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Novel Cyclourethane-Derived HIV Protease Inhibitors: A Ring-Closing Olefin Metathesis Based Strategy

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Abstract—A series of novel macrocyclic urethanes incorporating a (*R*)-hydroxyethylamine isostere was designed and synthesized. Ring size and substituent efffects have been investigated. Cyclourethanes containing 14- to 16-membered rings exhibited low nanomolar inhibitory potencies against HIV-1 protease.

The current treatment regimen for AIDS consists of HIV protease and reverse transcriptase inhibitors.[1] In the context of design and synthesis of protease inhibitors, a number of structurally diverse acyclic urethane derived inhibitors with improved pharmacological properties have been reported.[2] Unlike acyclic urethanes, the biological importance of cyclourethanes has been hitherto unexplored. We recently reported a series of very potent nonpeptide HIV protease inhibitors incorporating structure-based designed novel, high affinity P_2-ligands and (*R*)-(hydroxyethylamino)sulfonamide isosteres.[3] Of particular note, inhibitor **1** (UIC-PI also known as TMC-126)[4] incorporating bis-tetrahydrofuran as the P_2-ligand has shown remarkable enzyme inhibitory and antiviral potencies ($K_i = 15 \pm 1$ pM, $n = 4$ and $ID_{50} = 1.4 \pm 0.25$ nM, $n = 5$) compared to inhibitor **2**, which contains the hydroxyethylamine isostere of saquinavir ($K_i = 2$ nM and $ID_{50} = 50$ nM).[5,6] In an effort to introduce further structural diversity as well as to explore the biological potential of cyclourethanes, we have designed macrocyclic urethanes as P_1'–P_2'-ligands for these inhibitors. Preliminary modeling studies of various cyclourethanes based upon the X-ray structure of saquinavir-bound[7] HIV protease reveal that 14- to 16-membered cyclourethane carbonyls could effectively hydrogen bond with the critical tight-bound water molecule as well as fill in the S_1'–S_2' binding sites. Herein, we report our preliminary results of these investigations. Cyclourethanes are generally more potent than their acyclic counterparts and a number of cyclourethanes exhibited low nanomolar inhibitory potencies against HIV-1 protease. Various cyclourethanes were conveniently prepared by *N*,*N*′-disuccinimidyl carbonate (DSC) promoted alkoxycarbonylation of amines followed by efficient ring-closing metathesis of the resulting dienes utilizing Grubbs' catalyst.[8]

The general synthesis of various acyclic urethanes containing (*R*)-hydroxyethylamine isosteres is illustrated in Scheme 1. Enantiomerically pure azido epoxide **3** has been prepared in multigram quantities as described previously.[9] Regioselective opening of epoxide **3** with allylamine and 3-butenylamine in isopropanol at reflux provided amino alcohols **4** and **5** (80 and 85%, respectively). For preliminary investigation, we have prepared unsubstituted and substituted cyclourethanes derived from commercially available 9-decene-1-ol **6** and corresponding derivative **7**. Alcohol **7** was prepared by Swern oxidation of **6** followed by reaction of the resulting aldehyde with phenyl magnesium bromide (85%, two steps). Alcohols **6** and **7** were converted to the respective mixed carbonates **8** and **9** by using *N*,*N*′-disuccinimidyl carbonate in the presence of triethylamine. Reaction of these carbonates with amines **4** and **5** furnished the corresponding azido urethanes which, upon reduction with triphenylphosphine in aqueous THF, provided respective amines **10** and **11** (70–74%, two steps).[10] Amine **11** contains a 1:1 mixture of diastereomers at the

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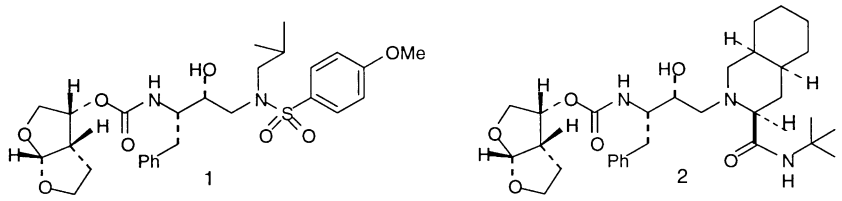
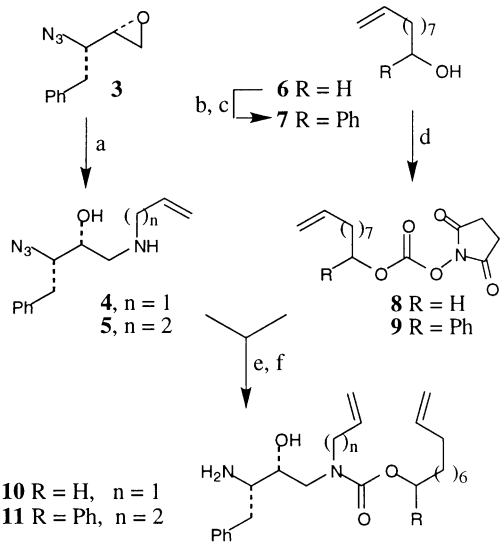
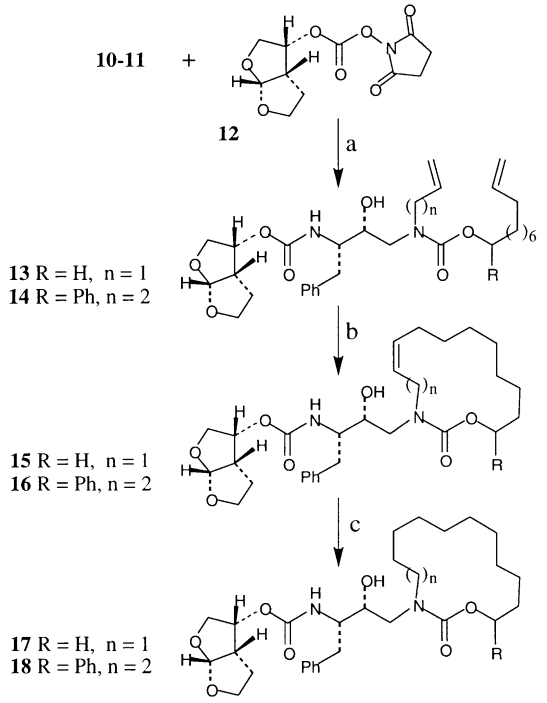


Figure 1.



Scheme 1. (a) $H_2N(CH_2)_nCH{=}CH_2$, *i*PrOH, 65 °C; (b) Swern oxidation, −60 °C; (c) PhMgBr, THF, 0 °C; (d) *N*,*N*′-disuccinimidylcarbonate, Et_3N, acetonitrile, 23 °C; (e) Et_3N, CH_2Cl_2, 23 °C; (f) Ph_3P, THF/H_2O (10:1), 23 °C.



Scheme 2. (a) Et_3N, CH_2Cl_2, 23 °C; (b) $Cl_2(PCy_3)_2{=}CHPh$ (10 mol%), $Ti(O^iPr)_4$ (30 mol%), CH_2Cl_2 (0.002 M solution), 23 °C; (c) H_2, 10% Pd/C, MeOH.

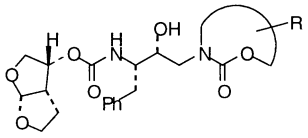
phenyl bearing center as racemic alcohol **7** was employed for urethane formation.

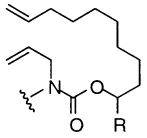
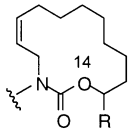
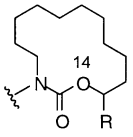
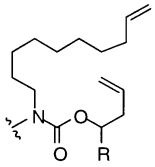
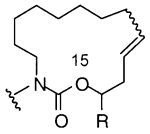
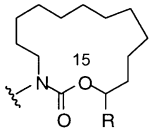
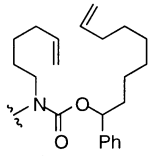
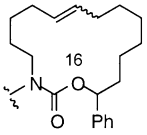
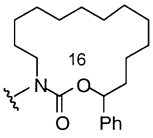
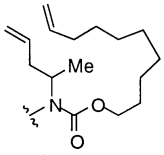
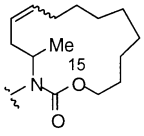
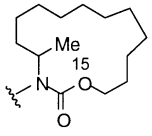
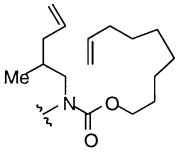
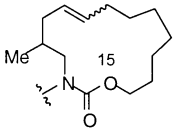
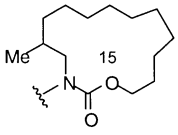
Preparations of the acyclic and corresponding cyclic macrourethanes derived from amines **10** and **11** are shown in Scheme 2. Alkoxycarbonylation of these amines with known optically active bis-tetrahydrofuranyl carbonate **12** afforded acyclic inhibitors **13** and **14** (1:1 mixture of diastereomers).

Exposure of acyclic urethanes **13** and **14** to commercial Grubbs' catalyst (10 mol%) in the presence of titanium isopropoxide (30 mol%) in CH_2Cl_2 (0.003 M solution) for 20 h at 23 °C afforded cyclourethanes **15** and **16** (1:1 *cis*/*trans* by ^1H NMR) after silica gel chromatography (69–78%).[11] Unsaturated cyclourethane **15** containing a 14-membered ring was obtained mainly as a single *cis*-isomer. Catalytic hydrogenation of the unsaturated cyclourethanes furnished saturated cyclic inhibitors **17** and **18**. Other inhibitors in Table 1 were prepared by analogous procedures.

The inhibitory potencies of various acyclic and cyclic urethanes in Table 1 were measured by the assay protocol of Toth and Marshall.[12] As can be seen, the acyclic inhibitors have shown very little inhibition. In contrast, the corresponding cyclic urethanes have shown significant activity against HIV protease. The saturated cyclourethanes are generally more potent than their corresponding unsaturated counterparts. Furthermore, ring size and substituents on the ring have pronounced effects on the inhibitory potencies. Both the 14- and 15-membered unsubstituted rings exhibited K_i values of 80 nM (**17**) and 14 nM (**24**), respectively. All alcohol **7**-derived 14- to 16-membered cyclourethanes have shown significant reduction in their respective K_i values. Since 15-membered cyclourethanes were the most potent, we have investigated the substituent effects of the corresponding α-alkyl cyclourethanes. The saturated α-methyl derivative is less potent than unsubstituted derivative **24**. Since the P_1'-isobutyl substitutent is optimum for inhibitors containing (*R*)-hydroxymethylsulfonamide isosteres, we have examined the substituent effect of the β-methyl cyclourethanes. For initial screening, a mixture of diastereomers (1:1) at the methyl bearing center of the cyclourethanes was evaluated in the HIV protease inhibition assay. Unsaturated (1:1 *cis*/*trans*) mixture **32** displayed a K_i value of 11 nM. The corresponding 15-membered saturated cyclourethanes **33**, containing a mixture of diastereomers

Table 1. Structure and inhibitory potencies of various acyclic and cyclic inhibitors[a]



Compd		K_i (nM)	Compd		K_i (nM)	Compd		K_i (nM)
13 R = H **19** R = Ph		> 1000 > 1000	**15** R = H **20** R = Ph		125 229	**17** R = H **21** R = Ph		80 189
22 R = H **14** R = Ph		> 1000 > 1000	**23** R = H **16** R = Ph		88 167	**24** R = H **18** R = Ph		14 357
25		444	**26**		162	**27**		268
28		> 1000	**29**		53	**30**		30
31		> 1000	**32**		11	**33**		6.1

[a]In-house prepared saquinavir[6] displayed $K_i = 0.12 \pm 0.01$ nM ($n = 3$) in this assay.

at the methyl center (K_i value of 6.1 nM), are significantly more potent than unsubstituted 15-membered cyclourethane **24**. Subsequently, stereodefined syntheses of both diastereomers of **33** were carried out from known 2-(*R*)- and 2-(*S*)-methyl-4-penten-1-ol.[13] The diastereomer-containing *S*-methyl configuration ($K_i = 8.9$ nM) is nearly 3-fold more potent than the *R*-isomer ($K_i = 25.8$ nM). Inhibitor **33** prevented the spread of HIV-1 in MT_4 human T-lymphoid cells infected with IIIB isolate at a concentration of 2.5 μM (ID_{50}).[14]

In summary, incorporation of cyclourethane functionality at P_1'–P_2' resulted in a novel series of structurally diverse protease inhibitors. Interestingly, cyclourethanes in general are considerably more potent than their acyclic counterparts. A substituent at the α-position on the ring appears detrimental to potency. Saturated 15-membered cyclourethane **33** is thus by far the most potent in this series with a K_i value of 6.1 nM. Chemical modifications of these inhibitors and further design are currently underway.

Acknowledgements

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