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SYNTHESIS AND EVALUATION OF DELTA LACTAMS AS NONPEPTIDE HIV-PROTEASE INHIBITORS

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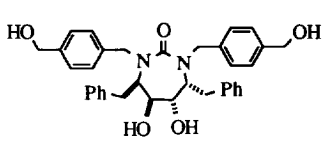
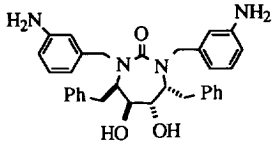
Abstract: The cyclization of the linear hydroxyethylene isostere based HIV-PR inhibitors gave the delta lactam **XQ921,** which was found to have a K_i = 9.4 uM. It is proposed that a major reason for the weaker potency of the lactam **XQ921** compared to cyclic urea based inhibitors is the lack of a P1' substituent that could interact with the S1' pocket of HIV-PR. © 1997 The DuPont Merck Pharmaceutical Company. Published by Elsevier Science Ltd.

The chemotherapeutic treatment[1] of AIDS has recently reached a milestone with the approval of the HIV-protease inhibitors Saquinavir (Roche), Ritonavir (Abbott), and Indinavir (Merck) by the FDA. In recent clinical studies these inhibitors have been shown to be very effective, especially in combination with reverse transcriptase (RT) inhibitors,[2] in reducing viral load and increasing $CD4^+$ lymphocyte counts. However, the ability of the virus to rapidly generate resistant mutants[3] suggests that there is an ongoing need for new, structurally diverse, HIV-PR inhibitors.

Workers at Dupont Merck recently described the rational design of a class of novel and highly potent cyclic urea inhibitors.[4] This work resulted in the identification of two clinical candidates in the cyclic urea series, **DMP 323**[5] and **DMP 450**.[6]



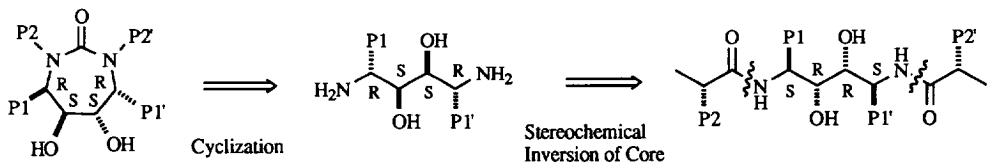
DMP 323



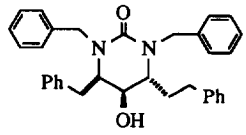
DMP 450

A "Reverse -Design Analysis" of the cyclic ureas revealed that it was "simply" a cyclized version of a potent linear inhibitor. It became apparent that in practice the sequence of events needed to get to the cyclic inhibitor starting from the linear inhibitor is (1) invert all the stereo centers of the transition state isostere core and (2) cyclize to give the cyclic compound (Figure 1). We became interested in investigating the generality of this cyclization process and in determining its scope. To address these issues we have applied this cyclization process to other linear HIV-PR inhibitors.

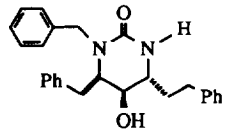
Figure 1



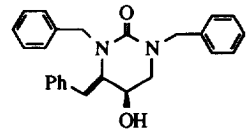
Recently, we reported our work on the cyclization of the diamino alcohol class of inhibitors to give tetrahydropyrimidinones, such as **1**, and showed that these 6-membered ring analogs were nearly equipotent to the 7-membered ring cyclic ureas.[7] In this paper we wish to report some of our results on applying this process to very common hydroxyethylene isostere class of linear HIV protease inhibitors.



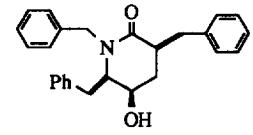
1
K_i = 15 nM



2
K_i = 66 nM



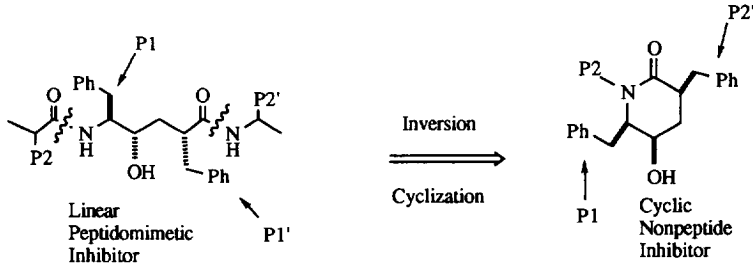
5
K_i = 2.5 uM



4
K_i = 9.4 uM

Inversion of the stereocenters of the hydroxyethylene isostere and cyclization of the carboxyl terminus to the amino end produces the lactam as shown in Figure 2. However, in doing so, what was the P1' substituent in the linear inhibitor now becomes the P2' substituent in the lactam. The new cyclic inhibitor does not have a P1' substituent. Alkylation of the lactam nitrogen can provide the P2 substituent. The resulting inhibitor would have three lipophilic interactions with the enzyme's S1/S2 and S2' specificity sites. We knew that this would not be optimal. However, in the tetrahydropyrimidinones series, three lipophilic interactions with the enzyme's S1/S1' and S2 sites (as with **2**) showed only a modest loss of potency (compared to **1**). To examine if the lactams would behave similarly we set out to synthesized a lactam analog and evaluated its HIV-PR inhibitory ability.

Figure 2



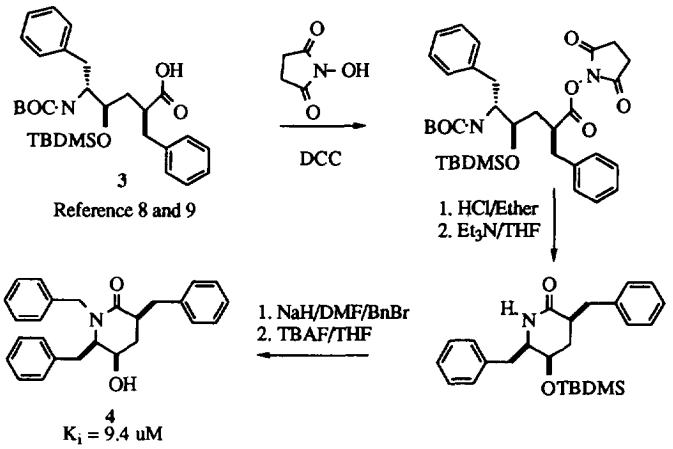
The synthesis of the lactam analog is summarized in Scheme 1. Following the literature[8] procedure, except starting with the enantiomeric amino acid, Boc-D-Phe was converted to the TBDMS protected hydroxy acid **3** in 8 steps using the previously described[9] procedure. The acid is activated as the succinimide ester, the amine is unmasked and cyclized to give the lactam. The lactam is treated with NaH in DMF and N-alkylated using benzyl bromide. The TBDMS group is removed with Bu_4NF to give the desired lactam **4**.

The HIV-PR activity of **4** was measured[10] and it was found to be a weak inhibitor with a K_i of 9.4 uM. The lack of a P1' substituent in the lactam series caused a much greater loss in potency than a lack of a P2' substituent in the tetrahydropyrimidinone series (compare **2** above). To ascertain if the magnitude of the loss in potency is principally due to the inherent importance of an S1 interaction over an S2 interaction or to the relative potency of the lactam series compared to the tetrahydropyrimidinone series; the analogous 6-membered ring cyclic urea **5** was synthesized as shown in Scheme 2.

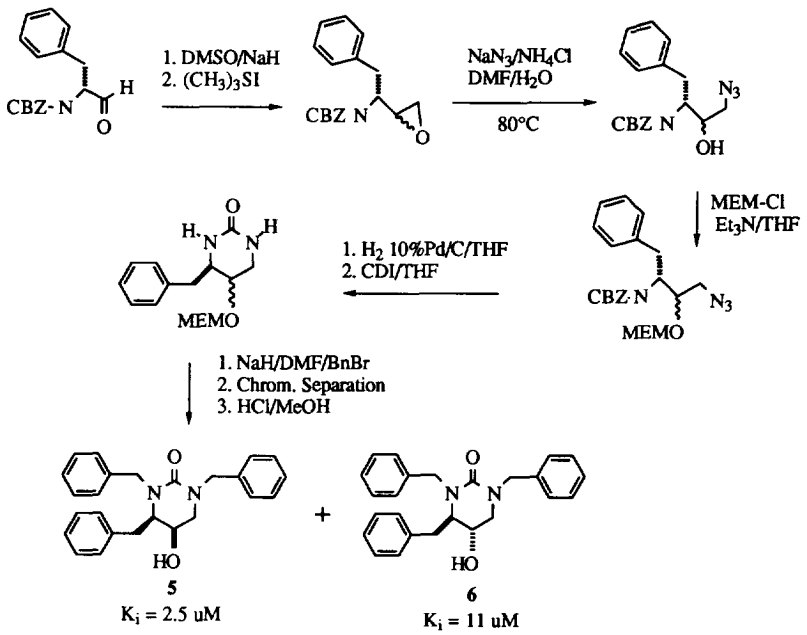
Comparing the potency of **5** with **2** it is apparent that a good lipophilic S1 interaction is much more important than a S2 interaction.[11] Since a P1' substituent is important for potency, most of the loss in activity

of the lactam **4** is probably due to the lack of a P1' substituent that can interact with the enzyme's S1' pocket and probably not due to the lactam being an inherently weaker inhibitor. Both the lactam **4** and the corresponding tetrahydropyrimidinone **5**, which can have similar S1/S2/S2' interactions with the enzyme, have similar potency.

Scheme 1



Scheme 2



This study suggests that if a proper P1' substituent is incorporated into the lactam **4**, it may improve the potency of these compounds significantly. We are currently addressing this issue and will report our findings in due course.

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