Predictions of pairs of drugs with synergistic activity against leukemia cell lines based on NCI-ALMANAC data

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Introduction

Drug resistance of tumor cells is one of the main problems in oncology. A combination of several drugs is used to overcome tumor resistance. It is not possible to test all combinations of pairs of approved drugs experimentally to identify synergy. We created classification SAR models for prediction of synergistic pair drug combinations against 6 leukemia cell lines using PASS DDI and GUSAR DDI software and the data from NCI-ALMANAC database (<https://ntp.cancer.gov/ncialmanac/>) which contains the results of experimental testing of 5232 drug pairs in cell lines of NCI-60 panel [1].

Methodology

Data. The data related with experimental results of synergistic antineoplastic activity against 6 leukemia cell-lines (RPMI-8226, MOLT-4, CCRF-CEM, SR, K-562 and HL60(TB)) were used for creation and validation of SAR models. The threshold in 50 points was used for dividing drug pairs actives, with synergistic action (≥ 50 points), and inactives without synergistic action (< 50 points). For example, the pair Bortezomib and Erlotinib is active for RPMI-8226 and MOLT-4 cell lines and inactive for others.

Software. The modified version for drug-drug interaction (DDI) modeling of PASS [2] (substructural PoSMNA (Pairs of Substances Multilevel Neighbourhoods of Atoms) descriptors and naïve Bayes-like algorithm) and GUSAR [3] (electro-topological QNA (Quantitative Neighbourhoods of Atoms) descriptors and self-consistent regression) software were used for the creation of SAR models.

Validation. 5-fold cross-validation.

Results

The accuracy of SAR models was verified using the 5-fold cross-validation procedure. For the best SAR models, AUC and balanced accuracy were more 0.85 and more 0.78, respectively.

Conclusion

The SAR models were used to screen potentially synergistic antitumor pairs of FDA approved drugs acting against 6 leukemia cell lines. Search for synergistic antitumor pairs by PASS models was made among 870 thousands pairs of 1320 FDA approved drugs from DrugBank. The figure below shows the numbers of drug pairs with prediction to be active more 0.7.

The analysis of the prediction results showed that the combination of Buclizine & Cabazitaxel was a drug pair with the highest probability to reveal synergistic activity against all 6 leukemic cell-lines.

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