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Homology Modelling as an Aid in Rational Synthesis of Nonclassical Cannabinoids.

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In absence of the crystal structure of cannabinoid receptors (CB_1 and CB_2), molecular modelling studies become one of the best sources of structural information on the active site. Providing in-silico predictions on the receptors' structure may facilitate the development of new ligands. In spite of numerous computational studies on cannabinoid ligand binding modes, models constructed so far do not give enough attention to nonclassical cannabinoids (such as CP-55,940).

Our main focus in this work is on constructing a reliable model for nonclassical cannabinoids affinity studies. Homology models of CB_1 and CB_2 based on bovine rhodopsin crystal structure were constructed and evaluated using high-affinity prototype ligands. Modelling involved constructing 7 TM helices, which are the core of the protein and can be modelled reliably, automated docking and further iterative improvements based on torsional restraints imposed on amino acid side chains and pharmacophore constraint to guide the docking procedure.

Further work is planned to examine novel GPCR X-ray structure – human β_2 adrenergic receptor, which shares higher sequence homology with both CB_1 and CB_2 than bovine rhodopsin. This might give further insight into cannabinoid receptors' structure and receptor-ligand interactions.

Thorough examination of obtained results and conclusions concerning SAR provides vital waypoints in designing novel cannabinoid receptors' agonists.

Acknowledgements: Project has been done as a part of students' practice at the Department of Medicinal Chemistry, Institute of Pharmacology, PAS, Smetna 12, 31-343 Krakow, Poland.