Toward Potent Ghrelin Receptor Ligands Based on Trisubstituted 1,2,4-Triazole Structure. 2. Synthesis and Pharmacological in Vitro and in Vivo Evaluations

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A series of ghrelin receptor ligands based on the trisubstituted 1,2,4-triazole structure were synthesized and evaluated for their in vitro binding and biological activity. In this study, we explored the significance of the aminoisobutyryl (Aib) moiety, a common feature in numerous growth hormone secretagogues described in the literature. Potent agonist and antagonist ligands of the growth hormone secretagogue receptor type 1a (GHS-R1a) were obtained, i.e., compounds **41** (JMV2894) and **17** (JMV3031). The best compounds were evaluated for their in vivo activity on food intake, after sc injection in rodents. Among the tested compounds, few of them were able to stimulate food intake and some others, i.e., compounds **4** (JMV2959), **17**, and **52** (JMV3021), acted as potent in vivo antagonist of hexarelin-stimulated food intake. These compounds did not stimulate growth hormone secretion in rats and furthermore did not antagonize growth hormone secretion induced by hexarelin, revealing that it is possible to modulate food intake without altering growth hormone secretion.

Introduction

Growth hormone secretagogues (GHSs[a]) or ghrelin receptor agonists are compounds able to stimulate growth hormone (GH) release in the pituitary. They were discovered by Bowers,[1] and they act in a totally independent pathway from GHRH. Their biological target named growth hormone secretagogue receptor type 1a (GHS-R1a)[2] and its natural ligand, ghrelin,[3] were later identified. GHS-R1a agonists are able to substitute direct administration of GH for treatment of various disorders caused by GH deficiency such as growth failure. Several peptide and non-peptide agonists of the ghrelin receptor have been reported (Figure 1). We have recently described a new family of ghrelin receptor ligands based on trisubstituted 1,2,4-triazoles.[4] In this study, we explore the significance of the α-aminoisobutyryl (Aib) moiety that is a common feature in almost all small GHS molecules described in the literature (Figure 2).[5−8]

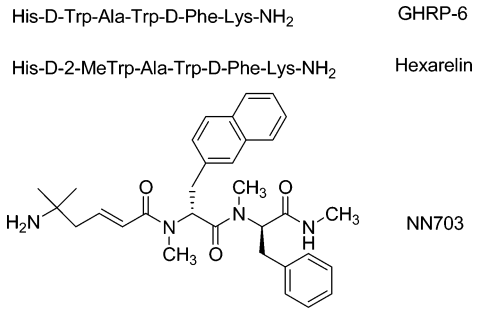

Figure 1. Peptide and pseudopeptide ghrelin receptor agonists.

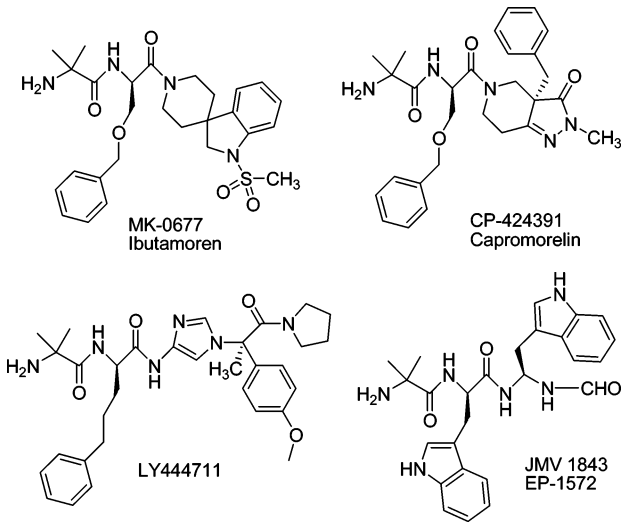

Figure 2. Structures of some known GHSs containing Aib residue.

Chemistry

To study the significance of Aib, 1,2,4-triazoles **D** were prepared as depicted in the general synthetic Scheme 1 and various substitutes of Aib were introduced and deprotected when necessary to yield final compounds **E**. Starting from Boc-D-Trp-OH, the first point of diversity was introduced by coupling with primary amines to yield intermediates **A**. After treatment with the Lawesson's reagent, the corresponding amides **A** were

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[a] Abbreviations: GHS-R1a, growth hormone secretagogue receptor type 1a; GH, growth hormone; GHS, growth hormone secretagogue; GHRH, growth hormone releasing hormone; Aib, α-aminoisobutyric acid; CHO, Chinese hamster ovary; BOP, (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate; DME, ethylene glycol dimethyl ether; DCM, dichloromethane; DMF, dimethylformamide; NMM, *N*-methylmorpholine; DMSO, dimethyl sulfoxide; EDTA, ethylenediaminetetraacetic acid.

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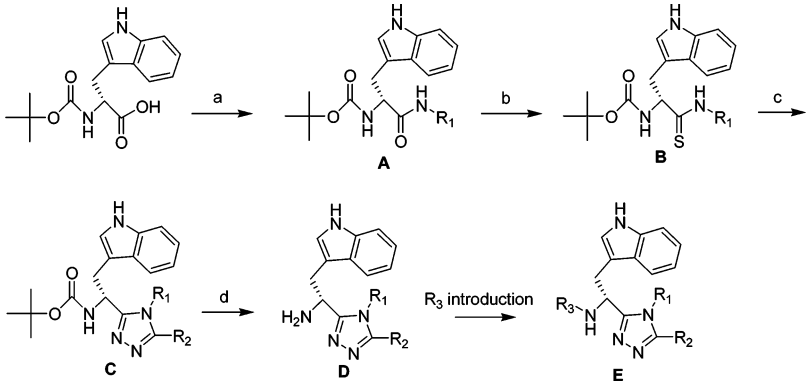
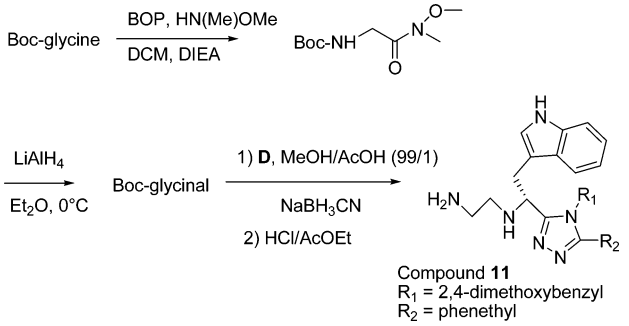
Scheme 1. General Synthetic Pathway to Trisubstituted 1,2,4-Triazoles[a]



[a] (a) BOP, H_2N-R_1, NMM, DCM; (b) Lawesson's reagent, DME, 85 °C; (c) H_2N-HN-COR_2, $Hg(OAc)_2$, room temp, THF; (d) HCl, AcOEt.

Scheme 2. Synthetic Route to Compound **11**



converted into thioamides **B**. The reaction of **B** with different hydrazides in the presence of a thiophile metal salt yielded trisubstituted 1,2,4-triazoles **C**. After deprotection of the Boc protecting group, the generated primary amine **D** reacted with acids, aldehydes, or sulfonyl chlorides to yield respectively amides, alkylamines, or sulfonylamides **E**. Starting from Boc-D-Trp-OH and within a few steps, we describe a route for the synthesis of 1,2,4-triazole derived compounds presenting three points of diversity, thus allowing a structure−activity relationship study.

In a previous study, we have shown that compound JMV1843 (Figure 2) was a very potent compound in stimulating GH secretion in rodents and dogs and by oral route in man.[8−10] All attempts to replace the Aib residue resulted in less potent compounds, indicating the significance of this residue for the stimulation of GH secretion. Recently, we reported that 1,2,4-triazole was a good scaffold to obtain potent GHS-R1a ligands of the ghrelin receptor, leading to agonists, partial agonists, or antagonists.[4] In this study, we showed that a benzyl group and particularly 4-methoxybenzyl or 2,4-dimethoxybenzyl groups in position 4 of the triazole ring and a two-carbon chain bearing a phenyl or an indole group in position 5 of the triazole led to potent ligands of the GHS-R1a. Starting from these results, we investigated the replacement of the Aib moiety in the R_3 position by natural or unnatural α-amino acids, piperidylcarboxyl, and piperazinecarboxyl groups. All these compounds **E** were obtained by coupling a carboxylic acid function on the primary amine **D** except for compound **11**, which was synthesized by reductive amination of the corresponding **D** product with Boc-glycinal as depicted in Scheme 2. All final compounds were purified by reversed-phase HPLC. The purity assessed by analytical reversed-phase C18 HPLC was found to be greater than 95% for target compounds and greater than 98% for key target compounds (compounds **4**, **16**, **17**, **35**, **39**, **40**, **41**, **52**), and the structure was confirmed by MS (electrospray), ^{1}H NMR, and ^{13}C NMR for the most interesting compounds.

Results and Discussion

The synthesized compounds were tested for their ability to displace ^{125}I-His^9-ghrelin from the cloned hGHS-1a receptor transiently expressed in LLC PK-1 cells. Binding affinities of human ghrelin and MK-0677 obtained using these cells were in accordance with the literature. The biological in vitro activity of the compounds (10^{-5} M) was then evaluated on intracellular calcium mobilization $[Ca^{2+}]_i$ using CHO cells transiently expressing GHS-R1a. Results are expressed as a percent of the maximal response induced by 10^{-7} M ghrelin (Table 1). The best compounds were tested in vivo for their ability to stimulate food intake or to inhibit hexarelin-stimulated food intake.

Compounds **1** and **2** containing the Aib residue are reported as reference compounds.[4] Aib was first replaced by glycine. A loss of affinity was observed (compounds **3**−**6**) but was not dramatic, the corresponding IC_{50} ranging from 30 to 150 nM (see Figure 3 for compound **4**). Replacement of 4-methoxybenzyl or 2,4-dimethoxybenzyl in the R_1 group by 4-ethylbenzyl, phenyl, 2,4-dimethoxyphenyl, or 4-ethylphenyl led to compounds **7**−**10** having decreased affinity. Introduction of a "reduced bond" replacing the amide bond led to compound **11** with an IC_{50} of 190 ± 10 nM. Substitution of glycine by alanine (reintroduction of one methyl group of Aib) did not lead to better compounds (**12**, **13**). Replacement of glycine by a β-alanine led to an analogue that exhibited an IC_{50} of 59 ± 16 nM (compound **14**). Replacement of glycine with phenylalanine (compound **15**) failed to increase affinity for the GHS-R1a. Because the Aib moiety is quite a hindered molecule, we decided to rigidify this part of the molecule by introducing a cyclic residue. (L)-Proline and (D)-proline were introduced with 4-methoxybenzyl as the R_1 group and 1*H*-indole-3-ylethyl or phenethyl as the R_2 group. Compounds **16**−**19** exhibited affinities comparable to those of compounds **1** and **2**, compound **16** being the most potent (IC_{50} = 9 ± 1 nM). Because the L-configuration for proline seemed better for interaction with the GHS-1a receptor, we explored in this series the R_1 substituent with 2,4-dimethoxybenzyl (compounds **20** and **21**), 4-ethylbenzyl (compound **22**), phenyl (compound **23**), and 4-ethylphenyl groups (compound **24**). As previously observed, the 2,4-dimethoxybenzyl group was well tolerated whereas 4-ethylbenzyl and 4-ethylphenyl groups led to less potent ligands. An inactive compound was obtained with a phenyl substituent in the R_1 position (compound **23**). Introduction of a hydroxyl group on the pyrrolidine cycle of proline (hydroxyproline) caused a significant decrease of binding affinity (compound **25**) when compared with compound **18**. The initial studies with the proline scaffold validated the constrained analogue approach and suggested to us to further explore other

Table 1. Binding Affinity Constants and Biological Activities of Trisubstituted 1,2,4-Triazoles

compd	R_1	R_2	R_3	IC_{50} (nM)[a]	% of max $[Ca^{2+}]_i$ response at 10 μM[b]	EC_{50} (nM)[c]	K_b (nM)[d]
1	benzyl	1*H*-indole-3-ylethyl	aminoisobutyryl	15 ± 5	73 ± 13	64 ± 14	
2	4-methoxybenzyl	1*H*-indole-3-ylethyl	aminoisobutyryl	6 ± 3	9 ± 11		4 ± 1
3	4-methoxybenzyl	1*H*-indole-3-ylethyl	glycyl	138 ± 23	2 ± 3		ND[f]
4	4-methoxybenzyl	phenethyl	glycyl	32 ± 3	0		19 ± 6
5	2,4-dimethoxybenzyl	1*H*-indole-3-ylethyl	glycyl	38 ± 6	0		27 ± 10
6	2,4-dimethoxybenzyl	phenethyl	glycyl	154 ± 44	0		ND[f]
7	4-ethylbenzyl	phenethyl	glycyl	759 ± 38	0		ND[f]
8	phenyl	phenethyl	glycyl	>1000	7 ± 1		ND[f]
9	2,4-dimethoxyphenyl	phenethyl	glycyl	>1000	27 ± 11	ND[f]	
10	4-ethylphenyl	1*H*-indole-3-ylethyl	glycyl	>1000	4 ± 1		ND[f]
11	2,4-dimethoxybenzyl	phenethyl	2-aminoethyl	190 ± 10	59 ± 12	279 ± 42	
12	4-methoxybenzyl	phenethyl	L-alaninyl	113 ± 29	13 ± 5	ND[f]	
13	4-ethylbenzyl	phenethyl	L-alaninyl	275 ± 50	1 ± 1		ND[f]
14	4-methoxybenzyl	phenethyl	3-aminopropanoyl (β-Ala)	59 ± 16	117 ± 15	256 ± 55	
15	4-methoxybenzyl	phenethyl	L-phenylalaninyl	175 ± 10	0		24 ± 7
16	4-methoxybenzyl	1*H*-indole-3-ylethyl	L-prolyl	9 ± 1	2 ± 2		6 ± 2
17	4-methoxybenzyl	1*H*-indole-3-ylethyl	D-prolyl	28 ± 9	7 ± 5		7 ± 2
18	4-methoxybenzyl	phenethyl	L-prolyl	9.5 ± 2	5 ± 3		13 ± 3
19	4-methoxybenzyl	phenethyl	D-prolyl	32 ± 4	3 ± 2		8 ± 2
20	2,4-dimethoxybenzyl	1*H*-indole-3-ylethyl	L-prolyl	5.6 ± 2	0		11 ± 4
21	2,4-dimethoxybenzyl	phenethyl	L-prolyl	44 ± 6	0		32 ± 10
22	4-ethylbenzyl	phenethyl	L-prolyl	490 ± 140	2 ± 2		ND[f]
23	phenyl	phenethyl	L-prolyl	>1000	24	ND[f]	
24	4-ethylphenyl	1*H*-indole-3-ylethyl	L-prolyl	350 ± 10	5 ± 5		ND[f]
25	4-methoxybenzyl	phenethyl	(2*S*,4*R*)-hydroxyprolyl	173 ± 98	87 ± 23	ND[f]	
26	2,4-dimethoxybenzyl	1*H*-indole-3-ylethyl	piperidyl-3-carboxyl[e]	6.5 ± 1	48 ± 19	5.3 ± 3	
27	benzyl	1*H*-indole-3-ylethyl	piperidyl-3-carboxyl[e]	13 ± 1	50 ± 18	9.9 ± 0.1	
28	2-methyl pyridine	phenethyl	piperidyl-3-carboxyl[e]	>1000	15	ND[f]	
29	4-methoxybenzyl	1*H*-indole-3-ylethyl	L-piperidyl-3-carboxyl	10 ± 2	11 ± 6	2.5 ± 1	
30	4-methoxybenzyl	phenethyl	L-piperidyl-3-carboxyl	16 ± 5	20 ± 9		10 ± 1
31	4-methoxybenzyl	phenethyl	D-piperidyl-3-carboxyl	7 ± 1	89 ± 1	36 ± 1.4	
32	4-ethylbenzyl	phenethyl	L-piperidyl-3-carboxyl	130 ± 1	11 ± 1	ND[f]	
33	2,4-dimethoxybenzyl	1*H*-indole-3-ylethyl	piperidyl-2-carboxyl[e]	53 ± 13	2 ± 1		18 ± 8
34	4-methoxybenzyl	phenethyl	L-piperidyl-2-carboxyl	11 ± 2	7 ± 1		27 ± 8
35	4-methoxybenzyl	1*H*-indole-3-ylethyl	D-piperidyl-2-carboxyl	29 ± 11	0		8 ± 1
36	4-methoxybenzyl	phenethyl	D-piperidyl-2-carboxyl	23 ± 5	3 ± 2		53 ± 7
37	2,4-dimethoxybenzyl	phenethyl	D-piperidyl-2-carboxyl	134 ± 4	0		ND[f]
38	4-ethylbenzyl	phenethyl	D-piperidyl-2-carboxyl	375 ± 6	0		ND[f]
39	4-methoxybenzyl	1*H*-indole-3-ylethyl	isonipecotyl	0.3 ± 0.2	93 ± 1	3.0 ± 1.3	
40	4-methoxybenzyl	phenethyl	isonipecotyl	0.6 ± 0.3	93 ± 4	1.6 ± 0.7	
41	2,4-dimethoxybenzyl	1*H*-indole-3-ylethyl	isonipecotyl	0.5 ± 0.3	77 ± 4	0.6 ± 0.0	
42	2,4-dimethoxybenzyl	phenethyl	isonipecotyl	0.9 ± 0.7	95 ± 14	6.1 ± 0.0	
43	benzyl	1*H*-indole-3-ylethyl	isonipecotyl	24 ± 2	75 ± 10	5.4 ± 2.4	
44	phenyl	phenethyl	isonipecotyl	468 ± 13	98 ± 11	ND[f]	
45	phenyl	1*H*-indole-3-ylethyl	isonipecotyl	70 ± 28	100 ± 0	2.3 ± 1.1	
46	4-ethylphenyl	1*H*-indole-3-ylethyl	isonipecotyl	96 ± 18	100 ± 0	15 ± 1.1	
47	4-ethylbenzyl	phenethyl	isonipecotyl	19 ± 6	101 ± 13	7.7 ± 1.2	
48	2,4-dimethoxyphenyl	phenethyl	isonipecotyl	63 ± 3	100 ± 0	14 ± 4	
49	2-methylpyridine	phenyl-methyl	isonipecotyl	>1000	78	ND[f]	
50	(thiophen-2-yl)methyl	phenethyl	isonipecotyl	255 ± 66	93 ± 13	ND[f]	
51	(furan-2-yl)methyl	phenethyl	isonipecotyl	560 ± 31	100 ± 0	183 ± 13	
52	4-methoxybenzyl	1*H*-indole-3-ylethyl	piperazine-2-carboxyl[e]	18 ± 3	37 ± 9	8.7 ± 1.1	
53	4-methoxybenzyl	phenethyl	piperazine-2-carboxyl[e]	54 ± 7	42 ± 11	12 ± 1.2	
54	2,4-dimethoxybenzyl	1*H*-indole-3-ylethyl	piperazine-2-carboxyl[e]	32 ± 13	2		5 ± 1
55	2,4-dimethoxybenzyl	phenethyl	piperazine-2-carboxyl[e]	35 ± 12	31 ± 17	19.6 ± 6	
56	4-ethylbenzyl	phenethyl	piperazine-2-carboxyl[e]	178 ± 47	68 ± 20	143 ± 27	
57	4-methoxybenzyl	phenethyl	tetrahydro-2*H*-pyran-4-carboxyl	6 ± 2	0		51 ± 8
58	4-methoxybenzyl	phenethyl	cyclohexylcarboxyl	18 ± 6	17 ± 7	390 ± 77	

[a] Specific binding was determined by incubation of membranes from GHS-R1a transfected LLC cells with ^{125}I-His^9-ghrelin in the presence of increasing concentrations of compounds. [b] The activation percentage for each compound (10^{-5} M) was assessed relative to the maximal response, obtained with ghrelin at 10^{-7} M (100%). [c] The signaling through the GHS-R1a, as determined by the accumulation of intracellular calcium and thus fluorescence output, was measured in the presence of increasing concentrations of agonists. [d] The ability of the antagonists to inhibit ghrelin signaling through the GHS-R1a (measurement of fluorescence output) was assessed using Schild plots, with increasing concentrations of ghrelin, alone, or in the presence of antagonist compound at 10^{-8}, 10^{-7}, or 10^{-6} M. [e] Racemic mixture. [f] ND: not determined.

heterocyclic templates. We then explored the possibility of extending the cycle size from 5 to 6 atoms, switching from proline to piperidine moiety and we also studied the influence of the nitrogen position in the cycle. Piperidyl-2-, piperidyl-3-, and piperidyl-4-carboxylic acids were introduced in place of the Aib moiety. Compounds containing the R_1 optimized groups (benzyl, 4-methoxybenzyl and 2,4-dimethoxybenzyl groups) with piperidyl-2-carboxyl and piperidyl-3-carboxyl substituents in the R_3 position exhibited high affinity constants in the range of 10−50 nM (compounds **26**, **27**, **29**−**31**, **33**−**36**) with the exception of compound **37**. No real influence of the piperidyl configuration was observed (compounds **30**, **31** and **34**, **36**).

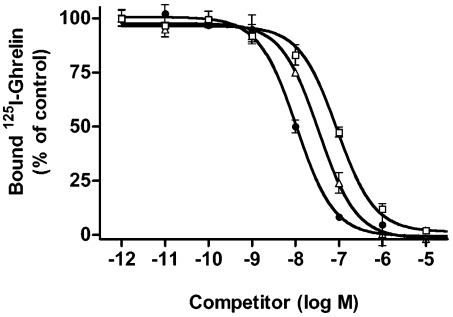


Figure 3. Specific binding was determined by incubation of membranes from GHS-R1a transfected LLC cells with ^{125}I-His^{9}-ghrelin in the presence of increasing concentrations of compound **4** (□), **16** (●), or **17** (Δ).

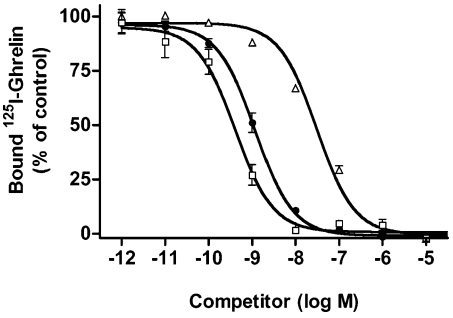


Figure 4. Specific binding was determined by incubation of membranes from GHS-R1a transfected LLC cells with ^{125}I-His^{9}-ghrelin in the presence of increasing concentrations of compound **41** (□), **42** (●), or **43** (Δ).

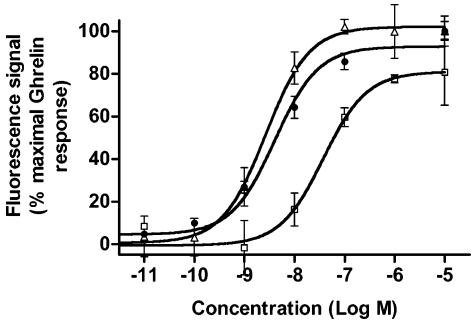


Figure 5. Signaling through the GHS-R1a, as determined by the accumulation of intracellular calcium and thus fluorescence output, was measured in the presence of increasing concentrations of agonists, compounds **31** (□), **39** (●), and **40** (Δ).

When the benzyl group in R_1 position was substituted with a 4-ethyl group, a decrease in binding affinity was observed (compounds **32** and **38**). Introduction of a nitrogen in position 2 of the R_1 benzyl group led to a complete loss of affinity (compound **28**). Compounds containing the isonipecotyl moiety in the R_3 substituent exhibited affinities in the subnanomolar range (compounds **39**−**42**, Figure 4 for compound **42**). The affinity decreased when R_1 substituents were not 4-methoxybenzyl and 2,4-dimethoxybenzyl (compounds **43**−**51**, Figure 4 for compound **43**). We postulated that the high binding affinity could be related to the nitrogen position on the piperidyl cycle that can create an extra interaction with the receptor. Introduction of a second nitrogen atom in the cycle did not improve the binding affinity as assessed by the results obtained with compounds **52**−**56**. The best binding affinity constants were obtained with compounds bearing a piperidine with a carboxylic acid in position 4 of the piperidine ring. We replaced the nitrogen atom by an oxygen atom (compound **57** versus compound **40**). We observed a 10-fold decrease in the affinity

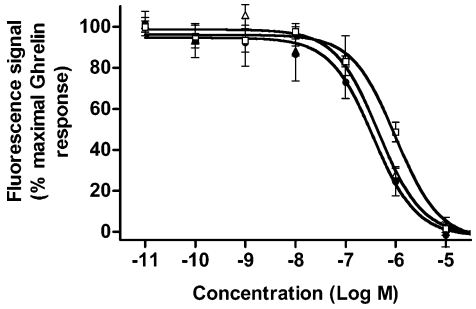


Figure 6. Ability of the antagonists to inhibit ghrelin signaling through the GHS-R1a (measurement of flurorescence output) was determined using increasing concentrations of compound **4** (□), **16** (●), or **17** (Δ) in the presence of a fixed concentration of ghrelin (10^{-7} M).

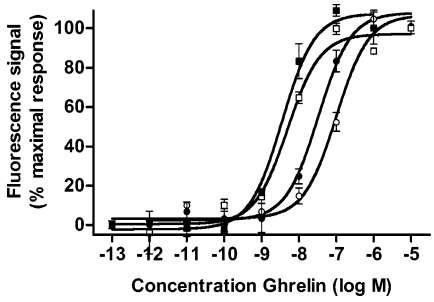


Figure 7. Ability of the antagonists to inhibit ghrelin signaling through the GHS-R1a (measurement of flurorescence output) was assessed using Schild plots, with increasing concentrations of ghrelin, alone (■), or in the presence of compound **4** at 10^{-8} M (□), 10^{-7} M (●), or 10^{-6} M (○).

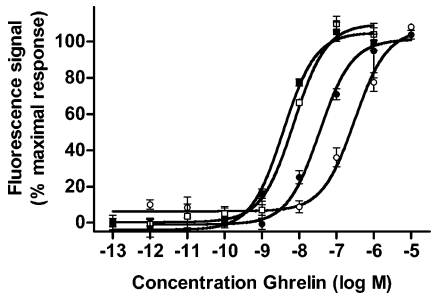


Figure 8. Ability of the antagonists to inhibit ghrelin signaling through the GHS-R1a (measurement of flurorescence output) was assessed using Schild plots, with increasing concentrations of ghrelin, alone (■), or in the presence of compound **17** at 10^{-8} M (□), 10^{-7} M (●), or 10^{-6} M (○).

value. The loss of affinity was more pronounced when the piperidyl ring was replaced by a cyclohexyl ring (compound **58** versus compound **40**) but was not so dramatic ($IC_{50} = 18 \pm 6$ nM for compound **58**).

The ability of these compounds to activate the GHS-R1a and to stimulate a biological response was determined by assessing the increase in intracellular calcium levels in CHO cells transiently transfected with the GHS-R1a. The activation percentage for each compound (10^{-5} M) was assessed relative to the maximal response obtained with ghrelin (10^{-7} M, 100%). For the most affine agonist compounds, EC_{50} values were determined as described in the Experimental Section and are reported in Table 1 (see Figure 5 as an example). We considered as potential antagonist any compound unable to elicit an increase of intracellular calcium level greater than 10% of the maximal response elicited by 10^{-7} M ghrelin. For antagonist compounds with high affinities, K_b values were determined as described in the Experimental Section and are reported in Table 1 (see Figure 6−8). In a previous study,[4] we postulated that the presence of

Table 2. Cumulative Food Intake in Rats after Subcutaneous Administration of 160 μg/kg Compound and/or 80 μg/kg Hexarelin

compd	cumulative food intake at 2 h for 160 μg of compound (cumulative food intake at 2 h for 80 μg of hexarelin)[a]	cumulative food intake at 2 h for 160 μg of compound + 80 μg of hexarelin[a]	cumulative food intake at 6 h for 160 μg of compound (cumulative food intake at 6 h for 80 μg of hexarelin)[a]	cumulative food intake at 6 h for 160 μg of compound + 80 μg of hexarelin[a]
saline	0.06 ± 0.02		0.16 ± 0.05	
4	0.01 ± 0.0 (0.53 ± 0.17)	0.01 ± 0.01	0.04 ± 0.01 (0.59 ± 0.17)	0.02 ± 0.01
5	0.01 ± 0.0 (0.29 ± 0.11)	0.39 ± 0.13	0.01 ± 0.0 (0.60 ± 0.15)	0.74 ± 0.33
6	0.01 ± 0.0 (0.57 ± 0.17)	1.26 ± 0.13	0.08 ± 0.05 (0.98 ± 0.19)	1.48 ± 0.32
7	0.01 ± 0.0 (0.32 ± 0.13)	0.79 ± 0.32	0.03 ± 0.0 (0.45 ± 0.16)	0.81 ± 0.40
14	0.01 ± 0.0(0.46 ± 0.15)	0.16 ± 0.12	0.12 ± 0.11(0.72 ± 0.17)	0.60 ± 0.20
16	0.05 ± 0.05 (0.55 ± 0.13)	0.44 ± 0.16	0.20 ± 0.09 (0.66 ± 0.14)	0.48 ± 0.18
17	0.01 ± 0.0 (0.32 ± 0.13)	0.05 ± 0.04	0.03 ± 0.0 (0.45 ± 0.16)	0.07 ± 0.04
19	0.01 ± 0.0 (0.53 ± 0.19)	0.35 ± 0.20	0.02 ± 0.0 (1.00 ± 0.19)	0.47 ± 0.19
25	0.01 ± 0.0 (0.28 ± 0.08)	0.02 ± 0.01	0.01 ± 0.0 (0.88 ± 0.26)	0.35 ± 0.21
26	0.01 ± 0.0 (0.70 ± 0.16)	0.33 ± 0.12	0.01 ± 0.0 (0.98 ± 0.16)	0.65 ± 0.31
27	0.52 ± 0.29 (0.26 ± 0.11)	0.16 ± 0.15	0.60 ± 0.30 (0.73 ± 0.11)	0.62 ± 0.22
29	0.01 ± 0.0 (0.27 ± 0.12)	0.62 ± 0.21	0.06 ± 0.02 (0.40 ± 0.12)	0.76 ± 0.26
33	0.02 ± 0.02 (0.70 ± 0.16)	0.84 ± 0.27	0.02 ± 0.02 (0.98 ± 0.16)	1.01 ± 0.27
34	0.01 ± 0.0 (1.01 ± 0.15)	0.85 ± 0.13	0.01 ± 0.0 (1.24 ± 0.06)	1.07 ± 0.08
35	0.04 ± 0.01 (0.41 ± 0.17)	1.25 ± 0.24	0.06 ± 0.01 (0.68 ± 0.29)	1.68 ± 0.14
36	0.01 ± 0.0 (0.26 ± 0.13)	0.06 ± 0.03	0.01 ± 0.0 (0.78 ± 0.24)	0.56 ± 0.21
39	0.01 ± 0.0 (0.26 ± 0.13)	0.40 ± 0.20	0.37 ± 0.21 (0.78 ± 0.24)	1.05 ± 0.26
40	0.43 ± 0.07 (1.01 ± 0.15)	1.27 ± 0.13	0.71 ± 0.15 (1.24 ± 0.06)	1.40 ± 0.12
41	0.01 ± 0.0 (0.44 ± 0.16)	0.11 ± 0.09	0.01 ± 0.0 (0.90 ± 0.18)	0.86 ± 0.22
42	0.01 ± 0.0 (0.41 ± 0.12)	0.17 ± 0.16	0.08 ± 0.06 (0.73 ± 0.21)	0.24 ± 0.16
43	0.01 ± 0.0 (0.44 ± 0.16)	0.38 ± 0.13	0.11 ± 0.10 (0.61 ± 0.18)	0.60 ± 0.23
47	0.03 ± 0.01 (0.41 ± 0.17)	1.40 ± 0.34	0.35 ± 0.18 (0.68 ± 0.29)	1.66 ± 0.35
52	0.02 ± 0.01 (0.70 ± 0.27)	0.02 ± 0.01	0.03 ± 0.01 (0.74 ± 0.27)	0.11 ± 0.08
53	0.01 ± 0.0 (0.70 ± 0.11)	0.85 ± 0.23	0.01 ± 0.0 (1.22 ± 0.06)	1.48 ± 0.25
54	0.01 ± 0.0 (0.70 ± 0.11)	0.63 ± 0.32	0.01 ± 0.0 (1.22 ± 0.06)	0.75 ± 0.31
58	0.01 ± 0.0 (0.43 ± 0.16)	0.21 ± 0.13	0.14 ± 0.12 (0.61 ± 0.18)	0.49 ± 0.26

[a] Expressed in g of food per 100 g of body weight.

Table 3. Dose-Response Study for Compounds **4**, **17**, and **52** on Food Intake Stimulated by 80 μg/kg Hexarelin[a]

compound	food intake	compound	food intake	compound	food intake
saline	0.16 ± 0.05	saline	0.16 ± 0.05	saline	0.07 ± 0.04
hexarelin, 80 μg	0.81 ± 0.09	hexarelin 80 μg	0.97 ± 0.20	hexarelin 80 μg	1.12 ± 0.06
+20 μg/kg **4**	0.63 ± 0.23	+20 μg/kg **17**	0.17 ± 0.12	+20 μg/kg **52**	0.66 ± 0.20
+80 μg/kg **4**	0.56 ± 0.18	+80 μg/kg **17**	0.15 ± 0.08	+80 μg/kg **52**	0.34 ± 0.15
+160 μg/kg **4**	0.28 ± 0.12	+160 μg/kg **17**	0.36 ± 0.16	+160 μg/kg **52**	0.83 ± 0.20
+320 μg/kg **4**	0.36 ± 0.14	+320 μg/kg **17**	0.58 ± 0.12	+320 μg/kg **52**	0.11 ± 0.05

[a] Cumulative food intake at 6 h expressed in g of food per 100 g of body weight.

a 4-methoxybenzyl substituent in the R_1 group led to antagonist compounds, all of them containing the Aib moiety at the N-terminus part. In this study, we have shown that when Aib was replaced by different groups, the presence of the 4-methoxybenzyl in the R_1 group was not sufficient to obtain full antagonists. Some of these compounds were able to stimulate $[Ca^{2+}]_i$ accumulation. This is particularly true for compound **11** with a 2-aminoethyl group replacing the Aib moiety (59% total response of 10^{-7} M ghrelin), compound **14** with a 3-aminopropanoyl group instead of Aib (117% total response), compound **25** with a hydroxyprolyl group (87% total response). When piperidyl-3-carboxyl (compounds **26**, **27**, and **31**) or isonipecotyl groups (compounds **39**−**51**) substituted Aib, compounds were also able to stimulate $[Ca^{2+}]_i$ accumulation (from 48% of the total response induced by 10^{-7} M ghrelin for compound **26** to 100% of the total response for compound **48**). The EC_{50} values of the best ligands for the GHS-1a receptor were determined (Table 1). Surprisingly, in the case of the isonipecotyl family, the 4-methoxy benzyl in the R_1 position can be replaced by a 4-ethyl group without a dramatic loss of activity (i.e., compound **47**, $EC_{50} = 7.7 \pm 1.2$ nM). Compounds containing a piperazine-2-carboxyl group exhibited good to modest biological activities (EC_{50} ranging from 8.7 ± 1.1 to 143 ± 27 nM, compounds **52**−**56**). When suppressing the NH moiety in the isonipecotyl group, we observed a decrease in the agonist efficacy [17% of the ghrelin response for compound **58** ($EC_{50} = 390 \pm 77$ nM) compared to 93% of the ghrelin response for compound **40** ($EC_{50} = 1.6 \pm 0.7$ nM) bearing the isonipecotyl group]. Replacement of the Aib moiety by glycyl, prolyl residues, or a piperidine-2-carboxyl group generally led to antagonist compounds. They were able to antagonize the ghrelin-induced $[Ca^{2+}]_i$ accumulation (Figure 6). Compounds **4**, ($K_b = 19 \pm 6$ nM), **16**, ($K_b = 6 \pm 2$ nM), **19**, ($K_b = 8 \pm 2$ nM), **35** ($K_b = 8 \pm 1$ nM), and **54** ($K_b = 5 \pm 1$ nM) were among the most potent ghrelin receptor antagonists. They were able to dose-dependently antagonize ghrelin-induced $[Ca^{2+}]_i$ accumulation in CHO cells transiently transfected with the GHS-R1a. Interestingly, in the presence of various increasing concentrations of compounds **4**, **16**−**18**, and **20**, the dose-response curves of ghrelin on $[Ca^{2+}]_i$ accumulation were shifted to the right in a parallel manner indicating a competitive antagonism (see Figures 7 and 8 for compounds **4** and **17** as examples). Introduction of an oxygen atom (compound **57**) in place of the nitrogen atom of compound **40** switched the agonist activity to antagonist activity (compound **57**, 0% total response, $K_b = 51 \pm 8$ nM) while a good affinity was conserved ($IC_{50} = 6 \pm 2$ nM). A proton that can be engaged in a hydrogen bond in the para position of the piperidine ring seems to be necessary to maintain the agonist activity when keeping similar R_1 and R_2 groups.

Selected compounds among the most active were tested in feeding behavior in rats. They were first evaluated alone for

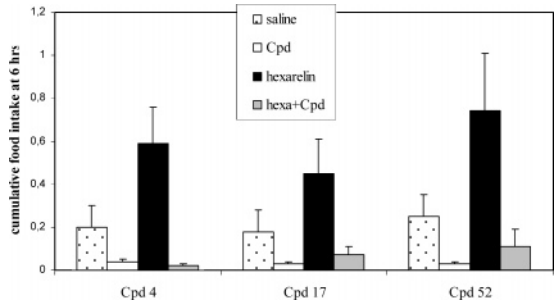


Figure 9. Inhibition of hexarelin (80 μg/kg) induced cumulative food intake (g of food/100 g of body weight) at 6 h by acute administration (sc) of compounds **4**, **17**, and **52** (160 μg/kg).

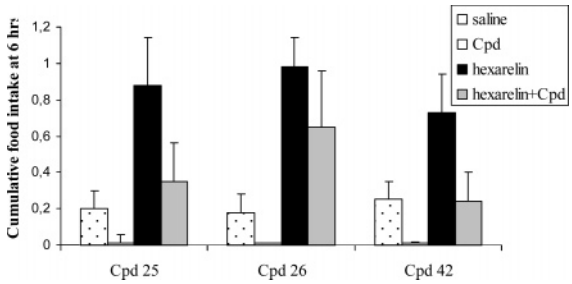


Figure 10. Partial inhibition of hexarelin (80 μg/kg) induced cumulative food intake (g of food/100 g of body weight) at 6 h by acute administration (sc) of GHS-R1a agonists **25**, **26**, and **42** (160 μg/kg).

their effect on food intake and compared to hexarelin and then for their ability to inhibit hexarelin-stimulated food intake. Results are gathered in Table 2. A significant increase in cumulative food intake at 6 h was found for compounds **27**, **39**, **40**, and **47** when compounds were administered alone. These compounds were also characterized as agonist compounds in vitro (EC_{50} values of 9.9, 3.0, 1.6, and 7.7 nM, respectively). Other potent in vitro agonists did not show any increase of cumulative food intake, suggesting either a poor in vivo bioavailability (for example, compound **41** with a EC_{50} value of 0.6 nM) or the presence of ghrelin receptor subtypes or a different mechanism of action of ghrelin receptor in vivo. As expected, when administered alone, in vitro antagonists did not increase food intake. When inhibition of food intake induced by hexarelin was evaluated, two compounds (**4** and **17**) were found to totally suppress food intake while compound **52** was also very potent in inhibiting hexarelin-stimulated food intake (Figure 9). The first two were characterized as antagonists in vitro, while compound **52** was found to be an agonist. In fact, there was no a clear correlation between in vitro and in vivo experiments for several compounds. Some of them characterized as full in vitro agonists were not very potent when administrered alone but potentiated hexarelin-stimulated food intake (compounds **39**, **40**), compound **47** being particularly potent, both at 2 and 6 h after injection (Table 2). Alternatively, in vitro agonist compounds such as **25** and **42** (Figure 10) or the partial agonists **26** and **52** were without effect on food intake when administered alone but were able to antagonize the effect of hexarelin on food intake both at 2 and 6 h after injection. On the other hand, compounds **4** and **17** characterized as in vitro antagonists did not exhibit any activity when administered alone and decreased food intake induced by hexarelin as expected. Compounds **33**, **35**, and **54**, also characterized as in vitro antagonists and with no proper activity, were unable to antagonize the effect of hexarelin on food intake. Compounds **6**, **7**, and **35** were even able to potentiate this effect (Figure 11, Table 2).

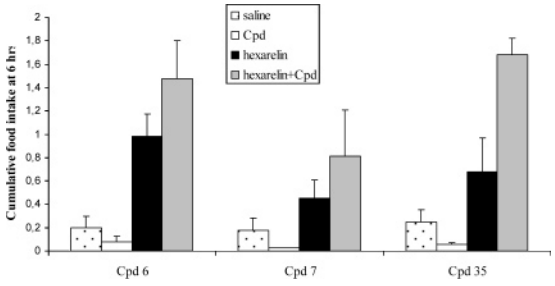


Figure 11. Stimulation of hexarelin (80 μg/kg) induced cumulative food intake (g of food/100 g of body weight) at 6 h by acute administration (sc) of GHS-R1a antagonists **6**, **7**, and **35** (160 μg/kg).

A dose-response study was performed for the three compounds (**4**, **17**, and **52**) able to totally inhibit the hexarelin-induced food intake at 6 h after sc administration. These results are gathered in Table 3. Compound **4** showed a well-correlated progressive inhibition of hexarelin stimulated cumulative food intake with increasing doses (20, 80, and 160 μg/kg). Almost total inhibition was observed at a dose of 80 μg/kg. The highest doses did not improve the inhibition. Compound **17** was found to be effective in suppressing feeding at very low doses (20 and 80 μg/kg), but surprisingly, its efficiency seemed to decrease at higher doses. For compound **52**, a dose-response curve could be obtained.

Information on the toxicity of the compounds could be obtained by the observation on the adult rats that received subcutaneous doses of the compounds (20−320 μg/kg) for assessing the effect on food intake. We did not obtain mortality with any of the tested compounds, and the observation of the animals during the 6 h of the food intake experiments did not reveal altered locomotion behavior.

Compound **4** has been evaluated in a chronic model of diet-induced obesity in mice that were treated for 2 weeks with subcutaneous daily doses of 1.5, 6, and 24 mg/kg. No signs of toxicity were noticed by the routine observation of the animals during the entire experiment.

From these observations we can infer that the tested compounds did not induce toxic effects at the tested doses in the food intake experiments.

The binding affinity of a model compound, compound **40**, was tested at 10 μM versus a panel of 92 GPCRs including cannabinoids, melanocortins, and NPY receptors (MDS Pharma Services' GPCR screen). Only GHS-R1a, CCKI, motilin, tachykinin 2, and vasopressin 1a receptors showed significant binding with this compound. However, the binding affinity to the ghrelin receptor GHS-R1a was 1000 times higher than the affinity to the other receptors.

Selected compounds were also evaluated for their activity on GH secretion in infant rats after sc administration, in the presence or not of hexarelin. Indeed, it is known that in the baby rats the pulsatility of the GH secretion is not yet activated at the hypothalamic level, and therefore, a constant GH blood level is measured in these young animals.

Results are reported in Table 4. As expected, when administered alone, GHS-R1a antagonists (compounds **4**, **17**, **19**, and **34**) did not significantly stimulate GH release. Compounds **40** and **41**, found to behave as full GHS-R1a in vitro agonists, stimulated GH secretion. Compound **52**, which was found to be a partial agonist in our in vitro test (with a total response value of 37%), gave a very low response on GH release (18.6 ng/mL vs 10.7 ng/mL for saline). However, GHS-R1a in vitro antagonists (compounds **4**, **17**, **19**, and **34**) were unable to antagonize hexarelin-stimulated GH secretion. The efficacy of

Table 4. GH Secretion in Infant Rat (sc Injection)[a]

compd	[rGH] (ng/mL)	compd	[rGH] (ng/mL)
saline	4.01 ± 0.47	saline	5.24 ± 0.73
hexarelin	162.84 ± 21.09	hexarelin	170.10 ± 13.23
19	5.66 ± 1.19	**4**	9.85 ± 1.04
19 + hexarelin	160.86 ± 13.52	**4** + hexarelin	164.46 ± 4.44
34	6.09 ± 2.09	saline	10.72 ± 2.02
34 + hexarelin	145.95 ± 12.16	hexarelin	253.82 ± 12.27
40	87.52 ± 15.07	**17**	16.86 ± 2.15
40 + hexarelin	100.52 ± 12.11	**17** + hexarelin	218.84 ± 19.72
41	119.94 ± 33.05	**52**	18.63 ± 2.93
41 + hexarelin	103.53 ± 14.09	**52** + hexarelin	216.57 ± 19.73

[a] Hexarelin was tested at a dose of 80 μg/kg, and compounds were tested at 160 μg/kg.

compounds **40** and **41** was similar in the presence or absence of hexarelin but remained lower than hexarelin itself. Compound **52** seemed to slightly inhibit hexarelin-stimulated GH secretion (216.57 ng/mL vs 253.82 ng/mL for hexarelin alone).

For in vitro results and both GH secretion and food intake stimulation, the situation is complex and no straightforward correlation can be drawn between in vitro results and in vivo experiments on GH secretion and food intake. Compounds **4** and **17** defined as in vitro GHS-R1a antagonists had no effect on GH secretion or food intake when administered alone. However, they were able to totally suppress hexarelin-induced food intake, while they were unable to inhibit GH secretion elicited by hexarelin. The same observation was made for compound **52**, which is a GHS-R1a agonist. Compounds **19** and **34**, also defined as in vitro GHS-R1a antagonists, partially inhibited food intake induced by hexarelin but not hexarelin-stimulated GH secretion. Compound **40**, a potent in vitro agonist, was able to stimulate food intake and GH secretion when administered alone. However, it was able to potentiate both hexarelin-stimulated food intake but not GH secretion. Compound **41**, another potent GHS-R1a agonist, had no effect on food intake when administered alone or with hexarelin but stimulated GH secretion.

All these findings strongly suggest the existence of either ghrelin receptor subtypes or a particular mechanism of action of the ghrelin receptor correlated with GH secretion on one side and food intake on the other side. This last hypothesis was recently suggested for ghrelin receptor inverse agonists that are biased toward a particular signaling pathway.[11]

Conclusion

A novel class of ghrelin receptor (GHS-R1a) ligands was identified from substituted 1,2,4-triazoles. The Aib moiety, often present in the described GHS structures, has been successfully replaced to yield very potent in vitro GHS-R1a agonists [compound **39** (JMV2952), $IC_{50} = 0.3 \pm 0.2$ nM, $EC_{50} = 3.0 \pm 1.3$ nM; **40** (JMV2951), $IC_{50} = 0.6 \pm 0.3$ nM, $EC_{50} = 1.6 \pm 0.7$ nM; **41** (JMV2894), $IC_{50} = 0.5 \pm 0.3$ nM, $EC_{50} = 0.6 \pm 0.0$ nM] and GHS-R1a antagonists [compound **4** (JMV2959), $IC_{50} = 32 \pm 3$ nM, $K_b = 19 \pm 6$ nM; **16** (JMV3030), $IC_{50} = 9 \pm 1$ nM, $K_b = 6 \pm 2$ nM; **17** (JMV3031), $IC_{50} = 28 \pm 9$ nM, $K_b = 7 \pm 2$ nM; **35** (JMV3029), $IC_{50} = 29 \pm 11$ nM, $K_b = 8 \pm 1$ nM]. The most potent compounds in this series were tested in vivo for their activity on hexarelin-stimulated food intake in the rat. Compounds **4**, **17**, and **52** (JMV3021) were found to be able to inhibit hexarelin-induced food intake. These compounds had no effect on GH secretion and were unable to inhibit hexarelin-stimulated GH secretion in the rat. Our results show for the first time that compounds characterized as in vitro GHS-R1a ligands can inhibit food intake without altering GH secretion. This study supports the concept of a specific pharmacological modulation of the ghrelin effect on appetite. To assess the medical relevance of this observation, these compounds will be tested in several other animal models.

Experimental Section

Chemistry. Ascending TLC was performed on precoated plates of silica gel 60 F_{254} (Merck). Peptide derivatives were located with charring reagent or ninhydrin. Column chromatography was performed with Kieselguhr Merck G silica gel, 0.04−0.063 mm. HPLC purifications were run on a Waters 4000 preparative apparatus on a C18 Deltapak column (100 mm × 40 mm, 15 μm, 100 Å), with a UV detection at 214 nm, at a flow rate of 50 mL/min of a mixture of A (water with 0.1% TFA) and B (acetonitrile with 0.1% TFA in gradient mode). Analytical HPLC chromatographs were obtained on a Beckman Gold apparatus composed of the 126 solvent module, the 168 detector, and the 32 Karat software; runs were performed on a VWR Chromolith column (50 mm × 3.9 mm) at a flow rate of 5 mL/min from solution A to solution B in a 3 min gradient (conditions A) or on a Symmetry Shield C18 column (50 mm × 4.6 mm, 3.5 μm) at a flow rate of 1 mL/min from solution A to solution B in a 15 min gradient (conditions B). ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 300 and 75 MHz or at 400 and 100 MHz, respectively, and at 300 K. Chemical shifts were reported as δ values (ppm) indirectly referenced to the solvent signal. Mass spectrum analyses were recorded on a Quatromicro (Micromass, Manchester, U.K.) triple quadrupole mass spectrometer fitted with an electrospray interface. The L- and D-aminoacids and derivatives were from Senn Chemicals, Iris Biotech GmbH, NeoMPS, or Advanced Chemtech. Human ghrelin was purchased from NeoMPS and iodinated in our laboratory. All reagents were of analytical grade.

General Procedure for Hydrazide Preparation. When hydrazides were not commercially available, they were synthesized in two steps via the corresponding esters as described before.[4]

General Procedure for Thioamide B Preparation. In a solution of DCM, amine (1.0 equiv), Boc-D-Trp (1.0 equiv), NMM (2.2 equiv) and BOP (1.0 equiv) were successively added. After 1 h stirring at room temperature, the mixture was concentrated in vacuo and dissolved in AcOEt. The organic layer was successively washed with aqueous solutions of 1 M $KHSO_4$, saturated $NaHCO_3$ and brine. The organic layer was then dried over Na_2SO_4, filtered and concentrated in vacuo to yield amide **A** that was used without purification. To 1.0 equiv. of amide **A** in DME (10 mmol/mL) was added the Lawesson's reagent (0.5 equiv) under argon. The reaction was heated to 85 °C for 2 h and then concentrated in vacuo. The residue was purified by chromatography on silica gel with a mixture of AcOEt/hexane 3/7 as eluent. The thioamide **B** was obtained as a white powder.

(*R*)-*tert*-Butyl 1-(2,4-Dimethoxybenzylamino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-ylcarbamate. 5.2 g (90%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.31 (s, 9H, CH_3 Boc), 2.94 (dd, 1H, $J = 14$ and 9 Hz, CH_2 βTrp), 3.11 (dd, 1H, $J = 14$ and 5 Hz, CH_2 βTrp), 3.71 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.23 (m, 3H, CH αTrp and CH_2 *o*,*p*-dimethoxybenzyl), 6.38 (dd, 1H, $J_o = 8$ Hz and $J_m = 2$ Hz, H_5 *o*,*p*-dimethoxybenzyl), 6.52 (d, 1H, $J_m = 2$ Hz, H_3 *o*,*p*-dimethoxybenzyl); 6.78 (d, 1H, $J_o = 8$ Hz, H_4 Trp), 6.96 (d, 1H, $J_o = 8$ Hz, H_6 *o*,*p*-dimethoxybenzyl), 6.97 (t, 1H, $J_o = 8$ Hz, H_5 Trp), 7.06 (t, 1H, $J_o = 7$ Hz, H_6 Trp), 7.12 (s, 1H, H_2 Trp), 7.34 (d, 1H, $J_o = 8$ Hz, H_7 Trp), 7.60 (d, 1H, $J = 8$ Hz, NH Boc), 8.09 (t, 1H, $J = 6$ Hz, NH amide), 10.79 (1H, s, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 28.3 (C βTrp), 28.5 (CH_3 Boc), 37.4 (CH_2 *o*,*p*-dimethoxybenzyl), 55.3 (OCH_3), 55.5 (C αTrp and OCH_3), 78.4 (Cq Boc), 98.5 (C_3 *o*,*p*-dimethoxybenzyl), 104.6 (C_5 *o*,*p*-dimethoxybenzyl), 110.7 (C_3 Trp), 111.7 (C_7 Trp), 118.6 (C_4 Trp), 118.9 (C_5 Trp), 119.2 (C_1 *o*,*p*-dimethoxybenzyl), 121.2 (C_6 Trp), 124.1 (C_2 Trp), 127.8 (C_9 Trp), 128.9 (C_6 *o*,*p*-dimethoxybenzyl), 136.5 (C_8 Trp), 155.6 (CO Boc), 158.0 (C_2 *o*,*p*-dimethoxybenzyl), 160.0 (C_4 *o*,*p*-dimethoxybenzyl), 172.3 (CO amide). MS (ES), *m/z*: 454.2 $[M + H]^+$, 398.2 $[M + H - {}^tBu]^+$, 354.2 $[M + H - Boc]^+$. HPLC t_R: 1.70 min (conditions A).

(*R*)-*tert*-Butyl 1-(4-Methoxybenzylamino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-ylcarbamate. Yield, 4.3 g (82%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.28 (s, 9H, CH_3 Boc), 2,88 (dd, 1H, J = 9 and 14 Hz, CH_2 βTrp), 3.04 (dd, 1H, J = 9 and 14 Hz, CH_2 βTrp), 3.68 (s, 3H, OCH_3), 4.17 (m, 3H, CH_2 *p*-methoxybenzyl and CH αTrp), 6.74 (d, 1H, J_o = 8 Hz, H_4 Trp), 6.79 (d, 2H, J_o = 8 Hz, H_3 and H_5 *p*-methoxybenzyl), 6.93 (t, 1H, J_o = 8 Hz, H_5 Trp), 7.02 (t, 1H, H_6 Trp), 7.02 (m, 3H, H_2 Trp, H_2 and H_6 *p*-methoxybenzyl), 7.30 (d, 1H, J_o = 8 Hz, H_7 Trp), 7.56 (d, 1H, J = 8 Hz, NH Boc), 8.27 (t, 1H, J = 5 Hz, NH amide), 10.76 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 28.2 (C βTrp), 28.5 (CH_3 Boc), 41.9 (*C*H_2-*p*-methoxybenzyl), 55.4 (OCH_3), 55.7 (C αTrp), 78.4 (Cq Boc), 110.6 (C_3 Trp), 111.6 (C_7 Trp), 112.0 (C_3 and C_5 *p*-methoxybenzyl), 118.5 (C_4 Trp), 118.9 (C_5 Trp), 121.2 (C_6 Trp), 124.1 (C_2 Trp), 127.7 (C_9 Trp), 128.7 (C_2 and C_6 *p*-methoxybenzyl), 131.7 (C_1 *p*-methoxybenzyl), 136.5 (C_8 Trp), 155.6 (CO Boc), 158.5 (C_4 *p*-methoxybenzyl), 172.3 (CO amide). MS (ES), *m/z*: 423.9 [M + H]$^+$, 367.8 [M + H − ^{t}Bu]$^+$, 324.0 [M + H − Boc]$^+$. HPLC t_R: 1.75 min (conditions A).

(*R*)-*tert*-Butyl 1-(Benzylamino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-ylcarbamate. Yield, 5.3 g (95%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.31 (s, 9H, CH_3 Boc), 2.95 (dd, 1H, J = 14 and 9 Hz, CH_2 βTrp), 3.11 (dd, 1H, J = 14 and 5 Hz, CH_2 βTrp), 4.28 (m, 3H, CH_2 benzyl and CH αTrp), 6.79 (d, 1H, J_o = 8 Hz, H_4 Trp), 6.96 (t, 1H, J_o = 7 Hz, H_5 Trp), 7.05 (t, 1H, J_o = 7 Hz, H_6 Trp), 7.12 (s, 1H, H_2 Trp), 7.15−7.27 (m, 5H, CHar benzyl), 7.33 (d, 1H, J_o = 8 Hz, H_7 Trp), 7.60 (d, 1H, J = 8 Hz, NH Boc), 8.40 (t, 1H, J = 6 Hz, NH amide), 10.82 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 28.2 (C βTrp), 28.6 (CH_3 Boc), 42.5 (CH_2 benzyl), 55.8 (C αTrp), 78.4 (Cq Boc), 110.6 (C_3 Trp), 111.7 (C_7 Trp), 118.6 (C_4 Trp), 118.9 (C_5 Trp), 121.2 (C_6 Trp), 124.1 (C_2 Trp), 127.0 (C_4 benzyl), 127.4 (C_2, C_3, C_5, and C_6 benzyl), 127.8 (C_9 Trp), 136.5 (C_8 Trp), 139.8 (C_1 benzyl), 155.6 (CO Boc), 172.5 (CO amide). MS (ES), *m/z*: 394.2 [M + H]$^+$, 338.2 [M + H − ^{t}Bu]$^+$, 294.2 [M + H − Boc]$^+$. HPLC t_R: 1.52 min (conditions A).

(*R*)-*tert*-Butyl 3-(1*H*-Indol-3-yl)-1-oxo-1-(pyridin-2-ylmethylamino)propan-2-ylcarbamate. Yield, 4.3 g (100%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.30 (s, 9H, CH_3 Boc), 2.93 (dd, 1H, J = 14 and 9 Hz, CH_2 βTrp), 3.11 (dd, 1H, J = 14 and 5 Hz, CH_2 βTrp), 4.25 (m, 1H, CH αTrp), 4.34 (d, 2H, J = 6 Hz, CH_2-*o*-pyridyl), 6.85 (d, 1H, J_o = 8 Hz, H_4 Trp), 6.95 (t, 1H, J_o = 8 Hz, H_5 Trp), 7.04 (t, 1H, J_o = 8 Hz, H_6 Trp), 7.12 (m, 2H, H_2 Trp and H_5 *o*-pyridyl), 7.21 (d, 1H, J_o = 7 Hz, H_3 *o*-pyridyl), 7.31 (d, 1H, J_o = 8 Hz, H_7 Trp), 7.59 (m, 2H, NH Boc and H_4 *o*-pyridyl), 8.45 (m, 2H, NH amide and H_6 *o*-pyridyl), 10.77 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 28.1 (C βTrp), 28.5 (CH_3 Boc), 44.8 (CH_2 *o*-pyridyl), 54.8 (C αTrp), 78.5 (Cq Boc), 110.6 (C_3 Trp), 111.7 (C_7 Trp), 118.6 (C_4 Trp), 118.9 (C_5 Trp), 121.0 (C_5 *o*-pyridyl), 121.2 (C_6 Trp), 122.4 (C_3 *o*-pyridyl), 124.5 (C_2 Trp), 127.7 (C_9 Trp), 136.5 (C_8 Trp), 136.9 (C_4 *o*-pyridyl), 149.1 (C_6 *o*-pyridyl), 155.7 (CO Boc), 158.9 (C_2 *o*-pyridyl), 172.7 (CO amide). MS (ES), *m/z*: 395.3 [M + H]$^+$, 339.3 [M + H − ^{t}Bu]$^+$, 295.3 [M + H − Boc]$^+$. HPLC t_R: 1.14 min (conditions A).

(*R*)-*tert*-Butyl 1-(4-Ethylbenzylamino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-ylcarbamate. Yield, 5.3 g (76%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.11 (t, 3H, J = 7 Hz, CH_3−CH_2−phenyl), 1.29 (s, 9H, CH_3 Boc), 2.53 (q, 2H, J = 7 Hz, CH_3−CH_2−phenyl), 2.89 (dd, 1H, J = 14 and 9 Hz, CH_2 βTrp), 3.06 (dd, 1H, J = 14 and 5 Hz, CH_2 βTrp), 4.21 (m, 3H, CH α Trp and CH_2 *p*-ethylbenzyl), 6.76 (d, 1H, J_o = 8 Hz, H_4 Trp), 6.94 (t, 1H, J_o = 7 Hz, H_5 Trp), 7.03 (t, 1H, J_o = 8 Hz, H_6 Trp), 7.07 (m, 5H, H_2 Trp and CHar *p*-ethylbenzyl), 7.30 (d, 1H, J_o = 8 Hz, H_7 Trp), 7.57 (d, 1H, J = 8 Hz, NH Boc), 8.30 (t, 1H, J = 6 Hz, NH amide), 10.77 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 16.2 (*C*H_3−CH_2−phenyl), 28.2 (CH_2 βTrp and CH_3-*C*H_2-phenyl), 28.6 (CH_3 Boc), 42.3 (*C*H_2 *p*-ethylbenzyl), 55.7 (C αTrp), 78.4 (Cq Boc), 110.6 (C_3 Trp), 111.7 (C_7 Trp), 118.6 (C_4 Trp), 118.9 (C_5 Trp), 121.2 (C_6 Trp), 124.1 (C_2 Trp), 127.5 (C_2 and C_6 *p*-ethylbenzyl), 127.8 (C_9 Trp), 127.9 (C_3 and C_5 *p*-ethylbenzyl), 136.5 (C_8 Trp), 137.0 (C_4 *p*-ethylbenzyl), 142.5 (C_1 *p*-ethylbenzyl), 155.6 (CO Boc), 172.4 (CO amide). MS (ES), *m/z*: 421.9 [M + H]$^+$, 365.9 [M + H − ^{t}Bu]$^+$, 322.0 [M + H − Boc]$^+$. HPLC t_R: 1.93 min (conditions A).

(*R*)-*tert*-Butyl 3-(1*H*-Indol-3-yl)-1-oxo-1-(thiophen-2-ylmethylamino)propan-2-ylcarbamate. Yield, 3.6 g (71%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.28 (s, 9H, CH_3 Boc), 2.89 (dd, 1H, J = 14 and 9 Hz, CH_2 βTrp), 3.06 (dd, 1H, J = 14 and 4 Hz, CH_2 βTrp), 4.20 (m, 1H, CH αTrp), 4.42 (m, 2H, CH_2-*o*-thiophenyl), 6.74 (d, 1H, J_o = 8 Hz, H_4 Trp), 6.90 (m, 2H, H_3 and H_4 *o*-thiophenyl), 6.94 (t, 1H, J_o = 7 Hz, H_5 Trp), 7.03 (t, 1H, J_o = 7 Hz, H_6 Trp), 7.08 (s, 1H, H_2 Trp), 7.30 (d, 1H, J_o = 8 Hz, H_7 Trp), 7.33 (dd, 1H, J = 4 and 2 Hz, H_5 *o*-thiophenyl), 7.58 (d, 1H, J = 8 Hz, NH Boc), 8.51 (brs, 1H, NH amide), 10.76 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 28.2 (C βTrp), 28.6 (CH_3 Boc), 37.7 (*C*H_2−*o*-thiophenyl), 55.6 (C αTrp), 78.4 (Cq Boc), 110.6 (C_3 Trp), 111.7 (C_7 Trp), 118.6 (C_4 Trp), 118.9 (C_5 Trp), 121.2 (C_6 Trp), 124.1 (C_2 Trp), 125.6 (C_5 *o*-thiophenyl), 127.0 (C_3 and C_4 *o*-thiophenyl), 127.7 (C_9 trp), 136.5 (C_8 Trp), 142.8 (C_2 *o*-thiophenyl), 155.6 (CO Boc), 172.3 (CO amide). MS (ES), *m/z*: 400.2 [M + H]$^+$, 344.2 [M + H − ^{t}Bu]$^+$, 300.2 [M + H − Boc]$^+$. HPLC t_R: 1.62 min (conditions A).

(*R*)-*tert*-Butyl 3-(1*H*-Indol-3-yl)-1-oxo-1-(phenylamino)propan-2-ylcarbamate. Yield, 5.6 g (88%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.32 (s, 9H, CH_3 Boc), 3.04 (dd, 1H, J = 14 and 9 Hz, CH_2 βTrp), 3.16 (dd, 1H, J = 14 and 5 Hz, CH_2 βTrp), 4.43 (m, 1H, CH αTrp), 6.87 (d, 1H, J_o = 8 Hz, H_4 Trp), 6.97 (t, 1H, J_o = 7 Hz, H_5 Trp), 7.05 (m, 2H, H_4 phenyl and H_6 Trp), 7.18 (s, 1H, H_2 Trp), 7.28 (t, 2H, J_o = 8 Hz, H_3 and H_5 phenyl), 7.33 (d, 1H, J_o = 8 Hz, H_7 Trp), 7.61 (d, 2H, J_o = 8 Hz, H_2 and H_6 phenyl), 7.66 (d, 1H, J = 8 Hz, NH Boc), 10.02 (s, 1H, NH amide), 10.80 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 28.3 (C βTrp), 28.6 (CH_3 Boc), 56.2 (C αTrp), 78.5 (Cq Boc), 110.4 (C_3 Trp), 111.7 (C_7 Trp), 118.6 (C_4 Trp), 119.0 (C_5 Trp), 119.9 (C_2 and C_6 phenyl), 121.3 (C_6 Trp), 123.7 (C_4 phenyl), 124.2 (C_2 Trp), 127.8 (C_9 Trp), 129.0 (C_3 and C_5 phenyl), 136.5 (C_8 Trp), 139.4 (C_1 phenyl), 155.7 (CO Boc), 171.5 (CO amide). MS (ES), *m/z*: 380.2 [M + H]$^+$, 324.2 [M + H − ^{t}Bu]$^+$, 280.2 [M + H − Boc]$^+$. HPLC t_R: 2.30 min (conditions A).

(*R*)-*tert*-Butyl 1-(2,4-Dimethoxybenzylamino)-3-(1*H*-indol-3-yl)-1-thioxopropan-2-ylcarbamate. Yield, 4.5 g (78%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.27 (s, 9H, CH_3 Boc), 2.97 (dd, 1H, J = 8 and 14 Hz, CH_2 βTrp), 3.30 (dd, 1H, J = 4 and 14 Hz, CH_2 βTrp), 3.71 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.58 (m, 3H, CH_2−*o*,*p*-dimethoxybenzyl and CH αTrp), 6.37 (dd, 1H, J_o = 8 Hz and J_m = 2 Hz, H_5 *o*,*p*-dimethoxybenzyl), 6.53 (d, 1H, J_m = 2 Hz, H_3 *o*,*p*-dimethoxybenzyl), 6.86 (d, 1H, J_o = 8 Hz, H_4 Trp), 6.87 (d, 1H, J_o = 8 Hz, H_6 *o*,*p*-dimethoxybenzyl), 6.95 (t, 1H, J_o = 7 Hz, H_5 Trp), 7.03 (t, 1H, J_o = 7 Hz, H_6 Trp), 7.11 (s, 1H, H_2 Trp), 7.30 (d, 1H, J_o = 8 Hz, H_7 Trp), 7.60 (m, 1H, NH Boc), 9.97 (t, 1H, J = 6 Hz, NH thioamide), 10.78 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 28.5 (CH_3 Boc), 31.3 (C βTrp), 44.2 (*C*H_2 *o*,*p*-dimethoxybenzyl), 55.6 (OCH_3), 55.9 (OCH_3), 61.9 (C αTrp), 78.6 (Cq Boc), 98.7 (C_3 *o*,*p*-dimethoxybenzyl), 104.8 (C_5 *o*,*p*-dimethoxybenzyl), 110.4 (C_3 Trp), 111.7 (C_7 Trp), 116.7 (C_1 *o*,*p*-dimethoxybenzyl), 118.6 (C_4 Trp); 118.9 (C_5 Trp), 121.2 (C_6 Trp), 124.4 (C_2 Trp), 127.8 (C_9 Trp), 130.1 (C_6 *o*,*p*-dimethoxybenzyl), 136.5 (C_8 Trp), 155.5 (CO Boc), 158.6 (C_2 *o*,*p*-dimethoxybenzyl), 161.1 (C_4 *o*,*p*-dimethoxybenzyl), 210.4 (CS thioamide). MS (ES), *m/z*: 470.0 [M + H]$^+$, 414.0 [M + H − ^{t}Bu]$^+$, 370.0 [M + H − Boc]$^+$. HPLC t_R: 1.97 min (conditions A).

(*R*)-*tert*-Butyl 1-(4-Methoxybenzylamino)-3-(1*H*-indol-3-yl)-1-thioxopropan-2-ylcarbamate. Yield, 4.4 g (83%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.27 (s, 9H, CH_3 Boc), 2.94 (dd, 1H, J = 9 and 14 Hz, CH_2 βTrp), 3.13 (dd, 1H, J = 5 and 14 Hz, CH_2 βTrp), 3.69 (s, 3H, OCH_3), 4.62 (m, 3H, CH_2 *p*-methoxybenzyl and CH αTrp), 6.76 (s, 4H, CHar *p*-methoxybenzyl), 6.94 (m, 2H, H_4 and H_5 Trp), 7.03 (t, 1H, H_6 Trp), 7.16 (s, 1H, H_2 Trp), 7.30 (d, 1H, J_o = 8 Hz, H_7 Trp), 7.59 (d, 1H, J = 8 Hz, NH Boc), 10.21 (t, 1H, J = 5 Hz, NH thioamide), 10.78 (s, 1H, NH indole Trp).

^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 28.5 (CH_3 Boc), 31.3 (C βTrp), 48.2 (CH_2 *p*-methoxybenzyl), 55.3 (OCH_3), 62.0 (C αTrp), 78.6 (Cq Boc), 110.4 (C_3 Trp), 111.7 (C_7 Trp), 114.0 (C_3 and C_5 *p*-methoxybenzyl), 118.6 (C_4 Trp), 118.9 (C_5 Trp), 121.2 (C_6 Trp), 124.3 (C_2 Trp), 127.7 (C_9 Trp), 129.0 (C_1 *p*-methoxybenzyl), 129.2 (C_2 and C_6 *p*-methoxybenzyl), 136.5 (C_8 Trp), 155.2 (CO Boc), 158.8 (C_4 *p*-methoxybenzyl), 204.8 (CS thioamide). MS (ES), *m/z*: 439.9 $[M + H]^+$, 383.9 $[M + H - {}^t\text{Bu}]^+$, 339.9 $[M + H - \text{Boc}]^+$. HPLC t_R: 2.01 min (conditions A).

(*R*)-*tert*-Butyl 1-(Benzylamino)-3-(1*H*-indol-3-yl)-1-thioxopropan-2-ylcarbamate. Yield, 5.2 g (77%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.30 (s, 9H, CH_3 Boc), 3.03 (dd, 1H, $J = 14$ and 8 Hz, CH_2 βTrp), 3.20 (dd, 1H, $J = 14$ and 5 Hz, CH_2 βTrp), 4.65−4.85 (m, 3H, CH_2 benzyl and CH αTrp), 6.79 (d, 1H, $J_o = 8$ Hz, H_4 Trp), 6.97 (t, 1H, $J_o = 7$ Hz, H_5 Trp), 7.06 (t, 1H, $J_o = 7$ Hz, H_6 Trp), 7.16 (m, 3H, H_2 and H_6 benzyl, H_2 Trp), 7.26 (m, 3H, H_3, H_4 and H_5 benzyl), 7.34 (d, 1H, $J_o = 8$ Hz, H_7 Trp), 7.64 (d, 1H, $J = 7$ Hz, NH Boc), 10.32 (t, 1H, $J = 5$ Hz, NH thioamide), 10.81 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 28.5 (CH_3 Boc), 31.3 (C βTrp), 48.6 (CH_2 benzyl), 62.1 (C αTrp), 78.6 (Cq Boc), 110.4 (C_3 Trp), 111.7 (C_7 Trp), 118.6 (C_4 Trp), 119.0 (C_5 Trp), 121.3 (C_6 Trp), 124.4 (C_2 Trp), 127.4 (C_4 benzyl), 127.8 (C_9 Trp), 128,8 (C_2 and C_6 benzyl), 128.6 (C_3 and C_5 benzyl), 136.5 (C_8 Trp), 137.3 (C_1 benzyl), 155.3 (CO Boc), 205.3 (CS thioamide). MS (ES), *m/z*: 410.0 $[M + H]^+$, 354.0 $[M + H - {}^t\text{Bu}]^+$, 310.0 $[M + H - \text{Boc}]^+$. HPLC t_R: 1.99 min (conditions A).

(*R*)-*tert*-Butyl 3-(1*H*-Indol-3-yl)-1-(pyridin-2-ylmethylamino)-1-thioxopropan-2-ylcarbamate. Yield, 2.5 g (49%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.29 (s, 9H, CH_3 Boc), 3.01 (dd, 1H, $J = 14$ and 8 Hz, CH_2 βTrp), 3.23 (dd, 1H, $J = 14$ and 5 Hz, CH_2 βTrp), 4.62 (m, 1H, CH αTrp), 4.89 (m, 2H, CH_2-*o*-pyridyl), 6.93 (m, 2H, H_4 and H_5 Trp), 7.01 (m, 2H, H_6 Trp and H_5 *o*-pyridyl), 7.17 (s, 1H, H_2 Trp), 7.32 (d, 1H, $J_o = 8$ Hz, H_7 Trp), 7.46 (d, 1H, $J_o = 8$ Hz, H_3 *o*-pyridyl), 7.61 (d, 1H, $J = 8$ Hz, NH Boc), 7.86 (t, 1H, $J_o = 8$ Hz, H_4 *o*-pyridyl), 8.60 (brs, 1H, H_6 *o*-pyridyl), 10.53 (brs,1H, NH thioamide), 10.83 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 28.5 (CH_3 Boc), 31.0 (C βTrp), 48.8 (CH_2−*o*-pyridyl), 62.4 (C αTrp), 78.8 (Cq Boc), 110.3 (C_3 Trp), 111.7 (C_7 Trp), 118.7 (C_4 Trp), 118.9 (C_5 Trp), 121.3 (C_6 Trp), 123.7 (C_5 *o*-pyridyl), 124.5 (C_3 *o*-pyridyl), 124.5 (C_2 Trp), 127.7 (C_9 Trp), 132.7 (C_4 *o*-pyridyl), 136.5 (C_8 Trp), 140.0 (C_6 *o*-pyridyl), 155.2 (CO Boc), 155.5 (C_2 *o*-pyridyl), 206.6 (CS thioamide). MS (ES), *m/z*: 411.0 $[M + H]^+$, 355.0 $[M + H - {}^t\text{Bu}]^+$, 311.0 $[M + H - \text{Boc}]^+$. HPLC t_R: 1.33 min (conditions A).

(*R*)-*tert*-Butyl 1-(4-Ethylbenzylamino)-3-(1*H*-indol-3-yl)-1-thioxopropan-2-ylcarbamate. Yield, 6.3 g (95%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.11 (t, 3H, $J = 8$ Hz, CH_3-CH_2-phenyl), 1.28 (s, 9H, CH_3 Boc), 2.53 (q, 2H, $J = 8$ Hz, CH_3−CH_2−phenyl), 2.97 (dd, 1H, $J = 14$ and 9 Hz, CH_2 βTrp), 3.15 (dd, 1H, $J = 14$ and 5 Hz, CH_2 βTrp), 4.68 (m, 3H, CH_2 *p*-ethylbenzyl and CH αTrp), 6.75 (d, 1H, $J_o = 8$ Hz, H_4 Trp), 6.85 (t, 1H, $J_o = 8$ Hz, H_5 Trp), 6.97 (t, 1H, $J_o = 8$ Hz, H_6 Trp), 6.99−7.10 (m, 4H, CHar *p*-ethylbenzyl), 7.13 (s, 1H, H_2 Trp), 7.31 (d, 1H, $J_o = 8$ Hz, H_7 Trp), 7.60 (d, 1H, $J = 8$ Hz, NH Boc), 10.24 (t, 1H, $J = 5$ Hz, NH thioamide), 10.79 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 16.1 (CH_3−CH_2−phenyl), 28.2 (CH_3−CH_2−phenyl), 28.5 (CH_3 Boc), 31.3 (C βTrp), 48.5 (CH_2 *p*-ethylbenzyl), 62.1 (C αTrp), 78.6 (Cq Boc), 110.4 (C_3 Trp), 111.7 (C_7 Trp), 118.6 (C_4 Trp), 118.9 (C_5 Trp), 121.2 (C_6 Trp), 124.4 (C_2 Trp), 127.7 (C_9 Trp), 127.9 (C_2, C_3, C_5 and C_6 *p*-ethylbenzyl), 134.5 (C_4 *p*-ethylbenzyl), 136.5 (C_8 Trp), 143.0 (C_1 *p*-ethylbenzyl), 155.2 (CO Boc), 205.0 (CS thioamide). MS (ES), *m/z*: 438.2 $[M + H]^+$, 382.2 $[M + H - {}^t\text{Bu}]^+$, 338.2 $[M + H - \text{Boc}]^+$. HPLC t_R: 2.17 min (conditions A).

(*R*)-*tert*-Butyl 3-(1*H*-Indol-3-yl)-1-(thiophen-2-ylmethylamino)-1-thioxopropan-2-ylcarbamate. Yield, 4.5 g (69%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.28 (s, 9H, CH_3 Boc), 2.95 (dd, 1H, $J = 14$ and 9 Hz, CH_2 βTrp), 3.12 (dd, 1H, $J = 14$ and 4 Hz, CH_2 βTrp), 4.55 (m, 1H, CH αTrp), 4.80 (m, 2H, CH_2−*o*-thiophenyl), 6.82 (d, 1H, $J_o = 8$ Hz, H_4 Trp), 6.90 (m, 2H, H_3 and H_4 *o*-thiophenyl), 6.94 (t, 1H, $J_o = 7$ Hz, H_5 Trp), 7.03 (t, 1H, $J_o = 7$ Hz, H_6 Trp), 7.08 (s, 1H, H_2 Trp), 7.30 (d, 1H, $J_o = 8$ Hz, H_7 Trp), 7.33 (dd, 1H, $J = 4$ and 2 Hz, H_5 *o*-thiophenyl), 7.58 (d, 1H, $J = 8$ Hz, NH Boc), 10.47 (brs, 1H, NH thioamide), 10.76 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 28.2 (C βTrp), 28.6 (CH_3 Boc), 45.4 (CH_2−*o*-thiophenyl), 62.0 (C αTrp), 78.4 (Cq Boc), 110.6 (C_3 Trp), 111.7 (C_7 Trp), 118.6 (C_4 Trp), 118.9 (C_5 Trp), 121.2 (C_6 Trp), 124.1 (C_2 Trp), 125.6 (C_5 *o*-thiophenyl), 127.0 (C_3 and C_4 *o*-thiophenyl), 127.7 (C_9 Trp), 136.5 (C_8 Trp), 142.8 (C_2 *o*-thiophenyl), 155.6 (CO Boc), 207.0 (CS thioamide). MS (ES), *m/z*: 416.2 $[M + H]^+$, 360.2 $[M + H - {}^t\text{Bu}]^+$, 316.2 $[M + H - \text{Boc}]^+$. HPLC t_R: 1.92 min (conditions A).

(*R*)-*tert*-Butyl 3-(1*H*-Indol-3-yl)-1-(phenylamino)-1-thioxopropan-2-ylcarbamate. Yield, 5.3 g (75%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.30 (s, 9H, CH_3 Boc), 3.09 (m, 1H, CH_2 βTrp), 3.17 (dd, 1H, $J = 14$ and 5 Hz, CH_2 βTrp), 4.74 (m, 1H, CH αTrp), 6.80 (d, 1H, $J_o = 7$ Hz, H_4 Trp), 6.96 (t, 1H, $J_o = 7$ Hz, H_5 Trp), 7.04 (t, 1H, $J_o = 7$ Hz, H_6 Trp), 7.20 (m, 2H, H_2 Trp and H_4 phenyl), 7.30 (d, 1H, $J_o = 8$ Hz, H_7 Trp), 7.35 (t, 2H, $J_o = 8$ Hz, H_2 and H_6 phenyl), 7.65 (m, 3H, H_3 and H_5 phenyl, NH Boc), 10.79 (s, 1H, NH thioamide), 11.42 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 28.6 (CH_3 Boc), 31.6 (C βTrp), 62.8 (C αTrp), 78.7 (Cq Boc), 110.2 (C_3 Trp), 111.7 (C_7 Trp), 118.6 (C_4 Trp), 119.0 (C_5 Trp), 121.2 (C_6 Trp), 123.9 (C_2 Trp and C_4 phenyl), 126.5 (C_2 and C_6 phenyl), 127.8 (C_9 Trp), 128.8 (C_3 and C_5 phenyl), 136.4 (C_8 Trp), 139.6 (C_1 phenyl), 155.3 (CO Boc), 204.7 (CS thioamide). MS (ES), *m/z*: 396.2 $[M + H]^+$, 340.2 $[M + H - {}^t\text{Bu}]^+$, 296.2 $[M + H - \text{Boc}]^+$. HPLC t_R: 1.85 min (conditions A).

General Procedure for Preparation of Triazole C. To a solution of 1.0 equiv of thioamide **B** in 5 mL of tetrahydrofuran (1 mmol/10 mL) were added 2.0 equiv of hydrazide and then 1.1 equiv of mercury(II) acetate at room temperature. After 2 days, the mixture was filtered on Celite and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel with a mixture of AcOEt/MeOH, 96/4, as eluent. The desired compounds were obtained as a white powder (yield ranging between 48% and 65%).

(*R*)-*tert*-Butyl 1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(2,4-dimethoxybenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethylcarbamate. Yield, 1.2 g (60%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.21 (s, 9H, CH_3 Boc), 2.90 (m, 4H, CH_2−CH_2−indole), 3.28 (m, 2H, CH_2 βTrp), 3.59 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 5.01 (m, 3H, CH_2−*o*,*p*-dimethoxyphenyl and CH αTrp), 6.26 (d, 1H, $J_o = 8$ Hz, H_5 *o*,*p*-dimethoxyphenyl), 6.49 (d, 1H, $J_o = 8$ Hz, H_6 *o*,*p*-dimethoxyphenyl), 6.51 (s, 1H, H_3 *o*,*p*-dimethoxyphenyl), 6.89 (m, 2H, H_5 Trp and H_5 indole), 7.02 (m, 2H, H_6 indole and H_6 Trp), 7.03 (s, 1H, H_2 indole), 7.05 (s, 1H, H_2 Trp), 7.26 (d, 1H, $J_o = 8$ Hz, H_4 Trp), 7.29 (m, 3H, H_4 and H_7 indole, H_7 Trp), 7.57 (d, 1H, $J = 9$ Hz, NH Boc), 10.79 (s, 1H, NH indole), 10.81 (1H, s, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300K): δ 22.4 (CH_2−CH_2−indole), 25.7 (CH_2−CH_2−indole), 28.4 (CH_3 Boc), 28,9 (C βTrp), 42.6 (CH_2−*o*,*p*-dimethoxyphenyl), 46.8 (C αTrp), 55.6 (OCH_3), 55.8 (OCH_3), 78.8 (Cq Boc), 98.9 (C_3 *o*,*p*-dimethoxyphenyl), 105.1 (C_5 *o*,*p*-dimethoxyphenyl), 110.0 (C_3 Trp), 111.7 (C_7 Trp), 111.8 (C_7 indole), 112.9 (C_3 indole), 114.8 (C_1 *o*,*p*-dimethoxyphenyl), 118.4 (C_4 indole and C_4 Trp), 118.7 (C_5 indole and C_5 Trp), 121.3 (C_6 Trp), 121.4 (C_6 indole), 123.0 (C_2 indole), 125.1 (C_2 Trp), 127.1 (C_9 indole), 127.5 (C_9 Trp), 128.5 (C_6 *o*,*p*-dimethoxyphenyl), 136.4 (C_8 Trp), 136.6 (C_8 indole), 155.5 (Cq triazole and CO Boc), 156.1 (Cq triazole), 157.8 (C_2 *o*,*p*-dimethoxyphenyl), 161.0 (C_4 *o*,*p*-dimethoxyphenyl). MS (ES), *m/z*: 621.0 $[M + H]^+$. HPLC t_R: 2.20 min (conditions A).

(*R*)-*tert*-Butyl 1-(4-(2,4-Dimethoxybenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethylcarbamate. Yield, 2.2 g (65%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.23 (s, 9H, CH_3 Boc), 2.81 (m, 2H, CH_2−CH_2−phenyl), 2.94 (m, 2H, CH_2−CH_2−phenyl), 3.28 (m, 2H, CH_2 βTrp), 3.58 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 5.05 (m, 3H, CH_2−*o*,*p*-dimethoxyphenyl and CH

αTrp), 6.30 (d, 1H, J_o = 8 Hz, H_5 *o,p*-dimethoxyphenyl), 6.51 (s, 1H, H_3 *o,p*-dimethoxyphenyl), 6.62 (d, 1H, J_o = 8 Hz, H_6 *o,p*-dimethoxyphenyl), 6.89 (t, 1H, J_o = 7 Hz, H_5 Trp), 7.02 (t, 1H, J_o = 8 Hz, H_6 Trp), 7.06 (d, 2H, J_o = 8 Hz, H_2 and H_6 phenyl), 7.08 (s, 1H, H_2 Trp), 7.17 (d, 1H, J_o = 7 Hz, H_4 Trp), 7.21−7.31 (m, 4H, H_7 Trp, H_3, H_4, and H_5 phenyl), 7.65 (d, 1H, J = 8 Hz, NH Boc), 10.85 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 26.1 (*C*H_2−CH_2−phenyl), 28.4 (CH_3 Boc), 28.7 (C *β*Trp), 32.0 (CH_2−*C*H_2−phenyl), 43.1 (*C*H_2−*o,p*-dimethoxyphenyl), 46.8 (C αTrp), 55.7 (OCH_3), 55.8 (OCH_3), 79.0 (Cq Boc), 99.0 (C_3 *o,p*-dimethoxyphenyl), 105.2 (C_5 *o,p*-dimethoxyphenyl), 109.7 (C_3 Trp), 111.8 (C_7 Trp), 114.2 (C_1 *o,p*-dimethoxyphenyl), 118.4 (C_4 Trp), 118.8 (C_5 Trp), 121.3 (C_6 Trp), 124.4 (C_2 Trp), 126.8 (C_6 *o,p*-dimethoxyphenyl), 127.4 (C_9 Trp), 128.6−129.1 (C_2, C_3, C_4, C_5, and C_6 phenyl), 136.4 (C_8 Trp), 140.0 (C_1 phenyl), 155.1 (Cq triazole), 155.5 (Cq triazole), 156.2 (CO Boc), 158.0 (C_2 *o,p*-dimethoxyphenyl), 161.2 (C_4 *o,p*-dimethoxyphenyl). MS (ES), *m/z*: 583.0 $[M + H]^+$. HPLC t_R: 1.97 min (conditions A).

(*R*)-*tert*-Butyl 1-(4-(4-Methoxybenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethylcarbamate. Yield, 1.7 g (65%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.21 (s, 9H, CH_3 Boc), 2.79 (m, 2H, C*H*$_2$−CH_2−phenyl), 2.88 (m, 2H, CH_2−C*H*$_2$−phenyl), 3.33 (m, 2H, C*H*$_2$ *β*Trp), 3.67 (s, 3H, OCH_3), 5.03 (m, 1H, CH αTrp), 5.17 (s, 2H, C*H*$_2$−*p*-methoxyphenyl), 6.72 (d, 2H, J_o = 8 Hz, H_3 and H_5 *p*-methoxyphenyl), 6.81 (d, 2H, J_o = 8 Hz, H_2 and H_6 *p*-methoxyphenyl), 6.88 (t, 1H, J_o = 8 Hz, H_5 Trp), 7.02 (t, 1H, J_o = 8 Hz, H_6 Trp), 7.04 (m, 2H, H_2 and H_6 phenyl), 7.06 (s, 1H, H_2 Trp), 7.16 (d, 1H, J_o = 7 Hz, H_4 Trp), 7.19−7.32 (m, 4H, H_7 Trp, H_3, H_4, and H_5 phenyl), 7.73 (d, 1H, J = 8 Hz, NH Boc), 10.84 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 26.2 (*C*H_2−CH_2−phenyl), 28.4 (CH_3 Boc), 28.7 (C *β*Trp), 32.0 (CH_2−*C*H_2−phenyl), 46.3 (*C*H_2−*p*-methoxyphenyl), 46.8 (C αTrp), 55.5 (OCH_3), 79.0 (Cq Boc), 109.7 (C_3 Trp), 111.8 (C_7 Trp), 114.5 (C_3 and C_5 *p*-methoxyphenyl), 118.4 (C_4 Trp), 118.8 (C_5 Trp), 121.3 (C_6 Trp), 124.5 (C_2 Trp), 126.7 (C_4 phenyl, C_9 Trp), 127.4 (C_1 *p*-methoxyphenyl), 128.2 (C_2 and C_6 *p*-methoxyphenyl), 128.8 (C_2, C_3, C_5, and C_6 phenyl), 136.4 (C_8 Trp), 140.1 (C_1 phenyl), 154.9 (CO Boc), 155.6 (Cq triazole), 156.0 (Cq triazole), 159.3 (C_4 *p*-methoxyphenyl). MS (ES), *m/z*: 552.1 $[M + H]^+$. HPLC t_R: 1.95 min (conditions A).

(*R*)-*tert*-Butyl 1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(4-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethylcarbamate. Yield, 1.4 g (62%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.20 (s, 9H, CH_3 Boc), 2.93 (m, 4H, C*H*$_2$−C*H*$_2$−indole), 3.32 (m, 2H, C*H*$_2$ *β*Trp), 3.66 (s, 3H, OCH_3), 5.02 (m, 1H, CH αTrp), 5.18 (m, 2H, C*H*$_2$−*p*-methoxyphenyl), 6.71 (d, 2H, J_o = 8 Hz, H_3 and H_5 *p*-methoxyphenyl), 6.81 (d, 2H, J_o = 8 Hz, H_2 and H_6 *p*-methoxyphenyl), 6.90 (t, 3H, J_o = 7 Hz, H_5 and H_6 Trp, H_5 indole), 7.00−7.07 (m, 4H, H_2 and H_6 indole, H_2 and H_4 Trp), 7.26−7.32 (m, 3H, H_4 and H_7 indole, H_7 Trp), 7.72 (d, 1H, J = 8 Hz, NH Boc), 10.80 (s, 1H, NH indole), 10.83 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 22.1 (CH_2−*C*H_2−indole), 25.7 (*C*H_2−CH_2−indole), 27.5 (CH_3 Boc), 27.7 (C *β*Trp), 46.5 (*C*H_2−*p*-methoxyphenyl), 46.9 (C αTrp), 55.5 (OCH_3), 79.0 (Cq Boc), 109.7 (C_3 Trp), 111.8 (C_7 Trp and C_7 indole), 112.6 (C_3 indole), 114.3 (C_3 and C_5 *p*-methoxyphenyl), 118.1 (C_4 Trp and C_4 indole), 119.1 (C_5 Trp and C_5 indole), 121.5 (C_6 Trp and C_6 indole), 123.1 (C_2 indole), 124.5 (C_2 Trp), 126.6 (C_9 indole), 127.0 (C_9 Trp), 127.4 (C_1 *p*-methoxyphenyl), 128.1 (C_2 and C_6 *p*-methoxyphenyl), 136.4 (C_8 Trp), 136.6 (C_8 indole), 155.4 (CO Boc), 155.5 (Cq triazole), 156.0 (Cq triazole), 162.2 (C_4 *p*-methoxyphenyl). MS (ES), *m/z*: 561.1 $[M + H]^+$. HPLC t_R: 1.98 min (conditions A).

(*R*)-*tert*-Butyl 1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethylcarbamate. Yield, 0.8 g (49%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.24 (s, 9H, CH_3 Boc), 2.73 (m, 2H, CH_2−C*H*$_2$−indole), 2.85 (m, 2H, C*H*$_2$−CH_2−indole), 3.04 (m, 2H, CH_2 *β*Trp), 4.51 (m, 1H, CH αTrp), 6.75 (m, 2H, H_5 indole and H_5 Trp), 6.83 (t, 2H, J_o = 7 Hz, H_6 indole and H_6 Trp), 6.92−7.04 (m, 7H, H_2 indole, H_2 Trp and CHar phenyl), 7.26 (d, 2H, J_o = 8 Hz, H_7 indole and H_7 Trp), 7.46 (m, 3H, NH Boc, H_4 indole and H_4 Trp), 10.70 (s, 2H, NH indole and NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 23.3 (CH_2−*C*H_2−indole), 26.2 (*C*H_2−CH_2−indole), 28.6 (CH_3 Boc), 30.1 (C *β*Trp), 47.7 (C αTrp), 78.4 (Cq Boc), 110.1 (C_3 Trp), 111.7 (C_7 Trp), 111.8 (C_7 indole), 113.2 (C_3 indole), 118.2 (C_4 indole and C_4 Trp), 118.6 (C_5 indole and C_5 Trp), 121.2 (C_6 indole), 121.3 (C_6 Trp), 122.8 (C_2 indole and C_2 Trp), 127.1 (C_9 indole), 127.4 (C_9 Trp), 127.7 (C_4 phenyl), 130.0 (C_2, C_3, C_5, and C_6 phenyl), 133.5 (C_1 phenyl), 136.4 (C_8 trp), 136.6 (C_8 indole), 154.3 (CO Boc), 155.3 (Cq triazole), 156.1 (Cq triazole). MS (ES), *m/z*: 547.3 $[M + H]^+$. HPLC t_R: 1.67 min (conditions A).

(*R*)-*tert*-Butyl 1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(4-ethylbenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethylcarbamate. Yield, 0.8 g (58%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.08 (t, 3H, J = 8 Hz, C*H*$_3$−CH_2−*p*-ethylphenyl), 1.16 (s, 9H, CH_3 Boc), 2.51 (q, 2H, J = 7 Hz, CH_3−C*H*$_2$−*p*-ethylphenyl), 2.92 (m, 4H, C*H*$_2$−C*H*$_2$−indole), 3.31 (m, 2H, C*H*$_2$ *β*Trp), 5.01 (m, 1H, CH αTrp), 5.22 (m, 2H, C*H*$_2$ *p*-ethylbenzyl), 6.79 (d, 2H, J_o = 8 Hz, H_3 and H_5 *p*-ethylbenzyl), 6.88 (t, 2H, J_o = 7 Hz, H_5 indole and H_5 Trp), 6.89 (d, 2H, J_o = 8 Hz, H_2 and H_6 *p*-ethylbenzyl), 6.99−7.11 (m, 5H, H_2 and H_6 indole, H_2, H_4, and H_6 Trp), 7.23 (d, 1H, J_o = 8 Hz, H_4 indole), 7.29 (d, 2H, J_o = 8 Hz, H_7 indole and H_7 Trp), 7.69 (d, 1H, J = 8 Hz, NH Boc), 10.79 (s, 1H, NH indole), 10.82 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 15.9 (*C*H_3−CH_2−*p*-ethylphenyl), 22.2 (CH_2−*C*H_2−indole), 25.7 (*C*H_2−CH_2−indole), 28.1 (CH_3−*C*H_2−*p*-ethylphenyl), 28.3 (CH_3 Boc), 28.6 (C *β*Trp), 46.7 (*C*H_2 *p*-ethylbenzyl), 46.8 (C αTrp), 79.0 (Cq Boc), 109.7 (C_3 Trp), 111.7 (C_7 Trp), 111.8 (C_7 indole), 112.6 (C_3 indole), 118.4 (C_4 Trp and C_4 indole), 118.7 (C_5 Trp and C_5 indole), 121.3 (C_6 indole), 121.4 (C_6 Trp), 123.1 (C_2 indole), 124.4 (C_2 Trp), 126.5 (C_3 and C_5 *p*-ethylbenzyl), 127.0 (C_9 Trp), 127.4 (C_9 indole), 128.5 (C_2 and C_6 *p*-ethylbenzyl), 132.1 (C_1 *p*-ethylbenzyl), 136.4 (C_8 Trp), 136.6 (C_8 indole), 143.9 (C_4 *p*-ethylbenzyl), 155.5 (2 Cq triazole), 156.1 (CO Boc). MS (ES), *m/z*: 589.3 $[M + H]^+$. HPLC t_R: 2.00 min (conditions A).

(*R*)-*tert*-Butyl 1-(4-(4-Ethylbenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethylcarbamate. Yield, 0.8 g (63%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.08 (t, 3H, J = 8 Hz, C*H*$_3$−CH_2−*p*-ethylphenyl), 1.17 (s, 9H, CH_3 Boc), 2.51 (q, 2H, J = 7 Hz, CH_3−C*H*$_2$−*p*-ethylphenyl), 2.86 (m, 4H, C*H*$_2$−C*H*$_2$−phenyl), 3.31 (m, 2H, C*H*$_2$ *β*Trp), 5.00 (m, 1H, CH αTrp), 5.20 (m, 2H, C*H*$_2$ *p*-ethylbenzyl), 6.78 (d, 2H, J_o = 8 Hz, H_3 and H_5 *p*-ethylbenzyl), 6.87 (t, 1H, J_o = 7 Hz, H_5 Trp), 7.02 (t, 1H, J_o = 8 Hz, H_6 Trp), 7.04 (m, 5H, H_2 Trp, H_2 and H_6 *p*-ethylbenzyl, H_2 and H_6 phenyl), 7.15 (d, 1H, J_o = 8 Hz, H_4 Trp), 7.18−7.31 (m, 4H, H_7 Trp, H_3, H_4, and H_6 phenyl), 7.69 (d, 1H, J = 8 Hz, NH Boc), 10.82 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 15.9 (*C*H_3−CH_2−*p*-ethylphenyl), 26.3 (CH_2−CH_2−phenyl), 28.1 (CH_3−*C*H_2−*p*-ethylphenyl), 28.3 (CH_3 Boc), 28.6 (C *β*Trp), 32.1 (CH_2−*C*H_2−phenyl), 46.5 (*C*H_2 *p*-ethylbenzyl), 46.8 (C αTrp), 78.9 (Cq Boc), 109.8 (C_3 Trp), 111.7 (C_7 Trp), 118.4 (C_4 Trp), 118.8 (C_5 Trp), 121.3 (C_6 Trp), 124.4 (C_2 Trp), 126.6 (C_3 and C_5 *p*-ethylbenzyl), 126.7 (C_4 phenyl), 127.4 (C_9 Trp), 128.5−128.8 (C_2 and C_6 *p*-ethylbenzyl, C_2, C_3, C_5, and C_6 phenyl), 132.3 (C_1 *p*-ethylbenzyl), 136.4 (C_8 Trp), 140.2 (C_1 phenyl), 143.9 (C_4 *p*-ethylbenzyl), 155.0 (CO Boc), 155,5 (Cq triazole), 156.0 (Cq triazole). MS (ES), *m/z*: 549.9 $[M + H]^+$. HPLC t_R: 2.03 min (conditions A).

(*R*)-*tert*-Butyl 1-(5-(3-(1*H*-Indol-3-yl)propyl)-4-benzyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethylcarbamate. Yield, 0.9 g (48%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.18 (s, 9H, CH_3 Boc), 1.85 (m, 2H, CH_2−C*H*$_2$−CH_2−indole), 2.53 (t, 2H, J = 7 Hz, C*H*$_2$−CH_2−CH_2−indole), 2.63 (t, 2H, J = 7 Hz, CH_2−CH_2−C*H*$_2$−indole), 3.32 (m, 2H, CH_2 *β*Trp), 4.89 (m, 1H, CH αTrp), 5.05 (s, 2H, CH_2 benzyl), 6.74 (d, 2H, J_o = 7 Hz, H_2 and H_6 benzyl), 6.86 (t, 1H, J_o = 7 Hz, H_5 Trp), 6.88−7.02 (m, 5H, H_2 and H_6 Trp, H_2, H_5, and H_6 indole), 7.14 (m, 3H, H_3, H_4, and H_5 benzyl), 7.28 (m, 3H, H_4 indole, H_4 and H_7 Trp), 7.39 (d, 1H, J_o = 8 Hz, H_7 indole), 7.50 (d, 1H, J = 7 Hz, NH Boc), 10.68 (s, 1H, NH indole), 10.73 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 24.3 (CH_2−CH_2−CH_2−indole), 24.5 (CH_2−

CH_2-CH_2-indole), 27.7 ($CH_2-CH_2-CH_2-$indole), 28.4 (CH_3 Boc), 29.3 (C βTrp), 45.7 (CH_2 benzyl), 46.8 (C αTrp), 78.5 (Cq Boc), 110.7 (C_3 Trp), 111.6 (C_7 indole and C_7 Trp), 114.2 (C_3 indole), 118.5 (C_4 indole and C_4 Trp), 118.7 (C_5 indole and C_5 Trp), 121.2 (C_6 indole and C_6 Trp), 122.7 (C_2 indole), 124.3 (C_2 Trp), 126.4 (C_4 benzyl), 127.5 (C_9 Trp), 127.6 (C_9 indole), 127.8 (C_2 and C_6 benzyl), 128.9 (C_3 and C_5 benzyl), 136.4 (C_8 indole and C_8 Trp), 136.7 (C_1 benzyl), 154.8 (CO Boc), 155.5 (Cq triazole), 155.6 (Cq triazole). MS (ES), *m/z*: 575.4 $[M + H]^+$. HPLC t_R: 1.82 min (conditions A).

General Procedure for Preparation of Compound E. The Boc protecting group of compound **C** was removed at room temperature for 1 h with a solution of AcOEt/HCl, 4 M. The mixture was then concentrated in vacuo, diluted with MeOH, and concentrated several times in vacuo. The residue was then coupled with the corresponding acid (1.1 equiv), in the presence of BOP (1.1 equiv) and NMM (2.2 equiv) for 2 h, in DCM. The mixture was then concentrated in vacuo and the residue dissolved in AcOEt. The organic layer was successively washed with aqueous solutions of 1 M $KHSO_4$, saturated $NaHCO_3$, and brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated in vacuo to yield the desired compound, which was then treated with 4 M AcOEt/HCl as already described. The final compound was purified by preparative HPLC on a C18 column using a water/acetonitrile/TFA, 0.1% gradient (yield around 50% for the three steps).

(*R*)-*N*-(1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-benzyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (1). ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): δ 1.29 (s, 3H, CH_3 Aib), 1.30 (s, 3H, CH_3 Aib), 2.88 (m, 2H, CH_2-CH_2-indole), 2.97 (m, 2H, CH_2-CH_2-indole), 3.37 (m, 2H, CH_2 βTrp), 5.11 (s, 2H, CH_2 benzyl), 5.21 (m, 1H, CH αTrp), 6.86 (t, 1H, $J = 7.4$, H_5 Trp), 6.88 (d, 2H, H_2 and H_6 benzyl), 6.92 (t, 1H, $J = 7.6$, H_5 indole), 7.03 (t, 1H, $J = 7.6$, H_6 Trp), 7.05 (2H, H_6 indole, H_2 indole), 7.09 (d, 1H, $J = 1.8$, H_2 Trp), 7.17 (d, 1H, $J = 7.9$, H_4 Trp), 7.26 (m, 2H, H_3 and H_5 benzyl), 7.27 (t, 1H, H_4 benzyl), 7.30 (d, 1H, H_4 indole), 7.32 (m, 2H, H_7 Trp and H_7 indole), 8.03 (brs, 3H, NH_2 Aib TFA salt), 8.95 (d, 1H, $J = 8.1$, NH amide), 10.77 (s, 1H, NH indole), 10.81 (s, 1H, NH indole Trp). ^{13}C NMR (100 MHz, DMSO-d_6, 300 K): δ 22.4 (CH_2-CH_2 indole), 23.1 (CH_3 Aib), 23.3 (CH_3 Aib), 25.4 (CH_2-CH_2 indole), 28.7 (C βTrp), 45.3 (C αTrp, CH_2 benzyl), 56.3 (Cq Aib), 109.5 (C_3 Trp), 111.3 (C_7 Trp, C_7 indole), 113.0 (C_3 indole), 117.8 (C_4 Trp), 118.0 (C_4 indole), 118.2 (C_5 indole), 118.3 (C_5 Trp), 120.9 (C_6 Trp, C_6 indole), 122.4 (C_2 indole), 124.3 (C_2 Trp), 125.9 (C_2, C_6 benzyl), 126.7 (C_9 Indole), 126.9 (C_9 Trp), 127.6 (C_4 benzyl), 128.8 (C_3, C_5 benzyl), 135.7 (C_1 benzyl), 136.0 (C_8 Trp), 136.1 (C_8 indole), 154.3 (Cq triazole), 154.5 (Cq triazole), 171.4 (CO amide).

(*R*)-*N*-(1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(4-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (2). ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): δ 1.30 (s, 3H, CH_3 Aib), 1.33 (s, 3H, CH_3 Aib), 2.91 (m, 2H, CH_2-CH_2-indole), 2.97 (m, 2H, CH_2-CH_2-indole), 3.37 (d, 2H, CH_2 βTrp), 3.71(s, 3H, OCH_3), 5.02 (s, 2H, CH_2 *p*-methoxybenzyl), 5.23 (m, 1H, CH αTrp), 6.78 (s, 4H, CHar *p*-methoxybenzyl), 6.87 (t, 1H, $J = 7.5$, H_5 Trp), 6.93 (t, 1H, $J = 7.5$, H_5 indole), 7.03 (t, 1H, H_6 Trp), 7.05 (t, 1H, H_6 indole), 7.07 (s, 1H, H_2 indole), 7.09 (s, 1H, H_2 Trp), 7.21 (d, 1H, $J = 8$, H_4 Trp), 7.32 (3H, H_4 and H_7 indole, H_7 Trp), 8.02 (brs, 3H, NH_2 Aib TFA salt), 8.97 (d, 1H, $J = 8.1$, NH amide), 10.77 (s, 1H, NH indole), 10.80 (s, 1H, NH indole Trp). ^{13}C NMR (100 MHz, DMSO-d_6, 300 K): δ 22.4 (CH_2-CH_2 indole), 23.1 (CH_3 Aib), 23.4 (CH_3 Aib), 25.5 (CH_2-CH_2 indole), 28.9 (C βTrp), 44.9 (CH_2 *p*-methoxybenzyl), 45.3 (C αTrp), 55.0 (OCH_3), 56.3 (Cq Aib), 109.5 (C_3 Trp), 111.3 (C_7 Trp, C_7 indole), 113.0 (C_3 indole), 114.1 (C_3, C_5 *p*-methoxybenzyl), 117.9 (C_4 Trp), 118.0 (C_4 indole), 118.2 (C_5 indole), 118.3 (C_5 Trp), 120.9 (C_6 indole, C_6 Trp), 122.0 (C_2 indole), 124.4 (C_2 Trp), 126.7 (C_9 indole), 126.9 (C_9 Trp), 127.3 (C_2, C_6 *p*-methoxybenzyl), 127.4 (C_1 *p*-methoxybenzyl), 135.9 (C_8 Trp), 136.1 (C_8 indole), 154.2 (Cq triazole), 154.5 (Cq triazole), 158.4 (C_4 *p*-methoxybenzyl), 171.4 (CO amide).

***N*-((*R*)-1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(4-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-aminoacetamide (3).** ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 2.86 (m, 4H, CH_2-CH_2-indole), 3.25 (dd, 1H, $J = 14$ Hz and 7 Hz, CH_2 βTrp), 3.38 (m, 3H, CH_2 βTrp and CH_2 αGly), 3.64 (s, 3H, OCH_3), 4.93 (m, 2H, CH_2 *p*-methoxybenzyl), 5.19 (m, 1H, CH αTrp), 6.63 (s, 4H, CHar *p*-methoxybenzyl), 6.89 (t, 1H, $J_o = 7$ Hz, H_5 indole), 6.86 (t, 1H, $J_o = 7$ Hz, H_5 Trp), 6.99−7.04 (m, 5H, H_2, H_4, and H_6 Trp, H_2 and H_6 indole), 7.22 (d, 1H, $J_o = 8$ Hz, H_4 indole), 7.30 (m, 2H, H_7 indole and H_7 Trp), 7.92 (brs, 3H, NH_2 Gly TFA salt), 9.18 (d, 1H, $J = 8$ Hz, NH amide), 10.74 (s, 1H, NH indole), 10.80 (d, 1H, $J = 2$ Hz, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 22.8 (CH_2-CH_2-indole), 25.8 (CH_2-CH_2-indole), 29.8 (C βTrp), 39.1 (CαGly), 45.4 (CH_2 *p*-methoxybenzyl and C αTrp), 55.4 (OCH_3), 109.7 (C_3 Trp), 111.8 (C_7 indole and C_7 Trp), 113.4 (C_3 indole), 114.5 (C_3 and C_5 *p*-methoxybenzyl), 118.3 (C_4 indole), 118.5 (C_4 Trp), 118.6 (C_5 indole), 118.8 (C_5 Trp), 121.3 (C_6 indole and C_6 Trp), 123.0 (C_2 indole), 124.6 (C_2 Trp), 127.2 (C_9 indole), 127.4 (C_9 Trp), 127.7 (C_2 and C_6 *p*-methoxybenzyl), 136.4 (C_8 Trp), 136.6 (C_8 indole), 154.7 (2Cq triazole), 159.0 (CO amide), 166.1 (C_4 *p*-methoxybenzyl).

(*R*)-*N*-(1-(4-(4-Methoxybenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-aminoacetamide Trifluoroacetate Salt (4). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 2.78 (m, 4H, CH_2-CH_2-phenyl), 3.26 (1H, dd, $J = 14$ Hz and 7 Hz, CH_2 βTrp), 3.39 (m, 3H, CH_2 βTrp and CH_2 αGly), 3.65 (s, 3H, OCH_3), 4.95 (m, 2H, CH_2-p-methoxybenzyl), 5.20 (m, 1H, CH αTrp), 6.63 (s, 4H, CHar *p*-methoxybenzyl), 6.86 (t, 1H, $J_o = 7$ Hz, H_5 Trp), 6.99 (s, 1H, H_2 Trp), 7.02 (t, 1H, $J_o = 7$ Hz, H_6 Trp), 7.10 (m, 2H, H_2, and H_6 phenyl), 7.15 (d, 1H, $J_o = 7$ Hz, H_4 Trp), 7.23 (m, 3H, H_3, H_4, and H_5 phenyl), 7.31 (d, 1H, $J_o = 8$ Hz, H_7 Trp), 7.95 (brs, 3H, NH_2 Gly, TFA salt), 9.20 (d, 1H, $J = 8$ Hz, NH amide), 10.82 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 26.5 (CH_2-CH_2-phenyl), 29.8 (C βTrp), 32.7 (CH_2-CH_2-phenyl), 39.0 (C αGly), 45.3 (CH_2 *p*-methoxybenzyl), 45.4 (C αTrp), 55.4 (OCH_3), 109.7 (C_3 Trp), 111.8 (C_7 Trp), 114.5 (C_3 and C_5 *p*-methoxybenzyl), 118.3 (C_4 Trp), 118.9 (C_5 Trp), 121.4 (C_6 Trp), 124.6 (C_2 Trp), 126.5 (C_4 phenyl), 127.3 (C_9 Trp), 127.7 (C_1 *p*-methoxybenzyl), 127.8 (C_2 and C_6 *p*-methoxybenzyl), 128.7 (C_2, C_3, C_5, and C_6 phenyl), 136.4 (C_8 Trp), 140.9 (C_1 phenyl), 154.3 (Cq triazole), 154.8 (Cq triazole), 159.0 (C_4 *p*-methoxybenzyl), 166.1 (CO amide).

(*R*)-*N*-(1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(2,4-dimethoxybenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-aminoacetamide Trifluoroacetate Salt (5). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 2.89 (m, 4H, CH_2-CH_2-indole), 3.25−3.43 (m, 4H, CH_2 βTrp and CH_2 αGly), 3.60 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 4.80 (d, 1H, $J = 17$ Hz, CH_2-o,p-dimethoxybenzyl), 4.97 (d, 1H, $J = 17$ Hz, CH_2-o,p-dimethoxybenzyl), 5.16 (m, 1H, CH αTrp), 6.15 (dd, 1H, $J_o = 8$ Hz and $J_m = 2$ Hz, H_5 *o,p*-dimethoxybenzyl), 6.25 (d, 1H, $J_o = 8$ Hz, H_6 *o,p*-dimethoxybenzyl), 6.49 (d, 1H, $J = 2$ Hz, H_3 *o,p*-dimethoxybenzyl), 6.89 (m, 2H, H_5 Trp and H_5 indole), 6.98−7.05 (m, 4H, H_2 and H_6 Trp, H_2 and H_6 indole), 7.17 (d, 1H, $J_o = 8$ Hz, H_4 Trp), 7.29 (m, 3H, H_4 and H_7 indole, H_7 Trp), 7.93 (brs, 3H, NH_2 Gly TFA salt), 9.16 (d, 1H, $J = 8$ Hz, NH amide), 10.76 (s, 1H, NH indole), 10.80 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 22.8 (CH_2-CH_2-indole), 25.8 (CH_2-CH_2-indole), 29.8 (C βTrp), 39.1 (CαGly), 41.7 (CH_2 *o,p*-dimethoxybenzyl), 45.5 (C αTrp), 55.6 (OCH_3), 55.9 (OCH_3), 98.9 (C_3 *o,p*-dimethoxybenzyl), 105.0 (C_5 *o,p*-dimethoxybenzyl), 109.8 (C_3 Trp), 111.8 (C_7 indole and C_7 Trp), 113.4 (C_3 indole), 115.5 (C_1 *o,p*-dimethoxybenzyl), 118.2 (C_4 indole), 118.4 (C_4 Trp), 118.6 (C_5 indole), 118.8 (C_5 Trp), 121.3 (C_6 indole and C_6 Trp), 123.0 (C_2 indole), 125.1 (C_2 Trp), 127.2 (C_9 indole and C_9 Trp), 127.9 (C_6 *o,p*-dimethoxybenzyl), 136.4 (C_8 indole and C_8 Trp), 154.9 (Cq triazole), 155.1 (Cq triazole), 157.6 (C_2 *o,p*-dimethoxybenzyl), 160.8 (C_4 *o,p*-dimethoxybenzyl), 166.0 (CO amide).

(*R*)-*N*-(1-(4-(2,4-Dimethoxybenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-aminoacetamide Trifluoroacetate Salt (6). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 2.81

(m, 4H, CH_2−CH_2−phenyl), 3.27 (t, 2H, J = 8 Hz, CH_2 αGly), 3.43 (m, 2H, CH_2 βTrp), 3.60 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 4.79 (d, 1H, J = 17 Hz, CH_2−*o*,*p*-dimethoxybenzyl), 4.96 (d, 1H, J = 17 Hz, CH_2−*o*,*p*-dimethoxybenzyl), 5.18 (m, 1H, CH αTrp), 6.18 (dd, 1H, J_o = 8 Hz and J_m = 2 Hz, H_5 *o*,*p*-dimethoxybenzyl), 6.29 (d, 1H, J_o = 8 Hz, H_6 *o*,*p*-dimethoxybenzyl), 6.49 (d, 1H, J_m = 2 Hz, H_3 *o*,*p*-dimethoxybenzyl), 6.85 (t, 1H, J_o = 8 Hz, H_5 Trp), 6.99 (m, 2H, H_2 and H_6 Trp), 7.11 (m, 2H, H_2 and H_6 phenyl), 7.18 (d, 1H, J_o = 8 Hz, H_4 Trp), 7.21 (m, 3H, H_3, H_4, and H_5 phenyl), 7.29 (d, 1H, J_o = 8 Hz, H_7 Trp), 7.93 (brs, 3H, NH_2 Gly TFA salt), 9.14 (d, 1H, J = 8 Hz, NH amide), 10.81 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 26.4 (*C*H_2−CH_2−phenyl), 29.8 (C βTrp), 32.7 (CH_2−*C*H_2−phenyl), 39.4 (CαGly), 41.7 (CH_2 *o*,*p*-dimethoxybenzyl), 45.5 (CH αTrp), 55.6 (OCH_3), 55.9 (OCH_3), 99.0 (C_3 *o*,*p*-dimethoxybenzyl), 105.1 (C_5 *o*,*p*-dimethoxybenzyl), 109.7 (C_3 Trp), 111.8 (C_7 Trp), 115.4 (C_1 *o*,*p*-dimethoxybenzyl), 118.2 (C_4 Trp), 118.8 (C_5 Trp), 121.4 (C_6 Trp), 124.6 (C_2 Trp), 127.9 (C_6 *o*,*p*-dimethoxybenzyl), 127.3 (C_9 Trp), 128.2 (C_4 phenyl), 128.7 (C_2, C_3, C_5, and C_6 phenyl), 136.4 (C_8 Trp), 140.8 (C_1 phenyl), 154.4 (Cq triazole), 155.1 (Cq triazole), 157.7 (C_2 *o*,*p*-dimethoxybenzyl), 160.8 (C_4 *o*,*p*-dimethoxybenzyl), 166.0 (CO amide).

(*S*)-*N*-((*R*)-1-(4-(4-Methoxybenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-aminopropanamide Trifluoroacetate Salt (12). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.09 (d, 3H, J = 7 Hz, CH_3 Ala), 2.84 (m, 4H, CH_2−CH_2−phenyl), 3.29 (m, 2H, CH_2 βTrp), 3.68 (s, 4H, OCH_3 and CH αAla), 5.06 (s, 2H, CH_2− *p*-methoxybenzyl), 5.19 (m, 1H, CH αTrp), 6.73 (s, 4H, CHar *p*-methoxybenzyl), 6.81 (t, 1H, J_o = 7 Hz, H_5 Trp), 6.99 (m, 2H, H_2 and H_6 Trp), 7.12−7.26 (m, 6H, H_4 Trp and CHar phenyl), 7.29 (d, 1H, J_o = 8 Hz, H_7 Trp), 7.97 (brs, 3H, NH_2 Ala TFA salt), 9.14 (d, 1H, J = 8 Hz, NH amide), 10.81 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 17.3 (CH_3 Ala), 26.4 (*C*H_2−CH_2−phenyl), 29.5 (C βTrp), 32.7 (CH_2−*C*H_2−phenyl), 45.0 (C αTrp), 45.5 (CH_2 *p*-methoxybenzyl), 48.9 (C αAla), 55.5 (OCH_3), 109.6 (C_3 Trp), 111.7 (C_7 Trp), 114.6 (C_3 and C_5 *p*-methoxybenzyl), 118.3 (C_4 Trp), 118.7 (C_5 Trp), 121.3 (C_6 Trp), 124.8 (C_2 Trp), 126.6 (C_4 phenyl), 127.3 (C_9 Trp), 127.8 (C_1 *p*-methoxybenzyl), 128.0 (C_2 and C_6 *p*-methoxybenzyl), 128.7 (C_2, C_3, C_5, and C_6 phenyl), 136.5 (C_8 Trp), 140.8 (C_1 phenyl), 154.3 (Cq triazole), 155.0 (Cq triazole), 159.2 (C_4 *p*-methoxybenzyl), 169.6 (CO amide).

(2*S*)-*N*-((*R*)-1-(4-(4-Ethylbenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-aminopropanamide Trifluoroacetate Salt (13). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.06 (d, 3H, J = 7 Hz, CH_3 Ala), 1.11 (t, 3H, J = 8 Hz, *C*H_3−CH_2− *p*-ethylphenyl), 2.53 (q, 2H, J = 8 Hz, CH_3−*C*H_2− *p*-ethylphenyl), 2.83 (m, 4H, CH_2−CH_2−phenyl), 3.26 (m, 2H, CH_2 βTrp), 4.65 (m, 1H, CH αAla), 5.10 (s, 2H, CH_2− *p*-ethylphenyl), 5.13 (m, 1H, CH αTrp), 6.74 (d, 2H, J_o = 8 Hz, H_3 and H_5 *p*-ethylphenyl), 6.80 (t, 1H, J_o = 7 Hz, H_5 Trp), 6.99 (t, 1H, J_o = 7 Hz, H_6 Trp), 7.0−7.17 (m, 6H, H_2 and H_4 Trp, H_2 and H_6 *p*-ethylphenyl, H_2 and H_6 phenyl), 7.20−7.29 (m, 4H, H_7 Trp, H_3, H_4, and H_5 phenyl), 7.90 (brs, 3H, NH_2 TFA salt), 9.09 (d, 1H, J = 8 Hz, NH amide), 10.76 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 15.9 (*C*H_3−CH_2−*p*-ethylphenyl), 17.3 (CH_3 Ala), 26.5 (*C*H_2−CH_2−phenyl), 28.1 (CH_3−*C*H_2−*p*-ethylphenyl), 29.6 (C βTrp), 32.8 (CH_2−*C*H_2−phenyl), 45.0 (C αTrp), 45.6 (CH_2−*p*-ethylphenyl), 48.5 (C αAla), 109.7 (C_3 Trp), 111.7 (C_7 Trp), 118.3 (C_4 Trp), 118.7 (C_5 Trp), 121.3 (C_6 Trp), 122.9 (C_2 Trp), 126.5 (C_3 and C_5 *p*-ethylphenyl, C_4 phenyl), 127.3 (C_9 Trp), 128.6 (C_2 and C_6 *p*-ethylphenyl, C_2, C_3, C_5 and C_6 phenyl), 133.5 (C_1 *p*-ethylphenyl), 136.5 (C_8 Trp), 141.0 (C_1 phenyl), 143.7 (C_4 *p*-ethylphenyl), 154.3 (Cq triazole), 155.0 (Cq triazole), 169.5 (CO amide).

(*R*)-*N*-(1-(4-(4-Methoxybenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-3-aminopropanamide Trifluoroacetate Salt (14). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 2.33 (m, 2H, CH_2−CH_2−NH_2), 2.78 (m, 6H, CH_2−CH_2−phenyl and CH_2−CH_2−NH_2), 3.26 (dd, 1H, J = 14 and 7 Hz, CH_2 βTrp), 3.40 (dd, 1H, J = 14 and 8 Hz, CH_2 βTrp), 3.64 (s, 3H, OCH_3), 4.91 (d, 1H, J = 17 Hz, CH_2 *p*-methoxybenzyl), 5.01 (d, 1H, J = 17 Hz, CH_2 *p*-methoxybenzyl), 5.21 (m, 1H, CH αTrp), 6.63 (s, 4H, CHar *p*-methoxybenzyl), 6.86 (t, 1H, J_o = 8 Hz, H_5 Trp), 6.97 (d, 1H, J = 2 Hz, H_2 Trp), 7.01 (t, 1H, J_o = 8 Hz, H_6 Trp), 7.08 (m, 2H, H_2 and H_6 phenyl), 7.15 (d, 1H, J_o = 7 Hz, H_4 Trp), 7.18−7.31 (m, 4H, H_7 Trp, H_3, H_4, and H_5 phenyl), 7.63 (brs, 3H, NH_2 TFA salt), 8.92 (d, 1H, J = 8 Hz, NH amide), 10.79 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 26.5 (CH_2−CH_2−phenyl), 29.4 (C βTrp), 32.2 (*C*H_2−CH_2−NH_2), 32.6 (CH_2−*C*H_2−phenyl), 35.4 (CH_2−*C*H_2−NH_2), 45.0 (C αTrp), 45.3 (CH_2 *p*-methoxybenzyl), 55.5 (OCH_3), 110.1 (C_3 Trp), 111.8 (C_7 Trp), 114.4 (C_3 and C_5 *p*-methoxybenzyl), 118.4 (C_4 Trp), 118.8 (C_5 Trp), 121.3 (C_6 Trp), 124.5 (C_2 Trp), 126.5 (C_4 phenyl), 127.4 (C_9 Trp, C_2 and C_6 *p*-methoxybenzyl), 127.7 (C_1 *p*-methoxybenzyl), 128.7 (*C*2_3, C_3, C_5, and C_6 phenyl), 136.4 (C_8 Trp), 140.8 (C_1 phenyl), 154.3 (Cq triazole), 155.1 (Cq triazole), 159.0 (C_4 *p*-methoxybenzyl), 169.5 (CO amide).

(*S*)-*N*-((*R*)-1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(4-methoxybenzyl)-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)pyrrolidine-2-carboxamide Trifluoroacetate Salt (16). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.42 (m, 1H, H_3 Pro), 1.52 (m, 1H, H_4 Pro), 1.72 (m, 1H, H_4 Pro), 2.07 (m, 1H, H_3 Pro), 2.94 (m, 4H, CH_2−CH_2−indole), 3.05 (t, 2H, J = 6 Hz, H_5 Pro), 3.30 (m, 2H, CH_2 βTrp), 3.67 (s, 3H, OCH_3), 3.96 (m, 1H, CH αPro), 5.02 (s, 2H, CH_2 *p*-methoxybenzyl), 5.19 (m, 1H, CH αTrp), 6.73 (s, 4H, CHar *p*-methoxybenzyl), 6.84 (t, 1H, J_o = 8 Hz, H_5 indole), 6.90 (t, 1H, J_o = 8 Hz, H_5 Trp), 6.93−7.06 (m, 4H, H_2 and H_6 indole, H_2 and H_6 Trp), 7.17 (d, 1H, J_o = 8 Hz, H_4 Trp), 7.29 (d, 3H, J_o = 8 Hz, H_4 and H_7 indole, H_7 Trp), 8.39 and 9.10 (2 m, 2H, NH Pro TFA salt), 9.25 (d, 1H, J = 8 Hz, NH amide), 10.76 (s, 1H, NH indole), 10.80 (d, 1H, J = 2 Hz, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 22.8 (CH_2−*C*H_2−indole), 23.5 (C_4 Pro), 25.8 (*C*H_2−CH_2−indole), 29.4 (C βTrp), 29.8 (C_3 Pro), 45.2 (C αTrp), 45.5 (CH_2 *p*-methoxybenzyl), 46.0 (C_5 Pro), 55.5 (OCH_3), 59.3 (C αPro), 109.6 (C_3 Trp), 111.8 (C_7 indole and C_7 Trp), 113.4 (C_3 indole), 114.6 (C_3 and C_5 *p*-methoxybenzyl), 118.4 (C_4 indole), 118.5 (C_4 Trp), 118.7 (C_5 indole and C_5 Trp), 121.4 (C_6 indole and C_6 Trp), 123.0 (C_2 Trp), 124.7 (C_2 indole), 127.2 (C_9 indole), 127.3 (C_9 Trp), 127.7 (C_1 *p*-methoxybenzyl), 127.8 (C_2 and C_6 *p*-methoxybenzyl), 126.5 (C_8 Trp), 136.6 (C_8 indole), 154.8 (Cq triazole), 154.9 (Cq triazole), 159.2 (C_4 *p*-methoxybenzyl), 168.2 (CO amide). MS (ES), *m/z*: 588.2 $[M + H]^+$. HPLC t_R: 1.60 min (conditions A).

(*R*)-*N*-((*R*)-1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(4-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)pyrrolidine-2-carboxamide Trifluoroacetate Salt (17). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.23 (m, 1H, H_3 Pro), 1.52 (m, 1H, H_4 Pro), 1.74 (m, 1H, H_4 Pro), 2.08 (m, 1H, H_3 Pro), 2.81 (m, 2H, H_5 Pro), 2.90−3,14 (m, 4H, CH_2−CH_2−indole), 3.31 (dd, 1H, J = 14 Hz and 7 Hz, CH_2 βTrp), 3.41 (dd, 1H, J = 14 Hz and 8 Hz, CH_2 βTrp), 3.63 (s, 3H, OCH_3), 4.05 (m, 1H, CH αPro), 4.86 (s, 2H, CH_2 *p*-methoxybenzyl), 5.21 (m, 1H, CH αTrp), 6.63 (s, 4H, CHar *p*-methoxybenzyl), 6.88 (t, 2H, J_o = 7 Hz, H_5 indole and H_5 Trp), 7.02 (m, 4H, H_2 and H_6 indole, H_2 and H_6 Trp), 7.26−7.34 (m, 4H, H_4 and H_7 indole, H_4 and H_7 Trp), 8.51 and 9.18 (2 m, 2H, NH Pro, TFA salt), 9.27 (d, 1H, J = 8 Hz, NH amide), 10.73 (s, 1H, NH indole), 10.80 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 22.8 (CH_2−*C*H_2−indole), 23.8 (C_4 Pro), 25.9 (*C*H_2−CH_2−indole), 29.7 (C βTrp and C_3 Pro), 45.4 (CH_2 *p*-methoxybenzyl), 45.8 (C αTrp), 46.1 (C_5 Pro), 55.5 (OCH_3), 59.2 (CH αPro), 109.7 (C_3 Trp), 111.8 (C_7 Trp), 111.9 (C_7 indole), 113.4 (C_3 indole), 114.4 (C_3 and C_5 *p*-methoxybenzyl), 118.3 (C_4 indole), 118.5 (C_4 Trp), 118.6 (C_5 indole), 118.9 (C_5 Trp), 121.4 (C_6 indole and C_6 Trp), 122.9 (C_2 indole and C_2 Trp), 127.2 (C_9 indole), 127.4 (C_9 Trp), 127.6 (C_1, C_2, and C_6 *p*-methoxybenzyl), 136.5 (C_8 Trp), 136.6 (C_8 indole), 154.4 (Cq triazole), 155.0 (Cq triazole), 159.1 (C_4 *p*-methoxybenzyl), 168.3 (CO amide).

(*S*)-*N*-((*R*)-1-(4-(4-Methoxybenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)pyrrolidine-2-carboxamide Trifluoroacetate Salt (18). ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): δ 1.46 (m, 1H, H_3 Pro), 1.58 (m, 1H, H_4 Pro), 1.76 (m, 1H, H_4

Pro), 2.12 (m, 1H, H_3 Pro), 2.88 (m, 4H, CH_2−CH_2−phenyl), 3.11 (m, 2H, H_5 Pro), 3.35 (m, 2H, CH_2 βTrp), 3.72 (s, 3H, OCH_3), 4.01 (m, 1H, CH αPro), 5.05 (s, 2H, CH_2 *p*-methoxybenzyl), 5.25 (m, 1H, CH αTrp), 6.77 (s, 4H, CHar *p*-methoxybenzyl), 6.88 (t, 1H, J_o = 8 Hz, H_6 Trp), 7.03 (t, 1H, J_o = 8 Hz, H_5 Trp), 7.04 (s, 1H, H_2 Trp), 7.22 (d, 1H, J_o = 8 Hz, H_4 Trp), 7.25−7.29 (m, 5H, CHar phenyl), 7.33 (d, 1H, J_o = 8 Hz, H_7 Trp), 8.44 and 9.16 (2 m, 2H, NH Pro TFA salt), 9.27 (d, 1H, *J* = 8 Hz, NH amide), 10.83 (s, 1H, NH indole Trp). ^{13}C NMR (100 MHz, DMSO-d_6, 300 K): δ 23.1 (C_4 Pro), 26.0 (*C*H_2−CH_2−phenyl), 29.0 (C βTrp), 29.3 (C_3 Pro), 32.3 (CH_2−*C*H_2−phenyl), 44.7 (C αTrp), 44.9 (CH_2 *p*-methoxybenzyl), 45.5 (C_5 Pro), 55.0 (OCH_3), 58.8 (C αPro), 109.3 (C_3 Trp), 111.2 (C_7 Trp), 114.1 (C_3 and C_5 *p*-methoxybenzyl), 117.9 (C_4 Trp), 118.3 (C_5 Trp), 120.9 (C_6 Trp), 124.2 (C_2 Trp), 126.0 (C_4 phenyl), 126.9 (C_9 Trp), 127.4 (C_1, C_2 and C_6 *p*-methoxybenzyl), 128.2 (C_2, C_3, C_5, and C_6 phenyl), 136.0 (C_8 Trp), 140.5 (C_1 phenyl), 153.9 (Cq triazole), 154.3 (Cq triazole), 158.7 (C_4 *p*-methoxybenzyl), 167.7 (CO amide).

(*S*)-*N*-((*R*)-1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(2,4-dimethoxybenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)pyrrolidine-2-carboxamide Trifluoroacetate Salt (20). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.40 (m, 1H, H_3 Pro), 1.53 (m, 1H, H_4 Pro), 1.71 (m, 1H, H_4 Pro), 2.09 (m, 1H, H_3 Pro), 2.90 (m, 4H, CH_2−CH_2−indole), 3.06 (t, 2H, *J* = 6 Hz, H_5 Pro), 3.28 (m, 2H, CH_2 βTrp), 3.40 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.80 (m, 1H, CH αPro), 4.88 (d, 1H, *J* = 17 Hz, CH_2 *o*,*p*-dimethoxybenzyl), 5.04 (d, 1H, *J* = 17 Hz, CH_2 *o*,*p*-dimethoxybenzyl), 5.21 (m, 1H, CH αTrp), 6.26 (dd, 1H, J_o = 8 Hz and J_m = 2 Hz, H_5 *o*,*p*-dimethoxybenzyl), 6.38 (d, 1H, J_o = 8 Hz, H_6 *o*,*p*-dimethoxybenzyl), 6.53 (d, 1H, J_m = 2 Hz, H_3 *o*,*p*-dimethoxybenzyl), 6.84 (t, 1H, H_5 indole), 6.91 (t, 1H, J_o = 8 Hz, H_5 Trp), 6.93−7.07 (m, 4H, H_2 and H_6 indole, H_2 and H_6 Trp), 7.16 (d, 1H, J_o = 8 Hz, H_4 Trp), 7.29 (m, 3H, H_4 and H_7 indole, H_7 Trp), 8.39 and 9.10 (2 m, 2H, NH Pro TFA salt), 9.22 (d, 1H, *J* = 8 Hz, NH amide), 10.76 (s, 1H, NH indole), 10.80 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 22.9 (CH_2−*C*H_2−indole), 23.5 (C_4 Pro), 25.8 (*C*H_2−CH_2−indole), 29.6 (C βTrp), 29.8 (C_3 Pro), 41.9 (CH_2−*o*,*p*-dimethoxybenzyl), 45.2 (C αTrp), 46.0 (C_5 Pro), 55.7 (OCH_3), 55.9 (OCH_3), 59.3 (C αPro), 99.0 (C_3 *o*,*p*-dimethoxybenzyl), 105.1 (C_5 *o*,*p*-dimethoxybenzyl), 109.7 (C_3 Trp), 111.8 (C_7 indole and C_7 Trp), 113.4 (C_3 indole), 115.6 (C_1 *o*,*p*-dimethoxybenzyl), 118.4 (C_4 indole and C_4 Trp), 118.7 (C_5 indole and C_5 Trp), 121.4 (C_6 indole and C_6 Trp), 123.0 (C_2 indole and C_2 Trp), 127.2 (C_9 indole), 127.3 (C_9 Trp), 128.1 (C_6 *o*,*p*-dimethoxybenzyl), 136.5 (C_8 Trp), 136.6 (C_8 indole), 155.0 (2Cq triazole), 157.8 (C_2 *o*,*p*-dimethoxybenzyl), 160.9 (C_4 *o*,*p*-dimethoxybenzyl), 168.1 (CO amide).

(*S*)-*N*-((*R*)-1-(4-(2,4-Dimethoxybenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)pyrrolidine-2-carboxamide Trifluoroacetate Salt (21). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.41 (m, 1H, H_3 Pro), 1.54 (m, 1H, H_4 Pro), 1.71 (m, 1H, H_4 Pro), 2.15 (m, 1H, H_3 Pro), 2.84 (m, 4H, CH_2−CH_2−phenyl), 3.06 (m, 2H, H_5 Pro), 3.27 (m, 2H, CH_2 βTrp), 3.65 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.98 (t, 1H, *J* = 7 Hz, CH αPro), 4.85 (d, 1H, *J* = 17 Hz, CH_2 *o*,*p*-dimethoxybenzyl), 5.02 (d, 1H, *J* = 17 Hz, CH_2−*o*,*p*-dimethoxybenzyl), 5.22 (m, 1H, CH αTrp), 6.27 (dd, 1H, J_o = 8 Hz and J_m = 2 Hz, H_5 *o*,*p*-dimethoxybenzyl), 6.40 (d, 1H, J_o = 8 Hz, H_6 *o*,*p*-dimethoxybenzyl), 6.54 (d, 1H, J_m = 2 Hz, H_3 *o*,*p*-dimethoxybenzyl), 6.84 (t, 1H, J_o = 8 Hz, H_5 Trp), 7.0 (t, 1H, J_o = 8 Hz, H_6 Trp), 7.01 (d, 1H, *J* = 2 Hz, H_2 Trp), 7.11−7.18 (m, 3H, H_4 Trp, H_2 and H_6 phenyl), 7.21−7.29 (m, 4H, H_7 Trp, H_3, H_4, and H_5 phenyl), 8.39 and 9.07 (2 m, 2H, NH Pro TFA salt), 9.21 (d, 1H, *J* = 8 Hz, NH amide), 10.79 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 23.5 (C_4 Pro), 26.5 (*C*H_2−CH_2−phenyl), 29.6 (C βTrp), 29.8 (C_3 Pro), 32.7 (CH_2−*C*H_2−phenyl), 41.8 (CH_2 *o*,*p*-dimethoxybenzyl), 45.2 (C αTrp), 46.0 (C_5 Pro), 55.7 (OCH_3), 55.9 (OCH_3), 59,3 (C αPro), 99.0 (C_3 *o*,*p*-dimethoxybenzyl), 105.2 (C_5 *o*,*p*-dimethoxybenzyl), 109.8 (C_3 Trp), 111.7 (C_7 Trp), 115.7 (C_1 *o*,*p*-dimethoxybenzyl), 118.3 (C_4 Trp), 118.7 (C_5 Trp), 121.3 (C_6 Trp), 124.4 (C_2 Trp), 126.6 (C_6 *o*,*p*-dimethoxybenzyl), 127.3 (C_9 Trp), 128.2 (C_4 phenyl), 128.7 (C_2, C_3, C_5, and C_6 phenyl), 136.5 (C_8 Trp), 141.0 (C_1 phenyl), 154.5 (Cq triazole), 155.0 (Cq triazole), 157.8 (C_2 *o*,*p*-dimethoxybenzyl), 160.9 (C_4 *o*,*p*-dimethoxybenzyl), 168.1 (CO amide).

(2*S*)-*N*-((*R*)-2-(1*H*-Indol-3-yl)-1-(5-phenethyl-4-phenyl-4*H*-1,2,4-triazol-3-yl)ethyl)pyrrolidine-2-carboxamide Trifluoroacetate Salt (23). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.52 (m, 1H, H_3 Pro), 1.60 (m, 1H, H_4 Pro), 1.75 (m, 1H, H_4 Pro), 2.17 (m, 1H, H_3 Pro), 2.71 (m, 4H, CH_2−CH_2−phenyl), 3.13 (m, 4H, CH_2 βTrp and H_5 Pro), 4.06 (1H, m, CH αPro), 4.79 (1H, m, CH αTrp), 6.77 (1H, t, J_o = 7 Hz, H_5 Trp), 6.84 (t, 1H, J_o = 8 Hz, H_6 Trp), 6.91 (s, 1H, H_2 Trp), 6.96−7,21 (m, 10H, CHar phenyl), 7.28 (d, 1H, J_o = 8 Hz, H_4 Trp), 7.47 (d, 1H, J_o = 7 Hz, H_7 Trp), 8.37 and 9.15 (2 m, 2H, NH Pro TFA salt), 9.34 (d, 1H, *J* = 8 Hz, NH amide), 10.78 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 23.7 (C_4 Pro), 26.8 (*C*H_2−CH_2−phenyl), 29.9 (C_3 Pro), 30.6 (C βTrp), 33.9 (CH_2−*C*H_2−phenyl), 46.0 (C_5 Pro), 46.2 (C αTrp), 59.3 (C αPro), 109.5 (C_3 Trp), 111.8 (C_7 Trp), 118.1 (C_4 Trp), 118.7 (C_5 Trp), 121.3 (C_6 Trp), 124.3 (C_2 Trp), 126.5 (C_4 phenyl from CH_2−CH_2−phenyl), 127.2 (C_9 Trp), 127.6 (C_4 phenyl), 128.6 and 130.1 (C_2, C_3, C_5, and C_6 phenyl and phenyl from CH_2−CH_2−phenyl), 133.2 (C_1 phenyl), 136.4 (C_8 Trp), 140.8 (C_1 phenyl from CH_2−CH_2−phenyl), 153.7 (Cq triazole), 155.1 (Cq triazole), 167.9 (CO amide).

(2*S*,4*R*)-*N*-((*R*)-1-(4-(4-Methoxybenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-4-hydroxypyrrolidine-2-carboxamide Trifluoroacetate Salt (25). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.50 (m, 1H, H_3 hydroxyprolyl), 2.10 (m, 1H, H_3 hydroxyprolyl), 2.80 (m, 4H, CH_2−CH_2−phenyl), 3.0 (m, 1H, H_5 hydroxyprolyl), 3.20 (m, 1H, H_5 hydroxyprolyl), 3.29 (d, 2H, *J* = 7 Hz, CH_2 βTrp), 3.63 (m, 1H, H_2 hydroxyprolyl), 3.67 (s, 3H, OCH_3), 4.50 (brs, 3H, OH and NH hydroxyprolyl TFA salt), 5.00 (s, 2H, CH_2 *p*-methoxybenzyl), 5.17 (m, 1H, CH αTrp), 6.72 (s, 4H, CHar *p*-methoxybenzyl), 6.84 (t, 1H, J_o = 8 Hz, H_5 Trp), 6.99 (m, 2H, H_2 and H_6 Trp), 7.09 (d, 1H, J_o = 8 Hz, H_4 Trp), 7.13−7.25 (5H, CHar phenyl), 7.29 (d, 1H, J_o = 8 Hz, H_7 Trp), 9.30 (d, 1H, *J* = 8 Hz, NH amide), 10.79 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 26.5 (*C*H_2−CH_2−phenyl), 29.5 (C βTrp), 32.8 (CH_2−CH_2−phenyl), 40.8 (C_3 hydroxyprolyl), 46.3 (C αTrp), 53.9 (CH_2 *p*-methoxybenzyl and C_5 hydroxyprolyl), 55.5 (OCH_3), 58.2 (C_2 hydroxyprolyl), 69.3 (C_4 hydroxyprolyl), 109.7 (C_3 Trp), 111.8 (C_7 Trp), 114.6 (C_3 and C_5 *p*-methoxybenzyl), 118.4 (C_4 Trp), 118.8 (C_5 Trp), 121.4 (C_6 Trp), 124.6 (C_2 Trp), 126.5 (C_4 phenyl), 127.3 (C_9 Trp), 127.8 (C_2 and C_6 *p*-methoxybenzyl), 128.7 (C_2, C_3, C_5, and C_6 phenyl), 136.4 (C_8 Trp), 141.0 (C_1 phenyl), 154.4 (Cq triazole), 154.7 (Cq triazole), 159.1 (C_4 *p*-methoxybenzyl), 168.2 (CO amide).

(*S*)-*N*-((*R*)-1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(4-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)piperidine-3-carboxamide Trifluoroacetate Salt (29). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.33 (m, 1H, H_4 piperidyl), 1.53 (m, 3H, H_3 and H_5 piperidyl), 2.72 (m, 2H, H_2 and H_6 piperidyl), 2.83 (m, 4H, CH_2−CH_2−indole), 3.03 (m, 2H, H_2 and H_6 piperidyl), 3.26 (dd, 1H, *J* = 14 and 7 Hz, CH_2 βTrp), 3.39 (dd, 1H, *J* = 14 and 8 Hz, CH_2 βTrp), 3.68 (s, 3H, OCH_3), 4.92 (s, 2H, CH_2 *p*-methoxybenzyl), 5.20 (m, 1H, CH αTrp), 6.65 (s, 4H, CHar *p*-methoxybenzyl), 6.87 (t, 2H, J_o = 7 Hz, H_5 indole and H_5 Trp), 7.00 (m, 4H, H_2 and H_6 indole, H_2 and H_6 Trp), 7.23−7.34 (m, 4H, H_4 and H_7 indole, H_4 and H_7 Trp), 8.53 (brs, 2H, NH piperidyl TFA salt), 8.88 (d, 1H, *J* = 8 Hz, NH amide), 10.75 (s, 1H, NH indole), 10.78 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 21.2 (C_5 piperidyl), 22.7 (CH_2−*C*H_2−indole), 25.9 (*C*H_2−CH_2−indole and C_4 piperidyl), 29.3 (C βTrp), 38.7 (C_3 piperidyl), 43.3 (C_6 piperidyl), 44.5 (C_2 piperidyl), 45.1 (C αTrp), 45.5 (CH_2 *p*-methoxybenzyl), 55.5 (OCH_3), 110.1 (C_3 Trp), 111.8 (C_7 indole and C_7 Trp), 113.2 (C_3 indole), 114.4 (C_3 and C_5 *p*-methoxybenzyl), 118.5 (C_4 indole and C_4 Trp), 118.6 (C_5 indole), 118.8 (C_5 Trp), 121.4 (C_6 indole and C_6 Trp), 123.0 (C_2 indole and C_2 Trp), 127.1 (C_1 *p*-methoxybenzyl), 127.5 (C_9 indole and C_9 Trp), 127.7 (C_2 and C_6 *p*-methoxybenzyl), 136.4 (C_8 Trp), 136.6 (C_8 indole), 155.0 (2Cq triazole), 159.1 (C_4 *p*-methoxybenzyl), 171.9 (CO amide).

(*S*)-*N*-((*R*)-1-(4-(4-Methoxybenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)piperidine-3-carboxamide Trifluoroacetate Salt (30). ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): δ 1.33 (m, 1H, H_4 piperidyl), 1.50 (m, 1H, H_5 piperidyl), 1.61 (m, 1H, H_4 piperidyl), 1.64 (m, 1H, H_5 piperidyl), 2.54 (m, 1H, H_3 piperidyl), 2.77 (m, 1H, H_2 piperidyl), 2.80 (m, 3H, H_6 piperidyl and CH_2-CH_2-phenyl), 2.84 (m, 2H, CH_2-CH_2-phenyl), 2.96 (m, 1H, H_2 piperidyl), 3.08 (m, 1H, H_6 piperidyl), 3.30 (dd, 1H, J = 14 and 7 Hz, CH_2 βTrp), 3.45 (dd, 1H, J = 14 and 8 Hz, CH_2 βTrp), 3.69 (s, 3H, OCH_3), 4.94 (m, 2H, CH_2 *p*-methoxybenzyl), 5.25 (m, 1H, CH αTrp), 6.70 (s, 4H, CHar *p*-methoxybenzyl), 6.91 (t, 1H, J_o = 8 Hz, H_6 Trp), 7.02 (d, 1H, J = 2 Hz, H_2 Trp), 7.05 (t, 1H, J_o = 8 Hz, H_5 Trp), 7.29−7.08 (m, 5H, CHar phenyl), 7.34 (d, 1H, J_o = 8 Hz, H_4 Trp), 7.39 (d, 1H, J_o = 8 Hz, H_7 Trp), 8.48 (brs, 2H, NH piperidyl TFA salt), 8.90 (d, 1H, J = 8 Hz, NH amide), 10.81 (s, 1H, NH indole Trp). ^{13}C NMR (100 MHz, DMSO-d_6, 300 K): δ 20.7 (C_5 piperidyl), 25.4 (C_4 piperidyl), 26.1 (CH_2-CH_2-phenyl), 28.9 (C βTrp), 32.2 (CH_2-CH_2-phenyl), 38.2 (C_3 piperidyl), 42.9 (C_6 piperidyl), 44.0 (C_2 piperidyl), 44.6 (C αTrp), 44.7 (CH_2 *p*-methoxybenzyl), 55.0 (OCH_3), 109.8 (C_3 Trp), 111.3 (C_7 Trp), 114.0 (C_3 and C_5 *p*-methoxybenzyl), 118.0 (C_4 Trp), 118.3 (C_5 Trp), 120.8 (C_6 Trp), 124.0 (C_2 Trp), 126.0 (C_4 phenyl), 127.1 (C_9 Trp), 127.2 (C_1, C_2 and C_6 *p*-methoxybenzyl), 128.2 (C_2, C_3, C_5, and C_6 phenyl), 136.0 (C_8 Trp), 140.4 (C_1 phenyl), 154.0 (Cq triazole), 154.4 (Cq triazole), 158.6 (C_4 *p*-methoxybenzyl), 171.4 (CO amide).

(*R*)-*N*-((*R*)-1-(4-(4-Methoxybenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)piperidine-3-carboxamide Trifluoroacetate Salt (31). ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): δ 1.27 (m, 1H, H_4 piperidyl), 1.49 (m, 2H, H_5 piperidyl), 1.65 (m, 1H, H_4 piperidyl), 2.53 (m, 1H, H_3 piperidyl), 2.70 (m, 1H, H_2 piperidyl), 2.75 (m, 1H, H_6 piperidyl), 2.79 (m, 1H, H_2 piperidyl), 2.83 (m, 2H, CH_2-CH_2-phenyl), 2.84 (m, 2H, CH_2-CH_2-phenyl), 3.01 (m, 1H, H_6 piperidyl), 3.33 (dd, 1H, J = 15 and 8 Hz, CH_2 βTrp), 3.38 (dd, 1H, J = 15 and 7 Hz, CH_2 βTrp), 3.71 (s, 3H, OCH_3), 5.06 (m, 2H, CH_2 *p*-methoxybenzyl), 5.26 (m, 1H, CH αTrp), 6.77 (s, 4H, CHar *p*-methoxybenzyl), 6.89 (t, 1H, J_o = 8 Hz, H_5 Trp), 7.03 (t, 1H, J_o = 8 Hz, H_6 Trp), 7.06 (d, 1H, J = 2 Hz, H_2 Trp), 7.29−7.08 (m, 5H, CHar phenyl), 7.29 (d, 1H, J_o = 8 Hz, H_4 Trp), 7.32 (d, 1H, J_o = 8 Hz, H_7 Trp), 8.54 and 8.88 (2 m, 2H, NH piperidyl TFA salt), 8.92 (d, 1H, J = 8 Hz, NH amide), 10.82 (s, 1H, NH indole Trp). ^{13}C NMR (100 MHz, DMSO-d_6, 300 K): δ 20.5 (C_5 piperidyl), 25.7 (C_4 piperidyl), 26.0 (CH_2-CH_2-phenyl), 28.6 (C βTrp), 32.2 (CH_2-CH_2-phenyl), 37.8 (C_3 piperidyl), 42.7 (C_6 piperidyl), 43.8 (C_2 piperidyl), 44.0 (C αTrp), 45.0 (CH_2 *p*-methoxybenzyl), 55.1 (OCH_3), 109.6 (C_3 Trp), 111.2 (C_7 Trp), 114.0 (C_3 and C_5 *p*-methoxybenzyl), 118.0 (C_4 Trp), 118.2 (C_5 Trp), 120.8 (C_6 Trp), 124.1 (C_2 Trp), 126.1 (C_4 phenyl), 127.1 (C_9 Trp), 127.2 (C_1, C_2, and C_6 *p*-methoxybenzyl), 128.2 (C_2, C_3, C_5, and C_6 phenyl), 136.0 (C_8 Trp), 140.4 (C_1 phenyl), 154.0 (Cq triazole), 154.4 (Cq triazole), 158.6 (C_4 *p*-methoxybenzyl), 171.5 (CO amide).

(3*S*)-*N*-((*R*)-1-(4-(4-Ethylbenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)piperidine-3-carboxamide Trifluoroacetate Salt (32). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.08 (t, 3H, J = 8 Hz, CH_3-CH_2-phenyl), 1.20 (m, 1H, H_4 piperidyl), 1.44 (m, 2H, H_5 piperidyl), 1.55 (m, 1H, H_4 piperidyl), 2.51 (q, 2H, J = 8 Hz, CH_3-CH_2-phenyl), 2.53 (m, 1H, H_3 piperidyl), 2.83 (m, 7H, CH_2-CH_2-phenyl, H_2 and H_6 piperidyl), 3.01 (m, 1H, H_6 piperidyl), 3.28 (m, 1H, CH_2 βTrp), 3.36 (m, 1H, CH_2 βTrp), 4.98 (s, 2H, CH_2 *p*-ethylbenzyl), 5.20 (m, 1H, CH αTrp), 6.65 (d, 2H, J_o = 8 Hz, H_3 and H_5 *p*-ethylbenzyl), 6.86 (t, 1H, J_o = 7 Hz, H_5 Trp), 6.97−7.07 (m, 7H, H_2, H_4, and H_6 Trp, H_2 and H_6 *p*-ethylbenzyl, H_2 and H_6 phenyl), 7.13−7.22 (m, 3H, H_3, H_4, and H_5 phenyl), 7.29 (d, 1H, J_o = 8 Hz, H_7 Trp), 8.46 (brs, 2H, NH piperidyl TFA salt), 8.85 (d, 1H, J = 8 Hz, NH amide), 10.78 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 15.9 (CH_3-CH_2-phenyl), 21.2 (C_5 piperidyl), 25.7 (C_4 piperidyl), 26.5 (CH_2-CH_2-phenyl), 28.1 (CH_3-CH_2-phenyl), 29.2 (C βTrp), 32.6 (CH_2-CH_2-phenyl), 38.7 (C_3 piperidyl), 43.3 (C_6 piperidyl), 44.5 (C_2 piperidyl), 45.0 (C αTrp), 45.6 (CH_2-p-ethylbenzyl), 110.2 (C_3 Trp), 111.7 (C_7 Trp), 118.5 (C_4 Trp), 118.7 (C_5 Trp), 121.3 (C_6 Trp), 124.4 (C_2 Trp), 126.2 (C_3 and C_5 *p*-ethylbenzyl), 126.5 (C_4 phenyl), 127.5 (C_9 Trp), 128.5 (C_2, C_3, C_5, and C_6 phenyl, C_2 and C_6 *p*-ethylbenzyl), 133.0 (C_1 *p*-ethylbenzyl), 136.4 (C_8 Trp), 140.8 (C_1 phenyl), 143.6 (C_4 *p*-ethylbenzyl), 154.5 (Cq triazole), 155.1 (Cq triazole), 171.9 (CO amide).

(*R*)-*N*-((*R*)-1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(4-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)piperidine-2-carboxamide Trifluoroacetate Salt (35). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.28 (m, 1H, H_3 piperidyl), 1.36 (m, 1H, H_4 piperidyl), 1.45 (m, 1H, H_5 piperidyl), 1.66 (m, 2H, H_4 and H_5 piperidyl), 1.90 (d, 1H, J = 13 Hz, H_3 piperidyl), 2.82 (m, 4H, CH_2-CH_2-indole), 2.89 (m, 1H, H_6 piperidyl), 3.14 (d, 1H, J = 12 Hz, H_6 piperidyl), 3.25 (dd, 1H, J = 14 and 7 Hz, CH_2 βTrp), 3.39 (dd, 1H, J = 14 and 8 Hz, CH_2 βTrp), 3.64 (s, 4H, OCH_3 and H_2 piperidyl), 4.88 (s, 2H, CH_2-p-methoxybenzyl), 5.19 (m, 1H, CH αTrp), 6.65 (s, 4H, CHar *p*-methoxybenzyl), 6.80 (m, 2H, H_5 indole and H_5 Trp), 7.02 (m, 5H, H_2, H_4, and H_6 Trp, H_2 and H_6 indole), 7.29 (m, 3H, H_4 and H_7 indole, H_7 Trp), 8.58 and 8.88 (2 m, 2H, NH piperidyl TFA salt), 9.22 (d, 1H, J = 8 Hz, NH amide), 10.73 (s, 1H, NH indole), 10.81 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 21.6 (C_5 piperidyl), 21.9 (C_4 piperidyl), 22.8 (CH_2-CH_2-indole), 25.9 (CH_2-CH_2-indole), 27.2 (C_3 piperidyl), 29.7 (C βTrp), 43.6 (C_6 piperidyl), 45.4 (CH_2-p-methoxybenzyl), 45.7 (C αTrp), 55.5 (OCH_3), 57.2 (C_2 piperidyl), 109.7 (C_3 Trp), 111.8 (C_7 Trp), 111.9 (C_7 indole), 113.4 (C_3 indole), 114.5 (C_3 and C_5 *p*-methoxybenzyl), 118.3 (C_4 indole), 118.5 (C_4 Trp), 118.6 (C_5 Trp), 118.9 (C_5 indole), 121.4 (C_6 indole and C_6 Trp), 122.9 (C_2 indole and C_2 Trp), 127.2 (C_9 indole), 127.3 (C_9 Trp), 127.5 (C_1 *p*-methoxybenzyl), 127.7 (C_2 and C_6 *p*-methoxybenzyl), 136.5 (C_8 Trp), 136.6 (C_8 indole), 154.5 (Cq triazole), 154.9 (Cq triazole), 159.1 (C_4 *p*-methoxybenzyl), 168.8 (CO amide).

(*R*)-*N*-((*R*)-1-(4-(4-Methoxybenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)piperidine-2-carboxamide Trifluoroacetate Salt (36). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.28 (m, 1H, H_3 piperidyl), 1.36 (m, 1H, H_4 piperidyl), 1.41 (m, 1H, H_5 piperidyl), 1.66 (m, 2H, H_4 and H_5 piperidyl), 1.90 (d, 1H, J = 14 Hz, H_3 piperidyl), 2.77 (m, 4H, CH_2-CH_2-phenyl), 2.86 (m, 1H, H_6 piperidyl), 3.15 (d, 1H, J = 12 Hz, H_6 piperidyl), 3.25 (dd, 1H, J = 14 and 7 Hz, CH_2 βTrp), 3.41 (dd, 1H, J = 14 and 8 Hz, CH_2 βTrp), 3.64 (s, 4H, OCH_3 and H_2 piperidyl), 4.86 (s, 2H, CH_2 *p*-methoxybenzyl), 5.19 (m, 1H, CH αTrp), 6.65 (s, 4H, CHar *p*-methoxybenzyl), 6.87 (t, 1H, J_o = 7 Hz, H_5 Trp), 7.01 (m, 2H, H_2 and H_6 Trp), 7.09 (d, 2H, J_o = 8 Hz, H_2 and H_6 phenyl), 7.14 (d, 1H, H_4 Trp), 7.18−7.33 (m, 4H, H_7 Trp, H_3, H_4, and H_5 phenyl), 8.60 and 8.89 (2 m, 2H, NH piperidyl TFA salt), 9.21 (d, 1H, J = 8 Hz, NH amide), 10.81 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 21.6 (C_5 piperidyl), 21.9 (C_4 piperidyl), 26.5 (CH_2-CH_2-phenyl), 27.3 (C_3 piperidyl), 29.8 (C βTrp), 32.7 (CH_2-CH_2-phenyl), 43.6 (C_6 piperidyl), 45.2 (CH_2 *p*-methoxybenzyl), 45.6 (C αTrp), 55.5 (OCH_3), 57.2 (C_2 piperidyl), 109.7 (C_3 Trp), 111.9 (C_7 Trp), 114.5 (C_3 and C_5 *p*-methoxybenzyl), 118.3 (C_4 Trp), 118.9 (C_5 Trp), 121.4 (C_6 Trp), 124.6 (C_2 Trp), 126.5 (C_4 phenyl), 127.3 (C_9 Trp), 127.6 (C_1 *p*-methoxybenzyl), 127.7 (C_2 and C_6 *p*-methoxybenzyl), 128.7 (C_2, C_3, C_5, and C_6 phenyl), 136.5 (C_8 Trp), 140.9 (C_1 phenyl), 154.4 (Cq triazole), 154.5 (Cq triazole), 159.1 (C_4 *p*-methoxybenzyl), 168.8 (CO amide).

(*R*)-*N*-(1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(4-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)piperidine-4-carboxamide Trifluoroacetate Salt (39). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.41 (m, 3H, H_3 and H_5 piperidyl), 1.54 (dd, 1H, J = 13 and 2 Hz, H_5 piperidyl), 2.23 (m, 1H, H_4 piperidyl), 2.72 (m, 2H, H_2 and H_6 piperidyl), 2.77−2.93 (m, 4H, CH_2-CH_2-indole), 3.06 (m, 2H, H_2 and H_6 piperidyl), 3.32 (m, 2H, CH_2 βTrp), 3.65 (s, 3H, OCH_3), 4.94 (s, 2H, CH_2 *p*-methoxybenzyl), 5.22 (m, 1H, CH αTrp), 6.68 (s, 4H, CHar *p*-methoxybenzyl), 6.87 (m, 3H, H_5 and H_6 Trp, H_5 indole), 6.98 (m, 4H, H_2 and H_6 indole, H_2 and H_4 Trp), 7.20−7.33 (m, 3H, H_4 and H_7 indole, H_7 Trp), 8.15 and 8.46 (2 m, 2H, NH piperidyl TFA salt), 8.64 (d, 1H, J = 8 Hz, NH amide), 10.74 (s, 2H, NH indole and NH indole Trp). ^{13}C NMR

(75 MHz, DMSO-d_6, 300 K): δ 22.9 (CH_2-CH_2-indole), 24.9 (C_3 piperidyl), 25.4 (C_5 piperidyl), 26.0 (CH_2-CH_2-indole), 29.3 (C βTrp), 39.1 (C_4 piperidyl), 42.7 (C_2 and C_6 piperidyl), 44.7 (C αTrp), 45.3 (CH_2 *p*-methoxybenzyl), 55.5 (OCH_3), 109.5 (C_3 Trp), 111.7 (C_7 indole and C_7 Trp), 113.5 (C_3 indole), 114.4 (C_3 and C_5 *p*-methoxybenzyl), 118.5 (C_4 indole and C_4 Trp), 118.6 (C_5 indole and C_5 Trp), 121.2 (C_6 indole), 121.3 (C_6 Trp), 122.9 (C_2 indole and C_2 Trp), 127.2 (C_9 indole), 127.6 (C_9 Trp, C_2 and C_6 *p*-methoxybenzyl), 127.9 (C_1 *p*-methoxybenzyl), 136.4 (C_8 Trp), 136.6 (C_8 indole), 154.9 (Cq triazole), 155.2 (Cq triazole), 159.0 (C_4 *p*-methoxybenzyl), 173.0 (CO amide).

(*R*)-*N*-(1-(4-(4-Methoxybenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)piperidine-4-carboxamide Trifluoroacetate Salt (40). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.42 (m, 3H, H_3 and H_5 piperidyl), 1.55 (m, 1H, H_5 piperidyl), 2.23 (m, 1H, H_4 piperidyl), 2.75 (m, 6H, H_2 and H_6 piperidyl and CH_2-CH_2-phenyl), 3.04 (m, 1H, H_6 piperidyl), 3.13 (m, 1H, H_2 piperidyl), 3.32 (m, 2H, CH_2 βTrp), 3.66 (s, 3H, OCH_3), 4.97 (m, 2H, CH_2-*p*-methoxybenzyl), 5.23 (m, 1H, CH αTrp), 6.70 (s, 4H, CHar *p*-methoxybenzyl), 6.87 (t, 1H, $J_o = 8$ Hz, H_5 Trp), 7.00 (m, 2H, H_2 and H_6 Trp), 7.07 (d, 2H, $J_o = 8$ Hz, H_2 and H_6 phenyl), 7.14 (d, 1H, $J_o = 7$ Hz, H_4 Trp), 7.18−7.30 (m, 4H, H_7 Trp, H_3, H_4, and H_5 phenyl), 8.16 and 8.46 (2 m, 2H, NH piperidyl TFA salt), 8.66 (d, 1H, $J = 8$ Hz, NH amide), 10.75 (1H, s, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 24.9 (C_3 piperidyl), 25.4 (C_5 piperidyl), 26.5 (CH_2-CH_2-phenyl), 29.2 (C βTrp), 32.7 (CH_2-CH_2-phenyl), 38.7 (C_4 piperidyl), 42.7 (C_2 and C_6 piperidyl), 44.7 (C αTrp), 45.3 (CH_2 *p*-methoxybenzyl), 55.5 (OCH_3), 110.2 (C_3 Trp), 111.7 (C_7 Trp), 114.4 (C_3 and C_5 *p*-methoxybenzyl), 118.5 (C_4 Trp), 118.7 (C_5 Trp), 121.3 (C_6 Trp), 124.4 (C_2 Trp), 126.5 (C_4 phenyl), 127.5 (C_9 Trp), 127.8 (C_1, C_2, and C_6 *p*-methoxybenzyl), 128.7 (C_2, C_3, C_5, and C_6 phenyl), 136.4 (C_8 Trp), 140.8 (C_1 phenyl), 155.3 (Cq triazole), 155.4 (Cq triazole), 159.1 (C_4 *p*-methoxybenzyl), 173.1 (CO amide).

(*R*)-*N*-(1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(2,4-dimethoxybenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)piperidine-4-carboxamide Trifluoroacetate Salt (41). ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): δ 1.43 (m, 1H, H_5 piperidyl), 1.48 (m, 2H, H_3 piperidyl), 1.59 (m, 1H, H_5 piperidyl), 2.27 (m, 1H, H_4 piperidyl), 2.77 (m, 2H, H_2 and H_6 piperidyl), 2.91 (m, 2H, CH_2-CH_2-indole), 2.94 (m, 2H, CH_2-CH_2-indole), 3.10 (m, 1H, H_6 piperidyl), 3.17 (m, 1H, H_2 piperidyl), 3.31 (dd, 1H, $J = 15$ and 8 Hz, CH_2 βTrp), 3.37 (dd, 1H, $J = 15$ and 7 Hz, CH_2 βTrp), 3.66 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 4.89 (d, 1H, $J = 17$ Hz, CH_2 *o*,*p*-dimethoxybenzyl), 5.0 (d, 1H, $J = 17$ Hz, CH_2 *o*,*p*-dimethoxybenzyl), 5.29 (m, 1H, CH αTrp), 6.26 (dd, 1H, $J_o = 8$ Hz and $J_m = 2$ Hz, H_5 *o*,*p*-dimethoxybenzyl), 6.39 (d, 1H, $J_o = 8$ Hz, H_6 *o*,*p*-dimethoxybenzyl), 6.54 (d, 1H, $J_m = 2$ Hz, H_3 *o*,*p*-dimethoxybenzyl), 6.92 (t, 1H, $J_o = 7$ Hz, H_5 Trp), 6.93 (t, 1H, $J_o = 7$ Hz, H_5 indole), 7.04 (t, 1H, $J_o = 8$ Hz, H_6 Trp), 7.05 (t, 1H, $J_o = 8$ Hz, H_6 indole), 7.06 (s, 1H, H_2 Trp), 7.07 (s, 1H, H_2 indole), 7.28 (d, 1H, $J_o = 8$ Hz, H_4 indole), 7.32 (m, 2H, H_7 indole and H_7 Trp), 7.34 (d, 1H, $J_o = 8$ Hz, H_4 Trp), 8.29 and 8.60 (2 m, 2H, NH piperidyl TFA salt), 8.65 (d, 1H, $J = 8$ Hz, NH amide), 10.80 (s, 1H, NH indole), 10.82 (s, 1H, NH indole Trp). ^{13}C NMR (100 MHz, DMSO-d_6, 300 K): δ 22.3 (CH_2-CH_2-indole), 24.5 (C_3 piperidyl), 24.9 (C_5 piperidyl), 25.3 (CH_2-CH_2-indole), 28.7 (C βTrp), 38.2 (C_4 piperidyl), 41.5 (CH_2 *o*,*p*-dimethoxybenzyl), 42.2 (C_2 andC_6 piperidyl), 44.3 (C αTrp), 55.2 (OCH_3), 55.4 (OCH_3), 98.5 (C_3 *o*,*p*-dimethoxybenzyl), 104.6 (C_5 *o*,*p*-dimethoxybenzyl), 109.7 (C_3 Trp), 111.2 (C_7 indole), 111.3 (C_7 Trp), 112.7 (C_3 indole), 114.9 (C_1 *o*,*p*-dimethoxybenzyl), 117.9 (C_4 indole), 118.0 (C_4 Trp), 118.2 (C_5 indole and C_5 Trp), 120.8 (C_6 indole), 120.9 (C_6 Trp), 122.5 (C_2 indole), 123.9 (C_2 Trp), 126.7 (C_9 indole), 127.1 (C_9 Trp), 127.5 (C_6 *o*,*p*-dimethoxybenzyl), 136.0 (C_8 Trp), 136.1 (C_8 indole), 154.7 (Cq triazole), 155.2 (Cq triazole), 157.2 (C_2 *o*,*p*-dimethoxybenzyl), 160.4 (C_4 *o*,*p*-dimethoxybenzyl), 172.6 (CO amide).

(*R*)-*N*-(1-(4-(2,4-Dimethoxybenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)piperidine-4-carboxamide Trifluoroacetate Salt (42). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.43 (m, 3H, H_3 and H_5 piperidyl), 1.56 (dd, 1H, $J = 13$ and 3 Hz, H_5 piperidyl), 2.24 (m, 1H, H_4 piperidyl), 2.67−2.83 (m, 6H, CH_2-CH_2-phenyl, H_2 and H_6 piperidyl), 3.09 (m, 2H, H_2 and H_6 piperidyl), 3.28 (m, 2H, CH_2 βTrp), 3.62 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 4.81 (d, 1H, $J = 17$ Hz, CH_2 *o*,*p*-dimethoxybenzyl), 4.94 (d, 1H, $J = 17$ Hz, CH_2 *o*,*p*-dimethoxybenzyl), 5.24 (m, 1H, CH αTrp), 6.24 (dd, 1H, $J_o = 8$ Hz and $J_m = 2$ Hz, H_5 *o*,*p*-dimethoxybenzyl), 6.35 (d, 1H, $J_o = 8$ Hz, H_6 *o*,*p*-dimethoxybenzyl), 6.50 (d, 1H, $J_m = 2$ Hz, H_3 *o*,*p*-dimethoxybenzyl), 6.87 (t, 1H, $J_o = 8$ Hz, H_5 Trp), 7.0 (m, 2H, H_2 and H_6 Trp), 7.08 (d, 2H, $J_o = 7$ Hz, H_2 and H_6 phenyl), 7.15 (d, 1H, $J_o = 7$ Hz, H_4 Trp), 7.19−7.30 (m, 4H, H_7 Trp, H_3, H_4, and H_5 phenyl), 8.35 (m, 1H, NH piperidyl TFA salt), 8.61 (d, 1H, $J = 8$ Hz, NH amide), 8.69 (m, 1H, NH piperidyl TFA salt), 10.78 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 22.3 (C_3 piperidyl), 25.0 (C_5 piperidyl), 25.3 (CH_2-CH_2-phenyl), 29.2 (C βTrp), 32.6 (CH_2-CH_2-phenyl), 38.7 (C_4 piperidyl), 41.9 (C_2 and C_6 piperidyl), 42.6 (CH_2 *o*,*p*-dimethoxybenzyl), 44.7 (C αTrp), 55.7 (OCH_3), 55.9 (OCH_3), 98.9 (C_3 *o*,*p*-dimethoxybenzyl), 105.1 (C_5 *o*,*p*-dimethoxybenzyl), 110.2 (C_3 Trp), 111.7 (C_7 Trp), 115.5 (C_1 *o*,*p*-dimethoxybenzyl), 118.5 (C_4 Trp), 118.7 (C_5 Trp), 121.3 (C_6 Trp), 124.4 (C_2 Trp), 126.6 (C_6 *o*,*p*-dimethoxybenzyl), 127.5 (C_9 Trp), 128.1 (C_4 phenyl), 128.7 (C_2, C_3, C_5 and C_6 phenyl), 136.4 (C_8 Trp), 140.7 (C_1 phenyl), 154.6 (Cq triazole), 155.6 (Cq triazole), 157.7 (C_2 *o*,*p*-dimethoxybenzyl), 160.8 (C_4 *o*,*p*-dimethoxybenzyl), 173.1 (CO amide).

***N*-((*R*)-2-(1*H*-Indol-3-yl)-1-(5-phenethyl-4-phenyl-4*H*-1,2,4-triazol-3-yl)ethyl)piperidine-4-carboxamide Trifluoroacetate Salt (44).** ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.50 (m, 3H, H_3 and H_5 piperidyl), 1.68 (m, 1H, H_5 piperidyl), 2.37 (m, 1H, H_4 piperidyl), 2.65 (m, 2H, H_2 and H_6 piperidyl), 2.79 (m, 4H, CH_2-CH_2-phenyl), 3.05−3.21 (m, 4H, CH_2 βTrp, H_2 and H_6 piperidyl), 4.77 (m, 1H, CH αTrp), 6.76 (t, 1H, $J_o = 7$ Hz, H_5 Trp), 6.82 (t, 1H, $J_o = 8$ Hz, H_6 Trp), 6.90 (s, 1H, H_2 Trp), 6.95−7.20 (m, 10H, CHar phenyl), 7.26 (d, 1H, $J_o = 8$ Hz, H_4 Trp), 7.45 (d, 1H, $J_o = 8$ Hz, H_7 Trp), 8.20 and 8.50 (2 m, 2H, NH piperidyl TFA salt), 8.64 (d, 1H, $J = 8$ Hz, NH amide), 10.72 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 25.3 (C_3 and C_5 piperidyl), 26.9 (CH_2-CH_2-phenyl), 30.2 (C βTrp), 33.0 (CH_2-CH_2-phenyl), 38.6 (C_4 piperidyl), 42.8 (C_2 and C_6 piperidyl), 45.9 (C αTrp), 110.0 (C_3 Trp), 111.7 (C_7 Trp), 118.2 (C_4 Trp), 118.6 (C_5 Trp), 121.2 (C_6 Trp), 124.3 (C_2 Trp), 126.5 (C_4 phenyl from CH_2-CH_2-phenyl), 127.3 (C_9 Trp), 127.6 (C_4 phenyl), 128.5 (C_2, C_3, C_5, and C_6 phenyl and phenyl from CH_2-CH_2-phenyl), 133.4 (C_1 phenyl), 136.4 (C_8 Trp), 140.8 (C_1 phenyl from CH_2-CH_2-phenyl), 153.7 (Cq triazole), 155.6 (Cq triazole), 172.9 (CO amide).

***N*-((*R*)-1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)piperidine-4-carboxamide Trifluoroacetate Salt (45)**. ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.54 (m, 3H, H_3 and H_5 piperidyl), 1.71 (m, 1H, H_5 piperidyl), 2.38 (m, 1H, H_4 piperidyl), 2.71 (m, 2H, H_2 and H_6 piperidyl), 2.83 (m, 4H, CH_2-CH_2-indole), 3.06−3.17 (m, 4H, CH_2 βTrp, H_1 and H_6 piperidyl), 4.77 (m, 1H, CH αTrp), 6.74−6.85 (m, 3H, H_5 indole, H_5 and H_6 Trp), 6.91 (d, 1H, $J = 2$ Hz, H_2 Trp), 6.95−7.02 (m, 7H, CHar phenyl, H_2 and H_6 indole), 7.26 (d, 2H, $J_o = 8$ Hz, H_7 indole and H_7 Trp), 7.43 (m, 2H, H_4 indole and H_4 Trp), 8.20 and 8.52 (2 m, 2H, NH piperidyl TFA salt), 8.64 (d, 1H, $J = 8$ Hz, NH amide), 10.71 (s, 2H, NH indole and NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 23.4 (CH_2-CH_2-indole), 25.3 (C_3 and C_5 piperidyl), 26.3 (CH_2-CH_2-indole), 30.2 (C βTrp), 38.6 (C_4 piperidyl), 42.8 (C_2 and C_6 piperidyl), 46.0 (C αTrp), 110.1 (C_3 Trp), 111.7 (C_7 indole and C_7 Trp), 113.3 (C_3 indole), 118.2 (C_4 indole and C_4 Trp), 118.6 (C_5 indole and C_5 Trp), 121.2 (C_6 indole), 121.3 (C_6 Trp), 122.8 (C_2 Trp), 124.3 (C_2 indole), 127.1 (C_9 indole), 127.4 (C_9 Trp), 127.7 (C_4 phenyl), 129.9 (C_2, C_3, C_5, and C_6 phenyl), 133.5 (C_1 phenyl), 136.6 (C_8 indole), 136.4 (C_8 Trp), 154.3 (Cq triazole), 155.6 (Cq triazole), 172.9 (CO amide).

(*R,S*)-*N*-((*R*)-1-(5-((1*H*-Indol-3-yl)methyl)-4-(4-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)piperazine-2-carboxamide Trifluoroacetate Salt (52). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 2.18 (m, 2H, NH piperazinyl), 2.96 (m, 6H, H_2, H_5, and H_6 piperazinyl), 3.34 (d, 2H, J = 7 Hz, CH_2 βTrp), 3.57 (m, 4H, CH_2−CH_2−indole), 3.61 (s, 3H, OMe), 3.64 (m, 1H, H_3 piperazinyl), 4.82 (m, 2H, CH_2 *p*-methoxybenzyl), 5.40 (m, 1H, CH αTrp), 6.45 (d, 2H, J_o = 8 Hz, H_3 and H_5 *p*-methoxybenzyl), 6.51 (d, 2H, J_o = 8 Hz, H_2 and H_6 *p*-methoxybenzyl), 6.65−7.47 (m, 10H, CHar, indole and indole Trp), 8.95 (m, 1H, NH amide), 10.88 (d, 1H, J = 2 Hz, NH indole), 10.91 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 22.5 (CH_2−*C*H_2−indole), 25.6 (*C*H_2−CH_2−indole), 31.3 (C βTrp), 41.9 (CH_2−*p*-methoxybenzyl), 47.7 (C αTrp, C_5 and C_6 piperazinyl), 55.5 (OCH_3 and C_2 piperazinyl), 61.1 (C_3 piperazinyl), 109.3 (C_3 Trp), 111.7 (C_7 indole and C_7 Trp), 114.0 (C_3 indole), 114.3 (C_3 and C_5 *p*-methoxybenzyl), 118.6 (C_4 indole), 118.7 (C_4 Trp), 118.9 (C_5 indole and C_5 Trp), 121.4 (C_6 indole), 121.5 (C_6 Trp), 123.9 (C_2 indole and C_2 Trp), 127.0 (C_9 indole), 127.2 (C_9 Trp), 127.7 (C_1 *p*-methoxybenzyl), 128.1 (C_2 and C_6 *p*-methoxybenzyl), 136.3 (C_8 Trp), 136.5 (C_8 indole), 155.5 (2Cq triazole), 162.2 (C_4 *p*-methoxybenzyl), 171.1 (CO amide).

(*R,S*)-*N*-((*R*)-1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(2,4-dimethoxybenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)piperazine-2-carboxamide Trifluoroacetate Salt (54). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 2.95 (m, 6H, H_2, H_5, and H_6 piperazinyl), 3.32 (m, 4H, CH_2 βTrp and NH piperazinyl), 3.62 (m, 10H, CH_2−CH_2−indole and OCH_3), 4.07 (m, 1H, H_3 piperazinyl), 4.84 (m, 2H, CH_2−*o,p*-dimethoxyphenyl), 5.16 (m, 1H, CH αTrp), 6.00−6.53 (m, 3H, CHar *o,p*-dimethoxyphenyl), 6.84−7.30 (m, 11H, CHar indole, CHar indole Trp and NH amide), 10.75 (s, 1H, NH indole), 10.79 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 22.9 (CH_2−*C*H_2−indole), 25.8 (*C*H_2−CH_2-indole), 29.8 (C βTrp), 41.2 (CH_2−*o,p*-dimethoxyphenyl), 47.7 (C αTrp, C_5 and C_6 piperazinyl), 55.6 (OCH_3 and C_2 piperazinyl), 58.4 (C_3 piperazinyl), 99.0 (C_3 *o,p*-dimethoxyphenyl), 105.0 (C_5 *o,p*-dimethoxyphenyl), 109.6 (C_3 Trp), 111.8 (C_7 indole and C_7 Trp), 113.4 (C_3 indole), 115.3 (C_1 *o,p*-dimethoxyphenyl), 118.2 (C_4 indole), 118.4 (C_4 Trp), 118.6 (C_5 indole), 118.8 (C_5 Trp), 121.4 (C_6 indole and C_6 Trp), 123.9 (C_2 indole and C_2 Trp), 127.2 (C_9 indole and C_9 Trp), 127.9 (C_6 *o,p*-dimethoxyphenyl), 136.5 (C_8 Trp), 136.6 (C_8 indole), 154.6 (Cq triazole), 154.8 (Cq triazole), 155.0 (CO amide), 157.6 (C_2 *o,p*-dimethoxyphenyl), 160.8 (C_4 *o,p*-dimethoxyphenyl).

***N*-((*R*)-1-(4-(4-Methoxybenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)tetrahydro-2*H*-pyran-4-carboxamide Trifluoroacetate Salt (57).** ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ 1.20 (m, 1H, H_5 tetrahydropyranyl), 1.30 (m, 3H, H_3 and H_5 tetrahydropyranyl), 2.17 (m, 1H, H_4 tetrahydropyranyl), 2.82 (m, 4H, CH_2−CH_2−phenyl), 3.16 (m, 2H, H_2 and H_6 tetrahydropyranyl), 3.31 (dd, 1H, J = 14 and 8 Hz, CH_2 βTrp), 3.35 (dd, 1H, J = 14 and 7 Hz, CH_2 βTrp), 3.66 (s, 3H, OCH_3), 3.72 (m, 2H, H_2 and H_6 tetrahydropyranyl), 5.08 (m, 2H, CH_2 *p*-methoxyphenyl), 5.26 (m, 1H, CH αTrp), 6.73 (s, 4H, CHar *p*-methoxyphenyl), 6.87 (t, 1H, J_o = 8 Hz, H_5 Trp), 7.02 (m, 2H, H_2 and H_6 Trp), 7.07 (d, 2H, J_o = 7 Hz, H_2 and H_6 phenyl), 7.18 (m, 3H, H_3, H_4, and H_5 phenyl), 7.30 (m, 2H, H_4 and H_7 Trp), 8.52 (d, 1H, J = 8 Hz, NH amide), 10.77 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 26.3 (*C*H_2−CH_2−phenyl), 28.8 (C_3 and C_5 tetrahydropyranyl), 29.2 (C βTrp), 32.2 (CH_2−*C*H_2−phenyl), 40.7 (C_4 tetrahydropyranyl), 44.8 (C αTrp), 45.9 (CH_2 *p*-methoxyphenyl), 55.5 (OCH_3), 66.6 (C_2 and C_6 tetrahydropyranyl), 109.8 (C_3 Trp), 111.7 (C_7 Trp), 114.5 (C_3 and C_5 *p*-methoxyphenyl), 118.4 (C_4 Trp), 118.7 (C_5 Trp), 121.3 (C_6 Trp), 124.5 (C_2 Trp), 126.7 (C_4 phenyl), 127.2 (C_9 Trp), 127.5 (C_1 *p*-methoxyphenyl), 128.8 (C_2 and C_6 phenyl), 128.7 (C_3 and C_5 phenyl), 127.9 (C_2 and C_6 *p*-methoxyphenyl), 136.4 (C_8 Trp), 140.4 (C_1 phenyl), 154.7 (Cq triazole), 155.7 (Cq triazole), 159.2 (C_4 *p*-methoxyphenyl), 174.2 (CO amide).

In Vitro Determination of the Binding Affinities for the Human GHS-R1a. Transient Transfection of LLC PK-1 Cells and Membrane Preparation: LLC PK-1 cells were grown at 37 °C, 5% CO_2 in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% FCS (v/v), glutamine (2 mM), and antibiotics (50 units/mL penicillin and 50 μg/mL streptomycin).

LLC PK-1 cells were transiently transfected with 1 μg of hGHS-R1a using electroporation (Easyject Optima apparatus, Equibio) according to the manufacturer's protocol (Equibio). Electroporation was carried out at room temperature according to the manufacturer's instructions with the following parameters: 250 V, 1500 μF, and infinite internal resistance. Transfected cells were plated in 10 cm culture dishes containing complete growth medium without phenol red. Approximately 48 h after transfection, cells were washed three times with phosphate-buffered saline, pH 6.95, once with 10 mL of homogenization buffer (HB) containing 50 mM Tris (pH 7.3), 5 mM $MgCl_2$, 2.5 mM EDTA, and 30 μg/mL bacitracin and were then collected by scrapping. The cells underwent two cycles of freeze−thawing and were then centrifuged at 10000*g* for 20 min at 4 °C. The membrane pellet was resuspended in a minimal volume of HB, aliquoted, and stored at −80 °C until use. Membrane protein concentrations were determined by the Bradford method using the Bio-Rad protein assay kit.

Receptor Binding Studies. Isolated plasma membranes from LLC PK-1 cells (10 μg of protein) were incubated in HB for 60 min at 25 °C (steady-state conditions) with 60 pM ^{125}I-His^9-ghrelin (Amersham) in the presence or absence of competing compounds. Nonspecific binding was defined using an excess (1 μM) of ghrelin. The binding reaction was stopped by addition of 4 mL of ice-cold HB followed by rapid filtration over Whatman GF/C filters presoaked with 0.5% polyethyleneimine to prevent excessive binding of radioligand to the filters. Filters were rinsed three times with 3 mL of ice-cold wash buffer (50 mM Tris (pH 7.3), 10 mM $MgCl_2$, 2.5 mM EDTA, and 0.015% (w/v) X-100 Triton), and the radioactivity bound to membranes was measured in a γ counter.

Intracellular Calcium Mobilization Assay. The calcium experiments were performed using the benchtop scanning fluorometer FlexStation II machine (Pharmacologie & Screening Plateform of the Institut Fédératif de Recherche 3, Montpellier, France).

CHO cells were transiently transfected with the hGHS-1a receptor, using electroporation, and were then plated into 96-well black-bottom plates (80 000 cells/well). Twenty-four hours later, the cells were washed with 150 μL of buffer A (Hank's balanced salt solution, 0.5% BSA, 20 mM $CaCl_2$, 2.5 mM probenecid, pH 7.4) and were then loaded with 1 μM fluorescent calcium indicator Fluo-4AM prepared in buffer A, containing 0.06% pluronic acid (a mild-ionic detergent that facilitates Fluo-4AM ester loading). The cells were left to incubate for 1 h in the dark at 37 °C.

Following the incubation, excess Fluo-4AM was removed from the cells by washing twice with 100 μL of buffer A, and 50 μL of the same buffer was then added to each well. The cells were left at room temperature for 30 min to allow complete de-esterification of intracellular Fluo-4AM esters. The black-bottom plate containing the cells and the plate containing the compounds to be tested were then placed into the temperature-regulated FlexStation machine.

The machine records the fluorescence output over a period of 60 s, with the compounds being automatically distributed into the wells containing the cells after 15 s. The Fluo-4AM exhibits a large fluorescence intensity increase on binding of calcium, and therefore, the fluorescence output is used directly as a measure of intracellular calcium mobilization. The excitation and emission wavelengths were 485 and 525 nm, respectively. The basal fluorescence intensity of dye-loaded cells was 800−1200 arbitrary units, and the fluorescence peak upon maximal response was 5000−7000 units.

To assess the ability of each of the compounds to induce calcium mobilization, they were tested at 10 μM in triplicate in at least two independent experiments. In each case, the change in fluorescence upon addition of the compound was compared with the basal fluorescence output measured with the control (addition of buffer A only). The maximum fluorescent output was equivalent to that achieved when the cells where stimulated with 0.1 μM ghrelin.

For the compounds behaving as agonists and displaying a high affinity binding for hGHS-R1a in radiolabeled binding experiments, the EC_{50} (the molar concentration of the agonist producing 50% of

the maximal possible effect of that agonist) was determined using a dose-response curve.

In the case of high-affinity antagonists, the IC_{50} and K_b were determined using antagonist inhibition curves in the presence of 0.1 μM ghrelin (submaximal concentration). The IC_{50} was calculated as the molar concentration of antagonist that reduced the maximal response of ghrelin by 50%, and an estimation of the K_b was made using the Cheng−Prusoff Equation. Schild analysis was also used to determine the EC_{50} of ghrelin in the presence of different concentrations of antagonist, and from this the pA_2 and the exact K_b were determined.

In Vivo Experiments in the Rat. Animals. Male 10-day-old Sprague-Dawley rats weighing about 25 g (Charles River, Calco, Italy) were used. Rats pups were received on the fifth day after birth and were housed in our facilities under controlled conditions (22 ± 2 °C, 65% humidity and artificial light from 06.00 to 20.00 h). A standard dry diet and water were available ad libitum to the dams. One hour before the experiments, pups were separated from their respective dams and were divided randomly into groups of eight each. All the experiments were performed in accordance with the Italian Guidelines for the Use of Animals in Medical Research.

Growth Hormone Assay. Pups were acutely challenged with solvent (DMSO, final dilution 1:300), hexarelin (80 μg/kg sc), or new compounds (160 μg/kg sc). For combined treatments (test compounds plus hexarelin), test compounds were administered 10 min before hexarelin. Pups were killed by decapitation 15 min later. Trunk blood was collected and centrifuged immediately. Plasma samples were stored at −20 °C until assayed for the determination of plasma GH concentrations. GH was assayed in plasma using a commercial rat GH enzyme immunoassay kit (Spibio, Montigny le Bretonneux, France). Values are expressed in terms of NIDDK-rat-GH-RP-2 standard (potency 2 IU/mg) as ng/mL plasma. The minimum detectable value of rat GH was about 1.0 ng/mL, and intra-assay variability was about 6%.

Experiments on Food Intake. Young-adult male Sprague-Dawley rats (Charles River Laboratories, Calco, Italy) weighing 125−150 g were used. All rats were housed in single cages under controlled conditions (22 ± 2 °C, 65% humidity, artificial light from 08.00 to 20.00 h) with ad libitum access to standard rat chow and water. Rats had 1 week of acclimation in individual home cages and animal room conditions. The following week, they were trained daily to mimic the experimental procedure. At the end of training, rats were administered sc (around 10.00−11.00 a.m.) with graded doses of the compounds to test (0, 20, 80, 160, 320 μg/kg) at time −10 min and with hexarelin (80 μg/kg) at time 0 to stimulate the feeding behavior. Immediately after, the animals were returned to their home cages, which contained a known amount of standard rat chow and ad libitum water. The remaining food was carefully collected and weighed to the nearest 0.1 g every hour for the following 6 h. Food intake was normalized for the body weight of the animals and expressed as grams of food eaten for 100 g of body weight.

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Supporting Information Available: RP HPLC chromatogramme tracings of compounds **4**, **16**, **17**, **35**, **39**−**41**, and **52**; displacement curves of ^{125}I-His^9-ghrelin for compounds **18**−**20**, **26**, **27**, **31**, **39**−**43**, **47**, **52**, and **55**; $[Ca^{2+}]_i$ accumulation curves in the presence of increasing concentration of agonists **26**, **27**, **29**, **41**−**43**, **47**, **52**, and **55**; inhibition curves of ghrelin-induced $[Ca^{2+}]_i$ accumulation by compounds **18**−**20**; Schild plots for compounds **16**, **18**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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