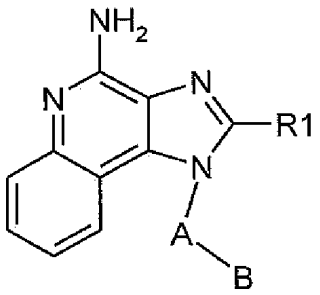
Summary of Invention:

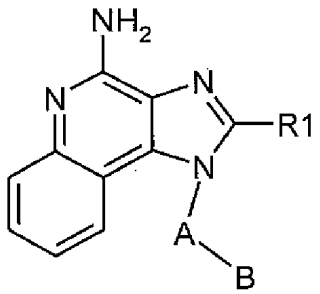
Small molecules, in particular imidazoquinolines-4-amine derivatives, have been found that are activators for TLR7 with high potency. These imidazoquinoline derivatives have favorable physicochemical and pharmacokinetic properties. Accordingly, the present disclosure provides compounds, which have been found to be activators for TLR7 and which are defined by general structure formula I:



(I)

wherein: R1, A and B are as defined below.

In one aspect, the present disclosure provides a compound of formula I:



(I)

wherein

R_1 is selected from the group consisting of:

-H, alkyl, alkynyl, aryl, alkoxy, heterocyclyl and heteroaryl,

wherein alkyl, alkynyl, aryl, alkoxy, heterocyclyl or heteroaryl may be unsubstituted or substituted by one or more substituents selected from the

group consisting of: -H, -OH, halogen, -CO-N(R_4)$_2$, -N(R_4)$_2$, -CO-C_{1-10} alkyl, -CO-O-C_{1-10} alkyl, -N_3, aryl, heterocyclyl,

wherein each R_4 is independently selected from the group consisting of: -H, -C_{1-10} alkyl, -C_{1-10} alkyl-aryl, or aryl;

A is C_1-C_6 alkyl;

B is -N(R_2)(R_3);

R_2 is H;

R_3 is selected from the group consisting of:

aryl, heteroaryl, cycloalkyl, and heterocyclyl,

wherein aryl, heteroaryls, cycloalkyl or heterocyclyl may be unsubstituted or substituted by one or more substituents selected from the group consisting of: -H, alkyl, alkenyl, alkoxy, halogen, -OH, -N_3, trifluromethyl, -alkyl-aryl, -O-alkyl-aryl, -CO-aryl, aryl, heterocyclyl, heteroaryl, -CO-heteroaryl, -CO-O-alkyl, -CO-N-alkyl, -CO-N-aryl,

or pharmaceutically acceptable solvates, salts, N-oxides or stereoisomers thereof, or combinations thereof.

In another aspect, the present disclosure provides a compound as disclosed herein for use as a medicament.

In another aspect, the present disclosure provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I as disclosed herein in combination with a pharmaceutically acceptable carrier.

In a further aspect, the present disclosure provides a use of a compound or a pharmaceutical composition as disclosed herein for the manufacture of a medicament for the treatment of a viral or neoplastic disease.

In another aspect, the present disclosure provides a use of a compound or a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a cancer selected from the group comprising cancer of the breast, bladder, bone, brain, central and peripheral nervous system, colon, endocrine glands, esophagus, endometrium, germ cells, head and neck, kidney, liver, lung, larynx and

hypopharynx, mesothelioma, sarcoma, ovary, pancreas, prostate, rectum, renal, small intestine, soft tissue, testis, stomach, skin, ureter, vagina and vulva; inherited cancers, retinomblastoma and Wilms tumor; leukemia, lymphoma, non-Hodgkins disease, chronic and acute myeloid leukaemia, acute lymphoblastic leukemia, Hodgkins disease, multiple myeloma and T-cell lymphoma; myelodysplastic syndrome, plasma cell neoplasia, paraneoplastic syndromes, cancers of unknown primary site and AIDS related malignancies.

In another aspect, the present disclosure provides a use of a compound or a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a medical condition selected from the group comprising genital warts; common warts; plantar warts; Hepatitis B; Hepatitis C; Herpes Simplex Type I and Type II; molluscum contagiosum; HIV; CMV; VZV; intraepithelial neoplasias including cervical intraepithelial neoplasia, human papillomavirus (HPV) and associated neoplasias; fungal diseases including candida, aspergillus, and cryptococcal meningitis; neoplastic diseases including basal cell carcinoma, hairy cell leukemia, Kaposi's sarcoma, renal cell carcinoma, squamous cell carcinoma, myelogenous leukemia, multiple myeloma, melanoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, and other cancers; parasitic diseases including pneumocystis carinii, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection, and leishmaniasis; bacterial infections including tuberculosis, and mycobacterium avium; eczema; eosinophilia; essential thrombocythaemia; leprosy; multiple sclerosis; Ommen's syndrome; discoid lupus; Bowen's disease; Bowenoid papulosis; atopic diseases including atopic dermatitis; asthma; allergy; allergic rhinitis; systemic lupus erythematosis; recurrent fungal diseases, periodontitis and chlamydia; or for the use as a vaccine adjuvant for cell mediated immunity; or for the use to enhance or stimulate the healing of wounds, including chronic wounds.

In yet another aspect, the present disclosure provides a use of a compound as disclosed herein in the manufacture of a medicament.

The compounds of formula I are useful as TLR7 activators.

The present disclosure further provides pharmaceutical compositions containing an effective amount of compound of formula I.

In addition, methods of synthesizing compounds of formula I are described.

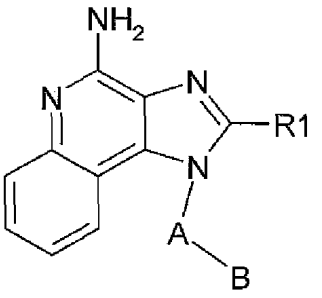
Description of Figures:

Figure 1 shows the effect of chloroquine on cytokine induction of TLR agonists in PCIR-1 cells. Expression of IL8 mRNA was measured with TaqMan PCR after 16 hours incubation of cells with H2006, LPS or Resiquimod alone and in combination with cloroquine.

Figure 2 shows the TLR agonist screening cascade.

Claims

1. A compound of formula I:



(I)

wherein

R_1 is selected from the group consisting of:

-H, alkyl, alkynyl, aryl, alkoxy, heterocyclyl and heteroaryl,

wherein alkyl, alkynyl, aryl, alkoxy, heterocyclyl or heteroaryl may be unsubstituted or substituted by one or more substituents selected from the group consisting of: -H, -OH, halogen, -CO-N(R_4)$_2$, -N(R_4)$_2$, -CO-C_{1-10} alkyl, -CO-O-C_{1-10} alkyl, -N_3, aryl, heterocyclyl,

wherein each R_4 is independently selected from the group consisting of: -H, -C_{1-10} alkyl, -C_{1-10} alkyl-aryl, or aryl;

A is C_1-C_6 alkyl;

B is -N(R_2)(R_3);

R_2 is H;

R_3 is selected from the group consisting of:

aryl, heteroaryl, cycloalkyl, and heterocyclyl,

wherein aryl, heteroaryls, cycloalkyl or heterocyclyl may be unsubstituted or substituted by one or more substituents selected from the group consisting of: -H, alkyl, alkenyl, alkoxy, halogen, -OH, -N_3, trifluromethyl, -alkyl-aryl, -O-alkyl-aryl, -CO-aryl, aryl, heterocyclyl, heteroaryl, -CO-heteroaryl, -CO-O-alkyl, -CO-N-alkyl, -CO-N-aryl,

or pharmaceutically acceptable solvates, salts, N-oxides or stereoisomers thereof, or combinations thereof.

2. The compound of formula I according to claim 1, wherein R_3 is heterocyclyl, which may be unsubstituted or substituted by one or more substituents selected from group consisting of: -H, alkyl, alkenyl, alkoxy, halogen, -OH, $-N_3$, trifluromethyl, -alkyl-aryl, -O-alkyl-aryl, -CO-aryl, aryl, heterocyclyl, heteroaryl, -CO-heteroaryl, -CO-O-alkyl, -CO-N-alkyl, -CO-N-aryl, preferably selected from group consisting of: -H, alkyl, alkenyl, halogen and -OH.

3. The compound of formula I accordingly to any of claims 1-2, wherein R_3 is selected from the group consisting of: dioxo-tetrahydrothiophenyl, piperidinyl, tetrahydrofuranyl, pyrididine, tetrahydropyranyl and azabicyclooctanyl, each of which may be optionally substituted by one or more groups, selected from the group comprising halogen, hydroxyl, aryl, alkyl, alkoxy, trifluoromethyl or combinations thereof.

4. The compound of formula I according to any of claims 1-3, wherein R_1 is alkyl, preferably ethyl.

5. The compound as claimed in claim 1 which is:
2-ethyl-1-[4-(tetrahydro-2H-pyran-4-ylamino)butyl]-1H-imidazo[4,5-c]quinolin-4-amine,
1-[4-(1-azabicyclo[2.2.2]oct-3-ylamino)butyl]-2-ethyl-1H-imidazo[4,5-c]quinolin-4-amine or
1-{4-[(1,1-dioxido-3,4-dihydro-2H-thiochromen-4-yl)amino]butyl}-2-ethyl-1H-imidazo[4,5-c]quinolin-4-amine

or pharmaceutically acceptable solvates, salts, N-oxides or stereoisomers thereof, or combinations thereof.

6. A compound as claimed in any one of claims 1 to 5 for use as a medicament.

7. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I as claimed in any one of claims 1 to 5 in combination with a pharmaceutically acceptable carrier.

8. A pharmaceutical composition according to claim 7 comprising an amount of the compound of formula I, or pharmaceutically acceptable solvates, salts, N-oxides or stereoisomers thereof, or combinations thereof, sufficient to provide a dose of 100 ng/kg to 50 mg/kg, preferably 10 μg/kg to 5 mg/kg of the compound to the subject.

9. Use of a compound according to any of claims 1 to 5 or a pharmaceutical composition according to claim 7 or 8 for the manufacture of a medicament for the treatment of a viral or neoplastic disease.

10. Use of a compound according to any of claims 1 to 5 or a pharmaceutical composition according to claim 7 or 8 in the manufacture of a medicament, for treating a cancer selected from the group comprising cancer of the breast, bladder, bone, brain, central and peripheral nervous system, colon, endocrine glands, esophagus, endometrium, germ cells, head and neck, kidney, liver, lung, larynx and hypopharynx, mesothelioma, sarcoma, ovary, pancreas, prostate, rectum, renal, small intestine, soft tissue, testis, stomach, skin, ureter, vagina and vulva; inherited cancers, retinomblastoma and Wilms tumor; leukemia, lymphoma, non-Hodgkins disease, chronic and acute myeloid leukaemia, acute lymphoblastic leukemia, Hodgkins disease, multiple myeloma and T-cell lymphoma; myelodysplastic syndrome, plasma cell neoplasia, paraneoplastic syndromes, cancers of unknown primary site and AIDS related malignancies.

11. Use of a compound according to any of claims 1 to 5 or a pharmaceutical composition according to claim 7 or 8 in the manufacture of a medicament, for treating a medical condition selected from the group comprising genital warts; common warts; plantar warts; Hepatitis B; Hepatitis C; Herpes Simplex Type I and Type II; molluscum contagiosum; HIV; CMV; VZV; intraepithelial neoplasias

including cervical intraepithelial neoplasia, human papillomavirus (HPV) and associated neoplasias; fungal diseases including candida, aspergillus, and cryptococcal meningitis; neoplastic diseases including basal cell carcinoma, hairy cell leukemia, Kaposi's sarcoma, renal cell carcinoma, squamous cell carcinoma, myelogenous leukemia, multiple myeloma, melanoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, and other cancers; parasitic diseases including pneumocystis carinii, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection, and leishmaniasis; bacterial infections including tuberculosis, and mycobacterium avium; eczema; eosinophilia; essential thrombocythaemia; leprosy; multiple sclerosis; Ommen's syndrome; discoid lupus; Bowen's disease; Bowenoid papulosis; atopic diseases including atopic dermatitis; asthma; allergy; allergic rhinitis; systemic lupus erythematosis; recurrent fungal diseases, periodontitis and chlamydia; or for the use as a vaccine adjuvant for cell mediated immunity; or for the use to enhance or stimulate the healing of wounds, including chronic wounds.

12. Use of a compound according to any of claims 1 to 5 in the manufacture of a medicament.