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Structure-based Development of Inhibitors of HCV NS5b

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Infection by the Hepatitis C virus (HCV) affects in the order of 150 million people world-wide with more than 300,000 dying each year from HCV-induced liver disease. The RNA-dependent RNA-polymerase of HCV, NS5b, is widely accepted as an ideal candidate for therapeutic development due to the lack of an equivalent enzymatic activity in normal human cells and the absolute dependence of viral replication on NS5b. Here we present the results of a fragment-based discovery program carried out as part of our research into NS5b inhibitors. A number of fragments identified as NS5b ligands through STD-NMR analysis, as well as structural analogues of these fragments, were soaked into crystals of HCV NS5b and the structures of the complexes determined. On the basis of the proximity of one of these compounds to the primer grip site of the enzyme, hybrid compounds linking the compound and a known inhibitor were designed and synthesised. These hybrid compounds were found to be potent inhibitors of the HCV replicon and NS5b enzymatic assay and were shown crystallographically to bind in the primer grip site in precisely the orientation predicted from modelling.

Keywords or phrases (comma separated)

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Summary

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