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Solid-phase synthesis and solution structure of bicyclic β-turn peptidomimetics: diversity at the i position

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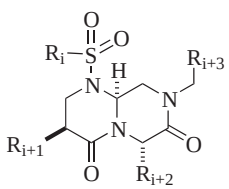
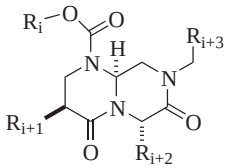
Abstract—A library of the urea type 6,6-bicyclic β-turn mimetics was conveniently prepared by using solid-phase chemistry with diversity at the i position in good yield and purity. The solution structure of the urea type scaffold was shown to mimic a type I β-turn structure.

The secondary structures of proteins control the three dimensional display of functional groups on their surfaces, which play an essential role in molecular recognition events in biological systems, such as receptor–ligand, enzyme–substrate, and antigen–antibody interactions.[1] Since most of these interactions are initiated or mediated by a key local structure in the protein or peptide, a small molecule bearing a similar local structural feature can effectively mimic the function of the protein or peptide as a ligand.[2] In addition, non-peptidic substances can potentially improve the undesirable therapeutic characteristics of peptides, which include poor bioavailability, short duration of action, and lack of oral activity.[3] Therefore, a methodology for the rapid and systematic preparation of secondary structure peptidomimetics, with complete control of their stereochemistry, would be a significant asset for drug discovery efforts.

Recently, we have developed bicyclic β-turn peptidomimetics **1** and **2** with four sites of diversity readily accessible through solid-phase synthesis from commercially available diversity components.[4] Libraries of the mimetics were screened against opioid receptors to identify potent μ-selective agonists.[5] In the synthetic scheme, however, diversity at the i position of the mimetic is limited to the commercially available sulfonyl chlorides or required the preparation of alkyl *p*-nitrophenyl carbonates in solution phase. It would enhance the value of our privileged nonpeptidic scaffolds for lead identification efforts if one could introduce a wide range of functional groups at the i position employing a solid-phase synthesis amenable to automation. Herein, we report an efficient method to furnish the diversity at the i position of our β-turn template compatible with automated solid-phase synthesis. The key modifications are utilization of a urea group for



1



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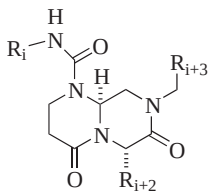

3

Keywords: peptide analogues/mimetics; combinatorial chemistry; bicyclic heterocyclic compounds.
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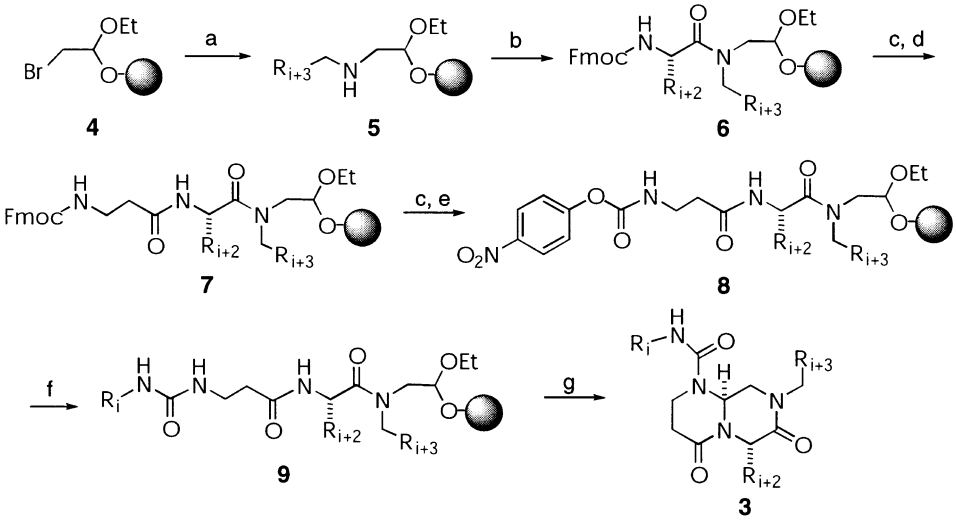


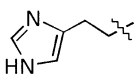
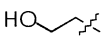
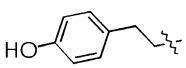
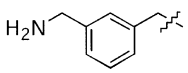
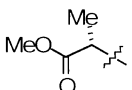
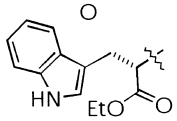
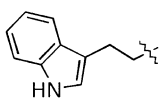
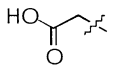
Scheme 1. (a) 2 M primary amine in DMSO (10–20 equiv.); (b) Fmoc-α-amino acid, DIC/HOAT in NMP (4 equiv.); (c) 20% piperidine in DMF; (d) Fmoc-β-alanine/HOBT/DIC (4 equiv.); (e) ClC(O)ONp/DIEA (5 equiv.); (f) R^iNH_2 (4 equiv.); (g) Formic acid at rt.

stereoselective tandem cyclization to produce the 1,6,8-substituted tetrahydro-2*H*-pyrazino[1,2-*a*]pyrimidine-4,7-dione **3** and the on-resin generation of *p*-nitrophenyl carbamate species that can be derivatized to the corresponding urea by the treatment with a variety of amines (Scheme 1).

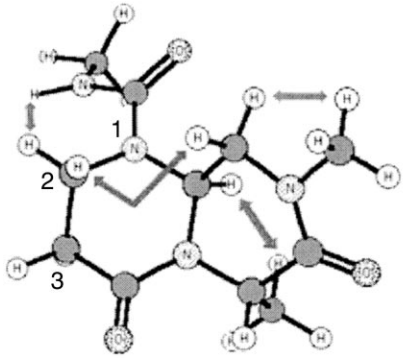
The solid-phase generation of **3** was carried out by employing commercially available bromoacetal resin **4**.[6] Nucleophilic displacement of the bromide with a number of primary amines gave the corresponding secondary amine **5**, which was then coupled with the appropriate Fmoc-α-amino acids using HOAT/DIC in NMP. Treatment of **6** with 20% piperidine in DMF followed by coupling with Fmoc-β-alanine afforded **7**. To introduce functionality at the i position, the Fmoc group was removed with 20% piperidine and subsequently treated with *p*-nitrophenyl chloroformate and DIEA in DCM/THF. The resulting *p*-nitrophenyl carbamate **8** was reacted with a variety of amines in DMF to give the corresponding urea derivatives **9**. Cleavage from the resin followed by stereoselective tandem cyclization was achieved by treatment with formic acid at room temperature. The bicyclic products **3** were observed as the major product by LC-MS and NMR analyses of the crude products except **3g**.

A wide range of amines can be applied to this derivatization of the i position, as shown in Table 1.[7] Alkylamines were successfully applied with good yield and purity (**3a–c**). Ethanolamine gave the formylated product as the major product, which was subsequently hydrolyzed by sodium carbonate to afford the desired hydroxyl derivative (**3d**). α,α′-Diamino-*m*-xylene, piperidine, tryptamine, histamine, and tyramine gave the bicyclic products in good yields (**3e–i**). Amino acid

Table 1. Preparation of mimetics **3** (R^{i+2}, Me; R^{i+3}, H)

	R^i	Yield (%)[a]		R^i	Yield (%)[a]
3a	Me	76			
3b	iBu	50	**3h**		73
3c	Bn	48			
3d		58	**3i**		66
3e		45	**3j**		63
3f		68	**3k**		59
3g		26	**3l**		65

a. Isolated yield for chromatographically purified compounds based on the initial loading of the solid support (bromoacetal resin[6])



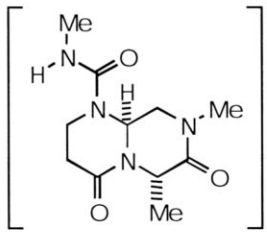


Figure 1. Proposed three-dimensional structure of **3a** and observed ROEs.

derivatives, e.g. alanine methyl ester, tryptophan ethyl ester, and glycine *t*-butyl ester, gave the corresponding bicyclic scaffolds in good yields (**3j–l**).

The 2D NMR study, i.e. DQF-COSY, TOCSY and ROESY, of **3a** in $CDCl_3$ at −20°C strongly suggests the ring conformation is the same as that of an X-ray structure previously determined,[4] in which we observed that the methyl group at the i+2 position and the proton at ring junction take pseudo-axial orientation to the convex face and that the methylene at position 2 was puckered toward the concave face. This ring conformation places the *pro-S* proton at position 3 in a pseudo-equatorial orientation. This orientation is suitable to mimic i+1 and i+2 functional groups of a type I β-turn. A strong ROE between the urea hydrogen and the *pro-S* hydrogen at position 2 was observed, suggesting the orientation of the urea NH bond to be *cis* to the N(1)–C(2) bond. The same cross-peaks, observed by ROESY experiment in DMSO-d_6/D_2O (1/1) at room temperature, suggest the core structure of our bicyclic template mimics a type I β-turn in aqueous solvent systems (Fig. 1).

In summary, we have successfully generated a library of urea type 6,6-bicyclic β-turn mimetics by using solid-phase chemistry with diversity at the i position in good yield and purity.

The solution structure of the urea type scaffold **3** was shown to mimic a type I β-turn structure similar to that observed for **1** and **2** by our previous study.[4] The generation of libraries of this β-turn template aimed at biologically significant targets and evaluation of their pharmacokinetic and pharmacodynamic profiles are underway and the results will be reported in due course.

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7. All compounds were characterized by ^1H NMR and MS (ESI). For a selected characterization: **3a**: ^1H NMR ($CDCl_3$, 500 MHz, −20°C): δ 1.47 (3H, d, $J=7.0$ Hz), 2.41 (1H, br.d, $J=16.5$ Hz), 2.54 (1H, m), 2.82 (3H, d, $J=3.0$ Hz), 2.95 (3H, s), 3.33 (1H, dd, $J=11.5$ and 4.0 Hz), 3.45 (1H, t, $J=14.5$ Hz), 3.57 (1H, t, $J=11.5$ Hz), 3.80 (1H, dd, $J=14.5$ and 5.0 Hz), 5.09 (1H, q, $J=7.0$ Hz), 5.57 (1H, br.s), 6.00 (1H, dd, $J=11.5$ and 4.0 Hz). ESI-MS (pos.); m/z, 255.1 $(M+H)^+$, ESI-MS (neg.); m/z, 253.2 $(M-H)^-$.