OD) δ 8.27 (d, J = 9.5 Hz, 1H), 7.22 (m, 1H), 7.08 (m, 2H), 6.86 (m, 1H), 4.96 (m, 1H), 4.05 (m, 1H), 4.10 (m, 4H), 3.70 (m, 1H), 3.42 (m, 1H), 2.65 (m, 1H), 2.55 (m, 1H), 2.12 (m, 2H), 1.82 (m, 1H), 1.46−1.70 (m, 4H), 1.23−1.39 (m, 5H), 0.91 (m, 7H), 0.82 (d, J = 6.6 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H), −0.56 (m, 1H); MS (ESI) m/z 543.3 $(M - H)^-$. Anal. ($C_{29}H_{44}N_4O_6 \cdot 0.25CF_3CO_2H$) C, H, N.

(6*S*,7*R*,10*S*)-*N*^{10}-[2-(3,3-Dimethyl-1-piperidinyl)-2-oxoethyl]-*N*^{6}-hydroxy-7-isobutyl-8-oxo-2-oxa-9-azabicyclo-[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54p): ^{1}H NMR (CD_3OD) δ 8.27 (d, J = 9.9 Hz, 1H), 7.23 (m, 1H), 7.08 (m, 2H), 6.86 (m, 1H), 4.96 (m, 1H), 4.10 (m, 4H), 3.40 (m, 3H), 3.20 (m, 2H), 2.65 (m, 1H), 2.15 (m, 1H), 1.60 (m, 3H), 1.23−1.46 (m, 7H), 0.90 (m, 7H), 0.82 (d, J = 6.2 Hz, 3H), 0.74 (d, J = 6.7 Hz, 3H), −0.57 (m, 1H); MS (ESI) m/z 543.2 $(M - H)^-$. Anal. ($C_{29}H_{44}N_4O_6 \cdot 1.2H_2O$) C, H, N.

(6*S*,7*R*,10*S*)-*N*^{6}-Hydroxy-7-isobutyl-*N*^{10}-[(1*S*)-1-methyl-2-(methylamino)-2-oxoethyl]-8-oxo-2-oxa-9-azabicyclo-[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54q): ^{1}H NMR (CD_3OD) δ 8.28 (d, J = 9.9 Hz, 1H), 7.25 (m, 1H), 7.08 (m, 2H), 6.85 (m, 1H), 4.95 (m, 1H), 4.30 (q, J = 7.0 Hz, 1H), 4.10 (m, 2H), 3.34 (m, 1H), 2.68 (m, 4H), 2.12 (m, 1H), 1.65 (m, 1H), 1.13−1.38 (m, 8H), 0.87 (m, 1H), 0.80 (d, J = 6.6 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H), −0.56 (m, 1H); MS (ESI) m/z 475 $(M - H)^-$; HRMS m/z 477.2693 $[(M + H)^+$ calcd for $C_{24}H_{37}N_4O_6$ 477.2713].

(6*S*,7*R*,10*S*)-*N*^{6}-Hydroxy-7-isobutyl-*N*^{10}-[(1*R*)-1-methyl-2-(methylamino)-2-oxoethyl]-8-oxo-2-oxa-9-azabicyclo-[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54r): ^{1}H NMR (CD_3OD) δ 8.31 (d, J = 9.5 Hz, 1H), 7.21 (m, 1H), 7.09 (m, 2H), 6.86 (m, 1H), 4.95 (m, 1H), 4.31 (q, J = 7.3 Hz, 1H), 4.10 (m, 2H), 3.34 (m, 1H), 2.70 (s, 3H), 2.65 (m, 1H), 2.14 (m, 1H), 1.66 (m, 1H), 1.12−1.42 (m, 8H), 0.86 (m, 1H), 0.82 (d, J = 6.6 Hz, 3H), 0.76 (d, J = 6.2 Hz, 3H), −0.56 (m, 1H); MS (ESI) m/z 475.2 $(M - H)^-$. Anal. ($C_{24}H_{36}N_4O_6 \cdot H_2O$) C, H, N.

(6*S*,7*R*,10*S*)-*N*^{6}-Hydroxy-7-isobutyl-*N*^{10}-[(1*S*)-1-(4-methoxybenzyl)-2-(methylamino)-2-oxoethyl]-8-oxo-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54s): ^{1}H NMR (CD_3OD) δ 7.22 (m, 1H), 7.09 (m, 4H), 6.85 (m, 3H), 4.95 (m, 1H), 4.46 (t, J = 7.3 Hz, 1H), 4.12 (m, 2H), 3.74 (s, 3H), 3.40 (m, 1H), 2.92 (m, 2H), 2.65 (s, 3H), 2.61 (m, 1H), 2.12 (m, 1H), 1.66 (m, 1H), 1.21−1.39 (m, 5H), 0.86 (m, 1H), 0.81 (d, J = 6.6 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H), −0.56 (m, 1H); MS (ESI) m/z 581.2 $(M - H)^-$. Anal. ($C_{31}H_{42}N_4O_7 \cdot H_2O$) C, H, N.

(6*S*,7*R*,10*S*)-*N*^{10}-[(1*S*)-1-(*tert*-Butoxymethyl)-2-(methylamino)-2-oxoethyl]-*N*^{6}-hydroxy-7-isobutyl-8-oxo-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54t): ^{1}H NMR (CD_3OD) δ 8.29 (d, J = 9.9 Hz, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.22 (m, 1H), 7.08 (m, 2H), 6,86 (m, 1H), 4.95 (m, 1H), 4.38 (m, 1H), 4.10 (m, 2H), 3.62 (m, 1H), 3.48 (m, 1H), 3.34 (m, 1H), 2.63−2.84 (m, 4H), 2.12 (m, 1H), 1.66 (m, 1H), 1.23−1.40 (m, 5H), 1.15 (s, 9H), 0.88 (m, 1H), 0.81 (d, J = 6.2 Hz, 3H), 0.76 (d, J = 6.6 Hz, 3H), −0.56 (m, 1H); MS (ESI) m/z 547.2 $(M - H)^-$. Anal. ($C_{28}H_{44}N_4O_7 \cdot 0.8H_2O$) C, H, N.

(6*S*,7*R*,10*S*)-*N*^{6}-Hydroxy-7-isobutyl-*N*^{10}-{(1*S*)-2-methyl-1-[(methylamino)carbonyl]propyl}-8-oxo-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (54u): ^{1}H NMR (CD_3OD) δ 8.27 (d, J = 9.9 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.22 (m, 1H), 7.08 (m, 2H), 6.85 (m, 1H), 4.94 (m, 1H), 4.10 (m, 3H), 3.32 (m, 1H), 2.73 (s, 3H), 2.65 (m, 1H), 2.10 (m, 1H), 2.01 (m, 1H), 1.66 (m, 1H), 1.23−1.39 (m, 5H), 0.86−0.92 (m, 7H), 0.80 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 6.6 Hz, 3H), −0.57 (m, 1H); MS (ESI) m/z 503.3 $(M - H)^-$. Anal. ($C_{26}H_{40}N_4O_6 \cdot 0.25CF_3CO_2H$) C, H, N.

Methyl (6*S*,7*R*,10*S*)-7-Hexyl-6-[(hydroxyamino)carbonyl]-8-oxo-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-triene-10-carboxylate (53): ^{1}H NMR (CD_3OD) δ 8.38 (d, 1H), 7.20 (m, 1H), 7.07 (m, 2H), 6.87 (m, 1H), 5.00 (dd, 1H), 4.14 (m, 2H), 3.75 (s, 3H), 3.47 (dd, 1H), 2.63 (t, 1H), 2.00 (m, 1H), 1.69 (m, 1H), 1.35−1.10 (m, 12H), 0.86 (t, 3H), 0.78 (m, 1H),

−0.55 (m, 1H); MS (ESI) *m/z* 435.3 (M + H)$^+$; HRMS (FAB) *m/z* 435.2515 [(M + H)$^+$, calcd for $C_{23}H_{35}N_2O_6$ 435.2495]. Anal. ($C_{23}H_{34}N_2O_6$) C, H, N.

(6*S*,7*R*,10*S*)-7-Hexyl-*N*^{6}-hydroxy-*N*^{10}-methyl-8-oxo-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (55a): ^{1}H NMR (CD_3OD) δ 8.17 (d, 1H), 7.20 (dd, 1H), 7.08 (m, 2H), 6.86 (dd, 1H), 4.85 (m, 1H), 4.14 (m, 2H), 3.17 (dd, 1H), 2.77 (s, 3H), 2.66 (t, 1H), 2.02 (m, 1H), 1.69 (m, 1H), 1.3−1.0 (m, 12H), 0.85 (t, 3H), 0.79 (m, 1H), −0.55 (m, 1H); MS (ESI) *m/z* 434.4 (M + H)$^+$; HRMS (FAB) *m/z* 434.2667 [(M + H)$^+$, calcd for $C_{23}H_{36}N_3O_5$ 434.2668]. Anal. ($C_{23}H_{35}N_3O_5$) C, H, N.

(6*S*,7*R*,10*S*)-*N*^{10}-Benzyl-7-hexyl-*N*^{6}-hydroxy-8-oxo-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (55b): ^{1}H NMR (CD_3OD) δ 7.36−7.20 (m, 6H), 7.07 (m, 2H), 6.86 (m, 1H), 4.93 (m, 1H), 4.40 (m, 2H), 4.13 (m, 2H), 3.32 (m, 1H), 2.69 (t, 1H), 2.02 (m, 1H), 1.72 (m, 1H), 1.32−1.00 (m, 12H), 0.82 (t, 3H), 0.77 (m, 1H), −0.55 (m, 1H); MS (ESI) *m/z* 510.5 (M + H)$^+$. Anal. ($C_{29}H_{39}N_3O_5$) C, H, N.

(6*S*,7*R*,10*S*)-*N*^{10}-{2-[4-(Aminosulfonyl)phenyl]ethyl}-7-hexyl-*N*^{6}-hydroxy-8-oxo-2-oxa-9-azabicyclo[10.2.2]-hexadeca-1(14),12,15-triene-6,10-dicarboxamide (55c): ^{1}H NMR (CD_3OD) δ 8.18 (d, 1H), 7.84 (d, 2H), 7.40 (d, 2H), 7.19 (m, 1H), 7.07 (m, 2H), 6.85 (m, 1H), 4.83 (m, 1H), 4.15 (m, 2H), 3.46 (m, 2H), 3.20 (m, 1H), 2.90 (m, 2H), 2.61 (t, 1H), 2.04 (m, 1H), 1.72 (m, 1H), 1.36−1.08 (m, 12H), 0.83 (t, 3H), 0.77 (m, 1H), −0.55 (m, 1H); MS (ESI) *m/z* 603.5 (M + H)$^+$; HRMS (FAB) *m/z* 603.2867 [(M + H)$^+$, calcd for $C_{30}H_{43}N_4O_7S$ 603.2866]. Anal. ($C_{30}H_{42}N_4O_7S$) C, H, N.

(6*S*,7*R*,10*S*)-7-Hexyl-*N*^{6}-hydroxy-*N*^{10}-[3-(1*H*-imidazol-1-yl)propyl]-8-oxo-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),-12,15-triene-6,10-dicarboxamide (55d): ^{1}H NMR (CD_3OD) δ 7.68 (s, 1H), 7.22 (m, 1H), 7.15 (s, 1H), 7.08 (m, 2H), 6.96 (s, 1H), 6.87 (m, 1H), 4.86 (m, 1H), 4.14 (m, 2H), 4.06 (t, 2H), 3.24 (m, 3H), 2.70 (t, 1H), 2.00 (m, 3H), 1.74 (m, 1H), 1.35−1.05 (m, 12H), 0.81 (m, 1H), 0.78 (t, 3H), −0.55 (m, 1H); MS (ESI) *m/z* 528.5 (M + H)$^+$; HRMS (FAB) *m/z* 528.3175 [(M + H)$^+$, calcd for $C_{28}H_{42}N_5O_5$ 528.3173]. Anal. ($C_{28}H_{41}N_5O_5\cdot H_2O$) C, H, N.

(6*S*,7*R*,10*S*)-7-Hexyl-*N*^{6}-hydroxy-*N*^{10}-[2-(methylamino)-2-oxoethyl]-8-oxo-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (55e): ^{1}H NMR (CD_3OD) δ 7.23 (m, 1H), 7.08 (m, 2H), 6.87 (m, 1H), 4.95 (m, 1H), 4.13 (m, 2H), 3.86 (m, 2H), 3.40 (m, 1H), 2.75 (s, 3H), 2.68 (t, 1H), 2.06 (m, 1H), 1.73 (m, 1H), 1.3−1.1 (m, 12H), 0.84 (t, 3H), 0.77 (m, 1H), −0.56 (m, 1H); MS (ESI) *m/z* 491.5 (M + H)$^+$. Anal. ($C_{25}H_{38}N_4O_6$) C, H, N.

(6*S*,7*R*,10*S*)-*N*^{10}-[(1*S*)-1-(*tert*-Butoxymethyl)-2-(methylamino)-2-oxoethyl]-7-hexyl-*N*^{6}-hydroxy-8-oxo-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (55f): ^{1}H NMR (CD_3OD) δ 7.23 (m, 1H), 7.10 (m, 2H), 6.88 (m, 1H), 4.94 (dd, 1H), 4.38 (t, 1H), 4.14 (m, 2H), 3.67 (dd, 1H), 3.53 (dd, 1H), 3.37 (dd, 1H), 2.76 (s, 3H), 2.67 (t, 1H), 2.03 (m, 1H), 1.72 (m, 1H), 1.17 (s, 9H), 1.35−1.05 (m, 12H), 0.85 (t, 3H), 0.77 (m, 1H), −0.54 (m, 1H); MS (ESI) *m/z* 577.6 (M + H)$^+$. Anal. ($C_{30}H_{48}N_4O_7$) C, H, N.

(6*S*,7*S*,10*R*)-*N*^{6}-Hydroxy-7-isobutyl-*N*^{10}-methyl-8-oxo-2-oxa-9-azabicyclo[1 1.2.2]heptadeca-1(15),13,16-triene-6,-10-dicarboxamide (56): ^{1}H NMR (CD_3OD) δ 7.88 (m, 1H), 7.74 (m, 1H), 7.19 (m, 1H), 7.08 (m, 2H), 6.78 (m, 1H), 4.18 (m, 3H), 2.96 (m, 1H), 2.67 (m, 3H), 2.55 (m, 1H), 1.85−2.18 (m, 3H), 1.70 (m, 1H), 1.26−1.48 (m, 5H), 0.90 (m, 1H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.73 (d, *J* = 6.6 Hz, 3H), 0.40 (m, 1H); HRMS *m/z* 420.2512 [(M + H)$^+$ calcd for $C_{22}H_{34}N_3O_5$ 420.2498].

(6*S*,7*S*,10*R*)-*N*^{6}-Hydroxy-7-isobutyl-*N*^{10}-methyl-8-oxo-2-oxa-9-azabicyclo[1 2.2.2]octadeca-1(16),14,17-triene-6,10-dicarboxamide (57): ^{1}H NMR (CD_3OD) δ 7.05 (m, 3H), 6.78 (m, 1H), 4.30 (m, 1H), 4.12 (m, 1H), 3.90 (m, 1H), 2.70 (m, 4H), 2.48 (m, 1H), 2.28 (m, 1H), 1.88 (m, 1H), 1.04−1.63 (m, 9H), 0.92 (m, 1H), 0.80 (d, *J* = 6.2 Hz, 3H), 0.75 (d, *J* = 6.2 Hz, 3H), 0.75 (m, 1H); MS (ESI) *m/z* 434 (M + H)$^+$; HRMS *m/z* 434.2655 [(M + H)$^+$ calcd for $C_{23}H_{36}N_3O_5$ 434.2655].

(6*S*,7*R*,10*S*)-*N*^{10}-{(1S)-5-amino-1-[(methylamino)carbonyl]pentyl}-*N*^{6}-hydroxy-7-isobutyl-8-oxo-2-oxa-9-azabicyclo[10.2.2]hexadeca-1(14),12,15-triene-6,10-dicarboxamide (58). Compound **54v** (50 mg) was dissolved in 50% TFA/CH_2Cl_2 (5 mL). After the solution was stirred at room temperature for 1 h, the volatiles were removed under reduced pressure and the residue was triturated with ether to provide **58** as a solid: ^{1}H NMR (CD_3OD) δ 7.22 (m, 1H), 7.08 (m, 2H), 6.86 (m, 1H), 4.94 (m, 1H), 4.35 (m, 1H), 4.10 (m, 2H), 3.36 (m, 1H), 2.65 (m, 3H), 2.16 (m, 1H), 1.24−1.87 (m, 12H), 0.87 (m, 1H), 0.80 (d, *J* = 6.2 Hz, 3H), 0.76 (d, *J* = 6.2 Hz, 3H), −0.57 (m, 1H); MS (ESI) *m/z* 520.3 (M + H)$^+$. Anal. ($C_{26}H_{41}N_5O_6\cdot 0.25CF_3CO_2H$) C, H, N.

(6*S*,7*R*,10*S*)-*N*^{10}-[(1*S*)-5-Amino-1-(aminocarbonyl)pentyl]-7-hexyl-*N*^{6}-hydroxy-8-oxo-2-oxa-9-azabicyclo[10.2.2]-hexadeca-1(14),12,15-triene-6,10-dicarboxamide (59). Compound **57** was obtained from **53g** following the procedure described for **56**: ^{1}H NMR (CD_3OD) δ 7.25 (m, 1H), 7.08 (m, 2H), 6.87 (m, 1H), 4.96 (dd, 1H), 4.37 (dd, 1H), 4.13 (m, 2H), 3.39 (dd, 1H), 2.71 (m, 3H), 2.07 (m, 1H), 1.83 (m, 1H), 1.70 (m, 2H), 1.56 (m, 2H), 1.43 (m, 2H), 1.35−1.08 (m, 12H), 0.85 (t, 3H), 0.77 (m, 1H), −0.56 (m, 1H); MS (ESI) *m/z* 548.6 (M + H)$^+$. Anal. ($C_{28}H_{45}N_5O_6\cdot 0.5H_2O$) C, H, N.

(2*S*)-2-{[(Benzyloxy)carbonyl]amino}-6-[(trifluoroacetyl)amino]hexanoic Acid (61). To a suspension of *N*$^\alpha$-Cbz-L-lysine (**60**) (5.6 g, 20 mmol) in H_2O (40 mL) and dioxane (5 mL) cooled in an ice bath was added K_2CO_3 (5.53 g, 40 mmol) followed by ethyl trifluoroacetate (7.14 mL, 60 mmol). The mixture was stirred for 1 h and diluted with water. The solution was extracted with ether 2×. The aqueous phase was acidified with 10% citric acid solution and extracted with EtOAc three times. The combined organic phase was washed with brine 3×, dried ($MgSO_4$), and concentrated to give 7.6 g (100%) of the lysine derivative **61**: MS (ESI) *m/z* 377.2 (M + H)$^+$.

Methyl (2*S*)-2-{[(Benzyloxy)carbonyl]amino}-6-[methyl(trifluoroacetyl)amino]hexanoate (62). A mixture of **61** (20 g, 53.1 mmol), K_2CO_3 (36.7 g, 265 mmol), and iodomethane (50 mL, 795 mmol) in DMF (150 mL) was stirred at 110 °C for 10 h. Insoluble materials were filtered off, and the solution was concentrated under reduced pressure. The residue was taken up in EtOAc. The resulting solution was washed with brine 6×, dried ($MgSO_4$), and concentrated to give 19.45 g (90%) of the ester **62**: MS (ESI) *m/z* 405.2 (M + H)$^+$. Anal. ($C_{18}H_{23}N_2O_5F_3$) C, H, N.

Methyl (2*S*)-2-{[(Benzyloxy)carbonyl]amino}-6-(methylamino)hexanoate (63). To a solution of **62** (2.02 g, 5 mmol) in THF (15 mL) was added a solution of 1 N LiOH (15 mL). The mixture was stirred at room temperature for 2 h and acidified with 1 N HCl (20 mL). The solvents were removed under reduced pressure, and the residue was taken up in MeOH (20 mL). To it was added 4 N HCl/dioxane (50 mL). The solution was stirred at room temperature overnight and concentrated under reduced pressure, affording the crude **63**, which was used for the next reaction without purification: MS (CI, NH_3) *m/z* 309.

1-Benzyl 4-*tert*-Butyl (2*R*,3*S*)-2-Isobutyl-3-(3-{[(4-nitrophenoxy)carbonyl]oxy}propyl)butanedioate (64). To a solution of **31a** (11.4 g, 33.1 mmol) and 4-nitrophenyl chloroformate (10.0 g, 50 mmol) in CH_2Cl_2 (50 mL) cooled in an ice bath was slowly added NMM (4.4 mL, 40 mmol), and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was taken up in EtOAc (200 mL). The solution was washed with brine 3×, dried ($MgSO_4$), and concentrated. Purification on a silica gel column eluting with 10% EtOAc/hexanes provided **64** (15.0 g, 91%) as a pale yellow solid: MS (CI, NH_3) *m/z* 561 (M + NH_4)$^+$. Anal. ($C_{29}H_{37}NO_9$) C, H, N.

17-Benzyl 16-*tert*-Butyl 5-Methyl (5*S*,16*S*,17*R*)-19-Methyl-3,11-dioxo-1-phenyl-2,12-dioxa-4,10-diazaicosane-5,16,-17-tricarboxylate (65a). To a solution of **64** (15.20 g, 27.28 mmol) and **63** (11.22 g, 32.78 mmol) in DMF (50 mL) was added K_2CO_3 (15 g, 109 mmol). The mixture was stirred at 50 °C for 2 h. Insoluble materials were filtered off, and the filtrate was diluted with EtOAc (300 mL). The resulting solution was washed with 10% citric acid, brine, $NaHCO_3$, and brine, dried

($MgSO_4$), and concentrated. Flash chromatography on silica gel eluting with 15% EtOAc/hexanes provided **65a** (17.0 g, 91%) as an oil: MS (ESI) *m/z* 699.5 $(M + H)^+$. Anal. ($C_{38}H_{54}N_2O_{10}$) C, H, N.

12-*tert*-Butyl 8-Methyl (8*S*,11*R*,12*S*)-11-Isobutyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxylate (66a). To a solution of **65a** (14.5 g, 20.8 mmol) in MeOH (100 mL) was added 10% Pd on carbon (1.5 g). The mixture was stirred under H_2 (balloon) for 1 h. The catalyst was filtered off, and the solvent was removed under reduced pressure. The residue was taken up in DMF (50 mL). This solution was dropwise added to a solution of BOP (9.2 g, 20.8 mmol) and DIEA (12 mL, 70 mmol) in $CHCl_3$ (1000 mL) cooled in an ice bath. The mixture was allowed to stir at room temperature overnight. The volatiles were removed under reduced pressure, and the residue was taken up in EtOAc. The resulting solution was washed with 5% citric acid, brine, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Purification on a silica gel column eluting with 7% MeOH/CH_2Cl_2 provided **66a** (6.6 g, 70%) as a powder: MS (ESI) *m/z* 457.4 $(M + H)^+$.

Methyl (8*S*,11*R*,12*S*)-12-{[(Benzyloxy)amino]carbonyl}-11-isobutyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8-carboxylate (67a). Compound **66a** (2.6 g, 5.5 mmol) was dissolved in 50% TFA in CH_2Cl_2 (20 mL). The solution was stirred for 1 h, and the volatiles were removed under reduced pressure. The residue was taken up in DMF (10 mL), and the solution was cooled in an ice bath. To it were added *O*-benzylhydroxylamine hydrochloride (0.96 g, 6.15 mmol), DIEA (4.3 mL, 24.6 mmol), and BOP (2.72 g, 6.15 mmol). The solution was allowed to stir at room temperature overnight and diluted with EtOAc. The resulting solution was washed with 5% citric acid, brine, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. The residue was triturated with ether to give **67a** (2.9 g, 90%) as a solid: MS (ESI) *m/z* 506.5 $(M + H)^+$.

(8*S*,11*R*,12*S*)-N^{12}-Hydroxy-11-isobutyl-N^8-[2-(4-morpholinyl)-2-oxoethyl]-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68y). To a solution of **67a** (1.1 g, 2 mmol) in THF (10 mL) was added 1 N LiOH (4 mL). The mixture was stirred at room temperature for 1 h and acidified with TFA. EtOAc was added, and the resulting solution was washed with brine 3×, dried ($MgSO_4$), and concentrated to give the acid as a solid. The solid was dissolved in DMF (10 mL), and the solution was cooled in an ice bath. To it were added *N*-glycinylmorpholine (0.55 g, 3 mmol), BOP (0.9 g, 2 mmol), and DIEA (1.75 mL, 10 mmol). The mixture was stirred at room temperature overnight and diluted with EtOAc. The resulting solution was washed with $NaHCO_3$ 3× and brine 3×, dried ($MgSO_4$), and concentrated to give a solid which was dissolved in MeOH (30 mL). To the solution was added Pd/$BaSO_4$ (0.5 g). The mixture was stirred under H_2 at 50 psi for 5 h. The catalyst was filtered off, and the solvent was removed under reduced pressure. Purification by reversed-phase HPLC afforded the hydroxamic acid **68y** (81 mg, 82%) as a powder: ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 1H), 8.20 (d, 1H), 7.70 (t, 1H), 6.95 (t, 1H), 4.20 (m, 1H), 3.95 (m, 4H), 3.55 (m, 4H), 3.40 (m, 4H), 3.00 (m, 2H), 2.45 (m, 1H), 2.00 (m, 1H), 1.6−1.2 (m, 12H), 0.90−0.75 (m, 7H); MS (ESI) *m/z* 528.5 $(M + H)^+$. Anal. ($C_{24}H_{41}N_5O_8$) C, H, N.

The following compounds were prepared in a manner analogous to that described for **68y**.

(8*S*,11*R*,12*S*)-N^{12}-Hydroxy-11-isobutyl-N^8-methyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68a): ^{1}H NMR (CD_3OD) δ 8.43 (d, 1H), 7.78 (s, 1H), 6.76 (t, 1H), 4.34 (m, 2H), 3.97 (m, 1H), 3.25−3.02 (m, 2H), 2.68 (d, 3H), 2.57 (m, 1H), 2.07 (m, 1H), 1.77−1.23 (m, 12H), 1.01 (m, 1H), 0.87 (d, 3H), 0.81 (d, 3H); MS (ESI) *m/z* 437.3 $(M + Na)^+$. Anal. ($C_{19}H_{34}N_4O_6 \cdot 0.1CH_2Cl_2$) C, H, N.

(8*S*,11*R*,12*S*)-N^{12}-Hydroxy-11-isobutyl-2,10-dioxo-N^8-(2,2,2-trifluoroethyl)-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68b): ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 1H), 8.81 (s, 1H), 8.37 (m, 1H), 8.17 (d, 1H), 6.96 (t, 1H), 4.31, (m, 1H), 4.16, (m, 1H), 4.02−3.73 (m, 3H), 3.10−2.86 (m, 2H), 2.49 (m, 1H), 1.95 (m, 1H), 1.68−1.15 (m, 12H), 0.87 (m, 1H), 0.80 (d, 3H), 0.72 (d, 3H); MS (ESI) *m/z* 505.3 $(M + Na)^+$. Anal. ($C_{20}H_{33}F_3N_4O_6$) C, H, N.

(8*S*,11*R*,12*S*)-N^{12}-Hydroxy-11-isobutyl-2,10-dioxo-N^8-phenyl-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68c): ^{1}H NMR (DMSO-d_6) δ 10.51 (s, 1H), 9.84 (s, 1H), 8.82 (s, 1H), 8.26 (d, 1H), 7.54 (d, 2H), 7.30 (t, 2H), 7.05−6.98 (m, 2H), 4.42 (m, 1H), 4.18 (m, 1H), 3.97 (m, 1H), 3.00 (m, 2H), 2.25 (m, 1H), 1.99 (m, 1H), 1.73−1.22 (m, 12H), 0.98−0.70 (m, 7H); MS (ESI) *m/z* 499.3 $(M + Na)^+$.

(8*S*,11*R*,12*S*)-N^{12}-Hydroxy-11-isobutyl-N^8-[4-(4-morpholinyl)phenyl]-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68d): ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 1H), 9.70 (s, 1H), 8.20 (d, 1H), 7.20 (d, 2H), 6.95 (d, 2H), 6.80 (t, 1H), 4.20 (m, 1H), 3.80 (m, 10H), 3.00 (m, 2H), 2.4−2.0 (m, 2H), 1.6−1.2 (m, 12H), 0.90−0.75 (m, 7H); MS (ESI) *m/z* 562.3 $(M + H)^+$. Anal. ($C_{28}H_{43}N_5O_7 \cdot CF_3CO_2H \cdot 0.4H_2O$) C, H, N.

(8*S*,11*R*,12*S*)-N^8-Benzyl-N^{12}-hydroxy-11-isobutyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68e): ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 1H), 8.81 (s, 1H), 8.14 (d, 1H), 8.05 (t, 1H), 7.32−7.19 (m, 5H), 6.95 (t, 1H), 4.25 (d, 2H), 4.23 (m, 2H), 3.97 (m, 1H), 3.10−2.88 (m, 2H), 2.43 (m, 1H), 1.95 (m, 1H), 1.65−1.22 (m, 12H), 0.86 (m, 1H), 0.73−0.68 (m, 6H); MS (ESI) *m/z* 513.4 $(M + Na)^+$. Anal. ($C_{25}H_{38}N_4O_6 \cdot 0.25H_2O$) C, H, N.

(8*S*,11*R*,12*S*)-N^{12}-Hydroxy-11-isobutyl-2,10-dioxo-N^8-(2-pyridinylmethyl)-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68f): ^{1}H NMR (DMSO-d_6) δ 10.51 (s, 1H), 8.82 (s, 1H), 8.48 (d, 1H), 8.35−8.19 (m, 2H), 7.73 (t, 1H), 7.24 (m, 2H), 6.96 (m, 1H), 4.32 (d, 2H), 4.33−4.08 (m, 2H), 3.93 (m, 1H), 3.15−2.80 (m, 2H), 2.52 (m, 1H), 1.95 (m, 1H), 1.78−1.11 (m, 12H), 0.86−0.67 (m, 7H); MS (ESI) *m/z* 492.3 $(M + H)^+$. Anal. ($C_{24}H_{37}N_5O_6 \cdot 0.4H_2O$) C, H, N.

(8*S*,11*R*,12*S*)-N^{12}-Hydroxy-11-isobutyl-2,10-dioxo-N^8-(3-pyridinylmethyl)-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68g): ^{1}H NMR (DMSO-d_6) δ 10.54 (s, 1H), 8.81 (s, 1H), 8.44 (bs, 2H), 8.37−8.11 (m, 2H), 7.59 (d, 1H), 7.31 (dd, 1H), 6.95 (m, 1H), 4.26 (d, 2H), 4.28−4.10 (m, 2H), 3.93 (m, 1H), 3.09−2.82 (m, 2H), 2.51 (m, 1H), 1.94 (m, 1H), 1.69−1.14 (m, 12H), 0.83 (m, 1H), 0.73 (d, 3H), 0.68 (d, 3H); MS (ESI) *m/z* 492.3 $(M + H)^+$. Anal. ($C_{24}H_{37}N_5O_6 \cdot 0.25H_2O$) C, H, N.

(8*S*,11*R*,12*S*)-N^{12}-Hydroxy-11-isobutyl-2,10-dioxo-N^8-(4-pyridinylmethyl)-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68h): ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 1H), 8.82 (s, 1H), 8.46 (dd, 2H), 8.30 (t, 1H), 8.18 (d, 1H), 7.19 (d, 2H), 6.97 (t, 1H), 4.35−4.10 (m, 2H), 4.27 (d, 2H), 3.93 (m, 1H), 3.16−2.85 (m, 2H), 2.49, (m, 1H), 1.95 (m, 1H), 1.72−1.15 (m, 12H), 0.87 (m, 1H), 0.75 (d, 3H), 0.69 (d, 3H); MS (ESI) *m/z* 492.3 $(M + H)^+$. Anal. ($C_{24}H_{37}N_5O_6 \cdot HCl \cdot 0.5MeOH$) C, H, N.

(8*S*,11*R*,12*S*)-N^{12}-Hydroxy-11-isobutyl-2,10-dioxo-N^8-[2-(2-pyridinyl)ethyl]-1-oxa-3,9-diazacyclopentadecane-8,-12-dicarboxamide (68i): ^{1}H NMR (DMSO-d_6) δ 10.47 (s, 1H), 8.77 (s, 1H), 8.45 (m, 1H), 8.02 (d, 1H), 7.64 (m, 2H), 7.18 (m, 2H), 6.90 (t, 1H), 4.13 (m, 2H), 3.88 (m, 1H), 3.34 (m, 2H), 3.08−2.87 (m, 2H), 2.78 (t, 2H), 2.42 (m, 1H), 1.90 (m, 1H), 1.60−1.03 (m, 12H), 0.83 (m, 1H), 0.75 (d, 3H), 0.69 (d, 3H); MS (ESI) *m/z* 506.4 $(M + H)^+$. Anal. ($C_{25}H_{39}N_5O_6 \cdot HCl \cdot H_2O$) C, H, N.

(8*S*,11*R*,12*S*)-N^{12}-Hydroxy-11-isobutyl-N^8-[2-(6-methoxy-1*H*-indol-3-yl)ethyl]-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68j): ^{1}H NMR (DMSO-d_6) δ 10.60 (s, 1H), 10.46 (s, 1H), 8.75 (s, 1H), 8.06 (m, 1H), 7.57 (m, 1H), 7.21 (d, 1H), 7.07 (s, 1H), 6.99 (s, 1H), 6.70 (m, 1H), 6.68 (d, 1H), 4.21 (m, 1H), 4.19 (m, 2H), 3.91 (m, 1H), 3.73 (s, 3H), 3.30 (m, 2H), 3.01 (m, 1H), 2.92 (m, 1H), 2.71 (m, 2H), 2.01 (m, 1H), 1.39−1.23 (m, 12H), 0.96 (m, 1H), 0.80 (d, 3H), 0.72 (d, 3H); HRMS (FAB) *m/z*. 574.325412 [$(M + H)^+$ calcd for $C_{29}H_{44}N_5O_7$ 574.325924]. Anal. ($C_{29}H_{43}N_5O_7 \cdot 0.1CF_3CO_2H$) C, H, N.

(8*S*,11*R*,12*S*)-N^{12}-Hydroxy-11-isobutyl-N^8-[2-(5-methoxy-1*H*-indol-3-yl)ethyl]-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68k): ^{1}H NMR (DMSO-d_6) δ 10.57 (s, 1H), 10.48 (s, 1H), 8.77 (s, 1H), 8.06 (m, 1H), 7.60

(m, 1H), 7.34 (m, 1H), 6.96 (s, 1H), 6.89 (m, 1H), 6.82 (s, 1H), 6.63 (m, 1H), 4.21 (m, 1H), 4.19 (m, 2H), 3.91 (m, 1H), 3.73 (s, 3H), 3.30 (m, 2H), 3.01 (m, 1H), 2.92 (m, 1H), 2.71 (m, 2H), 2.01 (m, 1H), 1.39−1.23 (m, 12H), 0.96 (m, 1H), 0.80 (d, 3H), 0.72 (d, 3H); HRMS (FAB) *m/z* 574.324074 [(M + H)$^+$ calcd for $C_{29}H_{44}N_5O_7$ 574.324279]. Anal. ($C_{29}H_{43}N_5O_7 \cdot 0.7H_2O$) C, H, N.

(8*S*,11*R*,12*S*)-*N*^{8}-[2-(5-Fluoro-1*H*-indol-3-yl)ethyl]-*N*^{12}-hydroxy-11-isobutyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68l): ^{1}H NMR (DMSO-d_6) δ 10.76 (s, 1H), 10.41 (s, 1H), 8.63 (s, 1H), 8.01 (s, 1H), 7.50 (m, 2H), 7.10 (m, 2H), 6.84 (s, 1H), 6.79 (s, 1H), 4.02 (m, 2H), 3.94 (m, 2H), 3.31 (m, 2H), 3.01 (m, 1H), 2.94 (m, 1H), 2.77 (m, 2H), 2.01 (m, 1H), 1.39−1.30 (m, 12H), 0.96 (m, 1H), 0.81 (d, 3H), 0.74 (d, 3H); HRMS (FAB) *m/z* 562.308110 [(M + H)$^+$ calcd for $C_{28}H_{41}FN_5O_6$ 562.306285]. Anal. ($C_{28}H_{40}FN_5O_6 \cdot 0.6CF_3CO_2H$) C, H, N.

(8*S*,11*R*,12*S*)-*N*^{12}-Hydroxy-11-isobutyl-*N*^{8}-[2-(5-methyl-1*H*-indol-3-yl)ethyl]-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68m): ^{1}H NMR (DMSO-d_6) δ 10.51 (s, 1H), 10.41 (s, 1H), 8.62 (s, 1H), 7.93 (s, 1H), 7.45 (s, 1H), 7.27 (s, 1H), 7.19 (s, 1H), 7.04 (s, 1H), 6.89 (s, 1H), 6.70 (s, 1H), 4.25 (m, 2H), 3.94 (m, 2H), 3.28 (m, 2H), 3.05 (m, 1H), 2.96 (m, 1H), 2.75 (m, 2H), 2.36 (s, 3H), 2.01 (m, 1H), 1.40−1.31 (m, 12H), 0.94 (m, 1H), 0.82 (d, 3H), 0.76 (d, 3H); HRMS (FAB) *m/z* 558.329160 [(M + H)$^+$ calcd for ($C_{29}H_{44}N_5O_6$)-558.327853]. Anal. ($C_{29}H_{43}N_5O_6 \cdot 0.8CF_3CO_2H$) C, H, N.

(8*S*,*11R*,*12S*)-*N*^{12}-Hydroxy-*N*^{8}-(2-hydroxy-2-phenylethyl)-11-isobutyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68n): ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 1H), 8.80 (s, 1H), 8.10 (d, 1H), 7.60 (t, 1H), 7.30 (m, 5H), 6.95 (t, 1H), 5.45 (m, 1H), 4.55 (m, 1H), 4.20 (m, 1H), 4.00 (m, 2H), 3.25 (m, 2H), 3.00 (m, 2H), 2.45 (m, 1H), 2.00 (m, 1H), 1.6−1.2 (m, 13H), 0.80 (m, 6H); MS (ESI) *m/z* 543.2 (M + Na)$^+$. Anal. ($C_{26}H_{40}N_4O_7 \cdot 0.7H_2O$) C, H, N.

Ethyl 4-[({(8*S*,11*R*,12*S*)-12-[(Hydroxyamino)carbonyl]-11-isobutyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecan-8-yl}carbonyl)amino]-1-piperidinecarboxylate (68o): ^{1}H NMR (DMSO-d_6) δ 10.40 (s, 1H), 8.62 (s, 1H), 7.93 (m, 1H), 7.28 (s, 1H), 6.70 (s, 1H), 4.23 (m, 2H), 4.05 (q, 2H), 3.99 (m, 1H), 3.83 (m, 2H), 3.79 (m, 1H), 3.05 (m, 1H), 2.96 (m, 3H), 2.00 (m, 1H), 1.71 (m, 2H), 1.69(m, 2H), 1.54−1.19 (m, 13H), 1.17 (t, 3H), 0.96 (m, 1H), 0.82 (d, 3H), 0.76 (d, 3H); HRMS (FAB) *m/z*. 556.334639 [(M + H)$^+$ calcd for $C_{26}H_{46}N_5O_8$ 556.334280]. Anal. ($C_{26}H_{45}N_5O_8$) C, H, N.

(8*S*,11*R*,12*S*)-*N*^{12}-Hydroxy-*N*^{8}-[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]-11-isobutyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68p): ^{1}H NMR (DMSO-d_6) δ 10.47 (s, 1H), 8.77 (s, 1H), 8.26 (d, 1H), 7.37 (t, 1H), 7.19−7.05 (m, 3H), 6.98 (d, 1H), 6.93 (t, 1H), 5.13 (m, 1H), 4.97 (d, 1H), 4.40−4.10 (m, 3H), 3.88 (m, 1H), 3.08−2.82 (m, 2H), 3.00 (dd, 1H), 2.75 (d, 1H), 2.45 (m, 1H), 1.92 (m, 1H), 1.62 (m, 3H), 1.47−1.11 (m, 9H), 0.69 (m 1H), 0.64 (d, 3H), 0.55 (d, 3H); MS (ESI) *m/z* 555.4 (M + Na)$^+$. Anal. ($C_{27}N_{40}N_4O_7$) C, H, N.

(8*S*,*11R*,*12S*)-*N*^{12}-Hydroxy-*N*^{8}-[(1R,2S)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]-11-isobutyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68q): ^{1}H NMR (DMSO-d_6) δ 10.48 (s, 1H), 8.78 (s, 1H), 8.26 (d, 1H), 7.42 (t, 1H), 7.21−7.01 (m, 4H), 6.92 (t, 1H), 5.07 (m, 1H), 4.98 (d, 1H), 4.34 (m, 2H), 4.18 (m, 1H), 3.89 (m, 1H), 3.11−2.85 (m, 2H), 2.99 (dd, 1H), 2.73 (d, 1H), 2.45 (m, 1H), 1.95 (m, 1H), 1.62 (m, 3H), 1.45−1.11 (m, 9H), 0.83 (m 1H), 0.72 (d, 3H), 0.65 (d, 3H); MS (ESI) *m/z* 555.4 (M + Na)$^+$. Anal. ($C_{27}H_{40}N_4O_7$) C, H, N.

(8*S*,*11R*,*12S*)-*N*^{12}-Hydroxy-11-isobutyl-2,10-dioxo-*N*^{8}-[(2*S*)-tetrahydro-2-furanylmethyl]-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68r): ^{1}H NMR (DMSO-d_6) δ 10.52 (s, 1H), 8.83 (s, 1H), 8.13 (d, 1H), 7.51 (t, 1H), 6.95 (t, 1H), 4.23 (m, 2H), 3.92 (m, 1H), 3.73 (m, 2H), 3.57−2.82 (m, 6H), 2.41 (m, 1H), 1.94 (m, 1H), 1.79 (m, 3H), 1.58−1.16 (m, 12H), 0.88 (m, 1H), 0.82 (d, 3H), 0.75 (d, 3H); MS (ESI) *m/z* 507.4 (M + Na)$^+$. Anal. ($C_{23}N_{40}N_4O_7$) C, H, N.

(8*S*,*11R*,*12S*)-*N*^{12}-Hydroxy-11-isobutyl-2,10-dioxo-*N*^{8}-[(2*R*)-tetrahydro-2-furanylmethyl]-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68s): ^{1}H NMR (DMSO-d_6) δ 10.53 (s, 1H), 8.78 (s, 1H), 8.07 (d, 1H), 7.51 (t, 1H), 6.91 (t, 1H), 4.16 (m, 2H), 3.89 (m, 1H), 3.71 (m, 3H), 3.57 (m, 1H), 3.15−2.80 (m, 4H), 2.45 (m, 1H), 1.94 (m, 1H), 1.76 (m, 3H), 1.60−1.05 (m, 12H), 0.84 (m, 1H), 0.77 (d, 3H), 0.71 (d, 3H); MS (ESI) *m/z* 507.4 (M + Na)$^+$. Anal. ($C_{23}N_{40}N_4O_7$) C, H, N.

(*8S*,*11R*,*12S*)-*N*^{12}-Hydroxy-11-isobutyl-*N*^{8}-[2-(methylamino)-2-oxoethyl]-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68t): ^{1}H NMR (DMSO-d_6) δ 10.51 (s, 1H), 8.82 (s, 1H), 8.23 (d, 1H), 7.93 (t, 1H), 7.73 (m, 1H), 6.97 (t, 1H), 4.19 (m, 2H), 3.94 (m, 1H), 3.61 (d, 2H), 3.11−2.88 (m, 2H), 2.56 (d, 3H), 2.52 (m, 1H), 1.98 (m, 1H), 1.64−1.16 (m, 12H), 0.86 (m 1H), 0.81 (d, 3H), 0.74 (d, 3H); MS (ESI) *m/z* 494.3 (M + Na)$^+$. Anal. ($C_{21}H_{37}N_5O_7$) C, H, N.

(8*S*,*11R*,*12S*)-*N*^{12}-Hydroxy-11-isobutyl-*N*^{8}-[(1*S*)-1-methyl-2-(methylamino)-2-oxoethyl]-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68u): ^{1}H NMR (DMSO-d_6) δ 10.51 (s, 1H), 8.82 (s, 1H), 8.17 (d, 1H), 7.84 (m, 1H), 7.54 (m, 1H), 6.95 (t, 1H), 4.16 (m, 2H), 4.01−3.79 (m, 2H), 3.11−2.84 (m, 2H), 2.56 (d, 3H), 2.49 (m, 1H), 1.95 (m, 1H), 1.64−1.15 (m, 12H), 1.13 (d, 3H), 0.88 (m 1H), 0.81 (d, 3H), 0.74 (d, 3H); MS (ESI) *m/z* 508.4 (M + Na)$^+$. Anal. ($C_{22}H_{39}N_5O_7$) C, H, N.

(8*S*,*11R*,*12S*)-*N*^{12}-Hydroxy-11-isobutyl-*N*^{8}-{(1*S*)-3-methyl-1-[(methylamino)carbonyl]butyl}-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68v): ^{1}H NMR (DMSO-d_6) δ 10.51 (s, 1H), 8.82 (s, 1H), 8.14 (d, 1H), 7.89 (m, 1H), 7.54 (m, 1H), 6.94 (t, 1H), 4.22 (m, 3H), 3.92 (m, 1H), 3.16−2.84 (m, 2H), 2.54 (d, 3H), 2.47 (m, 1H), 1.95 (m, 1H), 1.62−1.17 (m, 15H), 0.91−0.73 (m, 13H); MS (ESI) *m/z* 550.4 (M + Na)$^+$. Anal. ($C_{25}H_{45}N_5O_7 \cdot 0.1H_2O$) C, H, N.

***tert*-Butyl (5*S*)-5-[({(8*S*,11*R*,12*S*)-12-[(Hydroxyamino)carbonyl]-11-isobutyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecan-8-yl}carbonyl)amino]-6-(methylamino)-6-oxohexylcarbamate (68w)**: ^{1}H NMR (DMSO-d_6) δ 10.52 (s, 1H), 8.82 (s, 1H), 8.17 (d, 1H), 7.87 (m, 1H), 7.47 (m, 1H), 6.95 (t, 1H), 6.76 (t, 1H), 4.19 (m, 3H), 3.93 (m, 1H), 3.16−2.76 (m, 4H), 2.55 (d, 3H), 2.47 (m, 1H), 1.95 (m, 1H), 1.64−1.02 (m, 27H), 0.88 (m, 1H), 0.81 (d, 3H), 0.74 (d, 3H); MS (ESI) *m/z* 665.5 (M + Na)$^+$. Anal. ($C_{30}H_{54}N_6O_9$) C, H, N.

(8*S*,11*R*,12*S*)-*N*^{8}-{(1*S*)-2,2-Dimethyl-1-[(methylamino)carbonyl]propyl}-*N*^{12}-hydroxy-11-isobutyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68x) ^{1}H NMR (DMSO-d_6) δ 10.52 (s, 1H), 8.82 (s, 1H), 8.31 (d, 1H), 7.97 (m, 1H), 7.26 (m, 1H), 6.95 (t, 1H), 4.23 (m, 2H), 4.15 (d, 1H), 3.93 (m, 1H), 3.14−2.83 (m, 2H), 2.55 (d, 3H), 2.48 (m, 1H), 1.97 (m, 1H), 1.64−1.17 (m, 12H), 0.86−0.82 (m 13H), 0.74 (d, 3H); MS (ESI) *m/z* 550.4 (M + Na)$^+$. Anal. ($C_{25}H_{45}N_5O_7 \cdot 0.25H_2O$) C, H, N.

(8*S*,*11R*,*12S*)-*N*^{8}-[2-(2,6-Dimethyl-4-morpholinyl)-2-oxoethyl]-*N*^{12}-hydroxy-11-isobutyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68z): ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 1H), 8.15 (d, 1H), 7.65 (t, 1H), 6.95 (t, 1H), 4.2−3.3 (m, 11H), 3.00 (m, 2H), 2.30 (m, 1H), 2.00 (m, 1H), 1.6−1.2 (m, 12 H), 1.10 (d, 6H), 0.90−0.70 (m, 7H); MS (ESI) *m/z* 556.3 (M + H)$^+$. Anal. ($C_{26}H_{45}N_5O_8 \cdot 0.5H_2O$) C, H, N.

(8*S*,*11R*,*12S*)-*N*^{12}-Hydroxy-11-isobutyl-*N*^{8}-[2-(4-methyl-1-piperazinyl)-2-oxoethyl]-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68aa): ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 1H), 10.00 (br, 1H), 8.15 (d, 1H), 7.72 (t, 1H), 6.95 (t, 1H), 4.2−3.9 (m, 5H), 3.8−3.2 (m, 6H), 3.1−2.9 (m, 4H), 2.80 (s, 3H), 2.46 (m, 1H), 2.00 (m, 1H), 1.6−1.1 (m, 12H), 0.90−0.70 (m, 7H); MS (ESI) *m/z* 541.3 (M + H)$^+$. Anal. ($C_{25}H_{44}N_6O_7 \cdot 1.4CF_3CO_2H$) C, H, N.

(8*S*,*11R*,*12S*)-*N*^{12}-Hydroxy-11-isobutyl-2,10-dioxo-*N*^{8}-[2-oxo-2-(4-phenyl-1- piperazinyl)ethyl]-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68bb): ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 1H), 8.20 (d, 1H), 7.75 (t, 1H), 7.22 (m, 2H), 6.98 (m, 3H), 6.82 (t, 1H), 4.2−3.8 (m, 5H), 3.60 (m, 4H), 3.15 (m, 4H), 3.00 (m, 2H), 2.46 (m, 1H), 2.00 (m, 1H), 1.6−1.2 (m,

12H), 0.90−0.75 (m, 7H); MS (ESI) *m/z* 603.4 $(M + H)^+$. Anal. ($C_{30}H_{46}N_6O_7 \cdot 0.5CF_3CO_2H$) C, H, N.

(8*S*,11*R*,12*S*)-*N*^{12}-Hydroxy-11-isobutyl-2,10-dioxo-*N*^{8}-{2-oxo-2-[4-(2-pyridinyl)-1-piperazinyl]ethyl}-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68cc): ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 1H), 8.20 (d, 1H), 8.15 (d, 1H), 7.75 (t, 1H), 7.55 (t, 1H), 6.95 (t, 1H), 6.82 (d, 1H), 6.65 (t, 1H), 4.3−3.8 (m, 5H), 3.50 (m, 8H), 3.00 (m, 2H), 2.46 (m, 1H), 2.00 (m, 1H), 1.6−1.2 (m, 12H), 0.90−0.75 (m, 7H); MS (ESI) *m/z* 604.4 $(M + H)^+$. Anal. ($C_{29}H_{45}N_7O_7 \cdot CF_3CO_2H \cdot 0.5H_2O$) C, H, N.

Ethyl 4-{[({(8*S*,11*R*,12*S*)-12-[(Hydroxyamino)carbonyl]-11-isobutyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecan-8-yl}carbonyl)amino]acetyl}-1-piperazinecarboxylate (68dd): ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 1H), 8.18 (d, 1H), 7.75 (t, 1H), 6.95 (t, 1H), 4.4 (m, 1H), 4.20 (m, 2H), 4.02 (q, 2H), 3.95 (m, 2H), 3.40 (m, 8H), 3.00 (m, 2H), 2.45 (m, 1H), 2.00 (m, 1H), 1.6−1.2 (m, 12 H), 1.18 (t, 3H), 0.90−0.70 (m, 7H); MS (ESI) *m/z* 599.4 $(M + H)^+$. Anal. ($C_{27}H_{46}N_6O_9 \cdot 0.2CF_3CO_2H$) C, H, N.

(8*S*,11*R*,12*S*)-*N*^{12}-Hydroxy-*N*^{8}-[2-(4-hydroxy-1-piperidinyl)-2-oxoethyl]-11-isobutyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68ee): ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 1H), 8.18 (d, 1H), 7.62 (m, 1H), 6.95 (m, 1H), 4.20 (m, 2H), 3.90 (m, 3H), 3.60 (m, 2H), 3.05 (m, 6H), 2.45 (m, 1H), 2.00 (m, 1H), 1.7−1.2 (m, 16H), 0.90−0.75 (m, 7H); MS (ESI) *m/z* 542.4 $(M + H)^+$. Anal. ($C_{25}H_{43}N_5O_8 \cdot H_2O$) C, H, N.

(8*S*,11*R*,12*S*)-*N*^{12}-Hydroxy-11-isobutyl-*N*^{8}-{2-[4-(1-piperidinyl)-1-piperidinyl]-2-oxoethyl}-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68ff): ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 1H), 9.20 (br, 1H), 8.20 (d, 1H), 7.65 (t, 1H), 6.95 (t, 1H), 4.45 (m, 1H), 4.20 (m, 2H), 3.95 (m, 6H), 3.40 (m, 3), 3.00 (m, 4H), 2.55 (m, 1H), 2.00 (m, 1H), 1.8−1.2 (m, 22H), 0.90−0.75 (m, 7H); MS (ESI) *m/z* 609.4 $(M + H)^+$. Anal. ($C_{30}H_{52}N_6O_7 \cdot 1.9CF_3CO_2H$) C, H, N.

1-{[({(8*S*,11*R*,12*S*)-12-[(Hydroxyamino)carbonyl]-11-isobutyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecan-8-yl}carbonyl)amino]acetyl}-4-piperidinecarboxylic Acid (68gg): ^{1}H NMR (DMSO-d_6) δ 10.45 (s, 1H), 8.10 (d, 1H), 7.60 (t, 1H), 6.90 (t, 1H), 4.10 (m, 3H), 4.0−3.6 (m, 6H), 3.0−2.8 (m, 3H), 2.0−1.7 (m, 2H), 1.6−1.1 (m, 16H), 0.85−0.68 (m, 7H); MS (ESI) *m/z* 592.3 $(M + Na)^+$. Anal. ($C_{26}H_{43}N_5O_9 \cdot 0.4CF_3CO_2H$) C, H, N.

1-{[({(8*S*,11*R*,12*S*)-12-[(Hydroxyamino)carbonyl]-11-isobutyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecan-8-yl}carbonyl)amino]acetyl}-3-piperidinecarboxylic Acid (68hh): ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 1H), 8.18 (m, 1H), 7.62 (m, 1H), 6.95 (m, 1H), 4.2−3.6 (m, 9H), 3.3−2.7 (m, 3H), 2.40−1.8 (m, 4H), 1.7−1.2 (m, 14H), 0.90−0.75 (m, 7H); MS (ESI) *m/z* 592.2 $(M + Na)^+$. Anal. ($C_{26}H_{43}N_5O_9 \cdot 0.5CF_3CO_2H$) C, H, N.

(8*S*,11*R*,12*S*)-*N*^{12}-Hydroxy-11-isobutyl-*N*^{8}-[(1*S*)-1-methyl-2-(4-morpholinyl)-2-oxoethyl]-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68ii): ^{1}H NMR (DMSO-d_6) δ 10.52 (s, 1H), 8.80 (s, 1H), 8.20 (d, 1H), 7.74 (d, 1H), 6.95 (t, 1H), 4.70 (m, 1H), 4.20 (m, 2H), 3.95 (m, 1H), 3.50 (m, 8H), 3.00 (m, 2H), 2.46 (m, 1H), 2.00 (m, 1H), 1.6−1.2 (m, 12H), 1.08 (d, 3H), 0.90−0.75 (m, 7H); MS (ESI) *m/z* 564.3 $(M + Na)^+$. Anal. ($C_{25}H_{43}N_5O_8 \cdot 0.5H_2O$) C, H, N.

(8*S*,11*R*,12*S*)-*N*^{12}-Hydroxy-*N*^{8}-[(1*S*)-1-(hydroxymethyl)-2-(4-morpholinyl)-2-oxoethyl]-11-isobutyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68jj) ^{1}H NMR (DMSO-d_6) δ 10.52 (s, 1H), 8.18 (d, 1H), 7.60 (d, 1H), 6.95 (t, 1H), 4.75 (m, 1H), 4.20 (m, 2H), 3.90 (m, 2H), 3.50 (m, 10H), 3.00 (m, 2H), 2.46 (m, 1H), 2.00 (m, 1H), 1.6−1.2 (m, 12H), 0.90−0.75 (m, 7H); MS (ESI) *m/z* 570.2 $(M + Na)^+$. Anal. ($C_{25}H_{43}N_5O_9 \cdot 0.4CF_3CO_2H$) C, H, N.

(8*S*,*11R*,*12S*)-*N*^{12}-Hydroxy-11-isobutyl-*N*^{8}-[3-(4-morpholinyl)-3-oxopropyl]-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (68kk): ^{1}H NMR (DMSO-d_6) δ 10.52 (s, 1H), 8.10 (d, 1H), 7.56 (t, 1H), 6.95 (t, 1H), 4.20 (m, 1H), 3.9 (m, 2H), 3.6−3.2 (m, 8H), 3.15 (m, 2H), 3.00 (m, 2H), 2.45 (m, 3H), 2.00 (m, 1H), 1.6−1.2 (m, 12H), 0.90−0.75 (m, 7H); MS (ESI) *m/z* 564.3 $(M + Na)^+$. Anal. ($C_{25}H_{43}N_5O_8 \cdot 0.5H_2O$) C, H, N.

(8*S*,*11R*,*12S*)-*N*^{12}-Hydroxy-11-isobutyl-*N*^{8},3-dimethyl-2,10-dioxo-1-oxa-3,9- diazacyclopentadecane-8,12-dicarboxamide (69a): ^{1}H NMR (DMSO-d_6) δ 10.55 (s, 1H), 8.30 (d, 1H), 7.40 (m, 1H), 4.30 (m, 1H), 4.00 (m, 1H), 3.70 (m, 1H), 3.30 (m, 1H), 3.00 (m, 1H), 2.76 (s, 3H), 2.55 (d, 3H), 2.45 (m, 1H), 2.05 (m, 1H), 1.7−1.1 (m, 12H), 0.90−0.75 (m, 7H); MS (ESI) *m/z* 429.4 $(M + H)^+$. Anal. ($C_{20}H_{36}N_4O_6 \cdot 0.2H_2O$) C, H, N.

(8*S*,*11R*,*12S*)-*N*^{12}-Hydroxy-11-isobutyl-3-methyl-*N*^{8}-[2-(4-morpholinyl)-2-oxoethyl]-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (69b): ^{1}H NMR (DMSO-d_6) δ 10.55 (s, 1H), 8.32 (d, 1H), 7. 75 (m, 1H), 4.40 (m, 1H), 4.00 (m, 2H), 3.70 (m, 2H), 3.60 (m, 4H), 3.40 (m, 5H), 3.00 (m, 1H), 2.80 (s, 3H), 2.45 (m, 1H), 2.02 (m, 1H), 1.7−1.2 (m, 12H), 0.90−0.75 (m, 7H); MS (ESI) *m/z* 542.3 $(M + H)^+$. Anal. ($C_{25}H_{43}N_5O_8 \cdot 0.2CF_3CO_2H$) C, H, N.

(8*S*,*11R*,*12S*)-*N*^{12}-Hydroxy-*N*^{8}-[2-(4-hydroxy-1-piperidinyl)-2-oxoethyl]-11-isobutyl-3-methyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (69c): ^{1}H NMR (DMSO-d_6) δ 10.05 (s, 1H), 8.30 (d, 1H), 7.65 (t, 1H), 4.70 (m, 1H), 4.40 (m, 1H), 4.00 (m, 3H), 3.80 (m, 2H), 3.30 (m, 2H), 3.02 (m, 4H), 2.80 (s, 3H), 2.45 (m, 1H), 2.00 (m, 1H), 1.8−1.2 (m, 16H), 0.90−0.75 (m, 7H); MS (ESI) *m/z* 556.5 $(M + H)^+$. Anal. ($C_{26}H_{45}N_5O_8 \cdot 0.5CF_3CO_2H \cdot 0.8H_2O$) C, H, N.

(8*S*,*11R*,*12S*)-*N*^{12}-Hydroxy-11-isobutyl-3-methyl-*N*^{8}-[2-(4-methyl-1-piperazinyl)-2-oxoethyl]-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (69d): ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 1H), 8.30 (d, 1H), 7.95 (t, 1H), 4.40 (m, 2H), 4.00 (m, 4H), 3.70 (m, 1H), 3.40 (m, 4H), 3.00 (m, 4H), 2.81 (s, 3H), 2.78 (s, 3H), 2.45 (m, 1H), 2.00 (m, 1H), 1.6−1.2 (m, 12H), 0.90−0.73 (m, 7H); MS (ESI) *m/z* 555.5 $(M + H)^+$. Anal. ($C_{26}H_{46}N_6O_7 \cdot CF_3CO_2H \cdot 1.5H_2O$) C, H, N.

Ethyl 4-{[({(8*S*,11*R*,12*S*)-12-[(Hydroxyamino)carbonyl]-11-isobutyl-3-methyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecan-8-yl}carbonyl)amino]acetyl}-1-piperazinecarboxylate (69e): ^{1}H NMR (DMSO-d_6) δ 10.55 (s, 1H), 8.20 (d, 1H), 7.60 (d, 1H), 4.35 (m, 1H), 4.00 (m, 3H), 3.8−3.6 (m, 5H), 3.00 (m, 3H), 2.75 (s, 3H), 2.40 (m, 1H), 2.00 (m, 1H), 1.7−1.0 (m, 19H), 0.88−0.70 (m, 7H); MS (ESI) *m/z* 570.5 $(M + H)^+$. Anal. ($C_{27}H_{47}N_5O_8 \cdot 0.5CF_3CO_2H \cdot H_2O$) C, H, N.

(8*S*,11*R*,12*S*)-*N*^{8}-[2-(Dimethylamino)-2-oxoethyl]-*N*^{12}-hydroxy-11-isobutyl-3-methyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (69f): ^{1}H NMR (DMSO-d_6) δ 10.50 (s, 1H), 8.25 (d, 1H), 7.60 (t, 1H), 4.40 (m, 1H), 4.00 (m, 2H), 3.80 (m, 2H), 3.35 (m, 1H), 3.00 (m, 1H), 2.92 (s, 3H), 2.82 (s, 3H), 2.78 (s, 3H), 2.45 (m, 1H), 2.00 (m, 1H), 1.7−1.1 (m, 12H), 0.90−0.75 (m, 7H); MS (ESI) *m/z* 500.5 $(M + H)^+$. Anal. ($C_{23}H_{41}N_5O_7 \cdot 0.2CF_3CO_2H$) C, H, N.

(8*S*,11*R*,12*S*)-*N*^{12}-Hydroxy-11-isobutyl-3-methyl-2,10-dioxo-*N*^{8}-[2-oxo-2-(1- pyrrolidinyl)ethyl]-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (69g): ^{1}H NMR (DMSO-d_6) δ 10.55 (s, 1H), 8.32 (d, 1H), 7.70 (t, 1H), 4.42 (m, 1H), 4.02 (m, 2H), 3.80 (m, 2H), 3.30 (m, 5H), 3.00 (m, 1H), 2.80 (s, 3H), 2.45 (m, 1H), 2.02 (m, 1H), 1.80 (m, 4H), 1.7−1.2 (m, 12H), 0.90−0.75 (m, 7H); MS (ESI) *m/z* 526.5 $(M + H)^+$. Anal. ($C_{25}H_{43}N_5O_7 \cdot H_2O$) C, H, N.

(8*S*,11*R*,12*S*)-*N*^{12}-Hydroxy-11-isobutyl-3-methyl-*N*^{8}-[2-(methylamino)-2-oxoethyl]-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (69h): ^{1}H NMR (DMSO-d_6) δ 10.55 (s, 1H), 8.35 (d, 1H), 7.90 (t, 1H), 7.75 (q, 1H), 4.40 (m, 1H), 4.05 (m, 1H), 3.75 (m, 1H), 3.60 (d, 2H), 3.30 (m, 1H), 3.00 (m, 1H), 2.80 (s, 3H), 2.60 (d, 3H), 2.45 (m, 1H), 2.00 (m, 1H), 1.60 (m, 2H), 1.40 (m, 10H), 0.90−0.75 (m, 7H); MS (ESI) *m/z* 486.5 $(M + H)^+$. Anal. ($C_{22}H_{39}N_5O_7 \cdot 0.5CF_3CO_2H \cdot 0.4H_2O$) C, H, N.

(8*S*,*11R*,*12S*)-*N*^{8}-{(1*S*)-5-Amino-1-[(methylamino)carbonyl]pentyl}-*N*^{12}-hydroxy-11-isobutyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (70). To a solution of **68w** (51 mg, 0.079 mmol) in dioxane (1 mL) was added 4 N HCl in dioxane (2 mL). The solution was stirred at room temperature for 9 h and concentrated. The residue was

triturated with MeOH/ether to provide **70** (38 mg, 82%) as an HCl salt: ^{1}H NMR (DMSO-d_6) δ 10.52 (s, 1H), 8.19 (d, 1H), 7.91 (m, 1H), 7.76 (bs, 3H), 7.58 (d, 1H), 6.95 (t, 1H), 4.16 (m, 2H), 3.82 (m, 2H), 3.09−2.85 (m, 2H), 2.73 (m, 2H), 2.56 (d, 3H), 2.47 (m, 1H), 1.95 (m, 1H), 1.66−1.04 (m, 18H), 0.88 (m, 1H), 0.81 (d, 3H), 0.74 (d, 3H); MS (ESI) *m/z* 543.4 $(M + H)^+$. Anal. ($C_{25}H_{46}N_6O_7$·HCl·0.6MeOH) C, H, N.

***tert*-Butyl (8*S*,11*R*,12*S*)-11-Isobutyl-8-({[4-(2-methoxy-2-oxoethyl)-1,3-thiazol-2-yl]amino}carbonyl)-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-12-carboxylate (71)**. To a solution of **66a** (0.7 g, 1.53 mmol) in THF (5 mL) was added a solution of 1 N LiOH (5 mL). The solution was stirred at room temperature for 1 h. EtOAc (50 mL) was added followed by 1 N HCl (10 mL). The organic phase was separated, washed with brine 3×, dried ($MgSO_4$), and concentrated. The residue was taken up in DMF (5 mL). To it were added methyl 2-amino-4-thiazoleacetate hydrochloride salt (0.58 g, 2.8 mmol), BOP (0.80 g, 1.8 mmol), and DIEA (1.74 mL, 10 mmol). The solution was stirred at room temperature overnight. EtOAc (100 mL) was added. The solution was washed with brine 2×, 10% citric acid 2×, brine 2×, $NaHCO_3$ 2×, and brine 2×, dried ($MgSO_4$), and concentrated. The residue was triturated with ether to give **71** (700 mg, 78%) as a solid: MS (ESI) *m/z* 619.1 $(M + Na)^+$.

Methyl {2-[({(8*S*,11*R*,12*S*)-12-[(Hydroxyamino)carbonyl]-11-isobutyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecan-8-yl}carbonyl)amino]-1,3-thiazol-4-yl}acetate (73). Compound **71** (700 mg, 1.2 mmol) was dissolved in TFA/CH_2Cl_2 (1:1, 30 mL). After the solution was stirred for 2 h at room temperature, the solvents were removed under reduced pressure. The residue was taken up in DMF (5 mL), and the solution was cooled in an ice bath. To it were added hydroxylamine hydrochloride (278 mg, 4 mmol), BOP (664 mg, 1.5 mmol), and DIEA (1.04 mL, 6 mmol). The solution was stirred for 2 h and concentrated under reduced pressure. The residue was triturated with ether. The resulting solid was purified by reversed-phase HPLC to provide **73** (240 mg, 33%) as a powder: ^{1}H NMR (DMSO-d_6) δ 12.20 (s, 1H), 10.50 (s, 1H), 8.30 (d, 1H), 7.00 (t, 1H), 6.95 (s, 1H), 4.43 (m, 1H), 4.10 (m, 2H), 3.65 (s, 3H), 3.60 (s, 2H), 3.00 (m, 2H), 2.42 (m, 1H), 2.02 (m, 1H), 1.6−1.1 (m, 12H), 0.88−0.70 (m, 7H); MS (ESI) *m/z* 578.3 $(M + Na)^+$.

{2-[({(8*S*,11*R*,12*S*)-12-[(Hydroxyamino)carbonyl]-11-isobutyl-2,10-dioxo-1-oxa-3,9-diazacyclopentadecan-8-yl}carbonyl)amino]-1,3-thiazol-4-yl}acetic Acid (75). To a solution of **73** (55 mg, 0.1 mmol) in THF (2 mL) was added 1 N LiOH (1 mL). The solution was stirred at room temperature for 2 h and acidified with 1 N HCl. The volatiles were removed under reduced pressure, and the residue was purified by reversed-phase HPLC to provide **75** (35 mg) as a powder: ^{1}H NMR (DMSO-d_6) δ 12.20 (s, 1H), 10.50 (s, 1H), 8.30 (d, 1H), 7.00 (t, 1H), 6.95 (s, 1H), 4.45 (m, 1H), 4.10 (m, 2H), 3.60 (s, 2H), 3.00 (m, 2H), 2.40 (m, 1H), 2.00 (m, 1H), 1.6−1.2 (m, 12H), 0.88−0.72 (m, 7H); MS (ESI) *m/z* 542.2 $(M+H)^+$. Anal. ($C_{23}H_{35}N_5O_8S$·0.3CF_3CO_2H·0.8H_2O) C, H, N.

(8*S*,11*R*,12*S*)-*N*^{12}-Hydroxy-11-isobutyl-*N*^{8}-{4-[2-(4-morpholinyl)-2-oxoethyl]-1,3-thiazol-2-yl}-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (76). To a solution of **75** (50 mg, 0.092 mmol), morpholine (40 mg, 0.46 mmol), and DIEA (35 μL, 0.2 mmol) in DMF (2 mL) cooled in an ice bath was added BOP (44 mg, 0.1 mmol). The mixture was stirred for 2 h and purified by reversed-phase HPLC to provide **76** (35 mg) as a powder: ^{1}H NMR (DMSO-d_6) δ 12.1 (s, 1H), 10.50 (s, 1H), 8.35 (d, 1H), 7.00 (t, 1H), 6.90 (s, 1H), 4.45 (m, 1H), 4.10 (m, 2H), 3.70 (s, 2H), 3.50 (m, 8H), 3.00 (m, 2H), 2.40 (m, 1H), 2.00 (m, 1H), 1.6−1.2 (m, 12H), 0.90−0.75 (m, 7H); MS (ESI) *m/z* 611.2 $(M + H)^+$. Anal. ($C_{27}H_{42}N_6O_8S$·0.4CF_3CO_2H·2H_2O) C, H, N.

The following compounds were prepared in a manner analogous to that described for **73**.

(8*S*,11*R*,12*S*)-*N*^{12}-Hydroxy-11-isobutyl-3-methyl-2,10-dioxo-*N*^{8}-[2-oxo-2-(2-pyridinylamino)ethyl]-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (74a): ^{1}H NMR (DMSO-d_6) δ 10.50 (m, 2H), 8.30 (m, 2H), 8.00 (m, 2H), 7.75 (t, 1H), 7.05 (m, 1H), 4.40 (m, 1H), 3.95 (m, 2H), 3.80 (m, 2H), 3.30 (m, 1H), 3.00 (m, 1H), 2.75 (s, 3H), 2.45 (m, 1H), 2.00 (m, 1H), 1.60 (m, 2H), 1.35 (m, 10H), 0.88−0.72 (m, 7H); MS (ESI) *m/z* 549.5 $(M + H)^+$. Anal. ($C_{26}H_{40}N_6O_7$·CF_3CO_2H·2.4H_2O) C, H, N.

(8*S*,11*R*,12*S*)-*N*^{12}-Hydroxy-11-isobutyl-3-methyl-*N*^{8}-{2-[(4-methyl-1,3-thiazol-2-yl)amino]-2-oxoethyl}-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (74b): ^{1}H NMR (DMSO-d_6) δ 12.05 (s, 1H), 10.55 (s, 1H), 8.80 (br, 1H), 8.30 (d, 1H), 8.00 (t, 1H), 7.76 (s, 1H), 4.45 (m, 1H), 4.00 (m, 2H), 3.80 (m, 2H), 3.30 (m, 1H), 3.05 (m, 1H), 2.80 (s, 3H), 2.46 (m, 1H), 2.23 (s, 3H), 2.02 (m, 1H), 1.63 (m, 2H), 1.5−1.2 (m, 10H), 0.90−0.75 (m, 7H); MS (ESI) *m/z* 569.3 $(M + H)^+$. Anal. ($C_{25}H_{40}N_6O_7S$·0.2CF_3CO_2H) C, H, N.

(8*S*,11*R*,12*S*)-*N*^{12}-Hydroxy-11-isobutyl-3-methyl-2,10-dioxo-*N*^{8}-(2-pyridinyl)-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (74c): ^{1}H NMR (DMSO-d_6) δ 10.55 (s, 1H), 10.35 (s, 1H), 8.45 (d, 1H), 8.30 (d, 1H), 8.00 (d, 1H), 7.80 (t, 1H), 7.10 (t, 1H), 4.65 (m, 1H), 4.05 (m, 1H), 3.95 (m, 1H), 3.40 (m, 1H), 3.02 (m, 1H), 2.80 (s, 3H), 2.45 (m, 1H), 2.00 (m, 1H), 1.70 (m, 2H), 1.5−1.2 (m, 10H), 0.90−0.75 (m, 7H); MS (ESI) *m/z* 492.5 $(M + H)^+$. Anal. ($C_{24}H_{37}N_5O_6$·CF_3CO_2H·0.5H_2O) C, H, N.

(8*S*,*11R*,*12S*)-*N*^{12}-Hydroxy-11-isobutyl-3-methyl-2,10-dioxo-*N*^{8}-(3-pyridinyl)-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (74d): ^{1}H NMR (DMSO-d_6) δ 10.58 (m, 2H), 8.95 (s, 1H), 8.50 (d, 1H), 8.42 (d, 1H), 8.20 (d, 1H), 7.65 (t, 1H), 4.40 (m, 1H), 4.05 (m, 1H), 3.80 (m, 1H), 3.40 (m, 1H), 3.05 (m, 1H), 2.80 (s, 3H), 2.45 (m, 1H), 2.05 (m, 1H), 1.70 (m, 2H), 1.5−1.2 (m, 10H), 0.9−0.7 (m, 7H); MS (ESI) *m/z* 492.4 $(M + H)^+$. Anal. ($C_{24}H_{37}N_5O_6$·CF_3CO_2H·0.8H_2O) C, H, N.

(8*S*,*11R*,*12S*)-*N*^{12}-Hydroxy-11-isobutyl-3-methyl-2,10-dioxo-*N*^{8}-(4-pyridinyl)-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (74e): ^{1}H NMR (DMSO-d_6) δ 11.47 (s, 1H), 10.55 (s, 1H), 8.70 (d, 2H), 8.60 (d, 1H), 8.05 (d, 2H), 4.40 (m, 1H), 4.05 (m, 1H), 3.90 (m, 1H), 3.40 (m, 1H), 3.05 (m, 1H), 2.80 (s, 3H), 2.55 (m, 1H), 2.20 (m, 1H), 1.75 (m, 2H), 1.5−1.2 (m, 10H), 0.9−0.7 (m, 7H); MS (ESI) *m/z* 492.4 $(M + H)^+$. Anal. ($C_{24}H_{37}N_5O_6$·CF_3CO_2H·1.5H_2O) C, H, N.

(8*S*,*11R*,*12S*)-*N*^{12}-Hydroxy-11-isobutyl-3-methyl-*N*^{8}-(4-methyl-1,3-thiazol-2-yl)-2,10-dioxo-1-oxa-3,9-diazacyclopentadecane-8,12-dicarboxamide (74f): ^{1}H NMR (DMSO-d_6) δ 12.00 (s, 1H), 10.55 (s, 1H), 8.45 (d, 1H), 6.75 (s, 1H), 4.60 (m, 1H), 4.00 (m, 2H), 3.30 (m, 1H), 3.00 (m, 1H), 2.80 (s, 3H), 2.40 (m, 1H), 2.20 (s, 3H), 2.00 (m, 1H), 1.65 (m, 2H), 1.5−1.2 (m, 10H), 0.9−0.7 (m, 7H); MS (ESI) *m/z* 512.4 $(M + H)^+$. Anal. ($C_{23}H_{37}N_5O_6S$·0.9CF_3CO_2H) C, H, N.

TACE and MMP Assays. The enzymatic activity of porcine TACE was determined at 25 °C with partially purified porcine enzyme and a synthetic fluorogenic substrate, Mca-Pro-Leu-Ala-Gln-Ala-Val-Dpa-Arg-Ser-Ser-Ser-Agr-NH_2. (Mca = [7-methoxycoumarin-4-yl]acetyl, Dpa = *N*-3-[2,4-dinitrophenyl]-L-2,3-diaminopropionyl). Partially purified TACE was obtained from porcine spleen following a previously described procedure.[14] The enzymatic activities of MMPs were determined with recombinant human version catalytic domains (CHEMICON International, Inc., 28835 Single Oak Dr., Temecula, CA 92590) and a fluorogenic peptide substrate, Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2.[43] The peptide substrate was diluted to a final concentration of 10 μM in a buffer containing 50 mM Tricine (pH 7.5), 100 mM NaCl, 10 mM $CaCl_2$, and 1 mM $ZnCl_2$. Final enzyme concentrations in the assay were between 0.05 and 10 nM depending on the enzyme and the potency of the inhibitor. Fluorescence measurements were performed in a CytoFluor multiwell plate reader, series 4000. Cleavage of internal quenched substrate liberates emission-active Mca product, causing an increase in fluorescence emission at 395 nM (the excitation wavelength is 330 nM). The rate of emission change is proportional to enzyme activity. Initial velocities, in the presence or absence of inhibitor, were measured as slopes of the linear portion of the product progress curves. Apparent K_i values were determined by plotting the inhibitor

concentration dependence of the fractional velocity for each enzyme, and fitting the data by a tight binding inhibition equation.[44]

TNF-α Human Whole Blood Assay. Blood is drawn from normal donors into tubes containing 143 USP units of heparin/10 mL. The heparinized human blood (225 μL) was plated directly into 1 mL sterile polypropylene tubes. Compounds were diluted in DMSO/serum-free medium and added to the blood samples so the final concentrations of the compounds were 50, 10, 5, 1, 0.5, 0.1, and 0.01 μM. The final concentration of DMSO did not exceed 0.5%. Compounds were preincubated for 15 min before the addition of 100 ng/mL LPS. Plates were incubated for 5 h in an atmosphere of 5% CO_2 in air. At the end of 5 h, 750 μL of serum-free medium was added to each tube and the samples were spun at 1200 rpm for 10 min. The supernatant was collected off the top and assayed for TNF-α production by a standard sandwich ELISA. The ability of the compounds to inhibit TNF-α production by 50% compared to DMSO-treated cultures was given by the IC_{50} value.

TNF-α Mouse Model Studies. Test compounds were administered to mice po at time zero. Immediately following compound administration, mice received an ip injection of 20 mg of D-galactosamine plus 10 μg of LPS. One hour later, animals were anesthetized and bled by cardiac puncture. Blood plasma was evaluated for TNF-α levels by an ELISA specific for mouse TNF-α.

Pharmacokinetic Studies of SL422 and SP057 in Beagle Dogs. Nine male beagle dogs weighing approximately 10 kg were studied. SL422 (0.74 mg/kg) and SP057 (0.50 mg/kg) each was dosed intravenously to two animals in a 10% ethanol solution, and blood samples were taken at 6, 15, and 30 min prior to dosing, and at 1, 2, 4, 6, 8, 12, and 24 h postdosing. Two dogs were administered orally with SL422 (0.863 mg/kg), and three dogs were administered orally with SP057 (2.2 mg/kg) in a 0.5% methocell suspension. Blood samples were taken at 15, 30, and 45 min prior to dosing and at 1, 2, 4, 6, 8, 12, and 24 h postdosing. Plasma concentrations were determined by LC/MS/MS following solid-phase extraction. The limit of detection was 10 nM. Pharmacokinetic parameters were calculated using WINNONLIN, and the data given are expressed as the mean.

Acknowledgment. We thank Sherrill A. Nurnberg, Dianna L. Blessington, Persymphonie B. Miller, Theresa M. Dimeo, John Giannaras, Robert J. Collins, Tracy L. Taylor, and Paul J. Strzemienski for performing the in vitro and in vivo studies, and Thomas A. Emm for the pharmacokinetic studies.

Supporting Information Available: Proton NMR spectral data of nontarget compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM010127E