methyl ether, 138854-08-7; **42** allyl ether, 138854-09-8; **43a**, 138853-84-6; **43b**, 138853-85-7; **43b** hydrogenated, 139201-46-0; **44**, 139201-47-1; **45**, 138854-18-9; **45** 4-cyanophenoxy derivative, 138854-19-0; **46**, 133174-26-2; **46** benzyl ether, 138854-30-5; **47**, 139201-48-2; **47** benzyl ether, 138854-35-0; **48**, 139201-49-3; **49**, 138853-91-5; **49** benzyl ether, 138854-20-3; **50**, 139201-50-6; **50** benzyl ether, 139201-51-7; **51**, 138853-98-2; **51** benzyl ether, 139201-52-8; **52**, 139201-53-9; **53**, 139201-54-0; **53** benzyl ether, methyl ester, 138854-21-4; **53** methyl ester, 138854-22-5; **54**, 139201-55-1; **55**, 139201-56-2; **56**, 138854-29-2; **57**, 139201-57-3; **58**, 139201-58-4; **59**, 139201-59-5; **60**, 139201-60-8; **61**, 139201-61-9; **62**, 10242-08-7; **63**, 23145-19-9; **63** alcohol, 37603-26-2; (*E*)-**64**, 139201-62-0; (*Z*)-**64**, 139201-64-2; (*E*)-**64** alcohol, 139201-63-1; (*Z*)-**64** alcohol, 139201-65-3; **65**, 138853-86-8; **66**, 138853-90-4; **67**, 119794-95-5; **68**, 139201-66-4; **69**, 139201-67-5; **70**, 139242-71-0; **70** tri-*O*-acetyl methyl ester, 139201-68-6; LTB_4, 71160-24-2; p-$(OEt)_2P(O)CH_2C(O)C_6H_4Cl$, 18276-82-9; allyl bromide, 106-95-6; 3-methyl-2-buten-1-yl 4-methoxyphenyl ether, 34125-69-4; 3-methyl-2-buten-1-ol, 556-82-1; 2-(1,1-dimethyl-2,3-epoxypropyl)-4-methoxyphenyl *n*-butyrate, 138854-48-5; 2,3-dihydro-3,3-dimethyl-2-(hydroxymethyl)-5-benzofuranol, 138854-50-9; (4-methoxyphenyl)magnesium bromide, 13139-86-1; 4-bromoanisole, 104-92-7; 5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-[1-hydroxy-1-(4-methoxyphenyl)methyl]benzofuran, 139201-69-7; 5-(allyloxy)-2,3-dihydro-3,3-dimethyl-2-(4-methoxybenzyl)-benzofuran, 139201-70-0; diethyl (4-methoxybenzyl)phosphonate, 1145-93-3; benzyl chloride, 100-44-7; 5-(benzyloxy)-2,3-dihydro-3,3-dimethyl-2-[2-(4-methoxyphenyl)ethenyl]benzofuran, 138854-03-2; 5-(allyloxy)-2,3-dihydro-3,3-dimethyl-2-[2-(4-methoxyphenyl)ethyl]benzofuran, 139201-71-1; 5-(allyloxy)-2,3-dihydro-3,3-dimethyl-2-methoxybenzofuran, 138854-53-2; 6-allyl-2,3-dihydro-2,5-dihydroxy-3,3-dimethylbenzofuran, 138854-62-3; (carbethoxymethylene)triphenylphosphorane, 1099-45-2; 6-propyl-2-(carbethoxymethyl)-2,3-dihydro-3,3-dimethyl-5-benzofuranol, 139201-72-2; methyl 3-mercaptopropionate, 2935-90-2; 2-mercaptopyridine, 2637-34-5; [4-(methylthio)phenyl]magnesium bromide, 18620-04-7; 4-bromothioanisole, 104-95-0; phenol, 108-95-2; diethyl (2-oxo-2-phenylethyl)phosphonate, 3453-00-7; phenyl acetaldehyde, 122-78-1; 3-phenoxypropionaldehyde, 22409-86-5; methyl 4-hydroxybenzoate, 99-76-3; 4-cyanophenol, 767-00-0; 4-mercaptopyridine, 4556-23-4; 2-mercaptobenzothiazole, 149-30-4; 2,4-dihydroxy-3-propyl phenylmethyl ketone, 40786-69-4; 2-methoxy-3-carbomethoxy-7-mercaptoquinoline, 95903-63-2; benzaldehyde, 100-52-7; (4-chlorobenzyl)triphenylphosphonium chloride, 1530-39-8; 2,3-dihydro-6-(3-phenoxypropyl)-2-(2-phenethyl)-5-benzofuranol, 133174-26-2; methyl (tri-*O*-acetyl-α-D-glucopyranosyl bromide)uronate, 21085-72-3; 5-lipoxygenase, 80619-02-9.

Communications to the Editor

Intriguing Structure–Activity Relations Underlie the Potent Inhibition of HIV Protease by Norstatine-Based Peptides†

Human immunodeficiency virus (HIV) protease represents a compelling anti-viral target in that potent and specific inhibitors of this enzyme can be designed rationally using contemporary mechanistic and structural motifs.[1-3] Indeed, cell culture studies using inhibitors of HIV protease have established that this enzyme is essential for viral replication and infectivity, thereby providing a plausible biochemical rationale for the treatment of AIDS.[4] In accord with its role as an aspartyl proteinase, the enzyme has been profoundly inhibited by numerous peptide analogues incorporating features which mimic the proposed tetrahedral intermediates that are formed upon hydration of amide substrates of this class of proteinases.[5-11]

Yet, examples of (hydroxymethyl)carbonyl-based inhibitors (e.g. norstatine) of HIV protease have been conspicuously lacking until recently, when Raju and Deshpande[12] reported a number of moderately potent compounds $K_i \geq 3.3$ μM, and Mimoto et al.[13] described a heptapeptide, as well as a truncated variant,[14] with potent activity against synthetic [Ala^{67,95}] HIV protease. Their reports have prompted us to disclose a series of small phenylnorstatine-based peptides extending from the P_2 to P_1' positions, and having N and C terminals protected. With L-proline at the P_1' position and *S* stereochemistry of the (hydroxymethyl)carbonyl component (Table I), these inhibitors, prepared according to Scheme I,[15,16] exhibit impressive potency in the nanomolar range (IC_{50} = 0.58–7.4 nM).[17]

Specifically, the truncated peptide (1) possesses submicromolar activity (IC_{50} = 460 nM), which can be improved by extending the main chain in the N-terminal direction with either valine or asparagine at the P_2 position. Subnanomolar inhibition is achieved by capping the N-terminus with a (naphthyloxy)acetyl protecting group (cf.

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Table I[a]

no.	stereochem at -CH(OH)-	structure	IC_{50} (nM)
1	S	Z-Phe-Ψ[CH(OH)C(O)N]Pro-NHᵗBu	460
2	R	Z-Phe-Ψ[CH(OH)CH_2N]Pro-OᵗBu	6500[b]
3		Z-Phe-Ψ[C(O)C(O)N]Pro-NHᵗBu	600
4	S	Z-Asn-Phe-Ψ[CH(OH)C(O)N]Pro-NHᵗBu	7.4 (K_i = 4)[c]
5	R	Z-Asn-Phe-Ψ[CH(OH)C(O)N]Pro-NHᵗBu	3100
6		Z-Asn-Phe-Ψ[C(O)C(O)N]Pro-NHᵗBu	20
7	S	Z-Val-Phe-Ψ[CH(OH)C(O)N]Pro-NHᵗBu	4.3
8	S	Z-Asn-Phe-Ψ[CH(OH)C(O)N]PIC-NHᵗBu	26
9	S	Z-Asn-Phe-Ψ[CH(OH)C(O)N]DIQ-NHᵗBu	84
10	S	NoA-Asn-Phe-Ψ[CH(OH)C(O)N]Pro-NHᵗBu	0.58 (K_i = 0.4)
11	S	NoA-Val-Phe-Ψ[CH(OH)C(O)N]Pro-NHᵗBu	1.9
12	S	2-NoA-Asn-Phe-Ψ[CH(OH)C(O)N]Pro-NHᵗBu	1.3
13	S	QC-Asn-Phe-Ψ[CH(OH)C(O)N]Pro-NHᵗBu	1.1 (K_i = 0.9)
14	S	QC-Asn-Phe-Ψ[CH(OH)C(O)N]DIQ-NHᵗBu	27
15	R	Z-Asn-Phe-Ψ[CH(OH)CH_2N]Pro-OᵗBu	140,[b] 51,[d] 130[e]
16	R	Z-Asn-Phe-Ψ[CH(OH)CH_2N]Pro-Ile-Val-OMe	≫100[b]
17	R	Boc-Asn-Phe-Ψ[CH(OH)CH_2N]Pro-Ile-Val-OMe	850[d]
18	S	Z-Asn-Phe-Ψ[CH(OH)CH_2N]Pro-OᵗBu	300,[b] 450,[d] 180[e]
19	S	Z-Asn-Phe-Ψ[CH(OH)CH_2N]Pro-Ile-Val-OMe	13[b]
20	S	Boc-Asn-Phe-Ψ[CH(OH)CH_2N]Pro-Ile-Val-OMe	16[d]
21	S	Z-Asn-Phe-Ψ[CH(OH)C(O)N]Pro-Ile-Val-OMe	3.1
22	R	Z-Asn-Phe-Ψ[CH(OH)C(O)N]Pro-Ile-Val-OMe	25

[a] Abbreviations: PIC, piperidin-2(S)-ylcarbonyl; DIQ, [(4aS,8aS)-decahydroisoquinolin-3(S)-yl]carbonyl; NoA, (naphthyloxy)acetyl; QC, quinolin-2-ylcarbonyl. [b] Value reported by Roche group,[5,19] [c] K_i values were determined by Dixon analysis. [d] Values determined by Rich et al.[6] [e] This work.

10). For such proline-based inhibitors, the P_1-carbonyl imparts incremental gains in potency as exemplified by IC_{50} values for norstatines 1 and 4 vs hydroxyethylamines 2 and 15, respectively.

It is also interesting to note that the keto amides 3 and 6 are active with potencies comparable to those of the corresponding norstatine analogues 1 and 4, respectively. For an interaction which might be assumed to be analogous, Rich has established that the inhibition of pepsin by peptidyl ketones is due to the formation of a tight binding hydrate catalyzed by the enzyme.[18]

The most active epimer of each pair of norstatine stereoisomers has the S configuration around its essential carbinol function, which is identical in absolute configuration to that observed for potent members of the corre-

Scheme I

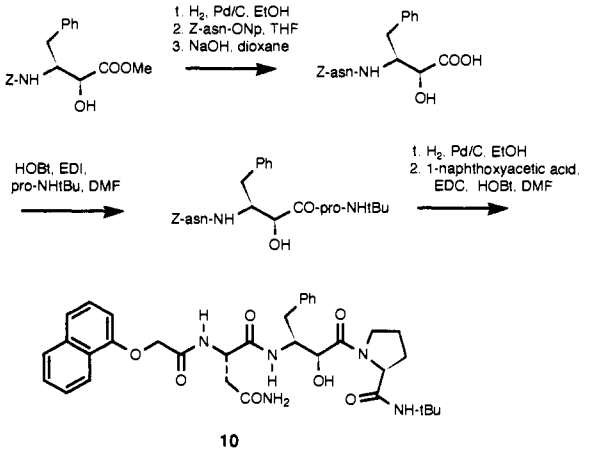

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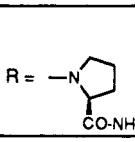
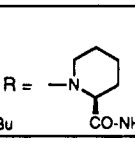
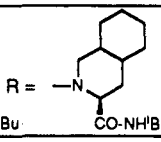
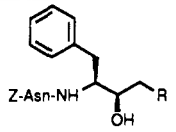
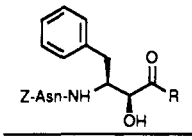
Table II. Variations in the P_1' Substituent: Effects on Potency Are Not Parallel for Hydroxyethylamine Isosteres and Hydroxyamide Isosteres[a]

	R = 	R = 	R = 
	210 nM[b] (23)	18 nM[b] (24)	<2.7 nM[b] (25)
	7 nM (4)	26 nM (8)	84 nM (9)

[a] All P_1' chiral centers in the table are *S*. [b] Values reported by Roche group.[5]

sponding hydroxyethylamine series prepared by Roche chemists (designated *R* in that series according to priority rules).[5] However, by contrast with the epimeric hydroxyethylamines, **15** and **18**, which have comparable activities, the IC_{50} values of norstatine epimers **4** and **5** differ significantly from each other (by a factor of 420). Furthermore, for the comparably potent epimeric hydroxyethylamines **15** and **18**, divergent effects on potency have been observed upon extension of such P_1'-terminal peptides to P_3' with Ile-Val (cf. **15** vs **16** or **17**, whereby IC_{50} increases significantly, with **18** vs **19** or **20**, whereby IC_{50} decreases significantly).[6,19] Lengthening of norstatine inhibitors **4** and **5** in the same fashion dramatically increases the potency of the *R* diastereomer, and leaves the IC_{50} of the *S* epimer essentially unchanged (Table I).

Another intriguing difference between the two systems is made manifest by replacing the pyrrolidine function with a homologous six-member ring (Table II). Roberts et al.[5] observed large incremental increases in potency with PIC [piperidin-2(*S*)-yl]carbonyl and DIQ [(4a*S*,8a*S*)-decahydroisoquinolin-3(*S*)-yl]carbonyl replacements of proline (compounds **24** and **25**, respectively). The trend we observe for norstatine-containing analogues (**8**, **9**, and **14**) runs counter to that reported for the hydroxyethylamine series. One possible explanation is that residues in the norstatine series are oriented differently in the P_1' pocket than are residues in the hydroxyethylamine series, because of the need to maintain a specific interaction for the P_1 carbonyl.

Intrinsic conformational effects may also contribute to the reduced potency (relative to proline) of this subset of inhibitors (**8**, **9**, and **14**). Six-member rings would normally assume thermodynamically favorable chair conformations placing substituents in equatorial positions to minimize steric interactions, *as observed for DIQ at the P_1' position of tight binding hydroxyethylamine isosteres.*[19] However, in the norstatine series, because of $A^{(1,3)}$ strain,[20-26] serious repulsive interactions between the *tert*-butylamide substituent and the adjacent *N*-acyl function must force the saturated rings in **8**, **9**, and **14** to deviate from normally preferred chairlike conformations carrying substituents equatorial. Therefore, even if rings in both series were similarly oriented in the P_1' pocket, the conformational requirements of the piperidine rings in the norstatine series might not permit optimal placement of functionality in the region of P_1' for tight binding to the enzyme.

In summary, suitably designed norstatine peptides possess a unique structure–activity profile and are potent inhibitors of HIV-1 protease. A reasonable working hypothesis is that the hydroxyamide carbonyl, by virtue of its proximity to essential carboxyl groups of the aspartyl protease, or alternatively, to a nearby water molecule[27] that connects inhibitors to the flap region, imposes constraints on the complex which accout for (1) the enhanced potency of **1** over **2** and (2) the unusual structure–activity relationships reported herein. A complete description of our investigations in this series will be discussed in a forthcoming full paper.

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