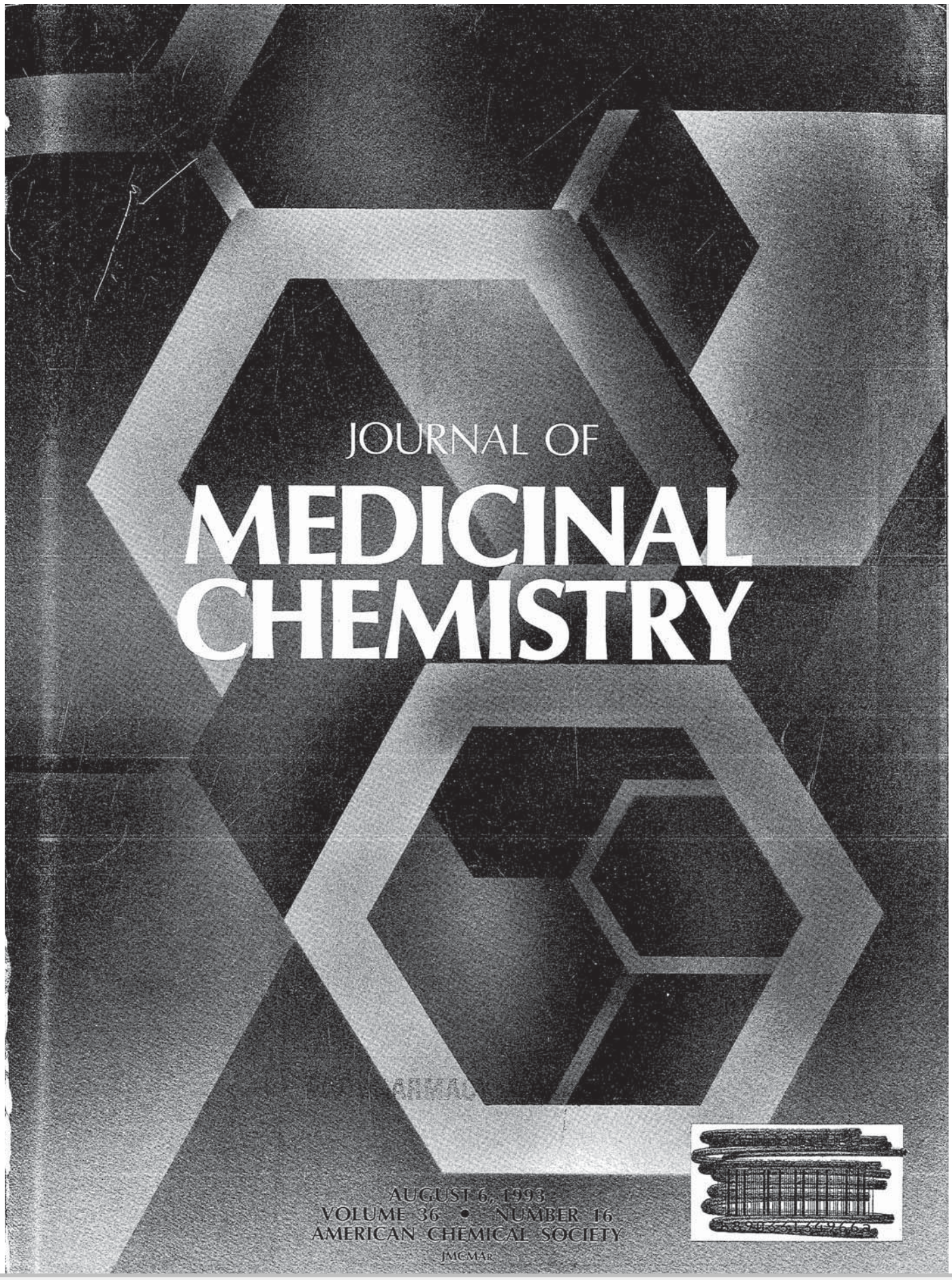

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Potent HIV Protease Inhibitors: The Development of Tetrahydrofuranylglycines as Novel P_2-Ligands and Pyrazine Amides as P_3-Ligands

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A series of protease inhibitors bearing constrained unnatural amino acids at the P_2-position and novel heterocycles at the P_3-position of compound **1** (Ro 31-8959) were synthesized, and their in vitro enzyme inhibitory and antiviral activities were evaluated. Replacement of P_2-asparagine of compound **1** with (2*S*,3′*R*)-tetrahydrofuranylglycine resulted in improvement in enzyme inhibitory as well as antiviral potencies (compound **23**). Interestingly, incorporation of (2*S*,3′*S*)-tetrahydrofuranylglycine at the P_2-position proved to be less effective. The resulting compound **24** was 100-fold less potent than the 2*S*,3*R*-isomer (compound **23**). This stereochemical preference indicated a hydrogen-bonding interaction between the tetrahydrofuranyl oxygen and the residues of the S_2-region of the enzyme active site. Furthermore, replacement of P_3-quinolinoyl ligand of **1** with various novel heterocycles resulted in potent inhibitors of HIV proteases. Of particular interest, compound **2** with (2*S*,3′*R*)-tetrahydrofuranylglycine at P_2 and pyrazine derivative at P_3 is one of the most potent inhibitors of HIV-1 (IC_{50} value 0.07 nM) and HIV-2 (IC_{50} value 0.18 nM) proteases. Another important result in this series is the identification of compound **27** in which the P_2–P_3-amide carbonyl has been removed. The resulting compound **27** has exhibited improvement in antiviral potency while retaining the enzyme inhibitory potency similar to compound **1**.

The inhibition of the enzyme HIV-1 protease, which cleaves the *gag* and *gag-pol* polyproteins into the functional proteins of infectious virions, continues to be a major therapeutic target for the treatment of AIDS and related ailments.[1] Of the numerous potent protease inhibitors that have been reported recently,[2] the present clinical candidate (2*S*,4a*S*,8a*S*,2′*R*,3′*S*)-*N*-*tert*-butyl-2-(2′-hydroxy-4′-phenyl-3′-((*N*-(2-quinolinylcarbonyl)-L-asparaginyl)-amino)butyl)decahydroisoquinoline-3-carboxamide (**1**) (Ro 31-8959) is particularly unique because of its effectiveness against both the enzymes HIV-1 and HIV-2 proteases.[3] Since these are the genetically most divergent strains of HIV known to exist to date, a protease inhibitor with this property may result in reduced susceptibility to clinical resistance. Subsequently, we have investigated the effect of incorporation of conformationally constrained unnatural amino acids in place of asparagine at the P_2 subsite of compound **1**. As reported in a recent paper,[4] the replacement of asparagine with (2*S*,3′*R*)-tetrahydrofuranylglycine not only increased the enzyme affinities for HIV-1 and HIV-2 proteases but led to significant enhancement of antiviral potencies compared to **1**. We now report the synthesis, enzyme inhibition, and antiviral potencies of a structurally novel class of protease inhibitors in which various constrained unnatural amino acids and novel heterocyclic derivatives were incorporated at the P_2- and P_3-positions of the present clinical candidate **1** (Ro 31-8959). This study has resulted in protease inhibitors with improved enzyme inhibitory and antiviral potencies. Particularly noteworthy is the inhibitor **2** which is very potent against HIV-1 (IC_{50} = 0.07 nM) and HIV-2 (IC_{50} = 0.18 nM).

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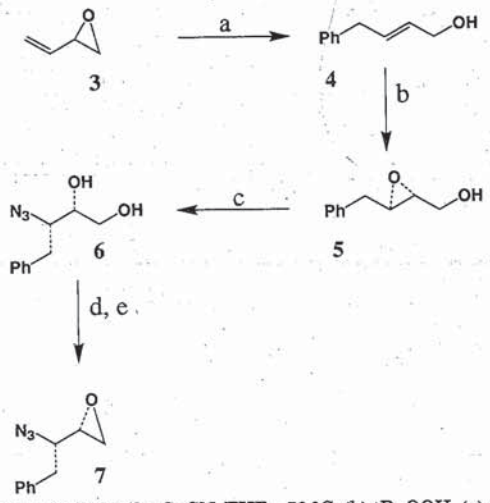
§ Department of Molecular Biology.
⊥ Department of Virus and Cell Biology.

Scheme I. Synthesis of Azido Epoxide[a]



[a] Key: (a) PhMgBr, CuCN, THF, −78 °C; (b) tBuOOH, (−)-DET, $Ti(OiPr)_4$, CH_2Cl_2, −22 °C; (c) $Ti(OiPr)_2(N_3)_2$, PhH, 80 °C; (d) $AcOCMe_2COCl$, $CHCl_3$, 23 °C; (e) NaOMe, THF, 23 °C.

Chemistry

The desired (2*R*,3*S*)-azido epoxide **7** was prepared as shown in Scheme I. The commercially available butadiene monoxide **3** was converted to allylic alcohol **4** by reaction with phenylmagnesium bromide in the presence of a catalytic amount of cuprous iodide. The allylic alcohol **4** was then subjected to the Sharpless epoxidation[5] condition with (−)-diethyl D-tartrate to furnish the epoxide **5**. Regioselective ring opening of epoxide **5** with diisopropoxytitanium diazide in benzene at 75 °C, as described by Sharpless and co-workers,[6] afforded the azidodiol **6** in very good yield. Azidodiol **6** was then converted efficiently to the desired azidoepoxide **7** by treatment with 2-acetox-

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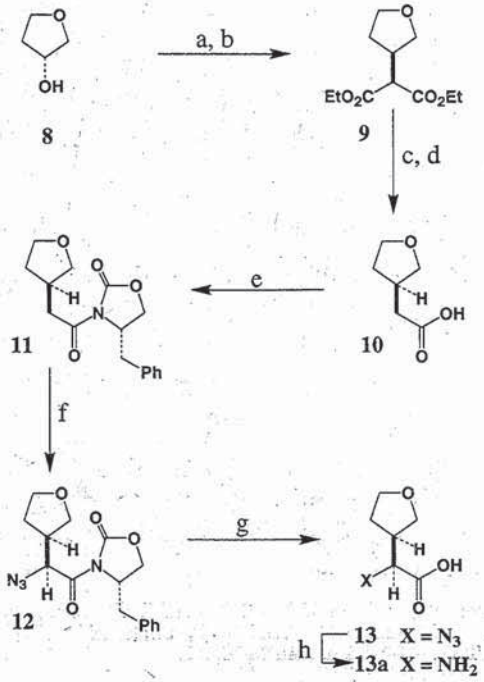
Scheme II. Synthesis of Amino Acid[a]

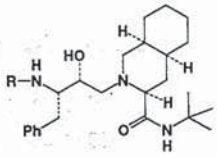


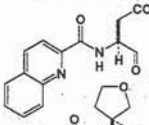
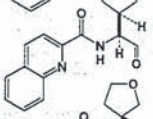
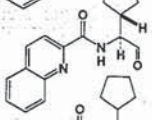
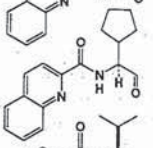
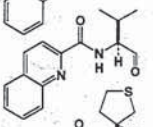
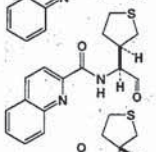
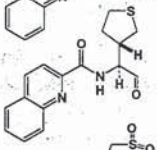
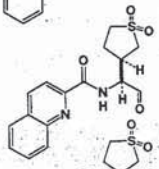
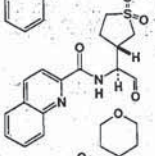
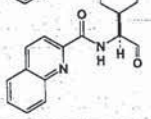
[a] Key: (a) MsCl, Et_3N, CH_2Cl_2, −10 °C; (b) NaH, $CH_2(CO_2Et)_2$, DMF; (c) 1 N NaOH then H_3O^+; (d) Cu_2O (cat), CH_3CN, 80 °C; (e) Me_3COCl, Et_3N, THF, −78 °C then *N*-lithio-(*S*)-(−)-4-benzyloxazolidinone; (f) $KN(TMS)_2$, THF, −78 °C, 30 min, then trisyl azide, −78 °C, 2 min, then AcOH, 30 °C, 1 h; (g) LiOH, THF–H_2O; (h) 5% Pd–C, EtOH–H_2O.

yisobutyryl chloride in chloroform at 23 °C followed by exposure of the resulting chloroacetate derivative to an excess of sodium methoxide in tetrahydrofuran at 23 °C for 3 h.[7]

The synthetic route leading to the (2*S*,3′*R*)-tetrahydrofuranylglycine equivalent is described in Scheme II. Readily prepared[8] enantiomerically pure (*S*)-(+)-3-hydroxytetrahydrofuran (**8**) was mesylated with mesyl chloride and triethylamine in methylene chloride at 0 °C for 20 min. Displacement[9] of the resulting mesylate with the sodium salt of diethyl malonate in DMF at 100 °C furnished the malonate derivative **9**. Ester hydrolysis followed by copper ion promoted decarboxylation[10] furnished the (*R*)-tetrahydrofuranylacetic acid (**10**) in very good yield. The highly diastereoselective azidation protocol developed by Evans[11] was then employed to introduce the α-amine functionality. Thus, deprotonation of the (*S*)-(−)-4-benzyloxazolidinone with n-BuLi followed by acylation with the mixed anhydride resulting from the reaction of acid **10** with pivaloyl chloride in the presence of triethylamine provided the carboximide **11** after silica gel chromatography. Treatment of this carboximide with potassium hexamethyldisilazide in tetrahydrofuran at −78 °C for 30 min provided the potassium enolate which was reacted with trisyl azide at −78 °C for 2 min and then quenched with glacial acetic acid and warmed to 30 °C. The α-azido carboximide thus obtained was purified by silica gel chromatography to furnish the azide **12** as a single diastereomer by HPLC and ^{1}H-NMR (400-MHz) analysis. Removal of the chiral auxiliary was effected by exposure to lithium hydroxide in aqueous tetrahydrofuran to provide the desired acid **13**. The resulting azido acid was hydrogenated over 5% palladium on charcoal in a mixture of ethanol and water (2:1) to furnish the amino acid **13a**. The corresponding (2*S*,3′*S*)-tetrahydrofuranylglycine equivalent was obtained utilizing (*R*)-(−)-3-hydroxytetrahydrofuran as the starting material. Similarly, diastereomeric azido acid **28** and other cyclic amino acids utilized in Table I were prepared following a similar course of reaction as described in Scheme II. Various pyrazine derivatives were synthesized as shown in Scheme III. The known[12] dichloropyrazine derivative **14** was heated with dimethylamine or 1-methyl piperazine in 2-propanol at 85 °C for 12 h to furnish the pyrazine derivative **15a** or **15b**. Hydrolysis of the corresponding methyl ester with aqueous NaOH in ethanol and subsequent acidification provided the acid derivative. For the preparation of pyrazine derivative **17**, pyrazine **15b** was first converted to bromide

Table I. Structure and Inhibitory Potencies of Various Constrained P_2-Ligands



Compd	R	IC_{50} (nM)	CIC_{95} (nM)
1.		0.23±0.1 (n=3)	22±7 (n=10)
23.		0.054±0.027 (n=4)	8±4 (n=8)
24.		5.4	100
25.		2.6	---
26.		0.7	100
31.		0.6	50
32.		3.3	>200
33.		0.5	---
34.		39	---
35.		67.9	---

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