

NS5A is highly phosphorylated by cellular protein kinases and the phosphorylation sites are conserved among HCV genotypes (Katze et al, 2001; Kim et al, 1999)

The discovery of novel antiviral strategies to selectively inhibit HCV replication has long been hindered by the lack of convenient cell culture models for the propagation of HCV (“Recent Advances in Nucleoside Monophosphate Prodrugs as Anti-hepatitis C Virus Agents” Bobeck, D. R.; Coats, S. J.; Schinazi, R. F. *Antivir. Ther.* **2010**; Book Chapter: “Approaches for the Development of Antiviral Compounds: The Case of Hepatitis C Virus.” Raymond F. Schinazi, Steven J. Coats, Leda C. Bassit, Johan Lennerstrand, James H. Nettles, and Selwyn J. Hurwitz in: *Handbook of Experimental Pharmacology*, vol. 189, 25-51: Antiviral Strategies; Edited by: Hans-Georg Kräusslich and Ralf Bartenschlager © Springer-Verlag Berlin Heidelberg 2009). This hurdle has been overcome first with the establishment of the HCV replicon system in 1999 (Bartenschlager, R., *Nat. Rev. Drug Discov.* **2002**, *1*, 911–916 and Bartenschlager, R., *J. Hepatol.* **2005**, *43*, 210–216) and, in 2005, with the development of robust HCV cell culture models (Wakita, T., et al., *Nat. Med.* **2005**, *11*, 791-6; Zhong, J., et al., *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 9294-9; Lindenbach, B.D., et al., *Science* **2005**, *309*, 623-6).

It would be advantageous to provide new antiviral agents, compositions including these agents, and methods of treatment using these agents, particularly to treat HCV and drug-resistant HCV. The present invention provides such agents, compositions and methods.

Summary

Disclosed herein are compounds, methods and compositions for treating or preventing HCV infection in a host. The methods involve administering a therapeutically or prophylactically-effective amount of at least one compound as described herein to treat or prevent an infection by, or an amount sufficient to reduce the biological activity of HCV infection. The pharmaceutical compositions include one or more of the compounds described herein, in combination with a pharmaceutically acceptable carrier or excipient, for treating a host infected with HCV. These compounds can be used in combination with nucleoside and non-nucleoside inhibitors of HCV. The formulations can further include at least one other therapeutic agent. In addition, the present invention includes processes for preparing such compounds.

In one example, the active compound is of Formula (I):

j is 0-4, and

x is 0-2.

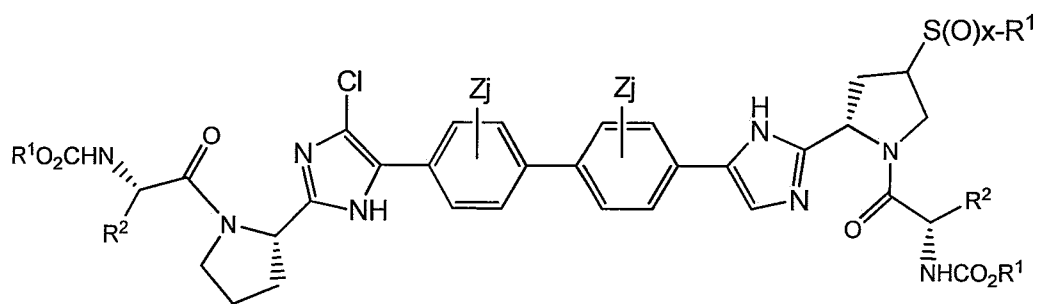
The compounds described herein can be in the form of the R- or S-configuration, or a mixture thereof, including a racemic or diastereomeric mixture thereof.

In one example, one or both of the R^2 substituents are phenyl or phenyl substituted with one or more substituents Z as defined herein.

In one example, one, two, or three of the R^1 substituents are $-CH_3$.

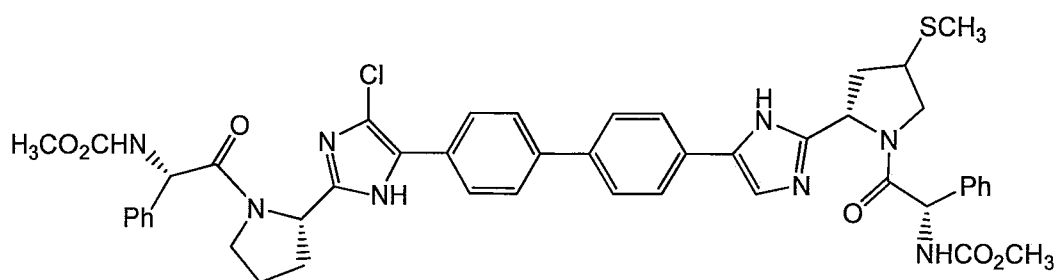
In one example, each R^1 is $-CH_3$ and both of the R^2 substituents are phenyl or phenyl substituted with one or more substituents Z as defined herein.

A subset of the compounds of Formula (I) is provided below as Formula (IA):



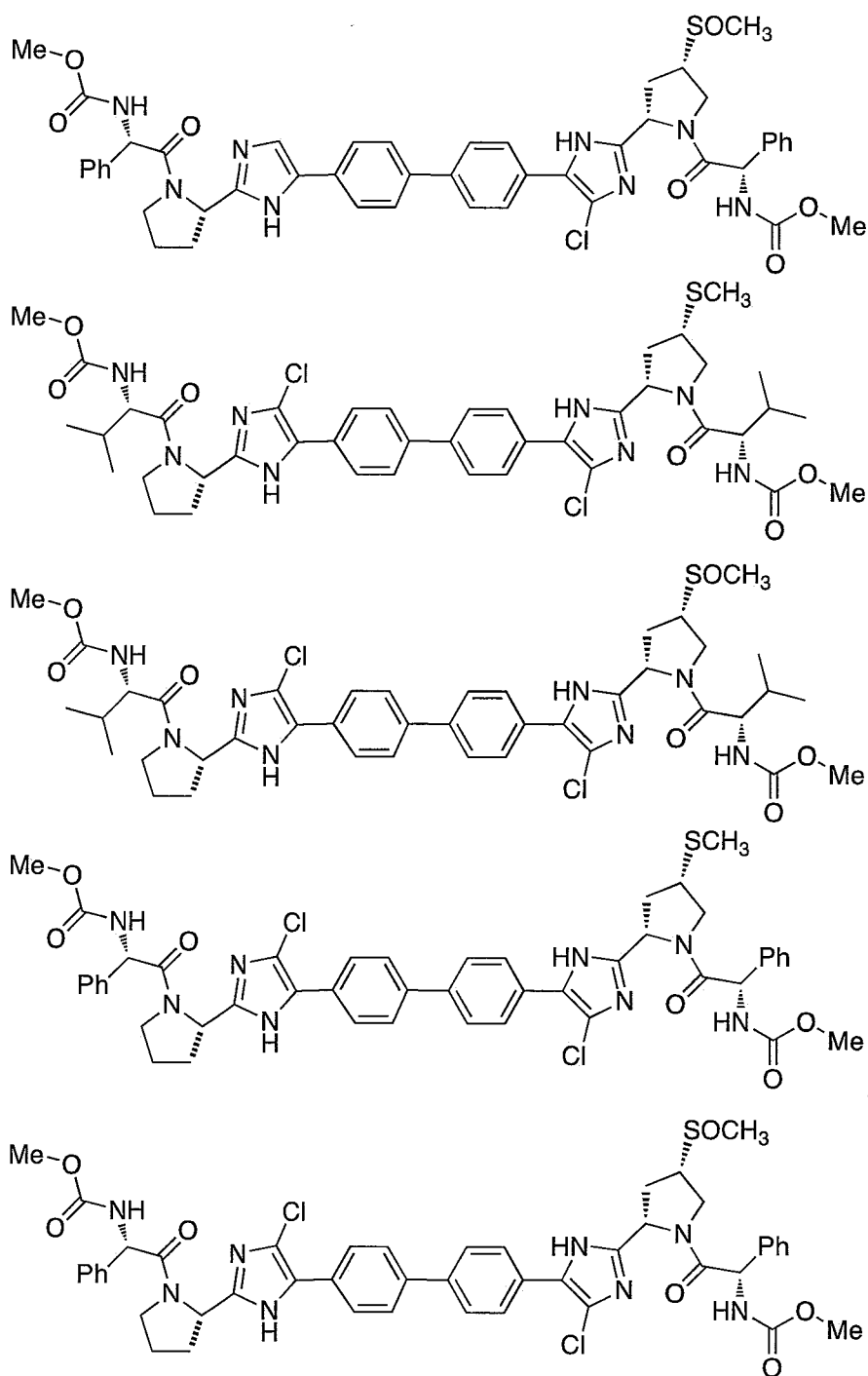
In which R^1 , R^2 , Z, R' , R'' , j, and x are as defined with respect to Formula (I).

Representative compounds include the following:



and all other diastereomers thereof, as well as $-S(O)-CH_3$ and $-S(O)_2-CH_3$ analogs thereof.

Further representative compounds have one of the following formulas:



and

and pharmaceutically-acceptable salts or prodrugs thereof.

In one example, there is provided the use of a compound as described herein in the preparation of a medicament for treating a host infected with HCV.

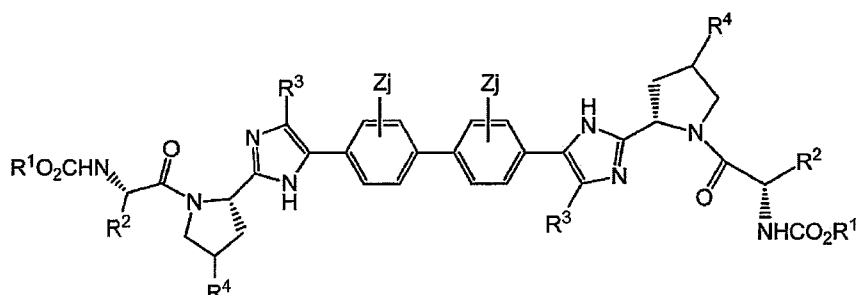
In one example, there is provided the use of a compound as described herein in the preparation of a medicament for preventing an infection from HCV.

In one example, there is provided the use of a compound as described herein in the preparation of a medicament for reducing the biological activity of an infection with HCV in a host.

In one example, there is provided the use of a compound as described herein in the preparation of a medicament for treating a host infected with HCV, wherein the medicament further comprises one, two, or three other anti-HCV agent(s).

In one example, there is provided the use of a compound as described herein in the preparation of a medicament for preventing an infection from HCV, wherein the medicament further comprises one, two, or three other anti-HCV agent(s).

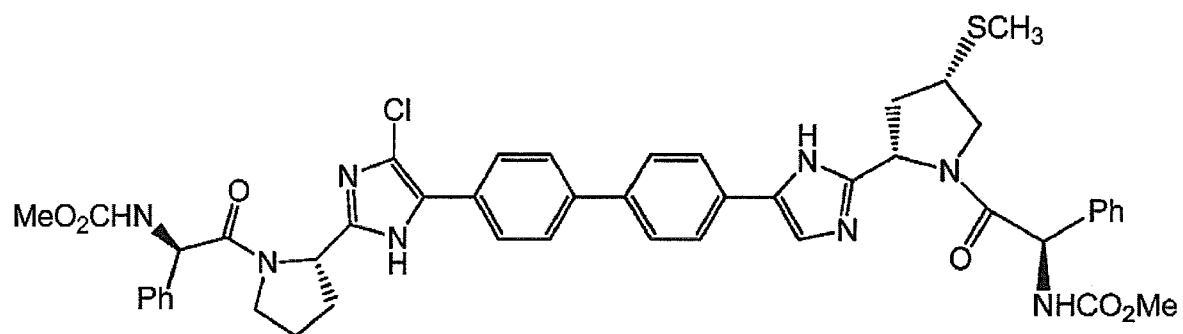
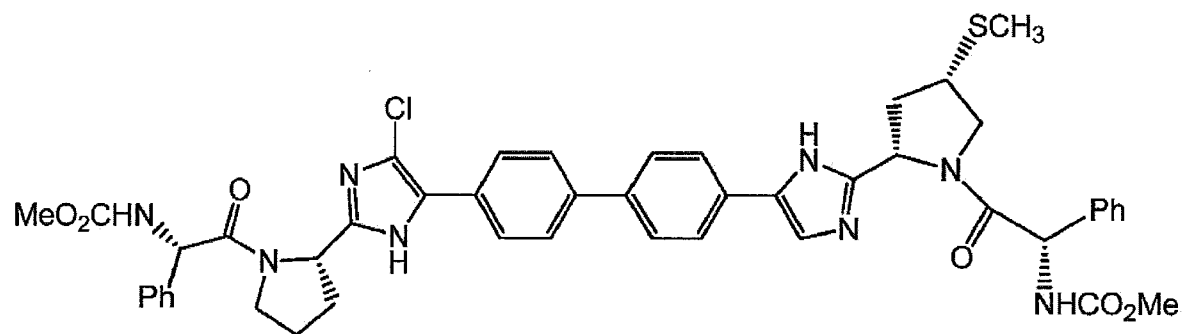
In one aspect, the present invention refers to a compound of Formula (I)

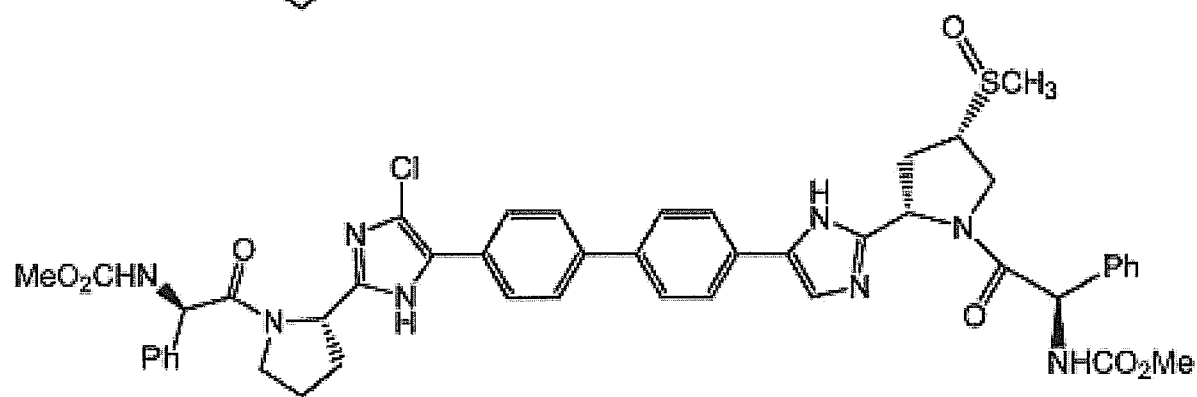
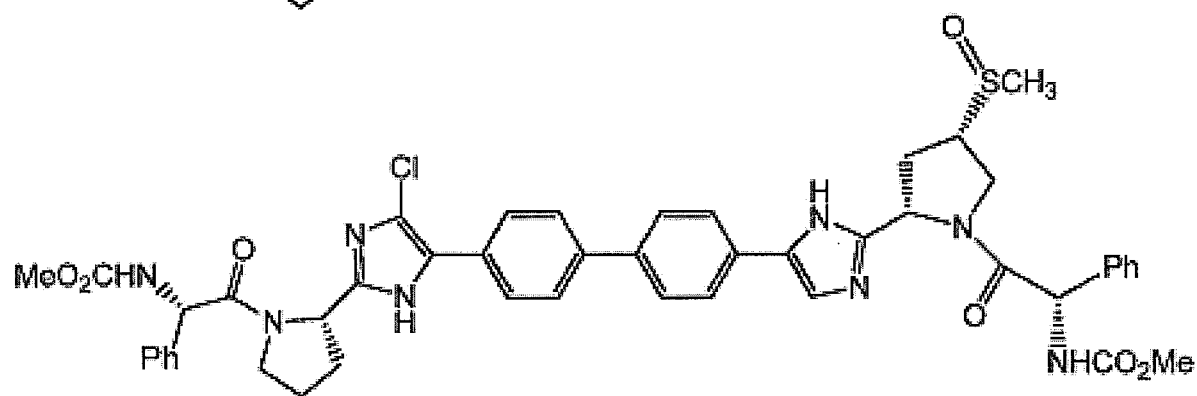
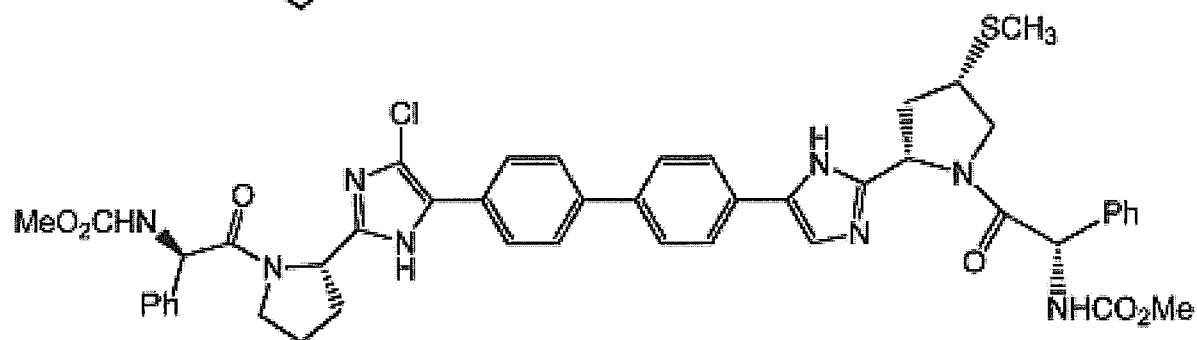
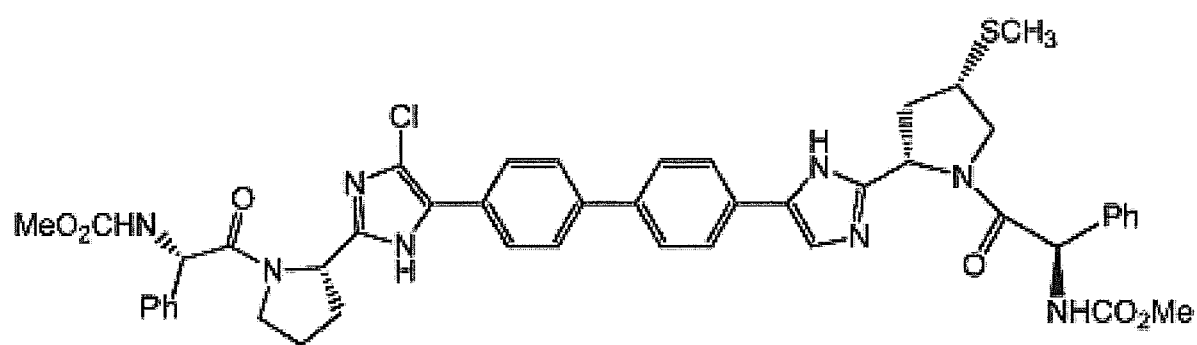


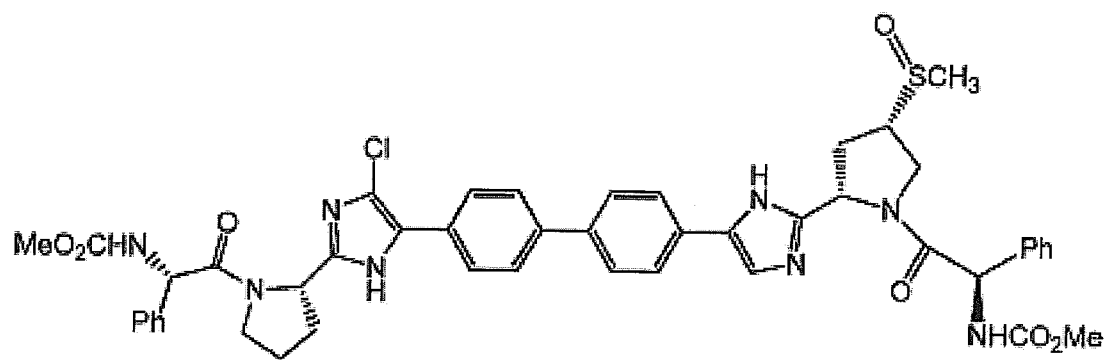
R^1 is, independently, H, C_{1-6} alkyl, aryl- C_{1-6} -alkyl, C_{1-6} alkyl-aryl, or aryl, R^2 is, independently, H, aryl- C_{1-6} -alkyl, C_{1-6} alkyl-aryl, aryl, C_{1-6} alkyl-guanidine, C_{1-6} alkylamino, C_{1-6} alkyl-S- C_{1-6} alkyl, C_{1-6} alkylthiol, C_{1-6} alkyl-hydroxy, C_{1-6} alkyl-amide, C_{1-6} alkyl-phenoxy, C_{1-6} alkyl-carboxy heteroaryl, and heteroaryl- C_{1-6} alkyl, wherein aryl rings can be substituted with from 1 to 3 substituents Z as defined herein, R^3 is, independently, H or Cl, with the proviso that at least one R^3 is Cl, R^4 is, independently, H or $-S(O)_xR^1$, with the proviso that at least one R^4 is $-S(O)_xR^1$, Z is selected from the group consisting of C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl heterocyclyl, aryl, heteroaryl, arylalkoxycarbonyl, carboxy, halo, haloalkyl, $-OR'$, $-NR'R''$, hydroxy, hydroxy- C_{1-6} alkyl, alkoxyalkyl(C_{2-8}), alkoxycarbonyl, $-CF_3$, $-CN$, $-NO_2$, $-C_2R'$, $-N_3$, $-C(=O)NR'R''$, $-NR'C(=O)R''$, $-C(=O)R'$, $-C(=O)OR'$, $-OC(=O)NR'R''$, $-NR'C(=O)OR''$, $-SO_2R'$, $-SO_2NR'R''$, $-NR'SO_2R''$, $N(R')_2$, SR' , $OCOR'$, $N(COR')R'$, $N(COR')COR'$, and $SCOR'$, Each R' and R'' are, independently, H, a C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, aryl- C_{1-6} -alkyl; or if two R' reside on the same nitrogen atom they can come together to form an alkyl ring (C_{3-6}) containing none or one heteroatom independently selected from N, O, and S; wherein the R' groups can be substituted with one or more Z substituents as defined above, j is 0-4, and x is 0-2, or a pharmaceutically acceptable salt

thereof, wherein the compound is in the form of the R- or S-configuration at any chiral center.

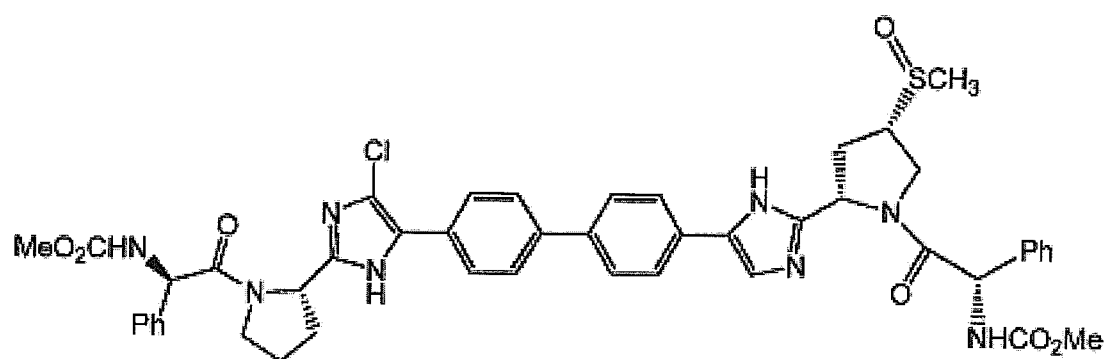
In another aspect, the present invention refers to a compound having one of the following formulas:



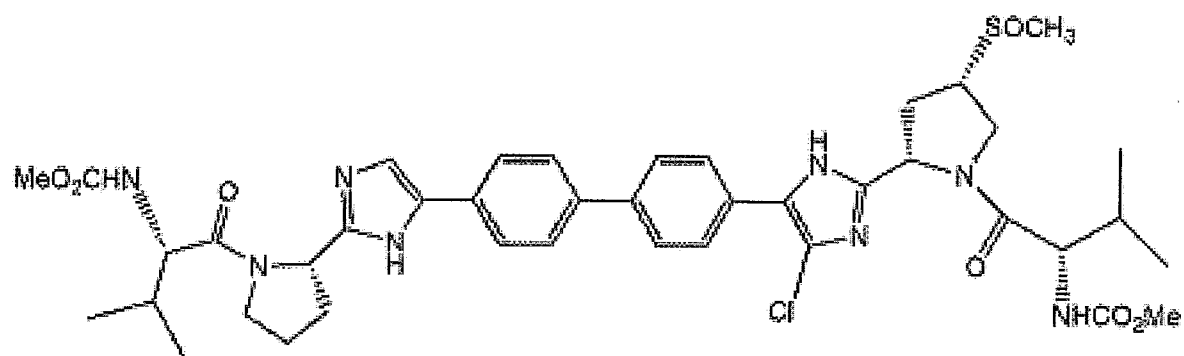
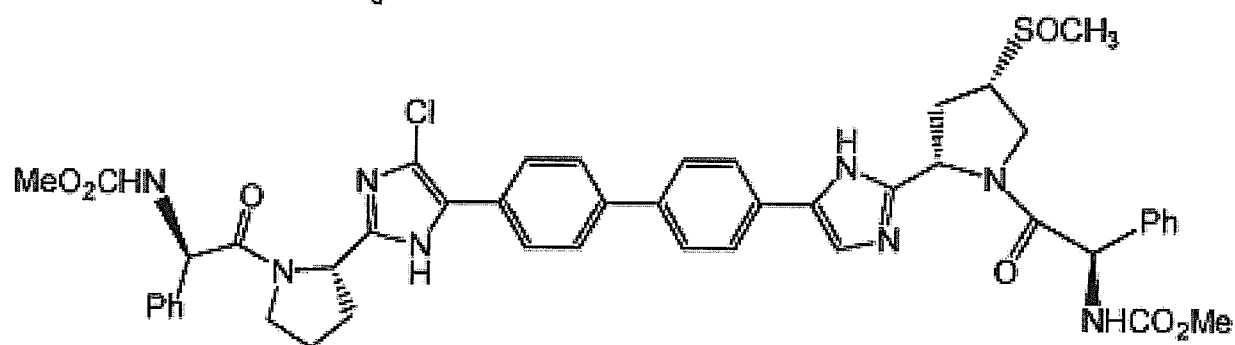
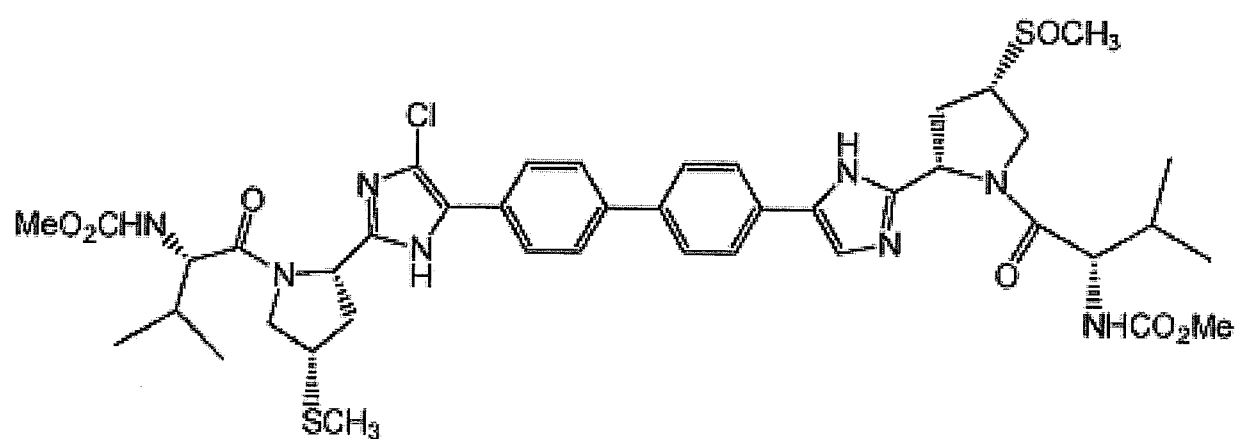


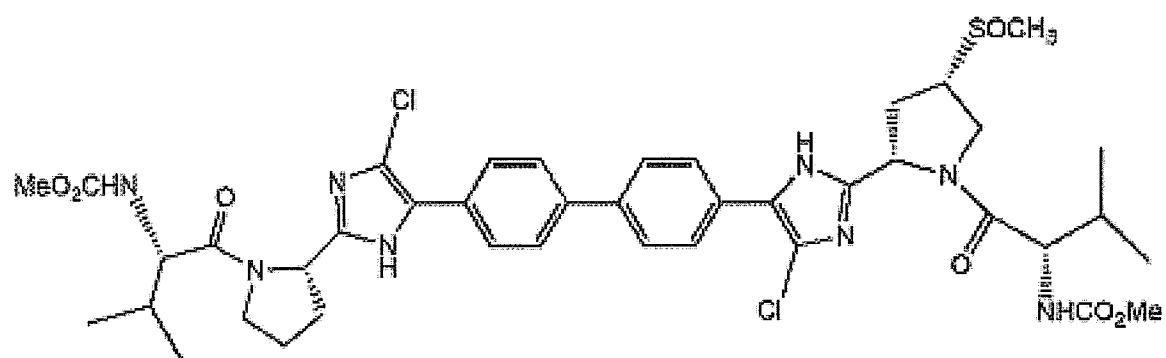
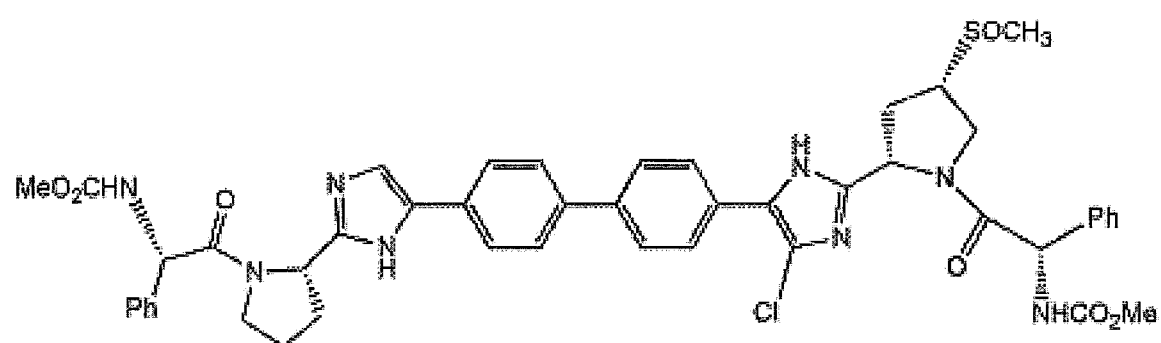
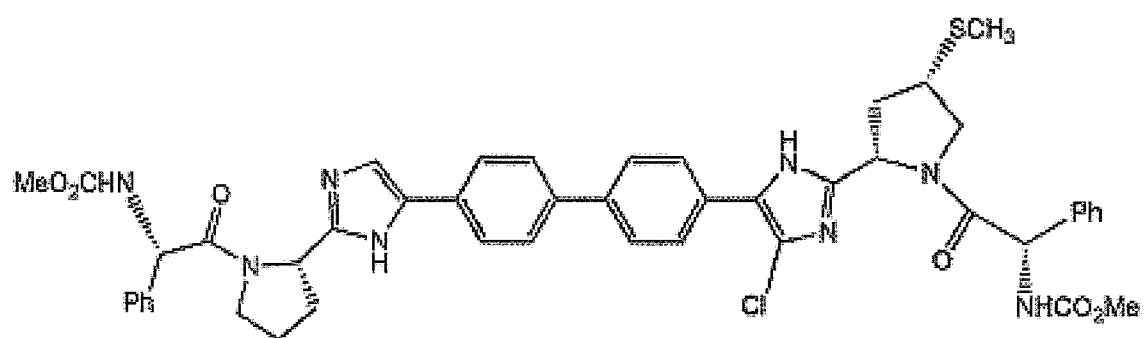


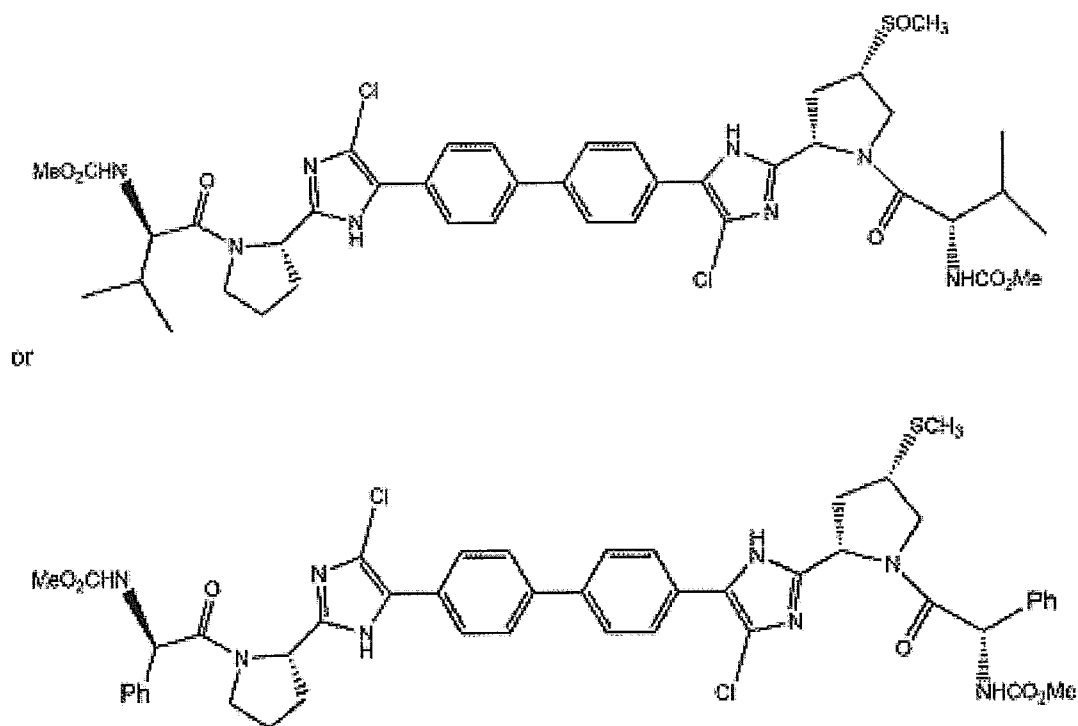
or



or a pharmaceutically acceptable salt thereof. In yet another aspect, the present invention refers to a compound having one of the following formulas:

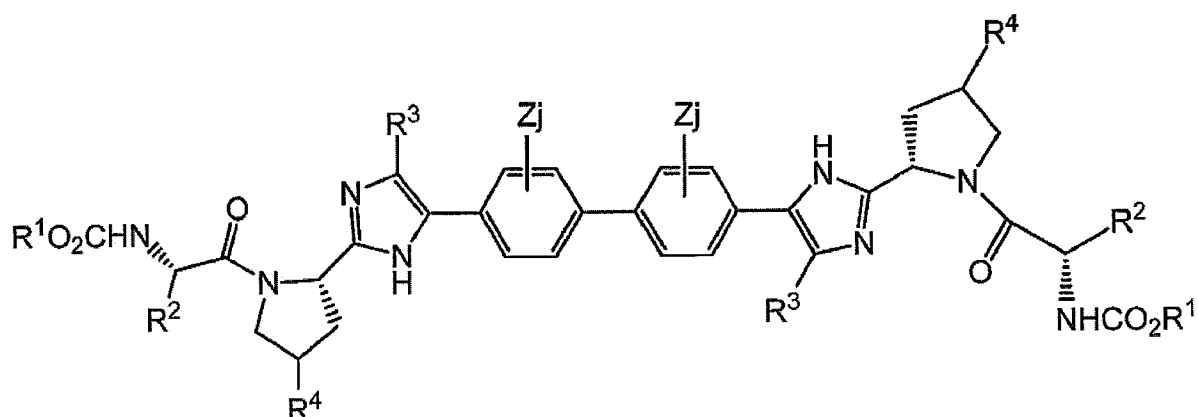






or a

pharmaceutically acceptable salt thereof. In a further aspect, the present invention refers to a composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In another aspect, the present invention refers to use of a compound as disclosed herein in the manufacture of a medicament for treating a host infected with HCV. In yet another aspect, the present invention refers to a compound of Formula (I):

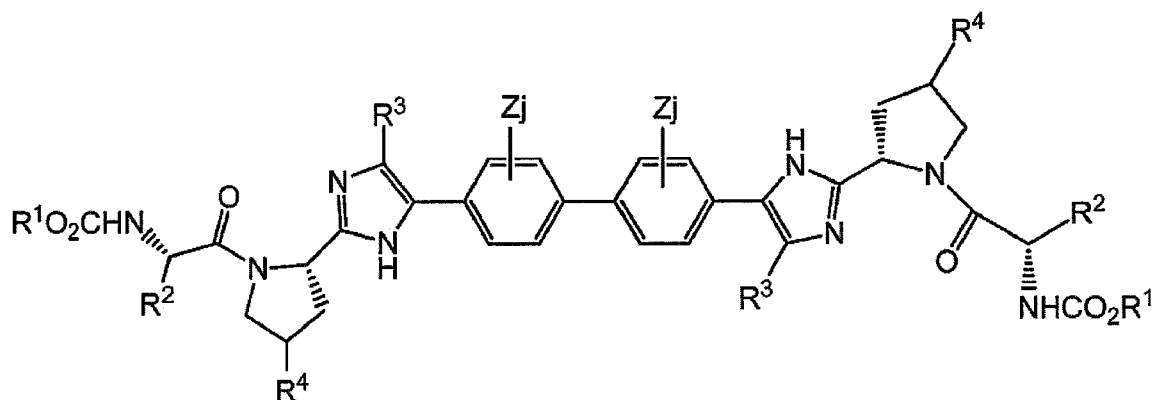


R^1 is, independently, H, C_{1-6} alkyl, aryl- C_{1-6} -alkyl, C_{1-6} alkyl-aryl, or aryl, R^2 is, independently, H, C_{1-6} alkyl, aryl- C_{1-6} -alkyl, C_{1-6} alkyl-aryl, aryl, C_{1-6} alkyl-guanidine, C_{1-6} alkylamino, C_{1-6} alkyl-S- C_{1-6} alkyl, C_{1-6} alkylthiol, C_{1-6} alkyl-hydroxy, C_{1-6} alkyl-amide, C_{1-6} alkyl-phenoxy, C_{1-6} alkyl-carboxy heteroaryl, and heteroaryl- C_{1-6} alkyl, wherein aryl rings can be substituted with from 1 to 3 substituents Z as defined herein, R^3 is, independently, H

or Cl, with the proviso that at least one R³ is Cl, R⁴ is, independently, H or -S(O)R¹, with the proviso that at least one R⁴ is -S(O)R¹, Z is selected from the group consisting of C₁₋₈ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl heterocyclyl, aryl, heteroaryl, arylalkoxycarbonyl, carboxy, halo, haloalkyl, -OR', -NR'R'', hydroxy, hydroxy-C₁₋₆ alkyl, alkoxyalkyl(C₂₋₈), alkoxycarbonyl, -CF₃, -CN, -NO₂, -C₂R', -N₃, -C(=O)NR'R'', -NR'C(=O)R'', -C(=O)R', -C(=O)OR', -OC(=O)NR'R'', -NR'C(=O)OR'', -SO₂R', -SO₂NR'R'', -NR'SO₂R'', N(R')₂, SR', OCOR', N(COR')R', N(COR')COR', and SCOR', Each R' and R'' are, independently, H, a C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, aryl-C₁₋₆-alkyl; or if two R' reside on the same nitrogen atom they can come together to form an alkyl ring (C₃₋₆) containing none or one heteroatom independently selected from N, O, and S; wherein the R' groups can be substituted with one or more Z substituents as defined above, j is 0-4, or a pharmaceutically acceptable salt thereof

The compounds can be used in combination therapy, for example, using conventional ribavirin/Pegasys therapy. Representative anti-HCV agents for use in combination therapy include, but are not limited to, a combination of Pegylated interferon (Pegasys) and ribavirin, polymerase inhibitors such as IDX-375 and IDX-184 (Idenix), PSI-7851 and PSI-7977 (Pharmasset) danoprevir (InterMune/Genentech), RG7128 (Pharmasset/Genentech), I

1. A compound of Formula (I):



R² is, independently, H, aryl-C₁₋₆-alkyl, C₁₋₆ alkyl-aryl, aryl, C₁₋₆ alkyl-guanidine, C₁₋₆ alkylamino, C₁₋₆ alkyl-S-C₁₋₆ alkyl, C₁₋₆ alkylthiol, C₁₋₆ alkyl-hydroxy, C₁₋₆ alkyl-amide, C₁₋₆ alkyl-phenoxy, C₁₋₆ alkyl-carboxy heteroaryl, and heteroaryl-C₁₋₆ alkyl, wherein aryl rings can be substituted with from 1 to 3 substituents Z as defined herein,

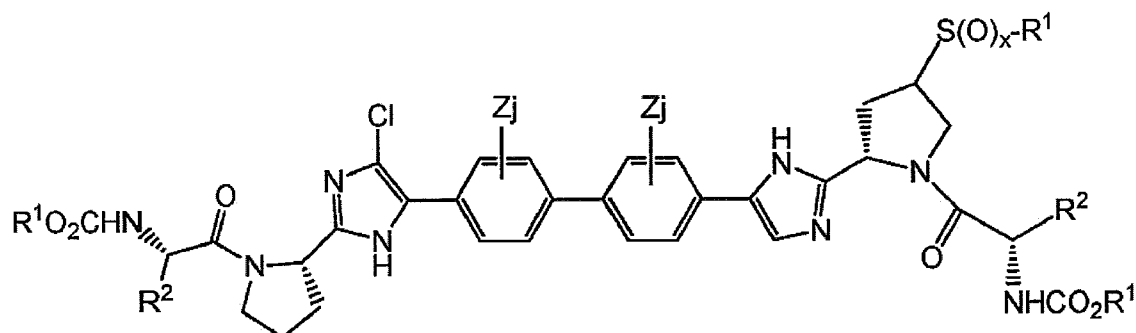
R^4 is, independently, H or $-S(O)_xR^1$, with the proviso that at least one R^4 is $-S(O)_xR^1$,

Each R' and R'' are, independently, H, a C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, aryl-C₁₋₆-alkyl; or if two R' reside on the same nitrogen atom they can come together to form an alkyl ring (C₃₋₆) containing none or one heteroatom independently selected from N, O, and S; wherein the R' groups can be substituted with one or more Z substituents as defined above,

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x is 0-2, or a pharmaceutically acceptable salt thereof, wherein the compound is in the form of the R- or S-configuration at any chiral center.

2. The compounds of claim 1, of the formula:



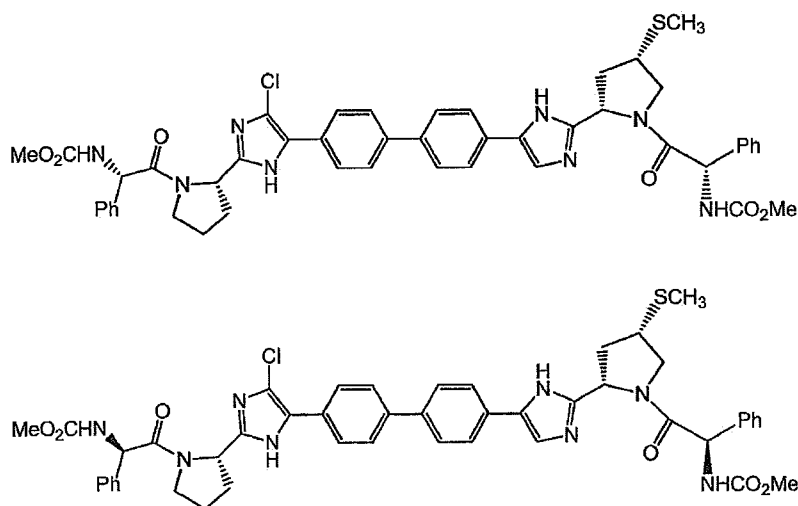
wherein R^1 , R^2 , Z, R' , R'' , j, and x are as defined with respect to Formula (I).

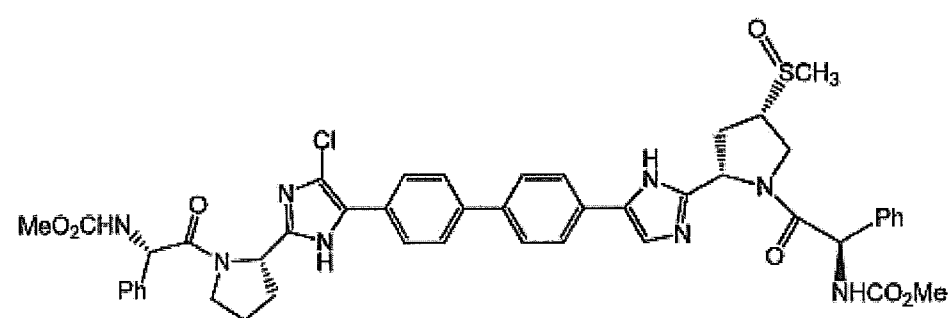
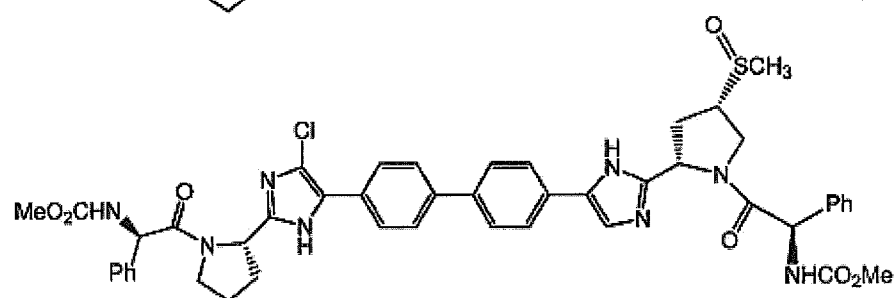
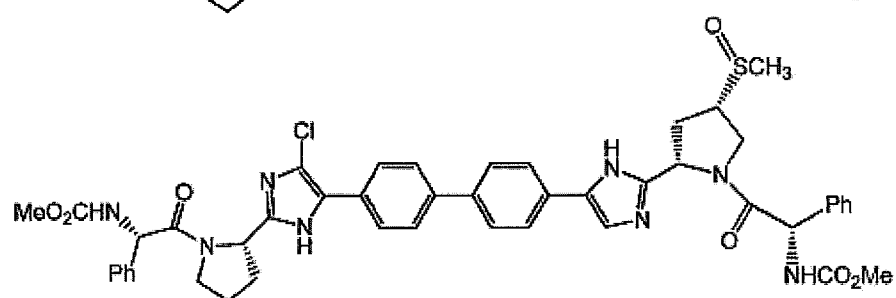
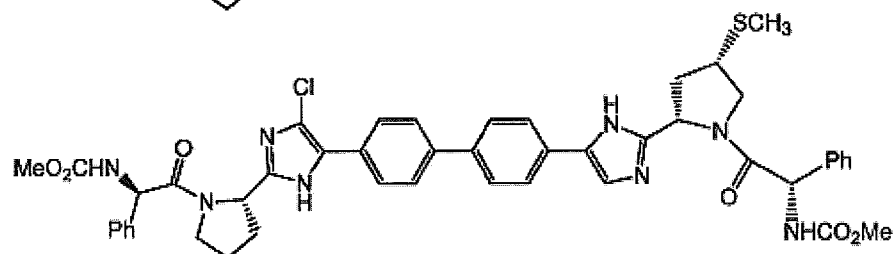
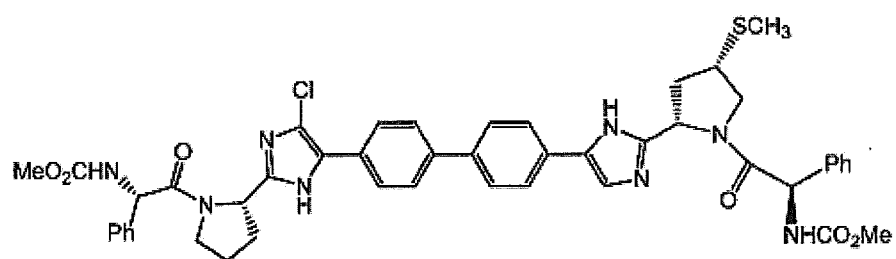
3. The compound of claim 1, wherein one or both of the R^2 substituents are phenyl or phenyl substituted with one or more substituents Z as defined herein.

4. The compound of claim 1, wherein one or two of the R^1 substituents are $-CH_3$.

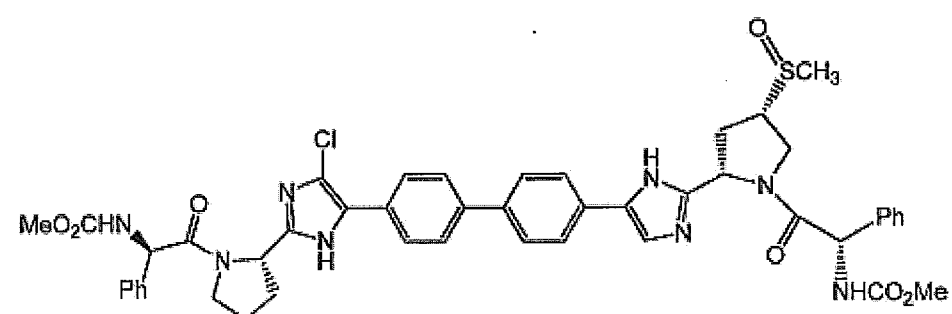
5. The compound of claim 1, wherein each R^1 is $-CH_3$ and both of the R^2 substituents are phenyl or phenyl substituted with one or more substituents Z.

6. A compound having one of the following formulas:



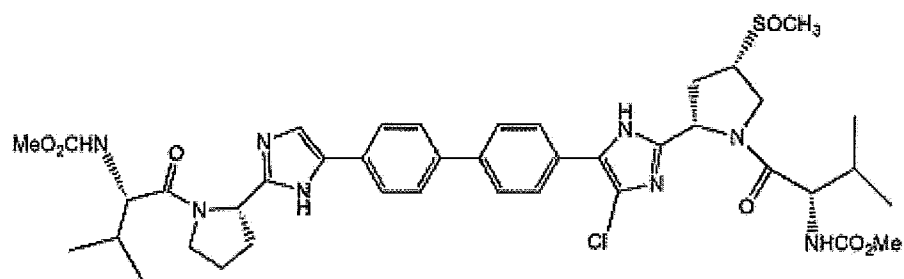
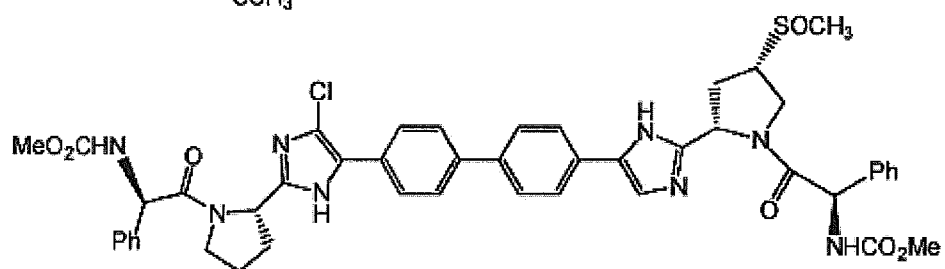
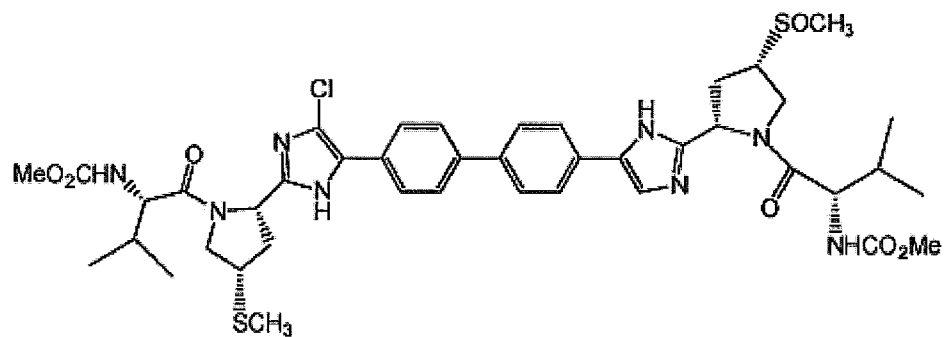


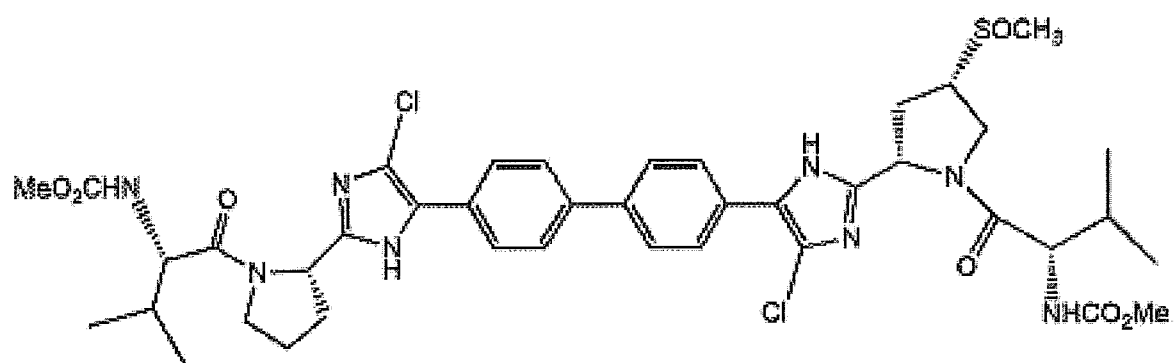
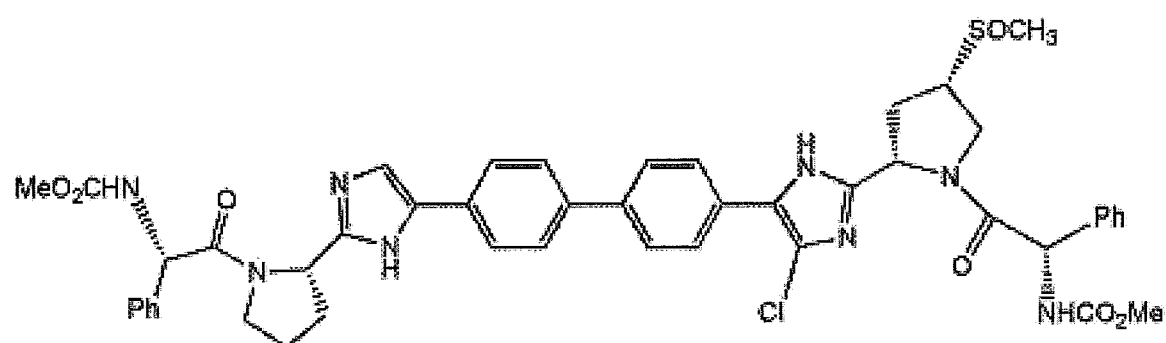
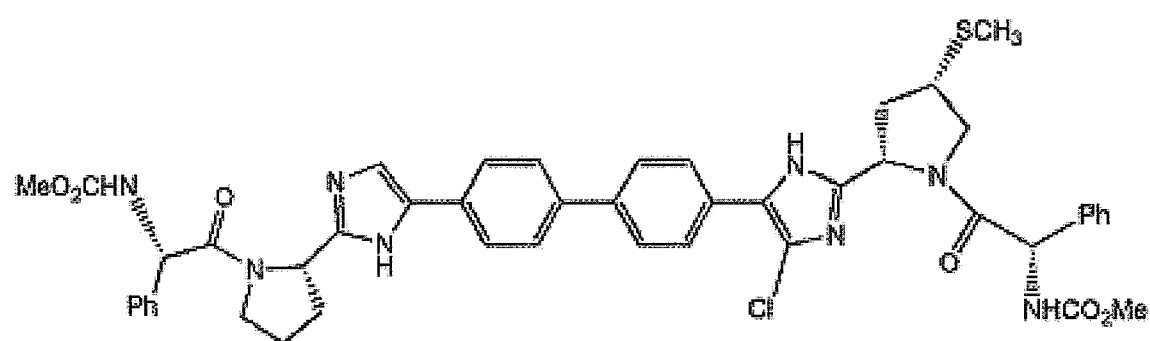
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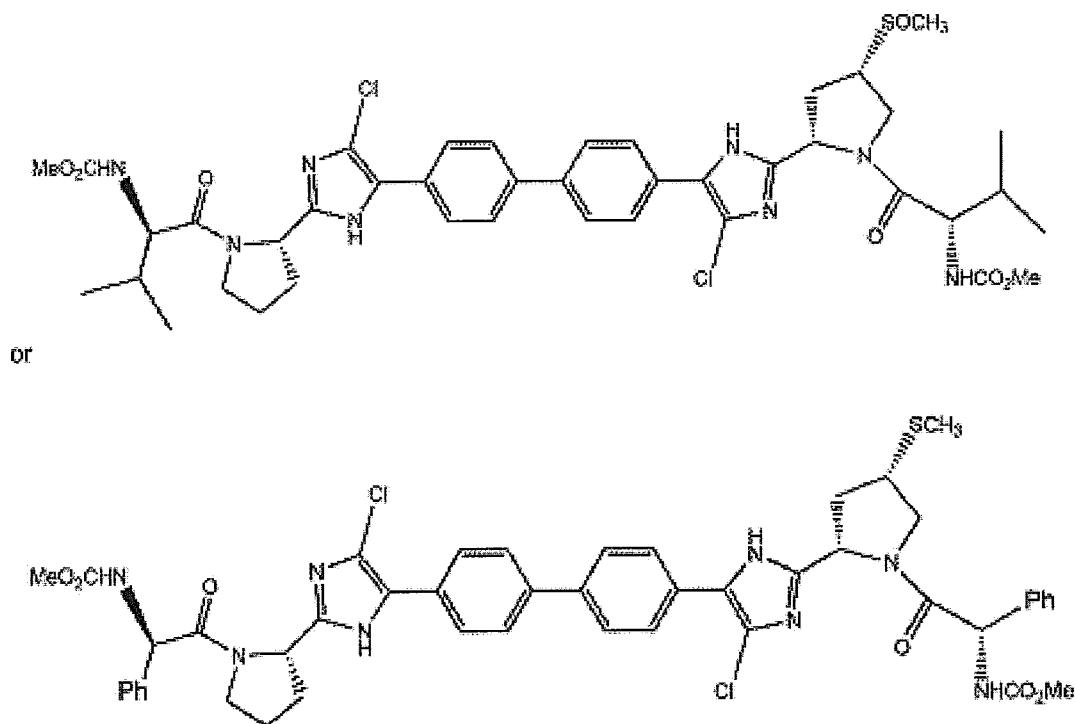


or a pharmaceutically acceptable salt thereof.

7. A compound having one of the following formulas:







or a pharmaceutically acceptable salt thereof.

8. A composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

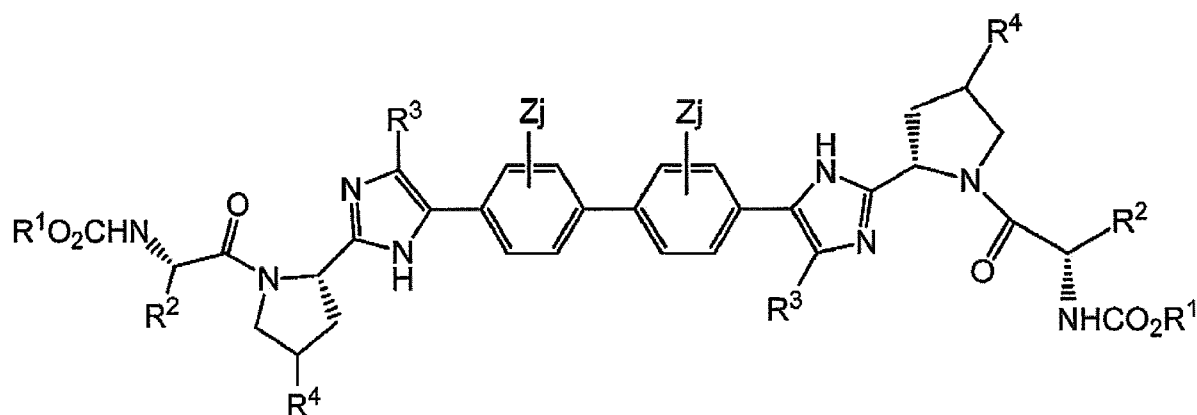
9. The composition of claim 8, further comprising one, two, or three additional compounds having anti-HCV activity.

10. Use of a compound of claim 1 in the manufacture of a medicament for treating a host infected with HCV.

11. The use of claim 10, wherein the compound is to be administered in combination with one, two, or three other anti-HCV agent(s).

12. The compound of claim 1, wherein one or both of R^2 are aryl, wherein each aryl ring can be substituted with from 1 to 3 substituents Z.

13. A compound of Formula (I):



R^1 is, independently, H, C_{1-6} alkyl, aryl- C_{1-6} -alkyl, C_{1-6} alkyl-aryl, or aryl,

R^2 is, independently, H, C_{1-6} alkyl, aryl- C_{1-6} -alkyl, C_{1-6} alkyl-aryl, aryl, C_{1-6} alkyl-guanidine, C_{1-6} alkylamino, C_{1-6} alkyl-S- C_{1-6} alkyl, C_{1-6} alkylthiol, C_{1-6} alkyl-hydroxy, C_{1-6} alkyl-amide, C_{1-6} alkyl-phenoxy, C_{1-6} alkyl-carboxy heteroaryl, and heteroaryl- C_{1-6} alkyl, wherein aryl rings can be substituted with from 1 to 3 substituents Z as defined herein,

R^3 is, independently, H or Cl, with the proviso that at least one R^3 is Cl,

R^4 is, independently, H or $-S(O)R^1$, with the proviso that at least one R^4 is $-S(O)R^1$,

Z is selected from the group consisting of C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl heterocyclyl, aryl, heteroaryl, arylalkoxycarbonyl, carboxy, halo, haloalkyl, $-OR'$, $-NR'R''$, hydroxy, hydroxy- C_{1-6} alkyl, alkoxyalkyl(C_{2-8}), alkoxycarbonyl, $-CF_3$, $-CN$, $-NO_2$, $-C_2R'$, $-N_3$, $-C(=O)NR'R''$, $-NR'C(=O)R''$, $-C(=O)R'$, $-C(=O)OR'$, $-OC(=O)NR'R''$, $-NR'C(=O)OR''$, $-SO_2R'$, $-SO_2NR'R''$, $-NR'SO_2R''$, $N(R')_2$, SR' , $OCOR'$, $N(COR')R'$, $N(COR')COR'$, and $SCOR'$,

Each R' and R'' are, independently, H, a C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, aryl- C_{1-6} -alkyl; or if two R' reside on the same nitrogen atom they can come together to form an alkyl ring (C_{3-6}) containing none or one heteroatom independently selected from N, O, and S; wherein the R' groups can be substituted with one or more Z substituents as defined above,

j is 0-4, or a pharmaceutically acceptable salt thereof.