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Searching for the 5-HT$_7$ receptor ligands in the series of new 1,2,3,4-tetrahydroisoquinolines with imide fragment

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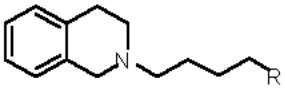
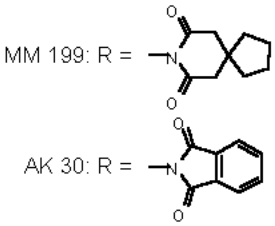
1,2,3,4-tetrahydroisoqunolines are of great importance to many different biological targets [1] and are frequently used as tool compounds to investigate the ligand–serotonergic receptor interactions [2,3]. The screening of our library of tetrahydroisoquinoline derivatives for 5-HT$_7$ receptor affinity led to the identification of MM 199 (tetrahydroisoquinoline analog of buspirone) and AK 30 (tetrahydroisoquinoline analog of NAN-190) having good 5-HT$_7$ receptor affinity.





To continue our studies on development of potent and selective 5-HT$_7$ receptor ligands we designed and synthesized a series of MM 199 and AK 30 analogs with modified tetrahydroisoquinoline fragment. We studied the effect of the introduction of methyl and benzyl substituent into the 2 position of amine moiety or spacer elongation on 5-HT$_7$ receptor affinity. Moreover, the structural variations included also changes of terminal imide fragments. The affinity for serotonergic receptor subtypes 5-HT$_7$ and 5-HT$_{1A}$ were determined and some structure–affinity relationships are discussed.

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Synthesis and molecular modeling of 1,2,3,4-tetrahydroisoquinoline-based arylsulfonamides as potential 5-HT$_7$ receptor ligands

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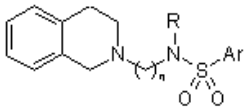
The 5-HT$_7$ receptor is the latest identified serotonin (5-hydroxytryptamine, 5-HT) receptor subtype. The brain distribution of 5-HT$_7$ receptors suggests their significant role in many mental diseases [1]. Thus, the novel and selective 5-HT$_7$ receptor ligands which may have potential therapeutic implications are a putative targets for novel drug discovery [2[.

Here we report the synthesis of a series of 1,2,3,4-tetrahydroisoquinolines with mono- or disubstituted arylsulfonamide moiety. The structure of new compounds was confirmed by ^{1}H NMR spectra as well as by C, H, N analysis. For all compounds the 5-HT$_7$ receptor affinity was determined and some structure-affinity relationships are discussed.



n = 2 - 4
R = H, $(CH_2)_2$-Y, $(CH_2)_3$-Y
Ar = phenyl, 1-naphthyl, 2-naphthyl

Molecular modeling techniques were used to rationalize the structure-activity relationships. The studied compounds were docked to the homology model of 5-HT$_7$ receptor and the binding modes were described.

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Uridine derivatives of 1-thioglycosides as analogs of glycosyltransferases natural substrates

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Complex oligosaccharides present in different classes of glycoconjugates are involved in numerous cell-cell recognition and communication processes. They are also responsible for intercellular adhesion in inflammation, bacterial or viral infection and activation of the immunity system. Formation of glycosidic linkage in biosynthesis of oligosaccharides usually occurs under action of glycosyltransferases (GTs). They catalyze sugar-transfer reaction in a regio- and stereospecific manner. Inhibition of GTs leads to the modulation of oligosaccharide biosynthesis and enables us to study their biological functions. Therefore some GTs inhibitors might be of therapeutic interest. GTs inhibitors are generally designed based on analogies between