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Original article

Design and synthesis of novel P2 substituents in diol-based HIV protease inhibitors

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ABSTRACT

The synthesis and SAR of HIV-1 protease inhibitors containing novel P2 structural elements are presented. The inhibitors were designed having hydrogen bond accepting P2 substituents to probe potential favorable interactions to Asp-29/Asp-30 of the HIV-1 protease backbone utilizing inhibitor **3** as a model template. Several inhibitors were synthesized from an L-Val methyl amide P2 motif by appending hydrogen bonding moieties from either the isopropyl side-chain or from the methyl amide portion. The most promising inhibitors **4a** and **4e** displayed K_i values of 1.0 nM and 0.7 nM respectively and EC_{50} values in the MT4 cell-based assay of 0.17 μM and 0.33 μM respectively, a slight loss in potency compared to lead inhibitor **3**. These inhibitors were also tested against an HIV protease inhibitor resistant strain carrying the M46I, V82F, and I84V mutations. Inhibitors **4a** and **4e** displayed a 3 and 4 fold change respectively compared with HIV wild type, whereas lead inhibitor **3** showed a higher 9 fold change. This study further demonstrate the chemical tractability of the approach where various P2 substituents can be introduced in just one chemical step from lactone **21** enabling facile modifications of the overall properties in this inhibitor class.

1. Introduction

Over two decades ago the human immunodeficiency virus (HIV) was identified as the etiologic agent of AIDS [1,2] and in 2008 it was estimated by UNAIDS [3] that 33 million people were afflicted by this disease. The HIV-1 genome encodes an aspartic protease [4,5] (HIV-1 PR) that is essential for the production of structural and functional viral proteins by processing of the *gag*- and *gag-pol* viral gene products [4,6]. Inhibition of the HIV-1 PR leads to the production of immature virus particles [7,8] and in clinical practice HIV-1 PR inhibitors has demonstrated high efficacy which has led to the development of efficacious treatment regimens.

Today ten HIV-1 protease inhibitors are approved by the FDA; Saquinavir, [9] Ritonavir, [10] Indinavir, [11,12] Nelfinavir, [13] Amprenavir, [14] Fosamprenavir, [15] Lopinavir, [16] Atazanavir, [17] Tiprinavir [18] and Darunavir [19] (compound **1**, Fig. 1). HIV-1 PR inhibitors in combination with nucleoside analogues, which targets the HIV-1 reverse transcriptase (RT), has emerged as one of the two major Highly Active Antiretroviral Therapy, HAART, treatment regimens [20,21].

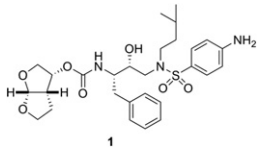

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Fig. 1. Compound **1**, Darunavir.

Current drug discovery efforts are now focusing on once daily HIV-1 PR inhibitors displaying improved efficacy, minor cross resistance towards clinical mutant resistant strains, high genetic barrier, low drug–drug interactions and an advantageous side effect profile. Cost is also a major issue with current HIV therapies and globally only ~20% of the HIV infected population is receiving adequate treatment [3].

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We have previously reported on the discovery of novel potent HIV–1 PR inhibitors, i.e. **2** [22] and **3** [23] (Fig. 2), displaying a C_2-symmetric diol-type central scaffold carrying P1/P1′ benzyloxy residues. In the C_2-symmetrical inhibitor **2** there are two amino-indanol P2/P2′ residues whereas in inhibitor **3** one of the amino-indanols has been replaced by L-Val methyl amide.

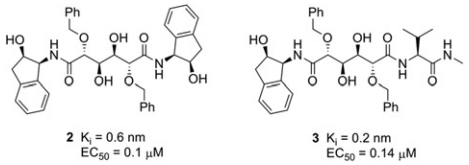


Fig. 2. Lead inhibitors **2** and **3**.

We now report on the synthesis and anti-HIV activities of a series of L-Val methyl amide analogues as P2 residues in inhibitor structure **3**, (i.e. **4a**–**h**, Fig. 3) containing potentially hydrogen interacting or accepting elements such as fluorine, methoxy groups and oxetane, with the aim to form positive interactions between these P2 residues and the N–H moiety in Asp-29 or Asp-30 of the HIV-1 protease backbone. The most promising inhibitor structures **4a** and **4e** displayed K_i values of 1.0 nM and 0.7 nM, respectively and EC_{50} values in the MT4 cell-based assay of 0.17 μM and 0.33 μM, respectively, a slight loss in potency compared to lead inhibitor **3**. Interestingly, these inhibitors displayed a 3 and 4 fold change in EC_{50} value, respectively, over HIV wild type when tested against an HIV PI multiple resistant strain, whereas inhibitor **3** showed a higher 9 fold change.

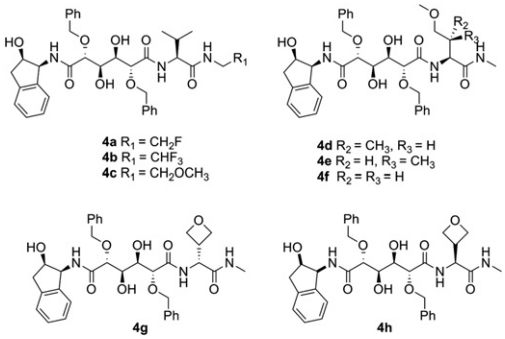
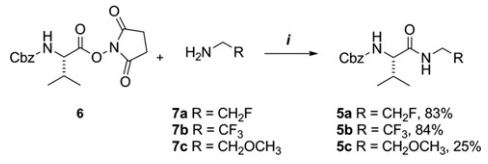


Fig. 3. Target structures **4a**–**h**.

2. Results and discussion

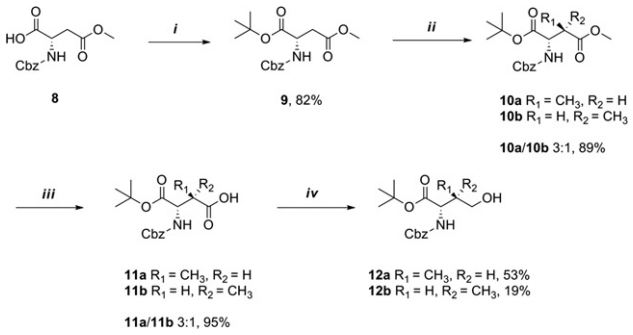
2.1. Chemistry

For the synthesis of the Cbz protected amines **5a**–**c** (Scheme 1) commercially available Cbz-L-Val-O-succinimide **6** was coupled with amines **7a**–**c** to generate **5a**–**c** [24] in 25–84% yield [22].



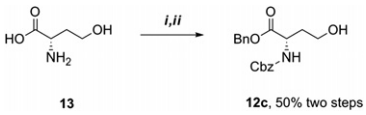
Scheme 1. Reagents and conditions: i: NMM, **7a**, **b** or **c**, THF.

Commercially available Cbz-L-Asp-OMe **8** was converted into its corresponding β-*tert*-butyl ester (Scheme 2) using isobutylene and a catalytic amount of H_2SO_4 [25] furnishing **9** [26] in 82% yield. Compound **9** was methylated [27,28] using LiHMDS and iodomethane to generate **10a**/**10b** [29] as an inseparable mixture of diastereomers in a 3:1 ratio in 89% yield. Selective hydrolysis [25] with NaOH (1 M) rendered the acids **11a**/**11b** as an inseparable mixture in 95% yield. The carboxylic acids **11a** and **11b** were activated with ethyl chloroformate and then reduced with sodium borohydride to generate the alcohols **12a** [30] and **12b** [30] that were easily separated by column chromatography in 53% and 19% yield, respectively.



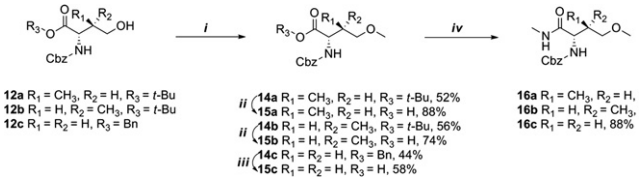
Scheme 2. Reagents and conditions: i: Isobutylene, H_2SO_4 (cat), CH_2Cl_2; ii: HMDS, BuLi, MeI, THF, 0 °C; iii: NaOH 1 M, MeOH; iv: a) Ethyl chloroformate, NMM, THF; b) $NaBH_4$, H_2O.

Commercially available L-homoserine **13** (Scheme 3) was Cbz and Bn protected [31] using $NaHCO_3$ and benzyl chloroformate, followed by treatment with NaOH and benzyl bromide to generate compound **12c** in 50% yield over two steps.



Scheme 3. Reagents and conditions: i: benzyl chloroformate, $NaHCO_3$; ii: NaOH, benzyl bromide.

The free hydroxyl groups of **12a**–**c** were converted into the corresponding methyl ethers **14a**–**c** (Scheme 4) in 44–56% yield using methyl triflate [32] and 2,6-di-*tert*-butyl-4-methylpyridine.



Scheme 4. Reagents and conditions: i: MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2; ii: TFA, TES, CH_2Cl_2; iii: NaOH (aq), THF/MeOH (13:10); iv: PyBOP, DIPEA, $MeNH_2$, CH_2Cl_2.

The *tert*-butyl esters **14a** and **14b** were cleaved using TFA [33] to render **15a** and **15b** in 88% and 74% yield respectively. The benzyl ester of **14c** was cleaved [34] with NaOH (0.59 M) to generate **14c** in 58% yield. The methylamides **16a**–**c** were obtained in 62–88% yield from **15a**–**c** using PyBOP [35], DIPEA and methylamine.