Discovery of a 2'-Fluoro-2'-*C*-Methyl *C*-Nucleotide HCV Polymerase Inhibitor and a Phosphoramidate Prodrug with Favorable Properties

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Discovery of a 2'-Fluoro-2'-*C*-Methyl *C*-Nucleotide HCV Polymerase Inhibitor and a Phosphoramidate Prodrug with Favorable Properties

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ABSTRACT

A series of 2'-fluorinated *C*-nucleosides were prepared and tested for anti-HCV activity. Among them, the triphosphate of 2'-fluoro-2'-*C*-methyl adenosine *C*-nucleoside (**15**) was a potent and selective inhibitor of the NS5B polymerase and maintained activity against the S282T resistance mutant. A number of phosphoramidate prodrugs were then prepared and evaluated leading to the identification of the 1-aminocyclobutane-1-carboxylic acid *iso*propyl ester variant (**53**) with favorable pharmacokinetic properties including efficient liver delivery in animals.

Keywords: Hepatitis C; Antiviral; C-nucleoside; NS5B polymerase

Hepatitis C Virus (HCV) infection is a major cause of chronic liver disease worldwide. When left untreated, it can lead to end stage liver diseases including cirrhosis and hepatocellular carcinoma. [1] Until 2011, the standard of care for patients with HCV infection was a regimen consisting of pegylated interferon-α and ribavarin, which has only limited efficacy. [2] More recently several direct-acting antivirals (DAAs) have been developed and licensed for use, resulting in combination regimens with markedly improved clinical outcomes. [3] A notable advance in this context was the discovery of the nucleotide prodrug sofosbuvir (**1**) (Figure 1). Combined with other DAAs, sofosbuvir affords high cure rates for infections across all genotypes of HCV. [4]