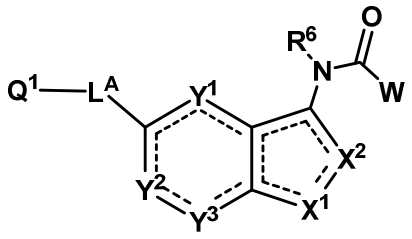
cancer) in a subject (e.g., a human). This disclosure also features compositions containing the same as well as methods of using and making the same.

An "antagonist" of STING includes compounds that, at the protein level, directly bind or modify STING such that an activity of STING is decreased, e.g., by inhibition, blocking or dampening agonist-mediated responses, altered distribution, or otherwise. STING antagonists include chemical entities, which interfere or inhibit STING signaling.

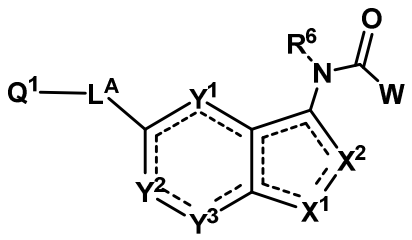
In one example, compounds of Formula (**I**), or a pharmaceutically acceptable salt thereof, are featured:



(**I**)

in which $\mathbf{Q^1}$, $\mathbf{L^A}$, $\mathbf{Y^1}$, $\mathbf{Y^2}$, $\mathbf{Y^3}$, $\mathbf{X^1}$, $\mathbf{X^2}$, $\mathbf{R^6}$, and **W** can be as defined anywhere herein.

In one aspect, the present disclosure refers to a compound of Formula **(I)**:



Formula I

or a pharmaceutically acceptable salt thereof or a tautomer thereof, wherein:

$\mathbf{L^A}$ is $-(\mathbf{L^1})_{\mathbf{a1}}\text{-}(\mathbf{L^2})_{\mathbf{a2}}\text{-}(\mathbf{L^3})_{\mathbf{a3}}\text{-}(\mathbf{L^4})_{\mathbf{a4}}\text{-}(\mathbf{L^5})_{\mathbf{a5}}\text{-}*$, wherein * represents the point of attachment to $\mathbf{Q^1}$;

a1, **a2**, **a3**, **a4**, and **a5** are each independently 0 or 1,

provided that $\mathbf{a1} + \mathbf{a2} + \mathbf{a3} + \mathbf{a4} + \mathbf{a5} \geq 1$, and

each of $\mathbf{L^1}$, $\mathbf{L^3}$, and $\mathbf{L^5}$ is independently selected from the group consisting of: -O-, -N(H)-, $-N(\mathbf{R^d})-$, $S(O)_{0\text{-}2}$, and –C(=O)-;

provided that when one or both of **a2** and **a4** is 0, then the combinations of $\mathbf{L^1}$, $\mathbf{L^3}$, and $\mathbf{L^5}$ cannot form O-O , N-O, N-N, O-S, S-S, or N-S(O)$_0$ bonds, and

each of $\mathbf{L^2}$ and $\mathbf{L^4}$ is independently selected from the group consisting of:

- straight-chain C_{1-6} alkylene, straight-chain C_{2-6} alkenylene, or straight-chain C_{2-6} alkynylene, each of which is optionally substituted with 1-6 $\mathbf{R^b}$;
- C_{3-10} cycloalkylene or C_{3-10} cycloalkenylene, each of which is optionally substituted with 1-3 $\mathbf{R^c}$ provided the C_{3-10} cycloalkylene or C_{3-10} cycloalkenylene is not directly connected to the 6-membered ring containing Y^1, Y^2, and Y^3; and
- heterocyclylene or heterocycloalkenylene, each having 4-10 ring atoms wherein 1-3 ring atoms are ring heteroatoms each independently selected from the group consisting of: N, N(H), N($\mathbf{R^d}$), O, and S(O)$_{0-2}$, wherein the heterocyclylene or heterocycloalkenylene is optionally substituted with 1-3 $\mathbf{R^c}$, provided the heterocyclylene or heterocycloalkenylene is not directly connected to the 6-membered ring containing Y^1, Y^2, and Y^3;

$\mathbf{Q^1}$ is $-\mathbf{R^g}$;

$\mathbf{Y^1}$, $\mathbf{Y^2}$, and $\mathbf{Y^3}$ are each independently selected from the group consisting of C$\mathbf{R^1}$, C(=O), N, and N$\mathbf{R^2}$;

$\mathbf{X^1}$ is selected from the group consisting of O, S, N, N$\mathbf{R^2}$, and C$\mathbf{R^1}$;

$\mathbf{X^2}$ is selected from the group consisting of O, S, N, N$\mathbf{R^4}$, and C$\mathbf{R^5}$;

each ---- is independently a single bond or a double bond, provided that the five-membered ring comprising $\mathbf{X^1}$ and $\mathbf{X^2}$ is heteroaryl, and that the six-membered ring comprising $\mathbf{Y^1}$, $\mathbf{Y^2}$, and $\mathbf{Y^3}$ is aryl or heteroaryl;

further provided that $\mathbf{L^A}$ cannot include a cyclic group directly attached to the 6-membered ring containing $\mathbf{Y^1}$, $\mathbf{Y^2}$, and $\mathbf{Y^3}$;

each occurrence of $\mathbf{R^1}$ and $\mathbf{R^5}$ is independently selected from the group consisting of: H; $\mathbf{R^c}$; $\mathbf{R^g}$; and $\mathbf{-(L^g)_{bg}-R^g}$;

each occurrence of $\mathbf{R^2}$ and $\mathbf{R^4}$ is independently selected from the group consisting of: H; $\mathbf{R^d}$; $\mathbf{R^g}$; and $\mathbf{-(L^g)_{bg}-R^g}$;

$\mathbf{R^6}$ is selected from the group consisting of: H; $\mathbf{R^d}$; and $\mathbf{R^g}$;

W is selected from the group consisting of:

- H;

- C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl, each of which is optionally substituted with 1-6 $\mathbf{R^{a2}}$, wherein one or more of the internal optionally substituted methylene group can be replaced by one or more heteroatom selected from O or S, wherein when **W** is alkenyl or alkynyl, the heteroatom is not directed connected to the sp^2 or sp carbon;
- monocyclic C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$; and
- monocyclic heterocyclyl or heterocycloalkenyl of 3-8 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$,

provided that when **W** is heterocyclyl or heterocycloalkenyl, it is attached to the C(=O)N$\mathbf{R^6}$ group via a ring carbon atom;

each occurrence of $\mathbf{R^a}$ and $\mathbf{R^{a2}}$ is independently selected from the group consisting of: –OH; -halo; –N$\mathbf{R^eR^f}$; C_{1-4} alkoxy; C_{1-4} haloalkoxy; -C(=O)O(C_{1-4} alkyl); -C(=O)(C_{1-4} alkyl); -C(=O)OH; -CON$\mathbf{R'R''}$; -$S(O)_{1-2}$N$\mathbf{R'R''}$; -$S(O)_{1-2}$(C_{1-4} alkyl); and cyano;

each occurrence of $\mathbf{R^b}$ and $\mathbf{R^c}$ is independently selected from the group consisting of: halo; cyano; C_{1-10} alkyl which is optionally substituted with 1-6 independently selected $\mathbf{R^a}$; C_{2-6} alkenyl; C_{2-6} alkynyl; C_{1-4} alkoxy; C_{1-4} haloalkoxy; -$S(O)_{1-2}$(C_{1-4} alkyl); -S(O)(=NH)(C_{1-4} alkyl); -N$\mathbf{R^eR^f}$; –OH; -$S(O)_{1-2}$N$\mathbf{R'R''}$; -C_{1-4} thioalkoxy; -NO_2; -C(=O)(C_{1-10} alkyl); -C(=O)O(C_{1-4} alkyl); -C(=O)OH; -C(=O)N$\mathbf{R'R''}$; -N$\mathbf{R'}$C(=O)(C_{1-4} alkyl) and –SF_5;

each occurrence of $\mathbf{R^d}$ is independently selected from the group consisting of: C_{1-6} alkyl optionally substituted with 1-3 independently selected $\mathbf{R^a}$; -C(O)(C_{1-4} alkyl); -C(O)O(C_{1-4} alkyl); -CON$\mathbf{R'R''}$; -$S(O)_{1-2}$N$\mathbf{R'R''}$; - $S(O)_{1-2}$(C_{1-4} alkyl); -OH; and C_{1-4} alkoxy;

each occurrence of $\mathbf{R^e}$ and $\mathbf{R^f}$ is independently selected from the group consisting of: H; C_{1-6} alkyl optionally substituted with 1-3 substituents each independently selected from the group consisting of N$\mathbf{R'R''}$, -OH, halo, C_{1-4} alkoxy, and C_{1-4} haloalkoxy; -

$C(O)(C_{1-4}$ alkyl); $-C(O)O(C_{1-4}$ alkyl); -CON**R'R''**; $-S(O)_{1-2}$N**R'R''**; $-S(O)_{1-2}(C_{1-4}$ alkyl); -OH; and C_{1-4} alkoxy;

each occurrence of $\mathbf{R^g}$ is independently selected from the group consisting of:

- C_{3-12} cycloalkyl or C_{3-12} cycloalkenyl, each of which is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, $\mathbf{R^c}$, and $\mathbf{R^h}$;
- heterocyclyl or heterocycloalkenyl of 3-12 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, $\mathbf{R^c}$, and $\mathbf{R^h}$;
- heteroaryl of 5-12 ring atoms, wherein 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, $\mathbf{R^c}$, and $\mathbf{R^h}$; and
- C_{6-10} aryl optionally substituted with 1-4 substituents independently selected from the group consisting of oxo, $\mathbf{R^c}$, and $\mathbf{R^h}$;

each occurrence of $\mathbf{R^h}$ is independently selected from the group consisting of:

- C_{3-12} cycloalkyl or C_{3-12} cycloalkenyl, each of which is optionally substituted with 1-4 $\mathbf{R^i}$;
- heterocyclyl or heterocycloalkenyl of 3-12 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with 1-4 $\mathbf{R^i}$;
- heteroaryl of 5-12 ring atoms, wherein 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0-2}$, and wherein the heteroaryl is optionally substituted with 1-4 $\mathbf{R^i}$; and
- C_{6-10} aryl optionally substituted with 1-4 $\mathbf{R^i}$;

each occurrence of $\mathbf{R^i}$ is independently selected from the group consisting of: C_{1-6} alkyl; C_{1-4} haloalkyl; C_{1-4} alkoxy; C_{1-4} haloalkoxy; and halo;

each occurrence of $\mathbf{L^g}$ is independently selected from the group consisting of: -O-, -NH-, -N$\mathbf{R^d}$, -S(O)$_{0-2}$, C(O), and C_{1-3} alkylene optionally substituted with 1-3 $\mathbf{R^a}$;

each occurrence of **bg** is independently 1, 2, or 3; and

each occurrence of **R'** and **R''** is independently selected from the group consisting of: H; -OH; and C_{1-4} alkyl.

In one example, pharmaceutical compositions are featured that include a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same) and one or more pharmaceutically acceptable excipients. In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

In one example, methods for inhibiting (e.g., antagonizing) STING activity are featured that include contacting STING with a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same). In one aspect, the present disclosure refers to a method for inhibiting STING activity, the method comprising contacting STING with a compound described herein, or a pharmaceutically acceptable salt thereof; or a pharmaceutical composition described herein. .Methods include *in vitro* methods, e.g., contacting a sample that includes one or more cells comprising STING (e.g., innate immune cells, e.g., mast cells, macrophages, dendritic cells (DCs), and natural killer cells) with the chemical entity. Methods can also include *in vivo* methods; e.g., administering the chemical entity to a subject (e.g., a human) having a disease in which increased (e.g., excessive) STING signaling contributes to the pathology and/or symptoms and/or progression of the disease.

In one example, methods of treating a condition, disease or disorder ameliorated by antagonizing STING are featured, e.g., treating a condition, disease or disorder in which increased (e.g., excessive) STING activation (e.g., STING signaling) contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g., cancer) in a subject (e.g., a human). The methods include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In another example, methods of treating cancer are featured that include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In a further example, methods of treating other STING-associated conditions are featured, e.g., type I interferonopathies (e.g., STING-associated vasculopathywith onset in infancy (SAVI)), Aicardi-Goutières Syndrome (AGS), genetic forms of lupus, and inflammation-associated disorders such as systemic lupus erythematosus, and rheumatoid arthritis. The methods include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In another example, methods of suppressing STING-dependent type I interferon production in a subject in need thereof are featured that include administering to the subject an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In a further example, methods of treating a disease in which increased (e.g., excessive) STING activation (e.g., STING signaling) contributes to the pathology and/or symptoms and/or progression of the disease are featured. The methods include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same). In one aspect, the present disclosure refers to a method of treatment of disease, disorder, or condition associated with STING, such as a disease, disorder, or condition, in which increased STING signaling, such as excessive STING signaling, contributes to the pathology and/or symptoms and/or progression of the disease, such as cancer, comprising administering to a subject in need of such treatment an effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described herein.

In another example, methods of treatment are featured that include administering an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same) to a subject; wherein the subject has (or is predisposed to have) a disease in which increased (e.g., excessive) STING activation (e.g., STING signaling) contributes to the pathology and/or symptoms and/or progression of the disease.

In a further example, methods of treatment that include administering to a subject a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same), wherein the chemical entity is administered in an amount effective to treat a disease in which increased (e.g., excessive) STING activation (e.g., STING signaling) contributes to the pathology and/or symptoms and/or progression of the disease, thereby treating the disease.

In one aspect, the present disclosure refers to a compound described herein or a pharmaceutically acceptable salt or tautomer thereof, or a pharmaceutical composition described herein, for use as a medicament.

In another example, there is provided is a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein, for use in the treatment of a disease, condition or disorder modulated by STING inhibition. In one aspect, the present disclosure refers to a compound described herein or a pharmaceutically acceptable salt or tautomer thereof, or a pharmaceutical composition described herein, for use in the treatment of a disease, condition or disorder modulated by STING inhibition.

In another example, there is provided a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for use in the treatment of a condition, disease or disorder associated with increased (e.g., excessive) STING activation.

In another example, there is provided a compound, or a pharmaceutically acceptable salt or tautomer thereof, described herein for use in the treatment of cancer.

In another example, there is provided a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for use in the treatment of cancer selected from the group consisting of melanoma, cervical cancer, breast cancer, ovarian cancer, prostate cancer, testicular cancer, urothelial carcinoma, bladder cancer, non-small cell lung cancer, small cell lung cancer, sarcoma, colorectal adenocarcinoma, gastrointestinal stromal tumors, gastroesophageal carcinoma, colorectal cancer, pancreatic cancer, kidney cancer, hepatocellular cancer, malignant mesothelioma, leukemia, lymphoma, myelodysplasia syndrome, multiple myeloma, transitional cell carcinoma, neuroblastoma, plasma cell neoplasms, Wilm's tumor, or hepatocellular carcinoma.

In another example, there is provided a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for use in the treatment of type I interferonopathies.

In another example, there is provided a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for use in the treatment of type I interferonopathies selected from STING-associated vasculopathywith onset in infancy (SAVI)), Aicardi-Goutières Syndrome (AGS), genetic forms of lupus, and inflammation-associated disorders such as systemic lupus erythematosus, and rheumatoid arthritis.

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein in the manufacture of a medicament for the treatment of a condition, disease or disorder associated with increased (e.g., excessive) STING activation.

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein in the manufacture of a medicament for the treatment of cancer.

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein in the manufacture of a medicament for the treatment of cancer selected from the group consisting of melanoma, cervical cancer, breast cancer, ovarian cancer, prostate cancer, testicular cancer, urothelial carcinoma, bladder cancer, non-small cell lung cancer, small cell lung cancer, sarcoma, colorectal adenocarcinoma, gastrointestinal stromal tumors, gastroesophageal carcinoma, colorectal cancer, pancreatic cancer, kidney cancer, hepatocellular cancer, malignant mesothelioma, leukemia, lymphoma, myelodysplasia syndrome, multiple myeloma, transitional cell carcinoma, neuroblastoma, plasma cell neoplasms, Wilm's tumor, or hepatocellular carcinoma.

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein in the manufacture of a medicament for the treatment of type I interferonopathies.

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for use in the manufacture of a medicament for the treatment of type I interferonopathies selected from STING-associated

vasculopathywith onset in infancy (SAVI)), Aicardi-Goutières Syndrome (AGS), genetic forms of lupus, and inflammation-associated disorders such as systemic lupus erythematosus, and rheumatoid arthritis.

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein, for the treatment of a disease, condition or disorder modulated by STING inhibition.

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for the treatment of a condition, disease or disorder associated with increased (e.g., excessive) STING activation.

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for the treatment of cancer.

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for the treatment of cancer selected from the group consisting of melanoma, cervical cancer, breast cancer, ovarian cancer, prostate cancer, testicular cancer, urothelial carcinoma, bladder cancer, non-small cell lung cancer, small cell lung cancer, sarcoma, colorectal adenocarcinoma, gastrointestinal stromal tumors, gastroesophageal carcinoma, colorectal cancer, pancreatic cancer, kidney cancer, hepatocellular cancer, malignant mesothelioma, leukemia, lymphoma, myelodysplasia syndrome, multiple myeloma, transitional cell carcinoma, neuroblastoma, plasma cell neoplasms, Wilm's tumor, or hepatocellular carcinoma.

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for the treatment of type I interferonopathies.

In another example, there is provided the use of a compound, or a pharmaceutically acceptable salt or tautomer thereof, as described herein for the treatment of type I interferonopathies selected from STING-associated vasculopathy with onset in infancy (SAVI)), Aicardi-Goutières Syndrome (AGS), genetic forms of lupus, and inflammation-associated disorders such as systemic lupus erythematosus, and rheumatoid arthritis.

Examples can include one or more of the following features.

The chemical entity can be administered in combination with one or more additional therapeutic agents and/or regimens. For examples, methods can further include administering one or more (e.g., two, three, four, five, six, or more) additional agents. In one aspect, the present disclosure refers to a combination comprising a compound described herein or a pharmaceutically acceptable salt or tautomer thereof, and one or more therapeutically active agents.

The chemical entity can be administered in combination with one or more additional therapeutic agents and/or regimens that are useful for treating other STING-associated conditions, e.g., type I interferonopathies (e.g., STING-associated vasculopathywith onset in infancy (SAVI)), Aicardi-Goutières Syndrome (AGS), genetic forms of lupus, and inflammation-associated disorders such as systemic lupus erythematosus, and rheumatoid arthritis.

The chemical entity can be administered in combination with one or more additional cancer therapies (e.g., surgery, radiotherapy, chemotherapy, toxin therapy, immunotherapy, cryotherapy or gene therapy, or a combination thereof; e.g., chemotherapy that includes administering one or more (e.g., two, three, four, five, six, or more) additional chemotherapeutic agents. Non-limiting examples of additional chemotherapeutic agents is selected from an alkylating agent (e.g., cisplatin, carboplatin, mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide and/or oxaliplatin); an anti-metabolite (e.g.,azathioprine and/or mercaptopurine); a terpenoid (e.g., a vinca alkaloid and/or a taxane; e.g., Vincristine, Vinblastine, Vinorelbine and/or Vindesine Taxol, Pacllitaxel and/or Docetaxel); a topoisomerase (e.g., a type I topoisomerase and/or a type 2 topoisomerase; e.g., camptothecins, such as irinotecan and/or topotecan;. amsacrine, etoposide, etoposide phosphate and/or teniposide); a cytotoxic antibiotic (e.g., actinomycin, anthracyclines, doxorubicin, daunorubicin, valrubicin, idarubicin, epirubicin, bleomycin, plicamycin and/or mitomycin); a hormone (e.g., a lutenizing hormone releasing hormone agonist; e.g., leuprolidine, goserelin, triptorelin, histrelin, bicalutamide, flutamide and/or nilutamide); an antibody (e.g., Abciximab, Adalimumab, Alemtuzumab, Atlizumab, Basiliximab, Belimumab, Bevacizumab, Bretuximab vedotin, Canakinumab, Cetuximab, Ceertolizumab pegol, Daclizumab, Denosumab, Eculizumab, Efalizumab, Gemtuzumab, Golimumab, Golimumab, Ibritumomab tiuxetan, Infliximab, Ipilimumab, Muromonab-CD3, Natalizumab, Ofatumumab, Omalizumab, Palivizumab, Panitumuab, Ranibizumab, Rituximab, Tocilizumab, Tositumomab and/or Trastuzumab); an anti-angiogenic agent; a cytokine; a thrombotic agent; a growth inhibitory agent; an anti-

helminthic agent; and an immune checkpoint inhibitor that targets an immune checkpoint receptor selected from the group consisting of CTLA-4, PD-1, PD-L1, PD-1 – PD-L1, PD-1 – PD-L2, interleukin-2 (IL-2), indoleamine 2,3-dioxygenase (IDO), IL-10, transforming growth factor-β (TGFβ), T cell immunoglobulin and mucin 3 (TIM3 or HAVCR2), Galectin 9 – TIM3, Phosphatidylserine – TIM3, lymphocyte activation gene 3 protein (LAG3), MHC class II – LAG3, 4-1BB–4-1BB ligand, OX40–OX40 ligand, GITR, GITR ligand – GITR, CD27, CD70-CD27, TNFRSF25, TNFRSF25–TL1A, CD40L, CD40–CD40 ligand, HVEM–LIGHT–LTA, HVEM, HVEM – BTLA, HVEM – CD160, HVEM – LIGHT, HVEM–BTLA–CD160, CD80, CD80 – PDL-1, PDL2 – CD80, CD244, CD48 – CD244, CD244, ICOS, ICOS–ICOS ligand, B7-H3, B7-H4, VISTA, TMIGD2, HHLA2–TMIGD2, Butyrophilins, including BTNL2, Siglec family, TIGIT and PVR family members, KIRs, ILTs and LIRs, NKG2D and NKG2A, MICA and MICB, CD244, CD28, CD86 – CD28, CD86 – CTLA, CD80 – CD28, CD39, CD73 Adenosine–CD39–CD73, CXCR4–CXCL12, Phosphatidylserine, TIM3, Phosphatidylserine – TIM3, SIRPA–CD47, VEGF, Neuropilin, CD160, CD30, and CD155 (e.g., CTLA-4 or PD1 or PD-L1).

The subject can have cancer; e.g., the subject has undergone and/or is undergoing and/or will undergo one or more cancer therapies.

Non-limiting examples of cancer include melanoma, cervical cancer, breast cancer, ovarian cancer, prostate cancer, testicular cancer, urothelial carcinoma, bladder cancer, non-small cell lung cancer, small cell lung cancer, sarcoma, colorectal adenocarcinoma, gastrointestinal stromal tumors, gastroesophageal carcinoma, colorectal cancer, pancreatic cancer, kidney cancer, hepatocellular cancer, malignant mesothelioma, leukemia, lymphoma, myelodysplasia syndrome, multiple myeloma, transitional cell carcinoma, neuroblastoma, plasma cell neoplasms, Wilm's tumor, or hepatocellular carcinoma. In certain examples, the cancer can be a refractory cancer.

The chemical entity can be administered intratumorally.

The methods can further include identifying the subject.

Other examples include those described in the Detailed Description and/or in the claims.

Additional Definitions

To facilitate understanding of the disclosure set forth herein, a number of additional terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well-known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Each of the patents, applications, published applications, and other publications that are mentioned throughout the specification and the attached appendices are incorporated herein by reference in their entireties.

As used herein, the term "STING" is meant to include, without limitation, nucleic acids, polynucleotides, oligonucleotides, sense and antisense polynucleotide strands, complementary sequences, peptides, polypeptides, proteins, homologous and/or orthologous STING molecules, isoforms, precursors, mutants, variants, derivatives, splice variants, alleles, different species, and active fragments thereof.

The term "acceptable" with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

"API" refers to an active pharmaceutical ingredient.

The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of a chemical entity being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case is determined using any suitable technique, such as a dose escalation study.

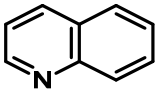
The term "excipient" or "pharmaceutically acceptable excipient" means a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, carrier, solvent, or encapsulating material. In one example, each component is "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. *See, e.g., Remington: The Science and Practice of Pharmacy, 21st ed.*; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients, 6th ed.*; Rowe *et al.*, Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives, 3rd ed.*; Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation, 2nd ed.*; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

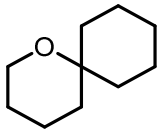
The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In certain instances, pharmaceutically acceptable salts are obtained by reacting a compound described herein, with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. In some instances, pharmaceutically acceptable salts are obtained by reacting a compound having acidic group described herein with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, *N*-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like, or by other methods previously determined. The pharmacologically acceptable salt s not specifically limited as far as it can be used in medicaments. Examples of a salt that the compounds described hereinform with a base include the following: salts thereof with inorganic bases such as sodium, potassium, magnesium, calcium, and aluminum; salts thereof with organic bases such as methylamine, ethylamine and ethanolamine; salts thereof with basic amino acids

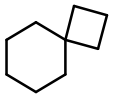
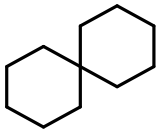
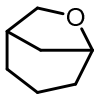
can either be unsubstituted or substituted with one or more substituents. Examples of heteroaryl include thienyl, pyridinyl, furyl, oxazolyl, oxadiazolyl, pyrrolyl, imidazolyl, triazolyl, thiodiazolyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thiazolyl benzothienyl, benzoxadiazolyl, benzofuranyl, benzimidazolyl, benzotriazolyl, cinnolinyl, indazolyl, indolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, purinyl, thienopyridinyl, pyrido[2,3-*d*]pyrimidinyl, pyrrolo[2,3-*b*]pyridinyl, quinazolinyl, quinolinyl, thieno[2,3-*c*]pyridinyl, pyrazolo[3,4-*b*]pyridinyl, pyrazolo[3,4-*c*]pyridinyl, pyrazolo[4,3-*c*]pyridinyl, pyrazolo[4,3-*b*]pyridinyl, tetrazolyl, chromanyl, 2,3-dihydrobenzo[*b*][1,4]dioxinyl, benzo[*d*][1,3]dioxolyl, 2,3-dihydrobenzofuranyl, tetrahydroquinolinyl, 2,3-dihydrobenzo[*b*][1,4]oxathiinyl, isoindolinyl, and others. In some examples, the heteroaryl is selected from thienyl, pyridinyl, furyl, pyrazolyl, imidazolyl, isoindolinyl, pyranyl, pyrazinyl, and pyrimidinyl.

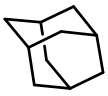
The term "heterocyclyl" refers to a mon-, bi-, tri-, or polycyclic saturated ring system with 3-16 ring atoms (e.g., 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system) having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic or polycyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2 or 3 atoms of each ring may be substituted by a substituent. Examples of heterocyclyl groups include piperazinyl, pyrrolidinyl, dioxanyl, morpholinyl, tetrahydrofuranyl, and the like. Heterocyclyl may include multiple fused and bridged rings. Non-limiting examples of fused/bridged heteorocyclyl includes: 2-azabicyclo[1.1.0]butanyl, 2-azabicyclo[2.1.0]pentanyl, 2-azabicyclo[1.1.1]pentanyl, 3-azabicyclo[3.1.0]hexanyl, 5-azabicyclo[2.1.1]hexanyl, 3-azabicyclo[3.2.0]heptanyl, octahydrocyclopenta[c]pyrrolyl, 3-azabicyclo[4.1.0]heptanyl, 7-azabicyclo[2.2.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 7-azabicyclo[4.2.0]octanyl, 2-azabicyclo[2.2.2]octanyl, 3-azabicyclo[3.2.1]octanyl, 2-oxabicyclo[1.1.0]butanyl, 2-oxabicyclo[2.1.0]pentanyl, 2-oxabicyclo[1.1.1]pentanyl, 3-oxabicyclo[3.1.0]hexanyl, 5-oxabicyclo[2.1.1]hexanyl, 3-oxabicyclo[3.2.0]heptanyl, 3-oxabicyclo[4.1.0]heptanyl, 7-oxabicyclo[2.2.1]heptanyl, 6-oxabicyclo[3.1.1]heptanyl, 7-oxabicyclo[4.2.0]octanyl, 2-oxabicyclo[2.2.2]octanyl, 3-oxabicyclo[3.2.1]octanyl, and the like. Heterocyclyl also

As used herein, when a ring is described as being "partially unsaturated", it means said ring has one or more additional degrees of unsaturation (in addition to the degree of unsaturation attributed to the ring itself; e.g., one or more double or tirple bonds between constituent ring atoms), provided that the ring is not aromatic. Examples of such rings include: cyclopentene, cyclohexene, cycloheptene, dihydropyridine, tetrahydropyridine, dihydropyrrole, dihydrofuran, dihydrothiophene, and the like.

For the avoidance of doubt, and unless otherwise specified, for rings and cyclic groups (e.g., aryl, heteroaryl, heterocyclyl, heterocycloalkenyl, cycloalkenyl, cycloalkyl, and the like described herein) containing a sufficient number of ring atoms to form bicyclic or higher order ring systems (e.g., tricyclic, polycyclic ring systems), it is understood that such rings and cyclic groups encompass those having fused rings, including those in which the points of fusion are located (i) on adjacent ring atoms (e.g., [x.x.0] ring systems, in which 0 represents a zero atom bridge (e.g., 

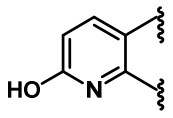
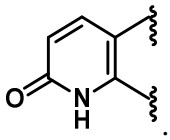
)); (ii) a single ring atom (spiro-fused ring systems) (e.g., 

, 
, or 
), or (iii) a contiguous array of ring atoms (bridged ring systems having all bridge lengths > 0) (e.g., 
, 

, or 
).

In addition, atoms making up the compounds of the present examples are intended to include all isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ^{13}C and ^{14}C.

In addition, the compounds generically or specifically disclosed herein are intended to include all tautomeric forms. Thus, by way of example, a compound containing the

moiety:  encompasses the tautomeric form containing the moiety: . Similarly, a pyridinyl or pyrimidinyl moiety that is described to be optionally substituted with hydroxyl encompasses pyridone or pyrimidone tautomeric forms.

As used herein, the phrase "optionally substituted" when used in conjunction with a structural moiety (e.g., alkyl) is intended to encompass both the unsubstituted structural moiety (i.e., none of the substitutable hydrogen atoms are replaced with one or more non-hydrogen substituents) and substituted structural moieties substituted with the indicated range of non-hydrogen substituents. For example, " C_1-C_4 alkyl optionally substituted with 1-4 $\mathbf{R^a}$" is intended to encompass both unsubstituted C_1-C_4 alkyl and C_1-C_4 alkyl substituted with 1-4 $\mathbf{R^a}$.

The details of one or more examples of the disclosure are set forth in the accompanying drawings and the description below. Other features and advantages of the disclosure will be apparent from the description and drawings, and from the claims.

DETAILED DESCRIPTION

This disclosure features chemical entities (e.g., a compound or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination of the compound) that inhibit (e.g., antagonize) Stimulator of Interferon Genes (STING). Said chemical entities are useful, e.g., for treating a condition, disease or disorder in which increased (e.g., excessive) STING activation (e.g., STING signaling) contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g., cancer) in a subject (e.g., a human). This disclosure also features compositions containing the same as well as methods of using and making the same.

Formula I Compounds

In one aspect, the disclosure features a compound of Formula **(I)**: