N-(Cbz- and Fmoc-α-aminoacyl)benzotriazoles: Stable Derivatives Enabling Peptide Coupling of Tyr, Trp, Cys, Met, and Gln with Free Amino Acids in Aqueous Media with Complete Retention of Chirality

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Abstract: Crystalline, chirally stable *N*-(Cbz- and Fmoc-α-aminoacyl)benzotriazoles **2a–f**, activated derivatives of Tyr, Trp, Cys, Met and Gln undergo peptide coupling in aqueous media with unprotected L-Ala-OH and L-Phe-OH to give the chiral dipeptides in 70–98% yield. A convenient and efficient procedure under mild reaction conditions for the preparation of **2a–f** in 72–95% yield utilizes *N*-Cbz- or *N*-Fmoc-protected α-amino acids **1a–f**.

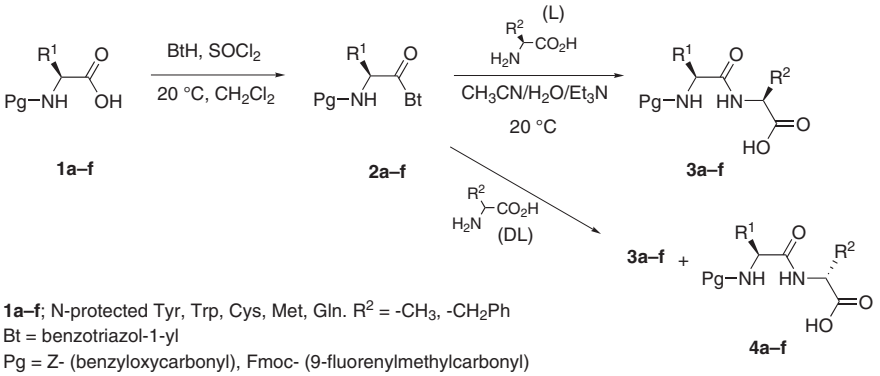
Key words: *N*-(protected α-aminoacyl)benzotriazole, benzotriazole, amino acid, acylating reagent, peptide coupling

Activation of the carboxylic acid function of N-protected α-amino acids has attracted considerable attention due to the importance of peptide bond formation. The many previous methods can be classified into (i) those in which no intermediate is isolated, for example carbodiimides (DCC or EDAC) with HOBt,[1a] or uronium salts,[1b] and (ii) isolated intermediates including N-protected α-amino acid chlorides,[1c] fluorides,[1d] azides and phenyl esters.[1a,1e–i] Although this type of chemistry for the formation of peptide bonds has been well-established, to date, no single method of choice has emerged.

Azides,[1e] *N*-hydroxysuccinimide esters,[2a,b] and *p*-nitrophenyl esters[3] were previously utilized to achieve peptide coupling between a C-terminal activated N-protected α-amino acid and a non-protected α-amino acid. *N*-Hydroxysuccinimide esters[2a,b] and *p*-nitrophenyl esters[3] were reported as isolable stable solids, sufficiently reactive to couple with α-amino acids, but mild enough to prevent undesired side-reactions with functional groups in amino acid side-chains, and examples have involved such esters of N-protected α-amino acids carrying alkyl side-chains (such as Ala, Val, Phe) as well as side-chains with some functionalities (such as Tyr, Trp, Gln, Thr[2c]).

N-Acylbenzotriazoles have been employed for: (i) N-acylation in the preparation of primary, secondary, and tertiary amides,[4a] and *N*-acylsulfonamides,[4b] (also see refs[4c–e]) (ii) O-acylation in additions to aldehydes to give esters,[5] (iii) S-acylation for the synthesis of thiol esters,[6] and (iv) C-acylation for the preparation of 1,3-,[7a] 1,2-diketones,[7b] α-cyano ketones,[7c] β-ketosulfones,[7d] enaminones,[7e] and C-acylated pyrroles, indoles,[7f] 2-methylfuran and thiophene.[7g]

We previously reported the preparation of *N*-(Boc-α-amino)amides from *N*-(Boc-α-aminoacyl)benzotriazoles and chiral amines in 82–99% yields with no detectable racemization[8a] and demonstrated the peptide coupling of several *N*-(Cbz-α-aminoacyl)benzotriazoles (Cbz-Ala-Bt, Cbz-Val-Bt, and Cbz-Phe-Bt) with unprotected amino acids in CH_3CN–H_2O with complete preservation of the original chirality.[8b] In continuation of our extensive research on N-(protected α-aminoacyl)benzotriazoles, we now report (i) the preparation of functionalized *N*-(Cbz- or Fmoc-α-aminoacyl)benzotriazoles **2a–f** carrying phenolic OH, NH of indole, SH, SMe, amide group, and (ii)



Scheme 1

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coupling reactions of **2a–f** with unprotected amino acids (L-Ala, D,L-Ala, L-Phe, D,L-Phe) with retention of chirality as d monstrated by NMR and HPLC (Scheme 1).

Table 1 Conversion of *N*-Cbz-α-Amino Acids into α-(*N*-Cbz-Aminoacyl) Benzotriazoles

Compound	Yield (%)[a]	$[\alpha]^{25}_D$	Mp (°C)
Cbz-L-Tyr-Bt (**2a**)	86	+46.5	165–166
Cbz-L-Trp-Bt (**2b**)	95	+35.2	100–101
Fmoc-L-Trp-Bt (**2c**)	90	+12.7	88–90
Cbz-L-Cys-Bt (**2d**)	76	−121.7	144–147
Fmoc-L-Met-Bt (**2e**)	87	−75.1	98–100
Cbz-L-Gln-Bt (**2f**)	72	−27.1	161–162

[a] Isolated yield.

Preparation of *N*-(Cbz- and Fmoc-α-Aminoacyl) Benzotriazoles

We recently developed a new method to prepare a wide range of *N*-acylbenzotriazoles utilizing 1 equivalent of a carboxylic acid with 4 equivalents of 1*H*-benzotriazole and 1 equivalent of thionyl chloride in THF or CH_2Cl_2 at 20 °C for two hours.[9] During our study of *N*-acylbenzotriazoles, we found that carboxyl groups can frequently be activated by this method without any side-reactions in the presence of potential reaction sites such as phenolic OH, thiol, indole NH and amide groups. The activation of the carboxyl group in tyrosine, cysteine, and glutamine derivatives without protection of -OH, -SH, and -$CONH_2$ groups at their side-chains was the main objective of this study. Therefore, the above protocol has now been applied to achieve the preparation of *N*-(Cbz- and Fmoc-α-aminoacyl)benzotriazoles **2a–f** with functionalized side-chains (Cbz-Tyr, Cbz-Trp, Cbz-Gln, Cbz-Cys, Fmoc-Trp, Fmoc-Met) in 72–95% yield (Table 1).

Cbz-Trp-Bt (**2b**), Fmoc-Trp-Bt (**2c**), and Fmoc-Met-Bt (**2e**) were prepared using the procedure of our previous report.[8b] However, in attempts to prepare Cbz-Tyr-Bt (**2a**) in this manner, the wash with Na_2CO_3 to remove BtH formed Tyr sodium phenolate and removed the product; however, a wash with 6 N HCl yielded the desired compound without its transfer to the aqueous layer. The crude product of Cbz-Cys-Bt (**2d**) was also washed with 6 N HCl to remove BtH to prevent the formation of thiol ester oligomers by known reactions of *N*-acylbenzotriazoles, including *N*-(Cbz-aminoacyl)benzotriazoles, with alphatic and aromatic mercaptans.[6] To obtain Cbz-Gln-Bt (**2f**), the crude mixture of **2f** and BtH was simply washed with EtOAc to remove BtH (**2f** was not very soluble in EtOAc).

N-(Cbz- and Fmoc-aminoacyl)benzotriazoles **2a–f** are novel, and were characterized by ^{1}H and ^{13}C NMR spectroscopy, elemental analysis, and ORP. The compounds **2a–f** are stable and can be stored at room temperature for months without special procedure to exclude air or moisture. In addition, the reagents involved in the preparation are inexpensive, thereby offering at the same time an overall cost effective methodology.

Preparation of Dipeptides (3a–f, 4a–f)

Peptide coupling was carried out using equimolar amount of **2a–f** and L-Ala-OH or L-Phe-OH in a partially aqueous medium (CH_3CN–H_2O, 2:1 in volume) in the presence of Et_3N (1 equiv) at 20 °C for 1 hour. After work-up, the L,L-dipeptides **3a–f** were obtained in almost pure form as indicated by the crude ^{1}H NMR spectra. Dipeptides **3a–f** were further purified by recrystallization, typically from $CHCl_3$–hexanes, to give yields of 85–95% (Table 2). Mixtures of L,L- and L,D-dipeptide diastereomers **3a–f** + **4a–f** were also prepared from each **2a–f** under the same condition utilizing enantiomixtures (Table 3), D,L-Ala-OH or D,L-Phe-OH, using the procedure described above for preparation of L,L-dipeptides **3a–f**.

Analysis of L,L-(3a–f) and L,D,L-Dipeptides (4a–f)

We previously described[8b] that the coupling reactions utilizing *N*-(Cbz-aminoacyl)benzotriazoles gave the resulting peptides with no detectable racemization demonstrated by ^{1}H NMR and HPLC analysis. Likewise, the crude dipeptides **3a–f** were analyzed in NMR, and showed no detectable racemization (> 95%). The ^{1}H NMR spectra of diastereo-mixtures **3a–f** + **4a–f** were typically complicated; however, the NH proton signal at Cbz and Fmoc groups around 8.2–8.5 ppm showed clearly two doublets for **3** + **4** (L,L-, L,D-mixture) when **3** (L,L) gave only one doublet. For instance, Cbz-L-Tyr-L-Phe-OH (**3a**) gave only one doublet at 8.37 ppm when Cbz-L-Tyr-D,L-Phe-OH (**3a** + **4a**) gave two doublets at 8.30 ppm and 8.37 ppm. It appeared that the NH proton signal for **3a–f** (L,L) showed their doublet in the magnetically lower field (higher ppm) than that of L,D-configuration. The methyl protons of alanine (Ala) fragment were also easily monitored in ^{1}H NMR. Cbz-L-Trp-L-Ala-OH (**3b**) gave a noticeable doublet for the methyl group at 1.32 ppm while Cbz-L-Trp-D,L-Ala-OH (**3b** + **4b**) indicated two doublets at 1.23 ppm and 1.32 ppm. By observing the methyl protons for **3b–e** and **4b–e**, compounds with L,L-configuration were found to have tendency to exhibit the peaks in the lower magnetic field (higher ppm) than compounds with L,D-conformation. In ^{13}C NMR for mixtures of **3a–f** + **4a–f**, all of the aliphatic and the carbonyl carbons typically displayed doublets, but aromatic carbons did not show significant differences.

The enantiopurity (> 99%) of the dipeptides **3a–f** (L,L-configuration) was further confirmed by HPLC analysis using Chirobiotic T column (detection at 254 nm, flow rate 0.5 mL/min, and solvent MeOH for all **3a–f**). The HPLC results obtained for the desired L,L-dipeptides **3a–f** are summarized in Table 1. HPLC results for the corresponding mixtures of L,L- and L,D-dipeptides prepared with D,L-amino acids as a second component is shown in

Table 2 Preparation of L,L-Dipeptides **3a–f** using **2a–f**

Reactant	Amino acid	Product	Yield (%)[a]	Retention time[b]
Cbz-L-Tyr-Bt (**2a**)	L-Phe-OH	Cbz-L-Tyr-L-Phe-OH (**3a**)	86	10.8
Cbz-L-Trp-Bt (**2b**)	L-Ala-OH	Cbz-L-Trp-L-Ala-OH (**3b**)	90	11.0
Fmoc-L-Trp-Bt (**2c**)	L-Ala-OH	Fmoc-L-Trp-L-Ala-OH (**3c**)	70	11.1
Cbz-L-Cys-Bt (**2d**)	L-Ala-OH	Cbz-L-Cys-L-Ala-OH (**3d**)	98	11.5
Fmoc-L-Met-Bt (**2e**)	L-Ala-OH	Fmoc-L-Met-L-Ala-OH (**3e**)	95	10.9
Cbz-L-Gln-Bt (**2f**)	L-Phe-OH	Cbz-L-Gln-L-Phe-OH (**3f**)	72	12.9

[a] Isolated yield.
[b] For conditions, see the experimental section.

Table 2. The L,L and L,D-mixtures (**3** + **4**) were clearly separated to show two peaks of L,L- and L,D-diastereomers using the chiral column; the L,L-compounds all have shorter retention time than L,D-compounds in these conditions.

In conclusion, the convenient preparation of *N*-(Cbz- or Fmoc-α-aminoacyl) benzotriazoles converted from *N*-Cbz- or Fmoc- protected amino acids (Tyr, Trp, Cys, Met, and Gln) has been demonstrated under mild conditions, and examples of peptide couplings utilizing non-protected amino acids in partially aqueous solution has been performed to produce the corresponding dipeptides with negligible racemization in NMR and HPLC studies. Our results in the preparation of dipeptides using Cbz-Tyr-Bt (**2a**), Cbz-Trp-Bt (**2b**), Fmoc-Trp-Bt (**2c**) are comparable to those in the conventional methods. However, Cbz-Cys-Bt (**2d**) is the first example of C-activated Cys derivative isolated without protection of the thiol group. Reactions of conventional Cbz-Gln active esters often require purification by column chromatography. Use of Cbz-Gln-Bt (**2f**) can simplify the process, and avoid the loss of products. Overall, the present method offers an advantageous and economical procedure utilizing inexpensive reagents (1*H*-benzotriazole, thionyl chloride) for the C-activation and shorter reaction times (< 2 h) than those (> 20 h) with esters of *N*-hydrosuccinimide or *p*-nitrophenol for the peptide couplings.

Melting points were determined on a capillary point apparatus equipped with a digital thermometer. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with TMS for ^1H (300 MHz) and ^{13}C (75 MHz) as the internal reference. HPLC analyses were performed on Beckman system gold programmable solvent module 126 using Chirobiotic T column (4.6 × 250 mm), detection at 254 nm, flow rate of 0.5 mL/min and MeOH as an eluting solvent. *N*-Cbz- and Fmoc-amino acids purchased from Fluka and amino acids purchased from Acros, were used without further purification.

Preparation of *N*-(Cbz- and Fmoc-Aminoacyl)benzotriazoles 2a–f; General Procedure

Thionyl chloride (5 mmol) was added to a solution of 1*H*-benzotriazole (20 mmol) in anhyd THF (15 mL) at 25 °C, and the reaction mixture was stirred for 20 min at 35–40 °C. The reaction mixture was cooled in an ice-bath, and the N-protected amino acid (5 mmol) dissolved in anhyd THF (5 mL) was added dropwise. After stirring for 2 h at 25 °C, the white precipitate formed during the reaction was filtered off, and the filtrate was concentrated under reduced pressure. The residue was diluted with EtOAc (100 mL) and the solution was washed with 6 N HCl solution (3 × 50 mL) for **2a** and **2d**, or sat. Na_2CO_3 solution (3 × 50 mL) for **2b**, **2c**, and **2e**, sat. NaCl solution (50 mL), and dried over anhyd $MgSO_4$. Removing solvents under reduced pressure gave the products **2a–e**. In case of **2f**, the product was obtained by simply washing the crude mixture with EtAOc after the concentration. Products **2a–f** were further recrystallized from $CHCl_3$–hexanes for elemental analysis.

Table 3 Preparation of Mixtures of L,D,L-Dipeptides **3a–f** + **4a–f**

Reactant	Amino acid	Product	Yield (%)[a]	Retention Time[b]	
				LL	LD
2a	D,L-Phe-OH	Cbz-L-Tyr-D, L-Phe-OH (**3a** + **4a**)	86	10.8	11.7
2b	D,L-Ala-OH	Cbz-L-Trp-D,L-Ala-OH (**3b** + **4b**)	90	11.0	12.9
2c	D,L-Ala-OH	Fmoc-L-Trp-D,L-Ala-OH (**3c** + **4c**)	68	11.3	13.6
2d	D,L-Ala-OH	Cbz-L-Cys-D,L-Ala-OH (**3d** + **4d**)	71	11.6	24.3
2e	D,L-Ala-OH	Fmoc-L-Met-D,L-Ala-OH (**3e** + **4e**)	72	10.9	15.9
2f	D,L-Phe-OH	Cbz-L-Gln-D,L-Phe-OH (**3f** + **4f**)	74	13.0	15.9

[a] Isolated yield.
[b] For conditions, see the experimental section.

Benzyl *N*-[(1*S*)-2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(4-hydroxybenzyl)-2-oxoethyl]carbamate [Cbz-L-Tyr-Bt (2a)]
White microcrystals (86%); mp 165–166 °C; $[\alpha]_D^{23}$ +46.5 (*c* = 1.5, DMF).

^{1}H NMR (DMSO-d_6): δ = 2.97 (dd, *J* = 13.7, 9.9 Hz, 1 H, CHCH_2Ar), 3.21 (dd, *J* = 13.7, 4.0 Hz, 1 H, CHCH_2Ar), 5.00 (s, 2 H, OCH_2Ph), 5.63–5.70 (unresolved m, 1 H, NC*H*CH$_2$), 6.65 (d, *J* = 8.0 Hz, 2 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 7.32–7.34 (m, 5 H), 7.64 (dd, *J* = 8.3, 6.9 Hz, 1 H, Bt), 7.82 (dd, *J* = 8.4, 6.9 Hz, 1 H, Bt), 8.23–8.34 [m, 2 H (Bt), 1 H (NH)], 9.27 (s, 1 H, OH).

^{13}C NMR ($CDCl_3$): δ = 35.7, 56.5, 65.8, 113.9, 115.1, 120.2, 126.8, 126.9, 127.7, 127.9, 128.3, 130.0, 130.5, 131.1, 136.6, 145.3, 156.1, 156.2, 171.9.

Anal. Calcd for $C_{23}H_{20}N_4O_4$: C, 66.34; H, 4.82; N, 13.45. Found: C, 66.35; H, 4.73; N, 13.20.

Benzyl *N*-[(1*S*)-2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(1*H*-indol-3-ylmethyl)-2-oxoethyl]carbamate [Cbz-L-Trp-Bt (2b)]
Pale yellow crystals (95%); mp 100–101 °C; $[\alpha]_D^{23}$ +35.2 (*c* = 1.5, DMF).

^{1}H NMR ($CDCl_3$): δ = 3.43 (dd, *J* = 14.7, 7.1 Hz, 1 H, ArCH_2CH), 3.61 (dd, *J* = 14.7, 7.1 Hz, 1 H, ArCH_2CH), 5.06 (s, 2 H, PhCH_2O), 5.70 (d, *J* = 7.5 Hz, 1 H, CH$_2$C*H*N), 6.13 (dd, *J* = 12.5, 7.0 Hz, 1 H, NH), 6.90–6.98 (m, 3 H), 7.08–7.13 (m, 1 H), 7.29 (m, 5 H), 7.40 (d, *J* = 7.8 Hz, 1 H), 7.47–7.52 (m, 1 H, Bt), 7.58–7.63 (m, 1 H, Bt), 8.12 (d, *J* = 8.2 Hz, 1 H, Bt), 8.16 (d, *J* = 8.2 Hz, 1 H, Bt), 8.22 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 28.7, 55.1, 67.2, 109.0, 111.2, 114.3, 118.3, 119.7, 120.2, 122.2, 123.1, 126.4, 127.1, 128.1, 128.4, 128.5, 130.7, 131.0, 135.9, 136.1, 145.9, 155.9, 171.1.

Anal. Calcd for $C_{25}H_{21}N_5O_3$: C, 68.33; H, 4.82; N, 15.94. Found: C, 68.18; H, 4.77; N, 16.12.

9*H*-Fluoren-9-ylmethyl *N*-[1-(1*H*-1,2,3-Benzotriazol-1-ylcarbonyl)-2-(indol-3-ylmethyl)]carbamate [Fmoc-L-Trp-Bt (2c)]
White microcrystals (90%); mp 88–90 °C; $[\alpha]_D^{23}$ +12.7 (*c* = 1.5, DMF).

^{1}H NMR (DMSO-d_6): δ = 3.27 (dd, *J* = 14.6, 9.9 Hz, 1 H, ArCH_2CH), 3.52 (dd, *J* = 14.6, 4.1 Hz, 1 H, ArCH_2CH), 4.15–4.30 (m, 3 H, CH$_2$, CH, Fmoc), 5.74–5.81 (unresolved m, 1 H, CH$_2$C*H*N), 6.97–7.09 (m, 2 H), 7.17–7.46 (m, 6 H), 7.61–7.84 (m, 5 H), 7.88 (d, *J* = 7.4 Hz, 2 H), 8.25 (d, *J* = 8.2 Hz, 1 H, Bt), 8.28 (d, *J* = 8.3 Hz, 1 H, Bt), 8.36 (d, *J* = 7.1 Hz, 1 H, NH), 10.89 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 27.1, 46.5, 55.6, 65.9, 109.2, 111.5, 114.0, 118.2, 118.5, 120.1, 120.2, 121.0, 124.4, 125.2, 126.7, 126.8, 127.1, 127.6, 130.6, 131.1, 136.1, 140.7, 143.6, 143.7, 145.3, 156.2, 172.2.

Anal. Calcd for $C_{32}H_{25}N_5O_3$: C, 72.85; H, 4.78; N, 13.27. Found: C, 72.55; H, 4.80; N, 12.97.

Benzyl *N*-[(1*S*)-2-(1*H*-1,2,3-Benzotriazol-1-yl)-2-oxo-1-(sulfanylmethyl)ethyl]carbamate [Cbz-L-Cys-Bt (2d)]
White microcrystals (76%); mp 144–147 °C; $[\alpha]_D^{23}$ –121.7 (*c* = 1.5, DMF).

^{1}H NMR (DMSO-d_6): δ = 3.17 (dd, *J* = 13.8, 9.9 Hz, 1 H, SCH_2CH), 3.54 (dd, *J* = 13.7, 4.1 Hz, 1 H, SCH_2CH), 5.04 (s, 2 H, PhCH_2O), 5.88 (unresolved m, 1 H, CH$_2$C*H*N), 7.34 (unresolved m, 5 H), 7.62 (dd, *J* = 7.7, 6.9 Hz, 1 H, Bt), 7.80 (dd, *J* = 7.7, 6.9 Hz, 1 H, Bt), 8.12 (d, *J* = 8.3 Hz, 1 H, Bt), 8.20 (d, *J* = 8.3 Hz, 1 H, Bt), 8.33 (d, *J* = 7.1 Hz, 1 H, NH); exchangeable 1 H (-SH) was missing.

^{13}C NMR (DMSO-d_6): δ = 37.2, 53.2, 66.0, 113.9, 120.2, 126.9, 127.8, 128.0, 128.4, 130.5, 131.3, 136.6, 145.3, 156.2, 170.3.

Anal. Calcd for $C_{17}H_{16}N_4O_3S$: C, 57.29; H, 4.52; N, 15.72. Found: C, 56.89; H, 4.20; N, 15.36.

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-1-(1*H*-1,2,3-benzotriazol-1-ylcarbonyl)-3-(methylsulfanyl)propyl]carbamate [Fmoc-L-Met-Bt (2e)]
White microcrystals (87%); mp 98–100 °C; $[\alpha]_D^{23}$ = –75.1 (*c* = 1.5, DMF).

^{1}H NMR (DMSO-d_6): δ = 2.08 (s, 3 H, CH_3S), 2.12–2.20 (m, 1 H, CH$_2$CH_2CH), 2.23–2.33 (m, 1 H, CH$_2$CH_2CH), 2.61–2.79 (m, 2 H, CH$_2$CH_2S), 4.23–4.31 (m, 1 H, CH, Fmoc), 4.38 (d, *J* = 6.8 Hz, 2 H, CH$_2$, Fmoc), 5.64–5.71 (m, 1 H), 7.30–7.48 (m, 4 H), 7.65 (dd, *J* = 7.7, 6.9 Hz, 1 H, Bt), 7.74 (d, *J* = 7.4 Hz, 2 H), 7.82 (dd. *J* = 7.5, 6.9 Hz, 1 H, Bt), 7.90 (d, *J* = 7.4 Hz, 2 H), 8.25 (d, *J* = 8.3 Hz, 1 H, Bt), 8.28–8.34 (m, 2 H, Bt, NH).

^{13}C NMR (DMSO-d_6): δ = 14.2, 29.6, 29.7, 46.6, 53.4, 65.9, 114.0, 120.1, 120.2, 125.2, 126.7, 127.1, 127.6, 130.7, 131.1, 140.7, 143.7, 145.3, 156.4, 171.9.

Anal. Calcd for $C_{26}H_{24}N_4O_3S$: C, 66.08; H, 5.12; N, 11.86. Found: C, 65.97; H, 5.08; N, 11.52.

Benzyl *N*-[(1*S*)-4-Amino-1-(1*H*-1,2,3-benzotriazol-1-ylcarbonyl)-4-oxobutyl]carbamate [Cbz-L-Gln-Bt (2f)]
Pale violet microcrystals (72%); mp 161–162 °C; $[\alpha]_D^{23}$ –27.1 (*c* = 1.5, DMF).

^{1}H NMR (DMSO-d_6): δ = 2.05–2.09 (m, 1 H, CH$_2$CH_2CH), 2.22–2.35 (m, 3 H, COCH_2CH_2CH), 5.06 (s, 2 H, PhCH_2O), 5.51–5.54 (unresolved m, 1 H, CH$_2$C*H*N), 6.83–6.92 (m, 2 H, NH_2), 7.36 (unresolved m, 5 H), 7.65 (dd, *J* = 8.2, 6.9 Hz, 1 H, Bt), 7.82 (dd, *J* = 8.2, 6.9 Hz, 1 H, Bt), 8.24 (d, *J* = 8.2 Hz, 1 H, NH), 8.31 (d, *J* = 7.8 Hz, 2 H, Bt).

^{13}C NMR (DMSO-d_6): δ = 26.5, 31.1, 54.1, 65.9, 114.1, 120.2, 126.8, 127.8, 127.9, 128.4, 130.6, 131.1, 136.7, 145.4, 156.3, 171.8, 173.1.

Anal. Calcd for $C_{23}H_{20}N_4O_4$: C, 59.84; H, 5.02; N, 18.36. Found: C, 59.59; H, 5.00; N, 18.11.

Preparation of Cbz- and Fmoc-L,L-dipeptides 3a–e; General Procedure
The starting material **2** (1 mmol) was added to a solution of an amino acid (1 mmol) with Et_3N (1 equiv) in CH_3CN–H_2O (10 mL/4 mL). The reaction mixture was stirred at r.t. for about 1 h (until TLC showed the absence of **2**). CH_3CN in the solution was removed under reduced pressure, and EtOAc was added. The organic solution was washed with 6 N HCl, and dried over $MgSO_4$. After evaporation of solvent, the residue was crystallized or precipitated out from $CHCl_3$–hexanes.

(2*S*)-2-{[(2*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-(4-hydroxyphenyl)propanoyl]amino}-3-phenyl-propanoic Acid [Cbz-L-Tyr-L-Phe-OH (3a)]
White microcrystals (86%); mp 149–151 °C; $[\alpha]_D^{23}$ –30.8 (*c* = 1.5, DMF).

^{1}H NMR (DMSO-d_6): δ = 2.60–2.64 (m, 1 H, ArCH_2CH), 2.88 (dd, *J* = 14.4, 3.3 Hz, 1 H, ArCH_2CH), 2.94–3.01 (m, 1 H, ArCH_2CH), 3.12 (dd, *J* = 14.0, 5.1 Hz, 1 H, ArCH_2CH), 4.20–4.25 (m, 1 H, COCHN), 4.45–4.48 (m, 1 H, COCHN), 4.96–5.01 (m, 2 H, PhCH$_2$O), 6.67 (d, *J* = 8.2 Hz, 2 H), 7.06 (s, 1 H, NH), 7.09 (s, 1 H, OH), 7.24–7.44 (m, 11 H), 8.28 (d, *J* = 7.7 Hz, 1 H), 9.22 (s, 1 H, NH), 12.77 (s, 1 H, CO_2H).

^{13}C NMR (DMSO-d_6): δ = 36.7, 47.2, 53.4, 56.3, 65.1, 114.8, 126.4, 127.3, 127.5, 127.6, 128.1, 128.2, 128.3, 129.2, 130.1, 137.0, 137.4, 155.7, 171.7, 172.4.

Anal. Calcd for $C_{26}H_{26}N_2O_6$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.65; H, 5.64; N, 5.73.

(2*S*)-2-{[(2*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-(1*H*-indol-3-yl)propanoyl]amino}propanoic Acid [Cbz-L-Trp-L-Ala-OH, (3b)]

White microcrystals (90%); mp 140–144 °C; $[\alpha]_D^{23}$ –22.5 (*c* = 1.5, DMF).

^{1}H NMR (DMSO-d_6): δ = 1.32 (d, *J* = 7.2 Hz, 3 H, CH_3CH), 2.90 (dd, *J* = 14.6, 10.4 Hz, 1 H, ArCH_2CH), 3.15 (dd, *J* = 14.6, 3.2 Hz, 1 H, ArCH_2CH), 4.22–4.38 (m, 2 H, 2 × COC*H*N), 4.88–4.98 (m, 2 H, PhCH_2O), 6.96–7.04 (m, 1 H), 7.06–7.09 (m, 1 H), 7.18 (s, 1 H), 7.22–7.38 (m, 7 H), 7.70 (d, *J* = 7.7 Hz, 1 H, NH), 8.38 (d, *J* = 7.1 Hz, 1 H, NH), 10.82 (s, 1 H, NH), 12.60 (s, 1 H, CO_2H).

^{13}C NMR (DMSO-d_6): δ = 17.2, 27.8, 47.6, 55.2, 65.2, 110.2, 111.3, 118.2, 116.6, 120.8, 124.0, 127.3, 127.5, 127.7, 128.3, 136.1, 137.0, 155.8, 171.8, 174.1.

Anal. Calcd for $C_{22}H_{23}N_3O_5$: C, 64.54; H, 5.66; N, 10.03. Found: C, 64.44; H, 5.66; N, 10.03.

(2*S*)-2-{[(2*S*)-2-{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}-3-(1*H*-indol-3-yl)propanoyl]amino}propanoic Acid [Fmoc-L-Trp-L-Ala-OH (3c)]

White microcrystals (70%); mp 155–156 °C; $[\alpha]_D^{23}$ –15.7 (*c* = 1.5, DMF).

^{1}H NMR (DMSO-d_6): δ = 1.31 (d, *J* = 7.1 Hz, 3 H, CH_3CH), 2.89–2.97 (m, 1 H, ArCH_2CH), 3.10–3.21 (m, 1 H, ArCH_2CH), 4.13 (apparent s, 2 H, CH_2, Fmoc), 4.19–4.33 (m, 3 H, CH (Fmoc), 2 × COCHN), 6.95–7.00 (m, 1 H), 7.03–7.08 (m, 1 H), 7.19–7.43 (m, 6 H), 7.51 (d, *J* = 8.5 Hz, 1 H), 7.59–7.66 (m, 2 H), 7.71 (d, *J* = 7.7 Hz, 1 H), 7.87 (d, *J* = 7.1 Hz, 2 H), 8.37 (d, *J* = 7.1 Hz, 1 H, NH), 10.82 (s, 1 H, NH), 12.57 (s, 1 H, CO_2H).

^{13}C NMR (DMSO-d_6): δ = 17.1, 27.8, 46.5, 47.5, 55.2, 65.6, 110.2, 111.3, 118.1, 118.6, 120.1, 120.8, 123.9, 125.4, 127.0, 127.3, 127.6, 136.1, 140.6, 143.7, 143.8, 155.8, 171.8, 174.1.

Anal. Calcd for $C_{29}H_{27}N_3O_5$: C, 70.01; H, 5.47; N, 8.45. Found: C, 69.68; H, 5.48; N, 8.25.

(2*S*)-2-({(2S)-2-[(3-Phenylpropanoyl)amino]-3-sulfanylpropanoyl}amino)propanoic Acid [Cbz-L-Cys-L-Ala-OH (3d)]

White microcrystals (98%); mp 161–164 °C; $[\alpha]_D^{23}$ –111.9 (*c* = 1.5, DMF).

^{1}H NMR (DMSO-d_6): δ = 1.29 (d, *J* = 7.1 Hz, 3 H, CH_3CH), 2.85–2.89 (m, 1 H, SCH_2CH), 3.14–3.20 (m, 1 H, SCH_2CH), 4.23 (t, *J* = 7.2 Hz, 1 H, COC*H*N), 4.34–4.39 (unresolved m, 1 H, COCHN), 5.04 (s, 2 H, PhCH_2O), 7.35–7.41 (unresolved m, 5 H), 7.69 (d, *J* = 8.2 Hz, 1 H, NH), 8.27–8.29 (m, 1 H, NH), 12.68 (br s, 1 H, CO_2H); exchangeable 1 H (-SH) was missing.

^{13}C NMR (DMSO-d_6): δ = 17.0, 47.7, 53.7, 65.0, 65.6, 127.7, 127.8, 128.4, 136.9, 156.0, 169.9, 173.8.

Anal. Calcd for $C_{15}H_{20}N_2O_5S$: C, 51.52; H, 5.56; N, 8.58. Found: C, 51.94; H, 5.36; N, 8.08.

(2*S*)-2-{[2-{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}-4-(methylsulfanyl)butanoyl]amino}propanoic Acid [Fmoc-L-Met-L-Ala-OH (3e)]

White microcrystals (95%); mp 155–156 °C; $[\alpha]_D^{23}$ –9.7 (*c* = 1.5, DMF).

^{1}H NMR (DMSO-d_6): δ = 1.29 (d, *J* = 7.1 Hz, 3 H, CH_3CH), 1.76–1.97 (m, 2 H, CHCH_2CH$_2$), 2.05 (s, 3 H, CH_3S), 2.45–2.50 (m, 2 H, CH_2CH_2S), 4.09–4.29 (m, 5 H), 7.30–7.35 (m, 2 H), 7.42–7.44 (m, 2 H), 7.58 (d, *J* = 8.3 Hz, 1 H, NH), 7.71–7.75 (m, 2 H), 7.89 (d, *J* = 7.7 Hz, 2 H), 8.25 (d, *J* = 6.9 Hz, 1 H, NH), 12.53 (br s, 1 H, CO_2H).

^{13}C NMR (DMSO-d_6): δ = 14.6, 17.0, 29.5, 31.9, 46.6, 47.5, 53.5, 65.6, 120.1, 125.3, 127.0, 127.6, 140.7, 143.7, 143.9, 155.9, 171.3, 174.0.

Anal. Calcd for $C_{23}H_{26}N_2O_5S$: C, 62.42; H, 5.92; N, 6.33. Found: C, 62.18; H, 6.06; N, 6.08.

(2*S*)-2-{[(2*S*)-5-Amino-2-{[(benzyloxy)carbonyl]amino}-5-oxopentanoyl]amino}-3-phenylpropanoic Acid [Cbz-L-Gln-L-Phe-OH (3f)]

White microcrystals (from water) (62%); mp 188–190 °C (lit.[3] 198–199 °C); $[\alpha]_D^{23}$ +3.6 (*c* = 1.5, DMF) [lit.[3] +4.7 (*c* = 1.0, DMF)].

^{1}H NMR (DMSO-d_6): δ = 1.64–1.69 (m, 1 H, CHCH_2CH$_2$), 1.83–1.90 (m, 1 H, CHCH_2CH$_2$), 2.01–2.17 (m, 2 H, ArCH_2CH), 2.86–2.95 (m, 1 H, CH$_2$CH_2CO), 3.02–3.10 (m, 1 H, CH$_2$CH_2CO), 3.96–4.00 (m, 3 H, $CONH_2$, COCHN), 4.43 (dd, *J* = 13.0, 8.0 Hz, 1 H, COCHN), 5.01 (s, 2 H, PHCH$_2$O), 6.78 (s, 1 H, NH), 7.18–7.28 (m, 5 H), 7.30–7.40 (m, 5 H), 8.13 (d, *J* = 7.7 Hz, 1 H, NH), 12.73 (s, 1 H, CO_2H).

^{13}C NMR (DMSO-d_6): δ = 27.8, 31.5, 36.7, 45.4, 54.2, 65.4, 126.4, 127.7, 127.8, 128.2, 128.4, 129.2, 137.0, 137.4, 155.8, 171.6, 172.8, 173.8.

Anal. Calcd for $C_{22}H_{25}N_3O_6$: C, 61.82; H, 5.89; N, 9.83. Found: C, 61.67; H, 5.98; N, 9.87.

2-{[(2*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-(4-hydroxyphenyl)propanoyl]amino}-3-phenylpropanoic Acid (Cbz-L-Tyr-D,L-Phe-OH, 3a + 4a)

White microcrystals (72%); mp 115–117 °C; $[\alpha]_D^{23}$ –13.3 (*c* = 1.5, DMF).

^{1}H NMR (DMSO-d_6): δ = 2.57–2.60 (m, 2 H, ArCH_2CH), 2.81–2.97 (unresolved m, 4 H, ArCH_2CH), 3.06–3.10 (unresolved m, 2 H, ArCH_2CH), 4.18–4.21 (unresolved m, 2 H, COCHN), 4.42–4.44 (unresolved m, 2 H, COCHN), 4.92–4.97 (unresolved m, 4 H, PhCH_2O), 6.59–6.71 (unresolved m, 4 H), 6.94–7.05 (m, 4 H), 7.09–7.39 (m, 22 H), 8.23 (d, *J* = 7.7 Hz, 1 H), 8.36 (d, *J* = 8.3 Hz, 1 H), 9.15–9.28 (m, 2 H, NH), 12.75 (s, 2 H, CO_2H).

^{13}C NMR (DMSO-d_6): δ = 14.0, 22.1, 31.0, 36.7, 36.8, 37.1, 53.2, 53.4, 56.3, 65.1, 65.2, 114.7, 114.8, 115.0, 115.1, 126.4, 127.3, 127.5, 127.6, 128.1, 128.2, 128.3, 129.2, 129.3, 130.0, 130.1, 137.1, 137.4, 155.7, 171.5, 171.7, 172.8, 172.9.

Anal. Calcd for $C_{26}H_{26}N_2O_6$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.18; H, 5.82; N, 5.68.

2-{[(2*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-(1*H*-indol-3-yl)propanoyl]amino}propanoic Acid (Cbz-L-Trp-D,L-Ala-OH, 3b + 4b)

White microcrystals (94%); mp 93–95 °C; $[\alpha]_D^{23}$ –19.5 (*c* = 1.5, DMF).

^{1}H NMR (DMSO-d_6): δ = 1.23 (d, *J* = 8.0 Hz, 3 H, CH_3CH), 1.31 (d, *J* = 7.5Hz, 3 H, CH_3CH), 2.85–2.95 (m, 2 H, ArCH_2CH), 3.05–3.15 (m, 2 H, ArCH_2CH), 4.16–4.37 (m, 4 H, COCHN), 4.92–4.94 (m, 4 H, PhCH_2O), 6.94–7.00 (m, 2 H), 7.03–7.08 (m, 2 H), 7.16 (unresolved m, 2 H), 7.23–7.37 (m, 14 H), 7.63–7.70 (m, 2 H), 8.30 (d, *J* = 7.4 Hz, 1 H), 8.36 (d, *J* = 7.4 Hz, 1 H, N H), 10.81 (s, 2 H, NH), 12.59 (s, 2 H, CO_2H).

^{13}C NMR (DMSO-d_6): δ = 14.0, 17.2, 17.3, 22.1, 27.8, 28.2, 31.0, 47.5, 55.2, 55.3, 65.2, 110.0, 110.1, 111.3, 118.1, 118.6, 120.8, 123.9, 124.0, 127.3, 127.4, 127.5, 127.7, 128.3, 136.0, 136.1, 137.0, 137.1, 155.7, 155.8, 171.5, 171.8, 174.0, 174.1.

Anal. Calcd for $C_{22}H_{23}N_3O_5$: C, 64.54; H, 5.66; N, 10.26. Found: C, 64.70; H, 6.06; N, 9.69.

2-{[(2*S*)-2-{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}-3-(1*H*-indol-3-yl)propanoyl]amino}propanoic Acid (Fmoc-L-Trp-D,L-Ala-OH, 3c + 4c)

White microcrystals (68%); mp 136–138 °C: $[\alpha]_D^{23}$ –0.6 (*c* = 1.5, DMF).

^{1}H NMR (DMSO-d_6): δ = 1.21 (d, *J* = 7.1 Hz, 3 H, CH_3CH), 1.32 (d, *J* = 7.1 Hz, 3 H, CH_3CH), 2.90–2.98 (m, 2 H, ArCH_2CH), 3.08–3.15 (m, 2 H, ArCH_2CH), 4.14 (m, 6 H, CH_2, CH in Fmoc), 4.19–4.26 (m, 2 H, COCHN), 4.28–4.34 (m, 2 H, COCHN), 6.97–7.00 (m, 2 H), 7.04–7.08 (m, 2 H), 7.19–7.43 (m, 12 H), 7.48–7.54 (m, 2 H), 7.60–7.72 (m, 6 H), 7.87 (d, *J* = 7.1 Hz, 4 H), 8.31 (d, *J* = 7.1 Hz, 1 H, NH), 8.38 (d, *J* = 7.1 Hz, 1 H, NH), 10.82 (s, 2 H, NH), 12.60 (s, 2 H, CO_2H).

^{13}C NMR (DMSO-d_6): δ = 17.2, 17.4, 27.8, 28.2, 46.6, 47.6, 55.2, 55.3, 65.7, 110.1, 110.3, 111.3, 118.2, 118.6, 120.1, 120.8, 123.9, 125.4, 127.1, 127.3, 127.4, 127.6, 136.0, 136.1, 140.6, 143.7, 143.8, 155.7, 155.8, 171.6, 171.9, 174.0, 174.1.

Anal. Calcd for $C_{29}H_{27}N_3O_5$: C, 70.01; H, 5.47; N, 8.45. Found: C, 70.03; H, 5.53; N, 7.70.

2-{[(2*S*)-2-[(3-phenylpropanoyl)amino]-3-sulfanyl propanoyl]amino}propanoic Acid (Cbz-L-Cys-D,L-Ala-OH, 3d + 4d)

White microcrystals (71%); mp 153–155 °C (lit.[10] 40–44 °C); $[\alpha]_D^{23}$ –99.9 (*c* = 1.5, DMF).

^{1}H NMR (DMSO-d_6): δ = 1.29–1.33 (m, 6 H, CH_3CH), 2.85–2.92 (m, 2 H, CHCH_2S), 3.13–3.17 (m, 2 H, CHCH_2S), 4.22–4.27 (m, 2 H, COCHN), 4.38 (unresolved m, 2 H, COCHN), 5.08 (s, 4 H, PhCH_2O), 7.36–7.60 (unresolved m, 10 H), 7.57–7.64 (m, 2 H, NH), 8.30–8.35 (m, 2 H, NH), 12.64 (s, 2 H, CO_2H).

^{13}C NMR (DMSO-d_6): δ = 17.0, 17.3, 47.7, 53.6, 65.0, 65.6, 127.7, 127.8, 128.3, 136.9, 156.0, 169.7, 169.9, 173.8, 173.9.

Anal. Calcd for $C_{14}H_{18}N_2O_5S$: C, 51.52; H, 5.56; N, 8.58. Found: C, 51.38; H, 5.17; N, 8.28.

2-{[2-{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}-4-(methylsulfanyl)butanoyl]amino}propanoic Acid (Fmoc-L-Met-D,L-Ala-OH, 3e + 4e)

White microcrystals (72%); mp 109–110 °C; $[\alpha]_D^{23}$ –7.8 (*c* = 1.5, DMF).

^{1}H NMR (DMSO-d_6): δ = 1.26 (d, *J* = 4.1 Hz, 3 H, CH_3CH), 1.28 (d, *J* = 4.4 Hz, 3 H, CH_3CH), 1.80–2.00 (m, 4 H, CHCH_2CH_2), 2.04 (s, 6 H, CH_3S), 2.41–2.51 (m, 4 H, CH_2CH_2S), 4.10–4.28 [m, 6 H (CH_2), CH (Fmoc), 4 H (COCHN)], 7.23–7.36 (m, 4 H), 7.39–7.44 (m, 4 H), 7.53–7.58 (m, 2 H), 7.71–7.75 (m, 4 H), 7.89 (d, *J* = 7.5 Hz, 4 H), 8.17 (d, *J* = 7.1 Hz, 1 H, NH), 8.24 (d, *J* = 7.1 Hz, 1 H, NH), 12.57 (s, 2 H, CO_2H).

^{13}C NMR (DMSO-d_6): δ = 14.6, 17.0, 17.4, 29.5, 29.6, 31.8, 46.6, 47.5, 53.5, 65.6, 120.1, 125.3, 127.0, 127.6, 140.7, 143.7, 143.9, 155.9, 171.1, 171.3, 173.9, 174.0.

Anal. Calcd for $C_{23}H_{26}N_2O_5S$: C, 62.42; H, 5.92; N, 6.33. Found: C, 62.26; H, 6.00; N, 6.01.

2-{[(2*S*)-5-amino-2-{[(Benzyloxy)carbonyl]amino}-5-oxopentanoyl]amino}-3-phenylpropanoic Acid (Cbz-L-Gln-D,L-Phe-OH, 3f + 4f)

White microcrystals (74%); mp 148–150 °C; $[\alpha]_D^{23}$ –0.5 (*c* = 1.5, DMF).

^{1}H NMR (DMSO-d_6): δ = 1.54–1.89 (m, 4 H, CHCH_2CH_2), 1.95–2.00 (m, 2 H, CH_2CH_2CO), 2.06–2.13 (m, 2 H, CH_2CH_2CO), 2.85–2.95 (m, 2 H, ArCH_2CH), 3.04–3.11 (m, 4 H, ArCH_2CH, $CONH_2$), 3.95–4.05 (unresolved m, 2 H, COCHN), 4.39–4.43 (m, 2 H, COCHN), 4.95–5.06 (m, 4 H, PhCH_2O), 6.74–6.76 (m, 2 H, NH), 7.18–7.23 [m, 10 H (ArH), 2 H (NH)], 7.28–7.42 (m, 10 H, ArH), 8.10–8.12 (m, 2 H, NH), 12.76 (s, 2 H, CO_2H).

^{13}C NMR (DMSO-d_6): δ = 8.6, 27.8, 31.3, 31.5, 36.7, 36.9, 45.6, 53.3, 53.4, 54.2, 54.3, 65.4, 126.4, 127.7, 127.8, 128.1, 128.3, 129.2, 137.0, 137.3, 155.8, 171.4, 171.6, 172.8, 173.6, 173.7.

Anal. Calcd for $C_{22}H_{25}N_3O_6$: C, 61.82; H, 5.89; N, 9.83. Found: C, 61.90; H, 5.91; N, 10.07.

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