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Preliminary SAR Studies on the Serotonin 5-HT$_7$ Receptor Activity in the Group of MM-77 Derived Compounds

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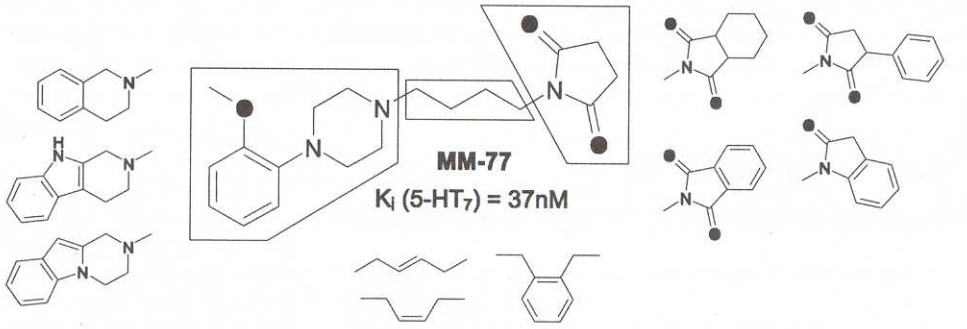
Following the emergence of new serotonin 5-HT$_7$ receptor subtype in 1993, it became clear that it plays an important role in several CNS functions and disorders i.e.: sleep, anxiety, depression and cognitive disturbances. These results indicated that development of novel agents, acting selectively at 5-HT$_7$ sites, as well as ligands which pharmacological profile include an interaction with this receptor, might be considered as a promising strategy of drug discovery process. Examination of the 5-HT$_7$ receptor revealed close similarities of its binding region shared with 5-HT$_{1A}$ subtype, and consequently many of described 5-HT$_{1A}$ ligands were found as a potent 5-HT$_7$ agents. Particularly in the group of the long chain arylpiperazines (LCAPs) a contribution of 5-HT$_7$ receptor activity has been observed. It was also confirmed by the screening of our compounds library for 5-HT$_7$ receptor affinity, where among *ortho*-methoxyphenylpiperazine (oMPP) derivatives, compounds displaying distinct potency to that binding sites were identified. Based on this results MM-77 was chosen as a lead structure for further modifications. The preliminary SAR studies concerned the modification within an amide terminus, methylene spacer and the change of oMPP fragment into isosteric: 1,2,3,4-tetrahydroizoquinoline (THIQ), 1,2,3,4-tetrahydro-β-carboline or 1,2,3,4-tetrahydropyrazino[1,2-a]indole.



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