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Oximinoarylsulfonamides as potent HIV protease inhibitors

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Abstract—The need for a potent HIV protease inhibitor (PI) to combat emerging PI-resistant viruses is anticipated. Analogs formulated from the combination of structural fragments of Ritonavir, Lopinavir, and Amprenavir were synthesized. Analogs containing the oxime pharmacophore were found to have improved activities against both wild type and resistant (A17) viruses. The synthesis and structure–activity relationships (SAR) based upon the in vitro IC_{50} of this series of compounds are reported.
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The introduction of the highly active anti-retroviral therapy (HAART) in 1996 has helped to significantly reduce AIDS disease progression and mortality among people living with HIV infection.[1] However, a portion of patients experience drug failure with resistance development, and the need for an effective salvaging agent in treating the HIV infections that are resistant to the current PIs has become increasingly important.[2a–c] Recent efforts in our research groups have focused on identifying a universal salvage agent, particularly for the successful HIV PI, Kaletra. By combining the structural elements from Ritonavir, Lopinavir, and Amprenavir (Fig. 1), we designed a novel series of compounds, which demonstrate interesting SAR and antiviral activity. This paper describes the optimization of the arylsulfonamide substituents in **1** resulting in analogs exhibiting good antiviral activities against viruses resistant to Lopinavir, the major constituent of Kaletra.

The synthesis of compounds **8**–**23** (Table 1) is outlined in Scheme 1. The sulfonamide bond in all but one (**8**) of these analogs was formed by direct sulfonylation of the secondary amine intermediate **7** with commercially available benzenesulfonyl chlorides. Amine **3** was prepared via the ring opening reaction of the commercially available epoxide **2** with isobutyl amine. Following removal of the Boc group in **3** with TFA, the diamine was selectively coupled under standard conditions with acid **6**[3]

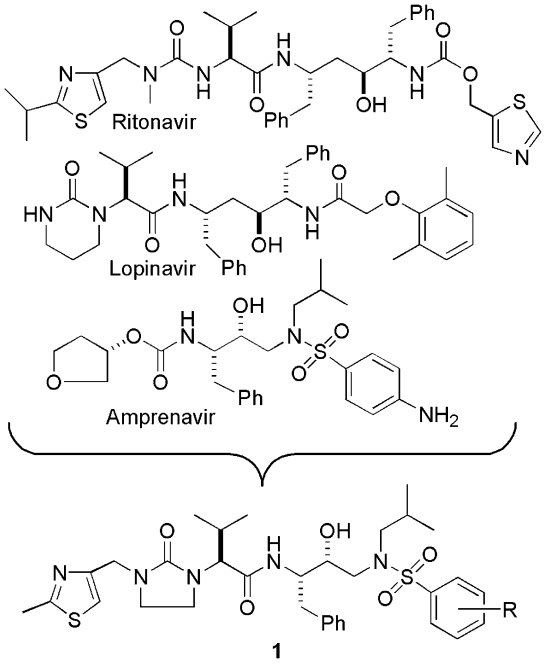

Figure 1. Design of hybrid analog.

to afford amine **7**. Sulfonylation of **7** with various *para*-substituted sulfonyl chlorides **4b**–**f** gave sulfonamide derivatives **11**–**14**, and **17**, respectively. An alternative route to **8** was necessary due to the incompatibility of the thiazole ring in **7** with the hydrogenolysis chemistry required in a later step for this analog. In this case, amine

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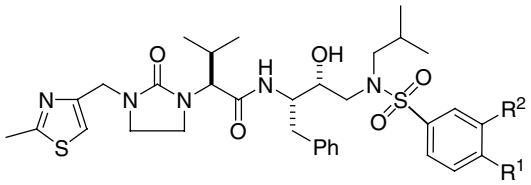
Table 1. Antiviral activity of benzenesulfonamide analogs



Compds[a]	R^1	R^2	Wild type IC_{50}, μM	A17 IC_{50}, μM
8	NH_2	H	0.031	0.311
9	NHCHO	H	0.168	2.41
10	$NHSO_2CH_3$	H	1.19	10
11	$NHCOCH_3$	H	0.312	1.52
12	CO_2H	H	10	9.44
13	$COCH_3$	H	0.039	0.68
14	CN	H	0.148	1.169
15	$CONH_2$	H	0.254	0.944
16	$C(NH_2)$=NOH	H	0.143	0.523
17	$CH=CH_2$	H	0.101	0.957
18	CHO	H	0.051	0.206
19	CH_2OH	H	0.016	0.099
20[b]	CH=NOH	H	0.005	0.031
21[b]	$CH=NOCH_3$	H	0.653	3.01
22	H	CH_2OH	0.045	0.91
23[b]	H	CH=NOH	0.016	0.222
Lopinavir			0.035	1.24
Amprenavir			0.109	3.72
Ritonavir			0.067	3.44

[a] All compounds were tested once except the following compounds: **20** and all three reference compounds-1 duplicate.
[b] *trans*-isomer only.

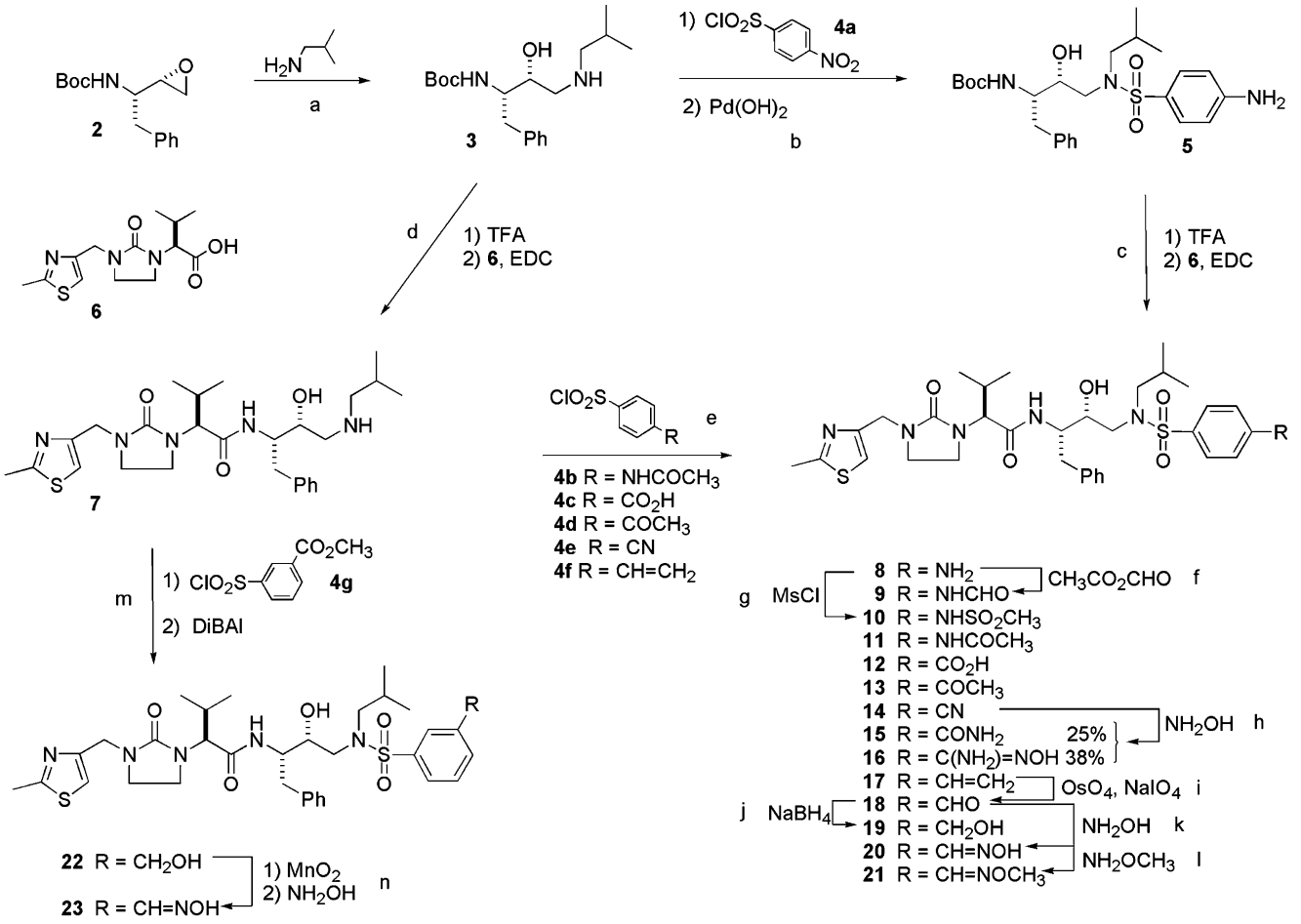
3 was directly sulfonylated with **4a**. Reduction with Pearlman's catalyst afforded the Boc-intermediate **5**. The conversion to compound **8** was accomplished by removal of the Boc group with TFA followed by an EDC coupling with the carboxylic acid **6**.

In two cases the product **8** underwent further modification. Derivatization of aniline **8** with acetic formic anhydride gave formamide **9**, while similar treatment of **8** with methanesulfonyl chloride afforded sulfonamide **10**. Derivatization of nitrile **14** with hydroxylamine hydrochloride gave a 2:3 mixture of compounds **15** and **16**, respectively. Oxidative cleavage of olefin **17** with osmium tetroxide and sodium periodate yielded the aldehyde **18**, which in turn, was reduced with sodium borohydride to afford alcohol **19**. Alternatively, treatment of **18** with hydroxylamine hydrochloride gave 1:20 mixture of the *cis* and *trans* oximes **20**. The *cis* oxime was found to be thermodynamically labile under acidic conditions relative to isomerization to the *trans* isomer, and this conversion takes place during silica gel purification. Because of the facility of this isomerization, pure samples of the *cis* isomer were not isolable. In a similar manner, aldehyde **18** was transformed into **21** by reaction with methoxylamine hydrochloride.

The *meta* oxime isomer can be obtained by sulfonylation of **7** with **4g** followed by diisobutylaluminum hydride reduction to the *meta*-hydroxymethyl analog **22** which was, in turn, oxidized with manganese dioxide and treated with hydroxylamine hydrochloride to give **23**.

The first hybrid analog **8** that was made in this series showed good wild type (WT) activity and approximately 4- to 12-fold improvement in IC_{50} against the resistant (A17) virus[4] over the control compounds, Lopinavir and Amprenavir (Table 1). The anilino group in Amprenavir[5] has been suggested to hydrogen bond with the Asp 30 side chain of HIV protease, and the aniline group in **8** was shown by X-ray crystallography to be similarly positioned. The enhancements in resistance profile are probably due to a combination of this interaction and the binding to the P3 elements.

Further modifications of the aniline group in **8** resulted in compounds that were much less active (formamide **9**, sulfonamide **10**, and acetamide **11**) with analogs exhibiting 5- to 38-fold loss in activity against both WT and resistant viruses activities. Acyl derivatives such as methylketone **13** and aldehyde **18** had similar WT and A17 activities (<2-fold changes) versus the anilino analog **8**, whereas the acid **12** showed poor antiviral activity (10 μM) against both viruses. Amide **15** exhibited reduced potency compared to the aldehyde **18**, and showed a 3- to 8-fold loss in WT and A17 antiviral activities versus **8**. Although the nitrile **14** and the olefin **17** are less sterically demanding groups, both show mediocre IC_{50} numbers. In an attempt to study the polarity and positioning of a hydrogen-bonding group such as the anilino group in the *para*-substituted benzenesulfonamide series, compound **19**, was prepared. This analog exhibited WT and A17 antiviral activities superior to that of the aniline **8**, perhaps reflecting a larger pocket



Scheme 1. Reagents and conditions: (a) *i*-PrOH, 3 h, 80 °C, 97%; (b) (i) Et_3N, DCM, 16 h, 90%, (ii) $Pd(OH)_2$, H_2, EtOAc, 4 h, 95%; (c) (i) 80% TFA/DCM, 4 h, 96%, (ii) EDC, HOBT, DMF, 16 h, 61%; (d) (i) 80% TFA/DCM, 5 h, 98%, (ii) EDC, 16 h, 74%; (e) Et_3N, DCM, 16 h, 22–72%; (f) THF, 1 h, 83%; (g) pyridine, DCM, 5 h, 87%; (h) Et_3N, EtOH, 3 h, 50 °C; (i) 5:1 THF/H_2O, 16 h, 82%; (j) EtOH, 1 h, 62%; (k) EtOH, 2 h, 41%; (l) EtOH, DIEA, 3 h, 46%; (m) (i) Et_3N, DCM, 16 h, 59%, (ii) DCM, −78 °C, 1 h, 80%; (n) (i) DCM, (ii) MeOH, 59% for two steps.

than previously thought or a conformational movement of the protein/Asp 30 side chain.

The most active analog in this series was the corresponding oxime **20** of aldehyde **18**. This group imparted a 6- to 10-fold enhancement in potency over the aniline **8** versus both the WT and A17 HIV activities and therefore, was the best group in this series against resistant virus. The presence of the proton of the oxime was very important in that replacement of this fragment with the methyloxime as in **21** resulted in greatly reduced antiviral activity. Other changes were not tolerated, such as the hydroxyamidine analog, **16**. The vector positioning of the oxime group was also critical for activity as replacement of the oxime at the *meta*-position as in **23** resulted in a 3-fold loss in WT activity and greater than a 7-fold loss in activity against resistant virus. The *meta*-hydroxymethyl **22** suffered a similar loss of antiviral activity.

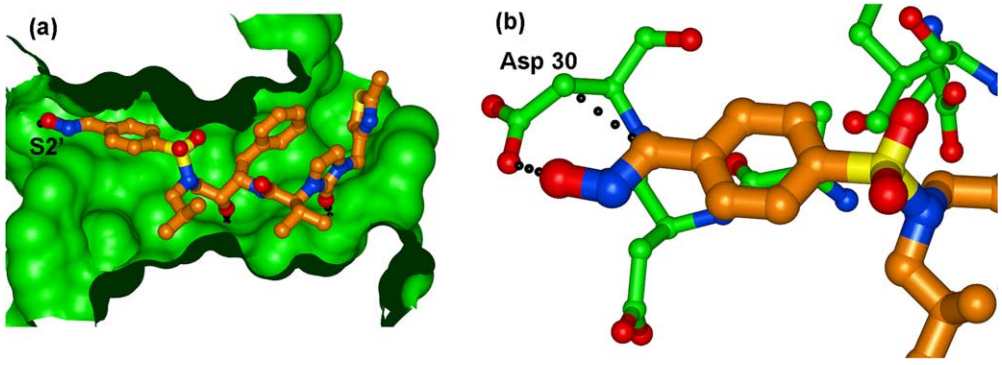


Figure 2. (a) Crystal structure of **20** bound to HIV protease indicating the oxime group projecting into S2′ cavity. (b) Crystal structure of **20** bound to HIV protease showing the H-bond of the oxime-OH with the side chain of Asp 30.

An X-ray crystal structure of oxime **20** bound in the HIV protease active site (Fig. 2)[6] revealed the potential interaction of the oxime hydroxyl group to form a favorable hydrogen bond with the Asp 30 side chain carbonyl with a distance of 2.66 Å. This interaction may be responsible for the excellent potency against both the WT and A17 resistant viruses.

In summary, we have discovered a novel series of hybrid arylsulfonamide HIV PIs that exhibit good in vitro potency against both the WT and A17 resistant viruses. The oximino group was identified as the optimal moiety in terms of resistant profile, and this activity may be attributed to its constructive hydrogen bonding with the Asp 30 side chain of the protease as shown by the X-ray crystallographic study. Further modifications on the left-hand side of the molecule are being pursued as a way to further enhance the antiviral and pharmacokinetic properties of this series.

References and notes

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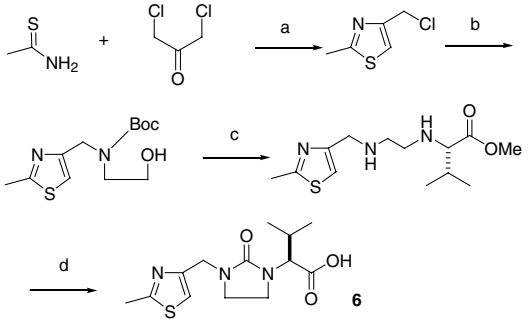
3. Unpublished results.



Reagents and conditions: (a) 60 °C, *i*-PrOH, 79%; (b) (i) ethanolamine, 16 h, rt, 73%, (ii) Boc_2O, 97%; (c) (i) oxalyl chloride, DMSO, (ii) L-ValOMe, $NaCNBH_3$, 1 h, rt, 63%, (iii) 50% TFA, 70%; (d) (i) CDI, THF, reflux, 3 h, 68%, (ii) LiOH, 59%.

4. A17 strain was generated by in vitro 17 passages with Lopinavir/Ritonavir and contains 6 mutations (L10F/V32I/M46I/I47V/Q58E/I84V). For assay procedure, see Ref. 11.
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6. HIV protease was purified and crystallized in the presence of compound **21** according to the procedures described by Stoll et al.[7] Data were collected on a Rigaku RU200 X-ray generator using a Mar 165 CCD detector. Data were processed using HKL2000.[8] The co-crystals of HIV protease and compound X belong to the orthorhombic space group *P*21212 with unit cell dimensions $a = 58.041$ Å, $b = 85.954$ Å, $c = 46.033$ Å. Calculation of initial electron density maps and refinement were done using CNX[9,10] and refined to a final $R_{work} = 27.75$ and $R_{free} = 35.31$ to 3.0 Å resolution. Coordinates for the crystal structure of protease complexed with **21** have been deposited in the RCSB protein data bank, PDB ID 1YT9.
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