

PYRIDONE DERIVATIVES FOR THE TREATMENT OF VIRAL INFECTIONS AND FURTHER DISEASES.

This invention relates to pyridone derivatives, processes for their preparation, pharmaceutical compositions, and their use in therapy.

- 5 The present invention relates to the use of pyridone 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
10 patterns via these TLRs expressed on the cell surface of certain types of immune cells. Recognition of foreign pathogens activates the production of cytokines and upregulation of co-stimulatory molecules on phagocytes. This leads to the modulation of T cell behaviour.

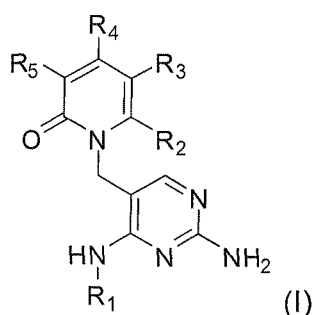
- It has been estimated that most mammalian species have between ten and fifteen types of Toll-like receptors. Thirteen TLRs (named simply TLR1 to TLR13) have been identified in humans
15 and mice together, and equivalent forms of many of these have been found in other mammalian species. However, equivalents 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
20 may express TLRs which are not found in humans. Other non-mammalian species may have 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 detailed reviews on toll-like receptors see the following journal articles. Hoffmann, J.A.,
25 Nature, 426, p33-38, 2003; Akira, S., Takeda, K., and Kaisho, T., Annual Rev. Immunology, 21, p335-376, 2003; Ulevitch, R. J., Nature Reviews: Immunology, 4, p512-520, 2004.

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.

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

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



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

R₁ is C₁₋₆ alkyl, optionally substituted by one or more substituents independently selected from aryl, halogen, hydroxyl, amino, carboxylic acid, carboxylic ester, carboxylic amide, acyl sulfonamide, C₁₋₃ alkyl, C₃₋₆ cycloalkyl, sulfone, sulfoxide, sulfonamide, heterocycle or nitrile;

R₂, R₃, R₄, and R₅ are independently selected from hydrogen, halogen, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₃₋₆ cycloalkyl, aryl, -CF₃ or heterocycle;

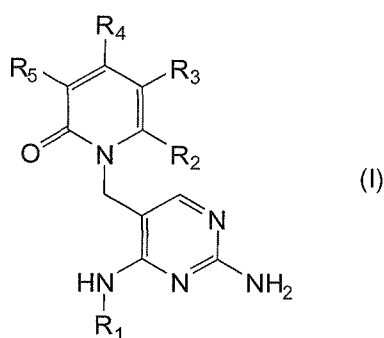
or wherein

R₂ is fused with R₃ to form a ring structure,

R₃ is fused with R₄ to form a ring structure or

R₄ is fused with R₅ to form a ring structure.

In one aspect the present disclosure provides a compound of formula (I)



or a pharmaceutically acceptable salt or solvate thereof, wherein

R₁ is C₁₋₆ alkyl, optionally substituted by one or more substituents independently selected from aryl, with aryl being an aromatic ring structure having 5, 6 or 7 ring atoms, halogen, hydroxyl, amino, carboxylic acid, carboxylic ester, carboxylic amide, acyl sulfonamide, C₁₋₃ alkyl, C₃₋₆ cycloalkyl, sulfone, sulfoxide, sulfonamide, saturated or partially saturated heterocycle or nitrile;

R₂, R₃, R₄, and R₅ are independently selected from hydrogen, halogen, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₃₋₆ cycloalkyl, aryl, with aryl being an aromatic ring structure having 5, 6 or 7 ring atoms, -CF₃ or saturated or partially saturated heterocycle;

or wherein

R₂ is fused with R₃ to form a 5-7 membered saturated or partially saturated monocyclic ring structure,

5 R₃ is fused with R₄ to form a 5-7 membered saturated or partially saturated monocyclic ring structure or

R₄ is fused with R₅ to form a 5-7 membered saturated or partially saturated monocyclic ring structure.

In a first embodiment the present disclosure provides compounds of formula (I) wherein R₁ is *n*-butyl and wherein R₂, R₃, R₄, and R₅ are hydrogen.

10 In a further embodiment the current disclosure relates to compounds of formula (I) wherein R₁ is *n*-butyl and wherein R₂ is fused with R₃ to form a ring structure, R₃ is fused with R₄ to form a ring structure or R₄ is fused with R₅ to form a ring structure.

15 The compounds of formula (I) and their pharmaceutically acceptable salt, solvate or polymorph thereof have activity as pharmaceuticals, in particular as modulators of Toll-Like Receptor TLR7 and/or TLR8 activity especially TLR7 activity.

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

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 the present disclosure provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined herein or a pharmaceutical composition as defined herein for use as a medicament.

5 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 or polymorph thereof can be used accordingly in the treatment of any disorder in which the modulation of TLR7 and /or TLR8 is involved.

10 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.

15 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.

The term "aryl" means an aromatic ring structure optionally comprising one or two heteroatoms selected from N, O and S, in particular from N and O. Said aromatic ring structure may have 5, 6 or 7 ring atoms. In particular, said aromatic ring structure may have 5 or 6 ring atoms.

20 The term "heterocycle" refers to molecules that are saturated or partially saturated and include ethyloxide, tetrahydrofuran, dioxane or other cyclic ethers. Heterocycles containing nitrogen include, for example azetidine, morpholine, piperidine, piperazine, pyrrolidine, and the like. Other heterocycles include, for example, thiomorpholine, dioxolanyl, and cyclic sulfones.

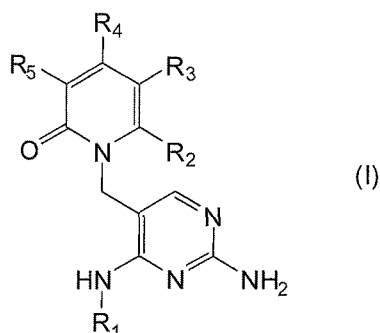
The term "ring structure" means a 5-7 membered, preferably 6-membered, saturated or partially
25 saturated monocyclic moiety optionally comprising one or more heteroatoms selected from nitrogen, oxygen or sulfur.

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.

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

Claims

1. A compound of formula (I)



- 5 or a pharmaceutically acceptable salt or solvate thereof, wherein

R_1 is C_{1-6} alkyl, optionally substituted by one or more substituents independently selected from aryl, with aryl being an aromatic ring structure having 5, 6 or 7 ring atoms, halogen, hydroxyl, amino, carboxylic acid, carboxylic ester, carboxylic amide, acyl sulfonamide, C_{1-3} alkyl, C_{3-6} cycloalkyl, sulfone, sulfoxide, sulfonamide, saturated or partially saturated heterocycle or nitrile;

R_2 , R_3 , R_4 , and R_5 are independently selected from hydrogen, halogen, C_{1-3} alkyl, C_{1-3} alkoxy, C_{3-6} cycloalkyl, aryl, with aryl being an aromatic ring structure having 5, 6 or 7 ring atoms, $-CF_3$ or saturated or partially saturated heterocycle;

or wherein

R_2 is fused with R_3 to form a 5-7 membered saturated or partially saturated monocyclic ring structure,

R_3 is fused with R_4 to form a 5-7 membered saturated or partially saturated monocyclic ring structure or

R_4 is fused with R_5 to form a 5-7 membered saturated or partially saturated monocyclic ring structure.

2. A compound of formula (I) according to claim 1 wherein R_1 is *n*-butyl and wherein R_2 , R_3 , R_4 , and R_5 are hydrogen.

3. A compound of formula (I) according to claim 1 wherein R_1 is *n*-butyl and wherein R_2 is fused with R_3 to form a ring structure, R_3 is fused with R_4 to form a ring structure or R_4 is fused with R_5 to form a ring structure.

4. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof according to one of 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 or solvate thereof according to one of claims 1-3 or a pharmaceutical composition according to claim 4

for use as a medicament.