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Novel lopinavir analogues incorporating heterocyclic replacements of six-member cyclic urea—synthesis and structure–activity relationships

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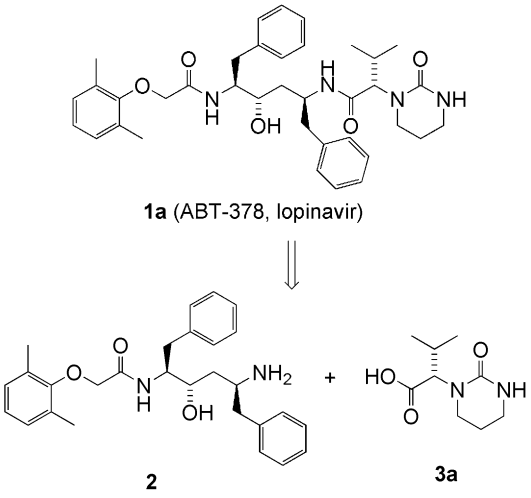
Abstract—The HIV protease inhibitor ABT-378 (lopinavir) has a six-member cyclic urea in the P-2 position. A series of analogues in which the six-member cyclic urea is replaced by various heterocycles was synthesized and the structure–activity relationships explored.

The human immunodeficiency virus (HIV) protease inhibitor lopinavir[1] (ABT-378, **1a**) is the antiviral component of Kaletra™ (approved by FDA in September 2000), one of the latest approved HIV protease inhibitors for the treatment of HIV infection. Lopinavir (**1a**) possesses high potency against wild type and mutant HIV proteases with K_i values ranging from 1.3–28 pM.[2] The synthesis of lopinavir[3] and its major metabolites,[4] as well as structure–activity relationships of P-1 (benzyl side chain),[5] and P-2′ (2,6-dimethylphenoxyacetyl)[6] positions of lopinavir have been reported. In this report, a series of lopinavir analogues in which the six-member cyclic urea at position P-2 is replaced by various heterocycles is described. The synthesis and structure–activity relationships of these analogues are reported.

The retrosynthetic analysis of lopinavir (**1a**) is shown in Scheme 1. Coupling of the carboxylic acid **3a** with amine **2** (synthesis of this amine is reported in Ref. 5) using EDAC/HOBt provided **1a**. Synthesis of lopinavir analogues **1b–j** are accomplished similarly by the coupling of the novel carboxylic acids **3b–j** with amine **2**. The synthesis of acids **3a–d** is outlined in Scheme 2. Deprotection of compound **4** with trifluoroacetic acid, followed by treatment with carbonyldiimidazole or thiocarbonyldiimidazole provided compound **5** (60–75% yield). Treatment of **5** ($n = 1$, X = O) with sodium



Scheme 1. Retrosynthetic schemes for lopinavir.

hydride, then methyl iodide resulted in **6** in 60% yield. Hydrolysis of the methyl esters of **5** and **6** provided the carboxylic acids **3a–d** (85–92% yield).

The synthesis of acids **3e–g** is illustrated in Scheme 3. Refluxing the benzyl ester of L-valine with succinic anhydride in chloroform gave **7** in 90% yield. Compound **7** was treated with EDAC/HOBt in DMF in the presence of 4-dimethylaminopyridine at room temperature for 4 days to cyclize to **8** (26% yield). Hydrogenolysis of **8** provided acid **3e** (95% yield). Reaction of

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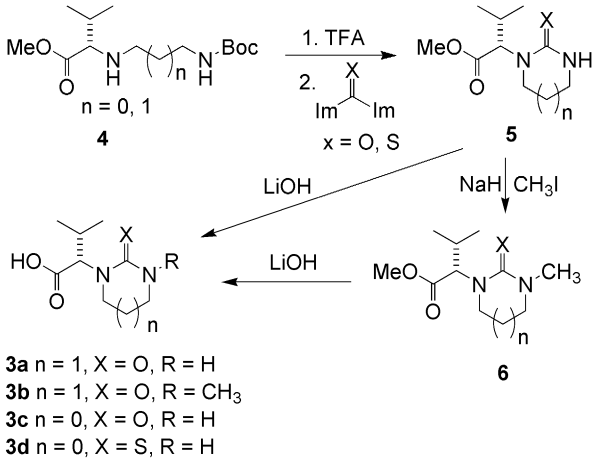
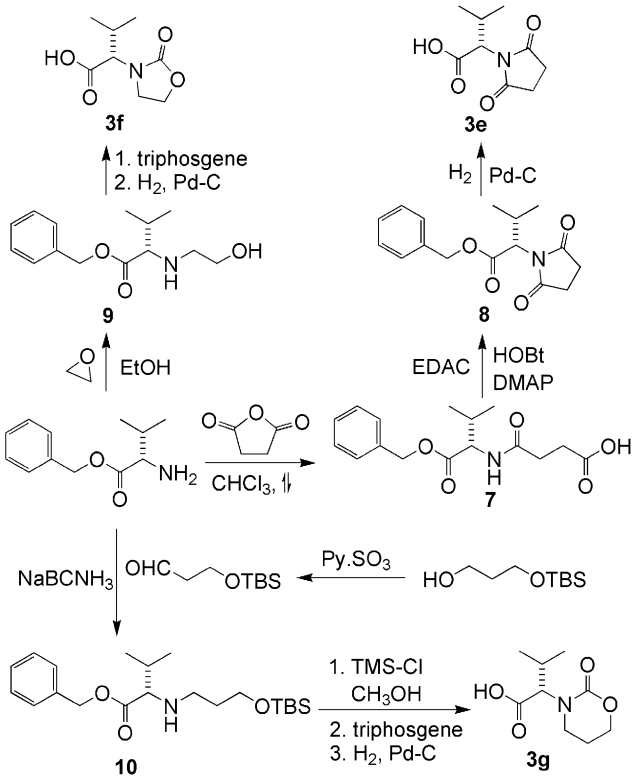
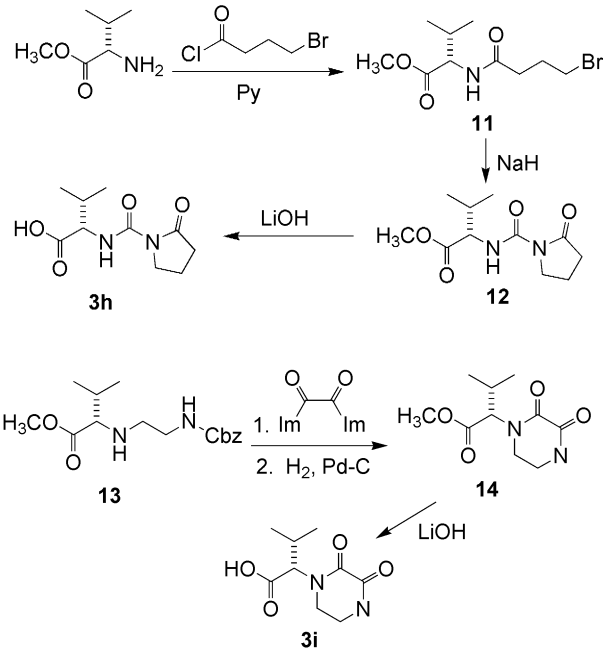


Scheme 2. Synthesis of acids **3a**–**d**.



Scheme 3. Synthesis of acids **3e**–**g**.

L-valine benzyl ester with excess ethylene oxide in ethanol gave **9** (75% yield). Treatment of **9** with triphosgene in methylene chloride, followed by hydrogenolysis afforded acid **3f** (70% for two steps). The mono-*t*-butyldimethylsilyl group protected 1,3-propanediol was oxidized with pyridinium sulfur trioxide in DMSO to give the corresponding aldehyde, which underwent reductive amination with L-valine benzyl ester to provide **10** (63% yield). Deprotection of **10** with in situ generated hydrogen chloride (TMS–Cl/methanol) followed by reaction with triphosgene and subsequent hydrogenolysis furnished acid **3g** in 70% yield.



Scheme 4. Synthesis of acids **3h**–**i**.

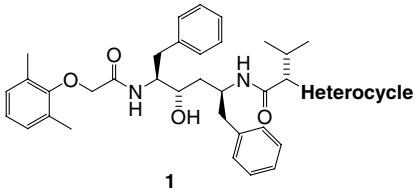
The synthesis of acids **3h**–**i** is shown in Scheme 4. Reaction of 4-bromobutanoyl chloride with L-valine methyl ester provided compound **11** in 86% yield. Treatment of **11** with sodium hydride, provided γ-lactam **12**. Hydrolysis of the methyl ester of **12** afforded acid **3h** (61% yield). Reaction of **13** with oxalyldiimidazole in toluene, followed by hydrogenolysis gave **14** (35% yield), which was hydrolyzed to provide **3i**. The synthesis of acid **3j** has been reported previously.

Coupling of the acids **3a**–**j** with amine **2** provided lopinavir and its analogues **1b**–**j**.

The HIV protease inhibitory potencies (%inhibition @ 0.5 nM) and the antiviral activities (against the cytopathic effects of HIV_{IIIB} in MT-4 cells) of the inhibitors **1a**–**j** are summarized in Table 1. Inhibitor **1c**, with a five-member cyclic urea, has very comparable activities to lopinavir (**1a**), but has inferior pharmacokinetic (PK) properties in rats, with a shorter half life (<0.5 h vs ~1 h for **1a**, F% = <15% vs 25% for **1a**), and lower AUC than **1a**. Removal of the hydrogen bonding capability of the cyclic urea via N-methylation (**1b**), or replacing the carbonyl with a thiocarbonyl (**1d**), or replacing the NH with CH_2 as in the case of lactam (**1h**), all seemed to reduce the activities of the inhibitors. Substituting the cyclic urea in **1a** with both the five- or six-membered cyclic carbamates reduced the activities only slightly. Inhibitor **1j**, though has the highest enzymatic potency, is less active than **1a** in the antiviral assay.

In summary, a series of HIV protease inhibitors in which the six-member cyclic urea of lopinavir (**1a**) is replaced by various heterocycles was synthesized. When compared to the analogues synthesized (Table 1), lopinavir (**1a**) has the best overall HIV protease inhibitory activity, antiviral potency, and pharmacokinetic profile in

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



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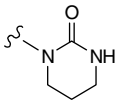
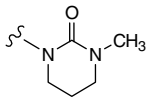
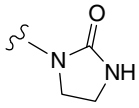
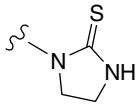
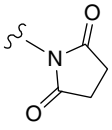
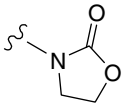
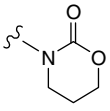
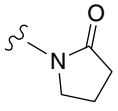
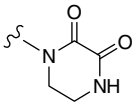
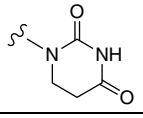
Compound	Heterocycle[7]	%Inhibition @ 0.5 nM	Antiviral EC_{50}[a] (μM)
1a (Lopinavir)		93	0.10
1b		80	1.06
1c		93	0.07
1d		63	3.80
1e		58	2.51
1f		87	0.11
1g		85	0.27
1h		87	0.31
1i		73	3.05
1j		100	0.14

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

several animal species, which led to its selection as the clinical candidate to enter clinical trials.

Acknowledgements

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7. All compounds reported have mass spectrum, NMR, and analytical data consistent with the structures.