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Design and Synthesis of New Orally Active Inhibitors of Human Neutrophil Elastase

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Abstract—To identify new orally active inhibitors, further modification of **1** (ONO-6818) was performed. Peptidic derivatives **4b**, **4c** and **4n** showed more potent inhibitory activity than nonpeptidic derivatives **3a**–**c**. As a result, a series of peptidic inhibitors, **4a**–**s** and **5a**–**v**, were discovered. Among these *N*-aryl derivatives **5a**–**g**, **5i**, **5m** and **5o**–**v** showed oral activity. Their oral activity showed good correlation with their metabolic stability. Compounds **5h** and **5j**–**l**, which were extremely metabolically unstable in hamster plasma, did not show oral activity. Oral activity was considered to be determined by a combination of at least two factors: oral absorption and metabolic stability.

Introduction

Human neutrophil elastase (HNE) has been implicated in initiation or exacerbation of a number of pathological conditions such as pulmonary emphysema,[1] cystic fibrosis,[2] chronic bronchitis,[3] adult respiratory distress syndrome,[4] chronic bowel disease,[5,6] myocarditis[7,8] and arthritis.[9] Several classes of orally active, nonpeptidic inhibitors of HNE have been described including trifluoromethyl ketones,[10–12] β-lactams[13,14] and pyrrolopyrrolones.[15] An attempt has also been made to identify peptidic inhibitors with the desired level of in vivo activity following oral administration.[16] However, orally active inhibitors with clinical potential are very rare.

Our studies to find a low molecular weight inhibitor of HNE resulted in the discovery of the orally active nonpeptidic inhibitor **1** (ONO-6818).[17] An orally active peptidic inhibitor **2** (ZD8321) was also indentified by Zeneca.[16]

In the process of our own screening program for an orally active inhibitor of HNE, a new series of inhibitors, **3a**–**c**, **4b**, **4c** and **4n**, were obtained by further chemical modification of α-keto-1,3,4-oxadiazole **1** (Chart 1). In this report, we describe the discovery of peptidyl α-keto-1,3,4-oxadiazolin-2-ones, which possess excellent oral activity.

Chemistry

Compounds **4a**–**s**, **5a**–**t** and **5v** were synthesized by the peptide formation of aminoalcohols **14a**–**s**, **19a**–**t** and **25** with carboxylic acid **16** followed by oxidation of the formed alcohols **15a**–**s**, **20a**–**t** and **26**, respectively.

The common intermediate **10a** was prepared as described in Scheme 1. Ring-opening reaction of *N*-protected aminoepoxide **6**[18] afforded **7**. The newly formed hydroxyl group was protected by formation of an acetonide to afford **8**. Methanolysis of *O*-acetate of **8** provided **9**, which was oxidized in good yield to afford carboxylic acid **10a**.

Compounds **4a**–**s** were prepared as described in Scheme 2. The compound **10b**, which was prepared by esterification of **10a**, was converted to acid hydrazide **11** by condensation reaction with hydrazine hydrate. Cyclization of the acid hydrazide function of **11** was accomplished by reaction with carbonyldiimidazole (CDI) in the presence of triethylamine to afford 1,3,4-oxadiazolin-2-one **12**.

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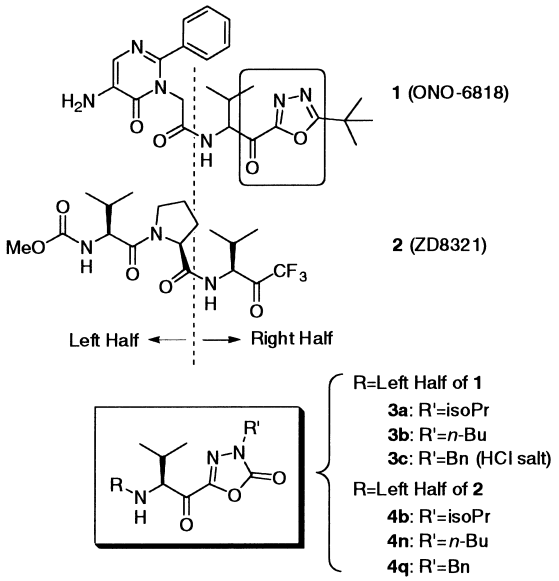
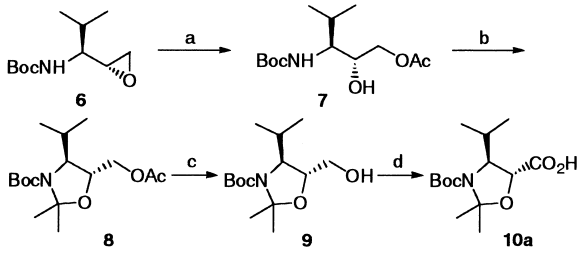


Chart 1. α-Keto-1,3,4-oxadiazolin-2-one as a new right half.

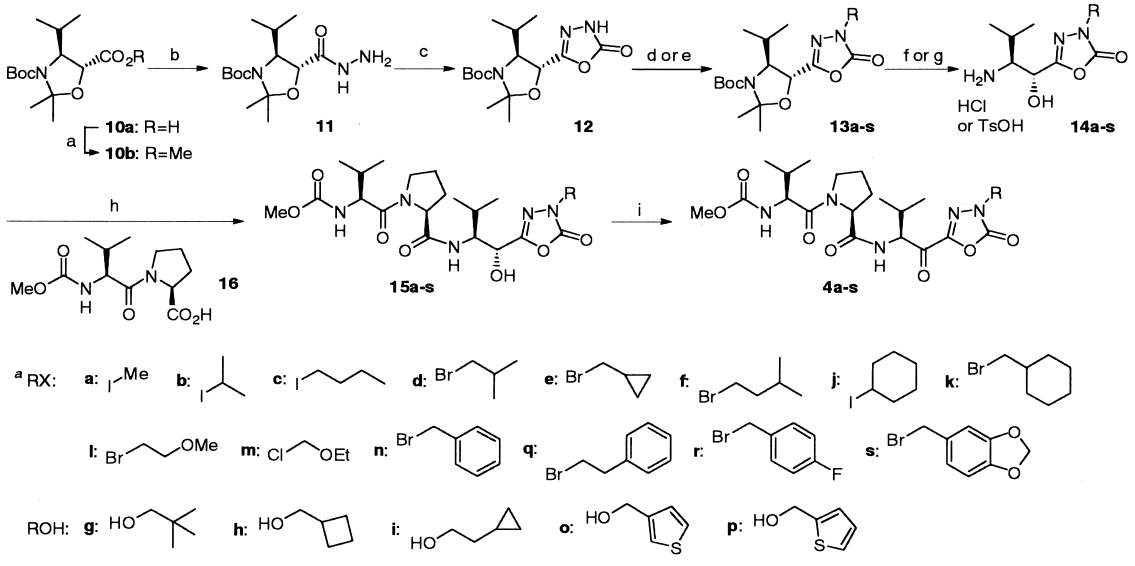


Scheme 1. Preparation of the common intermediate **10a.** Reagent: (a) AcOH, Li_2CO_3, DMF; (b) 2-methoxypropene, 10-camphorsulfonic acid, DMF; (c) K_2CO_3, MeOH; (d) $RuCl_3{\cdot}nH_2O$, $NaIO_4$, CCl_4, CH_3CN, H_2O.

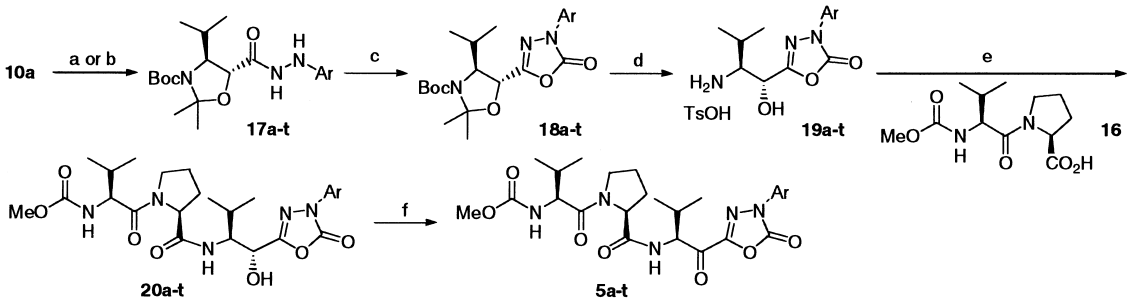
3*N*-Alkylation of the newly formed 1,3,4-oxadiazolin-2-one with alkyl halide in the presence of a base or with alkyl alcohol in the presence of diethyl azodicarboxylate (DEAD)/triphenylphosphine gave **13a–s**. Deprotection of the acetonide of **13a–s** under acidic conditions provided amino-alcohols **14a–s**, which were converted to the corresponding **15a–s**, respectively, by condensation with **16**.[19] Swern oxidation of the alcohols **15a–s** afforded **4a–s**.

Synthesis of **5a–u** was carried out as described in Schemes 3 and 4. *N*-Aryl-*N'*-acylhydrazide **17a–t** were prepared by condensation reaction of **10a** with the corresponding aryl hydrazine in the presence of EDC·HCl. Cyclization reaction of **17a–t** using CDI afforded **18a–t**, deprotection of which under acidic conditions provided **19a–t**, respectively. Peptide formation of **19a–t** with **16** provided **20a–t**, oxidation of which provided **5a–t**, respectively. Hydrogenolysis of the benzyl group of **5n** gave the phenol derivative **5u** (Scheme 4).

3-(4-Anilino)-1,3,4-oxadiazolin-2-one **5v** was prepared as described in Scheme 5. The acid hydrazide **21** was obtained from **10a** by the conventional method using 4-nitrophenylhydrazine. Cyclization of **21** using CDI was carried out by the same procedure as described above to afford **22**. Catalytic hydrogenation of **22** afforded **23**, which was alkylated to give **24**. Acidic deprotection of **24** provided the amino-alcohol **25**, peptide formation of which with **16** gave **26**. Swern oxidation of **26** afforded **5v**. Compounds **3a–c** were prepared as described in Scheme 6(a) and (b). Peptide formation of the aminoketones **14b,c** with **27a** afforded **28a,b**, respectively, which were converted to the corresponding ketones **29a,b** by Swern oxidation. Subsequent deprotection of **29a,b** by catalytic hydrogenation afforded **3a,b**, respectively (Scheme 6(a)). Replacement of the *N*-benzyloxycarbonyl group of **27b**,



Scheme 2. Preparation of 3-alkyl-1,3,4-oxadiazolin-2-ones **4a–s**. Reagent: (a) CH_2N_2–Et_2O, EtOAc; (b) $NH_2NH_2{\cdot}H_2O$, MeOH; (c) CDI, triethylamine, THF; (d) RX, K_2CO_3, DMF; (e) ROH, DEAD, Ph_3P, THF; (f) TFA–MeOH or TFA–H_2O, then HCl–EtOAc; (g) $TsOH{\cdot}H_2O$, EtOH; (h) **16**, EDC·HCl, $HOBt{\cdot}H_2O$, *N*-methylmorpholine, DMF; (i) oxalyl chloride, DMSO, *N*-methylmorpholine, CH_2Cl_2.

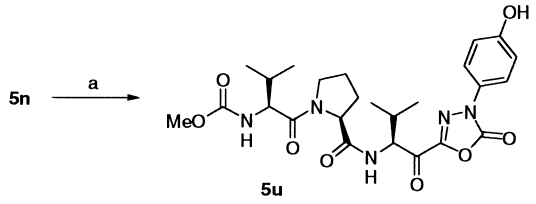


Scheme 3. Preparation of 3-Aryl-1,3,4-oxadiazolin-2-ones **5a**–**t**. Ar-: **a**, Ph-; **b**, 2-Me-Ph-; **c**, 3-Me-Ph-; **d**, 4-Me-Ph-; **e**, 2-MeO-Ph-; **f**, 4-MeO-Ph-; **g**, 2-CF_3-Ph-; **h**, 4-CF_3-Ph-; **i**, 4-F-Ph-; **j**, 4-Cl-Ph-; **k**, 4-CN-Ph-; **l**, 4-CF_3O-Ph-; **m**, 4-EtO-Ph-; **n**, 4-BnO-Ph-; **o**, 2-Me-4-MeO-Ph-; **p**, 2,4-diMeO-Ph-; **q**, 2-Me-4-F-Ph-; **r**, 2-MeO-4-F-Ph-; **s**, 2,4-diF-Ph-; **t**, 2,4-diMe-Ph-. Reagent: (a) $ArNHNH_2$, EDC·HCl, HOBt·H_2O, DMF; (b) $ArNHNH_2$·HCl, EDC·HCl, HOBt·H_2O, *N*-methylmorpholine, DMF; (c) CDI, triethylamine, THF; (d) TsOH·H_2O, EtOH; (e) **16**, EDC·HCl, HOBt·H_2O, *N*-methylmorpholine, DMF; (f) oxalyl chloride, DMSO, *N*-methylmorpholine, CH_2Cl_2.

prepared from **27a**, with a *N-tert*-butoxycarbonyl group was carried out by the conventional method to give **27c**. Peptide formation of **27c** with **14n** afforded **28c**, which was converted to **29c** by Swern oxidation. Acidic deprotection of **29c** provided **3c** (Scheme 6(b)).

Results and Discussion

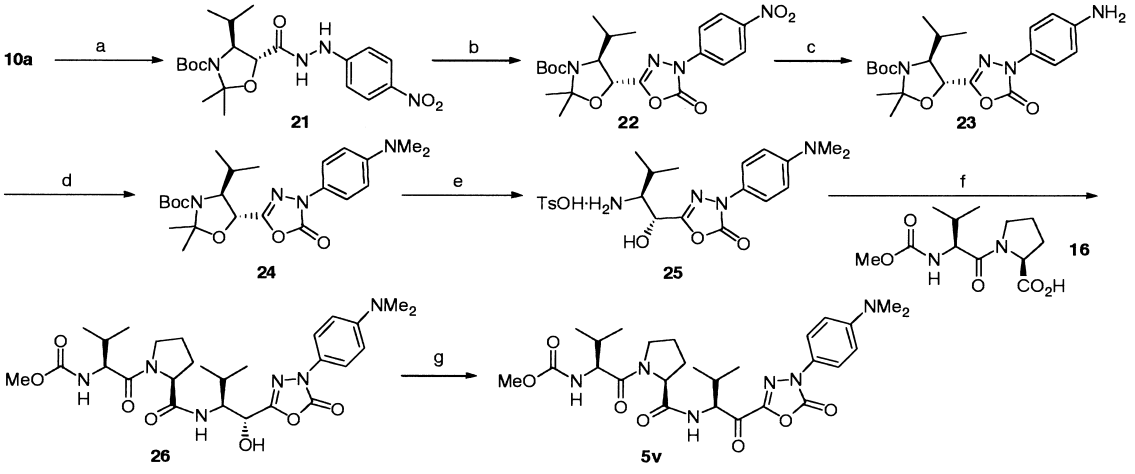
The compounds listed in Tables 1–5 were tested both in vitro and in vivo for their ability to inhibit elastase activity. In vitro testing consisted of determination of the K_i value corresponding to the compounds' ability to inhibit hydrolysis of the synthetic substrate MeO-Suc-Ala-Ala-Pro-Val-pNa.[20] In vivo testing was performed by acute hemorrhagic assay in hamsters.



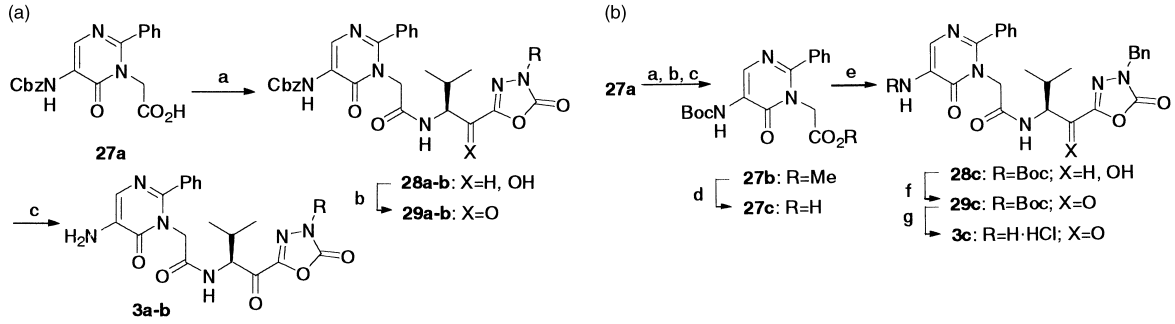
Scheme 4. Hydrogenolysis of benzyl group of **5n**. Reagent: (a) H_2, 10% $Pd(OH)_2$/C, MeOH.

This assay evaluates the ability of an orally administered inhibitor to protect the lungs from hemorrhage induced by a subsequent intratracheal challenge of a 10U/lung dose of HNE.

As shown in Table 1, replacement of 5-*tert*-butyl-1,3,4-oxadiazole of **1** with 3-alkyl-1,3,4-oxadiazolin-2-ones afforded **3a**–**c** with marked reduction of the inhibitory activity. Conversion of **3a**–**c** to their corresponding peptidic inhibitors **4b**, **4c** and **4n** restored the potent in vitro activity (Table 2). Based on these experimental results, a series of peptidic inhibitors, **4a**–**s**, were discovered to exhibit moderate to potent in vitro activity. More detailed chemical modification of this series of compounds was continued to obtain orally active inhibitors. Biological data of 3-alkyl-1,3,4-oxadiazolin-2-ones are shown in Table 2(a). Among the compounds tested, **4c** demonstrated the most potent in vitro activity, although it was not orally active. 3-Alkyl derivatives **4b**–**m** exhibited potent inhibitory activity, while 3-methyl derivative **4a** did not. Clear-cut SAR was not obtained within the chemical modifications described in Table 2(a). Unfortunately, none of the 3-alkyl-1,3,4-oxadiazolin-2-ones described in Table 2(a) was orally active despite their potent in vitro activities. The same extent of in vitro potency was obtained in the series of compounds



Scheme 5. Preparation of 3-(4-anilino)-1,3,4-oxadiazolin-2-one **5v**. Reagent: (a) 4-nitrophenylhydrazine, EDC·HCl, HOBt·H_2O, DMF; (b) CDI, triethylamine, THF; (c) H_2, 10% $Pd(OH)_2$/C, MeOH, dioxane; (d) HCHOaq, $NaBH_3CN$, AcOH, MeCN; (e) TsOH·H_2O, EtOH; (f) **16**, EDC·HCl, HOBt·H_2O, *N*-methylmorpholine, DMF; (g) oxalyl chloride, DMSO, *N*-methylmorpholine, CH_2Cl_2.



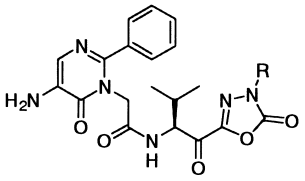
Scheme 6. (a) Preparation of **3a–b**. **a**, R = isoPr; **b**, R = *n*-Bu. Reagent: (a) **14b** or **14c**, EDC·HCl, HOBt·H_2O, *N*-methylmorpholine, DMF; (b) oxalyl chloride, DMSO, *N*-methylmorpholine, CH_2Cl_2; (c) H_2, 10% Pd/C (wet), HCl–EtOAc, MeOH; (b) preparation of **3c**. Reagent: (a) CH_2N_2, Et_2O, MeOH; (b) H_2, 10% Pd/C (wet), HCl–EtOAc, MeOH; (c) Boc_2O, THF reflux; (d) NaOHaq, MeOH; (e) **14n**, EDC·HCl, HOBt·H_2O, *N*-methylmorpholine, DMF; (f) oxalyl chloride, DMSO, *N*-methylmorpholine, CH_2Cl_2; (g) HCl–EtOAc.

4n–s as described in Table 2(b). None of the compounds possessing a 3-arylalkyl-1,3,4-oxadiazolin-2-one moiety were orally active, although they showed potent K_i values. Replacement of the phenyl moiety of **4n** with a 3-thienyl or 2-thienyl moiety afforded **4o** and **4p**, respectively, with slightly lower in vitro activities. Insertion of another methylene group in benzyl moiety afforded the phenethyl derivative **4q** with ca. 5-fold lower activity. Substitution of the phenyl moiety of **4n** with a 4-fluoro or 3,4-methylenedioxy group produced **4r** and **4s** with no marked changes on inhibitory activity.

Biological data of 3-phenyl-1,3,4-oxadiazolin-2-ones are shown in Table 3. Among the compounds tested, **5a–g** exhibited oral activity at a dose of 30 mg/kg, while **5h** was not orally active at the same dose. All the compounds retained potent inhibitory activity. The substitution pattern (*ortho*, *meta*, *para*) did not affect the in vitro or in vivo activity.

Biological data of other 3-(4-substituted-phenyl)-1,3,4-oxadiazolin-2-ones **5i–n**, **5u** and **5v** are shown in Table 4. Most of the compounds **5i**, **5m**, **5n**, **5u** and **5v** were orally active. Their potencies, however, did not show the expected correlation with their in vitro potencies. Especially, **5j** and **5n** did not show oral activity despite their potent in vitro activity. Again, clear-cut colleration was not obtained between their structure and activities.

Table 1. Biological data of 3-amino-6-phenylaminopyrimidinone-1,3,4-oxadiazolin-2-ones **3a–c**



Compound	R	K_i (nM)[a]
3a	isoPr	264
3b	*n*-Bu	42.8
3c	Bn (HCl salt)	111
1 (ONO-6818)		12.2

[a]Inhibition of HNE-catalyzed hydrolysis of the synthetic substrate MeO-Suc-Ala-Ala-Pro-Val-pNa.

Biological data of 3-(2,4-disubstituted-phenyl)-1,3,4-oxadiazolin-2-ones **5o–t** are shown in Table 5. All of these compounds were orally active. Asymmetrical substitution of the 3-phenyl moiety was speculated to improve their physicochemical properties such as water-solubility.

In summary, the compounds reported here could be clearly classified into two classes: orally active and inactive compounds. 3-Aryl-1,3,4-oxadiazolin-2-ones showed oral activity, while the other 3-alkyl and 3-arylalkyl-1,3,4-oxadiazolin-2-ones did not.

Tables 3–5 also demonstrate the results of in vitro metabolic study.

Table 3 shows the results of an in vitro study of metabolism of **5a–h**. Metabolic stability of the orally active inhibitors was investigated. Compounds **5a–h** were treated with hamster liver microsomes (MS) in the presence of NADPH for 30 min. All of these compounds except for **5c** were quite stable against in vitro metabolism with hamster liver MS. These compounds were also treated with hamster plasma for 60 min. Introduction of an *ortho*- or *para*-substituent to the phenyl group usually provided an increase in stability, while *meta*-substitution decreased the metabolic stability relative to **5a** as illustrated by **5c**. The order of stability was **5b** > **5e** > **5f** > **5a**, **5g** > **5h**. Among the compounds tested, **5b** exhibited the most potent activity after oral administration. The other compounds also showed oral activity. This result indicated that *meta*-substitution reduced the metabolic stability against both hamster liver MS and plasma relative to the corresponding *para*- and *ortho*-substitutions.

Table 4 shows the in vitro experimental results of the metabolic study of *para*-substituted phenyl derivatives. The same experiment as described above was carried out using *para*-substituted phenyl derivatives **5i–n**, **5u** and **5v**. Compounds **5h** and **5j–l**, which were not orally active, were extremely unstable in hamster plasma.

The rest of the compounds **5i**, **5m**, **5u** and **5v**, which were orally active, showed metabolic stability against both hamster liver MS and the hamster plasma. Among the compounds tested, **5v** exhibited the most potent oral

activity. Metabolic stability showed good correlation with respect to oral activity. Especially, polar groups such as 2-OMe, 4-OMe, 4-OH and 4-NMe_2 groups were effective for metabolic stabilization of the inhibitors. These results demonstrated that at least two factors, metabolic stability and oral absorption, are required to obtain good oral activity.

Table 5 shows the results of the in vitro study of the metabolic stability of 3-(2,4-disubstituted-phenyl) derivatives. Combination of the above-mentioned results produced *ortho*, *para*-disubstituted inhibitors **5o**–**t** with good metabolic stability and good oral activity. The compounds **5o** and **5p** showed the most potent oral activity, while **5s** was less orally active despite its potent inhibitory activity because of its unstability in hamster plasma.

Conclusion

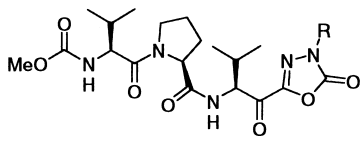
A series of tripeptidyl 3-phenyl-1,3,4-oxadiazolin-2-one derivatives have been identified as orally active inhibitors of HNE that exhibited good in vivo activity following oral administration in the HNE-induced lung injury model. Within the series of 3-phenyl-1,3,4-oxadiazolin-2-ones, the oral profile could be controlled by substitutions of the 3-phenyl group of the 1,3,4-oxadiazolin-2-ones. By replacing 3-phenyl group of **5a** with a 4-*N*,*N*-dimethylaminophenyl group or 2,4-disubstituted phenyl group, compounds with excellent oral potency were obtained. Our results demonstrated that oral activity of the inhibitors indicates good SAR with metabolic stability and oral absorption.

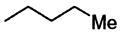
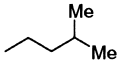
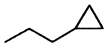
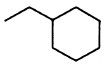
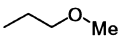
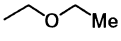
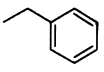
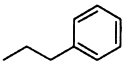
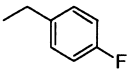
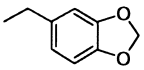
Experimental

General directions

Analytical samples were homogeneous as confirmed by TLC, and afforded spectroscopic results consistent with the assigned structures. All ^1H NMR spectra were obtained using a Varian Gemini-200, VXR-200s or Mercury300 spectrometer. Mass spectra were obtained on a Hitachi M1200H, JEOL JMS-DX303HF or PerSeptive Voyager Elite spectrometer. IR spectra were measured on a Perkin-Elmer FT-IR 1760X or Jasco FT/IR-430 spectrometer. Melting points were uncorrected. Elemental analyses for carbon, hydrogen, nitrogen and sulfur were carried out by the Analytical Section of Ono Pharmaceutical Co., Ltd. on a Perkin-Elmer PE2400 SeriesII CHNS/O analyzer. Optical rotations were measured using a Jasco DIP-1000 polarimeter. Column chromatography was carried out on silica gel (Merck silica gel 60 (0.063~0.200 mm) or Fuji Silysia FL60D). Thin layer chromatography was performed on silica gel (Merck TLC or HPTLC plates, silica gel 60 F_{254}). HPLC analyses were performed with an Alliance (2690 Separations Module, 486 Detector: Waters): (Capcell PAK C18 UG-120 (4.6×150 mm), 40 °C, 20 mM KH_2PO_4(pH 3)/CH_3CN, 1.0 mL/min, UV 220~245 nm). The following abbreviations are used: DME, ethylene

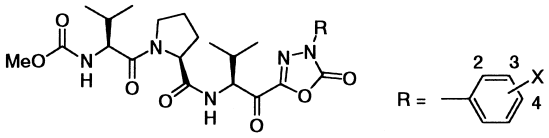
Table 2. Biological data of (a) 3-alkyl-1,3,4-oxadiazolin-2-ones **4a**–**m**; (b) 3-arylalkyl-1,3,4-oxadiazolin-2-ones **4n**–**s**



Compound	R	K_i (nM)[a]
a.		
4a		40.8
4b		4.73
4c		0.85
4d		1.87
4e		5.09
4f		10.4
4g		8.10
4h		5.00
4i		1.47
4j		6.04
4k		6.63
4l		14.7
4m		4.01
b.		
4n		1.67
4o		4.27
4p		4.79
4q		8.45
4r		2.50
4s		3.45

[a]Inhibition of HNE-catalyzed hydrolysis of the synthetic substrate MeO-Suc-Ala-Ala-Pro-Val-pNa.

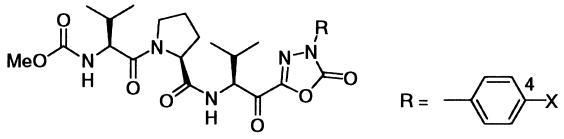
Table 3. Biological data and in vitro metabolic stability of 3-(unsubstituted or monosubstitutedphenyl)-1,3,4-oxadiazolin-2-ones **5a–h**



Compound	X	K_i (nM)[a]	Acute hemorrhagic assay		Remaining % of parent compound[c]	
			% Inhibition at 30 mg/kg, po[b]	ED_{50} (mg/kg)[b]	MS + NADPH (after 30 min)	Plasma (after 60 min)
5a	H	3.41	64	18.7	36	19
5b	2-Me	1.70	87	11.7	32	90
5c	3-Me	4.10	65	ND[d]	15	7
5d	4-Me	1.60	58	ND[d,e]	36	48
5e	2-OMe	3.20	68	21.5	56	74
5f	4-OMe	1.50	87	11.0	69	65
5g	2-CF_3	4.90	83	ND[d,e]	61	18
5h	4-CF_3	11.0	0	ND[d]	65	0
1 (ONO-6818)		12.2	100	5.1	82	100

[a]Inhibition of HNE-catalyzed hydrolysis of the synthetic substrate MeO-Suc-Ala-Ala-Pro-Val-pNa.
[b]Inhibition of HNE-induced lung hemorrhage in hamsters ($n = 6$–10). Test compounds were administered orally (as a solution in PEG400/distilled water/ethanol = 51/33/16) 1 h before intratracheal instillation of HNE (10 U/lung).
[c]Determined based on HPLC analysis: see Experimental.
[d]ND, not determined.
[e]Dose dependency was not observed.

Table 4. Biological data and in vitro metabolic stability of 3-(4-substituted phenyl)-1,3,4-oxadiazolin-2-ones **5i–n** and **5u–v**



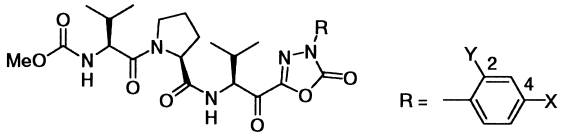
Compound	X	K_i (nM)[a]	Acute hemorrhagic assay		Remaining % of parent compound[c]	
			% Inhibition at 30 mg/kg, po[b]	ED_{50} (mg/kg)[b]	MS + NADPH (after 30 min)	Plasma (after 60 min)
5i	F	2.00	63	ND[d,e]	63	24
5j	Cl	2.20	32 (NS)[f]	ND[d]	37	3
5k	CN	1.90	0	ND[d]	30	0
5l	OCF_3	9.90	20 (NS)[f]	ND[d]	67	0
5m	OEt	8.90	72	ND[d]	37	78
5n	OBn	4.60	24 (NS)[f]	ND[d]	39	60
5u	OH	4.20	60	ND[d]	49	73
5v	NMe_2	6.40	96	7.5	51	100

[a]Inhibition of HNE-catalyzed hydrolysis of the synthetic substrate MeO-Suc-Ala-Ala-Pro-Val-pNa.
[b]Inhibition of HNE-induced lung hemorrhage in hamsters ($n = 6$–10). Test compounds were administered orally (as a solution in PEG400/distilled water/ethanol = 51/33/16) 1 h before intratracheal instillation of HNE (10 U/lung).
[c]Determined based on HPLC analysis: see Experimental.
[d]ND, not determined.
[e]Dose dependency was not observed.
[f]NS, not significant.

glycol dimethyl ether; EDC·HCl, 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride; HOBt·H_2O, *N*-hydroxybenzotriazole hydrate; DEAD, diethyl azodicarboxylate; CDI, carbonyldiimidazole; *m*-NBA, 3-nitrobenzylalcohol.

(3*S*,2*R*)-3-(*tert*-Butoxycarbonylamino)-2-hydroxy-4-methylpentyl acetate (7). A mixture of *tert*-butoxy-*N*-[(1*S*)-1-((2*R*)-oxiran-2-yl)-2-methylpropyl]carboxamide (**6**)[18] (41.3 g, 192 mmol), acetic acid (32.9 mL, 575 mmol) and Li_2CO_3 (42.6 g, 576 mmol) in DMF (384 mL) was heated at 100 °C for 17 h. The reaction mixture was poured into ice-cooled 10% citric acid, and extracted with EtOAc. The organic layer was washed with H_2O, saturated $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (Merck7734, EtOAc/*n*-hexane (1/9→1/1)) to afford **7** (31.0 g, 59%): TLC $R_f = 0.24$, EtOAc/*n*-hexane (1/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.86–4.75 (m, 1H), 4.20–3.96 (m, 4H), 3.31–3.20 (m, 1H), 2.10 (s, 3H), 2.00–1.86 (m, 1H), 1.44 (s, 9H), 0.98 and 0.96 (d×2, $J = 6.9$ Hz, 3H×2).

Table 5. Biological Data and In vitro metabolic Stability of 3-(2,4-disubstitutedphenyl)-1,3,4-oxadiazolin-2-ones **5o–t**



				Acute hemorrhagic assay		Remaining % of parent compound[c]	
Compound	X	Y	K_i (nM)[a]	% Inhibition at 30 mg/kg, po[b]	ED_{50} (mg/kg)[b]	MS + NADPH (after 30 min)	Plasma (after 60 min)
5o	OMe	Me	5.00	92	7.8	57	91
5p	OMe	OMe	5.10	92	11.9	66	76
5q	F	Me	3.10	71	ND[d]	61	96
5r	F	OMe	3.30	77	ND[d]	62	69
5s	F	F	1.70	74	16.9	59	9
5t	Me	Me	4.60	58	17.3	67	96

[a]Inhibition of HNE-catalyzed hydrolysis of the synthetic substrate MeO-Suc-Ala-Ala-Pro-Val-pNa.
[b]Inhibition of HNE-induced lung hemorrhage in hamsters ($n = 6$–10). Test compounds were administered orally (as a solution in PEG400/distilled water/ethanol = 51/33/16) 1 h before intratracheal instillation of HNE (10 U/lung).
[c]Determined based on HPLC analysis: see Experimental.
[d]ND, not determined.

[(4*S*,5*R*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-(methylethyl)-1,3-oxazolidin-5-yl]methyl acetate (8). To a stirred solution of **7** (9.66 g, 35.1 mmol) in DMF (40 mL) was added 2-methoxypropene (10.1 mL, 105 mmol) and 10-camphorsulfonic acid (405 mg, 1.75 mmol). After stirring at rt for 2 h, the reaction mixture was poured into ice-cooled saturated $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, concentrated in vacuo, and purified by silica gel column chromatography (FL60D, EtOAc/*n*-hexane (1/40→1/2)) to afford **8** (10.0 g, 90%): TLC $R_f = 0.72$, EtOAc/*n*-hexane (1/3); MS (MALDI, Pos.) $m/z = 216$ $(M-Boc+H)^+$; ^1H NMR (200 MHz, $CDCl_3$) δ 4.20–4.02 (m, 3H), 3.80–3.40 (m, 1H), 2.34–2.12 (m, 1H), 2.10 (s, 3H), 1.59 and 1.54 (s×2, 3H×2), 1.48 (s, 9H), 0.92 and 0.91 (d×2, $J = 6.8$ Hz, 3H×2).

***tert*-Butyl (4*S*,5*R*)-5-(hydroxymethyl)-2,2-dimethyl-4-(methylethyl)-1,3-oxazolidine-3-carboxylate (9).** A mixture of **8** (10.0 g, 31.8 mmol) and K_2CO_3 (4.83 g, 35.0 mmol) in MeOH (50 mL) was stirred at rt for 3 h. The reaction mixture was poured into crushed ice, and extracted with EtOAc. The organic layer was washed with H_2O, brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford **9** (8.74 g, quant). The product was used for the next reaction without further purification: TLC $R_f = 0.50$, EtOAc/*n*-hexane (1/2); MS (APCI, Pos. 20 V) $m/z = 174$ $(M-Boc+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 4.07–4.00 (m, 1H), 3.66–3.56 (m, 3H), 2.38–2.20 (m, 1H), 1.93 (m, 1H), 1.61 and 1.54 (s×2, 3H×2), 1.47 (s, 9H), 0.91 and 0.90 (d×2, $J = 6.9$ Hz, 3H×2); optical rotation $[\alpha]_D^{25}$ −2.6, (*c* 1.7, $CHCl_3$).

(4*S*,5*R*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-(methylethyl)-1,3-oxazolidine-5-carboxylic acid (10a). To a stirred solution of **9** (24.8 g, 90.8 mmol) in $CCl_4/CH_3CN/H_2O$ (2/2/3, 840 mL) were added $NaIO_4$ (58.3 g, 273 mmol) and then $RuCl_3 \cdot nH_2O$ (248 mg, 1 wt%) at rt. After stirring overnight, the reaction mixture was filtered through Celite to remove an insoluble material, which was washed with CH_2Cl_2. The filtrate was washed with H_2O, and dried over anhydrous Na_2SO_4. Concentration followed by trituration with *n*-hexane, gave **10a** (17.6 g, 68%). The resulting *n*-hexane solution was concentrated in vacuo, and purified by column chromatography on silica gel (FL60D, EtOAc/*n*-hexane (1/4→1/2)) to afford additional **10** (1.40 g, 5%) as an off-white powder: total 19.0 g, 73%: TLC $R_f = 0.33$, $MeOH/CHCl_3$ (1/9); ^1H NMR (300 MHz, $CDCl_3$) δ 4.38 (d, $J = 2.4$ Hz, 1H), 4.26–4.18 (m, 1H), 2.34–2.18 (m, 1H), 1.63 and 1.62 (s×2, 3H×2), 1.47 (s, 9H), 0.97 and 0.95 (d×2, $J = 7.2$ Hz, 3H×2).

Methyl (4*S*,5*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-(methylethyl)-1,3-oxazolidine-5-carboxylate (10b). A solution of **10a** (16.0 g, 55.7 mmol) in EtOAc (100 mL) was treated at 0 °C with CH_2N_2/Et_2O[21] until the evolution of gas subsided. The resulting solution was concentrated in vacuo to afford **10b** (17.5 g, quant) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 4.36 (d, $J = 2.4$ Hz, 1H), 4.28–4.05 (m, 1H), 3.78 (s, 3H), 2.38–2.10 (m, 1H), 1.58 (s, 6H), 1.47 (s, 9H), 0.95 and 0.93 (d×2, $J = 6.9$ Hz, 3H×2).

***tert*-Butyl (4*S*,5*R*)-5-(*N*-aminocarbamoyl)-2,2-dimethyl-4-(methylethyl)-1,3-oxazolidine-3-carboxylate (11).** A mixture of **10b** (17.1 g, 55.7 mmol) and $NH_2NH_2 \cdot H_2O$ (55.7 g, 1.11 mol) in MeOH (30 mL) was stirred at rt for 1 h. The reaction mixture was poured into ice water, and extracted with CH_2Cl_2. The organic layer was washed with H_2O (×2), brine, and dried over anhydrous Na_2SO_4. Concentration gave **11** (17.1 g, quant) as a beige solid: TLC $R_f = 0.51$, EtOAc; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (m, 1H), 4.30 (d, $J = 3.0$ H, 1H), 4.28–4.22 (m, 1H), 2.37–2.17 (m, 1H), 1.59 and 1.58 (s×2, 3H×2), 1.46 (s, 9H), 0.98 and 0.94 (d×2, $J = 6.9$ Hz, 3H×2).

***tert*-Butyl (4*S*,5*R*)-2,2-dimethyl-4-(methylethyl)-5-(2-oxo-1,3,4-oxadiazolin-5-yl)-1,3-oxazolidine-3-carboxylate (12).** To a stirred solution of **11** (369 mg, 1.22 mmol) in THF (25 mL) was added triethylamine (0.21 mL, 1.51 mmol)

and CDI (239 mg, 1.47 mmol) at 0 °C. The reaction mixture was stirred at rt overnight, then poured into ice water, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (FL60D, $CHCl_3$/MeOH (1/100)) to afford **12** (367 mg, 91%) as a white powder: TLC R_f = 0.27, EtOAc/*n*-hexane (1/3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.40–9.10 (m, 1H), 4.75 (d, J = 4.2 Hz, 1H), 4.50–4.15 (m, 1H), 2.46–2.15 (m, 1H), 1.59 and 1.53 (s×2, 3H×2), 1.49 (s, 9H), 0.96 and 0.92 (d×2, J = 6.6 Hz, 3H×2).

***tert*-Butyl (4*S*,5*R*)-5-(3-butyl-2-oxo-1,3,4-oxadiazolin-5-yl)-2,2-dimethyl-4-(methylethyl)-1,3-oxazolidine-3-carboxylate (13c).** To a stirred solution of **12** (304 mg, 0.93 mmol) in DMF (1 mL) was added K_2CO_3 (143 mg, 1.03 mmol) followed by *n*-BuI (0.12 mL, 1.03 mmol) at rt. The reaction mixture was stirred at rt for 2.5 h, then poured into ice water, and extracted with EtOAc. The organic layer was washed with 10% citric acid, saturated $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (FL60D, EtOAc/*n*-hexane (1/20)) to afford **13c** (347 mg, 97%) as a white solid: TLC R_f = 0.58, EtOAc/*n*-hexane (1/4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.74 (d, J = 3.0 Hz, 1H), 4.42–4.11 (m, 1H), 3.71 (t, J = 7.2 Hz, 2H), 2.44–1.80 (m, 1H), 1.78–1.66 (m, 2H), 1.59 and 1.53 (s×2, 3H×2), 1.48 (s, 9H), 1.43–1.26 (m, 2H), 0.95 and 0.93 (d×2, J = 7.0 Hz, 3H×2), 0.94 (t, J = 7.0 Hz, 3H).

5-[(2*S*,1*R*)-2-Amino-1-hydroxy-3-methylbutyl]-3-butyl-1,3,4-oxadiazolin-2-one *p*-toluenesulfonate (14c). A solution of **13c** (337 mg, 0.88 mmol) and TsOH·H_2O (234 mg, 1.23 mmol) in EtOH (18 mL) was stirred at 80 °C overnight, and then concentrated in vacuo to afford **14c** (428 mg) as TsOH salt quantitatively. The product was used for the next coupling reaction without further purification: TLC R_f = 0.29, $CHCl_3$/MeOH (9/1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.04–7.82 (m, 3H), 7.48 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 8.1 Hz, 2H), 7.01–6.90 (m, 1H), 4.80–4.76 (m, 1H), 3.65 (t, J = 6.6 Hz, 2H), 3.29–3.16 (m, 1H), 2.29 (s, 3H), 2.01–1.86 (m, 1H), 1.57–1.39 and 1.39–1.22 (m×2, 4H), 0.99 and 0.94 (d×2, J = 6.9 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H).

***N*-[(1*S*)-2-((2*S*)-2-{*N*-[(1*S*,2*R*)-2-(3-Butyl-2-oxo-1,3,4-oxadiazolin-5-yl)-2-hydroxy-1-(methylethyl)ethyl]carbamoyl}pyrrolidinyl)-1-(methylethyl)-2-oxoethyl]methoxycarboxamide (15c).** To a stirred solution of (2*S*)-1-[(2*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl]pyrrolidine-2-carboxylic acid (**16**)[19] (70 mg, 0.26 mmol), **14c** (TsOH salt: 126 mg, ca. 0.26 mmol) and HOBt·H_2O (49 mg, 0.32 mmol) in DMF (2 mL) was added EDC·HCl (60 mg, 0.31 mmol) and then *N*-methylmorpholine (0.055 mL, 0.50 mmol) at 0 °C. The reaction mixture was stirred at rt for 7 h, then poured into ice-cooled 10% citric acid, and extracted with EtOAc. The organic layer was washed with H_2O, saturated $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (FL60D, MeOH/$CHCl_3$ (1/100)) to afford **15c** (130 mg, quant) as a white amorphous powder: TLC R_f = 0.51, $CHCl_3$/MeOH (9/1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.74 (d, J = 9.6 Hz, 1H), 7.23 (d, J = 8.7 Hz, 1H), 5.99 (d, J = 5.7 Hz, 1H), 4.69–4.63 (m, 1H), 4.41–4.33 (m, 1H), 4.02–3.92 (m, 1H), 3.76–3.44 (m, 5H), 3.51 (s, 3H), 2.04–1.67 (m, 6H), 1.66–1.53 and 1.34–1.20 (m×2, 4H), 1.01–0.74 (m, 12H).

***N*-[(1*S*)-2-((2*S*)-2-{*N*-[(1*S*)-2-(3-Butyl-2-oxo-1,3,4-oxadiazolin-5-yl)-1-(methylethyl)-2-oxoethyl]carbamoyl}pyrrolidinyl)-1-(methylethyl)-2-oxoethyl]methoxycarboxamide (4c).** To a stirred solution of oxalyl chloride (0.045 mL, 0.51 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise a solution of DMSO in CH_2Cl_2 (1 M, 1.02 mL) at −70 °C. After 30 min, a solution of **15c** (130 mg, 0.26 mmol) in CH_2Cl_2 (1 mL) was added dropwise at −70 °C. After stirring at −70 °C for 2 h, the reaction mixture was treated with *N*-methylmorpholine (0.23 mL, 2.09 mmol), then stirred at −20 °C for 30 min. The reaction was quenched with ice-cooled 1 N HCl, and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (FL60D, $CHCl_3$/MeOH (100/1)) to afford **4c** (688 mg, 70%) as a white amorphous powder: TLC R_f = 0.23, EtOAc/*n*-hexane (2/1); MS (APCI, Pos. 20V) m/z = 496 $(M+H)^+$; IR (KBr) 1793, 1717, 1685, 1633, 1525 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 7.2 Hz, 1H), 5.36 (d, J = 9.0 Hz, 1H), 5.14 (dd, J = 7.2, 5.4 Hz, 1H), 4.61 (dd, J = 8.1, 3.0 Hz, 1H), 4.31 (dd, J = 9.0, 6.9 Hz, 1H), 3.83 (t, J = 7.2 Hz, 2H), 3.79–3.56 (m, 2H), 3.68 (s, 3H), 2.38–1.85 (m, 6H), 1.85–1.72 and 1.46–1.31 (m×2, 4H), 1.08–0.88 (m, 15H); optical rotation $[\alpha]_D^{25}$ −61.6 (*c* 0.3, MeCN). Anal. calcd for $C_{23}H_{37}N_5O_7 \cdot 0.2H_2O$: C, 55.34; H, 7.55; N, 14.03; found: C, 55.10; H, 7.59; N, 13.83.

Preparation of 4a–b, 4d–f, 4j–n and 4q–s. The following compounds were prepared according to the same procedures as described for the preparation of **4c**.

***N*-[(1*S*)-2-((2*S*)-2-{*N*-[(1*S*)-1-(Methylethyl)-2-(3-methyl-2-oxo-1,3,4-oxadiazolin-5-yl)-2-oxoethyl]carbamoyl}pyrrolidinyl)-1-(methylethyl)-2-oxoethyl]methoxycarboxamide (4a).** Derived from **12** and methyl iodide: white amorphous powder; TLC R_f = 0.22, $CHCl_3$/MeOH (50/1); MS (APCI, Pos. 20 V) m/z = 454 $(M+H)^+$; IR (KBr) 1795, 1714, 1684, 1635, 1526 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 7.2 Hz, 1H), 5.37 (d, J = 9.3 Hz, 1H), 5.10 (dd, J = 7.2, 5.7 Hz, 1H), 4.61 (dd, J = 8.4, 2.7 Hz, 1H), 4.31 (dd, J = 9.3, 7.2 Hz, 1H), 3.81–3.56 (m, 2H), 3.68 (s, 3H), 3.54 (s, 3H), 2.37–1.83 (m, 6H), 1.07–0.89 (m, 12 H); optical rotation $[\alpha]_D^{26}$ −60.0, (*c* 0.3, MeCN). Anal. calcd for $C_{20}H_{31}N_5O_7 \cdot 0.3H_2O$: C, 52.35; H, 6.94; N, 15.26; found: C, 52.56; H, 7.01; N, 14.86.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-1-(Methylethyl)-2-[3-(methylethyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (4b).** Derived from **12** and isopropyl iodide: white amorphous powder; TLC R_f = 0.24, EtOAc/*n*-hexane (2/1); MS (APCI, Pos. 20 V) m/z = 482 $(M+H)^+$; IR (KBr) 1791, 1718, 1686, 1632, 1529 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 7.8 Hz, 1H), 5.36 (d, J = 9.6 Hz, 1H), 5.19 (dd, J = 7.8, 5.4 Hz, 1H), 4.61 (dd, J = 8.1, 3.0 Hz, 1H), 4.49–4.37 (m, 1H), 4.32 (dd, J = 9.6, 6.6 Hz, 1H), 3.82–3.57 (m, 2H), 3.68 (s, 3H), 2.38–1.85 (m, 6H), 1.43 and 1.42 (d×2, J = 6.9 Hz, 3H×2), 1.01, 0.97 and 0.91 (d×3, J = 6.9 Hz, 12H). Anal. calcd for $C_{22}H_{35}N_5O_7$·0.4H_2O: C, 54.06; N, 7.38; N, 14.33; found: C, 53.74; H, 7.29; N, 14.01.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-1-(Methylethyl)-2-[3-(2-methylpropyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (4d).** Derived from **12** and 1-bromo-2-methylpropane: white amorphous powder; TLC R_f = 0.64, EtOAc; MS (MALDI, Pos.) m/z = 534 $(M+K)^+$, 518 $(M+Na)^+$, 496 $(M+H)^+$; IR (KBr) 1793, 1716, 1685, 1633, 1525 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 7.5 Hz, 1H), 5.38 (d, J = 9.2 Hz, 1H), 5.14 (dd, J = 7.5 and 5.4 Hz, 1H), 4.60 (dd, J = 8.1 and 2.7 Hz, 1H), 4.31 (dd, J = 9.2 and 6.6 Hz, 1H), 3.84–3.51 (m, 4H), 3.67 (s, 3H), 2.40–1.80 (m, 7H), 1.08–0.84 (m, 18H); optical rotation $[\alpha]_D^{26}$ −48.3 (*c* 0.26, MeCN). Anal. calcd for $C_{23}H_{37}N_5O_7$·0.2H_2O: C, 55.34; H, 7.55; N, 14.03; found: C, 55.10; H, 7.60; N, 13.83.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(Cyclopropylmethyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (4e).** Derived from **12** and cyclopropylmethyl bromide: white amorphous powder; TLC R_f = 0.50, EtOAc; MS (MALDI, Pos.) m/z = 532 $(M+K)^+$, 516 $(M+Na)^+$, 494 $(M+H)^+$; IR (KBr) 1791, 1715, 1685, 1633, 1526 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39 (d, J = 7.1 Hz, 1H), 5.38 (d, J = 9.0 Hz, 1H), 5.17 (dd, J = 7.1 and 5.0 Hz, 1H), 4.61 (dd, J = 8.2 and 3.4 Hz, 1H), 4.32 (dd, J = 9.0 and 6.6 Hz, 1H), 3.88–3.50 (m, 4H), 3.68 (s, 3H), 2.45–1.70 (m, 6H), 1.40–1.10 (m, 1H), 1.10–0.82 (m, 12H), 0.72–0.53 and 0.53–0.34 (m×2, 2H×2); optical rotation $[\alpha]_D^{26}$ −58.7 (*c* 0.3, MeCN). Anal. calcd for $C_{23}H_{35}N_5O_7$·0.2H_2O: C, 55.57; H, 7.18; N, 14.09; found: C, 55.29; H, 7.21; N, 13.89.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(3-Methylbutyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (4f).** Derived from **12** and 1-bromo-3-methylbutane: white amorphous powder; TLC R_f = 0.60, EtOAc; MS (MALDI, Pos.) m/z = 548 $(M+K)^+$, 532 $(M+Na)^+$, 510 $(M+H)^+$; IR (KBr) 1793, 1717, 1685, 1633, 1525 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 7.1 Hz, 1H), 5.36 (d, J = 9.2 Hz, 1H), 5.14 (dd, J = 7.1 and 5.4 Hz, 1H), 4.61 (dd, J = 8.1 and 3.0 Hz, 1H), 4.31 (dd, J = 9.2 and 6.6 Hz, 1H), 3.85 (t, J = 6.9 Hz, 2H), 3.84–3.54 (m, 2H), 3.68 (s, 3H), 2.40–1.80 (m, 6H), 1.75–1.48 (m, 3H), 1.10–0.83 (m, 18H); optical rotation $[\alpha]_D^{26}$ −51.5 (*c* 0.3, MeCN). Anal. calcd for $C_{24}H_{39}N_5O_7$: C, 56.57; H, 7.71; N, 13.74; found: C, 56.30; H, 7.94; N, 13.37.

***N*-[(1*S*)-2-((2*S*)-2-{*N*-[(1*S*)-2-(3-Cyclohexyl-2-oxo-1,3,4-oxadiazolin-5-yl)-1-(methylethyl)-2-oxoethyl]carbamoyl}-pyrrolidinyl)-1-(methylethyl)-2-oxoethyl]methoxycarboxamide (4j).** Derived from **12** and cyclohexyl iodide: white amorphous powder; TLC R_f = 0.36, EtOAc/*n*-hexane (2/1); MS (APCI, Pos. 20 V) m/z = 522 $(M+H)^+$; IR (KBr) 1789, 1715, 1685, 1633, 1525 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 7.5 Hz, 1H), 5.35 (d, J = 9.6 Hz, 1H), 5.18 (dd, J = 7.5, 4.8 Hz, 1H), 4.60 (dd, J = 8.1, 3.0 Hz, 1H), 4.32 (dd, J = 9.6, 7.2 Hz, 1H), 4.10–3.94 (m, 1H), 3.83–3.52 (m, 2H), 3.67 (s, 3H), 2.37–1.03 (m, 16H), 1.01, 0.96 and 0.91 (d×3, J = 6.9 Hz, 12H); optical rotation $[\alpha]_D^{25}$ −38.6 (*c* 0.2, MeCN). Anal. calcd for $C_{25}H_{39}N_5O_7$·0.1H_2O: C, 57.37; H, 7.55; N, 13.38; found: C, 56.99; H, 7.68; N, 13.05.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(Cyclohexylmethyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}-carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (4k).** Derived from **12** and bromomethylcyclohexane: clear viscous syrup; TLC R_f = 0.64, EtOAc; MS (MALDI, Pos.) m/z = 574 $(M+K)^+$, 558 $(M+Na)^+$, 536 $(M+H)^+$; IR (KBr) 1792, 1717, 1685, 1633, 1524 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 7.5 Hz, 1H), 5.37 (d, J = 9.5 Hz, 1H), 5.14 (dd, J = 7.5 and 5.7 Hz, 1H), 4.61 (dd, J = 8.4 and 3.0 Hz, 1H), 4.32 (dd, J = 9.5 and 6.9 Hz, 1H), 3.85–3.55 (m, 4H), 3.68 (s, 3H), 2.43–1.48 (m, 12H), 1.40–0.75 (m, 17H); optical rotation $[\alpha]_D^{26}$ −38.9 (*c* 0.2, MeCN). Anal. calcd for $C_{26}H_{41}N_5O_7$: C, 58.30; H, 7.71; N, 13.08; found: C, 57.93; H, 7.88; N, 12.73.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(2-Methoxyethyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (4l).** Derived from **12** and 2-bromo-1-methoxyethane: white amorphous powder; TLC R_f = 0.50, EtOAc; MS (APCI, Pos. 20 V) m/z = 498 $(M+H)^+$; IR (KBr) 1793, 1715, 1684, 1633, 1526 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 7.2 Hz, 1H), 5.35 (d, J = 9.6 Hz, 1H), 5.15 (dd, J = 7.2, 5.1 Hz, 1H), 4.60 (dd, J = 8.1, 2.7 Hz, 1H), 4.31 (dd, J = 9.6, 6.6 Hz, 1H), 4.05–3.97 (m, 2H), 3.82–3.55 (m, 4H), 3.67 (s, 3H), 3.36 (s, 3H), 2.35–1.80 (m, 6H), 1.01, 0.96 and 0.91 (d×3, J = 6.9 Hz, 12H); optical rotation $[\alpha]_D^{25}$ −55.8 (*c* 0.5, MeCN). Anal. calcd for $C_{22}H_{35}N_5O_8$·0.2H_2O: C, 52.73; H, 7.12; N, 13.97; found: C, 52.42; H, 7.16; N, 13.69.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(Ethoxymethyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (4m).** Derived from **12** and chloromethyl ethyl ether: white amorphous powder; TLC R_f = 0.55, EtOAc; MS (APCI, Pos. 20 V) m/z = 498 $(M+H)^+$; IR (KBr) 1798, 1718, 1685, 1633, 1625 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 6.9 Hz, 1H), 5.34 (d, J = 9.6 Hz, 1H), 5.21 (s, 2H), 5.12 (dd, J = 6.9, 5.1 Hz, 1H), 4.62 (dd, J = 8.1, 3.0 Hz, 1H), 4.31 (dd, J = 9.6, 6.9 Hz, 1H), 3.81–3.55 (m, 4H), 3.68 (s, 3H), 2.39–1.80 (m, 6H), 1.24 (t, J = 6.9 Hz, 3H), 1.02, 1.00, 0.96 and 0.93 (d×4, J = 6.9 Hz, 3H×4); optical rotation $[\alpha]_D^{27}$ −55.4 (*c* 0.3, MeCN). Anal. calcd for $C_{22}H_{35}N_5O_8$: C, 53.11; H, 7.09; N, 14.08; found: C, 52.72; H, 7.18; N, 13.81.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-1-(Methylethyl)-2-oxo-2-(2-oxo-3-benzyl-1,3,4-oxadiazolin-5-yl)}ethyl)carbamoyl]-pyrrolidinyl}-1-(methylethyl)-2-oxoethyl}methoxycarbox-**

amide (4n). Derived from **12** and benzyl bromide: white amorphous powder; mp 58–63 °C; TLC R_f = 0.46, $CHCl_3$/MeOH (19/1), MS (APCI, Pos.) m/z = 530 $(M+H)^+$; IR (KBr) 1791, 1718, 1684, 1613, 1527 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.47–7.30 (m, 1H), 7.37 (m, 5H), 5.39 (d, J = 9.2 Hz, 1H), 5.10 (dd, J = 7.2 Hz, 5.4 Hz, 1H), 4.97 (s, 2H), 4.62–4.52 (m, 1H), 4.30 (dd, J = 9.2 Hz, 7.0 Hz, 1H), 3.83–3.47 (m, 2H), 3.67 (s, 3H), 2.37–1.75 (m, 6H), 1.07–0.84 (m, 12H); optical rotation $[\alpha]_D^{27}$ −49.8 (*c* 0.6, MeCN). Anal. calcd for $C_{26}H_{35}N_5O_7 \cdot 0.6H_2O$: C, 57.79; H, 6.75; N, 12.96; found: C, 57.41; H, 6.63; N, 12.78.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-1-(Methylethyl)-2-oxo-2-[2-oxo-3-(2-phenylethyl)-1,3,4-oxadiazolin-5-yl]ethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (4q).** Derived from **12** and phenethyl bromide: clear viscous syrup; TLC R_f = 0.58, EtOAc; MS (APCI, Pos. 40 V) m/z = 544 $(M+H)^+$, 386, 354, 255, 229; IR (KBr) 1793, 1716, 1684, 1633, 1524 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 7.2 Hz, 1H), 7.38–7.09 (m, 5H), 5.35 (d, J = 8.9 Hz, 1H), 5.09 (dd, J = 7.2, 5.4 Hz, 1H), 4.60 (dd, J = 8.1, 3.0 Hz, 1H), 4.31 (dd, J = 8.9, 7.2 Hz, 1H), 4.23–3.96 (m, 2H), 3.86–3.47 (m, 2H), 3.68 (s, 3H), 3.11 (t, J = 7.2 Hz, 2H), 2.41–2.23 (m, 1H), 2.23–1.78 (m, 5H), 1.12–0.75 (m, 12H). Anal. calcd for $C_{27}H_{37}N_5O_7 \cdot 0.2H_2O$: C, 59.26; H, 6.89; N, 12.80; found: C, 58.90; H, 6.97; N, 12.43.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(4-Fluorophenyl)methyl-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (4r).** Derived from **12** and 4-fluorobenzyl bromide: white amorphous powder; TLC R_f = 0.56, $CHCl_3$/MeOH (19/1), MS (MALDI, Pos.) m/z = 586 $(M+K)^+$, 570 $(M+Na)^+$, 548 $(M+H)^+$; IR (KBr) 1792, 1716, 1684, 1633, 1513 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44–7.38 (m, 1H), 7.37 (dd, J = 8.4, 4.8 Hz, 1H), 7.06 (t, J = 8.4 Hz, 1H), 5.37 (d, J = 9.0 Hz, 1H), 5.09 (dd, J = 7.2, 5.7 Hz, 1H), 4.96 and 4.91 (d×2, J = 15.9 Hz, 1H×2), 4.57 (dd, J = 8.1, 3.0 Hz, 1H), 4.30 (dd, J = 9.0, 6.9 Hz, 1H), 3.73–3.54 (m, 2H), 3.67 (s, 3H), 2.34–1.81 (m, 6H), 1.00, 0.97, 0.96 and 0.89 (d×4, J = 6.9 Hz, 3H×4); optical rotation $[\alpha]_D^{25}$ −43.7 (*c* 0.8, MeCN). Anal. calcd for $C_{26}H_{34}FN_5O_7 \cdot H_2O$: C, 55.21; H, 6.42; N, 12.38; found: C, 54.90; H, 6.09; N, 12.28.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(2*H*-benzo[3,4-*d*]1,3-dioxolan-5-ylmethyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (4s).** Derived from **12** and 5-(bromomethyl)-2*H*-benzo[3,4-*d*]1,3-dioxolene:[22] white amorphous powder; TLC R_f = 0.63, EtOAc; MS (APCI, Pos. 40 V) m/z = 574 $(M+H)^+$, 386, 255, 229; IR (KBr) 1791, 1715, 1685, 1632, 1505 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 7.5 Hz, 1H), 6.90–6.83 (m, 2H), 6.78 (d, J = 8.7 Hz, 1H), 5.97 (s, 2H), 5.36 (d, J = 9.2 Hz, 1H), 5.10 (dd, J = 7.5, 5.4 Hz, 1H), 4.86 (s, 2H), 4.58 (dd, J = 7.5, 2.7 Hz, 1H), 4.31 (dd, J = 9.2, 6.9 Hz, 1H), 3.84–3.50 (m, 2H), 3.67 (s, 3H), 2.40–1.80 (m, 6H), 1.08–0.80 (m, 12H); optical rotation $[\alpha]_D^{26}$ −43.8 (*c* 0.3, MeCN). Anal. calcd for $C_{27}H_{35}N_5O_9 \cdot 0.9H_2O$: C, 54.98; H, 6.29; N, 11.87; found: C, 54.67; H, 6.04; N, 11.58.

***tert*-Butyl (4*S*,5*R*)-5-[3-(2-cyclopropylethyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-2,2-dimethyl-4-(methylethyl)-1,3-oxazolidine-3-carboxylate (13i).** To a stirred solution of **12** (374 mg, 1.14 mmol), 2-cyclopropylethanol (296 mg, 3.44 mmol) and triphenylphosphine (898 mg, 3.42 mmol) in THF (11.5 mL) was added dropwise DEAD (0.54 mL, 3.43 mmol) at rt. After 15 min, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (FL60D, EtOAc/*n*-hexane (1/19)) to afford **13i** (416 mg, 92%): TLC R_f = 0.50, EtOAc/*n*-hexane (1/4); MS (MALDI, Pos.) 418 $(M+Na)^+$, 296 $(M-Boc+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 4.74 (d, J = 3.3 Hz, 1H), 4.42–4.08 (m, 1H), 3.80 (t, J = 6.9 Hz, 1H), 2.42–2.17 (m, 1H), 1.70–1.57 (m, 2H), 1.59 and 1.54 (s×2, 3H×2), 1.48 (s, 9H), 0.95 and 0.92 (d×2, J = 6.9 Hz, 3H×2), 0.75–0.59 (m, 1H), 0.50–0.41 and 0.07–0.02 (m×2, 2H×2).

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(2-Cyclopropylethyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (4i).** Prepared from **13i** according to the same procedures as described for the preparation of **4c**: white amorphous powder; TLC R_f = 0.31, EtOAc/*n*-hexane (2/1); MS (APCI, Pos. 20V) m/z = 508 $(M+H)^+$; IR (KBr) 1793, 1716, 1685, 1633, 1525 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 7.5 Hz, 1H), 5.35 (d, J = 9.6 Hz, 1H), 5.13 (dd, J = 7.5, 5.4 Hz, 1H), 4.60 (dd, J = 8.1, 2.7 Hz, 1H), 4.31 (dd, J = 9.6, 6.9 Hz, 1H), 3.92 (t, J = 6.9 Hz, 2H), 3.82–3.56 (m, 2H), 3.68 (s, 3H), 2.38–1.80 (m, 6H), 1.73–1.63 (m, 2H), 1.01, 0.96 and 0.92 (d×3, J = 6.9 Hz, 12H), 0.76–0.60 (m, 1H), 0.52–0.43 and 0.10–0.03 (m×2, 2H×2); optical rotation $[\alpha]_D^{25}$ −53.5, (*c* 0.3, MeCN). Anal. calcd for $C_{24}H_{37}N_5O_7 \cdot 0.1H_2O$: C, 56.59; H, 7.36; N, 13.75; found: C, 56.23; H, 7.41; N, 13.41.

Preparation of 4g–h and 4o–p

The following compounds were prepared according to the same procedures as described for the preparation of **4i**.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(2,2-Dimethylpropyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (4g).** Derived from **12** and 2,2-dimethyl-1-propanol: white amorphous powder; TLC R_f = 0.58, EtOAc; MS (MALDI, Pos.) m/z = 548 $(M+K)^+$, 532 $(M+Na)^+$, 510 $(M+H)^+$; IR (KBr) 1793, 1716, 1685, 1633, 1525 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 7.1 Hz, 1H), 5.36 (d, J = 9.3 Hz, 1H), 5.15 (dd, J = 7.1, 5.1 Hz, 1H), 4.60 (dd, J = 8.1, 2.7 Hz, 1H), 4.31 (dd, J = 9.3, 6.6 Hz, 1H), 3.83–3.52 (m, 2H), 3.68 (s, 3H), 3.66 and 3.58 (d×2, J = 14.1 Hz, 1H×2), 2.40–1.79 (m, 6H), 1.10–0.78 (m, 12H), 1.01 (s, 9H); optical rotation $[\alpha]_D^{26}$ −50.0 (*c* 0.2, MeCN). Anal. calcd for $C_{24}H_{39}N_5O_7 \cdot 0.1H_2O$: C, 56.37; H, 7.73; N, 13.69; found: C, 56.06; H, 7.81; N, 13.41.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(Cyclobutylmethyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (4h).** Derived from **12** and cyclobutanemethanol:

white amorphous powder; TLC R_f = 0.62, EtOAc; MS (MALDI, Pos.) m/z = 546 $(M+K)^+$, 530 $(M+Na)^+$, 508 $(M+H)^+$; IR (KBr) 1792, 1715, 1685, 1633, 1525 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 6.9 Hz, 1H), 5.37 (d, J = 8.9 Hz, 1H), 5.14 (dd, J = 6.9, 5.1 Hz, 1H), 4.60 (dd, J = 8.1, 3.0 Hz, 1H), 4.31 (dd, J = 8.9, 6.9 Hz, 1H), 3.95–3.48 (m, 4H), 3.67 (s, 3H), 2.88–2.69 (m, 1H), 2.40–1.71 (m, 12H), 1.10–0.80 (m, 12H); optical rotation $[\alpha]_D^{26}$ −48.4 (*c* 0.3, MeCN). Anal. calcd for $C_{24}H_{37}N_5O_7$: C, 56.79; H, 7.35; N, 13.80; found: C, 56.40; H, 7.44; N, 13.50.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-1-(Methylethyl)-2-oxo-2-[2-oxo-3-(3-thienylmethyl)-1,3,4-oxadiazolin-5-yl]ethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (4o).** Derived from **12** and 3-thiophenemethanol: white amorphous powder; mp 58.1–59.9 °C; TLC R_f = 0.13 EtOAc/*n*-hexane (1/1); MS (APCI, Pos. 20 V) m/z = 536 $(M+H)^+$; IR (KBr) 1791, 1714, 1683, 1632, 1526 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.37 (d, J = 6.9 Hz, 1H), 7.57–7.54 (m, 2H), 7.26 (d, J = 8.4 Hz, 1H), 7.12–7.10 (m, 1H), 5.01 (s, 2H), 4.81 (t, J = 6.9 Hz, 1H), 4.43 (dd, J = 8.4, 4.2 Hz, 1H), 3.98 (t, J = 8.4 Hz, 1H), 3.76–3.67 and 3.55–3.45 (m×2, 5H), 2.26–2.14 and 2.02–1.66 (m×2, 6H), 0.92–0.84 (m, 12H); optical rotation $[\alpha]_D^{26}$ −52.2 (*c* 0.5, $CHCl_3$). Anal. calcd for $C_{24}H_{33}N_5O_7S{\cdot}0.3H_2O$: C, 53.28; H, 6.26; N, 12.94; S, 5.93; found: C, 53.00; H, 6.23; N, 12.66; S, 6.18.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-1-(Methylethyl)-2-oxo-2-[2-oxo-3-(2-thienylmethyl)-1,3,4-oxadiazolin-5-yl]ethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (4p).** Derived from **12** and 2-thiophenemethanol: white amorphous powder; mp 59.4–61.2 °C; TLC R_f = 0.34, $CHCl_3$/MeOH (20/1); MS (APCI, Neg. 20 V) m/z = 534 $(M-H)^-$; IR (KBr) 1793, 1715, 1684, 1632, 1525 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.39 (d, J = 7.0 Hz, 1H), 7.54 (dd, J = 5.0, 1.0 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 7.18 (d, J = 3.5 Hz, 1H), 7.02 (dd, J = 5.0, 3.5 Hz, 1H), 5.21 (s, 2H), 4.80 (t, J = 7.0 Hz, 1H), 4.44 (dd, J = 7.5, 4.0 Hz, 1H), 3.97 (t, J = 8.5 Hz, 1H), 3.75–3.67 and 3.58–3.46 (m×2, 5H), 2.25–2.14 and 2.02–1.65 (m×2, 6H), 0.92–0.85 (m, 12H); optical rotation $[\alpha]_D^{26}$ −58.3 (*c* 0.5, $CHCl_3$). Anal. calcd for $C_{24}H_{33}N_5O_7S{\cdot}0.4H_2O$: C, 53.10; H, 6.28; N, 12.90; S, 5.91; found: C, 52.75; H, 6.23; N, 12.72; S, 6.16.

***tert*-Butyl (4*S*,5*R*)-5-{*N*-[(4-methoxy-2-methylphenyl)amino]carbamoyl}-2,2-dimethyl-4-(methylethyl)-1,3-oxazolidine-3-carboxylate (17o).** To a stirred mixture of **10a** (678 mg, 2.36 mmol), 4-methoxy-2-methylphenylhydrazine[23] (445 mg, 2.36 mmol), HOBt·H_2O (433 mg, 2.83 mmol) and EDC·HCl (905 mg, 4.72 mmol) in DMF (5 mL) was added dropwise *N*-methylmorpholine (0.29 mL, 2.60 mmol) at 0 °C. After stirring at rt for 7 h, the reaction mixture was poured into ice-cooled 1N HCl, and extracted with EtOAc. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, H_2O, brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (FL60D, EtOAc/*n*-hexane (1/5→1/3)) to afford **17o** (813 mg, 82%) as a yellow viscous syrup: TLC R_f = 0.32, EtOAc/*n*-hexane (1/3); MS (APCI, Pos. 40 V) m/z = 422 $(M+H)^+$, 366; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 5.4 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 6.71–6.63 (m, 2H), 5.90 (d, J = 5.4 Hz, 1H), 4.38 (d, J = 3.0 Hz, 1H), 4.32–4.20 (m, 1H), 3.74 (s, 3H), 2.40–2.18 (m, 1H), 2.28 (s, 3H), 1.68 and 1.64 (s×2, 3H×2), 1.46 (s, 9H), 0.96 and 0.94 (d×2, J = 6.9 Hz, 3H×2).

***tert*-Butyl (4*S*,5*R*)-5-[3-(4-Methoxy-2-methylphenyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-2,2-dimethyl-4-(methylethyl)-1,3-oxazolidine-3-carboxylate (18o).** A mixture of **17o** (804 mg, 1.91 mmol), triethylamine (0.80 mL, 5.72 mmol) and CDI (1.54 g, 9.54 mmol) in THF (19 mL) was stirred at 80 °C for 15 h, then poured into 1N HCl, and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, H_2O, brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residual solid was washed with *n*-hexane containing a small amount of EtOAc to afford **18o** (501 mg, 59%) as a pale brown viscous syrup: TLC R_f = 0.42, EtOAc/*n*-hexane (1/3); MS (MALDI, Pos.) m/z = 486 $(M+K)^+$, 470 $(M+Na)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 9.0 Hz, 1H), 6.85–6.76 (m, 2H), 4.82 (d, J = 3.0 Hz, 1H), 4.50–4.27 (m, 1H), 3.82 (s, 3H), 2.50–2.14 (m, 1H), 2.25 (s, 3H), 1.62 and 1.60 (s×2, 3H×2), 1.48 (s, 9H), 0.98 and 0.95 (d×2, J = 6.0 Hz, 3H×2).

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(4-Methoxy-2-methylphenyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (5o).** Prepared from **18o** according to the same procedures as described for the preparation of **4c**: white amorphous solid; TLC R_f = 0.25, EtOAc/*n*-hexane (3/1); MS (APCI, Pos. 20 V) m/z = 560 $(M+H)^+$, 386; IR (KBr) 1793, 1717, 1685, 1635, 1508 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 7.1 Hz, 1H), 7.32–7.25 (m, 1H), 6.88–6.79 (m, 2H), 5.36 (d, J = 9.5 Hz, 1H), 5.14 (dd, J = 7.1, 5.7 Hz, 1H), 4.63 (dd, J = 8.4, 3.0 Hz, 1H), 4.31 (dd, J = 9.5, 6.9 Hz, 1H), 3.85–3.53 (m, 2H), 3.84 (s, 3H), 3.68 (s, 3H), 2.44–1.82 (m, 6H), 2.28 (s, 3H), 1.03, 0.99, 0.95 and 0.94 (d×4, J = 6.9 Hz, 3H×4); optical rotation $[\alpha]_D^{25}$ −41.2, (*c* 0.3, MeCN). Anal. calcd for $C_{27}H_{37}N_5O_8{\cdot}0.3H_2O$: C, 57.40; H, 6.71; N, 12.40; found: C, 57.54; H, 6.76; N, 12.01.

Preparation of 5a–n and 5p–t. The following compounds were prepared according to the same procedures as described for the preparation of **5o**.

***N*-[(1*S*)-2-((2*S*)-2-{*N*-[(1*S*)-1-(Methylethyl)-2-oxo-2-(2-oxo-3-phenyl-1,3,4-oxadiazolin-5-yl)ethyl]carbamoyl}pyrrolidinyl)-1-(methylethyl)-2-oxoethyl]methoxycarboxamide (5a).** Derived from **10a** and phenylhydrazine: white amorphous powder; TLC R_f = 0.40, EtOAc; MS (APCI, Pos. 20 V) m/z = 516 $(M+H)^+$; IR (KBr) 1794, 1717, 1685, 1632, 1598, 1570, 1524, 1503 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.56–7.44 (m, 3H), 7.39–7.31 (m, 1H), 5.35 (d, J = 8.7 Hz, 1H), 5.21 (dd, J = 7.5, 5.7 Hz, 1H), 4.63 (dd, J = 7.8, 3.0 Hz, 1H), 4.32 (dd, J = 8.7, 6.9 Hz, 1H), 3.85–3.53 (m, 2H), 3.68 (s, 3H), 2.40–1.82 (m, 6H), 1.06 and 1.01 (d×2, J = 6.6 Hz, 3H×2), 0.97 (d, J = 6.9 Hz, 6H); optical

rotation $[\alpha]_D^{27}$ −46.7 (*c* 0.5, MeCN). Anal. calcd for $C_{25}H_{33}N_5O_7 \cdot 0.2H_2O$: C, 57.84; H, 6.48; N, 13.49; found: C, 57.52; H, 6.50; N, 13.15.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-1-(Methylethyl)-2-[3-(2-methylphenyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (5b).** Derived from **10a** and 2-methylphenylhydrazine: white amorphous powder; TLC R_f = 0.29, EtOAc/*n*-hexane (2/1); MS (APCI, Pos. 20 V) *m*/*z* = 530 $(M+H)^+$; IR (KBr) 1795, 1718, 1685, 1634, 1523 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.2 Hz, 1H), 7.43–7.31 (m, 4H), 5.36 (d, *J* = 9.3 Hz, 1H), 5.15 (dd, *J* = 7.2, 5.4 Hz, 1H), 4.63 (dd, *J* = 8.4, 3.0 Hz, 1H), 4.31 (dd, *J* = 9.3, 6.9 Hz, 1H), 3.82–3.55 (m, 2H), 3.68 (s, 3H), 2.41–1.82 (m, 6H), 2.33 (s, 3H), 1.03, 0.99 and 0.95 (d×3, *J* = 6.9 Hz, 12H); optical rotation $[\alpha]_D^{26}$ −44.8 (*c* 0.8, MeCN). Anal. calcd for $C_{26}H_{35}N_5O_7 \cdot H_2O$: C, 57.03; H, 6.81; N, 12.79; found: C, 56.70; H, 6.51; N, 12.44.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-1-(Methylethyl)-2-[3-(3-methylphenyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (5c).** Derived from **10a** and 3-methylphenylhydrazine: white amorphous powder; TLC R_f = 0.30, EtOAc/*n*-hexane (2/1); MS (APCI, Pos. 20 V) *m*/*z* = 530 $(M+H)^+$; IR (KBr) 1793, 1718, 1685, 1633, 1523 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 5.37 (d, *J* = 9.0 Hz, 1H), 5.23 (dd, *J* = 7.2, 5.4 Hz, 1H), 4.63 (dd, *J* = 8.1, 3.0 Hz, 1H), 4.32 (dd, *J* = 9.0, 7.2 Hz, 1H), 3.85–3.55 (m, 2H), 3.68 (s, 3H), 2.43 (s, 3H), 2.40–1.83 (m, 6H), 1.06, 1.01, 0.97 and 0.96 (d×4, *J* = 6.9 Hz, 3H×4); optical rotation $[\alpha]_D^{25}$ −45.6 (*c* 0.2, MeCN). Anal. calcd for $C_{26}H_{35}N_5O_7 \cdot 0.5H_2O$: C, 57.98; H, 6.74; N, 13.00; found: C, 57.60; H, 6.63; N, 12.74.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-1-(Methylethyl)-2-[3-(4-methylphenyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (5d).** Derived from **10a** and 4-methylphenylhydrazine: white amorphous powder; TLC R_f = 0.30, EtOAc/*n*-hexane (2/1); MS (APCI, Pos. 20 V) *m*/*z* = 530 $(M+H)^+$; IR (KBr) 1796, 1718, 1685, 1632, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 5.37 (d, *J* = 9.3 Hz, 1H), 5.22 (dd, *J* = 7.2, 5.4 Hz, 1H), 4.63 (dd, *J* = 7.8, 2.7 Hz, 1H), 4.32 (dd, *J* = 9.3, 6.9 Hz, 1H), 3.82–3.55 (m, 2H), 3.68 (s, 3H), 2.39 (s, 3H), 2.38–1.83 (m, 6H), 1.05, 1.01, 0.97 and 0.96 (d×4, *J* = 6.9 Hz, 3H×4); optical rotation $[\alpha]_D^{27}$ −44.6, (*c* 0.5, MeCN). Anal. calcd for $C_{26}H_{35}N_5$-$O_7 \cdot 0.5H_2O$: C, 57.98; H, 6.74; N, 13.00; found: C, 57.63; H, 6.56; N, 12.73.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(2-Methoxyphenyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (5e).** Derived from **10a** and 2-methoxyphenylhydrazine: white amorphous powder; TLC R_f = 0.21, EtOAc/*n*-hexane (2/1); MS (APCI, Pos. 20 V) *m*/*z* = 546 $(M+H)^+$, 386; IR (KBr) 1799, 1717, 1684, 1634, 1507 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52–7.35 (m, 3H), 7.11–7.01 (m, 2H), 5.37 (d, *J* = 9.2 Hz, 1H), 5.18 (dd, *J* = 7.2, 5.4 Hz, 1H), 4.62 (dd, *J* = 8.4, 3.0 Hz, 1H), 4.31 (dd, *J* = 9.2, 7.2 Hz, 1H), 3.87 (s, 3H), 3.84–3.54 (m, 2H), 3.68 (s, 3H), 2.40–1.81 (m, 6H), 1.03, 0.99, 0.95 and 0.94 (d×4, *J* = 6.9 Hz, 3H×4); optical rotation $[\alpha]_D^{26}$ −47.8 (*c* 0.3, MeCN). Anal. calcd for $C_{26}H_{35}N_5O_8 \cdot 0.5H_2O$: C, 56.31; H, 6.54; N, 12.63; found: C, 56.65; H, 6.55; N, 12.26.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(4-Methoxyphenyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (5f).** Derived from **10a** and 4-methoxyphenylhydrazine: white amorphous powder; TLC R_f = 0.38, EtOAc/*n*-hexane (2/1); MS (APCI, Pos. 20 V) *m*/*z* = 516 $(M+H)^+$; IR (KBr) 1793, 1716, 1684, 1633, 1568, 1504 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.8 Hz, 2H), 7.56–7.44 (m, 3H), 7.35 (t, *J* = 7.8 Hz, 1H), 5.38 (d, *J* = 9.0 Hz, 1H), 5.22 (dd, *J* = 7.2, 5.4 Hz, 1H), 4.63 (dd, *J* = 8.1, 2.7 Hz, 1H), 4.32 (dd, *J* = 9.0, 7.2 Hz, 1H), 3.84–3.56 (m, 2H), 3.68 (s, 3H), 2.40–1.82 (m, 6H), 1.06 and 1.01 (d×2, *J* = 6.6 Hz, 3H×2), 0.97 (d, *J* = 6.9 Hz, 6H); optical rotation $[\alpha]_D^{27}$ −41.1 (*c* 0.8, MeCN). Anal. calcd for $C_{26}H_{35}N_5O_8 \cdot 0.2H_2O$: C, 56.86; H, 6.50; N, 12.75; found: C, 56.54; H, 6.54; N, 12.47.

***N*-((1*S*)-2-{(2*S*)-2-[*N*-((1*S*)-1-(Methylethyl)-2-oxo-2-{2-oxo-3-[2-(trifluoromethyl)phenyl]-1,3,4-oxadiazolin-5-yl}ethyl)carbamoyl]pyrrolidinyl}-1-(methylethyl)-2-oxoethyl)methoxycarboxamide (5g).** Derived from **10a** and 2-(trifluoromethyl)phenylhydrazine: white amorphous powder; TLC R_f = 0.25, EtOAc/*n*-hexane (3/1); MS (APCI, Pos. 40 V) *m*/*z* = 584 $(M+H)^+$, 386, 255, 229; IR (KBr) 1805, 1719, 1685, 1635, 1520 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.80–7.58 (m, 3H), 7.51 (d, *J* = 6.8 Hz, 1H), 5.35 (d, *J* = 9.3 Hz, 1H), 5.06 (dd, *J* = 6.8, 5.7 Hz, 1H), 4.63 (dd, *J* = 7.8, 2.7 Hz, 1H), 4.30 (dd, *J* = 9.3, 6.9 Hz, 1H), 3.83–3.51 (m, 2H), 3.67 (s, 3H), 2.42–1.80 (m, 6H), 1.09–0.87 (m, 12H); optical rotation $[\alpha]_D^{27}$ −38.8 (*c* 0.3, MeCN). Anal. calcd for $C_{26}H_{32}F_3N_5O_7$: C, 53.51; H, 5.53; N, 12.00; found: C, 53.21; H, 5.50; N, 11.66.

***N*-((1*S*)-2-{(2*S*)-2-[*N*-((1*S*)-1-(Methylethyl)-2-oxo-2-{2-oxo-3-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazolin-5-yl}ethyl)carbamoyl]pyrrolidinyl}-1-(methylethyl)-2-oxoethyl)methoxycarboxamide (5h).** Derived from **10a** and 4-(trifluoromethyl)phenylhydrazine: white amorphous powder; TLC R_f = 0.42, EtOAc/*n*-hexane (2/1); MS (APCI, Pos. 20 V) *m*/*z* = 584 $(M+H)^+$; IR (KBr) 1801, 1720, 1685, 1618, 1521 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.7 Hz, 2H), 7.76 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 6.6 Hz, 1H), 5.35 (d, *J* = 9.3 Hz, 1H), 5.16 (dd, *J* = 6.6, 5.7 Hz, 1H), 4.64 (dd, *J* = 8.4, 2.7 Hz, 1H), 4.32 (dd, *J* = 9.3, 6.9 Hz, 1H), 3.84–3.56 (m, 2H), 3.68 (s, 3H), 2.41–1.83 (m, 6H), 1.06, 1.01, 0.98 and 0.97 (d×4, *J* = 6.9 Hz, 3H×4); optical rotation $[\alpha]_D^{27}$ −41.9 (*c* 0.7, MeCN). Anal. calcd for $C_{26}H_{32}F_3N_5O_7 \cdot 0.6H_2O$: C, 52.54; H, 5.63; N, 11.78; found: C, 52.27; H, 5.36; N, 11.61.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(4-Fluorophenyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (5i).** Derived from **10a** and 4-fluorophenylhydrazine: white amorphous powder; TLC R_f = 0.39, EtOAc/*n*-hexane (2/1); MS (APCI, Pos. 20 V) m/z = 534 $(M+H)^+$; IR (KBr) 1800, 1719, 1685, 1636, 1511 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, J = 9.3, 4.5 Hz, 2H), 7.56 (d, J = 6.9 Hz, 1H), 7.18 (d, J = 9.3, 8.4 Hz, 2H), 5.35 (dd, J = 9.3 Hz, 1H), 5.18 (dd, J = 6.9, 5.7 Hz, 1H), 4.63 (dd, J = 7.8, 2.7 Hz, 1H), 4.32 (dd, J = 9.3, 6.9 Hz, 1H), 3.82–3.56 (m, 2H), 3.68 (s, 3H), 2.40–1.83 (m, 6H), 1.05, 1.01 and 0.97 (d×3, J = 6.9 Hz, 12H); optical rotation $[\alpha]_D^{27}$ −38.4 (*c* 0.5, MeCN). Anal. calcd for $C_{25}H_{32}FN_5O_7 \cdot 0.3H_2O$: C, 55.71; H, 6.10; N, 12.99; found: C, 55.40; H, 5.99; N, 12.61.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(4-Chlorophenyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (5j).** Derived from **10a** and 4-chlorophenylhydrazine: white amorphous powder; TLC R_f = 0.30, EtOAc/*n*-hexane (2/1); MS (APCI, Pos. 20 V) m/z = 550 $(M+H)^+$; IR (KBr) 1797, 1718, 1685, 1632, 1523 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 9.3 Hz, 2H), 7.57 (d, J = 7.2 Hz, 1H), 7.46 (d, J = 9.3 Hz, 2H), 5.36 (d, J = 9.3 Hz, 1H), 5.17 (dd, J = 7.2, 6.0 Hz, 1H), 4.63 (dd, J = 8.1, 3.0 Hz, 1H), 4.32 (dd, J = 9.3, 6.6 Hz, 1H), 3.83–3.57 (m, 2H), 3.68 (s, 3H), 2.40–1.82 (m, 6H), 1.05, 1.01 and 0.97 (d×3, J = 6.9 Hz, 12H); optical rotation $[\alpha]_D^{26}$ −38.7 (*c* 0.6, MeCN). Anal. calcd for $C_{25}H_{32}ClN_5O_7$: C, 54.59; H, 5.86; N, 12.73; found: C, 54.37; H, 5.86; N, 12.41.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(4-Cyanophenyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (5k).** Derived from **10a** and 4-cyanophenylhydrazine: white amorphous powder; mp 97.3–99.8 °C; TLC R_f = 0.60, $CHCl_3$/MeOH (10/1); MS (APCI, Pos. 20 V) m/z = 541 $(M+H)^+$; IR (KBr) 1802, 1719, 1685, 1635, 1513 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.49 (d, J = 6.9 Hz, 1H), 8.10–7.98 (m, 4H), 7.21 (d, J = 8.4 Hz, 1H), 4.92 (t, J = 6.9 Hz, 1H), 4.47 (dd, J = 8.1, 4.8 Hz, 1H), 3.98 (t, J = 8.4 Hz, 1H), 3.78–3.68 and 3.58–3.50 (m×2, 5H), 2.40–2.28 and 2.08–1.70 (m×2, 6H), 1.00–0.83 (m, 12H); optical rotation $[\alpha]_D^{26}$ −15.2 (*c* 0.3, $CHCl_3$). Anal. calcd for $C_{26}H_{32}N_6O_7 \cdot 0.5H_2O$: C, 56.82; H, 6.05; N, 15.29; found: C, 56.56; H, 5.89; N, 15.04.

***N*-((1*S*)-2-{(2*S*)-2-[*N*-((1*S*)-1-(Methylethyl)-2-oxo-2-{2-oxo-3-[4-(trifluoromethoxy)phenyl]-1,3,4-oxadiazolin-5-yl}ethyl)carbamoyl]pyrrolidinyl}-1-(methylethyl)-2-oxoethyl)methoxycarboxamide (5l).** Derived from **10a** and 4-(trifluoromethoxy)phenylhydrazine: white amorphous powder; TLC R_f = 0.45, EtOAc/*n*-hexane (2/1); MS (APCI, Pos. 20 V) m/z = 600 $(M+H)^+$; IR (KBr) 1797, 1719, 1685, 1634, 1511 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 9.0 Hz, 2H), 7.59 (d, J = 6.9 Hz, 1H), 7.34 (d, J = 9.0 Hz, 2H), 5.35 (d, J = 9.0 Hz, 1H), 5.16 (dd, J = 6.9, 5.7 Hz, 1H), 4.63 (dd, J = 8.1, 3.0 Hz, 1H), 4.32 (dd, J = 9.0, 6.6 Hz, 1H), 3.83–3.56 (m, 2H), 3.68 (s, 3H), 2.41–1.82 (m, 6H), 1.05, 1.01 and 0.97 (d×3, J = 6.9 Hz, 12H); optical rotation $[\alpha]_D^{27}$ −43.5 (*c* 0.7, MeCN). Anal. calcd for $C_{26}H_{32}F_3N_5O_8$: C, 52.09; H, 5.38; N, 11.68; found: C, 51.73; H, 5.33; N, 11.48.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(4-Ethoxyphenyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (5m).** Derived from **10a** and 4-ethoxyphenylhydrazine, which was prepared from ethoxybenzene according to the method described for preparation of 4-methoxy-2-methylphenylhydrazine: pale yellow amorphous powder; TLC R_f = 0.32, EtOAc/*n*-hexane (2/1); MS (APCI, Pos. 20 V) m/z = 560 $(M+H)^+$; IR (KBr) 1791, 1718, 1685, 1634, 1514 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 9.3 Hz, 2H), 7.50 (d, J = 6.9 Hz, 1H), 6.97 (d, J = 9.3 Hz, 2H), 5.37 (d, J = 9.3 Hz, 1H), 5.21 (dd, J = 6.9, 5.4 Hz, 1H), 4.63 (dd, J = 8.1, 3.0 Hz, 1H), 4.32 (dd, J = 9.3, 6.9 Hz, 1H), 4.07 (q, J = 6.9 Hz, 2H), 3.82–3.57 (m, 2H), 3.68 (s, 3H), 2.40–1.82 (m, 6H), 1.44 (t, J = 6.9 Hz, 3H), 1.05, 1.01, 0.97 and 0.96 (d×4, J = 6.9 Hz, 3H×4); optical rotation $[\alpha]_D^{26}$ −38.0 (*c* 0.2, MeCN). Anal. calcd for $C_{27}H_{37}N_5O_8 \cdot 1.4H_2O$: C, 55.45; H, 6.86; N, 11.98; found: C, 55.34; H, 6.74; N, 11.58.

***N*-((1*S*)-2-{(2*S*)-2-[*N*-((1*S*)-1-(Methylethyl)-2-oxo-2-{3-[4-(benzyloxy)phenyl]-2-oxo-1,3,4-oxadiazolin-5-yl}ethyl)carbamoyl]pyrrolidinyl}-1-(methylethyl)-2-oxoethyl)methoxycarboxamide (5n).** Derived from **10a** and 4-benzyloxyphenylhydrazine: pale yellow amorphous powder; TLC R_f = 0.38, EtOAc/*n*-hexane (2/1); MS (APCI, Pos. 20 V) m/z = 660 $(M+K)^+$, 644 $(M+Na)^+$, 622 $(M+H)^+$; IR (KBr) 1791, 1715, 1684, 1632, 1512 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 9.3 Hz, 2H), 7.50 (d, J = 6.9 Hz, 1H), 7.47–7.30 (m, 5H), 7.05 (d, J = 9.3 Hz, 2H), 5.36 (d, J = 9.0 Hz, 1H), 5.19 (dd, J = 6.9, 5.7 Hz, 1H), 5.10 (s, 2H), 4.63 (dd, J = 8.1, 2.7 Hz, 1H), 4.32 (dd, J = 9.0, 6.6 Hz, 1H), 3.82–3.56 (m, 2H), 3.68 (s, 3H), 2.40–1.83 (m, 6H), 1.05, 1.01, 0.97 and 0.96 (d×4, J = 6.9 Hz, 3H×4); optical rotation $[\alpha]_D^{26}$ −34.3 (*c* 0.5, MeCN). Anal. calcd for $C_{32}H_{39}N_5O_8 \cdot H_2O$: C, 60.08; H, 6.46; N, 10.95; found: C, 59.71; H, 6.16; N, 10.83.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(2,4-Dimethoxyphenyl)-2-oxo-1,3,4-oxadiazolin-5-yl]}-1-(methylethyl)-2-oxoethyl)carbamoyl]pyrrolidinyl}-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (5p).** Derived from **10a** and 2,4-dimethoxyphenylhydrazine, which was prepared from 1,3-dimethoxybenzene according to the method described for preparation of 4-methoxy-2-methylphenylhydrazine: white amorphous powder; TLC R_f = 0.22, EtOAc/*n*-hexane (3/1); MS (APCI, Pos. 20 V) m/z = 576 $(M+H)^+$, 386; IR (KBr) 1798, 1717, 1685, 1634, 1518 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40 (d, J = 7.3 Hz, 1H), 7.31 (d, J = 9.2 Hz, 1H), 6.61–6.51 (m, 2H), 5.37 (d, J = 9.0 Hz, 1H), 5.18 (dd, J = 7.3, 5.4 Hz, 1H), 4.62 (dd, J = 8.2, 3.4 Hz, 1H), 4.31 (dd, J = 9.0, 7.0 Hz, 1H), 3.91–3.48 (m, 2H), 3.86 and 3.83 (s×2, 3H×2), 3.68 (s, 3H), 2.46–1.77 (m, 6H), 1.02, 0.99, 0.95 and 0.93 (d×4, J = 6.6 Hz, 3H×4); optical rotation $[\alpha]_D^{26}$

−44.2 (*c* 0.2, MeCN). Anal. calcd for $C_{27}H_{37}N_5O_9 \cdot 0.3H_2O$: C, 55.82; H, 6.52; N, 12.05; found: C, 55.48; H, 6.40; N, 11.67.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(4-Fluoro-2-methylphenyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (5q).** Derived from **10a** and 4-fluoro-2-methylphenylhydrazine, which was prepared from 4-fluoro-2-methylphenylamine according to the method described for preparation of 4-fluoro-2-methoxyphenylhydrazine described below: white amorphous powder; TLC $R_f = 0.37$, EtOAc/*n*-hexane (2/1); MS (MALDI, Pos.) $m/z = 586$ $(M+K)^+$, 570 $(M+Na)^+$, 548 $(M+H)^+$; IR (KBr) 1798, 1718, 1684, 1633, 1504 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, $J = 6.9$ Hz, 1H), 7.37 (dd, $J = 8.7$, 5.4 Hz, 1H), 7.09–6.98 (m, 2H), 5.35 (d, $J = 9.3$ Hz, 1H), 5.12 (dd, $J = 6.9$, 5.4 Hz, 1H), 4.63 (dd, $J = 8.4$, 3.0 Hz, 1H), 4.31 (dd, $J = 9.3$, 6.9 Hz, 1H), 3.82–3.55 (m, 2H), 3.68 (s, 3H), 2.41–1.83 (m, 6H), 2.32 (s, 3H), 1.03, 0.99 and 0.95 (d×3, $J = 6.9$ Hz, 12H); optical rotation $[\alpha]_D^{26}$ −41.8 (*c* 0.7, MeCN). Anal. calcd for $C_{26}H_{34}FN_5O_7 \cdot H_2O$: C, 55.21; H, 6.42; N, 12.38; found: C, 54.81; H, 6.15; N, 12.21.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(4-Fluoro-2-methoxyphenyl)-2-oxo-1,3,4-oxadiazolin-5-yl]}-1-(methylethyl)-2-oxoethyl)carbamoyl]pyrrolidinyl}-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (5r).** Derived from **10a** and 4-fluoro-2-methoxyphenylhydrazine:[24] white amorphous powder; TLC $R_f = 0.37$, EtOAc/*n*-hexane (3/1); MS (FAB, Pos. Glycerol + *m*-NBA) $m/z = 564$ $(M+H)^+$; IR (KBr) 1802, 1717, 1685, 1618, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, $J = 7.5$ Hz, 1H), 7.38 (dd, $J = 9.2$, 5.9 Hz, 1H), 6.82–6.71 (m, 2H), 5.36 (d, $J = 9.0$ Hz, 1H), 5.15 (dd, $J = 7.5$, 5.4 Hz, 1H), 4.62 (dd, $J = 8.1$, 2.7 Hz, 1H), 4.31 (dd, $J = 9.0$, 6.6 Hz, 1H), 3.86 (s, 3H), 3.85–3.54 (m, 2H), 3.68 (s, 3H), 2.40–1.83 (m, 6H), 1.03, 0.99, 0.95 and 0.94 (d×4, $J = 6.6$ Hz, 3H×4); optical rotation $[\alpha]_D^{26}$ −41.8 (*c* 0.4, MeCN). Anal. calcd for $C_{26}H_{34}FN_5O_8 \cdot 0.1H_2O$: C, 55.23; H, 6.10; N, 12.39; found: C, 55.02; H, 6.10; N, 12.01.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(2,4-Difluorophenyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (5s).** Derived from **10a** and 2,4-difluorophenylhydrazine: white amorphous solid; mp 80.7–82.2 °C; TLC $R_f = 0.55$, $CHCl_3$/MeOH (10/1); MS (APCI, Pos. 20 V) 552 $(M+H)^+$; IR (KBr) 1806, 1718, 1684, 1633, 1520 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.47 (d, $J = 6.9$ Hz, 1H), 7.84–7.77 (m, 1H), 7.65–7.58 (m, 1H), 7.37–7.29 (m, 1H), 7.25 (d, $J = 8.4$ Hz, 1H), 4.80 (t, $J = 6.9$ Hz, 1H), 4.43 (dd, $J = 8.1$, 4.5 Hz, 1H), 3.98 (t, $J = 8.4$ Hz, 1H), 3.77–3.68 and 3.58–3.50 (m×2, 5H), 2.34–2.24 and 2.08–1.71 (m×2, 6H), 0.96–0.83 (m, 12H); optical rotation $[\alpha]_D^{27}$ −18.5 (*c* 0.3, $CHCl_3$). Anal. calcd for $C_{25}H_{31}F_2N_5O_7 \cdot H_2O$: C, 52.72; H, 5.84; N, 12.30; found: C, 52.45; H, 5.47; N, 12.09.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(2,4-Dimethylphenyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (5t).** Derived from **10a** and 2,4-dimethylphenylhydrazine: white amorphous powder; TLC $R_f = 0.34$, EtOAc/*n*-hexane (2/1); MS (APCI, Pos. 20 V) $m/z = 544$ $(M+H)^+$; IR (KBr) 1795, 1718, 1685, 1633, 1509 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, $J = 7.2$ Hz, 1H), 7.25 (d, $J = 8.7$ Hz, 1H), 7.15 (s, 1H), 7.12 (d, $J = 8.7$ Hz, 1H), 5.37 (d, $J = 9.0$ Hz, 1H), 5.15 (dd, $J = 7.2$, 5.4 Hz, 1H), 4.62 (dd, $J = 8.4$, 3.0 Hz, 1H), 4.31 (dd, $J = 9.0$, 6.6 Hz, 1H), 3.82–3.55 (m, 2H), 3.68 (s, 3H), 2.45–1.84 (m, 6H), 2.38 and 2.28 (s×2, 3H×2), 1.03, 0.99, 0.95 and 0.94 (d×4, $J = 6.9$ Hz, 3H×4); optical rotation $[\alpha]_D^{27}$ −42.6 (*c* 0.7, MeCN). Anal. calcd for $C_{27}H_{37}N_5O_7 \cdot 0.9H_2O$: C, 57.93; H, 6.99; N, 12.51; found: C, 57.56; H, 6.62; N, 12.26.

***N*-{(1*S*)-2-[(2*S*)-2-(*N*-{(1*S*)-2-[3-(4-Hydroxyphenyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-1-(methylethyl)-2-oxoethyl}carbamoyl)pyrrolidinyl]-1-(methylethyl)-2-oxoethyl}methoxycarboxamide (5u).** A mixture of **5n** (338 mg, 0.54 mmol) and 10% Pd-C (71 mg, 10 wt%) in MeOH (5.5 mL) was stirred under an atmosphere of H_2 gas at rt. After 7 h, the reaction mixture was filtered through Celite to remove the catalyst, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (FL60D, $CHCl_3$/MeOH (100/0→100/1)) to afford **5u** (283 mg, 98%) as a pale yellow amorphous powder: TLC $R_f = 0.24$, EtOAc/*n*-hexane (2/1); MS (MALDI, Pos.) $m/z = 570$ $(M+K)^+$, 554 $(M+Na)^+$, 532 $(M+H)^+$; IR (KBr) 1789, 1713, 1631, 1518 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, $J = 9.3$ Hz, 2H), 7.50 (d, $J = 7.2$ Hz, 1H), 6.89 (d, $J = 9.3$ Hz, 2H), 6.41 (s, 1H), 5.36 (d, $J = 9.3$ Hz, 1H), 5.20 (dd, $J = 7.2$, 5.4 Hz, 1H), 4.67–4.60 (m, 1H), 4.32 (dd, $J = 9.3$, 7.2 Hz, 1H), 3.85–3.57 (m, 2H), 3.68 (s, 3H), 2.39–1.86 (m, 6H), 1.05, 1.02 and 0.97 (d×3, $J = 6.9$ Hz, 12H); optical rotation $[\alpha]_D^{25}$ −40.0 (*c* 0.6, MeCN). Anal. calcd for $C_{25}H_{33}N_5O_8 \cdot 0.3C_4H_{10}O_2$: C, 56.40; H, 6.39; N, 12.55; found: C, 56.09; H, 6.41; N, 12.20.

***tert*-Butyl (4*S*,5*R*)-5-[3-(4-aminophenyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-2,2-dimethyl-4-(methylethyl)-1,3-oxazolidine-3-carboxylate (23).** Under an atmosphere of H_2 gas, a mixture of **22** (350 mg, 0.78 mmol), which was prepared from **10a** and 4-nitrophenylhydrazine according to the same procedures as described for preparation of **18o**, and 20% $Pd(OH)_2$/C (wet, 70 mg) in MeOH/dioxane (1/2, 6.9 mL) was stirred at rt for 2.5 h. The reaction mixture was filtered to remove the catalyst, and concentrated in vacuo to afford **23** (353 mg, quant) as a pale yellow viscous syrup. The product was used for the next reaction without further purification: TLC $R_f = 0.13$, EtOAc/*n*-hexane (1/3); MS (MALDI, Pos.) $m/z = 457$ $(M+K)^+$, 441 $(M+Na)^+$, 418 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 and 6.73 (d×2, $J = 8.7$ Hz, 2H×2), 4.82 (d, $J = 3.0$ Hz, 1H), 4.60–4.15 (m, 1H), 2.52–2.16 (m, 1H), 1.61 and 1.59 (s×2, 3H×2), 1.49 (s, 9H), 0.98 and 0.96 (d×2, $J = 6.6$ Hz, 3H×2).

***tert*-Butyl (4*S*,5*R*)-5-{3-[4-(dimethylamino)phenyl]-2-oxo-1,3,4-oxadiazolin-5-yl}-2,2-dimethyl-4-(methylethyl)-1,3-oxazolidine-3-carboxylate (24).** To a stirred solution of **23** (340 mg, 0.78 mmol) in CH_3CN (15 mL) was added

35% HCHOaq (0.4 mL) and $NaBH_3CN$ (78 mg, 1.25 mmol). After stirring at rt for 30 min, the reaction mixture was acidified to pH 4~5 with acetic acid, and stirred for 1 h. The reaction mixture was poured into saturated $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with H_2O, brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (FL60D, EtOAc/*n*-hexane, (1/9)) to afford **24** (219 mg, 63%) as a beige solid: TLC $R_f = 0.47$, EtOAc/*n*-hexane (1/3); MS (APCI, Pos. 40 V) $m/z = 447$ $(M+H)^+$, 391; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 and 6.75 (d×2, $J = 9.0$ Hz, 2H×2), 4.83 (d, $J = 2.7$ Hz, 1H), 4.57–4.16 (m, 1H), 2.97 (s, 6H), 2.57–2.10 (m, 1H), 1.61 and 1.59 (s×2, 3H×2), 1.49 (s, 9H), 0.98 and 0.96 (d×2, $J = 6.6$ Hz, 3H×2).

***N*-((1*S*)-2-{(2*S*)-2-[*N*-((1*S*)-2-{3-[4-(Dimethylamino)phenyl]-2-oxo-1,3,4-oxadiazolin-5-yl}-1-(methylethyl)-2-oxoethyl) carbamoyl]pyrrolidinyl}-1-(methylethyl)-2-oxoethyl)methoxycarboxamide (5v).** Prepared from **24** according to the same procedures as described for preparation of **4c**: orange amorphous solid; TLC $R_f = 0.29$, EtOAc/*n*-hexane (3/1); MS (APCI, Pos. 20 V) $m/z = 559$ $(M+H)^+$, 386; IR (KBr) 1789, 1717, 1685, 1633, 1523 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.64 (d, $J = 9.2$ Hz, 2H), 7.45 (d, $J = 7.4$ Hz, 1H), 6.75 (d, $J = 9.2$ Hz, 2H), 5.39 (d, $J = 9.0$ Hz, 1H), 5.23 (dd, $J = 7.4$, 5.4 Hz, 1H), 4.63 (dd, $J = 8.0$, 2.8 Hz, 1H), 4.32 (dd, $J = 9.0$, 6.6 Hz, 1H), 3.84–3.52 (m, 2H), 3.68 (s, 3H), 3.00 (s, 6H), 2.45–1.79 (m, 6H), 1.04, 1.01, 0.97 and 0.95 (d×4, $J = 6.6$ Hz, 3H×4); optical rotation $[\alpha]_D^{25}$ −30.7 (*c* 0.3, MeCN). Anal. calcd for $C_{27}H_{38}N_6O_7 \cdot 0.4H_2O$: C, 57.31; H, 6.91; N, 14.85; found: C, 57.64; H, 6.91; N, 14.46.

***N*-[(1*S*,2*R*)-2-(3-Butyl-2-oxo-1,3,4-oxadiazolin-5-yl)-2-hydroxy-1-(methylethyl)ethyl]-2-[5-(benzyloxycarbonylamino)-6-oxo-2-phenylhydropyrimidinyl]acetamide (28b).** A solution of **13c** (95 mg, 0.25 mmol) in MeOH/TFA (1/6, 3.5 mL) was stirred at rt for 18 h and at 40 °C for 2 h, then concentrated in vacuo. The residue was treated with 4 N HCl–EtOAc, followed by azeotropic removal of water with toluene to give **14c** (82 mg) as HCl salt quantitatively. The product was used for the next coupling reaction without further purification.

To a mixture of **14c** (82 mg, ca. 0.25 mmol), **27a** (76 mg, 0.20 mmol) and HOBt·H_2O (40 mg, 0.26 mmol) in DMF (2 mL) was added EDC·HCl (50 mg, 0.26 mmol) and *N*-methylmorpholine (0.035 mL, 0.32 mmol) at 0 °C. The reaction mixture was stirred at rt for 18 h, then poured into ice-cooled 10% citric acid, and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4. Concentration gave **28b** (109 mg, 90%) as a white solid. The product was used for the next reaction without further purification: TLC $R_f = 0.73$, MeOH/$CHCl_3$ (1/9); ^1H NMR (300 MHz, DMSO-d_6) δ 8.74 (s, 1H), 8.44 (s, 1H), 8.05 (d, $J = 9.3$ Hz, 1H), 7.55–7.30 (m, 10H), 6.06 (d, $J = 5.7$ Hz, 1H), 5.19 (s, 2H), 4.65–4.59 (m, 1H), 4.50 and 4.43 (br d×2, $J = 16.2$ Hz, 1H×2), 3.82–3.72 (m, 1H), 3.62–3.54 (m, 2H), 1.82–1.67 (m, 1H), 1.63–1.47 and 1.30–1.14 (m×2, 4H), 0.90 and 0.78 (d×2, $J = 6.6$ Hz, 3H×2), 0.83 (t, $J = 7.2$ Hz, 3H).

***N*-[(1*S*)-2-(3-Butyl-2-oxo-1,3,4-oxadiazolin-5-yl)-1-(methylethyl)-2-oxoethyl]-2-[5-(benzyloxycarbonylamino)-6-oxo-2-phenylhydropyrimidinyl]acetamide (29b).** To a stirred solution of oxalyl chloride (0.031 mL, 0.36 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise a solution of DMSO in CH_2Cl_2 (1 M, 0.71 mL) at −70 °C. After 30 min, a solution of **28b** (107 mg, 0.18 mmol) in DMSO/CH_2Cl_2 (1/5, 1.2 mL) was added dropwise at −70 °C. After stirring at −70 °C for 2 h, the reaction mixture was treated with *N*-methylmorpholine (0.16 mL, 1.45 mmol), then stirred at −20 °C for 30 min. The reaction mixture was poured into ice-cooled 1N HCl, and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (FL60D, MeOH/$CHCl_3$ (1/100)) to afford **29b** (104 mg, 98%): TLC $R_f = 0.50$, EtOAc/*n*-hexane (1/1), ^1H NMR (300 MHz, $CDCl_3$) δ 8.79 (br s, 1H), 7.61–7.30 (m, 11H), 6.47 (d, $J = 8.7$ Hz, 1H), 5.34 (dd, $J = 8.7$, 5.1 Hz, 1H), 5.23 (s, 2H), 4.63 and 4.56 (d×2, $J = 15.6$ Hz, 1H×2), 3.84 (t, $J = 7.2$ Hz, 2H), 2.35–2.20 (m, 1H), 1.85–1.72 and 1.46–1.32 (m×2, 4H), 1.04 and 0.86 (d×2, $J = 6.9$ Hz, 3H×2), 0.97 (t, $J = 7.2$ Hz, 3H).

***N*-[(1*S*)-2-(3-Butyl-2-oxo-1,3,4-oxadiazolin-5-yl)-1-(methylethyl)-2-oxoethyl]-2-(5-amino-6-oxo-2-phenylhydropyrimidinyl)acetamide (3b).** A mixture of **29b** (102 mg, 0.17 mmol), 1 N HCl–EtOAc (0.017 mL) and 10% Pd-C (50% wet, 21 mg) in MeOH (1.7 mL) was stirred under an atmosphere of H_2 gas for 3.5 h. The reaction mixture was filtered through Celite to remove the catalyst, and then concentrated in vacuo. The residual product was dissolved in EtOAc, washed with saturated $NaHCO_3$, H_2O, brine, dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by column chromatography on silica gel (FL60D, $CHCl_3$/MeOH (100/1)) to afford **3b** (67 mg, 85%) as a pale yellow amorphous solid: TLC $R_f = 0.39$, EtOAc; MS (APCI, Pos. 20 V) 469 $(M+H)^+$; IR (KBr) 1791, 1663, 1610, 1530 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60–7.35 (m, 6H), 6.68 (d, $J = 8.4$ Hz, 1H), 5.33 (dd, $J = 8.4$, 5.1 Hz, 1H), 4.63 and 4.56 (d×2, $J = 15.3$ Hz, 1H×2), 4.05 (m, 2H), 3.85 (t, $J = 7.2$ Hz, 2H), 2.36–2.18 (m, 1H), 1.85–1.72 and 1.47–1.32 (m×2, 4H), 1.05 and 0.88 (d×2, $J = 6.9$ Hz, 3H×2), 0.98 (t, $J = 7.2$ Hz, 3H). Anal. calcd for $C_{23}H_{28}N_6O_5$: C, 58.96; H, 6.02; N, 17.94; found: C, 58.60; H, 5.96; N, 17.62.

***N*-{(1*S*)-1-(Methylethyl)-2-[3-(methylethyl)-2-oxo-1,3,4-oxadiazolin-5-yl]-2-oxoethyl}-2-(5-amino-6-oxo-2-phenylhydropyrimidinyl)acetamide (3a).** This compound was prepared from **27a** and **14b** according to the same procedures as described for the preparation of **3b**: pale yellow powder; TLC $R_f = 0.40$, EtOAc; MS (APCI, Pos. 20 V) $m/z = 455$ $(M+H)^+$; IR (KBr) 1785, 1664, 1612, 1530 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.57–7.37 (m, 6H), 6.84 (d, $J = 8.4$ Hz, 1H), 5.36 (dd, $J = 8.4$, 5.0 Hz, 1H), 4.67 and 4.56 (d×2, $J = 15.6$ Hz, 1H×2), 4.57–4.36 (m, 1H), 4.10–3.10 (m, 2H), 2.38–2.16 (m, 1H), 1.44 (d, $J = 6.8$ Hz, 6H), 1.04 and 0.87 (d×2, $J = 7.0$ Hz, 3H×2). Anal. calcd for $C_{22}H_{26}N_6O_5 \cdot 0.4C_6H_{14}$: C, 59.94; H, 6.51; N, 17.19; found: C, 60.02; H, 6.17; N, 16.86.

Methyl 2-[5-(*tert*-butoxycarbonylamino)-6-oxo-2-phenylhydropyrimidinyl]acetate (27b). A solution of **27a** (1.76 g, 4.64 mmol) in MeOH (4 mL) was treated at 0 °C with CH_2N_2/Et_2O until the evolution of gas subsided. The resulting solution was concentrated in vacuo to afford the methyl ester (1.83 g, quant) as a white amorphous solid. The product was used for the next reaction without further purification: TLC $R_f = 0.30$, EtOAc/*n*-hexane (1/1); MS (APCI, Pos. 40V) $m/z = 394$ $(M+H)^+$, 260; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.78 (br s, 1H), 7.56–7.30 (m, 11H), 5.24 (s, 2H), 4.63 (s, 2H), 3.76 (s, 3H).

A mixture of the methyl ester (1.83 g, 4.64 mmol), 10% Pd-C (367 mg) and 1 N HCl–EtOAc (0.5 mL) in MeOH (50 mL) was stirred under an atmosphere of H_2 gas at rt. After 2 h, the reaction mixture was filtered through Celite to remove the catalyst. The filtrate was treated with 4 N HCl–EtOAc (10 mL), and concentrated in vacuo. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give the amine (1.15 g, 95%) as a yellow solid. The product was used for the next reaction without further purification: TLC $R_f = 0.82$, MeOH/$CHCl_3$ (1/4); MS (APCI, Pos. 40V) $m/z = 260$ $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.50–7.38 (m, 5H), 4.63 (s, 2H), 3.77 (s, 3H).

A mixture of the amine (879 mg, 3.39 mmol) and $(Boc)_2O$ (4.68 mL, 20.4 mmol) in THF (15 mL) was refluxed for 5 days, and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (FL60D, EtOAc/*n*-hexane (1/4)) to afford **27b** (1.14 g, 93%) as a clear viscous syrup: TLC $R_f = 0.53$, EtOAc/*n*-hexane (1/1); MS (APCI, Pos. 40V) $m/z = 360$ $(M+H)^+$, 304, 260; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.72 (br s, 1H), 7.48 (m, 6H), 4.63 (s, 2H), 3.77 (s, 3H), 1.53 (s, 9H).

2-[5-(*tert*-Butoxycarbonylamino)-6-oxo-2-phenylhydropyrimidinyl]acetic acid (27c). To a stirred solution of **27b** (1.11 g, 3.09 mmol) in MeOH (5 mL) was added 2N NaOH (1.85 mL, 3.70 mmol) at 0 °C. After stirring at rt for 2 h, the reaction mixture was cooled to 0 °C, then acidified with 1 N HCl, and extracted with EtOAc. The organic layer was washed with H_2O, brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford **27c** (1.07 g, quant) as a white amorphous solid: TLC $R_f = 0.21$, MeOH/$CHCl_3$ (1/4); ^{1}H NMR (200 MHz, $CDCl_3$ + several drops of CD_3OD) δ 8.70 (br s, 1H), 7.60–7.33 (m, 6H), 4.42 (s, 2H), 1.52 (s, 9H).

***N*-[(1*S*)-1-(Methylethyl)-2-oxo-2-(2-oxo-3-benzyl-1,3,4-oxadiazolin-5-yl)ethyl]-2-(5-amino-6-oxo-2-phenylhydropyrimidinyl)acetamide hydrochloride (3c).** A mixture of **29c** (60 mg, 0.10 mmol), which was prepared from **13n** and **27c** according to the same procedures as described for preparation of **29b**, and 4 N HCl–EtOAc (1 mL) in EtOAc (1 mL) was stirred at rt for 2 h, and then concentrated in vacuo. The residual product was washed with Et_2O to afford **3c** (47 mg, 88%) as a pale yellow powder: TLC $R_f = 0.48$, EtOAc; MS (APCI, Pos. 20 V) $m/z = 503$ $(M+H)^+$; IR (KBr) 1790, 1694, 1661, 1558 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.66 (d, $J = 7.8$ Hz, 1H), 7.55–7.24 (m, 11H), 5.03 (s, 2H), 4.93 (dd, $J = 7.8$, 5.4 Hz, 1H), 4.53 (s, 2H), 2.29–2.11 (m, 1H), 0.86 and 0.79 (d×2, $J = 6.9$ Hz, 3H×2). Anal. calcd for $C_{26}H_{27}ClN_6O_5$: C, 57.94; H, 5.05; N, 15.59; found: C, 57.92; H, 4.95; N, 15.49.

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