ANTIVIRAL COMPOUNDS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. § 119(e) of United States Provisional Application No. 61/560,654 filed on November 16, 2011, which is hereby incorporated by reference in its entirety.

BACKGROUND

Hepatitis C is recognized as a chronic viral disease of the liver which is characterized by liver disease. Although drugs targeting the liver are in wide use and have shown effectiveness, toxicity and other side effects have limited their usefulness. Inhibitors of hepatitis C virus (HCV) are useful to limit the establishment and progression of infection by HCV as well as in diagnostic assays for HCV.

There is a need for new HCV therapeutic agents. In particular, there is a need for HCV therapeutic agents that have broad activity against HCV genotypes (e.g. genotypes 1a, 1b, 2a, 3a, 4a). There is also a particular need for agents that are less susceptible to viral resistance. Resistance mutations to inhibitors have been described for HCV NS5A for genotypes 1a and 1b in Antimicrobial Agents and Chemotherapy, September 2010, Volume 54, p. 3641-3650.

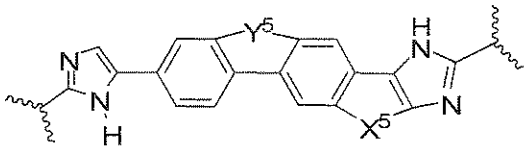
SUMMARY

In one aspect, there is provided~~embodiment the disclosure provides a compound of the disclosure which is~~ a compound of formula (I):

$$E^{1a}\text{-}V^{1a}\text{-}C(=O)\text{-}P^{1a}\text{-}W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}V^{1b}\text{-}E^{1b} \quad (I)$$

wherein:

W^{1a} is



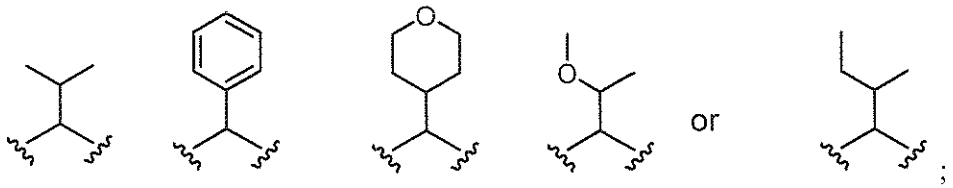
and W^{1a} is optionally substituted with one or more groups independently selected from halo, alkyl, haloalkyl, or cyano;

Y^5 is $-O-CH_2-$, or $-CH_2-O-$; X^5 is $-CH_2-CH_2-$ or $-CH=CH-$;

E^{1a} is -N(H)(alkoxycarbonyl), -N(H)(cycloalkylcarbonyl) or -N(H)(cycloalkyloxycarbonyl); or E^{1a}-V^{1a} taken together are R^{9a};

E^{1b} is -N(H)(alkoxycarbonyl), -N(H)(cycloalkylcarbonyl) or -N(H)(cycloalkyloxycarbonyl); or E^{1b}-V^{1b} taken together are R^{9b};

V^{1a} and V^{1b} are each independently selected from:



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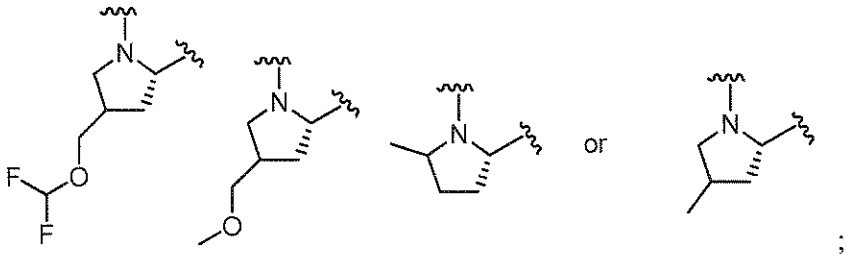
P^{1a} is selected from:



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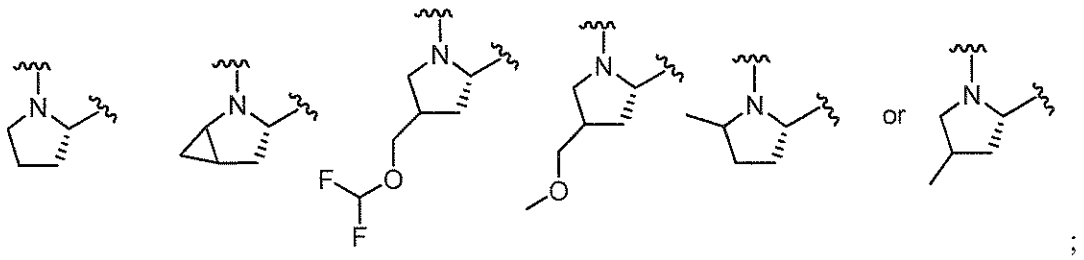
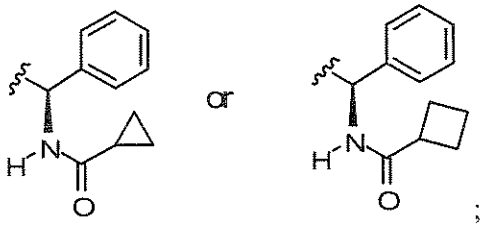
P^{1b} is selected from:



;

and

R^{9a} and R^{9b} are each independently:



;

or a pharmaceutically acceptable salt or prodrug thereof.

The disclosure also provides isotopically enriched compounds that are compounds of the disclosure that comprise an enriched isotope at one or more positions in the compound.

The present disclosure also provides a pharmaceutical composition comprising a compound of the disclosure or a pharmaceutically acceptable salt or prodrug thereof and at least one pharmaceutically acceptable carrier.

In one aspect, there is provided a pharmaceutical composition comprising the compound as described herein or a pharmaceutically acceptable salt thereof; and at least one pharmaceutically acceptable carrier.

In one aspect, there is provided a pharmaceutical composition comprising the compound as defined herein and a pharmaceutically acceptable carrier.

The present disclosure also provides a pharmaceutical composition for use in treating hepatits C (HCV). In one embodiment the composition comprises at least one additional therapeutic agent for treating HCV. In one embodiment, the therapeutic agent is selected from ribavirin, an NS3 protease inhibitor, a nucleoside or nucleotide inhibitor of HCV NS5B polymerase, an alpha-glucosidase 1 inhibitor, a hepatoprotectant, a non-nucleoside inhibitor of HCV polymerase, or combinations thereof.

In one embodiment, composition further comprises a nucleoside or nucleotide inhibitor of HCV NS5B polymerase. In one embodiment, the nucleoside or nucleotide inhibitor of HCV NS5B polymerase is selected from ribavirin, viramidine, levovirin, a L-nucleoside, or isatoribine.

In one aspect, there is~~embodiment in~~ provided a pharmaceutical composition comprising a compound as described herein, ~~and~~ at least one ~~one~~ nucleoside or nucleotide inhibitor of HCV NS5B polymerase, and at least one pharmaceutically acceptable carrier. In one embodiment, the composition further comprises an interferon, a pegylated interferon, ribavirin or combinations thereof. In one embodiment, the compound is the compound exemplified in Example PY. In one embodiment the the nucleoside or nucleotide inhibitor of HCV NS5B polymerase is sofosbuvir.

The present disclosure also provides a pharmaceutical composition further comprising an interferon or pegylated interferon.

The present disclosure also provides a pharmaceutical composition further comprising a nucleoside analog.

The present disclosure also provides for a pharmaceutical composition wherein said nucleoside analogue is selected from ribavirin, viramidine, levovirin, an L-nucleoside, and isatoribine and said interferon is α-interferon or pegylated α-interferon.

The present disclosure also provides for a method of treating hepatitis C, said method comprising administering to a human patient a pharmaceutical composition which comprises a therapeutically effective amount of a compound of the disclosure.

The present disclosure also provides a method of inhibiting HCV, comprising administering to a mammal afflicted with a condition associated with HCV activity, an amount of a compound of the disclosure, effective to inhibit HCV.

The present disclosure also provides a compound of the disclosure for use in medical therapy (e.g. for use in inhibiting HCV activity or treating a condition associated with HCV activity), as well as the use of a compound of the disclosure for the manufacture of a medicament useful for inhibiting HCV or the treatment of a condition associated with HCV activity in a mammal.

In one aspect, there is provided a compound as described herein or a pharmaceutically acceptable salt thereof for use in medical therapy.

In one aspect, there is provided the use of a compound as defined herein for preparing a medicament for treating hepatitis C or a hepatitis C associated disorder.

In one aspect, there is provided the use of a compound as described herein or a pharmaceutically acceptable salt thereof for preparing a medicament for treating hepatitis C or a hepatitis C associated disorder in an animal.

In one aspect, there is provided a compound as described herein or a pharmaceutically acceptable salt thereof for use in the prophylactic or therapeutic treatment of hepatitis C or a hepatitis C associated disorder.

The present disclosure also provides synthetic processes and novel intermediates disclosed herein which are useful for preparing compounds of the disclosure. Some of the compounds of the disclosure are useful to prepare other compounds of the disclosure.

In another ~~aspect~~embodiment the disclosure provides a compound of the disclosure, or a pharmaceutically acceptable salt or prodrug thereof, for use in the prophylactic or therapeutic treatment of hepatitis C or a hepatitis C associated disorder.

In another ~~aspect~~embodiment the disclosure provides a method of inhibiting HCV activity in a sample comprising treating the sample with a compound of the disclosure.

Compounds of formula (I) have been found to possess useful activity against HCV genotypes 1-Additionally certain compounds of formula (I) have significant potency against resistant variants in GT1.