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SYNTHESIS AND EVALUATION OF IMIDAZOLIDINONES AS NONPEPTIDE HIV-PROTEASE INHIBITORS

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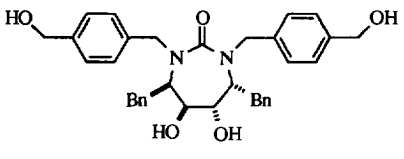
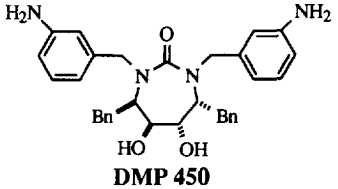
Abstract. Imidazolidinones were synthesized from 7-membered ring cyclic ureas via a sequential series of novel ring contraction reactions proceeding first through the tetrahydropyrimidinones and finally to the 5-membered ring heterocycle. These imidazolidinones are shown to be excellent HIV-PR inhibitors. The most potent compound **20** having a K_i = 17 nM.

In recent years there has been an intense international research effort to find therapies for acquired immunodeficiency syndrome (AIDS).[1] One of the prime targets has been the essential aspartic protease (PR) of the human immunodeficiency virus (HIV), the causative agent of AIDS. HIV-PR processes the viral *gag* and *gag-pol* polyproteins into structural and functional proteins. Inhibition of HIV-PR in vitro results in the production of progeny virions that are immature and non infectious.[2] In recent clinical studies, several HIV-PR inhibitors have been shown to be effective especially in combination with reverse transcriptase (RT) inhibitors.[3] Saquinavir (Roche), Ritonavir (Abbott), and Indinavir (Merck) have recently been approved by the FDA and are currently being used for AIDS therapy in combination with RT inhibitors.

Lam and coworkers 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 **DMP450**.[6]



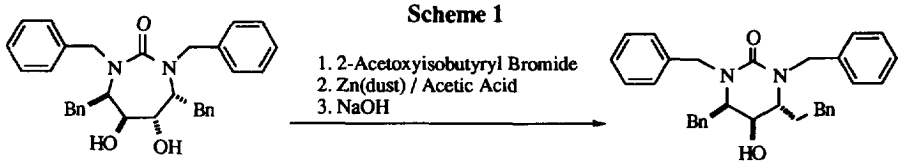
DMP 323



DMP 450

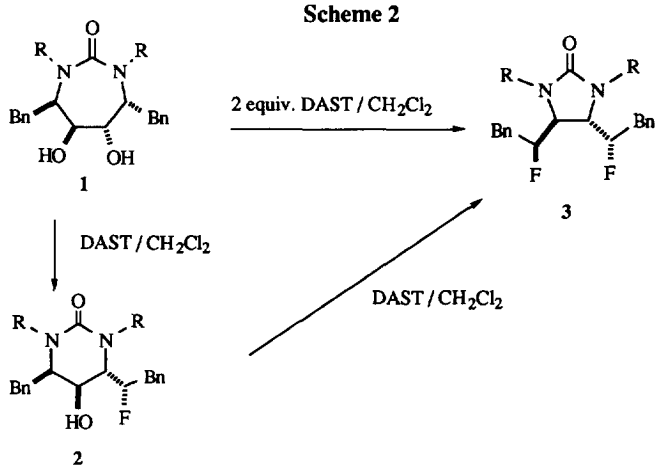
During our analoging efforts with the cyclic ureas we found that the cyclic ureas can undergo a facile ring contraction rearrangement reaction to give tetrahydropyrimidinones. We used this ability to design an efficient synthesis of tetrahydropyrimidinones (Scheme 1) and showed that these 6-membered ring analogs were nearly equipotent to the 7-membered ring cyclic ureas.[7]

Scheme 1



We subsequently have found that the tetrahydropyrimidinones can also undergo a second rearrangement to give imidazolidinones. This offered us the opportunity to further explore the effect of ring size on the structure activity relationship (SAR) of cyclic ureas as HIV-PR inhibitors. In this paper we wish to report our findings in this regard.

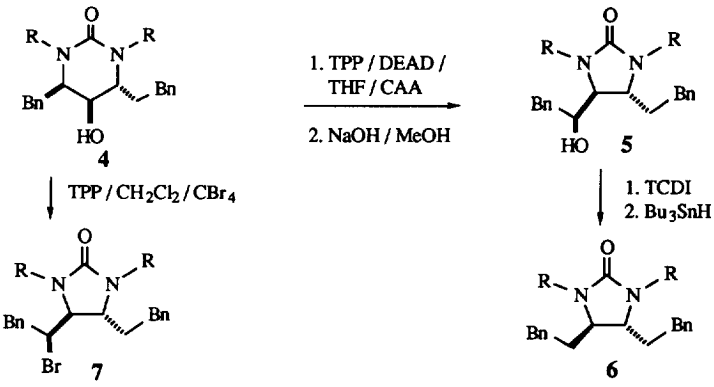
Scheme 2



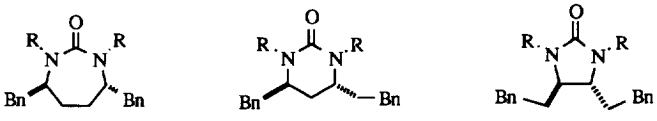
The synthesis of the imidazolidinones from the cyclic ureas and tetrahydropyrimidinones[8] is outline in Schemes 2 and 3. When the cyclic urea **1** is treated with 1 equivalent of the fluorinating agent diethylaminosulfur trifluoride (DAST) the rearranged fluoro-alcohol **2** is formed in good yield. The tetrahydropyrimidinone **2** can then be treated with a second equivalent to give the C_2 symmetric difluoro imidazolidinone **3**. Alternatively the cyclic urea **1** can be treated with excess DAST to give **3** directly. The sterochemistry of **2** and **3** is assumed by analogy to other rearrangement reactions (Scheme 1) that gives the bromo analog of **2** (Br instead of F) and for which the stereochemistry was confirmed by x-ray analysis.[7] Note that the rearrangement is stereospecific since the only product formed from the tetrahydropyrimidinone **2** is the C_2 symmetric imidazolidinone **3** (with none of the 1,2-difluoro-3-phenyl-propyl analog being formed).

This rearrangement seems to be fairly general and occurs under a variety of other conditions. For example, treatment of the tetrahydropyrimidinone **4** under Mitsunobu conditions [triphenylphosphine (TPP), diethyl azodicarboxylate (DEAD), chloroacetic acid (CAA)] gives the corresponding imidazolidinone chloroacetate intermediate which can then be hydrolyzed to give the alcohol **5** as outlined in Scheme 3. The alcohol functional group of **5** can be further reduced using Barton's radical deoxygenation procedure[9] [thiocarbonyldiimidazole (TCDI); Bu_3SnH reduction] to give the C_2 symmetrical phenethyl analogs **6**. The alcohol of **5** can also be treated with triphenylphosphine (TPP) and CBr_4 to give the corresponding rearranged bromo imidazolidinone **7**.

Scheme 3



The HIV-PR inhibitory activity of the imidazolidinones are summarized in Table 1. The compounds are not as potent as the cyclic ureas[5] or the tetrahydropyrimidinones.[7] However, the imidazolidinone analogs in Table 1 do not have a substituent that can interact effectively with the critical catalytic Asp 25/25' of HIV-PR and as such are weaker inhibitors. In spite of this, analogs capable of having appropriate hydrogen bonding interactions with the enzyme S2 subsites show excellent inhibition properties, the best being **20** with a K_i of 17 nM. Computer models of the imidazolidinones suggests that they are complementary to the enzyme active site and should have strong lipophilic interactions with the S1/S1' and S2/S2' sites on the enzyme. This was confirmed by the synthesis and evaluation of the analogous cyclic urea and tetrahydropyrimidinone analogs **21** and **22** and comparing them to the imidazolidinone **19**. These three analogs lack the hydroxyl substituent that interacts with the catalytic Asp and all three have comparable binding affinity to HIV-PR. Most of the loss in potency of the imidazolidinones is due to the lack of a transition-state isostere that can interact with the catalytic Asp 25/25'. A hydrogen bond donating substituent from the phenethyl side chain may be able to interact constructively with these catalytic residues. Computer models show that a simple hydroxyl group is not long enough to reach Asp25/Asp25' and would not be optimal and probably accounts for only the small improvement observed (compare **17/19** or **16/18**).



21 K_i = 170 nM

22 K_i = 99 nM

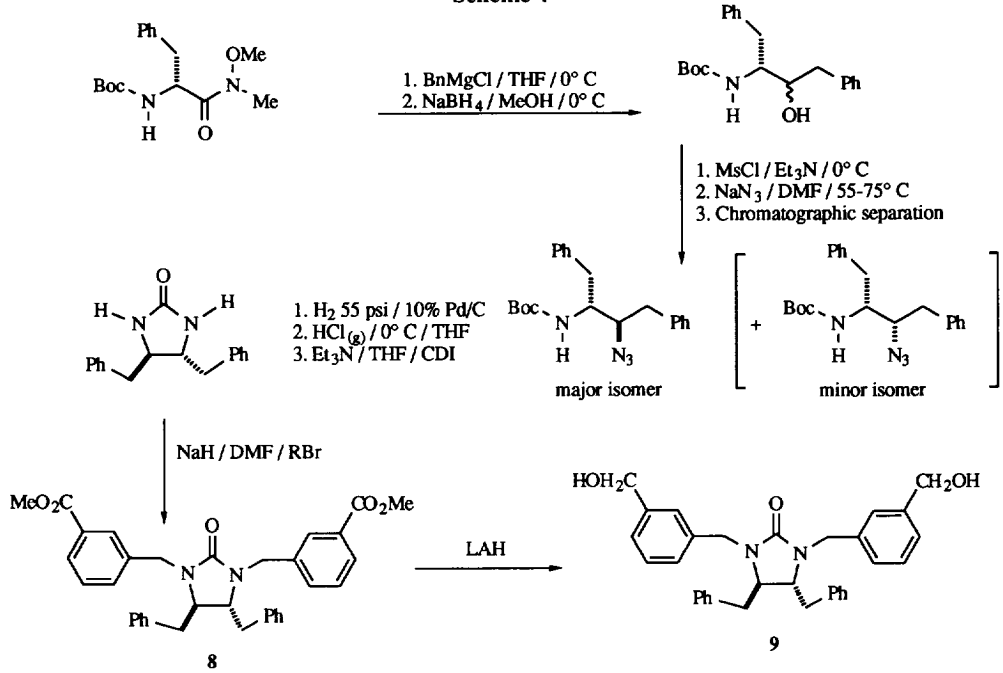
19 K_i = 55 nM

R = 3-(hydroxymethyl)benzyl
Bn = benzyl

Substitution of the P1 phenethyl side chain is generally not well tolerated (compare **15/18**) although substituents with hydrogen bonding capabilities do show some improvement (compare **16/18**). Computer models also suggest that the P1/P1' phenethyl substituents of the imidazolidinones is critical for potency. This

was confirmed by the synthesis of the P1/P1' benzyl analog as shown in Scheme 4. The stereochemistry of **9** was confirmed by single crystal X-ray[10] analysis. Compound **9** has a K_i of 15,500 nM which is almost 300X weaker than the corresponding phenethyl analog **19**.

Scheme 4



In conclusion we have shown that imidazolidinones can be prepare from 7-membered ring cyclic ureas via a sequential series of novel, stereospecific, ring contraction reactions. The cyclic ureas can be first converted to the tetrahydropyrimidinones (Scheme 1 and 2) and then to the 5-membered ring heterocycle (Scheme 2 and 3). The results presented here show that these imidazolidinones can serve as a good framework for designing potent, nonpeptide HIV-PR inhibitors. The 5-membered ring heterocycle provides a good nonpeptide scaffold for inhibitors of HIV-PR with good complementarity to the S1/S1' and S2/S2' subsites. However, because the 5-membered ring heterocycle is smaller than the 6 or 7-membered ring ureas, they lack the good interaction with the catalytic Asp25/Asp25' residues. Our current efforts are aimed at improving the potency of these compounds by optimizing hydrogen bonding interactions with the catalytic residues Asp25/25'. Computer models show that something at least as long as an hydroxymethyl substituent on the phenethyl side chain is needed to be able to reach the catalytic Asp residues and provide for an adequate interaction. Results of our continuing efforts to improve the potency of these compounds will be presented in due course.

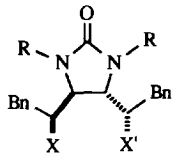


TABLE 1.

Compd.	R	X	X'	K_i (nM)[11]
10	3-(benzoxy)benzyl	F	F	425
11	3-hydroxylbenzyl	F	F	560
12	cyclopropylmethyl	F	F	980
13	2-naphthylmethyl	F	F	1400
14	allyl	F	F	2500
15	3-(carbomethoxy)benzyl	Br	H	920
16	3-(carbomethoxy)benzyl	OH	H	100
17	3-(hydroxymethyl)benzyl	OH	H	23
18	3-(carbomethoxy)benzyl	H	H	470
19	3-(hydroxymethyl)benzyl	H	H	55
20	3-(amidoxime)benzyl	H	H	17

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11. K_i's were measured by Mr. R. Klabe as described previously in: Erickson-Viitanen, S.; Klabe, R. M.; Cadwood, P. G.; O'Neal, P. L.; Meek, J. L. *Antimicrob. Agents Chemother.* **1994**, *38*, 1628.

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