2-Pyridyl P1′-Substituted Symmetry-Based Human Immunodeficiency Virus Protease Inhibitors (A-792611 and A-790742) with Potential for Convenient Dosing and Reduced Side Effects†

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A series of symmetry-based HIV protease inhibitors was designed and synthesized. Modification of the core regiochemistry and stereochemistry significantly affected the potency, metabolic stability, and oral bioavailability of the inhibitors, as did the variation of a pendent arylmethyl P3 group. Optimization led to the selection of two compounds, **10c** (A-790742) and **9d** (A-792611), for advancement to preclinical studies. Both compounds displayed low nanomolar potency against wild type HIV in the presence of human serum, low rates of metabolism in human liver microsomes, and high oral bioavailability in animal models. The compounds were examined in a preclinical model for the hyperbilirubinemia observed with some HIV PIs, and both exhibited less bilirubin elevation than comparator compounds. X-ray crystallographic analyses of the new cores were used to examine differences in their binding modes. The antiviral activity of the compounds against protease inhibitor resistant strains of HIV was also determined.

Introduction

Since the introduction of the first HIV protease inhibitors (PI[a]) more than a decade ago, they have continued to play a prominent role in highly active antiretroviral therapy (HAART), used in combination with two nucleoside reverse transcriptase inhibitors. Since that time, the efficacy and tolerability of this class have improved. Pharmacokinetic enhancement of protease inhibitors using low-dose ritonavir (RTV) is now widely used to maintain drug plasma levels leading to improved viral suppression while decreasing both the dosing frequency and pill count.[1] New HIV PIs with improved potencies and pharmacokinetics, however, could allow for a lower pill count using once-daily dosing. Drugs with improved resistance profiles have also been discovered. A long-term study of lopinavir (LPV)/RTV has demonstrated durable viral suppression over 7 years of therapy.[2] Tipranavir (TPV) and darunavir (DRV) have potent antiviral activity against drug resistant viruses harbored by PI-experienced patients.[3,4] Despite the advances, improvements are needed in reducing the side effects associated with HIV PI therapy. Indinavir (IDV) and atazanavir (ATV) cause elevations of unconjugated bilirubin (hyperbilirubinemia), leading to jaundice and scleral icterus in some patients, and we recently developed a preclinical model useful for screening new compounds for this effect.[5] Several PIs produce elevations of serum triglycerides, cholesterol, and low-density lipoproteins that may be associated with long-term cardiovascular risk.[6,7] While the exact mechanism(s) remain unclear, PI inhibition of human proteasome has been implicated as a possible link and recent studies have provided a means to screen compounds preclinically for this off-target activity.[8] It remains a challenge to identify protease inhibitors with improved potencies and pharmacokinetics, along with improved profiles for these off-target activities. We investigated compounds with 2-pyridyl P1′-substituted cores A, B, and C (Figure 1), which demonstrated higher potencies and higher metabolic stabilities than the unsubstituted pseudo-C_2-symmetric core of RTV. We also investigated additional cyclic-urea-linked P3 groups, which have provided potent inhibitors in several core series.[9] The central hydroxyl regiochemistry and P1′ stereochemistry as well as the P3 substituent affected the potency, metabolic stability, and oral bioavailability of the inhibitors. Herein, we report the optimization of the antiviral activity and pharmacokinetics of these compounds as well as the first use of our preclinical model for

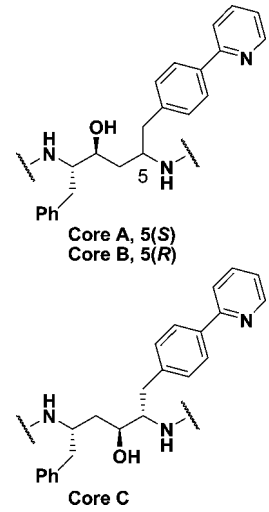

Figure 1. Symmetry-based HIV PI cores.

† X-ray coordinates have been deposited in the Protein Data Bank for HIV protease complexed with **10a** (PDB code 3GGX) and **11** (PDB code 3GGA).

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[a] Abbreviations: PI, protease inhibitor; HAART, highly active antiretroviral therapy; RTV, ritonavir; LPV, lopinavir; ATV, atazanavir; UGT, UDP-glucuronosyltransferase; 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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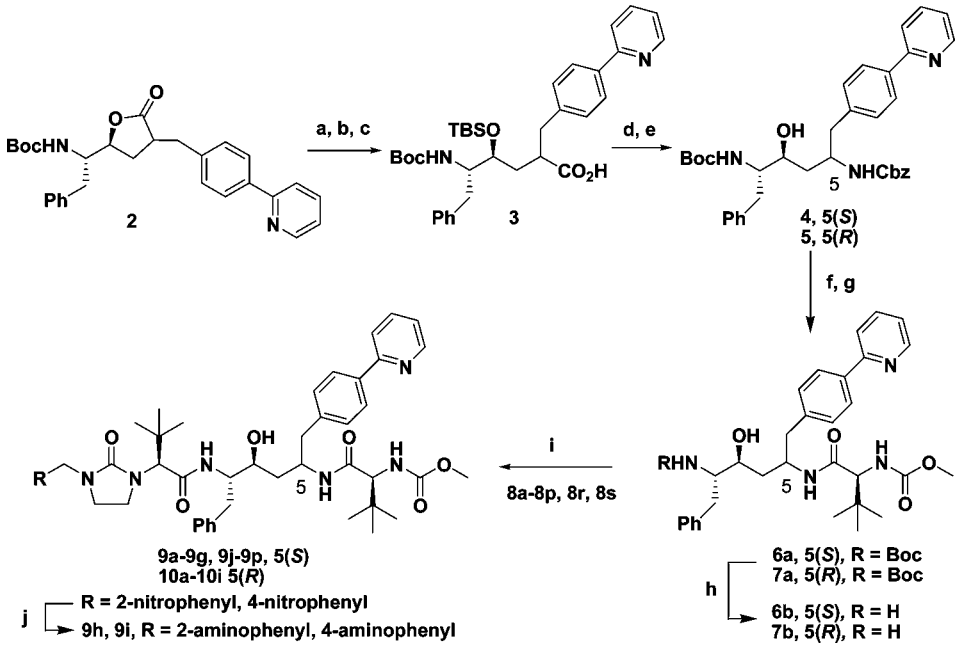
Scheme 1. Synthesis of Core A and Core B Analogues[a]



[a] Reagents and conditions: (a) NaOH; (b) TBSCl, imidazole; (c) AcOH; (d) (i) DPPA, toluene, reflux, (ii) benzyl alcohol; (e) TBAF; (f) $Pd(OH)_2$ on C, H_2; (g) DEPBT, MeO_2C-*t*-Bu-Gly-OH; (h) TFA; (i) DEPBT; (j) Pd on C, H_2.

hyperbilirubinemia to identify compounds with less potential for this side effect.

Chemistry

Core A and B compounds were prepared as shown in Scheme 1. The lactone **2** was prepared as described previously with the stereochemistry favoring the (4*S*)-isomer (1.6:1, *S*/*R*).[10] Opening of the lactone with hydroxide gave a mixture of acids **3**, which was subjected to Curtius rearrangement and reaction with benzyl alcohol. After treatment with TBAF, orthogonally protected intermediates **4** and **5** were obtained as a mixture at C-5 (1.6:1, respectively) and were separated by chromatography on silica gel. Removal of the Cbz group through hydrogenolysis, coupling with *tert*-butylglycine methyl carbamate, and removal of the Boc protecting group gave intermediates **6b** and **7b**. Final compounds (**9a**−**g**, **9j**−**p**, **10a**−**i**) were prepared by coupling with the appropriate arylmethyl-substituted cyclic urea acids **8a**−**g**, **8j**−**p**, **8r**, and **8s**, respectively. Compounds **9h** and **9i** were obtained through hydrogenation of the 2-nitrophenyl and 4-nitrophenyl intermediates, respectively.

Core C analogues were prepared starting from *p*-bromophenylalanine (Scheme 2), which was benzylated using benzyl chloride and potassium carbonate to give **12**. Palladium catalyzed coupling of **12** with 2-(tributylstannyl)pyridine gave **13**. Reaction of **13** with sodioacetonitrile resulted in nitrile **14**, which was treated with benzyl Grignard reagent to give the enaminone **15**. A high degree of stereocontrol was observed for the stepwise reduction of **15** by using the procedure reported for a similar enaminone to give **16**.[11] Removal of the benzyl protecting groups through hydrogenolysis gave the amine, which was coupled with *tert*-butylglycine methyl carbamate to give **17a**. Removal of the Boc protecting group gave intermediate **17b**, and final compounds (**18a**−**h**) were prepared by coupling with the appropriate arylmethyl-substituted cyclic urea acids **8a**−**g** and **8q**, respectively.

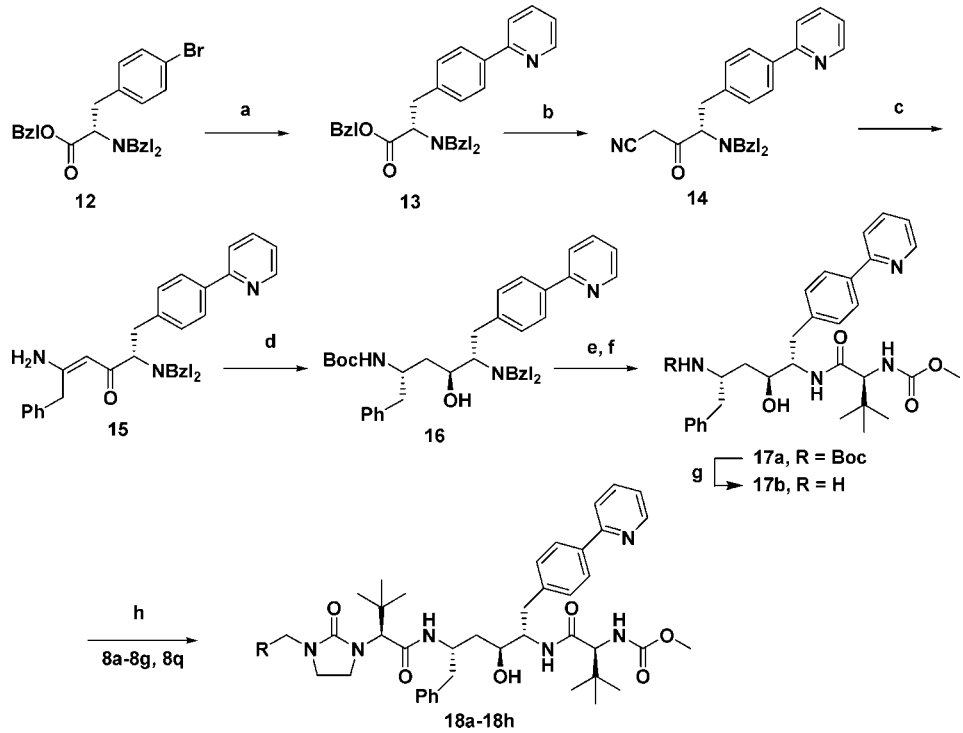
Cyclic urea acids **8a**, **8b**, **8d**−**q**, and **8s** were prepared from *N*-(2-aminoethyl)-(L)-*tert*-butylglycine *tert*-butyl ester (prepared as described previously)[9b] and the appropriate aryl aldehyde (Scheme 3) by reductive amination with $NaBH_4$, cyclization to form the urea, and removal of the *tert*-butyl protecting group. Acids **8c** and **8r** were prepared starting from **19** which was prepared from methyl 6-formylpicolinate under the standard conditions (Scheme 4). Reaction of **19** with excess methyl Grignard reagent gave the tertiary alcohol **20**, which was treated with TFA to give **8c**. Reaction of **19** with methyl Grignard reagent at −78 °C gave ketone **21**. Wittig olefination gave **22**, and the olefin was reduced to the isopropyl compound **23** by hydrogenation. Treatment with TFA gave the acid **8r**.

Results and Discussion

As mentioned, some HIV PIs elevate serum levels of unconjugated bilirubin clinically, including IDV and ATV.[12] Bilirubin is the major end-product of the catabolism of heme, and 300−400 mg is formed daily in humans. The main metabolic pathway for bilirubin excretion is glucuronidation catalyzed by UDP-glucuronosyltransferase 1A1 (UGT1A1). Bilirubin is highly protein bound, and unconjugated bilirubin has toxic side effects in humans if the serum bilirubin concentration exceeds the albumin concentration. Although the mechanism has not been unequivocally established, the above HIV PIs may elevate unconjugated bilirubin via direct inhibition of UGT1A1. Previously, we reported an in vivo model for assessing the potential for compounds to induce hyperbilirubinemia utilizing Gunn rats, which are heterozygous for an inherited deficiency in hepatic-bilirubin conjugating activity and are susceptible to bilirubin elevations.[5] In contrast to in vitro UGT1A1 inhibition measurements, the in vivo model data correlated well with the clinical observations.

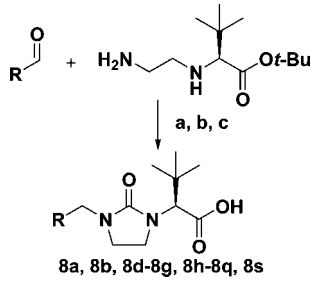
Five years ago, we evaluated exploratory HIV PI, **1a** (A-681799, Figure 2), as a potential drug candidate.[13] Compound **1a** demonstrated potent antiviral activity and high oral bioavailability with coadministration of RTV. Since **1a** shares the aza-core structure with ATV, the effect of **1a** on serum bilirubin levels was evaluated in the Gunn rat assay. Observed elevations

Scheme 2. Synthesis of Core C Analogues[a]



[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, LiCl, 2-(tributylstannyl)pyridine; (b) NaHMDS, CH_3CN; (c) BzlMgCl; (d) (i) $NaBH_4$, CH_3SO_3H, (ii) $NaBH_4$, TFA; (e) $Pd(OH)_2$ on C, H_2; (f) DEPBT, MeO_2C-*t*-Bu-Gly-OH; (g) TFA; (h) DEPBT.

Scheme 3. General Synthesis of Cyclic Urea Acids[a]



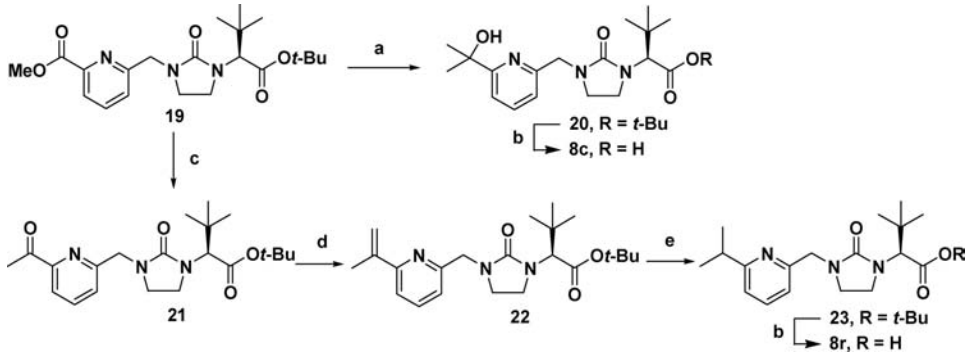
[a] Reagents and conditions: (a) (i) 50 °C, 16 h, (ii) $NaBH_4$; (b) *N*,*N*-disuccinimidyl carbonate, room temperature or bis(4-nitrophenyl)carbonate, reflux in toluene; (c) TFA.

of serum bilirubin were significantly greater for **1a** than those for ATV or IDV, and development of this compound was discontinued. In order to design a compound with lower potential for this side effect, we ascertained the structural features of **1a** associated with hyperbilirubinemia by examining multiple compounds in Gunn rats. Replacement of the P1′ pyridylbenzyl side chain of **1a** with an unsubstituted benzyl group as in **1b** did not significantly change the degree of bilirubin elevation (Figure 2). In contrast, compounds in which the aza core of **1a** was replaced with the symmetry-based all-carbon core of RTV,[14] such as **1c** (Figure 2), elevated bilirubin to a significantly lower extent, including compound **9a**, with the same P1′ pyridylbenzyl group contained in compound **1a**. This data suggested that the presence of the nitrogen atom in the aza core contributes to the hyperbilirubinemia observed with compounds **1a** and **1b**. In other screening assays, unsubstituted symmetry-based core compounds, such as **1c**, exhibited lower antiviral potency and were less stable in human liver microsomes (HLM) than **1a**, making them unlikely candidates for convenient dosing. While compound **9a** was less potent than **1a**, it displayed improved metabolic stability (see Table 1). In contrast to the aza core, the all-carbon core allowed for variation of both the position of the central hydroxyl group and the stereochemistry at the P1′ position. Consequently, we focused our structure−activity relationship (SAR) investigation on cores A, B, and C (Figure 1).

Antiviral activity and metabolic stability data for new compounds, along with reference compounds, are presented in Table 1. Compounds were screened in cell culture against wild type (WT) HIV-1 (pNL4-3 strain), both in the absence and presence of 50% human serum (HS), since it is known that the addition of serum reduces the potency of HIV PIs because of protein binding.[15] In addition, activity against a HIV PI resistant strain, A17 (protease mutations L10F, V32I, M46I, I47V, Q58E, I84V), which was generated by in vitro serial passage of LPV/RTV, was routinely determined.[16] The A17 mutant clone has several mutations that confer cross-resistance to other HIV PIs[17] and was highly resistant to LPV as well as other marketed PIs including RTV, ATV, amprenavir (APV), saquinavir (SQV), and DRV in antiviral assays. Consequently, the fold resistance to this multiple PI resistant mutant was monitored to gauge the potential effectiveness of new compounds in PI experienced patients.

As shown in Table 1, each of the cores (A, B and C in Figure 1) was combined with a series of arylmethyl-substituted P3 substituents. While the initial compound in the series **9a** lost 2-fold potency relative to **1a** in the presence of 50% HS, core B and C analogues **10a** and **18a** had 2-fold better potency than **9a** and nearly identical potency to **1a**. Generally, core B and C analogues displayed higher potency than the core A analogues. This trend was observed for the other P3 modifications, such as the 2-methyl-4-thiazole analogues (**9a**, **10b**, and **18b**) and 6-(2-methyl-2-hydroxyethyl)-2-pyridyl analogues (**9c**, **10c**, and **18c**). An exception was the phenyl analogue series, in which the core A and C compounds, **9d** and **18d**, respectively,

Scheme 4. Preparation of Cyclic Urea Acids **8c** and **8r**[a]



[a] Reagents and conditions: (a) excess MeMgBr, 0 °C; (b) TFA; (c) 1.2 equiv of MeMgBr, −78 °C; (d) $Me(PPh_3)Br$, *t*-BuOK; (e) Pd on C, H_2.

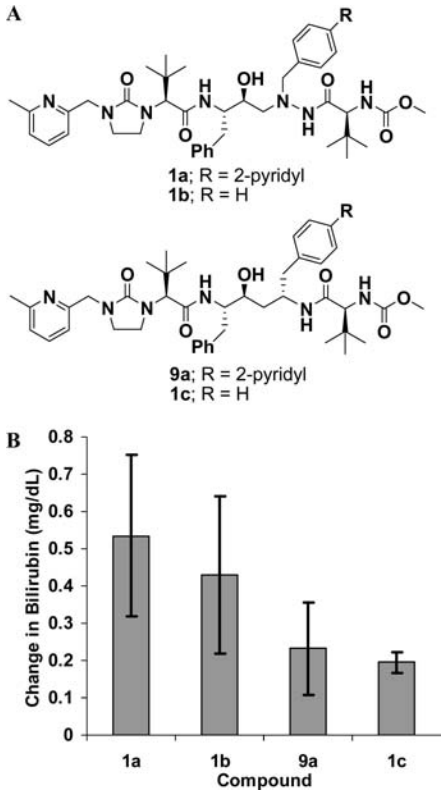


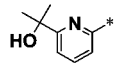
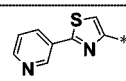
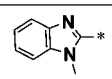
Figure 2. (A) Structures of aza-core analogues (**1a** and **1b)** and carbon-core analogues (**1c** and **9a**). (B) Mean change in serum bilirubin concentrations in the Gunn rat assay (error bars are standard deviation). All compounds were dosed orally along with 50 mg/kg RTV for pharmacokinetic enhancement.

displayed higher potencies than the core B analogue **10d**. Larger bicyclic heterocycles were also tolerated at the P3 position. For example, the 4-quinoline analogues (**9e**, **10e**, and **18e**) were uniformly potent against WT HIV, as were the 2-(pyridin-3-yl)-4-thiazole analogues (**9f**, **10f**, and **18f**). The benzimidazole analogue **9g**, however, was markedly less potent than the above bicyclic analogues. In general, the series of compounds (**9a**−**g**, **10a**−**g**, **18a**−**g**) demonstrated 5-fold to 10-fold reduction in potency with the addition of 50% HS. The compounds retained relatively high activity against the A17 mutant (<12-fold increase in EC_{50}, compared to WT HIV), with the core B analogues generally exhibiting slightly lower potency (i.e., larger fold change in EC_{50}) than core A or C analogues.

The potent antiviral activity of the core B analogues was unexpected on the basis of previous SAR of symmetry-based HIV PIs. HIV protease functions as a C_2-symmetric homodimer with a single active site, and the active site subsites (S1/S1′, S2/S2′, and S3/S3′) are symmetrically disposed around the symmetry axis that dissects the active site. The absolute stereochemistry of the P1 and P1′ side chains of core A and C analogues matches that of early C_2-symmetric inhibitors[18] and the pseudo-C_2-symmetry-based PIs exemplified by RTV and LPV.[14] Obtained as a side product from the synthesis of the desired core A analogues, core B analogues are epimeric at the P1′ (C-5) position. Because of the mismatch with the C_2-symmetric HIV protease binding site, these analogues were expected to be significantly less potent. In order to determine the binding mode, X-ray crystallographic analysis of core B analogue **10a** bound to HIV protease was conducted. Figure 3 depicts compound **10a** (in purple) overlaid with core A analogue **11**, which is capped at each end with *tert*-butylglycine methyl carbamate (in brown). The C-3 hydroxyl groups of both cores are similarly positioned to allow hydrogen-bonding interactions with the catalytic Asp residues 25 and 25′. To accommodate this binding mode, the conformations of the two cores differ significantly. While the core A compound **11** binds in a gauche conformation between C-3 and C-4, the core of **10a** adopts an all anti conformation. Both compounds form water mediated hydrogen bonds between the P2 side chain carbonyls and Ile 50 and 50′ (water shown in red, Figure 3), a feature common to all peptidomimetic inhibitors. To achieve this interaction, the C5−N bond of **10a** adopts a high energy conformation (the carbonyl carbon is gauche to C-4 and C-6), whereas compound **11** is in a lower energy conformation with the carbonyl carbon eclipsing the C-5 methine proton. Thus, both compounds require a gauche conformation to form the key hydrogen bonds in the center of the active site. The two cores project the pyridylbenzyl groups into the S1′ subsite of the enzyme at different angles, resulting in poor overlap between the P1′ pyridyl groups. However, this site is sufficiently large to accommodate both orientations. Overall, the crystal structures of both compounds are therefore consistent with their similar potencies.

In order to identify compounds with high potential for convenient dosing, the metabolic stability of new analogues was routinely screened in HLM by evaluating the disappearance of parent compound. Stability was determined for the compounds alone and in the presence of 0.4 μM RTV. The percentage inhibition of the metabolism by RTV provided an estimate of the potential effectiveness of PK enhancement by RTV. Improved stability in the absence of RTV provided insight into the potential for sustained plasma levels with a dose of RTV of 100 mg/day or less, in which inhibition of first pass metabolism by RTV is likely but systemic metabolism is relatively minimal. Such a compound might be advantageous in that lipid elevations

Table 1. In Vitro Cell Culture Potency and Metabolic Stability Data

Compound		Core	Cell Culture EC_{50} (nM)			Metabolism in HLM	
			WT[a]	WT	A17 (fold)[b]	% Disappearance (% Inh.)[c]	
no.	R		0% HS[d]	50% HS[d]	0% HS[d]	No RTV	0.4 μM RTV
LPV	Reference Compounds		18	152	1057 (59)	96	39 (59)
1a			2	30	17 (9)	44	5.2 (88)
1c			13	179	88 (7)	62	12 (80)
9a		A	13	62	15 (1)	24	6.2 (74)
10a		B	5	27	21 (4)	73	11 (85)
18a		C	5	30	5 (1)	70	4.9 (93)
9b		A	10	94	10 (1)	25	7.3 (71)
10b		B	3	15	12 (4)	56	13 (77)
18b		C	3	34	2 (<1)	40	6.5 (84)
9c		A	6	53	4 (<1)	20	7.5 (62)
10c		B	3	19	10 (3)	35	7.6 (78)
18c		C	4	19	2 (<1)	54	3.7 (93)
9d		A	2	12	22 (11)	11	6 (44)
10d		B	11	43	37 (3)	79	15.6 (80)
18d		C	1	10	4 (4)	73	6.7 (91)
9e		A	4	19	2 (<1)	60	14 (76)
10e		B	5	21	8 (2)	85	23 (73)
18e		C	2	15	1 (<1)	84	15 (83)
9f		A	8	26	8 (1)	35	15 (56)
10f		B	2	15	7 (4)	71	25 (65)
18f		C	2	18	1 (<1)	55	11 (79)
9g		A	140	346	32 (<1)	40	3.4 (91)
10g		B	3	33	20 (7)	40	13 (67)
18g		C	7	82	3 (<1)	68	11 (84)
9h	2-aminophenyl	A	4	20	21 (5)	26	17 (35)
9i	4-aminophenyl	A	10	63	30 (3)	17	7.2 (57)
9j	2-methoxyphenyl	A	4	17	49 (12)	38	16 (59)
9k	3-methoxyphenyl	A	14	65	53 (4)	33	13 (61)
9l	2-fluorophenyl	A	11	36	88 (2)	19	8.1 (58)
9m	3-fluorophenyl	A	4	28	38 (9)	24	8.6 (65)
9n	4-fluorophenyl	A	6	33	42 (7)	19	6.8 (64)
9o	2-methylphenyl	A	10	30	72 (7)	31	10.6 (66)
9p	3-methylphenyl	A	5	25	41 (8)	25	9.6 (62)
18h	2-iPr-4-thiazole	C	1	13	1 (1)	71	12 (82)
10h	6-iPr-2-pyridyl	B	15	105	66 (4)	61	7.0 (89)
10i	6-*t*Bu-2-pyridyl	B	15	311	151 (10)	40	3.8 (90)

[a] Wild type = pNL4-3. [b] Fold resistance. [c] % Inh. = percent inhibition of metabolism by RTV. [d] HS = human serum.

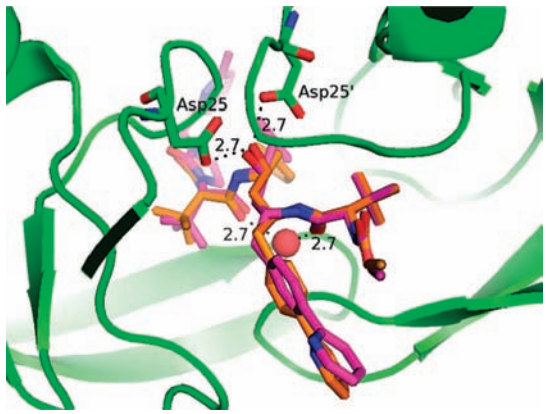


Figure 3. X-ray crystal structures of core B analogue **10a** (purple) analogue overlaid with core A analogue **11**, which is capped at each end with MeO_2C-*tert*-Bu-Gly (brown). Catalytic Asp 25 and Asp 25′ are highlighted, and water is shown in red.

by RTV are dose-dependent and relatively minimal at doses of <100 mg, b.i.d. It has been demonstrated in healthy volunteers that RTV (100 mg, b.i.d.) elevated LDL and HDL cholesterol levels as well as triglycerides.[19]

Trends in metabolic stability that emerged on the basis of the identity of the core and P3 groups are shown in Table 1. As mentioned earlier, compound **9a**, bearing the 2-pyridyl substituted benzyl group, was substantially more stable to microsomal metabolism than the unsubstituted version, **1c**. With only 24% disappearance under these conditions, compound **9a** was also more stable to metabolism than **1a**. Compounds **10a** and **18a**, the core B and core C analogues, however, were considerably less stable than **9a** to metabolism, exhibiting ≥70% disappearance. This trend was generally observed, with the core A analogues, **9a**−**9f**, demonstrating higher metabolic stability than the core B or C analogues. The phenyl analogue, **9d**, displayed the highest metabolic stability of the compound set in the absence of RTV (11% disappearance), and it was markedly more stable than core B and C analogues, **10d** and **18d**. The quinoline analogues (**9e**, **10e**, and **18e**) showed the highest rate of metabolism among the P3 analogues tested. RTV efficiently inhibited the metabolism of most of the compounds, with less than 50% inhibition observed with only analogue **9d**.

On the basis of their potencies and metabolic stabilities, compounds **9d**, **18b**, and **10c** were selected for additional P3 group SAR studies. The unadorned phenyl ring of **9d** was a potential liability in terms of metabolism and contributing to low aqueous solubility. SAR studies were targeted toward P3 groups that could improve potency, metabolic stability, or aqueous solubility. The 2-amino analogue **9h** displayed similar potency and metabolic stability to **9d**, while the 4-amino isomer

Table 2. Pharmacokinetic Data in Rats (5 mg/kg)

	iv		oral		
			no RTV		with RTV[a]
compd	$t_{1/2}$[b]	CL[c]	F (%)	AUC[d]	AUC[d]
10b	0.4	1.86	5.9	0.16	1.98
18b	0.5	1.90	11.2	0.32	8.40
9c	1.0	1.40	5.7	0.20	0.83
10c	0.5	1.35	4.9	0.18	12.93
18c	0.9	1.00	17.0	0.88	1.82
9d	1.0	1.15	3.4	0.15	3.50
9e	1.1	1.80	0.6	0.02	2.86
10e	0.6	2.50	0.0	0.00	9.20
18e	0.4	2.00	1.1	0.05	3.30
9f	0.7	2.05	0.8	0.02	0.12
18f	0.8	2.80	1.6	0.03	0.26
10g	0.7	3.24	0.1	0.00	1.17
9h	1.2	1.99	2.9	0.08	1.25
9j	1.2	2.16	3.1	0.07	9.38
9p	1.4	1.76	0.8	0.02	2.70

[a] Coadministered with 5 mg/kg RTV. [b] h. [c] L/(h·kg). [d] μg·h/mL.

9i was less potent. Similarly, the 2-methoxy analogue **9j**, but not the 3-methoxy analogue **9k**, exhibited similar potency to **9d**. Fluorinated analogues **9l**, **9m**, and **9n** and methylated analogues **9o** and **9p** were also similarly potent and comparably stable to **9d**. An analogue of compound **18b**, 2-isopropyl-4-thiazole **18h**, had improved potency compared to **18b** but was significantly less stable in HLM, with 71% disappearance. Analogues of compound **10c** included the structurally simpler analogues **10h** and **10i**, bearing 6-isopropyl and 6-*tert*-butyl substituents, respectively. Both compounds were less active than **10c**, and **10h** demonstrated decreased metabolic stability. The tertiary hydroxyl group of **10c** contributed to both its potency and metabolic stability.

Pharmacokinetic Evaluation. The pharmacokinetic profiles for select compounds were examined both alone and with coadministration of RTV. As shown in Table 2, all of the compounds showed high rates of clearance when dosed intravenously in the rat. The plasma levels from oral dosing alone were quite low, with oral bioavailability ranging from 0 to 17%. At the extremes, compound **18c** exhibited the highest plasma concentrations and the lowest clearance, while compound **10e** showed no detectable plasma levels upon oral dosing. Consistent with the predictions from the microsomal metabolism data, the plasma levels of all of the compounds were substantially enhanced upon oral coadministration with RTV, with AUCs increasing by 2- to 143-fold. Notably, compound **10e**, which showed no detectable plasma levels when dosed alone, showed high oral bioavailability upon coadministration with RTV.

Direct comparison of the effect of the core on the oral bioavailability was possible with two sets of analogues: (1) **9c**, **10c**, **18c** and (2) **9e**, **10e**, **18e**. In both cases the core B analogues, **10c** and **10e**, showed significantly higher plasma levels when coadministered with RTV than the core A or C analogues.

Several analogues of compound **9d** with substitution of the phenyl P3 group were also evaluated. Amino-substituted P3 analogue **9h** showed poor plasma levels even with RTV coadministration. The methoxy substituted analogue **9j**, on the other hand, showed 3-fold higher plasma levels than **9d**. The methyl-substituted analogue **9p** displayed similar pharmacokinetics to **9d**.

Characterization of 10c and 9d. On the basis of their potencies, metabolic stabilities, and oral bioavailabilities in our screening assays, two compounds, **10c** and **9d**, were selected for further pharmacokinetic and drug safety evaluation. While

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

	compd data			RTV data	
compd	AUC[a]	C_{max}[b]	C_{12h}[b]	dose[c]	AUC[a]
10c	0.02	0.04	0.00	0	0
	6.72	2.22	0.013	2.5	1.56
	10.64	2.56	0.058	5	8.8
9d	0.21	0.17	0.00	0	0
	18.96	3.91	0.068	2.5	0.71
	41.90	5.89	0.924	5	5.23

[a] μg·h/mL. [b] μg/mL. [c] mg/kg.

Table 4. Properties of **10c** and **9d**

assay	**10c**	**9d**
solubility (μg/mL)[a]	11.3	<0.15
protein binding[b]	98.2	99.66
Caco-2 permeability	moderate	moderate
CYP1A2 IC_{50} (μM)[c]	>5	>10
CYP2C9 IC_{50} (μM)[d]	>5	>10
CYP2C19 IC_{50} (μM)[e]	>5	>10
CYP2D6 IC_{50} (μM)[f]	>5	>10
CYP3A4 K_i (nM)[g]	66	18
HIV protease K_i (nM)	0.014	0.015
pepsin K_i (μM)	200	177
renin K_i (μM)	>20	>4
cathepsin D K_i (μM)	0.54	4.3

[a] pH 7.4 at 25 °C. [b] % bound in human plasma by equilibrium dialysis. [c] Phenacetin O-deethylation. [d] Tolbutamide hydroxylation. [e] *S*-Mephenytion hydroxylation. [f] Dextromethorphan O-demethylation. [g] Midazolam 1′-hydroxylation.

drug plasma levels of **9d** in rats were moderate after oral dosing, compound **9d** possessed both the highest potency of the series in the presence of 50% HS and the highest metabolic stability. The measured aqueous solubility for **9d** was quite low (see Table 4), suggesting the potential for improved oral exposure through formulation efforts. Although substituents on the phenyl ring of **9d** were accommodated in terms of potency, metabolic stability, and oral bioavailability (i.e., **9j** and **9p**), the analogues prepared in the series (**9h**−**p**) did not provide a significant advantage over **9d**. Compound **10c** was also selected for further evaluation, since it had nearly equivalent potency and metabolic stability compared to **9d**, but produced higher plasma levels upon oral administration with RTV. In addition, the structurally distinct core and P3 substituent of **10c** compared to **9d** offered the potential advantage of differentiated drug resistance and safety profiles for the two compounds.

Oral administration of either **10c** or **9d** alone in dogs resulted in low plasma levels and low oral bioavailability, similar to the observations from rats (Table 3). Coadministration with RTV (5 mg/kg), however, resulted in dramatic increases in the plasma levels and oral bioavailability of both compounds, with 500- and 200-fold increases in the AUC for **10c** and **9d**, respectively. Plasma exposures (AUC) were 3- to 4-fold higher for compound **9d** compared to compound **10c**, and at the 12 h time point **9d** provided plasma levels of approximately 1 μg/mL, whereas the concentrations of **10c** were significantly lower. At a lower dose of RTV (2.5 mg/kg), plasma levels of compound **9d** exceeded RTV levels by 27-fold, whereas the AUC of **10c** was only 4-fold higher than the RTV AUC. Compound **9d** thus provided a potential advantage in its sensitivity to pharmacokinetic enhancement by RTV, since a lower dose of RTV could be used to obtain the high levels of **9d**.

Further in vitro characteristics of compounds **10c** and **9d** are shown in Table 4. Both compounds exhibited low aqueous solubility at pH 7.4, with **10c** displaying higher solubility than **9d**. The compounds were highly protein bound in human plasma, and the Caco-2 permeability model predicted moderate

Table 5. Activity Against LPV-Resistant Strains

PI	cell culture EC_{50} (nM)			
	WT[a]	A17[b]	B26[c]	P25[d]
10c	3	10	25	45
9d	2	22	140	103
LPV	18	1057	3790	>10000
DRV	12	338	587	515
ATV	3	250	74	298

[a] pNL4-3. [b] A17: L10F, V32I, M46I, I47V, Q58E, and I84V. [c] B26: L33F, K45I, M46I, I50V, I54V, A71V, and V82F. [d] P25: L10F, G16E, V32I, M46I, I47A, H69Y, I84V, and T91S.

Table 6. Changes in Biliburin and Drug Concentrations in Gunn Rats

compd	dose[a]	change in bilirubin, mg/dL (SD)[b]		serum drug concn, μg/mL (SD)	
		day 1	day 2	day 1	day 2
1a	100	0.536(0.216)	0.685(0.415)	8.87(6.86)	8.88(5.35)
1b	250	0.429(0.212)	NA[c]	13.28(2.99)	NA[c]
9a	250	0.233(0.124)	NA[c]	5.83(4.98)	NA[c]
1c	250	0.195(0.029)	NA[c]	18.68(10.04)	NA[c]
10c	125	0.125(0.045)	NA[c]	9.37(3.93)	NA[c]
9d	125	0.144(0.107)	0.133(0.096)	2.45(0.71)	5.33(1.20)

[a] mg/kg. All compounds were coadministered with 50 mg/kg RTV. [b] SD = standard deviation. [c] NA = not available.

permeability for the compounds. The potential for drug−drug interactions for **10c** and **9d** was evaluated in vitro against a panel of cytochrome P450 (CYP) isoforms. No significant inhibition of CYP2C19, CYP1A2, CYP2C9, or CYP2D6 was observed at the highest concentrations tested. Both compounds exhibited potent inhibition of CYP3A4; however, the consequence of this inhibition is unclear, since both compounds are likely to require coadministration of RTV, a potent CYP3A4 inhibitor.

Compounds **10c** and **9d** demonstrated subnanomolar potency against WT HIV protease. Greater than 11000-fold selectivity for HIV protease inhibition was observed over the human aspartic proteinases pepsin, renin, and cathepsin D. Potencies of **10c** and **9d** against LPV resistant clones A17 (L10F, V32I, M46I, I47V, Q58E, I84V), B26 (L33F, K45I, M46I, I50V, I54V, A71V, V82F), and P25 (L10F, G16E, V32I, M46I, I47A, H69Y, I84V, T91S) are provided in Table 5. Compound **10c** maintained double-digit nanomolar potency against these viruses and displayed an advantage against these resistant mutant viruses compared to compound **9d**, LPV, ATV, or DRV. Additional studies of the resistance profile of **10c** including resistance selection and activity against clinical isolates have been described in detail elsewhere.[20]

Compound **9d** was examined in a gene microarray model for HIV PI-induced hyperlipidemia. Few proteasome genes were regulated by **9d**, while RTV strongly induced the expression of proteasome genes, and the results will be described elsewhere.[8d]

Evaluation of 10c and 9d in the Gunn Rat Model for Unconjugated Bilirubin. Compounds **10c** and **9d** were evaluated for their potential to elevate serum levels of unconjugated bilirubin in the Gunn rat assay. The results are presented in Table 6 along with data for reference compounds **1a**, **1b**, **1c**, and **9a**. The compounds were dosed in Gunn rats at 125 mg/kg along with 50 mg/kg RTV to enhance their plasma concentrations. Both compounds **10c** and **9d** caused only small increases in serum bilirubin concentrations on day 1, of a magnitude that is consistent with that caused by treatment with 50 mg of ritonavir alone and significantly less than that caused by **1a**, **1b**, or ATV. While compound **10c** achieved comparable plasma levels to **1a** on day 1, the plasma levels for **9d** were 75% lower than **1a**. Consequently, dosing was continued on day 2 to increase the plasma levels. Although the drug plasma levels of **9d** were doubled on day 2, no accompanying increase in serum bilirubin levels was observed. These results suggest that any elevation of unconjugated bilirubin in humans by **10c** and **9d** is likely to be clinically insignificant.

Conclusions

Investigation of HIV PI cores A, B, and C (Figure 1) revealed that the potency, metabolic stability, and pharmacokinetics could be modulated through the regiochemistry and stereochemistry of the core as well as through variation of the arylmethyl substituent appended to the cyclic urea P3 group. Through these modifications, we were able to identify two compounds, **10c** (A-790742) and **9d** (A-792611), for preclinical evaluation. Each has potent activity against WT HIV in the presence of 50% human serum and high oral bioavailability when coadministered with RTV. Compound **10c** retains potency against multiple PI-resistant strains of HIV. Unlike LPV, which exhibits rapid disappearance in HLM in the absence of RTV, both compounds are more stable than LPV in HLM, potentially allowing for the maintenance of high drug plasma levels using a lower dose of RTV than required for LPV in humans (200 mg/day). Finally, compounds **10c** and **9d** also demonstrated reduced potential for the common side effects of HIV PIs (bilirubin elevations and hyperlipidemia) in preclinical models.

Experimental Section

Chemistry. 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) by two methods. 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, 60Å) or Biotage KP-C18-HS cartridges. NMR spectra were determined with a Bruker ARX 300 MHz, Varian Unity 400 MHz, or Varian Unity INOVA 500 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane internal standard. Low-resolution mass spectral (MS) ESI and DCI data were determined on a Thermo-Finnigan SSQ7000 instrument. Combustion analysis was performed by Robertson Microlit Laboratories (Madison, NJ) or Quantitative Technologies Inc. (Whitehouse, NJ), and data were within 0.4% of calculated values.

***tert*-Butyl (1*S*)-1-((2*S*)-5-Oxo-4-(4-(pyridin-2-yl)benzyl)tetrahydrofuran-2-yl)-2-phenylethylcarbamate (2).** *tert*-Butyl (1*S*)-1-((2*R*)-oxiran-2-yl)-2-phenylethylcarbamate (10.0 g, 38.0 mmol) and diethyl malonate (5.8 mL, 38.2 mmol) were dissolved in ethanol (30 mL) and cooled at 0 °C as a solution of NaOEt (17 mL, 21% in ethanol) was added over 10 min. The mixture was warmed to room temperature and stirred for 2 h. At that time, additional diethyl malonate (0.58 mL, 3.4 mmol) was added and the mixture was stirred for 1 h. The mixture was recooled at 0 °C, and solid 2-(4-(bromomethyl)phenyl)pyridine (9.43 g, 38.0 mmol) was added in four increments over 10 min. To this suspension was added ethanol (20 mL), and the mixture was warmed to room temperature for 16 h. LiOH monohydrate (4.6 g, 109.6 mmol) solution in water (30 mL) was added followed by stirring at room temperature for 16 h. The mixture was cooled at 0 °C and then adjusted to pH 5 by addition of 4 N HCl and then partitioned between dichloromethane and water. The organic was washed with brine, dried over $MgSO_4$, filtered, and evaporated.

A solution of the crude product from the first step dissolved in toluene (100 mL) was then heated at reflux for 16 h. Evaporation of the solvent gave crude product (21.4 g), which was obtained as a 1.6:1 mixture of the (4*S*)- and (4*R*)-isomers, respectively, and was used without further purification. (4*S*)-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.37 (s, 9H), 1.76−1.92 (m, 1H), 2.06−2.18 (m, 1H), 2.66−2.79 (m, 1H), 2.79−3.00 (m, 3H), 3.28−3.39 (m, 1H), 3.87−4.02 (m, 1H), 4.29−4.38 (m, 1H), 4.62 (d, J = 9.83 Hz, 1H), 7.10−7.34 (m, 8H), 7.65−7.82 (m, 2H), 7.86−7.98 (m, 2H), 8.63−8.72 (m, 1 H). (4*R*)-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.36 (s, 9H), 1.92−2.03 (m, 1H), 2.19−2.32 (m, 1H), 2.79−3.09 (m, 3H), 3.15 (dd, J = 13.56, 4.41 Hz, 1H), 3.88−4.05 (m, 1H), 4.19−4.26 (m, 1H), 4.51 (d, J = 9.49 Hz, 1H), 7.10−7.34 (m, 8H), 7.66−7.79 (m, 2H), 7.87−7.98 (m, 2H), 8.64−8.72 (m, H). MS (ESI) *m*/*z* 473 $(M + H)^+$.

(4*S*,5*S*)-5-(*tert*-Butoxycarbonylamino)-4-(*tert*-butyldimethylsilyloxy)-6-phenyl-2-(4-(pyridin-2-yl)benzyl)hexanoic Acid (3). A solution containing **2** (21.4 g) in dioxane (100 mL) was treated with sodium hydroxide solution (57 mL, 1 N) for 30 min at room temperature. The dioxane was evaporated, the crude residue was cooled at 0 °C, and the mixture was acidified to pH 5 using 4 N HCl. The mixture was partitioned between dichloromethane and water, and the organic layer was washed with brine and dried over $MgSO_4$, and the solvents were evaporated to give 38 g of crude product.

The crude hydroxy acid from the first step was dissolved in DMF (100 mL) and treated with imidazole (21 g, 308.5 mmol) and *tert*-butyldimethylsilyl chloride (23 g, 152.6 mmol) at room temperature for 16 h. The solvent was evaporated, and the residue was combined with ice and acidified with 4 N HCl to pH 3. Ethyl acetate (50 mL) was added to permit stirring during the acidification. This mixture was extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, and filtered, and the solvents were evaporated. The residue was purified by chromatography on silica gel, eluting with a gradient of 20−100% ethyl acetate in chloroform, followed by elution with 5% methanol in ethyl acetate to give the product as a mixture of isomers (11.3 g, 49% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.06−0.16 (m, 6H), 0.94 (s, 9H), 1.33−1.39 (m, 9H), 1.52−1.99 (m, 2H), 2.59−3.09 (m, 4H), 3.66−4.09 (m, 2H), 4.57−4.83 (m, 1H), 7.07−7.39 (m, 8H), 7.64−7.79 (m, 2H), 7.81−7.91 (m, 2H), 8.56−8.72 (m, 1H). MS (ESI) *m*/*z* 605 $(M + H)^+$.

Benzyl (2*S*,4*S*,5*S*)-5-(*tert*-Butoxycarbonyl)amino-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylcarbamate (4) and Benzyl (2*R*,4*S*,5*S*)-5-(*tert*-Butoxycarbonyl)amino-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylcarbamate (5). To a solution of **3** (11.3 g, 18.7 mmol) in toluene (190 mL) were added diphenylphosphoryl azide (8.1 mL, 37.6 mmol) and triethylamine (5.2 mL, 37.3 mmol), and the mixture was heated at reflux for 2 h. Benzyl alcohol (5.8 mL, 56.0 mmol) was added, and the mixture was heated at reflux for an additional 16 h. The solvent was evaporated.

To the crude residue from the first step was added TBAF solution in THF (94 mL, 1 N), and the mixture was stirred at room temperature for 40 h. The THF was evaporated, and the mixture was partitioned between ethyl acetate and water. The organic was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica gel, eluting with 50% ethyl acetate in chloroform to give 2.6 g (23% yield) of the higher R_f product **5** by TLC (35% ethyl acetate in dichloromethane) and 4.2 g (38% yield) of the lower R_f product **4** by TLC. **4**: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.30 (s, 9H), 1.46−1.66 (m, 2H), 2.56−2.83 (m, 4H), 3.50−3.70 (m, 1H), 3.74−3.90 (m, 1H), 3.89−4.06 (m, 1H), 4.61 (d, J = 6.62 Hz, 1H), 4.85−5.00 (m, 2H), 6.32 (d, J = 9.56 Hz, 1H), 7.05−7.45 (m, 13H), 7.80−8.01 (m, 4H), 8.66 (d, J = 4.04 Hz, 1H). MS (ESI) *m*/*z* 596 $(M + H)^+$. **5**: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.28 (s, 9H), 1.39−1.56 (m, 2H), 2.53−2.87 (m, 4H), 3.49−3.63 (m, 1H), 3.84−3.97 (m, 1H), 4.51 (d, J = 6.25 Hz, 1H), 4.87−5.04 (m, 2H), 6.33 (d, J = 9.19 Hz, 1H), 7.10−7.37 (m, 13H), 7.77−8.04 (m, 4H), 8.65 (d, J = 4.04 Hz, 1H). MS (ESI) *m*/*z* 596 $(M + H)^+$.

Methyl (*S*)-1-((2*S*,4*S*,5*S*)-5-(*tert*-Butoxycarbonyl)amino-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (6a). To a solution containing **4** (4.2 g, 7.0 mmol) in a mixture of methanol (35 mL) and ethyl acetate (35 mL) were added $Pd(OH)_2$ on carbon (1.4 g, 20% Pd by weight) and HCl solution (1.8 mL, 4 N in dioxane), and the mixture was stirred under a hydrogen atmosphere (balloon pressure) for 16 h. The mixture was filtered through a bed of Celite and rinsed with methanol. The solvent was evaporated to give the crude product (3.7 g), which was used in the next step without further purification.

To a solution containing the product from the first step (3.7 g) in THF (75 mL) were added (*S*)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid (1.39 g, 7.4 mmol), DEPBT (3.3 g, 11.0 mmol), and *N*,*N*-diisopropylethylamine (6.4 mL, 36.7 mmol), and the mixture was stirred at room temperature for 16 h. The mixture was partitioned between ethyl acetate and 10% Na_2CO_3 solution. The organic was washed with additional 10% Na_2CO_3 solution and then brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica gel, eluting with a gradient of 33−100% ethyl acetate in chloroform to give the product (3.5 g, 75% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.81 (s, 9H), 1.28 (s, 9H), 1.51 (t, J = 7.00 Hz, 2H), 2.55−2.80 (m, 4H), 3.49 (s, 3H), 3.55−3.65 (m, 1H), 3.71−3.79 (m, 1H), 3.83 (d, J = 9.61 Hz, 1H), 4.09−4.24 (m, 1H), 4.57 (d, J = 6.86 Hz, 1H), 6.26 (d, J = 9.47 Hz, 1H), 6.63 (d, J = 9.88 Hz, 1H), 7.08−7.25 (m, 7H), 7.26−7.35 (m, 1H), 7.70−8.00 (m, 5H), 8.56−8.84 (m, 2H). MS (ESI) *m*/*z* 633 $(M + H)^+$.

Methyl (*S*)-1-((2*S*,4*S*,5*S*)-5-Amino-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (6b). To a solution containing **6a** (3.5 g, 5.5 mmol) in dichloromethane (40 mL) was added TFA (20 mL), and the mixture was stirred at room temperature for 1 h. The solvent was evaporated, and the mixture was partitioned between ethyl acetate and saturated $NaHCO_3$ solution. The organic was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The crude product (3.19 g) was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.99 (s, 9H), 1.54−1.67 (m, 1H), 1.70−1.80 (m, 1H), 2.48 (dd, J = 13.38, 9.13 Hz, 1H), 2.74−2.91 (m, 3H), 3.10 (dd, J = 13.45, 5.21 Hz, 1H), 3.38−3.50 (m, 1H), 3.66 (s, 3H), 3.85 (d, J = 9.06 Hz, 1H), 4.17−4.27 (m, 1H), 5.45 (d, J = 8.37 Hz, 1H), 6.66 (d, J = 5.76 Hz, 1H), 7.09−7.32 (m, 8H), 7.64−7.79 (m, 2H), 7.86−7.92 (m, 2H), 8.64−8.71 (m, 1H). MS (ESI) *m*/*z* 533 $(M + H)^+$.

Methyl (*S*)-1-((2*R*,4*S*,5*S*)-5-(*tert*-Butoxycarbonyl)amino-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (7a). 7a was prepared according to the procedure for **6a** from **5** (74% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.75 (s, 9H), 1.28 (s, 9H), 1.36−1.61 (m, 2H), 2.57−2.87 (m, 4H), 3.45−3.64 (m, 2H), 3.56 (s, 3H), 3.73−3.85 (m, 1H), 4.04−4.27 (m, 1H), 4.55 (d, J = 6.04 Hz, 1H), 6.31 (d, J = 9.47 Hz, 1H), 6.86 (d, J = 9.47 Hz, 1H), 7.05−7.41 (m, 8H), 7.76−8.00 (m, 5H), 8.51−8.69 (m, 1H). MS (ESI) *m*/*z* 633 $(M + H)^+$.

Methyl (*S*)-1-((2*R*,4*S*,5*S*)-5-Amino-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (7b). 7bwas prepared according to the procedure for **6b** from **7a**. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.73 (s, 9H), 1.51 (t, J = 10.85 Hz, 1H), 1.61−1.75 (m, 1H), 2.69−2.91 (m, 4H), 3.30−3.44 (m, 1H), 3.80 (d, J = 9.56 Hz, 1H), 4.08−4.29 (m, 1H), 6.90 (d, J = 9.56 Hz, 1H), 7.11−7.43 (m, 8H), 7.78−8.07 (m, 5H), 8.64 (d, J = 4.78 Hz, 1H). MS (ESI) *m*/*z* 533 $(M + H)^+$.

(*S*)-Benzyl 3-(4-bromophenyl)-2-(dibenzylamino)propanoate (12). To a suspension of (*S*)-2-amino-3-(4-bromophenyl)propanoic acid (5 g, 20.5 mmol) in a mixture of water and ethanol (2:1, respectively, 20 mL) were added potassium carbonate (9.3 g, 67.3 mmol) and benzyl chloride (7.77 mL, 67.5 mmol), and the mixture was heated at reflux for 16 h. The mixture was cooled to room temperature, and a mixture of hexanes and THF (1:1, 100 mL) was added followed by addition of water. The mixture was partitioned, and the organic was washed two times with a mixture of water

and methanol (2:1, respectively) and then with brine, dried over $MgSO_4$, filtered, and evaporated. The crude product (11.23 g) was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.84−2.98 (m, 1H), 2.99−3.17 (m, 1H), 3.47−3.56 (m, 2H), 3.61−3.69 (m, 1H), 3.90 (d, J = 13.97 Hz, 2H), 5.10−5.28 (m, 2H), 6.84 (d, J = 8.46 Hz, 2H), 7.06−7.15 (m, 4H), 7.17−7.44 (m, 13H). MS (ESI) m/z 516 $(M + H)^+$.

(*S*)-Benzyl 2-(Dibenzylamino)-3-(4-(pyridin-2-yl)phenyl)propanoate (13). To a solution containing **12** (11.0 g, 20.5 mmol) in DMF (90 mL) were added LiCl (8 g, 188.7 mmol), tetrakis(triphenylphosphine)palladium(0) (5 g, 4.3 mmol), and 2-(tributylstannyl)pyridine (22 g, 59.8 mmol), and the mixture was heated to 80 °C for 16 h. The mixture was cooled, filtered, and evaporated. The residue was partitioned between ethyl acetate and water, and the organic was washed with brine and dried over $MgSO_4$, filtered, and evaporated. The mixture was purified by chromatography on silica gel, eluting with a gradient of 0−25% ethyl acetate in hexanes to give the product (7.6 g, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.99−3.11 (m, 1H), 3.12−3.27 (m, 1H), 3.55 (d, J = 13.97 Hz, 2H), 3.75 (t, J = 7.72 Hz, 1H), 3.94 (d, J = 13.97 Hz, 2H), 5.07−5.17 (m, 1H), 5.20−5.32 (m, 1H), 7.05−7.28 (m, 14H), 7.32−7.42 (m, 4H), 7.67−7.81 (m, 2H), 7.85 (d, J = 8.09 Hz, 2H), 8.70 (d, J = 4.41 Hz, 1H). MS (ESI) m/z 513 $(M + H)^+$.

(*S*)-4-(Dibenzylamino)-3-oxo-5-(4-(pyridin-2-yl)phenyl)pentanenitrile (14). To a solution of sodium bis(trimethylsilyl)amide (1 M in THF, 50 mL) at −45 °C was added a solution of acetonitrile (2.81 mL, 53.4 mmol) in THF (10 mL) dropwise, and the mixture was stirred for 15 min at −45 °C and then cooled at −78 °C. A room temperature solution of **13** (7.6 g, 14.8 mmol) dissolved in THF (20 mL) was then added dropwise to the sodioacetonitrile solution above at −78 °C. After complete addition, the mixture was stirred at −45 °C for 1 h. Solid NH_4Cl (10 g) was added, and the mixture was warmed to 5 °C, followed by the addition of water. The mixture was allowed to warm to room temperature and was partitioned between ethyl acetate and water. The organic was washed with brine and dried over $MgSO_4$, filtered, and evaporated to give an oil. Precipitation from ethanol gave the product (4.3 g, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.96−3.13 (m, 2H), 3.19−3.36 (m, 1H), 3.49−3.65 (m, 3H), 3.81−3.96 (m, 3H), 7.14−7.48 (m, 13H), 7.62−7.79 (m, 2H), 7.89 (d, J = 8.46 Hz, 2H), 8.67 (d, J = 4.41 Hz, 1H). MS (ESI) m/z 446 $(M + H)^+$.

(*S*,*E*)-5-Amino-2-(dibenzylamino)-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hex-4-en-3-one (15). A solution containing **14** (4.3 g, 9.65 mmol) in THF (15 mL) was added dropwise to a solution of benzylmagnesium chloride (30 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 at 0 °C and quenched with 10% citric acid, followed by partitioning between ethyl acetate and water. The organic was washed with brine and dried over $MgSO_4$, filtered, and evaporated to give the crude product (6.18 g), which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.00 (dd, J = 13.42, 6.07 Hz, 1H), 3.20 (dd, J = 13.60, 7.72 Hz, 1H), 3.48 (d, J = 6.99 Hz, 2H), 3.51−3.56 (m, 1H), 3.61−3.70 (m, 2H), 3.77−3.85 (m, 2H), 5.04−5.13 (m, 1H), 7.12−7.44 (m, 18H), 7.66−7.77 (m, 2H), 7.85 (d, J = 8.09 Hz, 2H), 8.65−8.79 (m, 1 H). MS (ESI) m/z 538 $(M + H)^+$.

***tert*-Butyl (2*S*,4*S*,5*S*)-5-(Dibenzylamino)-4-hydroxy-1-phenyl-6-(4-(pyridin-2-yl)phenyl)hexan-2-ylcarbamate (16).** To a suspension of $NaBH_4$ (1.75 g, 46.3 mmol) in THF (45 mL) at −10 °C was added methanesulfonic acid (7.46 mL, 114.9 mmol) dropwise cautiously (gas evolution). After complete addition, a solution containing **15** (6.18 g, 9.65 mmol) in a mixture of THF (16 mL) and water (1.6 mL) was added and the mixture was stirred at −10 °C for 16 h.

To a suspension of $NaBH_4$ (1.75 g, 46.3 mmol) in THF (45 mL) at 0 °C was added TFA (4.4 mL, 57.1 mmol) dropwise cautiously (gas evolution), and the mixture was stirred at 0 °C for 30 min. The solution was then added to the mixture from the first step and allowed to warm to room temperature and was stirred for 16 h. $NaBH_4$ (1.75 g, 46.3 mmol) and TFA (4.4 mL, 57.1 mmol) were combined as described above and again added to the mixture at 0 °C, and the mixture was allowed to warm to room temperature and stirred for 16 h. The reaction was cooled at 0 °C and quenched cautiously by slow addition of NaOH solution (65 mL, 3 N), followed by partitioning between *tert*-butyl methyl ether and water. The organic was washed with NaOH solution (0.5 N), NH_4Cl solution, and brine, dried over $MgSO_4$, filtered, and evaporated to give the crude product, which was used without further purification.

To a solution containing the product from the second step (9.65 mmol) in *tert*-butyl methyl ether (50 mL) were added 10% K_2CO_3 (23 mL) and di-*tert*-butyl dicarbonate (3.5 g, 16.0 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was diluted with *tert*-butyl methyl ether, and the organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica gel, eluting with a gradient of 0−50% ethyl acetate in hexanes to give the product (2.7 g, 43% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.22 (s, 9H), 1.50−1.62 (m, 1H), 1.66−1.85 (m, 1H), 2.38−2.68 (m, 2H), 2.86−3.11 (m, 2H), 3.45−3.60 (m, 3H), 3.95−4.12 (m, 2H), 4.69 (d, J = 4.41 Hz, 1H), 6.43 (d, J = 8.09 Hz, 1H), 6.96−7.45 (m, 18H), 7.76−8.11 (m, 4H), 8.64 (d, J = 4.41 Hz, 1H). MS (ESI) m/z 642 $(M + H)^+$.

***tert*-Butyl (2*S*,4*S*,5*S*)-5-Amino-4-hydroxy-1-phenyl-6-(4-(pyridin-2-yl)phenyl)hexan-2-ylcarbamate (17a). 17a** was prepared according to the procedure for **6a** from **16**, except the hydrogenolysis was heated to 60 °C for 6 h (28% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.83 (s, 9H), 1.25 (s, 9H), 1.43−1.60 (m, 2H), 2.53−2.66 (m, 2H), 2.69−2.88 (m, 2H), 3.51 (s, 3H), 3.55−3.66 (m, 1H), 3.69−3.85 (m, 1H), 3.92 (d, J = 9.19 Hz, 1H), 4.08−4.24 (m, 1H), 4.79 (d, J = 5.52 Hz, 1H), 6.56 (d, J = 8.46 Hz, 1H), 6.80 (d, J = 9.93 Hz, 1H), 7.06−7.37 (m, 8H), 7.55 (d, J = 8.82 Hz, 1H), 7.80−8.01 (m, 4H), 8.63 (d, J = 4.04 Hz, 1H). MS (ESI) m/z 633 $(M + H)^+$.

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 (17b). 17b was prepared according to the procedure for **6b** from **17a**. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 0.84 (s, 9H), 1.57−1.80 (m, 2H), 2.72−3.03 (m, 4H), 3.48−3.57 (m, 1H), 3.53 (s, 3H), 3.79−3.89 (m, 2H), 4.03−4.15 (m, 1H), 7.13−7.39 (m, 8H), 7.74−7.95 (m, 4H), 8.58 (d, J = 5.15 Hz, 1 H). MS (ESI) m/z 533 $(M + H)^+$.

General Procedure for the Preparation of Carboxylic Acids 8. To a solution containing *N*-(2-aminoethyl)-L-*tert*-butylglycine *tert*-butyl ester (prepared as described previously)[9b] (0.230 g, 1.0 mmol) in a mixture of toluene (4.0 mL) and methanol (4.0 mL) was added the arylaldehyde (1.05 mmol), and the mixture was stirred at 50 °C for 16 h. The mixture was cooled to room temperature. Sodium borohydride (0.075 g, 2.0 mmol) was added, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with 1 M $NaHCO_3$ and stirred for 1 h. The mixture was partitioned between ethyl acetate and water, and the organic was washed with brine and dried over $MgSO_4$, filtered, and evaporated to give the product, which was used without further purification.

Urea Cyclization Method A. To a solution containing the crude product from the first step in 1,2-dichloroethane (15 mL) were added *N*,*N*-disuccinimidyl carbonate (0.308 g, 1.20 mmol) and triethylamine (0.169 mL, 1.20 mmol), and the mixture was stirred at room temperature for 16 h. The mixture was partitioned between 10% Na_2CO_3 and dichloromethane. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated to give the crude product.

Urea Cyclization Method B. To a solution containing the crude product from the first step in toluene (5.7 mL) was added bis(4-nitrophenyl)carbonate (0.365 g, 1.2 mmol), and the mixture was heated at reflux for 16 h. The mixture was cooled and partitioned between ethyl acetate and 10% K_2CO_3. The organic was washed with brine, dried over $MgSO_4$, filtered, and evaporated to give the crude product.

To a solution containing the crude product from cyclization method A or B in dichloromethane (2.5 mL) was added TFA (2.5 mL), and the mixture was stirred at room temperature for 2 h. The

solvent was evaporated and the product was purified by reversed phase (C18) chromatography, eluting with a gradient starting with water (0.1% TFA) and ending with acetonitrile to give the product.

(*S*)-3,3-Dimethyl-2-(3-((6-methylpyridin-2-yl)methyl)-2-oxoimidazolidin-1-yl)butanoic Acid (8a). 8a was prepared by the general procedure starting from 6-methyl-2-pyridinecarboxaldehyde using urea cyclization method A. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.04 (s, 9H), 2.57 (s, 3H), 3.33 (t, J = 7.93 Hz, 2H), 3.51−3.82 (m, 2H), 4.21 (s, 1H), 4.46 (s, 2H), 7.30 (d, J = 7.54 Hz, 1H), 7.43 (d, J = 7.93 Hz, 1H), 7.99 (t, J = 7.73 Hz, 1H). MS (ESI) m/z 306 $(M + H)^+$.

(*S*)-3,3-Dimethyl-2-(3-((2-methylthiazol-4-yl)methyl)-2-oxoimidazolidin-1-yl)butanoic Acid (8b). 8b was prepared by the general procedure starting from 2-methylthiazole-4-carbaldehyde (preparation has been described previously)[21] using urea cyclization method B. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.02 (s, 9H), 2.63 (s, 3H), 3.19−3.35 (m, 2H), 3.45−3.71 (m, 2H), 4.19 (s, 1H), 4.25−4.40 (m, 2H), 7.22 (s, 1H). MS (ESI) m/z 312 $(M + H)^+$.

Preparation of 8c. (*S*)-Methyl 6-((3-(1-*tert*-Butoxy-3,3-dimethyl-1-oxobutan-2-yl)-2-oxoimidazolidin-1-yl)methyl)picolinate (19). 19 was prepared by the general procedure (first two steps) from methyl 6-formylpicolinate (preparation has been described previously)[22] using urea cyclization method B (64% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.10 (s, 9H), 1.48 (s, 9H), 3.30−3.38 (m, 2H), 3.53−3.68 (m, 1H), 3.90 (q, J = 8.58 Hz, 1H), 4.00 (s, 3H), 4.42 (s, 1H), 4.64 (s, 2H), 7.52 (d, J = 7.72 Hz, 1H), 7.81 (t, J = 7.72 Hz, 1H), 8.03 (d, J = 7.72 Hz, 1H). MS (ESI) m/z 406 $(M + H)^+$.

(*S*)-*tert*-Butyl 2-(3-((6-(2-Hydroxypropan-2-yl)pyridin-2-yl)methyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanoate (20). A solution of **19** (9 g, 22.2 mmol) in THF (200 mL) at 0 °C was treated with 3 M methylmagnesium bromide in diethyl ether (37 mL, 111 mmol). The mixture was stirred for 1.5 h at 0 °C, quenched with 10% citric acid (20 mL), and extracted with ethyl acetate. The organic layer was decanted, evaporated, and the residue was purified by chromatography on silica gel, eluting with a gradient of 20−70% ethyl acetate in hexane give the product as a gummy solid (7.2 g, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.09 (s, 9H), 1.47 (s, 9H), 1.52 (s, 6H), 3.29−3.39 (m, 2H), 3.55−3.68 (m, 1H), 3.89 (q, J = 8.46 Hz, 1H), 4.42 (s, 1H), 4.45−4.62 (m, 2H), 5.20 (s, 1H), 7.16−7.29 (m, 2H), 7.68 (t, J = 7.72 Hz, 1H). MS (ESI) m/z 406 $(M + H)^+$.

(*S*)-2-(3-((6-(2-Hydroxypropan-2-yl)pyridin-2-yl)methyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanoic Acid (8c). 20 (7.2 g, 17.8 mmol) was treated with 90% TFA in water (30 mL) at 25 °C for 3 h. The solvent was evaporated and the residue was purified by chromatography on silica gel, eluting with 5% methanol in dichloromethane to give the product as a gummy solid (7.4 g, 90% yield). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.12 (s, 9H), 1.62 (s, 6H), 3.50 (t, J = 8.09 Hz, 2H), 3.70−3.81 (m, 1H), 3.92 (q, J = 8.70 Hz, 1H), 4.38 (s, 1H), 4.70 (s, 2H), 7.65 (d, J = 7.72 Hz, 1H), 7.87 (d, J = 8.09 Hz, 1H), 8.29 (t, J = 7.91 Hz, 1H). MS (ESI) m/z 450 $(M + H)^+$.

(*S*)-2-(3-Benzyl-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanoic Acid (8d). 8d was prepared by the general procedure starting from benzaldehyde using urea cyclization method A. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.03 (s, 9H), 3.06−3.22 (m, 2H), 3.47−3.67 (m, 2H), 4.22 (s, 1H), 4.23−4.36 (m, 2H), 7.18−7.42 (m, 5H). MS (ESI) m/z 291 $(M + H)^+$.

(*S*)-3,3-Dimethyl-2-(2-oxo-3-(quinolin-4-ylmethyl)imidazolidin-1-yl)butanoic Acid (8e). 8e was prepared by the general procedure starting from 4-quinolinecarboxaldehyde using urea cyclization method B. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.06 (s, 9H), 3.30−3.42 (m, 2H), 3.56−3.78 (m, 2H), 4.26 (s, 1H), 5.03 (s, 2H), 7.83 (d, J = 5.55 Hz, 1H), 7.89−7.96 (m, 1H), 8.06−8.14 (m, 1H), 8.39 (d, J = 8.72 Hz, 1H), 8.47 (d, J = 8.33 Hz, 1H), 9.21 (d, J = 5.16 Hz, 1H). MS (ESI) m/z 342 $(M + H)^+$.

Preparation of 8f. Ethyl 2-(Pyridin-3-yl)thiazole-4-carboxylate. To a solution containing thionicotinamide (30 g, 217.1 mmol) in ethanol (540 mL) was added ethyl bromopyruvate (30.3 mL, 241.4 mmol), and the mixture was heated to 70 °C for 3 h. The mixture was cooled to room temperature and evaporated. The mixture was partitioned between chloroform and saturated $NaHCO_3$, and the organic was washed with brine and dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica gel, eluting with a gradient of 0−15% methanol in chloroform containing 1% NH_4OH to give the product (36.3 g, 71% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.44 (t, J = 7.17 Hz, 3H), 4.47 (q, J = 7.35 Hz, 2H), 7.42 (dd, J = 8.46, 4.41 Hz, 1H), 8.23 (s, 1H), 8.31−8.40 (m, 1H), 8.70 (dd, J = 4.96, 1.65 Hz, 1H), 9.20 (d, J = 1.47 Hz, 1H). MS (ESI) m/z 235 $(M + H)^+$.

2-(Pyridin-3-yl)thiazole-4-carbaldehyde. To a solution containing ethyl 2-(pyridin-3-yl)thiazole-4-carboxylate (20 g, 85.5 mmol) in dichloromethane (340 mL) was added DIBAL (86 mL, 1 M in dichloromethane) dropwise at −78 °C, and the mixture was stirred at −78 °C for 2 h. Additional DIBAL (43 mL, 1 M in dichloromethane) was added, and the mixture was stirred at −78 °C for 1 h. Methanol (20 mL) was added at −78 °C, and the mixture was warmed to room temperature. Dichloromethane (250 mL), a saturated solution of aqueous sodium potassium tartrate (350 mL), and pH 7 buffer (300 mL) were added, and the mixture was stirred vigorously with a mechanical stirrer for 16 h. The mixture was filtered through Celite, and the layers were separated. The aqueous was washed with chloroform, and the combined organics were washed with brine and dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica gel, eluting with a gradient of 0−4% methanol in chloroform to give the product (11.61 g, 71% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.45 (dd, J = 8.09, 4.78 Hz, 1H), 8.24 (s, 1H), 8.29−8.42 (m, 1H), 8.67−8.81 (m, 1H), 9.22 (d, J = 2.57 Hz, 1H), 10.13 (s, 1H). MS (ESI) m/z 191 $(M + H)^+$.

(*S*)-3,3-Dimethyl-2-(2-oxo-3-((2-(pyridin-3-yl)thiazol-4-yl)methyl)imidazolidin-1-yl)butanoic Acid (8f). 8f was prepared by the general procedure starting from 2-(pyridin-3-yl)thiazole-4-carbaldehyde using urea cyclization method B. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.04 (s, 9H), 3.31−3.44 (m, 2H), 3.50−3.76 (m, 2H), 4.22 (s, 1H), 4.48 (s, 2H), 7.65 (s, 1H), 7.74 (dd, J = 7.93, 5.16 Hz, 1H), 8.52 (d, J = 7.93 Hz, 1H), 8.76 (d, J = 5.16 Hz, 1H), 9.20 (d, J = 1.98 Hz, 1H). MS (ESI) m/z 375 $(M + H)^+$.

(*S*)-3,3-Dimethyl-2-(3-((1-methyl-1*H*-benzo[*d*]imidazol-2-yl)methyl)-2-oxoimidazolidin-1-yl)butanoic Acid (8g). 8g was prepared by the general procedure from 1-methyl-2-formylbenzimidazole using urea cyclization method A. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.35 (s, 9H), 2.66−2.80 (m, 2H), 2.89−3.00 (m, 1H), 3.01−3.12 (m, 1H), 3.27 (s, 3H), 3.53 (s, 1H), 4.11−4.27 (m, 2H), 6.83−6.96 (m, 2H), 7.09−7.17 (m, 1H), 7.21−7.30 (m, 1H). MS (ESI) m/z 345 $(M + H)^+$.

(*S*)-3,3-Dimethyl-2-(3-(2-nitrobenzyl)-2-oxoimidazolidin-1-yl)butanoic Acid (8h). 8h was prepared by the general procedure starting from 2-nitrobenzaldehyde using urea cyclization method A. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.15 (s, 9H), 3.40−3.52 (m, 2H), 3.68−3.77 (m, 1H), 3.89−4.03 (m, 1H), 4.50 (s, 1H), 4.70−4.88 (m, 2H), 7.41−7.52 (m, 2H), 7.59−7.67 (m, 1H), 8.03 (d, J = 8.09 Hz, 1H). MS (ESI) m/z 336 $(M + H)^+$.

(*S*)-3,3-Dimethyl-2-(3-(4-nitrobenzyl)-2-oxoimidazolidin-1-yl)butanoic Acid (8i). 8i was prepared by the general procedure starting from 4-nitrobenzaldehyde using urea cyclization method A. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.04 (s, 9H), 3.16−3.29 (m, 2H), 3.52−3.73 (m, 2H), 4.22 (s, 1H), 4.43 (s, 2H), 7.51 (d, J = 8.72 Hz, 2H), 8.22 (d, J = 8.72 Hz, 2H). MS (ESI) m/z 336 $(M + H)^+$.

(*S*)-2-(3-(2-Methoxybenzyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanoic Acid (8j). 8j was prepared by the general procedure starting from *o*-anisaldehyde using urea cyclization method A. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.03 (s, 9H), 3.04−3.28 (m, 2H), 3.47−3.68 (m, 2H), 4.20 (s, 1H), 4.27 (s, 2H), 6.91 (t, J = 7.54 Hz, 1H), 7.00 (d, J = 8.46 Hz, 1H), 7.12 (d, J = 7.35 Hz, 1H), 7.21−7.32 (m, 1H). MS (ESI) m/z 321 $(M + H)^+$.

(*S*)-2-(3-(3-Methoxybenzyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanoic Acid (8k). 8k was prepared by the general procedure starting from *m*-anisaldehyde using urea cyclization method A. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.03 (s, 9H), 3.02−3.25 (m,

2H), 3.46−3.68 (m, 2H), 3.73 (s, 3H), 4.19−4.34 (m, 2H), 4.22 (s, 1H), 6.73−6.88 (m, 3H), 7.25 (t, J = 7.93 Hz, 1H). MS (ESI) m/z 321 $(M + H)^+$.

(*S*)-2-(3-(2-Fluorobenzyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanoic Acid (8l). 8l was prepared by the general procedure starting from 2-fluorobenzaldehyde using urea cyclization method A. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.02 (s, 9H), 3.12−3.26 (m, 2H), 3.47−3.69 (m, 2H), 4.20 (s, 1H), 4.35 (s, 2H), 7.11−7.25 (m, 2H), 7.25−7.41 (m, 2H). MS (ESI) m/z 309 $(M + H)^+$.

(*S*)-2-(3-(3-Fluorobenzyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanoic Acid (8m). 8m was prepared by the general procedure starting from 3-fluorobenzaldehyde using urea cyclization method A. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.03 (s, 9H), 3.10−3.25 (m, 2H), 3.49−3.71 (m, 2H), 4.22 (s, 1H), 4.31 (s, 2H), 6.97−7.18 (m, 3H), 7.32−7.47 (m, 1H). MS (ESI) m/z 309 $(M + H)^+$.

(*S*)-2-(3-(4-Fluorobenzyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanoic Acid (8n). 8n was prepared by the general procedure starting from 4-fluorobenzaldehyde using urea cyclization method A. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.02 (s, 9H), 3.05−3.21 (m, 2H), 3.47−3.69 (m, 2H), 4.21 (s, 1H), 4.27 (s, 2H), 7.08−7.22 (m, 2H), 7.23−7.31 (m, 2H). MS (ESI) m/z 309 $(M + H)^+$.

(*S*)-3,3-Dimethyl-2-(3-(2-methylbenzyl)-2-oxoimidazolidin-1-yl)butanoic Acid (8o). 8o was prepared by the general procedure starting from *o*-tolualdehyde using urea cyclization method A. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.03 (s, 9H), 2.24 (s, 3H), 3.03−3.23 (m, 2H), 3.44−3.71 (m, 2H), 4.22 (s, 1H), 4.28 (s, 2H), 7.14−7.21 (m, 4H). MS (ESI) m/z 305 $(M + H)^+$.

(*S*)-3,3-Dimethyl-2-(3-(3-methylbenzyl)-2-oxoimidazolidin-1-yl)butanoic Acid (8p). 8p was prepared by the general procedure starting from *m*-tolualdehyde using urea cyclization method A. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.03 (s, 9H), 2.28 (s, 3H), 3.04−3.25 (m, 2H), 3.45−3.67 (m, 2H), 4.22 (s, 1H), 4.25 (d, J = 2.38 Hz, 2H), 6.97−7.12 (m, 3H), 7.18−7.29 (m, 1H). MS (ESI) m/z 305 $(M + H)^+$.

(*S*)-2-(3-((2-Isopropylthiazol-4-yl)methyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanoic Acid (8q). 8q was prepared by the general procedure starting from 2-isopropylthiazole-4-carbaldehyde (preparation has been described previously)[14] using urea cyclization method B. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.02 (s, 9H), 1.31 (d, J = 6.99 Hz, 6H), 3.19−3.35 (m, 3H), 3.45−3.71 (m, 2H), 4.19 (s, 1H), 4.25−4.40 (m, 2H), 7.25 (s, 1H). MS (ESI) m/z 340 $(M + H)^+$.

Preparation of 8r. (*S*)-*tert*-Butyl 2-(3-((6-Acetylpyridin-2-yl)methyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanoate (21). A solution of **19** (1.95 g, 4.815 mmol) in THF (50 mL) at −78 °C was treated with methylmagnesium bromide in butyl ether (5.7 mL, 1 M). The mixture was stirred for 0.5 h at −78 °C, quenched with acetone (3 mL) and 10% citric acid. The mixture was partitioned between ethyl acetate and 1 N $NaHCO_3$, and the organic layer was decanted and evaporated. The residue was purified by chromatography on silica gel, eluting with a gradient of 25−50% ethyl acetate in hexane to give the product (1.6 g, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.10 (s, 9H), 1.48 (s, 9H), 2.70 (s, 3H), 3.33−3.49 (m, 2H), 3.56−3.77 (m, 1H), 3.94 (q, J = 8.46 Hz, 1H), 4.43 (s, 1H), 4.52−4.73 (m, 2H), 7.46 (d, J = 7.72 Hz, 1H), 7.79 (t, J = 7.54 Hz, 1H), 7.92 (d, J = 7.72 Hz, 1H). MS (ESI) m/z 390 $(M + H)^+$.

(*S*)-*tert*-Butyl 3,3-Dimethyl-2-(2-oxo-3-((6-(prop-1-en-2-yl)pyridin-2-yl)methyl)imidazolidin-1-yl)butanoate (22). To a solution of methyltriphenylphosphonium bromide (0.33 g, 0.923 mmol) in THF (2.5 mL) was added a solution of potassium *tert*-butoxide in THF (0.89 mL, 1 M) dropwise, and the mixture was stirred for 1 h at room temperature. A solution of **21** (0.116 g, 0.298 mmol) in THF (2 mL) was then added, and the mixture was stirred at room temperature for 30 min. The reaction was quenched with saturated NH_4Cl solution and partitioned between ethyl acetate and water, and the organic was washed with brine and dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica gel, eluting with a gradient of 15−25% ethyl acetate in hexane to give the product (0.040 g, 35% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.09 (s, 9 H), 1.47 (s, 9H), 2.20 (s, 3H), 3.34−3.43 (m, 2H), 3.55−3.67 (m, 1H), 3.88 (q, J = 8.46 Hz, 1H), 4.43 (s, 1H), 4.46−4.62 (m, 2H), 5.24−5.31 (m, 1H), 5.86−5.92 (m, 1H), 7.15 (d, J = 7.72 Hz, 1H), 7.34 (d, J = 7.72 Hz, 1H), 7.61 (t, J = 7.72 Hz, 1H). MS (ESI) m/z 388 $(M + H)^+$.

(*S*)-*tert*-Butyl 2-(3-((6-isopropylpyridin-2-yl)methyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanoate (23). To a solution containing **22** (0.038 g, 0.098 mmol) in methanol (1 mL) was added 10% Pd on carbon (0.005 g), and the mixture was stirred under an atmosphere of hydrogen (balloon pressure) for 2 h. The reaction was filtered, and the solvent was evaporated to give the product, which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.09 (s, 9H), 1.28 (d, J = 6.99 Hz, 6H), 1.47 (s, 9H), 2.95−3.10 (m, 1H), 3.32−3.40 (m, 2H), 3.56−3.65 (m, 1H), 3.87 (q, J = 8.46 Hz, 1H), 4.43 (s, 1H), 4.44−4.58 (m, 2H), 7.04 (d, J = 8.09 Hz, 1H), 7.07 (d, J = 7.72 Hz, 1H), 7.56 (t, J = 7.72 Hz, 1H). MS (ESI) m/z 390 $(M + H)^+$.

(*S*)-2-(3-((6-Isopropylpyridin-2-yl)methyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanoic Acid (8r). 8r was prepared from **23** by the general procedure for *tert*-butyl ester hydrolysis using TFA. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.11 (s, 9H), 1.41 (d, J = 6.99 Hz, 6H), 3.41−3.59 (m, 3H), 3.64−3.78 (m, 1H), 3.92 (q, J = 8.46 Hz, 1H), 4.39 (s, 1H), 4.70−4.93 (m, 2H), 7.64 (d, J = 8.09 Hz, 1H), 7.74 (d, J = 7.72 Hz, 1H), 8.32 (t, J = 7.91 Hz, 1H). MS (ESI) m/z 334 $(M + H)^+$.

(*S*)-2-(3-((6-*tert*-Butylpyridin-2-yl)methyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanoic Acid (8s). 8s was prepared by the general procedure starting from 6-*tert*-butylpicolinaldehyde (preparation has been described previously)[23] using urea cyclization method A. *tert*-Butyl ester: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.08 (s, 9H), 1.33 (s, 9H), 1.47 (s, 9H), 3.40 (t, J = 7.91 Hz, 2H), 3.54−3.67 (m, 1H), 3.86 (q, J = 8.70 Hz, 1H), 4.39−4.56 (m, 2H), 4.42 (s, 1H), 7.04 (d, J = 7.72 Hz, 1H), 7.18 (d, J = 8.09 Hz, 1H), 7.54 (t, J = 7.72 Hz, 1H). MS (ESI) m/z 404 $(M + H)^+$.

General Procedure for Preparation of Compounds 9a−p, 10a−i, 18a−h. Preparation of Methyl (*S*)-1-((2*S*,4*S*,5*S*)-5-((*S*)-3,3-Dimethyl-2-(3-((6-methylpyridin-2-yl)methyl)-2-oxoimidazolidin-1-yl)butanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (9a). To a solution containing **6b** (1.0 g, 1.88 mmol) in THF (19 mL) were added **8a** (0.83 g, 1.98 mmol), DEPBT (0.84 g, 2.8 mmol), and *N*,*N*-diisopropylethylamine (1.6 mL, 9.2 mmol), and the mixture was stirred at room temperature for 16 h. The mixture was partitioned between a mixture of dichloromethane and ethyl acetate (2:1, respectively) and 10% Na_2CO_3 solution. The organic was washed with additional 10% Na_2CO_3 solution and then brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica gel, eluting with a gradient of 0−100% ethyl acetate in dichloromethane, followed by elution with a gradient of 0−5% methanol in ethyl acetate to give the product as a white solid (1.15 g, 75% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83 (s, 9H), 0.90 (s, 9H), 1.55 (m, 2H), 2.38 (q, J = 9.44 Hz, 1H), 2.46 (s, 3H), 2.57 (m, 1H), 2.67 (d, J = 7.35 Hz, 2H), 2.79 (m, 1H), 2.97 (m, 1H), 3.09 (q, J = 8.95 Hz, 1H), 3.21 (m, 1H), 3.50 (s, 3H), 3.67 (m, 1H), 3.85 (d, J = 9.93 Hz, 1H), 4.12 (m, 3H), 4.35 (m, 2H), 4.54 (d, J = 7.72 Hz, 1H), 6.63 (d, J = 9.56 Hz, 1H), 7.09 (m, 7H), 7.22 (d, J = 8.09 Hz, 2H), 7.31 (m, 1H), 7.49 (d, J = 9.56 Hz, 1H), 7.69 (t, J = 7.54 Hz, 1H), 7.86 (m, 5H), 8.63 (d, J = 4.78 Hz, 1H). MS (ESI) m/z 820 $(M + H)^+$.

Compounds **9b−p**, **10a−i, 18a−h** were prepared by the above procedure, substituting **7b** and **17b** for **6b** as appropriate and coupling with the appropriate carboxylic acid **8a−s**.

Methyl (*S*)-1-((2*S*,3*S*,5*S*)-5-((*S*)-3,3-Dimethyl-2-(3-((6-methylpyridin-2-yl)methyl)-2-oxoimidazolidin-1-yl)butanamido)-3-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (18a). Yield 54%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83 (s, 9H), 0.86 (s, 9H), 1.25 (m, 1H), 1.53 (m, 2H), 2.41 (m, 1H), 2.46 (m, 3H), 2.66 (d, J = 10.66 Hz, 1H), 2.78 (d, J = 6.99 Hz, 2H), 2.96 (m, 1H), 3.07 (q, J = 8.70 Hz, 1H), 3.24 (m, 1H), 3.51 (s, 3H), 3.62 (m, 1H), 3.96 (m, 2H), 4.19 (m, 2H), 4.34 (m, 2H), 4.83 (d, J = 5.52 Hz, 1H), 6.79 (d, J = 9.56 Hz, 1H), 7.05 (m, 6H), 7.15 (d, J = 7.35

Hz, 1H), 7.30 (m, 3H), 7.58 (d, J = 9.19 Hz, 1H), 7.68 (t, J = 7.72 Hz, 1H), 7.86 (m, 5H), 8.63 (d, J = 4.78 Hz, 1H). HRMS (ESI) m/z calcd for $C_{47}H_{61}N_7O_6$ 820.4756; found 820.4756 ($\Delta \leq$ 0.1 ppm). Anal. ($C_{47}H_{61}N_7O_6$) C, H, N.

Methyl (*S*)-1-((2*R*,4*S*,5*S*)-5-((*S*)-3,3-Dimethyl-2-(3-((6-methylpyridin-2-yl)methyl)-2-oxoimidazolidin-1-yl)butanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (10a). Yield 65%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80 (s, 9H), 0.88 (s, 9H), 1.29 (m, 2H), 1.53 (m, 1H), 2.45 (s, 3H), 2.66 (m, 3H), 2.83 (dd, J = 13.79, 6.07 Hz, 1H), 3.03 (m, 2H), 3.23 (m, 1H), 3.53 (m, 4H), 3.84 (d, J = 9.56 Hz, 1H), 4.01 (m, 2H), 4.16 (m, 1H), 4.34 (m, 2H), 4.44 (d, J = 6.99 Hz, 1H), 6.88 (d, J = 9.56 Hz, 1H), 7.09 (m, 7H), 7.24 (d, J = 8.09 Hz, 2H), 7.32 (m, 1H), 7.54 (d, J = 9.56 Hz, 1H), 7.67 (t, J = 7.72 Hz, 1H), 7.89 (m, 5H), 8.64 (d, J = 4.04 Hz, 1H). MS (ESI) m/z 820 (M + H)$^+$.

Methyl (*S*)-1-((2*S*,4*S*,5*S*)-5-((*S*)-3,3-Dimethyl-2-(3-((2-methylthiazol-4-yl)methyl)-2-oxoimidazolidin-1-yl)butanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (9b). Yield 83%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83 (s, 9H), 0.88 (s, 9H), 1.54 (m, 2H), 2.36 (q, J = 9.31 Hz, 1H), 2.61 (m, 5H), 2.78 (m, 1H), 3.01 (m, 2H), 3.22 (m, 2H), 3.50 (s, 3H), 3.66 (m, 1H), 3.85 (d, J = 9.56 Hz, 1H), 4.17 (m, 4H), 4.41 (m, 1H), 4.54 (d, J = 7.35 Hz, 1H), 6.63 (d, J = 9.56 Hz, 1H), 7.06 (m, 5H), 7.21 (s, 1H), 7.24 (s, 2H), 7.31 (m, 1H), 7.45 (d, J = 9.56 Hz, 1H), 7.87 (m, 5H), 8.63 (d, J = 4.41 Hz, 1H). MS (ESI) m/z 826 (M + H)$^+$.

Methyl (*S*)-1-((2*S*,3*S*,5*S*)-5-((*S*)-3,3-Dimethyl-2-(3-((2-methylthiazol-4-yl)methyl)-2-oxoimidazolidin-1-yl)butanamido)-3-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (18b). Yield 70%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (s, 9H), 0.86 (s, 9H), 1.53 (m, 2H), 2.39 (m, 2H), 2.64 (m, 4H), 2.77 (d, J = 6.62 Hz, 2H), 3.00 (m, 2H), 3.19 (m, 1H), 3.51 (s, 3H), 3.61 (m, 1H), 3.96 (m, 2H), 4.32 (m, 4H), 4.82 (d, J = 5.52 Hz, 1H), 6.79 (d, J = 9.56 Hz, 1H), 7.04 (m, 5H), 7.21 (s, 1H), 7.30 (m, 3H), 7.58 (d, J = 8.82 Hz, 1H), 7.87 (m, 5H), 8.63 (d, J = 4.78 Hz, 1H). MS (ESI) m/z 826 (M + H)$^+$.

Methyl (*S*)-1-((2*R*,4*S*,5*S*)-5-((*S*)-3,3-Dimethyl-2-(3-((2-methylthiazol-4-yl)methyl)-2-oxoimidazolidin-1-yl)butanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (10b). Yield 94%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80 (s, 9H), 0.89 (s, 9H), 1.38 (m, 1H), 1.53 (m, 1H), 2.43 (m, 1H), 2.63 (m, 6H), 2.83 (m, 1H), 3.03 (m, 2H), 3.20 (m, 1H), 3.53 (m, 4H), 3.94 (m, 3H), 4.36 (m, 4H), 6.88 (d, J = 9.56 Hz, 1H), 7.05 (m, 5H), 7.24 (m, 3H), 7.32 (m, 1H), 7.51 (d, J = 9.56 Hz, 1H), 7.89 (m, 5H), 8.65 (d, J = 4.78 Hz, 1H). MS (ESI) m/z 826 (M + H)$^+$.

Methyl (*S*)-1-((2*S*,4*S*,5*S*)-4-Hydroxy-5-((*S*)-2-(3-((6-(2-hydroxypropan-2-yl)pyridin-2-yl)methyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanamido)-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (9c). Yield 86%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83 (s, 9H), 0.90 (s, 9H), 1.43 (d, J = 5.15 Hz, 6H), 1.53 (m, 2H), 2.36 (m, 1H), 2.65 (m, 3H), 2.79 (m, 1H), 2.99 (m, 1H), 3.20 (m, 3H), 3.50 (s, 3H), 3.65 (m, 1H), 3.85 (d, J = 9.93 Hz, 1H), 4.05 (m, 3H), 4.45 (m, 3H), 6.63 (d, J = 9.93 Hz, 1H), 7.08 (m, 6H), 7.22 (d, J = 8.09 Hz, 2H), 7.31 (m, 1H), 7.46 (d, J = 9.56 Hz, 1H), 7.54 (d, J = 7.72 Hz, 1H), 7.83 (m, 6H), 8.64 (d, J = 4.78 Hz, 1H). MS (ESI) m/z 864 (M + H)$^+$.

Methyl (*S*)-1-((2*S*,3*S*,5*S*)-3-Hydroxy-5-((*S*)-2-(3-((6-(2-hydroxypropan-2-yl)pyridin-2-yl)methyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanamido)-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (18c). Yield 64%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.82 (s, 9H), 0.86 (s, 9H), 1.42 (d, J = 4.78 Hz, 6H), 1.55 (m, 2H), 2.39 (m, 2H), 2.65 (d, J = 13.24 Hz, 1H), 2.78 (d, J = 6.25 Hz, 2H), 2.98 (m, 1H), 3.20 (m, 3H), 3.51 (s, 3H), 3.61 (m, 1H), 3.98 (m, 2H), 4.19 (m, 2H), 4.39 (m, 2H), 4.82 (d, J = 5.52 Hz, 1H), 6.78 (d, J = 9.19 Hz, 1H), 7.06 (m, 6H), 7.31 (m, 3H), 7.55 (m, 2H), 7.76 (t, J = 7.72 Hz, 1H), 7.86 (m, 5H), 8.63 (d, J = 4.04 Hz, 1H). MS (ESI) m/z 864 (M + H)$^+$.

Methyl (*S*)-1-((2*R*,4*S*,5*S*)-4-Hydroxy-5-((*S*)-2-(3-((6-(2-hydroxypropan-2-yl)pyridin-2-yl)methyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanamido)-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (10c). Yield 84%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80 (s, 9H), 0.88 (s, 9H), 1.39 (m, 10H), 2.64 (m, 3H), 2.83 (m, 1H), 3.01 (m, 1H), 3.20 (m, 2H), 3.54 (m, 4H), 3.83 (d, J = 9.56 Hz, 1H), 3.93 (m, 1H), 4.02 (s, 1H), 4.17 (m, 1H), 4.39 (m, 3H), 6.87 (d, J = 10.30 Hz, 1H), 7.08 (m, 6H), 7.24 (d, J = 8.46 Hz, 2H), 7.32 (m, 1H), 7.52 (m, 2H), 7.75 (t, J = 7.72 Hz, 1H), 7.89 (m, 5H), 8.64 (d, J = 4.78 Hz, 1H). MS (ESI) 864 m/z (M + H)$^+$. Anal. ($C_{49}H_{65}N_7O_7$) C, H, N.

Methyl (*S*)-1-((2*S*,4*S*,5*S*)-5-((*S*)-2-(3-Benzyl-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (9d). Yield 73%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83 (s, 9H), 0.89 (s, 9H), 1.56 (m, 2H), 2.33 (q, J = 9.07 Hz, 1H), 2.82 (m, 5H), 3.19 (m, 2H), 3.50 (s, 3H), 3.67 (m, 1H), 3.85 (d, J = 9.93 Hz, 1H), 4.09 (s, 1H), 4.19 (m, 2H), 4.31 (s, 2H), 4.55 (d, J = 7.72 Hz, 1H), 6.63 (d, J = 9.56 Hz, 1H), 7.07 (m, 5H), 7.31 (m, 8H), 7.47 (d, J = 9.56 Hz, 1H), 7.87 (m, 5H), 8.63 (d, J = 4.78 Hz, 1H). HRMS (ESI) m/z calcd for $C_{47}H_{60}N_6O_6$ 805.4647; found 805.4646 (Δ = 0.1 ppm). Anal. ($C_{47}H_{60}N_6O_6$) C, H, N.

Methyl (*S*)-1-((2*S*,3*S*,5*S*)-5-((*S*)-2-(3-Benzyl-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanamido)-3-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (18d). Yield 30%, white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.00 (s, 9H), 1.27 (m, 1H), 2.62 (dd, J = 13.79, 8.64 Hz, 1H), 2.85 (m, 5H), 3.03 (q, J = 8.58 Hz, 1H), 3.39 (m, 1H), 3.64 (m, 4H), 3.82 (d, J = 9.19 Hz, 1H), 3.94 (m, 1H), 4.00 (s, 1H), 4.11 (m, 2H), 4.35 (m, 2H), 5.31 (m, 1H), 6.13 (m, 2H), 7.10 (m, 5H), 7.21 (m, 2H), 7.33 (m, 7H), 7.74 (m, 2H), 7.89 (d, J = 8.46 Hz, 2H), 8.68 (d, J = 4.78 Hz, 1H). MS (ESI) m/z 805 (M + H)$^+$.

Methyl (*S*)-1-((2*R*,4*S*,5*S*)-5-((*S*)-2-(3-Benzyl-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (10d). Yield 73%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80 (s, 9H), 0.87 (s, 9H), 1.38 (t, J = 11.58 Hz, 1H), 1.54 (m, 1H), 2.41 (m, 1H), 2.64 (m, 3H), 2.87 (m, 3H), 3.19 (m, 1H), 3.53 (m, 4 H), 3.84 (d, J = 9.56 Hz, 1H), 3.95 (m, 1H), 4.04 (s, 1H), 4.18 (m, 1H), 4.29 (m, 2H), 4.45 (d, J = 7.35 Hz, 1H), 6.88 (d, J = 9.56 Hz, 1H), 7.05 (m, 5H), 7.30 (m, 8H), 7.53 (d, J = 9.56 Hz, 1H), 7.90 (m, 5H), 8.65 (d, J = 4.41 Hz, 1H). MS (ESI) m/z 805 (M + H)$^+$.

Methyl (*S*)-1-((2*S*,4*S*,5*S*)-5-((*S*)-3,3-Dimethyl-2-(2-oxo-3-(quinolin-4-ylmethyl)imidazolidin-1-yl)butanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (9e). Yield 67%, white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.82 (s, 9H), 0.90 (s, 9H), 1.45−1.64 (m, 2H), 2.16−2.32 (m, 1H), 2.54−2.69 (m, 3H), 2.78 (d, J = 10.25 Hz, 1H), 2.85 (dd, J = 8.06, 5.62 Hz, 1H), 3.00 (q, J = 8.30 Hz, 1H), 3.14−3.22 (m, 1H), 3.49 (s, 3H), 3.65 (d, J = 6.35 Hz, 1H), 3.84 (d, J = 8.79 Hz, 1H), 4.03−4.31 (m, 3H), 4.52 (d, J = 7.32 Hz, 1H), 4.64 (d, J = 15.63 Hz, 1H), 4.94 (d, J = 15.63 Hz, 1H), 6.58 (d, J = 8.79 Hz, 1H), 6.76−6.85 (m, 2H), 6.90 (t, J = 7.08 Hz, 1H), 6.96 (d, J = 7.32 Hz, 2H), 7.09−7.35 (m, 5H), 7.39−7.49 (m, 2H), 7.63 (t, J = 7.57 Hz, 1H), 7.72−7.95 (m, 7H), 8.06 (d, J = 7.81 Hz, 1H), 8.31 (d, J = 8.30 Hz, 1H), 8.62 (d, J = 3.42 Hz, 1H), 8.90 (d, J = 4.39 Hz, 1H). MS (ESI) m/z 856 (M + H)$^+$.

Methyl (*S*)-1-((2*S*,3*S*,5*S*)-5-((*S*)-3,3-Dimethyl-2-(2-oxo-3-(quinolin-4-ylmethyl)imidazolidin-1-yl)butanamido)-3-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (18e). Yield 37%, white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.83 (s, 9H), 0.85 (s, 9H), 1.61−1.50 (m, 2H), 2.41−2.31 (m, 2H), 2.69−2.59 (m, 1H), 2.78 (bs, 2H), 2.88 (m, 1H), 3.03−2.95 (m, 1H), 3.23−3.14 (m, 1H), 3.50 (s, 3H),

3.61 (m, 1H), 3.94 (m, 1H), 4.00 (s, 1H), 4.18 (m, 2H), 4.65 (d, J = 15.14 Hz, 1H), 4.81 (bs, 1H), 4.91 (d, J = 15.63 Hz, 1H), 6.87−6.73 (m, 4H), 6.96 (m, 2H), 7.29 (m, 3 H), 7.41 (bs, 1H), 7.61−7.54 (m, 2H), 7.89−7.77 (m, 5H), 8.05 (d, J = 7.81 Hz, 1H), 8.29 (d, J = 7.32 Hz, 1H), 8.62 (bs, 1H), 8.89 (bs, 1H). MS (ESI) m/z 856 $(M + H)^+$.

Methyl (*S*)-1-((2*R*,4*S*,5*S*)-5-((*S*)-3,3-Dimethyl-2-(2-oxo-3-(quinolin-4-ylmethyl)imidazolidin-1-yl)butanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (10e). Yield 65%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (s, 9H), 0.89 (s, 9H), 1.26 (m, 1H), 1.37 (m, 1H), 1.53 (m, 1H), 2.30 (m, 1H), 2.65 (m, 2H), 2.85 (m, 2H), 3.00 (m, 1H), 3.18 (m, 1H), 3.53 (m, 4H), 3.84 (d, J = 9.56 Hz, 1H), 3.94 (m, 1H), 4.05 (m, 1H), 4.19 (m, 1H), 4.44 (d, J = 7.35 Hz, 1H), 4.63 (d, J = 15.44 Hz, 1H), 4.95 (d, J = 15.44 Hz, 1H), 6.87 (m, 6H), 7.25 (d, J = 8.46 Hz, 2H), 7.32 (m, 1H), 7.43 (d, J = 4.41 Hz, 1H), 7.60 (m, 2H), 7.86 (m, 6H), 8.06 (d, J = 7.72 Hz, 1H), 8.30 (d, J = 8.09 Hz, 1H), 8.65 (m, 1H), 8.90 (d, J = 4.04 Hz, 1H). MS (ESI) m/z 856 $(M + H)^+$.

Methyl (*S*)-1-((2*S*,4*S*,5*S*)-5-((*S*)-3,3-Dimethyl-2-(2-oxo-3-((2-(pyridin-3-yl)thiazol-4-yl)methyl)imidazolidin-1-yl)butanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (9f). Yield 70%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83 (s, 9H), 0.89 (s, 9H), 1.54 (m, 2H), 2.34 (m, 1H), 2.63 (m, 2H), 2.79 (m, 1H), 3.16 (m, 4H), 3.50 (s, 3H), 3.65 (m, 1H), 3.85 (d, J = 9.93 Hz, 1H), 4.14 (m, 3H), 4.50 (m, 3H), 6.63 (d, J = 9.56 Hz, 1H), 6.98 (m, 1H), 7.06 (m, 4H), 7.22 (d, J = 8.09 Hz, 2H), 7.31 (m, 1H), 7.52 (m, 2H), 7.61 (s, 1H), 7.87 (m, 5H), 8.31 (m, 1H), 8.65 (m, 2H), 9.14 (d, J = 1.84 Hz, 1H). MS (ESI) m/z 889 $(M + H)^+$.

Methyl (*S*)-1-((2*S*,3*S*,5*S*)-5-((*S*)-3,3-Dimethyl-2-(2-oxo-3-((2-(pyridin-3-yl)thiazol-4-yl)methyl)imidazolidin-1-yl)butanamido)-3-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (18f). Yield 50%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.82 (s, 9H), 0.86 (s, 9H), 1.53 (m, 2H), 2.40 (m, 1H), 2.64 (d, J = 13.97 Hz, 1H), 2.77 (d, J = 6.62 Hz, 2H), 3.15 (m, 4H), 3.51 (s, 3H), 3.62 (m, 1H), 3.96 (m, 2H), 4.18 (m, 2H), 4.47 (m, 2H), 4.82 (d, J = 5.52 Hz, 1H), 6.79 (d, J = 9.56 Hz, 1H), 6.95 (m, 1H), 7.03 (m, 4H), 7.30 (m, 3H), 7.54 (m, 3H), 7.87 (m, 5H), 8.30 (m, 1H), 8.65 (m, 2H), 9.14 (d, J = 1.47 Hz, 1H). MS (ESI) m/z 889 $(M + H)^+$.

Methyl (*S*)-1-((2*R*,4*S*,5*S*)-5-((*S*)-3,3-Dimethyl-2-(2-oxo-3-((2-(pyridin-3-yl)thiazol-4-yl)methyl)imidazolidin-1-yl)butanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (10f). Yield 78%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80 (s, 9H), 0.88 (s, 9H), 1.46 (m, 2H), 2.44 (d, J = 8.82 Hz, 1H), 2.63 (m, 3H), 2.83 (m, 1H), 3.15 (m, 3H), 3.54 (m, 4H), 3.84 (d, J = 9.56 Hz, 1H), 3.93 (m, 1H), 4.04 (s, 1H), 4.18 (m, 1H), 4.46 (m, 3H), 6.88 (d, J = 9.56 Hz, 1H), 6.96 (m, 1H), 7.06 (m, 4H), 7.24 (d, J = 8.46 Hz, 2H), 7.32 (m, 1H), 7.53 (m, 2H), 7.60 (s, 1H), 7.89 (m, 5H), 8.29 (m, 1H), 8.65 (m, 2H), 9.13 (d, J = 1.47 Hz, 1H). MS (ESI) m/z 889 $(M + H)^+$.

Methyl (*S*)-1-((2*S*,4*S*,5*S*)-5-((*S*)-3,3-Dimethyl-2-(3-((1-methyl-1*H*-benzo[*d*]imidazol-2-yl)methyl)-2-oxoimidazolidin-1-yl)butanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (9g). Yield 14%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83 (s, 9H), 0.89 (s, 9H), 1.26 (m, 1H), 1.52 (m, 2H), 2.32 (m, 1H), 2.70 (m, 4H), 2.98 (m, 1H), 3.09 (m, 2H), 3.46 (s, 1H), 3.50 (s, 3H), 3.81 (s, 3H), 4.15 (m, 3H), 4.53 (dd, J = 11.40, 3.68 Hz, 2H), 4.70 (d, J = 15.44 Hz, 1H), 6.63 (d, J = 9.56 Hz, 1H), 6.93 (m, 3H), 7.07 (d, J = 6.62 Hz, 2H), 7.24 (m, 6H), 7.59 (m, 3H), 7.88 (m, 4H), 8.63 (d, J = 3.31 Hz, 1H). MS (ESI) m/z 859 $(M + H)^+$.

Methyl (*S*)-1-((2*S*,3*S*,5*S*)-5-((*S*)-3,3-Dimethyl-2-(3-((1-methyl-1*H*-benzo[*d*]imidazol-2-yl)methyl)-2-oxoimidazolidin-1-yl)butanamido)-3-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (18g). Yield 51%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.82 (s, 9H), 0.86 (s, 9H), 1.27 (m, 1H), 1.53 (m, 2H), 2.36 (m, 2H), 2.72 (m, 3H), 2.98 (m, 1H), 3.10 (m, 1H), 3.48 (d, J = 13.97 Hz, 3H), 3.61 (m, 1H), 3.80 (s, 3H), 3.93 (m, 2H), 4.16 (m, 2H), 4.60 (m, 2H), 4.83 (d, J = 5.52 Hz, 1H), 6.91 (m, 4H), 7.02 (m, 2H), 7.20 (m, 2H), 7.29 (m, 3H), 7.58 (m, 3H), 7.87 (m, 5H), 8.63 (d, J = 4.78 Hz, 1H). MS (ESI) m/z 859 $(M + H)^+$.

Methyl (*S*)-1-((2*R*,4*S*,5*S*)-5-((*S*)-3,3-Dimethyl-2-(3-((1-methyl-1*H*-benzo[*d*]imidazol-2-yl)methyl)-2-oxoimidazolidin-1-yl)butanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (10g). Yield 50%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (s, 9H), 0.88 (s, 9H), 1.38 (m, 1H), 1.53 (m, 1H), 2.40 (m, 1H), 2.64 (m, 3H), 2.83 (m, 1H), 3.12 (m, 4H), 3.54 (m, 4H), 3.82 (m, 3H), 3.95 (m, 1H), 4.03 (s, 1H), 4.18 (m, 1H), 4.43 (d, J = 6.99 Hz, 1H), 4.60 (m, 2H), 6.92 (m, 4H), 7.04 (m, 2H), 7.21 (m, 4H), 7.32 (m, 1H), 7.58 (m, 3H), 7.89 (m, 5H), 8.65 (d, J = 4.41 Hz, 1H). MS (ESI) m/z 859 $(M + H)^+$.

Methyl (*S*)-1-((2*S*,4*S*,5*S*)-5-((*S*)-2-(3-(2-Aminobenzyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (9h). Compounds **6b** and **8h**were coupled under the standard conditions to give the 2-nitro product (61% yield), which was hydrogenated using the procedure for **23** to give **9h** (0.014 g, 55% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.84 (s, 9H), 0.86 (s, 9H), 1.63−1.46 (m, 2H), 2.16−2.07 (m, 1H), 2.65−2.54 (m, 3H), 3.00−2.74 (m, 3H), 3.18−3.08 (m, 1H), 3.50 (s, 3H), 3.71−3.62 (m, 1H), 3.87−3.83 (d, J = 9.56 Hz, 1H), 4.05 (s, 1H), 4.28−4.10 (m, 4H), 4.53−4.51 (d, J = 7.72 Hz, 1H), 5.20 (s, 2H), 6.56−6.51 (t, J = 7.35 Hz, 1H), 6.68−6.64 (m, 2H), 7.08−6.92 (m, 7H), 7.24−7.21 (d, J = 8.09 Hz, 2H), 7.33−7.29 (m, 1H), 7.43−7.40 (d, J = 9.93 Hz, 1H), 7.91−7.82 (m, 5H), 8.64−8.63 (d, J = 4.41 Hz, 1H). MS (ESI) m/z 820 $(M + H)^+$.

Methyl (*S*)-1-((2*S*,4*S*,5*S*)-5-((*S*)-2-(3-(4-Aminobenzyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (9i). Compounds **6b** and **8i** were coupled under the standard conditions to give the 4-nitro product (56% yield), which was hydrogenated using the procedure for **23** to give **9i** (0.024 g, 39% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83 (s, 9H), 0.87 (s, 9H), 1.60−1.48 (m, 2H), 2.29−2.20 (m, 1H), 2.67−2.53 (m, 3H), 2.92−2.75 (m, 3H), 3.16−3.08 (m, 1H), 3.50 (s, 3H), 3.71−3.61 (m, 1H), 3.86−3.83 (d, J = 9.93 Hz, 1H), 4.07 (s, 1H), 4.11 (s, 2H), 4.23−4.09 (m, 2H), 4.56−4.53 (d, J = 7.72 Hz, 1H), 5.00 (s, 2H), 6.55−6.52 (d, J = 8.46 Hz, 2H), 6.67−6.64 (d, J = 9.93 Hz, 1H), 6.94−6.91 (d, J = 8.46 Hz, 2H), 7.10−7.02 (m, 5H), 7.23−7.21 (d, J = 8.46 Hz, 2H), 7.33−7.29 (m, 1H), 7.45−7.42 (d, J = 9.56 Hz, 1H), 7.91−7.82 (m, 5H), 8.64−8.62 (m, 1H). MS (ESI) m/z 820 $(M + H)^+$.

Methyl (*S*)-1-((2*S*,4*S*,5*S*)-4-Hydroxy-5-((*S*)-2-(3-(2-methoxybenzyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanamido)-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (9j). Yield 59%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83 (s, 9H), 0.89 (s, 9H), 1.26 (m, 1H), 1.38 (m, 1H), 1.54 (m, 2H), 2.33 (m, 1H), 2.83 (m, 5H), 3.18 (m, 1H), 3.50 (s, 3H), 3.66 (m, 1H), 3.83 (m, 4H), 4.25 (m, 4H), 4.53 (d, J = 7.72 Hz, 1H), 6.63 (d, J = 9.93 Hz, 1H), 6.95 (t, J = 6.99 Hz, 1H), 7.18 (m, 11H), 7.45 (d, J = 9.19 Hz, 1H), 7.86 (m, 5H), 8.63 (d, J = 4.41 Hz, 1H). MS (ESI) m/z 835 $(M + H)^+$.

Methyl (*S*)-1-((2*S*,4*S*,5*S*)-4-Hydroxy-5-((*S*)-2-(3-(3-methoxybenzyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanamido)-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (9k). Yield 59%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83 (s, 9H), 0.89 (s, 9H), 1.55 (m, 2H), 2.32 (m, 1H), 2.80 (m, 6H), 3.18 (m, 1H), 3.50 (s, 3H), 3.65 (m, 1H), 3.74 (s, 3H), 3.85 (d, J = 9.93 Hz, 1H), 4.20 (m, 5H), 4.54 (d, J = 7.72 Hz, 1H), 6.63 (d, J = 9.93 Hz, 1H), 6.85 (m, 3H), 7.08 (m, 5H), 7.28 (m, 4H), 7.48 (d, J = 9.56 Hz, 1H), 7.86 (m, 5H), 8.63 (d, J = 4.78 Hz, 1H). MS (ESI) m/z 835 $(M + H)^+$.

Methyl (*S*)-1-((2*S*,4*S*,5*S*)-5-((*S*)-2-(3-(2-Fluorobenzyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (9l). Yield 61%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83 (s, 9H), 0.88 (s, 9H), 1.58−1.49 (m,

2H), 2.35−2.27 (m, 1H), 2.61−2.54 (m, 1H), 2.67−2.65 (d, J = 6.99 Hz, 2H), 2.87−2.76 (m, 2H), 3.03−2.94 (q, J = 8.70 Hz, 1H), 3.20−3.16 (m, 1H), 3.50 (s, 3H), 3.70−3.63 (m, 1H), 3.86−3.83 (d, J = 9.93 Hz, 1H), 4.07 (s, 1H), 4.23−4.10 (m, 2H), 4.46−4.28 (m, 2H), 4.55−4.52 (d, J = 7.35 Hz, 1H), 6.65−6.62 (d, J = 9.56 Hz, 1H), 7.09−6.99 (m, 4H), 7.26−7.21 (m, 4H), 7.40−7.28 (m, 3H), 7.50−7.46 (d, J = 9.56 Hz, 1H), 7.91−7.82 (m, 5H), 8.64−8.63 (m, 1H). MS (ESI) m/z 823 $(M + H)^+$.

Methyl (*S*)-1-((2*S*,4*S*,5*S*)-5-((*S*)-2-(3-(3-Fluorobenzyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (9m). Yield 61%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83 (s, 9H), 0.89 (s, 9H), 1.58−1.49 (m, 2H), 2.39−2.30 (q, J = 9.19 Hz, 1H), 2.62−2.54 (m, 1H), 2.69−2.66 (d, J = 7.35 Hz, 2H), 2.90−2.77 (m, 2H), 3.02−2.93 (q, J = 8.7 Hz, 1H), 3.27−3.18 (m, 1H), 3.50 (s, 3H), 3.70−3.63 (m, 1H), 3.87−3.83 (d, J = 9.93 Hz, 1H), 4.09 (s, 1H), 4.19−4.14 (m, 2H), 4.39−4.27 (m, 2H), 4.56−4.54 (d, J = 7.72 Hz, 1H), 6.65−6.62 (d, J = 9.56 Hz, 1H), 7.15−7.04 (m, 8H), 7.24−7.21 (d, J = 8.46 Hz, 2H), 7.33−7.29 (m, 1H), 7.46−7.39 (m, 1H), 7.53−7.50 (d, J = 9.56 Hz, 1H), 7.91−7.82 (m, 4H), 8.65−8.62 (m, 1H). MS (ESI) m/z 823 $(M + H)^+$.

Methyl (*S*)-1-((2*S*,4*S*,5*S*)-5-((*S*)-2-(3-(4-Fluorobenzyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (9n). Yield 62%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83 (s, 9H), 0.88 (s, 9H), 1.58−1.49 (m, 2H), 2.37−2.28 (m, 1H), 2.61−2.54 (m, 1H), 2.68−2.66 (d, J = 7.35 Hz, 2H), 2.90−2.75 (m, 2H), 2.98−2.87 (q, J = 8.46 Hz, 1H), 3.20−3.16 (m, 1H), 3.50 (s, 3H), 3.70−3.63 (m, 1H), 3.86−3.83 (d, J = 9.93 Hz, 1H), 4.08 (s, 1H), 4.21−4.13 (m, 2H), 4.30 (s, 2H), 4.56−4.54 (d, J = 7.35 Hz, 1H), 6.65−6.62 (d, J = 9.56 Hz, 1H), 7.12−7.03 (m, 4H), 7.24−7.18 (m, 4H), 7.34−7.29 (m, 3H), 7.49−7.46 (d, J = 9.56 Hz, 1H), 7.91−7.82 (m, 5H), 8.64−8.63 (m, 1H). MS (ESI) m/z 823 $(M + H)^+$.

Methyl (*S*)-1-((2*S*,4*S*,5*S*)-5-((*S*)-3,3-Dimethyl-2-(3-(2-methylbenzyl)-2-oxoimidazolidin-1-yl)butanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (9o). Yield 49%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.83 (m, 9H), 0.89 (m, 9H), 1.62−1.48 (m, 2H), 2.31 (s, 3H), 2.34−2.24 (m, 1H), 2.62−2.53 (m, 1H), 2.68−2.65 (m, 2H), 2.84−2.73 (m, 2H), 2.97−2.88 (m, 1H), 3.22−3.12 (m, 1H), 3.50 (s, 3H), 3.70−3.62 (m, 1H), 3.87−3.83 (d, J = 9.93 Hz, 1H), 4.08 (s, 1H), 4.43−4.12 (m, 4H), 4.55−4.52 (d, J = 7.72 Hz, 1H), 6.65−6.62 (d, J = 9.56 Hz, 1H), 7.01−6.99 (m, 3H), 7.09−7.08 (m, 2H), 7.24−7.20 (m, 5H), 7.32−7.29 (m, 1H), 7.49−7.46 (d, J = 9.56 Hz, 1H), 7.91−7.82 (m, 5H), 8.64−8.63 (d, J = 4.41 Hz, 1H). MS (ESI) m/z 819 $(M + H)^+$.

Methyl (*S*)-1-((2*S*,4*S*,5*S*)-5-((*S*)-3,3-Dimethyl-2-(3-(3-methylbenzyl)-2-oxoimidazolidin-1-yl)butanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (9p). Yield 44%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83 (m, 9H), 0.89 (m, 9H), 1.62−1.48 (m, 2H), 2.31 (s, 3H), 2.34−2.24 (m, 1H), 2.62−2.53 (m, 1H), 2.68−2.65 (m, 2H), 2.97−2.73 (m, 3H), 3.22−3.12 (m, 1H), 3.50 (s, 3H), 3.70−3.62 (m, 1H), 3.87−3.83 (d, J = 9.93 Hz, 1H), 4.08 (s, 1H), 4.33−4.11 (m, 4H), 4.56−4.53 (d, J = 7.72 Hz, 1H), 6.65−6.62 (d, J = 9.56 Hz, 1H), 7.04−7.02 (m, 3H), 7.11−7.07 (m, 4H), 7.25−7.21 (m, 4H), 7.33−7.28 (m, 1H), 7.49−7.46 (d, J = 9.56 Hz, 1H), 7.91−7.82 (m, 4H), 8.64−8.63 (d, J = 4.04 Hz, 1H). MS (ESI) m/z 819 $(M + H)^+$.

Methyl (*S*)-1-((2*S*,3*S*,5*S*)-3-Hydroxy-5-((*S*)-2-(3-((2-isopropylthiazol-4-yl)methyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanamido)-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (18h). Yield 62%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (s, 9H), 0.86 (s, 9H), 1.32 (d, J = 6.99 Hz, 6H), 1.52 (m, 2H), 2.38 (m, 2H), 2.64 (d, J = 9.93 Hz, 1H), 2.77 (d, J = 6.99 Hz, 2H), 3.01 (m, 2H), 3.23 (m, 2H), 3.51 (s, 3H), 3.61 (m, 1H), 3.95 (m, 2H), 4.30 (m, 4H), 4.82 (d, J = 5.52 Hz, 1H), 6.79 (d, J = 9.19 Hz, 1H), 7.00 (m, 5H), 7.24 (s, 1H), 7.30 (m, 3H), 7.58 (d, J = 9.56 Hz, 1H), 7.87 (m, 5H), 8.63 (d, J = 4.41 Hz, 1H). MS (ESI) m/z 854 $(M + H)^+$.

Methyl (*S*)-1-((2*R*,4*S*,5*S*)-4-Hydroxy-5-((*S*)-2-(3-((6-isopropylpyridin-2-yl)methyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanamido)-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (10h). Yield 62%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80 (s, 9H), 0.88 (s, 9H), 1.27−1.25 (d, J = 6.99 Hz, 6H), 1.42−1.23 (m, 1H), 1.58−1.47 (m, 1H), 2.70−2.53 (m, 3H), 2.87−2.78 (m, 1H), 3.31−2.98 (m, 4H), 3.57−3.50 (m, 1H), 3.57 (s, 3H), 3.85−3.82 (d, J = 9.56 Hz, 1H), 3.99−3.87 (m, 1H), 4.03 (s, 1H), 4.23−4.13 (m, 2H), 4.45 (s, 2H), 6.91−6.87(d, J = 9.93 Hz, 1H), 7.10−7.06 (m, 5H), 7.28−7.21 (m, 4H), 7.44−7.37 (m, 2H), 7.58−7.55 (d, J = 9.19 Hz, 1H), 7.97−7.86 (m, 5H), 8.69−8.67 (m, 1H). MS (ESI) m/z 848 $(M + H)^+$.

Methyl (*S*)-1-((2*R*,4*S*,5*S*)-5-((*S*)-2-(3-((6-*tert*-Butylpyridin-2-yl)methyl)-2-oxoimidazolidin-1-yl)-3,3-dimethylbutanamido)-4-hydroxy-6-phenyl-1-(4-(pyridin-2-yl)phenyl)hexan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (10i). Yield 39%, white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80 (s, 9H), 0.88 (s, 9H), 1.30 (s, 9H), 1.42−1.23 (m, 1H), 1.58−1.47 (m, 1H), 2.47−2.42 (m, 1H), 2.73−2.55 (m, 2H), 2.87−2.78 (m, 1H), 3.05−2.99 (m, 1H), 3.31−3.18 (m, 1H), 3.57−3.50 (m, 1H), 3.57 (s, 3H), 3.85−3.82 (d, J = 9.56 Hz, 1H), 3.99−3.87 (m, 1H), 4.02 (s, 1H), 4.23−4.13 (m, 1H), 4.44−4.32 (m, 2H), 4.44−4.42 (d, J = 7.35 Hz, 1H), 6.90−6.87 (d, J = 9.19 Hz, 1H), 7.09−7.04 (m, 6H), 7.25−7.22 (d, J = 8.46 Hz, 2H), 7.34−7.29 (m, 2H), 7.54−7.51 (d, J = 9.91 Hz, 1H), 7.73−7.68 (t, J = 7.72 Hz, 1H), 7.90−7.83 (m, 3H), 7.97−7.94 (d, J = 8.09 Hz, 2H), 8.65−8.64 (m, 1H). MS (ESI) m/z 862 $(M + H)^+$.

Dimethyl (2*S*,2′*S*)-1,1′-((2*S*,3*S*,5*S*)-3-Hydroxy-1-phenyl-6-(4-(pyridin-2-yl)phenyl)hexane-2,5-diyl)bis(azanediyl)bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate (11). 11 was prepared from **6b** and (*S*)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid in 75% yield as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.79 (s, 9 H), 0.82 (s, 9 H), 1.51 (m, 2 H), 2.72 (m, 3 H), 3.49 (s, 3 H), 3.55 (s, 3 H), 3.63 (m, 1 H), 3.82 (d, J = 9.93 Hz, 1 H), 3.90 (d, J = 9.56 Hz, 1 H), 4.04 (m, 3 H), 4.86 (d, J = 5.88 Hz, 1 H), 6.60 (d, J = 9.93 Hz, 1 H), 6.78 (d, J = 9.19 Hz, 1 H), 7.16 (m, 7 H), 7.31 (m, 1 H), 7.54 (d, J = 8.46 Hz, 1 H), 7.83 (m, 5 H), 8.63 (d, J = 4.78 Hz, 1 H). MS (ESI) m/z 704 $(M + H)^+$.

Biological Evaluation. Procedures for EC_{50} determination against WT and mutant strains of HIV in MT-4 cells have been reported previously.[20]

Pharmacokinetic Analysis. Compounds were formulated as 5 mg/mL solutions in 5% dextrose containing 20% ethanol, 30% propylene glycol, and appropriate equivalents of methanesulfonic acid, and Sprague−Dawley-derived rats (Charles River, male; n = 3) and beagle dogs (male and female; n = 3) received doses by iv or oral gavage. Plasma samples, obtained as a function of time after dosing (rat, 10 time points over 8 h; dog, 12 time points over 12 h), were extracted into mixtures of ethyl acetate and hexane, concentrated, and analyzed by reversed-phase HPLC with an internal standard.

Metabolic Stability Screening. Inhibitors were incubated at 2 μM in a reaction mixture containing 100 mM potassium phosphate, pH 7.4, 0.5 mg/mL of pooled (HLM), 1 mM NADPH, 0.5% DMSO, and 0.5% acetonitrile in a final volume of 100 μL. Control samples received water instead of NADPH to start the reaction, and some samples received 0.4 μM RTV. All mixtures were incubated at 37 °C for 20 min and then terminated with the addition of cold acetonitrile/methanol (1:1) containing an internal standard in order to denature the protein and extract the compound. The extractions were allowed to progress to completion by storing the samples overnight at 4 °C, and samples were then centrifuged at 15000g for 10 min at 4 °C. The supernatants were analyzed by LC/MS/MS.

Hyperbilirubinemia Model. As described previously,[5] compounds for dosing in Gunn rats (n = 8−10 (rats/arm)/experiment) were formulated in 5% ethanol/95% propylene glycol with ap-

propriate equivalents of *p*-toluenesulfonic acid. Plasma samples were obtained 4 h after the first and second doses and were analyzed for drug concentration as described above for pharmacokinetic analysis and for bilirubin concentration to the nearest 0.01 mg/mL.

X-ray Crystallographic Analysis. HIV protease was purified and crystallized in the presence of compounds according to procedures previously described.[18b] 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 monoclinic space group *P*2(1), with unit cell dimensions $a = 67.08$ Å, $b = 61.50$ Å, $c = 87.68$ Å, $\alpha = 90.00°$, $\beta = 111.12°$, $\gamma = 90.00°$. The final structure of the HIV protease/**11** inhibited complex was refined using CNX,[24,25] an R_{free} set of 5.0%, and an $R = 22.70\%$, $R_{free} = 28.66\%$, at 2.5 Å resolution. The crystals of **10a** belong to the monoclinic space group *P*2(1), with unit cell dimensions $a = 42.65$ Å, $b = 195.57$ Å, $c = 50.37$ Å, $\alpha = 90.00°$, $\beta = 91.19°$, $\gamma = 90.00°$. The final structure of the HIV protease/**10a** inhibited complex was refined using CNX, an R_{free} set of 5.0%, and an $R = 22.11\%$, $R_{free} = 30.30\%$, at 2.7 Å resolution.

Acknowledgment. X-ray data were collected at beamline 17-ID in the facilities of the Industrial Macromolecular Crystallography Association Collaborative Access Team (IMCA-CAT) at the Advanced Photon Source. These facilities are supported by the companies of the Industrial Macromolecular Crystallography Association through a contract with Illinois Institute of Technology (IIT), executed through IIT's Center for Synchrotron Radiation Research and Instrumentation. Use of the Advanced Photon Source was supported by the U.S. Department of Energy, Basic Energy Sciences, Office of Science, under Contract No. W-31-109-Eng-38.

Supporting Information Available: HPLC purity data for compounds **1b**,**c**, **9a**−**p**, **10a**−**i**, **11**, **18a**−**h** and synthetic details for preparation of **1b** and **1c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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