

PREDICTION OF ACTIVITY SPECTRA FOR SUBSTANCES: TWENTY YEARS OF THE DEVELOPMENT

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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 about 9,000 researchers from 90 countries; and over 300,000 predictions were performed. More than 50 papers were published with confirmation of PASS predictions for compounds from diverse chemical series possessing different kinds of biological activity.

Using 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-arylidene-4-thiazolidinones as cyclooxygenase/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.

PASS application significantly increases the chances for discovery of new more safety and potent pharmaceutical agents, and allows formation of many collaborative projects with participation of multidisciplinary teams including computational organic and medicinal chemists, pharmacologists and toxicologists.

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