Synthesis S. Jung et al. Paper

Synthesis of Acetaminophen Analogues Containing α-Amino Acids and Fatty Acids for Inhibiting Hepatotoxicity

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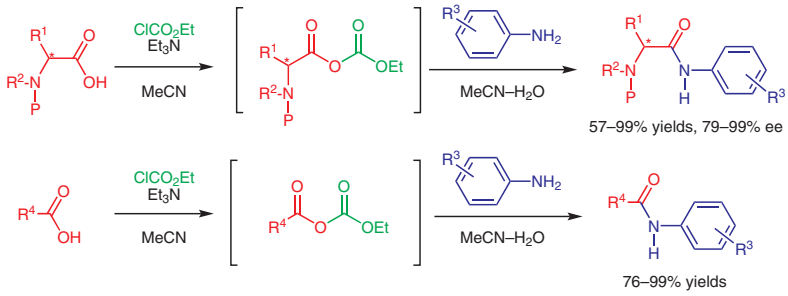
Dedicated to Professor E. J. Corey on the occasion of his 90th birthday.



Received: 13.05.2019
Accepted after revision: 27.06.2019
Published online: 15.07.2019
DOI: 10.1055/s-0037-1611893; Art ID: ss-2019-s0321-op

Abstract Acetaminophen is a popular antipyretic analgesic medicine that has weaker anti-inflammatory properties and lower incidence of side effects than nonsteroidal anti-inflammatory drugs (NSAIDs). However, acetaminophen causes hepatotoxicity due to the reactive metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI). We have obtained acetaminophen analogues in 57–99% yields by using aniline derivatives with protected α-amino acids and fatty acids via the corresponding mixed carbonic carboxylic anhydrides in aqueous MeCN. We have also succeeded in synthesizing AM404 analogues in 76–97% yields, which are expected to be promising candidates for reducing hepatotoxicity.

Key words acetaminophen, hepatotoxicity, α-amino acid, fatty acid, AM404

Medicines are metabolized and their chemical structures are changed after being taken into the body. The formation of reactive intermediates such as electrophiles and free radicals often induces various toxicities against the body; thus, much research on the reactive metabolites has been done to date. It is important to prevent the potential production of reactive metabolites from pharmaceuticals in the design manufacturing stages because they can cause a variety of toxic effects.[1]

Acetaminophen is a popular antipyretic analgesic medicine that has 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 a result, NAPQI accumulates, binds to intracellular macromolecules, and causes hepatocellular necrosis.[2] Furthermore, Zygmunt et al. have recently reported that the physiological action of acetaminophen is very similar to that of *N*-(4-hydroxyphenyl)arachidonamide (AM 404) (Figure 1).[3] AM 404 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.[4] Therefore, acetaminophen analogues of various fatty acids are interesting as AM404 analogues.

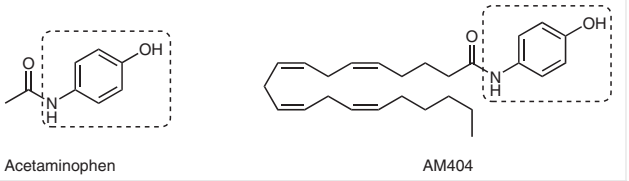


Figure 1

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 re-

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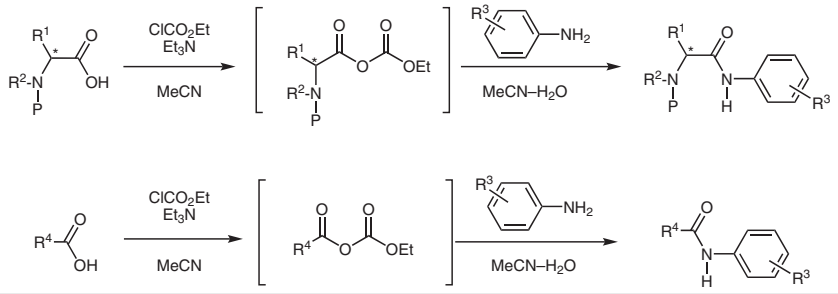


Scheme 1

spect to workup. Recently, Szostak demonstrated highly selective transition-metal-free transamidation of amides and amidation of esters in an interesting study.[5] We have also reported the syntheses of various amides from N-protected α-amino acids and N-protected dipeptides via the corresponding mixed carbonic carboxylic anhydrides.[6]

Herein, we describe in detail the synthesis of various acetaminophen analogues[6f] via the corresponding carbonic carboxylic anhydride. 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. We have also prepared AM404 analogues containing fatty acids (Scheme 1).

In a preliminary investigation, 3-phenylpropionic acid (**1**) was reacted with 1.1 equiv of 4-chloroaniline (**2a**) in the presence of 1.1 equiv of Et_3N and 1.4 equiv of $ClCO_2Et$ in aqueous tetrahydrofuran (THF) for 1.5 hours at 0 °C to give 57% yield of **3a** and 34% yield of by-product **4a**. The optimized conditions for the preparation of **3a** afforded 88% yield using 1.1 equiv of Et_3N, 1.1 equiv of $ClCO_2Et$, and 1.1 equiv of **2a**. The solvent effect of the amidation using **1** and **2a** was then examined for 24 hours at 0 °C. The amidation in aprotic polar solvents such as THF, acetone, and MeCN gave **3a** in excellent yields of 89–96%. However, the amidation in nonpolar solvent such as 1,4-dioxane and in protonic polar solvent such as EtOH and MeOH to give **3a** in 50% and 13% yield, respectively. MeCN was thus selected as an optimal solvent for synthesizing **3a** (96% yield) as described in the previously reported article.[6f]

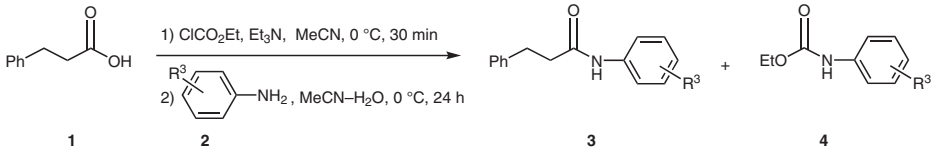
The reactions of **1** with various anilines **2a–r** were then carried out; the results are collected in Table 1. Acid **1** reacted with anilines **2a–f** and **2h–j**, containing an electron-withdrawing group, to produce the corresponding amides **3a–f** and **3h–j** in yields of 30–98% as described 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 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).

We also examined the condensation of α-amino acids and fatty acids using 4-aminophenol (**2m**), 2-ethoxyaniline (**2n**), and 4-ethoxyaniline (**2o**) for the synthesis of acetaminophen analogues. Table 2 shows the results of the condensation of various α-amino acids 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 2, 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 previous ones[6f] because the products were clearly separated by using a small amount of acetic acid with the eluents in order to avoid tailing of the products on silica gel during purification by column chromatography.

Finally, 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 Table 3 and Table 4, 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 hours by analyses using 2D TLC and ^1H NMR spectra, and no change was observed. Although unsaturated fatty acids are usually sensitive in air and at room temperature, it was found that the synthesized AM404 analogues were relatively stable.

Table 1 Reaction of 3-Phenylpropanoic Acid **1** with Aniline Derivatives **2**[a]

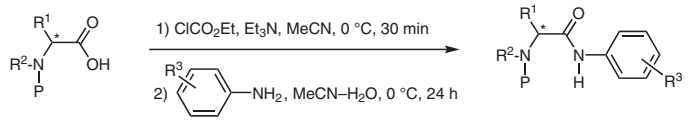


1 2 3 4

Entry	R^3	2	3	Yield of **3** (%)[b]	Yield of **4** (%)[b]
1[c]	4-Cl	**2a**	**3a**	96	trace
2[c]	4-F	**2b**	**3b**	97	0
3[c]	2,3,4,5,6-F_5	**2c**	**3c**	67	34
4[c]	4-EtO_2C	**2d**	**3d**	70	0
5[c]	4-O_2N	**2e**	**3e**	65	0
6[c]	3,5-$(O_2N)_2$	**2f**	**3f**	30	0
7[c]	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[c]	H	**2k**	**3k**	94	trace
12[c]	4-Me	**2l**	**3l**	95	1
13[c]	4-HO	**2m**	**3m**	92	3
14[c]	2-EtO	**2n**	**3n**	89	trace
15[c]	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] Reaction conditions: **1** (0.5 mmol), Et_3N (0.55 mmol), $ClCO_2Et$ (0.55 mmol), MeCN (10 mL). After stirring for 30 min at 0 °C, H_2O (0.75 mL) and **2** were added at 0 °C to the reaction mixture.
[b] Isolated yield.
[c] Described in the previously reported article.[6f]

Table 2 Synthesis of Acetaminophen Analogues **6** Containing α-Amino Acids **5**[a]



5 2 6

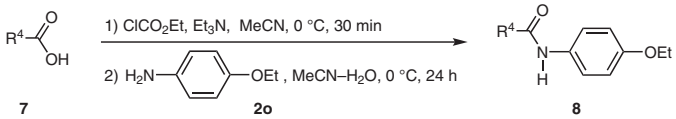
Entry	P	R^1	R^2	5	R^3	6	Yield (%)[b]	ee (%)[d]	Retention time (min)
1[c]	Cbz	$PhCH_2$ (L)	H	**5aL**	4-EtO	**6aLo**	96	>99	15
2[c]	Cbz	$PhCH_2$ (D)	H	**5aD**	4-EtO	**6aDo**	97	>99	17
3[c]	Cbz	$PhCH_2$ (L)	H	**5aL**	2-EtO	**6aLn**	91	>99	26
4[c]	Cbz	$PhCH_2$ (D)	H	**5aD**	2-EtO	**6aDn**	91	>99	51
5[c]	Cbz	$PhCH_2$ (L)	H	**5aL**	4-OH	**6aLm**	88	>99	26
6[c]	Cbz	$PhCH_2$ (D)	H	**5aD**	4-OH	**6aDm**	88	>99	30
7[c]	Cbz	Me_2CH (L)	H	**5bL**	4-EtO	**6bLo**	97	>99	10
8[c]	Cbz	Me_2CH (D)	H	**5bD**	4-EtO	**6bDo**	99	>99	11
9[c]	Cbz	Me (L)	H	**5cL**	4-EtO	**6cLo**	82	>99	14
10[c]	Cbz	Me (D)	H	**5cD**	4-EtO	**6cDo**	91	98	16

Table (continued)

Entry	P	R^1	R^2	5	R^3	6	Yield (%)[b]	ee (%)[d]	Retention time (min)
11[c]	Cbz	$MeS(CH_2)_2$ (L)	H	**5dL**	4-EtO	**6dLo**	85	>99	15
12[c]	Cbz	$MeS(CH_2)_2$ (D)	H	**5dD**	4-EtO	**6dDo**	88	>99	20
13[c]	Cbz	$(CH_2)_3$ (L)		**5eL**	4-EtO	**6eLo**	99	>99[e]	56
14[c]	Cbz	$(CH_2)_3$ (D)		**5eD**	4-EtO	**6eDo**	99	>99[e]	20
15[c]	Boc	$PhCH_2$ (L)	H	**5fL**	4-EtO	**6fLo**	99	>99	13
16[c]	Boc	$PhCH_2$ (D)	H	**5fD**	4-EtO	**6fDo**	99	95	8
17[c]	Fmoc	$PhCH_2$ (L)	H	**5gL**	4-EtO	**6gLo**	82	>99[f]	29
18[c]	Fmoc	$PhCH_2$ (D)	H	**5gD**	4-EtO	**6gDo**	95	>99[f]	11
19	Boc	$C_6H_5CH_2OCH_2$ (L)	H	**5hL**	4-EtO	**6hLo**	93	>99[g]	19
20	Boc	$C_6H_5CH_2OCH_2$ (D)	H	**5hD**	4-EtO	**6hDo**	95	98[g]	16
21	Fmoc	Ph_3CSCH_2 (L)	H	**5iL**	4-EtO	**6iLo**	77	79[f,h]	64
22	Fmoc	Ph_3CSCH_2 (D)	H	**5iD**	4-EtO	**6iDo**	79	86[f,h]	55
23	Cbz	*p*-$HOC_6H_4CH_2$ (L)	H	**5jL**	4-EtO	**6jLo**	65	>99[f]	62
24	Cbz	*p*-$HOC_6H_4CH_2$ (D)	H	**5jD**	4-EtO	**6jDo**	57	>99[f]	81
25	Cbz	$C_8H_6NCH_2$ (L)	H	**5kL**	4-EtO	**6kLo**	91	>99[e,i]	121
26	Cbz	$C_8H_6NCH_2$ (D)	H	**5kD**	4-EtO	**6kDo**	91	>99[e,i]	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] Reaction conditions: N-protected α-amino acid **5** (0.50 mmol), Et_3N (0.55 mmol), $ClCO_2Et$ (0.55 mmol), MeCN (10 mL). After stirring for 30 min at 0 °C, H_2O (0.75 mL) and aniline derivative **2** (0.55 mmol) were added at 0 °C to the reaction mixture.
[b] Isolated yield.
[c] Described in the previously reported article.[6f]
[d] Determined by HPLC analysis with a 90:10 mixture of hexane and isopropanol as eluent, using Chiralcel OD (1.0 mL/min).
[e] Determined by HPLC analysis with a 90:10 mixture of hexane and isopropanol as an eluent, using Chiralcel AS (1.0 mL/min).
[f] Determined by HPLC analysis with a 90:10 mixture of hexane and isopropanol as an eluent, using Chiralcel ADH (1.0 mL/min).
[g] Determined by HPLC analysis with a 95:5 mixture of hexane and isopropanol as an eluent, using Chiralcel OD (1.0 mL/min).
[h] The reactions were carried out at –15 °C.
[i] Cbz was deprotected.

Table 3 Synthesis of AM404 Analogues **8** Containing Fatty Acids **7**[a]



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

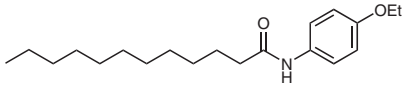
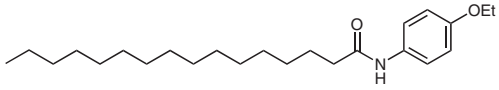
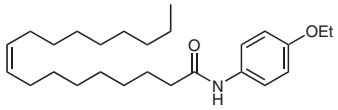
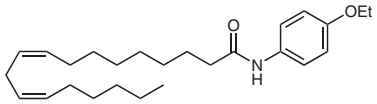
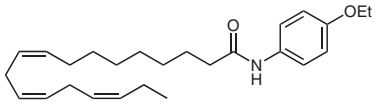
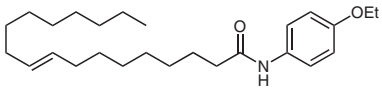
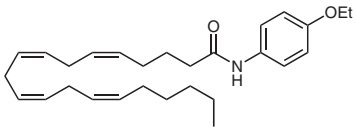
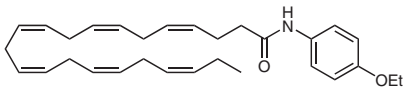
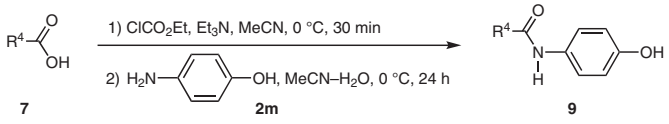
Entry	R^4-CO_2H	7		8	Yield (%)[b]
1[c]	lauric acid (c_{12})	**7a**		**8ao**	97
2[c]	palmitic acid (c_{16})	**7b**		**8bo**	98
3[c]	oleic acid (c_{18-1})	**7c**		**8co**	89

Table (continued)

Entry	R^4-CO_2H	7		8	Yield (%)[b]
4[c]	linoleic acid (c_{18-2})	**7d**		**8do**	93
5[c]	linolenic acid (c_{18-3})	**7e**		**8eo**	95
6	elaidic acid (c_{18-1})	**7f**		**8fo**	83
7[c]	arachidonic acid (c_{20-4})	**7g**		**8go**	93
8	docosahexaenoic acid (c_{22-6})	**7h**		**8ho**	99

[a] Reaction conditions: fatty acid **7** (1 equiv), Et_3N (1.1 equiv), $ClCO_2Et$ (1.1 equiv) in MeCN. After stirring for 30 min at 0 °C, H_2O and **2o** (1.1 equiv) were added at 0 °C to the reaction mixture.
[b] Isolated yield.
[c] Described in the previously reported article.[6f]

Table 4 Synthesis of AM404 Analogues **9** Containing Fatty Acids **7**[a]



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

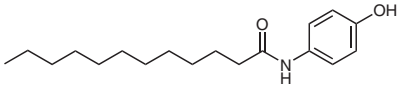
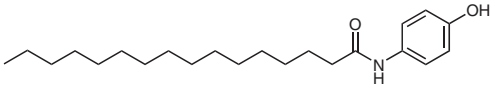
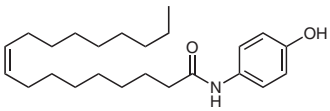
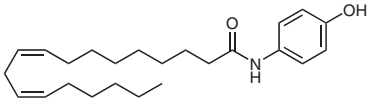
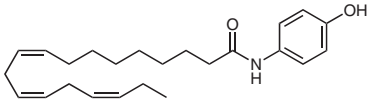
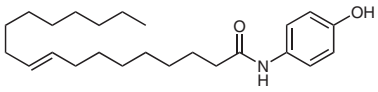
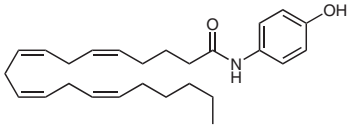
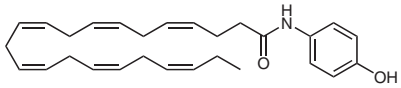
Entry	R^4-CO_2H	7		9	Yield (%)[b]
1	lauric acid (c_{12})	**7a**		**9am**	87
2	palmitic acid (c_{16})	**7b**		**9bm**	76
3	oleic acid (c_{18-1})	**7c**		**9cm**	79
4	linoleic acid (c_{18-2})	**7d**		**9dm**	94
5	linolenic acid (c_{18-3})	**7e**		**9em**	82

Table (continued)

Entry	R^4-CO_2H	7		9	Yield (%)[b]
6	elaidic acid (c_{18-1})	**7f**		**9fm**	97
7	arachidonic acid (c_{20-4})	**7g**		**9gm**	90
8	docosahexaenoic acid (c_{22-6})	**7h**		**9hm**	78

[a] Reaction conditions: fatty acid **7** (1 equiv), Et_3N (1.1 equiv), $ClCO_2Et$ (1.1 equiv) in MeCN. After stirring for 30 min at 0 °C, H_2O and **2m** (1.1 equiv) were added at 0 °C to the reaction mixture.
[b] Isolated yield.

In conclusion, we have synthesized acetaminophen analogues **6aLo–mDo** in 57–99% yields, AM404 analogues **8ao–ho** in 83–99% yields, and **9am–hm** in 76–97% yields, by using a convenient and economical procedure. 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 mild conditions. In particular, both of the activating agents (ethyl $ClCO_2Et$ 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 proceeded smoothly in aqueous organic solvent to afford the corresponding amides. Our synthetic method is also characterized by no racemization and low levels of by-product formation.

All reagents were used without further purification. The ^1H NMR and ^{13}C NMR spectra were measured with a Bruker Ultrashield TM 400 Plus spectrometer. The chemical shifts 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). 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 with a HORIBA FT-IR Fourier transform infrared spectrophotometer.

Amidation of 3-Phenylpropionic Acid (1) with 4-Chloroanilne (2a); Typical Procedure

To a colorless solution of 3-phenylpropionic acid **1** (75 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-chloroanilne **2a** (70 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 resulting suspension was extracted with EtOAc (50 mL), washed with brine (10 mL), and 1.0 M 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**.

N-(4-Chlorophenyl)-3-phenylpropanamide (3a)[6f]

Yield: 125 mg (96%); colorless powder; mp 137–139 °C.

IR (KBr): 3302 (NH), 1657 (CON) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.66 (t, *J* = 7.6 Hz, 2 H, CH_2CO), 3.05 (t, *J* = 7.6 Hz, 2 H, CH_2CH_2CO), 6.95 (br s, 1 H, NH), 7.21–7.38 (m, 9 H, 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): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{14}NOClNa$: 282.0656; found: 282.0667.

N-(4-Fluorophenyl)-3-phenylpropanamide (3b)[6f]

Yield: 118 mg (97%); colorless powder; mp 119–120 °C.

IR (KBr): 3289 (NH), 1652 (CON) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.65 (t, *J* = 7.4 Hz, 2 H, CH_2CO), 3.05 (t, *J* = 7.4 Hz, 2 H, CH_2CH_2CO), 6.96–7.02, 7.21–7.39 (m, m, 3 H, 7 H, 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): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{14}FNONa$: 266.0952; found: 266.0977.

_N_-(2,3,4,5,6-Pentafluorophenyl)-3-phenylpropanamide (3c)[6f]

Yield: 105 mg (67%); colorless powder; mp 128–129 °C.

IR (KBr): 3265 (NH), 1685 (CON) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.77 (t, *J* = 7.4 Hz, 2 H, CH_2CO), 3.07 (t, *J* = 7.4 Hz, 2 H, CH_2CH_2CO), 6.57 (br s, 1 H, NH), 7.22–7.34 (m, 5 H, 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): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{10}F_5NONa$: 338.0575; found: 338.0593.

Ethyl 4-(3-Phenylpropanamido)benzoate (3d)[6f]

Yield: 104 mg (70%); colorless powder; mp 132–133 °C.

IR (KBr): 3316 (NH), 1711 (CO_2), 1593 (CON) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2O), 2.69 (t, *J* = 7.4 Hz, 2 H, CH_2CO), 3.06 (t, *J* = 7.4 Hz, 2 H, CH_2CH_2CO), 4.53 (q, *J* = 7.1 Hz, 2 H, CH_3CH_2O), 7.21–7.33 (m, 6 H, NH, C_6H_5), 7.50, 7.98 (d, d, *J* = 8.7, 8.7 Hz, 2 H, 2 H, 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): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{19}NO_3Na$: 320.1257; found: 320.1250.

_N_-(4-Nitrophenyl)-3-phenylpropanamide (3e)[6f]

Yield: 88 mg (65%); yellow powder; mp 121–123 °C.

IR (KBr): 3249 (NH), 1670 (CON), 1504 (NO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.73 (t, *J* = 7.4 Hz, 2 H, CH_2CO), 3.08 (t, *J* = 7.4 Hz, 2 H, CH_2CH_2CO), 7.18 (br s, 1 H, NH), 7.23–7.35 (m, 5 H, C_6H_5), 7.59, 8.19 (d, d, *J* = 9.2, 9.2 Hz, 2 H, 2 H, 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): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}N_2O_3$: 271.1077; found: 271.1069.

_N_-(3,5-Dinitrophenyl)-3-phenylpropanamide (3f)[6f]

Yield: 47 mg (30%); yellow powder; mp 166–167 °C.

IR (KBr): 3357 (NH), 1710 (CON), 1540 (NO) cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 2.75 (t, *J* = 7.6 Hz, 2 H, CH_2CO), 3.02 (t, *J* = 7.6 Hz, 2 H, CH_2CH_2CO), 7.18 (br s, 1 H, NH), 7.14–7.29 (m, 5 H, C_6H_5), 8.64, 8.21 (t, d, *J* = 2.1, 2.1 Hz, 1 H, 2 H, C_6H_3).

^{13}C NMR (100 MHz, CD_3OD): 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): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{13}N_3O_5Na$: 338.0747; found: 338.0747.

_N_-(4-Bromophenyl)-3-phenylpropanamide (3h)

Yield: 148 mg (98%); colorless powder; mp 150–151 °C.

IR (KBr): 3298 (NH), 1658 (CON) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.65 (t, *J* = 7.5 Hz, 2 H, CH_2CO), 3.05 (t, *J* = 7.5 Hz, 2 H, CH_2CH_2CO), 7.00 (br s, 1 H, NH), 7.21–7.41 (m, 9 H, 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): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{14}NOBrNa$: 326.0151; found: 326.0112.

_N_-(4-Iodophenyl)-3-phenylpropanamide (3i)

Yield: 165 mg (94%); colorless powder; mp 163–165 °C.

IR (KBr): 3298 (NH), 1655 (CON) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.65 (t, *J* = 7.5 Hz, 2 H, CH_2CO), 3.04 (t, *J* = 7.5 Hz, 2 H, CH_2CH_2CO), 6.95 (br s, 1 H, NH), 7.19–7.32, 7.57–7.61 (m, m, 7 H, 2 H, 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): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{14}INONa$: 374.0012; found: 373.9984.

_N_-(4-Cyanophenyl)-3-phenylpropanamide (3j)

Yield: 109 mg (87%); colorless powder; mp 115–117 °C.

IR (KBr): 3257 (NH), 2218 (CN), 1672 (CON) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.68 (t, *J* = 7.6 Hz, 2 H, CH_2CO), 2.91 (t, *J* = 7.6 Hz, 2 H, CH_2CH_2CO), 7.18–7.30 (m, 5 H, C_6H_5), 7.72–7.90 (m, 4 H, C_6H_4), 10.36 (s, 1 H, 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): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_2O$: 251.1179; found: 251.1172.

***N*,3-Diphenylpropanamide (3k)**[6f]

Yield: 106 mg (94%); colorless powder; mp 130–133 °C.

IR (KBr): 3322 (NH), 1650 (CON) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.67 (t, *J* = 7.7 Hz, 3 H, CH_2CO), 3.07 (t, *J* = 7.7 Hz, 2 H, CH_2CH_2CO), 6.96 (br s, 1 H, NH), 7.08–7.44 (m, 10 H, 2 × C_6H_5).

^{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): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{15}NONa$: 248.1046; found: 248.1068.

_N_-(4-Methylphenyl)-3-phenylpropanamide (3l)[6f]

Yield: 114 mg (95%); colorless powder; mp 97–98 °C.

IR (KBr): 3300 (NH), 1657 (CON) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, CH_3), 2.30 (t, *J* = 7.4 Hz, 2 H, CH_2CO), 3.06 (t, *J* = 7.4 Hz, 2 H, CH_2CH_2CO), 6.90 (br s, 1 H, NH), 7.09–7.11, 7.20–7.33 (m, m, 2 H, 7 H, 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): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{17}NONa$: 262.1202; found: 262.1172.

_N_-(4-Hydroxyphenyl)-3-phenylpropanamide (3m)[6f]

Yield: 111 mg (92%); colorless powder; mp 143–145 °C.

IR (KBr): 3325 (OH), 1660 (CON) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.55 (t, J = 7.7 Hz, 2 H, CH_2CO), 2.88 (t, J = 7.7 Hz, 2 H, CH_2CH_2CO), 6.65–6.68, 7.15–7.34 (m, m, 2 H, 7 H, C_6H_4, C_6H_5), 9.14 (s, 1 H, NH), 9.63 (s, 1 H, 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): m/z [M + Na]$^+$ calcd for $C_{15}H_{15}NO_2Na$: 264.0995; found: 264.1019.

***N*-(2-Ethoxyphenyl)-3-phenylpropanamide (3n)**[6f]

Yield: 120 mg (89%); colorless powder; mp 79–80 °C.

IR (KBr): 3298 (NH), 1653 (CON) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (t, J = 7.0 Hz, 3 H, CH_3CH_2O), 2.71 (t, J = 7.8 Hz, 2 H, CH_2CO), 3.07 (t, J = 7.8 Hz, 2 H, CH_2CH_2CO), 4.07 (q, J = 7.0 Hz, 2 H, CH_3CH_2O), 6.83–7.32, 8.38–8.40 (m, m, 8 H, 1 H, C_6H_4, C_6H_5), 7.73 (br s, 1 H, 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): m/z [M + Na]$^+$ calcd for $C_{17}H_{19}NO_2Na$: 292.1308; found: 292.1268.

***N*-(4-Ethoxyphenyl)-3-phenylpropanamide (3o)**[6f]

Yield: 132 mg (98%); colorless powder; mp 131–133 °C.

IR (KBr): 3292 (NH), 1652 (CON) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, J = 7.0 Hz, 3 H, CH_3CH_2O), 2.64 (t, J = 7.4 Hz, 2 H, CH_2CO), 3.06 (t, J = 7.4 Hz, 2 H, CH_2CH_2CO), 4.00 (q, J = 7.0 Hz, CH_3CH_2O), 6.82–6.84, 7.18–7.36 (m, m, 3 H, 7 H, 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): m/z [M + Na]$^+$ calcd for $C_{17}H_{19}NO_2Na$: 292.1308; found: 292.1313.

***N*-(4-Mercaptophenyl)-3-phenylpropanamide (3p)**

Yield: 118 mg (92%); colorless powder; mp 197–199 °C.

IR (KBr): 3326 (NH), 1658 (CON) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.65 (t, J = 7.5 Hz, 2 H, CH_2CO), 3.05 (t, J = 7.5 Hz, 2 H, CH_2CH_2CO), 3.41 (s, 1 H, SH), 6.90 (br s, 1 H, NH), 7.22–7.33 (m, 9 H, 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): m/z [M + Na]$^+$ calcd for $C_{30}H_{28}N_2O_2S_2Na$: 535.1484; found: 535.1502.

***N*-(4-*tert*-Butylphenyl)-3-phenylpropanamide (3q)**

Yield: 135 mg (96%); colorless powder; mp 139–141 °C.

IR (KBr): 3282 (NH), 1655 (CON) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.25 (s, 9 H, 3 × CH_3), 2.59 (t, J = 7.7 Hz, 2 H, CH_2CO), 2.90 (t, J = 7.7 Hz, 2 H, CH_2CH_2CO), 7.18–7.31, 7.46–7.49 (m, m, 7 H, 2 H, C_6H_4, C_6H_5), 9.82 (s, 1 H, 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): m/z [M + H]$^+$ calcd for $C_{19}H_{24}NO$: 282.1852; found: 282.1866.

***N*-Mesityl-3-phenylpropanamide (3r)**

Yield: 100 mg (75%); colorless powder; mp 171–173 °C.

IR (KBr): 3228 (NH), 1646 (CON) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.97–199 (m, 6 H, 2 × CH_3), 2.20 (s, 3 H, CH_3), 2.62 (t, J = 7.5 Hz, 3 H, CH_2CO), 2.92 (t, J = 7.5 Hz, 2 H, CH_2CH_2CO), 6.83 (s, 2 H, C_6H_2), 7.19–7.29 (m, 5 H, C_6H_5), 9.09 (s, 1 H, 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): m/z [M + Na]$^+$ calcd for $C_{18}H_{21}NONa$: 290.1515; found: 290.1546.

Amidation of Cbz-L-Phe-OH (5aL) with 4-Ethoxyaniline (2o); Typical Procedure

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 1.0 M aqueous HCl to pH 2. The resulting suspension was extracted with EtOAc (50 mL), washed with brine (10 mL), and 1.0 M aqueous $NaHCO_3$ (5 mL), 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**).

Cbz-L-Phe-NHC_6H_4-4-OEt (6aLo)[6f]

Yield: 201 mg (96%); colorless powder; >99% ee; mp 178–179 °C; $[\alpha]_D^{30}$ +69.0 (c 0.99, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90:10): t_r = 15 min.

IR (KBr): 3292 (NH), 1693 (CON), 1653 (CON) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, J = 7.0 Hz, 3 H, CH_3CH_2O), 3.10 (dd, J = 6.0, 7.8 Hz, 1 H, $CH_AC_6H_5$), 3.21 (dd, J = 6.0, 6.3 Hz, 1 H, $CH_BC_6H_5$), 3.99 (q, J = 7.0 Hz, 3 H, CH_3CH_2O), 4.48 (m, 1 H, CHCO), 5.12 (s, 2 H, $OCH_2C_6H_5$), 5.42 (br s, 1 H, NH), 6.78–6.82, 7.18–7.37 (m, m, 2 H, 13 H, NH, C_6H_4, 2 × C_6H_5).

^{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): m/z [M + Na]$^+$ calcd for $C_{25}H_{26}N_2O_4Na$: 441.1785; found: 441.1795.

Cbz-D-Phe-NHC_6H_4-4-OEt (6aDo)[6f]

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

Cbz-L-Phe-NHC_6H_4-2-OEt (6aLn)[6f]

Yield: 190 mg (91%); colorless powder; >99% ee; mp 143–145 °C; $[\alpha]_D^{30}$ –17.8 (c 0.98, DMSO).

IR (KBr): 3303 (NH), 1680 (CON), 1597 (CON) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, J = 7.0 Hz, 3 H, CH_3CH_2O), 3.18 (d, J = 6.6 Hz, 2 H, $CH_2C_6H_5$), 3.97 (q, J = 7.0 Hz, 2 H, CH_3CH_2O), 4.58–4.59 (m, 1 H, CHCO), 5.11 (s, 2 H, $OCH_2C_6H_5$), 5.39 (br s, 1 H, NH), 6.80, 6.94, 7.02, 8.33 (d, t, t, d, J = 8.1, 7.8, 7.8, 8.0 Hz, 1 H, 1 H, 1 H, 1 H, C_6H_4), 7.20–7.32 (m, 10 H, 2 × C_6H_5), 8.11 (br s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{26}N_2O_4Na$: 441.1785; found: 441.1795.

The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90:10): t_r =26 min.

Cbz-D-Phe-NHC$_6$H$_4$-2-OEt (6aDn)[6f]

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

Cbz-L-Phe-NHC$_6$H$_4$-4-OH (6aLm)[6f]

Yield: 172 mg (88%); colorless powder; >99% ee; mp 184–185 °C; $[\alpha]_D^{29}$ +65.8 (*c* 1.02, DMSO).The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90:10): t_r = 26 min.

IR (KBr): 3649 (OH), 1687 (CON), 1660 (CON) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.83 (dd, *J* = 9.2, 10.3 Hz, 1 H, CH_AC$_6$H$_5$), 3.00 (dd, *J* = 9.2, 4.4 Hz, 1 H, CH_BC$_6$H$_5$), 4.36–4.37 (m, 1 H, CHCO), 4.96 (s, 2 H, OCH_2C$_6$H$_5$), 6.68–6.71, 7.18–7.37, 7.64–7.70 (m, m, m, 2 H, 12 H, 1 H, NH, C$_6$H$_4$, 2 × C$_6$H$_5$), 9.20 (s, 1 H, NH), 9.85 (s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{22}N_2O_4Na$: 413.1472; found: 413.1503.

Cbz-D-Phe-NHC$_6$H$_4$-4-OH (6aDm)[6f]

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.

Cbz-L-Val-NHC$_6$H$_4$-4-OEt (6bLo)[6f]

Yield: 179 mg (97%); colorless powder; >99% ee; mp 210–212 °C; $[\alpha]_D^{31}$ +37.1 (*c* 1.02, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90:10): t_r = 10 min.

IR (KBr) = 3300 (NH), 1689 (CON), 1654 (CON) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (d, d, *J* = 6.8, 6.8 Hz, 3 H, 3 H, (CH_3)$_2$CH), 1.39 (t, *J* = 7.0 Hz, 3 H, CH_3CH$_2$O), 2.18–2.26 (m, 1 H, CH(CH$_3$)$_2$), 4.00 (q, *J* = 7.0 Hz, 2 H, CH$_3$CH_2O), 4.07 (m, 1 H, CHCO), 5.11 (s, 2 H, OCH_2C$_6$H$_5$), 5.44 (br s, 1 H, NH), 6.81–6.83, 7.34–7.37 (m, m, 2 H, 7 H, C$_6$H$_4$, C$_6$H$_5$), 7.76 (br s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{26}N_2O_4Na$: 393.1785; found: 393.1732.

Cbz-D-Val-NHC$_6$H$_4$-4-OEt (6bDo)[6f]

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.

Cbz-L-Ala-NHC$_6$H$_4$-4-OEt (6cLo)[6f]

Yield: 140 mg (82%); colorless powder; >99% ee; mp 163–164 °C; $[\alpha]_D^{31}$ +1.2 (*c* 1.02, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90:10): t_r = 14 min.

IR (KBr): 3357 (NH), 1693 (CON), 1668 (CON) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, *J* = 7.0 Hz, 3 H, CH_3CH$_2$O), 1.46 (d, *J* = 7.0 Hz, 3 H, CH_3CH), 4.01 (q, *J* = 7.0 Hz, 2 H, CH$_3$CH_2O), 4.22–4.37 (m, 1 H, CHCO), 5.13 (s, 2 H, OCH_2C$_6$H$_5$), 5.28 (br s, 1 H, NH), 6.83–6.86, 7.32–7.38 (m, m, 2 H, 7 H, C$_6$H$_4$, C$_6$H$_5$), 7.94 (br s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{22}N_2O_4Na$: 365.1472; found: 365.1440.

Cbz-D-Ala-NHC$_6$H$_4$-4-OEt (6cDo)[6f]

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.

Cbz-L-Met-NHC$_6$H$_4$-4-OEt (6dLo)[6f]

Yield: 171 mg (85%); colorless powder; >99% ee; mp 129–130 °C; $[\alpha]_D^{31}$ +14.7 (*c* 0.98, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90:10): t_r = 15 min.

IR (KBr): 3288 (NH), 1689 (CON), 1653 (CON) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.30 (t, *J* = 6.9 Hz, 3 H, CH_3CH$_2$O), 1.86–1.91 (m, 4 H, CH$_2$CH$_2$S), 2.05 (s, 3 H, CH$_3$S), 3.98 (q, *J* = 6.9 Hz, 2 H, CH$_3$CH_2O), 4.20–4.21 (m, 1 H, CHCO), 5.03 (s, 1 H, OCH_2C$_6$H$_5$), 6.86, 7.49 (d, d, *J* = 8.4, 8.4 Hz, 2 H, 2 H, C$_6$H$_4$), 7.31–7.64 (m, 6 H, NH, C$_6$H$_5$), 9.90 (s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{26}N_2O_4Na$: 425.1505; found: 425.1554.

Cbz-D-Met-NHC$_6$H$_4$-4-OEt (6dDo)[6f]

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.

Cbz-L-Pro-NHC$_6$H$_4$-4-OEt (6eLo)[6f]

Yield: 182 mg (99%); colorless powder; >99% ee; mp 112–114 °C; $[\alpha]_D^{30}$ –38.3 (*c* 0.99, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel AS: hexane/2-propanol = 90:10): t_r = 56 min.

IR (KBr): 3269 (NH), 1709 (CON), 1664 (CON) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, *J* = 6.9 Hz, 3 H, CH_3CH$_2$O), 1.95–2.55, 3.46–3.53 (m, m, 4 H, 2 H, pyrrolidinyl H), 4.01 (q, *J* = 6.9 Hz, 2 H, CH$_3$CH_2O), 4.39–4.52 (m, 1 H, CHCO), 5.21 (s, 2 H, OCH_2C$_6$H$_5$), 6.81–6.83, 7.26–7.37 (m, m, 2 H, 8 H, NH, C$_6$H$_4$, C$_6$H$_5$), 8.97 (br s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{24}N_2O_4Na$: 391.1628; found: 391.1620.

Cbz-D-Pro-NHC$_6$H$_4$-4-OEt (6eDo)[6f]

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.

Boc-L-Phe-NHC$_6$H$_4$-4-OEt (6fLo)[6f]

Yield: 190 mg (99%); colorless powder; >99% ee; mp 159–161 °C; $[\alpha]_D^{31}$ +75.9 (*c* 0.98, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90:10): t_r = 13 min.

IR (KBr): 3344 (NH), 1691 (CON), 1664 (CON) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.23–1.32 (m, 12 H, C*H*$_3$CH$_2$O, (CH$_3$)$_3$C), 2.82 (dd, *J* = 10.3, 10.4 Hz, 1 H, C*H*$_A$C$_6$H$_5$), 2.97 (dd, *J* = 8.8, 10.3 Hz, 1 H, C*H*$_B$C$_6$H$_5$), 3.98 (q, *J* = 7.0 Hz, 2 H, CH$_3$C*H*$_2$O), 4.25–4.31 (m, 1 H, CHCO), 6.87, 7.46 (d, d, *J* = 9.0, 9.0 Hz, 2 H, 2 H, C$_6$H$_4$), 7.06–7.31 (m, 6 H, NH, C$_6$H$_5$), 9.87 (s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for C$_{22}$H$_{28}$N$_2$O$_4$Na: 407.1941; found: 407.1909.

Boc-D-Phe-NHC$_6$H$_4$-4-OEt (6fDo)[6f]

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

Fmoc-L-Phe-NHC$_6$H$_4$-4-OEt (6gLo)[6f]

Yield: 207 mg (82%); colorless powder; >99% ee; mp 218–220 °C; $[\alpha]_D^{29}$ +20.5 (*c* 1.00, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel ADH: hexane/2-propanol = 90:10): t_r = 29 min.

IR (KBr): 3307 (NH), 1691 (CON), 1654 (CON) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.31 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$CH$_2$O), 2.89 (dd, *J* = 10.2, 10.3 Hz, 1 H, C*H*$_A$C$_6$H$_5$), 3.02 (dd, *J* = 4.7, 10.2 Hz, 1 H, C*H*$_B$C$_6$H$_5$), 3.98 (q, *J* = 7.0 Hz, 2 H, CH$_3$C*H*$_2$O), 4.16–4.19 (m, 3 H, CHCH$_2$O), 4.38 (m, 1 H, CHCO), 6.86–6.88, 7.20–7.89 (m, m, 2 H, 16 H, NH, C$_6$H$_4$, C$_6$H$_5$, fluorenyl H), 9.97 (s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for C$_{32}$H$_{30}$N$_2$O$_4$Na: 529.2098; found: 529.2053.

Fmoc-D-Phe-NHC$_6$H$_4$-4-OEt (6gDo)[6f]

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

***O*-Benzyl-Boc-L-Ser-NHC$_6$H$_4$-4-OEt (6hLo)**

Yield: 193 mg (93%); colorless powder; >99% ee; mp 104–105 °C; $[\alpha]_D^{30}$ +13.8 (*c* 1.02, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95:5): t_r = 19 min.

IR (KBr): 3350 (NH), 1687 (CON), 1664 (CON) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.30 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$CH$_2$O), 1.39 (s, 9 H, (CH$_3$)$_3$C), 3.60–3.65 (m, 2 H, C*H*$_2$CHCO), 3.98 (q, *J* = 7.0 Hz, 2 H, CH$_3$C*H*$_2$O), 4.34–4.38 (m, 1 H, CHCO), 4.50 (s, 2 H, OC*H*$_2$C$_6$H$_5$), 6.87, 7.49 (d, d, *J* = 6.9, 6.9 Hz, 2 H, 2 H, C$_6$H$_4$), 6.98–7.33 (m, 6 H, NH, C$_6$H$_5$), 9.91 (s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for C$_{23}$H$_{30}$N$_2$O$_5$Na: 437.2047; found: 437.2057.

***O*-Benzyl-Boc-D-Ser-NHC$_6$H$_4$-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 = 16 min.

***S*-Trityl-Fmoc-L-Cys-NHC$_6$H$_4$-4-OEt (6iLo)**

Yield: 271 mg (77%); colorless powder; 79% ee; mp 191–193 °C; $[\alpha]_D^{30}$ –10.0 (*c* 0.98, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel ADH: hexane/2-propanol = 90:10): t_r = 64 min.

IR (KBr): 3292 (NH), 1685 (CON), 1662 (CON) cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.39 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$CH$_2$O), 2.71–2.79 (m, 2 H, SC*H*$_2$CHCO), 3.84–3.87 (m, 1 H, SCH$_2$C*H*CO), 3.99 (q, *J* = 7.0 Hz, 2 H, CH$_3$C*H*$_2$O), 4.18 (t, *J* = 6.8 Hz, 1 H, C*H*CH$_2$OCO), 4.42 (d, *J* = 6.8 Hz, 2 H, CHC*H*$_2$OCO), 5.01 (br s, 1 H, NH), 6.80–6.82, 7.18–7.76 (m, m, 2 H, 26 H, C$_6$H$_4$, NH, 3 × C$_6$H$_5$, 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): *m*/*z* [M + Na]$^+$ calcd for C$_{45}$H$_{40}$N$_2$O$_4$SNa: 727.2602; found: 727.2616.

***S*-Trityl-Fmoc-D-Cys-NHC$_6$H$_4$-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.

Cbz-L-Tyr-NHC$_6$H$_4$-4-OEt (6jLo)

Yield: 141 mg (65%); colorless powder; >99% ee; mp 170–171 °C; $[\alpha]_D^{30}$ +64.4 (*c* 1.01, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel ADH: hexane/2-propanol = 90:10): t_r = 62 min.

IR (KBr): 3413 (OH), 3313 (NH), 1710 (CON), 1668 (CON) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.31 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$CH$_2$O), 3.00 (dd, *J* = 5.1, 9.2 Hz, 1 H, C*H*$_A$C$_6$H$_4$), 3.14 (dd, *J* = 9.1, 9.2 Hz, C*H*$_B$C$_6$H$_4$), 3.98 (q, *J* = 7.0 Hz, 2 H, CH$_3$C*H*$_2$O), 4.42–4.44 (m, 1 H, CHCO), 4.97 (s, 2 H, OC*H*$_2$C$_6$H$_5$), 6.85–7.69 (m, 14 H, 2 × C$_6$H$_4$, NH, C$_6$H$_5$), 9.98 (s, 1 H, NH), 10.83 (s, 1 H, 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): *m*/*z* [M + 2Na]$^+$ calcd for C$_{25}$H$_{26}$N$_2$O$_5$Na$_2$: 480.1626; found: 480.1674.

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.

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). The enantiomeric ratio was determined by HPLC (Chiralcel AS: hexane/2-propanol = 99:1): t_r = 121 min.

IR (KBr): 3415 (NH), 3299 (NH), 1701 (CON), 1658 (CON) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.31 (t, *J* = 7.0 Hz, 3 H, CH_3CH$_2$O), 3.00 (dd, *J* = 9.3, 5.1 Hz, 1 H, CH_A-indole), 3.14 (dd, *J* = 5.1, 5.1 Hz, 1 H, CH_B-indole), 3.98 (q, *J* = 7.0 Hz, 2 H, CH$_3$CH_2O), 4.42–4.44 (m, 1 H, CH-CO), 4.97 (s, 2 H, OCH_2C$_6$H$_5$), 6.85–7.69 (m, 15 H, C$_6$H$_4$, NH, C$_6$H$_5$, indolyl H), 9.98 (s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for C$_{27}$H$_{27}$N$_3$O$_4$Na: 480.1894; found: 480.1883.

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.

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). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90:10): t_r = 19 min.

IR (KBr): 3388 (NH), 3336 (NH), 3194 (NH), 1681 (CON), 1654 (CON) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.30 (t, *J* = 7.0 Hz, 3 H, CH_3CH$_2$O), 1.38 (s, 9 H, (CH$_3$)$_3$C), 1.75–1.87 (m, 2 H, CH_2CH), 2.09–2.16 (m, 2 H, CH_2CH$_2$CH), 3.95–4.02 (m, 3 H, CH$_3$CH_2O, CHCO), 6.78 (s, 1 H, NH$_A$), 6.86, 7.48 (d, d, *J* = 9.0, 9.0 Hz, 2 H, 2 H, C$_6$H$_4$), 7.00 (d, *J* = 7.8 Hz, 1 H, NH), 7.29 (s, 1 H, NH$_B$), 9.80 (s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for C$_{18}$H$_{27}$N$_3$O$_5$Na: 388.1843; found: 388.1835.

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.

***N*$^\alpha$-Boc-*N*$^\varepsilon$-Cbz-L-Lys-NHC$_6$H$_4$-4-OEt (6mLo)**

Yield: 241 mg (94%); colorless powder; >99% ee; mp 139–140 °C; $[\alpha]_D^{30}$ +5.4 (*c* 1.00, DMSO). The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 90:10): t_r = 37 min.

IR (KBr): 3338 (NH), 1695 (CON), 1666 (CON) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.30 (t, *J* = 7.0 Hz, 3 H, CH_3CH$_2$O), 1.38 (s, 9 H, (CH$_3$)$_3$C), 1.54–1.58 (m, 6 H, NHCH$_2$(CH_2)$_3$), 2.95–2.99 (m, 2 H, NHCH_2(CH$_2$)$_3$), 3.95–4.02 (m, 3 H, CH$_3$CH_2O, CHCO), 4.99 (s, 2 H, OCH_2C$_6$H$_5$), 6.90, 7.48 (d, d, *J* = 9.0, 9.0 Hz, 2 H, 2 H, C$_6$H$_4$), 7.00 (d, *J* = 7.8, 1 H, N*H*CH), 9.80 (s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for C$_{27}$H$_{37}$N$_3$O$_6$Na: 522.2575; found: 522.2547.

***N*$^\alpha$-Boc-*N*$^\varepsilon$-Cbz-D-Lys-NHC$_6$H$_4$-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.

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 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$_3$ (5 mL), 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**.

***N*-(4-Ethoxyphenyl)lauramide (8ao)**[6f]

Yield: 155 mg (97%); colorless powder; mp 104–105 °C.

IR (KBr): 3302 (NH), 1653 (CON) cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3(CH$_2$)$_{10}$), 1.26–1.41 (m, 16 H, CH$_3$(CH_2)$_8$), 1.40 (t, *J* = 7.0 Hz, 3 H, CH_3CH$_2$O), 1.70–1.75 (m, 2 H, CH_2CH$_2$CO), 2.32 (t, *J* = 7.6 Hz, 2 H, CH$_2$CH_2CO), 4.01 (q, *J* = 7.0 Hz, 2 H, CH$_3$CH_2O), 6.84, 7.39 (d, d, *J* = 8.9, 8.9 Hz, 2 H, 2 H, C$_6$H$_4$), 7.03 (br s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for C$_{20}$H$_{33}$NO$_2$Na: 342.2404; found: 342.2403.

***N*-(4-Ethoxyphenyl)palmitamide (8bo)**[6f]

Yield: 184 mg (98%); colorless powder; mp 111–112 °C.

IR (KBr): 3302 (NH), 1658 (CON) cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.88 (t, *J* = 6.8, 3 H, CH_3(CH$_2$)$_{14}$), 1.25–1.41 (m, 24 H, CH$_3$(CH_2)$_{12}$), 1.40 (t, *J* = 7.0 Hz, 3 H, CH_3CH$_2$O), 1.70–1.71 (m, 2 H, CH_2CH$_2$CO), 2.32 (t, *J* = 7.6 Hz, 2 H, CH$_2$CH_2CO), 4.01 (q, *J* = 7.0 Hz, 2 H, CH$_3$CH_2O), 6.84, 7.39 (d, d, *J* = 9.0, 9.0 Hz, 2 H, 2 H, C$_6$H$_4$), 7.05 (br s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for C$_{24}$H$_{41}$NO$_2$Na: 398.3030; found: 398.3046.

***N*-(4-Ethoxyphenyl)oleamide (8co)**[6f]

Yield: 178 mg (89%); colorless powder; mp 66–67 °C.

IR (KBr): 3296 (NH), 1653 (CON) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.84 (t, *J* = 7.0 Hz, 3 H, CH_3(CH$_2$)$_7$), 1.23–1.31 (m, 23 H, CH_3CH$_2$O, CH$_3$(CH_2)$_6$, (CH_2)$_4$CH$_2$CH$_2$CO), 1.54–1.57 (m, 2 H, CH_2CH$_2$CO), 1.97–1.98 (m, 4 H, 2 × CH_2CH), 2.24 (t, *J* = 7.4 Hz, 2 H, CH$_2$CO), 3.97 (q, *J* = 7.0 Hz, 2 H, CH$_3$CH_2O), 5.28–5.36 (m, 2 H, 2 × CH), 6.83, 7.46 (d, d, *J* = 8.9, 8.9 Hz, 2 H, 2 H, C$_6$H$_4$), 9.67 (s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{43}NO_2Na$: 424.3186; found: 424.3218.

(9*Z*,12*Z*)-*N*-(4-Ethoxyphenyl)linoleamide (8do)[6f]

Yield: 186 mg (93%); yellow powder; mp 47–48 °C.

IR (KBr): 3302 (NH), 1655 (CON) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3 H, $CH_3(CH_2)_4$), 1.27–1.40 (m, 14 H, $CH_3(CH_2)_3$, $(CH_2)_4CH_2CH_2CO$), 1.39 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2O), 1.66–1.71 (m, 2 H, CH_2CH_2CO), 2.02–2.07 (m, 4 H, 2 × CH_2CH_2CH), 2.30 (t, *J* = 7.6 Hz, 2 H, CH_2CO), 2.75–278 (m, 2 H, $CHCH_2CH$), 3.99 (q, *J* = 7.0 Hz, 2 H, CH_3CH_2O), 5.29–5.40 (m, 4 H, 4 × CH), 6.81, 7.38 (d, d, *J* = 9.0, 9.0 Hz, 2 H, 2 H, C_6H_4), 7.42 (br s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{41}NO_2Na$: 422.3030; found: 422.3019.

(9*Z*,12*Z*,15*Z*)-*N*-(4-Ethoxyphenyl)linolenamide (8eo)[6f]

Yield: 189 mg (95%); yellow powder; mp 47–49 °C.

IR (KBr): 3300 (NH), 1655 (CON) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.5 Hz, 3 H, CH_3CH_2CH), 1.28–1.41 (m, 8 H, $(CH_2)_4CH_2CH_2CO$), 1.39 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2O), 1.66–1.73 (m, 2 H, CH_2CH_2CO), 2.03–2.11 (m, 4 H, CH_3CH_2CH, CH_2CH_2CH), 2.32 (t, *J* = 7.6 Hz, 2 H, CH_2CO), 2.75–2.82 (m, 4 H, 2 × $CHCH_2CH$), 4.00 (q, *J* = 7.0 Hz, 2 H, CH_3CH_2O), 5.30–5.41 (m, 6 H, 6 × CH), 6.84, 7.39 (d, d, *J* = 9.0, 9.0 Hz, 2 H, 2 H, C_6H_4), 7.11 (s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{39}NO_2Na$: 420.2873; found: 420.2862.

(*E*)-*N*-(4-Ethoxyphenyl)elaidamide (8fo)

Yield: 166 mg (83%); colorless powder; mp 87–88 °C.

IR (KBr): 3323 (NH), 1655 (CON) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H, $CH_3(CH_2)_7$), 1.26–1.41 (m, 20 H, $CH_3(CH_2)_6$, $(CH_2)_4CH_2CH_2CO$), 1.40 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2O), 1.67–1.75 (m, 2 H, CH_2CH_2CO), 1.94–1.97 (m, 4 H, 2 × CH_2CH), 2.32 (t, *J* = 7.6 Hz, 2 H, CH_2CO), 4.00 (q, *J* = 7.0 Hz, 2 H, CH_3CH_2O), 5.37–5.39 (m, 2 H, 2 × CH), 6.84, 7.39 (d, d, *J* = 9.0, 9.0 Hz, 2 H, 2 H, C_6H_4), 7.05 (br s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{43}NO_2Na$: 424.3186; found: 424.3218.

(5*Z*,8*Z*,11*Z*,14*Z*)-*N*-(4-Ethoxyphenyl)arachidonamide (8go)[6f]

Yield: 49 mg (93%); brown oil.

IR (KBr): 3292 (NH), 1655 (CON) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3 H, $CH_3(CH_2)_4$), 1.27–1.41 (m, 6 H, $CH_3(CH_2)_3$), 1.40 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2O), 1.81–1.85 (m, 2 H, CH_2CH_2CO), 2.03–2.20 (m, 4 H, 2 × CH_2CH_2CH), 2.33 (t, *J* = 7.6 Hz, 2 H, CH_2CO), 2.79–2.83 (m, 6 H, 3 × $CHCH_2CH$), 4.00 (q, *J* = 7.0 Hz, 2 H, CH_3CH_2O), 5.30–5.46 (m, 8 H, 8 × CH), 6.83, 7.38 (d, d, *J* = 9.0, 9.0 Hz, 2 H, 2 H, C_6H_4), 7.07 (br s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{41}NO_2Na$: 446.3030; found: 446.3061.

(4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-*N*-(4-Ethoxyphenyl)docosahexaenoamide (8ho)

Yield: 49 mg (99%); brown oil.

IR (KBr): 3296 (NH), 1655 (CON) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.5 Hz, 3 H, CH_3CH_2CH), 1.39 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2O), 2.04–2.11 (m, 2 H, CH_3CH_2CH), 2.36–2.40 (m, 2 H, CH_2CH_2CO), 2.48 (t, *J* = 6.7 Hz, 2 H, CH_2CO), 2.70–2.88 (m, 10 H, 5 × $CHCH_2CH$), 3.99 (q, *J* = 7.0 Hz, 2 H, CH_3CH_2O), 5.32–5.45 (m, 6 H, 12 × CH), 6.82, 7.37 (d, d, *J* = 9.0, 9.0 Hz, 2 H, 2 H, C_6H_4), 7.33 (s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for $C_{30}H_{41}NO_2Na$: 470.3030; found: 470.3023.

Amidation of Lauric Acid (7a) with 4-Aminophenol (2m); Typical Procedure

To a colorless solution of lauric acid **7a** (100 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-aminophenol **2m** (60 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 1.0 M aqueous HCl to pH 2. The resulting suspension was extracted with EtOAc (50 mL), washed with brine (10 mL), and 1.0 M aqueous $NaHCO_3$ (5 mL), 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**).

***N*-(4-Hydroxyphenyl)lauramide (9am)**

Yield: 127 mg (87%); colorless powder; mp 130–131 °C.

IR (KBr): 3313 (NH), 1653 (CON) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.85 (t, *J* = 6.8 Hz, 3 H, $CH_3(CH_2)_{10}$), 1.24–1.27 (m, 16 H, $CH_3(CH_2)_8$), 1.53–1.57 (m, 2 H, CH_2CH_2CO), 2.22 (t, *J* =7.4 Hz, 2 H, CH_2CO), 6.66, 7.34 (d, d, *J* = 8.9, 8.8 Hz, 2 H, 2 H, C_6H_4), 9.10 (s, 1 H, NHCO), 9.55 (s, 1 H, 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): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{29}NO_2Na$: 314.2091; found: 314.2099.

***N*-(4-Hydroxyphenyl)palmitamide (9bm)**

Yield: 132 mg (76%); colorless powder; mp 133–134 °C.

IR (KBr): 3315 (NH), 1653 (CON) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.85 (t, J = 7.0 Hz, 3 H, CH_3(CH$_2$)$_{14}$), 1.24–1.27 (m, 24 H, CH$_3$(CH_2)$_{12}$), 1.53–1.57 (m, 2 H, CH_2CH$_2$CO), 2.22 (t, J = 7.4 Hz, 2 H, CH$_2$CO), 6.66, 7.34 (d, d, J = 8.9, 8.9 Hz, 2 H, 2 H, C$_6$H$_4$), 9.10 (s, 1 H, NHCO), 9.55 (s, 1 H, 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): m/z [M + Na]$^+$ calcd for C$_{22}$H$_{37}$NO$_2$Na: 370.2717; found: 370.2760.

_N_-(4-Hydroxyphenyl)oleamide (9cm)

Yield: 147 mg (79%); colorless powder; mp 99–100 °C.

IR (KBr): 3278 (NH), 1649 (CON) cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.88 (t, J = 6.9 Hz, 3 H, CH_3(CH$_2$)$_7$), 1.27–1.32 (m, 20 H, CH$_3$(CH_2)$_6$, (CH_2)$_4$CH$_2$CH$_2$CO), 1.68–175 (m, 2 H, CH_2CH$_2$CO), 2.00–2.02 (m, 4 H, 2 × CH_2CH), 2.33 (t, J = 7.6 Hz, 2 H, CH$_2$CO), 5.33–5.36 (m, 2 H, 2 × CH), 5.50 (br s, 1 H, NHCO), 6.76, 7.29 (d, d, J = 8.8, 8.7 Hz, 2 H, 2 H, C$_6$H$_4$), 7.06 (br s, 1 H, 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): m/z [M + Na]$^+$ calcd for C$_{24}$H$_{39}$NO$_2$Na: 396.2873; found: 396.2899.

(9_Z_,12_Z_)-_N_-(4-Hydroxyphenyl)linoleamide (9dm)

Yield: 174 mg (94%); colorless powder; mp 86–87 °C.

IR (KBr): 3319 (NH), 1655 (CON) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.85 (t, J = 6.2 Hz, 3 H, CH_3(CH$_2$)$_4$), 1.26–1.33 (m, 14 H, CH$_3$(CH_2)$_3$, (CH_2)$_4$CH$_2$CH$_2$CO), 1.53–1.55 (m, 2 H, CH_2CH$_2$CO), 1.99–2.02 (m, 4 H, 2 × CH$_2$CH_2CH), 2.22 (t, J = 7.4 Hz, 2 H, CH$_2$CO), 2.72–2.75 (m, 2 H, CHCH_2CH), 5.24–5.38 (m, 4 H, 4 × CH), 6.66, 7.34 (d, d, J = 8.7, 8.7 Hz, 2 H, 2 H, C$_6$H$_4$), 9.10 (s, 1 H, NHCO), 9.55 (s, 1 H, 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): m/z [M + Na]$^+$ calcd for C$_{24}$H$_{37}$NO$_2$Na: 394.2717; found: 394.2704.

(9_Z_,12_Z_,15_Z_)-_N_-(4-Hydroxyphenyl)linolenamide (9em)

Yield: 152 mg (82%); colorless powder; mp 81–82 °C.

IR (KBr): 3319 (NH), 1655 (CON) cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.97 (t, J = 7.5 Hz, 3 H, CH_3CH$_2$CH), 1.26–1.32 (m, 8 H, (CH_2)$_4$CH$_2$CH$_2$CO), 1.66–1.74 (m, 2 H, CH_2CH$_2$CO), 2.02–2.11 (m, 4 H, CH$_3$CH_2CH, CH$_2$CH_2CH), 2.32 (t, J = 7.6 Hz, 2 H, CH$_2$-CO), 2.77–2.82 (m, 4 H, 2 × CHCH_2CH), 5.32–5.39 (m, 6 H, 6 × CH), 6.73, 7.23 (d, d, J = 8.8, 8.8 Hz, 2 H, 2 H, C$_6$H$_4$), 6.83 (s, 1 H, NHCO), 7.30 (s, 1 H, 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): m/z [M + Na]$^+$ calcd for C$_{24}$H$_{35}$NO$_2$Na: 392.2560; found: 392.2568.

(_E_)-_N_-(4-Hydroxyphenyl)elaidamide (9fm)

Yield: 181 mg (97%); colorless powder; mp 117–119 °C.

IR (KBr): 3332 (NH), 1655 (CON) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.85 (t, J = 6.9 Hz, 3 H, CH_3(CH$_2$)$_7$), 1.23–1.27 (m, 20 H, CH$_3$(CH_2)$_6$, (CH_2)$_4$ CH$_2$CH$_2$CO), 1.53–1.57 (m, 2 H, CH_2CH$_2$CO), 1.93–1.94 (m, 4 H, 2 × CH_2CH), 2.22 (t, J = 7.4 Hz, 2 H, CH$_2$CO), 5.35–5.37 (m, 2 H, 2 × CH), 6.66, 7.34 (d, d, J = 8.9, 8.9 Hz, 2 H, 2 H, C$_6$H$_4$), 9.10 (s, 1 H, NHCO), 9.55 (s, 1 H, 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): m/z [M + Na]$^+$ calcd for C$_{24}$H$_{39}$NO$_2$Na: 396.2873; found: 396.2899.

(5_Z_,8_Z_,11_Z_,14_Z_)-_N_-(4-Hydroxyphenyl)arachidonamide (AM404; 9gm)[4]

Yield: 124 mg (90%); colorless powder; mp 51–52 °C.

IR (KBr): 3315 (NH), 1653 (CON) cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.88 (t, J = 6.9 Hz, 3 H, CH_3(CH$_2$)$_4$), 1.25–1.39 (m, 6 H, CH$_3$(CH_2)$_3$), 1.77–1.85 (m, 2 H, CH_2CH$_2$CO), 2.02–2.08 (m, 2 H, CH$_3$(CH$_2$)$_3$CH_2), 2.14–2.18 (m, 2 H, CH_2(CH$_2$)$_2$CO), 2.34 (t, J = 7.6 Hz, 2 H, CH$_2$CO), 2.79–2.84 (m, 6 H, 3 × CHCH_2CH), 5.30–5.44 (m, 8 H, 8 × CH), 6.17 (br s, 1 H, NHCO), 6.74, 7.25 (d, d, J = 8.8, 7.4 Hz, 2 H, 2 H, C$_6$H$_4$), 7.15 (s, 1 H, 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): m/z [M + Na]$^+$ calcd for C$_{26}$H$_{37}$NO$_2$Na: 418.2717; found: 418.2767.

(4_Z_,7_Z_,10_Z_,13_Z_,16_Z_,19_Z_)-_N_-(4-Hydroxyphenyl)docosahexaenamide (9hm)

Yield: 36 mg (78%); brown oil.

IR (KBr): 3302 (NH), 1657 (CON) cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.97 (t, J = 7.5 Hz, 3 H, CH_3CH$_2$CH), 2.03–2.09 (m, 2 H, CH$_3$CH_2CH), 2.36–2.40 (m, 2 H, CH_2CH$_2$CO), 2.49 (t, J = 7.1 Hz, 2 H, CH$_2$CO), 2.79–2.85 (m, 10 H, 5 × CHCH_2CH), 5.32–5.43 (m, 13 H, 12 × CH, NHCO), 6.71, 7.19 (d, d, J = 8.6, 8.2 Hz, 2 H, 2 H, C$_6$H$_4$), 7.45 (br s, 1 H, 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): m/z [M + Na]$^+$ calcd for C$_{28}$H$_{37}$NO$_2$Na: 442.2717; found: 442.2695.

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