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CYCLIC SULFONE-3-CARBOXAMIDES AS NOVEL P_2-LIGANDS FOR Ro 31-8959 BASED HIV-1 PROTEASE INHIBITORS

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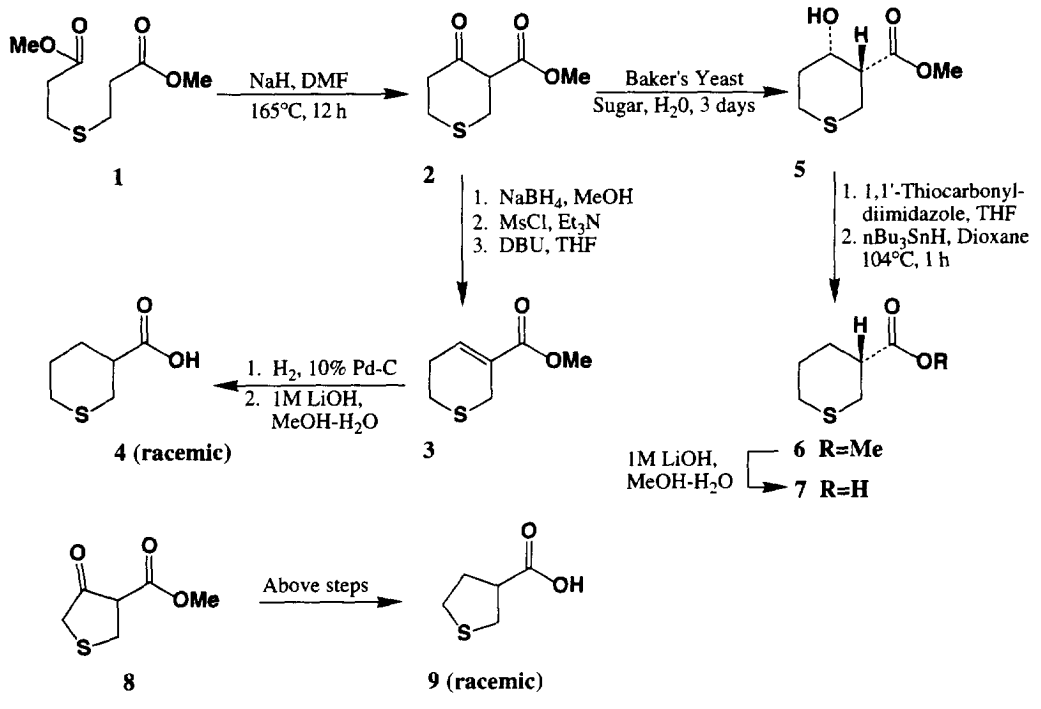
Abstract: Cyclic sulfone-3-carboxamides are effective P_2-ligands for HIV-1 protease inhibitors. Incorporation of 3S-tetrahydro-2H-thiopyrancarboxamide-1,1-dioxide in the hydroxyethylamine series resulted in inhibitor **14** (IC_{50}=9 nM, CIC_{95}=200 nM) with improved potency compared to its corresponding urethane derivative **18** (IC_{50}=2.0 μM).

As part of our continuing efforts in search of a suitable replacement for the N-terminus peptide group, we recently reported that the urethanes of 3-hydroxy tetrahydrofurans and sulfolanes are effective high affinity ligands for the HIV-1 protease substrate binding site.[1] Subsequently, we have searched for effective N-terminus heterocyclic amides as the P_2-ligands to replace the N-terminus peptides. In this letter, we report that the extension of our N-terminus cyclic sulfone urethanes to the corresponding N-terminus carboxamide leads to potent inhibitors of HIV-1 protease. Of particular interest, inhibitor **14** with 3S-tetrahydro-2H-thiopyrancarboxamide-1,1-dioxide as the P_2-ligand has exhibited a 190-fold enzyme inhibitory potency enhancement compared to its corresponding 3S- or 3R-tetrahydrothiopyranyloxycarbonyl derivatives. Presumably, the sulfone oxygens are involved in hydrogen bonding interactions with the residues in the S_2-region similar to the sulfone urethanes as described previously.[2]

The synthetic routes to various ligands are outlined in Scheme 1. Dieckman cyclization of the commercially available dimethyl-3,3'-thiodipropionate **1** with sodium hydride in refluxing DMF for 12 h afforded the b-ketoester **2** in 64% yield. The ketoester **2** was converted to dihydrothiopyran **3** by the following three-step sequence: (1) sodium borohydride reduction in methanol, (2) mesylation of the resulting alcohol with mesyl chloride and triethylamine, and (3) elimination of the corresponding mesylate with DBU in THF at 23°C for 12 h (35% from **2**). Catalytic hydrogenation of **3** over palladium on charcoal under 50 psi hydrogen pressure for 3

days furnished the corresponding saturated methyl ester which upon saponification with aqueous lithium hydroxide and acidification afforded the racemic acid **4** in 65% yield. The synthesis of racemic tetrahydrothiophene-3-carboxylic acid **9** was carried out from the known[3] thiolanone **8**, following the similar course of reactions as described above. Optically active 3R-tetrahydro-2H-thiopyrancarboxylic acid **7** was prepared from the b-ketoester **2**. Reduction of **2** by baker's yeast according to the procedure of Hoffmann and coworkers[4] afforded the hyroxy ester **5** in 71% yield (88% ee).[5] The deoxygenation of the 4-hydroxyl group was effected utilizing Barton's procedure.[6] Thus, reaction of hydroxyester **5** with 1.2 equiv. 1,1'-thiocarbonyldiimidazole in THF in the presence of 0.5 equiv. of pyridine afforded the corresponding thioimidazolide. Tri-n-butyltin hydride reduction of the imidazolide in refluxing dioxane in the presence of a catalytic amount of AIBN resulted in the deoxygenated product **6** (53% isolated yield in two steps) and a small amount (3-5%) **3** which was separated by silica gel chromatography.

Scheme 1



Various inhibitors with cyclic sulfone-3-carboxamides as the P_2-ligands were synthesized according to the Scheme 2. Coupling of the racemic acid **4** and the optically pure amine **10** with N-ethyl-N'-(3-(dimethylamino)-propyl)carbodiimide hydrochloride, triethylamine and 1-hydroxybenzotriazole hydrate in DMF furnished the mixture (1:1) of diastereomers **11** and **12** which were separated by silica gel chromatography.[7] The stereochemical assignment of the 3-position of the tetrahydrothiopyran rings of the isomers **11** and **12** was established following the coupling of the optically pure acid **7** with the amine **10** which has provided only the isomer **11**. Similarly, the assignment of stereochemistry of **19** and **20** was made based on comparison of ^1H NMR (300 MHz) spectra of **11** and **12**. The chemical shifts of the α-carboxamide ring protons of **11** and **12** were 2.4 and 2.5 ppm respectively. The corresponding chemical shifts of compounds **19** and **20** were 2.2 and 2.3 ppm.

Scheme 2

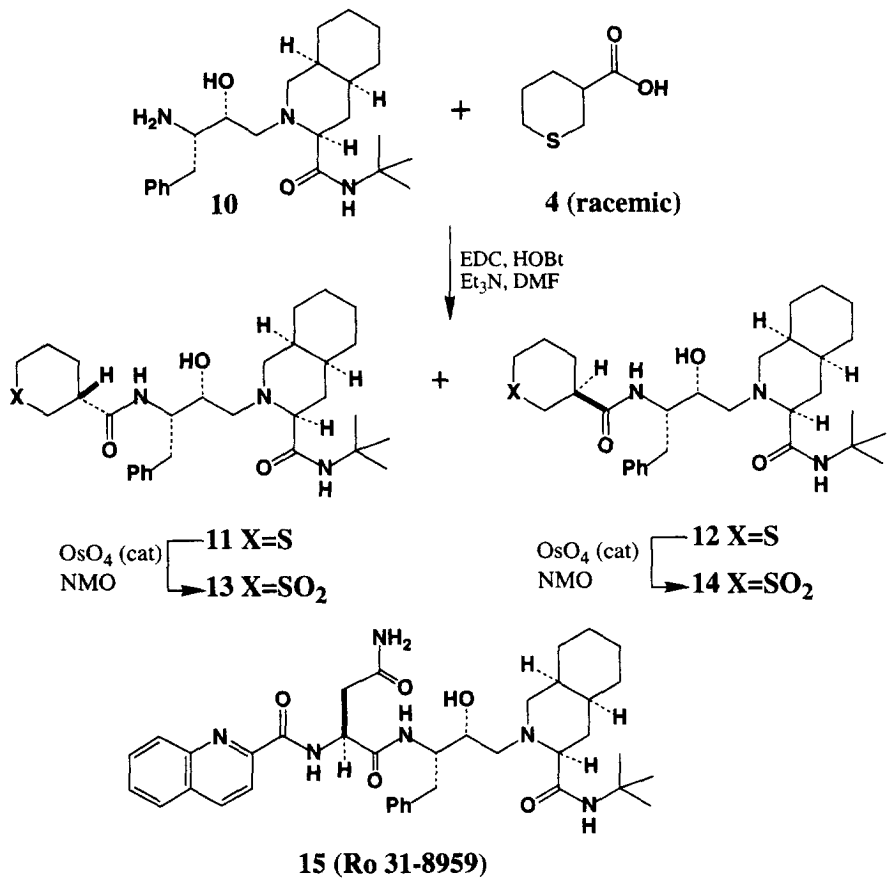
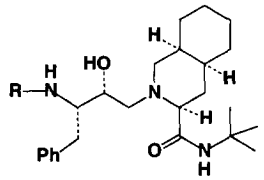
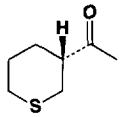
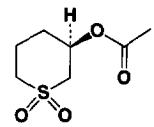
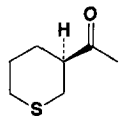
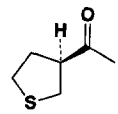
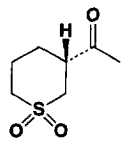
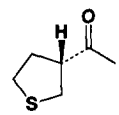
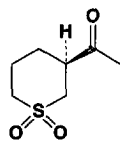
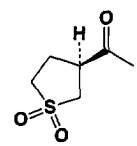
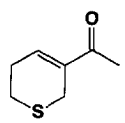
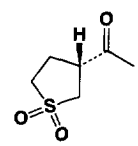
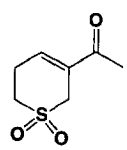
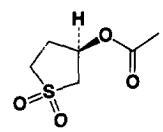
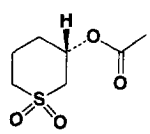
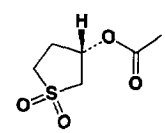


Table I: Structure and Inhibitory Potencies of Various Sulfone Derivatives



Comp.	R	IC_{50}[a] (nM)	Comp.	R	IC_{50}[a] (nM)
11.		98.8	**18.**		2068[b]
12.		78.4	**19.**		342
13.		23.5±2.5 (n=2)	**20.**		650
14.		9.2 ±0.2 (n=2)	**21.**		200
15.		167.4	**22.**		193
16.		54.7	**23.**		140[b]
17.		1745[b]	**24.**		76±12[b] (n=14)

[a] Inhibitor **14** (Ro-31-8959)[9] displayed an IC_{50} value of 0.23 nM (± 0.1, n=3) in this assay system.[10] [b] Previously published (see reference 1c).

The ring sulfur of these inhibitors was selectively oxidized to the corresponding sulfone derivative by exposure to a catalytic amount of OsO_4 and an excess of 4-methylmorpholine N-oxide in a mixture of acetone and water (3;1) as described previously.[1b,c]

As shown in Table I, incorporation of 3S- and 3R-tetrahydrothiopyran carboxamide as the P2-ligands provided the inhibitors **11** and **12** with enzyme inhibitory potencies (IC_{50}) of 78.4 nM and 98.8 nM respectively. As was observed in the urethane series, oxidation of the ring sulfur to the corresponding sulfone derivative resulted in significant potency enhancement. The inhibitor **13** has exhibited an IC_{50} value of 23.5 nM, a 4-fold increase over its sulfide **11**. The oxidation of the ring sulfur in **12** afforded the most potent compound in the present series. Compound **14** (IC_{50}=9 nM) has shown a greater than 8-fold improvement over its sulfide **12**. In contrast to its corresponding 3S- and 3R-urethanes (compounds **17** and **18**), inhibitor **14** with 3S-carboxamide has gained an impressive 190-fold potency enhancement. Also, it is 8-fold more potent than the unsubstituted sulfolane urethane **24** (IC_{50}=76 nM). In antiviral assay, inhibitors **13** and **14** have shown to prevent the spread of HIV-1 in MT4 lymphoid cells infected with IIIb isolate, at a concentration of 400 nM (CIC_{95}) and 200 nM respectively.[8] Based on our earlier observation in the urethane series, we presume that the reason for this improved inhibitory potency is due to favorable hydrophobic binding as well as hydrogen bonding interactions of the sulfone ring oxygens with the residues in the region. However, the actual understanding of such interactions should await the solution of the X-ray crystal structure of the protein-ligand complex. Incorporation of dihydrothiopyran carboxamide (compound **15**) and its sulfone derivative (compound **16**), both have exhibited reduction in potency. An examination of inhibitors **19-22** established that the five member ring sulfides and sulfones, unlike the urethane series, are much less preferred by the S_2-binding region of the enzyme active site than the corresponding six member heterocycles.

In summary, cyclic sulfone-3-carboxamides are effective replacements of the N-terminus peptides of which inhibitor **15** (Ro 31 8959)[9] is prototypical. Incorporation of 3S-tetrahydro-2H-thiopyran carboxamide as the P_2-ligand afforded the most potent inhibitor in the present series (compound **14** ; IC_{50}=9.2 nM; CIC_{95}=200 nM). Further optimization, particularly substitution of small alkyl chains in the sulfone ring as well as incorporation of these ligands in other transition-state isosteres may provide inhibitors with improved enzyme affinity and antiviral potency. Investigations along these lines are currently in progress.

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2. Examination of a preliminary X-ray crystal structure model of an enzyme-inhibitor complex of a sulfolane derivative (compound **43** in reference 1c) bound to HIV-1 protease revealed that the *cis* sulfone oxygen is within hydrogen bonding distance to the Asp 29 (distance 2.6 Å) and Asp 30 NH (distance 2.9 Å). Personal communication, Dr. Paula Fitzgerald, Merck Research Laboratories, Rahway, NJ 0765. Details of this experiment will be published in due course.
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