Bioorg. Med. Chem. Lett. 18 (2008) 5631–5634 describes immunostimulatory mono- and bis-phosphorothioate analogues of symmetrical bacterial CDN c-di-GMP.

WO 2014/189805 describes cyclic dinucleotide compounds that feature two purine nucleobases and at least one non-canonical 2',5' phosphodiester or phosphorothioate moiety and induce STING-dependent cytokine production.

WO 2015/185565 describes cyclic dinucleotide compounds that feature two purine nucleobases, one or two cyclopentane instead of ribose tetrahydrofurane rings and one non-canonical 2',5' phosphodiester moiety and modulate STING.

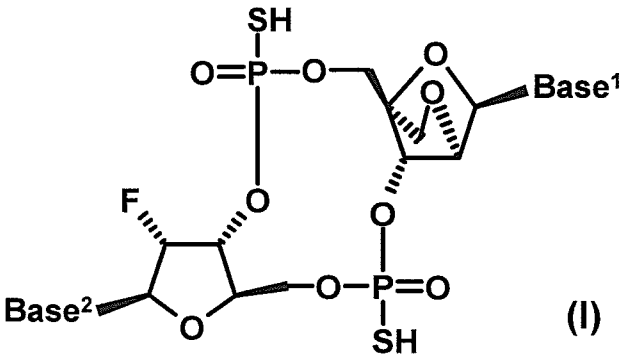
WO 2016/120305 describes cyclic dinucleotide compounds that feature two purine nucleobases, one ribose moiety in which the 2'-OH is replaced with a 2'-F and one non-canonical 2',5' phosphodiester moiety and modulate STING.

US 2014/0329889, WO 2014/099824, WO 2015/017652, Cell 154, 748–762 (2013), and Molecular Cell 51, 226–235 (2013) describe the cyclic dinucleotide 2'3'-cGAMP (cyclic [G(2',5')pA(3',5')p]) which features two purine nucleobases, one canonical 3',5' and one non-canonical 2',5' phosphodiester moieties. Non-canonically linked 2'3'-cGAMP binds to human STING with higher affinity than canonically linked 3'3'-cGAMP or symmetrical bacterial c-di-GMP and induces type I interferon production.

Further cyclic dinucleotides with 2',5'-2',5' or 2',5'-3',5' connectivity are disclosed as STING agonists in WO 2017/027645 and WO 2017/027646, respectively.

Summary

The present disclosure relates to a compound of formula (**I**)



(I)

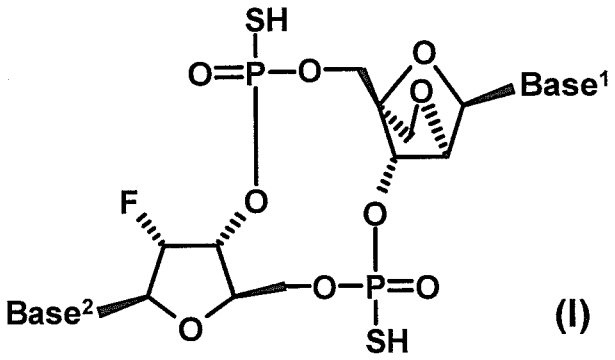
,

wherein

Base[1] and Base[2] are purine nucleobases independently selected from the group consisting of purine, adenine, guanine, xanthine, and hypoxanthine, connected through their N^9 nitrogen atoms,

the isoforms, tautomers, stereoisomers, metabolites, prodrugs, solvates, hydrates, and the salts thereof.

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



(I)

wherein

Base[1] and Base[2] are independently selected from the group consisting of purine, adenine, guanine, xanthine, and hypoxanthine, connected through their N^9 nitrogen atoms,

or a salt thereof.

In a second aspect, the present disclosure relates to a pharmaceutical composition comprising one or more compounds of formula (I), as defined hereinbefore or hereinafter, or pharmaceutically acceptable salts thereof, optionally together with one or more inert carriers and/or diluents.

In a third aspect, the present disclosure relates to a pharmaceutical composition comprising one or more compounds of formula (I), as defined hereinbefore or hereinafter, or pharmaceutically acceptable salts thereof, and one or more additional therapeutic agents, optionally together with one or more inert carriers and/or diluents.

In a fourth aspect, the present disclosure relates to a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as a medicament.

The present disclosure relates to the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as a vaccine adjuvant. In a fifth aspect, the present disclosure relates to a compound of formula (I), as defined hereinbefore or hereinafter, for use as a vaccine adjuvant. In a sixth aspect, the present disclosure relates to a vaccine comprising a compound of formula (I), as defined hereinbefore or hereinafter.

The present disclosure relates to a method for the treatment of diseases or conditions associated with or modulated by STING, particularly for the treatment of inflammation, allergic or autoimmune diseases, infectious diseases or cancer, in a patient in need thereof.

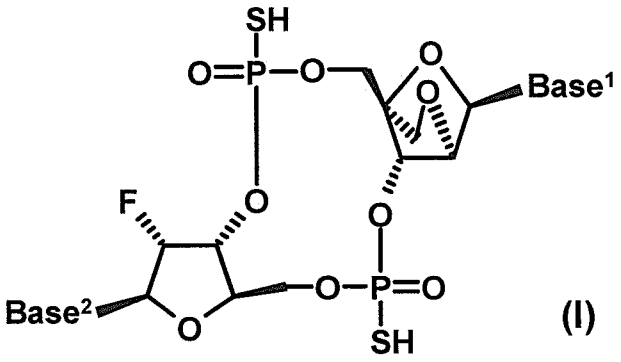
Also, the present disclosure relates to the use of one or more of said inhibitors in the manufacture of a medicament for the treatment of diseases or conditions associated with or modulated by STING, particularly for the treatment of inflammation, allergic or autoimmune diseases, infectious diseases or cancer, in a patient in need thereof. In a seventh aspect, the present disclosure relates to use of a compound of formula (I), as defined hereinbefore or hereinafter, in the preparation of a medicament for the treatment of diseases or conditions associated with or modulated by STING, particularly for the treatment of inflammation, allergic or autoimmune diseases, infectious diseases or cancer in a patient in need thereof.

Also, the present disclosure relates to a compound of formula (I), as defined hereinbefore or hereinafter, or a pharmaceutically acceptable salt thereof for use in a method for the treatment of diseases or conditions associated with or modulated by STING, particularly for the treatment of inflammation, allergic or autoimmune diseases, infectious diseases or cancer, in a patient in need thereof.

Other aspects of the present disclosure will become apparent to the person skilled in the art directly from the foregoing and following description and examples.

Claims

1. A compound of formula (I)



(I)

wherein

Base[1] and Base[2] are independently selected from the group consisting of purine, adenine, guanine, xanthine, and hypoxanthine, connected through their N^9 nitrogen atoms,

or a salt thereof.

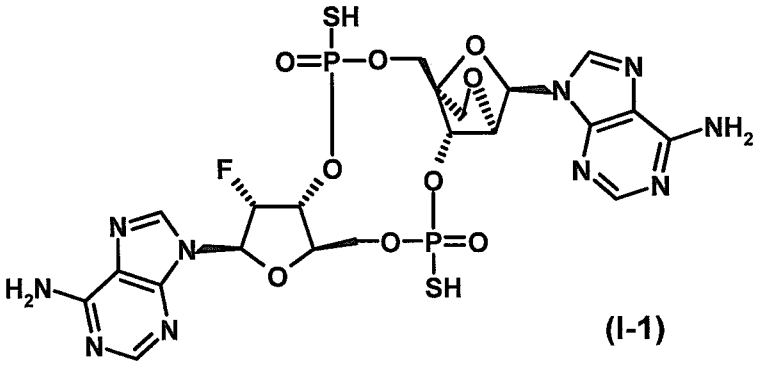
2. The compound according to claim 1 wherein Base[1] and Base [2] are adenine.

3. The compound according to claim 1 wherein Base[1] is adenine and Base[2] is guanine.

4. The compound according to claim 1 wherein Base[1] is guanine and Base[2] is adenine.

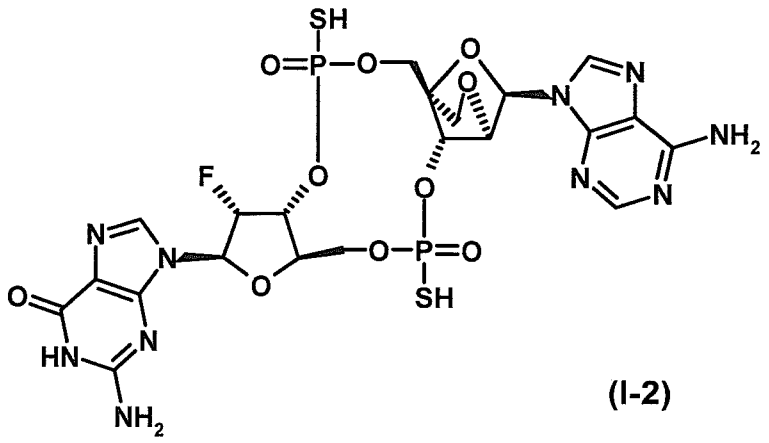
5. The compound according to claim 1 wherein Base[1] is adenine and Base[2] is hypoxanthine.

6. The compound according to claim 1 wherein the compound has the structure of formula (I-1):



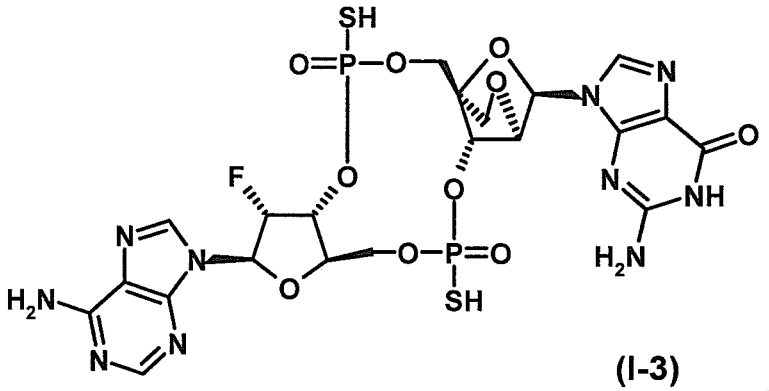
(I-1)

7. The compound according to claim 1 wherein the compound has the structure of formula (I-2):



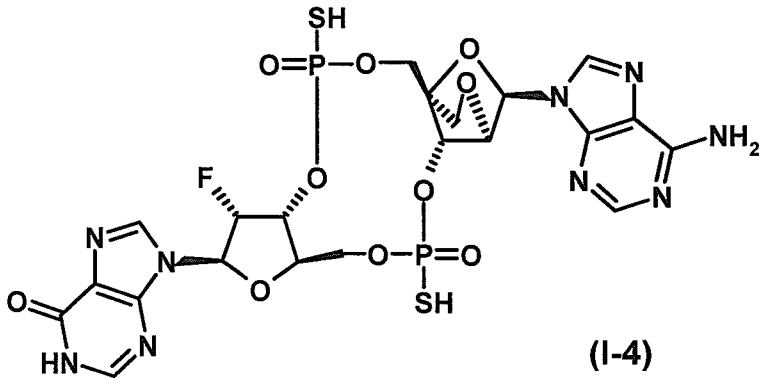
(I-2)

8. The compound according to claim 1 wherein the compound has the structure of formula (I-3):



(I-3)

9. The compound according to claim 1 wherein the compound has the structure of formula (I-4):



(I-4)

10. The compound according to one or more of claims 1 to 9, wherein the compound is a substantially pure (Sp,Sp), (Rp,Rp), (Sp,Rp), or (Rp,Sp) stereoisomer.

11. The compound according to one or more of claims 1 to 10, wherein the compound is a pharmaceutically acceptable salt.

12. A pharmaceutical composition comprising one or more compounds according to one or more of claims 1 to 10, or pharmaceutically acceptable salts thereof, optionally together with one or more inert carriers and/or diluents.

13. A vaccine comprising a compound according to one or more of claims 1 to 11.

14. A pharmaceutical composition comprising one or more compounds according to one or more of claims 1 to 10, or pharmaceutically acceptable salts thereof, and one or more additional therapeutic agents, optionally together with one or more inert carriers and/or diluents.

15. A pharmaceutical composition according to claim 14 comprising one compound according to one or more of claims 1 to 10 and one or more additional therapeutic agents.

16. A compound according to one or more of claims 1 to 11 for use as a medicament.

17. A compound according to one or more of claims 1 to 11 for use as a vaccine adjuvant.

18. Use of a compound according to one or more of claims 1 to 11 in the preparation of a medicament for the treatment of diseases or conditions associated with or modulated by STING, particularly for the treatment of inflammation, allergic or autoimmune diseases, infectious diseases or cancer in a patient in need thereof.