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Novel 1*H*-pyrrolo[3,2-*c*]quinoline derivatives as dual 5-HT_6/D_3 receptors antagonists with procognitive properties

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Cognitive impairment, which involves memory and attention disturbances, constitutes a common feature of various central nervous system disorders such as schizophrenia and Alzheimer's disease.[1] Although various procognitive drug candidates have been investigated in clinical trials for cognitive dysfunction, most of them failed to display clinically relevant effects. Recent results of advanced preclinical and clinical studies indicate the role of serotonin 5-HT_6 and dopamine D_3 receptor antagonists, in the control of cognitive functions.

We have recently described compound CPPQ ((*S*)-1-[(3-chlorophenyl)sulfonyl]-4-(pyrrolidine-3-yl-amino)-1*H*-pyrrolo[3,2-*c*]quinoline), a neutral 5-HT_6R antagonist (K_i = 3 nM, K_b = 0.41 nM). In the presented study CPPQ was used as a chemical template for the development of dual 5-HT_6/D_3 receptors antagonists.

Herein, we report chemical synthesis of novel *N*-alkylated analogs of CPPQ, their biological evaluation, followed by determination of neuroprotective properties and evaluation of procognitive properties in novel object recognition test (NOR) in rats. The study allowed for the identification of compound **16**, classified as dual 5-HT_6/D_3 receptors antagonist, which displayed neuroprotective properties against astrocyte damage with doxorubicin. Additionally, compound **16** reversed phencyclidine (PCP) induced memory deficits in NOR test in rats.

[1] Millan, M.J. *et. al. Nat. Rev. Drug Discov.* 11 (2012) 141-168
[2] Grychowska, K. *et al. ACS Chem. Neurosci* 20 (2016) 972-983

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