A. Dmitriev [1]
A. Rudik [1]
D. Filimonov [1]
A. Lagunin [1,2]
V. Poroikov [1]

PREDICTION OF THE METABOLIC NETWORK FOR XENOBIOTICS IN THE HUMAN ORGANISM

[1] Institute of Biomedical Chemistry, 10 Bldg. 8, Pogodinskaya Str., Moscow, 119121, Russia
[2] Medico-biological Faculty, Pirogov Russian National Research Medical University, 1 Ostrovityanova Str., Moscow, 117997, Russia
a.v.dmitriev@mail.ru

In the sixties, Richard Tecwyn Williams - one of the pioneers of investigations in the field of drug metabolism - postulated that the study of the fate of xenobiotics in humans and animals plays an increasingly important role in the assessment of the safety of drugs and other chemicals in the environment. It helps to increase our understanding of the mode of toxic action of such substances and should lead the way to produce more efficient and less toxic materials for human [1]. Toxicity and serious adverse effects are the primary cause of failures at the late stage of drug development. By the end of XX century, the impact of toxic effects in drug discovery projects' fiasco was estimated as 16%, while nowadays this number is appraised as 40% [2]. Toxic effects in the human organism may be caused not only by xenobiotic itself and its major final metabolites but also by intermediate and final metabolites, formed in trace quantities.

Thus the creation of the method for prediction of the metabolic network for xenobiotics in the human organism is very important but not yet solved problem. To address the issue of xenobiotics metabolism prediction several tasks was set.

First of all the specific training set was created. The training set contains the data on several thousands of xenobiotics biotransformations observed in humans or tissue-based and cell-based experiments. Specialized training set includes the data on 15 reaction classes from Phase I and Phase II of xenobiotics metabolism: aromatic hydroxylation, aliphatic hydroxylation, epoxidation, dehydrogenation, C-oxidation, N-dealkylation, N-oxidation, O-dealkylation, S-oxidation, N-acetylation, hydrolysis, N-glucuronidation, O-glucuronidation, O-sulfation and conjugation with glutathione. Reactions from the specific training set were analyzed to identify patterns of different reaction classes and for their inclusion into the database of fragments.

SAR model for the classes of biotransformation prediction was created using PASS algorithm [3].

Individual classification SAR models for the reacting atoms prediction were built. They utilize LMNA descriptors, which represent the substrates with marked atoms in which reactions occurred, and program SOMP [4] algorithm.

Using the database of fragments these 15 reaction classes was included in the list of reactions that uses for prediction of the metabolic network for xenobiotics in the human organism. The probability of a generated metabolite is calculated by using integrated assessment of preliminary prediction of biotransformation classes and prediction of the reacting atom of each of biotransformation classes. Methods of metabolic network generation are presented at the freely available via the Internet web resource MetaTox [5, 6].

1. Williams R.T. *Pure Appl. Chem*., 1969, **18**: 129-141.
2. Waring M.J. et al. *Nat. Rev. Drug Discov*., 2015, **14**: 475-486.
3. PASSOnline. – URL: http://www.way2drug.com/PASSOnline/.
4. SOMP. – URL: http://www.way2drug.com/SOMP/.
5. MetaTox. – URL: http://www.way2drug.com/mg/.
6. Rudik A.V. et al. *J. Chem. Inf. Model*., 2017, doi: 10.1021/acs.jcim.6b00662.

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