Non-nucleoside Inhibitors of NS5B Polymerase from HCV, Genotypes 1b and 2a

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Hepatitis C virus (HCV) is an important human pathogen affecting ~ 3% of the world's population. The current antiviral therapies (a combination of pegylated interferon and ribavirin) are of limited efficacy and often have severe adverse side effects. Structures of the RNA dependent RNA polymerases from HCV, genotypes 1b [1] and 2a complexed to a variety of non-nucleoside non-competitive inhibitors reveal a common binding site that is ~ 35 Å from the polymerase active site. Two crystal forms, I and II, of the 2a genotype unbound RdRp reveal a "closed" or active form of the polymerase and an "open" or inactive form, respectively. The difference in conformation lies in the relative orientation of the fingers and thumb domains of the molecule. Inhibitors bind only to the form I (active) conformation and will not bind to the form II (inactive) crystals. The binding of the inhibitors triggers the conformational changes from the active to the inactive conformation in the crystals. (Research supported in part by CIHR, AHFMR and Virochem Pharma Inc. MNGJ gratefully acknowledges the receipt of a Canada Research Chair).

[1] Wang M., Ng K.K., et al., *J. Biol. Chem.,* 2003, **278**, 9489.

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