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Synthesis of novel group of multireceptoral ligands with antipsychotic and pro-cognitive properties

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First-generation antipsychotics, like e.g. haloperidol or chlorpromazine, allowed to effectively treat positive symptoms of schizophrenia and related psychotic disorders, but they also revealed high rate of side effects, e.g. extrapyramidal symptoms [1]. Discovery of second-generation antipsychotics (olanzapine, risperidone, etc.) significantly reduced the range of the observed adverse effects, but those drugs did not eliminate cognitive deficits in schizophrenia [1]. Therefore new therapeutic agents with dual effect i.e. suppression of psychotic symptoms and elimination of cognition impairment are still needed [2].

We aimed at development of effective antipsychotic agents that would also ameliorate the cognitive deficits. The consistent series of about fifty compounds was synthesized and studied *in vitro* in binding and functional assays to identify compounds with receptor profile that could provide both antipsychotic and pro-cognitive features. The most promising lead compound showed high affinity for adrenergic α_1, α_{2c}, serotoninergic 5-HT_{2A}, 5-HT_{2C}, 5-HT_6 and dopaminergic D_1, D_2, D_3 receptors; and behaved as an 5-HT_{2A}/5-HT_6/D_2 antagonist. Antipsychotic and cognitive models assessing *in vivo* activity of these compounds included locomotor activity assays and novel object recognition assays. Like other antipsychotic agents, the lead compound reversed PCP-induced hyperactivity in animals and, in addition, it demonstrated pro-cognitive actions in the novel object recognition assay.

[1] Divac N., Prostran M., Jakovcevski I., Cerovac N. *Biomed. Res. Int.* (2014) 656370
[2] Lameh J., McFarland K. et al. *Naunyn. Schmiedebergs Arch. Pharmacol.* (2012) 385(3), 313-23.

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