Computational modeling of effective inhibitors of topoisomerase IA

Natallia Kulik[1], Aleksandr V. Kudriavtsev[2,3]
[1]*Center for Nanobiology and Structural Biology, Institute of Microbiology, Academy of Sciences of the Czech Republic, Nové Hrady, Czech Republic*
[2]*Biological Faculty, Lomonosov Moscow State University, Moscow, Russia*
[3]*Emanuel Institute of Biochemical Physics, Russian Academy of Science, Moscow, Russia*

Eukaryotic topoisomerases I (TOPO 1) are the targets of an increasing number of anti-cancer and anti-tumor drugs that act by inhibition these enzymes. Computational docking of potential active compounds would be appreciated for prediction of potential antimicrobial drugs, potentially lowering the experimental costs and time [1].

In our work we focused on the search of possible binding places for binding of different drugs, select prominent inhibitors and predict possible effects on enzyme action. Several approaches were used for search and analysis inhibitors, including characterization geometry of binding partners (Yasara [2], VMD), calculation of energy parameters such as binding affinity and charge distribution (Schrodinger [3]).

The potential inhibitors of TOPO 1 [1] where downloaded from PubChem database and used for building of pharmacophore. We also made screening of more than 325 mln entries from PubChem Database employing new approach based on filtering under MeSH classification with combination of different docking methods for inhibitor selection (rigid and flexible docking with, induced fit docking, MD simulation).
Based on our study we also proposed optimal work-flow which can be used for further search and selection other biologically active compounds.
Finally we had choose top-10 compounds based on this pharmacophore hypotheses and then we use it for rational manual construction of new compounds, that were not found in PubChem database.

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