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Synthesis and Anti-HIV Activities of Symmetrical N_1,N_3-dibenzyl-2-hydroxy-propane Derivatives

M. Medou,[1,2] M. Bouygues,[1,2] L. Rocheblave,[1,2] J.-C. Chermann[2], J.-L. Kraus.*[1,2]

1-Laboratoire de Chimie Biomoléculaire, Faculté des Sciences de Luminy, case 901, Université de la Méditerranée, 163 Avenue de Luminy, 13288 Marseille cédex 9, France.
2-INSERM U322 "Rétrovirus et Maladies associées", Campus Universitaire de Luminy, BP 33, 13273 Marseille cédex 9, France.

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Abstract
We report the synthesis and the anti-HIV activities of new C_2-symmetrical and achiral N_1,N_3-dibenzyl-2-hydroxy-propane isosteres. Some of them showed significant inhibitory activity with respect to HIV-infected MT4 cells (compound **6a** and **7a**, IC_{50} = 0.1 μM). These new structurally simple compounds represent new synthons which can be suitable for combinatorial chemistry purposes.

Introduction

The importance of HIV-protease inhibitors in the treatment of AIDS is now well established.[1,2] Recently, the concept of a single mechanism (e.g. a mixture of protease inhibitors) has attracted considerable interest.[3] Suggestions have been made that the best protection against the wild-type and mutant strains is obtained by maximizing structural diversity of protease inhibitors.[4] At the present time, numerous examples of potent inhibitors of HIV-protease involving the incorporation of a wide variety of isosteres at the cleavage site have been reported and reviewed.[5,6] Unfortunately, although many of peptidomimetic inhibitors possess potent antiviral activity *in vitro*, the low oral bioavailability, rapid biliary excretion and high cost synthesis have limited their potential utility as pharmaceutical agent. High molecular weight, numerous chiral centers, and high lipophilicity constitute significant obstacles to the development of peptidomimetic inhibitors.[7]

We have designed HIV-protease inhibitors with much reduced peptidic character, low lipophilicity, reduced number of chiral centers and low molecular weight. We adopted a simple approach based on the following findings: the design of numerous potent HIV-protease inhibitors was based on the unique C_2-symmetry of the homodimeric proteolytic enzyme.[8] For example, pseudo-symmetrical inhibitor **1** (fig.1) spanning specific P_2/P'_2 substituents [notation of Schechter and Berger][9] inhibits the HIV-protease with IC_{50} value of 3 nM.[8]

kraus@luminy.univ-mrs.fr
fax: (33) 491 82 93 04

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Starting from this simple example, we have selected the minimal symmetrical structure **2** which includes one secondary hydroxy function and reduced molecular weight due to the exclusion of the P_3/P'_3 ligands. We have investigated what would be the most appropriate substituent R which confers the best *in vitro* anti-HIV properties to the resulting compounds. The simplest and the most potent symmetrical pharmacophore could constitute active anti-HIV building block useful for solid phase combinatorial chemistry.

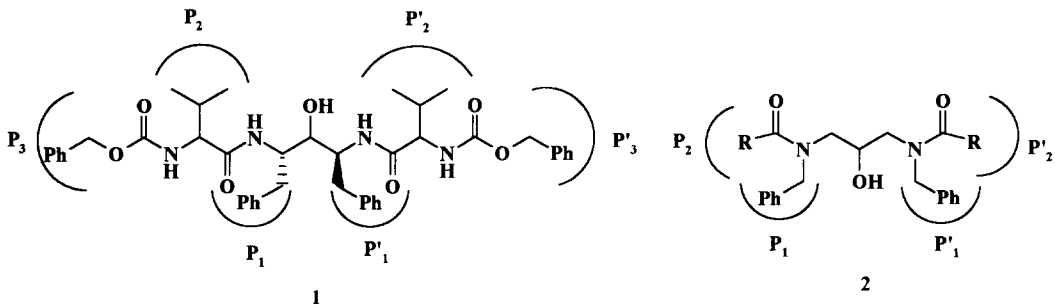


Figure 1

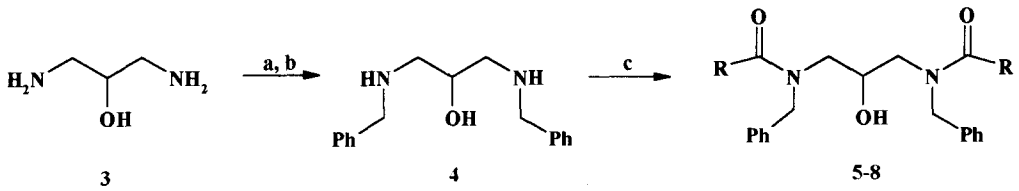
Our approach differs from the classical investigation since we directly proceed to the *in vitro* evaluation of anti-HIV activity of the new achiral analogs on HIV-infected MT4 cells (observation of *syncytia* formation). Indeed, although a compound can be strongly effective in purified enzyme inhibition assays, it can display weaker cellular antiviral activity.[4,10] In order to determine the lipophilic character of the new pharmacophores, we have calculated Log P (partition coefficient in octanol/water system) using ACD (Advanced Chemistry Development; Inc) software.[11] With the use of structure-based computer search (GenMol software[12]), we have evaluated the fit of the different structures docked into the active site of the HIV-protease.

Chemistry

The synthetic route leading to the N_1,N_3-dibenzyl-2-hydroxy-propane derivatives is outlined in Scheme **1**. 1,3-diamino-2-hydroxypropane **3** was condensed with benzaldehyde[13] and the resulting diimine was reduced with sodium borohydride in ethanol to the corresponding diamine **4** in quantitative yield.[14] Various urethanes and ureas were prepared by alkoxycarbonylation[15] and aminocarbonylation[16] of diamine **4** using the corresponding appropriate alcohols and amines.

The condensation of N_1,N_3-dibenzyl-2-hydroxy-propane **4** with alkylchloroformate in presence of triethylamine in dry methylene chloride at 0°C provided compounds **5a-d** in quantitative yield while the use of benzyl chloroformate resulted in only 40% yield. The use of benzylsuccinimidyl carbonate, prepared by the reaction of benzyl alcohol with N,N'-disuccinimidyl carbonate in presence of triethylamine in dry

acetonitrile provided the desired corresponding urethane **6a** in 93% yield after purification. Analogs **6b-d** were isolated from diamine **4** using the same method. Alternatively, preparation of urea analogs **7a-b** and **8a-b** required coupling of diamine **4** with the appropriate isocyanates (R-N=C=O) and carbamoylchlorides (RR'NCOCl). The corresponding analogs were obtained in quantitative yield.[17]



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Scheme 1:

(a) PhCHO, Na_2SO_4/CH_2Cl_2, 93 %; (b) $NaBH_4$, EtOH, quantitative; (c) alkylchloroformate, Et_3N/CH_2Cl_2, (**5a-5d**), quantitative; alkylsuccinimidyl carbonate Et_3N/CH_3CN, (**6a-6d**), 93%; alkyl isocyanate, CH_2Cl_2, (**7a-7b**), quantitative; alkyl carbamoylchloride, Et_3N/CH_2Cl_2, (**8a-8b**), quantitative.

Results and discussion

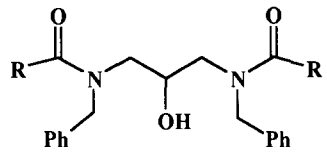
As already reported,[12] the concept which supports the design of symmetric inhibitors for HIV-protease must satisfy two major constraints. First, for a symmetric interaction between the inhibitor and the enzyme to occur, their C_2 axes should coincide. Second, the inhibitor should be able to fill the enzyme subsites that normally interact with the side chains of an asymmetric pseudopeptide substrate (compound **1**). Our goal was to conceive models which will not only embody the two mentioned constraints, but which will contain no other asymmetric carbons.

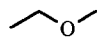
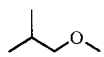
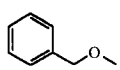
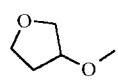
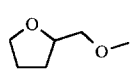
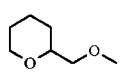
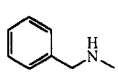
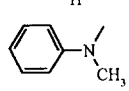
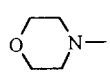
In model **2**, the two P_1/P'_1 chiral α-carbon centers were replaced by trigonal N-benzyl centers. In Table 1, inhibitions of viral spread T-lymphoid infected cells by the new N_1,N_3-dibenzyl-2-hydroxy-propane derivatives in HIV-BRU strains are reported. Some of the new analogs (**5b-d**, **6a**, **7a-b**, **8a**) showed good anti-HIV activities (IC_{50} ranging between 0.1 to 10 μM) while others, which only differ with the structure of the substituent R, were inactive (**5a**, **6b-d** and **8b**).

These results encouraged us to examine a possible correlation between the anti-HIV activity and lipophilicity represented by octanol/water partition coefficient of the new analogs. Using ACD software, the partition coefficient (Log P) were calculated for all of the derivatives and are reported in Table 1, but no correlation between lipophilicity and anti-HIV activity was found. Interestingly, since all the substituents at the carbonyl function in structure **2** were not tolerated, it can be deduced that interaction with the P_2 and P'_2 regions of the HIV-protease represents a absolute requisite for anti-HIV activity. Using GenMol software, we have calculated the interaction energy of the new analogs with the HIV-protease active site.[18]

Calculated fitting energies for all anti-HIV active compounds were up to 80% of that of reference compound **1**.

Table 1. Anti-HIV activities of new N_1,N_3-dibenzyl-2-hydroxy-propane derivatives



Compound	R	Log P[a]	IC_{50}, μM[b]	CC_{50}, μM[c]
5a		3.99 ± 0.64	inactive	50
5b	CH_3-$(CH_2)_6$-CH_2-O	10.35 ± 0.64	10	50
5c		5.75 ± 0.65	1	100
5d		5.39 ± 0.65	1-10	>100
6a		6.48 ± 0.65	< 0.1	10
6b		2.48 ± 0.66	inactive	50
6c		2.94 ± 0.66	inactive	50
6d		4.07 ± 0.66	inactive	50
7a		5.12 ± 0.65	0.1	>100
7b		4.12 ± 0.65	1	>100
8a		7.06 ± 0.51	1-10	>100
8b		0.04 ± 0.72	inactive	100

[a] Log P determinations were performed using ACD (Advanced Chemistry Development Inc.) /Log P 1.0 base calculations.
[b] IC_{50}= concentration required to inhibit *syncytia* formation by 50% in HIV-infected MT4 cells.
[c] CC_{50}= concentration required to cause 50% death of uninfected MT4 cells.

Consequently, this new class of symmetrical low molecular weight N_1,N_3-dibenzyl-2-hydroxy-propane derivatives which do not include chiral center in the P_1/P'_1 region, can represent promising candidates for lead optimisation through combinatorial chemistry.

Acknowledgments

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