ER to perinuclear endosomes (Liu et al, Science 347, Issue 6227, 2630-1 – 2630-14, 2015). Phosphorylation of the transcription factor IRF3 and NF-kB by TBK1 results in expression of multiple cytokines, including type I interferon (IFN).

Type I IFN production by antigen presenting cells, and other cell types, is considered a key event in the activation of T cells and thereby the differentiation of antigen specific effector CD4 and CD8 T cells. It was shown that the lack of type I IFN resulted in a reduced T cell dependent immune response against viral infections or tumor cells (Zitvogel et al, Nature Reviews Immunology 15, 405 - 414, 2015). On the other hand, the presence of a type I IFN signature during cancer therapy is associated with increased numbers of tumor infiltrating T cells and potentially favorable clinical outcome (Sistigu et al, Nature Medicine 20, 1301 – 1309, 2014).

Efficient secretion of type I IFN in the tumor microenvironment and the induction of a T cell dependent immune response against cancer cells depends on the presence of STING, as shown in recent studies in mice (Woo et al, Immunity 41, 5, 830 – 842, 2014; Corrales et al, Cell Reports 11, 1018 – 1030, 2015; Deng et al, Immunity 41, 5, 843 – 852, 2014). The deletion of STING resulted in reduced type I IFN levels in the tumor microenvironment and in a reduced anti-tumor effect in several mouse tumor models, thereby highlighting the importance of the presence of type I IFN. On the other hand, the specific activation of STING resulted in an improved, antigen specific T cell immune response against cancer cells.

Type I interferons can significantly enhance anti-tumor immune responses by inducing activation of both the adaptive and the innate immune cells.

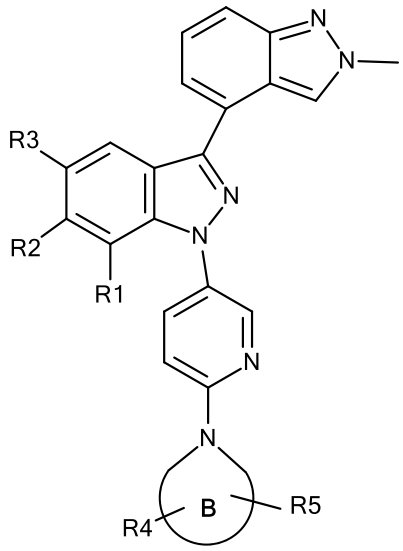
Given the importance of type I IFN in several malignancies including viral infections and cancer therapy, strategies that allow the specific activation of STING are of therapeutic interest. STING activation may be synergistic with various approved chemotherapeutic agents or other anti-cancer therapies such as radiotherapy (Wu et al., Med Res Rev 2020 May;40(3):1117-1141) or with infectious disease therapies.

In the prior art, small molecule modulators of STING are for example described in WO2020075790.

SUMMARY

Compounds according to the present disclosure are novel activators of STING as demonstrated in an *in vitro reporter* system using the THP1-Blue reporter cell line.

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



(I)

Wherein

B is a group selected from among the group consisting of

a 5-7-membered monocyclic heterocyclyl containing 1 or 2 N-atoms,

a 6-membered bicyclic heterocyclyl containing 1 N-atom, **and**

a 6-membered monocyclic heterocyclyl containing 1 N-atom and 1 heteroatom selected from the group consisting of O and S;

R^1 is -H or -C_{1-6}-alkyl;

R^2 is -H or -halogen;

R^3 is -H or -halogen;

provided that R^2 and/or R^3 is halogen;

R^4 is selected from among the group consisting of -H, -$S(O_2)$-C_{1-6}-alkyl, =O, -C(O)H, -C(O)OH, -C(O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-C(O)OH **and** -$C(O)NH_2$;

R^5 is absent **or** selected from among the group consisting of -H and =O

or a salt thereof.

The compounds of formula (I) or the salts thereof as defined herein are particularly suitable for the treatment of pathophysiological processes associated with or modulated by STING, particularly for the treatment of inflammation, allergic or autoimmune diseases, infectious diseases or cancer, or for the use as a vaccine adjuvants.

The disclosure relates to the method of treatment involving the compounds of formula (I) or the salts thereof. The disclosure relates to the use of a compound of general formula (I) as a medicament. In another aspect, the present disclosure relates to a compound as described herein or a pharmaceutically acceptable salt thereof for use as a medicament. In another aspect, the present disclosure relates to a compound as described herein or a pharmaceutically acceptable salt thereof for use in the treatment of a disease selected from among the group consisting of inflammation, allergic and autoimmune diseases, infectious diseases and cancer or for use as a vaccine adjuvants. In another aspect, the present disclosure relates to a compound as described herein or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, wherein the compound is to be administered after radiotherapy. In another aspect, the present disclosure relates to use of a compound as described herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease selected from among the group consisting of inflammation, allergic and autoimmune diseases, infectious diseases and cancer. In another aspect, the present disclosure relates to use of a compound as described herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer, wherein the compound is to be administered after radiotherapy. The disclosure

relates to a pharmaceutical composition comprising at least one compound of general formula (I). In another aspect, the present disclosure relates to a pharmaceutical composition comprising at least one compound as described herein or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. The disclosure relates to the use of a compound of general formula (I) in a medicament combination which comprises further active substances. In another aspect, the present disclosure relates to a medicament combination which comprises, besides one or more compounds as described herein, or a pharmaceutically acceptable salt thereof as further active substances a substance selected from the group consisting of cytostatic substances, cytotoxic substances, cell proliferation inhibitors, anti-angiogenic substances, steroids, viruses, immunogenic cell death inducers, cancer targeting agents, immuno-modulating agents, antibodies and nanobodies. The disclosure provides the general synthesis schemes for compounds of general formula (I) including examples and methods.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention exhibit several advantageous properties, such as favorable binding affinity to human STING, favorable cellular activity as measured by cellular EC50, i.e. in cells bearing different human STING alleles, and favorable permeability in cellular assays as described hereinafter.

Thus, in a first aspect the invention provides new compounds of formula (I), including salts thereof, which activate STING and therefore 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.

The compounds according to the present invention typically show a cellular EC50 on STING "HAQ" version of below 7 µM, preferably below 4 µM, more preferably below 2 µM, most preferably below 1 µM.

Furthermore, compounds according to the present invention also show a cellular EC50 of below 3 µM, preferably below 2 µM, more preferably below 1 µM, most preferably below 0.7 µM on the human STING variant "H232R" (sometimes also designated as wildtype, Yi et al., 2013; PLOS ONE 8(10)).

Furthermore, compounds according to the present invention also show a cellular EC50 of below 3 µM, preferably below 2 µM, more preferably below 1 µM, most preferably below 0.7 µM on the human STING variant "R232H".

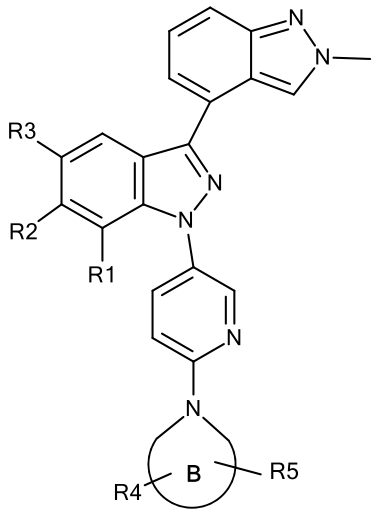
Furthermore, compounds according to the present invention also show a cellular EC50 of below 10 µM, preferably below 5 µM, more preferably below 3 µM, even more preferably below 2 µM, most preferably below 1 µM on the human STING variant "R293Q".

Furthermore, compounds according to the present invention also show a cellular EC50 of below 7 µM, preferably below 3 µM, more preferably below 2 µM, most preferably below 1 µM on the human STING variant "AQ".

"H232R", "R232H" and "R293Q" are single amino substitutions at the given position. "AQ" is a variant that consists of two substitutions, G230A and R293Q and "HAQ" is a STING

WHAT WE CLAIM

1. A compound of formula (I)



(I)

Wherein

B is a group selected from among the group consisting of

a 5-7-membered monocyclic heterocyclyl containing 1 or 2 N-atoms,

a 6-membered bicyclic heterocyclyl containing 1 N-atom, **and**

a 6-membered monocyclic heterocyclyl containing 1 N-atom and 1 heteroatom selected from the group consisting of O and S;

R^1 is -H or -C_{1-6}-alkyl;

R^2 is -H or -halogen;

R^3 is -H or -halogen;

provided that R^2 and/or R^3 is halogen;

R^4 is selected from among the group consisting of -H, -S(O_2)-C_{1-6}-alkyl, =O, -C(O)H, -C(O)OH, -C(O)O-C_{1-6}-alkyl, -C_{1-6}-alkylene-C(O)OH **and** -C(O)NH_2;

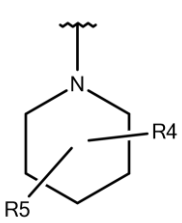
R^5 is absent **or** selected from among the group consisting of -H and =O

or a salt thereof.

2. A compound according to claim 1, wherein R^1 is -C_{1-3}-alkyl;

or a salt thereof.

3. A compound according to any one of claims 1-2 wherein **B** is selected from among the group consisting of



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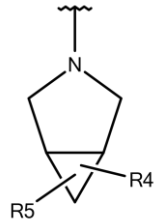

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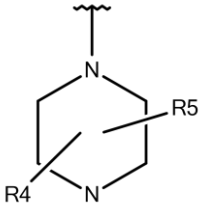

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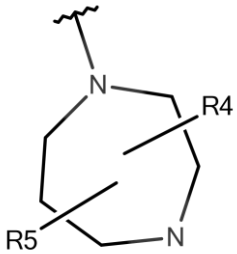

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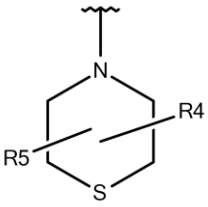

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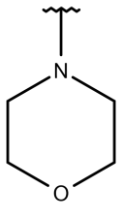

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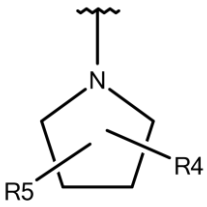
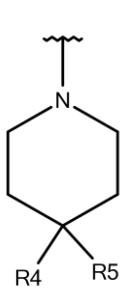


;

or a salt thereof.

4. A compound according to any one of claims 1-3, wherein **B** is selected from among the group consisting of



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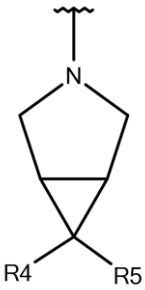

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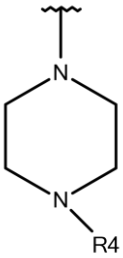

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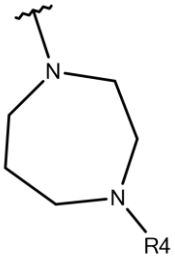

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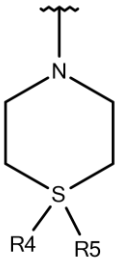


;

or a salt thereof.

5. A compound according to any one of claims 1-4, wherein $\mathbf{R^4}$ is selected from among the group consisting of -S(O_2)-C_{1-6}-alkyl, =O, -C(O)H **and** -C(O)OH;
or a salt thereof.

6. A compound according to any one of claims 1-5, wherein
$\mathbf{R^2}$ is selected from among the group consisting of -H, -F and -Cl;
$\mathbf{R^3}$ is selected from among the group consisting of -H, -F and -Cl**;**
or a salt thereof.

7. A compound according to any one of claims 1-6, wherein

R^2 is -F or -Cl;

R^3 is selected from among the group consisting of -H, -F and -Cl**;**

or a salt thereof.

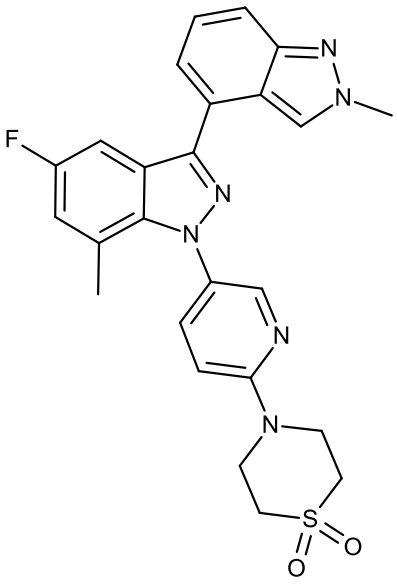
8. A compound according to any one of claims 1-6, wherein

R^2 is selected from among the group consisting of -H, -F and -Cl;

R^3 is -F or -Cl**;**

or a salt thereof.

9. A compound according to any one of claims 1-6, selected from the group consisting of



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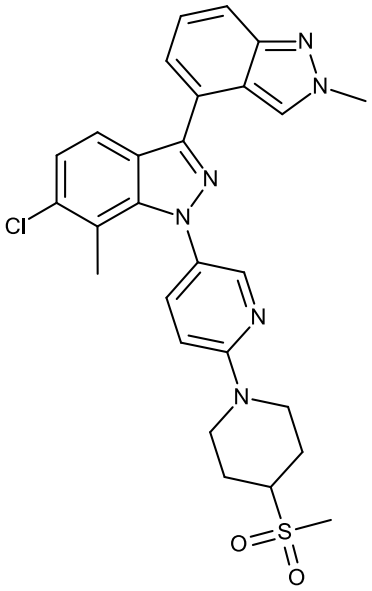

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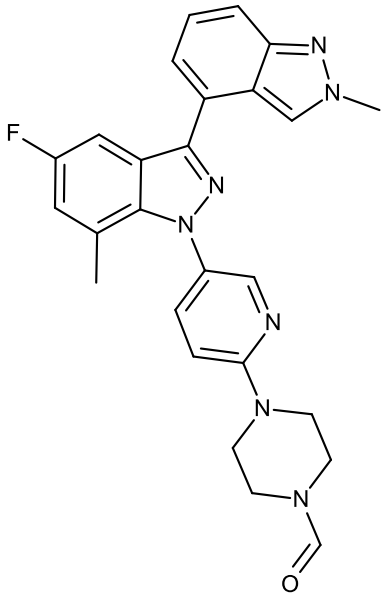
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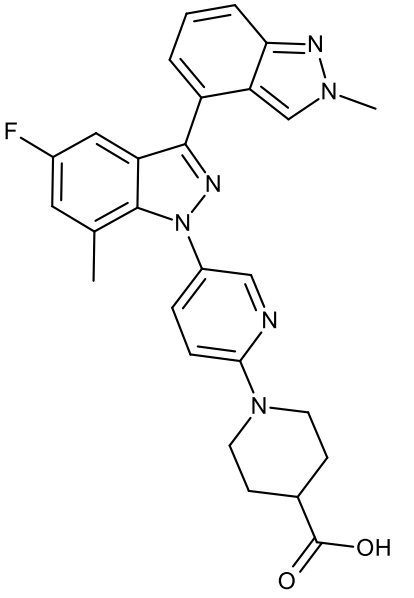
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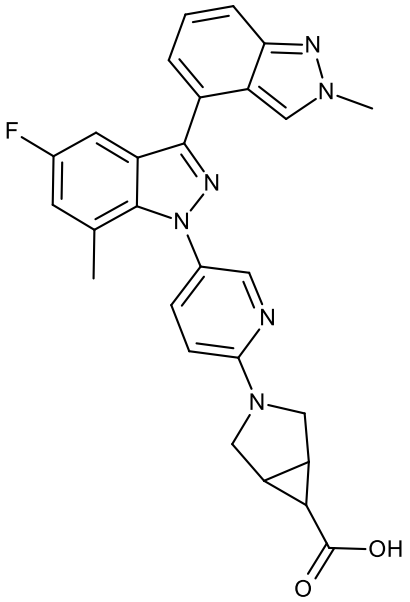
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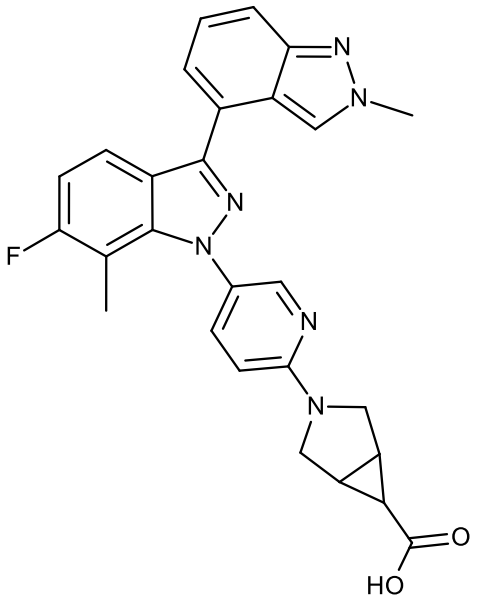
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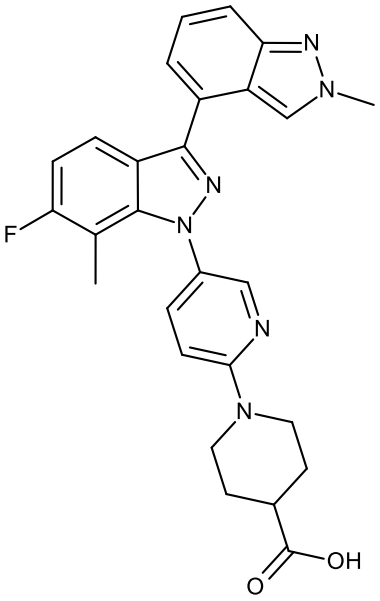
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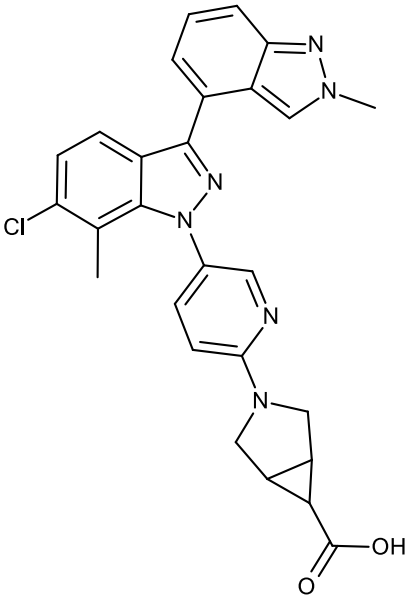
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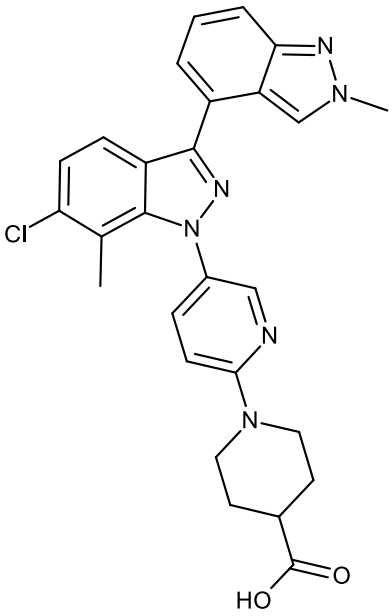
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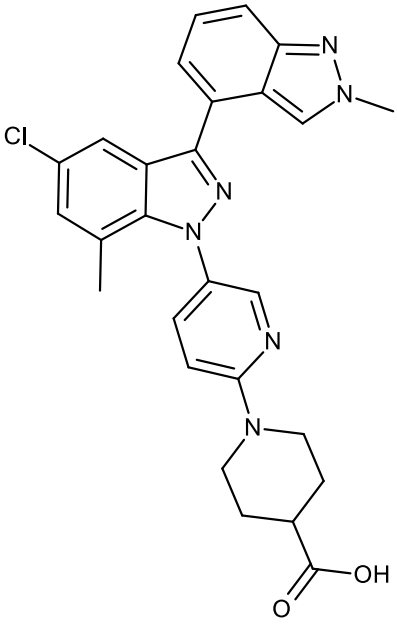
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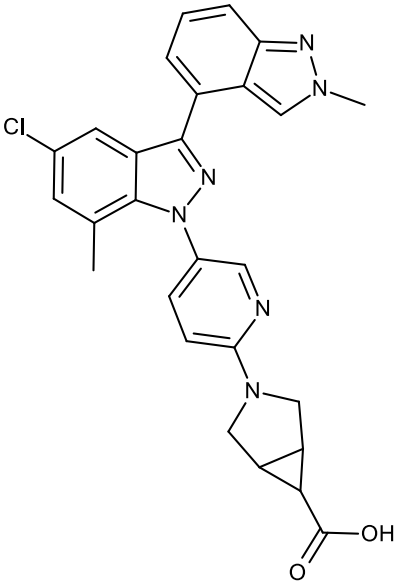

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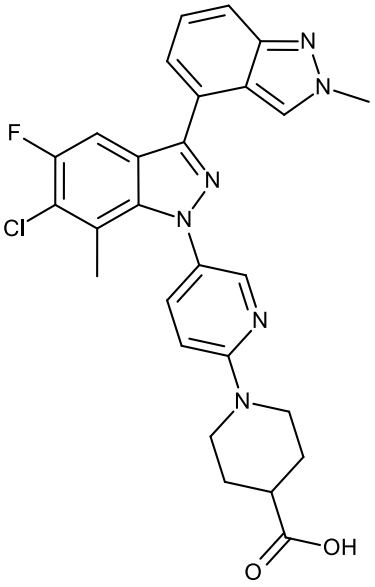

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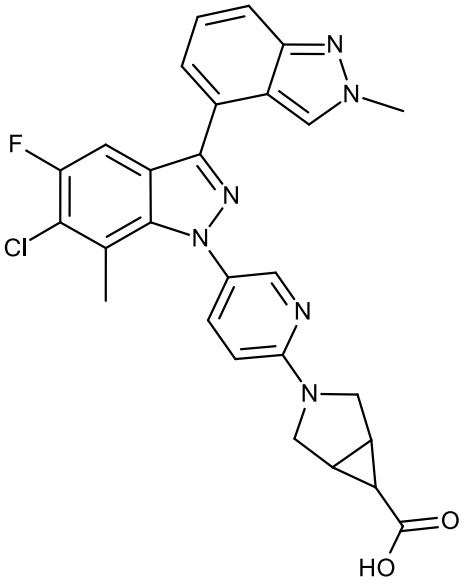

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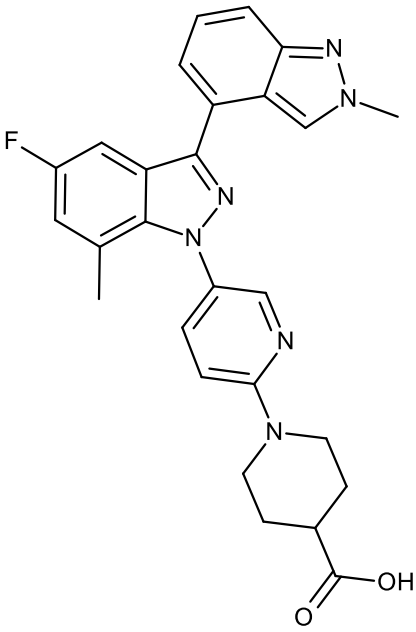
or a pharmaceutically acceptable salt thereof.

10. A compound according to any one of claims 1-6 and 9, selected from the group consisting of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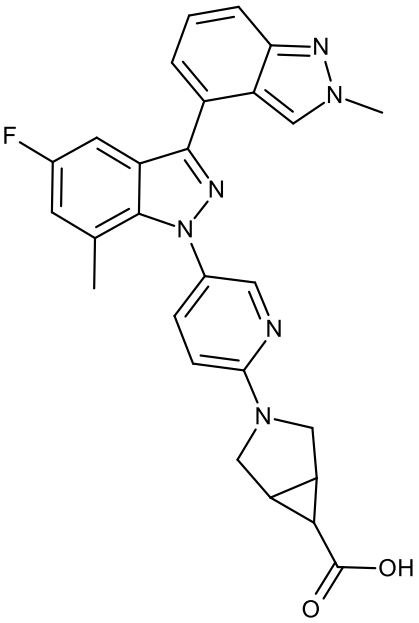
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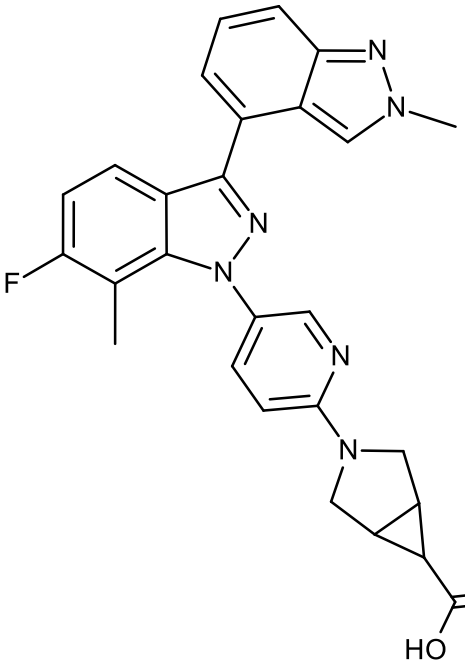
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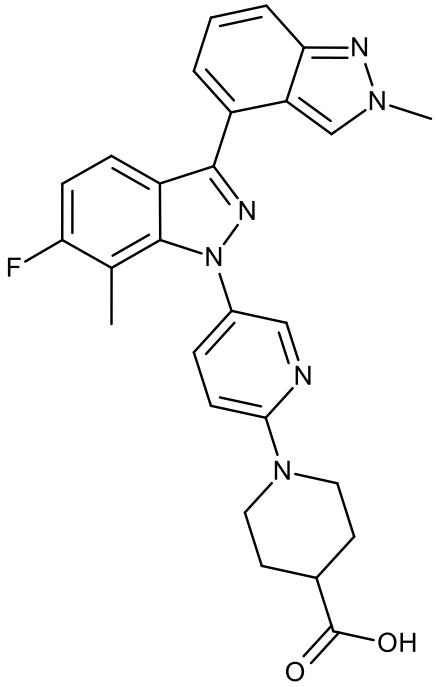
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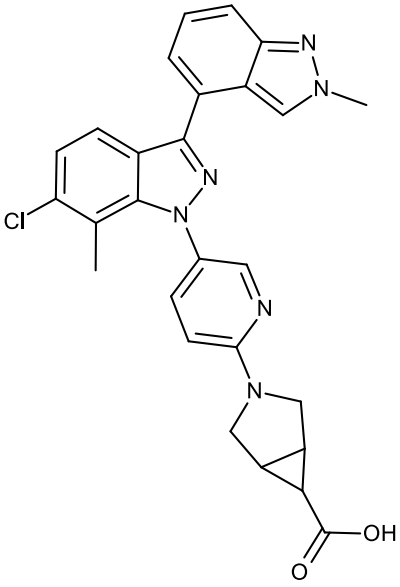
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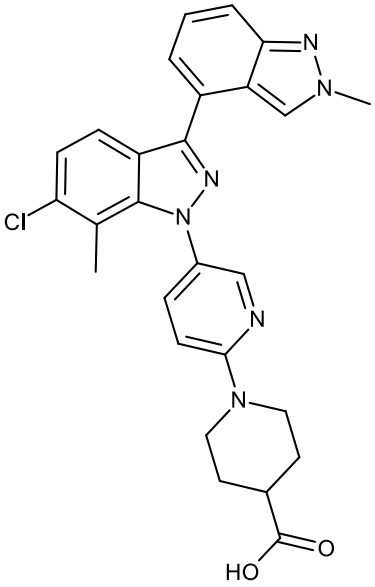
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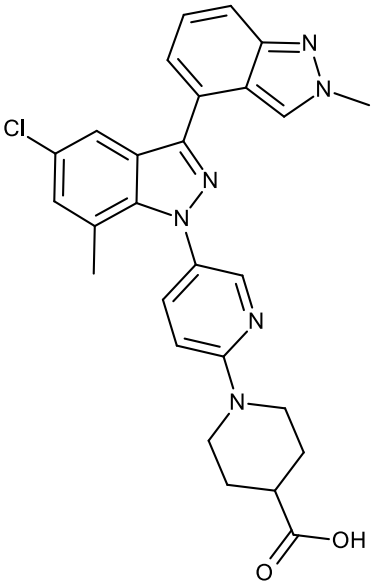
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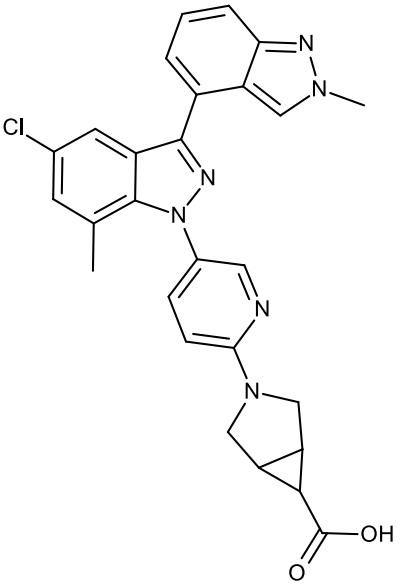
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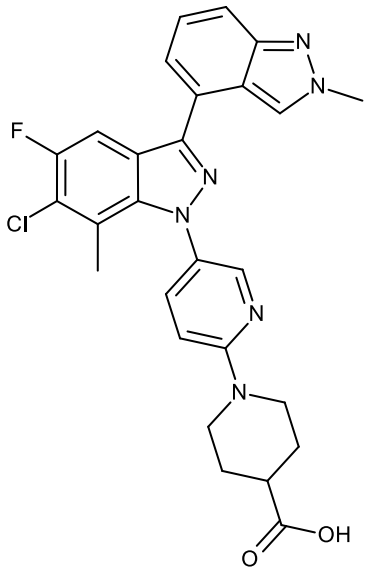

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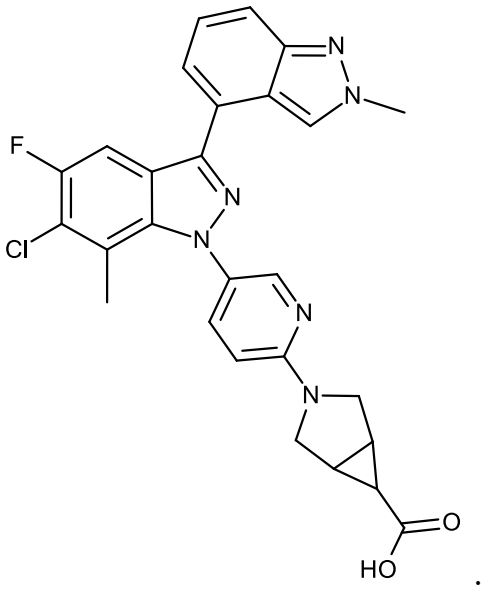

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or a pharmaceutically acceptable salt thereof.

11. A compound according to any one of the claims 1-10 in its salt free form.

12. A compound according to any one of claims 1-11 or a pharmaceutically acceptable salt thereof for use as a medicament.

13. A compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof for use in the treatment of a disease selected from among the group consisting of inflammation, allergic and autoimmune diseases, infectious diseases and cancer or for use as a vaccine adjuvants.

14. A compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, wherein the compound is to be administered after radiotherapy.

15. Use of a compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease selected from among the group consisting of inflammation, allergic and autoimmune diseases, infectious diseases and cancer.

16. Use of a compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer, wherein the compound is to be administered after radiotherapy.

17. A pharmaceutical composition comprising at least one compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

18. A medicament combination which comprises, besides one or more compounds according to one or more of claims 1 to 11, or a pharmaceutically acceptable salt thereof as further active substances a substance selected from the group consisting of cytostatic substances, cytotoxic substances, cell proliferation inhibitors, anti-angiogenic substances, steroids, viruses, immunogenic cell death inducers, cancer targeting agents, immuno-modulating agents, antibodies and nanobodies.