OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference on
Medicinal Chemistry & Computer Aided Drug Designing

October 15-17, 2013 Hampton Inn Tropicana, Las Vegas, NV, USA

Cluster-based molecular docking study for *in silico* identification of novel 6-fluoroquinolones as potential inhibitors against *Mycobacterium tuberculosis*

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A classical protein sequence alignment and homology modeling strategy were employed for building three *Mycobacterium tuberculosis*-DNA gyrase protein models using the available topoII-DNA-6FQ crystal structure complexes originating from different organisms. The recently determined *M. tuberculosis*-DNA gyrase apoprotein structures and topoII-DNA-6FQ complexes were used for defining the 6-FQs binding pockets. The quality of the generated model was initially validated by docking of the co-crystallized ligands into their binding site, and subsequently by quantitative evaluation of their discriminatory performances (identification of active/inactive 6-FQs) for a set of 145 6-FQs with known biological activity values. The *M. tuberculosis*-DNA gyrase model with the highest estimated discriminatory power was selected and used afterwards in an additional molecular docking experiment on a mixed combinatorial set of 427 drug-like 6-FQ analogs for which the biological activity values were predicted using a pre-built CP ANN model. A novel three-level Boolean-based (T/F (true/false)) clustering algorithm was used to assess the generated binding poses: level 1 (geometry properties assessment), level 2 (score-based clustering and selection of the (T)-signed highly-scored level 1 poses), and level 3 (activity-based clustering and selection of the most "active" (T)-signed level 2 hits). The frequency analysis of occurrence of the fragments attached at R1 and R7 position of the (T)-signed 6-FQs selected in level 3, revealed several novel attractive fragments and confirmed some previous findings. We believe that this methodology could be successfully utilized in establishing novel possible SAR recommendations in the 6-FQs optimization, which could be of great importance in the current anti-mycobacterial hit-to-lead processes.

Biography

Nikola Minovski has completed his Ph.D. in May 2011 at the Faculty of Pharmacy in Ljubljana, Slovenia. He is employed as a researcher at the Laboratory for Chemometrics, National Institute of Chemistry in Ljubljana, Slovenia since 2007. He is actively working on in silico development of novel 6-fluoroquinolone antibacterials for tuberculosis chemotherapy for more than 5 years. To date, he has published more than 10 papers in distinguished journals and has been serving as a reviewer as well.

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