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Solid-Phase Library Synthesis of Reversed-Statine Type Inhibitors of the Malarial Aspartyl Proteases Plasmepsin I and II

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Abstract—With the aim to develop inhibitors of the plasmepsin I and II aspartic proteases of the malaria parasite *Plasmodium falciparum*, we have synthesized sets of libraries from novel reversed-statine isosteres, using a combination of solution phase and solid phase chemistry. The synthetic strategy furnishes the library compounds in good to high overall yields and with excellent stereochemical control throughout the developed route. The products were evaluated for their plasmepsin I and II inhibiting properties and were found to exhibit modest but promising activity. The best inhibitor exhibits an in vitro activity of 28% inhibition of plasmepsin II at an inhibitor concentration of 0.5 μM (K_i for Plm II = 5.4 μM).

Introduction

Malaria, which is transmitted by the *Anopheles* mosquito, is a major health threat in the world today with enormous medical, social, and economic consequences. Annual mortality worldwide from malaria is estimated to be 2 million people. Over 40% of the world's population is possibly at risk, with 300–500 million individuals becoming infected each year.[1] There are four major species of the parasite, that is *Plasmodium falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*, of which *P. falciparum* is responsible for more than 95% of the malaria-related morbidity and mortality.[2]

The malaria parasite has a complex life cycle that requires a vertebrate host for the asexual reproduction cycle and a female *Anopheles* mosquito for completion of the sexual cycle.[3] In the erythrocytic stage the parasite invades the erythrocytes of its host, forms an acidic vacuolar membrane, and consumes the hemoglobin as a source of nutrients for growth and development.[4] The heme byproduct, which is toxic to the parasite, is formed in the process of the parasite's degradation of hemoglobin, and this byproduct is therefore polymerized, forming what is known as hemozoin. Some of the currently most widely used antimalarial drugs, for example the weakly basic quinoline derivatives chloroquine and mefloquine, exert their toxic effect on the parasite by interfering with this sequestration process.[3] Many of these drugs are no longer efficacious in most parts of the world, due to the increased incidence of drug resistant strains of *P. falciparum* able to restrict accumulation of weak bases in the parasite's digestive vacuole.[5] Other emerging antimalarial agents are artemisinin, involving free radical mechanisms causing damage to the parasite's digestive vacuoles,[3] and prophylactic drugs like proguanil, targeting the DNA synthesis of the parasite in the liver stage.[6]

This underscores the pressing need for new generations of safe, low cost drugs, effective against resistant malaria strains, which can be used for both prophylactic and therapeutic treatment of malaria.

The degradation of hemoglobin is mainly mediated by the cysteine proteases falcipain 1–3 and the aspartic proteases plasmepsin I and II (Plm I and II), expressed by the parasite.[3,7] Furthermore, it has been shown that

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inhibitors of aspartyl proteinases (plasmepsins) and cysteinyl proteinases (falcipains) from the malaria parasite *P. falciparum* are efficacious in cell and animal models of malaria, indicating that these enzymes may be suitable molecular targets for drug therapy.[7a,8] Today at least 10 aspartic protease genes have been identified in the *P. falciparum* genome, potentially complicating the picture of target selection and target redundancy.[9]

Potent peptide plasmepsin inhibitors have previously been described which incorporate the hydroxyethylamine core **I**, or the statine-derived core **II**, found in pepstatin A.[10,11] We now report on the design and synthesis of novel reversed-statine type isosteres, (*R*,*R*)-**III** and (*S*,*S*)-**III**, which introduces a C-terminus where only N-terminus isosteres previously have been explored (Fig. 1).

From carbohydrate-derived precursors, using high yielding solution-phase reaction sequences in combination with well optimized multi-step solid-phase reactions, a rapid and efficient synthetic route has been developed for these novel potential plasmepsin inhibitors. Good to high overall yields and excellent stereochemical control have been achieved. The compounds synthesized were evaluated for both Plm I and II inhibitory activity (Table 3), and to the best of our knowledge this is the first report describing a thorough evaluation of Plm I inhibitors.

Results and Discussion

The synthetic objective was to furnish four scaffolds which coupled to a solid support resin would be amenable to an array synthesis of compounds. For the synthesis of the methyl (2*R*,3*R*)-4-azido-2-bromobenzyloxy-3-hydroxy-butyrate scaffolds (+)-**7** (with bromo in the *para* position) and (+)-**8** (with bromo in the *meta* position) (Scheme 2) commercially available D-(−)-isoascorbic acid was reacted with racemic 10-camphorsulfonic acid (CSA) and 2,2-dimethoxypropane in acetone to afford compound **1**[12] in 98% yield (Scheme 1). Oxidative cleavage with H_2O_2,[13] acidic workup, followed by methylation, using MeI and Cs_2CO_3, provided the isopropylidene protected (2*R*,3*R*)-methyl ester (+)-**2**[14] in 90% yield (Scheme 1).

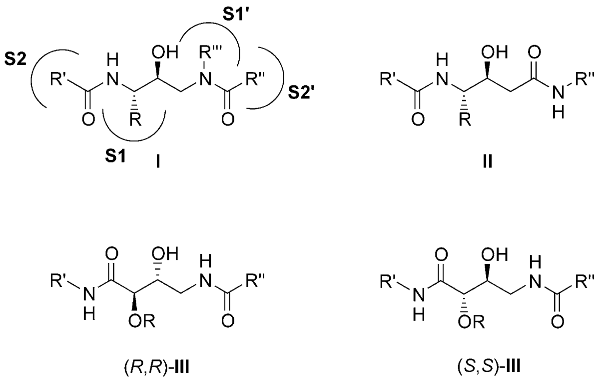
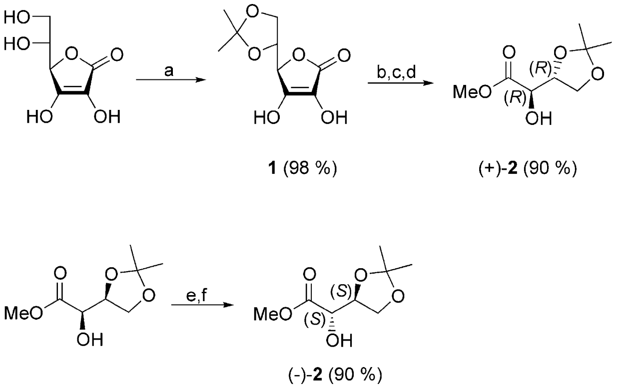
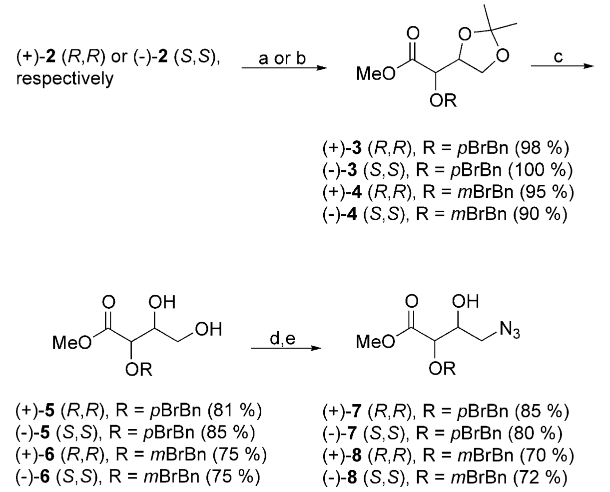


Figure 1. The structures of the hydroxyethylamine core (**I**) and the statine-derived core (**II**) used in previously reported Plm inhibitors. (*R*,*R*)-**III** and (*S*,*S*)-**III** represent the structures of the reversed-statine based Plm inhibitors presented in this report.



Scheme 1. (a) 2,2-Dimethoxypropane, 10-camphorsulfonic acid, acetone; (b) H_2O_2 (aq), $CaCO_3$, H_2O; (c) HCl (aq); (d) MeI, Cs_2CO_3, DMF; (e) DEAD, Ph_3P, *p*NO_2-benzoic acid, THF; (f) NaOMe, MeOH.



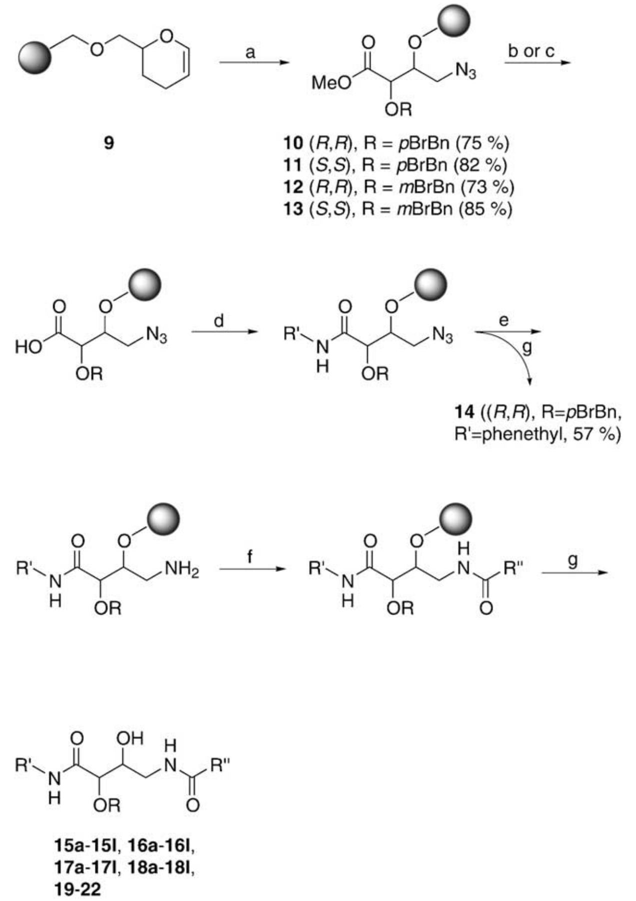
Scheme 2. (a) *p*BrBnBr, Ag_2O, KI, toluene; (b) *m*BrBnBr, Ag_2O, KI, toluene, 60 °C; (c) Dowex H^+, MeOH; (d) MsCl, pyridine, CH_2Cl_2, 0–8 °C; (e) NaN_3, DMF, 60 °C.

The enantiomer, the isopropylidene protected (2*S*,3*S*)-methyl ester (−)-**2**, used for the synthesis of the methyl (2*S*,3*S*)-4-azido-2-bromobenzyloxy-3-hydroxy-butyrate scaffolds (−)-**7** and (−)-**8** (with bromo in the *para* and *meta* position, respectively) (Scheme 2), was synthesized from commercially available methyl 3,4-*O*-isopropylidene-L-threonate by inverting the free hydroxyl group using Mitsunobu conditions with diethylazodicarboxylate (DEAD), Ph_3P, and *p*-nitrobenzoic acid, followed by cleavage of the obtained *p*-nitrobenzoate ester with NaOMe in MeOH to give (−)-**2**[15] in 90% yield (Scheme 1).

The free hydroxyl groups in (+)-**2** and (−)-**2** were subsequently bromobenzylated with either *p*- or *m*-bromobenzyl bromide using Ag_2O[16] and a catalytic amount of KI in toluene to give (+)-**3**, (−)-**3**, (+)-**4**, and (−)-**4** in yields ranging from 90 to 100%[17] (Scheme 2). The isopropylidene groups were removed by treatment with the acidic ion exchanger Dowex H^+ in MeOH, providing the diols (+)-**5**, (−)-**5**, (+)-**6**, and (−)-**6** in 75–85% yield.[18] Selective mesylation of the primary hydroxyl groups, using mesyl chloride and pyridine in CH_2Cl_2 at 0–8 °C, followed by displacement of the mesylate groups with azide, using NaN_3 in DMF, delivered the four target scaffolds (+)-**7**, (−)-**7**, (+)-**8**, and (−)-**8** in yields ranging from 70 to 85%[19] over two steps (Scheme 2).

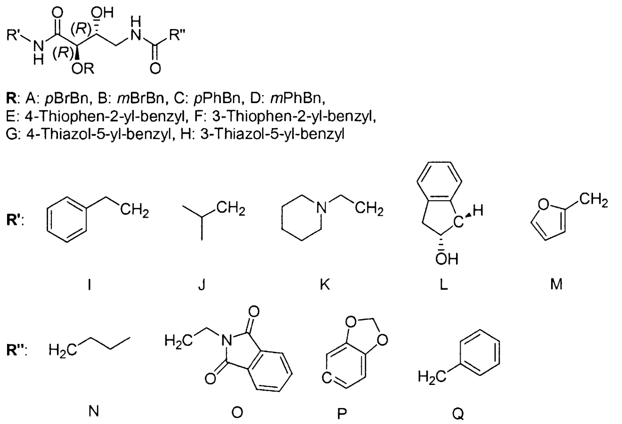
Ellman and coworkers have previously reported on the synthesis of the base stable DHP linker attached to a Merrifield polystyrene resin, useful for the attachment of hydroxyl groups.[20] Employing this procedure provided **9** in 87% yield (loading efficiency: 87%)[21] to which the scaffolds (+)-**7**, (−)-**7**, (+)-**8**, and (−)-**8** were coupled[20] to give the resins **10**, **11**, **12**, and **13** in 73–85% yield based on the loading efficiency (Scheme 3).

The solid-phase reaction sequence commenced by hydrolysis of the methyl esters, using either $KOSiMe_3$ in THF or LiOH in THF/MeOH/water.[22] The use of $KOSiMe_3$ in THF resulted in modest yields of final products. Notably, with LiOH in THF/MeOH/water excellent yields of final compounds were obtained (compounds **16j–16l**, **17a–17l**, and **19–22** in Tables 1 and 2).[23] The resin bound acids were coupled with several amines using benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) and *N*-methylmorpholine (NMM) in DMF. The amines used were selected based on similarity to amines reported in aspartic protease inhibitors.[10,24,25] The total yield over the two steps was determined through cleavage of a minor amount of product from the resin. In this case $KOSiMe_3$ in THF was used in the hydrolysis step. Cleavage was achieved through treatment with $TFA/CH_2Cl_2/EtOH$ to give compound **14** in 57% yield over three steps from **10** (including the cleavage step) (Scheme 3).



Scheme 3. (a) (+)-**7**, (−)-**7**, (+)-**8**, (−)-**8**, respectively, PPTS, 1,2-dichloroethane, 82 °C; (b) $KOSiMe_3$, THF; (c) LiOH, THF, MeOH, H_2O; (d) $R'NH_2$, PyBOP, NMM, DMF; (e) $SnCl_2$, PhSH, Et_3N, THF; (f) $R''CO_2H$, PyBOP, HOBt, DIEA, DMF; (g) TFA, CH_2Cl_2, EtOH.

Table 1. The identities and selected data of the target compounds with *R*,*R* configuration at the central core



Compd	R	R′	R″	Yield[a] (%)
15a	A	I	N	25
15b	A	I	O	25
15c	A	I	P	27
15d	A	J	N	31
15e	A	J	O	26
15f	A	J	P	27
15g	A	K	N	21
15h	A	K	O	19
15i	A	K	P	25
15j	A	L	N	30
15k	A	L	O	29
15l	A	L	P	32
17a	B	I	N	79
17b	B	I	O	90
17c	B	I	P	98
17d	B	J	N	95
17e	B	J	O	99
17f	B	J	P	99
17g	B	K	N	91
17h	B	K	O	84
17i	B	K	P	81
17j	B	L	N	81
17k	B	L	O	65
17l	B	L	P	96
19	A	M	Q	50
21	B	M	Q	90
23[b]	C	M	Q	70
25[b]	D	M	Q	81
27[b]	C	K	P	99
29[b]	D	I	N	51
30[c]	E	K	P	65
32[c]	F	I	N	45
33[c]	G	K	P	70
35[c]	H	I	N	90

[a] Total yield, including the cleavage step, from the loaded resins **10** and **12**, respectively (Scheme 3).

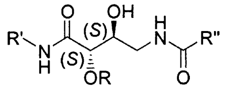
[b] Synthesized in solution from its corresponding bromo compound, using $PhB(OH)_2$, $(Ph_3P)_4Pd$, and aqueous sodium carbonate in refluxing 1,2-dimethoxyethane. The yields given refer to the last coupling step in solution.

[c] As b, but using thiophene or thiazole, $(Ph_3P)_4Pd$, and KOAc in *N*,*N*-dimethyl-acetamide at 120 °C.

Reduction of the azide functionality using $SnCl_2$, thiophenol, and Et_3N in THF,[26] followed by coupling of the free amine with selected carboxylic acids[10,25] using PyBOP, 1-hydroxybenzotriazole (HOBt), and *N*,*N*-diisopropylethylamine (DIEA) in DMF,[27] and subsequent cleavage furnished the final products **15a–15l**, **16a–16l**, **17a–17l**, **18a–18l**, and **19–22** from silica gel column chromatography (Scheme 3, Tables 1 and 2).

The bromo-aryl moiety of the final products provides a convenient handle to further diversify this set of compounds by introducing other functional groups in this position to probe interactions putatively extending from the S1 into the S3 pocket of the plasmepsins. In view of inhibition data of Plm I and II, compounds **15i**, **16j**, and **17a** were selected for substitution of the bromo-aryl moiety with phenyl, thiophen-2-yl, and thiazol-5-yl (Tables 1 and 2). Additionally, the slightly active compound **20** and its analogues **19**, **21**, and **22** were coupled with $PhB(OH)_2$ at the bromo-aryl moiety (Tables 1 and 2).

Table 2. The identities and selected data of the target compounds with *S*,*S* configuration at the central core



R,R',R": See Table 1

Compd	R	R′	R″	Yield[a] (%)
16a	A	I	N	23
16b	A	I	O	29
16c	A	I	P	31
16d	A	J	N	21
16e	A	J	O	35
16f	A	J	P	19
16g	A	K	N	24
16h	A	K	O	26
16i	A	K	P	25
16j	A	L	N	95
16k	A	L	O	99
16l	A	L	P	99
18a	B	I	N	22
18b	B	I	O	14
18c	B	I	P	14
18d	B	J	N	7
18e	B	J	O	14
18f	B	J	P	10
18g	B	K	N	11
18h	B	K	O	16
18i	B	K	P	16
18j	B	L	N	10
18k	B	L	O	9
18l	B	L	P	9
20	A	M	Q	82
22	B	M	Q	89
24[b]	C	M	Q	83
26[b]	D	M	Q	51
28[b]	C	L	N	95
31[c]	E	L	N	60
34[c]	G	L	N	67

[a] Total yield, including the cleavage step, from the loaded resins **11** and **13**, respectively (Scheme 3).

[b] Synthesized in solution from its corresponding bromo compound, using $PhB(OH)_2$, $(Ph_3P)_4Pd$, and aqueous sodium carbonate in refluxing 1,2-dimethoxyethane. The yields given refer to the last coupling step in solution.

[c] As b, but using thiophene or thiazole, $(Ph_3P)_4Pd$, and KOAc in *N*,*N*-dimethyl-acetamide at 120 °C.

In our hands, solid-phase Suzuki and Heck-like couplings resulted in very poor yields of the desired products. However, utilizing standard solution Suzuki conditions, that is reacting the cleaved off bromo compounds with $PhB(OH)_2$, $(Ph_3P)_4Pd$ and aqueous Na_2CO_3 in refluxing 1,2-dimethoxyethane (DME),[28] provided the biphenyls **23–29** in yields ranging from 51 to 99% from the corresponding bromo compounds **15i**, **16j**, **17a**, and **19–22** (Tables 1 and 2).

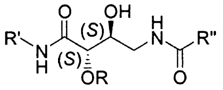
Compounds **15i**, **16j**, and **17a** were also successfully coupled with thiophene and thiazole in solution using Heck-like conditions, that is, the bromo compounds were treated with thiophene or thiazole, $(Ph_3P)_4Pd$, and KOAc in *N*,*N*-dimethylacetamide (DMA) at 120 °C[29] to give the thiophen-2-yl-benzyl and thiazol-5-yl-benzyl compounds **30–35** in 45–90% yield from the corresponding bromo compounds (Tables 1 and 2). The position of attachment at the thiazole moiety was determined by ^1H NMR.

Inhibition Data and Structure–Activity Relationships

All final compounds were tested for their plasmepsin inhibitory properties, and the data of the most potent inhibitors are outlined in Table 3.

K_i values were determined for only a few selected compounds, that is **15i** ($K_i = 5.4\,\mu M$ for Plm II) and **16j** ($K_i = 7.3\,\mu M$ for Plm II). From analysis of the data in Tables 1–3 it appears to be a requirement of *R*,*R* configuration in this carbohydrate based template series to achieve Plm I inhibitory activity, whereas both *R*,*R* and *S*,*S* configuration give compounds showing Plm II inhibitory activity. Additionally, it is evident that the presence of the phenethyl side chain I or the piperidine derived side chain K in the P2 position (see Table 1 and Fig. 1) seems to be preferred in terms of potency. Regarding the P1 and P2′ substituents, no structure–activity conclusions can be drawn from the inhibitory data presented above.

Table 3. Plasmepsin inhibitory properties of the most potent target compounds



R,R',R": See Table 1

Compd	Inh, Plm I[a] (%)	Inh, Plm II[a] (%)	Compd	Inh, Plm I[a] (%)	Inh, Plm II[a] (%)
15a	14	6	**17h**	11	0
15g	0	11	**17i**	15	11
15h	8	9	**18a**	0	6
15i	11	28	**18b**	0	6
16j	0	17	**20**	0	7
17a	22	9	**24**	0	13

[a] Inhibition at an inhibitor concentration of 0.5 µM.

Finally, the modestly potent but promising target compounds **15i**, **16j**, and **17a** appear to be well suited candidates for future optimization within this series of Plm I and II inhibitors. They are lead like[30a] and all fall within the property ranges predictive for oral bioavailability.[30] Moreover, they can readily be diversified using combinatorial synthesis to generate new focused libraries. Noteworthy, these newly developed carbohydrate templates are ideally suited to explore binding properties of different R-groups (Tables 1 and 2) to the Plm enzymes.

Conclusion

We have identified new small molecule lead inhibitors of the aspartic plasmepsin I and II proteases from carbohydrate derived retro-statine templates. The synthetic strategy has been focused on developing these templates and their chemistries in solution, followed by taking well optimized reaction sequences on to solid phase. The chemistry used readily provides the target compounds and offers the opportunity to easily diversify the sets of compounds presented in this report. Some members from the small libraries synthesized show modest but promising activity, with the best inhibitors having in vitro activities of 28% inhibition of Plm II (**15i**) and 22% inhibition of Plm I (**17a**) at 0.5 μM concentration. The introduction of P1′ substituents in the reversed-statine type inhibitors presented may be worth exploring in order to enhance the affinity for the plasmepsins.

Experimental

General methods

NMR spectra were recorded on a Varian 300 MHz instrument using $CDCl_3$ or MeOH-d_4 with TMS as an internal standard. Optical rotations were measured in $CHCl_3$ solutions on a Perkin–Elmer 141 polarimeter. TLC was carried out on Merck precoated 60 F_{254} plates using UV-light and charring with EtOH/H_2SO_4/HOAc/*p*-anisaldehyde 90:3:1:2 for visualisation. Column chromatography was performed using silica gel 60 (0.040–0.063 mm, Merck). Organic phases were dried over anhydrous magnesium sulfate. Concentrations were performed under diminished pressure (1–2 kPa) at a bath temperature of 40 °C. All target compounds were subjected to MALDI-TOF analyses, using a Voyager-DE STR Biospectrometry Workstation with α-cyano-4-hydroxycinnamic acid as reference.

Plasmepsin assay measurements

Pro-plasmepsin II was generously provided from Helena Danielson (Department of Biochemistry, Uppsala University, Uppsala, Sweden). The expression and purification of plasmepsin I will be published elsewhere.[31] The activities of plasmepsin I (Plm I) and plasmepsin II (Plm II) were measured essentially as described previously,[10] using a total reaction volume of 100 μL. The concentration of pro-Plm II was 3 nM and the amount of Plm I was adjusted to give similar catalytic activity. The pro-sequence of Plm II was cleaved off by preincubation in an assay reaction buffer (100 mM sodium acetate buffer (pH 4.5), 10% glycerol and 0.01% Tween 20) at room temperature for 40 min. The reaction was initiated by the addition of 3 μM substrate (DABCYL-Glu-Arg-Nle-Phe-Leu-Ser-Phe-Pro-EDANS, AnaSpec Inc, San Jose, CA, USA) and hydrolysis was recorded as the increase in fluorescence intensity over a 10-min time period, during which the rate increased linearly with time. Stock solutions of inhibitors in DMSO were serially diluted in DMSO and added directly before addition of substrate, giving a final DMSO concentration of 1%.

IC_{50}-values were obtained by assuming competitive inhibition and fitting a Langmuir isotherm ($v_i/v_o = 1/(1+[I]/IC_{50})$) to the dose response data (Grafit), where v_i and v_o are the initial velocities for the inhibited and uninhibited reaction respectively and [I] is the inhibitor concentration.[32] The K_i was subsequently calculated by using $K_i = IC_{50}/(1+[S]/K_m)$[33] and a K_m value determined according to Michaelis–Menten.

Solution phase experimentals

5,6-*O*-Isopropylidene-D-isoascorbic acid (1). To a suspension of D-(−)-isoascorbic acid (10.00 g, 56.8 mmol) in acetone (50 mL) were added 2,2-dimethoxypropane (12.0 mL, 10.2 g, 97.9 mmol) and 10-camphorsulfonic acid (CSA) (0.660 g, 2.84 mmol). The mixture was stirred for 1 h at room temperature after which the reaction was quenched with Et_3N (0.395 mL, 0.288 g, 2.84 mmol). The solvent was evaporated and the remainder was purified by flash column chromatography (EtOAc with 1% HOAc) to give compound **1** (12.06 g, 98%) as white crystals.

Methyl (2*R*,3*R*)-3,4-*O*-isopropylidene-2,3,4-trihydroxybutyrate [(+)-2]. Compound **1** (12.12 g, 56.1 mmol) and $CaCO_3$ (12.35 g, 123 mmol) were suspended in water (125 mL). The reaction mixture was stirred at 0 °C while H_2O_2 (30%, 20.0 mL, 176 mmol) was added dropwise during half an hour. The temperature was slowly raised to 40 °C. After 4 h, activated carbon (2.64 g) and Pd on activated carbon (10%, 0.148 g) were added and the mixture was heated at 85 °C until a negative peroxide test was obtained (after about 1 h). The resulting suspension was filtered and evaporated to a volume of 25 mL. Aqueous HCl (0.3 M) was added until pH 3 was reached, followed by several extractions with CH_2Cl_2 and EtOAc. The organic phases were pooled, dried, and evaporated and the obtained carboxylic acid was dissolved in DMF (100 mL). Cs_2CO_3 (32.90 g, 101 mmol) and MeI (5.24 mL, 11.95 g, 84.19 mmol) were added and the suspension was stirred at room temperature for two h. Water saturated with NH_4Cl was added and the mixture was extracted several times with Et_2O and EtOAc. The organic phases were pooled, dried, and evaporated and the remainder was purified by flash column chromatography (toluene/EtOAc 6:1) to yield (+)-**2** (9.59 g, 90%) as a slightly yellow oil.

Methyl (2*S*,3*S*)-3,4-*O*-isopropylidene-2,3,4-trihydroxybutyrate [(−)-2]. To a solution of methyl 3,4-*O*-isopropylidene-L-threonate (0.870 g, 4.58 mmol) in dry

THF (15 mL) were added *p*-nitrobenzoic acid (1.23 g, 7.36 mmol) and Ph_3P (1.91 g, 7.28 mmol). The reaction flask was placed in a water bath at room temperature, and a solution of diethyl azodicarboxylate (DEAD) (1.15 mL, 1.29 g, 7.41 mmol) in dry THF (15 mL) was added dropwise to the stirred solution during 30 min at room temperature. The reaction solution was stirred overnight at room temperature and was then evaporated and purified by flash column chromatography (toluene/EtOAc 6:1). The product was dissolved in MeOH (20 mL) and was allowed to react with NaOMe in MeOH (1 M, 2.3 mL, 2.3 mmol), which was slowly added dropwise into the stirred solution at room temperature. The solution was stirred at room temperature for 30 min, after which it was neutralized with HOAc, evaporated, and purified by flash column chromatography (toluene/EtOAc 6:1). This afforded compound (−)-**2** (0.780 g, 90%) as a colorless oil.

Methyl (2*R*,3*R*)-2-(4-bromobenzyloxy)-3,4-dihydroxy-3,4-*O*-isopropylidene- butyrate [(+)-3]. To a solution of compound (+)-**2** (0.683 g, 3.59 mmol) in toluene (15 mL) were added *p*-bromobenzyl bromide (3.18 g, 12.7 mmol), Ag_2O (2.52 g, 10.9 mmol), and KI (0.101 g, 0.608 mmol) and the mixture was stirred at room temperature for 15 min (some heat evolution was observed). The suspension was filtered, evaporated, and purified by flash column chromatography (toluene/EtOAc 6:1) to give compound (+)-**3** (1.27 g, 99%) as a colorless solid. (+)-**3**: $[\alpha]_D^{22}$ +41.7 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.34 (s, 3H), 1.41 (s, 3H), 3.76 (s, 3H), 3.97–4.07 (m, 3H), 4.34 (app dd, *J* = 5.4, 12.5 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 25.3, 26.5, 52.1, 66.1, 72.2, 75.9, 79.1, 110.0, 122.0, 129.6, 131.6, 136.0, 170.7. Anal. ($C_{15}H_{19}BrO_5$) C, H.

Methyl (2*S*,3*S*)-2-(4-bromobenzyloxy)-3,4-dihydroxy-3,4-*O*-isopropylidene-butyrate [(−)-3]. Compound (−)-**3** was synthesized from (−)-**2** in 100% yield according to the method for the preparation of (+)-**3**. (−)-**3**: $[\alpha]_D^{22}$ −40.0 (*c* 2.8, $CHCl_3$). Anal. ($C_{15}H_{19}BrO_5$) C, H.

Methyl (2*R*,3*R*)-2-(3-bromobenzyloxy)-3,4-dihydroxy-3,4-*O*-isopropylidene-butyrate [(+)-4]. Compound (+)-**4** was synthesized from (+)-**2** and *m*-bromobenzyl bromide in 95% yield according to the method for the preparation of (+)-**3**, with the exception that the reaction mixture was stirred overnight at 60 °C. (+)-**4**: $[\alpha]_D^{22}$ +37.6 (*c* 2.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.37 (s, 3H), 1.46 (s, 3H), 3.78 (s, 3H), 4.01–4.08 (m, 3H), 4.40 (app dd, *J* = 5.8, 11.3 Hz, 1H), 4.50 (d,*J* = 12.1 Hz, 1H), 4.66 (d, *J* = 12.1 Hz, 1H), 7.17–7.30 (m, 2H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.53 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 25.6, 26.8, 52.4, 66.3, 72.3, 76.1, 79.5, 110.2, 122.8, 126.6, 130.2, 131.1, 131.3, 139.6, 170.9. Anal. ($C_{15}H_{19}BrO_5$) C, H.

Methyl (2*S*,3*S*)-2-(3-bromobenzyloxy)-3,4-dihydroxy-3,4-*O*-isopropylidene- butyrate [(−)-4]. Compound (−)-**4** was synthesized from (−)-**2** in 90% yield according to the method for the preparation of (+)-**4**. (−)-**4**: $[\alpha]_D^{22}$ −36.5 (*c* 2.1, $CHCl_3$). Anal. ($C_{15}H_{19}BrO_5 \cdot 0.8CH_2Cl_2$) C, H.

Methyl (2*R*,3*R*)-2-(4-bromobenzyloxy)-3,4-dihydroxy-butyrate [(+)-5]. To a solution of compound (+)-**3** (1.25 g, 3.48 mmol) in MeOH (15 mL) was added a suspension of Dowex-H^+ (50×8, 20–50 mesh) in MeOH (9 mL). The mixture was shaken for 2 h at room temperature, after which the reaction mixture was filtered, neutralized with Et_3N, and evaporated. The crude product was purified by flash column chromatography (EtOAc/toluene 2:1) to give compound (+)-**5** (0.897 g, 81%) as a colorless solid. (+)-**5**: $[\alpha]_D^{22}$ +58.5 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.72–3.78 (m, 2H), 3.80 (s, 3H), 3.99–4.03 (m, 1H), 4.10–4.15 (m, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 52.3, 62.8, 71.7, 72.6, 79.6, 122.2, 129.7, 131.7, 136.2, 171.3. Anal. ($C_{12}H_{15}BrO_5 \cdot 0.3EtOAc$) C, H.

Methyl (2*S*,3*S*)-2-(4-bromobenzyloxy)-3,4-dihydroxy-butyrate [(−)-5]. Compound (−)-**5** was synthesized from (−)-**3** in 85% yield according to the method for the preparation of (+)-**5**. (−)-**5**: $[\alpha]_D^{22}$ −60.5 (*c* 0.4, $CHCl_3$). Anal. ($C_{12}H_{15}BrO_5$) C, H.

Methyl (2*R*,3*R*)-2-(3-bromobenzyloxy)-3,4-dihydroxy-butyrate [(+)-6]. Compound (+)-**6** was synthesized from (+)-**4** in 75% yield according to the method for the preparation of (+)-**5**. (+)-**6**: $[\alpha]_D^{22}$ +54.7 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.65–3.72 (m, 2H), 3.80 (s, 3H), 3.90–4.02 (m, 1H), 4.11–4.14 (m, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.72 (d, *J* = 11.7 Hz, 1H), 7.18–7.29 (m, 2H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 52.5, 63.0, 72.0, 72.7, 79.8, 122.8, 126.7, 130.3, 131.2, 131.5, 139.4, 171.5. Anal. ($C_{12}H_{15}BrO_5$) C, H.

Methyl (2*S*,3*S*)-2-(3-bromobenzyloxy)-3,4-dihydroxy-butyrate [(−)-6]. Compound (−)-**6** was synthesized from (−)-**4** in 75% yield according to the method for the preparation of (+)-**5**. (−)-**6**: $[\alpha]_D^{22}$ −53.0 (*c* 0.4, $CHCl_3$). Anal. ($C_{12}H_{15}BrO_5$) C, H.

Methyl (2*R*,3*R*)-4-azido-2-(4-bromobenzyloxy)-3-hydroxy-butyrate [(+)-7]. To a solution of compound (+)-**5** (0.741 g, 2.32 mmol) in dry CH_2Cl_2 (15 mL) was added dry pyridine (0.75 mL, 0.737 g, 9.33 mmol). The temperature was lowered to 0 °C and mesyl chloride (0.215 mL, 0.317 g, 2.77 mmol) was added dropwise. The solution was stirred at 0–8 °C overnight. The reaction mixture was evaporated and then coevaporated four times with toluene. Flash column chromatography (EtOAc/toluene 2:1) afforded the monomesylated product which was dissolved in dry DMF (10 mL). NaN_3 (0.609 g, 9.37 mmol) was added and the suspension was heated to 60 °C and stirred overnight. The mixture was cooled to room temperature, filtered, and evaporated. Finally, the remainder was purified by flash column chromatography (toluene/EtOAc 6:1) to give compound (+)-**7** (0.678 g, 85%) as a colorless oil. (+)-**7**: $[\alpha]_D^{22}$ +56.8 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.44–3.47 (m, 2H), 3.80 (s, 3H), 4.02–4.15 (m, 2H), 4.43 (d, *J* = 11.4 Hz, 1H), 4.70 (d, *J* = 11.4 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR

($CDCl_3$, 75.5 MHz): δ 52.4, 52.6, 71.3, 72.5, 78.8, 122.3, 129.8, 131.7, 135.7, 170.9. Anal. ($C_{12}H_{14}BrN_3O_4$) C, H, N.

Methyl (2*S*,3*S*)-4-azido-2-(4-bromobenzyloxy)-3-hydroxy-butyrate [(−)-7]. Compound (−)-**7** was synthesized from (−)-**5** in 80% yield according to the method for the preparation of (+)-**7**. (−)-**7**: $[\alpha]_D^{22}$ −55.9 (*c* 1.1, $CHCl_3$). Anal. ($C_{12}H_{14}BrN_3O_4$·0.1toluene·0.4DMF) C, H, N.

Methyl (2*R*,3*R*)-4-azido-2-(3-bromobenzyloxy)-3-hydroxy-butyrate [(+)-8]. Compound (+)-**8** was synthesized from (+)-**6** in 70% yield according to the method for the preparation of (+)-**7**. (+)-**8**: $[\alpha]_D^{22}$ +53.3 (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 3.36–3.52 (m, 2H), 3.77 (s, 3H), 4.02–4.12 (m, 2H), 4.42 (d, *J* = 11,7 Hz, 1H), 4.69 (d, *J* = 11,7 Hz, 1H), 7.20–7.26 (m, 2H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.48 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 52.3, 52.5, 71.1, 72.1, 79.0, 122.4, 126.4, 129.9, 130.8, 131.0, 138.9, 170.8. Anal. ($C_{12}H_{14}BrN_3O_4$) C, H, N.

Methyl (2*S*,3*S*)-4-azido-2-(3-bromobenzyloxy)-3-hydroxy-butyrate [(−)-8]. Compound (−)-**8** was synthesized from (−)-**6** in 72% yield according to the method for the preparation of (+)-**7**. (−)-**8**: $[\alpha]_D^{22}$ −52.0 (*c* 1.8, $CHCl_3$). Anal. ($C_{12}H_{14}BrN_3O_4$·0.2$CHCl_3$) C, H, N.

Preparation of DHP-resin

The DHP resin **9** was synthesized from the Merrifield Resin HL (25) (100–200 mesh, chlorine substitution 1.60 mmol/g, 1% cross-linking) according to the procedure described in ref 20. The loading and loading efficiency were determined to be 0.88 mmol/g and 87%, respectively, using the method outlined in ref 21.

Preparation of scaffold loaded resins 10, 11, 12 and 13

The scaffolds (+)-**7**, (−)-**7**, (+)-**8**, and (−)-**8** were coupled to the DHP-resin **9** according to the procedure described in ref 20. This gave the scaffold loaded resins **10**, **11**, **12**, and **13** with the loadings and loading efficiencies 0.63 mmol/g, 75%; 0.68 mmol/g, 82%; 0.61 mmol/g, 73%; and 0.71 mmol/g, 85%, respectively.

General procedures for solid-phase reactions

Hydrolysis of the methyl ester functionality (procedure a, used for compounds 15a–15l, 16a–16i and 18a–18l, typical procedure). The scaffold loaded resin was washed with THF (2×) followed by swelling in dry THF for 30 min. The resin was dried and a solution of $KOSiMe_3$ in THF (0.6 M) was added. The resin was shaken for 4 h and was then dried and washed with THF (5×), THF/HOAc (6:1) (4×), and THF (5×).

Hydrolysis of the methyl ester functionality, (procedure b, used for compounds 16j–16l, 17a–17l, and 19–22, typical procedure). The scaffold loaded resin was washed with THF (2×) followed by swelling in THF for 30 min. The resin was dried and a solution of THF/[1 M LiOH in ($MeOH/H_2O$ 7:1)] 3:1 was added. The slurry was shaken at room temperature for 72 h, followed by washing with $MeOH/H_2O$ 3:1 (3×), MeOH (3×), THF (3×), THF/HOAc 8:1 (5×), THF (3×), and MeOH (3×).

Peptide coupling no. 1 (typical procedure). The resin was washed with DMF (2×) and was then allowed to swell in DMF for 30 min. After drying a solution containing the amine $R'NH_2$ (0.4 M), benzotriazol-1-yl-oxytripyrrolidino-phosphonium hexafluorophosphate (PyBOP) (0.4 M) and *N*-methylmorpholine (NMM) (0.8 M) in DMF was added. The slurry was shaken overnight at room temperature and was then dried and washed with DMF (5×), MeOH (3×), and CH_2Cl_2 (5×).

Reduction of the azide functionality (typical procedure). The resin was washed with dry THF (2×) and was allowed to swell in dry THF for 30 min. It was then dried and a solution of anhydrous $SnCl_2$ (0.2 M), thiophenol (0.8 M), and Et_3N (1.0 M) in dry THF was added. After shaking for 4 h at room temperature the resin was dried and washed with THF/H_2O 2:1 (2×), THF (3×), DMF (2×), and CH_2Cl_2 (3×).

Peptide coupling no. 2 (typical procedure). The resin was washed with DMF (2×) and was then allowed to swell in DMF for 30 min. It was dried and a solution of the carboxylic acid $R''CO_2H$ (0.2 M), 1-hydroxybenzotriazole (HOBt) (0.2 M), PyBOP (0.2 M), and *N*,*N*-diisopropylethylamine (DIEA) (0.6 M) in DMF was added. The mixture was shaken overnight at room temperature and was then dried and washed with DMF (3×), CH_2Cl_2 (3×), and MeOH (3×).

Cleavage of the resins. Cleavage from the loaded resins was achieved through shaking the resins with TFA/CH_2Cl_2/99.5% EtOH 2:2:1 for 2 h at room temperature, followed by collection of the solvents. After washings with CH_2Cl_2 for 5 min and MeOH for 5 min all solvents were combined and evaporated. Coevaporation with toluene three times afforded the crude products.

The target compounds

Purifications. The targets were purified, to eliminate mostly residual polar baseline material, by silica column chromatography using $CHCl_3$/EtOH (99.5%) 19:1 as eluent in the vast majority of cases, the exceptions being the target compounds with basic side chains where the mobile phase $CHCl_3$/EtOH (99.5%) 19:1 + 3% MeOH saturated with NH_3 was utilized.

(2*R*,3*R*)-4-Azido-2-(4-bromobenzyloxy)-3-hydroxy-*N*-phenethyl-butyramide (14). Compound **14** was cleaved off after the first coupling step to establish the yield so far (57%).

(2*R*,3*R*)-2-(4-Bromobenzyloxy)-3-hydroxy-4-pentanoylamino-*N*-phenethyl-butyramide (15a). **15a**: $[\alpha]_D^{22}$ +26.7 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.23–1.40 (m, 2H), 1.49–1.63 (m, 2H), 2.19 (t, *J* = 7.7 Hz, 2H), 3.27–3.36 (m, 1H), 3.47–3.68 (m, 3H), 3.71 (d, *J* = 6.3 Hz, 1H), 3.82–3.90 (m, 1H), 4.35 (d, *J* = 11.2 Hz, 1H), 4.49 (d, *J* = 11.2 Hz, 1H), 6.01 (br s, 1H), 6.78 (br s, 1H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.13–7.35 (m, 5H), 7.45 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 13.9, 22.5, 28.0, 35.4, 36.5, 40.0, 41.4, 71.6, 73.6, 79.4, 122.7, 127.0, 128.9, 129.0, 130.1, 132.0, 135.8, 138.5, 171.2, 174.5. MS calcd for $C_{24}H_{32}BrN_2O_4$ $(M+H)^+$: 491.15. Found: 491.06. MS calcd for $C_{24}H_{31}BrN_2O_4Na$ $(M+Na)^+$: 513.14. Found: 513.04. MS calcd for $C_{24}H_{31}BrN_2O_4K$ $(M+K)^+$: 529.11. Found: 529.01.

(2*R*,3*R*)-2-(4-Bromobenzyloxy)-4-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionylamino]-3-hydroxy-*N*-phenethyl-butyramide (15b). 15b: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.62 (t, *J* = 7.2 Hz, 2H), 2.82 (t, *J* = 6.9 Hz, 2H), 3.25–3.40 (m, 1H), 3.42–3.65 (m, 3H), 3.75 (d, *J* = 6.6 Hz, 1H), 3.84–3.93 (m, 1H), 3.95 (t, *J* = 7.2 Hz, 2H), 4.35 (d, *J* = 11.3 Hz, 1H), 4.50 (d, *J* = 11.3 Hz, 1H), 6.21 (br s, 1H), 6.90 (br s, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 7.09–7.34 (m, 5H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.45–7.85 (m, 4H). MS calcd for $C_{30}H_{31}BrN_3O_6$ $(M+H)^+$: 608.14. Found: 608.11. MS calcd for $C_{30}H_{30}BrN_3O_6Na$ $(M+Na)^+$: 630.12. Found: 630.09. MS calcd for $C_{30}H_{30}BrN_3O_6K$ $(M+K)^+$: 646.10. Found: 646.07.

(2*R*,3*R*)-4-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-2-(4-bromobenzyloxy)-3-hydroxy-*N*-phenethyl-butyramide (15c). 15c: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.63 (d, *J* = 6.9 Hz, 2H), 3.46–3.70 (m, 3H), 3.73–3.85 (m, 1H), 3.79 (d, *J* = 6.3 Hz, 1H), 3.95–4.07 (m, 1H), 4.37 (d, *J* = 11.3 Hz, 1H), 4.55 (d, *J* = 11.3 Hz, 1H), 6.02 (s, 2H), 6.56–6.64 (m, 1H), 6.72–6.80 (m, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 2H), 7.12–7.34 (m, 7H), 7.42 (d, *J* = 8.5 Hz, 2H). MS calcd for $C_{27}H_{28}BrN_2O_6$ $(M+H)^+$: 555.11. Found: 555.08. MS calcd for $C_{27}H_{27}BrN_2O_6Na$ $(M+Na)^+$: 577.10. Found: 577.07. MS calcd for $C_{27}H_{27}BrN_2O_6K$ $(M+K)^+$: 593.07. Found: 593.04.

(2*R*,3*R*)-2-(4-Bromobenzyloxy)-3-hydroxy-*N*-isobutyl-4-pentanoylamino- butyramide (15d). 15d: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.89 (d, *J* = 6.9 Hz, 6H), 0.92 (t, *J* = 7.4 Hz, 3H), 1.22–1.43 (m, 2H), 1.53–1.67 (m, 2H), 1.66–1.82 (m, 1H), 2.20 (t, *J* = 7.4 Hz, 2H), 3.00–3.19 (m, 2H), 3.32–3.42 (m, 1H), 3.62–3.74 (m, 1H), 3.78 (d, *J* = 6.6 Hz, 1H), 3.88–3.98 (m, 1H), 4.52 (d, *J* = 11.3 Hz, 1H), 4.68 (d, *J* = 11.3 Hz, 1H), 5.97–6.06 (m, 1H), 6.77–6.86 (m, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H). MS calcd for $C_{20}H_{32}BrN_2O_4$ $(M+H)^+$: 443.15. Found: 443.18. MS calcd for $C_{20}H_{31}BrN_2O_4Na$ $(M+Na)^+$: 465.14. Found: 465.17. MS calcd for $C_{20}H_{31}BrN_2O_4K$ $(M+K)^+$: 481.11. Found: 481.14.

(2*R*,3*R*)-2-(4-Bromobenzyloxy)-4-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionylamino]-3-hydroxy-*N*-isobutyl-butyramide (15e). 15e: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.91 (d, *J* = 6.9 Hz, 6H), 1.69–1.82 (m, 1H), 2.62 (t, *J* = 7.0 Hz, 2H), 3.01–3.20 (m, 2H), 3.35–3.47 (m, 1H), 3.57–3.70 (m, 1H), 3.80 (d, *J* = 6.6 Hz, 1H), 3.88–3.95 (m, 1H), 4.00 (t, *J* = 7.0 Hz, 2H), 4.52 (d, *J* = 11.3 Hz, 1H), 4.66 (d, *J* = 11.3 Hz, 1H), 6.14–6.20 (m, 1H), 6.75–6.83 (m, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.63–7.85 (m, 4H). MS calcd for $C_{26}H_{31}BrN_3O_6$ $(M+H)^+$: 560.14. Found: 560.22. MS calcd for $C_{26}H_{30}BrN_3O_6Na$ $(M+Na)^+$: 582.12. Found: 582.21. MS calcd for $C_{26}H_{30}BrN_3O_6K$ $(M+K)^+$: 598.10. Found: 598.18.

(2*R*,3*R*)-4-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-2-(4-bromobenzyloxy)-3-hydroxy-*N*-isobutyl-butyramide (15f). 15f: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.89 (d, *J* = 6.9 Hz, 6H), 1.66–1.82 (m, 1H), 3.01–3.20 (m, 2H), 3.52–3.62 (m, 1H), 3.80–3.92 (m, 1H), 3.83 (d, *J* = 6.6 Hz, 1H), 4.01–4.09 (m, 1H), 4.57 (d, *J* = 11.3 Hz, 1H), 4.72 (d, *J* = 11.3 Hz, 1H), 6.02 (s, 2H), 6.62–6.71 (m, 1H), 6.78–6.84 (m, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.64–7.84 (m, 2H). MS calcd for $C_{23}H_{28}BrN_2O_6$ $(M+H)^+$: 507.11. Found: 507.11. MS calcd for $C_{23}H_{27}BrN_2O_6Na$ $(M+Na)^+$: 529.10. Found: 529.10. MS calcd for $C_{23}H_{27}BrN_2O_6K$ $(M+K)^+$: 545.07. Found: 545.06.

(2*R*,3*R*)-2-(4-Bromobenzyloxy)-3-hydroxy-4-pentanoylamino-*N*-(2-piperidin-1-yl-ethyl)-butyramide (15g). 15g: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.89 (t, *J* = 7.5 Hz, 3H), 1.22–1.63 (m, 10H), 2.15 (t, *J* = 7.2 Hz, 2H), 2.23–2.50 (m, 6H), 3.24–3.47 (m, 3H), 3.52–3.65 (m, 1H), 3.77 (d, *J* = 6.4 Hz, 1H), 3.86–3.97 (m, 1H), 4.54 (d, *J* = 11.3 Hz, 1H), 4.60 (d, *J* = 11.3 Hz, 1H), 6.10–6.21 (m, 1H), 7.05–7.15 (m, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H). MS calcd for $C_{23}H_{37}BrN_3O_4$ $(M+H)^+$: 498.20. Found: 498.26. MS calcd for $C_{23}H_{36}BrN_3O_4Na$ $(M+Na)^+$: 520.18. Found: 520.25.

(2*R*,3*R*)-2-(4-Bromobenzyloxy)-4-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionylamino]-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (15h). 15h: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.35–1.58 (m, 6H), 2.27–2.48 (m, 6H), 2.60 (t, *J* = 6.9 Hz, 2H), 3.28–3.53 (m, 3H), 3.54–3.63 (m, 1H), 3.80 (d, *J* = 6.5 Hz, 1H), 3.87–4.02 (m, 3H), 4.57 (d, *J* = 11.3 Hz, 1H), 4.60 (d, *J* = 11.3 Hz, 1H), 6.32–6.40 (m, 1H), 7.07–7.17 (m, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.47–7.87 (m, 4H). MS calcd for $C_{29}H_{36}BrN_4O_6$ $(M+H)^+$: 615.18. Found: 615.15. MS calcd for $C_{29}H_{35}BrN_4O_6Na$ $(M+Na)^+$: 637.16. Found: 637.14. MS calcd for $C_{29}H_{35}BrN_4O_6K$ $(M+K)^+$: 653.14. Found: 653.11.

(2*R*,3*R*)-4-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-2-(4-bromobenzyloxy)-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (15i). 15i: $[\alpha]_D^{22}$ +30.0 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.38–1.67 (m, 6H), 2.35–2.62 (m, 6H) 3.33–3.52 (m, 3H), 3.74–3.84 (m, 1H), 3.86 (d, *J* = 6.3 Hz, 1H), 4.02–4.08 (m, 1H), 4.55 (s, 2H), 6.02 (s, 2H), 6.72–6.83 (m, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 7.20–7.38 (m, 4H), 7.42 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 24.0, 25.3, 35.5, 42.2, 54.5, 57.4, 71.5, 73.1, 80.4, 101.8, 107.8, 108.1, 121.8, 122.4, 128.6, 130.2, 131.9, 135.9, 148.1, 150.5, 167.4, 171.4. MS calcd for $C_{26}H_{33}BrN_3O_6$ $(M+H)^+$: 562.16. Found: 562.12. MS calcd for $C_{26}H_{32}BrN_3O_6Na$ $(M+Na)^+$: 584.14. Found: 584.10. MS calcd for $C_{26}H_{32}BrN_3O_6K$ $(M+K)^+$: 600.11. Found: 600.08. Anal. ($C_{26}H_{32}BrN_3O_6$) C, H, N.

(2*R*,3*R*)-2-(4-Bromobenzyloxy)-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-4-pentanoylamino-butyramide (15j). 15j: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.01 (t, $J = 7.2$ Hz, 3H), 1.27–1.36 (m, 2H), 1.55–1.63 (m, 2H), 2.23 (t, $J = 6.8$ Hz, 2H), 2.85 (dd, $J = 1.9$, 16.8 Hz, 1H), 3.01 (dd, $J = 5.5$, 16.8 Hz, 1H), 3.20–3.31 (m, 1H), 3.43–3.53 (m, 1H), 3.91 (d, $J = 6.3$ Hz, 1H), 3.90–4.03 (m, 1H), 4.43 (d, $J = 11.3$ Hz, 1H), 4.48–4.55 (m, 1H), 4.58 (d, $J = 11.3$ Hz, 1H), 5.31 (dd, $J = 5.1$, 9.1 Hz, 1H), 6.11–6.20 (m, 1H), 6.86–6.98 (m, 1H), 7.13 (d, $J = 8.4$ Hz, 2H), 7.19–7.36 (m, 4H), 7.40 (d, $J = 8.4$ Hz, 2H). MS calcd for $C_{25}H_{32}BrN_2O_5$ $(M+H)^+$: 519.15. Found: 519.09. MS calcd for $C_{25}H_{31}BrN_2O_5Na$ $(M+Na)^+$: 541.13. Found: 541.06. MS calcd for $C_{25}H_{31}BrN_2O_5K$ $(M+K)^+$: 557.11. Found: 557.04.

(2*R*,3*R*)-2-(4-Bromobenzyloxy)-4-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionylamino]-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-butyramide (15k). 15k: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.60 (t, $J = 6.9$ Hz, 2H), 2.85 (dd, $J = 1.9$, 16.8 Hz, 1H), 3.01 (dd, $J = 5.5$, 16.8 Hz, 1H), 3.42–3.57 (m, 2H), 3.92 (t, $J = 6.9$ Hz, 2H), 4.02 (d, $J = 6.5$ Hz, 1H), 4.06–4.14 (m, 1H), 4.58 (d, $J = 11.3$ Hz, 1H), 4.63 (d, $J = 11.3$ Hz, 1H), 4.63–4.72 (m, 1H), 5.40 (dd, $J = 5.0$, 9.0 Hz, 1H), 6.39–6.45 (m, 1H), 6.74–6.80 (m, 1H), 7.09–7.32 (m, 4H), 7.18 (d, $J = 8.4$ Hz, 2H), 7.43 (d, $J = 8.4$ Hz, 2H), 7.63–7.80 (m, 4H). MS calcd for $C_{31}H_{31}BrN_3O_7$ $(M+H)^+$: 636.13. Found: 636.19. MS calcd for $C_{31}H_{30}BrN_3O_7Na$ $(M+Na)^+$: 658.12. Found: 658.18. MS calcd for $C_{31}H_{30}BrN_3O_7K$ $(M+K)^+$: 674.09. Found: 674.16.

(2*R*,3*R*)-4-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-2-(4-bromobenzyloxy)-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-butyramide (15l). 15l: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.92 (dd, $J = 1.8$, 16.7 Hz, 1H), 3.20 (dd, $J = 5.5$, 16.7 Hz, 1H), 3.60–3.72 (m, 1H), 3.79–3.87 (m, 1H), 3.90 (d, $J = 6.6$ Hz, 1H), 4.03–4.15 (m, 1H), 4.60 (d, $J = 11.3$ Hz, 1H), 4.61–4.67 (m, 1H), 4.63 (d, $J = 11.3$ Hz, 1H), 5.43 (dd, $J = 5.1$, 9.0 Hz, 1H), 6.03 (s, 2H), 6.57–6.63 (m, 1H), 6.78–6.85 (m, 1H), 6.81 (d, $J = 8.5$ Hz, 1H), 7.10–7.32 (m, 8H), 7.43 (d, $J = 8.4$ Hz, 2H). MS calcd for $C_{28}H_{28}BrN_2O_7$ $(M+H)^+$: 583.11. Found: 583.10. MS calcd for $C_{28}H_{27}BrN_2O_7Na$ $(M+Na)^+$: 605.09. Found: 605.08. MS calcd for $C_{28}H_{27}BrN_2O_7K$ $(M+K)^+$: 621.06. Found: 621.06.

(2*S*,3*S*)-2-(4-Bromobenzyloxy)-3-hydroxy-4-pentanoylamino-*N*-phenethyl-butyramide (16a). 16a: NMR data: see compound 15a. MS calcd for $C_{24}H_{32}BrN_2O_4$ $(M+H)^+$: 491.15. Found: 491.14. MS calcd for $C_{24}H_{31}BrN_2O_4Na$ $(M+Na)^+$: 513.14. Found: 513.12. MS calcd for $C_{24}H_{31}BrN_2O_4K$ $(M+K)^+$: 529.11. Found: 529.10.

(2*S*,3*S*)-2-(4-Bromobenzyloxy)-4-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionylamino]-3-hydroxy-*N*-phenethyl-butyramide (16b). 16b: NMR data: see compound 15b. MS calcd for $C_{30}H_{31}BrN_3O_6$ $(M+H)^+$: 608.14. Found: 608.12. MS calcd for $C_{30}H_{30}BrN_3O_6Na$ $(M+Na)^+$: 630.12. Found: 630.11. MS calcd for $C_{30}H_{30}BrN_3O_6K$ $(M+K)^+$: 646.10. Found: 646.08.

(2*S*,3*S*)-4-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-2-(4-bromobenzyloxy)-3-hydroxy-*N*-phenethyl-butyramide (16c). 16c: NMR data: see compound 15c. MS calcd for $C_{27}H_{28}BrN_2O_6$ $(M+H)^+$: 555.11. Found: 555.15. MS calcd for $C_{27}H_{27}BrN_2O_6Na$ $(M+Na)^+$: 577.10. Found: 577.13.

(2*S*,3*S*)-2-(4-Bromobenzyloxy)-3-hydroxy-*N*-isobutyl-4-pentanoylamino- butyramide (16d). 16d: NMR data: see compound 15d. MS calcd for $C_{20}H_{32}BrN_2O_4$ $(M+H)^+$: 443.15. Found: 443.20. MS calcd for $C_{20}H_{31}BrN_2O_4Na$ $(M+Na)^+$: 465.14. Found: 465.19. MS calcd for $C_{20}H_{31}BrN_2O_4K$ $(M+K)^+$: 481.11. Found: 481.16.

(2*S*,3*S*)-2-(4-Bromobenzyloxy)-4-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionylamino]-3-hydroxy-*N*-isobutyl-butyramide (16e). 16e: NMR data: see compound 15e. MS calcd for $C_{26}H_{31}BrN_3O_6$ $(M+H)^+$: 560.14. Found: 560.20. MS calcd for $C_{26}H_{30}BrN_3O_6Na$ $(M+Na)^+$: 582.12. Found: 582.19. MS calcd for $C_{26}H_{30}BrN_3O_6K$ $(M+K)^+$: 598.10. Found: 598.16.

(2*S*,3*S*)-4-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-2-(4-bromobenzyloxy)-3-hydroxy-*N*-isobutyl-butyramide (16f). 16f: NMR data: see compound 15f. MS calcd for $C_{23}H_{28}BrN_2O_6$ $(M+H)^+$: 507.11. Found: 507.17. MS calcd for $C_{23}H_{27}BrN_2O_6Na$ $(M+Na)^+$: 529.10. Found: 529.16. MS calcd for $C_{23}H_{27}BrN_2O_6K$ $(M+K)^+$: 545.07. Found: 545.13.

(2*S*,3*S*)-2-(4-Bromobenzyloxy)-3-hydroxy-4-pentanoylamino-*N*-(2-piperidin-1-yl-ethyl)-butyramide (16g). 16g: NMR data: see compound 15g. MS calcd for $C_{23}H_{37}BrN_3O_4$ $(M+H)^+$: 498.20. Found: 498.24. MS calcd for $C_{23}H_{36}BrN_3O_4Na$ $(M+Na)^+$: 520.18. Found: 520.23.

(2*S*,3*S*)-2-(4-Bromobenzyloxy)-4-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionylamino]-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (16h). 16h: NMR data: see compound 15h. MS calcd for $C_{29}H_{36}BrN_4O_6$ $(M+H)^+$: 615.18. Found: 615.24.

(2*S*,3*S*)-4-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-2-(4-bromobenzyloxy)-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (16i). 16i: NMR data: See compound 15i. MS calcd for $C_{26}H_{33}BrN_3O_6$ $(M+H)^+$: 562.16. Found: 562.23. MS calcd for $C_{26}H_{32}BrN_3O_6Na$ $(M+Na)^+$: 584.14. Found: 584.22.

(2*S*,3*S*)-2-(4-Bromobenzyloxy)-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-4-pentanoylamino-butyramide (16j). 16j: $[\alpha]_D^{22}$ −62.3 (*c* 0.8, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz): δ 0.98 (t, $J = 7.2$ Hz, 3H), 1.25–1.35 (m, 2H), 1.59–1.68 (m, 2H), 2.21 (t, $J = 6.8$ Hz, 2H), 2.87 (dd, $J = 1.9$, 16.8 Hz, 1H), 3.07 (dd, $J = 5.5$, 16.8 Hz, 1H), 3.24–3.35 (m, 1H), 3.44–3.55 (m, 1H), 3.93 (d, $J = 6.3$ Hz, 1H), 3.95–4.04 (m, 1H), 4.48 (d, $J = 11.3$ Hz, 1H), 4.46–4.53 (m, 1H), 4.58 (d, $J = 11.3$ Hz, 1H), 5.27 (dd, $J = 5.1$, 9.1 Hz, 1H), 6.17–6.25 (m, 1H), 6.85–6.96 (m, 1H), 7.11 (d, $J = 8.4$ Hz, 2H), 7.17–7.32 (m, 4H), 7.40 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 14.0, 22.7, 28.1, 35.6, 39.3, 40.0, 57.6, 71.8, 72.5, 73.5, 80.0, 122.7, 125.2, 126.1, 127.8, 129.0, 131.0, 132.5, 137.8, 141.6, 141.9, 171.2, 172.6. MS calcd for $C_{25}H_{32}BrN_2O_5$ $(M+H)^+$: 519.15. Found: 519.16. MS calcd for $C_{25}H_{31}BrN_2O_5Na$ $(M+Na)^+$: 541.13. Found: 541.14. MS calcd for $C_{25}H_{31}BrN_2O_5K$ $(M+K)^+$: 557.11. Found: 557.11. Anal. ($C_{25}H_{31}BrN_2O_5$) C, H, N.

(2*S*,3*S*)-2-(4-Bromobenzyloxy)-4-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionylamino]-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-butyramide (16k). **16k**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.58 (t, *J* = 6.9 Hz, 2H), 2.90 (dd, *J* = 1.9, 16.8 Hz, 1H), 3.00 (dd, *J* = 5.5, 16.8 Hz, 1H), 3.45–3.57 (m, 2H), 3.94 (t, *J* = 6.9 Hz, 2H), 4.05 (d, *J* = 6.5 Hz, 1H), 4.09–4.17 (m, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.65 (d, *J* = 11.5 Hz, 1H), 4.60–4.70 (m, 1H), 5.43 (dd, *J* = 5.2, 9.1 Hz, 1H), 6.35–6.43 (m, 1H), 6.71–6.78 (m, 1H), 7.10–7.29 (m, 4H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.65–7.82 (m, 4H). MS calcd for $C_{31}H_{31}BrN_3O_7$ $(M+H)^+$: 636.13. Found: 636.11. MS calcd for $C_{31}H_{30}BrN_3O_7Na$ $(M+Na)^+$: 658.12. Found: 658.10. MS calcd for $C_{31}H_{30}BrN_3O_7K$ $(M+K)^+$: 674.09. Found: 674.07.

(2*S*,3*S*)-4-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-2-(4-bromobenzyloxy)-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-butyramide (16l). **16l**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.90 (dd, *J* = 1.9, 16.8 Hz, 1H), 3.23 (dd, *J* = 5.4, 16.8 Hz, 1H), 3.63–3.72 (m, 1H), 3.80–3.89 (m, 1H), 3.92 (d, *J* = 6.5 Hz, 1H), 4.04–4.17 (m, 1H), 4.62 (d, *J* = 11.3 Hz, 1H), 4.63–4.67 (m, 1H), 4.68 (d, *J* = 11.3 Hz, 1H), 5.41 (dd, *J* = 5.1, 9.1 Hz, 1H), 6.01 (s, 2H), 6.50–6.61 (m, 1H), 6.75–6.84 (m, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 7.12–7.30 (m, 8H), 7.41 (d, *J* = 8.4 Hz, 2H). MS calcd for $C_{28}H_{28}BrN_2O_7$ $(M+H)^+$: 583.11. Found: 583.03. MS calcd for $C_{28}H_{27}BrN_2O_7Na$ $(M+Na)^+$: 605.09. Found: 605.02. MS calcd for $C_{28}H_{27}BrN_2O_7K$ $(M+K)^+$: 621.06. Found: 620.99.

(2*R*,3*R*)-2-(3-Bromobenzyloxy)-3-hydroxy-4-pentanoylamino-*N*-phenethyl-butyramide (17a). **17a**: $[\alpha]_D^{22}$ +29.2 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.91 (t, *J* = 7.2 Hz, 3H), 1.33 (m, 2H), 1.58 (m, 2H), 2.17 (t, *J* = 7.7 Hz, 2H), 2.83 (t, *J* = 6.8 Hz, 2H), 3.25–3.35 (m, 1H), 3.42–3.67 (m, 3H), 3.73 (d, *J* = 6.3 Hz, 1H), 3.89 (br s, 1H), 4.10–4.14 (m, 1H), 4.36 (d, *J* = 11.3 Hz, 1H), 4.53 (d, *J* = 11.3 Hz, 1H), 6.01 (br s, 1H), 6.77 (br s, 1H), 7.09–7.38 (m, 8H), 7.44 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 13.9, 22.5, 27.9, 35.5, 36.6, 40.0, 41.4, 71.7, 73.4, 79.8, 122.8, 126.8, 126.9, 128.8, 128.9, 130.4, 131.2, 131.5, 138.4, 139.0, 171.1, 174.5. MS calcd for $C_{24}H_{32}BrN_2O_4$ $(M+H)^+$: 491.15. Found: 491.20. MS calcd for $C_{24}H_{31}BrN_2O_4Na$ $(M+Na)^+$: 513.14. Found: 513.18. MS calcd for $C_{24}H_{31}BrN_2O_4K$ $(M+K)^+$: 529.11. Found: 529.16. Anal. ($C_{24}H_{31}BrN_2O_4$) C, H, N.

(2*R*,3*R*)-2-(3-Bromobenzyloxy)-4-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionylamino]-3-hydroxy-*N*-phenethyl-butyramide (17b). **17b**: NMR data: see compound **18b**. MS calcd for $C_{30}H_{31}BrN_3O_6$ $(M+H)^+$: 608.14. Found: 608.18. MS calcd for $C_{30}H_{30}BrN_3O_6Na$ $(M+Na)^+$: 630.12. Found: 630.16. MS calcd for $C_{30}H_{30}BrN_3O_6K$ $(M+K)^+$: 646.10. Found: 646.14.

(2*R*,3*R*)-4-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-2-(3-bromobenzyloxy)-3-hydroxy-*N*-phenethyl-butyramide (17c). **17c**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.65 (d, *J* = 6.9 Hz, 2H), 3.45–3.69 (m, 3H), 3.70–3.85 (m, 1H), 3.78 (d, *J* = 6.3 Hz, 1H), 3.95–4.05 (m, 1H), 4.34 (d, *J* = 11.3 Hz, 1H), 4.56 (d, *J* = 11.3 Hz, 1H), 6.01 (s, 2H), 6.55–6.65 (m, 1H), 6.68–6.81 (m, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 7.10–7.47 (m, 11H). MS calcd for $C_{27}H_{28}BrN_2O_6$ $(M+H)^+$: 555.11. Found: 555.08. MS calcd for $C_{27}H_{27}BrN_2O_6Na$ $(M+Na)^+$: 577.10. Found: 577.06. MS calcd for $C_{27}H_{27}BrN_2O_6K$ $(M+K)^+$: 593.07. Found: 593.03.

(2*R*,3*R*)-2-(3-Bromobenzyloxy)-3-hydroxy-*N*-isobutyl-4-pentanoylamino- butyramide (17d). **17d**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (d, *J* = 6.9 Hz, 6H), 0.94 (t, *J* = 7.4 Hz, 3H), 1.20–1.41 (m, 2H), 1.53–1.66 (m, 2H), 1.68–1.82 (m, 1H), 2.20 (t, *J* = 7.4 Hz, 2H), 3.01–3.20 (m, 2H), 3.32–3.43 (m, 1H), 3.61–3.72 (m, 1H), 3.80 (d, *J* = 6.6 Hz, 1H), 3.86–3.99 (m, 1H), 4.50 (d, *J* = 11.3 Hz, 1H), 4.65 (d, *J* = 11.3 Hz, 1H), 5.90–6.00 (m, 1H), 6.67–6.75 (m, 1H), 7.21–7.26 (m, 2H), 7.42–7.52 (m, 2H). MS calcd for $C_{20}H_{32}BrN_2O_4$ $(M+H)^+$: 443.15. Found: 443.16. MS calcd for $C_{20}H_{31}BrN_2O_4Na$ $(M+Na)^+$: 465.14. Found: 465.15. MS calcd for $C_{20}H_{31}BrN_2O_4K$ $(M+K)^+$: 481.11. Found: 481.12.

(2*R*,3*R*)-2-(3-Bromobenzyloxy)-4-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionylamino]-3-hydroxy-*N*-isobutyl-butyramide (17e). **17e**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.90 (d, *J* = 6.9 Hz, 6H), 1.71–1.83 (m, 1H), 2.61 (t, *J* = 7.0 Hz, 2H), 3.00–3.22 (m, 2H), 3.31–3.43 (m, 1H), 3.57–3.70 (m, 1H), 3.82 (d, *J* = 6.6 Hz, 1H), 3.89–3.93 (m, 1H), 4.02 (t, *J* = 7.0 Hz, 2H), 4.54 (d, *J* = 11.3 Hz, 1H), 4.68 (d, *J* = 11.3 Hz, 1H), 6.16–6.23 (m, 1H), 6.73–6.80 (m, 1H), 7.22–7.52 (m, 4H), 7.65–7.83 (m, 4H). MS calcd for $C_{26}H_{31}BrN_3O_6$ $(M+H)^+$: 560.14. Found: 560.19. MS calcd for $C_{26}H_{30}BrN_3O_6Na$ $(M+Na)^+$: 582.12. Found: 582.18. MS calcd for $C_{26}H_{30}BrN_3O_6K$ $(M+K)^+$: 598.10. Found: 598.15.

(2*R*,3*R*)-4-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-2-(3-bromobenzyloxy)-3-hydroxy-*N*-isobutyl-butyramide (17f). **17f**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.90 (d, *J* = 6.9 Hz, 6H), 1.65–1.80 (m, 1H), 3.01–3.19 (m, 2H), 3.50–3.59 (m, 1H), 3.81–3.90 (m, 1H), 3.81 (d, *J* = 6.6 Hz, 1H), 4.00–4.09 (m, 1H), 4.53 (d, *J* = 11.3 Hz, 1H), 4.70 (d, *J* = 11.3 Hz, 1H), 6.02 (s, 2H), 6.61–6.69 (m, 1H), 6.75–6.82 (m, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 7.19–7.33 (m, 4H), 7.42–7.52 (m, 2H). MS calcd for $C_{23}H_{28}BrN_2O_6$ $(M+H)^+$: 507.11. Found: 507.18. MS calcd for $C_{23}H_{27}BrN_2O_6Na$ $(M+Na)^+$: 529.10. Found: 529.17. MS calcd for $C_{23}H_{27}BrN_2O_6K$ $(M+K)^+$: 545.07. Found: 545.15.

(2*R*,3*R*)-2-(3-Bromobenzyloxy)-3-hydroxy-4-pentanoylamino-*N*-(2-piperidin-1-yl-ethyl)-butyramide (17g). **17g**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.90 (t, *J* = 7.5 Hz, 3H), 1.20–1.61 (m, 10H), 2.12 (t, *J* = 7.2 Hz, 2H), 2.23–2.49 (m, 6H), 3.25–3.49 (m, 3H), 3.52–3.64 (m, 1H), 3.79 (d, *J* = 6.4 Hz, 1H), 3.85–3.95 (m, 1H), 4.55 (d, *J* = 11.3 Hz, 1H), 4.60 (d, *J* = 11.3 Hz, 1H), 6.15–6.24 (m, 1H), 7.04–7.13 (m, 1H), 7.16–7.53 (m, 4H). MS calcd for $C_{23}H_{37}BrN_3O_4$ $(M+H)^+$: 498.20. Found: 498.27.

(2*R*,3*R*)-2-(3-Bromobenzyloxy)-4-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionylamino]-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (17h). **17h**: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.41–1.62 (m, 6H), 2.30–2.51 (m, 6H), 2.62 (t, *J* = 6.9 Hz, 2H), 3.29–3.55 (m, 3H), 3.57–3.65 (m, 1H), 3.81 (d, *J* = 6.5 Hz, 1H), 3.87–4.04 (m, 3H), 4.53 (d, *J* = 11.3 Hz, 1H), 4.65 (d, *J* = 11.3 Hz, 1H), 6.25–6.36 (m, 1H), 7.05–7.14 (m, 1H), 7.18–7.52 (m, 4H), 7.64–7.85 (m, 4H). MS calcd for $C_{29}H_{36}BrN_4O_6$ (M + H)$^+$: 615.18. Found: 615.27. MS calcd for $C_{29}H_{35}BrN_4O_6Na$ (M + Na)$^+$: 637.16. Found: 637.26.

(2*R*,3*R*)-4-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-2-(3-bromobenzyloxy)-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (17i). **17i**: $[\alpha]_D^{22}$ +23.2 (*c* 2.4, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.38–1.60 (m, 6H), 2.28–2.57 (m, 6H), 3.30–3.52 (m, 2H), 3.74–3.84 (m, 1H), 3.86 (d, *J* = 6.0 Hz, 1H), 4.03–4.10 (m, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.61 (d, *J* = 11.4 Hz, 1H), 6.01 (s, 2H), 6.75–6.85 (m, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 7.17–7.38 (m, 4H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.49 (s, 1H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 24.2, 25.6, 35.7, 42.2, 54.4, 57.3, 71.4, 73.0, 80.6, 101.8, 107.8, 108.1, 121.8, 122.7, 126.9, 128.6, 130.3, 131.2, 131.5, 139.2, 148.1, 150.5, 167.4, 171.2. MS calcd for $C_{26}H_{33}BrN_3O_6$ (M + H)$^+$: 562.16. Found: 562.22. MS calcd for $C_{26}H_{32}BrN_3O_6Na$ (M + Na)$^+$: 584.14. Found: 584.20.

(2*R*,3*R*)-2-(3-Bromobenzyloxy)-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-4-pentanoylamino-butyramide (17j). **17j**: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.01 (t, *J* = 7.2 Hz, 3H), 1.20–1.31 (m, 2H), 1.52–1.61 (m, 2H), 2.22 (t, *J* = 6.8 Hz, 2H), 2.87 (dd, *J* = 1.9, 16.8 Hz, 1H), 3.00 (dd, *J* = 5.5, 16.8 Hz, 1H), 3.20–3.31 (m, 1H), 3.43–3.55 (m, 1H), 3.87 (d, *J* = 6.3 Hz, 1H), 3.91–4.05 (m, 1H), 4.40 (d, *J* = 11.3 Hz, 1H), 4.48–4.57 (m, 1H), 4.61 (d, *J* = 11.3 Hz, 1H), 5.30 (dd, *J* = 5.1, 9.1 Hz, 1H), 6.10–6.20 (m, 1H), 6.75–6.88 (m, 1H), 7.17–7.32 (m, 5H), 7.40–7.50 (m, 3H). MS calcd for $C_{25}H_{32}BrN_2O_5$ (M + H)$^+$: 519.15. Found: 519.17. MS calcd for $C_{25}H_{31}BrN_2O_5Na$ (M + Na)$^+$: 541.13. Found: 541.16. MS calcd for $C_{25}H_{31}BrN_2O_5K$ (M + K)$^+$: 557.11. Found: 557.13.

(2*R*,3*R*)-2-(3-Bromobenzyloxy)-4-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionylamino]-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-butyramide (17k). **17k**: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.55 (t, *J* = 6.7 Hz, 2H), 2.92 (dd, *J* = 1.9, 16.7 Hz, 1H), 3.03 (dd, *J* = 5.5, 16.7 Hz, 1H), 3.40–3.54 (m, 2H), 3.92 (t, *J* = 6.7 Hz, 2H), 4.01 (d, *J* = 6.6 Hz, 1H), 4.10–4.19 (m, 1H), 4.62 (d, *J* = 11.5 Hz, 1H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.69–4.78 (m, 1H), 5.45 (dd, *J* = 5.2, 9.1 Hz, 1H), 6.30–6.40 (m, 1H), 6.69–6.78 (m, 1H), 7.12–7.87 (m, 12H). MS calcd for $C_{31}H_{31}BrN_3O_7$ (M + H)$^+$: 636.13. Found: 636.12. MS calcd for $C_{31}H_{30}BrN_3O_7Na$ (M + Na)$^+$: 658.12. Found: 658.10. MS calcd for $C_{31}H_{30}BrN_3O_7K$ (M + K)$^+$: 674.09. Found: 674.08.

(2*R*,3*R*)-4-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-2-(3-bromobenzyloxy)-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-butyramide (17l). **17l**: ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.92 (dd, *J* = 1.9, 16.8 Hz, 1H), 3.12 (dd, *J* = 5.4, 16.8 Hz, 1H), 3.65–3.73 (m, 2H), 4.07 (d, *J* = 5.0 Hz, 1H), 4.17–4.23 (m, 1H), 4.52–4.57 (m, 1H), 4.64 (s, 2H), 5.34 (dd, *J* = 5.0, 9.0 Hz, 1H), 6.00 (s, 2H), 6.50–6.57 (m, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.90–6.98 (m, 1H), 7.09–7.46 (m, 10H). MS calcd for $C_{28}H_{28}BrN_2O_7$ (M + H)$^+$: 583.11. Found: 583.08. MS calcd for $C_{28}H_{27}BrN_2O_7Na$ (M + Na)$^+$: 605.09. Found: 604.05. MS calcd for $C_{28}H_{27}BrN_2O_7K$ (M + K)$^+$: 621.06. Found: 621.03.

(2*S*,3*S*)-2-(3-Bromobenzyloxy)-3-hydroxy-4-pentanoylamino-*N*-phenethyl-butyramide (18a). **18a**: NMR data: see compound **17a**. MS calcd for $C_{24}H_{32}BrN_2O_4$ (M + H)$^+$: 491.15. Found: 491.16. MS calcd for $C_{24}H_{31}BrN_2O_4Na$ (M + Na)$^+$: 513.14. Found: 513.15. MS calcd for $C_{24}H_{31}BrN_2O_4K$ (M + K)$^+$: 529.11. Found: 529.12.

(2*S*,3*S*)-2-(3-Bromobenzyloxy)-4-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionylamino]-3-hydroxy-*N*-phenethyl-butyramide (18b). **18b**: $[\alpha]_D^{22}$ −21.0 (*c* 0.6, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.60 (t, *J* = 7.2 Hz, 2H), 2.83 (t, *J* = 6.9 Hz, 2H), 3.25–3.39 (m, 1H), 3.42–3.66 (m, 3H), 3.75 (d, *J* = 6.6 Hz, 1H), 3.84–3.92 (m, 1H), 3.97 (t, *J* = 7.2 Hz, 2H), 4.35 (d, *J* = 11.3 Hz, 1H), 4.51 (d, *J* = 11.3 Hz, 1H), 6.21 (br s, 1H), 6.75 (br s, 1H), 7.10–7.35 (m, 7H), 7.36 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.67–7.73 (m, 2H), 7.78–7.84 (m, 2H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ 34.8, 35.3, 35.8, 40.3, 41.7, 71.6, 73.6, 80.2, 123.0, 123.7, 127.1, 127.2, 129.1, 129.2, 130.7, 131.4, 131.8, 132.4, 134.4, 138.7, 139.3, 168.5, 171.1, 171.2. MS calcd for $C_{30}H_{31}BrN_3O_6$ (M + H)$^+$: 608.14. Found: 608.13. MS calcd for $C_{30}H_{30}BrN_3O_6Na$ (M + Na)$^+$: 630.12. Found: 630.12. MS calcd for $C_{30}H_{30}BrN_3O_6K$ (M + K)$^+$: 646.10. Found: 646.09.

(2*S*,3*S*)-4-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-2-(3-bromobenzyloxy)-3-hydroxy-*N*-phenethyl-butyramide (18c). **18c**: NMR data: see compound **17c**. MS calcd for $C_{27}H_{28}BrN_2O_6$ (M + H)$^+$: 555.11. Found: 555.15. MS calcd for $C_{27}H_{27}BrN_2O_6Na$ (M + Na)$^+$: 577.10. Found: 577.14. MS calcd for $C_{27}H_{27}BrN_2O_6K$ (M + K)$^+$: 593.07. Found: 593.12.

(2*S*,3*S*)-2-(3-Bromobenzyloxy)-3-hydroxy-*N*-isobutyl-4-pentanoylamino- butyramide (18d). **18d**: NMR data: see compound **17d**. MS calcd for $C_{20}H_{32}BrN_2O_4$ (M + H)$^+$: 443.15. Found: 443.21. MS calcd for $C_{20}H_{31}BrN_2O_4Na$ (M + Na)$^+$: 465.14. Found: 465.19. MS calcd for $C_{20}H_{31}BrN_2O_4K$ (M + K)$^+$: 481.11. Found: 481.16.

(2*S*,3*S*)-2-(3-Bromobenzyloxy)-4-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionylamino]-3-hydroxy-*N*-isobutyl-butyramide (18e). **18e**: NMR data: see compound **17e**. MS calcd for $C_{26}H_{31}BrN_3O_6$ (M + H)$^+$: 560.14. Found: 560.21. MS calcd for $C_{26}H_{30}BrN_3O_6Na$ (M + Na)$^+$: 582.12. Found: 582.19. MS calcd for $C_{26}H_{30}BrN_3O_6K$ (M + K)$^+$: 598.10. Found: 598.17.

(2*S*,3*S*)-4-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-2-(3-bromobenzyloxy)-3-hydroxy-*N*-isobutyl-butyramide (18f). **18f**: NMR data: see compound **17f**. MS calcd for $C_{23}H_{28}BrN_2O_6$ (M + H)$^+$: 507.11. Found: 507.17. MS calcd for $C_{23}H_{27}BrN_2O_6Na$ (M + Na)$^+$: 529.10. Found:

529.16. MS calcd for $C_{23}H_{27}BrN_2O_6K$ $(M+K)^+$: 545.07. Found: 545.12.

(2*S*,3*S*)-2-(3-Bromobenzyloxy)-3-hydroxy-4-pentanoylamino-*N*-(2-piperidin-1-yl-ethyl)-butyramide (18g). 18g: NMR data: see compound **17g**. MS calcd for $C_{23}H_{37}BrN_3O_4$ $(M+H)^+$: 498.20. Found: 498.19. MS calcd for $C_{23}H_{36}BrN_3O_4Na$ $(M+Na)^+$: 520.18. Found: 520.17.

(2*S*,3*S*)-2-(3-Bromobenzyloxy)-4-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionylamino]-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (18h). 18h: NMR data: see compound **17h**. MS calcd for $C_{29}H_{36}BrN_4O_6$ $(M+H)^+$: 615.18. Found: 615.16. MS calcd for $C_{29}H_{35}BrN_4O_6Na$ $(M+Na)^+$: 637.16. Found: 637.15.

(2*S*,3*S*)-4-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-2-(3-bromobenzyloxy)-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (18i). 18i: NMR data: see compound **17i**. MS calcd for $C_{26}H_{33}BrN_3O_6$ $(M+H)^+$: 562.16. Found: 562.22. MS calcd for $C_{26}H_{32}BrN_3O_6Na$ $(M+Na)^+$: 584.14. Found: 584.20.

(2*S*,3*S*)-2-(3-Bromobenzyloxy)-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-4-pentanoylamino-butyramide (18j). 18j: ^1H NMR ($CDCl_3$, 300 MHz): δ 1.01 (t, *J* = 7.2 Hz, 3H), 1.22–1.31 (m, 2H), 1.54–1.63 (m, 2H), 2.20 (t, *J* = 6.8 Hz, 2H), 2.84 (dd, *J* = 1.9, 16.9 Hz, 1H), 3.02 (dd, *J* = 5.5, 16.9 Hz, 1H), 3.19–3.31 (m, 1H), 3.40–3.51 (m, 1H), 3.86 (d, *J* = 6.3 Hz, 1H), 3.85–4.01 (m, 1H), 4.42 (d, *J* = 11.3 Hz, 1H), 4.46–4.57 (m, 1H), 4.63 (d, *J* = 11.3 Hz, 1H), 5.32 (dd, *J* = 5.0, 9.1 Hz, 1H), 6.13–6.21 (m, 1H), 6.72–6.85 (m, 1H), 7.19–7.33 (m, 5H), 7.39–7.49 (m, 3H). MS calcd for $C_{25}H_{32}BrN_2O_5$ $(M+H)^+$: 519.15. Found: 519.05. MS calcd for $C_{25}H_{31}BrN_2O_5Na$ $(M+Na)^+$: 541.13. Found: 541.03. MS calcd for $C_{25}H_{31}BrN_2O_5K$ $(M+K)^+$: 557.11. Found: 557.02.

(2*S*,3*S*)-2-(3-Bromobenzyloxy)-4-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionylamino]-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-butyramide (18k). 18k: ^1H NMR ($CDCl_3$, 300 MHz): δ 2.53 (t, *J* = 6.5 Hz, 2H), 2.94 (dd, *J* = 1.9, 16.7 Hz, 1H), 3.01 (dd, *J* = 5.5, 16.7 Hz, 1H), 3.41–3.54 (m, 2H), 3.95 (t, *J* = 6.5 Hz, 2H), 4.00 (d, *J* = 6.6 Hz, 1H), 4.11–4.19 (m, 1H), 4.60 (d, *J* = 11.4 Hz, 1H), 4.67 (d, *J* = 11.4 Hz, 1H), 4.70–4.78 (m, 1H), 5.42 (dd, *J* = 5.1, 9.1 Hz, 1H), 6.32–6.45 (m, 1H), 6.71–6.76 (m, 1H), 7.14–7.85 (m, 12H). MS calcd for $C_{31}H_{31}BrN_3O_7$ $(M+H)^+$: 636.13. Found: 636.15. MS calcd for $C_{31}H_{30}BrN_3O_7Na$ $(M+Na)^+$: 658.12. Found: 658.13. MS calcd for $C_{31}H_{30}BrN_3O_7K$ $(M+K)^+$: 674.09. Found: 674.10.

(2*S*,3*S*)-4-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-2-(3-bromobenzyloxy)-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-butyramide (18l). 18l: ^1H NMR ($CDCl_3$, 300 MHz): δ 2.90 (dd, *J* = 1.9, 16.9 Hz, 1H), 3.10 (dd, *J* = 5.5, 16.9 Hz, 1H), 3.63–3.71 (m, 2H), 4.05 (d, *J* = 5.0 Hz, 1H), 4.12–4.20 (m, 1H), 4.51–4.55 (m, 1H), 4.62 (s, 2H), 5.33 (dd, *J* = 5.1, 9.0 Hz, 1H), 6.01 (s, 2H), 6.51–6.56 (m, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 6.85–6.93 (m, 1H), 7.10–7.41 (m, 10H). MS calcd for $C_{28}H_{28}BrN_2O_7$ $(M+H)^+$: 583.11. Found: 583.06. MS calcd for $C_{28}H_{27}BrN_2O_7Na$ $(M+Na)^+$: 605.09. Found: 605.04. MS calcd for $C_{28}H_{27}BrN_2O_7K$ $(M+K)^+$: 621.06. Found: 621.00.

(2*R*,3*R*)-2-(4-Bromobenzyloxy)-*N*-(furan-2-yl-methyl)-3-hydroxy-4-phenylacetylamino-butyramide (19). 19: ^1H NMR (MeOH-d_4, 300 MHz): δ 3.35–3.40 (m, 2H), 3.45 (s, 2H), 3.87 (d, *J* = 4.6 Hz, 1H), 3.95–4.02 (m, 1H), 4.30 (d, *J* = 15.4 Hz, 1H), 4.43 (d, *J* = 15.4 Hz, 1H), 4.52 (d, *J* = 11.5 Hz, 1H), 4.61 Hz (d, *J* = 11.5 Hz, 1H), 6.21–6.26 (m, 1H), 6.30–6.34 (m, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.20–7.30 (m, 6H), 7.43 (d, *J* = 8.4 Hz, 2H). MS calcd for $C_{24}H_{26}BrN_2O_5$ $(M+H)^+$: 501.10. Found: 501.09. MS calcd for $C_{24}H_{25}BrN_2O_5Na$ $(M+Na)^+$: 523.08. Found: 523.07. MS calcd for $C_{24}H_{25}BrN_2O_5K$ $(M+K)^+$: 539.06. Found: 539.05.

(2*S*,3*S*)-2-(4-Bromobenzyloxy)-*N*-(furan-2-yl-methyl)-3-hydroxy-4-phenylacetylamino-butyramide (20). 20: NMR data: see compound **19**. MS calcd for $C_{24}H_{26}BrN_2O_5$ $(M+H)^+$: 501.10. Found: 501.04. MS calcd for $C_{24}H_{25}BrN_2O_5Na$ $(M+Na)^+$: 523.08. Found: 523.02. MS calcd for $C_{24}H_{25}BrN_2O_5K$ $(M+K)^+$: 539.06. Found: 539.01.

(2*R*,3*R*)-2-(3-Bromobenzyloxy)-*N*-(furan-2-yl-methyl)-3-hydroxy-4-phenylacetylamino-butyramide (21). 21: ^1H NMR (MeOH-d_4, 300 MHz): δ 3.37–3.42 (m, 2H), 3.47 (s, 2H), 3.86 (d, *J* = 4.7 Hz, 1H), 3.94–4.01 (m, 1H), 4.33 (d, *J* = 15.4 Hz, 1H), 4.46 (d, *J* = 15.4 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 4.60 Hz (d, *J* = 11.5 Hz, 1H), 6.22–6.26 (m, 1H), 6.31–6.35 (m, 1H), 7.17–7.50 (m, 10H). MS calcd for $C_{24}H_{26}BrN_2O_5$ $(M+H)^+$: 501.10. Found: 501.08. MS calcd for $C_{24}H_{25}BrN_2O_5Na$ $(M+Na)^+$: 523.08. Found: 523.06. MS calcd for $C_{24}H_{25}BrN_2O_5K$ $(M+K)^+$: 539.06. Found: 539.03.

(2*S*,3*S*)-2-(3-Bromobenzyloxy)-*N*-(furan-2-yl-methyl)-3-hydroxy-4-phenylacetylamino-butyramide (22). 22: NMR data: see compound **21**. MS calcd for $C_{24}H_{26}BrN_2O_5$ $(M+H)^+$: 501.10. Found: 501.05. MS calcd for $C_{24}H_{25}BrN_2O_5Na$ $(M+Na)^+$: 523.08. Found: 523.03. MS calcd for $C_{24}H_{25}BrN_2O_5K$ $(M+K)^+$: 539.06. Found: 539.00.

Suzuki coupling in solution, typical procedure. The bromo compound (76.6 μmol), aqueous Na_2CO_3 (2 M, 128 μL, 255 μmol), $PhB(OH)_2$ (28 mg, 230 μmol) and $(Ph_3P)_4Pd$ (6.9 mg, 6.0 μmol) were dissolved in freshly distilled and degassed 1,2-dimetoxyethane (DME) (6 mL). The solution was then refluxed overnight under an argon atmosphere. The mixture was evaporated and coevaporated with toluene three times, followed by purification by silica column chromatography (see above).

(2*R*,3*R*)-2-(Biphenyl-4-yl-methoxy)-*N*-(furan-2-yl-methyl)-3-hydroxy-4-phenylacetylamino-butyramide (23). 23: NMR data: see compound **24**. MS calcd for $C_{30}H_{30}N_2O_5Na$ $(M+Na)^+$: 521.20. Found: 521.25. MS calcd for $C_{30}H_{30}N_2O_5K$ $(M+K)^+$: 537.18. Found: 537.23.

(2*S*,3*S*)-2-(Biphenyl-4-yl-methoxy)-*N*-(furan-2-yl-methyl)-3-hydroxy-4-phenylacetylamino-butyramide (24). **24**: $[\alpha]_D^{22}$ −19.2 (*c* 1.3, $CHCl_3$); ^1H NMR (MeOH-d_4, 300 MHz): δ 3.37–3.42 (m, 2H), 3.47 (s, 2H), 3.86 (d, *J* = 4.7 Hz, 1H), 3.94–4.01 (m, 1H), 4.33 (d, *J* = 15.4 Hz, 1H), 4.46 (d, *J* = 15.4 Hz, 1H), 4.51 (d, *J* = 11.7 Hz, 1H), 4.60 Hz (d, *J* = 11.7 Hz, 1H), 6.22–6.26 (m, 1H), 6.31–6.35 (m, 1H), 7.18–7.43 (m, 7H), 7.50–7.66 (m, 8H); ^{13}C NMR (MeOH-d_4, 75.5 MHz): δ 35.7, 41.9, 42.7, 70.8, 72.6, 81.5, 107.0, 110.2, 126.8, 126.9, 127.3, 128.4, 128.7, 129.0, 131.8, 132.0, 132.6, 135.6, 136.4, 140.8, 142.1, 151.7, 170.9, 171.5. MS calcd for $C_{30}H_{31}N_2O_5$ $(M+H)^+$: 499.22. Found: 499.18. MS calcd for $C_{30}H_{30}N_2O_5Na$ $(M+Na)^+$: 521.20. Found: 521.14.

(2*R*,3*R*)-2-(Biphenyl-3-yl-methoxy)-*N*-(furan-2-yl-methyl)-3-hydroxy-4-phenylacetylamino-butyramide (25). **25**: ^1H NMR (MeOH-d_4, 300 MHz): δ 3.40–3.44 (m, 2H), 3.48 (s, 2H), 3.84 (d, *J* = 4.7 Hz, 1H), 3.92–4.02 (m, 1H), 4.30 (d, *J* = 15.4 Hz, 1H), 4.48 (d, *J* = 15.4 Hz, 1H), 4.51 (d, *J* = 11.3 Hz, 1H), 4.62 Hz (d, *J* = 11.3 Hz, 1H), 6.21–6.25 (m, 1H), 6.32–6.36 (m, 1H), 7.17–7.70 (m, 15H). MS calcd for $C_{30}H_{30}N_2O_5Na$ $(M+Na)^+$: 521.20. Found: 521.14. MS calcd for $C_{30}H_{30}N_2O_5K$ $(M+K)^+$: 537.18. Found: 537.11.

(2*S*,3*S*)-2-(Biphenyl-3-yl-methoxy)-*N*-(furan-2-yl-methyl)-3-hydroxy-4-phenylacetylamino-butyramide (26). **26**: NMR data: see compound **25**. MS calcd for $C_{30}H_{30}N_2O_5Na$ $(M+Na)^+$: 521.20. Found: 521.15. MS calcd for $C_{30}H_{30}N_2O_5K$ $(M+K)^+$: 537.18. Found: 537.14.

(2*R*,3*R*)-4-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-2-(biphenyl-4-yl-methoxy)-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-butyramide (27). **27**: ^1H NMR ($CDCl_3$, 300 MHz): δ 1.38–1.70 (m, 6H), 2.35–2.60 (m, 6H) 3.33–3.50 (m, 2H), 3.73–3.84 (m, 1H), 3.89 (d, *J* = 6.6 Hz, 1H), 4.08–4.14 (m, 1H), 4.63 (s, 2H), 5.98 (s, 2H), 6.72–6.83 (m, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 7.20–7.50 (m, 9H), 7.58 (d, *J* = 8.4 Hz, 2H). MS calcd for $C_{32}H_{38}N_3O_6$ $(M+H)^+$: 560.28. Found: 560.25. MS calcd for $C_{32}H_{37}N_3O_6Na$ $(M+Na)^+$: 582.26. Found: 582.24.

(2*S*,3*S*)-2-(Biphenyl-4-yl-methoxy)-3-hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-4-pentanoylamino-butyramide (28). **28**: ^1H NMR ($CDCl_3$, 300 MHz): δ 0.95 (t, *J* = 7.3 Hz, 3H), 1.25–1.35 (m, 2H), 1.58–1.65 (m, 2H), 2.20 (t, *J* = 6.9 Hz, 2H), 2.95 (dd, *J* = 1.8, 16.8 Hz, 1H), 3.20 (dd, *J* = 5.5, 16.8 Hz, 1H), 3.44–3.60 (m, 1H), 3.61–3.72 (m, 1H), 3.90 (d, *J* = 6.6 Hz, 1H), 3.95–4.05 (m, 1H), 4.60 (d, *J* = 11.3 Hz, 1H), 4.63–4.72 (m, 1H), 4.78 (d, *J* = 11.3 Hz, 1H), 5.39 (dd, *J* = 5.1, 9.1 Hz, 1H), 6.10–6.20 (m, 1H), 6.75–6.84 (m, 1H), 7.17–7.78 (m, 13H). MS calcd for $C_{31}H_{36}N_2O_5Na$ $(M+Na)^+$: 539.25. Found: 539.23. MS calcd for $C_{31}H_{36}N_2O_5K$ $(M+K)^+$: 555.23. Found: 555.20.

(2*R*,3*R*)-2-(Biphenyl-3-ylmethoxy)-3-hydroxy-4-pentanoylamino-*N*-phenethyl-butyramide (29). **29**: ^1H NMR ($CDCl_3$, 300 MHz): δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.34 (m, 2H), 1.60 (m, 2H), 2.15 (t, *J* = 7.6 Hz, 2H), 2.80 (t, *J* = 6.8 Hz, 2H), 3.30–3.40 (m, 1H), 3.43–3.67 (m, 3H), 3.78 (d, *J* = 6.4 Hz, 1H), 3.85–3.92 (m, 1H), 4.49 (d, *J* = 11.3 Hz, 1H), 4.63 (d, *J* = 11.3 Hz, 1H), 5.85–5.95 (m, 1H), 6.77–6.85 (m, 1H), 7.11–7.72 (m, 14H). MS calcd for $C_{30}H_{37}N_2O_4$ $(M+H)^+$: 489.28. Found: 489.30. MS calcd for $C_{30}H_{36}N_2O_4Na$ $(M+Na)^+$: 511.26. Found: 511.28. MS calcd for $C_{30}H_{36}N_2O_4K$ $(M+K)^+$: 527.23. Found: 527.25.

Heck-like coupling in solution, typical procedure. The bromo compound (21.3 μmol), thiophene or thiazol (211 μmol), KOAc (6.0 mg, 61 μmol) and $(Ph_3P)_4Pd$ (5.0 mg, 4.3 μmol) were dissolved in degassed *N*,*N*-dimethylacetamide (DMA) (2 mL). The solution was stirred overnight at 120 °C under an argon atmosphere, after which the solvent was evaporated. The crude product was purified by silica column chromatography (see above).

(2*R*,3*R*)-4-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-2-(4-thiophen-2-yl-benzyl)-butyramide (30). **30**: ^1H NMR ($CDCl_3$, 300 MHz): δ 1.38–1.70 (m, 6H), 2.30–2.58 (m, 6H) 3.33–3.55 (m, 2H), 3.55–3.84 (m, 2H), 3.86 (d, *J* = 6.6 Hz, 1H), 4.02–4.10 (m, 1H), 4.62 (s, 2H), 5.98 (s, 2H), 6.65–6.75 (m, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 7.10–7.28 (m, 5H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H). MS calcd for $C_{30}H_{36}N_3O_6S$ $(M+H)^+$: 566.23. Found: 566.22.

(2*S*,3*S*)-3-Hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-4-pentanoylamino-2-(4-thiophen-2-yl-benzyl)-butyramide (31). **31**: ^1H NMR ($CDCl_3$, 300 MHz): δ 0.95 (t, *J* = 7.4 Hz, 3H), 1.23–1.35 (m, 2H), 1.55–1.65 (m, 2H), 2.18 (t, *J* = 6.8 Hz, 2H), 2.95 (dd, *J* = 1.9, 16.8 Hz, 1H), 3.20 (dd, *J* = 5.5, 16.8 Hz, 1H), 3.50–3.57 (m, 1H), 3.62–3.70 (m, 1H), 3.84 (d, *J* = 6.4 Hz, 1H), 3.98–4.05 (m, 1H), 4.62 (d, *J* = 11.3 Hz, 1H), 4.64–4.72 (m, 1H), 4.70 (d, *J* = 11.3 Hz, 1H), 5.43 (dd, *J* = 5.0, 9.1 Hz, 1H), 5.89–5.95 (m, 1H), 6.81–6.90 (m, 1H), 7.07–7.33 (m, 7H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H). MS calcd for $C_{29}H_{34}N_2O_5SNa$ $(M+Na)^+$: 545.21. Found: 545.22.

(2*R*,3*R*)-3-Hydroxy-4-pentanoylamino-*N*-phenethyl-2-(3-thiophen-2-yl-benzyl)-butyramide (32). **32**: ^1H NMR ($CDCl_3$, 300 MHz): δ 0.95 (t, *J* = 7.4 Hz, 3H), 1.35 (m, 2H), 1.58 (m, 2H), 2.17 (t, *J* = 7.6 Hz, 2H), 2.82 (t, *J* = 6.7 Hz, 2H), 3.24–3.35 (m, 1H), 3.43–3.64 (m, 3H), 3.78 (d, *J* = 6.6 Hz, 1H), 3.90–3.99 (m, 1H), 4.41 (d, *J* = 11.3 Hz, 1H), 4.45 (d, *J* = 11.3 Hz, 1H), 6.10–6.19 (m, 1H), 6.71–6.78 (m, 1H), 7.12–7.71 (m, 12H). MS calcd for $C_{28}H_{35}N_2O_4S$ $(M+H)^+$: 495.23. Found: 495.24. MS calcd for $C_{28}H_{34}N_2O_4SNa$ $(M+Na)^+$: 517.21. Found: 517.23.

(2*R*,3*R*)-4-[(Benzo[1,3]dioxole-5-carbonyl)-amino]-3-hydroxy-*N*-(2-piperidin-1-yl-ethyl)-2-(4-thiazol-5-yl-benzyl)-butyramide (33). **33**: ^1H NMR ($CDCl_3$, 300 MHz): δ 1.31–1.62 (m, 6H), 2.30–2.55 (m, 6H) 3.33–3.53 (m, 2H), 3.55–3.65 (m, 1H), 3.82–3.87 (m, 1H), 3.89 (d, *J* = 6.6 Hz, 1H), 4.02–4.09 (m, 1H), 4.63 (s, 2H), 5.99 (s, 2H), 6.65–6.78 (m, 1H), 6.80 (d, $J=8.5$ Hz, 1H), 7.10–7.21 (m, 1H), 7.22–7.70 (m, 6H), 8.04 (s, 1H), 8.77 (s, 1H). MS calcd for $C_{29}H_{35}N_4O_6S$ $(M+H)^+$: 567.23. Found: 567.20.

(2*S*,3*S*)-3-Hydroxy-*N*-((1*S*,2*R*)-2-hydroxy-indan-1-yl)-4-pentanoylamino-2-(4-thiazol-5-yl-benzyl)-butyramide (34). 34: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.95 (t, $J=7.2$ Hz, 3H), 1.30–1.39 (m, 2H), 1.62–1.70 (m, 2H), 2.21 (t, $J=6.7$ Hz, 2H), 2.95 (dd, $J=1.8$, 16.8 Hz, 1H), 3.22 (dd, $J=5.5$, 16.8 Hz, 1H), 3.45–3.57 (m, 1H), 3.63–3.72 (m, 1H), 3.87 (d, $J=6.6$ Hz, 1H), 3.98–4.05 (m, 1H), 4.64 (d, $J=11.3$ Hz, 1H), 4.66–4.71 (m, 1H), 4.73 (d, $J=11.3$ Hz, 1H), 5.43 (dd, $J=5.0$, 9.0 Hz, 1H), 6.00–6.09 (m, 1H), 6.79–6.87 (m, 1H), 7.05–7.58 (m, 8H), 8.07 (s, 1H), 8.78 (s, 1H). MS calcd for $C_{28}H_{34}N_3O_5S$ $(M+H)^+$: 524.22. Found: 524.16. MS calcd for $C_{28}H_{33}N_3O_5SNa$ $(M+Na)^+$: 546.20. Found: 546.15. MS calcd for $C_{28}H_{33}N_3O_5K$ $(M+K)^+$: 562.18. Found: 562.12.

(2*R*,3*R*)-3-Hydroxy-4-pentanoylamino-*N*-phenethyl-2-(3-thiazol-5-yl-benzyl)-butyramide (35). 35: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.94 (t, $J=7.3$ Hz, 3H), 1.35 (m, 2H), 1.60 (m, 2H), 2.18 (t, $J=7.7$ Hz, 2H), 2.83 (t, $J=6.7$ Hz, 2H), 3.45–3.54 (m, 1H), 3.57–3.75 (m, 3H), 3.78 (d, $J=6.5$ Hz, 1H), 4.05–4.18 (m, 1H), 4.43 (d, $J=11.3$ Hz, 1H), 4.52 (d, $J=11.3$ Hz, 1H), 5.55–5.65 (m, 1H), 6.72–6.79 (m, 1H), 7.12–7.62 (m, 9H), 8.08 (s, 1H), 8.78 (s, 1H). MS calcd for $C_{27}H_{34}N_3O_4S$ $(M+H)^+$: 496.23. Found: 496.17. MS calcd for $C_{27}H_{33}N_3O_4SNa$ $(M+Na)^+$: 518.21. Found: 518.16.

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