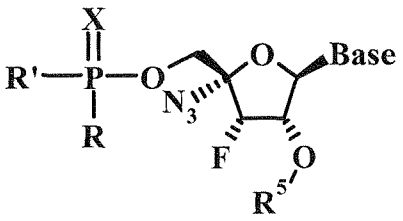
and shown to replicate with high efficiency. It is believed that the mechanism of RNA replication in these cell lines is identical to the replication of the full length HCV RNA genome in infected hepatocytes. The subgenomic HCV cDNA clones used for the isolation of these cell lines have formed the basis for the development of a cell-based assay for identifying nucleoside analogue inhibitors of HCV replication.

SUMMARY

[0006] The compounds of Formula I are useful for the treatment of diseases mediated by the Hepatitis C Virus (HCV) and for pharmaceutical compositions comprising such compounds.

[0007] The application provides a compound of Formula I:



I

wherein:

R is O-R^1 or $NR^4R^{1'}$;

R' is $N(R^4)C(R^{2a})(R^{2b})C(=O)OR^3$ or $-OR^3$;

$R^{1'}$ is $-C(R^{2a})(R^{2b})C(=O)OR^3$;

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

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

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

each R^{1c} is lower alkyl;

each R^{2a} and R^{2b} are independently H, lower alkyl, $-(CH_2)_rN(R^{1a})_2$, 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, $-(CH2)_mC(=O)R^{1b}$, aryl and aryl lower alkyl, wherein aryl may optionally be substituted with one or more hydroxy, lower alkyl, lower alkoxy, halo, nitro or cyano;

m is 0 to 3;

p is 0 to 2;

r is 1 to 6;

or R^{2a} is H and R^{2b} and R^4 together form $(CH_2)_n$;

n is 4 or 5;

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

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

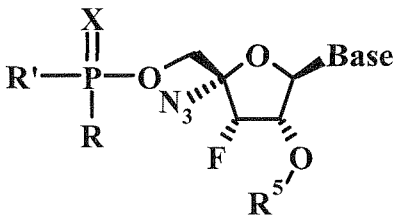
R^5 is H, $C(=O)R^{1c}$, $C(=O)R^{1b}$, $P(=O)(OR^1)(OR^{1a})$, or $P(=O)(OR^1)(NR^4R^7)$;

Base is uracil, cytosine, guanine, adenine, thymine, 7-deaza-7-fluoro adenosine or heterocycloalkyl, each of which may optionally substituted with one or more hydroxy, lower alkyl, lower alkoxy, halo, nitro or cyano; and

X is O or S;

or a pharmacologically acceptable salt thereof.

[0007a] In one aspect, there is provided a compound of Formula I:



I

wherein:

R is O-R^1 or $NR^4R^{1'}$;

R' is $N(R^4)C(R^{2a})(R^{2b})C(=O)OR^3$ or $-OR^3$;

$R^{1'}$ is $-C(R^{2a})(R^{2b})C(=O)OR^3$;

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

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

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

each R^{1c} is lower alkyl;

each R^{2a} and R^{2b} are independently H, lower alkyl, $-(CH_2)_rN(R^{1a})_2$, 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, $-(CH2)_mC(=O)R^{1b}$, aryl and aryl lower alkyl, wherein aryl may optionally be substituted with one or more hydroxy, lower alkyl, lower alkoxy, halo, nitro or cyano;

m is 0 to 3;

p is 0 to 2;

r is 1 to 6;

or R^{2a} is H and R^{2b} and R^4 together form $(CH_2)_n$;

n is 4 or 5;

R^3 is H, lower alkyl, lower haloalkyl, 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 $P(=O)(OR^1)(NR^4R^7)$;

Base is cytosine, which may optionally substituted with one or more hydroxy, lower alkyl, lower alkoxy, halo, nitro or cyano; and

X is O or S;

or a pharmacologically acceptable salt thereof.

[0007b] In another aspect, there is provided a compound selected from the group consisting of:

4'-Azido-3'-deoxy-3'-fluorouridine-5'-(*O*-phenyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl thiophosphoramidate;

4'-Azido-3'-deoxy-3'-fluorouridine-5'-(*O*-1-naphthyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl thiosphosphoramidate;

4'-Azido-3'-deoxy-3'-fluorouridine-5'-(*O*-2-naphthyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl thiosphosphoramidate;

4'-Azido-3'-deoxy-3'-fluorocytidine-5'-(*O*-phenyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl thiosphosphoramidate;

4'-Azido-3'-deoxy-3'-fluorocytidine-5'-(*O*-2-naphthyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl thiosphosphoramidate;

4'-Azido-3'-deoxy-3'-fluorocytidine-5'-(*O*-2-naphthyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl thiosphosphoramidate;

4'-Azido-3'-deoxy-3'-fluorouridine-5'-{*N,N'*-bis[(S)-1-(isopropoxylcarbonyl)ethyl]phosphorodiamidate;

4'-Azido-3'-deoxy-3'-fluorocytidine-5'-{*N,N'*-bis[(S)-1-(isopropoxylcarbonyl)ethyl]phosphorodiamidate;

4'-Azido-3'-deoxy-3'-fluorouridine-5'-{*N,N'*-bis[(S)-1-(isopropoxylcarbonyl)ethyl]thiphosphorodiamidate;

4'-Azido-3'-deoxy-3'-fluorocytidine-5'-{*N,N'*-bis[(S)-1-(benzyloxycarbonyl)ethyl]phosphorodiamidate;

4'-Azido-3'-deoxy-3'-fluorocytidine-5'-{*N,N'*-bis[(S)-1-(2,2-dimethylpropyloxylcarbonyl)ethyl]phosphorodiamidate;

4'-Azido-3'-deoxy-3'-fluorocytidine-5'-{*N,N'*-bis[(S)-1-(3,3-dimethylbutyloxylcarbonyl)ethyl]phosphorodiamidate;

4'-Azido-3'-deoxy-3'-fluorocytidine-5'-{*N,N'*-bis[(S)-1-(pentyloxylcarbonyl)ethyl]phosphorodiamidate; and

4'-Azido-3'-deoxy-3'-fluorocytidine-5'-{*N,N'*-bis[(S)-1-(cyclopentyloxylcarbonyl)ethyl]phosphorodiamidate.

[0008] The application provides a method for treating a Hepatitis C Virus (HCV) infection comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula I.

[0008a] In another aspect, there is provided a compound as defined herein for use in the treatment of a Hepatitis C Virus (HCV) infection.

[0008b] In another aspect, there is provided a combination of a compound as defined herein with an immune system modulator and/or an antiviral agent that inhibits replication of HCV for use in the treatment of a Hepatitis C Virus (HCV) infection.

[0008c] In another aspect, there is provided use of a compound as defined herein in the manufacture of a medicament for the treatment of a Hepatitis C Virus (HCV) infection.

[0008d] In another aspect, there is provided a compound as defined herein for use in inhibiting the replication of HCV in a cell.

[0008e] In another aspect, there is provided use of a compound as defined herein in the manufacture of a medicament for inhibiting the replication of HCV in a cell.

[0009] The application provides a composition comprising a compound of Formula I and a pharmaceutically acceptable excipient.

[0009a] In another aspect, there is provided a composition comprising the compound as defined herein, admixed with at least one carrier, diluent or excipient.

DETAILED DESCRIPTION OF THE INVENTION

[0010] The compounds of Formula I have been shown to be inhibitors of subgenomic Hepatitis C Virus replication in a hepatoma cell line. These compounds have the potential to be efficacious as antiviral drugs for the treatment of HCV infections in human.

[0011] The term "alkyl" as used herein denotes a straight or branched chain hydrocarbon residue containing 1 to 12 carbon atoms. Preferably, the term "alkyl" denotes a straight or branched chain hydrocarbon residue containing 1 to 7 carbon atoms. Most preferred are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl or pentyl. The alkyl may be unsubstituted or substituted. The substituents are selected from one or more of cycloalkyl, nitro, amino, alkyl amino, dialkyl amino, alkyl carbonyl and cycloalkyl carbonyl.

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

Base is cytosine, which may optionally substituted with one or more hydroxy, lower alkyl, lower alkoxy, halo, nitro or cyano; and

X is O or S;

or a pharmacologically acceptable salt thereof.

2. The compound of claim 1, wherein R is $O\text{-}R^1$.

3. The compound of claim 2, wherein R^5 is H.

4. The compound of claim 3, wherein R^1 is naphthyl or phenyl.

5. The compound of claim 4, wherein R' is $N(R^4)C(R^{2a})(R^{2b})C(=O)OR^3$.

6. The compound of claim 5, wherein R^{2a} is H and R^{2b} is methyl.

7. The compound of claim 6, wherein R^3 is isopropyl.

8. The compound of claim 7, wherein R^4 is H.

9. The compound of claim 8, wherein Base is cytosine.

10. The compound of claim 9, wherein X is O.

11. The compound of claim 9, wherein X is S.

12. A compound selected from the group consisting of:

4'-Azido-3'-deoxy-3'-fluorouridine-5'-(*O*-phenyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl thiophosphoramidate;

4'-Azido-3'-deoxy-3'-fluorouridine-5'-(*O*-1-naphthyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl thiosphosphoramidate;

4'-Azido-3'-deoxy-3'-fluorouridine-5'-(*O*-2-naphthyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl thiosphosphoramidate;

4'-Azido-3'-deoxy-3'-fluorocytidine-5'-(*O*-phenyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl thiosphosphoramidate;

4'-Azido-3'-deoxy-3'-fluorocytidine-5'-(*O*-2-naphthyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl thiosphosphoramidate;

4'-Azido-3'-deoxy-3'-fluorocytidine-5'-(*O*-2-naphthyl-*N*-(S)-1-(isopropoxycarbonyl)ethyl thiosphosphoramidate;

4'-Azido-3'-deoxy-3'-fluorouridine-5'-{*N,N'*-bis[(S)-1-(isopropoxylcarbonyl)ethyl]phosphorodiamidate;

4'-Azido-3'-deoxy-3'-fluorocytidine-5'-{*N,N'*-bis[(S)-1-(isopropoxylcarbonyl)ethyl]phosphorodiamidate;

4'-Azido-3'-deoxy-3'-fluorouridine-5'-{*N,N'*-bis[(S)-1-(isopropoxylcarbonyl)ethyl]thiphosphorodiamidate;

4'-Azido-3'-deoxy-3'-fluorocytidine-5'-{*N,N'*-bis[(S)-1-(benzyloxycarbonyl)ethyl]phosphorodiamidate;

4'-Azido-3'-deoxy-3'-fluorocytidine-5'-{*N,N'*-bis[(S)-1-(2,2-dimethylpropyloxylcarbonyl)ethyl]phosphorodiamidate;

4'-Azido-3'-deoxy-3'-fluorocytidine-5'-{*N,N'*-bis[(S)-1-(3,3-dimethylbutyloxylcarbonyl)ethyl]phosphorodiamidate;

4'-Azido-3'-deoxy-3'-fluorocytidine-5'-{*N,N'*-bis[(S)-1-(pentyloxylcarbonyl)ethyl]phosphorodiamidate; and

4'-Azido-3'-deoxy-3'-fluorocytidine-5'-{*N,N'*-bis[(S)-1-(cyclopentyloxylcarbonyl)ethyl]phosphorodiamidate.

13. A compound of claim 1 for use in the treatment of a Hepatitis C Virus (HCV) infection.

14. A combination of a compound of claim 1 with an immune system modulator and/or an antiviral agent that inhibits replication of HCV for use in the treatment of a Hepatitis C Virus (HCV) infection.

15. The combination of claim 14, wherein the immune system modulator is an interferon or chemically derivatized interferon.

16. The combination of claim 14, wherein the antiviral agent is selected from the group consisting of a HCV protease inhibitor, a HCV polymerase inhibitor, a HCV helicase inhibitor, a HCV primase inhibitor, a HCV fusion inhibitor, and a combination thereof.

17. Use of a compound of claim 1 in the manufacture of a medicament for the treatment of a Hepatitis C Virus (HCV) infection.

18. The use of claim 17, further comprising an immune system modulator or an antiviral agent that inhibits replication of HCV, or a combination thereof.

19. The use according to claim 18, wherein the immune system modulator is an interferon or chemically derivatized interferon.

20. The use according to claim 18, wherein the antiviral agent is selected from the group consisting of a HCV protease inhibitor, a HCV polymerase inhibitor, a HCV helicase inhibitor, a HCV primase inhibitor, a HCV fusion inhibitor, and a combination thereof.

21. A compound of claim 1 for use in inhibiting the replication of HCV in a cell.

22. Use of a compound 1 in the manufacture of a medicament for inhibition the replication of HCV in a cell.

23. A composition comprising the compound of claim 1, admixed with at least one carrier, diluent or excipient.