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

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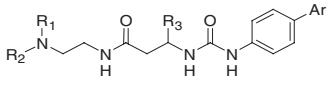
Abstract—Several β- and γ-amino acid derivatives were prepared as glycine transport inhibitors and their ability to block the uptake of [^{14}C]-glycine in COS7 cells transfected with human glycine transporter-2 (*h*GlyT-2) were evaluated. A range of lipophilic side chains were tolerated in the β-amino acid series (i.e., Ph, CH_2Ph, $CH(CH_3)_2$, and $CH_2CH(CH_3)_2$). 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 cyanogunaidine moiety was necessary for in vitro activity.

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_2Ph	Ph
5	CH_3	CH_3	CH_2Ph	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_2Ph	Ph
11	$(CH_2)_4$		CH_2Ph	OPh
12	$(CH_2)_4$		$(CH_3)_2CHCH_2$	Ph
13	$(CH_2)_4$		$(CH_3)_2CHCH_2$	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 carbodimide 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,

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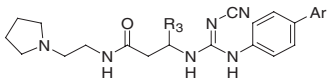
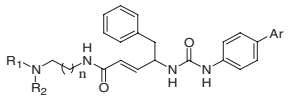


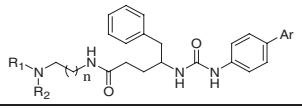
Compd	R_3	Ar
14	$CH_2CH(CH_3)_2$	Ph
15	CH_2Ph	Ph
16	CH_2Ph	OPh-4-Cl
17	Ph	Ph
18	Ph	OPh
19	Ph	OPh-4-Cl
20	Ph	OPh-4-CH_3
21	Ph	OPh-4-F

Figure 2. Cyanoguanidine β-amino acid derivatives.



Compd	R_1	R_2	n	Ar
22	H	H	1	Ph
23	H	H	1	OPh
24	H	H	2	Ph
25	CH_3	H	1	Ph
26	CH_3	H	1	OPh
27	CH_2CH_3	H	1	Ph
28	CH_3	CH_3	1	Ph
29	CH_3	CH_3	1	OPh
30	CH_3	CH_3	2	Ph
31	CH_2CH_3	CH_2CH_3	1	Ph
32	CH_2CH_3	CH_2CH_3	2	Ph
33	$(CH_2)_4$		1	Ph
34	$(CH_2)_4$		1	OPh
35	$(CH_2)_4$		2	Ph
36	$(CH_2)_4$		2	OPh

Figure 3. Unsaturated γ-amino acid derivatives.

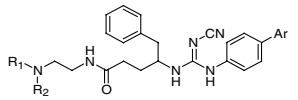


Compd	R_1	R_2	n	Ar
37	H	H	1	Ph
38	H	H	1	OPh
39	H	H	2	Ph
40	CH_3	H	1	Ph
41	CH_2CH_3	H	1	Ph
42	CH_3	CH_3	1	Ph
43	CH_2CH_3	CH_2CH_3	1	Ph
44	$(CH_2)_4$		1	Ph
45	$(CH_2)_4$		1	OPh

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



Compd	R_1	R_2	Ar
46	CH_3	CH_3	Ph
47	CH_2CH_3	CH_2CH_3	Ph
48	$CH(CH_3)_2$	H	Ph
49	$(CH_2)_4$		Ph
50	$(CH_2)_4$		OPh
51	$(CH_2)_4$		OPh-4-Cl
52	$(CH_2)_4$		OPh-4-F
53	$(CH_2)_4$		OPh-4-CH_3

Figure 5. Cyanoguanidine γ-amino acid derivatives.

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

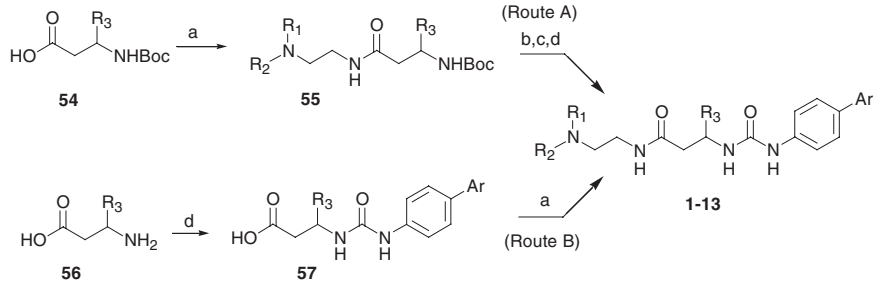
A general method for the synthesis of both D- and L-γ-amino acid analogs is illustrated in Scheme 3. Treatment of (*R*)-(+)-2-(*tert*-butoxycarbonylamino)-3-phenylpropanal (**62**) with methyl(triphenylphosphoranylidene)acetate in CH_2Cl_2 afforded the olefin adduct exclusively as the *trans*-isomer 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 component[8] 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 acid **33b** was achieved under Weinreb conditions (Scheme 4).[10]

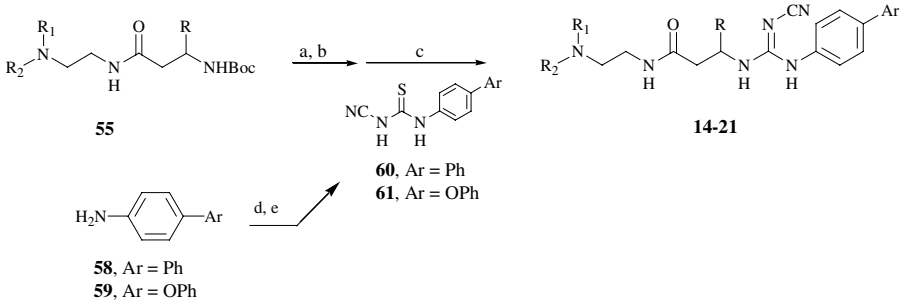
2.1. Cyanoguanidines

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).

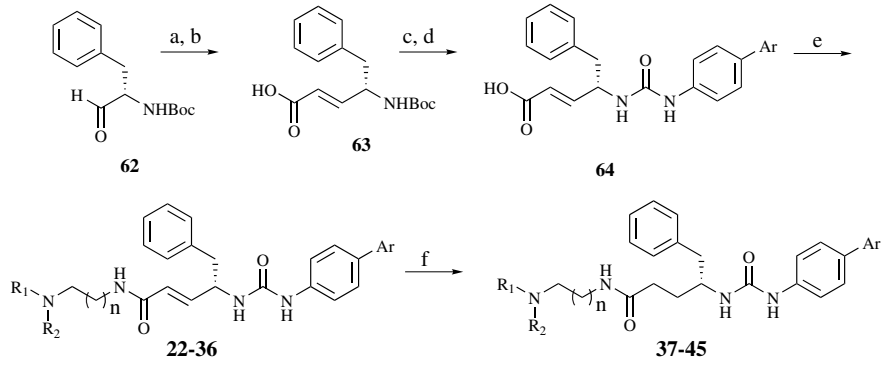
Carbodiimide mediated coupling of carboxylic acid **63** and the appropriate amines[11] provided the corresponding α,β-unsaturated amides **67**, which were subsequently reduced to the saturated intermediates **68**. Removal of the *N*-Boc-group followed by condensation with **60** or **61** as previously described provided the cyanoguanidine analogs **46**–**53**.



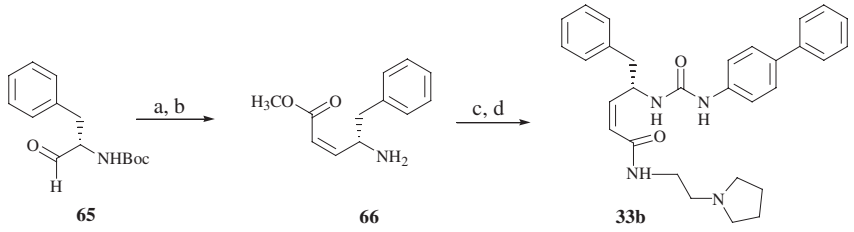
Scheme 1. Reagents: (a) $R_1R_2NCH_2CH_2NH_2$, EDCI, HOBt, DMF; (b) 4 M HCl/dioxane, CH_2Cl_2; (c) Dowex 550A anion exchange resin, MeOH; (d) ArPhNCO, Et_3N, CH_2Cl_2.



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.



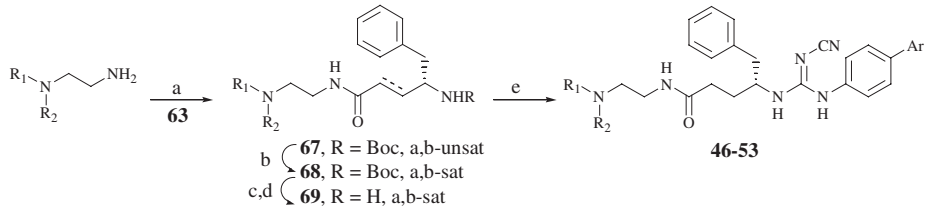
Scheme 3. Reagents: Only the L-enantiomer is shown for clarity. (a) $(Ph)_3PCHCO_2Me$, CH_2Cl_2; (b) LiOH, THF–H_2O; (c) 4 M HCl–dioxane; (d) ArPhNCO, Et_3N, $PhCH_3$; (e) $R_1R_2NCH_2CH_2NH_2$, EDCI, HOBt, DMF; (f) H_2, 10% Pd/C, EtOH.



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-Pyrrorlidinyl ethylamine, $AlMe_3$, toluene.

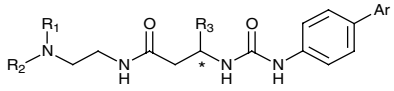
3. Results and discussion

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 (*h*GlyT-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



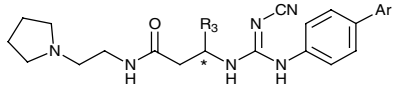
Compd	R_1	R_2	R_3	Ar	*Enant.	GlyT-2 IC_{50} (μM)
1	H	H	Ph	Ph	(±)	0.284
2	H	$(CH_3)_2CH$	Ph	Ph	(±)	0.059
3	CH_3	CH_3	Ph	Ph	(±)	0.184
4	CH_3	CH_3	CH_2Ph	Ph	L	0.342
5	CH_3	CH_3	CH_2Ph	OPh	L	0.333
6a	$(CH_2)_4$		Ph–4-CH_3	Ph	(±)	0.034
6b	$(CH_2)_4$		Ph–4-CH_3	Ph	L	0.027
6c	$(CH_2)_4$		Ph–4-CH_3	Ph	D	0.953
7b	$(CH_2)_4$		Ph	Ph	L	0.052
7c	$(CH_2)_4$		Ph	Ph	D	1.307
8	$(CH_2)_4$		$(CH_3)_2CH$	Ph	L	0.041
9	$(CH_2)_4$		$(CH_3)_2CH$	OPh	L	0.770
10	$(CH_2)_4$		CH_2Ph	Ph	L	0.134
11	$(CH_2)_4$		CH_2Ph	OPh	L	0.523
12	$(CH_2)_4$		$(CH_3)_2CHCH_2$	Ph	L	0.073
13	$(CH_2)_4$		$(CH_3)_2CHCH_2$	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.

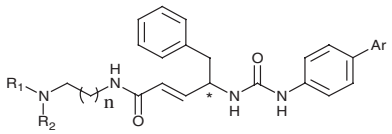
Examination of the γ-amino acid derivatives in Tables 3 and 4 reveal that the absolute configuration of the γ-substituent also has a pronounced effect on GlyT-2 inhibitory activity. For example, the two enantiomeric pairs listed in Table 3 (**24a/24b**, and **35a/35b**) and the one pair of enantiomers 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 2. GlyT-2 inhibitory activity for the cyanoguanidine analogs



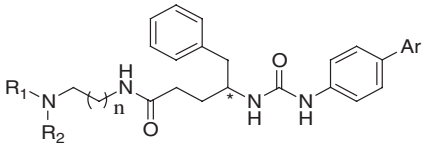
Compd	R_3	Ar	*Enant.	GlyT-2 IC_{50} (μM)
14	$CH_2CH(CH_3)_2$	Ph	L	0.368
15	CH_2Ph	Ph	(±)	0.103
16	CH_2Ph	OPh–4-Cl	(±)	0.127
17	Ph	Ph	(±)	0.060
18	Ph	OPh	(±)	0.062
19	Ph	OPh–4-Cl	(±)	0.068
20	Ph	OPh–4-CH_3	(±)	0.134
21	Ph	OPh–4-F	L	0.031

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



Compd	R_1	R_2	*n*	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_2CH_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_2CH_3	CH_2CH_3	1	Ph	L	0.048
32	CH_2CH_3	CH_2CH_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	*n*	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_2CH_3	H	1	Ph	L	0.140
42	CH_3	CH_3	1	Ph	L	0.272
43	CH_2CH_3	CH_2CH_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).

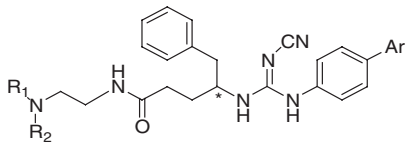
Lastly, direct comparison between urea derivatives **42**, **43**, and **44** in Table 4 with the corresponding cyanoguanidine derivatives **46**, **47**, and **49a** in Table 5 indicate that the GlyT-2 inhibitory activities were similar with less than a 2-fold difference being observed. The 5-fold difference 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 series[3] 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_2CH_3	CH_2CH_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-CI	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 (SiO_2; 40 g), Biotage 40M (SiO_2; 90 g), Biotage 40L (SiO_2; 120 g), Biotage 65M (SiO_2; 300 g) or ISCO Redisep (SiO_2; 10, 12, 35, 40, or 120 g). Preparative TLC was accomplished using PLC plates (20 × 20 cm silica gel 60 F_{254}, 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 CH_2Cl_2 (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 H_2O, and dried under vacuum to afford 0.87 g (83%) of the desired product as a white solid. MS (electrospray): mass calculated for $C_{23}H_{22}N_2O_3$, 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 N_2 at room temperature for 20 h. The solution was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine (40 mL), dried (Na_2SO_4), 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% NH_4OH)/CH_2Cl_2) to afford 0.12 g (63%) of the desired product as a white solid. Racemic compound: $R_f = 0.11$ (10% MeOH (1% NH_4OH)/CH_2Cl_2). 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 7.57–7.50 (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 $C_{29}H_{34}N_4O_2$, 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. H_2O (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 ($MgSO_4$), and concentrated. Purification by column chromatography [0–20% (1% NH_4OH/MeOH)/CH_2Cl_2] afforded 0.44 g (78%) of the desired product. 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).

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 CH_2Cl_2 (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 CH_2Cl_2 (3 mL). The reaction mixture was stirred at room temperature overnight, after which EtOAc (10 mL) and H_2O (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 ($MgSO_4$). The solvent was removed under reduced pressure. The residue was purified by column chromatography [0–20% (1% NH_4OH/MeOH)/CH_2Cl_2] 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 $C_{29}H_{34}N_4O_4$, 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 $C_{24}H_{26}N_4O_2$, 402.21; *m/z* found, 403.2 $[M+H]^+$, 425.2 $[M+Na]^+$, 827.4 $[2M+Na]^+$. ^1H NMR (400 MHz, CD_3OD) 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 $C_{22}H_{20}N_2O_3$, 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 $C_{27}H_{32}N_4O_2$, 444.25; *m/z* found, 445.2 $[M+H]^+$, 467.2 $[M+Na]^+$, 911.5 $[2M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (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 $C_{26}H_{30}N_4O_2$, 430.24; *m/z* found, 431.2 $[M+H]^+$, 453.2 $[M+Na]^+$, 883.5 $[2M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) 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-butyramide (4). Route B. [(*S*)-1-Benzyl-2-(2-dimethylamino-ethylcarbamoyl)-ethyl]-carbamic acid *tert*-butyl ester.

MS (electrospray): mass calculated for $C_{19}H_{31}N_3O_3$, 349.24; *m/z* found, 350.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) 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-butyramide.

MS (electrospray): mass calculated for $C_{27}H_{32}N_4O_2$, 444.57; *m/z* found, 445.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) 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-butyramide (5). Route B. (*S*)-*N*-(2-Dimethylamino-ethyl)-3-[3-(4-phenoxy-phenyl)-ureido]-4-phenyl-butyramide. 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)-butyramide (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)-butyramide (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 N_2 at room temperature for 20 h. The solution was diluted with H_2O (75 mL) and was extracted with EtOAc (3×75 mL). The combined extracts were washed with brine (100 mL), dried (Na_2SO_4) 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% NH_4OH)/CH_2Cl_2) to afford 0.65 g (88%) of the desired product as a white solid. $R_f = 0.34$ (10% MeOH (1% NH_4OH)/CH_2Cl_2). MS (electrospray): mass calculated for $C_{20}H_{31}N_3O_3$, 361.24; m/z found, 362.2 $[M+H]^+$, 745.4 $[2M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) 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 CH_2Cl_2 (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 N_2 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 (Na_2SO_4) 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% NH_4OH)/CH_2Cl_2) to afford 0.23 g (69%) of the desired product as a white solid. $R_f = 0.39$ (10% MeOH (1% NH_4OH)/CH_2Cl_2). MS (electrospray): mass calculated for $C_{29}H_{32}N_6O$, 480.26; m/z found, 481.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) 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 $C_{30}H_{34}ClN_6O$, 494.28; m/z found, 495.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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 $C_{14}H_{11}N_3OS$, 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)-propion-amide.

MS (electrospray): mass calculated for $C_{29}H_{32}N_6O_2$, 496.26; m/z found, 497.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) 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-cyano-thiourea.

1.8 g (98%) of the desired product was obtained. MS (electrospray): mass calculated for $C_{14}H_{10}ClN_3OS$, 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 $C_{29}H_{31}ClN_6O_2$, 530.22; m/z found, 531.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) 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*-tolyloxyphenyl)-guanidino]-3-phenyl-*N*-(2-pyrrolidin-1-yl-ethyl)-propionamide (20). 4-*p*-Tolyloxy-phenylisothiocyanate.

MS (electrospray): mass calculated for $C_{14}H_{11}NOS$, 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*-tolyloxy-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*-tolyloxy-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-Phenoxy-phenyl)-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-Phenoxy-phenyl)-ureido]-5-phenyl-pent-2-enoic acid (2-methylamino-ethyl)-amide. To a solution of (*E*)-(*S*)-4-[3-(4-phenoxy-phenyl)-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/iPrOH (3×40 mL). The combined organic extracts were washed with 1 N NaOH (1×30 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 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 $C_{29}H_{34}N_4O_2$, 470.27; m/z found, 471.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.81 (t, $J = 5.0$ Hz, 1H), 7.50–7.33 (m, 8H), 7.30–7.19 (m, 6H), 6.67 (dd, $J = 15.4$, 6.8 Hz, 1H), 6.54 (d, $J = 8.6$ Hz, 1H), 5.98 (d, $J = 17.6$ Hz, 1H), 4.88–4.81 (m, 1H), 3.47–3.29 (m, 2H), 2.96 (dd, $J = 13.6$, 7.0 Hz, 1H), 2.88 (dd, $J = 13.6$, 7.0 Hz, 1H), 2.34 (t, $J = 6.4$ 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 $C_{24}H_{22}N_2O_3$, 386.45; m/z found, 387.1 $[M+H]^+$, 409.1 $[M+Na]^+$. ^1H NMR (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 Hz, 1H), 6.41 (d, $J = 8.4$ Hz, 1H), 5.78 (dd, $J = 15.6$, 1.5 Hz, 1H), 4.63–4.69 (m, 1H), 2.94 (dd, $J = 13.7$, 6.2 Hz, 1H), 2.86 (dd, $J = 13.7$, 7.8 Hz, 1H). ^{13}C NMR (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 $C_{30}H_{36}N_4O_2$, 484.64; m/z found, 485.3 $[M+H]^+$, 507.2 $[M+Na]^+$. ^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, $J = 5.0$ Hz, 1H), 6.75 (dd, $J = 15.4$, 6.3 Hz, 1H), 6.51 (d, $J = 8.2$ Hz, 1H), 6.03 (dd, $J = 15.4$, 0.9 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, $J = 8.2$ 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 $C_{31}H_{38}N_4O_2$, 498.30; m/z found, 499.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.29 (t, $J = 4.8$ Hz, 1H), 7.52–7.36 (m, 8H), 7.31–7.20 (m, 6H), 6.70 (dd, $J = 15.4$, 6.8 Hz, 1H), 6.66 (d, $J = 9.7$ Hz, 1H), 5.97 (dd, $J = 15.4$, 0.9 Hz, 1H), 4.90–4.83 (m, 1H), 3.45–3.31 (m, 2H), 2.99 (dd, $J = 13.7$, 6.9 Hz, 1H), 2.89 (dd, $J = 13.7$, 7.2 Hz, 1H), 2.52–2.44 (m, 6H), 1.71–1.60 (m, 2H), 0.98 (t, $J = 7.1$ 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 $C_{30}H_{34}N_4O_2$, 482.27; m/z found, 483.3 $[M+H]^+$, 505.2 $[M+Na]^+$, 987.5 $[2M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.53 (d, $J = 7.4$ Hz, 2H), 7.49–7.37 (m, 7H), 7.32–7.20 (m, 5H), 6.80 (dd, $J = 15.3$, 5.1 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 Hz, 1H), 2.87 (dd, $J = 13.7$, 7.3 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 × 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 $C_{17}H_{23}NO_4$, 305.37; m/z found, 328.1 $[M+Na]^+$. ^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% NH_4OH/MeOH in CH_2Cl_2) to provide the desired product as a clear oil (0.02 g, 16%): MS (electrospray): mass calculated for $C_{22}H_{33}N_3O_3$, 387.25; m/z found, 388.2 $[M+H]^+$; 410.2 $[M+Na]^+$. ^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 $C_{30}H_{34}N_4O_2$, 482.62; m/z found, 483.3 $[M+H]^+$. ^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).

4.4.14. (*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 $C_{17}H_{23}NO_4$, 305.37; *m*/*z* found, 328.1 $[M+Na]^+$. ^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% NH_4OH/MeOH in CH_2Cl_2) to provide the desired product as a clear oil (0.02 g, 16%): MS (electrospray): mass calculated for $C_{22}H_{33}N_3O_3$, 387.25; *m*/*z* found, 388.2 $[M+H]^+$; 410.2 $[M+Na]^+$. ^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 $C_{30}H_{34}N_4O_2$, 482.62; *m*/*z* found, 483.3 $[M+H]^+$. ^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 $C_{30}H_{34}N_4O_3$, 498.26; *m*/*z* found, 499.2 $[M+H]^+$, 997.5.4 $[2M+H]^+$. ^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 $C_{31}H_{36}N_4O_2$, 496.28; *m*/*z* found, 497.3 $[M+H]^+$. ^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 $C_{31}H_{36}N_4O_3$, 512.28; *m*/*z* found, 513.3 $[M+H]^+$. ^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 $C_{24}H_{24}N_2O_3$, 388.46; *m*/*z* found, 389.2 $[M+H]^+$, 411.1 $[M+Na]^+$, 387.1 $[M-H]^-$. ^1H NMR (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 $C_{31}H_{38}N_4O_4$, 530.66; *m*/*z* found, 531.3 $[M+H]^+$, 553.3 $[M+Na]^+$. ^1H NMR (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-Phenoxy-phenyl)-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-Phenoxy-phenyl)-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-pentanoyl-amino]-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, 8 H), 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-tolyloxyphenyl)-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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References and notes

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