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Synthesis of C-2 Arylated Tryptophan Amino Acids and Related Compounds through Palladium-Catalyzed C−H Activation

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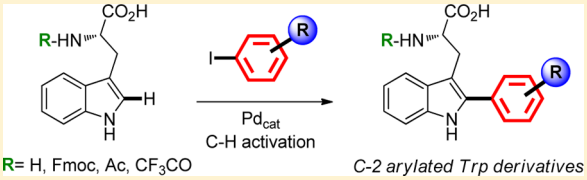
Supporting Information

ABSTRACT: Tryptophan (Trp) and tryptophan derivatives are C2-arylated. A C−H activation process allows the preparation of both protected and unprotected arylated-Trp amino acids, directly from the amino acid precursor and aryl iodides. The obtained compounds are suitable for standard solid-phase peptide synthesis.



Although tryptophan (Trp) shows a low relative abundance in peptide and protein sequences (around 1% of the overall amino acids), its presence is of crucial importance for the activity of these molecules. Furthermore, Trp is a common precursor to a wide range of biologically active compounds (natural products and drugs), and its structural, chemical, and biological roles make it an ideal site for selective chemical modifications. The access to modified Trp peptides would provide novel and useful applications in organic chemistry, drug discovery, and medicinal chemistry.[1] Furthermore, it would open the possibility of preparing new chemically modified peptides that are potentially useful in chemical biology. Right now, this goal is only achievable through de novo synthesis of the non-natural amino acid, by means of long stepwise syntheses,[2] with the exception of C- and N-allylations, which have been reported through Pd-catalyzed transformations.[3]

Indole, the heterocyclic residue of Trp, is probably one of the most abundant heterocycles in nature. Owing to the great structural diversity of biologically active indoles, it is not surprising that this ring system has become an important structural component in many pharmaceutical agents. Substituted indoles have been referred to as "privileged substructures" since they appear in many scaffolds capable of binding a variety of different receptors with high affinity.[4] Incidentally, the 2-arylindole moiety has gained relevance in medicinal chemistry and is considered a common scaffold.[5] Interestingly, the synthetic access to related drugs relies on its previous preparation. For well over a hundred years, the synthesis and functionalization of indoles has been a major area of focus for synthetic organic chemists, and numerous methods for the preparation of indoles have been described.[6]

Thus, the development of new synthetic methodologies for the selective chemical modification of Trp is of major importance. Particularly, the introduction of aromatic moieties into the indole ring of the Trp to modulate the structure and bioactivity of the selected biomolecules might be a challenging issue. Recently, the metal-catalyzed C−C coupling through direct C−H activation[7] for the functionalization of indoles has been extensively studied.[8]

Particularly relevant to our research was Larrosa's methodology for indole arylation using $Pd(OAc)_2$, Ag_2O, and *o*-nitrobenzoic acid (2-NO_2BzOH) in DMF.[8c] In this context, we described C-2 arylation of indoles in Trp derivatives and peptides through a Pd-catalyzed C−H activation protocol, allowing the preparation of a variety of peptide sequences with modified Trp moieties (Figure 1a).[9,10] In this work, it was determined that unprotected Trp was not reactive under the original conditions, and only the N^{α}-acetyl tryptophan methyl ester (Ac-Trp-OMe) could be properly arylated, using high-temperature microwave (MW) activation.[11] As the Ac is not a friendly group to mask the amino function, applicability of that methodology for the preparation of some peptides containing modified Trp units was restricted and, therefore, prompted us to tackle this problem (Figure 1b). Thus, a more convenient *N*-protecting group was tested next, and the N^{α}-trifluoroacetyl (Tfa) Trp **1a** could be successfully arylated (Table 1, entry 1). Although this group can be hydrolytically removed in solution, it was reluctant to standard deprotection methods in the solid phase,[12] which is the method of choice for the preparation of peptides.

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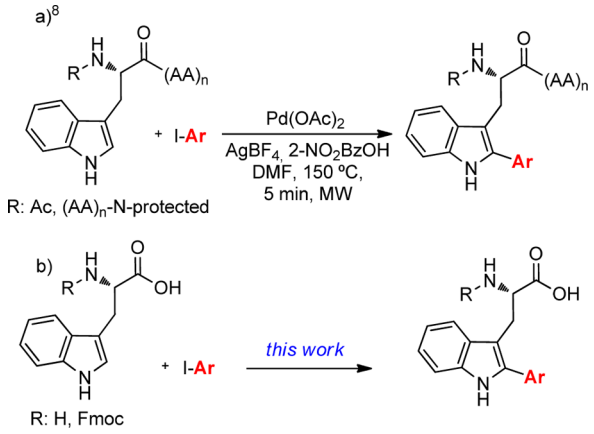
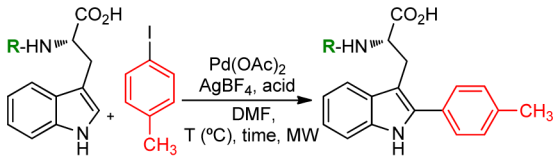


Figure 1. Arylation of indole in Trp derivatives.

As a starting point, we analyzed the reaction of native Trp **1b** using our standard conditions (2-NO_2BzOH, 150 °C, MW), but the arylated product was obtained just in traces in a complex mixture (Table 1, entry 2). Satisfactorily, the use of TFA alone (1 equiv) afforded 75% in 20 min (Table 1, entry 3). This result encouraged us to optimize the process using this acid, which apparently removes the incompatibility of a free amino group. In this regard, TFA is more convenient than other carboxylic acids, as it is water-soluble, has a low boiling point, and, therefore, can be conveniently removed, not hampering the stability and purification of the final products. Although traces of the acid could remain in the crude residue after standard evaporation, the use of TFA constitutes a practical improvement for this transformation, as it does not require chromatographic methods for the removal of the acid input. Also, it is evident that working at temperatures well below 150 °C is essential to keep the integrity of the Trp amino acids. Working at 90 °C under the same conditions allowed us to reduce the amount of aryl iodide while slightly increasing the conversion (87%, Table 1, entry 4). However, a slighltly higher temperature (100 °C) resulted in a less efficient transformation (Table 1, entry 5), probably fixing the practical limit of this reaction. Interestingly, the absence of an external acidic source still allowed the arylation process, although in lower conversion (Table 1, entry 6). Interestingly, a key parameter was the amount of Ag^+ salt present. Thus, using an excess of the Ag^+ salt (Table 1, entry 7) gave a practically quantitative reaction. Next, the Fmoc-Trp-OH derivative **1c**, which can be used directly in a solid-phase peptide synthesis, was assayed to be arylated (Table 1, entry 8), and again the use of 2 equiv of $AgBF_4$ afforded a quantitative transformation.[13] Incidentally, these optimized conditions lead to a total conversion of Tfa-Trp-OH derivative **1a** into **3** (Table 1, entry 9). Excess of TFA (up to 4 equiv) did not improve the yields, whereas the use of Ag_2CO_3 or different Pd sources [$Pd(TFA)_2$] was not beneficial. On the other hand, the presence of additives (LiCl, Cs_2CO_3, K_2CO_3) was detrimental to the reaction, leading to lower conversions.

A hypothetical mechanism for this C−H activation may proceed through a catalytic cycle involving Pd(II)/Pd(IV) species, taking into account the intramolecular coordination of the carboxylic acid moiety and the facilitated formation of the putative palladacycle (Scheme 1).[7a,14] However, alternative Pd(0)/Pd(II) pathways could also be considered in this context, starting with the Pd insertion into the C−I bond, the C−H activation taking place upon the metalated intermediate.[7c,8c] The role of silver salts and carboxylic acids seems to be critical for the fate of the catalytic cycle. First, coordination of Trp derivative **1** to the Pd^{II} species may evolve through indole palladation, presumably by a concerted metalation deprotonation mechanism[15] to generate Pd^{II} complex **I**. Insertion of this intermediate upon the C−I bond of the aryl halide by oxidative addition yields the palladium(IV) complex **II**, and then silver cation (I) acts as a halide scavenger, removing the iodide and setting up the reductive elimination to release the arylated products **3**−**5** and regenerate the Pd(II) catalyst.[16] Additionally, TFA is acidic enough (pK_a = 0.23) to protonate the amino group of the unprotected Trp, avoiding in this way an unproductive amino acid coordination.[17]

Table 1. Selected Optimization Results for the Arylation of Tryptophans (1) under Microwave Irradiation[a]



entry	R	T (°C)	time (min)	acid[b]	$AgBF_4$ (equiv)	I-Ar (equiv)	conv (%)[c]
1	Tfa[d]	150	5	2-NO_2BzOH	1.0	4.0	76
2	H	150	15	2-NO_2BzOH	1.0	4.0	<5
3	H	80	20	TFA	1.0	3.0	75
4[e]	H	90	20	TFA	1.0	1.5	87
5	H	100	20	TFA	1.0	1.5	78
6	H	100	20		1.0	1.5	49
7	H	90	20	TFA	2.0	1.5	>99
8	Fmoc	90	20	TFA	2.0	1.5	>99
9	Tfa	90	20	TFA	2.0	1.5	>99

[a]Unless otherwise noted, all reactions were carried out using 5 mol % $Pd(OAc)_2$ and 1.0 equiv of Trp in a 0.2 M solution. [b]1.5 equiv of 2-NO_2BzOH (entries 1 and 2) and 1.0 equiv of TFA were used. [c]Conversion measured by HPLC. [d]Tfa = trifluoroacetyl. [e]These reactions were also tested using PBS/DMF (1:1) as a solvent, and other silver salts, without any relevant improvement.

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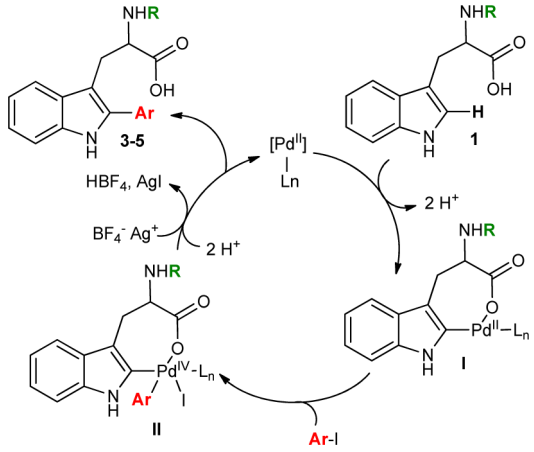
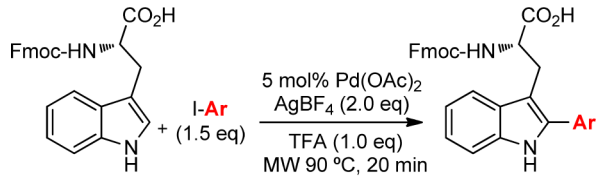
Scheme 1. Proposed Mechanism for the Reaction of Trp Amino Acid with Aryl Iodides



Furthermore, the trifluoroacetate anion can also coordinate with the metal to render it more electrophilic and also take part in the deprotonation and proton transfer steps. DMF seems to be very suitable for this process as it dissolves all the reactants involved and is also a ligand, capable to stabilize palladium intermediates as well.

We next examined the scope of the reaction with a variety of differently substituted aryl iodides. As shown in Table 2, excellent yields are obtained in the reaction of Fmoc-Trp-OH with several aryl iodides. Both electron-withdrawing (**5b**–**5f**) and electron-donating substitutents (**5g**–**5h**) are suitable groups for this transformation. Furthermore, a rather hindered pyrenyl fluorophore was introduced (**5i**), which would allow the synthesis of labeled Trp-containing peptides.[18] With respect to heterocyclic iodides, although an α-thienyl resiue can be attached to the Trp-2 position, the reactivity was low and purification problems precluded the isolation of the corresponding adduct (Table 2, entry 11). In this way, an array of arylated Fmoc-Trp derivatives were prepared in a direct manner with useful yields (Table 2) in scalable procedures (up to 500 mg of the Fmoc-Trp-OH was successfully arylated). Interestingly, the mild conditions allowed us to preserve the stereochemical integrity of the parent amino acid. Thus, the *S* and *R* enantiomers of the Fmoc-Trp-OH were separatedly subjected to the arylation reaction to yield compounds **5a** and **5a′**, respectively (entries 1 and 2, Table 2), whose chromatographic behavior (chiral HPLC, see the Supporting Information) confirmed the conservation of the initial absolute stereochemistry.[19]

Table 2. C-2 Arylation of Fmoc-Trp-OH Amino Acid 1c



entry	I-Ar	compound	yield (%)[a]
1	C_6H_5–	**5a**	56
2[b]	C_6H_5–	**5a′**	51
3	*p*-NO_2-C_6H_4–	**5b**	91
4	*p*-MeO_2C-C_6H_4–	**5c**	68
5	*p*-Br-C_6H_4–	**5d**	62
6	*m*-CF_3-C_6H_4–	**5e**	59
7	*o*-F-C_6H_4–	**5f**	77
8	*p*-Me-C_6H_4–	**5g**	81
9	*p*-MeO-C_6H_4–	**5h**	63
10	1-pyrenyl	**5i**	66
11	2-thienyl		[c]

[a]Yields are of the isolated pure material. [b]Opposite absolute stereochemistry (*R*). [c]Conversion lower than 15%; the thienyl-Trp was detected (^{1}H NMR, HPLC-MS) but not purified.

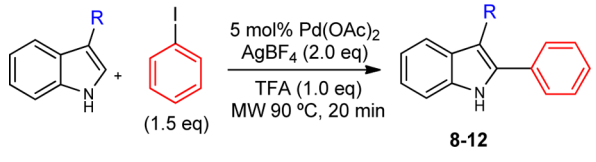
To prove the suitability for standard solid-phase peptide synthesis of the arylated-Trp amino acids, two peptide sequences were chosen as proof of principle (Table 3). The syntheses were performed using Fmoc-based SPPS on a 2-chlorotrityl chloride resin and standard coupling protocol. *N*-Terminal peptide chain elongation was carried out by anchoring the N^a-Fmoc protected amino acids with DIC/OxymaPure, followed by Fmoc deprotection in an iterative manner. Finally, sequences **6**–**7** were cleaved from the resin with 5% TFA in DCM, affording the corresponding peptides in high yield and purity (more than 99%), as determined by integration of the chromatographic peak areas of RP-HPLC-ESMS. The direct introduction of the Fmoc-arylated amino acid **5f** on the solid phase is very efficient and also overcomes the limitation encountered in previous studies regarding sequences containing sulfur-amino acids (Met or Cys). It also allows the selective preparation of arylated Trp peptides in sequences with multiple Trp units.[9]

Table 3. Solid-Phase Synthesis of Peptide Sequences Containing Arylated-Trp Amino Acids

entry	peptide	compound
1	H-Met-Gly-Trp(C2-*p*-methylphenyl)-Ala-OH	**6**
2	H-Trp-Gly-Trp(C2-*p*-methylphenyl)-Ala-OH	**7**

As the carboxylic acid moiety in Trp seems to actively promote the arylation by coordination with the palladium species, we extended this methodology to a series of indole-carboxylic acids having the CO_2H linked to the heteroaromatic ring by spacers of different lengths (1–4 bonds, Table 4). In this way, the corresponding arylated compounds **8**–**12** were obtained in high yields. However, remarkably, the indole 3-

Table 4. C-2 Arylation of Indole-Carboxylic Acids and Tryptamines



entry	R	compound	yield (%)[a]
1	CO_2H		
2	CH_2CO_2H	**8**	79
3	$CH_2CH_2CO_2H$	**9**	75
4	$CH_2CH_2CH_2CO_2H$	**10**	74
5	$CH_2CH_2NH_2$	**11**	48[b]
6	CH_2CH_2NHAc	**12**	73

[a]Yields are of the isolated pure material. [b]The reaction was carried out using two MW cycles, without adding TFA.

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carboxylic acid was not reactive under these conditions, and the expected adduct was not detected. Incidentally, indoleacetic acid is a natural plant hormone involved in growth and development, and indolebutyric acid is a synthetic and metabolically more stable analogue.[20] Taking into account the potential bioactivity of derivatives **8**−**10**, it is relevant to note the easy access to these compounds. Furthermore, compound **10** is also a patented IL-8 receptor antagonist,[21,22] whereas the other two phenyl-indole carboxylic acids **8** and **9** also showed interesting biological properties.[23] Interestingly, their preparation is reported through long stepwise synthetic sequences. Using our methodology, a more direct synthetic approach to this family of compounds can be feasible using cheap common indole precursors and a variety of commercially available aryl iodides in just one step.

Analogously, tryptamine was arylated under these acidic conditions (1 equiv TFA) to yield compound **11**, as expected in a low conversion (16%). However, when operating in the absence of TFA, an improved transformation (48%, Table 4, entry 5) was determined, suggesting that, in this case, the aminopalladacycle was an intermediate en route of the final compound.[24] In agreement with previous results,[9] the *N*-acetyltryptamine was satisfactorily arylated to yield derivative **12** (73%). This compound was prepared in higher yields and under much milder conditions than previously reported in a distinct C−H activation protocol.[25] Overall, the process is effective upon Trp, indole carboxylic acids, indole amines and amides. It has to be stated that, although different coordination modes are feasible depending on the substrate, TFA protonation allows the arylation of the free amino acids, which was not possible in the previous protocol.[9] Presumably, the formation of palladium−amino acid complexes is inhibited in these conditions, leading to productive catalytic cycles.

In conclusion, we have developed a synthetic methodology to α-arylated indoles in Trp, tryptamines, and β-substituted indole carboxylic acids, which is simple, high-yielding, versatile, and mild enough to allow the efficient transformation of biomolecules. Remarkably, the intramolecular ligand effect of the carboxylic acid seems to facilitate the process, as the conditions are milder than many C−H arylations previously reported upon 3-substituted indoles. Application of the newly synthesized amino acid derivatives to the preparation of modified Trp-containing peptides through solid-phase methodology has shown to be efficient.

EXPERIMENTAL SECTION

Reactions were monitored by RP-HPLC-ESMS at 220 nm and thin-layer chromatography using Merck silica gel 60 F254 TLC glass plates and visualized with UV at 254 nm. Chromatographic purification was performed with flash chromatography on silica 60A, 35−70 nm from SDS. Yields refer to chromatographically pure compounds. NMR spectra were recorded on a 400 spectrometer, operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C, and 376 MHz for ^{19}F. Chemical shifts (δ) are reported in parts per million. Multiplicities refer to the following abbreviations: s = singlet, d = doublet, t = triplet, dd = double doublet, dt = double triplet, q = quartet, p = pentuplet, and m = multiplet. IR spectra were obtained with an FTIR spectrometer and are reported in cm^{-1}. HRMS (ESI positive) were obtained with a linear ion trap mass analyzer. Optical rotation was performed using MeOH as solvent. All microwave reactions were carried out in 10 mL sealed glass tubes in a focused monomode microwave oven ("Discover" by CEM Corporation) featured with a surface sensor for internal temperature determination. Cooling was provided by compressed air ventilating the microwave chamber S3 during the reaction. The chiral chromatography was performed in a linear gradient of CH_3CN (+0.1% TFA) into H_2O (+0.1% TFA) from 50% to 90% CH_3CN, and a chiral HPLC column (Chiralpak ia, Amylose tris(3,5-dimethylphenylcarbamate) immobilized on 5 μm silica gel, 250 × 2 mm).

Preparation of (*S*)-3-(1*H*-Indol-3-yl)-2-(2,2,2-trifluoroacetamido)propanoic Acid (1a).[26] Compound **1a** was prepared using amino acid **1b** (1.0 g, 5.0 mmol). The system was purged with N_2, and the amino acid was dissolved in anhydrous MeOH (4.5 mL). With stirring, NEt_3 (696.5 μL, 5.0 mmol) was added, followed by ethyl trifluoroacetate (1.5 mL, 12.8 mmol) after 5 min. The reaction was left under vigorous agitation at r.t for 24 h. The solvent was removed under vacuum, and the crude product was dissolved in H_2O (46 mL) and acidified with concentrated HCl (1 mL). The precipitate was filtered by a filter plate, leaving **1a** as a white solid (1.22 g, 81%). ^{1}H NMR (400 MHz, DMSO): δ 10.84 (d, J = 2.5 Hz, 1H), 9.74 (d, J = 8.1 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.12 (d, J = 2.3 Hz, 1H), 7.08−7.02 (m, 1H), 6.97 (t, J = 7.4 Hz, 1H), 4.49 (ddd, J = 10.3, 7.9, 4.3 Hz, 1H), 3.30 (dd, J = 14.8, 4.4 Hz, 3H), 3.14 (dd, J = 14.8, 10.3 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO): δ 172.2, 157.3−156.6 (m), 136.5, 127.4, 124.0, 121.5, 120.5, 118.9, 118.4, 117.6, 114.8, 111.9, 110.1, 110.0, 54.1, 26.4 ppm.

Preparation of 1-Iodopyrene (2b).[27] Compound **2b** was prepared using 1-aminopyrene (973 mg, 4.47 mmol), which was suspended in aqueous HCl solution (3 M, 25 mL) with vigorous stirring at 0 °C. A solution of $NaNO_2$ (308.4 mg, 4.47 mmol) in H_2O (1.5 mL) was added in small portions. After 5 min, a solution of KI (742.4 mg, 4.47 mmol) in H_2O (3 mL) was added to the reaction mixture. The ice bath was removed, and the reaction mixture was stirred for 2 h at r.t and then heated to 60 °C for 1 h. The crude product was separated by filtration, dissolved in ether, and washed with a concentrated solution of Na_2SO_3. The ether solution was dried with $MgSO_4$ and concentrated under vacuum. The resulting product was purified by flash chromatography on silica gel (hexane/ethyl acetate) to obtain 1-iodopyrene **2b** as a white yellowish solid (598.8 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, J = 8.1 Hz, 1H), 8.16 (d, J = 9.2 Hz, 1H), 8.11−8.06 (m, 2H), 8.01−7.94 (m, 2H), 7.93−7.85 (m, 2H), 7.72 (d, J = 8.1 Hz, 1H) ppm.

General Procedure for the C2 Arylation of Trp Amino Acids (3−5). Unless stated otherwise, Trp amino acid (**1a**−**1c**) (0.117 mmol, 1 equiv), aryl iodide (1.5 equiv), $AgBF_4$ (2 equiv), TFA (1.0 equiv), and $Pd(OAc)_2$ (5% mol) were placed in a microwave reactor vessel in dry DMF (600 μL). The mixture was heated under microwave irradiation (250 W) at 90 °C for 20 min. Ethyl acetate (20 mL) was added, the resulting suspension was filtered through Celite, and the solvent was removed under vacuum. Unless otherwise quoted, the crude extract was purified by flash chromatography on silica gel (hexane/ethyl acetate) to obtain **3**−**5** as a pure product. Fractions containing the arylated tryptophans were collected, and the solvent was removed under reduced pressure. The residue was dissolved in CH_3CN/H_2O and lyophilized for 24 h to yield the pure product.

*(S)-3-(2-(p-Tolyl)-1H-indol-3-yl)-2-(2,2,2-trifluoroacetamido)-propanoic Acid (**3**).* Starting from amino acid **1a** (100 mg, 0.333 mmol) and 4-iodotoluene (110 mg, 0.500 mmol). Pale oil (65.9 mg, 51%). ^{1}H NMR (400 MHz, DMSO): δ 11.16 (s, 1H), 9.77 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.54−7.51 (m, 2H), 7.30 (td, J = 7.9, 0.9 Hz, 3H), 7.06 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 6.96 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 4.51 (td, J = 8.7, 5.1 Hz, 1H), 3.47 (dd, J = 14.7, 5.1 Hz, 1H), 3.32−3.23 (m, 1H), 2.35 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO): δ 171.3, 156.0, 155.7, 136.6, 135.5, 135.1, 129.6, 129.0, 128.6, 127.6, 121.1, 118.5, 118.4, 116.9, 114.0, 110.8, 106.7, 53.8, 25.8, 20.6 ppm. IR (film, cm^{-1}): ν = 3378.65, 3301.78, 2930.25, 1693.95 cm^{-1}. HRMS (ESI): m/z calcd 391.12640 ($C_{20}H_{18}F_3N_2O_3$), found 391.12592 $(M + H)^+$.

*(S)-2-Amino-3-(2-(p-tolyl)-1H-indol-3-yl)propanoic Acid (**4**).* Starting from amino acid **1b** (50.0 mg, 0.245 mmol) and 4-iodotoluene (80.2 mg, 0.368 mmol). The crude product was purified by flash chromatography on silica using hexane/ethyl acetate and then DCM/EtOH. Pale oil (39.9 mg, 56%). ^{1}H NMR (400 MHz, DMSO): δ 11.20 (s, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 7.8 Hz, 2H), 7.34 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 7.8 Hz, 2H), 7.08 (t, J = 7.5 Hz, 1H), 6.99 (t, J = 7.4 Hz, 1H), 3.68 (t, J = 7.2 Hz, 1H), 3.44 (dd, J = 14.9, 6.2 Hz,

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1H), 3.10 (dd, J = 14.8, 8.4 Hz, 1H), 2.34 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO): δ 170.9, 137.2, 136.4, 136.1, 130.2, 129.6, 129.1, 128.5, 121.8, 119.2, 119.0, 111.5, 106.5, 54.7, 27.5, 21.3 ppm. IR (film, cm^{-1}): ν = 3404.27, 3231.32, 3051.96, 2962.28, 2923.84, 1706.76 cm^{-1}. HRMS (ESI): m/z calcd 295.14410 ($C_{18}H_{19}N_2O_2$), found 295.14381 (M + H)$^+$.

*(S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(2-phenyl-1H-indol-3-yl)propanoic Acid (**5a**).* Starting from amino acid **1c** (50.0 mg, 0.117 mmol) and iodobenzene (26.2 μL, 0.234 mmol). Pale oil (32.9 mg, 56%). Scale-up: Starting from amino acid **1c** (0.5 g, 1.17 mmol) and iodobenzene (200 μL, 1.75 mmol) in dry DMF (2 mL). The general microwave process was performed six times, all the reaction mixtures were collected altogether, and the resulting crude was treated according to the general procedure. Pale oil (1.98 g, 56%). ^{1}H NMR (400 MHz, DMSO): δ 12.62 (s, 1H), 11.20 (s, 1H), 7.88−7.84 (m, 2H), 7.78 (d, J = 8.6 Hz, 1H), 7.72−7.60 (m, 5H), 7.47 (t, J = 7.7 Hz, 2H), 7.41−7.32 (m, 4H), 7.28 (td, J = 7.4, 1.1 Hz, 1H), 7.23 (td, J = 7.5, 1.1 Hz, 1H), 7.10−7.05 (m, 1H), 6.97 (ddd, J = 8.0, 6.9, 1.0 Hz, 1H), 4.31 (td, J = 8.6, 5.8 Hz, 1H), 4.15−4.06 (m, 3H), 3.40−3.34 (m, 1H), 3.18 (dd, J = 14.6, 8.7 Hz, 1H) ppm. IR (film, cm^{-1}): ν = 3372.24, 3321.00, 3051.96, 2955.87, 1693.95 cm^{-1}. RP-HPLC-ESMS: m/z (%) 503.22 (M + H)$^+$. $[\alpha]_D^{20}$ −5.9 (c 0.48, MeOH).

*(R)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(2-phenyl-1H-indol-3-yl)propanoic Acid (**5a′**).* Starting from amino acid **1c** (50.0 mg, 0.117 mmol) and iodobenzene (26.2 μL, 0.234 mmol). Pale oil (29.9 mg, 51%). ^{1}H NMR (400 MHz, DMSO): δ 12.64 (s, 1H), 11.20 (s, 1H), 7.86 (d, J = 7.6 Hz, 2H), 7.78 (d, J = 8.6 Hz, 1H), 7.72−7.60 (m, 5H), 7.47 (t, J = 7.7 Hz, 2H), 7.41−7.32 (m, 4H), 7.28 (td, J = 7.5, 1.2 Hz, 1H), 7.23 (td, J = 7.5, 1.2 Hz, 1H), 7.10−7.05 (m, 1H), 6.98 (t, J = 7.4 Hz, 1H), 4.31 (td, J = 8.5, 5.7 Hz, 1H), 4.15−4.06 (m, 3H), 3.37 (dd, J = 14.5, 5.8 Hz, 1H), 3.19 (dd, J = 14.6, 8.7 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO): δ 174.0, 156.3, 144.2, 144.12, 141.07, 136.3, 135.6, 133.2, 129.4, 129.1, 128.4, 128.05, 128.03, 127.8, 127.5, 125.8, 121.9, 120.5, 119.5, 119.2, 111.5, 108.4, 66.2, 55.7, 47.0, 27.4 ppm. IR (film, cm^{-1}): ν = 3372.24, 3321.00, 3051.96, 2955.87, 1693.95 cm^{-1}. HRMS (ESI): m/z calcd 503.19653 ($C_{32}H_{26}N_2O_4$), found 503.19761 (M + H)$^+$. $[\alpha]_D^{20}$ +13.2 (c 0.27, MeOH).

*(S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(2-(4-nitrophenyl)-1H-indol-3-yl)propanoic Acid (**5b**).* Starting from amino acid **1c** (100 mg, 0.234 mmol) and 1-iodo-4-nitrobenzene (89.4 mg, 0.352 mmol). Pale oil (116.7 mg, 91%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.50 (s, 1H), 8.31−8.26 (m, 2H), 7.96−7.92 (m, 2H), 7.86 (d, J = 7.6 Hz, 2H), 7.79 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.60 (dd, J = 7.5, 4.5 Hz, 2H), 7.41−7.36 (m, 3H), 7.29−7.20 (m, 2H), 7.19−7.13 (m, 1H), 7.03 (t, J = 7.5 Hz, 1H), 4.31 (td, J = 8.8, 5.3 Hz, 1H), 4.17−4.00 (m, 3H), 3.51−3.39 (m, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.31, 155.87, 145.92, 143.76, 143.65, 140.65, 139.32, 136.56, 132.78, 128.85, 128.52, 127.62, 127.01, 125.28, 123.87, 122.81, 120.07, 119.52, 119.34, 111.48, 111.10, 65.73, 54.99, 46.50, 26.92 ppm. IR (film, cm^{-1}): ν = 3404.27, 3327.40, 3058.36, 2943.06, 2917.44, 1700.36, 1508.19, 1348.04, 848.40, 733.10 cm^{-1}. RP-HPLC-ESMS: m/z (%): calcd 548.1816 ($C_{32}H_{26}N_3O_6$), found 548.18268 (M + H)$^+$. $[\alpha]_D^{20}$ −21.8 (c 0.50, MeOH).

*(S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(2-(4-(methoxycarbonyl)phenyl)-1H-indol-3-yl)propanoic Acid (**5c**).* Starting from amino acid **1c** (50 mg, 0.117 mmol) and methyl 4-iodobenzoate (46.1 mg, 0.176 mmol). Pale oil (44.8 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.63 (dd, J = 33.5, 7.4 Hz, 3H), 7.43−7.28 (m, 7H), 7.23−7.17 (m, 2H), 7.16−7.11 (m, 1H), 7.10−7.05 (m, 1H), 6.88−6.83 (m, 2H), 5.04 (d, J = 7.9 Hz, 1H), 4.55 (q, J = 6.8 Hz, 1H), 4.18−4.07 (m, 2H), 4.01 (t, J = 7.3 Hz, 1H), 3.70 (s, 3H), 3.43 (qd, J = 14.9, 6.3 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 166.8, 159.5, 143.8, 143.79, 143.72, 141.2, 136.0, 135.5, 135.0, 130.2, 129.7, 129.3, 128.1, 127.7, 127.0, 125.1, 123.2, 122.3, 120.5, 120.2, 119.91, 119.89, 119.2, 114.5, 111.1, 110.9, 108.2, 106.1, 67.1, 55.3, 54.4, 52.3, 47.0 ppm. IR (film, cm^{-1}): ν = 3410.68, 3340.21, 3058.36, 2949.47, 1713.17, 1693.95 cm^{-1}. HRMS (ESI): m/z calcd 561.20201 ($C_{34}H_{28}N_2O_6$), found 561.20365 (M + H)$^+$. $[\alpha]_D^{20}$ −15.9 (c 0.51, MeOH).

*(S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(2-(4-bromophenyl)-1H-indol-3-yl)propanoic Acid (**5d**).* Starting from amino acid **1c** (50.0 mg, 0.117 mmol) and 1-bromo-4-iodobenzene (50.8 mg, 0.176 mmol). Pale oil (42.5 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.72−7.65 (m, 2H), 7.64−7.57 (m, 1H), 7.44−7.36 (m, 4H), 7.37−7.27 (m, 2H), 7.29−7.21 (m, 3H), 7.26−7.17 (m, 2H), 7.16 (d, J = 7.9 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 5.04 (d, J = 8.0 Hz, 1H), 4.57 (q, J = 6.5 Hz, 1H), 4.22−4.00 (m, 3H), 3.45 (qd, J = 14.9, 6.0 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 155.7, 143.73, 143.67, 141.25, 141.23, 135.7, 135.2, 132.2, 131.6, 129.9, 129.0, 127.7, 127.0, 125.2, 122.9, 122.3, 120.4, 119.9, 119.0, 111.1, 107.2, 67.1, 54.3, 46.9, 26.8 ppm. IR (film, cm^{-1}): ν = 3378.65, 3314.59, 3058.36, 2949.47, 1687.54 cm^{-1}. HRMS (ESI): m/z calcd 581.10705 ($C_{32}H_{25}BrN_2O_4$), found 581.10888 (M + H)$^+$. $[\alpha]_D^{20}$ −8.1 (c 0.50, MeOH).

*(S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(2-(3-(trifluoromethyl)phenyl)-1H-indol-3-yl)propanoic Acid (**5e**).* Starting from amino acid **1c** (50.0 mg, 0.117 mmol) and 1-iodo-3-trifluoromethylbenzene (25.9 μL, 0.176 mmol). Pale oil (39.4 mg, 59%). ^{1}H NMR (400 MHz, DMSO): δ 12.67 (s, 1H), 11.39 (s, 1H), 8.01−7.95 (m, 2H), 7.89−7.79 (m, 3H), 7.74 (d, J = 8.1 Hz, 1H), 7.72−7.69 (m, 2H), 7.61 (dd, J = 11.1, 7.5 Hz, 2H), 7.41−7.35 (m, 3H), 7.30−7.20 (m, 2H), 7.12 (t, J = 7.8 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 4.30 (td, J = 8.6, 5.6 Hz, 1H), 4.15−4.04 (m, 3H), 3.40 (dd, J = 14.6, 5.7 Hz, 2H), 3.23 (dd, J = 14.7, 8.7 Hz, 1H) ppm. ^{19}F NMR (376 MHz, DMSO): δ −61.07 ppm. ^{13}C NMR (100 MHz, DMSO): δ 173.8, 156.3, 144.2, 144.1, 141.1, 136.5, 134.1, 133.7, 132.2, 130.22, 130.16, 129.3, 128.05, 128.03, 127.5, 125.7, 124.60, 124.56, 124.3, 122.5, 120.5, 119.8, 119.5, 111.7, 109.7, 66.2, 55.5, 46.9, 27.3 ppm. IR (film, cm^{-1}): ν = 3391.46, 3314.59, 3064.77, 2949.47, 1706.76 cm^{-1}. HRMS (ESI): m/z calcd 571.18392 ($C_{33}H_{25}F_3N_2O_4$), found 571.18559 (M + H)$^+$. $[\alpha]_D^{20}$ −12.1 (c 0.50, MeOH).

*(S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(2-(2-fluorophenyl)-1H-indol-3-yl)propanoic Acid (**5f**).* Starting from amino acid **1c** (100 mg, 0.234 mmol) and 2-fluoroiodobenzene (41.4 μL, 0.351 mmol). Pale oil (121.8 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.68 (d, J = 7.6 Hz, 2H), 7.62 (d, J = 7.9 Hz, 1H), 7.44−7.25 (m, 8H), 7.24−7.20 (m, 1H), 7.17−7.04 (m, 4H), 5.07 (d, J = 8.1 Hz, 1H), 4.63−4.53 (m, 1H), 4.21−4.06 (m, 2H), 4.03 (t, J = 7.4 Hz, 1H), 3.48− 3.30 (m, 2H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −114.0 to −114.2 (m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 158.7, 155.9, 144.0, 141.4, 136.1, 131.5, 130.6, 130.5, 130.3, 127.8, 127.2, 125.3, 124.84, 124.81, 123.1, 120.4, 120.1, 119.1, 116.6, 116.4, 111.2, 108.9, 67.3, 54.3, 47.1, 27.2. IR (film, cm^{-1}): ν = 3415.92, 3334.19, 3062.16, 2924.47, 1715.77 cm^{-1}. HRMS (ESI): m/z calcd 521.18711 ($C_{32}H_{25}FN_2O_4$), found 521.18728 (M + H)$^+$. $[\alpha]_D^{20}$ −2.9 (c 0.50, MeOH).

*(S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(2-(p-tolyl)-1H-indol-3-yl)propanoic Acid (**5g**).* Starting from amino acid **1c** (100 mg, 0.234 mmol) and 4-iodotoluene (76.7 mg, 0.351 mmol). Pale oil (97.4 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.69−7.65 (m, 2H), 7.59 (d, J = 7.9 Hz, 1H), 7.41−7.27 (m, 8H), 7.21−7.19 (m, 1H), 7.16−7.08 (m, 3H), 7.09−7.05 (m, 1H), 5.02 (d, J = 7.9 Hz, 1H), 4.54 (q, J = 6.9 Hz, 1H), 4.16−4.05 (m, 2H), 4.00 (t, J = 7.2 Hz, 1H), 3.54−3.35 (m, 2H), 2.26 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 155.8, 143.8, 143.7, 141.2, 138.2, 136.64, 135.60, 129.7, 129.6, 129.0, 128.3, 127.7, 127.6, 127.1, 127.0, 125.2, 122.5, 120.2, 120.0, 119.9, 118.7, 110.9, 106.4, 67.1, 54.5, 47.0, 26.8, 21.2 ppm. IR (film, cm^{-1}): ν = 3385.05, 3314.59, 3051.96, 2949.47, 1693.95 cm^{-1}. HRMS (ESI): m/z calcd 517.21218 ($C_{33}H_{28}N_2O_4$), found 517.21356 (M + H)$^+$. $[\alpha]_D^{20}$ −9.9 (c 0.50, MeOH).

*(S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(2-(4-methoxyphenyl)-1H-indol-3-yl)propanoic Acid (**5h**).* Starting from amino acid **1c** (50.0 mg, 0.117 mmol) and 4-iodoanisole (41.2 mg, 0.176 mmol). Pale oil (39.0 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.98−7.94 (m, 2H), 7.71−7.61 (m, 3H), 7.48 (d, J = 8.3 Hz, 2H), 7.42−7.28 (m, 5H), 7.23−7.16 (m, 3H), 7.09 (t, J = 7.5 Hz, 1H), 5.15 (d, J = 8.4 Hz, 1H), 4.60 (q, J = 6.6, 6.1 Hz, 1H), 4.18−4.07 (m, 2H), 3.99 (t, J = 7.3 Hz, 1H), 3.80 (s, 3H), 3.59−3.42 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 158.5, 154.8, 142.8,

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142.7, 140.19, 140.17, 134.5, 129.2, 128.7, 127.1, 126.6, 126.0, 124.2, 123.9, 121.3, 119.1, 118.90, 118.87, 117.6, 113.5, 109.9, 107.1, 105.1, 66.1, 54.2, 53.5, 51.2, 46.0 ppm. IR (film, cm^{-1}): ν = 3365.84, 3308.19, 3051.96, 2923.84, 1693.95 cm^{-1}. HRMS (ESI): m/z calcd 533.20710 ($C_{33}H_{28}N_2O_5$), found 533.20867 $(M + H)^+$. $[\alpha]_D^{20}$ −9.8 (c 0.45, MeOH).

*(S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(2-(pyren-1-yl)-1H-indol-3-yl)propanoic Acid (**5i**).* Starting from amino acid **1c** (100 mg, 0.234 mmol) and 1-iodopyrene 2b (115 mg, 0.352 mmol). Pale oil (94.2 mg, 66%). ^{1}H NMR (400 MHz, DMSO): δ 12.36 (s, 1H), 11.46 (s, 1H), 8.36−8.21 (m, 6H), 8.17−8.07 (m, 4H), 7.95 (d, J = 9.2 Hz, 1H), 7.86 (d, J = 7.6 Hz, 2H), 7.79 (d, J = 7.9 Hz, 1H), 7.52 (t, J = 7.1 Hz, 2H), 7.44−7.35 (m, 4H), 7.27−7.15 (m, 3H), 7.09 (t, J = 7.4 Hz, 1H), 4.13 (q, J = 7.8 Hz, 1H), 4.01−3.78 (m, 3H), 3.12 (s, 2H) ppm. ^{13}C NMR (100 MHz, DMSO): δ 173.2, 155.5, 143.7, 140.6, 136.2, 134.8, 130.8, 130.7, 130.4, 129.4, 128.8, 128.2, 128.0, 127.8, 127.7, 127.5, 127.3, 127.0, 126.4, 125.4, 125.3, 125.2, 124.5, 124.0, 123.8, 121.3, 120.0, 118.89, 118.86, 111.1, 109.8, 65.5, 54.8, 46.4, 26.8 ppm. IR (film, cm^{-1}): ν = 3417.33, 3308.19, 3043.35, 2923.54, 1714.91 cm^{-1}. HRMS (ESI): m/z calcd 627.22783 ($C_{42}H_{30}N_2O_4$), found 627.23025 $(M + H)^+$. $[\alpha]_D^{20}$ +7.6 (c 0.13, MeOH).

2-(2-Phenyl-1*H*-indol-3-yl)acetic Acid (8).[28] Starting from 2-(1*H*-indol-3-yl)acetic acid (42.0 mg, 0.240 mmol) and iodobenzene (40.3 μL, 0.360 mmol). Pale oil (47.8 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.60 (ddt, J = 7.8, 1.5, 0.7 Hz, 1H), 7.57−7.54 (m, 2H), 7.46−7.36 (m, 2H), 7.35−7.30 (m, 2H), 7.21−7.12 (m, 1H), 7.14−7.05 (m, 1H), 3.80 (s, 2H) ppm. HRMS (ESI): m/z calcd 252.10191 ($C_{16}H_{13}NO_2$), found 252.10168 $(M + H)^+$.

3-(2-Phenyl-1*H*-indol-3-yl)propanoic Acid (9).[29] Starting from 3-(1*H*-indol-3-yl)propanoic acid (45.4 mg, 0.240 mmol) and iodobenzene (41.1 μL, 0.360 mmol). Pale oil (47.6 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.58−7.55 (m, 1H), 7.48−7.45 (m, 2H), 7.43−7.38 (m, 2H), 7.33−7.28 (m, 2H), 7.15 (ddd, J = 8.1, 7.1, 1.2 Hz, 1H), 7.08 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H), 3.21−3.16 (m, 2H), 2.68−2.63 (m, 2H) ppm. HRMS (ESI): m/z calcd 266.11756 ($C_{17}H_{15}NO_2$), found 266.11729 $(M + H)^+$.

4-(2-Phenyl-1*H*-indol-3-yl)butanoic Acid (10).[30] Starting from 4-(1*H*-indol-3-yl)butanoic acid (83.7 mg, 0.412 mmol) and iodobenzene (69.2 μL, 0.618 mmol). Pale oil (84.8 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.57 (ddt, J = 7.8, 1.2, 0.7 Hz, 1H), 7.49−7.46 (m, 2H), 7.41−7.35 (m, 2H), 7.31−7.25 (m, 2H), 7.16−7.10 (m, 1H), 7.07 (ddt, J = 7.9, 6.9, 0.7 Hz, 1H), 2.91−2.87 (m, 2H), 2.33 (t, J = 7.3 Hz, 2H), 2.03−1.94 (m, 2H) ppm. HRMS (ESI): m/z calcd 280.13321 ($C_{18}H_{17}NO_2$), found 280.13287 $(M + H)^+$.

2-(2-Phenyl-1*H*-indol-3-yl)ethanamine (11).[31] Tryptamine (76.9 mg, 0.480 mmol), iodobenzene (80.6 μL, 0.720 mmol), $AgBF_4$ (186.9 mg, 0.960 mmol), and $Pd(OAc)_2$ (5.4 mg, 0.024 mmol) were placed in a microwave reactor vessel in dry DMF (2.4 mL). The mixture was heated under microwave irradiation (250 W) at 90 °C for 20 min. HPLC/MS analysis showed 29% of compound **11**. Incidentally, iodobenzene (80.6 μL, 0.720 mmol) and $Pd(OAc)_2$ (5.4 mg, 0.024 mmol) were added, and a second irradiation cycle was performed (250 W) at 90 °C for 20 min, thus increasing the conversion up to 89%, as shown in the HPLC/MS. Ethyl acetate (30 mL) was added, the resulting suspension was filtered through Celite, and the solvent was removed under vacuum. The crude product was purified by flash chromatography on silica using hexane/ethyl acetate and then DCM/MeOH to obtain **11** as an oil (54.4 mg, 48%). ^{1}H NMR (400 MHz, DMSO): δ 11.30 (s, 1H), 7.79 (s, 2H), 7.63−7.59 (m, 3H), 7.52 (t, J = 7.6 Hz, 2H), 7.44−7.35 (m, 2H), 7.15−7.10 (m, 1H), 7.08−7.02 (m, 1H), 3.15−3.09 (m, 2H), 3.09−2.98 (m, 2H) ppm. RP-HPLC-ESMS: m/z (%) 237.12 $(M + H)^+$.

***N*-(2-(2-Phenyl-1*H*-indol-3-yl)ethyl)acetamide (12).**[32] Starting from *N*-(2-(1*H*-indol-3-yl)ethyl)acetamide (98.0 mg, 0.485 mmol) and iodobenzene (80.6 μL, 0.720 mmol). Yellow solid (103.1 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.52−7.45 (m, 2H), 7.38 (t, J = 7.7 Hz, 2H), 7.33−7.26 (m, 2H), 7.17−7.12 (m, 1H), 7.09−7.05 (m, 1H), 5.41 (s, 1H), 3.46 (q, J = 6.5 Hz, 2H), 3.04 (t, J = 6.8 Hz, 2H), 1.67 (s, 3H) ppm. RP-HPLC-ESMS: 279.12 $(M + H)^+$.

General Procedure for SPPS. All peptides were manually synthesized in polystyrene syringes fitted with a polyethylene porous disc. The synthesis of the peptides were performed using Fmoc-based SPPS on a 2-chlorotrityl chloride resin. Solvents and soluble reagents were removed by suction. The Fmoc group was removed with piperidine-DMF (1:4, v/v) (1 × 1 min, 2 × 5 min). Peptide synthesis transformations and washes were performed at r.t.

Resin Loading. Fmoc-XX-OH (1 equiv) was attached to the resin (1 equiv) with DIPEA (3 equiv) in DCM at r.t for 10 min and then DIPEA (7 equiv) for 40 min. The remaining trityl groups were capped, adding 0.8 μL of MeOH/mg resin for 10 min. After that, the resin was filtered and washed with DCM (4 × 1 min) and DMF (4 × 1 min). The loading of the resin was determined by titration of the Fmoc group.[33]

Peptide Elongation. After the Fmoc group was eliminated, the resin was washed with DMF (4 × 1 min), DCM (3 × 1 min), and DMF (4 × 1 min). Amino acid coupling: Fmoc-XX-OH (3 equiv) was incorporated with a 5 min preactivation with DIPCDI (3 equiv) and OxymaPure (3 equiv) in DMF for 1h. The completion of the coupling was monitored with the ninhydrin test (free amine group).[34] The resin was then filtered and washed with DCM (4 × 1 min) and DMF (4 × 1 min), and the Fmoc group was eliminated.

Final Cleavage. The resin bound peptide was treated with 5% TFA in DCM (5 × 1 min). The resin was washed with DCM, and the combined eluates were evaporated under vacuum. The residue was then dissolved in ACN/H_2O and lyophilized, furnishing the corresponding peptide.

H-Met-Gly-Trp(C2-*p*-methylphenyl)-Ala-OH (6). Starting from 150 mg of 2-chlorotrityl resin (0.92 mmol/g). Pale solid (purity > 99%, HPLC). ^{1}H NMR (400 MHz, DMSO d_6): δ 12.51 (s, 1H), 11.09 (s, 1H), 8.53 (t, J = 5.6 Hz, 1H), 8.20−8.07 (m, 5H), 7.74 (d, J = 7.9 Hz, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.31−7.28 (m, 2H), 7.10−7.02 (m, 1H), 6.97 (t, J = 7.5 Hz, 1H), 4.76 (q, J = 7.6 Hz, 1H), 4.13 (p, J = 7.2 Hz, 1H), 3.85 (m, 1H), 3.78 (dd, J = 16.8, 5.4 Hz, 1H), 3.60 (dd, J = 16.8, 5.7 Hz, 1H), 3.26 (dd, J = 14.5, 5.7 Hz, 1H), 3.05 (dd, J = 14.5, 7.9 Hz, 1H), 2.48 (m, 2H), 2.37 (s, 3H), 2.03 (s, 3H), 1.99−1.88 (m, 2H), 1.22 (d, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, DMSO): δ 173.6, 170.7, 168.2, 167.5, 136.6, 135.8, 135.5, 129.9, 129.2, 129.0, 128.1, 121.2, 119.2, 118.5, 110.9, 107.0, 53.7, 51.5, 47.5, 41.6, 30.9, 28.3, 28.0, 20.8, 17.3, 14.4 ppm. HRMS (ESI): m/z calcd 554.2432 ($C_{28}H_{35}N_5O_5S$), found 554.2429 $(M + H)^+$.

H-Trp-Gly-Trp(C2-*p*-methylphenyl)-Ala-OH (7). Starting from 150 mg of 2-chlorotrityl resin (0.92 mmol/g). Pale solid (purity > 99%, HPLC). ^{1}H NMR (400 MHz, DMSO d_6): δ 11.10 (s, 1H), 10.98 (d, J = 2.5 Hz, 1H), 8.72 (t, J = 5.5 Hz, 1H), 8.16 (dd, J = 8.0, 5.8 Hz, 2H), 7.97 (m, 3H), 7.75 (d, J = 7.9 Hz, 1H), 7.68−7.63 (m, 1H), 7.60−7.54 (m, 2H), 7.36 (d, J = 8.1, 1H), 7.29 (d, J = 7.8 Hz, 2H), 7.19 (m, 1H), 7.08 (dddd, J = 8.1, 6.9, 5.8, 1.2 Hz, 2H), 6.98 (dddd, J = 8.0, 7.0, 4.4, 1.1 Hz, 2H), 4.79 (td, J = 8.3, 5.6 Hz, 1H), 4.14 (p, J = 7.2 Hz, 1H), 4.00 (m, 1H), 3.90 (dd, J = 16.9, 5.9 Hz, 1H), 3.45 (dd, J = 16.9, 5.0 Hz, 1H), 3.23 (ddd, J = 35.5, 14.7, 5.2 Hz, 2H), 3.04 (m, 2H), 2.36 (s, 3H), 1.22 (d, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, DMSO): δ 173.6, 170.8, 168.6, 167.5, 136.6, 136.3, 135.8, 135.6, 130.0, 129.2, 129.0, 128.1, 127.0, 125.0, 121.2, 119.2, 118.5, 118.4, 111.5, 110.9, 107.0, 106.8, 53.6, 52.5, 47.6, 41.8, 27.52 (2 C), 20.8, 17.3 ppm. HRMS (ESI): m/z calcd 609.2820 ($C_{34}H_{36}N_6O_5$), found 609.2820 $(M + H)^+$.

■ ASSOCIATED CONTENT

Supporting Information

Spectral and analytical data: copies of the ^{1}H, ^{13}C, and ^{19}F NMR spectra for all new compounds and chiral HPLC profiles of **5a** and **5a′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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