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Non-Peptide-Based Inhibitors of Human Immunodeficiency Virus-1 Protease

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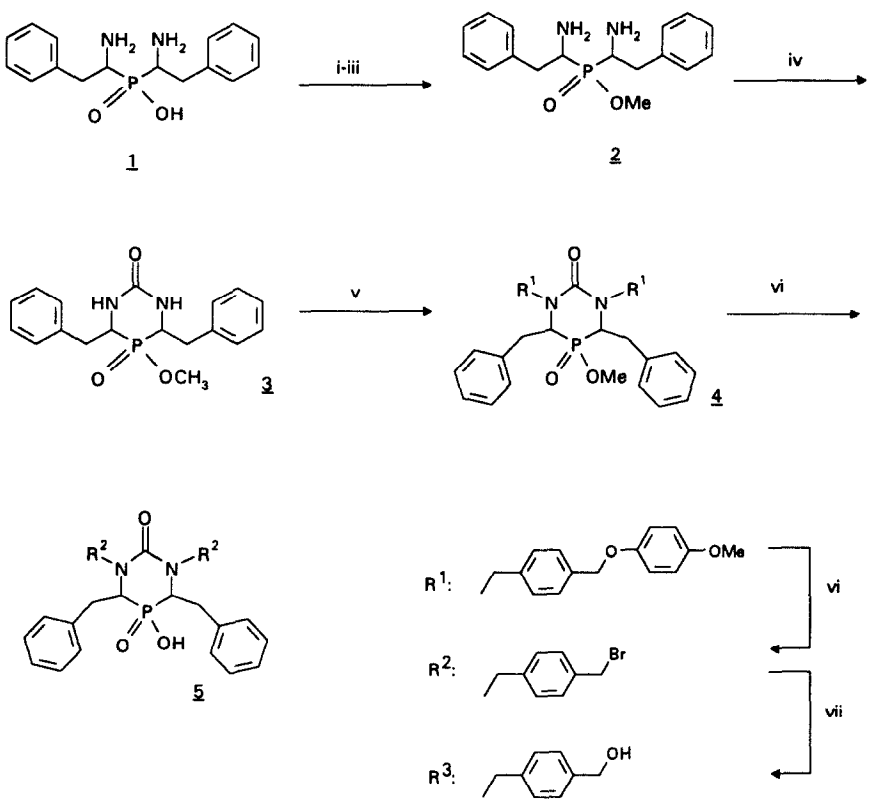
Abstract: The use of bis(α-aminoalkyl)phosphinic acids as analogs of the tetrahedral intermediate formed on the path to peptide hydrolysis in combination with a mimic for a structural water, which is found in HIV protease inhibitor complexes, leads to potent inhibitors of HIV-1 protease.

The virally encoded protease of the Human Immunodeficiency Virus (HIV) is one of the most interesting targets for HIV/AIDS chemotherapy [1]. The HIV protease, a member of the aspartyl protease family, plays a key role in processing the HIV polyproteins produced directly after translation, especially the gag and gag-pol polyproteins [1]. Blockade of these processing steps results in viral particles which are morphologically immature and noninfectious [2]. This led to the synthesis of a large number of peptide-based inhibitors of HIV protease [4]. HIV protease functions as a C_2-symmetrical homodimeric protein [3], and, interestingly, some excellent inhibitors have also C_2-symmetry like the enzyme [5-7]. Recently the unsatisfactory bioavailability and pharmakokinetics of most of these compounds triggered the development of low molecular weight nonpeptide inhibitors of HIV protease [8]. Structural features of these inhibitors include a diol transition state analog of peptide hydrolysis and, in addition, a prepositioned urea group to mimic a structural water molecule[3] found in HIV protease inhibitor complexes

We recently reported the synthesis of bis(α-aminoalkyl)phosphinic acids [7], which allow the placement of a phosphinic acid group into a peptide environment, where it acts as a transition state analog of peptide bond hydrolysis, leading to powerful inhibitors of HIV protease. Here we show that these phosphinic acid building blocks can be combined with the "structural water mimic" to form potent non-peptide inhibitors of HIV protease.

The bis(1-amino-2-phenylethyl)phosphinic acids **1** (scheme 1), separated into the meso and the racemic diastereomers, were first converted into the corresponding methyl esters **2** by benzyloxycarbonyl (Z) protection of the amino functions, esterification with diazomethane and subsequent removal of the Z groups. The resulting methyl esters **2** then were reacted with carbonyldiimidazole to give the cyclic ureas **3** which subsequently were N-alkylated using NaH in DMSO as base to **4** in with high yield. The free acid

can also be cyclized, however, alkylation is unsatisfactory, leading to several side products such as the alkylation of the phosphinic acid group



Scheme 1: Synthesis of the non-peptide HIV protease inhibitors **5**; i) Z-Cl, NaOH, quant.; ii) CH_2N_2, quant.; iii) H_2/Pd, quant.; iv) CDI, 40%; v) NaH/DMSO, R-Br, 70%; vi) HBr/AcOH, 90%; vii) $CaCO_3$/dioxan/water, 75%.

The phosphinic acid ester is cleaved with HBr in acetic acid or alternatively with bromotrimethylsilane to give the free acids **5** For the synthesis of the N-(4-hydroxymethyl)benzyl substituted compounds the alkylation in step v was carried out with 4-(4-methoxyphenoxymethyl)benzylbromide. However, the benzylether was also cleaved during the treatment with HBr. Therefore the resulting bromide had to be converted into the corresponding hydroxide by treatment with $CaCO_3$ in dioxan/water.

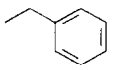
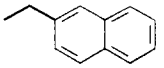
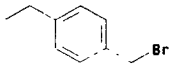
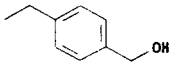
R^2	IC_{50} [μM] (meso 5)	IC_{50} [μM] (rac 5)
H	>100	>100
	21	---
	---	0,26
	18	0,70
	4,8	0,24

Table 1: Enzyme inhibiting activity of phosphinic acid inhibitors 5.

Inhibition of HIV protease was determined at pH 5.5 using a synthetic substrate[9], the results are shown in table 1 As expected the potency of inhibition strongly depends on the configuration of the benzyl groups: The racemic compounds (mixtures of [R,R]/[S,S]) are much better inhibitors than the meso-diastereomers. The free acid is needed for inhibition, the corresponding methyl esters 4 (not shown in table 1) do not show any activity. Inhibition is also strongly dependent on the presence of a nitrogen substituent Best results were obtained with the 4-hydroxymethylbenzyl substituent in both the meso and the racemic mixture series, although in racemic mixture the differences among various substituents are not very significant. However, it must be mentioned that the phosphinic acid inhibitors of the current work are as much as 100-fold weaker than the diols of ref. 8 which are part of a seven membered ring. It still needs to be determined whether this is caused by the six membered ring which cannot adopt a C_2-symmetrical conformation as easily as the seven membered ring, or if these inhibitors are somewhat less strong in replacing the active site water molecule as reported for the diol inhibitors in ref. 8.

We were able to show that the use of bis(α-aminoalkyl)phosphinic acids as transition state analogs of peptide hydrolysis in combination with a structural water mimic leads to good inhibitors of HIV-1 protease. It is likely that only one diastereomer of the racemic mixture is the active compound. This class of inhibitors will therefore be further improved by stereoselective synthesis and variation of the nitrogen substituents.

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Dedicated to Professor Christoph Ruchardt on the occasion of his sixty-fifth birthday

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