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Synthesis of β-turn mimics without stereogenic carbons: expanding the modular approach for diversity-oriented synthesis of tetrasubstituted benzotriazepinones

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Introduction

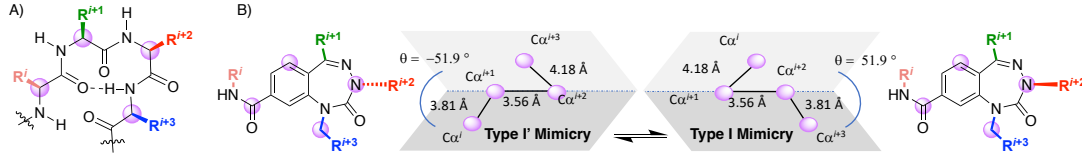


Figure 1. A) β-turn indicating α-carbons, B) dynamic turn mimicry by benzotriazepinone

Benzotriazepinones are "privileged structures" exhibiting promising biological and medicinal properties [1]. Benzotriazepinone crystal structures have shown that the N3 nitrogen is pyramidalized and exists in dynamic equilibrium between two configurations [2,3]. In the context of peptide science, X-ray analysis indicated tetrasubstituted benzotriazepinones replicate the topology of β-turn secondary structures [2]. Superimposing key atoms of the tetrasubstituted benzotriazepinone with the four α carbon atoms ($C\alpha^{i}$–$C\alpha^{i+1}$–$C\alpha^{i+2}$–$C\alpha^{i+3}$) within a tetrapeptide has demonstrated capacity to mimic both type I and I' β-turns which are topologically defined by the dihedral angle θ (Figure 1) [2,4].

A modular synthesis route to tetrasubstituted benzotriazepinones was developed starting from *tert*-butyl 4-acetyl-3-aminobenzoate (Figure 2) [2]. Aldol condensation provides the *i*+1 residue substituent. Annulation with an aza-glycine residue adds the *i*+2 substituent. The *i*+3 and *i* residue substituents are introduced by amide coupling and alkylation.

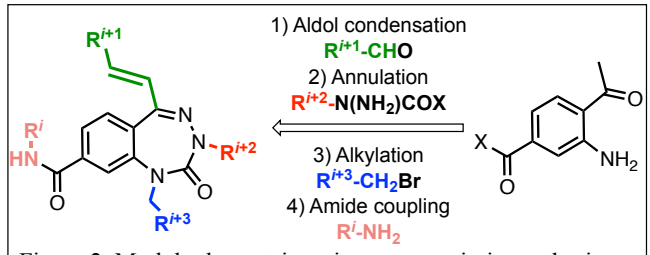
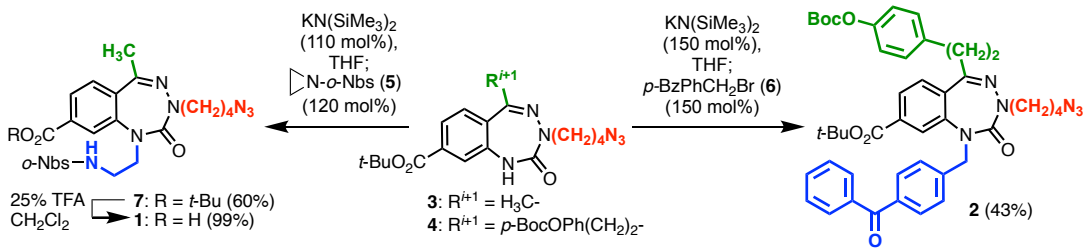


Figure 2. Modular benzotriazepinone turn mimic synthesis

A tetrasubstituted benzotriazepine library was rationally designed, synthesized, and shown to contain urotensin receptor (UT) allosteric modulators [2,5]. A G protein-coupled receptor, UT has two endogenous ligands, *h*UII and URP [5]. Differentiation of pathophysiological roles of *h*UII and URP has been pursued for medical applications, such as cardiovascular disease therapy. Tetrasubstituted benzotriazepinones exhibited respectively selective modulator ability on the activity of *h*UII and URP as positive and negative allosteric modulators with neutral activity on the ligand counterpart [5].

Results and Discussion

Diversity-oriented methods were studied to expand the modular route to β-turn *i*+1 and *i*+3 substituents by the synthesis of amino acid **1** and benzophenone analog **2** (Scheme).



Scheme. Synthesis of tetrasubstituted benzotriazepines **1** and **2**

Benzotriazepines **3** and **4** were respectively prepared from 4-keto-3-aminobenzoates using the reported annulation protocol [2]. The aza-glycinate derived from *p*-nitrophenyl chloroformate and benzophenone hydrazone reacted with 3-aminobenzoates, *i*-Pr_2EtN in CH_2Cl_2 to give glycinamides. Benzotriazepines **3** and **4** were obtained by glycinamide alkylation with $Br(CH_2)_4Cl$ and Et_4NOH in THF, annulation with 1N HCl, and chloride displacement with NaN_3 in 4:1 NMP:H_2O [2].

Respective alkylations of benzotriazepinones **3** and **4** using $KN(SiMe_3)_2$ in THF with *N*-*o*-nitrosulfonyl (*o*-Nbs)aziridine (**5**) [6] and *p*-benzoyl benzyl bromide (**6**) afforded *o*-Nbs-amino ethyl and benzophenone benzotriazepinones **7** (m/z = 601.2) and **2** (m/z = 771.5). Subsequent treatment of *o*-Nbs-amino ester **7** with F_3CCO_2H in CH_2Cl_2 gave acid **1**, which exhibited diastereotopic methylene proton signals at 3.41 and 4.30 ppm indicative of a chiral nitrogen center.

Modular synthesis of β-turn benzotriazepinone mimics has been expanded through diversification of the *i*+3 position substituent by novel alkylation chemistry which has respectively provided amino acid **1** and benzophenone **2** for applications in peptide synthesis and photoaffinity labeling.

Acknowledgments

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