Prediction of metabolite toxicity by meta-analysis

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The metabolism of drugs and xenobiotics is one of the most important aspect of the ADMET processes and its knowledge is very helpful in defining the safety of all chemical agents to which the animal and vegetal organisms can be deliberately or accidentally exposed. For this reason, metabolic and toxicological screenings are performed in the early phases of the drug discovery pipeline, with the clear aim to select (and develop) only drug-like compounds with an optimal pharmacokinetic behavior. In addition, one may consider that some xenobiotics are not intrinsically toxic, but are substrates of metabolic reactions whose products are reactive and/or toxic. From these considerations, the availability of computational tools able to predict the toxic metabolites can be a precious help in different industrial fields ranging from pharmaceutical to food industry.

Few years ago and with a view to supporting metabolic analyses, MetaPies database [1] was collected by primary literature and included the metabolic reactions of 1171 substrates which yield a total of 6767 different metabolites. Each metabolite was annotated and classified according to the metabolic reaction that generated it, the enzyme family that catalyzed the reaction and the toxicity/reactivity of the product. Since previous studies revealed that the physicochemical properties of a substrate can be successfully used to predict its metabolic fate, a similar approach was applied to predict the silent toxicity that can arise when a given xenobiotic is metabolized into toxic metabolites. Parameters based on semi-empirical calculations along with constitutional, geometrical and topological molecular descriptors were used to build predictive models through a machine learning approach in which a linear classifier and the cluster analysis were applied to reduce the weakness of information on the toxicity, since the parameters were calculated on the substrates and not on the products which are responsible of the potential toxicity. The obtained models proved successful in predicting the generation of toxic metabolites from a non-toxic compound with the maximum probability of 66 % and this appears to be an encouraging result when considering that such a prediction is based on the physicochemical properties of the substrates.

In this study, database handling and molecular descriptor calculations were carried out by VEGA ZZ [2, 3], an in-house freely available suite of programs which includes specific features for managing and interrogating chemical databases. Moreover, the latest VEGA ZZ release includes some features accessible through its user-friendly interface to perform QSAR analysis as required in the present study.

References

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