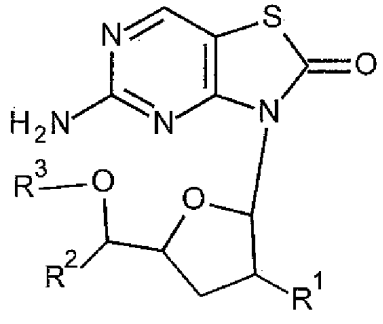
fact that the current therapies cannot elicit the appearance of neutralizing antibodies against HBsAg (anti-HBs), a sign of resolution of HBV infection, in most chronically infected patients. Hence, there is certainly a medical need for treatments with improved success rate of inducing HBsAg loss and/or seroconversion and promoting the production of anti-HBs.

SUMMARY

The present disclosure relates to a pharmaceutical composition comprising a TLR7 agonist and an HBV capsid assembly inhibitor, in a pharmaceutically acceptable carrier.

In one aspect, there is provided a pharmaceutical composition comprising a TLR7 agonist and an HBV capsid assembly inhibitor, in a pharmaceutically acceptable carrier, wherein the TLR7 agonist is a compound of formula (I):



(I),

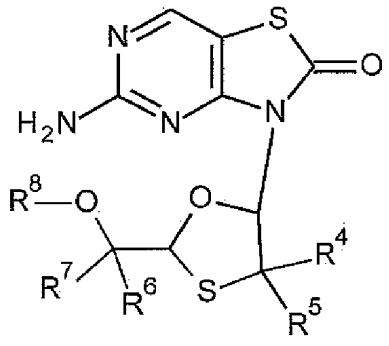
wherein

R^1 is hydroxy, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkylcarbonyl-O-, C_{1-6}alkyl-S-, azido, cyano, C_{2-6}alkenyl, C_{1-6}alkylsulfonyl-NH-, $(C_{1-6}alkyl)_2N$-, C_{1-6}alkylcarbonyl-NH- or heterocyclic amino;

R^2 is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{3-7}cycloalkyl, C_{2-6}alkynyl, C_{2-6}alkenyl, benzyl and thiophenyl;

R^3 is hydrogen or C_{1-6}alkylcarbonyl;

or wherein the TLR7 agonist is a compound of formula (II):



(II),

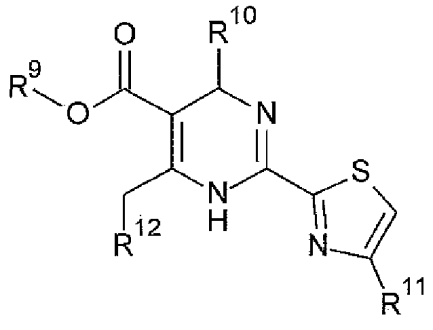
wherein

R^4 and R^5 are independently selected from hydrogen, C_{2-6}alkenyl and C_{1-6}alkyl;

R^6 and R^7 are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{2-6}alkynyl, C_{2-6}alkenyl, C_{2-6}alkynyl and 2-thiophenyl;

R^8 is hydrogen or C_{1-6}alkylcarbonyl;

and wherein the HBV capsid assembly inhibitor is a compound of formula (III):



(III),

wherein

R^9 is C_{1-6}alkyl;

R^{10} is phenyl, which is once or twice or three times substituted by halogen or C_{1-6}alkyl;

R^{11} is hydrogen or C_{1-6}alkyl;

R^{12} is monocyclic, bicyclic fused or bicyclic bridged heterocyclyl;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

The "TLR7 agonist" herein is a compound of formula (I), (II) or any one of the compounds disclosed in patent WO2006/066080, particularly the "TLR7 agonist" herein is [(1S)-1-[(2S,4R,5R)-5-(5-amino-2-oxo-thiazolo[4,5-d]pyrimidin-3-yl)-4-hydroxy-tetrahydrofuran-2-yl]propyl] acetate; [(S)-[(2S,5R)-5-(5-amino-2-oxo-thiazolo[4,5-d]pyrimidin-3-yl)-1,3-oxathiolan-2-yl]-cyclopropyl-methyl] acetate; 5-amino-3-(3'-deoxy-β-D-ribofuranosyl)-3H-thiazolo[4,5-d]pyrimidin-2-one; 5-amino-3-(2'-O-acetyl-3'-deoxy-β-D-ribofuranosyl)-3H-thiazolo[4,5-d]pyrimidin-2-one or 5-amino-3-(3'-deoxy-β-D-ribofuranosyl)-3H,6H-thiazolo[4,5-d]pyrimidin-2,7-dione, or pharmaceutically acceptable salt, enantiomer or diastereomer thereof. The HBV capsid assembly inhibitor herein is a compound of formula (III) or any one of the compounds disclosed in patent WO2014/037480, WO 2014/184328 and WO2015/132276, particularly the HBV capsid assembly inhibitor herein is 3-[(8aS)-7-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1H-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid; 3-[(8aS)-7-[[(4S)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-

3-oxo-5,6,8,8a-tetrahydro-1H-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid; 2-[(1R,3S,5S)-8-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid; 2-[(1S,3R,5R)-8-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid; or (*S*)-4-[(*R*)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

In another aspect, there is provided a method for manufacturing a medicament for treatment or prophylaxis of hepatitis B virus infection, characterized in that a TLR7 agonist of formula (I) or formula (II), or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof and an HBV capsid assembly inhibitor of formula (III), or pharmaceutically acceptable salt, enantiomer or diastereomer thereof are used in the medicament.

In another aspect, there is provided a kit comprising a container comprising a TLR7 agonist and an HBV capsid assembly inhibitor, wherein

the TLR7 agonist is

[(1S)-1-[(2S,4R,5R)-5-(5-amino-2-oxo-thiazolo[4,5-d]pyrimidin-3-yl)-4-hydroxy-tetrahydrofuran-2-yl]propyl] acetate;

[(S)-[(2S,5R)-5-(5-amino-2-oxo-thiazolo[4,5-d]pyrimidin-3-yl)-1,3-oxathiolan-2-yl]-cyclopropyl-methyl] acetate;

5-amino-3-(3'-deoxy-β-D-ribofuranosyl)-3H-thiazolo[4,5-d]pyrimidin-2-one;

5-amino-3-(2'-O-acetyl-3'-deoxy-β-D-ribofuranosyl)-3H-thiazolo[4,5-d]pyrimidin-2-one;

5-amino-3-(3'-deoxy-β-D-ribofuranosyl)-3H,6H-thiazolo[4,5-d]pyrimidin-2,7-dione; or

[(2R,3R,5S)-5-[(1S)-1-acetoxypropyl]-2-(5-amino-2,7-dioxo-6H-thiazolo[4,5-d]pyrimidin-3-yl)tetrahydrofuran-3-yl] acetate; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof; and

wherein the HBV capsid assembly inhibitor is

3-[(8aS)-7-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1H-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

3-[(8aS)-7-[[(4S)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1H-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

2-[(1R,3S,5S)-8-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3R,5R)-8-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

or (S)-4-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

In another aspect, there is provided the pharmaceutical composition as defined herein for use as an antiviral medicament, in particular as the medicament for treatment or prophylaxis of hepatitis B virus infection.

In another aspect, there is provided the use of a TLR7 agonist and an HBV capsid assembly inhibitor for the manufacture of pharmaceutical composition as defined herein as an antiviral medicament, in particular the medicament for treatment or prophylaxis of hepatitis B virus infection.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: HBV DNA and HBsAg levels from mice sera in AAV-HBV mouse model. Results were shown in Figure. 1 for mice with sustained level of HBV DNA and HBsAg treated

pharmaceutically acceptable salt, enantiomer or diastereomer thereof and an HBV capsid assembly inhibitor of formula (III), or pharmaceutically acceptable salt, enantiomer or diastereomer thereof are used in the medicament.

8. The method according to claim 7, wherein the TLR7 agonist and the HBV capsid assembly inhibitor are to be co-administered in the same formulation or different formulation.

9. The method according to claim 7 or 8, wherein the TLR7 agonist and the HBV capsid assembly inhibitor are intended for administration to a subject by the same route or different routes.

10. The method according to any one of claims 7 to 9, wherein the TLR7 agonist and the HBV capsid assembly inhibitor are intended for administration to a subject by parenteral or oral administration.

11. The method according to any one of claims 7 to 10, wherein the administration is to be simultaneous or sequential.

12. The method according to any one of claims 7 to 11, wherein the TLR7 agonist is

[(1S)-1-[(2S,4R,5R)-5-(5-amino-2-oxo-thiazolo[4,5-d]pyrimidin-3-yl)-4-hydroxy-tetrahydrofuran-2-yl]propyl] acetate;

[(S)-[(2S,5R)-5-(5-amino-2-oxo-thiazolo[4,5-d]pyrimidin-3-yl)-1,3-oxathiolan-2-yl]-cyclopropyl-methyl] acetate;

5-amino-3-(3'-deoxy-β-D-ribofuranosyl)-3H-thiazolo[4,5-d]pyrimidin-2-one;

5-amino-3-(2'-O-acetyl-3'-deoxy-β-D-ribofuranosyl)-3H-thiazolo[4,5-d]pyrimidin-2-one;

5-amino-3-(3'-deoxy-β-D-ribofuranosyl)-3H,6H-thiazolo[4,5-d]pyrimidin-2,7-dione; or

[(2R,3R,5S)-5-[(1S)-1-acetoxypropyl]-2-(5-amino-2,7-dioxo-6H-thiazolo[4,5-d]pyrimidin-3-yl)tetrahydrofuran-3-yl] acetate;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof;

and wherein

the HBV capsid assembly inhibitor is

3-[(8aS)-7-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1H-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

3-[(8aS)-7-[[(4S)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1H-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

2-[(1R,3S,5S)-8-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3R,5R)-8-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

or (*S*)-4-[(*R*)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

13. The method according to any one of claims 7 to 12, wherein the medicament additionally comprises one or more other antiviral agents selected from the group consisiting of lamivudine, adefovir, tenofovir, telbivudine and entecavir.

14. The method according to any one of claims 7 to 13, wherein the TLR7 agonist and the HBV capsid assembly inhibitor used in the medicament are:

[(1S)-1-[(2S,4R,5R)-5-(5-amino-2-oxo-thiazolo[4,5-d]pyrimidin-3-yl)-4-hydroxy-tetrahydrofuran-2-yl]propyl] acetate and 3-[(8aS)-7-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1H-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

15. A kit comprising a container comprising a TLR7 agonist and an HBV capsid assembly inhibitor, wherein

the TLR7 agonist is

[(1S)-1-[(2S,4R,5R)-5-(5-amino-2-oxo-thiazolo[4,5-d]pyrimidin-3-yl)-4-hydroxy-tetrahydrofuran-2-yl]propyl] acetate;

[(S)-[(2S,5R)-5-(5-amino-2-oxo-thiazolo[4,5-d]pyrimidin-3-yl)-1,3-oxathiolan-2-yl]-cyclopropyl-methyl] acetate;

5-amino-3-(3'-deoxy-β-D-ribofuranosyl)-3H-thiazolo[4,5-d]pyrimidin-2-one;

5-amino-3-(2'-O-acetyl-3'-deoxy-β-D-ribofuranosyl)-3H-thiazolo[4,5-d]pyrimidin-2-one;

5-amino-3-(3'-deoxy-β-D-ribofuranosyl)-3H,6H-thiazolo[4,5-d]pyrimidin-2,7-dione; or

[(2R,3R,5S)-5-[(1S)-1-acetoxypropyl]-2-(5-amino-2,7-dioxo-6H-thiazolo[4,5-d]pyrimidin-3-yl)tetrahydrofuran-3-yl] acetate; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof; and

wherein the HBV capsid assembly inhibitor is

3-[(8aS)-7-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1H-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

3-[(8aS)-7-[[(4S)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1H-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

2-[(1R,3S,5S)-8-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

2-[(1S,3R,5R)-8-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

or (*S*)-4-[(*R*)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid; or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

16. The kit according to claim 15, wherein the TLR7 agonist and the HBV capsid assembly inhibitor used in the container are:

[(1S)-1-[(2S,4R,5R)-5-(5-amino-2-oxo-thiazolo[4,5-d]pyrimidin-3-yl)-4-hydroxy-tetrahydrofuran-2-yl]propyl] acetate and 3-[(8aS)-7-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-ethoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1H-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

[(1S)-1-[(2S,4R,5R)-5-(5-amino-2-oxo-thiazolo[4,5-d]pyrimidin-3-yl)-4-hydroxy-tetrahydrofuran-2-yl]propyl] acetate and 3-[(8aS)-7-[[(4S)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1H-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

[(S)-[(2S,5R)-5-(5-amino-2-oxo-thiazolo[4,5-d]pyrimidin-3-yl)-1,3-oxathiolan-2-yl]-cyclopropyl-methyl] acetate and 3-[(8aS)-7-[[(4S)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1H-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid;

[(1S)-1-[(2S,4R,5R)-5-(5-amino-2-oxo-thiazolo[4,5-d]pyrimidin-3-yl)-4-hydroxy-tetrahydrofuran-2-yl]propyl] acetate and 2-[(1R,3S,5S)-8-[[(4R)-4-(2-chloro-3-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-6,6-difluoro-8-azabicyclo[3.2.1]octan-3-yl]acetic acid;

[(1*S*)-1-[(2*S*,4*R*,5*R*)-5-(5-amino-2-oxo-thiazolo[4,5-*d*]pyrimidin-3-yl)-4-hydroxy-tetrahydrofuran-2-yl]propyl] acetate and (*S*)-4-[(*R*)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid;

5-amino-3-(2'-O-acetyl-3'-deoxy-β-D-ribofuranosyl)-3H-thiazolo[4,5-d]pyrimidin-2-one and 3-[(8a*S*)-7-[[(4*S*)-5-ethoxycarbonyl-4-(3-fluoro-2-methyl-phenyl)-2-thiazol-2-yl-1,4-dihydropyrimidin-6-yl]methyl]-3-oxo-5,6,8,8a-tetrahydro-1H-imidazo[1,5-a]pyrazin-2-yl]-2,2-dimethyl-propanoic acid; or

5-amino-3-(2'-O-acetyl-3'-deoxy-β-D-ribofuranosyl)-3H-thiazolo[4,5-d]pyrimidin-2-one and (S)-4-[(R)-6-(2-Chloro-4-fluoro-phenyl)-5-methoxycarbonyl-2-thiazol-2-yl-3,6-dihydro-pyrimidin-4-ylmethyl]-morpholine-3-carboxylic acid;

in a pharmaceutically acceptable carrier.

17. The kit according to claim 15, further comprising a sterile diluent.

18. The kit according to any one of claims 15 to 17, further comprising a package insert comprising printed instructions directing a combined treatment of a TLR7 agonist and an HBV capsid assembly inhibitor for use in treatment or prophylaxis of hepatitis B virus infection.

19. The pharmaceutical composition according to any one of claims 1 to 6 for use as an antiviral medicament, in particular as the medicament for treatment or prophylaxis of hepatitis B virus infection.

20. The use of a TLR7 agonist and an HBV capsid assembly inhibitor for the manufacture of pharmaceutical composition according to any one of claims 1 to 6 as an antiviral medicament, in particular the medicament for treatment or prophylaxis of hepatitis B virus infection.