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Modifications of phenyl ring of 5-methyl-5-phenylhydantoin derivatives in search for selective 5-HT$_7$ agents with antidepressant action

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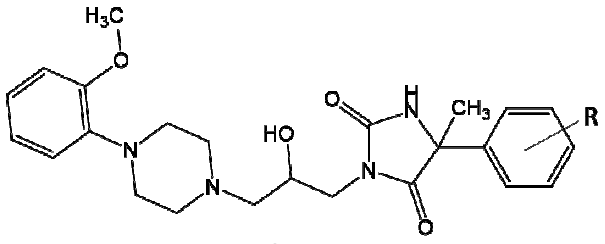
According to recent literature, serotoninergic 5-HT$_7$ receptors seem to be reasonable therapeutic target for treatment of CNS disorders such as schizophrenia, depression, migraine [1]. Our previous studies were focused on selection of the best substituent on piperazine moiety (Fig. 1) and resulted with synthesis of 14 novel 5-HT$_7$ antagonists with affinity (*Ki*) range from 3 nM to 79 nM [1,2].



R= H, F, Cl, Br, CH_3, OCH_3
Fig. 1

The second step was to find the most profitable substituent and its position on phenyl ring in position 5 of hydantoin (Fig. 1), which is presented within this work. Crystallographic analysis has been performed for one representative compound from the series (KKB23). Synthesized derivatives showed high to moderate affinity to 5-HT$_7$ (6nM<*K*i<94nm) in radioligand binding assays. Two of them (compounds KKB24 and KKB28) were evaluated in behavioral tests to check potential antidepressant activity. Both compounds reduce immobility time in forced swim test on mice.

[1] Handzlik et al. *Eur. J. Med. Chem*. 78 (2014) 324–339
[2] Kucwaj-Brysz et al. *Eur. J. Med. Chem*. 112 (2016) 258-269

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