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N-Substituted Glycines with Functional Side-Chains for Peptoid Synthesis

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N-Substituted glycines (NSG) constitute mimics of natural amino acids, and bring stability to peptide analogues. We developed a method to synthesize NSG bearing reactive secondary heterofunctionality. It was shown that persilylation could be used for temporary protection of reactive groups present on the substrate, with the aim of selectively alkylating the amine groups. NSG ready for peptide coupling were obtained by *C*-terminal deprotection and *N*-terminal protection of the resulting amino acid derivatives. This method was applied to prepare *N*-alkylated glycines as analogues of serine, cysteine, tyrosine and tryptophan. The last two derivatives were obtained in good yields and *N*-homotyrosine (*N*-hTyr) has been introduced into a peptide sequence of interest using automated solid-phase peptide synthesis (SPPS).

Introduction

Peptides are known for their efficiency as therapeutic drugs. However, their poor bioavailability and metabolic instability are still significantly problematic for their use as drugs. *N*-Substituted glycine oligomers, named peptoids, constitute an alternative to avoid these drawbacks.[1] In addition, as it has been recently reviewed,[2] incorporating various side chains on different amines offers the possibility of having in hand a large variety of *N*-substituted glycines (NSG). The resulting peptoids might maintain affinity towards targeted receptors while not being recognized by proteases. The NSG have already proved their biological interest when incorporated into peptide sequences.[3] They were successfully combined with glucosaminides to form glycopeptoids,[4] and were introduced into macrocycles, forming cyclic functionalized peptoids, which constitute promising templates for multimeric ligation of biologically active ligands.[5] Recently, linear oligomeric *N*-substituted aminomethyl-benzamides have been cyclized to form novel macrocycles enabling the determination of the first X-ray structures of arylopeptoid constructs.[6]

In addition, incorporation of *N*-substituted glycines enables translocation mutagenesis.[7] Other applications include drug candidates,[8] peptide mimics for studies of secondary structure,[9] catalysts,[10] sensors[11] and nanostructured materials.[12] They can also constitute starting materials for incorporating post-modifications on amino acid side chains into proteins.[13]

Peptoids can be synthesized according to different approaches. One of the first known methods consists of the reductive amination between an amine with glyoxylic acid.[1] In this case, Fmoc-*N*-alkylglycines have been synthesized with protected amino acid side chains.[14] The synthesis of oligomeric NSG was performed on solid support and named the submonomer solid-phase synthesis method.[15] A new approach to the synthesis of peptoids was described via photolithographic techniques,[16] and has already proved to be an interesting application for antibody replacements.[17] Oligomers of *N*-substituted glycines can also be obtained using microwave-assisted synthesis, especially for incorporation of electronically deactivated benzylic amines.[18] Apart from oligomeric NSG, some examples of bioactive peptide-peptoid hybrids have been reported as ligands of the SH2 domain involved in signal transduction,[19] or as membrane interactive agents.[20]

Peptoids can be designated according to different nomenclatures. For example, for the amine building block corresponding to tyrosine, some use the IUPAC nomenclature, *N*-[2-(*p*-hydroxyphenyl)methyl]glycine, whereas others apply the three letters codes related to amino acid abbreviations, for example, *N*-Tyr.[21]

Here we describe an efficient synthesis of *N*-substituted glycine analogues of a selection of functionalized natural amino acids like tyrosine, tryptophan, cysteine and serine. NSG that we prepared are the homologues of natural amino acids. Therefore, the nomenclature of these derivatives is *N*-hTyr, *N*-hTrp, *N*-hCys, *N*-hSer.[1]

To illustrate their utility in structure–activity relationships, *N*-hTyr has been introduced into a peptide sequence of interest, the neurotensin fragment called NT(8–13).

Results and Discussion

We have developed an alternative route to synthesize *N*-substituted glycines with functionalized side chains bearing heteroatoms. First, we focused on the synthesis of the NSG

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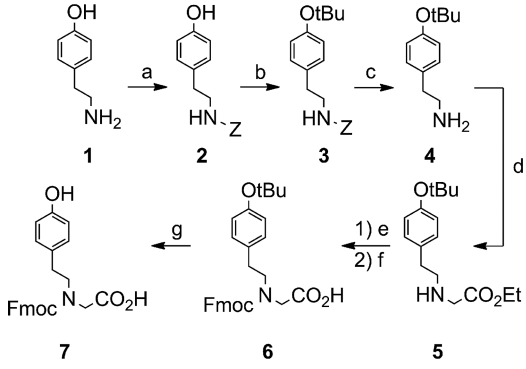
resembling a tyrosine homologue, called *N*-homotyrosine, which synthesis has been described in seven steps with 26% overall yield (Scheme 1).[22] To protect the side-chain functionality, this synthetic pathway involved a *tert*-butylation step using isobutene,[23] which often proceeds in low yield.[14,24]



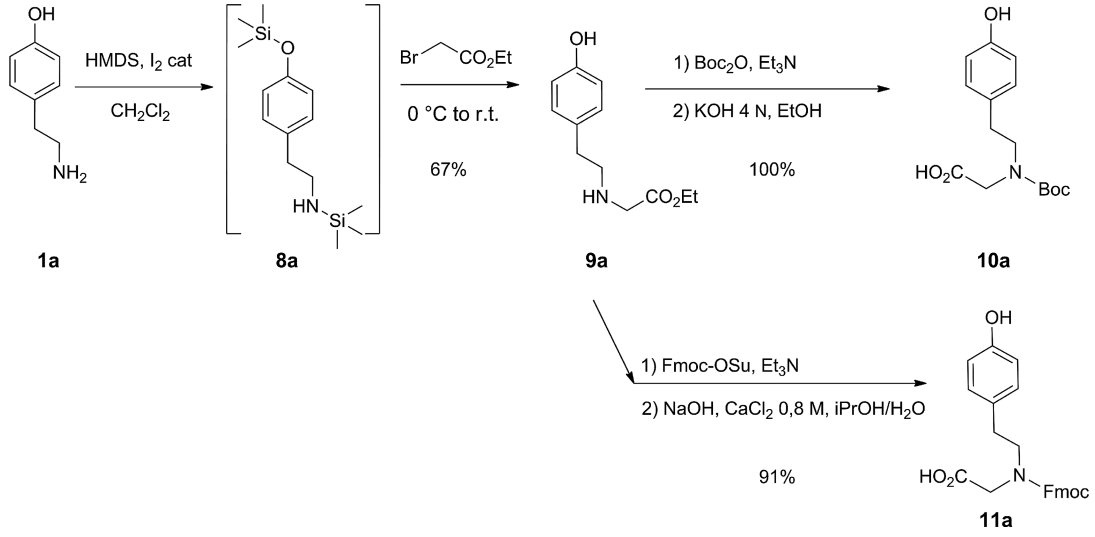
Scheme 1. Synthesis of Fmoc-*N*-hTyr described by Einsiedel.;[22] a: *N*-(benzyloxycarbonyloxy)succinimide, THF, 0 °C, for 1 h, then 25 °C for 3 h (96%); b: isobutylene, cat. conc. H_2SO_4, CH_2Cl_2/THF (4:1), –20 to 25 °C for 18 h (53%); c: H_2 (49 psi),10% Pd/C (100%); d: ethylbromoacetate, NEt_3, THF, 0 °C to room temp. then r.t. for 2 h (79%); e: NaOH, MeOH, room temp., 30 min; f: Fmoc-OSu, H_2O/dioxane, pH 8.5–9.0, 0 °C to room temp. room temp., 5 h (66%); g: TFA, room temp., 1 h.

An alternative method using a Lewis acid and di-*tert*-butyl dicarbonate was investigated to perform this tricky step.[25] Indeed, when magnesium perchlorate was used under refluxing dichloromethane, decarboxylation occurred and generated the *tert*-butylated phenolic ether.[26] Nevertheless, although yields were improved, the number of steps remained the same.

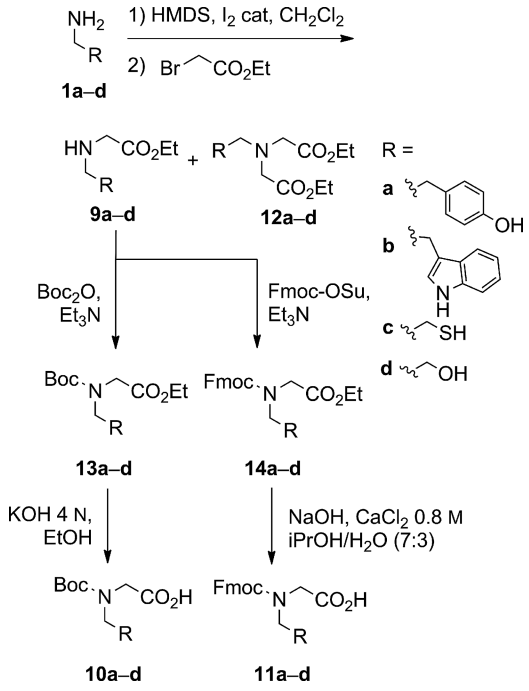
We thought that a shorter synthesis could be achieved using persilylation as a temporary protection, which is usually performed under acidic conditions with hexamethyldisilazane at high temperature together with trimethylsilyl chloride and triethylamine.[27] Thus, an efficient method of silylation under mild conditions catalyzed by iodine retained our attention.[28] We chose these persilylation conditions before performing alkylation with ethylbromoacetate at 0 °C directly on the silylated amine. Then, protection of the α-amino group with Boc and Fmoc groups and final ester hydrolysis gave access to building blocks ready for peptoid synthesis.

The persilylation reaction was performed on tyramine **1**, which was dissolved in dichloromethane in the presence of iodine, followed by slow addition of hexamethyldisilazane in dichloromethane.[28] One of the proposed hypotheses concerning the catalytic mechanism was that iodine could polarize the Si–N bond in HMDS to produce the reactive silylating agent $(Me_3Si)_2$-NH^+-I (I^- counter-anion). The reaction mixture was basic enough for the amine and hydroxy groups to react. However, addition of triethylamine, which traps HBr, allowed the intermediate **8a** to be observed by LC-MS monitoring. Usually, alkylation was performed one pot at 0 °C without additional base. The reaction was quenched after HPLC monitoring to minimize formation of the double alkylated product **12a**. The optimized mono **9a**/dialkylated **12a** amines ratio was improved to 95:5. The temporary silyl-protection on the hydroxy function was removed during the workup, and **9a** was isolated in 67% yield. The usual *N*-protection followed by saponification afforded the desired *N*-protected *N*-substituted glycines. Boc derivatives are generally used both in solution peptide synthesis and solid phase peptide synthesis (SPPS), and Fmoc derivatives are dedicated to SPPS. In the case of Fmoc derivative saponification, a solution of $CaCl_2$ [0.8 M in *i*PrOH/H_2O (7:3)] was used to allow both ester deprotection and preservation of the Fmoc protecting group.[29] Fmoc-*N*-homotyrosine **11a** was obtained in three steps in 61% overall yield (Scheme 2).

This strategy was extended to other amino acid analogues, like *N*-homotryptophan, *N*-homocysteine and *N*-homoserine (Scheme 3).



Scheme 2. Synthesis of Boc-*N*-hTyr **10a** and Fmoc-*N*-hTyr.**11a**.



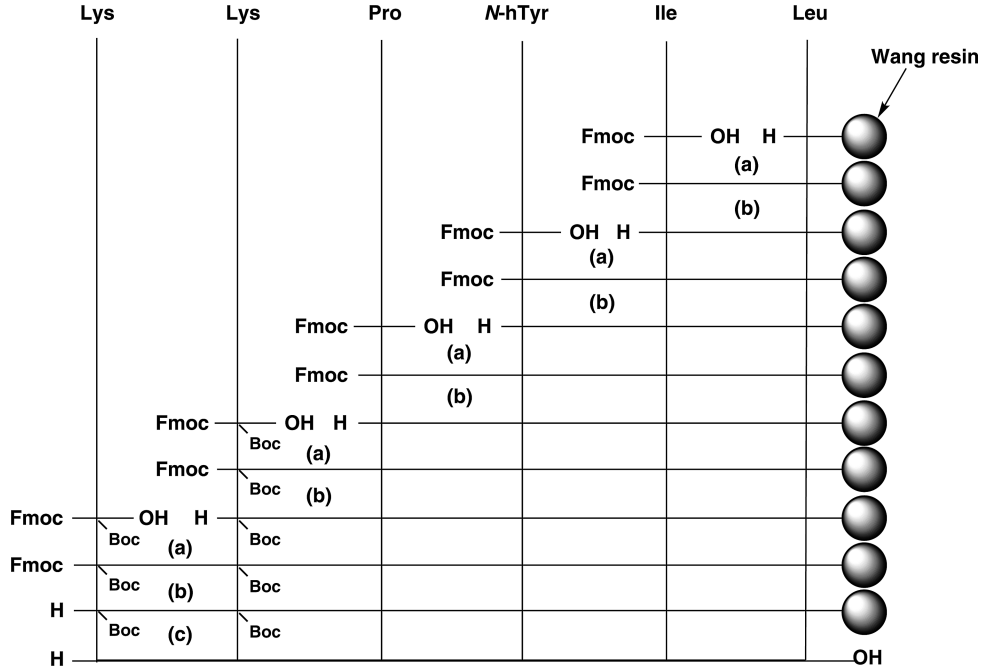
Scheme 3. Extension of the synthetic strategy.

The one pot persilylation/alkylation step was studied to evaluate the reaction yield for each side chain. *N*-homotyrosine **9a** and *N*-homotryptophan **9b** were isolated in 67% and 53% yield respectively. However, *N*-homocysteine **9c** and *N*-homoserine **9d** could not be clearly separated from their corresponding dialkylated products **12c–d** by chromatography. *N*-Protection of the crude mixtures allowed a better separation of *N*-protected amino esters (**13c–d** and **14c–d**) from dialkylated derivatives **12c–d**. Finally, compounds **10c–d** and **11c–d** were isolated in 7 to 26% overall yield (Table 1). These results could be explained by the low steric hindrance of the side chains that did not limit formation of di-alkylated product in addition to a high nucleophilic character of the side chain functional group.

Table 1. Overall yields per side chain.

Entry	Side-chain	**10**	**11**
1	**a**	67	61
2	**b**	52	44
3	**c**	26	18
4	**d**	7	8

We were then interested in the synthesis of modified peptides containing these NSG building blocks to exemplify their utility in structure–activity relationships. We chose the neurotensin fragment NT(8–13) that we are studying in another program.[30] It has been previously shown that replacement of tyrosine in a closely related sequence of NT(8–13) (JMV 438) by *N*-homotyrosine led to a highly NTS2-selective ligand.[22] After obtaining the *N*-substituted glycine **9a** as presented in Scheme 2, we used the Fmoc derivative **11a** in a SPPS strategy using a Liberty CEM™ microwave peptide synthesizer without any special conditions for peptoid building block coupling (Scheme 4). We obtained the desired pseudo-hexapeptide JMV 4961.



Scheme 4. Solid phase peptide synthesis of JMV 4961 using Fmoc-*N*-hTyr; (a) HBTU, DIEA, DMF; (b) piperidine 20%/DMF; (c) TFA, TIS, CH_2Cl_2.

Conclusions

We developed a rapid route to access *N*-substituted glycines in three steps in satisfactory yields depending on the nature of aliphatic or aromatic side chains. These *N*-protected building blocks in can be directly used in SPPS, in particular in the synthesis of peptide–peptoid hybrids.

Experimental Section

General: All reactions involving air-sensitive reagents were performed under nitrogen or argon. Purifications were performed with column chromatography using silica gel (Merck 60, 230–400 mesh) or with a Biotage instrument Isolera 4 using SNAP KP-SIL flash cartridges. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C-NMR) spectra were recorded with a Bruker Avance 200 spectrometer at 200 and 50 MHz, a Bruker Avance 300 spectrometer at 300 and 75 MHz or a Bruker 600 spectrometer at 600 and 150 MHz, respectively. All chemical shifts were recorded relative to internal tetramethylsilane when $CDCl_3$ was used as solvent. Low-resolution electrospray ionization (ESI) mass spectra were recorded with a Micromass platform electrospray mass spectrometer. Spectra were recorded in the positive mode (ESI^+). HPLC chromatography was performed using a Waters 2796 HPLC instrument equipped with a Phenomenex® Onyx Monolithic HD-C18 column (50 μm × 4.6 mm).

Alkylation Procedure for Homotyramine and Homotryptamine: To a stirred suspension of the amine (1 equiv.) and I_2 (0.01 equiv.) in CH_2Cl_2 (0.25 M) was added diluted HMDS (2 equiv.) in CH_2Cl_2 (0.8 M) dropwise within 5 min. The mixture became gradually homogeneous. After stirring at room temp. for 2 h and basic pH was verified , the reaction mixture was cooled to 0 °C and ethylbromoacetate (1 equiv.) was added dropwise. After stirring for 1.5 h at room temp., the reaction mixture was washed with a 10% citric acid solution. The pH of the aqueous layer was increased with potassium carbonate to a value of 8–9. Then, the monoalkylated amine was extracted with ethyl acetate. The organic layer was dried with $MgSO_4$ and then concentrated.

Compound 9a:.[31] Yield 67% ESI-MS: *m*/*z* = 224.1 $[M + H]^+$. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.24 (t, *J* = 9 Hz, 3 H, CH_2CH_3), 2.74 (d, *J* = 6 Hz, 2 H, CH_2Ph), 2.84 (d, *J* = 6 Hz, 2 H, CH_2NH), 3.39 (s, 3 H, CH_2CO_2), 4.15 (q, *J* = 9 Hz, 2 H, CH_2CH_3), 6.72 (d, *J* = 9 Hz, 2 H, C*H ortho*), 7.02 (d, *J* = 9 Hz, 2 H, C*H meta*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 14.2 (CH_2CH_3), 35.4 (CH_2CH_2NH), 50.8 (CH_2CH_2NH), 50.9 (CH_2CO_2), 60.9 (CH_2CH_3), 115.4 (C_m), 129.8 (C_o), 131.3 ($NHCH_2CH_2C$), 154.3 (C_p), 172.3 (CO2) ppm.

Compound 9b: Yield 53% ESI-MS: *m*/*z* = $[M + H]^+$ = 247.3 ^{1}H NMR ($CDCl_3$, 600 MHz, 0 °C): δ = 1.27 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 2.98–3.05 (m, 4 H, CH_2CH_2NH), 3.47 (s, 2 H, CH_2CO_2), 4.19 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 7.12 (d, *J* = 1.9 Hz, 1 H, C*H para*), 7.15–7.17 (m, 1 H, C*H meta*), 7.23–7.25 (m, 1 H, C*H ortho*), 7.40–7.42 (m, 1 H, C*H meta*′), 7.65–7.67 (m, 1 H, C*H*NH indole), 8.23 (br. s, 1 H, indole) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz, 25 °C): δ = 13.9 (CH_2CH_3), 25.6 (CH_2CH_2NH), 49.3 (CH_2CH_2NH), 50.8 (CH_2CO_2), 60.5 (CH_2CH_3), 110.91 ($C_{m'}$), 113.5 (*C*CHNH), 118.6 (C_o), 118.8 (C_m), 121.7 (C_p), 121.8 (C_o), 127.2 ($NHCH_2CH_2CC$), 136.1 (NH*C* indole), 172.2 (CO_2) ppm.

Alkylation Procedure for Homocysteamine and Homoethanolamine: To a stirred suspension of the amine hydrochloride (1 equiv.) in CH_2Cl_2 (0.25 M) was added triethylamine (1 equiv.). After 30 min, I_2 (0.01 equiv.) was added, followed by HMDS (2 equiv.) in CH_2Cl_2 (0.8 M) dropwise within 5 min. The mixture became gradually colourless. After 2 h stirring at room temp., the pH was checked and verified to be basic. The reaction mixture was cooled to 0 °C and ethyl bromoacetate (1 equiv.) was added dropwise. After 30 min stirring at room temp., the reaction mixture was washed with water. The organic layer, which contained the dialkylated product **13c**–**d** and the desired product **9c**–**d**, was dried with $MgSO_4$ and then concentrated. This crude product was directly engaged in the amine protection reaction.

Amine Group Protection for Homoalkylamines

***N*-Boc-Protection Procedure:** To a solution of monoalkylated amine **9** (1 equiv.) in THF (0.2 M) was added di-*tert*-butyl dicarbonate (1.2 equiv.) and triethylamine (1 equiv.). The reaction mixture was stirred overnight at room temp. After removing THF in vacuo, the crude product was dissolved in ethyl acetate. This organic layer was washed with a solution of potassium hydrogen sulfate (× 3) and a saturated solution of sodium hydrogen carbonate (× 3). Then, the organic layer was dried with $MgSO_4$ and concentrated.

Compound 13a: Yield 100%. ESI-MS: *m*/*z* = 324.4 $[M + H]^+$. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.30 (t, *J* = 6.9 Hz, 3 H, CH_2CH_3), 1.50 (s, 9 H, *t*Bu), 2.70–2.90 (m, 2 H, CH_2CH_2N), 3.40–3.50 (m, 2 H, CH_2CH_2N), 3.75 and 3.77 (2s, 2 H, CH_2CO_2), 4.20–4.30 (q, *J* = 6.9 Hz, 2 H, CH_2CH_3), 5.1 (br., 1 H, O*H*), 6.60–6.75 (m, 2 H, C*H meta*), 7.00–7.15 (m, 2 H, C*H ortho*) ppm.

Compound 13b: Yield 100%. ESI-MS: *m*/*z* = 347.4 $[M + H]^+$. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.24 (t, *J* = 6 Hz, 3 H, CH_2CH_3), 1.51 (s, 9 H, Boc), 2.95–3.03 (m, 2 H, CH_2CH_2N), 3.50–3.56 (m, 2 H, CH_2CH_2N), 3.76 and 3.89 (2s, rotamers, CH_2CO_2), 4.09–4.18 (q, *J* = 12 Hz, 2 H, CH_2CH_3), 6.98–7.02 (m, 1 H, C*H para*), 7.07–7.20 (m, 2 H, C*H ortho*, *meta*′), 7.33–7.36 (m, 1 H, C*H meta*), 7.57–7.62 (m, 1 H, C*H*NH indole), 7.99 (br. s, 1 H, indole) ppm.

Compound 13c: Purification by silica flash chromatography using cyclohexane/EtOAc 8:2 as the eluent. Yield 27% (2 steps) ESI-MS: *m*/*z* = 264.3 $[M + H]^+$. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.26 (t, *J* = 6 Hz, 3 H, CH_2CH_3), 1.41 (s, 9 H, Boc), 2.74 (t, *J* = 7.5 Hz, 2 H, CH_2CH_2N), 3.2 (s, 1 H, S*H*), 3.29–3.38 (m, 2 H, CH_2CH_2N), 3.20 (s, 2 H, CH_2CO_2), 4.16 (q, *J* = 6 Hz, 2 H, CH_2CH_3) ppm.

Compound 13d: Purification by silica flash chromatography, using cyclohexane/EtOAc 8:2 as the eluent. Yield 14% (2 steps). ESI-MS: *m*/*z* = 248.3 $[M + H]^+$, 270.3 [M + Na]. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.23–1.27 (m, 3 H, CH_2CH_3), 1.42 (d, *J* = 15 Hz, 9 H, Boc), 3.40–3.44 (m, 2 H, CH_2CH_2N), 3.62–3.78 (m, 2 H, CH_2CH_2N), 3.83 and 3.99 (2s, rotamers, 2 H, CH_2CO_2), 4.19 (q, *J* = 6 Hz, 2 H, CH_2CH_3) ppm.

***N*-Fmoc Protection Procedure:** To a solution of monoalkylated amine **9** (1 equiv.) in THF (0.2 M) was added *N*-(9-fluorenylmethoxycarbonyloxy)succinimide (1.3 equiv.) and triethylamine (1 equiv.). The reaction mixture was stirred for 5 h at room temp. After removing THF in vacuo, the residue was dissolved in ethyl acetate. This organic layer was washed with a solution of potassium hydrogen sulfate (× 3) and a saturated solution of sodium hydrogen carbonate (× 3). Then, the organic layer was dried with $MgSO_4$ and concentrated. The crude product was purified by silica flash chromatography using cyclohexane/ethyl acetate 8:2 as the eluent.

Compound 14a: Yield 91%. ESI-MS: *m*/*z* = 446.5 [M + H]$^+$. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.22 (t, *J* = 9 Hz, 3 H, CH_2CH_3), 2.63 (m, 2 H, CH_2CH_2N), 3.39 (m, 2 H, CH_2CH_2N),

3.76 and 3.80 (2s, rotamers, 2 H, CH_2CO_2), 4.08–4.15 (m, 2 H, CH_2CH_3), 4.42 (d, J = 6 Hz, 1 H, CH_2, Fmoc), 4.55 (d, J = 6 Hz, 1 H, CH, Fmoc), 5.35 (d, J = 12 Hz, 1 H, CH, Fmoc), 6.7–7.75 (m, 12 H, CH, aromatic) ppm.

Compound 14b: Yield 83%. ESI-MS: m/z = 469.5 $[M + H]^+$. ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.17 (t, J = 6 Hz, 3 H, CH_2CH_3), 2.89 (m, 2 H, CH_2CH_2N), 3.56 (m, 2 H, CH_2CH_2N), 3.79 and 3.84 (2s, rotamers, 2 H, CH_2CO_2), 4.03–4.13 (m, 3 H, CH_2CH_3, CH Fmoc), 4.42 (t, J = 9 Hz, 2 H, CH_2, Fmoc), 6.79–7.52 (m, 12 H, CH aromatic), 8.06 (br. s, 1 H, CHNH indole) ppm.

Compound 14c: Purification by silica flash chromatography, using cyclohexane/EtOAc 8:2 as the eluent. Yield 18%. ESI-MS: m/z = 386.5 $[M + H]^+$. ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.27 (t, J = 9 Hz, 3 H, CH_2CH_3), 2.71–2.83 (m, 2 H, CH_2CH_2N), 3.22 (s, 2 H, CH_2CO_2), 3.36–3.5 (m, 2 H, CH_2CH_2N), 4.14–4.25 (m, 3 H, CH_2CH_3 and CH Fmoc), 4.30–4.33 (d, J = 9 Hz, 1 H, CH_2 Fmoc), 5.29 (br. s, 1 H, NH), 7.27–7.76 (CH_{aro}) ppm.

Compound 14d: Yield 22%. ESI-MS: m/z = 370.4 $[M + H]^+$. ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.17–1.29 (m, 3 H, CH_2CH_3), 3.20 (m, 2 H, CH_2CH_2N), 3.48–3.60 (m, 2 H, CH_2CH_2N, SH), 3.88–3.92 (m, 2 H, CH_2CH_2N), 3.92 and 3.98 (2s, rotamers, 2 H, CH_2CO_2), 4.10–4.27 (m, 3 H, CH_2CH_3 and CH Fmoc), 4.43–4.49 (m, J = 18 Hz, 2 H, CH_2 Fmoc), 7.29–7.75 (CH aromatic) ppm.

Ester Saponification Procedure of Boc Derivatives 13

To a stirred solution of Boc ester derivative **13** (1 equiv.) in EtOH (0.2 M) was added a solution of KOH (4 N , 3 equiv.). The mixture was stirred at room temp. for 1.5 h. After HPLC monitoring, EtOH was removed in vacuo. The crude product was diluted in water, and the aqueous layer pH was decreased to 2–3 using solid citric acid. Then, this acidic aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with a saturated solution of sodium chloride , dried with $MgSO_4$ and concentrated.

Compound 10a: Yield 100%. ESI-MS: m/z = 296.3 $[M + H]^+$. ^1H NMR ([D$_6$]DMSO, 600 MHz, 25 °C): δ = 1.34 (s, 9 H, Boc), 2.61–2.65 (m, 2 H, CH_2CH_2N), 3.29–3.31 (m, 2 H, CH_2CH_2N), 3.75 and 3.77 (2s, rotamers, J = 13.3 Hz, 2 H, CH_2CO_2), 6.66–6.68 (m, 2 H, CH *meta*), 6.95–6.99 (m, 2 H, CH *ortho*) ppm. ^{13}C NMR ([D$_6$]DMSO, 150 MHz, 25 °C): δ = 27.9 (CH_3, *t*Bu), 33.4 (CH_2CH_2NH), 48.4 (CH_2CH_2N), 49.7 (CH_2CO_2), 78.7 [$C(CH_3)_3$], 115.1 (C_m), 129.2 (NCH_2CH_2C), 129.6 (C_o), 154.8 (CO_2, Boc), 155.6 (COH), 171.4 (CO_2H) ppm.

Compound 10b: Yield 100%. ESI-MS: m/z = 319.4 $[M + H]^+$. ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.35 (s, 9 H, Boc), 2.94–2.99 (m, 2 H, CH_2CH_2N), 3.54–3.59 (m, 2 H, CH_2CH_2N), 3.79 and 4.08 (2s, rotamers, 2 H, CH_2CO_2), 7–7.6 (m, 5 H, aromatic), 8.26 (br. s, 1 H, NH, indole) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.4 (CH_2CH_2N), 24.5 (CH_2CH_2N), 28.6 (CH_3, *t*Bu), 49.8 (CH_2CO_2), 81.2 [$C(CH_3)_3$], 111.7 (C Ar), 112.9 (C Ar), 118.9 (C Ar), 120.1 (C Ar), 122.3 (C Ar), 123.5 (C Ar), 127.7 (C cycle junction), 136.7 (C cycle junction), 156.8 (CO_2*t*Bu), 175.2 (CO_2 H) ppm.

Compound 10c: Yield 100%. ESI-MS: m/z = 236.3 $[M + H]^+$. ^1H NMR ([D$_6$]DMSO, 200 MHz, 25 °C): δ = 1.38 (s, 9 H, Boc), 2.57–2.64 (m, 2 H, CH_2CH_2N), 3.06–3.16 (m, 2 H, CH_2CH_2N), 3.23–3.25 (m, 2 H, CH_2CO_2), 12.5 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ = 28.2 (CH_3, *t*Bu), 31.5 (CH_2CH_2N), 32.9 (CH_2CH_2N), 77.7 (CH_2CO_2), 99.5 [$C(CH_3)_3$], 155.5 (CO_2 Boc), 171.5 (CO_2H) ppm.

Compound 10d: Yield 100%. ESI-MS: m/z = 220.2 $[M + H]^+$. ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 1.44–1.47 (2s, rotamers, 9 H, Boc), 3.40–3.45 (m, 2 H, CH_2CH_2N), 3.70–3.75 (m, 2 H, CH_2CH_2N), 3.94 and 3.99 (2s, rotamers, 2 H, CH_2CO_2) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 28.4 (CH_3, *t*Bu), 53.1 (CH_2CH_2N), 54.2 (CH_2CO_2), 58.5 (CH_2OH), 81.2 (C *t*Bu), 152.4 (CO_2, Boc), 178.4 (CO_2H) ppm.

Ester Deprotection Procedure of Fmoc Derivatives 14: Fmoc ester derivative **14** (1 equiv.) was dissolved in a $CaCl_2$ solution (0.8 M) prepared in *i*PrOH/H_2O (7:3). Solid sodium hydroxide (1.5 equiv.) was added, and the mixture was stirred at room temp. overnight. After HPLC monitoring, the solvent was removed in vacuo. The crude product was diluted in water, and the pH of the aqueous layer pH was decreased to 2–3 using solid citric acid. This acidic aqueous layer was extracted with ethyl acetate. The combined organic phases were washed with saturated a solution of sodium chloride , dried with $MgSO_4$ and concentrated.

Compound 11a: Yield 100%. ESI-MS: m/z = 418.5 = $[M + H]^+$. ^1H NMR ([D$_6$]DMSO, 300 MHz, 25 °C): δ = 2.29–2.33 (m, 1 H, CH_2CH_2N), 2.63–2.68 (m, 1 H, CH_2CH_2N), 3.04–3.09 (m, 1 H, CH_2CH_2N), 3.35–3.40 (m, 1 H, CH_2CH_2N), 3.76 and 3.88 (2s, rotamers, 2 H, CH_2CO_2), 4.16–4.23 (m, 2 H, CH_2 Fmoc), 4.50 (d, J = 6 Hz, 1 H, $CHCH_2$ Fmoc), 6.62–6.74 (m, 4 H, CH tyramine), 6.98–7.90 (m, 8 H, CH Fmoc) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz, 25 °C): δ = 33.5 (CH_2CH_2N), 47.1 (CH Fmoc), 49.2 (CH_2CH_2N), 50.1 (CH_2CO_2), 66.4 (CH_2 Fmoc), 115.3 (C *m* tyramine), 120.41 (C Fmoc), 124.9 (C Fmoc), 127.4 (C Fmoc), 129.3 (C *o* tyramine), 140.9 (C Fmoc), 141.2 (C Fmoc), 144.2 (C Fmoc), 155.5 (NCH_2CH_2C), 155.9 (CO_2 Fmoc), 171.3 (CO_2H) ppm.

Compound 11b: Yield 100%. ESI-MS: m/z = 441.5 $[M + H]^+$. ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 2.78–2.82 (m, 1 H, CH_2CH_2N), 2.96–3.01 (m, 1 H, CH_2CH_2N), 3.48–3.56 (m, 2 H, CH_2CH_2N), 3.75 and 3.85 (2s, rotamers, 2 H, CH_2CO_2), 4.1–4.25 (m, 1 H, $CHCH_2$ Fmoc), 4.46–4.48 (m, 2 H, CH_2 Fmoc), 7.02–7.69 (m, 14 H, CH Fmoc), 8.01 (br. d, 1 H, NH indole) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 25.0 (CH_2CH_2N), 47.9 (CH Fmoc), 49.9 (CH_2CH_2N), 68.3 (CH_2CO_2), 111.9 (CH_2 Fmoc), 113.2 (C Fmoc), 119.0 (C Fmoc), 120.2 (C Fmoc), 122.7 (C Fmoc), 127.8 (C Fmoc), 136.9 (C Fmoc), 141.9 (C Fmoc), 144.5 (C Fmoc), 157.5 (CO_2 Fmoc), 175.0 (CO_2H) ppm.

Compound 11c: Yield 100%. ESI-MS: m/z = 358.4 $[M + H]^+$, 380.4 [M + Na]. ^1H NMR ([D$_6$]DMSO, 600 MHz, 25 °C): δ = 2.64–2.66 (m, 1 H, NCH_2CH_2SH), 3.19–3.21 (m, 2 H, NCH_2CH_2SH), 3.35 (s, 2 H, CH_2CO_2), 4.2–4.22 (m, 1 H, $CHCH_2$ Fmoc), 4.30–4.31 (m, 2 H, $CHCH_2$ Fmoc), 6.91–7.94 (m, 9 H, CH Fmoc) ppm. ^{13}C NMR ([D$_6$]DMSO, 150 MHz, 25 °C): δ = 31.4 (NCH_2CH_2SH), 32.9 (CH Fmoc), 46.7 (NCH_2CH_2SH), 65.3 (CH_2 Fmoc), 120.1 (C Fmoc), 125.1 (C Fmoc), 127.1 (C Fmoc), 127.6 (C Fmoc), 140.7 (C Fmoc), 143.9 (C Fmoc), 156.1 (CO_2 Fmoc), 171.5 (CO_2 H) ppm.

Compound 11d: Yield 100%. ESI-MS: m/z = 342.4 $[M + H]^+$, 364.4 [M + Na]. ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 3.24–3.50 (m, 2 H, CH_2CO_2), 3.36–3.39 (m, 2 H, NCH_2CH_2OH), 3.50–3.55 (m, 2 H, NCH_2CH_2OH), 4.12–4.20 (m, 1 H, $CHCH_2$ Fmoc), 4.43–4.49 (m, 2 H, $CHCH_2$ Fmoc), 7.29–7.76 (m, 9 H, CH Fmoc) ppm. ^{13}C NMR ([D$_6$]DMSO, 150 MHz, 25 °C): δ = 48.7 (CH Fmoc), 51.2 (NCH_2CH_2OH), 56.4 (NCH_2CH_2OH), 66.7 (CH_2 Fmoc), 120.1 (C Fmoc), 126.3 (C Fmoc), 127.6 (C Fmoc), 128.3 (C Fmoc), 141.7 (C Fmoc), 143.6 (C Fmoc), 158.6 (CO_2 Fmoc), 173.5 (CO_2 H) ppm.

Supporting Information (see footnote on the first page of this article): ^1H NMR and ^{13}C NMR spectra of compounds, HPLC and HR-MS of peptides.

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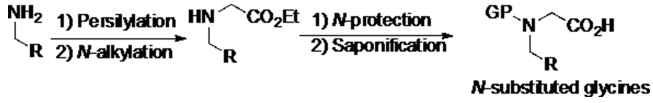

N-Substituted glycines (NSG) constitute mimics of natural amino acids that are used in peptoid synthesis. We developed a method to synthesize NSG bearing reactive secondary heterofunctionality. Persilylation was used as temporary protection, and analogues of serine, cysteine, tyrosine and tryptophan were prepared. *N*-Homotyrosine (*N*-hTyr) has been introduced into a peptide sequence of interest.

