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POTENT HIV PROTEASE INHIBITORS INCORPORATING HIGH-AFFINITY P_2-LIGANDS AND (*R*)-(HYDROXYETHYLAMINO)SULFONAMIDE ISOSTERE

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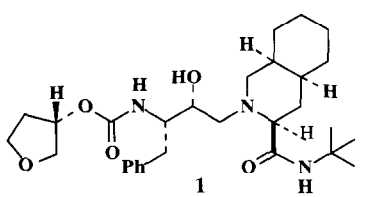
Abstract: Design and synthesis of a series of very potent nonpeptide HIV protease inhibitors are described. The inhibitors are derived from novel high affinity P_2-ligands and (*R*)-(hydroxyethylamino)sulfonamide isostere.

Recent approval of HIV protease inhibitors in combination with reverse transcriptase inhibitors has marked a new era of AIDS chemotherapy.[1] The new therapies have changed the course of HIV management and the progression of AIDS. However, the major new challenges are now to eliminate substantial 'peptide-like' character as well as to combat the emergence of resistance to these protease inhibitors.[2] In recognition of these problems, recent research efforts have been devoted to the design and synthesis of nonpeptidal protease inhibitors that are potent against mutant strains resistant to the currently approved protease inhibitors.[3] Successful execution of this approach may substantially delay the emergence of resistant clinical HIV strains and at the same time alleviate the problems of 'peptide-like' character.

As part of our continuing efforts, we recently designed a number of nonpeptidal high-affinity ligands for the HIV protease substrate binding site, based upon various available three-dimensional structures of the protein-ligand complexes.[4] One of the important elements of our ligand design is to incorporate stereochemically defined and conformationally constrained cyclic ether and cyclic sulfone functionalities that will replace peptide bonds and mimic the biological mode of action. As we have previously demonstrated, incorporation of these designed nonpeptidal ligands into Ro 31-8959[1a] based hydroxyethylamine isosteres resulted in HIV protease inhibitors that are potent, selective and orally bioavailable in laboratory animals.[4] As exemplified, a stereochemically



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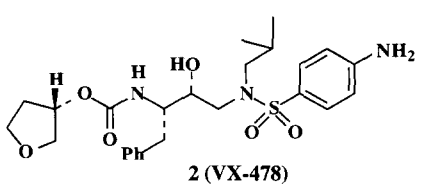

2 (VX-478)

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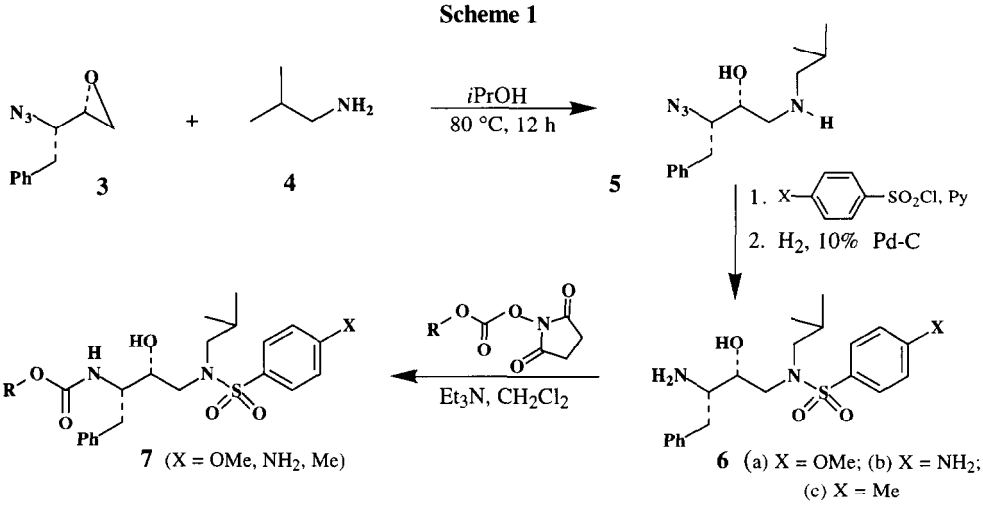
defined 3(*S*)-tetrahydrofuran ring can serve as a surrogate (inhibitor **1**, K_i = 87 nM) for the asparagine side chain of Ro 31-8959.[4h] Incorporation of this 3(*S*)-tetrahydrofuran ligand by Vertex Laboratories in (*R*)-(hydroxyethyl)sulfonamide based isostere however, afforded very potent and orally active inhibitor **2** (VX-478) which is currently in advanced clinical trials.[5] Encouraged by this report, we subsequently investigated the potency enhancing effect of other structurally novel high-affinity ligands in the in (*R*)-(hydroxyethyl)sulfonamide based isostere.[5,6] Herein we report that the incorporation of the novel P_2-ligands in sulfonamide isosteres provided a series of very potent and nonpeptidal HIV protease inhibitors.

The synthesis of various inhibitors with the novel P2-ligands is outlined in Scheme 1. The previously described[4f] azido epoxide **3** was reacted with isobutylamine in 2-propanol at 80 °C for 12 h to afford azidoalcohol **5**. Treatment of **5** with *p*-methoxybenzenesulfonyl chloride and *p*-nitrobenzenesulfonyl chloride in the presence of aqueous $NaHCO_3$ provided the corresponding azides. The resulting azides were hydrogenated over 10% Pd-C in ethyl acetate to afford the amine **6a**, **6c**, and diamines **6b**, respectively (75-78% overall from **3**). Above amines were transformed into the various target inhibitors **7** listed in Table 1 by an alkoxycarbonylation of the respective known[4] optically pure alcohol with the mixed carbonates in methylene chloride in the presence of 3 equiv of triethylamine at 23 °C for 12 h (80-85%).[7]

Scheme 1



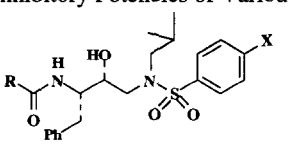
3 **4** **5**

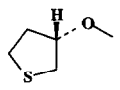
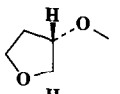
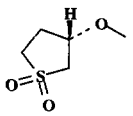
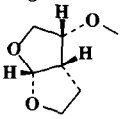
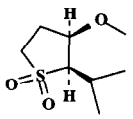
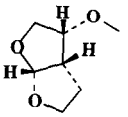
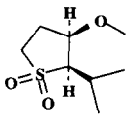
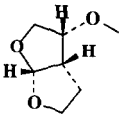
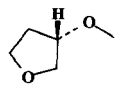
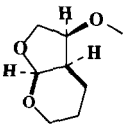
7 (X = OMe, NH_2, Me)

6 (a) X = OMe; (b) X = NH_2; (c) X = Me

As shown in Table 1, incorporation of urethane of 3(*S*)-hydroxytetrahydrothiophene as the P_2-ligands provided the inhibitor **8** with enzyme inhibitory potency (K_i) of 2.5 nM in enzyme inhibitory assay as developed by Toth and Marshall.[8] Inhibitor **8** has prevented the spread of HIV-1 in MT4 human T-lymphoid cells infected with IIIB isolate at a concentration of 47 nM (ID_{50}).[9, 10] Consistent with our earlier observation, oxidation of the ring sulfur to the sulfolane derivative **9** resulted in enhancement of both enzyme inhibitory as well as antiviral potencies.[4d] Incorporation of 2(*R*),3(*R*)-isopropylsulfolane has also resulted in potent protease inhibitors. Unlike Ro 31-8959 derived hydroxyethylamine series, incorporation of the *cis*-isopropyl substituent did not provide significant potency enhancement. Interestingly however, the 4-methoxybenzenesulfonamide derivative

Table 1. Structure and Inhibitory Potencies of Various Protease inhibitors[a]



Compd	R	X	K_i (nM)	ID_{50} (nM)	Compd	R	X	K_i (nM)	ID_{50} (nM)
8		OMe	2.5	47	**2**		NH_2	1.6	15
9		OMe	1.2	19	**13**		NH_2	2.1	4.5
10		OMe	1.4 ± 0.2 (n = 3)	18	**14**		OMe	1.1 ± 0.4 (n = 4)	1.4 ± 0.25 (n = 5)
11		NH_2	1.5	40	**15**		CH_3	1.2	3.5 (n = 2)
12		OMe	1.5	12	**16**		OMe	2.2	4.5

[a] Inhibitor **17** (Ro-31-8959)[1c] displayed, K_i = 1.4 ± 0.2 nM (n = 3) and ID_{50} = 18 nM (n = 2) in this assay.

10 (ID_{50} = 18 nM) has shown enhanced antiviral activity compared to inhibitor **11** (ID_{50} = 40 nM) which contains 4-aminobenzenesulfonamide similar to VX-478 sulfonamide isostere.[5] Consistent with this observation, 4-methoxysulfonamide derivative **12** exhibited enhanced antiviral potency compared to **2** (VX-478). Introduction of a stereochemically defined 3(*R*),3a(*S*),6a(*R*)-bis-tetrahydrofuranyl urethane (bis-THF) in the sulfonamide isostere afforded extremely potent inhibitor **14** with K_i = 1.1 ± 0.4 nM (n = 4) and ID_{50} = 1.4 ± 0.25 nM (n = 5).[11] Again, 4-methoxybenzenesulfonamide is more potent than the 4-aminobenzenesulfonamide **13** or the toluenesulfonamide **15**. Inhibitor **16** with 3(S),3a(S),7a(S)-hexahydrofuropyranyl urethane has also exhibited remarkable in vitro properties. In an effort to gain insight into the ligand binding site interactions, modeled energy-minimized structures of the inhibitors **13** and **14** were created in the VX-478 inhibited HIV-1 active site.[5] It appeared that both oxygen atoms of the bis-THF ligands of **13** and **14** are within hydrogen bonding distance to ASP 29 and Asp 30 NH and the 4-methoxyl oxygen of inhibitor **14** is within hydrogen-bonding distance to ASP 29' and Asp 30' NH and this may account for the potency enhancing effect of the 4-methoxy derivative.

In conclusion, incorporation of novel nonpeptidal ligands in the (*R*)-(hydroxyethyl)sulfonamide isostere has provided a series of very potent and structurally diverse protease inhibitors. Further optimization as well as in-depth biological studies of the selected protease inhibitors are the subject of our ongoing investigation.

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11. Inhibitor **14** has exhibited enzymatic K_i = 0.016 nM and antiviral cell RNA-IC_{90} = 0.71 nM in the assay protocol developed at the Dupont Merck Company; personal communication: Dr. Susan Erickson-Viitanen.