

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; LTB₄, 71160-24-2; *p*-(OEt)₂P(O)CH₂C(O)C₆H₄Cl, 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-bromothiobenzene, 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-phenylethyl)-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 Deshpande¹² reported a number of moderately potent compounds $K_i \geq 3.3 \mu\text{M}$, 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 P₂ to P₁' positions, and having N and C terminals protected. With L-proline at the P₁' 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 ($\text{IC}_{50} = 0.58\text{--}7.4 \text{ nM}$).¹⁷

Specifically, the truncated peptide (1) possesses sub-micromolar activity ($\text{IC}_{50} = 460 \text{ nM}$), which can be im-

proved by extending the main chain in the N-terminal direction with either valine or asparagine at the P₂ position. Subnanomolar inhibition is achieved by capping the N-terminus with a (naphthyl)acetyl protecting group (cf.

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[†]Contribution No. 353 from the Institute of Bioorganic Chemistry.

Table I^a

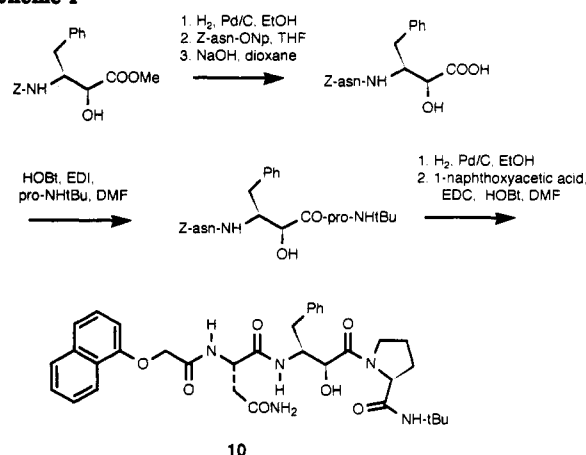
no.	stereochem at -CH(OH)-	structure	IC ₅₀ (nM)
1	S	Z-Phe-Ψ[CH(OH)C(O)N]Pro-NH ^t Bu	460
2	R	Z-Phe-Ψ[CH(OH)CH ₂ N]Pro-O ^t Bu	6500 ^b
3		Z-Phe-Ψ[C(O)C(O)N]Pro-NH ^t Bu	600
4	S	Z-Asn-Phe-Ψ[CH(OH)C(O)N]Pro-NH ^t Bu	7.4 (<i>K_i</i> = 4) ^c
5	R	Z-Asn-Phe-Ψ[CH(OH)C(O)N]Pro-NH ^t Bu	3100
6		Z-Asn-Phe-Ψ[C(O)C(O)N]Pro-NH ^t Bu	20
7	S	Z-Val-Phe-Ψ[CH(OH)C(O)N]Pro-NH ^t Bu	4.3
8	S	Z-Asn-Phe-Ψ[CH(OH)C(O)N]PIC-NH ^t Bu	26
9	S	Z-Asn-Phe-Ψ[CH(OH)C(O)N]DIQ-NH ^t Bu	84
10	S	NoA-Asn-Phe-Ψ[CH(OH)C(O)N]Pro-NH ^t Bu	0.58 (<i>K_i</i> = 0.4)
11	S	NoA-Val-Phe-Ψ[CH(OH)C(O)N]Pro-NH ^t Bu	1.9
12	S	2-NoA-Asn-Phe-Ψ[CH(OH)C(O)N]Pro-NH ^t Bu	1.3
13	S	QC-Asn-Phe-Ψ[CH(OH)C(O)N]Pro-NH ^t Bu	1.1 (<i>K_i</i> = 0.9)
14	S	QC-Asn-Phe-Ψ[CH(OH)C(O)N]DIQ-NH ^t Bu	27
15	R	Z-Asn-Phe-Ψ[CH(OH)CH ₂ N]Pro-O ^t Bu	140, ^b 51, ^d 130 ^e
16	R	Z-Asn-Phe-Ψ[CH(OH)CH ₂ N]Pro-Ile-Val-OMe	>>100 ^b
17	R	Boc-Asn-Phe-Ψ[CH(OH)CH ₂ N]Pro-Ile-Val-OMe	850 ^d
18	S	Z-Asn-Phe-Ψ[CH(OH)CH ₂ N]Pro-O ^t Bu	300, ^b 450, ^d 180 ^e
19	S	Z-Asn-Phe-Ψ[CH(OH)CH ₂ N]Pro-Ile-Val-OMe	13 ^b
20	S	Boc-Asn-Phe-Ψ[CH(OH)CH ₂ N]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, [(4*aS*,8*aS*)-decahydroisoquinolin-3(*S*)-yl]carbonyl; NoA, (naphthoxy)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 P₁-carbonyl imparts incremental gains in potency as exemplified by IC₅₀ 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

Scheme I



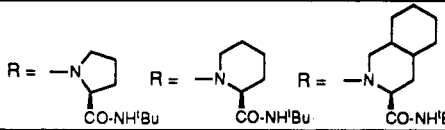
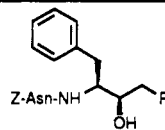
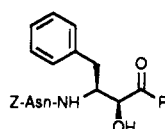
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corresponding norstatine analogues 1 and 4, respectively. For an interaction which might be assumed to be analogous, Rich has established that the inhibition of pepsin by peptidyl ketones is due to the formation of a tight binding hydrate catalyzed 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-

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Table II. Variations in the P₁' Substituent: Effects on Potency Are Not Parallel for Hydroxyethylamine Isosteres and Hydroxyamide Isosteres^a

		
210 nM ^b (23)	18 nM ^b (24)	<2.7 nM ^b (25)
		
7 nM (4)	26 nM (8)	84 nM (9)
		

^a All P₁' 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 IC₅₀ 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 P₁'-terminal peptides to P₃' with Ile-Val (cf. 15 vs 16 or 17, whereby IC₅₀ increases significantly, with 18 vs 19 or 20, whereby IC₅₀ 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 IC₅₀ 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 [(4*aS*,8*aS*)-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 P₁' pocket than are residues in the hydroxyethylamine series, because of the need to maintain a specific interaction for the P₁ 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 P₁' 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 sub-

stituent 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 P₁' pocket, the conformational requirements of the piperidine rings in the norstatine series might not permit optimal placement of functionality in the region of P₁' 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 molecule²⁷ that connects inhibitors to the flap region, imposes constraints on the complex which account 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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