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Synthesis and evaluation of a new indole-based series as non-basic 5-HT6 receptor ligands

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The majority of known 5-HT_6R ligands, like endogenous agonist – serotonin, possess positively charged at physiological pH basic nitrogen atom, which is considered to be necessary for effective interaction with the receptor. However, in last years, progressively grow new generations of 5-HT_6R ligands without a protonable nitrogen atom. The development of such molecules with novel, alternative binding mode, follows from the possibility of improving the pharmacokinetic properties of the known active compounds.[1] The 5-HT_6R ligands with reduced basicity developed so far revealed excellent selectivity over other monoaminergic GPCRs and low hERG affinity. The mechanism of a non-basic ligand-receptor interaction has been studied and some hypotheses were formulated but the phenomenon is still unclear.[2-4]

As a continuation of our investigations on the non-basic 5-HT_6R ligands, the new series of compounds has been synthesized based on structure of the two selected ligands from the previously developed series with 1-(phenylsulfonyl)-1H-indole fragment. The 5-HT_6, 5-HT_{1A}, 5-HT_{2A}, 5-HT_7 and D_2 receptor affinities for all the synthesized compounds were assessed in radioligand displacement experiments. The structure-affinity relationships and the results of molecular modelling experiments are discussed.

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