Development of Orally Active Nonpeptidic Inhibitors of Human Neutrophil Elastase

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5-Amino-2-phenylpyrimidin-6-ones, some of their desamino derivatives, and miscellaneous derivatives were synthesized and biologically evaluated on both in vitro activity and oral activity in an acute hemorrhagic assay. These compounds contained an α-keto-1,3,4-oxadiazole moiety to bind covalently to the Ser-195 hydroxy group of human neutrophil elastase (HNE). Among those tested, compounds **11a−c,e,i−l(F)**, **11d**,**e,k(H)**, **21d**,**e,k(F)**, and **21d**,**e(H)** showed a good oral profile. *RS*-Mixture **3(H)** was selected for clinical evaluation based on its oral potency, duration of action, enzyme selectivity, safety profile, and ease of synthesis. Structure−activity relationships (SARs) are discussed.

Introduction

Human neutrophil elastase (HNE) is a serine protease which is released from neutrophils in response to inflammatory stimuli.[1] HNE has a broad substrate specificity with the ability to degrade a variety of diverse structural proteins. Under normal conditions, the body protects itself from the potential damaging effects of extracellular HNE with the endogenous α_1-proteinase inhibitor (α_1-PI). If the balance between protease and antiprotease is in favor of protease due to a decrease in the level of α_1-PI, the excess HNE activity may lead to tissue damage and the development of a disease such as emphysema[2] due to chronic inflammation. The excess HNE produced by this imbalance hydrolyzes elastin, the structural protein which gives the lungs their elasticity, and is believed to initiate and/or contribute to the development of diseases such as pulmonary emphysema,[2] chronic bronchitis,[3] adult respiratory distress syndrome,[4] rheumatoid arthritis,[5] atherosclerosis,[6] cystic fibrosis,[7] chronic bowel disease,[8] and other inflammatory disorders.[9] It has been hypothesized that an appropriate, small-molecular-weight inhibitor of HNE could restore the imbalance between HNE and α_1-PI and would be therapeutically useful in the treatment of such diseases.[10] While a large number of synthetic HNE inhibitors have been developed,[11] only peptidyl trifluoromethyl ketones have emerged as leading candidates to demonstrate the clinical utility of low-molecular-weight synthetic proteinase inhibitors.[12]

Our research efforts have focused on the development of mechanism-based[13] inhibitors of elastase, in particular electrophilic ketones. A number of functional groups

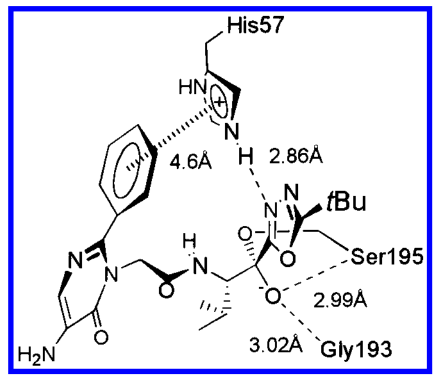

Figure 1. Covalent, hydrogen-bonding, and $\pi-\pi$ interactions between ONO-6818 and the catalytic site of PPE found in the crystal structure.[18]

which activate the carbonyl of peptidyl ketones for nucleophilic addition by the active-site Ser-195 hydroxyl group of HNE have been identified. Among the reported functional groups,[14] we focused our attention on α-ketoheterocycles such as α-keto-1,2,4-oxadiazole[15] and α-keto-1,3,4-oxadiazole. A predictable advantage of α-ketooxadiazole over other electrophilic ketones was that the better hydrophilic and/or electron-attracting properties of the oxadiazoles than the reported heterocycles[16] and other electron-attracting moieties would allow more subtle modulation of the physicochemical properties of the inhibitor by introducing lipophilic residues on their rings. As such, both the in vivo activity and the in vitro potency could be finely tuned.

We were also interested in the possibility that incorporation of an appropriately positioned nitrogen atom within the heterocyclic ring might further stabilize the covalent complex by participating in a hydrogen-bonding interaction with protonated active-site His-57 (Figure 1). This is analogous to the mechanism of inhibition observed in an α-ketobenzoxazole inhibitor complexed to PPE.[17] A hydrogen-bonding interaction between the

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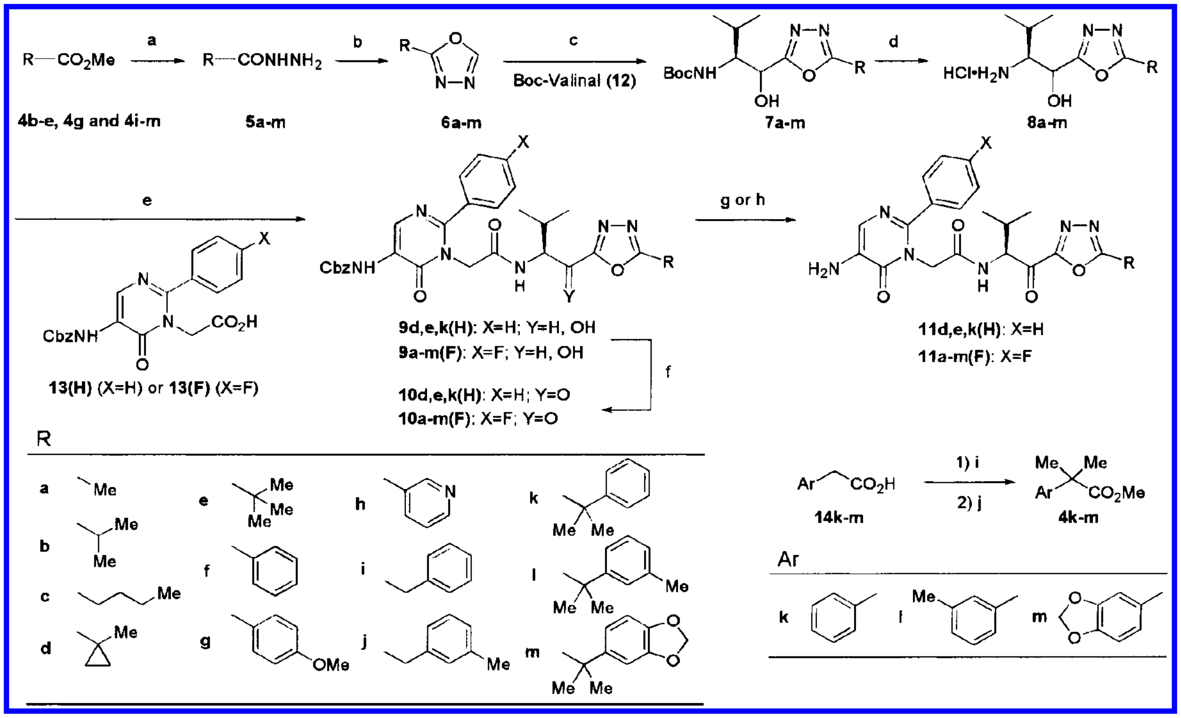
Scheme 1. Synthesis of Aminopyrimidinone Derivatives **11a−m**[a]



[a] Reagents: (a) hydrazine hydrate; (b) $HC(OMe)_3$ or $HC(OEt)_3$, $TsOH{\cdot}H_2O$; (c) (1) *n*-BuLi, $MgBr_2{\cdot}OEt_2$, THF, (2) **12**, THF; (d) 4 N HCl−dioxane; (e) **13(H)** or **13(F)**, EDC·HCl, $HOBt{\cdot}H_2O$, NMM, DMF; (f) Dess−Martin periodinane or Swern oxidation; (g) $AlCl_3$, anisole, CH_3NO_2, CH_2Cl_2; (h) 35% HBr/AcOH; (i) TMSCl, MeOH; (j) NaH, MeI, THF.

α-ketoheterocyclic inhibitors and His-57 was speculated to be beneficial for the fast and effective binding of the inhibitor to the enzyme in the covalent bond formation with Ser-195.

We report herein the synthesis and activities of a novel class of HNE inhibitors: the nonpeptidyl α-keto-1,3,4-oxadiazoles. A number of the compounds from this series are orally active inhibitors of HNE with potent K_i values in the nanomolar to subnanomolar range. The crystal structure of the inhibitor **3(H)** supports the hypothesis that binding interactions with both the enzyme active-site serine hydroxyl group and histidine imidazole ring (Figure 1) are important for optimal in vitro activity.[18]

Chemistry

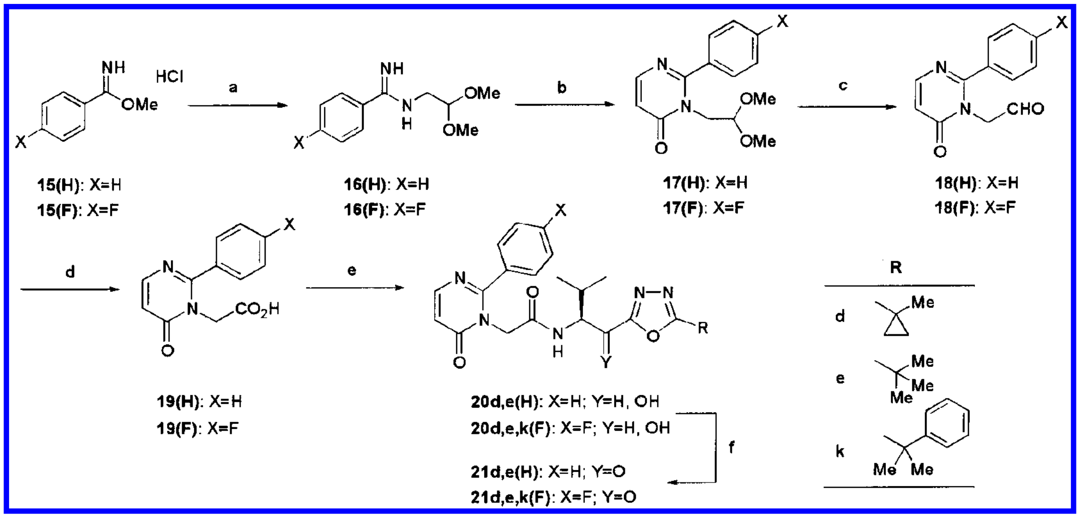
Compound **1a** can be structurally divided into two parts, a left half and a right half. Modifications were carried out on each part separately. Aminopyrimidinone derivatives **11a−m**, in which the right half was chemically modified, were prepared as outlined in Scheme 1. Oxadiazoles **6a−j** were synthesized from acyl hydrazides **5a−j**. Compounds **5a**,**f**,**h** were commercially available. Compounds **5b−e**,**g**,**i**,**j** were prepard from their corresponding esters **4b−e**,**g**,**i**,**j**, respectively. Methyl 2,2-dimethyphenylacetates **4k−m** were prepared by the *gem*-dialkylation of **14k−m**. Compounds **4b−e**,**g**,**i**,**j** and **14k−m** were commercially available. Addition of anions prepared from **6a−j** in the presence of *n*-BuLi/$MgBr_2{\cdot}OEt_2$ with **12**[19] afforded **7a−j**. Acidic deprotection of **7a−j** provided amino alcohols **8a−j**. Amide formation of **8a−j** with **13(H)**[20] or **13(F)**[20] gave **9d**,**e(H)** or **9a−j(F)**, respectively. Dess−Martin or Swern oxidation of **9d**,**e(H)** and **9a−j(F)** afforded **10d**,**e(H)** and **10a−j(F)**, respectively. Deprotection of **10d**,**e(H)** and **10a−j(F)** afforded **11d**,**e(H)** and **11a−j(F)** respectively. Compounds **11k(H)** and **11k−m(F)**[21] were sythesized from **4k−m** which were prepared from **14k−m**, respectively.

Synthesis of desaminopyrimidinone derivatives **21d**,**e(H)** and **21d**,**e**,**k(F)** is described in Scheme 2. Compounds **17(H)** and **17(F)** were synthesized from the corresponding amidines **16(H)** and **16(F)**, respectively, which were obtained from their corresponding imidates **15(H)** and **15(F)**, respectively. Deprotection of their dimethyl acetals **17(H)** and **17(F)** afforded **18(H)** and **18(F)**. These aldehydes were converted to the carboxylic acids **19(H)** and **19(F)** under oxidation conditions. Condensation of these carboxylic acids with **8d**,**e**,**k** afforded **20d**,**e(H)** and **20d**,**e**,**k(F)**, respectively. α-Ketooxadiazoles **21d**,**e(H)** and **21d**,**e**,**k(F)** were obtained from their corresponding alcohols by Dess−Martin or Swern oxidation.

Modification of the left half of **1a** was carried out as described in Schemes 3−5. Synthesis of **24a−c**,**e−g** is described in Scheme 3. Compounds **24a−c**,**e−g** were synthesized from **23a−c**,**e−g**, respectively, which were prepared by the condensation of **22a−c**,**e−g** with **8e** in the presence of EDC. Compounds **22a−c** were prepared from the urea **26a−c** which were obtained from their corresponding amino esters **25a−c** by a reaction with ethyl isocyanatoacetate. Compound **22e** was prepared by the deprotection of **39** which was prepared by *N*-methanesulfonylation of **38**. The carboxylic acid **22g** was obtained by alkaline hydrolysis of **41** which was prepared by *O*-alkylation of the pyridone **40** with ethyl bromoacetate.

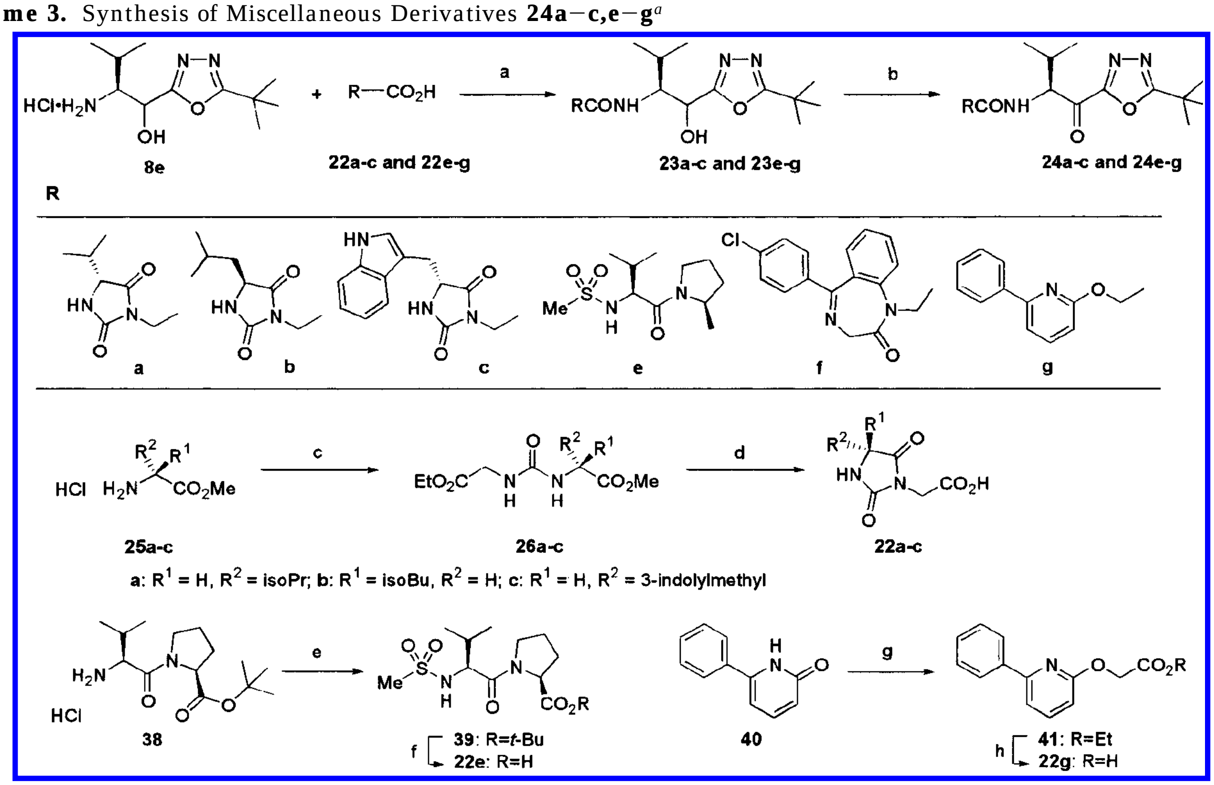
Synthesis of tetrahydroisoquinoline and of indoline derivatives **24h−m** is described in Scheme 4. Condensation of **27a**,**b** and the amino alcohol **8e** afforded **28a**,**b**. Acidic deprotection provided **29a**,**b** which were acylated again with isopropoxycarbonyl chloride to give **30a**,**b**.

Scheme 2. Synthesis of Desaminopyrimidinone Derivatives **21d,e,k**[a]



[a] Reagents: (a) aminoacetaldehyde dimethyl acetal, MeOH; (b) 3-ethoxyacrylic acid ethyl ester; (c) 1 N HCl(aq), THF; (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O; (e) **8d**, **8e**, or **8k**, EDC·HCl, HOBt·H_2O, NMM, DMF; (f) Dess–Martin periodinane or Swern oxidation.

Scheme 3. Synthesis of Miscellaneous Derivatives **24a–c,e–g**[a]



[a] Reagents: (a) EDC·HCl, HOBt·H_2O, NMM, DMF; (b) Dess–Martin periodinane or Swern oxidation; (c) ethyl isocyanatoacetate, triethylamine, EtOAc; (d) concd HCl; (e) methanesulfonyl chloride, NMM, CH_2Cl_2; (f) 90% TFA/H_2O; (g) ethyl bromoacetate, K_2CO_3, DMF; (h) 1 N LiOH(aq), DME.

Oxidation of **30a**,**b** afforded **24h**,**i**. Acylation of **29a**,**b** with **32**, which was prepared by the tritylation of **31**, in the presence of EDC afforded **33a**,**b**. Oxidation of **33a**,**b** gave α-ketooxadiazoles **34a**,**b** which were converted to **24j**,**k**, respectively, by acidic deprotection. *N*-Acylation of **29a**,**b** with Boc-L-valine afforded **35a**,**b** whose acidic deprotection provided **36a**,**b**. *N*-Acylation of **36a**,**b** with nicotinic acid gave **37a**,**b**. Oxidation of **37a**,**b** afforded **24l**,**m**, respectively.

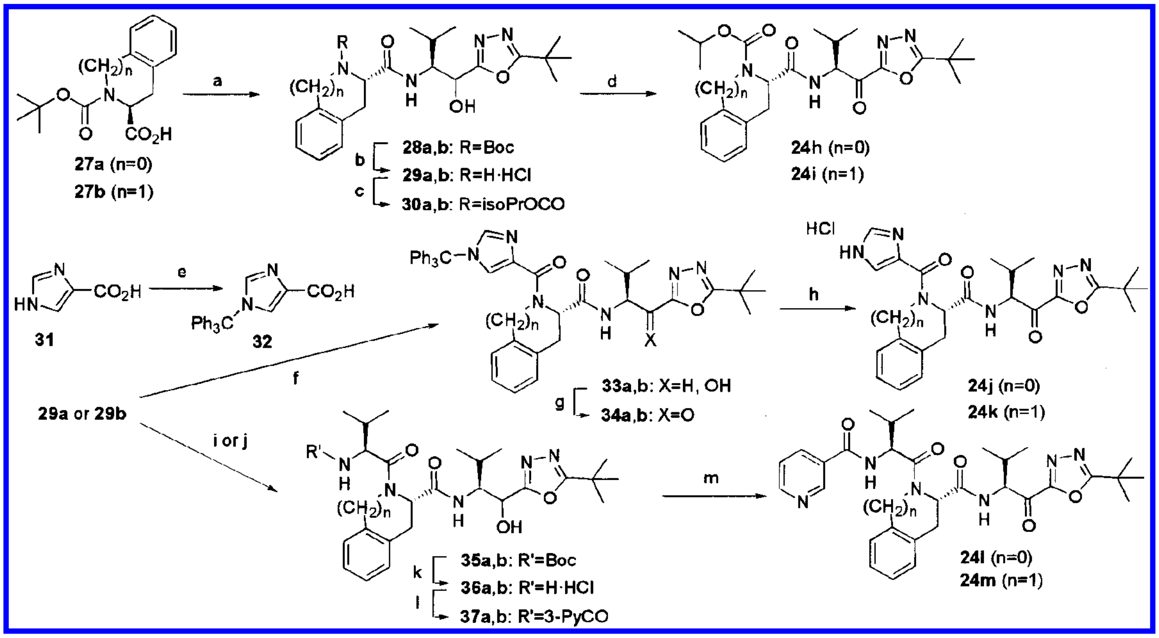
The 2-(pyridin-3-yl)pyrimidinone derivative **24d** was synthesized from **27** as outlined in Scheme 5. Compound **27**, which was prepared from 3-cyanopyridine by the same procedure used in the preparation of 2-phenylpyrimidin-6-one derivative,[20] was converted to **28** by a condensation reaction with **8e** in the presence of EDC. Oxidation of **28** afforded **29** which was converted to **24d** by deprotection with aluminum chloride.

Synthesis of **3(H)** (ONO-6818) was carried out as described in Scheme 6. Oxidation of optically active **9e(H)** followed by its epimerization under basic conditions afforded *RS*-mixture **42** which was converted to **3(H)** by deprotection with aluminum chloride.

Results and Discussion

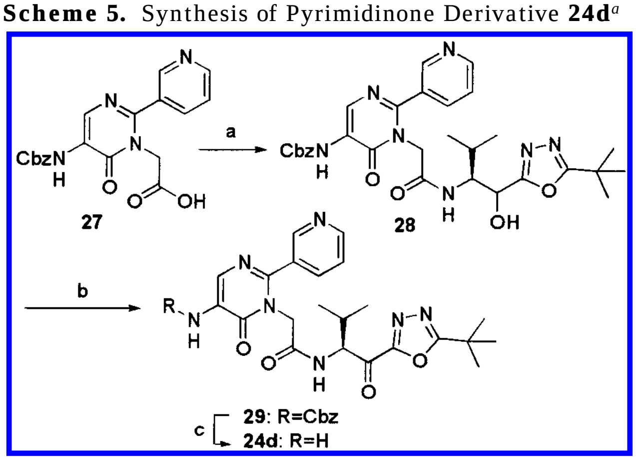
Two kinds of heterocycles were investigated for their ability to activate the carbonyl group of peptidyl ketone

Scheme 4. Synthesis of Tetrahydroisoquinoline and Indoline Derivatives **24h–m**[a]



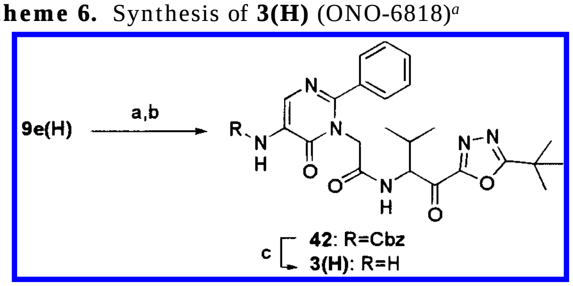
[a] Reagents: (a) **8e**, EDC·HCl, HOBt·H_2O, NMM, DMF; (b) 4 N HCl in EtOAc or dioxane; (c) isopropyl chloroformate, NMM, CH_2Cl_2; (d) Dess–Martin periodinane, CH_2Cl_2; (e) Ph_3CCl, pyridine, DMF; (f) **32**, EDC·HCl (HOBt·H_2O), NMM, DMF; (g) Dess–Martin periodinane, CH_2Cl_2; (h) (1) 95% TFA/H_2O, (2) 4 N HCl in EtOAc or dioxane; (i) BocValCOF, 2,6-di-*tert*-butylpyridine, DMAP, CH_2Cl_2; (j) Boc-L-valine, EDC·HCl, HOBt·H_2O, NMM, DMF; (k) 4 N HCl in EtOAc; (l) nicotinic acid, EDC·HCl, NMM, CH_2Cl_2; (m) Dess–Martin periodinane, CH_2Cl_2.

Scheme 5. Synthesis of Pyrimidinone Derivative **24d**[a]



[a] Reagents: (a) **8e**, EDC·HCl, HOBt·H_2O, NMM, DMF; (b) Dess–Martin periodinane; (c) $AlCl_3$, anisole, CH_3NO_2, CH_2Cl_2.

Scheme 6. Synthesis of **3(H)** (ONO-6818)[a]

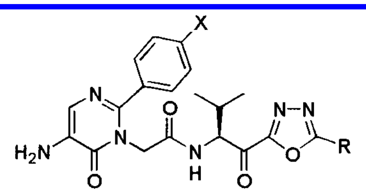


[a] Reagents: (a) oxalyl chloride, DMSO, CH_2Cl_2, −78 °C; (b) triethylamine, rt, 40 h; (c) $AlCl_3$, anisole, CH_3NO_2, CH_2Cl_2.

for nucleophilic addition by the hydroxyl group of Ser-195 of HNE. Among those tested, 1,3,4-oxadiazoles always exhibited more potent K_i values than the corresponding 1,2,4-oxadiazoles,[15] both of which showed very potent K_i values when the tripeptidyl backbone Cbz-Val-Pro-Val was used as a ketone scaffold. Since the final goal of this project was to identify a nonpeptidic, orally active inhibitor of HNE as a new clinical candidate, a variety of nonpeptidic portions for the tripeptide backbone Cbz-Val-Pro-Val were investigated for their ability to make the synthesized inhibitors orally active. Among the compounds tested, 5-amino-2-phenylpyrimidinones and corresponding desamino derivatives demonstrated good oral profiles as shown in Tables 1 and 2, respectively. The binding constants were derived from the inhibiton of the HNE-catalyzed hydrolysis of MeO-Suc-Ala-Ala-Pro-Val-pNa.[22] All of the inhibitors studied were competitive, reversible inhibitors of HNE and displayed fast-binding inhibition. The heterocyclic derivatives **1a**,**b** afforded extremely potent inhibitors of HNE (Chart 1). The 1,3,4-oxadiazole derivative **1a**, with a K_i of 0.025 nM, is the most potent of the series. Thus, the 1,3,4-oxadiazole is one of the most potent groups so far reported for activating peptidyl ketones.[20,23]

We focused our attention on the screening of a nonpeptidic substitute possessing a good oral profile for the tripeptide backbone Cbz-Val-Pro-Val. Structural hybridization of **1** and **2** reported by Zeneca[23] as an orally active elastase inhibitor afforded potent inhibitors of HNE (Table 1). All of the inhibitors **11a–m** described in Table 1 exhibited more potent in vivo activity than **2**. And 5-benzyl-1,3,4-oxadiazoles **11i–m** showed more potent in vitro activity than 5-alkyl-1,3,4-oxadiazoles **11a–e**. Introduction of a *m*-methyl group into the benzyl moiety of **11i(F)** afforded **11j(F)** with an increased inhibitory constant. *gem*-Dimethylation of the benzylic position of **11i,j(F)** afforded **11k,l(F)** with nearly the same and a slightly more potent K_i value, respectively. Substitution of the *m*- and *p*-positions of the benzylic phenyl portion with a methylenedioxy group produced **11m(F)** with slightly lower inhibitory activity than **11k(F)**. Replacement of the *p*-fluorine atom on the 5-amino-2-phenylpyrimidin-6-one of **11k(F)** with hydrogen pro-

Table 1. Biological Data of Aminopyrimidinone Derivatives **11a−m**

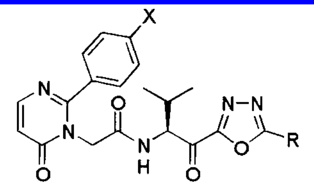


Compd.	X	R	K_i (nM)[a]	ED_{50} (mg/kg, po) or % inhibition at 30 mg/kg[b]
11a(F)	F	Me	14.0	47%
11b(F)	F	Me, Me	10.7	79%
11c(F)	F	Me	6.76	63%
11d(H)	H	Me	8.75	11
11d(F)	F		15.3	9.5
11e(H)	H	Me, Me, Me	3.59	6.7
11e(F)	F		6.38	6.5
11f(F)	F		24.8	9%(NS)[d]
11g(F)	F	OMe	21.2	13%(NS)[d]
11h(F)	F	N	13.9	0%
11i(F)	F		2.25	53%
11j(F)	F	Me	0.64[c]	13
11k(H)	H	Me, Me	2.55	25
11k(F)	F		0.52	10
11l(F)	F	Me, Me, Me	1.37	57%
11m(F)	F	Me, Me	1.18	50%(NS)[d]

[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 1 h before intratracheal instillation of HNE (10 U/lung). [c] See ref 15. [d] NS, not significant.

vided **11k(H)** with a decreased K_i value. Conversion of the benzylic moiety into a phenyl or *p*-methoxyphenyl moiety of **11i(F)** afforded **11f(F)** or **11g(F)** with significant loss of inhibitory activity. Replacement of the phenyl moiety on the oxadiazole of **11f(F)** with a pyridin-3-yl group gave **11h(F)** also with much lower inhibitory activity compared to **11i(F)**. Replacement of the benzylic portion of **11i−m** with an aliphatic moiety afforded **11a−e**. 5-Methyl-1,3,4-oxadiazole **11a(F)** exhibited a K_i of 14.0 nM. Introduction of an isopropyl and an *n*-butyl group instead of the methyl group into the oxadiazole gave **11b,c(F)**, respectively, with slightly more potent inhibitory activity. *tert*-Butyloxadiazole **11e(F)** which showed nearly the same K_i value as **11c(F)** was also investigated. Our scheme for its synthesis

Table 2. Biological Data of Desaminopyrimidinone Derivatives **21d,e(H)**, **21d,e(F)**, and **21k(F)**



Compd.	X	R	K_i (nM)[a]	ED_{50} (mg/kg, po) or % inhibition at 30 mg/kg[b]
21d(H)	H	Me	26.4	6.6
21d(F)	F		43.8	5.5
21e(H)	H	Me, Me, Me	23.5	4.0
21e(F)	F		44.3	6.8
21k(F)	F	Me, Me	3.35	61%

[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 1 h before intratracheal instillation of HNE (10 U/lung).

(Scheme 1) includes an anion formation at position-2 of the 5-substituted oxadiazole. It is easily predictable that selective anion formation at position-2 of the 5-substituted oxadiazoles causes a problem if the carbon atom attached to position-5 is not a tertiary one. Compound **11d(F)** was prepared for the same reason as described above and retained a potent K_i of 15.3 nM. Removal of the fluorine atom of **11d,e(F)** afforded **11d,e(H)**, respectively, with slightly higher inhibitory activity.

In an attempt to understand the factors responsible for oral potency in this set of compounds, we have divided these inhibitors into three groups on the basis of their structural features. The first group (**11a−e**) contains inhibitors with the oxadiazoles substituted with an aliphatic alkyl group such as a methyl, isopropyl, *n*-butyl, or *tert*-butyl. The second group (**11f−h**) contains inhibitors which have an aromatic group directly attached to the oxadiazole ring; these compounds exhibited relatively low K_i values compared with the members of the first group. The third group (**11i−m**) contains inhibitors possessing oxadiazoles substituted with benzyl groups, which exhibited the most potent in vitro activities of all. With respect to oral profiles, inhibitors of the first group demonstrated a relatively higher potency than those of the third group (**11i−m**) despite their lower K_i values. The inconsistency between oral potency and K_i values is presumed to result from the better solubility of the first group relative to that of the third group. According to our own investigation, solubility data of **11e,k(H)** under the same conditions (Table 6) clearly showed that inhibitors possessing alkyl substituents on their oxadiazoles such as **11e(H)** demonstrated better solubility than inhibitors possessing benzyl substituents on their oxadiazoles such as **11k(H)**. Inhibitors of the second group (**11f−h**) did not exhibit oral activity despite their potent K_i values. We speculate that a presumed lower solubility based on the longer conjugated system of the phenyloxadiazoles could be one of the reasons for their oral inactiv-

Chart 1. Structural Hybridization of **1** and **2**

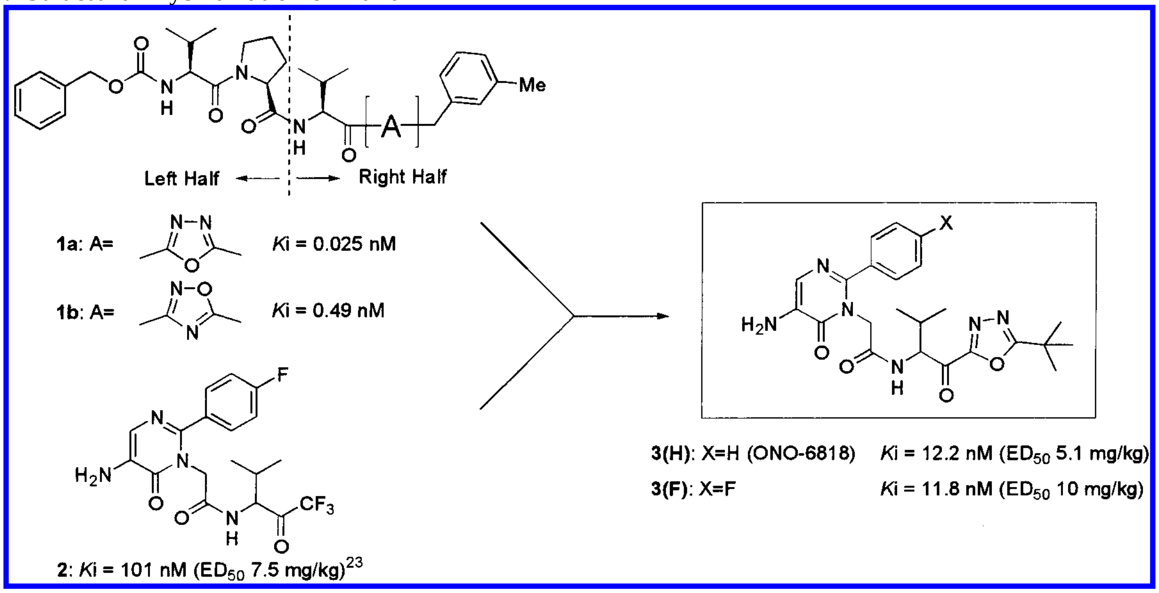
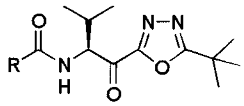
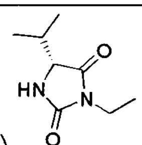
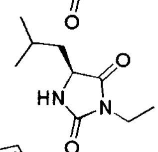
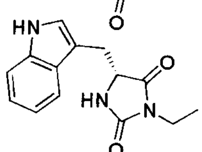
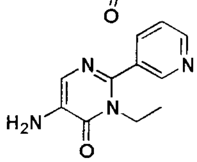
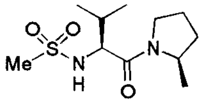
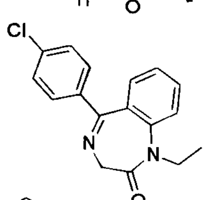
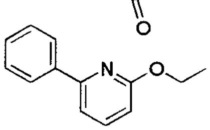


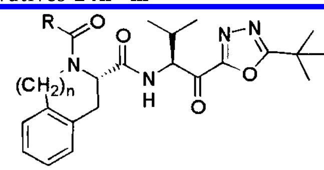
Table 3. Biological Data of Miscellaneous Derivatives **24a**−**g**

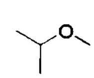
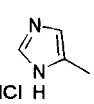
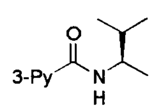


Compd.	R	*Ki* (nM)[a]	% inhibition (at 30 mg/kg, po)[b]
24a		836	0%
24b		730	0%
24c		163	22%(NS)[c]
24d		16.6	6%(NS)[c]
24e		12.0	17%(NS)[c]
24f		57.8	22%(NS)[c]
24g		4281	28%(NS)[c]

[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 1 h before intratracheal instillation of HNE (10 U/lung). [c] NS, not significant.

Table 4. Biological Data of Tetrahydroisoquinoline and Indoline Derivatives **24h**−**m**



Compd.	n	R	*Ki* (nM)[a]	ED_{50} (mg/kg, p.o.) or % inhibition (at 30 mg/kg)[b]
24h	0		114	NT[c]
24i	1		725	0%
24j	0	 HCl	79.7	81%[d]
24k	1		309	29%
24l	0		5.10	36%(NS)[e]
24m	1		1.66	14.2

[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 1 h before intratracheal instillation of HNE (10 U/lung). [c] NT, not tested. [d] Dose dependency was not observed. [e] NS, not significant.

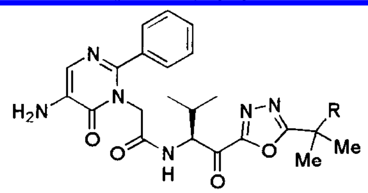
ity. As described in a previous paper, *RS*-mixture **3(H)**, *S*-isomer **11e(H)**, and its *R*-isomer **11n(H)**[24] exhibited nearly the same oral potency. This was ascribed to the presumed epimerization of the two enantiomers in the living body because of their easily enolizable structures. Supportive evidence is shown in Figure 2. Gradual racemization of both of the enantiomers **11e,n(H)**[24] was observed following their incubation in the whole blood of hamster. The evidence described above was also obtained in the whole blood of rat and human. On the basis of both of the oral profiles and reasons of synthesis, *RS*-mixture **3(H)** was selected as a clinical candidate (ONO-6818). The final ED_{50} value following oral dosing of **3(H)** (ONO-6818) was 1.4 mg/kg.[25]

Table 5. Pharmacokinetic Parameters[a] in Rat for **3(H)** (ONO-6818)[b]

Route	Fasted	Dose (mg/kg)	$T_{1/2}$[c] (h)	Cmax[d] (ng/mL)	Tmax[e] (h)	$AUC_{0-\infty}$[f] (ng·h/mL)	F[g] (%)
p.o.	+	1	5.1 ± 4.2	115 ± 18	0.31 ± 0.13	230 ± 52	
	+	3	4.5 ± 2.3	257 ± 110	0.63 ± 0.25	976 ± 313	50.5
	+	10	7.4 ± 5.4	351 ± 77	0.31 ± 0.13	2130 ± 950	
	+	30	8.7 ± 5.0	527 ± 232	0.44 ± 0.13	3050 ± 900	
	−	3	5.0 ± 1.8	174 ± 76	1.1 ± 0.3	760 ± 329	39.4
i.v.	+	3	3.0 ± 0.9[h]			1930 ± 210	

[a] Data are shown as mean ± SD (n = 4). [b] Compound was administered orally as a suspension in 0.5% CMC or intravenously as a solution in 35% HP-β-CD. [c] Pharmacokinetic half-life time was determined in the period 6−24 h after dosing. [d] Maximum concentration of unchanged drug in plasma recorded in the period 0−24 h after dosing. [e] Time of maximum concentration. [f] Integrated area under the concentration versus time curve. [g] Oral bioavailability was measured by the ratio of intravenous to oral AUC. [h] n = 3.

Table 6. Solubility of **11e,k(H)**



11e(H): R = Me
11k(H): R = Ph

	Solubility (μg/mL)			
	vehicle-1[a]	vehicle-2[b]	vehicle-3[c]	vehicle-4[d]
11e(H)	> 2000	NT[e]	1010	310
11k(H)	499	26	NT[e]	20

[a] First fluid (JP13th) (pH = ca. 1.2). [b] 1/14 M phosphate citrate buffer (pH = ca. 4.0). [c] Physiological saline (pH = ca. 5.5). [d] 1/14 M phosphate buffer (pH = ca. 7.4). [e] NT, not tested.

Compound **3(H)** (ONO-6818) exhibited highly potent oral activity, and sustained activity was observed for more than 8 h following oral dosing. Oral bioavailability was excellent in three species (rat, 51%; dog, 31%; monkey, 18%). As a representative example, oral profiles of **3(H)** are shown in Table 5. Compound **3(H)** was ineffective against a variety of proteases such as pancreatic elastase, proteinase 3, trypsin, murine macrophage elastase, *Pseudomonas aeruginosa* elastase, cathepsin G, plasmin, thrombin, and type I collagenase at a concentration 100 times that which inhibited HNE.

Biological data of several desaminopyrimidinone derivatives, **21d,e(H)** and **21d,e,k(F)**, were investigated. As shown in Table 2, all of the compounds exhibited lower K_i values than their corresponding aminopyrimidinone derivatives. Also in this case, compounds **21d,e(H)** and **21d,e(F)** possessing the oxadiazoles substituted with an aliphatic alkyl group demonstrated more potent oral activity (ED_{50}) than **21k(F)** possessing a 5-benzyloxadiazole, while they had much lower K_i values relative to that for **21k(F)**.

Many other peptidomimetics as a surrogate for Cbz-Val-Pro-Val were investigated (Tables 3, 4). Hydantoin derivatives **24a**−**c** demonstrated no activity in animal models as expected from their relatively weak in vitro activity. 5-Amino-2-(3-pyridyl)pyrimidinone **24d**, *N*-methanesulfonyl-Val-Pro derivative **24e**, and benzodiazepine derivative **24f** did not exhibit oral activity, while they showed quite potent in vitro activity. 6-Phenyl-2-alkoxypyridine derivative **24g** was not orally active as predicted from its weak K_i value.

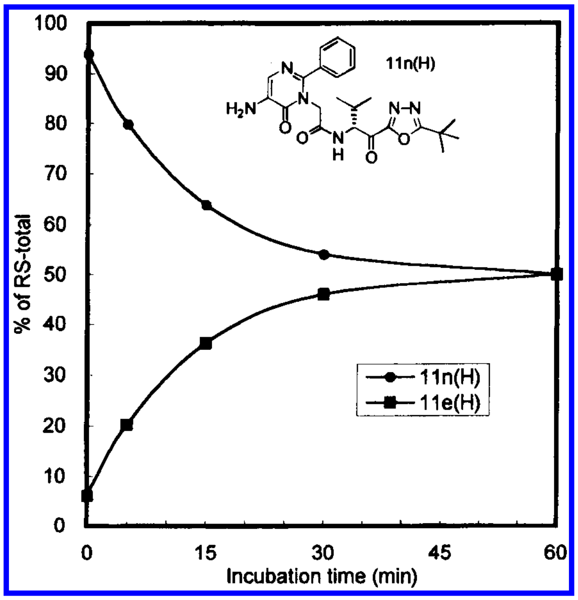


Figure 2. Racemization of **11n(H)** in hamster whole blood: To a solution of test compound in EtOH (1 μg/10 μL) was added 200 μL of blood (n = 3). The mixture, mixed well, was incubated for 60 min at 37 °C. After incubation for 0, 5, 15, 30, and 60 min, the reaction was quenched with water (0.5 mL)−benzene (2.5 mL). After centrifugation at ca. 1500g for 5 min, the organic layer was evaporated. A solution of the residue in the mobile phase [0.02 M KH_2PO_4 (pH 3)/EtOH (90/10)] was analyzed by HPLC [column: ULTRON ES-OVM, 4.6 × 150 mm (Shinwa Chemical Industries, Ltd.); detection: UV at 312 nm].

Biological data of the tetrahydroisoquinoline and indoline derivatives **24h**−**m** are shown in Table 4. *N*-Isopropoxycarbonylindoline derivative **24h** and *N*-isopropoxycarbonyltetrahydroisoquinoline derivative **24i** exhibited moderate and weak in vitro activity, respectively. *N*-Imidazolyl derivatives **24j**,**k** showed quite potent and moderate in vitro activity, respectively. The compound **24j** demonstrated 81% inhibition at a dose of 30 mg/kg (po), while it did not show dose-dependent efficacy. Nicotinoyl derivatives **24l**,**m** showed the most potent in vitro activity among the tested compounds of Tables 3 and 4, but neither of them showed significant oral efficacy.

Further experimental evidence for the proposed binding mechanism of this series was obtained from the X-ray crystal structure of an α-ketooxadiazole bound to PPE.[18] In this complex, one of the oxadiazole nitrogen atoms was observed to possess the appropriate geometry and distance (2.80 Å) from the nitrogen atom of His-57 to participate in a strong hydrogen-bonding interaction.

Summary

We have discovered a new series of nonpeptidic orally active HNE inhibitors which contain a 1,3,4-oxadiazole. A number of the 3-aminopyrimidinone α-keto-1,3,4-oxadiazoles, most notably **3(H)**, **3(F)**, **11d,e,j(H)**, and **11d,e,k(F)**, were extremely potent inhibitors of HNE. The data from this study combined with the crystal structure study[18] confirmed the importance of the hydrogen bond between the heterocyclic ring of the inhibitor and the imidazole ring of His-57 in the covalent enzyme−inhibitor complex. This is a report of the first clinical candidate for a nonpeptidic orally active HNE inhibitor.

Experimental Section

General Directions. Analytical samples were homogeneous on TLC and afforded spectroscopic results consistent with assigned structures. All ^{1}H NMR spectra were obtained using a Varian GEMINI-200, VXR-200s, or MERCURY300 spectrometer. Mass spectra were obtained on a HITACHI M1200H or JEOL JMS-DX303HF spectrometer. IR spectra were measured on a Perkin-Elmer FT-IR 1760X or JASCO FT/IR-430 spectrometer. Elemental analyses for carbon, hydrogen, and nitrogen were carried out by the Analytical Section of Ono Pharmaceutical Co., Ltd. on a Perkin-Elmer PE2400 SeriesII CHNS/O analyzer and are within ±0.4% of theory for the formulas given. Optical rotations were measured by 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}). The following abbreviations are used: THF, tetrahydrofuran; DMF, *N*,*N*-dimethylformamide; DME, ethylene glycol dimethyl ether; DMSO, dimethyl sulfoxide; EDC·HCl, 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride; HOBt·H_2O, *N*-hydroxybenzotriazole hydrate.

Pivalic Acid Hydrazide (5e). A mixture of methyl pivalate (**4e**) (11.5 mL, 86.4 mmol) and hydrazine hydrate (6.30 mL, 130 mmol) was refluxed for 28 h. After being cooled to room temperature, the reaction mixture was evaporated under reduced pressure, then dried by azeotropic removal of the solvent with toluene. The residue was dissolved in $CHCl_3$ and washed with brine. The aqueous layer was further extracted with $CHCl_3$ three times. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated to afford **5e** (6.03 g, 60%) as a white waxy solid: TLC R_f = 0.50, $CHCl_3$/MeOH (9/1); MS (APCI, pos. 40 V) m/z = 117 (M + H)$^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.09 (br s, 1H), 3.86 (br s, 2H), 1.19 (s, 9H).

2-*tert*-Butyl-1,3,4-oxadiazole (6e). In a round-bottomed flask equipped with a standard distillation apparatus, a mixture of the hydrazide **5e** (8.80 g, 76.0 mmol), trimethyl orthoformate (12.5 mL, 114 mmol) and *p*-toluenesulfonic acid monohydrate (217 mg, 1.14 mmol) was heated at 80−120 °C removing MeOH by distillation. Distillation in vacuo of the residue afforded the oxadiazole **6e** (6.58 g, 69%) as a pale yellow liquid: TLC R_f = 0.68, $CHCl_3$/MeOH (10/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.31 (s, 1H), 1.43 (s, 9H).

***tert*-Butyl *N*-[(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl]carbamate (7e).** To a stirred solution of the oxadiazole **6e** (62.1 g, 493 mmol) in THF (1.65 L) was added dropwise *n*-BuLi (493 mmol) in *n*-hexane under Ar at −70 °C. After 40 min, $MgBr_2$·OEt_2 (127 g, 493 mmol) was added. The reaction mixture was allowed to warm to −45 °C. The resulting white slurry was stirred at −45 °C for another 1.5 h, and treated with *N*-[(1*S*)-1-(methylethyl)-2-oxoethyl](*tert*-butoxy)carboxamide (**12**)[19] (90.0 g, 448 mmol) in THF (60 mL). The reaction temperature was raised to −20 °C. After being stirred for 3.5 h, the reaction mixture was quenched with saturated NH_4Cl, and extracted with EtOAc. The organic layer was washed with water (×3) and then brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel [Merck 7734, EtOAc/*n*-hexane (1/20 → 1/1)] to give the Boc alcohol **7e** (76.8 g, 53%) as a white amorphous solid: TLC R_f = 0.42, *n*-hexane/EtOAc (1/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.18−4.90 (m, 2H), 4.51 and 4.12 (m × 2, 1H), 3.91 and 3.66 (m × 2, 1H), 1.95 (m, 1H), 1.42, 1.41 and 1.34 (s × 3, 18H), 1.15−0.90 (m, 6H).

(2*S*)-2-Amino-1-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-3-methylbutan-1-ol Hydrochloride (8e). A mixture of the Boc alcohol **7e** (76.3 g, 233 mmol) and 4 N HCl in dioxane (1 L) diluted with dioxane (200 mL) was vigorously stirred at room temperature for 2 h. Concentration of the reaction mixture and then solidification with ether followed by azeotropic removal of water with benzene gave the amino alcohol **8e** (66.1 g) quantitatively. The formed product was used for the next reaction without further purification: TLC R_f = 0.30 and 0.26, $CHCl_3$/MeOH (10/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.34 and 8.24 (m × 2, 2H), 5.60 (m, 1H), 3.97−3.60 (m, 2H), 2.08 (m, 1H), 1.42 and 1.41 (s × 2, 9H), 1.25−0.95 (m, 6H).

***N*-[(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl]-2-{6-oxo-2-phenyl-5-[(phenylmethoxy)carbonylamino]hydropyrimidinyl}acetamide (9e(H)).** To a stirred mixture of 2-{6-oxo-2-phenyl-5-[(phenylmethoxy)carbonylamino]hydropyrimidinyl}acetic acid (**13(H)**) (30.0 g, 79.2 mmol), prepared according to Zeneca's procedure,[20] the amino alcohol **8e** (23.0 g, 87.1 mmol) and HOBt·H_2O (13.3 g, 87.1 mmol) in DMF (263 mL) were added EDC·HCl (16.7 g, 87.1 mmol) and then *N*-methylmorpholine (9.60 mL, 87.1 mmol) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 3.5 h, and then evaporated. The residue was dissolved in EtOAc and washed with water. The organic layer was washed successively with saturated NH_4Cl, saturated $NaHCO_3$, water and brine, and dried over anhydrous Na_2SO_4. Concentration of the organic layer afforded the alcohol **9e(H)** (50.1 g, quant) as a beige amorphous powder. The product was used for the next reaction without further purification: TLC R_f = 0.53 and 0.38, EtOAc; MS (APCI, pos. 40 V) m/z = 589 (M + H)$^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.81 and 8.71 (m × 2, 1H), 7.66−7.26 (m, 11H), 7.11 and 6.70 (d and m, J = 10.0 Hz, 1H), 5.20 (s, 2H), 5.15−5.00 (m, 1H), 4.70−4.22 and 4.15−3.60 (m × 2, 4H), 2.10−1.60 (m, 1H), 1.39 and 1.35 (s × 2, 9H), 1.12−0.87 (m, 6H).

***N*-[(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]-2-{6-oxo-2-phenyl-5-[(phenylmethoxy)-carbamido]hydropyrimidinyl}acetamide (10e(H)).** To a stirred solution of oxalyl chloride (0.790 mL, 9.08 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of DMSO (1.29 mL, 18.2 mmol) in CH_2Cl_2 (2 mL) under Ar at −70 to −60 °C. A solution of the alcohol **9e(H)** (2.62 g, ca. 4.17 mmol) in CH_2Cl_2 (20 mL) was added. After being stirred at −70 °C for 2 h, the reaction mixture was treated with *N*-methylmorpholine (3.99 mL, 36.3 mmol), then stirred at −20 °C for 30 min. The resulting mixture was acidified with 1 N HCl, and stirred vigorously at room temperature for a while, then extracted with EtOAc. The organic layer was washed successively with 1 N HCl, water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by silica gel column chromatography [FL60D, EtOAc/*n*-hexane (1/4)] gave the Cbz ketone **10e(H)** (2.13 g, 87% in 2 steps) as a white amorphous solid: TLC R_f = 0.40, EtOAc/*n*-hexane (1/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.78 (br s, 1H), 7.60−7.33 (m, 11H), 6.71 (d, J = 8.4 Hz, 1H), 5.44 (dd, J = 8.4, 4.8 Hz, 1H), 5.23 (s, 2H), 4.64 and 4.60 (d × 2, J = 15.0 Hz, 1H × 2), 2.50 (m, 1H), 1.47 (s, 9H), 1.06 and 0.87 (d × 2, J = 6.6 Hz, 3H × 2); optical rotation $[\alpha]^{26}_D$ −21.9 (*c* 0.7, MeCN).

***N*-[(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]-2-(5-amino-6-oxo-2-phenylhydropyrimidinyl)acetamide (11e(H)).** To a stirred solution of the Cbz ketone **10e(H)** (2.10 g, 3.58 mmol) and anisole (2.34 mL, 21.5 mmol) in CH_2Cl_2 (58 mL) was added dropwise a solution of aluminum chloride (2.87 g, 21.5 mmol) in CH_3NO_2 (28 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 2 h, then quenched with crushed ice, and extracted with EtOAc. The organic layer was washed with water and then brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by silica gel column chromatography [FL60D, MeOH/$CHCl_3$ (1/25 → 1/20)] gave the ketone **11e(H)** (1.42 g, 88%) as an off-white powder: TLC R_f = 0.49, MeOH/$CHCl_3$ (1/10); MS (APCI, pos. 40 V) *m/z* = 453 $(M + H)^+$; IR (KBr) 3457, 2975, 1661, 1614, 1542, 1441, 1304, 1205, 977, 706, 615 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.58−7.38 (m, 6H), 6.88 (br d, J = 8.4 Hz, 1H), 5.45 (dd, J = 8.4, 5.0 Hz, 1H), 4.66 and 4.60 (d × 2, J = 15.4 Hz, 1H × 2), 4.06 (m, 2H), 2.52 (m, 1H), 1.48 (s, 9H), 1.07 and 0.88 (d × 2, J = 6.8 Hz, 3H × 2); optical rotation $[\alpha]^{26}_D$ −9.0 (*c* 0.6, THF), −24.9 (*c* 0.5, MeCN). Anal. ($C_{23}H_{28}N_6O_4$·$0.2H_2O$) C, H, N.

Preparation of 11d(H) and 11a−j(F). Using essentially the same procedures as described for the preparation of **11e(H)**, the following compounds were prepared.

***N*-[(1*S*)-1-(Methylethyl)-2-(5-methyl-1,3,4-oxadiazol-2-yl)-2-oxoethyl]-2-[5-amino-2-(4-fluorophenyl)-6-oxohydropyrimidinyl]acetamide (11a(F)).** Derived from **13(F)** and **8a** which was prepared from **5a**: pale yellow powder; TLC R_f = 0.29, EtOAc; MS (FAB, pos. glycerol + *m*-NBA) *m/z* = 429 $(M + H)^+$, 246, 218, 206; IR (KBr) 3462, 3365, 3284, 3078, 2968, 2878, 1716, 1670, 1614, 1559, 1510, 1437, 1405, 1285, 1231, 1201, 1162, 1054, 1041, 979, 964, 899, 844, 816, 786, 758, 573, 531 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.63−7.43 (m, 3H), 7.22−7.03 (m, 2H), 6.97 (d, J = 7.6 Hz, 1H), 5.40 (dd, J = 8.2, 5.2 Hz, 1H), 4.61 (s, 2H), 4.07 (br s, 2H), 2.67 (m, 3H), 2.64−2.38 (m, 1H), 1.07 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H); optical rotation $[\alpha]^{25}_D$ −19.7 (*c* 0.5, CH_3CN). Anal. ($C_{20}H_{21}FN_6O_4$·$0.5H_2O$) C, H, N.

***N*-{(1*S*)-1-(Methylethyl)-2-[5-(methylethyl)-1,3,4-oxadiazol-2-yl]-2-oxoethyl}-2-[5-amino-2-(4-fluorophenyl)-6-oxohydropyrimidinyl]acetamide (11b(F)).** Derived from **13(F)** and **8b** which was prepared from **4b**: yellow amorphous solid; TLC R_f = 0.16, EtOAc; MS (APCI, pos. 40 V) *m/z* = 457 $(M + H)^+$, 377; IR (KBr) 3461, 3336, 2974, 2939, 2879, 1718, 1664, 1610, 1543, 1510, 1468, 1438, 1408, 1374, 1310, 1227, 1203, 1161, 1098, 1038, 1017, 981, 929, 900, 846, 818, 788, 753, 704, 532 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.60−7.48 (m, 2H), 7.49 (s, 1H), 7.19−7.06 (m, 2H), 6.90 (br d, J = 8.0 Hz, 1H), 5.42 (dd, J = 8.0, 5.0 Hz, 1H), 4.59 (s, 2H), 4.06 (br s, 2H), 3.29 (septet, J = 7.2 Hz, 1H), 2.52 (m, 1H), 1.45 (d, J = 7.2 Hz, 6H), 1.08 and 0.89 (d × 2, J = 7.0 Hz, 3H × 2); optical rotation $[\alpha]^{30}_D$ −20.0 (*c* 0.3, CH_3CN). Anal. ($C_{22}H_{25}FN_6O_4$·$0.2H_2O$) C, H, N.

***N*-[(1*S*)-2-(5-Butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]-2-[5-amino-2-(4-fluorophenyl)-6-oxohydropyrimidinyl]acetamide (11c(F)).** Derived from **13(F)** and **8c** which was prepared from **4c**: yellow amorphous solid; TLC R_f = 0.41, EtOAc; MS (APCI, pos. 40 V) *m/z* = 471 $(M + H)^+$; IR (KBr) 3338, 2965, 2876, 1720, 1664, 1610, 1548, 1510, 1468, 1437, 1407, 1302, 1227, 1161, 1098, 1024, 981, 901, 846, 818, 789, 733, 533 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.59−7.46 (m, 2H), 7.48 (s, 1H), 7.18−7.04 (m, 2H), 6.93 (br d, J = 8.0 Hz, 1H, NH), 5.42 (dd, J = 8.0, 5.2 Hz, 1H), 4.60 (s, 2H), 4.06 (br s, 2H), 2.95 (t, J = 7.7 Hz, 2H), 2.51 (m, 1H), 1.83 (m, 2H), 1.44 (m, 2H), 1.07 and 0.89 (d × 2, J = 7.0 Hz, 3H × 2), 0.96 (t, J = 7.1 Hz, 3H); optical rotation $[\alpha]^{29}_D$ −20.0 (*c* 0.8, CH_3CN). Anal. ($C_{23}H_{27}FN_6O_4$·$0.2H_2O$) C, H, N.

***N*-{(1*S*)-2-[5-(1-Methylcyclopropyl)-1,3,4-oxadiazol-2-yl]-1-(methylethyl)-2-oxoethyl}-2-(5-amino-6-oxo-2-phenylhydropyrimidinyl)acetamide (11d(H)).** Derived from **13(H)** and **8d** which was prepared from **4d**: yellow amorphous solid; TLC R_f = 0.37, EtOAc; MS (APCI, neg. 40 V) *m/z* = 449 $(M - H)^-$, 357, 313, 186, 123; IR (KBr) 3455, 3336, 2968, 2935, 1715, 1664, 1612, 1548, 1438, 1412, 1386, 1315, 1258, 1204, 1030, 819, 774, 705 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.60−7.34 (m, 6H), 6.87 (d, J = 8.2 Hz, 1H), 5.41 (dd, J = 8.2, 4.8 Hz, 1H), 4.66 (d, J = 15.4 Hz, 1H), 4.57 (d, J = 15.4 Hz, 1H), 4.33−3.72 (m, 2H), 2.62−2.37 (m, 1H), 1.61 (s, 3H), 1.51−1.39 (m, 2H), 1.14−0.99 (m, 5H), 0.87 (d, J = 6.8 Hz, 3H); optical rotation $[\alpha]^{26}_D$ −26.9 (*c* 0.5, CH_3CN). Anal. ($C_{23}H_{26}N_6O_4$·$0.2H_2O$) C, H, N.

***N*-{(1*S*)-2-[5-(1-Methylcyclopropyl)-1,3,4-oxadiazol-2-yl]-1-(methylethyl)-2-oxoethyl}-2-[5-amino-2-(4-fluorophenyl)-6-oxohydropyrimidinyl]acetamide (11d(F)).** Derived from **13(F)** and **8d** which was prepared from **4d**: pale yellow powder; TLC R_f = 0.41, EtOAc; MS (APCI, pos. 40 V) *m/z* = 469 $(M + H)^+$; IR (KBr) 3455, 3339, 3055, 2969, 2936, 2877, 1664, 1610, 1548, 1510, 1470, 1437, 1409, 1386, 1314, 1227, 1203, 1161, 1098, 1019, 981, 954, 928, 900, 846, 818, 788, 749, 734, 701, 638, 531 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.49 (s, 1H), 7.12 (t, J = 8.4 Hz, 2H), 6.92 (d, J = 8.0 Hz, 1H), 5.39 (dd, J = 8.0, 5.0 Hz, 1H), 4.60 (s, 2H), 4.07 (br s, 2H), 2.48 (m, 1H), 1.62 (s, 3H), 1.45 (m, 2H), 1.08 (m, 5H), 0.88 (d, J = 6.6 Hz, 3H); optical rotation $[\alpha]^{28}_D$ −28.2 (*c* 1.0, CH_3CN). Anal. ($C_{23}H_{25}FN_6O_4$) C, H, N.

***N*-[(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]-2-[5-amino-2-(4-fluorophenyl)-6-oxohydropyrimidinyl]acetamide (11e(F)).** Derived from **13(F)** and **8e** which was prepared from **4e**: off-white amorphous solid; TLC R_f = 0.29, EtOAc; MS (APCI, pos. 40 V) *m/z* = 471 $(M + H)^+$, 377; IR (KBr) 3461, 3314, 3076, 2976, 2937, 2878, 1714, 1695, 1641, 1609, 1543, 1508, 1463, 1435, 1408, 1393, 1370, 1302, 1222, 1205, 1162, 1111, 1098, 1048, 1017, 984, 969, 937, 895, 846, 825, 791, 761, 733, 695, 644, 606, 548, 534, 487, 423 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.60−7.48 (m, 2H), 7.49 (s, 1H), 7.19−7.06 (m, 2H), 6.90 (d, J = 8.6 Hz, 1H), 5.44 (dd, J = 8.2, 5.0 Hz, 1H), 4.60 (s, 2H), 4.07 (br s, 2H), 2.53 (m, 1H), 1.49 (s, 9H), 1.08 and 0.90 (d × 2, J = 6.9 Hz, 3H × 2); optical rotation $[\alpha]^{30}_D$ −23.4 (*c* 0.4, CH_3CN). Anal. ($C_{23}H_{27}FN_6O_4$) C, H, N.

***N*-[(1*S*)-1-(Methylethyl)-2-oxo-2-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl]-2-[5-amino-2-(4-fluorophenyl)-6-oxohydropyrimidinyl]acetamide (11f(F)).** Derived from **13(F)** and **8f** which was prepared from **5f**: yellow amorphous powder; TLC R_f = 0.29, EtOAc; MS (APCI, pos. 40 V) *m/z* = 491 $(M + H)^+$; IR (KBr) 3346, 3062, 2967, 1664, 1610, 1543, 1510, 1481, 1451, 1397, 1303, 1228, 1204, 1161, 1097, 1028, 982, 902, 845, 818, 787, 715, 691, 531, 492, 423, 406 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.18 (dd, J = 7.9, 1.7 Hz, 2H), 7.73 (d, J = 7.6 Hz, 1H), 7.66−7.48 (m, 5H), 7.47 (s, 1H), 7.11 (t, J = 8.5 Hz, 2H), 5.47 (dd, J = 7.8, 5.6 Hz, 1H), 4.64 (s, 2H), 4.14 (br s, 2H), 2.54 (m, 1H), 1.10 and 0.96 (d × 2, J = 6.7 Hz, 3H × 2); optical rotation $[\alpha]^{30}_D$ −64.1 (*c* 0.3, CH_3CN). Anal. ($C_{25}H_{23}FN_6O_4$·$0.3CH_3CO_2C_2H_5$) C, H, N.

***N*-{(1*S*)-2-[5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl]-1-(methylethyl)-2-oxoethyl}-2-[5-amino-2-(4-fluorophenyl)-6-oxohydropyrimidinyl]acetamide (11g(F)).** Derived from **13(F)** and **8g** which was prepared from **4g**: pale yellow powder; TLC R_f = 0.49, EtOAc; MS (APCI, pos. 40 V) *m/z* = 521 $(M + H)^+$, 246, 218, 206; IR (KBr) 3463, 3369, 3071, 2968, 1713, 1667, 1612, 1510, 1490, 1428, 1310, 1264, 1230, 1176, 1099, 1026, 842, 787, 750, 707, 621, 533 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.12 (m, 2H), 7.65−7.42 (m, 3H), 7.20−6.90 (m, 5H), 5.47 (dd, J = 8.4, 5.2 Hz, 1H), 4.62 (s, 2H), 4.06 (br s, 2H), 3.91 (s, 3H), 2.71−2.41 (m, 1H), 1.10 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H); optical rotation $[\alpha]^{25}_D$ −63.9 (*c* 0.5, CH_3CN). Anal. ($C_{26}H_{25}FN_6O_5$) C, H, N.

***N*-{(1*S*)-1-(Methylethyl)-2-oxo-2-[5-(3-pyridyl)-1,3,4-oxadiazol-2-yl]ethyl}-2-[5-amino-2-(4-fluorophenyl)-6-oxohydropyrimidinyl]acetamide (11h(F)).** Derived from **13(F)** and **8h** which was prepared from **5h**: yellow amorphous powder; TLC R_f = 0.37, $CHCl_3$/MeOH (10/1); MS (APCI, pos. 40 V) *m/z* = 492 $(M + H)^+$, 377, 148; IR (KBr) 3450, 3346, 3060, 2963, 2927, 1719, 1663, 1640, 1608, 1538, 1509, 1482, 1465, 1439, 1416, 1379, 1306, 1227, 1203, 1161, 1107, 1026, 982, 928, 901, 842, 817, 790, 753, 734, 704, 632, 574, 531, 424 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.41 (dd, J = 2.3, 0.7 Hz, 1H), 8.86 (dd, J = 4.9, 1.7 Hz, 1H), 8.46 (dt, 1H, J = 8.0, 2.0

Hz, 1H), 7.62−7.48 (m, 3H), 7.49 (s, 1H), 7.13 (t, $J = 8.6$ Hz, 2H), 6.99 (d, $J = 7.6$ Hz, 1H), 5.47 (dd, $J = 7.8$, 5.0 Hz, 1H), 4.62 (s, 2H), 4.06 (br s, 2H), 2.56 (m, 1H), 1.12 and 0.95 (d × 2, $J = 6.9$ Hz, 3H × 2); optical rotation $[\alpha]^{30}_{D}$ −34.6 (*c* 0.3, CH_3CN). Anal. ($C_{24}H_{22}FN_7O_4{\cdot}0.2CH_3CO_2C_2H_5$) C, H, N.

***N*-[(1*S*)-1-(Methylethyl)-2-oxo-2-(5-benzyl-1,3,4-oxadiazol-2-yl)ethyl]-2-[5-amino-2-(4-fluorophenyl)-6-oxohydropyrimidinyl]acetamide (11i(F)).** Derived from **13(F)** and **8i** which was prepared from **4i**: lemon yellow solid; TLC $R_f = 0.50$, etc; MS (APCI, pos. 40 V) $m/z = 505$ (M + H)$^+$, 377, 161; IR (KBr) 3465, 3367, 3075, 2969, 1716, 1670, 1611, 1544, 1510, 1457, 1436, 1405, 1312, 1280, 1229, 1202, 1161, 1097, 1024, 981, 899, 845, 817, 787, 731, 697, 534, 472 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.56−7.48 (m, 2H), 7.48 (s, 1H), 7.40−7.30 (m, 5H), 7.10 (t, $J = 8.5$ Hz, 2H), 6.94 (br d, $J = 8.6$ Hz, 1H), 5.39 (dd, $J = 8.6$, 5.2 Hz, 1H), 4.58 (s, 2H), 4.29 (s, 2H), 4.05 (br s, 2H), 2.49 (m, 1H), 1.06 and 0.87 (d × 2, $J = 6.8$ Hz, 3H × 2); optical rotation $[\alpha]^{27}_{D}$ −25.6 (*c* 0.6, CH_3CN). Anal. ($C_{26}H_{25}FN_6O_4$) C, H, N.

***N*-{(1*S*)-1-(Methylethyl)-2-[5-((3-methylphenyl)methyl)-1,3,4-oxadiazol-2-yl]-2-oxoethyl}-2-[5-amino-2-(4-fluorophenyl)-6-oxohydropyrimidinyl]acetamide (11j(F)).** Derived from **13(F)** and **8j** which was prepared from **4j**: white powder; TLC $R_f = 0.42$, EtOAc; MS (APCI, pos. 40 V) $m/z =$ 519 (M + H)$^+$, 246, 218, 206; IR (KBr) 3459, 3365, 3286, 2967, 1707, 1665, 1611, 1538, 1510, 1438, 1309, 1226, 1204, 1162, 1097, 1037, 980, 891, 846, 817, 787, 755, 695, 532 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.69 (d, $J = 7.0$ Hz, 1H,), 7.49−7.34 (m, 2H), 7.34−7.06 (m, 7H), 5.15 (br s, 2H), 5.11−4.99 (m, 1H), 4.52 (s, 2H), 4.36 (s, 2H), 2.35−2.11 (m, 1H), 2.29 (s, 3H), 0.89 (d, $J = 6.8$ Hz, 3H), 0.82 (d, $J = 6.8$ Hz, 3H); optical rotation $[\alpha]^{26}_{D}$ −23.7 (*c* 1.0, CH_3CN). Anal. ($C_{27}H_{27}FN_6O_4$) C, H, N.

Methyl 2-Methyl-2-phenylpropionate (4k). To a stirred solution of phenylacetic acid (**14k**) (15.0 g, 0.110 mol) in methanol (280 mL) was added dropwise chlorotrimethylsilane (31.0 mL, 0.24 mol). The resulting solution was stirred at room temperature for 5 h, and the solvent was removed by evaporation. The residue was dried by azeotropic removal of water with benzene and diluted with THF (100 mL). The solution was added dropwise to a stirred suspension of sodium hydride (60% in oil, 13.0 g, 0.33 mol) in THF (400 mL) under Ar. The resulting suspension was stirred for 30 min, and methyl iodide (16.5 mL, 0.26 mol) was added dropwise. The reaction mixture was stirred at room temperature overnight. To the reaction mixture was added Florisil (12 g), and the solid was removed by filtration through a pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was partitioned between EtOAc and water. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were washed with brine. After drying over anhydrous $MgSO_4$, the solvent was removed by evaporation. The residue was purified by silica gel column chromatography [Merck 7734, *n*-hexane/EtOAc (10/1)] to give **4k** (14.9 g, 76%) as a yellowish liquid: TLC $R_f = 0.33$, *n*-hexane/EtOAc (10/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38−7.18 (m, 5H), 3.65 (s, 3H), 1.58 (s, 6H).

2-Methyl-2-phenylpropione Hydrazide (5k). A mixture of the ester **4k** (14.9 g, 83.6 mmol) and hydrazine hydrate (41 mL, 0.85 mol) was heated under reflux with stirring for 6.5 h. The reaction mixture was cooled to room temperature, and concentrated. The hydrazine was removed by azeotropic distillation with toluene. The residue was purified by column chromatography [Merck 7734, $CHCl_3$/MeOH (10/1)] to give **5k** (14.7 g, 99%) as a yellowish gum: TLC $R_f = 0.50$, $CHCl_3$/MeOH (10/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41−7.22 (m, 5H), 3.92 (br s, 3H), 1.59 (s, 6H).

2-(1-Methyl-1-phenylethyl)-1,3,4-oxadiazole (6k). A mixture of the hydrazide **5k** (14.7 g, 82.5 mmol) and ethyl orthoformate (90 mL, 0.54 mol) was heated under reflux with stirring for 10 h. The reaction mixture was cooled to room temperature, and concentrated. The ethyl orthoformate was removed by azeotropic distillation with toluene. The residue was purified by silica gel column chromatography (Merck 7734, *n*-hexane/EtOAc), followed by azeotropic removal of water with toluene to give **6k** (10.06 g, 65%) as a slightly brown liquid: TLC $R_f = 0.58$, $CHCl_3$/MeOH (10/1); MS (APCI, pos. 40 V) m/z = 189 (M + H)$^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.40−7.19 (m, 5H), 1.85 (s, 6H).

***tert*-Butyl *N*-{(1*S*)-2-Hydroxy-1-(methylethyl)-2-[5-(1-methyl-1-phenylethyl)-1,3,4-oxadiazol-2-yl]ethyl}carbamate (7k).** To a stirred solution of the oxadiazole **6k** (1.69 g, 9.00 mmol) in THF (40 mL) was added dropwise *n*-BuLi (9.00 mmol) in *n*-hexane under Ar at −70 °C. After 1.5 h, $MgBr_2{\cdot}OEt_2$ (2.56 g, 9.90 mmol) was added, and then the reaction mixture was allowed to warm to −45 °C over 30 min. The resulting white slurry was stirred at −45 °C for 1 h, and treated with *tert*-butyl *N*-[(1*S*)-1-(methylethyl)-2-oxoethyl]carbamate (Boc-L-valinal) (**12**)[19] (603 mg, 3.00 mmol) in THF (13 mL). The reaction temperature was allowed to rise to −20 °C. The reaction mixture was stirred for another 1.5 h, then quenched with saturated NH_4Cl, and extracted with EtOAc. The organic layer was washed with water (×2) and then brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified twice by silica gel column chromatography [FL60D, EtOAc/*n*-hexane (1/10)] to give the Boc alcohol **7k** (922 mg, 2.37 mmol, ca. 79%) as a pale yellow amorphous solid: TLC (HPTLC) $R_f = 0.58$ and 0.55, EtOAc/*n*-hexane (1/1); MS (APCI, pos. 40 V) $m/z = 390$ (M + H)$^+$, 334, 189; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40−7.18 (m, 5H), 5.05−4.78 (m, 2H), 4.08−3.75 and 3.63−3.47 (m × 2, 2H), 2.05−1.68 (m, 7H), 1.41 and 1.35 (s × 2, 9H), 1.06−0.85 (m, 6H).

(2*S*)-2-Amino-3-methyl-1-[5-(1-methyl-1-phenylethyl)-1,3,4-oxadiazol-2-yl]butan-1-ol Hydrochloride (8k). A mixture of the Boc alcohol **7k** (393 mg, 1.01 mmol) and 4 N HCl in dioxane (30 mL) was stirred at room temperature for 1.5 h. The reaction mixture was concentrated in vacuo. The residue was dried by azeotropic removal of water with toluene to afford **8k** quantitatively. The product was used for the next reaction without further purification: TLC $R_f = 0.23$, MeOH/$CHCl_3$ (1/10); MS (APCI, pos. 40 V) $m/z = 290$ (M + H)$^+$, 219, 189; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.50−8.00 (m, 2H), 7.35−6.80 (m, 7H), 5.42−5.30 (m, 1H), 3.85−3.60 (m, 2H), 2.00−1.50 (m, 7H), 1.13−0.80 (m, 6H).

***N*-{(1*S*)-2-Hydroxy-1-(methylethyl)-2-[5-(1-methyl-1-phenylethyl)-1,3,4-oxadiazol-2-yl]ethyl}-2-{2-(4-fluorophenyl)-6-oxo-5-[(phenylmethoxy)carbamido]hydropyrimidinyl}acetamide (9k(F)).** To a stirred mixture of the carboxylic acid **13(F)** (333 mg, 0.84 mmol), the amino alcohol **8k** (ca. 1.01 mmol) and $HOBt{\cdot}H_2O$ (155 mg, 1.01 mmol) in DMF (2.5 mL), were added EDC·HCl (194 mg, 1.01 mmol) and then *N*-methylmorpholine (0.11 mL, 1.01 mmol) under Ar at 0 °C. After 15 min, the reaction mixture was stirred at room temperature for 12 h, and poured into saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with water, and dried over anhydrous $MgSO_4$. Evaporation followed by purification by silica gel column chromatography [FL60D, MeOH/$CHCl_3$ (0/100 → 1/10)] afforded Cbz alcohol **9k(F)** (551 mg, 98%) as a pale yellow amorphous solid: TLC $R_f = 0.46$ and 0.42, MeOH/$CHCl_3$ (1/10); MS (APCI, pos. 40 V) $m/z =$ 669 (M + H)$^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.78 and 8.71 (m × 2, 1H), 7.70−6.70 (m, 16H), 5.20 and 5.18 (s × 2, 2H), 5.05 and 4.98 (m × 2, 1H), 4.60−3.87 (m, 4H), 2.00−1.53 (m, 7H), 1.08−0.80 (m, 6H).

***N*-{(1*S*)-1-(Methylethyl)-2-[5-(1-methyl-1-phenylethyl)-1,3,4-oxadiazol-2-yl]-2-oxoethyl}-2-{2-(4-fluorophenyl)-6-oxo-5-[(phenylmethoxy)carbamido]hydropyrimidinyl}-acetamide (10k(F)).** To a suspension of Dess−Martin periodinane (ca. 77%, 491 mg, 0.89 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of Cbz alcohol **9k(F)** (542 mg, 0.81 mmol) in CH_2Cl_2 (8 mL) under Ar at room temperature. After 2 h, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and then brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by silica gel column chromatography [FL60D, EtOAc/*n*-hexane, (1/4 → 1/1)] gave Cbz ketone **10k(F)** (490 mg, 91%) as a pale yellow amorphous solid: TLC $R_f = 0.57$, EtOAc/*n*-hexane (1/1); MS

(APCI, pos. 40 V) *m/z* 667 (M + H)$^+$, 344, 173, 127; IR (KBr) 3386, 2973, 1723, 1663, 1608, 1526, 1504, 1398, 1368, 1301, 1216, 1191, 1162, 1093, 1016, 924, 847, 747, 699 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.75 (br s, 1H), 7.62−7.47 (m, 3H), 7.43−7.20 (m, 10H), 7.11 (t, J = 8.5 Hz, 2H), 6.75 (d, J = 8.0 Hz, 1H), 5.43 (dd, J = 8.0, 5.0 Hz, 1H), 5.22 (s, 2H), 4.58 (s, 2H), 2.49 (m, 1H), 1.88 (s, 6H), 1.04 and 0.84 (d × 2, J = 7.0 Hz, 3H × 2); optical rotation $[\alpha]^{24}_D$ −20.3, (*c* 1.0, MeCN).

***N*-{(1*S*)-1-(Methylethyl)-2-[5-(1-methyl-1-phenylethyl)-1,3,4-oxadiazol-2-yl]-2-oxoethyl}-2-[5-amino-2-(4-fluorophenyl)-6-oxohydropyrimidinyl]acetamide (11k(F)).** To a stirred solution of **10k(F)** (200 mg, 0.30 mmol) and anisole (0.20 mL, 1.80 mmol) in CH_2Cl_2 (6 mL) was added dropwise a solution of aluminum chloride (240 mg, 1.80 mmol) in CH_3NO_2 (3 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h, then quenched with crushed ice, and poured into water and extracted with EtOAc. The organic layer was washed with water and then brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification of the residue by silica gel column chromatography [FL60D, EtOAc/*n*-hexane (2/1)] gave **11k(F)** (153 mg, 97%) as a pale yellow amorphous powder: TLC R_f = 0.49, EtOAc; MS (FAB, pos.) *m/z* = 533 (M + H)$^+$, 246, 218, 206, 119; IR (KBr) 3448, 3348, 2972, 1719, 1664, 1610, 1533, 1510, 1438, 1227, 1161, 1033, 1017, 846, 700, 532 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62−7.42 (m, 3H), 7.42−7.18 (m, 5H), 7.18−7.03 (m, 2H), 7.00 (d, J = 8.3 Hz, 1H), 5.43 (dd, J = 8.3 and 5.0 Hz, 1H), 4.60 (s, 2H), 4.07 (br s, 2H), 2.63−2.35 (m, 1H), 1.88 (s, 6H), 1.05 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H); optical rotation $[\alpha]^{25}_D$ −25.2, (*c* 0.5, MeCN). Anal. ($C_{28}H_{29}FN_6O_4{\cdot}H_2O$) C, H, N.

Preparation of 11k(H) and 11l,m(F). The following compounds were prepared, using essentially the same procedures as described for the preparation of **11k(F)**.

***N*-{(1*S*)-1-(Methylethyl)-2-[5-(1-methyl-1-phenylethyl)-1,3,4-oxadiazol-2-yl]-2-oxoethyl}-2-(5-amino-6-oxo-2-phenylhydropyrimidinyl)acetamide (11k(H)).** Derived from **13(H)** and **8k** which was prepared from **14k**: white powder; TLC R_f = 0.51, EtOAc; MS (FAB, pos. glycerol + *m*-NBA) *m/z* = 515 (M + H)$^+$, 228, 200, 188, 119, 91; IR (KBr) 3463, 3319, 3060, 2977, 1695, 1664, 1610, 1531, 1438, 1371, 1301, 1247, 1204, 1032, 977, 897, 774, 700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.58−7.18 (m, 11H), 6.79 (d, J = 8.4 Hz, 1H), 5.44 (dd, J = 8.4, 5.0 Hz, 1H), 4.65 (d, J = 15.4 Hz, 1H), 4.55 (d, J = 15.4 Hz, 1H), 4.03 (br s, 2H), 2.62−2.36 (m, 1H), 1.89 (s, 6H), 1.06 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H); optical rotation $[\alpha]^{25}_D$ −27.2 (*c* 0.4, CH_3CN). Anal. ($C_{28}H_{30}N_6O_4$) C, H, N.

***N*-{(1*S*)-1-(Methylethyl)-2-[5-(1-methyl-1-(3-methylphenyl)ethyl)-1,3,4-oxadiazol-2-yl]-2-oxoethyl}-2-[5-amino-2-(4-fluorophenyl)-6-oxohydropyrimidinyl]acetamide (11l(F)).** Derived from **13(F)** and **8l** which was prepared from **14l**: pale yellow amorphous powder: TLC R_f = 0.51, AcOEt; MS (FAB, pos. glycerol + *m*-NBA) *m/z* = 547 (M + H)$^+$, 533, 246, 218, 206; IR (KBr) 3456, 3335, 2970, 2933, 1933, 1718, 1664, 1610, 1532, 1510, 1438, 1227, 1201, 1161, 1040, 1016, 845, 788, 103, 530 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62−7.39 (m, 3H), 7.31−6.92 (m, 7H), 5.44 (d, J = 8.6, 5.0 Hz, 1H), 4.60 (s, 2H), 4.07 (br s, 2H), 2.65−2.32 (m, 1H), 2.33 (s, 3H), 1.86 (s, 6H), 1.04 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H); optical rotation $[\alpha]^{25}_D$ −19.3 (*c* 0.5, CH_3CN). Anal. ($C_{29}H_{31}FN_6O_4{\cdot}0.4H_2O$) C, H, N.

***N*-{2-[5-(1-(2*H*-Benzo[3,4-*d*]1,3-dioxolan-5-yl)methylethyl)-1,3,4-oxadiazol-2-yl]-(1*S*)-1-(methylethyl)-2-oxoethyl}-2-[5-amino-2-(4-fluorophenyl)-6-oxohydropyrimidinyl]acetamide (11m(F)).** With respect to the final step for the synthesis of **11m(F)**, deprotection was carried out according to the procedure described as follows: A solution of **10m(F)** (66.0 mg, 0.093 mmol) in 30% HBr/AcOH (2.5 mL) was stirred at room temperature for 45 min. The reaction was quenched with water, and extracted three times with EtOAc. The combined organic layers were washed with water (×2) and then brine, and dried over anhydrous $MgSO_4$. The organic solution was diluted with *n*-hexane, and then purified by silica gel column chromatography [FL60D, *n*-hexane/EtOAc (1/1 → 1/2 → 0/1)] to give a yellow oil which was triturated with ether to afford **11m(F)**. The mother liquor was purified by silica gel column chromatography [FL60D, $CHCl_3$/MeOH (1/0 → 100/1)] to give an additional **11m(F)** as a pale yellow amorphous solid; total 40 mg (0.070 mmol, 75%): TLC R_f = 0.39, AcOEt; MS (EI, pos.) *m/z* = 576 (M+)$^+$; IR (KBr) 3346, 2973, 1664, 1610, 1533, 1509, 1436, 1243, 1161, 1112, 1039, 931, 897, 846, 817, 788, 532 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.58−7.46 (m, 2H), 7.48 (s, 1H), 7.11 (t, J = 8.6 Hz, 2H), 6.87 (br d, J = 8.4 Hz, 1H), 6.81 (d, J = 1.0 Hz, 1H), 6.76 (d, J = 1.2 Hz, 2H), 5.95 (s, 2H), 5.43 (dd, J = 8.3, 4.7 Hz, 1H), 4.62 and 4.53 (d × 2, J = 15.0 Hz, 1H × 2), 4.05 (br s, 2H), 2.51 (m, 1H), 1.84 (s, 6H), 1.07 and 0.87 (d × 2, J = 6.8 Hz, 3H × 2); optical rotation $[\alpha]^{30}_D$ −21.3 (*c* 0.3, CH_3CN). Anal. ($C_{29}H_{29}FN_6O_6{\cdot}0.5H_2O$) C, H, N.

***N*-(2,2-Dimethoxyethyl)benzamidine (16(H)).** To a stirred solution of methyl benzimidate hydrochloride (**15(H)**) (20.0 g, 116.6 mmol) in MeOH (100 mL) was added dropwise aminoacetaldehyde dimethylacetal (13.96 mL, 128.3 mmol) under Ar at 0 °C. The reaction mixture was stirred at 4 °C for 22 h, then concentrated in vacuo. The resulting white solid was treated with 1 N NaOH, and extracted with CH_2Cl_2. The organic layer was washed with 1 N NaOH (×6), dried over anhydrous $MgSO_4$, concentrated in vacuo, and dried by azeotropic removal of water with toluene. The resulting pale yellow syrup (amidine **16(H)**: 23.5 g, ca. 113.0 mmol) was used for the next reaction without further purification: TLC R_f = 0.22, MeOH/$CHCl_3$ (1/10); MS (APCI, pos. 40 V) *m/z* = 209 (M + H)$^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.59−7.38 (m, 5H), 4.62 (t, J = 5.6 Hz, 1H), 3.54 (d, J = 5.6 Hz, 2H), 3.44 (s, 6H).

3-(2,2-Dimethoxyethyl)-2-phenyl-3-hydropyrimidin-4-one (17(H)). A mixture of the crude amidine **16(H)** (15.5 g, ca. 74.4 mmol) and ethyl 3-ethoxyacrylate (11.3 mL, 78.1 mmol) was heated at 110−120 °C for 42 h, then cooled to room temperature. The reaction mixture was poured into saturated NH_4Cl and extracted with EtOAc. The organic layer was washed with water and then brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the crude product by silica gel column chromatography [Merck 7734, EtOAc/*n*-hexane (1/1)] gave the acetal **17(H)** (11.7 g, 58% in 2 steps) as a pale yellow solid: TLC R_f = 0.30, EtOAc/*n*-hexane (2/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.96 (d, J = 6.6 Hz, 1H), 7.63−7.40 (m, 5H), 6.45 (d, J = 6.6 Hz, 1H), 4.78 (t, J = 5.4 Hz, 1H), 4.11 (d, J = 5.4 Hz, 2H), 3.29 (s, 6H).

2-(6-Oxo-2-phenylhydropyrimidinyl)ethanal (18(H)). A mixture of the acetal **17(H)** (5.00 g, 19.2 mmol) in THF (35 mL) and 1 N HCl (21.7 mL) was refluxed overnight. The reaction mixture was neutralized with $NaHCO_3$ (solid), and extracted with EtOAc. The organic layer was washed with water and with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting brown oil (aldehyde **18(H)**: ca. 19.2 mmol) was used for the next reaction without further purification: TLC R_f = 0.42, EtOAc; MS (APCI, pos. 40 V) *m/z* = 215 (M + H)$^+$, 200, 168; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.61 (s, 1H), 8.02 (d, J = 6.6 Hz, 1H), 9.63−7.34 (m, 5H), 6.52 (d, J = 6.6 Hz, 1H), 4.75 (s, 2H).

2-(6-Oxo-2-phenylhydropyrimidinyl)acetic Acid (19(H)). To a stirred solution of the aldehyde **18(H)** (ca. 19.2 mmol.) in *tert*-butyl alcohol (31 mL) and water (7.8 mL) was added successively 2-methyl-2-butene (9.17 mL, 86.5 mmol), a solution of NaH_2PO_4 (2.77 g, 23.1 mmol) in water (7.8 mL) and a solution of $NaClO_2$ (80%, 7.61 g, 67.3 mmol) in water (17.8 mL) at 0 °C. After being stirred at room temperature for 4 h, the reaction mixture was evaporated under reduced pressure, and the resulting aqueous layer was washed with CH_2Cl_2 (×5), then acidified with 1 N HCl (pH 3). The resulting white precipitates were collected by filtration, and washed with ether. Drying under reduced pressure gave the carboxylic acid **19(H)** (2.57 g, 58% in 2 steps) as a white powder: TLC R_f = 0.18, $CHCl_3$/MeOH/AcOH (18/1/1); MS (APCI, pos. 40 V) *m/z* = 231 (M + H)$^+$, 202, 185, 168, 138, 122; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.03 (d, J = 6.6 Hz, 1H), 7.56−7.40 (m, 5H), 6.49 (d, J = 6.6 Hz, 1H), 4.46 (s, 2H).

***N*-[(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl]-2-(6-oxo-2-phenylhydropyrimidinyl)acetamide (20e(H)).** To a stirred solution of the carboxylic acid **19(H)** (262 mg, 1.14 mmol), the amino alcohol **8e** (364 mg, 1.38 mmol) and HOBt·H_2O (228 mg, 1.49 mmol) in DMF (15 mL) were added EDC·HCl (241 mg, 1.26 mmol) and then *N*-methylmorpholine (0.15 mL, 1.38 mmol) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 3.5 h, then poured into water and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl, saturated $NaHCO_3$, water and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by silica gel column chromatography [FL60D, MeOH/$CHCl_3$ (0/100 → 1/9)] to give the alcohol **20e(H)** (less polar isomer: 64 mg, more polar isomer: 242 mg; total: 306 mg, 61%) as a pale yellow amorphous solid. Less polar isomer: TLC (HPTLC) R_f = 0.34, $CHCl_3$/MeOH (9/1); MS (APCI, pos. 40 V) *m*/*z* = 440 (M + H)$^+$, 314, 176, 127; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.05 (d, *J* = 6.6 Hz, 1H), 7.76−7.61 (m, 2H), 7.59−7.42 (m, 3H), 7.07 (d, *J* = 10.4 Hz, 1H), 6.47 (d, *J* = 6.6 Hz, 1H), 5.10−4.94 (m, 1H), 4.61 and 4.45 (d × 2, *J* = 15.0 Hz, 1H × 2), 4.32 (dt, *J* = 4.0, 9.4 Hz, 1H), 4.22−4.00 (m, 1H), 1.89−1.60 (m, 1H), 1.43 (s, 9H), 0.95 and 0.93 (d × 2, *J* = 6.6 Hz, 3H × 2). More polar isomer: TLC (HPTLC) R_f = 0.27, $CHCl_3$/MeOH (9/1); MS (APCI, pos. 40 V) *m*/*z* = 440 (M + H)$^+$, 314, 176, 127; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98 (d, *J* = 6.6 Hz, 1H), 7.62−7.41 (m, 5H), 6.63 (d, *J* = 9.2 Hz, 1H), 6.43 (d, *J* = 6.6 Hz, 1H), 5.17−5.06 (m, 1H), 4.48 and 4.37 (d × 2, *J* = 15.4 Hz, 1H × 2), 4.37−4.23 (m, 1H), 4.05 (dt, *J* = 2.2, 8.6 Hz, 1H), 2.10−1.91 (m, 1H), 1.39 (s, 9H), 1.09 and 1.01 (d × 2, *J* = 6.6 Hz, 3H × 2).

***N*-[(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]-2-(6-oxo-2-phenylhydropyrimidinyl)acetamide (21e(H)).** To a stirred suspension of Dess−Martin periodinane (ca. 77%, 515 mg, 0.93 mmol) in CH_2Cl_2 (10 mL) was added a suspension of the alcohol **20e(H)** (a mixture of two isomers: 282 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) under Ar at room temperature. After 1 h, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with water, and then brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification by silica gel column chromatography [FL60D, EtOAc/*n*-hexane (1/1 → 1/0)] and washing with $CHCl_3$ gave **21e(H)** (242 mg, 86%) as a white amorphous powder: mp 79−85 °C; TLC R_f = 0.44, EtOAc; MS (APCI, neg. 40 V) *m*/*z* = 436 (M − H)$^-$, 342, 298, 171, 125; IR (KBr) 3299, 3061, 2974, 1936, 1876, 1685, 1525, 1493, 1465, 1447, 1424, 1406, 1390, 1371, 1252, 1193, 1048, 1017, 977, 834, 764, 704 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (d, *J* = 6.6 Hz, 1H), 7.65−7.40 (m, 5H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 6.6 Hz, 1H), 5.44 (dd, *J* = 8.4, 4.8 Hz, 1H), 4.66 (d, *J* = 15.2 Hz, 1H), 4.55 (d, *J* = 15.2 Hz, 1H), 2.65−2.39 (m, 1H), 1.48 (s, 9H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H); optical rotation $[\alpha]^{25}_D$ −12.40 (c 0.49, MeCN). Anal. ($C_{23}H_{27}N_5O_4$·0.3H_2O) C, H, N.

Preparation of 21d,e(H) and 21d,e,k(F). Using essentially the same procedures as described for the preparation of **21e(H)**, the following compounds were prepared.

***N*-{(1*S*)-2-[5-(1-Methylcyclopropyl)-1,3,4-oxadiazol-2-yl]-1-(methylethyl)-2-oxoethyl}-2-(6-oxo-2-phenylhydropyrimidinyl)acetamide (21d(H)).** Derived from **8d** and **19(H)** which was prepared from **15(H)**: yellowish amorphous solid; TLC R_f = 0.60, MeOH/$CHCl_3$ (1/10); MS (APCI, pos. 40 V) *m*/*z* = 436 (M + H)$^+$, 344, 125; IR (KBr) 3462, 3065, 2969, 2936, 1683, 1549, 1525, 1494, 1448, 1426, 1390, 1255, 1193, 1027, 977, 931, 903, 831, 787, 767, 705, 553 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.01 (d, *J* = 6.6 Hz, 1H), 7.61−7.40 (m, 5H), 6.84 (br d, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 6.6 Hz, 1H), 5.41 (dd, *J* = 8.4, 5.0 Hz, 1H), 4.62 and 4.57 (d × 2, *J* = 15.0 Hz, 1H × 2), 2.48 (m, 1H), 1.61 (s, 3H), 1.44 (m, 2H), 1.08 (m, 5H), 0.87 (d, *J* = 6.6 Hz, 3H); optical rotation $[\alpha]^{27}_D$ −32.2 (*c* 0.7, CH_3CN). Anal. ($C_{23}H_{25}N_5O_4$·0.2H_2O) C, H, N.

***N*-{(1*S*)-2-[5-(1-Methylcyclopropyl)-1,3,4-oxadiazol-2-yl]-1-(methylethyl)-2-oxoethyl}-2-[2-(4-fluorophenyl)-6-oxohydropyrimidinyl]acetamide (21d(F)).** Derived from **8d** and **19(F)** which was prepared from **15(F)**: ivory powder; TLC R_f = 0.38, EtOAc; MS (APCI, pos. 40 V) *m*/*z* = 454 (M + H)$^+$, 362, 125; IR (KBr) 3465, 3267, 3072, 2971, 1716, 1673, 1606, 1550, 1505, 1423, 1388, 1230, 1193, 1163, 1101, 1048, 978, 841, 805, 778, 738, 570, 459 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.00 (d, *J* = 6.6 Hz, 1H), 7.61 (dd, *J* = 8.8, 5.2 Hz, 2H), 7.15 (t, *J* = 8.8 Hz, 2H), 6.90 (br d, *J* = 8.2 Hz, 1H), 6.51 (d, *J* = 6.6 Hz, 1H), 5.39 (dd, *J* = 8.2, 5.1 Hz, 1H), 4.58 (s, 2H), 2.49 (m, 1H), 1.61 (s, 3H), 1.50−1.41 (m, 2H), 1.13−1.04 (m, 2H), 1.07 and 0.89 (d × 2, *J* = 6.8 Hz, 3H × 2).; optical rotation $[\alpha]^{24}_D$ −34.4 (*c* 0.7, CH_3CN). Anal. ($C_{23}H_{24}FN_5O_4$) C, H, N.

***N*-[(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]-2-[2-(4-fluorophenyl)-6-oxohydropyrimidinyl]acetamide (21e(F)).** Derived from **8e** and **19(F)** which was prepared from **15(F)**: ivory amorphous solid; TLC R_f = 0.42, EtOAc; MS (APCI, pos. 40 V) *m*/*z* = 456 (M + H)$^+$, 362; IR (KBr) 3444, 3063, 2974, 2937, 2877, 1685, 1606, 1531, 1505, 1466, 1426, 1408, 1371, 1228, 1192, 1163, 1100, 1048, 1017, 978, 902, 847, 807, 779, 761, 569 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.00 (d, *J* = 6.6 Hz, 1H), 7.64 (dd, *J* = 8.4, 5.1 Hz, 2H), 7.16 (t, *J* = 8.4 Hz, 2H), 6.92 (br d, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 6.6 Hz, 1H), 5.43 (dd, *J* = 8.4, 4.9 Hz, 1H), 4.64 and 4.55 (d × 2, *J* = 15.2 Hz, 1H × 2), 2.53 (m, 1H), 1.48 (s, 9H), 1.08 and 0.90 (d × 2, *J* = 6.7 Hz, 3H × 2); optical rotation $[\alpha]^{28}_D$ −14.8 (*c* 1.0, CH_3CN). Anal. ($C_{23}H_{26}FN_5O_4$·0.7H_2O) C, H, N.

***N*-{(1*S*)-1-(Methylethyl)-2-[5-(1-methyl-1-phenylethyl)-1,3,4-oxadiazol-2-yl]-2-oxoethyl}-2-[2-(4-fluorophenyl)-6-oxohydropyrimidinyl]acetamide (21k(F)).** Derived from **8k** and **19(F)** which was prepared from **15(F)**: ivory amorphous solid; TLC R_f = 0.50, EtOAc; MS (APCI, neg. 40 V) *m*/*z* = 516 (M − H)$^-$, 360, 189; IR (KBr) 3311, 3061, 2973, 2936, 2877, 1685, 1606, 1531, 1505, 1426, 1395, 1230, 1192, 1163, 1047, 1032, 1017, 978, 847, 700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.00 (d, *J* = 6.4 Hz, 1H), 7.72−7.51 (m, 2H), 7.46−7.04 (m, 7H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 6.4 Hz, 1H), 5.38 (dd, *J* = 8.4, 5.0 Hz, 1H), 4.61 (d, *J* = 15.4 Hz, 1H), 4.53 (d, *J* = 15.4 Hz, 1H), 2.65−2.38 (m, 1H), 1.89 (s, 6H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H); optical rotation $[\alpha]^{26}_D$ −29.4 (*c* 0.5, CH_3CN). Anal. ($C_{28}H_{28}FN_5O_4$·0.5H_2O) C, H, N.

Methyl (2*R*)-2-(3-Ethoxycarbonylmethylureido)-3-methylbutanoate (26a). To a stirred suspension of methyl (2*R*)-2-amino-3-methylbutanoate hydrochloride **(25a)** (2.59 g, 15.5 mmol) in EtOAc (85 mL) were added dropwise triethylamine (2.16 mL, 15.5 mmol) and then ethyl isocyanatoacetate (2.00 g, 15.5 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4.5 h, and poured into water and extracted with EtOAc. The organic layer was washed with 5% $KHSO_4$, water and then brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography [FL60D, MeOH/$CHCl_3$ (0/100 → 1/50)] to afford the urea **26a** (3.84 g, 95%) as a colorless liquid: TLC R_f = 0.69, $CHCl_3$/MeOH (9/1); MS (APCI, pos. 40 V) *m*/*z* = 261 (M + H)$^+$, 229, 215, 201, 183, 155, 132, 104; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.26 (d, *J* = 8.4 Hz, 1H), 5.19 (m, 1H), 4.42 (dd, *J* = 8.4, 4.8 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.06 and 3.94 (d × 2, *J* = 18.5 Hz, 1H × 2), 3.74 (s, 3H), 2.20−2.04 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H); optical rotation $[\alpha]^{25}_D$ +2.5 (*c* 1.9, MeCN).

2-[(4*R*)-4-(Methylethyl)-2,5-dioxoimidazolidinyl]acetic Acid (22a). A solution of the urea **26a** (3.24 g, 12.5 mmol) in concentrated HCl (70 mL) was refluxed for 18 h. After cooling to room temperature, the reaction mixture was diluted with water, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residual solid was dried by azeotropic removal of water with toluene, and then washed with ether to afford the hydantoin **22a** (2.04 g, quant.) as a white powder: TLC R_f = 0.16, $CHCl_3$/MeOH/AcOH (18/1/1); MS (APCI, neg. 40 V) *m*/*z* = 199 (M − H)$^-$, 155; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.62 (m, 0.3H), 4.23 (s, 2H), 4.05 (d, *J* = 3.8 Hz, 1H), 2.38−2.16 (m, 1H), 1.06 and

0.96 (d × 2, J = 7.0 Hz, 3H × 2); optical rotation $[\alpha]^{25}_D$ +2.5 (c 0.5, MeCN).

***N*-{(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl}-2-[(4*R*)-4-(methylethyl)-2,5-dioxoimidazolidinyl]acetamide (23a).** To a stirred mixture of the hydantoin **22a** (218 mg, 1.09 mmol), amino alcohol **8e** (317 mg, 1.20 mmol) and HOBt·H_2O (184 mg, 1.20 mmol) in DMF (3.5 mL), were added EDC·HCl (230 mg, 1.20 mmol) and then *N*-methylmorpholine (0.132 mL, 1.20 mmol) under Ar at 0 °C. After 15 min, the reaction mixture was stirred at room temperature for another 14 h, and poured into water and extracted with EtOAc. The organic layer was washed with 10% citric acid, saturated $NaHCO_3$, water and then brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the alcohol **23a** (ca. 1.09 mmol) as a pale yellow amorphous solid. The product was used for the next reaction without further purification: TLC R_f = 0.20, AcOH/*i*-PrOH/$CHCl_3$ (1/1/18); MS (APCI, pos. 40 V) m/z = 410 (M + H)$^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.13−6.89 (m, 1H), 6.73. 6.30, 6.20 and 6.10 (br s × 4, 1H), 5.14 and 5.01 (m × 2, 1H), 4.39−4.00 (m, 5H), 2.24 (m, 1H), 1.80 (m, 1H), 1.41 and 1.38 (s × 2, 9H), 1.16−0.80 (m, 12H).

***N*-{(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl}-2-[(4*R*)-4-(methylethyl)-2,5-dioxoimidazolidinyl]acetamide (24a).** To a stirred suspension of Dess−Martin periodinane (ca. 77%, 474 mg, 0.86 mmol) in CH_2Cl_2 (5.5 mL) was added a solution of the alcohol **23a** (ca. 0.78 mmol) in CH_2Cl_2 (10 mL) under Ar at room temperature. After 1 h, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by silica gel column chromatography [FL60D, MeOH/$CHCl_3$ (0/100 → 1/100)] gave the ketone **24a** (309 mg, 70% in 2 steps) as a white amorphous solid: TLC R_f = 0.41, MeOH/$CHCl_3$ (1/10); MS (APCI, pos. 40 V) m/z = 408 (M + H)$^+$; IR (KBr) 3318, 2971, 2937, 2877, 1776, 1718, 1543, 1452, 1393, 1371, 1356, 1321, 1297, 1257, 1155, 1018, 918, 829, 753, 624 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.65 (d, J = 7.4 Hz, 1H), 8.23 (br s, 1H), 5.09 (m, 1H), 4.04 (br s, 2H), 3.92 (br d, J = 3.8 Hz, 1H), 2.34 (m, 1H), 2.00 (m, 1H), 1.38 (s, 9H), 1.00−0.73 (m, 12H); optical rotation $[\alpha]^{26}_D$ −3.5 (c 1.1, MeCN). Anal. ($C_{19}H_{29}N_5O_5$·0.2$CH_3CO_2C_2H_5$) C, H, N.

Preparation of 24b,c. Using essentially the same procedures as described for the preparation of **24a**, the following compounds were prepared.

***N*-[(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]-2-[(4*S*)-4-(2-methylpropyl)-2,5-dioxoimidazolidinyl]acetamide (24b).** Derived from **8e** and **22b** which was prepared from **25b**: white amorphous solid; TLC (HPTLC) R_f = 0.62 MeOH/$CHCl_3$ (1/10); MS (APCI, pos. 40 V) m/z = 422 (M + H)$^+$; IR (KBr) 3318, 2968, 2875, 1780, 1718, 1543, 1455, 1390, 1370, 1336, 1254, 1206, 1157, 1047, 1017, 955, 924, 884, 826, 763, 624, 547 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.67 (br d, J = 6.8 Hz, 1H), 8.32 (br s, 1H), 5.08 (m, 1H), 4.03 (m, 3H), 2.32 (m, 1H), 1.75 (m, 1H), 1.60−1.25 (m, 11H), 0.87 (m, 12H); optical rotation $[\alpha]^{26}_D$ −6.8 (c 0.8, CH_3CN). Anal. ($C_{20}H_{31}N_5O_5$·0.3H_2O) C, H, N.

***N*-[(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]-2-[(4*R*)-4-(indol-3-ylmethyl)-2,5-dioxoimidazolidinyl]acetamide (24c).** Derived from **8e** and **22c** which was prepared from **25c**: yellow amorphous powder; TLC R_f = 0.46, EtOAc; MS (APCI, pos. 40 V) m/z = 495 (M + H)$^+$; IR (KBr) 3420, 2974, 2936, 1776, 1718, 1542, 1457, 1343, 1232, 1154, 1100, 1015, 924, 745, 624, 545, 424 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.90 (br s, 1H), 8.66 (d, J = 7.0 Hz, 1H), 8.23 (br s, 1H), 7.51 (br d, J = 7.3 Hz, 1H), 7.33 (br d, J = 7.3 Hz, 1H), 7.16 (d, J = 1.8 Hz, 1H), 7.06 (dt, J = 1.2, 7.3 Hz, 1H), 6.97 (dt, J = 1.2, 7.3 Hz, 1H), 5.10 (m, 1H), 4.38 (m, 1H), 3.93 (s, 2H), 3.16 (dd, J = 14.8, 4.8 Hz, 1H), 2.98 (dd, J = 14.8, 6.8 Hz, 1H), 2.34 (m, 1H), 1.41 and 1.40 (s × 2, 9H), 0.95 and 0.89 (d × 2, J = 6.6 Hz, 3H × 2); optical rotation $[\alpha]^{28}_D$ −3.0 (c 0.7, CH_3CN). Anal. ($C_{25}H_{30}N_6O_5$·0.3C_6H_{14}) C, H, N.

***N*-[(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]-2-[5-amino-6-oxo-2-(3-pyridyl)hydropyrimidinyl]acetamide (24d).** Derived from **8e** and **27** which was prepared by Zeneca's method:[20] brown yellow solid; TLC R_f = 0.12, EtOAc; MS (APCI, pos. 40 V) m/z = 454 (M + H)$^+$; IR (KBr) 3336, 3045, 2974, 2937, 2877, 1718, 1668, 1610, 1542, 1464, 1439, 1413, 1371, 1299, 1253, 1204, 1043, 1028, 979, 926, 900, 821, 787, 740, 716, 637, 479 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.79 (d, J = 1.8 Hz, 1H), 8.69 (dd, J = 4.8, 1.8 Hz, 1H), 7.94 (dt, J = 8.4, 1.8 Hz, 1H), 7.51 (s, 1H), 7.38 (dd, J = 8.4, 4.8 Hz, 1H), 7.07 (d, J = 8.5 Hz, 1H), 5.44 (dd, J = 8.5, 4.8 Hz, 1H), 4.63 (s, 2H), 4.16 (br s, 2H), 2.52 (m, 1H), 1.48 (s, 9H), 1.06 and 0.89 (d × 2, J = 6.8 Hz, 3H × 2); optical rotation $[\alpha]^{29}_D$ −22.9 (c 1.1, CH_3CN). Anal. ($C_{22}H_{27}N_7O_4$·0.1H_2O) C, H, N.

***tert*-Butyl (2*S*)-1-[(2*S*)-3-Methyl-2-(methylsulfonamido)butanoyl]pyrrolidine-2-carboxylate (39).** To a stirred ice-cooled solution of *tert*-butyl (2*S*)-1-((2*S*)-2-amino-3-methylbutanoyl)pyrrolidine-2-carboxylate hydrochloride **(38)** (1.00 g, 3.26 mmol) in CH_2Cl_2 (4 mL) were added dropwise with stirring methanesulfonyl chloride (0.28 mL, 3.6 mmol) and then *N*-methylmorpholine (0.79 mL, 7.2 mmol). The resulting solution was stirred for 1 h and then at room temperature for 3 h. The reaction mixture was cooled again with an ice bath, and additional methanesulfonyl chloride (0.125 mL, 1.6 mmol) and *N*-methylmorpholine (0.20 mL, 1.8 mmol) were added. The reaction mixture was stirred for another 1 h, and then at room temperature for 45 min. The reaction mixture was quenched with saturated NH_4Cl, and the product was extracted three times with EtOAc. The combined organic layers were washed with saturated $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography [FL60D, $CHCl_3$/MeOH (1/0 → 100/1)] to afford the *tert*-butyl ester **39** (639 mg, 56%): TLC R_f = 0.77, $CHCl_3$/MeOH (8/1); MS (APCI, pos. 20 V) m/z = 371 (M + Na)$^+$, 349 (M + H)$^+$, 293 (M − C_4H_9 + 2H)$^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.28 and 5.21 (br d × 2, J = 9.8 Hz, 1H), 4.42 (dd, J = 8.4, 5.0 Hz, 0.7H), 4.30 (dd, J = 8.0, 2.6 Hz, 0.3H), 3.99 (dd, J = 9.8, 4.9 Hz, 1H), 3.80−3.40 (m, 2H), 2.93 and 2.86 (s × 2, 3H), 2.40−1.80 (m, 5H), 1.49 and 1.45 (s × 2, 9H), 1.10 and 0.94 (d × 2, J = 7.0 Hz, 2.1H × 2), 1.07 and 0.85 (d × 2, J = 6.6 Hz, 0.9H × 2).

(2*S*)-1-[(2*S*)-3-Methyl-2-(methylsulfonamido)butanoyl]pyrrolidine-2-carboxylic Acid (22e). To a stirred *tert*-butyl ester **39** (453 mg, 1.30 mmol) was added ice-cooled 90% trifluoroacetic acid/water (5.4 mL) at 0 °C. The resulting solution was stirred at this temperature for 1.5 h, and concentrated. The residue was dried by azeotropic removal of water with toluene to give the carboxylic acid **22e** (423 mg, quant.). The crude product was used for the next step without further purification: TLC R_f = 0.41, $CHCl_3$/MeOH (9/1); MS (APCI, pos. 40 V) m/z = 293 (M + H)$^+$, 222; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.65 and 5.52 (br d × 2, J = 9.7 Hz, 1H), 4.59 (dd, J = 7.5, 5.3 Hz, 0.8H), 4.49 (dd, J = 8.1, 2.3 Hz, 0.2H), 4.00 (dd, J = 10.0, 5.8 Hz, 0.8 H), 3.88 (dd, J = 9.2, 4.2 Hz, 0.2 H), 3.82−3.42 (m, 2H), 2.96 and 2.91 (s × 2, 3H), 2.40−1.80 (m, 5H), 1.07, 0.96, and 0.89 (d × 3, J = 6.6 Hz, 6H).

{(2*S*)-1-[(2*S*)-3-Methyl-2-(methylsulfonamido)butanoyl]pyrrolidin-2-yl}-*N*-{(1*S*)-2-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl}carboxamide (23e). To a stirred mixture of the carboxylic acid **22e** (267 mg, 0.91 mmol), the amino alcohol **8e** (321 mg, 1.09 mmol) and HOBt·H_2O (181 mg, 1.18 mmol) in DMF (10 mL), were added EDC·HCl (192 mg, 1.00 mmol) and then *N*-methylmorpholine (0.120 mL, 1.09 mmol) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 2 h, then poured into water and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl, saturated $NaHCO_3$, water, and brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography [FL60D, $CHCl_3$/MeOH (50/1 → 20/1)] to afford the alcohol **23e** (310 mg, 68%) as a white amorphous solid. The product was used for the next reaction without further purification: TLC (HPTLC) R_f = 0.13, $CHCl_3$/MeOH (19/1); MS (APCI, pos. 40 V) m/z = 502 (M + H)$^+$, 376, 127; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43

and 7.10 (d × 2, J = 10.0 and 9.4 Hz, 1H), 6.73−6.56 and 5.97−5.78 (m × 2, 1H), 5.21−5.07 (m, 1H), 4.61−4.53 and 4.53−4.44 (m × 2, 1H), 4.29−4.18 and 4.05−3.92 (m × 2, 2H), 3.79−3.51 (m, 2H), 3.02 and 2.92 (s × 2, 3H), 2.30−1.67 (m, 6H), 1.42 and 1.38 (s × 2, 9H), 1.18−0.79 (m, 12H).

{(2*S*)-1-[(2*S*)-3-Methyl-2-(methylsulfonamido)butanoyl]-pyrrolidin-2-yl}-*N*-{(1*S*)-2-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl}carboxamide (24e). To a suspension of Dess−Martin periodinane (ca. 77%, 353 mg, 0.64 mmol) in CH_2Cl_2 (9 mL) was added a solution of the alcohol **23e** (292 mg, 0.58 mmol) in CH_2Cl_2 (12 mL) under Ar at room temperature. After 1 h, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by silica gel column chromatography [FL60D, EtOAc/*n*-hexane (1/2)] gave the ketone **24e** (260 mg, 90% in 2 steps) as a white amorphous solid: TLC R_f = 0.59, EtOAc; MS (APCI, neg. 40 V) m/z = 498 (M − H)$^-$, 404; IR (KBr) 3347, 2973, 2937, 2878, 1719, 1685, 1636, 1543, 1466, 1407, 1371, 1323, 1157, 1140, 1046, 1017, 983, 761, 521 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37 (d, J = 7.5 Hz, 1H), 5.58 (d, J = 9.8 Hz, 1H), 5.37 (dd, J = 7.5, 4.8 Hz, 1H), 4.69 (dd, J = 8.1, 2.9 Hz, 1H), 3.99 (dd, J = 9.8, 5.8 Hz, 1H), 3.86−3.43 (m, 2H), 2.92 (s, 3H), 2.63−1.80 (m, 6H), 1.47 (s, 9H), 1.06, 1.05, 0.97 and 0.93 (d × 4, J = 6.6, 6.6, 6.6 and 6.8 Hz, 3H × 4); optical rotation $[\alpha]^{24}_D$ −56.5, (c 0.515, MeCN). Anal. ($C_{22}H_{37}N_5O_6S{\cdot}0.1H_2O$) C, H, N, S.

***N*-[(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]-2-[5-(4-chlorophenyl)-1,2-dihydro-2-oxo-3*H*-1,4-benzo[*f*]diazepinyl]acetamide (24f).** Derived from **8e** and **22f** which was prepared according to a patented method:[26] white amorphous powder; TLC R_f = 0.28, EtOAc/*n*-hexane (1/1); MS (APCI, neg. 40 V) m/z = 534 (M − H)$^-$; IR (KBr) 3322, 2974, 2876, 1685, 1609, 1542, 1488, 1450, 1371, 1324, 1271, 1195, 1161, 1091, 1016, 934, 839, 762, 666 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.66−7.50 (m, 4H), 7.44−7.16 (m, 4.4H), 6.93 (d, J = 8.0 Hz, 0.6H), 5.42 and 5.31 (dd × 2, J = 8.0, 4.8 Hz, 1H), 4.89 and 4.86 (d × 2, J = 10.6 Hz, 1H), 4.83 and 4.73 (d × 2, J = 15.3 Hz, 1H), 4.22 and 4.10 (d × 2, J = 15.3 Hz, 1H), 3.94 and 3.88 (d × 2, J = 10.6 Hz, 1H), 2.66−2.34 (m, 1H), 1.48 and 1.44 (s × 2, 9H), 1.05 and 1.04 (d × 2, J = 7.0 Hz, 3H), 0.89 and 0.83 (d × 2, J = 7.0 Hz, 3H); optical rotation $[\alpha]^{25}_D$ −4.0 (c 0.5, CH_3CN). Anal. ($C_{28}H_{30}ClN_5O_4{\cdot}0.1C_6H_{14}$) C, H, N.

Ethyl 2-(6-Phenyl-2-pyridyloxy)acetate (41). A mixture of 6-phenyl-2-pyridone **40** (1.00 g, 5.85 mmol), ethyl bromoacetate (1.46 g, 8.77 mmol), K_2CO_3 (2.43 g, 17.55 mmol) and DMF (12 mL) was stirred at room temperature for 16 h, and then poured into water and extracted with EtOAc. The organic layer was washed with 1 N HCl, water and then brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residual yellow oil was purified by silica gel column chromatography [Merck 7734, EtOAc/*n*-hexane (1/9)] to give the ester **41** (1.47 g, 98%) as a clear syrup: TLC R_f = 0.80, EtOAc/*n*-hexane (1/2); MS (APCI, pos. 40 V) m/z = 258 (M + H)$^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.97 (m, 2H), 7.68 (dd, J = 8.0, 7.4 Hz, 1H), 7.50−7.38 (m, 4H), 6.83 (d, J = 8.0 Hz, 1H), 4.96 (s, 2H), 4.24 (q, J = 7.4 Hz, 2H), 1.26 (t, J = 7.4 Hz, 3H).

2-(6-Phenyl-2-pyridyloxy)acetic Acid (22g). To a stirred solution of the ester **41** (1.46 g, 5.68 mmol) in DME (34 mL) was added 1 N LiOH (17 mL) at 0 °C. After stirring for 1.5 h, the reaction mixture was acidified with 1 N HCl (34 mL), and extracted with EtOAc. The organic layer was washed with water and with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford the carboxylic acid **22g** (1.29 g, 99%): TLC R_f = 0.68, AcOH/*i*-PrOH/$CHCl_3$ (1/1/18); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.93 (m, 2H), 7.70 (t, J = 8.2 Hz, 1H), 7.45−7.30 (m, 4H), 6.83 (d, J = 8.2 Hz, 1H), 5.01 (s, 2H).

***N*-{(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl}-2-(6-phenyl-2-pyridyloxy)acetamide (23g).** To a stirred solution of the carboxylic acid **22g** (250 mg, 1.09 mmol), the amino alcohol **8e** (316 mg, 1.20 mmol) and HOBt·H_2O (184 mg, 1.20 mmol) in DMF (3.5 mL) were added EDC·HCl (230 mg, 1.20 mmol) and then *N*-methylmorpholine (0.13 mL, 1.20 mmol) under Ar at 0 °C. After 15 min, the reaction mixture was stirred at room temperature for 14 h, then poured into water and extracted with EtOAc. The organic layer was washed with 10% citric acid, saturated $NaHCO_3$, water, and finally brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting white amorphous solid (alcohol **23g**: ca. 1.09 mmol) was used for the next reaction without further purification: TLC R_f = 0.71 and 0.67, MeOH/$CHCl_3$ (1/10); MS (APCI, pos. 20 V) m/z = 439 (M + H)$^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.96 (m, 2H), 7.70 (m, 1H), 7.42 (m, 4H), 7.00 (m, 1H), 6.84 and 6.78 (d × 2, J = 8.0 Hz, 1H), 5.18−4.75 (m, 3H), 4.35−3.93 (m, 2H), 2.18−1.75 (m, 1H), 1.38 and 1.37 (s × 2, 9H), 1.02, 0.89, 0.84 and 0.81 (d × 4, J = 7.0 Hz, 6H).

***N*-{(1S)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl}-2-(6-phenyl-2-pyridyloxy)acetamide (24g).** To a stirred suspension of Dess−Martin periodinane (ca. 77%, 660 mg, 1.20 mmol) in CH_2Cl_2 (8 mL) was added a suspension of the alcohol **23g** (ca. 1.09 mmol) in CH_2Cl_2 (16 mL) under Ar at room temperature. After 2 h, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and then brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the crude product by silica gel column chromatography [FL60D, EtOAc/*n*-hexane (1/4)] gave the ketone **24g** (413 mg, 87% in 2 steps) as a white amorphous solid: TLC R_f = 0.64, EtOAc/*n*-hexane (1/1); MS (APCI, pos. 40 V) m/z = 437 (M + H)$^+$; IR (KBr) 3428, 2974, 1718, 1685, 1596, 1575, 1542, 1447, 1370, 1324, 1246, 1156, 1084, 1045, 880, 809, 766, 695, 623, 425, 408 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.99 (m, 2H), 7.74 (t, J = 8.2 Hz, 1H), 7.50−7.35 (m, 4H), 7.16 (br d, J = 9.0 Hz, 1H), 6.87 (d, J = 8.2 Hz, 1H), 5.49 (dd, J = 9 0.0, 5.2 Hz, 1H), 5.12 and 4.93 (d × 2, J = 15.6 Hz, 1H × 2), 2.47 (m, 1H), 1.45 (s, 9H), 0.97 and 0.79 (d × 2, J = 6.8 Hz, 3H × 2); optical rotation $[\alpha]^{25}_D$ +11.3 (c 1.03, MeCN). Anal. ($C_{24}H_{28}N_4O_4{\cdot}0.1H_2O$) C, H, N.

***tert*-Butyl (2*S*)-2-{*N*-[(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl]carbamoyl}-indolinecarboxylate (28a).** To a stirred mixture of the (2*S*)-1-(*tert*-butoxycarbonyl)indoline-2-carboxylic acid (**27a**) (6.58 g, 25.0 mmol), the amino alcohol **8e** (7.25 g, 27.5 mmol) and HOBt·H_2O (4.21 g, 27.5 mmol) in DMF (77 mL), were added EDC·HCl (5.27 g, 27.5 mmol) and then *N*-methylmorpholine (3.02 mL, 27.5 mmol) under Ar at 0 °C. After 10 min, the reaction mixture was stirred at room temperature for 20 h, and poured into water and extracted with EtOAc. The organic layer was washed with 10% citric acid, saturated $NaHCO_3$, water, and then brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residual beige solid by silica gel column chromatography [FL60D, EtOAc/*n*-hexane, (1/9 → 2/1)] gave the Boc alcohol **28a** (11.3 g, 96%) as a pale yellow amorphous powder: TLC R_f = 0.52 and 0.48, MeOH/$CHCl_3$ (1/10); MS (APCI, pos. 20 V) m/z = 473 (M + H)$^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.57 and 6.73 (m × 2, 1H), 7.27−6.90 (m, 4H), 5.11−4.75 (m, 2H), 4.35−3.92 (m, 2H), 3.65−3.00 (m, 2H), 2.00 and 1.70 (m × 2, 1H), 1.56, 1.46, 1.41 and 1.34 (s × 4, 18H), 1.05−0.80 (m, 6H).

(2*S*)-Indolin-2-yl-*N*-[(1*S*)-2-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl]carboxamide Hydrochloride (29a). A mixture of the Boc alcohol **28a** (10.3 g, 21.8 mmol) and 4 N HCl in dioxane (40 mL) was stirred at room temperature for 1 h. Concentration of the reaction mixture gave the amino alcohol **29a** (9.5 g) as a white powder quantitatively. The product was used for the next reaction without further purification: TLC R_f = 0.49 and 0.46, $CHCl_3$/MeOH (9/1); LC MS (APCI, pos. 40 V) m/z = 373 (M + H)$^+$; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.43 and 8.24 (d × 2, J = 10.0 Hz, 1H), 7.36−7.08 (m, 5H), 5.10−5.00, 4.75−4.58 and 3.95−3.83 (m × 3, 3H), 3.60−3.28, 3.00−2.85 and 2.65−2.57 (m × 2, 2H), 2.35−2.10 and 1.97−1.75 (m × 2, 1H), 1.18 and 1.11 (s × 2, 9H), 1.07−0.83 (m, 6H).

Methylethyl (2*S*)-2-{*N*-[(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl]carbamoyl}-indolinecarboxylate (30a). To a stirred solution of the amino alcohol **29a** (1.51 g, 3.69 mmol) in CH_2Cl_2 (20 mL) were added dropwise 1.0 M isopropyl chloroformate in toluene (4.06 mL, 4.06 mmol) and *N*-methylmorpholine (0.900 mL, 8.18 mmol) under Ar at 0 °C. After 1 h, the reaction mixture was stirred at room temperature for 3.5 h. Additional 1.0 M isopropyl chloroformate in toluene (1.22 mL, 1.22 mmol) and *N*-methylmorpholine (0.300 mL, 2.73 mmol) were added twice at 0 °C and the reaction mixture was stirred at room temperature. Then the reaction mixture was poured into ice-cooled 10% citric acid and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, and then brine, and dried over anhydrous Na_2SO_4. Concentration followed by purification by silica gel column chromatography [Merck 7734, *n*-hexane/EtOAc (1/1 → 1/2)] gave the alcohol **30a** (1.16 g, 69%) as a pale yellow amorphous powder: TLC R_f = 0.55 and 0.46, EtOAc/*n*-hexane (2/1); MS (APCI, pos. 20 V) *m*/*z* = 459 (M + H)$^+$; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.06−7.62 (m, 1H), 7.20−6.83 (m, 4H), 6.29 and 6.19 (d × 2, *J* = 6.2 Hz and *J* = 5.4 Hz, 1H), 5.06−4.60 (m, 3H), 4.30−4.10 and 3.97−3.80 (m × 2, 1H), 3.50−3.10 (m, 1H), 2.67−2.45, 2.37−2.01 and 1.95−1.67 (m × 3, 2H), 1.40−1.05 (m, 15H), 1.05−0.75 (m, 6H).

Methylethyl (2*S*)-2-{*N*-[(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]carbamoyl}indolinecarboxylate (24h). To a stirred suspension of Dess−Martin periodinane (ca. 70%; 1.32 g, 2.40 mmol) in CH_2Cl_2 (14 mL) was added a solution of the alcohol **30a** (1.09 g, 2.38 mmol) in CH_2Cl_2 (26 mL) under Ar at room temperature. After 1 h, the reaction mixture was poured into ice-cooled brine and extracted with EtOAc. The organic layer was concentrated in vacuo. Purification of the residue by silica gel column chromatography [FL60D, EtOAc/*n*-hexane (2/1)] gave the ketone **24h** (952 mg, 88%) as a white powder: TLC R_f = 0.22, EtOAc/*n*-hexane (1/3); MS (APCI, pos. 20 V) *m*/*z* = 457 (M + H)$^+$; IR (KBr) 3288, 2978, 1713, 1673, 1603, 1544, 1487, 1402, 1317, 1269, 1182, 1112, 1019, 907, 819, 751, 680 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.69 (m, 1H), 7.30−7.12 and 7.06−6.95 (m × 2, 4H), 5.37 (dd, *J* = 8.0, 4.8 Hz, 1H), 5.22−4.92 (m, 2H), 3.60−3.25 (m, 2H), 2.58−2.33 (m, 1H), 1.47 (s, 9H), 1.45−1.28 (m, 6H), 1.03−0.92 and 0.87−0.73 (m × 2, 3H); optical rotation $[\alpha]^{25}_D$ −75.7 (*c* 1.0, MeCN). Anal. ($C_{24}H_{32}N_4O_5$·$0.5H_2O$) C, H, N.

(2*S*)-1-{[1-(Triphenylmethyl)imidazol-4-yl]carbonyl}indolin-2-yl-*N*-[(1*S*)-2-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl]carboxamide (33a). To a stirred mixture of the carboxylic acid **32** (1.71 g, 4.84 mmol) and the amino alcohol **29a** (1.52 g, 3.72 mmol) in DMF (20 mL) were added EDC·HCl (928 mg, 4.85 mmol) and then *N*-methylmorpholine (0.532 mL, 4.84 mmol) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 60 h, and poured into 10% citric acid and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, and then brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residual solid by silica gel column chromatography [Merck 7734, EtOAc/*n*-hexane (1/1 → 2/1)] gave the alcohol **33a** (1.91 g, 73%) as a white amorphous powder: TLC R_f = 0.41 and 0.31, EtOAc/*n*-hexane (2/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.05−7.94 (m, 1H), 7.67−7.44 (m, 2H), 7.42−7.19, 7.18−7.00 and 6.80−6.71 (m × 3, 19H), 5.75−4.82 (m, 3H), 4.40−4.04 (m, 1H), 3.72−3.22 (m, 2H), 1.70−1.50 (m, 1H), 1.36 and 1.35 (s × 2, 9H), 0.87−0.50 (m, 6H).

(2*S*)-1-{[1-(Triphenylmethyl)imidazol-4-yl]carbonyl}indolin-2-yl-*N*-[(1*S*)-2-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]carboxamide (34a). To a stirred suspension of Dess−Martin periodinane (ca. 70%; 1.41 g, 2.55 mmol) in CH_2Cl_2 (16 mL) was added a solution of the alcohol **33a** (1.81 g, 2.55 mmol) in CH_2Cl_2 (33 mL) under Ar at room temperature. After 4.5 h, the reaction mixture was poured into ice-cooled brine and extracted with EtOAc. The organic layer was concentrated in vacuo. Purification of the residue by silica gel column chromatography [FL60D, EtOAc/*n*-hexane (1/2)] gave the ketone **34a** (1.36 g, 75%) as a pale yellow amorphous powder: TLC R_f = 0.26, EtOAc/*n*-hexane (1/2); MS (APCI, neg. 20 V) *m*/*z* = 705 (M − H)$^-$; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.64 (d, *J* = 7.2 Hz, 1H), 8.11 (m, 1H), 7.56−7.34, 7.24−7.06 and 7.03−6.94 (m × 3, 20H), 6.40−6.24 (m, 1H), 4.98 (t, *J* = 6.3 Hz, 1H), 3.70−3.55 and 3.08−2.97 (m × 2, 2H), 2.35−2.20 (m, 1H), 1.37 (s, 9H), 0.84 and 0.83 (d × 2, *J* = 6.6 Hz, 3H × 2).

(2*S*)-1-(Imidazol-4-ylcarbonyl)indolin-2-yl-*N*-[(1*S*)-2-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]carboxamide Hydrochloride (24j). A solution of the ketone **34a** (1.26 g, 1.79 mmol) in trifluoroacetic acid/water (19/1; 10 mL) was stirred at room temperature for 1 h. The reaction mixture was evaporated to remove the solvent and then treated with 4 N HCl in EtOAc followed by concentration in vacuo. The resulting solid was washed successively with ether, EtOAc and then *n*-hexane to afford the ketone **24j** (796 mg, 89%) as a white powder: TLC R_f = 0.46, $CHCl_3$/MeOH (9/1); MS (APCI, pos. 20 V) *m*/*z* = 465 (M + H)$^+$; IR (KBr) 3144, 2973, 2935, 2876, 2588, 1717, 1656, 1600, 1843, 1484, 1462, 1403, 1371, 1330, 1264, 1212, 1172, 1124, 1015, 849, 758 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 9.08 (d, *J* = 1.0 Hz, 1H), 8.00 (d, *J* = 1.0 Hz, 1H), 7.30−7.07 (m, 4H), 5.63−5.53 (m, 1H), 5.12 (d, *J* = 5.4 Hz, 1H), 3.87−3.73 and 3.35−3.22 (m × 2, 2H), 2.55−2.37 (m, 1H), 1.43 (s, 9H), 1.01−0.94 (m, 6H); optical rotation $[\alpha]^{25}_D$ −103.7 (*c* 1.0, DMF). Anal. ($C_{24}H_{29}ClN_6O_4$·$0.5H_2O$) C, H, N.

(2*S*)-1-[(2*S*)-2-(*tert*-Butoxycarbonylamino)-3-methylbutanoyl]indolin-2-yl-*N*-[(1*S*)-2-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl]carboxamide (35a). To a stirred solution of Boc-L-valine (1.30 g, 6.00 mmol) in CH_2Cl_2 (15 mL) were added dropwise pyridine (0.486 mL, 6.00 mmol) and then cyanuric fluoride (2.70 mL, 30.0 mmol) under Ar at −20 °C. After 2 h, the reaction was quenched with ice−water, and extracted with CH_2Cl_2. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford the (2*S*)-2-(*tert*-butoxycarbonylamino)-3-methylbutanoyl fluoride (1.20 g, 92%) as colorless needles: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.16−4.85 (m, 1H), 4.47−4.24 (m, 1H), 2.36−2.10 (m, 1H), 1.47 (s, 9H), 1.05 and 1.00 (d × 2, *J* = 7.0 Hz, 3H × 2).

To a stirred solution of the amino alcohol **29a** (1.65 g, 4.03 mmol) and 2,6-di-*tert*-butylpyridine (1.80 mL, 8.02 mmol) was added dropwise a solution of (2*S*)-2-(*tert*-butoxycarbonylamino)-3-methylbutanoyl fluoride (1.20 g, 5.50 mmol) in CH_2Cl_2 (5 mL) at −25 °C. After 1 h, the reaction mixture was treated with 4-(dimethylamino)pyridine (489 mg, 4.00 mmol), stirred at 0 °C for 48 h, then quenched with 10% citric acid and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ and then brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography [FL60D, $CHCl_3$/MeOH (200/1 → 100/1)] to afford the Boc alcohol **35a** (721 mg, 31%) as an off-white amorphous powder: TLC R_f = 0.53, $CHCl_3$/MeOH (1/9); MS (APCI, pos. 20 V) *m*/*z* = 572 (M + H)$^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.23 and 8.08 (d × 2, *J* = 8.6 Hz, 1H), 7.35−7.01 and 6.94−6.88 (m × 2, 5H), 5.35−4.74, 4.37−4.15 and 4.07−3.90 (m × 3, 5H), 3.73−3.30 (m, 2H), 2.23−1.65 (m, 2H), 1.55−0.42 (m, 30H).

(2*S*)-1-((2*S*)-2-Amino-3-methylbutanoyl)indolin-2-yl-*N*-[(1*S*)-2-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl]carboxamide Hydrochloride (36a). A solution of the Boc alcohol **35a** (700 mg, 1.23 mmol) in EtOAc (1 mL) was treated with 4 N HCl in dioxane (4 mL), and stirred at room temperature for 1 h, then concentrated in vacuo. The residue was dried by azeotropic removal of water with toluene to afford the amino alcohol **36a** (577 mg) as a yellowish amorphous powder quantitatively. The product was used for the next reaction without further purification: TLC R_f = 0.43 and 0.34, $CHCl_3$/MeOH (9/1); MS (APCI, pos. 20 V) *m*/*z* = 472 (M + H)$^+$; ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.60−8.25 and 8.15−8.04 (m × 2, 4H), 7.32−6.99 (m, 4H), 6.65−6.15 (m, 1H), 5.26−4.95 and 4.76−4.64 (m × 2, 2H), 4.23−4.15 and 3.96−3.80 (m × 2, 1H), 3.72−3.13 (m, 2H), 2.88−2.70, 2.45−2.10 and 2.10−1.70 (m × 3, 3H), 1.30−0.90 (m, 21H).

(2*S*)-1-[(2*S*)-3-Methyl-2-(3-pyridinecarbamido)butanoyl]indolin-2-yl-*N*-[(1*S*)-2-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl]carboxamide (37a). To a stirred solution of the amino alcohol **36a** (258 mg, 0.51 mmol) and nicotinic acid (69 mg, 0.56 mmol) in DMF (2 mL) were added EDC·HCl (108 mg, 0.57 mmol) and then *N*-methylmorpholine (0.062 mL, 0.56 mmol) under Ar at 0 °C. After 10 min, the reaction mixture was stirred at room temperature overnight. Additional nicotinic acid (13 mg, 0.10 mmol) and EDC·HCl (20 mg, 0.10 mmol) were added. After stirring at room temperature for another 3 h, the reaction mixture was poured into 10% citric acid and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ and then brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residual solid was purified by silica gel column chromatography [FL60D, $CHCl_3$/MeOH, (100/1 → 20/1)] to afford the alcohol **37a** (260 mg, 89%) as a pale yellow amorphous powder: TLC $R_f = 0.47$ and 0.44, $CHCl_3$/MeOH/AcOH (18/1/1); MS (APCI, pos. 20 V) $m/z = 577$ $(M + H)^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.10 and 8.96 (br s × 2, 1H), 8.84−8.65 (m, 1H), 8.28−7.94 (m, 2H), 7.50−6.97 (m, 6H), 5.64−5.38, 5.30−4.76 and 4.60−3.94 (m × 3, 5H), 3.76−3.34 (m, 2H), 2.40−1.60 (m, 2H), 1.38 and 1.18 (s × 2, 9H), 1.45−0.84, 0.70−0.63, 0.55−0.46 and 0.42−0.36 (m × 4, 12H).

(2*S*)-1-[(2*S*)-3-Methyl-2-(3-pyridinecarbamido)butanoyl]-indolin-2-yl-*N*-[(1*S*)-2-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]carboxamide (24l). To a stirred suspension of Dess−Martin periodinane (ca. 70%; 316 mg, 0.57 mmol) in CH_2Cl_2 (3 mL) was added a solution of the alcohol **37a** (235 mg, 0.41 mmol) in CH_2Cl_2 (7 mL) under Ar at room temperature. After 1 h, the reaction mixture was poured into ice-cooled brine and extracted with EtOAc. The organic layer was concentrated in vacuo. Purification by silica gel column chromatography [FL60D, EtOAc/*n*-hexane (1/1 → 2/1)] afforded the ketone **24l** (200 mg, 85%) as a white amorphous powder: TLC $R_f = 0.43$, $CHCl_3$/MeOH (9/1); MS (APCI, pos. 20 V) $m/z = 575$ $(M + H)^+$; IR (KBr) 3322, 2971, 2936, 2876, 1718, 1646, 1594, 1542, 1482, 1465, 1408, 1371, 1320, 1271, 1162, 1028, 949, 827, 707 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.06 and 8.96 (s × 2, 1H), 8.80−8.67 (m, 1H), 8.28−8.01 (m, 2H), 7.44−7.02 and 6.86−6.77 (m × 2, 6H), 5.63−5.54, 5.44−5.29, 5.34−5.04 and 4.76−4.66 (m × 4, 3H), 3.73−3.25 (m, 2H), 2.56−2.14 (m, 2H), 1.47 and 1.36 (s × 2, 9H), 1.31−0.78 and 0.64−0.54 (m × 2, 12H); optical rotation $[\alpha]^{25}_{D}$ −41.2 (*c* 0.4, MeCN). Anal. ($C_{31}H_{38}N_6O_5$·0.9H_2O) C, H, N.

***tert*-Butyl (3*S*)-3-{*N*-[(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl]carbamoyl}-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (28b).** To a stirred mixture of (3*S*)-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **(27b)** (4.97 g, 1.79 mmol), the amino alcohol **8e** (5.67 g, 21.5 mmol) and HOBt·H_2O (3.29 g, 21.5 mmol) in DMF (55 mL), were added EDC·HCl (4.12 g, 21.5 mmol) and then *N*-methylmorpholine (2.36 mL, 21.5 mmol) under Ar at 0 °C. After 15 min, the reaction mixture was stirred at room temperature for 18 h, and poured into water and extracted with EtOAc. The organic layer was washed with 10% citric acid, saturated $NaHCO_3$, water, and then brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residual pale yellow solid by silica gel column chromatography [Merck 7734, EtOAc/*n*-hexane, (1/1 → 4/1)] gave the Boc alcohol **28b** (8.00 g, 92%) as a white amorphous solid: TLC $R_f = 0.58$ and 0.51, EtOAc/*n*-hexane (4/1); MS (APCI, pos. 40 V) $m/z = 487$ $(M + H)^+$, 413, 387; ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6) δ 7.17 (m, 4H), 6.95−6.60 (m, 1H), 5.02−3.80 (m, 6H), 3.28−2.96 (m, 2H), 1.73 (m, 1H), 1.51, 1.43, 1.41 and 1.38 (s × 4, 18H), 0.95−0.40 (m, 6H).

[(3*S*)-3-(1,2,3,4-Tetrahydroisoquinolyl)]-*N*-[(1*S*)-2-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl]carboxamide Hydrochloride (29b). A mixture of the Boc alcohol **28b** (6.00 g, 12.3 mmol) and 4 N HCl in dioxane (40 mL) was stirred at room temperature for 1 h. The reaction mixture was concentrated in vacuo. The residue was dried by azeotropic removal of water with toluene to give the amino alcohol **29b** (5.35 g) as a white powder quantitatively. The product was used for the next reaction without further purification: TLC $R_f = 0.47$, MeOH/$CHCl_3$ (1/9); MS (APCI, pos. 40 V) $m/z = 387$ $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.12−9.89 and 9.42−9.14 (m × 2, 2H), 8.63 and 8.39 (d × 2, $J = 10.0$ Hz, 1H), 7.33−7.20 and 7.20−7.01 (m × 2, 4H), 5.05 and 4.73 (d × 2, $J = 3.9$ Hz and $J = 10.2$ Hz, 1H), 4.60−3.94 (m, 4H), 3.26−3.12, 2.90−2.66 and 2.60−2.36 (m × 3, 2H), 2.34−2.18 and 1.90−1.72 (m × 2, 1H), 1.35 and 1.34 (s × 2, 9H), 1.03−0.93 (m, 6H).

Methylethyl (3*S*)-3-{*N*-[(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl]carbamoyl}-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (30b). To a stirred solution of the amino alcohol **29b** (999 mg, 2.37 mmol) in CH_2Cl_2 (20 mL) were added dropwise 1.0 M isopropyl chloroformate in toluene (2.37 mL, 2.37 mmol) and *N*-methylmorpholine (0.520 mL, 4.73 mmol) at 0 °C. After 1 h, the reaction mixture was stirred at room temperature for 3.5 h. Additional 1.0 M isopropyl chloroformate in toluene (2.37 mL, 2.37 mmol) and *N*-methylmorpholine (0.520 mL, 4.73 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for another 3 h, then poured into ice-cooled 10% citric acid and extracted with EtOAc. The organic layer was washed with brine, with saturated $NaHCO_3$, and again brine, and dried over anhydrous Na_2SO_4. Concentration gave the alcohol **30b** (1.13 g) as a white amorphous powder quantitatively. The product was used for the next reaction without further purification: TLC $R_f = 0.42$ and 0.40, $CHCl_3$/MeOH (19/1); MS (APCI, pos. 40 V) $m/z = 473$ $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.66−7.47 (m, 1H), 7.26−6.98 (m, 4H), 6.23−6.05 (m, 1H), 4.95−4.05 and 3.90−3.60 (m × 2, 6H), 3.10−2.56 (m, 2H), 2.23−2.05 and 1.75−1.60 (m × 2, 1H), 1.37−1.05 (m, 15H), 0.95−0.60 (m, 6H).

Methylethyl (3*S*)-3-{*N*-[(1*S*)-2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]carbamoyl}-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (24i). To a stirred suspension of Dess−Martin periodinane (ca. 70%; 1.16 g, 2.12 mmol) in CH_2Cl_2 (14 mL) was added a solution of the alcohol **30b** (998 mg, 2.12 mmol) in CH_2Cl_2 (26 mL) under Ar at room temperature. After 4 h, the reaction mixture was poured into ice-cooled brine and extracted with EtOAc. The organic layer was concentrated in vacuo. Purification of the residue by silica gel column chromatography [Merck 7734, acetone/*n*-hexane (1/9)] gave the ketone **24i** (544 mg, 55% in 3 steps) as a yellowish amorphous powder: TLC $R_f = 0.33$, EtOAc/*n*-hexane (1/2); MS (APCI, pos. 40 V) $m/z = 471$ $(M + H)^+$; IR (KBr) 3331, 2977, 2936, 2876, 1703, 1543, 1525, 1462, 1387, 1373, 1342, 1317, 1222, 1181, 1112, 1042, 1017, 915, 749 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.48−8.32 (m, 1H), 7.24−7.05 (m, 4H), 4.96−4.34 (m, 5H), 3.18−2.87 (m, 2H), 2.38−2.23 (m, 1H), 1.39 (s, 9H), 1.32−0.98 and 0.92−0.74 (m × 2, 12H); optical rotation $[\alpha]^{24}_{D}$ −20.1 (*c* 1.0, MeCN). Anal. ($C_{25}H_{34}N_4O_5$·0.5H_2O) C, H, N.

1-(Triphenylmethyl)imidazole-4-carboxylic Acid (32). A mixture of imidazole-4-carboxylic acid (**31**) (2.24 g, 20.0 mmol) and triphenylmethyl chloride (6.13 g, 22.0 mmol) in pyridine (30 mL) and DMF (60 mL) was stirred at room temperature overnight, then quenched with water, and extracted with EtOAc. The organic layer was washed with water, 10% citric acid, and then brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting solid was washed with EtOAc to afford the carboxylic acid **32** (4.91 g, 70%) as a white powder: TLC $R_f = 0.33$, $CHCl_3$/MeOH (9/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68−7.04 (m, 18H).

(3*S*)-2-[1-(Triphenylmethyl)imidazol-4-yl]carbonyl-3-(1,2,3,4-tetrahydroisoquinolyl)-*N*-[(1*S*)-2-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl]carboxamide (33b). To a stirred mixture of the carboxylic acid **32** (1.69 g, 4.77 mmol), the amino alcohol **29b** (1.00 g, 2.37 mmol) and HOBt·H_2O (726 mg, 4.73 mmol) in DMF (20 mL), were added EDC·HCl (908 mg, 4.74 mmol) and then *N*-methylmorpholine (0.522 mL, 4.74 mmol) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 24 h, and poured into saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with 10% citric acid, and then brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residual pale yellow solid by silica gel column chromatography (Merck 7734, EtOAc/CH_2-

Cl_2 (1/9 → 1/1) gave the alcohol **33b** (1.04 g, 61%) as a white amorphous powder: TLC R_f = 0.48 and 0.42, $CHCl_3$/MeOH (9/1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.81−7.00 (m, 22H), 6.22−5.85 (m, 2H), 5.02−3.75 (m, 4H), 3.20−2.77 (m, 2H), 2.30−1.95 and 1.80−1.40 (m, totally 1H), 1.33−1.13 (m, 9H), 0.92−0.40 (m, 6H).

(3*S*)-2-{[1-(Triphenylmethyl)imidazol-4-yl]carbonyl}-3-(1,2,3,4-tetrahydroisoquinolyl)-*N*-[(1*S*)-2-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]carboxamide (34b). To a stirred suspension of Dess−Martin periodinane (ca. 70%; 751 mg, 1.36 mmol) in CH_2Cl_2 (9 mL) was added a solution of the alcohol **33b** (982 mg, 1.36 mmol) in CH_2Cl_2 (18 mL) under Ar at room temperature. After 2 h, the reaction mixture was poured into ice-cooled brine and extracted with EtOAc. The organic layer was concentrated in vacuo. Purification of the residue by silica gel column chromatography [FL60D, EtOAc/*n*-hexane (1/2)] gave the ketone **34b** (485 mg, 50%) as a white amorphous powder: TLC R_f = 0.61, $CHCl_3$/MeOH (19/1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.56−8.45 (m, 1H), 7.63−7.31 and 7.31−7.04 (m × 2, 21H), 6.22−5.94 (m, 1H), 5.25−4.75 and 4.50−4.38 (m × 2, 3H), 3.50−2.90 (m, 2H), 2.40−2.18 (m, 1H), 1.45−1.30 (m, 9H), 1.00−0.60 (m, 6H).

(3*S*)-2-(Imidazol-4-ylcarbonyl)-3-(1,2,3,4-tetrahydroisoquinolyl)-*N*-[(1*S*)-2-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]carboxamide Hydrochloride (24k). A solution of the ketone **34b** (433 mg, 0.602 mmol) in trifluoroacetic acid/water (19/1; 4 mL) was stirred at room temperature for 1 h. The reaction mixture was evaporated to remove the solvent, then treated with 4 N HCl in EtOAc, followed by concentration in vacuo. The resulting solid was washed with ether and then EtOAc to afford the ketone **24k** (176 mg, 57%) as a white powder: TLC R_f = 0.48, $CHCl_3$/MeOH (9/1); MS (APCI, pos. 20 V) m/z = 479 (M + H)$^+$; IR (KBr) 3423, 3113, 2975, 2934, 2874, 1718, 1622, 1542, 1481, 1425, 1369, 1307, 1282, 1227, 1188, 1166, 1114, 1042, 1016, 1001, 972, 952, 928, 822, 753, 693, 626 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 9.08 (br s, 1H), 8.31 (br s, 1H), 7.24 (m, 4H), 5.15−4.92 (m, 4H), 3.35−3.23 (m, 2H), 2.47−2.22 (m, 1H), 1.45 (s, 9H), 1.02−0.67 (m, 6H); optical rotation $[\alpha]^{25}_D$ −18.1 (c 0.4, DMF). Anal. ($C_{25}H_{31}ClN_6O_4{\cdot}0.8H_2O$) C, H, N.

(3*S*)-2-{(2*S*)-2-[(*tert*-Butoxy)carbonylamino]-3-methylbutanoyl}-3-(1,2,3,4-tetrahydroisoquinolyl)-*N*-[(1*S*)-2-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl]carboxamide (35b). To a stirred mixture of Boc-L-valine (1.54 g, 7.10 mmol), the amino alcohol **29b** (2.00 g, 4.73 mmol), and HOBt·H_2O (1.09 g, 7.10 mmol) in DMF (20 mL) were added EDC·HCl (1.36 g, 7.10 mmol) and then *N*-methylmorpholine (0.52 mL, 4.73 mmol) under Ar at 0 °C. After 10 min, the reaction mixture was stirred at room temperature for 24 h. Additional Boc-L-valine (1.54 g, 7.10 mmol), HOBt·H_2O (1.09 g, 7.10 mmol) and EDC·HCl (1.36 g, 7.10 mmol) were added at 0 °C. After stirring at room temperature for 24 h, Boc-L-valine (3.08 g, 14.2 mmol), HOBt·H_2O (2.18 g, 14.2 mmol) and EDC·HCl (2.72 g, 14.2 mmol) were added again at 0 °C. After stirring at room temperature for 32 h, the reaction was quenched with *N,N*-dimethylpropylenediamine (3.00 mL, 24.0 mmol) at 0 °C. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with 5% $KHSO_4$, water, and then brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification of the residual pale yellow solid by silica gel column chromatography [FL60D, EtOAc/*n*-hexane, (1/9 → 2/1)] gave the Boc alcohol **35b** (1.52 g, 55%) as a white amorphous solid: TLC R_f = 0.39, MeOH/$CHCl_3$ (1/10); MS (APCI, neg. 20 V) m/z = 584 (M − H)$^-$, 510; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45−6.90 (m, 5H), 5.29−2.80 (m, 10H), 2.10−1.70 (m, 2H), 1.50−0.30 (m, 30H).

(3*S*)-2-((2*S*)-2-Amino-3-methylbutanoyl)-3-(1,2,3,4-tetrahydroisoquinolyl)-*N*-[(1*S*)-2-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl]carboxamide Hydrochloride (36b). A mixture of the Boc alcohol **35b** (1.42 g, 2.44 mmol), 4 N HCl in EtOAc (25 mL) and EtOAc (2 mL) was stirred at room temperature for 1 h. Concentration of the reaction mixture followed by drying by azeotropic removal of water with toluene gave the amino alcohol **36b** (2.44 mmol) quantitatively. The product was used for the next reaction without further purification: MS (APCI, pos. 20 V) m/z = 485 (M + H)$^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.50 (m, 3H), 7.60−7.00 (m, 5H), 5.40−1.70 (m, 11H), 1.45−0.05 (m, 21H).

(3*S*)-2-[(2*S*)-3-Methyl-2-(3-pyridinecarbamido)butanoyl]-3-(1,2,3,4-tetrahydroisoquinolyl)-*N*-[(1*S*)-2-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-2-hydroxy-1-(methylethyl)ethyl]carboxamide (37b). To a stirred solution of the amino alcohol **36b** (500 mg, 0.96 mmol), nicotinic acid (142 mg, 1.15 mmol), and HOBt·H_2O (176 mg, 1.15 mmol) in DMF (3 mL), were added EDC·HCl (220 mg, 1.15 mmol) and then *N*-methylmorpholine (0.13 mL, 1.15 mmol) under Ar at 0 °C. After 10 min, the reaction mixture was stirred at room temperature for 2.5 h, and quenched with *N,N*-dimethylpropylendiamine (0.03 mL). After 1 min, the resulting mixture was poured into water and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl, water, saturated $NaHCO_3$, water, and then brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residual white amorphous solid was washed with EtOAc/ether/*n*-hexane (1/4/36) under sonication, and collected by filtration to give the alcohol **37b** (498 mg, 88%) as a white powder: TLC R_f = 0.36, MeOH/$CHCl_3$ (1/10); MS (APCI, pos. 40 V) m/z = 591 (M + H)$^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.17−8.90 (m, 1H), 8.71 (m, 1H), 8.20−7.91 (m, 1H), 7.70−7.00 (m, 7H), 5.47−2.88 (m, 9H), 2.36−1.80 (m, 2H), 1.47−0.19 (m, 21H).

(3*S*)-2-[(2*S*)-3-Methyl-2-(3-pyridinecarbamido)butanoyl]-3-(1,2,3,4-tetrahydroisoquinolyl)-*N*-[(1*S*)-2-(5-*tert*-butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]carboxamide (24m). To a stirred suspension of Dess−Martin periodinane (ca. 77%; 492 mg, 0.89 mmol) in CH_2Cl_2 (6 mL) was added a solution of the alcohol **37b** (479 mg, 0.81 mmol) in CH_2Cl_2 (12 mL) under Ar at room temperature. After 2.5 h, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and then brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residual white paste by silica gel column chromatography [FL60D, EtOAc/*n*-hexane (1/1 → 4/1)] gave the ketone **24m** (316 mg, 66%) as a white amorphous powder: TLC (HPTLC) R_f = 0.30, EtOAc; MS (APCI, pos. 20 V) m/z = 589 (M + H)$^+$; IR (KBr) 3427, 2971, 1716, 1638, 1592, 1541, 1419, 1369, 1221, 1158, 1027, 827, 745, 707 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.09 and 8.99 (m × 2, 1H), 8.73 (m, 1H), 8.20−8.00 (m, 1H), 7.65 and 7.45−6.87 (m × 2, 7H), 5.40 (dd, *J* = 8.2, 4.6 Hz, 1H), 5.27 (m, 1H), 5.16−4.96 and 4.86−4.53 (m × 2, 3H), 3.65−3.00 (m, 2H), 2.54−2.11 (m, 2H), 1.47 and 1.37 (s × 2, 9H), 1.25−0.60 (m, 12H); optical rotation $[\alpha]^{25}_D$ −6.7 (*c* 1.0, MeCN). Anal. ($C_{32}H_{40}N_6O_5{\cdot}0.4H_2O$) C, N, H.

***N*-[2-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]-2-{6-oxo-2-phenyl-5-[(phenylmethoxy)-carbamido]hydropyrimidinyl}acetamide (42).** To a stirred solution of oxalyl chloride (13.8 mL, 158 mmol) in CH_2Cl_2 (290 mL) was added dropwise a solution of DMSO (22.5 mL, 316 mmol) in CH_2Cl_2 (60 mL) under Ar at −70 to −60 °C. After being stirred for 1 h, a solution of the alcohol **9e(H)** (50.1 g, ca. 79.2 mmol) in DMSO (30 mL) and CH_2Cl_2 (230 mL) was added dropwise. After stirring at −70 °C for 2 h, the reaction mixture was treated with triethylamine (221 mL, 1.60 mol), then stirred at room temperature for 40 h. The reaction mixture was acidified with 2 N HCl (600 mL) at 0 °C. The organic layer was removed, and concentrated in vacuo. The residue was dissolved in EtOAc. The organic layer was washed with 1 N HCl, water, and then brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford the Cbz ketone **42** (47.6 g, quant). The product was used for the next reaction without further purification: TLC R_f = 0.36, *n*-hexane/EtOAc (1/1); MS (APCI, pos. 40 V) m/z = 587 (M + H)$^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.78 (br s, 1H), 7.67−7.24 (m, 11H), 6.74 (d, *J* = 8.4 Hz, 1H), 5.44 (dd, *J* = 8.4, 5.0 Hz, 1H), 5.23 (s, 2H), 4.68 and 4.58 (d × 2, *J* = 15.4 Hz, 1H × 2), 2.63−2.39 (m, 1H), 1.47 (s, 9H), 1.06 and 0.87 (d × 2, *J* = 6.8 Hz, 3H × 2).

2-(5-Amino-6-oxo-2-phenylhydropyrimidinyl)-*N*-[2-(5-

-*tert*-butyl-1,3,4-oxadiazol-2-yl)-1-(methylethyl)-2-oxoethyl]acetamide (3(H), ONO-6818). To a stirred solution of the ketone **42** (47.6 g, ca. 79.2 mmol) and anisole (51.6 mL, 475 mmol) in CH_2Cl_2 (1.25 L) was added dropwise a solution of aluminum chloride (63.0 g, 475 mmol) in CH_3NO_2 (630 mL) under Ar at 0 °C. The reaction mixture was stirred at room temperature for 2.5 h, then quenched with crushed ice, and extracted with CH_2Cl_2. The organic layer was washed with water and with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by silica gel column chromatography [Merck 7734, MeOH/$CHCl_3$ (0/100 → 1/19)] followed by washing with CH_2Cl_2 gave the ketone **3(H)** (ONO-6818) (26.0 g, 73% in 3 steps) as an off-white powder: TLC $R_f = 0.49$, $CHCl_3$/MeOH (10/1); MS (APCI, pos. 40 V) $m/z = 453\ (M + H)^+$; IR (KBr) 3466, 2976, 1695, 1641, 1611, 1543, 1439, 1303, 1205, 979, 703, 546 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.58−7.38 (m, 6H), 6.88 (br d, $J = 8.4$ Hz, 1H), 5.45 (dd, 1H, $J = 8.4, 5.0$ Hz), 4.66 and 4.60 (d × 2, $J = 15.4$ Hz, 1H × 2), 4.06 (m, 2H), 2.52 (m, 1H), 1.48 (s, 9H), 1.07 and 0.88 (d × 2, $J = 6.8$ Hz, 3H × 2). Anal. ($C_{23}H_{28}N_6O_4$) C, H, N.

Supporting Information Available: Elemental analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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