Direct amide formation from *N*-arylglycine ethyl esters and carboxylic acids catalysed by phenylboronic acid

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The phenylboronic acid-catalysed reaction of an *N*-arylglycine ethyl ester with various carboxylic acids, including *N*-acyl-*N*-phenylglycines, directly affords an amide or a dipeptide in 13–73% yields.

Keywords: direct amide formation, *N*-arylglycine, phenylboronic acid, amino acid, dipeptide

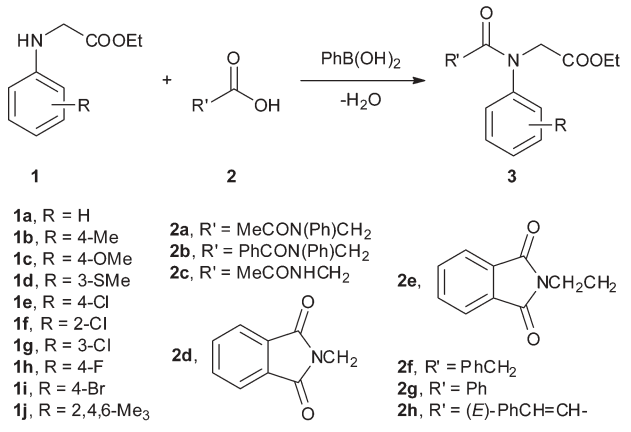
Amide bonds are the main chemical bonds that link amino acid building blocks together to give proteins which play a crucial role virtually in all biological processes.[1] Amide bond formation is one of the most commonly used reaction in synthesis of drugs, as a survey showed that among all reactions employed by medicinal chemists, about one in six was an amide formation.[2] Therefore, a vast number of methods[3,4] have been developed for the formation of amide bonds, but many of them require stoichiometric reagents to activate carboxylic acids, and thus are problematic in the context of atom-efficiency, recyclability and functional group tolerance.[5] Recently, boric acid or an arylboronic acid was found to promote or even catalyse the formation of an amide directly from a variety of carboxylic acids and amines.[6–16] To the best of our knowledge, however, this method has not been tested in the amide formation of *N*-arylglycines, which are known[17] to often suffer from low conversion by using traditional methods. Herein, we report direct amide formation catalysed d by phenylboronic acid from an *N*-arylglycine ethyl ester **1a–j** and carboxylic acids **2a–h** including *N*-acylglycines, as shown in Scheme 1.

Results and discussion

Initially we chose *N*-phenylglycine ethyl ester (**1a**) and *N*-acetyl-*N*-phenylglycine (**2a**) as model compounds to explore direct amide or peptide formation. The results are summarised in Table 1. When a mixture of **1a** (0.5 mmol), **2a** (0.5 mmol), and 25 mol % $PhB(OH)_2$ in toluene (20 mL) was refluxed with removal of water (4Å molecular sieves in a pressure equalising dropping funnel) for 10 h, dipeptide **3a** was obtained in 34% yield after isolation by preparative TLC (entry 1). Using a stoichiometric amount of $PhB(OH)_2$ just slightly increased the yield of **3a** to 44% (entry 2). An attempt to employ the cheaper $B(OH)_3$ led to a lower yield (12%, entry 3). Reducing the volume of toluene by half slightly increased the yield of **3a** to 40% (entry 4). To our delight, replacing toluene by xylene, the yield of **3a** increased to 73% (entry 5). Moreover, we found the usage of $PhB(OH)_2$ could be reduced to 10 mol % without decreasing the yield of **3a** (entry 6). Using mesitylene instead of xylene or increasing the reaction time to 15 h also led to almost the same yield of **3a** (entries 7 and 8). When the usage of $PhB(OH)_2$ was reduced to 5 mol % the yield of **3a** slightly decreased to 66% (entry 9). In a control experiment, in the absence of $PhB(OH)_2$, just a trace of **3a** was obtained and **1a** was recovered in 88% yield (entry 10), indicating a truly catalytic role of $PhB(OH)_2$ in direct amide formation. Based on the above results, we balanced the yield of **3a** against the usage of $PhB(OH)_2$, and reaction time and temperature, and finally chose the following optimal reaction conditions to further explore direct amide formation: 10 mol % $PhB(OH)_2$, xylene, and reflux for 10 h.

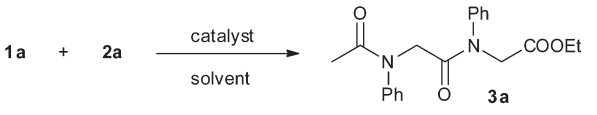
We then reacted a range of *N*-arylglycine ethyl esters **1a–j** with *N*-acetyl-*N*-phenylglycine **2a** using the optimal reaction conditions. As shown in Table 2, the reaction could tolerate a variety of substituents, whether electron-withdrawing or electron-donating or at different position, on the benzene ring of the *N*-arylglycine ethyl ester to afford the corresponding dipeptides 59–73% yields (entries 1–9), indicating that the electron effect on the benzene ring was not obvious. However, *N*-mesitylglycine ethyl ester **1j** gave a low yield of **3j** (entry 10), probably due to steric hindrance from two methyl groups at the *ortho* positions of mesitylamine moiety.

N-Phenylglycine ethyl ester **1a** was then reacted with a variety of carboxylic acids **2b–h**. *N*-Benzoyl-*N*-phenylglycine **2b** gave a slightly lower yield of **3k**, whereas *N*-acetylglycine **2c**



Scheme 1 Direct amide formation and structures of *N*-arylglycine ethyl ester and carboxylic acids used.

Table 1 Screening of reaction conditions for optimising phenylboronic acid-catalysed amide formation using *N*-phenylglycine ethyl ester **1a** and N-acetyl-N-phenylglycine **2a** as models[a]



Entry	Catalyst/mol %	Solvent/mL	Yieldof **3a**/%[b]
1	$PhB(OH)_2$ (25)	Toluene (20)	34
2	$PhB(OH)_2$ (100)	Toluene (20)	44
3	$B(OH)_3$ (25)	Toluene (20)	12
4	$PhB(OH)_2$ (25)	Toluene (10)	40
5	$PhB(OH)_2$ (25)	Xylene (10)	73
6	**$PhB(OH)_2$ (10)**	**Xylene (10)**	**72**
7	$PhB(OH)_2$ (10)	Mesitylene (10)	73
8	$PhB(OH)_2$ (10)	Xylene (10)	74[c]
9	$PhB(OH)_2$ (5)	Xylene (10)	66
10	-	Xylene (10)	<1[d]

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), $PhB(OH)_2$, solvent, and refluxed with removal of water for 10 h. [b]Isolated yield by preparative TLC. [c]Refluxed for 15 h. [d]**1a** was recovered in 88% yield.

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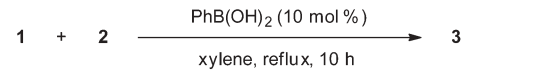
Table 2 Yields of amides or dipeptides **3a–q** from the phenylboronic acid-catalysed reaction of N-arylglycine ethyl esters **1a–j** with various carboxylic acids **2a–h** (Scheme 1)[a]



Entry	1	2	3	Yield/%[b] of 3
1	**1a**	**2a**	**3a**	72
2	**1b**	**2a**	**3b**	71
3	**1c**	**2a**	**3c**	67
4	**1d**	**2a**	**3d**	65
5	**1e**	**2a**	**3e**	70
6	**1f**	**2a**	**3f**	59
7	**1g**	**2a**	**3g**	73
8	**1h**	**2a**	**3h**	71
9	**1i**	**2a**	**3i**	69
10	**1j**	**2a**	**3j**	19
11	**1a**	**2b**	**3k**	54
12	**1a**	**2c**	**3l**	35
13	**1a**	**2d**	**3m**	22
14	**1a**	**2e**	**3n**	69
15	**1a**	**2f**	**3o**	58
16	**1a**	**2g**	**3p**	13
17	**1a**	**2h**	**3q**	29

[a]Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $PhB(OH)_2$ (0.05 mmol), xylene (10 mL), and refluxed with removal of water for 10 h. [b]Isolated yield by preparative TLC.

gave a low yield of **3l**, indicating that a free NH of the glycine moiety was unfavourable to direct amide formation (entries 11 and 12). While *N*-phthaloylglycine ethyl ester **2d** gave only a 22% yield of **3m**, *N*-phthaloyl-*β*-alanine ethyl ester **2e** gave **3n** in 69% yield (entries 13 and 14). Phenylacetic acid **2f** gave **3o** in 58% yield whereas benzoic acid **2g** and cinnamic acid **2h** gave **3p** and **3q** in 13 and 29% yields, respectively (entries 15–17).

In summary, we have demonstrated that *N*-arylglycine ethyl ester and carboxylic acids can undergo direct amide formation in the presence of catalytic $PhB(OH)_2$. When the carboxylic acid was *N*-acyl-*N*-phenylglycine, a range of dipeptides could be formed in reasonable yields. This direct amide formation seems to be independent of the substituent on the benzene ring of *N*-arylglycine ethyl ester but did depend on the structure of the carboxylic acid.

Experimental

NMR spectra were obtained on a MercuPlus 400 NMR spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) in $CDCl_3$ or DMSO-d_6 using TMS as internal standard. IR spectra were obtained on a Thermo Nicolet Avatar 360 IR spectrometer using KBr disks. High resolution electrospray ionisation mass spectra (HRMS-ESI) were obtained on an LCQ Advantage MAX (Finnigan) instrument. All melting points were measured on a melting apparatus with microscope and hot stage and are uncorrected. Compounds **1j**,[18] **2a**,[19] **2f**,[20] **2b**,[21] and **2d**[22] and were prepared according to the reported procedure. Phenylboronic acid and other reagents were purchased from a local company and used as received. All reactions were carried out under N_2. PE = petroleum ether (b.p. 60–90 °C).

Typical procedure for the synthesis of an N-arylglycine ethyl ester (method A)

K_2CO_3 (9.9 g, 0.071 mol) and $ClCH_2COOEt$ (8.3 g, 0.068 mol) were added to a solution of aniline (6.0 g, 0.065 mol) in DMF (15 mL). After this mixture had stirred for 30 min, $NaI{\cdot}2H_2O$ (6.0 g, 0.032 mol) was added. The resulting mixture was allowed to stir overnight under nitrogen. Then the mixture was poured into ice-water (ca. 100 mL), filtered by suction, and the precipitate washed sequentially with water (15 mL × 3), cold ethanol (3 mL × 3), and PE (5 mL × 3), to afford snow-white solids. Recrystallisation from EtOH/PE (9/1, v/v) gave ethyl 2-(phenylamino)acetate (**1a**) (8.9 g, 76%). Colourless flakes, m.p. 56–57 °C (lit.[23] 57 °C), IR: 3386 (NH), 1733 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.34 (t, J = 7.2 Hz, 3H, CH_2CH_3), 3.93 (s, 2H, CH_2COO), 4.27 (s, 1H, NH), 4.28 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.65 (d, J = 8.0 Hz, 2H, ArH), 6.80 (dd, J_1 = 7.4 Hz, J_2 = 7.4 Hz, 1H, ArH), 7.24 (dd, J_1 = 7.4 Hz, J_2 = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.2, 45.9, 61.3, 113.0, 118.2, 129.3, 147.0, 171.2. The following *N*-arylglycine ethyl ester was prepared according to the method A.

Ethyl 2-(p-tolylamino)acetate (**1b**): Colourless flakes (54%), m.p. 49–50 °C (lit.[24] 51 °C) (EtOH), IR: 3380 (NH), 1728 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.33 (t, J = 7.2 Hz, 3H, CH_2CH_3), 2.28 (s, 3H, $ArCH_3$), 3.91 (d, J = 5.6 Hz, 2 H, CH_2COO), 4.20 (brs, 1H, NH), 4.27 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.58 (d, J = 8.2 Hz, 2H, ArH), 7.04 (d, J = 8.2 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.2, 20.4, 46.3, 61.3, 113.2, 127.4, 129.8, 144.9, 171.3.

Ethyl 2-((4-methoxyphenyl)amino)acetate (**1c**): Colourless granules (70%), m.p. 59–60 °C (lit.[24] 59 °C) (EtOH), IR: 3383 (NH), 1730 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.31 (t, J = 7.2 Hz, 3H, CH_2CH_3), 3.77 (s, 3H, OCH_3), 3.88 (s, 2 H, NCH_2), 4.06 (brs, 1H, NH), 4.25 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.61 (d, J = 8.8 Hz, 2 H, ArH), 6.81 (d, J = 8.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$): 14.2, 46.9, 55.8, 61.2, 114.4, 114.9, 141.3, 152.6, 171.4.

Ethyl 2-((3-(methylthio)phenyl)amino)acetate (**1d**): White flakes (73%), m.p. 57–58 °C (EtOH), IR: 3379 (NH), 1728 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.32 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 2.48 (s, 3 H, SCH_3), 3.91 (s, 2H, NCH_2), 4.27 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.35 (brs, 1H, NH), 6.41 (dd, J_1 = 1.8 Hz, J_2 = 8.0 Hz, 1H, ArH), 6.52 (dd, J_1 = 1.6 Hz, J_2 = 1.8 Hz, 1H, ArH), 6.67 (d, J_1 = 1.6 Hz, J_2 = 7.8 Hz, 1H, ArH), 7.13 (dd, J_1 = 7.8 Hz, J_2 = 8.0 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.2, 15.7, 45.7, 61.4, 110.1, 110.8, 116.3, 129.6, 139.5, 147.4, 171.0; HRMS-ESI (positive) calcd for $C_{11}H_{15}NNaO_2S^+$ $[M + Na]^+$: 248.0716; found: 248.0719.

Ethyl 2-((3-chlorophenyl)amino)acetate (**1g**): Colourless flakes (82%), m.p. 114–115 °C (lit.[25] 113–114 °C) (EtOH), IR: 3380 (NH), 1725 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.33 (t, J = 7.2 Hz, 3H, CH_2CH_3), 3.89 (d, J = 5.6 Hz, 2 H, CH_2COO), 4.28 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.42 (brs, 1H, NH), 6.50 (dd, J_1 = 1.8 Hz, J_2 = 8.0 Hz, 1H, ArH), 6.59 (dd, J_1 = 1.5 Hz, J_2 = 1.8 Hz, 1H, ArH), 6.73 (dd, J_1 = 1.5 Hz, J_2 = 8.0 Hz, 1H, ArH), 7.11 (dd, J_1 = 8.0 Hz, J_2 = 8.0 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.2, 45.5, 61.5, 111.3, 112.6, 118.0, 130.3, 135.1, 148.1, 170.7.

Typical procedure for the synthesis of N-arylglycine ethyl ester (method B)

A mixture of $ClCH_2COOEt$ (1.06 g, 8.62 mmol), $NaI{\cdot}2H_2O$ (1.60 g, 8.62 mmol) in acetone (6 mL) was stirred at room temperature for 1 h. The reaction mixture was filtered by suction, and then the filtrate was evaporated to remove acetone. The obtained residue was dissolved in DMF (2 mL), and added to a mixture of 4-chloroaniline (1.00 g, 7.84 mmol), K_2CO_3 (1.19 g, 8.62 mmol), and DMF (3 mL). The resulting mixture was stirred overnight under nitrogen, and then poured into ice-water (50 mL). The white precipitates were collected after being filtered by suction, and washed sequentially by water (10 mL × 3), cold alcohol (1 mL × 3), and PE (3 mL × 3). Recrystallisation from EtOH gave ethyl 2-((4-chlorophenyl)amino)acetate **1e** (1.29 g, 77%). Colourless flakes, m.p. 94–95 °C (lit.[25] 92.5–93.5 °C), IR: 3376 (NH), 1722 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.32 (t, J = 7.2 Hz, 3H, CH_2CH_3), 3.88 (d, J = 5.2 Hz, 2H, CH_2COO), 4.27 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.34 (brs, 1H, NH), 6.54 (d, J = 8.8 Hz, 2H, ArH), 7.16 (d, J = 8.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.2, 45.8, 61.5, 114.1, 122.8, 129.2, 145.6, 170.9.

The following *N*-arylglycine ethyl esters were prepared by method B.

Ethyl 2-((2-chlorophenyl)amino)acetate (**1f**): Pale yellow oil (lit.[25] b.p. 116 °C/1 mm Hg), isolated by preparative TLC (eluted with PE/EtOAc (10/1, v/v), R_f = 0.52) in 21% yield, IR: 3408 (NH), 1742 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.33 (t, J = 7.2 Hz, 3H, CH_2CH_3), 3.97 (s, 2H, CH_2COO), 4.28 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.98 (s, 1H, NH), 6.56 (d, J = 7.8 Hz, 1H, ArH), 6.71 (dd, J_1 = 7.6 Hz, J_2 = 7.8 Hz, 1H, ArH), 7.16 (dd, J_1 = 7.6 Hz, J_2 = 7.8 Hz, 1H, ArH), 7.30 (d, J = 7.8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.2, 45.6, 61.5, 111.3, 118.1, 119.6, 127.8, 129.3, 143.0, 170.5.

Ethyl 2-((4-fluorophenyl)amino)acetate (**1h**): Colourless flakes (75%s), m.p. 73–74 °C (lit.[25] 73–74 °C) (EtOH), IR: 3383 (NH), 1727 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.31 (t, J = 7.2 Hz, 3H, CH_2CH_3), 3.87 (d, J = 5.6 Hz, 2H, CH_2COO), 4.21 (brs, 1H, NH), 4.26 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.53–6.59 (m, 2H, ArH), 6.88–6.96 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.2, 46.4, 61.4, 113.9 (d, $J_{F\text{-}C}$ = 7.6 Hz),

115.8 (d, $J_{F\text{-}C}$ = 22.5 Hz), 143.5 (d, $J_{F\text{-}C}$ = 1.9 Hz), 156.2 (d, $J_{F\text{-}C}$ = 234.2 Hz), 171.1.

Ethyl 2-((4-bromophenyl)amino)acetate (**1i**): Colourless flakes (69%), m.p. 95–96 °C (lit.[25] 94–95 °C) (EtOH), IR: 3376 (NH), 1721 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.32 (t, J = 7.2 Hz, 3H, CH_2CH_3), 3.87 (d, J = 5.6 Hz, 2H, NCH_2), 4.26 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.36 (t, J = 5.6 Hz, 1H, NH), 6.50 (d, J = 8.8 Hz, 2H, ArH), 7.29 (d, J = 8.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.2, 45.7, 61.5, 109.9, 114.5, 132.0, 146.0, 170.8.

3-(1,3-Dioxoisoindolin-2-yl)propanoic acid (**2e**): A mixture of β-alanine (5.0 g, 0.056 mol), phthalic anhydride (8.7 g, 0.059 mol), and DMF (20 mL) was refluxed under stirring for 3 h. The resulting mixture was cooled to room temperature, poured into ice-water (~100 mL), and then filtered by suction. The filter cake was sequentially washed with water (15 mL × 3), alcohol (3 mL × 3), and ether (10 mL × 2), and then dried *in vacuo* to give **2e** (9.9 g, 80%) as a white solid, m.p. 148–150 °C (lit.[26] 152 °C), IR: 1773 (C=O), 1699 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.61 (t, J = 7.2 Hz, 2H, CH_2COO), 3.79 (t, J = 7.2 Hz, 2H, NCH_2), 7.82–7.89 (m, 4H, ArH), 12.40 (brs, 1 H, COOH).

Direct amide formation catalysed by PhB(OH)$_2$; typical procedure

$PhB(OH)_2$ (6 mg, 0.05 mmol), and xylene (10 mL) were added to a round-bottom flask (100 mL), **1a** (90 mg, 0.5 mmol), **2a** (97 mg, 0.5 mmol). A pressure equalising dropping funnel, in which 4 Å molecular sieves (6 g) were placed, was installed onto the flask. Then a condenser was connected to the dropping funnel. After refluxing under stirring for 10 h, the reaction mixture was cooled down to room temperature, and evaporated to remove solvent. The resulting residue was dissolved in EtOAc (20 mL), and then sequentially washed with 0.1 M NaOH (20 mL), water (20 mL), and brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was subjected to preparative TLC (eluted with PE/acetone (2/1, v/v), R_f = 0.43) to afford ethyl 2-(N-phenyl-2-(N-phenylacetamido)acetamido)acetate **3a** (128 mg 72%) as a pale yellow oil, IR: 1751 (C=O), 1682 (C=O), 1658 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.24 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.89 (s, 3H, CH_3C=O), 4.15 (s, 2H, AcNCH_2), 4.17 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.39 (s, 2H, CH_2COO), 7.28–7.44 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.1, 51.5, 51.8, 61.3, 127.9, 128.0, 128.3, 128.7, 129.5, 129.9, 141.7, 143.8, 168.4, 168.9, 170.7; HRMS-ESI (positive) calcd for $C_{20}H_{22}N_2NaO_4^+$ [M + Na]$^+$: 377.1472; found: 377.1470.

Ethyl 2-(2-(N-phenylacetamido)-N-(p-toyl)acetamido)acetate (**3b**): Yellow oil (71%), IR: 1748 (C=O), 1667 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.19 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.84 (s, 3H, ArCH_3), 2.31 (s, 3H, CH_3C=O), 4.11 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.12 (s, 2H, AcNCH_2), 4.32 (s, 2H, CH_2COO), 7.15 (d, J = 8.2 Hz, 2 H, ArH), 7.25 (d, J = 8.2 Hz, 2H, ArH), 7.27–7.29 (m, 1H, ArH), 7.29–7.35 (m, 4H, ArH); ^{13}C NMR($CDCl_3$): δ 14.1, 21.1, 22.1, 51.5, 51.8, 61.1, 127.861, 127.936, 127.947, 129.5, 130.5, 138.6, 139.0, 143.8, 168.5, 168.9, 170.6; HRMS-ESI (positive) calcd for $C_{21}H_{24}N_2NaO_4^+$ [M + Na]$^+$: 391.1628; found: 391.1624; Eluent: PE/acetone (2/1, v/v), R_f = 0.30.

Ethyl 2-(N-(4-methoxyphenyl)-2-(N-phenylacetamido)acetamido)-acetate (**3c**): Light brown oil (67%), IR: 1746 (C=O), 1679 (C=O) cm^{-1}: ^{1}H NMR ($CDCl_3$): δ 1.18 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.82 (s, 3H, CH_3C=O), 3.73 (s, 3H, OCH_3), 4.09 (s, 2H, AcNCH_2), 4.10 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.29 (s, 2H, CH_2COO), 6.83 (d, J = 9.2 Hz, 2H, ArH), 7.22–7.31 (m, 7H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.1, 51.5, 51.7, 55.4, 61.1, 114.9, 127.8, 127.9, 129.3, 129.5, 134.2, 143.7, 159.5, 168.7, 168.9, 170.6; HRMS-ESI (positive) calcd for $C_{21}H_{24}N_2NaO_5^+$ [M + Na]$^+$: 407.1577; found: 407.1580; Eluent: PE/acetone (2/1, v/v), R_f = 0.26.

Ethyl 2-(N-(3-(methylthio)phenyl)-2-(N-phenylacetamido)acetamido)acetate (**3d**): Light yellow oil (65%), IR: 1749 (C=O), 1676 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.20 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.84 (s, 3H, CH_3C=O), 2.42 (s, 3H, SCH_3), 4.13 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.14 (s, 2H, AcNCH_2), 4.31 (s, 2H, CH_2COO), 7.12 (d, J = 8.0 Hz, 1H, ArH), 7.17 (d, J = 8.0 Hz, 1H, ArH), 7.23–7.29 (m, 3H, ArH), 7.29–7.35 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 14.1, 15.3, 22.1, 51.4, 51.7, 61.3, 124.4, 125.2, 126.1, 127.9, 128.0, 130.0, 130.1, 141.1, 142.2, 143.7, 168.3, 168.8, 170.6; HRMS-ESI (positive) calcd for $C_{21}H_{24}N_2NaO_4S^+$ [M + Na]$^+$: 423.1349; found: 423.1350; Eluent: PE/acetone (2/1, v/v), R_f = 0.34.

Ethyl 2-(N-(4-chlorophenyl)-2-(N-phenylacetamido)acetamido)-acetate (**3e**): Pale yellow oil (70%), IR: 1747 (C=O), 1685 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.18 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.82 (s, 3H, CH_3C=O), 4.08 (s, 2H, AcNCH_2), 4.11 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.30 (s, 2H, CH_2COO), 7.23–7.27 (m, 1H, ArH), 7.26–7.36 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.0, 51.3, 51.7, 61.3, 127.9, 128.0, 129.5, 129.7, 130.1, 134.5, 140.1, 143.6, 168.3, 168.7, 170.6; HRMS-ESI (positive) calcd for $C_{20}H_{21}ClN_2NaO_4^+$ [M + Na]$^+$: 411.1082; found: 411.1081; Eluent: PE/acetone (2/1, v/v), R_f = 0.44.

Ethyl 2-(N-(2-chlorophenyl)-2-(N-phenylacetamido)acetamido)-acetate (**3f**): Pale yellow oil(59%), IR: 1751 (C=O), 1690 (C=O), 1662 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.28 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.92 (s, 3H, CH_3C=O), 3.70 (d, J = 17.4 Hz, 1H, one proton of CH_2COO), 3.99 (d, J = 16.4 Hz, 1H, one proton of AcNCH_2), 4.16–4.24 (m, 2H, CH_2CH_3), 4.26 (d, J = 16.4 Hz, 1H, another proton of AcNCH_2), 5.04 (d, J = 17.4 Hz, 1H, another proton of CH_2COO), 7.32–7.42 (m, 7H, ArH), 7.49–7.53 (m, 1H, ArH), 7.70–7.74 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.1, 49.9, 51.4, 61.2, 127.9 (overlap, 2C), 128.2, 129.5, 130.3, 130.6, 131.6, 132.9, 138.4, 143.5, 168.4, 168.6, 170.6; HRMS-ESI (positive) calcd for $C_{20}H_{21}ClN_2NaO_4^+$ [M + Na]$^+$: 411.1082; found: 411.1079; Eluent: PE/acetone (2/1, v/v), R_f = 0.37.

Ethyl 2-(N-(3-chlorophenyl)-2-(N-phenylacetamido)acetamido)-acetate (**3g**): Light yellow oil (73%), IR: 1749 (C=O), 1689 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.19 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.83 (t, 3H, CH_3C=O), 4.11 (s, 2H, AcNCH_2), 4.12 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.30 (s, 2H, CH_2COO), 7.23–7.34 (m, 8H, ArH), 7.40 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.0, 30.9, 51.3, 51.7, 61.3, 126.7, 127.9, 128.0, 128.5, 129.0, 129.5, 130.9, 135.2, 142.8, 143.6, 168.2, 168.6, 170.6; HRMS-ESI (positive) calcd for $C_{20}H_{21}ClN_2NaO_4^+$ [M + Na]$^+$: 411.1082; found: 411.1083; Eluent: PE/acetone (2/1, v/v), R_f = 0.40.

Ethyl 2-(N-(4-fluorophenyl)-2-(N-phenylacetamido)acetamido)-acetate (**3h**): Pale yellow oil (71%), IR: 1747 (C=O), 1667 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.18 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.82 (s, 3H, CH_3C=O), 4.07 (s, 2H, AcNCH_2), 4.11 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.30 (s, 2H, CH_2COO), 6.99–7.05 (m, 2H, ArH), 7.23–7.28 (m, 1H, ArH), 7.28–7.34 (m, 4H, ArH), 7.36–7.40 (m, 2H, ArH): ^{13}C NMR ($CDCl_3$): δ 14.1, 22.0, 51.4, 51.7, 61.2, 116.7 (d, $J_{F\text{-}C}$ = 22.5 Hz), 127.9 (overlap, 2C), 129.5, 130.2 (d. $J_{F\text{-}C}$ = 8.7 Hz), 137.6 (d, $J_{F\text{-}C}$ = 3.0 Hz), 143.7, 162.2 (d, $J_{F\text{-}C}$ = 247.5 Hz), 168.5, 168.8, 170.6; HRMS-ESI (positive) calcd for $C_{20}H_{21}FN_2NaO_4^+$ [M + Na]$^+$: 395.1378; found: 395.1378; Eluent: PE/acetone (2/1, v/v), R_f = 0.39.

Ethyl 2-(N-(4-bromophenyl)-2-(N-phenylacetamido)acetamido)-acetate (**3i**): Pale yellow oil (69%), IR: 1748 (C=O), 1665 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.18 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.82 (s, 3 H, CH_3CO), 4.08 (s, 2 H, AcNCH_2), 4.11 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 4.31 (s, 2 H, CH_2COO), 7.22–7.34 (m, 7 H, ArH), 7.47 (d, J = 8.4 Hz, 2 H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.1, 22.1, 51.3, 51.8, 61.3, 122.6, 127.9, 128.0, 129.5, 130.1, 133.1, 140.7, 143.6, 168.2, 168.7, 170.6; HRMS-ESI (positive) calcd for $C_{20}H_{21}BrN_2NaO_4^+$ [M + Na]$^+$: 455.0577; found: 455.0579; Eluent: PE/acetone (2/1, v/v), R_f = 0.37.

Ethyl 2-(N-mesityl-2-(N-phenyacetamido)acetamido)acetate (**3j**): Red-brown oil (19%), IR: 1751 (C=O), 1668 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.25 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.89 (s, 3H, CH_3C=O), 2.27 (s, 9H, 3 x ArCH_3), 4.00 (s, 2H, CH_2COO), 4.14 (s, 2H, AcNCH_2), 4.19 (q, J = 7.2 Hz, 2H, CH_2CH_3), 6.91 (s, 2H, ArH), 7.28–7.39 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.1, 18.1, 20.9, 22.2, 51.46, 51.49, 61.1, 127.88, 127.92, 129.5, 130.0, 136.5, 137.0, 138.6, 143.8, 168.4, 168.9, 170.7; HRMS-ESI (positive) calcd for $C_{23}H_{28}N_2NaO_4^+$ [M + Na]$^+$: 419.1941; found: 419.1944; Eluent: PE/acetone (2/1, v/v), R_f = 0.33.

Ethyl 2-(N-phenyl-2-(N-phenylbenzamido)acetamido)acetate (**3k**): Pale yellow oil (54%), IR: 1749 (C=O), 1682 (C=O), 1651 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.25 (t, J = 7.2 Hz, 3H, CH_2CH_3), 4.19 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.42 (s, 2H, CH_2COO), 4.44 (s, 2H, NCH_2CON), 7.07–7.23 (m, 8H, ArH), 7.32–7.52 (m, 7H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.2, 51.5, 52.9, 61.3, 126.6, 127.2, 127.6, 128.3, 128.8, 128.9, 129.0, 129.7, 130.0, 135.4, 141.6, 144.3, 168.5, 169.0, 170.6; HRMS-ESI (positive) calcd for $C_{25}H_{24}N_2NaO_4^+$ [M + Na]$^+$: 439.1628; found: 439.1630; Eluent: PE/acetone (2/1, v/v), R_f = 0.48.

Ethyl 2-(2-benzamido-N-phenylacetamido)acetate (**3l**): White solids (35%), m.p. 128–130 °C, IR: 3433 (NH), 1746 (C=O), 1677 (C=O), 1654 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.27 (t, J = 7.2 Hz, 3H, CH_2CH_3), 4.02 (d, J = 4.0 Hz, 2H, NCH_2CON), 4.21 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.40 (s, 2H, CH_2COO), 7.24 (t, J = 4.0 Hz, 1 H, NH), 7.37–7.48 (m, 8H, ArH), 7.79 (d, J = 7.2 Hz, 2H, ArH); ^{13}C NMR

($CDCl_3$): δ 14.2, 42.5, 51.6, 61.5, 127.0, 128.0, 128.5, 129.3, 130.3, 131.5, 133.9, 140.6, 167.0, 168.7, 169.2; HRMS-ESI (positive) calcd for $C_{19}H_{20}N_2NaO_4^+$ [M + Na]$^+$: 363.1315; found: 363.1316; Eluent: PE/acetone (2/1, v/v), R_f = 0.23.

Ethyl 2-(2-(1,3-dioxoisoindolin-2-yl)-N-phenylacetamido)acetate (**3m**): Pale yellow solids (22%), m.p. 172–174 °C, IR: 1751 (C=O), 1724 (C=O), 1678 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.28 (t, J = 7.2 Hz, 3H, CH_2CH_3), 4.21 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.27 (s, 2H, CH_2CON), 4.40 (s, 2H, CH_2COO), 7.42–7.47 (m, 1H, ArH), 7.49–7.54 (m, 2 H, ArH), 7.56–7.59 (m, 2H, ArH), 7.71–7.74 (m, 2H, ArH), 7.85–7.88 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.1, 39.7, 51.6, 61.4, 123.5, 128.3, 129.1, 130.2, 132.2, 134.0, 141.1, 166.4, 167.7, 168.5; HRMS-ESI (positive) calcd for $C_{20}H_{18}N_2NaO_5^+$ [M + Na]$^+$: 389.1108; found: 389.1110; Eluent: PE/acetone (2/1, v/v), R_f = 0.37.

Ethyl 2-(3-(1,3-dioxoisoindolin-2-yl)-N-phenylpropanamido)acetate (**3n**): Pale yellow solids (69%), m.p. 115–116 °C, IR: 1769 (C=O), 1725 (C=O), 1665 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.28 (t, J = 7.2 Hz, 3H, CH_2CH_3), 2.56 (t, J = 7.6 Hz, 2H, CH_2CON), 3.98 (t, J = 7.6 Hz, 2H, NCH_2CH_2), 4.20 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.37 (s, 2H, CH_2COO), 7.33–7.44 (m, 5H, ArH), 7.68–7.71 (m, 2H, ArH), 7.80–7.83 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$): 14.1, 32.4, 34.1, 51.1, 61.2, 123.1, 128.1, 128.5, 129.9, 132.0, 133.9, 142.2, 167.9, 168.9, 170.3; HRMS-ESI (positive) calcd for $C_{21}H_{20}N_2NaO_5^+$ [M + Na]$^+$: 403.1264; found: 403.1265; Eluent: PE/acetone (2/1, v/v), R_f = 0.45.

Ethyl 2-(N,2-diphenylacetamido)acetate (**3o**): Light yellow oil (58%), IR: 1749 (C=O), 1671 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.26 (t, J = 7.2 Hz, 3H, CH_2CH_3), 3.54 (s, 2H, $PhCH_2$), 4.20 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.38 (s, 2H, CH_2COO), 7.08–7.10 (m, 2H, ArH), 7.17–7.27 (m, 3H, ArH), 7.28–7.32 (m, 2H, ArH), 7.34–7.42 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.2, 40.7, 51.6, 61.2, 126.6, 128.3, 128.37, 128.43, 129.1, 129.7, 135.1, 142.8, 169.1, 171.4; HRMS-ESI (positive) calcd for $C_{18}H_{19}NNaO_3^+$ [M + Na]$^+$: 320.1257; found: 320.1260; Eluent: PE/EtOAc (3/1, v/v), R_f = 0.23.

Ethyl 2-(N-phenylbenzamido)acetate (**3p**): Pale yellow oil (13%), IR: 1747 (C=O), 1653 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.31 (t, J = 7.2 Hz, 3H, CH_2CH_3), 4.25 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.62 (s, 2H, CH_2C=O), 7.14–7.29 (m, 8H, ArH), 7.36 (d, J = 7.6 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$): δ 14.2, 52.3, 61.4, 126.9, 127.5, 127.7, 128.8, 129.2 129.9, 135.1, 143.8, 169.1, 170.7. The spectra data are consistent with those reported.[27] Eluent: PE/EtOAc (3/1, v/v), R_f = 0.26.

Ethyl 2-(N-phenylcinnamamido)acetate (**3q**): Light yellow oil (29%), IR: 1745 (C=O), 1657 (C=O), 1620 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.30 (t, J = 7.2 Hz, 3H, CH_2CH_3), 4.24 (q, J = 7.2 Hz, 2H, CH_2CH_3), 4.52 (s, 2H, CH_2COO), 6.41 (d, J = 15.6 Hz, 1 H, $ArCH$=), 7.2807.35 (m, 5H, ArH), 7.38–7.42 (m, 3H, ArH), 7.44–7.49 (m, 2H, ArH), 7.74 (d, J = 15.6 Hz, 1H, =CHC=O); ^{13}C NMR ($CDCl_3$): δ 14.2, 51.7, 61.3, 117.9, 128.0, 128.1(overlap, 2C), 128.7, 129.67, 129.71, 135.0, 142.4, 142.8, 166.4, 169.1; HRMS-ESI (positive) calcd for $C_{19}H_{19}NNaO_3^+$ [M + Na]$^+$: 332.1257; found: 332.1254; Eluent: PE/acetone (2/1, v/v), R_f = 0.29.

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