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Molecular modeling, synthesis and anti-HCV Genotype-4 testing of various Peptidomimetic agents having potential HCV polymerase and HCV protease inhibitor activities

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HCV belongs to the Hepatitis C virus genus of the Flaviviridae family. It is a single-strand positive-sense RNA containing virus that propagates using an RNA-dependent RNA polymerase (RdRp). HCV genomes are classified into eleven major genotypes (designated 1-11). Genotypes 1-3 predominate in Northern Europe and North America, and in Southern and Eastern Europe and Japan, respectively. Type 3 is endemic in south-east Asia and is variably distributed in different countries. Genotype 4 is principally found in the Middle East, Egypt, and central Africa. Type 5 is almost exclusively found in South Africa, and genotypes 6-11 are distributed in Asia. The most important targeting for anti-HCV drug developments were HCV RNA-dependent RNA polymerase (RdRp) and HCV NS3 protease enzymes. The active site of the polymerase enzyme is structurally conserved in all polymerases. The HCV NS3 protease is a serine protease that utilizes three amino acids during the hydrolysis of a peptide bond; a histidine, an aspartic acid and a serine. These amino acids are recognized as the catalytic triad for peptide cleavage, and are numbered according to the HCV numbering system, His57, Asp81 and Ser139 and are conserved in genotype 1 & 4. Development of new anti-HCV-4 agents in our lab; in continuation of our strategy in drug discovery were monitored by docking of different proposed new molecules at the binding sites of HCV-polymerase & Protease enzymes. The polymerase crystal structure (code 2QE5) was downloaded from PDB, and various proposed molecules were docked, where it will help in predicting new active hits as polymerase inhibitors, which upon anti-HCV evaluation, they showed promising activities. Similarly, new HCV-4 protease inhibitors were designed by docking of HCV protease enzyme crystal structure (code 1w3c) with the various proposed peptidomimetic molecules, where it revealed that many compounds showed promising activities.

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