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Novel glycine transporter type-2 reuptake inhibitors. Part 1: α-amino acid derivatives

Ronald L. Wolin,* Hariharan Venkatesan, Liu Tang, Alejandro Santillán, Jr., Tristin Barclay, 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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Abstract—A variety of α-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) was evaluated. An array of substituents at the chiral center was studied and overall, L-phenylalanine was identified as the preferred amino acid residue. Compounds prepared from L-amino acids were more potent GlyT-2 inhibitors than analogs derived from the corresponding D-amino acids. Introducing an achiral amino acid such as glycine, or incorporating geminal substitution in the α-position, led to a significant reduction in GlyT-2 inhibitory properties.

1. Introduction

The two primary inhibitory neurotransmitters in the central nervous system (CNS) are γ-aminobutyric acid (GABA) and glycine. Radio-labeled strychnine binding studies[1] provide evidence that glycine is the major inhibitory amino acid in the brainstem and spinal cord of vertebrates, and exerts its effects post-synaptically at the strychnine-sensitive glycinergic receptor.[2] The binding of glycine to its specific receptor 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 glycine transporters, which provide a mechanism for the re-uptake of glycine from the synaptic cleft back into the pre-synaptic neuron and surrounding glial cells. Currently there are two known glycine transporters expressed in the CNS; GlyT-1 and GlyT-2.[3] Separate genes encode each transporter and the proteins produced from each gene have distinct pharmacologies associated with them as evidenced by their sensitivity to sarcosine (*N*-methylglycine).[4] The rat and human GlyT-2 transporters have been cloned and share ~93% sequence homology at the amino acid level.[5]

Compounds capable of inhibiting glycine transport function could provide various therapeutic benefits for a number of disorders associated with excessive neuronal activity, such as muscle spasticity, tinnitus, epilepsy, and neuropathic pain.[6,7] Therefore, molecular entities that are capable of blocking the glycine reuptake process should also be effective in enhancing inhibitory activity to the affected regions in the spinal cord. This paper describes the synthesis and biological activity of α-amino acid derivatives that were shown to be effective GlyT-2 reuptake inhibitors. The following paper[8] in this series describes our results with respect to β- and γ-amino acid homologs as GlyT-2 inhibitors (Fig. 1).

2. Chemistry

High-throughput-screening (HTS) of our internal compound collection identified conformationally restricted analogs of **III** as viable hits for conducting lead optimization studies directed at improving GlyT-2 inhibitory activity. The α-amino acid compounds prepared in this study were developed in conjunction with our overall SAR investigations, and are depicted in Figures 2–6. Three different approaches were employed to

* 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.

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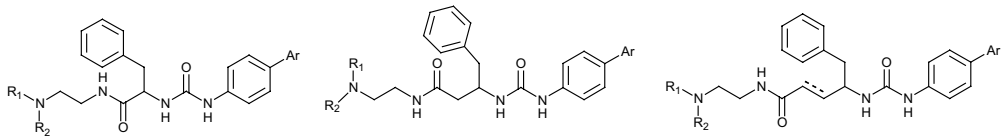
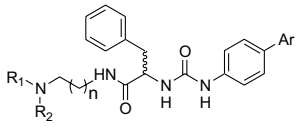


I, α-amino acid derivatives

II, β-amino acid derivatives

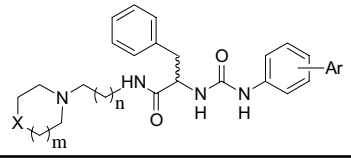
III, γ-amino acid derivatives

Figure 1.



Compd	R_1	R_2	n	A
1	H	H	1	H
2	H	H	1	Ph
3	H	H	2	Ph
4	H	H	3	Ph
5	H	H	1	OPh
6	H	H	2	OPh
7	CH_3	CH_3	1	Ph
8	CH_2CH_3	CH_2CH_3	1	Ph
9	CH_2CH_3	CH_2CH_3	2	Ph
10	$CH(CH_3)_2$	H	1	Ph
11	$CH(CH_3)_2$	$CH(CH_3)_2$	1	Ph
12	CH_3	CH_3	1	OPh
13	$CH(CH_3)_2$	$CH(CH_3)_2$	1	OPh
14	$CH(CH_3)_2$	$CH(CH_3)_2$	1	OPh-4-Cl

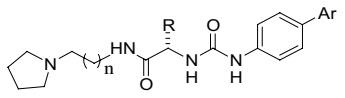
Figure 2. Terminal amino group and linker variations.



Compd	X	m	n	Ar
15	CH_2	0	1	*p*-Ph
16	CH_2	0	2	*p*-Ph
17	CH_2	1	1	*p*-Ph
18	O	0	1	*p*-Ph
19	NH	0	1	*p*-Ph
20	CH_2	0	1	*p*-OPh
21	CH_2	0	2	*p*-OPh
22	CH_2	0	2	*o*-OPh
23	CH_2	0	2	*m*-Ph
24	CH_2	0	1	*m*-OPh
25	CH_2	0	1	*p*-*t*-Bu
26	CH_2	0	1	*p*-OPh-4-Cl

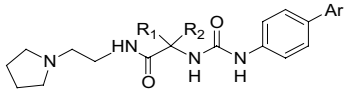
Figure 3. Aryl, linker, and amino group variations.

prepare the requisite α-amino acid analogs. Scheme 1 outlines a general solution-phase approach that was used for preparing a variety of D- and L-α-amino acid analogs. For derivatives that required an unsubstituted terminal amino group, a solid-phase approach employing Wang-based resin was utilized as illustrated in



Compd	R	n	Ar
27	$CH(CH_3)_2$	1	OPh
28	$CH(CH_3)_2$	1	Ph
29	$C(CH_3)_3$	1	OPh
30	$C(CH_3)_3$	1	Ph
31	Ph	2	Ph
32	Ph	2	OPh
33	CH_2-2-thienyl	1	OPh
34	CH_2-2-thienyl	1	Ph
35	CH_2-2-thienyl	2	OPh
36	CH_2-2-thienyl	2	Ph
37	CH_2SCH_2Ph	1	Ph
38	CH_2SCH_2Ph	1	OPh
39	CH_2-3-pyridyl	2	OPh
40	CH_2-3-pyridyl	2	Ph
41	CH_2-4-pyridyl	2	OPh
42	CH_2-4-pyridyl	2	Ph

Figure 4. Variations at the α-position.

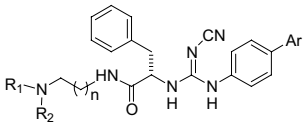


Compd	R_1	R_2	Ar
43	H	H	Ph
44	Ph	Ph	OPh
45	Ph	Ph	Ph
46	Propyl	Propyl	OPh
47	Propyl	Propyl	Ph
48	$(CH_2)_4$		OPh
49	$(CH_2)_4$		Ph
50	Indenyl		Ph

Figure 5. Analogs containing geminal substitution.

Scheme 2. Similarly, an indole-based resin was employed to prepare analogs requiring dialkyl-substitution at the terminal amino group, as shown in Scheme 3. Scheme 4 outlines the route used for assembling analogs requiring geminal-substitution in the α-position. The 4-phenoxyphenyl aniline segments used in this study (**74**–**77**) were prepared by displacing 4-fluoronitobenzene with the requisite phenol as illustrated in Scheme 5.[9]

Our synthetic efforts commenced with the assembly of a small library that was specifically designed to probe three features present in the α-amino acid scaffold: chain

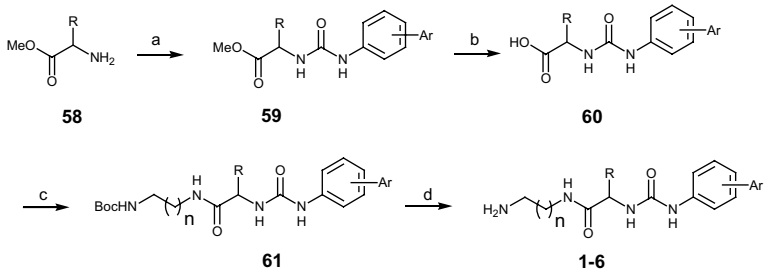


Compd	R_1	R_2	Ar	n
51	CH_3	CH_3	OPh-4-Cl	1
52	$(CH_3)_2CH$	$(CH_3)_2CH$	OPh-4-Cl	1
53	$(CH_2)_4$		OPh-4-Cl	1
54	$(CH_2)_4$		OPh-4-Cl	1
55	$(CH_2)_4$		OPh-4-Cl	2
56	$(CH_2)_4$		Ph	2
57	$(CH_2)_4$		Ph	2

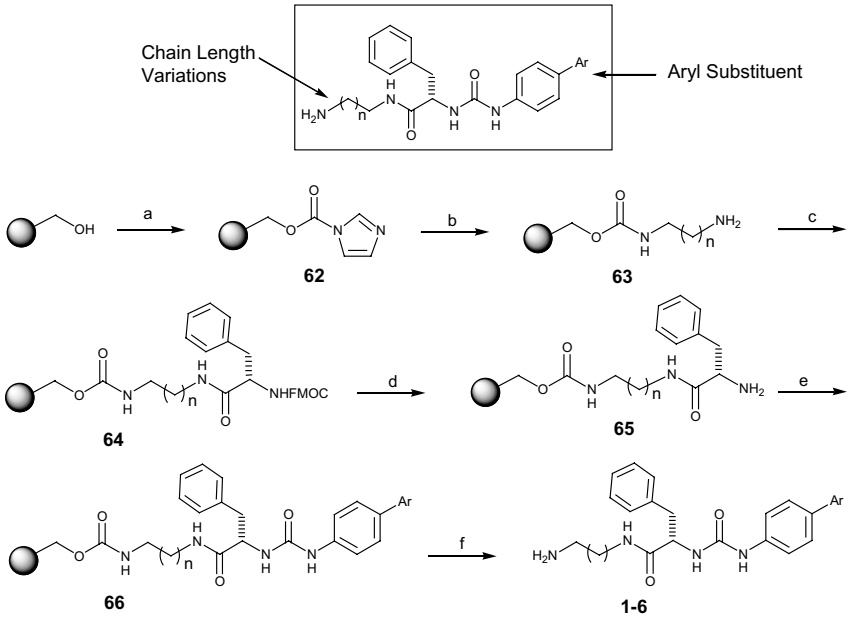
Figure 6. Cyanoguanidine analogs.

length, the α-substituent, and the nature of the aryl urea (Scheme 2).[10] Thus, Wang resin[11] was treated with carbonyldiimidazole in THF to provide carbamate **62** ($IR = 1755\,cm^{-1}$), which was subsequently treated with ethylene diamine or 1,3-diaminopropane in CH_2Cl_2 to afford the 2- and 3-carbon adducts **63**, respectively ($IR = 1700\,cm^{-1}$).[12] Carbodiimide mediated coupling of **63** with *N*-FMOC-L-Phe furnished the corresponding amides **64** (98% conversion as determined by ninhydrin analysis).[13] Removal of the FMOC group was accomplished using 20% piperidine, and the resulting amines **65** were treated with the requisite isocyanate to provide the corresponding aryl urea compounds **66**. The penultimate substrates were cleaved from the resin using trifluoroacetic acid in CH_2Cl_2 to afford the desired compounds **1**–**6** in enantiomerically pure form.[14]

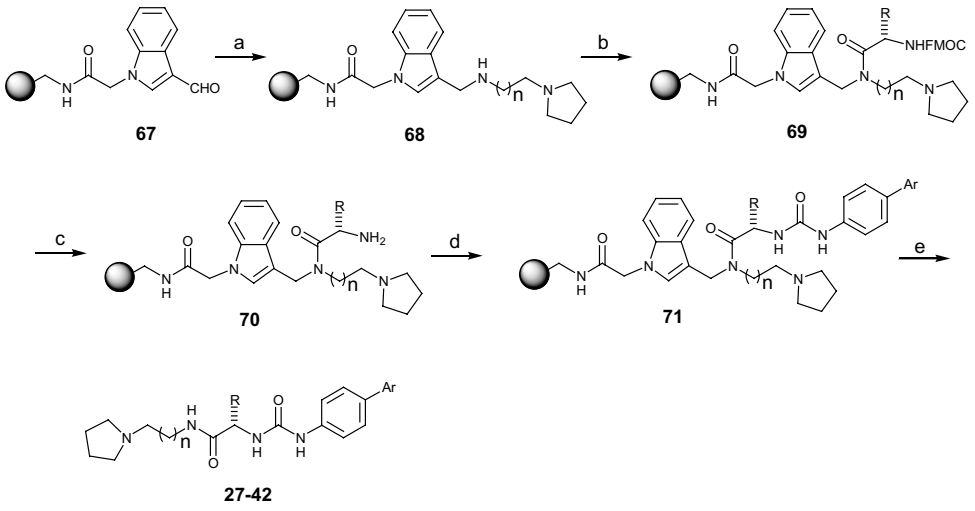
A second focused library was constructed in an effort to gain a more indepth understanding regarding the characteristics of the α-substituent, the terminal amino unit, and the aryl moiety (Scheme 3). For this approach, a polystyrene indole-based resin[15] was employed. Thus, indole **67** was subjected to reductive amination with 1,2-aminoethyl pyrrolidine using $Ti(iPrO)_4$ and $NaBH_4$ in EtOH to provide the resin bound amine **68**.[16] Carbodiimide mediated coupling with *N*-FMOC-L-Phe afforded the protected amide intermediate **69**, which was subsequently converted to the free amine **70** upon



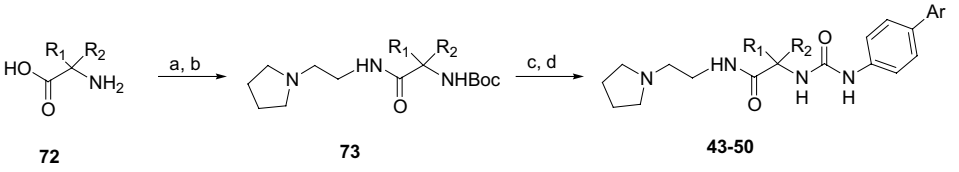
Scheme 1. Reagents: (a) ArNCO, Et_3N, toluene; (b) LiOH, THF–H_2O (3:1, v/v); (c) EDCI, HOBT, DMF, BocNH–$(CH_2)_n$–NH_2; (d) CF_3CO_2H, CH_2Cl_2.



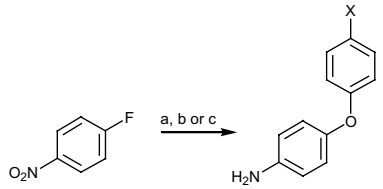
Scheme 2. Reagents: Only phenylalanine is illustrated for clarity (a) Wang resin, carbonyl diimidazole, THF; (b) ethylene diamine or 1,3-diaminopropane, DIPEA, CH_2Cl_2; (c) *N*-FMOC-Phe, diisopropyl carbodiimide, DMAP, 20% DMF/CH_2Cl_2; (d) 20% Piperidine, DMF; (e) ArPhNCO, DMF/CH_2Cl_2 (20:80 v/v); (f) CF_3CO_2H, CH_2Cl_2.



Scheme 3. Reagents: (a) appropriate amine, Ti(*i*PrO)$_4$, NaBH$_4$, EtOH; (b) appropriate FMOC-amino acid, DIC, DMAP; (c) 20% Piperidine, DMF; (d) ArPhNCO, CH_2Cl_2, DMF; (e) 50% CF_3CO_2H, CH_2Cl_2.



Scheme 4. Reagents: (a) $(BOC)_2O$, Me_4NOH–H_2O, CH_3CN; (b) 2-ethylpyrrolidine amine, EDCI, HOBT, DMF, NMM; (c) 4 M HCl/dioxane, CH_2Cl_2; (d) ArPhNCO, Et_3N, CH_2Cl_2.



Scheme 5. Reagents: (a) appropriate phenol, Cs_2CO_3, DMA; (b) H_2/Pd–C, EtOH; (c) $Na_2S_2O_4$, THF–H_2O (3:1, v/v).

treatment with 20% piperidine in dimethylformamide. Lastly, the targeted urea analogs **27**–**42** were obtained following condensation of **70** with 4-biphenyl isocyanate or 4-phenoxyphenyl isocyanate, and subsequent cleavage from the resin employing 50% trifluoroacetic acid in CH_2Cl_2.

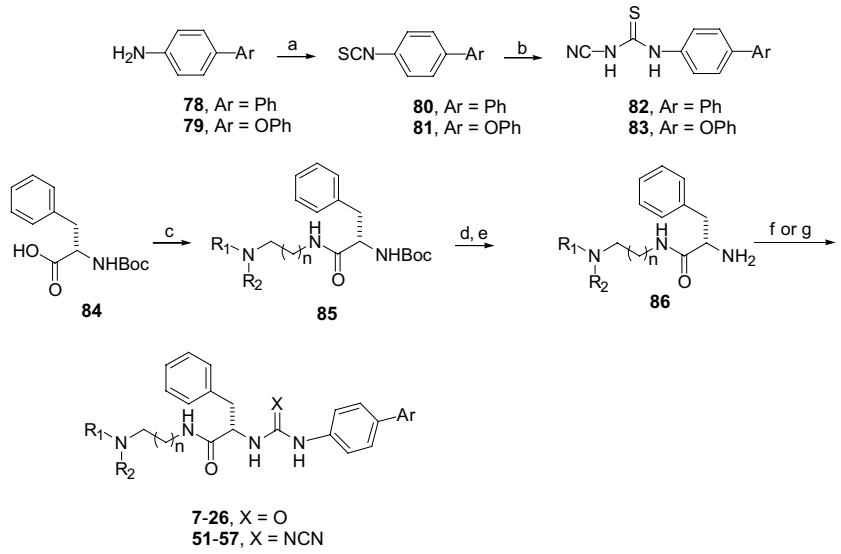
Next, geminal substitution at the α-position was examined. A general solution-phase method for the synthesis of these derivatives is illustrated in Scheme 4. Thus, the appropriately substituted amino acid **72** was protected as the *N*-Boc derivative, and then combined with 2-pyrrolidinyl ethylamine in a carbodiimide mediated coupling, to provide the corresponding intermediate **73**. Removal of the *N*-Boc group, followed by condensation with the requisite isocyanate provided analogs **43**–**50**.

The 4-phenoxyphenyl amine segments used in this study were prepared by displacing 4-fluoronitobenzene with the requisite phenol as illustrated in Scheme 5.[9] Subsequent reduction of the nitro group using sodium dithionate or hydrogen over Pd/C provided the desired anilines **74**–**77**.

We briefly evaluated alternatives to the urea linkage and found that a cyanoguanidine moiety served as a suitable replacement.[17] Towards that end, treatment of 4-(4-chlorophenoxy)phenylamine (**78**) or 4-aminobiphenyl (**79**) with thiocarbonyl diimidazole in CH_2Cl_2 afforded the corresponding isothiocyanates **80** and **81**. Employing the procedure of Atwal,[18] **80** and **81** were exposed to sodium cyanamide in EtOH to provide **82** and **83**. Coupling of **82** and **83** with the phenylalanine fragment **84** furnished intermediate **85**. The cyanoguanidine derivatives **51**–**57**, and the urea analogs **7**–**26** were both accessed from **85** as illustrated in Scheme 6.

3. Results and discussion

GlyT-2 inhibitory activity was determined by the ability of compounds to inhibit the uptake of [^{14}C]-glycine in COS-7 cells transfected with the human glycine transporter-2 (GlyT-2).[19] The data presented in Tables 1 and 2 illustrate several key points from this study. First, it

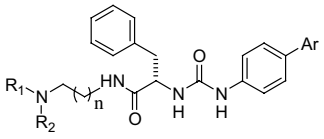


Scheme 6. Reagents: Only one enantiomer is illustrated for clarity (a) carbonyl diimidazole, CH_2Cl_2; (b) NaNHCN, EtOH; (c) appropriate amine, EDCI, HOBT, DMF, NMM; (d) 4 M HCl/dioxane in CH_2Cl_2; (e) Dowex 550A OH anion exchange resin, MeOH; (f) **82**–**83**, EDCI, DMF; (g) **75**–**77**, carbonyl diimidazole, CH_2Cl_2.

was necessary to have a second aromatic group (i.e., 4-phenyl or 4-phenoxy-phenyl) attached to the aryl urea in order to achieve GlyT-2 inhibitory activity. For example, the unsubstituted aryl urea derivatives, such as **1**, or the 4-*tert*-butylphenyl analog **25** were devoid of GlyT-2 inhibitory activity ($IC_{50} > 10\,\mu M$). Additionally, attachment of the second aromatic unit in the *para*-position was preferred by 4-fold over the *meta*-position, and more than 100-fold over the *ortho*-position ($n = 2$) as evidenced by compounds **20**, **24**, and **22**, respectively. Secondly, direct comparison between compounds containing varying tether lengths (i.e., **2**–**4**) indicated that a 3-carbon linker was slightly preferred over the 2-carbon linker, and extension to a 4-carbon linker caused a measurable decrease in inhibitory activity. Thus most of the SAR was carried out on compounds containing a 2- or 3-carbon linker.

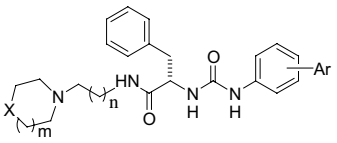
Thirdly, alkyl substitution on the terminal amino group was generally preferred over the corresponding unsubstituted derivatives, and compounds containing a pyrrolidine moiety or isopropyl unit tended to provide the best potencies and most consistent profiles overall. However, the nature of the aromatic moiety appended to the urea also influenced, which alkyl substituent was best (i.e., compare **2** vs **12** and **16** when Ar = Ph; and **5** vs **13** and **20** when Ar = OPh). Interestingly, the ring expanded piperidine analog **17** was only 3.5-fold less

Table 1. GlyT-2 inhibitory activity for urea analogs containing phenylalinine



Compd	R_1	R_2	Ar	*n*	Enant	GlyT-2 IC_{50} (μM)	GlyT-1 IC_{50} (μM)
1	H	H	H	1	L	>10	ND
2	H	H	Ph	1	(±)	0.560	>10
3	H	H	Ph	2	L	0.398	>10
4	H	H	Ph	3	(±)	1.000	>10
5	H	H	OPh	1	L	0.400	>10
6	H	H	OPh	2	L	1.400	>10
7	CH_3	CH_3	Ph	1	(±)	0.740	>10
8	CH_3	CH_3	OPh	1	L	0.091	ND
9	$(CH_3)_2CH$	H	Ph	1	L	0.041	ND
10	CH_2CH_3	CH_2CH_3	Ph	1	L	0.106	ND
11	CH_2CH_3	CH_2CH_3	Ph	2	L	0.046	ND
12	$(CH_3)_2CH$	$(CH_3)_2CH$	Ph	1	L	0.059	ND
13	$(CH_3)_2CH$	$(CH_3)_2CH$	OPh	1	L	0.028	ND
14	$(CH_3)_2CH$	$(CH_3)_2CH$	OPh-4-Cl	1	L	0.018	ND

Table 2. GlyT-2 inhibitory activity for urea analogs containing phenylalanine

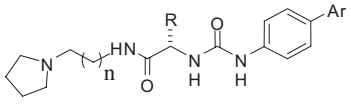


Compd	X	*m*	Ar	*n*	Enant	GlyT-2 IC_{50} (μM)	GlyT-1 IC_{50} (μM)
15	CH_2	0	*p*-Ph	1	L	0.122	2.50
16	CH_2	0	*p*-Ph	2	L	0.040	3.20
17	CH_2	1	*p*-Ph	1	(±)	0.450	7.00
18	O	0	*p*-Ph	1	(±)	>10	ND
19	NH	0	*p*-Ph	1	L	3.300	ND
20	CH_2	0	*p*-Ph	1	L	0.447	ND
21	NH	0	*p*-OPh	2	L	0.089	4.00
22	CH_2	0	*o*-OPh	2	L	>10	ND
23	CH_2	0	*m*-Ph	2	L	0.998	ND
24	CH_2	0	*m*-OPh	2	L	0.440	ND
25	CH_2	0	*p*-*t*-Bu	1	L	>10	ND
26	CH_2	0	*p*-OPh-4-Cl	1	L	0.079	1.60

potent than the pyrrolidine analog **15**, however, the morpholine analog **18** was more than 22-fold less potent than **15**. Lastly, from the array of 11 compounds that were evaluated against the GlyT-1 transporter, all displayed greater than 15-fold selectivity in preference of the GlyT-2 transporter.

The compounds listed in Table 3 illustrate the affect of the α-substituent on GlyT-2 inhibitory activity, and contain the *S*-configuration at the α-center for ease of comparison. Note that a variety of α-substituents are tolerated ranging from aliphatic substituents, such as isopropyl (**27**–**28**) and *tert*-butyl (**29**–**30**), to an aryl substituent (**31**–**32**). While several analogs containing nonnatural amino acids (thienylalanine, 3-pyridiylalanidne, 4-pyridylalinine, phenylglycine, phenylcystine, and *tert*-butylglycine) exhibited good to moderate GlyT-2 inhibitory activity, none of these substituents were markedly superior to those analogs derived from L-phenylalanine (Table 1). Moreover, relatively minor differences in potency were observed between analogs containing the 4-phenyl or 4-phenoxy appendage, with the largest difference being observed among the thienyl derivatives **35** and **36**.

Table 3. GlyT-2 inhibitory activity for analogs containing un-natural amino acids

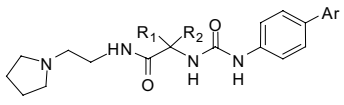


Compd	R	Ar	*n*	GlyT-2 IC_{50} (μM)
27	$CH(CH_3)_2$	OPh	1	0.246
28	$CH(CH_3)_2$	Ph	1	0.273
29	$C(CH_3)_3$	OPh	1	0.655
30	$C(CH_3)_3$	Ph	1	2.400
31	Ph	Ph	2	0.534
32	Ph	OPh	2	0.658
33	CH_2-2-thienyl	OPh	1	0.121
34	CH_2-2-thienyl	Ph	1	0.218
35	CH_2-2-thienyl	OPh	2	0.189
36	CH_2-2-thienyl	Ph	2	0.043
37	CH_2SCH_2Ph	Ph	1	0.530
38	CH_2SCH_2Ph	OPh	1	0.271
39	CH_2-3-pyridyl	OPh	2	2.400
40	CH_2-3-pyridyl	Ph	2	0.685
41	CH_2-4-pyridyl	OPh	2	3.000
42	CH_2-4-pyridyl	Ph	2	1.800

The data presented in Table 4 reveals the importance for retaining chirality at the α-position. This is most notably evidenced from comparing the phenylalanine derivative (**15**, $IC_{50} = 0.122\,\mu M$, Table 2) with the indenyl derivative (**50**, $IC_{50} > 10\,\mu M$), which is simply the restricted analog of **15**. This point is also illustrated with the glycine analog **43**. In general, the achiral analogs were much poorer inhibitors of GlyT-2 than their chiral counterparts.

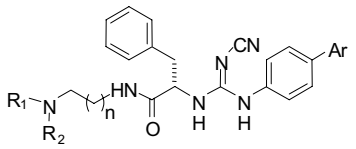
Table 5 highlights two important observations regarding the cyanoguanidine analogs. First, the urea group can successfully be replaced by a cyanoguanidine moiety without any loss in potency. Specifically, direct com-

Table 4. GlyT-2 inhibitory activity for achiral α-amino acids



Compd	R_1	R_2	Ar	GlyT-2 IC_{50} (μM)
43	H	H	Ph	>10
44	Ph	Ph	OPh	2.700
45	Ph	Ph	Ph	8.000
46	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	OPh	1.700
47	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	Ph	0.774
48	$(CH_2)_4$		OPh	5.000
49	$(CH_2)_4$		Ph	8.000
50	Indenyl		Ph	>10

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



Compd	R_1	R_2	Ar	*n*	Enant	GlyT-2 IC_{50} (μM)
51	CH_3	CH_3	OPh-4-Cl	1	L	0.073
52	$(CH_3)_2CH$	$(CH_3)_2CH$	OPh-4-Cl	1	L	0.030
53	$(CH_2)_4$		OPh-4-Cl	1	L	0.099
54	$(CH_2)_4$		OPh-4-Cl	1	D	0.207
55	$(CH_2)_4$		OPh-4-Cl	2	L	0.064
56	$(CH_2)_4$		Ph	2	L	0.011
57	$(CH_2)_4$		Ph	2	D	0.871

Table 6. Selectivity data for a bioisosteric pair of GlyT-2 inhibitors[a]

Compd	Na^+ Channel	DAT	5-HT2A	NET	(% Inhibition @ 1 μM)[b]
26	81	86	96	21	
53	58	71	73	68	

[a] DAT = dopamine transporter; 5-HT2A = serotonin transporter; NET = norepinephrine transporter.
[b] % Inhibition values are the average of two experiments.

parison between the urea analogs **14**, **16**, and **26** in Tables 1 and 2 with the analogous cyanoguanidine derivatives **52**, **56**, and **53** show that the cyanoguanidine analogs are at least equivalent in potency to the urea analogs. Secondly, the trend favoring analogs derived from the L-enantiomers was maintained in the cyanoguanidine series. This distinction was most notable between the enantiomeric pair **56** and **57**, which gives rise to approximately an 80-fold separation in activity.

Lastly, the two compounds presented in Table 6 are representative of the cross reactivity profile we observed for this series of peptidic compounds. When we screened against a panel of over 50 receptor targets that include prominent biogenic amine receptors, neuropeptide receptors, ion channels, and transporters, we detected minimal cross activity. The targets in which >50% inhibition was observed are depicted below and were monitored during our SAR development.

4. Conclusion

Based upon the results of this SAR study, we can make the following conclusions in regard to these series of compounds. Analogs derived from L-phenylalanine were clearly preferred over the corresponding D-enantiomers. Transformation of the carboxylic acid residue into a pyrrolidinyl ethyl amide afforded compounds with consistently good GlyT-2 inhibitory activity. Lastly, conversion of the amino group to an aryl-urea or aryl-cyanoguanidine moiety produced equally potent glycine transporter type-2 inhibitors, and selectivities ranging from 15- to 80-fold over the GlyT-1 transporter was realized.

5. Experimental

NMR spectra were obtained on either a Bruker model DPX400 (400 MHz) or DPX500 (500 MHz) 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, pre-packed 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).

5.1. General solution-phase procedure for the preparation of urea derivatives in the α-amino acid series: Method A

Step A. To a mixture of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (30 mmol), 1-hydroxybenzotriazole (HOBT) (30 mmol), and (*S*)-2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid (20 mmol) in DMF (80 mL), the appropriate amine (30 mmol) in DMF (10 mL) was added followed by *N*-methylmorpholine (40 mmol) in 10 mL of DMF at room temperature. The solution was stirred for 14 h at room temperature, or until complete by TLC and then diluted with ethyl acetate (500 mL). The organic layer was washed with saturated $NaHCO_3$ (2 × 100 mL), brine (3 × 100 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude residue was stirred in a mixture of 10% EtOAC/hexanes for 1 h to afford the desired product (87%).

Step B. To a solution of carbamic acid *tert*-butyl ester (0.4974 mmol) in CH_2Cl_2 (20 mL) neat TFA (0.66 mL, 8.56 mmol) was added, and the mixture was stirred for 17 h at room temperature. The solvents were removed under reduced pressure, and the residue was dissolved in

ethyl acetate (100 mL). The solution was washed with saturated $NaHCO_3$ (2×25 mL) and brine (25 mL), and dried (Na_2SO_4), and the solvents were removed under reduced pressure. Purification of the residue on silica gel by flash column chromatography using 0–20% MeOH (1% NH_4OH)/CH_2Cl_2 afforded the desired product (75%).

Step C. To a suspension of (*S*)-2-amino-3-phenylpropionic acid (6 mmol) in acetone–H_2O (1:1, 36 mL) was added TEA (9 mmol), and the mixture was stirred for 5 min at room temperature. A solution of 4-biphenyl isocyanate in THF (8 mL) was added, and the reaction mixture was stirred for 7 h, or until complete by TLC. The volume of the mixture was reduced in vacuo, and the pH of the solution was adjusted to approximately 2 using 10% HCl. The resulting white precipitate was filtered, washed with water and 10% CH_2Cl_2/hexanes, and dried under vacuum to afford (81%) of the desired product.

5.2. General solution-phase procedure for the preparation of urea derivatives in the α-amino acid series: Method B

Step A. TEA (15 mmol) was added to a suspension of (*S*)-2-amino-3-phenyl-propionic acid methyl ester hydrochloride (10 mmol) in toluene (30 mL) at 0 °C. After a few minutes, a solution of 4-biphenyl isocyanate (10.5 mmol) in CH_2Cl_2 was added dropwise to the mixture. After stirring for 6 h at room temperature, the mixture was poured into water (50 mL) and extracted with ethyl acetate (3×75 mL). The combined organics were washed with brine (25 mL), and dried (Na_2SO_4). Removal of the solvents under reduced pressure followed by flash column chromatography on silica gel using 10–50% ethyl acetate/hexanes yielded (86%) of pure product.

Step B. LiOH (4.5 mmol) was added to 2-(3-biphenyl-4-yl-ureido)-3-phenylpropionic acid methyl ester (3 mmol) in THF/MeOH/H_2O (28 mL, 1:2:2). After stirring for 4 h, the mixture was poured into H_2O (100 mL), and the pH was adjusted to 3–4 with 10% HCl. The aqueous layer was extracted with ethyl acetate (3×75 mL). The combined organics were washed with brine (50 mL) and dried (Na_2SO_4), and the solvents were removed under reduced pressure. The residue was recrystallized from 20% CH_2Cl_2/hexanes to yield (58%) of a white solid.

Step C. To a mixture of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (0.42 mmol), HOBT (0.42 mmol), and (*S*)-2-(3-biphenyl-4-yl-ureido)-3-phenyl-propionic acid (0.28 mmol) in DMF (3 mL), *N*′,*N*′-diethyl-propane-1,3-diamine (0.42 mmol) was added followed by *N*-methyl morpholine (0.55 mmol) at room temperature. The solution was stirred for 6 h, diluted with EtOAc (100 mL), washed with saturated $NaHCO_3$ (2×20 mL) and brine (2×20 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified on silica gel by flash column chromatography using 0–20% MeOH (1% NH_4OH)/CH_2Cl_2 to afford (76%) of the desired product.

5.3. General solid-phase (Wang) procedure for the preparation of urea derivatives in the α-amino acid series: Method C

Step A. To solid support resin (Wang, 1.3 mmol/g) in THF (1000 mL) was added carbonyl diimidazole (387 mmol) and the mixture was agitated for 5 h at room temperature. Subsequently, the resin was filtered off, washed with THF (3×), MeOH (3×), DCM (3×), and ether (3×), and dried under vacuum.

Step B. To the resin from step A (20 g) in DCM (500 mL), ethane 1,2-diamine (7.8 g) was added followed by diisopropyl ethylamine (16.25 g). The mixture was agitated for 24 h at room temperature. The resin was filtered off, washed with DCM (2×), DMF (2×), MeOH (2×), DCM (3×), and ether (3×), and dried under vacuum.

Step C. A solution of (*S*)-3-cyclohexyl-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)propionic acid (0.75 mmol) in *N*,*N*-dimethylformamide/dichloromethane (1:3, 2 mL) was added to a solution of diisopropyl carbodiimide (DIC) (0.75 mmol) in *N*,*N*-dimethylformamide/dichloromethane (1 mL) and was shaken for 2–3 min at room temperature. This solution was added to the resin from step B (0.156 mmol) followed by a small crystal of 4-dimethylaminopyridine (DMAP). The mixture was agitated for 20 h at room temperature, filtered, and the resin was washed with DMF (2×), DCM (2×), MeOH (2×), DCM (2×), and ether (2×).

Step D. To the resin from step C, a solution of piperidine in DMF (20%, 2 mL) was added and the mixture was agitated for 2 h at room temperature. The resin was filtered off, and washed with DMF (2×), DCM (2×), MeOH (2×), DCM (2×), and ether (2×).

Step E. To the resin from step D, a solution of 4-biphenyl isocyanate (1 mmol) in DMF (2 mL) was added, and the mixture was agitated for 20 h at room temperature. The resin was filtered off and washed with DMF (2×), DCM (2×), MeOH (2×), DCM (2×), and ether (2×).

Step F. (*S*)-*N*-(2-Amino-ethyl)-2-(3-biphenyl-4-yl-ureido)-3-cyclohexyl-propionamide. To the resin from step E, a solution of TFA in DCM (50%, 2 mL) was added and the mixture was agitated for 2.5 h at room temperature. The resin was filtered off and washed with DCM (2×). The filtrate and washings were collected, and the product was isolated by preparative reverse-phase HPLC.

5.4. General solid-phase (indole) procedure for the preparation of urea derivatives in the α-amino acid series: Method D

Step A. A mixture of solid support resin (PS-Indole-CHO, 500 mg, 0.5 mmol), Ti(O*i*Pr)$_4$ (1.0 mmol), and 3-pyrrolidin-1-yl-propylamine (1.0 mmol) in THF (4 mL) was agitated for 4 h at room temperature. Then 1.5 mL

(~0.75 M) of $NaBH_4$ in absolute EtOH was added, and the mixture was agitated again for 2.5 h. The resin was filtered off and washed with DMF (2×), MeOH (2×), DCM (2×), and ether (2×).

Step B. A solution of (*S*)-3-biphenyl-4-yl-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)propionic acid (0.66 mmol) in DMF/DCM (1:3, 2 mL) was added to a solution of diisopropyl carbodiimide (DIC) (0.66 mmol) in DMF/DCM (1 mL) and shaken for 2–3 min. This solution was added to the resin from step A (0.13 mmol) followed by a small crystal of DMAP. The mixture was agitated for 18 h and filtered, and the resin was washed with DMF (2×), DCM (2×), MeOH (2×), DCM (2×), and ether (2×).

Step C. A solution of piperidine in DMF (20%, 2 mL) was added to the resin from step B, and the mixture was agitated for 2 h. The resin was filtered off and washed with DMF (2×), DCM (2×), MeOH (2×), DCM (2×), and ether (2×).

Step D. A solution of 4-biphenyl isocyanate (0.73 mmol) in DMF (2 mL) was added to the resin from step C, and the mixture was agitated for 20 h. The resin was filtered off and washed with DMF (2×), DCM (2×), MeOH (2×), DCM (2×), and ether (2×).

Step E. A solution of TFA in DCM (50%, 1.5 mL) was added to the resin from step D, and the mixture was agitated for 1.5 h. The resin was filtered off and washed with DCM (2×), and the filtrate and the washings were collected. The crude product was purified by preparative reverse-phase HPLC.

5.5. (*S*)-*N*-(2-Amino-ethyl)-3-phenyl-2-(3-phenyl-ureido)-propionamide (1)

The title compound was prepared using Method C. MS (electrospray): mass calculated for $C_{18}H_{22}N_4O_2$, 326.17; *m/z* found, 327.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.31 (t, $J = 5.6$ Hz, 1H), 7.82 (br s, 3H), 7.35–7.18 (m, 9H), 6.88 (t, $J = 7.3$ Hz, 1H), 6.47 (d, $J = 7.8$ Hz, 1H), 4.42 (m, 1H), 3.29–3.26 (m, 2H), 3.02 (dd, $J = 13.8$, 5.3 Hz, 1H), 2.87–2.77 (m, 3H).

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

Prepared by Method C. MS (electrospray): mass calculated for $C_{29}H_{34}N_4O_4$, 502.26; *m/z* found, 503.3 $[M+H]^+$, 403.3 $[M-Boc]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.16 (t, $J = 5.3$ Hz, 1H), 7.61–7.19 (m, 14H), 6.75 (t, $J = 5.4$ Hz, 1H), 6.36 (d, $J = 8.2$ Hz, 1H), 4.46 (q, $J = 7.5$ Hz, 1H), 3.15–2.95 (m, 5H), 2.83 (dd, $J = 13.7$, 7.5 Hz, 1H), 1.37 (s, 9H). To a solution of {2-[2-(3-biphenyl-4-yl-ureido)-3-phenyl-propionylamino]-ethyl}-carbamic acid *tert*-butyl ester (0.25 g, 0.4974 mmol) in CH_2Cl_2 (20 mL) neat TFA (0.66 mL, 8.56 mmol) was added, and the mixture was stirred for 17 h at room temperature. The solvents were removed under reduced pressure, and the residue was dissolved in ethyl acetate (100 mL). The solution was washed with saturated $NaHCO_3$ (2×25 mL) and brine (25 mL), and dried (Na_2SO_4), and the solvents were removed under reduced pressure. Purification of the residue by flash column chromatography using 0–20% MeOH (1% NH_4OH)/CH_2Cl_2 afforded the desired product (0.15 g, 75%). MS (electrospray): mass calculated for $C_{24}H_{26}N_4O_2$, 402.21; *m/z* found, 403.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 7.58 (br s, 1H), 7.42–7.19 (m, 14H), 6.81 (d, $J = 7.6$ Hz, 1H), 4.7 (q, $J = 7.2$ Hz, 1H), 3.18 (br s, 2H), 3.06 (m, 2H), 2.67 (m, 2H), 2.50 (br s, 2H).

5.7. (*S*)-*N*-(2-Amino-ethyl)-2-[3-(4-phenoxy-phenyl)-ureido]-3-phenyl-propionamide (5)

Prepared by Method C. MS (electrospray): mass calculated for $C_{24}H_{26}N_4O_3$, 418.20; *m/z* found, 419.2 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 8.81 (s, 1H), 8.3 (t, $J = 5.6$ Hz, 1H), 7.83 (br s, 3H), 7.37–7.21 (m, 9H), 7.06 (m, 1H), 6.92 (m, 4H), 6.47 (d, $J = 7.8$ Hz, 1H), 4.42 (m, 1H), 3.29–3.25 (m, 2H), 3.03 (dd, $J = 13.8$, 5.3 Hz, 1H), 2.87–2.78 (m, 3H).

5.8. 2-(3-Biphenyl-4-yl-ureido)-*N*-(2-dimethylamino-ethyl)-3-phenyl-propionamide (7)

Prepared by Method B. MS (electrospray): mass calculated for $C_{26}H_{30}N_4O_2$, 430.24; *m/z* found, 431.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.46–7.15 (m, 14H), 4.4 (t, $J = 7.5$ Hz, 1H), 3.18 (m, 2H), 3.0 (dd, $J = 13.6$, 6.5 Hz, 1H), 2.89 (dd, $J = 13.6$, 7.6, 1H), 2.25 (m, 2H), 2.13 (s, 6H).

5.9. (*S*)-*N*-(2-Dimethylamino-ethyl)-2-[3-(4-phenoxy-phenyl)-ureido]-3-phenyl-propionamide (8)

Prepared by Method A. MS (electrospray): mass calculated for $C_{26}H_{30}N_4O_3$, 446.26; *m/z* found: 447.2, $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.01 (t, $J = 5.6$ Hz, 1H), 7.41–6.9 (m, 14H), 6.3 (d, $J = 8.3$ Hz, 1H), 4.46 (m, 1H), 3.1 (m, 2H), 2.97 (dd, $J = 13.6$, 5.6 Hz, 1H), 2.81 (dd, $J = 13.6$, 7.7 Hz, 1H), 2.23 (m, 2H), 2.20 (s, 3H), 2.13 (s, 3H).

5.10. (*S*)-2-(3-Biphenyl-4-yl-ureido)-*N*-(2-isopropyl-amino-ethyl)-3-phenyl-propionamide (9)

Prepared by Method B. Purification by flash column chromatography using 0–20% MeOH (1% NH_4OH)/CH_2Cl_2 to afford 0.07 g (57%) of the desired product. MS (electrospray): mass calculated for $C_{27}H_{32}N_4O_2$, 444.25; *m/z* found, 445.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.89 (s, 1H), 8.18 (t, $J = 5$ Hz, 1H), 7.61–7.2 (m, 14H), 6.53 (d, $J = 8$ Hz, 1H), 4.46 (m, 1H), 3.16 (m, 2H), 2.9 (dd, $J = 13.7$, 5.8 Hz, 1H), 2.86 (dd, $J = 13.7$, 7.72 Hz, 1H), 2.79 (m, 1H), 2.58 (m, 2H), 0.98 (d, $J = 6.2$ Hz, 6H).

5.11. (*S*)-2-(3-Biphenyl-4-yl-ureido)-*N*-(2-diethylamino-ethyl)-3-phenyl-propionamide (10)

Prepared by Method B. MS (electrospray): mass calculated for $C_{28}H_{34}N_4O_2$, 458.27; *m/z* found, 459.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 1H), 7.98 (t, $J = 5.4$ Hz, 1H), 7.74–7.04 (m, 14H), 6.43 (d, $J = 8.2$ Hz, 1H), 4.58 (q, $J = 7.8$ Hz, 1H), 3.1 (m, 2H), 2.99 (dd, $J = 13.7$, 5.7 Hz, 1H), 2.84 (dd, $J = 13.7$, 7.8 Hz, 1H), 2.45 (m, 6H), 0.92 (t, $J = 7.1$ Hz, 6H).

5.12. (*S*)-2-(3-Biphenyl-4-yl-ureido)-*N*-(3-diethylamino-propyl)-3-phenyl-propionamide (11)

To a suspension of (*S*)-2-amino-3-phenyl-propionic acid (0.99 g, 6 mmol) in CH_3COCH_3/H_2O (1:1, 36 mL) was added TEA (0.91 g, 9 mmol), and the mixture was stirred for 5 min. A solution of 4-isocyanato-biphenyl in THF (8 mL) was added, and the reaction mixture was stirred for 7 h. The volume of the mixture was reduced in vacuo, and the pH of the solution was adjusted to approximately 2 using 10% HCl. The resulting white precipitate was filtered, washed with water and 10% CH_2Cl_2/hexanes, and dried under vacuum to afford 1.7 g (81%) of the desired product. MS (electrospray): mass calculated for $C_{22}H_{20}N_2O_3$, 360.15; *m/z* found, 361.1 $[M+H]^+$, 383.1 $[M+Na]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.85 (br s, 1H), 8.81 (s, 1H), 7.66–7.21 (m, 14H), 6.37 (d, $J = 8$ Hz, 1H), 4.47 (m, 1H), 3.11 (dd, $J = 13.8$, 5 Hz, 1H), 2.97 (dd, $J = 13.8$, 7.6 Hz, 1H). (*S*)-2-(3-Biphenyl-4-yl-ureido)-*N*-(3-diethylamino-propyl)-3-phenyl-propionamide. To a mixture of EDCI (0.08 g, 0.42 mmol), HOBT (0.056 g, 0.42 mmol), and (*S*)-2-(3-biphenyl-4-yl-ureido)-3-phenyl-propionic acid (0.1 g, 0.28 mmol) in DMF (3 mL), *N*′,*N*′-diethyl-propane-1,3-diamine (0.054 g, 0.42 mmol) was added followed by *N*-methyl morpholine (0.056 g, 0.55 mmol) at room temperature. The solution was stirred for 6 h, diluted with EtOAc (100 mL), washed with saturated $NaHCO_3$ (2×20 mL) and brine (2×20 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography using 0–20% MeOH (1% NH_4OH)/CH_2Cl_2 to afford 0.1 g (76%) of the desired product. MS (electrospray): mass calculated for $C_{29}H_{36}N_4O_2$, 472.28; *m/z* found, 473.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.81 (s, 1H), 8.09 (t, $J = 5.4$ Hz, 1H), 7.61–7.2(m, 14H), 6.42 (d, $J = 8.3$ Hz, 1H), 4.43 (m, 1H), 3.10–3.03 (m, 2H), 2.98 (dd, $J = 5.8$ Hz, 13.7 Hz, 1H), 2.84 (dd, $J = 13.7$, 7.8 Hz, 1H), 2.46–2.4 (q, $J = 7.0$ Hz, 4H), 2.35 (t, $J = 7.2$ Hz, 2H), 1.47 (m, 2H), 0.92 (t, $J = 7.0$ Hz, 6H).

5.13. (*S*)-2-(3-Biphenyl-4-yl-ureido)-*N*-(2-diisopropyl-amino-ethyl)-3-phenyl-propionamide (12)

Prepared by Method A. 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, CD_3OD) δ 7.56–7.2 (m, 14H), 4.48 (t, $J = 7.4$ Hz, 1H), 3.47–2.99 (m, 6H), 2.44 (br s, 2H), 1.00 (d, $J = 6.4$ Hz, 12H).

5.14. (*S*)-*N*-(2-Diisopropylamino-ethyl)-2-[3-(4-phenoxy-phenyl)-ureido]-3-phenyl-propionamide (13)

To a solution of [(*S*)-1-(2-diisopropylamino-ethyl-carbamoyl)-2-phenyl-ethyl]-carbamic acid *tert*-butyl ester (0.1 g, 0.258 mmol) in CH_2Cl_2 (3 mL), a 4 M solution of HCl in dioxane (0.64 mL, 2.56 mmol) was added, and the mixture was stirred for 3 h at room temperature. The solvents were removed under reduced pressure, the residue was treated with CH_2Cl_2, and the solvent was removed again under reduced pressure. The crude product was dissolved in CH_2Cl_2 (3 mL), and triethylamine (0.037 g, 0.365 mmol) was added at 0 °C followed by 4-phenoxyphenyl isocyanate (0.059 g, 0.28 mmol). The mixture was warmed to room temperature over a period of 2 h and was then diluted with EtOAc (100 mL). The organic layer was washed with saturated $NaHCO_3$ (25 mL) and brine (25 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography using 0–20% MeOH (1% NH_4OH)/CH_2Cl_2 to afford 0.07 g (55%) of the desired product. MS (electrospray): mass calculated for $C_{30}H_{38}N_4O_3$, 502.29; *m/z* found, 503.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.3–7.19 (m, 9H), 7.04 (m, 1H), 6.91–6.85 (m, 4H), 4.47 (t, $J = 7.4$ Hz, 1H), 3.19–2.95 (m, 6H), 2.42 (br s, 2H), 1.02 (d, $J = 6.4$ Hz, 12H).

5.15. (*S*)-2-{3-[4-(4-Chloro-phenoxy)-phenyl]-ureido}-*N*-(2-diisopropylamino-ethyl)-3-phenyl-propionamide (14)

To 4-(4-chloro-phenoxy)-phenylamine (2.2 g, 10 mmol) in THF (30 mL) at 0 °C, pyridine (0.98 g, 12.5 mmol) was added followed by phenylchloroformate (1.61 g, 10.3 mmol). After the mixture was stirred for 10 min, the ice bath was removed. After further stirring for 2.5 h at room temperature, the mixture was diluted with EtOAc (150 mL) and washed sequentially with 10% HCl (40 mL), H_2O (40 mL), saturated $NaHCO_3$ (40 mL), and brine (40 mL). The organics were dried (Na_2SO_4), and the solvents were removed under reduced pressure. The residue was re-crystallized from CH_2Cl_2/hexanes to afford 2.8 g (85%) of the desired product. MS (electrospray): mass calculated for $C_{19}H_{14}ClNO_3$, 339.07; *m/z* found, 340.0 $[M+H]^+$, 362.0 $[M+Na]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.32 (br s, 1H), 7.57–6.96 (m, 13H). [(*S*)-1-(2-Diisopropylamino-ethylcarbamoyl)-2-phenyl-ethyl]-carbamic acid *tert*-butyl ester. HOBT (1.2 g, 8.49 mmol) and EDCI (1.6 g, 8.49 mmol) were added to a solution of (*S*)-2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid in DMF (11 mL). Following the addition of a solution of *N*′,*N*′-diisopropyl-ethane-1,2-diamine (0.978 g, 6.8 mmol) in DMF (2 mL), *N*-methyl-morpholine (1.1 g, 11.3 mmol) was added drop wise. 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 (3×30 mL). The combined organic layers were washed sequentially with 1 N NaOH (2×20 mL) and brine (40 mL), and dried ($MgSO_4$). The solvents were removed under reduced pressure. The crude product was purified by column chromatography [0–

20% (1% NH_4OH/MeOH)/CH_2Cl_2] to afford 1.6 g (72%) of the desired product. MS (electrospray): mass calculated for $C_{22}H_{37}N_3O_3$, 391.55; *m/z* found, 392.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.36–7.29 (m, 2H), 7.26–7.21 (m, 3H), 3.62–3.55 (m, 1H), 3.49 (d, $J = 5.5$ Hz, 1H), 3.27 (dd, $J = 4.1$, 13.6 Hz, 1H), 3.24 (d, $J = 6.2$ Hz, 1H), 3.22 (d, $J = 6.1$ Hz), 3.02–2.95 (m, 2H), 2.67 (dd, $J = 13.6$, 9.4 Hz, 1H), 2.54 (t, $J = 6.3$ Hz, 2H), 1.67 (s, 1H), 1.24 (d, $J = 5.6$ Hz, 2H), 0.98 (d, $J = 6.6$ Hz, 12H). (*S*)-2-{3-[4-(4-Chloro-phenoxy)-phenyl]-ureido}-*N*-(2-diisopropylamino-ethyl)-3-phenylpropion-amide. To a solution of [(*S*)-1-(2-diisopropylamino-ethylcarbamoyl)-2-phenyl-ethyl]-carbamic acid *tert*-butyl ester (0.2 g, 0.5 mmol) in CH_2Cl_2 (5 mL) was added 4 M HCl solution in 1,4-dioxane (3 mL). The mixture was stirred at room temperature for 4 h. Upon completion of the reaction, the solvent was removed under reduced pressure. The crude product was re-dissolved in MeOH (5 mL) and was treated with basic resin (Dowex 550A OH anion-exchange resin) for 2 h. The resin was filtered off, and the solvents were removed again under reduced pressure. To a stirred solution of the crude product in DMSO (1 mL) was added [4-(4-chloro-phenoxy)-phenyl]-carbamic acid phenyl ester (0.174 g, 0.5 mmol). The mixture was stirred at room temperature overnight. Excess EtOAc (50 mL) was then added, along with 0.1 N HCl (5 mL). The organic layers were washed sequentially with H_2O (10 mL), 1 N NaOH (10 mL), and brine (20 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure. Purification by column chromatography [0–20% of (1% NH_4OH/MeOH)/CH_2Cl_2] afforded 0.222 g (80%) of the desired product. MS (electrospray): mass calculated for $C_{30}H_{37}ClN_4O_3$, 536.26; *m/z* found, 537.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.32–7.24 (m, 9H), 6.91–6.88 (m, 4H), 4.47 (dd, $J = 7.5$, 6.7 Hz, 1H), 3.21–3.3.16 (m, 1H), 3.13–2.96 (m, 5H), 2.46 (s, 2H), 1.02 (d, $J = 6.5$ Hz, 12 H).

5.16. 2-(3-Biphenyl-4-yl-ureido)-3-phenyl-*N*-(2-pyrrolidin-1-yl-ethyl)-propionamide (15)

Prepared by Method A. MS (electrospray): mass calculated for $C_{28}H_{32}N_4O_2$, 456.25; *m/z* found 457.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.07 (t, $J = 4.2$ Hz, 1H), 7.8–7.03 (m, 14H), 6.37 (d, $J = 8.2$ Hz, 1H), 4.48 (q, $J = 7.4$ Hz, 1H), 3.15 (m, 2H), 2.97 (dd, $J = 13.7$, 7.5 Hz, 1H), 2.85 (dd, $J = 13.7$, 7.4 Hz, 1H), 2.43 (br s, 6H), 1.58 (br s, 4H).

5.17. (*S*)-2-(3-Biphenyl-4-yl-ureido)-3-phenyl-*N*-(3-pyrrolidin-1-yl-propyl)-propionamide (16)

Method A. To a solution of [(*S*)-2-phenyl-1-(3-pyrrolidin-1-yl-propylcarbamoyl)-ethyl]-carbamic acid *tert*-butyl ester (0.083 g, 0.22 mmol) in CH_2Cl_2 (3 mL), a 4 M solution of HCl in dioxane (0.55 mL, 2.2 mmol) was added, and the mixture was stirred for 3 h at room temperature. The solvents were removed under reduced pressure. The residue was treated with CH_2Cl_2, and the solvent was removed again under reduced pressure. The residue was dissolved in CH_2Cl_2 (3 mL), and at 0 °C, TEA (0.56 g, 0.55 mmol) was added followed by 4-biphenyl isocyanate (0.052 g, 0.264 mmol). The mixture was warmed to room temperature over a period of 2 h and was then diluted with EtOAc (100 mL). The organic layer was washed with saturated $NaHCO_3$ (25 mL) and brine (25 mL), and was dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography using 0–20% MeOH (1% NH_4OH)/CH_2Cl_2 to afford 0.08 g (77%) of the desired product. 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 7.56–7.48 (m, 4H), 7.42–7.36 (m, 4H), 7.33–7.22 (m, 6H), 4.47 (t, $J = 7.1$ Hz, 1H), 3.20–3.16 (m, 2H), 3.07 (dd, $J = 13.6$, 7.1 Hz, 1H), 2.99 (dd, $J = 13.6$, 7.1 Hz, 1H), 2.51 (br m, 4H), 2.42 (m, 2H), 1.77 (br m, 4H), 1.65 (m, 2H).

5.18. 2-(3-Biphenyl-4-yl-ureido)-3-phenyl-*N*-(2-piperidin-1-yl-ethyl)-propionamide (17)

Prepared by Method B. MS (electrospray): mass calculated for $C_{29}H_{34}N_4O_2$, 470.27; *m/z* found, 471.3 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 8.78 (s, 1H), 7.99 (t, $J = 5.4$ Hz, 1H), 7.61–7.05 (m, 14H), 6.37 (dd, $J = 8.2$, 2.3 Hz, 1H), 4.49–4.45 (m, 1H), 3.21–3.08 (m, 2H), 2.99 (dd, $J = 13.7$, 5.6 Hz, 1H), 2.85 (dd, $J = 13.7$, 7.7 Hz, 1H), 2.31–2.15 (m, 6H), 1.49–1.34 (m, 6H).

5.19. 2-(3-Biphenyl-4-yl-ureido)-*N*-(2-morpholin-4-yl-ethyl)-3-phenyl-propionamide (18)

Prepared by Method B. MS (electrospray): mass calculated for $C_{28}H_{32}N_4O_3$, 472.25; *m/z* found, 473.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.47–7.02 (m, 14H), 4.83 (m, 1H), 3.58 (m, 4H), 3.24 (m, 2H), 3.15 (dd, $J = 13.2$, 6.3 Hz, 1H), 3.02 (dd, $J = 13.2$, 8.9 Hz, 1H), 2.37–2.17 (m, 6H).

5.20. (*S*)-2-(3-Biphenyl-4-yl-ureido)-3-phenyl-*N*-(2-piperazin-1-yl-ethyl)-propionamide (19)

Prepared by Method B. MS (electrospray): mass calculated for $C_{28}H_{33}N_5O_2$, 471.26; *m/z* found, 472.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.56–7.07 (m, 14H), 4.5 (t, $J = 7.3$ Hz, 1H), 3.28 (m, 2H), 3.12 (dd, $J = 13.7$, 6.6 Hz, 1H), 3.07 (dd, $J = 13.7$, 7.6 Hz, 1H), 2.96 (m, 4H), 2.38 (m, 6H).

5.21. (*S*)-2-[3-(2-Phenoxy-phenyl)-ureido]-3-phenyl-*N*-(3-pyrrolidin-1-yl-propyl)-propionamide (22)

Prepared by Method A. MS (electrospray): mass calculated for $C_{29}H_{34}N_4O_3$, 486.26; *m/z* found, 487.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.06 (d, $J = 8.2$ Hz, 1H), 7.44–6.6 (m, 14H), 4.46 (t, $J = 7.0$ Hz, 1H), 3.13 (m, 2H), 3.01 (dd, $J = 13.6$, 6.9 Hz, 1H), 2.88 (dd, $J = 13.6$, 7.0 Hz, 1H), 2.45 (m, 4H), 2.36 (m, 2H), 1.74 (m, 4H), 1.57 (m, 2H).

5.22. (*S*)-2-(3-Biphenyl-3-yl-ureido)-3-phenyl-*N*-(3-pyrrolidin-1-yl-propyl)-propionamide (23)

Prepared by Method B. MS (electrospray): mass calculated for $C_{19}H_{15}NO_2$, 289.11; *m/z* found, 312.0 $[M+Na]^+$. (*S*)-2-(3-Biphenyl-3-yl-ureido)-3-phenyl-*N*-(3-pyrrolidin-1-yl-propyl)-propionamide. Prepared by Method B, using [(*S*)-2-phenyl-1-(3-pyrrolidin-1-yl-propylcarbamoyl)-ethyl]-carbamic acid *tert*-butyl ester 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 7.64 (t, $J = 2$ Hz, 1H), 7.55–7.15 (m, 13H), 4.50 (t, $J = 7.2$ Hz, 1H), 3.18 (m, 2H), 3.06 (dd, $J = 13.6$, 6.8 Hz, 1H), 2.98 (dd, $J = 13.6$, 7.2 Hz, 1H), 2.46 (br m, 4H), 2.35 (m, 2H), 1.68 (br m, 4H), 1.59 (m, 2H). To a suspension of 4-biphenyl isothiocyanate (0.72 g, 3.4 mmol) in EtOH (34 mL) was added sodium hydrogen cyanamide (0.22 g, 3.4 mmol), and the resulting suspension was stirred (70 °C, 1.5 h). During the course of the reaction a white solid precipitated. The precipitate was collected, washed with EtOH (100 mL), and dried in vacuo to provide the desired product (0.8 g, 93%). MS (electrospray): mass calculated for $C_{14}H_{11}N_3S$, 253.07; *m/z* found, 254.1 $[M+H]^+$, 276.0 $[M+Na]^+$; 252.1 $[M-H]^-$. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57–7.62 (m, 4H), 7.50–7.53 (m, 2H), 7.37–7.41 (m, 2H), 7.21–7.30 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 186.5, 140.6, 139.3, 135.7, 128.3, 126.4, 126.1, 121.9, 121.1, 121.0 ppm.

5.23. (*S*)-2-[3-(3-Phenoxy-phenyl)-ureido]-3-phenyl-*N*-(3-pyrrolidin-1-yl-propyl)-propionamide (24)

Prepared by Method B. MS (electrospray): mass calculated for $C_{29}H_{34}N_4O_3$, 486.26; *m/z* found, 487.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.05 (t, $J = 5.6$ Hz, 1H), 7.39–6.98 (m, 13H), 6.54 (m, 1H), 6.31 (d, $J = 8.3$ Hz, 1H), 4.38 (q, $J = 7.6$ Hz, 1H), 3.01 (m, 2H), 2.92 (dd, $J = 13.7$, 5.8 Hz, 1H), 2.8 (dd, $J = 13.6$, 7.6 Hz, 1H), 2.35 (m, 4H), 2.28 (m, 2H), 1.65 (m, 4H), 1.46 (m, 2H).

5.24. (*S*)-2-{3-[4-(4-Chloro-phenoxy)-phenyl]-ureido}-3-phenyl-*N*-(2-pyrrolidin-1-yl-ethyl)-propionamide (26)

Prepared by Method B. MS (electrospray): mass calculated for $C_{28}H_{31}ClN_4O_3$, 506.21; *m/z* found, 507.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.31–7.25 (m, 9H), 6.97–6.81 (m, 4H), 4.41–4.37 (m, 1H), 3.51–3.46 (m, 1H), 3.39–3.32 (m, 1H), 3.10 (dd, $J = 13.7$, 6.3 Hz, 1H), 2.97–2.89 (m, 7H), 1.91–1.89 (m, 5H).

5.25. (*S*)-3-Methyl-2-[3-(4-phenoxy-phenyl)-ureido]-*N*-(2-pyrrolidin-1-yl-ethyl)-butyramide (27)

Prepared by Method D. MS (electrospray): mass calculated for $C_{19}H_{29}N_3O_3$, 347.22; *m/z* found, 348.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.37–7.27 (m, 5H), 5.09 (s, 2H), 3.88 (d, $J = 6.8$ Hz, 1H), 3.39–3.33 (m, 2H), 2.65–2.53 (m, 6H), 2.10–2.01 (m, 1H), 1.82–1.78 (m, 4H), 0.95–0.91 (m, 6H). (*S*)-2-Amino-3-methyl-*N*-(2-pyrrolidin-1-yl-ethyl)-butyramide. To a solution of [(*S*)-2-methyl-1-(2-pyrrolidin-1-yl-ethylcarbamoyl)-propyl]-carbamic acid benzyl ester (0.6 g, 1.73 mmol) in EtOH (17 mL) was added 10% Pd/C (0.21 g). The resulting suspension was stirred under H_2 at room temperature overnight. The suspension was then filtered (Celite), and the filtrate was concentrated under reduced pressure. Column chromatography [10–20% (NH_4OH/MeOH)/CH_2Cl_2] afforded the desired product (0.2 g, 54%). MS (electrospray): mass calculated for $C_{11}H_{23}N_3O$, 213.18; *m/z* found, 214.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 3.39–3.35 (m, 2H), 3.34 (s, 1H), 3.05 (d, $J = 5.8$ Hz, 1H), 2.64 (d, $J = 6.9$ Hz, 2H), 2.63–2.59 (m, 4H), 1.95–1.89 (m, 1H), 1.84–1.80 (m, 4H), 0.95 (d, $J = 6.9$ Hz, 3H), 0.91 (d, $J = 6.8$ Hz, 3H). (*S*)-3-Methyl-2-[3-(4-phenoxyphenyl)-ureido]-*N*-(2-pyrrolidin-1-yl-ethyl)-butyramide. 4-Phenoxy-phenyl isocyanate (0.1 g, 0.47 mmol) was added to a solution of (*S*)-2-amino-3-methyl-*N*-(2-pyrrolidin-1-yl-ethyl)-butyramide (0.05 g, 0.23 mmol) in CH_2Cl_2 (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. Purification of the residue by flash column chromatography [0–20% MeOH (1% NH_4OH)/CH_2Cl_2] afforded 0.058 g (50%) of the desired product. MS (electrospray): mass calculated for $C_{24}H_{32}N_4O_3$, 424.5; *m/z* found, 425.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.05 (t, $J = 5.6$ Hz, 1H), 7.43–7.37 (m, 2H), 7.36–7.31 (m, 2H), 7.06 (t, $J = 7.4$ Hz, 1H), 6.95–6.91 (m, 4H), 6.3 (d, $J = 9.0$ Hz, 1H), 3.33 (s, 6H), 3.27–3.12 (m, 2H), 2.47–2.38 (m, 5H), 1.99–1.89 (m, 1H), 1.7–1.62 (m, 4H), 0.87 (d, $J = 6.8$ Hz, 3H), 0.84 (d, $J = 6.8$ Hz, 3H).

5.26. (*S*)-3,3-Dimethyl-2-[3-(4-phenoxy-phenyl)-ureido]-*N*-(3-pyrrolidin-1-yl-propyl)-butyramide (29)

Prepared by Method D. MS (electrospray): mass calculated for $C_{26}H_{36}N_4O_3$, 452.28; *m/z* found, 453.26 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.15 (t, $J = 5.6$ Hz, 1H), 7.43–7.21 (m, 4H), 6.95 (t, $J = 7.4$ Hz, 1H), 6.83–6.79 (m, 4H), 6.30 (d, $J = 9.1$ Hz, 1H), 3.88 (d, $J = 9.1$ Hz, 1H), 3.39 (br s, 2H), 2.98 (m, 4H), 2.83 (br s, 2H), 1.83–1.60 (m, 6H), 0.91 (s, 9H).

5.27. (*S*)-2-(3-Biphenyl-4-yl-ureido)-2-phenyl-*N*-(3-pyrrolidin-1-yl-propyl)-acetamide (31)

Prepared by Method D. MS (electrospray): mass calculated for $C_{28}H_{32}N_4O_2$, 456.25; *m/z* found, 457.26 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.38 (t, $J = 5.5$ Hz, 1H), 7.46–7.15 (m, 14H), 6.91 (d, $J = 7.6$ Hz, 1H), 5.14 (d, $J = 7.6$ Hz, 1H), 3.31–2.73 (m, 8H), 1.79–1.56 (m, 6H).

5.28. (*S*)-2-(3-Biphenyl-4-yl-ureido)-*N*-(2-pyrrolidin-1-yl-ethyl)-3-thiophen-2-yl-propionamide (34)

Prepared by Method D. MS (electrospray): mass calculated for $C_{26}H_{30}N_4O_2S$, 462.21; *m/z* found, 463.16 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.95 (s, 1H), 8.43 (t, $J = 5.6$ Hz, 1H), 7.62–7.36 (m, 10H), 6.98–6.90 (m, 2H), 6.57 (d, $J = 7.8$ Hz, 1H), 4.45 (m, 1H), 3.58–3.95 (m, 10H), 1.98 (br s, 2H), 1.84 (br s, 2H).

5.29. (*R*)-3-Benzylsulfanyl-2-[3-(4-phenoxy-phenyl)-ureido]-*N*-(2-pyrrolidin-1-yl-ethyl)-propionamide (38)

Prepared by Method D. MS (electrospray): mass calculated for $C_{21}H_{33}N_3O_3S$, 407.22; *m/z* found, 408.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.34–7.27 (m, 4H), 7.24–7.20 (m, 1H), 4.22 (t, $J = 6.7$ Hz, 1H), 3.75 (s, 2H), 3.37–3.34 (m, 3H), 2.82 (dd, $J = 13.8$, 5.8 Hz, 1H), 2.64–2.57 (m, 6H), 1.82–1.76 (m, 4H), 1.46 (s, 9H). (*R*)-3-Benzylsulfanyl-2-[3-(4-phenoxy-phenyl)-ureido]-*N*-(2-pyrrolidin-1-yl-ethyl)-propionamide. Prepared from [(*R*)-2-benzylsulfanyl-1-(2-pyrrolidin-1-yl-ethylcarbamoyl)-ethyl]-carbamic acid *tert*-butyl ester, MS (electrospray): mass calculated for $C_{29}H_{34}N_4O_3S$, 518.6; *m/z* found, 519 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.37–7.33 (m, 4H), 7.32–7.27 (m, 4H), 7.23–7.19 (m, 1H), 7.08–7.03 (m, 1H), 6.96–6.87 (m, 4H), 4.45 (t, $J = 6.8$ Hz, 1H), 3.78 (s, 2H), 3.38 (t, $J = 6.7$ Hz, 2H), 2.86 (dd, $J = 13.7$, 5.9 Hz, 1H), 2.76 (dd, $J = 13.7$, 6.9 Hz, 1H), 2.65 (dt, $J = 6.9$, 1.8 Hz, 2H), 2.61–2.59 (m, 4H), 1.81–1.76 (m, 4H).

5.30. (*S*)-2-(3-Biphenyl-4-yl-ureido)-3-pyridin-3-yl-*N*-(3-pyrrolidin-1-yl-propyl)-propionamide (40)

Prepared by Method D. MS (electrospray): mass calculated for $C_{28}H_{33}N_5O_2$, 471.26; *m/z* found, 472.21 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.47 (m, 2H), 8.29 (t, $J = 5.7$ Hz, 1H), 7.70 (d, $J = 7.8$ Hz, 1H), 7.59–7.28 (m, 11H), 6.59 (d, $J = 8.0$ Hz, 1H), 4.50 (m, 1H), 3.51 (br s, 2H), 3.19–2.88 (m, 8H), 1.98 (br s, 2H), 1.91 (br s, 2H), 1.77 (m, 2H).

5.31. (*S*)-2-(3-Biphenyl-4-yl-ureido)-3-pyridin-4-yl-*N*-(3-pyrrolidin-1-yl-propyl)-propionamide (42)

Prepared by Method D. MS (electrospray): mass calculated for $C_{28}H_{33}N_5O_2$, 471.26; *m/z* found, 472.24 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.66 (d, $J = 5.9$ Hz, 2H), 8.40 (t, $J = 5.7$ Hz, 1H), 7.82–7.32 (m, 11H), 6.71 (d, $J = 8.1$ Hz, 1H), 4.6 (m, 1H), 3.62 (m, 2H), 3.29–3.02 (m, 8H), 2.08–1.72 (m, 6H).

5.32. 2-[3-(4-Phenoxy-phenyl)-ureido]-2,2-diphenyl-*N*-(2-pyrrolidin-1-yl-ethyl)-acetamide (44)

Prepared by Method A. MS (electrospray): mass calculated for $C_{19}H_{21}NO_4$, 327.15; *m/z* found, 350.1 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.61–7.29 (m, 10H), 1.56–0.88 (m, 9H). [Diphenyl-(2-pyrrolidin-1-yl-ethylcarbamoyl)-methyl]-carbamic acid *tert*-butyl ester. MS (electrospray): mass calculated for $C_{25}H_{33}N_3O_3$, 423.25; *m/z* found, 424.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.43 (m, 4H), 7.38–7.30 (m, 6H), 6.61 (br s, 1H), 6.54 (br s, 1H), 3.34 (q, $J = 5.7$ Hz, 2H), 2.51 (t, $J = 6.2$ Hz, 2H), 2.40–2.31 (m, 4H), 1.70–1.61 (m, 4H), 1.39 (br s, 9H). 2-[3-(4-Phenoxy-phenyl)-ureido]-2,2-diphenyl-*N*-(2-pyrrolidin-1-yl-ethyl)-acetamide. MS (electrospray): mass calculated for $C_{33}H_{34}N_4O_3$, 534.65; *m/z* found, 535.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.46–7.43 (m, 4H), 7.36–7.27 (m, 10H), 7.06–7.02 (m, 1H), 6.91–6.86 (m, 4H), 3.39 (t, $J = 6.7$ Hz, 2H), 2.59 (t, $J = 6.5$ Hz, 2H), 2.51 (br s, 4H), 1.74–1.69 (m, 4H).

5.33. 2-(3-Biphenyl-4-yl-ureido)-2,2-diphenyl-*N*-(2-pyrrolidin-1-yl-ethyl)-acetamide (45)

Prepared by Method A. MS (electrospray): mass calculated for $C_{33}H_{34}N_4O_2$, 518.6, *m/z* found: 519.3, $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.61–7.50 (m, 4H), 7.46–7.44 (m, 4H), 7.40–7.25 (m, 11H), 3.45 (t, $J = 6.3$ Hz, 2H), 2.55–2.51 (m, 6H), 1.56–1.54 (m, 4H).

5.34. 2-[3-(4-Phenoxy-phenyl)-ureido]-2-propyl-pentanoic acid (2-pyrrolidin-1-yl-ethyl)-amide (46)

Prepared by Method A. To a solution of 2-amino-2-propyl-pentanoic acid (1 g, 6.28 mmol) in acetonitrile (30 mL) was added in tetramethylammonium hydroxide pentahydrate (1.2 g, 6.28 mmol). After 30 min of stirring, the reaction mixture became a solution. Di-*tert*-butyl dicarbonate (2 g, 9.4 mmol) was then added. The reaction mixture was stirred at room temperature for 3 days, after which more di-*tert*-butyl dicarbonate (0.685 g, 3.14 mmol) was added. After stirring overnight, EtOAc (30 mL) and Et_2O (30 mL) were added. Citric acid (10%) was used to adjust the pH to 2–3. The aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded 1 g (62%) of the desired product. MS (electrospray): mass calculated for $C_{13}H_{25}NO_4$, 259.18; *m/z* found, 258.1 $[M-H]^-$. ^1H NMR (400 MHz, CD_3OD) δ 2.11–2.05 (m, 2H), 1.77–1.70 (m, 2H), 1.43 (s, 9H), 1.31–1.26 (m, 2H), 1.17–1.08 (m, 2H), 0.928 (t, $J = 7.3$ Hz, 6H). [1-Propyl-1-(2-pyrrolidin-1-yl-ethylcarbamoyl)-butyl]-carbamic acid *tert*-butyl ester. Prepared from 2-*tert*-butoxycarbonylamino-2-propyl-pentanoic acid, and substituting 2-pyrrolidin-1-yl-ethylamine for 3-pyrrolidin-1-yl-propylamine. MS (electrospray): mass calculated for $C_{19}H_{37}N_3O_3$, 355.28; *m/z* found, 356.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 3.37–3.33 (m, 2H), 2.64–2.53 (m, 6H), 2.04–1.89 (m, 2H), 1.85–1.77 (m, 4H), 1.75–1.65 (m, 2H), 1.43 (s, 9H), 1.28–1.19 (m, 2H), 1.16–1.10 (m, 2H), 0.91–0.87 (m, 6H). 2-[3-(4-Phenoxy-phenyl)-ureido]-2-propyl-pentanoic acid (2-pyrrolidin-1-yl-ethyl)-amide. Prepared from

[1-propyl-1-(2-pyrrolidin-1-yl-ethylcarbamoyl)-butyl]-carbamic acid *tert*-butyl ester, and substituting 4-phenoxyphenyl isocyanate for 4-biphenyl isocyanate. MS (electrospray): mass calculated for $C_{27}H_{38}N_4O_3$, 466.29; m/z found, 467.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.33–7.28 (m, 4H), 7.07–7.03 (m, 1H), 6.94–6.89 (m, 4H), 3.41 (t, $J = 6.8$ Hz, 2H), 2.78–2.62 (m, 6H), 2.12 (dt, $J = 13.3$, 4.2 Hz, 2H), 1.83–1.73 (m, 6H), 1.35–1.27 (m, 2H), 1.21–1.14 (m, 2H), 0.92 (t, $J = 7.3$ Hz, 6H).

5.35. 2-(3-Biphenyl-4-yl-ureido)-2-propyl-pentanoic acid (2-pyrrolidin-1-yl-ethyl)-amide (47)

Prepared by Method A. MS (electrospray): mass calculated for $C_{27}H_{38}N_4O_2$, 450; m/z found, 451.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.60–7.52 (m, 4H), 7.43–7.37 (m, 4H), 7.29–7.25 (m, 1H), 3.42 (t, $J = 6.7$ Hz, 2H), 2.71 (m, 5H), 2.13 (td, $J = 4.1$, 13 Hz, 2H), 1.85–1.81 (m, 4H), 1.79–1.74 (m, 2H), 1.40–1.29 (m, 2H), 1.23–1.15 (m, 2H), 0.93 (t, $J = 7.31$ Hz, 6H).

5.36. 1-[3-(4-Phenoxy-phenyl)-ureido]-cyclopentane-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide (48)

Prepared by Method A. TEA (1.52 g, 15 mmol) was added dropwise to a solution of 1-amino-cyclopentanecarboxylic acid (1.24 g, 10 mmol) and 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile in acetone/water (40 mL, 1:1). After the reaction mixture was stirred for 4 h, the acetone was evaporated and the remaining aqueous layer was extracted with ether (3×40 mL). The aqueous layer was acidified to pH 3 with 10% HCl, and extracted with CH_2Cl_2 (3×70 mL). The combined organic layers were washed with brine (40 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure yielded the desired crude product. MS (electrospray): mass calculated for $C_{11}H_{19}NO_4$, 229.13; m/z found, 228.1 $[M-H]^-$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.45 (br s, 1H), 7.16 (br s, 1H), 1.94–1.85 (br m, 4H), 1.60–1.46 (br s, 4H), 1.36 (s, 9H). 1-[3-(4-Phenoxy-phenyl)-ureido]-cyclopentanecarboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide. Prepared by substituting 1-*tert*-butoxycarbonylamino-cyclopentanecarboxylic acid for 2-*tert*-butoxycarbonylamino-2-propyl-pentanoic acid and carrying the product of that step forward without purification. MS (electrospray): mass calculated for $C_{25}H_{32}N_4O_3$, 436.25; m/z found, 437.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.31 (t, $J = 5.9$ Hz, 1H), 7.31 (m, 4H), 7.05 (m, 1H), 6.92 (m, 4H), 3.57 (m, 4H), 3.30 (m, 2H), 3.08 (m, 2H), 2.22 (m, 2H), 2.02 (m, 2H), 1.84 (m, 8H).

5.37. 1-(3-Biphenyl-4-yl-ureido)-cyclopentanecarboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide (49)

Prepared by Method A. MS (electrospray): mass calculated for $C_{25}H_{32}N_4O_2$, 420.25; m/z found, 421.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.33 (t, $J = 5.81$ Hz, 1H), 7.76–7.27 (m, 9H), 3.78 (m, 4H), 3.30 (m, 2H), 3.02 (m, 2H), 2.07 (m, 2H), 2.01 (m, 2H), 1.88 (m, 8H).

5.38. 2-(3-Biphenyl-4-yl-ureido)-indan-2-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide (50)

Prepared by Method A. [2-(2-Pyrrolidin-1-yl-ethylcarbamoyl)-indan-2-yl]-carbamic acid *tert*-butyl ester. Prepared substituting 2-*tert*-butoxycarbonylamino-indan-2-carboxylic acid for 2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid, and 2-pyrrolidin-1-yl-ethylamine for 3-pyrrolidin-1-yl-propylamine. MS (electrospray): mass calculated for $C_{21}H_{31}N_3O_3$, 373.24; m/z found, 374.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.18–7.12 (m, 4H), 3.55 (d, $J = 16.4$ Hz, 2H), 3.37 (t, $J = 7.0$ Hz, 2H), 3.14 (d, $J = 16.5$ Hz, 2H), 2.64–2.57 (m, 6H), 1.84–1.76 (m, 4H), 1.42 (s, 9H). 2-(3-Biphenyl-4-yl-ureido)-indan-2-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide. MS (electrospray): mass calculated for $C_{29}H_{32}N_4O_2$, 468.2; m/z found, 469.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.56–7.53 (m, 2H), 7.51–7.48 (m, 2H), 7.41–7.36 (m, 4H), 7.28–7.26 (m, 1H), 7.25–7.22 (m, 2H), 7.19–7.12 (m, 2H), 3.65 (d, $J = 16.5$ Hz, 2H), 3.41 (t, $J = 6.8$ Hz, 2H), 3.21 (d, $J = 16.5$ Hz, 2H), 2.66 (t, $J = 6.7$ Hz, 2H), 2.59–2.57 (m, 4H), 1.82–1.71 (m, 4H). (*R*)-4-(3-Biphenyl-4-yl-ureido)-5-phenyl-pentanoic acid (2-amino-ethyl)-amide. MS (electrospray): mass calculated for $C_{26}H_{30}N_4O_2$, 430.54; m/z found, 431.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.52 (br s, 1H), 7.79 (br t, $J = 5.1$ Hz, 1H), 7.60 (d, $J = 7.3$ Hz, 2H), 7.53 (d, $J = 8.7$ Hz, 2H), 7.39–7.45 (m, 4H), 7.27–7.32 (m, 3H), 7.18–7.24 (m, 3H), 6.07 (d, $J = 8.6$ Hz, 1H), 3.84–3.90 (m, 1H), 2.91–3.02 (m, 2H), 2.75 (d, $J = 6.5$ Hz, 2H), 2.49 (br s, 2H), 2.13–2.18 (m, 2H), 1.68–1.76 (m, 1H), 1.49–1.59 (m, 1H).

5.39. (*S*)-2-{*N*′-[4-(4-Chloro-phenoxy)-phenyl]-*N*″-cyano-guanidino}-*N*-(2-dimethyl-aminoethyl)-3-phenyl-propionamide (51)

Prepared by Method A. MS (electrospray): mass calculated for $C_{27}H_{29}ClN_6O_2$, 504.2; m/z found, 505.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.39–7.35 (m, 2H), 7.32–7.22 (m, 3H), 7.19–7.17 (m, 2H), 7.02–6.93 (m, 6H), 4.62 (dd, $J = 8.6$, 5.9 Hz, 1H), 3.37–3.31 (m, 1H), 3.28–3.24 (m, 1H), 3.16 (dd, $J = 13.9$, 5.8 Hz, 1H), 2.93 (dd, $J = 13.9$, 8.8 Hz, 1H), 2.47–2.43 (m, 2H), 2.29 (s, 6H).

5.40. (*S*)-2-{*N*′-[4-(4-Chloro-phenoxy)-phenyl]-*N*″-cyano-guanidino}-*N*-(2-diisopropyl-amino-ethyl)-3-phenyl-propionamide (52)

Prepared by Method A. MS (electrospray): mass calculated for $C_{31}H_{37}ClN_6O_2$, 560.27; m/z found, 561.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.25 (m, 5H), 7.15–7.13 (m, 2H), 7.00–6.92 (m, 6H), 5.74 (d, $J = 5.1$ Hz, 1H), 4.54 (dd, $J = 7.0$, 14.0 Hz, 1H), 3.23–3.10 (m, 2H), 3.09–3.03 (m, 2H), 3.00–

2.90 (m, 2H), 2.62–2.45 (m, 2H), 0.98 (d, $J = 6.38$ Hz, 12H).

5.41. (*S*)-2-{*N*′-[4-(4-Chloro-phenoxy)-phenyl]-*N*″-cyano-guanidino}-3-phenyl-*N*-(2-pyrrolidin-1-yl-ethyl)-propionamide (53)

Prepared by Method A. 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, DMSO-d_6) δ 9.19 (s, 1H), 8.11 (t, $J = 5.3$ Hz, 1H), 7.5–6.98 (m, 13H), 6.92 (d, $J = 7.9$ Hz, 1H), 4.52 (m, 1H), 3.16 (m, 2H), 3.03 (dd, $J = 13.7$, 4.7 Hz, 1H), 2.93 (dd, $J = 13.7$, 9.2 Hz, 1H), 2.49 (br s, 6H), 1.68 (br m, 4H).

5.42. (*R*)-2-{*N*′-[4-(4-Chloro-phenoxy)-phenyl]-*N*″-cyano-guanidino}-3-phenyl-*N*-(2-pyrrolidin-1-yl-ethyl)-propionamide (54)

Prepared by Method A. 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, CD_3OD) δ 7.39–7.35 (m, 2H), 7.32–7.22 (m, 3H), 7.18–7.17 (m, 2H), 7.03–6.94 (m, 6H), 4.61 (dd, $J = 8.6$, 5.9 Hz, 1H), 3.38–3.33 (m, 2H), 3.15 (dd, $J = 13.9$, 5.9 Hz, 1H), 2.99–2.86 (m, 1H), 2.61–2.52 (m, 6H), 1.85–1.77 (m, 4H).

5.43. (*S*)-2-{*N*′-[4-(4-Chloro-phenoxy)-phenyl]-*N*″-cyano-guanidino}-3-phenyl-*N*-(3-pyrrolidin-1-yl-propyl)-propionamide (55)

Prepared by Method A. MS (electrospray): mass calculated for $C_{30}H_{33}ClN_6O_2$, 544.24; m/z found, 545.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.37–6.8 (m, 13H), 4.57 (m, 1H), 3.18 (m, 2H), 3.12 (dd, $J = 13.7$, 5.6 Hz, 1H), 2.93 (dd, $J = 13.7$, 8.6 Hz, 1H), 2.54 (br s, 4H), 2.46 (t, $J = 7.9$ Hz, 2H), 1.79 (br s, 4H), 1.68 (m, 2H).

5.44. (*S*)-2-(*N*′-Biphenyl-4-yl-*N*″-cyano-guanidino)-3-phenyl-*N*-(3-pyrrolidin-1-yl-propyl)-propionamide (56)

[(*S*)-2-Phenyl-1-(3-pyrrolidin-1-yl-propylcarbamoyl)-ethyl]-carbamic acid *tert*-butyl ester. To a mixture of EDCI (5.75 g, 30 mmol), HOBT (4.05 g, 30 mmol), and (*S*)-2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid (5.3 g, 20 mmol) in DMF (80 mL), 3-pyrrolidin-1-yl-propylamine (3.85 g, 30 mmol) in DMF (10 mL) was added followed by *N*-methylmorpholine (4.05 g, 40 mmol) in 10 mL of DMF at room temperature. The solution was stirred for 14 h and was diluted with ethyl acetate (500 mL). The organic layer was washed with saturated $NaHCO_3$ (2×100 mL), brine (3×100 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude residue was stirred in a mixture of 10% EtOAC/hexanes for 1 h to afford 6.5 g (87%) of the desired product as a white solid. MS (electrospray): mass calculated for $C_{21}H_{33}N_3O_3$, 375.25, m/z found, 376.2 $[M+H]^+$, 398.2 $[M+Na]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.25–7.18 (m, 5H), 4.22 (t, $J = 3.6$ Hz, 1H), 3.18–3.14 (m, 2H), 3.04 (dd, $J = 22.0$, 6.5 Hz, 1H), 2.83 (dd, $J = 22.0$, 8.3 Hz, 1H), 2.53–2.49 (m, 4H), 2.42 (t, $J = 7.9$ Hz, 1H), 1.81–1.76 (m, 4H), 1.65–1.61 (m, 2H), 1.37 (s, 9H). To a cooled solution (0 °C) of biphenyl-4-ylamine (0.67 g, 3.96 mmol) in anhydrous CH_2Cl_2 (70 mL) was added dropwise over a 2 h period a solution of 1,1'-thiocarbonyldiimidazole (2.0 g, 11.2 mmol) in CH_2Cl_2 (100 mL). The resulting solution was stirred (0 °C, 0.5 h) and then warmed (25 °C, 0.5 h). The solution was washed with saturated aqueous sodium bicarbonate (100 mL), brine (100 mL), and water (100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The yellow residue was purified by column chromatography using a gradient of 0–25% EtOAc/hexanes to provide the desired product as a tan solid (0.78 g, 93%): $R_f = 0.72$ (25%, EtOAc/hexanes). MS (electrospray): mass calculated for $C_{13}H_9NS$, 211.05; m/z found, 212.0 $[M+H]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.45–7.49 (m, 4H), 7.34–7.39 (m, 2H), 7.26–7.30 (m, 1H), 7.16–7.22 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.7, 140.1, 136.0, 130.7, 129.4, 128.6, 128.3, 124.4, 126.5. (*S*)-2-(*N*′-Biphenyl-4-yl-*N*″-cyano-guanidino)-3-phenyl-*N*-(3-pyrrolidin-1-yl-propyl)-propionamide. To a solution of [(*S*)-2-phenyl-1-(3-pyrrolidin-1-yl-propylcarbamoyl)-ethyl]-carbamic acid *tert*-butyl ester (1.35 g, 3.6 mmol) in CH_2Cl_2 (20 mL), a 4 M solution of HCl in dioxane (2.5 mL, 10 mmol) was added, and the mixture was stirred for 3 h at room temperature. The solvents were removed under reduced pressure, and the residue was treated with CH_2Cl_2. The solvents were removed again under reduced pressure. The residue was dissolved in MeOH and treated with strongly basic ion exchange resin. After the mixture was stirred for 10 min, the resin was filtered off, and the solvents were removed under reduced pressure. The residue was dissolved in DMF (18 mL), and 1-biphenyl-4-yl-3-cyano-thiourea (1.1 g, 4.36 mmol) was added followed by EDC (1.04 g, 5.45 mmol). The reaction mixture was stirred for 14 h, diluted with ethyl acetate (250 mL), and washed sequentially with saturated $NaHCO_3$ (2×50 mL) and brine (2×50 mL). After drying the mixture with Na_2SO_4, the solvents were removed under reduced pressure. Purification of the residue by flash column chromatography using 0–20% MeOH (1% NH_4OH)/CH_2Cl_2 afforded 1.03 g (57%) of the desired product. MS (electrospray): mass calculated for $C_{30}H_{34}N_6O$, 494.28, m/z found, 495.3 $[M+H]^+$, 517.3 $[M+Na]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.61–.55 (m, 4H), 7.45–7.42 (m, 2H), 7.36–7.18 (m, 6H), 7.09–7.06 (m, 2H), 4.6 (dd, $J = 8.5$, 6.2 Hz, 1H), 3.3–3.16 (m, 2H), 3.10 (dd, $J = 14.0$, 6.2 Hz, 1H), 2.94 (dd, $J = 14.0$, 8.5 Hz 1H), 2.53 (br m, 4H), 2.47 (m, 2H), 1.78 (br m, 4H), 1.71–1.65 (m, 2H).

5.45. (*R*)-2-(*N*′-Biphenyl-4-yl-*N*″-cyano-guanidino)-3-phenyl-*N*-(3-pyrrolidin-1-yl-propyl)-propionamide (57)

Prepared by Method A. MS (electrospray): mass calculated for $C_{30}H_{34}N_6O$, 494.28; m/z found, 495.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.14 (t, $J = 5.2$ Hz, 1H), 7.7–7.25 (m, 13H), 7.1 (d, $J = 8.5$ Hz,

2H), 4.57 (m, 1H), 3.15–2.9 (m, 4H), 2.39 (br s, 4H), 2.36 (m, 2H), 1.67 (br m, 4H), 1.53 (m, 2H).

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10. For clarity, only phenylalinine is illustrated in the Scheme 2. Other α-subtituents that were employed in this library were derived from; L-leucine, L-homoleucine, L-*tert*-leucine, 2-pyridylalanine, 3-pyridylalanine, 4-pyridylalanine, L-thienylglycine, 4-biphenyl, -phenylglycine, L-benzylserine, 2-naphthylglycine, L-homophenylalanine, 3-tryptophan.
11. Wang resin consists of polymer bound, 4-benzyloxybenzyl alcohol, CAS # [201058-08-4]. 100 mg of resin yielded 20 mg of product in enantiomeric pure form. Enantiomeric purity was determined using a Chiracel OD column with 100% MeOH.
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