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SYMMETRY-BASED HIV PROTEASE INHIBITORS CONTAINING A HYDROXY BIS-UREA ISOSTERE

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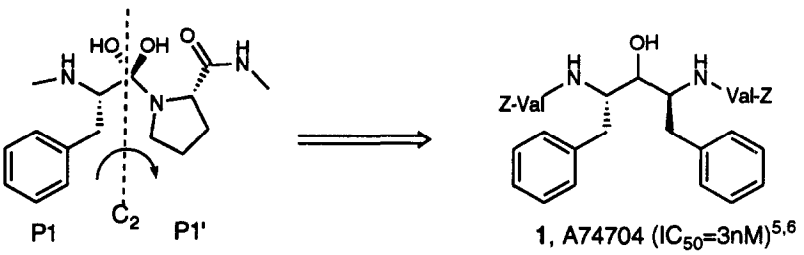
The human immunodeficiency virus type 1 (HIV) encodes an aspartic protease[1] which is essential for processing of viral polyproteins. Inhibition of HIV protease (HIV PR) results in the production of non-infectious virons.[2] Thus, the development of HIV PR inhibitors is an attractive strategy for the treatment of AIDS.[3] X-ray crystallography has revealed that HIV PR is a C_2-symmetric homodimeric enzyme.[4] Erickson *et al*[5] and Kempf *et al* [6] initially designed C_2 symmetry-based inhibitors to mimic the symmetry of the enzyme (Figure 1). Their approach involved deletion of the P' region followed by C_2 operation on the remainder of the substrate to generate a symmetric inhibitor. The resulting peptidomimetic compound **1**, contained a 1,3 diamino-2-hydroxypropane moiety as a transition state isostere and was a potent and selective inhibitor of HIV PR.

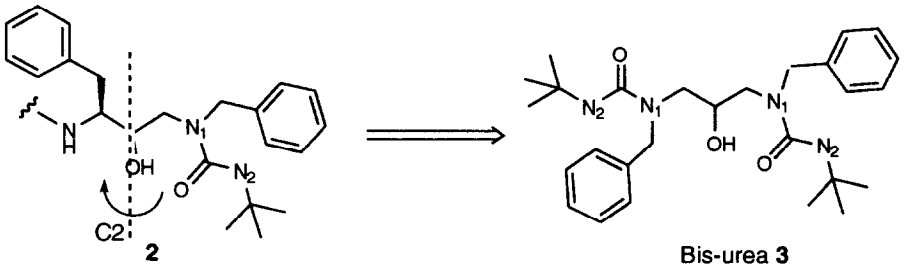
Figure 1



1, A74704 (IC_{50}=3nM)[5,6]

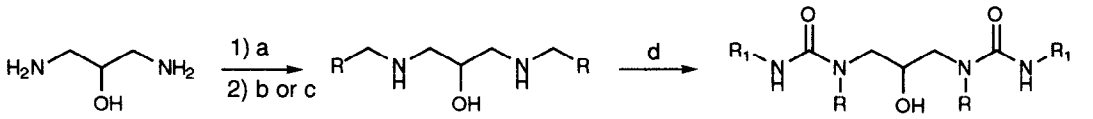
In this report we describe a novel series of C_2 symmetric inhibitors generated by deletion of the P region of a hydroxyethyl urea-containing substrate-based inhibitor[7], followed by a C_2 operation on the remainder. This operation on **2** generated the symmetric bis-urea containing inhibitor of general formula **3** (Figure **2**). We selected the urea part of the molecule for the C_2 operation because 1) it provides an inhibitor containing the same transition state isostere as in **1**; 2) suitable N-substituents can be added to provide subsite interactions; 3) the resulting bis-ureas **3** are achiral and can be readily synthesized.

Figure 2



The synthesis of these potential inhibitors is outlined in Scheme 1. Reaction of 1,3 diamino-2-propanol with a suitably substituted aromatic aldehyde in CH_2Cl_2 in the presence of 5Å molecular sieves gave stable bis-imines. When non-aromatic aldehydes were used, condensation was carried out in the presence of KOH and the resulting bis-imines were isolated by distillation and used immediately to avoid polymerization. Reduction of the Schiff's base with $NaBH_4$ or hydrogenation using catalytic PtO_2 provided the corresponding secondary amine **4**. Condensation of the resulting secondary amines with 2 mole equivalents of the representative isocyanates (R'NCO) provided the bis-ureas **3a-i** (Table 1). The ureas **3j-l** (Table 1) were prepared by

Scheme 1

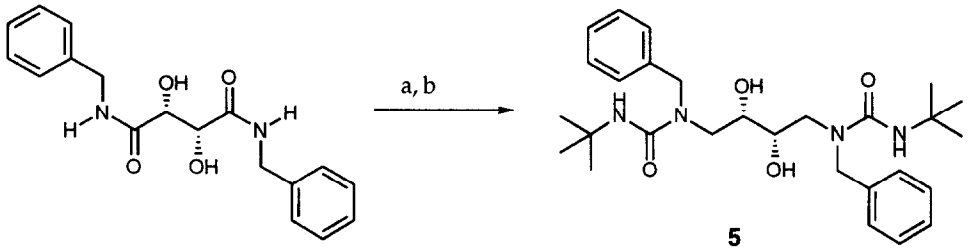


[a]RCHO/molecular Sieves/CH_2Cl_2/RT/6 hr; [b]$NaBH_4$/MeOH/RT/8-15hr.; [c]H_2/PtO_2/MeOH/RT/1hr.; [d]R_1NCO/THF/RT/4-8hr.

condensation of **4** with respective amines in the presence of triphosgene.[8] Reaction of **4** with di-*tert*-butyl dicarbonate afforded compound **3m**.

Symmety-based diol containing inhibitors are generally 10 to 100 fold more potent than the corresponding monols **1**[3,6]. Hence, the 1,4-diamino-2,3-dihydroxy derivative **5** was synthesized from (*S,S*)-N-benzyl tartaramide (Scheme **2**).

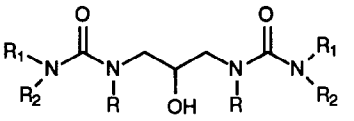
Scheme 2



[a]$BH_3.SMe_2$/THF/50°C/20 hr; [b]*tert*-butylisocyanate/THF/2hr.

Compounds **3a-m** and **5** were purified by filtration through a silica gel column and characterized by H^1NMR and mass spectroscopy. They were evaluated *in vitro* for inhibition of HIV PR[9] (Table 1). Compounds **3a-3m** and **5** showed weak inhibition.

Table 1: HIV PR Inhibition by C2 Symmetric Bis-Urea.



Compound	R	R_1	R_2	% Inhibition @ 10 μm
3a	H	$C(CH_3)_3$	H	8
3b	$CH_2CH(CH_3)_2$	$C(CH_3)_3$	H	25
3c	CH_2Ph	$C(CH_3)_3$	H	50
3d	CH_2Ph	CH_2Ph	H	19
3e	CH_2Ph	$CH_2CH_2CH_3$	H	38
3f	CH_2Ph	Ph	H	16
3g	$CH_2C_6H_4$ OH(*o*)	$C(CH_3)_3$	H	11
3h	$CH_2C_6H_4$ OH(*m*)	$C(CH_3)_3$	H	67
3i	$CH_2C_6H_3$ (OH)2(*o,m*)	$C(CH_3)_3$	H	67
3j	CH_2Ph	Val-OMe	H	36
3k	CH_2Ph	D-Val-OMe	H	16
3l	H	$C(CH_3)_3$	CH_2Ph	17.5 (50 μ m)
3m	CH_2Ph	Boc	H	28
5				78

Preliminary modeling studies with **3c** indicated that the rigidity of the urea moiety precludes optimal subsite binding of the benzyl and t-butyl groups on both the P and P' sides simultaneously. This may be a general problem with symmetric bis-ureas. Co-crystallization experiments using these compounds with HIV PR are in progress.

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Supplementary Material Available: Experimental details and spectroscopic data for compounds reported here are available from the authors.

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