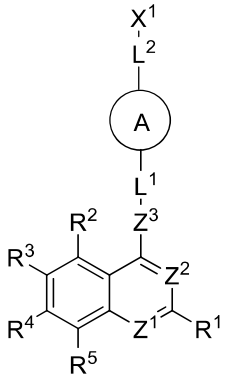
SUMMARY

[0005] Compounds, compositions and methods are provided for the inhibition of ENPP1. Aspects of the subject methods include contacting a sample with an ENPP1 inhibitor compound to inhibit the cGAMP hydrolysis activity of ENPP1. In some cases, the ENPP1 inhibitor compound is cell impermeable. ENPP1 inhibitor compounds can act extracellularly to block the degradation of cGAMP. Also provided are pharmaceutical compositions and methods for treating cancer. Aspects of the methods include administering to a subject a therapeutically effective amount of an ENPP1 inhibitor to treat the subject for cancer. In certain cases, the cancer is a solid tumor cancer. Also provided are methods of administering radiation therapy to a subject in conjunction with administering an ENPP1 inhibitor to the subject. The radiation therapy can be administered in the subject methods at a dosage and/or frequency effective to reduce radiation damage to the subject, but still instigate an immune response.

[0005a] In one aspect, the present disclosure refers to a compound of formula (I):



(I)

wherein,

X^1 is selected from the group consisting of phosphonate, phosphonate ester, phosphate, thiophosphate, thiophosphate ester, phosphoramidate, thiophosphoramidate, boronic acid or hydroxamic acid;

A is a ring system selected from aryl, heteroaryl, cycloalkyl, and heterocycle;

L^1 and L^2 are independently a covalent bond, or a (C_{1-6})alkyl linker;

Z^3 is absent or selected from NR^{22};

Z^2 is CR^{12};

Z^1 is CR^{11} or N;

R^1 is selected from H, alkyl, alkenyl, alkylaryl, alkylheteroaryl, alkenylaryl, alkenylheteroaryl, aryl, heteroaryl, and heterocycle;

R^{11} is selected from H, cyano, trifluoromethyl, halogen, and alkyl;

R^{12} is cyano;

R^{22} is selected from H and alkyl; and

R^2 to R^5 are independently selected from H, OH, alkyl, alkenyl, alkoxy, $-OCF_3$, halogen, cyano, amine, substituted amine, amide, heterocycle; or wherein R^2 and R^3, R^3 and R^4, or R^4 and R^5 together with the carbon atoms to which they are attached provide a fused ring selected from heterocycle, cycloalkyl, and aryl;

or a pharmaceutically acceptable salt or solvate thereof.

[0005b] In another aspect, the present disclosure refers to a pharmaceutical composition, comprising:

a compound as described herein; and

a pharmaceutically acceptable excipient.

[0006] These and other advantages and features of the disclosure will become apparent to those persons skilled in the art upon reading the details of the compositions and methods of use, which are more fully described below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] The invention is best understood from the following detailed description when read in conjunction with the accompanying figures. The patent or application file contains at least one figure executed in color. It is emphasized that, according to common practice, the various features of the figures are not to-scale. On the contrary, the dimensions of the various features are arbitrarily expanded or reduced for clarity. Included in the drawings are the following figures. It is understood that the figures, described below, are for illustration purposes only. The figures are not intended to limit the scope of the present teachings in any way.

[0008] **FIG. 1**, panels A to J, show experimental results that demonstrate cGAMP is exported from 293T cGAS ENPP1$^{-/-}$ cells as a soluble factor.

[0009] **FIG. 2**, panels A to C, show experimental results that demonstrate ENPP1 can regulate extracellular cGAMP.

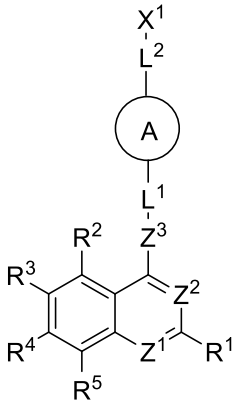
[0010] **FIG. 3**, panels A to F, illustrate the structure and activity in various cell assays of an exemplary ENPP1 inhibitor (compound 1).

[0011] **FIG. 4**, panels A to E, show experimental results that indicate cancer cells express cGAS and continuously export cGAMP in culture.

[0012] **FIG. 5**, panels A to I, show experimental results that indicate sequestration of extracellular cGAMP decreases tumor-associated dendritic cells in a tumor cGAS and host STING dependent manner.

What is claimed is:

1. A compound of formula (I):



(I)

wherein,

X^1 is selected from the group consisting of phosphonate, phosphonate ester, phosphate, thiophosphate, thiophosphate ester, phosphoramidate, thiophosphoramidate, boronic acid or hydroxamic acid;

A is a ring system selected from aryl, heteroaryl, cycloalkyl, and heterocycle;

L^1 and L^2 are independently a covalent bond, or a (C_{1-6})alkyl linker;

Z^3 is absent or selected from NR^{22};

Z^2 is CR^{12};

Z^1 is CR^{11} or N;

R^1 is selected from H, alkyl, alkenyl, alkylaryl, alkylheteroaryl, alkenylaryl, alkenylheteroaryl, aryl, heteroaryl, and heterocycle;

R^{11} is selected from H, cyano, trifluoromethyl, halogen and alkyl;

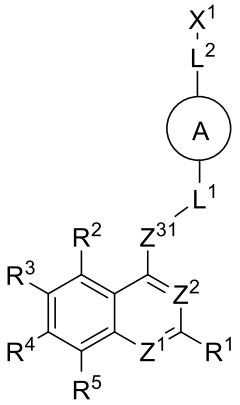
R^{12} is cyano;

R^{22} is selected from H and alkyl; and

R^2 to R^5 are independently selected from H, OH, alkyl, alkenyl substituted with pyridyl, alkoxy, $-OCF_3$, halogen, cyano, amine, amide, heterocycle; or wherein R^2 and R^3, R^3 and R^4, or R^4 and R^5 together with the carbon atoms to which they are attached provide a fused ring selected from heterocycle, cycloalkyl, and aryl;

or a pharmaceutically acceptable salt or solvate thereof.

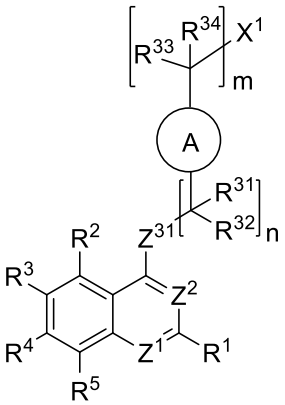
2. The compound of claim 1, wherein the compound is of formula (II):



(II)

wherein Z^{31} is NR^{22}.

3. The compound of claim 2 , wherein the compound is of formula (III):



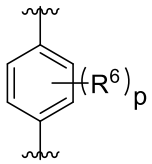
(III)

wherein each R^{31} to R^{34} is H; and

n and m are each independently an integer from 0 to 6.

4. The compound of claim 3, wherein n+m is 0 to 3.

5. The compound of claim 4, wherein the ring system A is selected from:



(A1)

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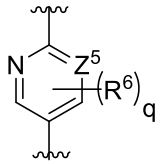

(A2)

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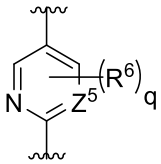
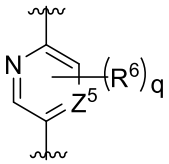


(A3)

and



(A4)

wherein:

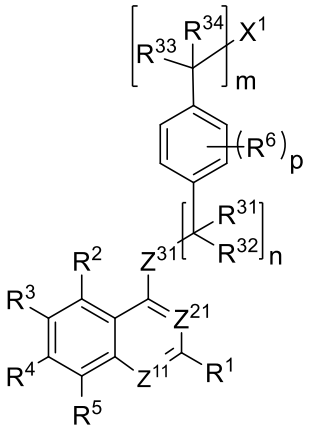
Z^5 is selected from N and CR^6;

each R^6 is hydrogen;

p is 4; and

q is 2.

6. The compound of any one of claims 3-5, wherein the compound is of formula (IV):



(IV)

wherein:

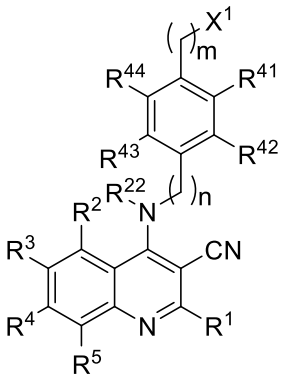
Z^{11} is selected from N and C(CN);

Z^{21} is C(CN); and

each R^6 is H; and

p is 4.

7. The compound of claim 6, wherein the compound is of formula (VIb):

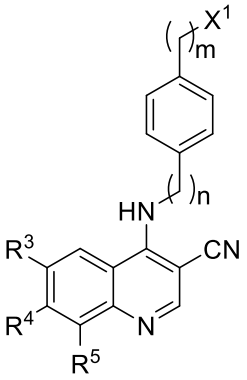


(VIb)

wherein R^{41} to R^{44} each are H.

8. The compound of any one of claims 1-7, wherein R^1 is selected from H and alkenyl substituted with pyridyl.

9. The compound of claim 7, wherein the compound is of formula (VIIb):

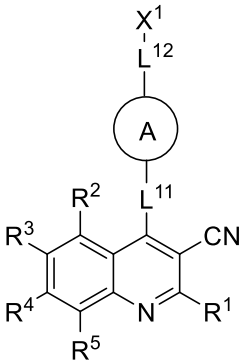


(VIIb).

10. The compound of any one of claims 1-9, wherein R^2 to R^5 are independently selected from H, OH, alkyl, alkoxy, -OCF_3, halogen, cyano, amine, amide and heterocycle.

11. The compound of claim 10, wherein R^2 to R^5 are independently selected from H, OH, $C_{(1-6)}$alkoxy, -OCF_3, F, Cl, Br and CN.

12. The compound of claim 1, wherein Z^3 is absent, wherein the compound is of Formula (X):

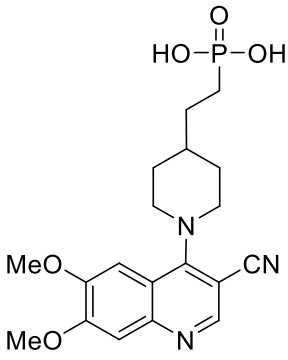


(X)

wherein L^{11} and L^{12} are independently covalent bond, or a (C_{1-6})alkyl linker.

13. The compound of claim 12, wherein the ring system A is selected from phenyl, pyridyl, pyrimidine, piperidine, piperazine, pyridazine, and cyclohexyl.

14. A compound of claim 1, wherein the compound is selected from the group consisting of:


HO–P–OH
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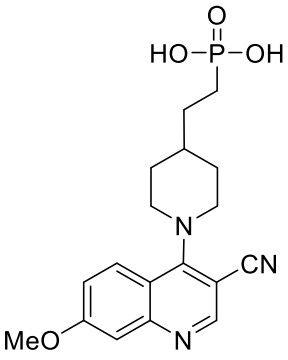
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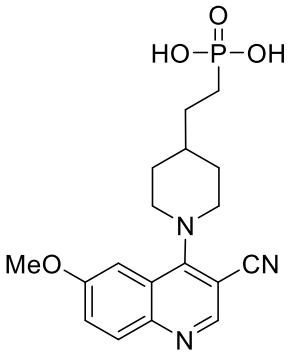
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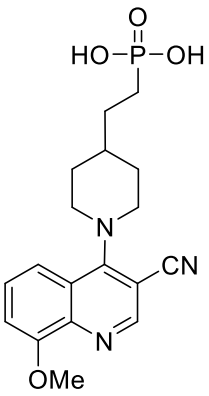
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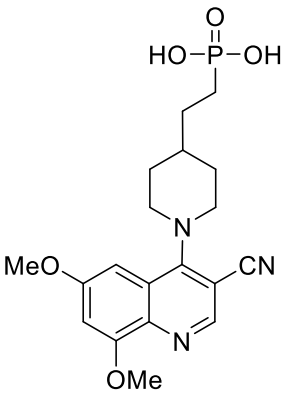
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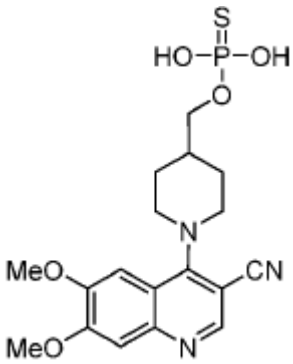
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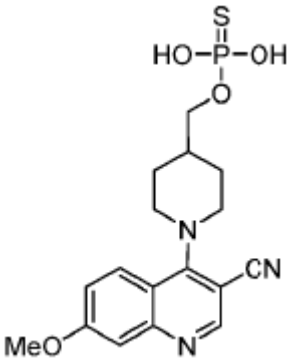
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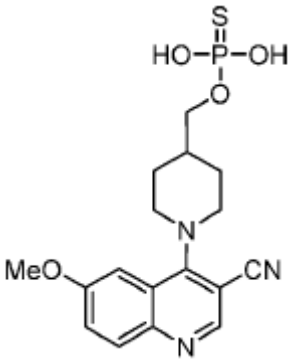
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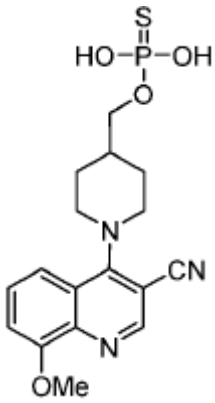
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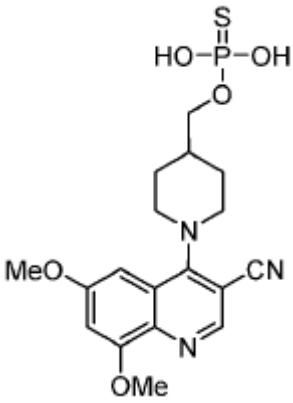
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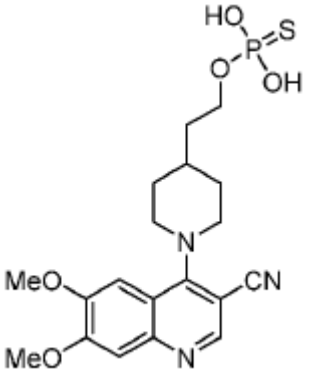
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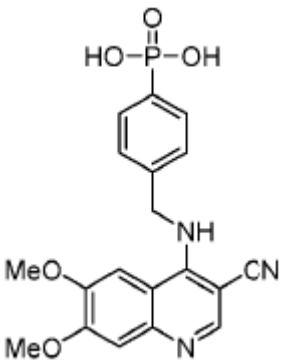
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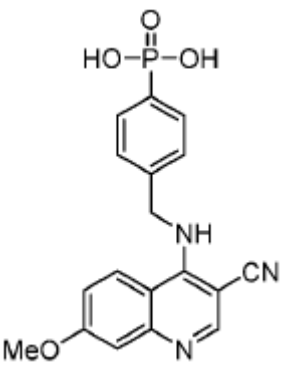
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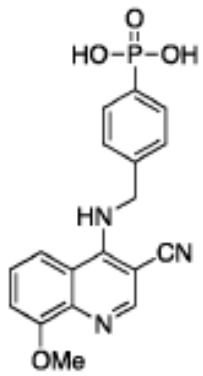
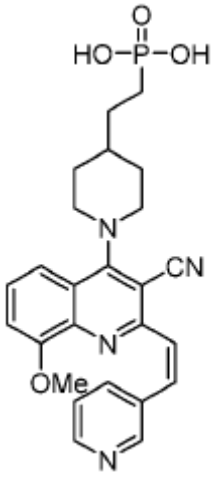
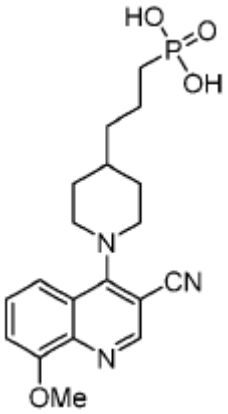
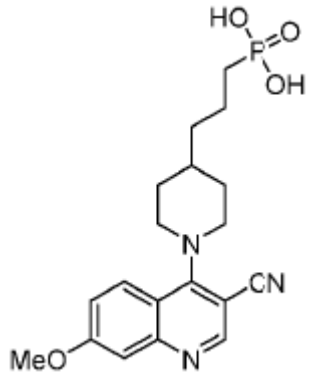
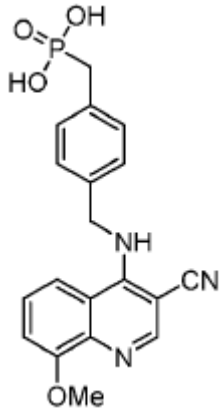
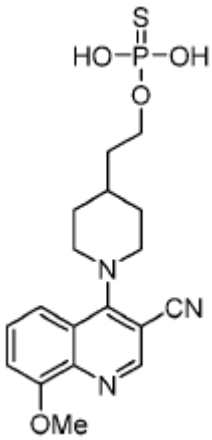
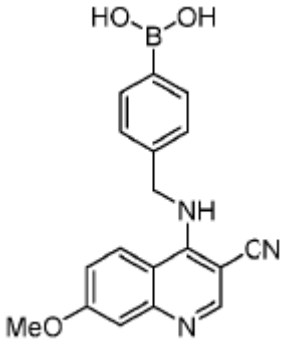
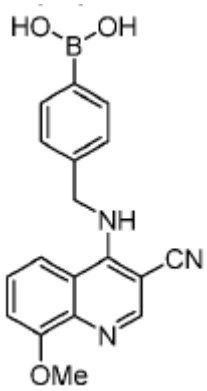
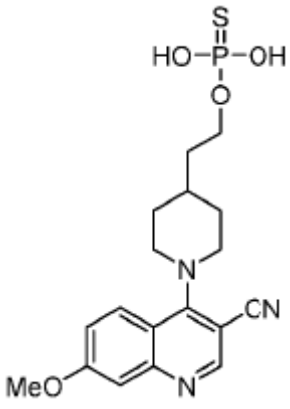
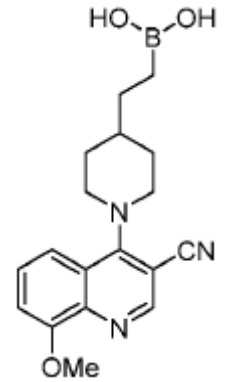
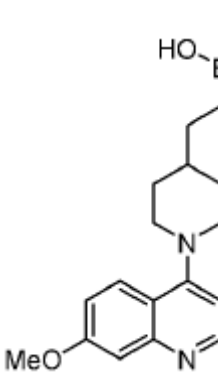
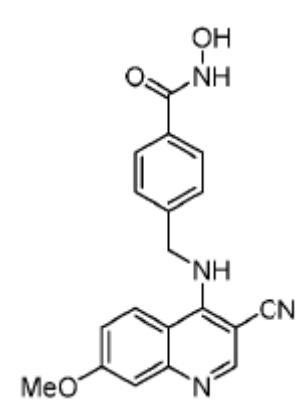

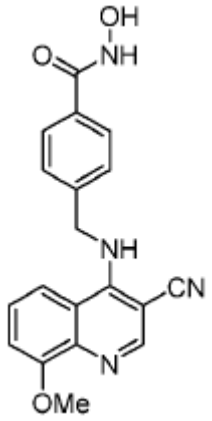

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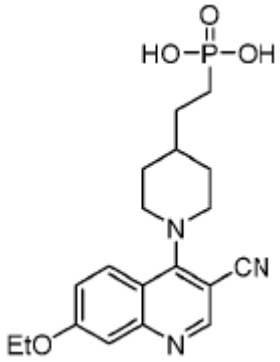

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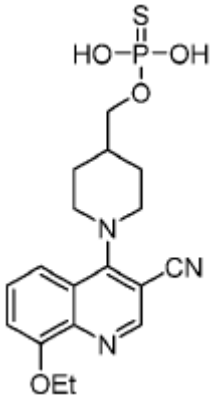
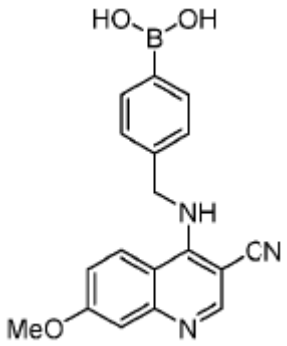


, or a pharmaceutically acceptable salt thereof.

15. A compound of claim 1, wherein the compound is selected from the group consisting of


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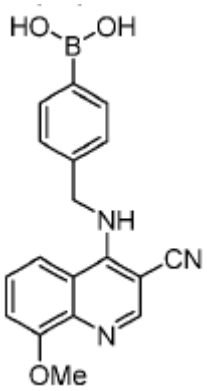

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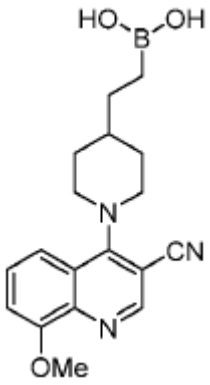

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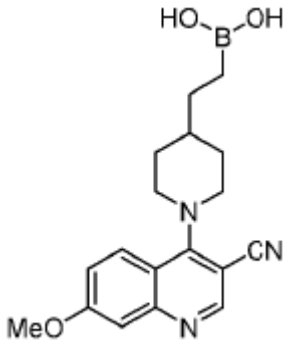

, or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition, comprising:
a compound of any one of claims 1-15; and
a pharmaceutically acceptable excipient.