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Design and synthesis of an orally active matrix metalloproteinase inhibitor

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Abstract—A series of 4-(4-phenoxy)benzoylamino-4-methoxymethyloxymethyl butyric acid hydroxamates, which were derived from L-glutamic acid, were synthesized and evaluated as matrix metalloproteinase inhibitors. Most of the compounds listed in Tables 1–3 exhibited strong inhibitory activity against MMP-2 and MMP-9, as well as even stronger inhibitory activity against MMP-3, but showed relatively weak inhibition of MMP-1. Structure–activity relationships are discussed.
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1. Introduction

Matrix metalloproteinases (MMPs) are postulated to regulate the homeostasis of a variety of tissues under the control of tissue inhibitors of metalloproteinases (TIMPs), which associate with and block the activity of MMPs. An imbalance between MMPs and their natural inhibitors (TIMPs) is believed to contribute to the manifestation of various pathological or physiological states involving the degradation of extracellular matrix (ECM) components, including osteoarthritis, rheumatoid arthritis, angiogenesis, cancer, pulmonary emphysema, corneal ulceration, rupture of atherosclerotic plaque, aortic aneurysm, and periodontal disease. For more than 30 years, MMPs have been heralded as promising targets for the treatment of such diseases.[1]

Nearly 20 members of this enzyme family, sharing significant sequence homology, have been reported.[2] They can be subdivided into: (1) collagenases (MMP-1, -8, -13, and -18); (2) gelatinases (MMP-2 and -9); (3) stromelysins (MMP-3, -10, and -11); and (4) membrane-type MMPs (MT-MMPs) (MMP-14, -15, -16, and -17).

Matrix metalloproteinase inhibitors (MMPIs) generally consist of two basic features, a zinc chelating ligand and a chemical moiety which binds the substrate recognition cleft of the enzyme. Widely utilized zinc binding moieties include: hydroxamic acid,[3] thiol,[4] carboxylic acid[5] phosphinic acid[6], and other chelators.[7] The structure with the substrate recognition site of MMPs has been designed from substrate of MMPs or structural information of MMP–inhibitor complex. Consequently, a large number of synthetic MMPIs have been reported.[8]

In our previous papers,we have reported on the discovery of a series of L-glutamic acid-based MMP inhibitors.[9] We have also reported that several *N*-benzoyl 4-aminobutyric acid hydroxamate analogs **1a**–**d** were identified as MMP inhibitors with increased activity against MMP-3.[10] Among them, the *N*-(4-phenoxy)benzoyl analogs exhibited relatively strong inhibitory activity against MMP-3 (stromelysin). In addition, we found that *N*-benzoyl 4-aminobutyric acid hydroxamate analogs with C2 or C4 substituents showed an increase of inhibitory activity against MMP-3 (Fig. 1).[10] Based on this information, C2 and C4 substitutions of **1a** were investigated to identify MMP inhibitors with strong inhibitory activity against MMP-3 as well as MMP-2 and MMP-9. We report here on the discovery of new orally active and L-glutamic acid-based MMP inhibitors that exhibit strong activity against MMP-3 in addition to MMP-2 and MMP-9.

Keywords: MMP; Matrix metalloproteinase inhibitor; Hydroxamate inhibitor; L-Glutamic acid.
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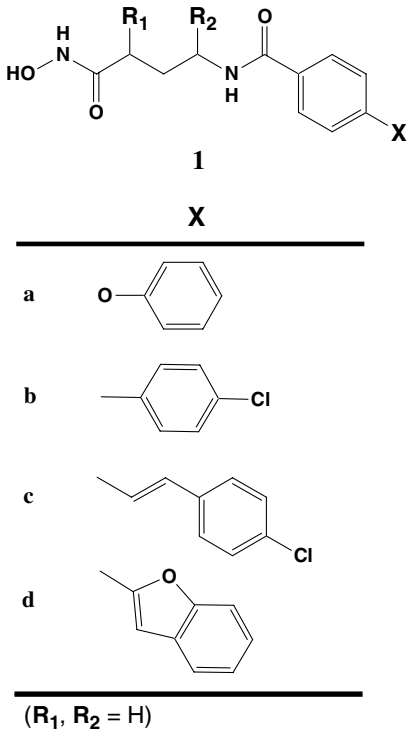


Figure 1. Structures with an increased inhibitory activity against MMP-3.

2. Chemistry

The test compounds listed in Tables 1–3 were synthesized as outlined in Schemes 1–6.

Synthesis of **2**–**15** is described in Scheme 1. Protection of the hydroxyl group of **24**[11] as a methoxymethyl ether gave **25**. Removal of the *N*-carbobenzyloxy group by a catalytic hydrogenation followed by N-acylation with a 4-phenoxybenzoic acid afforded **27**. Stereoselective C2-alkylation[12] of **25** resulted in **26a**–**e**. Catalytic hydrogenation followed by N-acylation with 4-phenoxybenzoic acid provided **28a**–**e**. Stereoselective C2-alkylation of **27** with an appropriate electrophile afforded **28f**–**g** and **i**–**m**, while catalytic hydrogenation of **28f** gave **28h**. Alkaline hydrolysis of **27** and **28a**–**m** led to their corresponding carboxylic acids. Condensation of **29a**–**l** and **29n** with O-protected hydroxylamine in the presence of EDC followed by acidic deprotection resulted in **2**–**12** and **14**, **15**, respectively. Condensation of **29m** with *O*-benzylhydroxylamine followed by catalytic hydrogenation produced **13**.

Synthesis of **16** and **19** is described in Scheme 2. Protection of the hydroxyl moiety of **24** as an ethoxymethyl ether and *tert*-butyldimethylsilyl ether afforded **30a** and **30b**, respectively. Stereoselective C2-methylation of **30a**,**b** provided **31a**,**b**. Deprotection of **31a**,**b** by catalytic hydrogenation followed by N-acylation with 4-phenoxybenzoic acid resulted in **32a**,**b**, respectively. Alkaline hydrolysis of **32a**,**b** provided the corresponding carboxylic acids **33a**,**b**, respectively. Condensation of **33a** with *O*-benzylhydroxylamine followed by deprotection via catalytic hydrogenation gave **16**. Condensation of **33b** with *O*-benzylhydroxylamine followed by deprotection with TBAF and catalytic hydrogenation resulted in **19**.

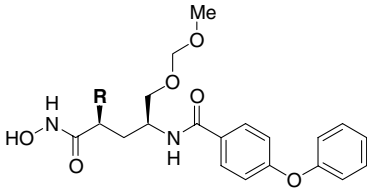
Synthesis of **17** and **18** is described in Scheme 3. Protection of the hydroxymethyl group of **34**[13] as a methoxyethoxymethylether or pivaloyl ester by conventional procedures gave **35a**,**b**, respectively. Stereoselective C2-alkylation of **35a**,**b** by the usual procedure afforded **36a**,**b**, respectively. Acidic deprotection of **36a**,**b** followed by N-acylation with 4-phenoxybenzoic acid led to production of **37a**,**b**, respectively. Catalytic hydrogenation of **37a**,**b** gave carboxylic acids **38a**,**b**, respectively. Condensation of **38a**,**b** with O-protected hydroxylamine followed by acidic deprotection resulted in **17** and **18**, respectively.

Synthesis of **20** is described in Scheme 4. C-Acylation of Meldrum's acid with **39** produced **40**, after which sodium borohydride reduction afforded **41**. Intramolecular cyclization and decarboxylation of **41** gave a five-membered lactam **42**, after which alkaline hydrolysis followed by esterification provided **43**. Acidic deprotection of **43** followed by N-acylation with 4-phenoxybenzoic acid resulted in **44**. Stereoselective C2-methylation followed by alkaline hydrolysis provided **46**, and condensation of **46** with O-protected hydroxylamine in the presence of EDC followed by acidic deprotection resulted in **20**.

Synthesis of **21** is described in Scheme 5. Acidic deprotection of **30a** followed by N-acylation with 4-phenoxybenzoic acid afforded **47**. Stereoselective C2-ethylation of **47** by the usual C-alkylation procedure provided **48**. Alkaline hydrolysis of **48** led to the corresponding carboxylic acid **49**, while condensation of **49** with *O*-benzylhydroxylamine in the presence of EDC followed by deprotection in the usual manner resulted in **21**.

Synthesis of **22** and **23** is described in Scheme 6. Acidic deprotection of **35a** followed by N-acylation with 4-phenoxybenzoic acid produced **50**. Stereoselective C2-ethylation of **50** by the usual C-alkylation procedure provided **52a**, while stereoselective C2-ethy-

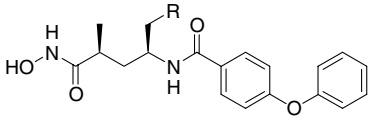
Table 1. Effect of the C2-substituent on the activity profiles of 4*S*-methoxymethyloxymethyl analogs

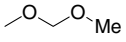
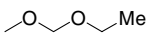
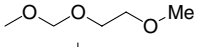
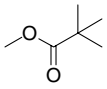


Compound	R	IC_{50}[a,b] (μM)			
		MMP-1	MMP-2	MMP-9	MMP-3
2	H	7.0	0.0035	0.0013	0.11
3	Me	2.8	0.0005	0.0013	0.047
4	Et	3.2	0.0011	0.0006	0.036
5	*n*-Pr	2.6	0.0017	0.0007	0.037
6	*i*-Bu	9.1	0.0035	0.0020	0.078
7	Bn	1.4	0.0005	0.0005	0.019
8	2-Pyridylmethyl	0.55	0.0007	0.0003	0.016
9	3-Pyridylmethyl	0.42	0.0006	0.0005	0.033
10	4-Pyridylmethyl	1.9	0.0004	0.0008	0.040
11	Allyl	1.5	0.0012	0.0007	0.018
12	1-Naphthylmethyl	0.95	0.0037	0.0015	0.029
13	CH_2CO_2-*t*-Bu	1.8	0.0017	0.0006	0.020
14	OH	5.8	0.0014	0.0031	0.11
15	SPh	2.4	0.0005	0.0005	0.0094

[a] Concentration required for 50% inhibition of enzyme activity.
[b] IC_{50} values were determined in a single experimental run in duplicate.

Table 2. Effect of the C4-substituent on the activity profiles of 2*S*-methyl analogs



Compound	R	IC_{50}[a,c] (μM)			
		MMP-1	MMP-2	MMP-9	MMP-3
3		2.8	0.0005	0.0013	0.047
16		2.5	0.0005	0.0008	0.026
17		2.6	0.0012	0.0005	0.038
18		NT[b]	0.0008	0.0014	0.065
19	OH	4.5	0.0007	0.0008	0.036
20	H	NT	0.071	0.11	6.4

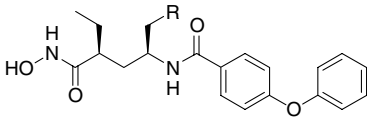
[a] Concentration required for 50% inhibition of enzyme activity.
[b] Not tested.
[c] IC_{50} values were determined in a single experimental run in duplicate.

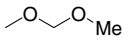
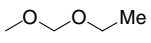
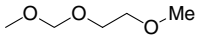
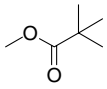
lation of **35b** afforded **51**. Acidic deprotection of **51** followed by N-acylation with 4-phenoxybenzoic acid led to **52b**. Catalytic hydrogenation of **52a**,**b** provided carboxylic acids **53a**,**b**, respectively. Condensation of **53a**,**b** with *O*-benzylhydroxylamine followed by catalytic hydrogenation resulted in **22** and **23**, respectively.

3. Results and discussion

The compounds listed in Tables 1–3 were tested for their inhibitory potency against MMP-1 (human collagenase), MMP-2 (human gelatinase A), MMP-9 (human gelatinase B), and MMP-3 (recombinant human stromelysin).[14]

Table 3. Effect of the C4-substituent on the activity profiles of 2*S*-ethyl analogs



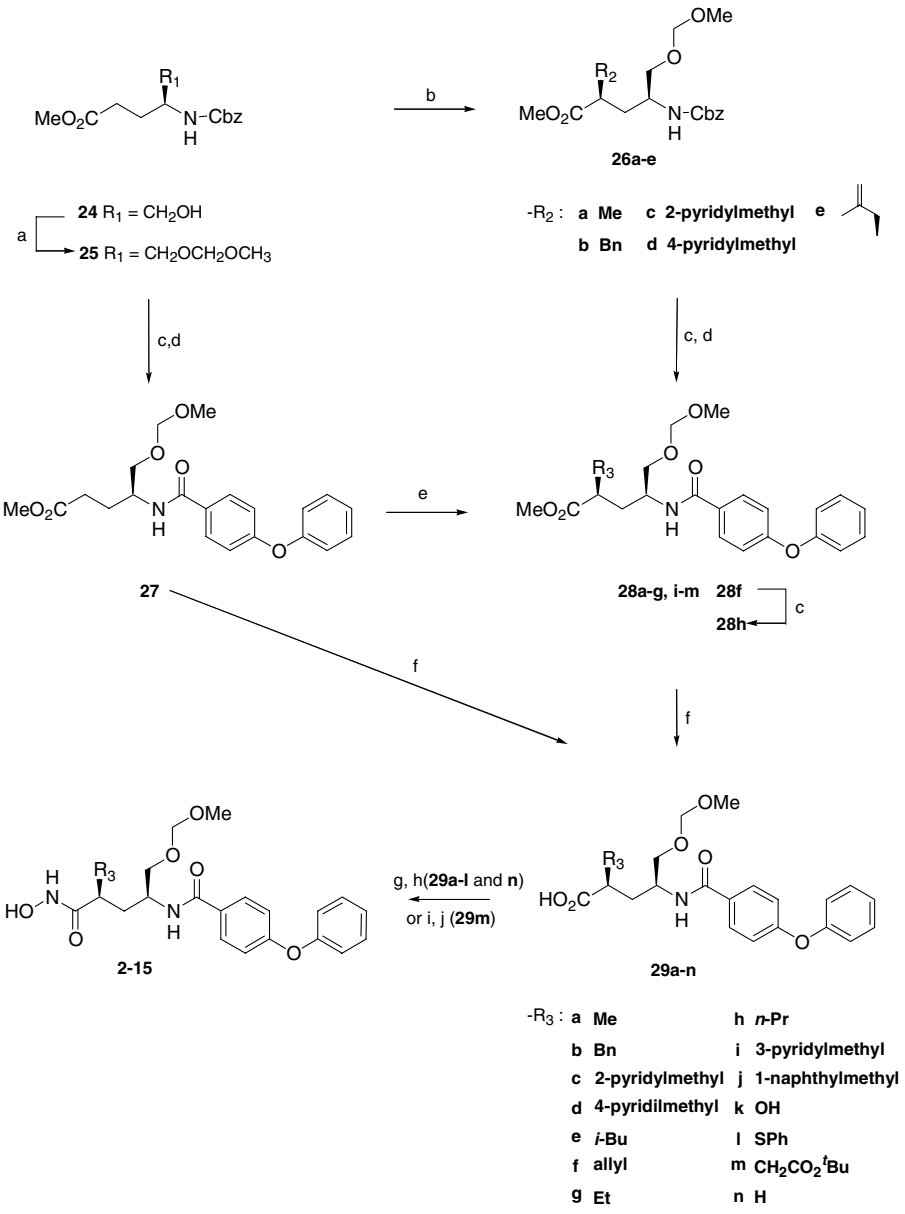
Compound	R	IC_{50} [a,b] (μM)			
		MMP-1	MMP-2	MMP-9	MMP-3
4		3.2	0.0011	0.0006	0.036
21		3.0	0.0005	0.0006	0.029
22		3.2	0.0006	0.0006	0.032
23		>10	0.0011	0.005	0.040

[a] Concentration required for 50% inhibition of enzyme activity.
[b] IC_{50} values were determined in a single experimental run in duplicate.

Since the discovery of the *N*-(4-phenoxy)benzoyl analog (**1a**) as a new chemical lead for MMP-3 inhibitors, further optimization of **1a** has been continued.

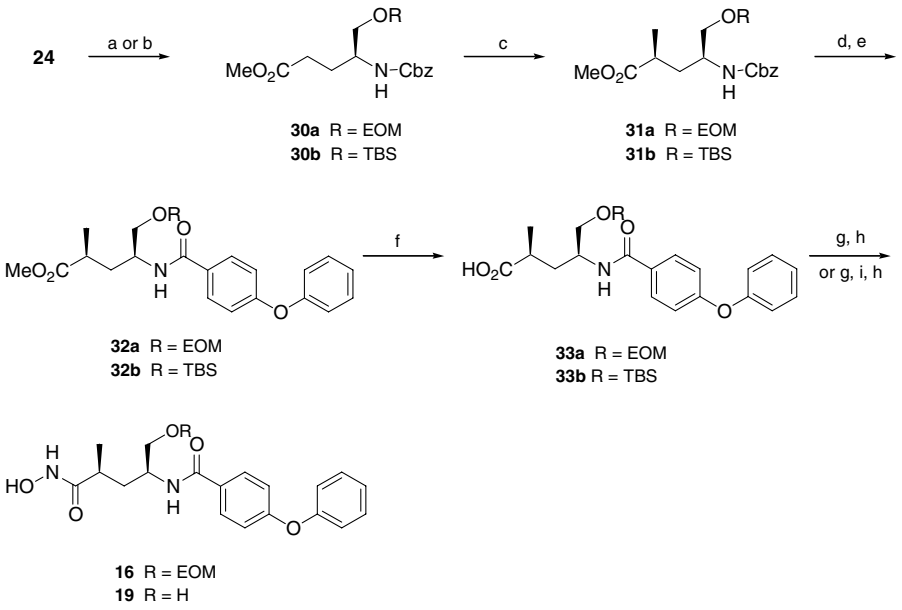
Introduction of the C4 substituents such as a methoxymethoxymethyl moiety into the *N*-benzoyl 4-aminobutyric acid hydroxamate resulted in the increased inhibition of MMP-3.[10]

Second, we focused on optimization of the C2 substituent, as shown in Table 1. Introduction of a 2*S*-methyl residue at the C2 position of **2** afforded **3**, which was 2.5-fold more potent, 7-fold more potent, and 2.3-fold more potent as an inhibitor of MMP-1, MMP-2, and MMP-3, respectively, while it showed the same activity against MMP-9. The corresponding 2*S*-ethyl and 2*S*-propyl analogs **4** and **5** were also synthesized and evaluated. Compound **4** exhibited 2.2-fold, 3.2-fold, 2.2-fold, and 3.1-fold more potent inhibitory activity against MMP-1, MMP-2, MMP-9, and MMP-3, respectively, relative to unsubstituted **2**. The 2*S*-propyl analog **5** showed nearly the same inhibitory spectrum as that of **4** with regard to all the MMP isoforms. Thus, analogs **3**–**5** tended to show increased activity against all of the MMP isoforms relative to unsubstituted analog **2**, while **3** retained its activity against MMP-9. Introduction of a 2*S*-isobutyl residue at the C2 position of **2** afforded **6**, which showed nearly equipotent activity against MMP-1, MMP-9, and MMP-3, while it retained the same activity against MMP-2. Introduction of a 2*S*-benzyl residue at the C2 position of **2** afforded **7**, which showed 5-fold, 7-fold, 2.6-fold, and 5.8-fold more potent inhibitory activity against MMP-1, MMP-2, MMP-9, and MMP-3, respectively. Thus, the 2*S*-benzyl analog **7** exhibited increased activity against all the MMP isoforms, while 2*S*-isobutyl analog **6** tended to show less and/or unchanged activity. Introduction of 2*R*- or 2*S*-pyridinylmethyl residues at the C2 position of **2** afforded **8**–**10**, with an increase of inhibitory activity against all of the MMP isoforms. The 2*R*-pyridin-2-ylmethyl analog **8** exhibited 13-fold, 5-fold, 4.3-fold, and 6.9-fold more potent activity against MMP-1, MMP-2, MMP-9, and MMP-3, respectively. In addition, the 2*S*-pyridin-3-ylmethyl analog **9** exhibited 17-fold, 5.8-fold, 2.6-fold, and 3.3-fold more potent activity against MMP-1, MMP-2, MMP-9, and MMP-3, respectively. Furthermore, the 2*S*-pyridin-4-ylmethyl analog **10** showed 3.7-fold, 8.8-fold, 1.6-fold, and 2.8-fold more potent activity against MMP-1, MMP-2, MMP-9, and MMP-3, respectively. Thus, basic pyridine moieties were also found to be accepted as illustrated by **8** (2*R*), **9** (2*S*), and **10** (2*S*). Introduction of a 2*S*-allyl residue into the C2 position of **2** afforded **11**, which also had increased activity against all of the MMP isoforms. Its inhibitory spectrum seemed to be close to that of 2*S*-benzyl analog **7**. Introduction of a 2*S*-naphthalene-1-ylmethyl moiety at the C2 position of **2** afforded **12**, which showed 7.8-fold and 3.8-fold more potent activity against MMP-1 and MMP-3, respectively, while it showed no change of activity against MMP-2 and MMP-9. Introduction of a 2*R*-*tert*-butyloxycarbonylmethyl residue at the C2 position of **2** provided **13**, with an increased activity against MMP-1, MMP-2, MMP-9, and MMP-3. Introduction of heteroatoms such as 2*S*-hydroxy and 2*S*-phenylthio residues at the C2 position of **2** afforded **14** and **15**. The 2*S*-hydroxy analog **14** exhibited equipotent, 2.5-fold more potent, and 2.4-fold less potent activity against MMP-1, MMP-2, and MMP-9 relative to **2**, respectively, while it retained activity against MMP-3. The 2*S*-phenylthio analog **15** exhibited 2.9-fold, 7-fold, 2.6-fold, and 12-fold more potent inhibition of MMP-1, MMP-2, MMP-9, and MMP-3, respectively, relative to **2**. Thus, all of these compounds listed in Table 1 showed very strong inhibitory activity against MMP-2 and MMP-9, while exhibiting moderate to weak activity against MMP-1. With regard to inhibition of MMP-3, most of the 2*S*-analogs **3**–**7**, **9**–**12**, **15** and 2*R*-analogs **8**, **13** exhibited more potent inhibitory activity compared with **2**. As a result, the 2*S*-methyl analog **3** and the 2*S*-ethyl analog **4** were selected as the chemical leads for further optimization because their synthesis was relatively simple.

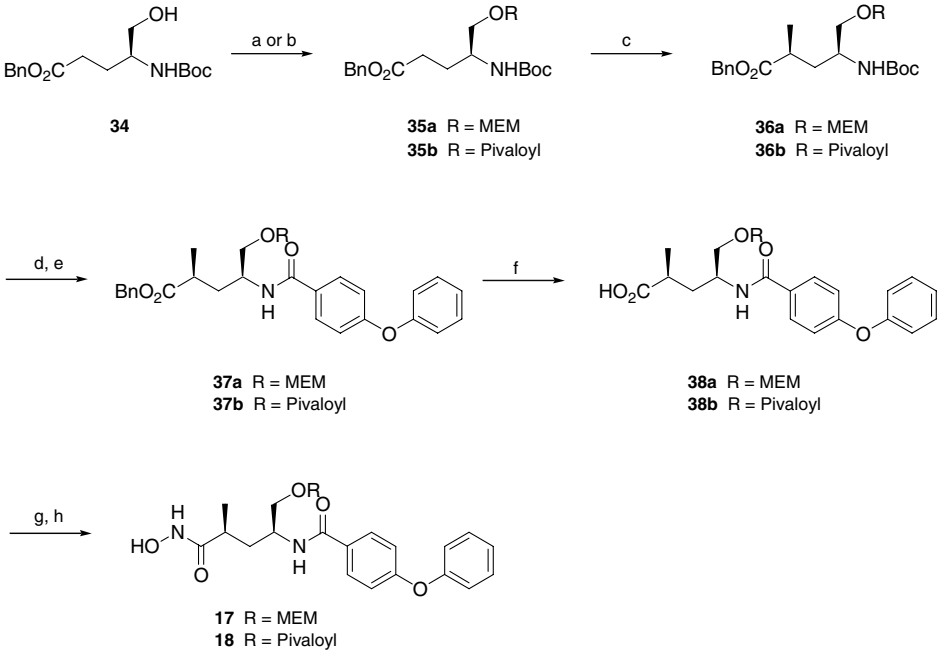


Scheme 1. Synthesis of **2**–**15**. Reagents and conditions: (a) MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2; (b) RBr or RI, LiHMDS, THF; (c) H_2, Pd/C, MeOH; (d) 4-phenoxybenzoic acid, EDC, HOBt, Et_3N, DMF; (e) RBr or RI or PhSSPh or 2-sulfonyl oxaziridine, LiHMDS, THF; (f) NaOH aq, THF–MeOH; (g) *O*-(2-methoxypropane-2-yl)hydroxylamine, EDC, HOBt, Et_3N, DMF; (h) HCl, MeOH; (i) *O*-benzylhydroxylamine, EDC, HOBt, Et_3N, DMF; (j) H_2, Pd/C, MeOH.

Then further optimization of the 2*S*-methyl analog **3** was conducted as described in Table 2. Replacement of the 4*S*-methoxymethyloxymethyl residue of **3** with a 4*S*-ethoxymethyloxymethyl residue afforded **16**, with slightly more potent inhibitory activity against MMP-9 and MMP-3, while it retained the equipotent activity against MMP-1 and MMP-2. Replacement of the 4*S*-methoxymethyloxymethyl residue of **3** with a 4*S*-methoxyethyloxymethyloxymethyl residue gave **17**, which showed 2.4-fold less potent and 2.6-fold more potent inhibitory activity against MMP-2 and MMP-9, respectively, while it retained the same activity against MMP-1 and MMP-3. Replacement of the 4*S*-methoxymethyloxymethyl residue of **3** with a pivaloyloxymethyl residue produced **18**, which was slightly less potent as an inhibitor of MMP-2 and MMP-3, while it retained the same activity against MMP-9. Deprotection of the methoxymethyl group of **3** afforded **19**, which showed nearly equipotent activity against MMP-1, MMP-2, MMP-9, and MMP-3, respectively. Replacement of the hydroxymethyl residue of **19** with a methyl residue led to **20**, which showed 101-fold less potent, 138-fold less potent, and 136-fold less potent inhibition of MMP-2, MMP-9, and MMP-3, respectively. Based on this information, an O-substitution in the 4*S*-substituent seems to be essential for potent activity. Thus, most of the chemical modifications described above resulted in a retention of the potent inhibitory activity although 4*S*-methyl analog **20** resulted in a decrease of the inhibitory activity relative to other analogs.

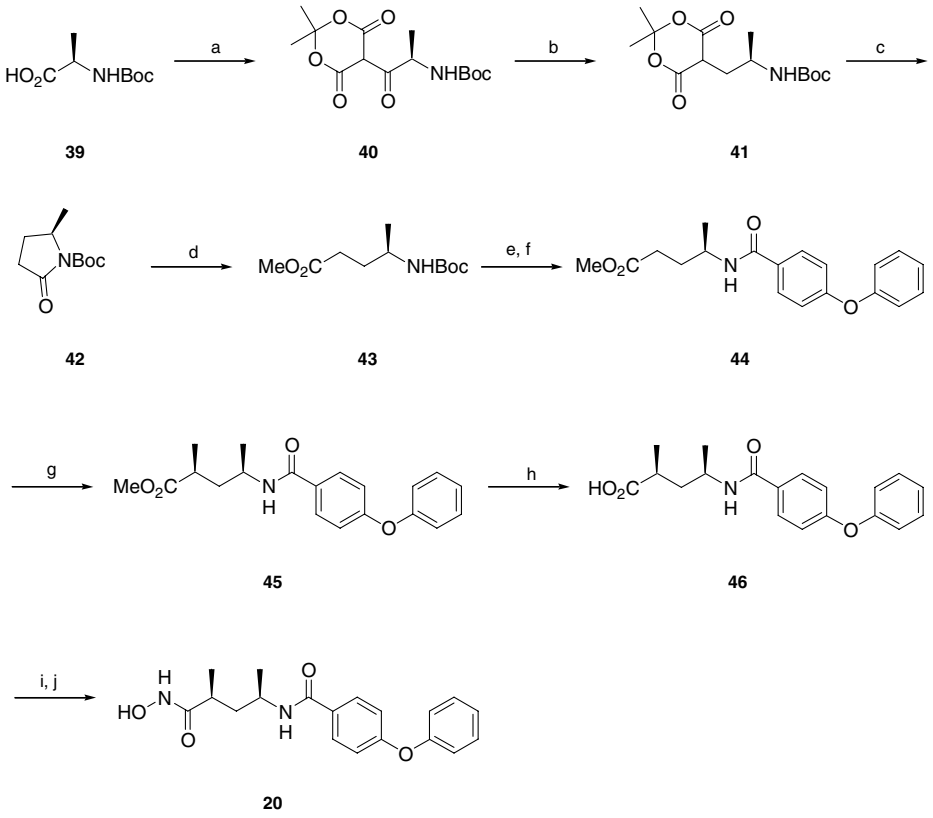


Scheme 2. Synthesis of **16** and **19**. Reagents and conditions: (a) EOMCl, $^{i}Pr_2NEt$, CH_2Cl_2; (b) TBSCl, imidazole, DMF; (c) MeI, LiHMDS, THF; (d) H_2, Pd/C, MeOH; (e) 4-phenoxybenzoic acid, EDC, HOBt, Et_3N, DMF; (f) NaOH aq, THF–MeOH; (g) *O*-benzylhydroxylamine, EDC, HOBt, Et_3N, DMF; (h) H_2, Pd/C, MeOH; (i) TBAF, THF.

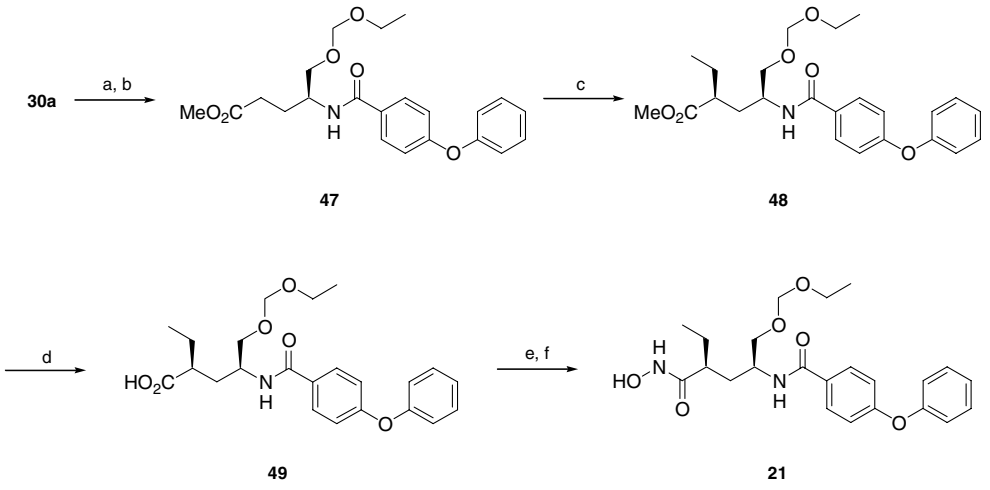


Scheme 3. Synthesis of **17** and **18**. Reagents and conditions: (a) MEMCl, $^{i}Pr_2NEt$, CH_2Cl_2; (b) PivCl, pyridine; (c) MeI, LiHMDS, THF; (d) TFA–H_2O, CH_2Cl_2; (e) 4-phenoxybenzoic acid, EDC, HOBt, Et_3N, DMF; (f) H_2, Pd/C, MeOH; (g) *O*-(2-methoxypropane-2-yl)hydroxylamine, EDC, HOBt, Et_3N, DMF; (h) HCl, MeOH.

Further optimization was also conducted for 2*S*-ethyl analog **4**. Chemical modification was again focused on optimization of the 4*S*-methoxymethyloxymethyl residue, as described in Table 3. Replacement of the 4*S*-methoxymethyloxymethyl residue of **4** with ethoxymethyloxymethyl or methoxyethyloxymethyloxymethyl residues afforded **21** and **22**, respectively. Compound **21** exhibited nearly equipotent inhibitory activity against MMP-2 and MMP-9 compared with **4**, while it retained its previous activity against MMP-1 and MMP-9. Compound **22** demonstrated nearly equipotent activity against MMP-2, while it retained the previous level of activity against other isoforms. Replacement of the 4*S*-methoxymethyloxymethyl residue with a pivaloyloxymethyl residue resulted in **23**, with 8.3-fold less potent activity against MMP-9, although it retained the previous level of activity against MMP-2 and MMP-3.



Scheme 4. Synthesis of **20**. Reagents and conditions: (a) Meldrum's acid, DMAP, DCC, CH_2Cl_2; (b) $NaBH_4$, AcOH, CH_2Cl_2; (c) toluene reflux; (d) i—NaOH aq, acetone; ii—CH_2N_2, MeOH; (e) 4 N HCl/EtOAc; (f) 4-phenoxybenzoic acid, EDC, HOBt, Et_3N, DMF; (g) MeI, LiHMDS, THF (h) NaOH aq, MeOH; (i) *O*-(2-methoxypropane-2-yl)hydroxylamine, EDC, HOBt, Et_3N, DMF; (j) HCl, MeOH.

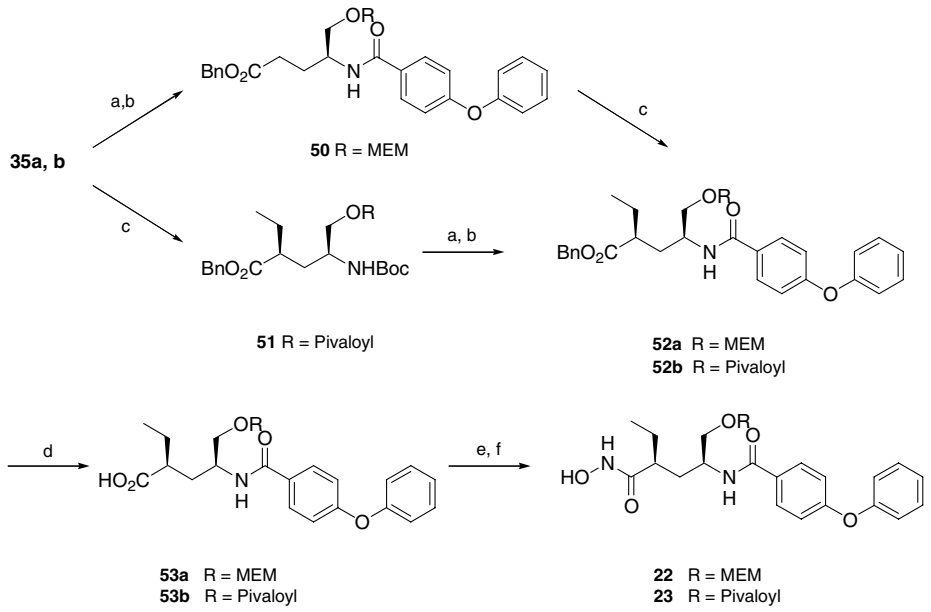


Scheme 5. Synthesis of **21**. Reagents and conditions: (a) H_2, Pd/C, MeOH; (b) 4-phenoxybenzoic acid, EDC, HOBt, Et_3N, DMF; (c) EtI, LiHMDS, THF; (d) NaOH aq, THF–MeOH; (e) *O*-benzylhydroxylamine, EDC, HOBt, Et_3N, DMF; (f) H_2, Pd/C, MeOH.

Our focus was placed on the compound **9** possessing broad inhibitory spectrum. As shown in Figure 2, an in vivo potential of **9** as a stromelysin inhibitor was evaluated based on its ability to inhibit stromelysin (MMP-3)-induced proteoglycan release in the knee joints of guinea pigs.[17] Compound **9** showed dose-dependent suppression of proteoglycan release from the knee joint cartilage after oral dosing. This finding strongly suggests that our inhibitors may have therapeutic potential for diseases where MMPs are overexpressed.

In summary, optimization of the C2-substituent was conducted in a series of 4-(4-phenoxy) benzoylamino-4-methoxymethyloxymethyl butyric acid hydroxamates. Most of the analogs listed in Table 1 exhibited strong inhibitory activity against MMP-2 and MMP-9 in addition to increased inhibition of MMP-3, while showing moderate to weak activity against MMP-1.

Further optimization of the 4*S* substituents of **3** and **4**, which were selected for their ease of synthesis and the



Scheme 6. Synthesis of **22** and **23**. Reagents and conditions: (a) TFA–H_2O, CH_2Cl_2; (b) 4-phenoxybenzoic acid, EDC, HOBt, Et_3N, DMF; (c) EtI, LiHMDS, THF; (d) H_2, Pd/C, MeOH; (e) *O*-benzylhydroxylamine, EDC, HOBt, Et_3N, DMF; (f) H_2, Pd/C, MeOH.

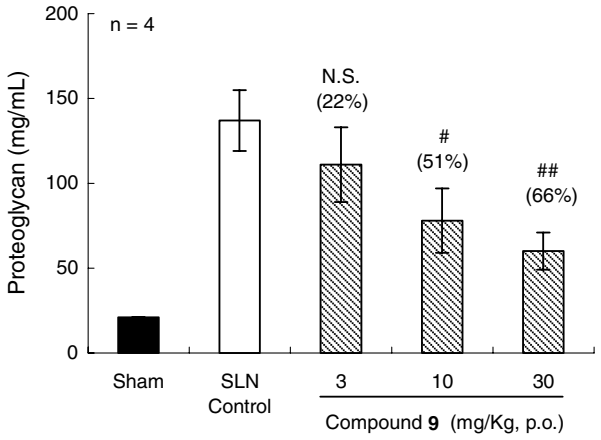


Figure 2. Effect of compound **9** on stromelysin (SLN)-induced proteoglycan release in the knee joints of guinea pigs. Each bar represents means ± standard error of four animals. (##) $p < 0.01$, significantly different from SLN control (Dunnett *t* test). (#) $p < 0.05$, significantly different from SLN control (Dunnett *t* test). NS, not significantly different from SLN control. The numbers in parentheses represent the percent inhibition of proteoglycan release to SLN control.

SAR study, was carried out as described in Tables 2 and 3, respectively. Among the compounds tested, **16**–**18** were also found to inhibit stromelysin (MMP-3)-induced proteoglycan release in the knee joints of guinea pigs.

4. Experimental

Analytical samples were homogeneous as confirmed by thin-layer chromatography (TLC) and yielded spectroscopic data consistent with the assigned structures. All ^1H NMR spectra were obtained with a Varian Gemini-200 or MERCURY-300 spectrometer. The chemical shift values are reported in parts per million (δ) and coupling constants (*J*) in hertz (Hz). Fast atom bombardment (FAB) and electron ionization (EI) mass spectra were obtained with a JEOL JMS-DX303HF or JMS-700 spectrometer. Atmospheric pressure chemical ionization (APCI) mass spectra were determined by a Hitachi M-1200 H spectrometer. Matrix-assisted laser desorption ionization (MALDI) mass spectra obtained on a PerSeptive Biosystems Voyager™ Elite spectrometer. IR spectra were measured using a Perkin-Elmer FTIR 1760X or JASCO FTIR-430 spectrometer. Column chromatography was carried out using silica gel [Merck silica gel 60 (0.063–0.200 mm), Wako Gel C200, Fuji Silysia FL60D, or Fuji Silysia BW-235]. TLC was also performed on silica gel (Merck TLC plate, silica gel 60 F254). The following abbreviations for solvents and reagents are used: THF, tetrahydrofuran; EtOAc, ethylacetate; MeOH, methanol; DMF, *N*,*N*-dimethylformamide; CH_2Cl_2, dichloromethane; $CHCl_3$, chloroform; EDC·HCl, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride; HOBt, 1-hydroxybenzotriazole; HMPA, hexamethylphosphoramide; DMSO, dimethylsulfoxide; AcOH, acetic acid; LiHMDS, lithium hexamethyldisilazane; FITC, fluorescein isothiocyanate; MOCAc, 7-methoxycoumarin-4-acetyl; Dpa, *N*-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl; Dnp, 2,4-dinitrophenyl.

4.1. Methyl (4*S*)-4-{[(benzyloxy)carbonyl]amino}-5-(methoxymethoxy)pentanoate (25)

To a stirred solution of **24** (93.6 g, 333 mmol) and *N*,*N*-(diisopropyl)ethylamine (170 mL, 999 mmol) in CH_2Cl_2 (170 mL) was added methoxymethyl chloride (38.0 mL, 500 mmol) cooling with an ice bath. The reaction mixture was stirred at room temperature for 2 h, quenched with aqueous NH_4Cl, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to give a crude product, which was purified by silica

gel chromatography with EtOAc–*n*-hexane (1:1) as an eluent to give **25** (83.5 g, 77%) as a white solid: TLC $R_f = 0.52$ (EtOAc–*n*-hexane, 1:1); ^{1}H NMR ($CDCl_3$): δ 7.40–7.26 (m, 5H), 5.10 (s, 2H), 5.03 (d, $J = 9.3$ Hz, 1H), 4.60 (s, 2H), 3.92–3.79 (m, 1H), 3.66 (s, 3H), 3.65–3.50 (m, 2H), 3.34 (s, 3H), 2.42 (t, $J = 7.5$ Hz, 2H), 2.00–1.80 (m, 2H).

4.2. Preparation of 26

Compounds **26a**–**e** were prepared from the compound **25** according to the general procedure described below.

4.2.1. General procedure for preparation of 26 from 25. To a stirred solution of LiHMDS (8.0 mmol, 1.0 M in THF) in dry THF (15 mL) was added a solution of compound **25** (3.6 mmol) in dry THF (10 mL) at −78 °C. After stirring for 1 h, alkyl halide (11 mmol) was added to the solution and stirred at −78 °C for 3 h. The reaction mixture was quenched with aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The resulting residue was purified by silica gel chromatography with EtOAc–*n*-hexane as an eluent to afford compound **26**.

4.2.2. Methyl (2*S*,4*S*)-4-{[(benzyloxy)carbonyl]amino}-5-(methoxymethoxy)-2-methylpentanoate (26a). Yield 67%; TLC $R_f = 0.46$ (EtOAc–*n*-hexane, 1:1); ^{1}H NMR ($CDCl_3$): δ 7.35–7.32 (m, 5H), 5.08 (s, 2H), 4.50 (s, 2H), 3.85–3.98 (m, 1H), 3.61 (s, 3H), 3.54–3.52 (m, 2H), 3.32 (s, 3H), 2.96–2.58 (m, 1H), 1.98 (ddd, $J = 14.4$ Hz, 10.5 Hz, and 7.2 Hz, 1H), 1.64 (m, 1H), 1.21 (d, $J = 6.9$ Hz, 3H).

4.2.3. Methyl (2*S*,4*S*)-2-benzyl-4-{[(benzyloxy)carbonyl]amino}-5-(methoxymethoxy)pentanoate (26b). Yield 92%; TLC $R_f = 0.48$ (EtOAc–*n*-hexane, 2:3); ^{1}H NMR ($CDCl_3$): δ 7.42–7.30 (m, 5H), 7.25–7.08 (m, 5H), 5.09 (s, 2H), 4.92 (d, $J = 10.0$ Hz, 1H), 4.56 (s, 2H), 4.00–3.80 (m, 1H), 3.58–3.40 (m, 5H), 3.29 (s, 3H), 2.98–2.65 (m, 3H), 2.02–1.87 (m, 1H), 1.72 (dt, $J = 14.4$, 5.0 Hz, 1H).

4.2.4. Methyl (2*R*,4*S*)-4-{[(benzyloxy)carbonyl]amino}-5-(methoxymethoxy)-2-(2-pyridinylmethyl)pentanoate (26c). Yield 92%; TLC $R_f = 0.14$ (EtOAc–*n*-hexane, 1:1); ^{1}H NMR ($CDCl_3$): δ 8.52–8.48 (m, 1H), 7.56 (dt, $J = 7.6$, 2.2 Hz, 1H), 7.37–7.28 (m, 5H), 7.14–7.08 (m, 2H), 5.08 (s, 2H), 5.07–5.01 (m, 1H), 4.56 (s, 2H), 3.96–3.82 (m, 1H), 3.60–3.47 (m, 5H), 3.29 (s, 3H), 3.17–2.95 (m, 3H), 2.02 (dt, $J = 14.0$, 8.1 Hz, 1H), 1.77 (dt, $J = 14.0$ Hz and 4.8 Hz, 1H).

4.2.5. Methyl (2*S*,4*S*)-4-{[(benzyloxy)carbonyl]amino}-5-(methoxymethoxy)-2-(4-pyridinylmethyl)pentanoate (26d). Yield 73%; TLC $R_f = 0.26$ (EtOAc–*n*-hexane, 9:1); ^{1}H NMR ($CDCl_3$): δ 8.49–8.44 (m, 2H), 7.40–7.28 (m, 5H), 7.10–7.00 (m, 2H), 5.14 (d, $J = 12.2$ Hz, 1H), 5.08 (d, $J = 12.2$ Hz, 1H), 4.99 (d, $J = 8.8$ Hz, 1H), 4.59 (s, 2H), 4.03–3.84 (m, 1H), 3.62–3.45 (m, 5H), 3.32 (s, 2H), 2.94–2.67 (m, 3H), 2.00 (ddd, $J = 14.4$ Hz, 9.8 Hz and 6.2 Hz, 1H), 1.71 (ddd, $J = 14.4$ Hz, 6.2 Hz and 4.8 Hz, 1H).

4.2.6. Methyl (2*S*)-2-[(2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-(methoxymethoxy)propyl]-4-methylpent-4-enoate (26e). Yield 73%; TLC $R_f = 0.37$ (EtOAc–*n*-hexane, 2:3); ^{1}H NMR ($CDCl_3$): δ 7.40–7.23 (m, 5H), 5.09 (s, 2H), 4.91 (d, $J = 9.2$ Hz, 1H), 4.76 (s, 1H), 4.59 (s, 2H), 4.00–3.78 (m, 1H), 3.61–3.42 (m, 5H), 3.33 (s, 3H), 2.77–2.58 (m, 1H), 2.34 (dd, $J = 13.8$, 8.4 Hz, 1H), 2.19 (dd, $J = 13.8$ Hz and 6.6 Hz, 1H), 1.93 (dt, $J = 14.0$ Hz and 9.8 Hz, 1H), 1.80–1.62 (m, 4H).

4.3. Methyl (4*S*)-5-(methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]pentanoate (27)

A solution of compound **25** (4.15 g, 12.8 mmol) in MeOH (20 mL) was vigorously stirred in the presence of 10% Pd/C (200 mg) under hydrogen atmosphere for 1 h. After removing the catalyst by filtration through a pad of Celite, the reaction mixture was concentrated in vacuo to afford a crude amine: TLC $R_f = 0.38$ ($CHCl_3$–MeOH, 9:1); ^{1}H NMR ($CDCl_3$): δ 4.64 (s, 2H), 3.68 (s, 3H), 3.51 (dd, $J = 9.6$, 4.0 Hz, 1H), 3.31 (dd, $J = 9.6$ Hz and 7.2 Hz, 1H), 3.02–2.89 (m, 1H), 2.59–2.31 (m, 2H), 1.92–1.73 (m, 1H), 1.70–1.50 (m, 1H).

A solution of the crude amine, EDC·HCl (2.68 g, 14.0 mmol), HOBt·H_2O (2.11 g, 14.0 mmol), 4-phenoxybenzoic acid (2.73 g, 12.8 mmol), and triethylamine (3.88 mL, 28.1 mmol) in DMF (30 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4 and evaporated. The resulting residue was triturated with diethyl ether to afford compound **27** as a white powder (4.47 g, 91%): TLC $R_f = 0.67$ (EtOAc–*n*-hexane, 4:1); ^{1}H NMR ($CDCl_3$): δ 7.77 (d, $J = 8.8$ Hz, 2H), 7.43–7.33 (m, 2H), 7.21–7.12 (m, 1H), 7.08–7.03 (m, 2H), 7.01 (d, $J = 8.8$ Hz, 2H), 6.63 (d, $J = 8.8$ Hz, 1H), 4.65 (s, 2H), 4.40–4.22 (m, 1H), 3.75 (dd, $J = 10.4$ Hz and 3.4 Hz, 1H), 3.63 (s, 3H), 3.61 (dd, $J = 10.4$ Hz and 4.0 Hz, 1H), 3.38 (s, 3H), 2.61–2.35 (m, 2H), 2.14–1.96 (m, 2H).

4.4. Preparation of compound 28

Compounds **28a**–**e** were prepared from the compounds **26a**–**e** according to the same procedure as described for the preparation of **27** from **25**, respectively. Compounds **28f**,**g** and **i**–**m** were prepared from **27** according to the general procedure for the preparation of **26** from **25**. Preparation of compound **28h** was described below.

4.4.1. Methyl (2*S*,4*S*)-5-(methoxymethoxy)-2-methyl-4-[(4-phenoxybenzoyl)amino]pentanoate (28a). Yield 92%; TLC $R_f = 0.42$ (EtOAc–*n*-hexane, 1:1); ^{1}H NMR ($CDCl_3$): δ 7.77–7.74 (m, 2H), 7.40–7.35 (m, 2H), 7.14 (t, $J = 7.5$ Hz, 1H), 7.05–6.98 (m, 4H), 6.43 (d, $J = 9.0$ Hz, 1H), 4.64 (d, $J = 6.9$ Hz, 1H), 4.62 (d, $J = 6.9$ Hz, 1H), 4.43–4.35 (m, 1H), 3.70 (dd, $J = 9.9$ Hz and 3.3 Hz, 1H), 3.60 (dd, $J = 9.9$ Hz and 3.9 Hz, 1H), 3.55 (s, 3H), 2.63–2.50 (m, 1H), 2.18 (ddd, $J = 14.4$ Hz, 10.8 Hz and 7.8 Hz, 1H), 1.72–1.61 (m, 1H), 1.24 (d, $J = 6.9$ Hz, 3H).

4.4.2. Methyl (2*S*,4*S*)-2-benzyl-5-(methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]pentanoate (28b). Yield 97%; TLC $R_f = 0.51$ (EtOAc–*n*-hexane, 1:1); ^{1}H NMR ($CDCl_3$): δ 7.75 (d, $J = 8.8$ Hz, 2H), 7.42–7.34 (m, 2H), 7.28–7.10 (m, 3H), 7.08–6.95 (m, 3H), 6.44 (d, $J = 9.0$ Hz, 1H), 4.62 (d, $J = 7.2$ Hz, 1H), 4.58 (d, $J = 7.2$ Hz, 1H), 4.44–4.28 (m, 1H), 3.68 (dd, $J = 10.2$ Hz and 3.2 Hz, 1H), 3.56 (dd, $J = 10.2$ Hz and 4.2 Hz, 1H), 3.40 (s, 3H), 3.29 (s, 3H), 3.00–2.70 (m, 3H), 2.15 (ddd, $J = 14.4$ Hz, 10.6 Hz and 8.8 Hz, 1H), 1.80 (dt, $J = 14.4$ Hz and 4.4 Hz, 1H).

4.4.3. Methyl (2*R*,4*S*)-5-(methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]-2-(2-pyridinylmethyl)pentanoate (28c). Yield 79%; TLC $R_f = 0.29$ (EtOAc–*n*-hexane, 9:1); ^{1}H NMR ($CDCl_3$): δ 8.55–8.44 (m, 1H), 7.77 (d, $J = 8.8$ Hz, 2H), 7.58 (dt, $J = 7.8$ Hz and 1.8 Hz, 1H), 7.42–7.30 (m, 2H), 7.21–6.96 (m, 7H), 6.69 (d, $J = 8.8$ Hz, 1H), 4.60 (s, 2H), 4.43–4.23 (m, 1H), 3.70 (dd, $J = 10.0$ Hz and 3.4 Hz, 1H), 3.59 (dd, $J = 10.0$ Hz and 4.0 Hz, 1H), 3.49 (s, 3H), 3.33 (s, 3H), 3.20–2.96 (m, 3H), 2.29–2.10 (m, 1H), 1.87 (dt, $J = 13.8$ Hz and 4.4 Hz, 1H).

4.4.4. Methyl (2*S*,4*S*)-5-(methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]-2-(4-pyridinylmethyl)pentanoate (28d). Yield 99%; TLC $R_f = 0.15$ (EtOAc–*n*-hexane, 9:1); ^{1}H NMR ($CDCl_3$): δ 8.51–8.46 (m, 2H), 7.77 (d, $J = 8.8$ Hz, 2H), 7.43–7.33 (m, 2H), 7.21–6.97 (m, 7H), 6.52 (d, $J = 8.8$ Hz, 1H), 4.64 (d, $J = 6.6$ Hz, 1H), 4.62 (d, $J = 6.6$ Hz, 1H), 4.55–4.36 (m, 1H), 3.72 (dd, $J = 10.8$ Hz and 3.4 Hz, 1H), 3.60 (dd, $J = 10.8$ Hz and 4.2 Hz, 1H), 3.43 (s, 3H), 3.36 (s, 3H), 3.02–2.74 (m, 3H), 2.17 (ddd, $J = 14.2$ Hz, 10.6 Hz and 7.6 Hz, 1H), 1.79 (ddd, $J = 14.2$ Hz, 5.4 Hz and 4.8 Hz, 1H).

4.4.5. Methyl (2*S*,4*S*)-2-isobutyl-5-(methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]pentanoate (28e). Yield 81%; TLC $R_f = 0.67$ (EtOAc–*n*-hexane, 1:1); ^{1}H NMR ($CDCl_3$): δ 7.76 (d, $J = 8.8$ Hz, 2H), 7.43–7.34 (m, 2H), 7.22–7.14 (m, 1H), 7.08–6.97 (m, 4H), 6.37 (d, $J = 9.2$ Hz, 1H), 4.63 (s, 2H), 4.43–4.24 (m, 1H), 3.71 (dd, $J = 10.0$ Hz and 3.4 Hz, 1H), 3.58 (dd, $J = 10.0$ Hz and 4.0 Hz, 1H), 3.49 (s, 3H), 3.37 (s, 3H), 2.65–2.49 (m, 1H), 2.00 (dt, $J = 14.4$ Hz and 10.4 Hz, 1H), 1.75 (dt, $J = 14.4$ Hz and 4.8 Hz, 1H), 1.66–1.44 (m, 2H), 1.42–1.28 (m, 1H), 0.89 (d, $J = 6.6$ Hz, 3H), 0.88 (d, $J = 6.6$ Hz, 3H).

4.4.6. Methyl (2*S*)-2-{(2*S*)-3-(methoxymethoxy)-2-[(4-phenoxybenzoyl)amino]propyl}-4-pentenoate (28f). Yield 93%; TLC $R_f = 0.54$ (EtOAc–*n*-hexane, 1:1); ^{1}H NMR ($CDCl_3$): δ 7.76–7.73 (m, 2H), 7.40–7.34 (m, 2H), 7.18–7.14 (m, 1H), 7.04–6.69 (m, 4H), 6.44 (d, $J = 9.0$ Hz, 1H), 5.79–5.65 (m, 1H), 5.09–5.02 (m, 2H), 4.65–4.60 (m, 2H), 4.41–4.30 (m, 1H), 3.69 (dd, $J = 10.2$ Hz and 3.3 Hz, 1H), 3.57 (dd, $J = 10.2$ Hz and 3.9 Hz, 1H), 3.49 (s, 3H), 3.36 (s, 3H), 2.63–2.29 (m, 2H), 2.19–2.08 (m, 1H), 1.84–1.77 (m, 1H).

4.4.7. Methyl (2*S*,4*S*)-2-ethyl-5-(methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]pentanoate (28g). Yield 75%; TLC $R_f = 0.59$ (EtOAc–*n*-hexane, 3:2); ^{1}H NMR ($CDCl_3$): δ 7.78–7.73 (m, 2H), 7.42–7.34 (m, 2H), 7.21–7.13 (m, 1H), 7.06 (m, 4H), 6.12 (d, $J = 8.8$ Hz, 1H), 4.63 (s, 2H), 4.43–4.28 (m, 1H), 3.70 (dd, $J = 13.2$ Hz and 3.4 Hz, 1H), 3.58 (dd, $J = 13.2$ Hz and 4.0 Hz, 1H), 3.56 (s, 3H), 3.36 (s, 3H), 2.50 (m, 1H), 2.21–2.04 (m, 2H), 1.83–1.57 (m, 3H), 0.89 (t, $J = 7.2$ Hz, 3H).

4.4.8. Methyl (2*S*,4*S*)-5-(methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]-2-propylpentanoate (28h). A solution of **28f** (640 mg, 1.49 mmol) in MeOH (5.0 mL) was vigorously stirred in the presence of 10% Pd/C (60 mg) under hydrogen atmosphere for 6 h. After removing the catalyst by filtration through a pad of Celite, the reaction mixture was evaporated. The resulting residue was purified by silica gel chromatography with EtOAc–*n*-hexane (1:4) as an eluent to afford **28h** (79%): TLC $R_f = 0.51$ (EtOAc–*n*-hexane, 1:1); ^{1}H NMR ($CDCl_3$): δ 7.76–7.73 (m, 2H), 7.40–7.26 (m, 2H), 7.19–7.14 (m, 1H), 7.05–6.98 (m, 4H), 6.56 (d, $J = 8.4$ Hz, 1H), 4.64 (d, $J = 6.6$ Hz, 1H), 4.62 (d, $J = 6.6$ Hz, 1H), 4.29–4.40 (m, 1H), 3.70 (dd, $J = 9.9$ Hz and 3.3 Hz, 1H), 3.57 (dd, $J = 9.9$ Hz and 3.9 Hz, 1H), 2.55–2.46 (m, 1H), 2.18–2.07 (m, 1H), 1.77 (dd, $J = 14.2$ Hz and 4.5 Hz, 1H), 1.65–1.48 (m, 2H), 1.36–1.23 (m, 2H), 0.89 (t, $J = 7.2$ Hz, 3H).

4.4.9. Methyl (2*S*,4*S*)-5-(methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]-2-(3-pyridinylmethyl)pentanoate (28i). Yield 84%; TLC $R_f = 0.19$ (EtOAc–*n*-hexane, 9:1); ^{1}H NMR ($CDCl_3$): δ 8.45 (dd, $J = 4.8$ Hz and 1.8 Hz, 1H), 8.43–8.40 (m, 1H), 7.76 (d, $J = 8.8$ Hz, 2H), 7.51 (dt, $J = 7.8$ Hz and 1.8 Hz, 1H), 7.44–7.33 (m, 2H), 7.25–7.13 (m, 2H), 7.09–7.03 (m, 2H), 7.01 (d, $J = 8.8$ Hz, 1H), 6.50 (d, $J = 9.2$ Hz, 1H), 4.64 (d, $J = 7.8$ Hz, 1H), 4.61 (d, $J = 7.8$ Hz, 1H), 4.55–5.36 (m, 1H), 3.71 (dd, $J = 10.2$ Hz and 3.0 Hz, 1H), 3.59 (dd, $J = 10.2$ Hz and 4.0 Hz, 1 H), 3.42 (s, 3H), 3.35 (s, 3H), 3.04–2.88 (m, 2H), 2.86–2.69 (m, 1H), 2.18 (ddd, $J = 14.0$ Hz, 10.4 Hz and 7.8 Hz, 1H), 1.81 (dt, $J = 14.0$ Hz and 5.0 Hz, 1H).

4.4.10. Methyl (2*S*,4*S*)-5-(methoxymethoxy)-2-(1-naphthylmethyl)-4-[(4-phenoxybenzoyl)amino]pentanoate (28j). Yield 95%; TLC $R_f = 0.51$ (EtOAc–*n*-hexane, 1:1); ^{1}H NMR ($CDCl_3$): δ 8.05–7.96 (m, 1H), 7.87–7.80 (m, 1H), 7.79–7.69 (m, 3H), 7.52–7.26 (m, 6H), 7.21–7.10 (m, 1H), 7.07–6.95 (m, 4H), 6.41 (d, $J = 9.0$ Hz, 1H), 4.57 (d, $J = 8.0$ Hz, 1H), 4.53 (d, $J = 8.0$ Hz, 1H), 4.46–4.25 (m, 1H), 3.64 (dd, $J = 10.2$ Hz and 3.4 Hz, 1H), 3.54 (dd, $J = 10.2$ Hz and 4.0 Hz, 1H), 3.41 (dd, $J = 13.8$ Hz and 8.2 Hz, 1H), 3.35 (s, 3H), 3.26 (dd, $J = 13.8$ Hz and 6.8 Hz, 1H), 3.24 (s, 3H), 3.08–2.88 (m, 1H), 2.27 (dt, $J = 14.0$ Hz and 9.8 Hz, 1H), 1.89 (dt, $J = 14.0$ Hz and 4.8 Hz, 1H).

4.4.11. Methyl (2*S*,4*S*)-2-hydroxy-5-(methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]pentanoate (28k). Yield 52%; TLC $R_f = 0.26$ (EtOAc–*n*-hexane, 9:1); ^{1}H NMR ($CDCl_3$): δ 7.80–7.76 (m, 2H), 7.43–7.35 (m, 2H), 7.22–7.14 (m, 1H), 7.08–6.99 (m, 5H), 4.70 (d, $J = 6.6$ Hz, 1H), 4.66 (d, $J = 6.6$ Hz, 1H), 4.55–4.44 (m, 1H), 4.45 (d, $J = 4.4$ Hz, 1H), 4.30 (ddd,

J = 10.6 Hz, 4.6 Hz and 2.6 Hz, 1H), 3.83 (dd, J = 10.2 Hz and 3.4 Hz, 1H), 3.77 (s, 3H), 3.73 (dd, J = 10.2 Hz and 3.4 Hz, 1H), 3.40 (s, 3H), 2.22 (ddd, J = 14.2 Hz, 10.5 Hz and 2.8 Hz, 1H), 1.90 (ddd, J = 14.2 Hz, 10.5 Hz and 3.6 Hz, 1H).

4.4.12. Methyl (2*S*,4*S*)-5-(methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]-2-(phenylthio)pentanoate (28l). Yield 35%; TLC R_f = 0.54 (EtOAc–*n*-hexane, 1:1); ^{1}H NMR ($CDCl_3$): δ 7.74–7.70 (m, 2H), 7.50–7.20 (m, 7H), 7.19–7.18 (m, 1H), 7.06–6.96 (m, 4H), 6.44 (d, J = 8.8 Hz, 1H), 4.63 (d, J = 6.6 Hz, 1H), 4.59 (d, J = 6.6 Hz, 1H), 4.65–4.48 (m, 1H), 3.79–3.56 (m, 3H), 3.44 (s, 3H), 3.34 (s, 3H), 2.40 (ddd, J = 14.5 Hz, 10.6 Hz and 8.8 Hz, 1H), 2.07 (ddd, J = 14.5 Hz, 5.6 Hz and 4.0 Hz, 1H).

4.4.13. 4-*tert*-Butyl 1-methyl (2*R*)-2-{(2*S*)-3-(methoxymethoxy)-2-[(4-phenoxybenzoyl)amino]propyl}succinate (28m). Yield 100%; TLC R_f = 0.25 (EtOAc–*n*-hexane, 1:1); ^{1}H NMR ($CDCl_3$): δ 7.76 (d, J = 8.7 Hz, 2H), 7.42–7.37 (m, 2 H), 7.21–7.13 (m, 1H), 7.08–7.01 (m, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.56 (d, J = 8.4 Hz, 1H), 4.63 (s, 2H), 4.42–4.30 (m, 2H), 3.75 (dd, J = 10.2 Hz and 3.3 Hz, 1H), 3.64–3.58 (m, 4H), 3.36 (s, 3H), 2.90–2.80 (m, 1H), 2.70–2.53 (m, 2H), 2.16 (ddd, J = 13.8 Hz, 9.9 Hz and 7.2 Hz, 1H), 1.81 (ddd, J = 13.8 Hz, 6.0 Hz and 4.8 Hz, 1H), 1.42 (s, 9H).

4.5. Preparation of 29

The compounds **29a**–**n** were prepared from the corresponding methyl esters **27** and **28a**–**m**, respectively, according to the general procedure.

4.5.1. General procedure for preparation of 29. To a stirred solution of **28** (1.43 mmol) in THF (10 mL) and MeOH (2 mL) was added 2 N NaOH (5 mL) at room temperature and stirring was continued for 4 h. The reaction mixture was neutralized with 1 N HCl and diluted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give compound **29**.

4.5.2. (2*S*,4*S*)-5-(Methoxymethoxy)-2-methyl-4-[(4-phenoxybenzoyl)amino]pentanoic acid (29a). Yield 100%; ^{1}H NMR (CD_3OD): δ 7.83–7.79 (m, 2H), 7.43–7.36 (m, 2H), 7.22–7.14 (m, 1H), 7.07–6.96 (m, 4H), 4.62 (s, 2H), 4.42–4.30 (m, 1H), 3.59 (d, J = 5.8 Hz, 2H), 3.32 (s, 3H), 2.59–2.41 (m, 1H), 2.11–2.19 (m, 1H), 1.73 (ddd, J = 14.0 Hz, 7.8 Hz and 4.2 Hz, 1H), 1.22 (d, J = 7.0 Hz, 3H).

4.5.3. (2*S*,4*S*)-2-Benzyl-5-(methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]pentanoic acid (29b). Yield 100%; TLC R_f = 0.35 ($CHCl_3$–MeOH, 19:1); ^{1}H NMR ($CDCl_3$): δ 7.72 (d, J = 8.8 Hz, 2H), 7.42–7.30 (m, 2H), 7.28–7.10 (m, 3H), 7.06–6.97 (m, 2H), 6.95 (d, J = 8.8 Hz, 2H), 6.63 (d, J = 9.2 Hz, 1H), 4.59 (d, J = 7.2 Hz, 1H), 4.57 (d, J = 7.2 Hz, 1H), 4.50–4.28 (m, 1H), 3.69 (dd, J = 10.2 Hz and 3.0 Hz, 1H), 3.56 (dd, J = 10.2 Hz and 3.6 Hz, 1H), 3.29 (s, 3H), 3.12–2.68 (m, 3H), 2.20–2.00 (m, 1H), 1.80 (dt, J = 14.4 Hz and 5.0 Hz, 1H).

4.5.4. (2*R*,4*S*)-5-(Methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]-2-(2-pyridinylmethyl)pentanoic acid (29c). Yield 69%; TLC R_f = 0.43 ($CHCl_3$–MeOH, 9:1); ^{1}H NMR ($CDCl_3$): δ 8.50–8.42 (m, 1H), 7.82–7.68 (m, 3H), 7.47–7.22 (m, 4H), 7.20–7.10 (m, 1H), 7.07–6.94 (m, 4H), 6.82 (d, J = 8.8 Hz, 1H), 4.60 (s, 2H), 4.50–4.28 (m, 1H), 3.64 (dd, J = 10.2 Hz and 3.6 Hz, 1H), 3.55 (dd, J = 10.2 Hz and 4.4 Hz, 1H), 3.33 (s, 3H), 3.31 (dd, J = 16.2 Hz and 8.4 Hz, 1H), 3.18 (dd, J = 16.2 Hz and 2.2 Hz, 1H), 2.98–2.82 (m, 1H), 2.40 (ddd, J = 14.2 Hz, 11.4 Hz and 6.0 Hz, 1H), 1.76 (ddd, J = 14.2 Hz, 7.8 Hz and 3.8 Hz, 1H), 3.20–2.96 (m, 3H), 2.29–2.10 (m, 1H), 1.87 (dt, J = 13.8 Hz and 4.4 Hz, 1H).

4.5.5. (2*S*,4*S*)-5-(Methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]-2-(4-pyridinylmethyl)pentanoic acid (29d). Yield 69%; TLC R_f = 0.17 ($CHCl_3$–MeOH, 9:1); ^{1}H NMR ($CDCl_3$): δ 12.28 (br s, 1H), 8.43 (d, J = 5.8 Hz, 2H), 8.24 (d, J = 9.2 Hz, 1H), 7.90 (d, J = 8.8 Hz, 2H), 7.50–7.38 (m, 2H), 7.24–7.14 (m, 3H), 7.13–6.99 (m, 4H), 4.62–4.48 (m, 2H), 4.43–4.23 (m, 1H), 3.60–3.43 (m, 2H), 3.24 (s, 3H), 2.94 (dd, J = 13.2 Hz and 4.8 Hz, 1H), 2.79 (dd, J = 13.2 Hz and 9.2 Hz, 1H), 2.70–2.56 (m, 1H), 1.92–1.64 (m, 2H).

4.5.6. (2*S*,4*S*)-2-Isobutyl-5-(methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]pentanoic acid (29e). Yield 92%; TLC R_f = 0.36 ($CHCl_3$–MeOH, 19:1); ^{1}H NMR ($CDCl_3$): δ 7.73 (d, J = 8.8 Hz, 2H), 7.42–7.30 (m, 2H), 7.21–7.11 (m, 1H), 7.07–7.02 (m, 2H), 6.97 (d, J = 8.8 Hz, 2H), 6.56 (d, J = 9.2 Hz, 1H), 4.65 (d, J = 7.8 Hz, 1H), 4.61 (d, J = 7.8 Hz, 1H), 4.48–4.30 (m, 1H), 3.74 (dd, J = 10.2 Hz and 3.0 Hz, 1H), 3.60 (dd, J = 10.2 Hz and 4.2 Hz, 1H), 3.36 (s, 3H), 2.63–2.49 (m, 1H), 2.08 (dt, J = 14.2 Hz and 9.4 Hz, 1H), 1.75 (dt, J = 14.2 Hz and 5.4 Hz, 1H), 1.70–1.50 (m, 2H), 1.46–1.30 (m, 1H), 0.90 (d, J = 6.2 Hz, 6H).

4.5.7. (2*S*)-2-{(2*S*)-3-(Methoxymethoxy)-2-[(4-phenoxybenzoyl)amino]propyl}-4-pentenoic acid (29f). Yield 82%; TLC R_f = 0.49 ($CHCl_3$–MeOH–AcOH, 100:5:1); ^{1}H NMR (CD_3OD): δ 7.83–7.78 (m, 2H), 7.43–7.30 (m, 2H), 7.21–7.14 (m, 1H), 7.07–6.96 (m, 4H), 5.88–5.68 (m, 1H), 5.13–4.99 (m, 2H), 4.62 (s, 2H), 4.43–4.28 (m, 1H), 3.62 (dd, J = 10.0 Hz and 5.4 Hz, 1H), 3.56 (dd, J = 10.0 Hz and 5.4 Hz, 1H), 3.32 (s, 3H), 2.55–2.33 (m, 3H), 1.99–1.86 (m, 2H).

4.5.8. (2*S*,4*S*)-2-Ethyl-5-(methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]pentanoic acid (29g). Yield 100%; TLC R_f = 0.50 ($CHCl_3$–MeOH–AcOH–H_2O, 100:10:1:1); ^{1}H NMR (CD_3OD): δ 7.89–7.78 (m, 2H), 7.44–7.36 (m, 2H), 7.22–7.14 (m, 1H), 7.06–6.96 (m, 4H), 4.62 (s, 2H), 4.40–4.26 (m, 1H), 3.62 (dd, J = 8.3 Hz and 5.0 Hz, 1H), 3.56 (dd, J = 8.3 Hz and 5.6 Hz, 1H), 3.33 (s, 3H), 2.29–2.24 (m, 1H), 2.02–1.56 (m, 4H), 0.93 (t, J = 7.2 Hz, 3H).

4.5.9. (2*S*,4*S*)-5-(Methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]-2-propylpentanoic acid (29h). Yield 100%; TLC R_f = 0.43 ($CHCl_3$–MeOH–AcOH, 100:10:1); ^{1}H NMR (CD_3OD): δ 7.83–7.79 (m, 2H), 7.44–7.36 (m,

2H), 7.22–7.14 (m, 1H), 7.07–6.97 (m, 4H), 4.62 (s, 2H), 4.46–4.27 (m, 1H), 3.62 (dd, J = 9.9 Hz and 5.4 Hz, 1H), 3.57 (dd, J = 9.9 Hz and 5.4 Hz, 1H), 3.33 (s, 3H), 2.51–2.38 (m, 1H), 2.03–1.75 (m, 2H), 1.65–1.28 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H).

4.5.10. (2*S*,4*S*)-5-(Methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]-2-(3-pyridinylmethyl)pentanoic acid (29i). Yield 90%; TLC R_f = 0.43 ($CHCl_3$–MeOH, 9:1); ^{1}H NMR (DMSO-d_6): δ 10.36 (s, 1H), 8.69 (s, 1H), 8.40–8.32 (m, 2H), 8.12 (d, J = 9.4 Hz, 1H), 7.91 (d, J = 8.8 Hz, 2H), 7.54–7.38 (m, 3H), 7.29–7.17 (m, 2H), 7.12–7.06 (m, 2H), 7.03 (d, J = 8.8 Hz, 2H), 4.56 (s, 2H), 4.40–4.20 (m, 1H), 3.60–3.42 (m, 2H), 3.22 (s, 3H), 2.87 (dd, J = 13.6 Hz and 4.8 Hz, 1H), 2.75 (d, J = 13.6 Hz and 9.6 Hz, 1H), 2.43–2.28 (m, 1H), 1.90–1.59 (m, 2H).

4.5.11. (2*S*,4*S*)-5-(Methoxymethoxy)-2-(1-naphthylmethyl)-4-[(4-phenoxybenzoyl)amino]pentanoic acid (29j). Yield 99%; TLC R_f = 0.33 ($CHCl_3$–MeOH, 19:1); ^{1}H NMR ($CDCl_3$): δ 8.08–7.98 (m, 1H), 7.85–7.77 (m, 1H), 7.76–7.62 (m, 3H), 7.51–7.27 (m, 6H), 7.20–7.09 (m, 1H), 7.03–6.98 (m, 2H), 6.93 (d, J = 8.8 Hz, 2H), 6.58 (d, J = 8.8 Hz, 1H), 4.50 (d, J = 10.0 Hz, 1H), 4.48 (d, J = 10.0 Hz, 1H), 4.42–4.27 (m, 1H), 3.63 (dd, J = 10.2 Hz and 3.0 Hz, 1H), 3.56–3.41 (m, 2H), 3.23 (dd, J = 13.8 Hz and 7.2 Hz, 1H), 3.15 (s, 3H), 3.10–2.90 (m, 1H), 2.21 (dt, J = 14.4 Hz and 9.2 Hz, 1H), 1.87 (dt, J = 14.4 Hz and 4.8 Hz, 1H).

4.5.12. (2*S*,4*S*)-2-Hydroxy-5-(methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]pentanoic acid (29k). Yield 100%; TLC R_f = 0.29 ($CHCl_3$–MeOH–AcOH–H_2O, 85:15:1:1); ^{1}H NMR (CD_3OD): δ 7.86–7.80 (m, 2H), 7.44–7.36 (m, 2H), 7.22–7.15 (m, 1H), 7.08–6.97 (m, 4H), 4.63 (s, 1H), 4.57–4.45 (m, 1H), 4.20 (dd, J = 10.2 Hz and 3.0 Hz, 1H), 3.67–3.64 (m, 2H), 3.33 (s, 3H), 2.22–2.08 (m, 1H), 1.97–1.83 (m, 1H).

4.5.13. (2S,4*S*)-5-(Methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]-2-(phenylthio)pentanoic acid (29l). Yield 100%; TLC R_f = 0.27 ($CHCl_3$–MeOH–AcOH, 100:5:1); ^{1}H NMR (CD_3OD): δ 7.81–7.75 (m, 2H), 7.52–7.36 (m, 4H), 7.30–7.18 (m, 4H), 7.07–6.95 (m, 4H), 4.61 (s, 2H), 4.57–4.37 (m, 1H), 3.67–3.58 (m, 3H), 3.31 (s, 3H), 2.38–2.03 (m, 2H).

4.5.14. (2*R*,4*S*)-2-(2-*tert*-Butoxy-2-oxoethyl)-5-(methoxymethoxy)-4-[(4-phenoxybenzoyl)amino]pentanoic acid (29m). Yield 94%; TLC R_f = 0.47 ($CHCl_3$–MeOH, 9:1); ^{1}H NMR ($CDCl_3$): δ 7.75 (d, J = 8.8 Hz, 2H), 7.41–7.37 (m, 2H), 76.21–7.11 (m, 1H), 7.08–7.00 (m, 2H), 6.98 (d, J = 8.8 Hz, 2H), 6.73 (d, J = 9.2 Hz, 1H), 4.62 (s, 2H), 4.48–4.31 (m, 1H), 3.77 (dd, J = 10.4 Hz and 3.0 Hz, 1H), 3.63 (dd, J = 10.4 Hz and 4.2 Hz, 1H), 3.36 (s, 3H), 2.97–2.78 (m, 1H), 2.77–2.56 (m, 2H), 2.17 (ddd, J = 14.2 Hz, 9.8 Hz and 7.0 Hz, 1H), 1.82 (ddd, J = 14.2 Hz, 7.0 Hz and 5.4 Hz, 1H), 1.42 (s, 9H).

4.5.15. (4*S*)-5-(Methoxymethoxy)-4-[(4-phenoxybenzoyl)-amino]pentanoic acid (29n). Yield 99%; ^{1}H NMR ($CDCl_3$): δ 7.84–7.80 (m, 2H), 7.43–7.36 (m, 2H), 7.23–7.13 (m, 1H), 7.07–6.97 (m, 4H), 4.62 (s, 2H), 4.35–4.21 (m, 1H), 3.62 (d, J = 5.4 Hz, 2H), 3.33 (s, 3H), 2.44–2.36 (m, 2H), 2.12–1.88 (m, 2H).

4.6. Preparation of compounds 2–15

Compounds **2**–**12** and **14**, **15** were prepared from the corresponding carboxylic acids **29a**–**l** and **29n**, respectively, according to the general procedure. Preparation of compound **13** was described below.

4.6.1. General procedure for preparation of 2–12, 14, and 15. A mixture of crude carboxylic acid **29** (0.51 mmol), EDC·HCl (1.5 mmol), HOBt·H_2O (1.5 mmol), and *O*-(2-methoxypropane-2-yl)hydroxylamine (4.3 mmol) in DMF (5 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and evaporated. To a stirred solution of the resulting residue in MeOH (10 mL) was added 2 N HCl (0.1 mL) at room temperature. After stirring for 15 min, the reaction mixture was concentrated under reduced pressure to give a crude hydroxamic acid, which was triturated with diethyl ether to afford compounds **2**–**12**, **14**, and **15**.

4.6.2. *N*-{(1*S*)-4-(Hydroxyamino)-1-[(methoxymethoxy)-methyl]-4-oxobutyl}-4-phenoxybenzamide (2). Yield 83%; TLC R_f = 0.36 ($CHCl_3$–MeOH–H_2O–AcOH, 100:10:1:1); MS (MALDI, pos.) m/z 427 $(M+K)^+$, 411 $(M+Na)^+$, 389 $(M+H)^+$; IR (KBr) 2878, 1632, 1588, 1550, 1489, 1316, 1251, 1172, 1150, 1103, 1039, 848, 752, 693 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.33 (s, 1H), 8.66 (s, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.46–7.38 (m, 2H), 7.22–7.15 (m, 2H), 7.07–6.99 (m, 4H), 4.54 (s, 2H), 4.19–3.94 (m, 1H), 3.49–3.45 (m, 2H), 3.22 (s, 3H), 2.07–1.57 (m, 4H); optical rotation $[\alpha]_D^{30}$ −30.46 (c 0.24, DMF); HRMS (FAB) calcd for $C_{20}H_{25}N_2O_6$: 389.1709. Found: 389.1713.

4.6.3. *N*-{(1*S*,3*S*)-4-(Hydroxyamino)-1-[(methoxymethoxy)methyl]-3-methyl-4-oxobutyl}-4-phenoxybenzamide (3). Yield 70%; TLC R_f = 0.49 ($CHCl_3$–MeOH–H_2O–AcOH, 100:10:1:1); MS (MALDI, pos.) m/z 441 $(M+K)^+$, 425 $(M+Na)^+$; IR (KBr) 3248, 2933, 1637, 1588, 1543, 1489, 1244, 1170, 1110, 1039, 963, 918, 876, 753, 692 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.38 (d, J = 1.5 Hz, 1H), 8.66 (d, J = 1.5 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.7 Hz, 2H), 7.45–7.40 (m, 2H), 7.22–7.17 (m, 1H), 7.08–7.01 (m, 4H), 4.55 (s, 2H), 4.21–4.08 (m, 1H), 3.52–3.44 (m, 2H), 3.22 (s, 3H), 2.25–2.09 (m, 1H), 1.67 (t, J = 7.2 Hz, 2H), 1.01 (d, J = 6.6 Hz, 3H); optical rotation $[\alpha]_D^{30}$ −4.56 (c 0.25, DMF); HRMS (FAB) calcd for $C_{21}H_{27}N_2O_6$: 403.1869. Found: 403.1871.

4.6.4. *N*-{(1*S*,3*S*)-3-[(Hydroxyamino)carbonyl]-1-[(methoxymethoxy)methyl]pentyl}-4-phenoxybenzamide (4). Yield 81%; TLC R_f = 0.62 ($CHCl_3$–MeOH–AcOH, 100:5:1); MS (MALDI, pos.) m/z 467 $(M+K)^+$, 451 $(M+Na)^+$, 429 $(M+H)^+$; IR (KBr) 3276, 2926, 1632, 1539, 1489, 1342, 1244, 1153, 1111, 1041, 960, 916, 878, 754, 692 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.43 (s, 1H), 8.66 (br s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.89–

7.85 (m, 2H), 7.47–7.38 (m, 2H), 7.23–7.15 (m, 1H), 7.09–6.99 (m, 4H), 5.73–5.60 (m, 1H), 5.05–4.92 (m, 2H), 4.54 (s, 2H), 4.19–4.05 (m, 1H), 3.52 (dd, J = 10.1 Hz and 5.2Hz, 1H), 3.44 (dd, J = 10.1 Hz and 5.2 Hz, 1H), 3.22 (s, 3H), 2.20–2.17 (m, 3H), 1.82–1.59 (m, 2H); optical rotation $[\alpha]_D^{30}$ −33.75 (c 0.40, DMF); HRMS (FAB) calcd for $C_{22}H_{29}N_2O_6$: 417.2026. Found: 417.2028.

4.6.5. *N*-{(1*S*,3*S*)-3-[(Hydroxyamino)carbonyl]-1-[(methoxymethoxy)methyl]hexyl}-4-phenoxybenzamide (5). Yield 89%; TLC R_f = 0.60 ($CHCl_3$–MeOH–H_2O–AcOH, 100:10:1:1); MS (MALDI, pos.) m/z 469 $(M+K)^+$, 453 $(M+Na)^+$, 431 $(M+H)^+$; IR (KBr) 3281, 2953, 1636, 1589, 1542, 1489, 1320, 1245, 1169, 1115, 1042, 916, 876, 753, 693 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.40 (s, 1H), 8.69 (d, J = 1.4 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.8 Hz, 2H), 7.46–7.37 (m, 2H), 7.23–7.15 (m, 1H), 7.08–6.98 (m, 4H), 4.54 (s, 2H), 4.16–4.00 (m, 1H), 3.48–3.44 (m, 2H), 3.21 (s, 3H), 2.14–1.99 (m, 1H), 1.78–1.58 (m, 2H), 1.45–1.28 (m, 2H), 1.27–1.07 (m, 2H), 0.80 (t, J = 7.2 Hz, 3H); optical rotation $[\alpha]_D^{30}$ −22.88 (c 0.20, DMF); HRMS (FAB) calcd for $C_{23}H_{31}N_2O_6$: 431.2182. Found: 431.2184.

4.6.6. *N*-{(1*S*,3*S*)-3-[(Hydroxyamino)carbonyl]-1-[(methoxymethoxy)methyl]-5-methylhexyl}-4-phenoxybenzamide (6). Yield 80%; TLC R_f = 0.36 ($CHCl_3$–MeOH, 19:1); MS (MALDI, pos.) m/z 483 $(M+K)^+$, 467 $(M+Na)^+$, 445 $(M+H)^+$; IR (KBr) 3237, 2954, 1636, 1588, 1542, 1489, 1243, 1170, 1110, 1038, 919, 876, 796, 753, 693, 493 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.46 (s, 1H), 8.72 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.8 Hz, 2H), 7.48–7.38 (m, 2H), 7.23–7.16 (m, 1H), 7.10–7.03 (m, 2H), 7.01 (d, J = 8.8 Hz, 2H), 4.56 (s, 2H), 4.22–4.01 (m, 1H), 3.60–3.40 (m, 2H), 3.24 (s, 3H), 2.25–2.08 (m, 1H), 1.78–1.60 (m, 2H), 1.58–1.32 (m, 2H), 1.28–1.07 (m, 1H), 0.82 (d, J = 6.0 Hz, 3H), 0.80 (d, J = 6.0 Hz, 3H); optical rotation $[\alpha]_D^{30}$ −26.99 (c 0.395, DMF); HRMS (FAB) calcd for $C_{24}H_{33}N_2O_6$: 445.2339. Found: 445.2339.

4.6.7. *N*-{(1*S*,3*S*)-3-Benzyl-4-(hydroxyamino)-1-[(methoxymethoxy)methyl]-4-oxobutyl}-4-phenoxybenzamide (7). Yield 65%; TLC R_f = 0.39 ($CHCl_3$–MeOH, 19:1); MS (MALDI, pos.) m/z 517 $(M+K)^+$, 501 $(M+Na)^+$, 479 $(M+H)^+$; IR (KBr) 3292, 2937, 1631, 1588, 1536, 1489, 1455, 1334, 1243, 1171, 1148, 1101, 1038, 965, 912, 878, 848, 798, 767, 754, 735, 694 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.36 (s, 1H), 8.09 (d, J = 8.6 Hz, 1H), 7.91 (d, J = 8.8 Hz, 2H), 7.50–7.38 (m, 2H), 7.30–7.08 (m, 8H), 7.03 (d, J = 8.8 Hz, 2H), 4.54 (s, 2H), 4.36–4.18 (m, 1H), 3.58–3.40 (m, 2H), 3.20 (s, 3H), 2.84–2.65 (m, 2H), 2.45–2.30 (m, 1H), 1.88–1.58 (m, 2H); optical rotation $[\alpha]_D^{30}$ −42.67 (c 0.76, DMF); HRMS (FAB) calcd for $C_{27}H_{31}N_2O_6$: 479.2182. Found: 479.2184.

4.6.8. *N*-[(1*S*,3*R*)-4-(Hydroxyamino)-1-[(methoxymethoxy)methyl]-4-oxo-3-(2-pyridinylmethyl)butyl]-4-phenoxybenzamide (8). Yield 29%; TLC R_f = 0.20 ($CHCl_3$–MeOH, 19:1); MS (APCI, neg. 40 V) m/z 478 $(M-H)^-$; IR (KBr) 3223, 2932, 1638, 1588, 1542, 1489, 1436, 1295, 1242, 1170, 1148, 1109, 1038, 915, 876, 754, 693 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.44 (s, 1H), 8.69 (s, 1H), 8.46–8.40 (m, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.8 Hz, 2H), 7.65 (td, J = 7.8 Hz and 1.8 Hz, 1H), 7.49–7.38 (m, 2H), 7.23–7.13 (m, 3H), 7.11–7.04 (m, 2H), 7.02 (d, J = 8.8 Hz, 2H), 4.52 (s, 2H), 4.23–4.06 (m, 1H), 3.49 (d, J = 5.4 Hz, 2H), 3.20 (s, 3H), 2.96 (dd, J = 13.8 Hz and 8.4 Hz, 1H), 2.85 (dd, J = 13.8 Hz and 6.6 Hz, 1H), 2.78–2.58 (m, 1H), 1.77 (t, J = 7.0 Hz, 2H); optical rotation $[\alpha]_D^{30}$ −42.43 (c 0.14, DMF); HRMS (FAB) calcd for $C_{26}H_{30}N_3O_6$: 480.2135. Found: 480.2135.

4.6.9. *N*-[(1*S*,3*S*)-4-(Hydroxyamino)-1-[(methoxymethoxy)methyl]-4-oxo-3-(3-pyridinylmethyl)butyl]-4-phenoxybenzamide (9). Yield 42%; TLC R_f = 0.43 ($CHCl_3$–MeOH, 9:1); MS (APCI, neg. 40 V) m/z 478 $(M-H)^-$; IR (KBr) 3224, 2930, 1638, 1587, 1542, 1489, 1307, 1242, 1170, 1109, 1038, 915, 876, 796, 754, 713, 693 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.36 (s, 1H), 8.69 (s, 1H), 8.40–8.32 (m, 2H), 8.12 (d, J = 9.4 Hz, 1H), 7.91 (d, J = 8.8 Hz, 2H), 7.54–7.38 (m, 3H), 7.29–7.17 (m, 2H), 7.12–7.06 (m, 2H), 7.03 (d, J = 8.8 Hz, 2H), 4.56 (s, 2H), 4.40–4.20 (m, 1H), 3.60–3.42 (m, 2H), 3.22 (s, 3H), 2.87 (dd, J = 13.6 Hz and 4.8 Hz, 1H), 2.75 (dd, J = 13.6 Hz and 9.6 Hz, 1H), 2.43–2.28 (m, 1H), 1.90–1.59 (m, 2H); optical rotation $[\alpha]_D^{30}$ −43.36 (c 0.14, DMF); HRMS (FAB) calcd for $C_{26}H_{30}N_3O_6$: 480.2135. Found: 480.2138.

4.6.10. *N*-[(1*S*,3S)-4-(Hydroxyamino)-1-[(methoxymethoxy)methyl]-4-oxo-3-(4-pyridinylmethyl)butyl]-4-phenoxybenzamide (10). Yield 73%; TLC R_f = 0.27 ($CHCl_3$–MeOH, 9:1); MS (MALDI, pos.) m/z 502 $(M+Na)^+$, 480 $(M+H)^+$; IR (KBr) 3275, 2928, 1636, 1609, 1588, 1542, 1489, 1304, 1245, 1170, 1109, 1038, 915, 850, 752, 692, 626, 542 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.44–10.30 (br s, 1H), 8.75–8.62 (br s, 1H), 8.40 (d, J = 6.0 Hz, 2H), 8.13 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.7 Hz, 2H), 7.48–7.38 (m, 2H), 7.22–7.18 (m, 1H), 7.13 (d, J = 6.0 Hz, 2H), 7.06 (d, J = 7.8 Hz, 2H), 7.02 (d, J = 8.7 Hz, 2H), 4.55 (s, 2H), 4.34–4.21 (m, 1H), 3.58–3.42 (m, 2H), 3.22 (s, 3H), 2.91–2.71 (m, 2H), 2.46–2.32 (m, 1H), 1.85–1.61 (m, 2H); optical rotation $[\alpha]_D^{30}$ −40.66 (c 0.355, DMF); HRMS (FAB) calcd for $C_{26}H_{30}N_3O_6$: 480.2135. Found: 480.2130.

4.6.11. *N*-{(1*S*,3*S*)-3-[(Hydroxyamino)carbonyl]-1-[(methoxymethoxy)methyl]-5-hexen-1-yl}-4-phenoxybenzamide (11). Yield 81%; TLC R_f = 0.62 ($CHCl_3$–MeOH–AcOH, 100:5:1); MS (MALDI, pos.) m/z 467 $(M+K)^+$, 451 $(M+Na)^+$, 429 $(M+H)^+$; IR (KBr) 3276, 2926, 1632, 1539, 1489, 1342, 1244, 1153, 1111, 1041, 960, 916, 878, 754, 692 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.43 (s, 1H), 8.66 (br s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.89–7.85 (m, 2H), 7.47–7.38 (m, 2H), 7.23–7.15 (m, 1H), 7.09–6.99 (m, 4H), 5.73–5.60 (m, 1H), 5.05–4.92 (m, 2H), 4.54 (s, 2H), 4.19–4.05 (m, 1H), 3.52 (dd, J = 10.1 Hz and 5.2 Hz, 1H), 3.44 (dd, J = 10.1 Hz and 5.2 Hz, 1H), 3.22 (s, 3H), 2.20–2.17 (m, 3H), 1.82–1.59 (m, 2H); optical rotation $[\alpha]_D^{30}$ −33.75 (c 0.40, DMF); HRMS (FAB) calcd for $C_{23}H_{29}N_2O_6$: 429.2026. Found: 429.2030.

4.6.12. *N*-[(1*S*,3*S*)-4-(Hydroxyamino)-1-[(methoxymethoxy)methyl]-3-(1-naphthylmethyl)-4-oxobutyl]-4-phenoxybenzamide (12). Yield 85%; TLC $R_f = 0.36$ ($CHCl_3$–MeOH, 19:1); MS (MALDI, pos.) *m*/*z* 567 $(M+K)^+$, 551 $(M+Na)^+$, 529 $(M+H)^+$; IR (KBr) 3223, 2931, 1638, 1587, 1539, 1488, 1395, 1242, 1170, 1108, 1036, 918, 876, 780, 753, 692 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.26 (s, 1H), 8.63 (s, 1H), 8.16 (d, $J = 8.4$ Hz, 1H), 8.04–7.82 (m, 4H), 7.80–7.70 (m, 1H), 7.52–7.16 (m, 7H), 7.14–6.96 (m, 4H), 4.52 (s, 2H), 4.50–4.28 (m, 1H), 3.61–3.40 (m, 2H), 3.25–3.02 (m, 5H), 2.69–2.52 (m, 1H), 2.00–1.78 (m, 2H); optical rotation $[\alpha]_D^{30}$ −66.46 (*c* 0.305, DMF); HRMS (FAB) calcd for $C_{31}H_{33}N_2O_6$: 529.2339. Found: 529.2341.

4.6.13. *tert*-Butyl (3*R*,5*S*)-3-[(hydroxyamino)carbonyl]-6-(methoxymethoxy)-5-[(4-phenoxybenzoyl)amino]hexanoate (13). A mixture of **29m** (595 mg, 1.20 mmol), EDC·HCl (348 mg, 1.83 mmol), HOBt·H_2O (274 mg, 1.83 mmol), *O*-benzylhydroxylamine hydrochloride (690 mg, 3.22 mmol), and triethylamine (506 μL, 1.83 mmol) in DMF (30 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$, H_2O, then brine, dried over Na_2SO_4, and evaporated. The resulting residue was triturated with diethyl ether to afford *O*-benzylhydroxamic acid (469 mg, 65%). The *O*-benzylhydroxamic acid (458 mg, 0.77 mmol) was dissolved in MeOH (10 mL), and vigorously stirred in the presence of 10% Pd/C (50 mg) under hydrogen atmosphere for 1 h. After removing the catalyst by filtration through a pad of Celite, the reaction mixture was evaporated. The resulting residue was triturated with diethyl ether to afford compound **13** (352 mg, 91%).

TLC $R_f = 0.54$ ($CHCl_3$–MeOH, 9:1); MS (MALDI, pos.) *m*/*z* 541 $(M+K)^+$, 525 $(M+Na)^+$, 503 $(M+H)^+$; IR (KBr) 3298, 2932, 1729, 1637, 1589, 1543, 1490, 1368, 1321, 1247, 1200, 1157, 1120, 1040, 957, 917, 877, 847, 792, 754, 693 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.47 (s, 1H), 8.75 (s, 1H), 8.05 (d, $J = 8.4$ Hz, 1H), 7.88 (d, $J = 8.7$ Hz, 2H), 7.47–7.40 (m, 2H), 7.23–7.17 (m, 1H), 7.10–7.04 (m, 2H), 7.03 (d, $J = 8.7$ Hz, 2H), 4.55 (s, 2H), 4.20–4.03 (m, 1H), 3.57–3.43 (m, 2H), 3.23 (s, 3H), 2.55–2.34 (m, 3H), 1.74–1.66 (m, 2H), 1.36 (s, 9H); optical rotation $[\alpha]_D^{30}$ −15.80 (*c* 0.30, DMF); HRMS (FAB) calcd for $C_{26}H_{35}N_2O_8$: 503.2393. Found: 503.2398.

4.6.14. *N*-{(1*S*,3*S*)-3-Hydroxy-4-(hydroxyamino)-1-[(methoxymethoxy)methyl]-4-oxobutyl}-4-phenoxybenzamide (14). Yield 74%; TLC $R_f = 0.57$ ($CHCl_3$–MeOH–AcOH, 85:15:1); MS (MALDI, pos.) *m*/*z* 443 $(M+K)^+$, 427 $(M+Na)^+$, 405 $(M+H)^+$; IR (KBr) 3298, 1626, 1551, 1491, 1335, 1248, 1156, 1113, 1041, 923, 849, 753, 695, 642 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.44 (s, 1H), 8.69 (br s, 1H), 8.19 (d, $J = 8.4$ Hz, 1H), 8.89 (d, $J = 8.8$ Hz, 2H), 7.48–7.38 (m, 2H), 7.22–7.16 (m, 1H), 7.09–7.01 (m, 4H), 5.36 (br s, 1H), 4.55 (s, 2H), 4.41–4.24 (m, 1H), 3.87 (dd, $J = 9.8$ Hz and 2.6 Hz, 1H), 3.56–3.42 (m, 2H), 3.22 (s, 3H), 1.96–1.66 (m, 2H); optical rotation $[\alpha]_D^{30}$ −53.02 (*c* 0.235, DMF); HRMS (FAB) calcd for $C_{20}H_{25}N_2O_7$: 405.1662. Found: 405.1663.

4.6.15. *N*-[(1*S*,3*S*)-4-(Hydroxyamino)-1-[(methoxymethoxy)methyl]-4-oxo-3-(phenylthio)butyl]-4-phenoxybenzamide (15). Yield 64%; TLC $R_f = 0.27$ ($CHCl_3$–MeOH–AcOH, 100:5:1); MS (MALDI, pos.) *m*/*z* 535 $(M+K)^+$, 519 $(M+Na)^+$, 497 $(M+H)^+$; IR (KBr) 3293, 1631, 1531, 1488, 1331, 1243, 1171, 1104, 1039, 913, 873, 847, 799, 755, 695 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.69 (s, 1H), 8.97 (s, 1H), 8.17 (d, $J = 8.0$ Hz, 1H), 7.86 (d, $J = 8.8$ Hz, 2H), 7.47–7.39 (m, 4H), 7.34–7.16 (m, 4H), 7.08–6.99 (m, 4H), 4.53 (s, 2H), 4.38–4.25 (m, 1H), 3.62–3.35 (m, 3H), 3.19 (s, 3H), 2.02 (t, $J = 6.8$ Hz, 2H); optical rotation $[\alpha]_D^{30}$ −92.93 (*c* 0.215, DMF); HRMS (FAB) calcd for $C_{26}H_{29}N_2O_6S$: 497.1746. Found: 497.1747.

4.7. Methyl (4*S*)-4-{[(benzyloxy)carbonyl]amino}-5-(ethoxymethoxy)pentanoate (30a)

Compound **30a** was prepared from **24** in 69% yield according to the same procedure as described for the preparation of **25** from **24**.

TLC $R_f = 0.59$ (EtOAc–*n*-hexane, 1:1); MS (MALDI, pos.) *m*/*z* 378 $(M+K)^+$, 362 $(M+Na)^+$, 340 $(M+H)^+$; ^1H NMR ($CDCl_3$): δ 7.37–7.28 (m, 5H), 5.10 (s, 2H), 5.05 (d, $J = 9.0$ Hz, 1H), 4.65 (s, 2H), 3.90–3.78 (m, 1H), 3.65 (s, 3H), 3.61–3.52 (m, 4H), 2.41 (t, $J = 7.6$ Hz, 2H), 1.94–1.84 (m, 2H), 1.20 (t, $J = 7.1$ Hz, 3H).

4.8. Methyl (4*S*)-4-{[(benzyloxy)carbonyl]amino}-5-{[*tert*-butyl(dimethyl)silyl]oxy}pentanoate (30b)

To a stirred solution of **24** (13.5 g, 48.0mmol) in DMF (48 mL) were added imidazole (7.20 g, 106 mmol) and TBSCl (15.2 g, 101 mmol) at 0 °C. After stirring at room temperature for 30 min, the reaction mixture was diluted with EtOAc. The organic layer was washed with 1 N HCl, H_2O, aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and evaporated. The resulting residue was purified by silica gel chromatography with EtOAc–*n*-hexane (1:10) as an eluent to give **30b** (14.0 g, 74%): TLC $R_f = 0.29$ (EtOAc–*n*-hexane, 1:4); ^1H NMR ($CDCl_3$): δ 7.41–7.32 (m, 5H), 5.09 (s, 2H), 4.93 (d, $J = 8.8$ Hz, 1H), 3.80–3.69 (m, 6H), 2.39 (t, $J = 7.2$ Hz, 2H), 2.04–1.78 (m, 2H), 0.87 (s, 9H), 0.03 (s, 6H).

4.9. Methyl (2*S*,4*S*)-4-{[(benzyloxy)carbonyl]amino}-5-(ethoxymethoxy)-2-methylpentanoate (31a)

Compound **31a** was prepared from **30a** in 65% yield according to the general procedure as described for the preparation of **26** from **25**.

TLC $R_f = 0.46$ (EtOAc–*n*-hexane, 1:1); MS (MALDI, pos.) *m*/*z* 392 $(M+K)^+$, 376 $(M+Na)^+$; ^1H NMR ($CDCl_3$): δ 7.39–7.30 (m, 5H), 5.10 (s, 2H), 4.92 (d, $J = 9.8$ Hz, 1H), 4.65 (s, 2H), 4.01–3.82 (m, 1H), 3.62 (s, 3H), 3.59–2.84 (m, 4H), 2.53 (sextet, $J = 7.1$ Hz, 1H), 2.70–1.90 (m, 1H), 1.66–1.53 (m, 1H), 1.26–1.16 (m, 6H).

4.10. Methyl (2*S*,4*S*)-4-{[(benzyloxy)carbonyl]amino}-5-{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylpentanoate (31b)

Compound **31b** was prepared from **30b** in 52% yield according to the general procedure as described for the preparation of **26** from **25**.

TLC $R_f = 0.64$ (EtOAc–*n*-hexane, 1:2); ^{1}H NMR ($CDCl_3$): δ 7.38–7.31 (m, 5H), 5.08 (s, 2H), 4.82 (d, $J = 9.3$ Hz, 1H), 3.82–3.71 (m, 1H), 3.62 (s, 3H), 3.62–3.55 (m, 2H), 2.51 (sextet, $J = 7.2$ Hz, 1H), 1.98–1.84 (m, 1H), 1.62–1.54 (m, 1H), 1.20 (d, $J = 6.9$ Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H).

4.11. Methyl (2*S*,4*S*)-5-(ethoxymethoxy)-2-methyl-4-[(4-phenoxybenzoyl)amino]pentanoate (32a)

Compound **32a** was prepared from **31a** in 37% yield according to the same procedure as described for the preparation of **27** from **25**.

TLC $R_f = 0.32$ (EtOAc–*n*-hexane, 1:1); ^{1}H NMR ($CDCl_3$): δ 7.77 (d, $J = 8.8$ Hz, 2H), 7.38 (m, 2H), 7.18 (m, 1H), 7.05 (d, $J = 7.7$ Hz, 2H), 7.01 (d, $J = 8.8$ Hz, 2H), 6.46 (d, $J = 8.8$ Hz, 1H), 4.71 (d, $J = 6.9$ Hz, 1H), 4.69 (d, $J = 6.9$ Hz, 1H), 4.40 (m, 1H), 3.72 (dd, $J = 10.2$ Hz and 3.3 Hz, 1H), 3.65–3.56 (m, 2H), 3.55 (s, 3H), 2.57 (m, 1H), 2.19 (ddd, $J = 14.3$ Hz, 10.9 Hz and 7.7 Hz, 1H), 1.69 (ddd, $J = 14.3$ Hz, 6.3 Hz and 4.1 Hz, 1H), 1.25 (d, $J = 6.9$ Hz, 3H), 1.21 (t, $J = 7.1$ Hz, 3H).

4.12. Methyl (2*S*,4*S*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-2-methyl-4-[(4-phenoxybenzoyl)amino]pentanoate (32b)

Compound **32b** was prepared from **31b** in 56% yield according to the same procedure as described for the preparation of **27** from **25**.

^{1}H NMR ($CDCl_3$): δ 7.73 (d, $J = 8.7$ Hz, 2H), 7.38 (t, $J = 7.7$ Hz, 2H), 7.18 (t, $J = 7.7$ Hz, 1H), 7.05 (d, $J = 7.7$ Hz, 2H), 7.00 (d, $J = 8.7$ Hz, 2H), 6.26 (d, $J = 9.0$ Hz, 1H), 4.31–4.21 (m, 1H), 3.69 (d, $J = 3.6$ Hz, 2H), 3.57 (s, 3H), 2.54 (m, 1H), 2.19–2.08 (m, 1H), 1.72–1.63 (m, 1H), 1.25 (d, $J = 6.9$ Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H).

4.13. (2*S*,4*S*)-5-(Ethoxymethoxy)-2-methyl-4-[(4-phenoxybenzoyl)amino]pentanoic acid (33a)

Compound **33a** was prepared from **32a** in 100% yield according to the general procedure for the preparation of **29** from **27** or **28a**–**m**.

TLC $R_f = 0.46$ (CH_2Cl_2–MeOH, 9:1); MS (APCI, neg. 20 V) *m*/*z* 400 $(M-H)^-$; ^{1}H NMR ($CDCl_3$): δ 12.04 (s, 1H), 8.12 (d, $J = 8.4$ Hz, 1H), 7.85 (d, $J = 8.7$ Hz, 2H), 7.40 (t, $J = 7.6$ Hz, 2H), 7.17 (t, $J = 7.6$ Hz, 1H), 7.04 (d, $J = 7.6$ Hz, 2H), 7.00 (d, $J = 8.7$ Hz, 2H), 4.57 (s, 2H), 4.24–4.13 (m, 1H), 3.52–3.42 (m, 4H), 2.37–2.26 (m, 1H), 1.93–1.84 (m, 1H), 1.62–1.53 (m, 1H), 1.10–1.01 (m, 6H).

4.14. (2*S*,4*S*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-methyl-4-[(4-phenoxybenzoyl)amino]pentanoic acid (33b)

Compound **33b** was prepared from **32b** in 100% yield according to the general procedure for the preparation of **29** from **27** or **28a**–**m**.

^{1}H NMR ($CDCl_3$): δ 11.67 (s, 1H), 8.01 (d, $J = 8.8$ Hz, 1H), 7.84 (d, $J = 8.8$ Hz, 2H), 7.40 (t, $J = 7.7$ Hz, 2H), 7.17 (t, $J = 7.7$ Hz, 1H), 7.04 (d, $J = 7.7$ Hz, 2H), 6.99 (d, $J = 8.8$ Hz, 2H), 4.12–3.95 (m, 1H), 3.81–3.71 (m, 1H), 3.62–3.48 (m, 1H), 2.39–2.26 (m, 1H), 1.96–1.58 (m, 2H), 1.04 (d, $J = 6.8$ Hz, 3H), 0.82 (s, 9H), 0.01 (s, 6H).

4.15. *N*-[(1*S*,3*S*)-1-[(Ethoxymethoxy)methyl]-4-(hydroxyamino)-3-methyl-4-oxobutyl]-4-phenoxybenzamide (16)

Compound **16** was prepared from **33a** in 85% yield according to the same procedure as described for the preparation of **13** from **29m**.

TLC $R_f = 0.40$ ($CHCl_3$–MeOH–AcOH–H_2O, 100:10:1:1); MS (APCI, neg. 40 V) *m*/*z* 415 $(M-H)^-$; IR (KBr) 3288, 1636, 1589, 1540, 1489, 1357, 1314, 1242, 1199, 1170, 1121, 1041, 967, 876, 843, 753, 692 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.37 (br, 1H), 8.66 (br, 1H), 8.03 (d, $J = 8.8$ Hz, 1H), 7.87 (d, $J = 8.8$ Hz, 2H), 7.43 (dd, $J = 7.4$ Hz and 8.5 Hz, 2H), 7.20 (t, $J = 7.4$ Hz, 1H), 7.06 (d, $J = 8.5$ Hz, 2H), 7.02 (d, $J = 8.8$ Hz, 2H), 4.59 (s, 2H), 4.14 (m, 1H), 3.50–3.45 (m, 4H), 3.32 (s, 2H), 2.17 (m, 1H), 1.66 (m, 2H), 1.09 (t, $J = 7.1$ Hz, 3H), 1.01 (d, $J = 6.9$ Hz, 3H); optical rotation $[\alpha]_D^{30}$ −5.46 (*c* 0.49, DMF); HRMS (FAB) calcd for $C_{22}H_{29}N_2O_6$: 417.2026. Found: 417.2039.

4.16. *N*-[(1*S*,3*S*)-4-(Hydroxyamino)-1-(hydroxymethyl)-3-methyl-4-oxobutyl]-4-phenoxybenzamide (19)

To a stirred solution of compound **33b** (437 mg, 0.96 mmol) in DMF (10 mL) were added *O*-benzylhydroxylamine hydrochloride (183 mg, 1.15 mmol), EDC·HCl (550 mg, 2.88 mmol), HOBt·H_2O (440 mg, 2.88 mmol), and triethylamine (0.4 mL, 2.88 mmol) at 0 °C. After stirring at room temperature for 2.5 h, the reaction mixture was diluted with EtOAc. The organic layer was washed with 1 N HCl, H_2O, aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and evaporated. To a stirred solution of the resulting residue in THF (5 mL) was added tetrabutylammonium fluoride (3 mL) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was diluted with EtOAc. The organic layer was washed with 1 N HCl, H_2O, aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and evaporated to afford *O*-benzylhydroxamic acid, a solution of which in MeOH (6.0 mL) was vigorously stirred in the presence of 5% Pd/C (90 mg) under hydrogen atmosphere for 45 min. After removing the catalyst by filtration through a pad of Celite, the reaction mixture was evaporated. The resulting residue was washed with diethyl ether to afford compound **19** (299 mg, 87%).

TLC $R_f = 0.14$ ($CHCl_3$–MeOH, 9:1); MS (MALDI, pos.) *m/z* 381 $(M+Na)^+$, 359 $(M+H)^+$; IR (KBr) 3290, 3095, 2964, 2875, 1636, 1588, 1550, 1503, 1489, 1359, 1322, 1247, 1199, 1171, 1085, 1048, 1033, 950, 877, 842, 752, 691, 659, 483 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.33 (s, 1H), 8.62 (s, 1H), 7.89–7.83 (m, 3 H), 7.41 (t, $J = 7.6$ Hz, 2H), 7.17 (t, $J = 7.6$ Hz, 1H), 7.04 (d, $J = 7.6$ Hz, 2H), 7.00 (d, $J = 8.7$ Hz, 2H), 4.68 (t, $J = 5.7$ Hz, 1H), 4.02–3.91 (m, 1H), 3.45–3.28 (m, 2H), 2.21–2.08 (m, 1H), 1.72–1.55 (m, 2H), 0.98 (t, $J = 6.6$ Hz, 3H); optical rotation $[\alpha]_D^{30}$ −15.2 (*c* 0.17, DMF); HRMS (FAB) calcd for $C_{19}H_{23}N_2O_5$: 359.1607. Found: 359.1611.

4.17. Benzyl (4*S*)-4-[(*tert*-butoxycarbonyl)amino]-5-[(2-methoxyethoxy)methoxy]pentanoate (35a)

Compound **35a** was prepared from **34** in 100% yield according to the same procedure as described for the preparation of **25** from **24**.

TLC $R_f = 0.40$ (EtOAc–*n*-hexane, 1:1); ^1H NMR ($CDCl_3$): δ 7.40–7.28 (m, 5H), 5.12 (s, 2H), 4.88–4.78 (m, 1H), 4.70 (s, 2H), 3.83–3.48 (m, 7H), 3.38 (s, 3H), 2.45 (t, $J = 7.8$ Hz, 2H), 1.98–1.75 (m, 2H), 1.43 (s, 9H).

4.18. Benzyl (4*S*)-4-[(*tert*-butoxycarbonyl)amino]-5-[(2,2-dimethylpropanoyl)oxy]pentanoate (35b)

To a stirred solution of compound **34** (3.0 g, 9.29 mmol) in pyridine (9 mL) was added pivaloyl chloride (2.2 g, 18.6 mmol) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was diluted with EtOAc. The organic layer was washed with 1 N HCl, H_2O, aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and evaporated. The resulting residue was purified by silica gel chromatography with EtOAc–*n*-hexane (1:6) as an eluent to afford compound **35b** (2.7 g, 72%).

TLC $R_f = 0.36$ (EtOAc–*n*-hexane, 1:4); ^1H NMR ($CDCl_3$): δ 7.39–7.32 (m, 5H), 5.12 (s, 2H), 4.52 (d, $J = 9.3$ Hz, 1H), 4.16–3.98 (m, 2H), 3.96–3.87 (m, 1H), 2.47 (t, $J = 7.7$ Hz, 2H), 1.95–1.83 (m, 1H), 1.79–1.66 (m, 1H), 1.42 (s, 9H), 1.20 (s, 9H).

4.19. Benzyl (2*S*,4*S*)-4-[(*tert*-butoxycarbonyl)amino]-5-[(2-methoxyethoxy)methoxy]-2-methylpentanoate (36a)

Compound **36a** was prepared from **35a** according to the general procedure for the preparation of **26** from **25**.

TLC $R_f = 0.22$ (EtOAc–*n*-hexane, 1:2); ^1H NMR ($CDCl_3$): δ 7.39–7.34 (m, 5H), 5.16 (d, $J = 12.5$ Hz, 2H), 5.08 (d, $J = 12.5$ Hz, 1H), 4.74–4.69 (m, 2H), 3.91–3.78 (m, 1H), 3.70–3.65 (m, 2H), 3.54 (t, $J = 4.7$ Hz, 4H), 3.38 (s, 3H), 2.58 (m, 1H), 2.02–1.89 (m, 1H), 1.65–1.56 (m, 1H), 1.42 (s, 9H), 1.22 (d, $J = 7.2$ Hz, 3H).

4.20. (2*S*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-5-[(2,2-dimethylpropanoyl)oxy]-2-methylpentanoate (36b)

Compound **36b** was prepared from **35b** according to the general procedure for the preparation of **26** from **25**.

^1H NMR ($CDCl_3$): δ 7.36–7.30 (m, 5H), 5.15 (d, $J = 12.6$ Hz, 1H), 5.09 (d, $J = 12.6$ Hz, 1H), 4.43 (d, $J = 10.0$ Hz, 1H), 4.07–4.00 (m, 2H), 2.68–2.44 (m, 1H), 1.96–1.80 (m, 1H), 1.62–1.49 (m, 1H), 1.42 (s, 9H), 1.23 (d, $J = 6.8$ Hz, 3H), 1.20 (s, 9H).

4.21. Benzyl (2*S*,4*S*)-5-[(2-methoxyethoxy)methoxy]-2-methyl-4-[(4-phenoxybenzoyl)amino]pentanoate (37a)

To a stirred solution of compound **36a** (1.0 g, 2.4 mmol) in CH_2Cl_2 (10 mL) were added TFA–H_2O (10:1) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was diluted with toluene and evaporated. To a stirred solution of the resulting residue in DMF (10 mL) was added EDC·HCl (1.4 g, 7.2 mmol), HOBt·H_2O (1.1 g, 7.2 mmol), 4-phenoxybenzoic acid (670 mg, 3.1 mmol), and triethylamine (1.0 mL, 7.2 mmol) at 0 °C. The reaction mixture was diluted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and evaporated. The resulting residue was purified by silica gel chromatography with EtOAc–*n*-hexane (1:1) as an eluent to afford compound **37a** (1.1 g, 85%).

TLC $R_f = 0.24$ (EtOAc–*n*-hexane, 1:1); ^1H NMR ($CDCl_3$): δ 7.76 (d, $J = 8.7$ Hz, 2H), 7.40–7.23 (m, 7H), 7.17 (t, $J = 7.4$ Hz, 1H), 7.02 (d, $J = 8.7$ Hz, 2H), 6.98 (d, $J = 8.7$ Hz, 2H), 6.57 (d, $J = 9.0$ Hz, 1H), 5.06 (d, $J = 12.3$ Hz, 1H), 4.92 (d, $J = 12.3$ Hz, 1H), 4.73 (d, $J = 10.5$ Hz, 1H), 4.71 (d, $J = 10.5$ Hz, 1H), 4.47–4.37 (m, 1H), 3.78–3.59 (m, 4H), 3.51 (t, $J = 4.7$ Hz, 2H), 3.27 (s, 3H), 2.60 (m, 1H), 2.26–2.15 (m, 1H), 1.74–1.65 (m, 1H), 1.26 (d, $J = 7.2$ Hz, 3H).

4.22. Benzyl (2*S*,4*S*)-5-[(2,2-dimethylpropanoyl)oxy]-2-methyl-4-[(4-phenoxybenzoyl)amino]pentanoate (37b)

Compound **37b** was prepared from **36b** in 84% yield according to the same procedure as described for the preparation of **37a** from **36a**.

TLC $R_f = 0.50$ (toluene–EtOAc, 4:1); ^1H NMR ($CDCl_3$): δ 7.71 (d, $J = 9.0$ Hz, 2H), 7.43–7.14 (m, 8H), 7.07–6.96 (m, 4H), 6.19 (d, $J = 9.0$ Hz, 1H), 5.05 (d, $J = 12.2$ Hz, 1H), 4.92 (d, $J = 12.2$ Hz, 1H), 4.62–4.45 (m, 1H), 4.25 (dd, $J = 11.4$ Hz and 5.8 Hz, 1H), 4.09 (dd, $J = 11.4$ Hz and 5.8 Hz, 1H), 2.61 (m, 1H), 2.16–1.95 (m, 1H), 1.73–1.60 (m, 1H), 1.27 (d, $J = 6.9$ Hz, 3H), 1.18 (s, 9H).

4.23. (2*S*,4*S*)-5-[(2-Methoxyethoxy)methoxy]-2-methyl-4-[(4-phenoxybenzoyl)amino]pentanoic acid (38a)

A solution of **37a** (1.06 g, 2.03 mmol) in MeOH (20 mL) was vigorously stirred in the presence of 5% Pd/C (300 mg) under hydrogen atmosphere for 40 min. After removing the catalyst by filtration through a pad of Celite, the reaction mixture was concentrated in vacuo to afford **38a**:^1H NMR (DMSO-d_6): δ 12.07 (br s, 1H), 8.11 (d, $J = 8.7$ Hz, 1H), 7.85 (d, $J = 8.7$ Hz, 2H), 7.40 (t, $J = 7.5$ Hz, 2H), 7.17 (t, $J = 7.5$ Hz, 1H), 7.06–6.97 (m, 4H), 4.60 (s, 2H),

4.26–4.11 (m, 1H), 3.55–3.38 (m, 6H), 3.19 (s, 3H), 2.38–2.24 (m, 1H), 1.92–1.81 (m, 1H), 1.61–1.52 (m, 1H), 1.05 (d, J = 6.9 Hz, 3H).

4.24. (2*S*,4*S*)-5-[(2,2-Dimethylpropanoyl)oxy]-2-methyl-4-[(4-phenoxybenzoyl)amino]pentanoic acid (38b)

Compound **38b** was prepared from **37b** in 86% yield according to the same procedure as described for the preparation of **38a** from **37a**.

^{1}H NMR (DMSO-d_6): δ 12.11 (br s, 1H), 8.15 (d, J = 8.7 Hz, 1H), 7.81 (d, J = 8.7 Hz, 2H), 7.41 (t, J = 7.7 Hz, 2H), 7.17 (t, J = 7.7 Hz, 1H), 7.04 (d, J = 7.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 4.36–4.25 (m, 1H), 4.08–3.94 (m, 2H), 2.38–2.23 (m, 1H), 1.93–1.82 (m, 1H), 1.55–1.45 (m, 1H), 1.17–1.05 (m, 12H).

4.25. *N*-[(1*S*,3*S*)-4-(Hydroxyamino)-1-{[(2-methoxyethoxy)methoxy]methyl}-3-methyl-4-oxobutyl]-4-phenoxybenzamide (17)

Compound **17** was prepared from **38a** in 69% yield according to the general procedure for the preparation of **2**–**15** from **29a**–**n**, respectively.

TLC R_f = 0.43 ($CHCl_3$–MeOH, 9:1); MS (APCI, neg. 40 V) m/z 445 $(M-H)^-$; IR (KBr) 3274, 3067, 2917, 1634, 1541, 1490, 1341, 1316, 1249, 1198, 1168, 1115, 1062, 1042, 954, 921, 870, 849, 754, 692, 489 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.35 (s, 1H), 8.64 (s, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 8.7 Hz, 2H), 7.41 (t, J = 7.7 Hz, 2H), 7.17 (t, J = 7.7 Hz, 1H), 7.04 (d, J = 7.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 4.59 (s, 2H), 4.18–4.06 (m, 1H), 3.55–3.37 (m, 6H), 3.19 (s, 3H), 2.15 (sextet, J = 7.1 Hz, 1H), 1.68–1.60 (2m, 2H), 0.99 (d, J = 6.6 Hz, 3H); optical rotation $[\alpha]_D^{30}$ −5.0 (c 0.46, DMF); HRMS (FAB) calcd for $C_{23}H_{31}N_2O_7$: 447.2131. Found: 447.2132.

4.26. (2*S*,4*S*)-5-(Hydroxyamino)-4-methyl-5-oxo-2-[(4-phenoxybenzoyl)amino]pentyl pivalate (18)

Compound **18** was prepared from **38b** in 77% yield according to the general procedure for the preparation of **2**–**15** from **29a**–**n**, respectively.

TLC R_f = 0.52 ($CHCl_3$–MeOH, 9:1); MS (MALDI, pos.) m/z 481 $(M+K)^+$, 465 $(M+Na)^+$, 443 $(M+H)^+$; IR (KBr) 3290, 3067, 2973, 2873, 1733, 1637, 1589, 1541, 1489, 1398, 1365, 1284, 1245, 1200, 1167, 1110, 1034, 1024, 1011, 988, 968, 953, 876, 849, 752, 691, 597, 492 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.38 (s, 1H), 8.07 (d, J = 9.0 Hz, 1H), 7.82 (d, J = 8.7 Hz, 2H), 7.41 (t, J = 7.7 Hz, 2H), 7.18 (t, J = 7.7 Hz, 1H), 7.07–6.99 (m, 4H), 4.30–4.18 (m, 1H), 4.07–3.94 (m, 2H), 2.20–2.11 (m, 1H), 1.73–1.49 (m, 2H), 1.06 (s, 9H), 0.99 (d, J = 6.6 Hz, 3H); optical rotation $[\alpha]_D^{30}$ +4.0 (c 0.45, DMF); HRMS (FAB) calcd for $C_{24}H_{31}N_2O_6$: 443.2182. Found: 443.2185.

4.27. *tert*-Butyl [(1*R*)-2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-1-methyl-2-oxoethyl]carbamate (40), *tert*-butyl [(1*R*)-2-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-1-methylethyl]carbamate (41), and *tert*-butyl (2*R*)-2-methyl-5-oxo-1-pyrrolidinecarboxylate (42)

To a stirred solution of compound **39** (5.0 g, 26.5 mmol) in CH_2Cl_2 (150 mL) were added 4-dimethylaminopyridine (8.1 g, 66.3 mmol), Meldrums' acid (7.6 g, 53 mmol), and N,N'-dicyclohexylcarbodiimide (10.9 g, 53 mmol) in CH_2Cl_2 (150 mL). After stirring at room temperature for 24 h, the solution was filtered, and then washed with 5% $KHSO_4$, and brine, dried over Na_2SO_4, and filtered. To a stirred solution of the filtrate were added AcOH (16.6 mL, 291 mmol) and $NaBH_4$ (2.5 g, 66 mmol) at 0 °C. After stirring for 1.5 h at 0 °C, the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with H_2O, and brine, dried over Na_2SO_4, and evaporated. The resulting residue was purified by silica gel chromatography with CH_2Cl_2–MeOH (9:1) as an eluent to afford compound **41**. A solution of compound **41** (1.74 g) in toluene was stirred at 110 °C for 5 h. The reaction mixture was diluted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and evaporated. The resulting residue was purified by silica gel chromatography with EtOAc–*n*-hexane (3:17) as an eluent to afford compound **42** (1.32 g, 25%).

TLC R_f = 0.53 (EtOAc–*n*-hexane, 1:1); ^{1}H NMR ($CDCl_3$): δ 4.29–4.19 (m, 1H), 2.60 (ddd, J = 16.3 Hz, 11.1 Hz and 9.0 Hz, 1H), 2.42 (ddd, J = 17.4 Hz, 9.0 Hz and 3.0 Hz, 1H), 2.23–2.09 (m, 1H), 1.68–1.58 (m, 1H), 1.52 (s, 9H), 1.31 (d, J = 6.6 Hz, 3H).

4.28. Methyl (4*R*)-4-[(*tert*-butoxycarbonyl)amino]pentanoate (43)

To a stirred solution of compound **42** (785 mg, 3.90 mmol) in acetone (5.0 mL) was added 1 N NaOH (2 mL) at room temperature. After stirring for 3 h, the reaction mixture was quenched with 1 N HCl and diluted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to afford a crude product. To a stirred solution of the crude product in MeOH (3 mL) was added CH_2N_2 (3 mL) and stirring was continued for 5 min. The reaction mixture was evaporated. The resulting residue was purified by silica gel chromatography with EtOAc–*n*-hexane (3:17) as an eluent to afford compound **43** (784 mg, 87%).

TLC R_f = 0.31 (EtOAc–*n*-hexane, 15:85); ^{1}H NMR ($CDCl_3$): δ 4.38–4.28 (m, 1H), 3.67 (s, 3H), 2.39–2.34 (m, 2H), 1.84–1.61 (m, 2H), 1.42 (s, 9H), 1.13 (d, J = 6.6 Hz, 3H).

4.29. Methyl (4*R*)-4-[(4-phenoxybenzoyl)amino]pentanoate (44)

To a stirred solution of compound **43** (650 mg, 2.8 mmol) in EtOAc (2 mL) was added 4 N HCl–EtOAc (6 mL) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was concentrated in vacuo to

afford a crude amine. To a stirred solution of the crude amine in DMF (6 mL) were added EDC·HCl (810 mg, 4.2 mmol), HOBt·H_2O (862 mg, 5.6 mmol), 4-phenoxybenzoic acid (722 mg, 3.4 mmol), and triethylamine (0.6 mL, 4.2 mmol) at 0 °C. The reaction mixture was diluted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and evaporated. The resulting residue was purified by silica gel chromatography with EtOAc–toluene (1:19) as an eluent to afford compound **44** (696 mg, 76%).

TLC $R_f = 0.25$ (EtOAc–*n*-hexane, 1:1); ^1H NMR ($CDCl_3$): δ 7.76–7.72 (m, 2H), 7.41–7.33 (m, 2H), 7.20–7.12 (m, 1H), 7.06–6.97 (m, 4H), 6.21 (d, $J = 8.8$ Hz, 1H), 4.26–4.10 (m, 1H), 2.51–2.38 (m, 2H), 1.95–1.84 (m, 2H), 1.26 (d, $J = 6.6$ Hz, 3H).

4.30. Methyl (2*S*,4*R*)-2-methyl-4-[(4-phenoxybenzoyl)-amino]pentanoate (45)

Compound **45** was prepared from **44** in 84% yield according to the general procedure for the preparation of **26** from **25**.

TLC $R_f = 0.50$ (EtOAc–*n*-hexane, 1:1); ^1H NMR ($CDCl_3$): δ 7.75–7.72 (m, 2H), 7.40–7.34 (m, 2H), 7.19–7.14 (m, 1H), 7.05–6.98 (m, 4H), 5.97 (d, $J = 8.4$ Hz, 1H), 4.35–4.20 (m, 1H), 3.55 (s, 3H), 2.61–2.49 (m, 1H), 2.00 (ddd, $J = 14.2$ Hz, 10.6 Hz and 8.1 Hz, 1H), 1.65–1.56 (m, 1H), 1.24 (d, $J = 6.3$ Hz, 3H), 1.22 (d, $J = 7.2$ Hz, 3H).

4.31. (2*S*,4*R*)-2-Methyl-4-[(4-phenoxybenzoyl)amino]-pentanoic acid (46) and *N*-[(1*R*,3*S*)-4-(hydroxyamino)-1,3-dimethyl-4-oxobutyl]-4-phenoxybenzamide (20)

Compound **46** was prepared from **45** in 100% yield according to the general procedure for preparation of **29**. Compound **46**: TLC $R_f = 0.48$ ($CHCl_3$–MeOH–AcOH, 100:5:1). Compound **20** was prepared from **46** in 89% yield (in two steps) according to the general procedure for the preparation of **2**–**15** from **29a**–**n**.

Compound **20**: TLC $R_f = 0.26$ ($CHCl_3$–MeOH–AcOH, 100:5:1); MS (MALDI, pos.) *m*/*z* 365 $(M+Na)^+$, 343 $(M+H)^+$; IR (KBr) 3282, 2969, 1632, 1589, 1541, 1489, 1354, 1246, 1169, 1015, 967, 870, 752, 692 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.39 (s, 1H), 8.68 (d, $J = 1.6$ Hz, 1H), 8.03 (d, $J = 8.4$ Hz, 1H), 7.88–7.84 (m, 2H), 7.47–7.39 (m, 2H), 7.23–7.15 (m, 1H), 7.08–6.99 (m, 4H), 4.08–3.92 (m, 1H), 2.21–2.07 (m, 1H), 1.75 (ddd, $J = 13.8$ Hz, 7.7 Hz and 6.6 Hz, 1H), 1.46 (ddd, $J = 13.8$ Hz, 7.7 Hz and 6.6 Hz, 1H), 1.11 (d, $J = 6.6$ Hz, 3H), 1.01 (d, $J = 6.6$ Hz, 3H); optical rotation $[\alpha]_D^{30}$ +19.84 (*c* 0.25, DMF); HRMS (FAB) calcd for $C_{19}H_{23}N_2O_4$: 343.1658. Found: 343.1663.

4.32. Methyl (4*S*)-5-(ethoxymethoxy)-4-[(4-phenoxy-benzoyl)amino]pentanoate (47)

Compound **47** was prepared from **30a** in 100% yield according to the same procedure as described for the preparation of **27** from **25**.

TLC $R_f = 0.38$ (EtOAc–*n*-hexane, 1:1); ^1H NMR ($CDCl_3$): δ 7.78–7.31 (m, 2H), 7.41–7.33 (m, 2H), 7.20–7.12 (m, 1H), 7.06–6.97 (m, 4H), 6.65 (d, $J = 8.8$ Hz, 1H), 4.69 (s, 2H), 4.40–4.22 (m, 1H), 3.75 (dd, $J = 10.2$ Hz and 3.2 Hz, 1H), 3.65–3.55 (m, 3H), 3.63 (s, 3H), 2.51–2.41 (m, 2H), 2.07–1.95 (m, 2H), 1.20 (t, $J = 7.0$ Hz, 3H).

4.33. Methyl (2*S*,4*S*)-5-(ethoxymethoxy)-2-ethyl-4-[(4-phenoxybenzoyl)amino]pentanoate (48)

Compound **48** was prepared from **47** in 100% yield according to the general procedure for the preparation of **26** from **25**.

TLC $R_f = 0.53$ (EtOAc–*n*-hexane, 1:1); ^1H NMR ($CDCl_3$): δ 7.78–7.73 (m, 2H), 7.41–7.33 (m, 2H), 7.20–7.13 (m, 1H), 7.06–6.97 (m, 1H), 6.42 (d, $J = 8.8$ Hz, 1H), 4.70 (d, $J = 6.6$ Hz, 1H), 4.60 (d, $J = 6.6$ Hz, 1H), 4.42–4.28 (m, 1H), 3.72 (dd, $J = 10.3$ Hz and 3.4 Hz, 1H), 3.62–3.57 (m, 1H), 3.60 (q, $J = 6.6$ Hz, 2H), 3.50 (s, 3H), 2.50–2.36 (m, 1H), 2.19–2.02 (m, 1H), 1.76 (ddd, $J = 14.4$ Hz, 4.4 Hz and 4.4 Hz, 1H), 1.70–1.56 (m, 2H), 1.19 (t, $J = 7.0$ Hz, 3H), 0.89 (t, $J = 7.8$ Hz, 3H).

4.34. (2*S*,4*S*)-5-(Ethoxymethoxy)-2-ethyl-4-[(4-phenoxy-benzoyl)amino]pentanoic acid (49)

Compound **49** was prepared from **48** in 100% yield according to the general procedure for the preparation of **29** from **27** or **28a**–**m**.

TLC $R_f = 0.44$ ($CHCl_3$–MeOH–AcOH–H_2O, 100:10:1:1); ^1H NMR (CD_3OD): δ 7.83–7.78 (m, 2H), 7.43–7.36 (m, 2H), 7.22–7.15 (m, 1H), 7.07–6.96 (m, 4H), 4.67 (s, 2H), 4.39–4.23 (m, 1H), 3.65–3.52 (m, 4H), 2.43–2.29 (m, 1H), 2.04–1.66 (m, 4H), 1.51 (t, $J = 7.2$ Hz, 3H), 0.92 (t, $J = 7.2$ Hz, 3H).

4.35. *N*-{(1*S*,3*S*)-1-[(Ethoxymethoxy)methyl]-3-[(hydroxy-amino)carbonyl]pentyl}-4-phenoxybenzamide (21)

Compound **21** was prepared from **49** in 85% yield according to the general procedure for the preparation of **2**–**15** from **29a**–**n**.

TLC $R_f = 0.33$ ($CHCl_3$–MeOH–AcOH, 100:5:1); MS (MALDI, pos.) *m*/*z* 469 $(M+K)^+$, 453 $(M+Na)^+$, 431 $(M+H)^+$; IR (KBr) 3276, 2928, 1634, 1589, 1542, 1489, 1244, 1171, 1116, 1046, 843, 753, 693 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.40 (s, 1H), 8.70 (d, $J = 0.8$ Hz, 1H), 8.02 (d, $J = 8.4$ Hz, 1H), 7.86 (d, $J = 8.8$ Hz, 2H), 7.46–7.38 (m, 2H), 7.23–7.15 (m, 1H), 7.08–6.99 (m, 4H), 4.59 (s, 2H), 4.19–4.01 (m, 1H), 3.52–3.42 (m, 2H), 3.47 (q, $J = 7.0$ Hz, 2H), 2.05–1.92 (m, 1H), 1.79–1.32 (m, 4H), 1.07 (t, $J = 7.2$ Hz, 3H), 0.76 (t, $J = 7.0$ Hz, 3H); optical rotation $[\alpha]_D^{30}$ −22.10 (*c* 0.20, DMF); HRMS (FAB) calcd for $C_{23}H_{31}N_2O_6$: 431.2182. Found: 431.2183.

4.36. Benzyl (4*S*)-5-[(2-methoxyethoxy)methoxy]-4-[(4-phenoxybenzoyl)amino]pentanoate (50)

Compound **50** was prepared from **35a** in 100% yield according to the same procedure as described for the preparation of **37a** from **36a**.

TLC $R_f = 0.53$ (EtOAc–*n*-hexane, 1:1); ^{1}H NMR ($CDCl_3$): δ 7.78 (d, $J = 8.8$ Hz, 2H), 7.42–7.26 (m 7H), 7.22–7.14 (m, 1H), 7.06–6.96 (m, 4H), 6.75 (d, J = 8.8 Hz, 2H), 5.16–5.00 (m, 2H), 4.78–4.68 (m, 2H), 4.42–4.23 (m, 1H), 3.80 (dd, $J = 10.6$, 3.6 Hz, 1H), 3.75–3.58 (m, 3H), 3.56–3.48 (m, 2H), 3.33 (s, 3H), 2.61–2.40 (m, 2H), 2.12–1.97 (m, 2H).

4.37. Benzyl (2*S*,4*S*)-4-[(*tert*-butoxycarbonyl)amino]-5-[(2,2-dimethylpropanoyl)oxy]-2-ethylpentanoate (51)

Compound **51** was prepared from **35b** in 55% yield according to the general procedure for the preparation of **26** from **25**.

TLC $R_f = 0.58$ (toluene–EtOAc, 4:1); ^{1}H NMR ($CDCl_3$): δ 7.40–7.32 (m, 5H), 5.21 (d, $J = 12.5$ Hz, 1H), 5.06 (d, $J = 12.5$ Hz, 1H), 4.43 (d, $J = 8.8$ Hz, 1H), 4.09–3.91 (m, 3H), 2.51–2.36 (m, 1H), 1.87–1.57 (m, 4H), 1.42 (s, 9H), 1.19 (s, 9H), 0.87 (t, $J = 7.3$ Hz, 3H).

4.38. Benzyl (2*S*,4*S*)-2-ethyl-5-[(2-methoxyethoxy)methoxy]-4-[(4-phenoxybenzoyl)amino]pentanoate (52a)

Compound **52a** was prepared from **50** in 96% yield according to the general procedure for the preparation of **26** from **25**.

TLC $R_f = 0.39$ (EtOAc–*n*-hexane, 1:1); ^{1}H NMR ($CDCl_3$): δ 7.76 (d, $J = 9.0$ Hz, 2H), 7.41–7.13 (m, 8H), 7.02 (d, $J = 8.4$ Hz, 2H), 6.98 (d, $J = 9.0$ Hz, 2H), 6.52 (d, $J = 8.7$ Hz, 1H), 5.05 (d, $J = 12.6$ Hz, 1H), 4.84 (d, $J = 12.6$ Hz, 2H), 4.73 (d, $J = 6.9$ Hz, 1H), 4.70 (d, $J = 6.9$ Hz, 1H), 4.43–4.31 (m, 1H), 3.75 (dd, $J = 10.2$ Hz and 3.6 Hz, 1H), 3.72–3.66 (m, 2H), 3.60 (dd, $J = 10.2$ Hz and 3.9 Hz, 1H), 3.54–3.49 (m, 2H), 3.34 (s, 3H), 2.53–2.40 (m, 1H), 2.14 (ddd, $J = 14.4$ Hz, 10.2 Hz and 8.7 Hz, 1H), 1.78 (dt, $J = 14.4$ Hz and 4.8 Hz, 1H), 1.72–1.60 (m, 2H), 0.87 (t, $J = 7.5$ Hz, 3H).

4.39. Benzyl (2*S*,4*S*)-5-[(2,2-Dimethylpropanoyl)oxy]-2-ethyl-4-[(4-phenoxybenzoyl)amino]pentanoate (52b)

Compound **52b** was prepared from **51** in 58% yield according to the same procedure as described for the preparation of **37a** from **36a**.

^{1}H NMR ($CDCl_3$): δ 7.70 (d, $J = 9.0$ Hz, 2H), 7.40–7.17 (m, 8H), 7.20 (d, $J = 7.8$ Hz, 2H), 6.98 (d, $J = 9.0$ Hz, 2H), 6.17 (d, $J = 9.0$ Hz, 1H), 5.05 (d, $J = 12.3$ Hz, 1H), 4.82 (d, $J = 12.3$ Hz, 1H), 4.56–4.44 (m, 1H), 4.28–4.22 (m, 1H), 4.13–4.06 (m, 1H), 2.53–2.44 (m, 1H), 2.09–1.97 (m, 1H), 1.78–1.63 (m, 3H), 1.19 (s, 9H), 0.88 (t, $J = 7.5$ Hz, 3H).

4.40. (2*S*,4*S*)-2-Ethyl-5-[(2-methoxyethoxy)methoxy]-4-[(4-phenoxybenzoyl)amino]pentanoic acid (53a)

Compound **53a** was prepared from **52a** in 94% yield according to the same procedure as described for the preparation of **38a** from **37a**.

TLC $R_f = 0.27$ ($CHCl_3$–MeOH, 19:1); ^{1}H NMR ($CDCl_3$): δ 7.76 (d, $J = 8.8$ Hz, 2H), 7.42–7.31 (m, 2H), 7.21–7.12 (m, 1H), 7.06–7.00 (m, 2H), 6.97 (d, $J = 8.8$ Hz, 2H), 6.69 (d, $J = 9.0$ Hz, 1H), 4.74 (d, $J = 7.0$ Hz, 2H), 4.70 (d, $J = 7.0$ Hz, 1H), 4.47–4.29 (m, 1H), 3.80 (dd, $J = 10.2$ Hz and 3.4 Hz, 1H), 3.74–3.67 (m, 2H), 3.62 (dd, $J = 10.2$ Hz and 3.6 Hz, 1H), 3.57–3.50 (m, 2H), 3.35 (s, 3H), 2.54–2.36 (m, 1H), 2.09 (dt, $J = 14.4$ Hz and 9.2 Hz, 1H), 1.80 (dt, $J = 14.4$ Hz and 5.4 Hz, 1H), 1.76–1.58 (m, 2H), 0.94 (t, $J = 7.4$ Hz, 3H).

4.41. (2*S*,4*S*)-5-[(2,2-Dimethylpropanoyl)oxy]-2-ethyl-4-[(4-phenoxybenzoyl)amino]pentanoic acid (53b)

Compound **53b** was prepared from **52b** in 100% yield according to the same procedure as described for the preparation of **38a** from **37a**.

^{1}H NMR (DMSO-d_6): δ 12.13 (br s, 1H), 8.14 (d, $J = 8.7$ Hz, 1H), 7.80 (d, $J = 8.7$ Hz, 2H), 7.41 (t, $J = 7.7$ Hz, 2H), 7.17 (t, $J = 7.7$ Hz, 2H), 7.04 (d, $J = 7.7$ Hz, 2H), 7.00 (d, $J = 8.7$ Hz, 2H), 4.32–4.20 (m, 1H), 4.08–3.94 (m, 2H), 2.26–2.17 (m, 1H), 1.83–1.72 (m, 1H), 1.66–1.43 (m, 2H), 1.06 (s, 9H), 0.80 (t, $J = 7.5$ Hz, 3H).

4.42. *N*-((1*S*,3*S*)-3-[(Hydroxyamino)carbonyl]-1-{[(2-methoxyethoxy)methoxy]methyl}pentyl)-4-phenoxybenzamide (22)

Compound **22** was prepared from **53a** in 88% yield according to the same procedure as described for the preparation of **13** from **29m**.

TLC $R_f = 0.43$ ($CHCl_3$–MeOH, 9:1); MS (APCI, neg. 40 V) *m*/*z* 445 $(M-H)^-$; IR (KBr) 3274, 3067, 2917, 1634, 1541, 1490, 1341, 1316, 1249, 1198, 1168, 1115, 1062, 1042, 954, 921, 870, 849, 754, 692, 489 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.35 (s, 1H), 8.64 (s, 1H), 8.01 (d, $J = 8.7$ Hz, 1H), 7.85 (d, $J = 8.7$ Hz, 2H), 7.41 (t, $J = 7.7$ Hz, 2H), 7.17 (t, $J = 7.7$ Hz, 1H), 7.04 (d, $J = 7.7$ Hz, 2H), 7.00 (d, $J = 8.7$ Hz, 2H), 4.59 (s, 2H), 4.18–4.06 (m, 1H), 3.55–3.37 (m, 6H), 3.19 (s, 3H), 2.15 (sextet, $J = 7.1$ Hz, 1H), 1.68–1.60 (m, 2H), 0.99 (d, $J = 6.6$ Hz, 3H); optical rotation $[\alpha]_D^{30}$ −5.0 (*c* 0.46, DMF); HRMS (FAB) calcd for $C_{24}H_{33}N_2O_7$: 461.2288. Found: 461.2301.

4.43. (2*S*,4*S*)-4-[(Hydroxyamino)carbonyl]-2-[(4-phenoxybenzoyl)amino]hexyl pivalate (23)

Compound **23** was prepared from **53b** in 73% yield according to the same procedure as described for the preparation of **13** from **29m**.

TLC $R_f = 0.69$ ($CHCl_3$–MeOH, 9:1); MS (MALDI, pos.) *m/z* 495 $(M+K)^+$, 479 $(M+Na)^+$, 457 $(M+H)^+$; IR (KBr) 3262, 3069, 2967, 2932, 2875, 1733, 1638, 1589, 1543, 1489, 1459, 1397, 1364, 1284, 1245, 1151, 1109, 1034, 975, 902, 876, 848, 751, 691, 595, 492 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.41 (s, 1H), 8.71 (s, 1H), 8.07 (d, $J = 8.7$ Hz, 1H), 7.81 (d, $J = 8.6$ Hz, 2H), 7.41 (t, $J = 7.6$ Hz, 2H), 7.17 (t, $J = 7.6$ Hz, 1H), 7.04 (d, $J = 7.6$ Hz, 2H), 7.00 (d, $J = 8.6$ Hz, 2H), 4.25–4.13 (m, 1H), 4.08–3.94 (m, 2H), 2.03–1.91 (m, 1H), 1.63 (t, $J = 6.9$ Hz, 2H), 1.48–1.36 (m, 2H), 1.06 (s, 9H), 0.75 (t, $J = 7.5$ Hz, 3H); optical rotation $[\alpha]_D^{30}$ −9.4 (*c* 0.15, DMF); HRMS (FAB) calcd for $C_{25}H_{33}N_2O_6$: 457.2339. Found: 457.2336.

5. Biological assay

5.1. MMP-1 assay

Commercially available assay kits (Yagai, Yamagata City, Japan) were used. The solutions provided in the kits were used unless otherwise stated. A 98 μL portion of enzyme solution (0.5 U/mL) and 2 μL of inhibitor solution (DMSO) were incubated with 100 μL of 0.5 mg/mL FITC-labeled type I collagen solution at 37 °C for 3 h. After incubation with 300 L of quenching solution on ice for 30 min, the reaction mixture was centrifuged at 2000*g* for 15 min. Supernatant was used for measurement of fluorescence by RF5300-PC. Excitation and emission wavelengths were 495 and 520 nm, respectively.

5.2. MMP-2 and MMP-9 assays[15]

A mixture of 130 μL of MOCAc-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2 (final concentration: 15 μM) and 20 μL of inhibitor solution was incubated at 37 °C for 5 min. Enzyme solution (50 μL) was added, and the reaction was performed at 37 °C for 10 min. Its fluorescence was measured by f_{max}. Excitation and emission wavelengths were 320 and 390 nm, respectively.

5.3. MMP-3 assay[16]

A mixture of 190 μL of MOCAc-Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg-Lys(Dnp)–NH_2 (final concentration:15 μM) and 10 μL of inhibitor solution was incubated at 37 °C for 5 min. Enzyme solution (50 μL) was added, and the reaction was performed at 37 °C for 10 min. Its fluorescence was measured by f_{max}. Excitation and emission wavelengths were 320 and 390 nm, respectively.

5.4. In vivo assay[17]

Compound **9** was orally administered to male Hartley guinea pigs (SLC, Shizuoka, Japan), weighing 221–375 g, at 60 min before the intra-articular injection of recombinant human stromelysin (SLN). (Sufficient enzyme was injected so that proteoglycan release was increased 6-fold relative to the control). Carboxymethyl cellulose (0.5%) was used as the solvent. Two hours after the injection of SLN, the animals were sacrificed under anesthesia, and then the knee joints were opened and washed with 500 μL of saline containing 0.38% sodium citrate. Next, the proteoglycan content of the washings was measured as a marker of cartilage destruction.[18] Briefly, the washings were treated with papain (Worthington Biochemical, NJ, USA). After the addition of dimethyl-methylene blue solution, the absorbance was measured at 540 nm and the proteoglycan content was calculated from the standard curve for chondroitin sulfate. Each group consisted of four animals. These experiments were carried out in accordance with the Guidelines for Animal Experiments of ONO Pharmaceutical Co., Ltd. (Osaka, Japan).

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