Design, Combinatorial Library Synthesis and Biological Evaluation of Nonpeptide Scaffold for Beta Turns

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The beta-turn has been implicated as an important conformation for biological recognition of peptides or proteins. We adapted the concept of general Cα atom positioning from the cluster analysis and recombination of each ideal beta-turn conformation pattern by Garland and Dean (J. Computer-Aided Molecular Design, 1999, 13, 469) as one strategy of designing non-peptide beta-turn scaffolds. Herein, the Cα positions of spiro-hydantoinylquinoline and tetrahydro-1,4-benzodiazepin-2-one scaffold were analyzed after the calculation of low energy conformer using a semi-empirical protocol. The synthesis of various synthons of 7'-hydroxy-2',3'-dihydro-1'H,2H,5H-spiro[imidazolidine-4,4'-quinoline]-2,5-dione with the introduction of several mimics of amino acid side-chains were developed, and the strategy was exemplified by derivatives that show agonist activity for the somatostatin type 2 receptor. For a combinatorial library synthesis, three points of corresponding Cα carbons for diverse substitutions in the benzodiazepine scaffold were designated and an efficient solid phase synthesis of the peptidomimetic library was developed. The scaffold itself was synthesized in solution phase starting from 4-hydroxy-2-nitro-benzoic acid and loaded to the PL-FDMP resin with high efficiency of reductive amination. Various building blocks for the derivatizations of 7-hydroxyl and N-1 amide nitrogen could be introduced as selective alkylation processes. Cleavage, parallel column chromatography and NMR analysis of 64 final compounds confirmed the feasibility of this peptidomimetic library synthesis.