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AROMATIC P_1 REPLACEMENTS FOR THE HIGHLY POTENT HIV-1 PROTEASE INHIBITOR CRIXIVAN®

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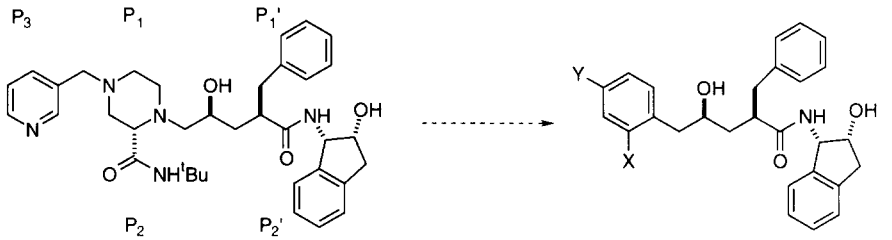
Abstract: A series of analogs of CRIXIVAN® containing various aromatic P_1 ligands were prepared and evaluated for inhibition of the HIV-1 protease enzyme. These new compounds were found to be effective inhibitors at nanomolar concentrations in the *in vitro* enzyme inhibition assay as well as the whole cell assay. Copyright © 1996 Elsevier Science Ltd

Human immunodeficiency virus protease (HIV PR) has been shown to be an essential enzyme in the life cycle of HIV and is responsible for the processing of the polyproteins required for viral replication.[1,2] Inhibition of this critically important enzyme utilizing peptidomimetic transition state isosteres remains a widely used strategy directed at halting viral replication.[3] We have employed this strategy to design a number of these isosteres that possess a hydroxylaminepentanamide subunit within the inhibitor. These efforts have culminated in the development of the extremely effective HIV PR inhibitor CRIXIVAN® (**1**).[4]

Figure 1



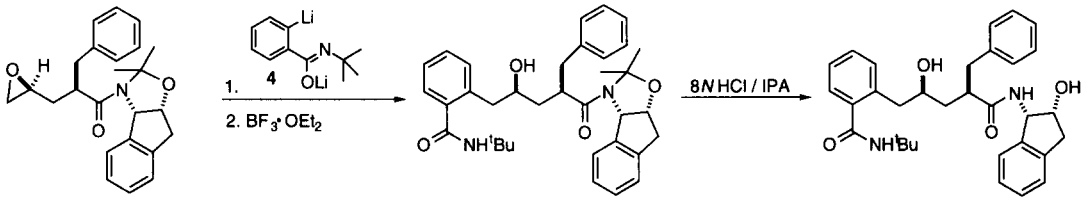
1; CRIXIVAN® **2**

As part of our program to explore structurally related inhibitors, we were interested in the replacement of the P_1/P_2 piperazine *tert*-butylcarboxamide moiety of **1** with various aromatic substituents while retaining the P', Phe-indane moiety.[5] In this paper, we describe the synthesis and activity profile of a number of these new protease inhibitors.

The synthetic route for the preparation of these compounds is shown in Scheme 1. Epoxide **3**[6] has been widely employed by us for the construction of diastereomerically pure hydroxyethylamine HIV PR inhibitors represented by **1.** We envisioned a similar strategy for the synthesis of a series of

2-arylethanols in which the *S*-configuration of the hydroxyl group would be derived from the epoxide prior to the introduction of the aromatic P_1 group. The success of the reaction scheme would then be based on a Lewis acid mediated opening of epoxide **3** by an appropriately substituted aromatic nucleophile.[7]

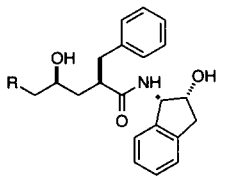
Scheme 1

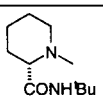
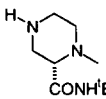


3 **5a** **2a**

Directed metallation of N-*tert*-butylbenzamide (2 equivalents n-BuLi/0 °C/2 h) afforded dilithio anion **4**, which was treated with a solution of epoxide **3** at -70 °C followed *immediately* by the addition of 1 equivalent of $BF_3{\cdot}OEt_2$. After work up the phenethyl alcohol adduct **5a** was isolated in good yield without any detectable racemization. Hydrolysis of the ketal protecting group was accomplished by the action of 8*N* HCl in isopropanol to afford title compound **2a** as a crystalline solid.[8]

Table 1: Effect of P_1 Replacement



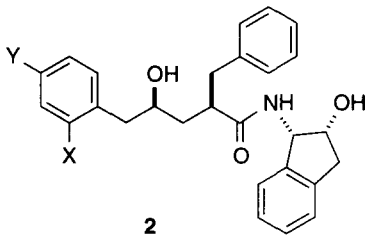
Compound	R	IC_{50}(nM)	CIC_{95}(nM)
6		80	nd[1]
7		38	3,000
2a		4.7	800

[1]not determined

Direct comparison of the aromatic P_1 inhibitor **2a** to several saturated cyclic isosteres revealed that this modification was favorable in both the *in vitro* assay and the whole cell assay (Table 1).[9] Encouraged by these results, we examined a number of substituted β-arylethanol inhibitors.

The short and efficient reaction scheme described above served well for the synthesis of a wide variety of arylethanols that contained the benzyl indanamide subunit (Table 2). Furthermore, we were able to convert some of the final compounds into a variety of modified P_2 derivatives. For example, anisole **2d** could be cleanly demethylated (BBr_3/DCM/rt) to afford phenol **2c** in 56% yield. Oxidation of thioanisole **2i** with 1.5 equivalents of Oxone® provided sulfone **2j**. Finally, dealkylation of *tert*-butylsulfonamide **2l** with 8*N* HCl in isopropanol provided access to primary sulfonamide **2k**.

Table 2: Aromatic P_1 Analogs



2

Compound	X	Y	IC_{50} (nM)
2b	H	H	1,200
2c	OH	H	1,600
2d	OCH_3	H	80
2e	OCH_3	OCH_3	105
2f	OCH_3	OPh	45
2g	O^{i}Bu	H	97
2h	OCH_2OCH_3	H	276
2i	SCH_3	H	95
2j	SO_2CH_3	H	314
2k	SO_2NH_2	H	290
2l	SO_2NH^tBu	H	6
2m	$CONH^tBu$	CH_3	1.7

The above compounds were evaluated for their ability to inhibit the HIV PR enzyme and the results are shown in table 2. Interestingly, the aryl ether and thioether compounds (**2d-2i**) were found to be fairly potent inhibitors *in vitro* (IC_{50} < 100 nM). However, phenol **2c** was 20-fold less active than its corresponding anisole analog. Sulfonamide **2l** and carboxamide **2a** were equipotent but removal of the lipophilic *t*-butyl group resulted in a significant drop in potency as evidenced in compound **2k**. Substitution of a methyl group *meta* to the carboxamide moiety gave the most potent compound thus far (**2m**; K_i = 1.7 nM), which was also reflected in whole cell assay (CIC_{95} = 400 nM). In conclusion, we have demonstrated that substitution of an aromatic group in P_1/P_2 of CRIXIVAN® can lead to highly active HIV PR inhibitors.

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