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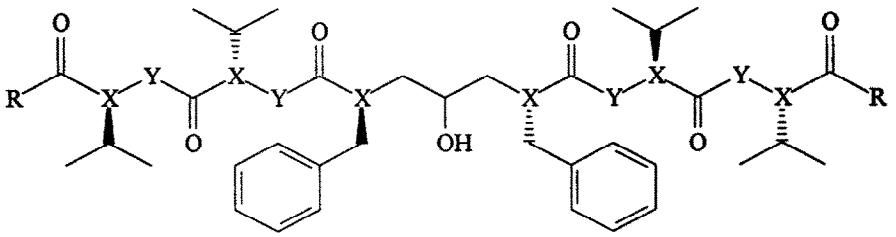
PEPTOID MIMICS OF A C_2-SYMMETRIC INHIBITOR OF THE HIV-1 PROTEASE.

Jean-Paul Mazaleyrat*, Isabelle Rage, Abdel Malek Mouna, Jaroslav Šavrda and Michel Wakselman
CNRS-CERCOA, 2, rue Henri Dunant, F-94320 Thiais, France
Raymond Boulay and Yves Lelièvre
Rhône-Poulenc Rorer, 13, quai Jules Guesde, F-94403 Vitry-sur-Seine, France

Abstract: Compounds **II**, designed as retro peptoid mimics of a known potent C_2-symmetric inhibitor **I** of the HIV protease, were synthesized in solution, using BOP as coupling reagent. They showed no significant inhibitory activity with respect to the HIV-1 protease.

A promising concept has been recently suggested as a new approach to the development of pharmaceuticals: N-substituted oligoglycine derivatives called "peptoids", in which the side chains on the α-carbon atoms of a peptide fragment are shifted along the peptide backbone to the adjacent nitrogen atoms, may mimic biologically active peptides. Advantages of these new structures could be increased resistance of the molecules to protease-catalyzed hydrolysis, high flexibility and absence of spatial restrictions associated to the chirality of the α-carbon atoms in peptides.[1,2] In previous studies, (L)-proline has been replaced by achiral N-substituted glycines to afford potent human leucocyte elastase and angiotensin converting enzyme inhibitors [3] and N-benzyl glycine has been considered as a structural isomer of phenylalanine in a bradykinin analog.[4] Concerning molecular recognition of true peptoid oligomers, peptoid versions of peptide ligands of three biological systems (bovine pancreatic α-amylase, hepatitis A virus 3C proteinase and HIV transactivator-responsive element RNA) have been found with affinities comparable to those of the corresponding peptides.[1] However, the widest collection of comparative data about the respective biological activities of peptide *vs* corresponding peptoid structures is needed in order to extend the experimental grounds for the peptoid concept.



I : X= CH; Y= NH; R= OMe

II : X= N; Y= CH_2; R= OtBu; OBzl; $(CH_2)_2COOH$; $(CH_2)_7CH{=}CH(CH_2)_7CH_3$

Figure 1

Inside of a research program on synthetic inhibitors of the HIV protease [5,6] in which we have been interested in the development of new C_2-symmetric structures,[6c] we considered that synthesis and biological evaluation of a peptoid mimic of a known potent C_2-symmetric inhibitor of this enzyme would be of interest within both peptoid and HIV fields. A number of C_2-symmetric or pseudosymmetric compounds containing

hydroxymethylene,[7,8] dihydroxyethylene,[7,8] 1,2-ethylenediamide (in penicillin-derived dimers) [9] and 4-hydroxy-2,6-bis-(phenylmethyl) heptanediamide [10] units as central linkers of two symmetrical moieties that incorporate binding elements of substrate, have been proven to be potent inhibitors of the HIV-1 protease. Compound **I** [10] (Fig. 1), which figures among the most efficient ones (IC_{50}= 5 nM), was chosen as a good candidate for a peptoid mimic **II**, because of the possible straightforward synthesis of a "retrosequence" in which the relative orientations of the carbonyl groups to the R groups are maintained.[1,2]

The derivatives **IIa-e** were prepared in solution. A convergent strategy was used, implying the prior synthesis of N-protected N,N'-di(isopropyl)-diglycine fragments (Fig. 2) and their coupling with the central N,N'-dibenzyl-2-hydroxy-1,3-propylenediamine unit **1** [11] (Fig. 3), readily obtained from 2-hydroxy-1,3-propylenediamine. Thus, Boc-N(isopropyl)glycine **2a** [12] was converted to its benzyl ester **3a** (93 %). N-deprotection of **3a** in TFA/CH_2Cl_2 followed by liberation of the free amine with 5 % $NaHCO_3$ and extraction with ether, led to **4** (74 %). Coupling of **2a** with **4** by the mixed anhydride method using ethyl chloroformate gave **5a** with only 35 % yield, the main product being ethyloxycarbonyl-N(isopropyl)glycine benzyl ester (45 %). However, when the same reaction was performed with BOP as coupling reagent,[13] with 1 equivalent triethylamine in acetonitrile at room temperature for 2 days, the compound **5a** was obtained with 61 % yield. In the same manner, BOP-mediated coupling of **4** with **2b**, obtained (67 % yield) by treatment of N(isopropyl)-glycine with benzyl chloroformate in 2N aq.NaOH, led to **5b** (82 %). N-deprotection of **5a** in HCl/EtOAc and coupling of the resulting crude ammonium hydrochloride **6** [14] with oleoic acid in the presence of BOP and 2 equivalents triethylamine, led to **5c** (55 %) Deprotection of the ester groups of **5a** (by hydrogenolysis), **5b** and **5c** (by saponification in MeOH/aq.NaOH) led to **6a** (93 %), **6b** (75 %) and **6c** (88 %), respectively.

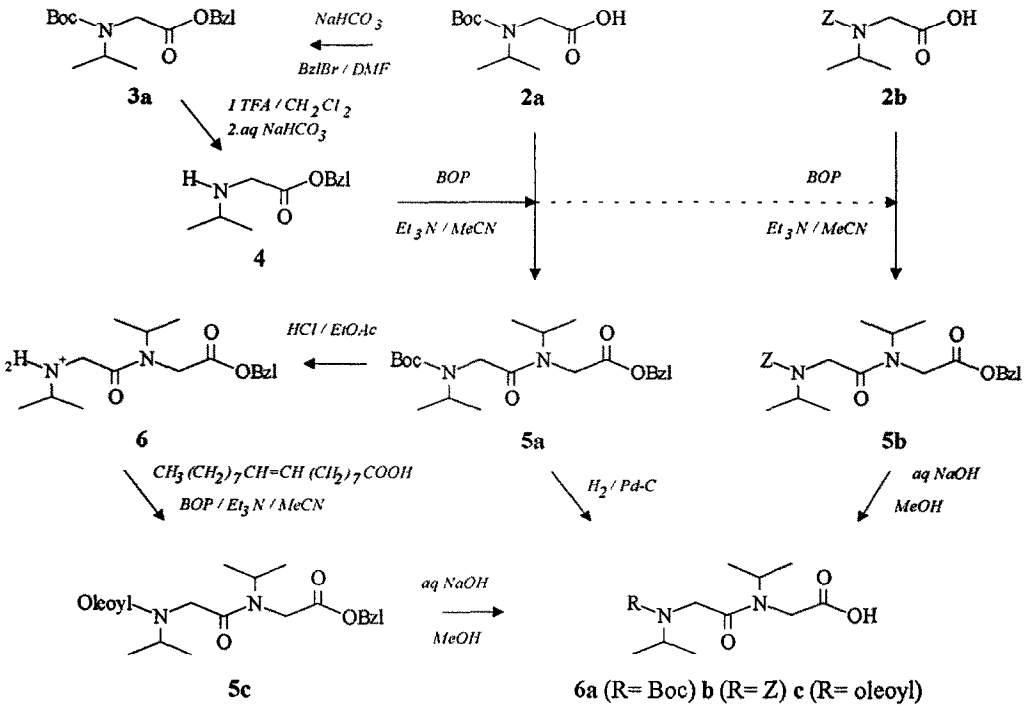


Figure 2

BOP-mediated coupling of the fragments **6a-c** with **1** (Fig. 3) gave **IIa** (70 %), **IIb** (36 %) and **IIc** (41 %). N-deprotection of **IIb** by hydrogenolysis gave **IId** (94 %), which was treated with succinic anhydride (2.4 equiv.) and triethylamine (4.8 equiv.) in DMF at room temperature for 4 days to give **IIe** (56 %).

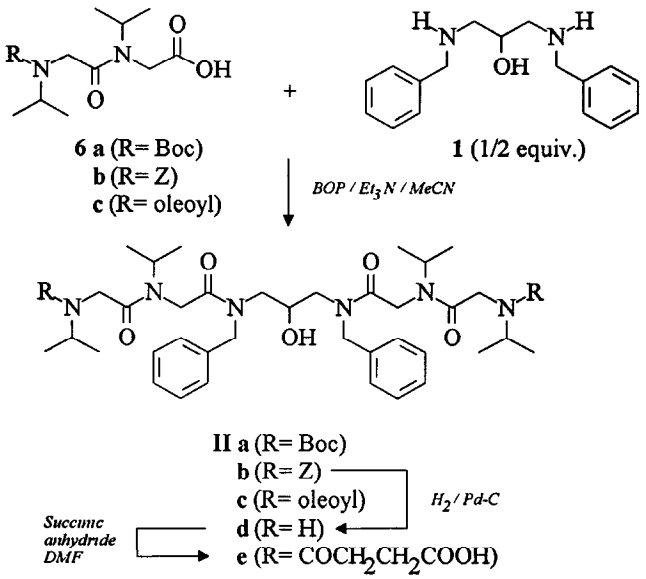
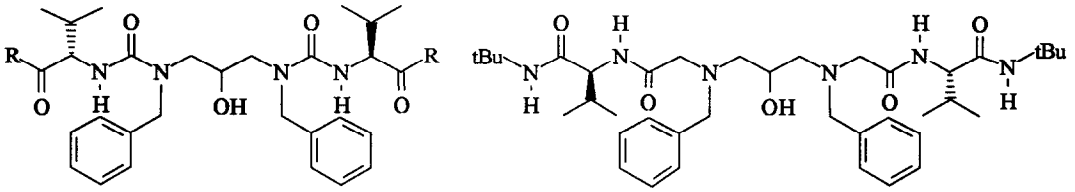


Figure 3



III IV

Figure 4

The derivatives **IIa-e**, when assayed at 10^{-5} M as inhibitors of the HIV-1 protease against three different substrates: TLNFPIS-AMC (Test I),[15] SQN-(*p*NO_2)F-PIV (Test II) and HKARVL-(*p*NO_2)F-EAnLS$_{NH2}$ (Test III),[16] showed no significant activity. The absence of anchor NH groups in the peptoids **II** could be the simplest explanation of these negative results, and in order to check this point, the synthesis of bis-urea derivatives of type **III** (Fig. 4), structurally closer to **I**, has now been undertaken. However, the first compound prepared **IIIa** (R= OMe) doesn't inhibit the HIV-1 protease either, suggesting that integrity of the central 4-hydroxy-2,6-bis-(phenylmethyl) heptanediamide linker present in **I** is of crucial importance too, as also illustrated by the reported absence of inhibitory activity of other series of parent 2,6-aza substituted compounds of type **IV**.[17]

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