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

SARS antiviral therapeutic development through structure and ligand-based drug design

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The human Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) is a human respiratory pathogen for which no effective antiviral treatment exists. The identification of a bat as the probable animal reservoir for SARS-CoV indicates that there is a continuing potential for re-emergence. The papain-like cysteine protease (PLpro) encoded by the SARS-CoV is essential for viral replication, and is a promising target for antiviral drug development. A high-throughput screening followed by a 3D-QSAR study led to the discovery and design of our recent inhibitors. The solution of the inhibitor-bound PL pro structures highlights the role of an extremely flexible six-residue loop in inhibitor binding. The high binding site plasticity is a major challenge in structure-based drug discovery/design efforts. From both conventional and accelerated molecular dynamics simulations, we find that only accelerated molecular dynamics simulation reproduces the experimentally observed conformational variability. Based on a series of the most diverse snapshots extracted from the molecular dynamic stimulation of both the open and closed form of the protein were used to build a computational solvent mapping based pharmacophore model that accommodates the protein flexibility, and permits structure based design. In summary, we have designed two series of inhibitors that show low micromolar SARS-CoV antiviral efficacy using an integrated approach that exploits both ligand and structure-based therapeutic design techniques. Metabolic stability and pharmacokinetic evaluation of one of these two series show ideal tissue distribution with promising biological characteristics. Details of drug design and efficacy evaluation will be discussed.

Biography

Rima Chaudhuri has completed her Ph.D. from University of Illinois at Chicago and postdoctoral studies in a joint program of computational biology at the Institute of Research in Biomedicine, Barcelona (IRB) and the Barcelona Supercomputing Center. During her Ph.D., she briefly worked at Pfizer Inc., as a computational chemist intern at their Global R&D division in CT,USA. Currently, she is a research officer at the Garvan Institute of Medical Research in Sydney, Australia. She is a co-inventor in one United States patent and one international patent application (from Europe) for her work in the field of CADD. In her leisure time, she is a scuba diver and a runner.

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