In this work the synthesis, conformational analysis and receptor docking of several 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-one (Aba) derivatives is discussed. These compounds are conformationally restricted phenylalanine analogs. Much effort has already been devoted to the design and synthesis of small peptide mimetics, especially mimetics of turn structures, because it has been shown that these compounds can have interesting biological activities. Conformational analysis by NMR spectroscopy and molecular modelling of the Ac-Xxx-Gly/β-Ala-NHMe (with Xxx = erythro-(4S*,5S*)-Me-Aba, threo-(4S*,5R*)-Me-Aba, 4(R,S)-Me-Aba, (S)-Aba, (S)-Abaw[CH2-NH]) pseudotetrapeptide models revealed that α-substitution of the Aba ring can orient the exocyclic groups favorably for turn formation, whereas C-1 or C-5 substitution does not. The synthesized Ac-(S)-Aba-β-Ala-NHMe derivative did not have turn inducing properties, whereas the attempt to influence the ring conformation of the 1,2,4,5-tetrahydro-4-amino-2-benzazepin-3-one scaffold by the reduction of the lactam amide was successful.

In addition the several conformationally restricted N-terminal tetrapeptide analogs of dermorphin (H-Tyr-D-Ala-Phe-Gly-Tyr-Pro-Ser-NH2) using solid-phase peptide synthesis SPPS (-CONH2 C-terminus) or synthesis in solution (-COOH C-terminus) is presented. The biological affinities and activities of the compounds were evaluated. It was observed that all of the synthesized peptides possessed higher affinity, in some cases in the subnanomolar range, for OPRM than for OPRD. Moreover, automated docking of several 4-amino-tetrahydro-2-benzazepin-3-one constrained peptide mimetics in OPRM and OPRD homology models was performed to explain experimental results of ligand-receptor interactions. The predicted selectivities were in good agreement with the experimental binding selectivities, with a few exceptions. Moreover, it was shown that when there was a factor >10 in the selectivity, it is possible that only a binding pose was found in the receptor for which the ligand had the highest affinity.