INTEGRAL ESTIMATION OF XENOBIOTICS' TOXICITY WITH REGARD TO THEIR METABOLISM IN HUMAN ORGANISM

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Most xenobiotics including pharmaceutical agents are metabolized in the human body by the biotransformation enzymes. The biological activity, toxicity, and other properties of the metabolites may differ significantly from those of the initial substances. Based on different principles computational methods are used for modeling of the individual stages of interaction between the xenobiotics and metabolic enzymes[1]; there are expert systems that allow building metabolic trees by prediction[2], and methods that predict only sites of metabolism, without generation of metabolites and metabolic trees. The purpose of our work is to develop a general approach to the assessment of xenobiotics' toxicity based on the prediction of their metabolism in the human body.

We have created a training set containing data about several thousands of reactions catalyzed by the major enzymes metabolizing xenobiotics in the human body. We developed methods for generating structures of metabolites and metabolic trees with estimation of the probability of each metabolite. Then, the general toxicity of xenobiotic is estimated taking into account toxicity of the initial substrate, intermediate and final products of the metabolites. We carried out the validation of the method and showed its applicability to solving practical problems. The advantages and limitations of computer methods of assessment of the toxicity of xenobiotics and scenarios of their use, to improve the safety and efficacy of new pharmaceutical agents, will be discussed.

References

1. Kirchmair J., Williamson M.J., Tyzack J.D., Tan L., Bond P.J., Bender A., Glen R.C. Journal of Chemical Information and Modeling, 2012, 52, 617.
2. Long A. Drug Discovery Today. Technologies, 2013, 10, 147.

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