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Ultra-potent P1 modified arylsulfonamide HIV protease inhibitors: The discovery of GW0385

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Abstract—A novel series of P1 modified HIV protease inhibitors was synthesized and evaluated for in vitro antiviral activity against wild-type virus and protease inhibitor-resistant viruses. Optimization of the P1 moiety resulted in compounds with femtomolar enzyme activities and cellular antiviral activities in the low nanomolar range culminating in the identification of clinical candidate GW0385.

Despite over two decades of intensive research directed toward the eradication of HIV/AIDS, the disease remains a global health crisis. The epidemic is particularly severe in the developing world, most notably sub-Saharan Africa where there are currently estimated to be 25 million people living with HIV.[1] Dramatic progress in the treatment of HIV was realized in the mid-1990s with the introduction of the HIV protease inhibitor class of drugs. The inclusion of protease inhibitors (PIs) as a component of highly active antiretroviral therapy or 'HAART' led to significantly improved clinical outcomes and was quickly adopted as the standard of care in HIV therapy.[2] In addition to their well-documented activity as potent inhibitors of viral polyprotein processing, more recent research suggests that HIV PIs may also play a role toward ameliorating protease mediated cytopathogenesis in $CD4^+$ T-cells.[3] Although they have seen considerable success in the management of HIV disease, PIs have several significant shortcomings. Chief among these is the emerging problem of drug resistance. Viral strains that are resistant to the currently available PIs have now developed and an increasing number of patients are failing PI therapy.[4] Therefore, the identification of agents with activity against drug resistant viral strains is of critical importance.

We recently reported three novel series of arylsulfonamide HIV-PIs obtained through iterative modification of the amprenavir scaffold.[5] Of these three series, the class containing aminoalkyl chain extensions attached to the *para* position of the P1 phenyl ring[5a] showed the most promising antiviral activity against wild-type virus and two PI-resistant viral strains (Fig. 1).

Herein, we describe our efforts to further optimize this chemical series by exploring additional modifications in the P1 position. In particular, we were interested in studying the effect of attaching various aryl and heteroaryl moieties to the P1 *para* oxygen atom. The diverse range of properties afforded by this class of substituents should, in principle, facilitate efficient lead optimization in this series.

All compounds were generated through the previously reported[5a] *O*-benzyl-protected, tyrosine-derived, intermediate **a**. Catalytic hydrogenation of **a** over Pd/C yielded phenolic intermediate **b**. Copper mediated aryl boronic acid coupling of **b** employing conditions previously reported by Evans et al.[6] provided diphenyl ether analogs **1**–**6** in modest yields (Method B1). In general,

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Keywords: Antiviral; Antiretroviral; Arylsulfonamide; Brecanavir; Drug resistance; GW0385; HIV protease.

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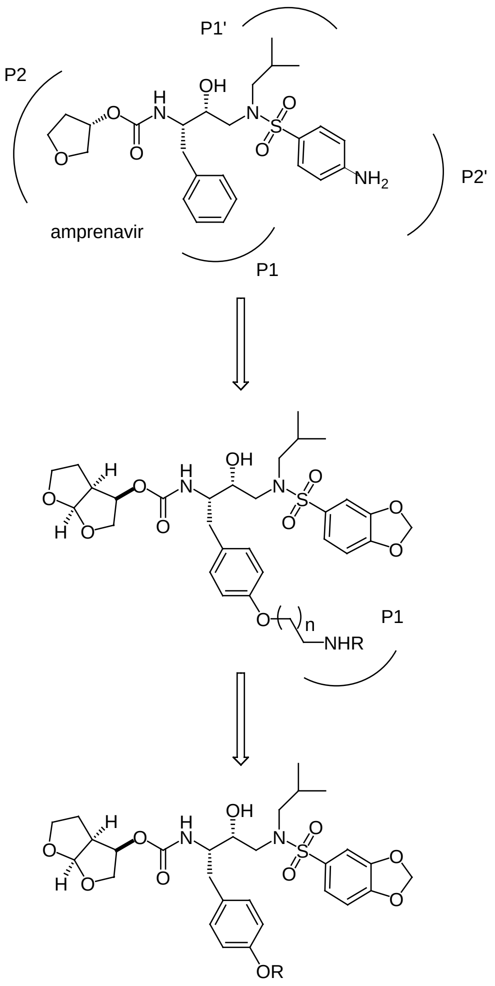


Figure 1.

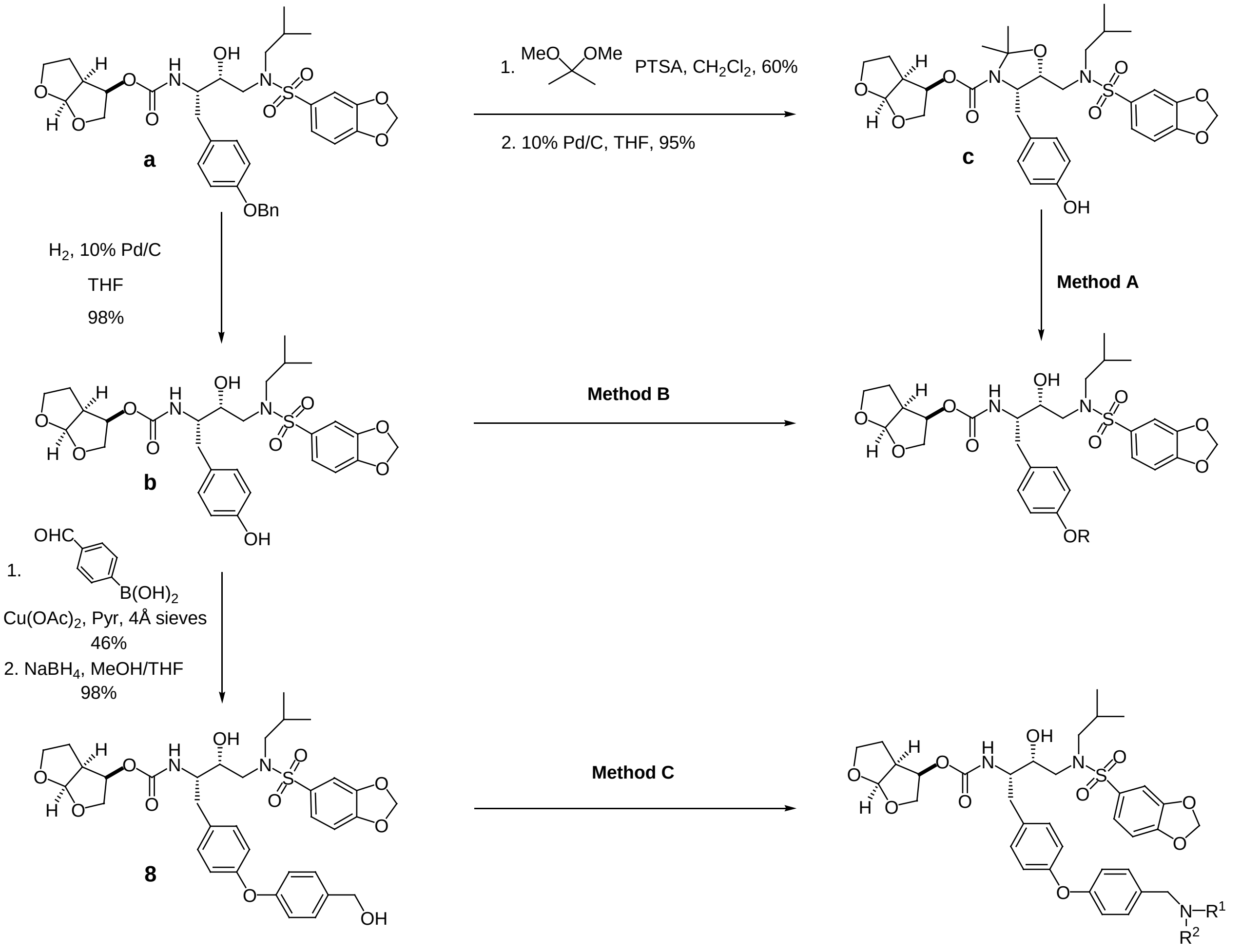
ortho-substituted aryl boronic acids failed to couple as did heteroaryl boronic acids excepting 3-pyridyl boronic acid which provided analog **6**, albeit in low yield. Analog **8** was prepared via coupling of **b** with benzaldehyde-4-boronic acid prior to borohydride reduction of the carboxaldehyde. Subsequent bromination of **8** and amine displacement provided analogs **9** and **10**. Alternatively, displacement of the intermediate bromide with ammonia followed by either acylation or sulfonylation provided analogs **11**–**13** (Method C). Pyrimidine analog **7** was prepared through direct phenolic displacement of 2,4-dichloropyrimidine with **b** followed by catalytic hydrogenation of the residual chloride (Method B2). Cesium carbonate mediated alkylation of **b** in DMF at room temperature with chloromethyl-substituted 2-pyridine and 2-quinoline provided analogs **21** and **22** (Method B3), respectively. Substrates requiring elevated temperatures gave rise to extensive degradation via oxazolidinone formation with concomitant loss of the chiral hydroxy furan. Therefore, prior protection of **a** as isopropylidene derivative **c** followed by benzyl deprotection, base-mediated alkylation, and final acid hydrolysis was required to provide analogs **15**, **20**, and **27** (Method A). The remaining analogs were prepared via Mitsunobu coupling of **b** with DtBAD, triphenylphosphine, and the appropriate alcohol (analogs **16**–**19** and **23**–**26**, Method B4) (Scheme 1).

Tables 1 and 2 illustrate the in vitro antiviral data for 27 new compounds in the P1 modified arylsulfonamide series. For comparison purposes, Table 2 shows analogous data for the structurally related competitor compound TMC114[7] and currently marketed PIs, also determined in our in-house assays. The antiviral IC_{50}s for wild-type HIV virus (HXB2)[8] and two multi-PI-resistant viruses (EP13 and D545701, see Table 4) were determined in a MT4 cell line.[9]

Within the aryl ether sub-series **1**–**13** substitution on the phenyl ring leads to modest increases in antiviral activity regardless of the substitution pattern. A comparison of the three isosteric derivatives **1**, **6**, and **7** is interesting. The activity trends across the viral strains are similar but the absolute potencies are greater for heteroaromatic analogs **6** and **7**. The aminomethyl-linked derivatives **9**–**13** show a general improvement in activity relative to parent compound **1** and its simpler substituted derivatives **2**–**5**. The data for *O*-benzyl derivatives **14** and **15** indicate that insertion of a methylene unit into the ether linkage of **1** yielded significant improvements in activity, particularly against the mutant viruses. Chain extension by an additional carbon atom, as exemplified by phenethyl analog **16**, leads to modest reductions in activity, most notably against the D545701 strain. Interestingly, the 2-substituted thiophene derivative **18** shows a 4-fold improvement in activity as compared to its 3-substituted congener **17**. Triazole **19** and imidazole **23** show significant reductions in wild-type activity, however, they show increases in activity against the mutant strains versus wild type. A comparison of compounds **14** and **20** indicates that benzo ring fusion exerts a deleterious effect on activity. Pyridyl derivative **21** and quinoline **22** show a similar but less pronounced activity relationship. As a class, thiazole derivatives **24**–**27** possess the most impressive activities with single-digit nanomolar IC_{50}s against all three viral strains.

Cellular antiviral activities are a composite of intrinsic enzyme activity and intracellular transport efficiency. In the absence of enzyme inhibition data, it is impossible to know the relative contributions of these two factors in determining antiviral activities. During the evolution of our HIV PI program, we reached a level of enzyme potency optimization at which the majority of compounds being synthesized had inhibitor binding constants below the lower limit (approximately 10 pM) measurable using standard steady-state kinetics techniques. As a result, the standard fluorometric assay[10] was no longer useful in driving our lead optimization efforts and we were forced to rely exclusively on cellular antiviral data.

To address this problem, we developed a radioligand binding assay which pushed the measurable K_i cutoff down into the femtomolar range.[11] However, due to lower effective compound throughput, we employed this assay not as a first line potency screen, but as a means of determining enzyme activities for a limited number of our more interesting lead molecules. Using this method, compounds **21** and **27** were found to have enzyme K_is against wild-type HIV protease of 6 and 15 fM,



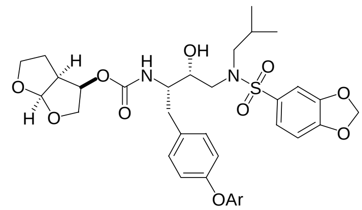
Scheme 1. Reagents: Method A: (a) Cs_2CO_3, DMF, R-Cl; (b) HCl, H_2O, dioxane. Method B: (1) $Cu(OAc)_2$, pyridine, 4 Å sieves or; (2) a–2,4-dichloropyrimidine, EtOH, $NaHCO_3$; b—5% Pd/C, EtOH, 2 M NH_3 in MeOH or; (3) Cs_2CO_3, DMF, chloride or (4) Di-*tert*-butylazodicarboxylate, PPh_3, alcohol, CH_2Cl_2. Method C: PBr_3, CH_2Cl_2, 46% then (1) 5 equiv amine, DMF or; (2) a—7 M NH_3 in MeOH, 94%; b—acetyl chloride, methanesulfonyl chloride or methyl chloroformate, DIEA, CH_2Cl_2.

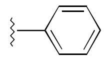
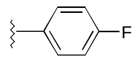
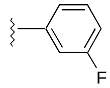
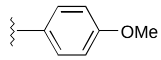
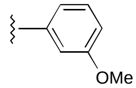
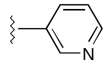
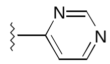
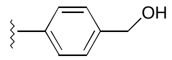
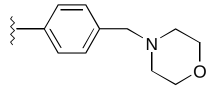
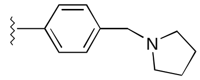
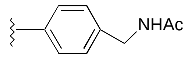
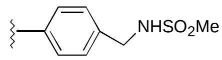
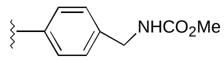
respectively. These data indicate a remarkable level of enzyme activity that ranges from 2400 to 6000 times that of amprenavir. It is interesting to note the disparity between the amprenavir/**27** enzyme differential (6000×) and the analogous cellular antiviral differential (185X). In addition, the data presented in Tables 1 and 2 indicate a relatively weak correlation of antiviral activity with the geometric and topological characteristics of the various substituents at P1. Taken together, these observations suggest that cell penetration may be a significant if not limiting factor in dictating antiviral activity.

To more rigorously address this possibility, we examined the relationship between antiviral activity and several calculated physicochemical parameters (polar surface area, C log *P*, and molar volume) for the 27 compounds in this study. While some limited correlation was gleaned from the polar surface area numbers, a rather well-defined relationship emerged between antiviral activity and C log *P*. No meaningful correlation was observed between antiviral activity and molar volume. Figure 2 shows a plot of D545701 IC_{50}s for our P1 modified derivatives and TMC114 against C log *P*.[12] The compounds with the best antiviral activities have C log *P* values in the 3.7–5.0 range (e.g., thiazoles **24**–**27** and pyridine **21**). Similar relationships were observed for the wild-type and EP13 viral strains. The observed functional dependence of biological activity on the hydrophobicity descriptor C log *P* suggests that membrane transport is the dominant factor governing antiviral activities in this compound series.

In the course of our lead optimization work in the P1 arylsulfonamide series, we examined a large number of compounds for oral pharmacokinetics in rats and/or dogs. The majority showed very low oral bioavailability as determined in single dose experiments. However, some did display modest % *F*s in the 10–20% range. Three selected examples are illustrated in Table 3. Thiazole derivative **27** yielded a 10% *F* and 20% *F* in rat and dog, respectively. However, when **27** was co-administered with 4 mg/kg of the cytochrome P450 (CYP450) inhibitor ritonavir, these values increased to 62% *F* and 86% *F*, respectively. Poor oral pharmacokinetics is one of the most problematic aspects of HIV PI therapy.

Table 1. Anti-HIV IC_{50}s ± standard error (*n*) for P1 modified diarylethers



Entry[a]	Ar	IC_{50}[b] (nM) HXB2	EP13	D545701	Synthetic sequence[c] (yield)
1		7.5 ± 1.6 (6)	21 ± 5 (6)	62 ± 7 (6)	B1 (32%)
2		3.3 ± 0.3 (5)	8.1 ± 1.0 (5)	29 ± 5 (5)	B1 (52%)
3		5.7 ± 1.2 (5)	17 ± 3 (5)	48 ± 10 (5)	B1 (42%)
4		2.1 ± 0.3 (5)	6.9 ± 2.3 (7)	27 ± 4 (7)	B1 (56%)
5		4.7 ± 1.1 (5)	16 ± 3 (5)	41 ± 9 (5)	B1 (54%)
6		1.1 ± 0.2 (5)	2.4 ± 0.5 (5)	9.5 ± 2.3 (6)	B1 (30%)
7		2.0 (1)	2.8 (1)	11 (1)	B2 (46%, 36%)
8		1.6 ± 0.4 (5)	1.6 ± 0.4 (5)	8.4 ± 1.1 (6)	see Scheme 1
9		1.2 ± 0.2 (5)	2.9 ± 0.6 (5)	13 ± 2 (6)	C1 (79%)
10		2.8 ± 0.2 (5)	4.6 ± 0.4 (5)	19 ± 3 (6)	C1 (68%)
11		6.2 ± 1.2 (6)	3.4 ± 0.6 (5)	6.3 ± 0.9 (6)	C2 (72%)
12		7.2 ± 1.1 (6)	5.3 ± 1.0 (5)	11 ± 2 (6)	C2 (68%)
13		1.3 ± 0.2 (5)	2.2 ± 0.4 (5)	6.8 ± 1.3 (6)	C2 (70%)

[a] All compounds were >95% pure by ^{1}H NMR and HPLC.

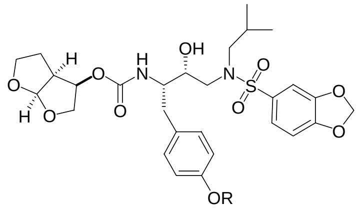
[b] IC_{50}, antiviral inhibition in MT-4 cell culture.

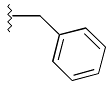
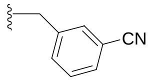
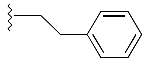
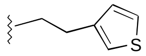
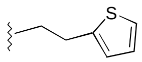
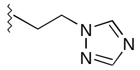
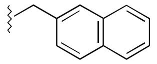
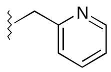
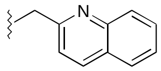
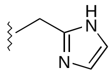
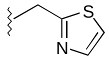
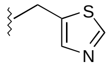
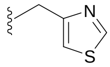
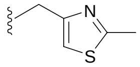
[c] See Scheme 1 for details.

In general, this problem is believed to be the result of a combination of extensive CYP450-mediated first-pass metabolism and variable cellular efflux by p-glycoprotein.[13] Co-administration with sub-therapeutic doses of ritonavir, also known as 'pharmacoenhancement,' has been successfully employed to increase systemic drug exposures in HIV PI therapy. The mechanisms by which ritonavir 'boosts' drug exposures are believed to be related to potent CYP450 inhibitory activity and possibly to its ability to inhibit p-glycoprotein mediated cellular efflux. Based on its success over the last several years, ritonavir-based PI boosting is now viewed as standard clinical practice by most HIV clinicians.[14]

In order to more rigorously assess the potential of analog **27** (GW0385) as a development candidate, the

Table 2. Anti-HIV IC_{50}s ± standard error (*n*) for P1-tethered aryl analogs



Entry[a]	R	IC_{50}[b] (nM)			Synthetic sequence[c]
		HXB2	EP13	D545701	
14		3.1 ± 0.7 (6)	5.9 ± 1.2 (6)	9.6 ± 2.4 (7)	Ref. 5a
15		1.2 ± 0.4 (3)	2.2 ± 0.8 (3)	2.2 ± 0.6 (4)	A1 (46%)
16		3.7 ± 0.7 (6)	8.7 ± 1.7 (5)	25 ± 5 (6)	B4 (72%)
17		9.5 ± 2.0 (6)	17 ± 3 (6)	44 ± 12 (4)	B4 (44%)
18		2.3 ± 0.5 (12)	3.4 ± 0.6 (12)	11 ± 2 (12)	B4 (71%)
19		21 ± 3 (5)	8.3 ± 0.8 (5)	12 ± 2 (5)	B4 (59%)
20		11 ± 1 (6)	30 ± 4 (6)	59 ± 16 (3)	A1 (92%)
21		1.2 ± 0.5 (6)	1.2 ± 0.3 (8)	4.5 ± 0.6 (8)	B3 (60%)
22		2.5 ± 0.6 (5)	5.2 ± 1.2 (5)	19 ± 3 (5)	B3 (44%)
23		69 ± 10 (5)	20 ± 3 (5)	16 ± 3 (5)	B4 (81%)
24		0.9 ± 0.2 (6)	1.5 ± 0.5 (6)	5.1 ± 1.0 (6)	B4 (38%)
25		1.9 ± 0.3 (5)	2.5 ±0.2 (5)	6.5 ±1.4 (5)	B4 (25%)
26		0.6 ± 0.2 (5)	1.2 ±0.2 (6)	3.5 ±0.4 (6)	B4 (47%)
27 (GW0385)		0.7 ± 0.1 (21)	1.1 ± 0.1 (24)	4.8 ± 0.5 (25)	A1 (36%)
TMC114	—	3.9 ± 1.6 (3)	6.8 ± 3.2 (3)	32 ± 10 (3)	—
Atazanavir	—	25	93	70	—
Lopinavir	—	40	400	>1000	—
Amprenavir	—	130	440	>1000	—
Saquinavir	—	60	80	603	—
Indinavir	—	50	330	440	—
Nelfinavir	—	320	450	>1000	—
Ritonavir	—	268	>1000	>1000	—

[a] All compounds were >95% pure by ^1H NMR and HPLC.

[b] IC_{50}, antiviral inhibition in MT-4 cell culture.

[c] See Scheme 1 for details.

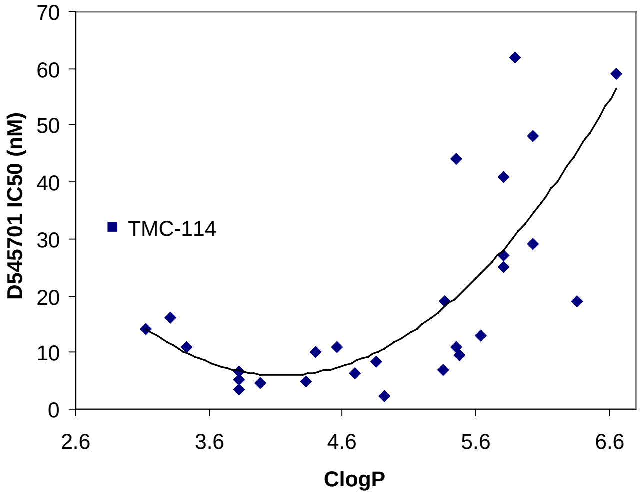


Figure 2. Plot of D545701 antiviral IC_{50} versus C log *P*.

Table 3. In vivo pharmacokinetic parameters for P1 modified arylsulfonamides dosed at 1 mg/kg

Entry	Species	IV clearance (mL/min/kg)	$t_{1/2}$ (h)	% *F*
18	Rat	27	2.2	15
18	Dog	22	0.50	18
21	Rat	20	0.91	21
27	Rat	10	1.4	10
27 + 4 mg/kg RTV	Rat	—	1.1	62[a]
27	Dog	19	0.87	20
27 + 4 mg/kg RTV	Dog	—	1.2	86[a]

RTV, ritonavir.

[a] Calculated by dividing the ritonavir-boosted oral AUC by the non-boosted IV AUC.

antiviral activity was examined in a more extensive panel of clinical and engineered resistant viral strains containing mutations in the aspartyl protease. Table 4 lists the amino acid substitutions present in each resistant virus along with antiviral activity as determined in MT4 cells.

Impressively, GW0385 exhibited single digit nanomolar, or less, potency against the entire screen. The largest drop of potency was observed in the clinically derived 468 amprenavir-resistant viral strain with an IC_{50} of ~8 nM. It is important to note that this broad-spectrum antiviral resistance profile is in contrast to analogs where even minor modifications were introduced at P1′, previously reported by our group.[5b,5c] For instance, decreases in antiviral potency against the multi-PI resistant D545701 strain in the *N*-alkoxy sulfonamides typically exceeded 20-fold.[5b] Figure 3 graphically depicts the comparison of potency in the same panel between GW0385 and currently marketed PIs along with structurally related TMC 114, using a cutoff of 200 nM for clarity. This comparison underscores the outstanding potential for this class of inhibitors in treating HIV patients infected with multi-PI resistant virus.

To fully investigate the effects of substitutions at P1, we solved X-ray crystal structures for GW0385 complexed in both the WT[15] and D545701[16] enzymes. Interestingly, although a general collapse of the P1 pocket is observed in the mutant enzyme, the P1 thiazolylmethyl tether is able to adopt an angled conformation that appears to produce an increase in van der Waals interactions with hydrophobic elements of the mutant protein without requiring additional hydrophilic interactions. This is consistent with our observations regarding the influence

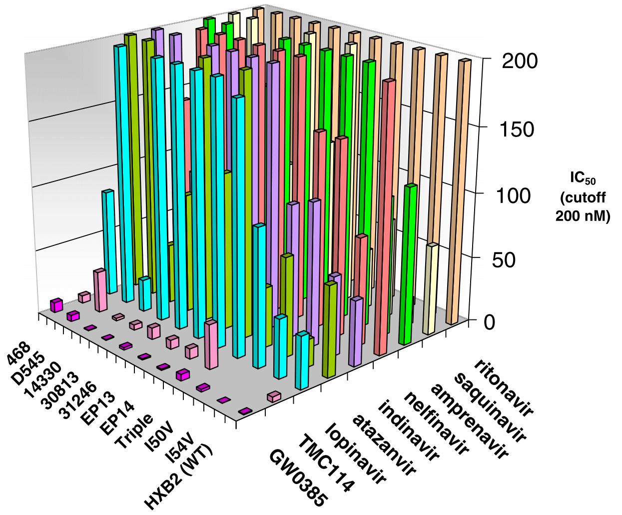


Figure 3. GW0385 antiviral resistance profile against current PIs.

Table 4. GW0385 resistance profile against PI-mutant virus

HIV-virus	Amino acid substitutions in the aspartyl protease gene	IC_{50} (nM)
HXB2–WT HIV-1		0.7
468 APV-r	I15V, E34G, M36I, S37E, I50V, L63P	8.2
D545701 Multi PI-r	L10I, L19Q, K20R, E35D, M36I, S37N, M46I, I50V, I54V, I62V, L63P, A71V, V82A, L90M	4.8
14330 NFV-r	D30N, E35D, M36I, S37D, I62V, L64P, I64M, N88D	0.45
30813 IDV-r	I15V, I54V, R57K, I62V, L63P, H69Y, A71T, I72E, V82A, I85V	0.46
31246 Multi PI-r	L10I, I54V, L63P, A71V, I72V, V77I, V82A, I84V, L90M, Q92K	1.7
EP13 Multi PI-r	M46I, L63P, A71V, V82F, I84V	1.1
EP14 Multi PI-r	L10R, M46I, L63P, V82T, I85V	0.77
Triple Multi PI-r	M46I, I47V, I50V	5.4
I50V	I50V	1.6
I54V	I54V	0.22

Abbreviations: NFV, nelfinavir; APV, amprenavir; IDV, indinavir.

of C log P in this series where substituents that introduced more hydrophilic character demonstrated a relative loss of antiviral potency. In addition, examination of the mutant structure suggests that there may be water mediated interactions between the thiazole nitrogen atom of the inhibitor and Arg 8 and Asp 29 side chains of the enzyme.

Following extensive preclinical testing, GW0385 successfully entered clinical trials for the treatment of HIV infection. The drug was generally safe and well tolerated. Pharmacoenhancement with ritonavir improved exposures 33- to 85-fold in humans, depending on dose, providing drug levels anticipated to be well above those estimated to effectively inhibit resistant viruses.[17] GW0385 (brecanavir[18]) has received fast track designation from the United States Food and Drug Administration and is currently being evaluated in Phase II studies in HIV-infected patients.

In summary, we have disclosed the synthesis and SAR of a novel series of P1-substituted arylsulfonamides culminating in the identification of the clinical candidate GW0385. Outstanding antiviral activity against both wild-type and mutant viruses, coupled with excellent bioavailability obtained when co-dosed with the CYP450 inhibitor ritonavir, highlights the therapeutic potential of this next generation PI. GW0385 is expected to proceed into Phase III clinical development for the treatment of HIV in 2006.

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