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Discovery of imidazolidine-2,4-dione-linked HIV protease inhibitors with activity against lopinavir-resistant mutant HIV

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Abstract—A new series of HIV protease inhibitors has been designed and synthesized based on the combination of the (*R*)-(hydroxyethylamino)sulfonamide isostere and the cyclic urea component of lopinavir. The series was optimized by replacing the 6-membered cyclic urea linker with an imidazolidine-2,4-dione which readily underwent N-alkylation to incorporate various methylene-linked heterocycle groups that bind favorably in site 3 of HIV protease. Significant improvements compared to lopinavir were seen in cell culture activity versus wild-type virus (pNL4-3) and the lopinavir-resistant mutant virus A17 (generated by *in vitro* serial passage of HIV-1 (pNL4-3) in MT-4 cells). Select imidazolidine-2,4-dione containing PIs were also more effective at inhibiting highly resistant patient isolates Pt1 and Pt2 than lopinavir. Pharmacokinetic data collected for compounds in this series varied considerably when coadministered orally in the rat with an equal amount of ritonavir (5 mg/kg each). The AUC values ranged from 0.144 to 12.33 μg h/mL.

1. Introduction

Lopinavir, a human immunodeficiency virus (HIV) type 1 protease inhibitor (PI), is a second-generation inhibitor designed to overcome some of the shortcomings of earlier drugs of this class. For example, binding to human serum proteins attenuates the *in vitro* potency of HIV PIs, leading to higher than anticipated EC_{50} values in the presence of human serum.[1,2] Second, many previous PIs had pharmacokinetic profiles that led to trough plasma drug levels that were only a few fold higher than their EC_{50} values. Lopinavir exhibits exceptional inhibition against wild-type virus (pNL4-3 strain), both with and without the presence of human serum (EC_{50} = 17 nM in the absence of human serum (HS), EC_{50} = 100 nM in the presence of 50% HS).[3] Lopinavir was also developed as a co-formulated product with ritonavir as a pharmacokinetic booster (Kaletra, 400 mg lopinavir/100 mg ritonavir).[4] As a result of lopinavir's high trough levels and improved potency in the presence of human serum, lopinavir/ritonavir (LPV/r) achieves an inhibitory quotient (IQ = C_{trough}/EC_{50}) of $\geqslant$75. The regimen has provided durable suppression of HIV in treatment-naïve and -experienced patients, with a large proportion of patients achieving undetectable viral loads. To date, no development of resistance to lopinavir has been reported in clinical trials in treatment-naïve patients after four years of therapy with LPV/r. However, in treatment-experienced patients, mutations in the protease gene are often present at the initiation of LPV/r therapy, resulting in lower response rates as well as the evolution of incremental resistance.[5,6] Key genetic changes that are associated with reduced susceptibility to lopinavir have been determined.[7]

Resistance to PIs occurs by accumulation of mutations in HIV protease, leading to reduced susceptibility to the drug. Mutations associated with individual PIs and those that confer cross-resistance to other PIs have been identified.[8] *In vitro* selection experiments were conducted with lopinavir as a means of predicting possible resistance patterns that may emerge *in vivo*. Serial passage of HIV-1 (pNL4-3) in MT-4 cells with increasing concentrations of lopinavir selected the following mutations sequentially: I84V, L10F, M46I, T91S, V32I, and I47V.[9] The I84V, L10F, M46I, V32I, and I47V mutations have been associated with resistance to other PIs,

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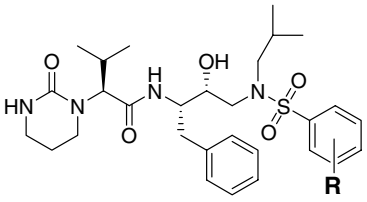
Table 1. Antiviral activity of HIV protease inhibitors **2a**–**2g**: P2′ modification



Compound	R	EC_{50} (μM) WT, 0% HS	EC_{50} (μM) WT, 50% HS	EC_{50} (μM) A17, 0% HS
1	LPV	0.025	0.213	1.01
2a	H	0.303	2.08	22.2
2b	4-NH_2	0.183	2.37	5.66
2c	3-NH_2	0.079	0.964	5.50
2d	4-MeO	0.074	0.182	6.65
2e	4-Cl	0.551	1.40	4.28
2f	4-Cl-3-NH_2	0.091	0.301	3.37
2g	4-OH	0.295	0.818	1.99

namely, indinavir, ritonavir, and amprenavir.[8] The mutant virus A17 (L10F/V32I/M46I/I47V/Q58E/I84V), obtained from the above *in vitro* selection, showed 40-fold reduced susceptibility to lopinavir compared to the wild-type virus (Table 1). It was our goal to design a potential salvage agent for patients failing multiple PI-based regimens, including LPV/r. We thus performed structure–activity studies of exploratory protease inhibitors using the A17 virus in our primary screening panel.

2. Results and discussion

The X-ray crystal structure of lopinavir bound to wild-type HIV protease[10] was used to model the way in which the mutations present in the A17 strain may affect the binding of lopinavir in the active site of the enzyme. A key active site mutation occurs at residue 84, which lies at the interface of the S1′ and S2 subsites of the enzyme (and C_2-symmetry related S1 and S2′ subsites) and forms part of each pocket. In addition, residues 32 and 47 occupy positions in the S2 subsite (and C_2-symmetry related S2′ subsite) of the enzyme and interact with the P2 cyclic urea unit and the P2′ 2,6-dimethylphenyl group of lopinavir. Thus, modifying the structural parts of lopinavir that interact with the subsites where mutations occur can be expected to have a significant impact on the resistance profile of new compounds.

Due to the relative ease of synthesis and the potential to prepare analogs with various P1′ and P2′ groups, the (*R*)-(hydroxyethylene)sulfonamide isostere was combined with the lopinavir 6-membered cyclic urea moiety to form the series of compounds shown in Table 1. Additionally, reports in the literature indicated that compounds containing the (*R*)-(hydroxyethylene)sulfonamide isostere possess good potency and oral bioavailability.[11,12]

The initial compound in the series (**2a**) was considerably less potent against both wild-type and A17 compared to lopinavir. However, substituting on the arylsulfonamide of **2a** with various polar groups at the *para* and *meta* positions enhanced the activity of the series in some cases. For example, the 4-hydroxy compound **2g** displayed more than 11-fold improved activity against A17 compared to **2a**. Substituting with 4-methoxy at the *para* position to give **2d** additionally improved the activity against wild-type and A17 strains compared to **2a**. Also notable was the improvement in activity observed for the 4-Cl-3-NH_2-substituted benzenesulfonamide analog **2f**, compared to analogs **2c** and **2e**, which were mono-substituted with 3-NH_2 and 4-Cl, respectively.

Modifications of the 6-membered cyclic urea group occupying S2 were investigated to further improve the activity of the series. This urea linkage is present in the structures of both lopinavir and ritonavir. Studies leading to ritonavir focused on acyclic urea compounds in which the urea linker was used to append a P3 heterocycle, with N-Me ureas exhibiting the best overall prop-

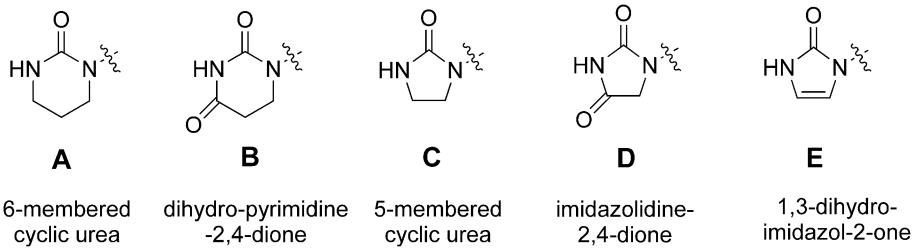


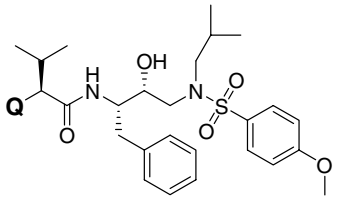
Figure 1. Six-membered cyclic urea replacement pieces.

erties.[13] The conformational constraint provided by the 6-membered cyclic urea of lopinavir led to a boost in potency compared to the acyclic versions.[3] Figure 1 shows the cyclic structural motifs proposed to replace the 6-membered cyclic urea in the current series. In addition to **A**, several other heterocycles were investigated in the context of lopinavir SAR studies, including structural motifs **B** and **C** in Figure 1.[14,15]

Table 2 summarizes the effect of replacing the 6-membered cyclic urea with structures **B**–**E** from Figure 1. In the case of compound **3a**, where **A** is replaced with **B**, the activity improves against both wild-type and A17 viruses. Reducing the size of the cyclic urea ring from six atoms to five atoms to give compound **3b** resulted in a sharp decrease in wild-type activity, while the activity against A17 remained relatively unchanged. Similarly, compound **3d** (the unsaturated version of **3b**) had very poor activity. Compound **3c** containing the imidazolidine-2,4-dione structure was ca. 2-fold more active against A17 than **2d** and had equal potency against wild-type in the presence of 0% HS. Compound **3c** experienced a significant serum effect that attenuated its wild-type activity.

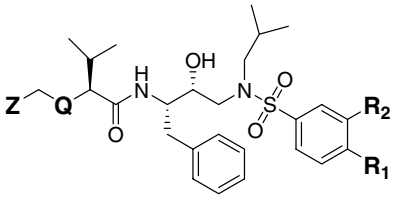
The increased activity observed when the 5- and 6-membered cyclic ureas were changed to **D** and **B**, respectively, prompted investigation of such compounds containing methylene-linked P3 groups. The increased acidity of the NH proton ($pK_a = 9.0$)[16] in structures **B**

Table 2. Antiviral activity of HIV protease inhibitors **2d** and **3a**–**3d**



Compound	Q	EC_{50} (μM) WT, 0%HS	EC_{50} (μM) WT, 50% HS	EC_{50} (μM) A17, 0% HS
2d	A	0.074	0.182	6.65
3a	B	0.035	0.125	2.42
3b	C	0.549	1.77	6.68
3c	D	0.075	0.474	3.46
3d	E	0.455	0.686	7.55

Table 3. Antiviral activity of HIV protease inhibitors **4a**–**7d**



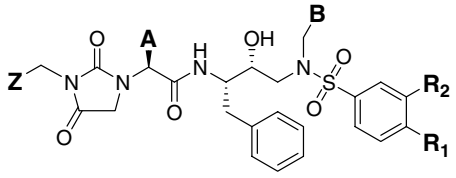
Compound	Z	Q	R_1	R_2	EC_{50} (nM) WT, 0% HS	EC_{50} (nM) A17, 0% HS	Fold
4a	2-Et-4-thz	B	OH	H	8	51	6
4b	2-Et-4-thz	C	OH	H	17	72	4
4c	2-Et-4-thz	D	OH	H	13	23	2
4d	2-Et-4-thz	E	OH	H	16	49	3
5a	2-Et-4-thz	B	NH_2	H	12	288	24
5b	2-Et-4-thz	C	NH_2	H	25	257	10
5c	2-Et-4-thz	D	NH_2	H	13	66	5
5d	2-Et-4-thz	E	NH_2	H	31	823	26
6a	2-Et-4-thz	B	Cl	NH_2	5	273	55
6b	2-Et-4-thz	C	Cl	NH_2	12	309	26
6c	2-Et-4-thz	D	Cl	NH_2	12	52	4
6d	2-Et-4-thz	E	Cl	NH_2	18	504	28
7a	2-Me-4-thz	B	OMe	H	21	767	36
7b	2-Me-4-thz	C	OMe	H	22	196	9
7c	2-Me-4-thz	D	OMe	H	5	75	15
7d	2-Me-4-thz	E	OMe	H	18	507	28

and **D** compared to the urea made them an attractive starting material for alkylation under basic conditions, allowing for a rapid survey of various P3 substituents. Analogous to the 2-isopropyl-4-thiazole group of ritonavir, 2-alkyl-4-thiazole groups were attached to the cyclic urea replacements **B**–**E**, as shown in Table 3. Four of the substituted benzenesulfonamide P2′ groups studied in Table 1 were also incorporated. As Table 3 indicates, there was an overall improvement in antiviral activity against wild-type and A17 viruses when a P3 group was incorporated into the molecule. Immediately apparent was the much lower fold resistance (A17/WT) observed with the 4-hydroxybenzenesulfonamide analogs **4a**–**4d** regardless of the nature of **Q**. The 4-hydroxybenzenesulfonamides also exhibited better activity against A17 than any of the other substituted benzenesulfonamides tested, such as the 4-NH_2 analogs **5a**–**5d**, the 4-Cl-3NH_2 analogs **6a**–**6d**, or the 4-MeO analogs **7a**–**7d**. Also apparent from Table 3 is that only the analogs containing imidazolidine **D** (**4c**, **5c**, **6c**, **7c**) retained their improved activities against A17, regardless of the benzenesulfonamide substituent used. For example, compound **5c** was at least 2-fold more potent than any of the compounds **5a**, **5b**, or **5d** versus A17, a trend that is continued for the 4-OH compound **4c**, the 4-Cl-3NH_2 compound **6c**, and the 4-MeO compound **7c**.

Due to their favorable resistance profiles, compounds **4c**–**7c** were identified as having the potential to meet the requirements for a LPV/r salvage agent, and were used as prototypes to further improve on qualities such as the antiviral activity in the presence of human serum, pharmacokinetic properties, and activities against additional resistant viruses. While compound **4c** showed excellent activity against A17, it suffered from high serum binding (50-fold loss in activity with 50% HS) that seriously attenuated its activity (Table 4). It was hoped that making structural changes to compound **4c** would reduce the serum binding effect. A slight reduction in the serum effect was observed for the 2-methyl thiazole and 2-methoxymethyl (MOM) thiazole analogs, **8** and **9**. It was determined, however, that the 4-OH analogs suffered from high *in vivo* clearance and poor oral bioavailability, with compound **8** showing almost undetectable plasma levels and a low AUC of 0.05 μg h/mL in rat. Compounds **10** and **7c**, the 4-Cl-3-NH2 and 4-OMe analogs of **8**, respectively, had reasonable potency in the presence of 50% HS and exhibited improved oral bioavailability. Further improvements in serum binding were made in compounds **11** and **12**, the 2-MOM-thiazole analogs of **10** and **7c**, which showed EC_{50} values in the presence of 50% HS several fold lower than lopinavir, in addition to good oral bioavailability in rat when co-dosed with ritonavir.

Further changes to this series at the P2 and P1′ positions led to compounds with considerably better potency overall. For example, changing the P2 valine group in **11** to isoleucine to give analog **13** resulted in a greater than 6-fold improvement in wild-type activity in the presence of 50% HS and a 36-fold improvement against A17, while maintaining good bioavailability. Good potency was also maintained by making changes to the P1′ group as shown by analogs **14** and **15**, which are *tert*-butyl and cyclopentyl amine versions, respectively, of compound **13**. However, the plasma concentrations after oral dosing in rats were exceedingly low for **14** and **15** compared to **13**.

Table 4. Antiviral activity and PK profile for HIV protease inhibitors **4c**–**20**



Compound	Z	A	B	R_1	R_2	EC_{50} (nM) WT, 0% HS	EC_{50} (nM) WT, 50% HS	EC_{50} (nM) A17, 0% HS (fold)	AUC (μg h/mL)[a]
4c	2-Et-4-thz	2-Propyl	2-Propyl	OH	H	13	650	23 (2)	N.A.
8	2-Me-4-thz	2-Propyl	2-Propyl	OH	H	54	434	28 (<1)	0.05
9	2-MOM-4-thz	2-Propyl	2-Propyl	OH	H	43	291	20 (<1)	N.A.
10	2-Me-4-thz	2-Propyl	2-Propyl	Cl	NH_2	5	227	68 (14)	12.33
7c	2-Me-4-thz	2-Propyl	2-Propyl	OMe	H	5	161	75 (15)	4.72
11	2-MOM-4-thz	2-Propyl	2-Propyl	OMe	H	28	46	181 (6)	8.19
12	2-MOM-4-thz	2-Propyl	2-Propyl	Cl	NH_2	6	25	63 (10)	3.47
13	2-MOM-4-thz	2-(*S*)-bu	2-Propyl	OMe	H	1	7	5 (5)	6.81
14	2-MOM-4-thz	2-(*S*)-bu	*tert*-Butyl	OMe	H	1	14	12 (12)	0.144
15	2-MOM-4-thz	2-(*S*)-bu	*c*-Pentyl	OMe	H	2	10	2 (1)	0.375
16	Phenyl	2-Propyl	2-Propyl	OMe	H	5	32	59 (12)	2.27
17	2-Quinoline	2-Propyl	2-Propyl	Cl	NH_2	4	42	174 (44)	2.88
18	2-Quinoline	2-Propyl	2-Propyl	OMe	H	3	42	224 (75)	2.48
19	1-Methyl-2-benzimidazole	2-Propyl	2-Propyl	Cl	NH_2	6	237	62 (10)	1.45
20	1-Methyl-2-benzimidazole	2-Propyl	2-Propyl	OMe	H	7	107	63 (9)	2.79

[a] AUC values reflect mean plasma levels in rats ($n = 3$) following a 5 mg/kg oral dose coadministered with a 5 mg/kg dose of ritonavir.

The effect of changing the P3 group was also examined. Compound **16**, a phenyl version of compound **7c**, displayed similar potency to the thiazole analog, with modest oral bioavailability. Examining heterocycles other than the thiazoles was also informative. For example, while 2-quinoline analogs, **17** and **18**, showed good potency against the wild-type virus, a lowered activity against A17 than the respective 2-methyl thiazole analogs, **10** and **7c**, was observed. By contrast, the 2-methyl benzoimidazole analogs, **19** and **20**, exhibited comparable potency against wild-type and A17 compared to the thiazole analogs. Oral bioavailability for these larger heterocycles was only moderate in each case.

Table 5. Activity of HIV PIs versus patient isolates Pt1 and Pt2

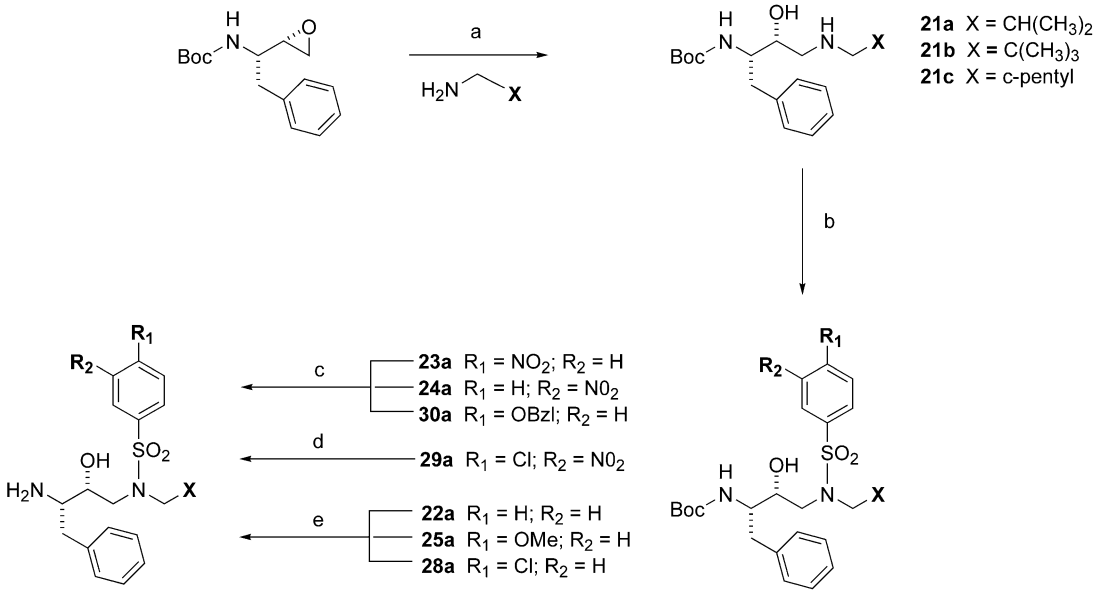
Compound	Pt1[a]			Pt2[b]	
	EC_{50} WT (nM)	EC_{50} (nM)	Fold	EC_{50} (nM)	Fold
LPV	7	420	60	1434	205
9	0.4	16	40	43	108
11	1	32	32	29	29
12	0.6	12	20	114	190
13	0.4	8.4	21	11.3	28
14	2	84	42	102	51
15	0.5	6	12	8	16

[a] Genotype of Pt1: L10I, M36I, M46I, I54V, L63P, A71V, I84V, L90M.
[b] Genotype of Pt2: L10I, L33F, M46I, I54V, L63P, A71L, V77I, V82A, L90M.

As stated earlier, resistance to HIV protease inhibitors occurs through the accumulation of primary and secondary mutations. Viruses observed clinically that are highly resistant to lopinavir generally contain numerous mutations in the protease. Select compounds from Table 4 were tested against two highly resistant patient isolates, Pt1 and Pt2, which were obtained from two PI-experienced subjects failing lopinavir/ritonavir therapy. The results are shown in Table 5. Representatives of the 4-OH, 4-OMe, and 4-Cl-3-NH_2 series each showed potent inhibition against Pt1 and Pt2. Compounds **11**–**13** were of particular interest since each of these PIs potently inhibited wild-type virus in the presence of 50% HS, as well as producing excellent plasma levels in rats when co-dosed with ritonavir. All three compounds showed good potency against Pt1 and Pt2 compared to lopinavir, with compound **13** having an overall advantage in terms of its activity profile and bioavailability.

3. Conclusion

A novel series of HIV protease inhibitors containing a 5-membered imidazolidine-2,4-dione moiety was designed with excellent potency against both wild-type



22 R_1 = H; R_2 = H; X = $CH(CH_3)_2$
23 R_1 = NH_2; R_2 = H; X = $CH(CH_3)_2$
24 R_1 = H; R_2 = NH_2; X = $CH(CH_3)_2$
25 R_1 = OMe; R_2 = H; X = $CH(CH_3)_2$
26 R_1 = OMe; R_2 = H; X = $C(CH_3)_3$
27 R_1 = OMe; R_2 = H; X = c-pentyl
28 R_1 = Cl; R_2 = H; X = $CH(CH_3)_2$
29 R_1 = Cl; R_2 = NH_2; X = $CH(CH_3)_2$
30 R_1 = OH; R_2 = H; X = $CH(CH_3)_2$

Scheme 1. Reagents and conditions: (a) alkyl amine (20 equiv), isopropanol, reflux; (b) R_1, R_2-benzenesulfonyl chloride, Et_3N, CH_2Cl_2; (c) i—$Pd(OH)_2$/C, H_2, ethyl acetate, ii—1:1 CH_2Cl_2/TFA; (d) i—Fe (4 equiv), 70 °C, ethyl acetate/acetic acid 1:1, ii—1:1 CH_2Cl_2/TFA; (e) 1:1 CH_2Cl_2/TFA.

virus and a mutant strain (A17) that is highly resistant to lopinavir. Compound **13** had the most favorable overall profile, with 1 nM activity against wild-type and 5 nM EC_{50} against the A17 strain, and an AUC in rat of 6.81. Compound **13** also performed comparatively well against the highly resistant patient isolates Pt1 and Pt2, with the EC_{50} values equal to 8.4 and 11.3 nM, respectively.

4. Chemistry

Synthesis of the protease inhibitors begins with construction of the amino sulfonamide cores **22**–**30** shown in Scheme 1. The commercially available epoxide was opened with excess alkyl amine in refluxing 2-propanol to provide amino alcohols **21a**–**c**. The amines were then sulfonylated with the appropriate substituted benzenesulfonyl chlorides. Nitro containing benzenesulfonamides **23a** and **24a** underwent catalytic hydrogenation to produce the 4-amino and 3-amino benzenesulfonamides, respectively. Debenzylation of **30a** to give the 4-hydroxybenzenesulfonamide was accomplished by the same hydrogenation method. The 4-chloro-3-nitro-substituted benzenesulfonamide intermediate **29a** required iron oxidation to make the 4-chloro-3-aminobenzenesulfonamide. Removal of the Boc protecting group using TFA:CH_2Cl_2 gave the free amine cores **22**–**30**.

Synthesis of the six-membered cyclic structure **B**, shown in Scheme 2, proceeded through the *tert*-butyl-protected valine amino acid, which was alkylated with acrylamide to give **31**. Cyclization of **31** was performed with CDI under basic conditions to make **32**. To make compounds **2a**–**g**, the ester was deprotected and coupled to the previously prepared amine cores from Scheme 1. In order to incorporate P3 groups into the molecule, **32** was alkylated with chloromethyl thiazoles. The *tert*-butyl group was then removed to give the acids **34** and **35**, which were coupled to the amine cores **23**, **25**, **29**, and **30** to give the protease inhibitors **4a**–**7a**.

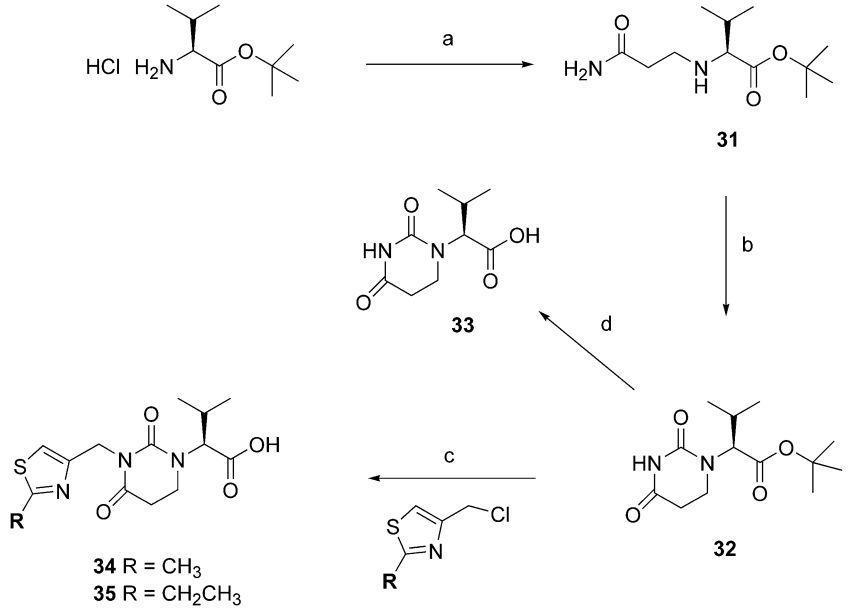
Like the six-membered cyclic structure **B**, synthesis of the imidazolidine **D** began with the *tert*-butyl-protected valine or isoleucine amino acids (Scheme 3). Reaction with ethylbromoacetate gave **36a**–**b**, which was subsequently reacted with chlorosulfonylisocyanate and cyclized under basic conditions to give **37a**–**37b**. To make inhibitor **3c**, the ester was deprotected and coupled with amine **25**. The imidazolidines **37a**–**37b** could be alkylated as previously described for **B**. Finally, deprotection gave the acid cores **39**–**45**, which were coupled with the amine cores from Scheme 1 using standard coupling conditions further detailed in Section.

The imidazolone **E** was constructed by combining commercially available aminoacetaldehyde diethyl acetal with the PNPO-valine methyl ester[13] to afford **47** (Scheme 4). Heating **47** in formic acid led to the imidazolone ester, which was hydrolyzed under basic conditions to provide **48**. Alkylation of the imidazolone using the same conditions that were employed to alkylate **B** and **D** was attempted but resulted in racemization at the chiral carbon, as determined by NMR analysis of the final coupled product. To circumvent this, the acetyl was combined with the chloromethyl thiazole to give **49a** and **50a**, which could then be converted to the imidazolone acids **49** and **50**. The acids were then coupled to the respective amine cores to give compounds **3c** and **4d**–**7d**.

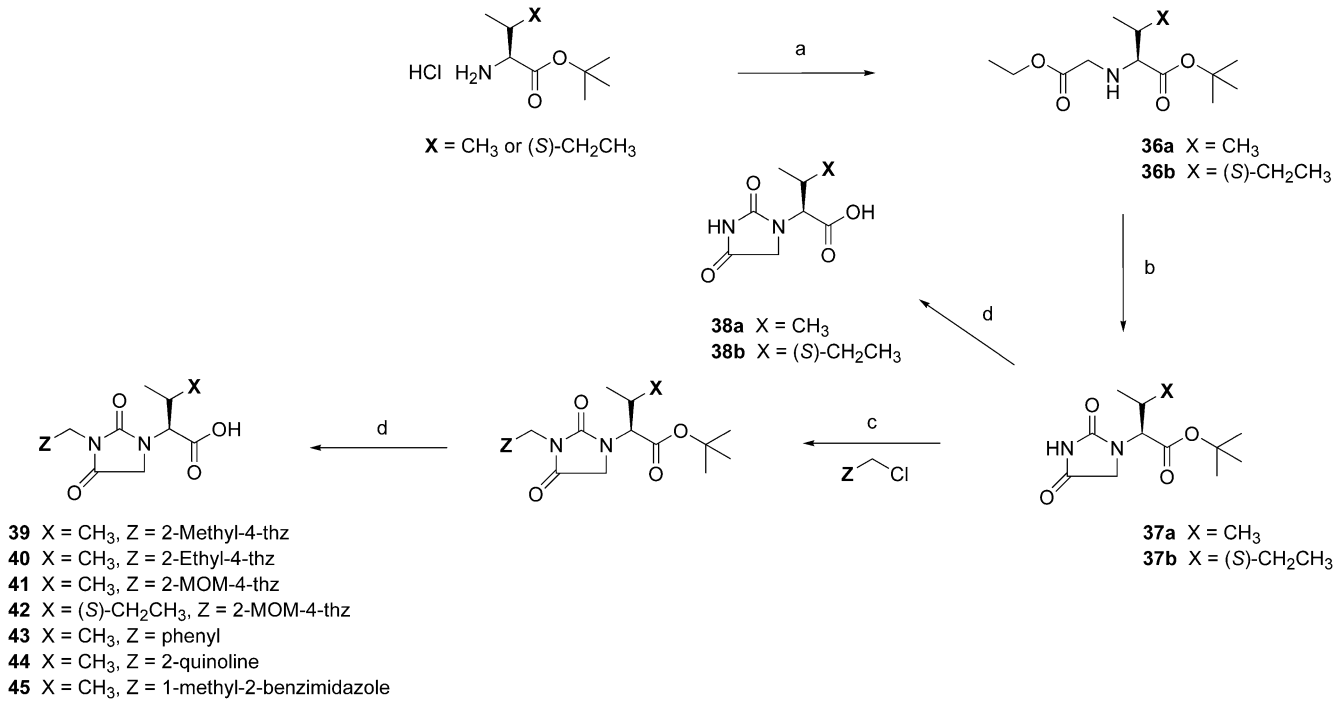
5. Experimental

5.1. General methods

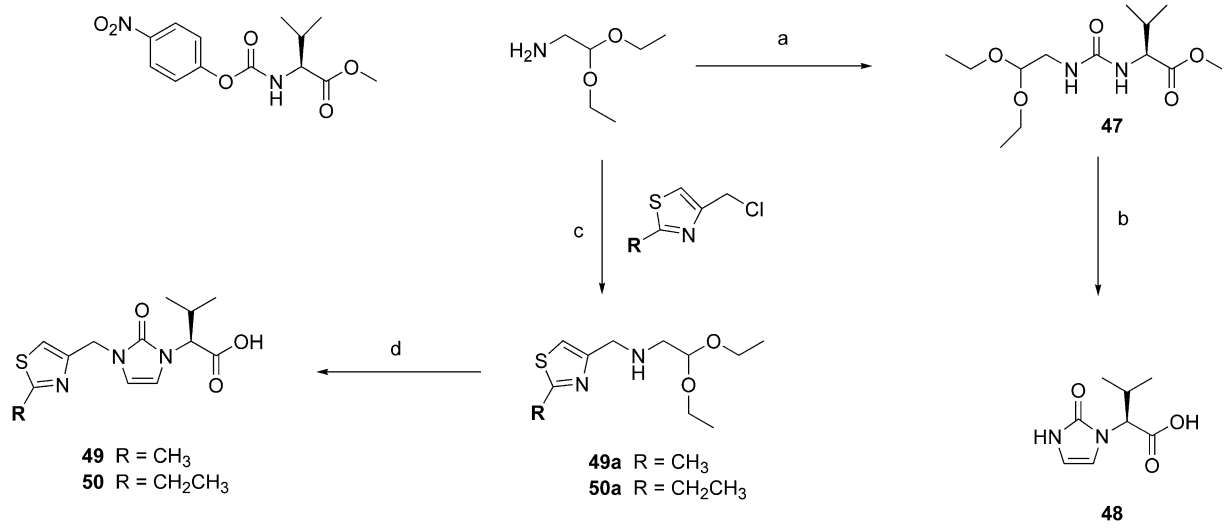
Solvents (including anhydrous) and reagents were obtained from commercial suppliers and were used without



Scheme 2. Reagents and conditions: (a) acrylamide (10 equiv), Et_3N, EtOH, 65 °C; (b) 1,1-carbonyldiimidazole, ET_3N, toluene, 100 °C; (c) i—NaHMDs, DMF, 70 °C, ii–1:1 CH_2Cl_2/TFA; (d) 1:1 CH_2Cl_2/TFA.



Scheme 3. Reagents and conditions: (a) ethylbromoacetate, Et_3N, DMF; (b) i—chlorosulfonylisocyanate, CH_2Cl_2, 0 °C, ii—H_2O, iii—Et_3N, MeOH; (c) i—NaHMDs, DMF, 70 °C; (d) 1:1 CH_2Cl_2/TFA.



Scheme 4. Reagents and conditions: (a) DMAP, Et_3N; (b) i—formic acid, 75 °C, ii—LiOH, 30% H_2O/THF; (c) THF, 18 h; (d) i—*N*-[[(4-nitrophenyl)-oxy]carbonyl]-L-valine methyl ester, DMAP, Et_3N, THF, 48 h, ii—formic acid, 18 h, iii—LiOH, 30%H_2O/THF.

further purification. Flash chromatography was performed using Biotage flash silica gel cartridges. ^1H NMR spectra were recorded at 300 MHz using a Bruker ARX 300 NMR spectrometer. Chemical shifts are in ppm (δ) relative to TMS. Mass Spectra were recorded using a Finnigan SSQ7000 mass spectrometer.

The two mutant clones Pt1 and Pt2 were generated by cloning the RT-PCR amplified DNA fragments spanning the protease region, the p7/p1 and p1/p6 cleavage sites into pNL4-3-Fluc-x. Drug susceptibility was determined using a single cycle assay by transfecting the mutant clones with a vesicular stomatitis virus (VSV) envelope expression vector into 293 cells.[17]

5.2. Synthesis of amine cores 22–30

5.2.1. *N*-((2*R*,3*S*)-3-Amino-2-hydroxy-4-phenyl-butyl)-*N*-isobutyl-4-methoxy benzenesulfonamide (25). To a solution of (2*R*,3*S*)-3-(*N*-*tert*-butoxycarbonyl)amino-1,2-epoxy-4-phenylbutane (6.0 g, 22.8 mmol) in 2-PrOH (115 mL) was added isobutylamine (45.3 mL, 456 mmol), and the mixture was heated at 80 °C for 2 h. The solvents were removed in vacuo to provide

crude product **21a**, which was dissolved in dichloromethane (115 mL) and treated with triethylamine (9.5 mL, 68.4 mmol) and 4-methoxybenzenesulfonyl chloride (5.18 g, 25.1 mmol). The mixture was stirred at rt for 4 h after which it was sequentially treated with a saturated solution of $NaHCO_3$, washed with water, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the Boc-protected amine core **25a**. The Boc group was removed by dissolving **25a** in 30 mL of dichloromethane, cooling to 0 °C, and treating with 30 mL trifluoroacetic acid. The mixture was allowed to warm to rt with continued stirring for 2 h. The reaction mixture was concentrated in vacuo, taken up in ethyl acetate, and washed with a saturated solution of $NaHCO_3$ (2×). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to provide 8.16 g (88%) of title compound **25**, which was used without further purification. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.89 (d, J = 6.62 Hz, 3H), 0.93 (d, J = 6.62 Hz, 3 H), 1.43 (br s, 2H), 1.81–1.95 (m, 1H), 2.49 (dd, J = 13.60, 9.93 Hz, 1H), 2.81–2.91 (m, 1H), 2.93–3.07 (m, 2H), 3.08–3.19 (m, 2H), 3.22 (d, J = 3.31 Hz, 1H), 3.27 (d, J = 8.82 Hz, 1H), 3.69–3.78 (m, 1H), 3.87 (s, 3H), 6.95–7.03 (m, 2H), 7.17–7.22 (m, 3H), 7.25–7.35 (m, 2H), 7.72–7.79 (m, 2H).

5.2.2. *N*-((2*R*,3*S*)-3-Amino-2-hydroxy-4-phenyl-butyl)-*N*-isobutyl-benzenesulfonamide (22). The title compound was prepared using the method described for the synthesis of **25** by substituting benzylsulfonyl chloride for 4-methoxybenzenesulfonyl chloride to provide **22** in 95% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.82–0.90 (m, 6H), 1.81–1.92 (m, 1H), 2.62 (dd, J = 13.42, 9.74 Hz, 1H), 2.85–2.96 (m, 2H), 2.96–3.05 (m, 2H), 3.25 (d, J = 5.88 Hz, 2H), 3.27–3.35 (m, 1H), 3.83–3.95 (m, 1H), 7.19–7.24 (m, 4H), 7.25–7.34 (m, 2H), 7.49–7.55 (m, 2H), 7.78–7.84 (m, 2H).

5.2.3. *N*-((2*R*,3*S*)-3-Amino-2-hydroxy-4-phenyl-butyl)-*N*-(2,2-dimethyl-propyl)-4-methoxy-benzenesulfonamide (26). The title compound was prepared using the method described for the synthesis of **25** by substituting neopentylamine for isobutylamine to provide **26** in 79% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.94 (s, 9H), 2.68 (dd, J = 13.97, 9.93 Hz, 1H), 2.89–2.96 (m, 1H), 2.99 (d, J = 7.72 Hz, 2H), 3.17 (d, J = 3.31 Hz, 1H), 3.21–3.29 (m, 1H), 3.30–3.38 (m, 2H), 3.48 (br s, 2H), 3.87 (s, 3H), 4.16–4.23 (m, 1H), 6.95–7.01 (m, 2H), 7.17–7.25 (m, 3H), 7.27–7.33 (m, 2H), 7.69–7.75 (m, 2H).

5.2.4. *N*-((2*R*,3*S*)-3-Amino-2-hydroxy-4-phenyl-butyl)-*N*-cyclopentylmethyl-4-methoxy- benzenesulfonamide (27). Cyclopentanecarbonitrile (5 mL, 47.9 mmol) in THF (6 mL) was treated with dropwise addition of a borane solution (52.7 mL, 1 M THF). The reaction was refluxed for 18 h, cooled to 0 °C, treated with methanol (65 mL), and HCl gas was bubbled into the solution for 30 min. The reaction was refluxed for 2 h and the solvents were removed in vacuo. Crystallization from ethyl acetate afforded 3.47 g (54%) of (cyclopentylmethyl)amine which was subsequently used to prepare the title compound using the method described for the synthesis of **25** to give **27** in 89% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 1.11–1.77 (m, 9H), 2.07–2.21 (m, 1H), 2.50 (dd, J = 13.42, 9.74 Hz, 1H), 2.90–3.05 (m, 2H), 3.07–3.21 (m, 2H), 3.23 (d, J = 3.31 Hz, 1H), 3.28 (d, J = 8.82 Hz, 1H), 3.70–3.83 (m, 1H), 3.87 (s, 3H), 6.94–7.06 (m, 2H), 7.16–7.40 (m, 5H), 7.70–7.82 (m, 2H).

5.2.5. *N*-((2*R*,3*S*)-3-Amino-2-hydroxy-4-phenyl-butyl)-4-chloro-*N*-isobutyl-benzenesulfonamide (28). The title compound was prepared using the method described for the synthesis of **25** by substituting benzylsulfonyl chloride for 4-chlorobenzenesulfonyl chloride to provide **28** in 92% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.86 (d, J = 6.62 Hz, 3H), 0.89 (d, J = 6.99 Hz, 3H), 1.80–1.93 (m, 1H), 2.30 (br s, 2H), 2.60 (dd, J = 13.60, 9.93 Hz, 1H), 2.85–3.04 (m, 3H), 3.19–3.31 (m, 3H), 3.76–3.90 (m, 1H), 7.18–7.35 (m, 5H), 7.49 (d, J = 8.46 Hz, 2H), 7.76 (d, J = 8.82 Hz, 2H).

5.2.6. 4-Amino-*N*-((2*R*,3*S*)-3-amino-2-hydroxy-4-phenyl-butyl)-*N*-isobutyl-benzenesulfonamide (23). To **21a** (640 mg, 1.9 mmol) in dichloromethane (20 mL) was added triethylamine (0.8 mL, 5.7 mmol) and 4-nitrobenzenesulfonyl chloride. The reaction mixture was stirred for 4 h at rt, after which it was sequentially treated with a saturated solution of $NaHCO_3$, washed with water, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give 0.88 g of **23a**. Reduction of the nitro group was performed by dissolving the crude material in ethyl acetate (17 mL) and adding $Pd(OH)_2$ on carbon (230 mg, 0.34 mmol). The reaction vessel was charged with hydrogen gas and reacted for 1 h under a hydrogen balloon atmosphere. The mixture was filtered through a pad of Celite and the solvent was removed in vacuo. Removal of the Boc group was performed as previously described to give 0.75 g of the title compound **23**, which was used without further purification. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.85 (d, J = 6.62 Hz, 3H), 0.88 (d, J = 6.62 Hz, 3H), 1.74–1.89 (m, 1H), 2.65 (dd, J = 13.97, 9.93 Hz, 1H), 2.81 (dd, J = 13.60, 6.99 Hz, 1H), 2.91 (d, J = 8.09 Hz, 1H), 2.95–3.07 (m, 2H), 3.14–3.25 (m, 2H), 3.28–3.38 (m, 1H), 3.83–3.95 (m, 1H), 4.13 (br s, 2H), 6.65–6.73 (m, 2H), 7.18–7.36 (m, 5 H), 7.53–7.60 (m, 2H).

5.2.7. 3-Amino-*N*-((2*R*,3*S*)-3-amino-2-hydroxy-4-phenyl-butyl)-*N*-isobutyl-benzenesulfonamide (24). The title compound was prepared using the method described for the synthesis of **23** by substituting 3-nitrobenzenesulfonyl chloride for 4-nitrobenzenesulfonyl chloride to provide **24** in 92% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.85 (d, J = 6.62 Hz, 3H), 0.88 (d, J = 6.62 Hz, 3H), 1.74–1.89 (m, 1H), 2.65 (dd, J = 13.97, 9.93 Hz, 1H), 2.81 (dd, J = 13.60, 6.99 Hz, 1H), 2.91 (d, J = 8.09 Hz, 1H), 2.95–3.07 (m, 2H), 3.14–3.25 (m, 2H), 3.28–3.38 (m, 1H), 3.83–3.95 (m, 1H), 4.13 (br s, 2H), 6.79–6.86 (m, 1H), 7.07–7.12 (m, 2H), 7.12–7.14 (m, 1H), 7.14–7.20 (m, 1H), 7.22–7.29 (m, 4H).

5.2.8. *N*-((2*R*,3*S*)-3-Amino-2-hydroxy-4-phenyl-butyl)-4-hydroxy-*N*-isobutyl-benzenesulfonamide (30). The title compound was prepared using the method described for the synthesis of **23** by substituting 4-benzyloxy-benzenesulfonyl chloride for 4-nitrobenzenesulfonyl chloride to provide **30** in 97% yield. ^{1}H NMR (300 MHz, methanol-d_4) δ ppm 0.85 (d, J = 6.62 Hz, 3H), 0.89 (d, J = 6.62 Hz, 3H), 1.89–2.00 (m, 1H), 2.60 (dd, J = 13.60, 9.19 Hz, 1H), 2.81 (d, J = 6.99 Hz, 1H), 2.90 (dd, J = 24.27, 7.72 Hz, 2H), 2.97–3.08 (m, 3H), 3.18–3.26 (m, 1H), 3.39 (dd, J = 14.71, 4.41 Hz, 1H), 3.75–3.90 (m, 1H), 6.85–6.93 (m, 2H), 7.21–7.28 (m, 1H), 7.28–7.37 (m, 4H), 7.60–7.68 (m, 2H).

5.2.9. 3-Amino-*N*-((2*R*,3*S*)-3-amino-2-hydroxy-4-phenyl-butyl)-4-chloro-*N*-isobutyl-benzenesulfonamide (29). To **21a** (640 mg, 1.9 mmol) in dichloromethane (20 mL) were added triethylamine (0.8 mL, 5.7 mmol) and 4-chloro-3-nitrobenzenesulfonyl chloride (0.54 g, 2.1 mmol). The reaction mixture was stirred for 4 h at rt and following standard workup gave 0.90 g **29a**. Reduction of the nitro group was performed by dissolving the crude material in ethanol/acetic acid (20 mL) and treating with iron powder (340 mg, 6.1 mmol). After stirring for 1 h at 70 °C, the solvent was removed in vacuo and the material was dissolved in ethyl acetate and washed with saturated $NaHCO_3$ solution (2×). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to give 0.91 g of crude material. The Boc group was removed as previously described to provide 0.80 g of the title compound **29**, which was used without further purification. ^{1}H NMR (300 MHz, methanol-d_4) δ ppm 0.86 (d, J = 6.62 Hz, 3H), 0.91 (d, J = 6.62 Hz, 3H), 1.29 (s, 2H), 1.89–2.02 (m, 1H), 2.68 (dd, J = 13.97, 9.56 Hz, 1H), 2.81–2.99 (m, 2H), 3.02 (d, J = 8.46 Hz, 1H), 3.04–3.15 (m, 2H), 3.32–3.41 (m, 1H), 3.45 (dd, J = 14.89, 4.96 Hz, 1H), 3.88–3.98 (m, 1H), 6.94–7.02 (m, 1H), 7.20–7.29 (m, 2H), 7.31–7.40 (m, 5H).

5.3. Synthesis of the imidazolidine-2,4-dione piece

5.3.1. (*S*)-2-(Ethoxycarbonylmethyl-amino)-3-methyl-butyric acid *tert*-butyl ester (36a). L-Valine *tert*-butyl ester hydrochloride (4.94 g, 23.6 mmol) was dissolved in DMF (55 mL) and treated with triethylamine (3.3 mL, 23.6 mmol) and stirred for 1 h. A white precipitate formed which was filtered off. To the collected filtrate was added triethylamine (9.9 mL, 70.7 mmol) followed by ethyl bromoacetate (7.8 mL, 70.7 mmol). After stirring for 2 h, the reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The remaining oil was taken up in EtOAc and washed sequentially with water (2×) and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel chromatography using 0–20% EtOAc/hexanes provided 4.48 g (78%) of **36a** as a clear oil. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.96 (d, J = 3.39 Hz, 3H), 0.98 (d, J = 3.39 Hz, 3H), 1.27 (t, J = 7.12 Hz, 3H), 1.47 (s, 9H), 1.89–2.03 (m, 1H), 2.91 (d, J = 5.76 Hz, 1H), 3.25–3.48 (m, 2H), 4.18 (q, J = 7.12 Hz, 2H).

5.3.2. (*S*)-2-(2,4-Dioxo-imidazolidin-1-yl)-3-methyl-butyric acid *tert*-butyl ester (37a). To **36a** (4.48 g, 18.3 mmol) in CH_2Cl_2 (30 mL) cooled to 0 °C, chlorosulfonyl isocyanate (2.07 mL, 23.7 mmol) was added dropwise. After stirring for 2 h, the reaction mixture was warmed to room temperature, water (30 mL) was added, and stirring was continued for 16 h. The layers were separated and the aqueous layer was back-extracted with EtOAc (2×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Complete conversion to the cyclized product was achieved by dissolving this material in MeOH (30 mL) and treating with triethylamine (5.1 mL, 36.5 mmol) while heating at 50 °C for 2 h. The solvents were removed in vacuo and purification by silica gel chromatography using 0–25% EtOAc/CH_2Cl_2 provided 2.97 g (63%) of **37a** as a white solid. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.96 (d, J = 6.78 Hz, 3H), 1.03 (d, J = 6.78 Hz, 3H), 1.48 (s, 9H), 2.07–2.22 (m, 1H), 3.92 (d, J = 17.97 Hz, 1H), 4.35 (d, J = 9.49 Hz, 1H), 4.38 (d, J = 17.97 Hz, 1H).

5.3.3. (2*S*,3*S*)-2-(Ethoxycarbonylmethyl-amino)-3-methyl-pentanoic acid *tert*-butyl ester (36b). The method described for the synthesis of **36a** was followed by substituting L-valine *tert*-butyl ester hydrochloride with L-isoluecine *tert*-butyl ester hydrochloride to provide **36b** in 93% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.93 (t, J = 7.46 Hz, 3H), 0.99 (d, J = 6.78 Hz, 3H), 1.27 (t, J = 7.12 Hz, 3H), 1.39–1.46 (m, 2H), 1.48 (s, 9H), 1.84–2.00 (m, 1H), 2.91 (d, J = 5.76 Hz, 1H), 3.25–3.48 (m, 2H), 4.18 (q, J = 7.12 Hz, 2H).

5.3.4. (2*S*,3*S*)-2-(2,4-Dioxo-imidazolidin-1-yl)-3-methyl-pentanoic acid *tert*-butyl ester (37b). The method described for the synthesis of **37a** was followed to provide **37b** in 47% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.93 (t, J = 7.46 Hz, 3H), 0.99 (d, J = 6.78 Hz, 3H), 1.27 (t, J = 7.12 Hz, 3H)1.39–1.46 (m, 2H), 1.48 (s, 9H), 1.84–2.00 (m, 1H), 3.89 (d, J = 17.63 Hz, 1H), 4.34–4.47 (m, 2H), 7.84 (br s, 1H).

5.3.5. (*S*)-2-(2,4-Dioxo-imidazolidin-1-yl)-3-methyl-butyric acid (38a). Deprotection of the ester **37a** was accomplished by stirring the material in a 0.1 M mixture of 1:1 dichloromethane:trifluoroacetic acid for 4 h. Removal of the solvents by evaporation afforded the desired acid **38a** in quantitative yield.

5.3.6. (2*S*,3*S*)-2-(2,4-Dioxo-imidazolidin-1-yl)-3-methyl-pentanoic acid (38b). Deprotection of the ester **37b** was accomplished by stirring the material in a 0.1 M mixture of 1:1 dichloromethane/trifluoroacetic acid for 4 h. Removal of the solvents by evaporation afforded the desired acid **38b** in quantitative yield.

5.4.Synthesis of the dihydro-pyrimidine-2,4-dione piece

5.4.1. (*S*)-2-(2,4-Dioxo-tetrahydro-pyrimidin-1-yl)-3-methyl-butyric acid *tert*-butyl ester (32). A mixture of L-valine *tert*-butyl ester hydrochloride (2.0 g, 9.5 mmol), acrylamide (6.8 g, 95 mmol), and triethylamine (2.6 mL, 19 mmol) in ethanol (40 mL) was heated to 65 °C and

stirred for 24 h. The solvent was removed in vacuo and purification by silica gel chromatography using 2% MeOH/$CHCl_3$ gave 2.33 g (99%) of **31** as a clear oil: ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.94 (d, J = 6.78 Hz, 3H), 0.97 (d, J = 6.78 Hz, 3H), 1.48 (s, 9H), 1.86–2.00 (m, 1H), 2.33–2.39 (m, 2H), 2.60–2.71 (m, 1H), 2.89 (d, J = 6.10 Hz, 1H), 2.91–2.98 (m, 1H). The amide (**31**) was treated with triethylamine (1.33 mL, 9.5 mmol) and 1,1′-carbonyldiimidazole (7.74 g, 47.5 mmol) in toluene (60 mL). The reaction mixture was stirred at 100 °C for 18 h under a nitrogen atmosphere. The solvent was removed in vacuo and purification by silica gel chromatography using 35% EtOAc/hexanes provided 1.74 g (67%) of **32** as a white solid. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.96 (d, J = 6.78 Hz, 3H), 1.05 (d, J = 6.44 Hz, 3H), 1.47 (s, 9H), 2.16–2.25 (m, 1H), 2.61–2.70 (m, 2H), 3.38–3.48 (m, 1H), 3.69–3.79 (m, 1H), 4.63 (d, J = 9.83 Hz, 1H).

5.4.2. (*S*)-2-(2,4-Dioxo-tetrahydro-pyrimidin-1-yl)-3-methyl-butyric acid (33). Deprotection of the ester **32** was accomplished by stirring the material in a 0.1 M mixture of 1:1 dichloromethane:trifluoroacetic acid for 4 h. Removal of the solvents by evaporation afforded the desired acid **33** in quantitative yield.

5.5. Alkylation of structures 32, 37a, and 37b

The procedure for making 4-(chloromethyl)-2-isopropylthiazole described in the literature[13] was applied toward the synthesis of 4-chloromethyl-2-methyl-thiazole, 4-chloromethyl-2-ethyl-thiazole, and 4-chloromethyl-2-methoxymethyl-thiazole, which were used in the synthesis of acids **34**–**35** and **39**–**42**. Benzyl chloride and 2-(chloromethyl)quinoline were purchased from Aldrich and used to synthesize acids **43** and **44**, respectively.

5.5.1. (*S*)-3-Methyl-2-[3-(2-methyl-thiazol-4-ylmethyl)-2,4-dioxo-imidazolidin-1-yl]-butyric acid (39). Compound **37a** (104 mg, 0.405 mmol) was dissolved in DMF (1 mL), cooled to 0 °C, and treated with dropwise addition of NaHMDS (1 M THF, 446 μL). After stirring for 30 min at 0 °C, the ice bath was removed. 4-chloro-2-methyl-thiazole (66 mg, 0.446 mmol) was added neat and the reaction mixture was heated to 75 °C with continued stirring for 1 h. A saturated solution of NH_4Cl (2 mL) was added and the aqueous layer was partitioned with EtOAc. The organic layer was sequentially washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel chromatography using 0–5% MeOH/CH_2Cl_2 gave 122 mg (82%) of the *tert*-butyl ester: ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.96 (d, J = 6.78 Hz, 3H), 1.03 (d, J = 6.78 Hz, 3 H), 1.46 (s, 9H), 2.09–2.23 (m, 1H), 2.66 (s, 3H), 3.92 (d, J = 17.63 Hz, 1H), 4.35 (d, J = 17.63 Hz, 1H), 4.40 (d, J = 9.49 Hz, 1H), 4.79 (s, 2H), 6.96 (s, 1H). Removal of the *tert*-butyl group was performed by dissolving the ester in CH_2Cl_2/TFA (2 mL) and stirring for 1 h. The solvents were removed in vacuo and the oil was purified by silica gel chromatography using 0–20% MeOH/CH_2Cl_2 to give 88 mg (93%) of **39**.

5.5.2. (*S*)-2-[3-(2-Ethyl-thiazol-4-ylmethyl)-2,4-dioxo-imidazolidin-1-yl]-3-methyl-butyric acid (40). The title compound was prepared using the method described for the synthesis of **39**, substituting 4-chloromethyl-2-ethyl-thiazole for 4-chloromethyl-2-methyl-thiazole. The following NMR data are for the *tert*-butyl ester precursor to **40**. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.96 (d, J = 6.78 Hz, 3H), 1.03 (d, J = 6.78 Hz, 3H), 1.35 (t, J = 7.46 Hz, 3H), 1.46 (s, 9H), 2.10–2.23 (m, 1H), 2.98 (q, J = 7.57 Hz, 2H), 3.92 (d, J = 17.63 Hz, 1H), 4.35 (d, J = 17.63 Hz, 1H), 4.41 (d, J = 9.49 Hz, 1H), 4.78–4.83 (m, 2H), 6.96 (s, 1H).

5.5.3. (*S*)-2-[3-(2-Methoxymethyl-thiazol-4-ylmethyl)-2,4-dioxo-imidazolidin-1-yl]-3-methyl-butyric acid (41). The title compound was prepared using the method described for the synthesis of **39**, substituting 4-chloromethyl-2-methoxymethyl-thiazole for 4-chloromethyl-2-methyl-thiazole. The following NMR data is for the *tert*-butyl ester precursor to **41**. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.95 (d, J = 6.78 Hz, 3H), 1.03 (d, J = 6.78 Hz, 3H), 1.46 (s, 9H), 2.09–2.25 (m, 1H), 3.47 (s, 3H), 3.87–3.99 (m, 1H), 4.29–4.45 (m, 2H), 4.69 (s, 2H), 4.82 (s, 2H), 7.15 (s, 1H).

5.5.4. (2*S*,3*S*)-2-[3-(2-Methoxymethyl-thiazol-4-ylmethyl)-2,4-dioxo-imidazolidin-1-yl]-3-methyl-pentanoic acid (42). The title compound was prepared using the method described for the synthesis of **39**, substituting 4-chloromethyl-2-methoxymethyl-thiazole for 4-chloromethyl-2-methyl-thiazole and **37b** for **37a**. The following NMR data is for the *tert*-butyl ester precursor to **42**. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.79 (t, J = 7.29 Hz, 3H), 0.94 (d, J = 6.78 Hz, 3H), 1.20–1.37 (m, 2H), 1.46 (s, 9H), 2.09–2.24 (m, 1H), 3.47 (s, 3H), 3.92 (d, J = 17.29 Hz, 1H), 4.35 (d, J = 17.29 Hz, 1H), 4.40 (d, J = 10.51 Hz, 1H), 4.69 (s, 2H), 4.82 (s, 2H), 7.15 (s, 1H).

5.5.5. (*S*)-2-(3-Benzyl-2,4-dioxo-imidazolidin-1-yl)-3-methyl-butyric acid (43). The title compound was prepared using the method described for the synthesis of **39**, substituting benzyl chloride for 4-chloromethyl-2-methyl-thiazole. The following NMR data is for the *tert*-butyl ester precursor to **43**. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.93 (d, J = 6.78 Hz, 3H), 1.02 (d, J = 6.78 Hz, 3H), 1.44 (s, 9H), 2.07–2.20 (m, 1H), 3.87 (d, J = 17.63 Hz, 1H), 4.29 (d, J = 17.63 Hz, 1H), 4.37 (d, J = 9.16 Hz, 1H), 4.68 (s, 2H), 7.27–7.42 (m, 5H).

5.5.6. (*S*)-2-(2,4-Dioxo-3-quinolin-2-ylmethyl-imidazolidin-1-yl)-3-methyl-butyric acid (44). The title compound was prepared using the method described for the synthesis of **39**, substituting 2-(chloromethyl)quinoline hydrochloride for 4-chloromethyl-2-methyl-thiazole. The following NMR data is for the *tert*-butyl ester precursor to **44**. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 1.04 (d, J = 6.95 Hz, 3H), 1.07 (d, J = 6.95 Hz, 3H), 1.48 (s, 9H), 2.15–2.30 (m, 1H), 4.05 (d, J = 17.63 Hz, 1H), 4.40–4.52 (m, 2H), 4.95–5.12 (m, 2H), 7.32 (d, J = 8.48 Hz, 1H), 7.45–7.54 (m, 1H), 7.62–7.70 (m, 1H), 7.77 (d, J = 8.14 Hz, 1H), 7.97 (d, J = 8.14 Hz, 1H), 8.11 (d, J = 8.48 Hz, 1H).

5.5.7. (*S*)-3-Methyl-2-[3-(1-methyl-1*H*-benzoimidazol-2-ylmethyl)-2,4-dioxo-imidazolidin-1-yl]-butyric acid (45). To a solution of commercially available 1-methyl-1*H*-benzoimidazole-2-carbaldehyde (254 mg, 1.58 mmol) in tetrahydrofuran (4 mL) cooled to 0 °C was added diisobutylaluminum hydride (1 M hexanes, 2.37 mL) dropwise. The reaction mixture was stirred for 1 h at 0 °C, quenched with a 10% solution of sodium potassium tartrate (12 mL) with stirring continued overnight at ambient temperature. The layers were separated and the aqueous layer back-extracted with dichloromethane (10 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Silica gel chromatography using 2–10% MeOH/CH_2Cl_2 gave 226 mg of the desired hydroxymethyl compound as a white solid (88%). ^{1}H NMR (300 MHz, MeOH) δ ppm 3.91 (s, 3H), 4.83 (s, 2H), 7.20–7.35 (m, 2H), 7.47–7.52 (m, 1H), 7.58–7.65 (m, 1H). To the alcohol (1.39 mmol) dissolved in CH_2Cl_2 (7 mL) was added $SOCl_2$ (0.66 mL, 9.0 mmol). The reaction mixture was stirred for 3 h and the solvent was removed in vacuo. The material was taken up in 10:1 CH_2Cl_2 (20 mL) and solid $NaHCO_3$ was added until neutral pH. The mixture was filtered and solvents were removed in vacuo. Silica gel chromatography was performed using 2–10% MeOH/CH_2Cl_2 to give 255 mg of 2-chloromethyl-1-methyl-1*H*-benzoimidazole as a white solid. This material (120 mg, 0.665 mmol) and **37a** (143 mg, 0.56 mmol) were combined in DMF (0.5 mL) and treated with NaHMDS (1 M THF, 567 μL). Following the previously described protocol for N-alkylation gave crude material which was purified by silica gel chromatography (0–25% EtOAc in CH_2Cl_2) to provide 199 mg (89%) of the ester precursor to **45** as a colorless oil: ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.98 (d, J = 6.78 Hz, 3H), 1.03 (d, J = 6.78 Hz, 3H), 1.46 (s, 9H), 2.09–2.23 (m, 1H), 3.87 (s, 3H), 3.99 (d, J = 17.63 Hz, 1H), 4.37 (s, 1H), 4.42 (d, J = 9.49 Hz, 1H), 4.90–5.03 (m, 2H), 7.19–7.35 (m, 3H), 7.69–7.75 (m, 1H). Removal of the *tert*-butyl ester was performed by dissolving the material in CH_2Cl_2:TFA (2 mL) and stirring for 1 h. The solvents were removed in vacuo to give the title compound **45**, which was used without further purification.

5.5.8. (*S*)-3-Methyl-2-[3-(2-methyl-thiazol-4-ylmethyl)-2,4-dioxo-tetrahydro-pyrimidin-1-yl]-butyric acid (34). The title compound was prepared using the method described for the synthesis of **39**, substituting **32** for **37a**. The following NMR data are for the *tert*-butyl ester precursor to **34**. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.94 (d, J = 6.78 Hz, 3H), 1.04 (d, J = 6.44 Hz, 3H), 1.45 (s, 9H), 2.16–2.26 (m, 1H), 2.65 (s, 3H), 2.69–2.80 (m, 2H), 3.33–3.45 (m, 1H), 3.63–3.73 (m, 1H), 4.65 (d, J = 9.83 Hz, 1H), 5.08 (s, 2H), 6.87 (s, 1H).

5.5.9. (*S*)-3-Methyl-2-[3-(2-methyl-thiazol-4-ylmethyl)-2,4-dioxo-tetrahydro-pyrimidin-1-yl]-butyric acid (35). The title compound was prepared using the method described for the synthesis of **39**, substituting **32** for **37a** and 4-chloromethyl-2-ethyl-thiazole for 4-chloromethyl-2-methyl-thiazole. The following NMR data are for the *tert*-butyl ester precursor to **35**. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.94 (d, J = 6.78 Hz, 3H), 1.04 (d, J = 6.44 Hz, 3H), 1.30–1.36 (m, 3H), 1.45 (s, 9H), 2.11–2.30 (m, 1H), 2.70–2.80 (m, 2H), 2.97 (q, J = 7.57 Hz, 2H), 3.32–3.47 (m, 1H), 3.61–3.77 (m, 1H), 4.66 (d, J = 9.83 Hz, 1H), 5.09 (s, 2H), 6.86 (s, 1H).

5.6. Synthesis of imidazolone

5.6.1. 3-Methyl-2-(2-oxo-2,3-dihydro-imidazol-1-yl)-butyric acid (48). To a solution of *N*-[[(4-nitrophenyl)-oxy]carbonyl]-L-valine methyl ester[13] (0.5 g, 1.69 mmol) in THF (7 mL) were added sequentially triethylamine (0.24 mL, 1.69 mmol), 2,2-diethoxy-ethylamine (0.27 mL, 1.86 mmol), and 4-(dimethylamino)pyridine (30 mg, 0.25 mmol). After stirring for 48 h, the solvents were removed in vacuo and the material was purified by silica gel chromatography using 0–50% EtOAc/CH_2Cl_2 to give 0.26 g (53%) of **47**: ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.90 (d, J = 6.78 Hz, 3H), 0.95 (d, J = 6.78 Hz, 3H), 1.17–1.26 (m, 6 H), 2.06–2.19 (m, 1H), 3.32 (t, J = 5.93 Hz, 3H), 3.50–3.62 (m, 2H), 3.64–3.78 (m, 4H), 4.39 (dd, J = 8.82, 4.75 Hz, 1H), 4.50 (t, J = 5.43 Hz, 1H), 4.64 (t, J = 5.76 Hz, 1H), 5.01 (d, J = 8.48 Hz, 1H). Cyclization of **47** was accomplished by treatment with 10 mL of formic acid and heating to 75 °C for 2 h. After removal of the solvents in vacuo, silica gel chromatography using 0–100% EtOAc/CH_2Cl_2 provided 152 mg (89%) of the methyl ester: ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.89 (d, J = 6.78 Hz, 3H), 1.01 (d, J = 6.78 Hz, 3H), 2.20–2.35 (m, 1H), 3.75 (s, 3H), 4.61 (d, J = 9.49 Hz, 1H), 6.30 (t, J = 2.54 Hz, 1H), 6.47–6.53 (m, 1H), 9.77 (br s, 1H). The ester was hydrolyzed with LiOH·H_2O (97 mg, 2.3 mmol) in 30% H_2O/THF (4 mL). After 1 h, the solvents were removed in vacuo to leave 141 mg (100%) of the title compound **48**.

5.7. Synthesis of N-alkylated imidazolones

5.7.1. (*S*)-3-Methyl-2-[3-(2-methyl-thiazol-4-ylmethyl)-2-oxo-2,3-dihydro-imidazol-1-yl]-butyric acid (49). To a solution of 2,2-diethoxy-ethylamine (5 mL, 34.4 mmol) in THF (15 mL) was added 4-chloromethyl-2-methyl-thiazole (0.5 g, 3.4 mmol). After 18 h of stirring, the solvent was removed in vacuo and the material was purified using 0–10% MeOH/CH_2Cl_2 to give 0.76 g (76%) of **49a**. To a solution of *N*-[[(4-nitrophenyl)-oxy]carbonyl]-L-valine methyl ester (0.92 g, 3.1 mmol) in THF (12 mL) were added triethylamine (0.43 mL, 3.1 mmol), DMAP (60 mg, 0.49 mmol), and **49a** (0.76 g, 3.1 mmol). After stirring for 48 h, the solvents were removed in vacuo. The reaction mixture was dissolved in EtOAc, washed with a 10% solution of Na_2CO_3 (4×), washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude urea intermediate was cyclized by dissolving in formic acid (30 mL) and stirring for 18 h at ambient temperature. Removal of the solvent and purification by silica gel chromatography (0–100% EtOAc/CH_2Cl_2) gave 0.51 g (53% over 2 steps) of the methyl ester: ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.89 (d, J = 6.44 Hz, 3H), 1.00 (d, J = 6.78 Hz, 3H), 2.20–2.34 (m, 1H), 2.69 (s, 3H), 3.73 (s, 3 H), 4.67 (d, J = 9.16 Hz, 1H), 4.88 (s, 2H), 6.37 (d, J = 3.05 Hz, 1H), 6.52 (d, J = 3.05 Hz, 1H), 6.93 (s,

1H). The methyl ester was hydrolyzed with $LiOH \cdot H_2O$ as previously described to give 0.48 g (100%) of the title compound **49**.

5.7.2. (*S*)-2-[3-(2-Ethyl-thiazol-4-ylmethyl)-2-oxo-2,3-dihydro-imidazol-1-yl]-3-methyl-butyric acid (50). The title compound was prepared using the method described for the synthesis of **49**, substituting 4-chloromethyl-2-ethyl-thiazole for 4-chloromethyl-2-methyl-thiazole to give **50** in 53% overall yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.89 (d, J = 6.78 Hz, 3H), 1.00 (d, J = 6.78 Hz, 3H), 1.38 (t, J = 7.46 Hz, 3H), 2.18–2.36 (m, 1H), 3.01 (q, J = 7.69 Hz, 2H), 3.74 (s, 3H), 4.67 (d, J = 9.16 Hz, 1H), 4.89 (s, 2H), 6.37 (d, J = 3.05 Hz, 1H), 6.52 (d, J = 3.05 Hz, 1H), 6.93 (s, 1H).

5.8. Synthesis of the 5- and 6-membered cyclic urea acids

Details for the synthesis of the 5- and 6-membered cyclic urea cores have been previously described.[14] The synthesis of 5- and 6-membered cyclic ureas containing P3 groups will be detailed in a future publication.[15]

5.9. Coupling of the acid and amine pieces

A number of different methods were used to couple the amine and acid cores to produce HIV protease inhibitors.

5.9.1. Method 1. To the acid core in THF (0.1 M) were added the amine core (1.0 equiv), 3-dimethoxyphosphoryloxy-1,2,3-benzo-triazin-4(3*H*)-one (1.5 equiv), and triethylamine (3.0 equiv). After 4 h, the solvent was removed and the reaction mixture was taken up in EtOAc, washed with a 10% solution of Na_2CO_3 (2×), washed with a brine solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Silica gel chromatography was performed using EtOAc and/or MeOH in CH_2Cl_2 to give the final product.

5.9.2. (*S*)-*N*-[(1*S*,2*R*)-3-(Benzenesulfonyl-isobutyl-amino)-1-benzyl-2-hydroxy-propyl]-3-methyl-2-(2-oxo-tetrahydro-pyrimidin-1-yl)-butyramide (2a). The six-membered cyclic urea carboxylic acid core and the amine core **52** were coupled using method 1 to give **2a** in 32% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.76–0.81 (m, 6H), 0.87 (d, J = 6.62 Hz, 3H), 0.92 (d, J = 6.62 Hz, 3H), 1.42–1.50 (m, 1H), 1.65–1.75 (m, 1H), 1.82–1.92 (m, 1H), 2.10–2.18 (m, 1H), 2.61–2.74 (m, 2H), 2.82–2.89 (m, 1H), 2.94–3.25 (m, 6 H), 3.74–3.79 (m, 1H), 4.15–4.22 (m, 2H), 4.66 (br s, 1H), 6.74 (d, J = 6.99 Hz, 1H), 7.12–7.22 (m, 1H), 7.22–7.25 (m, 4H), 7.49–7.61 (m, 3H), 7.81 (d, J = 6.99 Hz, 2H); MS (ESI) m/z 559.4 $[M+H]^+$, 581.4 $[M+Na]^+$.

5.9.3. (*S*)-*N*-{(1*S*,2*R*)-3-[(4-Amino-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-3-methyl-2-(2-oxo-tetrahydro-pyrimidin-1-yl)-butyramide (2b). The six-membered cyclic urea carboxylic acid core and the amine core **23** were coupled using method 1 to give **2b** in 45% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.78 (d, J = 1.47 Hz, 3H), 0.80 (d, J = 1.84 Hz, 3H), 0.87 (d, J = 6.62 Hz, 3H), 0.93 (d, J = 6.62 Hz, 3H), 1.39–1.54 (m, 1H), 1.61–1.77 (m, 1H), 1.78–1.91 (m, 1H), 2.07–2.22 (m, 1H), 2.60–2.81 (m, 3H), 2.92–3.25 (m, 6 H), 3.71–3.77 (m, 1H), 4.07–4.26 (m, 2H), 4.77 (br s, 1H), 6.56 (m, 1H), 6.68 (d, J = 8.82 Hz, 2H), 7.15–7.21 (m, 1H), 7.22–7.26 (m, 4H), 7.57 (d, J = 8.82 Hz, 2H); MS (ESI) m/z 574.4 $[M+H]^+$, 596.4 $[M+Na]^+$.

5.9.4. (*S*)-*N*-{(1*S*,2*R*)-3-[(3-Amino-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-3-methyl-2-(2-oxo-tetrahydro-pyrimidin-1-yl)-butyramide (2c). The six-membered cyclic urea carboxylic acid core and the amine core **24** were coupled using method 1 to give **2c** in 38% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.75–0.82 (m, 6H), 0.89 (d, J = 6.78 Hz, 3H), 0.93 (d, J = 6.44 Hz, 3H), 1.43–1.60 (m, 1H), 1.64–1.76 (m, 1H), 1.81–1.93 (m, 1H), 2.11–2.23 (m, 1H), 2.63–2.71 (m, 2H), 2.82–3.00 (m, 3H), 3.07–3.24 (m, 5H), 3.71–3.81 (m, 1H), 3.84 (d, J = 3.39 Hz, 1H), 4.03 (br s, 2H), 4.11–4.25 (m, 2H), 4.59 (br s, 1H), 6.68 (d, J = 8.82 Hz, 1H), 6.79–6.86 (m, 1H), 7.09–7.14 (m, 2H), 7.15–7.21 (m, 1H), 7.22–7.29 (m, 4H); MS (ESI) m/z 574.4 $[M+H]^+$, 596.4 $[M+Na]^+$.

5.9.5. (*S*)-*N*-{(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl-(4-methoxy-benzenesulfonyl)amino]-propyl}-3-methyl-2-(2-oxo-tetrahydro-pyrimidin-1-yl)-butyramide (2d). The six-membered cyclic urea carboxylic acid core and the amine core **25** were coupled using method 1 to give **2d** in 67% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.76–0.80 (m, 6H), 0.87 (d, J = 6.62 Hz, 3H), 0.93 (d, J = 6.25 Hz, 3H), 1.38–1.54 (m, 1H), 1.61–1.77 (m, 1H), 1.80–1.90 (m, 1H), 2.10- 2.18 (m, 1H), 2.59–2.72 (m, 2H), 2.76–2.83 (m, 1H), 2.93–3.03 (m, 2H), 3.03–3.12 (m, 2H), 3.13–3.26 (m, 2H), 3.68–3.79 (m, 1H), 3.87 (s, 3H), 4.12–4.21(m, 2H), 4.59 (br s, 1H), 6.67 (d, J = 8.09 Hz, 1H), 6.98 (d, J = 8.82 Hz, 2H), 7.13–7.21 (m, 1H), 7.22–7.25 (m, 4H), 7.74 (d, J = 8.82 Hz, 2H); MS (ESI) m/z 589.4 $[M+H]^+$, 611.4 $[M+Na]^+$.

5.9.6. (*S*)-*N*-{(1*S*,2*R*)-1-Benzyl-3-[(4-chloro-benzenesulfonyl)-isobutyl-amino]-2-hydroxy-propyl}-3-methyl-2-(2-oxo-tetrahydro-pyrimidin-1-yl)-butyramide (2e). The six-membered cyclic urea carboxylic acid core and the amine core **28** were coupled using method 1 to give **2e** in 50% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.75–0.83 (m, 6H), 0.87 (d, J = 6.62 Hz, 3H), 0.92 (d, J = 6.62 Hz, 3H), 1.40–1.52 (m, 1H), 1.59–1.77 (m, 1H), 1.80–1.95 (m, 1H), 2.08–2.21 (m, 1H), 2.61–2.76(m, 2H), 2.83–2.90 (m, 1H), 2.93–3.05 (m, 2H), 3.05–3.25 (m, 5H), 3.72–3.78 (m, 1H), 4.10–4.25 (m, 2H), 4.62 (br s, 1H), 6.79 (d, J = 7.72 Hz, 1H), 7.15–7.21 (m, 1H), 7.23–7.30 (m, 4H), 7.48 (d, J = 8.46 Hz, 2H), 7.74 (d, J = 8.46 Hz, 2H); MS (ESI) m/z 593.3 $[M+H]^+$, 615.3 $[M+Na]^+$.

5.9.7. (*S*)-*N*-{(1*S*,2*R*)-3-[(3-Amino-4-chloro-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-3-methyl-2-(2-oxo-tetrahydro-pyrimidin-1-yl)-butyramide (2f). The six-membered cyclic urea carboxylic acid core and the amine core **29** were coupled using method 1 to give **2f** in 37% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.77 (d, J = 6.25 Hz, 3H), 0.81 (d, J = 6.62 Hz,

3H), 0.89 (d, J = 6.62 Hz, 3H), 0.92 (d, J = 6.62 Hz, 3H), 1.44–1.55 (m, 1H), 1.62- 1.75 (m, 1H), 1.82–1.95 (m, 1H), 2.09–2.24 (m, 1H), 2.63–2.71 (m, 2H), 2.90 (d, J = 7.72 Hz, 2H), 2.95–3.02 (m, 1H), 3.08–3.22 (m, 5H), 3.77–3.83 (m, 1H), 4.16–4.25(m, 2H), 4.46–4.66 (m, 1H), 4.75 (br s, 1H), 6.84 (d, J = 8.46 Hz, 1H), 7.05 (dd, J = 8.09, 2.21 Hz, 1H), 7.13–7.21 (m, 1H), 7.22–7.25 (m, 4H), 7.35 (d, J = 8.46 Hz, 1H); MS (ESI) m/z 608.3 $[M+H]^+$, 630.3 $[M+Na]^+$.

5.9.8. (*S*)-*N*-{(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[(4-hydroxy-benzenesulfonyl)-isobutylamino]-propyl}-3-methyl-2-(2-oxo-tetrahydro-pyrimidin-1-yl)-butyramide (2g). The six-membered cyclic urea carboxylic acid core and the amine core **30** were coupled using method 1 to give **2g** in 49% yield. ^{1}H NMR (300 MHz, methanol-d_4) δ ppm 0.75–0.79 (m, 6H), 0.87 (d, J = 6.62 Hz, 3H), 0.91 (d, J = 6.62 Hz, 3H), 1.36–1.46 (m, 1H), 1.57–1.67 (m, 1H), 1.94–2.12 (m, 2H), 2.45–2.56 (m, 2H), 2.85–3.05 (m, 5H), 3.08–3.13 (m, 2H), 3.21 (dd, J = 13.97, 2.94 Hz, 1H), 3.33–3.39 (m, 1H), 3.69–3.76 (m, 1H), 4.04–4.15 (m, 1H), 4.19 (d, J = 11.03 Hz, 1H), 6.87–6.94 (m, 2H), 7.12–7.19 (m, 1H), 7.19–7.25 (m, 4H), 7.62–7.69 (m, 2H), 7.78 (d, J = 9.56 Hz, 1H); MS (ESI) m/z 575.4 $[M+H]^+$, 597.3 $[M+Na]^+$.

5.9.9. (*S*)-*N*-{(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl-(4-methoxy-benzenesulfonyl)amino]- propyl}-3-methyl-2-(2-oxo-2,3-dihydro-imidazol-1-yl)-butyramide (3d). Acid core **48** and amine core **25** were coupled using method 1 to give **3d** in 24% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.77 (d, J = 6.62 Hz, 3H), 0.80–0.91 (m, 9H), 1.75–1.89 (m, 1H), 2.23–2.39 (m, 1H), 2.71–2.90 (m, 4H), 2.99–3.20 (m, 4H), 3.78–3.88 (m, 3H), 3.87 (s, 3H), 4.06–4.21 (m, 2H), 6.15–6.21 (m, 1H), 6.24–6.34 (m, 1H), 6.92–6.99 (m, 2H), 7.06–7.15 (m, 1H), 7.13–7.21 (m, 2H), 7.63 (d, J = 9.19 Hz, 1H), 7.70–7.79 (m, 2H); MS (ESI) m/z 573.3 $[M+H]^+$, 595.3 $[M+Na]^+$.

5.9.10. Method 2. To the carboxylic acid core in CH_2Cl_2 (0.1 M) were added *N*-hydroxysuccinimide (1.5 equiv), 1,3-dicyclohexylcarbodiimide (1.5 equiv), and *N*-methylmorpholine (2.0 equiv). The amine core was then added (1.0 equiv) and additional DMF was added when necessary for solubility. After stirring for 18 h, the reaction mixture was filtered and the solvents were removed in vacuo. Silica gel chromatography was performed using EtOAc and/or MeOH in CH_2Cl_2 to give the final product.

5.9.11. (*S*)-*N*-{(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl-(4-methoxy-benzenesulfonyl)amino]-propyl}-2-(2,4-dioxo-tetrahydro-pyrimidin-1-yl)-3-methyl-butyramide (3a). Acid core **33** and amine core **25** were coupled using method 2 to give **3a** in 41% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.76–0.86 (m, 6 H), 0.88 (d, J = 6.44 Hz, 3H), 0.95 (d, J = 6.44 Hz, 3H), 1.80–1.91 (m, 1H), 2.04–2.20 (m, 2H), 2.31–2.44 (m, 1H), 2.52–2.70 (m, 2H), 2.75–2.84 (m, 1H), 2.85 (s, 1H), 2.96–3.09 (m, 3H), 3.16–3.28 (m, 2H), 3.73–3.84 (m, 2H), 3.88 (s, 3H), 4.19 (d, J = 11.19 Hz, 1H), 4.20–4.28 (m, 1H), 6.28 (d, J = 9.49 Hz, 1H), 6.95–7.04 (m, 2H), 7.14–7.25 (m, 5H), 7.41 (br s, 1H), 7.70–7.79 (m, 2H); MS (ESI) m/z 603.4 $[M+H]^+$, 625.4 $[M+Na]^+$.

5.9.12. (*S*)-*N*-{(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-propyl}-2-(2,4-dioxo-imidazolidin-1-yl)-3-methyl-butyramide (3c). Acid core **38a** and amine core **25** were coupled using method 2 to give **3c** in 37% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.82 (d, J = 6.44 Hz, 3H), 0.83 (d, J = 6.44 Hz, 3H), 0.87 (d, J = 6.44 Hz, 3H), 0.93 (d, J = 6.44 Hz, 3H), 1.80–1.91 (m, 1H), 1.98–2.10 (m, 1H), 2.63 (dd, J = 13.90, 10.85 Hz, 1H), 2.74–2.87 (m, 2H), 2.93–3.11 (m, 2H), 3.13–3.24 (m, 2H), 3.44 (dd, J = 96.64, 18.31 Hz, 2H), 3.75 (d, J = 2.71 Hz, 1H), 3.85–3.94 (m, 1H), 3.88 (s, 3H), 4.00 (d, J = 11.19 Hz, 1H), 4.17–4.32 (m, 1H), 6.74 (d, J = 9.83 Hz, 1H), 6.93–7.03 (m, 2H), 7.11–7.23 (m, 5H), 7.67–7.80 (m, 2H); MS (ESI) m/z 589.4 $[M+H]^+$, 611.4 $[M+Na]^+$.

5.9.13. (*S*)-*N*-{(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[(4-hydroxy-benzenesulfonyl)-isobutylamino]-propyl}-2-[3-(2-ethyl-thiazol-4-ylmethyl)-2,4-dioxo-tetrahydro-pyrimidin-1-yl]-3-methyl-butyramide (4a). Acid core **35** and amine core **30** were coupled using method 2 to give **4a** in 36% yield: ^{1}H NMR (300 MHz, MeOH) δ ppm 0.80 (d, 2.03 Hz, 3H), 0.82 (d, 2.03 Hz, 3H), 0.87 (d, J = 6.44 Hz, 3H), 0.91 (d, J = 6.78 Hz, 3H), 1.29–1.37 (m, 3H), 1.84–2.13 (m, 3H), 2.37–2.53 (m, 2H), 2.85–2.92 (m, 3 H), 2.96–3.03 (m, 4H), 3.06–3.15 (m, 1H), 3.22 (dd, J = 13.90, 3.05 Hz, 1H), 3.38 (dd, J = 14.92, 3.73 Hz, 1H), 3.72–3.80 (m, 1H), 4.08–4.18 (m, 1H), 4.28 (d, J = 11.19 Hz, 1H), 4.95–5.16 (m, 3H), 6.87–6.93 (m, 2H), 7.01–7.05 (m, 3H), 7.10–7.15 (m, 3H), 7.64–7.69 (m, 2H); MS (ESI) m/z 714.8 $[M+H]^+$.

5.9.14. (*S*)-*N*-{(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[(4-hydroxy-benzenesulfonyl)-isobutylamino]-propyl}-2-[3-(2-ethyl-thiazol-4-ylmethyl)-2-oxo-imidazolidin-1-yl]-3-methyl-butyramide (4b). The five-membered cyclic urea carboxylic acid core and the amine core **30** were coupled using method 2 to produce **4b**. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.74 (d, J = 6.44 Hz, 3H), 0.80 (d, J = 6.78 Hz, 3H), 0.89 (d, J = 6.78 Hz, 3H), 0.92 (d, J = 6.78 Hz, 3H), 1.38 (t, J = 7.12 Hz, 3H), 1.81–1.92 (m, 1H), 2.07–2.17 (m, 1H), 2.62–2.80 (m, 2H), 2.89–3.00 (m, 3H), 3.04–3.19 (m, 5H), 3.19–3.30 (m, 2H), 3.60 (d, J = 11.19 Hz, 1H), 3.73–3.82 (m, 1H), 4.00–4.13 (m, 1H), 4.34–4.52 (m, 2H), 6.43–6.58 (m, 1H), 6.92 (d, J = 8.48 Hz, 2H), 7.00 (s, 1H), 7.08–7.19 (m, 6 H), 7.65 (d, J = 8.48 Hz, 2H); MS (ESI) m/z 686.5 $[M+H]^+$, 709.5 $[M+Na]^+$.

5.9.15. (*S*)-*N*-{(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[(4-hydroxy-benzenesulfonyl)-isobutylamino]-propyl}-2-[3-(2-ethyl-thiazol-4-ylmethyl)-2,4-dioxo-imidazolidin-1-yl]-3-methyl butyramide (4c). The acid core **40** and amine core **30** were coupled using method 2 to produce **4c** in 27% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.74–0.84 (m, J = 6.61, 6.61 Hz, 6H), 0.88 (d, J = 6.44 Hz, 3H), 0.92 (d, J = 6.44 Hz, 3H), 1.32 (t, J = 7.63 Hz, 3H), 1.68–1.91 (m, 3H), 1.98–2.14 (m, 1H), 2.66 (dd, J = 14.24, 10.85 Hz, 1H), 2.83 (dd, J = 13.56, 6.78 Hz, 1H), 2.92–3.09 (m, 5H), 3.11–3.22 (m, 1H), 3.44 (dd, J = 101.73, 17.97 Hz, 2H), 3.78–3.87 (m, 2H), 3.89 (d, J = 11.19 Hz, 1H), 4.67–4.84 (m, 2H), 6.33 (d, J = 9.49 Hz, 1H), 6.87–6.97 (m, 2H), 7.04 (s, 1H),

7.06–7.13 (m, 5H), 7.59–7.71 (m, 2H); MS (ESI) *m*/*z* 700.4 $[M+H]^+$.

5.9.16. (*S*)-*N*-{(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[(4-hydroxy-benzenesulfonyl)-isobutylamino]-propyl}-2-[3-(2-ethyl-thiazol-4-ylmethyl)-2-oxo-2,3-dihydro-imidazol-1-yl]-3-methyl-butyramide (4d). The acid core **49** and amine core **30** were coupled using method 2 to produce **4d** in 54% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.65–0.76 (m, J = 7.12, 7.12 Hz, 6H), 0.87 (d, J = 6.78 Hz, 3H), 0.88 (d, J = 6.78 Hz, 3H), 1.37 (t, J = 7.46 Hz, 3H), 1.77–1.91 (m, 1H), 2.25–2.40 (m, 1H), 2.69–2.81 (m, 1H), 2.90 (dd, J = 7.46, 3.05 Hz, 2H), 2.95–3.12 (m, 5H), 3.75–3.83 (m, 2H), 3.86 (d, J = 10.85 Hz, 1H), 3.96–4.08 (m, 1H), 4.80–4.95 (m, 2H), 6.19 (d, J = 3.05 Hz, 1H), 6.32 (d, J = 2.71 Hz, 1H), 6.87–6.94 (m, 2H), 6.97 (s, 1H), 7.04–7.18 (m, 5H), 7.59–7.64 (m, 2H); MS (ESI) *m*/*z* 684.3 $[M+H]^+$, 706.3 $[M+Na]^+$.

5.9.17. (*S*)-*N*-{(1*S*,2*R*)-3-[(4-Amino-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-2-[3-(2-ethyl-thiazol-4-ylmethyl)-2,4-dioxo-tetrahydro-pyrimidin-1-yl]-3-methyl-butyramide (5a). The acid core **34** and amine core **23** were coupled using method 2 to produce **5a** in 65% yield. ^{1}H NMR (300 MHz, MeOH) δ ppm 0.78–0.85 (m, 6 H), 0.85–0.95 (m, 6 H), 1.33 (t, J = 7.46 Hz, 3H), 1.85–2.13 (m, 3H), 2.38–2.53 (m, 2H), 2.79–2.93 (m, 3H), 2.93–3.04 (m, 3H), 3.05–3.16 (m, 1H), 3.23 (dd, J = 13.90, 3.05 Hz, 1H), 3.30–3.43 (m, 1H), 3.71–3.82 (m, 1H), 4.04–4.25 (m, 2H), 4.28 (d, J = 10.85 Hz, 1H), 4.94–5.18 (m, 2H), 6.67–6.74 (m, 2H), 6.97–7.07 (m, 3H), 7.09–7.17 (m, 3H), 7.46–7.53 (m, 2H); MS (ESI) *m*/*z* 713.8 $[M+H]^+$.

5.9.18. (*S*)-*N*-{(1*S*,2*R*)-3-[(4-Amino-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-2-[3-(2-ethyl-thiazol-4-ylmethyl)-2-oxo-imidazolidin-1-yl]-3-methyl-butyramide (5b). The 5-membered cyclic urea carboxylic acid core and amine core **23** were coupled using method 2 to produce **5b**. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.78 (d, J = 6.44 Hz, 3H), 0.81 (d, J = 6.78 Hz, 3H), 0.86 (d, J = 6.44 Hz, 3H), 0.92 (d, J = 6.44 Hz, 3H), 1.38 (t, J = 7.63 Hz, 3H), 1.76–1.91 (m, 1H), 2.05–2.31 (m, 1H), 2.63–2.82 (m, 2H), 2.83 (s, 1H), 2.90–3.06 (m, 3H), 3.07–3.26 (m, 3H), 3.44–3.55 (m, 1H), 3.65 (d, J = 11.19 Hz, 1H), 3.70–3.80 (m, 1H), 3.90 (d, J = 3.05 Hz, 1H), 4.07–4.25 (m, 3H), 4.34–4.50 (m, 2H), 6.38 (d, J = 9.16 Hz, 1H), 6.63–6.73 (m, 2H), 6.95 (s, 1H), 7.11–7.22 (m, 5H), 7.52–7.59 (m, 2H); MS (ESI) *m*/*z* 685.4 $[M+H]^+$, 708.4 $[M+Na]^+$.

5.9.19. (*S*)-*N*-{(1*S*,2*R*)-3-[(4-Amino-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-2-[3-(2-ethyl-thiazol-4-ylmethyl)-2,4-dioxo-imidazolidin-1-yl]-3-methyl-butyramide (5c). The acid core **40** and amine core **23** were coupled using method 2 to produce **5c** in 41% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.79 (d, J = 6.78 Hz, 3H), 0.82 (d, J = 6.44 Hz, 3H), 0.87 (d, J = 6.44 Hz, 3H), 0.94 (d, J = 6.44 Hz, 3H), 1.33 (t, J = 7.63 Hz, 3H), 1.72–1.91 (m, 1H), 2.00–2.16 (m, 1H), 2.58–2.82 (m, 2H), 2.88–3.02 (m, 5H), 3.07 (dd, J = 13.90, 4.07 Hz, 1H), 3.13–3.23 (m, 1H), 3.41 (dd, J = 107.49, 17.97, 2H), 3.76–3.83 (m, 1H), 3.84 (s, 1H), 3.90 (d, J = 11.19 Hz, 1H), 4.13–4.31 (m, 3 H), 4.68–4.82 (m, 2H), 6.16 (d, J = 9.49 Hz, 1H), 6.64–6.73 (m, 2H), 7.00 (s, 1H), 7.06–7.14 (m, 5H), 7.52–7.60 (m, 2H); MS (ESI) *m*/*z* 699.5 $[M+H]^+$.

5.9.20. (*S*)-*N*-{(1*S*,2*R*)-3-[(4-Amino-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-2-[3-(2-ethyl-thiazol-4-ylmethyl)-2-oxo-2,3-dihydro-imidazol-1-yl]-3-methyl-butyramide (5d). The acid core **49** and amine core **23** were coupled using method 2 to produce **5d** in 51% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.71 (d, J = 6.78 Hz, 3H), 0.75 (d, J = 6.78 Hz, 3H), 0.83 (d, J = 6.78 Hz, 3H), 0.88 (d, J = 6.44 Hz, 3H), 1.37 (t, J = 7.46 Hz, 3H), 1.70–1.85 (m, 1H), 2.26–2.43 (m, 2H), 2.73-2.89 (m, 5H), 2.90-3.14(m, 6H), 3.71–3.84 (m, 1H), 3.92 (d, J = 10.85 Hz, 1H), 4.04–4.16 (m, 1H), 4.85 (s, 2H), 6.16 (d, J = 3.05 Hz, 1H), 6.31 (d, J = 3.05 Hz, 1H), 6.66 (d, J = 8.48 Hz, 2H), 6.95 (s, 1H), 7.03–7.20 (m, 5H), 7.49–7.57 (m, 2H); MS (ESI) *m*/*z* 683.3 $[M+H]^+$, 705.3 $[M+Na]^+$.

5.9.21. (*S*)-*N*-{(1*S*,2*R*)-3-[(3-Amino-4-chloro-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-2-[3-(2-ethyl-thiazol-4-ylmethyl)-2,4-dioxo-tetrahydro-pyrimidin-1-yl]-3-methyl-butyramide (6a). The acid core **34** and amine core **29** were coupled using method 2 to produce **6a** in 24% yield. ^{1}H NMR (300 MHz, MeOH) δ ppm 0.79 (d, J = 2.03 Hz, 3H), 0.81 (d, J = 2.37 Hz, 3H), 0.87–0.95 (m, 6 H), 1.33 (t, J = 7.46 Hz, 3H), 1.85–2.18 (m, 3H), 2.33–2.56 (m, 2H), 2.78–3.17 (m, 7H), 3.21 (dd, J = 13.73, 3.22 Hz, 1H), 3.40 (dd, J = 14.75, 3.90 Hz, 1H), 3.68–3.82 (m, 1H), 4.05–4.20 (m, 1H), 4.28 (d, J = 11.19 Hz, 1H), 4.92–5.17 (m, 2H), 6.97–7.08 (m, 4H), 7.09–7.17 (m, 3H), 7.26 (d, J = 2.03 Hz, 1H), 7.35 (d, J = 8.14 Hz, 1H); MS (ESI) *m*/*z* 748.3 $[M+H]^+$.

5.9.22. (*S*)-*N*-{(1*S*,2*R*)-3-[(3-Amino-4-chloro-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-2-[3-(2-ethyl-thiazol-4-ylmethyl)-2-oxo-imidazolidin-1-yl]-3-methyl-butyramide (6b). The 5-membered cyclic urea carboxylic acid core and amine core **29** were coupled using method 2 to produce **6b**. ^{1}H NMR (300 MHz, chloroform-D). δ ppm 0.78 (d, J = 6.44 Hz, 3H), 0.82 (d, J = 6.78 Hz, 3H), 0.90 (d, J = 3.39 Hz, 3H), 0.92 (d, J = 3.73 Hz, 3H), 1.37 (t, J = 7.63 Hz, 3H), 1.87 (m, 1H), 2.17 (m, 1H), 2.65 (q, J = 8.36 Hz, 1H), 2.78 (dd, J = 14.24, 10.51 Hz, 1H), 2.90 (dd, J = 7.46, 4.41 Hz, 2H), 3.00 (m, 2H), 3.12 (m, 2H), 3.23 (m, 1H), 3.72 (d, J = 3.73 Hz, 1H), 3.76 (d, J = 10.17 Hz, 1H), 3.83 (m, 1H), 4.24 (m, 1H), 4.42 (m, 2H), 4.57 (d, J = 6.78 Hz, 2H), 6.58 (d, J = 8.82 Hz, 1H), 6.94 (s, 1H), 7.01 (d, J = 2.03 Hz, 1H), 7.04 (t, J = 2.54 Hz, 1H), 7.17 (m, 7H), 7.35 (m, 1H); MS (ESI) *m*/*z* 719.8 $[M+H]^+$, 742.8 $[M+Na]^+$.

5.9.23. (*S*)-*N*-{(1*S*,2*R*)-3-[(3-Amino-4-chloro-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-2-[3-(2-ethyl-thiazol-4-ylmethyl)-2,4-dioxo-imidazolidin-1-yl]-3-methyl-butyramide (6c). The carboxylic acid core **40** and amine core **29** were coupled using method 2 to produce

6c in 31% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.76–0.83 (m, 6 H), 0.89 (d, J = 6.44 Hz, 3H), 0.94 (d, J = 6.44 Hz, 3H), 1.33 (t, J = 7.63 Hz, 3H), 1.79–1.90 (m, 1H), 2.03–2.14 (m, 1H), 2.67 (dd, J = 14.07, 10.68 Hz, 1H), 2.79–2.89 (m, 2H), 2.92–3.03 (m, 4H), 3.04–3.10 (m, 2H), 3.11–3.19 (m, 1H), 3.42 (dd, J = 104.44, 17.63 Hz, 2H), 3.64–3.66 (m, 1H), 3.80–3.87 (m, 1H), 4.19–4.29 (m, 1H), 4.43 (br s, 2H), 4.68–4.81 (m, 2H), 6.26 (d, J = 9.16 Hz, 1H), 7.01 (s, 1H), 7.04 (dd, J = 8.48, 2.03 Hz, 1H), 7.18 (d, J = 2.03 Hz, 1H), 7.22–7.30 (m, 5H), 7.37 (d, J = 8.48 Hz, 1H); MS (ESI) m/z 733.4 $[M+H]^+$.

5.9.24. (*S*)-*N*-{(1*S*,2*R*)-3-[(3-Amino-4-chloro-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-2-[3-(2-ethyl-thiazol-4-ylmethyl)-2-oxo-2,3-dihydro-imidazol-1-yl]-3-methyl-butyramide (6d). The carboxylic acid core **49** and amine core **29** were coupled using method 2 to produce **6d** in 50% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.69 (d, J = 6.78 Hz, 3H), 0.75 (d, J = 6.78 Hz, 3H), 0.87 (d, J = 1.36 Hz, 3H), 0.90 (d, J = 1.02 Hz, 3H), 1.36 (t, J = 7.46 Hz, 3H), 1.78–1.93 (m, 1H), 2.31–2.46 (m, 1H), 2.77–2.95 (m, 5H), 2.97–3.04 (m, 3H), 3.05-3.19 (m, 2H), 3.79–3.88 (m, 1H), 4.13 (d, J = 9.49 Hz, 1H), 4.16–4.27 (m, 1H), 4.79–4.94 (m, 2H), 6.02 (d, J = 3.05 Hz, 1H), 6.35 (d, J = 3.05 Hz, 1H), 6.95 (s, 1H), 6.98 (dd, J = 8.31, 2.20 Hz, 1H), 6.97 (d, J = 2.37 Hz, 1H), 7.12–7.20 (m, 7H), 7.33 (d, J = 8.14 Hz, 1H); MS (ESI) m/z 717.8 $[M+H]^+$, 739.8 $[M+Na]^+$.

5.9.25. (*S*)-*N*-{(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl-(4-methoxy-benzenesulfonyl)amino]-propyl}-3-methyl-2-[3-(2-methyl-thiazol-4-ylmethyl)-2,4-dioxo-tetrahydro-pyrimidin-1-yl]-butyramide (7a). The carboxylic acid core **34** and amine core **25** were coupled using method 2 to produce **7a** in 27% yield. ^{1}H NMR (300 MHz, MEOH) δ ppm 0.75–0.84 (m, 6 H), 0.87 (d, J = 6.78 Hz, 3H), 0.90 (d, J = 6.78 Hz, 3H), 1.86–2.14 (m, 3H), 2.38–2.53 (m, 2H), 2.65 (s, 3H), 2.78–3.15 (m, 6 H), 3.22 (dd, J = 13.90, 3.05 Hz, 1H), 3.40 (dd, J = 15.09, 3.56 Hz, 1H), 3.70–3.81 (m, 1H), 3.87 (s, 3H), 4.08–4.19 (m, 1H), 4.28 (d, J = 11.19 Hz, 1H), 4.90–5.16 (m, 2H), 7.00–7.17 (m, 7H), 7.19–7.26 (m, 1H), 7.75–7.81 (m, 2H); MS (ESI) m/z 714.8 $[M+H]^+$.

5.9.26. (*S*)-*N*-{(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-propyl}-3-methyl-2-[3-(2-methyl-thiazol-4-ylmethyl)-2-oxo-imidazolidin-1-yl]-butyramide (7b). The five-membered cyclic urea carboxylic acid core and amine core **25** were coupled using method 2 to produce **7b** in 57% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.67 (d, J = 6.44 Hz, 3H), 0.70 (d, J = 6.78 Hz, 3H), 0.80 (d, J = 6.78 Hz, 3H), 0.81 (d, J = 6.44 Hz, 3H), 1.87–2.01 (m, 2H), 2.42 (dd, J = 13.39, 11.02 Hz, 1H), 2.54–2.62 (m, 1H), 2.63 (s, 3H), 2.75–2.85 (m, 1H), 2.87–2.97 (m, 2H), 2.97–3.07 (m, 3H), 3.09–3.26 (m, 2H), 3.52–3.64 (m, 1H), 3.75 (d, J = 10.85 Hz, 1H), 3.83 (s, 3H), 3.85–3.96 (m, 1H), 4.26–4.40 (m, 2H), 4.93 (d, J = 6.44 Hz, 1H), 7.02–7.14 (m, 7H), 7.22 (s, 1H), 7.68–7.74 (m, 2H), 7.87 (d, J = 9.49 Hz, 1H); MS (ESI) m/z 686.3 $[M+H]^+$, 708.3 $[M+Na]^+$.

5.9.27. (*S*)-*N*-{(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-propyl}-3-methyl-2-[3-(2-methyl-thiazol-4-ylmethyl)-2,4-dioxo-imidazolidin-1-yl]-butyramide (7c). The carboxylic acid core **39** and amine core **25** were coupled using method 2 to produce **7c** in 65% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.79 (d, J = 6.78 Hz, 3H), 0.82 (d, J = 6.44 Hz, 3H), 0.87 (d, J = 6.44 Hz, 3H), 0.94 (d, J = 6.78 Hz, 3H), 1.75–1.90 (m, 1H), 2.00–2.15 (m, 1H), 2.62–2.65 (m, 1H), 2.65 (s, 3H), 2.73–2.83 (m, 2H), 2.85 (s, 1H), 2.98–3.02 (m, 1H), 3.02–3.12 (m, 1H), 3.14–3.19 (m, 1H), 3.40 (dd, J = 106.47, 17.97 Hz, 2H), 3.76–3.78 (m, 1H), 3.79–3.85 (m, 1H), 3.88 (s, 3H), 4.18–4.30 (m, 1H), 4.65–4.80 (m, 2H), 6.21 (d, J = 9.49 Hz, 1H), 6.95–7.02 (m, 3H), 7.05–7.14 (m, 5H), 7.69–7.77 (m, 2H); MS (ESI) m/z 700.3 $[M+H]^+$.

5.9.28. (S)-*N*-{(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-propyl}-3-methyl-2-[3-(2-methyl-thiazol-4-ylmethyl)-2-oxo-2,3-dihydro-imidazol-1-yl]-butyramide (7d). The carboxylic acid core **49** and the amine core **25** were coupled using method 2 to produce **7d** in 35% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.72 (d, J = 6.44 Hz, 3H), 0.73 (d, J = 6.78 Hz, 3H), 0.83 (d, J = 6.78 Hz, 3H), 0.87 (d, J = 6.78 Hz, 3H), 1.71–1.86 (m, 1H), 2.30–2.48 (m, 1H), 2.68 (s, 3H), 2.74–2.84 (m, 2H), 2.82–2.93 (m, 1H), 2.97–3.16 (m, 3H), 3.72–3.83 (m, 1H), 3.73–3.83 (m, 1H), 3.87 (s, 3H), 3.88–3.92 (m, 1H), 4.04–4.18 (m, 1H), 4.83 (s, 2H), 6.14 (d, J = 3.05 Hz, 1H), 6.30 (d, J = 3.05 Hz, 1H), 6.92 (s, 1H), 6.93–7.00 (m, 2H), 7.08–7.20 (m, 5H), 7.32 (d, J = 8.82 Hz, 1H), 7.65–7.75 (m, 2H); MS (ESI) m/z 684.3 $[M+H]^+$, 706.3 $[M+Na]^+$.

5.9.29. (*S*)-*N*-{(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[(4-hydroxy-benzenesulfonyl)-isobutyl-amino]-propyl}-3-methyl-2-[3-(2-methyl-thiazol-4-ylmethyl)-2,4-dioxo-imidazolidin1-yl]-butyramide (8). The carboxylic acid core **39** and the amine core **30** were coupled using method 2 to produce **8** in 52% yield. ^{1}H NMR (300 MHz, MeOH) δ ppm 0.77 (d, J = 6.78 Hz, 3H), 0.79 (d, J = 6.44 Hz, 3H), 0.87 (d, J = 6.78 Hz, 3H), 0.90 (d, J = 6.44 Hz, 3H), 1.92–2.08 (m, 2H), 2.39–2.52 (m, 1H), 2.65 (s, 3H), 2.82–2.93 (m, 2H), 2.93–3.07 (m, 2H), 3.23 (dd, J = 13.56, 3.39 Hz, 1H), 3.39 (dd, J = 14.58, 3.73 Hz, 1H), 3.68 (d, J = 18.31 Hz, 1H), 3.74–3.83 (m, 1H), 4.00 (d, J = 10.85 Hz, 1H), 4.07–4.21 (m, 1H), 4.66–4.80 (m, 2H), 6.87–6.93 (m, 2H), 6.95–7.01 (m, 3H), 7.10–7.15 (m, 2H), 7.23 (s, 1H), 7.62–7.70 (m, 2H), 8.21 (d, J = 9.83 Hz, 1H); MS (ESI) m/z 686.2 $[M+H]^+$.

5.9.30. (*S*)-*N*-{(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[(4-hydroxy-benzenesulfonyl)-isobutyl-amino]-propyl}-2-[3-(2-methoxy-methyl-thiazol-4-ylmethyl)-2,4-dioxo-imidazolidin-1-yl]-3-methyl-butyramide (9). The carboxylic acid core **41** and the amine core **30** were coupled using method 2 to produce **9** in 36% yield. ^{1}H NMR (300 MHz, MeOH) δ ppm 0.77 (d, J = 6.78 Hz, 3H), 0.79 (d, J = 6.44 Hz, 3H), 0.87 (d, J = 6.44 Hz, 3H), 0.90 (d, J = 6.44 Hz, 3H), 1.92–2.08 (m, 2H), 2.46 (dd, J = 13.56, 11.87 Hz, 1H), 2.82–2.93 (m, 1H), 2.93–2.96 (m, 1H), 2.96–3.08

(m, 2H), 3.23 (dd, J = 13.56, 3.39 Hz, 1H), 3.32–3.38 (m, 3H), 3.42 (s, 3H), 3.68 (d, J = 18.31 Hz, 1H), 3.73–3.82 (m, 1H), 4.00 (d, J = 10.85 Hz, 1H), 4.08–4.20 (m, 1H), 4.66 (s, 2H), 4.70–4.83 (m, 2H), 6.86–6.94 (m, 2H), 6.95–7.02 (m, 3H), 7.09–7.16 (m, 2H), 7.41 (s, 1H), 7.62–7.70 (m, 2H); MS (ESI) m/z 716.3 $[M+H]^+$, 738.3 $[M+Na]^+$.

5.9.31. (*S*)-*N*-{(1*S*,2*R*)-3-[(3-Amino-4-chloro-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-3-methyl-2-[3-(2-methyl-thiazol-4-ylmethyl)-2,4-dioxo-imidazolidin-1-yl]-butyramide (10). The carboxylic acid core **39** and the amine core **29** were coupled using method 2 to produce **10** in 50% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.77–0.83 (m, 6 H), 0.89 (d, J = 6.78 Hz, 3H), 0.94 (d, J = 6.44 Hz, 3H), 1.77–1.92 (m, 1H), 2.02–2.15 (m, 1H), 2.62–2.69 (m, 1H), 2.65 (s, 3H), 2.79–2.88 (m, 2H), 2.93–3.03 (m, 1H), 3.04–3.09 (m, 1H), 3.11–3.19 (m, 1H), 3.41 (dd, J = 107.15, 17.97 Hz, 2H), 3.62–3.67 (m, 1H), 3.79–3.88 (m, 1H), 3.92 (d, J = 10.85 Hz, 1H), 4.19–4.29 (m, 1H), 4.43 (br s, 2H), 4.65–4.80 (m, 2H), 6.30 (d, J = 9.16 Hz, 1H), 7.01 (s, 1H), 7.04 (dd, J = 8.31, 2.20 Hz, 1H), 7.08–7.15 (m, 5H), 7.18 (d, J = 2.37 Hz, 1H), 7.37 (d, J = 8.14 Hz, 1H); MS (ESI) m/z 719.8 $[M+H]^+$, 741.8 $[M+Na]^+$.

5.9.32. (*S*)-*N*-{(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl-(4-methoxy-benzenesulfonyl)amino]-propyl}-2-[3-(2-methoxymethyl-thiazol-4-ylmethyl)-2,4-dioxo-imidazolidin-1-yl]-3-methyl-butyramide (11). The carboxylic acid core **41** and the amine core **25** were coupled using method 2 to produce **11** in 30% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.78 (d, J = 6.78 Hz, 3H), 0.82 (d, J = 6.44 Hz, 3H), 0.87 (d, J = 6.44 Hz, 3H), 0.94 (d, J = 6.44 Hz, 3H), 1.75–1.90 (m, 1H), 2.02–2.15 (m, 1H), 2.66 (dd, J = 13.90, 10.85 Hz, 1H), 2.78 (dd, J = 13.39, 6.61 Hz, 1H), 2.91–3.12 (m, 3H), 3.14–3.28 (m, 2H), 3.45 (s, 3H), 3.58 (d, J = 17.97 Hz, 1H), 3.77–3.85 (m, 1H), 3.85–3.92 (m, 1H), 3.88 (s, 3H), 4.16–4.30 (m, 1H), 4.68 (s, 2H), 4.69–4.84 (m, 2H), 6.22 (d, J = 9.16 Hz, 1H), 6.95–7.02 (m, 2H), 7.04–7.14 (m, 5H), 7.19 (s, 1H), 7.68–7.77 (m, 2H); MS (ESI) m/z 730.2 $[M+H]^+$, 752.2 $[M+Na]^+$.

5.9.33. (*S*)-*N*-{(1*S*,2*R*)-3-[(3-Amino-4-chloro-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-2-[3-(2-methoxymethyl-thiazol-4-ylmethyl)-2,4-dioxo-imidazolidin-1-yl]-3-methyl-butyramide (12). The carboxylic acid core **41** and the amine core **29** were coupled using method 2 to produce **12** in 42% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.75–0.85 (m, 6 H), 0.89 (d, J = 6.78 Hz, 3H), 0.94 (d, J = 6.78 Hz, 3H), 1.77–1.91 (m, 1H), 2.01–2.14 (m, 1H), 2.68 (dd, J = 14.24, 10.85 Hz, 1H), 2.79–3.03 (m, 3H), 3.03–3.08 (m, 1H), 3.09–3.20 (m, 2H), 3.24–3.63 (dd, J = 99.52, 17.80 Hz, 2H), 3.44 (s, 3H), 3.78–3.88 (m, 1H), 3.91 (d, J = 10.85 Hz, 1H), 4.17–4.31 (m, 1H), 4.67 (s, 3H), 4.69–4.83 (m, 2H), 6.24 (d, J = 9.16 Hz, 1H), 7.04 (dd, J = 8.31, 2.20 Hz, 1H), 7.09–7.14 (m, 5H), 7.18 (d, J = 1.70 Hz, 1H), 7.19 (s, 1H), 7.35 (s, 1H), 7.38 (s, 1H); MS (ESI) m/z 749.4 $[M+H]^+$, 771.4 $[M+Na]^+$.

5.9.34. (2*S*,3*S*)-2-[3-(2-Methoxymethyl-thiazol-4-ylmethyl)-2,4-dioxo-imidazolidin-1-yl]-3-methyl-pentanoic acid {(1*S*,2*R*)-1-benzyl-2-hydroxy-3-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-propyl}-amide (13). The carboxylic acid core **42** and the amine core **25** were coupled using method 3 to produce **13** in 75% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.75–0.86 (m, 6 H), 0.87 (d, J = 6.62 Hz, 3H), 0.94 (d, J = 6.62 Hz, 3H), 1.17–1.34 (m, 2H), 1.75–1.96 (m, 2H), 2.66 (dd, J = 14.16, 10.85 Hz, 1H), 2.78 (dd, J = 13.60, 6.62 Hz, 1H), 2.92–3.11 (m, 3H), 3.14–3.22 (m, 1H), 3.41 (dd, J = 88.98, 18.02 Hz, 2H), 3.45 (s, 3H), 3.75–3.86 (m, 2H), 3.88 (s, 3H), 3.98 (d, J = 11.03 Hz, 1H), 4.16–4.32 (m, 1H), 4.67 (s, 2H), 4.69–4.83 (m, 2H), 6.20 (d, J = 9.56 Hz, 1H), 6.94–7.04 (m, 2H), 7.06–7.15 (m, 5H), 7.17 (s, 1H), 7.67–7.78 (m, 2H); MS (ESI) m/z 744.4 $[M+H]^+$.

5.9.35. Method 3. To the acid core in DMF (0.1 M) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) (1.5 equiv) and 1-hydroxybenzotriazole (HOBT) (1.5 equiv). After stirring for 30 min, the amine core was added (1 equiv) followed by triethylamine (3 equiv). After stirring for 18 h, the reaction mixture was diluted with EtOAc, washed with water followed by a brine solution, dried over $MgSO_4$, and filtered. Silica gel chromatography was performed using EtOAc and/or MeOH in CH_2Cl_2 to give the final product.

5.9.36. (*S*)-*N*-{(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-propyl}-3-methyl-2-(2-oxo-imidazolidin-1-yl)-butyramide (3b). The six-membered cyclic urea carboxylic acid core and amine core **25** were coupled using method 3 to give **3b** in 40% yield. ^{1}H NMR (300 MHz, MeOH) δ ppm 0.76 (d, J = 6.78 Hz, 3H), 0.78 (d, J = 6.44 Hz, 3H), 0.87 (d, J = 6.78 Hz, 3H), 0.90 (d, J = 6.78 Hz, 3H), 1.92–2.09 (m, 2H), 2.48 (dd, J = 13.56, 11.53 Hz, 1H), 2.59–2.69 (m, 1H), 2.85–3.00 (m, 3H), 3.03–3.11 (m, 3H), 3.13–3.25 (m, 3H), 3.39 (dd, J = 14.92, 3.73 Hz, 1H), 3.65 (d, J = 10.85 Hz, 1H), 3.70–3.78 (m, 1H), 3.87 (s, 3H), 4.05–4.17 (m, 1H), 7.05–7.10 (m, 2H), 7.12–7.19 (m, 1H), 7.18–7.23 (m, 4H), 7.73–7.79 (m, 2H), 7.91 (d, J = 9.49 Hz, 1H); MS (ESI) m/z 575.4 $[M+H]^+$, 597.4 $[M+Na]^+$.

5.9.37. (2*S*,3*S*)-2-[3-(2-Methoxymethyl-thiazol-4-ylmethyl)-2,4-dioxo-imidazolidin-1-yl]-3-methyl-pentanoic acid {(1*S*,2*R*)-1-benzyl-3-[(2,2-dimethyl-propyl)-(4-methoxy-benzenesulfonyl)-amino]-2-hydroxy-propyl}-amide (14). The carboxylic acid core **42** and the amine core **26** were coupled using method 3 to produce **14** in 64% yield. ^{1}H NMR (300 MHz, MeOH) δ ppm 0.70 (d, J = 6.78 Hz, 3H), 0.83 (t, J = 7.29 Hz, 3H), 0.93–0.99 (m, 3H), 1.00 (s, 9H), 1.20–1.37 (m, 1H), 1.73–1.88 (m, 1H), 2.44 (dd, J = 13.90, 11.53 Hz, 1H), 2.44 (dd, J = 13.90, 11.53 Hz, 1H), 2.92 (d, J = 3.73 Hz, 1H), 2.98 (d, J = 3.05 Hz, 1H), 3.05 (s, 1H), 3.08–3.21 (m, 3H), 3.34–3.40 (m, 1H), 3.43 (s, 3H), 3.65 (d, J = 18.31 Hz, 1H), 3.90–3.98 (m, 1H), 3.99–4.12 (m, 2H), 4.66 (s, 2H), 4.70–4.80 (m, 2H), 6.93–7.01 (m, 3H), 7.04–7.12 (m, 5H), 7.76–7.83 (m, 2H), 8.10 (d, J = 9.49 Hz, 1H); MS (ESI) m/z 760.2 $[M+H]^+$.

5.9.38. (2*S*,3*S*)-2-[3-(2-Methoxymethyl-thiazol-4-ylmethyl)-2,4-dioxo-imidazolidin-1-yl]-3-methyl-pentanoic acid {(1*S*,2*R*)-1-benzyl-3-[cyclopentylmethyl-(4-methoxy-benzenesulfonyl)-amino]-2-hydroxy-propyl}-amide (15). The carboxylic acid core **42** and the amine core **27** were coupled using method 3 to produce **15** in 48% yield. ^{1}H NMR (300 MHz, MeOH) δ ppm 0.75 (d, J = 6.44 Hz, 3H), 0.83 (t, J = 7.29 Hz, 3H), 1.22–1.35 (m, 2H), 1.49–1.62 (m, 4H), 1.60–1.76 (m, 4H), 1.77–1.90 (m, 1H), 2.19–2.32 (m, 1H), 2.47 (dd, J = 13.56, 11.87 Hz, 1H), 2.89–3.08 (m, 4H), 3.13–3.27 (m, 3H), 3.39–3.48 (m, 1H), 3.43 (s, 3H), 3.66 (d, J = 17.97 Hz, 1H), 3.75–3.84 (m, 1H), 3.87 (s, 3H), 4.11 (d, J = 11.19 Hz, 1H), 4.12–4.23 (m, 1H), 4.66 (s, 2H), 4.70–4.84 (m, 2H), 6.95–7.02 (m, 3H), 7.05–7.10 (m, 2H), 7.11–7.16 (m, 2H), 7.23 (s, 1H), 7.71–7.80 (m, 2H); MS (ESI) m/z 771.2 $[M+H]^+$.

5.9.39. (*S*)-2-(3-Benzyl-2,4-dioxo-imidazolidin-1-yl)-*N*-{(1*S*,2*R*)-1-benzyl-2-hydroxy-3-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-propyl}-3-methyl-butyramide (16). The carboxylic acid core **43** and the amine core **25** were coupled using method 3 to produce **16** in 43% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.75 (d, J = 6.78 Hz, 3H), 0.82 (d, J = 6.44 Hz, 3H), 0.87 (d, J = 6.78 Hz, 3H), 0.94 (d, J = 6.78 Hz, 3H), 1.75–1.89 (m, 1H), 1.99–2.10 (m, 1H), 2.63 (dd, J = 14.07, 10.68 Hz, 1H), 2.77 (dd, J = 13.56, 6.44 Hz, 1H), 2.89–2.99 (m, 1H), 2.99–3.09 (m, 2H), 3.12–3.25 (m, 2H), 3.53 (d, J = 17.97 Hz, 1H), 3.76–3.85 (m, 2H), 3.88 (s, 3H), 4.17–4.28 (m, 1H), 4.53–4.69 (m, 2H), 6.05 (d, J = 9.49 Hz, 1H), 6.91–7.01 (m, 4H), 7.02–7.11 (m, 4H), 7.27–7.38 (m, 3H), 7.39–7.46 (m, 2H), 7.69–7.76 (m, 2H); MS (ESI) m/z 680.0 $[M+H]^+$.

5.9.40. (*S*)-*N*-{(1*S*,2*R*)-3-[(3-Amino-4-chloro-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-2-(2,4-dioxo-3-quinolin-2-ylmethyl-imidazolidin-1-yl)-3-methyl-butyramide (17). The carboxylic acid core **44** and the amine core **29** were coupled using method 3, substituting PyBOP for EDC, to produce **17** in 65% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.77–0.98 (m, 12H), 1.74–1.90 (m, 1H), 2.08–2.25 (m, 1H), 2.69 (dd, J = 14.24, 10.51 Hz, 1H), 2.78 (dd, J = 13.39, 6.61 Hz, 1H), 2.92–3.01 (m, 2H), 3.06 (dd, J = 13.73, 9.32 Hz, 1H), 3.11–3.26 (m, 1H), 3.57 (dd, J = 101.73, 17.97 Hz, 2H), 3.79–3.86 (m, 2H), 3.88 (s, 3H), 3.92 (d, J = 10.85 Hz, 1H), 4.18–4.32 (m, 1H), 4.89–5.10 (m, 2H), 6.17 (d, J = 9.49 Hz, 1H), 6.94–7.02 (m, 2H), 7.12–7.20 (m, 5H), 7.33 (d, J = 8.48 Hz, 1H), 7.44–7.54 (m, 1H), 7.62–7.68 (m, 1H), 7.70–7.74 (m, 2H), 7.77 (d, J = 7.80 Hz, 1H), 7.95 (d, J = 8.48 Hz, 1H), 8.13 (d, J = 8.48 Hz, 1H); MS (ESI) m/z 750.6 $[M+H]^+$.

5.9.41. (*S*)-*N*-{(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-propyl}-2-(2,4-dioxo-3-quinolin-2-ylmethyl-imidazolidin-1-yl)-3-methyl-butyramide (18). The carboxylic acid core **44** and the amine core **25** were coupled using method 3, substituting PyBOP for EDC, to produce **18** in 96% yield. ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.80 (d, J = 6.44 Hz, 3H), 0.90 (m, 9H), 1.76–1.91 (m, 1H), 2.08–2.27 (m, 1H), 2.72 (dd, J = 14.07, 10.68 Hz, 1H), 2.79–3.00 (m, 2H), 3.02–3.22 (m, 3H), 3.39–3.79 (m, 3H), 3.81–3.90 (m, 1H), 3.96 (d, J = 10.85 Hz, 1H), 4.20–4.33 (m, 1H), 4.40 (br s, 1H), 4.88–5.08 (m, 2H), 6.26 (d, J = 9.16 Hz, 1H), 7.03 (dd, J = 8.31, 2.20 Hz, 1H), 7.10–7.20 (m, 5H), 7.34 (t, J = 8.14 Hz, 2H), 7.44–7.54 (m, 1H), 7.59–7.69 (m, 1H), 7.76 (d, J = 7.80 Hz, 1H), 7.94 (d, J = 8.48 Hz, 1H), 8.12 (d, J = 8.48 Hz, 1H); MS (ESI) m/z 730.9 $[M+H]^+$.

5.9.42. (*S*)-*N*-{(1*S*,2*R*)-3-[(3-Amino-4-chloro-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl}-3-methyl-2-[3-(1-methyl-1H-benzoimidazol-2-ylmethyl)-2,4-dioxo-imidazolidin-1-yl]-butyramide (19). The carboxylic acid core **45** and the amine core **29** were coupled using method 3, substituting PyBOP for EDC, to produce **19** in 70% yield. ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 0.68 (d, J = 6.78 Hz, 3H), 0.75 (d, J = 6.78 Hz, 3H), 0.82 (d, J = 6.10 Hz, 6 H), 1.86–2.06 (m, 2H), 2.38 (dd, J = 13.05, 11.70 Hz, 1H), 2.77–2.90 (m, 1H), 2.94 (dd, J = 8.99, 4.24 Hz, 1H), 2.97–3.12 (m, 2H), 3.17–3.27 (m, 1H), 3.59 (br s, 1H), 3.80 (m, 1H), 3.88 (s, 3H), 3.91–3.99 (m, 1H), 4.02 (d, J = 10.85 Hz, 1H), 4.95–5.05 (m, 2H), 5.81 (br s, 2H), 6.88 (dd, J = 8.48, 2.03 Hz, 1H), 6.93–7.02 (m, 1H), 7.08–7.18 (m, 5H), 7.17–7.28 (m, 4H), 7.32–7.38 (m, 1H), 7.48 (d, J = 8.14 Hz, 1H), 7.55 (d, J = 7.80 Hz, 1H), 8.23 (d, J = 9.83 Hz, 1H); MS (ESI) m/z 753.6 $[M+H]^+$.

5.9.43. (*S*)-*N*-{(1*S*,2*R*)-1-Benzyl-2-hydroxy-3-[isobutyl-(4-methoxy-benzenesulfonyl)-amino]-propyl}-3-methyl-2-[3-(1-methyl-1*H*-benzoimidazol-2-ylmethyl)-2,4-dioxo-imidazolidin-1-yl]-butyramide (20). The carboxylic acid core **45** and the amine core **25** were coupled using method 3, substituting PyBOP for EDC, to produce **20** in 69% yield: ^{1}H NMR (300 MHz, chloroform-D) δ ppm 0.77 (d, J = 6.44 Hz, 3H), 0.80 (d, J = 6.78 Hz, 3H), 0.86 (d, J = 6.44 Hz, 3H), 0.91 (d, J = 6.44 Hz, 3H), 1.74–1.92 (m, 1H), 1.97–2.17 (m, 1H), 2.71 (dd, J = 13.90, 10.85 Hz, 1H), 2.77–2.86 (m, 1H), 2.92–3.02 (m, 1H), 3.06 (dd, J = 8.31, 3.56 Hz, 1H), 3.11–3.25 (m, 1H), 3.36 (d, J = 17.97 Hz, 1H), 3.66 (d, J = 17.97 Hz, 1H), 3.84–3.87 (m, 4H), 3.88 (s, 3H), 3.96 (d, J = 10.85 Hz, 1H), 4.10–4.19 (m, 1H), 4.22–4.35 (m, 1H), 4.80–4.97 (m, 2H), 6.39 (d, J = 9.49 Hz, 1H), 6.93–7.01 (m, 2H), 7.03–7.11 (m, m, 2H), 7.19–7.23 (m, 1H), 7.23–7.28 (m, 2H), 7.29–7.36 (m, 1H), 7.66–7.77 (m, 3H), 7.13–7.18 (H); MS (ESI) m/z 733.8 $[M+H]^+$.

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