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New Submonomers for Poly *N*-Substituted Glycines (Peptoids)

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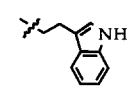
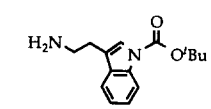
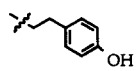
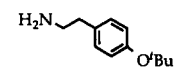
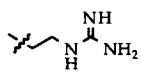
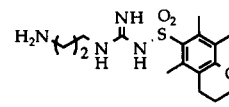
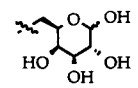
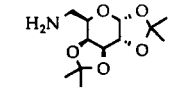
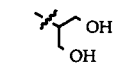
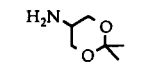
Abstract: Five protected submonomers for peptoid synthesis were prepared, including N^{in}-BOC-tryptamine, *O*-*t*-butyl tyramine, PMC-guanidino-propylamine, 6-amino-6-deoxy-D-galactopyranose diacetonide, and 5-amino-2,2-dimethyl-1,3-dioxane. The first three mimic natural aminoacid sidechains i.e. tryptophan, tyrosine, and arginine, while the last two provide hydrophilic sidechains. These submonomers were successfully used for preparation of oligo-peptoids by the submonomer synthesis method.

Poly *N*-substituted glycines (peptoids) are a novel class of sequence-specific heteropolymers that were originally developed for drug discovery.[1] Recently, peptoids have been shown to form stable helical secondary structures[2a], mediate the delivery of DNA to cells[2b] and increase the potency of ligands for SH3 domains[2c]. Peptoids are synthesized by the solid-phase submonomer method[3]. Thus, *N*-substituted glycine monomers are constructed on the growing chain of a resin-bound peptoid by repeating a two step cycle of (a) bromoacetylation of the N-terminal secondary amine, and (b) subsequent S_N2 displacement of the bromide by a desired primary amine (submonomer) (Scheme 1). The coupling efficiency of these two steps have been optimized to such a degree that peptoids as long as 36 residues[2a,2b] can be synthesized routinely. In order to introduce many interesting reactive or polar functionalities into peptoids, suitably protected amine submonomers need to be prepared. Table 1 shows the protected amines prepared in this study.

These submonomers include important amines such as tryptamine, tyramine and guanidinoalkylamines that mimic natural amino acid sidechains (**1**, **2**, **3**). In addition, submonomers with varing degrees of hydrophilicity were also prepared (**4**, **5**). For these monomers, we chose protecting groups that can be removed during the cleavage of the peptoid from resins with 95% [v/v] TFA in water. Furthermore, by-products of these protecting groups are volatile for easy removal from the crude product except for the by-products of the guanidine protecting group.[4]

To avoid side reaction of the indole system during peptoid synthesis, we chose the *t*-BOC group for indole nitrogen protection. N^{in}-*t*-BOC-tryptamine was prepared in three steps (**Figure 1**). The amino group of tryptamine was first protected with trifluoroacetic anhydride in pyridine/CH_2Cl_2 at room

Table 1

Sidechain[a)]	Submonomer	
		**1**
		**2**
		**3**
		**4**
		**5**

[a)] ⁄⁄ indicates the bond attached to the backbone N.

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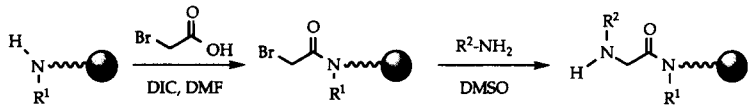
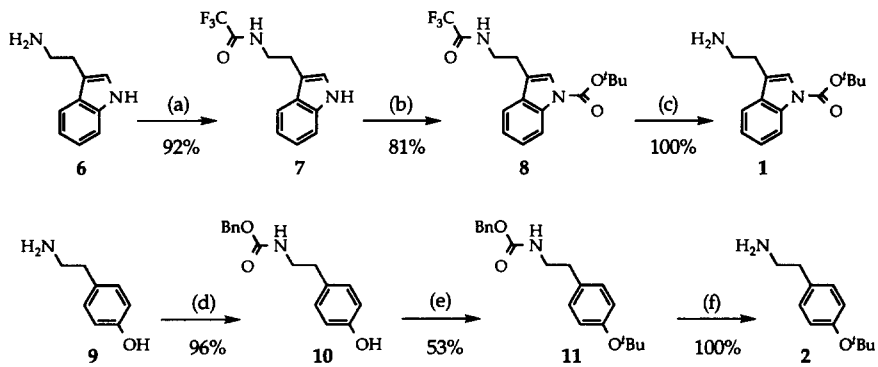
Scheme 1



temperature (92%). The BOC group was introduced using di-*t*-butyl dicarbonate in the presence of catalytic 4-*N*,*N*-dimethylaminopyridine in THF at 38 °C for 1 hour, affording a yellow solid in 81% yield after silica gel flash chromatograpy (CH_2Cl_2). The trifluoroacetyl group was selectively removed by treatment with potassium carbonate in H_2O/methanol, affording **1** in a total yield of 75% from **6**. We also tried the benzyloxycarbonyl (Cbz) group for the primary amine protection. However, its deprotection by hydrogenolysis (H_2/Pd) resulted in some overreduction of indole ring system.

Although tyramine can be used unprotected for shorter peptoids, protection of the phenolic hydroxyl group is desirable to prepare high-molecular weight peptoids. The phenolic hydroxyl group of tyramine was first protected with triisopropylsilyl group (TIPS), which is generally used for submonomers containing aliphatic hydroxyls.[1] Unfortunately, this TIPS ether was not entirely compatible with the submonomer synthesis conditions and produced an uncharacterizable mixture of products when a 36mer peptoid synthesis was attempted. Thus, the phenolic hydroxyl group was protected as the more robust *t*-butyl ether. Compound **2** was prepared by a method similar to the side chain protection of Cbz-tyrosine[5] (**Figure 1**). Thus, treatment of *N*-Cbz-tyramine with isobutylene in CH_2Cl_2 in the presence of conc. H_2SO_4 afforded desired **11** in a 53% yield after a silica gel flash chromatograpy (50% [v/v] ethyl acetate in hexane). The Cbz group was removed quantitatively by hydrogenolysis.

Figure 1

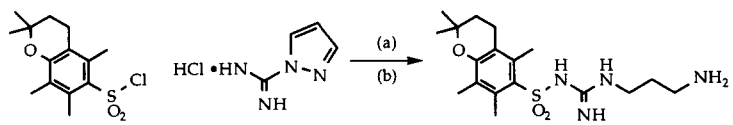


Preparation of protected tryptamine and tyramine submonomers. (a) 1.05 eq $(CF_3CO)_2O$, pyridine/CH_2Cl_2, 25 °C for 2 hr.; (b) 1.2 eq (Boc_2O, 0.05 eq 4-*N*,*N*-dimethylaminopyridine, THF, 38 °C for 1 hr.; (c) 5% K_2CO_3 in 70%[v/v] CH_3OH in H_2O, 25 °C for 18 hr.; (d) 1 eq *N*-(benzyloxycarbonyloxy)succinimide, THF, 0 °C for 1 hr, then 25 °C for 3 hr.; (e) 20 eq isobutylene, cat. conc H_2SO_4, CH_2Cl_2/THF (4/1), -20 to 25 °C for 18 hr.; (f) 10% Pd/C, H_2 (49 psi), EtOH, 25°C for 18 hr.

To introduce another important sidechain, τ-*N*-trityl and π-*N*-trityl histamine were prepared. Unfortunately, the trityl group failed to prevent an intramolecular S_N2 displacement of the bromide of the bromoacetamide by the remaining free imidazole nitrogen, resulting in the chain termination[6].

We prepared *N,N'*-bis-BOC-guanidinoethylamine and *N,N'*-bis-BOC-guanidinopropylamine by elaborating either mono-Cbz- ethylenediamine or 1,3-propanediamine with *N,N'*-bis-BOC-thiourea, respectively. To our surprise, these compounds underwent rapid intramolecular cyclization to produce 5- or 6-membered ring guanidine as soon as the Cbz protecting group was removed. Therefore, we decided to use the PMC group for the protection of the guanidino group (**Figure 2**). Compounds **3** was prepared by mixing 1H-pyrazole-1-carboxamidine hydrochloride with DIEA (2 eq.) and 2,2,5,7,8-pentamethylchroman-6-sulfonyl chloride for 16 hr. The reaction mixture was then added dropwise to a 1 M solution of 1,3-propanediamine in dioxane (5 eq.) to obtain **3** in 75% yield from **12**.

Figure 2

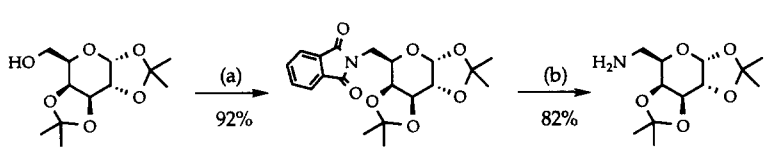


12 **13** **3**

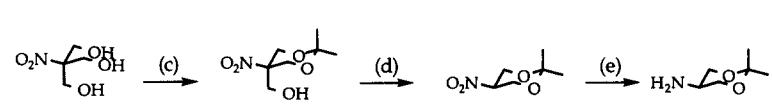
Preparation of protected guanidinopropyl submonomers. (a) DIEA (2 eq.) rt for 16 hr.; (b) 1,3-propanediamine (5 eq.), rt for 16 hr.

For polyhydroxyamines i.e. **4** and **5**, we have found cyclic acetals such as acetonides to be the protecting group of choice because of stability towards the submonomer peptoid synthesis, easy cleavage by TFA and easy removal of by-product (acetone). Importantly, the acetonide increases the molecular weight of submonomers much less than other common protecting groups such as the TIPS ether. Compound **4** was prepared in two steps with a Mitsunobu reaction as a key step (**Figure 3**). Thus, treatment of **17** with phthalimide, triphenylphosphine and diisopropyl azodicarboxylate (DIAD) at room temperature afforded **18** in a 92% yield after a silica gel flash chromatography (25% [v/v] ethyl acetate in hexane). Compound **5** was prepared[7] via 3 steps from tris(hydroxymethyl)nitromethane **19**. After the acetonide protection of **19**, the remaining free hydroxymethyl group in **20** was removed by a retro

Figure 3



17 **18** **4**



19 **20** **21** **5**

Preparation of protected polyhydroxylic submonomers. (a) 1 eq phthalimide, 1 eq Ph_3P, 1.05 eq DIAD, THF, 25 °C for 60 min.; (b) 3.5 eq NH_2NH_2 (35% [w/v] in H_2O), EtOH, 25 °C for 14 hr.; (c) acetone (3 eq.), BF_3-Et_2O (1 eq.); (d) NaOH, 60°C, 1h (e) ammonium formate Pd/C, MeOH, 3hr.

Henry-type aldol reaction. The nitro group in **21** was reduced to a primary amine by hydrogenation over palladium on carbon, resulting in desired submonomer **5**.

These amines were evaluated by incorporation into a series of oligomers. The coupling yield for each step was found to be greater than 98% when these protected amines were used as submonomers, and as long as 36-residue peptoids were prepared without difficulties in most cases. The crude and purified peptoids were analyzed by reverse phase HPLC and electrospray mass spectrometry. HPLC analysis generally indicated the purity of > 75% for the crude products. BOC group (**1**) and acetonide group (**4, 5**) were cleanly removed by 95% [v/v] TFA in H_2O within 20 minutes at room temperature, while the *t*-butyl ether group (**2**) required a longer reaction time of 2 hours for completion by the same reagent at room temperature. The removal of the PMC was performed using (TFA:H_2O:phenol:triisopropylsilane), (88:5:5:2) for 2 hours at room temperature.

In summary, these submonomers extend the range of hydrophilicity and charge that can be explored in peptoid oligomers prepared by the submonomer synthesis method.

Acknowledgments

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Reference and Notes

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4. In order to remove the PMC cleavage by-product, the crude product was lyophilized and dissolved in a solution of 20% [v/v] AcOH in H_2O. The acidic aqueous solution was washed with Et_2O and lyophilized again.
5. Boon, P. J.; Mous, J. F. M.; Ten Kortenaar, P. B. W.; Tesser, G. I. *Int. J. Peptide Protein Res.* **1986**, *28*, 477-492.
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7. Quirk, J. M.; Harsy, S. G., ; Hakansson, C. L. Eur. Patent 0 348 223 A3, 1989.
8. Selected spectroscopic data:
   1: ^{1}H NMR ($CDCl_3$) δ ppm 8.13 (1H, d, *J* = 7.9 Hz), 7.25 (4 H, m), 3.03 (2H, t, *J* = 6,7 Hz,), 2.93 (2H, t, *J* = 6.7 Hz), 1.76 (9H, s). ^{13}C NMR 149.5, 135.4, 130.4, 124.2, 123.0, 122.3,118.8, 118.0, 115.2, 83.4, 41.4, 28.9, 28.3.
   2: ^{1}H NMR ($CDCl_3$) δ ppm 6.95 (4H, m), 2.90 (4H, m), 1.26 (9H, s).
   3: ^{1}H NMR δ ppm 6.80 (2H, s), 6.45 (1H, s), 3.31 (2H, s), 2.78 (2H, t, *J*= 6.2 Hz), 2.64 (2H, t, *J*= 6.2 Hz), 2.58 (3H, s), 2.56 (3H, s), 2.15 (3H, s), 1.83 (2H, t, *J*= 6.5 Hz), 1.65 (2H, t, *J*= 6.5 Hz). 1.32 (6H, s).
   4: ^{1}H NMR δ ppm 5.53 (1H, d), 4.57 (1H, dd), 4.29 (1H, dd), 4.20 (1H, dd), 4.29 (1H, m), 3.68 (1H, m), 2.95 (1H, dd), 2.82 (1H, dd), 1.61 (2H, s), 1.51 (3H, s), 1.42 (3H,s), 1.31 (6H, s).