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The structure-selectivity relationship studies for hydantoin-derived 5-HT$_7$R ligands

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An achievement of high selectivity among GPCR ligands is a huge challenge. This problem especially concerns structures containing arylpiperazine moiety, which besides strong binding to desired protein, are also prone to interact with more than one receptor. This work is focused on searching for selective 5-HT$_7$R ligand among arylpiperazine hydantoin derivatives (Fig. 1). The choice of serotoninergic 5-HT$_7$R as a target is a consequence of recent studies which underline that regulation of this protein function may be essential in therapy of CNS disorders (e.g. depression, schizophrenia, anxiety).

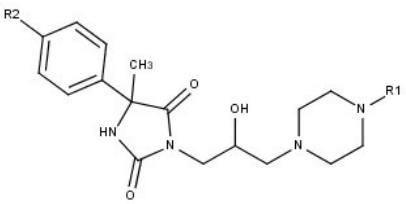

Fig. 1

To obtain the best results, organic synthesis was preceded by molecular modeling - selection of structures to prepare was performed by using following criteria: ligands position in docking rankings, potential selectivity evaluated in machine learning and synthesis difficulty level. As a consequence, the above-mentioned group of compounds which shows high activity to 5-HT$_7$R (3 nm<Ki<79nm) and also selectivity regards to 5-HT$_{1A}$R (23-71-fold) and D$_2$R (32-238-fold) has been synthesized.

[1] Handzlik, J., et al., Eur.J.Med.Chem, 2014, *78*, 324-339
[2] M. Leopoldo et al., Pharmacol. Ther. 2011, *129*, 120-148.

Acknowledgements

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