ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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2′,4′-Difluoro-2′-methyl Substituted Nucleoside Derivatives as Inhibitors of HCV RNA Replication

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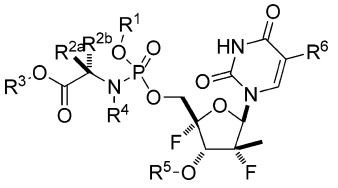
Title:	2′,4′-Difluoro-2′-methyl substituted nucleoside derivatives as inhibitors of HCV RNA replication		
Patent Application Number:	WO2013092481A1	**Publication date:**	June 27, 2013
Priority Application:	US61/577,707	**Priority date:**	December 20, 2011
Inventors:	Zhang, Jing; Zhang, Zhuming		
Assignee Company:	F. Hoffmann-La Roche, AG		
Disease Area:	Viral Infection	**Biological Target:**	Hepatitis C

Summary: The hepatitis C virus (HCV) remains a significant threat to human health. Globally, HCV is the largest contributor to chronic liver disease. HCV infection also substantially increases the risk of liver cirrhosis, hepatocellular carcinoma, and liver transplant. Modern therapies are limited to interferon-α and ribavirin. Additional, novel therapies will be required in order to develop a more effective treatment for HCV infection. It has been hypothesized that the majority of nonstructural proteins in the HCV genome are modulators of HCV replication. Subgenomic HCV clonal Human Hepatoma (Huh7) have been developed as screening tools for the identification of compounds capable of blocking viral replication, thereby blocking viral transmission and further infection. This disclosure describes a series of functionalized nucleoside analogues capable of inhibiting HCV replication and claims them for the treatment of HCV infection.

Important Compound Classes:



Definitions:

R^1 is H, lower halo alkyl, or aryl, wherein aryl is phenyl or naphthyl, optionally substituted with one or more lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, halo, lower halo alkyl, $-N(R^{la})_2$, acylamino, $-SO_2N(R^{la})_2$, $-COR^{1b}$, $-SO_2(R^{lc})$, $-NHSO_2(R^{lc})$, nitro, or cyano;

each R^{1a} is independently H or lower alkyl;

each R^{1b} is independently $-OR^{la}$ or $-N(R^{la})_2$;

each R^{1c} is lower alkyl;

R^{2a} and R^{2b} are (i) independently H, lower alkyl, $-(CH_2)_rN(R^{la})_2$, lower hydroxyalkyl, $-CH_2SH$, $-(CH_2)S(O)_pMe$, $-(CH_2)_3NHC(=NH)NH_2$, (1*H*-indol-3-yl)methyl, (1*H*-indol-4-yl)methyl, $-(CH_2)_mC(=O)R^{lb}$, aryl and aryl lower alkyl, wherein aryl may optionally be substituted with one or more hydroxy, lower alkyl, lower alkoxy, halo, nitro, or cyano; (ii) R^{2a} is H and R^{2b} and R^4 together form $(CH_2)_3$; (iii) R^{2a} and R^{2b} together form $(CH_2)_n$; or (iv) R^{2a} and R^{2b} both are lower alkyl;

R^3 is H, lower alkyl, lower halo alkyl, phenyl, or phenyl lower alkyl;

R^4 is H, lower alkyl, or R^{2b} and R^4 together form $(CH_2)_3$;

R^5 is H, $C(=O)R^{1c}$, $C(=O)R^{1b}$, $P(=O)(OR^1)(OR^{1a})$, or $P(=O)(OR^1)(NR^4R^7)$;

R^6 is H, methyl, or halo;

R^7 is $C(R^{2a}R^{2b})COOR^3$.

m is 0 to 3;

n is 4 or 5;

p is 0 to 2; and

r is 1 to 6;

Special Issue: HCV Therapies

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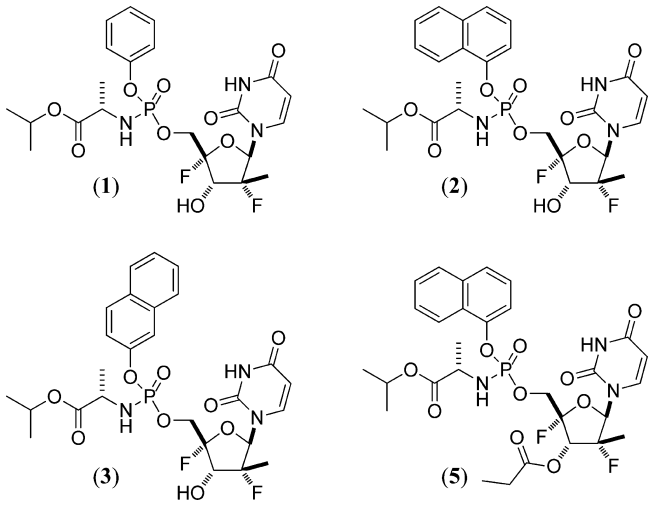
Key Structures:



Recent Review Articles:

1. Kwo, P. Y.; Vinayek, R. The therapeutic approaches for hepatitis C virus: protease inhibitors and polymerase inhibitors. *Gut Liver* **2011**, *5* (4), 406−417.
2. Shah, N.; Pierce, T.; Kowdley, K. V. Review of direct-acting antiviral agents for the treatment of chronic hepatitis C. *Expert Opin. Investig. Drugs* **2013**, *22* (9), 1107−1121.

Biological Assay:

HCV replicon assay, luciferase based.

WST-1 cytotoxicity assay (Roche Diagnostic, cat no. 1644807).

Biological Data:

Entry	HCV Replication	WST-1 Cytotoxicity	Entry	HCV Replication	WST-1 Cytotoxicity
	IC_{50} μM	CC_{50} μM		IC_{50} μM	CC_{50} μM
1	0.424	>100	3	0.15768	>100
2	0.1149	>100	5	0.1515	67.8

Claims:

20 Total claims.

14 Composition of matter claims.

6 Method of use claims.

AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.