

Novel glycine transporter type-2 reuptake inhibitors. Part 2: β - and γ -amino acid derivatives

Ronald L. Wolin,^{*} Alejandro Santillán, Jr., Tristin Barclay, Liu Tang,
Hariharan Venkatesan, Sandy Wilson, Doo Hyun Lee[†] and Timothy W. Lovenberg

Johnson & Johnson Pharmaceutical Research and Development, LLC, 3210 Merryfield Row, San Diego, CA 92121, USA

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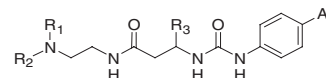
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Abstract—Several β - and γ -amino acid derivatives were prepared as glycine transport inhibitors and their ability to block the uptake of [¹⁴C]-glycine in COS7 cells transfected with human glycine transporter-2 (*h*GlyT-2) were evaluated. A range of lipophilic side chains were tolerated in the β -amino acid series (i.e., Ph, CH₂Ph, CH(CH₃)₂, and CH₂CH(CH₃)₂). In the γ -amino acid series, minimal differences in potency were observed between the α,β -unsaturated analogs and the corresponding saturated derivatives. In both series, a 4-biphenyl or 4-phenoxyphenyl substituent appended to the urea or cyanoguanidine moiety was necessary for in vitro activity.

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1. Introduction

The amino acid glycine is an important inhibitory neurotransmitter in the central nervous system (CNS) of vertebrates and exerts its action post-synaptically at the strychnine-sensitive glycinergic receptor.¹ When glycine binds to its specific receptor it induces the opening of a ligand-gated chloride channel, which results in an influx of chloride ion into the post-synaptic neuron. This process causes the neuron to become hyperpolarized and ultimately raises the threshold for neuronal signaling. The physiological effects of glycine are regulated by two glycine transporters (GlyT-1 and GlyT-2), which provide a mechanism for the re-uptake of glycine from the synaptic cleft back into the pre-synaptic neuron and surrounding glial cells. Inhibiting glycine transport (specifically GlyT-2 transport) may provide therapeutic benefits for a variety of ailments including neuropathic pain, muscle spasticity, tinnitus and epilepsy.^{2,3} This paper describes the synthesis and biological activity for a series of β - and γ -amino acids that were shown to be effective GlyT-2 reuptake inhibitors (Figs. 1–5). The previous paper in this series describes our results pertaining to α -amino acid derivatives.⁴



Compd	R ₁	R ₂	R ₃	Ar
1	H	H	Ph	Ph
2	H	CH(CH ₃) ₂	Ph	Ph
3	CH ₃	CH ₃	Ph	Ph
4	CH ₃	CH ₃	CH ₂ Ph	Ph
5	CH ₃	CH ₃	CH ₂ Ph	OPh
6		(CH ₂) ₄	Ph-4-CH ₃	Ph
7		(CH ₂) ₄	Ph	Ph
8		(CH ₂) ₄	CH(CH ₃) ₂	Ph
9		(CH ₂) ₄	CH(CH ₃) ₂	OPh
10		(CH ₂) ₄	CH ₂ Ph	Ph
11		(CH ₂) ₄	CH ₂ Ph	OPh
12		(CH ₂) ₄	(CH ₃) ₂ CHCH ₂	Ph
13		(CH ₂) ₄	(CH ₃) ₂ CHCH ₂	OPh

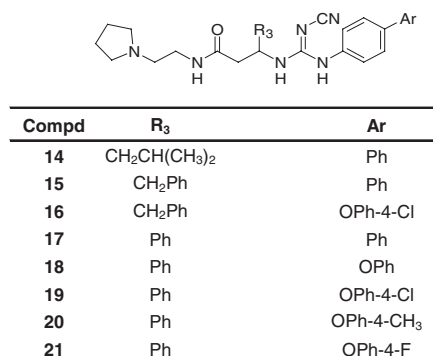
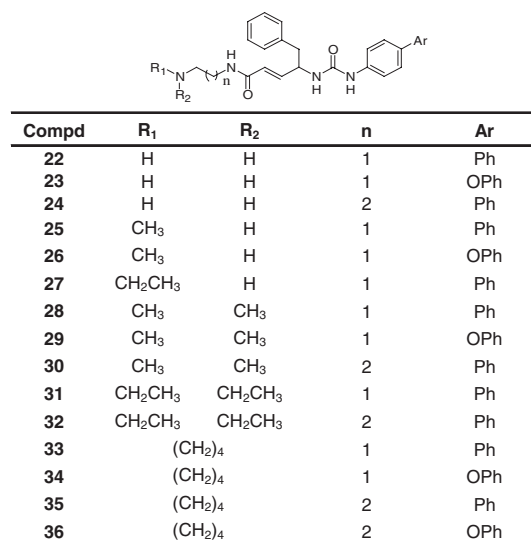
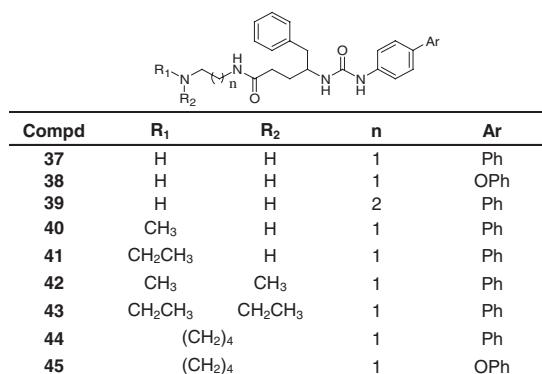
Figure 1. β -Amino acid derivatives.

2. Chemistry

Scheme 1 illustrates the two synthetic routes (A and/or B) that were employed for the preparation of the D- and L- β -amino acid analogs used in this study. Route A commenced with a carbodiimide mediated coupling between the appropriately substituted *N*-Boc amino acid **54** and one of the following diamines, 1-(2-aminoethyl)pyrrolidine, *N,N*-dimethyl ethylenediamine,

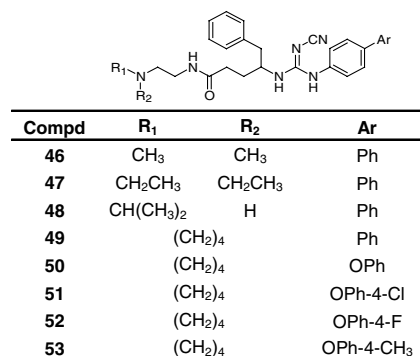
^{*} Corresponding author. Fax: +1-858-784-3116; e-mail: rwolin@prdus.jnj.com

[†] Present address: One Amgen Center Dr., Mail stop 29-2-B, Thousand Oaks, CA 91320, USA.

Figure 2. Cyanoguanidine β -amino acid derivatives.Figure 3. Unsaturated γ -amino acid derivatives.Figure 4. Saturated γ -amino acid derivatives.

N-isopropyl ethylenediamine, or *N*-Boc-ethylenediamine to afford adduct **55**. Removal of the *N*-Boc protecting group, followed by condensation with either 4-phenoxyphenyl or 4-biphenyl isocyanate provided the urea targets **1–13**.

Alternatively, treatment of the requisite amino acid **56** with the appropriate isocyanate afforded the urea intermediate **57**.⁵ Subsequent amide formation employ-

Figure 5. Cyanoguanidine γ -amino acid derivatives.

ing the diamines noted above led to the target analogs **1–13**.

The cyanoguanidine analogs shown in Scheme 2 were constructed from the reaction of amines **58** with *N*-cyano-*N*-biphenylthiourea (**61**) or *N*-cyano-*N*-phenoxyphenylthiourea (**62**) in the presence of EDCI, which provided the desired cyanoguanidine adducts **14–21**.⁶

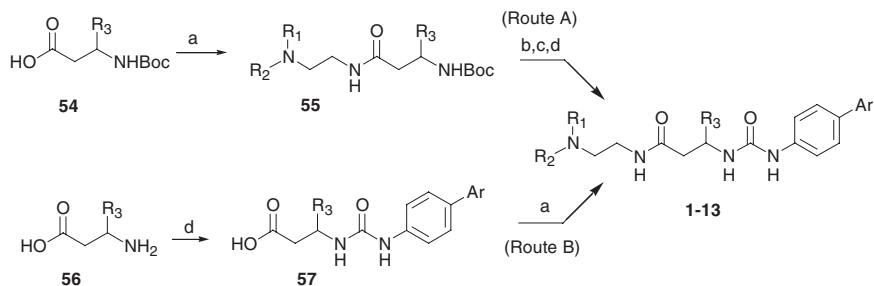
A general method for the synthesis of both D- and L- γ -amino acid analogs is illustrated in Scheme 3. Treatment of (*R*)-(+)-2-(*tert*-butoxycarbonylamino)-3-phenylpropanal (**62**) with methyl(triphenylphosphoranylidene)acetate in CH₂Cl₂ afforded the olefin adduct exclusively as the *trans*-isomer in 80% yield.⁷ Saponification to the carboxylic acid **63** was accomplished using aqueous 4 N LiOH in THF. Removal of the *N*-Boc group with HCl in dioxane gave the desired amines, which were condensed with 4-biphenyl isocyanate or 4-phenoxyphenyl isocyanate in toluene to afford the corresponding urea analogs **64**. Carbodiimide mediated coupling between **64** and the appropriate amine component⁸ provided the α,β -unsaturated- γ -amino acids **22–36**. The corresponding saturated analogs **37–45** were obtained via hydrogenation using 10% Pd/C in EtOH.

The *cis*- α,β -unsaturated intermediate **66** was obtained using the Still–Gennari olefination reaction.⁹ Subsequent conversion to the *cis*- α,β -unsaturated γ -amino amino acid **33b** was achieved under Weinreb conditions (Scheme 4).¹⁰

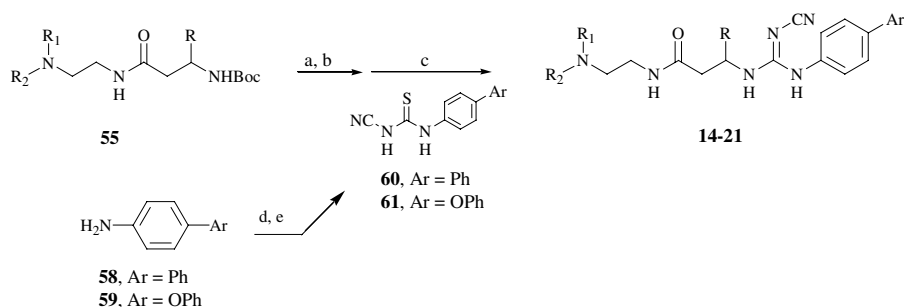
2.1. Cyanoguanidines

In our studies pertaining to α -amino acid derivatives,⁴ we found that cyanoguanidines were excellent surrogates for the urea linkage and often provided an improvement in potency. Thus, several analogs containing a cyanoguanidine moiety in the γ -amino acid series were synthesized for comparison (Scheme 5).

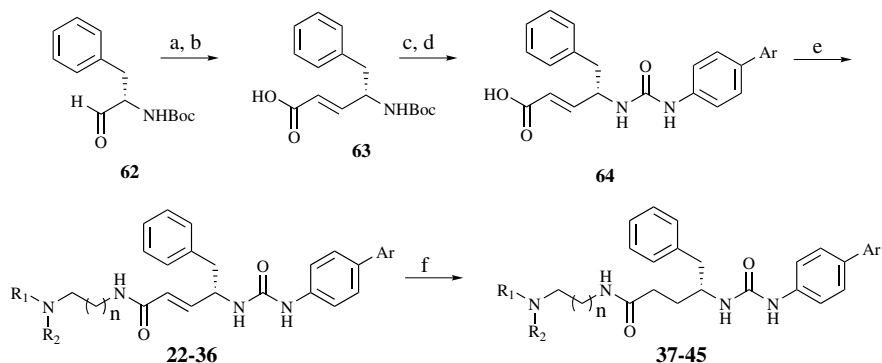
Carbodiimide mediated coupling of carboxylic acid **63** and the appropriate amines¹¹ provided the corresponding α,β -unsaturated amides **67**, which were subsequently reduced to the saturated intermediates **68**. Removal of the *N*-Boc-group followed by condensation with **60** or **61** as previously described provided the cyanoguanidine analogs **46–53**.



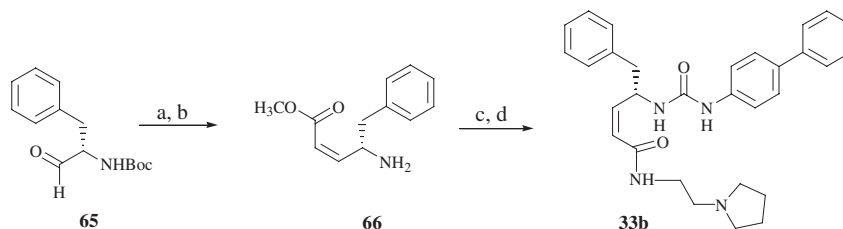
Scheme 1. Reagents: (a) $R_1R_2NCH_2CH_2NH_2$, EDCI, HOBT, DMF; (b) 4 M HCl/dioxane, CH_2Cl_2 ; (c) Dowex 550A anion exchange resin, MeOH; (d) ArPhNCO, Et_3N , CH_2Cl_2 .



Scheme 2. Reagents: (a) 4 M HCl/dioxane, CH_2Cl_2 ; (b) Dowex 550A OH anion-exchange resin, MeOH; (c) **60** or **61**, EDCI, DMF; (d) Thiocarbonyl diimidazole, CH_2Cl_2 ; (e) NaNHCN, EtOH.



Scheme 3. Reagents: Only the L-enantiomer is shown for clarity. (a) $(Ph)_3PCHCO_2Me$, CH_2Cl_2 ; (b) LiOH, THF– H_2O ; (c) 4 M HCl–dioxane; (d) ArPhNCO, Et_3N , $PhCH_3$; (e) $R_1R_2NCH_2CH_2NH_2$, EDCI, HOBT, DMF; (f) H_2 , 10% Pd/C, EtOH.

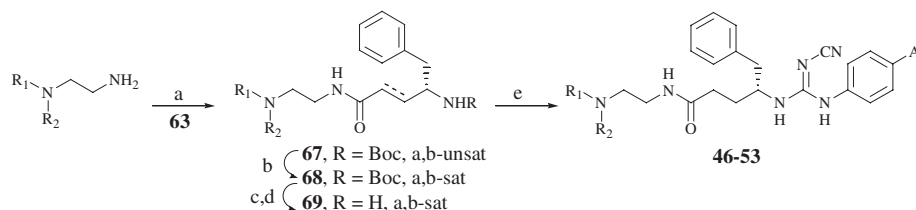


Scheme 4. Reagents: Only the L-enantiomer is shown for clarity. (a) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS/18-C-6, THF; (b) 4 M HCl/dioxane, CH_2Cl_2 ; (c) 4-Biphenylisocyanate, Et_3N , $PhCH_3$; (d) 2-Pyrrolidinyl ethylamine, $AlMe_3$, toluene.

3. Results and discussion

The GlyT-2 analogs synthesized in this study were evaluated for their ability to block the uptake of [^{14}C]-

glycine in COS7 cells transfected with human glycine transporter-2 (*hGlyT-2*).^{11,12} Three noteworthy observations from the data presented in Table 1 are that the L-enantiomers **6b** and **7b** are substantially more potent



Scheme 5. Reagents: Only the L-enantiomer is shown for clarity. (a) EDCI, HOBt, DMF; (b) H_2 , Pd/C, EtOH; (c) 4 M HCl/dioxane, CH_2Cl_2 ; (d) Dowex 550A OH an ion-exchange resin; (e) **60** or **61**, EDCI, DMF.

Table 1. GlyT-2 inhibitory activity for the urea analogs

Compd	R ₁	R ₂	R ₃	Ar	*Enant.	GlyT-2 IC ₅₀ (μM)
1	H	H	Ph	Ph	(±)	0.284
2	H	(CH ₃) ₂ CH	Ph	Ph	(±)	0.059
3	CH ₃	CH ₃	Ph	Ph	(±)	0.184
4	CH ₃	CH ₃	CH ₂ Ph	Ph	L	0.342
5	CH ₃	CH ₃	CH ₂ Ph	OPh	L	0.333
6a		(CH ₂) ₄	Ph-4-CH ₃	Ph	(±)	0.034
6b		(CH ₂) ₄	Ph-4-CH ₃	Ph	L	0.027
6c		(CH ₂) ₄	Ph-4-CH ₃	Ph	D	0.953
7b		(CH ₂) ₄	Ph	Ph	L	0.052
7c		(CH ₂) ₄	Ph	Ph	D	1.307
8		(CH ₂) ₄	(CH ₃) ₂ CH	Ph	L	0.041
9		(CH ₂) ₄	(CH ₃) ₂ CH	OPh	L	0.770
10		(CH ₂) ₄	CH ₂ Ph	Ph	L	0.134
11		(CH ₂) ₄	CH ₂ Ph	OPh	L	0.523
12		(CH ₂) ₄	(CH ₃) ₂ CHCH ₂	Ph	L	0.073
13		(CH ₂) ₄	(CH ₃) ₂ CHCH ₂	OPh	L	1.501

than their corresponding D-enantiomers **6c** and **7c** by 25- and 35-fold, respectively. Secondly, the nature of the substituent(s) attached to the terminal amino group and the β-position have a significant influence on GlyT-2 inhibitory activity. For example, comparison between the *N,N*-dimethyl derivatives **4** and **5** indicate that having either a 4-biphenyl or 4-phenoxyphenyl substituent produces compounds with equivalent GlyT-2 inhibitory activity. However, a 4-fold difference in activity was observed between derivatives **10** and **11** when a pyrrolidine group was present and 21-fold separation in activity was seen between the isobutyl derivatives **12** and **13**. Thirdly, aryl derivatives **6b** and **7b** indicate that direct attachment of a phenyl substituent in the β-position can produce GlyT-2 inhibitory affects that are equal to or better than the homologous benzyl derivatives **8** and **10**.

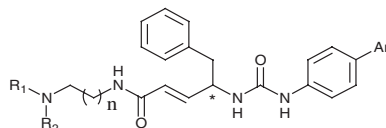
The data in Table 2 illustrate that the urea moiety can be replaced with a cyanoguanidine unit to afford compounds with similar or improved GlyT-2 inhibitory activities. For example, the cyanoguanidine analogs **15** and **17** possess comparable activities to their corresponding urea derivatives **10** and **7b**, respectively.

Examination of the γ-amino acid derivatives in Tables 3 and 4 reveal that the absolute configuration of the γ-substituent also has a pronounced effect on GlyT-2

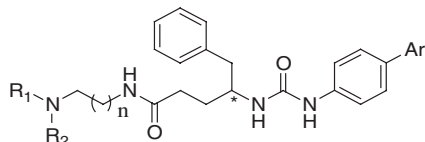
Table 2. GlyT-2 inhibitory activity for the cyanoguanidine analogs

Compd	R ₃	Ar	*Enant.	GlyT-2 IC ₅₀ (μM)
14	CH ₂ CH(CH ₃) ₂	Ph	L	0.368
15	CH ₂ Ph	Ph	(±)	0.103
16	CH ₂ Ph	OPh-4-Cl	(±)	0.127
17	Ph	Ph	(±)	0.060
18	Ph	OPh	(±)	0.062
19	Ph	OPh-4-Cl	(±)	0.068
20	Ph	OPh-4-CH ₃	(±)	0.134
21	Ph	OPh-4-F	L	0.031

inhibitory activity. For example, the two enantiomeric pairs listed in Table 3 (**24a/24b**, and **35a/35b**) and the one pair of enantiomers listed in Table 4 (**37a/37b**) reiterate that incorporation of the natural L-amino acid is preferred over the corresponding D-enantiomers. Secondly, only minor differences in potency were observed between derivatives containing the 4-biphenyl or 4-phenoxyphenyl substituent (Tables 3 and 4, **22a** vs **23**; **28** vs **29**; **33a** vs **33b**; **35** vs **36a** and **44** vs **45**). Thirdly, little or no difference in GlyT-2 inhibitory activity was observed between corresponding saturated and unsaturated analogs. Interestingly, GlyT-2 inhibitory activity

Table 3. GlyT-2 inhibitory activity for the unsaturated urea analogs

Compd	R ₁	R ₂	<i>n</i>	Ar	*Enant.	GlyT-2 IC ₅₀ (μM)
22	H	H	1	Ph	L	2.512
23	H	H	1	OPh	L	0.400
24a	H	H	2	Ph	L	1.000
24b	H	H	2	Ph	D	3.162
25	CH ₃	H	1	Ph	L	0.128
26	CH ₃	H	1	OPh	L	0.049
27	CH ₂ CH ₃	H	1	Ph	L	0.052
28	CH ₃	CH ₃	1	Ph	L	0.073
29	CH ₃	CH ₃	1	OPh	L	0.072
30	CH ₃	CH ₃	2	Ph	L	0.376
31	CH ₂ CH ₃	CH ₂ CH ₃	1	Ph	L	0.048
32	CH ₂ CH ₃	CH ₂ CH ₃	2	Ph	L	0.134
33a		(CH ₂) ₄	1	Ph	L	0.100
33b		(CH ₂) ₄	1	Ph	L	0.230
34		(CH ₂) ₄	1	OPh	L	0.158
35a		(CH ₂) ₄	2	Ph	L	0.500
35b		(CH ₂) ₄	2	Ph	D	1.400
36		(CH ₂) ₄	2	OPh	L	0.700

Table 4. GlyT-2 inhibitory activity for the saturated urea analogs

Compd	R ₁	R ₂	<i>n</i>	Ar	*Enant.	GlyT-2 IC ₅₀ (μM)
37a	H	H	1	Ph	L	0.315
37b	H	H	1	Ph	D	3.500
38	H	H	1	OPh	D	0.500
39	H	H	2	Ph	L	1.000
40	CH ₃	H	1	Ph	L	0.180
41	CH ₂ CH ₃	H	1	Ph	L	0.140
42	CH ₃	CH ₃	1	Ph	L	0.272
43	CH ₂ CH ₃	CH ₂ CH ₃	1	Ph	L	0.103
44		(CH ₂) ₄	1	Ph	L	0.158
45		(CH ₂) ₄	1	OPh	L	0.125

was not notably affected by the geometry of the α,β-unsaturated bond. (i.e., *trans*-**33a** vs *cis*-**33b**).

The structure–function differences begin to emerge when the chain length linking the amide and the terminal amino functionality was varied. For example, a 2-carbon tether (*n* = 1) was preferred relative to a 3-carbon tether (*n* = 2) in all cases examined. Additionally, GlyT-2 inhibitory activity remained fairly constant among the 2°- and 3°-amino analogs, however, the corresponding 1°-amino derivatives were generally 2–5-fold less potent (compare **22a** with **27**, **28**, **31** and **33a** in Table 3) and (**37a** with **40**, **41**, **43** and **44** in Table 4).

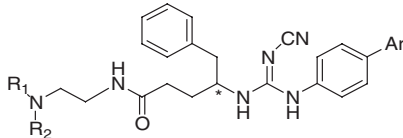
Lastly, direct comparison between urea derivatives **42**, **43**, and **44** in Table 4 with the corresponding cyanoguanidine derivatives **46**, **47**, and **49a** in Table 5 indicate

that the GlyT-2 inhibitory activities were similar with less than a 2-fold difference being observed. The 5-fold difference in potency between the L- and D-enantiomeric pair, **49a** and **49b**, respectively, illustrate the preference for incorporation of the natural amino acid.

In summary, a wide range of substituents were found to be well tolerated at the β-position in contrast to our observations from the homologous α-amino acid series³ and the γ-series. The optimal substituent in the γ-amino acid series was derived from phenylalanine.

4. Experimental

NMR spectra were obtained on either a Bruker model DPX400 (400 MHz) or DPX500 (500 MHz)

Table 5. GlyT-2 inhibitory activity for the cyanoguanidine analogs


Compd	R ₁	R ₂	Ar	*Enant.	GlyT-2 IC ₅₀ (μM)
46	CH ₃	CH ₃	Ph	L	0.448
47	CH ₂ CH ₃	CH ₂ CH ₃	Ph	L	0.226
48	CH(CH ₃) ₂	H	Ph	L	0.162
49a		(CH ₂) ₄	Ph	L	0.093
49b		(CH ₂) ₄	Ph	D	0.445
50		(CH ₂) ₄	OPh	L	0.188
51		(CH ₂) ₄	OPh-4-Cl	L	0.140
52		(CH ₂) ₄	OPh-4-F	L	0.170
53		(CH ₂) ₄	OPh-4-CH ₃	L	0.227

spectrometer. The format of the ¹H NMR data below is: chemical shift in ppm down field of the tetramethylsilane reference (multiplicity, coupling constant *J* in Hz, integration). Mass spectra were obtained on an Agilent series 1100 MSD using electrospray ionization (ESI) in either positive or negative mode as indicated. The 'mass calculated' for a molecular formula is the monoisotopic mass of the compound. Flash column chromatography was accomplished using the ISCO Foxy 200 system and one of the following commercially available, prepacked columns: Biotage 40S (SiO₂; 40 g), Biotage 40M (SiO₂; 90 g), Biotage 40L (SiO₂; 120 g), Biotage 65M (SiO₂; 300 g) or ISCO Rediseq (SiO₂; 10, 12, 35, 40, or 120 g). Preparative TLC was accomplished using PLC plates (20 × 20 cm silica gel 60 F₂₅₄, 0.5 mm).

4.1. General procedure for the preparation of urea derivatives 1–13, and exemplified for compound 6

4.1.1. Route A. (*R*)-3-(3-Biphenyl-4-yl-ureido)-*N*-(2-pyrrolidin-1-yl-ethyl)-3-*p*-tolyl-propionamide (6). Step A. 3-(3-Biphenyl-4-yl-ureido)-3-*p*-tolyl-propionic acid. To a solution of 3-amino-3-(*p*-tolyl)propionic acid (0.50 g, 2.79 mmol) and TEA (0.26 g, 2.56 mmol) in CH₂Cl₂ (28 mL) cooled to 0 °C, was added 4-biphenyl isocyanate (0.55 g, 2.79 mmol). The mixture was stirred at 0 °C for 30 min and was then brought to room temperature and stirred for an additional 3 h. The solvent was removed under reduced pressure, water (20 mL) was added to the clear residue, and the mixture was then chilled to 0 °C and acidified using 1 N HCl. The resulting precipitate was collected by filtration, washed with copious amounts of H₂O, and dried under vacuum to afford 0.87 g (83%) of the desired product as a white solid. MS (electrospray): mass calculated for C₂₃H₂₂N₂O₃, 374.16; *m/z* found, 413.0 [M+Na]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.74 (s, 1H), 7.65–7.29 (m, 9H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 6.64 (d, *J* = 8.5 Hz, 1H), 5.11–5.06 (m, 1H), 2.74–2.67 (m, 2H), 2.27 (s, 3H).

Step B. 3-(3-Biphenyl-4-yl-ureido)-*N*-(2-pyrrolidin-1-yl-ethyl)-3-*p*-tolyl-propionamide. To a solution of 3-(3-

biphenyl-4-yl-ureido)-3-*p*-tolyl-propionic acid (0.15 g, 0.40 mmol), 2-pyrrolidin-1-yl-ethylamine (0.05 g, 0.40 mmol) and HOBt (0.081 g, 0.60 mmol) in DMF (4 mL), was added EDCI (0.12 g, 0.60 mmol). The resulting solution was stirred under N₂ at room temperature for 20 h. The solution was diluted with H₂O (20 mL) and extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine (40 mL), dried (Na₂SO₄), and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel using a gradient of 0–20% (MeOH(1% NH₄OH)/CH₂Cl₂) to afford 0.12 g (63%) of the desired product as a white solid. Racemic compound: *R*_f = 0.11 (10% MeOH (1% NH₄OH)/CH₂Cl₂). MS (electrospray): mass calculated for C₂₉H₃₄N₄O₂, 470.27; *m/z* found, 471.3 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.57–7.50 (m, 4H), 7.43–7.37 (m, 4H), 7.29–7.25 (m, 3H), 7.16 (d, *J* = 7.9 Hz, 2H), 5.22 (t, *J* = 6.9 Hz, 1H), 3.28–3.23 (m, 2H), 2.68 (d, *J* = 6.4 Hz, 2H), 2.52–2.48 (m, 6H), 2.31 (s, 3H), 1.77–1.75 (m, 4H).

Step C. (*R*)-3-(3-Biphenyl-4-yl-ureido)-*N*-(2-pyrrolidin-1-yl-ethyl)-3-*p*-tolylpropion-amide. The enantiomers of the product obtained in step B were separated on a chiral O.D. (0.46 cm × 25 cm) column using 0.1% DEA/MeOH at a flow rate of 0.5 mL/min. The (*S*) and (*R*) enantiomers had retention times of 10.3 and 32.4 min, respectively. MS (electrospray): mass calculated for C₂₉H₃₄N₄O₂, 470.27; *m/z* found, 471.2 [M+H]⁺.

4.2. General procedure for the preparation of urea derivatives 1–13, and exemplified for compound 8

Route B. Step A. {(*R*)-2-Methyl-1-[(2-pyrrolidin-1-yl-ethylcarbamoyl)-methyl]-propyl}-carbamic acid *tert*-butyl ester. HOBt (0.351 g, 2.6 mmol) and EDCI (0.5 g, 2.6 mmol) were added to a solution of (*R*)-3-*tert*-butoxycarbonylamino-4-methyl-pentanoic acid (0.4 g, 1.7 mmol) in DMF (8.5 mL). Following the addition of a solution of 2-pyrrolidin-1-yl-ethylamine (0.3 g, 2.6 mmol) in DMF (2 mL), *N*-methyl-morpholine (0.26 g,

2.6 mmol) was added dropwise. The reaction mixture was stirred at room temperature overnight. H₂O (20 mL) and EtOAc (30 mL) were then added to the mixture. The aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with 1 N NaOH (2 × 20 mL) and brine (40 mL), dried (MgSO₄), and concentrated. Purification by column chromatography [0–20% (1% NH₄OH/MeOH)/CH₂Cl₂] afforded 0.44 g (78%) of the desired product. MS (electrospray): mass calculated for C₁₇H₃₃N₃O₃, 327.25; *m/z* found, 328.3 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 6.22 (s, 1H), 5.30 (d, *J* = 6.7 Hz, 1H), 3.66–3.59 (m, 1H), 3.44–3.36 (m, 1H), 3.35–3.27 (m, 1H), 2.59–2.56 (m, 2H), 2.52 (m, 4H), 2.42–2.40 (m, 2H), 1.87–1.74 (m, 8H), 1.43 (s, 9H), 0.93 (t, *J* = 6.3, 6H).

Step B. (*R*)-3-(3-Biphenyl-4-yl-ureido)-4-methyl-pentanoic acid (2-pyrrolidin-1-yl-ethyl)-amide. To a solution of {(*R*)-2-methyl-1-[(2-pyrrolidin-1-yl-ethylcarbamoyl)-methyl]-propyl}-carbamic acid *tert*-butyl ester (0.12 g, 0.37 mmol) in CH₂Cl₂ (4 mL) was added 4 M HCl solution in 1,4-dioxane (2 mL). The reaction mixture was stirred at room temperature for 4 h, and then the solvent was removed under reduced pressure. The residue was redissolved in MeOH (5 mL) and treated with basic resin (Dowex 550A OH anion-exchange resin) for 2 h. The resin was filtered off, and the solvents were removed under reduced pressure. 4-Biphenyl isocyanate (0.134 g, 0.68 mmol) was then added to a solution of the residue in CH₂Cl₂ (3 mL). The reaction mixture was stirred at room temperature overnight, after which EtOAc (10 mL) and H₂O (10 mL) were added. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), and dried (MgSO₄). The solvent was removed under reduced pressure. The residue was purified by column chromatography [0–20% (1% NH₄OH/MeOH)/CH₂Cl₂] to afford 0.124 g (86%) of the desired product.

4.2.1. *N*-(2-Amino-ethyl)-3-(3-biphenyl-4-yl-ureido)-3-phenyl-propionamide (1). Route A. {2-[3-(3-Biphenyl-4-yl-ureido)-3-phenyl-propionylamino]-ethyl}-carbamic acid *tert*-butyl ester.

MS (electrospray): mass calculated for C₂₉H₃₄N₄O₄, 502.26; *m/z* found, 503.3 [M+H]⁺, 525.3 [M+Na]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.81 (br t, *J* = 8.9 Hz, 1H), 7.94 (br t, *J* = 5.6 Hz, 1H), 7.51–7.66 (m, 5H), 7.39–7.47 (m, 4H), 7.30–7.32 (m, 5H), 6.94 (d, *J* = 9.2 Hz, 1H), 6.68 (br t, *J* = 5.6 Hz, 1H), 5.31 (dd, *J* = 14.8, 6.8 Hz, 1H), 2.93–3.05 (m, 2H), 2.81–2.90 (m, 2H), 2.58 (d, *J* = 6.7 Hz, 2H), 1.37 (s, 9H).

N-(2-Amino-ethyl)-3-(3-biphenyl-4-yl-ureido)-3-phenyl-propionamide.

MS (electrospray): mass calculated for C₂₄H₂₆N₄O₂, 402.21; *m/z* found, 403.2 [M+H]⁺, 425.2 [M+Na]⁺, 827.4 [2M+Na]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.55–7.48 (m, 4H), 7.44–7.32 (m, 8H), 7.28–7.21 (m, 2H),

3.31–3.30 (m, 1H), 3.17 (t, *J* = 6.0 Hz, 2H), 2.72 (dd, *J* = 3.0, 7.0 Hz, 2H), 2.59 (t, *J* = 6.0 Hz, 2H).

4.2.2. 3-(3-Biphenyl-4-yl-ureido)-*N*-(2-isopropylamino-ethyl)-3-phenyl-propionamide (2). Route A. 3-(3-Biphenyl-4-yl-ureido)-3-phenyl-propionic acid.

MS (electrospray): mass calculated for C₂₂H₂₀N₂O₃, 360.41; *m/z* found, 361.2 [M+H]⁺, 383.2 [M+Na]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.08 (br s, 1H), 8.73 (br s, 1H), 7.24–7.65 (m, 14H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.10–5.17 (m, 1H), 2.73–2.79 (m, 2H).

3-(3-Biphenyl-4-yl-ureido)-*N*-(2-isopropylamino-ethyl)-3-phenyl-propionamide.

MS (electrospray): mass calculated for C₂₇H₃₂N₄O₂, 444.25; *m/z* found, 445.2 [M+H]⁺, 467.2 [M+Na]⁺, 911.5 [2M+Na]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.70 (br s, 1H), 8.49 (br s, 1H), 7.45–7.43 (m, 3H), 7.39–7.22 (m, 11H), 5.69–5.61 (m, 1H), 3.41–3.30 (m, 2H), 3.10–3.01 (m, 1H), 2.91–2.82 (m, 1H), 2.67–2.58 (m, 3H), 0.92 (d, *J* = 2.3 Hz, 3H), 0.90 (d, *J* = 2.3 Hz, 3H).

4.2.3. 3-(3-Biphenyl-4-yl-ureido)-*N*-(2-dimethylamino-ethyl)-3-phenyl-propionamide (3). Route A. 3-(3-Biphenyl-4-yl-ureido)-*N*-(2-dimethylamino-ethyl)-3-phenyl-propionamide.

MS (electrospray): mass calculated for C₂₆H₃₀N₄O₂, 430.24; *m/z* found, 431.2 [M+H]⁺, 453.2 [M+Na]⁺, 883.5 [2M+Na]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.71 (s, 1H), 7.46–7.34 (m, 14H), 6.90 (br s, 1H), 6.72 (br s, 1H), 5.29–5.23 (m, 1H), 3.34–3.28 (m, 1H), 3.16–3.10 (m, 1H), 2.71 (dd, *J* = 14.1, 4.2 Hz, 1H), 2.62 (dd, *J* = 14.1, 8.0 Hz, 1H), 2.42–2.29 (m, 2H), 2.15 (t, *J* = 7.0 Hz, 6H).

4.2.4. (*S*)-3-(3-Biphenyl-4-yl-ureido)-*N*-(2-dimethylamino-ethyl)-4-phenyl-butylamide (4). Route B. [(*S*)-1-Benzyl-2-(2-dimethylamino-ethylcarbamoyl)-ethyl]-carbamic acid *tert*-butyl ester.

MS (electrospray): mass calculated for C₁₉H₃₁N₃O₃, 349.24; *m/z* found, 350.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.23–7.12 (m, 5H), 6.02 (br s, 1H), 5.66 (br s, 1H), 4.05–3.97 (m, 1H), 3.29–3.25 (m, 2H), 2.99–2.86 (m, 1H), 2.75–2.70 (m, 1H), 2.37–2.28 (m, 3H), 2.21–2.18 (m, 7H), 1.34 (s, 9H).

(*S*)-3-(3-Biphenyl-4-yl-ureido)-*N*-(2-dimethylamino-ethyl)-4-phenyl-butylamide.

MS (electrospray): mass calculated for C₂₇H₃₂N₄O₂, 444.57; *m/z* found, 445.3 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.42 (m, 4H), 7.36–7.32 (m, 4H), 7.26–7.14 (m, 6H), 6.32–6.25 (m, 1H), 6.00 (br s, 1H), 4.33–4.24 (m, 1H), 3.33–3.24 (m, 1H), 3.22–3.17 (m, 1H), 3.04 (dd, *J* = 13.5, 6.1 Hz, 1H), 2.74 (dd, *J* = 13.5, 8.6 Hz, 1H), 2.42 (dd, *J* = 14.8, 4.3 Hz, 1H), 2.35 (t, *J* = 5.9 Hz, 2H), 2.23 (dd, *J* = 14.8, 6.7 Hz, 1H), 2.16 (s, 6H).

4.2.5. (S)-N-(2-Dimethylamino-ethyl)-3-[3-(4-phenoxy-phenyl)-ureido]-4-phenyl-butylamide (5). Route B. (S)-N-(2-Dimethylamino-ethyl)-3-[3-(4-phenoxy-phenyl)-ureido]-4-phenyl-butylamide. MS (electrospray): mass calculated for $C_{27}H_{32}N_4O_3$, 460.57; m/z found, 461.3 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 6H), 7.25–7.23 (m, 3H), 7.10–7.07 (m, 1H), 6.99–6.94 (m, 4H), 6.55–6.49 (m, 1H), 6.12–6.05 (m, 1H), 4.4–4.32 (m, 1H), 3.51–3.36 (m, 1H), 3.32–3.25 (m, 1H), 3.09 (dd, $J = 13.5$, 6.9 Hz, 1H), 2.82 (dd, $J = 13.5$, 8.4 Hz, 1H), 2.51–2.43 (m, 3H), 2.32 (dd, $J = 14.8$, 7.1 Hz, 1H), 2.27 (s, 6H).

4.2.6. (R)-3-(3-Biphenyl-4-yl-ureido)-3-phenyl-N-(2-pyrrolidin-1-yl-ethyl)-propionamide (7b). Route A. (R)-3-(3-Biphenyl-4-yl-ureido)-3-phenyl-N-(2-pyrrolidin-1-yl-ethyl)-propionamide.

MS (electrospray): mass calculated for $C_{28}H_{32}N_4O_2$, 456.25; m/z found, 457.3 $[M+H]^+$, 479.2 $[M+Na]^+$, 935.4 $[2M+Na]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.56–7.49 (m, 4H), 7.43–7.32 (m, 8H), 7.29–7.23 (m, 2H), 5.27 (t, $J = 6.9$ Hz, 1H), 3.32–3.29 (m, 2H), 2.70 (d, $J = 6.6$ Hz, 2H), 2.62–2.57 (m, 6H), 1.79–1.76 (m, 4H).

4.2.7. (S)-3-(3-Biphenyl-4-yl-ureido)-3-phenyl-N-(2-pyrrolidin-1-yl-ethyl)-propionamide (7c). Route A. (S)-3-(3-Biphenyl-4-yl-ureido)-3-phenyl-N-(2-pyrrolidin-1-yl-ethyl)-propionamide.

MS (electrospray): mass calculated for $C_{28}H_{32}N_4O_2$, 456.25; m/z found, 457.3 $[M+H]^+$, 479.2 $[M+Na]^+$, 935.4 $[2M+Na]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.56–7.49 (m, 4H), 7.43–7.32 (m, 8H), 7.29–7.23 (m, 2H), 5.27 (t, $J = 6.9$ Hz, 1H), 3.32–3.29 (m, 2H), 2.70 (d, $J = 6.6$ Hz, 2H), 2.62–2.57 (m, 6H), 1.79–1.76 (m, 4H).

4.2.8. (R)-3-(3-Biphenyl-4-yl-ureido)-4-methyl-pentanoic acid (2-pyrrolidin-1-yl-ethyl)-amide (8). Route A. {(R)-2-Methyl-1-[(2-pyrrolidin-1-yl-ethylcarbamoyl)-methyl]-propyl}-carbamic acid *tert*-butyl ester.

MS (electrospray): mass calculated for $C_{17}H_{33}N_3O_3$, 327.25; m/z found, 328.3 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 6.22 (s, 1H), 5.30 (d, $J = 6.7$ Hz, 1H), 3.66–3.59 (m, 1H), 3.44–3.36 (m, 1H), 3.35–3.27 (m, 1H), 2.59–2.56 (m, 2H), 2.52 (m, 4H), 2.42–2.40 (m, 2H), 1.87–1.74 (m, 8H), 1.43 (s, 9H), 0.93 (t, $J = 6.3$, 6H).

(R)-3-(3-Biphenyl-4-yl-ureido)-4-methyl-pentanoic acid (2-pyrrolidin-1-yl-ethyl)-amide.

MS (electrospray): mass calculated for $C_{25}H_{34}N_4O_2$, 422.27; m/z found, 423.3 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.30 (m, 8H), 7.24–7.22 (1H), 6.57 (s, 1H), 3.89–3.82 (m, 1H), 3.36–3.25 (m, 2H), 2.53 (t, $J = 6.2$ Hz, 2H), 2.47 (d, $J = 3.8$ Hz, 1H), 2.44 (s, 3H), 2.33 (dd, $J = 14.8$, 8.6 Hz, 1H), 1.86–1.78 (m, 4H), 1.71–1.66 (m, 4H), 0.92 (d, $J = 4.4$ Hz, 3H), 0.90 (d, $J = 4.3$ Hz, 3H).

4.2.9. (R)-4-Methyl-3-[3-(4-phenoxyphenyl)-ureido]-pentanoic acid (2-pyrrolidin-1-yl-ethyl)-amide (9). Route B. MS (electrospray): mass calculated for $C_{25}H_{34}N_4O_3$, 438.26; m/z found, 439.21 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.21 (m, 4H), 7.0–6.96 (m, 1H), 6.90–6.86 (m, 4H), 6.49 (br s, 1H), 3.85–3.78 (m, 1H), 3.34–3.24 (m, 2H), 2.53–2.48 (m, 2H), 2.46–2.43 (m, 4H), 2.31 (dd, $J = 14.9$, 8.4 Hz, 1H), 1.83–1.76 (m, 4H), 1.74–1.66 (m, 4H), 0.89 (q, $J = 3.3$ Hz, 6H).

4.2.10. (S)-3-(3-Biphenyl-4-yl-ureido)-4-phenyl-N-(2-pyrrolidin-1-yl-ethyl)-butylamide (10). Route B. MS (electrospray): mass calculated for $C_{29}H_{34}N_4O_2$, 470.27; m/z found, 471.3 $[M+H]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.57–7.51 (m, 4H), 7.41–7.27 (m, 9H), 7.24–7.20 (m, 1H), 4.43–4.37 (m, 1H), 3.49–3.37 (m, 2H), 2.95–2.86 (m, 8H), 2.50 (dd, $J = 13.9$, 4.2 Hz, 1H), 2.31 (dd, $J = 13.9$, 9.0 Hz, 1H), 1.89–1.79 (m, 4H).

4.2.11. (S)-3-[3-(4-Phenoxyphenyl)-ureido]-4-phenyl-N-(2-pyrrolidin-1-yl-ethyl)-butylamide (11). Route B. MS (electrospray): mass calculated for $C_{14}H_{12}ClNO_3$, 486.3; m/z found, 487.3 $[M+H]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.33–7.19 (m, 9H), 7.07–7.04 (m, 1H), 6.93–6.88 (m, 4H), 4.39–4.33 (m, 1H), 3.37 (t, $J = 6.62$ Hz, 2H), 2.88 (d, $J = 7$ Hz, 2H), 2.79 (t, $J = 6.09$ Hz, 6H), 2.46 (dd, $J = 4.7$, 14.1 Hz, 1H), 2.33 (dd, $J = 8.5$, 14.1 Hz, 1H), 1.83–1.76 (m, 4H).

4.2.12. (S)-3-(3-Biphenyl-4-yl-ureido)-5-methylhexanoic acid (2-pyrrolidin-1-yl-ethyl)-amide (12). Route B. MS (electrospray): mass calculated for $C_{26}H_{36}N_4O_2$, 436; m/z found, 437.3 $[M+H]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.58–7.51 (m, 4H), 7.44–7.34 (m, 4H), 7.30–7.26 (m, 1H), 4.23–4.16 (m, 1H), 3.36 (t, $J = 6.8$ Hz, 2H), 2.70–2.65 (m, 6H), 2.67 (dd, $J = 5.45$, 13.9 Hz, 1H), 2.34 (dd, $J = 7.4$, 13.9 Hz, 1H), 1.79–1.76 (m, 4H), 1.74–1.69 (m, 1H), 1.54–1.46 (m, 1H), 1.38–1.31 (m, 1H), 0.96 (d, $J = 6.8$, 6H).

4.2.13. (S)-5-Methyl-3-[3-(4-phenoxyphenyl)-ureido]-hexanoic acid (2-pyrrolidin-1-yl-ethyl)-amide (13). Route B. MS (electrospray): mass calculated for $C_{26}H_{36}N_4O_3$, 452; m/z found, 453.3 $[M+H]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.35–7.23 (m, 4H), 7.08–7.03 (m, 1H), 6.96–6.88 (m, 4H), 4.20–4.13 (m, 1H), 3.44–3.34 (m, 2H), 2.63–2.49 (m, 6H), 2.38–2.37 (m, 2H), 1.80–1.76 (m, 4H), 1.74–1.65 (m, 1H), 1.52–1.45 (m, 1H), 1.37–1.27 (m, 1H), 0.96 (d, $J = 1.06$ Hz, 3H), 0.94 (d, $J = 0.75$ Hz, 3H).

4.3. General procedure for the preparation of cyanoguanidine derivatives 14–21, and exemplified for compound 17

4.3.1. (R)-3-(N-Biphenyl-4-yl-N''-cyanoguanidino)-3-phenyl-N-(2-pyrrolidin-1-yl-ethyl)-propionamide (17). Step A. [(R)-1-Phenyl-2-(2-pyrrolidin-1-yl-ethylcarbamoyl)-ethyl]-carbamic acid *tert*-butyl ester. To a solution of (R)-3-

tert-butoxycarbonylamino-3-phenyl-propionic acid (0.54 g, 2.04 mmol), 2-pyrrolidin-1-yl-ethylamine (0.35 g, 3.06 mmol), HOBt (0.41 g, 3.06 mmol) and 4-methylmorpholine (0.41 g, 4.08 mmol) in DMF (10 mL), was added EDCI (0.59 g, 3.06 mmol), and the resulting solution was stirred under N₂ at room temperature for 20 h. The solution was diluted with H₂O (75 mL) and was extracted with EtOAc (3 × 75 mL). The combined extracts were washed with brine (100 mL), dried (Na₂SO₄) and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel using a gradient of 2–30% (MeOH (1% NH₄OH)/CH₂Cl₂) to afford 0.65 g (88%) of the desired product as a white solid. *R*_f = 0.34 (10% MeOH (1% NH₄OH)/CH₂Cl₂). MS (electrospray): mass calculated for C₂₀H₃₁N₃O₃, 361.24; *m/z* found, 362.2 [M+H]⁺, 745.4 [2M+Na]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.32–7.28 (m, 4H), 7.24–7.20 (m, 1H), 6.37 (br s, 1H), 6.14 (br s, 1H), 5.01 (br s, 1H), 3.21 (dd, *J* = 11.2, 5.7 Hz, 2H), 2.74–2.67 (m, 1H), 2.59 (dd, *J* = 14, 5.9 Hz, 1H), 2.49–2.38 (m, 6H), 1.76–1.67 (m, 4H), 1.41 (s, 9H).

Step B. (*R*)-3-(*N'*-Biphenyl-4-yl-*N''*-cyano-guanidino)-3-phenyl-*N*-(2-pyrrolidin-1-yl-ethyl)-propionamide. To a solution of [(*R*)-1-phenyl-2-(2-pyrrolidin-1-yl-ethylcarbamoyl)-ethyl]-carbamic acid *tert*-butyl ester (0.25 g, 0.69 mmol) in CH₂Cl₂ (6.9 mL) was added 4 M HCl in 1,4-dioxane (2.4 mL), and the resulting solution was stirred at room temperature for 1.5 h. The solvent was removed under reduced pressure, and the resulting residue was dissolved in MeOH (7 mL) and treated with basic resin (Dowex 550A OH anion-exchange resin). The resulting suspension was stirred at room temperature for 30 min. The resin was filtered off and washed with MeOH (7 mL). The filtrate and washings were concentrated under reduced pressure, and the resulting free amine was dried under vacuum. To a solution of the free amine and 1-biphenyl-4-yl-3-cyanothiourea (0.21 g, 0.83 mmol) in DMF (3.5 mL), was added EDCI (0.2 g, 1.04 mmol). The resulting solution was stirred under N₂ at room temperature for 2 h. The solution was diluted with EtOAc (70 mL) and washed with 1 N NaOH (2 × 50 mL). The organic layer was dried (Na₂SO₄) and filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel using a gradient of 5–10% (MeOH (1% NH₄OH)/CH₂Cl₂) to afford 0.23 g (69%) of the desired product as a white solid. *R*_f = 0.39 (10% MeOH (1% NH₄OH)/CH₂Cl₂). MS (electrospray): mass calculated for C₂₉H₃₂N₆O, 480.26; *m/z* found, 481.2 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.67–7.16 (m, 4H), 7.45–7.41 (m, 2H), 7.35–7.24 (m, 8H), 5.38 (t, *J* = 6.4 Hz, 1H), 3.23 (t, *J* = 6.8 Hz, 2H), 2.71 (d, *J* = 6.4 Hz, 2H), 2.47–2.42 (m, 6H), 1.77–1.69 (m, 4H).

4.3.2. (*S*)-3-(*N'*-Biphenyl-4-yl-*N''*-cyanoguanidino)-4-phenyl-*N*-(2-pyrrolidin-1-yl-ethyl)-butyramide (15). MS (electrospray): mass calculated for C₃₀H₃₄ClN₆O, 494.28; *m/z* found, 495.3 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.60–7.56 (m, 4H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.38–7.25 (m, 8H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.62 (br s, 1H), 4.5–

4.42 (m, 1H), 3.44–3.28 (m, 2H), 3.11 (dd, *J* = 13.6, 7.0 Hz, 1H), 2.94–2.8 (m, 1H), 2.60–2.57 (m, 2H), 2.55–2.4 (m, 6H), 1.84–1.75 (m, 4H).

4.3.3. 3-[*N'*-Cyano-*N''*-(4-phenoxyphenyl)-guanidino]-3-phenyl-*N*-(2-pyrrolidin-1-yl-ethyl)-propionamide (18). 4-Phenoxy-phenyl isothiocyanate.

¹H NMR (400 MHz, CDCl₃) δ 7.43 (t, *J* = 8.0 Hz, 2H), 7.19–7.24 (m, 3H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 9.0 Hz, 2H).

1-Cyano-3-(4-phenoxy-phenyl)-thiourea.

MS (electrospray): mass calculated for C₁₄H₁₁N₃OS, 227.04; *m/z* found, 268.0 [M–H][–]. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.21 (br s, 1H), 7.36 (d, *J* = 9.0 Hz, 2H), 7.33–7.36 (m, 2H), 7.06 (t, *J* = 7.4 Hz, 1H), 6.85–6.93 (m, 4H).

3-[*N'*-Cyano-*N''*-(4-phenoxy-phenyl)-guanidino]-3-phenyl-*N*-(2-pyrrolidin-1-yl-ethyl)-propionamide.

MS (electrospray): mass calculated for C₂₉H₃₂N₆O₂, 496.26; *m/z* found, 497.3 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.04 (br s, 1H), 7.27–7.15 (m, 9H), 7.05–7.01 (m, 1H), 6.97–6.94 (m, 4H), 6.41 (br s, 1H), 5.26–5.21 (m, 1H), 3.12 (d, *J* = 4.8 Hz, 2H), 2.66–2.52 (m, 2H), 2.44–2.28 (m, 6H), 1.67–1.58 (m, 4H).

4.3.4. 3-{*N'*-[4-(4-Chlorophenoxy)-phenyl]-*N''*-cyanoguanidino}-3-phenyl-*N*-(2-pyrrolidin-1-yl-ethyl)-propionamide (19). 1-[4-(4-Chloro-phenoxy)-phenyl]-3-cyanothiourea.

1.8 g (98%) of the desired product was obtained. MS (electrospray): mass calculated for C₁₄H₁₀ClN₃OS, 303.02; *m/z* found, 304.0 [M+H]⁺, 326.0 [M+Na]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.27 (s, 1H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H).

3-{*N'*-[4-(4-Chloro-phenoxy)-phenyl]-*N''*-cyano-guanidino}-3-phenyl-*N*-(2-pyrrolidin-1-yl-ethyl)-propionamide.

MS (electrospray): mass calculated for C₂₉H₃₁ClN₆O₂, 530.22; *m/z* found, 531.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.42 (br s, 1H), 7.41 (br s, 1H), 7.33–7.23 (m, 9H), 7.02–6.96 (m, 4H), 6.48 (br s, 1H), 5.36–5.32 (m, 1H), 3.19 (d, *J* = 3.6 Hz, 2H), 2.72–2.68 (m, 2H), 2.50–2.36 (m, 6H), 1.73–1.67 (m, 4H).

4.3.5. 3-[*N'*-Methyl-*N''*-(4-*p*-tolylloxyphenyl)-guanidino]-3-phenyl-*N*-(2-pyrrolidin-1-yl-ethyl)-propionamide (20). 4-*p*-Tolylloxy-phenylisothiocyanate.

MS (electrospray): mass calculated for C₁₄H₁₁NOS, 241.06; *m/z* found, [M+H]⁺. ¹H NMR (500 MHz,

DMSO- d_6) δ 7.43–7.40 (m, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.98–6.95 (m, 4H), 2.30 (s, 3H).

1-Cyano-3-(4-*p*-tolylloxy-phenyl)-thiourea.

MS (electrospray): mass calculated for $C_{15}H_{13}N_3OS$, 283.08; m/z found, 282.1, $[M-H]^-$. 1H NMR (500 MHz, DMSO- d_6) δ 9.18 (s, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 6.83–6.81 (m, 4H), 2.26 (s, 3H).

3-[*N'*-Methyl-*N''*-(4-*p*-tolylloxy-phenyl)-guanidino]-3-phenyl-*N*-(2-pyrrolidin-1-yl-ethyl)-propionamide.

MS (electrospray): mass calculated for $C_{30}H_{34}N_6O_2$, 510.27; m/z found, 511.3 $[M+H]^+$, 533.2 $[M+Na]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.34–7.23 (m, 7H), 7.16 (d, J = 8.1 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 6.46 (br s, 1H), 5.35–5.30 (m, 1H), 3.22–3.18 (m, 2H), 2.74–2.63 (m, 2H), 2.51–2.39 (m, 6H), 2.35 (s, 3H), 1.76–1.68 (m, 4H).

4.3.6. 3-{*N'*-[4-(4-Fluorophenoxy)-phenyl]-*N''*-cyanoguanidino}-3-phenyl-*N*-(2-pyrrolidin-1-yl-ethyl)-propionamide (21). MS (electrospray): mass calculated for $C_{29}H_{31}FN_6O_2$, 514.25; m/z found, 515.2 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.24 (m, 7H), 7.06–6.98 (m, 6H), 6.46 (br s, 1H), 5.34–5.30 (m, 1H), 3.19 (d, J = 4.0 Hz, 2H), 2.72–2.68 (m, 2H), 2.50–2.36 (m, 6H), 1.72–1.66 (m, 4H).

4.4. General procedure for the preparation of urea derivatives 22–36, and exemplified for compound 26

4.4.1. (*E*)-(S)-4-[3-(4-Phenoxyphenyl)-ureido]-5-phenyl-pent-2-enoic acid (2-methyl-aminoethyl)-amide (26). Step A. (*E*)-(S)-4-[3-(4-Phenoxyphenyl)-ureido]-5-phenyl-pent-2-enoic acid. To a solution of (*E*)-(S)-4-*tert*-butoxycarbonylamino-5-phenyl-pent-2-enoic acid (Example 11, step A) (2.12 g, 7.26 mmol) in CH_2Cl_2 (73 mL) was added 4 M HCl in 1,4-dioxane (25 mL), and the resulting solution was stirred at room temperature for 15 min. The solvent was removed under reduced pressure. To a solution of the resulting residue and TEA (0.74 g, 7.26 mmol) in THF (73 mL) cooled to 0 °C, was added 4-phenoxy phenyl isocyanate (1.53 g, 7.26 mmol), and the mixture was stirred for 30 min. The solution was brought to room temperature and was stirred for an additional 3 h. The solvent was removed under reduced pressure, and the resulting yellow oil was purified by column chromatography on silica gel using a gradient of 0–35% (MeOH (10% acetic acid)/ CH_2Cl_2). The purified product was recrystallized from CH_2Cl_2 and was washed with hexanes to afford 1.45 g (50%) of the desired product as a grey solid. R_f = 0.47 (5% MeOH (1% NH_4OH)/ CH_2Cl_2). MS (electrospray): mass calculated for $C_{24}H_{22}N_2O_4$, 402.16; m/z found, 403.1 $[M+H]^+$, 425.1 $[M+Na]^+$, 827.3 $[2M+Na]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 12.34 (br s, 1H), 8.51 (s, 1H), 7.40–7.20 (m, 9H), 7.08–7.05 (m, 1H), 6.93–6.91 (m, 4H), 6.86 (d, J = 5.0 Hz, 1H), 6.35 (d, J = 8.5 Hz, 1H), 5.77 (dd,

J = 15.6, 1.6 Hz, 1H), 4.70–4.61 (m, 1H), 2.93 (dd, J = 13.7, 6.1 Hz, 1H), 2.84 (dd, J = 13.7, 7.9 Hz, 1H).

Step B. (*E*)-(S)-4-[3-(4-Phenoxyphenyl)-ureido]-5-phenyl-pent-2-enoic acid (2-methylamino-ethyl)-amide. To a solution of (*E*)-(S)-4-[3-(4-phenoxyphenyl)-ureido]-5-phenyl-pent-2-enoic acid (0.20 g, 0.49 mmol), *N'*-methyl-ethane-1,2-diamine (0.04 g, 0.54 mmol) and HOBt (0.01 g, 0.732 mmol) in DMF (4.9 mL), was added EDCI (0.14 g, 0.732 mmol). The resulting solution was stirred under N_2 at room temperature for 20 h. The solution was diluted with H_2O (30 mL) and extracted with 3:1 EtOAc/*i*PrOH (3 $\times$ 40 mL). The combined organic extracts were washed with 1 N NaOH (1 $\times$ 30 mL), dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using a gradient of 0–15% (MeOH (1% NH_4OH)/ CH_2Cl_2) to obtain 0.04 g (18%) of the desired product as a clear oil. R_f = 0.20 (10% MeOH (1% NH_4OH)/ CH_2Cl_2). MS (electrospray): mass calculated for $C_{27}H_{30}N_4O_3$, 458.23; m/z found, 459.3 $[M+H]^+$, 481.2 $[M+Na]^+$, 917.4 $[2M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.45 (br t, J = 5.6 Hz, 1H), 7.23–7.06 (m, 9H), 6.98–6.94 (m, 1H), 6.84–6.78 (m, 4H), 6.64 (dd, J = 15.4, 5.5 Hz, 1H), 6.05 (br d, J = 6.4 Hz, 1H), 5.82 (dd, J = 15.4, 1.2 Hz, 1H), 4.67–4.61 (m, 1H), 3.37–2.28 (m, 1H), 3.20–3.14 (m, 1H), 2.79–2.70 (m, 2H), 2.64–2.54 (m, 3H), 2.25 (s, 3H).

4.4.2. (*E*)-(R)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoic acid (2-amino-ethyl)-amide (22b). (*E*)-(R)-4-*tert*-Butoxycarbonylamino-5-phenyl-pent-2-enoic acid methyl ester.

MS (electrospray): mass calculated for $C_{17}H_{23}NO_4$, 305.16; m/z found, 328.1 $[M+Na]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.16–7.31 (m, 5H), 6.92 (dd, J = 15.7, 5.1 Hz, 1H), 5.90 (d, J = 15.7 Hz, 1H), 4.79 (br s, 1H), 4.61 (br s, 1H), 3.70 (s, 3H), 2.88 (d, J = 6.4 Hz, 2H), 1.39 (s, 9H).

(*E*)-(R)-4-*tert*-Butoxycarbonylamino-5-phenyl-pent-2-enoic acid.

MS (electrospray): mass calculated for $C_{16}H_{21}NO_4$, 291.15; m/z found, 314.1 $[M+Na]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.22–7.26 (m, 2H), 7.08–7.11 (m, 2H), 6.93 (dd, J = 15.5, 4.7 Hz, 1H), 5.79 (d, J = 15.5 Hz, 1H), 4.58 (br s, 1H), 4.48 (br s, 1H), 2.84 (d, J = 6.8 Hz, 2H), 1.33 (s, 9H), remaining peak in the aromatic region was not detected and is believed to overlap with the solvent peak at 7.56 ppm.

(*E*)-(R)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoic acid.

MS (electrospray): mass calculated for $C_{24}H_{22}N_2O_3$, 386.16; m/z found, 387.1 $[M+H]^+$, 409.1 $[M+Na]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 12.33 (br s, 1H), 8.59 (br s, 1H), 7.59–7.62 (m, 2H), 7.52–7.55 (m, 2H), 7.39–7.47 (m, 4H), 7.20–7.34 (m, 6H), 6.89 (dd, J = 15.7, 5.1 Hz, 1H), 6.40 (d, J = 8.4 Hz, 1H), 5.78 (dd, J = 15.7, 1.6 Hz,

1H), 4.66 (br s, 1H), 2.94 (dd, $J = 13.7, 6.2$ Hz, 1H), 2.86 (dd, $J = 13.7, 8.0$ Hz, 1H).

{2-[(*E*)-(*R*)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoylamino]-ethyl}-carbamic acid *tert*-butyl ester.

MS (electrospray): mass calculated for $C_{31}H_{36}N_4O_4$, 528.65; m/z found, 529.3 $[M+H]^+$, 551.1 $[M+Na]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.49–7.60 (m, 4H), 7.36–7.40 (m, 4H), 7.21–7.30 (m, 6H), 6.79 (dd, $J = 15.4, 5.6$ Hz, 1H), 5.99 (d, $J = 15.4$ Hz, 1H), 4.72 (dd, $J = 12.3, 6.2$ Hz, 1H), 3.29 (br t, $J = 6.1$ Hz, 1H), 3.15 (br t, $J = 6.1$ Hz, 1H), 2.97 (dd, $J = 13.7, 6.5$ Hz, 1H), 2.89 (dd, $J = 13.7, 7.8$ Hz, 1H), 1.36 (s, 9H).

(*E*)-(*R*)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoic acid (2-amino-ethyl)-amide.

MS (electrospray): mass calculated for $C_{26}H_{28}N_4O_2$, 428.22; m/z found, 429.2 $[M+H]^+$. 1H NMR (CD_3OD , 400 MHz) δ 7.40–7.47 (m, 4H), 7.27–7.31 (m, 4H), 7.12–7.22 (m, 6H), 6.72 (dd, $J = 15.4, 5.6$ Hz, 1H), 5.92 (dd, $J = 15.4, 1.5$ Hz, 1H), 4.62 (dd, $J = 12.4, 6.2$ Hz, 1H), 3.27 (br t, $J = 6.2$ Hz, 1H), 2.89 (dd, $J = 13.7, 6.7$ Hz, 1H), 2.82 (dd, $J = 13.7, 7.8$ Hz, 1H), 2.59 (br t, $J = 6.2$ Hz, 1H).

4.4.3. (*E*)-(*S*)-4-[3-(4-Phenoxyphenyl)-ureido]-5-phenyl-pent-2-enoic acid (2-amino-ethyl)-amide (23). {2-[(*E*)-(*S*)-4-[3-(4-Phenoxy-phenyl)-ureido]-5-phenyl-pent-2-enoylamino]-ethyl}-carbamic acid *tert*-butyl ester.

MS (electrospray): mass calculated for $C_{31}H_{26}N_4O_5$, 544.27; m/z found, 567.2 $[M+Na]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ 8.49 (br s, 1H), 8.05 (br t, $J = 5.9$ Hz, 1H), 7.29–7.38 (m, 6H), 7.19–7.25 (m, 3H), 7.04–7.08 (m, 1H), 6.89–6.93 (m, 4H), 6.81 (br t, $J = 5.8$ Hz, 1H), 6.66 (dd, $J = 15.5, 5.4$ Hz, 1H), 6.27 (d, $J = 8.4$ Hz, 1H), 5.92 (dd, $J = 15.5, 1.3$ Hz, 1H), 4.58 (br s, 1H), 3.09–3.14 (m, 2H), 2.93–2.99 (m, 2H), 2.91 (dd, $J = 13.7, 6.2$ Hz, 1H), 2.80 (dd, $J = 13.7, 8.1$ Hz, 1H), 1.36 (s, 9H).

(*E*)-(*S*)-4-[3-(4-Phenoxy-phenyl)-ureido]-5-phenyl-pent-2-enoic acid (2-amino-ethyl)-amide. MS (electrospray): mass calculated for $C_{26}H_{28}N_4O_3$, 444.22; m/z found, 445.2 $[M+H]^+$, 467.2 $[M+Na]^+$, 889.4 $[2M+H]^+$, 911.4 $[2M+Na]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.45 (br t, $J = 5.6$ Hz, 1H), 7.20–7.04 (m, 8H), 6.96–6.92 (m, 2H), 6.86–6.76 (m, 4H), 6.66 (dd, $J = 15.3, 5.5$ Hz, 1H), 6.14 (d, $J = 7.7$ Hz, 1H), 5.88 (d, $J = 15.0$ Hz, 1H), 4.65–4.57 (m, 1H), 3.21–3.14 (m, 1H), 3.11–3.03 (m, 1H), 2.75 (d, $J = 7.0$ Hz, 2H), 2.63–2.59 (m, 2H), (2.08 br s, 2H).

4.4.4. (*E*)-(*S*)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoic acid (3-amino-propyl)-amide (24a). MS (electrospray): mass calculated for $C_{27}H_{30}N_4O_2$, 442.24; m/z found, 443.2 $[M+H]^+$, 885.5 $[2M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.45–7.11 (m, 14H), 6.62 (dd, $J = 6.2, 15.3$ Hz, 1H), 5.94 (d, $J = 7.2$ Hz, 1H),

5.85 (d, $J = 15.3$ Hz, 1H), 4.74–4.67 (m, 1H), 3.33–3.22 (m, 2H), 2.89–2.78 (m, 2H), 2.70–2.63 (m, 2H), 1.58 (br s, 2H), 1.52 (t, $J = 6.4$ Hz, 2H).

4.4.5. (*E*)-(*R*)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoic acid (3-amino-propyl)-amide (24b). {3-[(*E*)-(*R*)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoylamino]-propyl}-carbamic acid *tert*-butyl ester.

MS (electrospray): mass calculated for $C_{32}H_{38}N_4O_4$, 542.29; m/z found, 443.2 $[M-BOC]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.33–7.39 (m, 4H), 7.26–7.30 (m, 4H), 7.15–7.21 (m, 4H), 7.11–7.13 (m, 2H), 6.86 (t, $J = 5.7$ Hz, 1H), 6.67 (dd, $J = 15.3, 5.1$ Hz, 1H), 5.93 (d, $J = 8.2$ Hz, 1H), 5.83 (d, $J = 15.3$ Hz, 1H), 4.96 (br s, 1H), 4.71 (br s, 1H), 3.23–3.33 (m, 1H), 2.97–3.12 (m, 3H), 2.74–2.85 (m, 2H), 1.48–1.55 (b, 2H), 1.34 (s, 9H).

(*E*)-(*R*)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoic acid (3-amino-propyl)-amide.

MS (electrospray): mass calculated for $C_{27}H_{30}N_4O_2$, 442.24; m/z found, 443.2 $[M+H]^+$, 465.2 $[M+Na]^+$, 885.5 $[2M+H]^+$, 907.4 $[2M+Na]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.38–7.09 (m, 14H), 6.63 (dd, $J = 15.3, 6.0$ Hz, 1H), 6.20 (d, $J = 7.7$ Hz, 1H), 5.87 (d, $J = 15.3$ Hz, 1H), 4.71–4.67 (m, 1H), 3.26–3.22 (m, 2H), 2.85–2.76 (m, 2H), 2.62–2.53 (m, 2H), 1.79 (br s, 2H), 1.47 (t, $J = 5.6$ Hz, 2H).

4.4.6. (*E*)-(*S*)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoic acid (2-methylamino-ethyl)-amide (25). MS (electrospray): mass calculated for $C_{27}H_{30}N_4O_2$, 442.24; m/z found, 443.2 $[M+H]^+$, 465.2 $[M+Na]^+$, 885.4 $[2M+H]^+$, 907.4 $[2M+Na]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 8.23 (br s, 1H), 7.46 (br t, $J = 5.0$ Hz, 1H), 7.40–7.26 (m, 9H), 7.21–7.06 (m, 5H), 6.65 (dd, $J = 15.3, 5.3$ Hz, 1H), 6.19 (d, $J = 7.8$ Hz, 1H), 5.85 (d, $J = 14.9$ Hz, 1H), 4.68–4.62 (m, 1H), 3.35–3.30 (m, 1H), 3.19–3.14 (m, 1H), 2.76–2.54 (m, 5H), 2.24 (s, 3H).

4.4.7. (*E*)-(*S*)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoic acid (2-dimethylamino-ethyl)-amide (28). MS (electrospray): mass calculated for $C_{28}H_{32}N_4O_2$, 456.25; m/z found, 457.2 $[M+H]^+$, 479.2 $[M+Na]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.37–7.04 (m, 14H), 6.65 (dd, $J = 15.3, 5.7$ Hz, 1H), 6.28 (d, $J = 8.1$ Hz, 1H), 5.88 (dd, $J = 15.3, 0.8$ Hz, 1H), 4.70–4.63 (m, 1H), 3.31–3.25 (m, 1H), 3.21–3.15 (m, 1H), 2.80–2.69 (m, 2H), 2.37–2.26 (m, 2H), 2.09 (s, 6H).

4.4.8. (*E*)-(*S*)-4-[3-(4-Phenoxyphenyl)-ureido]-5-phenyl-pent-2-enoic acid (2-dimethylamino-ethyl)-amide (29). MS (electrospray): mass calculated for $C_{28}H_{32}N_4O_3$, 472.59; m/z found, 473.2 $[M+H]^+$, 495.2 $[M+Na]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.20–7.07 (m, 9H), 6.97–6.92 (m, 1H), 6.84–6.78 (m, 1H), 6.64 (dd, $J = 15.3, 5.7$ Hz, 1H), 5.95 (d, $J = 8.4$ Hz, 1H), 5.85 (dd,

$J = 15.3, 1.2 \text{ Hz, 1H}$), 4.71–4.62 (m, 1H), 3.38–3.31 (m, 1H), 3.20–3.15 (m, 1H), 2.80–2.39 (m, 2H), 2.39–2.27 (m, 2H), 2.13 (s, 6H).

4.4.9. (E)-(S)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoic acid (3-dimethylamino-propyl)-amide (30). MS (electrospray): mass calculated for $\text{C}_{29}\text{H}_{34}\text{N}_4\text{O}_2$, 470.27; m/z found, 471.3 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 8.13 (s, 1H), 7.81 (t, $J = 5.0 \text{ Hz, 1H}$), 7.50–7.33 (m, 8H), 7.30–7.19 (m, 6H), 6.67 (dd, $J = 15.4, 6.8 \text{ Hz, 1H}$), 6.54 (d, $J = 8.6 \text{ Hz, 1H}$), 5.98 (d, $J = 17.6 \text{ Hz, 1H}$), 4.88–4.81 (m, 1H), 3.47–3.29 (m, 2H), 2.96 (dd, $J = 13.6, 7.0 \text{ Hz, 1H}$), 2.88 (dd, $J = 13.6, 7.0 \text{ Hz, 1H}$), 2.34 (t, $J = 6.4 \text{ Hz, 2H}$), 2.17 (s, 6H), 1.69–1.63 (m, 2H).

4.4.10. (E)-(S)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoic acid (2-diethylamino-ethyl)-amide (31). (E)-(S)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoic acid.

MS (electrospray): mass calculated for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_3$, 386.45; m/z found, 387.1 $[\text{M}+\text{H}]^+$, 409.1 $[\text{M}+\text{Na}]^+$. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 12.32 (br s, 1H), 8.55 (s, 1H), 7.53–7.64 (m, 5H), 7.40–7.48 (m, 4H), 7.16–7.34 (m, 5H), 6.86 (dd, $J = 15.6, 5.1 \text{ Hz, 1H}$), 6.41 (d, $J = 8.4 \text{ Hz, 1H}$), 5.78 (dd, $J = 15.6, 1.5 \text{ Hz, 1H}$), 4.63–4.69 (m, 1H), 2.94 (dd, $J = 13.7, 6.2 \text{ Hz, 1H}$), 2.86 (dd, $J = 13.7, 7.8 \text{ Hz, 1H}$). ^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz) δ 166.9, 154.2, 148.7, 138.8, 139.6, 137.6, 132.8, 129.2, 128.9, 128.2, 128.3, 128.0, 126.9, 126.1, 120.7, 118.4, 51.6, 51.2 ppm.

(E)-(S)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoic acid (2-diethylamino-ethyl)-amide. MS (electrospray): mass calculated for $\text{C}_{30}\text{H}_{36}\text{N}_4\text{O}_2$, 484.64; m/z found, 485.3 $[\text{M}+\text{H}]^+$, 507.2 $[\text{M}+\text{Na}]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.39 (br s, 1H), 7.36–7.50 (m, 8H), 7.18–7.31 (m, 6H), 7.03 (br t, $J = 5.0 \text{ Hz, 1H}$), 6.75 (dd, $J = 15.4, 6.3 \text{ Hz, 1H}$), 6.51 (d, $J = 8.2 \text{ Hz, 1H}$), 6.03 (dd, $J = 15.4, 0.9 \text{ Hz, 1H}$), 4.78–4.85 (m, 1H), 3.28–3.44 (m, 2H), 2.81–2.95 (m, 2H), 2.53–2.65 (m, 6H), 1.00 (t, $J = 8.2 \text{ Hz, 6H}$).

4.4.11. (E)-(S)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoic acid (3-diethylamino-propyl)-amide (32). MS (electrospray): mass calculated for $\text{C}_{31}\text{H}_{38}\text{N}_4\text{O}_2$, 498.30; m/z found, 499.3 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 8.29 (s, 1H), 8.29 (t, $J = 4.8 \text{ Hz, 1H}$), 7.52–7.36 (m, 8H), 7.31–7.20 (m, 6H), 6.70 (dd, $J = 15.4, 6.8 \text{ Hz, 1H}$), 6.66 (d, $J = 9.7 \text{ Hz, 1H}$), 5.97 (dd, $J = 15.4, 0.9 \text{ Hz, 1H}$), 4.90–4.83 (m, 1H), 3.45–3.31 (m, 2H), 2.99 (dd, $J = 13.7, 6.9 \text{ Hz, 1H}$), 2.89 (dd, $J = 13.7, 7.2 \text{ Hz, 1H}$), 2.52–2.44 (m, 6H), 1.71–1.60 (m, 2H), 0.98 (t, $J = 7.1 \text{ Hz, 6H}$).

4.4.12. (E)-(S)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoic acid (2-pyrrolidin-1-yl-ethyl)-amide (33). MS (electrospray): mass calculated for $\text{C}_{30}\text{H}_{34}\text{N}_4\text{O}_2$, 482.27; m/z found, 483.3 $[\text{M}+\text{H}]^+$, 505.2 $[\text{M}+\text{Na}]^+$, 987.5 $[2\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 7.99 (s, 1H), 7.53 (d, $J = 7.4 \text{ Hz, 2H}$), 7.49–7.37 (m, 7H), 7.32–7.20

(m, 5H), 6.80 (dd, $J = 15.3, 5.1 \text{ Hz, 1H}$), 5.97–5.93 (m, 2H), 4.89–4.83 (m, 1H), 4.51–4.45 (m, 1H), 3.63–3.55 (m, 1H), 3.28–3.21 (m, 1H), 2.95 (dd, $J = 13.7, 7.3 \text{ Hz, 1H}$), 2.87 (dd, $J = 13.7, 7.3 \text{ Hz, 1H}$), 2.72–2.65 (m, 2H), 2.53–2.45 (m, 4H), 1.78–1.69 (m, 4H).

4.4.13. (Z)-(S)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoic acid (2-pyrrolidin-1-yl-ethyl)-amide (33a). Step A. (Z)-(S)-4-*tert*-Butoxycarbonylamino-5-phenyl-pent-2-enoic acid methyl ester. To a solution of bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)-phosphonate (0.32 g, 1.0 mmol) in THF (10 mL) was added 18-crown-6 (0.265 g, 1.0 mmol), and the resulting solution was cooled (-78°C). The solution was treated with potassium bis(trimethylsilyl)amide (0.2 g, 1.0 mmol) and ((S)-1-benzyl-2-oxo-ethyl)-carbamic acid *tert*-butyl ester (0.25 g, 1.0 mmol), and stirred (-78°C , 0.5 h). The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc ($2 \times 50 \text{ mL}$). The organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography using 0–40% (EtOAc/hexanes) to provide the desired product as a white solid (0.185 g, 59%); MS (electrospray): mass calculated for $\text{C}_{17}\text{H}_{23}\text{NO}_4$, 305.37; m/z found, 328.1 $[\text{M}+\text{Na}]^+$. ^1H NMR (CDCl_3 , 400 MHz) δ 7.31–7.38 (m, 2H), 7.20–7.26 (m, 3H), 6.23 (br s, 1H), 5.86 (dd, $J = 11.6, 1.0 \text{ Hz, 1H}$), 5.36 (br s, 1H), 4.79 (br s, 1H), 3.75 (s, 3H), 2.99–3.04 (m, 1H), 2.91 (br s, 1H), 1.39 (s, 9H).

Step B. [(Z)-(S)-1-Benzyl-3-(2-pyrrolidin-1-yl-ethylcarbamoyl)-allyl]-carbamic acid *tert*-butyl ester. To a solution of (Z)-(S)-4-*tert*-butoxycarbonylamino-5-phenyl-pent-2-enoic acid methyl ester (0.10 g, 0.33 mmol) in toluene (3.6 mL) was added aminoethylpyrrolidine (0.041 g, 0.36 mmol) and trimethylaluminum (2 M in hexanes, 0.026 g, 0.36 mmol), and the solution was stirred (25°C , 4 h). The solvent was removed in vacuo, and the residue was partitioned with 1 N NaOH and CH_2Cl_2 (50 mL each). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography using 0–20% (1% $\text{NH}_4\text{OH}/\text{MeOH}$ in CH_2Cl_2) to provide the desired product as a clear oil (0.02 g, 16%); MS (electrospray): mass calculated for $\text{C}_{22}\text{H}_{33}\text{N}_3\text{O}_3$, 387.25; m/z found, 388.2 $[\text{M}+\text{H}]^+$, 410.2 $[\text{M}+\text{Na}]^+$. ^1H NMR (CDCl_3 , 400 MHz) δ 7.20–7.25 (m, 2H), 7.13–7.18 (m, 3H), 5.72–5.81 (m, 2H), 5.08 (br s, 1H), 4.94 (br s, 1H), 3.28–3.45 (m, 2H), 2.91 (dd, $J = 13.4, 5.6 \text{ Hz, 1H}$), 2.77–2.86 (m, 1H), 2.51–2.61 (m, 2H), 2.42–2.47 (m, 4H), 1.65–1.71 (m, 4H), 1.32 (s, 9H).

Step C. (Z)-(S)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoic acid (2-pyrrolidin-1-yl-ethyl)-amide. Prepared by a route similar to Example 11, step C. MS (electrospray): mass calculated for $\text{C}_{30}\text{H}_{34}\text{N}_4\text{O}_2$, 482.62; m/z found, 483.3 $[\text{M}+\text{H}]^+$. ^1H NMR (CDCl_3 , 400 MHz) δ 7.45–7.49 (m, 4H), 7.39–7.42 (m, 2H), 7.33 (t, $J = 7.3 \text{ Hz, 2H}$), 7.18–7.26 (m, 3H), 7.11–7.17 (m, 3H), 5.71–5.77 (m, 2H), 5.45 (br s, 1H), 3.38–3.46 (m, 2H), 3.24–3.35 (m, 1H), 2.87 (dd, $J = 13.6, 6.8 \text{ Hz, 1H}$), 2.76

(dd, $J = 13.6, 6.8$ Hz, 1H), 2.54–2.64 (m, 2H), 2.48 (br s, 4H), 1.71 (br s, 4H).

4.4.14. (Z)-(S)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoic acid (2-pyrrolidin-1-yl-ethyl)-amide (33b). Step A. (Z)-(S)-4-*tert*-Butoxycarbonylamino-5-phenyl-pent-2-enoic acid methyl ester. To a solution of bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)-phosphonate (0.32 g, 1.0 mmol) in THF (10 mL) was added 18-crown-6 (0.265 g, 1.0 mmol), and the resulting solution was cooled (-78°C). The solution was treated with potassium bis(trimethylsilyl)amide (0.2 g, 1.0 mmol) and ((S)-1-benzyl-2-oxo-ethyl)-carbamic acid *tert*-butyl ester (0.25 g, 1.0 mmol), and stirred (-78°C , 0.5 h). The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (2×50 mL). The organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography using 0–40% (EtOAc/hexanes) to provide the desired product as a white solid (0.185 g, 59%): MS (electrospray): mass calculated for $\text{C}_{17}\text{H}_{23}\text{NO}_4$, 305.37; m/z found, 328.1 $[\text{M}+\text{Na}]^+$. ^1H NMR (CDCl_3 , 400 MHz) δ 7.31–7.38 (m, 2H), 7.20–7.26 (m, 3H), 6.23 (br s, 1H), 5.86 (dd, $J = 11.6, 1.0$ Hz, 1H), 5.36 (br s, 1H), 4.79 (br s, 1H), 3.75 (s, 3H), 2.99–3.04 (m, 1H), 2.91 (br s, 1H), 1.39 (s, 9H).

Step B. [(Z)-(S)-1-Benzyl-3-(2-pyrrolidin-1-yl-ethylcarbamoyl)-allyl]-carbamic acid *tert*-butyl ester. To a solution of (Z)-(S)-4-*tert*-butoxycarbonylamino-5-phenyl-pent-2-enoic acid methyl ester (0.10 g, 0.33 mmol) in toluene (3.6 mL) was added aminoethylpyrrolidine (0.041 g, 0.36 mmol) and trimethylaluminum (2 M in hexanes, 0.026 g, 0.36 mmol), and the solution was stirred (25°C , 4 h). The solvent was removed in vacuo, and the residue was partitioned with 1 N NaOH and CH_2Cl_2 (50 mL each). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography using 0–20% (1% $\text{NH}_4\text{OH}/\text{MeOH}$ in CH_2Cl_2) to provide the desired product as a clear oil (0.02 g, 16%): MS (electrospray): mass calculated for $\text{C}_{22}\text{H}_{33}\text{N}_3\text{O}_3$, 387.25; m/z found, 388.2 $[\text{M}+\text{H}]^+$; 410.2 $[\text{M}+\text{Na}]^+$. ^1H NMR (CDCl_3 , 400 MHz) δ 7.20–7.25 (m, 2H), 7.13–7.18 (m, 3H), 5.72–5.81 (m, 2H), 5.08 (br s, 1H), 4.94 (br s, 1H), 3.28–3.45 (m, 2H), 2.91 (dd, $J = 13.4, 5.6$ Hz, 1H), 2.77–2.86 (m, 1H), 2.51–2.61 (m, 2H), 2.42–2.47 (m, 4H), 1.65–1.71 (m, 4H), 1.32 (s, 9H).

Step C. (Z)-(S)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoic acid (2-pyrrolidin-1-yl-ethyl)-amide. Prepared by a route similar to Example 11, step C. MS (electrospray): mass calculated for $\text{C}_{30}\text{H}_{34}\text{N}_4\text{O}_2$, 482.62; m/z found, 483.3 $[\text{M}+\text{H}]^+$. ^1H NMR (CDCl_3 , 400 MHz) δ 7.45–7.49 (m, 4H), 7.39–7.42 (m, 2H), 7.33 (t, $J = 7.3$ Hz, 2H), 7.18–7.26 (m, 3H), 7.11–7.17 (m, 3H), 5.71–5.77 (m, 2H), 5.45 (br s, 1H), 3.38–3.46 (m, 2H), 3.24–3.35 (m, 1H), 2.87 (dd, $J = 13.6, 6.8$ Hz, 1H), 2.76 (dd, $J = 13.6, 6.8$ Hz, 1H), 2.54–2.64 (m, 2H), 2.48 (br s, 4H), 1.71 (br s, 4H).

4.4.15. (E)-(S)-4-[3-(4-Phenoxyphenyl)-ureido]-5-phenyl-pent-2-enoic acid (2-pyrrolidin-1-yl-ethyl)-amide (34). MS (electrospray): mass calculated for $\text{C}_{30}\text{H}_{34}\text{N}_4\text{O}_3$, 498.26; m/z found, 499.2 $[\text{M}+\text{H}]^+$, 997.54 $[2\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 8.31 (s, 1H), 7.59 (br t, $J = 5.2$ Hz, 1H), 7.34–7.31 (m, 2H), 7.30–7.24 (m, 4H), 7.20–7.18 (m, 3H), 7.07–7.03 (m, 1H), 6.93–6.88 (m, 4H), 6.75 (dd, $J = 15.3, 5.2$ Hz, 1H), 6.21 (d, $J = 8.2$ Hz, 1H), 5.95 (dd, $J = 15.3, 1.3$ Hz, 1H), 4.78–4.72 (m, 1H), 3.53–3.45 (m, 1H), 3.33–3.25 (m, 1H), 2.88 (dd, $J = 13.7, 7.5$ Hz, 1H), 2.81 (dd, $J = 13.7, 7.2$ Hz, 1H), 2.76–2.70 (m, 1H), 2.66–2.58 (m, 5H), 1.82–1.74 (m, 4H).

4.4.16. (E)-(R)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoic acid (3-pyrrolidin-1-yl-propyl)-amide (35b). MS (electrospray): mass calculated for $\text{C}_{31}\text{H}_{36}\text{N}_4\text{O}_2$, 496.28; m/z found, 497.3 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 8.22 (s, 1H), 7.99 (t, $J = 5.4$ Hz, 1H), 7.50–7.35 (m, 8H), 7.30–7.18 (m, 6H), 6.69 (dd, $J = 15.3, 6.5$ Hz, 1H), 6.55 (d, $J = 8.5$ Hz, 1H), 5.94 (dd, $J = 15.3, 1.0$ Hz, 1H), 4.87–4.80 (m, 1H), 3.45–3.29 (m, 2H), 2.98–2.89 (m, 2H), 2.54 (t, $J = 6.6$ Hz, 2H), 2.45 (br s, 4H), 1.77–1.67 (m, 6H).

4.4.17. (E)-(S)-4-[3-(4-Phenoxyphenyl)-ureido]-5-phenyl-pent-2-enoic acid (3-pyrrolidin-1-yl-propyl)-amide (36). MS (electrospray): mass calculated for $\text{C}_{31}\text{H}_{36}\text{N}_4\text{O}_3$, 512.28; m/z found, 513.3 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 8.51 (s, 1H), 7.93 (br t, $J = 5.0$ Hz, 1H), 7.31–7.15 (m, 9H), 7.05–7.01 (m, 1H), 6.91–6.85 (m, 4H), 6.69 (dd, $J = 15.4, 5.8$ Hz, 1H), 6.50 (d, $J = 8.0$ Hz, 1H), 5.96 (dd, $J = 14.6, 0.72$ Hz, 1H), 4.77–4.70 (m, 1H), 3.35–3.21 (m, 2H), 2.91–2.79 (m, 2H), 2.60 (s, 6H), 1.76–1.68 (m, 6H).

4.5. General procedure for the preparation of urea derivatives 37–45, and exemplified for compound 37

4.5.1. (R)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pentanoic acid (2-amino-ethyl)-amide (37a). Step A. (R)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pentanoic acid.

MS (electrospray): mass calculated for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_3$, 388.46; m/z found, 389.2 $[\text{M}+\text{H}]^+$, 411.1 $[\text{M}+\text{Na}]^+$, 387.1 $[\text{M}-\text{H}]^-$. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 12.00 (br s, 1H), 8.44 (br s, 1H), 7.52–7.62 (m, 4H), 7.40–7.47 (m, 4H), 7.28–7.32 (m, 4H), 7.18–7.24 (m, 2H), 6.06 (d, $J = 8.6$ Hz, 1H), 3.85–3.94 (m, 1H), 2.72–2.80 (m, 2H), 2.20–2.38 (m, 2H), 1.71–1.79 (m, 1H), 1.49–1.57 (m, 1H).

Step B. {2-[(R)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pentanoylamino]-ethyl}-carbamic acid *tert*-butyl ester.

MS (electrospray): mass calculated for $\text{C}_{31}\text{H}_{38}\text{N}_4\text{O}_4$, 530.66; m/z found, 531.3 $[\text{M}+\text{H}]^+$, 553.3 $[\text{M}+\text{Na}]^+$. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 8.64 (br s, 1H), 7.84 (br s, 1H), 7.60 (d, $J = 8.1$ Hz, 2H), 7.53 (d, $J = 8.5$ Hz, 2H), 7.40–7.47 (m, 4H), 7.28–7.32 (m, 3H), 7.18–7.23

(m, 3H), 6.77 (br t, $J = 5.4$ Hz, 1H), 6.03 (d, $J = 8.6$ Hz, 1H), 3.86 (br s, 1H), 3.02–3.07 (m, 2H), 2.94–2.99 (m, 2H), 2.74 (d, $J = 6.4$ Hz, 2H), 2.08–2.19 (m, 2H), 1.70–1.75 (m, 1H), 1.51–1.56 (m, 1H), 1.36 (s, 9H).

4.5.2. (S)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pentanoic acid (2-amino-ethyl)-amide (37b). Step A. {2-[(S)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pentanoylamino]-ethyl}-carbamic acid *tert*-butyl ester.

MS (electrospray): mass calculated for $C_{32}H_{38}N_4O_4$, 530.66; m/z found, 531.3 $[M+H]^+$, 553.2 $[M+Na]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.44–7.47 (m, 2H), 7.39–7.42 (m, 2H), 7.27–7.31 (m, 4H), 7.06–7.21 (m, 6H), 3.87–3.94 (m, 2H), 3.14–3.18 (m, 1H), 3.00–3.10 (m, 3H), 2.68–2.77 (m, 2H), 2.18 (t, $J = 7.4$ Hz, 2H), 1.75–1.84 (m, 1H), 1.53–1.62 (m, 1H), 1.30 (s, 9H).

Step B. (S)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pentanoic acid (2-amino-ethyl)-amide.

MS (electrospray): mass calculated for $C_{26}H_{30}N_4O_2$, 430.24; m/z found, 431.2 $[M+H]^+$, 453.2 $[M+Na]^+$, 883.4 $[2M+Na]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.56 (br s, 1H), 7.47–7.13 (m, 14H), 6.70–6.66 (m, 1H), 5.22 (d, $J = 5.9$ Hz, 1H), 4.08–4.01 (m, 1H), 3.27–3.18 (m, 2H), 2.81 (dd, $J = 13.6$, 6.1 Hz, 1H), 2.73–2.67 (m, 3H), 2.29–2.12 (m, 2H), 1.79 (br s, 2H), 1.74–1.63 (m, 2H).

4.5.3. (R)-4-[3-(4-Phenoxyphenyl)-ureido]-5-phenyl-pentanoic acid (2-amino-ethyl)-amide (38). (2-{[(R)-4-[3-(4-Phenoxyphenyl)-ureido]-5-phenyl-pentanoylamino]}-ethyl)-carbamic acid *tert*-butyl ester.

MS (electrospray): mass calculated for $C_{31}H_{38}N_4O_5$, 546.28; m/z found, 547.2 $[M+H]^+$, 569.3 $[M+Na]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.54 (br s, 1H), 7.14–7.21 (m, 5H), 7.05–7.11 (m, 6H), 6.96 (t, $J = 7.3$ Hz, 1H), 6.77–6.85 (m, 4H), 5.55 (br d, $J = 7.8$ Hz, 1H), 5.30 (br s, 1H), 3.95 (br s, 1H), 3.03–3.29 (m, 4H), 2.64–2.74 (m, 2H), 2.17 (br t, $J = 6.8$ Hz, 1H), 1.70–1.79 (m, 1H), 1.54–1.64 (m, 1H), 1.32 (s, 9H).

(R)-4-[3-(4-Phenoxyphenyl)-ureido]-5-phenyl-pentanoic acid (2-amino-ethyl)-amide.

MS (electrospray): mass calculated for $C_{26}H_{30}N_4O_3$, 446.23; m/z found, 447.2 $[M+H]^+$, 469.2 $[M+Na]^+$, 915.4 $[2M+Na]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.77 (br s, 1H), 7.24–7.08 (m, 8H), 7.00–6.93 (m, 2H), 6.88–6.79 (m, 4H), 5.49 (d, $J = 8.6$ Hz, 1H), 4.03–3.94 (m, 1H), 3.20–3.11 (m, 2H), 2.75 (dd, $J = 6.4$, 3.6 Hz, 1H), 2.70–2.65 (m, 3H), 2.25–2.13 (m, 2H), 1.80–1.71 (m, 2H).

4.5.4. (R)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pentanoic acid (3-amino-propyl)-amide (39). {3-[(E)-(S)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pent-2-enoylamino]-propyl}-carbamic acid *tert*-butyl ester.

MS (electrospray): mass calculated for $C_{32}H_{38}N_4O_4$, 542.67; m/z found, 543.2 $[M+H]^+$. 1H NMR (400 MHz,

$DMSO-d_6$) δ 8.62 (br s, 1H), 8.03 (br t, $J = 5.7$ Hz, 1H), 7.60–7.66 (m, 5H), 7.42–7.48 (m, 4H), 7.25–7.33 (m, 5H), 6.79 (br t, $J = 5.7$ Hz, 1H), 6.68 (dd, $J = 15.2$, 5.2 Hz, 1H), 6.36 (d, $J = 8.6$ Hz, 1H), 5.95 (dd, $J = 15.2$, 1.4 Hz, 1H), 4.62 (br s, 1H), 3.05–3.13 (m, 2H), 2.80–2.95 (m, 4H), 1.47–1.55 (m, 2H), 1.36 (s, 9H).

{3-[(R)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pentanoylamino]-propyl}-carbamic acid *tert*-butyl ester.

MS (electrospray): mass calculated for $C_{32}H_{40}N_4O_4$, 544.69; m/z found, 545.3 $[M+H]^+$, 567.3 $[M+Na]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.39–7.47 (m, 4H), 7.27–7.31 (m, 4H), 3.86–3.93 (m, 1H), 3.00–3.10 (m, 2H), 2.90–2.95 (m, 2H), 2.72 (d, $J = 6.9$ Hz, 2H), 2.14–2.22 (m, 4H), 1.74–1.83 (m, 1H), 1.47–1.63 (m, 3H), 1.31 (s, 9H).

(R)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pentanoic acid (3-amino-propyl)-amide.

MS (electrospray): mass calculated for $C_{27}H_{32}N_4O_2$, 444.25; m/z found, 445.2 $[M+H]^+$, 467.2 $[M+Na]^+$, 911.5 $[2M+Na]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 8.04 (br s, 1H), 7.50–7.32 (m, 8H), 7.23–7.10 (m, 6H), 7.05 (t, $J = 5.1$ Hz, 1H), 5.64 (br d, $J = 7.6$ Hz, 1H), 4.06–3.95 (m, 1H), 3.30–3.13 (m, 2H), 2.84 (dd, $J = 13.5$, 5.9 Hz, 1H), 2.67 (dd, $J = 13.5$, 5.7 Hz, 1H), 2.60 (t, $J = 5.7$ Hz, 2H), 2.26–2.11 (m, 2H), 2.00 (br s, 2H), 1.75–1.63 (m, 2H), 1.46 (t, $J = 5.9$ Hz, 2H).

4.5.5. (R)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pentanoic acid (2-methylamino-ethyl)-amide (40). MS (electrospray): mass calculated for $C_{27}H_{32}N_4O_2$, 444.25; m/z found, 445.2 $[M+H]^+$, 467.2 $[M+Na]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 8.50 (br s, 1H), 7.71 (s, 1H), 7.40–7.34 (m, 4H), 7.30–7.19 (m, 6H), 7.15–7.04 (m, 4H), 6.14 (d, $J = 8.7$ Hz, 1H), 3.94–3.86 (m, 1H), 3.55–3.46 (m, 1H), 3.26–3.18 (m, 1H), 2.98–2.90 (m, 1H), 2.73–2.62 (m, 3H), 2.40 (s, 3H), 2.29–2.11 (m, 2H), 1.91–1.80 (m, 1H), 1.50–1.36 (m, 1H).

4.5.6. (R)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pentanoic acid (2-diethylamino-ethyl)-amide (43). MS (electrospray): mass calculated for $C_{30}H_{38}N_4O_2$, 486.30; m/z found, 487.3 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.44–7.29 (m, 8H), 7.23–7.09 (m, 6H), 6.74 (br s, 1H), 5.84 (br s, 1H), 4.05–3.96 (m, 1H), 3.30–3.22 (m, 1H), 3.17–3.10 (m, 1H), 2.83 (dd, $J = 13.6$, 6.0 Hz, 1H), 2.66 (dd, $J = 13.6$, 7.2 Hz, 1H), 2.47–2.41 (m, 6H), 2.22 (t, $J = 7.0$ Hz, 2H), 1.79–1.72 (m, 1H), 1.67–1.59 (m, 1H), 0.88 (t, $J = 7.2$ Hz, 6H).

4.5.7. (S)-4-(N'-Biphenyl-4-yl-N'-cyanoguanidino)-5-phenyl-pentanoic acid (2-pyrrolidin-1-yl-ethyl)-amide (44). [(E)-(R)-1-Benzyl-3-(2-pyrrolidin-1-yl-ethylcarbamoyl)-allyl]-carbamic acid *tert*-butyl ester. MS (electrospray): mass calculated for $C_{22}H_{33}N_3O_3$, 387.25; m/z found, 388.3 $[M+H]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.33–7.14 (m, 5H), 6.70 (dd, $J = 5.5$, 15.3 Hz, 1H), 5.88 (d,

$J = 15.3$ Hz, 1H), 4.43–4.40 (m, 1H), 3.93 (m, 2H), 2.95–2.83 (m, 2H), 2.77–2.43 (m, 6H), 1.90–1.85 (m, 4H), 1.36 (s, 9H).

[(*S*)-1-Benzyl-3-(2-pyrrolidin-1-yl-ethylcarbamoyl)-propyl]-carbamic acid *tert*-butyl ester.

MS (electrospray): mass calculated for $C_{22}H_{35}N_3O_3$, 389.27; m/z found, 390.3 $[M+H]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.26–7.13 (m, 5H), 3.70–3.59 (m, 1H), 3.35–3.27 (m, 2H), 2.71 (d, $J = 7.2$ Hz, 2H), 2.61–2.56 (m, 6H), 2.29–2.14 (m, 2H), 1.85–1.80 (m, 4H), 1.650–1.58 (m, 1H), 1.37 (s, 9H).

(*S*)-4-(*N'*-Biphenyl-4-yl-*N''*-cyano-guanidino)-5-phenyl-pentanoic acid (2-pyrrolidin-1-yl-ethyl)-amide.

MS (electrospray): mass calculated for $C_{31}H_{36}N_6O$, 508.30; m/z found, 509.3 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.57–7.51 (m, 4H), 7.43 (t, $J = 7.6$ Hz, 2H), 7.35–7.21 (m, 8H), 6.81 (br s, 1H), 4.26–4.18 (m, 1H), 3.38–3.29 (m, 2H), 2.88 (d, $J = 4.4$ Hz, 2H), 2.58 (t, $J = 6.0$ Hz, 2H), 2.51 (br s, 4H), 2.37–2.29 (m, 1H), 2.28–2.22 (m, 1H), 1.90–1.82 (m, 2H), 1.76 (br s, 4H).

4.5.8. (*R*)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pentanoic acid (2-pyrrolidin-1-yl-ethyl)-amide (44). MS (electrospray): mass calculated for $C_{30}H_{36}N_4O_2$, 484.28; m/z found, 485.2 $[M+H]^+$, 507.2 $[M+Na]^+$, 991.5 $[2M+Na]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.52–7.37 (m, 9H), 7.32–7.14 (m, 5H), 6.06 (br d, $J = 6.6$ Hz, 1H), 4.13–4.05 (m, 1H), 3.99 (br s, 1H), 3.42–3.36 (m, 1H), 3.33–3.25 (m, 1H), 2.89 (dd, $J = 13.4$, 6.2 Hz, 1H), 2.75 (dd, $J = 13.4$, 7.0 Hz, 1H), 2.61 (t, $J = 6.0$ Hz, 2H), 2.57–2.51 (m, 4H), 2.31 (t, $J = 7.0$ Hz, 2H), 1.90–1.83 (m, 1H), 1.77–1.64 (m, 5H).

4.5.9. (*R*)-4-[3-(4-Phenoxyphenyl)-ureido]-5-phenyl-pentanoic acid (2-pyrrolidin-1-yl-ethyl)-amide (45). MS (electrospray): mass calculated for $C_{30}H_{36}N_4O_3$, 500.28; m/z found, 501.3 $[M+H]^+$, 523.2 $[M+Na]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.74 (br s, 1H), 7.23–7.17 (m, 6H), 7.13–7.09 (m, 3H), 6.97 (t, $J = 7.4$ Hz, 1H), 6.87–6.82 (m, 4H), 5.68 (br d, $J = 4.8$ Hz, 1H), 3.99–3.95 (m, 1H), 3.85 (br s, 1H), 3.34–3.30 (m, 1H), 3.23–3.18 (m, 1H), 2.80 (dd, $J = 13.6$, 6.2 Hz, 1H), 2.66 (dd, $J = 13.6$, 7.0 Hz, 1H), 2.56 (t, $J = 6.0$ Hz, 2H), 2.52–2.48 (m, 4H), 2.24–2.19 (m, 2H), 1.78–1.73 (m, 1H), 1.71–1.67 (m, 4H), 1.62–1.55 (m, 1H).

4.6. The procedure for preparing the cyanoguanidine derivatives 46–53 was analogous to that for compound 17

4.6.1. (*R*)-4-(*N'*-Biphenyl-4-yl-*N''*-cyanoguanidino)-5-phenyl-pentanoic acid (2-dimethylamino-ethyl)-amide (46). [(*E*)-(*S*)-1-Benzyl-3-(2-dimethylamino-ethylcarbamoyl)-allyl]-carbamic acid *tert*-butyl ester. MS (electrospray): mass calculated for $C_{20}H_{31}N_3O_3$, 361.48; m/z found, 362.2 $[M+H]^+$, 384.2 $[M+Na]^+$. 1H NMR ($CDCl_3$,

400 MHz) δ 7.17–7.31 (m, 5H), 6.78 (dd, $J = 14.5$, 5.2 Hz, 1H), 6.25 (br s, 1H), 5.82 (dd, $J = 15.5$, 1.6 Hz, 1H), 4.70 (d, $J = 8.9$ Hz, 1H), 4.59 (br s, 1H), 3.34–3.42 (m, 2H), 2.88–2.93 (m, 2H), 2.40–2.44 (m, 2H), 2.22 (s, 6H), 1.40 (s, 9H).

[(*R*)-1-Benzyl-3-(2-dimethylamino-ethylcarbamoyl)-propyl]-carbamic acid *tert*-butyl ester.

MS (electrospray): mass calculated for $C_{20}H_{33}N_3O_3$, 363.50; m/z found, 364.2 $[M+H]^+$, 386.2 $[M+Na]^+$. 1H NMR ($CDCl_3$, 400 MHz) δ 7.09–7.22 (m, 5H), 6.15 (br s, 1H), 4.52 (br d, $J = 8.5$ Hz, 1H), 3.72 (br s, 1H), 3.21–3.24 (m, 1H), 2.75 (dd, $J = 13.3$, 6.1 Hz, 1H), 2.66 (dd, $J = 13.3$, 6.7 Hz, 1H), 2.31 (t, $J = 6.0$ Hz, 1H), 2.13 (s, 6H), 1.32 (s, 9H).

(*R*)-4-(*N'*-Biphenyl-4-yl-*N''*-cyano-guanidino)-5-phenyl-pentanoic acid (2-dimethylamino-ethyl)-amide.

MS (electrospray): mass calculated for $C_{29}H_{34}N_6O$, 482.62; m/z found, 483.3 $[M+H]^+$. 1H NMR ($CDCl_3$, 400 MHz) δ 9.63 (br s, 1H), 7.23–7.58 (m, 15H), 6.54 (br s, 1H), 4.20–4.25 (m, 1H), 3.30 (br s, 2H), 2.86–2.89 (br s, 2H), 2.32–2.42 (m, 3H), 2.23–2.27 (m, 1H), 2.23 (s, 6H), 1.84–1.88 (br s, 2H).

4.6.2. (*R*)-4-(*N'*-Biphenyl-4-yl-*N''*-cyanoguanidino)-5-phenyl-pentanoic acid (2-diethylamino-ethyl)-amide (47). [(*E*)-(*S*)-1-Benzyl-3-(2-diethylamino-ethylcarbamoyl)-allyl]-carbamic acid *tert*-butyl ester.

MS (electrospray): mass calculated for $C_{22}H_{35}N_3O_3$, 389.53; m/z found, 390.3 $[M+H]^+$, 412.3 $[M+Na]^+$. 1H NMR ($CDCl_3$, 400 MHz) δ 7.17–7.31 (m, 5H), 6.75–6.79 (m, 1H), 6.19 (br s, 1H), 5.80 (d, $J = 15.1$ Hz, 1H), 4.62 (br s, 2H), 3.32–3.42 (m, 2H), 2.88–2.93 (m, 2H), 2.48–2.56 (m, 6H), 1.40 (s, 9H), 1.00 (t, $J = 7.1$ Hz, 6H).

[(*R*)-1-Benzyl-3-(2-diethylamino-ethylcarbamoyl)-propyl]-carbamic acid *tert*-butyl ester.

MS (electrospray): mass calculated for $C_{22}H_{37}N_3O_3$, 391.55; m/z found, 392.3 $[M+H]^+$, 414.3 $[M+Na]^+$. 1H NMR ($CDCl_3$, 400 MHz) δ 7.18–7.32 (m, 5H), 6.28 (br s, 1H), 4.58 (br d, $J = 8.8$ Hz, 1H), 3.80–3.83 (br s, 1H), 3.29–3.32 (m, 2H), 2.85 (dd, $J = 13.5$, 6.0 Hz, 1H), 2.75 (dd, $J = 13.5$, 6.8 Hz, 1H), 2.49–2.57 (m, 6H), 2.17–2.30 (m, 2H), 1.84–1.89 (m, 1H), 1.62–1.71 (m, 1H), 1.41 (s, 9H), 1.00 (t, $J = 7.1$ Hz, 6H).

(*R*)-4-(*N'*-Biphenyl-4-yl-*N''*-cyano-guanidino)-5-phenyl-pentanoic acid (2-diethylamino-ethyl)-amide.

MS (electrospray): mass calculated for $C_{31}H_{33}N_6O$, 510.68; m/z found, 511.3 $[M+H]^+$. 1H NMR ($CDCl_3$, 400 MHz) δ 9.66 (br s, 1H), 7.24–7.59 (m, 14H), 6.42 (br s, 1H), 5.60 (br s, 1H), 4.20–4.26 (m, 1H), 2.30 (br s, 2H), 2.86–2.89 (br s, 2H), 2.52–2.57 (m, 6H), 2.37 (br s, 1H), 2.19–2.26 (m, 1H), 2.85–2.88 (br s, 2H), 1.02 (t, $J = 7.1$ Hz, 6H).

4.6.3. (R)-4-(N'-Biphenyl-4-yl-N''-cyanoguanidino)-5-phenyl-pentanoic acid (2-isopropylamino-ethyl)-amide (48). [(E)-(S)-1-Benzyl-3-(2-isopropylamino-ethylcarbamoyl)-allyl]-carbamic acid *tert*-butyl ester. MS (electrospray): mass calculated for $C_{21}H_{33}N_3O_3$, 375.25; m/z found, 376.3 $[M+H]^+$, 398.3 $[M+Na]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.16–7.27 (m, 5H), 6.74 (dd, $J = 15.3$, 5.6 Hz, 1H), 5.97 (d, $J = 15.3$ Hz, 1H), 4.43 (br s, 1H), 3.36 (t, $J = 6.7$ Hz, 2H), 2.75–2.89 (m, 3H), 2.69 (t, $J = 6.7$ Hz, 2H), 1.36 (s, 9H), 1.05 (d, $J = 6.3$ Hz, 6H).

[(R)-1-Benzyl-3-(2-isopropylamino-ethylcarbamoyl)-propyl]-carbamic acid *tert*-butyl ester.

MS (electrospray): mass calculated for $C_{21}H_{35}N_3O_3$, 377.27; m/z found, 376.3 $[M-H]^-$. 1H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.31–7.12 (m, 5H), 6.73 (dd, $J = 15.3$, 5.6 Hz, 1H), 5.97 (d, $J = 15.3$ Hz, 1H), 4.43 (m, 1H), 2.94 (s, 2H), 2.95–2.75 (m, 3H), 2.69 (t, $J = 6.4$ Hz, 2H), 1.29 (s, 9H), 1.04 (d, $J = 6.4$ Hz, 6H).

(R)-4-(N'-Biphenyl-4-yl-N''-cyano-guanidino)-5-phenyl-pentanoic acid (2-isopropylamino-ethyl)-amide.

MS (electrospray): mass calculated for $C_{30}H_{36}N_6O$, 496.66; m/z found, 497.2 $[M+H]^+$, 519.2 $[M+Na]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.51–7.44 (m, 4H), 7.39–7.34 (m, 2H), 7.30–7.11 (m, 8H), 6.40 (br s, 1H), 5.29 (br s, 1H), 4.18–4.08 (m, 1H), 3.30–3.23 (m, 2H), 2.83–2.78 (m, 1H), 2.77–2.70 (m, 2H), 2.67 (t, $J = 5.8$ Hz, 2H), 2.34–2.23 (m, 1H), 2.19–2.12 (m, 1H), 1.80–1.76 (m, 2H), 0.99 (d, $J = 6.4$ Hz, 6H).

4.6.4. (R)-4-(N'-Biphenyl-4-yl-N''-cyanoguanidino)-5-phenyl-pentanoic acid (2-pyrrolidin-1-yl-ethyl)-amide (49a). MS (electrospray): mass calculated for $C_{13}H_{36}N_6O$, 508.66; m/z found, 509.3 $[M+H]^+$, 531.2 $[M+Na]^+$. 1H NMR ($CDCl_3$, 400 MHz) δ 7.57 (br t, $J = 9.5$ Hz, 5H), 7.46 (br t, $J = 7.6$ Hz, 2H), 7.13–7.30 (m, 8H), 6.34 (br s, 1H), 5.36 (br s, 1H), 4.14 (dt, $J = 7.3$, 7.0 Hz, 1H), 3.24–3.40 (m, 2H), 2.72–2.84 (m, 2H), 2.62 (t, $J = 6.0$ Hz, 1H), 2.25 (br s, 4H), 2.28–2.30 (m, 1H), 2.13–2.18 (m, 1H), 1.68–1.80 (m, 6H).

4.6.5. (R)-4-[N'-Cyano-N''-(4-phenoxyphenyl)-guanidino]-5-phenyl-pentanoic acid (2-pyrrolidin-1-yl-ethyl)-amide (50). MS (electrospray): mass calculated for $C_{31}H_{36}N_6O_2$, 524.29; m/z found, 525.3 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.10 (m, 10H), 7.02 (d, $J = 7.9$ Hz, 2H), 6.94 (d, $J = 8.7$ Hz, 2H), 6.58 (br s, 1H), 4.21–4.08 (m, 1H), 3.39–3.30 (m, 2H), 2.85 (d, $J = 6.4$ Hz, 2H), 2.58 (t, $J = 6.0$ Hz, 2H), 2.53–2.49 (m, 4H), 2.41–2.30 (m, 1H), 2.25–2.18 (m, 1H), 1.84–1.73 (m, 6H).

4.6.6. (R)-4-[N'-[4-(4-Chlorophenoxy)-phenyl]-N''-cyano-guanidino]-5-phenyl-pentanoic acid (2-pyrrolidin-1-yl-ethyl)-amide (51). MS (electrospray): mass calculated for $C_{31}H_{35}ClN_6O_2$, 558.25; m/z found, 560.3 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.23–7.10 (m, 9H), 6.88–

6.82 (m, 4H), 6.39 (br s, 1H), 4.12–4.03 (m, 1H), 3.29–3.23 (m, 2H), 2.78 (d, $J = 5.6$ Hz, 2H), 2.50 (t, $J = 6.0$ Hz, 2H), 2.47–2.43 (m, 4H), 2.31–2.22 (m, 1H), 2.16–2.09 (m, 1H), 1.76–1.69 (m, 6H).

4.6.7. (R)-4-[N'-[4-(4-Fluorophenoxy)-phenyl]-N''-cyano-guanidino]-5-phenyl-pentanoic acid (2-pyrrolidin-1-yl-ethyl)-amide (52). MS (electrospray): mass calculated for $C_{31}H_{35}FN_6O_2$, 542.28; m/z found, 543.2 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.22–7.90 (m, 11H), 6.81 (d, $J = 8.6$ Hz, 2H), 6.43 (br s, 1H), 4.10–4.03 (m, 1H), 3.29–3.19 (m, 2H), 2.76 (d, $J = 4.8$ Hz, 2H), 2.51 (t, $J = 6.0$ Hz, 2H), 2.47–2.41 (m, 4H), 2.30–2.21 (m, 1H), 2.16–2.11 (m, 1H), 1.75–1.68 (m, 6H).

4.6.8. (R)-4-[N'-Cyano-N''-(4-p-tolylloxyphenyl)-guanidino]-5-phenyl-pentanoic acid (2-pyrrolidin-1-yl-ethyl)-amide (53). MS (electrospray): mass calculated for $C_{32}H_{38}N_6O_2$, 538.31; m/z found, 539.3 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.02 (m, 9H), 6.94–6.89 (m, 4H), 6.52 (br s, 1H), 4.21–4.08 (m, 1H), 3.42–3.26 (m, 2H), 2.81 (d, $J = 5.6$ Hz, 2H), 2.60 (t, $J = 6.0$ Hz, 2H), 2.56–2.50 (m, 4H), 2.35 (s, 3H), 2.34–2.29 (m, 1H), 2.25–2.18 (m, 1H), 1.83–1.78 (m, 6H).

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