SYNTHESIS AND SAR STUDIES OF 1,2,3,4-TETRAHYDRO-β-CARBOLINE DERIVATIVES AS NEW 5-HT_7/5-HT_{1A} RECEPTOR LIGANDS

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Since its discovery in 1993, the 5-HT_7 receptor is gaining increasing interest as a potential drug target. Studies utilizing recently developed selective antagonists revealed that 5-HT_7 receptors play a role in thermoregulation, learning and memory, hippocampal activity, sleep, circadian rhythms and mood. Due to a relatively limited number of papers describing structure-activity relationship (SAR) studies of 5-HT_7 receptor ligands further research in this field is of particular interest.

It is known that pharmacophoric arylpiperazine fragment is well recognized by 5-HT_{1A}, 5-HT_{2A} as well as 5-HT_7 receptors. Indeed, 1-(2-methoxyphenyl)piperazine (oMPP) derivatives were among the most active 5-HT_7 receptor ligands identified by the screening of our compounds library. In the structure of a few selected compounds oMPP fragment was replaced with a 1,2,3,4-tetrahydroisoquinoline, 1,2,3,4-tetrahydro-β-carboline (THBC) or 9-methylcarbamoylmethyl-THBC moiety. The impact of the applied structural modifications on the 5-HT_7 affinity and selectivity for 5-HT_{1A} receptor is discussed. For three selected compounds their functional profile, at both receptors, was determined in electrophysiological experiments. The extracelelural recording of epileptiform activity of hippcocampal CA3 neurons was used. To induce that activity the brain slices were perfused with physiological salt devoid of magesium ions, and the frequency of bursting events was the measured parameter.

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