Optimization of metabolic stability of ligands of serotonin receptor 5-HT7 using SHAP values

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Background

The process of drug design and development is very complex and involves multiples stages. After detection of compounds active towards considered target, scientists must also optimize its physicochemical and pharmacokinetic properties, so as it reaches the desirable therapeutic area, it does not undergo fast decomposition and it does not produce toxic effects. In the study, we focused on metabolic stability – very important parameter influencing the compound potential to become a future drug. After entering organism, the drug undergoes a number of processes, which might lead to modification of its structure, and therefore, evaluation of metabolic stability *in silico* is very complex and difficult task.

Aim of the study

The aim of the project is to construct a web-based service for evaluation of metabolic stability of compounds with the special focus on the assessment of the structural contributions to particular predictions. It was obtained via the application of SHapley Additive exPlanations (SHAP) values. The service is available at https://metstab-shap.matinf.uj.edu.pl/

Results

The workflow of the developed methodology is presented in Figure 1. It involves preparation of the dataset on the basis of information present in the ChEMBL database, representation of compounds with the use of two substructural fingerprints: MACCSFP and Klekota&Roth Fingerprint (KRFP), development of machine learning-based predictive models, and calculation of SHAP values.

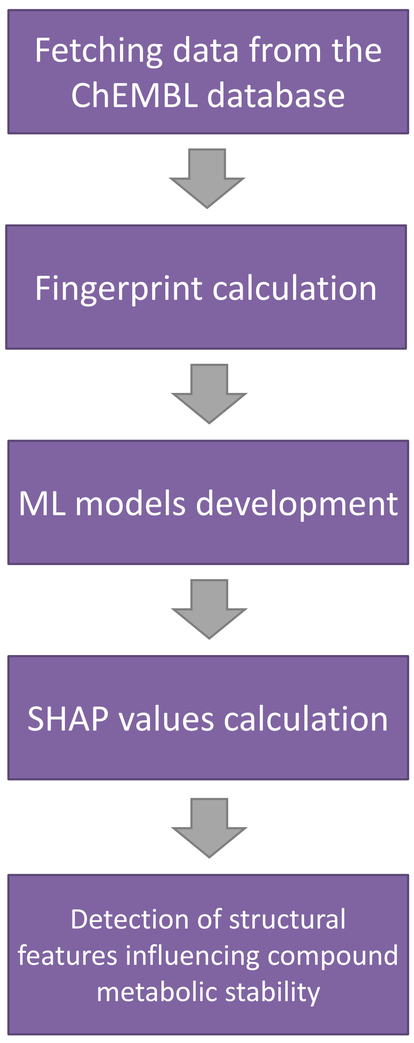


Figure 1. Scheme of the developed protocol for optimization of compound metabolic stability

The machine learning algorithms used in the study were Naive Bayes, Support Vector Machines and trees.

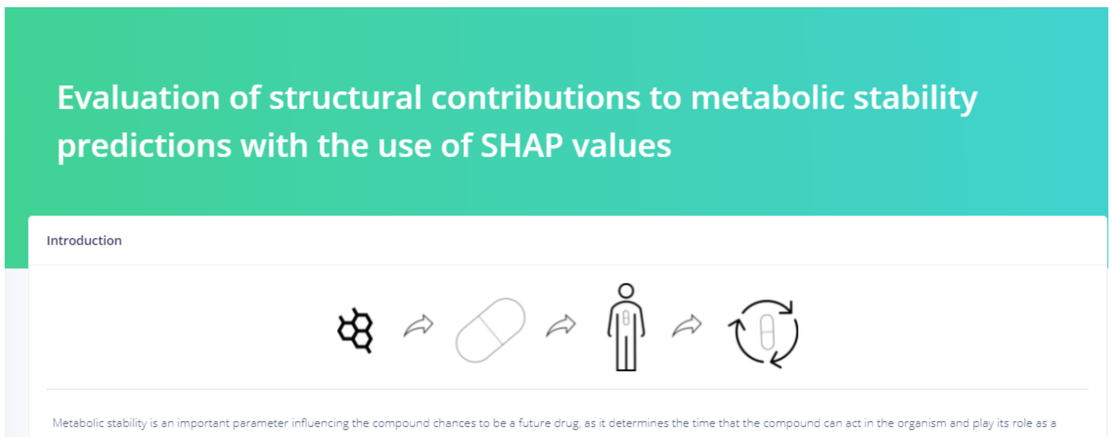
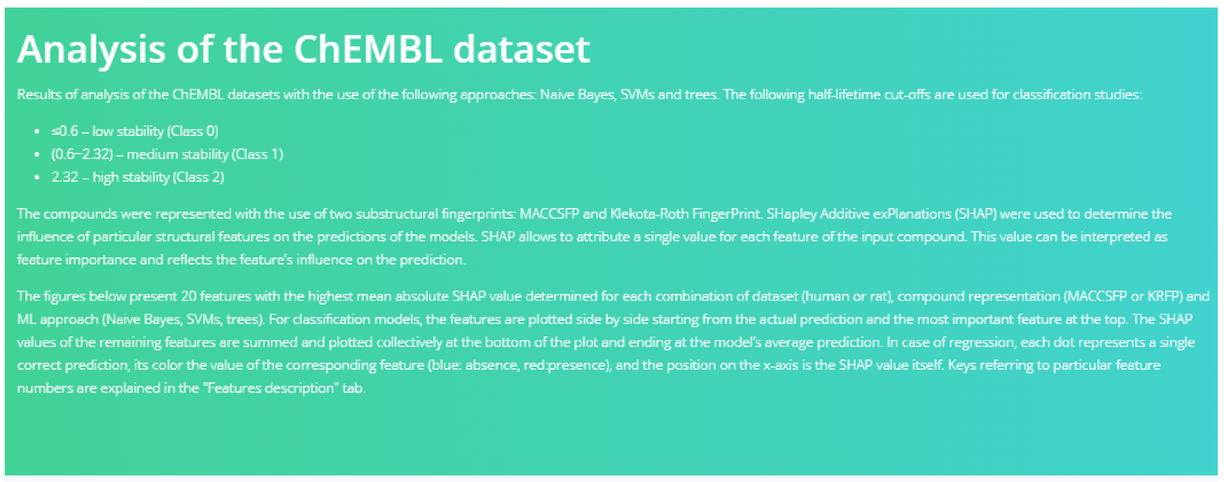
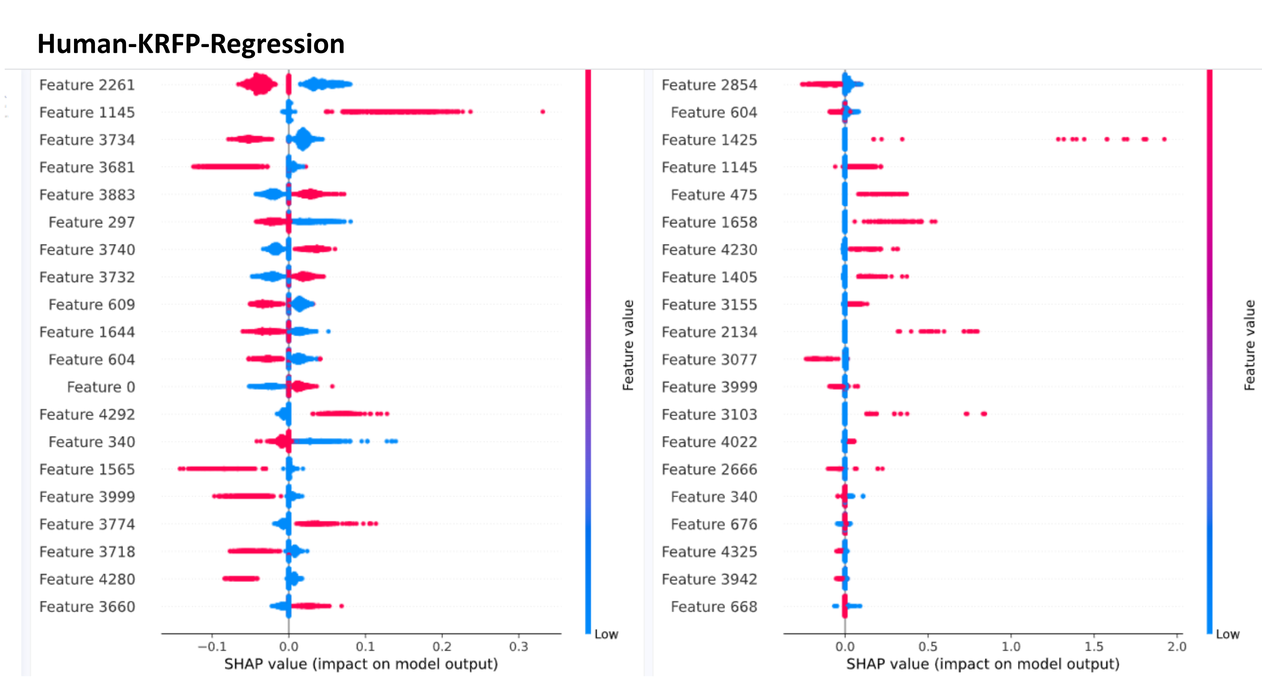
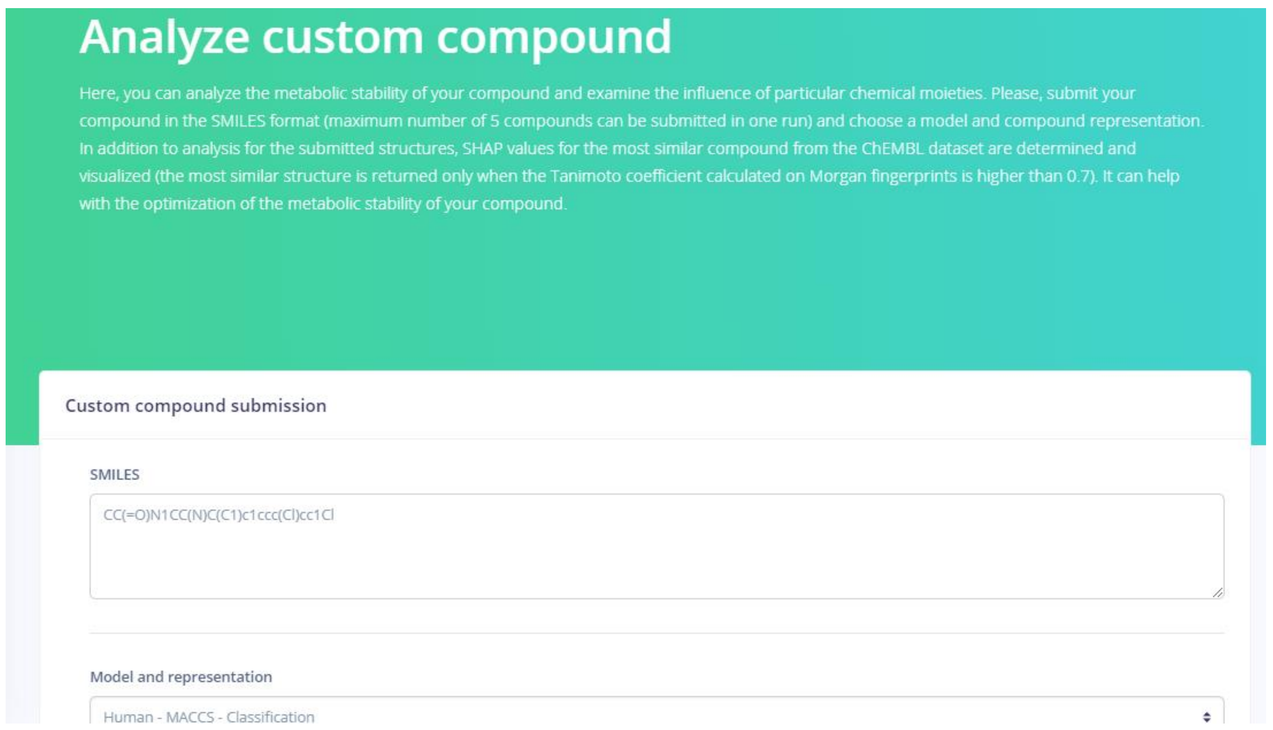


Figure 2. Screen of the main page of the prepared web service.







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