PP18

Novel 1*H*-pyrrolo[3,2-*c*]quinoline derivatives as 5-HT$_6$ receptor antagonists with procognitive properties

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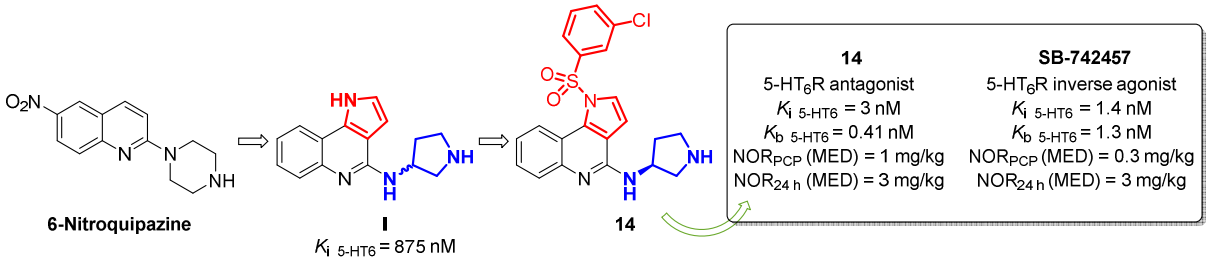
Alzheimer's disease, an irreversible neurodegenerative disorder, constitutes one of the most frequent forms of dementia worldwide. AD is characterized by progressive detoriation of cognitive functions, including memory and thinking. In the recent years 5-HT$_6$ receptor (5-HT$_6$R) has emerged as a promising molecular target for the treatment of cognitive deficits in AD.[1]

Herein we present the design, synthesis and pharmacological evaluation of novel class of 5-HT$_6$R antagonists based on 1*H*-pyrrolo[3,2-*c*]quinoline core. The study allowed for identification of compound **14** (*S*)-1-[(3-chlorophenyl)sulfonyl]-4-(pyrrolidine-3-yl-amino)-1*H*-pyrrolo[3,2-*c*]quinoline (K_i = 3nM and K_b = 0.41 nM), a more selective and potent 5-HT$_6$R antagonist than the reference compound SB-742457. Further evaluation of the 5-HT$_6$Rs constitutive activity at Gs signaling revealed that **14** behaved as a neutral antagonist, while SB-742457 was classified as an inverse agonist.[2]



Compounds **14** and SB-742457 reversed phencyclidine memory deficits and displayed procognitive properties in cognitively unimpaired animals (3 mg/kg) in NOR tasks. Additionally, compound **14** has demonstrated a higher anxiolytic effect (MED = 3 mg/kg) than SB-742457 in the Vogel test and showed similar antidepressant-like properties in 3-fold higher dose (MED = 10 mg/kg) than SB-742457 (MED = 3 mg/kg) in FST.
These results support the therapeutic potential of 5-HT$_6$R antagonists and inverse agonists in the treatment of cognitive decline and other symptoms associated with AD. More detailed biochemical studies would provide additional information about the action of 5-HT$_6$R antagonists and inverse agonists.

[1] Claeysen, S. et.al. *ACS Chem. Neurosci.* 6 (2015) 940–943.
[2] Grychowska, K. et. al. *ACS Chem. Neurosci.* 2016, DOI: 10.1021/acschemneuro.6b00090.