## CLAIMS

We claim:

1. A modulator of cGAS having a structure comprising the following features:

A ----- L ----- B

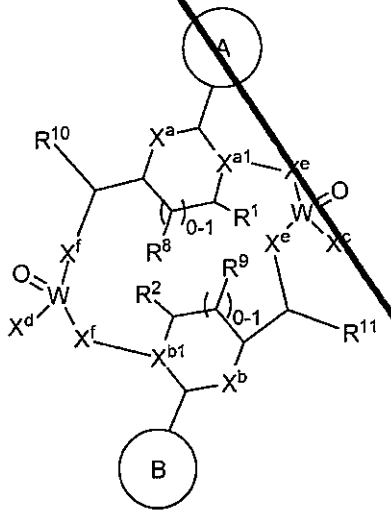
wherein:

A is or comprises a moiety that fits in the cGAS adenosine binding site;

B is or comprises a moiety that fits in the cGAS guanosine binding site; and

L is a linker moiety linking A and B in a manner which allows A and B to adopt appropriate interactions to bind cGAS.

2. A compound of Formula I:

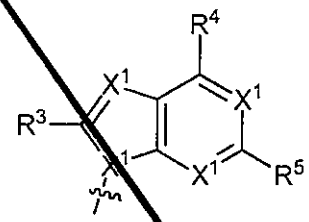
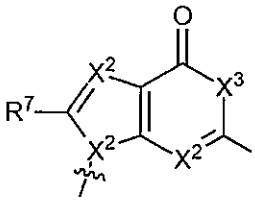
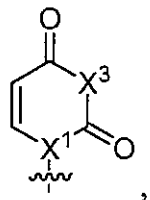
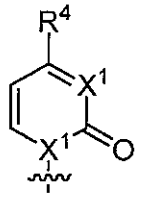



I

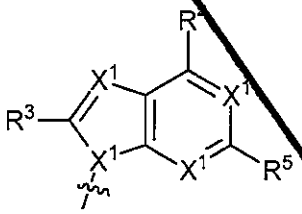
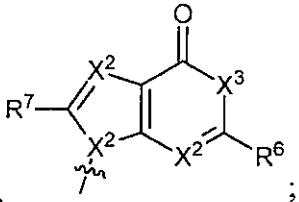
or a pharmaceutically acceptable salt thereof,

wherein:

Ring A is selected from the group consisting of:


, 
, 
, and 
;

Ring B is selected from the group consisting of:


and 
;

each $X^1$ and $X^2$ is independently –CR- or –N-;

$X^3$ is –$C(R)_2$-, -O-, or –NR-;

$X^a$ and $X^b$ are independently –$C(R)_2$-, -C(R)=C(R)-, -O-, -S-, -S(O)-, -$S(O)_2$-, or -N(R)-;

$X^{a1}$ and $X^{b1}$ are independently –C(R)- or –N-;

$X^c$ and $X^d$, when present, are independently optionally substituted oxygen, optionally substituted sulfur, a substituted nitrogen atom, $BH_3$, or optionally substituted $C_{1-12}$ aliphatic;

each $X^e$ and $X^f$ is independently –O-, -S-, or -N(R)-;

each W is independently P or S;

each $R^1$ and $R^2$ is independently selected from the group consisting of hydrogen, halogen, –$NO_2$, –CN, –$OR^a$, –SR, –$N(R)_2$, -C(O)R, -$CO_2$R, -C(O)C(O)R, –$C(O)CH_2C(O)R$, –S(O)R, –$S(O)_2$R, –$C(O)N(R)_2$, -$SO_2N(R)_2$, -OC(O)R, -N(R)C(O)R, –$N(R)N(R)_2$, -$N(R)C(=NR)N(R)_2$, -$C(=NR)N(R)_2$, –C=NOR, -$N(R)C(O)N(R)_2$, –$N(R)SO_2N(R)_2$, –$N(R)SO_2$R, -$OC(O)N(R)_2$, and optionally substituted $C_{1-12}$ aliphatic or $C_{1-4}$ alkoxy-$C_{1-4}$ alkyl;

each $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^{10}$, and $R^{11}$ is independently selected from the group consisting of hydrogen, halogen, –$NO_2$, –CN, –OR, –SR, –$N(R)_2$, -C(O)R, -$CO_2$R, -C(O)C(O)R, –$C(O)CH_2C(O)R$, –S(O)R, –$S(O)_2$R, –$C(O)N(R)_2$, -$SO_2N(R)_2$, -OC(O)R, -N(R)C(O)R, –$N(R)N(R)_2$, -$N(R)C(=NR)N(R)_2$, -$C(=NR)N(R)_2$, –C=NOR, -$N(R)C(O)N(R)_2$, –$N(R)SO_2N(R)_2$, –$N(R)SO_2$R, -$OC(O)N(R)_2$, or an optionally substituted group selected from $C_{1-12}$ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-10 membered saturated or partially unsaturated bicyclic carbocyclic ring, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2

heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

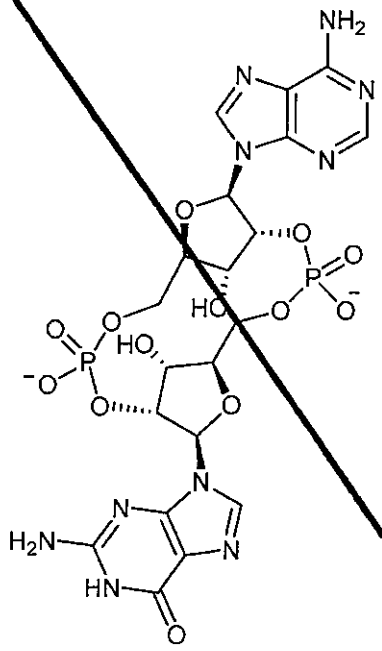
each $R^8$ and $R^9$, when present, is independently selected from the group consisting of hydrogen, halogen, $-NO_2$, $-CN$, $-OR^a$, $-SR$, $-N(R)_2$, $-C(O)R$, $-CO_2R$, $-C(O)C(O)R$, $-C(O)CH_2C(O)R$, $-S(O)R$, $-S(O)_2R$, $-C(O)N(R)_2$, $-SO_2N(R)_2$, $-OC(O)R$, $-N(R)C(O)R$, $-N(R)N(R)_2$, $-N(R)C(=NR)N(R)_2$, $-C(=NR)N(R)_2$, $-C=NOR$, $-N(R)C(O)N(R)_2$, $-N(R)SO_2N(R)_2$, $-N(R)SO_2R$, $-OC(O)N(R)_2$, and an optionally substituted $C_{1-12}$ aliphatic;

each R is independently selected from the group consisting of hydrogen or an optionally substituted group selected from $C_{1-6}$ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two R groups on the same nitrogen are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated, partially unsaturated, or heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

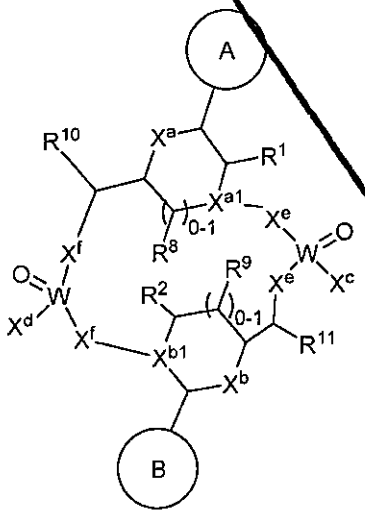
$R^a$ is an oxygen protecting group or R;

with the proviso that the compound is other than:



or a pharmaceutically acceptable salt thereof.

3. A compound of Formula II:

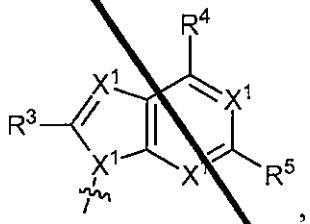
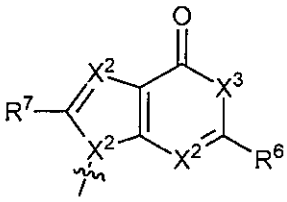
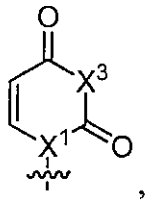
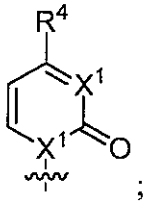


II

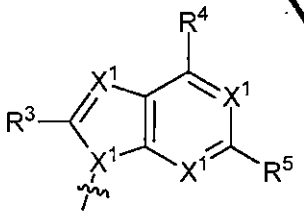
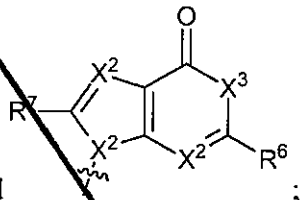
or a pharmaceutically acceptable salt thereof,

wherein:

Ring A is selected from the group consisting of:


, 
, 
, and 
;

Ring B is selected from the group consisting of:


and 
;

each $X^1$ and $X^2$ is independently –CR– or –N–;

$X^3$ is $–C(R)_2–$, -O-, or –NR–;

$X^a$ and $X^b$ are independently $–C(R)_2–$, $-C(R)=C(R)-$, -O-, -S-, -S(O)-, $-S(O)_2-$, or -N(R)-;

$X^{a1}$ and $X^{b1}$ are independently –C(R)- or –N–;

$X^c$ and $X^d$, when present, are independently optionally substituted oxygen, optionally substituted sulfur, a substituted nitrogen atom, $BH_3$, or optionally substituted $C_{1-12}$ aliphatic;

each $X^e$ and $X^f$ is independently –O-, -S-, or -N(R)-;

each W is independently P or S;

each $R^1$ and $R^2$ is independently selected from the group consisting of hydrogen, halogen, $–NO_2$, –CN, $–OR^a$, –SR, $–N(R)_2$, -C(O)R, $-CO_2R$, -C(O)C(O)R, $–C(O)CH_2C(O)R$, –S(O)R, $–S(O)_2R$, $–C(O)N(R)_2$, $-SO_2N(R)_2$, -OC(O)R, -N(R)C(O)R, $–N(R)N(R)_2$, $-N(R)C(=NR)N(R)_2$, $-C(=NR)N(R)_2$, –C=NOR, -N(R)C(O)N(R)$_2$, $–N(R)SO_2N(R)_2$, $–N(R)SO_2R$, $-OC(O)N(R)_2$, and optionally substituted $C_{1-12}$ aliphatic or $C_{1-4}$ alkoxy-$C_{1-4}$ alkyl;

each $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^{10}$, and $R^{11}$ is independently selected from the group consisting of hydrogen, halogen, $–NO_2$, –CN, –OR, –SR, $–N(R)_2$, -C(O)R, $-CO_2R$, -C(O)C(O)R, $–C(O)CH_2C(O)R$, –S(O)R, $–S(O)_2R$, $–C(O)N(R)_2$, $-SO_2N(R)_2$, -OC(O)R, -N(R)C(O)R, $–N(R)N(R)_2$, $-N(R)C(=NR)N(R)_2$, $-C(=NR)N(R)_2$, –C=NOR, -N(R)C(O)N(R)$_2$, $–N(R)SO_2N(R)_2$, $–N(R)SO_2R$, $-OC(O)N(R)_2$, or an optionally substituted group selected from $C_{1-12}$ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic

carbocyclic ring, a 7-10 membered saturated or partially unsaturated bicyclic carbocyclic ring, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

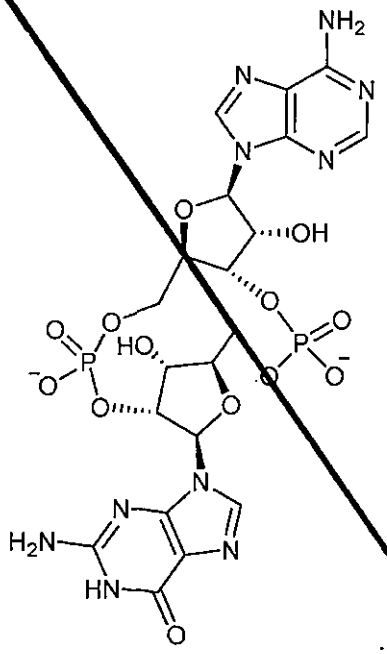
each $R^8$ and $R^9$, when present, is independently selected from the group consisting of hydrogen, halogen, $-NO_2$, $-CN$, $-OR^a$, $-SR$, $-N(R)_2$, $-C(O)R$, $-CO_2R$, $-C(O)C(O)R$, $-C(O)CH_2C(O)R$, $-S(O)R$, $-S(O)_2R$, $-C(O)N(R)_2$, $-SO_2N(R)_2$, $-OC(O)R$, $-N(R)C(O)R$, $-N(R)N(R)_2$, $-N(R)C(=NR)N(R)_2$, $-C(=NR)N(R)_2$, $-C=NOR$, $-N(R)C(O)N(R)_2$, $-N(R)SO_2N(R)_2$, $-N(R)SO_2R$, $-OC(O)N(R)_2$, and optionally substituted $C_{1-12}$ aliphatic;

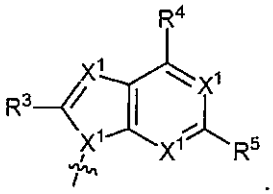
each R is independently selected from the group consisting of hydrogen or an optionally substituted group selected from $C_{1-6}$ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

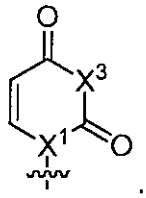
two R groups on the same nitrogen are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated, partially unsaturated, or heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

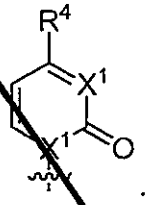
$R^a$ is an oxygen protecting group or R;

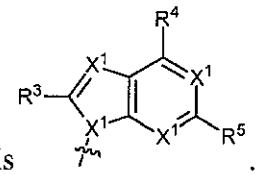
with the proviso that the compound is other than:

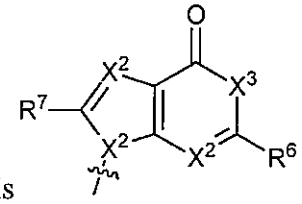


4. The compound of any one of the preceding claims, wherein Ring A is .

5. The compound of any one of the preceding claims, wherein Ring A is .

6. The compound of any one of the preceding claims, wherein Ring A is .

7. The compound of any one of the preceding claims, wherein Ring B is .

8. The compound of any one of the preceding claims, wherein Ring B is .

9. The compound of any one of the preceding claims, wherein each $X^1$ is –N-.

10. The compound of any one of preceding claims, wherein each $X^2$ is –N-.

11. The compound of any one of the preceding claims, wherein $X^3$ is –NR-.

12. The compound of any one of the preceding claims, wherein $X^a$ is –O-.

13. The compound of any one of the preceding claims, wherein $X^b$ is –O-.

14. The compound of any one of the preceding claims, wherein $X^{a1}$ and $X^{b1}$ are –C(R)-.

15. The compound of any one of the preceding claims, wherein $X^c$ and $X^d$ are both oxygen.

16. The compound of any one of the preceding claims, wherein $X^e$ and $X^f$ are both oxygen.

17. The compound of any one of the preceding claims, wherein $R^1$ is selected from the group consisting of hydrogen, halogen, $–OR^a$, -SR, $-N(R)_2$, and optionally substituted $C_{1-12}$ aliphatic or $C_{1-4}$ alkoxy-$C_{1-4}$ alkyl.

18. The compound of claim 17, wherein $R^1$ is –OH.

19. The compound of any one of the preceding claims, wherein $R^2$ is selected from the group consisting of hydrogen, halogen, $-OR^a$, -SR, $-N(R)_2$, and optionally substituted $C_{1-12}$ aliphatic or $C_{1-4}$ alkoxy-$C_{1-4}$ alkyl.

20. The compound of claim 19, wherein $R^2$ is –OH.

21. The compound of claim 17 or 19, wherein $R^a$ is R.

22. The compound of any one of the preceding claims, wherein each $R^3$, $R^5$, and $R^7$ is independently selected from the group consisting of hydrogen, halogen, and optionally substituted $C_{1-6}$ aliphatic.

23. The compound of claim 22, where each of $R^3$, $R^5$, and $R^7$ is hydrogen.

24. The compound of any one the preceding claims, wherein each of $R^4$ and $R^6$ is independently selected from the group consisting of hydrogen, halogen, and $-N(R)_2$.

25. The compound of claim 24, wherein $R^4$ and $R^6$ are each $–NH_2$.

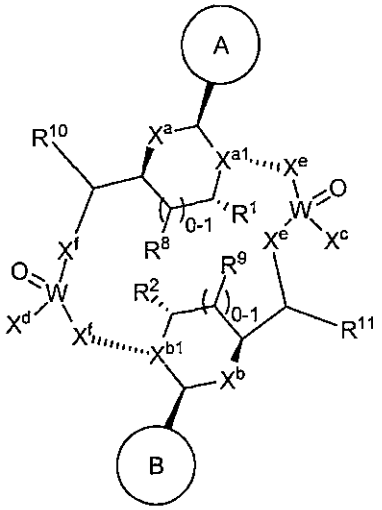
26. The compound of any one of the preceding claims, wherein $R^8$ and $R^9$ are hydrogen.

27. The compound of any one of the preceding claims, wherein $R^{10}$ and $R^{11}$ are hydrogen.

28. The compound of any one of the preceding claims, wherein W is P.

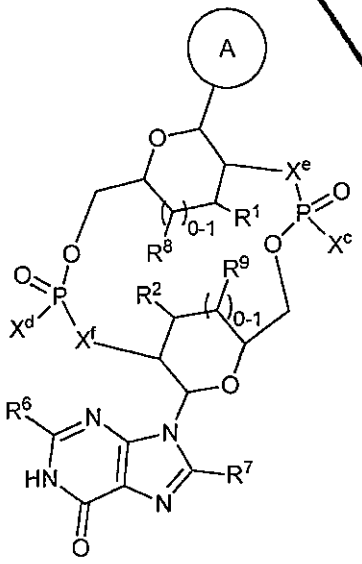
29. The compound of any one of the preceding claims, wherein R is hydrogen.

30. The compound of any one of claims 1, 2, or 4-29, wherein the compound is of formula I-a:

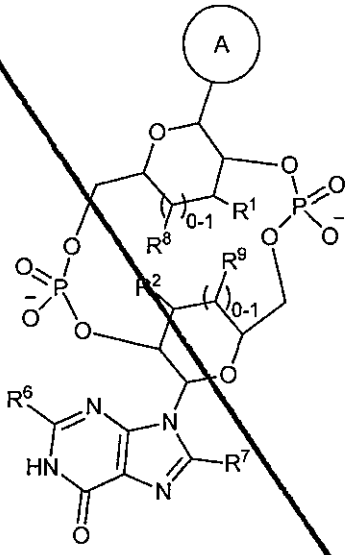



I-a

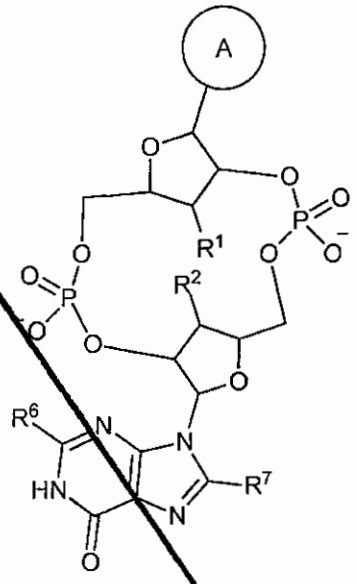
31. The compound of any one of claims 1, 2, or 4-29, wherein the compound is of formula III, IV, V, VI, VII, VIII, or IX:



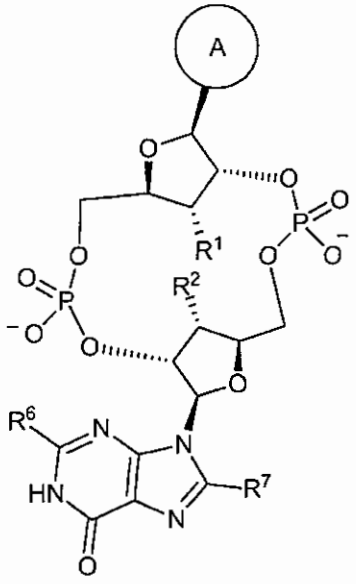

III



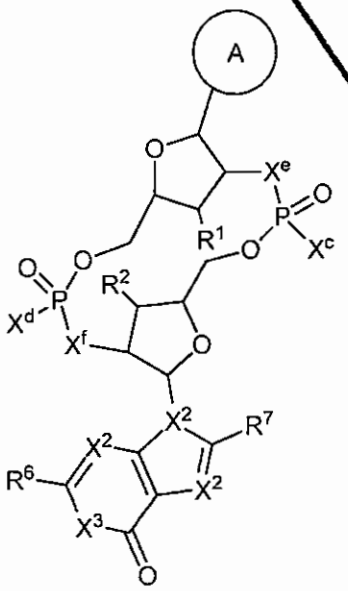

IV



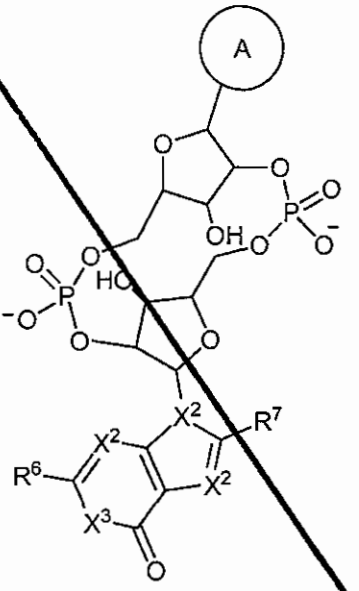
V



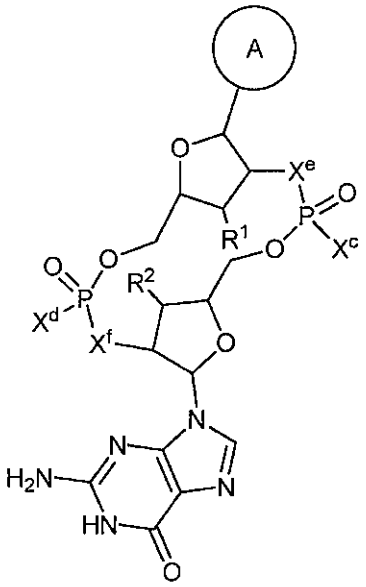
VI



VII



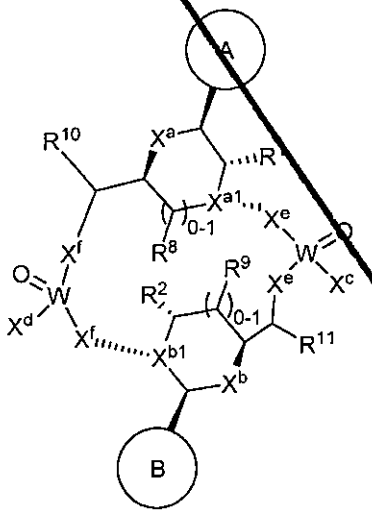
VIII



IX

or a pharmaceutically acceptable salt thereof.

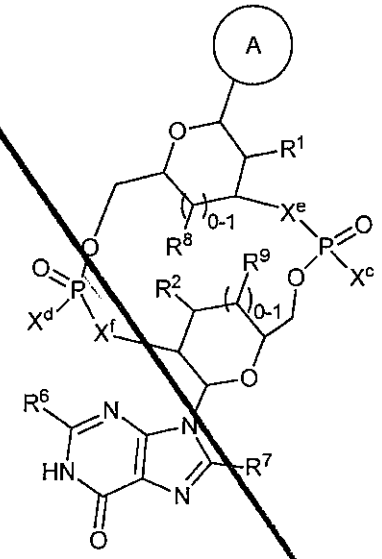
32. The compound of any one of claims 1 or 3-29, wherein the compound is of formula II-a:



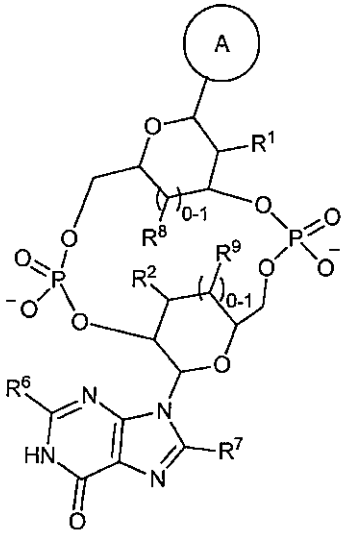
II-a

or a pharmaceutically acceptable salt thereof.

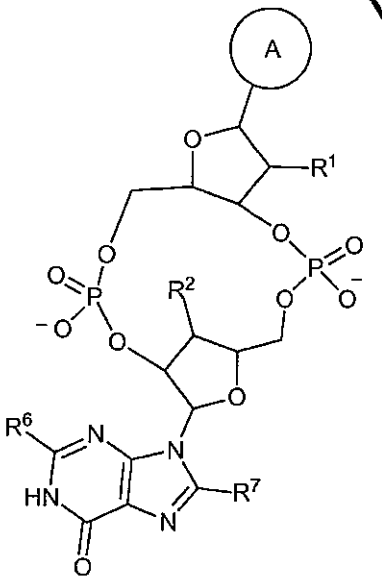
33. The compound of any one of claims 1 or 3-29, wherein the compound is of formula X, XI, XII, XIII, XIV, XV, or XVI:



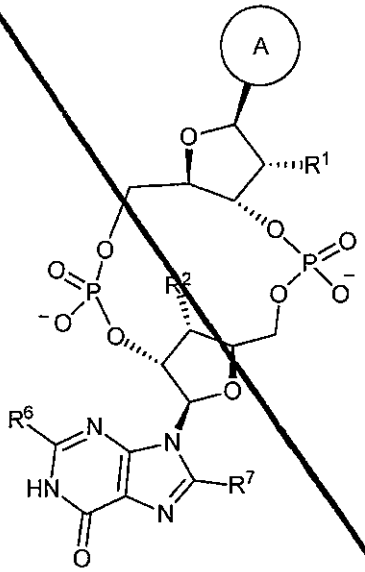
X



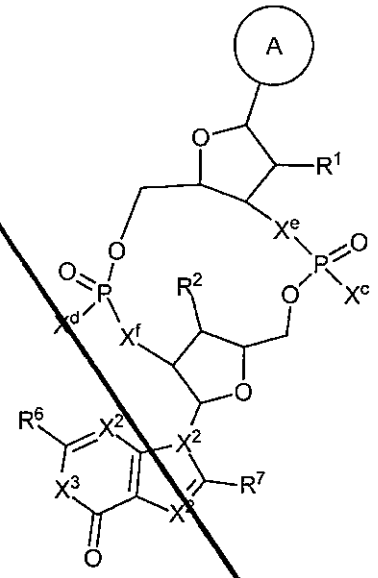
XI



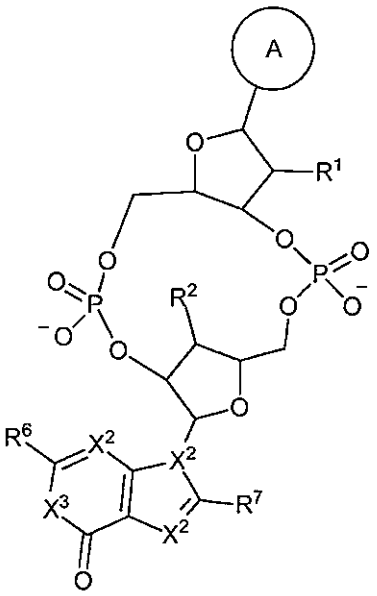
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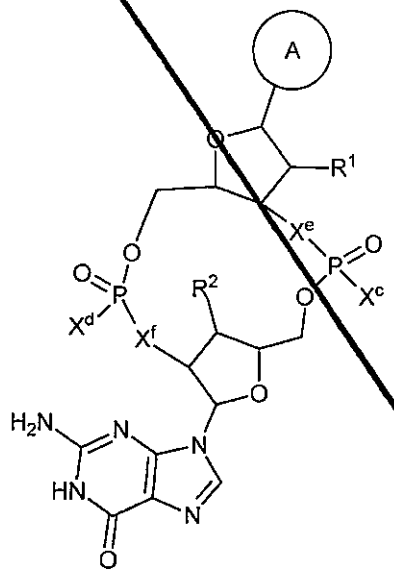
XIII



XIV



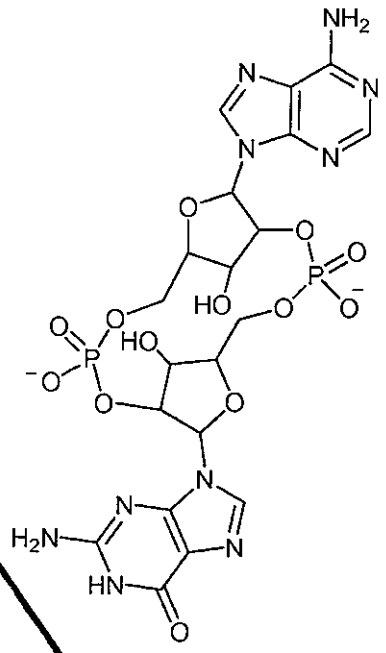
XV



XVI

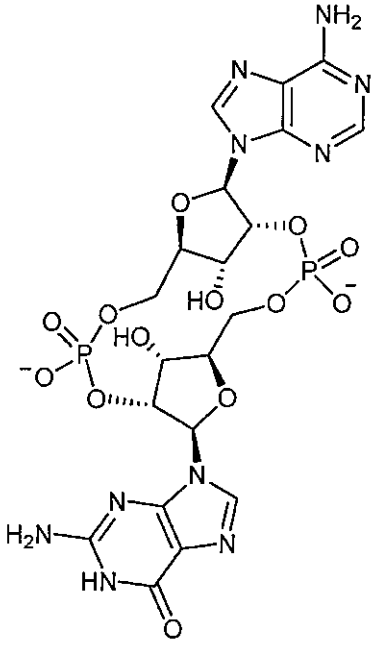
or a pharmaceutically acceptable salt thereof.

34. A compound:



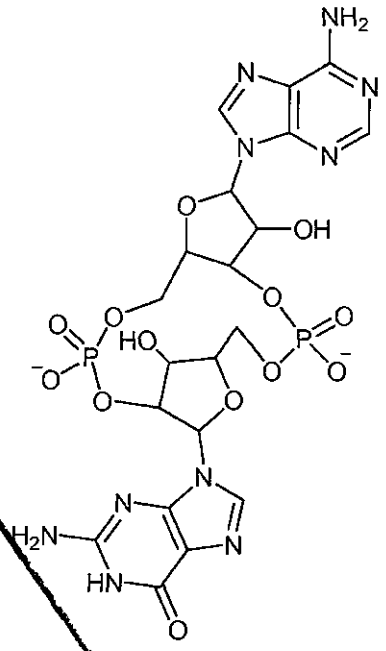
or a pharmaceutically acceptable salt thereof.

35. The compound of claim 34, wherein the compound is:



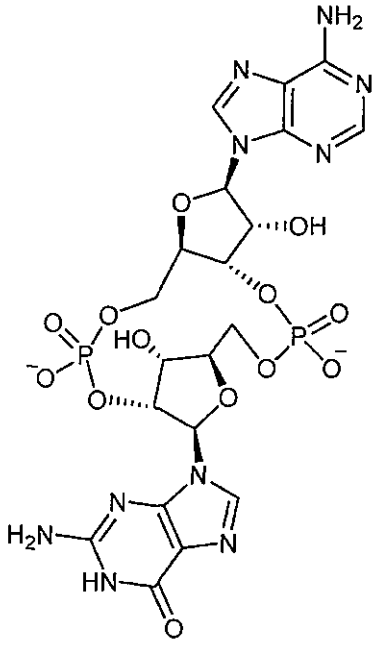
or a pharmaceutically acceptable salt thereof.

36. A compound:



or a pharmaceutically acceptable salt thereof.

37. The compound of claim 36, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

38. The compound of any one of claims 34-37, in isolated form.

39. The compound of claim 38, in purified form.

40. A pharmaceutical composition comprising a compound of any one of claims 1-39 and a pharmaceutically acceptable carrier.

41. A method for treatment or prevention of an immune disease, disorder, or condition comprising administering to a subject in need thereof a compound of any one of claims 1-39 or the pharmaceutical composition of claim 40.

42. The method of claim 41, wherein the immune disease, disorder, or condition is an autoimmune disease, disorder, or condition.

43. The method of claim 41 of 42, wherein the immune disease, disorder, or condition is selected from the group consisting of systemic lupus erythematosus, Sjögren's syndrome, and Aicardi-Goutières syndrome.

44. The method of claim 41, wherein the immune disease, disorder, or condition is characterized by inflammation.

45. The method of claim 41, wherein the immune disease, disorder, or condition is caused by, sustained by, or related to cGAS activation.

46. The method of claim 41, wherein the immune disease, disorder, or condition is caused by, sustained by, or related to STING activation.

47. The method of claim 41, wherein the administration of the compound results in a decrease of cGAS activity.

48. The method of claim 41, wherein the administration of the compound results in a decrease of STING activity.

49. The method of any one of claims 41-48, wherein the compound is prepared by chemical synthesis.

50. A method of inhibiting cGAS comprising contacting cGAS with a compound of any one of claims 1-39.

51. A method of inhibiting STING comprising contacting STING with a compound of any one of claims 1-39.

52. A method of designing or characterizing a cGAS modulator comprising the steps of:
a) providing an image of a cGAS crystal that includes at least one potential interaction site;
b) docking in the image at least one moiety that is a potential cGAS modulator structural element; and
c) assessing one or more features of a potential moiety-interaction site interaction.

53. The method of claim 52, wherein the at least one potential interaction site includes a site selected from the group consisting of Ser199, Ser420, Lys402, Glu211, Asp213, Asp307, Tyr421, Arg364, and combinations thereof.

54. The method of claim 52 or 53, wherein the at least one potential interaction site includes a site selected from the group consisting of Tyr421, Thr197, Ser366, Ser368, Arg364, and combinations thereof.

55. The method of claim 52, 53, or 54, wherein the at least one potential interaction site includes a site selected from the group consisting of Tyr421, Asp213, Asp307, Arg364, and combinations thereof.

56. The method of claim 52, wherein the at least one potential interaction site includes Arg161.

57. The method of any one of claims 52-55, wherein the modulator is a compound of any one of claims 1-39.

58. The method of any one of claims 52-57, wherein the one or more features include at least one feature selected from the group consisting of: spatial separation between the moiety and the potential interaction site; energy of the potential moiety-interaction site interaction, and/or combinations thereof.

59. The method of any one of claims 52-57, further comprising a step of providing an image of a potential cGAS modulator comprising the moiety docked with the image of the cGAS crystal.

60. The method of claim 59, further comprising the step of comparing the image with that of a cGAS crystal including a bound known modulator, substrate, or product.

61. A system comprising a computer or computer readable medium in which a cGAS crystal structure, or coordinates thereof, is embedded and/or displayed.

62. A method of designing and/or characterizing an cGAS modulator, which method comprises steps of:
(i) using the system of claim 51 to assess one or more structural features of the cGAS modulator; and
(ii) performing one or more *in vitro, in vivo* or cell-based assays to characterize the cGAS modulator.

63. The method of any one of claims 52-60 or 62, further comprising the step of performing a competition experiment between the cGAS modulator and a known cGAS modulator, substrate, or product.

64. The method of claim 63, wherein the method further comprises the step of defining the three-dimensional shape of the inhibitor.

65. An inhibitor of cGAS characterized in that it binds in the binding pocket having a three-dimensional structure characterized by the structure coordinates of any one of Tables 1, 2, 3, 4, 5, 6, or 7.

66. A designed cGAS inhibitor, comprising the crystallography coordinates of any one of Tables 1, 2, 3, 4, 5, 6, or 7, wherein the crystallography coordinates are within about a root mean square deviation of not more than about 1.5 Å from the backbone atoms of the amino acids according to Tables 1, 2, 3, 4, 5, 6, or 7.

67. A computer system containing a set of information to perform a design or characterization of an cGAS inhibitor having a user interface comprising a display unit, the set of information comprising:
(i) logic for inputting an information regarding a binding of a cGAS protein to a moiety known to bind cGAS protein;
(ii) logic for design a candidate cGAS inhibitor based on the binding of the cGAS protein to the moiety known to bind cGAS protein;
(iii) logic for determining an information regarding a binding of the cGAS protein to the candidate cGAS inhibitor; and
(iv) logic for making a conclusion regarding a cGAS inhibitory properties of the candidate cGAS inhibitor based on the determination of step (iii).

68. A computer-readable storage medium containing a set of information for a general purpose computer having a user interface comprising, a display unit, the set of information comprising:
(i) logic for inputting an information regarding a binding of a cGAS protein to a chemical known to binding cGAS protein;
(ii) logic for design a candidate cGAS inhibitor based on the binding of the cGAS protein to the chemical known to bind cGAS protein;

(iii) logic for determining an information regarding a binding of the cGAS protein to the candidate cGAS inhibitor; and
(iv) logic for making a conclusion regarding a cGAS inhibitory properties of the candidate cGAS inhibitor based on the determination step of step (iii).

69. An electronic signal or carrier wave that is propagated over the internet between computers comprising a set of information for a general purpose computer having a user interface comprising a display unit, the set of information comprising a computer-readable storage medium containing a set of information for a general purpose computer having a user interface comprising a display unit, the set of information comprising:
(i) logic for inputting an information regarding a binding of a cGAS protein to a chemical known to bind cGAS protein;
(ii) logic for designing a candidate cGAS inhibitor based on the binding of the cGAS protein to the chemical known to bind cGAS protein;
(iii) logic for determining an information regarding a binding of the cGAS protein to the candidate cGAS inhibitor; and
(iv) logic for making a conclusion regarding a cGAS inhibitory properties of the candidate cGAS inhibitor based on the determination of step (iii).

70. A method of modulating activity of an cGAS polypeptide, the method comprising contacting the cGAS polypeptide with a cGAS modulator of claim 52 which modulating agent is not a known modulator, substrate, or product of cGAS.

71. The method of claim 70, wherein the modulating agent is a compound of any one of claims 1-39.

72. A crystalline or crystallizable composition comprising or consisting of an cGAS polypeptide.

73. A method of making the composition of claim 72.

74. A method of using the composition of claim 72.

75. A method of reducing the level of interferon in a subject comprising contacting said subject with an antagonist of cGAS.

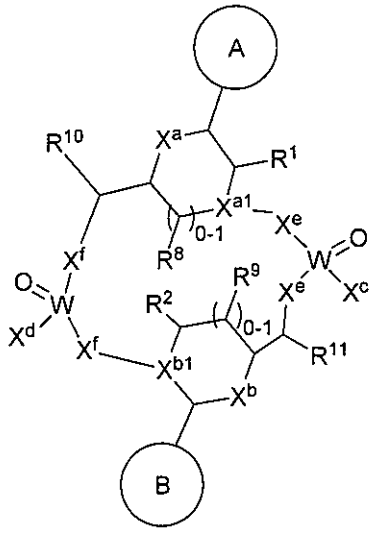
76. The method of claim 75, wherein the antagonist is an analog, mimic or variant of an isomer of the cGAMP family of molecules.

77. A method of altering cytokine profile in an individual, comprising contacting the individual with a cGAS antagonist which is an analog, mimic or variant of an isomer of the cGAMP family of molecules.

78. A kit comprising one or more cGAMP compounds and optionally one or more cGAS molecules.

## CLAIMS

1. A compound of Formula II:

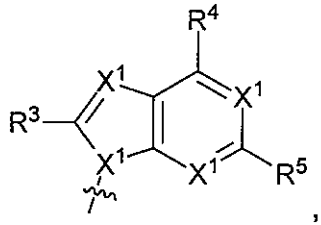
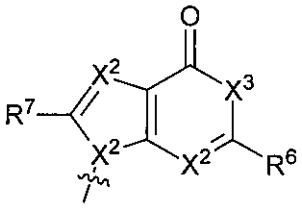
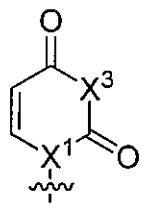
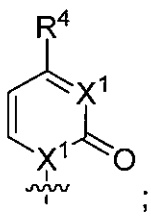


II

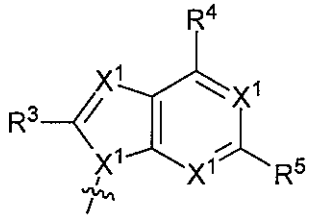
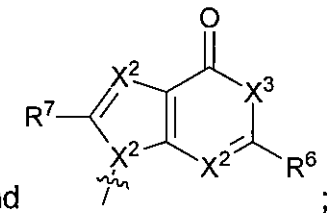
or a pharmaceutically acceptable salt thereof,

wherein:

Ring A is selected from the group consisting of:


, 
, 
, and 
;

Ring B is selected from the group consisting of:


and 
;

each $X^1$ and $X^2$ is independently –CR- or –N-;

$X^3$ is $–C(R)_2$-, -O-, or –NR-;

$X^a$ and $X^b$ are independently $–C(R)_2$-, -C(R)=C(R)-, -O-, -S-, -S(O)-, $-S(O)_2$-, or -N(R)-;

$X^{a1}$ and $X^{b1}$ are independently –C(R)- or –N-;

$X^c$ and $X^d$, when present, are independently optionally substituted oxygen, optionally substituted sulfur, a substituted nitrogen atom, $BH_3$, or optionally substituted $C_{1-12}$ aliphatic;

each $X^e$ and $X^f$ is independently –O-, -S-, or -N(R)-;

each W is independently P or S;

each $R^1$ and $R^2$ is independently selected from the group consisting of hydrogen, halogen, $–NO_2$, –CN, $–OR^a$, –SR, $–N(R)_2$, -C(O)R, $-CO_2R$, -C(O)C(O)R, –$C(O)CH_2C(O)R$, –S(O)R, $–S(O)_2R$, –$C(O)N(R)_2$, $-SO_2N(R)_2$, -OC(O)R, -N(R)C(O)R, $–N(R)N(R)_2$, -$N(R)C(=NR)N(R)_2$, -$C(=NR)N(R)_2$, –C=NOR, -N(R)C(O)$N(R)_2$, –$N(R)SO_2N(R)_2$, $–N(R)SO_2R$, -$OC(O)N(R)_2$, and optionally substituted $C_{1-12}$ aliphatic or $C_{1-4}$ alkoxy-$C_{1-4}$ alkyl;

each $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^{10}$, and $R^{11}$ is independently selected from the group consisting of hydrogen, halogen, $–NO_2$, –CN, –OR, –SR, –$N(R)_2$, -C(O)R, $-CO_2R$, -C(O)C(O)R, $–C(O)CH_2C(O)R$, –S(O)R, $–S(O)_2R$, –$C(O)N(R)_2$, $-SO_2N(R)_2$, -OC(O)R, -N(R)C(O)R, $–N(R)N(R)_2$, -$N(R)C(=NR)N(R)_2$, -$C(=NR)N(R)_2$, –C=NOR, -N(R)C(O)$N(R)_2$, –$N(R)SO_2N(R)_2$, $–N(R)SO_2R$, -$OC(O)N(R)_2$, or an optionally substituted group selected from $C_{1-12}$ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-10 membered saturated or partially unsaturated bicyclic carbocyclic ring, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each $R^8$ and $R^9$, when present, is independently selected from the group consisting of hydrogen, halogen, $–NO_2$, –CN, $–OR^a$, –SR, –$N(R)_2$, -C(O)R, $-CO_2R$, -C(O)C(O)R, $–C(O)CH_2C(O)R$, –S(O)R, $–S(O)_2R$, –$C(O)N(R)_2$, $-SO_2N(R)_2$, -OC(O)R, -N(R)C(O)R, $–N(R)N(R)_2$, -

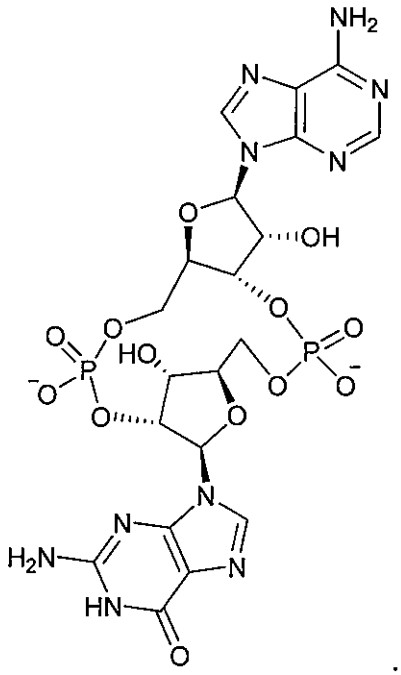
$N(R)C(=NR)N(R)_2$, $-C(=NR)N(R)_2$, $-C=NOR$, $-N(R)C(O)N(R)_2$, $-N(R)SO_2N(R)_2$, $-N(R)SO_2R$, $-OC(O)N(R)_2$, and optionally substituted $C_{1-12}$ aliphatic;

each R is independently selected from the group consisting of hydrogen or an optionally substituted group selected from $C_{1-6}$ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

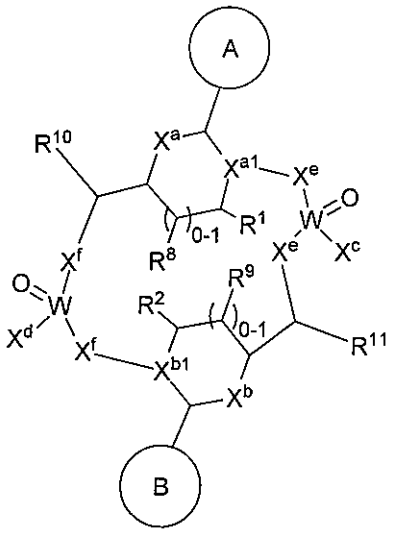
two R groups on the same nitrogen are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated, partially unsaturated, or heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

$R^a$ is an oxygen protecting group or R;

with the proviso that the compound is other than:



2. A compound of Formula I:

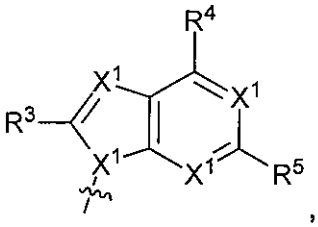
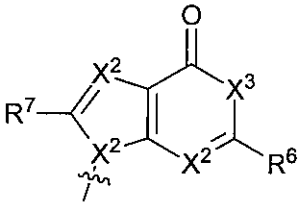
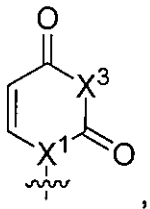
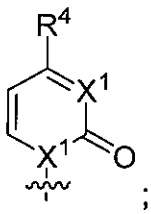


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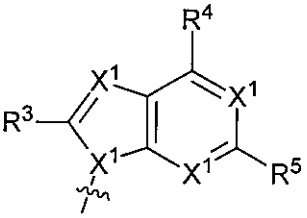
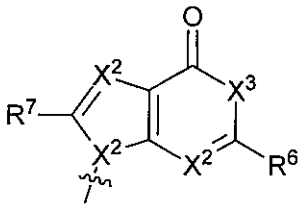
or a pharmaceutically acceptable salt thereof,

wherein:

Ring A is selected from the group consisting of:


,

,

, and

;

Ring B is selected from the group consisting of:


and

;

each $X^1$ and $X^2$ is independently –CR- or –N-;

$X^3$ is $–C(R)_2$-, -O-, or –NR-;

$X^a$ and $X^b$ are independently $–C(R)_2$-, -C(R)=C(R)-, -O-, -S-, -S(O)-, $-S(O)_2$-, or -N(R)-;

$X^{a1}$ and $X^{b1}$ are independently –C(R)- or –N-;

$X^c$ and $X^d$, when present, are independently optionally substituted oxygen, optionally substituted sulfur, a substituted nitrogen atom, $BH_3$, or optionally substituted $C_{1-12}$ aliphatic;

each $X^e$ and $X^f$ is independently –O-, -S-, or -N(R)-;

each W is independently P or S;

each $R^1$ and $R^2$ is independently selected from the group consisting of hydrogen, halogen, $–NO_2$, –CN, $–OR^a$, –SR, $–N(R)_2$, -C(O)R, $-CO_2R$, -C(O)C(O)R, –$C(O)CH_2C(O)R$, –S(O)R, $–S(O)_2R$, –$C(O)N(R)_2$, $-SO_2N(R)_2$, -OC(O)R, -N(R)C(O)R, $–N(R)N(R)_2$, -$N(R)C(=NR)N(R)_2$, $-C(=NR)N(R)_2$, –C=NOR, $-N(R)C(O)N(R)_2$, –$N(R)SO_2N(R)_2$, $–N(R)SO_2R$, $-OC(O)N(R)_2$, and optionally substituted $C_{1-12}$ aliphatic or $C_{1-4}$ alkoxy-$C_{1-4}$ alkyl;

each $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^{10}$, and $R^{11}$ is independently selected from the group consisting of hydrogen, halogen, $–NO_2$, –CN, –OR, –SR, –$N(R)_2$, -C(O)R, $-CO_2R$, -C(O)C(O)R, –$C(O)CH_2C(O)R$, –S(O)R, $–S(O)_2R$, –$C(O)N(R)_2$, $-SO_2N(R)_2$, -OC(O)R, -N(R)C(O)R, $–N(R)N(R)_2$, -$N(R)C(=NR)N(R)_2$, $-C(=NR)N(R)_2$, –C=NOR, $-N(R)C(O)N(R)_2$, –$N(R)SO_2N(R)_2$, $–N(R)SO_2R$, $-OC(O)N(R)_2$, or an optionally substituted group selected from $C_{1-12}$ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 7-10 membered saturated or partially unsaturated bicyclic carbocyclic ring, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

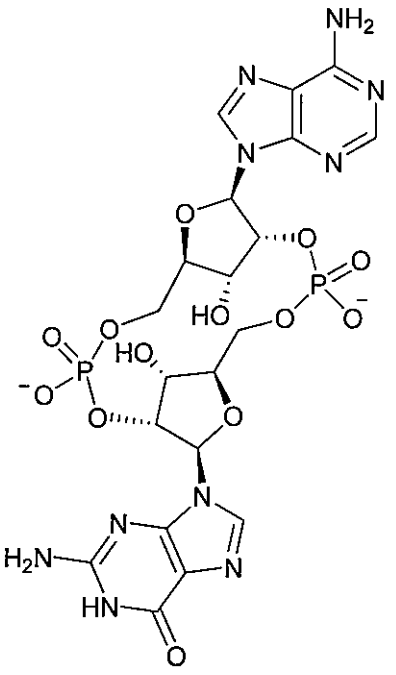
each $R^8$ and $R^9$, when present, is independently selected from the group consisting of hydrogen, halogen, $–NO_2$, –CN, $–OR^a$, –SR, –$N(R)_2$, -C(O)R, $-CO_2R$, -C(O)C(O)R, –$C(O)CH_2C(O)R$, –S(O)R, $–S(O)_2R$, –$C(O)N(R)_2$, $-SO_2N(R)_2$, -OC(O)R, -N(R)C(O)R, $–N(R)N(R)_2$, -$N(R)C(=NR)N(R)_2$, $-C(=NR)N(R)_2$, –C=NOR, $-N(R)C(O)N(R)_2$, –$N(R)SO_2N(R)_2$, $–N(R)SO_2R$, $-OC(O)N(R)_2$, and an optionally substituted $C_{1-12}$ aliphatic;

each R is independently selected from the group consisting of hydrogen or an optionally substituted group selected from $C_{1-6}$ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or:

two R groups on the same nitrogen are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated, partially unsaturated, or heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

$R^a$ is an oxygen protecting group or R;

with the proviso that the compound is other than:



or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 or 2, wherein:

(a) each $X^1$ is –N-, and/or

(b) each $X^2$ is –N-, and/or

(c) $X^3$ is –NR-, and/or

(d) $X^a$ is –O-, and/or

(e) $X^b$ is –O-, and/or

(f) $X^{a1}$ and $X^{b1}$ are –C(R)-, and/or

(g) $X^c$ and $X^d$ are both oxygen, and/or

(h) $X^e$ and $X^f$ are both oxygen, and/or

(i) $R^1$ is selected from the group consisting of hydrogen, halogen, $-OR^a$, -SR, $-N(R)_2$, and optionally substituted $C_{1-12}$ aliphatic or $C_{1-4}$ alkoxy-$C_{1-4}$ alkyl, optionally wherein $R^1$ is –OH, optionally $R^a$ is R, and/or

(j) $R^2$ is selected from the group consisting of hydrogen, halogen, $-OR^a$, -SR, $-N(R)_2$, and optionally substituted $C_{1-12}$ aliphatic or $C_{1-4}$ alkoxy-$C_{1-4}$ alkyl, optionally wherein $R^2$ is –OH, or optionally wherein $R^a$ is R, and/or

(k) each $R^3$, $R^5$, and $R^7$ is independently selected from the group consisting of hydrogen, halogen, and optionally substituted $C_{1-6}$ aliphatic, optionally where each of $R^3$, $R^5$, and $R^7$ is hydrogen, and/or

(l) each of $R^4$ and $R^6$ is independently selected from the group consisting of hydrogen, halogen, and $-N(R)_2$, optionally wherein $R^4$ and $R^6$ are each $–NH_2$, and/or

(m) $R^8$ and $R^9$ are hydrogen, and/or

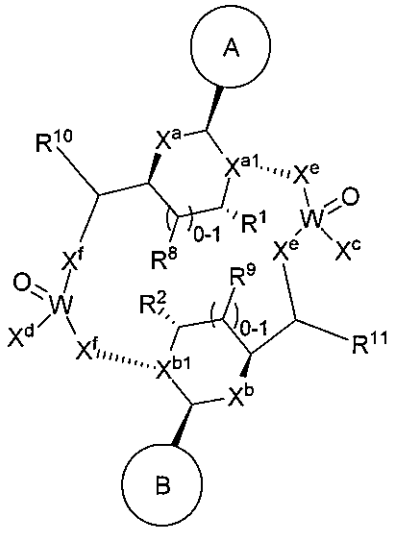
(n) $R^{10}$ and $R^{11}$ are hydrogen, and/or

(o) W is P, and/or

(p) R is hydrogen.

4. The compound of claim 2 or 3, wherein the compound is of

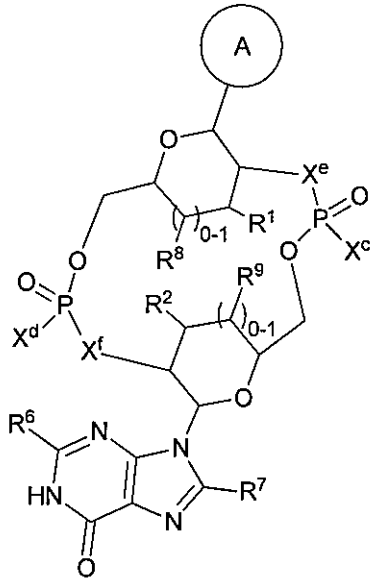
(a) formula I-a:



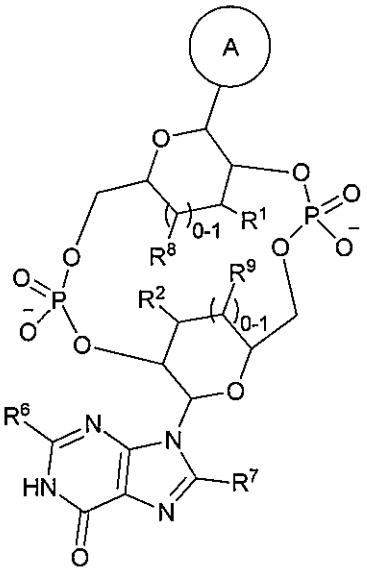

, or

**I-a**

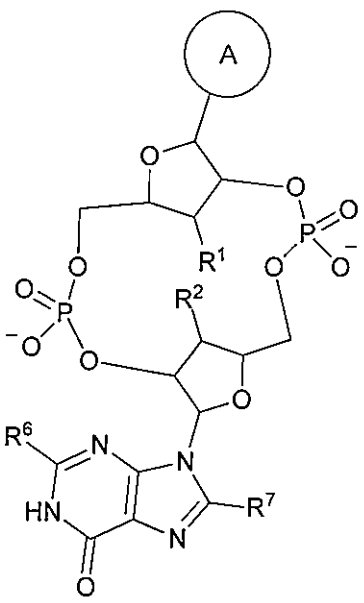
(b) formula III, IV, V, VI, VII, VIII, or IX:



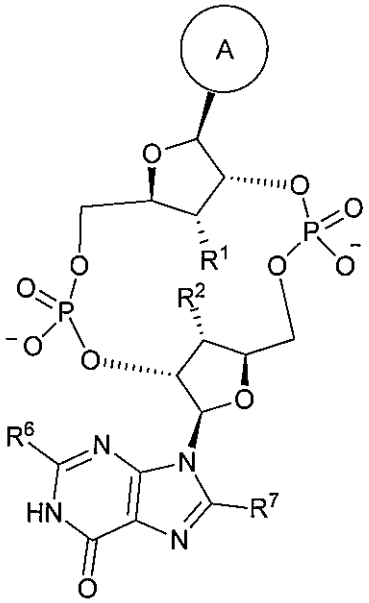

**III**



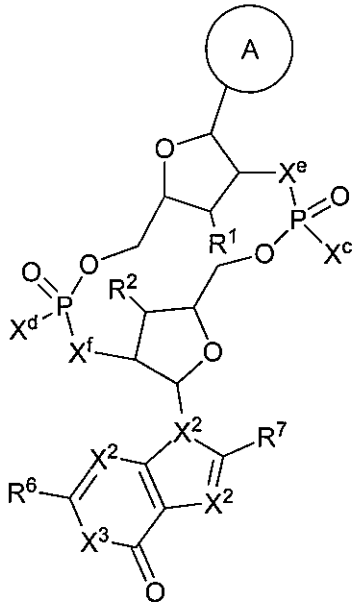

**IV**



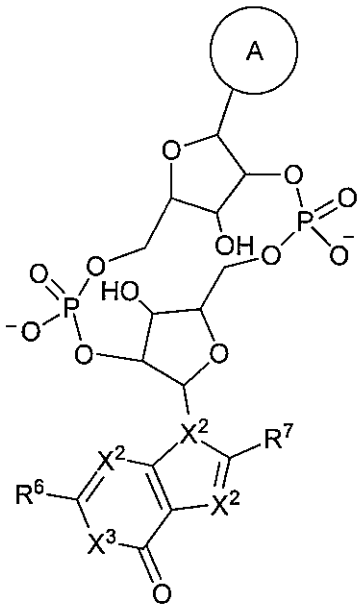
V



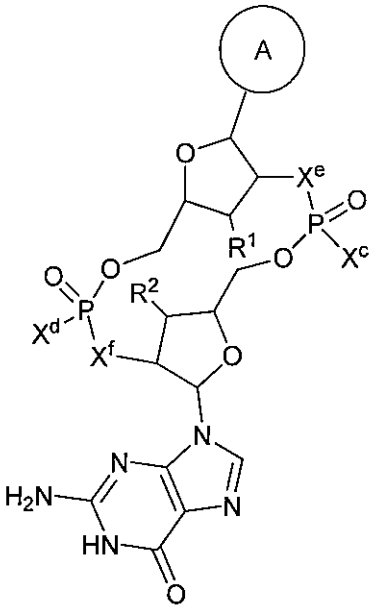
VI



VII



VIII

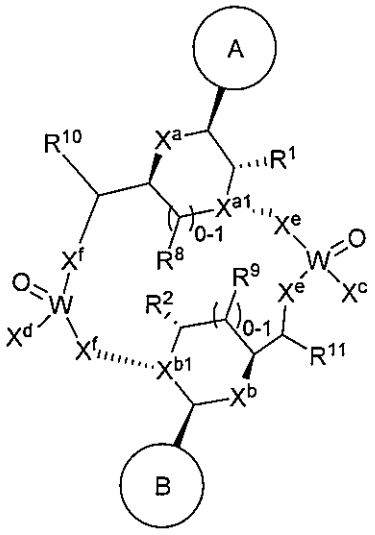


**IX**

or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1 or 3, wherein the compound is of

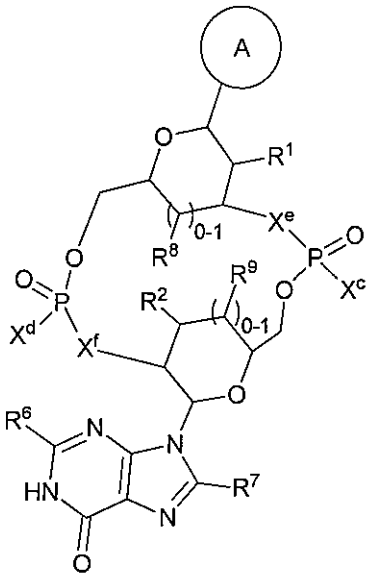
(a) formula II-a:



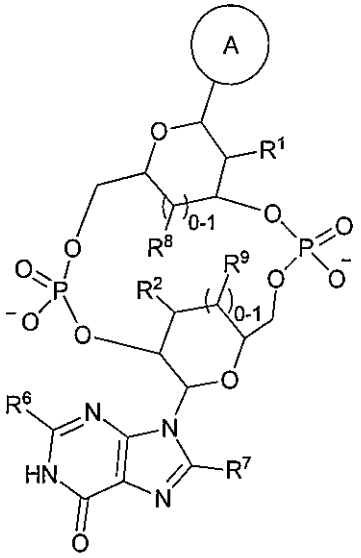
**II-a**

or a pharmaceutically acceptable salt thereof, or

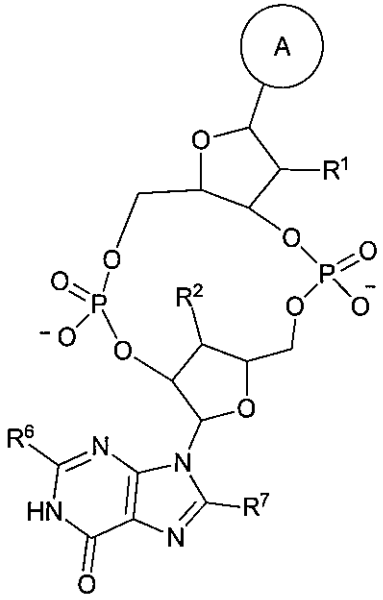
(b) formula X, XI, XII, XIII, XIV, XV, or XVI:



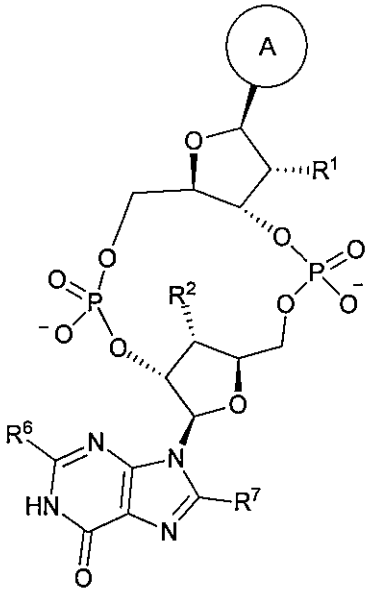
X



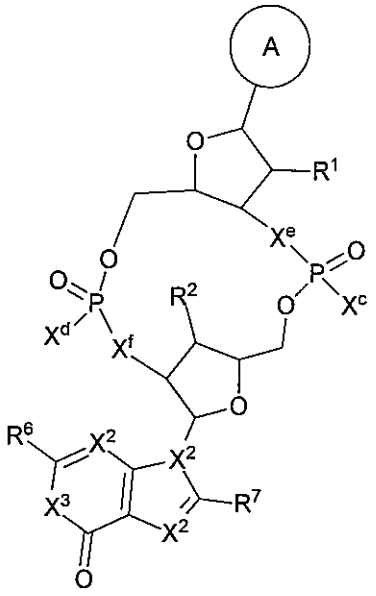
XI



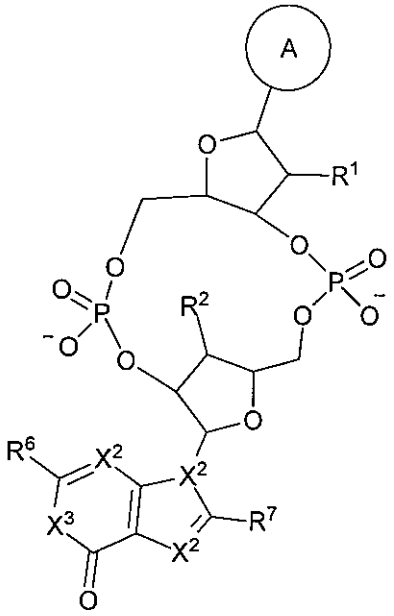
XII



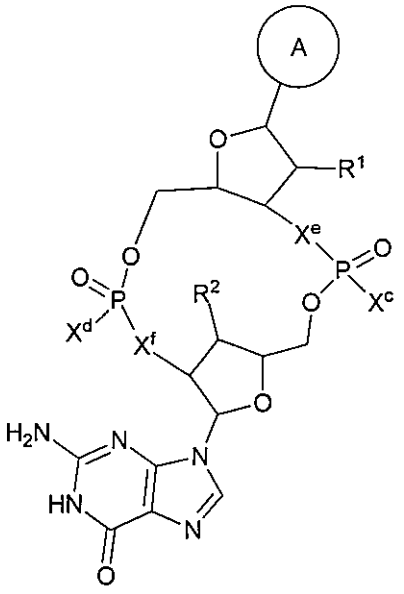
XIII



**XIV**



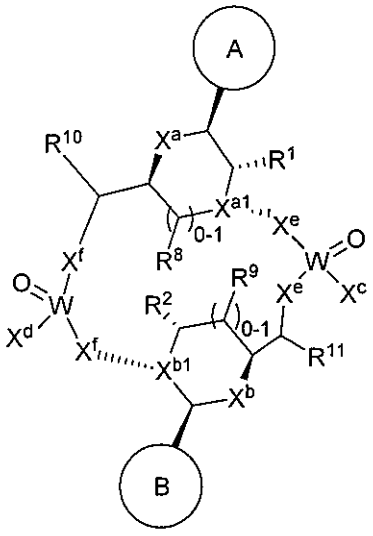
**XV**



**XVI**

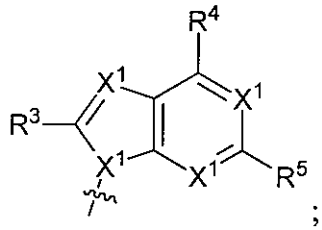
or a pharmaceutically acceptable salt thereof.

6. The compound of claim 5, wherein the compound is of formula II-a,

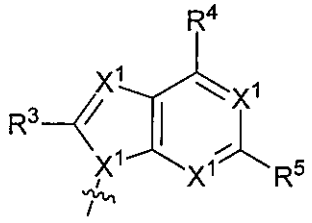
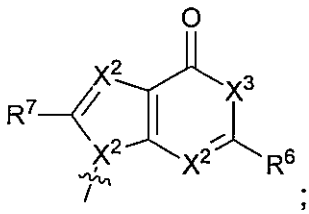



**II-a**

or a pharmaceutically acceptable salt thereof, wherein

Ring A is  ;

Ring B is selected from the group consisting of:

 and  ;

each $X^1$ is N;

$R^3$ and $R^5$ are hydrogen;

$R^4$ is $NH_2$;

W is P;

$X^a$ and $X^b$ are O;

$X^c$ and $X^d$, when present, are independently optionally substituted oxygen, optionally substituted sulfur, a substituted nitrogen atom, $BH_3$, or optionally substituted $C_{1-12}$ aliphatic;

$X^e$ and $X^f$ are O;

$R^1$ and $R^2$ are OH;

$X^{a1}$ and $X^{b1}$ are CH;

$R^{10}$ and $R^{11}$ are hydrogen; and

$R^8$ and $R^9$ are hydrogen.

7. The compound of claim 6, wherein:

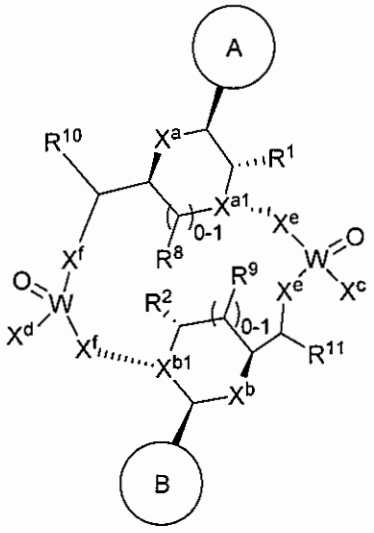
$X^c$ is oxygen or sulfur; and/or

$X^d$ is oxygen or sulfur; and/or

$CHR^8$ is absent; and/or

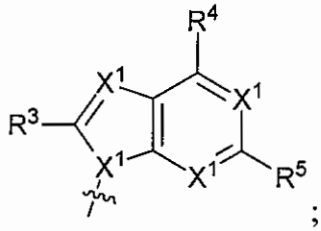
$CHR^9$ is absent.

8. The compound of claim 5, wherein the compound is of formula II-a,

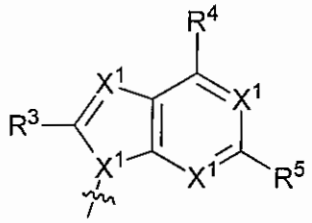


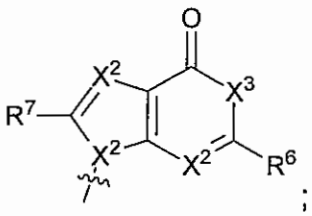

**II-a**

or a pharmaceutically acceptable salt thereof, wherein

Ring A is  ;

Ring B is selected from the group consisting of:



and


;

each $X^1$ is N;

$R^3$ and $R^5$ are hydrogen;

$R^4$ is $NH_2$;

W is P;

$X^a$ and $X^b$ are O;

$X^c$ and $X^d$, are independently oxygen or sulfur;

$X^e$ and $X^f$ are O;

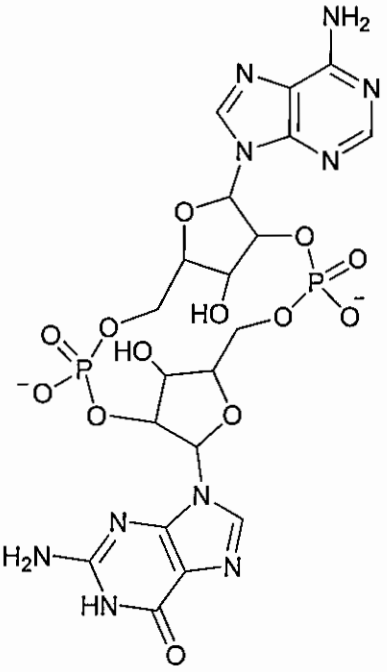
$R^1$ and $R^2$ are OH;

$X^{a1}$ and $X^{b1}$ are CH;

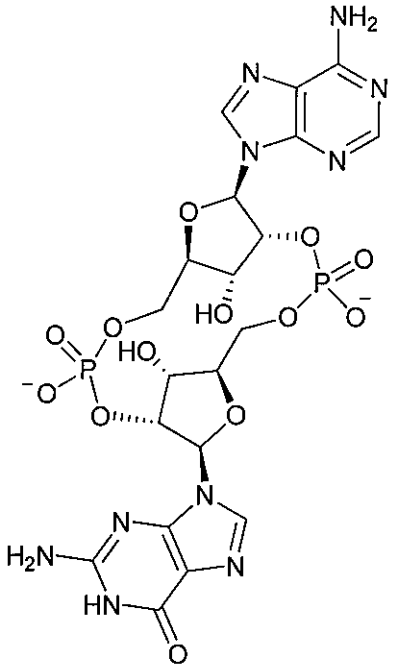
$R^{10}$ and $R^{11}$ are hydrogen; and

$CHR^8$ and $CHR^9$ are absent.

9. A compound:

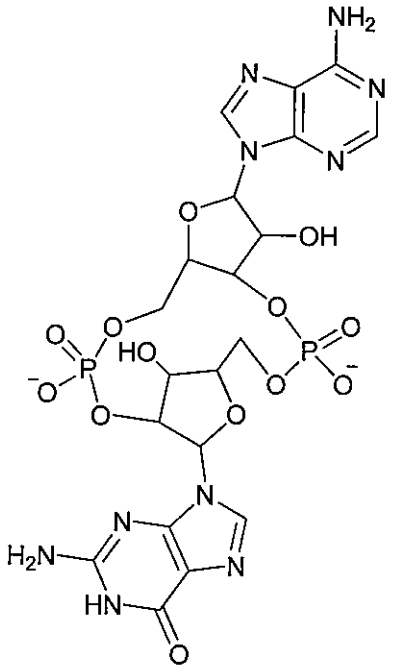



or a pharmaceutically acceptable salt thereof, optionally wherein the compound is:

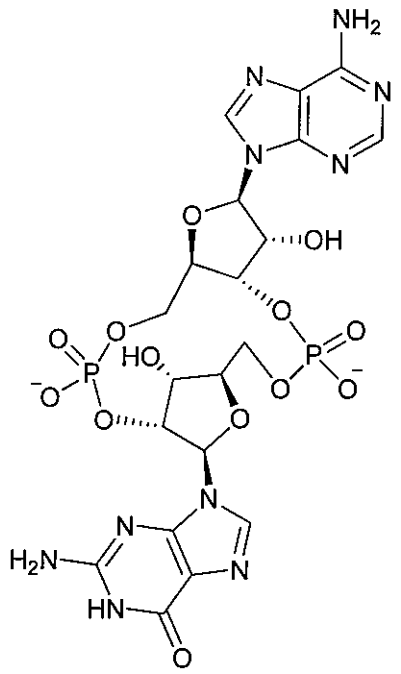


or a pharmaceutically acceptable salt thereof.

10. A compound:



or a pharmaceutically acceptable salt thereof, optionally wherein the compound is:



or a pharmaceutically acceptable salt thereof.

11. The compound of claim 9 or 10 in isolated form, optionally in purified form.

12. A modulator of cGAS having a structure comprising the following features:

A ----- L ----- B

wherein:
A is or comprises a moiety that fits in the cGAS adenosine binding site;
B is or comprises a moiety that fits in the cGAS guanosine binding site; and
L is a linker moiety linking A and B in a manner which allows A and B to adopt appropriate interactions to bind cGAS.

13. A pharmaceutical composition comprising the compound of any one of claims 1-11, or the modulator of claim 12, and a pharmaceutically acceptable carrier.

14. A method for treatment or prevention of cancer, comprising administering to a subject in need thereof the compound of any one of claims 1-11, or the modulator of claim 12, or the pharmaceutical composition of claim 13.

15. The compound according to any one of claims 1-11, or the modulator of claim 12, or the pharmaceutical composition according to claim 13 for use in treating or preventing an immune disease, disorder, or condition, optionally wherein the immune disease, disorder, or condition is

(a) an autoimmune disease, disorder, or condition, optionally wherein the immune disease, disorder, or condition is selected from the group consisting of systemic lupus erythematosus, Sjögren's syndrome, and Aicardi-Goutières syndrome;

(b) is characterized by inflammation;

(c) is caused by, sustained by, or related to cGAS activation; or

(d) is caused by, sustained by, or related to STING activation.

16. The compound, or modulator, or pharmaceutical composition for use according to claim 15, wherein administration of the compound, or modulator, or pharmaceutical composition results in a decrease of cGAS activity or STING activity, optionally wherein the compound or modulator is prepared by chemical synthesis.

17. An in vitro method of inhibiting cGAS or STING comprising contacting cGAS or STING with the compound of any one of claims 1-11, or the modulator of claim 12.

18. A method of designing or characterizing a cGAS modulator comprising the steps of:

a) providing an image of a cGAS crystal that includes at least one potential interaction site;

b) docking in the image at least one moiety that is a potential cGAS modulator structural element; and

c) assessing one or more features of a potential moiety-interaction site interaction.

19. The method of claim 18, wherein the at least one potential interaction site includes a site selected from the group consisting of:

(a) Ser199, Ser420, Lys402, Glu211, Asp213, Asp307, Tyr421, Arg364, and combinations thereof; and/or

(b) Tyr421, Thr197, Ser366, Ser368, Arg364, and combinations thereof; and/or

(c) Tyr421, Asp213, Asp307, Arg364, and combinations thereof;

optionally wherein the at least one potential interaction site includes Arg161.

20. The method of claim 18 or 19, wherein

the modulator is the compound of any one of claims 1-11 or the modulator of claim 12, and/or

the one or more features include at least one feature selected from the group consisting of: spatial separation between the moiety and the potential interaction site; energy of the potential moiety-interaction site interaction, and/or combinations thereof, and/or

further comprising a step of providing an image of a potential cGAS modulator comprising the moiety docked with the image of the cGAS crystal, and/or further comprising the step of comparing the image with that of a cGAS crystal including a bound known modulator, substrate, or product.

21. A system comprising a computer or computer readable medium in which a cGAS crystal structure, or coordinates thereof, is embedded and/or displayed.

22. A method of designing and/or characterizing an cGAS modulator, which method comprises steps of:

(i) using the system of claim 21 to assess one or more structural features of the cGAS modulator; and

(ii) performing one or more *in vitro, in vivo* or cell-based assays to characterize the cGAS modulator.

23. The method of any one of claims 18-20 or 22, further comprising the step of performing a competition experiment between the cGAS modulator and a known cGAS modulator, substrate, or product, optionally wherein the method further comprises the step of defining the three-dimensional shape of the inhibitor.

24. An inhibitor of cGAS characterized in that it binds in the binding pocket having a three-dimensional structure characterized by the structure coordinates of any one of Tables 1, 2, 3, 4, 5, 6, or 7.

25. A designed cGAS inhibitor, comprising the crystallography coordinates of any one of Tables 1, 2, 3, 4, 5, 6, or 7, wherein the crystallography coordinates are within about a root mean square deviation of not more than about 1.5 Å from the backbone atoms of the amino acids according to Tables 1, 2, 3, 4, 5, 6, or 7.

26. A computer system, a computer-readable storage medium or an electronic signal or carrier wave that is propagated over the internet between computers, which contains a set of information to perform a design or characterization of an cGAS inhibitor having a user interface comprising a display unit, the set of information comprising:
(i) logic for inputting an information regarding a binding of a cGAS protein to a moiety known to bind cGAS protein;
(ii) logic for design a candidate cGAS inhibitor based on the binding of the cGAS protein to the moiety known to bind cGAS protein;
(iii) logic for determining an information regarding a binding of the cGAS protein to the candidate cGAS inhibitor; and
(iv) logic for making a conclusion regarding a cGAS inhibitory properties of the candidate cGAS inhibitor based on the determination of step (iii).

27. An in vitro method of modulating activity of an cGAS polypeptide, the method comprising contacting the cGAS polypeptide with a cGAS modulator obtained by the method of claim 18 which modulating agent is not a known modulator, substrate, or product of cGAS, optionally wherein the modulating agent is the compound of any one of claims 1-11 or the modulator of claim 12.

28. A crystalline or crystallizable composition comprising or consisting of an cGAS polypeptide.

29. A method of making or using the composition of claim 28.

30. An antagonist of cGAS for use in reducing the level of interferon in a subject, optionally wherein the antagonist is an analog, mimic or variant of an isomer of the cGAMP family of molecules.

31. A cGAS antagonist for use in altering the cytokine profile in an individual, wherein the cGAS antagonist is an analog, mimic or variant of an isomer of the cGAMP family of molecules.

32. A kit comprising one or more cGAMP compounds and optionally one or more cGAS molecules.