令和２年度

博　士　論　文

Green synthesis of various medicine analogues containing α-amino acids or dipeptides without racemization or epimerization under the extremely mild conditions

千葉科学大学

大学院薬学研究科

薬学専攻

鄭　昇姬

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List of abbreviations

The following abbreviations are used in this paper.

2D	two-dimensional space
Ala	alanine
AM404	*N*-(4-hydroxyphenyl)arachidonamide
aq.	aqueous
Asp	aspartic acid
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad singlet (spectral)
^{o}C	degrees Celsius
Cbz	benzyloxycarbonyl
Cys	cysteine
d	doublet (spectral)
de	diastereomeric excess
DCC	dicyclohexylcarbodiimide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
eq	equivalent
ER	endoplasmic reticulum
ESI	electronspray ionization
Et	ethyl
FDA	the U.S. Food and Drug Administration
Fmoc	9-fluorenylmethyloxycarbonyl
g	gram (s)
Gln	glutamine
Gly	glycine
h	hour (s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
Hz	hertz
IR	Infrared Spectroscopy
i-Bu	*iso*-butyl
IR	infrared spetroscopy
J	coupling constant (in NMR)

L	liter (s)
Leu	leucine
Lys	lysine
m	milli, multiplet (spectral)
M	moles per liter
m/z	mass to change ratio (in mass spectrometry)
Me	methyl
Met	methionine
mol	mole (s)
MS	mass spectroscopy
NAPQI	*N*-acetyl-*p*-benzoquinone imine
NMR	nuclear magnetic resonance
NSAIDs	nonsteroidal anti-inflammatory drugs
Ph	phenyl
Phe	phenylalanine
Phg	phenylglycine
Pro	proline
q	quartet (spectral)
rt	room temperature
s	singlet (spectral)
Ser	serine
t	triplet (spectral)
t-Bu	*tert*-butyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	tetramethylsilane
TOF	time-of-flight
Trp	tryptophan
Tyr	tyrosine
Val	valine
δ	chemical shift in parts per million downfield from tetramethylsilane
μ	micro

Contents

Introduction 1

Chapter 1. Synthesis of acetaminophen analogues containing α-amino acids and fatty acid for inhibiting hepatotoxicity 3

Section 1. Preparation of various anilines containing 3-phenylpropionic acid via mixed carbonic carboxylic anhydrides under mild conditions 4

Section 2. Amidation of α-amino acids and fatty acids via the mixed carbonic carboxylic anhydrides and its application to synthesis of acetaminophen analogues and AM404 analogues 6

Chapter 2. Green synthesis of various medicine analogues containing dipeptides without epimerization under the extremely mild conditions 11

Section 1. Preparation of amidation of Cbz-Phg-OH and Cbz-Phe-Phe-OH via mixed carbonic carboxylic anhydrides without racemization and epimerization under extremely mild conditions 11

Section 2. Amidation of dipeptides via the mixed carbonic carboxylic anhydrides and its application to synthesis of various medicine analogues 15

Conclusion 20

Experimental 23

Acknowledgement 62

References 63

Introduction

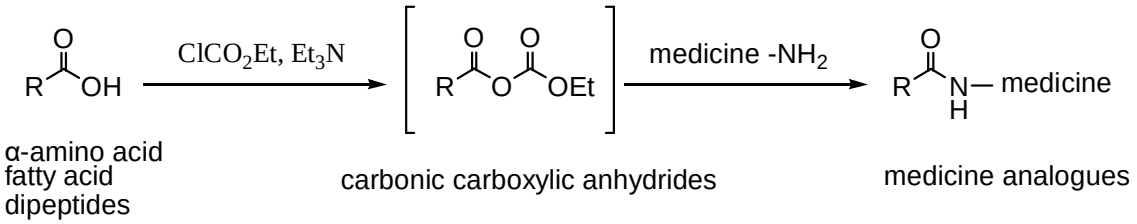
Medicines are metabolized and these chemical structures are changed after being taken in bodies. The formation of reactive intermediates such as electrophiles and free radicals often induces various toxicities against the bodies. So much research about the reactive metabolites has been done so far. It is important to exclude the by-produced reactive metabolites from pharmaceuticals in the manufacturing stages because they cause a variety of toxicities.[1] Furthermore, various efforts in development of new medicines include reducing the amount of chemical waste, saving energy, and minimizing the amount of used and discharged hazardous substances. Green chemistry is defined as "Technology that designs a process for producing chemical products while minimizing the use and generation of hazardous or environmentally polluting substances".[2] The United States of America awards the "Green Chemistry Presidential Award" for companies and scientists who have successfully contributed to green chemistry every year. For example, *Eastman* won the Green Chemistry Award for development of the enzyme-based esterification in 2009.[3] The methods include milder reaction conditions and less amount of solvents and by-products than conventional synthetic ones.

Here I describe an eco-friendly, economical and convenient synthesis method by synthesizing various medicine analogues capable of suppressing side effects through amidation via the corresponding mixed carbonic carboxylic anhydrides (Scheme 1). Although amidation in pharmaceutical synthesis often involves the reaction of active acyl chlorides with amines, acyl chlorides are usually unstable in water and it is necessary to avoid moisture during the reaction. The use of *N*, *N*-dicyclohexylcarbodiimide (DCC) as an alternative condensing agent is not cheap and introduces difficulties with respect to workup. Recently, Szostak demonstrated highly selective transition-metal-free transamidation of amides and amidation of esters in an interesting study.[4]

Our group has recently developed amidations of various *N*-protected α-amino acids with unprotected α-amino acids, NH_4Cl, and aniline derivatives via the mixed carbonic carboxylic anhydrides to provide the corresponding dipeptides, primary amide, and anilides in excellent yield.[5] In these reports, our group has showed that primary amines and ammonia work as an active nucleophile on the reaction of mixed carbonic carboxylic anhydrides in aqueous organic solvent. Aniline derivatives are less active than ammonia as a nucleophile, so it is very exciting to examine the reactivity of aniline derivatives on the reaction of mixed carbonic carboxylic anhydrides in aqueous organic solvent.[6] Although amidation via activated carboxylic acid is generally carried out under anhydrous conditions, it is very unique that the reaction of activated carboxylic anhydride proceeds smoothly in an aqueous organic solvent to obtain the corresponding amide. In addition, the two activators ($ClCO_2Et$ and Et_3N) are very inexpensive and the by-products obtained in an efficient way are triethylamine hydrochloride, carbon dioxide and the corresponding alcohols, which are very environmentally safe.

Herein, I describe eco-friendly, economical, and convenient synthesis of various medicine analogues containing α-amino acids or dipeptides without racemization or epimerization using amidation via

corresponding mixed carbonic carboxylic anhydrides under the extremely mild conditions. The following two contents are presented: (I) Synthesis of acetaminophen analogues containing α-amino acids and fatty acids for inhibiting hepatotoxicity,[7a,7e] (II) Green synthesis of various medicine analogues containing dipeptides without epimerization under the extremely mild conditions.[7d,7g]



Scheme 1. Convenient synthesis of various medicine analogues via mixed carbonic carboxylic anhydrides

Chapter 1. Synthesis of acetaminophen analogues containing α-amino acids and fatty acids for inhibiting hepatotoxicity

Acetaminophen is a popular antipyretic analgesic medicine that has a weaker anti-inflammatory properties and lower incidence of side effects than nonsteroidal anti-inflammatory drugs (NSAIDs). However, it is well known that acetaminophen causes severe hepatotoxicity due to the reactive metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI) upon overdose. Recently, the U.S. Food and Drug Administration (FDA) has reduced the maximum recommended daily dose of acetaminophen from 4000 to 3000 mg to avoid Stevenson Johnson syndrome and hepatotoxicity, and recommends reducing the dose of acetaminophen to 325 mg.

In a possible metabolic pathway, acetaminophen is converted into the corresponding sulfate or glucuronate at the usual dosage and excreted without producing NAPQI as a reactive metabolite. However, the metabolic process is saturated in the case of overdose and the oxidative metabolism by cytochrome P-450 proceeds to afford the reactive NAPQI. Although NAPQI is detoxified by glutathione stored in the liver, it depletes the liver-derived glutathione upon acute overdose. As the result, NAPQI accumulates, binds to intracellular macromolecules, and causes hepatocellular necrosis.[8] Furthermore, Zygmunt et al. have recently reported that the physiological action of acetaminophen is very similar to that of *N*-(4-hydroxyphenyl)arachidonamide (AM404) (Figure 1).[9] AM404 has a strong agonistic action in $TRPV_1$, which is an ion channel, and affects the cannabinoid CB_1 receptor. These receptors are also involved with pain and thermoregulatory systems and have received considerable attention as analgesic and anti-inflammatory therapeutic targets in recent years.[10] Therefore, acetaminophen analogues of various fatty acids are quite interesting as AM404 analogues.

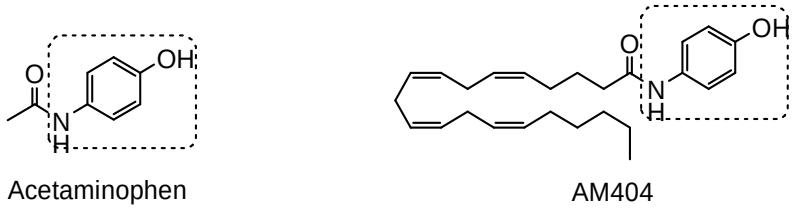
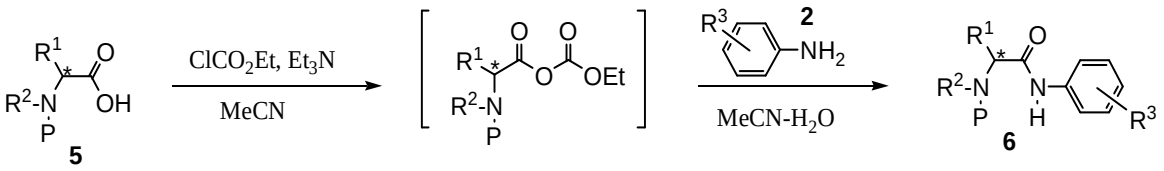


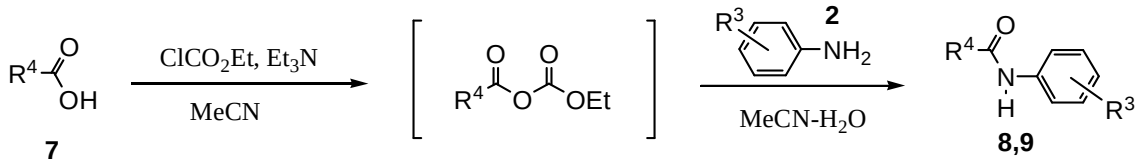
Figure 1

Herein, I describe in detail the synthesis of various acetaminophen analogues via the corresponding carbonic carboxylic anhydride (Scheme 2). The acetyl group of acetaminophen was replaced with bulkier α-amino acid to construct a derivative of NAPQI that is less susceptible to nucleophilic attack by intracellular macromolecules. I have also prepared AM404 analogues containing fatty acids (Scheme 3).



P = Cbz, Boc, Fmoc

Scheme 2. Synthesis of acetaminophen analogues **6** containing α-amino acid **5**



Scheme 3. Synthesis of AM404 analogues **8,9** containing fatty acid **7**

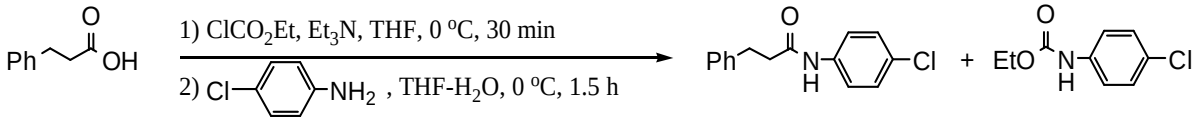
Section 1. Preparation of various anilides containing 3-phenylpropionic acid via mixed carbonic carboxylic anhydrides under mild conditions

In a preliminary investigation, the reaction of 3-phenylpropionic acid (**1**) with 1.1 equivalents of 4-chloroaniline (**2a**) in the presence of 1.4 equivalents of $ClCO_2Et$ and 1.1 equivalents of Et_3N in aqueous tetrahydrofuran (THF) afforded *N*-(4-chlorophenyl)-3-phenylpropanamide (**3a**) in 57% yield along with the by-product **4a** of 34% yield based on **2a** as indicated in entry 1 of Table 1. Effect of the quantity of **2a**, ethyl chloroformate, triethylamine on the amidation of **1** in aqueous THF at 0 ^oC for 1.5 h was examined, and the results are collected in Table 1. The best result (88% yield, entry 3) among them was obtained using 1.1 equivalents of **2a**, 1.1 equivalents of $ClCO_2Et$, and 1.1 equivalents of Et_3N.

Next, effect of solvent on the amidation of **1** at 0 ^oC for 24 h was checked, and the results are summarized in Table 2. The reactions of **1** in aqueous THF, 1,4-dioxane, acetone, MeCN, EtOH, or MeOH afforded the corresponding primary amide **3a** in 92%, 19%, 89%, 96%, 50%, and 13% yields, respectively. The best yield (96%) was obtained when the reaction was carried out in aqueous MeCN.

The reactions of **1** with various anilines **2a-r** were then carried out; the results are collected in Table 3. Acid **1** reacted with anilines **2a-f** and **2h-j,** containing an electron-withdrawing group, to produce the corresponding amides **3a-f** and **3h-j** in yields of 30-98% as described in entries 1-6 and 8-10. Unfortunately, the reaction of **1** with 2,4-dinitroaniline **2g** (entry 7) did not afford the corresponding amide **3g** at all and the starting material **2g** was recovered. Acid **1** reacted readily with aniline (**2k**) to yield the amide **3k** in 94%, as shown in entry 11. The reactions of **1** with the anilines **2l-r,** containing an electron-donating group, proceeded smoothly to give the corresponding anilines **3l-r** in high yields of 75-98% (entries 12-18).

Table 1. Effect of the quantity of 4-chloroaniline **2a**, ethyl chloroformate, triethylamine on the amidation of 3-phenylpropanoic acid **1**[a]

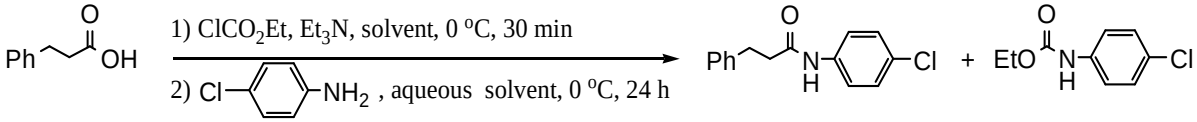


1 **2a** **3a** **4a**

Entry	Et_3N (equiv)	$ClCO_2Et$ (equiv)	**2a** (equiv)	Yield of **3a** (%)[b]	Yield of **4a** (%)[b]
1	1.1	1.4	1.1	57	34
2	1.5	1.1	1.1	83	2
3	1.1	1.1	1.1	88	13
4	1.1	1.05	1.1	77	9
5	1.1	1.05	1.05	74	11
6	1.1	1.0	1.05	79	5
7	1.1	1.0	1.0	83	4

[a] All reactions were carried out with 1.0 mmol of **1** in 20 mL of THF. After stirring for 30 min at 0 °C, 1.5 mL of water and **2a** were added at 0 °C to the reaction mixture. [b] Isolated yield.

Table 2. Effect of solvent on the amidation of 3-phenylpropanoic acid **1**[a]

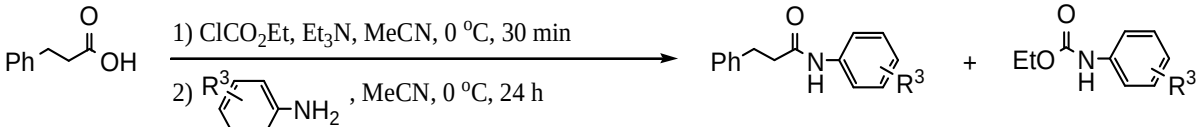


1 **2a** **3a** **4a**

Entry	Solvent	Yield of **3a** (%)[b]	Yield of **3a** (%)[b]
1	THF	92	4
2	1,4-dioxane	19	8
3	acetone	89	3
4	MeCN	96	trace
5	EtOH	50	35
6	MeOH	13	70

[a] All reactions were carried out with 1.0 mmol of **1**, 1.1 mmol of Et_3N, and 1.1 mmol of $ClCO_2Et$ in 20 mL of solvent. After stirring for 30 min at 0 °C, 1.5 mL of water and 1.1 mmol of **2a** were added at 0 °C to the reaction mixture. [b] Isolated yield.

Table 3. Reaction of 3-phenylpropanoic acid **1** with aniline derivatives **2**[a]



1 **2** **3** **4**

Entry	R^3	**2**	**3**	Yield of **3** (%)[b]	Yield of **4** (%)[b]
1	4-Cl	**2a**	**3a**	96	trace
2	4-F	**2b**	**3b**	97	0
3	2,3,4,5,6-F_5	**2c**	**3c**	67	34
4	4-EtO_2C	**2d**	**3d**	70	0
5	4-O_2N	**2e**	**3e**	65	0
6	3,5-$(O_2N)_2$	**2f**	**3f**	30	0
7	2,4-$(O_2N)_2$	**2g**	**3g**	0	0
8	4-Br	**2h**	**3h**	98	2
9	4-I	**2i**	**3i**	94	5
10	4-CN	**2j**	**3j**	87	0
11	H	**2k**	**3k**	94	trace
12	4-Me	**2l**	**3l**	95	1
13	4-HO	**2m**	**3m**	92	3
14	2-EtO	**2n**	**3n**	89	trace
15	4-EtO	**2o**	**3o**	98	2
16	4-SH	**2p**	**3p**	92	7
17	4-*tert*-Bu	**2q**	**3q**	96	0
18	2,4,6-Me_3	**2r**	**3r**	75	4

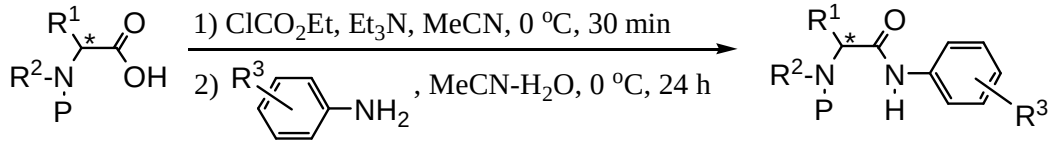
[a] All reactions were carried out with 0.5 mmol of **1**, 0.55 mmol of Et_3N, and 0.55 mmol of $ClCO_2Et$ in 10 mL of MeCN. After stirring for 30 min at 0 ^oC, 0.75 mL of water and **2** were added at 0 ^oC to the reaction mixture. [b] Isolated yield.

Section 2. Amidation of α-amino acids and fatty acids via mixed carbonic carboxylic anhydrides and its application to synthesis of acetaminophen analogues and AM404 analogues

I also examined the condensation of α-amino acids and fatty acids using 4-aminophenol (**2m**), 2-ethoxyaniline (**2n**), and 4-ethoxyaniline (**2o**) for synthesis of acetaminophen analogues. Table 4 shows the results of the condensation of various N-protected with Cbz, Boc, and Fmoc groups via the corresponding mixed carbonic carboxylic anhydrides, with **2m**, **2n**, and **2o**. The reaction proceeded without racemization (95-99% ee) except for the substrates listed in entries 21-22, and good yield (57-99%) although the yields given in entries 23 and 24 (65% and 57%) were lower due to low solubility in MeCN.

It is presumed that the reduction of the enantioselectivities in the reactions shown in Table 4, entries 21 and 22 is attributable to the weakened reactivity of the corresponding mixed carbonic carboxylic anhydrides by the steric hindrance of the trityl group. The yields were slightly improved in several cases compared with the eluents in order to avoid tailing of the products on silica gel during purification by column chromatography.

Table 4. Synthesis of acetaminophen analogues **6** containing α-amino acid **5**[a]

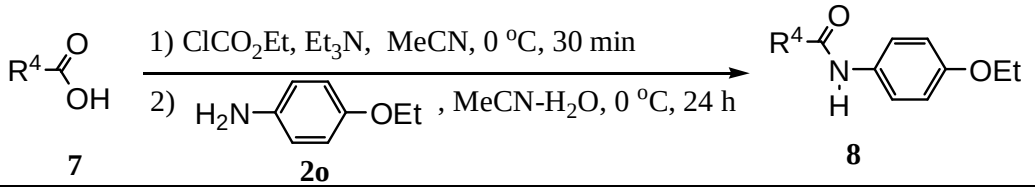


5 **2** **6**

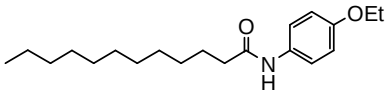
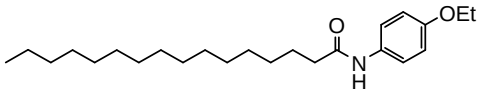
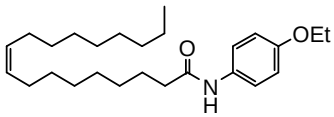
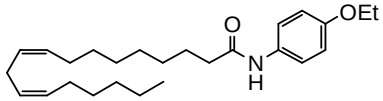
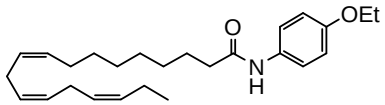
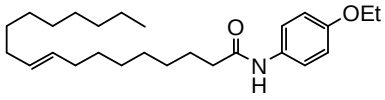
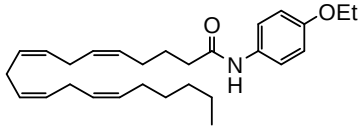
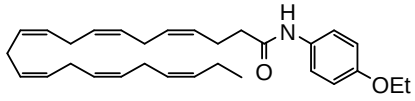
Entry	P	R^1	R^2	**5**	R^3	**6**	Yield (%)[b]	% ee[c]	Retention time (min)
1	Cbz	$PhCH_2$ (L)	H	**5aL**	4-EtO	**6aLo**	96	>99	15
2	Cbz	$PhCH_2$ (D)	H	**5aD**	4-EtO	**6aDo**	97	>99	17
3	Cbz	$PhCH_2$ (L)	H	**5aL**	2-EtO	**6aLn**	91	>99	26
4	Cbz	$PhCH_2$ (D)	H	**5aD**	2-EtO	**6aDn**	91	>99	51
5	Cbz	$PhCH_2$ (L)	H	**5aL**	4-OH	**6aLm**	88	>99	26
6	Cbz	$PhCH_2$ (D)	H	**5aD**	4-OH	**6aDm**	88	>99	30
7	Cbz	Me_2CH (L)	H	**5bL**	4-EtO	**6bLo**	97	>99	10
8	Cbz	Me_2CH (D)	H	**5bD**	4-EtO	**6bDo**	99	>99	11
9	Cbz	Me (L)	H	**5cL**	4-EtO	**6cLo**	82	>99	14
10	Cbz	Me (D)	H	**5cD**	4-EtO	**6cDo**	91	98	16
11	Cbz	$MeS(CH_2)_2$ (L)	H	**5dL**	4-EtO	**6dLo**	85	>99	15
12	Cbz	$MeS(CH_2)_2$ (D)	H	**5dD**	4-EtO	**6dDo**	88	>99	20
13	Cbz	$(CH_2)_3$ (L)		**5eL**	4-EtO	**6eLo**	99	>99[d]	56
14	Cbz	$(CH_2)_3$ (D)		**5eD**	4-EtO	**6eDo**	99	>99[d]	20
15	Boc	$PhCH_2$ (L)	H	**5fL**	4-EtO	**6fLo**	99	>99	13
16	Boc	$PhCH_2$ (D)	H	**5fD**	4-EtO	**6fDo**	99	95	8
17	Fmoc	$PhCH_2$ (L)	H	**5gL**	4-EtO	**6gLo**	82	>99[e]	29
18	Fmoc	$PhCH_2$ (D)	H	**5gD**	4-EtO	**6gDo**	95	>99[e]	11
19	Boc	$C_6H_5CH_2OCH_2$ (L)	H	**5hL**	4-EtO	**6hLo**	93	>99[f]	19
20	Boc	$C_6H_5CH_2OCH_2$ (D)	H	**5hD**	4-EtO	**6hDo**	95	98[f]	16
21	Fmoc	Ph_3CSCH_2 (L)	H	**5iL**	4-EtO	**6iLo**	77	79[e,g]	64
22	Fmoc	Ph_3CSCH_2 (D)	H	**5iD**	4-EtO	**6iDo**	79	86[e,g]	55
23	Cbz	*p*-$HOC_6H_4CH_2$ (L)	H	**5jL**	4-EtO	**6jLo**	65	>99[e]	62
24	Cbz	*p*-$HOC_6H_4CH_2$ (D)	H	**5jD**	4-EtO	**6jDo**	57	>99[e]	81
25	Cbz	$C_8H_6NCH_2$ (L)	H	**5kL**	4-EtO	**6kLo**	91	>99[d,h]	121
26	Cbz	$C_8H_6NCH_2$ (L)	H	**5kD**	4-EtO	**6kDo**	91	>99[d,h]	87
27	Boc	$H_2NCOCH_2CH_2$ (L)	H	**5lL**	4-EtO	**6lLo**	79	>99	19
28	Boc	$H_2NCOCH_2CH_2$ (D)	H	**5lD**	4-EtO	**6lDo**	80	>99	14
29	Boc	Cbz-$NH(CH_2)_4$ (L)	H	**5mL**	4-EtO	**6mLo**	94	>99	37
30	Boc	Cbz-$NH(CH_2)_4$ (D)	H	**5mD**	4-EtO	**6mDo**	97	>99	15

[a] All reactions were carried out with 0.5 mmol of **1**, 0.55 mmol of Et_3N, and 0.55 mmol of $ClCO_2Et$ in 10 mL of MeCN. After stirring for 30 min at 0 °C, 0.75 mL of water and **2** were added at 0 °C to the reaction mixture. [b] Isolated yield. [c] Determined by HPLC analysis with a 90:10 mixture of hexane and isopropanol as an eluent using Chiralcel OD (1.0 mL/min). [d] Determined by HPLC analysis with a 90:10 mixture of hexane and isopropanol as an eluent using Chiralcel AS (1.0 mL/min). [e] Determined by HPLC analysis with a 90:10 mixture of hexane and isopropanol as an eluent using Chiralcel ADH (1.0 mL/min). [f] Determined by HPLC analysis with a 95:5 mixture of hexane and isopropanol as an eluent using Chiralcel OD (1.0 mL/min). [g] The reactions were carried out at -15 °C. [h] Cbz was deprotected.

Table 5. Synthesis of AM404 analogues **8** containing fatty acid **7**[a]

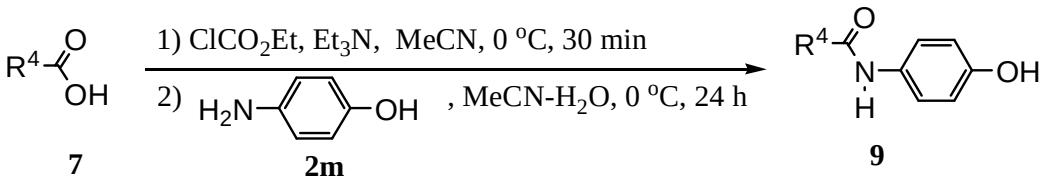


7 **2o** **8**

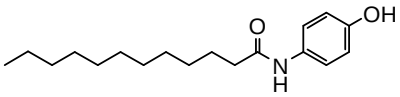
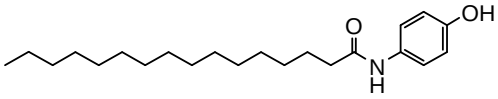
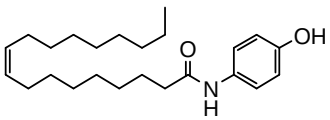
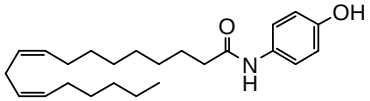
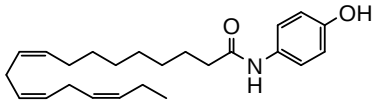
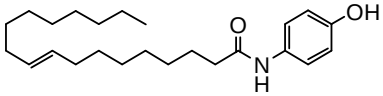
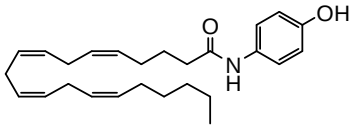
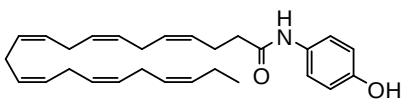
Entry	R^4-CO_2H	**7**		**8**	Yield (%)[b]
1	Lauric acid (C_{12})	**7a**		**8ao**	97
2	Palmitic acid (C_{16})	**7b**		**8bo**	98
3	Oleic acid (C_{18-1})	**7c**		**8co**	89
4	Linoleic acid (C_{18-2})	**7d**		**8do**	93
5	Linolenic acid (C_{18-3})	**7e**		**8eo**	95
6	Elaidic acid (C_{18-1})	**7f**		**8fo**	83
7	Arachidonic acid (C_{20-4})	**7g**		**8go**	93
8	Docosaheaenoic acid (C_{22-6})	**7h**		**8ho**	99

[a] All reactions were carried out with 1 equiv of fatty acid **7**, 1.1 equiv of Et_3N, and 1.1 equiv of $ClCO_2Et$ in MeCN. After stirring for 30 min at 0 °C, H_2O and 1.1 equiv of **2o** were added at 0 °C to the reaction mixture. [b] Isolated yield.

Table 6. Synthesis of AM404 analogues **9** containing fatty acid **7**[a]



7 **2m** **9**

Entry	R^4-CO_2H	**7**		**9**	Yield (%)[b]
1	Lauric acid (C_{12})	**7a**		**9am**	87
2	Palmitic acid (C_{16})	**7b**		**9bm**	76
3	Oleic acid (C_{18-1})	**7c**		**9cm**	79
4	Linoleic acid (C_{18-2})	**7d**		**9dm**	94
5	Linolenic acid (C_{18-3})	**7e**		**9em**	82
6	Elaidic acid (C_{18-1})	**7f**		**9fm**	97
7	Arachidonic acid (C_{20-4})	**7g**		**9gm**	90
8	Docosaheaenoic acid (C_{22-6})	**7h**		**9hm**	78

[a] All reactions were carried out with 1 equiv of fatty acid **7**, 1.1 equiv of Et_3N, and 1.1 equiv of $ClCO_2Et$ in MeCN. After stirring for 30 min at 0 °C, H_2O and 1.1 equiv of **2m** were added at 0 °C to the reaction mixture. [b] Isolated yield.

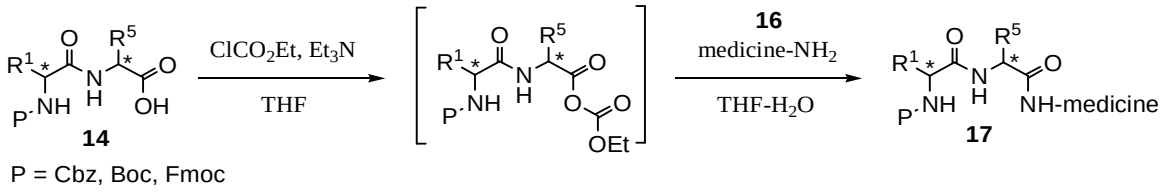
Next, various AM404 analogues **8ao-ho** and **9am-hm** were synthesized by the condensation of fatty acids **7a-h** with 4-ethoxyaniline (**2o**) and 4-aminophenol (**2m**); the results are summarized in Tables 5 and Table 6, respectively. The reactions of various fatty acids **7a-h** with **2o** and **2m** via the mixed carbonic acid carboxylic anhydrides gave the corresponding AM404 analogues **8ao-ho** in 83-99% yields and **9am-hm** in 76-97% yields, respectively. The stability of the synthesized AM404 analogues **9am-hm** was checked at 0 °C and 22 °C after 240 h by analyses using 2D TLC and ^{1}H NMR spectra, and no change was observed. Although unsaturated fatty acids are usually sensitive in air at room temperature, it was found that the synthesized AM404 analogues were relatively stable.

Chapter 2. Green synthesis of various medicine analogues containing dipeptides without epimerization under the extremely mild conditions

Although amidation is most important in peptide synthesis, it makes problems such as utilization of a large amount of expensive condensation agent and generation of a large amount of waste.[11] In addition, linkage of amino acids in high yields would be a significant research because of easy racemization. Cysteine, histidine, and phenylglycine are more susceptible to racemize than the other amino acids. In particular, synthesis of peptides containing phenylglycine remains a challenging task because it has been reported that phenylglycine easily causes racemization about 60 times compared with alanine.[12] After Vaughan and Boissonnas initially developed the mixed carbonic carboxylic anhydrides as active carboxylic acid derivatives for the preparation of peptides,[13] Kovacs described the interesting kinetic studies on the *N*-protected methionine and glycylmethionine active esters to determine the racemization rate constants.[14]

Recently, we,[5] Verarado,[15] and Fuse[16] have successively reported the convenient amidations of various *N*-protected α-amino acids with unprotected α-amino acids via the mixed carbonic carboxylic anhydrides in aqueous organic solvents to provide the corresponding dipeptides in excellent yield. On the other hand, peptide medicines have attracted much attention due to the realization of oral administration, targeting of biomolecules in cells, and low side effects compared with antibody medicines.

We have also developed amidations of various *N*-protected α-amino acids with NH_4Cl and aniline derivatives via the mixed carbonic carboxylic anhydrides to provide the corresponding primary amide and anilides in excellent yield.[7] Herein, we describe green and convenient synthesis of dipeptides-containing various medicine analogues and dipeptides without epimerization at -15 ^oC via the mixed carbonic carboxylic anhydrides from the corresponding carboxylic acids as indicated in Scheme 4.



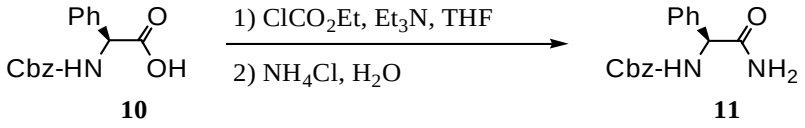
Scheme 4. Synthesis of various medicine analogues **17** containing dipeptides **14**

Section 1. Preparation of amidation of Cbz-Phg-OH and Cbz-Phe-Phe-OH via mixed carbonic carboxylic anhydrides without racemization and epimerization under extremely mild conditions

In a preliminary investigation, the reaction of Cbz-L-Phg-OH (**10**) with 1.5 equivalents of NH_4Cl in the presence of 1.4 equivalents of $ClCO_2Et$ and 3.0 equivalents of Et_3N in aqueous tetrahydrofuran (THF) at ice-cooled temperature (5 ^oC) afforded Cbz-L-Phg-NH_2 (**10**) in 43% yield with 46% ee as indicated in entry 1 of Table 7. When the reaction was carried out for 0.5 h at 0 ^oC on the step 2), the ee was improved to 67%

(entry 3). When the reaction temperature was decreased to -5 °C on both steps 1) and 2), the corresponding primary amide **11** was obtained with 83% ee as shown in entry 6. Effect of decreasing the reaction temperature until -15 °C was amazingly well and an excellent enantioselectivity (93% ee) was observed.

Table 7. Primary amidation of Cbz-L-Phg-OH (**10**)[a]

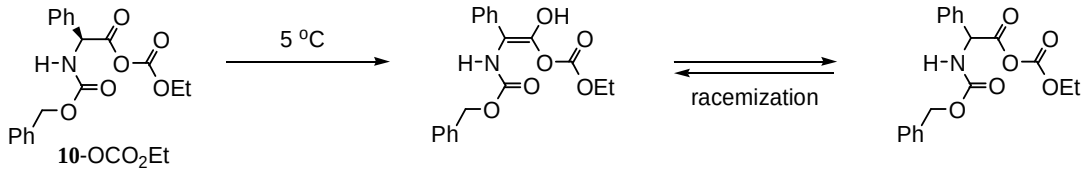


10 **11**

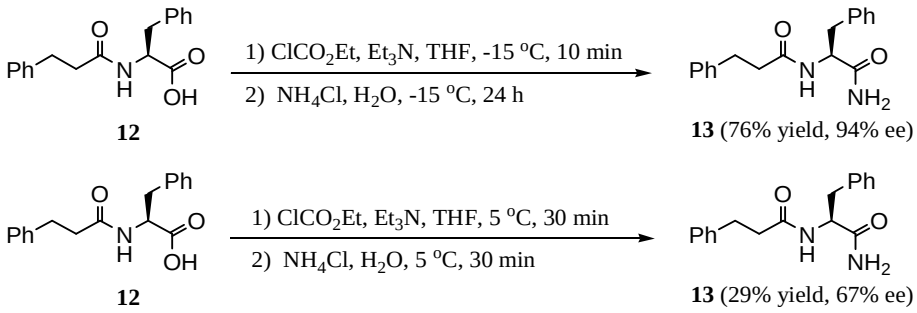
Entry	Step 1)		Step 2)		Yield[d] (%)	% ee[e]
	Temp. (°C)	Time (min)	Temp. (°C)	Time (h)		
1	5	30	5	0.5	43	46
2[b]	5	30	5	0.5	44	47
3	5	30	0	0.5	47	67
4	5	30	0	24	58	51
5	0	30	0	24	59	59
6	-5	30	-5	24	63	83
7	-10	30	-10	24	63	86
8	-15	30	-15	24	68	93
9[c]	-15	30	-15	24	79	92
10[c]	-15	5	-15	24	73	99
11[c]	-15	10	-15	24	83	99
12[c]	-15	15	-15	24	89	97
13[c]	-15	60	-15	24	58	75
14[c]	-15	120	-15	24	32	26
15[c]	-15	10	-15	0.5	73	99
16[c]	-15	10	-15	3	77	99
17[c]	-15	10	-15	48	82	98

[a] All reactions were carried out with 0.5 mmol of **10**, 0.7 mmol of $ClCO_2Et$ and 1.5 mmol of Et_3N in 10 mL of THF. After stirring for 30 min, 0.75 mmol of 1.0 M aqueous solution of NH_4Cl was added to the reaction mixture. [b] The D-form was used instead of Cbz-L-Phg-OH. [c] $ClCO_2Et$ and 1.0 M aqueous solution of NH_4Cl precooled at -15 °C were added at -15 °C to the prepared solutions on the steps 1) and 2), respectively. [d] Isolated yield. [e] Determined by HPLC analysis with 4 : 1 mixture of hexane and isopropanol as an eluent using Chiralcel AD.

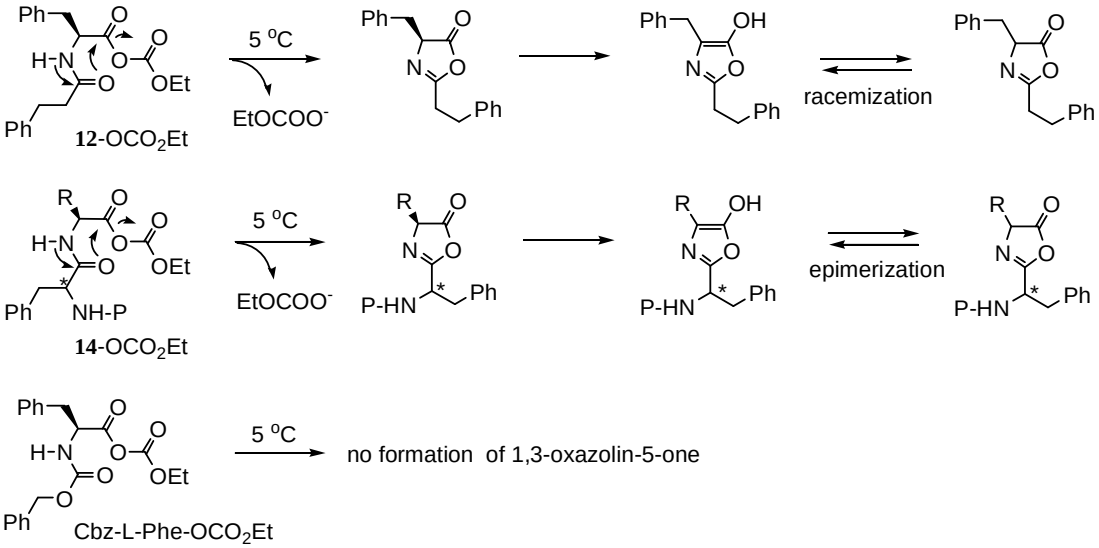
The reaction conditions were further optimized by using precooled reagents on both steps 1) and 2) and the best results (83% yield, 99% ee) were obtained when the reaction was carried out for 10 min at -15 °C on the step 1) and for 24 h at -15 °C on the step 2) as described in entry 11. In order to make sure that the optimized reaction conditions are best, the reaction time was checked on 15, 60, 120 min for the step 1) and on 0.5, 3, 48 h for the step 2) as indicated in entries 12-17. Longer reaction times of the step 1) decreased



Scheme 5. Possible pathway for racemization of **10**-OCO_2Et.



Scheme 6. The amidation of **12** with NH_4Cl at 5 °C or -15 °C.



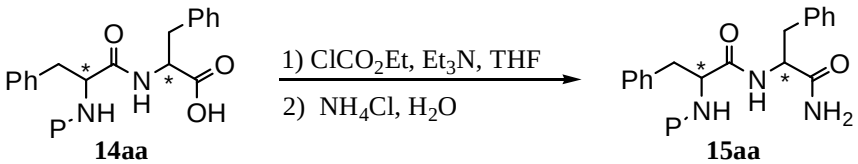
Scheme 7. Possible pathway for racemization of **12**-OCO_2Et and for epimerization of **14**-OCO_2Et.

the enantiomer excesses (97-26% ee, entries 12, 13 and 14). Then, shorter reaction times of the step 2) decreased the reaction yields (77-73% yields, entries 16 and 15) and longer reaction time of the step 2) did not give any change about both of the yield and the enantiomer excess (entry 17). It is well known that Cbz-L-Phg-OH (**10**) is easily racemized under various kinds of reaction conditions because of the reactivity on the benzyl position on it as shown in Scheme 5.

As showed in Scheme 6, the reaction of N-phenethyl-L-Phe-OH (**12**) with NH_4Cl in the presence of $ClCO_2Et$ at 5 °C proceeded with racemization via the easier formation of the corresponding 1,3-oxazol-5-one and 2,4-disubstituted 1,3-oxazolin-5-ol.[18] In addition, the unprotected side of dipeptides **14** is epimerized on the basis of the similar reason as indicated in Scheme 7. On the other hand,

Cbz-L-Phe-OCO_2Et was not converted to the corresponding 1,3-oxazol-5-one and was not racemized by the stronger electron-donating effect of the benzyloxy group compared with the phenethyl group of **12**-OCO_2Et and **14**-OCO_2Et.

Table 8. Optimization of the reaction conditions on the primary amidation of Cbz-Phe-Phe-OH (**14aa**)[a]



14aa **15aa**

Entry	**14aa**	Yield[d] (%)	% de[e]	% de[f]	Ratio of product[g] (%)			
					LL	DL	DD	LD
1	Cbz-$_L$-Phe-$_L$-Phe-OH	63	52	48	73.8	0	0	26.2
2	Cbz-$_L$-Phe-$_D$-Phe-OH	66	88	83	8.6	0	0	91.4
3[b]	Cbz-$_L$-Phe-$_L$-Phe-OH	94	13	15	57.7	0	0	42.3
4[b]	Cbz-$_L$-Phe-$_D$-Phe-OH	86	67	68	16.1	0	0	83.9
5[b]	Cbz-$_D$-Phe-$_L$-Phe-OH	90	59	58	0	79.0	21.0	0
6[b]	Cbz-$_D$-Phe-$_D$-Phe-OH	86	23	25	0	37.7	62.3	0
7[c]	Cbz-$_L$-Phe-$_L$-Phe-OH	84	>99	>99	>99	0	0	0
8[c]	Cbz-$_L$-Phe-$_D$-Phe-OH	90	>99	>99	0	0	0	>99
9[c]	Cbz-$_D$-Phe-$_L$-Phe-OH	92	>99	>99	0	>99	0	0
10[c]	Cbz-$_D$-Phe-$_D$-Phe-OH	89	>99	>99	0	0	>99	0

[a] All reactions were carried out with 0.30 mmol of **14aa**, 0.42 mmol of $ClCO_2Et$ and 0.90 mmol of Et_3N in 6 mL of THF. After stirring for 30 min at 5 ^oC, 0.45 mmol of 1.0 M aqueous solution of NH_4Cl was added at 5 ^oC to the reaction mixture. [b] The reaction time on the step 2) was 24 h. [c] $ClCO_2Et$ and 1.0 M aqueous solution of NH_4Cl precooled at -15 ^oC were added at -15 ^oC to the prepared solutions on the steps 1) and 2), respectively. Then, the reaction times on the steps 1) and 2) were 10 min and 24 h, respectively. [d] Isolated yield. [e] Determined by ^1H NMR analysis. [f] Determined by HPLC analysis with a 95 : 5 : 0.05 mixture of hexane, ethanol anddiethylamine as an eluent using Chiralcel OD (1.0 mL/min). [g] Retention times of LL-, DL-, DD- and LD-forms on HPLC analysis were 34,5, 41.2, 49.5 and 53.6 min, respectively.

Next, the results of the primary amidation of Cbz-Phe-Phe-OH (**14aa**) using NH_4Cl via the corresponding mixed carbonic carboxylic anhydride are collected in Table 8. The reactions of Cbz-L-Phe-L-Phe-OH (**14aLaL**) and Cbz-L-Phe-D-Phe-OH (**14aLaD**) in our original conditions (for 30 min at 5 ^oC on the step 1) then for 30 min at 5 ^oC on the step 2)) afforded the corresponding primary amides (**15aLaL** and **15aLaD**) in 63% and 66% yields, respectively (entries 1 and 2). Unfortunately, these diastereomer excesses were not good (52% de and 88% de, respectively) by epimerization. The reactions of **14aLaL** and **14aDaD** for 24 h at 5 ^oC on the step 2) proceeded further epimerization to afford worse diastereomer excesses (13% de and 23% de, respectively) as shown in entries 3 and 6. The reaction conditions were optimized well by using precooled reagents at -15 ^oC on both steps 1) and 2) and the results (84-92% yields, >99% de) were drastically improved as described in entries 7-10.

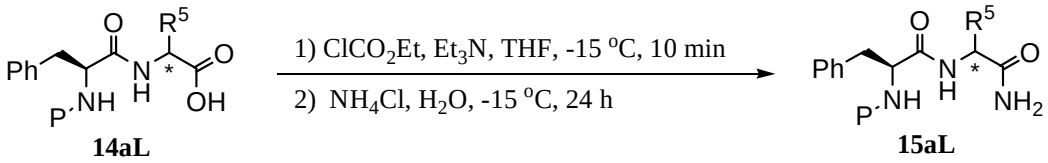
Section 2. Amidation of dipeptides via mixed carbonic carboxylic anhydrides and its application to synthesis of various medicine analogues

The reactions of various dipeptides **14aL** with NH_4Cl in aqueous THF at -15 ^oC were then carried out; the results are collected in Table 9. Boc-L-Phe-L-Phe-OH (**14'aLaL**) and Boc-L-Phe-D-Phe-OH (**14'aLaD**) reacted with NH_4Cl to produce the corresponding amides Boc-L-Phe-L-Phe-NH_2 (**15'aLaL**) and Boc-L-Phe-D-Phe-NH_2 (**15'aLaD**) in 85% yield with 81% de and 94% yield with >99% de, respectively (entries 3 and 4). The reaction of Fmoc-protected dipeptides **14"aLaL** and **14"aLaD** afforded **15"aLaL** and **15"aLaD** in 90% yield with 96% de and 95% yield with >99% de, respectively (entries 5 and 6). Then, various Cbz-L-Phe-containing dipeptides **14aLbL-aLfD** reacted readily with NH_4Cl to yield **15aLbL-aLfD** in 76-99% with 70->99% de (entries 7-16). Unfortunately, the reaction of Cys-containing dipeptides **14aLgL** and **14aLgD** with NH_4Cl did not afford the corresponding amide **15aLgL** and **15aLgD** at all, respectively and the starting materials **14aLgL** and **14aLgD** were recovered (entries 17 and 18). I also examined the condensation of various Cbz-protected dipeptides **14cLbL-mLaD** using NH_4Cl. Table 10 shows the results of the condensation of various Cbz-protected dipeptides **14cLbL-mLaD** with NH_4Cl in aqueous THF at -15 ^oC. The reactions smoothly proceeded to give the corresponding amides **15cLbL-mLaD** in 76-99% yields with 72->99% de.

Subsequently, various dipeptides-containing medicine analogues **17aLaLa-aLaDe** were synthesized by condensation of dipeptides **14aLa** with amino group-substituted medicines such as 4-aminophenol **16a**, dopamine **16b**, amantazine **16c**, (±)-rimantadine **16d**, and memantine **16e** and the results were summarized in Table 11. The reactions of dipeptides Cbz-L-Phe-L-Phe-OH (**14aLaL**) and Cbz-L-Phe-D-Phe-OH (**14aLaD**) with 4-aminophenol **16a** afforded 97% with 96% de and 94% yield with 97% de, respectively (entries 1 and 2). Cbz-L-Phe-L-Phe-OH (**14aLaL**) and Cbz-L-Phe-D-Phe-OH (**14aLaD**) reacted with dopamine **16b** to produce the corresponding amides Cbz-L-Phe-L-Phe-dopamine (**17aLaLb**) and Cbz-L-Phe-D-Phe-dopamine (**17aLaDb**) in 98% yield with 82% de and 99% yield with 88% de, respectively (entries 3 and 4). The other reactions of dipeptides **14aLaL** and **14aLaD** with **16c-e** also proceeded smoothly to produce **17aLaLc-aLaDe** in 74-93% yields with 79-97% de (entries 5-10).

Finally, reactions of various tripeptides **19aLcL** with NH_4Cl in aqueous THF at -15 ^oC were then carried out; the results are collected in Table 12. Cbz-L-Phe-L-Val-L-Phe-OH (**19aLcLaL**) and Cbz-L-Phe-L-Val-D-Phe-OH (**19aLcLaD**) reacted with NH_4Cl to produce the corresponding amides Cbz-L-Phe-L-Val-L-Phe-NH_2 (**20aLcLaL**) and Cbz-L-Phe-L-Val-L-Phe-NH_2 (**20aLcLaD**) in 95% yield with 76% de and 94% yield with 72% de, respectively (entries 1 and 2). The other reactions of tripeptides **19aLcLbL-aLcLdD** with NH_4Cl also proceeded smoothly to produce **20aLcLbL-aLcLdD** in 77-97% yields (entries 3-8).

Table 9. Preparation of primary amides derived from various P-L-Phe- α-amino acid **14aL**[a]

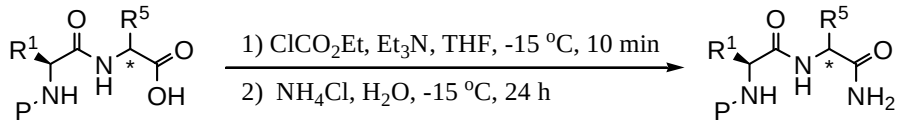


14aL **15aL**

Entry	P	R^5	**15**	Yield (%)[b]	% de[c]
1	Cbz	$PhCH_2$ (L)	**15aLaL**	84	>99[d]
2	Cbz	$PhCH_2$ (D)	**15aLaD**	90	>99[d]
3	Boc	$PhCH_2$ (L)	**15'aLaL**	85	81[e]
4	Boc	$PhCH_2$ (D)	**15'aLaD**	94	>99[e]
5	Fmoc	$PhCH_2$ (L)	**15''aLaL**	90	96
6	Fmoc	$PhCH_2$ (D)	**15''aLaD**	95	>99
7	Cbz	Me (L)	**15aLbL**	89	84
8	Cbz	Me (D)	**15aLbD**	76	>99
9	Cbz	Me_2CH (L)	**15aLcL**	93	>99
10	Cbz	Me_2CH (D)	**15aLcD**	90	>99
11	Cbz	$MeS(CH)_2$ (L)	**15aLdL**	94	>99
12	Cbz	$MeS(CH)_2$ (D)	**15aLdD**	99	>99
13	Cbz	Ph (L)	**15aLeL**	93	>99
14	Cbz	Ph (D)	**15aLeD**	84	>99
15	Cbz	CH_2OH (L)	**15aLfL**	80	70
16	Cbz	CH_2OH (D)	**15aLfD**	89	95
17	Cbz	CH_2SH (L)	**15aLgL**	0	-
18	Cbz	CH_2SH (D)	**15aLgD**	0	-

[a] All reactions were carried out with 0.30 mmol (1 equiv) of **14aL**, 40 μL (0.42 mmol, 1.4 equiv) of a precooled $ClCO_2Et$, and 126 μL (0.90 mmol, 3 equiv) of a precooled Et_3N in 6 mL of anhydrous THF. After stirring for 10 min at -15 °C, 0.45 mL (0.45 mmol, 1.5 equiv) of a precooled 1.0M aqueous solution of NH_4Cl was added dropwise at -15 °C to the reaction mixture. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Determined by HPLC analysis with a 95 : 5 : 0.05 mixture of hexane, EtOH, and Et_2NH as an eluent using Chiralcel OD (1.0 mL/min). [e] Determined by HPLC analysis with a 4 : 1 mixture of hexane and 2-propanol as an eluent using Chiralcel OD (1.0 mL/min).

Table 10. Preparation of primary amides derived from various dipeptides **14**[a]

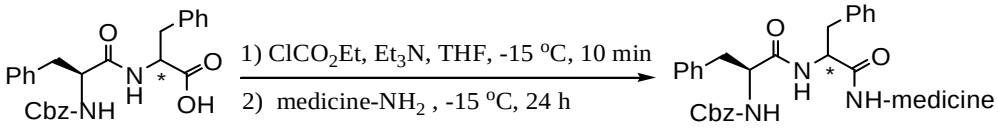


14 **15**

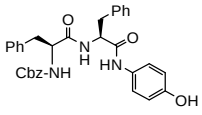
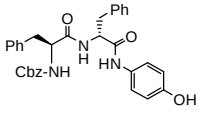
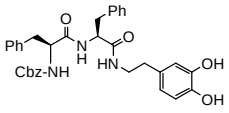
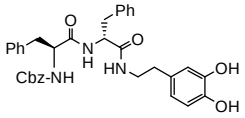
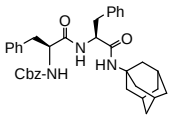
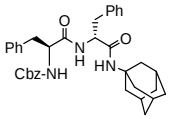
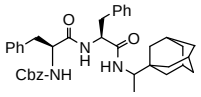
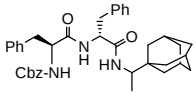
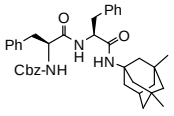
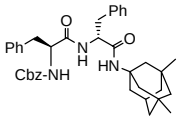
Entry	P	R^1	R^5	**15**	Yield[b] (%)	%de[c]
1	Cbz	Me	Me (L)	**15cLbL**	76	86
2	Cbz	Me	Me (D)	**15cLbD**	86	90
3	Cbz	Me	Me_2CH (L)	**15cLcL**	85	>99
4	Cbz	Me	Me_2CH (D)	**15cLcD**	99	>99
5	Cbz	Me	$MeS(CH_2)_2$ (L)	**15cLdL**	85	>99
6	Cbz	Me	$MeS(CH_2)_2$ (D)	**15cLdD**	83	89
7	Cbz	Me_2CH	Me (L)	**15bLbL**	99	>99
8	Cbz	Me_2CH	Me (D)	**15bLbD**	97	>99
9	Cbz	Me_2CH	Me_2CH (L)	**15bLcL**	93	92
10	Cbz	Me_2CH	Me_2CH (D)	**15bLcD**	94	72
11	Cbz	Me_2CH	$MeS(CH_2)_2$ (L)	**15bLdL**	99	>99
12	Cbz	Me_2CH	$MeS(CH_2)_2$ (D)	**15bLdD**	92	89
13	Cbz	$MeS(CH_2)_2$	Me (L)	**15dLbL**	97	94
14	Cbz	$MeS(CH_2)_2$	Me (D)	**15dLbD**	97	76
15	Cbz	$MeS(CH_2)_2$	Me_2CH (L)	**15dLcL**	86	>99
16	Cbz	$MeS(CH_2)_2$	Me_2CH (D)	**15dLcD**	84	>99
17	Cbz	$MeS(CH_2)_2$	$MeS(CH_2)_2$ (L)	**15dLdL**	77	97
18	Cbz	$MeS(CH_2)_2$	$MeS(CH_2)_2$ (D)	**15dLdD**	90	>99
19	Boc	$C_6H_5CH_2OCH_2$	$PhCH_2$ (L)	**15hLaL**	96	97
20	Boc	$C_6H_5CH_2OCH_2$	$PhCH_2$ (D)	**15hLaD**	96	91
21	N^{α}-Boc-N^{ε}-Cbz	$(CH_2)_4$	$PhCH_2$ (L)	**15mLaL**	86	97
22	N^{α}-Boc-N^{ε}-Cbz	$(CH_2)_4$	$PhCH_2$ (D)	**15mLaD**	89	96

[a] All reactions were carried out with 0.30 mmol (1 equiv) of **14**, 40 μL (0.42 mmol, 1.4 equiv) of a precooled $ClCO_2Et$, and 126 μL (0.90 mmol, 3 equiv) of a precooled Et_3N in 6 mL of anhydrous THF. After stirring for 10 min at -15 °C, 0.45 mL (0.45 mmol, 1.5 equiv) of a precooed 1.0M aqueous solution of NH_4Cl was added dropwise at -15 °C to the reaction mixture. [b] Isolated yield. [c] Determined by ^1H NMR analysis.

Table 11. Synthesis of various medicine analogues containing dipeptides **14**[a]

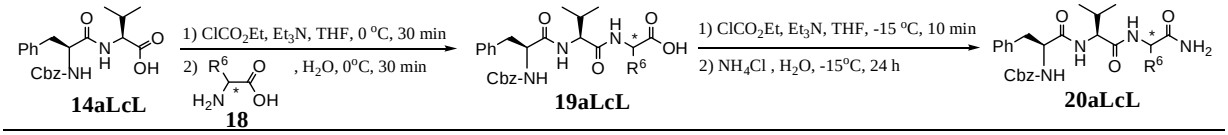


14aLa **16** **17aLa**

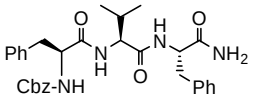
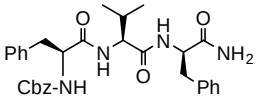
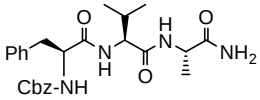
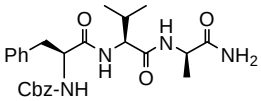
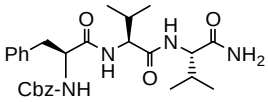
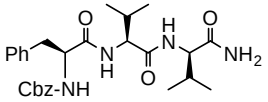
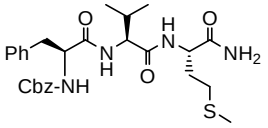
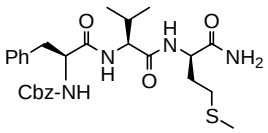
Entry	Medicine-NH_2 **16**		**17**	Yield[b] (%)	%de[c]
1	4-aminophenol **16a**		**17aLaLa**	97	96
2	4-aminophenol **16a**		**17aLaDa**	94	97
3	dopamine **16b**		**17aLaLb**	98	82
4	dopamine **16b**		**17aLaDb**	99	88
5	amantazine **16c**		**17aLaLc**	83	88
6	amantazine **16c**		**17aLaDc**	89	95
7	(±)-rimantadine **16d**		**17aLaLd**	86	79
8	(±)-rimantadine **16d**		**17aLaDd**	93	91
9	memantine **16e**		**17aLaLe**	74	85
10	memantine **16e**		**17aLaDe**	82	97

[a] All reactions were carried out with 0.30 mmol (1 equiv) of **14aLa**, 40 μL (0.42 mmol, 1.4 equiv) of a precooled $ClCO_2Et$, and 126 μL (0.90 mmol, 3 equiv) of a precooled Et_3N in 6 mL of anhydrous THF. After stirring for 10 min at -15 °C, 0.45 mL (0.45 mmol, 1.5 equiv) of 1.0M aqueous solution of NH_4Cl was added dropwise at -15 °C to the reaction mixture. [b] Isolated yield. [c] Determined by 1H NMR analysis.

Table 12. Preparation of primary amides derived from various tripeptides **19**[a]



14aLcL **18** **19aLcL** **20aLcL**

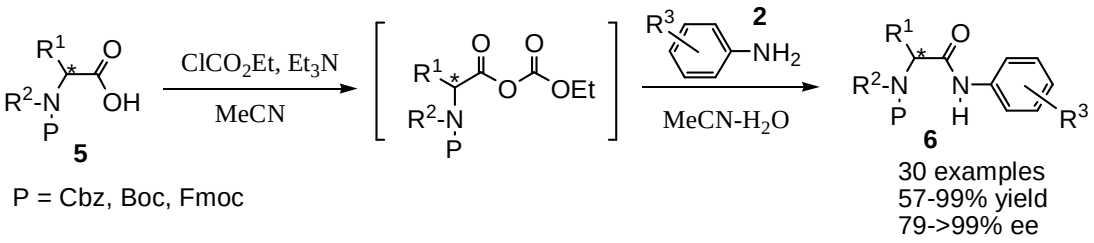
Entry	R^6	**19aLcL**		**20aLcL**	Yield[b] (%)	%de[c]
1	$PhCH_2$ (L)	**19aLcLaL**		**20aLcLaL**	95	76
2	$PhCH_2$ (D)	**19aLcLaD**		**20aLcLaD**	94	72
3	Me (L)	**19aLcLbL**		**20aLcLbL**	89	-[d]
4	Me (D)	**19aLcLbD**		**20aLcLbD**	85	-[d]
5	Me_2CH (L)	**19aLcLcL**		**20aLcLcL**	84	-[d]
6	Me_2CH (D)	**19aLcLcD**		**20aLcLcD**	77	-[d]
7	$MeS(CH_2)_2$ (L)	**19aLcLdL**		**20aLcLdL**	97	-[d]
8	$MeS(CH_2)_2$ (D)	**19aLcLdD**		**20aLcLdD**	94	-[d]

[a] All reactions were carried out with 0.30 mmol (1 equiv) of **19aLcL**, 40 μL (0.42 mmol, 1.4 equiv) of a precooled $ClCO_2Et$, and 126 μL (0.90 mmol, 3 equiv) of a precooled Et_3N in 6 mL of anhydrous THF. After stirring for 10 min at -15 °C, 0.45 mL (0.45 mmol, 1.5 equiv) of a precooled 1.0M aqueous solution of NH_4Cl was added dropwise at -15 °C to the reaction mixture. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Not determined neither by ^1H NMR analysis nor HPLC analysis.

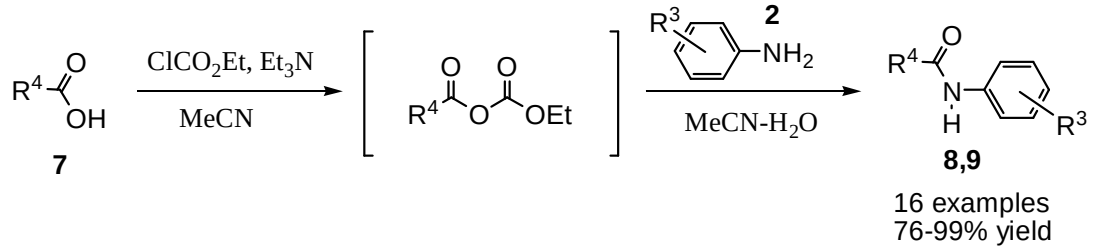
Conclusion

Chapter 1. Synthesis of acetaminophen analogues containing α-amino acids and fatty acids for inhibiting hepatotoxicity

I have synthesized acetaminophen analogues **6aLo-mDo** (Table 4) in 57-99% yields, AM404 analogues **8ao-ho** (Table 5) in 83-99% yields, and **9am-hm** (Table 6) in 76-97% yields, by using a convenient and economical procedure (Scheme 8, 9). These analogues would be useful *p*-aminophenol donors and are expected to act as novel antipyretic analgesics like acetaminophen. Various amides were obtained in high to excellent yields with excellent enantioselectivities after purification by silica gel column chromatography, by using $ClCO_2Et$ and Et_3N under the mild conditions. In particular, both of the activating agents ($ClCO_2Et$ and Et_3N) are relatively inexpensive and the by-products obtained by our efficient method are triethylamine hydrochloride, carbon dioxide, and the corresponding alcohols, which are relatively environmentally benign. Although amidations via activated carboxylic acids are usually carried out under anhydrous conditions, it is quite unique that the reaction of the activated carbonic carboxylic anhydride smoothly in aqueous organic solvent to afford the corresponding amides. Our synthetic method is also characterized by no racemization and low levels of by-products formation.



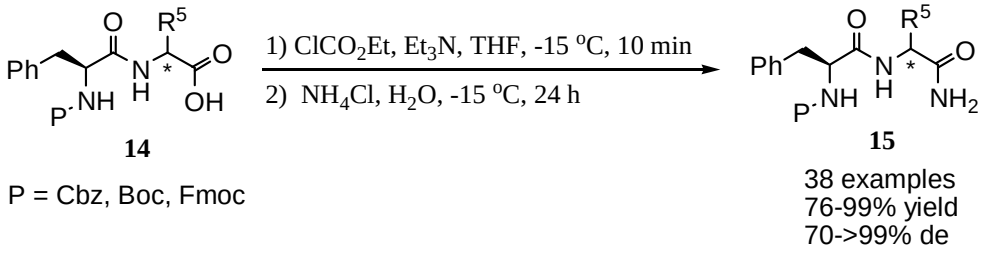
Scheme 8. Synthesis of acetaminophen analogues **6** containing α-amino acid **5**



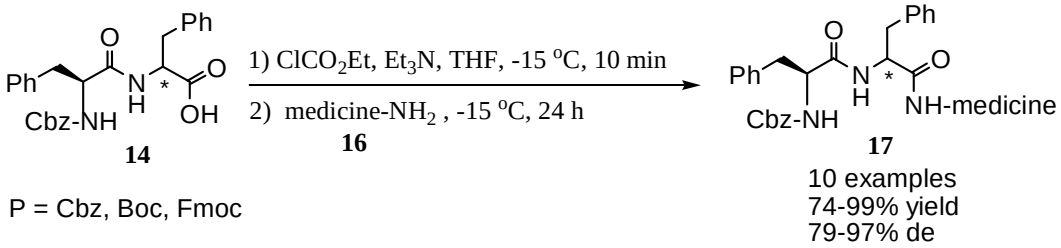
Scheme 9. Synthesis of AM404 analogues **8,9** containing fatty acid **7**

Chapter 2. Green synthesis of various medicine analogues containing dipeptides without epimerization under the extremely mild conditions

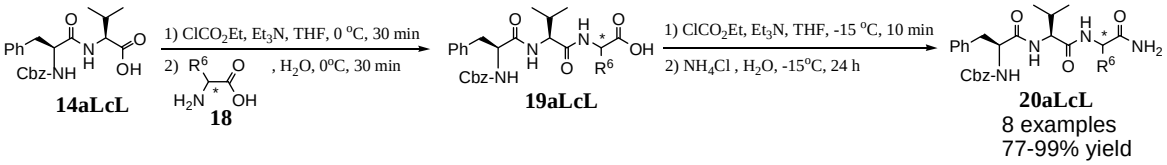
In conclusions, various dipeptides **15aLaL-mLaD** (Table 9, 10) and tripeptides **20aLcLaL-aLcLdD** (Table 12) were prepared in 76-99% yields with 70->99% de and 77-97% yields, respectively (Scheme 10, 12). Then, the various dipeptides-containing medicine analogues **17aLaLa-aLaDe** (Table 11) were synthesized in 74-99% yields with 79-97% de (Scheme 11). As a result, I succeeded green and economical synthesis of various dipeptides-containing medicine analogues **17aLaLa-aLaDe** (Table 11), dipeptides **15aLaL-mLaD** (Table 9, 10), and tripeptides **20aLcLaL-aLcLdD** (Table 12) in aqueous THF at -15 ^{o}C via the mixed carbonic carboxylic anhydrides by the activation of the corresponding carboxylic acids. It is noted that the results were obtained by precisely controlling the reaction temperature during the activation of the corresponding carboxylic acids. Particularly, it is amazing that racemization or epimerization does not proceed as a result of controlling the reaction temperature by our developed precooled dropping method. In addition, both of the activating agents ($ClCO_2Et$ and Et_3N) are quite cheap and the by-products obtained by our efficient method are triethylamine hydrochloride, carbon dioxide, and the corresponding alcohols, which are quite safe environmentally. Although amidations via activated carboxylic acids are usually carried out under anhydrous conditions, it is quite unique that the reaction of the activated mixed carbonic carboxylic anhydride smoothly proceeded in aqueous organic solvent to afford the corresponding amides. Furthermore, the dipeptides-containing medicine analogues **17aLaLa-aLaDe** (Table 11) have recently attracted much attention for inhibiting side effect in the clinical field and are expected to be useful donors of peptide medicines.



Scheme 10. Preparation of primary amides derived from various dipeptides **14**



Scheme 11. Synthesis of various medicine analogues **17** containing dipeptides **14**



Scheme12. Preparation of primary amides derived from various tripeptides **19**

Experimental

1. General

All reagents were used without purification. The ^{1}H NMR and ^{13}C NMR spectra were measured with a Bruker Ultrashield TM 400 Plus spectrometer. The chemical shifts of ^{1}H NMR spectra are expressed in parts per million downfield from tetramethylsilane (δ = 0.00 ppm) as an internal standard. Chemical shifts (δ) are reported in ppm, and spin-spin coupling constants (*J*) are given in hertz (Hz). Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). The high-resolution mass spectra (HRMS) of the compounds with a high molecular weight were recorded with a Waters LCT Premier (ESI-TOF-MS) spectrometer. Reactions were monitored using thin-layer chromatography with silica gel 60 F_{254}. Purification of the reaction products was carried out by column chromatography using silica gel (64-210 mesh). HPLC analysis was carried out with Chiralcel OD (10 mm, 46 × 250 mm), Chiralcel AS (10 mm, 46 × 250 mm), and Chiralcel AD-H (5 mm, 46 × 250 mm) coupled to a photodiode array detector or a dual λ absorbance detector, and HPLC grade solvents were used for HPLC analysis. Melting points were determined with a hot plate apparatus. Optical rotations were measured with a digital polarimeter with a sodium lamp at room temperature. Infrared (IR) spectra were recorded on HORIBA FT-IR Fourier transform infrared spectrophotometer.

2. Typical Procedure for amidation of 3-phenylpropionic acid (1) with 4-chloroanilne 2a

To a colorless solution of 3-phenylpropionic acid **1** (75 mg, 0.50 mmol) in MeCN (10ml) were added at 0 ℃ Et_3N (77 μL, 0.55 mmol, 1.1 equiv) and $ClCO_2Et$ (53 μL, 0.55 mmol, 1.1 equiv). After stirring for 30 min at 0 ℃, a solution of 4-chloroanilne **2a (**70 mg, 0.55 mmol, 1.1 equiv) in H_2O (0.75 mL) was added at 0 ℃ to the colorless suspension. The mixture was stirred for 24 h at 0 ℃ and concentrated in vacuo. To the residue was added a 1.0 M of aqueous HCl to pH 2. The resulted suspension was extracted with EtOAc (50 mL), washed with brine (10 mL), and 1.0 M of aqueous $NaHCO_3$ (5 mL), and dried over $MgSO_4$. The crude product was purified by chromatography on silica gel with a 1:1 mixture of hexane and EtOAc to afford 125 mg (96% yield) of *N*-(4-chlorophenyl)-3-phenylpropanamide **3a**.

2.1. *N*-(4-chlorophenyl)-3-phenylpropanamide 3a

Yield: 125 mg (96%); colorless powder; mp: 137-139 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.66 (t, *J* = 7.6, 2H, CH_2CO), 3.05 (t, *J* = 7.6, 2H, CH_2CH_2CO), 6.95 (brs, 1H, NH), 7.21-7.38 (m, 9H, C_6H_4, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.5, 39.3, 121.3, 126.5, 128.0, 128.3, 128.9, 129.3, 136.3, 140.4, 170.7; HRMS (ESI-TOF): Calcd for $C_{15}H_{14}NOClNa$ $(M+Na)^+$: 282.0656, found: 282.0667; IR (KBr, ν_{max}/cm^{-1}) = 3302 (NH), 1657 (CON).

2.2. *N*-(4-fluorophenyl)-3-phenylpropanamide, 3b

Yield: 118 mg (97%); colorless powder; mp: 119-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.65 (t, *J* = 7.4, 2H, CH_2CO), 3.05 (t, *J* = 7.4, 2H, CH_2CH_2CO), 6.96-7.02, 7.21-7.39 (m, m, 3H, 7H, NH, C_6H_4, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.6, 39.4, 115.5, 115.7, 121.7, 121.8, 126.5, 128.4, 128.7,133.7, 140.6, 160.6, 170.3; HRMS (ESI-TOF): Calcd for $C_{15}H_{14}FNONa$ $(M+Na)^+$: 266.0952, found: 266.0977; IR (KBr, ν_{max}/cm^{-1}) = 3289 (NH), 1652 (CON).

2.3. *N*-(2,3,4,5,6-pentafluorophenyl)-3-phenylpropanamide, 3c

Yield: 105 mg (67%); colorless powder; mp: 128-129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.77 (t, *J* = 7.4, 2H, CH_2CO), 3.07 (t, *J* = 7.4, 2H, CH_2CH_2CO), 6.57 (brs, 1H, NH), 7.22-7.34 (m, 5H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.3, 38.0, 126.6, 128.3, 128.8, 140.0, 170.5; HRMS (ESI-TOF): Calcd for $C_{15}H_{10}F_5NONa$ $(M+Na)^+$: 338.0575, found: 338.0593; IR (KBr, ν_{max}/cm^{-1}) = 3265 (NH), 1685 (CON).

2.4. ethyl 4-(3-phenylpropanamido)benzoate, 3d

Yield: 104 mg (70%); colorless powder; mp: 132-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (t, *J* = 7.1, 3H, CH_3CH_2O), 2.69 (t, *J* = 7.4, 2H, CH_2CO), 3.06 (t, *J* = 7.4, 2H, CH_2CH_2CO), 4.53 (q, *J* = 7.1, 2H, CH_3CH_2O), 7.21-7.33 (m, 6H, NH, C_6H_5), 7.50, 7.98 (d, d, *J* = 8.7, 8.7, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 31.4, 39.6, 60.9, 118.8, 126.0, 126.5, 128.4, 128.7, 130.8, 140.4, 141.8, 166.1, 170.5; HRMS (ESI-TOF): Calcd for $C_{18}H_{19}NO_3Na$ $(M+Na)^+$: 320.1257, found: 320.1250; IR (KBr, ν_{max}/cm^{-1}) = 3316 (NH), 1711 (CO_2), 1593 (CON).

2.5. *N*-(4-nitrophenyl)-3-phenylpropanamide, 3e

Yield: 88 mg (65%); yellow powder; mp: 121-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.73 (t, *J* = 7.4, 2H, CH_2CO), 3.08 (t, *J* = 7.4, 2H, CH_2CH_2CO), 7.18 (brs, 1H, NH), 7.23-7.35 (m, 5H, C_6H_5), 7.59, 8.19 (d, d, *J* = 9.2, 9.2, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.3, 39.6, 119.0, 125.1, 126.7, 128.4, 128.8, 140.1, 143.5, 143.5, 170.7; HRMS (ESI-TOF): Calcd for $C_{15}H_{15}N_2O_3$ $(M+H)^+$: 271.1077, found: 271.1069; IR (KBr, ν_{max}/cm^{-1}) = 3249 (NH), 1670 (CON), 1504 (NO).

2.6. *N*-(3,5-dinitrophenyl)-3-phenylpropanamide, 3f

Yield: 47 mg (30%); yellow powder; mp: 166-167 °C; ^{1}H NMR (400 MHz, MeOD-d^4): δ = 2.75 (t, *J* = 7.6, 2H, CH_2CO), 3.02 (t, *J* = 7.6, 2H, CH_2CH_2CO), 7.18 (brs, 1H, NH), 7.14-7.29 (m, 5H, C_6H_5), 8.64, 8.21 (t, d, *J* = 2.1, 2.1, 1H, 2H, C_6H_3); ^{13}C NMR (100 MHz, MeOD-d^4): δ = 32.3, 39.8, 113.7, 119.9, 127.4, 129.5,

129.6, 142.0, 142.6, 150.1, 174.2; HRMS (ESI-TOF): Calcd for $C_{15}H_{13}N_3O_5Na$ $(M+Na)^+$: 338.0747, found: 338.0747; IR (KBr, ν_{max}/cm^{-1}) = 3357 (NH), 1710 (CON), 1540 (NO).

2.7. *N*-(4-bromophenyl)-3-phenylpropanamide, 3h

Yield: 148 mg (98%); colorless powder; mp: 150-151 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.65 (t, *J* = 7.5, 2H, CH_2CO), 3.05 (t, *J* = 7.5, 2H, CH_2CH_2CO), 7.00 (brs, 1H, NH), 7.21-7.41(m, 9H, C_6H_4, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.5, 39.5, 116.9, 121.4, 126.5, 128.4, 128.7, 131.9, 136.8, 140.5, 170.3; HRMS (ESI-TOF): Calcd for $C_{15}H_{14}NOBrNa$ $(M+Na)^+$: 326.0151, found: 326.0112; IR (KBr, ν_{max}/cm^{-1}) = 3298 (NH), 1658 (CON).

2.8. *N*-(4-iodophenyl)-3-phenylpropanamide, 3i

Yield: 165 mg (94%); colorless powder; mp: 163-165 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.65 (t, *J* = 7.5, 2H, CH_2CO), 3.04 (t, *J* = 7.5, 2H, CH_2CH_2CO), 6.95 (brs, 1H, NH), 7.19-7.32, 7.57-7.61 (m, m, 7H, 2H, C_6H_4, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.5, 39.6, 87.4, 121.7, 126.5, 128.4, 128.7, 137.5, 137.9, 140.5, 170.3; HRMS (ESI-TOF): Calcd for $C_{15}H_{14}INONa$ $(M+Na)^+$: 374.0012, found: 373.9984; IR (KBr, ν_{max}/cm^{-1}) = 3298 (NH), 1655 (CON).

2.9. *N*-(4-cyanophenyl)-3-phenylpropanamide, 3j

Yield: 109 mg (87%); colorless powder; mp: 115-117 °C; ^1H NMR (400 MHz, DMSO-d^6): δ = 2.68 (t, *J* = 7.6, 2H, CH_2CO), 2.91 (t, *J* = 7.6, 2H, CH_2CH_2CO), 7.18-7.30 (m, 5H, C_6H_5), 7.72-7.90 (m, 4H, C_6H_4), 10.36 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 30.4, 37.9, 104.6, 118.9, 119.0, 125.9, 128.1, 128.2, 133.2, 140.9, 143.3, 171.2; HRMS (ESI-TOF): Calcd for $C_{16}H_{15}N_2O$ $(M+H)^+$: 251.1179, found: 251.1172; IR (KBr, ν_{max}/cm^{-1}) = 3257 (NH), 2218 (CN), 1672 (CON).

2.10. *N*,3-diphenylpropanamide, 3k

Yield: 106 mg (94%); colorless powder; mp: 130-133 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.67 (t, *J* = 7.7, 3H, CH_2CO), 3.07 (t, *J* = 7.7, 2H, CH_2CH_2CO), 6.96 (brs, 1H, NH), 7.08-7.44 (m, 10H, C_6H_5×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.6, 39.5, 119.9, 124.3, 126.4, 128.4, 128.7, 129.0, 137.7, 140.6, 170.3; HRMS (ESI-TOF): Calcd for $C_{15}H_{15}NONa$ $(M+Na)^+$: 248.1046, found: 248.1068; IR (KBr, ν_{max}/cm^{-1}) = 3322 (NH), 1650 (CON).

2.11. *N*-(4-methylphenyl)-3-phenylpropanamide, 3l

Yield: 114 mg (95%); colorless powder; mp: 97-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3H, CH_3), 2.30 (t, *J* = 7.4, 2H, CH_2CO), 3.06 (t, *J* = 7.4, 2H, C*H*$_2$CH$_2$CO), 6.90 (brs, 1H, NH), 7.09-7.11, 7.20-7.33 (m, m, 2H, 7H, C_6H_4, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 31.6, 39.5, 120.0, 126.4, 128.4, 128.7, 129.5, 134.0, 135.1, 140.7, 170.1; HRMS (ESI-TOF): Calcd for $C_{16}H_{17}NONa$ $(M+Na)^+$: 262.1202, found: 262.1172; IR (KBr, ν_{max}/cm^{-1}) = 3300 (NH), 1657 (CON).

2.12. *N*-(4-hydroxyphenyl)-3-phenylpropanamide, 3m

Yield: 111 mg (92%); colorless powder; mp: 143-145 °C; ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 2.55 (t, *J* = 7.7, 2H, CH_2CO), 2.88 (t, *J* = 7.7, 2H, C*H*$_2$CH$_2$CO), 6.65-6.68, 7.15-7.34 (m, m, 2H, 7H, C_6H_4, C_6H_5), 9.14 (s, 1H, NH), 9.63 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 30.9, 37.7, 114.9, 120.7, 125.8, 128.1, 128.2, 130.8, 141.2, 153.0, 169.5; HRMS (ESI-TOF): Calcd for $C_{15}H_{15}NO_2Na$ $(M+Na)^+$: 264.0995, found: 264.1019; IR (KBr, ν_{max}/cm^{-1}) = 3325 (OH), 1660 (CON).

2.13. *N*-(2-ethoxyphenyl)-3-phenylpropanamide, 3n

Yield: 120 mg (89%); colorless powder; mp: 79-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (t, *J* = 7.0, 3H, C*H*$_3$CH$_2$O), 2.71 (t, *J* = 7.8, 2H, CH_2CO), 3.07 (t, *J* = 7.8, 2H, C*H*$_2$CH$_2$CO), 4.07 (q, *J* = 7.0, 2H, CH$_3$C*H*$_2$O), 6.83-7.32, 8.38-8.40 (m, m, 8H, 1H, C_6H_4, C_6H_5), 7.73 (brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8, 31.5, 39.7, 64.1, 110.8 119.8, 121.0, 123.5, 126.3, 127.7, 128.4, 128.6, 140.8, 146.9, 170.1; HRMS (ESI-TOF): Calcd for $C_{17}H_{19}NO_2Na$ $(M+Na)^+$: 292.1308, found: 292.1268; IR (KBr, ν_{max}/cm^{-1}) = 3298 (NH), 1653 (CON).

2.14. *N*-(4-ethoxyphenyl)-3-phenylpropanamide, 3o

Yield: 132 mg (98%); colorless powder; mp: 131-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, *J* = 7.0 Hz, 3H, C*H*$_3$CH$_2$O), 2.64 (t, *J* = 7.4, 2H, CH_2CO), 3.06 (t, *J* = 7.4, 2H, C*H*$_2$CH$_2$CO), 4.00 (q, *J* = 7.0, CH$_3$C*H*$_2$O), 6.82-6.84, 7.18-7.36 (m, m, 3H, 7H, NH, C_6H_4, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8, 31.7, 39.4, 63.7, 114.8, 121.9, 126.4, 128.4, 128.7, 130.7, 140.7, 155.9,170.1; HRMS (ESI-TOF): Calcd for $C_{17}H_{19}NO_2Na$ $(M+Na)^+$: 292.1308, found: 292.1313; IR (KBr, ν_{max}/cm^{-1}) = 3292 (NH), 1652 (CON).

2.15. *N*-(4-mercaptophenyl)-3-phenylpropanamide, 3p

Yield: 118 mg (92%); colorless powder; mp: 197-199 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.65 (t, *J* = 7.5, 2H, CH_2CO), 3.05 (t, *J* = 7.5, 2H, C*H*$_2$CH$_2$CO), 3.41 (s, 1H, SH), 6.90 (brs, 1H, NH), 7.22-7.33 (m, 9H, C_6H_4, C_6H_5); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 30.6, 37.8, 119.7, 125.9, 128.1, 128.2, 129.3, 130.0,

139.3, 141.0, 170.5; HRMS (ESI-TOF): Calcd for $C_{30}H_{28}N_2O_2S_2Na$ $(M+Na)^+$: 535.1484, found: 535.1502; IR (KBr, ν_{max}/cm^{-1}) = 3326 (NH), 1658 (CON).

2.16. *N*-(4-*tert*-butylphenyl)-3-phenylpropanamide, 3q

Yield: 135 mg (96%); colorless powder; mp: 139-141 °C; ^1H NMR (400 MHz, DMSO-d^6): δ = 1.25 (s, 9H, CH_3×3), 2.59 (t, 2H, *J* = 7.7, CH_2CO), 2.90 (t, 2H, *J* = 7.7, C$H_2$$CH_2CO$), 7.18-7.31, 7.46-7.49 (m, m, 7H, 2H, C_6H_4, C_6H_5), 9.82 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 30.8, 31.1, 33.9, 118.8, 125.1, 125.8, 128.1, 128.2, 136.6, 141.1, 145.2, 170.0; HRMS (ESI-TOF): Calcd for $C_{19}H_{24}NO$ $(M+H)^+$: 282.1852, found: 282.1866; IR (KBr, ν_{max}/cm^{-1}) = 3282 (NH), 1655 (CON).

2.17. *N*-mesityl-3-phenylpropanamide, 3r

Yield: 100 mg (75%); colorless powder; mp: 171-173 °C; ^1H NMR (400 MHz, DMSO-d^6): δ = 1.97-199 (m, 6H, CH_3×2), 2.20 (s, 3H, CH_3), 2.62 (t, *J* = 7.5, 3H, CH_2CO), 2.92 (t, *J* = 7.5, 2H, C$H_2$$CH_2CO$), 6.83 (s, 2H, C_6H_2), 7.19-7.29(m, 5H, C_6H_5), 9.09 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 17.8, 20.4, 31.1, 36.7, 125.8, 128.1, 128,1, 128.2, 128.6, 132.5, 134.7, 135.1135.7, 141.1, 169.8; HRMS (ESI-TOF): Calcd for $C_{18}H_{21}NONa$ $(M+Na)^+$: 290.1515, found: 290.1546; IR (KBr, ν_{max}/cm^{-1}) = 3228 (NH), 1646 (CON).

3. Typical Procedure for amidation of Cbz-$_L$-Phe-OH (5aL) with 4-ethoxyaniline 2o

To a colorless solution of Cbz-$_L$-Phe-OH **5aL** (150 mg, 0.50 mmol) in MeCN (10 mL) were added at 0 °C Et_3N (77 μL, 0.55 mmol, 1.1 equiv) and $ClCO_2Et$ (53 μL, 0.55 mmol, 1.1 equiv). After stirring for 30 min at 0 °C, a solution of 4-ethoxyaniline **2o** (75 mg, 0.55 mmol, 1.1 equiv) in H_2O (0.75 mL) was added at 0 °C to the colorless suspension. The mixture was stirred for 24 h at 0 °C and concentrated in vacuo. To the residue was added a 1.0 M aqueous HCl to pH 2. The resulted suspension was extracted with EtOAc (50 mL), washed with brine (10 mL), and 1.0 M aqueous $NaHCO_3$ (5ml), and dried over $MgSO_4$. The crude product was purified by chromatography on silica gel with a 3:1 mixture of hexane and EtOAc including a small amount of acetic acid to afford 201 mg (96% yield) of Cbz-$_L$-Phe-NHC_6H_4-4-OEt **6aLo**.

3.1. Cbz-L-Phe-NHC_6H_4-4-OEt 6aLo

Yield: 201 mg (96%); colorless powder; >99% ee; mp: 178-179 °C; $[\alpha]_D^{30}$ = +69.0 (*c* 0.99, DMSO); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, *J* = 7.0, 3H, C$H_3$$CH_2O$), 3.10 (dd, *J* = 6.0, 7.8, 1H, C$H_A$$C_6H_5$), 3.21 (dd, *J* = 6.0, 6.3, 1H, C$H_B$$C_6H_5$), 3.99 (q, *J* = 7.0, 3H, $CH_3$$CH_2O$), 4.48 (m, 1H, CHCO), 5.12 (s, 2H, OC$H_2$$C_6H_5$), 5.42 (brs, 1H, NH), 6.78-6.82, 7.18-7.37 (m, m, 2H, 13H, NH, C_6H_4, C_6H_5×2); ^{13}C NMR (100

MHz, $CDCl_3$): δ = 14.8, 38.7, 57.0, 63.7, 67.3, 114.7, 122.0 127.2, 128.1, 128.3, 128.6, 128.9, 129.4, 129.9, 136.0, 156.1, 168.7; HRMS (ESI-TOF): Calcd for $C_{25}H_{26}N_2O_4Na$ $(M+Na)^+$: 441.1785, found: 441.1795; IR (KBr, ν_{max}/cm^{-1}) = 3292 (NH), 1693 (CON), 1653 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90/10): T_r 15 min.

3.2. Cbz-D-Phe-NHC$_6$H$_4$-4-OEt 6aDo

Yield: 203 mg (97%); colorless powder; >99% ee; mp: 178-179 ℃; $[\alpha]_D^{31}$ = -70.0 (*c* 0.98, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90/10): T_r 17 min.

3.3. Cbz-L-Phe-NHC$_6$H$_4$-2-OEt 6aLn

Yield: 190 mg (91%); colorless powder; >99% ee; mp: 143-145 ℃; $[\alpha]_D^{30}$ = -17.8 (*c* 0.98, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.0, 3H, C*H*$_3$CH$_2$O), 3.18 (d, *J* = 6.6, 2H, C*H*$_2$C$_6$H$_5$), 3.97 (q, *J* = 7.0, 2H, CH$_3$C*H*$_2$O), 4.58-4.59 (m, 1H, CHCO), 5.11 (s, 2H, OC*H*$_2$C$_6$H$_5$), 5.39 (brs, 1H, NH), 6.80, 6.94, 7.02, 8.33 (d, t, t, d, *J* = 8.1, 7.8, 7.8, 8.0 Hz, 1H, 1H, 1H, 1H, C$_6$H$_4$), 7.20-7.32 (m, 10H, C$_6$H$_5$×2), 8.11 (brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7, 38.8, 64.2, 67.2, 111.0, 119.7, 120.9, 124.1, 127.1, 128.0, 128.2, 128.6, 128.8, 129.3, 136.1, 136.3, 147.4, 168.7; HRMS (ESI-TOF): Calcd for $C_{25}H_{26}N_2O_4Na$ $(M+Na)^+$: 441.1785, found: 441.1795; IR (KBr, ν_{max}/cm^{-1}) = 3303 (NH), 1680 (CON), 1597 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90/10): T_r 26 min.

3.4. Cbz-D-Phe-NHC$_6$H$_4$-2-OEt 6aDn

Yield: 190 mg (91%); colorless powder; >99% ee; mp: 143-145 ℃; $[\alpha]_D^{30}$ = +17.8 (*c* 0.98, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90/10): T_r 51 min.

3.5. Cbz-L-Phe-NHC$_6$H$_4$-4-OH 6aLm

Yield: 172 mg (88%); colorless powder; >99% ee; mp: 184-185 ℃; $[\alpha]_D^{29}$ = +65.8 (*c* 1.02, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 2.83 (dd, *J* = 9.2, 10.3, 1H, C*H*$_A$C$_6$H$_5$), 3.00 (dd, *J* = 9.2, 4.4, 1H, C*H*$_B$C$_6$H$_5$), 4.36-4.37 (m, 1H, CHCO), 4.96 (s, 2H, OC*H*$_2$C$_6$H$_5$), 6.68-6.71, 7.18-7.37, 7.64-7.70 (m, m, m, 2H, 12H, 1H, NH, C$_6$H$_4$, C$_6$H$_5$×2), 9.20 (s, 1H, NH), 9.85 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 37.6, 56.7, 65.2, 115.0, 121.0, 126.2, 127.4, 127.6, 128.0, 128.2, 129.2, 130.4, 137.9, 153.3, 155.8, 169.7; HRMS (ESI-TOF): Calcd for $C_{23}H_{22}N_2O_4Na$ $(M+Na)^+$: 413.1472, found: 413.1503; IR (KBr, ν_{max}/cm^{-1}) = 3649 (OH), 1687 (CON), 1660 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90/10): T_r 26 min.

3.6. Cbz-D-Phe-NHC$_6$H$_4$-4-OH 6aDm

Yield: 172 mg (88%); colorless powder; >99% ee; mp: 184-185 °C; $[\alpha]_D^{29}$ = -65.5 (*c* 1.00, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90/10): T_r 30 min.

3.7. Cbz-L-Val-NHC$_6$H$_4$-4-OEt 6bLo

Yield: 179 mg (97%); colorless powder; >99% ee; mp: 210-212 °C; $[\alpha]_D^{31}$ = +37.1 (*c* 1.02, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (d, d, *J* = 6.8, 6.8, 3H, 3H, (C*H*$_3$)$_2$CH), 1.39 (t, *J* = 7.0, 3H, C*H*$_3$CH$_2$O), 2.18-2.26 (m, 1H, C*H*(CH$_3$)$_2$), 4.00 (q, *J* = 7.0, 2H, CH$_3$C*H*$_2$O), 4.07 (m, 1H, CHCO), 5.11 (s, 2H, OC*H*$_2$C$_6$H$_5$), 5.44 (brs, 1H, NH), 6.81-6.83, 7.34-7.37 (m, m, 2H, 7H, C$_6$H$_4$, C$_6$H$_5$), 7.76 (brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8, 18.0, 19.4, 30.9, 61.3, 63.7, 67.3, 114.8, 122.0, 128.1, 128.3, 128.6, 130.3, 136.1, 156.1, 156.7, 169.4; HRMS (ESI-TOF): Calcd for $C_{21}H_{26}N_2O_4Na$ $(M+Na)^+$: 393.1785, found: 393.1732; IR (KBr, ν_{max}/cm^{-1}) = 3300 (NH), 1689 (CON), 1654 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90/10): T_r 10 min.

3.8. Cbz-D-Val-NHC$_6$H$_4$-4-OEt 6bDo

Yield: 183 mg (99%); colorless powder; >99% ee; mp: 210-212 °C; $[\alpha]_D^{31}$ = -36.0 (*c* 1.00, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90/10): T_r 11 min.

3.9. Cbz-L-Ala-NHC$_6$H$_4$-4-OEt 6cLo

Yield: 140 mg (82%); colorless powder; >99% ee; mp: 163-164 °C; $[\alpha]_D^{31}$ = +1.2 (*c* 1.02, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, *J* = 7.0, 3H, C*H*$_3$CH$_2$O), 1.46 (d, *J* = 7.0, 3H, C*H*$_3$CH), 4.01 (q, *J* = 7.0, 2H, CH$_3$C*H*$_2$O), 4.22-4.37 (m, 1H, CHCO), 5.13 (s, 2H, OC*H*$_2$C$_6$H$_5$), 5.28 (brs, 1H, NH), 6.83-6.86, 7.32-7.38 (m, m, 2H, 7H, C$_6$H$_4$, C$_6$H$_5$), 7.94 (brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8, 18.3, 51.1, 63.7, 67.3, 114.7, 121.8, 128.0, 128.3, 128.5, 128.6, 130.6, 136.0, 155.9, 170.3; HRMS (ESI-TOF): Calcd for $C_{19}H_{22}N_2O_4Na$ $(M+Na)^+$: 365.1472, found: 365.1440; IR (KBr, ν_{max}/cm^{-1}) = 3357 (NH), 1693 (CON), 1668 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90/10): T_r 14 min.

3.10. Cbz-D-Ala-NHC$_6$H$_4$-4-OEt 6cDo

Yield: 156 mg (91%); colorless powder; 98% ee; mp: 163-164 °C; $[\alpha]_D^{31}$ = -1.1 (*c* 0.98, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90/10): T_r 16 min.

3.11. Cbz-L-Met-NHC$_6$H$_4$-4-OEt 6dLo

Yield: 171 mg (85%); colorless powder; >99% ee; mp: 129-130 °C; $[\alpha]_D^{31}$ = +14.7 (*c* 0.98, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 1.30 (t, *J* = 6.9, 3H, C*H*$_3$CH$_2$O), 1.86-1.91 (m, 4H, CH$_2$CH$_2$S), 2.05 (s, 3H, CH$_3$S), 3.98 (q, *J* = 6.9, 2H, CH$_3$C*H*$_2$O), 4.20-4.21 (m, 1H, CHCO), 5.03 (s, 1H, OC*H*$_2$C$_6$H$_5$), 6.86, 7.49 (d, d, *J* = 8.4, 8.4, 2H, 2H, C$_6$H$_4$), 7.31-7.64 (m, 6H, NH, C$_6$H$_5$), 9.90 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 14.5, 14.6, 29.7, 31.5, 54.5, 63.0, 65.4, 114.3, 120.8, 126.9, 127.6, 127.7, 128.2, 131.8, 136.9, 154.4, 156.0, 169.9; HRMS (ESI-TOF): Calcd for $C_{21}H_{26}N_2O_4Na$ $(M+Na)^+$: 425.1505, found: 425.1554; IR (KBr, ν_{max}/cm^{-1}) = 3288 (NH), 1689 (CON), 1653 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90/10): T_r 15 min.

3.12. Cbz-D-Met-NHC$_6$H$_4$-4-OEt 6dDo

Yield: 177 mg (88%); colorless powder; >99% ee; mp: 129-130 °C; $[\alpha]_D^{30}$ = -13.8 (*c* 1.00, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90/10): T_r 20 min.

3.13. Cbz-L-Pro-NHC$_6$H$_4$-4-OEt 6eLo

Yield: 182 mg (99%); colorless powder; >99% ee; mp: 112-114 °C; $[\alpha]_D^{30}$ = -38.3 (*c* 0.99, DMSO); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.40 (t, *J* = 6.9, 3H, C*H*$_3$CH$_2$O), 1.95-2.55, 3.46-3.53 (m, m, 4H, 2H, pyrrolidinyl H), 4.01(q, *J* = 6.9, 2H, CH$_3$C*H*$_2$O), 4.39-4.52 (m, 1H, CHCO), 5.21 (s, 2H, OC*H*$_2$C$_6$H$_5$), 6.81-6.83, 7.26-7.37 (m, m, 2H, 8H, NH, C$_6$H$_4$, C$_6$H$_5$), 8.97 (brs, 1H, NH); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 14.8, 24.7, 27.7, 47.1, 61.0, 61.4, 63.7, 67.6, 114.7, 121.4, 128.0, 128.2, 128.4, 128.6, 131.2, 136.3, 155.5, 156.7, 169.2; HRMS (ESI-TOF): Calcd for $C_{21}H_{24}N_2O_4Na$ $(M+Na)^+$: 391.1628, found: 391.1620; IR (KBr, ν_{max}/cm^{-1}) = 3269 (NH), 1709 (CON), 1664 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel AS: hexane/2-propanol = 90/10): T_r 56 min.

3.14. Cbz-D-Pro-NHC$_6$H$_4$-4-OEt 6eDo

Yield: 182 mg (99%); colorless powder; >99% ee; mp: 112-114 °C; $[\alpha]_D^{30}$ = +40.8 (*c* 1.02, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel AS: hexane/2-propanol = 90/10): T_r 20 min.

3.15. Boc-L-Phe-NHC$_6$H$_4$-4-OEt 6fLo

Yield: 190 mg (99%); colorless powder; >99% ee; mp: 159-161 °C; $[\alpha]_D^{31}$ = +75.9 (*c* 0.98, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 1.23-1.32 (m, 12H, C*H*$_3$CH$_2$O, (CH$_3$)$_3$C), 2.82 (dd, *J* = 10.3, 10.4, 1H, C*H*$_A$C$_6$H$_5$), 2.97 (dd, *J* = 8.8, 10.3, 1H, C*H*$_B$C$_6$H$_5$), 3.98 (q, *J* = 7.0, 2H, CH$_3$C*H*$_2$O), 4.25-4.31 (m, 1H,

CHCO), 6.87, 7.46 (d, d, J = 9.0, 9.0, 2H, 2H, C_6H_4), 7.06-7.31 (m, 6H, NH, C_6H_5), 9.87 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 14.6, 28.1, 56.3, 63.0, 77.9, 114.3, 120.7, 126.2, 127.9, 129.1, 131.9, 137.9, 154.4, 155.3, 170.1; HRMS (ESI-TOF): Calcd for $C_{22}H_{28}N_2O_4Na$ $(M+Na)^+$: 407.1941, found: 407.1909; IR (KBr, ν_{max}/cm^{-1}) = 3344 (NH), 1691 (CON), 1664 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90/10): T_r 13 min.

3.16. Boc-D-Phe-NHC$_6$H$_4$-4-OEt 6fDo

Yield: 190 mg (99%); colorless powder; 95% ee; mp: 159-161 ℃; $[\alpha]_D^{31}$ = -75.6 (*c* 0.99, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90/10): T_r 8 min.

3.17. Fmoc-L-Phe-NHC$_6$H$_4$-4-OEt 6gLo

Yield: 207 mg (82%); colorless powder; >99% ee; mp: 218-220 ℃; $[\alpha]_D^{29}$ = +20.5 (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 1.31 (t, J = 7.0, 3H, CH_3CH$_2$O), 2.89 (dd, J = 10.2, 10.3, 1H, CH_AC$_6$H$_5$), 3.02 (dd, J = 4.7, 10.2, 1H, CH_BC$_6$H$_5$), 3.98 (q, J = 7.0, 2H, CH$_3$CH_2O), 4.16-4.19 (m, 3H, CHCH$_2$O), 4.38 (m, 1H, CHCO), 6.86-6.88, 7.20-7.89 (m, m, 2H, 16H, NH, C_6H_4, C_6H_5, fluorenyl H), 9.97 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 14.6, 37.5, 46.5, 56.7, 63.0, 65.6, 114.3, 120.0, 120.7, 125.2, 125.3, 126.2, 126.9, 127.5, 128.0, 129.2, 131.8, 137.9, 140.6, 143.6, 143.7, 154.5, 155.8, 169.8; HRMS (ESI-TOF): Calcd for $C_{32}H_{30}N_2O_4Na$ $(M+Na)^+$: 529.2098, found: 529.2053; IR (KBr, ν_{max}/cm^{-1}) = 3307 (NH), 1691 (CON), 1654 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel ADH: hexane/2-propanol = 90/10): T_r 29 min.

3.18. Fmoc-D-Phe-NHC$_6$H$_4$-4-OEt 6gDo

Yield: 240 mg (95%); colorless powder; >99% ee; mp: 218-220 ℃; $[\alpha]_D^{29}$ = -15.6 (*c* 1.00, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel ADH: hexane/2-propanol = 90/10): T_r 11 min.

3.19. *O*-benzyl-Boc-L-Ser-NHC$_6$H$_4$-4-OEt 6hLo

Yield: 193 mg (93%); colorless powder; >99% ee; mp: 104-105 ℃; $[\alpha]_D^{30}$ = +13.8 (*c* 1.02, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 1.30 (t, J = 7.0, 3H, CH_3CH$_2$O), 1.39 (s, 9H, (CH$_3$)$_3$C), 3.60-3.65 (m, 2H, CH_2CHCO), 3.98 (q, J = 7.0, 2H, CH$_3$CH_2O), 4.34-4.38 (m, 1H, CHCO), 4.50 (s, 2H, OCH_2C$_6$H$_5$), 6.87, 7.49 (d, d, J = 6.9, 6.9, 2H, 2H, C_6H_4), 6.98-7.33 (m, 6H, NH, C_6H_5), 9.91 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 14.6, 28.1, 54.8, 63.0, 69.8, 72.0, 78.2, 114.3, 120.7, 127.3, 128.1, 131.8, 138.1, 154.5, 155.1, 168.3; HRMS (ESI-TOF): Calcd for $C_{23}H_{30}N_2O_5Na$ $(M+Na)^+$: 437.2047, found: 437.2057; IR

(KBr, ν_{max}/cm^{-1}) = 3350 (NH), 1687 (CON), 1664 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5): T_r 19 min.

3.20. *O*-benzyl-Boc-D-Ser-NHC_6H_4-4-OEt 6hDo

Yield: 197 mg (95%); colorless powder; 98% ee; mp: 104-105 °C; $[\alpha]_D^{30}$ = -12.8 (*c* 1.00, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5): T_r 16min.

3.21. *S*-trityl-Fmoc-L-Cys-NHC_6H_4-4-OEt 6iLo

Yield: 271 mg (77%); colorless powder; 79% ee; mp: 191-193 °C; $[\alpha]_D^{30}$ = -10.0 (*c* 0.98, DMSO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, *J* = 7.0, 3H, C*H*$_3$CH$_2$O), 2.71-2.79 (m, 2H, SC*H*$_2$CHCO), 3.84-3.87 (m, 1H, SCH$_2$C*H*CO), 3.99 (q, *J* = 7.0, 2H, CH$_3$C*H*$_2$O), 4.18 (t, *J* = 6.8, 1H, C*H*CH$_2$OCO), 4.42 (d, *J* = 6.8, 2H, CHC*H*$_2$OCO), 5.01 (brs, 1H, NH), 6.80-6.82, 7.18-7.76 (m, m, 2H, 26H, C_6H_4, NH, C_6H_5×3, fluorenyl H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8, 33.6, 47.1, 54.7, 64.0, 67.1, 67.5, 114.7, 120.0, 121.7, 125.0, 127.0, 127.1, 127.8, 128.1, 129.6, 130.1, 141.3, 143.6, 144.3, 156.0, 167.9; HRMS (ESI-TOF): Calcd for $C_{45}H_{40}N_2O_4SNa$ $(M+Na)^+$: 727.2602, found: 727.2616; IR (KBr, ν_{max}/cm^{-1}) = 3292 (NH), 1685 (CON), 1662 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel ADH: hexane/2-propanol = 90/10): T_r 64 min.

3.22. *S*-trityl-Fmoc-D-Cys-NHC_6H_4-4-OEt 6iDo

Yield: 278 mg (79%); colorless powder; 86% ee; mp: 191-193 °C; $[\alpha]_D^{29}$ = +13.5 (*c* 1.00, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel ADH: hexane/2-propanol = 90/10): T_r 55 min.

3.23. Cbz-$_L$-Tyr-NHC_6H_4-4-OEt 6jLo

Yield: 141 mg (65%); colorless powder; >99% ee; mp: 170-171 °C; $[\alpha]_D^{30}$ = +64.4 (*c* 1.01, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 1.31 (t, *J* = 7.0, 3H, C*H*$_3$CH$_2$O), 3.00 (dd, *J* = 5.1, 9.2, 1H, C*H*$_A$C$_6$H$_4$), 3.14 (dd, *J* = 9.1, 9.2, C*H*$_B$C$_6$H$_4$), 3.98 (q, *J* = 7.0, 2H, CH$_3$C*H*$_2$O), 4.42-4.44 (m, 1H, CHCO), 4.97 (s, 2H, OC*H*$_2$C$_6$H$_5$), 6.85-7.69 (m, 14H, C_6H_4×2, NH, C_6H_5), 9.98 (s, 1H, NH), 10.83 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 14.6, 27.8, 56.0, 63.0, 65.2, 109.8, 111.2, 114.2, 118.1, 118.5, 120.8, 120.8, 123.8, 127.1, 127.5, 127.6, 128.2, 131.9, 135.9, 136.9, 154.4, 155.8, 170.2; HRMS (ESI-TOF): Calcd for $C_{25}H_{26}N_2O_5Na_2$ $(M+2Na)^+$: 480.1626, found: 480.1674; IR (KBr, ν_{max}/cm^{-1}) = 3413 (OH), 3313 (NH), 1710 (CON), 1668 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel ADH: hexane/2-propanol = 90/10): T_r 62 min.

3.24. Cbz-$_D$-Tyr-NHC$_6$H$_4$-4-OEt 6jDo

Yield: 124 mg (57%); colorless powder; >99% ee; mp: 170-171 °C; $[\alpha]_D^{30}$ = -62.1 (*c* 1.02, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel ADH: hexane/2-propanol = 90/10): T_r 81 min.

3.25. Cbz-$_L$-Trp-NHC$_6$H$_4$-4-OEt 6kLo

Yield: 208 mg (91%); colorless powder; >99% ee; mp: 181-182 °C; $[\alpha]_D^{30}$ = +51.5 (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 1.31 (t, *J* = 7.0, 3H, C*H*$_3$CH$_2$O), 3.00 (dd, *J* = 9.3, 5.1, 1H, C*H*$_A$-indole), 3.14 (dd, *J* = 5.1, 5.1, 1H, C*H*$_B$-indole), 3.98 (q, *J* = 7.0, 2H, CH$_3$C*H*$_2$O), 4.42-4.44 (m, 1H, CHCO), 4.97 (s, 2H, OC*H*$_2$C$_6$H$_5$), 6.85-7.69 (m, 15H, C$_6$H$_4$, NH, C$_6$H$_5$, indolyl H), 9.98 (s, 1H, NHCO), 10.83 (s, indole NH); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 14.6, 27.8, 56.0, 63.0, 65.2, 109.9, 111.2, 114.2, 118.1, 118.5, 120.8, 120.9, 123.8, 127.2, 127.5, 127.6, 128.2, 131.9, 136.0, 136.9, 154.4, 155.8, 170.3; HRMS (ESI-TOF): Calcd for $C_{27}H_{27}N_3O_4Na$ $(M+Na)^+$: 480.1894, found: 480.1883; IR (KBr, ν_{max}/cm^{-1}) = 3415 (NH), 3299 (NH), 1701 (CON), 1658 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel AS: hexane/2-propanol = 99/1): T_r 121 min.

3.26. Cbz-$_D$-Trp-NHC$_6$H$_4$-4-OEt 6kDo

Yield: 208 mg (91%); colorless powder; >99% ee; mp: 181-182 °C; $[\alpha]_D^{30}$ = -51.1 (*c* 1.02, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel AS: hexane/2-propanol = 90/10): T_r 87 min.

3.27. Boc-$_L$-Gln-NHC$_6$H$_4$-4-OEt 6lLo

Yield: 144 mg (79%); colorless powder; >99% ee; mp: 176-178 °C; $[\alpha]_D^{30}$ = +6.8 (*c* 1.01, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 1.30 (t, *J* = 7.0, 3H, C*H*$_3$CH$_2$O), 1.38 (s, 9H, (CH$_3$)$_3$C), 1.75-1.87 (m, 2H, C*H*$_2$CH), 2.09-2.16 (m, 2H, C*H*$_2$CH$_2$CH), 3.95-4.02 (m, 3H, CH$_3$C*H*$_2$O, CHCO), 6.78 (s, 1H, NH$_A$), 6.86, 7,48 (d, d, *J* = 9.0, 9.0, 2H, 2H, C$_6$H$_4$), 7.00 (d, *J* = 7.8, 1H, NH), 7.29 (s, 1H, NH$_B$), 9.80 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 14.6, 27.6, 28.1, 31.5, 54.6, 63.0, 78.0, 114.3, 120.7, 131.9, 154.4, 155.3, 170.3, 173.5; HRMS (ESI-TOF): Calcd for $C_{18}H_{27}N_3O_5Na$ $(M+Na)^+$: 388.1843, found: 388.1835; IR (KBr, ν_{max}/cm^{-1}) = 3388 (NH), 3336 (NH), 3194 (NH), 1681 (CON), 1654 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90/10): T_r 19 min.

3.28. Boc-$_D$-Gln-NHC$_6$H$_4$-4-OEt 6lDo

Yield: 146 mg (80%); colorless powder; >99% ee; mp: 176-178 °C; $[\alpha]_D^{30}$ = -6.4 (*c* 1.01, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90/10): T_r 14 min.

3.29. N^{α}-Boc-N^{ε}-Cbz-$_L$-Lys-NHC_6H_4-4-OEt 6mLo

Yield: 241 mg (94%); colorless powder; >99% ee; mp: 139-140 °C; $[\alpha]_D^{30}$ = +5.4 (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 1.30 (t, *J* = 7.0, 3H, C*H*$_3$CH$_2$O), 1.38 (s, 9H, (CH$_3$)$_3$C), 1.54-1.58 (m, 6H, NHCH$_2$(C*H*$_2$)$_3$), 2.95-2.99 (m, 2H, NHC*H*$_2$(CH$_2$)$_3$), 3.95-4.02 (m, 3H, CH$_3$C*H*$_2$O, CHCO), 4.99 (s, 2H, OC*H*$_2$C$_6$H$_5$), 6.90, 7.48 (d, d, *J* = 9.0, 9.0, 2H, 2H, C$_6$H$_4$), 7.00 (d, *J* = 7.8, 1H, N*H*CH), 9.80 (s, 1H, NHCO); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 14.6, 22.8, 28.1, 29.0, 31.5, 54.9, 63.0, 65.0, 77.9, 114.3, 120.6, 127.6, 128.2, 132.0, 137.2, 154.3, 155.4, 156.0, 170.7; HRMS (ESI-TOF): Calcd for $C_{27}H_{37}N_3O_6Na$ $(M+Na)^+$: 522.2575, found: 522.2547; IR (KBr, ν_{max}/cm^{-1}) = 3338 (NH), 1695 (CON), 1666 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90/10): T_r 37 min.

3.30. N^{α}-Boc-N^{ε}-Cbz-$_D$-Lys-NHC_6H_4-4-OEt 6mDo

Yield: 249 mg (97%); colorless powder; >99% ee; mp: 139-140 °C; $[\alpha]_D^{30}$ = -5.5 (*c* 1.02, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90/10): T_r 15 min.

4. Typical Procedure for amidation of lauric acid 7a with 4-ethoxyaniline 2o

To a colorless solution of lauric acid **7a** (100 mg, 0.50 mmol) in MeCN (10 mL) were added at 0 °C Et$_3$N (77 μL, 0.55 mmol, 1.1 equiv) and ClCO$_2$Et (53 μL, 0.55 mmol, 1.1 equiv). After stirring for 30 min at 0 °C, a solution of 4-ethoxyaniline **2o** (75 mg, 0.55 mmol, 1.1 equiv) in H$_2$O (0.75 mL) was added at 0 °C to the colorless suspension. The mixture was stirred for 24 h at 0 °C and concentrated in vacuo. To the residue was added a 1.0 M aqueous HCl to pH 2. The resulted suspension was extracted with EtOAc (50 mL), washed with brine (10 mL), and 1.0 M aqueous NaHCO$_3$ (5ml), and dried over MgSO$_4$. The crude product was purified by chromatography on silica gel with a 2:1 mixture of hexane and EtOAc to afford 155 mg (97% yield) of *N*-(4-ethoxyphenyl)lauramide **8ao**.

4.1. *N*-(4-ethoxyphenyl)lauramide 8ao

Yield: 155 mg (97%); colorless powder; mp: 104-105 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.88 (t, *J* = 6.8, 3H, C*H*$_3$(CH$_2$)$_{10}$), 1.26-1.41 (m, 16H, CH$_3$(C*H*$_2$)$_8$), 1.40 (t, *J* = 7.0, 3H, C*H*$_3$CH$_2$O), 1.70-1.75 (m, 2H, C*H*$_2$CH$_2$CO), 2.32 (t, *J* = 7.6, 2H, CH$_2$C*H*$_2$CO), 4.01 (q, *J* = 7.0, 2H, CH$_3$C*H*$_2$O), 6.84, 7.39 (d, d, *J* = 8.9, 8.9, 2H, 2H, C$_6$H$_4$), 7.03 (brs, 1H, NHCO); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 14.1, 14.8, 22.7, 25.7, 29.3, 29.3, 29.4, 29.5, 29.6, 31.9, 37.7, 63.7, 114.8, 121.7, 131.0, 155.7, 171.2; HRMS (ESI-TOF): Calcd for $C_{20}H_{33}NO_2Na$ $(M+Na)^+$: 342.2404, found: 342.2403; IR (KBr, ν_{max}/cm^{-1}) = 3302 (NH), 1653 (CON).

4.2. *N*-(4-ethoxyphenyl)palmitamide 8bo

Yield: 184 mg (98%); colorless powder; mp: 111-112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8, 3H, C*H*$_3$(CH$_2$)$_{14}$), 1.25-1.41 (m, 24H, CH$_3$(C*H*$_2$)$_{12}$), 1.40 (t, *J* = 7.0, 3H, C*H*$_3$CH$_2$O), 1.70-1.71 (m, 2H, C*H*$_2$CH$_2$CO), 2.32 (t, *J* = 7.6, 2H, CH$_2$C*H*$_2$CO), 4.01 (q, *J* = 7.0, 2H, CH$_3$C*H*$_2$O), 6.84, 7.39 (d, d, *J* = 9.0, 9.0, 2H, 2H, C_6H_4), 7.05 (brs, 1H, NHCO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 14.8, 22.7, 25.7, 29.3, 29.4, 29.4, 29.5, 29.6, 29.7, 29.7, 31.9, 37.7, 63.7, 114.8, 121.7, 131.0, 155.7, 171.3; HRMS (ESI-TOF): Calcd for $C_{24}H_{41}NO_2Na$ $(M+Na)^+$: 398.3030, found: 398.3046; IR (KBr, ν_{max}/cm^{-1}) = 3302 (NH), 1658 (CON).

4.3. *N*-(4-ethoxyphenyl)oleamide 8co

Yield: 178 mg (89%); colorless powder; mp: 66-67 °C; ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 0.84 (t, *J* = 7.0, 3H, C*H*$_3$(CH$_2$)$_7$), 1.23-1.31 (m, 23H, C*H*$_3$CH$_2$O, CH$_3$(C*H*$_2$)$_6$, (C*H*$_2$)$_4$CH$_2$CH$_2$CO), 1.54-1.57 (m, 2H, C*H*$_2$CH$_2$CO), 1.97-1.98 (m, 4H, C*H*$_2$CH×2), 2.24 (t, *J* = 7.4, 2H, CH$_2$CO), 3.97 (q, *J* = 7.0, 2H, CH$_3$C*H*$_2$O), 5.28-5.36 (m, 2H, CH×2), 6.83, 7.46 (d, d, *J* = 8.9, 8.9, 2H, 2H, C_6H_4), 9.67 (s, 1H, NHCO); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 13.9, 14.6, 22.1, 25.2, 26.6, 26.6, 28.6, 28.6, 28.7, 28.8, 29.1, 31.3, 36.3, 63.0, 114.2, 120.5, 129.5, 129.6, 132.5, 154.2, 170.6; HRMS (ESI-TOF): Calcd for $C_{26}H_{43}NO_2Na$ $(M+Na)^+$: 424.3186, found: 424.3218; IR (KBr, ν_{max}/cm^{-1}) = 3296 (NH), 1653 (CON).

4.4. (9*Z*,12*Z*)-*N*-(4-ethoxyphenyl)linoleamide 8do

Yield: 186 mg (93%); yellow powder; mp: 47-48 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9, 3H, C*H*$_3$(CH$_2$)$_4$), 1.27-1.40 (m, 14H, CH$_3$(C*H*$_2$)$_3$, (C*H*$_2$)$_4$CH$_2$CH$_2$CO), 1.39 (t, *J* = 7.0, 3H, C*H*$_3$CH$_2$O), 1.66-1.71 (m, 2H, C*H*$_2$CH$_2$CO), 2.02-2.07 (m, 4H, CH$_2$C*H*$_2$CH×2), 2.30 (t, *J* = 7.6, 2H, CH$_2$CO), 2.75-278 (m, 2H, CHC*H*$_2$CH), 3.99 (q, *J* = 7.0, 2H, CH$_3$C*H*$_2$O), 5.29-5.40 (m, 4H, CH×4), 6.81, 7.38 (d, d, *J* = 9.0, 9.0, 2H, 2H, C_6H_4), 7.42 (brs, 1H, NHCO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 14.8, 22.6, 25.7, 25.7, 29.2, 29.3, 29.3, 29.4, 29.6, 31.5, 37.6, 63.7, 114.8, 115.1, 121.8, 130.1, 130.2, 131.1, 155.7, 171.4; HRMS (ESI-TOF): Calcd for $C_{26}H_{41}NO_2Na$ $(M+Na)^+$: 422.3030, found: 422.3019; IR (KBr, ν_{max}/cm^{-1}) = 3302 (NH), 1655 (CON).

4.5. (9*Z*,12*Z*,15*Z*)-*N*-(4-ethoxyphenyl)linolenamide 8eo

Yield: 189 mg (95%); yellow powder; mp: 47-49 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.5, 3H, C*H*$_3$CH$_2$CH), 1.28-1.41 (m, 8H, (C*H*$_2$)$_4$CH$_2$CH$_2$CO), 1.39 (t, *J* = 7.0, 3H, C*H*$_3$CH$_2$O), 1.66-1.73 (m, 2H, C*H*$_2$CH$_2$CO), 2.03-2.11 (m, 4H, CH$_3$C*H*$_2$CH, CH$_2$C*H*$_2$CH), 2.32 (t, *J* = 7.6, 2H, CH$_2$CO), 2.75-2.82 (m, 4H,

CHCH_2CH×2), 4.00 (q, J = 7.0, 2H, CH_3CH_2O), 5.30-5.41 (m, 6H, CH×6), 6.84, 7.39 (d, d, J = 9.0, 9.0, 2H, 2H, C_6H_4), 7.11 (s, 1H, NHCO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 14.8, 20.6, 25.5, 25.6, 25.7, 27.2, 29.1, 29.3, 29.6, 37.7, 63.7, 114.8, 121.7, 127.1, 127.6, 128.3, 128.3, 130.3, 130.9, 132.0, 155.7, 171.2; HRMS (ESI-TOF): Calcd for $C_{26}H_{39}NO_2Na$ $(M+Na)^+$: 420.2873, found: 420.2862; IR (KBr, ν_{max}/cm^{-1}) = 3300 (NH), 1655 (CON).

4.6. (*E*)-*N*-(4-ethoxyphenyl)elaidamide 8fo

Yield: 166 mg (83%); colorless powder; mp: 87-88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.9, 3H, $CH_3(CH_2)_7$), 1.26-1.41 (m, 20H, $CH_3(CH_2)_6$, $(CH_2)_4CH_2CH_2CO$), 1.40 (t, J = 7.0, 3H, CH_3CH_2O), 1.67-1.75 (m, 2H, CH_2CH_2CO), 1.94-1.97 (m, 4H, CH_2CH×2), 2.32 (t, J = 7.6, 2H, CH_2CO), 4.00 (q, J = 7.0, 2H, CH_3CH_2O), 5.37-5.39 (m, 2H, CH×2), 6.84, 7.39 (d, d, J = 9.0, 9.0, 2H, 2H, C_6H_4), 7.05 (brs, 1H, NHCO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 14.8, 22.7, 25.7, 29.0, 29.2, 29.3, 29.3, 29.5, 29.6, 29.7, 31.9, 32.6, 32.6, 37.7, 63.7, 114.8, 121.7, 130.2, 130.5, 131.0, 155.7, 171.2; HRMS (ESI-TOF): Calcd for $C_{26}H_{43}NO_2Na$ $(M+Na)^+$: 424.3186, found: 424.3218; IR (KBr, ν_{max}/cm^{-1}) = 3323 (NH), 1655 (CON).

4.7. (5*Z*,8*Z*,11*Z*,14*Z*)-*N*-(4-ethoxyphenyl)arachidonamide 8go

Yield: 49 mg (93%); brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, J = 6.9, 3H, $CH_3(CH_2)_4$), 1.27-1.41 (m, 6H, $CH_3(CH_2)_3$), 1.40 (t, J = 7.0, 3H, CH_3CH_2O), 1.81-1.85 (m, 2H, CH_2CH_2CO), 2.03-2.20 (m, 4H, CH_2CH_2CH×2), 2.33 (t, J = 7.6, 2H, CH_2CO), 2.79-2.83 (m, 6H, CHCH_2CH×3), 4.00 (q, J = 7.0, 2H, CH_3CH_2O), 5.30-5.46 (m, 8H, CH×8), 6.83, 7.38 (d, d, J = 9.0, 9.0, 2H, 2H, C_6H_4), 7.07 (brs, 1H, NHCO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 14.8, 22.6, 25.4, 25.7, 26.5, 27.2, 29.3, 31.3, 36.9, 63.7, 114.8, 121.7, 127.5, 127.9, 128.2, 128.3, 128.6, 129.1, 130.5, 130.9, 155.8, 170.9; HRMS (ESI-TOF): Calcd for $C_{28}H_{41}NO_2Na$ $(M+Na)^+$: 446.3030, found: 446.3061; IR (KBr, ν_{max}/cm^{-1}) = 3292 (NH), 1655 (CON).

4.8. (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-*N*-(4-ethoxyphenyl)docosahexaeno-amide 8ho

Yield: 49 mg (99%); brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, J = 7.5, 3H, CH_3CH_2CH), 1.39 (t, J = 7.0, 3H, CH_3CH_2O), 2.04-2.11 (m, 2H, CH_3CH_2CH), 2.36-2.40 (m, 2H, CH_2CH_2CO), 2.48 (t, J = 6.7, 2H, CH_2CO), 2.70-2.88 (m, 10H, CHCH_2CH×5), 3.99 (q, J = 7.0, 2H, CH_3CH_2O), 5.32-5.45 (m, 6H, CH×12), 6.82, 7.37 (d, d, J = 9.0, 9.0, 2H, 2H, C_6H_4), 7.33 (s, 1H, NHCO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 14.8, 20.6, 23.4, 25.6, 25.7, 37.2, 63.7, 114.7, 121.8, 127.0, 128.0, 128.1, 128.1, 128.3, 128.3, 128.4,

128.6, 129.6, 130.9, 155.8, 170.6; HRMS (ESI-TOF): Calcd for $C_{30}H_{41}NO_2Na$ $(M+Na)^+$: 470.3030, found: 470.3023; IR (KBr, ν_{max}/cm^{-1}) = 3296 (NH), 1655 (CON).

5. Typical Procedure for amidation of lauric acid 7a with 4-aminophenol 2m

To a colorless solution of lauric acid **7a** (100 mg, 0.50 mmol) in MeCN (10 mL) were added at 0 ℃ Et_3N (77 μL, 0.55 mmol, 1.1 equiv) and $ClCO_2Et$ (53 μL, 0.55 mmol, 1.1 equiv). After stirring for 30 min at 0 ℃, a solution of 4-ethoxyaniline **2m** (75 mg, 0.55 mmol, 1.1 equiv) in H_2O (0.75 mL) was added at 0 ℃ to the colorless suspension. The mixture was stirred for 24 h at 0 ℃ and concentrated in vacuo. To the residue was added a 1.0 M aqueous HCl to pH 2. The resulted suspension was extracted with EtOAc (50 mL), washed with brine (10 mL), and 1.0 M aqueous $NaHCO_3$ (5ml), and dried over $MgSO_4$. The crude product was purified by chromatography on silica gel with a 2:1 mixture of hexane and EtOAc to afford 127 mg (87% yield) of *N*-(4-hydroxyphenyl)lauramide **9am**.

5.1. *N*-(4-hydroxyphenyl)lauramide 9am

Yield: 127 mg (87%); colorless powder; mp: 130-131 ℃; ^{1}H NMR (400 MHz, DMSO-d^6): δ = 0.85 (t, *J* = 6.8, 3H, CH_3(CH_2)$_{10}$), 1.24-1.27 (m, 16H, CH_3(CH_2)$_8$), 1.53-1.57 (m, 2H, C$H_2$$CH_2$CO), 2.22 (t, *J* =7.4, 2H, CH_2CO), 6.66, 7.34 (d, d, *J* = 8.9, 8.8, 2H, 2H, C_6H_4), 9.10 (s, 1H, NHCO), 9.55 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 13.9, 22.0, 25.2, 28.6, 28.6, 28.7, 28.4, 28.9, 28.9, 31.2, 36.2, 114.9, 120.8, 131.0, 153.0, 170.4; HRMS (ESI-TOF): Calcd for $C_{18}H_{29}NO_2Na$ $(M+Na)^+$: 314.2091, found: 314.2099; IR (KBr, ν_{max}/cm^{-1}) = 3313 (NH), 1653 (CON).

5.2. *N*-(4-hydroxyphenyl)palmitamide 9bm

Yield: 132 mg (76%); colorless powder; mp: 133-134 ℃; ^{1}H NMR (400 MHz, DMSO-d^6): δ = 0.85 (t, *J* = 7.0, 3H, CH_3(CH_2)$_{14}$), 1.24-1.27 (m, 24H, CH_3(CH_2)$_{12}$), 1.53-1.57 (m, 2H, C$H_2$$CH_2$CO), 2.22 (t, *J*= 7.4, 2H, CH_2CO), 6.66, 7.34 (d, d, *J* = 8.9, 8.9, 2H, 2H, C_6H_4), 9.10 (s, 1H, NHCO), 9.55 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 13.8, 22.0, 25.2, 28.6, 28.7, 28.8, 28.9, 28.9, 31.2, 114, 9, 120.8, 130.9, 153.0, 170.5; HRMS (ESI-TOF): Calcd for $C_{22}H_{37}NO_2Na$ $(M+Na)^+$: 370.2717, found: 370.2760; IR (KBr, ν_{max}/cm^{-1}) = 3315 (NH), 1653 (CON).

5.3. *N*-(4-hydroxyphenyl)oleamide 9cm

Yield: 147 mg (79%); colorless powder; mp: 99-100 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9, 3H, CH_3(CH_2)$_7$), 1.27-1.32 (m, 20H, CH_3(CH_2)$_6$, (CH_2)$_4$$CH_2CH_2$CO), 1.68-175 (m, 2H, C$H_2$$CH_2$CO),

2.00-2.02 (m, 4H, C*H*$_2$CH×2), 2.33 (t, *J* = 7.6, 2H, CH$_2$CO), 5.33-5.36 (m, 2H, CH×2), 5.50 (brs, 1H, NHCO), 6.76, 7.29 (d, d, 2H, 2H, *J* = 8.8, 8.7, C$_6$H$_4$), 7.06 (brs, 1H, OH); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 14.1, 22.7, 25.7, 27.2, 27.3, 29.2, 29.3, 29.3, 29.3, 29.5, 29.7, 29.8, 31.9, 37.6, 115.8, 122.6, 129.8, 130.0, 130,4, 153.1, 171.8; HRMS (ESI-TOF): Calcd for C$_{24}$H$_{39}$NO$_2$Na (M+Na)$^+$: 396.2873, found: 396.2899; IR (KBr, ν_{max}/cm^{-1}) = 3278 (NH), 1649 (CON).

5.4. (9*Z*,12*Z*)-*N*-(4-hydroxyphenyl)linoleamide 9dm

Yield: 174 mg (94%); colorless powder; mp: 86-87 °C; ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 0.85 (t, *J* = 6.2, 3H, C*H*$_3$(CH$_2$)$_4$), 1.26-1.33 (m, 14H, CH$_3$(C*H*$_2$)$_3$, (C*H*$_2$)$_4$CH$_2$CH$_2$CO), 1.53-1.55 (m, 2H, C*H*$_2$CH$_2$CO), 1.99-2.02 (m, 4H, CH$_2$C*H*$_2$CH×2), 2.22 (t, *J* = 7.4, 2H, CH$_2$CO), 2.72-2.75 (m, 2H, CHC*H*$_2$CH), 5.24-5.38 (m, 4H, CH×4), 6.66, 7.34 (d, d, *J* = 8.7, 8.7, 2H, 2H, C$_6$H$_4$), 9.10 (s, 1H, NHCO), 9.55 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 13.8, 21.9, 25.1, 25.2, 26.5, 26.5, 28.5, 28.6, 28.6, 28.9, 30.8, 36.2, 114.9, 120.8, 127.7, 127.7, 129.6, 129.7, 130.9, 153.0, 170.4; HRMS (ESI-TOF): Calcd for C$_{24}$H$_{37}$NO$_2$Na (M+Na)$^+$: 394.2717, found: 394.2704; IR (KBr, ν_{max}/cm^{-1}) = 3319 (NH), 1655 (CON).

5.5. (9*Z*,12*Z*,15*Z*)-*N*-(4-hydroxyphenyl)linolenamide 9em

Yield: 152 mg (82%); colorless powder; mp: 81-82 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.97 (t, *J* = 7.5, 3H, C*H*$_3$CH$_2$CH), 1.26-1.32 (m, 8H, (C*H*$_2$)$_4$CH$_2$CH$_2$CO), 1.66-1.74 (m, 2H, C*H*$_2$CH$_2$CO), 2.02-2.11 (m, 4H, CH$_3$C*H*$_2$CH, CH$_2$C*H*$_2$CH), 2.32 (t, *J* = 7.6, 2H, CH$_2$CO), 2.77-2.82 (m, 4H, CHC*H*$_2$CH×2), 5.32-5.39 (m, 6H, CH×6), 6.73, 7.23 (d, d, *J* = 8.8, 8.8, 2H, 2H, C$_6$H$_4$), 6.83 (s, 1H, NHCO), 7.30 (s, 1H, OH); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 20.6, 22.6, 22.7, 25.5, 25.6, 25.8, 27.2, 29.2, 29.3, 29.3, 29.3, 29.6, 29.6, 29.8, 31.5, 31.9, 37.4, 116.2, 127.1, 127.7, 127.9, 128.0, 128.3, 128.3, 129.6, 130.1, 130.3, 130.3, 132.0, 153.7, 172.6; HRMS (ESI-TOF): Calcd for C$_{24}$H$_{35}$NO$_2$Na (M+Na)$^+$: 392.2560, found: 392.2568; IR (KBr, ν_{max}/cm^{-1}) = 3319 (NH), 1655 (CON).

5.6. (*E*)-*N*-(4-hydroxyphenyl)elaidamide 9fm

Yield: 181 mg (97%); colorless powder; mp: 117-119 °C; ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 0.85 (t, *J* = 6.9, 3H, C*H*$_3$(CH$_2$)$_7$), 1.23-1.27 (m, 20H, CH$_3$(C*H*$_2$)$_6$, (C*H*$_2$)$_4$ CH$_2$CH$_2$CO), 1.53-1.57 (m, 2H, C*H*$_2$CH$_2$CO), 1.93-1.94 (m, 4H, C*H*$_2$CH×2), 2.22 (t, *J* = 7.4, 2H, CH$_2$CO), 5.35-5.37 (m, 2H, CH×2), 6.66, 7.34 (d, d, *J* = 8.9, 8.9, 2H, 2H, C$_6$H$_4$), 9.10 (s, 1H, NHCO), 9.55 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 13.9, 22.0, 25.1, 28.3, 28.4, 28.6, 28.6, 28.7, 28.9, 31.2, 31.9, 114.6, 120.7, 130.0, 130.0, 131.0, 153.0, 170.4;

HRMS (ESI-TOF): Calcd for $C_{24}H_{39}NO_2Na$ $(M+Na)^+$: 396.2873, found: 396.2899; IR (KBr, ν_{max}/cm^{-1}) = 3332 (NH), 1655 (CON).

5.7. (5*Z*,8*Z*,11*Z*,14*Z*)-*N*-(4-hydroxyphenyl)arachidonamide 9gm

Yield: 124 mg (90%); colorless powder; mp: 51-52 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9, 3H, C*H*$_3$(CH$_2$)$_4$), 1.25-1.39 (m, 6H, CH$_3$(C*H*$_2$)$_3$), 1.77-1.85 (m, 2H, C*H*$_2$CH$_2$CO), 2.02-2.08 (m, 2H, CH$_3$(CH$_2$)$_3$C*H*$_2$), 2.14-2.18 (m, 2H, C*H*$_2$(CH$_2$)$_2$CO), 2.34 (t, *J* = 7.6, 2H, CH$_2$CO), 2.79-2.84 (m, 6H, CHC*H*$_2$CH×3), 5.30-5.44 (m, 8H, CH×8), 6.17 (brs, 1H, NHCO), 6.74, 7.25 (d, d, 2H, 2H, *J* = 8.8, 7.4, C_6H_4), 7.15 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.6, 25.4, 25.7, 26.6, 27.2, 29.3, 31.5, 36.8, 115.8, 122.6, 127.5, 127.9, 128.1, 128.3, 128.6, 129.0, 130.2, 130.6, 153.2, 171.6; HRMS (ESI-TOF): Calcd for $C_{26}H_{37}NO_2Na$ $(M+Na)^+$: 418.2717, found: 418.2767; IR (KBr, ν_{max}/cm^{-1}) = 3315 (NH), 1653 (CON).

5.8. (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-*N*-(4-hydroxyphenyl)docosahexaen-amide 9hm

Yield: 36 mg (78%); brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.5, 3H, C*H*$_3$CH$_2$CH), 2.03-2.09 (m, 2H, CH$_3$C*H*$_2$CH), 2.36-2.40 (m, 2H, C*H*$_2$CH$_2$CO), 2.49 (t, *J* = 7.1, 2H, CH$_2$CO), 2.79-2.85 (m, 10H, CHC*H*$_2$CH×5), 5.32-5.43 (m, 13H, CH×12, NHCO), 6.71, 7.19 (d, d, *J* = 8.6, 8.2, 2H, 2H, C_6H_4), 7.45 (brs, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 20.6, 23.4, 25.6, 25.7, 37.1, 115.6, 123.0, 127.0, 127.9, 128.0, 128.1, 128.3, 128.3, 128.4, 128.6, 129.7, 129.8, 132.1, 153.7, 171.6; HRMS (ESI-TOF): Calcd for $C_{28}H_{37}NO_2Na$ $(M+Na)^+$: 442.2717, found: 442.2695; IR (KBr, ν_{max}/cm^{-1}) = 3302 (NH), 1657 (CON).

6. Typical procedure of the primary amidation of Cbz-L-Phg-OH 10 with NH_4Cl

To a colorless solution of 142 mg (0.50 mmol, 1 equiv) of Cbz-L-Phg-OH **10** in 10 mL of anhydrous THF were added dropwise at -15 °C 209 μL (1.5 mmol, 3.0 equiv) of a precooled Et_3N and 67 μL (0.7 mmol, 1.4 equiv) of a precooled $ClCO_2Et$. After stirring for 10 min at -15 °C, 0.75 mL (0.75 mmol, 1.5 equiv) of a precooled 1.0M aqueous solution of NH_4Cl was added at -15 °C to the colorless suspension. The mixture was stirred for 24 h at -15 °C and 15mL of H_2O was added dropwise at -15 °C to the resulted mixture. The suspension was extracted with 100 mL of EtOAc, washed with 10 mL of brine, and dried over anhydrous $MgSO_4$. The crude product was chromatographed on silica gel with a 1:1 mixture of hexane and EtOAc to afford 118 mg (83% yield) of Cbz-$_L$-Phg-NH_2 **11**.

6.1. Cbz-L-Phg-NH_2 11

Yield: 118 mg (83%); colorless powder; 99% ee; mp: 173-174 °C; $[\alpha]_D^{26}$ = +85.3 (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 5.03 (s, 2H, OC*H*$_2$C$_6$H$_5$), 5.17 (d, *J* = 8.5, 1H, C*H*C$_6$H$_5$), 7.15 (s, 1H,

NH_A), 7.26-7.44 (m, 10H, C_6H_5×2), 7.60 (s, 1H, NH_B), 7.80 (d, J = 8.5, 1H, $NHCO_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 58.1, 65.5, 127.2, 127.5, 127.6, 127.8, 128.2, 128.3, 137.0, 138.8, 155.6, 171.7; HRMS (ESI-TOF): Calcd for $C_{16}H_{16}N_2O_3Na$ $(M+Na)^+$: 307.1053, Found: 307.1031; IR (KBr, ν_{max}/cm^{-1}) = 3420 (NH), 3332 (NH), 3275 (NH), 3203 (NH), 1658 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 80/20): T_r 26 min.

6.2. Cbz-D-Phg-NH_2 11D

Yield: 109 mg (77%); colorless powder; 99% ee; $[\alpha]_D^{26}$ = -80.4 (*c* 1.01, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel AD: hexane/2-propanol = 80/20): T_r 18 min.

7. Typical procedure of the primary amidation of Cbz-L-Phe-L-Phe-OH 14aLaL with NH_4Cl

To a colorless solution of 134 mg (0.30 mmol) of Cbz-L-Phe-L-Phe-OH (**14aLaL**) in 6 mL of anhydrous THF were added dropwise at -15 °C 126 μL (0.9 mmol, 3.0 equiv) of a precooled Et_3N and 40 μL (0.42 mmol, 1.4 equiv) of a precooled $ClCO_2Et$. After stirring for 10 min at -15 °C, 0.45 mL (0.45mmol, 1.5 equiv) of a precooled 1.0M aqueous solution of NH_4Cl was added dropwise at -15 °C to the colorless suspension. The mixture was stirred for 24 h at -15 °C and 15mL of H_2O was added dropwise at -15 °C to the resulted mixture. The suspension was extracted with 100 mL of EtOAc, washed with 10 mL of brine, and dried over anhydrous $MgSO_4$. The crude product was chromatographed on silica gel with a 1:1 mixture of hexane and EtOAc to afford 96 mg (85% yield) of Cbz-L-Phe-L-Phe-NH_2 **15aLaL**.

7.1. Cbz-L-Phe-L-Phe-NH_2 15aLaL

Yield: 112 mg (84%); colorless powder; >99% de; mp: 234-235 °C; $[\alpha]_D^{27}$ = -4.1 (*c* 0.99, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 2.67 (dd, J = 10.7, 13.8, 1H, CH_AC$_6$H$_5$), 2.84 (dd, J = 8.7, 13.7, 1H, CH_A'C$_6$H$_5$), 2.92 (dd, J = 3.9, 13.7, 1H, CH_BC$_6$H$_5$), 3.01 (dd, J = 5.1, 13.8, 1H, CH_B'C$_6$H$_5$), 4.19-4.25 (m, 1H, CHCO), 4.43-4.49 (m, 1H, CHNHCO$_2$), 4.93 (s, 2H, OCH_2C$_6$H$_5$), 7.13 (brs, 1H, NH_A), 7.16-7.35 (m, 15H, C_6H_5×3), 7.41 (brs, 1H, NH_B), 7.51 (d, J = 8.7, 1H, NHCO), 8.05 (d, J = 8.2, 1H, $NHCO_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 37.4, 37.7, 53.7, 56.2, 65.2, 126.3, 127.4, 127.7, 128.0, 128.3, 129.2, 129.3, 137.0, 137.7, 138.1, 155.7, 171.2, 172.6; HRMS (ESI-TOF): Calcd for $C_{26}H_{25}N_3O_4Na$ $(M+Na)^+$: 468.1894, Found: 468.1841; IR (KBr, ν_{max}/cm^{-1}) = 3375 (NH), 3319 (NH), 3213 (NH), 1695 (CON), 1643 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/EtOH/Et_2NH = 95/5/0.05): T_r 35 min.

7.2. Cbz-L-Phe-D-Phe-NH_2 15aLaD

Yield: 120 mg (90%); colorless powder; >99% de; mp: 201-203 ^{o}C; $[\alpha]_D^{27}$ = +17.4 (*c* 0.99, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 2.36 (dd, *J* = 10.7, 13.6, 1H, CH_AC$_6$H$_5$), 2.54 (dd, *J* = 3.5, 13.6, 1H, CH_A·C$_6$H$_5$), 2.68 (dd, *J* = 10.1, 13.6, 1H, CH_BC$_6$H$_5$), 2.96 (dd, *J* = 4.3, 13.6, 1H, CH_B·C$_6$H$_5$), 4.12-4.18 (m, 1H, CHCO), 4.39-4.45 (m, 1H, C*H*NHCO$_2$), 4.83 (s, 2H, OCH_2C$_6$H$_5$), 7.07-7.23 (m, 16H, NH$_A$, C$_6$H$_5$×3), 7.36 (d, *J* = 8.5, 1H, NHCO), 7.39 (brs, 1H, NH$_B$), 8.28 (d, *J* = 8.7, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 37.4, 37.8, 53.6, 56.2, 65.2, 126.2, 126.3, 127.5, 127.7, 128.0, 128.0, 128.3, 129.2, 129.3, 137.0, 137.9, 138.1, 155.9, 171.2, 173.0; HRMS (ESI-TOF): Calcd for $C_{26}H_{25}N_3O_4Na$ $(M+Na)^+$: 468.1894, Found: 468.1841; IR (KBr, ν_{max}/cm^{-1}) = 3427 (NH), 3292 (NH), 3201 (NH), 1693 (CON), 1637 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/EtOH/Et$_2$NH = 95/5/0.05): T_r 54 min.

7.3. Cbz-D-Phe-L-Phe-NH$_2$ 15aDaL

Yield: 123 mg (92%); colorless powder; >99% de; $[\alpha]_D^{27}$ = -25.7 (*c* 0.99, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/EtOH/Et$_2$NH = 95/5/0.05): T_r 41 min.

7.4. Cbz-D-Phe-D-Phe-NH$_2$ 15aDaD

Yield: 119 mg (89%); colorless powder; >99% de; $[\alpha]_D^{26}$ = +11.1 (*c* 1.01, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/EtOH/Et$_2$NH = 95/5/0.05): T_r 50 min.

8. Typical procedure of the primary amidation of Cbz-L-Phe-L-Phe-OH 14aLaL with NH$_4$Cl

To a colorless solution of 134 mg (0.30 mmol) of Cbz-L-Phe-L-Phe-OH (**14aLaL**) in 6 mL of anhydrous THF were added dropwise at -15 ^{o}C 126 μL (0.9 mmol, 3.0 equiv) of a precooled Et$_3$N and 40 μL (0.42 mmol, 1.4 equiv) of a precooled ClCO$_2$Et. After stirring for 10 min at -15 ^{o}C, 0.45 mL (0.45mmol, 1.5 equiv) of a precooled 1.0M aqueous solution of NH$_4$Cl was added dropwise at -15 ^{o}C to the colorless suspension. The mixture was stirred for 24 h at -15 ^{o}C and 15mL of H$_2$O was added dropwise at -15 ^{o}C to the resulted mixture. The suspension was extracted with 100 mL of EtOAc, washed with 10 mL of brine, and dried over anhydrous MgSO$_4$. The crude product was chromatographed on silica gel with a 1:1 mixture of hexane and EtOAc to afford 96 mg (85% yield) of Cbz-L-Phe-L-Phe-NH$_2$ **15aLaL**.

8.1. Cbz-L-Phe-L-Phe-NH$_2$ 15aLaL

Yield: 112 mg (84%); colorless powder; >99% de; mp: 234-235 ^{o}C; $[\alpha]_D^{27}$ = -4.1 (*c* 0.99, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 2.67 (dd, *J* = 10.7, 13.8, 1H, CH_AC$_6$H$_5$), 2.84 (dd, *J* = 8.7, 13.7, 1H, CH_A·C$_6$H$_5$),

2.92 (dd, *J* = 3.9, 13.7, 1H, C*H*$_B$C$_6$H$_5$), 3.01 (dd, *J* = 5.1, 13.8, 1H, C*H*$_B$·C$_6$H$_5$), 4.19-4.25 (m, 1H, CHCO), 4.43-4.49 (m, 1H, C*H*NHCO$_2$), 4.93 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.13 (brs, 1H, NH$_A$), 7.16-7.35 (m, 15H, C$_6$H$_5$×3), 7.41 (brs, 1H, NH$_B$), 7.51 (d, *J* = 8.7, 1H, NHCO), 8.05 (d, *J* = 8.2, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 37.4, 37.7, 53.7, 56.2, 65.2, 126.3, 127.4, 127.7, 128.0, 128.3, 129.2, 129.3, 137.0, 137.7, 138.1, 155.7, 171.2, 172.6; HRMS (ESI-TOF): Calcd for $C_{26}H_{25}N_3O_4Na$ $(M+Na)^+$: 468.1894, Found: 468.1841; IR (KBr, ν_{max}/cm^{-1}) = 3375 (NH), 3319 (NH), 3213 (NH), 1695 (CON), 1643 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/EtOH/Et$_2$NH = 95/5/0.05): T_r 35 min.

8.2. Cbz-L-Phe-D-Phe-NH$_2$ 15aLaD

Yield: 120 mg (90%); colorless powder; >99% de; mp: 201-203 ^{o}C; $[\alpha]_D^{27}$ = +17.4 (*c* 0.99, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 2.36 (dd, *J* = 10.7, 13.6, 1H, C*H*$_A$C$_6$H$_5$), 2.54 (dd, *J* = 3.5, 13.6, 1H, C*H*$_A$·C$_6$H$_5$), 2.68 (dd, *J* = 10.1, 13.6, 1H, C*H*$_B$C$_6$H$_5$), 2.96 (dd, *J* = 4.3, 13.6, 1H, C*H*$_B$·C$_6$H$_5$), 4.12-4.18 (m, 1H, CHCO), 4.39-4.45 (m, 1H, C*H*NHCO$_2$), 4.83 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.07-7.23 (m, 16H, NH$_A$, C$_6$H$_5$×3), 7.36 (d, *J* = 8.5, 1H, NHCO), 7.39 (brs, 1H, NH$_B$), 8.28 (d, *J* = 8.7, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 37.4, 37.8, 53.6, 56.2, 65.2, 126.2, 126.3, 127.5, 127.7, 128.0, 128.0, 128.3, 129.2, 129.3, 137.0, 137.9, 138.1, 155.9, 171.2, 173.0; HRMS (ESI-TOF): Calcd for $C_{26}H_{25}N_3O_4Na$ $(M+Na)^+$: 468.1894, Found: 468.1841; IR (KBr, ν_{max}/cm^{-1}) = 3427 (NH), 3292 (NH), 3201 (NH), 1693 (CON), 1637 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/EtOH/Et$_2$NH = 95/5/0.05): T_r 54 min.

8.3. Boc-L-Phe-L-Phe-NH$_2$ 15'aLaL

Yield: 105 mg (85%); colorless powder; 81% de; mp: 200-201 ^{o}C; $[\alpha]_D^{26}$ = -4.2 (*c* 0.98, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 1.28 (s, 9H, (CH$_3$)$_3$C), 2.65 (dd, *J* = 10.4, 13.7, 1H, C*H*$_A$C$_6$H$_5$), 2.82-2.87 (m, 2H, C*H*$_A$·C$_6$H$_5$, C*H*$_B$C$_6$H$_5$), 3.01 (dd, *J* = 5.0, 13.7, 1H, C*H*$_B$·C$_6$H$_5$), 4.06-4.11 (m, 1H, CHCO), 4.43-4.48 (m, 1H, C*H*NHCO$_2$), 6.95 (d, *J* = 8.5, 1H, NHCO), 7.11 (brs, 1H, NH$_A$), 7.15-7.26 (m, 10H, C$_6$H$_5$×2), 7.38 (brs, 1H, NH$_B$), 7.88 (d, *J* = 8.2, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 28.1, 37.4, 37.7, 53.5, 56.0, 78.2, 126.1, 126.2, 128.0, 128.0, 129.1, 129.3, 137.7, 138.1, 155.1, 171.2, 172.6; HRMS (ESI-TOF): Calcd for $C_{23}H_{29}N_3O_4Na$ $(M+Na)^+$: 434.2050, Found: 434.2096; IR (KBr, ν_{max}/cm^{-1}) = 3381 (NH), 3336 (NH), 3309 (NH), 3213 (NH), 1687 (CON), 1653 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 80/20): T_r 8 min.

8.4. Boc-L-Phe-D-Phe-NH$_2$ 15'aLaD

Yield: 116 mg (94%); colorless powder; >99% de; mp: 185-186 ^{o}C; $[\alpha]_D^{26}$ = +24.3 (*c* 0.99, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 1.29 (s, 9H, $(CH_3)_3C$), 2.64 (dd, *J* = 10.2, 13.7, 1H, C*H*$_A$C$_6$H$_5$), 2.82-2.87 (m, 2H, C*H*$_A$·C$_6$H$_5$, C*H*$_B$C$_6$H$_5$), 3.01 (dd, *J* = 5.0, 13.7, 1H, C*H*$_B$·C$_6$H$_5$), 4.05-4.11 (m, 1H, CHCO), 4.43-4.48 (m, 1H, C*H*NHCO$_2$), 6.97 (d, *J* = 8.4, 1H, NHCO), 7.13 (brs, 1H, NH$_A$), 7.16-7.27 (m, 10H, C$_6$H$_5$×2), 7.40 (brs, 1H, NH$_B$), 7.89 (d, *J* = 8.2, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 28.1, 37.2, 37.6, 53.7, 56.0, 78.1, 126.1, 126.3, 127.9, 128.0, 129.2, 129.2, 138.0, 138.1, 155.4, 171.4, 172.9; HRMS (ESI-TOF): Calcd for $C_{23}H_{29}N_3O_4Na$ $(M+Na)^+$: 434.2050, Found: 434.2096; IR (KBr, ν_{max}/cm^{-1}) = 3381 (NH), 3344 (NH), 3311 (NH), 3209 (NH), 1683 (CON), 1654 (CON), 1644 (CON). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 80/20): T_r 9 min.

8.5. Fmoc-L-Phe-L-Phe-NH$_2$ 15''aLaL

Yield: 144 mg (90%); colorless powder; 96% de; mp: 231-233 ^{o}C; $[\alpha]_D^{26}$ = -7.1 (*c* 0.98, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 2.71 (dd, *J* = 10.6, 13.6, 1H, C*H*$_A$C$_6$H$_5$), 2.84 (dd, *J* = 8.6, 13.6, 1H, C*H*$_A$·C$_6$H$_5$), 2.93 (dd, *J* = 3.8, 13.6, 1H, C*H*$_B$C$_6$H$_5$), 3.00 (dd, *J* = 5.0, 13.6, 1H, C*H*$_B$·C$_6$H$_5$), 4.08-4.24 (m, 4H, CHCO, CHCH$_2$O), 4.46-4.49 (m, 1H, C*H*NHCO$_2$), 7.16-7.89 (m, 21H, C$_6$H$_5$×2, fluorenyl H, NHCO, NH$_2$), 8.05 (d, *J* = 8.2, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 37.4, 37.7, 46.5, 53.6, 56.2, 65.7, 120.1, 125.2, 125.3, 126.2, 127.1, 127.6, 128.0, 129.2, 129.2, 137.7, 138.1, 140.6, 143.7, 143.7, 155.7, 171.2, 172.6; HRMS (ESI-TOF): Calcd for $C_{33}H_{31}N_3O_4Na$ $(M+Na)^+$: 556.2207, Found: 556.2179; IR (KBr, ν_{max}/cm^{-1}) = 3367 (NH), 3294 (NH), 3197 (NH), 1695 (CON), 1670 (CON), 1652 (CON).

8.6. Fmoc-L-Phe-D-Phe-NH$_2$ 15''aLaD

Yield: 152 mg (95%); colorless powder; >99% de; mp: 219-221 ^{o}C; $[\alpha]_D^{27}$ = +12.9 (*c* 0.98, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 2.53 (dd, J = 10.7, 13.6, 1H, C*H*$_A$C$_6$H$_5$), 2.63 (dd, *J* = 3.4, 13.5, 1H, C*H*$_A$·C$_6$H$_5$), 2.76 (dd, *J* = 10.2, 13.6, 1H, C*H*$_B$C$_6$H$_5$), 3.04 (dd, *J* = 4.3, 13.5, 1H, C*H*$_B$·C$_6$H$_5$), 4.07-4.25 (m, 4H, CHCO, CHCH$_2$O), 4.49-4.53 (m, 1H, C*H*NHCO$_2$), 7.15-7.87 (m, 21H, C$_6$H$_5$×2, fluorenyl H, NHCO, NH$_2$), 8.38 (d, *J* = 8.2, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 37.4, 37.9, 46.5, 53.6, 56.1, 65.7, 120.1, 125.3, 125.3, 126.2, 126.3, 127.0, 127.6, 128.0, 129.2, 129.3, 137.9, 138.1, 140.7, 143.7, 143.8, 155.8, 171.2, 172.9; HRMS (ESI-TOF): Calcd for $C_{33}H_{31}N_3O_4Na$ $(M+Na)^+$: 556.2207, Found: 556.2179; IR (KBr, ν_{max}/cm^{-1}) = 3284 (NH), 3201 (NH), 1695 (CON), 1647 (CON).

8.7. Cbz-L-Phe-L-Ala-NH$_2$ 15aLbL

Yield: 99 mg (89%); colorless powder; 84% de; mp: 211-212 ^{o}C; $[\alpha]_D^{27}$ = +19.9 (*c* 1.02, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 1.22 (d, *J* = 7.1, 3H, C*H*$_3$CH), 2.71 (dd, *J* = 10.9, 13.7, 1H, C*H*$_A$C$_6$H$_5$), 3.03 (dd, *J* = 3.7, 13.7, 1H, C*H*$_B$C$_6$H$_5$), 4.18-4.29 (m, 2H, CHCO, C*H*NHCO$_2$), 4.93 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.04 (brs, 1H, NH$_A$), 7.20-7.35 (m, 11H, NH$_B$, C$_6$H$_5$×2), 7.54 (d, *J* = 8.6, 1H, NHCO), 8.07 (d, *J* = 7.5, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 18.5, 37.3, 48.0, 56.1, 65.2, 126.2, 127.4, 127.7, 128.0, 128.3, 129.2, 137.0, 138.2, 155.9, 171.0, 174.0; HRMS (ESI-TOF): Calcd for $C_{20}H_{23}N_3O_4Na$ $(M+Na)^+$: 392.1581, Found: 392.1606; IR (KBr, v_{max}/cm^{-1}) = 3381 (NH), 3321 (NH), 3292 (NH), 1691 (CON), 1647 (CON).

8.8. Cbz-L-Phe-D-Ala-NH$_2$ 15aLbD

Yield: 84 mg (76%); colorless powder; >99% de; mp: 196-198 ^{o}C; $[\alpha]_D^{27}$ = -4.8 (*c* 0.99, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 1.12 (d, *J* = 7.1, 3H, C*H*$_3$CH), 2.75 (dd, *J* = 9.9, 13.5, 1H, C*H*$_A$C$_6$H$_5$), 2.94 (dd, *J* = 5.0, 13.5, 1H, C*H*$_B$C$_6$H$_5$), 4.17-4.28 (m, 2H, CHCO, C*H*NHCO$_2$), 4.95 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.08 (brs, 1H, NH$_A$), 7.19-7.35 (m, 11H, NH$_B$, C$_6$H$_5$×2), 7.58 (d, *J* = 8.1, 1H, NHCO), 8.15 (d, *J* = 7.7, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 18.2, 37.4, 47.8, 56.2, 65.3, 126.2, 127.5, 127.7, 128.0, 128.3, 129.3, 136.9, 137.9, 155.9, 170.9, 174.0; HRMS (ESI-TOF): Calcd for $C_{20}H_{23}N_3O_4Na$ $(M+Na)^+$: 392.1581, Found: 392.1606; IR (KBr, v_{max}/cm^{-1}) = 3429 (NH), 3290 (NH), 3209 (NH), 1691 (CON), 1670 (CON), 1633 (CON).

8.9. Cbz-L-Phe-L-Val-NH$_2$ 15aLcL

Yield: 111 mg (93%); colorless powder; >99% de; mp: 242-243 ^{o}C; $[\alpha]_D^{27}$ = +19.5 (*c* 1.01, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 0.84, 0.86 (d, d, *J* = 7.0, 8.0, 3H, 3H, (C*H*$_3$)$_2$CH), 1.92-2.01 (m, 1H, (CH$_3$)$_2$C*H*), 2.74 (dd, *J* = 11.0, 13.8, 1H, C*H*$_A$C$_6$H$_5$), 3.03 (dd, *J* = 3.8, 13.8, 1H, C*H*$_B$C$_6$H$_5$), 4.14-4.18 (m, 1H, CHCO), 4.29-4.35 (m, 1H, C*H*NHCO$_2$), 4.94 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.08 (brs, 1H, NH$_A$), 7.18-7.34 (m, 10H, C$_6$H$_5$×2), 7.38 (brs, 1H, NH$_B$), 7.57 (d, *J* = 8.6, 1H, NHCO), 7.78 (d, *J* = 9.0, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 17.8, 19.2, 30.7, 37.2, 56.2, 57.3, 65.2, 126.2, 127.4, 127.6, 128.0, 128.3, 129.2, 137.0, 138.1, 155.8, 171.3, 172.7; HRMS (ESI-TOF): Calcd for $C_{22}H_{27}N_3O_4Na$ $(M+Na)^+$: 420.1894, Found: 420.1867; IR (KBr, v_{max}/cm^{-1}) = 3400 (NH), 3294 (NH), 3207 (NH), 1685 (CON), 1678 (CON).

8.10. Cbz-L-Phe-D-Val-NH$_2$ 15aLcD

Yield: 107 mg (90%); colorless powder; >99% de; mp: 233-236 ^{o}C; $[\alpha]_D^{27}$ = -25.0 (*c* 1.01, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 0.76 (d, *J* = 6.8, 6H, (C*H*$_3$)$_2$CH), 1.91-1.99 (m, 1H, (CH$_3$)$_2$C*H*), 2.75 (dd, *J* = 10.5, 13.5, 1H, C*H*$_A$C$_6$H$_5$), 2.96 (dd, *J* = 4.6, 13.5, 1H, C*H*$_B$C$_6$H$_5$), 4.12-4.16 (m, 1H, CHCO), 4.38-4.41

(m, 1H, C*H*NHCO$_2$), 4.94 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.10 (brs, 1H, NH$_A$), 7.19-7.35 (m, 10H, C$_6$H$_5$×2), 7.40 (brs, 1H, NH$_B$), 7.58 (d, *J* = 8.4, 1H, NHCO), 8.01 (d, *J* = 9.1, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 17.7, 19.2, 30.4, 37.7, 56.2, 57.1, 65.2, 126.2, 127.5, 127.7, 128.0, 128.3, 129.3, 137.0, 137.9, 155.9, 171.4, 172.8; HRMS (ESI-TOF): Calcd for $C_{22}H_{27}N_3O_4Na$ $(M+Na)^+$: 420.1894, Found: 420.1867; IR (KBr, ν_{max}/cm^{-1}) = 3367 (NH), 3323 (NH), 3290 (NH), 3199 (NH), 1687 (CON), 1645 (CON).

8.11. Cbz-L-Phe-L-Met-NH$_2$ 15aLdL

Yield: 122 mg (94%); colorless powder; >99% de; mp: 214-216 ^{o}C; $[\alpha]_D^{27}$ = +9.4 (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 1.74-2.20 (m, 2H, C*H*$_2$CH$_2$S), 2.03 (s, 3H, CH$_3$S), 2.33-2.44 (m, 2H, CH$_2$C*H*$_2$S), 2.74 (dd, *J* = 10.5, 13.7, 1H, C*H*$_A$C$_6$H$_5$), 3.02 (dd, *J* = 4.1, 13.7, 1H, C*H*$_B$C$_6$H$_5$), 4.24-4.31 (m, 2H, CHCO, C*H*NHCO$_2$), 4.95 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.10 (brs, 1H, NH$_A$), 7.18-7.35 (m, 11H, NH$_B$, C$_6$H$_5$×2), 7.55 (d, *J* = 8.5, 1H, NHCO), 8.07 (d, *J* = 8.2, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 14.7, 29.5, 32.0, 37.2, 51.7, 56.2, 65.2, 126.3, 127.4, 127.7, 128.0, 128.3, 129.2, 137.0, 138.1, 155.9, 171.4, 172.9; HRMS (ESI-TOF): Calcd for $C_{22}H_{27}N_3O_4SNa$ $(M+Na)^+$: 452.1614, Found: 452.1674; IR (KBr, ν_{max}/cm^{-1}) = 3373 (NH), 3327 (NH), 3309 (NH), 3197 (NH), 1693 (CON), 1647 (CON), 1623 (CON).

8.12. Cbz-L-Phe-D-Met-NH$_2$ 15aLdD

Yield: 128 mg (99%); colorless powder; >99% de; mp: 191-193 ^{o}C; $[\alpha]_D^{27}$ = +27.7 (*c* 0.99, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 1.64-1.90 (m, 2H, C*H*$_2$CH$_2$S), 1.98 (s, 3H, CH$_3$S), 2.13-2.19 (m, 2H, CH$_2$C*H*$_2$S), 2.78 (dd, *J* = 9.1, 13.5, 1H, C*H*$_A$C$_6$H$_5$), 2.92 (dd, *J* = 6.4, 13.5, 1H, C*H*$_B$C$_6$H$_5$), 4.19-4.29 (m, 2H, CHCO, C*H*NHCO$_2$), 4.96 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.15 (brs, 1H, NH$_A$), 7.18-7.37 (m, 11H, NH$_B$, C$_6$H$_5$×2), 7.65 (d, *J* = 7.5, 1H, NHCO), 8.24 (d, *J* = 8.3, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 14.5, 29.5, 31.4, 37.4, 51.5, 56.4, 65.4, 126.3, 127.6, 127.8, 128.0, 128.3, 129.2, 136.9, 137.6, 160.0, 171.4, 173.1; HRMS (ESI-TOF): Calcd for $C_{22}H_{27}N_3O_4SNa$ $(M+Na)^+$: 452.1614, Found: 452.1674; IR (KBr, ν_{max}/cm^{-1}) = 3421 (NH), 3290 (NH), 3205 (NH), 1695 (CON), 1670 (CON), 1635 (CON).

8.13. Cbz-L-Phe-L-Phg-NH$_2$ 15aLeL

Yield: 120 mg (93%); colorless powder; >99% de; mp: 192-193 ^{o}C; $[\alpha]_D^{27}$ = +24.2 (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 2.74 (dd, *J* = 11.2, 13.6, 1H, C*H*$_A$C$_6$H$_5$), 3.03 (dd, *J* = 3.6, 13.6, 1H, C*H*$_B$C$_6$H$_5$), 4.36-4.42 (m, 1H, C*H*NHCO$_2$), 4.94 (s, 2H, OC*H*$_2$C$_6$H$_5$), 5.39 (d, *J* = 7.8, 1H, C*H*C$_6$H$_5$), 7.18-7.46 (m, 16H, NH$_A$, C$_6$H$_5$×3), 7.63 (d, *J* = 8.8, 1H, NHCO$_2$), 7.73 (brs, 1H, NH$_B$), 8.51 (d, *J* = 7.8, 1H, N*H*CHC$_6$H$_5$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 37.3, 56.0, 56.1, 65.2, 126.2, 126.8, 127.0, 127.4,

127.5, 127.7, 127.9, 128.0, 128.3, 128.3, 129.2, 137.0, 138.1, 138.9, 155.9, 171.0, 171.4; HRMS (ESI-TOF): Calcd for $C_{25}H_{25}N_3O_4Na$ $(M+Na)^+$: 454.1737, Found: 454.1748; IR (KBr, ν_{max}/cm^{-1}) = 3392 (NH), 3309 (NH), 3209 (NH), 1676 (CON), 1653 (CON), 1637 (CON).

8.14. Cbz-L-Phe-D-Phg-NH_2 15aLeD

Yield: 108 mg (84%); colorless powder; >99% de; mp: 243-244 ^oC; $[\alpha]_D^{27}$ = -30.0 (*c* 0.99, DMSO); ^1H NMR (400 MHz, DMSO-d^6): δ = 2.68 (dd, *J* = 10.8, 13.6, 1H, CH_AC$_6$H$_5$), 2.95 (dd, *J* = 4.4, 13.6, 1H, CH_BC$_6$H$_5$), 4.40-4.46 (m, 1H, C*H*NHCO$_2$), 4.95 (s, 2H, OCH_2C$_6$H$_5$), 5.42 (d, *J* = 8.0, 1H, C*H*C$_6$H$_5$), 7.15-7.37 (m, 16H, NH_A, C_6H_5×3), 7.57 (d, *J* = 8.6, 1H, NHCO$_2$), 7.74 (brs, 1H, NH_B), 8.68 (d, *J* = 8.0, 1H, N*H*CHC$_6$H$_5$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 37.4, 55.8, 56.0, 65.2, 126.2, 126.8, 127.3, 127.4, 127.7, 127.9, 128.2, 128.3, 128.3, 129.3, 137.0, 137.9, 139.1, 155.9, 171.0, 171.4; HRMS (ESI-TOF): Calcd for $C_{25}H_{25}N_3O_4Na$ $(M+Na)^+$: 454.1737, Found: 454.1748; IR (KBr, ν_{max}/cm^{-1}) = 3448 (NH), 3315 (NH), 3301 (NH), 1672 (CON), 1635 (CON).

8.15. Cbz-L-Phe-L-Ser-NH_2 15aLfL

Yield: 93 mg (80%); colorless powder; 70% de; mp: 168-169 ^oC; $[\alpha]_D^{27}$ = +17.2 (*c* 0.99, DMSO); ^1H NMR (400 MHz, DMSO-d^6): δ = 2.73 (dd, *J* = 11.0, 13.7, 1H, CH_AC$_6$H$_5$), 3.06 (dd, *J* = 3.7, 13.7, 1H, CH_BC$_6$H$_5$), 3.51-3.65 (m, 2H, CH_2OH), 4.20-4.24 (m, 1H, C*H*CH$_2$OH), 4.29-4.35 (m, 1H, C*H*NHCO$_2$), 4.83-4.98 (m, 3H, CH$_2$O*H*, OCH_2C$_6$H$_5$), 7.12 (brs, 1H, NH_A), 7.20-7.33 (m, 11H, NH_B, C_6H_5×2), 7.55 (d, *J* = 8.6, 1H, NHCO), 7.99 (d, *J* = 7.8, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 37.4, 55.0, 56.2, 61.7, 65.2, 126.2, 127.4, 127.7, 128.0, 128.3, 129.2, 137.0, 138.1, 155.9, 171.4, 171.8; HRMS (ESI-TOF): Calcd for $C_{20}H_{23}N_3O_5Na$ $(M+Na)^+$: 408.1530, Found: 408.1506; IR (KBr, ν_{max}/cm^{-1}) = 3481 (NH), 3334 (NH), 3298 (NH), 1732 (CON), 1639 (CON).

8.16. Cbz-L-Phe-D-Ser-NH_2 15aLfD

Yield: 103 mg (89%); colorless powder; 95% de; mp: 128-130 ^oC; $[\alpha]_D^{27}$ = -13.2 (*c* 0.99, DMSO); ^1H NMR (400 MHz, DMSO-d^6): δ = 2.75 (dd, *J* = 10.5, 13.7, 1H, CH_AC$_6$H$_5$), 3.01 (dd, *J* = 4.3, 13.7, 1H, CH_BC$_6$H$_5$), 3.47-3.60 (m, 2H, CH_2OH), 4.18-4.23 (m, 1H, C*H*CH$_2$OH), 4.30-4.36 (m, 1H, C*H*NHCO$_2$), 4.87-4.98 (m, 3H, CH$_2$O*H*, OCH_2C$_6$H$_5$), 7.16 (brs, 1H, NH_A), 7.19-7.35 (m, 11H, NH_B, C_6H_5×2), 7.56 (d, *J* = 8.3, 1H, NHCO), 8.06 (d, *J* = 8.2, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 37.3, 54.9, 56.2, 61.6, 65.3, 126.2, 127.5, 127.7, 128.0, 128.3, 129.3, 136.9, 138.0, 156.0, 171.4, 171.9; HRMS (ESI-TOF):

Calcd for $C_{20}H_{23}N_3O_5Na$ $(M+Na)^+$: 408.1530, Found: 408.1506; IR (KBr, ν_{max}/cm^{-1}) = 3404 (NH), 3375 (NH), 3246 (NH), 1703 (CON), 1633 (CON).

9. Typical procedure of the primary amidation of Cbz-L-Ala-L-Ala-OH 14cLbL with NH_4Cl

To a colorless solution of 88 mg (0.30 mmol) of Cbz-L-Ala-L-Ala-OH (**14cLbL**) in 6 mL of anhydrous THF were added dropwise at -15 °C 126 μL (0.9 mmol, 3.0 equiv) of a precooled Et_3N and 40 μL (0.42 mmol, 1.4 equiv) of a precooled $ClCO_2Et$. After stirring for 10 min at -15 °C, 0.45 mL (0.45mmol, 1.5 equiv) of a precooled 1.0M aqueous solution of NH_4Cl was added dropwise at -15 °C to the colorless suspension. The mixture was stirred for 24 h at -15 °C and 15mL of H_2O was added dropwise at -15 °C to the resulted mixture. The suspension was extracted with 100 mL of EtOAc, washed with 10 mL of brine, and dried over anhydrous $MgSO_4$. The crude product was chromatographed on silica gel with a 1:1 mixture of hexane and EtOAc to afford 96 mg (85% yield) of Cbz-L-Ala-L-Ala-NH_2 **15cLbL**.

9.1. Cbz-L-Ala-L-Ala-NH_2 15cLbL

Yield: 67 mg (76%); colorless powder; 86% de; mp: 216-217 °C; $[\alpha]_D^{28}$ = +4.4 (*c* 0.99, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 1.17-1.21 (m, 6H, CH_3CH×2), 4.00-4.07 (m, 1H, CHCO), 4.15-4.22 (m, 1H, C*H*NHCO$_2$), 5.02 (s, 2H, OCH_2C$_6$H$_5$), 7.00 (brs, 1H, NH_A), 7.28 (brs, 1H, NH_B), 7.29-7.39 (m, 5H, C_6H_5), 7.48 (d, *J* = 7.3, 1H, NHCO), 7.83 (d, *J* = 7.5, 1H, $NHCO_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 18.0, 18.4, 47.8, 50.1, 65.4, 127.7, 127.7, 128.3, 137.0, 155.7, 171.9, 174.0; HRMS (ESI-TOF): Calcd for $C_{14}H_{19}N_3O_4Na$ $(M+Na)^+$: 316.1268, Found: 316.1261; IR (KBr, ν_{max}/cm^{-1}) = 3392 (NH), 3307 (NH), 3276 (NH), 1684 (CON), 1645 (CON).

9.2. Cbz-L-Ala-D-Ala-NH_2 15cLbD

Yield: 76 mg (86%); colorless powder; 90% de; mp: 215-216 °C; $[\alpha]_D^{28}$ = +7.5 (*c* 1.02, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 1.18-1.20 (m, 6H, CH_3CH×2), 4.01-4.08 (m, 1H, CHCO), 4.14-4.21 (m, 1H, C*H*NHCO$_2$), 5.02 (s, 2H, OCH_2C$_6$H$_5$), 7.06 (brs, 1H, NH_A), 7.24 (brs, 1H, NH_B), 7.31-7.37 (m, 5H, C_6H_5), 7.51 (d, *J* = 7.0, 1H, NHCO), 8.01 (d, *J* = 7.6, 1H, $NHCO_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 17.9, 18.2, 47.9, 50.1, 65.4, 127.7, 127.8, 128.3, 155.8, 172.0, 174.1; HRMS (ESI-TOF): Calcd for $C_{14}H_{19}N_3O_4Na$ $(M+Na)^+$: 316.1268, Found: 316.1261; IR (KBr, ν_{max}/cm^{-1}) = 3390 (NH), 3311 (NH), 3282 (NH), 1674 (CON), 1637 (CON).

9.3. Cbz-L-Ala-L-Val-NH_2 15cLcL

Yield: 82 mg (85%); colorless powder; >99% de; mp: 258-259 ^{o}C; $[\alpha]_D^{28}$ = -3.1 (*c* 1.02, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 0.82, 0.84 (d, d, *J* = 6.9, 6.9, 3H, 3H, (C*H*$_3$)$_2$CH), 1.20 (d, *J* = 7.0, 3H, C*H*$_3$CH), 1.91-1.96 (m, 1H, C*H*(CH$_3$)$_2$), 4.10-4.14 (m, 2H, CHCO, C*H*NHCO$_2$), 5.02 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.05 (brs, 1H, NH$_A$), 7.40 (brs, 1H, NH$_B$), 7.35-7.58 (m, 7H, C$_6$H$_5$, NHCO, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 17.8, 18.0, 19.2, 30.7, 50.2, 57.1, 65.4, 127.7, 127.7, 128.3, 137.0, 155.6, 172.2, 172.7; HRMS (ESI-TOF): Calcd for $C_{16}H_{23}N_3O_4Na$ $(M+Na)^+$: 344.1581, Found: 344.1584; IR (KBr, ν_{max}/cm^{-1}) = 3392 (NH), 3309 (NH), 3280 (NH), 1684 (CON), 1645 (CON).

9.4. Cbz-L-Ala-D-Val-NH$_2$ 15cLcD

Yield: 95 mg (99%); colorless powder; >99% de; mp: 197-199 ^{o}C; $[\alpha]_D^{28}$ = +0.4 (*c* 1.02, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 0.79, 0.83 (d, d, *J* = 6.8, 6.8, 3H, 3H, (C*H*$_3$)$_2$CH), 1.20 (d, *J* = 7.1, 3H, C*H*$_3$CH), 1.96-2.00 (m, 1H, C*H*(CH$_3$)$_2$), 4.11-4.16 (m, 2H, CHCO, C*H*NHCO$_2$), 5.01 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.08 (brs, 1H, NH$_A$), 7.31-7.38 (m, 6H, NH$_B$, C$_6$H$_5$), 7.48 (d, *J* = 7.4, 1H, NHCO), 7.74 (d, *J* = 9.2, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 17.6, 18.4, 19.3, 30.5, 50.2, 57.0, 65.4, 127.7, 127.8, 128.4, 137.0, 155.7, 172.5, 172.8; HRMS (ESI-TOF): Calcd for $C_{16}H_{23}N_3O_4Na$ $(M+Na)^+$: 344.1581, Found: 344.1584; IR (KBr, ν_{max}/cm^{-1}) = 3319 (NH), 3276 (NH), 1685 (CON), 1645 (CON).

9.5. Cbz-L-Ala-L-Met-NH$_2$ 15cLdL

Yield: 90 mg (85%); colorless powder; >99% de; mp: 187-189 ^{o}C; $[\alpha]_D^{27}$ = +1.8 (*c* 1.01, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 1.20 (d, *J* = 7.2, 3H, C*H*$_3$CH), 1.76-1.97 (m, 2H, C*H*$_2$CH$_2$S), 2.02 (s, 3H, CH$_3$S), 2.38-2.45 (m, 2H, CH$_2$C*H*$_2$S), 4.03-4.06 (m, 1H, CHCO), 4.24-4.29 (m, 1H, C*H*NHCO$_2$), 5.02 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.09 (brs, 1H, NH$_A$), 7.32-7.39 (m, 6H, NH$_B$, C$_6$H$_5$), 7.51 (d, *J* = 7.2, 1H, NHCO), 7.89 (d, *J* = 8.1, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 14.6, 17.9, 29.5, 32.0, 50.2, 51.6, 65.4, 127.7, 127.8, 128.3, 137.0, 155.8, 172.4, 173.0; HRMS (ESI-TOF): Calcd for $C_{16}H_{23}N_3O_4SNa$ $(M+Na)^+$: 376.1301, Found: 376.1338; IR (KBr, ν_{max}/cm^{-1}) = 3313 (NH), 3294 (NH), 1684 (CON), 1674 (CON).

9.6. Cbz-L-Ala-D-Met-NH$_2$ 15cLdD

Yield: 88 mg (83%); colorless powder; 89% de; mp: 163-164 ^{o}C; $[\alpha]_D^{27}$ = +6.6 (*c* 1.01, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 1.20 (d, *J* = 7.1, 3H, C*H*$_3$CH), 1.74-1.97 (m, 2H, C*H*$_2$CH$_2$S), 2.02 (s, 3H, CH$_3$S), 2.36-2.42 (m, 2H, CH$_2$C*H*$_2$S), 4.03-4.07 (m, 1H, CHCO), 4.23-4.28 (m, 1H, C*H*NHCO$_2$), 5.02 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.14 (brs, 1H, NH$_A$), 7.30-7.39 (m, 6H, NH$_B$, C$_6$H$_5$), 7.53 (d, *J* = 6.8, 1H, NHCO), 8.07 (d, *J* = 8.2, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 14.6, 17.9, 29.6, 31.5, 50.5, 51.5, 65.4, 127.7,

172.8, 128.4, 136.9, 155.8, 172.5, 173.1; HRMS (ESI-TOF): Calcd for $C_{16}H_{23}N_3O_4SNa$ $(M+Na)^+$: 376.1301, Found: 376.1338; IR (KBr, ν_{max}/cm^{-1}) = 3282 (NH), 3197 (NH), 1689 (CON), 1653 (CON).

9.7. Cbz-L-Val-L-Ala-NH_2 15bLbL

Yield: 95 mg (99%); colorless powder; >99% de; mp: 237-238 ^oC; $[\alpha]_D^{26}$ = +27.2 (*c* 0.99, DMSO); ^1H NMR (400 MHz, DMSO-d^6): δ = 0.83, 0.86 (d, d, *J* = 6.8, 6.8, 3H, 3H, $(CH_3)_2CH$), 1.20 (d, *J* = 7.0, 3H, CH_3CH), 1.94-2.03 (m, 1H, $CH(CH_3)_2$), 3.85-3.89 (m, 1H, CHCO), 4.19-4.26 (m, 1H, $CHNHCO_2$), 5.03 (s, 2H, $OCH_2C_6H_5$), 7.00 (brs, 1H, NH_A), 7.30-7.37 (m, 7H, C_6H_5, NH_B, NHCO), 7.88 (d, *J* = 7.4, 1H, $NHCO_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 18.0, 18.5, 19.2, 30.3, 46.8, 60.1, 65.4, 127.6, 127.8, 128.3, 137.1, 156.2, 170.6, 174.0; HRMS (ESI-TOF): Calcd for $C_{16}H_{23}N_3O_4Na$ $(M+Na)^+$: 344.1581, Found: 344.1549; IR (KBr, ν_{max}/cm^{-1}) = 3421 (NH), 3304 (NH), 3207 (NH), 1684 (CON), 1635 (CON).

9.8. Cbz-L-Val-D-Ala-NH_2 15bLbD

Yield: 93 mg (97%); colorless powder; >99% de; mp: 232-234 ^oC; $[\alpha]_D^{27}$ = +11.2 (*c* 0.98, DMSO); ^1H NMR (400 MHz, DMSO-d^6): δ = 0.84, 0.86 (d, d, *J* = 6.7, 6.6, 3H, 3H, $(CH_3)_2CH$), 1.20 (d, *J* = 7.1, 3H, CH_3CH), 1.89-1.97 (m, 1H, $CH(CH_3)_2$), 3.81-3.85 (m, 1H, CHCO), 4.20-4.24 (m, 1H, $CHNHCO_2$), 5.03 (s, 2H, $OCH_2C_6H_5$), 7.06 (brs, 1H, NH_A), 7.26 (brs, 1H, NH_B), 7.31-7.41 (m, 6H, C_6H_5, NHCO), 8.11 (d, *J* = 7.7, 1H, $NHCO_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 18.3, 18.4, 19.1, 30.0, 47.8, 60.5, 65.5, 127.7, 127.8, 128.4, 137.0, 156.3, 170.9, 174.1; HRMS (ESI-TOF): Calcd for $C_{16}H_{23}N_3O_4Na$ $(M+Na)^+$: 344.1581, Found: 344.1584; IR (KBr, ν_{max}/cm^{-1}) = 3327 (NH), 3278 (NH), 1684 (CON), 1647 (CON).

9.9. Cbz-L-Val-L-Val-NH_2 15bLcL

Yield: 97 mg (93%); colorless powder; 92% de; mp: 252-253 ^oC; $[\alpha]_D^{27}$ = +10.3 (*c* 0.98, DMSO); ^1H NMR (400 MHz, DMSO-d^6): δ = 0.82-0.86 (m, 12H, $(CH_3)_2CH\times2$), 1.90-1.99 (m, 2H, $CH(CH_3)_2\times2$), 3.88-3.92 (m, 1H, CHCO), 4.11-4.15 (m, 1H, $CHNHCO_2$), 5.04 (s, 2H, $OCH_2C_6H_5$), 7.05 (brs, 1H, NH_A), 7.74 (brs, 1H, NH_B), 7.29-7.45 (m, 6H, C_6H_5, NHCO), 7.63 (d, *J* = 8.9, 1H, $NHCO_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 18.0, 18.2, 19.3, 30.1, 30.6, 57.2, 60.5, 65.4, 127.6, 127.7, 128.3, 137.1, 156.1, 171.0, 172.7; HRMS (ESI-TOF): Calcd for $C_{18}H_{27}N_3O_4Na$ $(M+Na)^+$: 372.1894, Found: 372.1863; IR (KBr, ν_{max}/cm^{-1}) = 3377 (NH), 3303 (NH), 1674 (CON), 1639 (CON).

9.10. Cbz-L-Val-D-Val-NH_2 15bLcD

Yield: 99 mg (94%); colorless powder; 72% de; mp: 255-256 ^{o}C; $[\alpha]_D^{27}$ = -12.2 (*c* 1.02, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 0.81-0.87 (m, 12H, (C*H*$_3$)$_2$CH×2), 1.92-2.05 (m, 2H, C*H*(CH$_3$)$_2$×2), 3.97-3.99 (m, 1H, CHCO), 4.11-4.14 (m, 1H, C*H*NHCO$_2$), 5.02 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.08 (brs, 1H, NH$_A$), 7.30-7.39 (m, 7H, C$_6$H$_5$, NH$_B$, NHCO), 7.87 (d, *J* = 8.9, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 17.7, 18.2, 19.3, 19.4, 30.0, 30.1, 57.3, 60.4, 65.4, 127.7, 127.8, 128.3, 137.0, 156.3, 171.4, 172.9; HRMS (ESI-TOF): Calcd for $C_{18}H_{27}N_3O_4Na$ $(M+Na)^+$: 372.1894, Found: 372.1863; IR (KBr, ν_{max}/cm^{-1}) = 3384 (NH), 3317 (NH), 3273 (NH), 1672 (CON), 1641 (CON).

9.11. Cbz-L-Val-L-Met-NH$_2$ 15bLdL

Yield: 113 mg (99%); colorless powder; >99% de; mp: 242-244 ^{o}C; $[\alpha]_D^{28}$ = +11.7 (*c* 1.02, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 0.83, 0.86 (d, d, *J* = 6.8, 6.8, 6H, (C*H*$_3$)$_2$CH), 1.76-2.00 (m, 3H, (CH$_3$)$_2$C*H*, C*H*$_2$CH$_2$S), 2.02 (s, 3H, CH$_3$S), 2.37-2.45 (m, 2H, CH$_2$C*H*$_2$S), 3.84-3.88 (m, 1H, CHCO), 4.27-4.33 (m, 1H, C*H*NHCO$_2$), 5.03 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.07 (brs, 1H, NH$_A$), 7.24-7.39 (m, 7H, NH$_B$, C$_6$H$_5$, NHCO), 7.90 (d, *J* = 7.9, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 14.6, 18.1, 19.2, 29.5, 30.0, 31.9, 51.5, 60.4, 65.4, 127.6, 127.7, 128.3, 137.0, 156.2, 171.0, 172.8; HRMS (ESI-TOF): Calcd for $C_{17}H_{25}N_3O_4SNa$ $(M+Na)^+$: 404.1614, Found: 404.1645; IR (KBr, ν_{max}/cm^{-1}) = 3313 (NH), 3282 (NH), 1674 (CON), 1637 (CON).

9.12. Cbz-L-Val-D-Met-NH$_2$ 15bLdD

Yield: 105 mg (92%); colorless powder; 89% de; mp: 225-227 ^{o}C; $[\alpha]_D^{27}$ = +33.2 (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 0.85, 0.86 (d, d, *J* = 6.5, 5.8, 6H, (C*H*$_3$)$_2$CH), 1.75-1.81 (m, 1H, (CH$_3$)$_2$C*H*), 1.90-1.98 (m, 2H, C*H*$_2$CH$_2$S), 2.01 (s, 3H, CH$_3$S), 2.38-2.50 (m, 2H, CH$_2$C*H*$_2$S), 3.79-3.83 (m, 1H, CHCO), 4.25-4.30 (m, 1H, C*H*NHCO$_2$), 5.02 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.12 (brs, 1H, NH$_A$), 7.26 (brs, 1H, NH$_B$), 7.24-7.37 (m, 5H, C$_6$H$_5$), 7.44 (d, *J* = 7.9, 1H, NHCO), 8.22 (d, *J* = 8.1, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 14.5, 18.5, 19.1, 29.7, 31.1, 51.4, 60.7, 65.5, 127.8, 127.8, 128.4, 136.9, 156.4, 171.5, 173.2; HRMS (ESI-TOF): Calcd for $C_{17}H_{25}N_3O_4SNa$ $(M+Na)^+$: 404.1614, Found: 404.1645; IR (KBr, ν_{max}/cm^{-1}) = 3402 (NH), 3323 (NH), 3275 (NH), 1672 (CON), 1645 (CON).

9.13. Cbz-L-Met-L-Ala-NH$_2$ 15dLbL

Yield: 103 mg (97%); colorless powder; 94% de; mp: 223-224 ^{o}C; $[\alpha]_D^{27}$ = +12.3 (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 1.21 (d, *J* = 7.0, 3H, C*H*$_3$CH), 1.76-1.91 (m, 2H, C*H*$_2$CH$_2$S), 2.03 (s, 3H, CH$_3$S), 2.45-2.51 (m, 2H, CH$_2$C*H*$_2$S), 4.06-4.12 (m, 1H, CHCO), 4.18-4.22 (m, 1H, C*H*NHCO$_2$), 5.03 (s,

2H, OCH_2C$_6$H$_5$), 7.02 (brs, 1H, NH$_A$), 7.25-7.39 (m, 6H, NH$_B$, C$_6$H$_5$), 7.54 (d, *J* = 10.0, 1H, NHCO), 7.93 (d, *J* = 7.4, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 14.6, 18.4, 29.6, 31.7, 47.9, 53.9, 65.4, 127.6, 127.8, 128.3, 137.0, 156.0, 170.9, 174.0; HRMS (ESI-TOF): Calcd for $C_{16}H_{23}N_3O_4SNa$ $(M+Na)^+$: 376.1301, Found: 376.1338; IR (KBr, ν_{max}/cm^{-1}) = 3392 (NH), 3317 (NH), 1672 (CON), 1637 (CON).

9.14. Cbz-L-Met-D-Ala-NH$_2$ 15dLbD

Yield: 103 mg (97%); colorless powder; 76% de; mp: 233-234 ^{o}C; $[\alpha]_D^{27}$ = +4.6 (*c* 1.02, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 1.20 (d, *J* = 7.1, 3H, C*H*$_3$CH), 1.75-1.91 (m, 2H, C*H*$_2$CH$_2$S), 2.02 (s, 3H, CH$_3$S), 2.37-2.45 (m, 2H, CH$_2$C*H*$_2$S), 4.10-4.11 (m, 1H, CHCO), 4.16-4.23 (m, 1H, C*H*NHCO$_2$), 5.03 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.08 (brs, 1H, NH$_A$), 7.27 (brs, 1H, NH$_B$), 7.25-7.39 (m, 5H, C$_6$H$_5$), 7.57 (d, *J* = 7.7, 1H, NHCO), 8.06 (d, *J* = 7.6, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 14.6, 18.3, 29.6, 31.4, 47.9, 54.0, 65.5, 127.7, 127.8, 128.4, 136.9, 156.1, 171.0, 174.0; HRMS (ESI-TOF): Calcd for $C_{16}H_{23}N_3O_4SNa$ $(M+Na)^+$: 376.1301, Found: 376.1338; IR (KBr, ν_{max}/cm^{-1}) = 3384 (NH), 3309 (NH), 1684 (CON), 1637 (CON).

9.15. Cbz-L-Met-L-Val-NH$_2$ 15dLcL

Yield: 98 mg (86%); colorless powder; >99% de; mp: 231-232 ^{o}C; $[\alpha]_D^{27}$ = +0.5 (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 0.82, 0.84 (d, d, *J* = 6.8, 6.7, 6H, (C*H*$_3$)$_2$CH), 1.78-1.96 (m, 3H, (CH$_3$)$_2$C*H*, C*H*$_2$CH$_2$S), 2.02 (s, 3H, CH$_3$S), 2.43-2.47 (m, 2H, CH$_2$C*H*$_2$S), 4.10-4.16 (m, 2H, CHCO, C*H*NHCO$_2$), 5.03 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.07 (brs, 1H, NH$_A$), 7.43 (brs, 1H, NH$_B$), 7.31-7.38 (m, 5H, C$_6$H$_5$), 7.59 (d, *J* = 8.2, 1H, NHCO), 7.63 (d, *J* = 8.9, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 14.6, 17.8, 19.3, 29.7, 30.7, 31.7, 54.1, 57.2, 65.4, 127.6, 127.8, 128.3, 137.0, 155.9, 171.2, 172.7; HRMS (ESI-TOF): Calcd for $C_{18}H_{27}N_3O_4SNa$ $(M+Na)^+$: 404.1614, Found: 404.1645; IR (KBr, ν_{max}/cm^{-1}) = 3298 (NH), 3209 (NH), 1680 (CON), 1643 (CON).

9.16. Cbz-L-Met-D-Val-NH$_2$ 15dLcD

Yield: 96 mg (84%); colorless powder; >99% de; mp: 244-246 ^{o}C; $[\alpha]_D^{27}$ = +9.8 (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 0.80, 0.83 (d, d, *J* = 6.8, 6.8, 6H, (C*H*$_3$)$_2$CH), 1.76-2.02 (m, 3H, (CH$_3$)$_2$C*H*, C*H*$_2$CH$_2$S), 2.02 (s, 3H, CH$_3$S), 2.43-2.48 (m, 2H, CH$_2$C*H*$_2$S), 4.14-4.21 (m, 2H, CHCO, C*H*NHCO$_2$), 5.03 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.09 (brs, 1H, NH$_A$), 7.30-7.37 (m, 6H, C$_6$H$_5$, NH$_B$), 7.54 (d, *J* = 7.9, 1H, NHCO), 7.79 (d, *J* = 9.0, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 14.6, 17.6, 19.3, 29.7, 30.4, 31.8, 54.1, 57.1, 65.4, 127.7, 127.8, 128.3, 136.9, 156.0, 171.4, 172.7; HRMS (ESI-TOF): Calcd for $C_{18}H_{27}N_3O_4SNa$

$(M+Na)^+$: 404.1614, Found: 404.1645; IR (KBr, ν_{max}/cm^{-1}) = 3338 (NH), 3286 (NH), 1734 (CON), 1641 (CON).

9.17. Cbz-L-Met-L-Met-NH_2 15dLdL

Yield: 95 mg (77%); colorless powder; 97% de; mp: 195-197 °C; $[\alpha]_D^{28}$ = -1.9 (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 1.77-1.98 (m, 4H, C*H*$_2$CH$_2$S×2), 2.03 (s, 6H, CH$_3$S×2), 2.39-2.49 (m, 4H, CH$_2$C*H*$_2$S×2), 4.08-4.12 (m, 1H, CHCO), 4.25-4.30 (m, 1H, C*H*NHCO$_2$), 5.03 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.09 (brs, 1H, NH$_A$), 7.31-7.39 (m, 6H, C$_6$H$_5$, NH$_B$), 7.55 (d, *J* = 7.8, 1H, NHCO), 7.95 (d, *J* = 8.0, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 14.6, 29.5, 29.6, 31.5, 31.9, 51.7, 54.0, 65.5, 127.7, 127.8, 128.3, 136.9, 156.0, 171.3, 172.9; HRMS (ESI-TOF): Calcd for $C_{18}H_{27}N_3O_4S_2Na$ $(M+Na)^+$: 436.1335, Found: 436.1365; IR (KBr, ν_{max}/cm^{-1}) = 3305 (NH), 3282 (NH), 1693 (CON), 1647 (CON).

9.18. Cbz-L-Met-D-Met-NH_2 15dLdD

Yield: 112 mg (90%); colorless powder; >99% de; mp: 181-182 °C; $[\alpha]_D^{27}$ = +20.5 (*c* 0.98, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 1.75-1.88 (m, 4H, C*H*$_2$CH$_2$S×2), 2.02 (s, 6H, CH$_3$S×2), 2.37-2.47 (m, 4H, CH$_2$C*H*$_2$S×2), 4.10-4.12 (m, 1H, CHCO), 4.24-4.29 (m, 1H, C*H*NHCO$_2$), 5.02 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.14 (brs, 1H, NH$_A$), 7.28 (brs, 1H, NH$_B$), 7.30-7.39 (m, 5H, C$_6$H$_5$), 7.59 (d, *J* = 7.3, 1H, NHCO), 8.16 (d, *J* = 8.2, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 14.6, 29.6, 29.6, 31.4, 31.9, 51.5, 54.1, 65.5, 127.7, 127.8, 128.4, 136.9, 156.1, 171.5, 173.0; HRMS (ESI-TOF): Calcd for $C_{18}H_{27}N_3O_4S_2Na$ $(M+Na)^+$: 436.1335, Found: 436.1365; IR (KBr, ν_{max}/cm^{-1}) = 3307 (NH), 3286 (NH), 1674 (CON), 1639 (CON).

9.19. *N*-Boc-*O*-Bn-L-Ser-L-Phe-NH_2 15hLaL

Yield: 127 mg (96%); colorless powder; 97% de; mp: 121-122 °C; $[\alpha]_D^{27}$ = +10.0 (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 1.38 (s, 9H, (CH$_3$)$_3$C), 2.83 (dd, *J* = 8.7, 13.7, 1H, C*H*$_A$C$_6$H$_5$), 3.02 (dd, *J* = 4.7, 13.7, 1H, C*H*$_B$C$_6$H$_5$), 3.48-3.50 (m, 2H, C*H*$_2$OCH$_2$C$_6$H$_5$), 4.15-4.18 (m, 1H, CHCO), 4.36-4.62 (m, 3H, C*H*NHCO$_2$, OC*H*$_2$C$_6$H$_5$), 6.96 (d, *J* = 7.8, 1H, NHCO), 7.15-7.39 (m, 12H, C$_6$H$_5$×2, NH$_2$), 7.93 (d, *J* = 8.1, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 28.2, 37.5, 53.5, 54.6, 69.8, 72.0, 78.4, 126.2, 127.4, 127.5, 128.0, 128.2, 129.2, 137.7, 138.1, 155.2, 169.4, 172.5; HRMS (ESI-TOF): Calcd for $C_{24}H_{31}N_3O_5Na$ $(M+Na)^+$: 464.2156, Found: 464.2163; IR (KBr, ν_{max}/cm^{-1}) = 3427 (NH), 3282 (NH), 3197 (NH), 1695 (CON), 1637 (CON).

9.20. *N*-Boc-*O*-Bn-L-Ser-D-Phe-NH_2 15hLaD

Yield: 127 mg (96%); colorless powder; 91% de; mp: 112-113 ^{o}C; $[\alpha]_D^{28}$ = +1.3 (*c* 1.02, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 1.38 (s, 9H, $(CH_3)_3C$), 2.88 (dd, *J* = 9.7, 13.7, 1H, $CH_AC_6H_5$), 3.04 (dd, *J* = 4.7, 13.7, 1H, $CH_BC_6H_5$), 3.36-3.39 (m, 2H, $CH_2OCH_2C_6H_5$), 4.10-4.23 (m, 1H, CHCO), 4.36-4.48 (m, 3H, $CHNHCO_2$, $OCH_2C_6H_5$), 6.85 (d, *J* = 7.8, 1H, NHCO), 7.02-7.41 (m, 12H, C_6H_5×2, NH_2), 8.16 (d, *J* = 8.4, 1H, $NHCO_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 28.1, 37.3, 53.8, 54.3, 69.7, 71.8, 78.3, 126.2, 127.3, 127.4, 127.9, 128.0, 128.1, 129.1, 137.9, 138.1, 155.3, 169.6, 172.7; HRMS (ESI-TOF): Calcd for $C_{24}H_{31}N_3O_5Na$ $(M+Na)^+$: 464.2156, Found: 464.2163; IR (KBr, ν_{max}/cm^{-1}) = 3456 (NH), 3365 (NH), 3334 (NH), 1684 (CON), 1637 (CON).

9.21. N^{α}-Boc-N^{ε}-Cbz-L-Lys-L-Phe-NH_2 15mLaL

Yield: 136 mg (86%); colorless powder; 97% de; mp: 120-121 ^{o}C; $[\alpha]_D^{27}$ = -7.0 (*c* 1.02, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 1.08-1.33 (m, 6H, $NHCH_2(CH_2)_3$), 1.37 (s, 9H, $(CH_3)_3C$), 2.82 (dd, *J* = 8.9, 13.6, 1H, $CH_AC_6H_5$), 2.89-2.94 (m, 2H, $NHCH_2(CH_2)_3$), 2.99 (dd, *J* = 4.6, 13.6, 1H, $CH_BC_6H_5$), 3.72-3.79 (m, 1H, CHCO), 4.42-4.47 (m, 1H, $CHNHCO_2$), 5.00 (s, 2H, $OCH_2C_6H_5$), 6.95 (d, *J* = 7.5, 1H, NHCO), 7.13-7.38 (m, 12H, C_6H_5×2, NH_2), 7.72 (d, *J* = 8.3, 1H, $NHCO_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 22.7, 28.2, 29.1, 31.4, 37.5, 53.2, 55.0, 65.1, 78.2, 126.2, 127.7, 128.0, 128.4, 129.2, 137.3, 137.7, 155.4, 156.1, 171.8, 172.8; HRMS (ESI-TOF): Calcd for $C_{28}H_{38}N_4O_6Na$ $(M+Na)^+$: 549.2684, Found: 549.2712; IR (KBr, ν_{max}/cm^{-1}) = 3435 (NH), 3329 (NH), 1695 (CON), 1647 (CON).

9.22. N^{α}-Boc-N^{ε}-Cbz-L-Lys-D-Phe-NH_2 15mLaD

Yield: 141 mg (89%); colorless powder; 96% de; mp: 165-167 ^{o}C; $[\alpha]_D^{28}$ = -1.7 (*c* 0.98, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 0.88-1.28 (m, 6H, $NHCH_2(CH_2)_3$), 1.36 (s, 9H, $(CH_3)_3C$), 2.73 (dd, *J* = 10.8, 13.4, 1H, $CH_AC_6H_5$), 2.84-2.89 (m, 2H, $NHCH_2(CH_2)_3$), 3.11 (dd, *J* = 3.7, 13.4, 1H, $CH_BC_6H_5$), 3.78-3.83 (m, 1H, CHCO), 4.36-4.42 (m, 1H, $CHNHCO_2$), 5.01 (s, 2H, $OCH_2C_6H_5$), 6.87 (d, *J* = 7.1, 1H, NHCO), 7.15-7.39 (m, 12H, C_6H_5×2, NH_2), 8.16 (d, *J* = 8.6, 1H, $NHCO_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 22.3, 28.2, 29.1, 31.0, 37.2, 53.8, 54.4, 65.1, 78.1, 126.2, 127.7, 128.0, 128.3, 129.1, 137.3, 138.1, 155.6, 156.0, 172.0, 173.0; HRMS (ESI-TOF): Calcd for $C_{28}H_{38}N_4O_6Na$ $(M+Na)^+$: 549.2684, Found: 549.2712; IR (KBr, ν_{max}/cm^{-1}) = 3334 (NH), 3195 (NH), 1687 (CON), 1649 (CON).

10. Typical procedure of the amidation of Cbz-L-Phe-L-Phe-OH 14aLaL with 4-aminophenol 16a

To a colorless solution of 134 mg (0.30 mmol, 1 equiv) of Cbz-L-Phe-L-Phe-OH (**14aLaL**) in 6 mL of anhydrous THF were added dropwise at -15 ^{o}C 126 μL (0.9 mmol, 3.0 equiv) of a precooled Et_3N and 40

μL (0.42 mmol, 1.4 equiv) of a precooled $ClCO_2Et$. After stirring for 10 min at -15 °C, 49 mg (0.45 mmol, 1.5 equiv) of 4-aminophenol (**16a**) and 1 mL of H_2O were added at -15 °C to the colorless suspension. The mixture was stirred for 24 h at -15 °C and 15mL of H_2O was added dropwise at -15 °C to the resulted mixture. The suspension was extracted with 100 mL of EtOAc, washed with 10 mL of brine, and dried over anhydrous $MgSO_4$. The crude product was chromatographed on silica gel with a 1:1 mixture of hexane and EtOAc to afford 156 mg (97% yield) of Cbz-L-Phe-L-Phe-4-aminophenol **17aLaLa**.

10.1. Cbz-L-Phe-L-Phe-4-aminophenol 17aLaLa

Yield: 156 mg (97%); colorless powder; 96% de; mp: 219-222 °C; $[\alpha]_D^{27}$ = +25.3 (*c* 0.99, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 2.68 (dd, *J* = 10.6, 13.6, 1H, CH_AC$_6$H$_5$), 2.90-2.95 (m, 2H, CH_A·C$_6$H$_5$, CH_BC$_6$H$_5$), 3.06 (dd, *J* = 5.6, 13.6, 1H, CH_B·C$_6$H$_5$), 4.25-4.30 (m, 1H, CHCO), 4.63-4.69 (m, 1H, C*H*NHCO$_2$), 4.94 (s, 2H, OCH_2C$_6$H$_5$), 6.70, 7.17-7.35 (d, m, *J* = 8.8, 2H, 17H, C$_6$H$_4$, C$_6$H$_5$×3), 7.47 (d, *J* = 8.6, 1H, NHCO), 8.26 (d, *J* = 8.0, 1H, NHCO$_2$), 9.22 (s, 1H, OH), 9.81 (s, 1H, CON*H*C$_6$H$_4$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 37.5, 38.0, 54.6, 56.1, 65.2, 115.1, 121.2, 126.2, 126.4, 127.4, 127.7, 128.0, 128.1, 128.3, 129.2, 129.3, 130.3, 137.0, 137.4, 138.0, 153.5, 155.7, 169.0, 171.3; HRMS (ESI-TOF): Calcd for $C_{32}H_{31}N_3O_5Na$ $(M+Na)^+$: 560.2156, Found: 560.2169; IR (KBr, ν_{max}/cm^{-1}) = 3293 (OH), 1695 (CON), 1623 (CON).

10.2. Cbz-L-Phe-D-Phe-4-aminophenol 17aLaDa

Yield: 141 mg (94%); colorless powder; 97% de; mp: 200-202 °C; $[\alpha]_D^{27}$ = +19.4 (*c* 1.01, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 2.47 (dd, *J* = 10.8, 13.5, 1H, CH_AC$_6$H$_5$), 2.63 (dd, *J* = 3.4, 13.5, 1H, CH_A·C$_6$H$_5$), 2.85 (dd, *J* = 10.0, 13.5, 1H, CH_BC$_6$H$_5$), 3.07 (dd, *J* = 4.5, 13.5, 1H, CH_B·C$_6$H$_5$), 4.26-4.31 (m, 1H, CHCO), 4.67-4.73 (m, 1H, C*H*NHCO$_2$), 4.92 (s, 2H, OCH_2C$_6$H$_5$), 6.72, 7.41 (d, d, *J* = 8.9, 8.9, 2H, 2H, C$_6$H$_4$), 7.17-7.32 (m, 16H, C$_6$H$_5$×3, NHCO), 8.58 (d, *J* = 8.6, 1H, NHCO$_2$), 9.24 (s, 1H, OH), 9.86 (s, 1H, CON*H*C$_6$H$_4$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 37.4, 38.1, 54.5, 56.1, 65.2, 115.1, 121.1, 126.2, 126.4, 127.5, 127.7, 128.0, 128.0, 128.3, 129.2, 129.3, 130.3, 136.9, 137.7, 138.1, 153.5, 155.9, 169.2, 171.4; HRMS (ESI-TOF): Calcd for $C_{32}H_{31}N_3O_5Na$ $(M+Na)^+$: 560.2156, Found: 560.2169; IR (KBr, ν_{max}/cm^{-1}) = 3292 (OH), 1693 (CON), 1645 (CON).

10.3. Cbz-L-Phe-L-Phe-dopamine 17aLaLb

Yield: 171 mg (98%); colorless powder; 82% de; mp: 70-71 °C; $[\alpha]_D^{27}$ = +11.1 (*c* 0.98, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 2.43-2.47 (m, 2H, CH_2CH$_2$C$_6$H$_3$), 2.67 (dd, *J* = 10.9, 13.6, 1H, CH_AC$_6$H$_5$), 2.82

(dd, *J* = 8.5, 13.6, 1H, CH_A,C_6H_5), 3.12-3.20 (m, 2H, C$H_B$$C_6H_5$, C$H_B$,$C_6H_5$), 3.11-3.23 (m, 2H, $CH_2CH_2C_6H_3$), 4.23-4.27 (m, 1H, CHCO), 4.44-4.49 (m, 1H, C*H*$NHCO_2$), 4.94 (s, 2H, $OCH_2C_6H_5$), 6.40-6.63 (m, 3H, C_6H_3), 7.17-7.33 (m, 15H, C_6H_5×3), 7.46 (d, *J* = 8.7, 1H, NHCO), 7.95-8.02 (m, 1H, N*H*CH_2CH_2), 8.08 (d, *J* = 8.2, 1H, $NHCO_2$), 9.65 (s, 1H, OH), 9.74 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 34.5, 37.4, 38.0, 40.6, 53.9, 56.1, 65.2, 115.5, 115.9, 119.2, 126.2, 126.2, 127.4, 127.6, 128.2, 128.3, 129.2, 129.3, 130.0, 137.0, 137.6, 138.0, 143.5, 145.1, 155.7, 170.4, 171.1; HRMS (ESI-TOF): Calcd for $C_{33}H_{33}N_3O_5Na$ $(M+Na)^+$: 604.2428, Found: 604.2474; IR (KBr, ν_{max}/cm^{-1}) = 3398 (OH), 1705 (CON), 1647 (CON).

10.4. Cbz-L-Phe-D-Phe-dopamine 17aLaDb

Yield: 173 mg (99%); colorless powder; 88% de; mp: 76-77 ^oC; $[\alpha]_D^{27}$ = +5.3 (*c* 0.99, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 2.43 (dd, *J* = 3.0, 13.6, 1H, C$H_A$$C_6H_5$), 2.45-2.52 (m, 2H, C$H_2CH_2C_6H_3$), 2.62 (dd, *J* = 3.6, 13.6, 1H, CH_A,C_6H_5), 2.73 (dd, *J* = 4.9, 13.6, 1H, C$H_B$$C_6H_5$), 2.96 (dd, *J* = 4.6, 13.6, 1H, C$H_B$$C_6H_5$), 3.15-3.25 (m, 2H, $CH_2CH_2C_6H_3$), 4.24-4.27 (m, 1H, CHCO), 4.47-4.53 (m, 1H, C*H*$NHCO_2$), 4.93 (s, 2H, $OCH_2C_6H_5$), 6.42-6.64 (m, 3H, C_6H_3), 7.14-7.29 (m, 15H, C_6H_5×3), 7.30 (d, *J* = 7.3, 1H, NHCO), 8.05-8.08 (m, 1H, N*H*CH_2CH_2), 8.39 (d, *J* = 8.7, 1H, $NHCO_2$), 8.65 (s, 1H, OH), 8.74 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 34.5, 37.4, 38.1, 40.6, 48.6, 53.9, 56.1, 65.2, 115.5, 115.9, 119.2, 126.1, 126.2, 127.4, 127.7, 127.9, 128.0, 128.3, 129.2, 129.3, 130.0, 137.0, 137.8, 138.0, 143.6, 145.1, 155.8, 170.7, 171.2; HRMS (ESI-TOF): Calcd for $C_{14}H_{19}N_3O_4Na$ $(M+Na)^+$: 604.2428, Found: 604.2474; IR (KBr, ν_{max}/cm^{-1}) = 3290 (OH), 1697 (CON), 1647 (CON).

10.5. Cbz-L-Phe-L-Phe-amantazine 17aLaLc

Yield: 144 mg (83%); colorless powder; 88% de; mp: 73-75 ^oC; $[\alpha]_D^{28}$ = -2.2 (*c* 1.02, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 1.57-1.63 (m, 6H, CH_2×3 of adamantane), 1.86-1.90 (m, 6H, CH_2×3 of adamantane), 1.91-1.97 (m, 3H, CH×3 of adamantane), 2.68 (dd, *J* = 10.4, 13.7, 1H, C$H_A$$C_6H_5$), 2.82 (dd, *J* = 8.3, 13.7, 1H, CH_A,C_6H_5), 2.89-2.93 (m, 2H, C$H_B$$C_6H_5$, C$H_B$,$C_6H_5$), 4.22-4.25 (m, 1H, CHCO), 4.46-4.51 (m, 1H, C*H*$NHCO_2$), 4.95 (s, 2H, $OCH_2C_6H_5$), 7.18-7.34 (m, 16H, C_6H_5×3, NH-adamantane), 7.45 (d, *J* = 8.6, 1H, NHCO), 7.95 (d, *J* = 8.2, 1H, $NHCO_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 28.8, 36.0, 37.4, 38.2, 40.8, 50.8, 54.0, 56.2, 65.2, 79.2, 126.2, 127.3, 127.6, 127.9, 128.0, 128.2, 129.1, 129.4, 137.0, 137.9, 155.7, 169.6, 170.9; HRMS (ESI-TOF): Calcd for $C_{36}H_{41}N_3O_4Na$ $(M+Na)^+$: 602.2989, Found: 602.2994; IR (KBr, ν_{max}/cm^{-1}) = 3275 (NH), 2908 (NH), 1707 (CON), 1647 (CON).

10.6. Cbz-L-Phe-D-Phe-amantazine 17aLaDc

Yield: 155 mg (89%); colorless powder; 95% de; mp: 77-78 ^{o}C; $[\alpha]_D^{28}$ = +15.1 (*c* 0.98, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 1.57-1.63 (m, 6H, CH_2×3 of adamantane), 1.86-1.90 (m, 6H, CH_2×3 of adamantane), 1.91-1.99 (m, 3H, CH×3 of adamantane), 2.47 (dd, *J* = 11.1, 13.5, 1H, CH_AC$_6$H$_5$), 2.61 (dd, *J* = 3.4, 13.5, 1H, CH_A·C$_6$H$_5$), 2.74 (dd, *J* = 9.6, 13.5, 1H, CH_BC$_6$H$_5$), 2.96 (dd, *J* = 4.8, 13.6, 1H, CH_B·C$_6$H$_5$), 4.20-4.26 (m, 1H, CHCO), 4.48-4.53 (m, 1H, C*H*NHCO$_2$), 4.94 (s, 2H, OCH_2C$_6$H$_5$), 7.12-7.34 (m, 16H, C$_6$H$_5$×3, NH-adamantane), 7.43 (d, *J* = 8.5, 1H, NHCO), 8.28 (d, *J* = 8.6, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 28.8, 36.0, 37.3, 38.1, 40.9, 50.8, 54.0, 56.2, 65.1, 126.1, 126.2, 127.3, 127.8, 127.9, 128.2, 129.2, 129.4, 137.0, 137.8, 138.1, 155.8, 169.8, 171.2; HRMS (ESI-TOF): Calcd for $C_{36}H_{41}N_3O_4Na$ $(M+Na)^+$: 602.2989, Found: 602.2994; IR (KBr, ν_{max}/cm^{-1}) = 3273 (NH), 2908 (NH), 1732 (CON), 1639 (CON).

10.7. Cbz-L-Phe-L-Phe-(±)-rimantadine 17aLaLd

Yield: 157 mg (86%); colorless powder; 79% de; mp: 95-98 ^{o}C; $[\alpha]_D^{28}$ = -7.9 (*c* 1.01, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 0.80 and 0.92 (d and d, *J* = 6.8, 6.9, 3H, CH_3), 1.30-1.64 (m, 12H, CH_2×6 of adamantane), 1.85-1.90 (m, 3H, CH×3 of adamantane), 2.97 (dd, *J* = 10.8, 13.4, 1H, CH_AC$_6$H$_5$), 2.83-2.92 (m, 2H, CH_BC$_6$H$_5$, CH_A·C$_6$H$_5$), 2.83-2.92 (dd, *J* = 6.2, 13.5, 1H, CH_BC$_6$H$_5$), 3.45-3.49 (m, 1H, C*H*CH$_3$), 4.22-4.28 (m, 1H, CHCO), 4.57-4.64 (m, 1H, C*H*NHCO$_2$), 4.93 (s, 2H, OCH_2C$_6$H$_5$), 7.15-7.48 (m, 16H, C$_6$H$_5$×3, NH-adamantane), 7.56 (d, *J* = 9.4, 1H, NHCO), 8.16 (d, *J* = 8.2, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 13.9, 14.1, 27.7, 27.8, 35.4, 35.5, 36.5, 36.6, 37.5, 37.7, 37.8, 38.3, 52.2, 52.2, 53.9, 54.1, 56.1, 56.2, 65.2, 126.2, 127.4, 127.6, 127.9, 128.0, 129.1, 129.3, 136.9, 137.5, 137.6, 137.9, 137.9, 155.6, 155.7, 169.9, 171.0, 171.1; HRMS (ESI-TOF): Calcd for $C_{38}H_{45}N_3O_4Na$ $(M+Na)^+$: 630.3302, Found: 630.3305; IR (KBr, ν_{max}/cm^{-1}) = 3275 (NH), 2902 (NH), 1705 (CON), 1647 (CON).

10.8. Cbz-L-Phe-D-Phe-(±)-rimantadine 17aLaDd

Yield: 169 mg (93%); colorless powder; 91% de; mp: 89-91 ^{o}C; $[\alpha]_D^{28}$ = +12.3 (*c* 0.98, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 0.87 and 0.96 (d and d, *J* = 6.9, 6.9, 3H, CH_3), 1.34-1.59 (m, 12H, CH_2×6 of adamantane), 1.88-1.91 (m, 3H, CH×3 of adamantane), 2.42-2.48 (m, 1H, CH_A·C$_6$H$_5$), 2.55-2.61 (m, 1H, CH_A·C$_6$H$_5$), 2.74-2.81 (m, 1H, CH_BC$_6$H$_5$), 2.97-3.05 (m, 1H, CH_B·C$_6$H$_5$), 3.49-3.52 (m, 1H, C*H*CH$_3$), 4.23-4.27 (m, 1H, CHCO), 4.54-4.67 (m, 1H, C*H*NHCO$_2$), 4.92 (s, 2H, OCH_2C$_6$H$_5$), 7.13-7.43 (m, 16H, C$_6$H$_5$×3, NH-adamantane), 7.54 (d, *J* = 9.5, 1H, NHCO), 8.41 (d, *J* = 8.4, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 13.9, 14.1, 27.4, 27.8, 35.5, 35.6, 36.5, 36.6, 37.8, 37.8, 52.2, 52.3, 53.9, 56.2, 65.1,

126.1, 126.2, 127.3, 127.4, 127.6, 127.9, 128.2, 129.2, 136.9, 137.8, 137.9, 138.1, 155.7, 155.8, 170.0, 171.3; HRMS (ESI-TOF): Calcd for $C_{38}H_{45}N_3O_4Na$ $(M+Na)^+$: 630.3302, Found: 630.3305; IR (KBr, ν_{max}/cm^{-1}) = 2902 (NH), 1707 (CON), 1641 (CON).

10.9. Cbz-L-Phe-L-Phe-memantine 17aLaLe

Yield: 135 mg (74%); colorless powder; 85% de; mp: 91-93 °C; $[\alpha]_D^{28}$ = +0.8 (*c* 0.99, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 0.80 (s, 6H, CH_3×2), 1.07-1.13 (m, 6H, CH_2×3 of adamantane), 1.48-1.74 (m, 6H, CH_2×3 of adamantane), 1.99-2.09 (m, 1H, CH of adamantane), 2.69 (dd, *J* = 10.3, 13.7, 1H, CH_AC$_6$H$_5$), 2.83 (dd, *J* = 8.4, 13.6, 1H, CH_A'C$_6$H$_5$), 2.89-2.96 (m, 2H, CH_BC$_6$H$_5$, CH_B'C$_6$H$_5$), 4.19-4.25 (m, 1H, CHCO), 4.44-4.50 (m, 1H, C*H*NHCO$_2$), 4.95 (s, 2H, OCH_2C$_6$H$_5$), 7.17-7.36 (m, 16H, C$_6$H$_5$×3, NH-adamantane), 7.45 (d, *J* = 8.6, 1H, NHCO), 7.94 (d, *J* = 8.2, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 29.4, 30.0, 31.8, 37.4, 38.1, 42.2, 46.8, 46.9, 50.2, 52.4, 54.0, 56.2, 65.2, 126.2, 127.3, 127.6, 127.9, 128.0, 128.3, 129.1, 129.4, 137.0, 137.5, 137.9, 155.7, 169.7, 170.9; HRMS (ESI-TOF): Calcd for $C_{38}H_{45}N_3O_4Na$ $(M+Na)^+$: 630.3302, Found: 630.3305; IR (KBr, ν_{max}/cm^{-1}) = 3305 (NH), 2900 (NH), 1709 (CON), 1645 (CON).

10.10. Cbz-L-Phe-D-Phe-memantine 17aLaDe

Yield: 149 mg (82%); colorless powder; 97% de; mp: 80-82 °C; $[\alpha]_D^{28}$ = +7.9 (*c* 1.02, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 0.80 (s, 6H, CH_3×2), 1.08-1.13 (m, 6H, CH_2×3 of adamantane), 1.51-1.78 (m, 6H, CH_2×3 of adamantane), 2.05-2.06 (m, 1H, CH of adamantane), 2.46 (dd, *J* = 10.6, 13.5, 1H, CH_AC$_6$H$_5$), 2.59 (dd, *J* = 3.7, 13.7, 1H, CH_A'C$_6$H$_5$), 2.72 (dd, *J* = 9.6, 13.5, 1H, CH_BC$_6$H$_5$), 2.96 (dd, *J* = 4.8, 13.7, 1H, CH_B'C$_6$H$_5$), 4.18-4.24 (m, 1H, CHCO), 4.44-4.49 (m, 1H, C*H*NHCO$_2$), 4.94 (s, 2H, OCH_2C$_6$H$_5$), 7.13-7.33 (m, 16H, C$_6$H$_5$×3, NH-adamantane), 7.43 (d, *J* = 8.4, 1H, NHCO), 8.27 (d, *J* = 8.6, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 29.5, 30.0, 31.8, 37.2, 38.0, 42.2, 46.9, 50.2, 52.4, 554.1, 56.3, 65.1, 126.1, 127.3, 127.6, 127.8, 127.9, 128.3, 129.1, 129.3, 136.9, 137.8, 138.0, 155.9, 169.9, 171.2; HRMS (ESI-TOF): Calcd for $C_{38}H_{45}N_3O_4Na$ $(M+Na)^+$: 630.3302, Found: 630.3305; IR (KBr, ν_{max}/cm^{-1}) = 3275 (NH), 2900 (NH), 1705 (CON), 1637 (CON).

11. Typical procedure of the primary amidation of Cbz-L-Phe-L-Val-L-Phe-OH 19aLcLaL with NH_4Cl

To a colorless solution of 163 mg (0.30 mmol) of Cbz-L-Phe-L-Val-L-Phe-OH (**19aLcLaL**) in 6 mL of anhydrous THF were added dropwise at -15 °C 126 μL (0.9 mmol, 3.0 equiv) of a precooled Et_3N and 40

μL (0.42 mmol, 1.4 equiv) of a precooled $ClCO_2Et$. After stirring for 10 min at -15 °C, 0.45 mL (0.45 mmol, 1.5 equiv) of a precooled 1.0M aqueous solution of NH_4Cl was added dropwise at -15 °C to the colorless suspension. The mixture was stirred for 24 h at -15 °C and 15mL of H_2O was added dropwise at -15 °C to the resulted mixture. The suspension was extracted with 100 mL of EtOAc, washed with 10 mL of brine, and dried over anhydrous $MgSO_4$. The crude product was chromatographed on silica gel with a 1:1 mixture of hexane and EtOAc to afford 155 mg (95% yield) of Cbz-L-Phe-L-Val-L-Phe-NH_2 **20aLcLaL**.

11.1. Cbz-L-Phe-L-Val-L-Phe-NH_2 20aLcLaL

Yield: 155 mg (95%); colorless powder; 76% de; mp: 247-249 °C; $[\alpha]_D^{27}$ = -2.3 (*c* 1.01, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 0.79 (d, *J* = 5.6, 6H, $(CH_3)_2CH$), 1.90-1.98 (m, 1H, $(CH_3)_2CH$), 2.70 (dd, *J* = 11.0, 13.7, 1H, $CH_AC_6H_5$), 2.81 (dd, *J* = 8.9, 13.8, 1H, $CH_A{\cdot}C_6H_5$), 2.93 (dd, *J* = 3.3, 13.7, 1H, $CH_BC_6H_5$), 2.99 (dd, *J* = 5.2, 13.8, 1H, $CH_B{\cdot}C_6H_5$), 4.14-4.18 (m, 1H, $CHCH(CH_3)_2$), 4.28-4.33 (m, 1H, $CHCONH_2$), 4.45-4.51 (m, 1H, $CHNHCO_2$), 4.94 (s, 2H, $OCH_2C_6H_5$), 7.06 (brs, 1H, NH_A), 7.13-7.34 (m, 15H, C_6H_5×3), 7.39 (brs, 1H, NH_B), 7.55 (d, *J* = 8.7, 1H, NHCO), 7.86 (d, *J* = 8.9, 1H, $NHCHCONH_2$), 7.98 (d, *J* = 8.2, 1H, $NHCO_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 18.0, 19.1, 30.7, 37.2, 37.6, 53.5, 56.0, 57.7, 65.1, 126.2, 127.4, 127.6, 128.0, 128.3, 129.1, 129.2, 137.0, 137.8, 155.8, 170.5, 171.4, 172.6; HRMS (ESI-TOF): Calcd for $C_{31}H_{36}N_4O_5Na$ $(M+Na)^+$: 567.2578, Found: 567.2554; IR (KBr, ν_{max}/cm^{-1}) = 3296 (NH), 1670 (CON), 1635 (CON).

11.2. Cbz-L-Phe-L-Val-D-Phe-NH_2 20aLcLaD

Yield: 153 mg (94%); colorless powder; 72% de; mp: 254-256 °C; $[\alpha]_D^{27}$ = +17.9 (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ = 0.57 (d, *J* = 6.6, 6H, $(CH_3)_2CH$), 1.72-1.98 (m, 1H, $(CH_3)_2CH$), 2.67-2.76 (m, 2H, $CH_AC_6H_5$, $CH_A{\cdot}C_6H_5$), 2.93 (dd, *J* = 3.5, 13.8, 1H, $CH_BC_6H_5$), 3.08 (dd, *J* = 3.8, 13.6, 1H, $CH_B{\cdot}C_6H_5$), 4.10-4.14 (m, 1H, $CHCH(CH_3)_2$), 4.27-4.33 (m, 1H, $CHCONH_2$), 4.45-4.49 (m, 1H, $CHNHCO_2$), 4.93 (s, 2H, $OCH_2C_6H_5$), 7.13 (brs, 1H, NH_A), 7.15-7.34 (m, 15H, C_6H_5×3), 7.43 (brs, 1H, NH_B), 7.53 (d, *J* = 8.6, 1H, NHCO), 7.86 (d, *J* = 8.4, 1H, $NHCHCONH_2$), 8.28 (d, *J* = 8.6, 1H, $NHCO_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 17.7, 19.0, 30.5, 37.2, 37.5, 53.9, 56.0, 57.8, 65.2, 126.1, 127.4, 127.6, 128.0, 128.0, 128.3, 129.1, 129.2, 137.0, 138.1, 138.1, 155.8, 170.6, 171.6, 173.1; HRMS (ESI-TOF): Calcd for $C_{31}H_{36}N_4O_5Na$ $(M+Na)^+$: 567.2578, Found: 567.2554; IR (KBr, ν_{max}/cm^{-1}) = 3284 (NH), 1697 (CON), 1631 (CON).

11.3. Cbz-L-Phe-L-Val-L-Ala-NH_2 20aLcLbL

Yield: 125 mg (89%); colorless powder; mp: 266-268 ^{o}C; $[\alpha]_D^{28}$ = +2.2 (*c* 1.02, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 0.84, 0.88 (d, d, *J* = 6.9, 7.0, 3H, 3H, (C*H*$_3$)$_2$CH), 1.20 (d, *J* = 7.0, 3H, C*H*$_3$CH), 1.97-2.05 (m, 1H, (CH$_3$)$_2$C*H*), 2.74 (dd, *J* = 11.2, 13.7, 1H, C*H*$_A$C$_6$H$_5$), 3.01 (dd, *J* = 3.2, 13.7, 1H, C*H*$_B$C$_6$H$_5$), 4.20-4.24 (m, 2H, C*H*CH(C*H*$_3$)$_2$, C*H*CONH$_2$), 4.31-4.36 (m, 1H, C*H*NHCO$_2$), 4.94 (s, 2H, OC*H*$_2$C$_6$H$_5$), 6.69 (brs, 1H, NH$_A$), 7.18-7.74 (m, 11H, C$_6$H$_5$×2, NH$_B$), 7.54 (d, *J* = 8.6, 1H, NHCO), 7.91 (d, *J* = 8.8, 1H, N*H*CHCONH$_2$), 7.96 (d, *J* = 7.2, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 17.9, 18.4, 19.2, 30.7, 37.3, 47.9, 56.1, 57.5, 65.2, 126.2, 127.4, 127.6, 128.0, 129.2, 127.4, 127.6, 128.0, 128.3, 129.2, 137.0, 138.1, 155.8, 170.2, 171.5, 173.9; HRMS (ESI-TOF): Calcd for $C_{25}H_{32}N_4O_5Na$ $(M+Na)^+$: 491.2265, Found: 491.2302; IR (KBr, ν_{max}/cm^{-1}) = 3284 (NH), 1697 (CON), 1630 (CON).

11.4. Cbz-L-Phe-L-Val-D-Ala-NH$_2$ 20aLcLbD

Yield: 119 mg (85%); colorless powder; mp: 184-186 ^{o}C; $[\alpha]_D^{28}$ = +1.5 (*c* 0.98, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 0.56, 0.58 (d, d, *J* = 6.6, 6.6, 3H, 3H, (C*H*$_3$)$_2$CH), 1.20 (d, *J* = 7.0, 3H, C*H*$_3$CH), 1.91-2.04 (m, 1H, (CH$_3$)$_2$C*H*), 2.75 (dd, *J* = 10.5, 13.7, 1H, C*H*$_A$C$_6$H$_5$), 3.01 (dd, *J* = 8.6, 13.7, 1H, C*H*$_B$C$_6$H$_5$), 4.14-4.40 (m, 3H, C*H*CH(C*H*$_3$)$_2$, C*H*CONH$_2$, C*H*NHCO$_2$), 4.94 (s, 2H, OC*H*$_2$C$_6$H$_5$), 6.98 (brs, 1H, NH$_A$), 7.03-7.57 (m, 12H, C$_6$H$_5$×2, NH$_B$, NHCO), 7.76 (d, *J* = 9.1, 1H, N*H*CHCONH$_2$), 7.95 (d, *J* = 9.0, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 17.8, 19.0, 19.2, 29.0, 30.7, 37.2, 56.2, 57.1, 57.3, 65.2, 126.2, 127.3, 127.5, 127.6, 128.0, 128.0, 128.3, 129.2, 129.2, 137.0, 138.1, 155.8, 171.3, 172.7, 174.0; HRMS (ESI-TOF): Calcd for $C_{25}H_{32}N_4O_5Na$ $(M+Na)^+$: 491.2265, Found: 491.2302; IR (KBr, ν_{max}/cm^{-1}) = 3292 (NH), 1697 (CON), 1647 (CON).

11.5. Cbz-L-Phe-L-Val-L-Val-NH$_2$ 20aLcLcL

Yield: 125 mg (84%); colorless powder; mp: 268-269 ^{o}C; $[\alpha]_D^{28}$ = -1.4 (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-*d*^{6}): δ = 0.76-0.91 (m, 12H, (C*H*$_3$)$_2$CH×2), 1.93-2.04 (m, 2H, (CH$_3$)$_2$C*H*), 2.74 (dd, *J* = 11.0, 13.7, 1H, C*H*$_A$C$_6$H$_5$), 3.00 (dd, *J* = 3.3, 13.7, 1H, C*H*$_B$C$_6$H$_5$), 4.11-4.15 (m, 1H, C*H*CH(C*H*$_3$)$_2$), 4.23-4.27 (m, 1H, C*H*CONH$_2$), 4.31-4.37 (m, 1H, C*H*NHCO$_2$), 4.94 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.04 (brs, 1H, NH$_A$), 7.19-7.33 (m, 11H, C$_6$H$_5$×2, NH$_B$), 7.53 (d, *J* = 8.6, 1H, NHCO), 7.71 (d, *J* = 8.8, 1H, N*H*CHCONH$_2$), 7.99 (d, *J* = 8.8, 1H, NHCO$_2$); ^{13}C NMR (100 MHz, DMSO-*d*^{6}): δ = 17.9, 18.1, 19.2, 19.3, 30.5, 30.5, 37.2, 56.0, 57.4, 57.8, 65.2, 126.2, 127.4, 127.6, 128.0, 128.3, 129.2, 137.0, 138.1, 155.8, 170.6, 171.5, 172.7; HRMS (ESI-TOF): Calcd for $C_{27}H_{36}N_4O_5Na$ $(M+Na)^+$: 519.2578, Found: 519.2504; IR (KBr, ν_{max}/cm^{-1}) = 3294 (NH), 1670 (CON), 1637 (CON).

11.6. Cbz-L-Phe-L-Val-D-Val-NH_2 20aLcLcD

Yield: 115 mg (77%); colorless powder; mp: 271-273 ^oC; $[\alpha]_D^{28}$ = +0.2 (*c* 0.99, DMSO); ^1H NMR (400 MHz, DMSO-d^6): δ = 0.76-0.87 (m, 12H, $(CH_3)_2CH\times2$), 1.98-2.07 (m, 2H, $(CH_3)_2CH$), 2.74 (dd, *J* = 11.1, 13.5, 1H, $CH_AC_6H_5$), 2.99 (dd, *J* = 3.5, 13.6, 1H, $CH_BC_6H_5$), 4.15-4.19 (m, 1H, $CHCH(CH_3)_2$), 4.31-4.37 (m, 2H, $CHCONH_2$, $CHNHCO_2$), 4.95 (s, 2H, $OCH_2C_6H_5$), 7.07 (brs, 1H, NH_A), 7.18-7.34 (m, 10H, $C_6H_5\times2$), 7.37 (brs, 1H, NH_B), 7.55 (d, *J* = 8.6, 1H, NHCO), 7.95 (d, *J* = 8.8, 1H, $NHCHCONH_2$), 7.97 (d, *J* = 8.8, 1H, $NHCO_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 17.7, 17.8, 17.9, 19.2, 19.4, 30.1, 30.7, 37.3, 56.0, 57.3, 57.9, 65.2, 126.2, 127.4, 127.5, 127.6, 128.0, 128.3, 129.2, 137.0, 138.0, 155.8, 170.9, 171.5, 172.7, 172.9; HRMS (ESI-TOF): Calcd for $C_{27}H_{36}N_4O_5Na$ $(M+Na)^+$: 519.2578, Found: 519.2504; IR (KBr, ν_{max}/cm^{-1}) = 3292 (NH), 1697 (CON), 1623 (CON).

11.7. Cbz-L-Phe-L-Val-L-Met-NH_2 20aLcLdL

Yield: 153 mg (97%); colorless powder; mp: 221-223 ^oC; $[\alpha]_D^{27}$ = +20.0 (*c* 0.99, DMSO); ^1H NMR (400 MHz, DMSO-d^6): δ = 0.84, 0.87 (d, d, *J* = 5.6, 6.6, 3H, 3H, $(CH_3)_2CH$), 1.77-2.02 (m, 3H, CH_2CH_2S, $(CH_3)_2CH$), 2.03 (s, 3H, CH_3S), 2.40-2.46 (m, 2H, CH_2CH_2S), 2.72 (dd, *J* = 10.9, 13.7, 1H, $CH_AC_6H_5$), 3.00 (dd, *J* = 3.5, 13.7, 1H, $CH_BC_6H_5$), 4.14-4.21 (m, 1H, $CHCH(CH_3)_2$), 4.27-4.36 (m, 2H, $CHCONH_2$, $CHNHCO_2$), 4.94 (s, 2H, $OCH_2C_6H_5$), 7.07 (brs, 1H, NH_A), 7.20-7.33 (m, 12H, $C_6H_5\times2$, NH_B, NHCO), 7.54 (d, *J* = 8.5, 1H, $NHCHCONH_2$), 7.96 (d, *J* = 8.6, 1H, $NHCO_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 14.5, 14.6, 18.1, 19.2, 29.6, 30.5, 31.9, 37.2, 56.0, 57.8, 65.2, 126.2, 127.4, 127.5, 127.7, 128.0, 128.3, 129.2, 137, 51.7.0, 138.1, 155.8, 170.7, 171.6, 172.8; HRMS (ESI-TOF): Calcd for $C_{27}H_{36}N_4O_5SNa$ $(M+Na)^+$: 551.2299, Found: 551.2222; IR (KBr, ν_{max}/cm^{-1}) = 3284 (NH), 1676 (CON), 1635 (CON).

11.8. Cbz-L-Phe-L-Val-D-Met-NH_2 20aLcLdD

Yield: 149 mg (94%); colorless powder; mp: 248-250 ^oC; $[\alpha]_D^{27}$ = +30.6 (*c* 0.99, DMSO); ^1H NMR (400 MHz, DMSO-d^6): δ = 0.75, 0.87 (d, d, *J* = 5.6, 6.6, 3H, 3H, $(CH_3)_2CH$), 1.77-2.00 (m, 3H, CH_2CH_2S, $(CH_3)_2CH$), 2.02 (s, 3H, CH_3S), 2.38-2.47 (m, 2H, CH_2CH_2S), 2.76 (dd, *J* = 10.8, 13.8, 1H, $CH_AC_6H_5$), 3.95 (dd, *J* = 10.2, 13.8, 1H, $CH_BC_6H_5$), 4.11-4.17 (m, 1H, $CHCH(CH_3)_2$), 4.27-4.33 (m, 2H, $CHCONH_2$, $CHNHCO_2$), 4.94 (s, 2H, $OCH_2C_6H_5$), 7.10 (s, 1H, NH_A), 7.17-7.36 (m, 12H, $C_6H_5\times2$, NH_B, NHCO), 7.55 (d, *J* = 8.6, 1H, $NHCHCONH_2$), 8.23 (d, *J* = 8.2, 1H, $NHCO_2$); ^{13}C NMR (100 MHz, DMSO-d^6): δ = 14.5, 14.6, 17.6, 18.3, 19.1, 29.7, 29.7, 30.0, 30.4, 31.3, 37.2, 52.4, 51.8, 56.0, 56.2, 57.9, 58.3, 65.2, 65.4, 126.2, 126.3, 127.4, 127.6, 127.8, 128.0, 128.3, 128.3, 129.2, 129.3, 136.8, 137.0, 137.6, 138.0, 155.8, 170.9,

171.8, 172.2, 173.1, 173.2; HRMS (ESI-TOF): Calcd for $C_{27}H_{36}N_4O_5SNa$ $(M+Na)^+$: 551.2299, Found: 551.2336; IR (KBr, ν_{max}/cm^{-1}) = 3284 (NH), 1676 (CON), 1635 (CON).

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