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

Combinatorially-generated library of benzamide-containing aminonitriles as promising cathepsin K inhibitors: A molecular docking study

Jure Borisek and Marjana Novic
National Institute of Chemistry, Slovenia

Cathepsin K (Cat K) is a lysosomal cysteine protease that plays an important role in many severe diseases, which makes inhibition of Cat K a potentially attractive therapeutic approach. Several compounds, including balicatib, passed preclinical studies and were tested in clinical trials as perspective Cat K inhibitors. Balicatib proved as a potent inhibitor, however, the side effects caused by the accumulation of drug candidate in the lysosomes (lysosomotrophism) of human skin fibroblast as a consequence of its P3 basic nature prevented further drug development.

The aim of our work was to design structural analogues of balicatib like benzamide-containing aminonitriles by virtual combinatorial chemistry approach and to perform molecular docking study on obtained combinatorial dataset. The covalent molecular docking studies were carried out by GOLD Suite v5.1 docking package. Crystal structure of Cat K was derived from PDB with entry code 4DMX. Post-docking analyses comprised both, ligand fitness and orientation assessment in protein binding site, which enabled the inspection of intermolecular distances between ligands and protein key amino acid residues. The virtual combinatorial dataset of 254 compounds was obtained using the virtual combinatorial chemistry approach. Interatomic distance measurement between docked compound features and protein key amino acid residues yielded 12/254 correct compounds for virtual combinatorial dataset. Some of resulted compounds had P3 weak or non- basic nature, which could be of importance to avoid lysosomotrophic related side effects.

Biography

Jure Borisek has graduated as Master of Pharmacy in 2011 from the University of Ljubljana. He is a Ph.D. student in the field of Biomedicine, working on QSAR and molecular modeling at the Laboratory of Chemometrics at the National institute of Chemistry, Slovenia.

jure.borisek@ki.si