Novel 5-HT7 receptor ligands N-terminated with quinolinesulfoamoyl moieties

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Of 14 serotonin receptors, a recently identified 5-HT7R subtype has focused considerable attention. Correlation between distribution pattern and its function in CNS, followed by identification of selective ligands allowed to outline its therapeutical potential. Moreover, it has been suggested that 5-ht7 receptor antagonism, at least in part, may account for antidepressant properties of several psychotropic drugs.1

Among several classes of 5-HT7R ligands a prominent position represent aromatic sulfonamides and sulfones connected via aliphatic spacer of different length to aryl- or alkyl-amine fragments.2 Herein, we report on solid-supported synthesis of a new series of quinolinesulfonamides and solution synthesis of some of their N-alkylated analogs, followed by their biological evaluation for 5-HT1A, 5-HT2A, 5-HT6, and 5-HT7 receptors and pharmacological estimation in animal model of depression (FST, forced swim test).

The study revealed, that 5-HT7 receptor affinity benefits from increasing the distance between basic center (embedded in PHIQ) and terminal Ar group and introduction of hydrophobic fragment at the nitrogen of sulfonamide group. Compound PZ-376 was identified in vitro as a potent 5-HT7 antagonist (Ki = 13 nM, KB = 140 nM) with acceptable selectivity over other receptors tested. When evaluated in FST in mice it reduced immobility similarly to the selective 5-HT7 antagonist SB-269970.

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