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HYDANTOIN DERIVATIVES AS SELECTIVE SEROTONIN 5-HT$_7$ RECEPTOR LIGANDS

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Recent lines of evidence indicates relevant role of 5-HT$_7$ receptor in thermoregulation process, memory and learning, hormonal regulation and also in hippocampus activity, circadian rhythm and mechanism of depression. Already synthesized ligands of this receptor, despite the high affinity, cause side effects as a consequence of lack of selectivity, which is still very challenging to achieve among GPCRs [1]. Our studies allowed to find first selective 5-HT$_7$R ligand among aminoalkyl derivatives of hydantoin [2]. Although the structure contains arylpiperazine fragment which is known to interact with many GPCRs, putatively geometry of hydantoin is relevant to achieve selectivity. However, obtained compound was an orphan, that is why synthesis of its analogues was vital to identify structural fragments which are responsible for selectivity with simultaneous maintaining high affinity to 5-HT$_7$. For this moment, about 20 new compounds have been obtained. Their general structure is presented in Fig.1:

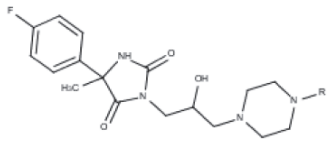

Fig. 1

The new compounds were synthesized in three-step pathway (Bucherer-Berg condensation, Mitsunobu reaction, condensation using microwave irradiation). Among this group of compounds, there are highly active compounds (3 nm < K_i < 234 nm). It turned up that when R-group is biphenylmethyl moiety, the highest selectivity regards to 5-HT$_{1A}$ is observed, moreover all the synthesized derivatives show selectivity regards to D_2R. Organic synthesis is supported with molecular modeling techniques: homology modeling, fit induced docking and machine learning, which allow us to study protein-ligand interactions and predict selectivity. Our studies lead to choose new selective 5-HT$_7$ ligand among hydantoin derivatives, which will be ready for biofunctional and *in vivo* studies. It may have significant meaning in future CNS diseases therapy. Partly supported by Polish program K/ZDS/003323.

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References:

1.) M. Leopoldo et al. , Pharmacol. Ther. **2011**, *129*, 120-148.

2.) Handzlik, J., et al., Eur.J.Med.Chem, **2014**, *78*, 324-339