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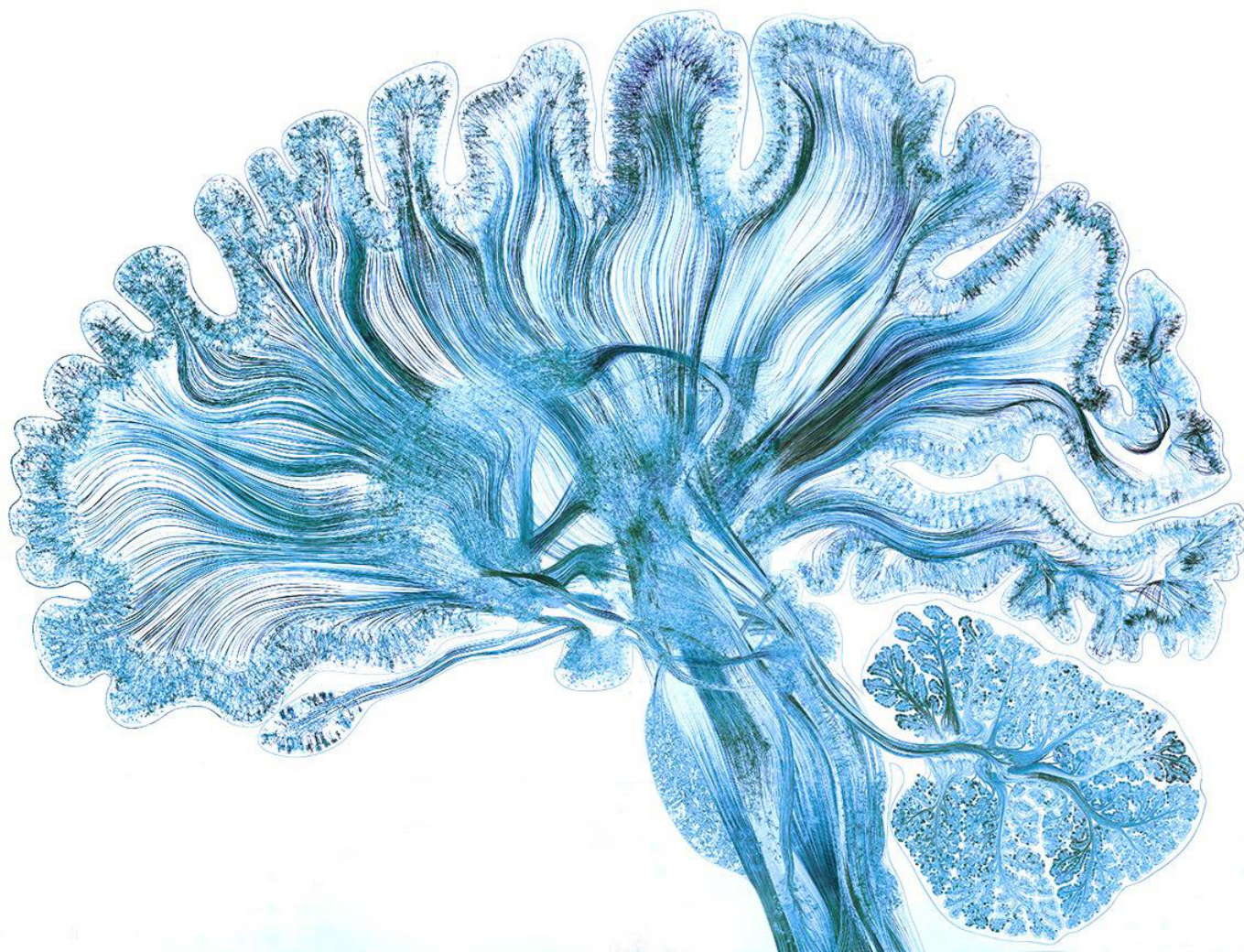
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2. Simpozijum iz biomedicine: bazična i klinička Neuronauka

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ABSTRACT BOOK

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Abnormally folded alpha-synuclein protein, dysfunctional mitochondria, increased oxidative stress and reduced dopamine neurotransmitter synthesis are a

II extremely well characterized phenomena in Parkinson's disease (PD) and are thought to be interconnected. While direct targeting of these areas has demonstrated neuroprotection *in vitro* and *in vivo*, there has been a major lack of success in clinical trials. A critical component in the failure of these clinical trials is the inability to specifically target drugs to dopamine producing neurons in the brain.

New drugs targeting the dopaminergic neurons by specific uptake through the human dopamine transporter (hDAT) could represent a viable strategy for establishing selective neuroprotection. Molecules able to increase the bioactive amount of extracellular dopamine, thereby enhancing and compensating a loss of dopaminergic neurotransmission, and to exert neuroprotective response because of their accumulation in the cytoplasm, are required.

By means of homology modeling, molecular docking and molecular dynamics simulations, we have generated 3D structure models of hDAT in complex with substrate and inhibitors. Our results clearly reveal differences in binding kinetics of these compounds to the hDAT in the open and closed conformations, critical for future drug design. The established *in silico* approach allowed the identification of three promising substrate compounds that were subsequently analyzed for their efficiency in inhibiting hDAT-dependent fluorescent substrate uptake, through *in vitro* live cell imaging experiments. Taken together, our work presents the first implementation of a combined *in silico/in vitro*-approach enabling the selection of promising dopaminergic neuron specific substrates.

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Identification of potential dual histamine H₃ receptor antagonist and serotonin reuptake inhibitors through ligand-based and structure-based approaches

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The major depressive disorder (MDD), routinely treated with selective serotonin reuptake inhibitors (SSRIs), is the second leading cause of disability worldwide. However, the treatment of MDD is complicated by high prevalence of residual symptoms connected to increased risk of relapse. Some of the most common residual symptoms are cognitive dysfunction and fatigue. Histamine H₃ receptor (H₃R) antagonists are both, pro-cognitive and wake-promoting agents. In pre-clinical study it was suggested that dual histamine H₃R antagonist and SSRI may have utility as a more efficient antidepressant therapy. The aim of this *in silico* study was identification of novel dual SSRI/H₃R antagonist using ligand-based and structure-based drug design techniques. Starting from structures and activities of known dual ligands, two GRIND-based 3D-QSAR models have been developed, SERT model ($R^2 = 0.97$; $Q^2 = 0.79$; SDEP= 0.124) and H₃R model ($R^2 = 0.86$; $Q^2 = 0.75$; SDEP= 0.184), and 3D-pharmacophores were constructed. Further, homology model of H₃R was built and refined with molecular dynamics. The hypotheses of binding modes for dual ligands were generated with molecular docking on H₃R model and X-ray structure of SERT. In the second part of this study, ligand-based and structure-based virtual screening models were generated and validated. Prospective screening of ZINC database was performed in order to extract novel chemotypes of dual ligands. Final selection of ligands was performed based on generated pharmacophore and docking models as well as predicted pharmacokinetic properties. Few novel compounds were emphasized as promising starting point for development of new classes of dual antidepressants.

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Structure and ligand based drug design strategies in the development of novel serotonin 5-HT_{2A} receptor antagonists

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The serotonin 5-HT_{2A} receptors are widely distributed throughout the central and the peripheral nervous system where they play a key role in many physiological functions. Abnormal activity of 5-HT_{2A} receptors is associated with various neurological disorders, such as depression, schizophrenia, anxiety, and Parkinson disease. In order to analyze 3D-structure of the