FIGHTING WITH HIV-1 RESISTANCE TO REVERSE TRANSCRIPTASE INHIBITORS BY COMPUTER-AIDED APPROACH

O.A. Tarasova*, D.A. Karasev, D.A. Filimonov, V.V. Poroikov
Institute of Biomedical Chemistry, Moscow, Russia
e-mail: olga.a.tarasova@gmail.com
*Corresponding author

Keywords: HIV reverse transcriptase inhibitors, resistance, PASS.

Motivation and Aim: HIV reverse transcriptase (RT) inhibitors are important components of the highly active antiretroviral therapy [1]. Response to treatment with HIV RT inhibitors agents often depends on viral drug resistance development. There are a lot of clinical and biochemical data on the relationships between the occurring of the single point mutations in pol gene of HIV and the resistance of the particular variants of the RT to the nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). The aim of our study is the development of the computer-aided approach to the search for HIV-1 RT inhibitors, active against the resistant RT variants.
Methods and Algorithms: We propose an application of PASS algorithm [2] to the (i) prediction of the amino acid changes, potentially involved in the resistance of HIV-1 and (ii) integrated approach based on usage of small molecules descriptors and the descriptors of the amino acid sequences of the protein to the search for the compounds with activity against the HIV resistant strains.
Results: We used over 3200 variants of the HIV-1 RT from the publicly accessible HIV Drug Resistance Database tested against the ten anti-HIV drugs in two susceptibility assays (Phenosense and Antivirogram). Two classes of the variants were considered: "susceptible" and "resistant". The average balanced accuracy of prediction obtained in the leave-one-out procedure for the Phenosense data set was about 82%, and for the Antivirogram data set was about 87%. For further computational experiments, we selected over 500 sequences, for which the complete amino acid sequences can be retrieved from NCBI Protein database. We have developed and tested an approach based on the integration of (i) estimated probability of the specific pentapeptide to occur in the amino acid sequence of the particular variant of HIV RT and (ii) estimated probability of the ligand descriptors (multilevel neighborhoods of atoms, MNA [2]) to arise in the particular ligand. The average balanced accuracy of prediction obtained in the leave-one-out procedure was about 84%.
Conclusion: The computer-aided approach to finding new HIV-1 RT inhibitors provides the possibility to predict the (i) amino acid changes, potentially involved in resistance and (ii) probability of the compound to be active against the particular HIV-1 variant with average balanced accuracy about 84%.
Availability: Detailed description of the algorithm description may be provided on request.
Acknowledgements: This work was supported by RFBR grant No. 16-34-60187.
References:
1. Geronikaki A. et al., *Topics in Medicinal Chemistry,* 2016, 1-59. DOI:10.1007/7355_2015_5001.
2. Filimonov D. et al., *Chemistry of Heterocyclic Compounds,* 2014, 50 (3), 444-457.