NOVEL 5-HT6 RECEPTOR ANTAGONISTS/D2 RECEPTOR PARTIAL AGONISTS TARGETING BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

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All dementia patients suffer from impairment of cognitive functions and up to 90% of them show also behavioral and psychological symptoms (BPSD) such as: depression, anxiety, agitation, aggression, irritability or psychosis. Those symptoms were found to be even more disturbing than cognitive decline and are the most common cause of patient's institutionalization. In view of lack of specific treatments, BPSD have been commonly treated using antipsychotic drugs, which display only partial efficacy. Moreover, they were found to exacerbate preexisting cognitive deficits, as well as cause serious cardiovascular and motor side effects, and thus are not approved for the treatment of BPSD [1]. Therefore, development of an effective and safe therapy of BPSD remains an increasing clinical and social unmet need.

Pharmacological studies revealed procognitive role of 5-HT6 receptor (5-HT6R) antagonists, and indicated their potential anxiolytic and antidepressant-like activity [2,3]. Moreover recent clinical findings confirm their utility in treatment of Alzheimer’s disease [4]. Similarly, a growing body of evidence suggests the high therapeutical potential of D2 receptor (D2R) partial agonists as both antipsychotic and antidepressant agents, with a favorable safety profile [5].

In this study we present design, synthesis and pharmacological evaluation of a series of innovative hybrid molecules acting as 5HT6R antagonists and D2R partial agonists. Based on molecular modeling studies we combined indoleamine moieties characteristic for 5-HT6 antagonists with aryloxy fragments providing D2 partial agonism [6].

A series of molecules was synthesized and characterized for affinity towards 5-HT6, D2 and M3 receptors as well as hERG channels. The most promising compounds displayed a desired profile of 5-HT6/D2 activity with only a negligible affinity for antitargets. Lead molecules were characterized in rodent models of anxiety and depression and possessed a more favourable activity than the selective 5-HT6R antagonist SB-271046. Pharmacological profile of novel indoleamine-based hybrid molecules indicates their relevance for BPSD drug discovery.