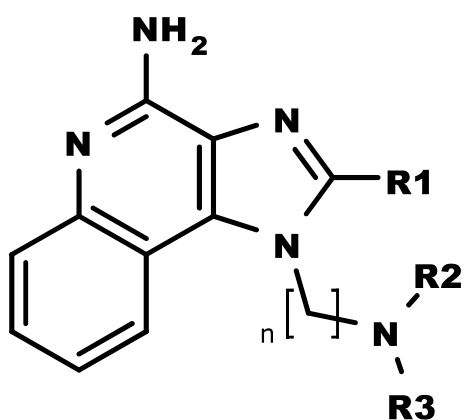


Summary of the Disclosure:

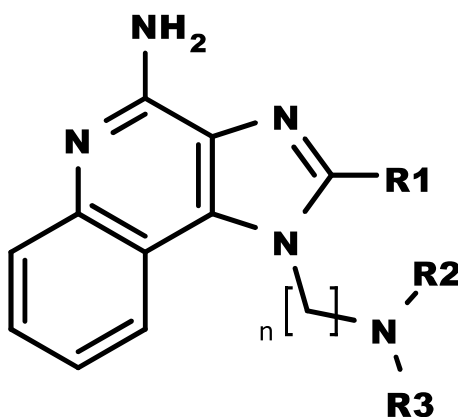
The present disclosure provides imidazoquinoline-4-amine compounds with certain specific substituents, physiologically functional derivatives, solvates and salts thereof, as further described in the following. Said compounds are agonists or
5 activators for TLR7 and may serve as cytokine inducing compounds. Said compounds have the general Formula (I):



10 (I)

wherein: R_1 , R_2 , R_3 and n are as defined below.

In one aspect, the present disclosure provides a compound having the general Formula (I):



wherein

- 5 R1 is selected from the group consisting of -H, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₃-alkoxy-C₁₋₃-alkyl, C₁₋₆-alkylthio, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, 4- to 10-membered heterocycloalkyl, C₃₋₁₀-cycloalkyl, C₆₋₁₀-aryl, C₆₋₁₀-aryl-C₁₋₂-alkyl and 5- to 10-membered heteroaryl, wherein said C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₃-alkoxy-C₁₋₃-alkyl, C₁₋₆-alkylthio, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, C₆₋₁₀-aryl, 4- to 10-membered heterocycloalkyl, C₃₋₁₀-cycloalkyl, C₆₋₁₀-aryl-C₁₋₂-alkyl and 5- to 10-membered heteroaryl is optionally substituted by one or more groups independently selected from the group consisting of C₁₋₄-alkyl, -OH, halogen, -CO-N(R₄)₂, -N(R₄)₂, -CO-R₄, -COO-R₄, -N₃, -NO₂, and -CN;
- 10 R2 is selected from the group consisting of -CO-R₅, -CONH-R₅, and -COO-R₅;
- 15 R3 is 1,1-dioxothietan-3-yl, which is optionally substituted by one or more groups independently selected from the group consisting of C₁₋₄-alkyl, -OH, and halogen;
- R4 is each independently selected from the group consisting of H and C₁₋₄-alkyl;
- 20 n is an integer from 3 to 6; and
- R5 is selected from the group consisting of -H, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₃-alkoxy-C₁₋₃-alkyl, C₁₋₆-alkylthio, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, C₆₋₁₀-aryl, 4- to 10-membered heterocycloalkyl, C₃₋₁₀-cycloalkyl and 5- to 10-membered heteroaryl, wherein said C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₃-alkoxy-C₁₋₃-alkyl, C₁₋₆-alkylthio, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, C₆₋₁₀-aryl, 4- to 10-membered heterocycloalkyl, C₃₋₁₀-cycloalkyl and 5- to 10-membered heteroaryl is optionally substituted by one or more groups independently selected from the group consisting of C₁₋₄-alkyl, -OH, halogen, -CO-N(R₄)₂, -N(R₄)₂, -CO-R₄, -COO-R₄, -N₃, -NO₂, and -CN;
- 25 30 or a physiologically functional derivative, solvate or salt thereof,

wherein the physiologically functional derivative is a prodrug of said compound, wherein at least one of the following groups is derivatized as specified in the following:

- 5 (i) a carboxylic acid (-COOH) group is derivatized into an ester having the formula -COOR₈, wherein R₈ is selected from the group consisting of -H, alkyl, alkoxy, alkoxyalkyl, alkylthio, alkylthioalkyl, alkylaminoalkyl, aryl, heterocycloalkyl, cycloalkyl and heteroaryl, wherein said alkyl, alkoxy, alkoxyalkyl, alkylthio, alkylthioalkyl, alkylaminoalkyl, aryl, heterocycloalkyl, cycloalkyl and heteroaryl groups are optionally substituted
10 by one or more groups independently selected from the group consisting of C₁₋₄-alkyl, -OH, halogen, -CO-N(R₉)₂, -N(R₉)₂, -CO-R₉, -COO-R₉, -N₃, -NO₂, and -CN, wherein R₉ is each independently selected from the group consisting of H and C₁₋₄-alkyl;
- 15 (ii) a hydroxyl (-OH) group is derivatized into an ester having the formula -COOR₈;
- (iii) a carboxylic acid is derivatized into an amide having the formula -CONH-R₈;
- (iv) an amine (-NH₂) is derivatized into an amide having the formula -CONH-R₈; and
20 (v) a hydroxyl group is derivatized into a phosphate ester having the formula -OP(O)(OR₁₀)₂, wherein R₁₀ is each independently selected from the group consisting of H and C₁₋₄-alkyl.

25 In another example, the present disclosure provides methods for the preparation of certain compounds of Formula (I), physiologically functional derivatives, solvates or salts thereof, as detailed further herein below.

In another example, the present disclosure provides methods for the treatment or prevention of certain medical conditions, the method comprising the administration of compounds of Formula (I), physiologically functional derivatives, solvates or salts
30 thereof, to a subject in need thereof, as detailed further herein below.

In another example, the present disclosure provides the use of compounds of Formula (I), physiologically functional derivatives, solvates or salts thereof, in the

manufacture of a medicament for the treatment or prevention of certain medical conditions, as detailed further herein below.

In another example, the present disclosure provides compounds of Formula (I), physiologically functional derivatives, solvates or salts thereof, for use as medicament, in particular for use in the treatment or prevention of certain medical conditions, as detailed further herein below.

In another aspect, the present disclosure provides pharmaceutical compositions comprising compounds of Formula (I), physiologically functional derivatives, solvates or salts thereof and one or more pharmaceutically acceptable excipients.

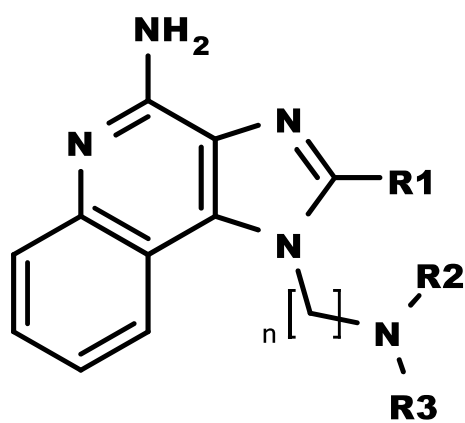
In yet another aspect, the present disclosure provides a compound, physiologically functional derivative, solvate or salt thereof as described herein or a pharmaceutical composition as described herein for use as medicament. In a further aspect, the present disclosure provides use of the compound, physiologically functional derivative, solvate or salt thereof as defined herein or the pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment or prevention of a medical condition selected from the group consisting of proliferative diseases, in particular cancer.

The compounds of Formula (I) are for instance useful as TLR7 activators.

Detailed Description of Invention:

It has been found that the imidazoquinoline derivatives of Formula (I), physiologically functional derivatives, solvates or salts thereof, which are described in greater detail below, are particularly effective TLR7 agonists and have surprising and particularly advantageous properties.

The present invention provides compounds of Formula (I):



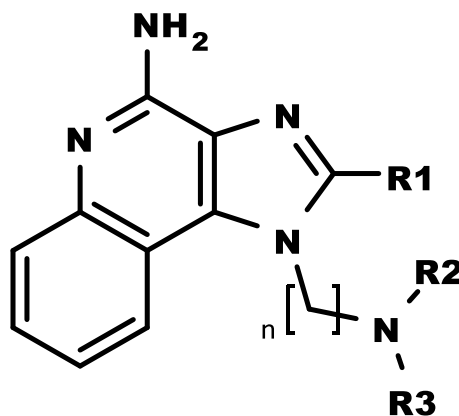
(I)

wherein

- 5 R_1 is selected from the group consisting of -H, C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-3} -alkoxy- C_{1-3} -alkyl, C_{1-6} -alkylthio, C_{1-3} -alkylthio- C_{1-3} -alkyl, C_{1-3} -alkylamino-

Claims

1. A compound having the general Formula (I):



5

wherein

- R1 is selected from the group consisting of -H, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₃-alkoxy-C₁₋₃-alkyl, C₁₋₆-alkylthio, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, 4- to 10-membered heterocycloalkyl, C₃₋₁₀-cycloalkyl, C₆₋₁₀-aryl, C₆₋₁₀-aryl-C₁₋₂-alkyl and 5- to 10-membered heteroaryl, wherein said C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₃-alkoxy-C₁₋₃-alkyl, C₁₋₆-alkylthio, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, C₆₋₁₀-aryl, 4- to 10-membered heterocycloalkyl, C₃₋₁₀-cycloalkyl, C₆₋₁₀-aryl-C₁₋₂-alkyl and 5- to 10-membered heteroaryl is optionally substituted by one or more groups independently selected from the group consisting of C₁₋₄-alkyl, -OH, halogen, -CO-N(R₄)₂, -N(R₄)₂, -CO-R₄, -COO-R₄, -N₃, -NO₂, and -CN;
- R2 is selected from the group consisting of -CO-R₅, -CONH-R₅, and -COO-R₅;
- R3 is 1,1-dioxathietan-3-yl, which is optionally substituted by one or more groups independently selected from the group consisting of C₁₋₄-alkyl, -OH, and halogen;
- R4 is each independently selected from the group consisting of H and C₁₋₄-alkyl;
- n is an integer from 3 to 6; and

- 5 R5 is selected from the group consisting of -H, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₃-alkoxy-C₁₋₃-alkyl, C₁₋₆-alkylthio, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, C₆₋₁₀-aryl, 4- to 10-membered heterocycloalkyl, C₃₋₁₀-cycloalkyl and 5- to 10-membered heteroaryl, wherein said C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₃-alkoxy-C₁₋₃-alkyl, C₁₋₆-alkylthio, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, C₆₋₁₀-aryl, 4- to 10-membered heterocycloalkyl, C₃₋₁₀-cycloalkyl and 5- to 10-membered heteroaryl is optionally substituted by one or more groups independently selected from the group consisting of C₁₋₄-alkyl, -OH, halogen, -CO-N(R₄)₂, -N(R₄)₂, -CO-R₄, -COO-R₄, -N₃, -NO₂, and -CN;
- 10 or a physiologically functional derivative, solvate or salt thereof, wherein the physiologically functional derivative is a prodrug of said compound, wherein at least one of the following groups is derivatized as specified in the following:
- 15 (i) a carboxylic acid (-COOH) group is derivatized into an ester having the formula -COOR₈, wherein R₈ is selected from the group consisting of -H, alkyl, alkoxy, alkoxyalkyl, alkylthio, alkylthioalkyl, alkylaminoalkyl, aryl, heterocycloalkyl, cycloalkyl and heteroaryl, wherein said alkyl, alkoxy, alkoxyalkyl, alkylthio, alkylthioalkyl, alkylaminoalkyl, aryl, heterocycloalkyl, cycloalkyl and heteroaryl groups are optionally substituted by one or more groups independently selected from the group consisting of C₁₋₄-alkyl, -OH, halogen, -CO-N(R₉)₂, -N(R₉)₂, -CO-R₉, -COO-R₉, -N₃, -NO₂, and -CN, wherein R₉ is each independently selected from the group consisting of H and C₁₋₄-alkyl;
- 20 (ii) a hydroxyl (-OH) group is derivatized into an ester having the formula -COOR₈;
- 25 (iii) a carboxylic acid is derivatized into an amide having the formula -CONH-R₈;
- (iv) an amine (-NH₂) is derivatized into an amide having the formula -CONH-R₈; and
- 30 (v) a hydroxyl group is derivatized into a phosphate ester having the formula -OP(O)(OR₁₀)₂, wherein R₁₀ is each independently selected from the group consisting of H and C₁₋₄-alkyl.

2. The compound, physiologically functional derivative, solvate or salt thereof according to claim 1, wherein R1 is selected from the group consisting of C₁₋₆-alkyl, C₁₋₃-alkoxy-C₁₋₃-alkyl, C₁₋₃-alkylthio-C₁₋₃-alkyl, and C₁₋₃-alkylamino-C₁₋₃-alkyl, wherein said C₁₋₆-alkyl, C₁₋₃-alkoxy-C₁₋₃-alkyl, C₁₋₃-alkylthio-C₁₋₃-alkyl, or C₁₋₃-alkylamino-C₁₋₃-alkyl is optionally substituted by one or more groups independently selected from the group consisting of -OH and halogen.
5
3. The compound, physiologically functional derivative, solvate or salt thereof according to claim 2, wherein R1 is selected from the group consisting of C₁₋₆-alkyl, C₁₋₃-alkoxy-C₁₋₃-alkyl, and C₁₋₃-alkylamino-C₁₋₃-alkyl, wherein said C₁₋₆-alkyl, C₁₋₃-alkoxy-C₁₋₃-alkyl, and C₁₋₃-alkylamino-C₁₋₃-alkyl is optionally substituted by one or more groups independently selected from the group consisting of -OH and halogen.
10
4. The compound, physiologically functional derivative, solvate or salt thereof according to any one of claims 1 to 3, wherein R1 is selected from the group consisting of ethyl, methyl, propyl, butyl, methoxyethyl, and ethylaminomethyl, each of which is optionally substituted by one or more groups independently selected from the group consisting of -OH and halogen.
15
5. The compound, physiologically functional derivative, solvate or salt thereof according to any of claims 1 to 4, wherein R2 is selected from the group consisting of -CO-R5, -COO-R5, and -CONH-R5.
20
6. The compound, physiologically functional derivative, solvate or salt thereof according to claim 5, wherein R2 is selected from the group consisting of -CO-R5 and -CONH-R5.
25
7. The compound, physiologically functional derivative, solvate or salt thereof according to claim 5 or 6, wherein R2 is -CO-R5.
- 30 8. The compound, physiologically functional derivative, solvate or salt thereof according to any of claims 1 to 7, wherein R3 is unsubstituted 1,1-dioxothietan-3-yl.

9. The compound, physiologically functional derivative, solvate or salt thereof according to any of claims 1 to 8, wherein n is an integer from 3 to 5.
- 5 10. The compound, physiologically functional derivative, solvate or salt thereof according to claim 9, wherein n is 4.
11. The compound, physiologically functional derivative, solvate or salt thereof according to any of claims 1 to 10, selected from the group consisting of:
- 10 N-(4-(4-amino-2-ethyl-1H-imidazo[4,5-c]quinolin-1-yl)butyl)-N-(1,1-dioxidothietan-3-yl)acetamide;
methyl (4-(4-amino-2-ethyl-1H-imidazo[4,5-c]quinolin-1-yl)butyl)(1,1-dioxidothietan-3-yl)carbamate;
1-(4-(4-amino-2-ethyl-1H-imidazo[4,5-c]quinolin-1-yl)butyl)-1-(1,1-dioxidothietan-3-yl)urea;
- 15 N-(4-(4-amino-2-((ethylamino)methyl)-1H-imidazo[4,5-c]quinolin-1-yl)butyl)-N-(1,1-dioxidothietan-3-yl)acetamide;
methyl (4-(4-amino-2-((ethylamino)methyl)-1H-imidazo[4,5-c]quinolin-1-yl)butyl)(1,1-dioxidothietan-3-yl)carbamate;
- 20 1-(4-(4-amino-2-((ethylamino)methyl)-1H-imidazo[4,5-c]quinolin-1-yl)butyl)-1-(1,1-dioxidothietan-3-yl)urea;
N-(4-(4-amino-2-(2-methoxyethyl)-1H-imidazo[4,5-c]quinolin-1-yl)butyl)-N-(1,1-dioxidothietan-3-yl)acetamide;
methyl (4-(4-amino-2-(2-methoxyethyl)-1H-imidazo[4,5-c]quinolin-1-yl)butyl)(1,1-dioxidothietan-3-yl)carbamate;
- 25 1-(4-(4-amino-2-(2-methoxyethyl)-1H-imidazo[4,5-c]quinolin-1-yl)butyl)-1-(1,1-dioxidothietan-3-yl)urea;
and a physiologically functional derivative, solvate or salt thereof.
- 30 12. A pharmaceutical composition comprising a compound, physiologically functional derivative, solvate or salt thereof according to any of claims 1 to 11 and one or more pharmaceutically acceptable excipients.

13. A compound, physiologically functional derivative, solvate or salt thereof according to any of claims 1 to 11 or a pharmaceutical composition according to claim 12 for use as medicament.
- 5 14. Use of the compound, physiologically functional derivative, solvate or salt thereof as defined in any of claims 1 to 11 or the pharmaceutical composition as defined in claim 12 in the manufacture of a medicament for the treatment or prevention of a medical condition selected from the group consisting of proliferative diseases, in particular cancer.
- 10 15. The use according to claim 14, wherein the medical condition is cancer.