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Modeling studies of HCV protease inhibitors: Understanding their efficacy in mutant forms

Vema Aparna
Sree Chaitanya Institute of Pharmaceutical Sciences, India

Hepatitis C virus (HCV) infection is a major cause of liver infection and is believed to be the major reason for liver transplantations worldwide. The expansion of drug resistant strains of HCV might aggravate anti-HCV therapy and is an issue to consider when developing new drugs. HCV NS3 protease is an important drug target, for which several inhibitors are in clinical trials. Because of the high-mutation rate of the virus, resistance against any HCV-specific drug is likely to become a substantial problem. Structure-activity data for the major resistant variants are therefore needed to guide future designs of protease inhibitors. With this preview, molecular modeling studies were carried out for a series of Tripeptide NS3 protease inhibitors against both wild type and A156T and D168V mutant forms of HCV NS3 protease. Biological assay results show that Inhibitors with a P2 proline and P1 vinyl cyclo propyl carboxylic acid substituent loose much of their potency on the resistant forms when compared to P2 phenyl glycine based inhibitors. Molecular modeling studies identify an enforced change in the binding conformation for the P2 proline based inhibitors due to steric hindrance raised by the mutant forms. However, such steric hindrance is not seen with the P2 phenyl glycine based inhibitors in the mutant forms. P2 phenyl glycine based inhibitors show an altogether different binding profile compared to other inhibitors in the study. Thus, the basis of the activity of the P2 phenyl glycine based inhibitors against the A156T and D168A mutant forms of HCV was identified. This could help in the design and synthesis of much potent HCV protease inhibitors.

Biography

Vema Aparna has completed her Ph.D at the age of 29 years from University of Hyderabad and postdoctoral studies from Department of Medicinal Chemistry, Uppsala University. She is the Principal/Head of Sree Chaitanya Institute of Pharmaceutical Sciences. She has published more than 10 papers in reputed journals and presented more than 12 papers in several national and international conferences.

vemaparna@gmail.com