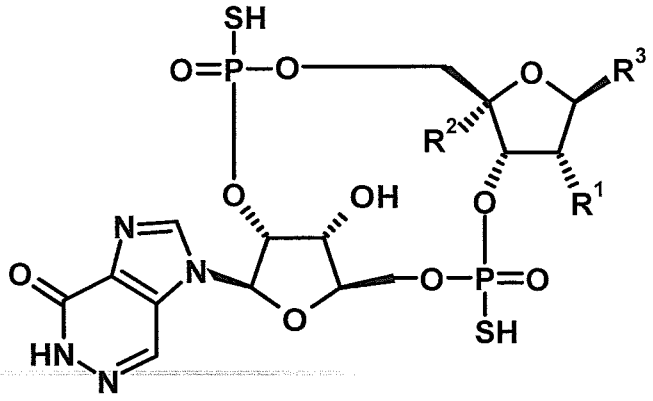
WO 2016/096174 and WO 2016/145102 describe cyclic dinucleotide compounds that feature two purine nucleobases and two canonical 3',5' phosphodiester or phosphorothioate moieties and induce STING-dependent cytokine production.

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

Summary

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



I,

wherein

R^1 is selected from the group consisting of H, F, -O-C_{1-3}alkyl and OH, and

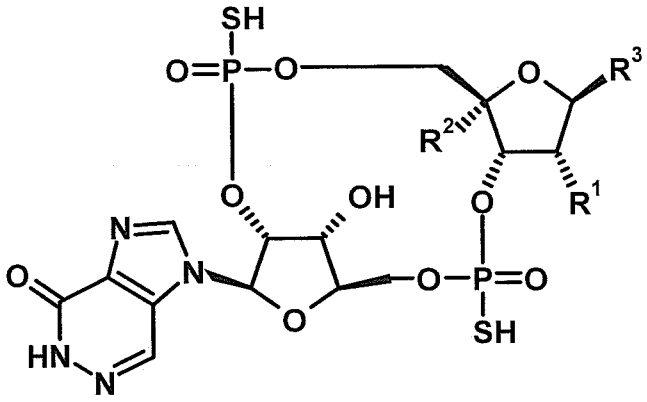
R^2 is H, or

R^2 is -CH_2- and R^1 is –O–, forming together a -CH_2-O- bridge, and

R^3 is a purine nucleobase selected from the group consisting of purine, adenine, guanine, xanthine, hypoxanthine, connected through its N^9 nitrogen,

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

In a first embodiment, the disclosure provides cyclic dinucleotide compounds of formula I



I,

wherein

R^1 is selected from the group consisting of H, F, -O-C_{1-3}-alkyl and OH, and

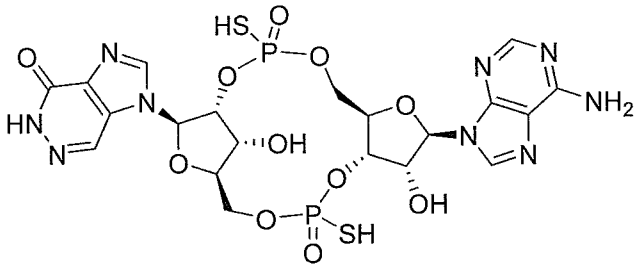
R^2 is H, or

R^2 is -CH_2- and R^1 is –O–, forming together a -CH_2-O- bridge ("Locked Nucleic Acid"; "LNA"), and

R^3 is a purine nucleobase selected from the group consisting of purine, adenine, guanine, xanthine, hypoxanthine, connected through its N^9 nitrogen;

the isoforms, tautomers, stereoisomers, metabolites, prodrugs, solvates, hydrates, and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic bases, or the combinations thereof.

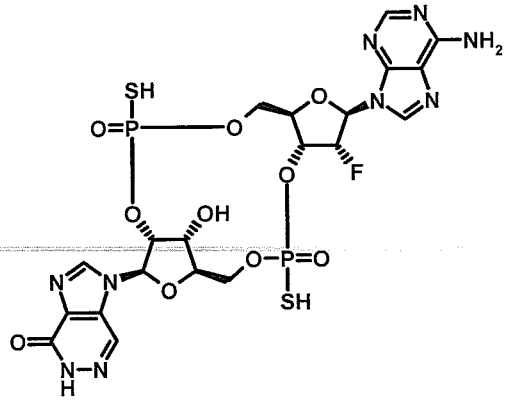
In another aspect, the disclosure provides cyclic (imidazopyridazinon-β-D-ribofuranoside-(2'→5')-phosphorothioate-adenosine-(3'→5')-phosphorothioate),



,

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

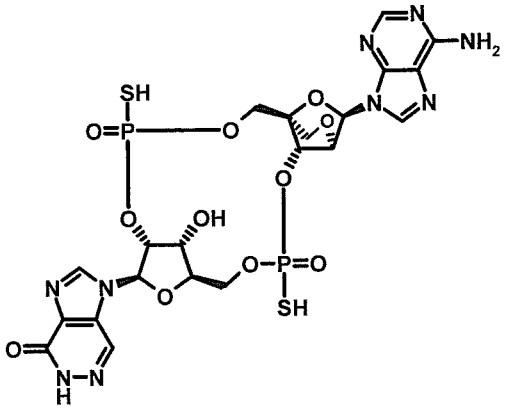
In another aspect, the disclosure provides cyclic (imidazopyridazinon-β-D-ribofuranoside-(2'→5')-phosphorothioate-2'-F-2'-deoxyadenosine-(3'→5')-phosphorothioate,



,

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

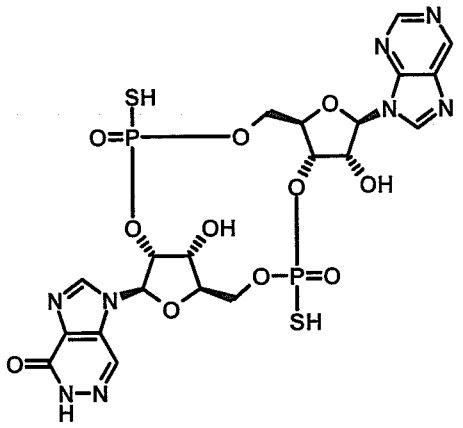
In another aspect, the disclosure provides cyclic (imidazopyridazinon-β-D-ribofuranoside-(2'→5')-phosphorothioate-LNA-adenine-(3'→5')-phosphorothioate),



,

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

In another aspect, the disclosure provides cyclic (imidazopyridazinon-β-D-ribofuranoside-(2'→5')-phosphorothioate-purine-β-D-ribofuranoside-(3'→5')-phosphorothioate),



,

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

In an embodiment, the disclosure provides new compounds of formula **I**, including pharmaceutically acceptable salts thereof, which induce cytokine production in STING-dependent fashion *in vitro* and/or *in vivo* and possess suitable pharmacological and pharmacokinetic properties for use in therapy, i.e. for use as medicaments.

In a further embodiment, the disclosure provides new compounds of formula **I**, including pharmaceutically acceptable salts thereof, for use in the treatment of a disease or condition associated with or modulated by STING.

In a further embodiment, the disclosure provides new compounds of formula **I**, or pharmaceutically acceptable salts thereof, for the treatment of inflammation, allergic or autoimmune diseases, for example allergic rhinitis or asthma, for the treatment of infectious diseases or of cancer, or for the use as vaccine adjuvants.

In a further embodiment, the disclosure provides a method of treatment of a disease or condition associated with or modulated by STING, in a subject comprising administering a therapeutically effective amount of a compound of formula **I**, or a pharmaceutically acceptable salt thereof, to the subject.

In an embodiment, the disclosure provides a method of treatment of inflammation, allergic or autoimmune diseases, for example allergic rhinitis or asthma, for the treatment of infectious diseases or of cancer, in a patient in need thereof, comprising administering a therapeutically effective amount of a compound of formula **I**, or a pharmaceutically acceptable salt, thereof to the patient.

In a further embodiment, the disclosure provides pharmaceutical compositions comprising a compound of formula **I**, or a pharmaceutically acceptable salt thereof, and one or more of pharmaceutically acceptable excipients.

In another aspect, the disclosure provides a pharmaceutical composition comprising one or more compounds as disclosed herein, optionally together with one or more inert carriers and/or diluents.

In another aspect, the disclosure provides a pharmaceutical composition as disclosed herein, for use in the treatment of diseases or conditions selected from inflammation, allergic diseases, autoimmune diseases, infectious diseases or cancer.

In a further embodiment, the disclosure provides the use of a compound of formula **I**, including pharmaceutically acceptable salts thereof, in the manufacture of a medicament for use in the treatment of a disease or condition in which modulation of STING is beneficial or for use in the treatment of a disease or condition associated with or modulated by STING.

In another aspect, the disclosure provides a vaccine comprising a compound as disclosed herein.

In another aspect, the disclosure provides use of a compound as disclosed herein, for the production of vaccine adjuvants.

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

In a further embodiment, the disclosure provides the use of a compound of formula **I**, or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for use in the treatment of inflammation, allergic or autoimmune diseases, for example allergic rhinitis or asthma, for the treatment of infectious diseases or of cancer, or for the use as vaccine adjuvants.

In a further embodiment, the disclosure provides a combination comprising a compound of formula **I**, or a pharmaceutically acceptable salt thereof, and at least one further therapeutic agent.

A further object of the present disclosure is to provide a pharmaceutical composition comprising a compound of formula **I**, or a pharmaceutically acceptable salt thereof, and at least one further therapeutic agent and one or more of pharmaceutically acceptable excipients.

In a further embodiment, the disclosure provides a combination comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and at least one further therapeutic agent for use in therapy.

In a further embodiment, the disclosure provides a combination comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and at least one further therapeutic agent for use in the treatment of a disease or condition in which modulation of STING is beneficial or for use in the treatment of a disease or condition associated with or modulated by STING.

In a further embodiment, the disclosure provides a combination comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and at least one further therapeutic agent for use in the treatment of inflammation, allergic and autoimmune diseases, infectious diseases and cancer.

In a further embodiment, the disclosure provides a method of treatment of a disease or condition in which modulation of STING is beneficial or of a disease or condition associated with or modulated by STING, in a patient, comprising administering to the patient a therapeutically effective amount of a combination comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and at least one further therapeutic agent.

In a further embodiment, the disclosure provides a method of treatment of inflammation, allergic or autoimmune diseases, infectious diseases or cancer, in a patient, comprising administering to the patient a therapeutically effective amount of a combination comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and at least one further therapeutic agent.

In a further embodiment, the disclosure provides a vaccine adjuvant comprising a compound of formula I, or a pharmaceutically acceptable salt thereof.

In a further embodiment, the disclosure provides an immunogenic composition comprising an antigen or antigen composition and a compound of formula I, or a pharmaceutically acceptable salt thereof.

In a further embodiment, the disclosure provides an immunogenic composition comprising an antigen or antigen composition and a compound of formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of a disease.

In a further embodiment, the disclosure provides the use of a compound of formula **I**, or a pharmaceutically acceptable salt thereof, for the manufacture of an immunogenic composition comprising an antigen or antigen composition, for the treatment or prevention of a disease.

In a further embodiment, the disclosure provides a method of treating or preventing a disease comprising the administration to a human subject suffering from or susceptible to a disease, an immunogenic composition comprising an antigen or antigen composition and a compound of formula **I**, or a pharmaceutically acceptable salt thereof.

In a further embodiment, the disclosure provides a vaccine composition comprising an antigen or antigen composition and a compound of formula **I**, or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of a disease.

In a further embodiment, the disclosure provides the use of a compound of formula **I**, or a pharmaceutically acceptable salt thereof, for the manufacture of a vaccine composition comprising an antigen or antigen composition, for the treatment or prevention of a disease.

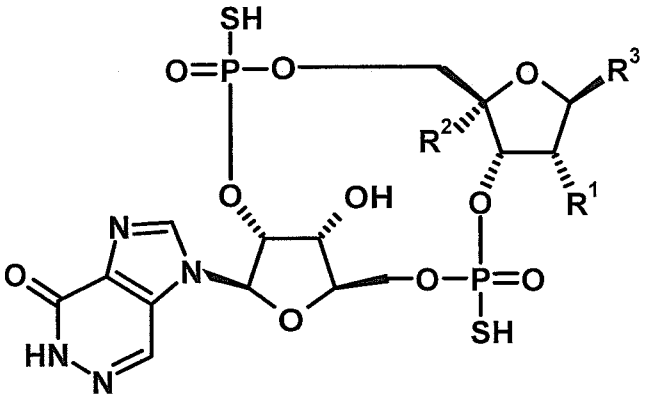
In a further embodiment, the disclosure provides a method of treating or preventing a disease comprising the administration to a human subject suffering from or susceptible to disease, a vaccine composition comprising an antigen or antigen composition and a compound of formula **I**, or a pharmaceutically acceptable salt thereof.

Further objects of the present disclosure become apparent to the one skilled in the art by the description hereinbefore and in the following and by the examples.

The compounds of the present disclosure exhibit several advantages, such as favorable binding affinity to human STING, favorable cellular activity, i.e. in cells

Claims

1. A compound of formula **I**



I,

wherein

R^1 is selected from the group consisting of H, F, -O-C_{1-3}alkyl and OH, and

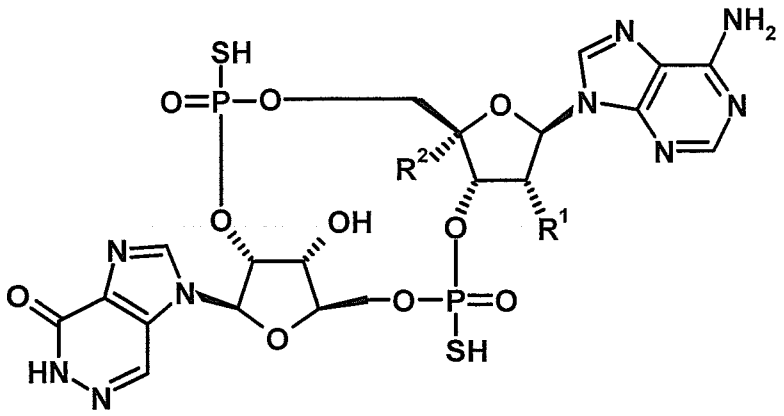
R^2 is H, or

R^2 is -CH_2- and R^1 is –O–, forming together a -CH_2-O- bridge, and

R^3 is a purine nucleobase selected from the group consisting of purine, adenine, guanine, xanthine, hypoxanthine, connected through its N^9 nitrogen,

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

2. A compound according to claim 1 of formula **Ia**

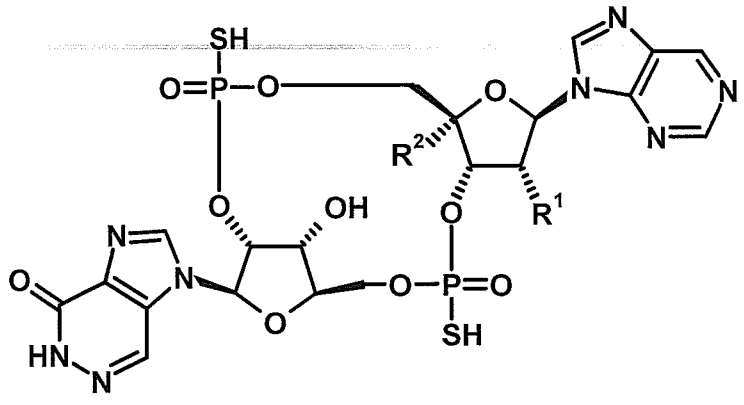


Ia,

wherein R^1 and R^1 are defined as claim 1,

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

3. A compound according to claim 1 of formula **Ib**

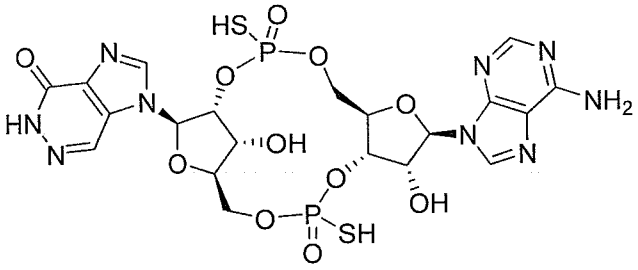


Ib,

wherein R^1 and R^1 are defined as claim 1,

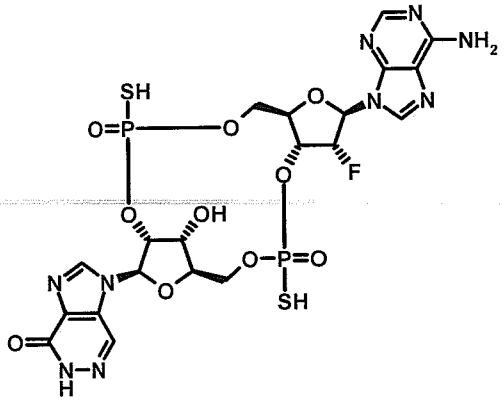
or a pharmaceutically acceptable salt, solvate or hydrate thereof.

4. Cyclic (imidazopyridazinon-β-D-ribofuranoside-(2'→5')-phosphorothioate-adenosine-(3'→5')-phosphorothioate),



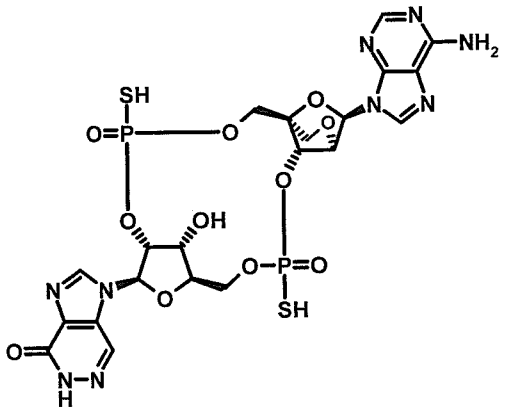
or a pharmaceutically acceptable salt, solvate or hydrate thereof.

5. Cyclic (imidazopyridazinon-β-D-ribofuranoside-(2'→5')-phosphorothioate-2'-F-2'-deoxyadenosine-(3'→5')-phosphorothioate,



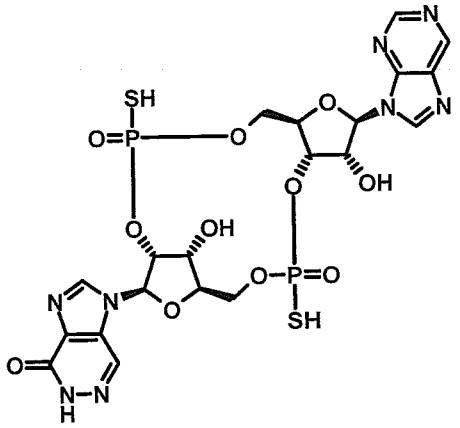
or a pharmaceutically acceptable salt, solvate or hydrate thereof.

6. Cyclic (imidazopyridazinon-β-D-ribofuranoside-(2'→5')-phosphorothioate-LNA-adenine-(3'→5')-phosphorothioate),



or a pharmaceutically acceptable salt, solvate or hydrate thereof.

7. Cyclic (imidazopyridazinon-β-D-ribofuranoside-(2'→5')-phosphorothioate-purine-β-D-ribofuranoside-(3'→5')-phosphorothioate),



,

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

8. A sodium salt of a compound of claim 4, 5, 6, or 7.

9. A (Sp,Sp), (Rp,Rp), (Sp,Rp), or (Rp,Sp) stereoisomer of a compound according to any of claims 1 to 8.

10. A (Rp,Rp) stereoisomer of a compound according to any of claims 1 to 8.

11. A pharmaceutical composition comprising one or more compounds according to any of claims 1 to 10, optionally together with one or more inert carriers and/or diluents.

12. A pharmaceutical composition according to claim 11, for use in the treatment of diseases or conditions selected from inflammation, allergic diseases, autoimmune diseases, infectious diseases or cancer.

13. A vaccine comprising a compound according any of claims 1 to 10.

14. Use of a compound according to any of claims 1 to 10, for the production of vaccine adjuvants.

15. Use of a compound according to any of claims 1 to 10, for the production of a medicament.

16. A pharmaceutical composition according to claim 11 or 12, further comprising one or more additional therapeutic agents.

17. A pharmaceutical composition according to claim 16, wherein the composition comprises one compound according to any of claims 1 to 10.

18. Use according to claim 15, wherein the medicament is to be used for the treatment of diseases or conditions selected from inflammation, allergic diseases, autoimmune diseases, infectious diseases or cancer.