DESIGN AND SYNTHESIS OF AMINERGIC GPCR's LIGANDS

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Streszczenie: GPCR's (G-protein coupled receptors, 7-transmembrane domain receptors) constitute the largest by number family of cell surface receptors. GPCR's are involved in etiology of numerous diseases thus comprise over 40% of drug targets [Nichols et al., 2008]. Serotonin (5-HT), one of the evolutionary oldest neurotransmitters, plays a variety of physiological roles including developmental, cardiovascular, gastrointestinal, and endocrine function, sensory perception, behaviors such as aggression, appetite, sex, sleep, mood, cognition, and memory. 5-HT_6 receptor has been proposed as a target for Alzheimer's Disease therapheutics [Holenz et al., 2006]. We have developed two series of 5-HT_6 ligands. Serie 1 consists of 40 compounds, 38 of which exhibit very high binding affinities and excellent selectivities over 5-HT_{1A}, 5-HT_{2A}, 5-HT_7 and D_2 receptors. Additional tests performed on chosen derivatives have shown low risk of genotoxicity, fair metabolic stability, lack of hERG binding and good selectivities over a broad range of CNS targets. Serie 2, consisting of 62 compounds, has stemed out from a known 5-HT_{2A}R ligand series (lead compound 25I-NBOMe) with additional 5-HT_6R component [ChEMBL, 2015]. A non-classical bioisosteric substitution led to compounds with moderate binding affinities and selectivities toward 5-HT_6R. Novel, selective 5-HT_{1A}R hit compounds were found within serie 2.

Literatura:

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