NOVEL 5-HT$_6$R LIGANDS IN A GROUP OF PYRROLOQUINOLINES - INFLUENCE OF TYPE OF CONDENSATION ON RECEPTOR AFFINITY

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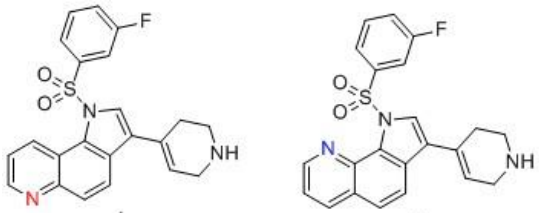
Pyrroloquinolines have been widely explored as a structural core of biologically active compounds, including anticancer, antimalarial and CNS acting agents.[1] Their biological activity depends on the type of condensation and substitution pattern of the tricyclic aromatic ring system.

We have previously described the application of 1*H*-pyrrolo[3,2-*c*]quinoline scaffold for the development of serotonin 5-HT$_6$R antagonists with potential application in the treatment of cognitive decline associated with Alzheimer's disease.[2,3]



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[3,2-*h*]quinoline cores, modified with various arylsulfonyl fragments in position 1 and 4-(1,2,3,6)-tetrahydropiridine in position 3 of pyrroloquinoline.

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 position of quinoline nitrogen atom in the planar pyrroloquinoline skeleton.

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References:

1. Yamashkin, S.A. et al. *Chem. Heterocycl. Compd*. **2001**, *37*, 1439–1460.
2. Grychowska, K. et al. ACS *Chem. Neurosci.* **2016**, *7*, 972–983.
3. Zajdel, P. et. al. WO/2015/012704.