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Aryl-containing compounds with 1,3,5-triazine core as a new grateful family of serotonin 5-HT$_6$ receptor agents

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The serotonin 5-HT$_6$ receptor (5-HT$_6$R), one of a younger member of serotonin receptors' family, was discovered almost 25 years ago. Due a special location in CNS, the 5-HT$_6$R is able to regulate the balance between excitatory and inhibitory signaling [1]. Results of pre-clinical data indicate a potential usage of 5-HT$_6$R ligands in the treatment of cognitive dysfunctions associated with Alzheimer's disease (AD) and schizophrenia, obesity and feeding behavior impairments and/or mood disorders [1, 2]. Various research teams have been focused on search for both 5-HT$_6$R agonists and antagonists. However, no selective 5-HT$_6$ agent has reached pharmacological market to date. Thus, the search for new 5-HT$_6$R agents is still a challenge for medicinal chemistry. In this context, we have explored a new series of 1,3,5-triazine derivatives that provided three different lead structures (Fig.1) [3].

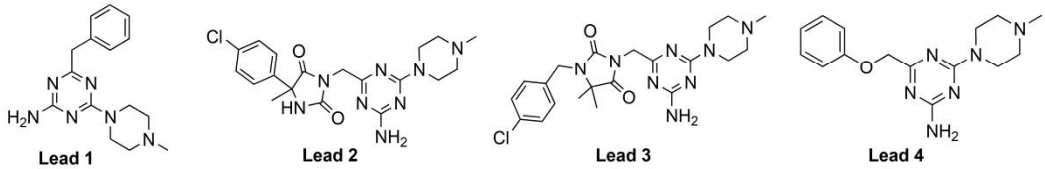

Fig.1

Parallel modifications of the leads provided a series of active 5-HT$_6$R agents, with Ki<5nM for the best ones. The compounds displayed antagonistic action in functional assays, antidepressant, procognitive and anti-obesity properties *in vivo* as well as profitable CNS-drugability. SAR analysis, supported by docking studies, allowed to explain the role of both, aromatic moiety and linker, for the pharmacological action observed.

[1] A. Wesołowska, *et al*,. Int Rev Neurobiol, 2011, 96, 49-71
[2] K. Hirano,. *et al*., Life Sci 2009, 84, 558-62
[3] D. Łażewska,. *et al.* Eur J Med Chem 2017,135, 117-124

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