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MS5-P4 Structure analysis of arylpiperazine derivatives displaying affinity towards 5-HT_{1A} and 5-HT_7 receptors

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Serotonin (5-HT, 5-hydroxytryptamine) is one of the evolutionary oldest biogenic monoamines, which regulates various physiological functions in the human body. The serotonin receptor family was divided into 7 main classes among which, depending on the classification, at least 14 distinct classes may be distinguished. Six out of seven main classes belong to the G protein-coupled receptors (GPCRs) family. The member of the last main class, 5-HT_7 receptor, was found to be involved in regulation of temperature, circadian rhythm and proper functioning of memory. The lack of an accurate experimental structural data for most 5-HT receptor family members is a challenge in the process of designing selective and safe agonists and antagonists for individual classes. The selectivity problem is particularly important and visible in designing selective 5-HT_{1A} and 5-HT_7 ligands, because the 5-HT_7 receptor shares a high sequence similarity to 5-HT_{1A} receptor, especially in the binding pocket region.

Arylpiperazine is one of the most universal fragments found in ligands acting on various central nervous system receptors. Arylpiperazines are also a noteworthy scaffold component in 5-HT receptor ligands. Depending on the aryl part and its potential substituents, they can demonstrate diverse intrinsic activity and manifest different selectivity among the distinct 5-HT receptor classes. Substituents may variously affect the electronic features of the aromatic ring, which may result in different preferential mutual orientation of the aryl ring in regards with the piperazine moiety.

In this work, structures of selected long chain arylpiperazine derivatives are presented. Each compound contains a theophylline moiety connected to the piperazine with an alkyl linker. The crystal structure analysis is accompanied by molecular docking and structure-affinity relationship investigation.

Keywords: long chain arylpiperazines, serotonin receptors, structure-activity relationship, molecular docking