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Heterocyclic amines for the construction of peptoid oligomers bearing multi-dentate ligands

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Abstract—Peptoids are oligomers of N-substituted glycine that can be readily assembled using haloacetic acids and primary amines as synthons. Here, we report the synthesis and characterization of three new heterocyclic amines, 2-(2,2′:6′,2″-terpyridine-4′-yloxy)ethylamine, 2-(1,10-phenanthroline-5-yloxy)ethylamine and 8-hydroxy-2-quinolinemethylamine, and their incorporation into a series of different peptoid oligomer sequences. Since the heterocycles are all known to coordinate metal ions, the peptidomimetic products are designed to bind metal species with the potential for applications in catalysis and materials science.
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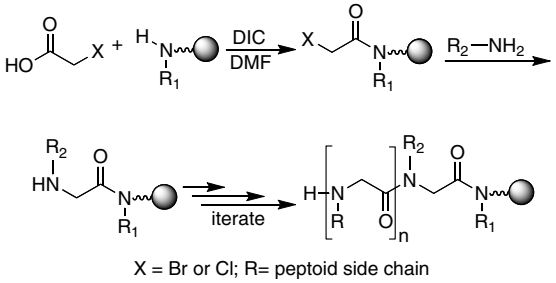
N-Substituted glycine peptoid oligomers, or 'peptoids', are abiotic polypeptide mimics that are capable of adopting stable secondary structures.[1] By employing a solid-phase synthesis protocol,[2] a wide variety of side chains can be incorporated into peptoid sequences, as shown in Scheme 1. This 'submonomer' protocol enables the generation of peptoid oligomers possessing a wide range of chemical and structural diversity.[3] For example, the incorporation of nitrogen-containing heterocyclic side chains (imidazole, pyridine, etc.) in peptoid oligomers has been reported previously.[4] Multidentate ligands for metal coordination such as terpyridine, phenanthroline, and hydroxyquinoline,[5] however, have not yet been explored in the context of peptoid synthesis. Such ligands, especially bipyridine and terpyridine, have been incorporated into other oligomeric scaffolds (e.g., PNA) and utilized for metal binding.[6] Hence, the incorporation of such ligands as side chains in peptoids will enable their use for metal coordination and may further expand the functional diversity of peptoids for applications in catalysis and materials science. We report here, for the first time, the synthesis of three primary amines: 2-(2,2′:6′,2″-terpyridine-4′-yloxy)ethylamine, 2-(1,10-phenanthroline-5-yloxy)ethylamine and 8-hydroxy-2-quinolinemethylamine, and their utilization as reagents in the solid-phase synthesis of peptoid oligomers.



Scheme 1. Solid-phase 'submonomer' peptoid synthesis.

Primary amines **1**–**3** were synthesized in simple one-step reactions from commercially available starting materials. Compound **1**, 2-(2,2′:6′,2″-terpyridine-4′-yloxy)ethylamine, was synthesized similarly to a known procedure,[7] by adding 4′-chloro-2,2′:6′,2″-terpyridine and ethanolamine to a suspension of powdered KOH in DMSO, and stirring at 40 °C for 2 h.[8] Compound **2**, 2-(1,10-phenanthroline-5-yloxy)ethylamine, was synthesized accordingly, but because 5-chloro-1,10-phenanthroline is much less reactive than 4′-chloro-2,2′:6′,2″-terpyridine, a higher temperature (80 °C) and a longer reaction time (6 h) were required.[9] Compound **3**, 8-hydroxy-2-quinolinemethylamine, was synthesized by reduction of 8-hydroxy-2-quinolinecarbonitrile with molecular hydrogen using palladium on carbon as a catalyst.[10] Conversion of the nitrile to the amine was confirmed by the ^{1}H NMR spectrum, showing a characteristic

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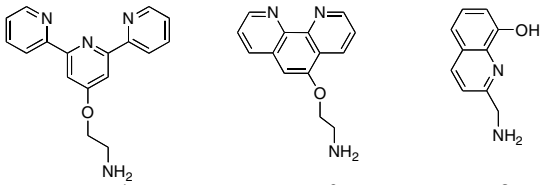
Table 1. Peptoid oligomer sequences

Peptoid	Oligomer sequence	Oligomer length	Molecular weight Calcd:found	Purity[a] (%)
4	*N*etp–*N*pm–*N*me	3mer	611.7:612.4	>95
5	*N*pm–*N*etp–*N*pm–*N*me	4mer	758.9:759.5	>95
6	*N*me–*N*pm–*N*etp–*N*pm–*N*me	5mer	874.0:874.5	>95
7	*N*me–*N*pm–*N*eph–*N*pm–*N*me	5mer	820.9:821.5	>90
8	*N*me–*N*pm–*N*hq–*N*pm–*N*me	5mer	755.9:756.4	87
9	*N*spe–*N*etp–*N*spe	3mer	671.8:672.3	95
10	*N*spe–*N*eph–*N*spe	3mer	618.7:619.3	87
11	*N*spe–*N*hq–*N*spe	3mer	553.6:554.3	56

[a] As determined by analytical HPLC of crude product. Compounds **9**–**11** were subsequently purified by preparative HPLC to >95%. *N*me = 2-methoxyethylamine; *N*pm = benzylamine; *N*etp = 2-(2,2′:6′,2″-terpyridine-4′-yloxy)ethylamine; *N*eph = 2-(1,10-phenanthroline-5-yloxy)ethylamine and *N*hq = 8-hydroxy-2-quinolinemethylamine.

singlet signal for the methylene amine hydrogen molecules (CH_2–NH_2) at δ 4.03 ppm.



1 **2** **3**

N-Substituted glycine oligomers **4**–**11** (Table 1) were synthesized as C-terminal amides in good yields and high purities by using haloacetic acids and the following primary amines: **1** (*N*etp); **2** (*N*eph); **3** (*N*hq); (*S*)-(−)-1-phenylethylamine (*N*spe); 2-methoxyethylamine (*N*me); and benzylamine (*N*pm).[11] The test sequence, *N*me–*N*pm–*N*etp–*N*pm–*N*me was evaluated at various stages of the synthesis to ensure compatibility of the heterocycles with oligomer synthesis. Figure 1 shows high performance liquid chromatographic (HPLC) characterization following incorporation of *N*etp (trimer **4**), *N*pm (tetramer **5**), and *N*me (pentamer **6**).

As shown in Figure 1, 2-(2,2′:6′,2″-terpyridine-4′-yloxy)ethylamine was incorporated successfully into the peptoid sequence, resulting in peptoid **6**, with high purity. Accordingly, amines **2** and **3** were incorporated in similar sequences to form the peptoids *N*me–*N*pm–*N*eph–*N*pm–*N*me (**7**) and *N*me–*N*pm–*N*hq–*N*pm–*N*me (**8**).

Due to the fact that only peptoid oligomers containing bulky α-chiral side chains are known to form stable secondary structures,[1a,d] we were interested in evaluating amines **1**–**3** in the synthesis of peptoids incorporating structure-inducing (*S*)-(−)-1-phenylethyl glycine (*N*spe) monomers. Therefore, we further synthesized peptoids **9**–**11**, with the sequences *N*spe–*N*etp–*N*spe, *N*spe–*N*eph–*N*spe, and *N*spe–*N*hq–*N*spe, respectively.

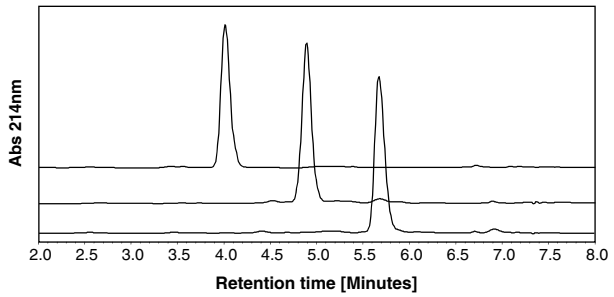
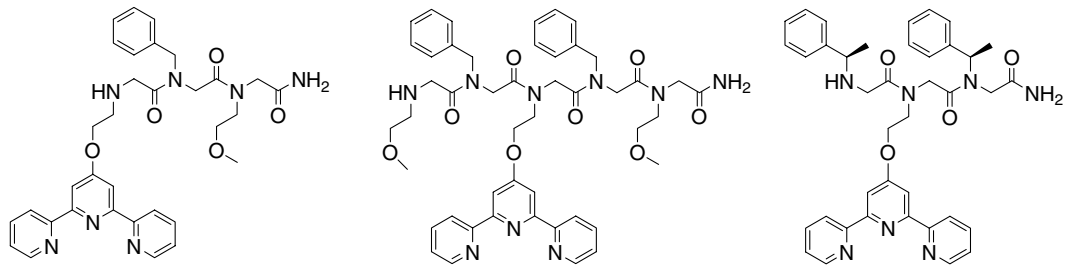


Figure 1. HPLC traces of crude peptoid oligomers **4**–**6** prior to purification (offset in *y*-dimension only). Top: *N*etp–*N*pm–*N*me trimer (**4**); middle: *N*pm–*N*etp–*N*pm–*N*me tetramer (**5**); bottom: *N*me–*N*pm–*N*etp–*N*pm–*N*me pentamer (**6**).

Crude oligomer purities ranging from 56% to 95% were obtained, as determined by HPLC. Low peptoid yields were observed with the incorporation of 8-hydroxy-2-quinolinemethylamine. Diminished yields may arise due to the variations in the length of the spacer between the heterocycle and the reactive amine functionality. In the case of 8-hydroxy-2-quinolinemethylamine, the heterocycle is positioned closer to the peptoid backbone, which may enhance side reactions such as acylation of the heterocyclic nitrogen center. Molecular weights were



4 **6** **9**

*N*etp-*N*pm-*N*me *N*me-*N*pm-*N*etp-*N*pm-*N*me *N*spe-*N*etp-*N*spe

confirmed by electrospray mass spectrometry and were in agreement with the expected values (Table 1).

The study presented here establishes the compatibility of terpyridine, phenanthroline and hydroxyquinoline groups with the solid-phase synthesis of peptoid oligomers. Furthermore, we demonstrate the feasibility of incorporating these heterocyclic ligands in peptoids of various lengths and sequences. The results establish the opportunity for realizing peptoid metal complexes, using late transition metal ions (e.g., Co and Cu) as a starting point. The ability to place one or two monomers incorporating metal coordinating centers at specific positions in the context of a peptidomimetic scaffold will be exploited to direct the formation of intermolecular or intramolecular metal complexes. This may enable the control of peptoid structure and will point the way to the formation of peptoid podands, as well as foldamers with unique secondary, tertiary, or quaternary structures. We have recently obtained metal complexes of peptoids bearing such ligands, which are currently under investigation in our laboratory.

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8. 4′-Chloro-2,2′:6′,2″-terpyridine (286 mg, 1 mmol) and ethanolamine (100 μl, 1.1 mmol) were added to a stirred suspension of powdered KOH (280 mg, 5 mmol) in DMSO (5 ml) and stirred at 40 °C for 2 h. The reaction mixture was then added to 40 ml of methylene chloride and washed with water (3×). The methylene chloride solution was dried over Na_2SO_4 and the solvent was removed. 2-(2,2′:6′,2″-Terpyridine-4′-yloxy) ethylamine (286 mg, 0.97 mmol) was obtained as a light yellow solid in 97% yield and used subsequently without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.9$ (t, 2H, H_α), 4.8 (t, 2H, H_β), 7.25 (t, 2H, $H_{5,5''}$), 7.75 (t, 2H, $H_{4,4''}$), 8.05 (s, 2H, $H_{3',5'}$), 8.55 (d, 2H, $H_{3,3''}$), 8.65 (d, 2H, $H_{6,6''}$) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 40.9$ (C_α), 77.1 (C_β), 107.4 ($C_{5,5''}$), 121.3 ($C_{4,4''}$), 123.8 ($C_{3,3''}$), 136.7 ($C_{3',5'}$), 149.0 ($C_{6,6''}$), 155.87 ($C_{2,2''}$), 156.5 ($C_{2',6'}$), 166.8 ($C_{4'}$) ppm. ESI-MS: $m/z = 293.1$ (M^+), 315.2 ($M+Na^+$).
9. 5-Chloro-1,10-phenanthroline (560 mg, 2.6 mmol) and ethanolamine (175 μl, 2.9 mmol) were added to powder KOH (730 mg, 13 mmol) in DMSO (10 ml) and stirred at 80 °C for 6 h. The reaction mixture was then added to 100 ml of methylene chloride and washed with water (4×). The methylene chloride solution was dried over Na_2SO_4 and the solvent was removed. The brown solid was purified from warm methylene chloride (2×) and 2-(1,10-phenanthroline-5-yloxy) ethylamine (442 mg, 1.85 mmol) was obtained as a light brown solid in 71% yield and used subsequently without further purification. ^{1}H NMR δ (400 MHz, DMSO): $\delta = 9.03$ (dd, 2H, $H_{2,9}$), 8.42 (dd, 2H, $H_{4,7}$), 7.9 (s, 1H, H_6), 7.7 (dd, 2H, $H_{3,8}$) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 40.0$ (C_α), 79.5 (C_β), 123.3 ($C_{3,8}$), 126.6 (C_6), 129.1 (C_{6a}), 130.8 (C_{4a}), 136.2 ($C_{4,7}$), 145.8 and 147.3 ($C_{10a,b}$), 150.1 ($C_{2,9}$) 151.4 (C_5) ppm. ESI-MS: $m/z = 240.0$ (M^+), 262.1 ($M+Na^+$).
10. 8-Hydroxy-2-quinolinecarbonitrile (1 g, 5.9 mmol) was dissolved in acetic acid (43 ml). Pd/C (10%, 220 mg) was added and the solution was treated with H_2 (1 atm) for 14 h. The catalyst was filtered and the solvent was removed. The crude product was re-crystallized from a mixture of $CHCl_3$ and Et_2O. The light brown solid was filtered, dissolved in $CHCl_3$ (160 ml), and treated with a 1 M potassium bicarbonate solution (4 ml). The product was extracted with $CHCl_3$, dried over Na_2SO_4, and the solvent was removed. 8-Hydroxy-2-quinolinemethylamine (66 mg, 3.8 mmol) was obtained as a light brown solid in 65% yield and used subsequently without further purification. ^{1}H NMR (400 MHz, DMSO): $\delta = 8.2$ (d, 1H, H_7), 7.5 (d, 1H, H_2), 7.35 (dt, 2H, $H_{5,6}$), 7.08 (dd, 1H, H_3), 5.2 (br s, 2H, NH_2), 4.03 (s, 2H, H_α) ppm. ^{13}C NMR (400 MHz, DMSO): $\delta = 46.35$ (C_α), 110.0 (C_7), 116.4 (C_5), 119.5 (C_3), 125.7 (C_6), 126.5 (C_{4a}), 135.1 (C_4), 136.4 (C_{8a}),

151.9 (C_8) 159.6 (C_2) ppm. ESI-MS: $m/z = 174.9$ (M^+).

11. Peptoid oligomers were synthesized manually on Rink amide resin using the submonomer approach.[2] Typically, 100 mg of resin was deprotected with 2 ml of 20% piperidine in *N*,*N*-dimethylformamide (DMF) for 20 min. This was followed by a two-step monomer addition cycle for each residue—acylation and nucleophilic amine displacement. For the haloacylation step, 0.85 ml of a 0.4 M solution of bromoacetic acid and 0.2 ml of neat *N*,*N*′-diisopropylcarbodiimide (DIC) were added to the resin and mixed at room temperature for 20 min. For the displacement steps, a 1.0 M solution of the desired amine was prepared in DMF. From this solution, 1 ml was added to the resin and mixed for 20 min at room temperature. This two-step addition cycle was modified as follows: after incorporation of heterocyclic amines **1**–**3**, chloroacetic acid was used in place of bromoacetic acid, and for the next displacement steps, 2.0 M solutions of the desired amine were used and the displacement was done in 35 °C for 1 h.[4]