WAY2DRUG PLATFORM
LIGAND-BASED APPROACH TO DRUG REPURPOSING

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Introduction

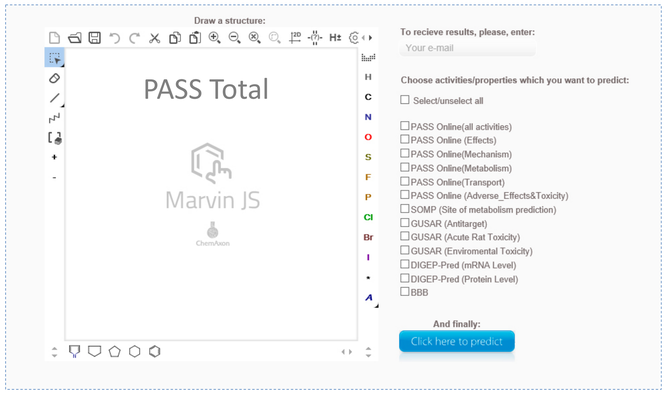
Drug repositioning has gained attention from both academia and pharmaceutical companies as an auxiliary process to conventional drug discovery. Lack of knowledge about chemical-biological interactions is one of the most significant problems in developing more effective and safe drugs, in particular, we often poorly imagine the mechanism of action of existing and created drugs and the violation of various regulatory pathways associated with the development of the disease. The current work is a result of our interest in developing the efficient computational methods for identifying the promising pharmacological targets, for searching and designing their ligands, and the integration of the established computational approaches into a unified platform Way2Drug [1]. Development of repurpusing-specific open source web portal appear to be important as its primary objective is to integrate all the literature, data, computational tools including chemoinformatics and bioinformatics, in a single platform which are also publicly available.

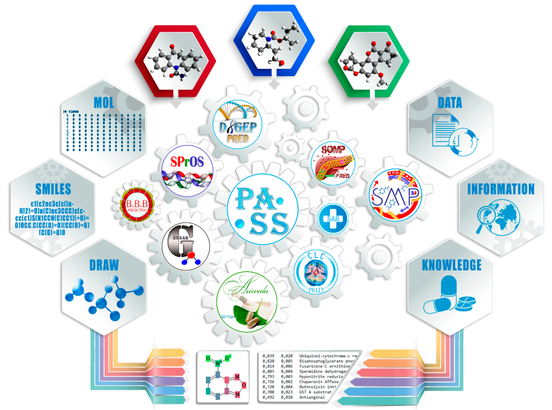
Material and Methods

Way2Drug provides several tools for *in silico* drug discovery, including PASS (Prediction of Biological Activity for Substances), PASSTargets (interaction with pharmacological targets), GUSAROnline (acute rat toxicity and interaction with antitargets), CLC-Pred (cytotoxicity for tumor and non-tumor cell lines), Meta-Pred (metabolism of drug-like molecules); etc. The scientific base of a platform is the concept of local conformity from which activity of drug-like compounds is based on the recognition of the ligand atoms of the target atoms. Using this concept, we have developed a consistent system of atom-centered neighborhoods of atoms descriptors including MNA, QNA, and LMNA, and have implemented them in several SAR/QSAR/QSPR modeling approaches. We have created a drug targets knowledge base, the impact on which is used to treat selected diseases, and are also considered promising in the development of new drugs. At present, world wide database of medicines approved by HC (Canada), MHPRA (UK), CDSCO (India), CFDA (China), FDA (USA), EMA (Europe), PMDA (Japan), KFDA (Korea), DFS (Russia); knowledge base on the drug targets are available for use by registered users, the impact of which used/discovered for the treatment of socially significant disease.

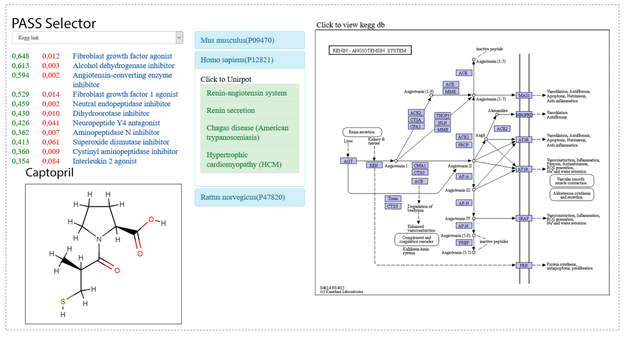
Results

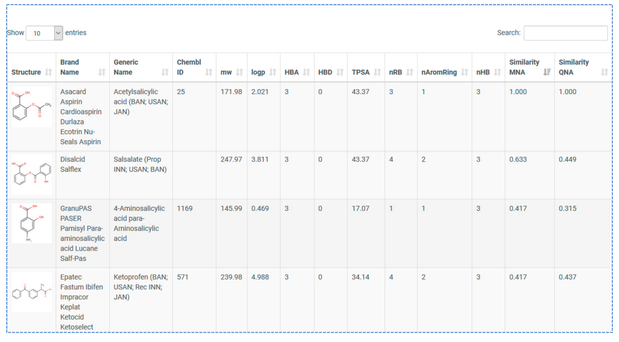
Platform provides the prediction of interaction with molecular targets, influence on gene expression, pharmacotherapeutic and side effects, metabolism, acute toxicity in rats with four modes of administration, cytotoxicity, etc., by the structural formula. Users may search for similarity using SimMNA and SimQNA methods. This functionality is built on the basis of MNA and QNA descriptors and allows user to estimate how much your perspective compound is similar to those already allowed for clinical use.
All of this were collected under PassTotal – is the system which has been created that integrates previously developed methods of computer-aided ligand based drug design, which provides for the user the ability to select the characteristics of biological activity in the framework of his specific project and to receive the results of the prediction in the form of a PDF file via email. PASS Selector is a logical extension of PASS total in frame of our project. We tried, on the one hand, to combine the results of the prediction spectrum of biological activities and the regulatory pathways to which they affect, on the other, to allow the user to systematize the obtained knowledge by selecting the results within the of diseases. Data are presented for mice, rats and humans. At the moment, numbers of selectors are limited only by antidiabetic and anti-tuberculosis activity, as well as by sorting by biological activities for which there are some records in the KeGG database. Implemented hypertext links provide associations between pharmacological targets, the impact of which is predicted by PASS Online program, with UniProt, KEGG and PDB databases.





It was implemented the molecule functional property diagnostic suit (MPDS) [2] function that allows on the initial stages of the estimation of a molecules to evaluate the multifarious aspects of drug-likelikeness of any given molecule in order to diagnose their potential application as drug. As a result, from Way2Drug portal the user can use the FDA PCP Search service to validate the values of physicochemical parameters for further validation of the compounds under study. This service implements a similarity search algorithm among structures with a given threshold of some physical and chemical parameters of the World wide Approved Drugs database of the Way2Drug portal.





Conclusion

We have developed web services for predicting interactions with ~ 80% of the molecular targets that are being studied in the target pharmacotherapeutic area. Physicochemical and ADMET characteristics may be estimated for the compound under study using the MPDS computational tools.

Acknowledgements

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References

1. http://www.way2drug.com/dr
2. http://mpds.osdd.net