COMPUTER-AIDED PREDICTION OF BIOLOGICAL ACTIVITY SPECTRA FOR SUBSTANCES

Vladimir Poroikov

Institute of Biomedical Chemistry of Rus. Acad. Med. Sci.; 10 Pogodinskaya Str., Moscow, 119121, Russia; E-mail: vladimir.poroikov@ibmc.msk.ru

Biological activity is one of the most important properties of organic compounds, which may become a reason for both medical use of the compound and its toxic action on human organism and environment. Despite the significant part of currently known pharmaceuticals were discovered by random screening, rational computational methods are widely applied now for discovery and optimisation of new leads and drug-candidates.

When the information about structure and properties of compounds with a certain biological activity is available, ligand-based methods can be used for further drug design and discovery. As one example of such approach we will consider computer program PASS, which predicts about 4000 pharmacological effects, mechanisms of action, specific toxicities, interaction with metabolic systems, on the basis of structural formula of chemical compound [1]. Prediction is based on the analysis of structure-activity relationships for about 270,000 biologically active compounds belonging to different chemical classes. Average accuracy of prediction is about 95% (leave one out cross-validation for all compounds from the training set with all appropriate biological activities). Using PASS predictions new pharmacological agents were discovered with anxiolytic, cognition enhancing, antiulcer, anti-inflammatory and some other actions [1, 2].

To extend the circle of PASS users, we developed an Internet version of the program – PASS INet [3]. After the the registration and receipt of the appropriate password, to obtain PASS INet prediction, the user has to submit the structural formula of compound presented as a MOL-file, which can be prepared with many chemical editors. By January 1st, 2011 the number of registered users exceeded 7,500; and more than 200,000 predictions were performed. Based on the prediction results, the researchers selected the most prospective substances for chemical synthesis and biological testing. Comparison of PASS predictions with the subsequent experiments provides an independent validation of the approach versus compounds from different chemical series with various kinds of biological activity. About forty papers, showing the coincidence of PASS predictions with the experiment, have been published (some of them were reviewed in: [4]).

Using computer program PharmaExpert [5] one can select the molecules with the required profiles of biological activity including multitargeted ligands, and to identify the compounds containing a significant number of new chemical descriptors, which might be the potential NCEs. Using recently developed computer program GUSAR [6] quantitative structure-activity and structure-property relationships can be determined and further used for prediction of activities/properties of new pharmaceutical agents.

Possibilities and limitations of computer-aided predictions utilization for estimating safety and efficacy of new pharmaceutical agents will be discussed.

References

1. PASS program package, © Filimonov D.A., Poroikov V.V., Gloziozova T.A., Lagunin A.A. *Russian State Patent Agency,* No. 2006613275 of 15.09.2006.
2. Filimonov D.A., Poroikov V.V. (2008). Probabilistic approach in activity prediction. In: Chemoinformatics Approaches to Virtual Screening. Eds. Alexandre Varnek and Alexander Tropsha. Cambridge (UK): RSC Publishing, p.182-216.
3. http://pharmaexpert.ru/passonline
4. Geronikaki A., Druzhilovsky D., Zakharov A., Poroikov V. Prediction of biological activity via Internet. Medicinal chemist's point of view. *SAR and QSAR in Environm. Res.*, 2008, **19** (1 & 2), 27-38.
5. PharmaExpert program package, © Lagunin A.A., Poroikov V.V., Filimonov D.A., Gloziozova T.A. *Russian State Patent Agency*, No. 2006613590 of 16.10.2006.
6. Filimonov D.A., Zakharov A.V., Lagunin A.A., Poroikov V.V. (2009). QNA based "Star Track" QSAR approach. *SAR and QSAR Environ. Res.*, **20** (7-8), 679-709.