VIRTUAL SCREENING AND DESIGN OF NEW PHARMACEUTICAL AGENTS USING PASS APPROACH

Vladimir Poroikov, Dmitry Filimonov, Alexey Lagunin, Tatyana Gloriozova, Olga Tarasova

Orekhovich Institute of Biomedical Chemistry of Russian Academy of Medical Sciences, Pogodinskaya Str., 10/8, Moscow, 119121, Russia

Among the numerous tools currently used for virtual screening PASS occupies a special place because its development has been started over 20 years ago, and during the past time it is improved and extended permanently [1, 2]. Current version of PASS (Prediction of Activity Spectra for Substances) predicts 6,400 biological activities of drug-like compounds with a mean accuracy of about 95% based on analysis of structure-activity relationships for the training set consisted of 330,000 biologically active compounds.

PASS online resource (http://pharmaexpert.ru/passonline) is used by 9,000 researchers from 90 countries; and over 300,000 predictions were performed. More that 50 papers were published with confirmation of PASS predictions for compounds from diverse chemical series possessing different kinds of biological activity. Based on PASS predictions, novel pharmaceutical agents have been discovered with anxiolytic, anti-inflammatory, antihypertensive, anticancer and other actions.

By application of PASS to the launched pharmaceuticals, we identified a nootropic action in known antihypertensive drugs Perindopril, Quinapril and Monopril [3]. The observed nootropic effect of some ACE inhibitors is likely to be unrelated to their antihypertensive effect since the nootropic action took place only at relatively low doses of perindopril, quinapril, and monopril and was not observed with further increase of the dose.

Based on PASS approach we developed a new fragment-based drug design method. This method was validated in the virtual experiments [4] and in the design of novel 2-benzo/benzisothiazolimino-5-aryliden- 4-thiazolidinones as cycloxygenase/lipoxygenase inhibitors [5]. Synthesis of novel compounds, and the in vitro/in vivo biological testing confirmed the results of computational studies. The benzothiazolyl moiety was proved to be of great significance for developing more potent inhibitors [5].

Since PASS calculations for 50,000 structures take a few minutes on an ordinary PC, PASS is applicable to chemical libraries containing millions of compounds. To find new anticancer agents, we have analyzed dozens of millions of structures from ChemNavigator database and selected a few dozen compounds for biological testing. Two out of eleven tested compounds were found to be potent anticancer NCEs, which demonstrated a synergistic activity with known p53 reactivator RITA. Currently these structures are optimized by a new startup company ALab, which is the resident of Skolkovo Foundation.

PASS application for virtual screening of HIV-1 microbicides not only allowed to identify the hits with probable anti-HIV action, but also to estimate the novelty of the selected molecules in comparison with the known anti-HIV agents at different phases of development (launched, clinical, preclinical, biological testing) [6].

Acknowledgement: This work was partially supported by FP7 grant No. LSHB-CT-2007-037590 and RFBR/NIH grant No. 12-04-91445-NIH_a/RUB1-31081-MO-12.

1) Poroikov V.V., Filimonov D.A., Boudunova A.P. (1993) Comparison of the results of prediction of the spectra of biological activity of chemical compounds by experts and the PASS system. Automatic Documentation and Mathematical Linguistics. Allerton Press, Inc., 27 (3), 40-43.
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) Kryzhanovskii S.A., Salimov R.M., Lagunin A.A., Filimonov D.A., Gloriozova T.A., Poroikov V.V. (2012). Nootropic action of some antihypertensive drugs: computer predicting and experimental testing. Pharmaceut. Chem. J., 45 (10), 605-611.
4) Filz O.A., Lagunin A.A., Filimonov D.A., Poroikov V.V. (2012). In silico fragment-based drug design using PASS approach. SAR & QSAR Environ. Res., 23 (3-4), 279-296.
5) Eleftheriou P., Geronikaki A., Hadjipavlou-Litina D., Vicini P., Filz O., Filimonov D., Poroikov V., Chaudhaery S.S., Roy K.K., Saxena A. (2012). Fragment-based design, docking, synthesis, biological evaluation and structure–activity relationships of 2-benzo/benzisothiazolimino–5–aryliden–4-thiazolidinones as cycloxygenase/lipoxygenase inhibitors. Eur. J. Med. Chem., 47 (1), 111-124.
6) Poroikov V.V., Filimonov D.A., Lagunin A.A., Gloriozova T.A., Tarasova O.A., Pogodin P.V., Nicklaus M.C. Virtual high-throughput screening of novel pharmacological agents based on PASS predictions. Abstracts of the 245th ACS National Meeting, New Orleans, April 7-11, 2013.