Synthesis and Pharmacological in Vitro and in Vivo Evaluations of Novel Triazole Derivatives as Ligands of the Ghrelin Receptor. 1

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A new series of growth hormone secretagogue (GHS) analogues based on the 1,2,4-triazole structure were synthesized and evaluated for their in vitro binding and their ability to stimulate intracellular calcium release to the cloned *h*GHS-1a ghrelin receptor expressed in LLC PK-1 cells. We have synthesized potent ligands of this receptor, some of them behaving as agonists, partial agonists, or antagonists. Some compounds among the most potent, i.e., agonist **29c** (JMV2873), partial agonists including **21b** (JMV2810), antagonists **19b** (JMV2866) and **19c** (JMV2844), were evaluated for their in vivo activity on food intake, after sc injection in rodents. Some compounds were found to stimulate food intake like hexarelin; some others were identified as potent hexarelin antagonists in this assay. Among the tested compounds, **21b** was identified as an in vitro ghrelin receptor partial agonist, as well as a potent in vivo antagonist of hexarelin-stimulated food intake in rodents. Compound **21b** was without effect on GH release from rat. However, in this series of compounds, it was not possible to find a clear correlation between in vitro and in vivo results.

Introduction

Growth hormone (GH) is an important endocrine regulator of growth and anabolic processes.[1] The use of recombinant human GH is beneficial in the treatment of GH-deficient children[2] and has been shown to reverse some of the effects of aging in the elderly.[3] In recent years, the GH releasing peptides (GHRPs) and peptidomimetics have received considerable attention as potential alternatives to the expensive recombinant human GH. During their studies on enkephalin analogues Bowers et al. discovered a series of peptides able to stimulate GH release from rat pituitary, and in doing so, they opened a new avenue for research.[4] This new family of peptides[5] including GHRP-6, GHRP-1, GHRP-2, and hexarelin promotes the release of GH in humans. This GH releasing mechanism was found to be different from that of the endogenous growth hormone releasing hormone (GHRH)[6] and to be mediated through a G-protein coupled receptor named growth hormone secretagogue receptor type1a (GHS-R1a).[7] The natural ligand for this receptor, named ghrelin, has been isolated and recently characterized from rat stomach[8] and further identified in humans.[9] It is constituted of a 28 amino acid peptide in which serine in position 3 is n-octanoylated. Several classes of small nonpeptide molecule secretagogues (benzolactam biphenyl tetrazoles,[10] camphor derivatives,[11] and 4-spiropiperidines[12]) have been described and are able to release GH from the pituitary. Various peptide molecules, based on the GHRP-6 sequence, have been reported as potent GHRPs. Starting from a tripeptide EP-51389, Aib-(D)-2-Me-Trp-(D)-2-Me-Trp-NH_2,[13] we recently described a new potent growth hormone secretagogue, namely, JMV1843[14] (EP-1572),[15] which is orally active in humans. As JMV1843 is a peptide derivative, we wanted to limit the inherent flexibilities of the peptide backbone and side chains. For this purpose we decided to introduce a cyclic structure as scaffold bearing the three major pharmacophores contained in JMV1843: a basic amino group (in our case included in an amino-isobutyric acid residue) and two hydrophobic regions (indole rings). Several cyclic scaffolds were tested such as piperazines, keto-piperazines, piperidines, and triazinones (unpublished results). 1,2,4-Triazoles were found to be the best templates. In this paper, we report on the identification of a new series of potent nonpeptide analogues that acted as ghrelin receptor ligands and exhibited agonist, partial agonist, or antagonist properties.

1,2,4-Triazoles have gained considerable interest among medicinal chemists because they display a wide range of antifungal[16] and antibacterial[17] activities. This moiety was also found in a series of potent agonist or antagonist G-protein coupled receptor ligands.[18−21] 1,2,4-Triazole derivatives have been used as mimics[20−23] or isosteres[24,25] of the amide bond in an attempt to increase the bioavailability of the parent bioactive molecules. They have also been incorporated into peptides to surrogate cis amide bonds.[26]

Chemistry

Triazole derivatives were synthesized in five steps as shown in Scheme 1, starting from Boc−(D)-Trp−OH. After coupling to an amine, the formed amide **1** was transformed into the thioamide **2** using Lawesson's reagent. The obtained thioamide **2** was then treated with 2.0 equiv of hydrazide and 1.1 equiv of mercury(II) acetate in THF, according to Hitotsuyanagi et al.[27] to obtain the cyclized triazole derivatives.[28] Completion of this step was monitored by reversed-phase HPLC, which showed that cyclization into triazoles **3** was achieved within 2

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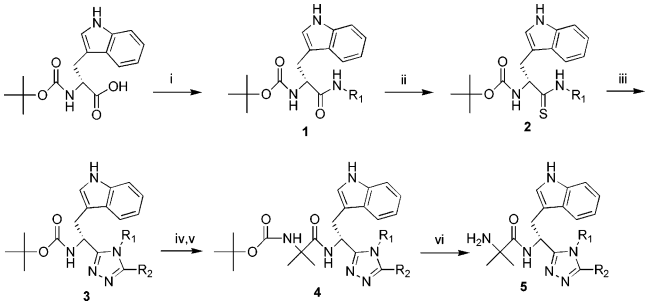
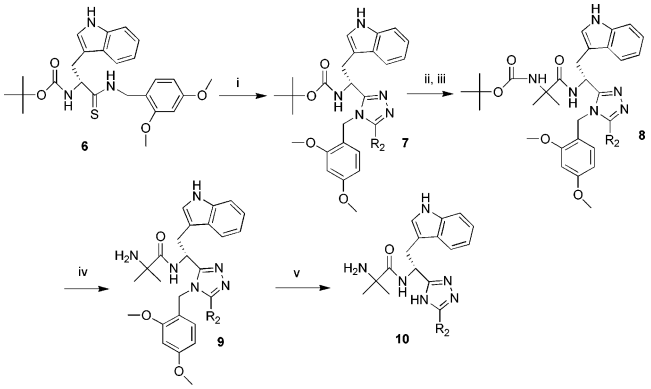
Scheme 1. General Synthetic Scheme for the Synthesis of 3,4,5-Trisubstituted 1,2,4-Triazoles[a]



[a] (i) BOP, H_2N-R_1, NMM, DCM; (ii) Lawesson's Reagent, DME, 85 °C; (iii) $H_2N-HN-COR_2$, $Hg(OAc)_2$, room temperature, THF; (iv) HCl, AcOEt; (v) Boc−Aib−OH, BOP, DIPEA, DCM; (vi) HCl, AcOEt.

Scheme 2. General Synthetic Scheme for the Synthesis of 3,5-Disubstituted 1,2,4-Triazoles[a]



[a] (i) $H_2N-HN-COR_2$, $Hg(OAc)_2$, room temperature, THF; (ii) HCl, AcOEt; (iii) Boc−Aib−OH, BOP, DIPEA, DCM; (iv) HCl, AcOEt; (v) TFA, DCM.

days. Compounds were purified by silica gel column chromatography. Removing of the Boc protecting group by 4 M HCl in AcOEt and coupling with Boc−Aib−OH in the presence of BOP[a29] and NMM in DCM produced the N-protected desired compounds **4**. The final compounds **5** were obtained after 4 M HCl in AcOEt.

When R_1 was a hydrogen atom, formation of the triazole moiety was not observed. Careful examination of LC/MS spectra revealed the presence of the corresponding nitrile derivative. This "desulfuration" of nonsubstituted thioamides already described on simple aliphatic and aromatic primary thioamides[30] illustrates that this synthetic pathway was not suitable for the preparation of 3,5-disubstituted 1,2,4-triazoles. We therefore decided to introduce a protecting group on the primary amide function that could be cleaved after formation of the desired triazole moiety (Scheme 2). For this purpose, 2,4-dimethoxybenzylamine was chosen as a protecting group that did not interfere with the formation of the triazole moiety **7**. After completion of the synthesis compounds **9** and **10** were obtained, substituted or not in position 4 of the triazole moiety.

A set of six initial compounds (**11**−**16**, Figure 1) were synthesized as depicted in Schemes 1 and 2, all bearing an indole group in position 5 of the triazole cycle with one or two carbon atoms between the indole and the triazole.

[a] Abbreviations: BOP, (benzotriazol-1-yloxy)-tris(dimethylamino)-phosphonium hexafluorophosphate; DME, ethylene glycol dimethyl ether; DCM, dichloromethane; NMM, *N*-methyl-morpholine. Other abbreviations used were those recommended by the IUPAC-IUB Commission [*Eur. J. Biochem.* **1984**, *138*, 9−37].

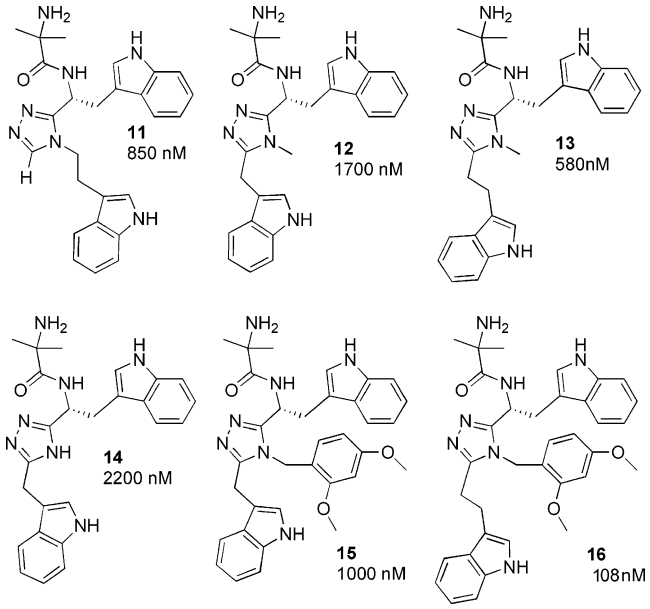


Figure 1. Structure and IC_{50} of the first synthesized triazoles.

Results and Discussion

Compounds **11**−**16** were tested for their ability to displace $^{125}I-His^9-$ghrelin from the cloned *h*GHS-1a receptor transiently expressed in LLC PK-1 cells. Their binding affinities were found in the micromolar range. Interestingly, comparison between compounds **12**, **13**, **14**, and **15**, respectively, showed that a two-carbon chain bearing the indole group in position 5 was well accepted by the ghrelin receptor. Substitution of the nitrogen at position 4 also had a beneficial effect (i.e., compound **16**, IC_{50} 108 nM) (Figure 1). According to the observations that affinity for the ghrelin receptor could be modulated by substitutions at the position 4 and 5 of the triazole moiety, several compounds were synthesized to explore R_1 and R_2. Various aryl and/or alkyl groups were introduced in positions 4 and 5 (R_1 and R_2 groups). These compounds were synthesized according to Schemes 1 and 2. The synthesized compounds were tested for their ability to displace $^{125}I-His^9-$ghrelin from the cloned *h*GHS-1a receptor transiently expressed in LLC PK-1 cells. Binding affinities of human ghrelin and MK-0677 obtained with this model were in accordance with the literature. Their biological in vitro activity was then evaluated on $[Ca^{2+}]_i$ mobilization in GHS-R1a at a concentration of 10^{-5} M of each compound and 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.

The results of their biological activity at the GHS-1a receptor are reported in Table 1. R_1 aromatic groups in position 4 of the triazole moiety were generally well tolerated for interaction with the GHS-1a receptor. As shown for compounds **16**−**20**, methoxy substitutions on the aromatic moiety led to potent ghrelin receptor ligands, the best compounds in this series bearing a 4-methoxybenzyl (**19b**, IC_{50} 11 ± 4 nM; **19c**, IC_{50} 6 ± 3 nM) or a 3-methoxybenzyl group (**18a**, IC_{50} 18 ± 5 nM; **18b**, IC_{50} 22 ± 4 nM) (Table 1). 2-Methoxybenzyl and dimethoxybenzyl substitution at position 4 of the triazole moiety led to derivatives presenting less affinity for the GHS-R1a compared to that of the corresponding 3- or 4-methoxy derivatives (Table 1). We then introduced various benzyl groups in position 4 of the triazole moiety. Bromide-, fluoride-, and chloride-substituted benzyl derivatives yielded less potent ligands for the GHS-1a receptor (compounds **22a**−**c**, **23a**−**c**, and **24a**−**c**). Electron-

Table 1. Binding Affinities and Biological Activities of Compounds of General Formula **5** in Scheme 1

compds	R_1	R_2	binding IC_{50} (nM)[a]	% of max $[Ca^{2+}]i$ response at 10 μM[b]	biological activity (nM)
16	2,4-dimethoxybenzyl	1*H*-indole-3-yl-ethyl	108 ± 17	0	antagonist; K_b, 14 ± 2
16a	2,4-dimethoxybenzyl	benzyl	560 ± 130	0	antagonist
16b	2,4-dimethoxybenzyl	1*H*-indole-3-yl-propyl	750 ± 100	27 ± 1	partial agonist
16c	2,4-dimethoxybenzyl	phenethyl	60 ± 10	0	antagonist; K_b, 17 ± 7
17a	3,5-dimethoxybenzyl	1*H*-indole-3-yl-ethyl	150 ± 31	22 ± 1	partial agonist
17b	3,5-dimethoxybenzyl	phenethyl	>1000	0	antagonist
17c	3,5-dimethoxybenzyl	benzyl	110 ± 30	29 ± 1	partial agonist
18a	3-methoxybenzyl	1*H*-indole-3-yl-ethyl	**18 ± 5**	63 ± 13	partial agonist; EC_{50}, 4 ± 1
18b	3-methoxybenzyl	1*H*-indole-3-yl-propyl	22 ± 4	66 ± 11	partial agonist; EC_{50}, 18 ± 3
18c	3-methoxybenzyl	phenethyl	78 ± 15	82 ± 31	partial agonist; EC_{50}, 45 ± 6
18d	3-methoxybenzyl	benzyl	120 ± 20	50 ± 18	partial agonist
19a	4-methoxybenzyl	1*H*-indole-3-yl-methyl	660 ± 40	0	antagonist
19b	4-methoxybenzyl	phenethyl	11 ± 4	0	antagonist; K_b, 5 ± 1
19c	4-methoxybenzyl	1*H*-indole-3-yl-ethyl	6 ± 3	0	antagonist; K_b, 4 ± 1
19d	4-methoxybenzyl	phenylpropyl	12 ± 3	0	antagonist; K_b, 14 ± 4
19e	4-methoxybenzyl	benzyl	121 ± 33	0	antagonist
19f	4-methoxybenzyl	1*H*-indole-3-yl-propyl	145 ± 30	0	antagonist; K_b, 12 ± 0.2
20a	2-methoxybenzyl	benzyl	410 ± 110	66	partial agonist
20b	2-methoxybenzyl	1*H*-indole-3-yl-ethyl	96 ± 13	50	partial agonist
20c	2-methoxybenzyl	phenethyl	56 ± 18	80 ± 25	partial agonist; EC_{50}, 98 ± 17
21a	benzyl	1*H*-indole-3-yl-ethyl	**15 ± 5**	73 ± 13	partial agonist, EC_{50}, 64 ± 14
21b	benzyl	1*H*-indole-3-yl-propyl	33 ± 7	30 ± 4	partial agonist; EC_{50}, 49 ± 14
21c	benzyl	benzyl	500 ± 70	44 ± 10	partial agonist
22a	4-bromobenzyl	1*H*-indole-3-yl-ethyl	100 ± 30	27 ± 13	partial agonist
22b	4-bromobenzyl	1*H*-indole-3-yl-propyl	150 ± 30	25 ± 9	partial agonist
22c	4-bromobenzyl	benzyl	440 ± 50	16 ± 5	partial agonist
23a	4-fluorobenzyl	1*H*-indole-3-yl-ethyl	66 ± 11	59 ± 16	partial agonist; EC_{50}, 210 ± 40
23b	4-fluorobenzyl	benzyl	170 ± 60	60 ± 3	partial agonist
23c	4-fluorobenzyl	phenethyl	400 ± 130	20 ± 9	partial agonist
24a	3,4-dichlorobenzyl	1*H*-indole-3-yl-ethyl	55 ± 8	28 ± 1	partial agonist
24b	3,4-dichlorobenzyl	benzyl	520 ± 50	64 ± 12	partial agonist
24c	3,4-dichlorobenzyl	phenethyl	640 ± 10	53 ± 9	partial agonist
25a	phenethyl	1*H*-indole-3-yl-ethyl	80 ± 10	25 ± 6	partial agonist
25b	phenethyl	1*H*-indole-3-yl-methyl	300 ± 60	88 ± 30	partial agonist
25c	phenethyl	1*H*-indole-3-yl-propyl	11 ± 4	18 ± 3	partial agonist; EC_{50}, 15 ± 2
25d	phenethyl	benzyl	>1000	85 ± 26	partial agonist
25e	phenethyl	phenethyl	310 ± 30	63 ± 13	partial agonist
26a	2,2-diphenylethyl	benzyl	>1000	60 ± 20	partial agonist
26b	2,2-diphenylethyl	1*H*-indole-3-yl-ethyl	640 ± 250	62 ± 7	partial agonist
27a	(naphtalen-1-yl)methyl	benzyl	220 ± 30	78 ± 26	partial agonist
27b	(naphtalen-1-yl)methyl	1*H*-indole-3-yl-propyl	140 ± 3	62 ± 2	partial agonist
27c	(naphtalen-1-yl)methyl	1*H*-indole-3-yl-ethyl	125 ± 50	54 ± 1	partial agonist
27d	(naphtalen-1-yl)methyl	phenethyl	130 ± 1	40 ± 12	partial agonist
28a	*n*-hexyl	benzyl	470 ± 40	67 ± 6	partial agonist
28b	*n*-hexyl	1*H*-indole-3-yl-ethyl	195 ± 35	62 ± 33	partial agonist
28c	*n*-hexyl	1*H*-indole-3-yl-propyl	240 ± 50	32 ± 3	partial agonist
29a	1*H*-indole-3-yl-ethyl	benzyl	700 ± 120	95 ± 9	agonist
29b	1*H*-indole-3-yl-ethyl	1*H*-indole-3-yl-ethyl	150 ± 5	82 ± 17	partial agonist
29c	1*H*-indole-3-yl-ethyl	1*H*-indole-3-yl-propyl	14 ± 2	85 ± 22	agonist; EC_{50}, 140 ± 30
30a	4-methylbenzyl	phenylpropyl	21 ± 2	16 ± 3	partial agonist; EC_{50}, 12 ± 0.7
30b	4-methylbenzyl	benzyl	840 ± 220	28 ± 4	partial agonist
30c	4-methylbenzyl	1*H*-indole-3-yl-ethyl	28 ± 5	69 ± 6	partial agonist; EC_{50}, 630 ± 190
30d	4-methylbenzyl	phenethyl	140 ± 30	19 ± 15	partial agonist
31	4-ethylbenzyl	phenethyl	44 ± 17	26 ± 5	partial agonist; EC_{50}, 11 ± 5
32	4-nitrobenzyl	phenethyl	>1000	10 ± 4	weak agonist
33a	(pyridin-2-yl)methyl	benzyl	>1000	78 ± 3	partial agonist
33b	(pyridin-2-yl)methyl	phenethyl	>1000	59 ± 20	partial agonist
34	4-methoxyphenethyl	phenethyl	550 ± 50	82 ± 40	partial agonist
35	(thiophen-2-yl)methyl	phenethyl	570 ± 40	91 ± 9	agonist
36	(furan-2-yl)methyl	phenethyl	420 ± 100	97 ± 6	agonist; EC_{50}, 23 ± 2
37	phenyl	1*H*-indole-3-yl-ethyl	140 ± 20	91 ± 4	agonist; EC_{50}, 41 ± 3

[a] Inhibition of $^{125}I-His^9-$ghrelin binding to membranes from *h*GHS-R1a transfected LLC cells. [b] Maximum calcium flux activity is reported relative to ghrelin at 0.1 μM.

withdrawing groups such as 4-nitro or electron-donating groups such as 4-methyl or 4-ethyl on the benzyl ring were also introduced in position 4 of the triazole moiety. It clearly appeared that electron-withdrawing groups were not tolerated at this position of the molecule (compound **32**), while electron-donating groups were privileged (**30a**−**d**, **31**). The significance of the length of the carbon chain between the triazole and the phenyl rings was studied. Phenyl, benzyl, and phenethyl groups were introduced as R_1 substituents (**37**, **21a**, and **25a**). The benzyl group led to the compounds that exhibited the better affinity for the GHS-1a receptor. Naphtalen-1-yl-methyl and 2,2-diphenylethyl groups (**26a**,**b**, **27a**−**d**) were introduced. The affinity of the obtained compounds was lower than that of the benzyl-containing derivatives. Pyridin-2-yl-methyl, thiophen-2-yl-methyl, and furan-2-yl-methyl substituents led to compounds (**33a**,**b**, **35**, and **36**) of low affinity for the GHS-1a

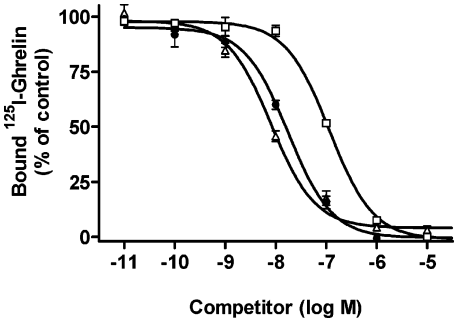


Figure 2. Ability of compounds **16** (□), **19b** (△), or **25c** (●) to inhibit binding of ^{125}I−His^{9}−ghrelin to membranes from *h*GHS-R1a-transfected LLC cells. Results are expressed as the percentage of radioactivity bound in the absence of added nonradioactive compounds. In each experiment, each value was determined in triplicate, and the results given are means from at least three separate experiments. Nonspecific binding was determined in the presence of 10 μM ghrelin and was always less than 20% of total binding.

receptor. An indole group was also introduced at position 4 (**29a** and **29b**) without improving the affinity for the ghrelin receptor. A three-carbon chain bearing the indole group in position 5 of the triazole yielded compound **29c** with an improved binding affinity when compared with that of compound **29b**. Introducing a lipophilic chain (compounds **28a**−**c**) at the 4 position of the indole moiety to mimic the octanoyl group of the natural ghrelin ligand led to compounds having less affinity.

In position 5 of the triazole moiety (R_2 group), six different phenyl and indole-derived substituents were explored linked to the triazole moiety by an aliphatic chain composed of one, two, or three carbon atoms. The best compounds were obtained with a two-carbon chain length (**18a**, **19b**, **19c**, **21a**, **30c**, **31**) (IC_{50} ranging from 6 ± 3 nM for compound **19c** to 44 ± 17 nM for compound **31**). In some derivatives, a three-carbon length chain was well tolerated yielding analogues (**16b**, **18b**, **19d**, **19f**, **21b**, **22b**, **25c**, **27b**, **28c**, **29c**, and **30a**) with IC_{50} ranging from 11 ± 4 for compound **25c** to 750 ± 100 nM for compound **16b** (Table 1). When triazole derivatives substituted by benzyl or 1*H*-indol-3-yl-methyl groups in position R_2 were compared, no precise rule could be defined in terms of structure−activity relationships. In some cases compounds having a benzyl group had a better affinity (**19e**, IC_{50} 121 ± 33 vs **19a**, IC_{50} 660 ± 40), in some others those having a 1*H*-indol-3-yl-methyl group exhibited better affinity for the GHS-1a receptor (**25b**, IC_{50} 300 ± 60 vs **25d**, IC_{50} > 1000 nM). In general, 1*H*-indole-3-yl-ethyl-containing compounds at the R_2 position were found better ligands than those with phenethyl moieties (**18a**, IC_{50} 18 ± 5 vs **18c**, IC_{50} 78 ± 15; **23a**, IC_{50} 66 ± 11 vs **23c**, IC_{50} 400 ± 130; **24a**, IC_{50} 55 ± 8 vs **24c**, IC_{50} 640 ± 10; **25a**, IC_{50} 80 ± 10 vs **25e**, IC_{50} 310 ± 30), although it was not always the case (**19b**, IC_{50} 11 ± 4 vs **19c**, IC_{50} 6 ± 3). However, when a three-carbon chain was placed between the triazole ring and the aromatic cycle, phenyl-containing compounds seemed to have slightly better affinity for the GHS-1a receptor (**19d**, IC_{50} 12 ± 3 vs **19f**, IC_{50} 145 ± 30). As examples of competition studies, displacement curves for compounds **16**, **19b**, and **25c** (Figure 2) are reported.

When tested for their ability to induce intracellular calcium release, most of the compounds containing a 4-methoxy group in R_1 position were not able to stimulate intracellular calcium levels (i.e., compounds **16**, **16a**, **16c**, **19a**−**f**). Compounds with a different substitution in the R_1 position were able to stimulate $[Ca^{2+}]_i$ accumulation, but a large majority were not fully efficacious, inducing only 16 ± 3% (for compound **30a**) to 88% (for compound **25b**) of the total response of ghrelin. The EC_{50} of the best ligands for the GHS-1a receptor of these partial agonists were determined (**18a**, 63% total response, EC_{50} 4 ± 1 nM, **18b**, 66% total response, 18 ± 3 nM, **25c**, 18% total response, 15 ± 2 nM, **30a**, 16% total response, 12 ± 0.7 nM) (Table 1). As an example, the dose−response curves of compounds **18a**, **18b**, and **30a** are reported (Figure 3). On the basis of these biological results, it was not possible to establish a clear structure−activity relationship for these partial agonists. Among the compounds that behaved as full agonists (i.e., **25b**, **25d**, **29a**−**c**, **35**, **36**, and **37**), only **29c** exhibited high affinity for the GHS-1a receptor (IC_{50} 14 ± 2) and moderate potency on $[Ca^{2+}]_i$ accumulation (EC_{50} 120 ± 30 nM). However, it is quite clear that the presence of a phenyl, 3-methoxybenzyl, 2-methoxybenzyl, 4-fluorobenzyl, phenethyl, 2,2-diphenylethyl, (naphtalen-1-yl)-methyl, *n*-hexyl, and 1*H*-indole-3-yl-ethyl group in the R_1 position was sufficient to generate derivatives with the best efficacy (particularly in the case of the 1*H*-indole-3-yl-ethyl group in the R_2 position). As an example, the dose−response curve for compound **29c** is reported in Figure 4. Some of the compounds that were synthesized were not able to promote $[Ca^{2+}]_i$ accumulation, although they were able to recognize the GHS-1a receptor. For all these compounds, the R_1 group was either a 4-methoxybenzyl or a 2,4-dimethoxybenzyl (i.e., **16**, **16a**, **16c**, **19a**−**f**) (Table 1). These compounds were able to antagonize the $[Ca^{2+}]_i$ accumulation induced by ghrelin. Compounds **16** (K_b 14 ± 2 nM), **19b** (K_b 5 ± 1 nM),

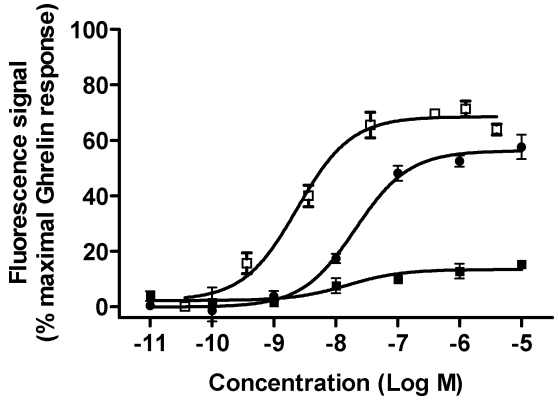


Figure 3. Effects of compounds **18a** (□), **18b** (●), and **30a** (■) on $[Ca^{2+}]_i$ accumulation in CHO cells expressing the *h*GHS-R1a. The results are expressed as the percentage of the fluorescence signal compared to the maximal response induced by 10 μM ghrelin. In each experiment, each value was determined in triplicate, and the results given are means from at least three separate experiments.

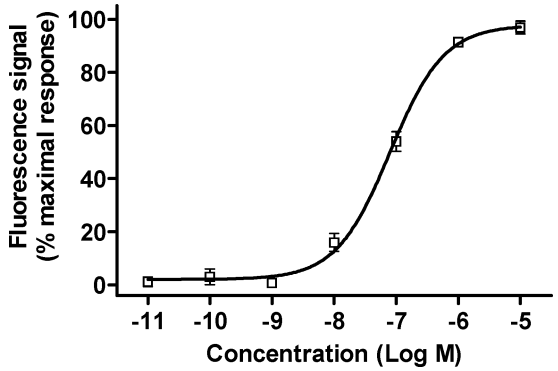


Figure 4. Effects of compound **29c** (□) on $[Ca^{2+}]_i$ accumulation in CHO cells expressing the *h*GHS-R1a. The results are expressed as the percentage of the fluorescence signal compared to the maximal response induced by 10 μM ghrelin. In each experiment, each value was determined in triplicate, and the results given are means from at least three separate experiments.

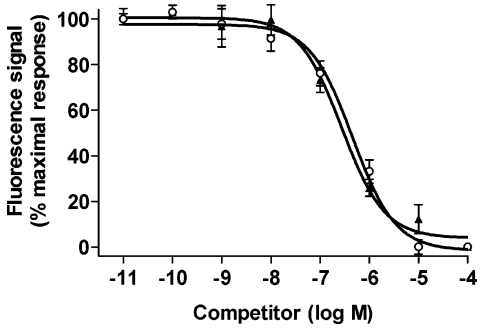


Figure 5. Ability of compounds **19c** (▲) and **19d** (○) to inhibit 0.1 μM ghrelin-induced $[Ca^{2+}]_i$ accumulation in CHO cells expressing the *h*GHS-R1a. Values are expressed as the percentage of the fluorescence signal induced by 10 μM ghrelin with no added antagonist. In each experiment, each value was determined in duplicate, and the results given are means from at least three separate experiments.

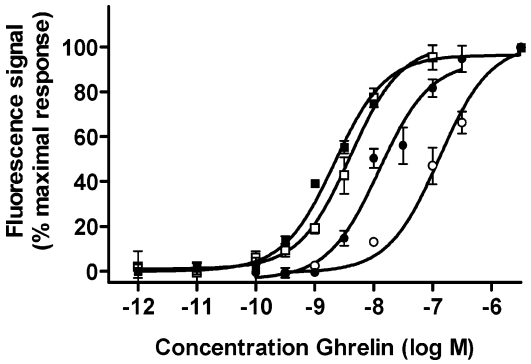


Figure 6. Effects of compound **19b** on ghrelin-induced $[Ca^{2+}]_i$ accumulation in CHO cells expressing the *h*GHS-R1a. Cells were incubated with various concentrations of ghrelin in the absence of compounds (■) or in the presence of indicated concentrations of compound **19b** at 10^{-8} (□), 10^{-7} (●), or 10^{-6} M (○). Values are expressed as the percentage of the fluorescence signal induced by 10 μM ghrelin with no added antagonist. In each experiment, each value was determined in duplicate, and the results given are means from at least three separate experiments.

19c (K_b 4 ± 1 nM), and **19d** (K_b 14 ± 4 nM) were among the most potent ghrelin receptor antagonists (Figure 5 for compounds **19c** and **19d**). They were able to antagonize dose dependently ghrelin-induced $[Ca^{2+}]_i$ accumulation in CHO cells transiently transfected with the GHS-R1a. Interestingly, in the presence of various concentrations of compounds **16**, **19b**, **19c**, or **19d**, the dose−response curves of ghrelin on $[Ca^{2+}]_i$ accumulation were shifted in a parallel manner indicating a competitive antagonism (see Figure 6 for compound **19b** as an example).

Some of the compounds were tested for their activity on food intake (Table 2). Each compound was sc injected (160 μg/kg) in the rat. We selected some agonist (**29c**), partial agonists (**18c**, **20c**, **21a**, **21b**, **24a**, **25c**, **29b**, **30c**), and antagonists (**16**, **19b**, **19c**, **19e**) compounds according to their in vitro activity on the GHS-1a receptor. Compound **29c** that has been reported to be an in vitro agonist at the GHS-R1a was unable to stimulate food intake when administered alone. However, when administered with hexarelin, cumulative food intake at 6 h was increased with a variation of about 50% when compared with that of hexarelin alone. As reported in Table 2, when administered alone, compounds **24a**, **25c**, and **30a** (all in vitro partial agonists) elicited a significant increase in cumulative food intake, while all other compounds were found without effect. When administered with hexarelin, all compounds, with the exception of compounds **21a** which was without any effect and as already reported compound **29c**, were able to inhibit hexarelin-induced food intake in the rat with different potencies that were not in accordance with their in vitro potency or efficacy. Unexpectedly, the most potent compound in this series (**21b**) for the inhibition of hexarelin-stimulated food intake was not the compound presenting the best affinity for the GHS-1a receptor (IC_{50} 33 ± 7 nM), nor was it found the most potent in vitro agonist (30 ± 4% of the maximal response on $[Ca^{2+}]_i$ accumulation, EC_{50} 49 ± 14 nM). There was no clear correlation between in vitro and in vivo results, some very potent partial agonists in recognizing the GHS-1a receptor having weak effects on food intake (i.e., **21a**), some potent partial agonist on $[Ca^{2+}]_i$ accumulation being potent antagonist of hexarelin-stimulated food intake (i.e., **20c**). A dose−response study for the most active compound (**21b**) that was able to antagonize the effects of hexarelin on food intake is reported in Table 3. A clear dose−effect could be found, compound **21b** being already active at the dose of 20 μg/kg.

Compound **21b** was evaluated for its activity on GH secretion after sc injection in the rat. As can be seen in Table 4, compound **21b** did not have any proper effect on GH release. On the other

Table 2. Cumulative Food Intake at 6 h after sc Administration of Compounds Alone or with Hexarelin[a]

compds	cumulative food intake (g/100 g bw) at 6 h for 160 μg compd (cumulative food intake at 6 h for 80 μg hexarelin)	cumulative food intake (g/100 g bw) at 6 h for 160 μg compd + 80 μg hexarelin	% variation vs hexarelin[b]
saline	0.19 ± 0.11	0.28 ± 0.12	
16	0.06 ± 0.03 (0.90 ± 0.38)	0.33 ± 0.22	−63
18c	0.01 ± 0.0 (0.76 ± 0.20)	0.48 ± 0.23	−37
19b	0.20 ± 0.19 (0.70 ± 0.21)	0.63 ± 0.20	−10
19c	0.06 ± 0.02 (0.70 ± 0.21)	0.48 ± 0.22	−31
19e	0.17 ± 0.17 (1.14 ± 0.11)	0.79 ± 0.33	−31
20c	0.29 ± 0.18 (1.10 ± 0.40)	0.47 ± 0.41	−57
21a	0.02 ± 0.01 (0.67 ± 0.26)	0.64 ± 0.01	−4
21b	0.01 ± 0.00 (0.60 ± 0.17)	0.02 ± 0.01	−97
24a	0.41 ± 0.37 (0.78 ± 0.22)	0.43 ± 0.20	−45
25c	0.75 ± 0.35 (0.67 ± 0.26)	0.53 ± 0.33	−21
29b	0.27 ± 0.17 (1.14 ± 0.11)	0.85 ± 0.41	−25
29c	0.22 ± 0.20 (0.59 ± 0.30)	0.91 ± 0.36	+54
30a	0.74 ± 0.31 (1.10 ± 0.22)	0.49 ± 0.17	−55
30c	0.30 ± 0.13 (1.10 ± 0.22)	0.56 ± 0.21	−49

[a] Results are expressed as g of food intake per 100 g of body weight (mean ± SEM). [b] (Cumulative food intake at 6 h for compound minus cumulative food intake at 6 h for hexarelin)/cumulative food intake at 6 h for hexarelin.

Table 3. Inhibition of Hexarelin-Stimulated Cumulative Food Intake at Various sc Doses of Compound **21b** (mean ± SEM)[a]

compds	food intake at 6 h (g/100 g bw)
hexarelin 80 μg	1.01 ± 0.19
+20 μg compound **21b**	0.46 ± 0.11
+80 μg compound **21b**	0.25 ± 0.13
+160 μg compound **21b**	0.25 ± 0.13
+320 μg compound **21b**	0.08 ± 0.05

[a] Values are the mean of 7−8 determinations. Experiments have been repeated three times.

Table 4. Effect of Compound **21b** on GH Secretion in the Rat (sc Injection)[a,b]

compd	[GH] ng/mL
solvent	2.2 ± 0.1
hexarelin (80 μg)	170 ± 13
21b (160 μg)	13 ± 2
hexarelin + **21b** (160 μg)	183 ± 17

[a] GH concentration was determined as described in the Experimental Section (mean ± SEM). [b] Values are the mean of 5−7 determinations. Experiments have been repeated three times.

hand, compound **21b** (160 μg/kg) was not able to modify hexarelin-stimulated GH release. Results on GH secretion are reported in Table 4.

These results indicate that compound **21b** works efficiently on the hexarelin-stimulated food intake (about 90% decrease in the cumulative 6 h period) and is without effect on GH secretion. The discrepancies observed between in vivo and in vitro activity might result from different pharmacokinetic and/or pharmacodynamic properties of compound **21b**.

Conclusion

A novel class of ghrelin receptor (GHS-R1a) ligands was identified from substituted 1,2,4-triazoles. These compounds were easily synthesized from commercially available materials. They contain only one asymmetric center that was selected at the beginning of the synthesis from the starting amino acid residue and conserved throughout the synthesis. SAR studies allowed us to improve in vitro binding affinity and to discover potent agonists, partial agonists, and antagonists for the GHS-1a receptor. The best in vitro receptor antagonists of this series were found to be compounds **19c** (JMV2844) (IC_{50} of 6 $\pm$ 3 nM, K_b of 4 $\pm$ 1 nM) and **19b** (JMV2866) (IC_{50} of 11 $\pm$ 4 nM, K_b of 5 $\pm$ 1 nM). The most potent compounds in this series were tested in vivo for their activity on food intake in the rat. Compound **21b** (JMV2810) that was defined in vitro as a partial agonist at the GHS-R1a was found the most potent compound in inhibiting hexarelin-stimulated food intake in the rat. However, it did not show any activity on GH secretion in the rat. Considering that some of the compounds tested are antagonists and some partial agonists in vitro at the GHS-1a receptor, this should infer that the receptor involved in the modulation of the food intake by the tested compounds depends on a more complicated mechanism.

Experimental Section

General Procedures. Ascending TLC was performed on precoated plates of silica gel 60 F_{254} (Merck). Peptide derivatives were located with charring reagent or ninhydrine. Column chromatography was performed with silica gel Kieselguhr Merck G 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 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 chromatography was performed 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. (L),(D)-Amino acids and derivatives were from Senn Chemicals, NeoMPS, or Advanced Chemtech. Human ghrelin was purchased from NeoMPS and iodinated in our laboratory. All reagents were of analytical grade.

All final compounds were purified by reversed-phase HPLC; the purity assessed by analytical reversed-phase C18 HPLC was found superior to 95%, and the structure was confirmed by MS (electrospray) and ^{1}H NMR and ^{13}C NMR for the most interesting compounds.

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

Ester Preparation. An amount of 1.0 equiv of carboxylic acid was dissolved in acetonitrile (0.5 mol/L). Then 1.2 equiv of DBU and 5.0 equiv of methyl iodide were added dropwise consecutively under stirring. After 8 h under reflux, the solvent was removed in vacuo. The residue was diluted in dichloromethane, washed with aqueous potassium hydrogen sulfate (1 M), saturated aqueous sodium hydrogen carbonate, and saturated aqueous sodium chloride. The organic layer was dried over sodium sulfate, filtered, and the solvent was removed in vacuo to afford the corresponding ester, as a colorless oil.

Methyl 3-Phenylpropanoate: 3.7 g (84%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.58 (t, 2H, J = 7 Hz, CH_2−CH_2−phenyl), 2.84 (t, 2H, J = 7 Hz, CH_2−CH_2−phenyl), 3.55 (s, 3H, OCH_3), 7.21 (m, 5H, CH phenyl); ^{13}C NMR (75 MHz, DMSO-d_6) δ 30.7 (CH_2−CH_2−phenyl), 35.3 (CH_2−CH_2−phenyl), 51.5 (OCH_3), 126.4 (C_4 phenyl), 128.5 (C_2 and C_6 phenyl), 128.7 (C_3 and C_5 phenyl), 140.9 (C_1 phenyl), 173.0 (CO ester); MS (ES) m/z 165.0 $[M + H]^+$; HPLC t_R, 1.51 min (conditions A).

Methyl 3-(1*H*-Indol-3-yl)propanoate: 4.0 g (94%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.64 (t, 2H, J = 8 Hz, CH_2−CH_2−indole), 2.94 (t, 2H, J = 8 Hz, CH_2−CH_2−indole), 3.55 (s, 3H, OCH_3), 6.95 (t, 1H, J = 7 Hz, H_5 indole), 7.04 (t, 1H, J = 7 Hz, H_6 indole), 7.08 (s, 1H, H_2 indole), 7.32 (d, 1H, J = 8 Hz, H_4 indole), 7.48 (d, 1H, J = 8 Hz, H_7 indole), 10.78 (brs, 1H, NH indole); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.7 (CH_2−CH_2−indole), 34.7 (CH_2−CH_2−indole), 51.2 (OCH_3), 111.8 (C_7 indole), 113.5 (C_3 indole), 118.5 (C_4 and C_5 indole), 121.3 (C_6 indole), 122.7 (C_2 indole), 127.3 (C_9 indole), 136.6 (C_8 indole), 173.5 (CO ester); MS (ES) m/z 204.1 $[M + H]^+$; HPLC t_R, 1.50 min (conditions A).

Methyl 4-Phenylbutanoate: 1.1 g (100%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.79 (m, 2H, CH_2−CH_2−CH_2−phenyl), 2.26 (t, 2H, J = 7 Hz, CH_2−CH_2−CH_2−phenyl), 2.54 (t, 2H, J = 7 Hz, CH_2−CH_2−CH_2−phenyl), 3.55 (s, 3H, OCH_3), 7.13−7.16 (m, 3H, H_3, H_4, and H_5 phenyl), 7.22−7.27 (m, 2H, H_2, and H_6 phenyl); ^{13}C NMR (75 MHz, DMSO-d_6) δ 26.6 (CH_2−CH_2−CH_2−phenyl), 33.1 (CH_2−CH_2−CH_2−phenyl), 34.7 (CH_2−CH_2−CH_2−phenyl), 51.5 (OCH_3), 126.2 (C_4 phenyl), 128.6 (C_2, C_3, C_5, and C_6 phenyl), 141.7 (C_1 phenyl), 173.4 (CO ester); MS (ES) m/z 179.1 $[M + H]^+$. HPLC t_R, 1.68 min (conditions A).

Methyl 2-(1*H*-Indol-3-yl)acetate: 0.78 g (72%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.58 (s, 3H, OCH_3), 3.73 (s, 2H, CH_2−indole), 6.97 (t, 1H, J = 8 Hz, H_5 indole), 7.07 (t, 1H, J = 7 Hz, H_6 indole), 7.23 (d, 1H, J = 2 Hz, H_2 indole), 7.35 (d, 1H, J = 8 Hz, H_4 indole), 7.47 (d, 1H, J = 8 Hz, H_7 indole), 10.92 (s, 1H, NH indole); ^{13}C NMR (75 MHz, DMSO-d_6) δ 31.0 (CH_2−indole), 51.9 (OCH_3), 107.4 (C_3 indole), 111.8 (C_7 indole), 118.8 (C_4 indole), 118.9 (C_5 indole), 121.5 (C_6 indole), 124.5 (C_2 indole), 127.5 (C_9 indole), 136.5 (C_8 indole), 172.5 (CO ester); MS (ES) m/z 190.1 $[M + H]^+$; HPLC t_R, 1.37 min (conditions A).

Methyl 4-(1*H*-Indol-3-yl)butanoate: 0.69 g (52%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.87 (m, 2H, CH_2−CH_2−CH_2−indole), 2.32 (t, 2H, J = 7 Hz, CH_2−CH_2−CH_2−indole), 2.67 (t, 2H, J = 7 Hz, CH_2−CH_2−CH_2−indole), 3.55 (s, 3H, OCH_3), 6.94 (t, 1H, J = 7 Hz, H_5 indole), 7.03 (t, 1H, J = 7 Hz, H_6 indole), 7.07 (d, 1H, J = 2 Hz, H_2 indole), 7.31 (d, 1H, J = 8 Hz, H_4 indole), 7.47 (d, 1H, J = 8 Hz, H_7 indole), 10.74 (s, 1H, NH indole); ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.4 (CH_2−CH_2−CH_2−indole), 25.7 (CH_2−CH_2−CH_2−indole), 33.4 (CH_2−CH_2−CH_2−indole), 51.5 (OCH_3), 111.7 (C_7 indole), 114.1 (C_3 indole), 118.5 (C_4 indole), 118.6 (C_5 indole), 121.2 (C_6 indole), 122.7 (C_2 indole), 127.5 (C_9 indole), 136.5 (C_8 indole), 173.8 (CO ester); MS (ES) m/z 218.1 $[M + H]^+$; HPLC t_R, 1.64 min (conditions A).

Hydrazide Preparation. An amount of 1.0 equiv of the corresponding ester and 10.0 equiv of hydrazine monohydrate were dissolved in ethanol (0.3 mol/L). The mixture was stirred overnight at reflux. The solvent was then removed in vacuo, and the residue was washed with diethylether and dried in vacuo to afford the corresponding hydrazide as a white powder.

3-Phenylpropanehydrazide: 3.3 g (91%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.28 (t, 2H, J = 7 Hz, CH_2−CH_2−phenyl), 2.77 (t, 2H, J = 7 Hz, CH_2−CH_2−phenyl), 3.69 (brs, 2H, NH_2), 7.11−7.26 (m, 5H, CH aromatic), 8.94 (brs, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 31.4 (CH$_2$−*C*H$_2$−phenyl), 35.5 (*C*H$_2$−CH$_2$−phenyl), 126.3 (C_4 phenyl), 128.6 (C_2 and C_6 phenyl), 128.7 (C_3 and C_5 phenyl), 140.1 (C_1 phenyl), 173.1 (CO); MS (ES) *m*/*z* 165.1 [M + H]$^+$; HPLC t_R, 0.77 min (conditions A).

3-(1*H*-Indol-3-yl)propanehydrazide: 3.1 g (76%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.41 (m, 2H, CH_2−CH$_2$−indole), 2.90 (m, 2H, CH$_2$−CH_2−indole), 5.72 (brs, 2H, NH_2), 6.93 (t, 1H, J = 7 Hz, H_5 indole), 7.02 (t, 1H, J = 8 Hz, H_6 indole), 7.07 (s, 1H, H_2 indole), 7.31 (d, 1H, J = 8 Hz, H_4 indole), 7.48 (d, 1H, J = 8 Hz, H_7 indole), 9.03 (brs, 1H, NH hydrazide), 10.79 (brs, 1H, NH indole); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.4 (CH$_2$−*C*H$_2$−indole), 34.7 (*C*H$_2$−CH$_2$−indole), 111.7 (C_7 indole), 114.1 (C_3 indole), 118.5 (C_4 indole), 118.7 (C_5 indole), 121.3 (C_6 indole), 122.5 (C_2 indole), 127.4 (C_9 indole), 136.6 (C_8 indole), 171.9 (CO); MS (ES) *m*/*z* 204.1 [M + H]$^+$; HPLC t_R, 0.85 min (conditions A).

4-Phenylbutanehydrazide: 1.1 g (100%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.84 (m, 2H, CH$_2$−CH_2−CH$_2$−phenyl), 2.00 (t, 2H, J = 7 Hz, CH_2−CH$_2$−CH$_2$−phenyl), 2.53 (t, 2H, J = 8 Hz, CH$_2$−CH$_2$−CH_2−phenyl), 4.40 (brs, 2H, NH_2), 7.09−7.16 (m, 3H, H_2, H_4, and H_6 phenyl), 7.21−7.26 (m, 2H, H_3, and H_5 phenyl), 8.90 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.4 (CH$_2$−*C*H$_2$−CH$_2$−phenyl), 33.3 (CH$_2$−CH$_2$−*C*H$_2$−phenyl), 35.1 (*C*H$_2$−CH$_2$−CH$_2$−phenyl), 126.1 (C_4 phenyl), 128.7 (C_2, C_3, C_5, and C_6 phenyl), 142.1 (C_1 phenyl), 171.7 (CO); MS (ES) *m*/*z* 179.1 [M + H]$^+$; HPLC t_R, 0.86 min (conditions A).

2-(1*H*-Indol-3-yl)acetohydrazide: 0.5 g (59%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.46 (s, 2H, CH$_2$−indole), 4.25 (brs, 2H, NH_2), 6.96 (t, 1H, J = 7 Hz, H_5 indole), 7.05 (t, 1H, J = 8 Hz, H_6 indole), 7.18 (s, 1H, H_2 indole), 7.33 (d, 1H, J = 8 Hz, H_4 indole), 7.57 (d, 1H, J = 8 Hz, H_7 indole), 9.20 (brs, 1H, NH hydrazide), 10.86 (s, 1H, NH indole); ^{13}C NMR (75 MHz, DMSO-d_6) δ 31.2 (CH$_2$−indole), 109.1 (C_3 indole), 111.7 (C_7 indole), 118.7 (C_4 indole), 119.2 (C_5 indole), 121.3 (C_6 indole), 124.2 (C_2 indole), 127.6 (C_9 indole), 136.5 (C_8 indole), 170.7 (CO); MS (ES) *m*/*z* 190.2 [M + H]$^+$; HPLC t_R, 0.78 min (conditions A).

4-(1*H*-Indol-3-yl)butanehydrazide: 1.0 g (90%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.83 (m, 2H, CH$_2$−CH_2−CH$_2$−indole), 2.06 (t, 2H, J = 7 Hz, CH_2−CH$_2$−CH$_2$−indole), 2.62 (t, 2H, J = 8 Hz, CH$_2$−CH$_2$−CH_2−indole), 4.35 (brs, 2H, NH_2), 6.92 (t, 1H, J = 7 Hz, H_5 indole), 7.02 (t, 1H, J = 7 Hz, H_6 indole), 7.06 (s, 1H, H_2 indole), 7.29 (d, 1H, J = 8 Hz, H_4 indole), 7.46 (d, 1H, J = 8 Hz, H_7 indole), 8.93 (brs, 1H, NH hydrazide), 10.72 (s, 1H, NH indole); ^{13}C RMN (75 MHz, DMSO-d_6) δ 24.8 (CH$_2$−*C*H$_2$−CH$_2$−indole), 26.5 (CH$_2$−CH$_2$−*C*H$_2$−indole), 33.7 (*C*H$_2$−CH$_2$−CH$_2$−indole), 111.7 (C_7 indole), 114.5 (C_3 indole), 118.5 (C_4 indole), 118.7 (C_5 indole), 121.2 (C_6 indole), 122.6 (C_2 indole), 127.6 (C_9 indole), 136.7 (C_8 indole), 172.0 (CO); MS (ES) *m*/*z* 218.1 [M + H]$^+$; HPLC t_R, 0.93 min (conditions A).

General Procedure for Thioamide 2 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 of 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 **1** that was used without purification. To 1.0 equiv of amide **1** in DME (10 mL/mmol) was added Lawesson's reagent (0.5 equiv) under argon. The reaction mixture 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 **2** was obtained as a white powder (yields between 35% and 70% for the two steps).

***tert*-Butyl (*R*)-1-(2-(1*H*-Indol-3-yl)ethylthiocarbamoyl)-2-(1*H*-indol-3-yl)ethylcarbamate (2a).** Obtained from Boc−D-Trp and tryptamine: 1.1 g (67%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ 1.27 (s, 9H, CH_3 Boc), 2.86 (m, 2H, CH$_2$−CH_2−indole), 2.95 (dd, 1H, J = 14 and 8 Hz, CH$_2$ βTrp), 3.11 (dd, 1H, J = 14 and 5 Hz, CH$_2$ βTrp), 3.75 (m, 2H, CH_2−CH$_2$−indole), 4.53 (m, 1H, CH αTrp), 6.68 (d, 1H, J_o = 8 Hz, H_4 Trp), 6.95 (t, 1H, J_o = 7 Hz, H_5 Trp), 6.96 (t, 1H, J_o = 8 Hz, H_5 indole), 7.03 (t, 1H, J_o = 6 Hz, H_6 Trp), 7.04 (m, 2H, H_6 and H_2 indole), 7.10 (d, 1H, J = 2 Hz, H_2 Trp), 7.12 (d, 1H, J_o = 8 Hz, H_4 indole), 7.30 (d, 2H, J_o = 8 Hz, H_7 indole and H_7 Trp), 7.57 (d, 1H, J = 7 Hz, NH Boc), 9.95 (brs, 1H, NH thioamide), 10.79 (s, 2H, NH indole and NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ 21.2 (CH$_2$−*C*H$_2$−indole), 28.5 (CH_3 Boc), 31.5 (C βTrp), 46.1 (*C*H$_2$−CH$_2$−indole), 62.0 (C αTrp), 78.6 (Cq Boc), 110.5 (C_3 indole and C_3 Trp), 111.7 (C_7 indole and C_7 Trp), 118.6 (C_4 Trp), 118.7 (C_4 indole), 119.0 (C_5 indole and C_5 Trp), 121.2 (C_6 Trp), 121.3 (C_6 indole), 123.1 (C_2 indole and C_2 Trp), 127.5 (C_9 indole), 127.8 (C_9 Trp), 136.5 (C_8 Trp), 136.7 (C_8 indole), 155.2 (CO Boc), 204.1 (CS thioamide). MS (ES) *m*/*z* 363.29 [M + H − 100]$^+$, 406.9 [M + H − 56]$^+$, 463.1 [M + H]$^+$, 925.4 [2M + H]$^+$. HPLC t_R, 2.01 min (conditions A).

***tert*-Butyl (*R*)-1-(Methylthiocarbamoyl)-2-(1*H*-indol-3-yl)ethylcarbamate (2b).** Obtained from Boc−D-Trp and methylamine: 0.3 g (69%). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ 1.27 (s, 9H, CH_3 Boc), 2.91 (d, 3H, J = 4 Hz, NH−CH_3), 2.97 (m, 1H, CH$_2$ βTrp), 3.14 (dd, 1H, J = 14 and 5 Hz, CH$_2$ βTrp), 4.49 (m, 1H, CH αTrp), 6.64 (d, 1H, J_o = 8 Hz, H_4 Trp), 6.93 (t, 1H, J_o = 8 Hz, H_5 Trp), 7.03 (t, 1H, J_o = 8 Hz, H_6 Trp), 7.11 (s, 1H, H_2 Trp), 7.29 (d, 1H, J_o = 8 Hz, H_7 Trp), 7.58 (d, 1H, J = 8 Hz, NH Boc), 9.86 (d, 1H, J = 4 Hz, NH thioamide), 10.75 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ 28.5 (CH_3 Boc), 31.5 (C βTrp), 32.7 (NH−*C*H$_3$), 61.8 (C αTrp), 78.6 (Cq Boc), 110.5 (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), 127.8 (C_9 Trp), 136.5 (C_8 Trp), 155.2 (CO Boc), 204.8 (CS thioamide). MS (ES) *m*/*z* 234.4 [M + H − 100]$^+$, 277.7 [M + H − 56]$^+$, 334.2 [M + H]$^+$, 667.3 [2M + H]$^+$, 689.1 [2M + Na]$^+$. HPLC t_R, 1.93 min (conditions A).

***tert*-Butyl (*R*)-1-(2,4-Dimethoxybenzylcarbamoyl)-2-(1*H*-indol-3-yl)ethylcarbamate (2c).** Obtained from Boc−D-Trp and 2,4-dimethoxybenzylamine. ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.27 (s, 9H, CH_3 Boc), 2.97 (dd, 1H, ^3J = 8 and 14 Hz, CH$_2$ βTrp), 3.30 (dd, 1H, ^3J = 4 and 14 Hz, CH$_2$ βTrp), 3.71 (s, 3H, CH_3O), 3.75 (s, 3H, CH_3O), 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 Trp), 9.97 (t, 1H, J = 6 Hz, N*H*−thioamide), 10.78 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 28.5 (CH_3 Boc), 31.3 (CH$_2$ βTrp), 44.2 (*C*H$_2$−*o*,*p*-dimethoxybenzyl), 55.6 (OCH_3), 55.9 (OCH_3), 61.9 (CH 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]$^+$. HPLC t_R, 1.97 min (conditions A).

General Procedure for Preparation of Triazole 3. To a solution of 1.0 equiv of thioamide **2** of tetrahydrofuran (10 mL/mmol) was 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 40% and 60%).

***tert*-Butyl (*R*)-1-(4-(2-(1*H*-Indol-3-yl)ethyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3yl)ethylcarbamate (3a).** Obtained from **2a** and formic hydrazide. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (s, 9H, Boc), 2.84 (m, 2H, CH$_2$−CH_2−indole), 3.29 (m, 2H, CH$_2$ βTrp),

4.05 (m, 2H, CH_2−CH_2−indole), 4.95 (m, 1H, CH αTrp), 6.83 (brs, 1H, H indole), 6.88−6.97 (m, 2H, H indole), 6.98−7.10 (m, 3H, H indole), 7.31 (d, 1H, J = 8 Hz, H indole), 7.32 (d, 1H, J = 8 Hz, H indole), 7.40 (d, 1H, J = 8 Hz, H indole), 7.48 (d, 1H, J = 8 Hz, H indole), 7.63 (d, 1H, J = 8 Hz, NH Trp), 8.21 (brs, 1H, H triazole), 10.80 (brs, 1H, NH indole), 10.85 (brs, 1H, NH indole). MS (ES) m/z 415.0 $[M + H - 56]^+$, 471.3 $[M + H]^+$, 941.3 $[2M + H]^+$.

***tert*-Butyl (*R*)-1-(5-((1*H*-Indol-3-yl)methyl)-4-methyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethylcarbamate (3b).** Obtained from **2b** and 2-(1*H*-indol-3-yl)acetohydrazide. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (s, 9H, CH_3 Boc), 3.10−3.30 (m, 5H, 3H N−CH_3 and 2H $CH_2\beta$), 4.15 (m, 2H, CH_2−indole), 4.90 (m, 1H, CH αTrp), 6.90−7.10 (m, 6H, H indole), 7.33 (d, 1H, J = 8 Hz, H indole), 7.35 (d, 1H, J = 8 Hz, H indole), 7.41−7.58 (3H, 2H indole, NH Trp), 10.75 (1H, s, NH indole), 10.90 (1H, s, NH indole). MS (ES) m/z 471.4 $[M + H]^+$, 941.3 $[2M + H]^+$.

***tert*-Butyl (*R*)-1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-methyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethylcarbamate (3c).** The title compound was obtained as previously described by reacting thioamide **2b** with 3-(1*H*-indol-3-yl)propanehydrazide. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (s, 9H, CH_3 Boc), 2.85−3.10 (m, 4H, CH_2−CH_2−indole), 3.20 (s, 3H, N−CH_3), 3.22−3.40 (m, 2H, $CH_2\beta$Trp), 4.92 (m, 1H, CH αTrp), 6.93−7.02 (m, 2H, H indole), 7.04−7.10 (m, 2H, H indole), 7.13 (s, 1H, H indole), 7.16 (s, 1H, H indole), 7.32−7.38 (m, 2H, H indole), 7.42−7.52 (m, 3H, 2H indole and NH Trp), 10.85 (brs, 2H, NH indole). MS (ES) m/z 485,3 $[M + H]^+$.

***tert*-Butyl (*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)ethylcarbamate (3d).** The title compound was obtained as previously described by reacting thioamide **2c** with 3-(1*H*-indol-3-yl)propanehydrazide: 1.2 g (65%). ^{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*-dimethoxybenzyl and CH αTrp), 6.26 (d, 1H, J_o = 8 Hz, H_5 *o*,*p*-dimethoxybenzyl), 6.49 (d, 1H, J_o = 8 Hz, H_6 *o*,*p*-dimethoxybenzyl), 6.51 (s, 1H, H_3 *o*,*p*-dimethoxybenzyl), 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 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) 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*-dimethoxybenzyl), 46.8 (C αTrp), 55.6 (OCH_3), 55.8 (OCH_3), 78.8 (Cq Boc), 98.9 (C_3 *o*,*p*-dimethoxybenzyl), 105.1 (C_5 *o*,*p*-dimethoxybenzyl), 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*-dimethoxybenzyl), 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*-dimethoxybenzyl), 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*-dimethoxybenzyl), 161.0 (C_4 *o*,*p*-dimethoxybenzyl). MS (ES) m/z 621.0 $[M + H]^+$. HPLC t_R, 2.20 min (conditions A).

General Procedure for Preparation of Compound 5. The Boc protecting group of compound **3** 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 Boc−Aib (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 was 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 AcOEt/HCl 4 M 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-(4-(2-(1*H*-Indol-3-yl)ethyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (11). Obtained from **3a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (s, 3H, CH_3 Aib), 1.35 (s, 3H, CH_3 Aib), 2.85 (m, 1H, 1H N−CH_2−CH_2−indole), 2.89 (m, 1H, 1H, N−CH_2−CH_2−indole), 3.28 (dd, 1H, J = 14 Hz, J = 7 Hz, CH_2 βTrp), 3.40 (dd, 1H, J = 14 Hz and J = 8 Hz, CH_2 βTrp), 4.10 (m, 2H,N−CH_2−CH_2−In), 5.25 (m, 1H, CH αTrp), 6.85 (d, 1H, J = 2 Hz, H_2 indole), 6.90−6.98 (m, 2H, H_5 indole), 7.01 (d, 1H, J = 2 Hz, H_2 indole), 7.02−7.12 (m, 2H, H_6 indole), 7.30 (d, 1H, J = 8.2 Hz, H_7 indole), 7.33 (d, 1H, J = 8 Hz, H_7 indole), 7.40 (d, 1H, J = 8 Hz, H_4 indole), 7.47 (d, 1H, J = 8 Hz, H_4 indole), 8.04 (brs, 3H, NH_2 Aib, TFA salt), 8.42 (s, 1H, H triazole), 9.01 (d, 1H, J = 8 Hz, NH Trp), 10.81 (s, 1H, NH indole), 10.90 (s, 1H, NH indole).

(*R*)-*N*-(1-(5-((1*H*-Indol-3-yl)methyl)-4-methyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (12). Obtained from **3b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.20 (s, 3H, CH_3 Aib), 1.28 (s, 3H, CH_3 Aib), 3.32 (d, 3H, N−CH_3), 3.30−3.45 (m, 2H, CH_2 βTrp), 4.22 (s, 2H, CH_2−indole), 5.30 (m, 1H, CH αTrp), 6.91 (t, 1H, J = 8 Hz, H_5 indole), 6.94 (d, 1H, J = 8 Hz, H_5 indole), 7.02 (t, 1H, J = 8 Hz, H_6 indole), 7.05 (t, 1H, J = 8 Hz, H_6 indole), 7.08 (d, 1H, J = 2 Hz, H_2 indole), 7.12 (d, 1H, J = 2 Hz, H_2 indole), 7.29 (d, 1H, J = 8 Hz, H_7 indole), 7.33 (d, 1H, J = 8 Hz, H_7 indole), 7.48 (d, 1H, J = 8 Hz, H_4 indole), 7.57 (d, 1H, J = 8 Hz, H_4 indole), 8.00 (brs, 3H, NH_2 Aib, TFA salt), 8.85 (d, 1H, J = 8 Hz, NH amide), 10.82 (s, 1H, NH indole), 10.98 (s, 1H, NH indole).

(*R*)-*N*-(1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-methyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (13). Obtained from **3c**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (s, 3H, CH_3 Aib), 1.40 (s, 3H, CH_3 Aib), 3.00−3.20 (m, 4H, CH_2−CH_2−indole), 3.36 (s, 3H, N−CH_3), 3.45−3.50 (m, 2H, CH_2 βTrp), 5.30 (m, 1H, CH αTrp), 6.95−7.04 (t, 2H, H_5 indole), 7.06−7.13 (m, 2H, H_6 indole), 7.18 (brs, 2H, H_2 indole), 7.34 (d, 1H, J = 8 Hz, H_7 indole), 7.36 (d, 1H, J = 8 Hz, H_7 indole), 7.48 (d, 1H, J = 8 Hz, H_4 indole), 7.58 (d, 1H, J = 8 Hz, H_4 indole), 8.10 (brs, 3H, NH_2 Aib, TFA salt), 8.95 (d, 1H, J = 8 Hz, NH amide), 10.95 (s, 1H, NH indole), 10.96 (s, 1H, NH indole). ^{13}C NMR (100 MHz, DMSO-d_6) 22.9 (CH_2−CH_2−indole), 24.1 (CH_3 Aib), 24.3 (CH_3 Aib), 25.9 (CH_2−CH_2−indole), 28.8 (C βTrp), 30.7 (NCH_3), 46.2 (C αTrp), 57.2 (Cq Aib), 110.2 (C_3 indole), 112.3 ($2C_7$ indole), 113.5 (C_3 indole), 118.9−119.2 ($2C_5$, $2C_4$ indole), 121.9 ($2C_6$ indole), 123.6 (C_2 indole), 125.3 (C_2 indole), 127.7 (C_9 indole), 128.0 (C_9 indole), 136.9 (C_8 indole), 137.1 (C_8 indole), 155.3 (Cq triazole), 155.8 (Cq triazole), 172.2 (CO Aib).

(*R*)-*N*-(1-(5-((1*H*-Indol-3-yl)methyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (14). Compound **14** was obtained by treatment of compound **15** with TFA. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (s, 3H, CH_3 Aib), 1.42 (s, 3H, CH_3 Aib), 3.19 (dd, 1H, J = 15 Hz and J = 10 Hz, CH_2 βTrp), 3.35 (dd, 1H, J = 15 Hz, J = 5 Hz, CH_2 βTrp), 4.15 (s, 2H, CH_2 indole), 5.26 (m, 1H, CH αTrp), 6.95 (t, 1H, H_5 Trp), 6.96 (t, 1H, H_5 indole), 7.05 (t, 1H, H_6 Trp), 7.06 (s, 1H, H_2 Trp), 7.07 (t, 1H, H_6 indole), 7.21 (s, 1H, H_2 indole), 7.32 (d, 1H, H_7 Trp), 7.37 (d, 1H, H_7 indole), 7.51 (d, 1H, J = 8 Hz, H_4 indole), 7.58 (d, 1H, J = 8 Hz, H_4 Trp), 8.00 (s, 3H, NH_2 Aib, TFA salt), 8.64 (d, 1H, J = 9 Hz, NH amide), 10.77 (s, 1H, NH indole Trp), 10.92 (s, 1H, NH indole). ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.9 (CH_2−indole), 23.2 (CH_3 Aib), 23.3 (CH_3 Aib), 29.4 (C βTrp), 48.3 (C αTrp), 56.3 (Cq Aib), 109.7 (C_3 indole), 110.3 (C_3 Trp), 111.2 (C_7 Trp), 111.3 (C_7 indole), 118.1 (C_4 Trp, C_5 Trp), 118.3 (C_4 indole), 118.4 (C_5 indole), 120.7 (C_6 Trp), 121.0 (C_6 indole), 123.4 (C_2 indole), 123.6 (C_2 Trp), 126.8 (C_9 indole), 127.1 (C_9 Trp), 136.0 (C_8 Trp), 136.2 (C_8 indole), 157.5 (Cq triazole), 161.7 (Cq triazole), 170.8 (CO Aib).

(*R*)-*N*-(1-(5-((1*H*-Indol-3-yl)methyl)-4-(2,4-dimethoxybenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (15). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.27 (s, 3H, CH_3 Aib), 1.29 (s, 3H, CH_3 Aib), 3.25 (dd, 1H, J = 14 Hz, J = 6 Hz, CH_2 βTrp), 3.38 (dd, 1H, J = 14

Hz and $J = 9$ Hz, CH_2 βTrp), 3.68 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 4.10 (d, 1H, $J = 17$ Hz, CH_2−indole), 4.16 (d, 1H, $J = 17$ Hz, CH_2−indole), 4.96 (d, 1H, $J = 17$ Hz, CH_2 *o*,*p*-dimethoxybenzyl), 5.12 (d, 1H, $J = 17$ Hz, CH_2 *o*,*p*-dimethoxybenzyl), 5.16 (m, 1H, CH αTrp), 6.21 (dd, 1H, $J = 9$ Hz and $J = 2$ Hz, H_5 *o*,*p*-dimethoxybenzyl), 6.27 (d, 1H, $J = 9$ Hz, H_6 *o*,*p*-dimethoxybenzyl), 6.57 (d, 1H, $J = 2$ Hz, H_3 *o*,*p*-dimethoxybenzyl), 6.83 (t, 1H, H_5 Trp), 6.94 (t, 1H, H_5 indole), 7.02 (t, 1H, H_6 Trp), 7.05 (s, 1H, H_2 indole),7.06 (t, 1H, H_6 indole), 7.07 (s, 1H, H_2 Trp), 7.07 (d, 1H, H_4 Trp), 7.31 (d, 1H, H_7 Trp), 7.33 (d, 1H, H_7 indole), 7.36 (d, 1H, $J = 8$ Hz, H_4 indole), 8.00 (brs, 3H, NH_2 Aib, TFA salt), 8.92 (d, 1H, $J = 8$ Hz, NH amide), 10.79 (s, 1H, NH indole Trp), 10.89 (s, 1H, NH indole). ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.2 (CH_2 indole), 23.1 (CH_3 Aib), 23.2 (CH_3 Aib), 28.6 (C βTrp), 41.4 (N−CH_2 *o*,*p*-dimethoxybenzyl), 45.1 (C αTrp), 55.2 (OCH_3), 55.4 (OCH_3), 56.2 (Cq Aib), 98.5 (C_3 *o*,*p*-dimethoxybenzyl), 104.6 (C_5 *o*,*p*-dimethoxybenzyl), 107.9 (C_3 indole), 109.5 (C_3 Trp), 111.2 (C_7 Trp), 111.3 (C_7 indole), 115.1 (C_1 *o*,*p*-dimethoxybenzyl), 117.8 (C_4 Trp), 118.1 (C_5 Trp), 118.3 (C_4 indole), 118.4 (C_5 indole), 120.8 (C_6 Trp), 121.1 (C_6 indole), 123.5 (C_2 indole), 124.3 (C_2 Trp), 126.6 (C_9 indole), 126.8 (C_9 Trp), 127.2 (C_6 *o*,*p*-dimethoxybenzyl), 136.0 (C_8 Trp), 136.2 (C_8 indole), 157.5 (Cq triazole), 154.9 (Cq triazole), 157.2 (C_2 *o*,*p*-dimethoxybenzyl), 160.3 (C_4 *o*,*p*-dimethoxybenzyl), 171.2 (CO Aib).

(*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-amino-2-methylpropanamide Trifluoroacetate Salt (16). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (s, 3H, CH_3 Aib), 1.36 (s, 3H, CH_3 Aib), 2.93 (m, 2H, CH_2−CH_2−indole), 2.97 (m, 2H, CH_2−CH_2−indole), 3.31 (dd, 1H, $J = 15$ Hz and $J = 6$ Hz, CH_2 βTrp), 3.38 (dd, 1H, $J = 15$ Hz and $J = 9$ Hz, CH_2 βTrp), 3.66 (s, 3H, *o*-OCH_3), 3.72 (s, 3H, *p*-OCH_3), 4.93 (d, 1H, $J = 17$ Hz, CH_2 *o*,*p*-dimethoxybenzyl), 5.10 (d, 1H, $J = 17$ Hz, CH_2 *o*,*p*-dimethoxybenzyl), 5.23 (m, 1H, CH αTrp), 6.31 (dd, 1H, $J = 9$ Hz and $J = 2$ Hz, H_5 *o*,*p*-dimethoxybenzyl), 6.45 (d, 1H, $J = 9$ Hz, H_6 *o*,*p*-dimethoxybenzyl), 6.59 (d, 1H, $J = 2$ Hz, H_3 *o*,*p*-dimethoxybenzyl), 6.88 (t, 1H, $J = 8$ Hz, H_5 Trp), 6.94 (t, 1H, $J = 8$ Hz, H_5 indole), 7.04 (t, 1H, H_6 Trp), 7.06 (t, 1H, H_6 indole), 7.08 (s, 1H, H_2 indole), 7.11 (s, 1H, H_2 Trp), 7.18 (d, 1H, $J = 8$, H_4 Trp), 7.33 (3H, H_4, H_7 indole, H_7 Trp), 8.05 (s, 3H, NH_2 Aib, TFA salt), 8.95 (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) δ 22.4 (CH_2−CH_2 indole), 23.2 (CH_3 Aib), 23.3 (CH_3 Aib), 25.4 (CH_2−CH_2 indole), 28.7 (C βTrp), 41.3 (CH_2−*o*,*p*-dimethoxybenzyl), 45.3 (C αTrp), 55.2 (*p*-OCH_3), 55.4 (*o*-OCH_3), 56.3 (Cq Aib), 98.6 (C_3 *o*,*p*-dimethoxybenzyl), 104.7 (C_5 *o*,*p*-dimethoxybenzyl), 109.5 (C_3 Trp), 111.3 (C_7 Trp, C_7 indole), 112.9 (C_3 indole), 115.2 (C_1 *o*,*p*-dimethoxybenzyl), 117.8 (C_4 indole), 117.9 (C_4 Trp), 118.2 (C_5 Trp, C_5 indole), 120.9 (C_6 Trp, C_6 indole), 122.4 (C_2 indole), 124.3 (C_2 Trp), 126.8 (C_9 Indole), 126.9 (C_9 Trp), 127.5 (C_6 *o*,*p*-dimethoxybenzyl), 136.0 (C_8 Trp), 136.2 (C_8 indole), 154.6 (2Cq triazole), 157.3 (C_2 *o*,*p*-dimethoxybenzyl), 160.4 (C_4 *o*,*p*-dimethoxybenzyl), 171.3 (CO Aib).

(*R*)-*N*-(1-(4-(2,4-Dimethoxybenzyl)-5-benzyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (16a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (s, 3H, CH_3 Aib), 1.33 (s, 3H, CH_3 Aib), 3.26 (dd, 1H, $J = 14$ Hz and $J = 6$ Hz, CH_2 βTrp), 3.38 (dd, 1H, $J = 14$ Hz and $J = 9$ Hz, CH_2 βTrp), 3.69 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 4.02 (s, 2H, CH_2−benzyl), 4.87 (d, 1H, $J = 17$ Hz, CH_2−*o*,*p*-dimethoxybenzyl), 5.08 (d, 1H, $J = 17$ Hz, CH_2 *o*,*p*-dimethoxybenzyl), 5.17 (m, 1H, CH αTrp), 6.24 (dd, 1H, $J = 8$ Hz, $J = 2$ Hz, H_5 *o*,*p*-dimethoxybenzyl), 6.28 (d, 1H, $J = 8$ Hz, H_6 *o*,*p*-dimethoxybenzyl), 6.56 (d, 1H, $J = 2$ Hz, H_3 *o*,*p*-dimethoxybenzyl), 6.85 (t, 1H, $J = 8$ Hz, H_5 Trp), 7.02 (t, 1H, H_6 Trp), 7.07 (m, 2H, H_2, H_6 benzyl), 7.08 (s, 1H, H_2 Trp), 7.09 (d, 1H, H_4 Trp), 7.16−7.29 (m, 3H, H_3, H_4, H_5 benzyl), 7.31 (d, 1H, $J = 8$ Hz, H_7 Trp), 8.01 (s, 3H, NH_2 Aib, TFA salt), 8.92 (d, 1H, $J = 8$ Hz, NH amide), 11.79 (s, 1H, NH indole Trp). ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.2 (2CH_3 Aib), 28.7 (C βTrp), 30.2 (CH_2−benzyl), 41.3 (CH_2−*o*,*p*-dimethoxybenzyl), 45.2 (C αTrp), 55.2 (OCH_3), 55.4 (OCH_3), 56.2 (Cq Aib), 98.5 (C_3 *o*,*p*-dimethoxybenzyl), 104.7 (C_5 *o*,*p*-dimethoxybenzyl), 109.5 (C_3 Trp), 111.3 (C_7 Trp), 115.1 (C_1 *o*,*p*-dimethoxybenzyl), 117.8 (C_4 Trp), 118.2 (C_5 Trp), 120.8 (C_6 Trp), 124.3 (C_2 Trp), 126.5 (C_4 benzyl), 126.8 (C_9 Trp), 127.3 (C_6 *o*,*p*-dimethoxybenzyl), 128.3 (C_2,C_3, C_5, C_6 benzyl), 135.8 (C_1 benzyl), 136.0 (C_8 Trp), 153.4 (Cq triazole), 155.0 (Cq triazole), 157.2 (C_2 *o*,*p*-dimethoxybenzyl), 160.3 (C_4 *o*,*p*-dimethoxybenzyl), 171.3 (CO Aib).

(*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-amino-2-methylpropanamide Trifluoroacetate Salt (16c). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.26 (s, 3H, CH_3 Aib), 1.30 (s, 3H, CH_3 Aib), 2.82 (m, 4H, CH_2−CH_2−phenyl), 3.29 (t, 2H, $J = 8$ Hz, CH_2 βTrp), 3.61 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 4.85 (d, 1H, $J = 17$ Hz, CH_2−*o*,*p*-dimethoxybenzyl), 5.02 (d, 1H, $J = 17$ Hz, CH_2−*o*,*p*-dimethoxybenzyl), 5.18 (m, 1H, CH αTrp), 6.29 (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), 6.55 (d, 1H, $J_m = 2$ Hz, H_3 *o*,*p*-dimethoxybenzyl), 6.82 (t, 1H, $J_o = 8$ Hz, H_5 Trp), 6.99 (t, 1H, $J_o = 8$ Hz, H_6 Trp), 7.05 (s, 1H, H_2 Trp), 7.09−7.24 (m, 6H, H_4 Trp and CHar phenyl), 7.27 (d, 1H, $J_o = 8$ Hz, H_7 Trp), 7.99 (s3H, large, NH_2 Aib TFA salt), 8.89 (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 (ppm) 23.6 (CH_3 Aib), 23.7 (CH_3 Aib), 26.5 (CH_2−CH_2−phenyl), 29.2 (CH_2 βTrp), 32.7 (CH_2−CH_2−phenyl), 41.6 (CH_2−*o*,*p*-dimethoxybenzyl), 45.7 (CH αTrp), 55.7 (OCH_3), 55.9 (OCH_3), 56.7 (Cq Aib), 99.1 (C_3 *o*,*p*-dimethoxybenzyl), 105.2 (C_5 *o*,*p*-dimethoxybenzyl), 110.0 (C_3 Trp), 111.8 (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), 126.5 (C_2 Trp and C_6 *o*,*p*-dimethoxybenzyl), 127.3 (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), 140.9 (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), 171.7 (CO amide).

(*R*)-*N*-(1-(4-(3,5-Dimethoxybenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (17b). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.24 (s, 3H, CH_3 Aib), 1.27 (s, 3H, CH_3 Aib), 2.83 (s, 4H, CH_2−CH_2−phenyl), 3.32 (m, 2H, CH_2 βTrp), 3.61 (s, 6H, OCH_3), 5.02 (m, 2H, CH_2−*m*-dimethoxybenzyl), 5.18 (m, 1H, CH αTrp), 6.07 (d, 2H, $J_m = 2$ Hz, H_2 and H_6 *m*-dimethoxybenzyl), 6.42 (brs, 1H, H_4 *m*-dimethoxybenzyl), 6.83 (t, 1H, $J_o = 7$ Hz, H_5 Trp), 6.99 (t, 1H, $J_o = 8$ Hz, H_6 Trp), 7.08 (d, 1H, $J = 2$ Hz, H_2 Trp), 7.13 (t, 3H, $J_o = 8$ Hz, H_3, H_4 and H_5 phenyl), 7.20 (d, 3H, $J_o = 7$ Hz, H_2 and H_6 phenyl, H_4 Trp), 7.28 (d, 1H, $J_o = 8$ Hz, H_7 Trp), 7.99 (brs, 3H, NH_2 Aib), 8.92 (d, 1H, $J = 8$ Hz, NH amide), 10.77 (s, 1H, NH indole). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 23.5 (CH_3 Aib), 23.8 (CH_3 Aib), 26.5 (CH_2−CH_2−phenyl), 29.2 (CH_2 βTrp), 32.7 (CH_2−CH_2−phenyl), 45.6 (CH αTrp), 45.8 (CH_2− *m*-dimethoxybenzyl), 55.6 (OCH_3), 56.8 (Cq Aib), 99.6 (C_4 *m*-dimethoxybenzyl), 104.6 (C_2 and C_6 *m*-dimethoxybenzyl), 109.9 (C_3 Trp), 111.8 (C_7 Trp), 118.2 (C_4 Trp), 118.7 (C_5 Trp), 121.3 (C_6 Trp), 124.8 (C_2 Trp), 126.5 (C_4 phenyl), 127.3 (C_9 Trp), 128.7 (C_2, C_3, C_5 and C_6 phenyl), 136.4 (C_8 Trp), 138.6 (C_1 *m*-dimethoxybenzyl), 140.9 (C_1 phenyl), 154.6 (Cq triazole), 154.8 (Cq triazole), 161.4 (C_3 and C_5 *m*-dimethoxybenzyl), 171.8 (CO amide).

(*R*)-*N*-(1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(3-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (18a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (s, 3H, CH_3 Aib), 1.30 (s, 3H, CH_3 Aib), 2.92 (m, 2H, CH_2−CH_2−indole), 2.98 (m, 2H, CH_2−CH_2−indole), 3.33 (dd, 1H, $J = 15$ Hz and $J = 6$ Hz, CH_2 βTrp), 3.40 (dd, 1H, $J = 15$ Hz and $J = 9$ Hz, CH_2 βTrp), 3.66 (s, 3H, OCH_3), 5.09 (m, 2H, CH_2−*m*-methoxybenzyl), 5.22 (m, 1H, CH αTrp), 6.38 (d, 1H, $J = 8$ Hz, H_6 *m*-methoxybenzyl), 6.59 (s, 1H, H_2 *m*-methoxybenzyl), 6.86 (t, 1H, H_5 Trp), 6.87 (d, 1H, H_4 *m*-methoxybenzyl), 6.92 (t, 1H, $J = 7.5$ Hz, H_5 indole), 7.03 (t, 1H, $J = 7.9$ Hz, H_6 Trp), 7.05 (t, 1H, H_6 indole), 7.07 (s, 1H, H_2 indole), 7.11 (s, 1H, H_2 Trp), 7.18 (t, 1H, H_5 *m*-methoxybenzyl), 7.19 (d, 1H, H_4 Trp), 7.31 (1H, H_4 indole), 7.32 (2H, H_7 Trp, H_7 indole), 8.00 (s, 3H, NH_2 Aib,

TFA salt), 8.96 (d, 1H, $J = 8$ Hz, NH amide), 10.78 (s, 1H, NH indole), 10.80 (s, 1H, NH indole Trp). ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.4 (*C*H$_2$−CH$_2$−indole), 23.1 (CH$_3$ Aib), 23.3 (CH$_3$ Aib), 25.4 (CH$_2$−*C*H$_2$ indole), 28.7 (C βTrp), 45.3 (CH$_2$ *m*-methoxybenzyl), 45.4 (C αTrp), 55.0 (OCH$_3$), 56.3 (Cq Aib), 109.5 (C$_3$ Trp), 111.3 (C$_7$ Trp, C$_7$ indole), 112.0 (C$_2$ *m*-methoxybenzyl), 113.0 (C$_4$ *m*-methoxybenzyl, C$_3$ indole), 117.8 (C$_4$ Trp, C$_6$ *m*-methoxybenzyl), 118.0 (C$_4$ indole), 118.2 (C$_5$ indole), 118.3 (C$_5$ Trp), 120.8 (C$_6$ indole), 120.9 (C$_6$ Trp), 122.4 (C$_2$ indole), 124.3 (C$_2$ Trp), 126.7 (C$_9$ indole), 126.9 (C$_9$ Trp), 130.0 (C$_5$ *m*-methoxybenzyl), 136.0 (C$_8$ indole), 136.1 (C$_8$ Trp), 137.2 (C$_1$ *m*-methoxybenzyl), 154.3 (2Cq triazole), 159.6 (C$_3$ *m*-methoxybenzyl), 171.4 (CO amide).

(*R*)-*N*-(1-(5-(3-(1*H*-Indol-3-yl)propyl)-4-(3-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (18b). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.27 (s, 3H, CH$_3$ Aib), 1.30 (s, 3H, CH$_3$ Aib), 1.92 (m, 2H, CH$_2$−*C*H$_2$−CH$_2$−indole), 2.62 (m, 2H, *C*H$_2$−CH$_2$−CH$_2$−indole), 2.68 (m, 2H, CH$_2$−CH$_2$−*C*H$_2$−indole), 3.24 (dd, 1H, $J =$ 14.5, $J = 5.8$, CH$_2$ βTrp), 3.39 (dd, 1H, $J = 14.5$, $J = 9.0$, CH$_2$ βTrp), 3.66 (s, 3H, *m*-OCH$_3$), 5.07 (s, 2H, CH$_2$ *m*-methoxybenzyl), 5.18 (m, 1H, CH α Trp), 6.35 (d, 1H, $J = 7.5$, H$_6$ *m*-methoxybenzyl), 6.54 (brs, 1H, H$_2$ *m*-methoxybenzyl), 6.84 (t, 1H, $J = 7.5$, H$_5$ Trp), 6.87 (dd, 1H, $J = 8.0$, $J = 2.1$, H$_4$ *m*-methoxybenzyl), 6.94 (t, 1H, $J = 7.3$, H$_5$ indole), 7.02 (t, 1H, H$_6$ Trp), 7.02 (s, 1H, H$_2$ indole), 7.05 (t, 1H, $J = 7.8$, H$_6$ indole), 7.08 (d, 1H, $J = 2.1$, H$_2$ Trp), 7.13 (d, 1H, $J = 8.1$, H$_4$ Trp), 7.17 (t, 1H, $J = 8.1$, H$_5$ *m*-methoxybenzyl), 7.30 (d, 1H, H$_7$ Trp), 7.32 (d, 1H, $J = 8$, H$_7$ indole), 7.42 (d, 1H, $J = 7.6$, H$_4$ indole), 7.98 (brs, 3H, NH$_2$ Aib, TFA salt), 8.93 (d, 1H, $J = 8.2$, NH amide), 10.71 (s, 1H, NH indole), 10.77 (s, 1H, NH indole Trp). ^{13}C NMR (100 MHz,DMSO-d_6) δ 23.1 (CH$_3$ Aib), 23.3 (CH$_3$ Aib), 23.9 (*C*H$_2$−CH$_2$−CH$_2$−indole), 24.3 (CH$_2$−CH$_2$−*C*H$_2$−indole), 27.4 (CH$_2$−*C*H$_2$−CH$_2$ indole), 28.8 (C βTrp), 45.2 (*C*H$_2$− *m*-methoxybenzyl), 45.4 (C αTrp), 55.1 (*m*-OCH$_3$), 56.3 (Cq Aib), 109.5 (C$_3$ Trp), 111.3 (C$_7$ Trp, C$_7$ indole), 111.8 (C$_2$ *m*-methoxybenzyl), 113.0 (C$_4$ *m*-methoxybenzyl), 113.8 (C$_3$ indole), 117.8 (C$_6$ *m*-methoxybenzyl), 117.9 (C$_4$ Trp), 118.1 (C$_5$ indole), 118.2 (C$_5$ Trp, C$_4$ indole), 120.8 (C$_6$ Trp), 120.9 (C$_6$ indole), 122.2 (C$_2$ indole), 124.3 (C$_2$ Trp), 126.8 (C$_9$ Trp), 127.0 (C$_9$ indole), 130.0 (C$_5$ *m*-methoxybenzyl), 136.0 (C$_8$ Trp), 136.2 (C$_8$ indole), 137.4 (C$_1$ *m*-methoxybenzyl), 154.3 (Cq triazole), 154.6 (Cq triazole), 159.7 (C$_3$ *m*-methoxybenzyl), 171.4 (CO amide).

(*R*)-*N*-(1-(4-(3-Methoxybenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (18c). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.24 (s, 3H, CH$_3$ Aib), 1.27 (s, 3H, CH$_3$ Aib), 2.82 (m, 4H, C*H*$_2$−C*H*$_2$−phenyl), 3.32 (m, 2H, CH$_2$ βTrp), 3.63 (s, 3H, OCH$_3$), 5.08 (m, 2H, C*H*$_2$−*m*-methoxybenzyl), 5.18 (m, 1H, CH αTrp), 6.35 (d, 1H, $J_o = 8$ Hz, H$_6$ *m*-methoxybenzyl), 6.57 (s, 1H, H$_2$ *m*-methoxybenzyl), 6.82 (t, 1H, $J_o = 8$ Hz, H$_5$ Trp), 6.84 (d, 1H, $J_o = 8$ Hz, H$_4$ *m*-methoxybenzyl), 6.99 (t, 1H, $J_o = 8$ Hz, H$_6$ Trp), 7.08 (m, 1H, H$_4$ phenyl), 7.11−7,16 (m, 5H, H$_2$ and H$_4$ Trp, H$_2$ and H$_6$ phenyl, H$_5$ *m*-methoxybenzyl), 7.20 (m, 2H, H$_3$ and H$_5$ phenyl), 7.27 (d, 1H, $J_o = 8$ Hz, H$_7$ Trp), 8.01 (brs, 3H, NH$_2$ Aib, TFA salt), 8.96 (d, 1H, $J = 8$ Hz, NH amide), 10.81 (d, 1H, $J =$ 2 Hz, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 23.5 (CH$_3$ Aib), 23.8 (CH$_3$ Aib), 26.4 (*C*H$_2$−CH$_2$−phenyl), 29.1 (CH$_2$ βTrp), 32.7 (CH$_2$−*C*H$_2$−phenyl), 45.7 (CH αTrp), 45.8 (CH$_2$−*m*-methoxybenzyl), 55.5 (OCH$_3$), 56.7 (Cq Aib), 109.8 (C$_3$ Trp), 111.8 (C$_7$ Trp), 112.5 (C$_2$ *m*-methoxybenzyl), 113.5 (C$_4$ *m*-methoxybenzyl), 118.2 (C$_4$ Trp), 118.4 (C$_6$ *m*-methoxybenzyl), 118.7 (C$_5$ Trp), 121.3 (C$_6$ Trp), 124.8 (C$_2$ Trp), 126.5 (C$_4$ phenyl), 127.3 (C$_9$ Trp), 128.7 (C$_2$, C$_3$, C$_5$, and C$_6$ phenyl), 130.5 (C$_5$ *m*-methoxybenzyl), 136.4 (C$_8$ Trp), 137.7 (C$_1$ *m*-methoxybenzyl), 140.9 (C$_1$ phenyl), 154.6 (Cq triazole), 154.9 (Cq triazole), 160.1 (C$_3$ *m*-methoxybenzyl), 171.9 (CO amide).

(*R*)-*N*-(1-(4-(3-Methoxybenzyl)-5-benzyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (18d). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (s, 3H, CH$_3$ Aib), 1.29 (s, 3H, CH$_3$ Aib), 3.24 (dd, 1H, $J = 14.3$, $J = 5.8$, CH$_2$ βTrp), 3.38 (dd, 1H, $J = 14.3$, $J = 9.1$, CH$_2$ βTrp), 3.61 (s, 3H, *m*-OCH$_3$), 4.04 (m, 2H, CH$_2$ benzyl), 5.07 (d, 1H, $J =$ 17.4, CH$_2$ *m*-methoxybenzyl), 5.13 (d, 1H, $J = 17.4$, CH$_2$ *m*-methoxybenzyl), 5.14 (m, 1H, CH αTrp), 6.32 (d, 1H, $J = 7.8$, H$_6$ *m*-methoxybenzyl), 6.40 (m, 1H, H$_2$ *m*-methoxybenzyl), 6.82 (t, 1H, H$_5$ Trp), 6.83 (d, 1H, $J = 7.8$, H$_4$ *m*-methoxybenzyl), 7.01 (t, 1H, $J = 8.2$, H$_6$ Trp), 7.04 (d, 1H, $J = 8.2$, H$_4$ Trp), 7.06 (d, 1H, $J = 2.0$, H$_2$ Trp), 7.12 (m, 2H, H$_2$, H$_6$ benzyl), 7.13 (t, 1H, $J =$ 7.9, H$_5$ *m*-methoxybenzyl), 7.20 (m, 1H, H$_4$ benzyl), 7.24 (m, 2H, H$_3$, H$_5$ benzyl), 7.29 (d, 1H, $J = 8.2$, H$_7$ Trp), 7.99 (brs, 3H, NH$_2$ Aib, TFA salt), 8.92 (d, 1H, $J = 8.2$, NH amide), 10.77 (s, 1H, NH indole Trp). ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.0 (CH$_3$ Aib), 23.3 (CH$_3$ Aib), 28.6 (Cβ Trp), 30.1 (CH$_2$ benzyl), 45.2 (Cα Trp), 45.6 (*C*H$_2$− *m*-methoxybenzyl), 54.9 (*m*-OCH$_3$), 56.2 (Cq Aib), 109.4 (C$_3$ Trp), 111.2 (C$_7$ Trp), 111.7 (C$_2$ *m*-methoxybenzyl), 113.1 (C$_4$ *m*-methoxybenzyl), 117.9 (C$_4$ Trp, C$_6$ *m*-methoxybenzyl), 118.2 (C$_5$ Trp), 120.8 (C$_6$ Trp), 124.3 (C$_2$ Trp), 126.6 (C$_4$ benzyl), 126.8 (C$_9$ Trp), 128.3 (C$_3$, C$_5$ benzyl), 128.4 (C$_2$, C$_6$ benzyl), 129.9 (C$_5$ *m*-methoxybenzyl), 135.9 (C$_1$ benzyl, C$_8$ Trp), 137.0 (C$_1$ *m*-methoxybenzyl), 153.5 (Cq triazole), 154.8 (Cq triazole), 159.5 (C$_3$ *m*-methoxybenzyl), 171.3 (CO amide).

(*R*)-*N*-(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)-2-amino-2-methylpropanamide Trifluoroacetate Salt (19a). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 1.22 (s, 3H, CH$_3$ Aib), 1.25 (s, 3H, CH$_3$ Aib), 3.22 (dd, 1H, $J =$ 14 and 6 Hz, CH$_2$ βTrp), 3.34 (dd, 1H, $J =$ 14 and 9 Hz, CH$_2$ βTrp), 3.68 (s, 3H, OCH$_3$), 4.11 (m, 2H, C*H*$_2$− indole), 5.09 (m, 3H, CH αTrp and C*H*$_2$−*p*-methoxybenzyl), 6.70 (s, 4H, CHar *p*-methoxybenzyl), 6.78 (m, 2H, H$_5$ indole and H$_5$ Trp), 6.93 (m, 2H, H$_6$ indole and H$_6$ Trp), 7.01−7,06 (m, 3H, H$_2$ indole, H$_2$ and H$_4$ Trp), 7.31 (m, 3H, H$_4$ and H$_7$ indole, H$_7$ Trp), 7.98 (brs, 3H, NH$_2$ Aib, TFA salt), 8.92 (d, 1H, $J = 8$ Hz, NH amide), 10.77 (s, 1H, NH indole), 10.89 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 21.7 (*C*H$_2$−indole), 23.5 (CH$_3$ Aib), 23.7 (CH$_3$ Aib), 28.9 (C βTrp), 45.6 (C αTrp), 45.8 (*C*H$_2$−*p*-methoxybenzyl), 55.5 (OCH$_3$), 56.7 (Cq Aib), 108.1 (C$_3$ indole), 109.7 (C$_3$ Trp), 111.7 (C$_7$ Trp), 111.9 (C$_7$ indole), 114.5 (C$_3$ and C$_5$ *p*-methoxybenzyl), 118.3 (C$_4$ Trp), 118.7 (C$_4$ indole), 118.8 (C$_5$ indole), 118.9 (C$_5$ Trp), 121.3 (C$_6$ indole), 121.6 (C$_6$ Trp), 124.2 (C$_2$ indole), 125.3 (C$_2$ Trp), 127.1 (C$_9$ indole), 127.2 (C$_9$ Trp), 127.6 (C$_1$ *p*-methoxybenzyl), 127.8 (C$_2$ and C$_6$ *p*-methoxybenzyl), 136.4 (C$_8$ Trp), 136.7 (C$_8$ indole), 154.2 (Cq triazole), 155.2 (Cq triazole), 159.2 (C$_4$ *p*-methoxybenzyl), 171.9 (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)-2-amino-2-methylpropanamide Trifluoroacetate Salt (19b). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 1.28 (s, 3H, CH$_3$ Aib), 1.32 (s, 3H, CH$_3$ Aib), 2.46 (m, 2H, C*H*$_2$−CH$_2$−phenyl), 2.82 (m, 2H, CH$_2$−C*H*$_2$−phenyl), 3.35 (d, 2H, $J =$ 7 Hz, CH$_2$ βTrp), 3.68 (s, 3H, OCH$_3$), 5.02 (s, 2H, C*H*$_2$−*p*-methoxybenzyl), 5.22 (m, 1H, CH αTrp), 6.73−6.81 (s, 4H, CHar *p*-methoxybenzyl), 6.84 (t, 1H, $J_o = 7$ Hz, H$_5$ Trp), 7.00 (t, 1H, J_o $= 7$ Hz, H$_6$ Trp), 7.05−7.11 (m, 4H, H$_2$ and H$_6$ phenyl, H$_2$ and H$_4$ Trp), 7.14−7.22 (m, 3H, H$_3$, H$_4$ and H$_5$ phenyl), 7.29 (d, 1H, $J_o =$ 8 Hz, H$_7$ Trp), 8.09 (brs, 3H, NH$_2$ Aib, TFA salt), 8.99 (d, 1H, J $= 8$ Hz, NH amide), 10.83 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 23.5 (CH$_3$ Aib), 23.8 (CH$_3$ Aib), 26.5 (*C*H$_2$−CH$_2$−phenyl), 29.1 (C βTrp), 32.6 (CH$_2$−*C*H$_2$−phenyl), 45.5 (*C*H$_2$−*p*-methoxybenzyl), 45.7 (C αTrp), 55.5 (OCH$_3$), 56.8 (Cq Aib), 109.7 (C$_3$ Trp), 111.8 (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), 124.9 (C$_2$ Trp), 126.6 (C$_4$ phenyl), 127.3 (C$_9$ Trp), 127.6 (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), 136.4 (C$_8$ Trp), 140.8 (C$_1$ phenyl), 154.5 (Cq triazole), 154.8 (Cq triazole), 159.2 (C$_4$ *p*-methoxybenzyl), 172.0 (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 (19c). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (s, 3H, CH$_3$ Aib), 1.33 (s, 3H, CH$_3$ Aib), 2.91 (m, 2H, C*H*$_2$−CH$_2$−indole), 2.97 (m, 2H, CH$_2$−C*H*$_2$−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 = 8 Hz, H_5 Trp), 6.93 (t, 1H, J = 8 Hz, 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 Hz, H_4 Trp), 7.32 (3H, H_4, H_7 indole, H_7 Trp), 8.02 (brs, 3H, NH_2 Aib, TFA salt), 8.97 (d, 1H, J = 8 Hz, NH amide), 10.77 (s, 1H, NH indole), 10.80 (s, 1H, NH indole Trp). ^{13}C NMR (100 MHz, DMSO-d_6) 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).

(*R*)-*N*-(1-(4-(4-Methoxybenzyl)-5-(3-phenylpropyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (19d). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.27 (s, 3H, CH_3 Aib), 1.31 (s, 3H, CH_3 Aib), 1.73 (m, 2H, $CH_2-CH_2-CH_2-$phenyl), 2.47 (m, 2H, $CH_2-CH_2-CH_2-$phenyl), 2.52 (t, 2H, ^3J = 7 Hz, $CH_2-CH_2-CH_2-$phenyl), 3.35 (d, 2H, J = 7 Hz, CH_2 βTrp), 3.68 (s, 3H, OCH_3), 4.98 (s, 2H, CH_2-p-methoxybenzyl), 5.20 (m, 1H, CH αTrp), 6.75 (s, 4H, CHar *p*-methoxybenzyl), 6.82 (t, 1H, J_o = 7 Hz, H_5 Trp), 6.99 (t, 1H, J_o = 7 Hz, H_6 Trp), 7.04−7.07 (m, 4H, H_2 and H_6 phenyl, H_2 and H_4 Trp), 7.13−7.24 (m, 3H, H_3, H_4, and H_5 phenyl), 7.29 (d, 1H, J_o = 8 Hz, H_7 Trp), 8.03 (brs, 3H, NH_2 Aib, TFA salt), 8.96 (d, 1H, J = 8 Hz, NH amide), 10.80 (d, 1H, J = 2 Hz, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 23.6 (CH_3 Aib), 23.6 (CH_3 Aib), 24.06 ($CH_2-CH_2-CH_2-$phenyl), 28.5 ($CH_2-CH_2-CH_2-$phenyl), 29.2 (CH_2 βTrp), 34.7 ($CH_2-CH_2-CH_2-$phenyl), 45.5 (CH_2-p-methoxybenzyl), 45.8 (CH αTrp), 55.5 (OCH_3), 56.8 (Cq Aib), 109.8 (C_3 Trp), 111.8 (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), 124.9 (C_2 Trp), 126.2 (C_4 phenyl), 127.3 (C_9 Trp), 127.8 (C_1 *p*-methoxybenzyl), 127.9 (C_2 and C_6 *p*-methoxybenzyl), 128.7 (C_2, C_3, C_5, and C_6 phenyl), 136.4 (C_8 Trp), 141.7 (C_1 phenyl), 154.8 (2Cq triazole), 159.2 (C_4 *p*-methoxybenzyl), 171.9 (CO amide).

(*R*)-*N*-(1-(4-(4-Methoxybenzyl)-5-benzyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (19e). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.24 (s, 3H, CH_3 Aib), 1.28 (s, 3H, CH_3 Aib), 3.26 (dd, 1H, ^3J = 14 and 6 Hz, CH_2 βTrp), 3.31 (dd, 1H, ^3J = 14 and 9 Hz, CH_2 βTrp), 3.67 (s, 3H, OCH_3), 3.99 (s, 2H, CH_2 benzyl), 4.99 (s, 2H, CH_2-p-methoxybenzyl), 5.12 (m, 1H, CH αTrp), 6.67 (s, 4H, CHar *p*-methoxybenzyl), 6.80 (t, 1H, J_o = 8 Hz, H_5 Trp), 6.98 (t, 1H, J_o = 8 Hz, H_6 Trp), 7.02−7.06 (m, 4H, H_2 and H_6 benzyl, H_2 and H_4 Trp), 7.12−7.25 (m, 3H, H_3, H_4, and H_5 benzyl), 7.26 (d, 1H, J_o = 8 Hz, H_7 Trp), 8.01 (brs, 3H, NH_2 Aib, TFA salt), 8.92 (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 (ppm) 23.5 (CH_3 Aib), 23.7 (CH_3 Aib), 29.1 (CH_2 βTrp), 30.6 (CH_2-benzyl), 45.7 (CH_2-p-methoxybenzyl), 45.7 (CH αTrp), 55.5 (OCH_3), 56.7 (Cq Aib), 109.8 (C_3 Trp), 111.7 (C_7 Trp), 114.5 (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), 127.1 (C_2 and C_6 benzyl), 127.3 (C_9 Trp), 127.6 (C_1 *p*-methoxybenzyl), 127.8 (C_2 and C_6 *p*-methoxybenzyl), 128.8 (C_3, C_4, and C_5 benzyl), 136.3 (C_1 benzyl), 136.4 (C_8 Trp), 153.8 (Cq triazole), 155.2 (Cq triazole), 159.1 (C_4 *p*-methoxybenzyl), 171.9 (CO amide).

(*R*)-*N*-(1-(5-(3-(1*H*-Indol-3-yl)propyl)-4-(4-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (19f). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.27 (s, 3H, CH_3 Aib), 1.30 (s, 3H, CH_3 Aib), 1.84 (m, 2H, $CH_2CH_2CH_2-$indole), 2.58 (m, 2H, $CH_2CH_2CH_2-$indole), 2.65 (m, 2H, $CH_2CH_2CH_2-$indole), 3.34 (d, 2H, ^3J = 7 Hz, CH_2 βTrp), 3.67 (s, 3H, OCH_3), 4.96 (s, 2H, CH_2-p-methoxybenzyl), 5.19 (m, 1H, CH αTrp), 6.71 (s, 4H, CH ar *p*-methoxybenzyl), 6.89 (t, 1H, J_o =7 Hz, H_5 Trp), 6.92 (t, 1H, J_o =7 Hz, H_5 indole), 6.96 (m, 2H, H_6 indole, H_6 Trp), 7.02 (s, 1H, H_2 indole), 7.05 (s, 1H, H_2 Trp), 7.14 (d, 1H, J_o = 8 Hz, H_4 Trp), 7.33 (m, 3H, H_4 indole, H_7 Trp, H_7 indole), 7.90 (d, 1H, J = 8 Hz, NH amide), 8.02 (brs, 3H, NH_2 Aib, TFA salt), 10.73 (s, 1H, NH indole), 10.79 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 23.6 (CH_3 Aib), 23.8 (CH_3 Aib), 24.3 ($CH_2-CH_2CH_2-$indole), 24.8 ($CH_2CH_2CH_2-$indole), 27.7 ($CH_2CH_2CH_2-$indole), 29.1 (C βTrp), 45.5 (CH_2-p-methoxybenzyl), 45.8 (C αTrp), 55.5 (OCH_3), 56.8 (Cq Aib), 109.8 (C_3 Trp), 111.7 (C_7 Trp, C_7 indole), 114.0 (C_3 indole), 114.5 (C_3, C_5 *p*-methoxybenzyl), 118.3 (C_4 indole, C_4 Trp), 118.5 (C_5 indole), 118.8 (C_5 Trp), 121.3 (C_6 indole, C_6 Trp), 127.3 (C_9 indole), 127.4 (C_9 Trp), 127.6 (C_1 *p*-methoxybenzyl), 127.9 (C_2, C_6 *p*-methoxybenzyl, C_2 Trp, C_2 indole), 136.1 (C_8 indole), 136.4 (C_8 Trp), 154.7 (Cq triazole), 155.1 (Cq triazole), 159.2 (C_4 *p*-methoxybenzyl), 171.9 (CO amide).

(*R*)-*N*-(1-(4-(2-Methoxybenzyl)-5-benzyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (20a). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.24 (s, 3H, CH_3 Aib), 1.27 (s, 3H, CH_3 Aib), 3.20 (dd, 1H, J = 14 and 5 Hz, CH_2 βTrp), 3.33 (dd, 1H, J = 14 and 9 Hz, CH_2 βTrp), 3.68 (s, 3H, OCH_3), 4.00 (s, 2H, CH_2-phenyl), 4.95 (d, 1H, J = 17 Hz, CH_2-o-methoxybenzyl), 5.07 (m, 1H, CH αTrp), 5.18 (d, 1H, J = 17 Hz, CH_2-o-methoxybenzyl), 6.27 (d, 1H, J_o = 8 Hz, H_3 *o*-methoxybenzyl), 6.67 (t, 1H, J_o = 7 Hz, H_5 Trp), 6.77 (t, 1H, J_o = 6 Hz, H_6 Trp), 6.92−7.05 (m, 6H, H_2 Trp, H_2 and H_6 phenyl, H_4, H_5, and H_6 *o*-methoxybenzyl), 7.14−7.26 (m, 5H, H_4 and H_7 Trp, H_3, H_4, and H_5 phenyl), 8.03 (brs, 3H, NH_2 Aib, TFA salt), 8.91 (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 (ppm) 23.5 (CH_3 Aib), 23.6 (CH_3 Aib), 29.1 (C βTrp), 30.5 (CH_2-phenyl), 42.1 (CH_2-o-methoxybenzyl), 45.7 (CH α Trp), 55.9 (OCH_3), 56.7 (Cq Aib), 109.8 (C_3 Trp), 111.3 (C_3 *o*-methoxybenzyl), 111.7 (C_7 Trp), 118.2 (C_4 Trp), 118.7 (C_5 Trp), 120.9 (C_5 *o*-methoxybenzyl), 121.2 (C_6 Trp), 123.3 (C_1 *o*-methoxybenzyl), 124.8 (C_2 Trp), 126.6 (C_4 phenyl), 127.1 (C_4 *o*-methoxybenzyl), 127.2 (C_9 Trp), 128.8 (C_2, C_3, C_5 and C_6 phenyl), 129.5 (C_6 *o*-methoxybenzyl), 136.0 (C_1 phenyl), 136.4 (C_8 Trp), 154.0 (Cq triazole), 155.6 (Cq triazole), 156.5 (C_2 *o*-methoxybenzyl), 171.8 (CO amide).

(*R*)-*N*-(1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(2-methoxy)benzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (20b). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.27 (s, 3H, CH_3 Aib), 1.29 (s, 3H, CH_3 Aib), 2.90 (m, 2H, CH_2-CH_2-indole), 2.96 (m, 2H, CH_2-CH_2-indole), 3.29 (m, 2H, CH_2 βTrp), 3.65 (s, 3H, OCH_3), 5.09 (m, 3H, CH_2-o-methoxybenzyl and CH αTrp), 6.49 (d, 1H, J_o = 8 Hz, H_3 *o*-methoxybenzyl), 6.76 (t, 1H, J_o = 8 Hz, H_5 Trp), 6.81 (t, 1H, J_o = 8 Hz, H_5 indole), 6.89 (t, 1H, J_o = 7 Hz, H_6 Trp), 6.96 (t, 1H, J_o = 8 Hz, H_6 indole), 6.98 (s, 1H, H_2 indole), 7.02 (m, 3H, H_4, H_5, and H_6 *o*-methoxybenzyl), 7.07 (d, 1H, J_o = 6 Hz, H_4 Trp), 7.18 (d, 1H, H_4 indole), 7.29 (m, 2H, H_7 indole and H_7 Trp), 8.07 (brs, 3H, NH_2 Aib, TFA salt), 8.97 (d, 1H, J = 8 Hz, NH amide), 10.80 (s, 1H, NH indole), 10.82 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 22.8 (CH_2-CH_2-indole), 23.6 (CH_3 Aib), 23.7 (CH_3 Aib), 25.8 (CH_2-CH_2-indole), 29.1 (C βTrp), 42.3 (CH_2-o-methoxybenzyl), 45.7 (C αTrp), 55.8 (OCH_3), 56.7 (Cq Aib), 109.8 (C_3 Trp), 111.5 (C_3 *o*-methoxybenzyl), 111.8 (C_7 indole and C_7 Trp), 113.2 (C_3 indole), 118.2 (C_4 Trp), 118.4 (C_4 indole), 118.7 (C_5 indole and C_5 Trp), 121.0 (C_6 indole), 121.3 (C_6 Trp), 121.4 (C_5 *o*-methoxybenzyl), 123.0 (C_2 indole and C_2 Trp), 123.3 (C_1 *o*-methoxybenzyl), 127.0 (C_4 *o*-methoxybenzyl), 127.1 (C_9 indole), 127.3 (C_9 Trp), 129.8 (C_6 *o*-methoxybenzyl), 136.4 (C_8 indole), 136.6 (C_8 Trp), 155.2 (2Cq triazole), 156.6 (*C*2 *o*-methoxybenzyl), 171.9 (CO amide).

(*R*)-*N*-(1-(4-(2-Methoxybenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (20c). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.26 (s, 3H, CH_3 Aib), 1.29 (s, 3H, CH_3 Aib), 2.78−2.92 (m, 4H, CH_2-CH_2-phenyl), 3.29 (m, 2H, CH_2 βTrp), 3.65 (s, 3H, OCH_3), 4.97−5.21 (m, 3H, CH αTrp and CH_2-o-methoxybenzyl), 6.52 (d, 1H, J_o = 7 Hz, H_3 *o*-methoxybenzyl), 6.78 (t, 1H, J_o = 7

Hz, H_5 Trp), 6.82 (t, 1H, J_o = 8 Hz, H_6 Trp), 6.84−7.04 (m, 3H, H_2 and H_6 phenyl, H_2 Trp), 7.04−7.10 (m, 3H, H_4, H_5, and H_6 *o*-methoxybenzyl), 7.15 (d, 1H, J_o = 7 Hz, H_4 Trp), 7.19−7.29 (m, 4H, H_3, H_4 and H_5 phenyl, H_7 Trp), 8.03 (brs, 3H, NH_2 Aib, TFA salt), 8.94 (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 (ppm) 23.6 (CH_3 Aib), 23.7 (CH_3 Aib), 26.3 (*C*H_2−CH_2−phenyl), 29.0 (C βTrp), 32.5 (CH_2−*C*H_2−phenyl), 42.3 (CH_2−*o*-methoxybenzyl), 45.7 (C αTrp), 55.8 (OCH_3), 56.7 (Cq Aib), 109.7 (C_3 Trp), 111.5 (C_7 Trp), 111.8 (C_3 *o*-methoxybenzyl), 118.2 (C_4 Trp), 118.7 (C_5 Trp), 121.0 (C_6 Trp), 121.3 (C_5 *o*-methoxybenzyl), 123.2 (C_1 *o*-methoxybenzyl), 124.9 (C_2 Trp), 126.6 (C_4 phenyl), 127.2 (C_9 Trp and C_4 *o*-methoxybenzyl), 128.7 (C_2, C_3, C_5 and C_6 phenyl), 129.9 (C_6 *o*-methoxybenzyl), 136.4 (C_8 Trp), 140.6 (C_1 phenyl), 154.8 (Cq triazole), 155.2 (Cq triazole), 156.7 (C_2 *o*-methoxybenzyl), 171.9 (CO amide).

(*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 (21a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (s, 3H, CH_3 Aib), 1.30 (s, 3H, CH_3 Aib), 2.88 (m, 2H, C*H*$_2$−CH_2−indole), 2.97 (m, 2H, CH_2−C*H*$_2$−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 Hz, H_5 Trp), 6.88 (2H, H_2, H_6 benzyl), 6.92 (t, 1H, *J* = 8 Hz, H_5 indole), 7.03 (t, 1H, *J* = 8 Hz, H_6 Trp), 7.05 (2H, H_6 indole, H_2 indole), 7.09 (d, 1H, *J* = 2 Hz, H_2 Trp), 7.17 (d, 1H, *J* = 8 Hz, H_4 Trp), 7.26 (2H, H_3, H_5 benzyl), 7.27 (1H, H_4 benzyl), 7.30 (1H, H_4 indole), 7.32 (2H, H_7 Trp, H_7 indole), 8.03 (brs, 3H, NH_2 Aib, TFA salt), 8.95 (d, 1H, *J* = 8 Hz, NH amide), 10.77 (s, 1H, NH indole), 10.81 (s, 1H, NH indole Trp). ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.4 (CH_2−*C*H_2 indole), 23.1 (CH_3 Aib), 23.3 (CH_3 Aib), 25.4 (*C*H_2−CH_2 indole), 28.7 (C βTrp), 45.3 (C αTrp, *C*H_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_4 benzyl), 126.7 (C_9 indole), 126.9 (C_9 Trp), 127.6 (C_2, C_6 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-(3-(1*H*-Indol-3-yl)propyl)-4-benzyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (21b). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (s, 3H, CH_3 Aib), 1.31 (s, 3H, CH_3 Aib), 1.90 (m, 2H, CH_2−*C*H_2−CH_2−indole), 2.61 (m, 2H, *C*H_2−CH_2−CH_2−indole), 2.69 (m, 2H, CH_2−CH_2−*C*H_2−indole), 3.37 (m, 2H, CH_2 βTrp), 5.09 (s, 2H, CH_2 Bzl), 5.20 (m, 1H, CH αTrp), 6.85 (m, 3H, H_2, H_6 Bzl, H_5 Trp), 6.94 (t, 1H, *J* = 7.5, H_5 indole), 7.01 (s, 1H, H_2 indole), 7.02 (t, 1H, *J* = 7.8, H_6 Trp), 7.05 (t, 1H, *J* = 8, H_6 indole), 7.08 (d, 1H, *J* = 2.0, H_2 Trp), 7.14 (d, 1H, *J* = 8.0, H_4 Trp), 7.25 (m, 3H, H_3, H_4, H_5 benzyl), 7.31 (d, 1H, *J* = 8.0, H_7 Trp), 7.32 (d, 1H, *J* = 8.0, H_7 indole), 7.42 (d, 1H, *J* = 7.8, H_4 indole), 8.03 (brs, 3H, NH_2 Aib, TFA salt), 8.95 (d, 1H, *J* = 8.1, NH Trp), 10.73 (s, 1H, NH indole), 10.80 (d, 1H, *J* = 2.0, NH indole Trp). ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.1 (CH_3 Aib), 23.3 (CH_3 Aib), 23.8 (*C*H_2−CH_2−CH_2−indole), 24.1 (CH_2−CH_2−*C*H_2−indole), 27.2 (CH_2−*C*H_2−CH_2−indole), 28.7 (C βTrp), 45.4 (C αTrp), 45.5 (CH_2 benzyl), 56.3 (Cq Aib), 109.4 (C_3 Trp), 111.3 (C_7 Trp, C_7 indole), 113.6 (C_3 indole), 117.8 (C_4 Trp), 118.0 (C_5 indole), 118.2 (C_4 indole), 118.3 (C_5 Trp), 120.8 (C_6 indole, C_6 Trp), 122.2 (C_2 indole), 124.3 (C_2 Trp), 125.9 (C_4 benzyl), 126.8 (C_9 Trp), 127.0 (C_9 indole), 127.7 (C_2, C_6 benzyl), 128.7 (C_3, C_5 benzyl), 135.5 (C_1 benzyl), 136.0 (C_8 Trp), 136.2 (C_8 indole), 154.3 (Cq triazole), 154.7 (Cq triazole), 171.4 (CO amide).

2-Amino-*N*-((*R*)-1-(4,5-dibenzyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-methylpropanamide Trifluoroacetate Salt (21c). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.23 (s, 3H, CH_3 Aib), 1.26 (s, 3H, CH_3 Aib), 3.23 (dd, 1H, *J* = 14 and 6 Hz, CH_2 βTrp), 3.35 (dd, 1H, *J* = 14 and 9 Hz, CH_2 βTrp), 3.99 (s, 2H, C−C*H*$_2$−phenyl), 5.10 (m, 3H, N−C*H*$_2$−phenyl and CH αTrp), 6.77 (m, 3H, H_5 Trp, H_2 and H_6 phenyl from N−CH_2−phenyl), 6.99 (m, 2H, H_2 and H_6 Trp), 7.01−7.07 (m, 3H, H_4 Trp, H_2 and H_6 from C−CH_2−phenyl), 7.15−7.23 (m, 6H, H_3, H_4, and H_5 phenyl from N−CH_2−phenyl and from C−CH_2−phenyl), 7.25 (d, 1H, *J* = 8 Hz, H_7 Trp), 8.01 (brs, 3H, NH_2 Aib, TFA salt), 8,91 (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 (ppm) 23.5 (CH_3 Aib), 23.7 (CH_3 Aib), 29.0 (C βTrp), 30.6 (C−CH_2−phenyl), 45.7 (C αTrp), 46.1 (N−*C*H_2−phenyl), 56.7 (Cq Aib), 109.8 (C_3 Trp), 111.7 (C_7 Trp), 118.3 (C_4 Trp), 118.7 (C_5 Trp), 121.2 (C_6 Trp), 124.8 (C_2 Trp), 126.3 (C_4 phenyl from N−CH_2−phenyl), 127.0 (C_4 phenyl from C−CH_2−phenyl), 127.2 (C_9 Trp), 128.0 (C_2, C_6 phenyl from N−CH_2−phenyl), 128.8 (C_2, C_3, C_5, and C_6 from C−CH_2−phenyl), 128.9 (C_3 and C_5 phenyl from N−CH_2−phenyl), 135.8 (C_1 phenyl from N−CH_2−phenyl), 136.2 (C_1 phenyl from C−CH_2−phenyl), 136.4 (C_8 Trp), 153.9 (Cq triazole), 155.3 (Cq triazole), 171.9 (CO amide).

(*R*)-*N*-(1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(4-bromobenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (22a). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (s, 3H, CH_3 Aib), 1.30 (s, 3H, CH_3 Aib), 2.90 (m, 2H, *C*H_2−CH_2−indole), 3.00 (m, 2H, CH_2−*C*H_2−indole), 3.37 (m, 2H, CH_2 βTrp), 5.10 (s, 2H, CH_2 *p*-bromobenzyl), 5.13 (m, 1H, CH αTrp), 6.75 (d, 2H, *J* = 8.1, H_2, H_6 *p*-bromobenzyl), 6.88 (t, 1H, *J* = 7.3, H_5 Trp), 6.93 (t, 1H, *J* = 7.5, H_5 indole), 7.03 (t, 1H, *J* = 7.0, H_6 Trp), 7.05 (m, 1H, H_6 indole), 7.07 (d, 1H, *J* = 1.7, H_2 indole), 7.09 (d, 1H, *J* = 1.8, H_2 Trp), 7.12 (d, 1H, *J* = 8.2, H_4 Trp), 7.28 (d, 1H, *J* = 7.9, H_4 indole), 7.32 (d, 2H, *J* = 8.2, H_7 Trp, H_7 indole), 7.41 (d, 2H, *J* = 8.1, H_3, H_5 *p*-bromobenzyl), 8.01 (brs, 3H, NH_2 Aib, TFA salt), 8.95 (d, 1H, *J* = 7.9, NH amide), 10.77 (brs, 1H, NH indole), 10.80 (brs, 1H, NH indole Trp). ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.4 (CH_2−*C*H_2 indole), 23.1 (CH_3 Aib), 23.4 (CH_3 Aib), 25.4 (*C*H_2−CH_2 indole), 28.7 (C βTrp), 44.8 (*C*H_2 *p*-bromobenzyl), 45.2 (C αTrp,), 56.3 (Cq Aib), 109.4 (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), 120.8 (C_4 *p*-bromobenzyl), 120.9 (C_6 Trp, C_6 indole), 122.5 (C_2 indole), 124.4 (C_2 Trp), 126.7 (C_9 indole), 126.8 (C_9 Trp), 128.0 (C_2, C_6 *p*-bromobenzyl), 131.6 (C_3, C_5 *p*-bromobenzyl), 135.1 (C_1 *p*-bromobenzyl), 136.1 (C_8 Trp, C_8 indole), 154.2 (Cq triazole), 154.5 (Cq triazole), 171.4 (CO amide).

***N*-((*R*)-1-(4-(4-Bromobenzyl)-5-benzyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (22c).** ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm)1.23 (s, 3H, CH_3 Aib), 1.25 (s, 3H, CH_3 Aib), 3.26 (dd, 1H, ^3J = 14 and 6 Hz, CH_2 Trp), 3.34 (dd, 1H, ^3J = 14 and 9 Hz, CH_2 βTrp), 4.01 (m, 2H, CH_2−benzyl), 5.01 (m, 1H, CH αTrp), 5.08 (s, 2H, CH_2−*p*-bromobenzyl), 6.59 (d, 2H, J_o = 8 Hz, H_2 and H_6 *p*-bromobenzyl), 6.81 (t, 1H, J_o = 7 Hz, H_5 Trp), 6.94 (s, 1H, H_2 Trp), 6.98 (t, 1H, J_o = 7 Hz, H_6 Trp), 7.06 (m, 2H, H_2 and H_6 benzyl), 7.12 (d, 1H, J_o = 7 Hz, H_4 Trp), 7.16−7.20 (m, 3H, H_3, H_4, and H_5 benzyl), 7.26 (d, 1H, J_o = 8 Hz, H_7 Trp), 7.29 (d, 2H, J_o = 8 Hz, H_3 and H_5 *p*-bromobenzyl), 8.00 (brs, 3H, NH_2 Aib, TFA salt), 8.92 (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 (ppm) 23.5 (CH_3 Aib), 23.8 (CH_3 Aib), 29.0 (C βTrp), 30.5 (CH_2−benzyl), 45.6 (*CH*$_2$− *p*-bromobenzyl), 45.7 (C αTrp), 56.7 (Cq Aib), 109.7 (C_3 Trp), 111.8 (C_7 Trp), 118.2 (C_4 Trp), 118.7 (C_5 Trp), 121.2 (C_4 *p*-bromobenzyl), 121.3 (C_6 Trp), 124.9 (C_2 Trp), 127.0 (C_2 and C_6 benzyl), 127.2 (C_9 Trp), 128.4 (C_2 and C_6 *p*-bromobenzyl), 128.9 (C_3, C_4 and C_5 benzyl), 131.9 (C_3 and C_5 *p*-bromobenzyl), 135.2 (C_1 *p*-bromobenzyl), 136.2 (C_8 Trp), 136.4 (C_1 benzyl), 153.9 (Cq triazole), 155.3 (Cq triazole), 171.9 (CO amide).

(*R*)-*N*-(1-(4-(4-Fluorobenzyl)-5-benzyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (23b). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.27 (s, 3H, CH_3 Aib), 1.29 (s, 3H, CH_3 Aib), 3.33 (m, 2H, CH_2 βTrp), 4.02 (s, 2H, CH_2−benzyl), 5.10 (m, 3H, CH_2−*p*-fluorobenzyl and CH αTrp), 6.71 (m, 2H, H_3 and H_5 *p*-fluorobenzyl), 6.80 (t, 1H, J_o = 8 Hz, H_5 Trp), 6.90 (d, 2H, J_o = 8 Hz, H_2 and H_6 *p*-fluorobenzyl), 6.94 (t, 1H, J_o = 8 Hz, H_6 Trp), 6.99−7.10 (m, 4H, H_2 and H_4 Trp, H_2 and H_6 benzyl), 7.20 (m, 3H, H_3, H_4 and H_5 benzyl), 7.27 (d, 1H, J_o = 8 Hz, H_7 Trp), 8.09 (brs, 3H, NH_2 Aib, TFA salt), 8.97 (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 (ppm) 23.5 (CH_3 Aib), 23.8 (CH_3 Aib), 29.0 (C βTrp), 31.1 (CH_2− benzyl), 45.7 (CH_2− *p*-fluorobenzyl), 45.8 (C αTrp), 56.8 (Cq Aib), 109.6 (C_3 Trp), 111.8 (C_7 Trp), 115.6 and 115.9 (C_3 and C_5 *p*-fluorobenzyl), 118.2 (C_4 Trp), 118.7 (C_5 Trp), 121.3 (C_6 Trp), 124.8 (C_2 Trp), 127.1 (C_4 benzyl), 127.2 (C_9 Trp), 128.8 and 128.9 (C_2 and C_6 *p*-fluorobenzyl), 129.4 (C_2, C_3, C_5, and C_6 benzyl), 131.6 (C_1 *p*-fluorobenzyl), 135.9 (C_1 benzyl), 136.4 (C_8 Trp), 154.0 (C_4 *p*-fluorobenzyl), 155.3 (2Cq triazole), 172.0 (CO amide).

***N*-((*R*)-1-(4-(4-Fluorobenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (23c).** ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.27 (s, 3H, CH_3 Aib), 1.28 (s, 3H, CH_3 Aib), 2.82 (m, 4H, C*H*$_2$−C*H*$_2$−phenyl), 3.34 (m, 2H, CH_2 βTrp), 5.06 (s, 2H, CH_2−*p*-fluorobenzyl), 5.16 (m, 1H, CH αTrp), 6.85 (m, 3H, H_5 Trp, H_3 and H_5 *p*-fluorobenzyl), 6.98−7.04 (m, 4H, H_2 and H_6 Trp, H_2 and H_6 phenyl), 7.09−7.11 (m, 2H, H_2 and H_6 *p*-fluorobenzyl), 7.15 (d, 1H, J_o = 6 Hz, H_4 Trp), 7.19 (t, 3H, J_o = 8 Hz, H_3, H_4 and H_5 phenyl), 7.29 (d, 1H, J_o = 8 Hz, H_7 Trp), 8.01 (brs, 3H, NH_2 Aib, TFA salt), 8.94 (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 (ppm) 23.5 (CH_3 Aib), 23.8 (CH_3 Aib), 26.5 (*C*H$_2$−CH$_2$−phenyl), 29.2 (C βTrp), 32.7 (CH$_2$−*C*H$_2$−phenyl), 45.4 (CH$_2$−*p*-fluorobenzyl), 45.7 (C αTrp), 56.8 (Cq Aib), 109.8 (C_3 Trp), 111.8 (C_7 Trp), 115.9 and 116.2 (C_3 and C_5 *p*-fluorobenzyl), 118.3 (C_4 Trp), 118.7 (C_5 Trp), 121.3 (C_6 Trp), 124.8 (C_2 Trp), 126.5 (C_4 phenyl), 127.3 (C_9 Trp), 128.5 (C_2 and C_6 *p*-fluorobenzyl), 128.7 (C_2, C_3, C_5 and C_6 phenyl), 132.2 (C_1 *p*-fluorobenzyl), 136.4 (C_8 Trp), 140.9 (C_1 phenyl), 154.5 (Cq triazole), 154.7 (Cq triazole), 160.3 (C_4 *p*-fluorobenzyl), 171.9 (CO amide).

(*R*)-*N*-(1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(3,4-dichlorobenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (24a). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.26 (s, 6H, CH_3 Aib), 2.87 (m, 2H, C*H*$_2$−CH$_2$−indole), 2.96 (m, 2H, CH$_2$−C*H*$_2$−indole), 3.32 (m, 2H, CH_2 βTrp), 5.13 (m, 3H, CH αTrp and CH$_2$−*m*,*p*-dichlorobenzyl), 6.58 (d, 1H, J_o = 8 Hz, H_6 *m*,*p*-dichlorobenzyl), 6.85 (t, 1H, J_o = 7 Hz, H_5 Trp), 6.96 (t, 1H, J_o = 7 Hz, H_5 indole), 7.01 (m, 2H, H_6 indole and H_6 Trp), 7.04 (s, 1H, H_2 Trp), 7.08 (s, 1H, H_2 indole), 7.13 (d, 1H, J_o = 8 Hz, H_5 *m*,*p*-dichlorobenzyl), 7.20−7.30 (m, 4H, H_4 and H_7 indole, H_7 Trp and H_2 *m*,*p*-dichlorobenzyl), 7.36 (d, 1H, J_o = 8 Hz, H_4 Trp), 8.08 (brs, 3H, NH_2 Aib, TFA salt), 8.98 (d, 1H, J = 8 Hz, NH amide), 10.80 (s, 1H, NH indole), 10.82 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 22.8 (CH$_2$−*C*H$_2$−indole), 23.4 (CH_3 Aib), 23.8 (CH_3 Aib), 25.8 (*C*H$_2$−CH$_2$−indole), 29.0 (C βTrp), 44.8 (CH$_2$−*m*,*p*-dichlorobenzyl), 45.6 (C αTrp), 56.8 (Cq Aib), 109.7 (C_3 indole), 111.8 (C_7 indole and C_7 Trp), 113.3 (C_3 Trp), 118.1 (C_4 Trp), 118.4 (C_5 indole), 118.6 (C_4 indole and C_5 Trp), 121.3 (C_6 indole and C_6 Trp), 123.0 (C_2 indole and C_2 Trp), 126.4 (C_6 *m*,*p*-dichlorobenzyl), 127.1 (C_9 Trp), 127.3 (C_9 indole), 128.6 (C_2 *m*,*p*-dichlorobenzyl), 130.9 (C_4 *m*,*p*-dichlorobenzyl),131.3 (C_5 *m*,*p*-dichlorobenzyl), 132.0 (C_3 *m*,*p*-dichlorobenzyl), 136.4 (C_8 Trp), 136.6 (C_8 indole), 137.2 (C_1 *m*,*p*-dichlorobenzyl), 154.7 (Cq triazole), 155.1 (Cq triazole), 172.0 (CO amide).

***N*-((*R*)-1-(4-(3,4-Dichlorobenzyl)-5-benzyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (24b).** ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.24 (s, 3H, CH_3 Aib), 1.25 (s, 3H, CH_3 Aib), 3.33 (m, 2H, CH_2 βTrp), 4.04 (s, 2H, C*H*$_2$−benzyl), 5.05 (m, 1H, CH αTrp), 5.12 (s, 2H, CH$_2$−*m*,*p*-dichlorobenzyl), 6.49 (dd, 1H, J_o = 8 Hz and J_m = 2 Hz, H_6 *m*,*p*-dichlorobenzyl), 6.80 (t, 1H, J_o = 8 Hz, H_5 Trp), 6.87 (d, 1H, J_m = 2 Hz, H_2 Trp), 6.98 (t, 1H, J_o = 7 Hz, H_6 Trp), 7.02−7.10 (m, 3H, H_2 and H_6 benzyl, H_5 *m*,*p*-dichlorobenzyl), 7.18 (m, 4H, H_3, H_4 and H_5 benzyl, H_2 *m*,*p*-dichlorobenzyl), 7.26 (m, 2H, H_4 and H_7 Trp), 8.04 (brs, 3H, NH_2 Aib, TFA salt), 8.94 (d, 1H, J = 9 Hz, NH amide), 10.81 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 23.4 (CH_3 Aib), 23.8 (CH_3 Aib), 29.0 (C βTrp), 30.4 (*C*H$_2$−benzyl), 45.1 (*C*H$_2$− *m*,*p*-dichlorobenzyl), 45.6 (C αTrp), 56.7 (Cq Aib), 109.6 (C_3 Trp), 111.8 (C_7 Trp), 118.1 (C_4 Trp), 118.6 (C_5 Trp), 121.3 (C_6 Trp), 124.9 (C_2 Trp), 126.4 (C_6 *m*,*p*-dichlorobenzyl and C_4 benzyl), 127.0 (C_2 *m*,*p*-dichlorobenzyl), 127.2 (C_9 Trp), 128.4 (C_2, C_3, C_5 and C_6 benzyl), 130.7 (C_4 and C_5 *m*,*p*-dichlorobenzyl), 131.8 (C_3 *m*,*p*-dichlorobenzyl), 136.0 (C_1 benzyl), 136.4 (C_8 Trp), 136.7 (C_1 *m*,*p*-dichlorobenzyl), 154.1 (Cq triazole), 155.2 (Cq triazole), 172.0 (CO amide).

***N*-((*R*)-1-(4-(3,4-Dichlorobenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (24c).** ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.25 (s, 3H, CH_3 Aib), 1.26 (s, 3H, CH_3 Aib), 2.84 (m, 4H, C*H*$_2$−C*H*$_2$−phenyl), 3.34 (d, 2H, J = 7 Hz, CH_2 βTrp), 5.11 (m, 3H, CH αTrp and CH$_2$−*m*,*p*-dichlorobenzyl), 6.63 (dd, 1H, J_o = 8 Hz and J_m = 2 Hz, H_6 *m*,*p*-dichlorobenzyl), 6.83 (t, 1H, J_o = 8 Hz, H_5 Trp), 6.99 (t, 1H, J_o = 8 Hz, H_6 Trp), 7.05 (d, 1H, J = 2 Hz, H_2 Trp), 7.12 (m, 5H, CHar phenyl), 7.17 (d, 1H, J_o = 8 Hz, H_4 Trp), 7.21 (s, 1H, H_2 *m*,*p*-dichlorobenzyl), 7.27 (d, 1H, J_o = 8 Hz, H_5 *m*,*p*-dichlorobenzyl), 7.39 (d, 1H, J_o = 8 Hz, H_7 Trp), 8.02 (brs, 3H, NH_2 Aib, TFA salt), 8.94 (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 (ppm) 23.5 (CH_3 Aib), 23.8 (CH_3 Aib), 26.4 (*C*H$_2$−CH$_2$−phenyl), 29.1 (C βTrp), 32.6 (CH$_2$−*C*H$_2$−phenyl), 44.7 (CH$_2$−*m*,*p*-dichlorobenzyl), 45.6 (C αTrp), 56.7 (Cq Aib), 109.7 (C_3 Trp), 111.8 (C_7 Trp), 118.1 (C_4 Trp), 118.7 (C_5 Trp), 121.3 (C_6 Trp), 124.9 (C_2 Trp), 126.5 (C_4 phenyl and C_6 *m*,*p*-dichlorobenzyl), 127.2 (C_9 Trp), 128.7 (C_2, C_3, C_5, and C_6 phenyl, C_2 *m*,*p*-dichlorobenzyl), 130.9 (C_4 *m*,*p*-dichlorobenzyl), 131.4 (C_5 *m*,*p*-dichlorobenzyl), 132.0 (C_3 *m*,*p*-dichlorobenzyl), 136.4 (C_8 Trp), 137.2 (C_1 *m*,*p*-dichlorobenzyl), 140.8 (C_1 phenyl), 154.5 (Cq triazole), 154.7 (Cq triazole), 171.9 (CO amide).

***N*-((*R*)-1-(5-((1*H*-Indol-3-yl)methyl)-4-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (25b).** ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.27 (s, 3H, CH_3 Aib), 1.29 (s, 3H, CH_3 Aib), 2.39−2.53 (m, 4H, C*H*$_2$−C*H*$_2$−phenyl), 3.74 (m, 1H, CH_2 βTrp), 3.92 (m, 1H, CH_2 βTrp), 3.99 (s, 2H, CH_2−indole), 5.21 (m, 1H, CH αTrp), 6.74 (m, 2H, H_5 indole and H_5 Trp), 6.90 (t, 1H, J_o = 8 Hz, H_6 Trp), 6.92 (t, 1H, J_o = 8 Hz, H_6 indole), 7.01−7.06 (m, 4H, H_2 and H_6 phenyl, H_2 indole and H_2 Trp), 7.16 (m, 3H, H_3, H_4 and H_5 phenyl), 7.27 (d, 1H, J_o = 8 Hz, H_4 Trp), 7.32 (d, 1H, J_o = 8 Hz, H_7 Trp), 7.36 (d, 1H, J_o = 8 Hz, H_7 indole), 7.50 (d, 1H, J_o = 8 Hz, H_4 indole), 7.99 (brs, 3H, NH_2 Aib, TFA salt), 9.02 (s, 1H, J = 8 Hz, NH amide), 10.79 (s, 1H, NH indole Trp), 10.94 (s, 1H, NH indole). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 21.4 (*C*H$_2$−indole), 23.5 (CH_3 Aib), 23.8 (CH_3 Aib), 29.5 (C βTrp), 35.8 (CH$_2$−*C*H$_2$−phenyl), 44.5 (*C*H$_2$−CH$_2$−phenyl), 45.8 (C αTrp), 56.7 (Cq Aib), 108.5 (C_3 indole), 109.9 (C_3 Trp), 114.0 (C_7 indole and C_7 Trp), 118.4 (C_4 Trp), 118.8 (C_4 indole and C_5 Trp), 119.0 (C_5 indole), 121.4 (C_6 Trp), 121.7 (C_6 indole), 124.0 (C_2 indole and C_2 Trp), 127.1 (C_4 phenyl), 127.7 (C_9 indole and C_9 Trp), 128.8 (C_2 and C_6 phenyl), 129.1 (C_3 and C_5 phenyl), 136.5 (C_8 Trp), 136.6 (C_8 indole), 137.5 (C_1 phenyl), 153.6 (Cq triazole), 155.0 (Cq triazole), 171.8 (CO amide).

(*R*)-*N*-(1-(5-(3-(1*H*-Indol-3-yl)propyl)-4-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (25c). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 1.32 (s, 3H, CH_3 Aib), 1.37 (s, 3H, CH_3 Aib), 1.86 (m, 2H, CH$_2$−C*H*$_2$−CH$_2$−indole), 2.38 (m, 2H, C*H*$_2$−CH$_2$−CH$_2$−indole), 2.65 (m, 4H, CH$_2$−CH$_2$−C*H*$_2$−indole and CH$_2$−C*H*$_2$−phenyl), 3.38 (m, 2H, C*H*$_2$−CH$_2$−phenyl), 3.74 (m, 1H, CH_2 βTrp), 3.92 (m, 1H, CH_2 βTrp), 5.23 (m, 1H, CH αTrp), 6.78 (m, 2H, H_5 indole and H_5 Trp), 6.93 (t, 1H, J_o = 8 Hz, H_6 Trp), 7.01 (m, 3H, H_6 indole, H_2 and H_6 phenyl), 7.05 (d, 1H, J = 2 Hz, H_2 Trp), 7.08 (d, 1H, J = 2 Hz, H_2 indole), 7.15 (m, 3H, H_3, H_4 and H_5 phenyl), 7.29 (d, 1H, J_o = 8 Hz, H_4 Trp), 7.31 (d, 1H, J_o = 8 Hz, H_7 Trp), 7.44 (d, 1H, J_o = 8 Hz, H_7 indole), 7.46 (d, 1H, J_o = 8 Hz, H_4 indole), 8.06 (brs, 3H, NH_2 Aib, TFA salt), 9.05 (d, 1H, 8 Hz, NH amide), 10.76 (s, 1H, NH indole), 10.85 (d, 1H, J = 2 Hz, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 23.5 (CH_3 Aib), 23.6 (*C*H$_2$−CH$_2$−CH$_2$−indole), 23.9 (CH_3 Aib), 24.5 (CH$_2$−CH$_2$−*C*H$_2$−indole), 27.3 (CH$_2$−*C*H$_2$−CH$_2$−indole), 29.4 (C βTrp), 35.7 (CH$_2$−*C*H$_2$−phenyl), 44.5 (*C*H$_2$−CH$_2$−phenyl), 46.1 (C

αTrp), 56.8 (Cq Aib), 109.6 (C_3 Trp), 111.8 (C_7 Trp), 111.9 (C_7 indole), 113.9 (C_3 indole), 118.3 (C_4 Trp), 118.6 (C_5 indole), 118.7 (C_4 indole), 118.9 (C_5 Trp), 121.3 (C_6 Trp), 121.4 (C_6 indole), 122.8 (C_2 indole and C_2 Trp), 127.1 (C_4 phenyl), 127.3 (C_9 Trp), 127.5 (C_9 indole), 128.8 (C_2 and C_6 phenyl), 129.1 (C_3 and C_5 phenyl), 136.5 (C_1 phenyl), 136.8 (C_8 Trp), 137.2 (C_8 indole), 154.7 (2Cq triazole), 172.0 (CO amide).

***N*-((*R*)-2-(1*H*-Indol-3-yl)-1-(4,5-diphenethyl-4*H*-1,2,4-triazol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (25e).** ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.32 (s, 3H, CH_3 Aib), 1.37 (s, 3H, CH_3 Aib), 2.59 (m, 4H, C−CH_2−CH_2−phenyl), 2.83 (t, 2H, J = 8 Hz, N−CH_2−CH_2−phenyl), 3.38 (m, 2H, N−CH_2−CH_2−phenyl), 3.84 (m, 1H, CH_2 βTrp), 3.94 (m, 1H, CH_2 βTrp), 5.23 (m, 1H, CH αTrp), 6.84 (m, 2H, H_4 phenyl from C−CH_2−CH_2−phenyl and H_4 phenyl from N−CH_2−CH_2−phenyl), 6.93 (t, 1H, J_o = 8 Hz, H_5 Trp), 7.00 (t, 1H, J_o = 8 Hz, H_6 Trp), 7.07 (d, 1H, J = 2 Hz, H_2 Trp), 7.11−7.27 (m, 9H, H_2, H_3, H_5 and H_6 phenyl from C−CH_2−CH_2−phenyl, H_2, H_3, H_5 and H_6 phenyl from N−CH_2−CH_2−phenyl and H_4 Trp), 7.50 (d, 1H, J_o = 8 Hz, H_7 Trp), 8.07 (brs, 3H, NH_2 Aib, TFA salt), 9.04 (d, 1H, J = 8 Hz, NH amide), 10.85 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 23.5 (CH_3 Aib), 23.8 (CH_3 Aib), 25.9 (C−*C*H_2−CH_2−phenyl), 29.5 (C βTrp), 32.4 (C−CH_2−*C*H_2−phenyl), 35.8 (N−CH_2−*C*H_2−phenyl), 44.2 (N−*C*H_2−CH_2−phenyl), 45.9 (C αTrp), 56.8 (Cq Aib), 109.7 (C_3 Trp), 111.9 (C_7 Trp), 118.4 (C_4 Trp), 118.9 (C_5 Trp), 121.4 (C_6 Trp), 124.8 (C_2 Trp), 126.6 (C_4 phenyl from C−CH_2−CH_2−phenyl), 127.2 (C_4 phenyl from N−CH_2−CH_2−phenyl), 127.4 (C_9 Trp), 128.7 (C_2 and C_6 phenyl from C−CH_2−CH_2−phenyl, C_2 and C_6 phenyl from N−CH_2−CH_2−phenyl), 128.8 (C_3 and C_5 phenyl from C−CH_2−CH_2−phenyl, C_3 and C_5 phenyl from N−CH_2−CH_2−phenyl), 136.5 (C_1 phenyl from N−CH_2−CH_2−phenyl), 137.5 (C_1 phenyl from C−CH_2−CH_2−phenyl), 140.8 (C_8 Trp), 154.1 (Cq triazole), 154.7 (Cq triazole), 171.9 (CO amide).

2-Amino-*N*-((*R*)-1-(5-benzyl-4-(2,2-diphenylethyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-methylpropanamide Trifluoroacetate Salt (26a). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.29 (s, 3H, CH_3 Aib), 1.34 (s, 3H, CH_3 Aib), 3.37 (m, 4H, CH_2 βTrp and CH_2−benzyl), 3.74 (t, 1H, J = 7 Hz, CH_2−C*H*(Phe)$_2$), 4.21 (dd, 1H, J = 14 and 8 Hz, CH_2−CH(Phe)$_2$), 4.51 (dd, 1H, J = 14 and 8 Hz, CH_2−CH(Phe)$_2$), 5.08 (m, 1H, CH αTrp), 6.72 (m, 2H, H_2 and H_6 benzyl), 6.86−6.93 (m, 5H, H_3, H_4 and H_5 benzyl, H_5 and H_6 Trp), 7.03 (s, 1H, H_2 Trp), 7.06−7.25 (m, 10H, CHar phenyl from CH(Phe)$_2$), 7.33 (d, 1H, J_o = 8 Hz, H_4 Trp), 7.47 (d, 1H, J_o = 8 Hz, H_7 indole), 8.10 (brs, 3H, NH_2 Aib, TFA salt), 8.98 (d, 1H, J = 8 Hz, NH amide), 10.94 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 23.5 (CH_3 Aib), 23.7 (CH_3 Aib), 29.4 (C βTrp), 30.1 (*C*H_2−benzyl), 46.0 (C αTrp), 47.7 (*C*H_2−CH(Phe)$_2$), 51.3 (*C*H(Phe)$_2$), 56.8 (Cq Aib), 109.8 (C_3 Trp), 112.0 (C_7 Trp), 118.5 (C_4 Trp), 119.0 (C_5 Trp), 121.5 (C_6 Trp), 124.8 (C_2 Trp), 127.1 (C_4 phenyl from CH(Phe)$_2$), 127.4 (C_9 Trp, C_4 benzyl), 128.3 (C_2 and C_6 phenyl from CH(Phe)$_2$), 128.8−129.1 (C_3 and C_5 phenyl from CH(Phe)$_2$, C_2, C_3, C_5, and C_6 benzyl), 136.2 (C_1 benzyl), 136.5 (C_8 Trp), 141.0 (C_1 phenyl from CH(Phe)$_2$), 153.5 (Cq triazole), 155.1 (Cq triazole), 172.0 (CO amide).

***N*-((*R*)-1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(2,2-diphenylethyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (26b).** ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.34 (s, 3H, CH_3 Aib), 1.38 (s, 3H, CH_3 Aib), 2.06 (m, 1H, CH_2−CH_2−indole), 2.30 (m, 1H, CH_2−CH_2−indole), 2.78 (m, 2H, CH_2−CH_2−indole), 3.35 (dd, 1H, J = 14 and 7 Hz, CH_2 βTrp), 3.46 (dd, 1H, J = 14 and 9 Hz, CH_2 βTrp), 3.58 (t, 1H, J = 7 Hz, CH_2−C*H*(Phe)$_2$), 4.14 (dd, 1H, J = 14 and 8 Hz, CH_2−CH(Phe)$_2$), 4.39 (dd, 1H, J = 14 and 7 Hz, CH_2−CH(Phe)$_2$), 5.12 (m, 1H, CH αTrp), 6.50 (m, 2H, H_5 indole and H_5 Trp), 6.76 (m, 2H, H_6 indole and H_6 Trp), 6.87 (m, 2H, H_2 indole and H_2 Trp), 6.89−6.96 (m, 2H, H_4 phenyl), 7.03−7,15 (m, 8H, H_2, H_3, H_5 and H_6 phenyl), 7.33 (m, 3H, H_4 indole, H_4 and H_7 Trp), 7.47 (d, 1H, J = 8 Hz, H_7 indole), 8.11 (brs, 3H, NH_2 Aib, TFA salt), 9.04 (d, 1H, J = 8 Hz, NH amide), 10.76 (s, 1H, NH indole), 10.96 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 22.4 (CH_2−*C*H_2−indole), 23.6 (CH_3 Aib), 23.8 (CH_3 Aib), 24.9 (*C*H_2−CH_2−indole), 29.6 (*C* βTrp), 46.1 (C αTrp), 47.5 (*C*H_2−CH(Phe)$_2$), 51.5 (CH_2−*C*H(Phe)$_2$), 56.8 (Cq Aib), 109.8 (C_3 Trp), 111.8 (C_7 Trp), 112.1 (C_7 indole), 113.5 (C_3 indole), 118.4 (C_4 Trp), 118.7 (C_4 and C_5 indole), 119.0 (C_5 Trp), 121.4 (C_6 indole and C_6 Trp), 122.8 (C_2 indole), 125.0 (C_2 Trp), 127.2 (C_9 indole and C_9 Trp), 127.3 (C_4 phenyl), 128.2 (C_2 and C_6 phenyl), 128.7 (C_3 and C_5 phenyl), 136.6 (C_8 indole and C_8 Trp), 141.0 (C_1 phenyl), 154.6 (2 Cq triazole), 172.0 (CO amide).

(*R*)-2-Amino-*N*-(1-(5-benzyl-4-(naphthalen-1-ylmethyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-methylpropanamide Trifluoroacetate Salt (27a). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.18 (s, 3H, CH_3 Aib), 1.24 (s, 3H, CH_3 Aib), 3.17 (dd, 1H, J = 14 and 5 Hz, CH_2 βTrp), 3.36 (dd, 1H, J = 14 and 9 Hz, CH_2 βTrp), 4.05 (m, 2H, CH_2−benzyl), 4.90 (m, 1H, CH αTrp), 5.65 (d, 1H, J = 18 Hz, CH_2−naphtyl), 5.81 (d, 1H, J = 18 Hz, CH_2−naphtyl), 6.12 (d, 1H, J_o = 7 Hz, H_2 naphtyl), 6.38 (t, 1H, J_o = 7 Hz, H_5 Trp), 6.47 (d, 1H, J_o = 8 Hz, H_4 Trp), 6.85 (t, 1H, J_o = 8 Hz, H_6 Trp), 7.03 (d, 1H, J = 2 Hz, H_2 Trp), 7.05−7.12 (m, 5H, CHar benzyl), 7.15 (d, 1H, J_o = 8 Hz, H_7 Trp), 7.19 (d, 1H, J_o = 8 Hz, H_3 naphtyl), 7.58 (m, 2H, H_6 and H_7 naphtyl), 7.81 (d, 1H, J_o = 8 Hz, H_4 naphtyl), 7.89−8.01 (m, 5H, NH_2 Aib TFA salt, H_5 and H_8 naphtyl), 8.92 (d, 1H, J = 8 Hz, NH amide), 10.73 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 23.5 (CH_3 Aib), 23.6 (CH_3 Aib), 29.2 (C βTrp), 30.5 (*C*H_2−benzyl), 44.0 (*C*H_2−naphtyl), 45.6 (C αTrp), 56.6 (Cq Aib), 109.7 (C_3 Trp), 111.7 (C_7 Trp), 117.9 (C_4 Trp), 118.4 (C_5 Trp), 121.1 (C_6 Trp), 122.1 (C_2 naphtyl), 122.8 (C_8 naphtyl), 124.9 (C_2 Trp), 125.7 (C_3 naphtyl), 126.7 (C_6 naphtyl), 126.9 (C_9 Trp), 127.0 (C_7 naphtyl), 128.2 (C_4 benzyl), 128.7−129.1 (C_2, C_3, C_5, and C_6 benzyl, C_4 and C_5 naphtyl), 129.9 (C_9 naphtyl), 131.5 (C_1 naphtyl), 133.5 (C_{10} naphtyl), 136.2 (C_1 benzyl), 136.4 (C_8 Trp), 154.2 (Cq triazole), 155.7 (Cq triazole), 171.9 (CO amide).

(*R*)-*N*-(1-(5-(3-(1*H*-Indol-3-yl)propyl)-4-(naphthalen-1-ylmethyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (27b). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.20 (s, 3H, CH_3 Aib), 1.25 (s, 3H, CH_3 Aib), 1.93 (m, 2H, CH_2−CH_2−CH_2−indole), 2.66 (m, 4H, CH_2−CH_2−CH_2−indole), 3.25 (dd, 1H, J = 14 and 5 Hz, CH_2 βTrp), 3.40 (dd, 1H, J = 14 and 9 Hz, CH_2 βTrp), 4.95 (m, 1H, CH αTrp), 5.66 (d, 1H, J = 18 Hz, CH_2−naphtyl), 5.81 (d, 1H, J = 18 Hz, CH_2−naphtyl), 6.37 (d, 1H, J_o = 7 Hz, H_2 naphtyl), 6.43 (t, 1H, J_o = 7 Hz, H_5 Trp), 6.59 (d, 1H, J_o = 8 Hz, H_4 Trp), 6.86 (m, 3H, H_5 and H_6 indole, H_6 Trp), 6.95 (d, 1H, J = 2 Hz, H_2 indole), 7.00 (d, 1H, J_o = 8 Hz, H_4 indole), 7.06 (d, 1H, J = 2 Hz, H_2 Trp), 7.20−7.33 (m, 3H, H_7 indole, H_7 Trp, H_3 naphtyl), 7.60 (m, 2H, H_6 and H_7 naphtyl), 7.87 (d, 1H, J_o = 8 Hz, H_4 naphtyl), 7.99 (m, 5H, NH_2 Aib TFA salt, H_5 and H_8 naphtyl), 8.95 (d, 1H, J = 8 Hz, NH amide), 10.70 (s, 1H, NH indole), 10.77 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 23.5 (CH_3 Aib), 23.6 (CH_3 Aib), 24.1 (*C*H_2−CH_2−CH_2−indole), 24.5 (CH_2−CH_2−*C*H_2−indole), 27.6 (CH_2−*C*H_2−CH_2−indole), 29.1 (C βTrp), 44.1 (*C*H_2−naphtyl), 45.7 (C αTrp), 56.7 (Cq Aib), 109.7 (C_3 Trp), 111.7 (C_7 indole and C_7 Trp), 113.9 (C_3 indole), 117.9 (C_4 Trp), 118.5 (C_4 indole, C_5 Trp), 118.6 (C_5 indole), 121.1 (C_6 Trp), 121.2 (C_6 indole), 122.1 (C_2 naphtyl), 122.7 (C_2 indole), 122.9 (C_8 naphtyl), 125.0 (C_2 Trp), 125.9 (C_3 naphtyl), 126.8 (C_6 naphtyl), 127.0 (C_9 indole), 127.1 (C_7 naphtyl), 127.4 (C_9 Trp), 128.5 (C_4 naphtyl), 129.2 (C_5 naphtyl), 129.9 (C_9 naphtyl), 131.6 (C_1 naphtyl), 133.6 (C_{10} naphtyl), 136.4 (C_8 Trp), 136.7 (C_8 indole), 155.4 (2Cq triazole), 171.9 (CO amide).

(*R*)-*N*-(1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-(naphthalen-1-ylmethyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (27c). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (s, 3H, CH_3 Aib), 1.28 (s, 3H, CH_3 Aib), 2.93 (m, 2H, *C*H_2−CH_2−indole), 3.01 (m, 2H, CH_2−*C*H_2−indole), 3.30 (dd, 1H, J = 14.3, J = 5.8, CH_2 βTrp), 3.40 (dd, 1H, J = 14.3, J = 8.8, CH_2 βTrp), 5.03 (m, 1H, CαH Trp), 5.62 (d, 1H, J = 18.0, CH_2−naphtyl), 5.76 (d, 1H, J = 18.0, CH_2−naphtyl), 6.36 (d, 1H, J = 7.2, H_2 naphtyl), 6.51 (t, 1H, J = 7.4, H_5 Trp), 6.72 (d, 1H, J

= 7.9, H_4 Trp), 6.76 (t, 1H, J = 7.5, H_5 indole), 6.92 (t, 1H, J = 7.5, H_6 Trp), 7.0 (t, 1H, J = 7.5, H_6 indole), 7.02 (d, 1H, J = 2.0, H_2 indole), 7.09 (d, 1H, J = 2.0, H_2 Trp), 7.13 (d, 1H, J = 7.9, H_4 indole), 7.26 (d, 1H, J = 7.9, H_7 Trp), 7.27 (t, 1H, J = 8.2, H_3 naphtyl), 7.29 (d, 1H, H_7 indole), 7.58−7.64 (m, 2H, H_6, H_7 naphtyl), 7.88 (d, 1H, J = 8.2, H_4 naphtyl), 7.93 (d, 1H, J = 7.9, H_8 naphtyl), 7.98 (brs, 2H, NH_2 Aib, TFA salt), 8.03 (d, 1H, J = 8.2, H_5 naphtyl), 8.96 (d, 1H, J = 7.9, NH Trp), 10.75 (brs, 1H, NH indole), 10.77 (brs, 1H, NH indole Trp). ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.6 (CH_2-CH_2 indole), 23.1 (CH_3 Aib), 23.2 (CH_3 Aib), 25.3 (CH_2-CH_2 indole), 28.8 (C βTrp), 43.3 (CH_2-naphtyl), 45.3 (C αTrp), 56.2 (Cq Aib), 109.4 (C_3 Trp), 111.2 (C_7 Trp, C_7 indole), 112.9 (C_3 indole), 117.5 (C_4 Trp), 117.8 (C_4 indole), 118.0 (C_5 Trp), 118.1 (C_5 indole), 120.7 (C_6 Trp), 120.8 (C_6 indole), 121.6 (C_2 naphtyl), 122.5 (C_2 indole, C_8 naphtyl), 124.4 (C_2 Trp), 125.4 (C_3 naphtyl), 126.3 (C_6 naphtyl), 126.6 (C_9 Indole, C_9 Trp, C_7 naphtyl), 127.9 (C_4 naphtyl), 128.6 (C_5 naphtyl), 129.5 (C_9 naphtyl), 131.4 (C_1 naphtyl), 133.1 (C_{10} naphtyl), 135.9 (C_8 Trp), 136.1 (C_8 indole), 154.7 (2Cq triazole), 171.4 (CO amide).

(*R*)-*N*-(2-(1*H*-Indol-3-yl)-1-(4-(naphthalen-1-ylmethyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (27d). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.21 (s, 3H, CH_3 Aib), 1.25 (s, 3H, CH_3 Aib), 2.46 (m, 2H, CH_2-CH_2-phenyl), 2.88 (m, 2H, CH_2-CH_2-phenyl), 3.26 (dd, 2H, ^3J = 14 and 6 Hz, CH_2 βTrp), 3.36 (dd, 2H, ^3J = 14 and 9 Hz, CH_2 βTrp), 4.99 (m, 1H, CH αTrp), 5.65 (d, 1H, ^3J = 18 Hz, CH_2-naphtyl), 5.78 (d, 1H, ^3J = 18 Hz, CH_2-naphtyl), 6.29 (d, 1H, J_o = 7 Hz, H_2 naphtyl), 6.45 (t, 1H, J_o = 7 Hz, H_5 Trp), 6.62 (d, 1H, J_o = 8 Hz, H_4 Trp), 6.88 (t, 1H, J_o = 8 Hz, H_6 Trp), 7.04−7.06 (m, 4H, H_2 and H_7 Trp, H_2 and H_6 phenyl), 7.07−7.25 (m, 4H, H_3 naphtyl, H_3, H_4 and H_5 phenyl), 7.57−7.60 (m, 2H, H_6 and H_7 naphtyl), 7.86 (d, 1H, J_o = 8 Hz, H_4 naphtyl), 7.98−8.00 (m, 5H, H_5 and H_8 naphtyl, NH_2 Aib, TFA salt), 8.96 (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 (ppm) 23.5 (CH_3 Aib), 23.6 (CH_3 Aib), 26.3 (CH_2CH_2-phenyl), 29.2 (C βTrp), 32.6 (CH_2-CH_2-phenyl), 43.8 (CH_2-naphtyl), 45.6 (C αTrp), 56.7 (Cq Aib), 109.7 (C_3 Trp), 111.7 (C_7 Trp), 117.9 (C_4 Trp), 118.4 (C_5 Trp), 121.1 (C_6 Trp), 122.1 (C_2 naphtyl), 123.0 (C_8 naphtyl), 124.9 (C_2 Trp), 125.9 (C_3 naphtyl), 126.5 (C_6 naphtyl), 126.9 (C_4 phenyl), 127.0 (C_9 Trp and C_7 naphtyl), 127.1 (C_4 naphtyl), 128.4 (C_5 naphtyl), 128.7 (C_2, C_3, C_5, and C_6 phenyl), 130.0 (C_9 naphtyl), 131.7 (C_1 naphtyl), 133.6 (C_{10} naphtyl), 136.4 (C_8 Trp), 140.8 (C_1 phenyl), 154.8 (Cq triazole), 155.3 (Cq triazole), 171.9 (CO amide).

2-Amino-*N*-((*R*)-1-(5-benzyl-4-hexyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-methylpropanamide Trifluoroacetate Salt (28a). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 0.71 (t, 3H, ^3J = 7 Hz, $(CH_2)_5-CH_3$), 0.87 (m, 4H, 2 CH_2), 0.95 (m, 2H, CH_2-CH_3), 1.00 (m, 2H, $N-CH_2-CH_2$), 1.36 (s, 6H, CH_3 Aib), 3.36 (dd, 1H, ^3J = 14 and 7 Hz, CH_2 βTrp), 3.41 (dd, 1H, ^3J = 14 and 7 Hz, CH_2 βTrp), 3.50 (m, 1H, $N-CH_2$), 3.65 (m, 1H, $N-CH_2$), 4.11 (s, 2H, CH_2-benzyl), 5.14 (m, 1H, CH αTrp), 6.90 (t, 1H, J_o = 7 Hz, H_5 Trp), 7.01 (t, 1H, J_o = 7 Hz, H_6 Trp), 7.04 (s, 1H, H_2 Trp), 7.09 (m, 2H, H_2 and H_6 benzyl), 7.17−7.29 (m, 4H, H_4 Trp, H_3, H_4 and H_5 benzyl), 7.47 (d, 1H, J_o = 8 Hz, H_7 Trp), 8.10 (brs, 3H, NH_2 Aib, TFA salt), 9.05 (d, 1H, J = 7 Hz, NH amide), 10.84 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 14.1 ($(CH_2)_5-CH_3$), 22.1 (CH_2-CH_3), 23.8 (CH_3 Aib), 23.5 (CH_3 Aib), 25.8 ($CH_3-CH_2-CH_2-CH_2$), 29.5 (C βTrp), 30.3 ($N-CH_2-CH_2$), 30.8 (CH_2-benzyl and $CH_3-CH_2-CH_2$), 43.3 ($N-CH_2-CH_2$), 46.1 (C αTrp), 56.8 (Cq Aib), 109.6 (C_3 Trp), 111.9 (C_7 Trp), 118.2 (C_4 Trp), 118.8 (C_5 Trp), 121.4 (C_6 Trp), 124.7 (C_2 Trp), 127.2 (C_4 benzyl), 127.3 (C_9 Trp), 128.8 (C_2, C_3, C_5 and C_6 benzyl), 136.2 (C_1 benzyl), 136.5 (C_8 Trp), 153.1 (Cq triazole), 155.1 (Cq triazole), 171.9 (CO amide).

(*R*)-*N*-(1-(5-(2-(1*H*-Indol-3-yl)ethyl)-4-hexyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (28b). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.77 (t, 3H, J = 7.2 $(CH_2)_5-CH_3$), 1.01 (m, 4H, $2CH_2$), 1.11 (m, 2H, CH_2-CH_3), 1.14 (m, 1H, $N-CH_2-CH_2$), 1.33 (m, 1H, $N-CH_2-CH_2$), 1.40 (s, 3H, CH_3 Aib), 1.42 (s, 3H, CH_3 Aib), 3.05 (m, 2H, CH_2-CH_2-indole), 3.10 (m, 2H, CH_2-CH_2-indole), 3.37 (dd, 1H, J = 14.2, J = 7.6, CH_2 βTrp), 3.44 (dd, 1H, J = 14.2, J = 7.6, CH_2 βTrp), 3.58 (m, 1H, 1H $N-CH_2$), 3.71 (m, 1H, $N-CH_2$), 5.21 (m, 1H, CH αTrp), 6.96 (t, 1H, H_5 Trp), 6.97 (t, 1H, H_5 indole), 7.06 (t, 2H, H_6 Trp, H_6 indole), 7.09 (s, 1H, H_2 Trp), 7.13 (s, 1H, H_2 indole), 7.34 (d, 2H, H_7 Trp, H_7 indole),7.48 (d, 1H, d, H_4 indole), 7.50 (d, 1H, H_4 Trp), 8.14 (brs, 3H, NH_2 Aib, TFA salt), 9.08 (d, 1H, J = 7.8, NH amide), 10.84 (s, 1H, NH indole), 10.88 (s, 1H, NH indole Trp). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.7 $(CH_2)_5-CH_3$), 21.7 (CH_2-CH_3), 22.4 (CH_2-CH_2 indole), 23.1 (CH_3 Aib), 23.3 (CH_3 Aib), 25.1 (CH_2-CH_2 indole), 25.5 ($CH_3-CH_2-CH_2-CH_2$), 29.1 (C βTrp), 29.3 ($N-CH_2-CH_2$), 30.4 ($CH_3-CH_2-CH_2$), 42.6 ($N-CH_2-CH_2$), 45.6 (C αTrp), 56.3 (Cq Aib), 109.2 (C_3 Trp), 111.4 (C_7 Trp, C_7 indole), 112.8 (C_3 indole), 117.7 (C_4 Trp), 118.0 (C_5 indole), 118.2 (C_4 indole), 118.4 (C_5 Trp), 120.9 (C_6 indole, C_6 Trp), 122.6 (C_2 indole), 124.3 (C_2 Trp), 126.8 (C_9 Trp), 126.9 (C_9 indole), 136.0 (C_8 Trp), 136.2 (C_8 indole), 154.0 (Cq triazole), 154.1 (Cq triazole), 171.4 (CO amide).

(*R*)-*N*-(1-(5-(3-(1*H*-Indol-3-yl)propyl)-4-hexyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (28c). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 0.74 (t, 3H, J = 6 Hz, $CH_3-CH_2-CH_2-CH_2-CH_2-CH_2$), 0.95 (brs, 4H, $CH_3-CH_2-CH_2-CH_2-CH_2-CH_2$), 1.06 (m, 3H, $CH_3-CH_2-CH_2-CH_2-CH_2-CH_2$ and $N-CH_2-CH_2$), 1.38 (s, 7H, CH_3 Aib and $N-CH_2-CH_2$), 1.97 (m, 2H, $CH_2-CH_2-CH_2-$indole), 2.71 (m, 4H, $CH_2-CH_2-CH_2-$indole), 3.37 (m, 2H, CH_2 βTrp), 3.56 (m, 2H, $N-CH_2$), 5.15 (m, 1H, CH αTrp), 6.91 (m, 2H, H_5 indole and H_5 Trp), 7.00 (m, 2H, H_6 indole and H_6 Trp), 7.07 (s, 2H, H_2 indole and H_2 Trp), 7.29 (d, 2H, J_o = 8 Hz, H_7 indole and H_7 Trp), 7.45 (d, 2H, J = 7 Hz, H_4 indole and H_4 Trp), 8.15 (brs, 3H, NH_2 Aib, TFA salt), 9.10 (d, 1H, J = 6 Hz, NH amide), 10.77 (s, 1H, NH indole), 10.85 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 14.2 ($CH_3-CH_2-CH_2-CH_2-CH_2-CH_2$), 22.2 ($CH_3-CH_2-CH_2-CH_2-CH_2-CH_2$ and $CH_2-CH_2-CH_2-$indole), 23.6 (CH_3 Aib), 23.7 (CH_3 Aib), 24.5 ($CH_2-CH_2-CH_2-$indole), 25.9 ($CH_3-CH_2-CH_2-CH_2-CH_2-CH_2$), 27.5 (C βTrp and $CH_2-CH_2-CH_2-$indole), 29.7 ($N-CH_2-CH_2$), 30.8 ($CH_3-CH_2-CH_2-CH_2-CH_2-CH_2$), 43.2 ($N-CH_2$), 46.1 (C αTrp), 56.8 (Cq Aib), 109.5 (C_3 Trp), 111.8 (C_7 Trp), 111.9 (C_7 indole), 113.9 (C_3 indole), 118.1 (C_4 Trp), 118.5 (C_5 indole), 118.6 (C_4 indole), 118.9 (C_5 Trp), 121.3 (C_6 indole and C_6 Trp), 122.8 (C_2 indole and C_2 Trp), 127.3 (C_9 Trp), 127.4 (C_9 indole), 136.5 (C_8 Trp), 136.8 (C_8 indole), 154.7 (2Cq triazole), 172.0 (CO amide).

***N*-((*R*)-1-(4-(2-(1*H*-Indol-3-yl)ethyl)-5-benzyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (29a).** ^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ (ppm) 1.31 (s, 3H, CH_3 Aib), 1.35 (s, 3H, CH_3 Aib), 2.51 (m, 2H, CH_2-CH_2-indole), 3.37 (m, 2H, CH_2 βTrp), 3.76−3.90 (m, 4H, CH_2-benzyl and CH_2-CH_2-indole), 5.25 (m, 1H, CH αTrp), 6.88 (t, 2H, J_o = 7 Hz, H_5 indole and H_5 Trp), 6.95 (t, 2H, J_o = 7 Hz, H_6 indole and H_6 Trp), 7.03 (m, 4H, H_2 Trp, H_2 indole, H_2 and H_6 benzyl), 7.16 (d, 2H, J_o = 8 Hz, H_4 indole and H_4 Trp), 7.20−7,30 (m, 4H, H_7 indole, H_3, H_4 and H_5 benzyl), 7.47 (d, 1H, J_o = 8 Hz, H_7 Trp), 8.05 (brs, 3H, NH_2 Aib, TFA salt), 9.05 (d, 1H, J = 8 Hz, NH amide), 10.83 (s, 1H, NH indole), 10.88 (s, 1H, NH indole Trp). ^{13}C NMR (100 MHz, DMSO-d_6, 300 K) δ (ppm) 23.5 (CH_3 Aib), 23.7 (CH_3 Aib), 29.6 (C βTrp), 30.3 (CH_2-benzyl and CH_2-CH_2-indole), 44.1 (CH_2-CH_2-indole), 46.1 (C αTrp), 56.8 (Cq Aib), 109.8 (C_3 Trp), 109.9 (C_3 indole), 111.9 (C_7 indole and C_7 Trp), 118.3 (C_4 Trp), 118.4 (C_4 indole), 118.9 (C_5 indole and C_5 Trp), 121.3 (C_6 Trp), 121.5 (C_6 indole), 123.7 (C_2 indole), 124.7 (C_2 Trp), 127.0 (C_9 indole), 127.2 (C_4 benzyl), 127.4 (C_9 Trp), 128.8 (C_3 and C_5 benzyl), 129.0 (C_2 and C_6 benzyl), 136.3 (C_1 benzyl), 136.4 (C_8 indole and C_8 Trp), 153.1 (Cq triazole), 155.3 (Cq triazole), 171.8 (CO amide).

(*R*)-*N*-(1-(4,5-bis(2-(1*H*-Indol-3-yl)ethyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (29b). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.30 (s, 3H, CH_3 Aib), 1.37 (s, 3H, CH_3 Aib), 2.50 (m, 2H, $N-CH_2-CH_2-$indole), 2.68 (t, 2H, J_o = 8 Hz, $C-CH_2-CH_2-$

indole), 2.91 (t, 2H, J_o = 8 Hz, C−CH_2−CH_2−indole), 3.34 (m, 2H, N−CH_2−CH_2−indole), 3.93 (m, 2H, CH_2 βTrp), 5.25 (m, 1H, CH αTrp), 6.72−6.94 (m, 4H, H_5 and H_6 Trp, H_5 indole from C−CH_2−CH_2−indole and H_5 indole from N−CH_2−CH_2−indole), 6.98−7.04 (m, 4H, H_2 Trp, H_6 indole from C−CH_2−CH_2−indole, H_2 and H_6 indole from N−CH_2−CH_2−indole), 7.11 (s, 1H, H_2 indole from C−CH_2−CH_2−indole), 7.19 (d, 1H, J_o = 8 Hz, H_4 indole from N−CH_2−CH_2−indole), 7.28 (m, 3H, H_4 and H_7 Trp, H_7 indole from N−CH_2−CH_2−indole), 7.40 (d, 1H, J_o = 8 Hz, H_7 indole from C−CH_2−CH_2−indole), 7.44 (d, 1H, J_o = 8 Hz, H_4 indole from C−CH_2−CH_2−indole), 8.04 (brs, 3H, NH_2 Aib, TFA salt), 9.69 (d, 1H, J = 8 Hz, NH amide), 10.73 (s, 1H, NH indole from C−CH_2−CH_2−indole), 10.82 (d, 1H, J = 2 Hz, NH indole Trp), 10.84 (s, 1H, NH indole from N−CH_2−CH_2−indole). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 22.7 (C−CH_2−CH_2−indole), 23.6 (CH_3 Aib), 23.8 (CH_3 Aib), 25.4 (C−CH_2−CH_2−indole), 26.0 (N−CH_2−CH_2−indole), 29.6 (C βTrp), 43.9 (N−CH_2−CH_2−indole), 46.0 (C αTrp), 56.8 (Cq Aib), 109.5 (C_3 indole from N−CH_2−CH_2−indole), 109.9 (C_3 Trp), 111.7 (C_7 Trp), 111.9 (C_7 indole from N−CH_2−CH_2−indole and C_7 indole from C−CH_2−CH_2−indole), 113.5 (C_3 indole from C−CH_2−CH_2−indole), 118.3 (C_4 indole from N−CH_2−CH_2−indole), 118.4 (C_4 Trp), 118.5 (C_5 indole from C−CH_2−CH_2−indole), 118.7 (C_4 indole from C−CH_2−CH_2−indole), 118.9 (C_5 Trp), 119.0 (C_5 indole from N−CH_2−CH_2−indole), 121.3 (C_6 Trp), 121.5 (C_6 indole from C−CH_2−CH_2−indole and C_6 indole from N−CH_2−CH_2−indole), 122.8 (C_2 Trp, C_2 indole from C−CH_2−CH_2−indole and C_2 indole from N−CH_2−CH_2−indole), 127.1 (C_9 Trp), 127.2 (C_9 indole from C−CH_2−CH_2−indole), 127.4 (C_9 indole from N−CH_2−CH_2−indole), 136.5 (C_8 Trp and C_8 indole from C−CH_2−CH_2−indole), 136.6 (C_8 indole from N−CH_2−CH_2−indole), 154.5 (Cq triazole), 154.8 (Cq triazole), 171.8 (CO amide).

(*R*)-*N*-(1-(4-(2-(1*H*-Indol-3-yl)ethyl)-5-(3-(1*H*-indol-3-yl)propyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (29c). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 1.29 (s, 3H, CH_3 Aib), 1.35 (s, 3H, CH_3 Aib), 1.78 (m, 2H, CH_2−CH_2−CH_2−indole), 2.34 (m, 2H, CH_2−CH_2−CH_2−indole), 2.48 (m, 2H, N−CH_2−CH_2−indole), 2.80 (m, 2H, CH_2−CH_2−CH_2−indole), 3.34 (m, 2H, N−CH_2−CH_2−indole), 3.94 (m, 2H, CH_2 βTrp), 5.27 (m, 1H, CH αTrp), 6.73−6.94 (m, 4H, H_5 and H_6 Trp, H_5 indole from N−CH_2−CH_2−indole and H_5 indole from CH_2−CH_2−CH_2−indole), 6.99−7.04 (m, 5H, H_2 Trp, H_2 and H_6 indole from N−CH_2−CH_2−indole, H_2 and H_6 indole from CH_2−CH_2−CH_2−indole), 7.20 (d, 1H, J_o = 8 Hz, H_4 indole from N−CH_2−CH_2−indole), 7.29 (m, 3H, H_4 and H_7 Trp, H_7 indole from N−CH_2−CH_2−indole), 7.40 (d, 1H, J_o = 8 Hz, H_7 indole from CH_2−CH_2−CH_2−indole), 7.44 (d, 1H, J_o = 8 Hz, H_4 indole from CH_2−CH_2−CH_2−indole), 8.05 (brs, 3H, NH_2 Aib, TFA salt), 9.07 (d, 1H, J = 8 Hz, NH amide), 10.75 (s, 1H, NH indole from CH_2−CH_2−CH_2−indole), 10.86 (s, 1H, NH indole Trp), 10.90 (s, 1H, NH indole from N−CH_2−CH_2−indole). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 23.6 (CH_3 Aib), 23.8 (CH_3 Aib), 24.5 (CH_2−CH_2−CH_2−indole), 25.8 (CH_2−CH_2−CH_2−indole), 27.2 (CH_2−CH_2−CH_2−indole), 29.4 (C βTrp), 44.1 (N−CH_2−CH_2−indole), 46.0 (C αTrp), 52.9 (N−CH_2−CH_2−indole), 56.8 (Cq Aib), 109.7 (C_3 Trp and C_3 indole from N−CH_2−CH_2−indole), 111.8 (C_7 Trp), 111.9 (C_7 indole from N−CH_2−CH_2−indole and C_7 indole from CH_2−CH_2−CH_2−indole), 114.0 (C_3 indole from CH_2−CH_2−CH_2−indole), 118.2 (C_4 indole from N−CH_2−CH_2−indole), 118.3 (C_4 Trp), 118.5 (C_5 indole from CH_2−CH_2−CH_2−indole), 118.6 (C_4 indole from CH_2−CH_2−CH_2−indole), 118.9 (C_5 Trp), 119.0 (C_5 indole from N−CH_2−CH_2−indole), 121.3 (C_6 Trp), 121.4 (C_6 indole from CH_2−CH_2−CH_2−indole), 121.6 (C_6 indole from N−CH_2−CH_2−indole), 122.7 (C_2 Trp, C_2 indole from N−CH_2−CH_2−indole and C_2 indole from CH_2−CH_2−CH_2−indole), 127.1 (C_9 Trp), 127.4 (C_9 indole from N−CH_2−CH_2−indole and C_9 indole from CH_2−CH_2−CH_2−indole), 136.4 (C_8 Trp), 136.5 (C_8 indole from CH_2−CH_2−CH_2−indole), 136.7 (C_8 indole from N−CH_2−CH_2−indole), 154.7 (2 Cq triazole), 171.9 (CO amide).

(*R*)-*N*-(1-(4-(4-Methylbenzyl)-5-(3-phenylpropyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (30a). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 1.25 (s, 3H, CH_3 Aib), 1.28 (s, 3H, CH_3 Aib), 1.73 (m, 2H, CH_2−CH_2−CH_2−phenyl), 2.23 (s, 3H, CH_3 *p*-methylbenzyl), 2.49−2.54 (m, 4H, CH_2−CH_2−CH_2−phenyl), 3.33 (m, 2H, CH_2 βTrp), 5.04 (s, 2H, CH_2−*p*-methylbenzyl), 5.16 (m, 1H, CH αTrp), 6.74 (d, 2H, J_o = 8 Hz, H_3 and H_5 *p*-methylbenzyl), 6.80 (t, 1H, J_o = 7 Hz, H_5 Trp), 6.98 (t, 1H, J_o = 7 Hz, H_6 Trp), 7.03 (d, 1H, J = 2 Hz, H_2 Trp), 7.06 (m, 5H, CHar phenyl), 7.14 (d, 1H, J_o = 7 Hz, H_4 Trp), 7.20 (d, 2H, J_o = 7 Hz, H_2 and H_6 *p*-methylbenzyl), 7.27 (d, 1H, J_o = 8 Hz, H_7 Trp), 8.01 (brs, 3H, NH_2 Aib, TFA salt), 8.95 (d, 1H, J = 8 Hz, NH amide), 10.80 (d, 1H, J = 2 Hz, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 21.0 (CH_3 *p*-methylbenzyl), 23.5 (CH_3 Aib), 23.8 (CH_3 Aib), 24.0 (CH_2−CH_2−CH_2−phenyl), 28.5 (CH_2−CH_2−CH_2−phenyl), 29.1 (C βTrp), 34.7 (CH_2−CH_2−CH_2−phenyl), 45.7 (C αTrp), 45.8 (CH_2−*p*-methylbenzyl), 56.8 (Cq Aib), 109.8 (C_3 Trp), 111.8 (C_7 Trp), 118.3 (C_4 Trp), 118.7 (C_5 Trp), 121.3 (C_6 Trp), 124.9 (C_2 Trp), 126.2 (C_4 phenyl), 126.4 (C_3 and C_5 *p*-methylbenzyl), 127.3 (C_9 Trp), 128.7 (C_2, C_3, C_5 and C_6 phenyl), 129.8 (C_2 and C_6 *p*-methylbenzyl), 133.0 (C_1 *p*-methylbenzyl), 136.4 (C_8 Trp), 137.5 (C_4 *p*-methylbenzyl), 141.7 (C_1 phenyl), 154.8 (2Cq triazole), 171.9 (CO amide).

(*R*)-*N*-(1-(4-(4-Methylbenzyl)-5-(3-benzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (30b). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.22 (s, 3H, CH_3 Aib), 1.27 (s, 3H, CH_3 Aib), 2.22 (s, 3H, CH_3 *p*-methylbenzyl), 3.22 (dd, 1H, J = 14 and 6 Hz, CH_2 βTrp), 3.33 (dd, 1H, J = 14 and 9 Hz, CH_2 βTrp), 3.99 (s, 2H, CH_2−benzyl), 5.04 (s, 2H, CH_2−*p*-methylbenzyl), 5.09 (m, 1H, CH αTrp), 6.64 (d, 2H, J_o = 8 Hz, H_3 and H_5 *p*-methylbenzyl), 6.78 (t, 1H, J_o = 7 Hz, H_5 Trp), 6.98 (t, 4H, J_o = 7 Hz, H_6 Trp, H_3, H_4 and H_5 benzyl), 7.01 (d, 1H, J = 2 Hz, H_2 Trp), 7.07 (d, 2H, J_o = 7 Hz, H_2 and H_6 *p*-methylbenzyl), 7.20 (m, 3H, H_4 Trp, H_2 and H_6 benzyl), 7.26 (d, 1H, J_o = 8 Hz, H_7 Trp), 7.98 (brs, 3H, NH_2 Aib, TFA salt), 8.89 (d, 1H, J = 8 Hz, NH amide), 10.74 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 21.0 (CH_3 *p*-methylbenzyl), 23.5 (CH_3 Aib), 23.7 (CH_3 Aib), 29.1 (C βTrp), 30.6 (CH_2−benzyl), 45.7 (C αTrp), 46.0 (CH_2−*p*-methylbenzyl), 56.7 (Cq Aib), 109.8 (C_3 Trp), 111.7 (C_7 Trp), 118.3 (C_4 Trp), 118.6 (C_5 Trp), 121.2 (C_6 Trp), 124.8 (C_2 Trp), 126.3 (C_3 and C_5 *p*-methylbenzyl), 127.0 (C_4 benzyl), 127.2 (C_9 Trp), 128.9 (C_2, C_3, C_5, and C_6 benzyl), 129.7 (C_2 and C_6 *p*-methylbenzyl), 132.9 (C_1 *p*-methylbenzyl), 136.3 (C_4 *p*-methylbenzyl), 136.4 (C_8 Trp), 137.4 (C_1 benzyl), 153.9 (Cq triazole), 155.3 (Cq triazole), 171.8 (CO amide).

(*R*)-*N*-(1-(5-(2-(1*H*-Indol-2-yl)ethyl)-4-(4-methylbenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (30c). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.25 (s, 3H, CH_3 Aib), 1.28 (s, 3H, CH_3 Aib), 2.23 (s, 3H, CH_3−*p*-methylbenzyl), 2.84−2.97 (m, 4H, CH_2−CH_2−indole), 3.32 (m, 2H, CH_2 βTrp), 5.04 (s, 2H, CH_2−*p*-methylbenzyl), 5.16 (m, 1H, CH αTrp), 6.79−6.86 (m, 4H, CH ar *p*-methylbenzyl), 6.99−7.05 (m, 4H, H_5 and H_6 indole, H_5 and H_6 Trp), 7.08 (m, 3H, H_2 indole, H_2 and H_4 Trp), 7.25−7.30 (m, 3H, H_4 and H_7 indole, H_7 Trp), 8.00 (brs, 3H, NH_2 Aib, TFA salt), 8.94 (d, 1H, J = 8 Hz, NH amide), 10.76 (s, 1H, NH indole), 10.78 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 21.0 (CH_3− *p*-methylbenzyl), 22.8 (CH_2−CH_2−indole), 23.8 (CH_3 Aib), 23.9 (CH_3 Aib), 25.9 (CH_2−CH_2−indole), 28.5 (C βTrp), 45.7 (CH_2− *p*-methylbenzyl and C αTrp), 56.7 (Cq Aib), 109.9 (C_3 Trp), 111.8 (C_7 indole and C_7 Trp), 113.4 (C_3 indole), 118.1 (C_4 Trp), 118.3 (C_4 indole), 118.5 (C_5 indole), 118.7 (C_5 Trp), 120.9 (C_6 indole and C_6 Trp), 121.3 (C_2 indole and C_2 Trp), 126.3 (C_3 and C_5 *p*-methylbenzyl), 127.2 (C_9 indole), 127.3 (C_9 Trp), 129.8 (C_2 and C_6 *p*-methylbenzyl), 133.1 (C_1 *p*-methylbenzyl), 135.8 (C_8 indole, C_8 Trp), 136.4 (C_4 *p*-methylbenzyl), 154.8 (Cq triazole), 155.0 (Cq triazole), 171.9 (CO amide).

(*R*)-*N*-(1-(4-(4-Methylbenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (30d). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.25 (s, 3H, CH_3 Aib), 1.28 (s, 3H, CH_3 Aib), 2.23 (s,

3H, CH_3 *p*-methylbenzyl), 2.83 (m, 4H, C*H*$_2$−C*H*$_2$−phenyl), 3.32 (m, 2H, CH_2 βTrp), 5.05 (s, 2H, CH_2−*p*-methylbenzyl), 5.18 (m, 1H, CH αTrp), 6.75 (d, 2H, $J_o = 8$ Hz, H_3 and H_5 *p*-methylbenzyl), 6.82 (t, 1H, $J_o = 8$ Hz, H_5 Trp), 6.99 (t, 1H, $J_o = 8$ Hz, H_6 Trp), 7.02−7.11 (m, 6H, H_2 Trp and CHar phenyl), 7.15 (d, 1H, $J_o = 7$ Hz, H_4 Trp), 7.20 (d, 2H, $J_o = 7$ Hz, H_2 and H_6 *p*-methylbenzyl), 7.28 (d, 1H, $J_o = 8$ Hz, H_7 Trp), 8.01 (brs, 3H, NH_2 Aib, TFA salt), 8.93 (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 (ppm) 21.0 (CH_3 *p*-methylbenzyl), 23.6 (CH_3 Aib), 23.8 (CH_3 Aib), 26.5 (*C*H$_2$−CH$_2$−phenyl), 29.1 (C βTrp), 32.7 (CH$_2$−*C*H$_2$−phenyl), 45.7 (C αTrp and CH$_2$−*p*-methylbenzyl), 56.8 (Cq Aib), 109.8 (C_3 Trp), 111.8 (C_7 Trp), 118.3 (C_4 Trp), 118.7 (C_5 Trp), 121.3 (C_6 Trp), 124.8 (C_2 Trp), 126.4 (C_3 and C_5 *p*-methylbenzyl), 126.6 (C_4 phenyl), 127.3 (C_9 Trp), 128.7 (C_2, C_3, C_5, and C_6 phenyl), 129.8 (C_2 and C_6 *p*-methylbenzyl), 133.0 (C_1 *p*-methylbenzyl), 136.4 (C_8 Trp), 137.5 (C_4 *p*-methylbenzyl), 140.9 (C_1 phenyl), 154.5 (Cq triazole), 154.9 (Cq triazole), 171.9 (CO amide).

(*R*)-*N*-(1-(4-(4-Ethylbenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (31). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.10 (t, 3H, $J = 8$ Hz, C*H*$_3$−CH$_2$ *p*- ethylbenzyl), 1.25 (s, 3H, CH_3 Aib), 1.28 (s, 3H, CH_3 Aib), 2.53 (q, 2H, $J = 8$ Hz, CH$_3$−C*H*$_2$ *p*-ethylbenzyl), 2.83 (m, 4H, C*H*$_2$−C*H*$_2$−phenyl), 3.34 (m, 2H, CH_2 βTrp), 5.07 (s, 2H, C*H*$_2$−*p*-ethylbenzyl), 5.19 (m, 1H, CH αTrp), 6.77 (d, 2H, $J_o = 8$ Hz, H_3 and H_5 *p*-ethylbenzyl), 6.81 (t, 1H, $J_o = 7$ Hz, H_5 Trp), 6.99 (t, 1H, $J_o = 8$ Hz, H_6 Trp), 7.05−7.10 (m, 7H, CHar phenyl, H_2 and H_6 *p*-ethylbenzyl), 7.13 (d, 1H, $J = 2$ Hz, H_2 Trp), 7.20 (d, 1H, $J_o = 7$ Hz, H_4 Trp), 7.28 (d, 1H, $J_o = 8$ Hz, H_7 Trp), 8.03 (brs, 3H, NH_2 Aib, TFA salt), 8.94 (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 (ppm) 15.9 (*C*H$_3$−CH$_2$ *p*-ethylbenzyl), 23.5 (CH_3 Aib), 23.8 (CH_3 Aib), 26.5 (*C*H$_2$−CH$_2$−phenyl), 28.1 (CH$_3$−*C*H$_2$ *p*-ethylbenzyl), 29.1 (C βTrp), 32.7 (CH$_2$−*C*H$_2$−phenyl), 45.7 (C αTrp), 45.8 (*C*H$_2$−*p*-ethylbenzyl), 56.8 (Cq Aib), 109.8 (C_3 Trp), 111.8 (C_7 Trp), 118.3 (C_4 Trp), 118.7 (C_5 Trp), 121.3 (C_6 Trp), 124.9 (C_2 Trp), 126.5 (C_3 and C_5 *p*-ethylbenzyl), 126.6 (C_4 phenyl), 127.3 (C_9 Trp), 128.6 (C_2 and C_6 *p*-ethylbenzyl, C_2, C_3, C_5, and C_6 phenyl), 133.1 (C_1 *p*-ethylbenzyl), 136.5 (C_8 Trp), 140.8 (C_1 phenyl), 143.8 (C_4 *p*-ethylbenzyl), 154.6 (Cq triazole), 154.9 (Cq triazole), 171.9 (CO amide).

***N*-((*R*)-1-(4-(4-Nitrobenzyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (32).** ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.28 (s, 3H, CH_3 Aib), 1.29 (s, 3H, CH_3 Aib), 2.77−2.94 (m, 4H, C*H*$_2$−C*H*$_2$−phenyl), 3.28 (dd, 1H, $^3J = 14$ and 8 Hz, CH_2 βTrp), 3.43 (dd, 1H, $^3J = 14$ and 7 Hz, CH_2 βTrp), 5.05 (m, 1H, CH αTrp), 5.25 (d, 2H, $J = 7$ Hz, C*H*$_2$−*p*-nitrobenzyl), 6.72 (t, 1H, $J_o = 7$ Hz, H_5 Trp), 6.89 (d, 2H, $J_o = 9$ Hz, H_2 and H_6 *p*-nitrobenzyl), 6.92 (t, 1H, $J_o = 7$ Hz, H_6 Trp), 7.00 (d, 1H, $J_m = 2$ Hz, H_2 Trp), 7.08−7.15 (m, 4H, H_4 and H_7 Trp, H_2 and H_6 phenyl), 7.17 (t, 2H, $J_o = 7$ Hz, H_3 and H_5 phenyl), 7.24 (t, 1H, $J_o = 8$ Hz, H_4 phenyl), 7.92 (d, 2H, $J_o = 9$ Hz, H_3 and H_5 *p*-nitrobenzyl), 8.06 (brs, 3H, NH_2 Aib, TFA salt), 8.98 (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 (ppm) 23.5 (CH_3 Aib), 23.8 (CH_3 Aib), 26.4 (*C*H$_2$−CH$_2$−phenyl), 29.1 (C βTrp), 32.6 (CH$_2$−*C*H$_2$−phenyl), 45.3 (*C*H$_2$−*p*-nitrobenzyl), 45.7 (C αTrp), 56.8 (Cq Aib), 109.6 (C_3 Trp), 111.8 (C_7 Trp), 118.1 (C_4 Trp), 118.5 (C_5 Trp), 121.2 (C_6 Trp), 124.1 (C_2 and C_6 *p*-nitrobenzyl), 124.8 (C_2 Trp), 126.5 (C_4 phenyl), 127.2 (C_9 Trp, C_3 and C_5 *p*-nitrobenzyl), 128.7 (C_2, C_3, C_5, and C_6 phenyl), 136.4 (C_8 Trp), 140.8 (C_1 phenyl), 143.5 (C_1 *p*-nitrobenzyl), 147.1 (C_4 *p*-nitrobenzyl), 154.5 (Cq triazole), 154.8 (Cq triazole), 172.0 (CO amide).

(*R*)-2-Amino-*N*-(1-(5-benzyl-4-(pyridin-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-methylpropanamide Trifluoroacetate Salt (33a). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.23 (s, 3H, CH_3 Aib), 1.27 (s, 3H, CH_3 Aib), 3.34 (dd, 1H, $J = 14$ and 6 Hz, CH_2 βTrp), 3.43 (dd, 1H, $J = 14$ and 9 Hz, CH_2 βTrp), 4.13 (s, 2H, C*H*$_2$−benzyl), 5.22 (s, 1H, CH αTrp), 5.35 (s, 2H, CH_2−*o*-pyridyl), 6.80 (t, 1H, $J_o = 8$ Hz, H_5 Trp), 6.92 (t, 1H, $J_o = 8$ Hz, H_5 pyridyl), 6.97 (t, 1H, $J_o = 8$ Hz, H_6 Trp), 7.04 (d, 1H, $J_o = 8$ Hz, H_4 Trp), 7.07 (d, 1H, $J = 2$ Hz, H_2 Trp), 7.10−7.16 (m, 5H, CHar benzyl), 7.19 (s, 1H, H_3 *o*-pyridyl), 7.26 (d, 1H, $J_o = 8$ Hz, H_7 Trp), 7.57 (t, 1H, $J_o = 9$ Hz, H_4 *o*-pyridyl), 8.16 (brs, 3H, NH_2 Aib, TFA salt), 8.36 (d, 1H, $J_{\alpha\beta} = 5$ Hz, H_6 *o*-pyridyl), 9.01 (d, 1H, $J = 8$ Hz, NH amide), 10.85 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 23.4 (CH_3 Aib), 23.7 (CH_3 Aib), 28.6 (C βTrp), 30.4 (CH_2−benzyl), 45.7 (C αTrp), 47.7 (CH_2− *o*-pyridyl), 56.7 (Cq Aib), 109.8 (C_3 Trp), 111.8 (C_7 Trp), 118.3 (C_4 Trp), 118.6 (C_5 Trp), 121.2 (C_6 Trp), 121.7 (C_3 *o*-pyridyl), 123.3 (C_5 *o*-pyridyl), 124.8 (C_2 Trp), 127.1 (C_4 benzyl), 127.3 (C_9 Trp), 128.8 (C_2 and C_6 benzyl), 129.0 (C_3 and C_5 benzyl), 135.6 (C_1 benzyl), 136.4 (C_8 Trp), 137.5 (C_4 *o*-pyridyl), 149.5 (C_6 *o*-pyridyl), 154.1 (Cq triazole), 154.2 (Cq triazole), 155.7 (C_2 *o*-pyridyl), 172.0 (CO amide).

(*R*)-2-Amino-*N*-(1-(5-phenethyl-4-(pyridin-2-ylmethyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-methylpropanamide Trifluoroacetate Salt (33b). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.26 (s, 3H, CH_3 Aib), 1.29 (s, 3H, CH_3 Aib), 2.95 (m, 4H, C*H*$_2$−C*H*$_2$−phenyl), 3.40 (m, 2H, CH_2 βTrp), 5.26 (m, 1H, CH αTrp), 5.37 (s, 2H, CH_2−*o*-pyridyl), 6.83 (t, 1H, $J_o = 7$ Hz, H_5 Trp), 6.98 (t, 1H, $J_o = 8$ Hz, H_6 Trp), 7.11−7.30 (m, 10H, H_2, H_4 and H_7 Trp, CHar phenyl, H_3 and H_5 *o*-pyridyl), 7.71 (t, 1H, $J_o = 7$ Hz, H_4 *o*-pyridyl), 8.22 (brs, 3H, NH_2 Aib, TFA salt), 8.42 (d, 1H, $J_{\alpha\beta} = 4$ Hz, H_6 *o*-pyridyl), 9.05 (d, 1H, $J = 8$ Hz, NH amide), 10.87 (s, 1H, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 23.4 (CH_3 Aib), 23.7 (CH_3 Aib), 26.4 (*C*H$_2$−CH$_2$−phenyl), 28.6 (C βTrp), 32.5 (CH$_2$−*C*H$_2$−phenyl), 45.7 (C αTrp), 47.6 (CH_2 *o*-pyridyl), 56.8 (Cq Aib), 109.8 (C_3 Trp), 111.8 (C_7 Trp), 118.3 (C_4 Trp), 118.6 (C_5 Trp), 121.2 (C_6 Trp), 122.0 (C_3 *o*-pyridyl), 123.6 (C_5 *o*-pyridyl), 126.3 (C_2 Trp), 126.6 (C_4 phenyl), 127.3 (C_9 Trp), 128.7 (C_2, C_3, C_5, and C_6 phenyl), 136.4 (C_8 trypophane), 137.7 (C_4 *o*-pyridyl), 140.7 (C_1 phenyl), 150.1 (C_6 *o*-pyridyl), 154.9 (Cq triazole), 155.2 (Cq triazole), 158.7 (C_2 *o*-pyridyl), 172.0 (CO amide).

***N*-((*R*)-1-(4-(4-Methoxyphenethyl)-5-phenethyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethyl)-2-amino-2-methylpropanamide Trifluoroacetate Salt (34).** ^{1}H NMR (300 MHz, DMSO-d_6, 300 K) δ (ppm) 1.30 (s, 3H, CH_3 Aib), 1.35 (s, 3H, CH_3 Aib), 2.55 (m, 4H, C*H*$_2$−CH$_2$−phenyl and CH$_2$−C*H*$_2$−*p*-methoxybenzyl), 2.83 (t, 2H, $J = 8$ Hz, CH$_2$−C*H*$_2$−phenyl), 3.37 (m, 2H, C*H*$_2$−CH$_2$−*p*-methoxybenzyl), 3.65 (s, 3H, OCH_3), 3.77 (m, 1H, CH_2 βTrp), 3.89 (m, 1H, CH_2 βTrp), 5.20 (m, 1H, CH αTrp), 6.72 (s, 4H, CHar *p*-methoxybenzyl), 6.94 (t, 1H, $J_o = 7$ Hz, H_5 Trp), 7.02 (t, 1H, $J_o = 8$ Hz, H_6 Trp), 7.05 (d, 1H, $J = 2$ Hz, H_2 Trp), 7.11 (d, 2H, $J_o = 7$ Hz, H_2 and H_6 phenyl), 7.16 (d, 1H, $J_o = 7$ Hz, H_4 Trp), 7.25 (m, 3H, H_3, H_4, H_5 phenyl), 7.50 (d, 1H, $J_o = 8$ Hz, H_7 Trp), 8.05 (brs, 3H, NH_2 Aib, TFA salt), 9.02 (d, 1H, $J = 8$ Hz, NH amide), 10.83 (d, 1H, $J = 2$ Hz, NH indole Trp). ^{13}C NMR (75 MHz, DMSO-d_6, 300 K) δ (ppm) 23.5 (CH_3 Aib), 23.8 (CH_3 Aib), 26.0 (*C*H$_2$−CH$_2$−phenyl), 29.5 (C βTrp), 32.5 (CH$_2$−*C*H$_2$−phenyl), 35.0 (CH$_2$−*C*H$_2$−*p*- methoxybenzyl), 44.4 (*C*H$_2$−CH$_2$−*p*-methoxybenzyl), 45.8 (C αTrp), 55.4 (OCH_3), 56.8 (Cq Aib), 109.9 (C_3 Trp), 111.9 (C_7 Trp), 114.2 (C_3 and C_5 *p*-methoxybenzyl), 118.4 (C_4 Trp), 118.9 (C_5 Trp), 121.4 (C_6 Trp), 124.7 (C_2 Trp), 126.5 (C_4 phenyl), 127.4 (C_9 Trp), 128.7 (C_2, C_3, C_5, and C_6 phenyl), 129.4 (C_1 *p*-methoxybenzyl), 130.3 (C_2 and C_6 *p*-methoxybenzyl), 136.5 (C_8 Trp), 141.0 (C_1 phenyl), 154.0 (Cq triazole), 154.5 (Cq triazole), 158.6 (C_4 *p*-methoxybenzyl), 171.8 (CO amide).

In Vitro *h*GHSR-1a Evaluation. Transient transfection of LLC PK-1 cells and membrane preparation were performed as previously described.[31] 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 *h*GHS-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 post-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 10 000*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 concentration was 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 and was always less than 20% of total binding. 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) Triton X-100), 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 and screening plateform of the Institut Fédératif de Recherche 3, Montpellier, France). CHO cells were transiently transfected with the *h*GHS-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 buffer A (Hanks' balanced salt solution, 0.5% BSA, 20 mM $CaCl_2$, 2.5 mM probenecid, pH 7.4) and were then loaded with 1 μM of the fluorescent calcium indicator Fluo-4AM prepared in buffer A, containing 0.06% pluronic acid (a mild ionic detergent which 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, as well as the plate containing the compounds to be tested, was 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 a concentration of 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 1 μM ghrelin. For the compounds behaving as agonists and displaying a high affinity binding for *h*GHS-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.[32] Schild analysis[33] 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. A. Growth Hormone Assay. Compounds were dissolved in DMSO (10^{-2} M) and brought to the final volume with saline. Animals, male 10-day-old Sprague−Dawley rats weighing about 25 g (Charles River, Calco, Italy), were used. Rat 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.

Pups were acutely challenged with solvent (DMSO, final dilution 1:300), hexarelin (80 μg/kg sc), or the compound to be tested (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−GHRP-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%.

B. 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 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. In all the experiments hexarelin stimulated the intake of about 1 g of standard dry pellet food per 100 g of body weight of rats. Food intake was normalized for the body weight of the animals and expressed as g of food eaten for 100 g of body weight. Statistical analysis of food intake eaten in the first 2 h and in the total period of observation of 6 h was performed by one-way ANOVA followed by Dunnett's *t* test for multiple comparisons. A *P* value less than 0.05 was considered significant.

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Supporting Information Available: Displacement curves of ^{125}I−His^9−ghrelin for compounds **18a**, **19d**, **21a**, and **29c**; inhibition curves of ghrelin-induced $[Ca^{2+}]_i$ accumulation by compounds **16** and **19b**; $[Ca^{2+}]_i$ accumulation dose−response curves of ghrelin in the presence of increasing concentrations of compounds **16**, **19c**, and **19d**; physicochemical properties of all final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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