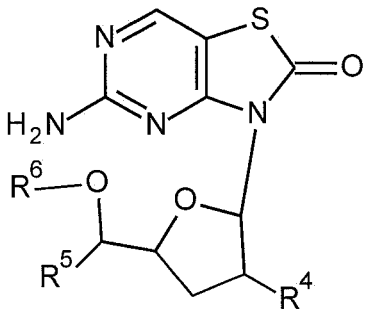
R^6 is hydrogen or C_{1-6}alkylcarbonyl;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof; with the proviso that 5-amino-3-[3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]thiazolo[4,5-d]pyrimidin-2-one; [2-(5-amino-2-oxo-thiazolo[4,5-d]pyrimidin-3-yl)-5-(hydroxymethyl)tetrahydrofuran-3-yl] acetate; [4-acetoxy-5-(5-amino-2-oxo-thiazolo[4,5-d]pyrimidin-3-yl)tetrahydrofuran-2-yl]methyl acetate and their diastereomers are excluded.

In another aspect, there is provided a compound of formula (II),



(II)

wherein

R^4 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^5 is 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;

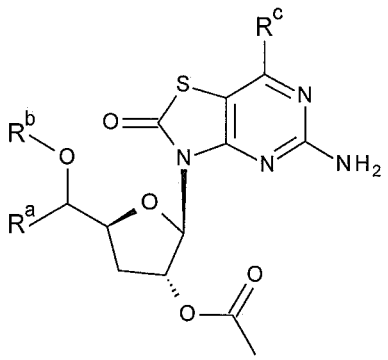
R^6 is hydrogen or C_{1-6}alkylcarbonyl;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

The disclosure also relates to their manufacture, medicaments based on a compound in accordance with the disclosure and their production as well as the use of compounds of formula (I) or (Ia) or their prodrugs, formula (II) or (IIa), thereof as TLR7 agonist. Accordingly, the compounds of formula (I) and (Ia) or their prodrugs of formula (II) and (IIa) are useful for the treatment or prophylaxis of HBV and/or HCV infection with Toll-like receptors agonism.

In another aspect, there is provided a process for the preparation of a compound as defined herein comprising one of the following steps:

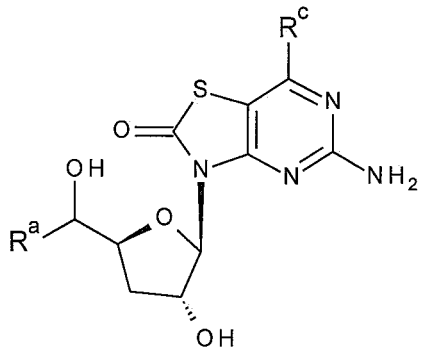
(a) the reaction of a compound of formula (X),



(X),

with a base or fluoride reagent, wherein R^a is R^2 or R^5; R^b is acyl, benzoyl, *tert*-butyl(dimethyl)silyl or *tert*-butyl(diphenyl)silyl; R^c is hydrogen or hydroxy;

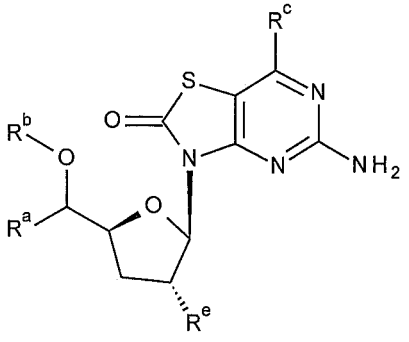
(b) the reaction of a compound of formula (P1),



(P1),

with an acid anhydride or acid chloride, wherein R^a is R^2 or R^5; R^c is hydrogen or hydroxy;

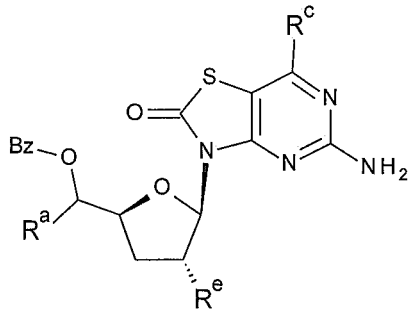
(c) the reaction of a compound of formula (XIV),



(XIV),

with a base or a fluoride reagent, wherein R^a is R^2 or R^5; R^b is acyl, benzoyl or *tert*-butyl(diphenyl)silyl; R^c is hydrogen or hydroxy; R^d is trifluoromethylsulfonyl or p-tolylsulfonyl; R^e is R^1 or R^4;

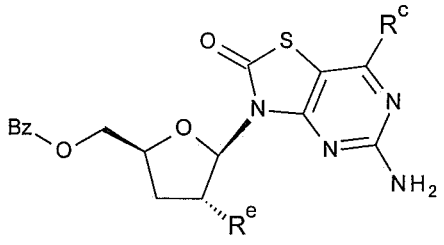
(d) the reaction of a compound of formula (XXIII),



(XXIII),

with a base, wherein R^a is R^2 or R^5; R^c is hydrogen or hydroxy; R^e is R^1 or R^4; or

(e) the reaction of a compound of formula (XXVI),



(XXVI),

with a base, wherein R^c is hydrogen or hydroxy; R^e is R^1 or R^4;

wherein R^1, R^2, R^4 and R^5 are as defined herein.

In another aspect, there is provided a compound or pharmaceutically acceptable salts, enantiomers or diastereomers as defined herein for use as therapeutically active substance.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a therapeutically inert carrier.

In another aspect, there is provided use of a compound as defined herein for the preparation of a medicament for the treatment or prophylaxis of hepatitis B virus infection.

In another aspect, there is provided a compound as defined herein as a TLR7 agonist.

In another aspect, there is provided a compound as defined herein to induce production of interferon-α.

In another aspect, there is provided a compound or pharmaceutically acceptable salts, enantiomers or diastereomers as defined herein for use in the treatment or prophylaxis of hepatitis B virus infection.

DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Furthermore, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention.

DEFINITIONS

As used herein, the term "C_{1-6}alkyl" denotes a saturated, linear or branched chain alkyl group containing 1 to 6, particularly 1 to 4 carbon atoms, for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl and the like. Particular "C_{1-6}alkyl" groups are methyl, ethyl and n-propyl.

The term "halogen" and "halo" are used interchangeably herein and denote fluoro, chloro, bromo, or iodo.

The term "haloC_{1-6}alkyl" refers to an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloC_{1-6}alkyl include monofluoro-, difluoro- or trifluoro-methyl, -ethyl or -propyl, for example 3,3,3-trifluoropropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl, difluoromethyl and trifluoromethyl.

5-Amino-3-[(2*R*,3*R*,5*S*)-5-[(1*S*)-1-hydroxybut-2-ynyl]-3-methyl-tetrahydrofuran-2-yl]-6*H*-thiazolo[4,5-*d*]pyrimidine-2,7-dione;

5-Amino-3-[(2*R*,3*R*,5*S*)-5-[(*S*)-cyclopropyl(hydroxy)methyl]-3-methyl-tetrahydrofuran-2-yl]-6*H*-thiazolo[4,5-*d*]pyrimidine-2,7-dione;

5-Amino-3-[(2*R*,3*R*,5*S*)-5-[(1*S*)-1-hydroxyethyl]-3-methyl-tetrahydrofuran-2-yl]-6*H*-thiazolo[4,5-*d*]pyrimidine-2,7-dione;

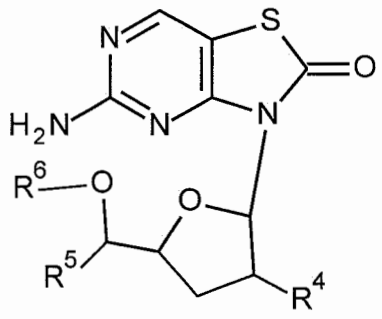
5-Amino-3-[(2*R*,3*R*,5*S*)-5-(hydroxymethyl)-3-pyrrolidin-1-yl-tetrahydrofuran-2-yl]-6*H*-thiazolo[4,5-*d*]pyrimidine-2,7-dione;

5-Amino-3-[(2*R*,3*R*,5*S*)-5-(hydroxymethyl)-3-methylsulfanyl-tetrahydrofuran-2-yl]-6*H*-thiazolo[4,5-*d*]pyrimidine-2,7-dione;

and [(1*S*)-1-[(2*S*,4*R*,5*R*)-5-(5-Amino-2,7-dioxo-6*H*-thiazolo[4,5-*d*]pyrimidin-3-yl)-4-hydroxy-tetrahydrofuran-2-yl]propyl] 2-methylpropanoate;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

21. A compound of formula (II),



(II)

wherein

R^4 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^5 is 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^6 is hydrogen or C_{1-6}alkylcarbonyl;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

22. A compound according to claim 21, wherein

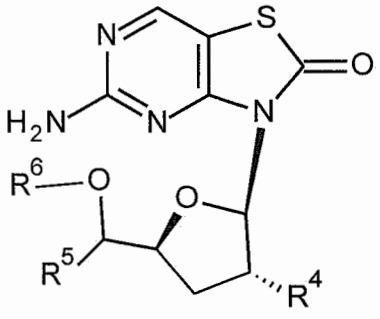
R^4 is hydroxy, methyl, n-propyl, fluoroisopropyl, acetyloxy, methylsulfanyl, azido, cyano, allyl, 2-methylallyl, methylsulfonylamino, dimethylamino, acetylamino, pyrrolidinyl, morpholinyl or piperidinyl;

R^5 is methyl, ethyl, propyl, butyl, cyclopropyl, cyclopentyl, vinyl, allyl, benzyl, ethynyl, 1-propynyl, methoxymethyl or thiophenyl;

R^6 is hydrogen, acetyl or isobutyryl;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

23. A compound of formula (IIa) according to claim 21 or 22,



(IIa)

wherein

R^4 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^5 is 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^6 is hydrogen or C_{1-6}alkylcarbonyl;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

24. A compound according to any one of claims 21 to 23, wherein

R^4 is hydroxy, methyl, n-propyl, fluoroisopropyl, acetyloxy, methylsulfanyl, azido, cyano, allyl, 2-methylallyl, methylsulfonylamino, dimethylamino, acetylamino, pyrrolidinyl, morpholinyl or piperidinyl;

R^5 is methyl, ethyl, propyl, butyl, cyclopropyl, cyclopentyl, vinyl, allyl, benzyl, ethynyl, 1-propynyl, methoxymethyl or thiophenyl;

R^6 is hydrogen, acetyl or isobutyryl;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

25. A compound according to any one of claims 21 to 24, wherein

R^4 is hydroxy, C_{1-6}alkyl, C_{1-6}alkyl-S-, azido or C_{2-6}alkenyl;

R^5 is C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{2-6}alkynyl or C_{2-6}alkenyl;

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

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

26. A compound according to any one of claims 21 to 24, wherein

R^4 is hydroxy, methyl, propyl, methylsulfanyl, azido or allyl;

R^5 is methyl, ethyl, propyl, cyclopropyl, vinyl, ethynyl or 1-propynyl;

R^6 is hydrogen or isobutyryl;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

27. A compound according to any one of claims 21 to 24, wherein

R^4 is hydroxy or C_{1-6}alkylcarbonyl-O-;

R^5 is C_{1-6}alkyl or C_{3-7}cycloalkyl;

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

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

28. A compound according to any one of claims 21 to 25, wherein

R^4 is hydroxy or acetyloxy;

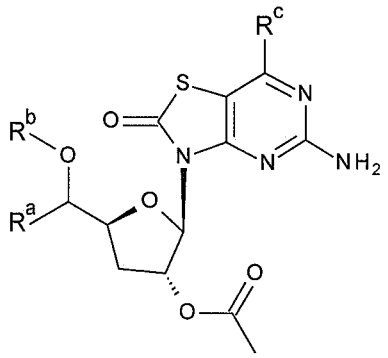
R^5 is ethyl or cyclopropyl;

R^6 is hydrogen or acetyl;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

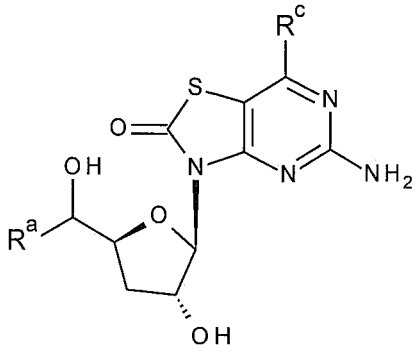
29. A compound according to any one of claims 21 to 28 selected from:
5-Amino-3-[(2*R*,3*R*,5*S*)-3-hydroxy-5-(1-hydroxypropyl)tetrahydrofuran-2-yl]thiazolo[4,5-*d*]pyrimidin-2-one;
[(2*R*,3*R*,5*S*)-2-(5-amino-2-oxo-thiazolo[4,5-*d*]pyrimidin-3-yl)-5-(1-hydroxypropyl)tetrahydrofuran-3-yl] acetate;
1-[(2*S*,4*R*,5*R*)-5-(5-amino-2-oxo-thiazolo[4,5-*d*]pyrimidin-3-yl)-4-hydroxy-tetrahydrofuran-2-yl]propyl acetate;
[(*S*)-[(2*S*,4*R*,5*R*)-5-(5-amino-2-oxo-thiazolo[4,5-*d*]pyrimidin-3-yl)-4-hydroxy-tetrahydrofuran-2-yl]-cyclopropyl-methyl] acetate;
and 5-Amino-3-[(2*R*,3*R*,5*S*)-5-[cyclopropyl(hydroxy)methyl]-3-hydroxy-tetrahydrofuran-2-yl]thiazolo[4,5-*d*]pyrimidin-2-one;
or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

30. A process for the preparation of a compound according to any one of claims 1 to 29 comprising one of the following steps:
(a) the reaction of a compound of formula (X),



(X),

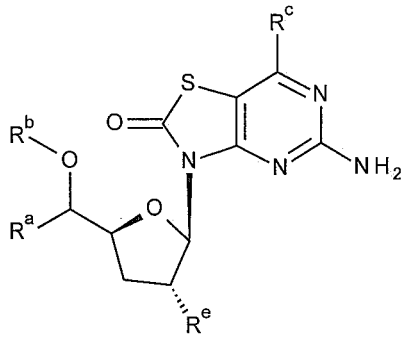
with a base or fluoride reagent, wherein R^a is R^2 or R^5; R^b is acyl, benzoyl, *tert*-butyl(dimethyl)silyl or *tert*-butyl(diphenyl)silyl; R^c is hydrogen or hydroxy;
(b) the reaction of a compound of formula (P1),



(P1),

with an acid anhydride or acid chloride, wherein R^a is R^2 or R^5; R^c is hydrogen or hydroxy;

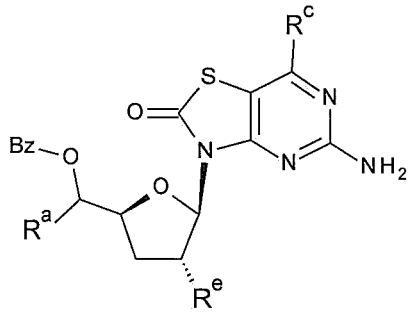
(c) the reaction of a compound of formula (XIV),



(XIV),

with a base or a fluoride reagent, wherein R^a is R^2 or R^5; R^b is acyl, benzoyl or *tert*-butyl(diphenyl)silyl; R^c is hydrogen or hydroxy; R^d is trifluoromethylsulfonyl or p-tolylsulfonyl; R^e is R^1 or R^4;

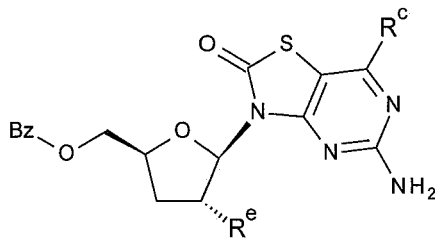
(d) the reaction of a compound of formula (XXIII),



(XXIII),

with a base, wherein R^a is R^2 or R^5; R^c is hydrogen or hydroxy; R^e is R^1 or R^4; or

(e) the reaction of a compound of formula (XXVI),



(XXVI),

with a base, wherein R^c is hydrogen or hydroxy; R^e is R^1 or R^4;

wherein R^1 and R^2 are defined as in any one of claims 1 to 18 and R^4 and R^5 are as defined in any one of claims 21-28.

31. A compound or pharmaceutically acceptable salts, enantiomers or diastereomers according to any one of claims 1 to 29 for use as therapeutically active substance.

32. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 29 and a therapeutically inert carrier.

33. The use of a compound according to any one of claims 1 to 29 for the preparation of a medicament for the treatment or prophylaxis of hepatitis B virus infection.

34. A compound according to any one of claims 1 to 29 as a TLR7 agonist.

35. A compound according to any one of claims 1 to 29 to induce production of interferon-α.

36. A compound or pharmaceutically acceptable salts, enantiomers or diastereomers according to any one of claims 1 to 29 for use in the treatment or prophylaxis of hepatitis B virus infection.