BI- AND MONOCYCLIC NUCLEOSIDE ANALOGS FOR TREATMENT OF HEPATITIS E

BACKGROUND

Hepatitis E virus (HEV) is believed to be the cause of about 20 million human infections a year and the most common cause of acute hepatitis and jaundice worldwide. Immuno-compromised patients are a significant population at risk for chronic HEV infection. Acute HEV infections tend to be self-limiting, but HEV genotype 3 can persist in immune-compromised patients, especially organ transplant recipients, leading to chronic hepatitis, cirrhosis and/or liver failure.

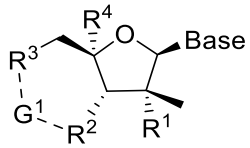
HEV is a positive-sense, single-stranded, nonenveloped, RNA icosahedral virus classified in the genus Orthohepevirus and the family Hepeviridae. Although HEV genotype 1 and 2 infect only humans, genotypes 3 and 4 also infect swine and other types of animals. Each of the four genotypes is classified into multiple subtypes.

HEV infections have been treated by ribavirin (RBV) and pegylated interferon-α with varying success. Accordingly, there is still a need for safe, tolerable and effective treatment options for HEV infections.

SUMMARY

Provided herein are compounds, more particularly methods of ameliorating and/or treating a Hepatitis E (HEV) infection, as well as compounds for use in such treatment.

Provided herein are compounds, more particularly compounds for use in treating a hepatitis E infection in a subject in need thereof, wherein the compound is a compound of formula (I):



(I) ;

or a pharmaceutically acceptable salt thereof;

wherein:

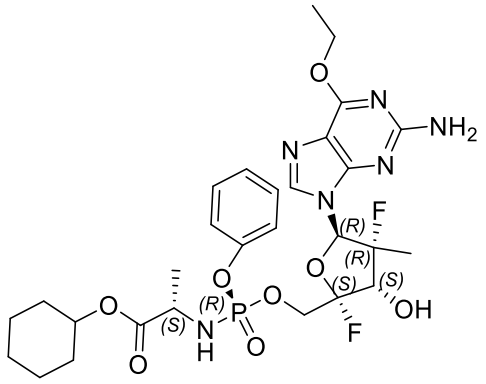
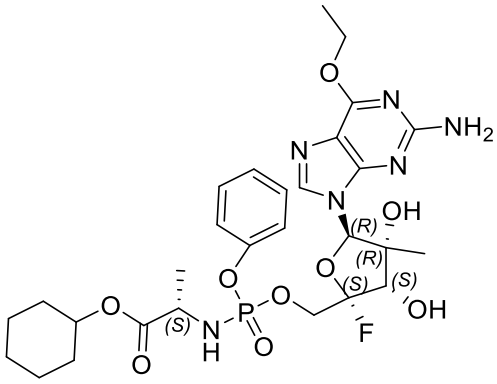
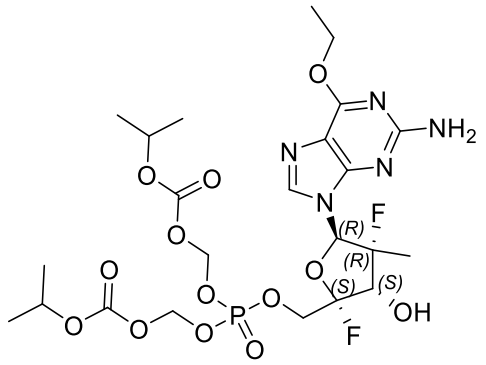
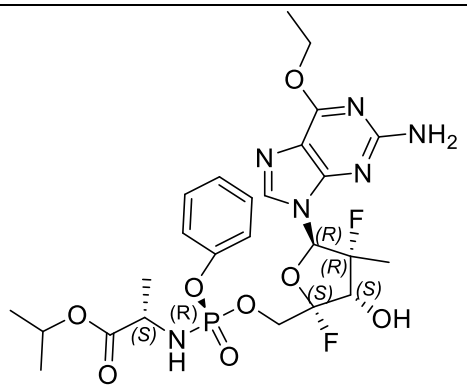
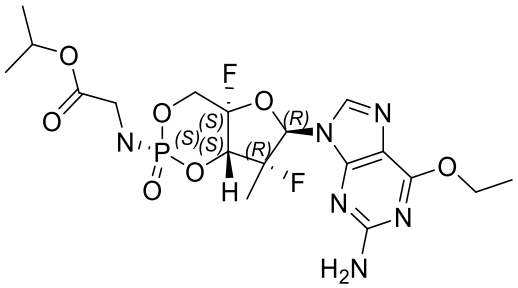
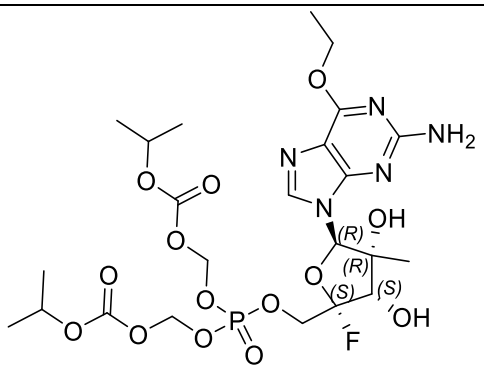
Base is selected from the group consisting of (b-1), (b-2), (b-3), (b-4), (b-5), (b-6), (b-7), and (b-8):

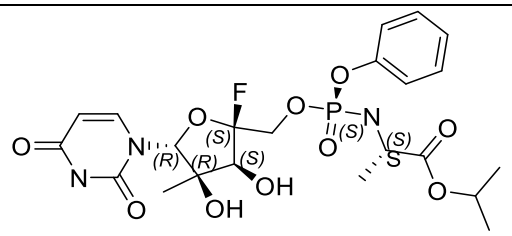
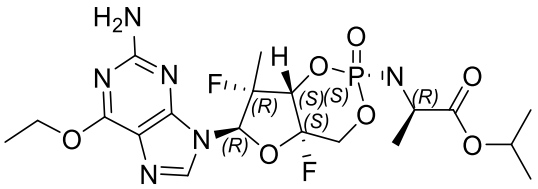
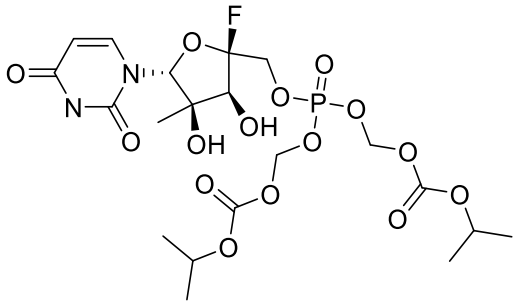
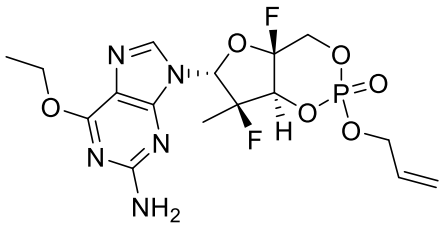
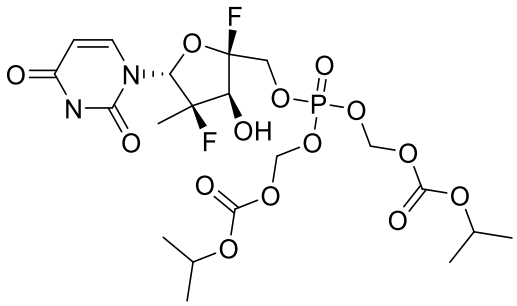
R^3 is O; and

R^4 is selected from the group consisting of H and F.

In an example, Base is selected from the group consisting of (b-1) and (b-6). In another example wherein G^1 is absent, R^3 is selected from the group consisting of (f-1) and (f-2). In yet another example, G^1 is (g-1) and R^8 is C_{1-4}alkyl. In still another example, G^1 is (g-2). In another example, G^1 is (g-3) and R^{10} is selected from C_{1-4}alkyl and C_{2-3}alkenyl.

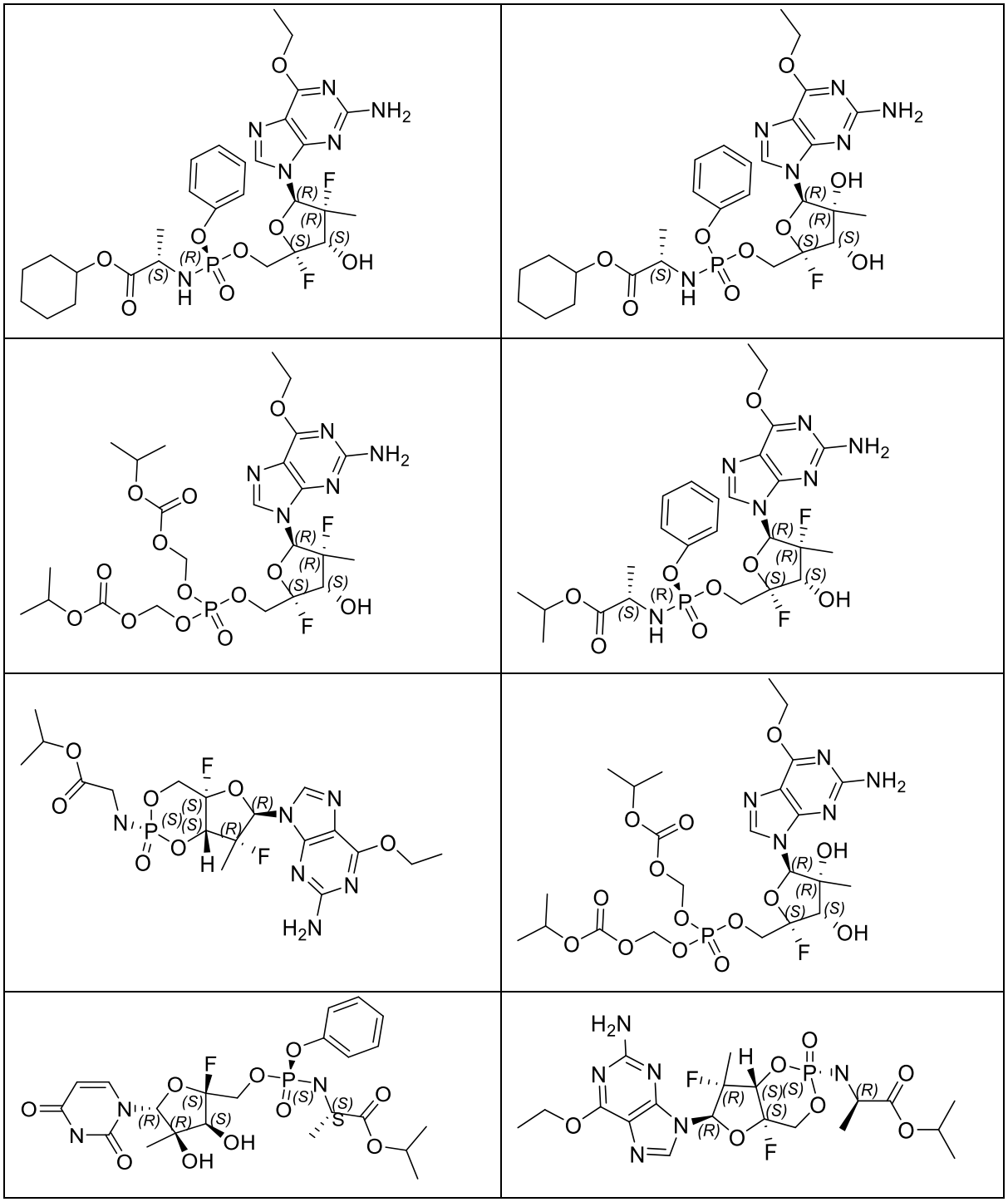
In an example, the compound is selected from the group consisting of:

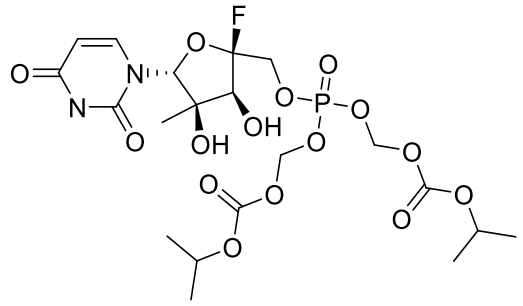
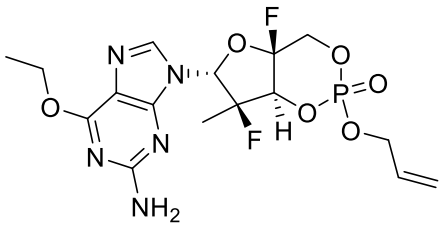
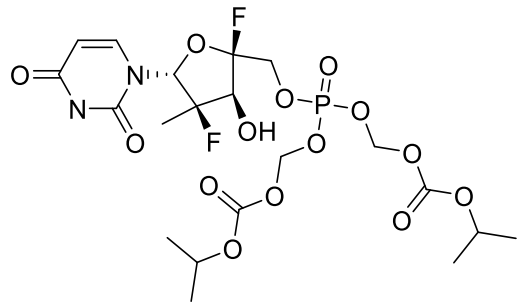
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or pharmaceutically acceptable salts thereof.

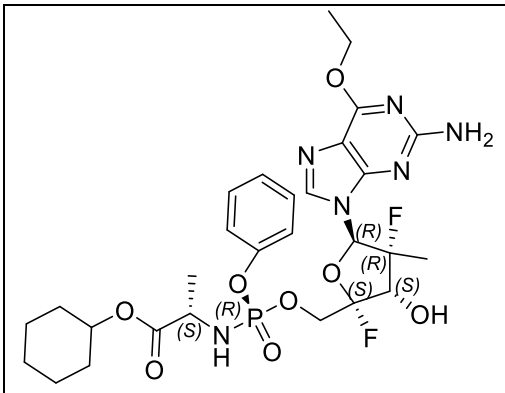
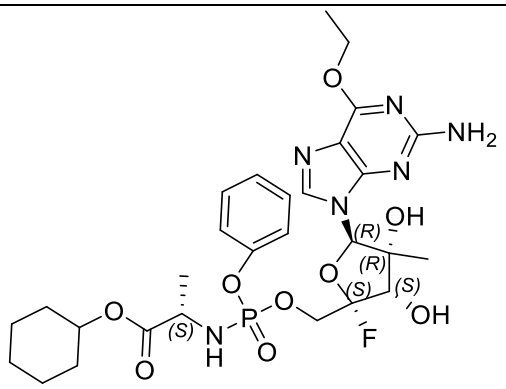
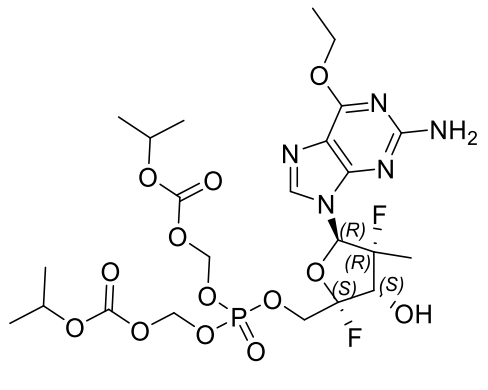
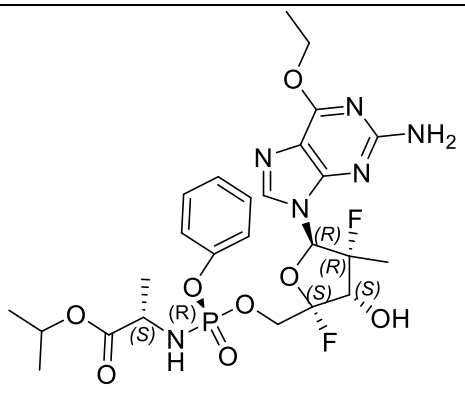
In an aspect, provided herein is a compound for use in treating a hepatitis E infection in a subject in need thereof, wherein the compound is selected from the group consisting of:

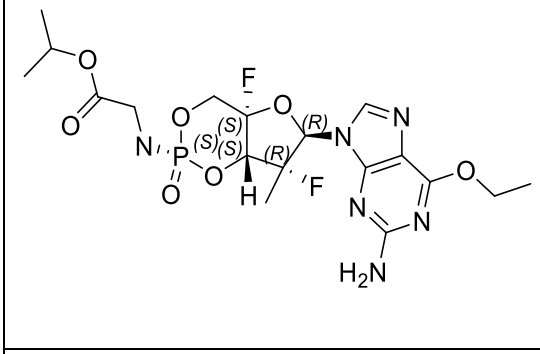
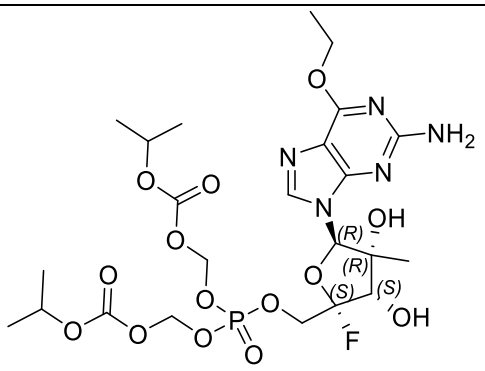
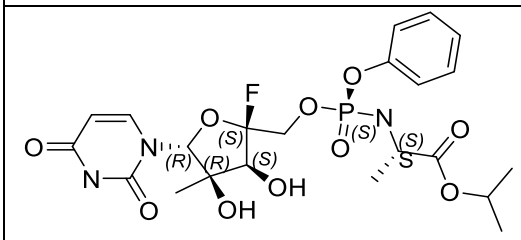
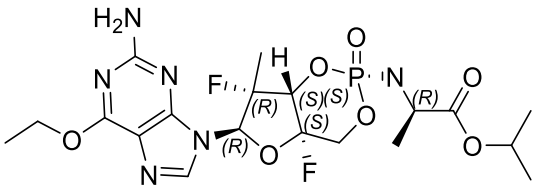
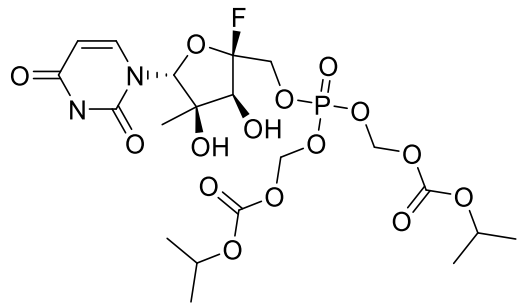
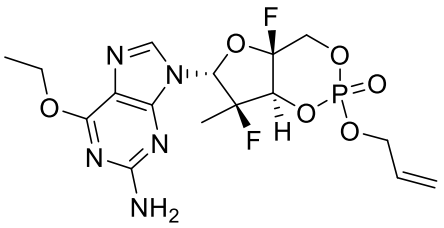
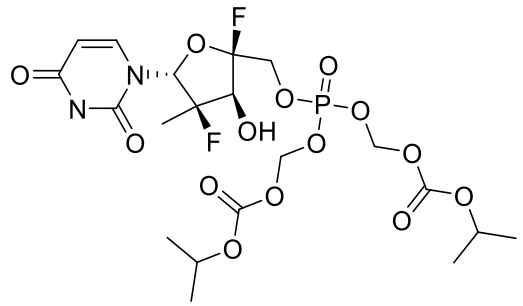


In another aspect, provided herein are pharmaceutical compositions for use in treating a hepatitis E infection in a subject in need thereof, which comprises the compounds disclosed herein, and a pharmaceutically acceptable vehicle.

In another aspect, provided herein is use of a compound selected from the group consisting of:

in the manufacture of a medicament for the treatment of a hepatitis E infection in a subject.In another aspect, provided herein is use of a pharmaceutical composition which comprises the compound disclosed herein, and a pharmaceutically acceptable vehicle, in the manufacture of a medicament for the treatment of a hepatitis E infection in a subject.

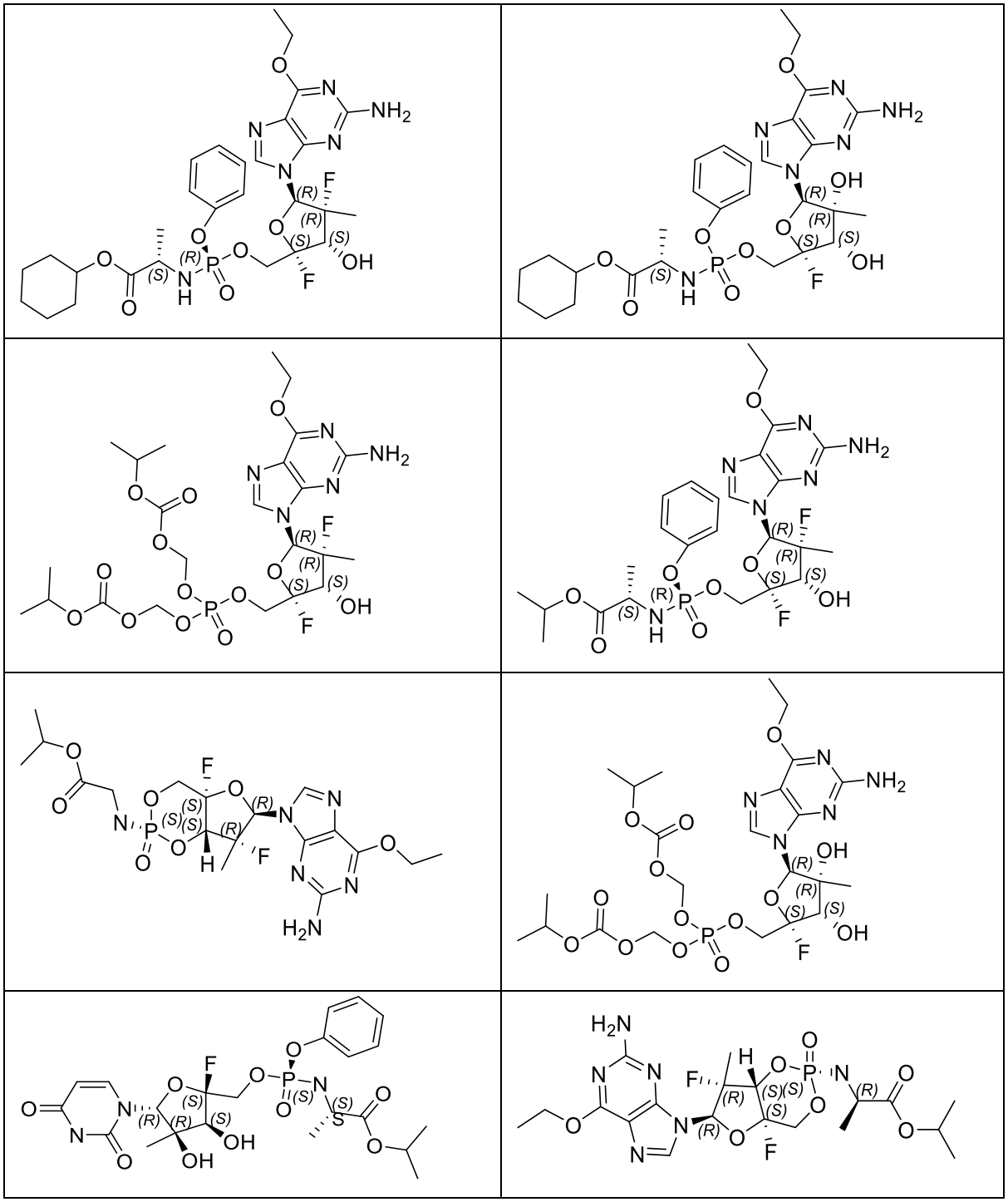
In an example, the hepatitis E infection is a chronic HEV infection. In another example, the HEV infection is of genotype 1, genotype 2 or genotype 3. In yet another example, the subject is a pregnant woman, an immune-compromised subject or immune-deficient subject.

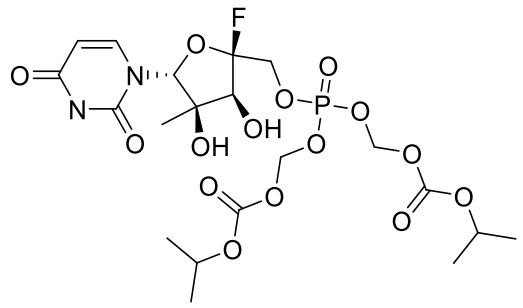
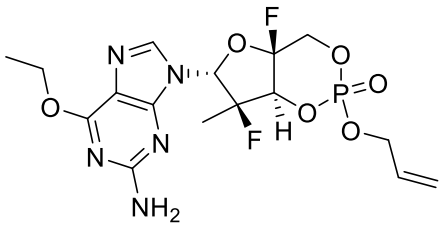
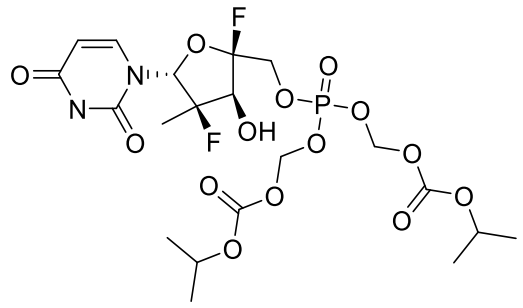
DETAILED DESCRIPTION

Provided herein are compounds, more particularly methods of ameliorating and/or treating a Hepatitis E (HEV) infection, as well as compounds for use in such treatment. In an aspect, provided herein are compounds of Formula (I) which can be used for treatment of Hepatitis E viral infections. Also provided herein are pharmaceutical compositions comprising compounds of Formula (I).

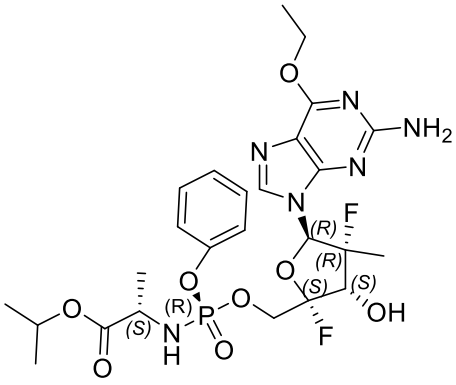
CLAIMS

1. A compound for use in treating a hepatitis E infection in a subject in need thereof, wherein the compound is selected from the group consisting of:



2. The compound for the use of claim 1, wherein the compound is:



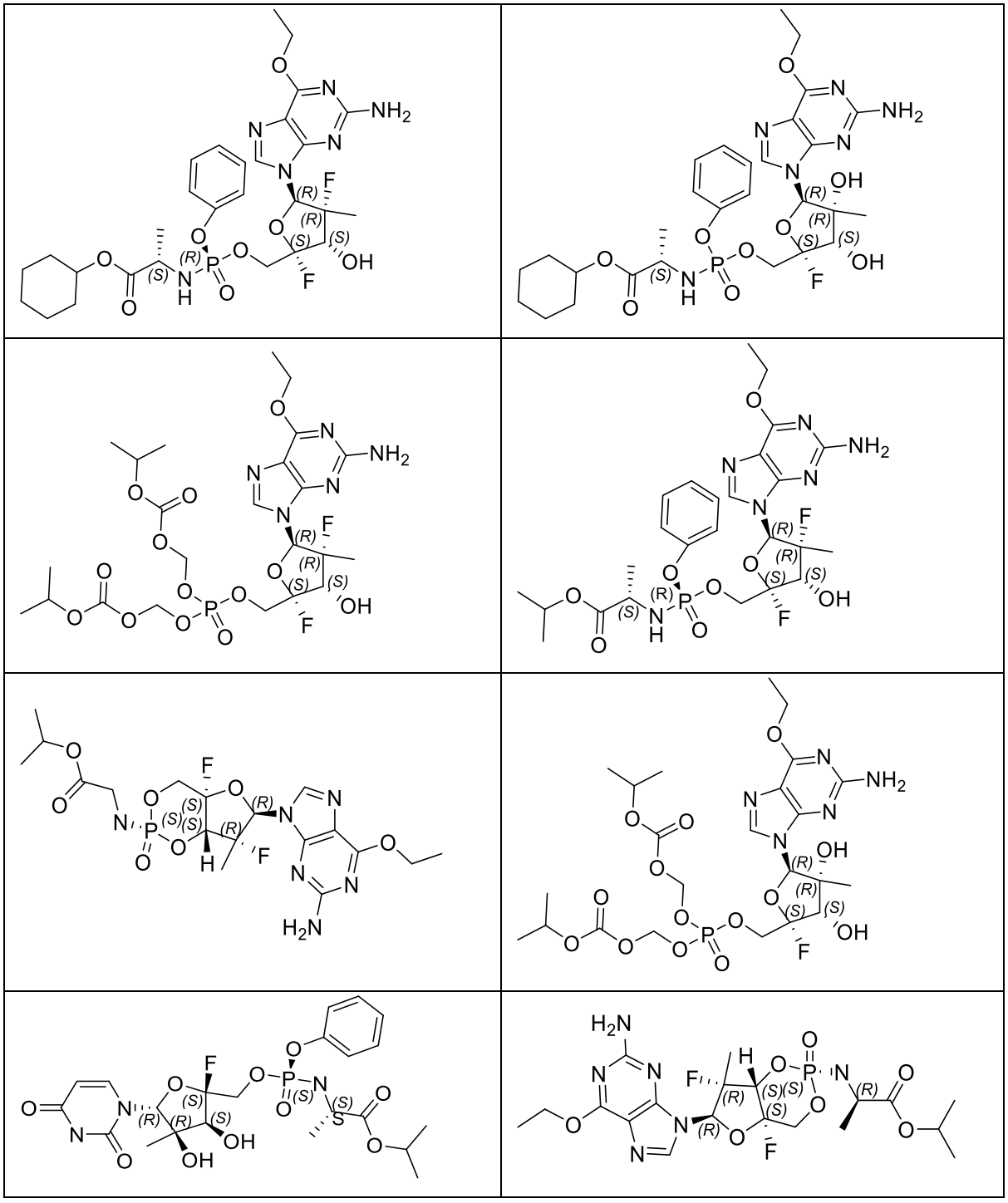
3. A pharmaceutical composition for use in treating a hepatitis E infection in a subject in need thereof, which comprises the compound as defined in claim 1 or 2, and a pharmaceutically acceptable vehicle.

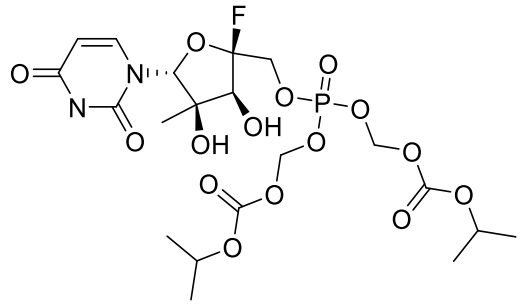
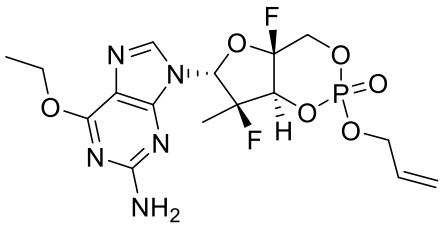
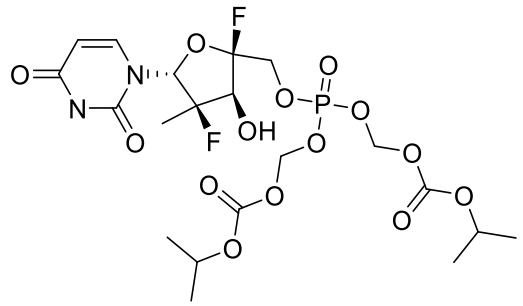
4. The compound for the use of claim 1 or 2, or the pharmaceutical composition for the use of claim 3, wherein the hepatitis E infection is a chronic HEV infection.

5. The compound for the use of claim 1 or 2, or the pharmaceutical composition for the use of claim 3, wherein the HEV infection is of genotype 1, genotype 2 or genotype 3.

6. The compound for the use of claim 1 or 2, or the pharmaceutical composition for the use of claim 3, wherein the subject is a pregnant woman, an immune-compromised subject or immune-deficient subject.

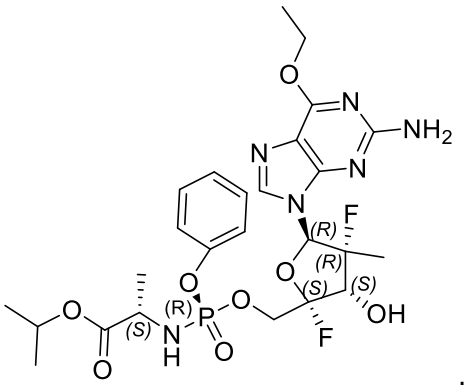
7. Use of a compound selected from the group consisting of:



in the manufacture of a medicament for the treatment of a hepatitis E infection in a subject.

8. The use of claim 7, wherein the compound is:



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9. Use of a pharmaceutical composition which comprises the compound as defined in claim 7 or 8, and a pharmaceutically acceptable vehicle, in the manufacture of a medicament for the treatment of a hepatitis E infection in a subject.

10. The use of any one of claims 7 to 9, wherein the hepatitis E infection is a chronic HEV infection.

11. The use of any one of claims 7 to 9, wherein the HEV infection is of genotype 1, genotype 2 or genotype 3.

12. The use of any one of claims 7 to 9, wherein the subject is a pregnant woman, an immune-compromised subject or immune-deficient subject.