WEB SERVICE FOR PREDICTING STRUCTURE AND TOXICITY OF XENOBIOTICS' METABOLITES

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Many xenobiotics, including drugs, are metabolized in the human organism by multiple enzyme systems. Formed metabolites could significantly affect toxicity profile of the parent compound [1].
We created Metabolite Generator (http://way2drug.com/mg) that predicts metabolites, which are formed by the nine reaction classes (aliphatic and aromatic hydroxylation, N- and O-glucuronidation, N-, S- and C-oxidation, and N- and O-dealkylation). These reactions are catalyzed by five human cytochromes of P450s (1A2, 2C19, 2C9, 2D6, 3A4) and by all human UDP-glucuronosyltransferase isoforms. All considered enzymes metabolize the majority of drugs [2].
Generation of the metabolites includes two steps. During the first step, the most probable biotransformation reactions are predicted for the studied compounds. Then, the reacting atoms for these reactions are predicted [3] and metabolite structures are generated. Both predictions are based on the PASS algorithm [4]. The average accuracy of prediction estimated by leave-one-out cross-validation procedure calculated separately for both steps is about 0.85.
The probability of metabolite formation is calculated by using two steps of integrated assessment. Before generation, the user can specify the number of the generation levels, logP threshold and top-level for the reacting atoms. The user could modify the generated net of metabolites by including new or by removing of the obtained metabolites.
Prediction of LD50 values for rats with intravenous route of administration is calculated using GUSAR software [5] for every metabolite and the parent compound. The comprehensive assessment of the toxicity is based on the prediction of LD50 values and probability of metabolite formation in the generated net of metabolites.
The details of the generation of the net of metabolism of xenobiotics and examples will be presented.

Acknowledgements. The project was supported by Russian Science Foundation grant 14-15-00449.

References

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