METATOX: WEB RESOURCE FOR PREDICTION OF THE METABOLIC NETWORK FOR XENOBIOTICS IN THE HUMAN ORGANISM

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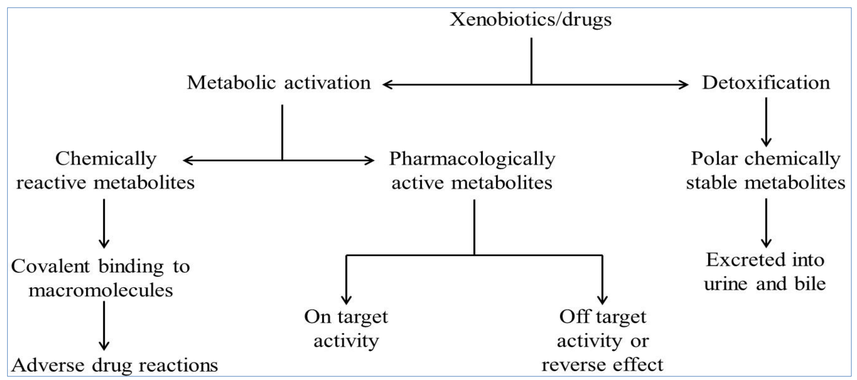
INTRODUCTION

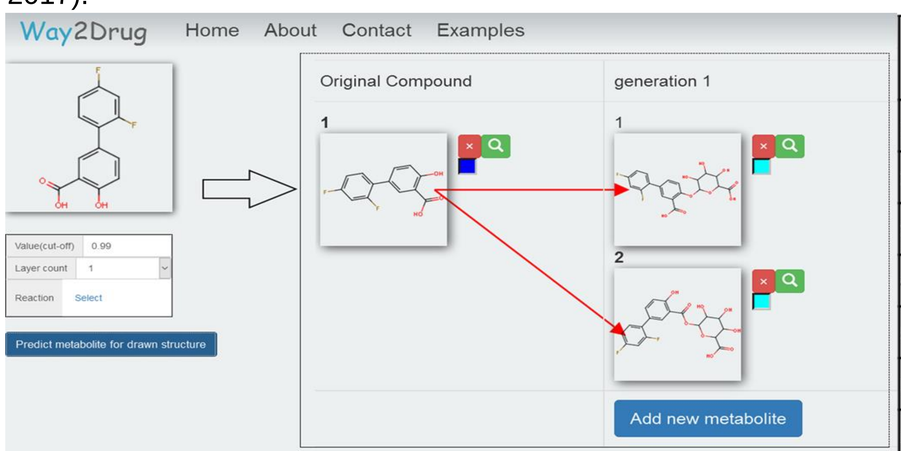
Biotransformations affect both safety and efficacy of drugs and other xenobiotics for a human. Taking into account the restrictions for the study of the xenobiotics' metabolism in the human body and known drawbacks for experimental testing in various in vitro and in vivo assays, a computational approach is currently "the method of choice" (Kirchmair J. et al., 2015).



Our research aims to create the method for computational estimation of xenobiotics' metabolites and their toxicity in the human organism.

METATOX

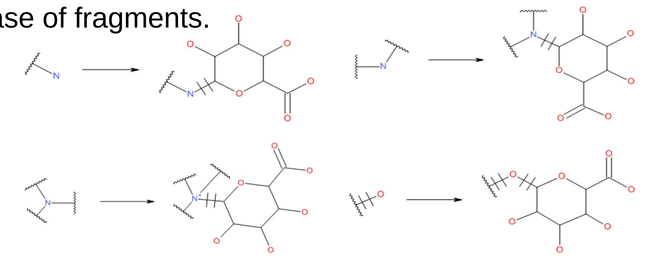
We developed the metabolic network generation method as the freely-available MetaTox service (http://www.way2drug.com/MG/). The likelihood of each generated metabolite is calculated using the combined assessment of probabilities for the predicted biotransformation classes and the particular reacting atoms (Rudik A. et al., 2017). Prediction of acute rat toxicity (i.v. administration) is performed for the parent compound and each of the generated metabolites (Lagunin A. et al., 2011). A heat map visualizes the toxicity class for each metabolite (Rudik A. et al., 2017). Besides, we implemented the computational estimation of integral xenobiotics' toxicity (Dmitriev A.V. et al., 2017).



	LD50, mg/kg (i.v.)	
1 class	≤0.7	
2 class	(0.7:7]	
3 class	(7:40]	
4 class	(40:300]	
5 class	(300:700]	
Low toxic	>700	
No result		

MATERIALS AND METHODS

The training set contains the data on several thousand xenobiotics biotransformations observed in humans, and tissue-based and cell-based experiments. It includes the information on 15 reaction classes from Phase I and Phase II of xenobiotics metabolism. We analyzed those reactions to identify the patterns of different transformations and for their inclusion into the database of fragments.

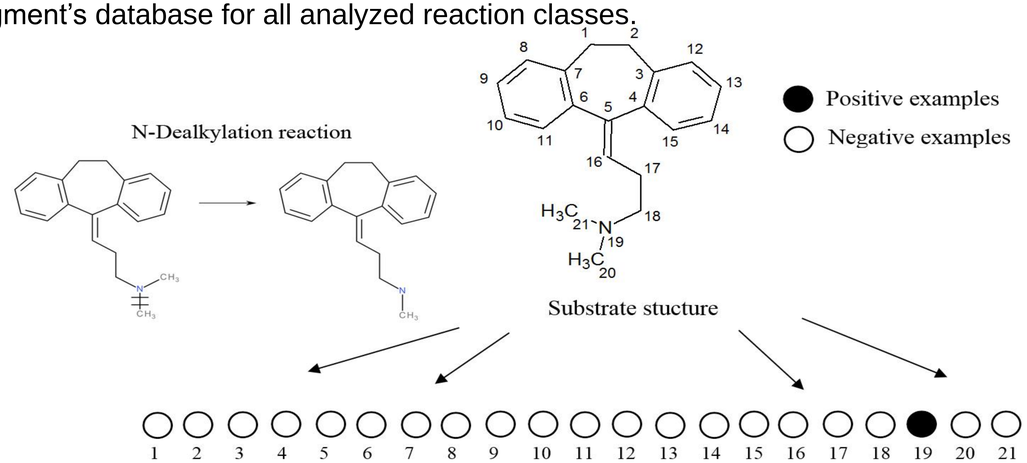


Fragments of N-glucuronidation and O-glucuronidation reactions

List of reactions:

(1) Aromatic hydroxylation;
(2) Aliphatic hydroxylation;
(3) Epoxidation;
(4) Dehydrogenation;
(5) C-oxidation;
(6) N-dealkylation;
(7) N-oxidation;
(8) O-dealkylation;
(9) S-oxidation;
(10) N-acetylation;
(11) Hydrolysis;
(12) N-glucuronidation;
(13) O-glucuronidation;
(14) O-sulfation;
(15) Glutathione conjugation

SAR models for the classes of biotransformation prediction were created using PASS algorithm (http://www.way2drug.com/PASSOnline/). Individual classification SAR models for the reacting atoms prediction utilize LMNA (Labelled Multilevel Neighborhoods of Atoms) descriptors that represent the substrates with the marked atoms in which reactions occurred and SOMP algorithm (Rudik A. et al., 2015; Rudik et al., 2016). Generation of the metabolic network is performed using the fragment's database for all analyzed reaction classes.



Positive and negative examples of N-Dealkylation reaction

Conclusions. The MetaTox is the first freely-available web application where metabolism pathway generation is integrated with the prediction of acute toxicity, which will be useful in the early drug discovery process.

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References: Dmitriev A.V. et al. *Pure Appl. Chem.*, **2017**, in press. DOI 10.1515/pac-2016-1205. Kirchmair J. et al. *Nat. Rev. Drug Discov.*, **2015**, *14*: 387. Lagunin A. et al. *Mol. Inf.*, **2011**, *30*: 241. Rudik A. et al. *Bioinformatics*, **2015**, 31: 2046. Rudik A. et al. *J. Chemoinformatics*, **2016**, 8: 68. Rudik A. et al. *J. Chem. Inf. Comput. Sci.*, **2017**, *57*: 638.