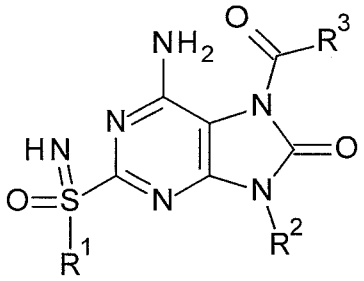
refractory metastatic melanoma, respectively. ANA773 is an oral pro-drug TLR7 agonist, developed for the treatment of patients with chronic hepatitis C virus (HCV) infection and chronic hepatitis B infection. GS-9620 is an orally available TLR7 agonist. A phase Ib study demonstrated that treatment with GS-9620 was safe, well tolerated and resulted in dose-dependent ISG15 mRNA induction in patients with chronic hepatitis B (E. J. Gane *et al*, Annu Meet Am Assoc Study Liver Dis (November 1-5, Washington, D.C.) 2013, Abst 946). Therefore there is high unmet clinical need for developing potent and safe TLR7 agonists as new HBV treatment to offer more therapeutic solutions or replace existing partly effective treatment.

SUMMARY

The present disclosure provides a series of novel 6-amino-2-sulfonimidoyl-9-substituted-7-substituted-purin-8-one compounds that have Toll-like receptor agonism activity and their prodrugs. The disclosure also provides the bio-activity of such compounds to induce SEAP level increase by activating Toll-like receptors, such as TLR7 receptor, the metabolic conversion of prodrugs to parent compounds in the presence of human hepatocytes, and the therapeutic or prophylactic use of such compounds and their pharmaceutical compositions comprising these compounds and their prodrugs to treat or prevent infectious disease like HBV or HCV. The present disclosure also provides compounds with superior activity. In addition, the compounds of formula (I) also show good solubility and PK profiles.

The present disclosure, in one aspect, relates to novel compounds of formula (I),



(I),

wherein

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

R^2 is benzyl, said benzyl being unsubstituted or substituted by one, two or three substituents independently selected from halogen and C_{1-6}alkyl;

R^3 is $-NR^4R^5$, wherein

R^4 is C_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl;

R^5 is $(C_{1-6}alkyl)_2NCOOC_{1-6}$alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxycarbonyl(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkoxycarbonyl(phenyl)C_{1-6}alkyl, C_{1-6}alkoxycarbonylC_{1-6}alkyl, C_{1-6}alkoxycarbonyloxyC_{1-6}alkyl, C_{1-6}alkyl, C_{1-}

$_6$alkylcarbonyl(C_{1-6}alkyl)aminoC_{1-6}alkyl or pyrrolidinylcarbamoyloxyC_{1-6}alkyl; or

R^4 and R^5 together with the nitrogen they are attached to form a heterocyclyl;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof;

with the proviso that

6-amino-9-benzyl-2-(propylsulfonimidoyl)-7-(pyrrolidine-1-carbonyl)purin-8-one;

6-amino-9-benzyl-7-(piperidine-1-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

6-amino-9-benzyl-7-(morpholine-4-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

6-amino-9-benzyl-7-(3,3-dimethylpyrrolidine-1-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

ethyl 1-[6-amino-9-benzyl-8-oxo-2-(propylsulfonimidoyl)purine-7-carbonyl]pyrrolidine-2-carboxylate;

6-amino-7-(2-azaspiro[3.3]heptane-2-carbonyl)-9-benzyl-2-(propylsulfonimidoyl)purin-8-one;

6-amino-9-benzyl-7-(2-oxa-6-azaspiro[3.3]heptane-6-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

6-amino-9-benzyl-7-(3,3-difluoropyrrolidine-1-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

6-amino-9-benzyl-7-(3-fluoro-3-methyl-pyrrolidine-1-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

and their enantiomers or diastereomers are excluded.

The present disclosure, in another aspect, relates to a compound selected from:

6-Amino-9-benzyl-N-methyl-8-oxo-N-propyl-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-9-benzyl-N-(2-methoxyethyl)-N-methyl-8-oxo-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-9-benzyl-*N*-ethyl-8-*oxo*-*N*-propyl-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-9-benzyl-7-[4-(1-piperidyl)piperidine-1-carbonyl]-2-(propylsulfonimidoyl)purin-8-one;

6-Amino-9-benzyl-*N*-ethyl-*N*-(2-methoxyethyl)-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-9-benzyl-*N*-butyl-*N*-ethyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-9-benzyl-*N*-(2-methoxyethyl)-8-*oxo*-*N*-propyl-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-9-benzyl-*N*,*N*-bis(2-methoxyethyl)-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-7-(azetidine-1-carbonyl)-9-benzyl-2-(propylsulfonimidoyl)purin-8-one;

6-Amino-9-benzyl-*N*-isopropyl-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-9-benzyl-7-(4-methylpiperazine-1-carbonyl)-2-(propylsulfonimidoyl)purin-8-one;

6-Amino-9-benzyl-*N*-(3-methoxypropyl)-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-9-benzyl-*N*-isobutyl-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

Ethyl 2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]acetate;

Ethyl 3-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]propanoate;

tert-Butyl 3-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]propanoate;

Ethyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]propanoate;

tert-Butyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-4-methyl-pentanoate;

Isopropyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-4-methyl-pentanoate;

Ethyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-3-methyl-butanoate;

Ethyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-4-methyl-pentanoate;

Ethyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-3-phenyl-propanoate;

Isopropyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-3-phenyl-propanoate;

tert-Butyl (2*S*)-2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]-3-phenyl-propanoate;

N-[2-[Acetyl(methyl)amino]ethyl]-6-amino-9-benzyl-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

Methyl *N*-[2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl]-*N*-methyl-carbamate;

tert-Butyl *N*-[2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl]-*N*-methyl-carbamate;

Ethyl *N*-[2-[[6-amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl]-*N*-methyl-carbamate;

2-[[6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl *N*-butyl-*N*-methyl-carbamate;

2-[[6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl pyrrolidine-1-carboxylate;

2-[[6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl *N*-methyl-*N*-propyl-carbamate;

2-[[6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl *N*,*N*-diethylcarbamate;

2-[[6-Amino-9-benzyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carbonyl]-methyl-amino]ethyl ethyl carbonate;

6-Amino-N-butyl-9-[(4-chlorophenyl)methyl]-N-methyl-8-oxo-2-[S(S)-propylsulfonimidoyl]purine-7-carboxamide;

6-amino-N-butyl-9-[(4-chlorophenyl)methyl]-N-methyl-8-oxo-2-[S(S)-propylsulfonimidoyl]purine-7-carboxamide;

6-Amino-9-[(4-chlorophenyl)methyl]-*N*-ethyl-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)purine-7-carboxamide;

6-Amino-*N*-methyl-8-*oxo*-*N*-propyl-2[S(*S*)-propylsulfonimidoyl]-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-*N*-methyl-8-*oxo*-*N*-propyl-2[S(*R*)-propylsulfonimidoyl]-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-2-[S(*S*)-propylsulfonimidoyl]-9-(*p*-tolylmethyl)-7-(pyrrolidine-1-carbonyl)purin-8-one;

6-Amino-2-[S(*R*)-propylsulfonimidoyl]-9-(*p*-tolylmethyl)-7-(pyrrolidine-1-carbonyl)purin-8-one;

6-Amino-*N*-(2-methoxyethyl)-*N*-methyl-8-*oxo*-2-[S(*S*)-propylsulfonimidoyl]-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-*N*-(2-methoxyethyl)-*N*-methyl-8-*oxo*-2-[S(*R*)-propylsulfonimidoyl]-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-*N*-ethyl-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-*N*-butyl-*N*-methyl-8-*oxo*-2-(propylsulfonimidoyl)-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-9-[(4-chlorophenyl)methyl]-2-[S(*R*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-9-[(4-chlorophenyl)methyl]-2-[S(*S*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-9-[(4-chlorophenyl)methyl]-*N*-ethyl-2[S(*S*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide;

6-Amino-9-[(4-chlorophenyl)methyl]-*N*-ethyl-2-[S(*R*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide;

6-Amino-2-[S(*S*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-*N*-propyl-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-2-[S(*R*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-*N*-propyl-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-*N*-ethyl-2[S(*S*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-*N*-ethyl-2-[S(*R*)-ethylsulfonimidoyl]-*N*-methyl-8-*oxo*-9-(*p*-tolylmethyl)purine-7-carboxamide;

6-Amino-2-[S(*S*)ethylsulfonimidoyl]-9-[(4-fluorophenyl)methyl]-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-2-[S(*R*)ethylsulfonimidoyl]-9-[(4-fluorophenyl)methyl]-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-*N*-ethyl-2-(ethylsulfonimidoyl)-9-[(4-fluorophenyl)methyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide;

6-Amino-*N*-ethyl-2-[S(*S*)-(ethylsulfonimidoyl)]-9-[(4-fluorophenyl)methyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide;

6-Amino-*N*-ethyl-2-[S(*R*)-(ethylsulfonimidoyl)]-9-[(4-fluorophenyl)methyl]-*N*-methyl-8-*oxo*-purine-7-carboxamide;

6-Amino-9-[(4-bromophenyl)methyl]-2-(ethylsulfonimidoyl)-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-2-[S(*R*)-ethylsulfonimidoyl]-9-[(4-bromophenyl)methyl]-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-2-[S(*S*)-ethylsulfonimidoyl]-9-[(4-bromophenyl)methyl]-*N*-methyl-8-*oxo*-*N*-propyl-purine-7-carboxamide;

6-Amino-9-[(4-bromophenyl)methyl]-*N*-ethyl-2-(ethylsulfonimidoyl)-*N*-methyl-8-*oxo*-purine-7-carboxamide;

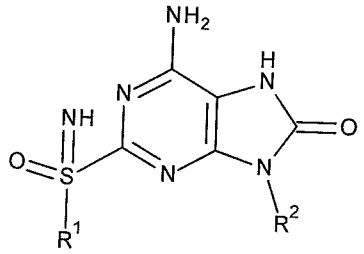
6-Amino-9-[(4-bromophenyl)methyl]-*N*-ethyl-2-[S(*S*)-(ethylsulfonimidoyl)]-*N*-methyl-8-*oxo*-purine-7-carboxamide; and

6-Amino-9-[(4-bromophenyl)methyl]-*N*-ethyl-2-[S(*R*)-(ethylsulfonimidoyl)]-*N*-methyl-8-*oxo*-purine-7-carboxamide;

or pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

The present disclosure, in another aspect, relates to a process for the preparation of a compound as defined herein comprising the following step:

the reaction of a compound of formula (II),



(II),

with carbamoyl chloride in the presence of a mixed base;

wherein the mixed base is pyridine and triethylamine, pyridine and DIPEA, DMAP and triethylamine, or DMAP and DIPEA; R^1 and R^2 are defined herein.

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) thereof as TLR7 agonist. Accordingly, the compounds of formula (I) are useful for the treatment or prophylaxis of HBV and/or HCV infection with Toll-like receptors agonism.

The present disclosure, in another aspect, relates to a compound or pharmaceutically acceptable salt, enantiomer or diastereomer as defined herein for use as therapeutically active substance.

The present disclosure, in another aspect, relates to a pharmaceutical composition comprising a compound as defined herein and a therapeutically inert carrier.

The present disclosure, in another aspect, relates to use of a compound as defined herein for the preparation of a medicament for the treatment or prophylaxis of hepatitis B virus infection.

The present disclosure, in another aspect, relates to the compound as defined herein for use as a TLR7 agonist.

The present disclosure, in another aspect, relates to the compound as defined herein for use to induce production of interferon-α.

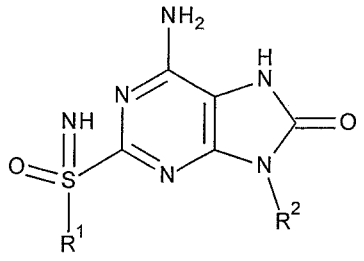
The present disclosure, in another aspect, relates to a compound or pharmaceutically acceptable salt, enantiomer or diastereomer as defined herein for use in the treatment or prophylaxis of hepatitis B virus infection.

The present disclosure, in another aspect, relates to a compound or pharmaceutically acceptable salt, enantiomer or diastereomer as defined herein, when manufactured according to a process as defined herein.

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



(II),

with carbamoyl chloride in the presence of a mixed base;
wherein the mixed base is pyridine and triethylamine, pyridine and DIPEA, DMAP and triethylamine, or DMAP and DIPEA; R^1 and R^2 are defined as in any one of claims 1 to 14.

16. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 14 for use as therapeutically active substance.

17. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 14 and a therapeutically inert carrier.

18. The use of a compound according to any one of claims 1 to 14 for the preparation of a medicament for the treatment or prophylaxis of hepatitis B virus infection.

19. The compound according to any one of claims 1 to 14 for use as a TLR7 agonist.

20. The compound according to any one of claims 1 to 14 for use to induce production of interferon-α.

21. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 14 for use in the treatment or prophylaxis of hepatitis B virus infection.

22. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 14, when manufactured according to a process of claim 15.