An Efficient Synthesis of N$^{\alpha}$-Protected Amino and Peptide Acid Aryl Amides via Iodine-Mediated Oxidative Acylation of N$^{\alpha}$-Protected Amino and Peptide Thioacids

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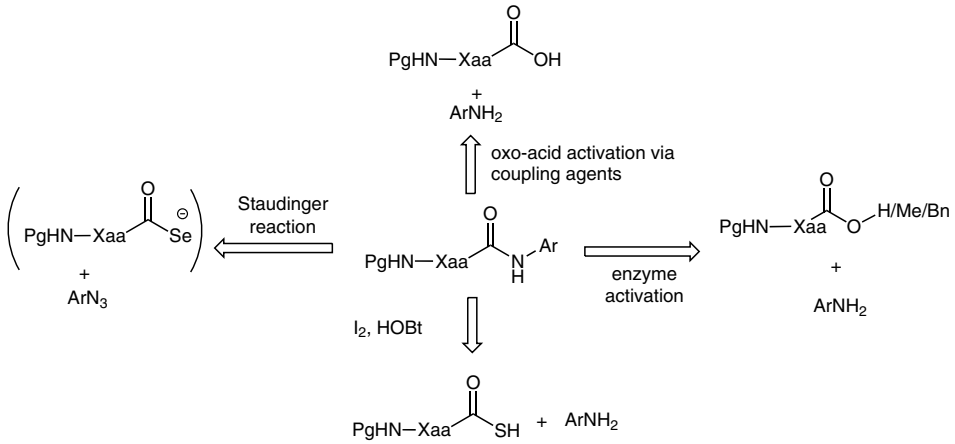
Abstract: Thioacids derived from N-protected amino or dipeptide and tripeptide acids undergo facile N-acylation with aromatic amines to afford N-protected amino or peptide aryl amides in good to excellent yields and enantiopurities. The method also furnishes difficult-to-prepare *N*-Fmoc amino acid 4-nitroanilides in good yields. This simple oxidative N$^{\alpha}$-acylation of thioacids with aromatic amines proceeds in the presence of iodine, 1-hydroxybenzotriazole and *N*,*N*-diisopropylethylamine at room temperature in tetrahydrofuran.

Key words: thioacids, acylation, aryl amides, iodine

Amide bond formation is an important reaction in organic synthesis as this moiety occurs widely in Nature.[1] Hence, there has been significant research on the development of novel and efficient methods toward the formation of amides.[2] The most popular strategy for the generation of amide bonds relies on the reactions of activated carboxylic acids with amines.[3] However, studies have also been directed to the use of thioacids as efficient acylating agents.[4] Thioacids have been used as precursors to thioesters, which participate in ligation reactions in the chemical synthesis of proteins.[5,6] Due to the challenges in preparing thioesters (especially in Fmoc chemistry),[7] research has focused on N-protected amino/peptide thioacids as alternatives to thioesters in native chemical ligation. This is not only because of their easy preparation, but also on account of the numerous advantages over their carboxylic acid (RCOOH) counterparts, such as solubility, acidity and enhanced nucleophilicity.[8] Thus, amino/peptide thioacids have been the subject of major endeavors devoted toward the chemical assembly of polypeptides and a variety of proteins.[9] Thioacids, similar to oxo-acids, do not undergo acylation directly with amines; they need to be activated prior to treatment with an amine. Importantly, the activation of a thioacid is very mild and does not require any coupling reagent,[10] and sometimes not even a base.[11] Such inherent advantages of thioacids have been explored for the preparation of amides[12] and peptidomimetics.[13]

Among pharmaceutical compounds possessing amide bonds, aryl amides are an example of carboxamides, which have generated significant interest in varied applications.[14,15]

Substituted aniline derivatives, in particular those possessing electron-withdrawing groups, do not undergo straightforward condensation with carboxylic acids. Therefore, a number of strategies have been developed for the synthesis of C-terminal amino acid or peptide acid aryl amides (Scheme 1). Aryl amides of *tert*-butoxycarbonyl (Boc) or benzyloxycarbonyl (Cbz) amino acids are prepared from carboxylic acids via the mixed anhydride



Scheme 1 Retrosynthetic analysis of aryl amides through various approaches

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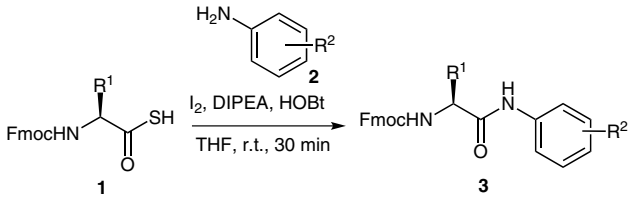
method, or by using carbodiimides or other expensive coupling reagents.[16] Alternative procedures include the Staudinger-type reaction in which azides are treated with in situ generated N-protected amino acid selenocarboxylates.[17] However, the preparation of selenocarboxylates is cumbersome. Liskamp's group have developed an elegant protocol for the acylation of *N*-Cbz protected amino acids/esters with amines mediated by Alcalase-CLEA enzyme.[18] Although enantiomerically pure products were obtained, the long reaction times and high temperature were not suited to the general applicability of this protocol. Many aniline derivatives, being the amine components for the preparation of the title compounds, have basicities in the range of pH 8–9, and thus are not suitable for 9-fluorenylmethoxycarbonyl (Fmoc) chemistry at high temperature. Some attempts have been made to prepare Fmoc-protected 4-nitroanilides,[16f,g] however, low yields of products were obtained.



Scheme 2 Synthesis of N-protected amino acid aryl amides **3**

Table 1 Optimization of the Solvent for the Synthesis of **3a**[a]

Entry	Solvent	Base	Time[b]	Yield (%)[c]
1	DMSO	DIPEA	5 h	54
2	DMSO	NMM	5 h	58
3	MeCN	DIPEA	4 h	61
4	DMF	DIPEA	2 h	63
5	CH_2Cl_2	DIPEA	4 h	59
6	THF	DIPEA	30 min	91
7	THF	NMM	45 min	86

[a] Reactions were conducted at r.t.
[b] The reaction was monitored by TLC until thioacid **1a** had been fully consumed.
[c] Yield of isolated product after column chromatography.

Table 2 Investigation of the Coupling of **1a** with Aniline[a]

Entry	Additive	Solvent	Yield (%)
1	none	I_2, DMSO	58
2	HOBt (2.0 equiv)	DMSO	20
3	HOBt (2.0 equiv)	I_2, DMSO	54
4	HOBt (2.0 equiv)	I_2, THF	91

[a] Reactions were conducted at r.t. with DIPEA as the base.

We report herein a rapid, high-yielding and racemization-free synthesis of aryl amides via iodine-mediated oxidative acylation of N-protected thioacids with substituted anilines. The protocol is compatible with the three commonly employed peptide protecting groups (Fmoc, Boc and Cbz), as well as several bifunctional amino acids, peptides and a diverse range of substituted aniline derivatives. In addition, N-protected amino acids such as serine, threonine and tyrosine have been converted into the corresponding aryl amides without protection of the hydroxyl group. Iodine is a cheap and easily available reagent, which has been used extensively in a number of reactions.[19] Danishefsky's group have previously reported the total chemical synthesis of complex glycoproteins via iodine-mediated oxidative acylation of amino and peptide thioacids.[9] In an earlier study, we prepared two dipeptides, Fmoc-(L)-Phg-Ala-OMe and Fmoc-(D)-Phg-Ala-OMe, and studied their enantiopurities.[20] These results established that thioacids could be employed to acylate aryl amines at room temperature in the presence of iodine and 1-hydroxybenzotriazole (HOBt) (Scheme 2). On the basis of these studies, we initiated an investigation on the reaction of N-protected thioacids with aniline derivatives.

The required N-protected amino and peptide thioacids **1** were prepared using our previously reported protocol.[20] We have also reviewed the advantages of propanephosphonic acid anhydride (T3P®) over other traditional coupling reagents in a variety of reactions.[21] Hence, a procedure involving T3P®-mediated activation of a carboxylic acid followed by treatment with sodium sulfide (Na_2S) was employed to prepare thioacids **1**. Our study began with the condensation of Fmoc-Ala-SH (**1a**, R^1 = Me) with aniline in the presence of iodine and HOBt at room temperature in dimethyl sulfoxide (DMSO) as the solvent (Table 1, entries 1 and 2). After five hours, the expected product **3a** was isolated in a yield of 54–58%. Solvents including acetonitrile, *N*,*N*-dimethylformamide, dichloromethane and tetrahydrofuran were tested in this reaction (Table 1, entries 3–7). Tetrahydrofuran was found to be the best solvent, leading to the desired product **3a** in 91% yield in 30 minutes. The use of *N*-methylmorpholine (NMM) as the tertiary base had no beneficial influence on the reaction rate, therefore we used *N*,*N*-diisopropylethylamine (DIPEA) as the base (Table 1, entry 6). In order to ascertain the role of HOBt in the coupling reaction, a control experiment was carried out in which aniline was coupled to **1a** in the absence of HOBt. Under these conditions, the product yield was reduced significantly to 58% (Table 2, entry 1), and the level of epimerization increased to 12%. Thus, HOBt played a vital role in suppressing racemization as well as increasing the yield. According to the mechanism established by Danishefsky[9] (Scheme 3), thioacylation can be achieved in dimethyl sulfoxide, even in the absence of iodine. Consequently, thioacid **1a** was treated with aniline and HOBt in dimethyl sulfoxide (Table 2, entry 2), however, it was interesting to note that only 20% of the desired aryl amide **3a** was detected after five hours. In contrast, thioacylation of **1a** with aniline mediated by iodine and HOBt in di-

methyl sulfoxide, led to an increase in the yield of **3a** (Table 2, entry 3). Although, dimethyl sulfoxide assists in the formation of the intermediate diacyl disulfide, it is less efficient than tetrahydrofuran for formation of the *O*-benzotriazolyl (OBt) ester or amide product derived from the diacyl disulfide.

To demonstrate the scope of the optimized protocol, a series of N-protected thioacids was acylated with aniline

Table 3 Synthesis of N-Protected Aryl Amides **3**

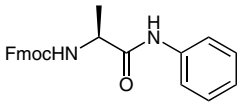
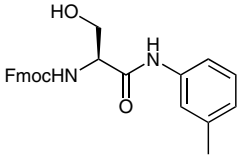
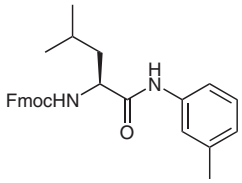
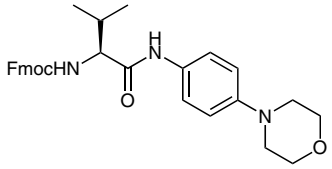
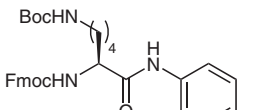
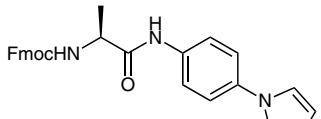
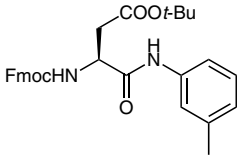
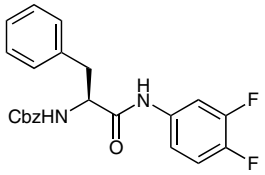
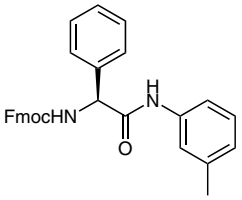
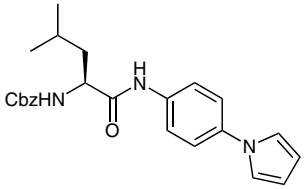
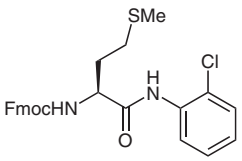
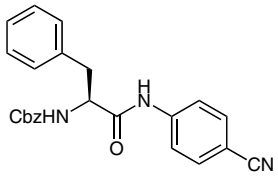
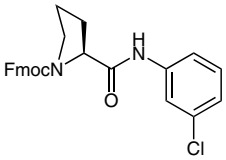
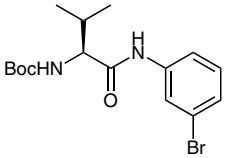
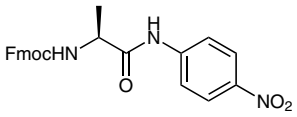
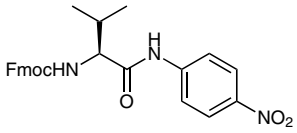
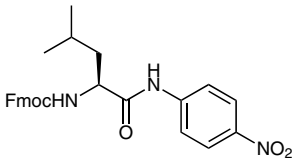
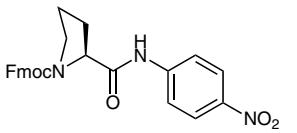
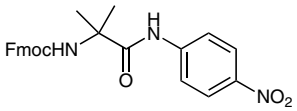
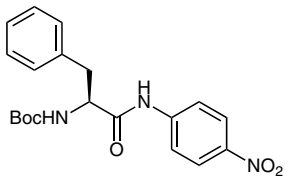
Entry	Aryl amide	Yield (%)	Mp (°C)	Entry	Aryl amide	Yield (%)	Mp (°C)
1	 **3a**	91	191–193	8	 **3h**	87	190–192
2	 **3b**	88	179	9	 **3i**	83	213–215
3	 **3c**	79	176–178	10	 **3j**	76	227–229
4	 **3d**	81	132	11	 **3k**	65	161–163
5	 **3e**	86	218	12	 **3l**	81	219–221
6	 **3f**	85	187–188	13	 **3m**	78	170
7	 **3g**	77	180–184	14	 **3n**	89	154–155

Table 4 Synthesis of N-Protected 4-Nitroanilides **4**

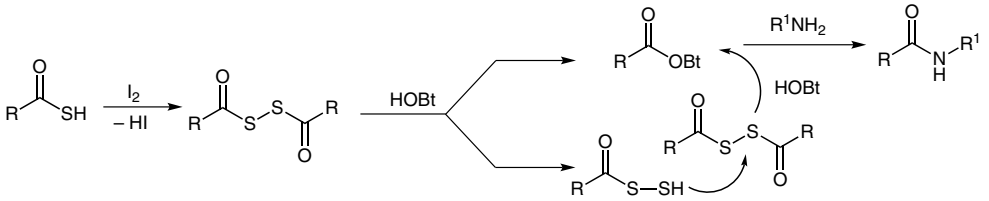
Entry	4-Nitroanilide	Yield (%)	Mp (°C)
1	 **4a**	81	181–183
2	 **4b**	75	185–187
3	 **4c**	80	190
4	 **4d**	69	183–184
5	 **4e**	63	197–199
6	 **4f**	78	172–173

derivatives containing electron-donating or electron-withdrawing substituents. The results are summarized in Table 3. It was found that the coupling of anilines with electron-donating groups gave the corresponding products in higher yields than those possessing electron-withdrawing groups. The aniline substrates containing *ortho*, *para*, and *meta* substituents had no effect on the product yield. Various Fmoc-, Boc- and Cbz-protected amino thioacids were well-tolerated under the optimized reaction conditions, leading to the desired aryl amides **3** in good to excellent yields.

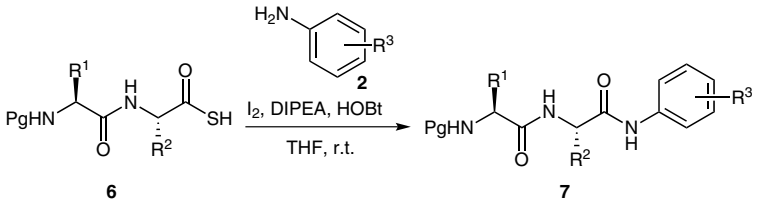
N-Protected amino acid 4-nitroanilides play a significant role in biology and medicine.[22] However, a number of the reported methods for their synthesis result in low yields. Despite the procedure employing phosphorus(V) oxychloride ($POCl_3$) giving 4-nitroanilides in almost 80% yield,[16g] this reagent is not employed commonly as an acylating agent in peptide chemistry because of the inherent disadvantages associated with sensitive protecting groups. Thus, we focused our studies on the synthesis of Fmoc-protected 4-nitroanilides **4a**–**f** via the condensation of Fmoc-protected amino thioacids with 4-nitroaniline. The products were obtained in satisfactory yields after recrystallization from diethyl ether–THF (Table 4). Interestingly, the reaction occurred efficiently with sterically hindered amino thioacids such as Fmoc-Val, Fmoc-Pro and Fmoc-Aib, affording the corresponding 4-nitroanilides in high purities (as confirmed by HPLC analysis).

Due to the wide functional group tolerance of the T3P®-mediated thioacid preparation,[20] we also addressed the compatibility of the present protocol with unprotected bifunctional amino acids. For this investigation, thioacids derived from Fmoc-Ser, Fmoc-Thr, Fmoc-Tyr and Fmoc-His were employed without protection of the side chain functionalities. The aryl amides **5a**–**d** derived from these thioacids were obtained in good yields (Table 5).

In order to broaden the scope of the present methodology, the synthesis of N-protected dipeptide and tripeptide acid aryl amides was carried out (Scheme 4). The required thioacids **6** were synthesized via T3P® activation of the re-

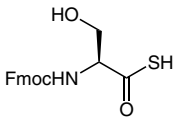
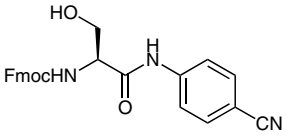
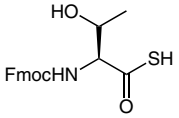
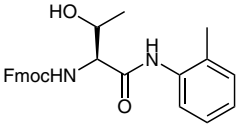
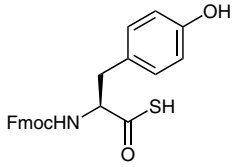
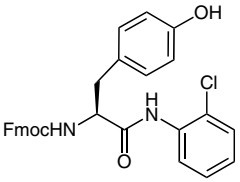
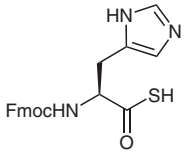
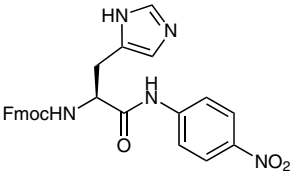


Scheme 3 A plausible mechanism for the formation of an amide bond using thioacids



Scheme 4 Synthesis of N-protected peptide acid aryl amides **7**

Table 5 Synthesis of Unprotected Bifunctional Amino Acid Aryl Amides **5**

Entry	Thioacid	Aryl amide	Yield (%)
1		 **5a**	79
2		 **5b**	82
3		 **5c**	88
4		 **5d**	75

spective oxo-acids. In general, the reactions of peptide thioacids **6** with aniline derivatives were satisfactory, however, the reaction times were longer, taking up to an hour. In all cases, the peptidyl aryl amides **7** were isolated in moderate to good yields (Table 6).

In conclusion, a general and efficient synthesis of enantiopure N-protected amino/peptide aryl amides has been described. The coupling of N-protected amino, dipeptide and tripeptide thioacids with aniline derivatives occurs in the presence of iodine, HOBt and *N*,*N*-diisopropylethylamine at room temperature in tetrahydrofuran. The scope of this new protocol has been demonstrated using a variety of *N*-urethane protecting groups, and side-chain functionalized and sterically hindered amino acids.

All solvents were freshly distilled before use. Amino acids were used as received from Sigma-Aldrich. All the reactions were monitored by TLC using Merck precoated silica gel plates. Column chromatography was performed with Merck silica gel (200–300 mesh) at normal atmospheric pressure. Melting points were recorded on a Kofler hot block in open capillary tubes and are uncorrected. IR spectra were recorded on a Nicolet Impact 400D FT-IR spectrophotometer (KBr pellets, 3 cm^{-1} resolution). Optical rotation values were recorded on a JASCO P-2000 digital polarimeter. ^1H NMR (400 MHz) and ^{13}C NMR (75 MHz) were recorded on a Bruker AMX 400 MHz instrument with tetramethylsilane (TMS) as the internal standard. HRMS analyses were recorded on a Q-Tof Micromass spectrometer.

N-Protected Amino/Peptide Thioacids; General Procedure

To a soln of the appropriate carboxylic acid (1.0 mmol) and T3P® (2.2 mmol) in anhyd MeCN (8.0 mL) was added Et_3N (1.5 mmol) at 0 °C, followed by finely ground Na_2S (3.0 mmol). The resulting mixture was stirred for 2–3 h until the reaction was complete (TLC monitoring), concentrated and then diluted with H_2O. The mixture was acidified with aq citric acid soln (10%) and the product was extracted with EtOAc (10 mL). The organic layer was washed with H_2O (2 × 10 mL) and brine (10 mL), and then dried over anhyd Na_2SO_4. The solvent was evaporated in vacuo to afford the corresponding amino thioacid in quant. yield.

N-Protected Amino/Peptide Acid Aryl Amides; General Procedure

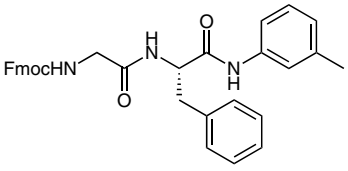
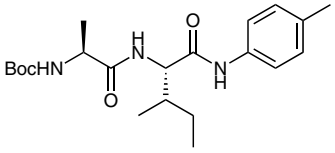
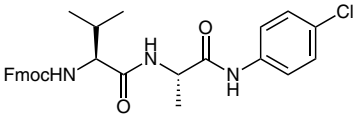
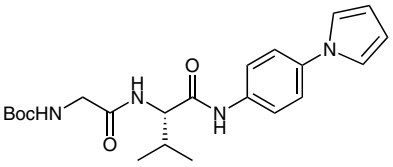
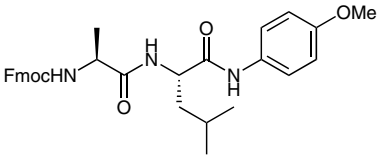
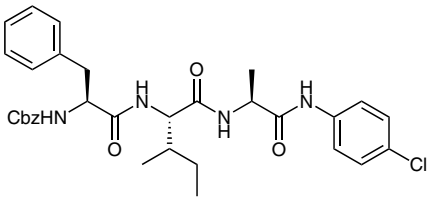
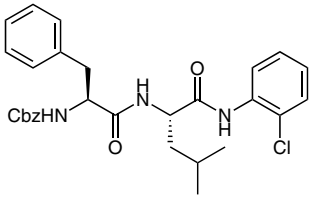
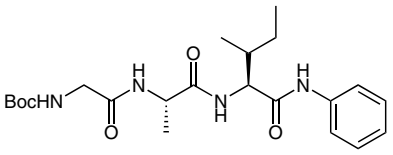
To a stirred suspension of thioacid (1.0 mmol) in THF (5 mL) were added I_2 (0.6 mmol, 152 mg), DIPEA (1.2 mmol, 0.156 mL) and HOBt (2.0 mmol, 270 mg) at r.t., followed by the appropriate amine (1.1 mmol). The reaction mixture was stirred for 0.5 to 1 h as analyzed by TLC (until complete disappearance of the thioacid was observed). After the reaction was complete, the solvent was evaporated under vacuum and diluted with EtOAc (20 mL). The organic phase was washed with 10% HCl (2 × 10 mL), 1 N Na_2CO_3 (3 × 10 mL), H_2O (2 × 10 mL) and brine (10 mL) and then dried over anhydrous Na_2SO_4. The solvent was filtered and evaporated under reduced pressure. The crude reaction mixture was purified under column chromatography using hexane–EtOAc (7:3) as the eluent to afford the desired product.

Fmoc-Ala-anilide (3a)

Yield: 0.355 g (91%); white solid; mp 191–193 °C; $[\alpha]_D^{25}$ –27.5 (*c* 0.1, $CHCl_3$).

IR (neat): 3359, 1689, 1528 cm^{-1}.

Table 6 Synthesis of N-Protected Peptide Aryl Amides **7**

Entry	Peptide aryl amide	Yield (%)	Entry	Peptide aryl amide	Yield (%)
1	 **7a**	83	5	 **7e**	76
2	 **7b**	86	6	 **7f**	80
3	 **7c**	79	7	 **7g**	75
4	 **7d**	81	8	 **7h**	76

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.27 (d, J = 7.6 Hz, 3 H), 4.13–4.24 (m, 4 H), 6.90 (d, J = 7.6 Hz, 2 H), 7.25–7.81 (m, 12 H), 9.94 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 16.4, 45.9, 51.3, 69.2, 122.3, 124.1, 127.1, 128.1, 128.6, 129.3, 139.1, 141.2, 143.7, 156.2, 172.1.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{24}H_{22}N_2O_3Na$: 409.1528; found: 409.1531.

Fmoc-Leu-3-methylanilide (3b)
Yield: 0.39 g (88%); white solid; mp 179 °C; $[\alpha]_D^{25}$ –35.1 (c 0.1, $CHCl_3$).

IR (neat): 3288, 1686, 1530, 1258 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.97 (d, J = 7.8 Hz, 6 H), 1.87–1.92 (m, 3 H), 2.34 (s, 3 H), 4.28–4.33 (m, 2 H), 4.61 (d, J = 7.2 Hz, 2 H), 6.89 (d, J = 5.8 Hz, 1 H), 7.19–7.80 (m, 12 H), 9.29 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.9, 24.2, 40.3, 48.1, 51.7, 67.8, 119.1, 121.7, 123.9, 125.4, 127.8, 128.1, 128.7, 137.3, 138.1, 139.8, 143.3, 156.2, 171.8.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{28}H_{30}N_2O_3Na$: 465.2154; found: 465.2151.

Fmoc-Lys(Boc)-4-methylanilide (3c)
Yield: 0.44 g (79%); white solid; mp 176–178 °C; $[\alpha]_D^{25}$ –25.3 (c 0.1, $CHCl_3$).

IR (neat): 3353, 1663, 1530, 1251 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.23–1.27 (m, 2 H), 1.39 (s, 9 H), 1.62–1.67 (m, 2 H), 1.92–1.96 (m, 2 H), 2.25 (s, 3 H), 2.81–2.85 (m, 2 H), 4.35–4.41 (m, 1 H), 4.42 (t, J = 5.6 Hz, 1 H), 4.64 (d, J = 6.8 Hz, 2 H), 6.90 (br s, 2 H), 7.08–7.55 (m, 12 H), 8.91 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9, 22.9, 24.1, 28.9, 30.0, 30.2, 32.2, 47.6, 55.9, 67.7, 117.5, 120.5, 121.1, 125.5, 125.8, 127.6, 128.2, 129.3, 139.4, 141.8, 144.2, 156.7, 156.9, 168.2, 170.5.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{33}H_{39}N_3O_5Na$: 580.2787; found: 580.2789.

Fmoc-Asp(*t*-Bu)-3-methylanilide (3d)
Yield: 0.4 g (81%); white solid; mp 132 °C; $[\alpha]_D^{25}$ –38.5 (c 0.1, $CHCl_3$).

IR (neat): 3288, 1656, 1535, 1258 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 2.33 (s, 3 H), 2.95–3.00 (m, J = 3.6 Hz, 2 H), 4.20 (t, J = 6.8 Hz, 1 H), 4.46 (d, J = 6.8 Hz, 2 H), 4.58–4.65 (m, 1 H), 6.10 (br s, 1 H), 6.94 (d, J = 7.6 Hz, 1 H), 7.20–7.70 (m, 11 H), 8.48 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 28.5, 38.0, 47.6, 52.2, 67.8, 82.7, 117.6, 120.6, 121.1, 125.5, 125.9, 127.6, 128.3, 129.3, 137.9, 139.4, 141.8, 144.1, 156.8, 169.0, 171.8.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{30}H_{32}N_2O_5Na$: 523.2209; found: 523.2212.

Fmoc-Phg-3-methylanilide (3e)
Yield: 0.4 g (86%); white solid; mp 218 °C; $[\alpha]_D^{25}$ –32.1 (*c* 0.1, $CHCl_3$).

IR (neat): 3277, 1656, 1535, 1258 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.25 (s, 3 H), 4.22–4.28 (m, 3 H), 5.43 (d, *J* = 8.0 Hz, 1 H), 6.80 (d, *J* = 7.2 Hz, 1 H), 7.15–8.20 (m, 17 H), 10.24 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.2, 46.3, 66.1, 119.3, 120.9, 125.1, 126.3, 127.4, 128.3, 128.8, 129.1, 129.6, 138.3, 138.7, 156.2, 169.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{27}N_2O_3$: 463.2022; found: 463.2019.

Fmoc-Met-2-chloroanilide (3f)
Yield: 0.41 g (85%); white solid; mp 187–188 °C; $[\alpha]_D^{25}$ –29.2 (*c* 0.1, $CHCl_3$).

IR (neat): 3295, 1678, 1532, 1256 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.13 (s, 3 H), 2.65–2.61 (m, 2 H), 2.74 (t, *J* = 6.0 Hz, 2 H), 4.24 (t, *J* = 6.4 Hz, 1 H), 4.45–4.46 (m, 3 H), 5.60 (d, *J* = 8.0 Hz, 1 H), 6.10 (br s, 1 H), 7.05–7.70 (m, 11 H), 8.80 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.9, 28.7, 32.3, 45.4, 55.1, 69.1, 123.8, 126.1, 126.8, 127.3, 128.4, 128.7, 129.6, 131.5, 137.3, 140.9, 144.7, 155.9, 169.7.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{25}ClN_2O_3SNa$: 503.1172; found: 503.1171.

Fmoc-Pro-3-chloroanilide (3g)
Yield: 0.34 g (77%); white solid; mp 180–184 °C; $[\alpha]_D^{25}$ –26.4 (*c* 0.1, $CHCl_3$).

IR (neat): 3332, 1672, 1545, 1421 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.82–1.87 (m, 2 H), 2.01–2.07 (m, 2 H), 3.14 (t, *J* = 4.8 Hz, 2 H), 4.10 (t, *J* = 5.4 Hz, 1 H), 4.35 (t, *J* = 5.0 Hz, 1 H), 4.89 (d, *J* = 7.4 Hz, 2 H), 6.93 (d, *J* = 7.2 Hz, 1 H), 7.23–7.56 (m, 11 H), 8.92 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 28.5, 47.6, 48.1, 61.5, 68.5, 118.1, 120.2, 120.5, 124.4, 125.4, 127.5, 127.6, 128.3, 130.2, 134.9, 139.7, 141.8, 144.1, 157.3, 170.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{23}ClN_2O_3Na$: 469.1295; found: 469.1291.

Fmoc-Ser-3-methylanilide (3h)
Yield: 0.36 g (87%); white solid; mp 190–192 °C; $[\alpha]_D^{25}$ –21.5 (*c* 0.1, $CHCl_3$).

IR (neat): 3272, 1654, 1535, 1257 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.27 (s, 3 H), 3.64 (d, *J* = 6.0 Hz, 2 H), 4.21–4.30 (m, 4 H), 6.86 (d, *J* = 6.8 Hz, 1 H), 7.10–7.90 (m, 11 H), 8.10 (s, 1 H), 9.90 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.7, 47.1, 62.2, 116.9, 120.2, 120.6, 124.4, 125.8, 127.6, 128.1, 129.0, 138.3, 139.4, 141.2, 144.3, 144.4, 156.4, 172.6.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{24}N_2O_4Na$: 439.1634; found: 439.1634.

Fmoc-Val-4-morpholino-anilide (3i)
Yield: 0.42 g (83%); white solid; mp 213–215 °C; $[\alpha]_D^{25}$ –32.1 (*c* 0.1, $CHCl_3$).

IR (neat): 3287, 1682, 1537, 1254 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 0.97 (d, *J* = 7.4 Hz, 6 H), 2.51–2.58 (m, 1 H), 3.20 (t, *J* = 4.6 Hz, 4 H), 3.71 (t, *J* = 4.6 Hz, 4 H), 4.32 (t, *J* = 5.2 Hz, 1 H), 4.57 (d, *J* = 6.4 Hz, 2 H), 4.72–4.85 (m, 1 H), 6.57 (d, *J* = 7.2 Hz, 2 H), 6.80 (br s, 1 H), 7.28–7.78 (m, 10 H), 10.21 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 17.4, 28.9, 44.7, 46.8, 57.4, 63.2, 68.1, 114.7, 121.3, 125.8, 127.3, 128.4, 128.7, 129.4, 140.1, 142.7, 144.4, 156.2, 170.7.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{30}H_{33}N_3O_4Na$: 522.2369; found: 522.2364.

Fmoc-Ala-4-pyrazolo-anilide (3j)
Yield: 0.34 g (76%); white solid; mp 227–229 °C; $[\alpha]_D^{25}$ –37.1 (*c* 0.1, $CHCl_3$).

IR (neat): 3293, 1725, 1668, 1533 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.32 (d, *J* = 6.4 Hz, 3 H), 2.80–2.86 (m, 1 H), 4.24 (t, *J* = 4.8 Hz, 1 H), 4.47 (d, *J* = 7.2 Hz, 2 H), 5.90 (br s, 1 H), 6.34 (d, *J* = 6.8 Hz, 1 H), 7.23–7.80 (m, 14 H), 8.92 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 16.5, 46.3, 66.9, 109.1, 121.3, 122.7, 125.9, 126.2, 127.8, 128.4, 133.4, 136.7, 140.4, 143.2, 156.6, 171.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{24}N_4O_3Na$: 475.1746; found: 475.1748.

Cbz-Phe-3,4-difluoroanilide (3k)[16i]
Yield: 0.26 g (65%); white solid; mp 162–164 °C; $[\alpha]_D^{25}$ –25.6 (*c* 0.1, $CHCl_3$).

IR (neat): 3284, 1653, 1530, 1283 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.88 (d, *J* = 6.8 Hz, 2 H), 4.29 (t, *J* = 5.2 Hz, 1 H), 5.14 (s, 2 H), 6.92 (d, *J* = 7.2 Hz, 1 H), 7.20–7.38 (m, 11 H), 7.60–7.80 (m, 2 H), 10.25 (br s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 36.3, 55.1, 66.0, 110.4, 116.5, 118.2, 125.8, 126.7, 127.3, 128.1, 128.5, 129.4, 136.3, 138.8, 140.2, 146.2, 148.4, 156.7, 172.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{20}F_2N_2O_3Na$: 433.1340; found: 433.1337.

Cbz-Leu-4-pyrrolylanilide (3l)[16i]
Yield: 0.33 g (81%); white solid; mp 219–221 °C; $[\alpha]_D^{25}$ –27.1 (*c* 0.1, $CHCl_3$).

IR (neat): 3284, 1685, 1594, 1531 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 0.84 (d, *J* = 7.2 Hz, 6 H), 1.14–1.19 (m, 1 H), 1.44–1.52 (m, 2 H), 4.00 (t, *J* = 4.2 Hz, 1 H), 5.01 (s, 2 H), 5.58 (br s, 1 H), 6.22 (d, *J* = 6.4 Hz, 2 H), 7.12–7.65 (m, 11 H), 10.06 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.8, 22.3, 41.7, 50.3, 66.1, 110.3, 121.5, 122.2, 123.9, 127.0, 127.8, 129.4, 135.3, 137.1, 140.9, 156.2, 171.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{27}N_3O_3Na$: 428.1950; found: 428.1952.

Cbz-Phe-4-cyanoanilide (3m)[18]
Yield: 0.31 g (78%); white solid; mp 170 °C; $[\alpha]_D^{25}$ –35.7 (*c* 0.1, $CHCl_3$).

IR (neat): 3325, 2235, 1530, 1251 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.87 (d, *J* = 7.2 Hz, 2 H), 3.05 (t, *J* = 4.4 Hz, 1 H), 4.97 (s, 2 H), 7.14–7.56 (m, 12 H), 7.79 (d, *J* = 6.6 Hz, 2 H), 8.09 (br s, 1 H), 10.46 (br s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 37.2, 56.9, 65.3, 111.4, 118.5, 121.9, 123.8, 126.3, 126.9, 127.4, 127.6, 128.0, 128.2, 129.1, 130.1, 136.8, 137.5, 139.4, 155.9, 171.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{21}N_3O_3Na$: 422.1481; found: 422.1483.

Boc-Val-3-bromoanilide (3n)
Yield: 0.33 g (89%); white solid; mp 154–155 °C; $[\alpha]_D^{25}$ –33.4 (*c* 0.1, $CHCl_3$).

IR (neat): 3314, 1683, 1532, 1249 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.03 (d, J = 7.2 Hz, 6 H), 1.37 (s, 9 H), 2.66–2.78 (m, 1 H), 4.04–4.07 (m, 1 H), 7.13–7.52 (m, 4 H), 7.92 (br s, 1 H), 9.80 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 17.8, 27.9, 32.4, 58.2, 78.5, 120.4, 120.9, 123.4, 127.1, 130.7, 139.2, 155.8, 172.3.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{16}H_{23}BrN_2O_3Na$: 393.0790; found: 393.0785.

Fmoc-Ala-4-nitroanilide (4a)[16f]
Yield: 0.35 g (81%); white solid; mp 181–183 °C; $[\alpha]_D^{25}$ –30.5 (c 0.1, $CHCl_3$).

IR (neat): 2983, 1737, 1372, 1234 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.31 (d, J = 4.2 Hz, 3 H), 4.11 (t, J = 6.0 Hz, 1 H), 4.43 (d, J = 5.6 Hz, 2 H), 4.65–4.70 (m, 1 H), 5.11 (br s, 1 H), 7.11–8.12 (m, 12 H), 10.80 (br s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 16.5, 45.5, 49.6, 66.3, 120.4, 121.6, 125.8, 126.4, 127.1, 127.8, 140.1, 141.2, 143.2, 143.8, 155.8, 171.2.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{24}H_{21}N_3O_5Na$: 454.1379; found: 454.1368.

Fmoc-Val-4-nitroanilide (4b)[16g]
Yield: 0.34 g (75%); white solid; mp 185–187 °C; $[\alpha]_D^{25}$ –39.1 (c 0.1, $CHCl_3$).

IR (neat): 3329, 1685, 1533, 1383 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 0.96 (d, J = 7.2 Hz, 6 H), 2.45–2.53 (m, 1 H), 4.21–4.28 (m, 2 H), 4.51 (d, J = 5.8 Hz, 2 H), 5.29 (br s, 1 H), 7.18–8.15 (m, 12 H), 9.80 (br s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 16.8, 30.5, 45.7, 58.5, 67.6, 121.2, 121.6, 125.5, 126.8, 127.4, 127.8, 140.0, 141.5, 143.3, 143.9, 155.0, 171.1.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{26}H_{25}N_3O_5Na$: 482.1692; found: 482.1680.

Fmoc-Leu-4-nitroanilide (4c)[16f]
Yield: 0.38 g (80%); white solid; mp 190 °C; $[\alpha]_D^{25}$ –36.4 (c 0.1, $CHCl_3$).

IR (neat): 3299, 1635, 1538, 1372 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 0.98 (d, J = 8.4 Hz, 6 H), 1.75–1.81 (m, 3 H), 4.22–4.31 (m, 2 H), 4.61 (d, J = 5.8 Hz, 2 H), 5.55 (br s, 1 H), 7.11–8.21 (m, 12 H), 10.60 (br s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.8, 22.0, 40.2, 46.5, 50.8, 66.8, 120.8, 121.5, 126.4, 126.8, 127.0, 128.0, 139.7, 141.0, 142.8, 143.4, 155.0, 170.7.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{27}H_{27}N_3O_5Na$: 496.1848; found: 496.1831.

Fmoc-Pro-4-nitroanilide (4d)[16f]
Yield: 0.32 g (69%); white solid; mp 183–184 °C; $[\alpha]_D^{25}$ –53.4 (c 0.1, $CHCl_3$).

IR (neat): 3315, 1658, 1543, 1425 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.22–1.27 (m, 2 H), 1.85–1.94 (m, 2 H), 3.21–3.26 (m, 2 H), 4.12–4.18 (m, 1 H), 4.28 (t, J = 7.2 Hz, 1 H), 4.57 (d, J = 6.8 Hz, 2 H), 7.10–8.12 (m, 12 H), 9.60 (br s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.8, 28.5, 46.8, 47.0, 61.5, 67.0, 121.5, 121.9, 127.2, 127.8, 128.0, 128.2, 139.9, 141.5, 143.1, 143.5, 155.2, 170.8.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{26}H_{23}N_3O_5Na$: 480.1535; found: 480.1530.

Fmoc-Aib-4-nitroanilide (4e)
Yield: 0.28 g (63%); white solid; mp 197–199 °C.

IR (neat): 3318, 1669, 1539, 1382 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.41 (s, 6 H), 4.30 (t, J = 4.2 Hz, 1 H), 4.55 (d, J = 4.9 Hz, 2 H), 5.11 (br s, 1 H), 7.11–8.15 (m, 12 H), 10.23 (br s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.7, 45.8, 47.1, 66.8, 121.2, 121.7, 126.4, 127.8, 128.0, 128.2, 139.5, 141.0, 143.6, 143.8, 155.1, 171.2.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{25}H_{23}N_3O_5Na$: 468.1535; found: 468.1522.

Boc-Phe-4-nitroanilide (4f)[16g]
Yield: 0.3 g (78%); white solid; mp 172–173 °C; $[\alpha]_D^{25}$ –42.6 (c 0.1, $CHCl_3$).

IR (neat): 3289, 1663, 1534, 1381 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.32 (s, 9 H), 2.85–2.91 (m, 2 H), 4.77–4.85 (m, 1 H), 5.08 (br s, 1 H), 7.01–8.05 (m, 9 H), 9.80 (br s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 27.5, 37.2, 54.1, 79.2, 121.1, 121.8, 125.7, 127.2, 128.1, 139.1, 144.0, 144.1, 155.7, 172.1.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{20}H_{23}N_3O_5Na$: 408.1535; found: 408.1519.

Fmoc-Ser-4-cyanoanilide (5a)
Yield: 0.34 g (79%); white solid; mp 173–175 °C; $[\alpha]_D^{25}$ –34.5 (c 0.1, $CHCl_3$).

IR (neat): 3312, 2225, 1672, 1542 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.80 (d, J = 5.6 Hz, 2 H), 4.24 (t, J = 8.0 Hz, 1 H), 4.48 (d, J = 6.4 Hz, 2 H), 4.68–4.75 (m, 1 H), 6.20 (br s, 1 H), 7.20–7.80 (m, 12 H), 9.80 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 45.3, 53.1, 60.8, 67.2, 108.9, 113.7, 121.8, 125.3, 127.4, 128.0, 128.6, 131.5, 140.2, 141.8, 143.2, 156.4, 172.8.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{25}H_{21}N_3O_4Na$: 450.1430; found: 450.1427.

Fmoc-Thr-2-methylanilide (5b)
Yield: 0.35 g (82%); white solid; mp 190 °C; $[\alpha]_D^{25}$ –35.7 (c 0.1, $CHCl_3$).

IR (neat): 3285, 1654, 1535, 1235 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.30 (d, J = 6.4 Hz, 3 H), 2.31 (s, 3 H), 3.91–4.01 (m, 1 H), 4.37 (t, J = 4.8 Hz, 1 H), 4.64–4.71 (m, 3 H), 5.86 (br s, 1 H), 6.87–7.03 (m, 3 H), 7.23–7.50 (m, 9 H), 9.95 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.7, 18.2, 46.9, 59.4, 66.9, 68.1, 121.8, 123.7, 125.9, 126.3, 127.8, 128.1, 128.5, 129.7, 133.8, 137.2, 140.3, 143.5, 155.8, 171.3.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{26}H_{26}N_2O_4Na$: 453.1790; found: 453.1735.

Fmoc-Tyr-2-chloroanilide (5c)
Yield: 0.45 g (88%); white solid; mp 194–196 °C; $[\alpha]_D^{25}$ –43.2 (c 0.1, $CHCl_3$).

IR (neat): 3159, 1657, 1538, 1446 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.10–3.18 (m, 2 H), 4.41 (t, J = 5.2 Hz, 1 H), 4.63 (d, J = 6.2 Hz, 2 H), 4.78–4.85 (m, 1 H), 5.63 (br s, 1 H), 6.62 (s, 2 H), 6.85 (s, 2 H), 7.15–7.55 (m, 12 H), 10.25 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 36.3, 47.1, 53.8, 67.9, 114.3, 122.7, 125.1, 125.5, 126.5, 126.9, 127.8, 128.3, 128.9, 129.4, 130.2, 132.7, 137.4, 140.0, 142.5, 155.4, 156.2, 171.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{30}H_{25}ClN_2O_4Na$: 535.1401; found: 535.1408.

Fmoc-His-4-nitroanilide (5d)
Yield: 0.37 g (75%); white solid; mp 225–228 °C; $[\alpha]_D^{25}$ –38.5 (*c* 0.1, $CHCl_3$).

IR (neat): 3105, 2856, 1854, 1628 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.51 (d, *J* = 6.4 Hz, 2 H), 4.47 (t, *J* = 5.4 Hz, 1 H), 4.63 (d, *J* = 7.2 Hz, 2 H), 4.80 (t, *J* = 6.2 Hz, 1 H), 6.30 (br s, 1 H), 6.75 (s, 1 H), 7.28–7.87 (m, 11 H), 8.15 (d, *J* = 6.8 Hz, 2 H), 9.70 (s, 1 H), 12.30 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.7, 46.4, 51.7, 66.9, 118.5, 120.9, 122.2, 126.7, 127.8, 128.6, 133.8, 135.1, 141.2, 143.0, 144.1, 144.8, 156.5, 172.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{23}N_5O_5Na$: 520.1597; found: 520.1591.

Fmoc-Gly-Phe-3-methylanilide (7a)
Yield: 0.44 g (83%); white solid; mp 235–237 °C; $[\alpha]_D^{25}$ –93.6 (*c* 0.1, $CHCl_3$).

IR (neat): 3314, 2922, 1640, 1536 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.31 (s, 3 H), 3.05–3.16 (m, 2 H), 3.72 (s, 2 H), 4.32 (t, *J* = 5.4 Hz, 1 H), 4.42–4.61 (m, 3 H), 6.78 (d, *J* = 6.4 Hz, 1 H), 7.15–7.79 (m, 18 H), 9.10 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.1, 35.3, 41.7, 46.9, 53.4, 67.4, 119.4, 121.3, 123.4, 126.1, 126.5, 127.1, 127.8, 128.3, 128.7, 129.1, 137.9, 138.3, 139.8, 140.7, 143.2, 156.4, 169.6, 172.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{33}H_{31}N_3O_4Na$: 556.2212; found: 556.2222.

Fmoc-Val-Ala-4-chloroanilide (7b)
Yield: 0.45 g (86%); white solid; mp 243 °C; $[\alpha]_D^{25}$ +79.3 (*c* 0.1, $CHCl_3$).

IR (neat): 3298, 2955, 1675, 1535 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.07 (d, *J* = 7.2 Hz, 6 H), 1.32 (d, *J* = 6.6 Hz, 3 H), 2.48–2.56 (m, 1 H), 4.43–4.50 (m, 2 H), 4.63 (d, *J* = 6.8 Hz, 2 H), 4.78–4.85 (m, 1 H), 6.80 (br s, 1 H), 7.25–7.90 (m, 13 H), 9.72 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 16.8, 17.4, 30.2, 46.8, 48.2, 58.7, 67.2, 123.7, 126.4, 127.8, 128.0, 128.3, 128.7, 129.4, 137.6, 139.5, 143.1, 156.5, 170.3, 171.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{29}H_{30}ClN_3O_4Na$: 542.1823; found: 542.1825.

Fmoc-Ala-Leu-4-methoxyanilide (7c)
Yield: 0.42 g (79%); white solid; mp 253–255 °C; $[\alpha]_D^{25}$ +18.3 (*c* 0.1, $CHCl_3$).

IR (neat): 3307, 2825, 1682, 1538 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.95 (d, *J* = 7.2 Hz, 6 H), 1.39 (d, *J* = 6.2 Hz, 3 H), 1.81–1.87 (m, 3 H), 3.68 (s, 3 H), 4.42–4.53 (m, 3 H), 4.63 (d, *J* = 6.8 Hz, 2 H), 6.71 (d, *J* = 7.0 Hz, 2 H), 7.25–7.51 (m, 12 H), 8.95 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 17.5, 21.3, 22.4, 40.9, 48.4, 50.3, 50.8, 56.2, 68.1, 114.6, 122.3, 126.0, 127.6, 128.2, 131.4, 141.2, 143.1, 156.3, 156.7, 170.5, 172.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{31}H_{35}N_3O_5Na$: 552.2474; found: 552.2471.

Cbz-Phe-Leu-2-chloroanilide (7d)
Yield: 0.42 g (81%); white solid; mp 231–232 °C; $[\alpha]_D^{25}$ –123.5 (*c* 0.1, $CHCl_3$).

IR (neat): 3283, 2846, 1698, 1535 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.10 (d, *J* = 7.4 Hz, 6 H), 1.80–1.83 (m, 2 H), 2.85 (d, *J* = 6.6 Hz, 2 H), 4.35–4.42 (m, 3 H), 5.27 (s, 2 H), 5.80 (br s, 1 H), 6.90–7.21 (m, 14 H), 7.42 (br s, 1 H), 9.72 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 16.1, 21.3, 22.7, 36.8, 42.5, 50.4, 53.7, 123.7, 125.4, 125.9, 126.8, 127.1, 127.5, 127.9, 128.3, 128.8, 129.3, 131.2, 135.3, 139.1, 141.7, 156.3, 169.8, 171.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{29}H_{32}ClN_3O_4Na$: 544.1979; found: 544.1975.

Boc-Ala-Ile-4-methylanilide (7e)
Yield: 0.3 g (76%); white solid; mp 218–221 °C; $[\alpha]_D^{25}$ –58.5 (*c* 0.1, $CHCl_3$).

IR (neat): 3292, 2916, 1613, 1529 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.85 (t, *J* = 5.2 Hz, 3 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 1.18–1.21 (m, 2 H), 1.37 (s, 9 H), 1.45 (d, *J* = 7.4 Hz, 3 H), 2.25–2.34 (m, 1 H), 2.36 (s, 3 H), 4.40 (d, *J* = 6.2 Hz, 1 H), 5.61 (br s, 1 H), 6.80 (br s, 1 H), 7.15 (d, *J* = 5.6 Hz, 2 H), 7.62 (d, *J* = 5.6 Hz, 2 H), 8.63 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.1, 15.2, 18.4, 23.5, 24.6, 28.1, 35.4, 49.7, 54.1, 78.5, 120.8, 129.1, 133.5, 135.1, 156.7, 170.1, 172.3

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{33}N_3O_4Na$: 414.2369; found: 414.2372.

Boc-Gly-Val-4-pyrrolylanilide (7f)
Yield: 0.33 g (80%); white solid; mp 227–279 °C; $[\alpha]_D^{25}$ –29.7 (*c* 0.1, $CHCl_3$).

IR (neat): 3297, 2928, 1625, 1532 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.13 (d, *J* = 7.2 Hz, 6 H), 1.35 (s, 9 H), 2.31–2.37 (m, 1 H), 3.73 (d, *J* = 6.6 Hz, 2 H), 4.41 (d, *J* = 7.0 Hz, 1 H), 5.57 (br s, 1 H), 6.13 (d, *J* = 5.8 Hz, 2 H), 6.83 (d, *J* = 5.8 Hz, 2 H), 7.21 (d, *J* = 6.2 Hz, 2 H), 7.65 (d, *J* = 6.2 Hz, 2 H), 7.80 (br s, 1 H), 9.85 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 17.8, 27.3, 31.5, 46.1, 55.7, 78.9, 109.2, 121.7, 122.5, 124.1, 134.6, 135.4, 156.1, 170.3, 171.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{30}N_4O_4Na$: 437.2165; found: 437.2158.

Cbz-Phe-Ile-Ala-4-chloroanilide (7g)
Yield: 0.45 g (75%); white solid; mp 235 °C; $[\alpha]_D^{25}$ +23.4 (*c* 0.1, $CHCl_3$).

IR (neat): 3311, 2954, 2925, 1631 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.03 (t, *J* = 7.2 Hz, 3 H), 1.15 (d, *J* = 6.6 Hz, 3 H), 1.32–1.40 (m, 2 H), 1.53 (d, *J* = 7.0 Hz, 3 H), 2.25–2.34 (m, 1 H), 2.85 (d, *J* = 5.8 Hz, 2 H), 3.84 (d, *J* = 5.4 Hz, 1 H), 4.45–4.53 (m, 1 H), 4.72–4.81 (m, 1 H), 5.21 (s, 2 H), 5.80 (br s, 1 H), 6.64 (br s, 1 H), 7.18–7.52 (m, 14 H), 9.85 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 11.3, 15.1, 17.6, 26.1, 38.1, 38.6, 45.4, 53.1, 55.8, 64.3, 122.6, 125.4, 126.8, 127.4, 128.8, 129.5, 129.7, 134.5, 138.3, 140.2, 155.3, 168.8, 170.5, 142.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{32}H_{37}ClN_4O_5Na$: 615.2350; found: 615.2348.

Boc-Gly-Ala-Ile-anilide (7h)
Yield: 0.33 g (76%); white solid; mp 241–243 °C; $[\alpha]_D^{25}$ +68.3 (*c* 0.1, $CHCl_3$).

IR (neat): 3295, 2961, 2884, 1626 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.87 (t, *J* = 4.8 Hz, 3 H), 1.09 (d, *J* = 6.4 Hz, 3 H), 1.20–1.27 (m, 2 H), 1.34 (s, 9 H), 1.48 (d, *J* = 6.8 Hz, 3 H), 2.80–2.89 (m, 1 H), 3.51 (s, 2 H), 4.43 (d, *J* = 7.6 Hz, 1 H), 4.78–4.85 (m, 1 H), 5.23 (br s, 1 H), 6.82 (br s, 1 H), 7.10–7.35 (m, 5 H), 10.23 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.1, 14.3, 16.8, 26.2, 28.4, 38.2, 43.2, 47.8, 56.5, 79.7, 120.6, 123.9, 129.4, 136.3, 155.72, 169.4, 171.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{34}N_4O_5Na$: 457.2427; found: 457.2454.

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