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Synthesis of α-helix mimetics with four side-chains

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ABSTRACT

The synthesis of a heterocyclic piperazine-based scaffold that mimics the *i*, *i* + 4, *i* + 8, *i* + 11 side-chain projections of an α-helix is described. The synthesis is designed to be modular to allow the targeting of a range of protein–protein interactions involving α-helices.

The α-helix motif is one of the most abundant secondary protein structures and is often involved in protein–protein recognition. The projecting amino-acid residues in *i*, *i* + 4, *i* + 7/*i* + 8, *i* + 11 positions appear at the same side of the α-helix and define a surface interface for intermolecular interactions with other proteins.[1] (Fig. 1) Since protein–protein interactions are involved in several cell-regulatory processes, significant efforts have been directed towards the synthesis of smaller molecules that can efficiently disrupt these interactions.[1,2]

Hamilton and coworkers pioneered the area of non-peptide-based α-helix mimetics and developed small-molecule libraries based on terphenyl **A**, terephtalimide, and oligopyridine scaffolds that display side-chain functionalities with similar spatial and angular orientation to those found in an α-helix (Fig. 2).[3] These scaffolds were shown to efficiently disrupt protein–protein interactions in biologically relevant systems such as Bak/Bcl-X_L[4] and p53-HDM2.[5] Recently, König and coworkers described the synthesis of functionalized 1,4-dipiperazino benzenes **B** and demonstrated that these compounds adopt a staggered conformation with the projecting side-chains closely resembling an α-helix.[6] Our efforts toward the synthesis of structurally similar inhibitors for protein–protein interactions have revolved around heterocyclic compounds **C** containing a central pyridazine ring functionalized with hydrophobic amino-acid side-chains which were intended to reproduce the projecting *i*, *i* + 4, *i* + 7 residues of an α-helix.[7] These compounds were intended to mimic the amphiphilic nature of α-helices by displaying a hydrophilic surface rich in hydrogen-bonding towards the solution and a hydrophobic surface interacting with the protein target.

These scaffolds all present three hydrophobic side-chains effectively mimicking the side-chain projections of two turns of an α-helix (Fig. 2). Recently, Hamilton and coworkers have described synthetic foldamers that mimic longer sections of the α-helix.[8] Here, we describe the synthesis of an extended class of α-helix mimetics **7**. They present four hydrophobic residues and reproduce the *i*, *i* + 4, *i* + 8, *i* + 11 side-chains, that is, three turns of an α-helix.

The general synthetic approach is outlined in Scheme 1. The synthesis is modular and allows the incorporation of structurally different hydrophobic side-chains in the scaffold. The synthesis of **7** commenced with Cu(I)-catalyzed N-arylation of **1** with L-valine or L-phenylalanine which proceeded in high yields to give **2**.[9] Treatment of **2** with 4-(benzyloxy)-2-methylaniline under

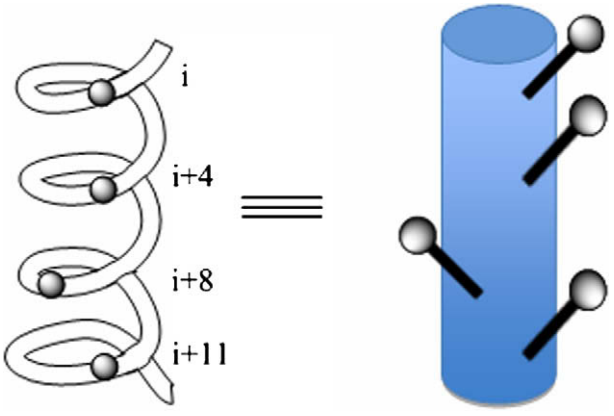

Figure 1. Orientation of the *i*, *i* + 4, *i* + 8, *i* + 11 residues in an idealized α-helix.

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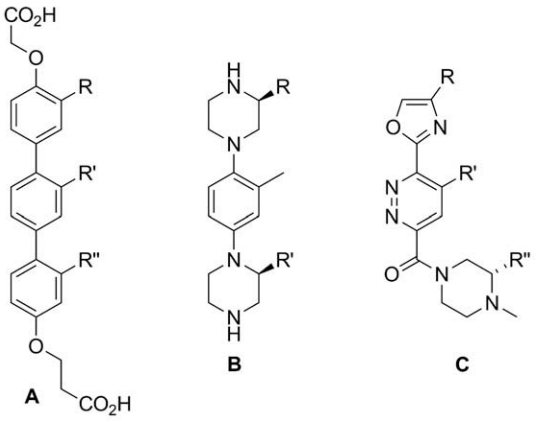


Figure 2. Examples of α-helix mimetics: Hamilton's terphenyl scaffold **A**, König's 1,4-dipiperazino benzenes **B**, and the oxazole-pyridazine-based scaffold **C**.

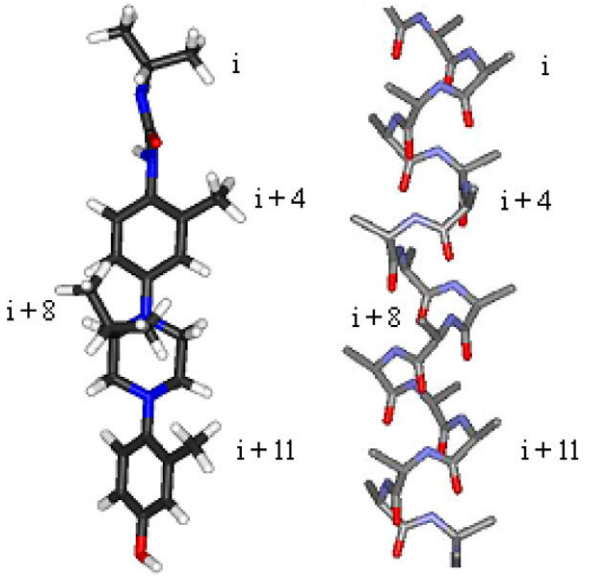
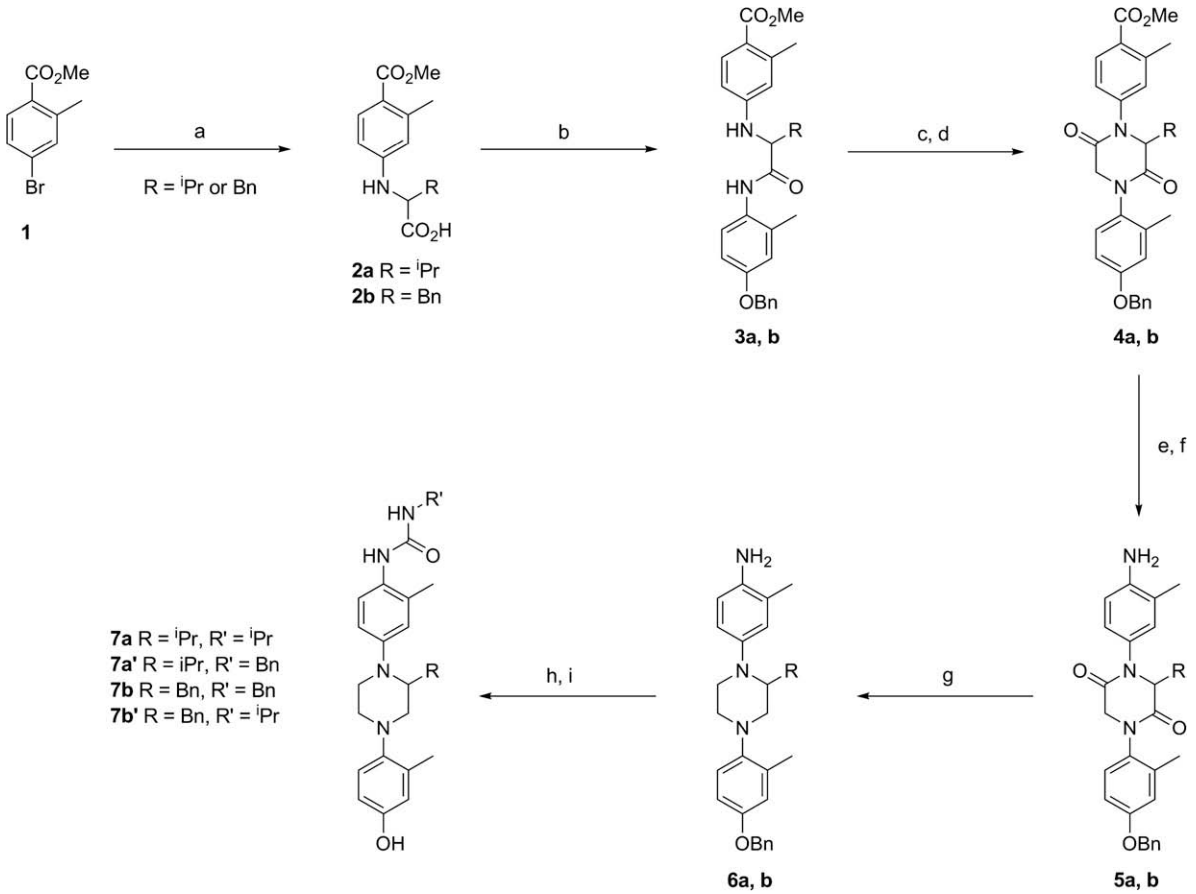


Figure 3. Minimized representations of α-helix mimetic **7a** and an idealized alanine α-helix (Hyper Chem 7.0 semi-empirical, AM1).

standard amide-bond forming conditions afforded amide **3**, which was subsequently transformed into keto-piperazine **4**.[10] Saponification of **4** using LiOH followed by a Curtius rearrangement delivered aniline **5**, possessing a handle for further functionalization. Reduction of **5** with $LiAlH_4$[11] resulted in partial deprotection of the benzyloxy ether. This problem could be circumvented by using BH_3 DMS as reductant, which delivered amine **6** in high yield. Reaction of **6** with ^{i}PrNCO or BnNCO followed by catalytic hydrogenolysis of the phenolic protecting group yielded the mimetics **7** in excellent yields.

Figure 3 shows a minimized representation of **7a** along with an idealized α-helix consisting of alanine α-amino acids. The dis-



Scheme 1. Reagents and conditions: (a) R-CH(NH_2)CO_2H, CuI, K_2CO_3, DMF, 100 °C , 70% (R = ^{i}Pr), 75% (R = Bn), (b) 4-(benzyloxy)-2-methylaniline, EDCI, HOBt, CH_2Cl_2, rt, 75% (R = ^{i}Pr), 82% (R = Bn), (c) bromo-acetylbromide, $NaHCO_3$(aq), EtOAc, rt, (d) $CsCO_3$, DMF, 0 °C, 72% (2 steps, R = ^{i}Pr), 61% (2 steps, R = Bn), (e) LiOH, THF:H_2O, rt, 88% (R = ^{i}Pr), 92% (R = Bn), (f) DPPA, NEt_3, DMF, rt → 100 °C 74% (R = ^{i}Pr), 68% (R = Bn), (g) BH3 DMS, THF, reflux, 91% (R = ^{i}Pr), 82% (R = Bn), (h) R′-NCO, CH_2Cl_2, rt, (i) Pd-black, H_2 (1 atm), THF:MeOH, 95% (R = ^{i}Pr, R′ = ^{i}Pr), 89% (*R* = ^{i}Pr, *R*′ = 97), X% (*R* = Bn, R′ = ^{i}Pr), 91% (R = Bn, R′ = Bn).

tances between the substituents in the key positions of **7a** [*i* to *i* + 4 = 5.3 Å, *i* + 4 to *i* + 8 = 6.2 Å, i to *i* + 8 = 9.8 Å, *i* + 4 to *i* + 11 = 9.0 Å, and *i* + 8 to *i* + 11 = 5.1 Å] compares favorably to those of an idealized alanine α-helix: [*i* to *i* + 4 = 6.3 Å, *i* + 4 to *i* + 8 = 6.2 Å, *i* to *i* + 8 = 11.9 Å, *i* + 4 to *i* + 11 = 10.2 Å, and *i* + 8 to *i* + 11 = 5.5 Å]. The central piperazine ring adopts a flattened chair conformation with the Bn- or ^{i}Pr group occupying an axial position. This conformation has previously been observed by X-ray diffraction analysis of a similar system.[6] The minimized representation also shows that **7a** adopts a staggered conformation in close analogy to Hamilton's terphenyl[3a] and König's 1,4-dipiperazino-benzene[6] scaffolds and projects the side-chain residues appropriately to replicate those of an α-helix.

To conclude, we have prepared a new series of α-helix mimetics in few synthetic steps, which mimics the *i*, *i* + 4, *i* + 8, *i* + 11 residues of an α-helix. The synthetic methodology reported in this letter should be applicable for the synthesis of a broader and more general set of α-helix mimetics possessing hydrophobic side-chains tailored to target specific protein–protein interactions. Work in this direction along with biological screening of these compounds is currently underway in our laboratory and will be reported in due course.

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