Preparation of N^{β}-Fmoc-Protected Aza-β^3-Amino Acids with Nonproteinogenic Hydrophobic Side Chains for Solid-Phase Syntheses of Pseudopeptides

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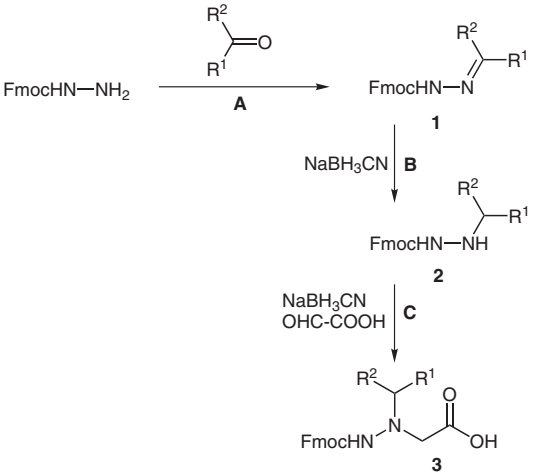
Abstract: The preparation of twelve new N^{β}-Fmoc-protected aza-β^3-amino acids (aza-β^3aa) with nonproteinogenic hydrophobic side chains is described.

Key words: aza-β^3-amino acid, Fmoc protecting group, peptidomimetics, hydrophobic side chains, non-natural amino acid

Due to proteolytic degradation, peptides are not ideal candidates for pharmaceutical development. For this reason, numerous research groups try to develop non-natural peptidic analogues in order to enhance metabolic stability, bioavailability, and biological absorption.[1–4] In this class of peptidomimetics, pseudopeptides either consisting exclusively or including aza-β^3-amino acids have emerged as a promising new class of compounds that favor hydrogen bond formation and can enhance biological activities.[5–7] N^{β}-Fmoc-protected aza-β^3-amino acids with both nonfunctionalized and functionalized side chains that are analogues of natural proteinogenic amino acids have been already published,[8–10] and we have demonstrated that pseudopeptides including aza-β^3-amino acids can be more active than the natural parent peptides.[6] In light of the instability of aza-β^3-Tyr and aza-β^3-Trp analogues in a strongly acidic medium, and in the context of our ongoing projects on the synthesis of antimicrobial pseudopeptides, we needed to develop N^{β}-Fmoc-protected aza-β^3-amino acid building blocks with non-proteinogenic side chains that are more hydrophobic than natural side chains and more stable. We already know that Trp residues can be replaced by naphthylalanine, pyridylalanine, biphenylalanine residues and many other compounds.[11–13] Furthermore, lipophilic long alkyl chains are very useful for enhancing or modifying antimicrobial activities and cytotoxicity.[14–17] Additionally, the incorporation of fluorinated amino acids have generated great interest since such modifications can enhance the activity of antimicrobial peptides. Such modifications can also allow structural NMR studies since fluorine labels are very suitable for analyzing molecular orientations.[18–20]

Thus, we describe here a detailed preparation of twelve new aza-β^3-amino acid derivatives (Table 1), with the side chains of 9-anthracenylalanine (9-Ath), 4,4′-biphenylalanine (4-Bip), cyclohexylalanine (Cha), diphenylalanine (Dip), dodecylalanine (Dod), 4-fluorophenylalanine (4-F-Phe), 4-fluoro-1-naphthylalanine (4-F-1-Nal), 1-naphthylalanine (1-Nal), 2-naphthylalanine (2-Nal), octylalanine (Oct), 4-pyridylalanine (4-Pal), and 3-pyridylalanine (3-Pal).

We have previously reported a method with which to prepare aza-β^3-amino acids via reductive amination of glyoxylic acid.[21] First, N-substituted Fmoc hydrazones **1** were obtained by condensing fluoren-9-ylmethyl carbazate with the appropriate aldehyde or ketone (Scheme 1). For 4-fluoro-1-naphthylalanine, since the corresponding aldehyde was not commercially available, 4-fluoro-1-naphthalenecarbaldehyde was first synthesized following the procedure described by Boswell et al.[22] Most of these hydrazones were not soluble in dichloromethane and precipitated immediately after their formation, thus driving the reaction through a shift in the equilibrium. All these reactions afforded very good yields (Table 2). The condensation of fluoren-9-ylmethyl carbazate and benzophenone required heating to reflux in toluene with a Dean–Stark trap.



Scheme 1 Synthesis of Fmoc-aza-β^3-amino acids. See Table 1 for R^1 and R^2

In a recent publication on the synthesis of aza-amino acids, Boeglin et al. described the reduction of acyl hydrazone intermediates of 1-naphthylalanine, 2-naphthylalanine and 4,4′-biphenylalanine with 10% mol of $Pd(OH)_2$ on carbon (20% wt) in tetrahydrofuran (THF)

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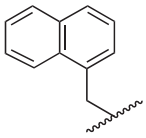
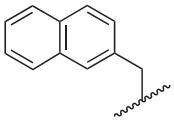
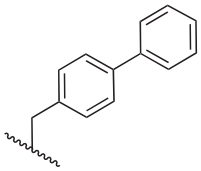
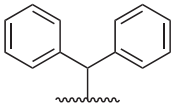
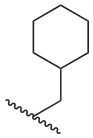
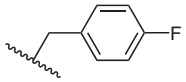
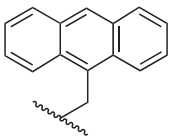
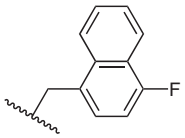
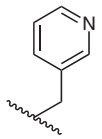
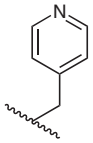
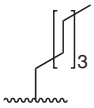
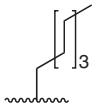
Table 1 Hydrophobic Non-Proteinogenic Side Chains (R^1 and R^2) of Aza-β^3-Amino Acids

a 1-Nal 1-naphthylalanine		**b 2-Nal** 2-naphthylalanine	
c 4-Bip 4′-biphenylalanine			
d Dip diphenylalanine		**e Cha** cyclohexylalanine	
f 4-Fpa 4-fluorophenylalanine			
g 9-Ath 9-anthracenylalanine		**h 4-F-1-Nal** 4-fluoro-1-naphthylalanine	
i 3-Pal 3-pyridylalanine			
j 4-Pal 4-pyridylalanine		**k Oct** octylalanine	
l Dod dodecylalanine			

under 100 psi H_2 pressure.[23] The authors reported that attempts to reduce the acyl hydrazone intermediates with sodium cyanoborohydride were not successful. However, reduction of these hydrazones with sodium cyanoborohydride in methanol could be performed with the use of an additional solvent: *N*,*N*-dimethylformamide (DMF).

In fact, the acyl hydrazone intermediates were insoluble in many solvents, including dichloromethane and methanol, and it is this insolubility that prevents the action of the reductive agent. Thus, hydrazones **1** were solubilized in the minimum amount of DMF and then methanol and sodium cyanoborohydride (1.5 equiv) were added. Immediately after the addition, the pH of the solution was adjusted to pH 3 and the reaction occurred. This addition of DMF is not necessary for the reduction of all hydrazones and can be replaced by dichloromethane for the reduction of diphenylalanine, octyl and dodecylalanine hydrazones. For all side chains, yields of hydrazone reduction were very good (>95%; Table 2) except for the two pyridyl residues. Effectively, protonation of the heterocycle during these reactions could explain the two low yields. We could isolate the two protonated forms of the acyl hydrazone intermediates and *N*′-alkyl fluoren-9-ylmethyl carbazates of 4-pyridylalanine, and 3-pyridylalanine.

With the entire series of twelve *N*′-alkyl fluoren-9-ylmethyl carbazates **2** in hand, we could realize the final reductive amination in the presence of glyoxilic acid to provide the twelve new N^{β}-Fmoc-protected aza-β^3-amino acids **3**. The reactions gave the expected products with good to excellent yields from 70 to 98% (Table 2). All conditions were the same except for Fmoc-aza-β^3-9-anthracenylalanine, for which addition of some DMF was necessary in order to solubilize the *N*′-anthracen-9-yl fluoren-9-ylmethylcarbazate before adding the reagents.

Table 2 Yields of the Reactions A, B and C

Side chain type	A	B	C
1-Nal	99%	96%	96%
2-Nal	97%	96%	98%
Dip	95%	99%	85%
4-Bip	98%	99%	93%
Cha	96%	91%	92%
4-Fpa	97%	98%	96%
9-Ath	96%	99%	94%
4-F-1-Nal	87%	99%	96%
3-Pal	87%	57%	85%
4-Pal	99%	45%	86%
Oct	87%	88%	92%
Dod	91%	91%	95%

In conclusion, we have shown that Fmoc-aza-β^3-amino acids, with chemically diverse hydrophobic side chains, could be conveniently prepared via reductive amination of glyoxylic acid. As in our precedent works, these monomers could be anchored to resin, allowing the preparation of mixed pseudopeptides on solid-phase support. The solid-phase synthesis of antimicrobial hybrid peptides incorporating these analogues will be published later.

NMR spectra were recorded at 200 MHz or 300 MHz (^{1}H) and 75 MHz (^{13}C). ^{1}H chemical shifts are reported in δ values in ppm relative to $CHCl_3$ (δ = 7.24 ppm) as internal standard; ^{13}C chemical shifts are reported in ppm relative to $CDCl_3$ (δ = 77.0 ppm). Multi-

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plicities in ^{1}H NMR are reported as: (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, and (m) multiplet. For the assignment of signals ^{1}H, ^{13}C, and ^{1}H–^{13}C heteronuclear single quantum correlation (HSQC) spectroscopy experiments were used. The analytical laboratory from the Centre Régional de Mesures Physiques de l'Ouest performed elemental analyses and electrospray mass spectrometry (HR-MS, ESI) studies using an MS/MS mass spectrometer ZAB Spec TOF. Thin layer chromatography was performed on silica gel 60 F_{254} plates (Merck). Flash chromatography was performed on SP silica gel 60 (230–600) mesh ASTM.

Condensation; General Procedure

A stirred solution of fluoren-9-ylmethyl carbazate (10.17 g, 40 mmol) in CH_2Cl_2 (500 mL) and aldehyde (1.1 equiv) was maintained under stirring overnight. The mixture was concentrated and the resulting white powder was triturated in Et_2O to give hydrazone **1**, which was pure enough for the following steps. If the hydrazone remains soluble, purification by chromatography on silica gel (CH_2Cl_2–EtOAc, 9:1) was required.

Hydrazone 1-Nal (1a)

Yield: 99%; mp 219–220 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 4.38 (t, *J* = 6.8 Hz, 1 H, CH), 4.57 (d, *J* = 6.8 Hz, 2 H, CH_2), 7.29–8.05 (m, 14 H, ArH), 8.76 (d, *J* = 7.2 Hz, 1 H, ArH), 8.82 (s, 1 H, CH), 11.32 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 154.0, 144.6, 144.2, 141.3, 134.0, 130.6, 130.5, 130.1, 129.2, 128.2, 127.7, 127.6, 126.7, 126.0, 125.6, 124.6, 120.7, 66.3, 47.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{20}N_2O_2Na$: 415.14225; found: 415.1418.

Hydrazone 2-Nal (1b)

Yield: 97%; mp 235–236 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 4.33 (t, *J* = 6.8 Hz, 1 H, CH), 4.53 (d, *J* = 6.8 Hz, 2 H, CH_2), 7.32–7.92 (m, 14 H, ArH), 8.04 (d, *J* = 7.2 Hz, 1 H, ArH), 8.25 (s, 1 H, CH), 11.34 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 153.4, 144.4, 143.7, 140.8, 133.5, 132.8, 132.1, 128.1, 128.2, 128.0, 127.7, 127.1, 126.9, 126.6, 125.1, 122.4, 120.1, 65.7, 46.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{20}N_2O_2Na$: 415.14225; found: 415.1419.

Hydrazone 4-Bip (1c)

Yield: 98%; mp 240–241 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 4.32 (t, *J* = 6.7 Hz, 1 H, CH), 4.55 (d, *J* = 6.7 Hz, 2 H, CH_2), 7.35–7.83 (m, 15 H, ArH), 7.90 (d, *J* = 6.8 Hz, 2 H, ArH), 8.10 (s, 1 H, CH), 11.26 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 153.3 (s), 143.9, 143.7, 141.1, 140.8, 139.3, 133.5, 128.8, 127.7, 127.7, 127.2, 127.1, 126.9, 126.6, 125.1, 120.1, 65.7, 46.6.

Hydrazone Dip (1d)

Yield: 95%; mp 163–164 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.38 (t, *J* = 7.4 Hz, 1 H, CH), 4.45 (d, *J* = 7.4 Hz, 2 H, CH_2), 7.27–7.92 (m, 18 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.9, 152.0, 143.7, 141.4, 137.1, 131.8, 130.0, 129.9, 129.7, 128.5, 128.4, 127.8, 127.6, 127.1, 125.5, 120.1, 67.9, 47.0.

Hydrazone Cha (1e)

Yield: 96%; mp 207–208 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.23 (m, 4 H, CH_2), 1.60 (m, 2 H, CH_2), 1.71 (m, 4 H, CH_2), 2.19 (m, 1 H, CH), 4.30 (t, *J* = 6.8 Hz, 1 H, CH), 4.42 (d, *J* = 6.8 Hz, 2 H, CH_2), 7.2–7.6 (m, 5 H, ArH + CH), 7.66–7.83 (d, *J* = 7 Hz, 2 H, ArH), 7.90 (d, *J* = 7 Hz, 2 H, ArH), 10.71 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 153.8, 152.4, 144.2, 141.2, 128.1, 127.5, 125.7, 120.6, 65.9, 47.1, 40.4, 30.2, 26.0, 25.5.

Hydrazone 4-Fpa (1f)

Yield: 97%; mp 200–201 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.35 (t, *J* = 6.3 Hz, 1 H, CH), 4.54 (d, *J* = 6.3 Hz, 2 H, CH_2), 7.25–7.48 (m, 6 H, ArH), 7.7–7.8 (m, 4 H, ArH), 7.92 (d, *J* = 6.9 Hz, 2 H, ArH), 8.10 (s, 1 H, CH), 11.29 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.95, 161.68 (s), 153.88 (s), 144.18 (s), 143.7, 141.3, 131.49 (s), 129.56, 129.1, 128.16 (d), 127.57 (d), 125.65 (d), 120.6, 116.4, 116.12, 66.26 (t), 47.1.

Hydrazone 9-Ath (1g)

Yield: 96%; mp 249–250 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 4.36 (t, *J* = 6.9 Hz, 1 H, CH), 4.59 (d, *J* = 6.9 Hz, 2 H, CH_2), 7.20–7.50 (m, 4 H, ArH), 7.50–7.70 (m, 4 H, ArH), 7.80 (d, *J* = 7.2 Hz, 2 H, ArH), 7.89 (d, *J* = 7.2 Hz, 2 H, ArH), 8.11 (d, *J* = 6.5 Hz, 2 H, ArH), 8.65 (m, 3 H, ArH + CH), 9.27 (m, 1 H, ArH), 11.49 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 154.0, 144.2, 143.8, 141.3, 131.4, 129.9, 129.6, 129.4, 128.2, 127.6, 127.48 (d), 125.9, 125.8, 125.6, 125.2, 120.7, 66.3, 47.2.

Hydrazone 4-F-1-Nal (1h)

Yield: 87%; mp 221–222 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 4.34 (t, *J* = 6.2 Hz, 1 H, CH), 4.53 (d, *J* = 6.2 Hz, 2 H, CH_2), 7.30–7.47 (m, 5 H, ArH), 7.67–7.91 (m, 7 H, ArH), 8.11 (m, 1 H, ArH), 8.64 (s, 1 H, CH), 8.85 (m, 1 H, ArH), 11.31 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.8, 157.5, 153.9, 144.3, 144.2, 141.3, 131.9, 131.8, 128.8, 128.2, 127.6, 127.5, 126.9, 126.8, 125.6, 125.0, 123.7, 123.5, 121.1, 121.0, 120.6, 110.3, 110.0, 66.4, 47.1.

Hydrazone 3-Pal (1i)

Yield: 87%; mp 215–216 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 4.35 (t, *J* = 6.7 Hz, 1 H, CH), 4.53 (d, *J* = 6.7 Hz, 2 H, CH_2), 7.30–8.12 (m, 11 H, ArH + CH), 8.59 (d, *J* = 7 Hz, 1 H, ArH), 8.84 (s, 1 H, ArH), 11.45 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 153.8, 150.7, 148.74, 144.1, 142.0, 141.3, 133.5, 130.8, 128.2, 127.6, 125.6, 124.4, 120.6, 66.3, 47.1.

Hydrazone 4-Pal (1j)

Yield: 99%; mp 215–216 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 4.37 (t, *J* = 6.7 Hz, 1 H, CH), 4.62 (d, *J* = 6.7 Hz, 2 H, CH_2), 7.30–8.00 (m, 10 H, ArH), 8.15 (s, 1 H, CH), 8.69 (d, *J* = 6.1 Hz, 2 H, ArH), 11.90 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 153.8, 150.6, 144.1, 142.4, 142.1, 141.3, 128.2, 127.6, 125.6, 121.4, 120.6, 66.7, 47.1.

Hydrazone Oct (1k)

Yield: 87%; mp 137–138 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 6.4 Hz, 3 H, CH_3), 1.32 (m, 8 H, CH_2), 1.54 (m, 2 H, CH_2), 2.32 (m, 2 H, CH_2), 4.31 (t, *J* = 7 Hz, 1 H, CH), 4.54 (d, *J* = 7 Hz, 2 H, CH_2), 6.75 (m, 1 H, NH), 7.2 (t, *J* = 5.6 Hz, 1 H, CH), 7.29–7.5 (m, 4 H, ArH), 7.67 (d, *J* = 7.2 Hz, 2 H, ArH).

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^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.8, 149.2, 143.7, 141.3, 128.8, 127.1, 125.2, 120.0, 67.1, 47.0, 32.3, 31.7, 29.2, 29.1, 26.6, 22.7, 14.1.

Hydrazone Dod (1l)
Yield: 91%; mp 133–134 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 6.4 Hz, 3 H, CH_3), 1.30 (m, 16 H, CH_2), 1.56 (m, 2 H, CH_2), 2.36 (m, 2 H, CH_2), 4.32 (t, *J* = 6.9 Hz, 1 H, CH), 4.56 (d, *J* = 6.9 Hz, 2 H, CH_2), 6.76 (m, 1 H, NH), 7.22 (t, *J* = 5.6 Hz, 1 H, CH), 7.30–7.5 (m, 4 H, ArH), 7.67 (d, *J* = 7.1 Hz, 2 H, ArH), 7.81 (d, *J* = 7.1 Hz, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.7, 148.9, 143.7, 141.3, 127.8, 127.1, 125.1, 120.0, 67.4, 47.0, 32.2, 31.9, 29.6, 29.5, 29.4, 29.4, 29.2, 26.6, 22.7, 14.1.

Reduction of Hydrazone 1; General Procedure
To a stirred solution of hydrazone **1** (35 mmol) in DMF–MeOH (50:150 mL), $NaBH_3CN$ (2.7 g, 1.2 equiv) was added fractionally into the above mixture and the pH was adjusted to pH 3 with HCl (2N). This mixture was maintained under stirring for 1 h, then the pH was adjusted to pH 1 over 10 min and finally increased to pH 7 with sat. $NaHCO_3$. The mixture was filtered, concentrated, taken up in EtOAc (150 mL) and washed with H_2O (2 × 100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4 and concentrated to give a crude foam, which was triturated in Et_2O to give hydrazine **2** as a white powder, which was pure enough for the following step. For characterization, the crude material was purified by chromatography on silica gel (CH_2Cl_2–EtOAc, 9:1).

***N′*-(1-Naphthylmethyl)fluorenylmethyl Carbazate (2a)**
Yield: 96%; mp 136–137 °C (Lit.[23] 136–137 °C).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.27 (t, *J* = 6.7 Hz, 1 H, CH), 4.51 (m, 4 H, 2 × CH_2), 6.43 (br, 1 H, NH), 7.30–7.39 (m, 2 H, ArH), 7.40–7.49 (m, 4 H, ArH), 7.50–7.70 (m, 4 H, ArH), 7.75–7.96 (m, 4 H, ArH), 8.31 (d, *J* = 8.4 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.9, 53.1, 66.7, 119.7, 123.6, 124.7, 125.0, 125.5, 126.1, 126.8, 127.5, 127.6, 128.2, 128.3, 131.7, 132.4, 133.5, 141.0, 143.3, 156.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{22}N_2O_2Na$: 417.15790; found: 417.1581.

***N′*-(2-Naphthylmethyl)fluorenylmethyl Carbazate (2b)**
Yield: 96%; mp 128–129 °C (Lit.[23] 128–129 °C).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.20 (m, 2 H, CH_2), 4.25 (t, *J* = 6.8 Hz, 1 H, CH), 4.49 (m, 2 H, CH_2), 6.45 (br, 1 H, NH), 7.39–7.38 (m, 2 H, ArH), 7.44 (t, *J* = 7.4 Hz, 2 H, ArH), 7.48–7.55 (m, 3 H, ArH), 7.57–7.63 (m, 2 H, ArH), 7.77–7.81 (m, 2 H, ArH), 7.82–7.91 (m, 3 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.9, 143.3, 141.0, 134.5, 133.0, 132.6, 127.9, 127.5, 127.4, 126.8, 126.6, 125.8, 125.6, 124.7, 119.7, 66.7, 55.4, 46.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{23}N_2O_2$: 395.1754; found: 395.1755.

***N′*-(Biphenyl-4-ylmethyl)fluorenylmethyl Carbazate (2c)**
Yield: 99%; mp 140–141 °C (Lit.[23] 140–141 °C).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.09 (m, 2 H, CH_2), 4.27 (m, 1 H, CH), 4.51 (m, 2 H, CH_2), 6.44 (br, 1 H, NH), 7.30–7.52 (m, 9 H, ArH), 7.55–7.68 (m, 6 H, ArH), 7.80 (d, *J* = 7.5 Hz, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.8, 143.3, 141.0, 140.4, 140.2, 136.0, 129.1, 128.5, 127.5, 127.4, 127.0, 126.9, 126.8, 124.7, 119.7, 66.6, 55.0, 46.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{25}N_2O_2$: 421.1910; found: 421.1910.

***N′*-(Diphenyl)fluorenylmethyl Carbazate (2d)**
Yield: 99%; translucent oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.24 (t, *J* = 6.6 Hz, 1 H, CH), 4.45 (d, *J* = 6.6 Hz, 2 H, CH_2), 5.40 (br, 1 H, CH), 6.46 (br, 1 H, NH), 7.27–7.82 (m, 18 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.3, 143.7, 141.4, 141.2, 128.7, 127.8, 127.7, 127.15, 125.1, 120.1, 68.2, 67.1, 46.2.

***N′*-(Cyclohexylmethyl)fluorenylmethyl Carbazate (2e)**
Yield: 91%; mp 133–134 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (m, 2 H, CH_2), 1.11–1.33 (m, 3 H, CH_2), 1.46 (m, 1 H, CH), 1.68–1.78 (m, 5 H, CH_2), 2.72 (m, 2 H, CH_2), 4.25 (t, *J* = 6.7 Hz, 1 H, CH), 4.47 (d, *J* = 6.7 Hz, 2 H, CH_2), 6.47 (s, 1 H, NH), 7.2–7.6 (m, 4 H, ArH), 7.61 (d, *J* = 7.1 Hz, 2 H, ArH), 7.79 (d, *J* = 7.1 Hz, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.3, 143.8, 141.4, 127.8, 127.1, 125.0, 120.0, 66.9, 58.6, 47.2, 36.3, 31.3, 26.6, 26.0.

***N′*-(4-Fluorophenylmethyl)fluorenylmethyl Carbazate (2f)**
Yield: 97%; mp 159–160 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.97 (s, 2 H, CH_2), 4.24 (t, *J* = 6.8 Hz, 1 H, CH), 4.49 (d, *J* = 6.8 Hz, 2 H, CH_2), 6.29 (s, 1 H, NH), 7.03 (m, 2 H, ArH), 7.28–7.46 (m, 6 H, ArH), 7.58 (d, *J* = 7.2 Hz, 2 H, ArH), 7.79 (d, *J* = 7.2 Hz, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4, 157.2, 143.8, 141.4, 133.1, 130.7, 130.6, 127.8, 127.1, 124.95, 120.1, 115.5, 115.2, 66.9, 54.9, 47.2.

***N′*-(9-Anthracenylmethyl)fluorenylmethyl Carbazate (2g)**
Yield: 99%; mp 208–210 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 4.26 (t, *J* = 6.9 Hz, 1 H, CH), 4.44 (d, *J* = 6.9 Hz, 2 H, CH_2), 4.87 (s, 2 H, CH_2), 7.28–7.58 (m, 8 H, ArH), 7.71 (d, *J* = 7.2 Hz, 2 H, ArH), 7.88 (d, *J* = 7.2 Hz, 2 H, ArH), 8.07 (d, *J* = 8 Hz, 2 H, ArH), 8.53 (s, 1 H, ArH), 8.56 (s, 2 H, ArH), 8.98 (br, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 157.9, 144.3, 141.2, 135.0, 131.5, 131.1, 129.2, 128.1, 127.7, 127.55, 126.4, 125.8, 125.55, 125.3, 120.6, 66.3, 53.45, 47.3.

***N′*-(4-Fluoro-1-naphthylmethyl)fluorenylmethyl Carbazate (2h)**
Yield: 99%; mp 150–152 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.13 (t, *J* = 6.7 Hz, 1 H, CH), 4.30 (s, 2 H, CH_2), 4.39 (d, *J* = 5.9 Hz, 2 H, CH_2), 6.23 (br, 1 H, NH), 6.96 (m, 1 H, ArH), 7.15–7.68 (m, 10 H, ArH), 8.02–8.06 (m, 2 H, ArH), 8.15 (d, *J* = 7 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.5, 157.2, 143.6, 141.4, 133.35, 128.7, 127.8, 127.7, 127.3, 127.1, 126.15, 125.0, 124.1, 124.1, 121.15, 120.1, 108.75, 67.0, 58.0, 53.0, 47.2.

N′-(3-Pyridylmethyl)fluorenylmethyl Carbazate (2i)
Yield: 57%; mp 133–134 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.03 (s, 2 H, CH_2), 4.23 (t, *J* = 6.7 Hz, 1 H, CH), 4.49 (d, *J* = 6.7 Hz, 2 H, CH_2), 7.03 (s, 1 H, NH), 7.20–7.47 (m, 5 H, ArH), 7.58 (m, 2 H, ArH), 7.65 (s, 1 H, ArH), 7.78 (d, *J* = 7 Hz, 2 H, ArH), 8.47 (d, *J* = 4 Hz, 1 H, ArH), 8.57 (s, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4, 150.2, 148.7, 143.7, 141.3, 136.7, 133.3, 127.8, 127.1, 125.0, 123.4, 120.4, 66.8, 52.9, 47.2.

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N'-(4-Pyridylmethyl)fluorenylmethyl Carbazate (2j)
Yield: 45%; mp 127–128 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.99 (s, 2 H, CH_2), 4.21 (t, J = 6.4 Hz, 1 H, CH), 4.51 (d, J = 6.4 Hz, 2 H, CH_2), 6.92 (s, 1 H, NH), 7.20–7.50 (m, 5 H, ArH), 7.59 (m, 2 H, ArH), 7.75 (s, 1 H, ArH), 7.78 (d, J = 7.1 Hz, 2 H, ArH), 8.47 (d, J = 6.1 Hz, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4, 149.7, 147.0, 143.6, 141.4, 127.8, 127.1, 124.9, 123.7, 120.6, 66.8, 54.2, 47.2.

N'-(Octyl)fluorenylmethyl Carbazate (2k)
Yield: 88%; mp 111–112 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, J = 6.3 Hz, 3 H, CH_3), 1.32 (m, 10 H, CH_2), 1.47 (m, 2 H, CH_2), 2.88 (m, 2 H, CH_2), 4.27 (t, J = 6.7 Hz, 1 H, CH), 4.50 (d, J = 6.7 Hz, 2 H, CH_2), 6.42 (s, 1 H, NH), 7.30–7.5 (m, 4 H, ArH), 7.63 (d, J = 7 Hz, 2 H, ArH), 7.81 (d, J = 7 Hz, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.25 (s), 143.75 (s), 141.36 (s), 127.78 (d), 127.09 (d), 125.01 (d), 120.04 (d), 66.95 (t), 52.06 (t), 47.24 (d), 31.86 (t), 29.53 (t), 29.28 (t), 27.79 (t), 27.08 (t), 22.70 (t), 14.15 (q).

N'-(Dodecyl)fluorenylmethyl Carbazate (2l)
Yield: 91%; mp 105–106 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, J = 6.8 Hz, 3 H, CH_3), 1.32 (m, 18 H, CH_2), 1.47 (m, 2 H, CH_2), 2.89 (m, 2 H, CH_2), 4.27 (t, J = 6.6 Hz, 1 H, CH), 4.5 (d, J = 6.6 Hz, 2 H, CH_2), 6.60 (s, 1 H, NH), 7.30–7.5 (m, 4 H, ArH), 7.63 (d, J = 7 Hz, 2 H, ArH), 7.8 (d, J = 7 Hz, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.3, 143.8, 141.4, 127.8, 127.1, 125.0, 120.0, 66.9, 52.1, 47.3, 32.0, 29.8, 29.75, 29.7, 29.65, 29.6, 29.4, 27.8, 27.1, 22.8, 14.2.

Reductive Amination; General Procedure
To a stirred solution of substituted fluorenylmethyl carbazate (32 mmol) in CH_2Cl_2–MeOH (80:150 mL), glyoxylic acid monohydrate (1.2 equiv) was added. $NaBH_3CN$ (1.5 equiv) was added fractionally into the above mixture, which was maintained under stirring for 1 h, then the pH was adjusted to pH 1 over 10 min and finally increased to pH 4 with sat. $NaHCO_3$. The mixture was filtered, concentrated, taken into EtOAc (100 mL) and washed with acid water (0.5 M HCl; 2 × 100 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4 and concentrated to give a crude foam, which was triturated in Et_2O to give the crude product (13.7 g). All monomers were purified by chromatography on silica gel (CH_2Cl_2–MeOH, 9:1).

Fmoc-aza-β^3-1-Nal-OH (3a)
Yield: 96%; mp 175–176 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 3.75 (s, 2 H, CH_2), 4.08–4.27 (m, 3 H, CH_2 + CH), 4.52 (d, J = 6.7 Hz, 2 H, CH_2), 7.28–7.74 (m, 8 H, ArH), 7.77 (d, J = 7 Hz, 2 H, ArH), 7.80–7.98 (m, 4 H, ArH), 8.62 (d, J = 7.3 Hz, 1 H, ArH), 8.78 (br, 1 H, NH), 12.58 (br, 1 H, COOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.72, 155.73, 144.20, 141.17, 133.83, 133.57, 132.64, 128.59, 128.34, 128.09, 127.53, 126.35, 126.14, 125.76, 125.68, 125.62, 120.52, 65.96, 57.97, 57.50, 58.60, 47.14.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{28}H_{25}N_2O_4$: 453.18143; found: 453.1806.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{28}H_{24}N_2O_4Na$: 475.16338; found: 475.1637.

Fmoc-aza-β^3-2-Nal-OH (3b)
Yield: 98%; mp 130–132 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 3.69 (s, 2 H, CH_2), 4.05–4.30 (m, 5 H, 2 × CH_2 and CH), 7.18–7.96 (m, 15 H, ArH), 8.73 (br, 1 H, NH), 12.51 (br, 1 H, COOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.1, 155.1, 143.6, 140.6, 135.3, 132.75, 132.35, 127.6, 127.5, 127.4, 127.3, 127.25, 127.0, 125.9, 125.6, 125.2, 120.0, 65.4, 59.5, 57.3, 46.6.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{28}H_{25}N_2O_4Na$: 475.1634; found: 475.1636.

HRMS (ESI): m/z $[M + K]^+$ calcd for $C_{28}H_{24}N_2O_4K$: 491.1373; found: 491.1382.

Fmoc-aza-β^3-4-Bip-OH (3c)
Yield: 93%; mp 144–146 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 3.66 (s, 2 H, CH_2), 4.11–4.25 (m, 5 H, 2 × CH_2 and CH), 7.22–7.96 (m, 17 H, ArH), 8.75 (br, 1 H, NH), 12.51 (br, 1 H, COOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.5, 155.15, 143.7, 140.7, 139.9, 138.9, 136.9, 129.5, 128.8, 127.5, 127.2, 127.0, 126.5, 126.3, 125.2, 120.0, 65.4, 59.1, 57.6, 46.6.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{30}H_{26}N_2O_4Na$: 501.1790; found: 501.1789.

HRMS (ESI): m/z $[M + K]^+$ calcd for $C_{30}H_{26}N_2O_4K$: 517.1530; found: 517.1540.

Fmoc-aza-β^3-Dip-OH (3d)
Yield: 85%; mp 138–140 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.75 (s, 2 H, CH_2), 4.06 (t, J = 7 Hz, 1 H, CH), 4.28 (d, J = 7 Hz, 2 H, CH_2), 5.37 (s, 1 H, CH), 6.72 (br, 1 H, NH), 7.27–7.92 (m, 18 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4, 156.7, 143.4, 141.2, 140.2, 128.95, 127.8, 127.7, 127.15, 125.1, 119.9, 74.3, 67.7, 55.9, 47.0.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{30}H_{26}N_2O_4Na$: 501.1790; found: 501.1800.

HRMS (ESI): m/z $[M + K]^+$ calcd for $C_{30}H_{26}N_2O_4K$: 517.1530; found: 517.1519.

Fmoc-aza-β^3-Cha-OH (3e)
Yield: 92%; translucent oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (m, 2 H, CH_2), 1.11–1.33 (m, 2 H, CH_2), 1.38 (m, 1 H, CH), 1.64 (m, 4 H, CH_2), 1.81 (m, 2 H, CH_2), 2.67 (d, J = 6.1 Hz, 2 H, CH_2), 3.62 (s, 2 H, CH_2), 4.16 (t, J = 6.7 Hz, 1 H, CH), 4.42 (d, J = 6.7 Hz, 2 H, CH_2), 7.17 (s, 1 H, NH), 7.24–7.40 (m, 4 H, ArH), 7.53 (d, J = 7.2 Hz, 2 H, ArH), 7.71 (d, J = 7.2 Hz, 2 H, ArH), 10.45 (br, 1 H, COOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.85, 157.0, 143.6, 141.3, 127.8, 127.1, 125.0, 120.0, 67.1, 64.5, 59.3, 47.1, 35.8, 31.2, 26.5, 25.9.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{24}H_{28}N_2O_4Na$: 431.1947; found: 431.1950.

Fmoc-aza-β^3-4-Fpa-OH (3f)
Yield: 96%; mp 135–136 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.56 (s, 2 H, CH_2), 3.90 (s, 2 H, CH_2), 4.01 (t, J = 6.6 Hz, 1 H, CH), 4.28 (d, J = 6.6 Hz, 2 H, CH_2), 6.74 (s, 1 H, NH), 6.85 (m, 2 H, ArH), 7.02–7.52 (m, 8 H, ArH), 7.63 (d, J = 7 Hz, 2 H, ArH), 8.82 (br, 1 H, COOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 162.5, 156.4, 143.5, 141.35, 133.1, 131.0, 127.9, 127.1, 124.9, 120.1, 115.5, 67.2, 60.2, 56.7, 47.1.

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HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{21}N_2O_4FNa$: 443.1383; found: 443.1378.

HRMS (ESI): *m*/*z* [M + K]$^+$ calcd for $C_{24}H_{21}N_2O_4FK$: 459.1122; found: 459.1126.

Fmoc-aza-β^3-9-Ath-OH (3g)
Yield: 94%; mp 219–220 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 3.71 (s, 2 H, CH_2), 4.07 (t, *J* = 6.8 Hz, 1 H, CH), 4.18 (d, *J* = 6.8 Hz, 2 H, CH_2), 5.05 (m, 2 H, CH_2), 7.23–7.60 (m, 8 H, ArH), 7.80 (d, *J* = 7.3 Hz, 2 H, ArH), 7.83 (d, *J* = 7.3 Hz, 2 H, ArH), 8.05 (d, *J* = 8.5 Hz, 2 H, ArH), 8.57 (br, 1 H, ArH), 8.73 (br, 2 H, ArH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.6, 155.4, 143.6, 140.6, 131.2, 130.9, 128.6, 128.2, 127.7, 127.5, 127.0, 125.9, 125.2, 125.1, 125.0, 120.0, 65.6, 56.2, 51.4, 46.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{32}H_{26}N_2O_4Na$: 525.1790; found: 525.1777.

HRMS (ESI): *m*/*z* [M + 2Na]$^+$ calcd for $C_{28}H_{25}N_2O_4Na_2$: 547.1610; found: 547.1644.

Fmoc-aza-β^3-4-Fluo-1-Nal-OH (3h)
Yield: 96%; mp 190–192 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 3.72 (s, 2 H, CH_2), 4.13 (m, 1 H, CH), 4.22 (br, 2 H, CH_2), 4.44 (br, 2 H, CH_2), 7.14–7.60 (m, 9 H, ArH), 7.84 (d, *J* = 7.2 Hz, 2 H, ArH), 8.04 (d, *J* = 7.2 Hz, 2 H, ArH), 8.62 (d, *J* = 7.8 Hz, 1 H, ArH), 8.71 (br, 1 H, NH), 12.58 (br, 1 H, COOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.2, 159.4, 156.1, 155.2, 143.65, 140.6, 133.4, 129.55 130.0, 127.85, 127.75, 127.55, 127.0, 126.3, 125.5, 125.2, 123.1, 122.9, 120.0, 119.9, 108.8, 108.5, 65.3, 59.7, 57.0, 46.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{23}N_2O_4FNa$: 493.1540; found: 493.1537.

HRMS (ESI): *m*/*z* [M + K]$^+$ calcd for $C_{28}H_{23}N_2O_4FK$: 509.1279; found: 509.1270.

Fmoc-aza-β^3-3-Pal-OH (3i)
Yield: 85%; white foam.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.75 (s, 2 H, CH_2), 4.11 (s, 2 H, CH_2), 4.21 (t, *J* = 6.4 Hz, 1 H, CH), 4.35 (d, *J* = 6.4 Hz, 2 H, CH_2), 7.27–7.81 (m, 10 H, ArH), 8.42 (d, *J* = 4.2 Hz, 1 H, ArH), 8.65 (s, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 155.9, 147.5, 146.1, 143.7, 141.3, 139.6, 134.4, 127.8, 127.1, 125.0, 124.4, 120.0, 66.9, 57.7, 57.2, 47.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{21}N_3O_4Na$: 426.1430; found: 426.1448.

Fmoc-aza-β^3-4-Pal-OH (3j)
Yield: 86%; white foam.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.67 (s, 2 H, CH_2), 4.05 (s, 2 H, CH_2), 4.16 (t, *J* = 6.6 Hz, 1 H, CH), 4.31 (d, *J* = 6.6 Hz, 2 H, CH_2), 7.20–7.80 (m, 10 H, ArH), 8.45 (d, *J* = 6.3 Hz, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 156.2, 150.2, 146.6, 143.6, 141.4, 127.8, 127.1, 124.9, 124.6, 120.0, 66.8, 59.6, 57.4, 47.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{22}N_3O_4$: 404.1610; found: 404.1609.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{21}N_3O_4Na$: 426.1430; found: 426.1432.

HRMS (ESI): *m*/*z* [M + K]$^+$ calcd for $C_{23}H_{21}N_3O_4K$: 442.1170; found: 442.1194.

Fmoc-aza-β^3-Oct-OH (3k)
Yield: 92%; mp 102 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78 (t, *J* = 6 Hz, 3 H, CH_3), 1.16 (m, 10 H, CH_2), 1.35 (m, 2 H, CH_2), 2.74 (t, *J* = 7 Hz, 2 H, CH_2), 3.54 (s, 2 H, CH_2), 4.10 (t, *J* = 6.7 Hz, 1 H, CH), 4.40 (d, *J* = 6.7 Hz, 2 H, CH_2), 6.54 (br, 1 H, NH), 7.16–7.36 (m, 4 H, ArH), 7.47 (d, *J* = 7.1 Hz, 2 H, ArH), 7.66 (d, *J* = 7.1 Hz, 2 H, ArH), 8.78 (br, 1 H, COOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 156.9, 143.5, 141.3, 127.8, 127.1, 125.0, 120.0, 67.2, 58.8, 57.7, 47.2, 31.8, 29.4, 29.2, 27.1, 26.9, 22.6, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{32}N_2O_4Na$: 447.2260; found: 447.2274.

HRMS (ESI): *m*/*z* [M + K]$^+$ calcd for $C_{25}H_{32}N_2O_4K$: 463.1999; found: 463.2013.

Fmoc-aza-β^3-Dod-OH (3l)
Yield: 95%; mp 100 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 6.3 Hz, 3 H, CH_3), 1.28 (m, 18 H, CH_2), 1.48 (m, 2 H, CH_2), 2.88 (t, *J* = 7 Hz, 2 H, CH_2), 3.68 (s, 2 H, CH_2), 4.22 (t, *J* = 6.6 Hz, 1 H, CH), 4.51 (d, *J* = 6.6 Hz, 2 H, CH_2), 6.83 (s, 1 H, NH), 7.30–7.45 (m, 4 H, ArH), 7.59 (d, *J* = 7.2 Hz, 2 H, ArH), 7.77 (d, *J* = 7.2 Hz, 2 H, ArH), 11.19 (s, 1 H, COOH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 156.9, 143.6, 141.4, 127.85, 127.1, 125.0, 120.1, 67.2, 58.6, 57.5, 47.2, 32.0, 29.7, 29.7, 29.7, 29.65, 29.5, 29.4, 26.9, 22.8, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{29}H_{40}N_2O_4Na$: 503.2886; found: 503.2873.

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