COMPREHENSIVE ASSESSMENT OF THE TOXICITY OF XENOBIOTICS TAKING INTO ACCOUNT THEIR METABOLISM IN THE HUMAN ORGANISM

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Most xenobiotics, which include drugs, food additives, cosmetic ingredients, industrial chemicals, etc., are metabolized by enzymes in the human organism. Information about the metabolites of xenobiotics is critical because their toxicity, biological activity, bioavailability and other properties may significantly differ from those of the parent substances [1].

There are some computational methods for modeling of enzyme-substrate interaction, expert systems, which allow building the metabolism trees, and the methods for prediction of sites of metabolism, which do not predict metabolites and metabolism pathways [2]. Metabolites' toxicity is estimated by some other methods, but it is not a comprehensive assessment, which takes into account the toxicity of the parent compound, intermediate metabolites, and the final products.

We have created a new ligand-based method for the prediction of sites of metabolism (SOMs) for xenobiotics using the LMNA (Labelled Multilevel Neighbourhoods of Atoms) descriptors [3], but the prediction of SOM does not always correspond to the particular atom that is modified by the enzyme, and rather is associated with a group of atoms. To overcome this problem, we propose to operate with the term "reacting atom," corresponding to a single atom in the substrate that is modified during the biotransformation reaction. We used LMNA descriptors for describing of reacting atoms and algorithm of PASS software [4] for the reacting atoms prediction. The obtained in leave-one-out and 20-fold cross-validation procedures average IAP (invariant accuracy of prediction) for five human isoforms of cytochrome P450 and all isoforms of UDP-glucuronosyltransferase varies from 0.86 to 0.99 (0.96 on average).

On this basis, we created the metabolite generator that predicts for the studied compounds the most probable biotransformation reactions and the reacting atoms for these reactions, and then the metabolite structures are generated. As a result, the net of possible metabolites is formed [5].

The comprehensive assessment of the toxicity is based on the calculated using GUSAR software LD50 values for rats with intravenous route of administration [6]. The simplest estimate is the least value of LD50 among all generated metabolites and parent compound without taking into account possibilities of existence of metabolite in reality. Others estimates are calculated for each generation of metabolites separately using predicted LD50 values and probabilities of metabolites as integral LD50 values for each generation. It is possible also to predict biological activity spectra for every of metabolite in the generated net of metabolites, e.g., probable targets of action.

The details of the comprehensive assessment of the toxicity of xenobiotics, examples, and validation results will be presented.

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