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Optimization of pyrrolidinone based HIV protease inhibitors

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Abstract—Optimization of P1-substituted pyrrolidinone based HIV protease inhibitors has yielded analogs with very potent antiviral activity.
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1. Introduction

The HIV pandemic continues unabated. However, in the western world, HAART (Highly Active Anti-Retroviral Therapy) has made dramatic impacts on both the mortality and morbidity associated with HIV infection. HIV protease inhibitors were pivotal in early triple combination therapy trials and continue to be a critical component of HIV therapy.[1]

Our efforts in this field of research led to the generation of a novel series of inhibitors where a 3,5-disubstituted pyrrolidinone occupies the P1/P2 pocket of the active site of the viral protease.[2] The 2,5-dibenzyl substituted pyrrolidinone **1a** (Fig. 1) demonstrated exceptional enzyme inhibition ($IC_{50} = 0.050\,nM$). Unfortunately, the antiviral activity ($ED_{50} = 0.72\,\mu M$) of this analog in cell based assays failed to match prototypical inhibitors such as the marketed drug, amprenavir ($ED_{50} = 0.15\,\mu M$).

Researchers at Merck have previously reported that polar, hydrophilic, phenolic substituents tethered to the P1 or P1′ phenyl groups of indinavir progenitors could enhance antiviral potency.[3] Similarly, we sought to optimize substitutions at these positions within our inhibitor in order to demonstrate increased antiviral potency. Using molecular modeling derived from the crystal structure[4] of a similar analog bound to the HIV protease protein where the P1 position was unsubstituted, we

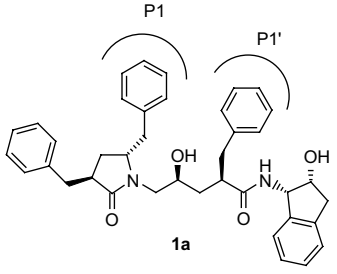

Figure 1.

rationalized that the *para*-position of the P1-benzyl group would be near to the exterior of the active site and therefore might tolerate additional functionalization (Fig. 2). Similarly, Merck researchers identified the *para*-position of the P1′-benzyl[3] as having similar attributes in an identical hydroxyethylene backbone.

2. Chemistry

The general synthetic strategy for construction of these analogs (see Fig. 3) involved a diastereoselective synthesis of the P1/P2 pyrrolidinone scaffolds **7a** and **7c** followed by addition to epoxides **8a** and **8b**. Preparation of the *N*1-unsubstituted 3,5-dibenzyl pyrrolidinone intermediates was accomplished through Wittig olefination of either *N*-Boc-L-phenylalaninal (**3a**) or *N*-Boc-O-benzyl-L-tyrosinal (**3b**) with known phosphorane **2**,[5] available through alkylation of methyl triphenylphosphorylideneacetate with benzyl bromide. As expected, the

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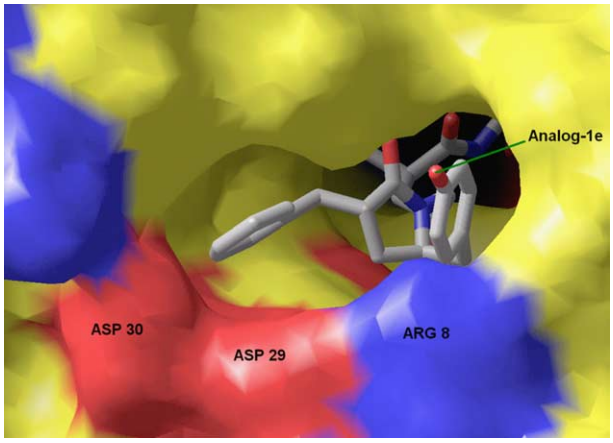


Figure 2.

olefination yielded exclusively the *E*-isomer of enoates **4a** and **4b** in good yields. Diastereoselectivity, induced through 1,3-allylic strain,[6] was achieved in the subsequent catalytic reduction of the olefin bond to give predominantly the desired *anti*-isomer. Reduction of tyrosine derived enoate **4b** provided a 2:1 mixture of *anti* and *syn* isomers, **5b** and **6b**, in essentially quantitative yield with concomitant loss of the benzyl protecting group. On the other hand, phenylalanine derived enoate **4a** provided a 5:1 mixture of *anti* and *syn* isomers **5a** and **6a**, although we could not readily rationalize the improved diastereoselectivity observed. Neither mixture of diastereomers could be resolved by chromatography at this juncture.

Acidic deprotection of the Boc group on the diastereomeric mix of **5** and **6** followed by basification to induce cyclization provided pyrrolidinones **7a** and **7b**. The minor *cis* epimer of 2,5-dibenzyl pyrrolidinones **7a** was chromatographically removed using TLC mesh silica gel. The relative stereochemistry of **7a** was assigned based on 2D-NMR analysis and later confirmed through single-crystal X-ray diffraction. We had previously established the preferred stereochemistry as the *trans* isomer.[2] The phenolic pyrrolidinone **7b** was inseparable from the contaminating diastereomer. Therefore, the 2:1 mixture of *trans* and *cis* isomers was carried through the remainder of the sequence following installation of the methoxymethyl ether protecting group on the phenol as **7c**.

Epoxide **8a** was prepared identically to known epoxide **8b**, used in the manufacturing of indinavir.[7] However, 3-[4-(benzyloxy)phenyl]propionic acid[8] was substituted for phenylpropionic acid as starting material.

Addition of pyrrolidinones **7a** and **7c** to epoxides **8a** and **8b**, respectively, using P4-phosphazene base at −20 °C followed by acid deprotection of the acetonide with HCl generated the complete hydroxyethylene backbone of analogs **1b** and **1e**. The deprotection protocol concomitantly removed the methoxymethyl ether protecting group at P1 yielding phenol analog **1e**. The benzyl protecting group at the P1′ position was removed using catalytic hydrogenation to provide phenol **1d**.

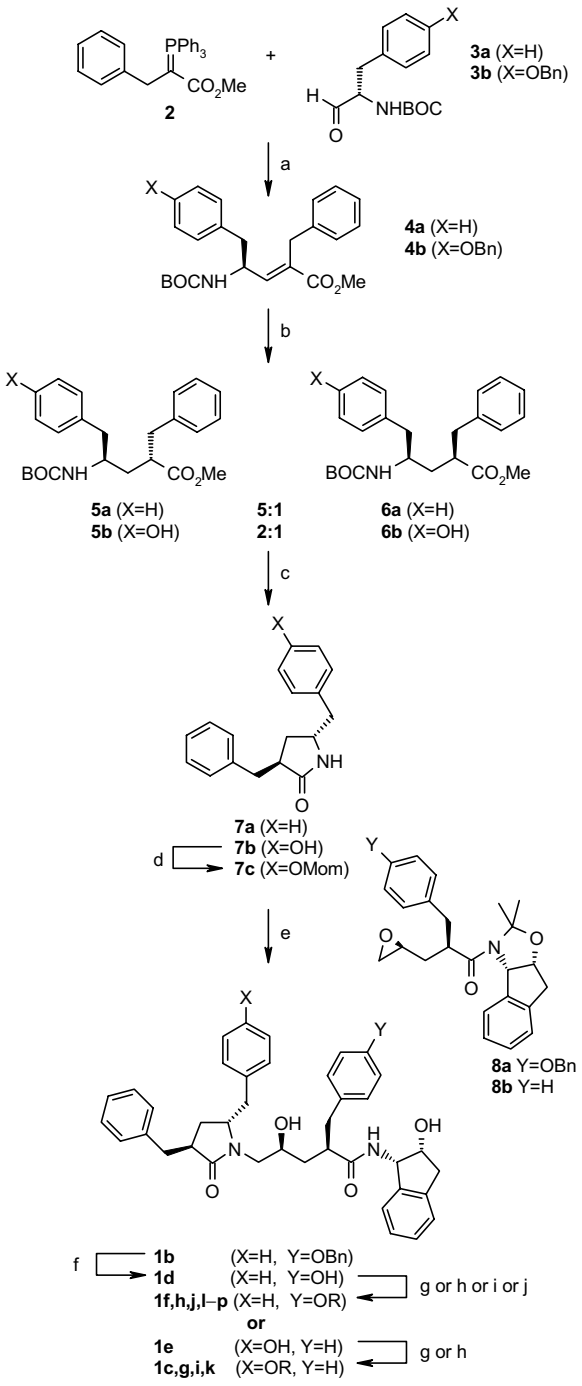


Figure 3. (a) $CHCl_3$, rt; for **4a**: 77%, for **4b** 71%; (b) 5% Pd/C, H_2 (1 atm), MeOH; for **5a/6a** and **5b/6b** 100%; (c) i. TFA/CH_2Cl_2 (1:1); ii. K_2CO_3 (4 equiv), MeOH; for **7a** 69%, for **7b** 100%; (d) NaH, DMF, methoxymethyl chloride, 74%; (e) i. P4-phosphazene, −20 °C, THF; ii. 21–26 equiv concd HCl, IPA, rt; for **1b**: 85 and 93%, respectively; for **1e**: 76% and 60%, respectively; (f) $Pd(OH)_2$/C, EtOH, 92%, for **1d**; (g) Cs_2CO_3, dioxane, halide Z, 80 °C, 28–98%; for **1c** Z = benzyl bromide, for **1f** and **1g** Z = *N*-chloroethyl-morpholine, for **1j** and **1k** Z = *N*-(bromoacetyl)morpholine,[9] for **1m** Z = 2-bromoethyl 2-methoxyethyl ether, for **1n** Z = 4-morpholinecarboxylic acid, 2-bromoethyl ester;[10] (h) for **1h** and **1i**; i. methyl bromoacetate Cs_2CO_3, dioxane, 80 °C, 63–64%; ii. $LiBH_4$, THF 36–67%; (i) for **1l**, 2-pyridinemethanol, DEAD, PPh_3, THF, 16%; (j) i. methyl bromoacetate Cs_2CO_3, dioxane, 80° C, 64%; for **1o**: ii. THF/H_2O/TEA 3/1.5/0.75 at reflux; 39%; iii. EDC, HOBT, DMF, *N*-methylpiperazine, 24%; or for **1p**: ii. 2 M NH_3 in MeOH, 64%.

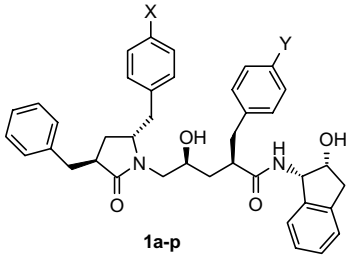
Tethered analogs **1f**,**g**,**j**,**k**,**m**,**n** were prepared through alkylation of the phenol and the appropriate halide with Cs_2CO_3 in dioxane at 80 °C. Analog **1l** was prepared via Mitsonobu coupling of **1d** with 2-pyridylmethanol. Ethoxy analogs **1h** and **1i** were prepared via alkylation of phenols **1d** and **1e**, respectively, with methyl bromoacetate followed by $LiBH_4$ reduction of the intermediate ester. Similarly, amide analogs **1o** and **1p** were prepared by initial alkylation of phenol **1d** with methyl bromoacetate. Direct aminolysis of the intermediate ester yielded acetamide **1p** whereas basic hydrolysis of the ester and carbodiimide coupling of the acid with *N*-methylpiperazine yielded **1o**.

3. Results and discussion

Initially, we sought to focus our efforts toward either the P1 or P1′ position through synthesis of a representative set of comparative analogs. For this purpose, we chose four substituents which had previously imparted increased antiviral efficacy in HIV protease inhibitors with an identical ethanolamine backbone:[3] the phenols, **1d** and **1e**; the morpholinoethoxy ethers, **1f** and **1g**; the ethoxy ethers **1h** and **1i**; and the morpholineacetamides, **1j** and **1k**.

Each of the P1 substituted phenols demonstrated decreased enzyme potency. Antiviral potency relative to the unsubstituted phenyl analog **1a**, was either similar or decreased excepting morpholineacetamide **1k** and phenol **1e**, which both demonstrated increased antiviral activity of 0.20 μM versus 0.72 μM from the parent. Of particular note, the morpholinoethoxy analog **1g** displayed a greater than 20-fold loss in enzyme potency with a concomitant loss of antiviral activity to 0.96 μM. The measured loss of enzyme and antiviral potency at P1 could not be rationalized by the presence of the contaminating one third inactive diastereomer in these analogs. Apparently, the greater conformational constraint inherent in the pyrrolidinone system did not allow optimal placement of even small, flexible substituents at this position. For these reasons, we elected to focus the remainder of our efforts on P1′ substituted analogs (Table 1).

Table 1.



Analog[a]	X[b]	Y	K_i (nM)[c]	IC_{50} (μM)[d]
amprenavir			0.04	0.15 (±0.01)
1a	H	H	0.05	0.72 (±0.11)
1b	H	OBn	0.11	0.92 (±0.09)
1c	OBn	H	0.13	0.55 (±0.05)
1d	H	OH	0.06	0.32 (±0.04)
1e	OH	H	0.13	0.20 (±0.05)
1f	H	–OCH_2CH_2-N⟨O⟩	0.14	0.083 (±0.02)
1g	–OCH_2CH_2-N⟨O⟩	H	1.30	0.96 (±0.14)
1h	H	–OCH_2CH_2OH	0.02	0.094 (±0.01)
1i	–OCH_2CH_2OH	H	0.30	0.48 (±0.03)
1j	H	–OCH_2CON⟨O⟩	0.02	0.063 (±0.02)
1k	–OCH_2CON⟨O⟩	H	0.10	0.20 (±0.02)
1l	H	–OCH_2–⟨N⟩	0.07	0.38 (±0.04)
1m	H	–$O(CH_2CH_2O)_2CH_3$	0.02	0.093 (±0.02)
1n	H	–$OCH_2CH_2OC(O)N$⟨O⟩	0.05	0.24 (±0.02)
1o	H	–OCH_2CON⟨NMe⟩	0.05	0.13 (±0.03)
1p	H	–OCH_2CONH_2	0.07	0.36 (±0.03)

[a] All compounds were >95% pure by ^1H NMR and HPLC.
[b] Analogs where X ≠ H are 2:1 mixture of *trans*:*cis* pyrrolidinone.
[c] K_i, enzyme inhibition constant,[11] %CV 0.15–1.15.
[d] IC_{50}, antiviral inhibition against HIV-1 in MT-4 cell culture;[12] N ⩾ 6.

The P1′ substituted phenols, in contrast, demonstrated similar or increased enzyme inhibition relative to the unsubstituted analog. More importantly, each of the P1′ analogs with the exception of the benzyl analog **1b** demonstrated increased antiviral activity in our cell based assay. As observed for the P1 substituted analog, the morpholinoethoxy analog **1f** also demonstrated the most dramatic loss in enzyme potency, 0.14 versus 0.05 nM. However, an enhanced antiviral potency was recorded for this compound, 0.08 μM versus 0.72 μM for the parent. Particularly noteworthy, analogs **1f**, **1h**, **1j** and **1m** all demonstrated somewhat improved antiviral efficacy relative to the marketed protease inhibitor, amprenavir.

In summary, we have disclosed a series of optimized 2,5-dibenzyl pyrrolidine based HIV protease inhibitors which demonstrate improved antiviral potency through modifications at P1′. These analogs demonstrated comparable antiviral efficacy to currently marketed agents, such as amprenavir.

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