NEW PERSPECTIVES IN SEROTONERGIC SIGNAL TRANSDUCTION STUDIES. 3-(1-ALKYL-1H-IMIDAZOL-5-YL)-1H-INDOLES, POWERFUL TOOLS TO STUDY THE 5-HT7 RECEPTOR FUNCTION.

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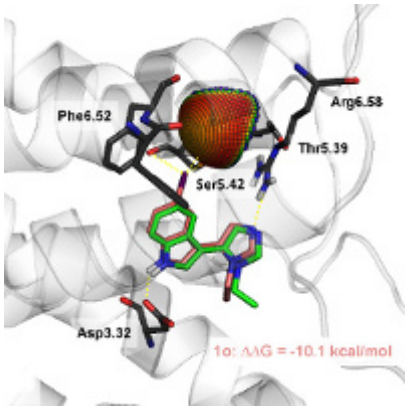
The serotonin system has been the subject of intensive studies since the discovery of serotonin in 1937 and LSD in 1943. It was believed, that abnormalities of the serotonin system underlay certain neurological conditions such as schizophrenia and depression. These hypotheses, while partially true, have not yielded any breakthrough in the CNS diseases treatment since the discovery of antipsychotics and SSRI type antidepressants. Despite great efforts, the serotonin receptors are still underexplored, mainly due to the lack of appropriate methods and tools. Many of the serotonin receptor subtypes lack any selective agonists which makes it rather difficult to study their active conformation.
New areas in GPCR research such as the studies of biased agonism and receptor oligomerisation as well as the emerging crystal structures of the receptors implicate that novel serotonergic therapeutics are yet to come.
New perspectives in serotonergic transduction studies arise with the discovery of low-basicity serotonin receptor agonists. An example of such compounds is the series of 3-(1-alkyl-1*H*-imidazol-5-yl)-1*H*-indoles, 5-HT$_7$ ligands, which are notably one of the very few known examples of low-basicity aminergic receptor agonists. The compounds were synthesized concisely using van Leusen multi-component protocol. A distinctive mode of action renders the compounds extremely selective, while preserving the full agonist function and high water solubility.



The most potent compounds within the series exhibit 2≤K_i≤30 nM as well as high efficacy as agonists, excellent selectivity over related CNS targets and high metabolic stability. 3-(1-ethyl-1*H*-imidazol-5-yl)-5-iodo-1*H*-indole K_i = 6 nM exhibits perfect pharmacokinetic profile, i.e. rapid absorption into the brain with very high peak concentrations. The compounds were found active in the NOR assay conducted on mice. The compounds fulfill most of the requirements needed for a PET radioligand as well as molecular probes for electrophysiology, behavioural assays and signal transduction studies.

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References

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