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Potent inhibitors of the HIV-1 protease incorporating cyclic urea P1–P2 scaffold

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Abstract—We have developed synthetic approaches to novel analogues of 2-imidazolidinone scaffold **2**, which was found to be an effective P1–P2 mimetic in HIV-1 protease inhibitor **4**. This enabled a rapid synthesis of analogues of **4** and subsequently allowed us to evaluate and rationalize the SAR. Accordingly, *trans* relationship of P1 and P2 substituents in the P1–P2 mimetic, as found in a related 2-pyrrolidone-based scaffold **1**, was found necessary for high potency against HIV-1 protease. Results of this study provided further rationale towards subsequent optimization of 2-pyrrolidone-based lead **3**, which led us to potent and drug-like HIV-1 protease inhibitors described in a follow-on report (*Bioorg. Med. Chem. Lett*. **2004**, *14*, in press. doi:10.1016/j.bmcl.2004.08.039).

The discovery of HIV-1 protease inhibitors (PI), has been widely accepted as a key factor contributing to the decrease of AIDS-related mortality rates in the developed world. However, the relatively large pill burden of the highly active antiretroviral therapy (HAART) might be a factor in sometimes inconsistent patient adherence to drug regimen. This in turn limits the benefits of HAART by allowing the rebound of viral load and potential emergence of viral resistance. Since much of the pill burden associated with PIs is a direct consequence of their limited aqueous solubility, our laboratories have been involved in discovery efforts towards novel PIs with improved solubility, potency and viral resistance profiles.[1–7] We recently disclosed *spiro-pyrrolidone*[3] and *spiro-morpholinone*[4] motifs that can serve as P1–P2 mimetics in marketed HIV protease inhibitors, such as Amprenavir[8] or Indinavir (Fig. 1). In this and a follow-up[9] report we are describing new synthetic protocols developed towards additional P1–P2 scaffolds, *mono-substituted pyrrolidine* **1** and 2-*imidazolidinone* **2**. Not only are scaffolds **1** and **2** more synthetically accessible than the spiro-molecules, but these motifs are also potentially more attractive synthetic targets due to high potency of lead compounds **3** and **4** (Fig. 1).[1]

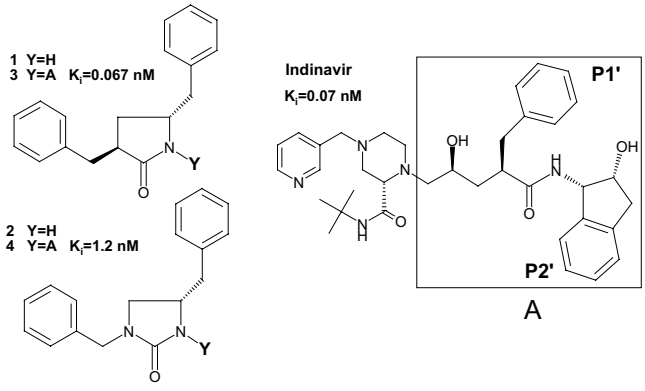

Figure 1. P1–P2 mimetics 2-pyrrolidone **1** and 2-imidazolinone **2** and associated HIV-1 protease inhibitors **3** and **4** incorporating the indanolamine-based P1′–P2′ scaffold **A**.

Our initial efforts focused on 2-imidazolidinone scaffold **2**,[8] the synthesis of which involved conversion of Boc-phenylalanine to amide **5**, which was then reduced with borane to diamine **6** and cyclized to the

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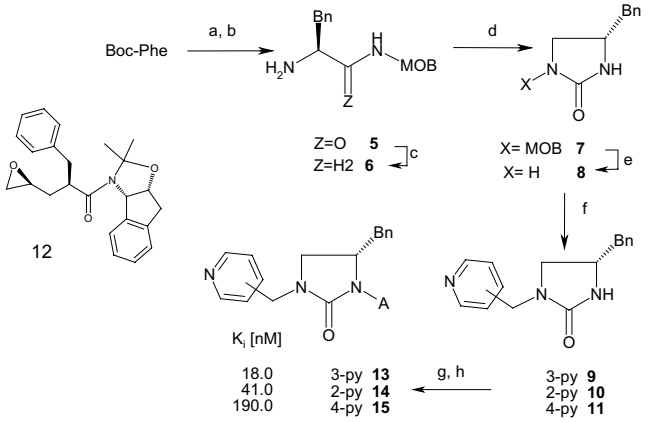

Figure 2. Reagents and conditions: (a) EDCI, HOBt, *p*-methoxybenzylamine; (b) TFA; (c) BH_3·THF in THF; (d) CDI, THF; (e) CAN; (f) 2-, 3- and 4-picolyl chlorides, KO-*t*-Bu; (g) NaH/DMF, **12**; (h) 4 N HCl in dioxane/water (95:5, v/v).

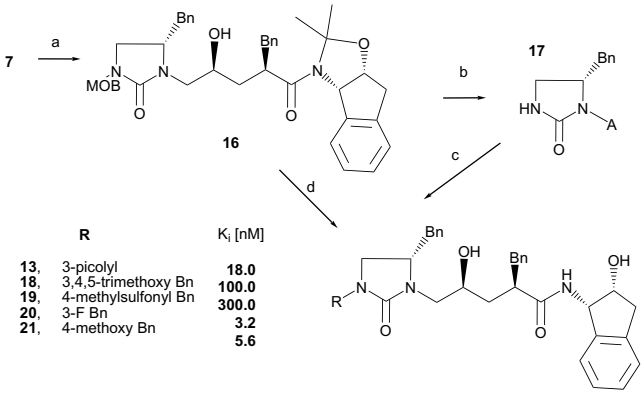

Figure 3. Reagents and conditions: (a) NaH/DMF, epoxide **12**, 95%; (b) neat TFA followed by basic workup, 65.6%; (c) *t*-Bu-OK, DMF, Bn–X, 60–85%; (d) 4 N HCl in dioxane/water (95:5, v/v), 93%.

p-methoxybenzyl (MOB)-protected urea **7** (Fig. 2). Subsequent deprotection of **7** and alkylation of 2-imidazolinone **8** with 2-, 3- and 4-picolyl chlorides yielded the desired 2-, 3- and 4-picolyl derivatives **9**–**11**, albeit in low yields. Considerable quantities of the unwanted N3-alkyl regioisomers and of N1-, N3-bis-alkylation products were also formed, necessitating laborious chromatographic purifications in order to secure small quantities of **9**–**11**.[10] Anions derived from **9** to **11** were then alkylated with epoxide **12**,[11] and the resulting intermediate acetonides were deprotected under acidic conditions,[12] yielding target inhibitors **13**–**15** (Fig. 2).

Evaluation of **13**–**15** in the HIV-1 protease enzyme assay indicated that these picolyl P2 substituent-bearing inhibitors were substantially less potent than benzyl **4**, suggesting that the solubilizing picolyl moiety was incompatible with the enzyme active site. We desired to explore additional benzyl-substituted derivatives of **2**. To overcome the synthetic hurdles encountered in the synthesis of **13**–**15**, we explored schemes, which did not allow the formation of N3-alkyl and N1-, N3-bis-alkyl products. The new route, starts with the coupling of intermediates **7** and **12**, to produce MOB-protected **16**. We then intended to selectively deprotect the MOB group in **16** under conditions, which would preserve the N-,O-acetonide moiety, and then N1-alkylate such a derivative with a wide variety of benzyl halides. However, all attempts to deprotect **16** involving cerium ammonium nitrate (CAN), including those previously employed in the synthesis of **8** (Fig. 2), failed to produce the desired product and instead yielded complex mixtures. Further experimentation led us to an observation that the treatment of **16** with neat TFA for 5 h, followed by acid removal and basic workup[13] resulted in intermediate **17** in good yield and purity. Rewardingly, **17** underwent facile alkylations with benzyl halides, allowing us to rapidly synthesize a number of analogues, including inhibitors **13** and **18**–**20**[10] (Fig. 3). In addition, deprotection of acetonide **16** yielded 4-methoxy derivative **21** (Fig. 3).

In contrast to the original route in Figure 2, the new approach to **13** and related compounds described in Figure 3 eliminates extensive and laborious purification, yielding ample quantities of products. These inhibitors were then evaluated in the HIV-1 protease enzyme assay, but none proved more potent than the parent **4**. This SAR was also confirmed in the antiviral MT-4 cell assay in which compounds **13**, **16** and **18**–**21** were less potent (2.2–10 μM) than **4** (1.4 μM). Molecular modelling of inhibitors of the type **18**–**21** in the context of the HIV-1 protease active site led us to rationalize that the relatively planar projection of the P2 substituent from N1 in 2-imidazolidonone **2** precluded strong interactions with the S2 pocket in the HIV-1 protease. Effective P1–P2 mimicry requires a more angular (sp^3) projection of P2 into the S2, as identified in 2-pyrrolidone motif **1**. Consistent with this observation, adding a *cis*-Me group in **3** resulted in a largely inactive HIV-1 protease inhibitor.[14]

This communication describes the development of a robust synthetic protocol, which enabled rapid synthesis of analogues of 2-imidazolone-based **4**. Attempts to optimize P2 substituents in this series and the emerging SAR strongly suggest that successful P1–P2 mimicry requires *trans* relationship of both P1 and P2 substituents in the P1–P2 scaffold in order to maximize the interactions with both S1 and S2 subsites.

Among the putative P1–P2 mimetics examined in the course of this work, such as morpholinone, 1,2,5-thiadiazolidine 1,1-dioxide, isothiazolidine 1,1-dioxide, 2-imidazolidinone and 2-pyrrolidone scaffolds,[1–7] we conclude that the latter is the most promising P1–P2 mimetic. Our follow-up report[9] discloses chemistry and SAR developed in the 2-pyrrolidone scaffold **1** series, leading to potent HIV-1 protease inhibitors with enhanced drug-like properties.

Acknowledgement

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10. ^{1}H and ^{13}C NMR spectral and mass spectroscopy data for all compounds support the proposed structures.
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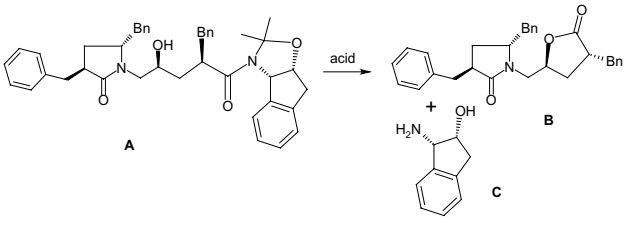
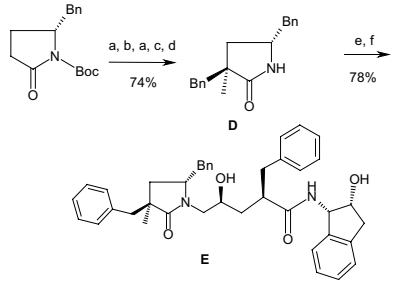
12. The deprotection of N-,O-acetonide **A** with TFA results in substantial amounts of cyclitive cleavage products, lacton **B** and indanolamine **C**. Additional experimens revealed that under conditions of 4 N HCl in dioxane (95%) and water (5%) formation of **B** and **C** is dramatically suppressed.



13. Excessive (longer than 5 h) exposure to the trifluoroacetic acid results in decomposition of **16** to products of the type **B** and **C** (Ref. 12). While shorter reaction time prevents formation of **B** and **C**, we found out that the desired product is obtained as a complex mixture of trifluoroacetyl esters and trifluorocetylated amides. These can be converted to the desired **17** by workup with aqueous sodium carbonate. Compound **17**: 0.30 g of **16** was dissolved in 10 mL of TFA and stirred for 5 h at room temperature. After in vacuo rotary evaporation, the solid residue was treated with 10% Na_2CO_3 in methanol/water for 10 min, yielding 0.15 g of **17** (yield 65.6%). ^{1}H NMR of **17** ($CDCl_3$, 300 MHz): δ 8.10 (1H, d, J = 8.4 Hz), 7.24 (10H, m), 7.05 (5H, m), 5.28 (1H, m), 4.10 (1H, m), 3.97 (1H, m), 3.53 (1H, m), 3.39 (2H, m), 2.95 (5H, m), 2.69 (2H, m), 2.54 (1H, m), 2.17 (1H, m), 1.92 (1H, m), 1.78 (1H, m). Compound **13**: 20 mg of **17** (0.039 mmol) in 1 mL DMF were stirred with potassium *t*-butoxide (26.3 mg, 0.234 mmol, 6 equiv) for 10 min, followed by addition of 6.3 mg of 3-picolyl chloride in 1 mL DMF. The reaction was stirred for 20 min, solvents removed in vacuo and the product purified on HPLC yielding 14.2 mg of **13** (yield 60.2%). ^{1}H NMR of **13** (d_6-acetone, 400 MHz): δ 8.57 (1H, d, J = 5.3 Hz), 8.42 (1H, s), 8.01 (1H, d, J = 8.0 Hz), 7.80 (1H, m), 7.20 (14H, m), 6.92 (1H, d, J = 8.8 Hz), 5.23 (1H, m), 4.29 (1H, d, J = 16.2 Hz), 4.29 (1H, m), 4.11 (1H, d, J = 16.2 Hz), 3.98 (2H, m), 3.48 (1H, dd), 3.18 (2H, m), 3.00 (4H, m), 2.75 (3H, m), 1.93 (1H, m), 1.88 (1H, m), 1.66 (1H, m).
14. For example, analogue **E** with the 3-methyl-substituent (P2) *cis* to 5-benzyl (P1) was much less potent (K_i = 170 nM) than **3** (K_i = 0.05 nM).



(a) LHMDS −78 °C; (b) MeI; (c) Bn–Br; (d) TFA; (e) Ref. 1; (f) 4 N HCl in dioxane/water (95:5, v/v).