

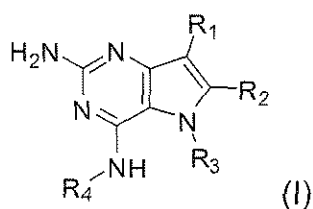
- 5 Compounds indicating activity on Toll-Like receptors have been previously described such as heterocyclic derivatives in WO2000006577, adenine derivatives in WO 98/01448 and WO 99/28321, and pyrimidines in WO 2009/067081.

10 In the treatment of certain viral infections, regular injections of interferon (IFN- α) can be administered, as is the case for hepatitis C virus (HCV) (Fried et. al. Peginterferon- α plus ribavirin for chronic hepatitis C virus infection, *N Engl J Med* 2002; 347: 975-82). Orally available small molecule IFN inducers offer the potential advantages of reduced immunogenicity and convenience of administration. Thus, novel IFN inducers are potentially effective new class of
15 drugs for treating virus infections. For an example in the literature of a small molecule IFN inducer having antiviral effect see De Clercq, E.; Descamps, J.; De Somer, P. *Science* 1978, 200, 563-565.

Interferon alpha is also given to patients in combination with other drugs in the treatment of certain types of cancer (Eur. J. Cancer (46) p 2849–57, and
20 Cancer Res. 1992 (52) p.1056). TLR 7/8 agonists are also of interest as vaccine adjuvants because of their ability to induce pronounced Th1 response (Hum.Vaccines, 2009 (5), 381–394).

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

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



and their pharmaceutically acceptable salt, solvate prodrug, stereoisomers or
30 polymorph thereof wherein

R_1 is H, fluorine or methyl;

R_2 is H, halogen or C_{1-3} alkyl;

5 R_3 is C_{1-6} alkyl optionally substituted by aryl optionally further substituted by one or more substituents independently selected from aryloxy, halogen, aryl, alkylamino, dialkylamino, heterocycloalkyl, C_{1-6} cycloalkyl, C_{1-6} alkyl, carboxylic acid, carboxylic ester, carboxylic amide, nitrile, or C_{1-6} alkoxy; or

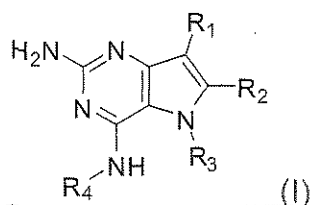
R_3 is C_{1-6} alkyl optionally substituted by C_{1-6} alkene, C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl; or

R_3 is C_{1-6} alkyl optionally substituted by C_{1-6} alkoxy optionally further substituted by aryl;

15 R_4 is C_{1-8} alkyl optionally substituted by one or more substituents independently selected from hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, aryl, heteroaryl optionally further substituted by C_{1-6} alkyl, and C_{3-7} cycloalkyl optionally further substituted by C_{1-6} alkyl;

with the proviso that 2-amino-4-(N-butylamino)-5-(α -methylbenzyl)pyrrolo[3,2-d] pyrimidine is excluded.

20 In one aspect, the present disclosure relates to a compound of formula (I)



and their pharmaceutically acceptable salt, solvate or polymorph thereof wherein

R_1 is H, fluorine or methyl;

25 R_2 is H, halogen or C_{1-3} alkyl;

R_3 is C_{1-6} alkyl optionally substituted by aryl optionally further substituted by one or more substituents independently selected from aryloxy, halogen, aryl, alkylamino, dialkylamino, C_{1-6} alkyl, carboxylic acid, carboxylic ester, carboxylic amide, nitrile, or C_{1-6} alkoxy; or

30 R_3 is C_{1-6} alkyl optionally substituted by C_{1-6} alkene, C_{3-7} cycloalkyl or C_{3-7} heterocycloalkyl; or

5 R₃ is C₁₋₆ alkyl optionally substituted by C₁₋₆ alkoxy optionally further substituted by aryl;

R₄ is C₁₋₈ alkyl optionally substituted by one or more substituents independently selected from hydroxyl, C₁₋₆ alkoxy, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₂₋₆ alkenyl, aryl, heteroaryl optionally further substituted by C₁₋₆ alkyl, and C₃₋₇ cycloalkyl optionally further substituted by C₁₋₆ alkyl;

10 cycloalkyl optionally further substituted by C₁₋₆ alkyl;

with the proviso that 2-amino, 4-(N-butylamino)-5-(alphamethylbenzyl)pyrrolo[3,2-d] pyrimidine is excluded.

Preferred compounds are those of formula (I) wherein R₃ is a C₁₋₃ alkyl group substituted with an aryl (substituted or unsubstituted), and R₁, R₂, and R₄ are described as above.

15

In a second embodiment are the compounds of formula (I) wherein R₃ and R₄ are a C₁₋₃ alkyl substituted by an aryl, optionally further substituted as described above.

In a further embodiments are those of formula (I) wherein R₁ is hydrogen, R₂ is fluorine, and R₃ and R₄ are described as above.

20

Other preferred embodiments are those of formula (I) wherein R₁ is fluorine, R₂ is hydrogen, and R₃ and R₄ are described as above.

The compounds, as listed in Tables I and II, having the following numbers # 89, 94, 101, 144, 154, 156, 175, 192, 209, 213 and 215 are of special interest because of their properties according to the ~~invention-disclosed~~disclosed herein.

25

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 (especially TLR7 and/or TLR8) activity.

5 In a further aspect the present ~~disclosure invention~~ 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.

10 Furthermore a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to the current ~~disclosure invention~~, 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. Another aspect of the present disclosure provides 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.

20 The present disclosure also relates to ~~Another aspect of the invention 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 that can be used accordingly in the treatment of any disorder in which the modulation of TLR7 and /or TLR8 is involved.

25 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 "alkenyl" refers to an alkyl as defined above consisting of at least two carbon atoms and at least one carbon-carbon double bond.

30 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.

35 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. Said aromatic ring structure

- 5 may also be fused to another aryl ring affording a bicyclic structure (examples include but are not limited to: quinoline, isoquinoline, quinazoline, benzoxazole).

- 5 4. A compound of formula (I) according to claim 1 wherein R₁ is fluorine, R₂
is hydrogen, and R₃ and R₄ are as described in claim 1.
- 10 5. A pharmaceutical composition comprising a compound of formula (I) or a
pharmaceutically acceptable salt, solvate or polymorph thereof
according to claim 1 together with one or more pharmaceutically
acceptable excipients, diluents or carriers.
- 15 6. A compound of formula (I) or a pharmaceutically acceptable salt, solvate
or polymorph thereof according to claim 1, or a pharmaceutical
composition comprising said compound of formula (I) or a
pharmaceutically acceptable salt, solvate or polymorph thereof
according to claim 5 for use as a medicament.
- 20 ~~7. A compound of formula (I) or a pharmaceutically acceptable salt,
solvate or polymorph thereof according to claim 1 or said pharmaceutical
composition comprising said compound of formula (I) or a
pharmaceutically acceptable salt, solvate or polymorph thereof
according to claim 5 for use in the treatment of any disorder in which the
modulation of TLR7 and /or TLR8 is involved.~~