Abstract
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Title: Preparation and Evaluation of New Ligands Targeting Organic Cation Transporters in the Central Nervous System for the Treatment of Depression

Brain organic cation transporters (OCT2, OCT3) are polyspecific facilitated diffusion transporters that regulate aminergic tonus and have a complementary role to high-affinity monoamine transporters (serotonine transporter SERT, noradrenaline transporter NET and dopamine transporter DAT) in monoamine clearance in the brain. Their complementary characteristics compared to the high-affinity transporters (widespread distribution, broader pharmacological profile) and their involvement in mood-related functions make brain OCT relevant and original targets for the development of novel antidepressants.

H2-cyanome is a newly developed prodrug of cyanome that targets OCT. This prodrug showed promising antidepressant efficacy in a rodent model of chronic depression. Despite the positive impact of this prodrug on antidepressant efficacy, its limitation is its high affinity for α_1 adrenergic receptors that may confer potential cardiovascular side effects. The aim of this project was therefore to prepare designed hybrid derivative of cyanome and its analogues that would overcome the above-mentioned disadvantage while maintaining selectivity to brain OCT and antidepressant efficacy.

Interaction of two novel designed and synthesized compounds with brain OCT were predicted via molecular docking and scoring in BIOVIA Discovery Studio software using previously generated homology models of OCT2, OCT3 and α adrenoreceptors. TLC, NMR spectroscopy, MS and HRMS analysis were used for characterization of prepared compounds. One of these compounds was assessed for potential toxic effects in cell viability assays using a colorimetric CCK-8 assay, flow cytometry and a trypan blue exclusion test, and its antidepressant-like efficacy was evaluated in the forced swim test (FST) in mice.

The predicted virtual affinities of the designed and synthesized compounds showed high selectivity to OCT3 and α_{2C} adrenoreceptors and lack of binding at α_1 adrenoreceptors. The viability assays revealed some toxicity on the cell lines HEK-293T and CHO-K1. Gradual dose escalation, up to 3 mg/kg (i.p.) over four days in test mice showed no lethal toxicity. Acute administration of this compound at 0.2 mg/kg showed significant antidepressant-like effect in the FST, a classical test for antidepressant activity. It therefore appears to be a very promising compounds for further testing in a rodent model of chronic depression. In terms of predicted affinities, the second molecule as well appears suitable for chemical synthesis and further evaluation.