

PURINE DERIVATIVES FOR THE TREATMENT OF VIRAL INFECTIONS

The current invention relates to purine derivatives, processes for their preparation, pharmaceutical compositions, and their use in treating viral infections.

5 The present invention relates to the use of purine derivatives in the treatment of viral infections, immune or inflammatory disorders, whereby the modulation, or agonism, of toll-like-receptors (TLRs) is involved. Toll-Like Receptors are primary transmembrane proteins characterized by an extracellular leucine rich domain and a cytoplasmic extension that contains a conserved region. The innate immune system can recognize pathogen-associated molecular patterns via these TLRs expressed on the cell surface of certain types of immune cells. Recognition of
10 foreign pathogens activates the production of cytokines and upregulation of co-stimulatory molecules on phagocytes. This leads to the modulation of T cell behaviour.

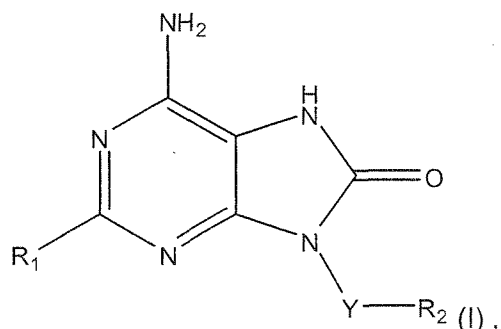
It has been estimated that most mammalian species have between ten and fifteen types of Toll-like receptors. Thirteen TLRs (named TLR1 to TLR13) have been identified in humans and mice together, and equivalent forms of many of these have been found in other mammalian species.
15 However, equivalents of certain TLR found in humans are not present in all mammals. For example, a gene coding for a protein analogous to TLR10 in humans is present in mice, but appears to have been damaged at some point in the past by a retrovirus. On the other hand, mice express TLRs 11, 12, and 13, none of which are represented in humans. Other mammals may express TLRs which are not found in humans. Other non-mammalian species may have
20 TLRs distinct from mammals, as demonstrated by TLR14, which is found in the Takifugu pufferfish. This may complicate the process of using experimental animals as models of human innate immunity.

For a review on toll-like receptors see for instance the following journal article: Hoffmann, J.A., Nature, 426, p33-38, 2003.

25 Compounds indicating activity on Toll-Like receptors have been previously described such as purine derivatives in WO 2006/117670, adenine derivatives in WO 98/01448 and WO 99/28321, and pyrimidines in WO 2009/067081.

However, there exists a strong need for novel Toll-Like receptor modulators having preferred selectivity, higher potency, higher metabolic stability, higher solubility and an improved safety
30 profile compared to the compounds of the prior art.

~~In accordance with a first aspect, the~~ The present disclosure provides compounds of formula (I)



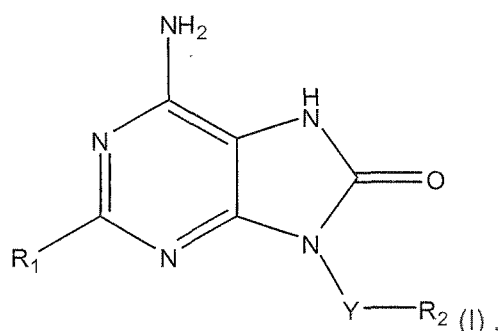
or a pharmaceutically acceptable salt, solvate or polymorph thereof, wherein

Y is (C₁₋₄)alkylene,

R₁ is a heteroaryl¹ and

5 R₂ an aryl² or a heterocyclyl.

In a first aspect, there is provided a compound compound of formula (I)



or a pharmaceutically acceptable salt, solvate or polymorph thereof, wherein Y is (C₁₋₄) alkylene,

R₁ is selected from the group comprising an imidazolyl, a pyrazolyl or a pyridinyl each of which

10 is optionally substituted by one or more substituents independently selected from halogen,

hydroxyl, C₁₋₆ alkyl, C₁₋₄ alkoxy or C₃₋₆ cycloalkyl and R₂ is an aryl² or a heterocyclyl; wherein

the term "aryl²" includes phenyl, naphtyl, anthracenyl and phenanthrenyl, which is optionally

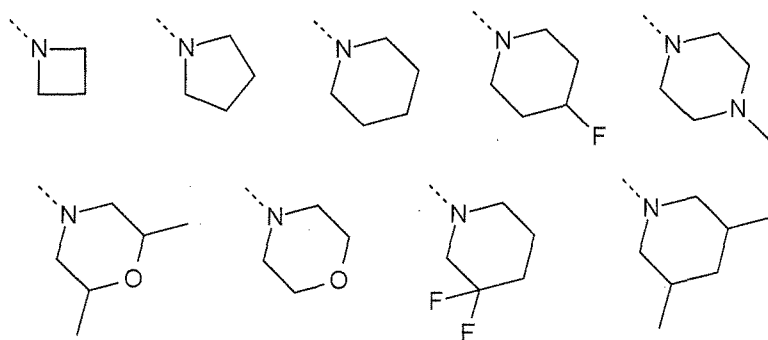
substituted by one or more substituents independently selected from hydroxyl, C₁₋₆ alkyl, C₁₋₄

alkoxy, trifluoromethyl, CO₂R₃, R₄R₅N-C₁₋₄-alkyl-, halogen, hydroxyl- C₁₋₄ alkyl-, NR₆R₇, C(O)R₆,

15 C(O)NR₆R₇, C₁₋₄alkyl-diethoxyphosphoryl or C₁₋₄alkyl-phosphonic acid, whereby R₃ is selected

from H and C₁₋₆ alkyl, R₄ and R₅ taken together with the nitrogen, to which they are both

attached, form a heterocycle selected from the group consisting of:



and R_6 and R_7 are

each independently selected from H, C_{1-6} -alkyl or C_{1-4} alkoxy; wherein

the term "heterocyclyl" refers to tetrahydropyran and heteroaryl², whereby the term "heteroaryl²" includes pyridyl, tetrahydroisoquinolyl, imidazopyridinyl, quinolyl,

- 5 isoquinolyl, pyrazinyl, pyrimidyl, naphthyridinyl, pyridazinyl, benzimidazolyl, benzothiazolyl, pyrazolyl, thiazolyl, imidazolyl, indazolyl, which is optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C_{1-6} alkyl, C_{1-4} alkoxy, oxy- C_{1-4} alkylamine or pyrrolidinyl-methanone; and wherein

the term "solvate" refers to a molecular complex comprising the compound of formula

- 10 (I) and one or more pharmaceutically acceptable solvent molecules.

The term heteroaryl¹ means imidazolyl, pyridyl, pyrimidyl, pyrrolyl, pyrazolyl, furyl, oxazolyl, oxadiazolyl, isoxazolyl, pyrazinyl or thiazolyl. Heteroaryl¹ is optionally substituted by one or more substituents independently selected from hydroxyl, C_{1-6} alkyl, C_{1-4} alkoxy, trifluoromethyl, C_{3-6} cycloalkyl, phenyl, halogen, hydroxyl- C_{1-4} alkyl,

15 C_{1-4} -alkoxy- C_{1-4} -alkyl-, or C_{1-4} alkyl-diethoxyphosphoryl.

The term aryl² includes phenyl, naphtyl, anthracenyl and phenanthrenyl and is preferably phenyl. Aryl² is optionally substituted by one or more substituents independently selected from hydroxyl, C_{1-6} alkyl, C_{1-4} alkoxy, trifluoromethyl, CO_2R_3 , $R_4R_5N-C_{1-4}$ -alkyl-, halogen, hydroxyl- C_{1-4} alkyl-, NR_6R_7 , $C(O)R_6$, $C(O)NR_6R_7$, C_{1-4} alkyl-diethoxyphosphoryl or C_{1-4} alkyl-phosphonic acid.

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R_3 is selected from H and C_{1-6} alkyl.

R_4 and R_5 taken together with the nitrogen, to which they are both attached, form a heterocycle selected from the group consisting of:

mentioned for use in the treatment of a disorder in which the modulation of TLR7 is involved.

In a fourth aspect, the disclosure provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof as defined herein in the manufacture of a medicament for the treatment of viral infections.

The term "alkyl" refers to a straight-chain or branched-chain saturated aliphatic hydrocarbon containing the specified number of carbon atoms.

The term "halogen" refers to fluorine, chlorine, bromine or iodine.

The term "cycloalkyl" refers to a carbocyclic ring containing the specified number of carbon atoms.

The term "alkoxy" refers to an alkyl (carbon and hydrogen chain) group singular bonded to oxygen like for instance a methoxy group or ethoxy group.

Pharmaceutically acceptable salts of the compounds of formula (I) include the acid addition and base salts thereof. Suitable acid addition salts are formed from acids which form non-toxic salts. Suitable base salts are formed from bases which form non-toxic salts.

The compounds of the disclosure may also exist in unsolvated and solvated forms. The term "solvate" is used herein to describe a molecular complex comprising the compound of the disclosure and one or more pharmaceutically acceptable solvent molecules, for example, ethanol.

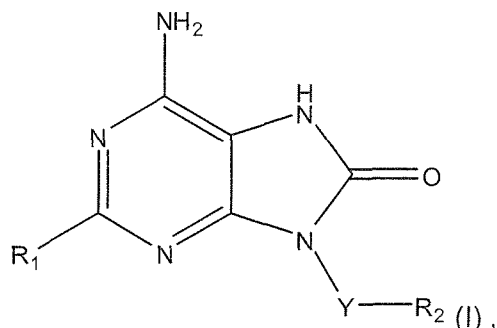
The term "polymorph" refers to the ability of the compound of the disclosure to exist in more than one form or crystal structure.

The compounds of the disclosure can be present in a so-called "tautomer(s)" formation referring to isomers of organic compounds that readily interconvert by a chemical reaction called tautomerization. This reaction results in the formal migration of a hydrogen atom or proton, accompanied by a switch of a single bond and adjacent double bond.

The compounds of the present disclosure may be administered as crystalline or amorphous products. They may be obtained for example as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. They may be administered alone or in combination with one or more other compounds of the disclosure or in combination with one or more other drugs. Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound(s) of the disclosure. The choice of

Claims

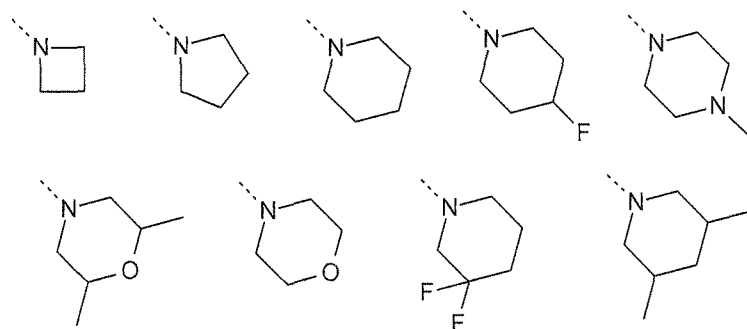
1. A compound of formula (I)



or a pharmaceutically acceptable salt, solvate or polymorph thereof, wherein Y is (C₁₋₄)

alkylene, R₁ is a heteroaryl¹ selected from the group comprising an imidazolyl, a pyrazolyl or a pyridinyl each of which is optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C₁₋₆ alkyl, C₁₋₄ alkoxy or C₃₋₆ cycloalkyl and R₂ is an aryl² or a heterocyclyl; wherein

the term "aryl²" includes phenyl, naphthyl, anthracenyl and phenanthrenyl, which is optionally substituted by one or more substituents independently selected from hydroxyl, C₁₋₆ alkyl, C₁₋₄ alkoxy, trifluoromethyl, CO₂R₃, R₄R₅N-C₁₋₄-alkyl-, halogen, hydroxyl- C₁₋₄ alkyl-, NR₆R₇, C(O)R₆, C(O)NR₆R₇, C₁₋₄alkyl-diethoxyphosphoryl or C₁₋₄alkyl-phosphonic acid, whereby R₃ is selected from H and C₁₋₆ alkyl, R₄ and R₅ taken together with the nitrogen, to which they are both attached, form a heterocycle selected from the group consisting of:



and R₆ and R₇ are each independently selected from H, C₁₋₆-alkyl or C₁₋₄alkoxy; wherein

the term "heterocyclyl" refers to tetrahydropyran and heteroaryl², whereby the term "heteroaryl²" includes pyridyl, tetrahydroisquinoliny, imidazopyridinyl, quinoliny, isoquinoliny, pyrazinyl, pyrimidyl, naphthyridinyl, pyridazinyl, benzimidazolyl, benzothiazolyl, pyrazolyl, thiazolyl, imidazolyl, indazolyl, which is optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C₁₋₆ alkyl, C₁₋₄ alkoxy, oxy-C₁₋₄alkylamine or pyrrolidinyl-methanone; and wherein

the term "solvate" refers to a molecular complex comprising the compound of formula (I) and one or more pharmaceutically acceptable solvent molecules.

2. ~~A compound of formula (I) according to claim 1 wherein R₁ is selected from the group comprising an imidazolyl, a pyrazolyl or a pyridinyl each of which is optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C₁₋₆ alkyl, C₁₋₄ alkoxy or C₃₋₆ cycloalkyl.~~

3.2. ~~A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to claim 1 or 2 together with one or more pharmaceutically acceptable excipients, diluents or carriers.~~

4.3. ~~A compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to claim 1 or 2, or a pharmaceutical composition according to claim 3.2 for use as a medicament.~~

5.4. ~~A compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to claim 1 or 2, or a pharmaceutical composition according to claim 3.2, for use in the treatment of a disorder in which the modulation of TLR7 is involved.~~

5. Use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to claim 1 in the manufacture of a medicament for the treatment of viral infections.