ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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HCV Polymerase Inhibitors

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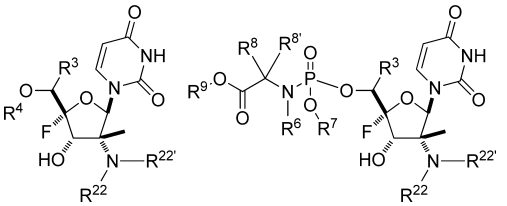
Title:	HCV Polymerase Inhibitors		
Patent Application Number:	WO2013084165A1	**Publication date:**	June 13, 2013
Priority Application:	SE1151157.3	**Priority date:**	December 5, 2011
	SE1250458−5		May 7, 2012
Inventors:	Klasson, Bjorn; Eneroth, Anders; Nilson, Magnus; Pinho, Pedro; Samuelsson, Bertil; Sund, Christian		
Assignee Company:	Medivir AB		
Disease Area:	Viral Infection	**Biological Target:**	Hepatitis C

Summary: Hepatitis C viral infection remains a major health issue, despite the development of pegylated interferon-α and the antiviral agent ribavirin. HCV is a member of the Flaviviridae family of viruses with a single stranded, positive-sense RNA. It employs RNA polymerase as an essential aspect of its replication. The vast majority of HCV infected patients develop chronic hepatitis after an initial acute infection as a result of HCV's ability to replicate in hepatocytes without direct cytopathic activity. Ultimately, long-term HCV infection increases liver fibrosis, cirrhosis, and liver cancer and is the leading contributor to liver transplants. Efforts to develop novel treatments for HCV infection led to the development of both nucleoside analogue and non-nucleoside inhibitors of RNA polymerase. Nucleoside analogues are typically incorporated into viral replication process and terminate RNA chain growth, thus blocking viral replication. This patent application describes a series of nucleoside analogues capable of inhibiting HCV replication and claims them for the treatment of HCV infection.

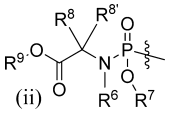
Important Compound Classes:



Definitions:

R^3 is H or CH_3;

R^4 is a mono-, di-, or triphosphate ester, or a group of formula (ii):



(ii)

R^6 is H or together with the adjacent R^8 and the atoms to which they are attached forms a pyrrolidinylene ring;

R^7 is H or C_1-C_6alkyl, or R^7 is phenyl, pyridyl, indolyl, quinolinyl, or naphthyl, which phenyl, pyridyl, indolyl, quinolinyl, or naphthyl group is optionally substituted with 1, 2, or 3 substituents each independently selected from halo, C_1-C_6haloalkyl, C_1-C_6alkyl C_1-C_6alkenyl, C_1-C_6alkoxy, hydroxy, amino, $NHS(=O)_2Me$, $N(Me)S(=O)_2Me$, $S(=O)_2Me$, $S(=O)_2NH_2$, $S(=O)_2NHMe$, $S(=O)_2NMe_2$, and $C(=O)Me$;

R^8 and $R^{8\prime}$ are each independently selected from H, C_1-C_6alkyl, and benzyl; or R^8 and $R^{8\prime}$ together with the carbon atom to which they are attached from a C_3-C_7 cycloalkylene group; or R^8 is H, and $R^{8\prime}$ together with the adjacent R6 and the atoms to which they are attached form a pyrrolidinylene ring;

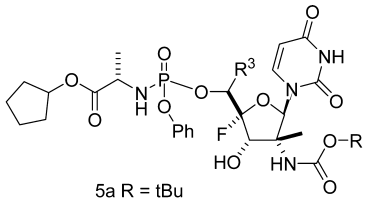
R^9 is C_1-C_{10}alkyl, C_1-C_{10}haloalkyl, C_3-C_7cycloalkyl, benzyl, or phenyl, any of which is optionally substituted with 1, 2, or 3 substituents each independently selected from hydroxy C_1-C_6alkoxy, amino, and mono- and di-C_1-C_6alkylamino;

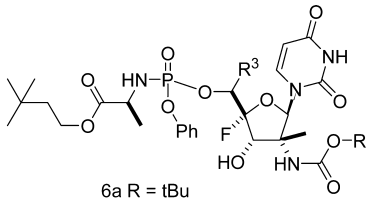
R^{22} and $R^{22\prime}$ are independently H, C_1-C_6alkyl, $C(=O)OC_1-C_4$alkyl. or $C(=O)OC_3-C_6$cycloalkyl.

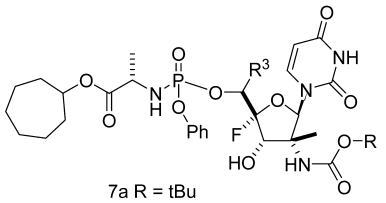
Special Issue: HCV Therapies

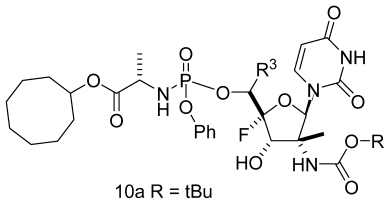
Received: October 26, 2013
Published: November 13, 2013

Key Structures:









Recent Review Articles:

1. Kiser, J. J.; Flexner, C. Direct-acting antiviral agents for hepatitis C virus infection. *Annu. Rev. Pharmacolo. Toxicol.* **2013**, *53*, 427−449.
2. Casey, L. C.; Lee, W. M. Hepatitis C virus therapy update 2013. *Curr. Opin. Gastroenterol.* **2013**, *29* (3), 243−249.

Biological Assay: HCV NS5B-21 scintillation proximity assay.

Biological Data:

Entry	HCV replication EC_{50} (μM)	Entry	HCV replication EC_{50} (μM)
5a	4.7	7a	3
5b	0.47	7b	0.19
6a	2.3	10a	15
6b	0.49	10b	0.29

Claims: 23 Total claims.
17 Composition of matter claims.
5 Method of use claims.

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Notes
The authors declare no competing financial interest.