P-50

SYNTHESIS, STRUCTURE-ACTIVITY RELATIONSHIPS, AND MOLECULAR MODELING STUDIES OF NEW LONG-CHAIN CHLOROARYLPIPERAZINES DERIVATIVES AS 5-HT$_7$ AND 5-HT$_{1A}$ RECEPTOR LIGANDS

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Diversity in the variety of functions that serotonin plays in the human body is undoubtedly related to the fact that serotonin receptors have a number of connections with other neurotransmitter systems. However, the 5-HT$_{1A}$ receptors fulfill the key role because they are crucial in pathogenesis and treatment of depression and anxiety.[1-3] The research conducted in recent years has proved that the increased density of 5-HT$_7$ receptors in limbic structure of CNS may be connected with the occurrence of affective disorders.[4,5] Numerous findings in the literature prove that the active ligands of 5-HT$_7$ receptors can play a crucial therapeutic role in treating depression and insomnia.[6]
Based on our previous studies of structure activity relationships on *N*-hexyl-arylpiperazine derivatives, in this work, we synthesized a new set of long-chain arylpiperazines in order to explain whether certain structural modifications involving substitution of hydrogen in arylpiperazine by chlorine may affect the binding affinity for the 5-HT$_7$ receptors and 5-HT$_{1A}$ receptors. It is known that hexyl-2-chloroarypiperazine shows high affinity for the 5-HT$_{1A}$ receptors 5-HT$_{1A}$ (K_i = 2.67 nM[7]), therefore we have started the synthesis of ligands from a group containing this moiety. In the terminal part of these ligands, we tested phtalimide and comparative amide fragment. All ligands were prepared by a new synthetic reaction in the presence of microwave radiation. Analysis of results from *in vitro* studies shows that the most active ligands for the 5-HT$_{1A}$ receptor in the group of hexyl-phtalimides are ligands which have a substituent 2-chloroarylpiperazine group, and binding decreases in a series of 2-chloro > 3-chloro > 4-chloro > 2,3-dichloro > 3,5-dichloro arylpiperazines. However, the most active ligands for the 5-HT$_7$ have 3-chloroarylpiperazine moieties. In the case of conversion of the phtalimide on salicylamide moiety, we observed several-fold increase in the activity of both 5-HT$_{1A}$ and 5-HT$_7$. For the most active ligands, we also performed an assessment of the bioactive conformation in the receptors binding site.

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