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SIMPLE *cis*-EPOXIDE-BASED INHIBITORS OF HIV-1 PROTEASE

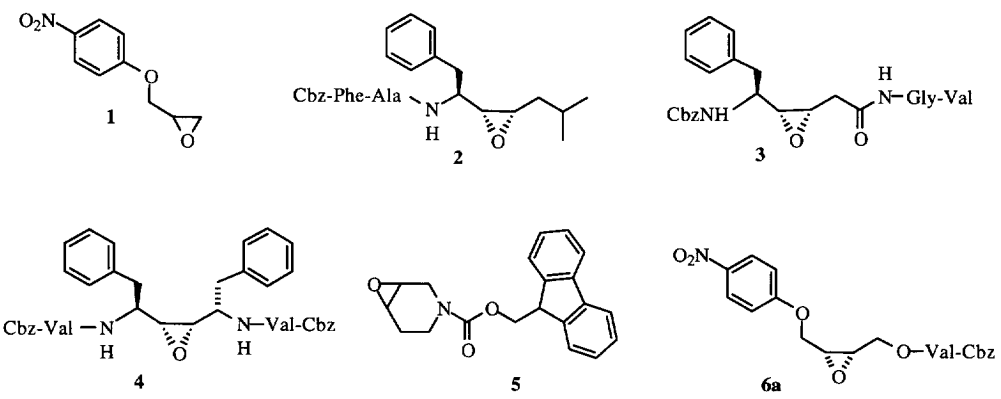
Andrew D. Abell,*[a] Deborah A. Hoult,[a] Douglas A. Bergman,[b] and David P. Fairlie[b]

aDepartment of Chemistry, University of Canterbury, Christchurch, New Zealand
bCentre for Drug Design and Development, University of Queensland, Brisbane, Qld. 4072 Australia

Abstract: The 4-nitrophenoxy-based epoxide **6a**, conveniently synthesized using Sharpless epoxidation chemistry, has been shown to be an irreversible inhibitor of HIV-1 protease (K_{inact} 1.8 μM, pH 6.5, I = 0.1 M). Related analogues, differing in the mode of attachment to the epoxide core, have also been prepared and assayed against HIV-1 protease. © 1997 Elsevier Science Ltd.

The use of inhibitors of HIV-1 protease is now established as a viable treatment for patients with acquired immunodeficiency syndrome (AIDS).[1] Many peptidomimetic transition state analogue inhibitors of this enzyme have been identifed with nanomolar and subnanomolar K_i values and a number of these have now been approved for the treatment of AIDS.[1] However, the need still exists to identify new inhibitors of HIV protease to combat problems associated with the appearance of drug resistant strains of HIV[2] and the expense and difficulties associated with the available treatments.[3] To this end, we have embarked on a programme to identify novel and simple leads for the development of potent inhibitors of HIV-1 protease.

To date, a few epoxide-based inhibitors of HIV-1 protease have been reported. 1,2-Epoxy-3-(4-nitrophenoxy)propane (EPNP; **1**) is a nonspecific, irreversible inhibitor of HIV-1 protease (K_{inact} 11 mM).[4] The nitrophenoxy group of EPNP is thought to reside in the S1 pocket of the enzyme active site. The tripeptidomimetic epoxide **2** was subsequently developed, based on the known specificity of HIV-1 protease, to span the S3-S1′ substrate-binding sites with the epoxy group binding in place of the scissile P1-P1′ peptide bond (K_{inact} = 20 μM).[5] *Cis* epoxide-based inhibitors of the type **3** have also been recently reported as time-dependent, irreversible inhibitors of HIV-1 protease.[6] An increase in the potency of these inhibitors was obtained by extending the peptide sequence to span the S2-S3′ binding domains. C_2-Symmetric epoxides of the type **4** are reversible inhibitors of HIV-1 protease (K_i = 75 nM)[7] while the non-peptidic epoxide **5** is an irreversible, active-site directed inhibitor of HIV-1 protease (K_{inact} = 65 μM).[8] Compound **5** was designed using the known non-peptidic inhibitor, haloperidol, as the lead structure.

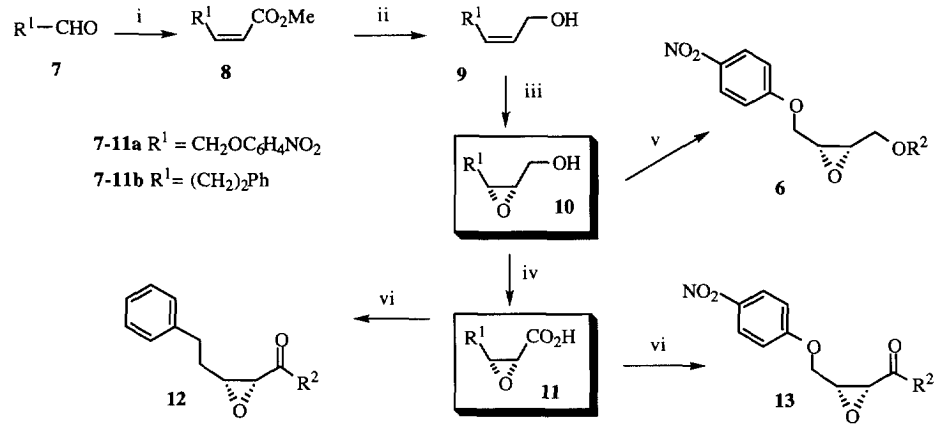


In this paper, we wish to report our initial studies on the synthesis and inhibition of HIV-1 protease by two series of simple *cis*-epoxides. The two series differ in the mode of amino acid attachment to an epoxide core structure, either **10** or **11**. Compounds **6** have an ester linkage to **10**, while **12** and **13** have an amide linkage to **11**. These compounds were designed to combine the nitrophenoxy group of EPNP (**1**) with a *cis*-epoxide, which is common to all the before mentioned literature inhibitors. We also required the compounds to be readily prepared, as single isomers, from simple starting materials.

The synthesis of compounds **6**, **12**, and **13** is given in the Scheme. A Horner–Wittig olefination of separate samples of the aldehydes **7a** and **7b** gave the *cis* α,β-unsaturated esters **8** (traces of the *trans* isomers were readily separable by chromatography). A diisobutylaluminium hydride (DIBAL) reduction of **8** gave the allylic alcohols **9**, which were converted into the key epoxides **10** under Sharpless conditions.[9] Condensation of **10a** with either Cbz-Val or Cbz-Val-Val, under Mitsunobu conditions,[10] then gave **6a** and **6b** (step v). Oxidation of **10a** and **10b** gave **11a** and **11b**, which underwent a BOP catalysed coupling with the methyl esters of either Val or Leu, to give compounds **12** and **13** (step vi).

The Table shows preliminary data for the inhibition of HIV-1 protease by compounds **6**, **12**, and **13** (a K_{inact} value was determined for the most potent derivative, **6a**). The first point about the data is that compounds of type **6** are more potent than the amide-linked analogues, **12** and **13**. Compound **6a** inhibited HIV-1 protease in a time-dependent manner. This inactivation was irreversible since enzyme activity was not recovered by exhaustive dialysis. A double reciprocal plot of inactivation rates (k_{obs}) versus inhibitor concentration[4] yielded values of 1.8 μM for K_{inact} (the concentration of inhibitor giving the half-maximum inactivation rate), 0.26 min^{-1} for V_{inact} (the maximal inactivation rate) and 1.4×10^5 M^{-1} min^{-1} for V_{inact}/K_{inact} (the bimolecular rate constant), which makes it significantly more potent than model epoxide EPNP. The addition of a reversible competitive inhibitor (DMP323, 100 nM)[12] protected the enzyme from inactivation by 10 mM of compound **6a**,

causing a 7.5-fold reduction in the apparent bimolecular rate constant. This result is consistent with compound **6a** reacting with an active-site residue.



(i) $[PhO)_2POCCO_2Me]Li^+$, –78 °C; (ii) DIBAL, –78 °C; (iii) $Ti(OiPr)_4$, L-DIPT, TBHP; (iv) $RuCl_3$, H_5IO_6; (v) RCO_2H, Ph_3P, DEAD; (vi) $Cl{\cdot}H_3NCHRCO_2Me$, BOP.

The incorporation of a second Val, as in **6b**, resulted in a significant decrease in potency towards HIV-1 protease. A nitrophenoxymethyl group, as in **6** and **13**, would appear to provide slightly more potent compounds than a phenylethyl group, as in **12**. Ongoing work is directed towards optimising the substituents and configuration of this new and readily prepared series of HIV-1 protease inhibitors.

Table. Inhibition of HIV-1 protease.[11]

Compound	R^2	% Inhibition[a]
6a	Val-NHCbz	88%[b] (K_{inact} = 1.8 μM)
6b	Val-Val-NHCbz	25%[b]
12	Leu-OMe	19%
13a	Val-OMe	22%
13b	Leu-OMe	30%

[a]After 1 min, pH 6.5, I 0.1 M, 37 °C, 50 μM [S], 200 μM [I].
[b]At 20 μM [I].

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