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Long-Chain Arylpiperazine Derivatives with Cyclic Amino Acid Amide Fragments as Potential 5-HT$_7$ Receptor Ligands.

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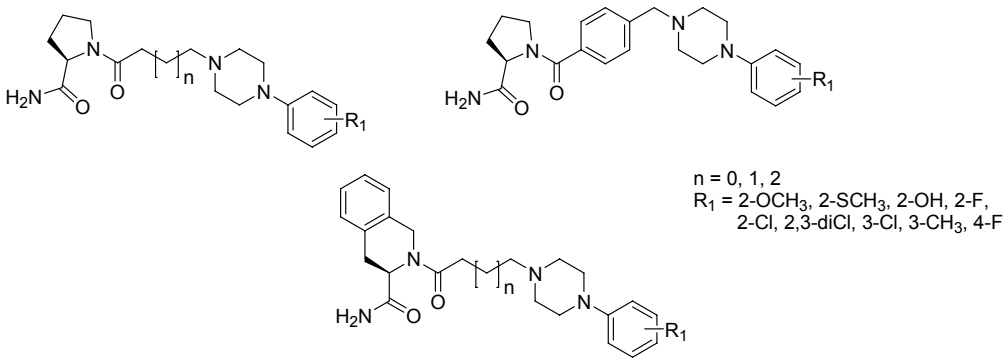
Recently, the 5-HT$_7$ receptor (5-HT$_7$R) has emerged as a new target with a potential for the treatment of psychiatric disorders. It was evidenced that the antidepressant-like effects of well-known atypical antipsychotics amisulpride and aripiprazole are mediated by 5-HT$_7$R antagonism [1]. More recently, it was shown that the 5-HT$_7$Rs may significantly influence cognitive dysfunction and therefore represent a potential therapeutic target for the treatment of memory dysfunction in cognitive disorders (Alzheimer's disease, age-related decline) [2].
As a part of our efforts in identifying selective 5-HT$_7$ receptor ligands with arylpiperazine structure we designed and a series of LCAPs containing amino acid amide fragments (pyrrolidine-2-carboxamide, 1,2,3,4-tetrahydroisoquinoline-3-carboxamide). Herein we present our initial data on design, solid-phase synthesis and biological evaluation of a 48 member library.



Selected library representatives displayed high-to low affinity for 5-HT$_{1A}$ (K_i = 0.2–6307 nM), 5-HT$_7$ (K_i = 18–3134 nM), and D$_2$ (K_i = 25–2892 nM) receptors. Herein, we examine an influence of position and character of a series of electronic and polar substituents and discuss on structural features determining 5-HT$_{1A}$ and 5-HT$_7$ receptor affinity and selectivity.

[1] Leopoldo M., *et al.*: *Pharmacol. Ther*. **129** (2011), 120-148.
[2] Matthys A., *et al.*: *Mol. Neurobiol*. **43** (2011), 228–253.

This study was partly supported by the Polish Ministry of Science and Higher Education (MNiSW), Grant No. N N405 671540.