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Abstract

Optimization of Metabolic Stability of Ligands of Serotonin Receptor 5-HT7 Using SHAP Values †

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There are numerous computational tools, which support the design of new potential ligands. They assist in the evaluation of potential compound activity, as well as they help in the optimization of compound physicochemical and pharmacokinetic properties. Nowadays, they are indispensable element of drug design process, as thanks to their application, both time and money can be saved. In the study, we applied methodology based on SHAP (SHapley Additive exPlanations) values to assess metabolic stability of a series of newly designed derivatives of ligands of serotonin receptor 5-HT7. This protein is a representative of G protein-coupled receptors and constitute an important drug target, mainly for the treatment of central nervous system disorders, such as depression, cognitive disorders, anxiety and Alzheimer's disease. The aim of application of SHAP values is to provide explanation of prediction by machine learning models, and to evaluate contributions of particular features. In the study, we used two key-based fingerprints for compound representation: MACCS keys and Klekota&Roth Fingerprint. At first, we evaluated compounds with known metabolic stability from the ChEMBL database. Then, using information provided by SHAP values from models constructed on known data, we selected features, which are important (according to the model) for metabolic stability. These information was used for the generation of new ligands of serotonin receptor 5-HT7 with the input constituted by known ligands of these receptor gathered in the ChEMBL database. After evaluation of their 5-HT7R activity via docking, the best compounds will undergo visual inspection and will be selected for purchasing and/or synthesis.

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