THE MOST LIKELY BINDING CONFORMATION AND 3D STRUCTURE OF THE BINDING POCKET FOR BENZOXAZINE OXYTOCIN ANTAGONISTS

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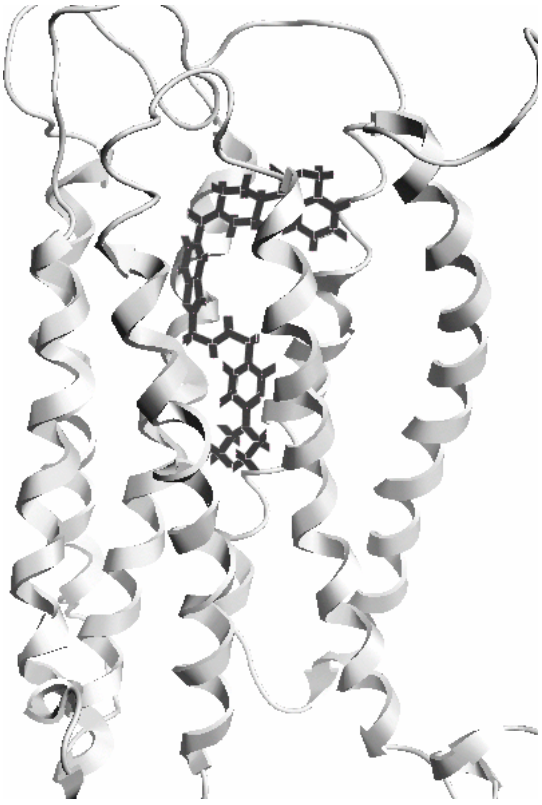
Molecular docking and 3D-QSAR studies were performed to determine the binding mode for a series of benzoxazine oxytocin antagonists taken from the literature [1,2]. Structural hypotheses were generated by docking the most active compound to the rigid receptor by means of AutoDock 3.05. The cluster analysis yielded 7 possible binding conformations.

These structures were refined by using constrained simulated annealing, and the further ligands were aligned in the refined receptor by molecular docking. A good correlation was found between the estimated ΔG_{bind} and the pK_i values for complex **F**. The Connolly-surface analysis, CoMFA and CoMSIA models ($q^2_{CoMFA} = 0.653$, $q^2_{CoMSIA} = 0.630$ and $r^2_{pred,CoMFA} = 0.852$, $r^2_{pred,CoMSIA} = 0.815$) confirmed the scoring function results. The structural features of the receptor-ligand complex and the CoMFA and CoMSIA fields are in closely connected. These results suggest that receptor-ligand complex **F** is the most likely binding hypothesis for the studied benzoxazine analogs.



[1] Wyatt, P. G., Allen, M. J., Chilcott, J., Foster, A., Livermore, D. G., Mordaunt, J. E., Scicinski, J., Woollard, P., Bioorg. Med. Chem. Lett. 12 (2002) 1399.

[2] Wyatt, P. G., Allen, M. J., Chilcott, J., Gardner, C. J., Livermore, D. G., Mordaunt, J. E., Nerozzi, F., Patel, M., Perren, M.J., Weingarten, G. G., Shabbir, S., Wollard, P. M., Zhou, P., Bioorg. Med. Chem. Lett. 12 (2002) 1405.