

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
10 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.

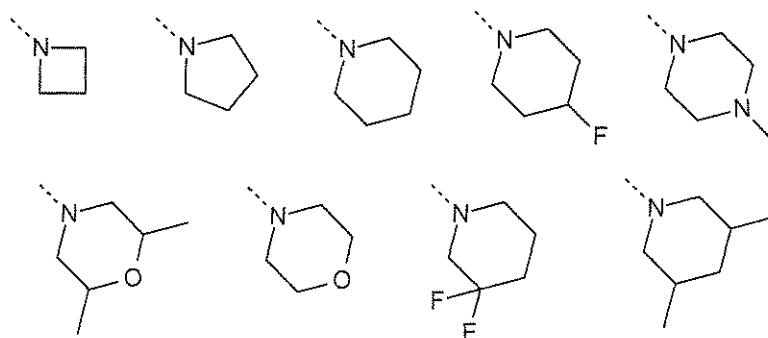
It has been estimated that most mammalian species have between ten and fifteen types of Toll-like receptors. Thirteen TLRs (named TLR1 to TLR13) have been
15 identified in humans and mice together, and equivalent forms of many of these have been found in other mammalian species. However, equivalents 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
20 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 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.

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

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, higher potency, higher metabolic stability, higher solubility and an improved safety profile compared to the compounds of the prior art.

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



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

The term "heterocyclyl" refers to tetrahydropyran and heteroaryl².

The term heteroaryl² includes pyridyl, tetrahydroisoquinolyl, imidazopyridinyl, quinolyl, isoquinolyl, pyrazinyl, pyrimidyl, naphthyridinyl, pyridazinyl, benzimidazolyl, benzothiazolyl, pyrazolyl, thiazolyl, imidazolyl, indazolyl. Heteroaryl² 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.

In a further embodiment the current disclosure encompasses a compound of formula (I) 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.

Preferred compounds according to the disclosure are compounds listed in Table 1 and Table 2 respectively under the heading of the following numbers: 1, 4, 9, 23, 24, 25, 26, 35, 36, 48, 49, 50, 51 and 54.

Furthermore, in a second aspect, to the disclosure provides invention belongs 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 a third aspect, the disclosure provides ~~Part of the invention is also a~~ compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof or a pharmaceutical composition above mentioned for use as a medicament.

In a fourth aspect, the disclosure provides ~~The invention also related to a~~ compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof or a pharmaceutical composition above

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

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

- 5 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.

- 10 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.

- 15 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.

- 20 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.

- 25 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
30 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

excipient depends largely on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

The compounds of the present disclosure or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate

5 compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this disclosure, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of

10 preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, for example, for oral, rectal, or percutaneous administration. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as

15 suspensions, syrups, elixirs, emulsions, and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. Also

20 included are solid form preparations that can be converted, shortly before use, to liquid forms. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives

25 may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. The compounds of the present disclosure may also be administered via inhalation or insufflation by means of methods and formulations employed in the art for administration via this way. Thus, in

30 general the compounds of the present disclosure may be administered to the lungs in the form of a solution, a suspension or a dry powder.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary

35 dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required

pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

Those of skill in the treatment of infectious diseases will be able to determine the effective amount from the test results presented hereinafter. In general it is contemplated that an effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, more preferably from 0.1 mg/kg to 10 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, and in particular 5 to 200 mg of active ingredient per unit dosage form.

The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that the effective amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant disclosure. The effective amount ranges mentioned above are therefore only guidelines and are not intended to limit the scope or use of the disclosure to any extent.