COMPUTER-AIDED APPROACHES TO VIRTUAL SCREENING AND RATIONAL DESIGN OF MULTITARGETED DRUGS

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Many diseases have a complex etiology, which treatment often requires multiple actions on several pharmacological targets. On the contrary, the majority of current drugs were designed to interact with a single target, which sometimes leads to activation/blockade of other elements in the appropriate signal regulatory pathway. As a consequence of negative feedbacks, expected pharmacotherapeutic effect may be significantly decreased or even completely suppressed. Therefore, the multitargeted drugs, due to their additive, synergistic or antagonistic action, might have some advantages comparing to the monotargeted medicines. The purpose of our study was to develop computer-assisted methods for identification of the most promising targets; finding and rational design of multitargeted agents with the required biological activity profiles.

The following computer-aided tools were used in this work. **Net2Drug** – software for simulation of behavior of signal regulatory pathways and identification of the most promising targets and their combinations. **PASS** (Prediction of Activity Spectra for Substances, http://pharmaexpert.ru/passonline/) - software, which predicts about 4000 kinds of biological activity on the basis of structural formula with mean accuracy about 95%. **PharmaExpert** – software for analysis of **PASS** predicted biological activity spectra and selection of compounds with the required biological activity profiles.

As a result, we identified the promising targets for treatment of breast cancers by analysis of signal regulatory pathways. Based on computer prediction of biological activity for 24 mln chemical compounds 64 molecules were selected for experimental testing. 26 samples were purchased and antineoplastic activity was confirmed experimentally in some molecules. Therefore, it was shown that computer-aided methods are rather useful in discovery of the most prospective pharmacological targets and their ligands.

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