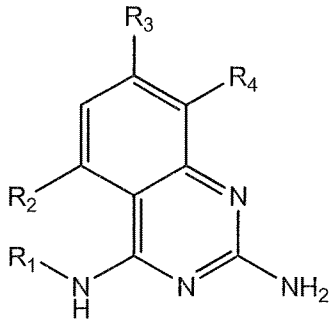
Compounds indicating activity on Toll-Like receptors have been previously described such as purine derivatives in WO 2006/117670, adenine derivatives in WO 98/01448 and WO 99/28321, and pyrimidines in WO 2009/067081.

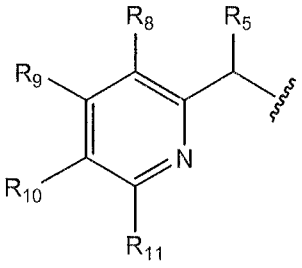
However, there exists a strong need for novel Toll-Like receptor modulators having preferred selectivity, higher potency, higher metabolic stability, and an improved safety profile compared to the compounds of the prior art.

In accordance with one aspect, the present ~~invention~~ disclosure relates to a compound of formula (I) ~~is provided~~



or a pharmaceutically acceptable salt, tautomer(s), stereo-isomeric forms, solvate or polymorph thereof, wherein

R_1 is any of the following structures



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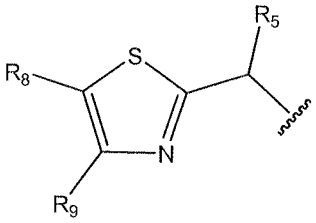

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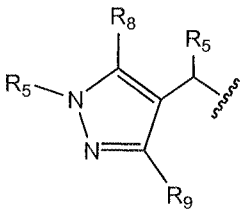

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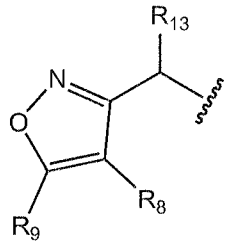
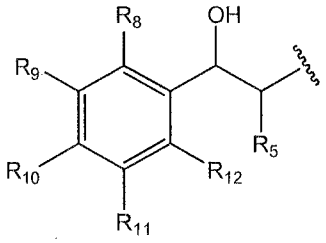
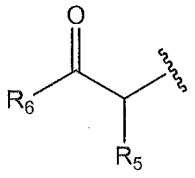
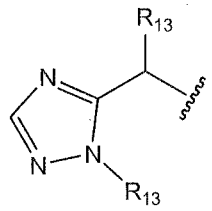
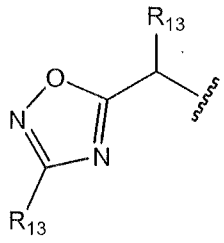






or ;

R_2 is hydrogen, -O-(C_{1-3})-alkyl, halogen, (C_{1-3})-alkyl, -O-(C_{1-3})-alkyl-O-(C_{1-3})-alkyl or CH_2OH;

R_3 is hydrogen, -O-(C_{1-3})-alkyl, halogen, (C_{1-3})-alkyl or –C(=O)-R_7 wherein R_7 is -O-(C_{1-3})-alkyl, NH_2, $NH(CH_3)$, $N(CH_3)_2$, $N(CH_3)$(C_{1-3})-alkyl, N((C_{1-3})-alkyl)$_2$ or pyrolidine;

R_4 is hydrogen or fluorine;

R_5 is (C_{1-3})-alkyl, (C_{1-3})-fluoro-alkyl or CH_2OH;

R_6 is NH_2, $NH(CH_3)$ or $N(CH_3)_2$, (hetero)-anilines optionally substituted with one or more R_8, R_9, R_{10} R_{11} or R_{12} or (hetero)-benzylamines optionally substituted with one or more R_8, R_9, R_{10} R_{11} or R_{12},

R_8, R_9, R_{10}, R_{11} and R_{12} which are the same or different, are each independently selected from hydrogen, (C_{1-3})-alkyl, -O-(C_{1-3})-alkyl or halogen

and

R_{13} is hydrogen, (C_{1-3})-alkyl or (C_{1-3})-fluoro-alkyl.

Preferred compounds according to the ~~invention~~ disclosure are compounds with the numbers 12 and 29 as depicted in Table II.

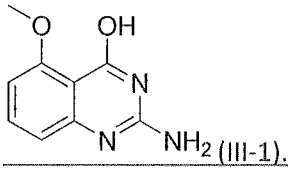
The compounds of formula (I) and their pharmaceutically acceptable salts, tautomer(s), stereo-isomeric forms, solvate or polymorph thereof have activity as pharmaceuticals, in particular as modulators of Toll-Like Receptors (especially TLR7 and/or TLR8 activity).

In a further aspect the present ~~invention~~ disclosure provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt, tautomer, stereo-isomeric form, solvate or polymorph thereof together with one or more pharmaceutically acceptable excipients, diluents or carriers.

In a further aspect, the present disclosure provides ~~Furthermore~~ a compound of formula (I) or a pharmaceutically acceptable salt, solvate, tautomer, stereo-isomeric form or polymorph thereof according to the current ~~invention~~disclosure, or a pharmaceutical composition comprising said compound of formula(I) or a pharmaceutically acceptable salt, solvate, tautomer, stereo-isomeric form or polymorph thereof for ~~can be~~ used as a medicament.

Another aspect of the ~~invention~~ disclosure provides ~~is that~~ a compound of formula (I) or its pharmaceutically acceptable salt, solvate, tautomer, stereo-isomeric form or polymorph thereof, or said pharmaceutical composition comprising said compound of formula (I) or a pharmaceutically acceptable salt, solvate, tautomer, stereo-isomeric form or polymorph thereof for ~~can be~~ used ~~accordingly~~ in the treatment of a disorder in which the modulation of TLR7 and /or TLR8 is involved.

Another aspect of the disclosure provides a substituted 2-amino-4-hydroxyquinazoline having the following formula



(III-1).

The term "(C_{1-3})-alkyl" refers to a straight-chain, branched-chain or cyclic saturated aliphatic hydrocarbon containing the specified number of carbon atoms.

The term "(C_{1-3})-fluoro-alkyl" refers to a straight-chain, branched-chain or cyclic saturated aliphatic hydrocarbon containing the specified number of carbon atoms where one or more hydrogen atoms was replaced by a fluorine atom.

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

The term "aniline" refers a compound with the formula $C_6H_5NR_{13}$- consisting of a phenyl group attached to an amino group; with "(hetero)-aniline" is meant that in the aromatic ring 1-3 nitrogen atoms, preferably 1 nitrogen atom, are present.

The term "benzylamine" means a compound of the formula $C_6H_5CH_2NR_{13}$- consisting of a benzyl group, $C_6H_5CH_2$, attached to an amine functional group; with "(hetero)-benzylamine" is meant that in the aromatic ring 1-3 nitrogen atoms, preferably 1 nitrogen atom, are present.