PYRROLOQUINOLINE DERIVATIVES AS 5-HT$_6$R LIGANDS - INFLUENCE OF TYPE OF CONDENSATION ON RECEPTOR AFFINITY

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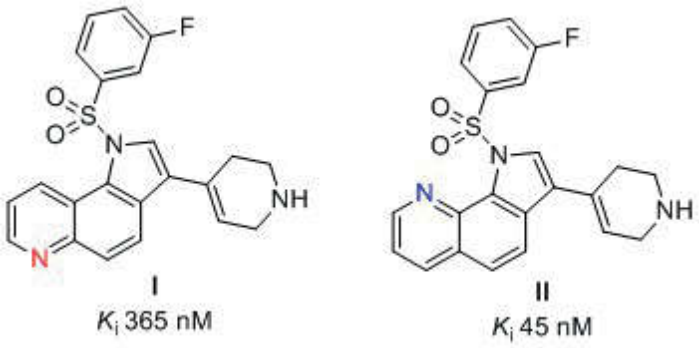
Serotonin 5-HT$_6$Rs belong to the G-protein coupled receptors superfamily and are almost exclusively localized in the central nervous system. It has been demonstrated that 5-HT$_6$Rs are engaged in the formation of neuronal circuits. Moreover, a number of preclinical and clinical studies indicate the therapeutic potential of 5-HT$_6$R modulators in the treatment of cognitive disorders associated with Alzheimer's disease.[1,2]

Pyrroloquinoline core has been widely explored as a privileged structure in medicinal chemistry, including the development of CNS acting drugs.[3] Their biological activity depends on the type of condensation and substitution pattern of the tricyclic aromatic ring system.



We have previously described the application of 1*H*-pyrrolo[3,2-*c*]quinoline scaffold for the development of 5-HT$_6$R antagonists.[4] Herein we report the design, synthesis and biological evaluation of novel 5-HT$_6$R ligands, based on 1*H*-pyrrolo[2,3-*f*]quinoline and 1*H*-pyrrolo[2,3-*h*]quinoline cores. The structural modifications comprised introduction of various substituents in the arylsulfonyl fragment in position 1 and 4-(1,2,3,6)-tetrahydropiridine in position 3 of pyrroloquinoline.

The obtained derivatives displayed high-to-moderate affinity for the 5-HT$_6$R in the radioligand binding studies (K_i = 45-711 nM). The receptor affinity of the evaluated compounds depended mainly on the type of condensation of pyrrole and quinoline rings. As revealed by molecular modeling studies, position of quinoline nitrogen atom in the planar pyrroloquinoline skeleton might affect the spatial orientation of the arylsulfonamide fragment. The possible binding mode of both pyrroloquinolines isomers is discussed.

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References

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