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Indinavir Analogues with Blocked Metabolism Sites as HIV Protease Inhibitors with Improved Pharmacological Profiles and High Potency Against PI-Resistant Viral Strains

Yuan Cheng,[a,*] Fengqi Zhang,[a] Thomas A. Rano,[a] Zhijian Lu,[a] William A. Schleif,[b] Lori Gabryelski,[b] David B. Olsen,[c] Mark Stahlhut,[c] Carrie A. Rutkowski,[c] Jiunn H. Lin,[d] Lixia Jin,[d] Emilio A. Emini,[b] Kevin T. Chapman[a] and James R. Tata[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA*
[b]*Department of Viral Vaccine Research, Merck Research Laboratories, West Point, PA 19486, USA*
[c]*Department of Biological Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[d]*Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, USA*

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Abstract—Indinavir analogues with blocked metabolism sites show highly improved pharmacokinetic profiles in animals. The *cis*-aminochromanol substituted analogues exhibited excellent potency against both the wild-type (NL4-3) virus and protease inhibitor-resistant HIV strains.

In the past decade, extensive research has focused on identifying HIV protease (PR) inhibitors for the treatment of human immunodeficiency virus (HIV-1) infection.[1] Several HIV protease inhibitors, including Indinavir, have been approved by the US Food and Drug Administration as key therapeutic agents for the treatment of HIV infection and AIDS.[1,2] Although these drugs represent a major advance in the management of HIV disease, they suffer, to some extent, from first-pass metabolism and/or food restrictions. In addition, a number of patients develop resistance to multiple protease inhibitors through viral mutations.[3] There are two approaches to develop drugs that are efficacious against resistant mutants: one is to improve pharmacokinetic profiles by blocking the metabolic sites and another is to improve potency of HIV PR inhibitors. In an effort to develop a second-generation drug with better pharmacokinetic parameters and improved activity against resistant mutants, we launched an investigation to modify the Indinavir class of protease inhibitors by varying the P_2' and P_3 moieties.

The benzylic position of the aminoindanol moiety in the P_2' position as well as the pyridine nitrogen and the methylene linker in P_3 have been identified as the major metabolic sites in Indinavir (Fig. 1).[4] As such we first incorporated a *gem*-dimethylpyridyl substituent into the P_3 position. The resulting compound, **1**, had a C_{max} more than 20 times greater than that of Indinavir when dosed orally in rats. The $t_{1/2}$ of **1** is more than twice as long as Indinavir in both rats and dogs. Encouraged by these results, we reviewed historical data and found that pyridylfuran derivative **2** prepared during the initial

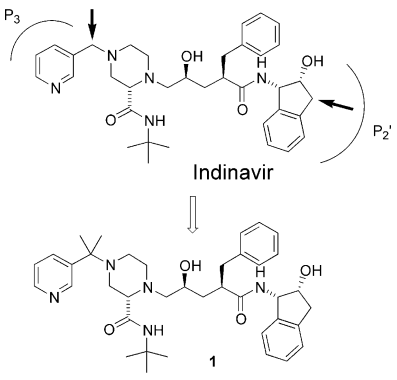

Figure 1. ← Denotes metabolism by CYP3A4.

*Corresponding author. Fax: +1-732-594-9556; e-mail: yuan_cheng@merck.com

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protease program had reasonable potency and bioavailability. We were interested in combining the *gem*-dimethyl concept with the pyridylfuran of **2** and additionally replacing the aminoindanol to address the metabolic liability of the benzylic position with a more robust aminochromanol moiety (Fig. 2). In this communication, we report the successful execution of this strategy that resulted in compounds with improved pharmacokinetic profiles and increased potency against PI-resistant viral strains.

The synthetic strategy for incorporation of the *gem*-dimethylpyridyl substituent is shown in Scheme 1. We started with intermediate **5**[5] that was first treated with TFA to remove the Boc protecting group. Copper mediated alkylation with 3-chloro-3-methyl-butyne gave intermediate **6**.[6] Reaction of **6** with diiodo-hydroxypyridine **7** under Castro–Stevens conditions[7] resulted in smooth cyclization to provide pyridylfuran lactone **8**. The lactone in intermediate **8** was opened with LiOH in dioxane and the hydroxyl group was protected with TBSOTf affording, after hydrolysis of the TBS ester with THF/H_2O, acid **9**. Aminoindanol **10** was coupled to acid **9** using HBTU and HOBt to afford **11**. The iodine was removed by hydrogenation with Pd/C in ethanol and the TBS group was removed with HF/pyridine to give **3**.

In order to block the metabolic site on the aminoindanol, we synthesized aminochromanol[8] as illustrated in Scheme 2. 4-Chromanone was brominated with bromine in CH_2Cl_2. Although a mixture of mono- and di-bromo products at α-ketone position was obtained, the di-bromo product **12** could be quantitatively converted to mono-bromo product **13** by treatment with Na_2SO_3 in wet acetic acid. Bromoketone **13** was reduced with $NaBH_4$ to afford bromo alcohol **14**. Using Ritter reaction[9] conditions, **14** was converted to amino alcohol **15**.[10] The desired 3*S*,4*S* enantiomer **16** was isolated by crystallization from ethanol with (*S*)-mandelic acid. Coupling of aminochromanol **16** to acid **9** provided compound **4**.

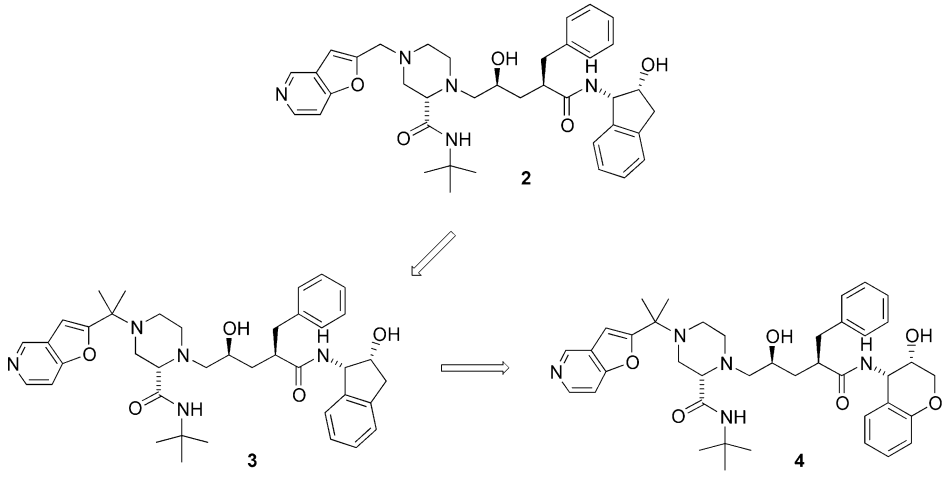
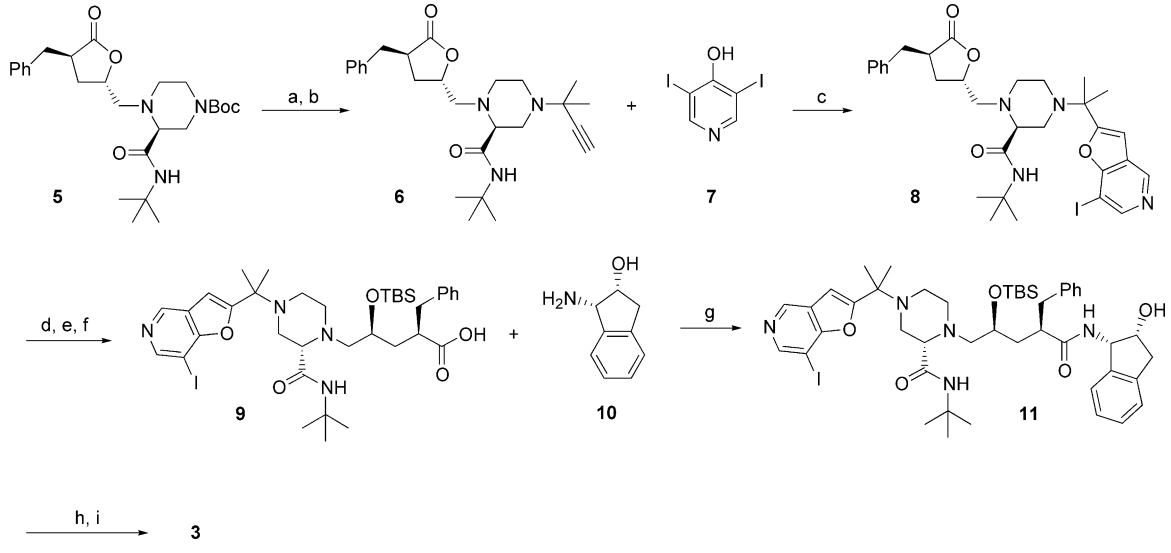
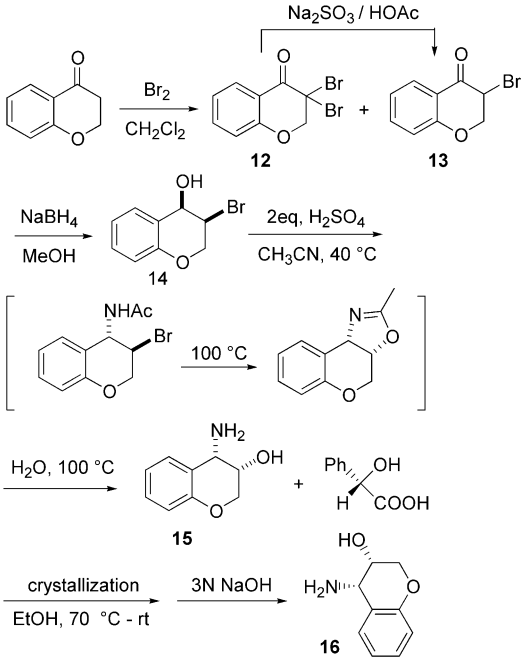


Figure 2. Approaches to block metabolism sites of pyridylfuran derivative.



Scheme 1. Reagents and conditions: (a) TFA/CH_2Cl_2 30%, 1 h; (b) 3-chloro-3-methyl-1-butyne, Cu, CuCl, Et_3N, THF; (c) CuI, *N*-ethylpiperidine, DMF; (d) LiOH, dioxane; (e) TBSOTf, DIEA, THF; (f) H_2O/THF 1:1; (g) HBTU, HOBt, DIEA, DMF; (h) H_2, Pd/C 10%, ethanol; (i) HF/pyridine, THF.



Scheme 2. Synthesis of (3*S*,4*S*)-aminochromanol.

Compounds **1**, **3**, and **4** were tested along with Indinavir for their ability to inhibit cleavage of a substrate by the wild-type HIV-1 protease enzyme and to inhibit the spread of viral infection in MT4 human T-lymphoid cells infected by the NL4-3 virus (Table 1). The *gem*-dimethyl derivative of Indinavir, **1**, was as potent as Indinavir in viral spread assay, although it was about 2-fold less active in the enzyme inhibition assay. The *gem*-dimethyl pyridylfuran derivative **3** exhibited the same potency as its unsubstituted analogue **2** in both the enzyme inhibition assay and viral spread assay. These results demonstrate that compounds with the *gem*-dimethyl substitution retain the high potency of their unsubstituted counterparts. Gratifyingly, the aminochromanol derivative **4** showed enhanced potency over the aminoindanol derivative **3** in the viral spread assay (<8 nM vs 15 nM).

Encouraged by these findings we further investigated the impact of the aminochromanol substituent on the potency of Indinavir analogues by testing a set of compounds against PI-resistant viral constructs (Table 2). The viral constructs used in the viral spread assay were engineered from clinical viral isolates of patients infected with multiply PI-resistant HIV.[11] The results clearly show that replacement of aminoindanol with aminochromanol leads to significant improvements in potency against a variety of PI cross-resistant viral constructs. While Indinavir and the pyridylfuran analogue **3** are inactive against most of the resistant viral strains, compound **4** shows increased potency across all strains tested.

With these more potent compounds in hand the pharmacokinetic profiles of compounds **3** and **4**, in dogs, were then examined (Table 3). The in vivo properties of both **3** and **4** were more favorable relative to Indinavir. Compound **3** had twice the AUC and C_{max} of Indinavir (corrected for dose) while compound **4** exhibited slightly

Table 1. In vitro potency against wild-type HIV virus

Compd	Enzyme inhibition IC_{50} (nM)	Viral spread CIC_{95} (nM)
Indinavir	0.59	50
1	1.16	50
2	0.23	15
3	0.15	15
4	0.075	<8

Table 2. In vitro potency of compounds against HIV mutant strains

Compd	Viral spread data (CIC_{95}, NM)				
	WT	4X Virus	K-60C	Q-60C	V-18C
Indinavir	50.5	500	>3000	>1000	1500
3	15	625	>1000	>1000	>1000
4	<8	31	500	250	250

Table 3. Pharmacokinetics in dogs

Compd	Dose (po dose mpk)	C_{max} (μM)	AUC (μM h)	F (%)	$t_{1/2}$ (min)
Indinavir	Dog (10)	11.4	12.5	71.6	38
3	Dog (5)	16.6	14.1	44.3	47
4	Dog (5)	8.85	7.43	81	62.4

improved values. The half lives ($t_{1/2}$) of compounds **3** and **4** were also improved over that of Indinavir (47, 62, and 38 min, respectively).

In summary, we have demonstrated that we can improve the pharmacokinetic profile of Indinavir analogues by blocking sites of metabolism. In addition substitution of aminoindanol with aminochromanol afforded compounds with greater potency against both the wild-type (NL4-3) virus and PI-resistant HIV strains.

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