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Novel Lopinavir Analogues Incorporating Non-Aromatic P-1 Side Chains—Synthesis and Structure–Activity Relationships

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Abstract—The HIV protease inhibitor Lopinavir has a pseudosymmetric core unit incorporating benzyl groups at both P-1, P-1′ positions. A series of analogues incorporating non-aromatic side chains at the P-1 position were synthesized and the structure–activity relationships explored.

The HIV protease inhibitor Lopinavir[1] (ABT-378) is the anti-viral component of Kaletra™ (approved by FDA in September, 2000), the latest approved HIV protease inhibitor for the treatment of human immunodeficiency virus (HIV) infection. The pseudo-C_2-symmetrical diamino-diphenylhexanol P-1/P-1′ core unit of lopinavir is identical to that of ritonavir[2] and both have their structural roots in our early reports of C_2-symmetric and pseudo-C_2-symmetric inhibitors of HIV protease, such as compounds **1**–**4**[3–5] shown in Figure 1.

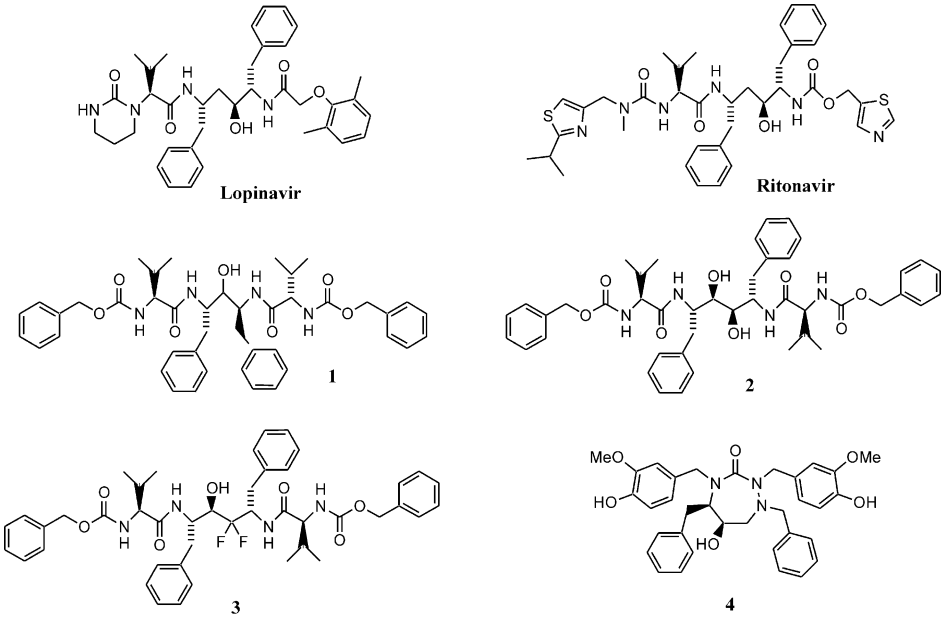

Figure 1. HIV protease inhibitors.

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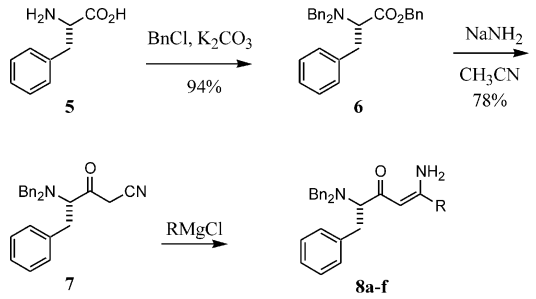
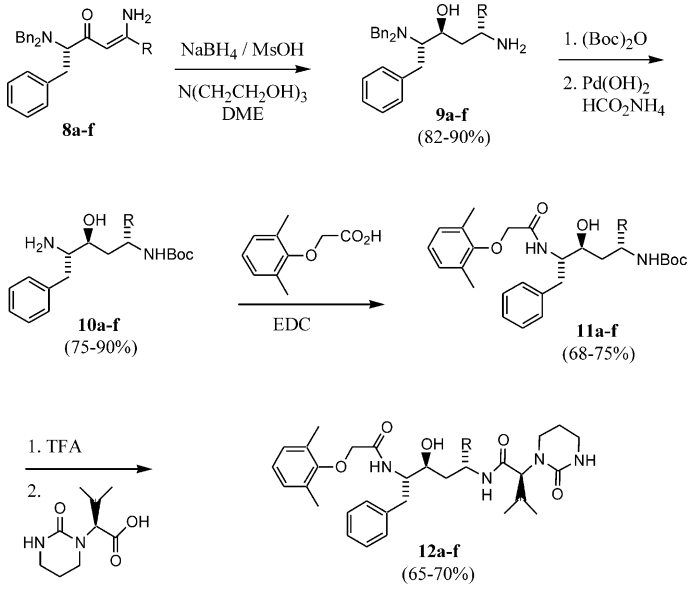


Scheme 1. Synthetic scheme for the core unit. R: (a) benzyl, (b) butyl, (c) isopropyl, (d) isobutyl, (e) 3-methylbutyl, (f) 2-ethylbutyl.

Inspection of the structures of the HIV protease inhibitors in Figure 1 shows that all of them have the aromatic benzyl group in both the P-1 and P-1′ position. In order to further desymmetrize the core unit and explore the resulting structure–activity relationships, we synthesized a series of novel analogues of lopinavir in which the P-1 benzyl side chain was replaced with non-aromatic alkyl groups. The synthesis of the core unit with non-aromatic side chains is shown in Scheme 1, following the same route reported for the benzyl side chain.[6] The key reaction, treatment of the cyanomethyl ketone with a Grignard reagent to give the corresponding enaminone, proceeds in 94% for benzyl Grignard. The alkyl Grignards used in Scheme 1 give yields ranging from 82–91% for this transformation.

The reduction of **8a** to give **9a** has been reported.[6,7] The reduction of **8b–f** to provide the diamino compounds **9b–f** followed similar procedures and is shown in Scheme 2. The resulting amines were protected with a Boc group. Catalytic debenzylation using transfer hydrogenation provided the amines **10a–f**. Coupling of the amines with 2,6-dimethylphenoxyacetic acid[8] using standard procedures provided **11a–f**. Removal of the Boc protecting group using trifluoroacetic acid and coupling of the resulting amines with the cyclic urea derived from L-valine[8] provided the final products **12a–f**.

The HIV protease inhibitory potencies[2] (% inhibition @ 0.5 nM) and the anti-viral activities (against the cytopathic effects of HIV_{IIIB} in MT-4 cells) of the inhibitors **12a–f** are reported in Table 1. The anti-viral activities were assayed in the presence of 50% human serum so as to better assess the effect of plasma protein binding on activities. All the compounds[9] with alkyl side chains have enzymatic inhibitory potencies comparable to that of lopinavir. However, in the anti-viral assay (in the presence of 50% human serum), lopinavir has the best potency. In addition, its good pharmacokinetic profiles[1] in several animal species led to its selection as the candidate to enter clinical trials.



Scheme 2. Reduction of enaminone and synthesis of HIV protease inhibitors **12a–f**.

Table 1. Inhibition of HIV protease and anti-viral activities in MT-4 cells

Compd	R	% Inhibiton @ 0.5 nM	Antiviral EC_{50},[a] μM	Cytotoxicity IC_{50}, μM
12a (lopinavir)	Benzyl	93	0.10	17.8
12b	Butyl	87	0.92	32.9
12c	Isopropyl	93	0.26	56.2
12d	Isobutyl	64	0.32	34.4
12e	3-Methylbutyl	97	0.34	18.7
12f	2-Ethylbutyl	87	2.8	17.8

[a]In the presence of 50% human serum.

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9. All compounds reported have mass, NMR, and analytical data consistent with the structures assigned.