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# Design and Synthesis of Highly Potent HIV Protease Inhibitors with Activity Against Resistant Virus

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**Abstract**—A series of highly potent HIV protease inhibitors have been designed and synthesized. These compounds are active against various clinical viral isolates as well as wild-type virus. The synthesis and biological activity of these HIV protease inhibitors are discussed.


The AIDS epidemic has spread around the world at an alarming rate. Although the first generation of HIV protease inhibitors,[1] including indinavir, nelfinavir, saquinavir and ritonavir, were initially effective against HIV infection, the fast emerging resistance to above agents has been a substantial and persistent problem in the treatment of AIDS.[2] Attempts to address the resistance issue with 'salvage therapy' consisting of high doses of multiple protease inhibitors have only been moderately successful due to the high level of cross resistance and toxicities associated with the protease inhibitors. Accordingly, there remains a need for new protease inhibitors having improved effectiveness against the resistant viral variants.

In an effort to search for a new structure-type of HIV protease inhibitors, we took advantage of the $C_2$ symmetry of the protease by preparing hybrid inhibitors combining the P3P2P1 ligand of the α-hydroxy amide based inhibitor **JE-2147**[3] with the P1′P3′ portion of indinavir (Fig. 1).

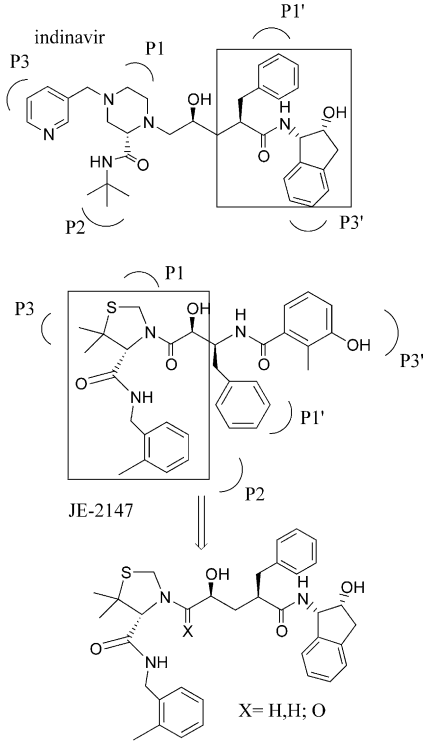


**Figure 1.** Design of a hybrid between indinavir and JE-2147.

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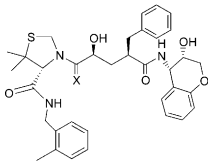
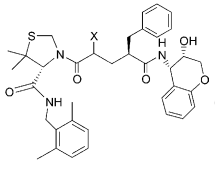
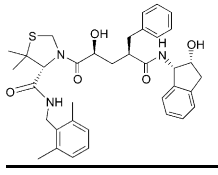
In order to explore the scope of the proposed hybrid series, several compounds were initially synthesized. Surprisingly this combination resulted in HIV protease inhibitors (PI) that exhibited high potency in both the protease enzyme inhibition assay ($IC_{50}$) and the spread assay (inhibition of the spread of viral infection in MT4 human T-lymphoid cells, $CIC_{95}$).[4] They were also tested against highly PI-resistant viral constructs that were engineered from clinic viral isolates of patients infected with multiply PI-resistant HIV.[5] As shown in Table 1, the results show that all compounds but **2** are more potent than indinavir; the α-hydroxy amide **1** is 10-fold more potent than the hydroxy ethylene amine moiety **2**.

Aminochromanol[7] moiety is twice as effective as the aminoindanol (**3** vs **5**); *o*-disubstituted-benzyl amide **3** is twice as potent as *o*-mono-substituted-benzyl amide **1**. The stereochemistry of the hydroxyl group also plays an important role for activity. An analogue of *S* configuration **3** is 3–14-fold more potent than that of the *R* isomer **4**. On the basis of the initial studies, we decided to investigate the SARs of the lead **3** and the results are discussed below.

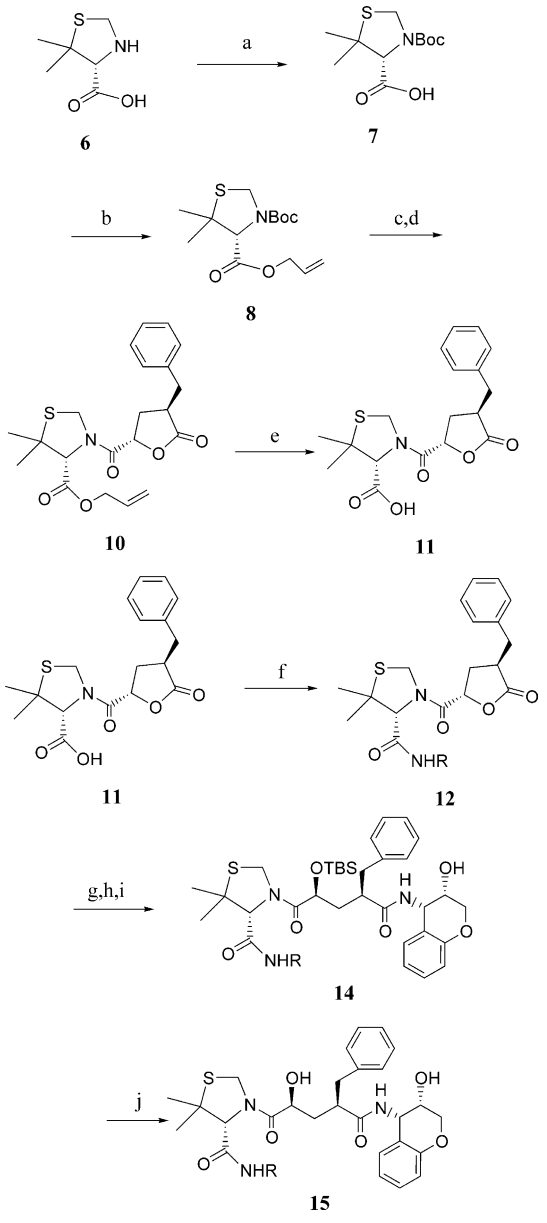
Synthesis of this series of compounds is generalized in Scheme 1. Commercially available acid **6** was protected with Boc anhydride under basic conditions in 42% yield. Treatment of resulting acid **7** with allyl bromide and triethyl amine in DMF afforded compound **8** (80%). Deprotection of the Boc group, followed by Py.Brop (bromo-tris-pyrrolidino-phosphonium hexafluorophosphate) coupling of acid **9**,[6] gave amide **10** in 47% overall yield. Catalytic removal of the allyl group with tetrakis(triphenylphosphine) palladium afforded acid **11** (85%). EDC coupling with various amines **16** (see Table 2) or **17** provided amides **12** (40–70%). Treatment of **12** with 1M aqueous LiOH solution in dioxane, followed by treatment of TBSOTf and hydrolysis, gave acids which were coupled with 4-amino-3-chromanol[7] (**13**) leading to compound **14**. Deprotection of the TBS group with 1 M tetrabutylammonium fluoride solution provided final products **15** in 95% yield.

**Table 1.** Antiviral activities of hybrid series

| | | $IC_{50}$ (nM) | | | $CIC_{95}$ (nM) | | |
|---|---|---|---|---|---|---|---|
| | X | WT | K-60C | V-18C | WT | K-60C | V-18C |
| Indinavir | | 0.6 | 61.2 | 43.6 | 45 | 1000 | 890 |
|  | O, **1** | 0.07 | 0.83 | 0.4 | 19 | 125 | 41 |
| | H,H, **2** | 0.52 | 7.90 | 8.8 | 250 | >1000 | 1000 |
|  | OH, *S*, **3** | 0.03 | 0.1 | 0.08 | 15 | 70 | 15 |
| | OH, *R*, **4** | 0.28 | 1.9 | 1.14 | 47 | 500 | 62 |
|  | **5** | 0.04 | 0.062 | 0.062 | 31 | 125 | 31 |

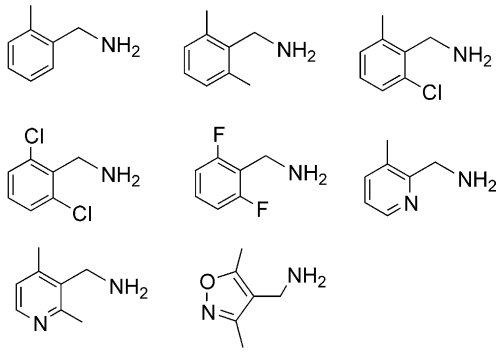
The amines that were used in this study are listed in Table 2. The synthesis of 3,5-dimethylisothiazole-4-methyl amine (**17**) is outlined in Scheme 2, and is representative of how all the amines were prepared.

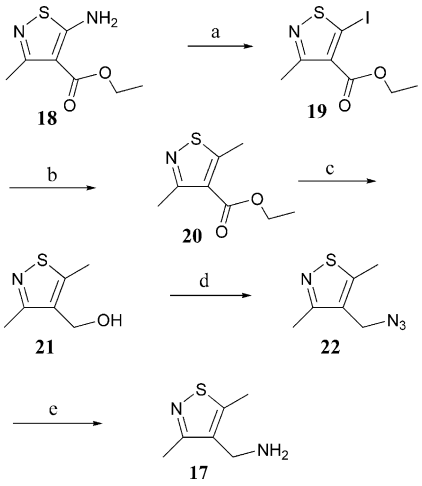
Commercially available ethyl 5-amino-3-methyl-isothiazole-4-carboxylate **18** was treated with isoamyl nitrite and iodine in chloroform under refluxing condi-




**Scheme 1.** (a) $Boc_2O$, $NaOH/H_2O/i$-PrOH, 42%; (b) allyl bromide, $Et_3N$, DMF, rt, 80%; (c) $TFA/CH_2Cl_2$, 100%; (d) Py.Brop, HOAT, DIEA, **9**, $CH_2Cl_2$, rt, 47%; (e) $Pd(PPh_3)_4$, morpholine, THF, rt, 85%; (f) **16**, or **17**, EDC, HOAT, DIEA, $CH_2Cl_2$, rt, 40–70%; (g) LiOH/$H_2O$/dioxane, rt; (h) TBSOTf/EtOAc, DIEA, rt; $H_2O$/THF; (i) **13**, *O*-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyl-uronium hexafluorophosphate (HBTU), DIEA, 1-hydroxy-7-azabenzotrizole (HOAT) (cat), DMF, rt (j) $Bu_4NF$, THF, rt, 95%.

**Table 2.** A list of amines used



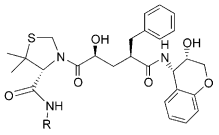


**Scheme 2.** (a) Isoamyl nitrite, $I_2$, $CHCl_3$, reflux, 50%; (b) $(CH_3)_4Sn$, $PdCl_2(PPh_3)_2$, toluene, reflux, 83%; (c) $LiAlH_4$, THF, 0 °C→rt, 57%; (d) $CBr_4$, $Ph_3P$, $NaN_3$, DMF, rt, 83%; (e) $Ph_3P$, THF/$H_2O$, rt, 84%.

tions to give **19** in 50% yield. The Castro–Stevens reaction[8] afforded compound **20** (83%). $LiAlH_4$ reduction of **20** provided alcohol **21** (57%) which was then converted to azide **22** in good yield. Reduction of **22** gave the desired amine **17** in 84% yield.

SAR study of the lead **3** was carried out and the influence of different substituents on in vitro potency against mutant variants[9] is summarized in Table 3. Searching for other types of substituents on the phenyl ring and exploring heterocycles have been the focus of this study. Replacement of one of the methyl groups with a chlorine atom on the phenyl ring results in another highly potent protease inhibitor **23**, with slight loss of the spread activity. Dichloro substituted analogue **24**[10] appears to be one of the most potent compounds in this series in the spread assay. However, difluoro substituted analogue **25** apparently is less potent than methyl or chloro-substituted analogues due to smaller size. On the other hand, methyl substituted pyridyl methyl amides are less active than the substituted phenyl analogues. The 2-pyridyl analogue is more active than the 3-pyridyl analogue (**26** vs **27**). The substituted 5-membered heterocycles were also investigated. Compounds **28** and **29** are two most potent analogues. Especially, compound **29**[11] is comparable to the most potent substituted phenyl analogue **24**. Indinavir is much less active against the resistant virus in the study.

**Table 3.** Influence of substituents on antiviral activities



| Compd | R | $IC_{50}$ (nM) | | | $CIC_{95}$ (nM) | | |
|---|---|---|---|---|---|---|---|
| | | WT | K-60C | V-18C | WT | K-60C | V-18C |
| Indinavir | | 0.6 | 61.2 | 43.6 | 45 | 1000 | 890 |
| 3 |  | 0.03 | 0.1 | 0.08 | 15 | 70 | 15 |
| 23 |  | 0.03 | 0.11 | 0.08 | 31 | 46 | 23 |
| 24 |  | **0.04** | **0.23** | **0.12** | **<8** | **250** | **16** |
| 25 |  | 0.24 | 2.0 | 1.48 | 23 | 250 | 62 |
| 26 |  | 0.13 | 0.6 | 0.26 | 39 | 187 | 46 |
| 27 |  | 0.16 | 2.37 | 0.72 | 187 | 250 | 125 |
| 28 |  | 0.07 | 0.21 | 0.9 | 156 | 250 | 62 |
| 29 |  | **0.05** | **0.24** | **0.11** | **16** | **250** | **31** |

In summary, we have designed and synthesized a new series of highly active HIV protease inhibitors against various clinic isolates. The successful incorporation of substituted 5-membered heterocycles provides us with another option to study the antiviral activity of this class of compounds.

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Graham, P. I.; Condra, J. H.; Gotlib, L.; Holloway, M. K.; Lin, J.; Chen, I.-W.; Vastag, K.; Ostovic, D.; Anderson, P. S.; Emini, E. A.; Huff, J. R. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4096.

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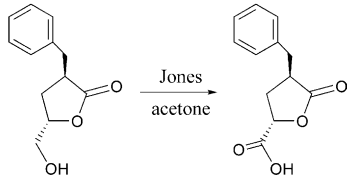
6. Compound **9** was obtained by treatment of compound **30** (see reference herein) with Jones' reagent in acetone.




**30** **9**

Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I.-W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1994**, *37*, 3443.

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9. For viral isolate protease genotypes corresponding to those employed in this study, see: Condra, J. H.; Holder, D. J.; Schleif, W. A.; Blahy, O. M.; Danovich, R. M.; Gabyelski, L. J.; Graham, D. J.; Laird, D.; Quintero, J. C.; Rhodes, A.; Robbins, H. L.; Roth, E.; Shivaprakash, M.; Yang, T.; Chodakewitz, J. A.; Deutsch, P. J.; Leavitt, R. Y.; Massari, F. E.; Mellors, J. W.; Squires, K. E.; Steigbigel, R. T.; Teppler, H.; Emini, E. A. *J. Virol.* **1996**, *70*, 8270.

10. **Data for compound 24:** $^1$H NMR ($CDCl_3$, 500 MHz): 1:1 mixture of rotamers: 6.80–7.70 (m, 12H), 6.00 (m, 2H), 5.18 (m, 1H), 4.85 (m, 3H), 4.70 (s, 1/2H), 4.61 (m, 1H), 4.40 (s, 1/2H), 4.38 (m, 1H), 4.05 (m, 3H), 3.78 (m, 1H), 2.80–3.10 (m, 4H), 2.20 (m, 1H), 1.61 (m, 1H), 1.60 (s, 3/2H), 1.57 (s, 3/2H), 1.40 (s, 3/2H), 1.39 (s, 3/2H). LC–MS (ES) 686.1 (M + 1).

11. **Data for compound 29:** $^1$H NMR ($CDCl_3$, 500 MHz): 1:1 mixture of rotamers: 6.80–7.40 (m, 9H), 5.88 (br.S, 1H), 5.10 (m, 1H), 4.90 (m, 1H), 4.65 (s, 1/2H), 4.40 (3/2H), 4.29 (m, 1H), 4.05 (m, 2H), 3.72 (m, 1H), 2.88 (m, 4H), 2.53 (s, 3/2H), 2.50 (s, 3/2H), 2.40 (s, 3H), 2.08 (m, 1H), 1.59 (s, 3/2H), 1.56 (s, 3/2H), 1.42 (s, 3/2H), 1.36 (s, 3/2H). LC–MS (ES) 653.1 (M + 1).