Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 3, pp. 499-504, 1994
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0960-894X/94 $6.00+0.00

0960-894X(93)E0113-F

Conformationally Constrained HIV-1 Protease Inhibitors

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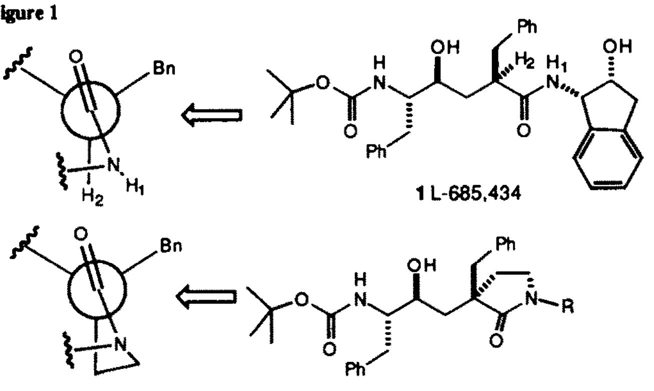
Abstract. The synthesis and structure activity relationships of conformationally constrained analogs of the HIV-1 protease inhibitor L-685,434 are described. In addition, the X-ray crystal structure of a complex between L-700,497 and the HIV-1 protease is shown.

The human immunodeficiency virus type-1 (HIV-1) protease plays a key role in the HIV viral life cycle by posttranslational processing of *gag* and *gag-pol* polyproteins into viral core components.[1] Genetic inactivation of the protease resulted in the production of non-infectious virions in cell culture.[2] Accordingly, the HIV-1 protease was recognized as a key target for developing anti-AIDS chemotherapy.[3] To date, most of the potent HIV-1 protease inhibitors reported[4] are peptidomimetic transition-state mimic analogs, and very few have reached the clinic as a result of poor oral bioavailability in animal models. A number of hydroxyethylene derived inhibitors (represented by L-685,434 (1)) that contain an amino-indanol as a novel P_2' amino acid surrogate were recently reported.[5,6] Unfortunately, compounds from this class lacked oral bioavailability in animals, possibly a result of the proteolytic instability of the indan amide bond. A successful strategy for increasing the stability of this amide bond while further decreasing the peptide-like nature of the compound entails constraining the amide group into a lactam ring.[6] The successful application of this strategy to L-685,434 was aided by examination of a molecular model of 1 docked into the native HIV-1 protease active site.[7] In this model, the inhibitor occupied the active site in an extended conformation with the indan and t-Boc group filling the P_2' and P_2 pockets respectively. Figure 1 shows an isolated view of the conformation of the P_1' carbonyl relative to the adjacent carbon in which the indan NH_1 and C-2

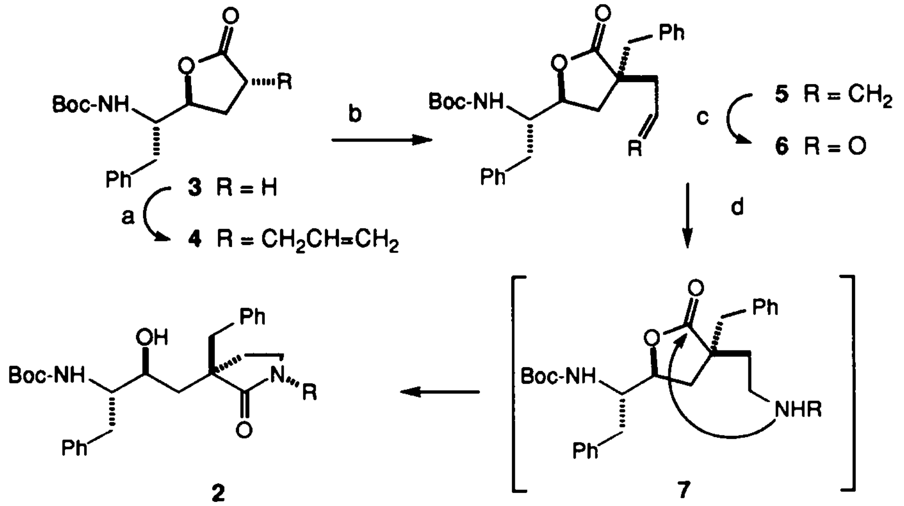
Figure 1



1 L-685,434

2

Scheme 1



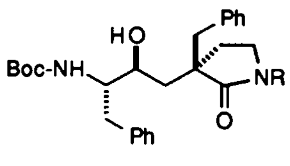
Reagents: a) 2.05 eq. LDA, -78°C, THF; allylbromide; b) 2.05 eq. LDA, -78°C, THF; benzyl iodide (64% from **3**); c) O_3, -78°C, CH_2Cl_2/MeOH; Dimethyl sulfide (65%); d) RNH_2, MeOH, AcOH, $NaBH_3CN$; HOBT, 110°C, 2-5 hrs, toluene.

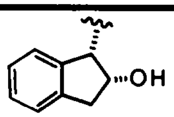
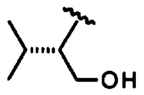
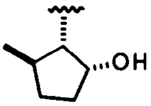
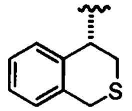
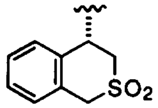
proton (H_2) are in an eclipsed relationship. This was viewed as an ideal position to form a five-membered lactam ring. In addition to improving the stability of the amide bond, the conformational constraint introduced was expected to enforce the bioactive conformation, thus compensating to some degree for the loss of any important inhibitor/enzyme interactions. A stereoselective route to compounds of general structure **2** is shown in Scheme 1.

Lactone **3**[8] was alkylated with allyl bromide to give **4** as the exclusive product. Subsequent alkylation of **4** with benzyl iodide afforded lactone **5** in good yield (64% from **3**). Alkylation occurred from the alpha face of the molecule, opposite to the bulky Boc-amino group.[9] The terminal olefin of **5** was converted to aldehyde **6** which was reductively aminated[10] with an appropriate amine. In some cases, the intermediate amine **7** spontaneously cyclized upon the lactone group to afford the lactam **2**, while in other cases, isolated **7** required heating in toluene with catalytic HOBT to effect closure.

Several analogs of compound **2** were evaluated as HIV-1 inhibitors in a peptide cleavage assay,[11] and the results are shown in Table 1. Amino-indan **8** was less potent than its acyclic analog **1** (37 nM vs 0.3 nM) possibly due to the loss of a critical hydrogen bond to Gly 27. Compound **9**, which contains valinol in the P_2' position, was equipotent to amino-indan **8**. Hydroxycyclopentane **10**, which is a conformationally constrained isostere for valinol,[12] was almost three times as potent as alcohol **8**. A decrease in activity occurred upon substitution of an isothiabenzopyran group[13] (**11**) for the aminoindan in **8**. Oxidation of sulfide **11** (Oxone®, MeOH/H_2O (1:1) 25°C, 5hr, 87%) to the corresponding sulfone

Table I P_2' Ligand Replacements



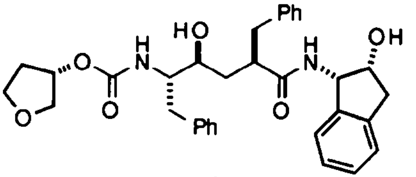
Compound	% Yield	R	IC_{50} (nM)
8	45		37
9	89^a		35
10	85^a		14
11	75		111
12	87^b		17

a) Required heating 7 in toluene with 10% HOBT.; b) Yield after oxidation of sulfide **11** See text.

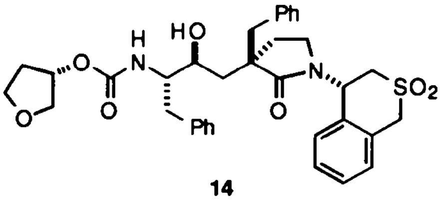
12 resulted in an increase in activity (17 nM). The isothiabenzopyran sulfone in compound **12** is a representative from a new class of non-peptide P_2' ligands which will be published in due course.[14]

Compound **13** (Fig. 2), which contains a 3(S)-tetrahydrofuranyl carbamate as a novel P_2 ligand, has been reported to be a potent HIV-1 protease inhibitor (IC_{50} =0.06 nM).[15] Incorporation of this potency enhancing group into compound **12** gave inhibitor **14** (L-700,497, IC_{50} = 1.8 nM).

Figure 2



13



14

In an effort to gain insight into interactions of this series with the HIV-1 protease, compound **14** was co-crystallized with the enzyme, and the crystal structure was analyzed at 2.25 Å resolution.[16] Figure 3 shows a stereoview of **14** in the HIV-1 protease active site. The transition-state mimic hydroxyl group is situated between the two catalytic aspartic acid groups of the enzyme. The two inhibitor benzyl side chains occupy the P_1 and P_1' sites. The isothiabenzopyran group is in the P_2' pocket, and one of the sulfone oxygens is within hydrogen bonding distance of an Asp 29 NH group (3.2 Å). The reason for the tenfold increase in potency upon substitution of the THF group is not apparent from this structure. As in all HIV-1 protease/inhibitor crystal structures, the two carbonyl groups of the inhibitor form hydrogen bonds to a water molecule which in turn interacts with the flap Ile 50 NH groups.

Figure 4 illustrates the superposition of compounds **14** (yellow) and L-689,502[6] (magenta, a P_1' analog of L-685,434) generated by aligning both crystal structure complexes in the same frame of reference. The indan and isothiabenzopyran groups occupy the P_2' positions and both the indan's hydroxyl group and sulfone's axial oxygen make an interaction with Asp 29 NH. As expected, the Boc and THF groups occupy the P_2 pocket. The main difference between the two compounds is that the indan-amide NH of L-689,502 is able to make a hydrogen bond with Gly 27 of the enzyme while lactam **14**, which contains a carbon atom in this position, cannot form this hydrogen bond. This may provide at least a partial explanation for the loss in potency of the lactam series versus the corresponding acyclic compounds. In addition, the lactam ring appears to experience non-bonded interactions that force the P_1' lactam carbonyl group to be raised up by one angstrom relative to the L-689,502 P_1' carbonyl group. It is also evident that in the lactam-enzyme complex (yellow), the Gly 27 carbonyl oxygen is displaced one angstrom from the position of the Gly 27 carbonyl in the L-689,502 structure (magenta).

In summary, a concise and efficient synthesis of a new HIV protease inhibitor class has been accomplished. A full account of this series' structure activity relationships, as well as pharmacokinetic data for selected inhibitors, will be published in due course.[17]

Acknowledgments: The author gratefully appreciates the technical assistance of J. P. Moreau, H. Ramjit, S. Britcher, L. Payne and B. Schaefer for manuscript preparation.

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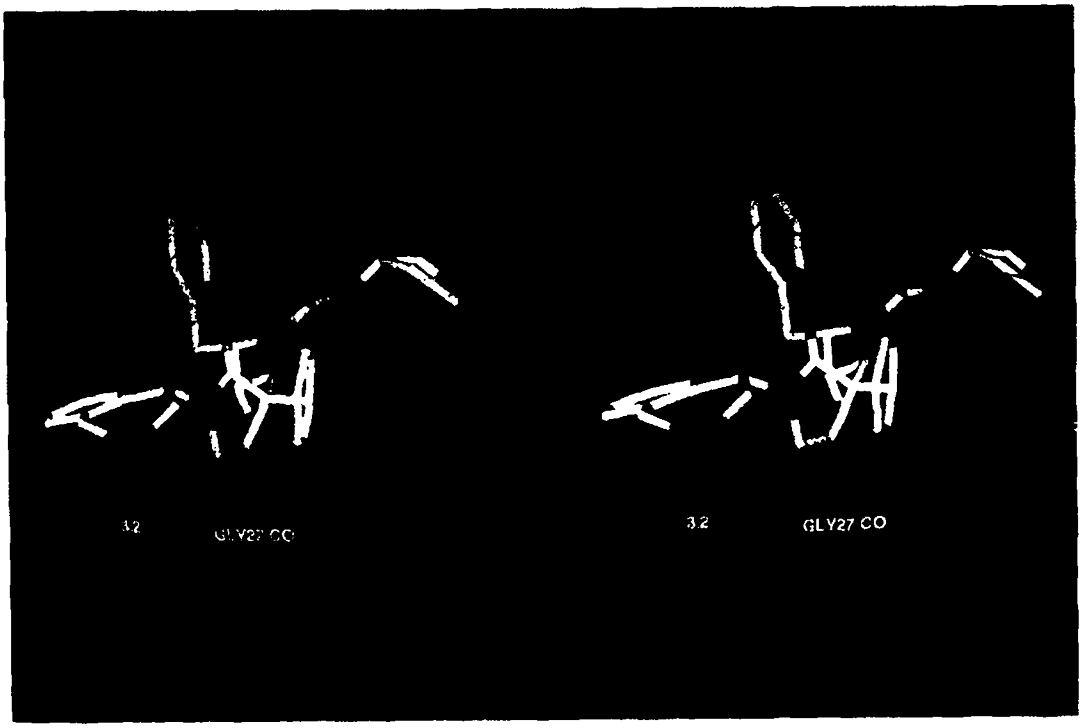

Figure 3 X-ray complex between L-700,497 (**14**, green) and HIV-1 protease. The sulfone oxygen of **14** is within 3.2 Å of Asp 29 NH of the protease.

Figure 4 Superposition of the X-ray complexes of compound **14** (yellow) with L-689,502 (magenta).

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(16) A complex between **14** (L-700,497) and HIV-1 protease was crystallized in space group $P2_12_12$, a=59.41, b=87.30, c=46.61 Å. A model for the complex was refined against data extending from 10.0 to 2.25 Å in resolution; the R-value for the final model was 0.169 and deviations from ideal bond distances were 0.018 Å. Full details of the crystallographic analysis will be published elsewhere.

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(*Received in USA* 9 *November* 1993; *accepted* 6 *December* 1993)