Design, Synthesis, and Evaluation of Proline and Pyrrolidine Based Melanocortin Receptor Agonists. A Conformationally Restricted Dipeptide Mimic Approach

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The design, synthesis, and structure−activity relationships (SAR) of a series of novel proline and pyrrolidine based melanocortin receptor (MCR) agonists are described. To validate a conformationally constrained Arg-Nal dipeptide analogue strategy, we first synthesized and evaluated a test set of *cis*-(2*R*,4*R*)-proline analogues (**21a**−**g**). All of these compounds showed significant binding and agonist potency at the hMC1R, hMC3R, and hMC4R. Potent *cis*-(2*S*,4*R*)-pyrrolidine based MCR agonists (**35a**−**g**) were subsequently developed by means of this design approach. A SAR study directed toward probing the effect of the two chiral centers in the pyrrolidine ring on biological activity revealed the importance of the (*S*) absolute configuration at the 2-position for binding affinity, agonist potency, and receptor selectivity. Among the four sets of the pyrrolidine diastereomers investigated, analogues with the (2*S*,4*R*) configuration were the most potent agonists across the three receptors, followed by those possessing the (2*S*,4*S*) configuration.

The melanocortin receptors (MCRs)[a] are a family of five seven-transmembrane G-protein-coupled receptors (MC1R−MC5R) that have been identified and cloned. These receptors are activated by endogenous peptide ligands, α,*β*,*γ*-melanocyte stimulating hormones (MSH), and adrenocorticotropin (ACTH), which are derived from a common precursor protein, proopiomelanocortin (POMC), by post-translational cleavage.[1,2] All of these ligands feature a conserved tetrapeptide sequence, His-Phe-Arg-Trp, which has been identified as the minimal peptide fragment necessary for activating the receptors.[3,4] In addition, two endogenous antagonists, namely, the agouti protein and agouti-related peptide (AgRP),[5] of the melanocortin receptor family have been discovered. The MCRs mediate a variety of physiological responses that include skin pigmentation (MC1R),[6] inflammation (MC1R),[7−9] steroidogenesis (MC2R),[10,11] feeding behavior (MC3R and MC4R),[12−14] sexual function (MC4R),[15] and exocrine gland secretion (MC5R).[16,17] Consequently, the melanocortin system has become an attractive therapeutic target for drug development. Over the past decade, significant progress has been made toward the design of peptidic and nonpeptidic ligands as potential therapeutic agents for treatment of melanocortin-mediated diseases.[18−20] The MC4R, in particular, has attracted an enormous level of attention as a potential therapeutic target for obesity, sexual dysfunction, and involuntary weight loss associated diseases.[21,22] Recently, many research groups have disclosed their efforts in the design of potent and selective nonpeptidic small-molecule MC4 agonists[23−35] and antagonists.[36−42]

One successful approach in the design and synthesis of MC4R agonists has been the use of privileged structures.[43,44] The first potent and selective small-molecule MC4R agonist **1** (Figure 1), reported by Sebhat and co-workers,[35] resulted from the optimization of the initial lead **2**, which was derived by the coupling of a dipeptide to a spiroindoline privileged structure, a key component of the growth hormone secretagogue MK-0677.[43,45] The effectiveness of this design concept has also been demonstrated in the discovery of a number of potent and selective piperazine-based MC4R agonists.[42,46,47] The initial lead compound containing an arylsulfonamide unit (**3**) in the series was identified through iterative directed screening of several libraries generated by employing a GPCR privileged structure, an aryl piperazine scaffold. In fact, piperidine and piperazine cores have been the key structural templates for the majority of the potent MC4 agonists reported to date. In another distinct approach, Fostch and co-workers[48] used a set of low-energy structures derived from NMR data for the peptide ligand to identify ring systems that could position key functional groups in proximity to the side chains of the D-Phe-Arg-Trp tripeptide, which led to the synthesis of a 1,4-diaminocyclohexyl ring containing peptidomimetic MCR agonist with single-nanomolar potency at MC4R.

During the course of our efforts to develop peptidomimetic MCR agonists with significantly reduced peptide character on the basis of the tetrapeptide leads derived from His-D-Phe-Arg-Trp, we have explored a conceptually different strategy. It involves the incorporation of conformational constraint between two adjacent amino acids through the ring formation. A key objective of this approach would be to identify the appropriate constraining mode and cyclic scaffold that could enhance receptor binding and functional potency while allowing for both replacement of the amide bonds and truncation of the peptide terminus.

Our early work in the design of melanocortin ligands by means of the Tyr-D-Phe dipeptide mimic approach provided preliminary evidence for the validity for the strategy described above. The use of proline as a cyclic scaffold to conformationally restrict two phenyl rings intended to mimic the D-Phe and Tyr side chains produced dipeptide mimic **4** (Figure 2).[49] The coupling of **4** with a capped Arg residue led to the discovery of a series of ligands that displayed significant binding affinity at the MC4R. As exemplified by **5**, these analogues are

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[a] Abbreviations used: MCR, melanocortin receptor; ECDI, ethyldimethylaminopropyl carbodiimide; HOBt, 1*H*-benzotriazole; NMM, 4-methylmorpholine; DMEM, Dulbecco's modified Eagel's medium; BSA, bovine serum albumin. MK-0677, (*R*)-2-amino-*N*-(3-(benzyloxy)-1-(1-(methylsulfonyl)spiro[indoline-3,4′-piperidine]-1′-yl)-1-oxopropan-2-yl)-2-methylpropanamide.

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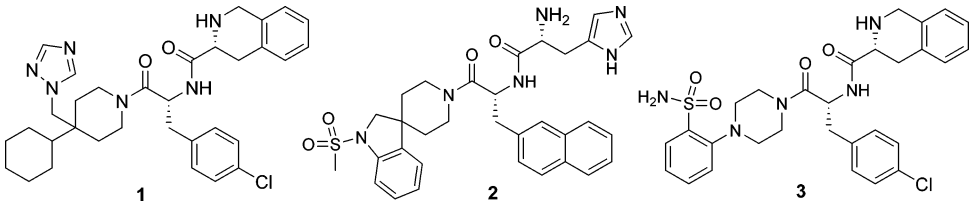


Figure 1. Piperidine and piperazine scaffolds identified through the privileged structure approach.

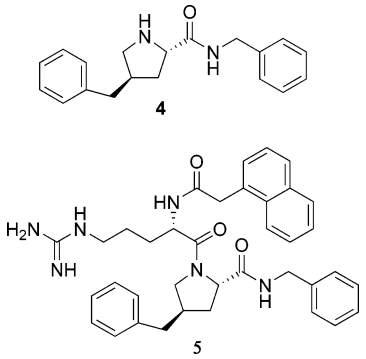


Figure 2. Proline based Tyr-D-Phe dipeptide mimic.

structurally different from the tetrapeptide templates. Subsequent efforts directed toward conformationally constraining the two C-terminal amino acids (Arg-2-Nal) of the tetrapeptide lead resulted in the identification of a privileged constraining mode for the design of novel peptidomimetics as potent melanocortin agonists. Herein, we report the design and synthesis of both proline and pyrrolidine based Arg-2-Nal dipeptide mimics and their use in the development of melanocortin agonists.

As illustrated in Figure 3, the constrained dipeptide surrogates we identified were derived by inserting a methylene group between the two amide nitrogen atoms (**7**) and subsequently substituting the amide bond between two amino acids with a CH_2-CH_2 linkage and deleting the C-terminus (**8**). While the C-2 guanidine side chain was used for mimicking the Arg residue, the naphthyl ring was employed to mimic the 2-Nal and Trp residues. It has been demonstrated by Haskell-Luevano and co-workers that replacement of the Trp in tetrapeptide **9** with 2-Nal maintained agonist potency across MC1R, MC3R, and MC4R.[50] We also found that substitution of the Trp-NH_2 residue of **9** for 2-Nal-$NHCH_3$ (**10**) resulted in ~8-fold and 3-fold better affinity at MC4R and MC1R, respectively (Table 1). Moreover, the selectivity for MC4R over MC1R was dramatically enhanced by replacing the His of **7** with Tyr (**11**). In addition to the beneficial effect on potency, the use of a 2-naphthyl ring provided a significant synthetic advantage due to its chemical inertness compared to the indole ring of the Trp moiety. The absolute stereochemistry depicted at C-2 of the five-membered ring of **8** correlates with the (*S*) configuration of L-Arg. Inversion of this chirality would provide the correspond-

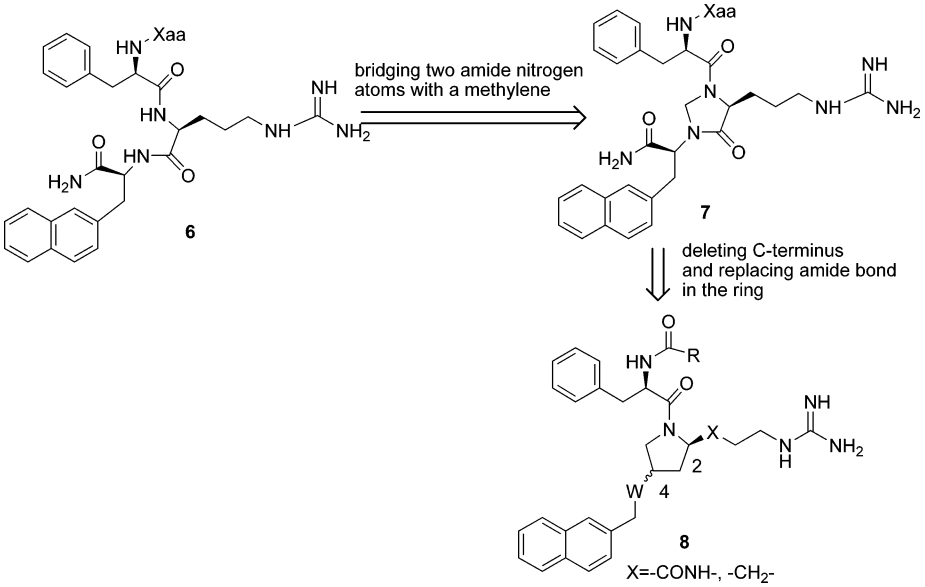


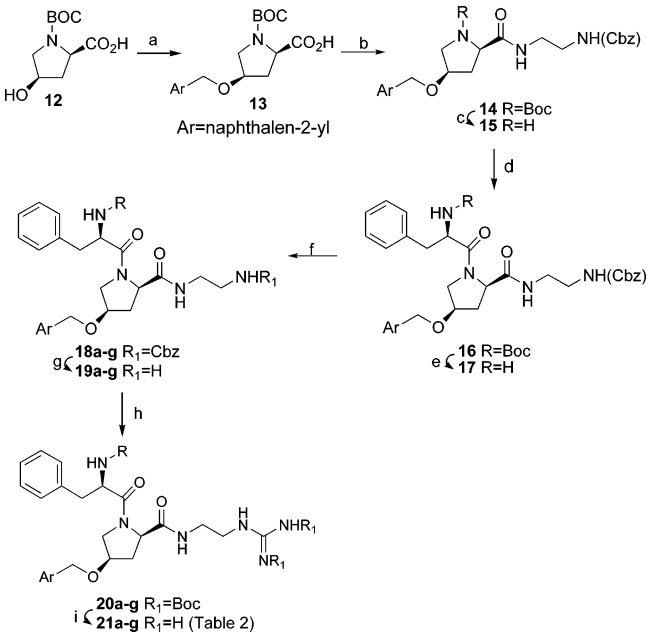
Figure 3. Design of five-membered ring constrained Arg-2-Nal dipeptide mimetics.

Table 1. Binding Affinity and Agonist Potency for Tetrapeptides **9**−**11**

9 Ac-His-D-Phe-Arg-Trp-NH_2
10 Ac-His-D-Phe-Arg-2-Nal-$NHCH_3$
11 Ac-Tyr-D-Phe-Arg-2-Nal-$NHCH_3$

Compd	MC1R		MC3R		MC4R	
	Ki, nM	EC50(Emax, %), nM	Ki, nM	EC50 (Emax, %), nM	Ki , nM	EC50(Emax, %), nM
9	35±9	14±0.6(104)	2865±1075	248±26(102)	246±40.8	59±9.8(105)
10	13±2	14±1(98)	1195±326	541±88(106)	29±5	5.7±0.7(101)
11	4520±1257	20000(83)	1727±67	20000(51)	104±10	44±5(84)

Scheme 1[a]



[a] Reagents and conditions: (a) sodium hydride, 2-bromomethyl naphthalene, DMF; (b) $NH_2CH_2CH_2NH(Cbz)$, HOBt, EDCI, NMM, DMF; (c) TFA, CH_2Cl_2; (d) BOC-D-Phe-OH, HOBt, EDCI, NMM, DMF; (e) TFA, CH_2Cl_2; (f) acids (ROH), EDCI, HOBt, NMM, DMF; (g) H_2, pyridine, Pd/C, CH_3OH; (h) 1,3-bis(*tert*-butoxycarbonyl)2-methyl-2-thiopseudourea, $HgCl_2$, Et_3N, DMF; (i) TFA/anisole/CH_2Cl_2.

ing configuration of a D-Arg mimic at this position. On the other hand, the C-4 chiral center was created by replacing the amide nitrogen with a carbon and was thus not related to the chirality of Nal or Trp. The stereochemical requirement at C-4 of the ring could not be defined by a topographical comparison with the tetrapeptide counterpart or computer modeling. Therefore, both (*R*) and (*S*) isomers at this position were synthesized and investigated in response to the potential critical impact of this chiral center on biological activity.

Chemistry

The *cis*-proline analogues were prepared from (2*R*,4*R*)-Boc-4-hydroxyproline using the route shown in Scheme 1. Alkylation of the 4-hydroxyl group of **12** by treatment with sodium hydride and bromomethylnaphthalene yielded 4-naphthyl methyl ether **13**, which was then coupled with *N*-1-Cbz-1,2-diaminoethane to give **14**. Removal of the Boc group with TFA followed by EDCI-mediated coupling of the amine with Boc-D-Phe-OH afforded dipeptide **17**, which was then deprotected and coupled with appropriate acids chosen to answer specific SAR questions. Selective cleavage of the Cbz group was accomplished by means of hydrogenation with 10 wt % Pd/C in the presence of a catalytic amount of pyridine. It was found that the addition of pyridine to the reaction mixture was critical for the desired transformation because concomitant cleavage of the naphthyl methyl ether and the Cbz group was observed without pyridine. The guanidination of the resulting amines **19** with 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea and $HgCl_2$ produced the protected guanidines **20**, which were then treated with TFA to give the desired target compounds **21**.

The synthetic route developed for *cis*-(2*S*,4*R*)-pyrrolidine analogues is outlined in Scheme 2. The synthesis began with (*R*)-*tert*-butyl 3-hydroxypyrrolidine-1-carboxylate (**22**). Allylation of **22** using the procedure reported by Gallagher and coworkers[51] gave a mixture of **23a** and **23b** in a ~1:1 ratio. Since it was difficult to separate **23a** and **23b** by chromatography on silica gel, a mixture of two isomers was treated with sodium hydride and bromomethylnaphthalene to alkylate the C-4 hydroxyl group of the pyrrolidine ring. Subsequent hydroboration of the olefins, **24a** and **24b**, afforded a mixture of diastereomers **25** and **26**, which could be separated readily by column chromatography. Both alcohols were converted to the azides **28** and **37** by means of a two-step sequence. Mesylate formation from isomer **25** followed by treatment with sodium azide at 70 °C in DMSO produced the azide **28**, which was then deprotected. The coupling of **29** with Boc-D-Phe-OH followed by cleavage of the Boc group generated the amine **31**, which was reacted with acids (ROH) to give the dipeptide **32**. The selective reduction of the azido group of **32** was accomplished with Pd/C (10 wt %) in the presence of pyridine while leaving the naphthyl ether intact. Guanidination of **33** followed by removal of the Boc group from the guanidine moiety or (*R*) amino acids afforded the desired analogues **35**. The transformation of trans isomer **26** to the targeted (2*R*,4*R*)-pyrrolidine analogues **42a**−**e** was carried out using the same sequence of reactions as illustrated for the synthesis of cis isomers.

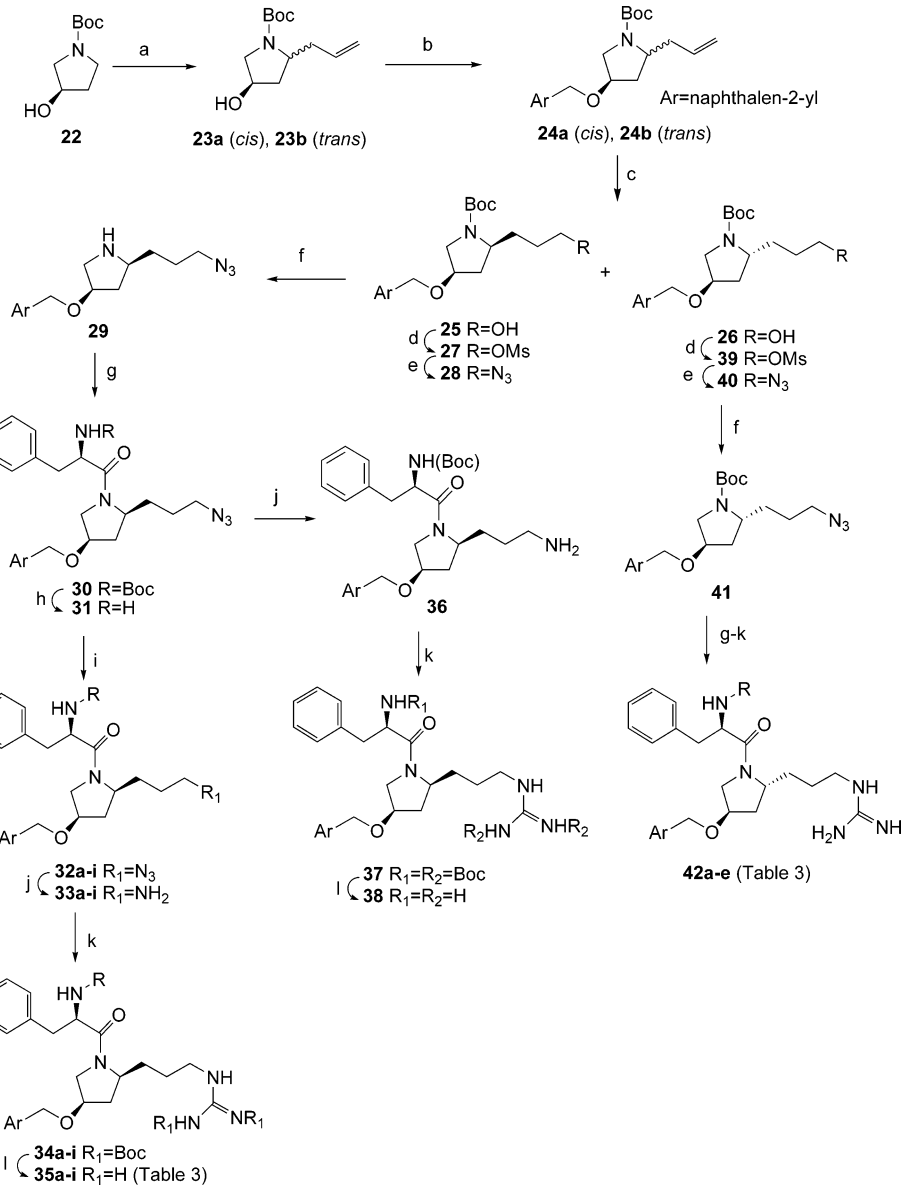
Alternatively, the key intermediate **25** could be prepared from 4-(naphthalen-2-ylmethoxy)proline **13** by means of two-carbon chain elongation (Scheme 3). The coupling of **5** with Meldrum's acid under EDCI activation produced **43**, which was deoxygenated with sodium borohydride in the presence of acetic acid to afford **44**. The attempted cleavage and decarboxylation of **44** in the presence of Cu in pyridine under reflux[52] gave the desired methyl ester **45** in a low yield, with extensive decomposition of **44** being observed upon prolonged heating. We found, however, that heating **44** in a mixture of toluene/EtOH (5:1) at 100 °C promoted smooth ring opening to give the ethyl ester **46**, which underwent decarboxylation when heated in toluene at reflux to yield **47**. Reduction of **47** with lithium aluminum hydride afforded **25**, which was identical in every respect to that prepared using the route shown in Scheme 1, thus allowing for the assignment of the stereochemistry for isomers **25** and **26**. The stereochemistry for diastereomers **23a** and **23b** and diastereomers **24a** and **24b** was also established by converting pure **23a** to **25** via an alkylation and hydroboration sequence.

The (2*R*,4*S*) isomers **56a**−**e** and (2*S*,4*S*) isomers **60a**−**e** were prepared from (*R*)-*tert*-butyl 3-hydroxypyrrolidine-1-carboxylate (**48**) using the reaction sequences shown in Scheme 2 (Scheme 4).

Results and Discussion

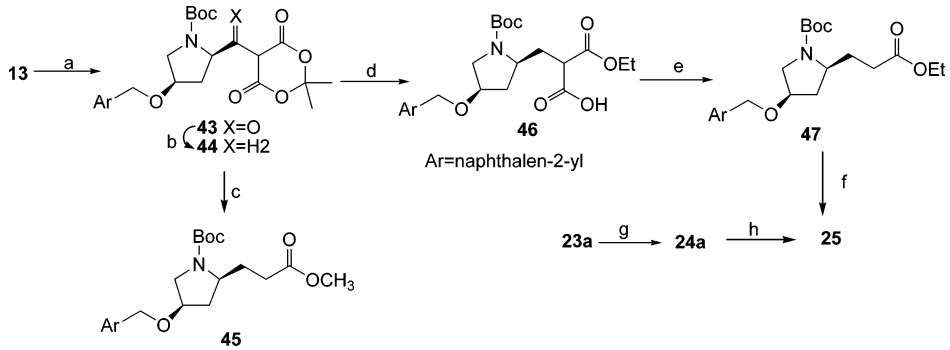
All analogues were purified by reverse-phase preparative HPLC (purity >98%) and screened in binding and functional assays against the human MC1R, MC3R, and MC4R. Binding affinity (calculated as IC_{50} and K_i values) was determined by measuring the displacement of a constant concentration of europium labeled NDP-α-MSH with competing unlabeled ligands. The agonist activity of the MCR analogues was evaluated at three human MCRs using a cell-based assay that is specific for each subtype of MCR (MC1R, MC3R, MC4R). Each subtype was stably transfected into HEK293 cells. The MCR expressing cells were stably transfected with a reporter system consisting of a cyclic-AMP responsive element (CRE) coupled to a luciferase reporter gene. Responses were compared to the effect of NDP-MSH (MT-I) and expressed as a percentage of maximum activity. The detailed procedures are provided in the Experimental Section.

Scheme 2[a]



[a] Reagents and conditions: (a) *s*-BuLi, −78 °C; TMEDA, allyl bromide, THF; (b) NaH, 2-bromomethylnaphthalene, DMF; (c) BH_3−THF, H_2O_2, THF, NaOH, H_2O; (d) MsCl, Et_3N, CH_2Cl_2; (e) NaN_3, DMSO, 70 °C; (f) TFA, CH_2Cl_2; (g) BOC-D-Phe-OH, HOBt, EDCI, NMM, DMF; (h) TFA, CH_2Cl_2; (i) acids (ROH), EDCI, HOBt, NMM, DMF; (j) H_2, pyridine, Pd/C, CH_3OH; (k) 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea, $HgCl_2$, Et_3N, DMF; (l) TFA/anisole/CH_2Cl_2.

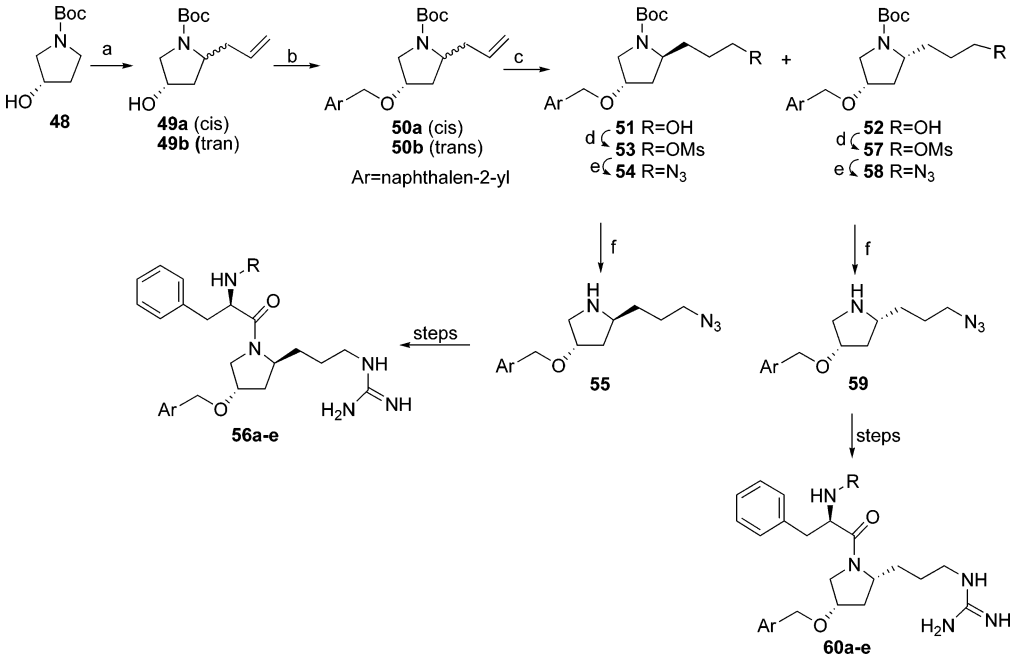
Scheme 3[a]



[a] Reagents and conditions: (a) Meldrum's acid, EDCI, DMAP, CH_2Cl_2; (b) $NaBH_4$, acetic acid, CH_3OH; (c) Cu, pyridine, CH_3OH; (d) toluene/EtOH (5:1), 100 °C; (e) toluene, reflux; (f) LAH, THF; (g) NaH, 2-(bromomethyl)naphthalene, THF; (h) BH_3−THF, H_2O_2, NaOH, H_2O, THF.

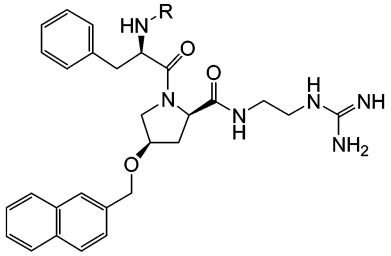
Proline Analogues. As an initial proof of concept study, we set out to synthesize and evaluate a series of synthetically accessible proline analogues that would demonstrate the validity of our design strategy. Table 2 summarizes a list of initial proline-based target compounds along with their corresponding binding affinity and functional activity at MC1R, MC3R, and

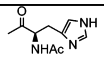
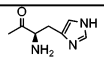
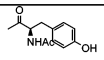
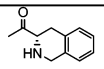
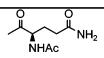
Scheme 4[a]



[a] Reagents and conditions: (a) *s*-BuLi, −78 °C; TMEDA, allyl bromide, THF; (b) NaH, 2-bromomethylnaphthalene, DMF; (c) BH_3−THF, H_2O_2, THF, NaOH, H_2O; (d) MsCl, Et_3N, CH_2Cl_2; (e) NaN_3, DMSO, 70 °C; (f) TFA, CH_2Cl_2.

Table 2. Binding Affinity and Agonist Potency of *cis*-Proline Analogues **21a**−**g**[a]



		MC1R		MC3R		MC4R	
Compd	**R**	Ki, nM	EC50(Emax,%), nM	Ki, nM	EC50(Emax,%), nM	Ki, nM	EC50(Emax,%), nM
21a		13±4.4	3±1(113)	824±115	340±16(93)	1578±604	152±41(80)
21b		15±3.8	24±12(116)	703±320	266±3(135)	760±176	249±24(89)
21c		2047±168	1337±11(112)	501±40	1218±12 (51)	559±59	254±66(142)
21d		1615±112	539±160(108)	4393±1507	825±284(75)	411±123	97±37(82)
21e		631±156	390±45(117)	3852±1452	1774±329(97)	1376±365	292±67(120)
21f		121±12	104± 14(108)	3177± 910	2474±533(44)	1016±289	501± 104(99)
21g		893±170	328±62(107)	1488±133	563±24(117)	632±160	184±85(103)

[a] The data represent the mean of the at least three experiments ± SEM.

MC4R. We were delighted to find that **21a** showed single-nanomolar agonist potency (EC_{50}, 3 nM) at MC1R with a K_i of 13 nM, comparable to those of the corresponding linear analogue **9**. Constrained analogue **21a**, however, exhibited a significantly improved selectivity for MC1R over MC4R (~120-fold, on the basis of binding affinity). In addition, the noncapped His

analogue **21b** showed binding affinity at MC1R and MC3R similar to those of analogue **21a** and 2-fold better affinity at MC4R than **21a**. The permeability of **21a** was also measured across the Caco-2 cell monolayer. It appeared to be passively absorbed at a permeability rate lower than that of mannitol (absorptive and exsorptive permeability coefficients of 0.6×10^{-4} and 0.3×10^{-4} cm/min, respectively, vs 1.3×10^{-4} and 1.1×10^{-4} cm/min of mannitol, respectively).

Encouraged by these promising preliminary results, we moved on to explore other amino acids in place of the His residue to gain insight into the structure−activity relationship of the top side chain appended to the constrained proline based dipeptide mimic (Table 2). In general, all other amino acids surveyed in this work to replace the His residue produced analogues that demonstrated significant binding and functional activity across all three receptors. However, because of the significantly reduced binding and agonist potency at MC1R observed with these analogues compared to the His analogue **21a**, the selectivity for MC1R over MC4R was markedly reduced. Among these compounds, the Tyr analogue **21c** showed the weakest affinity at MC1R but was ∼4-fold selective for MC4R over MC1R. In comparison with **21a**, **21c** had a ∼300-fold reduced affinity at MC1R but exhibited 3-fold better affinity at MC4R and comparable affinity at MC3R. The use of a constrained Phe analogue (Tic) gave an analogue (**21d**) exhibiting ∼4-fold selectivity for MC4R over MC1R and MC3R. The aromatic ring of the Tic moiety of **21d** seems to have an impact on the receptor selectivity because the Pip analogue **21e** exhibited 3-fold better binding affinity at MC1R and ∼2-fold decreased affinity at MC4R compared to **21d**. An α-amino acid capping group of the D-Phe residue was important but not obligatory for biological activity. Moving the piperidine nitrogen from the 2 (**21e**) to the 4 position (**21f**) led to a ∼4-fold increase in binding and agonist potency for MC1R and a marginal decrease in potency at MC3R and MC4R. The analogue **21g**, containing linear amino acid Gln, also had K_i values below 900 nM at MC1R and MC4R and was a full agonist of these two receptors.

The initial studies with the proline scaffold validated our constrained dipeptide analogue approach and motivated us to further explore this design strategy by using other heterocyclic templates. As a next step, we expanded our effort to include pyrrolidine analogues illustrated in Figure 3. To this end, a series of (2*S*,4*R*)-pyrrolidine analogues bearing a guanidine moiety at the 2-position and a naphthyl ring at the 4-position were synthesized and screened. It was remarkable to find that a seemingly minor change, replacing of the amide bond of the C-2 side chain with a methylene group, had such a profound effect on binding affinity and functional activity across the MC1R, MC3R, and MC4R, as shown by the data listed in Table 3. The His analogue **35a** showed subnanomolar affinity (0.65 nM) and agonist potency (0.3 nM) at MC1R, representing a 20-fold and 10-fold improvement over the proline His analogue **21a**. Moreover, **35a** had ∼90-fold and ∼30-fold better binding affinity at MC4R and MC3R, respectively, than **21a**. These dramatic increases in binding affinity and functional potency across all three receptors were also achieved with Tyr, Tic, Pip, and Gln analogues within this class. In contrast with the corresponding proline counterparts, all four analogues had potent functional activity at the three receptors. In addition, moderate selectivity for MC4R over MC1 was seen with the Tyr analogue **35b** (∼4-fold) and the Tic analogue **35d** (∼8-fold). The removal of the aromatic moiety from the Tic residue of **35d** slightly reduced affinity at the MC4R while maintaining affinity at the MC1R (**35e**), thus decreasing the MC4/MC1 selectivity. The five-membered ring proline analogue **35f** showed comparable binding affinity and functional potency profiles to those of six-membered ring piperidine **35e**.

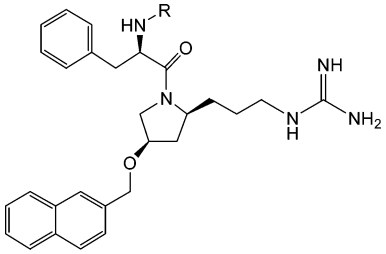
In comparison with the Tyr analogue **35b**, the Phe analogue **35g** showed ∼2-fold to 3-fold reduced affinity at the MC1R and MC4R, suggesting that the hydroxyl group on the aromatic ring of the Tyr moiety plays a role in binding either by forming a hydrogen bond with receptors or by sterically affecting a key receptor pocket. However, deletion of the N-terminal group (−NHAc) from the Phe moiety **35g** led to a ∼2-fold to 3-fold loss in binding affinity. This structural change was more detrimental to agonist potency at the MC3R and MC4R, and the resulting analogue **35h** became a partial agonist at these two receptors. A similar trend was also seen with the acetyl analogue **35i**, which was a partial agonist at MC3R and MC4R but retained significant binding affinity across the three receptors. Nevertheless, acetyl analogue **35i** showed significantly improved Caco-2 permeability than the His analogue **21a** (absorptive and exsorptive permeability coefficients of 4.5×10^{-4} and $3.7 \times 10-4$ cm/min, respectively, vs 0.6×10^{-4} and $0.3 \times 10-4$ cm/min of **21a**, respectively). These results clearly indicated the importance of the N-terminus for agonist potency at all three receptors. To better understand the effect of capping the NH_2 group of the D-Phe residue with an amino acid or a simple acid, the tripeptidomimetic **38** was also evaluated. While **38** showed significantly reduced binding affinity and functional potency than analogues containing a D-Phe-Xaa dipeptide as the top side chain, it was a full agonist across all three receptors with EC_{50} values of 151 and 291 nM, respectively, at MC1R and MC4R. On the other hand, the corresponding linear tripeptide D-Phe-Arg-2-Nal-$NHCH_3$ (**61**) was inactive at MC1R and MC3R and had a K_i of 2013 nM at MC4R, compared to 305 nM of **38**. The discovery of these (2*S*,4*R*)-pyrrolidine analogues with high binding affinity and agonist potency at MC1R and MC4R provided further compelling evidence supporting our strategy of designing conformationally restricted Arg-2-Nal dipeptide mimics.

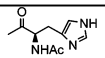
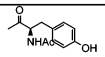
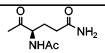
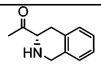
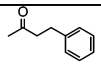
To further explore the pyrrolidine based Arg-Trp dipeptide mimetics, we next focused on the effect of stereochemistry at the two chiral centers of the pyrrolidine ring on binding affinity, functional activity, and receptor selectivity profile across the MC1R, MC3R, and MC4R. A study of stereochemical modification of tetrepeptide **9** and tripeptide Ac-D-Phe-Arg-Trp-NH_2 has demonstrated the importance of the chirality related to the amino acid residues for binding affinity and functional activity.[53] To this end, we set out to synthesize and evaluate three other sets of (2*R*,4*R*)-, (2*R*,4*S*)-, (2*S*,4*S*)-pyrrolidine diastereomers by using His, Tyr, Tic, Pip, and Gln as the capping groups of the D-Phe moiety as depicted in Figure 4.

The binding affinity and agonist potency of three sets of diastereomers are listed in Table 4. The potent and selective MC1R agonists were identified within the trans (2*R*,4*R*) series. With the exception of the Tyr analogue **42a**, all four of the other compounds showed significant affinity and agonist potency at MC1R and weak affinity on MC3R and MC4R. The His analogue **42b** had a K_i value of 4.7 nM and an EC_{50} value of 8.2 nM at MC1R with 3100- and 1480-fold selectivity for MC1R over MC3R and MC4R, respectively. These data indicated that inverting the C-2 chirality of *cis*-pyrrolidine **35a** resulted in a ∼60-fold increase in selectivity for MC1R over MC4R. Similarly, the Tic analogue **42c** also exhibited high affinity (K_i, 19 nM) and functional potency (EC_{50}, 19 nM) as well as excellent selectivity (>200-fold) for MC1R over MC4R.

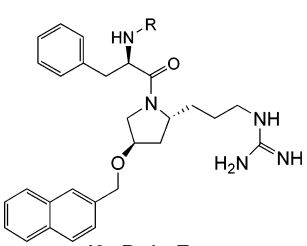
Within the trans (2*S*,4*S*) series, five analogues exhibited

Table 3. Binding Affinity and Agonist Potency of (2*R*,4*R*)-Pyrrolidine Analogues[a]

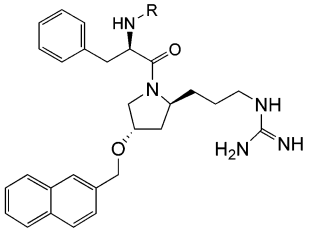


		MC1R		MC3R		MC4R	
Compd	**R**	Ki, nM	EC50(Emax, %), nM	Ki , nM	EC50 (Emax, %), nM	Ki, nM	EC50 (Emax, %), nM
35a		0.65±0.17	0.3±0.09(105)	26±3	15±2(140)	17±3	3.7±0.3(121)
35b		85±7	88±19(118)	42±8	85±17(97)	21±3	14±5(119)
35c		35±3	45±7(78)	50±6	42±7(130)	18±7	4.3±0.3(111)
35d		42±1	98±6(90)	86±12	232±15(41)	10±3	10±2(84)
35e		40±3	30±5(79)	156±42	260±89(69)	31±2	14±4(88)
35f		55±6	52±7(80)	219±36	593±92(64)	46±3	17±4 (84)
35g		182±25	201±16(110)	154±25	313±101(95)	59±16	20±4(111)
35h		611±124	585±81(103)	403±55	2051±1064(19)	137±23	266±98(41)
35i		463±88	232±32(92)	289±20	1384±399(19)	90±15	317±53(30)
38	H	381±16	151±15(95)	1244±234	871±45(90)	305±10	291±13(81)
61		4384±820	20000±0(26)	22562±10874	20000±0(24)	1248±185	809±122(77)

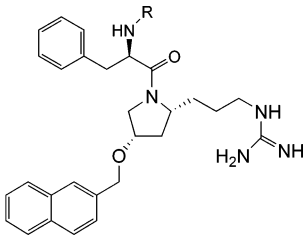
[a] The data represent the mean of the at least three experiments ± SEM.



42a R=Ac-Tyr
42b R=Ac-His
42c R=Tic
42d R=Pip
42e R=Ac-Gln



56a R=Ac-Tyr
56b R=Ac-His
56c R=Tic
56d R=Pip
56e R=Ac-Gln



60a R=Ac-Tyr
60b R=Ac-His
60c R=Tic
60d R=Pip
60e R=Ac-Gln

Figure 4. Pyrrolidine analogues with (2*R*,4*R*), (2*R*,4*S*), and (2*S*,4*S*) configurations.

moderate to good binding affinity and functional potency across the three MCRs. In comparison with the corresponding cis (2*S*,4*R*) analogues, compounds from this series (**56a**−**e**) were only slightly less potent and possessed similar receptor selectivity profiles. These results might suggest that an (*S*) configuration at the C-2 position is critical for significant binding affinity and agonist potency while both (*R*) and (*S*) configurations at the C-4 position are tolerated.

In contrast with the corresponding cis (2*S*,4*R*) analogues, the cis (2*R*,4*S*) analogues showed significantly reduced affinity and functional potency across all three receptors, with the exception of the His analogue **60b**. Within this series, the most notable SAR observation was that the His analogue **60b** exhibited a K_i of 14 nM and an EC_{50} of 9 nM and was >150-fold and >100-fold selective for MC4 over MC1R and MC3R, respectively. The importance of the stereochemistry at the C-4 position was further revealed by comparing **60b** with the His analogue **42b** from the (2*R*,4*R*) series; inversion of the (*R*) configuration of **60b** to (*S*)-(**42b**) converted a potent and selective MC4R agonist to a potent and selective MC1R agonist.

Table 4. Binding Affinity and Agonist Potency of **42a**−**e**, **56a**−**e**, and **60a**−**e**[a]

Compd	MC1R		MC3R		MC4R	
	Ki, nM	EC50(Emax,%), nM	Ki, nM	EC50(Emax, %), nM	Ki, nM	EC50(Emax, %), nM
42a	1687±721	1751±124(117)	19213±4279	20000±0(46)	2353±370	20000±0(46)
42b	4.7±0.9	8±2(112)	7226±1202	3720±990(60)	2879±378	986±108(102)
42c	19±3	19±3(94)	8102±379	1474±372(104)	4390±529	1093±45(85)
42d	340±85	449±102(90)	7441±718	20000±0 (13)	1712±104	10846±5288(46)
42e	443±101	402±25(102)	15358±3584	20000±0(45)	6666±252	20000±0(58)
56a	138±63	71±5(106)	425±66	68±9(109)	248±98	39±2(96)
56b	1.3±0.3	0.045±0.025(101)	117±14	1.3±0.3(109)	57±14	2.3±0.3(94)
56c	562±122	72±14(103)	529±19	214±14(96)	97±21	36±4(90)
56d	125±80	28±3(101)	1263±474	286±3(102)	121±2	54±12(90)
56e	103±21	4.3±0.3(105)	835±75	10±1(108)	187±13	8±2(93)
60a	2454±577	1815±25(83)	2884±359	1171±430(38)	492±94	252±23(102)
60b	2968±1116	1220±5(87)	1958±581	1134±266(63)	14±1	9±3(112)
60c	1403±446	1362±13(88)	4180±628	3152±998 (48)	670±60	457±66(95)
60d	1793±669	1070±235(99)	7163±837	20000±0(26)	2258±258	515±137(72)
60e	1572±26	521±36(99)	29064±8009	2986± 111(89)	8158±1369	1617±510(79)

[a] The data represent the mean of the at least three experiments ± SEM.

Conclusions

We have designed and synthesized a series of novel proline and pyrrolidine based Arg-Nal dipeptide mimics in which two specific amino acid side chains, the guanidine and naphthyl moieties, are conformationally restricted by a five-membered ring template. The coupling of pyrrolidine-derived dipeptide mimics with a variety of Xaa-D-Phe dipeptides led to the discovery of a number of potent peptidomimetic MCR agonists. The stereochemistry at the two chiral centers of the pyrrolidine ring has been demonstrated to play an important role in affinity, agonist potency, and selectivity profiles across the MC1R, MC3R, and MC4R. Among four sets of diastereomers investigated, cis (2*S*,4*R*) analogues showed the best binding affinity and agonist potency at the three receptors and trans (2*S*,4*S*) analogues displayed moderate to good affinity and agonist potency. On the other hand, (2*R*,4*S*) and (2*R*,4*R*) analogues exhibited significantly reduced potency at MC1R, MC3R, MC4R compared to the other two sets of analogues with the (*S*) configuration at the 2-position of the pyrrolidine ring, with the exception of the His analogues. The His analogue **42b** within the (2*R*,4*R*) series was a potent and selective MC1R agonist, while the corresponding stereoisomer **60b** in the (2*R*,4*S*) series was a potent and selective MC4R agonist. The SAR insights described in this paper established the viability of the constrained dipeptide (Arg-Nal) mimic approach for designing peptidomimetic melanocortin agonists. These constrained dipeptide mimics could serve as novel templates for the development of small-molecule melanocortin agonists as potential therapeutic agents. Our subsequent efforts at further optimization of the constrained dipeptide (Arg-Nal) mimic demonstrated that the bulky naphthyl group could be replaced with a phenyl group, thus offering an additional opportunity for further reduction of molecular weight. These results and the extension of the design strategy described above to other cyclic scaffolds will be reported in due course.

Experimental Section

General. Unless otherwise indicated, all reagents were purchased from commercial suppliers and used without further purification. TLC analyses were carried out on precoated silica gel plates (Diamond MK6F). Flash column chromatography was performed on Merck silica gel 60A (230−400) mesh. Reverse-phase preparative HPLC purification was carried out using a Varian 320 and a Varian-A 10 μm (250 mm × 500 mm) column. Analytical HPLC was performed using an Agilent Polaris C18-A 3 μm column with 15 min linear gradient from 95:5 to 1:99 0.1% H_3PO_4/CH_3CN at a flow rate of 1 mL/min with UV detection at 215 and 254 nm. ^{1}H NMR spectra were recorded on a Varian INOVA-300 NMR spectrometer and were reported as parts per million (ppm) relative to Me_4Si as internal reference. Mass spectra data were determined on a Micromass ZMD-4000. Elemental analyses (C, H, N) were performed on a LECO CHNS-932 elemental analyzer.

Binding and Functional Assays. The agonist activity of MCR ligands was evaluated at three human MCR using a cell based assay that is specific for each subtype of MCR (MC1R, MC3R, MC4R). Each subtype of receptor was stably transfected into HEK293 cells. The MCR expressing cells were next stably transfected with a reporter system consisting of a cyclic-AMP responsive element (CRE) coupled to a luciferase reporter gene. Agonist activity was determined by assaying cells in 96-well plates. Cells were seeded at 2 × 10^4/well in 200 μL of DMEM containing 10% FBS, 1% amino acids, 0.1% L-glutamine and incubated at 37 °C plus 5% CO_2. The next day the media was removed from the cells and replaced with 100 μL of diluted compound in DMEM containing 0.01% BSA. After plates were incubated for 4 h at 37 °C and 5% CO_2, the compounds were removed and 30 μL of Steady Glo luciferase reagent (Promega E 2650) was added to each well. After 20 min at room temperature, the luciferase luminescence was determined on a Wallac TriLux reader. Responses were compared to the effect of NDP-MSH (MT-I) and expressed as a percentage of maximum activity of MT-1 (Emax). MT-1 is considered to be a full agonist at each of the three MCR subtypes.

Binding activity was measured using a cell based assay specific for each subtype of MCR (MC1R, MC3R, MC4R) stably expressed

in HEK293 cells. Cells were seeded in 96-well poly-L-lysine coated plates as described above. The media were removed from the cells the next day and replaced with 100 μL of diluted compound in DMEM, 10% SeaBlock (Pierce 37527), and 10 nM of NDP-MSH-EU (Perkin-Elmer CR339-100). Plates were incubated at room temperature for 90 min and washed four times with PBS. An amount of 100 μL of enhancement solution (Wallac 1244−105) was added, and plates were shaken for 20 min at room temperature. Europium fluorescence was detected using time-resolved fluorometry on Wallac Victor. Binding activity (calculated as IC_{50} and K_i values) was determined by measuring the displacement of a constant concentration of europium labeled NDP-α-MSH with competing unlabeled ligands.

(2*R*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(naphthalen-2-ylmethoxy)-pyrrolidine-2-carboxylic Acid (13). To a solution of Boc-*cis*-4-hydroxy-D-proline (7.25 g, 31.4 mmol) in THF (50 mL) was added sodium hydride (60% in oil, 2.76 g, 69.0 mmol) in portions at 0 °C. The reaction mixture was stirred for 45 min, and a solution of 2-(bromomethyl)naphthalene (15.6 g, 70.6 mmol) in THF (20 mL) was slowly added. The mixture was stirred at room temperature for 20 h, quenched with H_2O (100 mL), and extracted with Et_2O. The aqueous layer was acidified with 6 N HCl and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated to give a pale-yellow oil (8.1 g), which was used for the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65−7.90 (m, 4H), 7.30−7.60 (m, 3H), 4.30−4.80 (m, 3H), 4.13 (m, 1H), 3.45−3.80 (m, 2H), 2.00−2.80 (m, 2H), 1.48 (d, 9H); MS (ESI) *m*/*z* 272 (M + H).

(2*R*,4*R*)-*tert*-Butyl 2-(2-(Benzyloxycarbonylamino)ethylcarbamoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-1-carboxylate (14). To a solution of **13** (8.1 g, 21.8 mmol) in DMF (80 mL) were added *N*-1-CBZ-1,2-diaminoethane·HCl (4.75 g, 20.6 mmol), HOBt (5.06 g, 37.5 mmol), NMM (10.7 g, 105.5 mmol), and EDCI (4.44 g, 23.1 mmol) consecutively, and the reaction mixture was stirred for 3.5 h. It was quenched with aqueous NH_4Cl and extracted with EtOAc. The extract was dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed (silica gel, eluent CH_2Cl_2/acetone, 8:1) to give the amide **14** as a viscous oil (5.8 g, 34% yield over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.90 (m, 4H), 7.20−7.60 (m, 8H), 5.10−5.40 (m, 1H), 5.05 (s, 2H), 4.50−4.70 (m, 2H), 4.37 (m, 1H), 4.16 (m, 1H), 3.00−4.10 (m, 6H), 2.40−2.90 (m, 1H), 2.10−2.40 (s, 1H), 1.46 (s, 9H); MS (ESI) *m*/*z* 548 (M + H).

Benzyl 2-((2*R*,4*R*)-4-(Naphthalen-2-ylmethoxy)pyrrolidine-2-carboxamido)ethylcarbamate (15). To a solution of **14** (2.47 g, 4.52 mmol) in CH_2Cl_2 (10 mL) was added TFA (2 mL), and the reaction mixture was stirred for 3.0 h. It was then concentrated and further dried under high vacuum to give a pale-yellow oil, which was used for the next reaction without further purification (2.40 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (m, 1H), 7.70−7.85 (m, 4H), 7.25−7.54 (m, 8H), 5.05 (s, 2H), 4.66 (d, J = 12.2 Hz, 2H), 4.56 (d, J = 12.2 Hz, 1H), 3.82 (dd, J = 9.6, 3.0 Hz, 1H), 3.42 (m, 1H), 3.12−3.30 (m, 5H), 2.42−2.56 (m, 2H), 2.14 (m, 1H); MS (ESI) *m*/*z* 448 (M + H).

***N*-(*tert*-Butoxycarbonyl)-D-phenylalanyl-(4*R*)-*N*-(2-{[(benzyloxy)carbonyl]amino}ethyl)-4-(2-naphthylmethoxy)-D-prolinamide (16).** To a solution of the TFA salt of amine **15** (2.40 g, 4.39 mmol) in DMF (10 mL) were added BOC-D-Phe-OH (1.44 g, 5.43 mmol), HOBt (1.34 g, 9.92 mmol), NMM (2.30 g, 22.68 mmol), and EDCI (1.04 g, 5.43 mmol) consecutively, and the reaction mixture was stirred for 3.0 h. It was quenched with aqueous NH_4Cl solution and extracted with EtOAc. The extract was dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed (silica gel, eluent CH_2Cl_2/acetone, 15:1) to give the amide **16** as a pale-yellow oil (2.95 g, 96% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10−8.00 (m, 17 H), 5.40−5.70 (m, 2H), 4.90−5.20 (m, 2H), 4.00−4.80 (m, 4H), 2.80−4.00 (m, 9H), 2.58 (m, 1H), 1.90−2.10 (m, 1H), 1.20−1.50 (m, 9H); MS (ESI) *m*/*z* 695 (M + H).

Benzyl 2-((2*R*,4*R*)-1-((*R*)-2-Amino-3-phenylpropanoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-2-carboxamido)ethylcarbamate (17). To a solution of the BOC substrate **16** (2.95 g, 4.25 mmol) in CH_2Cl_2 (20 mL) was added TFA (5 mL), and the reaction mixture was stirred for 3.0 h. It was then concentrated, and the residue was dried under high vacuum to give amine **17** as a pale-yellow oil in a quantitative yield. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.20−7.55 (m, 13H), 5.04−5.10 (m, 2H), 4.40−4.70 (m, 3H), 4.26 (m, 1H), 3.00−4.10 (m, 9H), 1.60−2.50 (m, 2H); MS (ESI) *m*/*z* 596 (M + H).

Benzyl 2-((2*R*,4*R*)-1-((*R*)-2-((*S*)-2-Acetamido-3-(1-trityl-1*H*-imidazol-4-yl)propanamido)-3-phenylpropanoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-2-carboxamido)ethylcarbamate (18a). To a solution of amine **17** (347 mg, 0.49 mmol) in DMF (3 mL) were added Ac-His(1-Trt)-OH (258 mg, 0.59 mmol), HOBt (149 mg, 1.10 mmol), NMM (303 mg, 3.00 mmol), and EDCI (105 mg, 0.59 mmol) consecutively, and the reaction mixture was stirred for 3.0 h. It was quenched with aqueous NH_4Cl and extracted with EtOAc. The extract was dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed (silica gel, eluent CH_2Cl_2/acetone, 15:1) to give **18a** as a white solid (180 mg, 36% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.40−8.40 (m, 34H), 2.70−5.10 (m, 18H), 2.40−2.70 (m, 1H), 1.90−2.10 (m, 4H); MS (ESI) *m*/*z* 1016 (M + H).

***N*-(*tert*-Butoxycarbonyl)-1-trityl-L-histidyl-D-phenylalanyl-(4*R*)-*N*-(2-{[(benzyloxy)carbonyl]amino}ethyl)-4-(2-naphthylmethoxy)-D-prolinamide (18b). 18b** was synthesized from **17** as described for preparation of **18a** in 69% yield as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.10−8.00 (m, 34H), 4.90−5.10 (m, 2H), 4.10−4.70 (m, 4H), 2.20−4.10 (m, 14H), 1.30−1.42 (m, 9H); MS (ESI) *m*/*z* 1074 (M + H).

Benzyl 2-((2*R*,4*R*)-1-((*R*)-2-((*S*)-2-Acetamido-3-(4-hydroxyphenyl)propan-amido)-3-phenylpropanoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-2-carboxamido)ethylcarbamate (18c). 18c was synthesized from **17** as described for preparation of **18a** in 31% yield as a foam. ^{1}H NMR (300 MHz, CD_3OD) δ 7.60−7.90 (m, 4H), 6.60−7.50 (m, 17H), 5.00−5.10 (m, 2H), 4.40−4.90 (m, 4H), 2.60−4.30 (m, 12H), 1.30−2.50 (m, 5H); MS (ESI) *m*/*z* 800 (M + H).

(*S*)-*tert*-Butyl 3-((*R*)-1-((2*R*,4*R*)-2-(2-(Benzyloxycarbonylamino)ethylcarbamoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (18d). 18d was synthesized from **17** as described for preparation of **18a** in 30% yield as a foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00−8.00 (m, 21H), 4.20−5.20 (m, 10H), 2.70−4.00 (m, 10H), 1.20−2.70 (m, 11H); MS (ESI) *m*/*z* 854 (M + H).

(*S*)-*tert*-Butyl 2-((*R*)-1-((2*R*,4*R*)-2-(2-(Benzyloxycarbonylamino)ethylcarbamoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamoyl)piperidine-1-carboxylate (18e). 18e was synthesized from **17** as described for preparation of **18a** in 31% yield as a foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10−8.00 (m, 17H), 4.4 0−5.00 (m, 6H), 2.80−4.20 (m, 12H), 2.64 (m, 1H), 1.20−2.30 (m, 16H); MS (ESI) *m*/*z* 806 (M + H).

***tert*-Butyl 4-((*R*)-1-((2*R*,4*R*)-2-(2-(Benzyloxycarbonylamino)-ethylcarbamoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamoyl)piperidine-1-carboxylate (18f). 18f** was synthesized from **17** as described for preparation of **18a** in 34% yield as a foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10−8.00 (m, 12H), 4.90−5.10 (m, 2H), 4.30−4.60 (m, 3H), 3.60−4.20 (m, 5H), 3.30−3.50 (m, 1H), 2.90−3.30 (m, 8H), 1.20−2.30 (m, 16H); MS (ESI) *m*/*z* 806 (M + H).

Benzyl 2-((2*R*,4*R*)-1-((*R*)-2-((*S*)-2-Acetamido-5-amino-5-oxopentanamido)-3-phenylpropanoyl)-4-(naphthalen-2-ylmethoxy)-pyrrolidine-2-carboxamido)ethylcarbamate (18g). 18g was synthesized from **17** as described for preparation of **18a** in 37% yield as a foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80−8.00 (m, 17H), 4.20−5.20 (m, 7H), 2.70−4.10 (m, 9H), 1.20−2.70 (m, 9H); MS (ESI) *m*/*z* 765 (M + H).

(2*R*,4*R*)-1-((*R*)-2-((*S*)-2-Acetamido-3-(1-trityl-1*H*-imidazol-4-yl)propanamido)-3-phenylpropanoyl)-*N*-(2-aminoethyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-2-carboxamide (19a). To a solution of the Cbz substrate **18a** (180 mg, 0.18 mmol)) in methanol (5 mL) were added Pd/C (70 mg) and pyridine (0.02 mL, 0.26 mmol), and the reaction mixture was stirred for 3.0 h. The mixture

was then filtered through a short pad of Celite, and the filtrate was concentrated to give the title compound (140 mg, 89% yield) as a white solid, which was used for the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00−8.40 (m, 29 H), 2.80−5.10 (m, 16H), 1.80−2.50 (m, 5H); MS (ESI) *m*/*z* 882 (M + H).

***tert*-Butyl (*S*)-1-((*R*)-1-((2*R*,4R)-2-(2-Aminoethylcarbamoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylamino)-1-oxo-3-(1-trityl-1*H*-imidazol-4-yl)propan-2-ylcarbamate (19b). 19b** was synthesized from **18b** as described for **19a** in 96% yield as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.10−8.00 (m, 29H), 4.20−4.70 (m, 4H), 2.10−4.20 (m, 14H), 1.36−1.46 (m, 9H); MS (ESI) *m*/*z* 940 (M + H).

(2*R*,4*R*)-1-((*R*)-2-((*S*)-2-Acetamido-3-(4-hydroxyphenyl)propanamido)-3-phenylpropanoyl)-*N*-(2-aminoethyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-2-carboxamide (19c). 19c was synthesized from **18c** as described for **19a** in 96% yield as a foam. ^{1}H NMR (300 MHz, CD_3OD) δ 6.60−8.00 (m, 16H), 2.50−4.90 (m, 16H), 1.20−2.50 (m, 5H); MS (ESI) *m*/*z* 666 (M + H).

(*S*)-*tert*-Butyl 3-((*R*)-1-((2*R*,4*R*)-2-(2-Aminoethylcarbamoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)carboxylate (19d). 19d was synthesized from **18d** as described for **19a** in 79% yield as a foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00−8.00 (m, 16H), 4.00−5.00 (m, 6H), 2.50−4.00 (m, 12H), 1.20−2.40 (m, 11H); MS (ESI) *m*/*z* 720 (M + H).

(*S*)-*tert*-Butyl 2-((*R*)-1-((2*R*,4*R*)-2-(2-Aminoethylcarbamoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamoyl)piperidine-1-carboxylate (19e). 19e was synthesized from **18e** as described for **19a** in 90% yield as a foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10−8.00 (m, 12H), 4.30−5.00 (m, 4H), 2.80−4.40 (m, 12H), 1.10−2.50 (m, 16H); MS (ESI) *m*/*z* 672 (M + H).

***tert*-Butyl 4-((*R*)-1-((2*R*,4*R*)-2-(2-Aminoethylcarbamoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamoyl)piperidine-1-carboxylate (19f). 19f** was synthesized from **18f** as described for **19a** in 99% yield as a foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00−8.00 (m, 12H), 4.30−4.70 (m, 2H), 3.30−4.30 (m, 7H), 2.40−3.30 (m, 8H), 1.20−2.40 (m, 16H); MS (ESI) *m*/*z* 672 (M + H).

(*S*)-2-Acetamido-*N*1-((*R*)-1-((2*R*,4*R*)-2-(2-aminoethylcarbamoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)pentanediamide (19g). 19g was synthesized from **18g** as described for **19a** in 99% yield as a foam. ^{1}H NMR (300 MHz, CD_3OD) δ 7.00−8.00 (m, 12H), 2.70−4.90 (m, 14H), 1.20−2.70 (m, 9H); MS (ESI) *m*/*z* 631 (M + H).

(*Z*)-*tert*-Butyl 1-((2*R*,4*R*)-1-((*R*)-2-((*S*)-2-acetamido-3-(1-trityl-1*H*-imidazol-4-yl)propanamido)-3-phenylpropanoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-2-yl)-10,10-dimethyl-1,8-dioxo-9-oxa-2,5,7-triazaundecan-6-ylidenecarbamate (20a). To a solution of amine **19a** (140 mg, 0.31 mmol) in DMF (2 mL) were added *N*, *N*′-di-Boc-(*S*)-methylisothiourea (56 mg, 0.19 mmol), $HgCl_2$ (54 mg, 0.20 mmol), and triethylamine (49 mg, 0.48 mmol) consecutively, and the reaction mixture was stirred for 3.0 h. It was filtered through a short pad of Celite, and the filtrate was concentrated. The residue was subjected to column chromatography (silica gel, CH_2Cl_2/acetone, 15:1) to give the amide **20a** (120 mg, 69% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00−8.40 (m, 29 H), 2.90−5.10 (m, 16H), 1.40−2.60 (m, 23H); MS (ESI) *m*/*z* 1125 (M + H).

***N*-(*tert*-Butoxycarbonyl)-1-trityl-L-histidyl-D-phenylalanyl-(4*R*)-*N*-[2-({(*Z*)-[*tert*-butoxycarbonyl)amino][(*tert*-butoxycarbonyl)imino]methyl}amino)ethyl]-4-(2-naphthylmethoxy)-D-prolinamide (20b). 20b** was synthesized from **19b** as described for **20a** in 63% yield as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10−8.00 (m, 29H), 4.20−4.70 (m, 4H), 2.10−4.10 (m, 14H), 1.30−1.60 (m, 27H); MS (ESI) *m*/*z* 1182 (M + H).

(*Z*)-*tert*-Butyl 1-((2*R*,4*R*)-1-((*R*)-2-((*S*)-2-Acetamido-3-(4-hydroxyphenyl)propanamido)-3-phenylpropanoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-2-yl)-10,10-dimethyl-1,8-dioxo-9-oxa-2,5,7-triazaundecan-6-ylidenecarbamate (20c). 20c was synthesized from **19c** as described for **20a** in 84% yield as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 6.60−8.00 (m, 16H), 3.90−4.80 (m, 5H), 2.60−3.80 (m, 11H), 1.30−2.60 (m, 23H); MS (ESI) *m*/*z* 908 (M + H).

(*S*)-*tert*-Butyl 3-((*R*)-1-((2*R*,4*R*)-2-(2-((*Z*)-2,3-Bis(*tert*-butoxycarbonyl)guanidino)ethylcarbamoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (20d). 20d was synthesized from **19d** as described for **20a** in 55% yield as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00−8.00 (m, 16H), 2.80−5.00 (m, 18H), 1.20−2.70 (m, 29H); MS (ESI) *m*/*z* 962 (M + H).

(*S*)-*tert*-Butyl 2-((*R*)-1-((2*R*,4*R*)-2-(2-((*Z*)-2,3-Bis(*tert*-butoxycarbonyl)guanidino)ethylcarbamoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamoyl)piperidine-1-carboxylate (20e). 20e was synthesized from **19e** as described for **20a** in 49% yield as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10−8.00 (m, 12H), 4.30−5.00 (m, 4H), 2.50−4.30 (m, 12H), 1.20−2.40 (m, 35H); MS (ESI) *m*/*z* 914 (M + H).

***tert*-Butyl 4-((*R*)-1-((2*R*,4*R*)-2-(2-((*Z*)-2,3-Bis(*tert*-butoxycarbonyl)guanidino)ethylcarbamoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamoyl)piperidine-1-carboxylate (20f). 20f** was synthesized from **19f** as described for **20a** in 55% yield as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20−8.00 (m, 12H), 3.90−4.60 (m, 6H), 2.40−3.80 (m, 11H), 1.20−2.40 (m, 34H); MS (ESI) *m*/*z* 914 (M + H).

(*Z*)-*tert*-Butyl 1-((2*R*,4*R*)-1-((*R*)-2-((*S*)-2-Acetamido-5-amino-5-oxopentanamido)-3-phenylpropanoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-2-yl)-10,10-dimethyl-1,8-dioxo-9-oxa-2,5,7-triazaundecan-6-ylidenecarbamate (20g). 20g was synthesized from **19g** as described for **20a** in 74% yield as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.20−7.60 (m, 8H), 4.00−4.80 (m, 5H), 2.90−3.90 (m, 9H), 1.20−2.60 (m, 27H); MS (ESI) *m*/*z* 775 (M + H).

(2*R*,4*R*)-1-((*R*)-2-((*S*)-2-Acetamido-3-(1*H*-imidazol-4-yl)propanamido)-3-phenylpropanoyl)-*N*-(2-guanidinoethyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-2-carboxamide (21a). To a solution of the Boc substrate **20a** (230 mg, 0.19 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (2 mL), and the reaction mixture was stirred for 4.0 h. It was then concentrated, and the residue was subjected to reverse-phase HPLC purification to give a TFA salt of the title compound (65 mg). ^{1}H NMR (300 MHz, CD_3OD) δ 8.30−8.90 (m, 1H), 7.70−7.90 (m, 4H), 7.00−7.60 (m, 9H), 4.30−4.80 (m, 5H), 4.00−4.20 (m, 1H), 3.60−3.80 (m, 2H), 2.80−3.30 (m, 8H), 1.40−2.60 (m, 5H); MS (ESI) *m*/*z* 682 (M + H). Anal. ($C_{34}H_{41}N_9O_4 \cdot 3.2CF_3CO_2H$) C, H, N.

(2*R*,4*R*)-1-((*R*)-2-((*S*)-2-Amino-3-(1*H*-imidazol-4-yl)propanamido)-3-phenylpropanoyl)-*N*-(2-guanidinoethyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-2-carboxamide (21b). 21b was synthesized from **20b** as described for **21a**. ^{1}H NMR (300 MHz, CD_3OD) δ 8.70−8.90 (m, 1H), 7.70−7.95 (m, 4H), 7.20−7.60 (m, 9H), 4.10−4.80 (m, 6H), 3.50−3.90 (m, 2H), 2.20−3.40 (m, 10H); MS (ESI) *m*/*z* 640 (M + H). Anal. ($C_{34}H_{41}N_9O_4 \cdot 4.3CF_3CO_2H$) C, H, N.

(2*R*,4*R*)-1-((*R*)-2-((*S*)-2-Acetamido-3-(4-hydroxyphenyl)propanamido)-3-phenylpropanoyl)-*N*-(2-guanidinoethyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-2-carboxamide (21c). 21c was synthesized from **20c** as described for **21a**. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.15−7.60 (m, 10H), 6.60−6.80 (m, 2H), 4.20−4.70 (m, 5H), 4.00−4.20 (m, 1H), 3.50−3.75 (m, 2H), 2.60−3.40 (m, 8H), 1.30−2.50 (m, 5H); MS (ESI) *m*/*z* 708 (M + H). Anal. ($C_{39}H_{45}N_7O_6 \cdot 1.6CF_3CO_2H$) C, H, N.

(*S*)-*N*-((*R*)-1-((2*R*,4*R*)-2-(2-Guanidinoethylcarbamoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (21d). 21d was synthesized from **20d** as described for **21a**. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.20−7.50 (m, 12H), 4.00−4.90 (m, 8H), 2.90−3.80 (m, 10H), 1.50−2.60 (m, 2H); MS (ESI) *m*/*z* 662 (M + H). Anal. ($C_{38}H_{43}N_7O_4 \cdot 3.0CF_3CO_2H$) C, H, N.

(*S*)-*N*-((*R*)-1-((2*R*,4*R*)-2-(2-Guanidinoethylcarbamoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)piperidine-2-carboxamide (21e). 21e was synthesized from **20e** as described for **21a**. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−8.00 (m, 3H), 7.15−7.60 (m, 9H), 4.30−5.00 (m, 4H), 2.80−4.30 (m,

12H), 1.20−2.40 (m, 8H); MS (ESI) *m*/*z* 614 (M + H). Anal. ($C_{34}H_{43}N_7O_4 \cdot 3.0CF_3CO_2H$) C, H, N.

***N*-((*R*)-1-((2*R*,4*R*)-2-(2-Guanidinoethylcarbamoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)piperidine-4-carboxamide (21f). 21f** was synthesized from **20f** as described for **21a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10−8.00 (m, 12H), 4.50−4.80 (m, 4H), 4.00−4.20 (m, 1H), 2.80−3.80 (m, 12H), 1.30−2.80 (m, 7H); MS (ESI) *m*/*z* 614 (M + H). Anal. ($C_{34}H_{43}N_7O_4 \cdot 2.5CF_3CO_2H$) C, H, N.

(*S*)-2-Acetamido-*N*1-((*R*)-1-((2*R*,4*R*)-2-(2-guanidinoethylcarbamoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)pentanediamide (21g). 21g was synthesized from **20g** as described for **21a**. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.00−7.50 (m, 8H), 4.00−4.80 (m, 5H), 2.90−3.40 (m, 9H), 1.20−2.80 (m, 9H). MS (ESI) *m*/*z* 673 (M + H). Anal. ($C_{35}H_{44}N_8O_6 \cdot 1.9CF_3CO_2H$) C, H, N.

(2*S*,4*R*)-*tert*-Butyl 2-Allyl-4-hydroxypyrrolidine-1-carboxylate (23a) and (2*R*,4*R*)-*tert*-Butyl 2-Allyl-4-hydroxypyrrolidine-1-carboxylate (23b). To a solution of 4-hydroxylpyrrolidine **22** (3.0 g, 16.0 mmol) and TMEDA (6.4 mL, 40.1 mmol) was added a solution of *sec*-butyllithium (1.3 M, 50 mL) in cyclohexanes at −78 °C with stirring. The resultant orange mixture was warmed to −40 °C and stirred for 2.75 h. The mixture was then cooled to −78 °C, and allyl bromide (3.1 mL, 35.3 mmol) was added. The reaction mixture was slowly warmed to room temperature with stirring over 4.5 h. It was quenched with aqueous NH_4Cl solution and extracted with ethyl acetate (150 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The oil residue was purified by chromatography (silica gel, eluent CH_2Cl_2/acetone, 4:1) to give a mixture of **23a** and **23b** (2.1 g, 58% yield) as a clear oil. The small amount of the mixture was purified by preparative reverse-phase HPLC to give pure isomers **23a** and **23b** for characterization.

***cis*-23a.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.12 (m, 2H), 4.44 (m, 1H), 3.88 (m, 1H), 3.70 (dd, J = 11.9, 5.6 Hz, 1H), 3.32 (ddd, J = 11.9, 3.3, 1.2 Hz, 1H), 2.68 (m, 1H), 2.45 (m, 1H), 2.18 (m, 1H), 1.80−1.98 (m, 2H), 1.50 (s, 9H); MS (ESI) *m*/*z* 172 (M + H − 56).

***trans*-23b.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (m, 1H), 5.11 (m, 2H), 4.41 (m, 1H), 4.03 (m, 1H), 3.57 (m, 1H), 3.40 (dd, J = 11.9, 3.8 Hz, 1H), 2.53 (m, 1H), 2.31 (m, 1H), 2.05 (m, 1H), 1.89 (m, 1H), 1.50 (s, 9H); MS (ESI) *m*/*z* 172 (M + H − 56).

(2*S*,4*R*)-*tert*-Butyl 2-Allyl-4-(naphthalen-2-ylmethoxy)pyrrolidine-1-carboxylate (24a) and (2*R*,4*R*)-*tert*-Butyl 2-Allyl-4-(naphthalen-2-ylmethoxy)pyrrolidine-1-carboxylate (24b). To a stirred solution of **23** (2.0 g, 8.8 mmol) in DMF (10 mL) was added sodium hydride (408 mg, 11.5 mmol) in portions at 0 °C, and the reaction mixture was stirred for 20 min. A solution of 2-(bromomethyl)naphthalene (2.9 g, 13.2 mmol) in DMF (5 mL) was then added, and the resulting solution was stirred for 5.0 h at room temperature. The reaction mixture was quenched with aqueous NH_4Cl solution and extracted with ethyl acetate. The extract was dried over Na_2SO_4, filtered, and evaporated to a yellow oil. The oil residue was purified by chromatography (silica gel, eluent hexanes/EtOAc, 4:1) to give a mixture of **24a** and **24b** (2.7 g, 84%) as a clear oil.

***cis*-24a.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.90 (m, 4H), 7.45−7.60 (m, 3H), 5.83 (m, 1H), 5.14 (m, 2H), 4.71(m, 2H), 4.17 (m, 1H), 3.50−4.00 (m, 3H), 2.60−2.80 (m, 1H), 2.47 (m, 1H), 2.10 (m, 2H), 1.52 (s, 9H); MS (ESI) *m*/*z* 368 (M + H).

***trans*-24b.** MS (ESI) *m*/*z* 368 (M + H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.90 (m, 4H), 7.45−7.60 (m, 3H), 5.77 (m, 1H), 5.13 (m, 2H), 4.00−4.20 (m, 2H), 3.40−4.00 (m, 2H), 2.40−2.70 (m, 1H), 2.00−2.40 (m, 2H), 1.93 (m, 1H), 1.53 (s, 9H); MS (ESI) *m*/*z* 368 (M + H).

(2*S*,4*R*)-*tert*-Butyl 2-(3-Hydroxypropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-1-carboxylate (25) and (2*R*,4*R*)-*tert*-Butyl 2-(3-Hydroxypropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-1-carboxylate (26). To a solution of **24** (2.70 g, 7.36 mmol) in THF (15 mL) was added slowly a solution of borane−tetrahydrofuran complex in THF (1.0 M, 11.0 mL), and the reaction mixture was stirred for 0.5 h. Water (4.1 mL) was added dropwise followed by the addition of aqueous NaOH solution (3.0 M, 7.3 mL) and 33% H_2O_2 (5.0 mL). The mixture was stirred for 2 h and extracted with EtOAc (50 mL). The organic layer was then dried over Na_2SO_4, filtered, and evaporated to a yellow oil. The oil residue was purified by chromatography (silica gel, eluent hexanes/EtOAc, 1:1) to give **25** (712 mg, 25% yield) and **26** (879 mg, 33% yield) as clear oils.

***cis*-25.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.90 (m, 4H), 7.45−7.55 (m, 3H), 4.70 (s, 2H), 4.18 (m, 1H), 3.93 (m, 1H), 3.72 (m, 2H), 3.49 (dd, J = 12.2, 2.8 Hz, 1H), 1.90−2.25 (m, 3H), 1.50−1.80 (m, 3H), 1.49 (s, 9H); MS (ESI) *m*/*z* 386 (M + 1).

***trans*-26.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.90 (m, 4H), 7.40−7.55 (m, 3H), 4.72 (d, J = 11.8 Hz, 1H), 4.66 (d, J = 11.8 Hz, 1H), 4.19 (m, 1H), 4.03 (m, 1H), 3.65−3.78 (m, 3H), 3.44 (dd, J = 11.8, 4.9 Hz, 1H), 1.40−2.30 (m, 15H); MS (ESI) *m*/*z* 386 (M + 1).

(2*S*,4*R*)-*tert*-Butyl 2-(3-Azidopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-1-carboxylate (28). To a stirred solution of **25** (712 mg, 1.85 mmol) in dichloromethane (6 mL) were added triethylamine (0.39 mL, 2.77 mmol) and methanesulfonyl chloride (0.215 mL, 2.77 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 0.75 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted twice with dichloromethane (25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to give **27** as an oil that was sufficiently pure for the next reaction without further purification.

Sodium azide (361 mg, 5.50 mmol) was added to a solution of **27** (856 mg) in DMSO (7 mL), and the reaction mixture was stirred at 70 °C for 3 h. The reaction was quenched with H_2O and extracted with EtOAc (30 mL). The extract was dried over Na_2SO_4, filtered, and evaporated to an orange oil. The oil residue was purified by chromatography (silica gel, eluent hexanes/EtOAc, 3:1) to give **28** (584 mg, 78%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.90 (m, 4 H), 7.40−7.55 (m, 3H), 4.71 (s, 2H), 4.18 (m, 1H), 3.85 (m, 1H), 3.71 (dd, J = 12.0, 5.4 Hz, 1H), 3.49 (dd, J = 12.0, 3.0 Hz, 1H), 3.31 (m, 2H), 2.10−2.30 (m, 1H), 1.80−2.05 (m, 2H), 1.60−1.80 (m, 3H), 1.50 (s, 9H); MS (ESI) *m*/*z* 411 (M + 1).

(2*R*,4*R*)-*tert*-Butyl 2-(3-Azidopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-1-carboxylate (40). 40 was synthesized from **24b** as described for preparation of **28**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75−7.90 (m, 4H), 7.40−7.55 (m, 3H), 4.68 (m, 2H), 4.18 (m, 1H), 3.99 (m, 1H), 3.78 (d, J = 12.0 Hz, 1H), 3.40 (dd, J = 12.0, 4.8 Hz, 1H), 3.32 (m, 2H), 2.20−2.30 (m, 1H), 1.75−2.00 (m, 2H), 1.40−1.70 (m, 12H); MS (ESI) *m*/*z* 411 (M + 1).

(2*S*,4*R*)-2-(3-Azidopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine (29). The Boc analogue **28** (2.85 g, 6.95 mmol) was dissolved into a prepared solution of TFA/H_2O/CH_2Cl_2 (1:0.1:1, 20 mL), and the reaction mixture was stirred for 1.0 h. The mixture was concentrated to give **29** (3.0 g, 100%) as a TFA salt. The crude oil was carried forward for the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75−8.00 (m, 4H), 7.40−7.60 (m, 3H), 4.60−4.80 (m, 2H), 4.33 (m, 1H), 3.68 (m, 1H), 3.51 (m, 1H), 3.39 (m, 3H), 2.30−2.50 (m, 1H), 1.60−2.20 (m, 6H); MS (ESI) *m*/*z* 311 (M + H).

(2*R*,4*R*)-2-(3-Azidopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine (41). 41 was synthesized from **40** as described for preparation of **29**. ^{1}H NMR (300 MHz, $CDCl_3$) 7.75−7.90 (m, 4H), 7.40−7.60 (m, 3H), 4.60−4.80 (m, 2H), 4.34 (m, 1H), 3.88 (m, 1H), 3.82 (m, 2H), 3.34 (t, J = 6.3 Hz, 2H), 2.40 (dd, J = 13.6, 5.6 Hz, 1H), 1.50−2.00 (m, 5H); MS (ESI) *m*/*z* 311 (M + 1).

***tert*-Butyl (*R*)-1-((2*S*,4*R*)-2-(3-Azidopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamate (30).** To a solution of **29** (1.0 g, 2.36 mmol) in DMF (9.4 mL) were added Boc-D-Phe-OH (625 mg, 2.36 mmol), HOAt (641 mg, 4.72 mmol), NMM (0.8 mL, 7.07 mmol), and EDCI (506 mg, 2.83 mmol) consecutively, and the reaction mixture was stirred for 1.25 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (75 mL). The organic layer was washed with H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and evaporated to a brown oil. The crude oil residue was purified by column chromatography (silica gel, eluent hexanes/

EtOAc, 3:2) to give **30** (986 mg, 75%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10−7.95 (m, 12H), 4.45−4.75 (m, 3H), 3.50−4.20 (m, 3H), 2.90−3.40 (m, 5H), 1.40−2.10 (m, 15H); MS (ESI) *m*/*z* 558 (M + H).

(*R*)-2-Amino-1-((2*S*,4*R*)-2-(3-azidopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-3-phenylpropan-1-one (31). The Boc analogue **30** (986 mg, 1.77 mmol) was dissolved into a prepared solution of TFA/CH_2Cl_2/H_2O (1:1:0.1, 10 mL), and the reaction mixture was stirred for 1.0 h. It was then concentrated to give a TFA salt of **31** (1.0 g, 99%) as a clear oil, which was sufficiently pure for the next reaction without purification. ^{1}H NMR (300 MHz, $CDCl_3$) 7.10−7.95 (m, 12H), 4.30−4.70 (m, 3H), 3.50−4.20 (m, 3H), 3.00−3.50 (m, 5H), 1.40−2.10 (m, 6H); MS (ESI) *m*/*z* 458 (M + H).

(*S*)-2-Acetamido-*N*-((*R*)-1-((2*S*,4*R*)-2-(3-azidopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-3-(4-hydroxyphenyl)propanamide (32b). To a solution of amine **31** (1.5 g, 2.63 mmol) in DMF (8.8 mL) were added Ac-Tyr-OH (586 mg, 2.63 mmol), HOBt (709 mg, 5.25 mmol), NMM (0.9 mL, 7.88 mmol), and EDCI (564 mg, 3.15 mmol) consecutively, and the reaction mixture was stirred for 1.0 h. The reaction was quenched with aqueous NH_4Cl and extracted twice with EtOAc (75 mL). The combined organic layers were washed with H_2O (80 mL) and brine (80 mL), dried over Na_2SO_4, filtered, and evaporated to an oil. The oil residue was purified by column chromatography (silica gel, eluent acetone/CH_2Cl_2, 3:2) to give **32b** (1.03 g, 60% yield) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) 7.70−8.00 (m, 4H), 7.00−7.60 (m, 10H), 6.74 (m, 2H), 4.40−4.80 (m, 4H), 3.80−4.20 (m, 2H), 2.70−3.40 (m, 8H), 1.75−2.10 (m, 6H), 1.40−1.55 (m, 3H); MS (ESI) *m*/*z* 663 (M + H).

(*S*)-2-Acetamido-*N*-((*R*)-1-((2*S*,4*R*)-2-(3-azidopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-3-(1-trityl-1*H*-imidazol-4-yl)propanamide (32a). 32a was synthesized from **31** and Ac-His-(1-Trt)-OH as described for **32b**. ^{1}H NMR (300 MHz, CD_3OD) δ 7.00−8.00 (m, 29H), 4.40−4.80 (m, 4H), 3.80−4.20 (m, 3H), 2.70−3.50 (m, 8H), 1.70−2.10 (m, 6H), 1.30−1.55 (m, 3H); MS (ESI) *m*/*z* 901 (M + Na).

(*S*)-2-Acetamido-*N*1-((*R*)-1-((2*S*,4*R*)-2-(3-azidopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl-)pentanediamide (32c). 32c was synthesized from **31** and Ac-Gln-OH in 60% yield as a foam. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.00−7.60 (m, 8H), 4.30−4.80 (m, 4H), 3.85−4.20 (m, 2H), 2.90−3.60 (m, 6H), 1.70−2.20 (m, 13H); MS (ESI) *m*/*z* 628 (M + H).

(*S*)-*tert*-Butyl 3-((*R*)-1-((2*S*,4*R*)-2-(3-Azidopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (32d). 32d was synthesized from **31** and BOC−Tic-OH as described for **32b** in 64% yield as a foam. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.00−7.60 (m, 12H), 4.40−4.80 (m, 5H), 2.80−4.20 (m, 11H), 1.20−2.00 (m, 15H); MS (ESI) *m*/*z* 717 (M + H).

(*S*)-*tert*-Butyl 2-((*R*)-1-((2*S*,4*R*)-2-(3-Azidopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamoyl)piperidine-1-carboxylate (32e). 32e was synthesized from **31** and BOC-Pip-OH as described for **32b** in 75% yield as a foam. ^{1}H NMR (300 MHz, CD_3OD) δ 7.75−7.90 (m, 4H), 7.40−7.55 (m, 3H), 7.00−7.30 (m, 5H), 4.50−4.90 (m, 4H), 3.45−4.25 (m, 4H), 2.90−3.40 (m, 6H), 1.10−2.20 (m, 21H); MS (ESI) *m*/*z* 669 (M + H).

(*S*)-*tert*-Butyl 2-((*R*)-1-((2*S*,4*R*)-2-(3-Azidopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (32f). 32f was synthesized from **31** and BOC-proline as described for **32b** in 72% yield as a foam. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.40−7.55 (m, 3H), 7.00−7.30 (m, 5H), 4.56 (m, 2H), 3.80−4.30 (m, 3H), 2.80−3.60 (m, 9H), 1.10−2.20 (m, 19H); MS (ESI) *m*/*z* 655 (M + H).

(*S*)-2-Acetamido-*N*-((*R*)-1-((2*S*,4*R*)-2-(3-azidopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-3-phenylpropanamide (32g). 32g was synthesized from **31** and Ac-Tyr-OH as described for **32b** in 62% yield as a foam. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.00−7.60 (m, 13H), 4.40−4.90 (m, 4H), 3.80−4.20 (m, 2H), 2.70−3.40 (m, 8H), 1.70−2.10 (m, 6H), 1.35−1.55 (m, 3H); MS (ESI) *m*/*z* 647 (M + H).

***N*-((*R*)-1-((2*S*,4*R*)-2-(3-Azidopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-3-phenylpropanamide (32h). 32h** was synthesized from **31** and 3-phenylpropanoic acid as described for **32b** in 85% yield as a foam. ^{1}H NMR (300 MHz, CD_3OD) δ 7.75−7.90 (m, 4H), 7.40−7.60 (m, 3H), 7.00−7.30 (m, 10H), 4.40−4.80 (m, 3H), 3.80−4.20 (m, 2H), 2.80−3.60 (m, 8H), 2.53 (q, J = 7.8 Hz, 2H), 1.70−2.10 (m, 3H), 1.30−1.55 (m, 3H); MS (ESI) *m*/*z* 590 (M + H);

***N*-((*R*)-1-((2*S*,4*R*)-2-(3-Azidopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)acetamide (32i). 32i** was synthesized from **31** and acetic acid in 88% yield as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10−8.00 (m, 12H), 4.80−5.10 (m, 1H), 4.50−4.70 (m, 2H), 2.80−4.20 (m, 8H), 1.40−2.30 (m, 9H); MS (ESI) *m*/*z* 500 (M + H).

(*S*)-2-Acetamido-*N*-((*R*)-1-((2S,4*R*)-2-(3-aminopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-3-(4-hydroxyphenyl)propanamide (33b). A solution of **32b** (1.03 g, 1.56 mmol) and pyridine (0.07 mL, 0.78 mmol) in methanol (5.0 mL) was purged with argon, and palladium on carbon (10% by wt, 500 mg) was then added. This reaction mixture was stirred at a hydrogen atmosphere for 5.0 h. It was filtered through a short pad of Celite, and the filtrate was concentrated under the reduced pressure to yield **33b** (871 mg, 88%) as a white solid, which was used directly for the next reaction without further purification. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−8.00 (m, 4H), 7.40−7.60 (m, 3H), 7.00−7.30 (m, 7H), 6.74 (m, 2H), 4.50−4.80 (m, 4H), 3.85−4.20 (m, 2H), 2.55−3.40 (m, 8H), 1.75−2.10 (m, 6H), 1.40−1.55 (m, 3H); MS (ESI) *m*/*z* 637 (M + 1).

(*S*)-2-Acetamido-*N*-((*R*)-1-((2S,4*R*)-2-(3-aminopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-3-(1-trityl-1*H*-imidazol-4-yl)propanamide (33a). 33a was synthesized from **32a** as described for **33b** in 97% yield as a foam. ^{1}H NMR (300 MHz, CD_3OD) δ 7.00−8.00 (m, 29H), 4.50−4.80 (m, 4H), 3.90−4.20 (m, 2H), 2.60−3.50 (m, 8H), 1.70−2.10 (m, 6H), 1.30−1.60 (m, 3H); MS (ESI) *m*/*z* 853 (M + H).

(*S*)-2-Acetamido-*N*1-((*R*)-1-((2S,4*R*)-2-(3-aminopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl-)pentanediamide (33c). 33c was synthesized from **32c** as described from **33b** in 98% yield as a foam. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.00−7.60 (m, 8H), 4.35−4.80 (m, 4H), 3.90−4.20 (m, 2H), 2.60−3.80 (m, 6H), 1.40−2.40 (m, 13H); MS (ESI) *m*/*z* 602 (M + H).

(*S*)-*tert*-Butyl 3-((*R*)-1-((2S,4*R*)-2-(3-Aminopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (33d). 33d was synthesized from **32d** as described for **33b** in 95% yield as a foam. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.00−7.60 (m, 12H), 4.40−4.90 (m, 5H), 2.60−4.20 (m, 11H), 1.20−2.00 (m, 15H); MS (ESI) *m*/*z* 691 (M + H).

(*S*)-*tert*-Butyl 2-((*R*)-1-((2S,4*R*)-2-(3-Aminopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamoyl)piperidine-1-carboxylate (33e). 33e was synthesized from **32e** as described for **33b** in 97% yield as a foam. ^{1}H NMR (300 MHz, CD_3OD) δ 7.75−7.90 (m, 4H), 7.40−7.55 (m, 3H), 7.10−7.35 (m, 5H), 4.50−5.00 (m, 4H), 3.80−4.30 (m, 3H), 2.90−3.60 (m, 7H), 1.10−2.20 (m, 21H); MS (ESI) *m*/*z* 643 (M + H).

(*S*)-*tert*-Butyl 2-((*R*)-1-((2S,4*R*)-2-(3-Aminopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (33f). 33f was synthesized from **32f** as described for **33b** in 96% yield as a foam. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.40−7.55 (m, 3H), 7.10−7.35 (m, 5H), 4.58 (m, 2H), 3.80−4.30 (m, 3H), 3.10−3.70 (m, 5H), 2.50−3.10 (m, 4H), 1.60−2.30 (m, 7H), 1.20−1.60 (m, 12H); MS (ESI) *m*/*z* 629 (M + H).

(*S*)-2-Acetamido-*N*-((*R*)-1-((2S,4*R*)-2-(3-aminopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-3-phenylpropanamide (33g). 33g was synthesized from **32g** as described for **33b** in 99% yield as a foam. ^{1}H NMR (300 MHz,

CD_3OD) δ 7.70−7.90 (m, 4H), 7.00−7.60 (m, 13H), 4.40−5.00 (m, 4H), 3.80−4.20 (m, 2H), 2.60−3.60 (m, 8H), 1.30−2.10 (m, 9H); MS (ESI) *m*/*z* 621 (M + H).

***N*-((*R*)-1-((2*S*,4*R*)-2-(3-Aminopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-3-phenylpropanamide (33h). 33h** was synthesized from **32h** as described for **33b** in 96% yield as a foam. ^{1}H NMR (300 MHz, CD_3OD) δ 7.75−7.90 (m, 4H), 7.00−7.60 (m, 13H), 4.40−4.80 (m, 3H), 3.80−4.20 (m, 2H), 2.80−3.60 (m, 6H), 2.40−2.70 (m, 4H), 1.70−2.10 (m, 3H), 1.30−1.50 (m, 3H); MS (ESI) *m*/*z* 564 (M + H).

***N*-((*R*)-1-((2*S*,4*R*)-2-(3-Aminopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)acetamide (33i). 33i** was synthesized from **32i** as described for **33b** in 91% yield as a foam. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.00−7.60 (m, 8H), 4.40−5.00 (m, 3H), 2.70−4.30 (m, 8H), 1.20−2.20 (m, 9H); MS (ESI) *m*/*z* 474 (M + H).

(*Z*)-*tert*-Butyl (3-((2*S*,4*R*)-1-((*R*)-2-((*S*)-2-Acetamido-3-(4-hydroxyphenyl)propanamido)-3-phenylpropanoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-2-yl)propylamino)(*tert*-butoxycarbonylamino)methylenecarbamate (34b). To a solution of amine **33b** (125 mg, 0.20 mmol) in DMF (2.0 mL) were added 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (57 mg, 0.2 mmol), triethylamine (0.1 mL, 0.59 mmol), and mercury(II) chloride (64 mg, 0.24 mmol), and the reaction mixture was stirred at 0 °C for 1.0 h. It was then diluted with EtOAc and filtered through a short pad of Celite. The filtrate was concentrated under the reduced pressure to give an oil residue, which was purified by column chromatography (silica gel, eluent CH_2Cl_2/methanol,14:1) to give **34b** (170 mg, 98%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.00−7.60 (m, 10H), 6.74 (m, 2H), 4.45−4.80 (m, 4H), 3.85−4.20 (m, 2H), 2.70−3.60 (m, 8H), 1.40−2.00 (m, 18H); MS (ESI) *m*/*z* 879 (M + H).

(*Z*)-*tert*-Butyl (3-((2*S*,4*R*)-1-((*R*)-2-((*S*)-2-Acetamido-3-(1-trityl-1*H*-imidazol-4-yl)propanamido)-3-phenylpropanoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-2-yl)propylamino)(*tert*-butoxycarbonylamino)methylenecarbamate (34a). 34a was synthesized from **33a** as described for **34b** in 65% yield as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−8.00 (m, 4H), 7.00−7.60 (m, 25H), 4.50−4.80 (m, 4H), 3.90−4.30 (m, 2H), 2.80−3.60 (m, 8H), 1.80−2.10 (m, 6H), 1.30−1.60 (m, 12H); MS (ESI) *m*/*z* 1095 (M + H).

(*Z*)-*tert*-Butyl (3-((2*S*,4*R*)-1-((*R*)-2-((*S*)-2-Acetamido-5-amino-5-oxopentanamido)-3-phenylpropanoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-2-yl)propylamino)(*tert*-butoxycarbonylamino)-methylenecarbamate (34c). 34c was synthesized from **33c** as described for **34b** in 53% yield as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.35−7.60 (m, 3H), 7.10−7.30 (m, 5H), 4.30−4.80 (m, 4H), 3.90−4.20 (m, 2H), 2.60−3.80 (m, 7H), 1.75−2.49 (m, 14H), 1.40−1.70 (m, 17H); MS (ESI) *m*/*z* 866 (M + Na).

(*S*)-*tert*-Butyl 3-((*R*)-1-((2*S*,4*R*)-2-(3-((*E*)-2,3-Bis(*tert*-butoxycarbonyl)guanidino)propyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (34d). 34d was synthesized from **33d** as described for **34b** in 41% yield as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.00−7.60 (m, 12H), 4.40−4.90 (m, 5H), 2.80−4.20 (m, 11H), 1.20−2.00 (m, 33H); MS (ESI) *m*/*z* 933 (M + H).

(*S*)-*tert*-Butyl 2-((*R*)-1-((2*S*,4*R*)-2-(3-((*Z*)-2,3-Bis(*tert*-butoxycarbonyl)guanidino)propyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamoyl)piperidine-1-carboxylate (34e). 34e was synthesized from **33e** as described for **34b** in 51% yield as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.75−8.00 (m, 4H), 7.40−7.60 (m, 3H), 7.10−7.35 (m, 5H), 4.50−5.00 (m, 4H), 3.80−4.30 (m, 3H), 2.90−3.60 (m, 7H), 1.10−2.20 (m, 39H); MS (ESI) *m*/*z* 886 (M + H).

(*S*)-*tert*-Butyl 2-((*R*)-1-((2*S*,4*R*)-2-(3-((*Z*)-2,3-Bis(*tert*-butoxycarbonyl)guanidino)propyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (34f). 34f was synthesized from **33f** as described for **34b** in 62% yield as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−8.00 (m, 4H), 7.10−7.60 (m, 8H), 4.50−5.00 (m, 3H), 3.80−4.30 (m, 3H), 2.80−3.60 (m, 9H), 1.20−2.30 (m, 37H); MS (ESI) *m*/*z* 871 (M + H).

(*Z*)-*tert*-Butyl (3-((2*S*,4*R*)-1-((*R*)-2-((*S*)-2-Acetamido-3-phenylpropanamido)-3-phenylpropanoyl)-4-(naphthalen-2-ylmethoxy)-pyrrolidin-2-yl)propylamino)(*tert*-butoxycarbonylamino)methylenecarbamate (34g). 34g was synthesized from **33g** as described for **34b** in 76% yield as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.00−7.60 (m, 13H), 4.50−5.00 (m, 4H), 3.80−4.20 (m, 2H), 2.70−3.70 (m, 8H), 1.40−2.10 (m, 27H); MS (ESI) *m*/*z* 863 (M + H).

(*Z*)-*tert*-Butyl (*tert*-Butoxycarbonylamino)(3-((2*S*,4*R*)-4-(naphthalen-2-ylmethoxy)-1-((*R*)-3-phenyl-2-(3-phenylpropanamido)-propanoyl)pyrrolidin-2-yl)propylamino)methylenecarbamate (34h). 34h was synthesized from **33h** as described for **34b** in 64% yield as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.75−7.90 (m, 4H), 7.35−7.60 (m, 3H), 7.00−7.30 (m, 10H), 4.50−4.90 (m, 3H), 3.80−4.20 (m, 2H), 2.80−3.60 (m, 8H), 2.55 (q, J = 7.60 Hz, 2H), 1.70−2.10 (m, 3H), 1.30−1.60 (m, 21H); MS (ESI) *m*/*z* 807 (M + H).

(*Z*)-*tert*-Butyl (3-((2*S*,4*R*)-1-((*R*)-2-Acetamido-3-phenylpropanoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-2-yl)propylamino)(*tert*-butoxycarbonylamino)methylenecarbamate (34i). 34i was synthesized from **33i** as described for **34b** in 59% yield as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−8.00 (m, 4H), 7.10−7.60 (m, 8H), 4.40−5.00 (m, 3H), 3.80−4.30 (m, 2H), 2.80−3.70 (m, 6H), 1.20−2.20 (m, 27H); MS (ESI) *m*/*z* 716 (M + H).

(*S*)-2-Acetamido-*N*-((*R*)-1-((2*S*,4*R*)-2-(3-guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-3-(4-hydroxyphenyl)propanamide (35b). The Boc analogue **34b** (170 mg, 0.19 mmol) was dissolved into a prepared solution of TFA/CH_2Cl_2/anisole (40:55:5, 3.0 mL), and the reaction mixture was stirred for 3.0 h. It was then concentrated, and the residue was purified by reverse-phase preparative HPLC to give **35b** (57 mg, 44% yield) as a white powder. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.40−7.60 (m, 3H), 7.00−7.30 (m, 7H), 6.74 (m, 2H), 4.50−4.80 (m, 4H), 3.85−4.20 (m, 2H), 2.70−3.30(m, 8H), 1.40−2.10 (m, 9H); MS (ESI) *m*/*z* 679 (M + H). Anal. ($C_{39}H_{46}N_6O_5 \cdot 2.5CF_3CO_2H$) C, H, N.

(*S*)-2-Acetamido-*N*-((*R*)-1-((2*S*,4*R*)-2-(3-guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-3-(1*H*-imidazol-4-yl)propanamide (35a). 35a was synthesized from **34a** as described for **35b** as a TFA salt. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−8.00 (m, 4H), 7.40−7.60 (m, 3H), 7.10−7.35 (m, 7H), 4.50−4.90 (m, 4H), 3.90−4.30 (m, 3H), 2.90−3.60 (m, 8H), 1.80−2.20 (m, 6H), 1.40−1.60 (m, 3H); MS (ESI) *m*/*z* 653 (M + H). Anal. ($C_{36}H_{44}N_8O_4 \cdot 3.3CF_3CO_2H$) C, H, N.

(*S*)-2-Acetamido-*N*1-((*R*)-1-((2*S*,4*R*)-2-(3-guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)pentanediamide (35c). 35c was synthesized from **34c** as described for **35b** as a TFA salt (white solid). ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.10−7.60 (m, 8H), 4.30−4.80 (m, 4H), 3.90−4.25 (m, 2H), 2.90−3.80 (m, 6H), 1.75−2.40 (m, 10H), 1.40−1.60 (m, 3H); MS (ESI) *m*/*z* 644 (M + H). Anal. ($C_{35}H_{45}N_7O_5 \cdot 2.8CF_3CO_2H$) C, H, N.

(*S*)-*N*-((*R*)-1-((2*S*,4*R*)-2-(3-Guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (35d). 35d was synthesized from **34d** as described for **35b** as a TFA salt. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.10−7.60 (m, 12H), 4.92 (m, 2H), 4.68 (m, 2H), 4.40 (m, 2H), 4.00−4.30 (m, 4H), 2.90−3.50 (m, 6H), 1.80−2.20 (m, 3H), 1.58 (m, 3H); MS (ESI) *m*/*z* 633 (M + H). Anal. ($C_{38}H_{44}N_6O_3 \cdot 2.5CF_3CO_2H$) C, H, N.

(*S*)-*N*-((*R*)-1-((2*S*,4*R*)-2-(3-guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)piperidine-2-carboxamide (35e). 35e was synthesized from **34e** as described for **35b** as a TFA salt (white solid). ^{1}H NMR (300 MHz, CD_3OD) δ 7.75−8.00 (m, 4H), 7.10−7.60 (m, 8H), 4.50−5.00 (m, 4H), 3.90−4.30 (m, 2H), 2.90−3.85 (m, 8H), 1.30−2.20 (m, 12H); MS (ESI) *m*/*z* 886 (M + H). Anal. ($C_{34}H_{44}N_6O_3 \cdot 2.8CF_3CO_2H$) C, H, N.

(*S*)-*N*-((*R*)-1-((2*S*,4*R*)-2-(3-Guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)pyrrolidine-2-carboxamide (35f). 35f was synthesized from **34f** as described for **35b** as a TFA salt (white solid). ^{1}H NMR (300 MHz, CD_3OD) δ 7.75−8.00 (m, 4H), 7.10−7.60 (m, 8H), 4.63 (m, 2H), 4.30 (m, 2H), 2.90−4.20 (m, 10H), 2.36 (m, 1H), 1.20−2.20 (m, 9H); MS (ESI) *m*/*z* 571 (M + H). Anal. ($C_{33}H_{42}N_6O_3 \cdot 2.7CF_3CO_2H$) C, H, N.

(*S*)-2-Acetamido-*N*-((*R*)-1-((2*S*,4*R*)-2-(3-guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-3-phenylpropanamide (35g). 35g was synthesized from **34g** as described for **35b** as a TFA salt. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−8.00 (m, 4H), 7.00−7.60 (m, 13H), 4.50−5.00 (m, 4H), 3.80−4.20 (m, 2H), 2.70−3.70 (m, 8H), 1.60−2.10 (m, 6H), 1.48 (m, 3H); MS (ESI) *m*/*z* 663 (M + H). Anal. ($C_{39}H_{46}N_6O_4 \cdot 2.7CF_3CO_2H$) C, H, N.

***N*-((*R*)-1-((2*S*,4*R*)-2-(3-Guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-3-phenylpropanamide (35h). 35h** was synthesized from **34h** as described for **35b** as a TFA salt (white solid). ^{1}H NMR (300 MHz, CD_3OD) δ 7.75−7.90 (m, 4H), 7.10−7.60 (m, 13H), 4.50−4.90 (m, 3H), 3.80−4.20 (m, 2H), 2.80−3.60 (m, 8H), 2.56 (m, 2H),), 1.70−2.10 (m, 3H), 1.30−1.60 (m, 3H); MS (ESI) *m*/*z* 606 (M + H). Anal. ($C_{37}H_{43}N_5O_3 \cdot 1.3CF_3CO_2H$) C, H, N.

***N*-((*R*)-1-((2*S*,4*R*)-2-(3-Guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)acetamide (35i). 35i** was synthesized from **34i** as described for **35b** as a TFA salt (white solid). ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−8.00 (m, 4H), 7.10−7.60 (m, 8H), 4.40−5.00 (m, 3H), 3.90−4.30 (m, 2H), 2.90−3.70 (m, 6H), 1.20−2.20 (m, 9H); MS (ESI) *m*/*z* 516 (M + H). Anal. ($C_{30}H_{37}N_5O_3 \cdot 1.6CF_3CO_2H$) C, H, N.

***tert*-Butyl (*R*)-1-((2*S*,4*R*)-2-(3-Aminopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamate (36). 36** was synthesized from **30** as described for **33b** in 94% yield as a foam. ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.00−7.60 (m, 8H), 3.20−4.90 (m, 6H), 2.60−3.20 (m, 5H), 1.10−2.10 (m, 15H); MS (ESI) *m*/*z* 532 (M + H).

Di-*tert*-butyl[(*Z*)-({3-[(2*S*,4*R*)-1-[*N*-(*tert*-butoxycarbonyl)-D-phenylalanyl]-4-(2-naphthylmethoxy)pyrrolidin-2-yl]propyl}-amino)methylylidene]biscarbamate (37). 37 was synthesized from **36** as described for **34b** in 30% yield as a white solid. ^{1}H NMR (300 MHz, CD_3OD) 7.70−8.00 (m, 4H), 7.10−7.60 (m, 8H), 4.40−5.00 (m, 3H), 3.80−4.30 (m, 2H), 2.80−3.70 (m, 6H), 1.20−2.20 (m, 33H); MS (ESI) *m*/*z* 774 (M + H).

1-(3-((2*S*,4*R*)-1-((*R*)-2-Amino-3-phenylpropanoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-2-yl)propyl)guanidine (38). 38 was synthesized from **37** as described for **35b** as a TFA salt (white solid). ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−8.00 (m, 4H), 7.10−7.60 (m, 8H), 4.00−4.80 (m, 4H), 2.70−3.80 (m, 7H), 1.20−2.20 (m, 6H); MS (ESI) *m*/*z* 474 (M + H). Anal. ($C_{28}H_{35}N_5O_2 \cdot 2.6CF_3CO_2H$) C, H, N.

(*S*)-2-Acetamido-*N*-((*R*)-1-((2*R*,4*R*)-2-(3-guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-3-(4-hydroxyphenyl)propanamide (42a). White solid; ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.30−7.50 (m, 3H), 7.00−7.30 (m, 5H), 6.95 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 4.10−4.80 (m, 6H), 2.90−3.70 (m, 5H), 2.50−2.90 (m, 3H), 1.60−2.20 (m, 6H), 1.30−1.60 (m, 3H); MS (ESI) *m*/*z* 679 (M + 1). Anal. ($C_{39}H_{46}N_6O_5 \cdot 2.5CF_3CO_2H$) C, H, N.

(*S*)-2-Acetamido-*N*-((*R*)-1-((2*R*,4*R*)-2-(3-guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-3-(1H-imidazol-4-yl)propanamide (42b). White solid; ^{1}H NMR (300 MHz, CD_3OD) δ 7.00−8.90 (m, 14H), 4.10−4.90 (m, 6H), 2.80−3.80 (m, 8H), 1.80−2.30 (m, 6H), 1.20−1.70 (m, 3H); MS (ESI) *m*/*z* 653 (M + 1). Anal. ($C_{36}H_{44}N_8O_4 \cdot 3.2CF_3CO_2H$) C, H, N.

(*S*)-*N*-((*R*)-1-((2*R*,4*R*)-2-(3-Guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (42c). White solid; ^{1}H NMR (300 MHz, CD_3OD) δ 7.80−7.90 (m, 4H), 7.42−7.54 (m, 3H), 7.10−7.40 (m, 9H), 4.60−5.00 (m, 3H), 4.10−4.50 (m, 5H), 2.60−3.80 (m, 8H), 1.80−2.40 (m, 3H), 1.30−1.70 (m, 3H); MS (ESI) *m*/*z* 633 (M + H). Anal. ($C_{38}H_{44}N_6O_3 \cdot 3.0CF_3CO_2H$) C, H, N.

(*S*)-*N*-((*R*)-1-((2*R*,4*R*)-2-(3-Guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)piperidine-2-carboxamide (42d). White solid; ^{1}H NMR (300 MHz, CD_3OD) δ 7.80−8.00 (m, 4H), 7.40−7.60 (m, 3H), 7.10−7.40 (m, 5H), 2.80−5.00 (m, 14H), 1.20−2.30 (m, 12H); MS (ESI) *m*/*z* 585 (M + H). Anal. ($C_{34}H_{44}N_6O_3 \cdot 2.4CF_3CO_2H$) C, H, N.

(*S*)-2-Acetamido-*N*1-((*R*)-1-((2*R*,4*R*)-2-(3-guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)pentanediamide (42e). White solid; ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.10−7.60 (m, 8H), 4.10−4.90 (m, 6H), 2.80−3.80 (m, 6H), 1.20−2.20 (m, 13H); MS (ESI) *m*/*z* 644 (M + H). Anal. ($C_{35}H_{45}N_7O_5 \cdot 1.4CF_3CO_2H$) C, H, N.

(2*R*,4*S*)-*tert*-Butyl 2-allyl-4-hydroxypyrrolidine-1-carboxylate (49a) and (2*S*,4*S*)-*tert*-Butyl 2-allyl-4-hydroxypyrrolidine-1-carboxylate (49b). To a solution of 3-(*S*)-hydroxypyrrolidine-1-carboxylic acid *tert*-butyl ester (**48**) (3.0 g, 16.0 mmol) in THF (50 mL) were added TMEDA (6.4 mL, 40.1 mmol) and a solution of *sec*-butyllithium in THF (1.3 M, 31 mL) at −78 °C, and the resultant orange mixture was warmed to −40 °C and stirred at that temperature for 2.75 h. The mixture was then cooled to −78 °C, and allyl bromide (3.1 mL, 35.3 mmol) was added. This mixture was stirred and warmed to 0 °C over 4.5 h. The reaction was quenched with aqueous NH_4Cl solution and extracted with ethyl acetate (150 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated to a brown oil. The oil residue was purified by column chromatography (silica gel, eluent CH_2Cl_2/acetone, 4:1) to give a mixture of **49a** and **49b** (2.2 g, 61%) as a clear oil. A small amount of the mixture was purified using reverse-phase preparative HPLC to give pure **49a** and **49b** for characterization.

***cis*-49a.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.12 (m, 2H), 4.44 (m, 1H), 3.88 (m, 1H), 3.70 (dd, J = 11.70, 5.70 Hz, 1H), 3.32 (ddd, J = 12.0, 3.3, 1.2 Hz, 1H), 2.68 (m, 1H), 2.45 (m, 1H), 2.10−2.30 (m, 2H), 1.84 (m, 1H), 1.50 (m, 9H); MS (ESI) *m*/*z* 172 (M + H − 56).

***trans*-49b.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (m, 1H), 5.11 (m, 2H), 4.40 (m, 1H), 4.02 (m, 1H), 3.57 (m, 2H), 3.40 (dd, J = 11.8, 3.8 Hz, 1H), 2.53 (m, 1H), 2.31 (m, 1H), 2.04 (m, 1H), 1.89 (m, 1H), 1.49 (m, 9H); MS (ESI) *m*/*z* 172 (M + H − 56).

(2*R*,4*S*)-*tert*-Butyl 2-Allyl-4-(naphthalen-2-ylmethoxy)pyrrolidine-1-carboxylate (50a) and (2*S*,4*S*)-*tert*-Butyl 2-Allyl-4-(naphthalen-2-ylmethoxy)pyrrolidine-1-carboxylate (50b). Sodium hydride (458 mg, 11.45 mmol) was added in portions to a stirred solution of **49** (2.0 g, 8.81 mmol) in DMF (18 mL) at 0 °C. After the reaction mixture was stirred for 20 min, 2-(bromomethyl)-naphthalene (2.9 g, 13.22 mmol) in DMF (5 mL) was added, and the resulting solution was stirred overnight at room temperature. The reaction was quenched with aqueous NH_4Cl solution and extracted twice with ethyl acetate. The extract was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by chromatography (silica gel, eluent hexanes/EtOAc, 6:1) to give **50** (2.7 g, 84% yield) as a clear oil. A small amount of the mixture was purified using reverse-phase preparative HPLC to give pure **50a** and **50b** for characterization.

***cis*-50a.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.90 (m, 4H), 7.40−7.60 (m, 3H), 5.81 (m, 1H), 5.11 (m, 2H) 4.69 (m, 2H), 4.16 (m, 1H), 3.89 (m, 1H), 3.70 (m, 1H), 3.50 (m, 1H), 2.66 (m, 1H), 2.43 (m, 1H), 2.07 (m, 2H), 1.49 (m, 9H); MS (ESI) *m*/*z* 368 (M + H).

***trans*-50b.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75−7.90 (m, 4H), 7.40−7.60 (m, 3H), 5.75 (m, 1H), 5.10 (m, 2H), 4.69 (m, 2H), 3.40−4.20 (m, 4H), 2.10−2.70 (m, 3H), 1.92 (m, 1H), 1.51 (m, 9H); MS (ESI) *m*/*z* 368 (M + H).

(2*S*,4*S*)-*tert*-Butyl 2-(3-Hydroxypropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-1-carboxylate (51) and (2*R*,4*S*)-*tert*-Butyl 2-(3-Hydroxypropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-1-carboxylate (52). To a solution of **50** (2.7 g, 7.36 mmol) in THF (15 mL) was slowly added 1.0 M solution of borane−tetrahydrofuran complex in THF (11.0 mL), and the reaction mixture was

stirred for 0.5 h. Water (4.1 mL) was then added dropwise followed by the addition of aqueous NaOH (3.0 M, 7.3 mL) and 33% H_2O_2 (5.0 mL). The mixture was stirred for 2.0 h and extracted with EtOAc (150 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography (silica gel, eluent hexanes/EtOAc, 1:1) to afford **51** (1.1 g) and **52** (1.0 g) as clear oils.

***trans*-51.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.90 (m, 4H), 7.40−7.60 (m, 3H), 4.60−4.80 (m, 2H), 4.19 (m, 1H), 4.05 (m, 1H), 3.60−3.95 (m, 3H), 3.46 (m, 1H), 3.09 (m, 1H), 2.25 (m, 1H), 1.80−2.00 (m, 2H), 1.40−1.70 (m, 12H); MS (ESI) *m*/*z* 386 (M + 1).

***cis*-52.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.90 (m, 4H), 7.45−7.55 (m, 3H), 4.70 (s, 2H), 4.17 (m, 1H), 3.92 (m, 1H), 3.70 (m, 2H), 3.49 (dd, J = 12.0, 3.3 Hz, 1H), 1.90−2.25 (m, 3H), 1.40−1.80 (m, 12H); MS (ESI) *m*/*z* 386 (M + 1).

(2*S*,4*S*)-*tert*-Butyl 2-(3-Azidopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-1-carboxylate (54). 54 was synthesized from **51** as described for **28** in 83% yield as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75−7.90 (m, 4H), 7.45−7.55 (m, 3H), 4.69 (m, 2H), 4.18 (m, 1H), 3.40 (m, 1H), 3.77 (m, 1H), 3.25−3.50 (m, 2H), 2.25 (m, 1H), 1.40−2.00 (m, 14H); MS (ESI) *m*/*z* 433 (M + Na).

(2*R*,4*S*)-*tert*-Butyl 2-(3-Azidopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine-1-carboxylate (58). 58 was synthesized from **52** as described for **28** in 78% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−8.00 (m, 4H), 7.40−7.70 (m, 3H), 4.70 (s, 2H), 4.18 (m, 1H), 3.87 (m, 1H), 3.70 (m, 1H), 3.49 (m, 1H), 3.30 (m, 2H), 1.90−2.30 (m, 3H), 1.20−1.90 (m, 12H); MS (ESI) *m*/*z* 411 (M + 1).

(2*S*,4*S*)-2-(3-Azidopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine (55). 55 was synthesized from **54** as described for **29** in a quantitative yield as a TFA salt, which was used directly for the next reaction without further purification. ^{1}H NMR (300 MHz, CD_3OD) δ 7.80−8.00 (m, 4H), 7.45−7.55 (m, 3H), 4.71 (s, 2H), 4.39 (m, 1H), 3.83 (m, 1H), 3.30−3.60 (m, 4H), 2.47 (dd, J = 6.0, 1.4 Hz, 1H), 1.60−2.00 (m, 6H); MS (ESI) *m*/*z* 311 (M + H).

(2*R*,4*S*)-2-(3-Azidopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidine (59). 59 was synthesized from **58** as described for **29** in a quantitative yield as a TFA salt, which was used directly for the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−8.00 (m, 7H), 4.72 (m, 2H), 4.35 (m, 1H), 3.20−3.90 (m, 5H), 1.30−2.60 (m, 6H); MS (ESI) *m*/*z* 311 (M + H).

(*S*)-2-Acetamido-*N*-((*R*)-1-((2*S*,4*S*)-2-(3-guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-3-(4-hydroxyphenyl)propanamide (56a). 56a was synthesized from (*Z*)-*tert*-butyl (3-((2*S*,4*S*)-1-((*R*)-2-((*S*)-2-acetamido-3-(4-hydroxyphenyl)propanamido)-3-phenylpropanoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-2-yl)propylamino)(*tert*-butoxycarbonylamino)methylenecarbamate as described for **35b**. ^{1}H NMR (300 MHz, CD_3OD) δ 7.80−7.90 (m, 4H), 7.40−7.55 (m, 3H), 6.90−7.30 (m, 7H), 6.72 (m, 2H), 4.50−4.90 (m, 4H), 2.60−4.20 (m, 11H), 1.10−2.20 (m, 9H); MS (ESI) *m*/*z* 679 (M + H). Anal. ($C_{39}H_{46}N_6O_5 \cdot 1.6CF_3CO_2H$) C, H, N.

(*S*)-2-Acetamido-*N*-((*R*)-1-((2*S*,4*S*)-2-(3-guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-3-(1*H*-imidazol-4-yl)propanamide (56b). 56b was synthesized from (*Z*)-*tert*-butyl (3-((2*S*,4*S*)-1-((*R*)-2-((*S*)-2-acetamido-3-(1-trityl-1*H*-imidazol-4-yl)propanamido)-3-phenylpropanoyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-2-yl)propylamino)(*tert*-butoxycarbonylamino)methylenecarbamate as described for **35b**. White solid; ^{1}H NMR (300 MHz, CD_3OD) δ 8.70−8.90 (m, 1H), 7.80−8.00 (m, 5H), 7.40−7.55 (m, 3H), 7.20−7.40 (m, 5H), 4.60−5.00 (m, 4H), 2.80−4.20 (m, 11H), 1.10−2.30 (m, 9H); MS (ESI) *m*/*z* 653 (M + H). Anal. ($C_{36}H_{44}N_8O_4 \cdot 2.2CF_3CO_2H$) C, H, N.

(*S*)-*N*-((*R*)-1-((2*S*,4*S*)-2-(3-Guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (56c). White solid; ^{1}H NMR (300 MHz, CD_3OD) δ 7.80−8.00 (m, 4H), 7.20−7.60 (m, 12H), 4.76 (m, 2H), 4.00−4.50 (m, 6H), 2.80−3.40 (m, 8H), 2.24 (m, 1H), 1.80−2.00 (m, 2H), 1.10−1.65 (m, 3H); MS (ESI) *m*/*z* 633 (M + H). Anal. ($C_{38}H_{44}N_6O_3 \cdot 2.3CF_3CO_2H$) C, H, N.

(*S*)-*N*-((*R*)-1-((2*S*,4*S*)-2-(3-Guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)piperidine-2-carboxamide (56d). White solid; ^{1}H NMR (300 MHz, CD_3OD) δ 7.80−7.95 (m, 4H), 7.45−7.60 (m, 3H), 7.20−7.40 (m, 5H), 4.60−5.10 (m, 4H), 4.00−4.40 (m, 3H), 2.80−3.90 (m, 7H), 1.10−2.30 (m, 12H); MS (ESI) *m*/*z* 585 (M + H). Anal. ($C_{34}H_{44}N_6O_3 \cdot 3.0CF_3CO_2H$) C, H, N.

(*S*)-2-Acetamido-*N*1-((*R*)-1-((2*S*,4*S*)-2-(3-guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)pentanediamide (56e). White solid; ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.42−7.60 (m, 3H), 7.10−7.30 (m, 5H), 4.60−4.80 (m, 2H), 4.00−4.50 (m, 4H), 2.90−3.80 (m, 6H), 1.10−2.40 (m, 13H). MS (ESI) *m*/*z* 644 (M + H). Anal. ($C_{35}H_{45}N_7O_5 \cdot 1.4CF_3CO_2H$) C, H, N.

(*S*)-2-Acetamido-*N*-((*R*)-1-((2*R*,4*S*)-2-(3-guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-3-(4-hydroxyphenyl)propanamide (60a). White solid; ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.70 (m, 4H), 7.40−7.60 (m, 3H), 7.10−7.40 (m, 5H), 7.10 (m, 2H), 6.74 (m, 2H), 4.40−4.90 (m, 4H), 2.70−4.20 (m, 10H), 1.40−2.10 (m, 9H). MS (ESI) *m*/*z* 679 (M + H). Anal. ($C_{39}H_{46}N_6O_5 \cdot 1.7CF_3CO_2H$) C, H, N.

(*S*)-2-Acetamido-*N*-((*R*)-1-((2*R*,4*S*)-2-(3-guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-3-(1*H*-imidazol-4-yl)propanamide (60b). White solid; ^{1}H NMR (300 MHz, CD_3OD) δ 7.75−7.90 (m, 4H), 7.40−7.60 (m, 3H), 7.10−7.35 (m, 7H), 4.40−4.90 (m, 5H), 2.80−4.30 (m, 9H), 1.40−2.20 (m, 9H); MS (ESI) *m*/*z* 652 (M + H). Anal. ($C_{36}H_{44}N_8O_4 \cdot 4.2CF_3CO_2H$) C, H, N.

(*S*)-*N*-((*R*)-1-((2*R*,4*S*)-2-(3-Guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (60c). White solid; ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.40−7.60 (m, 3H), 7.10−7.40 (m, 9H), 4.60−4.80 (m, 2H), 4.38 (s, 2H), 3.90−4.30 (m, 3H), 2.80−3.90 (m, 9H), 1.40−2.10 (m, 6H); MS (ESI) *m*/*z* 633 (M + H). Anal. ($C_{38}H_{44}N_6O_3 \cdot 3.2CF_3CO_2H$) C, H, N.

(*S*)-*N*-((*R*)-1-((2*R*,4*S*)-2-(3-Guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)piperidine-2-carboxamide (60d). White solid; ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.40−7.60 (m, 3H), 7.20−7.40 (m, 5H), 2.80−4.90 (m, 14H), 1.20−2.30 (m, 12H); MS (ESI) *m*/*z* 585 (M + H). Anal. ($C_{34}H_{44}N_6O_3 \cdot 3.5CF_3CO_2H$) C, H, N.

(*S*)-2-Acetamido-*N*1-((*R*)-1-((2*R*,4*S*)-2-(3-guanidinopropyl)-4-(naphthalen-2-ylmethoxy)pyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)pentanediamide (60e). White solid; ^{1}H NMR (300 MHz, CD_3OD) δ 7.70−7.90 (m, 4H), 7.42−7.60 (m, 3H), 7.10−7.30 (m, 5H), 4.60−4.80 (m, 2H), 2.90−4.50 (m, 10H), 1.10−2.40 (m, 13H); MS (ESI) *m*/*z* 644 (M + 1). Anal. ($C_{35}H_{45}N_7O_5 \cdot 1.3CF_3CO_2H$) C, H, N.

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Supporting Information Available: Experimental procedures and analytical data for analogues **42a**−**e**, **43**−**47**, **56a**−**e**, **60a**−**e** and elemental analysis results for final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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