AN ANALYSIS OF A NON-BASIC 5-HT$_6$R LIGANDS BINDING MODE

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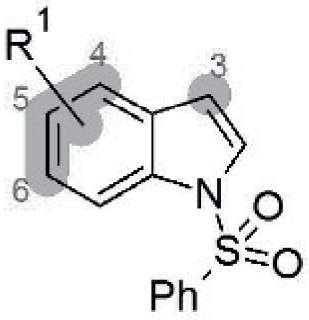
The subtype six serotonin receptor (5-HT$_6$) is a seven transmembrane receptor coupled to G$_s$ and is positively coupled to adenylyl cyclase. It is located mostly in the limbic and extrapyramidal areas of the brain such as: olfactory tubercle, cerebral cortex (frontal and entorhinal regions), nucleus accumbens, striatum, caudate nucleus, hippocampus, and the molecular layer of the cerebellum. Localization of the 5-HT$_6$ receptor suggests its role primarily in consolidation of short and long-term memory and cognition.[1] This statement was confirmed by numerous *in vivo* studies, which additionally showed that blockade of 5-HT$_6$R increases cognitive functions.[2,3]

Several thousands of the 5-HT$_6$R ligands have been obtained so far, however the emergence of non-basic compounds exhibiting high affinity toward 5-HT$_6$R caused a common binding mode (protonable nitrogen – hydrophobic core – dual hydrogen bond acceptor – aromatic moiety) questionable.[4] To investigate this matter we designed a series of indole-based non-basic analogues (Fig. 1.) and evaluated their binding affinity towards the 5-HT$_6$R. The most active non-basic ligand, with 4-pirydine at C6 position of indole, exhibited K_i = 38 nM. Its analogues substituted at C3, C4 and C5 positions, were 3- to 40-fold less active. Surprisingly, analogues with *N* -Ac-piperazine substituted at C3 and C6 positions exhibited K_i = 97 nM, whereas compounds substituted at C4 and C5 were 7- to 50-fold less active. Molecular modeling studies proposed a very interesting explanation of the observed structure-activity relationships.



R^1 = H, piperazine, N-Ac-piperazine, N-(2,2,2-trifluoroetyl)-piperazine, piperidine, N,N-dimethylamine, phenyl, 4-pirydynyl

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References

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