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Abstract

Optimization of Pharmacokinetic Compound Profile of Serotonin Receptor Ligands via Machine Learning †

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During the search for new active compounds, at first, the focus is put mainly on the provision of compound activity towards considered targets. However, at the same time, or in the subsequent stages, the compound need to be adequately profiled in terms of its physicochemistry and ADMET properties. Here, we present a tool for optimization of physicochemical and pharmacokinetic properties based on the application of machine learning tools. It considered several compound properties: solubility, metabolic stability, biological membranes permeability, hERG channels blocking, and mutagenicity. Separate models are constructed for each property and the predictive power of the models is verified on the ligands of serotonin receptor 5-HT7. The models use various fingerprints for compound representation (including interaction fingerprints in the cases, where docking to the target protein can be performed). Serotonin receptor 5-HT7 is a representative of G protein-coupled receptors – the largest and the most diverse group of proteins in the human genome. The endogenous ligand of serotonin receptor 5-HT7 (Serotonin) plays important functions in the organism, such as regulation of mood, sleep, temperature, appetite and other physiological processes and therefore, the 5-HT7R constitute important drug target for a wide range of disorders. The results obtained within the study will be used for the design of new serotonin receptor ligands with optimized physicochemical and ADMET profile.

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