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P1-Substituted Symmetry-Based Human Immunodeficiency Virus Protease Inhibitors with Potent Antiviral Activity against Drug-Resistant Viruses

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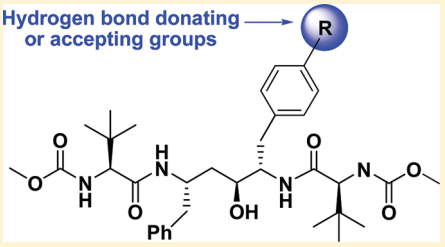
ABSTRACT: Because there is currently no cure for HIV infection, patients must remain on long-term drug therapy, leading to concerns over potential drug side effects and the emergence of drug resistance. For this reason, new and safe antiretroviral agents with improved potency against drug-resistant strains of HIV are needed. A series of HIV protease inhibitors (PIs) with potent activity against both wild-type (WT) virus and drug-resistant strains of HIV was designed and synthesized. The incorporation of substituents with hydrogen bond donor and acceptor groups at the P1 position of our symmetry-based inhibitor series resulted in significant potency improvements against the resistant mutants. By this approach, several compounds, such as **13**, **24**, and **29**, were identified that demonstrated similar or improved potencies compared to **1** against highly mutated strains of HIV derived from patients who previously failed HIV PI therapy. Overall, compound **13** demonstrated the best balance of potency against drug resistant strains of HIV and oral bioavailability in pharmacokinetic studies. X-ray analysis of an HIV PI with an improved resistance profile bound to WT HIV protease is also reported.



INTRODUCTION

The treatment of HIV infection with highly active antiretroviral therapy (HAART) has dramatically reduced the rate of disease progression to AIDS and the morbidity and mortality rate associated with it.[1] Because no cure for HIV infection is available, however, patients must remain on long-term drug therapy, leading to concerns over potential drug side effects and the emergence of drug resistance. Consequently, a need exists to develop new and safe antiretroviral agents with improved potency against drug-resistant strains of HIV. Significant progress has been made toward the discovery of HIV PIs with improved resistance profiles compared to the first generation of compounds. For example, the analysis of crystal structures of HIV protease in enzyme−ligand complexes has enabled structure-based drug design and has contributed to the understanding of the molecular basis for drug resistance.[2] Several marketed HIV protease inhibitors (PIs), including lopinavir, darunavir, and tipranavir (Figure 1), have improved potency against drug-resistant mutants compared to the first generation of drugs.[3,4] In addition, several reports on preclinical compounds with improved resistance profiles have also appeared.[5−8] We recently reported on compound **1** (A-790742, Figure 1), which demonstrated excellent potency against HIV PI-resistant clinical isolates.[9,10] A unique structural feature of compound **1** that contributed to its superior resistance profile was the P3 tertiary hydroxyl group. X-ray analysis of compound **1** bound to WT HIV protease (Figure 2) demonstrated that this hydroxyl functional group occupies a solvent exposed region adjacent to the hydrophobic S1 binding site, with the P3 pyridine ring interacting with the Arg8 residue via π stacking. The analysis also suggested that the tertiary alcohol binding region could potentially be accessed by substituents attached to the P1 group, due to their close spatial proximity. We speculated that the introduction of functional groups at the P1 position of our previously described pseudo-C_2-symmetric cores that could mimic the interactions of the tertiary hydroxyl group of **1** might provide an alternative approach for the discovery of HIV PIs with improved resistance profiles. We chose to study P1-substituted analogues of one of our previously described pseudo-C_2-symmetric cores (Figure 1), obtained by capping the P2 group with a methyl carbamate. While the hydroxyl group regiochemistry and P1′ stereochemistry of the new analogues differ from **1**, we showed previously that both of the core configurations result in potent compounds against the WT virus and that the P3 group was critical for activity against the drug-resistant viruses.[9] As expected, the initial analogue **10** with the 2-pyridyl P1 group was not highly active against drug-resistant HIV mutants, although subsequent analogues with modified P1 groups demonstrated improved resistance profiles. In this report, the synthesis and biological evaluation of HIV PIs having P1 groups substituted with hydrogen bond donor and acceptor groups are described.

CHEMISTRY

As shown in Scheme 1, compounds **10**−**30** were synthesized from the triflates **6**, **7**, **8**, or **9** through palladium-mediated

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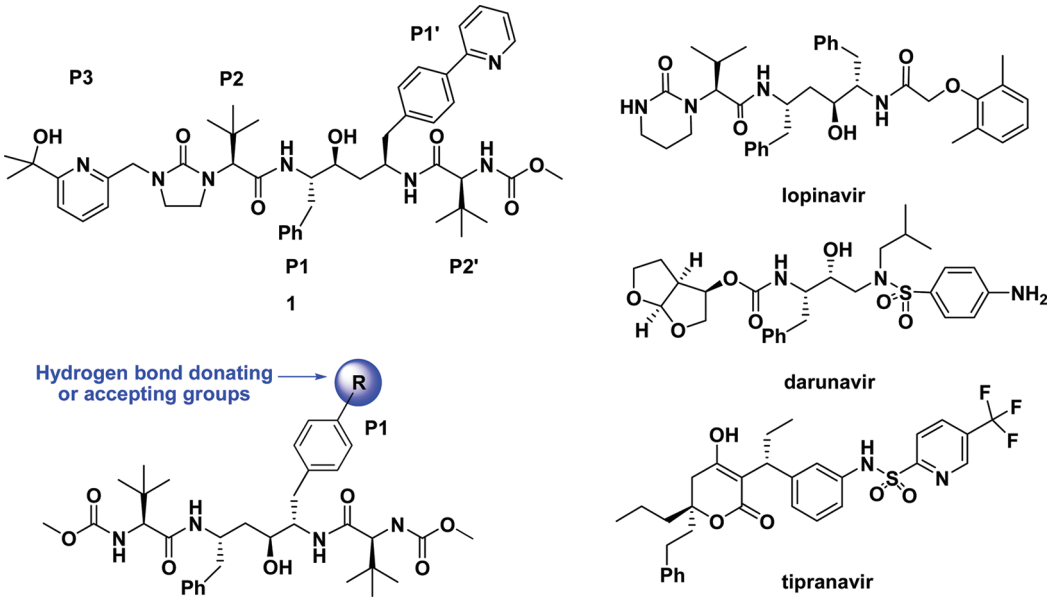

Figure 1. Structures of **1**, some marketed HIV PIs, and the design of P1-substituted HIV PIs.

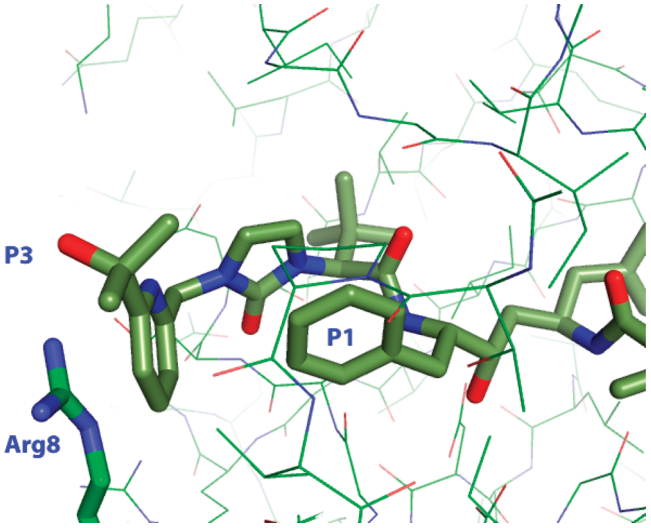

Figure 2. X-ray of **1** bound to WT HIV protease. Residue Arg 8 is highlighted to illustrate the π stacking interaction with the P3 pyridine ring. The P1 and P3 groups are in close proximity, suggesting that substituents attached to P1 may access the S3 binding region.

coupling with the appropriate boronic acid or stannane reagent. Tyrosine was benzylated as previously reported,[11] and reaction with sodioacetonitrile resulted in nitrile **2**, which was treated with benzyl Grignard reagent to give the enaminone **3**. A high degree of stereocontrol was observed for the stepwise reduction of **3** by using a similar procedure to that reported[12] for an analogous enaminone to give **4**, following Boc protection of the resulting amine. Removal of the benzyl protecting groups through hydrogenolysis gave the amine **5**. The triflates were generated using *N*-phenyl-bis(trifluoromethanesulfonimide), and a number of protection schemes, such as those found in **6**, **7**, **8**, and **9**, were compatible with either Suzuki or Stille coupling reactions. Compound **6** was employed initially based on the consideration that it would be beneficial to mask the central hydroxyl group and carbamate nitrogen during the palladium catalyzed coupling. While **6** reacted smoothly in Stille coupling reactions, it was subsequently discovered that a more direct synthesis with a simpler protection scheme was possible. For example, **7** reacted efficiently in Suzuki cross coupling reactions, and similar yields of coupled products were obtained by employing **8** or **9**, which had one or both of the *tert*-leucine peptide end-caps already in place. Deprotection of products resulting from palladium catalyzed couplings with **6**, **7**, and **8** using standard conditions followed by coupling with the *tert*-leucine end-caps gave the final products, while palladium catalyzed coupling with **9** gave the final products directly.

RESULTS AND DISCUSSION

Biological data for these compounds were summarized in Table 1. Antiviral activity was evaluated against WT virus with and without the addition of 50% human serum (HS), as well as against two resistant mutants, A17 and B26, derived from in vitro selection with lopinavir (LPV).[10] Attenuation of potency by binding to human serum proteins has been shown to be clinically relevant for HIV PIs, and measurement of in vitro EC_{50}s in the presence of 50% HS has demonstrated utility in the context of pharmacokinetic−pharmacodynamic modeling.[13] As described previously,[10] the mutant viruses had key mutations in the protease at positions that confer resistance to marketed HIV PIs, including lopinavir, atazanavir, and darunavir. Compound **10**, which was substituted with a 2-pyridyl group at the P1 position, demonstrated potency against the WT virus, although the fold resistance observed against the mutants was 4- to 7-fold higher than that observed for **1**. Altering the position of the pyridine nitrogen to either the 3- or 4-position as in compounds **11** and **12**, respectively, resulted in a slight decrease in WT potency and improvement in activity against the resistant mutants, which demonstrated only 2- to 3-fold resistance to **11** and **12**. An X-ray crystal structure of **11** bound to WT HIV protease (Figure 3) was obtained in an effort to understand the origins of its improved resistance profile. While no direct

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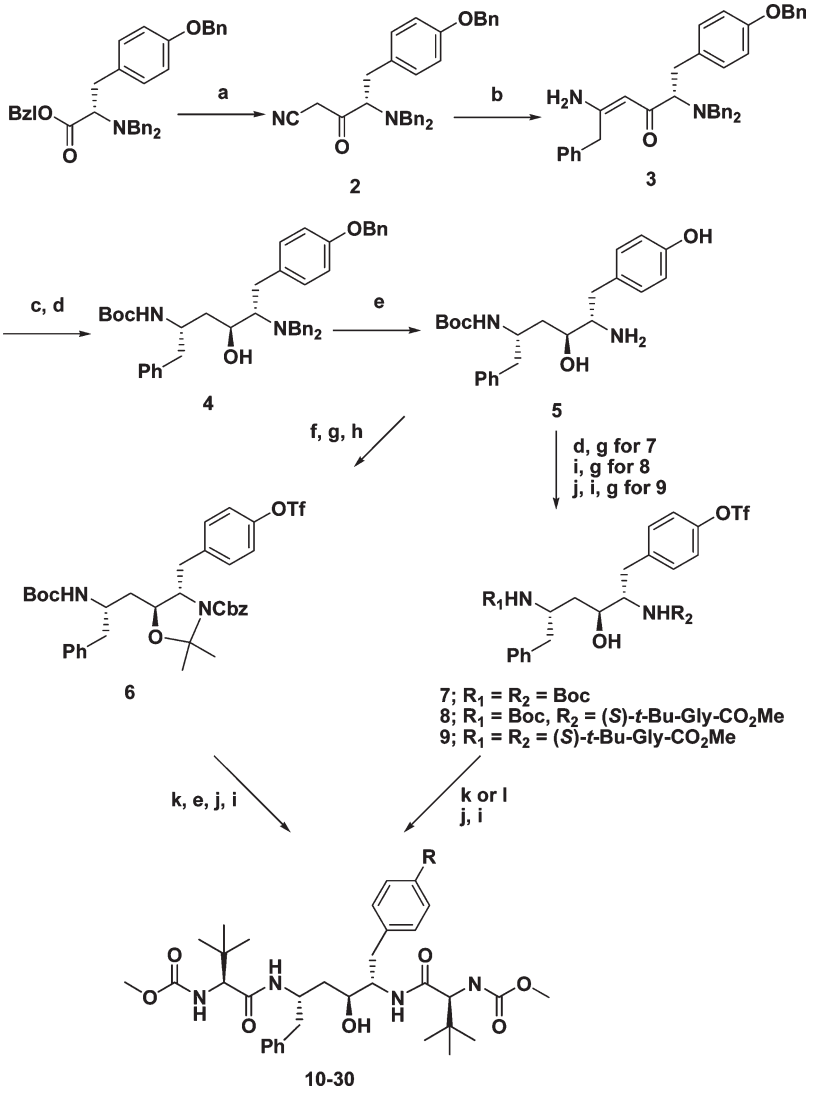
Scheme 1. Synthesis of HIV PIs 10−30[a]



[a] Reagents and conditions: (a) NaHMDS, CH_3CN; (b) BnMgCl; (c) (i) $NaBH_4$, CH_3SO_3H, (ii) $NaBH_4$, TFA; (d) Boc_2O; (e) $Pd(OH)_2$ on C, H_2; (f) Cbz-Osu; (g) *N*-phenyl-bis(trifluoromethanesulfonimide); (h) 2,2-dimethoxypropane; (i) DEPBT, MeO_2C-*t*-Bu-Gly-OH; (j) 4 N HCl in dioxane; (k) $Cl_2Pd(PPh_3)_2$, LiCl, $RSn(Bu)_3$, DMF; (l) $Cl_2Pd(PPh_3)_2$, $RB(OH)_2$, Na_2CO_3, DMF.

hydrogen bounds between **11** and the enzyme were observable, the region occupied by the pyridine ring was exposed to the aqueous environment. Consequently, the 3-pyridyl nitrogen atom of **11** may be more accessible for the formation of water-mediated hydrogen bonds with the protein or to contribute to solvent anchoring effects.[7] The X-ray analysis also indicated that the twist angle of 20−30° for the 3-phenylpyridine P1 side chain of **11** was larger than the relatively planar angle (approximately 5°) observed for the 2-phenylpyridine P1′ group of **1**, an observation supported by the literature.[14] The larger twist angle of the pyridine of **11** may allow for increased van der Waals interactions with Pro81, and this increased interaction with the protein may have greater impact for resistant viruses where neighboring residues are mutated in A17 (I84 V) and B26 (V82F).

Substitution of compound **11** with a fluorine at the 3-position resulted in compound **13**, which had improved WT potency and maintained low-fold resistance for the mutants. In contrast, substitution of electron withdrawing substituents at the 2-position, such as fluorine (**14**) and cyano (**16**), resulted in decreased potency against the resistant mutants, while the WT potency was maintained. Substitution of such groups at the 2-position more significantly reduces the basicity of the pyridine ring than substitution at the 3-position,[15] suggesting that the charged group may enhance the resistance profile. A similar reduction in potency against the mutant viruses was observed when compound **12** was substituted with a fluorine at the 2-position, as in compound **15**.

Because subtle structural changes to the pyridine ring system affected the resistance profile, the effect of substituting the P1 position with additional nitrogen-based heterocycles was examined. For example, the pyrazine analogue **18** lost potency against the WT virus and the resistant mutants, while the pyrimidine analogue **19** retained WT potency and had significantly higher-fold resistance against the resistant mutants. Both of these heterocycles are significantly less basic than the pyridines found in **11** or **12**, again suggesting that the protonated forms may

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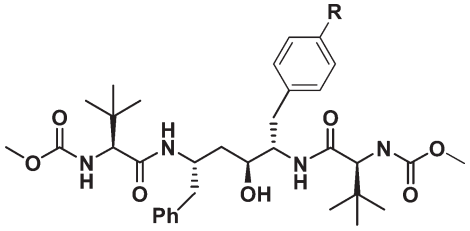
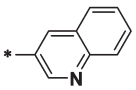
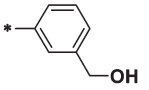
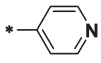
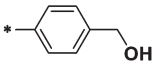
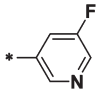
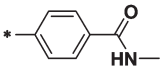
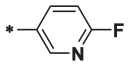
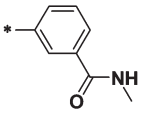
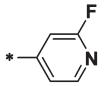
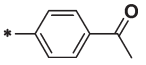
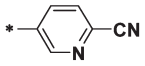
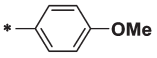
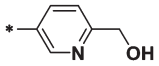
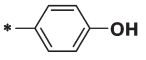
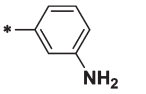
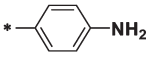
Table 1. In Vitro Cell Culture Potency



Compound		EC_{50} (nM)		Fold Change Relative to WT		Compound		EC_{50} (nM)		Fold Change Relative to WT	
No.	R	WT[a] 0% HS	WT[b] 50% HS	A17[c] 0% HS	B26[d] 0% HS	No.	R	WT[a] 0% HS	WT[b] 50% HS	A17[c] 0% HS	B26[d] 0% HS
LPV		18	152	59	211	**20**		2	18	14	21
1		3	19	3	7						
10		6	19	20	29	**21**	Ph	4	95	21	12
11		11	35	2	3	**22**		21	92	1	1
12		13	34	2	3	**23**		5	18	2	2
13		4	24	3	3	**24**		4	56	1	1
14		3	14	12	14	**25**		159	842	0.4	0.5
15		2	7	10	10	**26**		1	3	9	8
16		6	23	8	12	**27**		1	3	48	30
17		14	45	0.2	0.6	**28**		13	71	3	3
18		54	151	7	4	**29**		5	20	3	3
19		2	58	41	74	**30**		6	38	7	9

[a] pNL4−3, no HS added. [b] pNL4−3, 50% HS added. [c] A17 contains the mutations L10F, V32I, M46I, I47V, Q58E, and I84V. [d] B26 contains the mutations L33F, K45I, M46I, I50V, I54V, A71V, and V82F.

contribute to the potency of the pyridine analogues. Compound **20** which was substituted with a quinoline group retained WT potency, although its potency against the resistant mutants was diminished.

In general, the addition of polar functional groups with hydrogen bonding donor or acceptor groups to the P1 biaryl system was well-tolerated for potency against the WT virus and several compounds had improved potency against the resistant

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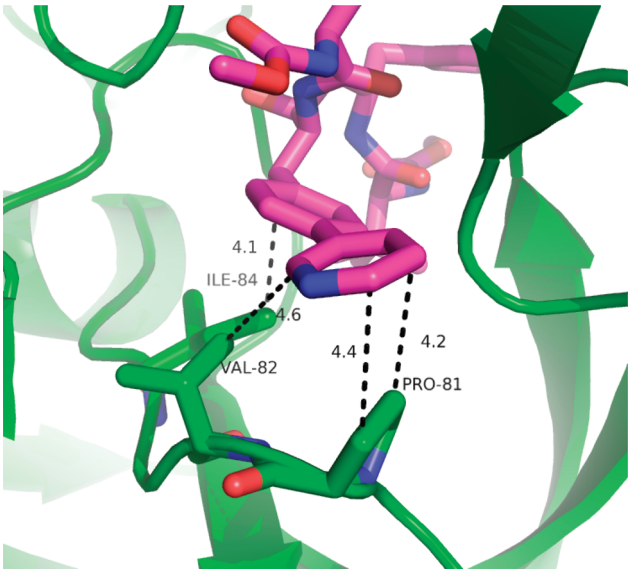

Figure 3. X-ray crystal structure of **11** bound to WT HIV protease. The biaryl twist angle of 20−30° may enhance hydrophobic contacts with Pro81, while the 3-phenylpyridine nitrogen is accessible for interactions with solvent water molecules. Distances are shown in Å.

mutants. For example, compound **17**, which resulted from the addition of a hydroxymethyl group at the 2-position of compound **11**, maintained potency against the WT virus, while the resistant mutants demonstrated hypersensitivity to this compound. In addition to the heterocyclic P1 groups described above, a variety of substituted biphenyl compounds were also surveyed. While the unsubstituted parent compound **21** had similar potency to compound **10** against the WT and the drug-resistant viruses, the introduction of hydrogen bond donating groups, such as hydroxymethyl (**21** and **23**), phenol (**28**), and amines (**29** and **30**), generally resulted in improved potency against the resistant mutants. Compounds **23** and **29** combined the attractive features of excellent potency against the WT virus along with low-fold resistance versus the mutants. Compounds with hydrogen bond accepting groups alone, such as acetate (**26**) and methoxy (**27**), demonstrated superior potency against the WT virus but lacked any improvement against the resistant mutants. Compounds bearing an amide which provided both hydrogen bond donor and acceptor groups, such as **24** and **25**, exhibited a lack of resistance for the mutant viruses, while the para-substituted isomer (**24**) was 40-fold more potent than the meta-substituted isomer (**25**) against the WT virus.

Viruses obtained from patients who have failed HIV PI therapy often have proteases with a large number of mutations, in addition to those found in the A17 and B26 mutants.[10,16] To determine the potential effectiveness of these compounds at inhibiting this type of drug-resistant virus, compounds that demonstrated low-fold resistance against the A17 and B26 viruses were also tested against two HIV molecular clones containing protease genes derived from patient isolates (Table 2). Viruses 1 and 2 were highly resistant to LPV, while virus 1 was highly resistant and virus 2 was susceptible to compound **1**. Several of the new compounds showed similar activity against viruses 1 and 2 compared to compound **1**, such as **13**, **15**, **22**, **23**, and **26**. Four of the compounds (**16**, **17**, **24**, and **29**), however, showed improvement in their activity against virus

Table 2. Activity against HIV-1 Molecular Clones Containing Proteases Derived from PI-Resistant Patient Isolates

	fold change in EC_{50} relative to WT	
no.	virus 1[a]	virus 2[b]
LPV	62	234
1	57	2
11	29	17
13	38	2
14	58	7
15	30	2
16	16	3
17	12	2
20	33	12
22	52	4
23	45	2
24	7	1
26	28	4
27	34	18
29	9	1
30	45	7

[a] Virus 1 contains the mutations L10I, E35D, N37D, M46I, I54V, G57R, L63P, A71V, T74P, I84V, L90M, I93L. [b] Virus 2 contains the mutations L10I, I13V, G16A, Q18H, L33F, N37D, M46I, I54V, G57R, Q61H, I62V, L63P, A71L, I72T, L76V, V77I, V82A, N88G, L90M, I93L.

Table 3. Oral Pharmacokinetic Data in Rats (5 mg/kg)

	no RTV			w/RTV[a]		
no.	F (%)	C_{max}[b]	AUC[c]	F (%)[d]	C_{max}[b]	AUC[c]
10	7	0.28	0.19	>100	1.55	4.88
11	5	0.18	0.16	25	0.43	0.74
13	13	0.11	0.16	>100	0.47	3.22
20	1	0.02	0.03	63	0.22	1.85
23	0	0	0	0.3	0.01	0.01
26	0	0	0	27	0.05	0.22
27	0	0	0	14	0.05	0.27
29	1	0.1	0.02	5	0.10	0.07

[a] Coadministered with 5 mg/kg RTV. [b] μg/mL. [c] μg·h/mL. [d] Relative to IV dose without RTV coadministration.

1 compared to LPV or compound **1**. Against virus 2, all of the compounds demonstrated superior potency compared to LPV. Two compounds, **24** and **29**, demonstrated less than 10-fold resistance to both of these highly resistant clones.

Compounds with potent activities against the WT virus in the presence of HS and promising resistance profiles were selected for further pharmacokinetic and drug safety evaluation (Table 3). Similar to compounds in our P3-substituted series, our P1-substituted analogues showed moderate stability in human liver microsomes (HLM) in vitro (30−40% disappearance in 20 min) and significantly higher clearance rates in rat liver microsomes. Microsomal stability was greatly improved in the presence of 0.4 μM ritonavir (RTV), a potent inhibitor of CYP3A mediated metabolism. For example, while compounds **10**, **11**, and **13** demonstrated similar microsomal stability in vitro (40% disappearance in HLM with 20 min incubation), no appreciable metabolism

was observed in the presence of RTV. In rat pharmacokinetic studies, 2-pyridyl compound **10** demonstrated low plasma exposures when dosed alone orally and a 25-fold increase in AUC upon coadministration with RTV. In contrast, 3-pyridyl compound **11** demonstrated relatively low exposures when dosed alone orally ($F = 5\%$) or with coadmininstration of RTV ($F = 25\%$). While compound **13** showed similarly low exposures when dosed alone orally ($F = 12\%$), it demonstrated much higher plasma exposures than **11** with coadmininstration of RTV. Compound **20** also demonstrated significant pharmacokinetic enhancement upon coadministration of RTV, although it was less potent against the drug-resistant mutants. Other compounds bearing hydrogen bond acceptor groups on the P1 substituent, such as **26** and **27**, also demonstrated improved plasma levels upon coadministration with RTV, although the exposures were significantly less that those observed for **13**. Compounds bearing hydrogen bond donor groups on the P1 substituent, such as **23** and **29**, generally showed poor oral bioavailability and low plasma exposures, even with coadministration of RTV. Overall, compound **13** demonstrated the best balance of potency against drug resistant strains of HIV and oral bioavailability in the rat. As a result, compound **13** was characterized in dog pharmacokinetic studies and it demonstrated comparable plasma levels to **1** when coadministered orally with RTV (5 mg/kg **13** with 5 mg/kg RTV, AUC = 7.0). Additional profiling of compound **13** revealed that, like many HIV PIs, it demonstrated inhibition of CYP3A4 (IC_{50} = 0.14 μM). In addition, **13** demonstrated moderate permeability (7.3 × 10−6 cm/s) and comparable aqueous solubility to **1** (10.4 μM).

CONCLUSIONS

There remains a need to discover new drugs that are potent against drug-resistant strains of HIV. Upon the basis of observations with compound **1**, it was hypothesized that compounds with similar or improved resistance profiles could be designed by mimicking the interactions of the P3 tertiary hydroxyl side chain of **1** with compounds bearing P1 side chains capable of forming hydrogen bonds. The compounds were screened against WT and resistant strains of HIV. By this approach, several compounds, such as **13**, **24**, and **29**, were identified that demonstrated similar or improved potencies compared to **1** against highly mutated strains of HIV derived from patients who previously failed HIV PI therapy. Overall, compound **13** demonstrated the best balance of potency against drug-resistant strains of HIV and oral bioavailability in rat pharmacokinetic studies. On the basis of our observations, modification of the P1 position of this class of HIV PIs represents a promising approach toward the design of new drugs with improved resistance profiles.

EXPERIMENTAL SECTION

Biological Evaluation. Procedures for EC_{50} determination against WT and mutant strains of HIV in MT-4 cells have been reported previously.[10]

Pharmacokinetic Evaluation. Compounds were formulated and dosed in animals as reported previously.[9]

Chemistry.

General Procedures. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents were obtained from Aldrich (Milwaukee, WI) and used directly. All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen or argon atmosphere. All final compounds were purified to >95% purity as determined by high-performance liquid chromatography (HPLC). Silica gel chromatography was performed using either glass columns packed with silica gel 60 (230−400 mesh) or prepacked silica gel cartridges (Biotage, 32−63 μm). Preparative reverse phase HPLC was conducted on a Waters 600 system using Waters Nova-Pak C18 (6 μm, 60 Å) or Biotage KP-C18-HS cartridges. NMR spectra were determined with Bruker ARX 300 MHz, Varian Unity 400 MHz, or Varian Unity INOVA 500 MHz spectrometers. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane internal standard. Mass spectral (MS) ESI data were determined on a Thermo-Finnigan SSQ7000 instrument. Analytical LC-MS was performed on an Agilent series 1100 HPLC system equipped with an autosampler and coupled to a Finnegan Thermoquest atmospheric pressure chemical ionization (APCI) mass spectrometer. HPLC was performed on a Phenomenex Luna C8(2) column (2.0 mm × 30 mm, 5 μm, 100 Å) using a linear gradient of 10−100% MeCN and 0.1% trifluoroacetic acid in water over 3 min at 1.5 mL/min.

*(4S)-5-[4-(Benzyloxy)phenyl]-4-(dibenzylamino)-3-oxopentanenitrile (**2**).* A solution of sodium bis(trimethylsilyl) amide (1 M in THF, 414 mL) at −45 °C was treated dropwise with a solution of acetonitrile (24 mL, 460 mmol) in THF (50 mL), and the mixture was stirred for 15 min at −45 °C. The resulting solution was added via cannula to a solution of benzyl (2*S*)-3-[4-(benzyloxy)phenyl]-2-(dibenzylamino) propanoate (prepared as described previously,[11] 75.7 g, 140 mmol) in THF (150 mL) at −45 °C, stirred for 1 h, treated with solid NH_4Cl and warmed to 5 °C, and then quenched with water. The mixture was partitioned between ethyl acetate and water. The organic phase was washed with brine and dried over $MgSO_4$, filtered, and concentrated. Precipitation from ethanol gave **2** (39 g, 60% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.92 (dd, J = 13.60, 3.31 Hz, 1 H) 3.04 (d, J = 19.49 Hz, 1 H) 3.14 (dd, J = 13.60, 9.56 Hz, 1 H) 3.48 (dd, J = 9.56, 3.68 Hz, 1 H) 3.56 (d, J = 13.60 Hz, 2 H) 3.83 (d, J = 13.6 Hz, 2 H) 3.85 (d, J = 19.49 Hz, 1 H) 5.03 (s, 2 H) 6.83−6.92 (m, 2 H) 7.01−7.11 (m, 2 H) 7.24−7.46 (m, 15 H). MS (ESI) m/z 475 $(M + H)^+$.

*(2S)-5-Amino-1-[4-(benzyloxy)phenyl]-2-(dibenzylamino)-6-phenyl-4-hexen-3-one (**3**).* A solution containing **2** (19.0 g, 40.1 mmol) in THF (48 mL) was treated dropwise with a solution of benzyl magnesium bromide (120 mL, 1 M in ether) at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 16 h. The reaction was cooled to 0 °C and quenched with 10% citric acid, followed by partitioning between ethyl acetate and water. The organic phase was washed with brine and dried over $MgSO_4$, filtered, and concentrated to give crude **3** (23.2 g), which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.90 (dd, J = 6.42, 13.59 Hz, 1 H) 3.06 (dd, J = 7.72, 13.98 Hz, 1 H) 3.39−3.55 (m, 3 H) 3.61 (d, J = 13.97 Hz, 2 H) 3.79 (d, J = 14.34 Hz, 2 H) 4.88 (s, 1 H) 5.00−5.11 (m, 3 H) 6.80−6.91 (m, 2 H) 6.96−7.08 (m, 2 H) 7.14−7.48 (m, 20 H) 9.80 (s, 1 H). MS (ESI) m/z 567 $(M + H)^+$.

*tert-Butyl (1S,3S,4S)-1-Benzyl-5-[4-(benzyloxy)phenyl]-4-(dibenzylamino)-3-hydroxypentylcarbamate (**4**). Step 1.* A suspension of $NaBH_4$ (6.07 g, 160.4 mmol) in THF (170 mL) at −10 °C was treated with methansulfonic acid (26.0 mL, 401.0 mmol) dropwise (Caution: gas evolution). After complete addition, a solution containing **3** (23.2 g, 40.1 mmol) in a mixture of THF (60 mL) and water (6 mL) was added and the mixture was stirred at −10 °C for 18 h.

Step 2. A suspension of $NaBH_4$ (6.07 g, 160.4 mmol) in THF (170 mL) at 0 °C was treated dropwise with trifluoroacetic acid (15.4 mL, 200.5 mmol) (caution: gas evolution), stirred at 0 °C for 30 min, treated with the solution from step 1, warmed to room temperature, stirred for 3 h, treated with a mixture of $NaBH_4$ (6.07 g, 160.4 mmol) and trifluoroacetic acid (15.4 mL, 200.5 mmol) prepared as described above, warmed to room temperature, and stirred for 2 h. The reaction was cooled to 0 °C and quenched cautiously by slow addition of NaOH solution (300 mL, 3 N), followed by partitioning between *tert*-butyl methyl ether and water. The organic phase was washed with NaOH solution (0.5 N), NH_4Cl solution,

and brine, dried over $MgSO_4$, filtered, and concentrated to give the crude product (22.9 g), which was used without further purification.

Step 3. A solution containing the product from step 2 (22.9 g, 40.1 mmol) in *tert*-butyl methyl ether (200 mL) was treated with 10% K_2CO_3 (95 mL) and di-*tert*-butyl dicarbonate (14.0 g, 64.2 mmol), and stirred at room temperature for 2 h. The organic phase layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel eluting with 20% hexanes in chloroform and then with 10% ethyl acetate in chloroform to give **4** (12.3 g, 46% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.10−1.23 (m, 1 H) 1.40 (s, 9 H) 2.51 (dd, J = 14.52, 6.43 Hz, 1 H) 2.61−2.86 (m, 3 H) 2.98 (dd, J = 14.34, 6.25 Hz, 1 H) 3.36 (d, J = 13.24 Hz, 2 H) 3.54−3.67 (m, 1 H) 3.73−3.84 (m, 1 H) 3.88 (d, J = 13.24 Hz, 2 H) 4.37 (s, 1 H) 4.85 (s, 1 H) 5.08 (s, 2 H) 6.83−6.93 (m, 2 H) 6.96−7.50 (m, 20 H). MS (ESI) m/z 671 $(M + H)^+$.

*(4S,5S)-Benzyl 5-((S)-2-(tert-Butoxycarbonylamino)-3-phenylpropyl)-2,2-dimethyl-4-(4-(trifluoromethylsulfonyloxy)benzyl)oxazolidine-3-carboxylate (**6**).*

Step 1. A solution containing **4** (12.3 g, 18.4 mmol) in THF (169 mL) was treated with 10% Pd on carbon (2.5 g) and ammonium formate (6.9 g, 109.4 mmol), and the mixture was heated at reflux for 1.5 h. Additional 10% Pd on carbon (1.25 g) and NH_4CO_2H (3.45 g) were added, and the mixture was heated at reflux for 2.5 h. The reaction was concentrated and partitioned between chloroform and water, and the solution was adjusted to pH 10 with $NaHCO_3$ solution. The organic phase was washed with brine and dried over $MgSO_4$, filtered, and concentrated to give **5** (6.1 g, 82% yield), which was used without further purification. MS (APCI) m/z 401 $(M + H)^+$.

Step 2. A solution containing 5 (6.1 g, 15.2 mmol) in THF (150 mL) was treated with *N*-(benzyloxycarbonyloxy)succinimide (3.4 g, 13.6 mmol) and *N*,*N*-diisopropylethylamine (3.3 mL, 19.0 mmol), stirred at room temperature for 68 h, and concentrated. The residue was purified by chromatography on silica gel eluting with 33% ethyl acetate in chloroform and then with 10% methanol in chloroform to give benzyl (1*S*,2*S*,4*S*)-4-[(*tert*-butoxycarbonyl)amino]-2-hydroxy-1-(4-hydroxybenzyl)-5-phenylpentylcarbamate (5.1 g, 63% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.29 (s, 9 H) 1.40−1.52 (m, 2 H) 2.52−2.68 (m, 4 H) 3.50−3.61 (m, 1 H) 3.71−3.93 (m, 2 H) 4.53 (d, J = 6.25 Hz, 1 H) 4.80−5.12 (m, 2 H) 6.55−6.69 (m, 3 H) 6.74 (d, J = 9.19 Hz, 1 H) 6.94−7.39 (m, 12 H) 9.09 (s, 1 H). MS (ESI) m/z 535 $(M + H)^+$.

Step 3. A solution containing the product step 2 (5.1 g, 9.6 mmol) in dichloromethane (50 mL) was treated with *N*-phenyl-bis(trifluoromethanesulfonimide) (4.1 g, 11.5 mmol) and DMAP (1.4 g, 11.5 mmol), heated at reflux for 1 h, cooled to room temperature, and purified by chromatography on silica gel eluting with 0−50% ethyl acetate in chloroform to give 4-{(2*S*,3*S*,5*S*)-2-{[(benzyloxy)carbonyl]amino}-5-[(*tert*-butoxycarbonyl)amino]-3-hydroxy-6-phenylhexyl}phenyl trifluoromethanesulfonate (4.7 g, 74% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.29 (s, 9 H) 1.42−1.58 (m, 2 H) 2.53−2.65 (m, 2 H) 2.76 (d, J = 6.62 Hz, 2 H) 3.49−3.66 (m, 1 H) 3.74−3.97 (m, 2 H) 4.61−4.75 (m, 1 H) 4.91 (s, 2 H) 6.64 (d, J = 8.82 Hz, 1 H) 6.88 (d, J = 9.19 Hz, 1 H) 7.00−7.47 (m, 14 H). MS (ESI) m/z 667 $(M + H)^+$.

Step 4. A solution containing the product from step 3 (4.7 g, 7.1 mmol) in 2,2-dimethoxypropane (70 mL) was treated with *p*-toluenesulfonic acid monohydrate (0.067 g, 0.35 mmol), and the mixture was stirred at room temperature for 1 h. Triethylamine (0.3 mL, 2.15 mmol) was added, and the reaction was partitioned between ethyl acetate and water. The organic phase was washed with brine and dried over $MgSO_4$, filtered, and concentrated to give **6** (4.83 g, 97% yield), which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm broad 1.39 (s, 9 H) 1.46−1.67 (m, 7 H) 2.64−2.80 (m, 2 H) 2.81−3.12 (m, 2 H) 3.69−3.88 (m, 2 H) 3.89−4.05 (m, 1 H) 4.31−4.52 (m, 1 H) 5.03−5.31 (m, 2 H) 6.97−7.15 (m, 6 H) 7.17−7.29 (m, 4 H) 7.33−7.44 (m, 4 H). MS (APCI) m/z 707 $(M + H)^+$.

*4-((2S,3S,5S)-2,5-Bis(tert-butoxycarbonylamino)-3-hydroxy-6-phenylhexyl)phenyl trifluoromethanesulfonate (**7**).* To a room temperature solution of **5** (1.0 g, 2.50 mmol) in THF (25 mL) were added di-*tert*-butyl dicarbonate (0.60 g, 2.75 mmol) and triethylamine (0.70 mL, 5.02 mmol), and the mixture was stirred for 16 h. The solvent was evaporated, and the residue was dissolved in dichloromethane (10 mL), followed by the addition of *N*-phenyl-bis(trifluoromethanesulfonimide) (1.07 g, 3.00 mmol) and DMAP (0.37 g, 3.03 mmol), and the mixture was heated to 40 °C for 2 h. The mixture was diluted with ethyl acetate and washed with 10% citric acid, water, and then brine. The organic was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica gel eluting with 0−25% ethyl acetate in dichloromethane to give **7** (0.99 g, 63% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.27 (s, 9 H) 1.29 (s, 9 H) 1.42−1.58 (m, 2 H) 2.52−2.81 (m, 4 H) 3.47−3.61 (m, 1 H) 3.68−3.93 (m, 2 H) 4.58 (d, J = 6.62 Hz, 1 H) 6.29 (d, J = 9.56 Hz, 1 H) 6.63 (d, J = 8.82 Hz, 1 H) 7.09−7.29 (m, 5 H) 7.31−7.45 (m, 4 H). MS (APCI) m/z 633 $(M + H)^+$

*4-((2S,3S,5S)-5-(tert-Butoxycarbonylamino)-3-hydroxy-2-((S)-2-(methoxycarbonylamino)-3,3-dimethylbutanamido)-6-phenylhexyl)-phenyl trifluoromethanesulfonate (**8**).* Following the general procedure for peptide coupling reactions, **5** (12.65 g, 6.62 mmol) was reacted with (*S*)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid (1.4 g, 7.41 mmol). The crude product was dissolved in dichloromethane (26 mL), followed by the addition of *N*-phenyl-bis(trifluoromethanesulfonimide) (2.84 g, 7.95 mmol) and DMAP (1.00 g, 8.20 mmol), and the mixture was heated to 40 °C for 2 h. The mixture was diluted with ethyl acetate and washed with 10% citric acid, water, and then brine. The organic was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica gel eluting with 0−50% ethyl acetate in dichloromethane to give **8** (3.61 g, 77% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 (s, 9 H) 1.27 (s, 9 H) 1.45−1.57 (m, 2 H) 2.52−2.65 (m, 2 H) 2.74−2.84 (m, 2 H) 3.52−3.63 (m, 1 H) 3.54 (s, 3 H) 3.73−3.84 (m, 1 H) 3.87 (d, J = 9.65 Hz, 1 H) 4.17−4.26 (m, 1 H) 4.85 (d, J = 5.10 Hz, 1 H) 6.60 (d, J = 9.00 Hz, 1 H) 6.83 (d, J = 9.65 Hz, 1 H) 7.09−7.18 (m, 3 H) 7.19−7.31 (m, 4 H) 7.38 (d, J = 8.57 Hz, 2 H) 7.52 (d, J = 9.22 Hz, 1 H). MS (ESI) m/z 704 $(M + H)^+$.

*4-((2S,3S,5S)-3-Hydroxy-2,5-bis((S)-2-(methoxycarbonylamino)-3,3-dimethylbutanamido)-6-phenylhexyl)phenyl trifluoromethanesulfonate (**9**).* Compound **7** (0.050 g, 0.079 mmol) was treated with 4 N HCl in dioxane (0.5 mL) for 0.5 h. The solvent was evaporated, and the crude product was reacted with *tert*-butyl (*S*)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid (0.033 g, 0.175 mmol) following the general procedure for peptide coupling reactions. The product was purified by chromatography on silica gel eluting with 0−100% ethyl acetate in dichloromethane to provide **9** (0.038 g, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (s, 18 H) 1.57−1.70 (m, 2 H) 2.70−2.89 (m, 4 H) 3.49−3.59 (m, 1 H) 3.67 (s, 3 H) 3.68 (s, 3 H) 3.75 (t, J = 9.38 Hz, 2 H) 3.90−4.01 (m, 1 H) 4.05−4.20 (m, 2 H) 5.22 (d, J = 9.19 Hz, 1 H) 5.30 (d, J = 9.19 Hz, 1 H) 5.99 (d, J = 7.72 Hz, 1 H) 6.20 (d, J = 8.82 Hz, 1 H) 7.04−7.33 (m, 9 H). MS (ESI) m/z 704 $(M + H)^+$.

*General Procedure for Peptide Coupling Reactions:. Preparation of Methyl (1S,4S,5S,7S,10S)-7-Benzyl-1,10-ditert-butyl-5-hydroxy-2,9,12-trioxo-4-[4-(2-pyridinyl)benzyl]-13-oxa-3,8,11-triazatetradec-1-ylcarbamate (**10**)* A solution of methyl (*S*)-1-((2*S*,3*S*,5*S*)-5-amino-3-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (prepared as described previously,[9] 0.025 g, 0.047 mmol) in THF (0.5 mL) was treated with the (*S*)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid (0.010 g, 0.053 mmol), DEPBT (0.020 g, 0.067 mmol), and *N*,*N*-diisopropylethylamine (0.040 mL, 0.229 mmol), stirred at room temperature for 16 h, and partitioned between ethyl acetate and 10% Na_2CO_3 solution. The organic phase was washed with additional 10% Na_2CO_3 solution and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel eluting with 0−100% ethyl acetate in dichloromethane to give **10** (0.015 g,

45% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.77 (s, 9 H) 0.83 (s, 9 H) 1.40−1.61 (m, 2 H) 2.66−2.81 (m, 3 H) 3.50 (s, 3 H) 3.54 (s, 3 H) 3.60−3.68 (m, 1 H) 3.79 (d, J = 9.19 Hz, 1 H) 3.93 (d, J = 9.56 Hz, 1 H) 4.01−4.18 (m, 2 H) 4.85 (d, J = 5.88 Hz, 1 H) 6.60 (d, J = 9.93 Hz, 1 H) 6.75 (d, J = 9.93 Hz, 1 H) 7.06−7.19 (m, 5 H) 7.26−7.37 (m, 3 H) 7.59 (d, J = 9.19 Hz, 1 H) 7.74 (d, J = 8.82 Hz, 1 H) 7.80−7.97 (m, 4 H) 8.59−8.69 (m, 1 H). MS (APCI) m/z 704.3 $(M + H)^+$.

General Procedure for Palladium Catalyzed Coupling of 6 with Stannanes and Conversion to Final Products. *Preparation of Methyl (1S,4S,5S,7S,10S)-7-Benzyl-1,10-ditert-butyl-5-hydroxy-2,9,12-trioxo-4-[4-(3-pyridinyl)benzyl]-13-oxa-3,8,11-triazatetradec-1-ylcarbamate (**11**). Step 1.* A solution containing **6** (0.200 g, 0.283 mmol) in DMF (3 mL) was treated with LiCl (0.120 g, 2.83 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.060 g, 0.085 mmol), and 3-tri-*n*-butylstannylpyridine (0.200 mL, 0.870 mmol), heated at 100 °C for 16 h, cooled, and partitioned between ethyl acetate and water. The organic phase was washed with brine and dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel eluting with 0−25% ethyl acetate in dichloromethane to give (4*S*,5*S*)-benzyl 5-((*S*)-2-(*tert*-butoxycarbonylamino)-3-phenylpropyl)-2,2-dimethyl-4-(4-(pyridin-3-yl)benzyl)oxazolidine-3-carboxylate (0.130 g, 72% yield). ^{1}H NMR (300 MHz, DMSO-d_6) rotamers δ ppm 1.1, 1.19 (2s, 3 H) 1.28 (s, 9 H) 1.40−1.58 (m, 4 H) 1.57−1.74 (m, 1 H) 2.53−2.72 (m, 2 H) 2.90−3.02 (m, 2 H) 3.54−3.74 (m, 1 H) 3.72−3.89 (m, 1 H) 3.99−4.14 (m, 1 H) 5.08 (s, 2 H) 6.69−6.83 (m, 1 H) 7.03−7.27 (m, 8 H) 7.31−7.44 (m, 4 H) 7.47 (dd, J = 7.91, 4.96 Hz, 1 H) 7.61 (d, J = 8.09 Hz, 2 H) 8.04 (d, J = 8.09 Hz, 1 H) 8.55 (dd, J = 4.78, 1.47 Hz, 1 H) 8.86 (d, J = 2.21 Hz, 1 H). MS (APCI) m/z 636 $(M + H)^+$.

Step 2. A solution containing the product from step 1 (0.059 g, 0.093 mmol) in a mixture of methanol (3 mL) and aqueous HCl (1 mL, 1 N) was stirred at 50 °C for 2 h and concentrated to give benzyl (1*S*,2*S*,4*S*)-4-amino-2-hydroxy-5-phenyl-1-[4-(3-pyridinyl)benzyl]pentylcarbamate as the hydrochloride salt, which was used without further purification.

Step 3. A solution containing the product from step 2 (0.093 mmol) in methanol (2 mL) was treated with $Pd(OH)_2$ on carbon (0.050 g, 20% Pd by wt) and HCl solution (0.040 mL, 4N in dioxane), stirred under a hydrogen atmosphere (balloon pressure) at room temperature for 2 h, filtered through a bed of Celite, rinsed with methanol, and concentrated to give (2*S*,3*S*,5*S*)-2,5-diamino-6-phenyl-1-[4-(3-pyridinyl)phenyl]-3-hexanol as the hydrochloride salt, which was used without further purification.

Step 4. A solution containing the product from step 3 (0.093 mmol) in THF (1 mL) was treated with *tert*-butyl (*S*)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid (0.040 g, 0.211 mmol), DEPBT (0.085 g, 0.284 mmol), and *N*,*N*-diisopropylethylamine (0.175 mL, 1.00 mmol), stirred at room temperature for 1 h, and partitioned between ethyl acetate and 10% Na_2CO_3 solution. The organic phase was washed with additional 10% Na_2CO_3 solution and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel eluting with 0−100% ethyl acetate in dichloromethane, followed by 0−5% methanol in ethyl acetate, to give **11** (0.035 g, 55% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.77 (s, 9 H) 0.83 (s, 9 H) 1.41−1.59 (m, 2 H) 2.66−2.81 (m, 3 H) 3.48 (s, 3 H) 3.54 (s, 3 H) 3.59−3.71 (m, 1 H) 3.80 (d, J = 10.30 Hz, 1 H) 3.93 (d, J = 9.19 Hz, 1 H) 4.03−4.19 (m, 2 H) 4.84 (d, J = 5.52 Hz, 1 H) 6.61 (d, J = 9.56 Hz, 1 H) 6.78 (d, J = 8.82 Hz, 1 H) 7.04−7.19 (m, 5 H) 7.32 (d, J = 8.09 Hz, 2 H) 7.47 (dd, J = 7.72, 5.15 Hz, 1 H) 7.51−7.62 (m, 3 H) 7.73 (d, J = 8.46 Hz, 1 H) 7.97−8.05 (m, 1 H) 8.54 (dd, J = 4.60, 1.65 Hz, 1 H) 8.84 (d, J = 1.84 Hz, 1 H). MS (ESI) m/z 704.3 $(M + H)^+$.

General Procedures for the Coupling of 7, 8, and 9 with Boronic Acids and Conversion to Final Products. *Preparation of Dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-3-Hydroxy-6-phenyl-1-(4-(quinolin-3-yl)phenyl)hexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate (**20**). Step 1.* A degassed (nitrogen sparge) mixture of **8** (0.050 g, 0.071 mmol) and quinolin-3-ylboronic acid (0.020 g, 0.116 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.010 g, 0.014 mmol), and 2 M Na_2CO_3 (0.120 mL) in DMF (0.40 mL) was heated to 80 °C for 2 h. After cooling to room temperature, ethyl acetate was added and solid was removed by filtration through Celite. The filtrate was washed with 10% Na_2CO_3 and brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica gel eluting with 0−100% ethyl acetate in dichloromethane to give methyl (*S*)-1-((2*S*,3*S*,5*S*)-5-(*tert*-butoxycarbonylamino)-3-hydroxy-6-phenyl-1-(4-(quinolin-3-yl)phenyl)-hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (0.027 g, 56% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.85 (s, 9 H) 1.25 (s, 9 H) 1.44−1.61 (m, 2 H) 2.53−2.69 (m, 2 H) 2.76−2.88 (m, 2 H) 3.49 (s, 3 H) 3.58−3.70 (m, 1 H) 3.71−3.86 (m, 1 H) 3.94 (d, J = 9.56 Hz, 1 H) 4.12−4.26 (m, 1 H) 4.82 (d, J = 5.52 Hz, 1 H) 6.58 (d, J = 8.82 Hz, 1 H) 6.85 (d, J = 9.56 Hz, 1 H) 7.08−7.28 (m, 5 H) 7.39 (d, J = 8.09 Hz, 2 H) 7.59−7.80 (m, 5 H) 8.05 (d, J = 8.46 Hz, 2 H) 8.58 (d, J = 1.84 Hz, 1 H) 9.21 (d, J = 2.21 Hz, 1 H). MS (APCI) m/z 683 $(M + H)^+$.

Step 2. The product from step 1 (0.025 g, 0.037 mmol) was dissolved in 4 N HCl in dioxane (0.5 mL) at room temperature and stirred for 30 min. Methanol was added, and the mixture was evaporated. The residue was reacted with *tert*-butyl (*S*)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid (0.008 g, 0.042 mmol) following the general procedure for peptide coupling reactions. The product was purified by chromatography on silica gel, eluting with 0−100% ethyl acetate in dichloromethane to provide **20** (0.028 g, quantitative). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.78 (s, 9 H) 0.84 (s, 9 H) 1.40−1.65 (m, 2 H) 2.69−2.86 (m, 3 H) 3.48 (s, 3 H) 3.54 (s, 3 H) 3.61−3.72 (m, 1 H) 3.80 (d, J = 9.56 Hz, 1 H) 3.95 (d, J = 10.30 Hz, 1 H) 4.06−4.20 (m, 2 H) 4.87 (d, J = 5.52 Hz, 1 H) 6.62 (d, J = 9.56 Hz, 1 H) 6.80 (d, J = 9.56 Hz, 1 H) 7.03−7.20 (m, 5 H) 7.37 (d, J = 8.09 Hz, 2 H) 7.56−7.84 (m, 6 H) 8.05 (d, J = 9.19 Hz, 2 H) 8.59 (d, J = 2.21 Hz, 1 H) 9.21 (d, J = 2.21 Hz, 1 H). MS (APCI) m/z 754.2 $(M + H)^+$.

*Methyl (1S,4S,5S,7S,10S)-7-Benzyl-1,10-di-tert-butyl-5-hydroxy-2,9,12-trioxo-4-[4-(4-pyridinyl)benzyl]-13-oxa-3,8,11-triazatetradec-1-ylcarbamate (**12**).* Using the general procedures, **12** was prepared from **6** and 4-tri-*n*-butylstannylpyridine. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.77 (s, 9 H) 0.82 (s, 9 H) 1.39−1.59 (m, 2 H) 2.66−2.83 (m, 3 H) 3.49 (s, 3 H) 3.54 (s, 3 H) 3.64 (q, J = 6.74 Hz, 1 H) 3.80 (d, J = 9.93 Hz, 1 H) 3.93 (d, J = 9.56 Hz, 1 H) 4.05−4.17 (m, 2 H) 4.85 (d, J = 5.52 Hz, 1 H) 6.60 (d, J = 9.19 Hz, 1 H) 6.76 (d, J = 10.30 Hz, 1 H) 7.05−7.18 (m, 5 H) 7.33 (d, J = 8.09 Hz, 2 H) 7.54−7.68 (m, 5 H) 7.73 (d, J = 9.19 Hz, 1 H) 8.57−8.65 (m, 2 H). MS (APCI) m/z 704.3 $(M + H)^+$.

*Dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-1-(4-(5-Fluoropyridin-3-yl)phenyl)-3-hydroxy-6-phenylhexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate (**13**).* Using the general procedures, **13** was prepared from **8** and 5-fluoropyridin-3-ylboronic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.77 (s, 9 H) 0.83 (s, 9 H) 1.39−1.59 (m, 2 H) 2.67−2.80 (m, 3 H) 3.48 (s, 3 H) 3.54 (s, 3 H) 3.60−3.69 (m, 1 H) 3.80 (d, J = 9.93 Hz, 1 H) 3.92 (d, J = 9.56 Hz, 1 H) 4.03−4.18 (m, 2 H) 4.86 (d, J = 5.88 Hz, 1 H) 6.62 (d, J = 9.93 Hz, 1 H) 6.78 (d, J = 9.93 Hz, 1 H) 7.04−7.19 (m, 5 H) 7.33 (d, J = 8.09 Hz, 2 H) 7.56−7.64 (m, 3 H) 7.74 (d, J = 8.46 Hz, 1 H) 7.95−8.03 (m, 1 H) 8.54 (d, J = 2.94 Hz, 1 H) 8.75 (t, J = 1.65 Hz, 1 H). MS (ESI) m/z 722.2 $(M + H)^+$.

*Dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-1-(4-(6-Fluoropyridin-3-yl)phenyl)-3-hydroxy-6-phenylhexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate (**14**).* Using the general procedures, **14** was prepared from **7** and 6-fluoropyridin-3-ylboronic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.77 (s, 9 H) 0.83 (s, 9 H) 1.39−1.65 (m, 2 H) 2.66−2.84 (m, 3 H) 3.48 (s, 3 H) 3.54 (s, 3 H) 3.58−3.68 (m, 1 H) 3.80 (d, J = 9.56 Hz, 1 H) 3.93 (d, J = 9.56 Hz, 1 H) 4.01−4.18 (m, 2 H) 4.85 (d, J = 5.52 Hz, 1 H) 6.62 (d, J = 9.93 Hz, 1 H) 6.78 (d, J = 9.19 Hz, 1 H) 7.05−7.19 (m, 5 H) 7.23−7.35 (m, 3 H) 7.53 (d, J = 8.09 Hz, 2 H) 7.59 (d, J = 8.82 Hz, 1 H) 7.74 (d, J = 8.82 Hz, 1 H) 8.16−8.27 (m, 1 H) 8.49 (d, J = 2.57 Hz, 1 H). MS (ESI) m/z 722.2 $(M + H)^+$.

*Dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-1-(4-(2-Fluoropyridin-4-yl)phenyl)-3-hydroxy-6-phenylhexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate (**15**).* Using the general procedures, **15** was prepared from **8** and 2-fluoropyridin-4-ylboronic acid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.77 (s, 9 H) 0.83 (s, 9 H) 1.43−1.61 (m, 2 H) 2.68−2.83 (m, 4 H) 3.49 (s, 3 H) 3.54 (s, 3 H) 3.59−3.67 (m, 1 H) 3.79 (d, J = 9.28 Hz, 1 H) 3.92 (d, J = 9.77 Hz, 1 H) 4.05−4.17 (m, 2 H) 4.85 (s, 1 H) 6.56 (d, J = 10.25 Hz, 1 H) 6.73 (d, J = 9.77 Hz, 1 H) 7.04−7.20 (m, 5 H) 7.35 (d, J = 7.81 Hz, 2 H) 7.45 (s, 1 H) 7.58 (d, J = 8.79 Hz, 1 H) 7.63−7.73 (m, 4 H) 8.28 (d, J = 5.37 Hz, 1 H). MS (ESI) m/z 722.3 $(M + H)^+$.

*Dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-1-(4-(6-Cyanopyridin-3-yl)phenyl)-3-hydroxy-6-phenylhexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate (**16**).* Using the general procedures, **16** was prepared from **8** and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinonitrile. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.77 (s, 9 H) 0.82 (s, 9 H) 1.39−1.65 (m, 2 H) 2.65−2.83 (m, 3 H) 3.47 (s, 3 H) 3.54 (s, 3 H) 3.58−3.71 (m, 1 H) 3.80 (d, J = 9.93 Hz, 1 H) 3.92 (d, J = 9.56 Hz, 1 H) 4.05−4.20 (m, 2 H) 4.86 (d, J = 5.52 Hz, 1 H) 6.62 (d, J = 9.19 Hz, 1 H) 6.77 (d, J = 9.56 Hz, 1 H) 7.04−7.19 (m, 5 H) 7.36 (d, J = 8.09 Hz, 2 H) 7.60 (d, J = 9.93 Hz, 1 H) 7.66 (d, J = 8.09 Hz, 2 H) 7.74 (d, J = 8.09 Hz, 1 H) 8.11 (d, J = 8.46 Hz, 1 H) 8.30 (dd, J = 8.09, 2.21 Hz, 1 H) 9.06 (d, J = 2.21 Hz, 1 H). MS (APCI) m/z 729.3 $(M + H)^+$.

*Dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-3-Hydroxy-1-(4-(6-(hydroxymethyl)pyridin-3-yl)phenyl)-6-phenylhexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate (**17**).* *tert*-Butyl (2*S*,3*S*,5*S*)-1-(4-(6-cyanopyridin-3-yl)phenyl)-3-hydroxy-6-phenylhexane-2,5-diyldicarbamate (0.065 g, 0.111 mmol, prepared from reaction of **7** with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinonitrile using the general procedure) was dissolved in dichloromethane and cooled to −78 °C, followed by dropwise addition of diisobutylaluminum hydride in hexanes (1 M, 0.26 mL). After 2 h, a saturated solution of sodium potassium tartrate was added and the mixture was stirred for 30 min and warmed to room temperature. The reaction was diluted with ethyl acetate, and the organic was separated, dried over $MgSO_4$, filtered, and evaporated. The crude aldehyde was dissolved in methanol (0.25 mL) and treated with excess sodium borohydride (0.02 g) at room temperature for 1 h. The mixture was extracted with ethyl acetate and washed with water and brine. The resulting crude alcohol was converted to **17** by the general procedures. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.77 (s, 9 H) 0.83 (s, 9 H) 1.41−1.58 (m, 2 H) 2.67−2.84 (m, 3 H) 3.49 (s, 3 H) 3.54 (s, 3 H) 3.59−3.70 (m, 1 H) 3.80 (d, J = 9.56 Hz, 1 H) 3.93 (d, J = 9.19 Hz, 1 H) 4.04−4.19 (m, 2 H) 4.60 (d, J = 5.88 Hz, 2 H) 4.85 (d, J = 5.52 Hz, 1 H) 5.43 (t, J = 5.88 Hz, 1 H) 6.62 (d, J = 9.93 Hz, 1 H) 6.79 (d, J = 9.56 Hz, 1 H) 7.02−7.17 (m, 5 H) 7.31 (d, J = 8.09 Hz, 2 H) 7.53 (d, J = 8.09 Hz, 3 H) 7.59 (d, J = 8.82 Hz, 1 H) 7.74 (d, J = 8.46 Hz, 1 H) 8.02 (dd, J = 8.09, 2.57 Hz, 1 H) 8.73 (d, J = 2.21 Hz, 1 H). MS (APCI) m/z 734.1 $(M + H)^+$.

*Dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-3-Hydroxy-6-phenyl-1-(4-(pyrazin-2-yl)phenyl)hexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate (**18**).* Using the general procedures, **18** was prepared from **7** and 2-(tributylstannyl)pyrazine. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 0.84 (s, 9 H) 0.89 (s, 9 H) 1.67 (t, J = 7.17 Hz, 2 H) 2.60 (dd, J = 13.42, 9.01 Hz, 1 H) 2.77−3.03 (m, 3 H) 3.55 (s, 3 H) 3.65 (s, 3 H) 3.73−3.83 (m, 2 H) 3.91 (s, 1 H) 4.24−4.40 (m, 2 H) 7.08−7.22 (m, 5 H) 7.41 (d, J = 8.46 Hz, 2 H) 7.94 (d, J = 8.09 Hz, 2 H) 8.49 (d, J = 2.57 Hz, 1 H) 8.61−8.67 (m, 1 H) 9.06 (s, 1 H). MS (APCI) m/z 705.2 $(M + H)^+$.

*Dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-3-Hydroxy-6-phenyl-1-(4-(pyrimidin-5-yl)phenyl)hexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate (**19**).* Using the general procedures, **19** was prepared from **7** and pyrimidin-5-ylboronic acid. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 0.85 (s, 9 H) 0.89 (s, 9 H) 1.67 (t, J = 6.99 Hz, 2 H) 2.61 (dd, J = 13.42, 9.01 Hz, 1 H) 2.79−2.98 (m, 3 H) 3.54 (s, 3 H) 3.65 (s, 3 H) 3.73−3.84 (m, 2 H) 3.91 (s, 1 H) 4.24−4.37 (m, 2 H) 7.09−7.25 (m, 5 H) 7.43 (d, J = 8.09 Hz, 2 H) 7.56 (d, J = 8.09 Hz, 2 H) 9.03 (s, 2 H) 9.11 (s, 1 H). MS (APCI) m/z 705 $(M + H)^+$. MS (ESI) m/z 705.2 $(M + H)^+$.

*Dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-1-(Biphenyl-4-yl)-3-hydroxy-6-phenylhexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate (**21**).* Using the general procedures, **21** was prepared from **7** and phenylboronic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.78 (s, 9 H) 0.83 (s, 9 H) 1.38−1.60 (m, 2 H) 2.66−2.81 (m, 3 H) 3.49 (s, 3 H) 3.54 (s, 3 H) 3.59−3.72 (m, 1 H) 3.80 (d, J = 9.93 Hz, 1 H) 3.93 (d, J = 9.56 Hz, 1 H) 4.03−4.20 (m, 2 H) 4.84 (d, J = 5.52 Hz, 1 H) 6.62 (d, J = 9.93 Hz, 1 H) 6.79 (d, J = 9.19 Hz, 1 H) 7.04−7.19 (m, 5 H) 7.25−7.31 (m, 2 H) 7.34 (d, J = 7.35 Hz, 1 H) 7.40−7.50 (m, 4 H) 7.55−7.65 (m, 3 H) 7.74 (d, J = 8.46 Hz, 1 H). MS (ESI) m/z 703.3 $(M + H)^+$.

*Dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-3-Hydroxy-1-(3′-(hydroxymethyl)-biphenyl-4-yl)-6-phenylhexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate (**22**).* Using the general procedures, **22** was prepared from **7** and 3-(hydroxymethyl)phenylboronic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.78 (s, 9 H) 0.83 (s, 7 H) 1.38−1.62 (m, 2 H) 2.67−2.81 (m, 3 H) 3.50 (s, 3 H) 3.54 (s, 3 H) 3.58−3.70 (m, 1 H) 3.80 (d, J = 9.93 Hz, 1 H) 3.94 (d, J = 9.56 Hz, 1 H) 4.01−4.17 (m, 2 H) 4.55 (d, J = 5.52 Hz, 2 H) 4.84 (d, J = 5.52 Hz, 1 H) 5.22 (t, J = 5.70 Hz, 1 H) 6.62 (d, J = 9.19 Hz, 1 H) 6.79 (d, J = 9.93 Hz, 1 H) 7.03−7.18 (m, 5 H) 7.27 (d, J = 8.09 Hz, 3 H) 7.39 (t, J = 7.54 Hz, 1 H) 7.43−7.51 (m, 3 H) 7.53−7.63 (m, 2 H) 7.74 (d, J = 7.72 Hz, 1 H). MS (ESI) m/z 733.2 $(M + H)^+$.

*Dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-3-Hydroxy-1-(4′-(hydroxymethyl)-biphenyl-4-yl)-6-phenylhexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate (**23**).* Using the general procedures, **23** was prepared from **7** and 4-(hydroxymethyl)phenylboronic acid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.78 (s, 9 H) 0.83 (s, 9 H) 1.36−1.62 (m, 2 H) 2.66−2.79 (m, 3 H) 3.50 (s, 3 H) 3.54 (s, 3 H) 3.60−3.70 (m, 1 H) 3.80 (d, J = 9.93 Hz, 1 H) 3.94 (d, J = 9.56 Hz, 1 H) 3.98−4.19 (m, 2 H) 4.52 (d, J = 5.52 Hz, 2 H) 4.84 (d, J = 5.52 Hz, 1 H) 5.19 (t, J = 5.70 Hz, 1 H) 6.62 (d, J = 9.56 Hz, 1 H) 6.80 (d, J = 9.19 Hz, 1 H) 7.01−7.18 (m, 5 H) 7.26 (d, J = 8.09 Hz, 2 H) 7.38 (d, J = 8.09 Hz, 2 H) 7.47 (d, J = 8.09 Hz, 2 H) 7.53−7.63 (m, 3 H) 7.74 (d, J = 8.82 Hz, 1 H). MS (APCI) m/z 733.3 $(M + H)^+$.

*Dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-3-Hydroxy-1-(4′-(methylcarbamoyl)biphenyl-4-yl)-6-phenylhexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate (**24**).* Using the general procedures, **24** was prepared from **9** and 4-(methylcarbamoyl) phenylboronic acid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (s, 9 H) 0.94 (s, 9 H) 1.53−1.72 (m, 2 H) 2.21 (s, 3 H) 2.71−2.81 (m, 2 H) 2.82−2.91 (m, 2 H) 3.61 (s, 3 H) 3.67 (s, 3 H) 3.73 (d, J = 9.19 Hz, 1 H) 3.80 (d, J = 9.19 Hz, 1 H) 3.88 (d, J = 3.68 Hz, 1 H) 3.92−4.04 (m, 1 H) 4.07−4.19 (m, 1 H) 5.30 (d, J = 8.46 Hz, 2 H) 6.00 (d, J = 7.35 Hz, 1 H) 6.18 (d, J = 8.82 Hz, 1 H) 7.04−7.09 (m, 2 H) 7.11−7.29 (m, 5 H) 7.44 (d, J = 8.09 Hz, 2 H) 7.50−7.60 (m, 4 H). MS (ESI) m/z 760.7 $(M + H)^+$.

*Dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-3-Hydroxy-1-(3′-(methylcarbamoyl)-biphenyl-4-yl)-6-phenylhexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate (**25**).* Using the general procedures, **25** was prepared from **7** and 3-(methylcarbamoyl)phenylboronic acid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.78 (s, 9 H) 0.83 (s, 9 H) 1.41−1.58 (m, 2 H) 2.06 (s, 3 H) 2.67−2.81 (m, 3 H) 3.50 (s, 3 H) 3.55 (s, 3 H) 3.60−3.68 (m, 1 H) 3.80 (d, J = 9.77 Hz, 1 H) 3.92 (d, J = 9.77 Hz, 1 H) 4.02−4.17 (m, 2 H) 4.82 (d, J = 5.49 Hz, 1 H) 6.56 (d, J = 9.77 Hz, 1 H) 6.76 (d, J = 9.77 Hz, 1 H) 7.08 (d, J = 6.71 Hz, 2 H) 7.10−7.17 (m, 3 H) 7.23−7.32 (m, 3 H) 7.35 (t, J = 7.93 Hz, 1 H) 7.42 (d, J = 7.93 Hz, 2 H) 7.52 (d, J = 7.93 Hz, 1 H) 7.55 (d, J = 9.16 Hz, 1 H) 7.72 (d, J = 8.54 Hz, 1 H) 7.86 (s, 1 H) 9.97 (s, 1 H). MS (ESI) m/z 760.5 $(M + H)^+$.

*Dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-1-(4′-Acetylbiphenyl-4-yl)-3-hydroxy-6-phenylhexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate (**26**).* Using the general procedures, **26**

was prepared from **8** and 4-acetylphenylboronic acid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (s, 9 H) 0.94 (s, 9 H) 1.58−1.69 (m, 2 H) 2.64 (s, 3 H) 2.73−2.82 (m, 2 H) 2.89 (d, J = 6.25 Hz, 2 H) 3.60 (s, 3 H) 3.67 (s, 3 H) 3.74 (d, J = 8.82 Hz, 1 H) 3.81 (d, J = 9.19 Hz, 1 H) 3.95−4.06 (m, 2 H) 4.10−4.21 (m, 1 H) 5.30 (t, J = 9.56 Hz, 2 H) 6.01 (d, J = 7.35 Hz, 1 H) 6.21 (d, J = 8.82 Hz, 1 H) 7.07 (d, J = 6.62 Hz, 2 H) 7.12−7.32 (m, 5 H) 7.52 (d, J = 8.09 Hz, 2 H) 7.67 (d, J = 8.46 Hz, 2 H) 8.02 (d, J = 8.46 Hz, 2 H). MS (ESI) m/z 745.6 $(M + H)^+$.

*Dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-3-Hydroxy-1-(4′-methoxybiphenyl-4-yl)-6-phenylhexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate (**27**).* Using the general procedures, **27** was prepared from **7** and 4-methoxyphenylboronic acid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.78 (s, 9 H) 0.83 (s, 9 H) 1.41−1.56 (m, 2 H) 2.68−2.79 (m, 3 H) 3.50 (s, 3 H) 3.54 (s, 3 H) 3.60−3.67 (m, 1 H) 3.77−3.82 (m, 4 H) 3.93 (d, J = 9.77 Hz, 1 H) 4.02−4.15 (m, 2 H) 4.80 (s, 1 H) 6.55 (d, J = 9.77 Hz, 1 H) 6.75 (d, J = 9.77 Hz, 1 H) 6.98−7.04 (m, 2 H) 7.05−7.17 (m, 5 H) 7.24 (d, J = 7.93 Hz, 2 H) 7.42 (d, J = 7.93 Hz, 2 H) 7.52−7.57 (m, 3 H) 7.71 (d, J = 8.54 Hz, 1 H). MS (ESI) m/z 733.4 $(M + H)^+$.

*Dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-3-Hydroxy-1-(4′-hydroxybiphenyl-4-yl)-6-phenylhexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate (**28**).* Using the general procedures, **28** was prepared from **7** and 4-hydroxyphenylboronic acid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.78 (s, 9 H) 0.83 (s, 9 H) 1.41−1.57 (m, 2 H) 2.66−2.76 (m, 3 H) 3.50 (s, 3 H) 3.54 (s, 3 H) 3.60−3.67 (m, 1 H) 3.79 (d, J = 9.16 Hz, 1 H) 3.92 (d, J = 9.77 Hz, 1 H) 4.00−4.18 (m, 2 H) 4.81 (d, J = 5.49 Hz, 1 H) 6.56 (d, J = 9.16 Hz, 1 H) 6.76 (d, J = 9.77 Hz, 1 H) 6.82 (d, J = 8.54 Hz, 2 H) 7.04−7.17 (m, 5 H) 7.21 (d, J = 7.93 Hz, 2 H) 7.38 (d, J = 7.93 Hz, 2 H) 7.41 (d, J = 8.54 Hz, 2 H) 7.54 (d, J = 9.16 Hz, 1 H) 7.71 (d, J = 8.54 Hz, 1 H) 9.47 (s, 1 H). MS (ESI) m/z 719.5 $(M + H)^+$.

*Dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-1-(3′-Aminobiphenyl-4-yl)-3-hydroxy-6-phenylhexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate (**29**).* Using the general procedures, dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-3-hydroxy-1-(3′-nitrobiphenyl-4-yl)-6-phenylhexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate was prepared from **8** and 3-nitrophenylboronic acid. The resulting nitro compound (0.082 g, 0.110 mmol) was dissolved in a mixture of ethyl acetate (1.0 mL) and methanol (1.0 mL), and palladium hydroxide (0.020 g) was added followed by stirring under hydrogen (balloon pressure) for 1 h. The reaction was filtered through Celite, and the filtrate was evaporated. The residue was purified by chromatography on silica gel eluting with a 0−100% ethyl acetate in dichloromethane to give **29** (0.060 g, 76% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.78 (s, 9 H) 0.83 (s, 9 H) 1.39−1.58 (m, 2 H) 2.66−2.80 (m, 3 H) 3.51 (s, 3 H) 3.54 (s, 3 H) 3.58−3.69 (m, 1 H) 3.80 (d, J = 9.93 Hz, 1 H) 3.93 (d, J = 9.93 Hz, 1 H) 3.99−4.18 (m, 2 H) 4.84 (d, J = 5.52 Hz, 1 H) 5.11 (s, 2 H) 6.48−6.55 (m, 1 H) 6.62 (d, J = 10.30 Hz, 1 H) 6.72 (d, J = 7.72 Hz, 1 H) 6.77−6.85 (m, 2 H) 7.02−7.18 (m, 6 H) 7.23 (d, J = 8.09 Hz, 2 H) 7.37 (d, J = 8.09 Hz, 2 H) 7.56 (d, J = 8.82 Hz, 1 H) 7.74 (d, J = 8.82 Hz, 1 H). MS (ESI) m/z 718.3 $(M + H)^+$.

*Dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-1-(4′-Aminobiphenyl-4-yl)-3-hydroxy-6-phenylhexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate (**30**).* Using the general procedures, dimethyl (2S,2′S)-1,1′-((2S,3S,5S)-3-hydroxy-1-(4′-nitrobiphenyl-4-yl)-6-phenylhexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate was prepared from **8** and 4-nitrophenylboronic acid. The resulting nitro compound was reduced by the procedure used for **29** to give **30**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.78 (s, 9 H) 0.84 (s, 9 H) 1.37−1.62 (m, 2 H) 2.65−2.80 (m, 3 H) 3.51 (s, 3 H) 3.54 (s, 3 H) 3.58−3.69 (m, 1 H) 3.80 (d, J = 9.93 Hz, 1 H) 3.93 (d, J = 9.56 Hz, 1 H) 3.96−4.19 (m, 2 H) 4.82 (d, J = 5.15 Hz, 1 H) 5.15 (s, 2 H) 6.61 (m, 3 H) 6.81 (d, J = 9.56 Hz, 1 H) 7.02−7.24 (m, 7 H) 7.24−7.40 (m, 4 H) 7.55 (d, J = 8.82 Hz, 1 H) 7.73 (d, J = 8.46 Hz, 1 H). MS (ESI) m/z 718.2 $(M + H)^+$.

X-ray Crystallographic Analysis. HIV protease was purified and crystallized in the presence of compounds according to procedures previously described.[17] Data were collected at the Argonne National Laboratory synchrotron on the IMCA ID17 beamline using a Mar 165 CCD detector. Data were processed using HKL2000. The crystals of **11** belong to the space group $P1$, with unit cell dimensions a = 59.478 Å, b = 66.512 Å, c = 87.595 Å, α = 110.41, β = 91.49, γ = 93.64. The final structure of the HIV protease/**11** inhibited complex was refined in REFMAC[18] resulting in R_f = 28.52% and R = 23.46% to a resolution of 2.8 Å, and the coordinates have been deposited in the Protein Data Bank.

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ABBREVIATIONS USED

PI, protease inhibitor; HAART, highly active antiretroviral therapy; LPV, lopinavir; RTV, ritonavir; WT, wild type; HS, human serum; HLM, human liver microsomes; DEPBT, 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one

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