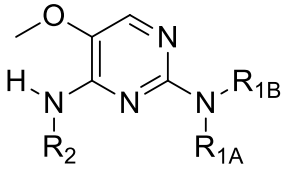
PYRIMIDINE PRODRUGS FOR THE TREATMENT OF VIRAL INFECTIONS AND FURTHER DISEASES.

The present invention relates to pyrimidine prodrug derivatives and the use of said pyrimidine prodrug derivatives in the treatment of viral infections, immune disorders, and cancer, or as a vaccine adjuvant, whereby the induction of a T helper 1 (Th1) immune response is desired.

For instance, in the treatment of chronic hepatitis B (HBV), a Th1 response to reinvigorate exhausted virus-specific $CD8^+$ T cells in the infected organs would be highly beneficial (*Science* **1999**, *284*, 825-829; *J. Virol.* **2003**, *77*, 68-76). Such a response is induced by the innate immune system, in particular by stimulating Toll-like receptors (TLR) such as TLR3, 4, 7, 8 and 9 (*Clin. Transl. Immunol.* **2016**, 5(5):e85). TLR8 agonists induce one of the strongest Th1 response in human cells, *via* the secretion of IL-12p70 and the upregulation of CD40 or OX40L activation markers and indirectly IFNγ (*J Immunol.* **2006**,176(12):7438-46; *Hum Immunol*. **2011** Jan;72(1):24-31; *J Leukoc Biol.* **2012**, 91(1):105-17), which have shown their potential *ex vivo* to treat chronic HBV (*PLoS Pathog.* **2013**, *9*, e1003208; *J. Exp. Med.* **2014**, *211*, 2047-2059; *PLoS Path.* **2013**, *9*, e1003490; *PLoS Pathog.* **2014**, *10*, e1004210).

Only one TLR8 agonist, administered by subcutaneous injection, is currently in development for cancer indications (*Clin. Cancer Res.* **2014**, *20*, 3683; *Cancer Immunol. Immunother.* **2013**, *62*, 1347; WO2012/045089. See also US20080234251, US20100029585). Therefore, there exists a strong need for orally-available TLR8 agonists to treat infections such as chronic HBV.

In accordance with the present disclosure, a compound of formula (I) is provided



(I)

or a pharmaceutically acceptable salt, solvate or polymorph thereof, wherein

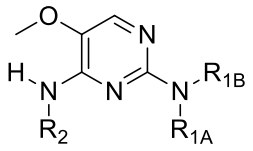
R_{1A} is selected from hydrogen, a substituted or unsubstituted C_{1-3} alkyl, heterocycle, or a substituted or unsubstituted phosphoramidate,

R_{1B} is selected from hydrogen, a substituted or unsubstituted C_{1-3} alkyl, heterocycle, or a substituted or unsubstituted phosphoramidate,

with the exception that R_{1A} and R_{1B} are not both hydrogen, and wherein

R_2 is a C_{1-8} alkyl, which is optionally substituted by a hydroxyl group.

In accordance with the present disclosure, in one aspect, a compound of formula (I) is provided



(I)

or a pharmaceutically acceptable salt, solvate or polymorph thereof, wherein

R_{1A} is selected from hydrogen, a substituted or unsubstituted C_{1-3} alkyl, heterocycle, or a substituted or unsubstituted phosphoramidate,

R_{1B} is selected from hydrogen, a substituted or unsubstituted C_{1-3} alkyl, heterocycle, or a substituted or unsubstituted phosphoramidate,

with the exception that R_{1A} and R_{1B} are not both hydrogen, and wherein

R_2 is a C_{1-8} alkyl, which is substituted by a hydroxyl group.

The present disclosure concerns a prodrug composition of a pharmaceutical compound. The pharmaceutical compound is characterized by bioavailability of 50% or less and a molecular weight in the range of 100-1000 Daltons. Also described is a method of delivering a pharmaceutical compound to an individual including the step of orally administering said prodrug to an individual. The prodrug moiety is attached to the pharmaceutical compound wherein the modification allows the TLR8 agonist potential to be attenuated. The prodrug is enzymatically cleaved prior to or at the site of the liver to yield the pharmaceutical compound, such that the pharmaceutical compound is delivered to the individual limiting TLR8 agonism prior to the liver.

In a first embodiment the present disclosure provides compounds of formula (I) wherein R_{1A} and/ or R_{1B} are a substituted or unsubstituted phosphoramidate and wherein R_2 is a C_{1-6} alkyl preferably substituted by a hydroxyl group.

In a second embodiment the present disclosure provides compounds of formula (I) wherein R_{1A} and/or R_{1B} are methyl and wherein R_2 is a C_6-alkyl substituted by a hydroxyl group.

The compounds of formula (I) in any stereochemical form and their pharmaceutically acceptable salt, solvate or polymorph thereof have activity as pharmaceuticals, in particular as inducers of interferon.

So, in a further aspect the present disclosure provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof as defined herein together with one or more pharmaceutically acceptable excipients, diluents or carriers.

In another aspect of the present disclosure, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof as defined herein, or a pharmaceutical composition comprising said compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof as defined herein for use as a medicament.

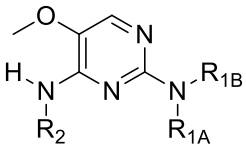
Furthermore a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to the current disclosure, or a pharmaceutical composition comprising said compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof can be used as a medicament.

In another aspect of the present disclosure, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof as defined herein, or a pharmaceutical composition comprising said compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof as defined herein for use in the treatment of a disorder in which the induction of interferon is involved.

Another embodiment of the disclosure is that a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof, or said pharmaceutical composition comprising said compound of formula (I) or a pharmaceutically acceptable salt, solvate

Claims

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt, solvate or polymorph thereof, wherein

R_{1A} is selected from hydrogen, a substituted or unsubstituted C_{1-3} alkyl, heterocycle, or a substituted or unsubstituted phosphoramidate,

R_{1B} is selected from hydrogen, a substituted or unsubstituted C_{1-3} alkyl, heterocycle, or a substituted or unsubstituted phosphoramidate,

with the exception that R_{1A} and R_{1B} are not both hydrogen, and wherein

R_2 is a C_{1-8} alkyl, which is substituted by a hydroxyl group.

2. A compound according to claim 1 wherein R_{1A} and/ or R_{1B} are a substituted or unsubstituted phosphoramidate and wherein R_2 is a C_{1-6} alkyl preferably substituted by a hydroxyl group.

3. A compound according to claim 1 wherein R_{1A} and/or R_{1B} are methyl and wherein R_2 is a C_6-alkyl substituted by a hydroxyl group.

4. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to any one of the claims 1-3 together with one or more pharmaceutically acceptable excipients, diluents or carriers.

5. A compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to any one of the claims 1-3, or a pharmaceutical composition comprising said compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to claim 4 for use as a medicament.

6. A compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to any one of the claims 1-3, or a pharmaceutical composition comprising said compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to claim 4 for use in the treatment of a disorder in which the induction of interferon is involved.

7. Use of compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to any one of the claims 1-3, or a pharmaceutical composition comprising said compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to claim 4, in the manufacture of a medicament for the treatment of viral infections, immune disorders or cancer.