N-(1,2,3,4-TETRAHYDRONAPHTHALEN-1-YL)-4-ARYL-1-PIPERAZINEALKYLAMIDES AS 5-HT$_7$ RECEPTOR AGENTS

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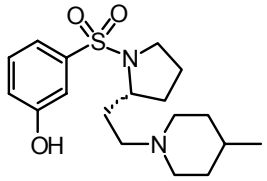
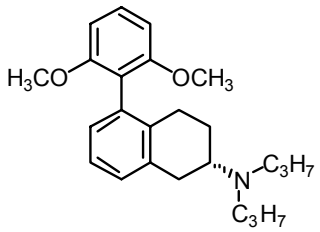
The 5-HT$_7$ receptor (5-HT$_7$R) has been found by the application of molecular cloning and it has been identified in rat, mouse, human, pig, and guinea pig. Although the biological functions of the 5-HT$_7$Rs are poorly understood, preliminary evidence suggests that it may be involved in depression, control of circadian rhythms, and relaxation of vascular smooth muscles. For these reasons the 5-HT$_7$R has become a target for the development of novel drugs. During the last decade considerable research efforts have been directed towards the identification of selective 5-HT$_7$R ligands, allowing the identification of several antagonists, such as SB-269970 (**1**) and a limited number of agonists, as compound **2**. [1]



SB-269970 (**1**)



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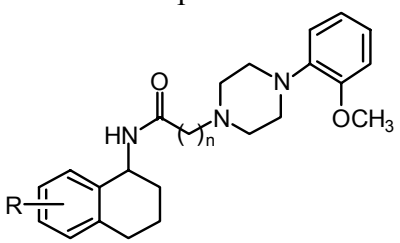
However, the reported 5-HT$_7$R agents display low potency, modest selectivity, and low metabolic stability. Therefore, the search for selectively-acting 5-HT$_7$R ligands as pharmacological tools or potential drugs is still open. In a recent paper [2], we have described the identification of a series of high affinity 5-HT$_7$R ligands based on the *N*-(1,2,3,4-tetrahydronaphthalen-1-yl)-4-aryl-1-piperazinealkylamide structure **3**. In particular, we observed that all structural modifications introduced on either the 1,2,3,4-tetrahydronaphthalenyl nucleus or on the linker between this particular group and the *N*-(2-methoxyphenyl)piperazine moiety influenced only the 5-HT$_7$R affinity and not the selectivity over 5-HT$_{1A}$ receptor. In contrast, modifications of the aryl group linked to the piperazine ring resulted in major changes in 5-HT$_7$R affinity. For this reason, we have further evaluated other substituents on the arylpiperazine moiety with the aim of modulating the activity on 5-HT$_7$ receptors of these ligands (structure **4**). The outcomes of this research will be presented.



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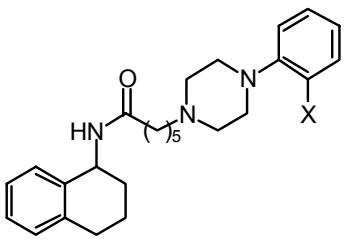

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[1] Leopoldo, M. *Curr. Med. Chem.* **2004**, *11*, 629-661.
[2] Leopoldo, M.; Berardi, F.; Colabufo, N. A.; Contino, M.; Lacivita, E.; Niso, M.; Perrone, R.; Tortorella, V. *J. Med. Chem.* **2004**, *47*, 6616-6624.