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Synthesis, antiviral activity, and pharmacokinetic evaluation of P3 pyridylmethyl analogs of oximinoarylsulfonyl HIV-1 protease inhibitors

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Abstract—As a continuation of the recently communicated discovery of oximinoarylsulfonamides as potent inhibitors of HIV-1 aspartyl protease, compounds bearing pyridylmethyl substituents at P3 were designed and synthesized. Potent analogs in this series provided low single-digit nanomolar EC_{50} values against both wild-type HIV and resistant mutant virus (A17), attenuated some 3- to 12-fold in the presence of 50% human serum. Pharmacokinetic results for compounds in this series showed good to excellent exposure when co-administered orally with an equal amount of ritonavir (5 mg/kg each) in the rat, with average AUC >8 μg h/mL. Similar dosing in dog resulted in significantly lower plasma levels (average AUC <2 μg h/mL). The 3-pyridylmethyl analog **30** gave the best overall exposure (rat AUC = 7.1 μg h/mL and dog AUC = 4.9 μg h/mL), however, this compound was found to be a potent inhibitor of cytochrome P450 3A (K_i = 2.4 nM).

1. Introduction

Inhibitors of HIV-1 aspartyl protease play a critical role in the treatment of HIV infection and have helped to transform this fatal disease into a chronic condition through the use of effective combination therapy regimens. Although tremendous success in the clinic has been achieved with the current line of protease inhibitors (PIs), several challenges remain for research aimed at improved agents.[1] One such challenge is the need to develop new PIs to combat mutant viruses that are resistant to currently available antiretrovirals.[1a,2] Following the introduction of our second-generation antiretroviral agent Kaletra,[3] we began a program to identify novel PIs that might be useful as salvage agents for patients who develop resistance to lopinavir,[4] the active component of Kaletra.

We recently described a novel series of HIV protease inhibitors[5] exhibiting potent antiviral activity against the A17 virus, a strain of mutant virus selected by and highly resistant to lopinavir in vitro.[6] The core region of these compounds is derived from amprenavir, to which has been appended an arylmethyl-substituted imidazolidin-2-one or imidazolidin-2,4-dione group at the P3 position.[7] Early medicinal chemistry studies of structure–activity relationships (SARs) in the series identified substituted thiazoles, such as **1** (Table 1), as potent analogs. The simple benzyl analog **2** was found to be equally active, but suffered from relatively poor aqueous solubility that complicated the evaluation of its pharmacokinetic properties. As was observed with other analogs in the series,[5] activity for the benzyl analog was greatly improved by replacement of the 4-methoxy substituent at the 4-position of the P2′-benzenesulfonamide group with an *E*-oximinomethyl group (see **3**). An X-ray crystal structure of an enzyme/inhibitor complex revealed that the oxime portion of compounds in this series forms a hydrogen

Keywords: HIV; Aspartyl protease inhibitors; Lopinavir resistant virus; Peptidomimetic.
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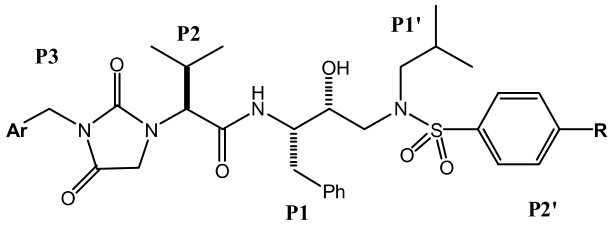
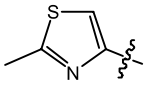
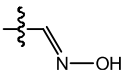
Table 1. Comparison of antiviral activities of P3 4-thiazolyl and benzyl analogs



Compound	Ar	R	EC_{50}[a] (nM)		
			0% HS	50% HS	A17
1		OMe	5	161	75
2	Ph	OMe	5	32	59
3	Ph		1	25	16

[a] For assay methods, see Ref. 9. Activity against wild-type virus was determined both in the absence of human serum (0% HS) and in the presence of 50% human serum (50% HS). A17 is a mutant strain of virus highly resistant to lopinavir.[6]

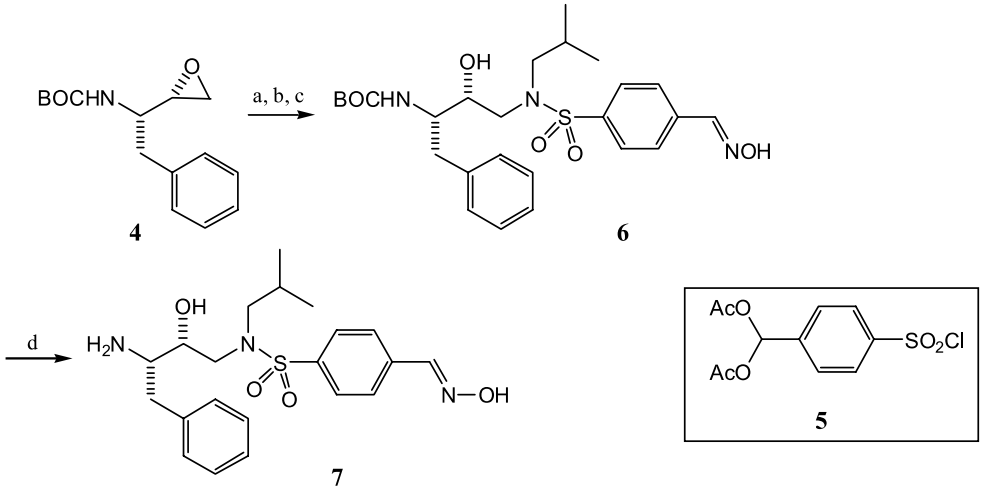
bond with Asp-30, while the heterocyclic appendage at the far end of the molecule occupies the S3 subsite.[5]

2. Chemical synthesis

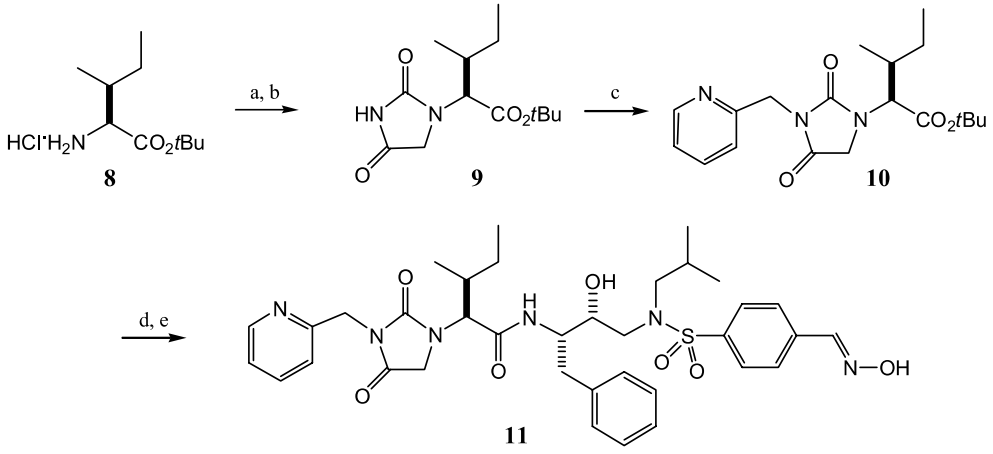
Compounds were synthesized using methods presented in Schemes 1–3. Scheme 1 presents a synthesis of the P1–P2′ portion of the inhibitors. The known epoxide[8] **4** was allowed to react with a primary alkyl amine (isobutylamine shown), followed by sulfonylation with sulfonyl chloride **5**. The resulting 4-(diacetoxymethyl)benzenesulfonamide was treated with hydroxylamine hydrochloride to give oxime **6** as a mixture of *E*- and *Z*-oxime isomers. Removal of the Boc-protecting group, followed by acid-promoted isomerization of the oxime group to the thermodynamically preferred *E*-isomer, provided **7**, a common intermediate in the synthesis of many of the inhibitors described.

Scheme 2 presents the method used to synthesize inhibitors bearing an imidazolidin-2,4-dione linkage between P2 and P3. The *tert*-butylester of L-isoleucine (**8**) was first converted, as shown, to imidazolidinedione **9**.[7b] Deprotonation of **9**, followed by alkylation with 2-(bromomethyl)pyridine, gave **10**, which is hydrolyzed to the acid and coupled with amine **7** to produce the target inhibitor **11**.

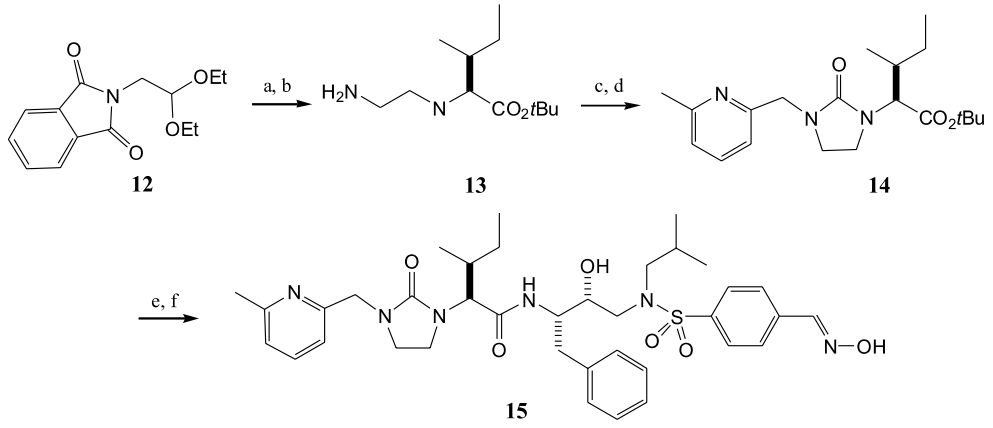
A method for the synthesis of compounds bearing an imidazolidin-2-one linkage between P2 and P3 groups



Scheme 1. Reagents and conditions: (a) isobutylamine, 2-PrOH, 80 °C; (b) **5**, TEA, THF; (c) $HONH_2$·HCl, TEA, EtOH; (d) i—4:1 TFA, CH_2Cl_2; ii—1:19 TFA, CH_2Cl_2.



Scheme 2. Reagents and conditions: (a) ethyl bromoacetate, TEA, DMF; (b) i—chlorosulfonylisocyanate, $ClCH_2CH_2Cl$, 0 °C; ii—H_2O; iii—TEA, MeOH; (c) i—sodium bis(trimethylsilyl)amide, DMF, −40 °C; ii—2-(bromomethyl)pyridine hydrobromide; (d) 2:1 TFA, CH_2Cl_2; (e) **7**, EDCI, HOBT, Hunig's base, DMF.



Scheme 3. Reagents and conditions: (a) 10% aq HCl, THF, 75 °C; (b) i—**8**, $NaCNBH_3$, AcOH, MeOH; ii—$H_2NNH_2{\cdot}H_2O$, EtOH, 70 °C; (c) i—6-methyl-2-pyridinecarboxaldehyde, $MgSO_4$, CH_2Cl_2; ii—$NaBH_4$, MeOH; (d) bis(4-nitrophenyl)carbonate, DMF, 50 °C; (e) 2:1 TFA, CH_2Cl_2; (f) **7**, EDCI, HOBT, Hunig's base, DMF.

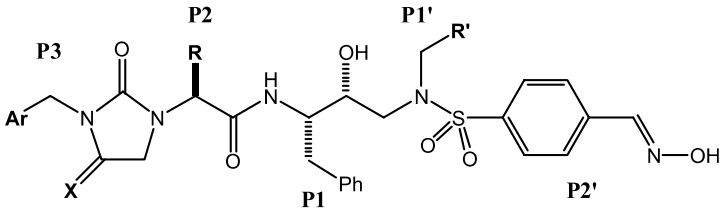
is shown in Scheme 3. Phthalimidoacetaldehyde diethylacetal (**12**) was hydrolyzed to the aldehyde and aminated with **8** under standard reducing conditions, followed by removal of the phthalimide group, to give diamine **13**. Regioselective monoalkylation at the primary amino position of **13** was affected by reaction with 6-methyl-2-pyridinecarboxaldehyde to give an imine, which is reduced with sodium borohydride. Cyclization to imidazolidinone **14** was accomplished using bis-(4-nitrophenyl)carbonate. Finally, ester hydrolysis and coupling to amine **7** provided the target inhibitor **15**.

3. Results and discussion

In order to address the solubility problem with the benzyl analogs, a series of compounds bearing a pyridylmethyl substituent in place of the benzyl group at P3 was prepared (Table 2). Pyridyl analogs **16** and **17** were somewhat less active than benzyl analog **3** against wild-type HIV,[9] although the activities for all three compounds against resistant virus (A17) were approximately the same. Replacement of the valine amino acid at P2 with isoleucine resulted in significant improvements in potency against A17 and improved activity against wild-type virus in the presence of 50% human serum. The position of the pyridine nitrogen did not appear to have a great effect on activity against wild-type virus, although the 2-pyridyl analog **11** was somewhat less active against the A17 strain than the 3- and 4-pyridyl analogs **18** and **19**, respectively.

Table 2 also presents data from pharmacokinetic studies in rat via oral dosing,[10] in which the test compounds (5 mg/kg) were co-administered with ritonavir (5 mg/kg) in order to enhance blood levels by inhibiting drug metabolism.[10,11] For example, the AUC of the 2-pyridyl analog **11** was 9-fold higher than that of the 4-pyridyl analog **19**. The cyclic urea (X = 2H) analog **20** provided significantly higher plasma levels than the cyclic imide (X = O) **19**, although **20** was significantly less active against the A17 viral mutant strain. In general, the cyclic urea analogs (**X** = 2H) were found to have improved aqueous solubility over their imide counterparts

Table 2. SAR for P3 pyridylmethyl analogs



Compound	Ar	X	R	R′	EC_{50}[a] (nM)			Rat PK[b]		
					0% HS	50% HS	A17	AUC	C_{max}	C_{8h}
16	4-pyr	O	2-Pr	2-Pr	16	42	15			
17	2-pyr	O	2-Pr	2-Pr	5	59	25			
11	2-pyr	O	2-(*S*)-Bu	2-Pr	3	14	6	4.52	1.06	0.11
18	3-pyr	O	2-(*S*)-Bu	2-Pr	4	16	1			
19	4-pyr	O	2-(*S*)-Bu	2-Pr	5	13	1	0.52	0.30	—
20	4-pyr	2H	2-(*S*)-Bu	2-Pr	6	23	8	1.29	0.59	0.01
21	2-pyr	2H	2-(*S*)-Bu	2-Pr	5	16	12	5.88	0.86	0.41
22	3-pyr	2H	2-(*S*)-Bu	2-Pr	4	29	8	4.47	1.58	0.2
15	6-Me-2-pyr	2H	2-(*S*)-Bu	2-Pr	2	24	7	11.97	1.88	0.52
23	6-MOM-2-pyr	2H	2-(*S*)-Bu	2-Pr	3	22	3	5.59	1.13	0.56
24	6-(2-Pr)-2-pyr	2H	2-(*S*)-Bu	2-Pr	3	26	5	11.49	1.32	0.87
25	2-Me-3-pyr	2H	2-(*S*)-Bu	2-Pr	2	16	19	19.28	3.38	0.47
26	6-Me-3-pyr	2H	2-(*S*)-Bu	2-Pr	2	25	13	19.31	3.36	0.70
27	4-Me-3-pyr	2H	2-(*S*)-Bu	2-Pr	6	42	12	9.59	3.06	0.05
28	2,4-Di-Me-3-pyr	2H	2-(*S*)-Bu	2-Pr	3	13	6	3.08	0.77	0.20
29	6-MeO-3-pyr	2H	2-(*S*)-Bu	2-Pr	1	10	1	1.97	0.75	0.75
30	3-pyr	2H	*t*-Bu	2-Pr	1	12	1	7.14	2.02	0.08
31	3-pyr	2H	2-(*S*)-Bu	*c*-Pent	2	11	1	5.62	1.60	0.13
32	6-Me-2-pyr	2H	2-(*S*)-Bu	*c*-Pent	0.5	4	0.4	4.88	0.89	0.57
33	2-Me-3-pyr	2H	2-(*S*)-Bu	*c*-Pent	2	10	2	11.23	1.48	0.62
34	6-Me-3-pyr	2H	*t*-Bu	2-Pr	1	12	2	9.81	1.19	0.34
35	4-Me-3-pyr	2H	2-(*S*)-Bu	*c*-Pent	1	14	1			
36	6-MOM-2-pyr	2H	2-(*S*)-Bu	*c*-Pent	2	26	1	10.29	0.95	0.70
37	6-MOM-2-pyr	2H	*t*-Bu	2-Pr	2	23	2.5	4.93	0.92	0.12

[a] For assay methods, see Ref. 9. Activity against wild-type virus was determined both in the absence of human serum (0% HS) and in the presence of 50% human serum (50% HS). A17 is a mutant strain of virus highly resistant to lopinavir.[6]

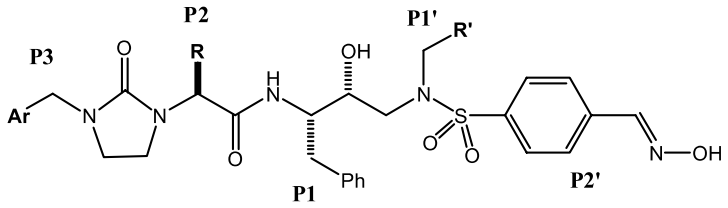
[b] Pharmacokinetic results in rat for oral co-dose of test compound and ritonavir (5 mg/kg each). AUC = total plasma concentration over 8 h following dosing (μg h/mL); C_{max} = maximum measured plasma concentration (μg/mL); C_{8h} = plasma concentration 8 h following dosing (μg/mL).

(**X** = O). This difference may contribute to the observation that compounds in the urea series generally gave better overall exposure in the rat. This difference was also apparent with **21**, which produced a slightly improved AUC relative to **11** due to increased duration of blood levels (C_{8h} = 0.41 for **21** vs C_{8h} = 0.11 for **11**). The 3-pyridyl analog **22** gave a higher maximum exposure (C_{max}) than the 2- and 4-pyridyl analogs.

Attempts to optimize the activity and pharmacokinetic properties of these compounds were focused on the 2- and 3-pyridyl analogs. A small substituent on the pyridine ring was observed to significantly affect both parameters. The 6-methyl-2-pyridyl analog **15** showed a 2-fold improvement in activity relative to unsubstituted analog **21** against both wild-type and A17 viruses, although the effect of serum on activity was more pronounced in the case of **15**. More importantly, the pharmacokinetics of **15** were improved relative to **21**, with AUC and C_{max} values roughly two times better for the 6-methyl-2-pyridyl derivative. Further increasing the size of the substituent at the 6-position (see, e.g., 6-methoxymethyl analog **23** and 6-isopropyl analog **24**) gave compounds that showed no significant improvements relative to **15**. Substitution of the 3-pyridyl analog with a single methyl substituent (see 2-methyl-3-pyridyl analog **25** and 6-methyl-3-pyridyl analog **26**) resulted in a dramatic improvement in plasma levels (relative to unsubstituted analog **22**), with each of these compounds, as well as the 4-methyl-3-pyridyl analog **27**, giving very high maximum exposures ($C_{max} > 3.0$). Unfortunately, all of the methyl-3-pyridyl analogs displayed only modest potency against the A17 virus. Other substituted 3-pyridyl analogs prepared, such as dimethyl analog **28** and methoxy analog **29**, gave relatively poor plasma levels in rats.

Further optimization in the series was obtained by modifying substituents at the P2 and P1′ positions. Replacement of isoleucine at P2 with a *tert*-butyl glycine resulted in a significant improvement in activity against both wild-type and resistant viruses (compare 3-pyridyl analogs **30** and **22**). Activities were similarly improved by replacing the isoamyl group at P1′ with cyclopentylmeth-

Table 3. Comparison of rat and dog PK



Compound	Ar	R	R′	Rat PK[a] AUC	Dog PK[a]				CYP 3A K_i[b]
					AUC	C_{max}	C_{12h}	F%	
22	3-pyr	2-(*S*)-Bu	2-Pr	4.47	2.30	1.27	0.02	30	2.3
30	3-pyr	*t*-Bu	2-Pr	7.14	4.92	3.07	0.02	71	2.4
15	6-Me-2-pyr	2-(*S*)-Bu	2-Pr	11.97	1.27	0.85	—	38	
23	6-MOM-2-pyr	2-(*S*)-Bu	2-Pr	5.59	1.09	0.53	0.01	29	32.4
25	2-Me-3-pyr	2-(*S*)-Bu	2-Pr	19.28	0.38	0.26	—	12	16.3
33	2-Me-3-pyr	2-(*S*)-Bu	*c*-Pent	11.23	0.24	0.16	—		
34	6-Me-3-pyr	*t*-Bu	2-Pr	9.81	1.84	0.81	0.06		28.0

[a] Pharmacokinetic results in rat and dog for oral co-dose of test compound and ritonavir (5 mg/kg each). AUC = total plasma concentration over 8 h (rat) or 12 h (dog) following dosing (μg h/mL); C_{max} = maximum measured plasma concentration (μg/mL); C_{12h} = plasma concentration 12 h following dosing (μg/mL).

[b] K_i (nM) for inhibition of CYP 3A mediated midazolam hydroxylation (for methods used, see Ref. 12).

yl (compare **31** with **22**). The potencies of the methyl-substituted 2- and 3-pyridyl analogs also increased with these structural changes. Most notably, the EC_{50} of the 6-methyl-2-pyridyl analog **32** against both wild-type and A17 viruses was subnanomolar, although the pharmacokinetic behavior of this compound was inferior to that of the less-potent analog **15**. Methyl-3-pyridyl analogs modified at P2 or P1′ also followed this general trend of improved activity (especially against the A17 strain), but with some decrease in oral bioavailability (compare **33** with **25** and **34** with **26**).

An evaluation of pharmacokinetics in dog was also conducted for the most promising compounds in the series.[10] A comparison of plasma exposures following oral dosing (5 mg/kg test compound co-administered with 5 mg/kg ritonavir) is provided in Table 3. Overall, exposures in the dog were significantly lower than in the rat. The 3-pyridyl analogs **22** and **30** gave the best performance in dog, with AUC values within 2-fold of those obtained in rat. All of the compounds bearing an additional substituent on the pyridine ring gave AUC values in dog 5–50 times lower than the AUC in rat. Bioavailabilities were also relatively low for compounds co-dosed with ritonavir (each of the compounds shown in Table 3 gave $F\% > 100$ when co-dosed with ritonavir in rat), suggesting significant differences in the metabolism of these compounds in rat and dog.

Compounds were also evaluated for their abilities to inhibit human cytochrome P450 3A in human liver microsomes (see CYP 3A in final column of Table 3).[12] The higher plasma levels of **22** and **30** may be in part attributable to more potent inhibition of CYP 3A by these two compounds (CYP K_i = 2.3 and 2.4 nM, respectively), which rivals that of ritonavir (CYP K_i = 3.2 nM). Notably, placement of a methyl substituent on the pyridine ring *ortho* to the ring nitrogen had a significant effect on CYP K_i (compare **22** with **25** and **30** with **34**), indicating an important role for the pyridine ring in binding to CYP 3A.

4. Conclusion

The series of novel HIV protease inhibitors described are potent inhibitors or replication of both wild-type virus and a strain of mutant virus (A17) that is highly resistant to lopinavir. The fold-resistance for the A17 virus was <2 for most of the compounds in this series. Activity values in the presence of 50% human serum were attenuated some 3- to 12-fold relative to activities in the absence of human serum. The most active compounds in the series have serum-adjusted EC_{50} values for both wild-type and A17 viruses in the 10–15 nM range. Most of the compounds in this activity range bear either a *tert*-butyl glycine group at P2 or a cyclopentylmethyl group at P1′. The position of the nitrogen in the pyridine ring at P3 did not have a significant effect on activity, however, it was important in vivo. Pharmacokinetic results in rat revealed that 2-pyridyl and 3-pyridyl analogs gave better overall exposure. Further, substitution on the pyridine ring also had a significant effect on the pharmacokinetic properties. Placement of a single methyl substituent on the 3-pyridyl ring resulted in very high exposure in the rat. In dog, only the unsubstituted 3-pyridyl analogs resulted in good blood levels. Compound **30** gave perhaps the best overall performance, with 1 nM activity against both wild-type and resistant viruses (12 nM in the presence of human serum), and AUC in rat and dog of 7.1 and 4.9, respectively. Compound **30** was also found to be a potent inhibitor of CYP 3A, with CYP K_i = 2.4 nM, which may play a role in the overall pharmacokinetic performance for this compound.

5. Experimental

5.1. General procedures

Solvents (including anhydrous) and reagents were used as supplied by commercial sources. Non-commercially available pyridine carboxaldehydes were prepared from the readily available hydroxymethyl analogs by the action of MnO_2 in CH_2Cl_2. Flash chromatography was performed using either Alltech Extract-Clean or Biotage Flash-40 silica gel cartridges. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz using a Bruker ARX 300 NMR spectrometer. Chemical shifts are in parts per million (δ) relative to TMS. Mass spectra were recorded using a Finnigan SSQ7000 mass spectrometer.

5.1.1. 4-(Diacetoxymethyl)benzenesulfonyl chloride (5). To a solution of *p*-toluenesulfonyl chloride (40.2 g, 0.21 mol) in acetic acid:acetic anhydride (800 mL, 1:1) at 0 °C was added concd sulfuric acid (64 mL, 1.2 mol). Chromium trioxide (80 g, 0.80 mol) was added at such a rate that the temperature remained below 10 °C, and the resulting mixture was stirred at 5–10 °C until the reaction was complete, as indicated by TLC. The reaction was quenched with ice water (2 L), and the solids were filtered, washed with water, and dried. The solids were added to saturated $NaHCO_3$ (1 L), stirred at rt for 2 h, filtered, dissolved in dichloromethane (1 L), dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in hot acetone/pentane and cooled to provide **5**, which was collected by vacuum filtration (24 g, 38%): mp = 110–112 °C (lit.[13] mp = 112–113 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, J = 9 Hz, 2 H), 7.77 (d, J = 9 Hz, 2H), 7.73 (s, 1H), 2.16 (s, 6H).

5.1.2. ((1*S*,2*R*)-1-Benzyl-2-hydroxy-3-{[4-(hydroxyiminomethyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-carbamic acid *tert*-butyl ester (6). To a solution of ((*S*)-1-(*S*)-oxiranyl-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester (**4**)[8] (10.0 g, 38.0 mmol) in 2-PrOH (100 mL) was added isobutylamine (11.4 mL, 114.7 mmol), and the mixture was heated at 80 °C for 2.5 h. Solvents were removed in vacuo, and the crude product was dissolved in anhydrous THF (95 mL). To this solution was added triethylamine (15.9 mL, 114.1 mmol), followed by a solution of **5** (14.0 g, 45.6 mmol) in anhydrous THF (95 mL). The mixture was stirred at rt for 4 h, treated with a saturated solution of $NaHCO_3$ (125 mL), extracted with EtOAc (3× 100 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was dissolved in EtOH (254 mL) and treated sequentially with hydroxylamine hydrochloride (5.29 g, 76.1 mmol) and triethylamine (21.2 mL, 152.1 mmol). The resulting mixture was stirred at 75 °C for 4 h, cooled to rt, and concentrated. The residue was diluted with EtOAc (200 mL) and washed sequentially with water (3× 100 mL), brine, and the organic layer was separated and concentrated in vacuo. The resulting solid was dissolved in boiling EtOAc (50 mL), cooled to rt, and triturated with hexanes to give **6** as a colorless solid (14.38 g, 73%): ^{1}H NMR (300 MHz, $CDCl_3$). δ 8.16 (s, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.25 (m, 5H), 4.63 (d, J = 5.8 Hz, 1H), 3.87 (s, 1H), 3.80 (s, 2H), 3.13 (m, 2H), 2.95 (m, 2H), 2.94 (s, 1H), 1.85 (m, 1H), 1.35 (s, 9H), 0.89 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H); MS (ESI) m/z 518.3 $[M-H]^-$, 520.1 $[M+H]^+$, 542.1 $[M+Na]^+$.

5.1.3. *N*-((2*R*,3*S*)-3-Amino-2-hydroxy-4-phenyl-butyl)-4-(*E*-hydroxyimino-methyl)-*N*-isobutyl-benzenesulfonamide (7). Compound **6** (4.92 g, 9.47 mmol) was dissolved in 4:1 trifluoroacetic acid:CH_2Cl_2, and the resulting solution was stirred at 0 °C for 3 h. The solvents were evaporated, and the residue was dissolved in 1:19 trifluoroacetic acid:CH_2Cl_2 (20 mL) and stirred at 25 °C for 16 h. The solvents were evaporated, the residue was partitioned between ethyl acetate (100 mL) and 1 N $NaHCO_3$ (50 mL), and the organic layer was separated and concentrated in vacuo. The residue was flashed on silica gel using 94:5:1 EtOAc:MeOH:NH_4OH and concentrated to give a colorless solid consisting predominantly of the *E*-oxime isomer (3.62 g, 91%). The pure *E*-oxime **7** was obtained by crystallization from 5% MeOH in EtOAc as a colorless, crystalline solid: mp = 155–156 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 8.13 (s, 1H), 7.79 (m, 4H), 7.26 (m, 5H), 3.73 (m, 1H), 3.44 (dd, J = 14.8, 3.6 Hz, 1H), 3.14 (dd, J = 14.9, 8.5 Hz, 1H), 3.06 (m, 2H), 2.95 (m, 2H), 2.54 (dd, J = 13.4, 9.0 Hz, 1H), 1.98 (m, 1H), 0.87 (m, 6H); MS (ESI) m/z 418.2 $[M-H]^-$, 420.0 $[M+H]^+$.

5.1.4. (2*S*,3*S*)-2-(2,4-Dioxo-imidazolidin-1-yl)-3-methyl-pentanoic acid *tert*-butyl ester (9). A solution of L-isoleucine *tert*-butyl ester hydrochloride (**8**) (10.0 g, 44.7 mmol) in anhydrous DMF (100 mL) and triethylamine (18.7 mL, 134.1 mmol) was treated dropwise over 15 min with ethyl bromoacetate (10.0 mL, 90.2 mmol). The mixture was stirred at rt for 16 h and was partitioned between EtOAc (200 mL) and H_2O (2× 200 mL), and dried over Na_2SO_4. Column chromatography on silica gel using 1:4 EtOAc:hexanes gave a colorless oil (12.07 g, 44.2 mmol), which was dissolved in anhydrous CH_2Cl_2 (100 mL), cooled to 0 °C, and treated dropwise with chlorosulfonylisocyanate (4.6 mL, 52.8 mmol) over 5 min. The mixture was stirred at 0 °C for 3 h and then allowed to warm to rt. H_2O (80 mL) was slowly added (heat!), and the resulting mixture was stirred at rt for 5 h. The layers were separated, the aqueous layer was washed with CH_2Cl_2 (2× 50 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in MeOH (100 mL), treated with triethylamine (10 mL), and the resulting mixture was stirred at rt for 16 h. The mixture was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel using 1:3 EtOAc:hexanes. The title compound **9** was obtained as a colorless gum (4.20 g, 35%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (br s, 1 H), 4.41 (m, 2H), 3.89 (d, J = 18.0 Hz, 1H), 1.87 (m, 1H), 1.48 (s, 9H), 1.20 (m, 2H), 1.00 (d, J = 6.8 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H); MS (ESI) m/z 269.1 $[M-H]^-$, 270.9 $[M+H]^+$, 288.0 $[M+NH_4]^+$, 293.0 $[M+Na]^+$.

5.1.5. (2*S*,3*S*)-2-(2,4-Dioxo-3-pyridin-2-ylmethyl-imidazolidin-1-yl)-3-methyl-pentanoic acid *tert*-butyl ester (10). A solution of **9** (0.20 g, 0.74 mmol) in anhydrous DMF (4 mL) at −40 °C was treated dropwise with a solution of sodium bis(trimethylsilyl)amide (1.0 M in THF, 1.5 mL, 1.5 mmol). The resulting mixture was stirred at −40 °C for 15 min, followed by the addition of 2-(bromomethyl)pyridine hydrogen bromide (0.19 g, 0.75 mmol). The mixture was stirred at −40 °C for 10 min and then stirred at 0 °C for 2 h. A saturated solution of NH_4Cl (5 mL) was added, and the mixture was partitioned between H_2O (50 mL) and EtOAc (2× 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated, and the crude product was purified by column chromatography on silica gel using 2:1 EtOAc:hexanes. The title compound **10** was obtained as a colorless, amorphous solid (0.22 g, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J = 5.1 Hz, 1H), 7.63 (m, 1H), 7.18 (m, 2H), 4.84 (m, 2H), 4.49 (d, J = 9.2 Hz, 1H), 4.39 (d, J = 17.6 Hz, 1H), 3.94 (d, J = 17.6 Hz, 1H), 1.95 (m, 1H), 1.47 (s, 9H), 1.18 (m, 2H), 1.00 (d, J = 6.8 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H); MS (ESI) m/z 362.0 $[M+H]^+$, 384.0 $[M+Na]^+$.

5.2. General method for peptide coupling

5.2.1. (2*S*,3*S*)-2-(2,4-Dioxo-3-pyridin-2-ylmethyl-imidazolidin-1-yl)-3-methyl-pentanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (11). A solution of **10** (0.10 g, 0.28 mmol) in 2:1 TFA:CH_2Cl_2 (0.9 mL) was stirred at rt 90 min and concentrated in vacuo. The residue was repeatedly concentrated from CH_2Cl_2 (2× 2 mL) and dried in vacuo. To a solution of the resulting residue in anhydrous DMF (2 mL) at 0 °C were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (64 mg, 0.33 mmol), 1-hydroxybenzotriazole (57 mg, 0.42 mmol). The resulting mixture was stirred at 0 °C for 20 min, after which time **7** (0.13 g, 0.31 mmol) and diisopropylethylamine (0.10 mL, 0.57 mmol) were added. The resulting mixture was stirred at rt for 16 h and was partitioned between H_2O (20 mL) and EtOAc (3× 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated, and the crude product was purified by column chromatography on silica gel using 98:2 $CHCl_3$:MeOH. The title compound **11** was obtained as a colorless, amorphous solid (85 mg, 43%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J = 3.7 Hz, 1H), 8.16 (s, 1H), 7.85 (m, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H), 7.64 (m, 1H), 7.22 (m, 2H), 7.15 (s, 5H), 6.23 (d, J = 9.5 Hz, 1H), 4.80 (m, 2H), 4.25 (m, 1H), 3.99 (d, J = 10.9 Hz, 1H), 3.83 (m, 1H), 3.75 (br s, 1H), 3.67 (d, J = 18.0 Hz, 1H), 3.44 (d, J = 17.6 Hz, 1H), 3.21 (m, 1H), 3.04 (m, 3H), 2.85 (dd, J = 13.6, 6.8 Hz, 1H), 2.71 (dd, J = 14.1, 10.3 Hz, 1H), 1.88 (m, 2H), 1.29 (m, 1H), 0.96 (m, 1H), 0.92 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 7.1 Hz, 3H), 0.76 (d, J = 6.7 Hz, 3H); MS (ESI) m/z 705.3 $[M-H]^-$, 707.3 $[M+H]^+$, 729.2 $[M+Na]^+$.

5.2.2. (*S*)-2-(2,4-Dioxo-3-pyridin-4-ylmethyl-imidazolidin-1-yl)-3-methyl-butanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (16). The title compound was prepared using the method described for the synthesis of **11**, substituting 4-(bromomethyl)pyridine for 2-(bromomethyl)pyridine, and substituting **38** for **9** (19% overall yield from **38**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (br s, 2H), 8.16 (s, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.51 (m, 2H), 7.14 (m, 5H), 6.45 (d, J = 7.8 Hz, 1H), 4.71 (m, 2H), 4.28 (m, 1H), 3.92 (m, 2H), 3.69 (d, J = 18.0 Hz, 1H), 3.49 (d, J = 18.0 Hz, 1H), 3.22 (m, 1H), 3.04 (m, 3H), 2.87 (m, 1H), 2.74 (m, 1H), 2.09 (m, 1H), 1.86 (m, 1H), 0.91 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H), 0.84 (d, J = 6.4 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H); MS (ESI) m/z 691.3 $[M-H]^-$, 693.2 $[M+H]^+$, 715.2 $[M+Na]^+$.

5.2.3. (*S*)-2-(2,4-Dioxo-3-pyridin-2-ylmethyl-imidazolidin-1-yl)-3-methyl-butanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (17). The title compound was prepared using the method described for the synthesis of **11**, substituting **38** for **9** (38% overall yield from **38**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (br s, 1H), 8.16 (s, 1H), 7.80 (d, J = 8.8 Hz, 2H), 7.71 (m, J = 8.5 Hz, 3H), 7.26 (m, 2H), 7.17 (m, 5H), 6.38 (s, 1H), 4.85 (m, 2H), 4.27 (m, 1H), 3.93 (d, J = 10.5 Hz, 1H), 3.85 (m, 1H), 3.71 (d, J = 18.0 Hz, 1H), 3.47 (d, J = 18.3 Hz, 1H), 3.20 (m, 1H), 3.07 (m, 2H), 2.98 (m, 1H), 2.86 (m, 1H), 2.75 (m, 1H), 2.13 (m, J = 10.17 Hz, 1H), 1.87 (m, 1H), 0.91 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H), 0.81 (d, J = 6.8, 3H), 0.80 (d, J = 6.8 Hz, 3H); MS (ESI) m/z 691.2 $[M-H]^-$, 693.1 $[M+H]^+$, 715.2 $[M+Na]^+$.

5.2.4. (2*S*,3*S*)-2-(2,4-Dioxo-3-pyridin-3-ylmethyl-imidazolidin-1-yl)-3-methyl-pentanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (18). The title compound was prepared using the method described for the synthesis of **11**, substituting 3-(bromomethyl)pyridine for 2-(bromomethyl)pyridine (25% overall yield from **9**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 8.57 (br s, 1H), 8.17 (s, 1H), 8.09 (br s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H), 7.32 (m, 1H), 7.05 (m, 5H), 6.12 (d, J = 8.8 Hz, 1H), 4.23 (m, 1H), 4.63 (m, 2H), 3.93 (d, J = 11.2 Hz, 1H), 3.78 (m, 1H), 3.62 (br s, 1H), 3.56 (d, J = 18.0 Hz, 1H), 3.31 (d, J = 17.6 Hz, 1H), 3.20 (m, 1H), 3.04 (m, 3H), 2.86 (dd, J = 13.6, 6.8 Hz, 1H), 2.64 (dd, J = 14.1, 10.7 Hz, 1H), 1.85 (m, 2H), 1.19 (m, 1H), 0.92 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H), 0.82 (d, J = 7.5 Hz, 3H), 0.77 (d, J = 6.8 Hz, 3H); MS (ESI) m/z 705.4 $[M-H]^-$, 707.3 $[M+H]^+$, 729.3 $[M+Na]^+$.

5.2.5. (2*S*,3*S*)-2-(2,4-Dioxo-3-pyridin-4-ylmethyl-imidazolidin-1-yl)-3-methyl-pentanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (19). The title compound was prepared using the method described for the synthesis of **11**, substituting 4-(bromomethyl)pyridine for 2-(bromomethyl)pyridine (44% overall yield from **9**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (br s, 2H), 8.17 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H), 7.26 (m, 2H), 7.11 (m, 5H), 6.14 (d, J = 9.2 Hz, 1H),

4.64 (m, 2H), 4.57 (m, 1H), 4.26 (m, 1H), 3.96 (d, J = 11.2 Hz, 1H), 3.85 (m, 1H), 3.61 (d, J = 18.3 Hz, 2H), 3.41 (d, J = 18.0 Hz, 1H), 3.22 (m, 1H), 3.04 (m, 3H), 2.84 (dd, J = 13.6, 6.4 Hz, 1H), 2.70 (dd, J = 14.2, 10.5 Hz, 1H), 1.84 (m, 2H), 1.18 (s, 1H), 0.93 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H), 0.81 (m, 6H); MS (ESI) m/z 705.4 $[M-H]^-$, 707.3 $[M+H]^+$, 729.3 $[M+Na]^+$.

5.2.6. (*S*)-2-(2,4-Dioxo-3-benzyl-imidazolidin-1-yl)-3-methyl-butanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (3). The title compound was prepared using the method described for the synthesis of **11**, substituting benzylbromide for 2-(bromomethyl)pyridine, and substituting **38** for **9** (13% overall yield from **38**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H), 7.41 (m, 2H), 7.32 (m, 3H), 7.02 (m, 5H), 6.06 (d, J = 9.8 Hz, 1H), 4.62 (m, 2H), 4.23 (m, 1H), 3.86 (d, J = 11.2Hz, 1H), 3.81 (m, 1H), 3.54 (d, J = 18.0 Hz, 1H), 3.20 (m, 2H), 3.01 (m, 3H), 2.84 (m, 1H), 2.64 (dd, J = 14.2, 10.9 Hz, 1H), 2.05 (m, 1H), 1.86 (m, 1H), 0.93 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.4 Hz, 3H), 0.76 (d, J = 6.8 Hz, 3H); MS (ESI) m/z 690.3 $[M-H]^-$, 692.2 $[M+H]^+$, 714.2 $[M+Na]^+$.

5.2.7. (*S*)-2-(2,4-Dioxo-3-benzyl-imidazolidin-1-yl)-3-methyl-butanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-methoxy-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (2). The title compound was prepared using an analogous procedure to that described for the synthesis of **3**, substituting ((1*S*,2*R*)-1-Benzyl-2-hydroxy-3-{[4-methoxy-benzenesulfonyl]-isobutyl-amino}-propyl)-carbamic acid *tert*-butyl ester[14] for **6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (m, 2H), 7.42 (m, 2H), 7.33 (m, 3H), 7.02 (m, 7H), 6.05 (d, J = 9.5 Hz, 1H), 4.62 (m, 2H), 4.22 (m, 1H), 3.88 (s, 3H), 3.80 (m, 2H), 3.53 (d, J = 18.0 Hz, 1H), 3.18 (m, 2H), 2.98 (m, 3H), 2.77 (dd, J = 13.6, 6.4 Hz, 1H), 2.63 (dd, J = 14.1, 10.7 Hz, 1H), 2.05 (m, 1H), 1.81 (m, 1H), 0.94 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.4 Hz, 3H), 0.75 (d, J = 6.8 Hz, 3H); MS (ESI) m/z 677.3 $[M-H]^-$, 679.2 $[M+H]^+$.

5.2.8. (*S*)-2-(2,4-Dioxo-3-(2-methyl-thiazol-4-ylmethyl)-imidazolidin-1-yl)-3-methyl-butanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-methoxy-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (1). The title compound was prepared using an analogous procedure to that described for the synthesis of **2**, substituting 4-chloromethyl-2-methylthiazole[15] for benzylbromide: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (m, 2H), 7.10 (m, 5H), 6.99 (m, 2H), 6.20 (d, J = 9.5 Hz, 1H), 4.73 (m, J = 7.1 Hz, 2H), 4.22 (m, 1H), 3.88 (s, 3H), 3.82 (m, 1H), 3.55 (m, 1H), 3.20 (m, 2H), 3.00 (m, 3H), 2.78 (dd, J = 13.4, 6.6 Hz, 1H), 2.66 (s, 3H), 2.07 (m, 1H), 1.83 (m, 1H), 0.93 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H), 0.80 (m, 6H); MS (ESI) m/z 698.3 $[M-H]^-$, 700.3 $[M+H]^+$, 722.3 $[M+Na]^+$.

5.2.9. *N*-(2-Aminoethyl)-L-isoleucine *tert*-butyl ester (13). To a solution of *N*-(2,2-diethoxyethyl)-phthalimide (**12**) (14.2 g, 53.9 mmol) in THF (30 mL) was added 10% aq HCl (30 mL), and the mixture was stirred at 75 °C for 10 h. The mixture was concentrated to ~30 mL in vacuo, followed by slow addition of saturated $NaHCO_3$ (100 mL). The mixture was extracted with EtOAc (3× 100 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting crude aldehyde was dissolved in MeOH (200 mL) and treated with **8** (13.1 g, 58.7 mmol), $NaCNBH_3$ (7.4 g, 117.8 mmol), and AcOH (2 mL). The resulting mixture was stirred at rt for 2 h and was concentrated in vacuo. The residue was partitioned between saturated $NaHCO_3$ (200 mL) and CH_2Cl_2 (3× 200 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by column chromatography on silica gel using 1:2 EtOAc:hexanes to give a colorless oil (11.5 g). This material was dissolved in EtOH (250 mL) and treated with hydrazine hydrate (10 mL), and the resulting mixture was stirred at 60 °C for 1 h. The mixture was cooled to rt to give a solid colorless mass, which was treated with 0.5 M NaOH (250 mL). The mass slowly dissolved with stirring, and the solution was extracted with CH_2Cl_2 (3× 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give the title compound **13** as a yellowish oil (6.88 g, 55%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 (d, J = 6.1 Hz, 1H), 2.73 (m, 3H), 2.47 (m, 1H), 1.61 (m, 2H), 1.47 (s, 9H), 1.20 (m, 1H), 0.90 (m, 6H); MS (ESI) m/z 231.1 $[M+H]^+$.

5.2.10. (2*S*,3*S*)-3-Methyl-2-[3-(6-methyl-pyridin-2-yl-methyl)-2-oxo-imidazolidin-1-yl]-pentanoic acid *tert*-butyl ester (14). A solution of **13** (0.25 g, 1.1 mmol) and 6-methyl-2-pyridinecarboxaldehyde (0.13 g, 1.1 mmol) in anhydrous CH_2Cl_2 (5 mL) was treated with $MgSO_4$ (~0.1 g), and the resulting mixture was stirred at rt for 2 h. The mixture was filtered and concentrated in vacuo, and the residue was dissolved in anhydrous MeOH (5 mL) and treated with $NaBH_4$ (60 mg, 1.6 mmol). The resulting mixture was stirred at rt for 1 h, acetone (1 mL) was added, and the solvent was removed in vacuo. The residue was partitioned between H_2O (20 mL) and EtOAc (2× 25 mL), and the combined organic layers were dried over Na_2SO_4. The drying agent was filtered off, and the solvent was removed in vacuo to give an oil, which was dissolved in anhydrous DMF (22 mL) and treated with bis(4-nitrophenyl) carbonate (0.39 g, 1.3 mmol). The resulting mixture was stirred at 50 °C for 3 h, cooled to rt, and partitioned between H_2O (100 mL) and EtOAc (100 mL). The organic layer was washed with saturated $NaHCO_3$ (3× 100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 3:2 EtOAc:hexanes to give the title compound **14** as a colorless oil (0.32 g, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.11 (d, J = 7.8 Hz, 1H), 7.04 (d, J = 7.5 Hz, 1H), 4.50 (m, 2H), 4.29 (d, J = 9.5 Hz, 1H), 3.71 (m, 1H), 3.34 (m, 3H), 2.54 (s, 3H), 1.92 (m, 1H), 1.47 (m, 9H), 1.16 (m, 1H), 0.98 (d, J = 6.8 Hz, 3H), 0.92 (t, J = 7.5 Hz, 3H); MS (ESI) m/z 362.1 $[M+H]^+$.

5.2.11. (2*S*,3*S*)-3-Methyl-2-[3-(6-methyl-pyridin-2-yl-methyl)-2-oxo-imidazolidin-1-yl]-pentanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (15). Using the general method for peptide coupling described above for the conversion of **10** to **11**, compound **14** (50 mg, 0.14 mmol) was converted to the title compound **15**, obtained as a colorless, amorphous solid (56 mg, 57%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (br s, 1H), 8.16 (s, 1H), 7.79 (d, J = 8.5Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.58 (m, 1H), 7.18 (m, 5H), 7.06 (m, 2H), 6.49 (d, J = 8.8 Hz, 1H), 4.59 (d, J = 15.6 Hz, 1H), 4.38 (d, J = 15.6 Hz, 1H), 4.12 (m, 1H), 3.88 (d, J = 3.4 Hz, 1H), 3.80 (m, 2H), 3.13 (m, 6H), 2.94 (m, 1H), 2.83 (m, 1H), 2.74 (dd, J = 14.2, 10.2 Hz, 1H), 2.56 (s, 3H), 1.96 (m, 1H), 1.86 (m, 1H), 1.35 (m, 1H), 1.03 (m, 1H), 0.91 (d, J = 6.4 Hz, 3H), 0.85 (m, 6H), 0.73 (d, J = 6.4 Hz, 3H); MS (ESI) m/z 705.4 $[M-H]^-$, 707.3 $[M+H]^+$, 729.3 $[M+Na]^+$.

5.2.12. (2*S*,3*S*)-3-Methyl-2-[2-oxo-3-pyridin-4-ylmethyl-imidazolidin-1-yl]-pentanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (20). The title compound was prepared using the method described for the synthesis of **15**, substituting 4-pyridinecarboxaldehyde for 6-methyl-2-pyridinecarboxaldehyde (12% overall yield from **13**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (br s, 2H), 8.16 (s, 1H), 7.80 (d, J = 8.1 Hz, 2H), 7.69 (d, J = 8.5 Hz, 2H), 7.30 (m, 2H), 7.20 (m, 5H), 6.53 (d, J = 8.8 Hz, 1H), 4.49 (d, J = 15.9 Hz, 1H), 4.27 (d, J = 15.9 Hz, 1H), 4.23 (m, 1H), 3.79 (m, 2H), 2.96 (m, 9H), 2.00 (m, 1H), 1.87 (m, 2H), 1.37 (m, 1H), 1.01 (m, 1H), 0.87 (m, 9H), 0.76 (d, J = 6.4 Hz, 3H); MS (ESI) m/z 691.4 $[M-H]^-$, 693.3 $[M+H]^+$, 715.3 $[M+Na]^+$.

5.2.13. (2*S*,3*S*)-3-Methyl-2-[2-oxo-3-pyridin-2-ylmethyl-imidazolidin-1-yl]-pentanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (21). The title compound was prepared using the method described for the synthesis of **15**, substituting 2-pyridinecarboxaldehyde for 6-methyl-2-pyridinecarboxaldehyde (43% overall yield from **13**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J = 4.1 Hz, 1H), 8.16 (s, 2H), 7.79 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 3H), 7.68 (m, 1H), 7.22 (m, 7H), 6.53 (d, J = 8.8 Hz, 1H), 4.59 (d, J = 15.6 Hz, 1H), 4.40 (d, J = 15.6 Hz, 1H), 4.16 (m, 1H), 3.90 (m, 1H), 3.79 (m, 1H), 3.77 (d, J = 10.9 Hz, 1H), 3.14 (m, 5H), 2.99 (m, 1H), 2.87 (m, 2H), 2.75 (dd, J = 14.2, 10.2 Hz, 1H), 1.97 (m, 1H), 1.87 (m, 1H), 1.39 (m, 1H), 1.01 (m, 1H), 0.89 (m, 9H), 0.73 (d, J = 6.4 Hz, 3H); MS (ESI) m/z 691.3 $[M-H]^-$, 693.3 $[M+H]^+$, 715.2 $[M+Na]^+$.

5.2.14. (2*S*,3*S*)-3-Methyl-2-[2-oxo-3-pyridin-3-ylmethyl-imidazolidin-1-yl]-pentanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (22). The title compound was prepared using the method described for the synthesis of **15**, substituting 3-pyridinecarboxaldehyde for 6-methyl-2-pyridinecarboxaldehyde (40% overall yield from **13**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (br s, 2H), 8.16 (s, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 7.8 Hz, 1H), 7.37 (m, 1H), 7.19 (m, 7H), 6.53 (d, J = 8.5 Hz, 1H), 4.48 (d, J = 15.3 Hz, 1H), 4.23 (d, J = 15.3 Hz, 1H), 4.18 (m, 1H), 3.83 (m, 2H), 3.74 (d, J = 10.9 Hz, 1H), 3.12 (m, 4H), 3.04 (m, 1H), 2.95 (m, 1H), 2.88 (m, 1H), 2.75 (dd, J = 14.2, 10.1 Hz, 1H), 1.98 (m, 1H), 1.86 (m, 1H), 1.35 (m, 1H), 0.97 (m, 1H), 0.92 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H), 0.83 (m, J = 7.5 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H); MS (ESI) m/z 691.5 $[M-H]^-$, 693.3 $[M+H]^+$, 715.3 $[M+Na]^+$.

5.2.15. (2*S*,3*S*)-3-Methyl-2-[3-(6-methoxymethyl-pyridin-2-ylmethyl)-2-oxo-imidazolidin-1-yl]-pentanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (23). The title compound was prepared using the method described for the synthesis of **15**, substituting 6-methoxymethyl-2-pyridinecarboxaldehyde for 6-methyl-2-pyridinecarboxaldehyde (60% overall yield from **13**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.15 (br s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.68 (m, 3H), 7.32 (d, J = 7.8 Hz, 1H), 7.17 (m, 5H), 6.50 (d, J = 8.5 Hz, 1H), 4.60 (d, J = 15.9 Hz, 1H), 4.56 (s, 2H), 4.37 (d, J = 15.6 Hz, 1H), 4.17 (m, 1H), 3.81 (m, 3H), 3.48 (s, 3H), 3.14 (m, 6H), 2.99 (m, 1H), 2.84 (m, 2H), 2.75 (dd, J = 14.4, 10.0 Hz, 1H), 1.98 (m, 1H), 1.88 (m, 1H), 1.39 (m, 1H), 1.01 (m, 1H), 0.91 (d, J = 6.8 Hz, 3H), 0.85 (m, 6H), 0.74 (d, J = 6.8 Hz, 3H); MS (ESI) m/z 735.4 $[M-H]^-$, 737.3 $[M+H]^+$, 759.3 $[M+Na]^+$.

5.2.16. (2*S*,3*S*)-3-Methyl-2-[3-(6-isopropyl-pyridin-2-yl-methyl)-2-oxo-imidazolidin-1-yl]-pentanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (24). The title compound was prepared using the method described for the synthesis of **15**, substituting 6-isopropyl-2-pyridinecarboxaldehyde for 6-methyl-2-pyridinecarboxaldehyde (18% overall yield from **13**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.69 (m, 2H), 7.19 (m, 5H), 7.08 (m, 2H), 6.50 (d, J = 8.8 Hz, 1H), 4.58 (m, 1H), 4.39 (m, 1H), 4.12 (m, 1H), 3.86 (m, 1H), 3.75 (m, 2H), 3.02 (m, 11H), 2.75 (m, 1H), 1.87 (m, 2H), 1.29 (m, 6H), 1.01 (m, 1H), 0.88 (m, 9H), 0.73 (d, J = 6.4 Hz, 3H); MS (ESI) m/z 733.5 $[M-H]^-$, 735.3 $[M+H]^+$, 757.5 $[M+Na]^+$.

5.2.17. (2*S*,3*S*)-3-Methyl-2-[3-(2-methyl-pyridin-3-yl-methyl)-2-oxo-imidazolidin-1-yl]-pentanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (25). The title compound was prepared using the method described for the synthesis of **15**, substituting 2-methyl-3-pyridinecarboxaldehyde for 6-methyl-2-pyridinecarboxaldehyde (39% overall yield from **13**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (dd, J = 5.0, 1.7 Hz, 1H), 8.16 (s, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2H), 7.45 (dd, J = 7.7, 1.5 Hz, 1H), 7.17 (m, 6H), 6.49 (d, J = 8.8 Hz, 1H), 4.42 (d, J = 15.1 Hz, 1H), 4.26 (d, J = 15.4 Hz, 1H), 4.20 (m, 1H), 3.79 (m, 2H), 3.02 (m, 9H), 2.78 (dd, J = 14.3, 9.9 Hz, 1H), 2.55 (s, 3H), 1.99 (m, 1H), 1.85 (m, 1H), 1.33 (m, 1H), 1.00 (m, 1H), 0.90 (d, J = 6.6 Hz, 3H), 0.85 (m, 6H), 0.75 (d, J = 6.6 Hz,

3H); MS (ESI) *m/z* 705.3 $[M-H]^-$, 707.4 $[M+H]^+$, 729.5 $[M+Na]^+$.

5.2.18. (2*S*,3*S*)-3-Methyl-2-[3-(6-methyl-pyridin-3-yl-methyl)-2-oxo-imidazolidin-1-yl]-pentanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (26). The title compound was prepared using the method described for the synthesis of **15**, substituting 6-methyl-3-pyridinecarboxaldehyde for 6-methyl-2-pyridinecarboxaldehyde (36% overall yield from **13**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, J = 2.6 Hz, 1H), 8.16 (m, 2H), 7.80 (d, J = 8.5Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H), 7.49 (dd, J = 7.9, 2.4 Hz, 1H), 7.18 (m, 5H), 6.45 (d, J = 8.8 Hz, 1H), 4.41 (d, J = 15.1 Hz, 1H), 4.19 (m, 2H), 3.76 (m, 2H), 3.08 (m, 7H), 2.88 (m, 1H), 2.76 (m, 2H), 2.55 (s, 3H), 1.90 (m, 2H), 1.31 (m, 1H), 0.99 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H), 0.84 (m, 6H), 0.73 (d, J = 6.6 Hz, 3H); MS (ESI) *m/z* 705.3 $[M-H]^-$, 707.4 $[M+H]^+$, 729.4 $[M+Na]^+$.

5.2.19. (2*S*,3*S*)-3-Methyl-2-[3-(4-methyl-pyridin-3-yl-methyl)-2-oxo-imidazolidin-1-yl]-pentanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (27). The title compound was prepared using the method described for the synthesis of **15**, substituting 4-methyl-3-pyridinecarboxaldehyde for 6-methyl-2-pyridinecarboxaldehyde (15% overall yield from **13**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (m, 3H), 8.16 (s, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2H), 7.19 (m, 6H), 6.49 (d, J = 8.8 Hz, 1H), 4.44 (d, J = 14.9 Hz, 1H), 4.28 (d, J = 14.9 Hz, 1H), 4.17 (m, 1H), 3.81 (m, 1H), 3.76 (d, J = 10.9 Hz, 1H), 3.09 (m, 6H), 2.88 (m, 3H), 2.75 (dd, J = 14.2, 9.8 Hz, 1H), 2.34 (s, 3H), 1.99 (m, 1H), 1.87 (m, 1H), 1.33 (m, 1H), 1.00 (m, 1H), 0.90 (d, J = 6.4 Hz, 3 H), 0.84 (m, 6H), 0.73 (d, J = 6.4 Hz, 3H); MS (ESI) *m/z* 705.4 $[M-H]^-$, 707.3 $[M+H]^+$, 729.3 $[M+Na]^+$.

5.2.20. (2*S*,3*S*)-3-Methyl-2-[3-(2,4-dimethyl-pyridin-3-ylmethyl)-2-oxo-imidazolidin-1-yl]-pentanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (28). The title compound was prepared using the method described for the synthesis of **15**, substituting 2,4-dimethyl-3-pyridinecarboxaldehyde for 6-methyl-2-pyridinecarboxaldehyde (40% overall yield from **13**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 5.2 Hz, 2H), 8.16 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.20 (m, 5H), 6.97 (d, J = 5.2 Hz, 1H), 6.52 (d, J = 8.5 Hz, 1H), 4.48 (d, J = 14.7 Hz, 1H), 4.39 (d, J = 14.7 Hz, 1H), 4.20 (m, 1H), 3.79 (m, 2H), 3.10 (m, 4H), 2.92 (m, 4H), 2.77 (m, 2H), 2.59 (s, 3H), 2.34 (s, 3H), 1.97 (m, 1H), 1.85 (m, 1H), 1.31 (m, 1H), 0.97 (m, 1H), 0.90 (d, J = 6.3 Hz, 3H), 0.84 (m, 6H), 0.74 (d, J = 6.3 Hz, 3 H); MS (ESI) *m/z* 719.4 $[M-H]^-$, 721.4 $[M+H]^+$.

5.2.21. (2*S*,3*S*)-3-Methyl-2-[3-(6-methoxy-pyridin-3-yl-methyl)-2-oxo-imidazolidin-1-yl]-pentanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (29). The title compound was prepared using the method described for the synthesis of **15**, substituting 6-methoxy-3-pyridinecarboxaldehyde for 6-methyl-2-pyridinecarboxaldehyde (19% overall yield from **13**): ^{1}H NMR (300 MHz, CD_3OD). δ 8.14 (s, 1H), 8.08 (m, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.63 (dd, J = 8.6, 2.4 Hz, 1H), 7.14 (m, 2H), 7.05 (m, 3H), 6.81 (d, J = 8.5 Hz, 1H), 4.39 (d, J = 15.1 Hz, 1H), 4.24 (d, J = 15.1 Hz, 1H), 4.12 (m, 1H), 3.90 (s, 3H), 3.84 (m, 1H), 3.74 (m, 1H), 3.44 (m, 1H), 3.18 (m, 1H), 3.04 (m, 7H), 2.51 (m, 2H), 2.01 (m, 1H), 1.83 (m, 1H), 1.28 (m, 1H), 0.97 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H), 0.85 (m, 6H), 0.71 (d, J = 6.6 Hz, 3H); MS (ESI) *m/z* 721.4 $[M-H]^-$, 723.4 $[M+H]^+$, 745.4 $[M+Na]^+$.

5.2.22. (*S*)-3,3-Dimethyl-2-(2-oxo-3-pyridin-3-ylmethyl-imidazolidin-1-yl)-butanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (30). The title compound was prepared using the method described for the synthesis of **15**, substituting 3-pyridinecarboxaldehyde for 6-methyl-2-pyridinecarboxaldehyde, and substituting **39** for **13** (46% overall yield from **39**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (m, 2H), 8.17 (s, 1H), 7.80 (d, J = 8.5 Hz, 3H), 7.72 (d, J = 8.5 Hz, 2H), 7.62 (m, 1H), 7.30 (dd, J = 7.4, 4.4 Hz, 1H), 7.13 (m, 5H), 6.24 (d, J = 9.2 Hz, 1H), 4.46 (d, J = 15.1 Hz, 1H), 4.27 (d, J = 15.1 Hz, 1H), 4.23 (m, 1H), 4.00 (s, 1H), 3.79 (m, 1H), 3.32 (m, 1H), 3.14 (m, 3H), 3.01 (m, 2H), 2.89 (m, 2H), 2.70 (dd, J = 14.2, 10.5 Hz, 1H), 2.59 (q, J = 9.0 Hz, 1H), 1.87 (m, 1H), 0.96 (s, 9H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); MS (ESI) *m/z* 691.3 $[M-H]^-$, 693.4 $[M+H]^+$, 715.4 $[M+Na]^+$.

5.2.23. (2*S*,3*S*)-3-Methyl-2-(2-oxo-3-pyridin-3-ylmethyl-imidazolidin-1-yl)-pentanoic acid ((1*S*,2*R*)-1-benzyl-3-{cyclopentylmethyl-[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-amino}-2-hydroxy-propyl)-amide (31). The title compound was prepared using the method described for the synthesis of **15**, substituting 3-pyridinecarboxaldehyde for 6-methyl-2-pyridinecarboxaldehyde, and substituting **40** for **7** (36% overall yield from **13**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (m, 2H), 8.16 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2H), 7.60 (m, 1H), 7.29 (m, 1H), 7.17 (m, 5H), 6.50 (d, J = 8.8 Hz, 1H), 4.45 (d, J = 15.1 Hz, 1H), 4.22 (m, 2H), 3.79 (m, 2H), 3.09 (m, 8H), 2.79 (m, 2H), 2.11 (m, 1H), 1.96 (m, 1H), 1.64 (m, 4H), 1.31 (m, 5H), 0.97 (m, 1H), 0.84 (t, J = 7.4Hz, 3H), 0.74 (d, J = 6.6 Hz, 3H); MS (ESI) *m/z* 717.3 $[M-H]^-$, 719.4 $[M+H]^+$, 741.4 $[M+Na]^+$.

5.2.24. (2*S*,3*S*)-3-Methyl-2-(3-(6-methyl-pyridin-2-yl-methyl)-2-oxo-imidazolidin-1-yl)-pentanoic acid ((1*S*,2*R*)-1-benzyl-3-{cyclopentylmethyl-[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-amino}-2-hydroxy-propyl)-amide (32). The title compound was prepared using the method described for the synthesis of **15**, substituting **40** for **7** (57% overall yield from **13**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (br s, 1H), 8.16 (s, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.58 (m, 1H), 7.21 (m, 4H), 7.16 (m, 1H), 7.06 (m, 2H), 6.52 (d,

J = 8.8 Hz, 1H), 4.59 (d, J = 15.6 Hz, 1H), 4.40 (m, 1H), 4.36 (d, J = 15.6 Hz, 1H), 4.15 (m, 1H), 3.79 (m, 3H), 3.15 (m, 6H), 3.00 (m, 1H), 2.79 (m, 2H), 2.55 (s, 3H), 2.13 (m, 1H), 1.97 (m, 1H), 1.64 (m, 4H), 1.39 (m, 2H), 1.26 (m, 2H), 1.16 (m, 1H), 1.00 (m, 1H), 0.86 (m, 3H), 0.74 (d, J = 6.8 Hz, 3H); MS (ESI) *m/z* 731.4 $[M-H]^-$, 733.5 $[M+H]^+$, 755.5 $[M+Na]^+$.

5.2.25. (2*S*,3*S*)-3-Methyl-2-(3-(2-methyl-pyridin-3-yl-methyl)-2-oxo-imidazolidin-1-yl)-pentanoic acid ((1*S*,2*R*)-1-benzyl-3-{cyclopentylmethyl-[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-amino}-2-hydroxy-propyl)-amide (33). The title compound was prepared using the method described for the synthesis of **15**, substituting 2-methyl-3-pyridinecarboxaldehyde for 6-methyl-2-pyridinecarboxaldehyde, and substituting **40** for **7** (37% overall yield from **13**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J = 3.7 Hz, 1H), 8.25 (br s, 1H), 8.16 (s, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 6.6 Hz, 1H), 7.17 (m, 5H), 6.52 (d, J = 8.8 Hz, 1H), 4.43 (d, J = 15.4 Hz, 1H), 4.24 (m, 2H), 3.81 (m, 3H), 3.04 (m, 8H), 2.88 (m, 1H), 2.80 (m, 1H), 2.54 (s, 3H), 2.11 (m, 1H), 1.99 (m, 1H), 1.58 (m, 4H), 1.26 (m, 4H), 1.00 (m, 2H), 0.85 (t, J = 7.4Hz, 3H), 0.76 (d, J = 6.6 Hz, 3H); MS (ESI) *m/z* 731.4 $[M-H]^-$, 733.5 $[M+H]^+$, 755.4 $[M+Na]^+$.

5.2.26. (*S*)-3,3-Dimethyl-2-(3-(6-methyl-pyridin-3-ylmethyl)-2-oxo-imidazolidin-1-yl)-butanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (34). The title compound was prepared using the method described for the synthesis of **15**, substituting 6-methyl-3-pyridinecarboxaldehyde for 6-methyl-2-pyridinecarboxaldehyde, and substituting **39** for **13** (49% overall yield from **39**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (m, 1H), 8.17 (s, 1H), 7.87 (m, 1H), 7.80 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H), 7.51 (dd, J = 7.7, 2.2 Hz, 1H), 7.14 (m, 5H), 6.18 (d, J = 9.2 Hz, 1H), 4.42 (m, 1H), 4.20 (m, 2H), 4.00 (s, 1H), 3.77 (m, 2H), 3.31 (m, 1H), 3.15 (m, 3H), 3.00 (m, 2H), 2.89 (m, 2H), 2.69 (m, 1H), 2.56 (s, 3H), 1.85 (m, 1H), 0.96 (s, 9H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); MS (ESI) *m/z* 705.4 $[M-H]^-$, 707.4 $[M+H]^+$, 729.4 $[M+Na]^+$.

5.2.27. (2*S*,3*S*)-3-Methyl-2-(3-(4-methyl-pyridin-3-yl-methyl)-2-oxo-imidazolidin-1-yl)-pentanoic acid ((1*S*,2*R*)-1-benzyl-3-{cyclopentylmethyl-[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-amino}-2-hydroxy-propyl)-amide (35). The title compound was prepared using the method described for the synthesis of **15**, substituting 4-methyl-3-pyridinecarboxaldehyde for 6-methyl-2-pyridinecarboxaldehyde, and substituting **40** for **7** (16% overall yield from **13**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (m, 2H), 8.16 (s, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2H), 7.17 (m, 6H), 6.51 (d, J = 8.8 Hz, 1H), 4.45 (d, J = 14.9 Hz, 1H), 4.28 (d, J = 15.3 Hz, 1H), 4.22 (m, 1H), 3.79 (m, 2H), 3.04 (m, 7H), 2.80 (m, 2H), 2.34 (s, 3H), 2.11 (m, 1H), 1.96 (m, 1H), 1.59 (m, 4H), 1.34 (m, 2H), 1.16 (m, 2H), 0.99 (m, 1H), 0.84 (t, J = 7.5 Hz, 3H), 0.74 (d, J = 6.4 Hz, 3H); MS (ESI) *m/z* 731.4 $[M-H]^-$, 733.5 $[M+H]^+$, 755.5 $[M+Na]^+$.

5.2.28. (2*S*,3*S*)-3-Methyl-2-(3-(6-methoxymethyl-pyridin-2-ylmethyl)-2-oxo-imidazolidin-1-yl)-pentanoic acid ((1*S*,2*R*)-1-benzyl-3-{cyclopentylmethyl-[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-amino}-2-hydroxy-propyl)-amide (36). The title compound was prepared using the method described for the synthesis of **15**, substituting 6-methoxymethyl-2-pyridinecarboxaldehyde for 6-methyl-2-pyridinecarboxaldehyde, and substituting **40** for **7** (45% overall yield from **13**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.68 (m, 3H), 7.45 (m, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.17 (m, 6H), 6.66 (d, J = 9.2 Hz, 1H), 4.61 (d, J = 15.6 Hz, 1H), 4.56 (s, 2H), 4.37 (d, J = 15.9 Hz, 1H), 4.20 (m, 1H), 3.86 (m, 1H), 3.80 (d, J = 10.9 Hz, 1H), 3.47 (s, 3H), 3.11 (m, 7H), 2.78 (m, 2H), 2.13 (m, 2H), 1.96 (m, 2H), 1.59 (m, 6H), 1.34 (m, 2H), 1.17 (m, 1H), 0.98 (m, 1H), 0.83 (t, J = 7.12 Hz, 3H), 0.73 (d, J = 6.4 Hz, 3H); MS (ESI) *m/z* 761.5 $[M-H]^-$, 763.4 $[M+H]^+$, 785.3 $[M+Na]^+$.

5.2.29. (*S*)-3,3-Dimethyl-2-(3-(6-methoxymethyl-pyridin-2-ylmethyl)-2-oxo-imidazolidin-1-yl)-butanoic acid ((1*S*,2*R*)-1-benzyl-2-hydroxy-3-{[4-(*E*-hydroxyimino-methyl)-benzenesulfonyl]-isobutyl-amino}-propyl)-amide (37). The title compound was prepared using the method described for the synthesis of **15**, substituting 6-methoxymethyl-2-pyridinecarboxaldehyde for 6-methyl-2-pyridinecarboxaldehyde, and substituting **39** for **13** (6% overall yield from **39**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.02 (s, 1H), 7.80 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 6.3 Hz, 2H), 7.68 (m, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.15 (m, 5H), 6.18 (d, J = 9.2 Hz, 1H), 4.64 (d, J = 15.8 Hz, 1H), 4.57 (s, 2H), 4.39 (d, J = 15.8 Hz, 1H), 4.16 (m, 1H), 4.00 (s, 1H), 3.79 (m, 1H), 3.48 (s, 3H), 3.34 (m, 1H), 3.09 (m, 5H), 2.87 (dd, J = 13.4, 6.8 Hz, 1H), 2.71 (dd, J = 14.3, 10.3 Hz, 1H), 2.61 (q, J = 9.2 Hz, 1H), 1.84 (m, 1H), 1.53 (m, 1H), 0.97 (s, 9H), 0.92 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); MS (ESI) *m/z* 735.3 $[M-H]^-$, 737.4 $[M+H]^+$, 759.4 $[M+Na]^+$.

5.2.30. (2*S*,3*S*)-2-(2,4-Dioxo-imidazolidin-1-yl)-2-methyl-butanoic acid *tert*-butyl ester (38). The title compound was prepared using the method described for the synthesis of **9**, substituting L-valine *tert*-butyl ester hydrochloride for **8** (51% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (m, 2H), 3.92 (d, J = 17.6 Hz, 1H), 2.15 (m, 1H), 1.48 (s, 9H), 1.03 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H); MS (ESI) *m/z* 255.0 $[M-H]^-$, 257.0 $[M+H]^+$, 274.0 $[M+NH_4]^+$, 279.0 $[M+Na]^+$.

5.2.31. *N*-(2-Aminoethyl)-L-*tert*-butylglycine *tert*-butyl ester (39). The title compound was prepared using the method described for the synthesis of **13**, substituting L-*tert*-butylglycine *tert*-butyl ester for **8** (62% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.72 (m, 3H), 2.43 (m, 1H), 1.47 (s, 9H), 1.20 (m, 1H), 0.96 (s, 9H); MS (ESI) *m/z* 231.2 $[M+H]^+$.

5.2.32. *N*-((2*R*,3*S*)-3-Amino-2-hydroxy-4-phenyl-butyl)-4-(*E*-hydroxyimino-methyl)-*N*-cyclopentylmethyl-benzenesulfonamide (40). The title compound was prepared

using the method described for the synthesis of **7**, substituting cyclopentylmethylamine for isobutylamine (32% overall yield from **4**): ^{1}H NMR (300 MHz, CD_3OD) δ 8.16 (s, 1H), 7.81 (m, 4H), 7.28 (m, 5H), 3.82 (m, 1H), 3.46 (m, 1H), 3.17 (m, 3H), 3.04 (m, 2H), 2.61 (dd, J = 13.7, 9.0 Hz, 1H), 2.21 (m, 1H), 1.60 (m, 6H), 1.21 (m, 2H); MS (ESI) *m/z* 446.2 $[M+H]^+$, 468.2 $[M+Na]^+$.

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