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Combinatorial Library of Indinavir Analogues: Replacement for the Aminoindanol at P_2'

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Abstract—A 1X22X41 combinatorial library or 902 compounds of indinavir analogues was synthesized on the solid support to identify a replacement for the aminoindanol moiety at P_2'. 2,6-Dimethyl-4-hydroxy phenol was discovered to be a good replacement for aminoindanol.

Human immunodeficiency virus (HIV) protease cleaves the *gag* and *gag-pol* polyproteins required by the infectious virus to mature. Inhibition of HIV protease results in immature virons that are incapable of replication.[1] Protease inhibitors (PI) used in combination with reverse-transcriptase inhibitors have slowed disease progression in AIDS patients.[2] Nevertheless all the currently approved PI's suffer from various drawbacks leading to patient non-compliance. Furthermore, multidrug resistant viruses have recently emerged jeopardizing current PI therapies.[3] Indinavir is one of the most efficacious PI currently available. Despite its clinical success the need to identify a second generation of compounds possessing greater intrinsic potency (particularly against mutants), metabolic stability, and longer half life remains.

Indinavir is rapidly metabolized by the cytochrome p450 family of isozymes and in particular, by cytochrome p450 3A4. The two major metabolism pathways that have been observed are *N*-dealkylation of the pyridyl methyl moiety and hydroxylation of the aminoindanol (Fig. 1).[4] Our goal was to find a replacement for the metabolically labile aminoindanol moiety. This communication describes the synthesis of a 1X22X41 combinatorial library of indinavir analogues wherein the aminoindanol moiety was diversified.

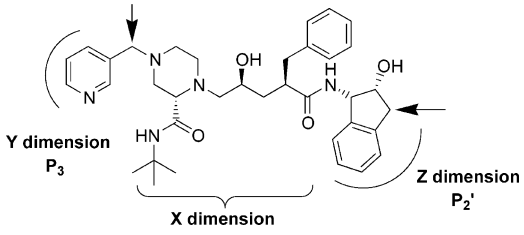

Figure 1. Arrows denote the major sites of metabolism.

Solid-phase, combinatorial library synthesis was accomplished by dividing Indinavir into three parts: the central hydroxyethylene core bearing the piperazine (**X** dimension), the pyridyl methyl fragment at P_3 (**Y** dimension), and aminoindanol fragment at P_2' (**Z** dimension). The library was prepared using the resin archive, iterative deconvolution format.[5] The **X** dimension comprised of a single subunit the hydroxyl ethylene core structure. For the **Y** dimension 22 subunits demonstrated to give potent compounds when used with aminoindanol were selected. These included aldehydes, sulfonyl chlorides and acids (Fig. 2).[6]

Molecular modeling was used to select **Z** subunits that would fit in the S_2 binding pocket and make the same

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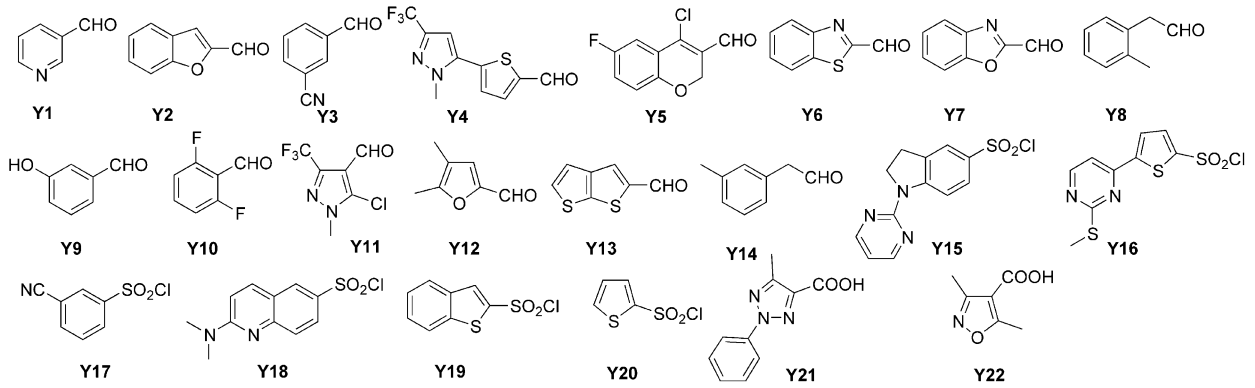


Figure 2. Y Subunits of the library.

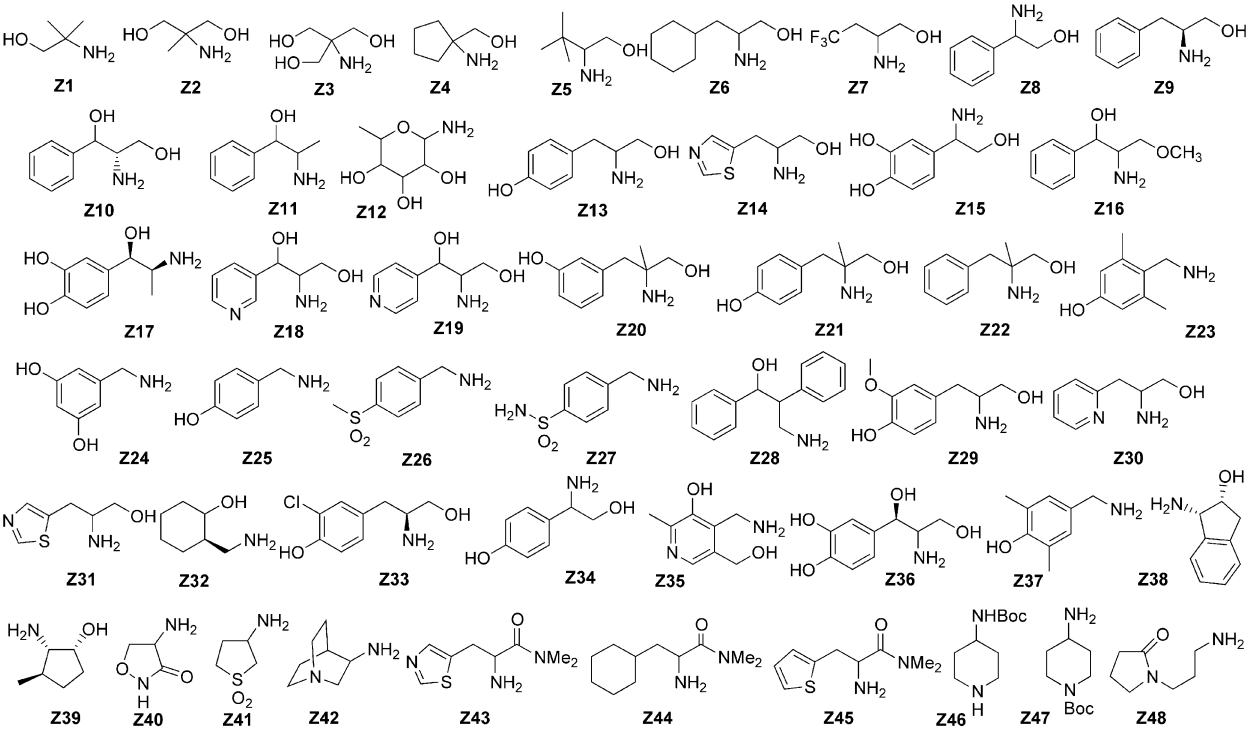
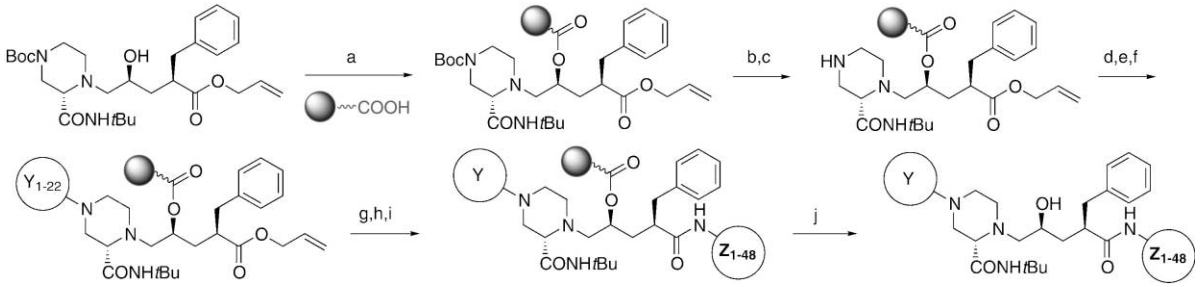


Figure 3. Z Subunits of the library.

kinds of interactions with HIV protease enzyme as aminoindanol. These include a diverse set of aliphatic and aromatic amino alcohols and amines. Molecular modeling also suggested the possibility of utilizing some new interactions with the peptide backbone in the S_2 binding pocket of the enzyme. To address this, some sulfones, phenols, and basic amines were included (Fig. 3). Aminoindanol (**Z-38**) and 3-methyl-cyclopentyl amino alcohol (**Z-39**) were included as control pools in the library.

Scheme 1 illustrates the synthesis of the library. The orthogonally protected **X** subunit[6b] was attached to the Rapp TentaGel S-COOH resin as an ester linkage via the central hydroxyl group with EDC, HOBt and DMAP. The resin was then split equally by weight into 22 tubes. The Boc group on the piperazine was removed by treatment with TFA. After deprotection the resin was neutralized with TEA/DCM. Tubes 1–14 were treated with aldehydes **Y1**–**Y14** and sodium triacetoxy borohydride in 1% AcOH/DMF. Tubes **15**–**20** were treated with the sulfonyl chlorides **Y15**–**Y20**, respectively, in the presence of DIEA in DCM. Tubes 21–22 were treated with the acids **Y21** and **Y22**, respectively, HOBt and pyBOP. After completion of the reaction a portion of the resin in each tube was archived and the remaining resin was thoroughly mixed and the split equally by weight into 48 tubes.

Each of these tubes was treated with 1,3-dimethylbarbituric acid and $Pd(Ph_3)_4$ in DCM. After 3 h the resin was washed thoroughly and treated with each of the **Z** subunits **Z1**–**Z48** in the presence of EDC, HOBt, and DIEA. After 24 h, the resin was washed exhaustively.[7] The final products were cleaved from the resin by treatment with 10% triethyl amine in methanol. Each pool



Scheme 1. Reagents and conditions: (a) EDC, DMAP, CH_2Cl_2, 24 h; (b) distribute resin; (c) 30% TFA/CH_2Cl_2, 1 h; (d) RCHO (**Y1**–**Y14**), $NaBH(OAc)_3$, 1% AcOH/DMF 16 h; (e) RSO_2Cl_2 (**Y15**–**Y20**), DIEA, CH_2Cl_2, 16 h; (f) RCOOH (**Y21**–**Y22**), pyBOP, HOBt, DMF, 16 h; (g) archive resin, mix and redistribute resin; (h) DMBA, $Pd(Ph_3)_4$, CH_2Cl_2, 3 h; (i) Amine (**Z1**–**Z48**), EDC, HOBt, DIEA, DMF, 24 h; (j) 10% Et_3N, MeOH, 60 °C, 16 h.

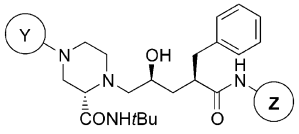
contained a mixture of 22 compounds (not including diastereomers), and was analyzed by LC/MS.

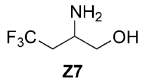
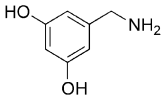
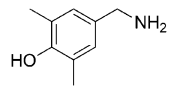
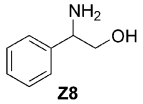
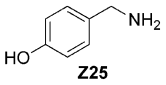
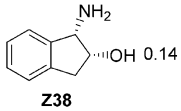
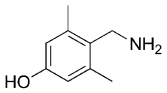
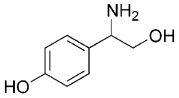
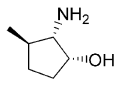
Four of the 48 **Z** subunits failed to couple completely and three of the **Z** subunits coupled only partially. The reason for this is probably due to the bulky nature of the amines in these particular subunits. These pools were removed from the library. The remainder 41 pools were tested for their ability to prevent cleavage of a substrate by the HIV protease wild-type enzyme (IC_{50}) and the mutant A-44 enzyme.[8a] In addition, the pools were tested for their ability to inhibit the spread of viral infection in MT4 human T-lymphoid cells infected with the IIIb isolate (CIC_{95}).[8b]

The biological activity of the pools is highlighted in Table 1. The **Z-23** (2,6-dimethyl 4-hydroxy-benzyl amine) pool exhibited good activity with an IC_{50} of 0.82 nM. For the wild-type enzyme **Z-23** had IC_{50} activity that was between the two control pools **Z-38** and **Z-39**. Furthermore, for the A-44 mutant enzyme **Z-23** had the same IC_{50} activity as **Z-38** and was 8-fold more potent than **Z-39**. The enzyme inhibition data revealed some interesting SAR. It is clear that the two methyl groups in **Z-23** are important for activity. Removal of the methyl groups results in 30-fold loss in activity (cf., with **Z-25**). Furthermore, the location of the methyl groups on the phenyl ring is also important. Placement of the methyl groups next to the hydroxyl group results in significant loss in activity (cf., with **Z-37**). The hydroxyl group in the meta position of the phenyl ring results in weaker activity compared to the hydroxyl in the para position (cf., with **Z-34**).

Phenyl glycinol (**Z-8**) was the second most active pool after **Z-23**. Interestingly, introduction of a hydroxyl group in the para position of this subunit (**Z-34**) resulted in dramatic loss in activity (from 6.3 to 185 nM). **Z-7** (β-CF_3 alaninol) pool had an IC_{50} of 18 nM. However, replacement of the CF_3 with a phenyl group **Z-9** (phenyl

Table 1. In vitro potency data for selected Z pools



Z Subunit	IC_{50} (nM)		CIC_{95} (nM)	Z Subunit	IC_{50} (nM)		CIC_{95} (nM)	Z Subunit	IC_{50} (nM)		CIC_{95} (nM)
	wt	9×	wt		wt	9×	wt		wt	9×	wt
 **Z7**	18	120	>1000	 **Z24**	10.5	26	1250	 **Z37**	1400	—	>1000
 **Z8**	6.3	6.3	>1000	 **Z25**	26	48	1250	 **Z38**	0.14	3.2	78
 **Z23**	0.89	3.2	156.3	 **Z34**	185	120	>1000	 **Z39**	1.7	26	78

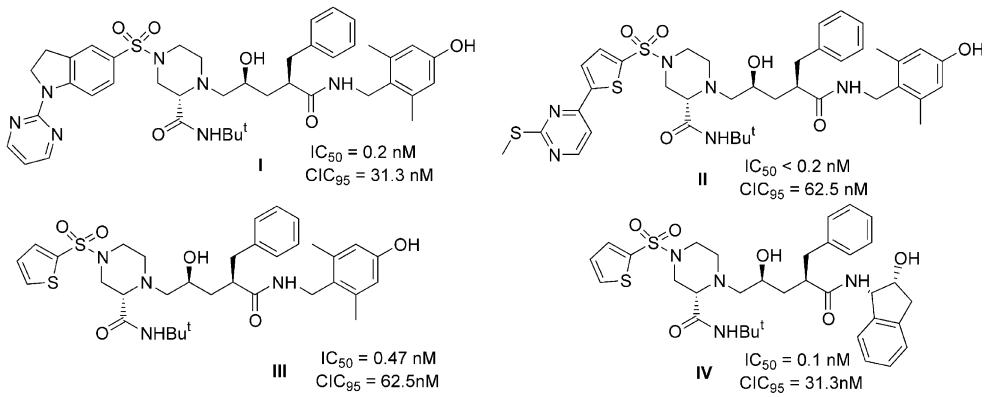


Figure 4. In vitro potency for the sulfonamides.

alaninol) resulted in a drop in activity to 1400 nM. **Z-23** (2,6-dimethyl 4-hydroxy benzyl amine) pool had a CIC_{95} of 156 nM which was only twofold less than that for the aminoindanol pool. The remaining pools had modest activity in the HIV viral spread assay. **Z-23** was chosen for further deconvolution.

The deconvolution were performed by starting with a portion of the 'Y archive' resin from the initial library synthesis. The **Z-23** subunit was added to each of the 22 archive samples. This resulted in 22 single compounds with defined **XYZ** structures. These compounds were tested in the PepCleav and HIV spread assay.

Our hope was to find a subunit that was more active and structurally different from the metabolically labile pyridyl methyl moiety in the **Y** dimension. In fact, the combination of the **Y1Z23** had a rather modest activity ($IC_{50} = 8.2$ nM, $CIC_{95} = 1$ μM). All the aldehyde subunits when used in combination with **Z-23** had weak activity in the viral spread assay with CIC_{95} ranging from 250–1000 nM. However, the sulfonamides exhibited very good enzyme inhibition and antiviral activity. In particular, **Y-15**, **Y-16**, and **Y-20**, stood out with their CIC_{95} activity ranging from 31.3 to 62.5 nM. Furthermore, the activity of these compounds was comparable to the combination of **Y-15**, **Y-16**, and **Y-20** with aminoindanol (Fig. 4).

A 1X22X41 combinatorial library or 902 compounds of indinavir analogues was synthesized on the solid support using the mix and split strategy. Based on screening the library, **Z-23** 2,6-dimethyl 4-hydroxy benzyl amine was found to be the most active subunit besides aminoindanol. Further deconvolution of this pool identified three compounds **I** with and $IC_{50} = 0.2$ nM (wt) and $CIC_{95} = 31.3$ nM, **II** with an $IC_{50} < 0.1$ nM and CIC_{95} of 62.5 nM and **III** $IC_{50} = 0.47$ nM and $CIC_{95} = 62.5$ nM.

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