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SEARCH FOR 5-HT$_6$ RECEPTOR AGENTS AMONG TRIAZINE DERIVATIVES OF HYDANTOIN

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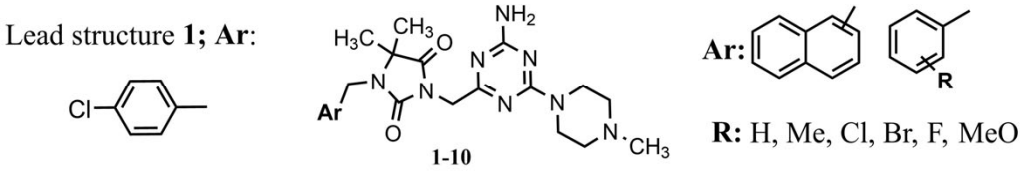
The 5-HT$_6$ receptors are a relatively new subgroup of serotonin receptors that are quite different from other members. The significant interest in 5-HT$_6$ receptors is related to the therapeutic ability of their ligands as potential anti-dementia, antipsychotic, antidepressant or anti-obese drugs.[1] Several families of compounds displaying action on 5-HT$_6$R found previously allowed to postulate pharmacophore features.[2] Reviewing the library of our compounds, we stumbled on two hydantoin 1,3,5-triazine derivatives that display some features corresponding to those of the pharmacophore of the 5-HT$_6$R ligand and we decided to evaluate their affinities for 5-HT$_6$R in the radioligand binding assay.The compounds differed in the co-position of both, triazine and benzyl moieties, in respect to the hydantoin core. Thus, the compound with 1,3,5-triazine at position 3 of hydantoin and benzyl at position 1 (**1**, Figure) had nanomolar 5-HT$_6$R affinity, whereas the compound with triazine at 1 and the benzyl substitution at position 3 had weak micromolar activity.



Thus, the compound **1** was selected as a lead structure for further modifications to search for new 5-HT$_6$R agents **2**-**10** (Figure). The new compounds were obtained within 3-step synthesis, including: (i) an intruduction of ester at position 3, (ii) an alkylation at position 1, and (iii) cyclic condensations with biguanide to give 1,3,5-triazine moiety. The compounds were examined on their affinities to 5-HT$_6$R in the radioligand binding assay. Docking to the homology model of 5-HT$_6$R was performed. The best compounds displayed significant affinities for the serotonin 5-HT$_6$R (K_i < 200 nM). Docking studies provided new interesting information about poses of the hydantoin-triazines (**1**-**10**) within the ligand binding pocket of this important serotonin receptor.

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[1] D. Marazziti, S. Baroni, F. Borsini, M. Picchetti, E. Vatteroni, V. Falaschi, M. Catena-Dell'Osso, *Curr. Med. Chem.,* **2013**, *20*, 371.
[2] B. Benhamú, M. Martín-Fontecha, H. Vázquez-Villa, L. Pardo, M.L. López-Rodríguez, *J. Med. Chem.,* **2014**, *57*, 7160.