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Targeting the HCV RNA Polymerase: Study of Two Types of Non Nucleoside Analogs that Inhibit HCV Replication by Binding In-and-Outside of the Catalytic Site. Nanhua Yao, Todd Appleby, Shunqi Yan, Yili Ding, Valeant Pharmaceuticals International, Costa Mesa, CA.

Hepatitis C virus (HCV) nonstructural protein 5B (NS5B) is an RNA-dependent RNA polymerase that is essential for the viral replication. It is a valid target for anti-HCV therapy. High-throughput screening identifies two novel series of HCV RNA polymerase inhibitors. X-ray crystallographic study reveals two different binding sites. Subsequent study uncovers two different mechanisms of action. One analog, bound near the center of polymerase close to the catalytic site, interferes with the primer binding. Another analog, bound within a narrow cleft in the “thumb” domain on the surface, is an allosteric inhibitor. It locks the polymerase conformation and perturbs fluctuation within polymerase sub-domains. Structure-activity relationships (SAR) studies are carried out for both series as well.