



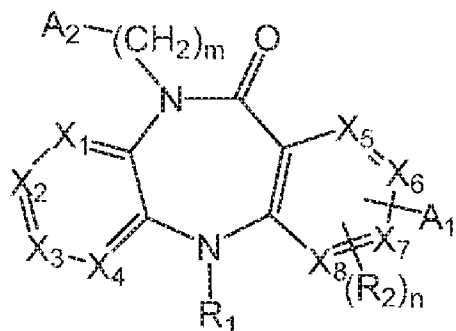
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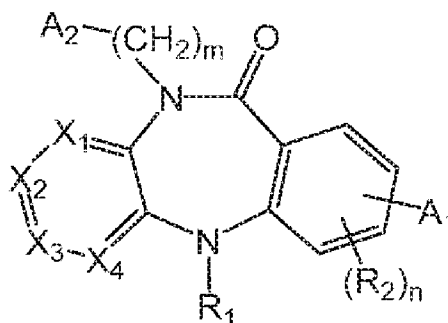
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(71) Demandeur/Applicant:
DANA-FARBER CANCER INSTITUTE, INC., US
(72) Inventeurs/Inventors:
GRAY, NATHANAEL S., US;
DE CLERCQ, DRIES, US;
JANG, JAEBONG, US;
JANNE, PASI, US;
TO, CIRIC, US;
ECK, MICHAEL, US;
PARK, EUNYOUNG, US;
HEPPNER, DAVID, US
(74) Agent: SMART & BIGGAR LLP

(54) Titre : INHIBITEURS D'EGFR ET LEURS PROCEDES D'UTILISATION
(54) Title: INHIBITORS OF EGFR AND METHODS OF USE THEREOF



(Ia) or



(Ib),

(57) **Abrégé/Abstract:**

The application relates to a compound having Formula Ia or Ib: (Ia) or (Ib), or a pharmaceutically acceptable salt, hydrate, or solvate thereof, which modulates the activity of EGFR, a pharmaceutical composition comprising the compound, and a method of treating or preventing a disease in which EGFR plays a role.

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(71) Applicant: **DANA-FARBER CANCER INSTITUTE, INC.** [US/US]; 450 BROOKLINE AVENUE, Boston, Massachusetts 02215 (US).

(72) Inventors: **GRAY, Nathanael S.**; 26 Greenview Avenue, Boston, Massachusetts 02130 (US). **DE CLERCQ, Dries**; 1575 Tremont Street, Apt. 901, Boston, Massachusetts 02120 (US). **JANG, Jaebong**; 1 Emerson Place, 11D, Boston, Massachusetts 02114 (US). **JANNE, Pasi**; 9 Savoy Road, Needham, Massachusetts 02492 (US). **TO, Ciric**; 450 Brookline Avenue, Boston, Massachusetts 02215 (US). **ECK, Michael**; 450 Brookline Avenue, Boston, Massachusetts 02215 (US). **PARK, Eunyoung**; 450 Brookline Avenue, Boston, Massachusetts 02215 (US). **HEPPNER, David**; 450 Brookline Avenue, Boston, Massachusetts 02215 (US).

(74) Agent: **COUGHLIN, Sean, M.** et al.; Lathrop Gage LLP, 28 State Street, Boston, MA 02109 (US).

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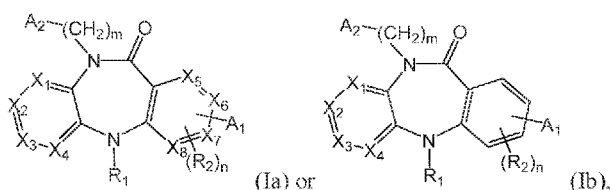
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(57) Abstract: The application relates to a compound having Formula Ia or Ib: (Ia) or (Ib), or a pharmaceutically acceptable salt, hydrate, or solvate thereof, which modulates the activity of EGFR, a pharmaceutical composition comprising the compound, and a method of treating or preventing a disease in which EGFR plays a role.



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INHIBITORS OF EGFR AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to, and the benefit of, U.S. Provisional Application Nos. 62/632,819, filed on February 20, 2018 and 62/744,086, filed on October 10, 2018, the entire
5 contents of each of which are incorporated herein by reference.

GOVERNMENT SUPPORT

The work described herein was supported by the National Institutes of Health, NIH Grant No. R01 CA201049. The U.S. Government has certain rights to the claimed invention.

10

BACKGROUND

The epidermal growth factor receptor (EGFR, Erb-B1) belongs to a family of proteins involved in cell proliferation. EGFR overexpression is present in at least 70% of human cancers, such as non-small cell lung carcinoma (NSCLC), breast cancer, glioma, and prostate cancer. The
15 EGFR-TK is therefore widely recognized as a target for the design and development of therapies that can specifically bind and inhibit tyrosine kinase activity and its signal transduction pathway in cancer cells, and thus can serve as diagnostic or therapeutic agents.

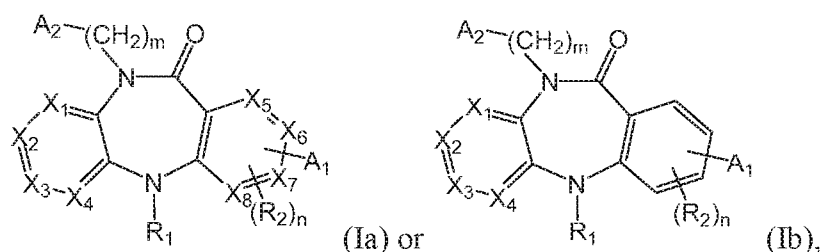
EGFR tyrosine kinase inhibitors (TKIs) are effective clinical therapies for *EGFR* mutant advanced non-small cell lung cancer (NSCLC) patients. However, the vast majority of patients
20 develop disease progression following successful treatment with an EGFR TKI. The most common mechanism of acquired resistance is a secondary mutation T790M, which leads to an increase in ATP affinity, thus making it more difficult for reversible EGFR TKIs gefitinib and erlotinib to bind the EGFR TKI domain. Covalent EGFR inhibitors have emerged as strategies to inhibit *EGFR* T790M containing cancers. Afatinib is a potent inhibitor of both mutant and
25 wild type (WT) EGFR, but is only effective in EGFR TKI naive *EGFR* mutant cancers, has a RR of < 10% in patients with NSCLC resistant to gefitinib or erlotinib, and suffers from toxicities from inhibition of WT EGFR. Other irreversible EGFR inhibitors, such as WZ4002, CO-1686, and AZD9291, overcome many of the limitations of afatinib. They are not only more potent on EGFR T790M, but also selectively inhibit mutant over WT EGFR.

However, all current EGFR TKIs target the ATP binding site, and are rendered impotent by the C797S mutation arising in treated patients. Cetuximab, an anti-EGFR antibody that blocks receptor dimerization is not effective in EGFR-mutant NSCLC, because mutational activation of the kinase is effectively “downstream” of receptor dimerization. Hence, alternative strategies to inhibit EGFR are needed. Thus, there is a need for novel and potent small molecule EGFR inhibitors with alternative mechanisms of action targeting mutant EGFR. The present application addresses the need.

SUMMARY

The present application relates to dibenzodiazepinone allosteric inhibitors of EGFR that are capable of inhibiting drug resistant forms of EGFR. The application features methods of treating or preventing a disease in which EGFR plays a role in a subject in need thereof by administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof. The methods of the application can be used to treat or prevent diseases in which EGFR plays a role by inhibiting the kinase activity of EGFR.

A first aspect of the application relates to a compound of Formula Ia or Ib:



or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein each of the variables in Formula Ia or Ib is described herein in detail below.

Another aspect of the present application relates to a pharmaceutical composition comprising a compound of Formula Ia or Ib, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and a pharmaceutically acceptable carrier. In another aspect, the pharmaceutical composition further comprises a second agent that prevents EGFR dimer formation, and a pharmaceutically acceptable carrier.

Another aspect of the present application relates to a method of inhibiting a kinase (*e.g.*, EGFR). The method comprises administering to a subject in need thereof an effective amount of

a compound of Formula Ia or Ib, or a pharmaceutically acceptable salt, hydrate, or solvate thereof. In one aspect, the method further comprises administering to the subject a second agent that prevents EGFR dimer formation.

Another aspect of the present application relates to a method of treating or preventing a disease (*e.g.*, a disease in which EGFR plays a role). The method comprises administering to a subject in need thereof an effective amount of a compound of Formula Ia or Ib, or a pharmaceutically acceptable salt, hydrate, or solvate thereof. In another aspect, the method further comprises administering to the subject a second agent that prevents EGFR dimer formation.

Another aspect of the present application relates to a method of treating or preventing a disease resistant to an EGFR targeted therapy, such as a therapy with gefitinib, erlotinib, afatinib, AZD9291, CO-1686, or WZ4002. The method comprises administering to a subject in need thereof an effective amount of a compound of Formula Ia or Ib, or a pharmaceutically acceptable salt, hydrate, or solvate thereof. In another aspect, the method further comprises administering to the subject a second agent that prevents EGFR dimer formation.

Another aspect of the present application relates to a method of treating or preventing cancer, wherein the cell of the cancer comprises an activated EGFR. The method comprises administering to a subject in need thereof an effective amount of a compound of Formula Ia or Ib, or a pharmaceutically acceptable salt, hydrate, or solvate thereof. In another aspect, the method further comprises administering to the subject a second agent that prevents EGFR dimer formation.

Another aspect of the present application relates to a method of treating or preventing cancer in a subject, wherein the subject is identified as being in need of EGFR inhibition for the treatment or prevention of cancer. The method comprises administering to the subject an effective amount of a compound of Formula Ia or Ib, or a pharmaceutically acceptable salt, hydrate, or solvate thereof. In another aspect, the method further comprises administering to the subject a second agent that prevents EGFR dimer formation.

Another aspect of the present application relates to a method of treating or preventing cancer, wherein the cell of the cancer comprises an activated ERBB2. The method comprises administering to a subject in need thereof an effective amount of a compound of Formula Ia or Ib, or a pharmaceutically acceptable salt, hydrate, or solvate thereof. In another aspect, the

method further comprises administering to the subject a second agent that prevents ERBB2 dimer formation.

Another aspect of the present application relates to a method of treating or preventing cancer in a subject, wherein the subject is identified as being in need of ERBB2 inhibition for the treatment or prevention of cancer. The method comprises administering to the subject an effective amount of a compound of Formula Ia or Ib, or a pharmaceutically acceptable salt, hydrate, or solvate thereof. In another aspect, the method further comprises administering to the subject a second agent that prevents ERBB2 dimer formation.

Another aspect of the present application relates to a kit comprising a compound of Formula Ia or Ib, or a pharmaceutically acceptable salt, hydrate, or solvate thereof. In another aspect, the kit further comprises a second agent that prevents EGFR dimer formation.

Another aspect of the present application relates to a compound of Formula Ia or Ib, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for use in the manufacture of a medicament for

inhibiting a kinase (*e.g.*, EGFR) in a subject in need thereof,
treating or preventing a disease (*e.g.*, a disease in which EGFR plays a role) in a subject in need thereof,

treating or preventing a disease resistant to an EGFR targeted therapy, such as a therapy with gefitinib, erlotinib, afatinib, AZD9291, CO-1686, or WZ4002, in a subject in need thereof,

treating or preventing cancer in a subject in need thereof, wherein the cell of the cancer comprises an activated EGFR or an activated ERBB2, or

treating or preventing cancer in a subject, wherein the subject is identified as being in need of EGFR inhibition or ERBB2 inhibition for the treatment or prevention of cancer.

In another aspect, the present application relates to a compound of Formula Ia or Ib, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and a second agent that prevents EGFR dimer formation, for use in the manufacture of a medicament for

inhibiting a kinase (*e.g.*, EGFR) in a subject in need thereof,
treating or preventing a disease (*e.g.*, a disease in which EGFR plays a role) in a subject in need thereof,

treating or preventing a disease resistant to an EGFR targeted therapy, such as a therapy with gefitinib, erlotinib, afatinib, AZD9291, CO-1686, or WZ4002, in a subject in need thereof,

treating or preventing cancer in a subject in need thereof, wherein the cell of the cancer comprises an activated EGFR or an activated ERBB2, or

treating or preventing cancer in a subject, wherein the subject is identified as being in need of EGFR inhibition or ERBB2 inhibition for the treatment or prevention of cancer.

5 Another aspect of the present application relates to a compound of Formula Ia or Ib, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for

inhibiting a kinase (*e.g.*, EGFR) in a subject in need thereof,

treating or preventing a disease (*e.g.*, a disease in which EGFR plays a role) in a subject in need thereof,

10 treating or preventing a disease resistant to an EGFR targeted therapy, such as a therapy with gefitinib, erlotinib, afatinib, AZD9291, CO-1686, or WZ4002, in a subject in need thereof,

treating or preventing cancer in a subject in need thereof, wherein the cell of the cancer comprises an activated EGFR or an activated ERBB2, or

15 treating or preventing cancer in a subject, wherein the subject is identified as being in need of EGFR inhibition or ERBB2 inhibition for the treatment or prevention of cancer.

Another aspect of the present application relates to a compound of Formula Ia or Ib, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and a second agent that prevents EGFR dimer formation, for

inhibiting a kinase (*e.g.*, EGFR) in a subject in need thereof,

20 treating or preventing a disease (*e.g.*, a disease in which EGFR plays a role) in a subject in need thereof,

treating or preventing a disease resistant to an EGFR targeted therapy, such as a therapy with gefitinib, erlotinib, afatinib, AZD9291, CO-1686, or WZ4002, in a subject in need thereof,

25 treating or preventing cancer in a subject in need thereof, wherein the cell of the cancer comprises an activated EGFR or an activated ERBB2, or

treating or preventing cancer in a subject, wherein the subject is identified as being in need of EGFR inhibition or ERBB2 inhibition for the treatment or prevention of cancer.

Another aspect of the present application relates to use of a compound of Formula Ia or Ib, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, in the manufacture of a
30 medicament for

inhibiting a kinase (*e.g.*, EGFR) in a subject in need thereof,

treating or preventing a disease (*e.g.*, a disease in which EGFR plays a role) in a subject in need thereof,

treating or preventing a disease resistant to an EGFR targeted therapy, such as a therapy with gefitinib, erlotinib, afatinib, AZD9291, CO-1686, or WZ4002, in a subject in need thereof,

5 treating or preventing cancer in a subject in need thereof, wherein the cell of the cancer comprises an activated EGFR or an activated ERBB2, or

treating or preventing cancer in a subject, wherein the subject is identified as being in need of EGFR inhibition or ERBB2 inhibition for the treatment or prevention of cancer.

10 In another aspect, the present application relates to use of a compound of Formula Ia or Ib, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and a second agent that prevents EGFR dimer formation, in the manufacture of a medicament for

inhibiting a kinase (*e.g.*, EGFR) in a subject in need thereof,

treating or preventing a disease (*e.g.*, a disease in which EGFR plays a role) in a subject in need thereof,

15 treating or preventing a disease resistant to an EGFR targeted therapy, such as a therapy with gefitinib, erlotinib, afatinib, AZD9291, CO-1686, or WZ4002, in a subject in need thereof,

treating or preventing cancer in a subject in need thereof, wherein the cell of the cancer comprises an activated EGFR or an activated ERBB2, or

20 treating or preventing cancer in a subject, wherein the subject is identified as being in need of EGFR inhibition or ERBB2 inhibition for the treatment or prevention of cancer.

Another aspect of the present application relates to use of a compound of Formula Ia or Ib, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, in

inhibiting a kinase (*e.g.*, EGFR) in a subject in need thereof,

25 treating or preventing a disease (*e.g.*, a disease in which EGFR plays a role) in a subject in need thereof,

treating or preventing a disease resistant to an EGFR targeted therapy, such as a therapy with gefitinib, erlotinib, afatinib, AZD9291, CO-1686, or WZ4002, in a subject in need thereof,

treating or preventing cancer in a subject in need thereof, wherein the cell of the cancer comprises an activated EGFR or an activated ERBB2, or

30 treating or preventing cancer in a subject, wherein the subject is identified as being in need of EGFR inhibition or ERBB2 inhibition for the treatment or prevention of cancer.

Another aspect of the present application relates to use of a compound of Formula Ia or Ib, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and a second agent that prevents EGFR dimer formation, in

inhibiting a kinase (*e.g.*, EGFR) in a subject in need thereof,

5 treating or preventing a disease (*e.g.*, a disease in which EGFR plays a role) in a subject in need thereof,

treating or preventing a disease resistant to an EGFR targeted therapy, such as a therapy with gefitinib, erlotinib, afatinib, AZD9291, CO-1686, or WZ4002, in a subject in need thereof,

10 treating or preventing cancer in a subject in need thereof, wherein the cell of the cancer comprises an activated EGFR or an activated ERBB2, or

treating or preventing cancer in a subject, wherein the subject is identified as being in need of EGFR inhibition or ERBB2 inhibition for the treatment or prevention of cancer.

The present application provides inhibitors of EGFR, such as EGFR containing one or more mutations, that are therapeutic agents in the treatment or prevention of diseases such as
15 cancer and metastasis.

The present application further provides compounds and compositions with an improved efficacy and/or safety profile relative to known EGFR inhibitors. The present application also provides agents with novel mechanisms of action toward EGFR kinases in the treatment or prevention of various types of diseases including cancer and metastasis.

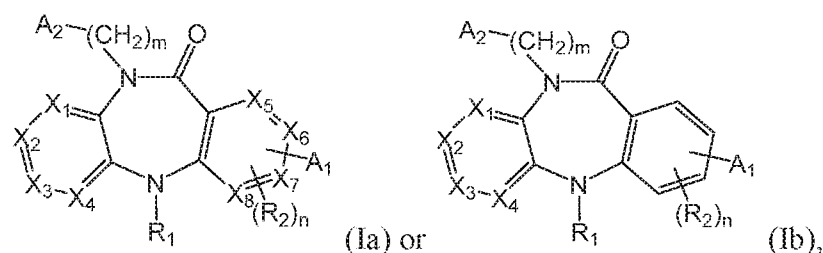
20 The details of the application are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present application, illustrative methods and materials are now described. Other features, objects, and advantages of the application will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms
25 also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this application belongs. The contents of all references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated herein in
30 their entireties by reference.

DETAILED DESCRIPTION

Compounds of the Application

The compounds of the present application are dibenzodiazepinone-based compounds that modulate EGFR allosterically. In one aspect, the present application relates to a compound of

5 Formula Ia or Ib:



or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein:

A₁ is phenyl or heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl or heteroaryl is substituted with one or more R_{A1};

10 each R_{A1} is independently C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, halogen, CN, phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently
15 selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, and halogen, or

two R_{A1}, together with the adjacent atoms to which they are attached, form phenyl, C₃-C₆ cycloalkyl, or a 5- or 6-membered heteroaryl or heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is
20 optionally substituted with one or more substituents independently selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, and halogen;

n is 0, 1, 2, or 3;

each R₂ is independently C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, halogen, or CN;

25 each m is independently 0, 1, 2, or 3;

A₂ is phenyl or heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl or heteroaryl is optionally substituted with one or more R_{A2};

each R_{A2} is independently C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, halogen, CN, phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, and halogen,

or

two R_{A2}, together with the adjacent atoms to which they are attached, form phenyl, C₃-C₆ cycloalkyl, or a 5- or 6-membered heteroaryl or heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, and halogen;

R₁ is H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, halogen, CN, or (CH₂)_m-A₃;

A₃ is phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, halogen, and W;

X₁, X₂, X₃, and X₄ are each independently N or CR_X, provided that at least two of X₁, X₂, X₃, and X₄ are CR_X;

X₅, X₆, X₇, and X₈ are each independently N or CR_X;

each R_X is independently W, H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, halogen, CN, phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents

independently selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, and halogen;

R₃ is H or C₁-C₄ alkyl;

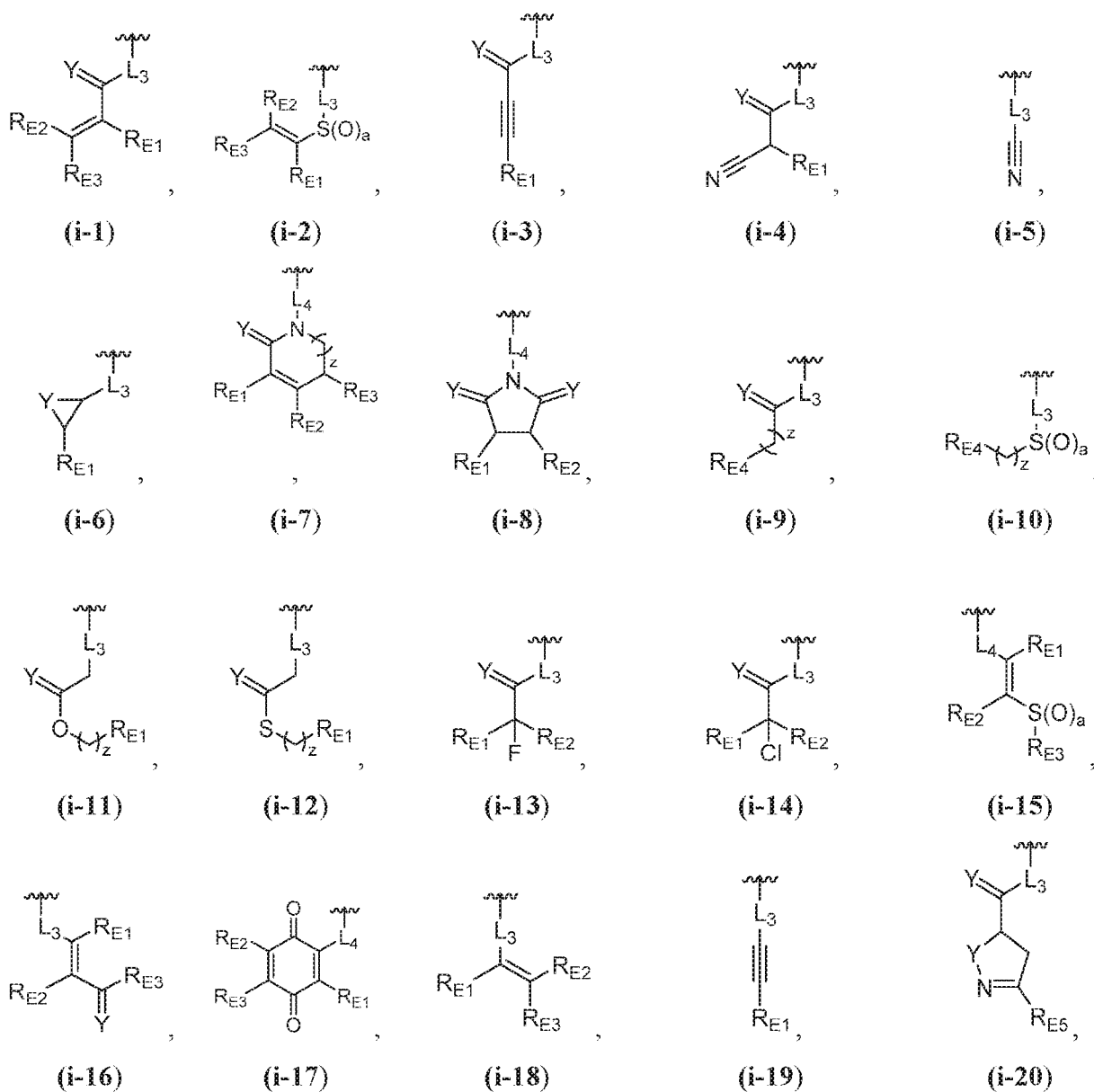
R₄ is C₁-C₄ alkyl substituted with one or more R₅ or C₂-C₄ alkenyl optionally substituted

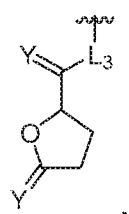
5 with one or more R₅;

each R₅ is independently halogen or NR_{n1}R_{n2};

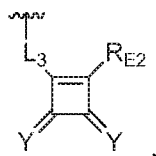
each R_{n1} and each R_{n2} are independently H or C₁-C₄ alkyl;

W is NR₃C(O)R₄, C(O)R₄, or is of formula:

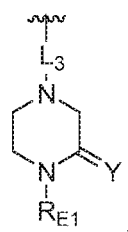




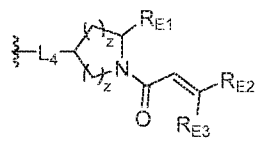
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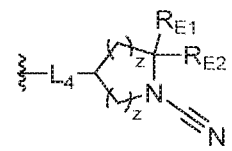
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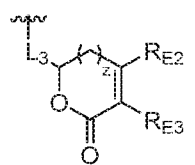
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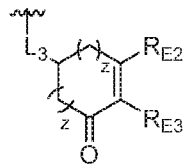
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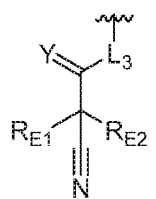
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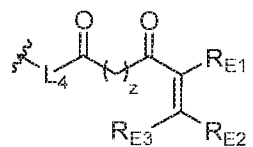
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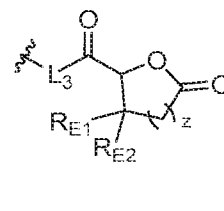
(i-27)



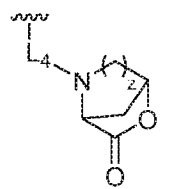
(i-28)



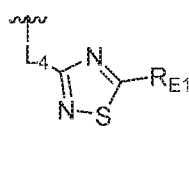
(i-29)



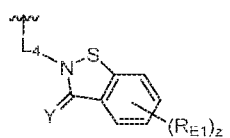
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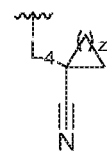
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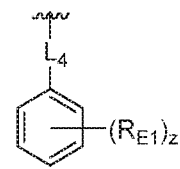
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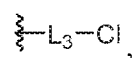
(i-33)



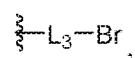
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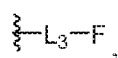
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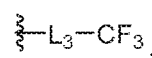
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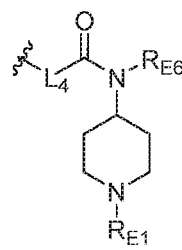
(i-37)



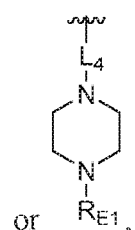
(i-38)



(i-39)



(i-40)



(i-41)

L₃ is a bond or an optionally substituted C₁-C₄ hydrocarbon chain, optionally wherein one or more carbon units of the hydrocarbon chain are independently replaced with -C(=O)-, -O-, -S-, -NR_{L3a}-, -NR_{L3a}C(=O)-, -C(=O)NR_{L3a}-, -SC(=O)-, -C(=O)S-, -OC(=O)-, -C(=O)O-, -NR_{L3a}C(=S)-, -C(=S)NR_{L3a}-, *trans*-CR_{L3b}=CR_{L3b}-, *cis*-CR_{L3b}=CR_{L3b}-, -C≡C-, -S(=O)-, -S(=O)O-, -OS(=O)-, -S(=O)NR_{L3a}-, -NR_{L3a}S(=O)-, -S(=O)₂-, -S(=O)₂O-, -OS(=O)₂-, -S(=O)₂NR_{L3a}-, or -NR_{L3a}S(=O)₂-;

R_{L3a} is H, optionally substituted C₁-C₆ alkyl, or a nitrogen protecting group;

each R_{L3b} is independently H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S, optionally substituted C_6 - C_{10} aryl, or optionally substituted heteroaryl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S, or two R_{L3b} groups are joined to form an optionally substituted C_3 - C_8 carbocycle or optionally substituted 4- to 7-membered heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S;

L_4 is a bond or an optionally substituted C_1 - C_6 hydrocarbon chain;

each of R_{E1} , R_{E2} , and R_{E3} is independently H, halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S, optionally substituted C_6 - C_{10} aryl, or optionally substituted heteroaryl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S, CN, CH_2OR_{EE} , $CH_2N(R_{EE})_2$, CH_2SR_{EE} , OR_{EE} , $N(R_{EE})_2$, $Si(R_{EE})_3$, or SR_{EE} , or R_{E1} and R_{E3} , or R_{E2} and R_{E3} , or R_{E1} and R_{E2} are joined to form an optionally substituted C_3 - C_8 carbocycle or optionally substituted 4- to 7-membered heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S;

R_{E4} is halogen, optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S, optionally substituted C_6 - C_{10} aryl, or optionally substituted heteroaryl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S, CN, CH_2OR_{EE} , $CH_2N(R_{EE})_2$, CH_2SR_{EE} , OR_{EE} , $N(R_{EE})_2$, $Si(R_{EE})_3$, or SR_{EE} ;

each R_{EE} is independently H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_1 - C_6 alkoxy, optionally substituted C_2 - C_6 alkenyl, optionally substituted C_2 - C_6 alkynyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S, optionally substituted C_6 - C_{10} aryl, or optionally substituted heteroaryl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S, or two R_{EE} are joined to form an optionally substituted 4- to 7-membered heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S;

RE5 is halogen;

RE6 is H, optionally substituted C₁-C₆ alkyl, or a nitrogen protecting group;

each Y is independently O, S, or NR_{E7};

RE7 is H, optionally substituted C₁-C₆ alkyl, or a nitrogen protecting group;

5 a is 1 or 2; and

each z is independently 0, 1, 2, 3, 4, 5, or 6,

provided that at least one of R_x and R₁ is a moiety comprising W, and not both of R_x and R₁ are a moiety comprising W.

10 For a compound of Formula Ia or Ib, where applicable, each of the variables can be a group as described below.

(I1) In one embodiment, A₁ is phenyl.

(I2) In one embodiment, A₁ is heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S.

15 (I3) In one embodiment, A₁ is heteroaryl comprising one 5-membered ring and 1-3 heteroatoms selected from N, O, and S. In one embodiment, A₁ is heteroaryl comprising one 5-membered ring and 1 or 2 heteroatoms selected from N, O, and S. In one embodiment, A₁ is heteroaryl comprising one 5-membered ring and 1 or 2 heteroatoms selected from N and O. In one embodiment, A₁ is heteroaryl selected from pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, and
20 tetrazolyl. In one embodiment, A₁ is pyrazolyl or imidazolyl.

(I4) In one embodiment, A₁ is heteroaryl comprising one 6-membered ring and 1-3 heteroatoms selected from N, O, and S. In one embodiment, A₁ is heteroaryl comprising one 6-membered ring and 1 or 2 heteroatoms selected from N, O, and S. In one embodiment, A₁ is heteroaryl comprising one 6-membered ring and 1 or 2 heteroatoms selected from N and O. In
25 one embodiment, A₁ is heteroaryl selected from pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranlyl, thiopyranlyl, diazinyl, thiazinyl, dioxinyl, and triazinyl.

(II1) In one embodiment, each R_{A1} is independently C₁-C₆ straight-chain or C₃-C₆ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), C₁-C₆ straight-chain or C₃-C₆ branched haloalkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl,
30 n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), C₁-C₆ straight-chain or C₃-C₆ branched alkoxy (*e.g.*, methoxy,

ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy), C₁-C₆ straight-chain or C₃-C₆ branched haloalkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), OH, halogen (*e.g.*, F, Cl, Br, or I), CN, phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C₁-C₆ straight-chain or C₃-C₆ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), C₁-C₆ straight-chain or C₃-C₆ branched haloalkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), C₁-C₆ straight-chain or C₃-C₆ branched alkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy), C₁-C₆ straight-chain or C₃-C₆ branched haloalkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), OH, and halogen (*e.g.*, F, Cl, Br, or I).

(II2) In one embodiment, each R_{A1} is independently C₁-C₄ straight-chain or C₃-C₄ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, or t-butyl), C₁-C₄ straight-chain or C₃-C₄ branched haloalkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, or t-butyl, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), C₁-C₄ straight-chain or C₃-C₄ branched alkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, or t-butoxy), C₁-C₄ straight-chain or C₃-C₄ branched haloalkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, or t-butoxy, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), OH, halogen (*e.g.*, F, Cl, Br, or I), CN, phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted as described herein (*e.g.*, as in (II1)).

(II3) In one embodiment, each R_{A1} is independently phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or two R_{A1} , together with the adjacent atoms to which they are attached, form phenyl, C₃-C₆ cycloalkyl, or a 5- or 6-membered heteroaryl or heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C₁-C₆ straight-chain or C₃-C₆ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), C₁-C₆ straight-chain or C₃-C₆ branched haloalkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), C₁-C₆ straight-chain or C₃-C₆ branched alkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy), C₁-C₆ straight-chain or C₃-C₆ branched haloalkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), OH, and halogen (*e.g.*, F, Cl, Br, or I).

(II4) In one embodiment, at least one R_{A1} is C₁-C₄ straight-chain or C₃-C₄ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, or t-butyl), C₁-C₄ straight-chain or C₃-C₄ branched haloalkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, or t-butyl, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), C₁-C₄ straight-chain or C₃-C₄ branched alkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, or t-butoxy), C₁-C₄ straight-chain or C₃-C₄ branched haloalkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, or t-butoxy, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), OH, halogen (*e.g.*, F, Cl, Br, or I), or CN.

(II5) In one embodiment, at least one R_{A1} is phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted as described herein (*e.g.*, as in (II1)).

(II6) In one embodiment, at least one R_{A1} is phenyl, and is optionally substituted as described herein (*e.g.*, as in (III)).

(II7) In one embodiment, at least one R_{A1} is C₃-C₆ cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), and is optionally substituted as described herein (*e.g.*, as in (III)).

(II8) In one embodiment, at least one R_{A1} is heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (III)).

(II9) In one embodiment, at least one R_{A1} is heteroaryl comprising one 5-membered ring and 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (III)). In one embodiment, at least one R_{A1} is heteroaryl comprising one 5-membered ring and 1 or 2 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (III)). In one embodiment, at least one R_{A1} is heteroaryl comprising one 5-membered ring and 1 or 2 heteroatoms selected from N and O, and is optionally substituted as described herein (*e.g.*, as in (III)). In one embodiment, at least one R_{A1} is heteroaryl selected from pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, and tetrazolyl, each of which is optionally substituted as described herein (*e.g.*, as in (III)). In one embodiment, at least one R_{A1} is pyrazolyl or imidazolyl, each of which is optionally substituted as described herein (*e.g.*, as in (III)).

(II10) In one embodiment, at least one R_{A1} is heteroaryl comprising one 6-membered ring and 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (III)). In one embodiment, at least one R_{A1} is heteroaryl comprising one 6-membered ring and 1 or 2 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (III)). In one embodiment, at least one R_{A1} is heteroaryl comprising one 6-membered ring and 1 or 2 heteroatoms selected from N and O, and is optionally substituted as described herein (*e.g.*, as in (III)). In one embodiment, at least one R_{A1} is heteroaryl selected from pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, thiopyranyl, diazinyl, thiazinyl, dioxinyl, and triazinyl, each of which is optionally substituted as described herein (*e.g.*, as in (III)).

(III1) In one embodiment, at least one R_{A1} is heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (II1)).

(III2) In one embodiment, at least one R_{A1} is heterocyclyl comprising one 5-membered
5 ring and 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (II1)). In one embodiment, at least one R_{A1} is heterocyclyl comprising one 5-membered ring and 1 or 2 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (II1)). In one embodiment, at least one R_{A1} is heterocyclyl comprising one 5-membered ring and 1 or 2 heteroatoms selected from N and O, and is
10 optionally substituted as described herein (*e.g.*, as in (II1)). In one embodiment, at least one R_{A1} is heterocyclyl selected from pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, triazolidinyl, oxadiazolidinyl, isoxadiazolidinyl, thiadiazolidinyl, and isothiadiadiazolidinyl, each of which is optionally substituted as described herein (*e.g.*, as in (II1)).

(III3) In one embodiment, at least one R_{A1} is heterocyclyl comprising one 6-membered
15 ring and 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (II1)). In one embodiment, at least one R_{A1} is heterocyclyl comprising one 6-membered ring and 1 or 2 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (II1)). In one embodiment, at least one R_{A1} is heterocyclyl comprising one 6-membered ring and 1 or 2 heteroatoms selected from N and O, and is
20 optionally substituted as described herein (*e.g.*, as in (II1)). In one embodiment, at least one R_{A1} is heterocyclyl selected from piperidinyl, piperazinyl, tetrahydropyranyl, hexahydropyridazinyl, hexahydropyrimidinyl, morpholinyl, and triazinanyl, each of which is optionally substituted as described herein (*e.g.*, as in (II1)). In one embodiment, at least one R_{A1} is piperidinyl or
25 piperazinyl, each of which is optionally substituted as described herein (*e.g.*, as in (II1)).

(III4) In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form phenyl optionally substituted as described herein (*e.g.*, as in (II3)).

(III5) In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form C_3 - C_6 cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl)
30 optionally substituted as described herein (*e.g.*, as in (II3)).

(III16) In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a 5- or 6-membered heteroaryl or heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (II3)).

(III17) In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a 5- or 6-membered heteroaryl ring comprising 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (II3)).

(III18) In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a 5-membered heteroaryl ring comprising 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (II3)). In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a 5-membered heteroaryl ring comprising 1 or 2 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (II3)). In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a 5-membered heteroaryl ring comprising 1 or 2 heteroatoms selected from N and O, and is optionally substituted as described herein (*e.g.*, as in (II3)). In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a 5-membered heteroaryl ring selected from pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, and tetrazolyl, each of which is optionally substituted as described herein (*e.g.*, as in (II3)). In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a pyrrolyl ring optionally substituted as described herein (*e.g.*, as in (II3)).

(III19) In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a 6-membered heteroaryl ring comprising 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (II3)). In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a 6-membered heteroaryl ring comprising 1 or 2 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (II3)). In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a 6-membered heteroaryl ring comprising 1 or 2 heteroatoms selected from N and O, and is optionally substituted as described herein (*e.g.*, as in (II3)). In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a 6-membered heteroaryl ring selected from pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl,

pyranyl, thiopyranyl, diazinyl, thiazinyl, dioxinyl, and triazinyl, each of which is optionally substituted as described herein (*e.g.*, as in (II3)).

(II20) In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a 5- or 6-membered heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S and is optionally substituted as described herein (*e.g.*, as in (II3)).

(II21) In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a 5-membered heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (II3)). In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a 5-membered heterocyclyl ring comprising 1 or 2 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (II3)). In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a 5-membered heterocyclyl ring comprising 1 or 2 heteroatoms selected from N and O, and is optionally substituted as described herein (*e.g.*, as in (II3)). In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a 5-membered heterocyclyl ring selected from pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, triazolidinyl, oxadiazolidinyl, isoxadiazolidinyl, thiadiazolidinyl, and isothiadiazolidinyl, each of which is optionally substituted as described herein (*e.g.*, as in (II3)).

(II22) In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a 6-membered heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (II3)). In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a 6-membered heterocyclyl ring comprising 1 or 2 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (II3)). In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a 6-membered heterocyclyl ring comprising 1 or 2 heteroatoms selected from N and O, and is optionally substituted as described herein (*e.g.*, as in (II3)). In one embodiment, two R_{A1} , together with the adjacent atoms to which they are attached, form a 6-membered heterocyclyl ring selected from piperidinyl, piperazinyl, tetrahydropyranyl, hexahydropyridazinyl, hexahydropyrimidinyl, morpholinyl, and triazinanyl, each of which is optionally substituted as described herein (*e.g.*, as in (II3)).

(III1) In one embodiment, n is 0, 1, or 2.

(III2) In one embodiment, n is 0 or 1.

(III3) In one embodiment, n is 0.

(IV1) In one embodiment, at least one R_2 is C_1 - C_6 straight-chain or C_3 - C_6 branched alkyl (e.g., methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, pentyl, or hexyl), C_1 - C_6 straight-chain or C_3 - C_6 branched haloalkyl (e.g., methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, pentyl, or hexyl, each of which is substituted with one or more halogen (e.g., F, Cl, Br, or I)), C_1 - C_6 straight-chain or C_3 - C_6 branched alkoxy (e.g., methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, *t*-butoxy, pentoxy, or hexyloxy), C_1 - C_6 straight-chain or C_3 - C_6 branched haloalkoxy (e.g., methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, *t*-butoxy, pentoxy, or hexyloxy, each of which is substituted with one or more halogen (e.g., F, Cl, Br, or I)), OH, halogen (e.g., F, Cl, Br, or I), or CN.

(V1) In one embodiment, A_2 is unsubstituted phenyl.

(V2) In one embodiment, A_2 is phenyl substituted with one or more R_{A2} .

(V3) In one embodiment, A_2 is unsubstituted heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S.

(V4) In one embodiment, A_2 is heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, substituted with one or more R_{A2} .

(V5) In one embodiment, A_2 is heteroaryl comprising one 5-membered ring and 1-3 heteroatoms selected from N, O, and S, and is optionally substituted with one or more R_{A2} . In one embodiment, A_2 is heteroaryl comprising one 5-membered ring and 1 or 2 heteroatoms selected from N, O, and S, and is optionally substituted with one or more R_{A2} . In one embodiment, A_2 is heteroaryl comprising one 5-membered ring and 1 or 2 heteroatoms selected from N and O, and is optionally substituted with one or more R_{A2} . In one embodiment, A_2 is heteroaryl selected from pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, and tetrazolyl, each of which is optionally substituted with one or more R_{A2} . In one embodiment, A_2 is thiazolyl optionally substituted with one or more R_{A2} .

(V6) In one embodiment, A_2 is heteroaryl comprising one 6-membered ring and 1-3 heteroatoms selected from N, O, and S, and is optionally substituted with one or more R_{A2} . In one embodiment, A_2 is heteroaryl comprising one 6-membered ring and 1 or 2 heteroatoms selected from N, O, and S, and is optionally substituted with one or more R_{A2} . In one

embodiment, A₂ is heteroaryl comprising one 6-membered ring and 1 or 2 heteroatoms selected from N and O, and is optionally substituted with one or more R_{A2}. In one embodiment, A₂ is heteroaryl selected from pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, thiopyranyl, diazinyl, thiazinyl, dioxinyl, and triazinyl, each of which is optionally substituted with one or more R_{A2}. In one embodiment, A₂ is pyridinyl optionally substituted with one or more R_{A2}.

(VII) In one embodiment, each R_{A2} is independently C₁-C₆ straight-chain or C₃-C₆ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), C₁-C₆ straight-chain or C₃-C₆ branched haloalkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), C₁-C₆ straight-chain or C₃-C₆ branched alkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy), C₁-C₆ straight-chain or C₃-C₆ branched haloalkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), OH, halogen (*e.g.*, F, Cl, Br, or I), CN, phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C₁-C₆ straight-chain or C₃-C₆ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), C₁-C₆ straight-chain or C₃-C₆ branched haloalkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), C₁-C₆ straight-chain or C₃-C₆ branched alkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy), C₁-C₆ straight-chain or C₃-C₆ branched haloalkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), OH, and halogen (*e.g.*, F, Cl, Br, or I).

(VI2) In one embodiment, each R_{A2} is independently C₁-C₄ straight-chain or C₃-C₄ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, or t-butyl), C₁-C₄ straight-chain or C₃-C₄ branched haloalkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, or t-butyl, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br,

or I)), C₁-C₄ straight-chain or C₃-C₄ branched alkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, or t-butoxy), C₁-C₄ straight-chain or C₃-C₄ branched haloalkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, or t-butoxy, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), OH,
 5 halogen (*e.g.*, F, Cl, Br, or I), CN, phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted as described herein (*e.g.*, as in (VI1)).

10 (VI3) In one embodiment, each R_{A2} is independently phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or two R_{A2}, together with the adjacent atoms to which they are attached, form phenyl, C₃-C₆ cycloalkyl, or a 5- or 6-membered heteroaryl or heterocyclyl ring comprising 1-3 heteroatoms
 15 selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C₁-C₆ straight-chain or C₃-C₆ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), C₁-C₆ straight-chain or C₃-C₆ branched haloalkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl, each of which is substituted
 20 with one or more halogen (*e.g.*, F, Cl, Br, or I)), C₁-C₆ straight-chain or C₃-C₆ branched alkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy), C₁-C₆ straight-chain or C₃-C₆ branched haloalkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), OH, and halogen (*e.g.*, F, Cl, Br,
 25 or I).

(VI4) In one embodiment, at least one R_{A2} is C₁-C₄ straight-chain or C₃-C₄ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, or t-butyl), C₁-C₄ straight-chain or C₃-C₄ branched haloalkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, or t-butyl, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), C₁-
 30 C₄ straight-chain or C₃-C₄ branched alkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, or t-butoxy), C₁-C₄ straight-chain or C₃-C₄ branched haloalkoxy

(*e.g.*, methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, or *t*-butoxy, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), OH, halogen (*e.g.*, F, Cl, Br, or I), or CN.

(VI5) In one embodiment, at least one R_{A2} is phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted as described herein (*e.g.*, as in (VII))

(VI6) In one embodiment, at least one R_{A2} is phenyl, and is optionally substituted as described herein (*e.g.*, as in (VII)).

(VI7) In one embodiment, at least one R_{A2} is C₃-C₆ cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), and is optionally substituted as described herein (*e.g.*, as in (VII)).

(VI8) In one embodiment, at least one R_{A2} is heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (VII)).

(VI9) In one embodiment, at least one R_{A2} is heteroaryl comprising one 5-membered ring and 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (VII)). In one embodiment, at least one R_{A2} is heteroaryl comprising one 5-membered ring and 1 or 2 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (VII)). In one embodiment, at least one R_{A2} is heteroaryl comprising one 5-membered ring and 1 or 2 heteroatoms selected from N and O, and is optionally substituted as described herein (*e.g.*, as in (VII)). In one embodiment, at least one R_{A2} is heteroaryl selected from pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, and tetrazolyl, each of which is optionally substituted as described herein (*e.g.*, as in (VII)).

(VII0) In one embodiment, at least one R_{A2} is heteroaryl comprising one 6-membered ring and 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (VII)). In one embodiment, at least one R_{A2} is heteroaryl comprising one 6-membered ring and 1 or 2 heteroatoms selected from N, O, and S, and is optionally as described herein (*e.g.*, as in (VII)). In one embodiment, at least one R_{A2} is heteroaryl comprising one 6-

membered ring and 1 or 2 heteroatoms selected from N and O, and is optionally substituted as described herein (*e.g.*, as in (VII)). In one embodiment, at least one R_{A2} is heteroaryl selected from pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, thiopyranyl, diazinyl, thiazinyl, dioxinyl, and triazinyl, each of which is optionally substituted as described herein (*e.g.*, as in (VII)).

(VII1) In one embodiment, at least one R_{A2} is heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (VII)).

(VII2) In one embodiment, at least one R_{A2} is heterocyclyl comprising one 5-membered ring and 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (VII)). In one embodiment, at least one R_{A2} is heterocyclyl comprising one 5-membered ring and 1 or 2 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (VII)). In one embodiment, at least one R_{A2} is heterocyclyl comprising one 5-membered ring and 1 or 2 heteroatoms selected from N and O, and is optionally substituted as described herein (*e.g.*, as in (VII)). In one embodiment, at least one R_{A2} is heterocyclyl selected from pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, triazolidinyl, oxadiazolidinyl, isoxadiazolidinyl, thiadiazolidinyl, and isothiadiadiazolidinyl, each of which is optionally substituted as described herein (*e.g.*, as in (VII)).

(VII3) In one embodiment, at least one R_{A2} is heterocyclyl comprising one 6-membered ring and 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (VII)). In one embodiment, at least one R_{A2} is heterocyclyl comprising one 6-membered ring and 1 or 2 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (VII)). In one embodiment, at least one R_{A2} is heterocyclyl comprising one 6-membered ring and 1 or 2 heteroatoms selected from N and O, and is optionally substituted as described herein (*e.g.*, as in (VII)). In one embodiment, at least one R_{A2} is heterocyclyl selected from piperidinyl, piperazinyl, tetrahydropyranyl, hexahydropyridazinyl, hexahydropyrimidinyl, morpholinyl, and triazinanyl, each of which is optionally substituted as described herein (*e.g.*, as in (VII)).

(VII4) In one embodiment, two R_{A2}, together with the adjacent atoms to which they are attached, form phenyl optionally substituted as described herein (*e.g.*, as in (VI3)).

(VI15) In one embodiment, two R_{A2} , together with the adjacent atoms to which they are attached, form C₃-C₆ cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl) optionally substituted as described herein (*e.g.*, as in (VI3)).

(VI16) In one embodiment, two R_{A2} , together with the adjacent atoms to which they are attached, form a 5- or 6-membered heteroaryl or heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (VI3)).

(VI17) In one embodiment, two R_{A2} , together with the adjacent atoms to which they are attached, form a 5- or 6-membered heteroaryl ring comprising 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (VI3)).

(VI18) In one embodiment, two R_{A2} , together with the adjacent atoms to which they are attached, form a 5-membered heteroaryl ring comprising 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (VI3)). In one embodiment, two R_{A2} , together with the adjacent atoms to which they are attached, form a 5-membered heteroaryl ring comprising 1 or 2 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (VI3)). In one embodiment, two R_{A2} , together with the adjacent atoms to which they are attached, form a 5-membered heteroaryl ring comprising 1 or 2 heteroatoms selected from N and O, and is optionally substituted as described herein (*e.g.*, as in (VI3)). In one embodiment, two R_{A2} , together with the adjacent atoms to which they are attached, form a 5-membered heteroaryl ring selected from pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, and tetrazolyl, each of which is optionally substituted as described herein (*e.g.*, as in (VI3)).

(VI19) In one embodiment, two R_{A2} , together with the adjacent atoms to which they are attached, form a 6-membered heteroaryl ring comprising 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (VI3)). In one embodiment, two R_{A2} , together with the adjacent atoms to which they are attached, form a 6-membered heteroaryl ring comprising 1 or 2 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (VI3)). In one embodiment, two R_{A2} , together with the adjacent atoms to which they are attached, form a 6-membered heteroaryl ring comprising 1 or 2 heteroatoms selected from N and O, and is optionally substituted as described herein (*e.g.*, as in (VI3)). In one embodiment, two R_{A2} , together with the adjacent atoms to which they are

attached, form a 6-membered heteroaryl ring selected from pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, thiopyranyl, diazinyl, thiazinyl, dioxinyl, and triazinyl, each of which is optionally substituted as described herein (*e.g.*, as in (VI3)).

(VI20) In one embodiment, two R_{A2} , together with the adjacent atoms to which they are attached, form a 5- or 6-membered heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S and is optionally substituted as described herein (*e.g.*, as in (VI3)).

(VI21) In one embodiment, two R_{A2} , together with the adjacent atoms to which they are attached, form a 5-membered heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (VI3)). In one embodiment, two R_{A2} , together with the adjacent atoms to which they are attached, form a 5-membered heterocyclyl ring comprising 1 or 2 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (VI3)). In one embodiment, two R_{A2} , together with the adjacent atoms to which they are attached, form a 5-membered heterocyclyl ring comprising 1 or 2 heteroatoms selected from N and O, and is optionally substituted as described herein (*e.g.*, as in (VI3)). In one embodiment, two R_{A2} , together with the adjacent atoms to which they are attached, form a 5-membered heterocyclyl ring selected from pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, triazolidinyl, oxadiazolidinyl, isoxadiazolidinyl, thiadiazolidinyl, and isothiadiadiazolidinyl, each of which is optionally substituted as described herein (*e.g.*, as in (VI3)).

(VI22) In one embodiment, two R_{A2} , together with the adjacent atoms to which they are attached, form a 6-membered heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (VI3)). In one embodiment, two R_{A2} , together with the adjacent atoms to which they are attached, form a 6-membered heterocyclyl ring comprising 1 or 2 heteroatoms selected from N, O, and S, and is optionally substituted as described herein (*e.g.*, as in (VI3)). In one embodiment, two R_{A2} , together with the adjacent atoms to which they are attached, form a 6-membered heterocyclyl ring comprising 1 or 2 heteroatoms selected from N and O, and is optionally substituted as described herein (*e.g.*, as in (VI3)). In one embodiment, two R_{A2} , together with the adjacent atoms to which they are attached, form a 6-membered heterocyclyl ring selected from piperidinyl, piperazinyl, tetrahydropyranyl, hexahydropyridazinyl, hexahydropyrimidinyl, morpholinyl, and triazinanyl, each of which is optionally substituted as described herein (*e.g.*, as in (VI3)).

(VII1) In one embodiment, each m is independently 0, 1, or 2.

(VII2) In one embodiment, each m is independently 0 or 1.

(VII3) In one embodiment, m is 0.

(VII4) In one embodiment, m is 1.

5 (VIII1) In one embodiment, R_1 is H.

(VIII2) In one embodiment, R_1 is C_1 - C_6 straight-chain or C_3 - C_6 branched alkyl (*e.g.*, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, pentyl, or hexyl), C_1 - C_6 straight-chain or C_3 - C_6 branched haloalkyl (*e.g.*, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, pentyl, or hexyl, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), C_1 - C_6 straight-chain or C_3 - C_6 branched alkoxy (*e.g.*, methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, *t*-butoxy, pentoxy, or hexyloxy), C_1 - C_6 straight-chain or C_3 - C_6 branched haloalkoxy (*e.g.*, methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, *t*-butoxy, pentoxy, or hexyloxy, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), OH, halogen (*e.g.*, F, Cl, Br, or I), CN, or $(CH_2)_m-A_3$.

15 (VIII3) In one embodiment, R_1 is C_1 - C_4 straight-chain or C_3 - C_4 branched alkyl (*e.g.*, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, or *t*-butyl), C_1 - C_4 straight-chain or C_3 - C_4 branched haloalkyl (*e.g.*, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, or *t*-butyl, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), C_1 - C_4 straight-chain or C_3 - C_4 branched alkoxy (*e.g.*, methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, or *t*-butoxy), C_1 - C_4 straight-chain or C_3 - C_4 branched haloalkoxy (*e.g.*, methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, or *t*-butoxy, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), OH, halogen (*e.g.*, F, Cl, Br, or I), or CN.

(VIII4) In one embodiment, R_1 is $(CH_2)_m-A_3$.

(VIII5) In one embodiment, R_1 is A_3 .

25 (VIII6) In one embodiment, R_1 is $(CH_2)-A_3$.

(VIII7) In one embodiment, R_1 is $(CH_2)_2-A_3$.

(IX1) In one embodiment, A_3 is phenyl, C_3 - C_6 cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C_1 - C_6 straight-chain or C_3 - C_6 branched alkyl (*e.g.*, methyl, ethyl, *n*-

propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), C₁-C₆ straight-chain or C₃-C₆ branched haloalkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), C₁-C₆ straight-chain or C₃-C₆ branched alkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy), C₁-C₆ straight-chain or C₃-C₆ branched haloalkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), OH, halogen (*e.g.*, F, Cl, Br, or I), and W.

(IX2) In one embodiment, A₃ is phenyl optionally substituted as described herein (*e.g.*, as in (IX1)).

(IX3) In one embodiment, A₃ is C₃-C₆ cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl) optionally substituted as described herein (*e.g.*, as in (IX1)).

(IX4) In one embodiment, A₃ is heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S (*e.g.*, pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, thiopyranyl, diazinyl, thiazinyl, dioxinyl, or triazinyl), wherein the heteroaryl is optionally substituted as described herein (*e.g.*, as in (IX1)).

(IX5) In one embodiment, A₃ is heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S (*e.g.*, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, triazolidinyl, oxadiazolidinyl, isoxadiazolidinyl, thiadiazolidinyl, isothiadiadiazolidinyl, piperidinyl, piperazinyl, tetrahydropyranyl, hexahydropyridazinyl, hexahydropyrimidinyl, morpholinyl, or triazinanyl), wherein the heterocyclyl is optionally substituted as described herein (*e.g.*, as in (IX1)).

(X1) In one embodiment, X₁, X₂, X₃, and X₄ are each CR_X.

(X2) In one embodiment, one of X₁, X₂, X₃, and X₄ is N, and the remainder of X₁, X₂, X₃, and X₄ are each CR_X.

(X3) In one embodiment, two of X₁, X₂, X₃, and X₄ are N, and the remainder of X₁, X₂, X₃, and X₄ are each CR_X.

(X4) In one embodiment, X₁ is N, and X₂, X₃, and X₄ are each CR_X.

(X5) In one embodiment, X₂ is N, and X₁, X₃, and X₄ are each CR_X.

(X6) In one embodiment, X₃ is N, and X₁, X₂, and X₄ are each CR_X.

(X7) In one embodiment, X₄ is N, and X₁, X₂, and X₃ are each CR_X.

(X8) In one embodiment, X₅, X₆, X₇, and X₈ are each CR_X.

5 (X9) In one embodiment, one of X₅, X₆, X₇, and X₈ is N, and the remainder of X₅, X₆, X₇, and X₈ are each CR_X.

(X10) In one embodiment, two of X₅, X₆, X₇, and X₈ are N, and the remainder of X₅, X₆, X₇, and X₈ are each CR_X.

(X11) In one embodiment, X₅ is N, and X₆, X₇, and X₈ are each CR_X.

10 (X12) In one embodiment, X₆ is N, and X₅, X₇, and X₈ are each CR_X.

(X13) In one embodiment, X₇ is N, and X₅, X₆, and X₈ are each CR_X.

(X14) In one embodiment, X₈ is N, and X₅, X₆, and X₇ are each CR_X.

(XI1) In one embodiment, one of R_X is W, and the remaining one or more R_X are each independently H, C₁-C₆ straight-chain or C₃-C₆ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), C₁-C₆ straight-chain or C₃-C₆ branched haloalkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), C₁-C₆ straight-chain or C₃-C₆ branched alkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy), C₁-C₆ straight-chain or C₃-C₆ branched haloalkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), OH, halogen (*e.g.*, F, Cl, Br, or I), CN, phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C₁-C₆ straight-chain or C₃-C₆ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), C₁-C₆ straight-chain or C₃-C₆ branched haloalkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), C₁-C₆ straight-chain or C₃-C₆ branched alkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy), C₁-C₆

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straight-chain or C₃-C₆ branched haloalkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), OH, and halogen (*e.g.*, F, Cl, Br, or I).

(XI2) In one embodiment, one of R_x is W, and the remaining one or more R_x are each H.

5 (XI3) In one embodiment, one of R_x is W, and the remaining one or more R_x are each independently H, C₁-C₆ straight-chain or C₃-C₆ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), C₁-C₆ straight-chain or C₃-C₆ branched haloalkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), C₁-C₆ straight-chain or C₃-C₆ branched alkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy), C₁-C₆ straight-chain or C₃-C₆ branched haloalkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy, each of which is substituted with one or more halogen (*e.g.*, F, Cl, Br, or I)), OH, halogen (*e.g.*, F, Cl, Br, or I), or CN.

15 (XI4) In one embodiment, one of R_x is W, and the remaining one or more R_x are each independently H, OH, halogen (*e.g.*, F, Cl, Br, or I), or CN.

(XI5) In one embodiment, one of R_x is W, and the remaining one or more R_x are each independently H or halogen (*e.g.*, F, Cl, Br, or I).

20 (XI6) In one embodiment, one of R_x is W, and the remaining one or more R_x are each independently H, phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted as described herein (*e.g.*, as in (XI1)).

25 (XI7) In one embodiment, one of R_x is W, and the remaining one or more R_x are each independently H, or phenyl optionally substituted as described herein (*e.g.*, as in (XI1)).

(XI8) In one embodiment, one of R_x is W, and the remaining one or more R_x are each independently H, or C₃-C₆ cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl) optionally substituted as described herein (*e.g.*, as in (XI1)).

30 (XI9) In one embodiment, one of R_x is W, and the remaining one or more R_x are each independently H, or heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S (*e.g.*, pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl,

isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, thiopyranyl, diazinyl, thiazinyl, dioxinyl, or triazinyl), wherein the heteroaryl is optionally substituted as described herein (*e.g.*, as in (XI)).

(XI10) In one embodiment, one of R_x is W, and the remaining one or more R_x are each independently H, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S (*e.g.*, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, triazolidinyl, oxadiazolidinyl, isoxadiazolidinyl, thiadiazolidinyl, isothiadiadiazolidinyl, piperidinyl, piperazinyl, tetrahydropyranyl, hexahydropyridazinyl, hexahydropyrimidinyl, morpholinyl, or triazinanyl), wherein the heterocyclyl is optionally substituted as described herein (*e.g.*, as in (XI)).

(XII1) In one embodiment, W is $NR_3C(O)R_4$ or $C(O)R_4$.

(XII2) In one embodiment, W is selected from formulae (i-1)-(i-5), (i-9)-(i-16), (i-18), (i-19), (i-28), (i-29), and (i-36)-(i-39).

(XII3) In one embodiment, W is selected from formulae (i-1), (i-3), (i-9), (i-13), (i-14), (i-16), (i-18), (i-19), (i-29), and (i-36)-(i-39).

(XII4) In one embodiment, W is selected from formulae (i-2), (i-10), (i-15), (i-28), and (i-34).

(XII5) In one embodiment, W is selected from formulae (i-4), (i-5), and (i-10).

(XII6) In one embodiment, W is selected from formulae (i-11) and (i-12).

(XII7) In one embodiment, W is selected from formulae (i-6)-(i-8), (i-17), (i-20)-(i-27), (i-30)-(i-35), (i-40), and (i-41).

(XII8) In one embodiment, W is selected from formulae (i-6)-(i-8), (i-17), (i-20)-(i-27), (i-30), (i-34), (i-40), and (i-41).

(XIII1) In one embodiment, R_3 is H.

(XIII2) In one embodiment, R_3 is C_1 - C_4 alkyl selected from methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, and t-butyl.

(XIV1) In one embodiment, R_4 is C_1 - C_4 alkyl selected from methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, and t-butyl, each of which is substituted with one or more R_5 . In a further embodiment, R_4 is methyl or ethyl, each of which is substituted with one or more R_5 .

(XIV2) In one embodiment, R₄ is C₂-C₄ alkenyl selected from ethenyl, n-propenyl, i-propenyl, n-butenyl, i-butenyl, and s-butenyl, each of which is optionally substituted with one or more R₅. In a further embodiment, R₄ is ethenyl or n-propenyl, each of which is optionally substituted with one or more R₅.

5 (XV1) In one embodiment, each R₅ is independently NR_{n1}R_{n2}, wherein R_{n1} and R_{n2} are each H.

(XV2) In one embodiment, each R₅ is independently NR_{n1}R_{n2}, wherein R_{n1} and R_{n2} are each independently H or C₁-C₄ alkyl selected from methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, and t-butyl.

10 (XV3) In one embodiment, each R₅ is independently halogen (*e.g.*, F, Cl, Br, or I).

(XVI1) In one embodiment, L₃ is a bond.

(XVI2) In one embodiment, L₃ is an optionally substituted C₁-C₄ hydrocarbon chain (*e.g.*, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, or -CH₂CH₂CH₂CH₂-), optionally wherein one or more carbon units of the hydrocarbon chain are independently replaced with -C(=O)-, -O-, -S-, -NR_{L3a}-, -NR_{L3a}C(=O)-, -C(=O)NR_{L3a}-, -SC(=O)-, -C(=O)S-, -OC(=O)-, -C(=O)O-, -NR_{L3a}C(=S)-, -C(=S)NR_{L3a}-, *trans*-CR_{L3b}=CR_{L3b}-, *cis*-CR_{L3b}=CR_{L3b}-, -C≡C-, -S(=O)-, -S(=O)O-, -OS(=O)-, -S(=O)NR_{L3a}-, -NR_{L3a}S(=O)-, -S(=O)₂-, -S(=O)₂O-, -OS(=O)₂-, -S(=O)₂NR_{L3a}-, or -NR_{L3a}S(=O)₂-.

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(XVI3) In one embodiment, L₃ is an optionally substituted C₁-C₄ hydrocarbon chain (*e.g.*, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, or -CH₂CH₂CH₂CH₂-), optionally wherein one or more carbon units of the hydrocarbon chain are independently replaced with -C(=O)-, -O-, -S-, -NR_{L3a}-, -NR_{L3a}C(=O)-, -C(=O)NR_{L3a}-, -SC(=O)-, -C(=O)S-, -OC(=O)-, -C(=O)O-, -S(=O)-, -S(=O)O-, -OS(=O)-, -S(=O)NR_{L3a}-, -NR_{L3a}S(=O)-, -S(=O)₂-, -S(=O)₂O-, -OS(=O)₂-, -S(=O)₂NR_{L3a}-, or -NR_{L3a}S(=O)₂-.

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(XVI4) In one embodiment, L₃ is an optionally substituted C₁-C₄ hydrocarbon chain (*e.g.*, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, or -CH₂CH₂CH₂CH₂-), optionally wherein one or more carbon units of the hydrocarbon chain are independently replaced with *trans*-CR_{L3b}=CR_{L3b}-, *cis*-CR_{L3b}=CR_{L3b}-, or -C≡C-.

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(XVI5) In one embodiment, L₃ is an optionally substituted C₁-C₄ hydrocarbon chain (*e.g.*, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, or -CH₂CH₂CH₂CH₂-), optionally wherein one or more carbon

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units of the hydrocarbon chain are independently replaced with $-\text{C}=\text{O}-$, $-\text{O}-$, $-\text{S}-$, $-\text{NR}_{\text{L3a}}-$, $-\text{NR}_{\text{L3a}}\text{C}(=\text{O})-$, $-\text{C}(=\text{O})\text{NR}_{\text{L3a}}-$, $-\text{SC}(=\text{O})-$, $-\text{C}(=\text{O})\text{S}-$, $-\text{OC}(=\text{O})-$, or $-\text{C}(=\text{O})\text{O}-$.

(XVIII1) In one embodiment, R_{L3a} is H.

(XVIII2) In one embodiment, R_{L3a} is optionally substituted C_1 - C_6 straight-chain or C_3 - C_6 branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

(XVIII3) In one embodiment, R_{L3a} is a nitrogen protecting group.

(XVIII1) In one embodiment, each R_{L3b} is H.

(XVIII2) In one embodiment, at least one R_{L3b} is halogen (*e.g.*, F, Cl, Br, or I), optionally substituted C_1 - C_6 straight-chain or C_3 - C_6 branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), optionally substituted C_2 - C_6 straight-chain or C_3 - C_6 branched alkenyl (*e.g.*, ethenyl, n-propenyl, i-propenyl, n-butenyl, i-butenyl, s-butenyl, pentenyl, or hexenyl), optionally substituted C_2 - C_6 straight-chain or C_4 - C_6 branched alkynyl (*e.g.*, ethynyl, n-propynyl, i-propynyl, n-butynyl, i-butynyl, pentynyl, or hexynyl), optionally substituted C_3 - C_8 cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl), optionally substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S (*e.g.*, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, triazolidinyl, oxadiazolidinyl, isoxadiazolidinyl, thiadiazolidinyl, or isothiadiazolidinyl), optionally substituted C_6 - C_{10} aryl (*e.g.*, phenyl), or optionally substituted heteroaryl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S (*e.g.*, pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, thiopyranyl, diazinyl, thiazinyl, dioxinyl, or triazinyl).

(XVIII3) In one embodiment, at least one R_{L3b} is halogen (*e.g.*, F, Cl, Br, or I), optionally substituted C_1 - C_6 straight-chain or C_3 - C_6 branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), optionally substituted C_2 - C_6 straight-chain or C_3 - C_6 branched alkenyl (*e.g.*, ethenyl, n-propenyl, i-propenyl, n-butenyl, i-butenyl, s-butenyl, pentenyl, or hexenyl), or optionally substituted C_2 - C_6 straight-chain or C_4 - C_6 branched alkynyl (*e.g.*, ethynyl, n-propynyl, i-propynyl, n-butynyl, i-butynyl, pentynyl, or hexynyl).

(XVIII4) In one embodiment, two R_{L3b} groups are joined to form an optionally substituted C_3 - C_8 carbocycle (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl), or optionally substituted 4- to 7-membered heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S (*e.g.*, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, triazolidinyl, oxadiazolidinyl, isoxadiazolidinyl, thiadiazolidinyl, or isothiadiiazolidinyl).

(XIX1) In one embodiment, L_4 is a bond.

(XIX2) In one embodiment, L_4 is an optionally substituted C_1 - C_6 hydrocarbon chain (*e.g.*, - CH_2 -, - CH_2CH_2 -, - $CH_2CH_2CH_2$ -, - $CH_2CH_2CH_2CH_2$ -, - $CH_2CH_2CH_2CH_2CH_2$ -, or - $CH_2CH_2CH_2CH_2CH_2CH_2$ -).

(XX1) In one embodiment, each R_{E1} is H.

(XX2) In one embodiment, at least one R_{E1} is halogen (*e.g.*, F, Cl, Br, or I), optionally substituted C_1 - C_6 straight-chain or C_3 - C_6 branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), optionally substituted C_2 - C_6 straight-chain or C_3 - C_6 branched alkenyl (*e.g.*, ethenyl, n-propenyl, i-propenyl, n-butenyl, i-butenyl, s-butenyl, pentenyl, or hexenyl), optionally substituted C_2 - C_6 straight-chain or C_4 - C_6 branched alkynyl (*e.g.*, ethynyl, n-propynyl, i-propynyl, n-butynyl, i-butynyl, pentynyl, or hexynyl), optionally substituted C_3 - C_8 cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl), optionally substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S (*e.g.*, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, triazolidinyl, oxadiazolidinyl, isoxadiazolidinyl, thiadiazolidinyl, or isothiadiiazolidinyl), optionally substituted C_6 - C_{10} aryl (*e.g.*, phenyl), optionally substituted heteroaryl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S (*e.g.*, pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, thiopyranyl, diazinyl, thiazinyl, dioxinyl, or triazinyl), CN, CH_2OR_{EE} , $CH_2N(R_{EE})_2$, CH_2SR_{EE} , OR_{EE} , $N(R_{EE})_2$, $Si(R_{EE})_3$, or SR_{EE} .

(XX3) In one embodiment, at least one R_{E1} is halogen (*e.g.*, F, Cl, Br, or I), optionally substituted C_1 - C_6 straight-chain or C_3 - C_6 branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl,

n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), optionally substituted C₂-C₆ straight-chain or C₃-C₆ branched alkenyl (*e.g.*, ethenyl, n-propenyl, i-propenyl, n-butenyl, i-butenyl, s-butenyl, pentenyl, or hexenyl), or optionally substituted C₂-C₆ straight-chain or C₄-C₆ branched alkynyl (*e.g.*, ethynyl, n-propynyl, i-propynyl, n-butynyl, i-butynyl, pentynyl, or hexynyl).

5 (XX4) In one embodiment, each R_{E2} is H.

(XX5) In one embodiment, at least one R_{E2} is halogen (*e.g.*, F, Cl, Br, or I), optionally substituted C₁-C₆ straight-chain or C₃-C₆ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), optionally substituted C₂-C₆ straight-chain or C₃-C₆ branched alkenyl (*e.g.*, ethenyl, n-propenyl, i-propenyl, n-butenyl, i-butenyl, s-butenyl, pentenyl, or hexenyl), optionally substituted C₂-C₆ straight-chain or C₄-C₆ branched alkynyl (*e.g.*, ethynyl, n-propynyl, i-propynyl, n-butynyl, i-butynyl, pentynyl, or hexynyl), optionally substituted C₃-C₈ cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl), optionally substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S (*e.g.*, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, triazolidinyl, oxadiazolidinyl, isoxadiazolidinyl, thiadiazolidinyl, or isothiadiadiazolidinyl), optionally substituted C₆-C₁₀ aryl (*e.g.*, phenyl), optionally substituted heteroaryl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S (*e.g.*, pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, thiopyranyl, diazinyl, thiazinyl, dioxinyl, or triazinyl), CN, CH₂OR_{EE}, CH₂N(R_{EE})₂, CH₂SR_{EE}, OR_{EE}, N(R_{EE})₂, Si(R_{EE})₃, or SR_{EE}.

(XX6) In one embodiment, at least one R_{E2} is halogen (*e.g.*, F, Cl, Br, or I), optionally substituted C₁-C₆ straight-chain or C₃-C₆ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), optionally substituted C₂-C₆ straight-chain or C₃-C₆ branched alkenyl (*e.g.*, ethenyl, n-propenyl, i-propenyl, n-butenyl, i-butenyl, s-butenyl, pentenyl, or hexenyl), or optionally substituted C₂-C₆ straight-chain or C₄-C₆ branched alkynyl (*e.g.*, ethynyl, n-propynyl, i-propynyl, n-butynyl, i-butynyl, pentynyl, or hexynyl).

(XX7) In one embodiment, each R_{E3} is H.

30 (XX8) In one embodiment, at least one R_{E3} is halogen (*e.g.*, F, Cl, Br, or I), optionally substituted C₁-C₆ straight-chain or C₃-C₆ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl,

n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), optionally substituted C₂-C₆ straight-chain or C₃-C₆ branched alkenyl (*e.g.*, ethenyl, n-propenyl, i-propenyl, n-butenyl, i-butenyl, s-butenyl, pentenyl, or hexenyl), optionally substituted C₂-C₆ straight-chain or C₄-C₆ branched alkynyl (*e.g.*, ethynyl, n-propynyl, i-propynyl, n-butynyl, i-butynyl, pentynyl, or hexynyl), optionally substituted C₃-C₈ cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl), optionally substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S (*e.g.*, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, triazolidinyl, oxadiazolidinyl, isoxadiazolidinyl, thiadiazolidinyl, or isothiadiiazolidinyl), optionally substituted C₆-C₁₀ aryl (*e.g.*, phenyl), optionally substituted heteroaryl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S (*e.g.*, pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, thiopyranyl, diazinyl, thiazinyl, dioxinyl, or triazinyl), CN, CH₂OR_{EE}, CH₂N(R_{EE})₂, CH₂SR_{EE}, OR_{EE}, N(R_{EE})₂, Si(R_{EE})₃, or SR_{EE}.

(XX9) In one embodiment, at least one R_{E3} is halogen (*e.g.*, F, Cl, Br, or I), optionally substituted C₁-C₆ straight-chain or C₃-C₆ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), optionally substituted C₂-C₆ straight-chain or C₃-C₆ branched alkenyl (*e.g.*, ethenyl, n-propenyl, i-propenyl, n-butenyl, i-butenyl, s-butenyl, pentenyl, or hexenyl), or optionally substituted C₂-C₆ straight-chain or C₄-C₆ branched alkynyl (*e.g.*, ethynyl, n-propynyl, i-propynyl, n-butynyl, i-butynyl, pentynyl, or hexynyl).

(XX10) In one embodiment, R_{E1} and R_{E3} are joined to form an optionally substituted C₃-C₈ carbocycle (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl), or optionally substituted 4- to 7-membered heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S (*e.g.*, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, triazolidinyl, oxadiazolidinyl, isoxadiazolidinyl, thiadiazolidinyl, or isothiadiiazolidinyl).

(XX11) In one embodiment, R_{E2} and R_{E3} are joined to form an optionally substituted C₃-C₈ carbocycle (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl), or optionally substituted 4- to 7-membered heterocyclyl ring comprising 1-3

heteroatoms selected from N, O, and S (*e.g.*, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, triazolidinyl, oxadiazolidinyl, isoxadiazolidinyl, thiadiazolidinyl, or isothiadiiazolidinyl).

5 (XX12) In one embodiment, RE_1 and RE_2 are joined to form an optionally substituted C_3 - C_8 carbocycle (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl), or optionally substituted 4- to 7-membered heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S (*e.g.*, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, triazolidinyl, oxadiazolidinyl, isoxadiazolidinyl, thiadiazolidinyl, or
10 isothiadiiazolidinyl).

(XX13) In one embodiment, RE_4 is halogen (*e.g.*, F, Cl, Br, or I), optionally substituted C_1 - C_6 straight-chain or C_3 - C_6 branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), optionally substituted C_2 - C_6 straight-chain or C_3 - C_6 branched alkenyl (*e.g.*, ethenyl, n-propenyl, i-propenyl, n-butenyl, i-butenyl, s-butenyl, pentenyl, or hexenyl), optionally substituted C_2 - C_6 straight-chain or C_4 - C_6 branched alkynyl (*e.g.*, ethynyl, n-propynyl, i-propynyl, n-butynyl, i-butynyl, pentynyl, or hexynyl), optionally substituted C_3 - C_8 cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl), optionally substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1-4
20 heteroatoms selected from N, O, and S (*e.g.*, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, triazolidinyl, oxadiazolidinyl, isoxadiazolidinyl, thiadiazolidinyl, or isothiadiiazolidinyl), optionally substituted C_6 - C_{10} aryl (*e.g.*, phenyl), optionally substituted heteroaryl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N,
25 O, and S (*e.g.*, pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, thiopyranyl, diazinyl, thiazinyl, dioxinyl, or triazinyl), CN, CH_2OR_{EE} , $CH_2N(R_{EE})_2$, CH_2SR_{EE} , OR_{EE} , $N(R_{EE})_2$, $Si(R_{EE})_3$, or SR_{EE} .

(XX14) In one embodiment, RE_4 is halogen (*e.g.*, F, Cl, Br, or I), optionally substituted
30 C_1 - C_6 straight-chain or C_3 - C_6 branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), optionally substituted C_2 - C_6 straight-chain or C_3 - C_6

branched alkenyl (*e.g.*, ethenyl, n-propenyl, i-propenyl, n-butenyl, i-butenyl, s-butenyl, pentenyl, or hexenyl), or optionally substituted C₂-C₆ straight-chain or C₄-C₆ branched alkynyl (*e.g.*, ethynyl, n-propynyl, i-propynyl, n-butynyl, i-butynyl, pentynyl, or hexynyl).

(XXI1) In one embodiment, each R_{EE} is H.

5 (XXI2) In one embodiment, at least one R_{EE} is halogen (*e.g.*, F, Cl, Br, or I), optionally substituted C₁-C₆ straight-chain or C₃-C₆ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), optionally substituted C₁-C₆ straight-chain or C₃-C₆ branched alkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy), optionally substituted C₂-C₆ straight-chain or C₃-C₆ branched alkenyl (*e.g.*, ethenyl, n-propenyl, i-propenyl, n-butenyl, i-butenyl, s-butenyl, pentenyl, or hexenyl), optionally substituted C₂-C₆ straight-chain or C₄-C₆ branched alkynyl (*e.g.*, ethynyl, n-propynyl, i-propynyl, n-butynyl, i-butynyl, pentynyl, or hexynyl), optionally substituted C₃-C₈ cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl), optionally substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1-4
10 heteroatoms selected from N, O, and S (*e.g.*, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, triazolidinyl, oxadiazolidinyl, isoxadiazolidinyl, thiadiazolidinyl, or isothiadiazolidinyl), optionally substituted C₆-C₁₀ aryl (*e.g.*, phenyl), or optionally substituted heteroaryl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S (*e.g.*, pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, thiopyranyl, diazinyl, thiazinyl, dioxinyl, or triazinyl).
20

(XXI3) In one embodiment, at least one R_{EE} is halogen (*e.g.*, F, Cl, Br, or I), optionally substituted C₁-C₆ straight-chain or C₃-C₆ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl), optionally substituted C₁-C₆ straight-chain or C₃-C₆ branched alkoxy (*e.g.*, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentoxy, or hexyloxy), optionally substituted C₂-C₆ straight-chain or C₃-C₆ branched alkenyl (*e.g.*, ethenyl, n-propenyl, i-propenyl, n-butenyl, i-butenyl, s-butenyl, pentenyl, or hexenyl), or optionally substituted C₂-C₆ straight-chain or C₄-C₆ branched alkynyl (*e.g.*, ethynyl, n-propynyl, i-propynyl, n-butynyl, i-butynyl, pentynyl, or hexynyl).
25
30

(XXI4) In one embodiment, two R_{EE} are joined to form an optionally substituted 4- to 7-membered heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S (*e.g.*, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, triazolidinyl, oxadiazolidinyl, isoxadiazolidinyl, thiadiazolidinyl, or isothiadiazolidinyl).

(XXII1) In one embodiment, R_{E5} is halogen (*e.g.*, F, Cl, Br, or I).

(XXIII1) In one embodiment, R_{E6} is H.

(XXIII2) In one embodiment, R_{E6} is optionally substituted C₁-C₆ straight-chain or C₃-C₆ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

(XXIII3) In one embodiment, R_{E6} is a nitrogen protecting group.

(XXIV1) In one embodiment, each Y is O.

(XXIV2) In one embodiment, each Y is S.

(XXIV3) In one embodiment, each Y is NR_{E7}.

(XXIV4) In one embodiment, at least one Y is O.

(XXIV5) In one embodiment, at least one Y is S.

(XXIV6) In one embodiment, at least one Y is NR_{E7}.

(XXIV7) In one embodiment, at least one Y is O, and at least one Y is S.

(XXIV8) In one embodiment, at least one Y is O, and at least one Y is NR_{E7}.

(XXIV9) In one embodiment, at least one Y is S, and at least one Y is NR_{E7}.

(XXV1) In one embodiment, R_{E7} is H.

(XXV2) In one embodiment, R_{E7} is optionally substituted C₁-C₆ straight-chain or C₃-C₆ branched alkyl (*e.g.*, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, or hexyl).

(XXV3) In one embodiment, R_{E7} is a nitrogen protecting group.

(XXVI1) In one embodiment, a is 1.

(XXVI2) In one embodiment, a is 2.

(XXVII1) In one embodiment, each z is independently 0, 1, 2, or 3.

(XXVII2) In one embodiment, each z is independently 1, 2, or 3.

(XXVII3) In one embodiment, each z is independently 0, 1, or 2.

Any of the substituents described herein for any of A₁, A₂, A₃, W, X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈, R_{A1}, R_{A2}, R₁, R₂, R₃, R₄, R₅, R_{n1}, R_{n2}, R_X, m, n, L₃, L₄, R_{L3a}, R_{L3b}, R_{E1}, R_{E2}, R_{E3}, R_{E4}, R_{EE}, R_{E5}, R_{E6}, R_{E7}, Y, a, and z can be combined with any of the substituents described herein for one or more of the remainder of A₁, A₂, A₃, W, X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈, R_{A1}, R_{A2}, R₁, R₂, R₃,
 5 R₄, R₅, R_{n1}, R_{n2}, R_X, m, n, L₃, L₄, R_{L3a}, R_{L3b}, R_{E1}, R_{E2}, R_{E3}, R_{E4}, R_{EE}, R_{E5}, R_{E6}, R_{E7}, Y, a, and z.

(1) In one embodiment, A₁ is as described in (I1), and A₂ is as described in (V1) or (V2).

(2) In one embodiment, A₁ is as described in (I1), and A₂ is as described in (V3), (V4), (V5), or (V6).

(3) In one embodiment, A₁ is as described in (I2), (I3), or (I4), and A₂ is as described in
 10 (V1) or (V2).

(4) In one embodiment, A₁ is as described in (I2), (I3), or (I4), and A₂ is as described in (V3), (V4), (V5), or (V6).

(5) In one embodiment, A₁ is as described in (I1), and R_{A1} is as described in (II1) or (II2).

(6) In one embodiment, A₁ is as described in (I1), and R_{A1} is as described in (II4)

15 (7) In one embodiment, A₁ is as described in (I1), and R_{A1} is as described in (II3).

(8) In one embodiment, A₁ is as described in (I1), and R_{A1} is as described in any one of (II5)-(II13).

(9) In one embodiment, A₁ is as described in (I1), and R_{A1} is as described in (II11), (II12), or (II13).

20 (10) In one embodiment, A₁ is as described in (I1), and R_{A1} is as described in any one of (II14)-(II22).

(11) In one embodiment, A₁ is as described in (I1), and R_{A1} is as described in (II17), (II18), or (II19).

(12) In one embodiment, A₁ is as described in (I2), (I3), or (I4), and R_{A1} is as described in
 25 (II1) or (II2).

(13) In one embodiment, A₁ is as described in (I2), (I3), or (I4), and R_{A1} is as described in (II4)

(14) In one embodiment, A₁ is as described in (I2), (I3), or (I4), and R_{A1} is as described in (II3).

30 (15) In one embodiment, A₁ is as described in (I2), (I3), or (I4), and R_{A1} is as described in any one of (II5)-(II13).

(16) In one embodiment, A_1 is as described in (I2), (I3), or (I4), and R_{A1} is as described in (III1), (III2), or (III3).

(17) In one embodiment, A_1 is as described in (I2), (I3), or (I4), and R_{A1} is as described in any one of (III4)-(II22).

5 (18) In one embodiment, A_1 is as described in (I2), (I3), or (I4), and R_{A1} is as described in (III7), (III8), or (III9).

(19) In one embodiment, A_1 and R_{A1} are each as described in any one of (5)-(18), and A_2 is as described in (V1) or (V2).

10 (20) In one embodiment, A_1 and R_{A1} are each as described in any one of (5)-(18), and A_2 is as described in (V3), (V4), (V5), or (V6).

(21) In one embodiment, A_1 , A_2 , and R_{A1} are each as described, where applicable, in any one of (1)-(20), and m is as described in (VII2), (VII3), or (VII4).

(22) In one embodiment, A_1 , A_2 , and R_{A1} are each as described, where applicable, in any one of (1)-(20), and m is as described in (VII4).

15 (23) In one embodiment, A_1 , A_2 , R_{A1} , and m are each as described, where applicable, in any one of (1)-(22), and R_1 is as described in (VIII1).

(24) In one embodiment, A_1 , A_2 , R_{A1} , and m are each as described, where applicable, in any one of (1)-(22), and R_1 is as described in (VIII2).

20 (25) In one embodiment, A_1 , A_2 , R_{A1} , and m are each as described, where applicable, in any one of (1)-(22), and R_1 is as described in (VIII3).

(26) In one embodiment, A_1 , A_2 , R_{A1} , and m are each as described, where applicable, in any one of (1)-(22), and R_1 is as described in any one of (VIII4)-(VIII7).

(27) In one embodiment, A_1 , A_2 , R_{A1} , R_1 , and m are each as described, where applicable, in any one of (1)-(26), and R_X is as described in (XI2).

25 (28) In one embodiment, A_1 , A_2 , R_{A1} , R_1 , and m are each as described, where applicable, in any one of (1)-(26), and R_X is as described in any one of (XI1) and (XI3)-(XI5).

(29) In one embodiment, A_1 , A_2 , R_{A1} , R_1 , and m are each as described, where applicable, in any one of (1)-(26), and R_X is as described in any one of (XI6)-(XI10).

30 (30) In one embodiment, A_1 , A_2 , R_{A1} , R_1 , R_X , and m are each as described, where applicable, in any one of (1)-(29), and W is as described in (XII1).

(31) In one embodiment, A_1 , A_2 , R_{A1} , R_1 , R_X , and m are each as described, where applicable, in any one of (1)-(29), and W is as described in (XII2).

(32) In one embodiment, A_1 , A_2 , R_{A1} , R_1 , R_X , and m are each as described, where applicable, in any one of (1)-(29), and W is as described in (XII3).

5 (33) In one embodiment, A_1 , A_2 , R_{A1} , R_1 , R_X , and m are each as described, where applicable, in any one of (1)-(29), and W is as described in (XII4).

(34) In one embodiment, A_1 , A_2 , R_{A1} , R_1 , R_X , and m are each as described, where applicable, in any one of (1)-(29), and W is as described in (XII5).

10 (35) In one embodiment, A_1 , A_2 , R_{A1} , R_1 , R_X , and m are each as described, where applicable, in any one of (1)-(29), and W is as described in (XII6).

(36) In one embodiment, A_1 , A_2 , R_{A1} , R_1 , R_X , and m are each as described, where applicable, in any one of (1)-(29), and W is as described in (XII7).

(37) In one embodiment, A_1 , A_2 , R_{A1} , R_1 , R_X , and m are each as described, where applicable, in any one of (1)-(29), and W is as described in (XII8).

15 (38) In one embodiment, W is as described in (XIII1), and R_4 is as described in (XIV1).

(39) In one embodiment, W is as described in (XIII1), and R_4 is as described in (XIV2).

(40) In one embodiment, A_1 , A_2 , W , R_{A1} , R_1 , R_X , and m are each as described, where applicable, in any one of (1)-(30), and R_4 is as described in (XIV1).

20 (41) In one embodiment, A_1 , A_2 , W , R_{A1} , R_1 , R_X , and m are each as described, where applicable, in any one of (1)-(30), and R_4 is as described in (XIV2).

(42) In one embodiment, A_1 , A_2 , W , R_{A1} , R_1 , R_4 , R_X , and m are each as described, where applicable, in any one of (1)-(30) and (38)-(41), and R_5 is as described in (XV1).

(43) In one embodiment, A_1 , A_2 , W , R_{A1} , R_1 , R_4 , R_X , and m are each as described, where applicable, in any one of (1)-(30) and (38)-(41), and R_5 is as described in (XV2).

25 (44) In one embodiment, A_1 , A_2 , W , R_{A1} , R_1 , R_4 , R_X , and m are each as described, where applicable, in any one of (1)-(30) and (38)-(41), and R_5 is as described in (XV3).

(45) In one embodiment, A_1 , A_2 , W , R_{A1} , R_1 , R_4 , R_5 , R_X , and m are each as described, where applicable, in any one of (1)-(44), and X_1 , X_2 , X_3 , and X_4 are as described in (X1).

30 (46) In one embodiment, A_1 , A_2 , W , R_{A1} , R_1 , R_4 , R_5 , R_X , and m are each as described, where applicable, in any one of (1)-(44), and X_1 , X_2 , X_3 , and X_4 are as described in (X2).

(47) In one embodiment, A₁, A₂, W, R_{A1}, R₁, R₄, R₅, R_X, and m are each as described, where applicable, in any one of (1)-(44), and X₁, X₂, X₃, and X₄ are as described in (X3).

(48) In one embodiment, A₁, A₂, W, R_{A1}, R₁, R₄, R₅, R_X, and m are each as described, where applicable, in any one of (1)-(44), and X₁, X₂, X₃, and X₄ are as described in (X4).

5 (49) In one embodiment, A₁, A₂, W, R_{A1}, R₁, R₄, R₅, R_X, and m are each as described, where applicable, in any one of (1)-(44), and X₁, X₂, X₃, and X₄ are as described in (X5).

(50) In one embodiment, A₁, A₂, W, R_{A1}, R₁, R₄, R₅, R_X, and m are each as described, where applicable, in any one of (1)-(44), and X₁, X₂, X₃, and X₄ are as described in (X6).

10 (51) In one embodiment, A₁, A₂, W, R_{A1}, R₁, R₄, R₅, R_X, and m are each as described, where applicable, in any one of (1)-(44), and X₁, X₂, X₃, and X₄ are as described in (X7).

(52) In one embodiment, A₁, A₂, W, R_{A1}, R₁, R₄, R₅, R_X, m, X₁, X₂, X₃, and X₄ are each as described, where applicable, in any one of (1)-(51), and X₅, X₆, X₇, and X₈ are as described in (X8).

15 (53) In one embodiment, A₁, A₂, W, R_{A1}, R₁, R₄, R₅, R_X, m, X₁, X₂, X₃, and X₄ are each as described, where applicable, in any one of (1)-(51), and X₅, X₆, X₇, and X₈ are as described in (X9).

(54) In one embodiment, A₁, A₂, W, R_{A1}, R₁, R₄, R₅, R_X, m, X₁, X₂, X₃, and X₄ are each as described, where applicable, in any one of (1)-(51), and X₅, X₆, X₇, and X₈ are as described in (X10).

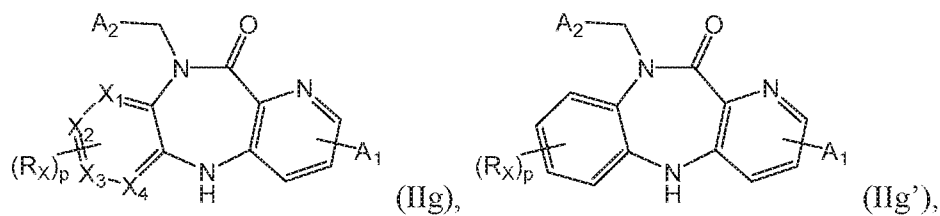
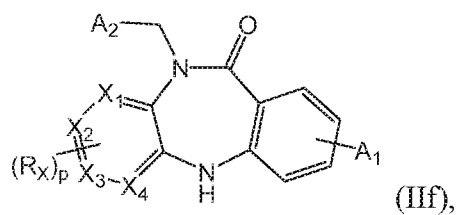
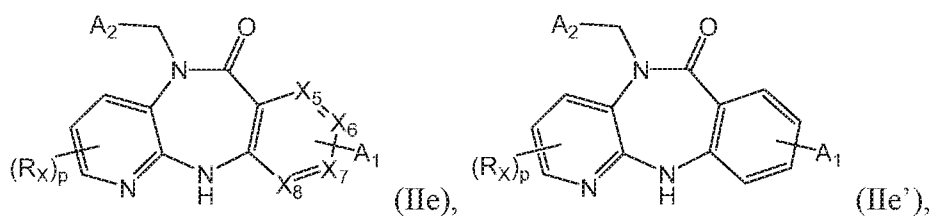
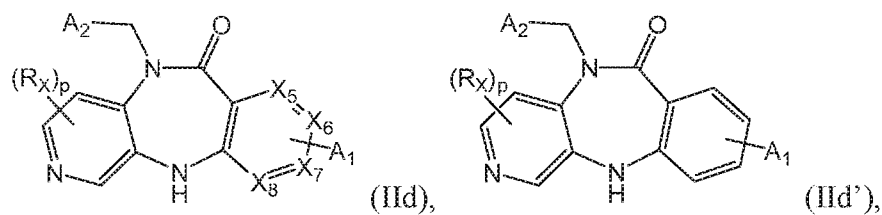
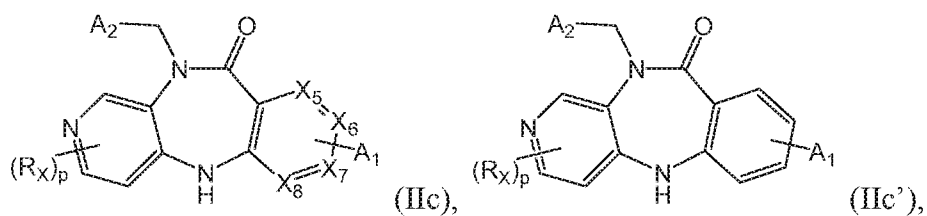
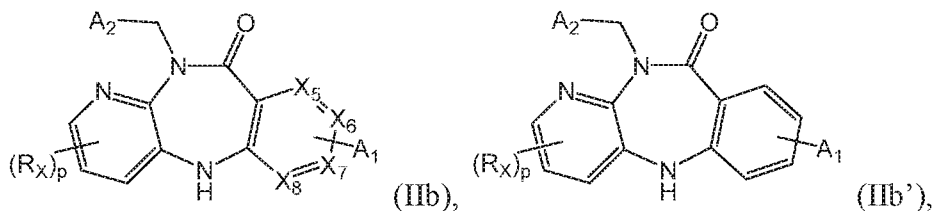
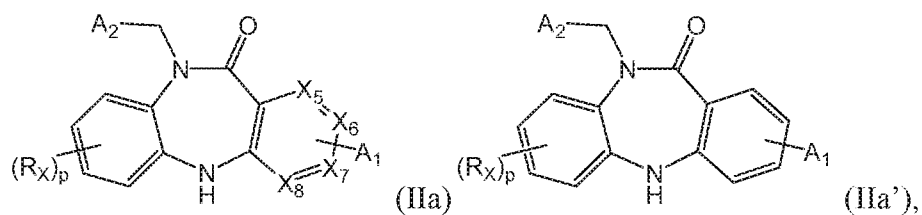
20 (55) In one embodiment, A₁, A₂, W, R_{A1}, R₁, R₄, R₅, R_X, m, X₁, X₂, X₃, and X₄ are each as described, where applicable, in any one of (1)-(51), and X₅, X₆, X₇, and X₈ are as described in (X11).

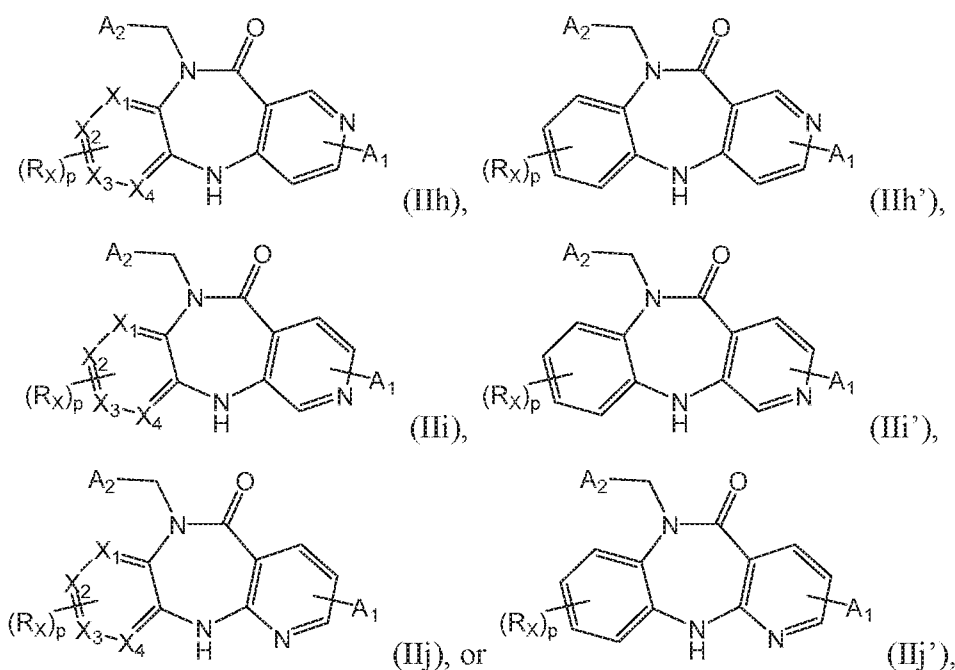
(56) In one embodiment, A₁, A₂, W, R_{A1}, R₁, R₄, R₅, R_X, m, X₁, X₂, X₃, and X₄ are each as described, where applicable, in any one of (1)-(51), and X₅, X₆, X₇, and X₈ are as described in 25 (X12).

(57) In one embodiment, A₁, A₂, W, R_{A1}, R₁, R₄, R₅, R_X, m, X₁, X₂, X₃, and X₄ are each as described, where applicable, in any one of (1)-(51), and X₅, X₆, X₇, and X₈ are as described in (X13).

30 (58) In one embodiment, A₁, A₂, W, R_{A1}, R₁, R₄, R₅, R_X, m, X₁, X₂, X₃, and X₄ are each as described, where applicable, in any one of (1)-(51), and X₅, X₆, X₇, and X₈ are as described in (X14).

In one embodiment, a compound of Formula Ia or Ib is of Formula IIa, IIa', IIb, IIb', IIc, IIc', IId, IId', IIe, IIe', IIg, IIg', IIh, IIh', Ili, Ili', IIj, or IIj':





or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein:

- 5 A₁, A₂, X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈, W, R_{A1}, R_{A2}, R₃, R₄, R₅, R_{n1}, R_{n2}, R_X, L₃, L₄, R_{L3a}, R_{L3b}, R_{E1}, R_{E2}, R_{E3}, R_{E4}, R_{EE}, R_{E5}, R_{E6}, R_{E7}, Y, a, and z are each as defined in Formula Ia or Ib; and

p is 1, 2, or 3.

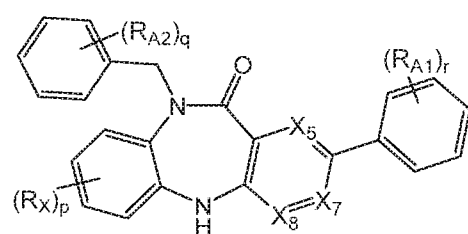
In one embodiment, p is 1 or 2.

- 10 In one embodiment, p is 1.

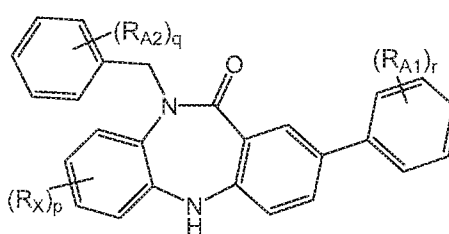
In one embodiment, p is 2.

- Any of the substituents described herein for any of A₁, A₂, X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈, W, R_{A1}, R_{A2}, R₃, R₄, R₅, R_{n1}, R_{n2}, R_X, L₃, L₄, R_{L3a}, R_{L3b}, R_{E1}, R_{E2}, R_{E3}, R_{E4}, R_{EE}, R_{E5}, R_{E6}, R_{E7}, Y, a, z, and p, for example, in Formula Ia or Ib and any of Formulae IIa, IIa', IIb, IIb', IIc, IIc', IId, IId', IIe, IIe', IIg, IIg', IIh, IIh', Ili, Ili', Iij, and Iij', can be combined with any of the substituents described herein for one or more of the remainder of A₁, A₂, X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈, W, R_{A1}, R_{A2}, R₃, R₄, R₅, R_{n1}, R_{n2}, R_X, L₃, L₄, R_{L3a}, R_{L3b}, R_{E1}, R_{E2}, R_{E3}, R_{E4}, R_{EE}, R_{E5}, R_{E6}, R_{E7}, Y, a, z, and p, for example, in any of Formula Ia or Ib and any of Formulae IIa, IIa', IIb, IIb', IIc, IIc', IId, IId', IIe, IIe', IIg, IIg', IIh, IIh', Ili, Ili', Iij, and Iij'.

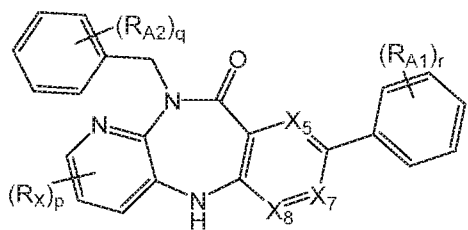
- 20 In one embodiment, a compound of Formula Ia or Ib is of Formula IIIa, IIIa', IIIb, IIIb', IIIc, IIIc', IIId, IIId', IIIe, or IIIe':



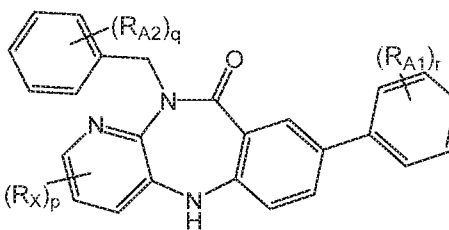
(IIIa),



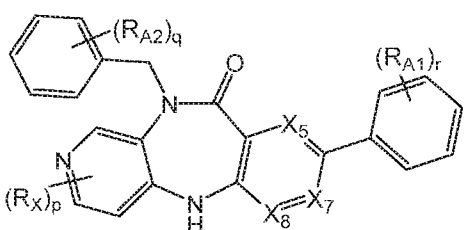
(IIIa'),



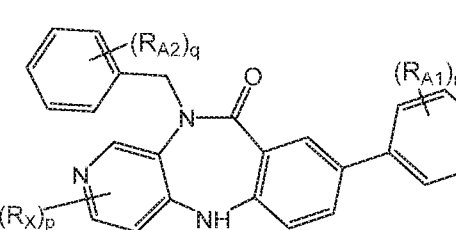
(IIIb),



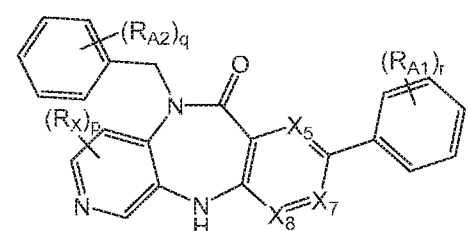
(IIIb'),



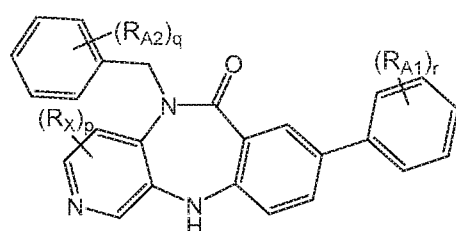
(IIIc),



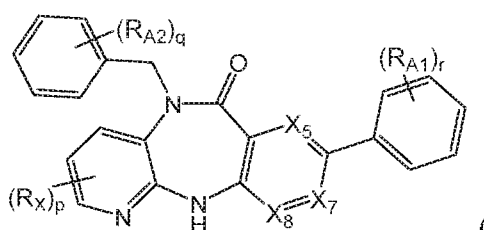
(IIIc'),



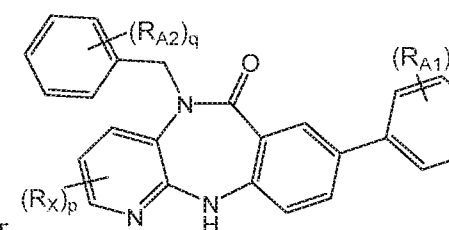
(IIId),



(IIId'),



(IIIe), or



(IIIe'),

or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein:

X₅, X₇, X₈, W, R_{A1}, R_{A2}, R₃, R₄, R₅, R_{n1}, R_{n2}, R_X, L₃, L₄, R_{L3a}, R_{L3b}, R_{E1}, R_{E2}, R_{E3}, R_{E4}, R_{EE}, R_{E5}, R_{E6}, R_{E7}, Y, a, and z are each as defined in Formula Ia or Ib;

p is 1, 2, or 3;

q is 0, 1, 2, 3, 4, or 5; and

r is 0, 1, 2, 3, 4, or 5.

In one embodiment, p is 1 or 2.

In one embodiment, p is 1.

In one embodiment, p is 2.

In one embodiment, q is 0 or 1.

In one embodiment, q is 0.

In one embodiment, q is 1.

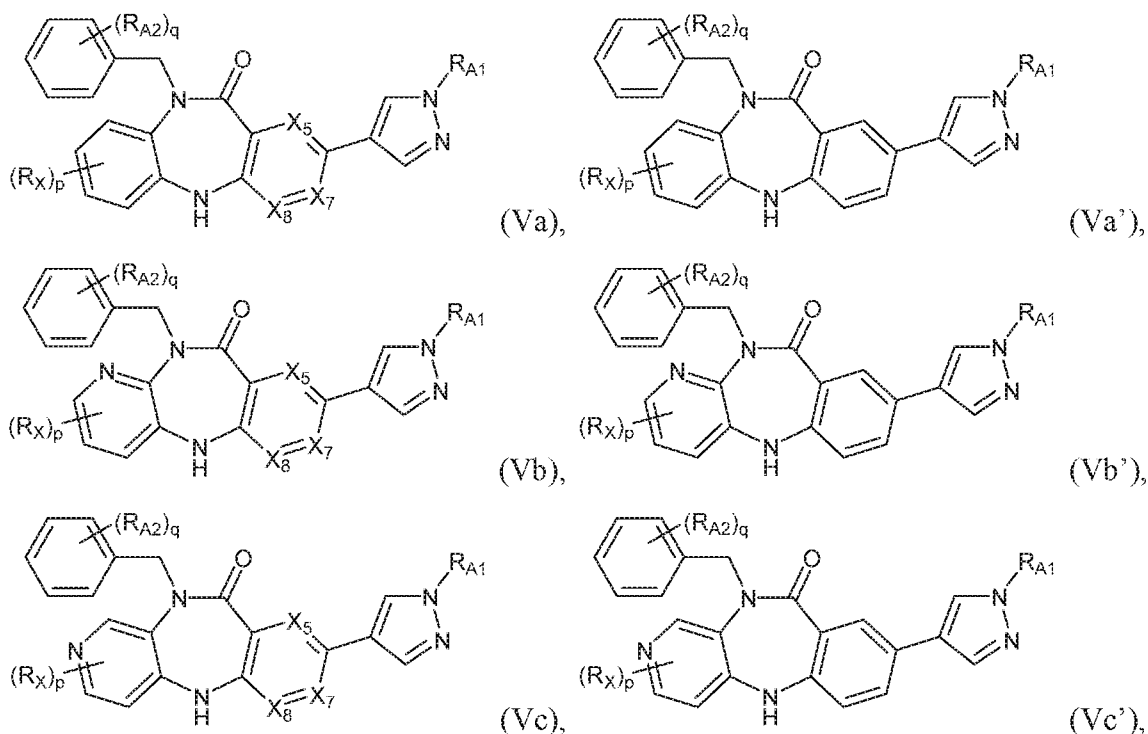
5 In one embodiment, r is 0 or 1.

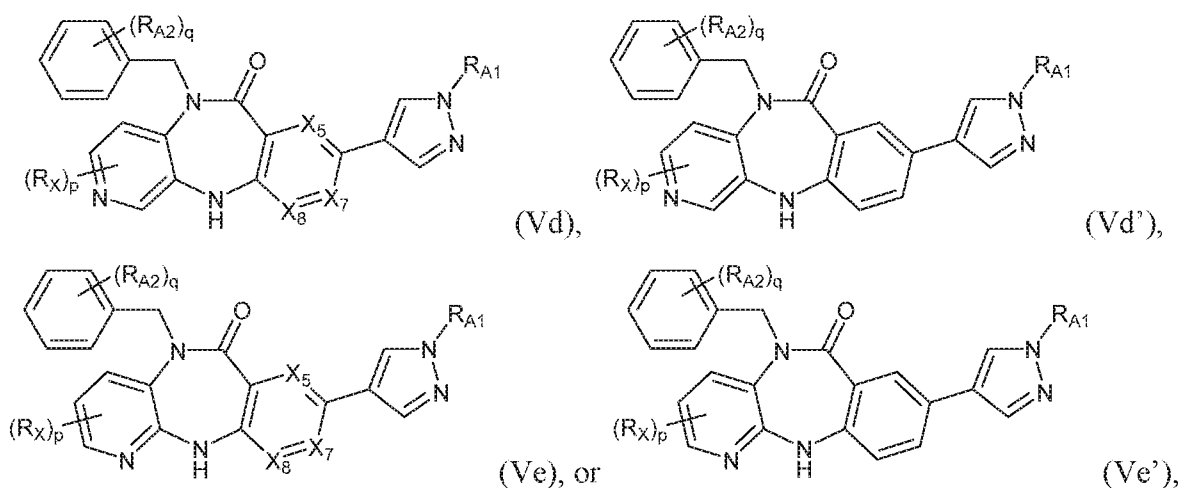
In one embodiment, r is 0.

In one embodiment, r is 1.

Any of the substituents described herein for any of X₅, X₇, X₈, W, R_{A1}, R_{A2}, R₃, R₄, R₅, R_{n1}, R_{n2}, R_X, L₃, L₄, R_{L3a}, R_{L3b}, R_{E1}, R_{E2}, R_{E3}, R_{E4}, R_{EE}, R_{E5}, R_{E6}, R_{E7}, Y, a, z, p, q, and r, for example, in Formula Ia or Ib and any of Formulae IIIa, IIIa', IIIb, IIIb', IIIc, IIIc', IIId, IIId', IIIe, and IIIe', can be combined with any of the substituents described herein for one or more of the remainder of X₅, X₇, X₈, W, R_{A1}, R_{A2}, R₃, R₄, R₅, R_{n1}, R_{n2}, R_X, L₃, L₄, R_{L3a}, R_{L3b}, R_{E1}, R_{E2}, R_{E3}, R_{E4}, R_{EE}, R_{E5}, R_{E6}, R_{E7}, Y, a, z, p, q, and r, for example, in any of Formula Ia or Ib and any of Formulae IIIa, IIIa', IIIb, IIIb', IIIc, IIIc', IIId, IIId', IIIe, and IIIe'.

15 In one embodiment, a compound of Formula Ia or Ib is of Formula Va, Va', Vb, Vb', Vc, Vc', Vd, Vd', Ve or Ve':





or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein:

X_5 , X_7 , X_8 , R_{A1} , R_{A2} , R_{n1} , R_{n2} , R_3 , R_4 , and R_X are each as defined in Formula Ia or Ib;

p is 0, 1, 2, or 3; and

q is 0, 1, 2, 3, 4, or 5.

In one embodiment, p is 0 or 1.

In one embodiment, p is 0.

In one embodiment, p is 1.

In one embodiment, q is 0 or 1.

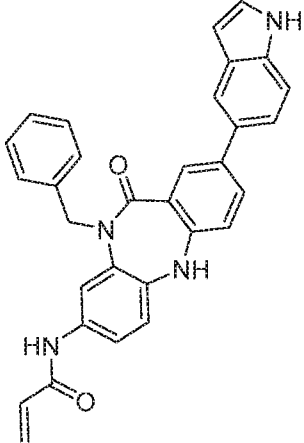
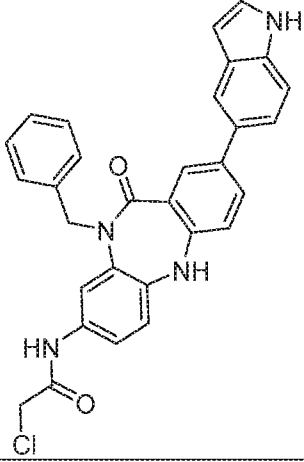
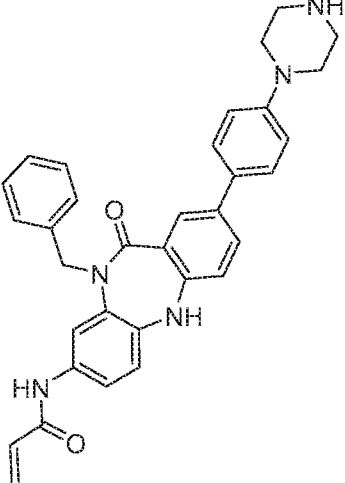
In one embodiment, q is 0.

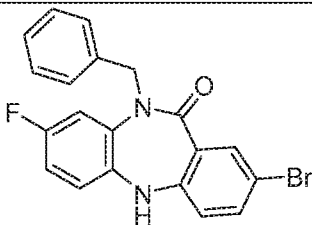
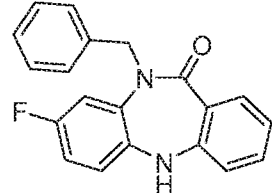
In one embodiment, q is 1.

Any of the substituents described herein for any of X_5 , X_7 , X_8 , R_{A1} , R_{A2} , R_{n1} , R_{n2} , R_3 , R_4 , R_X , p , q , and r , for example, in Formula Ia or Ib and any of Formulae Va, Va', Vb, Vb', Vc, Vc', Vd, Vd', Ve, and Ve', can be combined with any of the substituents described herein for one or more of the remainder of X_5 , X_7 , X_8 , R_{A1} , R_{A2} , R_{n1} , R_{n2} , R_3 , R_4 , R_X , p , q , and r , for example, in any of Formula Ia or Ib and any of Formulae Va, Va', Vb, Vb', Vc, Vc', Vd, Vd', Ve, and Ve'.

Non-limiting illustrative compounds of the application are included in Table A:

Table A

Compound ID	Structure
I-1	
I-2	
I-3	

Compound ID	Structure
I-a	
I-b	

A compound that binds to an allosteric site in EGFR, such as the compounds of the present application (*e.g.*, the compounds of the formulae disclosed herein), optionally in combination with a second agent that prevents EGFR dimer formation, are capable of modulating (*e.g.*, inhibiting or decreasing) EGFR activity. In some embodiments, the compounds of the present application are capable of inhibiting or decreasing EGFR activity, without a second agent (*e.g.*, an antibody such as cetuximab, trastuzumab, or panitumumab). In other embodiments, the compounds of the present application, in combination with a second agent that prevents EGFR dimer formation (*e.g.*, an antibody such as cetuximab, trastuzumab, or panitumumab), are capable of inhibiting or decreasing EGFR activity. In some embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

In some embodiments, the compounds of the present application are capable of modulating (*e.g.*, inhibiting or decreasing) the activity of EGFR containing one or more mutations. In some embodiments, the mutant EGFR contains one or more mutations selected from T790M, L718Q, L844V, V948R, L858R, I941R, C797S, Del (*e.g.*, deletion in exon 19), and Insertion (*e.g.*, insertion in exon 20). In some embodiments, the mutant EGFR contains C797S. In other embodiments, the mutant EGFR contains a combination of mutations, wherein the combination is selected from Del/L718Q, Del/L844V, Del/T790M, Del/T790M/L718Q, Del/T790M/L844V, L858R/L718Q, L858R/L844V, L858R/T790M, L858R/T790M/I941R, Del/T790M, Del/T790M/C797S, L858R/T790M/C797S, and L858R/T790M/L718Q. In other

embodiments, the mutant EGFR contains a combination of mutations, wherein the combination is selected from Del/L844V, L858R/L844V, L858R/T790M, L858R/T790M/I941R, L858R/T790M/C797S, Del/T790M, and Del/T790M/C797S. In other embodiments, the mutant EGFR contains a combination of mutations, wherein the combination is selected from
5 L858R/T790M, L858R/T790M/I941R, L858R/T790M/C797S, Del/T790M, Del/T790M/C797S, and L858R/T790M.

In some embodiments, the compounds of the present application in combination with a second agent that prevents EGFR dimer formation are capable of modulating (*e.g.*, inhibiting or decreasing) the activity of EGFR containing one or more mutations (*e.g.*, the EGFR containing
10 one or more mutations described herein). In some embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

In some embodiments, the compounds of the present application are capable of
15 modulating (*e.g.*, inhibiting or decreasing) the activity of EGFR containing one or more mutations, but do not affect the activity of a wild-type EGFR.

In other embodiments, the compounds of the present application in combination with a second agent that prevents EGFR dimer formation are capable of modulating (*e.g.*, inhibiting or decreasing) the activity of EGFR containing one or more mutations, but do not affect the activity
20 of a wild-type EGFR. In some embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

Modulation of EGFR containing one or more mutations, such as those described herein,
25 but not a wild-type EGFR, provides a novel approach to the treatment, prevention, or amelioration of diseases including, but not limited to, cancer and metastasis, inflammation, arthritis, systemic lupus erythematosus, skin-related disorders, pulmonary disorders, cardiovascular disease, ischemia, neurodegenerative disorders, liver disease, gastrointestinal disorders, viral and bacterial infections, central nervous system disorders, Alzheimer's disease,
30 Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, and peripheral neuropathy.

In some embodiments, the compounds of the application exhibit greater inhibition of EGFR containing one or more mutations as described herein relative to a wild-type EGFR. In certain embodiments, the compounds of the application exhibit at least 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold or 100-fold greater inhibition of EGFR containing one or more mutations as described herein relative to a wild-type EGFR. In various embodiments, the compounds of the application exhibit up to 1000-fold greater inhibition of EGFR containing one or more mutations as described herein relative to a wild-type EGFR. In various embodiments, the compounds of the application exhibit up to 10000-fold greater inhibition of EGFR having a combination of mutations described herein relative to a wild-type EGFR.

In other embodiments, the compounds of the application in combination with a second agent that prevents EGFR dimer formation exhibit greater inhibition of EGFR containing one or more mutations as described herein relative to a wild-type EGFR. In certain embodiments, the compounds of the application in combination with a second agent that prevents EGFR dimer formation exhibit at least 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold or 100-fold greater inhibition of EGFR containing one or more mutations as described herein relative to a wild-type EGFR. In various embodiments, the compounds of the application in combination with a second agent that prevents EGFR dimer formation exhibit up to 1000-fold greater inhibition of EGFR containing one or more mutations as described herein relative to a wild-type EGFR. In various embodiments, the compounds of the application in combination with a second agent that prevents EGFR dimer formation exhibit up to 10000-fold greater inhibition of EGFR having a combination of mutations described herein relative to a wild-type EGFR. In some embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

In some embodiments, the compounds of the application exhibit from about 2-fold to about 10-fold greater inhibition of EGFR containing one or more mutations as described herein relative to a wild-type EGFR. In various embodiments, the compounds of the application exhibit from about 10-fold to about 100-fold greater inhibition of EGFR containing one or more mutations as described herein relative to a wild-type EGFR. In various embodiments, the compounds of the application exhibit from about 100-fold to about 1000-fold greater inhibition

of EGFR containing one or more mutations as described herein relative to a wild-type EGFR. In various embodiments, the compounds of the application exhibit from about 1000-fold to about 10000-fold greater inhibition of EGFR containing one or more mutations as described herein relative to a wild-type EGFR.

5 In other embodiments, the compounds of the application in combination with a second agent that prevents EGFR dimer formation exhibit from about 2-fold to about 10-fold greater inhibition of EGFR containing one or more mutations as described herein relative to a wild-type EGFR. In other embodiments, the compounds of the application in combination with a second agent that prevents EGFR dimer formation exhibit from about 10-fold to about 100-fold greater
10 inhibition of EGFR containing one or more mutations as described herein relative to a wild-type EGFR. In other embodiments, the compounds of the application in combination with a second agent that prevents EGFR dimer formation exhibit from about 100-fold to about 1000-fold greater inhibition of EGFR containing one or more mutations as described herein relative to a wild-type EGFR. In other embodiments, the compounds of the application in combination with a
15 second agent that prevents EGFR dimer formation exhibit from about 1000-fold to about 10000-fold greater inhibition of EGFR containing one or more mutations as described herein relative to a wild-type EGFR. In other embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that
20 prevents EGFR dimer formation is cetuximab.

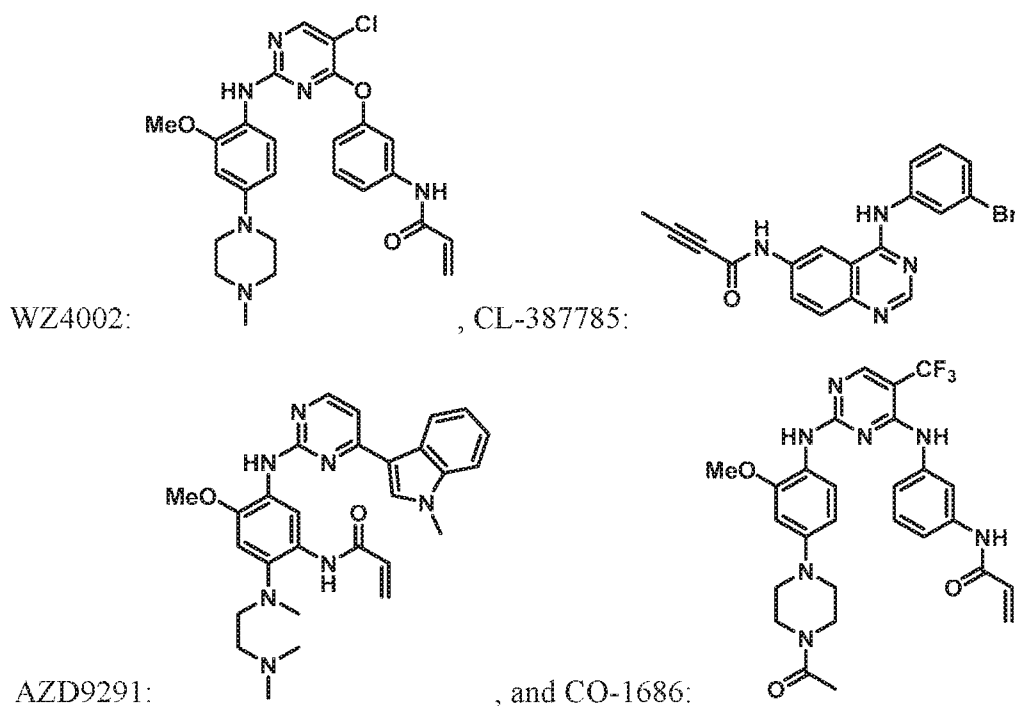
In some embodiments, the inhibition of EGFR activity is measured by IC_{50} .

In some embodiments, the inhibition of EGFR activity is measured by EC_{50} .

In some embodiments, the compounds of the application bind to an allosteric site in EGFR. In some embodiments, the compounds of the application interact with at least one amino
25 acid residue of EGFR selected from Lys745, Leu788, and Ala 743. In other embodiments, the compounds of the application interact with at least one amino acid residue of EGFR selected from Cys755, Leu777, Phe856, and Asp855. In other embodiments, the compounds of the application interact with at least one amino acid residue of EGFR selected from Met766, Ile759, Glu762, and Ala763. In other embodiments, the compounds of the application interact with at
30 least one amino acid residue of EGFR selected from Lys745, Leu788, and Ala 743, at least one amino acid residue of EGFR selected from Cys755, Leu777, Phe856, and Asp855, and at least

one amino acid residue of EGFR selected from Met766, Ile759, Glu762, and Ala763. In other embodiments, the compounds of the application do not interact with the any of the amino acid residues of EGFR selected from Met793, Gly796, and Cys797.

In some embodiments, the application provides a compound (*e.g.*, an allosteric kinase inhibitor), wherein the compound is a more potent inhibitor of a drug-resistant EGFR mutant relative to a wild type EGFR. For example, the compound can be at least about 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold or about 100-fold more potent at inhibiting the kinase activity of the drug-resistant EGFR mutant relative to a wild-type EGFR. In some embodiments, the drug-resistant EGFR mutant is resistant to one or more known EGFR inhibitors, including but not limited to gefitinib, erlotinib, afatinib, lapatinib, neratinib,



In some embodiments, the drug-resistant EGFR mutant comprises a sensitizing mutation, such as Del and L858R.

In some embodiments, the application provides a compound (*e.g.*, an allosteric kinase inhibitor) in combination with a second agent that prevents EGFR dimer formation, wherein the compound is a more potent inhibitor of a drug-resistant EGFR mutant relative to a wild type EGFR. For example, the compound in combination with a second agent that prevents EGFR dimer formation can be at least about 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold or about 100-fold more potent at inhibiting the kinase activity of the drug-resistant EGFR mutant relative

to a wild-type EGFR. In some embodiments, the drug-resistant EGFR mutant is resistant to one or more known EGFR inhibitors, including but not limited to gefitinib, erlotinib, afatinib, lapatinib, neratinib, WZ4002, CL-387785, AZD9291, and CO-1686. In some embodiments, the drug-resistant EGFR mutant comprises a sensitizing mutation, such as Del and L858R. In some
5 embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

 In some embodiments, the application provides a compound (*e.g.*, an allosteric kinase
10 inhibitor), wherein the compound inhibits kinase activity of a drug-resistant EGFR mutant harboring a sensitizing mutation (*e.g.*, Del and L858R) and a drug-resistance mutation (*e.g.*, T790M, L718Q, C797S, and L844V) with less than a 10-fold difference in potency (*e.g.*, as measured by IC₅₀) relative to an EGFR mutant harboring the sensitizing mutation but not the drug-resistance mutation. In some embodiments, the difference in potency is less than about 9-
15 fold, 8-fold, 7-fold, 6-fold, 5-fold, 4-fold, 3-fold, or 2-fold.

 In other embodiments, the application provides a compound (*e.g.*, an allosteric kinase inhibitor) in combination with a second agent that prevents EGFR dimer formation, wherein the compound in combination with the second agent inhibits kinase activity of a drug-resistant EGFR mutant harboring a sensitizing mutation (*e.g.*, Del and L858R) and a drug-resistance
20 mutation (*e.g.*, T790M, L718Q, C797S, and L844V) with less than a 10-fold difference in potency (*e.g.*, as measured by IC₅₀) relative to an EGFR mutant harboring the sensitizing mutation but not the drug-resistance mutation. In some embodiments, the difference in potency is less than about 9-fold, 8-fold, 7-fold, 6-fold, 5-fold, 4-fold, 3-fold, or 2-fold. In some
25 embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

 In some embodiments, the application provides a compound (*e.g.*, an allosteric kinase inhibitor), wherein the compound is more potent than one or more known EGFR inhibitors,
30 including but not limited to gefitinib, erlotinib, afatinib, lapatinib, neratinib, WZ4002, CL-387785, AZD9291, and CO-1686, at inhibiting the activity of EGFR containing one or more

mutations as described herein. For example, the compound can be at least about 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold or about 100-fold more potent (*e.g.*, as measured by IC₅₀) than gefitinib, erlotinib, afatinib, lapatinib, neratinib, WZ4002, CL-387785, AZD9291, and CO-1686 at inhibiting the activity of the EGFR containing one or more mutations as described herein.

5 In other embodiments, the application provides a compound (*e.g.*, an allosteric kinase inhibitor) in combination with a second agent that prevents EGFR dimer formation, wherein the compound in combination with the second agent is more potent than one or more known EGFR inhibitors, including but not limited to gefitinib, erlotinib, afatinib, lapatinib, neratinib, WZ4002, CL-387785, AZD9291, and CO-1686, at inhibiting the activity of EGFR containing one or more
10 mutations as described herein, such as T790M, L718Q, L844V, L858R, C797S, and Del. For example, the compound in combination with a second agent that prevents EGFR dimer formation can be at least about 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold or about 100-fold more potent (*e.g.*, as measured by IC₅₀) than gefitinib, erlotinib, afatinib, lapatinib, neratinib, WZ4002, CL-387785, AZD9291, and CO-1686 at inhibiting the activity of the EGFR containing one or
15 more mutations as described herein. In some embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

In some embodiments, the application provides a compound (*e.g.*, an allosteric kinase
20 inhibitor), wherein the compound is less potent than one or more known EGFR inhibitors, including but not limited to gefitinib, erlotinib, afatinib, lapatinib, neratinib, WZ4002, CL-387785, AZD9291, and CO-1686, at inhibiting the activity of a wild-type EGFR. For example, the compound can be at least about 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold or about 100-fold less potent (*e.g.*, as measured by IC₅₀) than gefitinib, erlotinib, afatinib, lapatinib, neratinib,
25 WZ4002, CL-387785, AZD9291, and CO-1686, at inhibiting the activity of a wild-type EGFR.

In other embodiments, the application provides a compound (*e.g.*, an allosteric kinase
inhibitor) in combination with a second agent that prevents EGFR dimer formation, wherein the compound in combination with the second agent is less potent than one or more known EGFR
inhibitors, including but not limited to gefitinib, erlotinib, afatinib, lapatinib, neratinib, WZ4002,
30 CL-387785, AZD9291, and CO-1686, at inhibiting the activity of a wild-type EGFR. For example, the compound in combination with a second agent that prevents EGFR dimer formation

can be at least about 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold or about 100-fold less potent (e.g., as measured by IC₅₀) than gefitinib, erlotinib, afatinib, lapatinib, neratinib, WZ4002, CL-387785, AZD9291, and CO-1686, at inhibiting the activity of a wild-type EGFR. In some embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further
5 embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

Potency of the inhibitor can be determined by EC₅₀ value. A compound with a lower EC₅₀ value, as determined under substantially similar conditions, is a more potent inhibitor
10 relative to a compound with a higher EC₅₀ value. In some embodiments, the substantially similar conditions comprise determining an EGFR-dependent phosphorylation level, *in vitro* or *in vivo* (e.g., in 3T3 cells expressing a wild type EGFR, a mutant EGFR, or a fragment of any thereof).

Potency of the inhibitor can also be determined by IC₅₀ value. A compound with a lower IC₅₀ value, as determined under substantially similar conditions, is a more potent inhibitor
15 relative to a compound with a higher IC₅₀ value. In some embodiments, the substantially similar conditions comprise determining an EGFR-dependent phosphorylation level, *in vitro* or *in vivo* (e.g., in 3T3 cells expressing a wild type EGFR, a mutant EGFR, or a fragment of any thereof).

An EGFR sensitizing mutation comprises without limitation L858R, G719S, G719C, G719A, L861Q, a deletion in exon 19 and/or an insertion in exon 20. A drug-resistant EGFR
20 mutant can have without limitation a drug resistance mutation comprising T790M, T854A, L718Q, C797S, or D761Y.

The selectivity between wild-type EGFR and EGFR containing one or more mutations as described herein can also be measured using cellular proliferation assays where cell proliferation is dependent on kinase activity. For example, murine Ba/F3 cells transfected with a suitable
25 version of wild-type EGFR (such as VIII, containing a WT EGFR kinase domain), or Ba/F3 cells transfected with L858R/T790M, Del/T790M/L718Q, L858R/T790M/L718Q, L858R/T790M/C797S, Del/T790M/C797S, L858R/T790M/I941R, or Exon 19 deletion/T790M can be used. Proliferation assays are performed at a range of inhibitor concentrations (e.g., 10 μM, 3 μM, 1.1 μM, 330 nM, 110 nM, 33 nM, 11 nM, 3 nM, 1 nM) and an EC₅₀ is calculated.

30 An alternative method to measure effects on EGFR activity is to assay EGFR phosphorylation. Wild type or mutant (L858R/T790M, Del/T790M, Del/T790M/L718Q,

L858R/T790M/C797S, Del/T790M/C797S, L858R/T790M/I941R, or L858R/T790M/L718Q) EGFR can be transfected into cells which do not normally express endogenous EGFR and the ability of the inhibitor (using concentrations as above) to inhibit EGFR phosphorylation can be assayed. Cells are exposed to increasing concentrations of inhibitor and stimulated with EGF.

5 The effects on EGFR phosphorylation are assayed by Western Blotting using phospho-specific EGFR antibodies.

In another aspect, the present application relates to a compound that binds to an allosteric site in EGFR, wherein the compound exhibits greater than 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold, 100-fold, or 1000-fold inhibition of EGFR containing one or more mutations as described herein (*e.g.*, L858R/T790M, Del/T790M, Del/T790M/L718Q, L858R/T790M/C797S, 10 Del/T790M/C797S, L858R/T790M/I941R, or L858R/T790M/L718Q) relative to a wild-type EGFR.

In other embodiments, the application provides a compound that binds to an allosteric site in EGFR in combination with a second agent that prevents EGFR dimer formation, wherein the 15 compound in combination with the second agent greater than 2-fold, 3-fold, 5-fold, 10-fold, 25-fold, 50-fold, 100-fold, or 1000-fold inhibition of EGFR containing one or more mutations as described herein (*e.g.*, L858R/T790M, Del/T790M, Del/T790M/L718Q, Del/T790M/C797S, L858R/T790M/C797S, L858R/T790M/I941R, or L858R/T790M/L718Q) relative to a wild-type EGFR. In some embodiments, the second agent that prevents EGFR 20 dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

Another aspect is an isotopically labeled compound of any of the formulae delineated herein. Such compounds have one or more isotope atoms which may or may not be radioactive 25 (*e.g.*, ^3H , ^2H , ^{14}C , ^{13}C , ^{18}F , ^{35}S , ^{32}P , ^{125}I , and ^{131}I) introduced into the compound. Such compounds are useful for drug metabolism studies and diagnostics, as well as therapeutic applications.

The application also provides for a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, together with 30 a pharmaceutically acceptable carrier.

In another aspect, the application provides a kit comprising a compound capable of inhibiting EGFR activity selected from one or more compounds of disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, optionally in combination with a second agent that prevents EGFR dimer formation and instructions for use in treating cancer.

5 In another aspect, the application provides a method of synthesizing a compound disclosed herein. The synthesis of the compounds of the application can be found herein and in the schemes and Examples below. Other embodiments are a method of making a compound of any of the formulae herein using any one, or combination of, reactions delineated herein. The method can include the use of one or more intermediates or chemical reagents delineated herein.

10 The compounds of the application are defined herein by their chemical structures and/or chemical names. Where a compound is referred to by both a chemical structure and a chemical name, and the chemical structure and chemical name conflict, the chemical structure is determinative of the compound's identity.

The recitation of a listing of chemical groups in any definition of a variable herein
15 includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

Definitions

20 Listed below are definitions of various terms used to describe this application. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

The term "alkyl," as used herein, refers to saturated, straight- or branched-chain hydrocarbon radicals containing, in certain embodiments, between one and six, or one and eight
25 carbon atoms, respectively. Examples of C₁-C₆ alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, *tert-butyl*, neopentyl, n-hexyl radicals; and examples of C₁-C₈ alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, *tert-butyl*, neopentyl, n-hexyl, heptyl, octyl radicals.

The term "alkenyl," as used herein, denotes a monovalent group derived from a
30 hydrocarbon moiety containing, in certain embodiments, from two to six, or two to eight carbon atoms having at least one carbon-carbon double bond. The double bond may or may not be the

point of attachment to another group. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, heptenyl, octenyl and the like.

The term "alkynyl," as used herein, denotes a monovalent group derived from a hydrocarbon moiety containing, in certain embodiments, from two to six, or two to eight carbon atoms having at least one carbon-carbon triple bond. The alkynyl group may or may not be the point of attachment to another group. Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1-propynyl, 1-butyne, heptynyl, octynyl and the like.

The term "alkoxy" refers to an -O-alkyl radical.

The term "aryl," as used herein, refers to a mono- or poly-cyclic carbocyclic ring system having one or more aromatic rings, fused or non-fused, including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like.

The term "aralkyl," as used herein, refers to an alkyl residue attached to an aryl ring. Examples include, but are not limited to, benzyl, phenethyl and the like.

The term "cycloalkyl," as used herein, denotes a monovalent group derived from a monocyclic or polycyclic saturated or partially unsaturated carbocyclic ring compound. Examples of C₃-C₈ cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; and examples of C₃-C₁₂-cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl. Also contemplated is a monovalent group derived from a monocyclic or polycyclic carbocyclic ring compound having at least one carbon-carbon double bond by the removal of a single hydrogen atom. Examples of such groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like.

The term "heteroaryl," as used herein, refers to a mono- or poly-cyclic (*e.g.*, bi-, or tri-cyclic or more) fused or non-fused, radical or ring system having at least one aromatic ring, having from five to ten ring atoms of which one ring atom is selected from S, O, and N; zero, one, or two ring atoms are additional heteroatoms independently selected from S, O, and N; and the remaining ring atoms are carbon. Heteroaryl includes, but is not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzooxazolyl, quinoxalinyl, and the like.

The term "heteroaralkyl," as used herein, refers to an alkyl residue attached to a heteroaryl ring. Examples include, but are not limited to, pyridinylmethyl, pyrimidinylethyl and the like.

The term "heterocyclyl," or "heterocycloalkyl," as used herein, refers to a non-aromatic 3-, 4-, 5-, 6- or 7-membered ring or a bi- or tri-cyclic group fused of non-fused system, where (i) each ring contains between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, (ii) each 5-membered ring has 0 to 1 double bonds and each 6-membered ring has 0 to 2 double bonds, (iii) the nitrogen and sulfur heteroatoms may optionally be oxidized, and (iv) the nitrogen heteroatom may optionally be quaternized. Representative heterocycloalkyl groups include, but are not limited to, [1,3]dioxolane, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl.

The term "alkylamino" refers to a group having the structure $\text{-NH}(\text{C}_1\text{-C}_{12} \text{ alkyl})$, *e.g.*, $\text{-NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$, where $\text{C}_1\text{-C}_{12}$ alkyl is as previously defined.

The term "dialkylamino" refers to a group having the structure $\text{-N}(\text{C}_1\text{-C}_{12} \text{ alkyl})_2$, *e.g.*, $\text{-NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$, where $\text{C}_1\text{-C}_{12}$ alkyl is as previously defined.

The term "acyl" includes residues derived from acids, including but not limited to carboxylic acids, carbamic acids, carbonic acids, sulfonic acids, and phosphorous acids. Examples include aliphatic carbonyls, aromatic carbonyls, aliphatic sulfonyls, aromatic sulfinyls, aliphatic sulfinyls, aromatic phosphates and aliphatic phosphates. Examples of aliphatic carbonyls include, but are not limited to, acetyl, propionyl, 2-fluoroacetyl, butyryl, 2-hydroxy acetyl, and the like.

In accordance with the application, any of the aryls, substituted aryls, heteroaryls and substituted heteroaryls described herein, can be any aromatic group. Aromatic groups can be substituted or unsubstituted.

The terms "hal," "halo," and "halogen," as used herein, refer to an atom selected from fluorine, chlorine, bromine and iodine.

As described herein, compounds of the application may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the application. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted."

In general, the term "substituted", whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. The terms "optionally substituted", "optionally substituted alkyl", "optionally substituted alkenyl", "optionally substituted alkynyl", "optionally substituted cycloalkyl", "optionally substituted cycloalkenyl", "optionally substituted aryl", "optionally substituted heteroaryl", "optionally substituted aralkyl", "optionally substituted heteroaralkyl", "optionally substituted heterocycloalkyl", and any other optionally substituted group as used herein, refer to groups that are substituted or unsubstituted by independent replacement of one, two, or three or more of the hydrogen atoms thereon with substituents including, but not limited to:

-F, -Cl, -Br, -I, -OH, protected hydroxy, -NO₂, -CN, -NH₂, protected amino, -NH-C₁-C₁₂-alkyl, -NH-C₂-C₁₂-alkenyl, -NH-C₂-C₁₂-alkenyl, -NH-C₃-C₁₂-cycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -dialkylamino, -diarylramino, -diheteroarylramino, -O-C₁-C₁₂-alkyl, -O-C₂-C₁₂-alkenyl, -O-C₂-C₁₂-alkenyl, -O-C₃-C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)-C₁-C₁₂-alkyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₃-C₁₂-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -CONH₂, -CONH-C₁-C₁₂-alkyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₃-C₁₂-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO₂-C₁-C₁₂-alkyl, -OCO₂-C₂-C₁₂-alkenyl, -OCO₂-C₂-C₁₂-alkenyl, -OCO₂-C₃-C₁₂-cycloalkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCO₂-heterocycloalkyl, -OCONH₂, -OCONH-C₁-C₁₂-alkyl, -OCONH-C₂-C₁₂-alkenyl, -OCONH-C₂-C₁₂-alkenyl, -OCONH-C₃-C₁₂-cycloalkyl, -OCONH-aryl, -OCONH-heteroaryl, -OCONH-heterocycloalkyl, -NHC(O)-C₁-C₁₂-alkyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₃-C₁₂-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -NHCO₂-C₁-C₁₂-alkyl, -NHCO₂-C₂-C₁₂-alkenyl, -NHCO₂-C₂-C₁₂-alkenyl, -NHCO₂-C₃-C₁₂-cycloalkyl, -NHCO₂-aryl, -NHCO₂-heteroaryl, -NHCO₂-heterocycloalkyl, -NHC(O)NH₂, -NHC(O)NH-C₁-C₁₂-alkyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₃-C₁₂-cycloalkyl, -NHC(O)NH-aryl,

- NHC(O)NH-heteroaryl, NHC(O)NH-heterocycloalkyl, -NHC(S)NH₂,
 -NHC(S)NH-C₁-C₁₂-alkyl, -NHC(S)NH-C₂-C₁₂-alkenyl,
 -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl,
 -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂,
 5 -NHC(NH)NH-C₁-C₁₂-alkyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₂-C₁₂-alkenyl,
 -NHC(NH)NH-C₃-C₁₂-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl,
 -NHC(NH)NH-heterocycloalkyl, -NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₁₂-alkenyl,
 -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₃-C₁₂-cycloalkyl, -NHC(NH)-aryl,
 -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C₁-C₁₂-alkyl,
 10 -C(NH)NH-C₂-C₁₂-alkenyl, -C(NH)NH-C₂-C₁₂-alkenyl, C(NH)NH-C₃-C₁₂-cycloalkyl,
 -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl,
 -S(O)-C₁-C₁₂-alkyl, -S(O)-C₂-C₁₂-alkenyl, -S(O)-C₂-C₁₂-alkenyl,
 -S(O)-C₃-C₁₂-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-heterocycloalkyl -SO₂NH₂,
 -SO₂NH-C₁-C₁₂-alkyl, -SO₂NH-C₂-C₁₂-alkenyl, -SO₂NH-C₂-C₁₂-alkenyl,
 15 -SO₂NH-C₃-C₁₂-cycloalkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -SO₂NH-heterocycloalkyl,
 -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₂-C₁₂-alkenyl,
 -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl,
 -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl,
 -C₃-C₁₂-cycloalkyl, polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH,
 20 -S-C₁-C₁₂-alkyl, -S-C₂-C₁₂-alkenyl, -S-C₂-C₁₂-alkenyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl,
 -S-heteroaryl, -S-heterocycloalkyl, or methylthiomethyl.

It is understood that the aryls, heteroaryls, alkyls, and the like can be substituted.

- The term "cancer" includes, but is not limited to, the following cancers: epidermoid Oral:
 buccal cavity, lip, tongue, mouth, pharynx; Cardiac: sarcoma (angiosarcoma, fibrosarcoma,
 25 rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma, and teratoma;
 Lung: bronchogenic carcinoma (squamous cell or epidermoid, undifferentiated small cell,
 undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial
 adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal:
 esophagus (squamous cell carcinoma, larynx, adenocarcinoma, leiomyosarcoma, lymphoma),
 30 stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma,
 insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel or small

intestines (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel or large intestines (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), colon, colon-rectum, colorectal, rectum; Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma),
 5 lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma,
 10 hemangioma, biliary passages; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocyoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma,
 15 hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical
 20 dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma),
 25 breast; Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma) hairy cell; lymphoid disorders; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, keratoacanthoma, moles dysplastic nevi, lipoma,
 30 angioma, dermatofibroma, keloids, psoriasis, Thyroid gland: papillary thyroid carcinoma, follicular thyroid carcinoma; medullary thyroid carcinoma, undifferentiated thyroid cancer,

multiple endocrine neoplasia type 2A, multiple endocrine neoplasia type 2B, familial medullary thyroid cancer, pheochromocytoma, paraganglioma; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

5 The term "EGFR" herein refers to epidermal growth factor receptor kinase.

 The term "HER" or "Her", herein refers to human epidermal growth factor receptor kinase.

 The term "subject" as used herein refers to a mammal. A subject therefore refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, and the like. Preferably the subject is a
10 human. When the subject is a human, the subject may be referred to herein as a patient.

 "Treat", "treating" and "treatment" refer to a method of alleviating or abating a disease and/or its attendant symptoms.

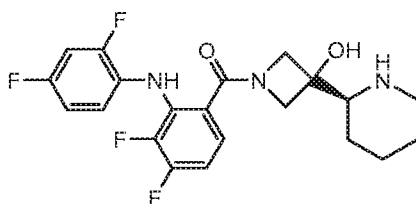
 As used herein, "preventing" or "prevent" describes reducing or eliminating the onset of the symptoms or complications of the disease, condition or disorder.

15 As used herein, the term "allosteric site" refers to a site on EGFR other than the ATP binding site, such as that characterized in a crystal structure of EGFR. An "allosteric site" can be a site that is close to the ATP binding site, such as that characterized in a crystal structure of EGFR. For example, one allosteric site includes one or more of the following amino acid residues of EGFR: Lys745, Leu788, Ala 743, Cys755, Leu777, Phe856, Asp855, Met766,
20 Ile759, Glu762, and/or Ala763.

 As used herein, the term "allosteric EGFR inhibitor" refers to a compound that inhibits EGFR activity through binding to one or more allosteric sites on EGFR.

 As used herein, the term "agent that prevents EGFR dimer formation" refers to an agent that prevents dimer formation in which the C-lobe of the "activator" subunit impinges on the N-
25 lobe of the "receiver" subunit. Examples of agents that prevent EGFR dimer formation include, but are not limited to, cetuximab, cobimetinib, trastuzumab, panitumumab, and Mig6.

 As used herein the term "GDC0973" or "Cobimetinib" refers to a compound having the chemical structure:



As used herein, the term "pharmaceutically acceptable salt" refers to those salts of the compounds formed by the process of the present application which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.*, describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 66: 1-19 (1977). The salts can be prepared *in situ* during the final isolation and purification of the compounds of the application, or separately by reacting the free base function with a suitable organic acid.

Examples of pharmaceutically acceptable include, but are not limited to, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

As used herein, the term "pharmaceutically acceptable ester" refers to esters of the compounds formed by the process of the present application which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds formed by the process of the present application which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the present application. "Prodrug", as used herein means a compound which is convertible *in vivo* by metabolic means (*e.g.*, by hydrolysis) to afford any compound delineated by the formulae of the instant application. Various forms of prodrugs are known in the art, for example, as discussed in Bundgaard, (ed.), *Design of Prodrugs*, Elsevier (1985); Widder, *et al.*, (ed.), *Methods in Enzymology*, vol. 4, Academic Press (1985); Krogsgaard-Larsen, *et al.*, (ed.) *Design and Application of Prodrugs, Textbook of Drug Design and Development*, Chapter 5, 113-191 (1991); Bundgaard, *et al.*, *Journal of Drug Deliver Reviews*, 8:1-38(1992); Bundgaard, J. of Pharmaceutical Sciences, 77:285 et seq. (1988); Higuchi and Stella (eds.) *Prodrugs as Novel Drug Delivery Systems*, American Chemical Society (1975); and Bernard Testa & Joachim Mayer, "Hydrolysis In Drug And Prodrug Metabolism: Chemistry, Biochemistry And Enzymology," John Wiley and Sons, Ltd. (2002).

This application also encompasses pharmaceutical compositions containing, and methods of treating disorders through administering, pharmaceutically acceptable prodrugs of compounds of the application. For example, compounds of the application having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (*e.g.*, two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of the application. The amino acid residues include but

are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Additional types of prodrugs are also encompassed. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxy carbonyls, as outlined in *Advanced Drug Delivery Reviews*, 1996, 19, 1-15. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in *J. Med. Chem.* 1996, 39, 10. Free amines can also be derivatized as amides, sulfonamides or phosphonamides. All of these prodrug moieties may incorporate groups including but not limited to ether, amine and carboxylic acid functionalities

Combinations of substituents and variables envisioned by this application are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

In addition, some of the compounds of this application have one or more double bonds, or one or more asymmetric centers. Such compounds can occur as racemates, racemic mixtures, single enantiomers, individual diastereomers, diastereomeric mixtures, and cis- or trans- or *E*- or *Z*- double isomeric forms, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-, or as (D)- or (L)- for amino acids. All such isomeric forms of these compounds are expressly included in the present application.

"Isomerism" means compounds that have identical molecular formulae but differ in the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereoisomers", and stereoisomers that are

non-superimposable mirror images of each other are termed “enantiomers” or sometimes optical isomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a “racemic mixture”.

A carbon atom bonded to four non-identical substituents is termed a “chiral center”.

5 “Chiral isomer” means a compound with at least one chiral center. Compounds with more than one chiral center may exist either as an individual diastereomer or as a mixture of diastereomers, termed “diastereomeric mixture”. When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The
10 substituents attached to the chiral center under consideration are ranked in accordance with the *Sequence Rule* of Cahn, Ingold and Prelog. (Cahn *et al.*, *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn *et al.*, *Angew. Chem.* 1966, 78, 413; Cahn and Ingold, *J. Chem. Soc.* 1951 (London), 612; Cahn *et al.*, *Experientia* 1956, 12, 81; Cahn, *J. Chem. Educ.* 1964, 41, 116).

“Geometric isomer” means the diastereomers that owe their existence to hindered
15 rotation about double bonds. These configurations are differentiated in their names by the prefixes cis and trans, or Z and E, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

Furthermore, the structures and other compounds discussed in this application include all atropic isomers thereof. “Atropic isomers” are a type of stereoisomer in which the atoms of two
20 isomers are arranged differently in space. Atropic isomers owe their existence to a restricted rotation caused by hindrance of rotation of large groups about a central bond. Such atropic isomers typically exist as a mixture, however as a result of recent advances in chromatography techniques; it has been possible to separate mixtures of two atropic isomers in select cases.

“Tautomer” is one of two or more structural isomers that exist in equilibrium and is
25 readily converted from one isomeric form to another. This conversion results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds. Tautomers exist as a mixture of a tautomeric set in solution. In solid form, usually one tautomer predominates. In solutions where tautomerization is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including
30 temperature, solvent and pH. The concept of tautomers that are interconvertable by tautomerizations is called tautomerism.

Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs. Ring-chain tautomerism arises as a result of the aldehyde group (-CHO) in a sugar chain molecule reacting with one of the hydroxy groups (-OH) in the same molecule to give it a cyclic (ring-shaped) form as exhibited by glucose. Common tautomeric pairs are: ketone-enol, amide-nitrile, lactam-lactim, amide-imidic acid tautomerism in heterocyclic rings (*e.g.*, in nucleobases such as guanine, thymine and cytosine), amine-enamine and enamine-enamine.

The compounds of this application may also be represented in multiple tautomeric forms, in such instances, the application expressly includes all tautomeric forms of the compounds described herein (*e.g.*, alkylation of a ring system may result in alkylation at multiple sites, the application expressly includes all such reaction products). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration unless the text so states; thus a carbon-carbon double bond depicted arbitrarily herein as *trans* may be *cis*, *trans*, or a mixture of the two in any proportion. All such isomeric forms of such compounds are expressly included in the present application.

In the present specification, the structural formula of the compound represents a certain isomer for convenience in some cases, but the present application includes all isomers, such as geometrical isomers, optical isomers based on an asymmetrical carbon, stereoisomers, tautomers, and the like.

Furthermore, so-called metabolite which is produced by degradation of the present compound *in vivo* is included in the scope of the present application.

The term "crystal polymorphs", "polymorphs" or "crystal forms" means crystal structures in which a compound (or a salt or solvate thereof) can crystallize in different crystal packing arrangements, all of which have the same elemental composition. Different crystal forms usually have different X-ray diffraction patterns, infrared spectral, melting points, density hardness, crystal shape, optical and electrical properties, stability and solubility. Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to

dominate. Crystal polymorphs of the compounds can be prepared by crystallization under different conditions.

Additionally, the compounds of the present application, for example, the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Non-limiting examples of hydrates include monohydrates, dihydrates, *etc.* Non-limiting examples of solvates include ethanol solvates, acetone solvates, *etc.*

“Solvate” means solvent addition forms that contain either stoichiometric or non stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate; and if the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one molecule of the substance in which the water retains its molecular state as H₂O.

Method of Synthesizing the Compounds

The compounds of the present application may be made by a variety of methods, including standard chemistry. The synthetic processes of the application can tolerate a wide variety of functional groups, therefore various substituted starting materials can be used. The processes generally provide the desired final compound at or near the end of the overall process, although it may be desirable in certain instances to further convert the compound to a pharmaceutically acceptable salt, ester or prodrug thereof. Suitable synthetic routes are depicted in the schemes below.

Compounds of the present application can be prepared in a variety of ways using commercially available starting materials, compounds known in the literature, or from readily prepared intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or which will be apparent to the skilled artisan in light of the teachings herein. Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be obtained from the relevant scientific literature or from standard textbooks in the field. Although not limited to any one or several sources, classic texts such as Smith, M. B., March, J., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th edition, John Wiley & Sons: New York, 2001; and Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley &

Sons: New York, 1999, incorporated by reference herein, are useful and recognized reference textbooks of organic synthesis known to those in the art. The following descriptions of synthetic methods are designed to illustrate, but not to limit, general procedures for the preparation of compounds of the present application.

5 The compounds of disclosed herein may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthetic schemes. In the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999).
10 These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection processes, as well as the reaction conditions and order of their execution, shall be consistent with the preparation of compounds of disclosed herein.

15 Those skilled in the art will recognize if a stereocenter exists in the compounds of disclosed herein. Accordingly, the present application includes both possible stereoisomers (unless specified in the synthesis) and includes not only racemic compounds but the individual enantiomers and/or diastereomers as well. When a compound is desired as a single enantiomer or diastereomer, it may be obtained by stereospecific synthesis or by resolution of the final
20 product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be affected by any suitable method known in the art. See, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

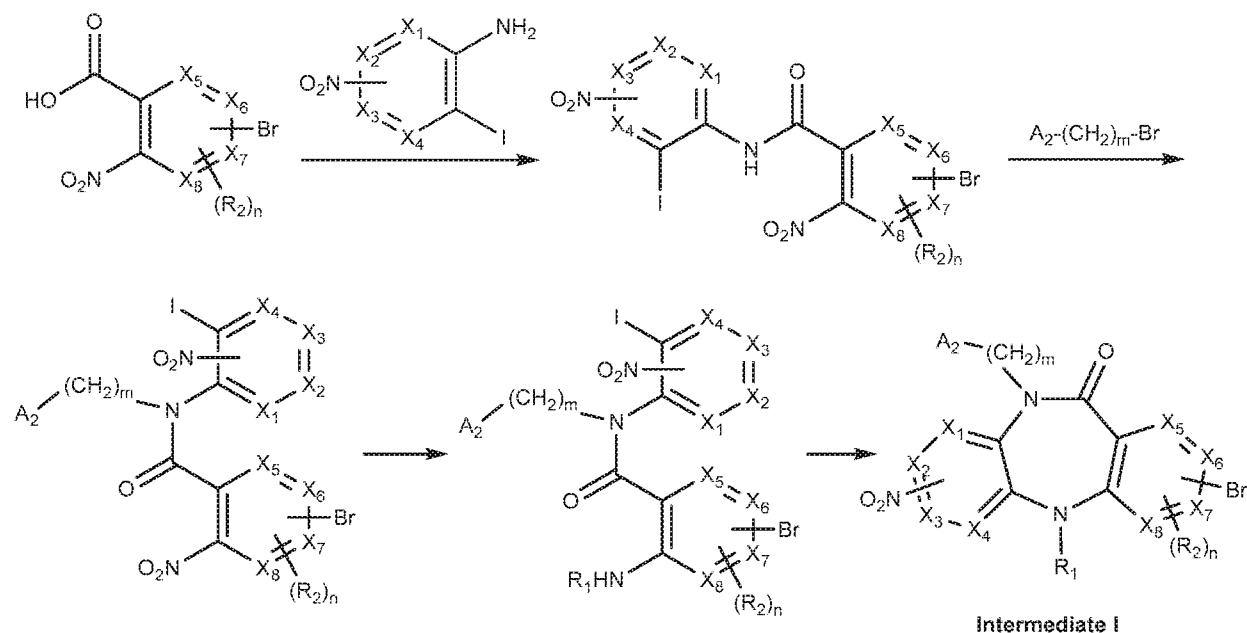
25 All the abbreviations used in this application are found in "Protective Groups in Organic Synthesis" by John Wiley & Sons, Inc, or the MERCK INDEX by MERCK & Co., Inc, or other chemistry books or chemicals catalogs by chemicals vendor such as Aldrich, or according to usage known in the art.

30 The compounds of the present application can be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, compounds of the present application can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as

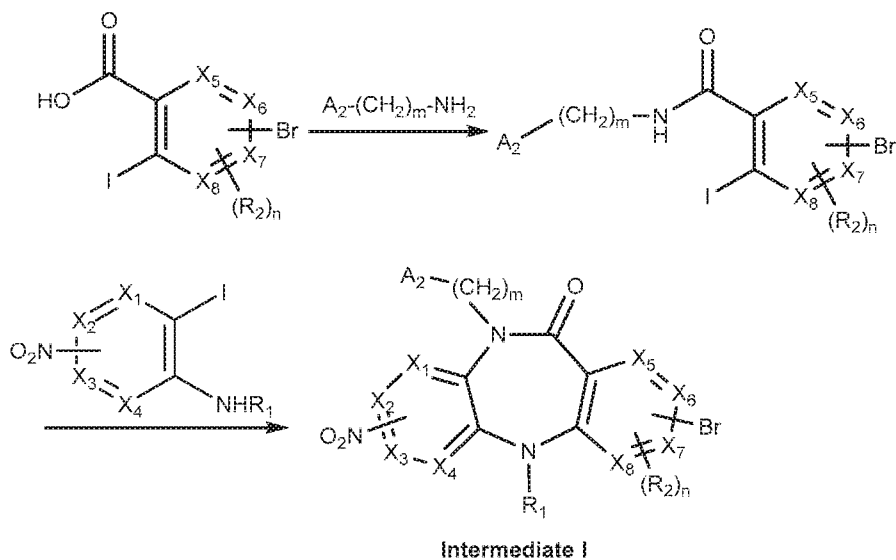
appreciated by those skilled in the art. Preferred methods include but are not limited to those methods described below. Compounds of the present application can be synthesized by following the steps outlined in General Schemes 1-4 which comprise different sequences of assembling intermediates and compounds of the application. Starting materials are either

5 commercially available or made by known procedures in the reported literature or as illustrated.

General Scheme 1

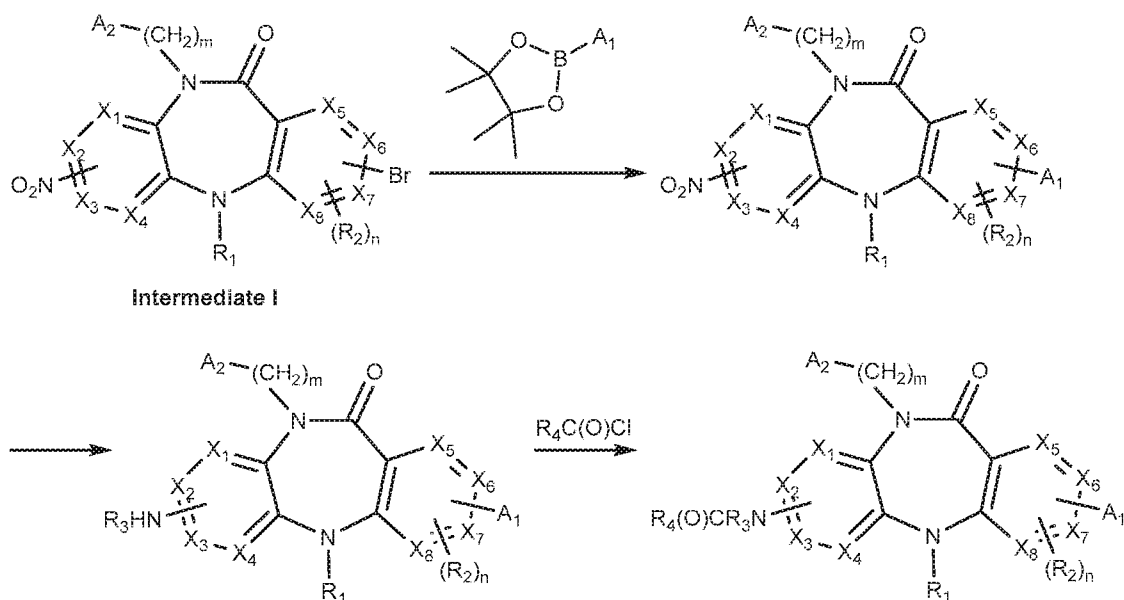


General Scheme 2



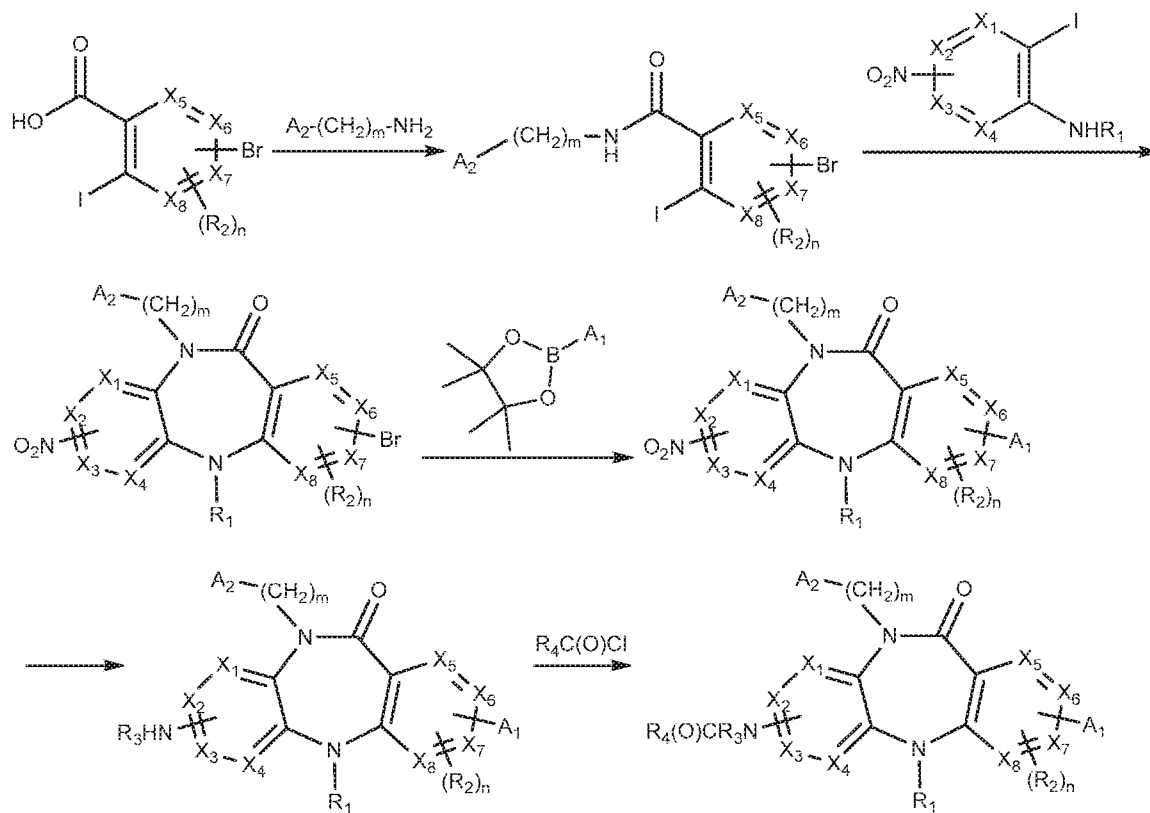
Intermediate I may be prepared according to General Scheme 1 or 2 under appropriate conditions, such as those exemplified in the Examples.

General Scheme 3



- 5 Compounds of the application (e.g., a compound of Formula Ia) may be prepared according to General Scheme 3 under appropriate conditions, such as those exemplified in the Examples.

General Scheme 4



Compounds of the application (e.g., a compound of Formula Ia) may be prepared according to General Scheme 4 under appropriate conditions, such as those exemplified in the Examples.

A mixture of enantiomers, diastereomers, and/or cis/trans isomers resulting from the processes described above can be separated into their single components by chiral salt technique, chromatography using normal phase, or reverse phase or chiral column, depending on the nature of the separation.

It should be understood that in the description and formulae shown above, the various groups and other variables are as defined herein, except where otherwise indicated. Furthermore, for synthetic purposes, the compounds of General Schemes are mere representatives with elected radicals to illustrate the general synthetic methodology of the compounds of disclosed herein.

A compound of the application can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of the application can be prepared by reacting the free acid form of the compound

with a pharmaceutically acceptable inorganic or organic base. Alternatively, the salt forms of the compounds of the application can be prepared using salts of the starting materials or intermediates.

5 The free acid or free base forms of the compounds of the application can be prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound of the application in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (*e.g.*, ammonium hydroxide solution, sodium hydroxide, and the like). A compound of the application in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (*e.g.*, hydrochloric acid, 10 *etc.*).

Prodrugs of the compounds of the application can be prepared by methods known to those of ordinary skill in the art (*e.g.*, for further details see Saulnier *et al.*, (1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of the application with a suitable 15 carbamylating agent (*e.g.*, 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like).

Protected derivatives of the compounds of the application can be made by means known to those of ordinary skill in the art. A detailed description of techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, "Protecting 20 Groups in Organic Chemistry", 3rd edition, John Wiley and Sons, Inc., 1999.

Compounds of the present application can be conveniently prepared, or formed during the process of the application, as solvates (*e.g.*, hydrates). Hydrates of compounds of the present application can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

25 Acids and bases useful in the methods herein are known in the art. Acid catalysts are any acidic chemical, which can be inorganic (*e.g.*, hydrochloric, sulfuric, nitric acids, aluminum trichloride) or organic (*e.g.*, camphorsulfonic acid, p-toluenesulfonic acid, acetic acid, ytterbium triflate) in nature. Acids are useful in either catalytic or stoichiometric amounts to facilitate chemical reactions. Bases are any basic chemical, which can be inorganic (*e.g.*, sodium 30 bicarbonate, potassium hydroxide) or organic (*e.g.*, triethylamine, pyridine) in nature. Bases are useful in either catalytic or stoichiometric amounts to facilitate chemical reactions.

Optical isomers may be prepared from their respective optically active precursors by the procedures described herein, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some combination of these techniques which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, *et al.*, *Enantiomers, Racemates, and Resolutions* (John Wiley & Sons, 1981).

The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. As can be appreciated by the skilled artisan, further methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. In addition, the solvents, temperatures, reaction durations, *etc.* delineated herein are for purposes of illustration only and one of ordinary skill in the art will recognize that variation of the reaction conditions can produce the desired bridged macrocyclic products of the present application. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), and subsequent editions thereof.

The compounds of this application may be modified by appending various functionalities via any synthetic means delineated herein to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (*e.g.*, blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

Biological Assays

Biochemical Assays

EGFR biochemical assays are carried out using a homogeneous time-resolved fluorescence (HTRF) assay. The reaction mixtures contain biotin-Lck-peptide substrate, wild type, or mutant EGFR enzyme in reaction buffer. Enzyme concentrations are adjusted to accommodate varying kinase activity and ATP concentrations. Compounds of the present application are diluted into the assay mixture and IC₅₀ values are determined using 12-point inhibition curves.

Phospho-EGFR Target Modulation Assays and ELISA

Cells are lysed with lysis buffer containing protease and phosphatase inhibitors and the plates are shaken. An aliquot from each well is then transferred to prepared ELISA plates for analysis. Once harvested and plated, the cells are pre-treated with media with or without EGF. The compounds of the present application are then added and IC₅₀ values are determined using an EGFR biochemical assay described above.

Solid high-binding ELISA plates are coated with goat anti-EGFR capture antibody. Plates are then blocked with BSA in a buffer, and then washed. Aliquots of lysed cell are added to each well of the ELISA plate and the plate is incubated. An anti-phospho-EGFR is then added and is followed by further incubation. After washing, anti-rabbit-HRP is added and the plate is again incubated. Chemiluminescent detection is carried out with SuperSignal ELISA Pico substrate. Signal is read on EnVision plate reader using built-in UltraLUM setting.

Western blotting

Cell lysates are equalized to protein content and loaded onto a gel with running buffer. Membranes are probed with primary antibodies and are then washed. HRP-conjugated secondary antibodies are added and after washing. HRP is detected using a HRP substrate reagent and recorded with an imager.

Cell Proliferation Assays

Cell lines are plated in media. The compounds of the present application are then serially diluted and transferred to the cells. Cell viability is measured via a luminescent readout. Data is analyzed by non-linear regression curve-fitting.

Methods of the Application

In another aspect, the application provides a method of inhibiting a kinase, comprising contacting the kinase with a compound disclosed herein, or a pharmaceutically acceptable salt,

hydrate, or solvate thereof. In some embodiments, the kinase comprises a mutated cysteine residue. In further embodiments, the mutated cysteine residue is located in or near the position equivalent to Cys 797 in EGFR, including such position in Jak3, Blk, Bmx, Btk, HER2 (ErbB2), HER4 (ErbB4), Itk, Tec, and Txk. In some embodiments, the kinase is EGFR. In some
5 embodiments, the kinase is a Her-kinase. In other embodiments, the method further comprises a second agent that prevents kinase dimer formation. In some embodiments, the second agent that prevents kinase dimer formation is an antibody. In further embodiments, the second agent prevents EGFR dimer formation. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the
10 second agent that prevents EGFR dimer formation is cetuximab.

In another aspect, the application provides a method of inhibiting a kinase, the method comprising administering to a subject in need thereof an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof. In some
15 embodiments, the kinase is EGFR. In some embodiments, the kinase is a Her-kinase. In other embodiments, the method further comprises administering a second agent that prevents dimer formation of the kinase. In some embodiments, the second agent that prevents kinase dimer formation is an antibody. In further embodiments, the second agent prevents EGFR dimer formation. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that
20 prevents EGFR dimer formation is cetuximab.

In still another aspect, the application provides a method of inhibiting EGFR, the method comprising administering to a subject in need thereof an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof. In some
25 embodiments, the method further comprises administering a second agent that prevents EGFR dimer formation. In some embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

Another aspect of the application provides a method of treating or preventing a disease,
30 the method comprising administering to a subject in need thereof an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof. In

some embodiments, the disease is mediated by a kinase. In further embodiments, the kinase comprises a mutated cysteine residue. In further embodiments, the mutated cysteine residue is located in or near the position equivalent to Cys 797 in EGFR, including such positions in Jak3, Blk, Bmx, Btk, HER2 (ErbB2), HER4 (ErbB4), Itk, Tec, and Txk. In some embodiments, the method further comprises administering a second agent that prevents dimer formation of the kinase. In some embodiments, the second agent that prevents kinase dimer formation is an antibody. In further embodiments, the second agent prevents EGFR dimer formation. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

In some embodiments, the disease is mediated by EGFR (*e.g.*, EGFR plays a role in the initiation or development of the disease). In further embodiments, the EGFR is a Her-kinase. In further embodiments, the Her-kinase is HER1, HER2, or HER4. In some embodiments, the EGFR comprises one or more mutations, as described herein.

In certain embodiments, the disease is cancer or a proliferation disease.

In further embodiments, the disease is lung cancer, colon cancer, breast cancer, prostate cancer, liver cancer, pancreas cancer, brain cancer, kidney cancer, ovarian cancer, stomach cancer, skin cancer, bone cancer, gastric cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, hepatocellular carcinoma, papillary renal carcinoma, head and neck squamous cell carcinoma, leukemias, lymphomas, myelomas, or solid tumors.

In other embodiments, the disease is inflammation, arthritis, rheumatoid arthritis, spondyarthropathies, gouty arthritis, osteoarthritis, juvenile arthritis, and other arthritic conditions, systemic lupus erthematosus (SLE), skin-related conditions, psoriasis, eczema, burns, dermatitis, neuroinflammation, allergy, pain, neuropathic pain, fever, pulmonary disorders, lung inflammation, adult respiratory distress syndrome, pulmonary sarcoisosis, asthma, silicosis, chronic pulmonary inflammatory disease, and chronic obstructive pulmonary disease (COPD), cardiovascular disease, arteriosclerosis, myocardial infarction (including post-myocardial infarction indications), thrombosis, congestive heart failure, cardiac reperfusion injury, as well as complications associated with hypertension and/or heart failure such as vascular organ damage, restenosis, cardiomyopathy, stroke including ischemic and hemorrhagic stroke, reperfusion injury, renal reperfusion injury, ischemia including stroke and brain ischemia, and ischemia

resulting from cardiac/coronary bypass, neurodegenerative disorders, liver disease and nephritis, gastrointestinal conditions, inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, ulcerative diseases, gastric ulcers, viral and bacterial infections, sepsis, septic shock, gram negative sepsis, malaria, meningitis, HIV infection, opportunistic infections, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), pneumonia, herpes virus, myalgias due to infection, influenza, autoimmune disease, graft vs. host reaction and allograft rejections, treatment of bone resorption diseases, osteoporosis, multiple sclerosis, cancer, leukemia, lymphoma, colorectal cancer, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma), basal cell carcinoma, adenocarcinoma, gastrointestinal cancer, lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer, skin cancer, squamous cell and/or basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that affect epithelial cells throughout the body, chronic myelogenous leukemia (CML), acute myeloid leukemia (AML) and acute promyelocytic leukemia (APL), angiogenesis including neoplasia, metastasis, central nervous system disorders, central nervous system disorders having an inflammatory or apoptotic component, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, and peripheral neuropathy, or B-Cell Lymphoma.

In further embodiments, the disease is inflammation, arthritis, rheumatoid arthritis, spondylarthropathies, gouty arthritis, osteoarthritis, juvenile arthritis, and other arthritic conditions, systemic lupus erythematosus (SLE), skin-related conditions, psoriasis, eczema, dermatitis, pain, pulmonary disorders, lung inflammation, adult respiratory distress syndrome, pulmonary sarcoidosis, asthma, chronic pulmonary inflammatory disease, and chronic obstructive pulmonary disease (COPD), cardiovascular disease, arteriosclerosis, myocardial infarction (including post-myocardial infarction indications), congestive heart failure, cardiac reperfusion injury, inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, leukemia or lymphoma.

Another aspect of the application provides a method of treating a kinase mediated disorder, the method comprising administering to a subject in need thereof an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate

thereof. In other embodiments, the compound is an inhibitor of HER1, HER2, or HER4. In other embodiments, the subject is administered an additional therapeutic agent. In other embodiments, the compound and the additional therapeutic agent are administered simultaneously or sequentially.

5 In another aspect, the application provides a method of treating a kinase mediated disorder, the method comprising administering to a subject in need thereof an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and a second agent that prevents EGFR dimer formation. In other embodiments, the compound is an inhibitor of HER1, HER2, or HER4. In other embodiments, the subject is
10 administered an additional therapeutic agent. In other embodiments, the compound, the second agent that prevents EGFR dimer formation, and the additional therapeutic agent are administered simultaneously or sequentially. In some embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the
15 second agent that prevents EGFR dimer formation is cetuximab.

In other embodiments, the disease is cancer. In further embodiments, the cancer is lung cancer, colon cancer, breast cancer, prostate cancer, liver cancer, pancreas cancer, brain cancer, kidney cancer, ovarian cancer, stomach cancer, skin cancer, bone cancer, gastric cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, hepatocellular carcinoma, papillary renal
20 carcinoma, head and neck squamous cell carcinoma, leukemias, lymphomas, myelomas, or solid tumors.

In another aspect, the application provides a method of treating or preventing cancer, wherein the cancer cell comprise activated EGFR, comprising administering to a subject in need thereof an effective amount of a compound disclosed herein, or a pharmaceutically acceptable
25 salt, hydrate, or solvate thereof.

In another aspect, the application provides a method of treating or preventing cancer, wherein the cancer cell comprise activated EGFR, comprising administering to a subject in need thereof an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof and a second agent that prevents EGFR dimer formation. In
30 some embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab,

trastuzumab, or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

In certain embodiments, the EGFR activation is selected from mutation of EGFR, amplification of EGFR, expression of EGFR, and ligand mediated activation of EGFR.

5 Another aspect of the application provides a method of treating or preventing cancer in a subject, wherein the subject is identified as being in need of EGFR inhibition for the treatment of cancer, comprising administering to the subject an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

10 In another aspect, the application provides a method of treating or preventing cancer in a subject, wherein the subject is identified as being in need of EGFR inhibition for the treatment of cancer, comprising administering to the subject an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and optionally a second agent that prevents EGFR dimer formation. In some embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further
15 embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

In certain embodiments, the subject identified as being in need of EGFR inhibition is resistant to a known EGFR inhibitor, including but not limited to, gefitinib, erlotinib, afatinib, AZD9291, CO-1686, or WZ4002. In certain embodiments, a diagnostic test is performed to
20 determine if the subject has an activating mutation in EGFR. In certain embodiments, a diagnostic test is performed to determine if the subject has an EGFR harboring an activating and a drug resistance mutation, such as those described herein. Activating mutations comprise without limitation L858R, G719S, G719C, G719A, L718Q, L861Q, a deletion in exon 19 and/or an insertion in exon 20. Drug resistant EGFR mutants can have without limitation a drug
25 resistance mutation comprising T790M, T854A, L718Q, C797S, or D761Y. The diagnostic test can comprise sequencing, pyrosequencing, PCR, RT-PCR, or similar analysis techniques known to those of skill in the art that can detect nucleotide sequences.

In another aspect, the application provides a method of treating or preventing cancer, wherein the cancer cell comprises an activated ERBB2, comprising administering to a subject in
30 need thereof an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof. In certain embodiments, the ERBB2 activation is

selected from mutation of ERBB2, expression of ERBB2 and amplification of ERBB2. In further embodiments, the mutation is a mutation in exon 20 of ERBB2.

In another aspect, the application provides a method of treating or preventing cancer, wherein the cancer cell comprises an activated ERBB2, comprising administering to a subject in need thereof an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and a second agent that prevents ERBB2 dimer formation. In certain embodiments, the ERBB2 activation is selected from mutation of ERBB2, expression of ERBB2 and amplification of ERBB2. In further embodiments, the mutation is a mutation in exon 20 of ERBB2. In some embodiments, the second agent that prevents ERBB2 dimer formation is an antibody. In further embodiments, the second agent that prevents ERBB2 dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents ERBB2 dimer formation is cetuximab.

In another aspect, the application provides a method of treating cancer in a subject, wherein the subject is identified as being in need of ERBB2 inhibition for the treatment of cancer, comprising administering to the subject in need thereof an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In another aspect, the application provides a method of treating cancer in a subject, wherein the subject is identified as being in need of ERBB2 inhibition for the treatment of cancer, comprising administering to the subject in need thereof an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and optionally a second agent that prevents ERBB2 dimer formation. In some embodiments, the second agent that prevents ERBB2 dimer formation is an antibody. In further embodiments, the second agent that prevents ERBB2 dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents ERBB2 dimer formation is cetuximab.

Another aspect of the application provides a method of preventing resistance to a known EGFR inhibitor, including but not limited to, gefitinib, erlotinib, afatinib, lapatinib, neratinib, WZ4002, CL-387785, AZD9291, and CO-1686, in a disease, comprising administering to a subject in need thereof an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

Another aspect of the application provides a method of preventing resistance to a known EGFR inhibitor, including but not limited to, gefitinib, erlotinib, afatinib, lapatinib, neratinib,

WZ4002, CL-387785, AZD9291, and CO-1686, in a disease, comprising administering to a subject in need thereof an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and a second agent that prevents EGFR dimer formation. In some embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

In certain embodiments, the application provides a method of treating any of the disorders described herein, wherein the subject is a human. In certain embodiments, the application provides a method of preventing any of the disorders described herein, wherein the subject is a human.

In another aspect, the application provides a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for use in the manufacture of a medicament for treating or preventing a disease in which EGFR plays a role.

In another aspect, the application provides a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and a second agent that prevents EGFR dimer formation for use in the manufacture of a medicament for treating or preventing a disease in which EGFR plays a role. In some embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

In still another aspect, the application provides the use of a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, in the treatment or prevention of a disease in which EGFR plays a role.

In another aspect, the application provides the use of a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and a second agent that prevents EGFR dimer formation in the treatment or prevention of a disease in which EGFR plays a role. In some embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

As inhibitors of EGFR kinases, the compounds and compositions of this application are particularly useful for treating or lessening the severity of a disease, condition, or disorder where a protein kinase is implicated in the disease, condition, or disorder. In one aspect, the present application provides a method for treating or lessening the severity of a disease, condition, or disorder where a protein kinase is implicated in the disease state. In another aspect, the present application provides a method for treating or lessening the severity of a kinase disease, condition, or disorder where inhibition of enzymatic activity is implicated in the treatment of the disease. In another aspect, this application provides a method for treating or lessening the severity of a disease, condition, or disorder with compounds that inhibit enzymatic activity by binding to the protein kinase. Another aspect provides a method for treating or lessening the severity of a kinase disease, condition, or disorder by inhibiting enzymatic activity of the kinase with a protein kinase inhibitor.

In some embodiments, said method is used to treat or prevent a condition selected from autoimmune diseases, inflammatory diseases, proliferative and hyperproliferative diseases, immunologically-mediated diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cardiovascular diseases, hormone related diseases, allergies, asthma, and Alzheimer's disease. In other embodiments, said condition is selected from a proliferative disorder and a neurodegenerative disorder.

One aspect of this application provides compounds that are useful for the treatment of diseases, disorders, and conditions characterized by excessive or abnormal cell proliferation. Such diseases include, but are not limited to, a proliferative or hyperproliferative disease, and a neurodegenerative disease. Examples of proliferative and hyperproliferative diseases include, without limitation, cancer. The term "cancer" includes, but is not limited to, the following cancers: breast; ovary; cervix; prostate; testis, genitourinary tract; esophagus; larynx, glioblastoma; neuroblastoma; stomach; skin, keratoacanthoma; lung, epidermoid carcinoma, large cell carcinoma, small cell carcinoma, lung adenocarcinoma; bone; colon; colorectal; adenoma; pancreas, adenocarcinoma; thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma; seminoma; melanoma; sarcoma; bladder carcinoma; liver carcinoma and biliary passages; kidney carcinoma; myeloid disorders; lymphoid disorders, Hodgkin's, hairy cells; buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx; small intestine; colonrectum, large intestine, rectum, brain and central nervous system; chronic myeloid

leukemia (CML), and leukemia. The term "cancer" includes, but is not limited to, the following cancers: myeloma, lymphoma, or a cancer selected from gastric, renal, or and the following cancers: head and neck, oropharangeal, non-small cell lung cancer (NSCLC), endometrial, hepatocarcinoma, Non-Hodgkins lymphoma, and pulmonary.

5 The term "cancer" refers to any cancer caused by the proliferation of malignant neoplastic cells, such as tumors, neoplasms, carcinomas, sarcomas, leukemias, lymphomas and the like. For example, cancers include, but are not limited to, mesothelioma, leukemias and lymphomas such as cutaneous T-cell lymphomas (CTCL), noncutaneous peripheral T-cell lymphomas, lymphomas associated with human T-cell lymphotropic virus (HTLV) such as adult T-cell
10 leukemia/lymphoma (ATLL), B-cell lymphoma, acute nonlymphocytic leukemias, chronic lymphocytic leukemia, chronic myelogenous leukemia, acute myelogenous leukemia, lymphomas, and multiple myeloma, non-Hodgkin lymphoma, acute lymphatic leukemia (ALL), chronic lymphatic leukemia (CLL), Hodgkin's lymphoma, Burkitt lymphoma, adult T-cell leukemia lymphoma, acute-myeloid leukemia (AML), chronic myeloid leukemia (CML), or
15 hepatocellular carcinoma. Further examples include myelodysplastic syndrome, childhood solid tumors such as brain tumors, neuroblastoma, retinoblastoma, Wilms' tumor, bone tumors, and soft-tissue sarcomas, common solid tumors of adults such as head and neck cancers (*e.g.*, oral, laryngeal, nasopharyngeal and esophageal), genitourinary cancers (*e.g.*, prostate, bladder, renal, uterine, ovarian, testicular), lung cancer (*e.g.*, small-cell and non-small cell), breast cancer,
20 pancreatic cancer, melanoma and other skin cancers, stomach cancer, brain tumors, tumors related to Gorlin's syndrome (*e.g.*, medulloblastoma, meningioma, *etc.*), and liver cancer. Additional exemplary forms of cancer which may be treated by the subject compounds include, but are not limited to, cancer of skeletal or smooth muscle, stomach cancer, cancer of the small intestine, rectum carcinoma, cancer of the salivary gland, endometrial cancer, adrenal cancer,
25 anal cancer, rectal cancer, parathyroid cancer, and pituitary cancer.

 Additional cancers that the compounds described herein may be useful in preventing, treating and studying are, for example, colon carcinoma, familial adenomatous polyposis carcinoma and hereditary non-polyposis colorectal cancer, or melanoma. Further, cancers include, but are not limited to, labial carcinoma, larynx carcinoma, hypopharynx carcinoma,
30 tongue carcinoma, salivary gland carcinoma, gastric carcinoma, adenocarcinoma, thyroid cancer (medullary and papillary thyroid carcinoma), renal carcinoma, kidney parenchyma carcinoma,

cervix carcinoma, uterine corpus carcinoma, endometrium carcinoma, chorion carcinoma, testis carcinoma, urinary carcinoma, melanoma, brain tumors such as glioblastoma, astrocytoma, meningioma, medulloblastoma and peripheral neuroectodermal tumors, gall bladder carcinoma, bronchial carcinoma, multiple myeloma, basalioma, teratoma, retinoblastoma, choroidea
5 melanoma, seminoma, rhabdomyosarcoma, craniopharyngeoma, osteosarcoma, chondrosarcoma, myosarcoma, liposarcoma, fibrosarcoma, Ewing sarcoma, and plasmocytoma. In one aspect of the application, the present application provides for the use of one or more compounds of the application in the manufacture of a medicament for the treatment of cancer, including without limitation the various types of cancer disclosed herein.

10 In some embodiments, the compounds of this application are useful for treating cancer, such as colorectal, thyroid, breast, and lung cancer; and myeloproliferative disorders, such as polycythemia vera, thrombocythemia, myeloid metaplasia with myelofibrosis, chronic myelogenous leukemia, chronic myelomonocytic leukemia, hypereosinophilic syndrome, juvenile myelomonocytic leukemia, and systemic mast cell disease. In some embodiments, the
15 compounds of this application are useful for treating hematopoietic disorders, in particular, acute-myelogenous leukemia (AML), chronic-myelogenous leukemia (CML), acute-promyelocytic leukemia, and acute lymphocytic leukemia (ALL).

This application further embraces the treatment or prevention of cell proliferative disorders such as hyperplasias, dysplasias and pre-cancerous lesions. Dysplasia is the earliest
20 form of pre-cancerous lesion recognizable in a biopsy by a pathologist. The subject compounds may be administered for the purpose of preventing said hyperplasias, dysplasias or pre-cancerous lesions from continuing to expand or from becoming cancerous. Examples of pre-cancerous lesions may occur in skin, esophageal tissue, breast and cervical intra-epithelial tissue.

Examples of neurodegenerative diseases include, without limitation,
25 Adrenoleukodystrophy (ALD), Alexander's disease, Alper's disease, Alzheimer's disease, Amyotrophic lateral sclerosis (Lou Gehrig's Disease), Ataxia telangiectasia, Batten disease (also known as Spielmeyer-Vogt-Sjogren-Batten disease), Bovine spongiform encephalopathy (BSE), Canavan disease, Cockayne syndrome, Corticobasal degeneration, Creutzfeldt-Jakob disease, Familial fatal insomnia, Frontotemporal lobar degeneration, Huntington's disease, HIV-
30 associated dementia, Kennedy's disease, Krabbe's disease, Lewy body dementia, Neuroborreliosis, Machado-Joseph disease (Spinocerebellar ataxia type 3), Multiple System

Atrophy, Multiple sclerosis, Narcolepsy, Niemann Pick disease, Parkinson's disease, Pelizaeus-Merzbacher Disease, Pick's disease, Primary lateral sclerosis, Prion diseases, Progressive Supranuclear Palsy, Refsum's disease, Sandhoff disease, Schilder's disease, Subacute combined degeneration of spinal cord secondary to Pernicious Anaemia, Spielmeyer-Vogt-Sjogren-Batten disease (also known as Batten disease), Spinocerebellar ataxia (multiple types with varying characteristics), Spinal muscular atrophy, Steele-Richardson-Olszewski disease, Tabes dorsalis, and Toxic encephalopathy.

Another aspect of this application provides a method for the treatment or lessening the severity of a disease selected from a proliferative or hyperproliferative disease, or a neurodegenerative disease, comprising administering an effective amount of a compound, or a pharmaceutically acceptable composition comprising a compound, to a subject in need thereof. In other embodiments, the method further comprises administering a second agent that prevents EGFR dimer formation. In some embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

As inhibitors of EGFR kinases, the compounds and compositions of this application are also useful in biological samples. One aspect of the application relates to inhibiting protein kinase activity in a biological sample, which method comprises contacting said biological sample with a compound of the application or a composition comprising said compound. The term "biological sample", as used herein, means an *in vitro* or an *ex vivo* sample, including, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof. Inhibition of protein kinase activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ- transplantation, and biological specimen storage.

Another aspect of this application relates to the study of EGFR kinases in biological and pathological phenomena; the study of intracellular signal transduction pathways mediated by such protein kinases; and the comparative evaluation of new protein kinase inhibitors. Examples of such uses include, but are not limited to, biological assays such as enzyme assays and cell-based assays.

The activity of the compounds and compositions of the present application as EGFR kinase inhibitors may be assayed *in vitro*, *in vivo*, or in a cell line. *In vitro* assays include assays that determine inhibition of either the kinase activity or ATPase activity of the activated kinase. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to the protein kinase and may be measured either by radio labelling the inhibitor prior to binding, isolating the inhibitor/kinase complex and determining the amount of radio label bound, or by running a competition experiment where new inhibitors are incubated with the kinase bound to known radioligands. Detailed conditions for assaying a compound utilized in this application as an inhibitor of various kinases are set forth in the Examples below.

In accordance with the foregoing, the present application further provides a method for preventing or treating any of the diseases or disorders described above in a subject in need of such treatment, which method comprises administering to said subject a therapeutically effective amount of a compound of the application, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and optionally a second agent that prevents EGFR dimer formation. For any of the above uses, the required dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired.

In other embodiments, the compound and the second agent that prevents EGFR dimer formation are administered simultaneously or sequentially.

Pharmaceutical Compositions

In another aspect, the application provides a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, together with a pharmaceutically acceptable carrier.

In another aspect, the application provides a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and a second agent that prevents EGFR dimer formation together with a pharmaceutically acceptable carrier. In some embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

Compounds of the application can be administered as pharmaceutical compositions by any conventional route, in particular enterally, *e.g.*, orally, *e.g.*, in the form of tablets or capsules, or parenterally, *e.g.*, in the form of injectable solutions or suspensions, topically, *e.g.*, in the form of lotions, gels, ointments or creams, or in a nasal or suppository form. Pharmaceutical compositions comprising a compound of the present application in free form or in a pharmaceutically acceptable salt form in association and optionally a second agent that prevents EGFR dimer formation with at least one pharmaceutically acceptable carrier or diluent can be manufactured in a conventional manner by mixing, granulating or coating methods. For example, oral compositions can be tablets or gelatin capsules comprising the active ingredient together with a) diluents, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired d) disintegrants, *e.g.*, starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions can be aqueous isotonic solutions or suspensions, and suppositories can be prepared from fatty emulsions or suspensions. The compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Suitable formulations for transdermal applications include an effective amount of a compound of the present application with a carrier. A carrier can include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. Matrix transdermal formulations may also be used. Suitable formulations for topical application, *e.g.*, to the skin and eyes, are preferably aqueous solutions, ointments, creams or gels well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

Compounds and compositions of the application can be administered in therapeutically effective amounts in a combinational therapy with one or more therapeutic agents (pharmaceutical combinations) or modalities, *e.g.*, a second agent that prevents EGFR dimer formation, non-drug therapies, *etc.* For example, synergistic effects can occur with agents that prevents EGFR dimer formation, other anti-proliferative, anti-cancer, immunomodulatory or anti-inflammatory substances. Where the compounds of the application are administered in conjunction with other therapies, dosages of the co-administered compounds will of course vary depending on the type of co-drug employed, on the specific drug employed, on the condition being treated and so forth.

Combination therapy includes the administration of the subject compounds in further combination with one or more other biologically active ingredients (such as, but not limited to, a second agent that prevents EGFR dimer formation, a second and different antineoplastic agent) and non-drug therapies (such as, but not limited to, surgery or radiation treatment). For instance, the compounds of the application can be used in combination with other pharmaceutically active compounds, preferably compounds that are able to enhance the effect of the compounds of the application. The compounds of the application can be administered simultaneously (as a single preparation or separate preparation) or sequentially to the other drug therapy or treatment modality. In general, a combination therapy envisions administration of two or more drugs during a single cycle or course of therapy.

In one aspect of the application, the compounds may be administered in combination with one or more agents that prevent EGFR dimer formation. In some embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

In another aspect of the application, the compounds may be administered in combination with one or more separate pharmaceutical agents, *e.g.*, a chemotherapeutic agent, an immunotherapeutic agent, or an adjunctive therapeutic agent. In one embodiment, the chemotherapeutic agent reduces or inhibits the binding of ATP with EGFR (*e.g.*, gefitinib, erlotinib, afatinib, lapatinib, nerabinib, CL-387785, AZD9291, CO-1686 or WZ4002).

The pharmaceutical compositions of the present application comprise a therapeutically effective amount of a compound of the present application formulated together with one or more

pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The pharmaceutical compositions of this application can be administered to humans and other animals orally, rectally, parenterally, intracisternally, 5 intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray. In other embodiments, the composition further comprises administering a second agent that prevents EGFR dimer formation. In some embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further 10 embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl 15 alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, com, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying 20 and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a 25 solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

30 In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a

liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

5 Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this application with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

10 Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

 The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and
15 granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids
20 such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents.

 Dosage forms for topical or transdermal administration of a compound of this application include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable
25 carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this application.

 The ointments, pastes, creams and gels may contain, in addition to an active compound of this application, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and
30 zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this application, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

5 Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

10 According to the methods of treatment of the present application, disorders are treated or prevented in a subject, such as a human or other animal, by administering to the subject a therapeutically effective amount of a compound of the application, in such amounts and for such time as is necessary to achieve the desired result. The term "therapeutically effective amount" of a compound of the application, as used herein, means a sufficient amount of the compound so as
15 to decrease the symptoms of a disorder in a subject. As is well understood in the medical arts a therapeutically effective amount of a compound of this application will be at a reasonable benefit/risk ratio applicable to any medical treatment.

In general, compounds of the application will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in
20 combination with one or more therapeutic agents. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5 mg/kg per body weight. An indicated daily dosage in the larger mammal, *e.g.*, humans, is in the range from about 0.5 mg to
25 about 100 mg, conveniently administered, *e.g.*, in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 50 mg active ingredient.

In certain embodiments, a therapeutic amount or dose of the compounds of the present application may range from about 0.1 mg/Kg to about 500 mg/Kg, alternatively from about 1 to
30 about 50 mg/Kg. In general, treatment regimens according to the present application comprise administration to a patient in need of such treatment from about 10 mg to about 1000 mg of the

compound(s) of this application per day in single or multiple doses. Therapeutic amounts or doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents.

Upon improvement of a subject's condition, a maintenance dose of a compound,
5 composition or combination of this application may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. The subject may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

10 It will be understood, however, that the total daily usage of the compounds and compositions of the present application will be decided by the attending physician within the scope of sound medical judgment. The specific inhibitory dose for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed;
15 the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

The application also provides for a pharmaceutical combinations, *e.g.*, a kit, comprising
20 a) a first agent which is a compound of the application as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent. The kit can comprise instructions for its administration.

The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and
25 are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active
30 ingredients, *e.g.*, a compound of the application and a co- agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed

combination" means that the active ingredients, *e.g.*, a compound of the application and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, *e.g.*, the administration of three or more active ingredients.

In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents. For example, an agent that prevents EGFR dimer formation, chemotherapeutic agents or other antiproliferative agents may be combined with the compounds of this application to treat proliferative diseases and cancer.

Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylenepolyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes, oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate, agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water, isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. The protein kinase inhibitors or pharmaceutical salts thereof may be formulated into pharmaceutical compositions for administration to animals or humans. These pharmaceutical compositions, which comprise an amount of the protein inhibitor effective to treat or prevent a protein kinase-

mediated condition and a pharmaceutically acceptable carrier, are other embodiments of the present application.

In another aspect, the application provides a kit comprising a compound capable of inhibiting kinase activity selected from one or more compounds of disclosed herein, or
5 pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers thereof, and instructions for use in treating cancer. In certain embodiments, the kit further comprises components for performing a test to determine whether a subject has activating and/or drug resistance mutations in EGFR.

In another aspect, the application provides a kit comprising a compound capable of
10 inhibiting EGFR activity selected from a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In another aspect, the application provides a kit comprising a compound capable of inhibiting kinase activity selected from one or more compounds of disclosed herein, or
pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomers
15 thereof, a second agent that prevents EGFR dimer formation, and instructions for use in treating cancer. In certain embodiments, the kit further comprises components for performing a test to determine whether a subject has activating and/or drug resistance mutations in EGFR. In some embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab,
20 or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

In another aspect, the application provides a kit comprising a compound capable of inhibiting EGFR activity selected from a compound disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof and second agent wherein the second agent prevents
25 EGFR dimer formation. In some embodiments, the second agent that prevents EGFR dimer formation is an antibody. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab, trastuzumab, or panitumumab. In further embodiments, the second agent that prevents EGFR dimer formation is cetuximab.

The application is further illustrated by the following examples and synthesis schemes,
30 which are not to be construed as limiting this application in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate

certain embodiments and that no limitation to the scope of the application is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present application and/or scope of the appended claims.

5

EXAMPLES

Analytical Methods, Materials, and Instrumentation

Starting materials, reagents and solvents were purchased from commercial suppliers and were used without further purification unless otherwise noted. All reactions were monitored using a Waters Acquity UPLC/MS system (Waters PDA eλ Detector, QDa Detector, Sample manager – FL, Binary Solvent Manager) using Acquity UPLC® BEH C18 column (2.1 x 50 mm, 1.7 μm particle size): solvent gradient = 85 % A at 0 min, 1 % A at 1.6 min; solvent A = 0.1 % formic acid in Water; solvent B = 0.1 % formic acid in Acetonitrile; flow rate : 0.6 mL/min. Reaction products were purified by flash column chromatography using CombiFlash®Rf with Teledyne Isco RediSep®Rt columns (4 g, 12 g, 24 g, 40 g, or 80 g) and Waters HPLC system using SunFire™ Prep C18 column (19 x 100 mm, 5 μm particle size): solvent gradient = 80 % A at 0 min, 10 % A at 25 min; solvent A = 0.035 % TFA in Water; solvent B = 0.035 % TFA in MeOH; flow rate : 25 mL/min. ¹H NMR spectra were recorded on 500 MHz Bruker Avance III spectrometers. Chemical shifts are reported relative to methanol (δ = 3.30), chloroform (δ = 7.24) or dimethyl sulfoxide (δ = 2.50) for ¹H NMR and ¹³C NMR. Data are reported as (*br* = broad, *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet).

20

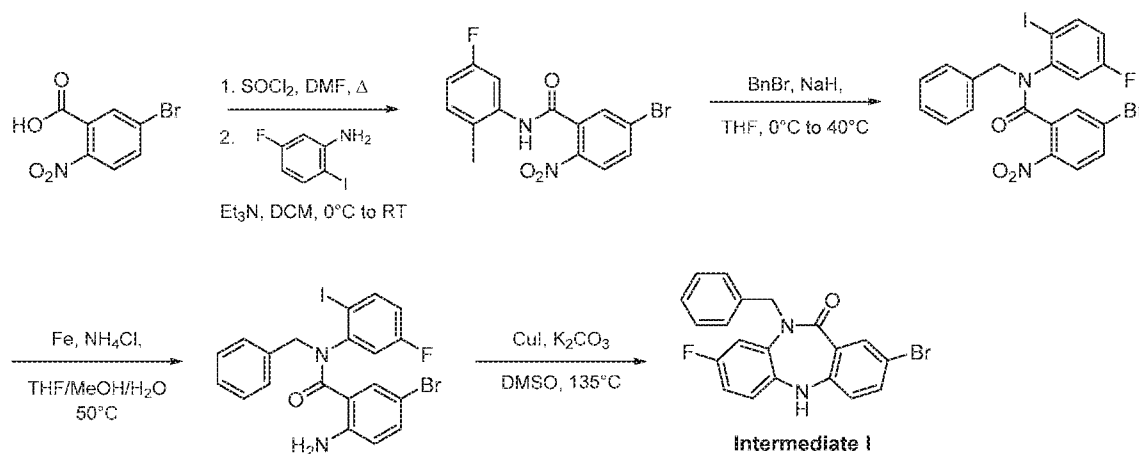
Abbreviations used in the following examples and elsewhere herein are:

	atm	atmosphere
	br	broad
25	DIPEA	<i>N,N</i> -diisopropylethylamine
	DMA	<i>N,N</i> -dimethylacetamide
	DMF	<i>N,N</i> -dimethylformamide
	DMSO	dimethyl sulfoxide
	ESI	electrospray ionization
30	EtOAc	ethyl acetate
	HCl	hydrochloric acid
	h	hour(s)

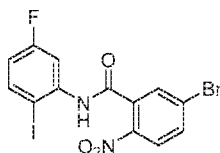
	HATU	bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>]pyridinium 3-oxide hexafluoro-phosphate
	HPLC	high-performance liquid chromatography
	LCMS	liquid chromatography–mass spectrometry
5	m	multiplet
	MeOH	methanol
	MHz	megahertz
	min	minutes
	MS	mass spectrometry
10	NMR	nuclear magnetic resonance
	Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
	ppm	parts per million
	THF	tetrahydrofuran
	TLC	thin layer chromatography
15	Xphos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Example 1: Synthesis of Intermediate I

Intermediate I for the preparation of the compounds of the application can be synthesized according to the procedures below.

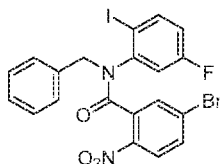


Step 1: 5-Bromo-*N*-(5-fluoro-2-iodophenyl)-2-nitrobenzamide



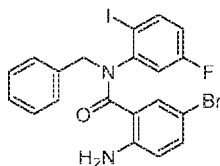
To a solution of 5-bromo-2-nitrobenzoic acid (103 mg, 0.42 mmol) in thionyl chloride (4 mL) was added a catalytic amount of *N,N*-dimethylformamide. After refluxing for 2 hr, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was re-dissolved in anhydrous DCM (1.5 mL) and cooled on ice. To this solution was added dropwise a solution of 5-fluoro-2-iodoaniline (100 mg, 0.42 mmol) and triethylamine (88 μ L, 0.63 mmol) in anhydrous DCM (0.5 mL). The resulting reaction mixture was stirred for 4 hr, allowing the temperature to rise to room temperature, and subsequently washed with sat. NaHCO₃. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (EtOAc : DCM = 0 : 100 to 100 : 0) to afford 5-bromo-*N*-(5-fluoro-2-iodophenyl)-2-nitrobenzamide (160 mg, 81 %).

Step 2: *N*-Benzyl-5-bromo-*N*-(5-fluoro-2-iodophenyl)-2-nitrobenzamide



To an ice-cooled solution of 5-bromo-*N*-(5-fluoro-2-iodophenyl)-2-nitrobenzamide (160 mg, 0.34 mmol) in anhydrous THF (3.5 mL) was added sodium hydride (60 % dispersion in mineral oil, 33 mg, 0.85 mmol) and the mixture was stirred at room temperature for 1 hr. The mixture was cooled on ice again and benzyl bromide (81 μ L, 0.68 mmol) was added. The resulting reaction mixture was warmed to room temperature and subsequently heated to 40 °C for 4 hr. The solution was cooled to room temperature, quenched by dropwise addition of water and concentrated under reduced pressure. The residue was re-dissolved in DCM and washed repeatedly with water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was used in the next step without further purification.

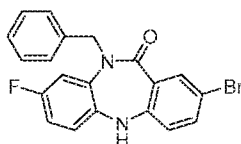
Step 3: 2-Amino-*N*-benzyl-5-bromo-*N*-(5-fluoro-2-iodophenyl)benzamide



N-Benzyl-5-bromo-*N*-(5-fluoro-2-iodophenyl)-2-nitrobenzamide (189 mg, 0.34 mmol), iron powder (95 mg, 1.70 mmol), and ammonium chloride (182 mg, 3.40 mmol) were suspended in a mixture of THF/MeOH/H₂O (5:2:1, 3.5 mL). The resulting mixture was vigorously stirred

at 50 °C for 1 hr. The reaction mixture was cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the residue was re-dissolved in EtOAc and washed repeatedly with sat. NaHCO₃. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (DCM : 1.75 *N*NH₃ in MeOH = 100 : 0 to 80 : 20) to give 2-amino-*N*-benzyl-5-bromo-*N*-(5-fluoro-2-iodophenyl)benzamide (120 mg, 68 %, two steps).

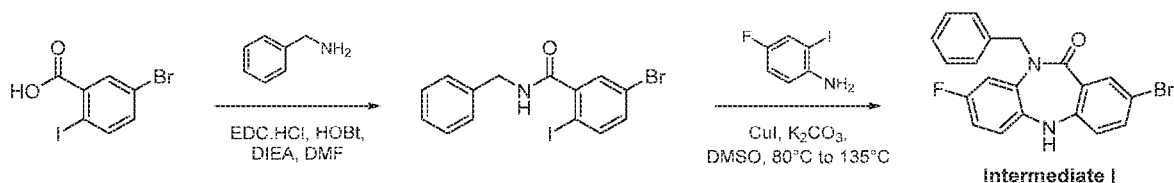
Step 4: 10-Benzyl-2-bromo-8-fluoro-5,10-dihydro-11*H*-dibenzo[*b,e*][1,4]diazepin-11-one (Intermediate I)



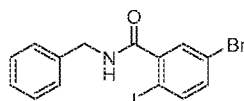
2-Amino-*N*-benzyl-5-bromo-*N*-(5-fluoro-2-iodophenyl)benzamide (60 mg, 0.11 mmol), copper(I) iodide (4 mg, 0.022 mmol), and potassium carbonate (38 mg, 0.275 mmol) were taken up in anhydrous DMSO (1 mL) and the resulting reaction mixture was stirred at 135°C for 2 hr. After cooling to room temperature, the mixture was diluted with an excess of Et₂O and washed with water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (EtOAc : DCM = 0 : 100 to 30 : 70) to give 10-benzyl-2-bromo-8-fluoro-5,10-dihydro-11*H*-dibenzo[*b,e*][1,4]diazepin-11-one (28 mg, 64 %) as a light yellow solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.06 (s, 1H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.54 (dd, *J* = 2.4, 8.5 Hz, 1H), 7.30 - 7.24 (m, 5H), 7.22 - 7.17 (m, 1H), 7.09 (dd, *J* = 6.0, 8.7 Hz, 1H), 7.04 (d, *J* = 8.9 Hz, 1H), 6.91 (td, *J* = 2.7, 8.4 Hz, 1H), 5.26 (s, 2H); LC/MS (ESI) *m/z* 396.73 [M+H]⁺.

Example 2: Synthesis of Intermediate I

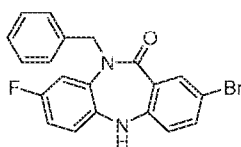


Step 1: *N*-Benzyl-5-bromo-2-iodobenzamide



5-Bromo-2-iodobenzoic acid (409 mg, 1.25 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (288 mg, 1.5 mmol), 1-hydroxybenzotriazole (135 mg, 1.0 mmol), *N,N*-diisopropylethylamine (523 μ L, 3.0 mmol), and benzylamine (109 μ L, 1.0 mmol) were dissolved in anhydrous DMF (5 mL) and stirred at room temperature for 16 hr. The reaction mixture was diluted with an excess of EtOAc and washed five times with water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (EtOAc : DCM = 0 : 100 to 30 : 70) to give *N*-benzyl-5-bromo-2-iodobenzamide (361 mg, 87 %) as a white solid.

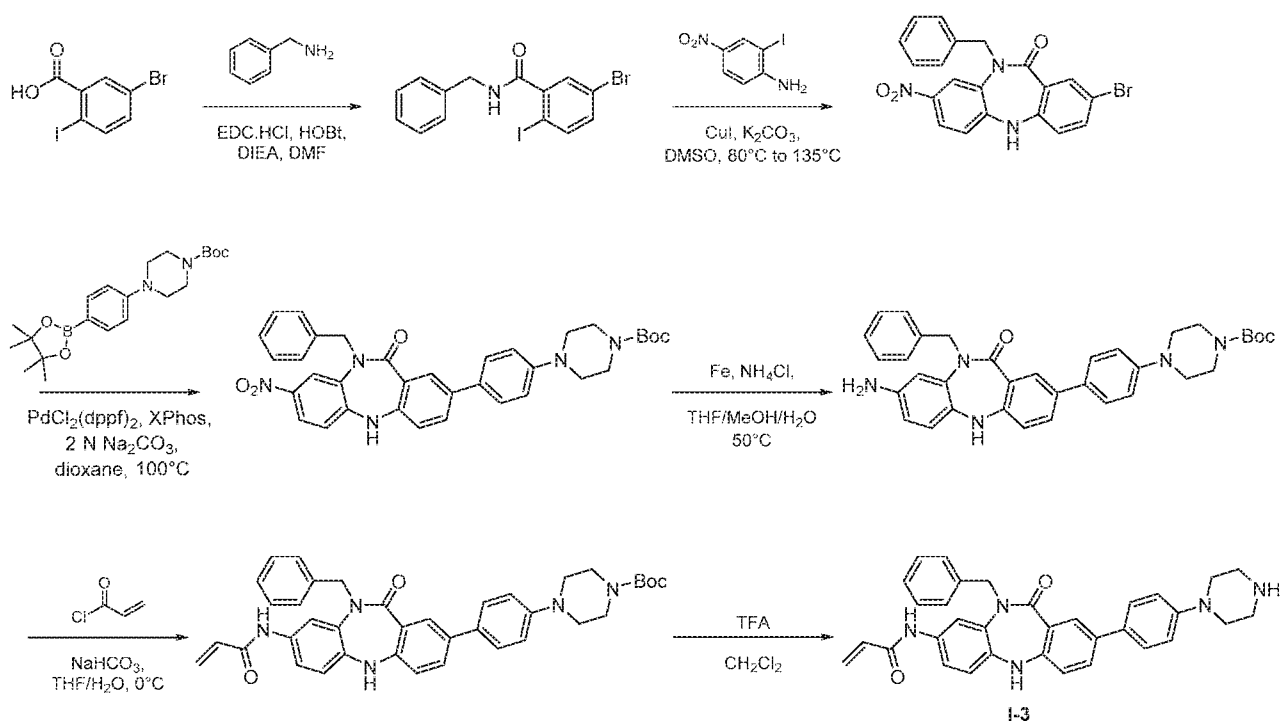
Step 2: 10-Benzyl-2-bromo-8-fluoro-5,10-dihydro-11*H*-dibenzo[*b,e*][1,4]diazepin-11-one (Intermediate I)



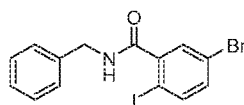
N-Benzyl-5-bromo-2-iodobenzamide (125 mg, 0.30 mmol), 4-fluoro-2-iodoaniline (29 μ L, 0.25 mmol), copper(I) iodide (10 mg, 0.05 mmol), and potassium carbonate (86 mg, 0.63 mmol) were taken up in anhydrous DMSO (1.5 mL). The resulting reaction mixture was first stirred at 80 °C for 2 hr, followed by heating to 135 °C for another 10 hr. After cooling to room temperature, the mixture was diluted with an excess of Et₂O and washed with water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (EtOAc : Hex = 0 : 100 to 100 : 0; EtOAc : DCM = 0 : 100 to 30 : 70) to give 10-benzyl-2-bromo-8-fluoro-5,10-dihydro-11*H*-dibenzo[*b,e*][1,4]diazepin-11-one (43 mg, 44 %) as a light yellow solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.06 (s, 1H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.54 (dd, *J* = 2.4, 8.5 Hz, 1H), 7.30 - 7.24 (m, 5H), 7.22 - 7.17 (m, 1H), 7.09 (dd, *J* = 6.0, 8.7 Hz, 1H), 7.04 (d, *J* = 8.9 Hz, 1H), 6.91 (td, *J* = 2.7, 8.4 Hz, 1H), 5.26 (s, 2H); LC/MS (ESI) *m/z* 396.73 [M+H]⁺.

Example 3: Synthesis of Compound I-3

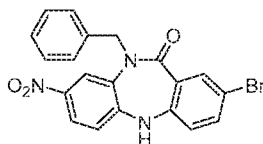


Step 1: *N*-Benzyl-5-bromo-2-iodobenzamide



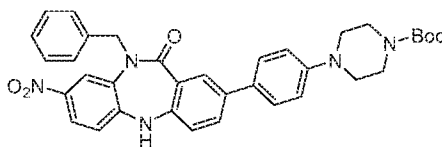
N-Benzyl-5-bromo-2-iodobenzamide was synthesized as described above (see Example 2).

Step 2: 10-Benzyl-2-bromo-8-nitro-5,10-dihydro-11*H*-dibenzo[*b,e*][1,4]diazepin-11-one



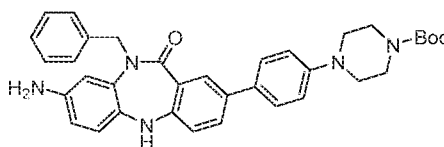
N-Benzyl-5-bromo-2-iodobenzamide (805 mg, 1.93 mmol), 2-iodo-4-nitroaniline (425 mg, 1.61 mmol), copper(I) iodide (123 mg, 0.65 mmol), and potassium carbonate (1.11 g, 8.0 mmol) were taken up in anhydrous DMSO (11 mL). The resulting reaction mixture was first stirred at 80°C for 2 hr, followed by heating to 135 °C for another 16 hr. After cooling to room temperature, the mixture was diluted with an excess of Et₂O and washed with water. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (EtOAc : Hex = 0 : 100 to 100 : 0) to give 10-benzyl-2-bromo-8-nitro-5,10-dihydro-11*H*-dibenzo[*b,e*][1,4]diazepin-11-one (179 mg, 26 %).

Step 3: *tert*-butyl 4-(4-(10-benzyl-8-nitro-11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-2-yl)phenyl)piperazine-1-carboxylate



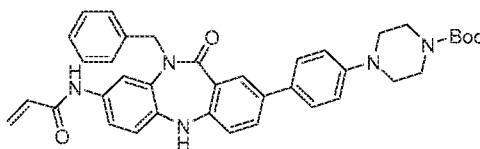
A mixture of 10-benzyl-2-bromo-8-nitro-5,10-dihydro-11*H*-dibenzo[*b,e*][1,4]diazepin-11-one (179 mg, 0.42 mmol), *tert*-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine-1-carboxylate (245 mg, 0.63 mmol) and a 2 *N* aqueous solution of sodium carbonate (1.1 mL, 2.1 mmol) in 1,4-dioxane (5 mL) was degassed by nitrogen bubbling for 10 min and heated to 100 °C. Then, PdCl₂(dppf)₂ (34 mg, 0.042 mmol) and XPhos (30 mg, 0.063 mmol) were added and the resulting reaction mixture was stirred at 100 °C for 2 hr. The reaction mixture was cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the residue was re-dissolved in DCM and washed repeatedly with brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (EtOAc : Hex = 0 : 100 to 100 : 0) to give *tert*-butyl 4-(4-(10-benzyl-8-nitro-11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-2-yl)phenyl)piperazine-1-carboxylate (233 mg, 90%).

Step 4: *tert*-butyl 4-(4-(8-amino-10-benzyl-11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-2-yl)phenyl)piperazine-1-carboxylate



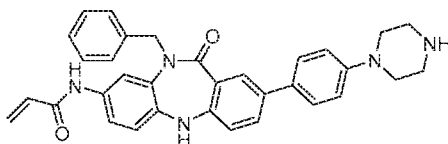
tert-Butyl 4-(4-(10-benzyl-8-nitro-11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-2-yl)phenyl)piperazine-1-carboxylate (233 mg, 0.38 mmol), iron powder (106 mg, 1.90 mmol), and ammonium chloride (203 mg, 3.80 mmol) were suspended in a mixture of THF/MeOH/H₂O (5:2:1, 4 mL). The resulting mixture was vigorously stirred at 50 °C for 45 min. The reaction mixture was cooled to room temperature and filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (DCM : 1.75 *N* NH₃ in MeOH = 100 : 0 to 80 : 20) to give *tert*-butyl 4-(4-(8-amino-10-benzyl-11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-2-yl)phenyl)piperazine-1-carboxylate (194 mg, 89 %).

Step 5: *tert*-Butyl 4-(4-(8-acrylamido-10-benzyl-11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-2-yl)phenyl)piperazine-1-carboxylate



To an ice-cooled solution of *tert*-butyl 4-(4-(8-amino-10-benzyl-11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-2-yl)phenyl)piperazine-1-carboxylate (194 mg, 0.34 mmol) in a THF/sat. NaHCO₃ mixture (1:1, 3 mL) was added dropwise acryloyl chloride (33 μ L, 0.41 mmol). After stirring for 30 min, the reaction mixture was diluted with DCM and washed with water. The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc : Hex = 0 : 100 to 100 : 0) to give *tert*-butyl 4-(4-(8-acrylamido-10-benzyl-11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-2-yl)phenyl)piperazine-1-carboxylate (179 mg, 82 %) as a light yellow solid.

Step 6: *N*-(10-Benzyl-11-oxo-2-(4-(piperazin-1-yl)phenyl)-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-8-yl)acrylamide (Compound I-3)



To a solution of *tert*-butyl 4-(4-(8-acrylamido-10-benzyl-11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-2-yl)phenyl)piperazine-1-carboxylate (179 mg, 0.28 mmol) in dichloromethane (4 mL) was added trifluoroacetic acid (1 mL). The resulting reaction mixture was stirred for 1 hr, after which the solution was concentrated and trifluoroacetic acid was removed under reduced pressure. The residue was purified by preparative RP-HPLC to afford *N*-(10-benzyl-11-oxo-2-(4-(piperazin-1-yl)phenyl)-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-8-yl)acrylamide (29 mg, 19%) as a light yellow solid.

¹H NMR (500 MHz, DMSO-*d*₆) δ 10.05 (s, 1H), 7.89 (s, 1H), 7.80 (d, *J* = 2.4 Hz, 1H), 7.71 (d, *J* = 2.1 Hz, 1H), 7.60 (dd, *J* = 2.4, 8.5 Hz, 1H), 7.45 (d, *J* = 8.9 Hz, 2H), 7.35 - 7.32 (m, 2H), 7.31 - 7.28 (m, 3H), 7.22 - 7.18 (m, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 7.07 (d, *J* = 8.9 Hz, 1H), 6.98 - 6.95 (m, 2H), 6.38 - 6.32 (m, 1H), 6.23 - 6.18 (m, 1H), 5.73 - 5.69 (m, 1H), 5.23 (s, 2H), 3.09 - 3.06 (m, 4H), 2.86 - 2.83 (m, 4H); LC/MS (ESI) *m/z* 530.25 [M+H]⁺.

Example 4: Synthesis of compounds of the application

Compounds in Table 1 were synthesized according to the procedures outlined in the Example 1-3.

Table 1

Cmpd ID	¹ H NMR and/or MS (m/z) data
I-1	¹ H NMR (500 MHz, DMSO-d ₆) δ 11.11 (s, 1H), 10.06 (s, 1H), 7.90 (s, 1H), 7.87 (d, <i>J</i> = 2.1 Hz, 1H), 7.72 (dd, <i>J</i> = 2.0, 9.3 Hz, 2H), 7.67 (dd, <i>J</i> = 2.3, 8.4 Hz, 1H), 7.44 (d, <i>J</i> = 8.5 Hz, 1H), 7.36 - 7.34 (m, 3H), 7.33 - 7.28 (m, 4H), 7.23 - 7.19 (m, 1H), 7.15 (d, <i>J</i> = 8.2 Hz, 1H), 7.09 (d, <i>J</i> = 8.5 Hz, 1H), 6.47 - 6.45 (m, 1H), 6.39 - 6.32 (m, 1H), 6.23 - 6.18 (m, 1H), 5.73 - 5.69 (m, 1H), 5.24 (s, 2H); LC/MS (ESI) <i>m/z</i> 485.32 [M+H] ⁺ .
I-2	¹ H NMR (500 MHz, DMSO-d ₆) δ 11.11 (s, 1H), 10.19 (s, 1H), 7.91 (s, 1H), 7.87 (d, <i>J</i> = 2.4 Hz, 1H), 7.74 - 7.73 (m, 1H), 7.69 - 7.66 (m, 1H), 7.59 (d, <i>J</i> = 2.4 Hz, 1H), 7.45 - 7.42 (m, 1H), 7.36 - 7.33 (m, 3H), 7.33 - 7.29 (m, 3H), 7.26 (dd, <i>J</i> = 2.3, 8.7 Hz, 1H), 7.23 - 7.19 (m, 1H), 7.15 (d, <i>J</i> = 8.2 Hz, 1H), 7.09 (d, <i>J</i> = 8.5 Hz, 1H), 6.46 (ddd, <i>J</i> = 0.9, 1.9, 3.0 Hz, 1H), 5.23 (s, 2H), 4.18 (s, 2H); LC/MS (ESI) <i>m/z</i> 507.45 [M+H] ⁺ .
I-a	¹ H NMR (500 MHz, DMSO-d ₆) δ 8.06 (s, 1H), 7.74 (d, <i>J</i> = 2.4 Hz, 1H), 7.54 (dd, <i>J</i> = 2.4, 8.5 Hz, 1H), 7.30 - 7.24 (m, 5H), 7.22 - 7.17 (m, 1H), 7.09 (dd, <i>J</i> = 6.0, 8.7 Hz, 1H), 7.04 (d, <i>J</i> = 8.9 Hz, 1H), 6.91 (td, <i>J</i> = 2.7, 8.4 Hz, 1H), 5.26 (s, 2H); LC/MS (ESI) <i>m/z</i> 396.73 [M+H] ⁺ .
I-b	¹ H NMR (500 MHz, DMSO-d ₆) δ 7.88 (s, 1H), 7.66 (dd, <i>J</i> = 1.5, 7.9 Hz, 1H), 7.39 - 7.35 (m, 1H), 7.32 - 7.26 (m, 4H), 7.23 (dd, <i>J</i> = 2.9, 10.5 Hz, 1H), 7.21 - 7.17 (m, 1H), 7.12 - 7.06 (m, 2H), 6.99 (t, <i>J</i> = 7.2 Hz, 1H), 6.89 (td, <i>J</i> = 2.7, 8.4 Hz, 1H), 5.27 (s, 2H); LC/MS (ESI) <i>m/z</i> 318.96 [M+H] ⁺ .

5

Example 5: Biochemical/Biological Studies*Ba/F3 cell proliferation models*

The EGFR mutant L858R, Del E746_A750, L858R/T790M, DelE746_A750/T790M, L858R/T790M/C797S and Del/T790M/C797S Ba/F3 cells were previously described (Zhou *et al.*, *Nature* 462, (2009), 1070-1074). All cell lines were maintained in RPMI 1640 (Cellgro; Mediatech Inc., Herndon, CA) supplemented with 10% FBS 100 units/mL penicillin, 100 units/mL streptomycin, and 2 mM glutamine. L858R cells were maintained in ACL-4 media (Invitrogen, Carlsbad, CA) supplemented with 5% FBS, 100 units/mL penicillin, 100 units/mL streptomycin, and 2 mM glutamine. The EGFR I941R mutation was introduced via site directed mutagenesis using the Quick Change Site-Directed Mutagenesis kit (Stratagene; La Jolla, CA) according to the

15

manufacturer's instructions. All constructs were confirmed by DNA sequencing. The constructs were shuttled into the retroviral vector JP1540 using the BD Creator™ System (BD Biosciences). Ba/F3 cells were infected with retrovirus and according to standard protocols, as described previously (Zhou 2009). Stable clones were obtained by selection in puromycin (2
5 µg/ml).

Growth and inhibition of growth was assessed by MTS assay and was performed according to previously established methods (Zhou 2009). The MTS assay is a colorimetric method for determining the number of viable cells that is based on the bioreduction of MTS by cells to a formazan product that is soluble in cell culture medium and can be detected
10 spectrophotometrically. Ba/F3 cells of different *EGFR* genotypes were exposed to treatment and the number of cells used per experiment determined empirically and has been previously established (Zhou 2009). All experimental points were set up in six wells and all experiments were repeated at least three times. The data was graphically displayed using GraphPad Prism version 5.0 for Windows (GraphPad Software). The curves were fitted using a non-linear
15 regression model with a sigmoidal dose response.

The inhibition of cell proliferation by compounds of the application is shown in Tables 2A-2D.

Table 2A: Inhibition of proliferation of EGFR T790M/L858R Ba/F3 cell line by compounds of the application at a concentration of 1 µM (% inhibition: $0 \leq A < 25$, $25 \leq B < 50$, $50 \leq C < 75$, $75 \leq D$).

Compound ID	Activity (% DMSO control)
I-1	A

Table 2C: Inhibition of proliferation of EGFR L858R/T790M/C797S Ba/F3 cell line by compounds of the application at a concentration of 1 µM (% inhibition: $0 \leq A < 25$, $25 \leq B < 50$, $50 \leq C < 75$, $75 \leq D$).

Table 2B: Inhibition of proliferation of EGFR T790M/L858R Ba/F3 cell line by compounds of the application at a concentration of 1 µM in the presence of 1 µg/mL cetuximab (% inhibition: $0 \leq A < 25$, $25 \leq B < 50$, $50 \leq C < 75$, $75 \leq D$).

Compound ID	Activity (% cetuximab)
I-1	A

Table 2D: Inhibition of proliferation of EGFR L858R/T790M/C797S cell line by compounds of the application at a concentration of 1 µM in the presence of 1 µg/mL cetuximab (% inhibition: $0 \leq A < 25$, $25 \leq B < 50$, $50 \leq C < 75$, $75 \leq D$).

inhibition: $0 \leq A < 25$, $25 \leq B < 50$, $50 \leq C < 75$, $75 \leq D$).

Compound ID	Activity (% DMSO control)
I-1	C

Compound ID	Activity (% cetuximab)
I-1	A

The antiproliferative activity of compounds of the application is shown in Table 3.

Table 3: Antiproliferative activity (EC_{50}) of compounds of the application against EGFR

T790M/L858R Ba/F3 cell line in the absence and presence of 1 μ g/mL cetuximab (EC_{50} : $0 < A < 250$ nM; 250 nM $\leq B < 500$ nM; 500 nM $\leq C < 750$ nM; 750 nM $\leq D$).

Compound ID	Ba/F3 cellular activity (EC_{50})	
	T790M/L858R	T790M/L858R + Cetuximab
I-1	D	C
I-2	A	A
I-3	D	D
I-a	D	B
I-b	D	C

EGFR protein expression and purification

Constructs spanning residues 696-1022 of the human EGFR (including wild type and L858R, L858R/T790M, T790M, and T790M/V948R mutant sequences) were prepared in a GST-fusion format using the pTriEX system (Novagen) for expression in Sf9 insect cells essentially as described (Yun *et al.*, *PNAS* 105, 2070-2075 (2008); Yun *et al.*, *Cancer Cell* 11, 217-227 (2007)). EGFR kinase proteins were purified by glutathione-affinity chromatography followed by size-exclusion chromatography after cleavage with TEV or thrombin to remove the GST fusion partner following established procedures. (Yun 2008; Yun 2007).

High-throughput screening

Purified EGFR-L858R/T790M enzyme was screened against compounds of the present application using HTRF-based biochemical assay format. The screening was performed at 1 μ M ATP using a single compound concentration (12.5 μ M). 1322 top hits were picked for follow-up IC_{50} confirmation. IC_{50} values were determined at both 1 μ M and 1 mM ATP to identify both ATP competitive and non-competitive compounds. Hits were also counter-screened against wild type EGFR to evaluate the mutant selectivity.

The HTRF-based screen was carried out using 1 μ M ATP, and active compounds were counter-screened at 1 mM ATP and against wild type EGFR to identify those that were potentially non-ATP-competitive and mutant selective. This strategy identified several compounds of distinct chemical classes that were both selective for the L858R/T790M mutant over WT EGFR and relatively insensitive to ATP concentrations, suggesting an allosteric mechanism of action.

HTRF-based EGFR biochemical assays

EGFR biochemical assays were carried out using a homogeneous time-resolved fluorescence (HTRF) assay as described previously. The reaction mixtures contained 1 μ M biotin-Lck-peptide substrate, wild type or mutant EGFR enzyme in reaction buffer (50mM HEPES pH 7.1, 10 mM MgCl₂, 0.01% BSA, 1 mM TCEP and 0.1 mM Na₃VO₄) at a final volume of 10 μ L. Enzyme concentrations were adjusted to accommodate varying kinase activity and ATP concentrations (0.2-0.4 nM L858R/T790M; or 2-4 nM L858R, or 2-4 nM T790M, or 40 nM WT). All reactions were carried out at room temperature in white ProxiPlate™ 384-well Plus plates (PerkinElmer) and were quenched with 5 μ L of 0.2 M EDTA at 60 min. Five μ L per well of the detection reagent containing 2.5 ng PT66K (Cis-bio) and 0.05 μ g SAXL (Prozyme) were added, and the plates were then incubated at room temperature for 1 hour and read with an EnVision plate reader. For IC₅₀ determinations, compounds of the present application were diluted into assay mixture (final DMSO 0.5%), and IC₅₀ values were determined by 12-point inhibition curves (from 50 to 0.000282 μ M) in duplicate under the assay conditions as described above.

The biochemical inhibitory activity (HTRF, IC₅₀) of compounds of the application is shown in Table 4.

Table 4: Biochemical inhibitory activity (HTRF, IC₅₀) of compounds of the application against recombinant EGFR T790M/L858R kinase (IC₅₀: 0 < A < 250 nM; 250 nM $\leq$ B < 500 nM; 500 nM $\leq$ C < 750 nM; 750 nM $\leq$ D).

Compound ID	HTRF (IC ₅₀) T790M/L858R
I-1	D
I-2	D
I-3	D
I-a	A
I-b	A

*H1975, H3255 & HaCaT Target Modulation Assays**Tissue Culture*

5 Cells were maintained in 10% FBS/RPMI supplemented with 100 µg/mL Penicillin/Streptomycin (Hyclone #SH30236.01). The cells were harvested with 0.25% Trypsin/EDTA (Hyclone #SH30042.1), re-suspended in 5% FBS/RPMI Pen/Strep and plated at 7,500 cells per well in 50 µL of media in a 384-well black plate with clear bottoms (Greiner #789068G). The cells were allowed to incubate overnight in a 37 °C, 5% CO₂ humidified tissue culture incubator. The 12-point serial diluted test compounds were transferred to the plate containing cells by using a 50 nL Pin Head device (Perkin Elmer) and the cells were placed back in the incubator for 3 hours.

Phospho-EGFR (Y1173) Target Modulation Assay

15 HaCaT cells were stimulated with 10 ng/mL EGF (Peprotech # AF-100-15) for 5 minutes at room temperature. Constitutively activated EGFR mutant cell lines (H1975 and H3255) were not stimulated with EGF. The media was reduced to 20 µL using a Bio-Tek ELx 405 Select™ plate washer. Cells were lysed with 20 µL of 2X Lysis buffer containing protease and phosphatase inhibitors (2% Triton X-100, 40 mM Tris, pH 7.5, 2 mM EDTA, 2 mM EGTA, 300 mM NaCl, 2X complete cocktail inhibitor (Roche #11 697 498 001), 2X Phosphatase Inhibitor 20 Cocktail Set II and Set III (Sigma #P5726 and #P0044)). The plates were shaken for 20 minutes. An aliquot of 25 µL from each well was transferred to prepared ELISA plates for analysis.

For the experiment studying the effect of EGF pre-treatment on compound (*e.g.*, compounds of the present application) target modulation, H1975 cells were harvested and plated in 0.5% FBS/RPMI Pen/Strep. On the following day, cells were pre-treated with 0.5% 25 FBS/RPMI media with or without 10 ng EGF/mL for 5 minutes. Compound (*i.e.*, compounds of the present application) was added and assay was carried out as described above.

Phospho-EGFR (Y1173) ELISA

30 Solid white 384-well high-binding ELISA plates (Greiner #781074) were coated with 5 µg/mL goat anti-EGFR capture antibody overnight in 50 mM carbonate/bicarbonate pH 9.5 buffer. Plates were blocked with 1% BSA (Sigma #A7030) in PBS for 1 hour at room temperature, and washes were carried out with a Bio-Tek ELx405 Select™ using 4 cycles of

100 μ L TBS-T (20 mM Tris, 137 mM NaCl, 0.05% Tween-20) per well. A 25 μ L aliquot of lysed cell was added to each well of the ELISA plate and incubated overnight at 4 °C with gentle shaking. A 1:1,000 anti-phospho-EGFR in 0.2% BSA/TBS-T was added and incubated for 2 hours at room temperature. After washing, 1:2,000 anti-rabbit-HRP in 0.2% BSA/TBS-T was added and incubated for 1 hour at room temperature. Chemiluminescent detection was carried out with SuperSignal ELISA Pico substrate. Signal was read on EnVision plate reader using built-in UltraLUM setting.

Western blotting

Cell lysates were equalized to protein content determined by Coomassie Plus™ Protein Assay Reagent (ThermoScientific #1856210) and loaded onto 4-12% NuPAGE Bis-Tris gels with MOPS running buffer with LDS Sample buffer (supplemented with DTT). Gel proteins were transferred to PVDF membranes with an iBlot® Gel Transfer Device. 1X Casein-blocked membranes were probed with primary antibodies overnight at 4 °C on an end-over-end rotisserie. Membranes were washed with TBS-T and HRP-conjugated secondary antibodies were added for 1 hour at room temperature. After washing, HRP was detected using Luminata™ Forte Western HRP Substrate reagent and recorded with a Bio-Rad VersaDoc imager.

Proliferation Assay

H1975, H3255 and HaCaT cell lines were plated in solid white 384-well plates (Greiner) at 500 cells per well in 10% FBS RPMI P/S media. Using a Pin Tool, 50 nL of serial diluted compounds of the present application were transferred to the cells. After 3 days, cell viability was measured by CellTiter-Glo (Promega) according to manufacturer's instructions. Luminescent readout was normalized to 0.1% DMSO-treated cells and empty wells. Data was analyzed by non-linear regression curve-fitting and EC₅₀ values were reported.

Considering the allosteric mechanism of action the compounds of the present application, the extent to which ligand stimulation would affect potency of inhibition of the mutant receptor was studied. To this end, inhibition of EGFR phosphorylation in H1975 cells in the presence and absence of EGF using the quantitative ELISA-based assay was examined.

In the EGFR asymmetric dimer, the C-lobe of the "activator" subunit impinges on the N-lobe of the "receiver" subunit, inducing an active conformation in the receiver by reorienting the regulatory C-helix to its inward, catalytically functional position. In wild-type EGFR, only the receiver subunit is activated. Oncogenic mutations in the EGFR kinase domain induce an active

conformation even in the absence of ligand stimulation, thus both subunits of a ligand-bound mutant receptor are expected to be catalytically active. In the receiver subunit but not the activator, outward displacement of the C-helix is impeded by the asymmetric dimer interaction. Because the mutant receptor favors dimer formation and could promote dimerization even in the absence of ligand, this effect could explain the apparent disconnect in biochemical and cellular potencies of the allosteric inhibitor (Red Brewer *et al.*, *PNAS* 110, E3595-3604, doi:10.1073/pnas.1220050110 (2013); Shan *et al.*, *Cell* 149, 860-870, doi:10.1016/j.cell.2012.02.063 (2012)). To test this notion, an I941R point mutation in the C-lobe of the kinase, which is known to block the asymmetric dimer interaction, was exploited. (Zhang 2006; Cho *et al.*, *Cancer Res* 73, 6770-6779, doi:10.1158/0008-5472.CAN-13-1145 (2013)). The activity of the L858R/T790M mutant is dimerization-independent, and as expected Ba/F3 cells bearing the L858R/T790M/I941R triple mutant EGFR proliferated in the absence of IL-3. The dimerization-defective mutant was dramatically more sensitive to the allosteric inhibitor.

One therapeutic antibody, cetuximab, targets the extracellular portion of the EGF receptor, blocking ligand binding and preventing dimer formation. The antibody is not effective clinically in EGFR-mutant NSCLC, and in cell-based studies cetuximab alone does not inhibit L858R/T790M or Del/T790M mutant EGFR, because their activity is dimerization independent.

Mouse efficacy studies

EGFR-TL (T790M/L858R) and EGFR-TD (exon 19 deletion-T790M) mice were generated as previously described. The *EGFR-L858R;T790M;C797S* ("TLCS") mutant mouse cohort was established briefly as follows: The full-length HuTLCS cDNA was generated by site-directed mutagenesis using the Quickchange site directed mutagenesis kit (Agilent Technologies) and further verified by DNA sequencing. Sequence-verified targeting vectors were co-electroporated with an FLPe recombinase plasmid into v6.5 C57BL/6J (female) x 129/sv (male) embryonic stem cells (Open Biosystems) as described elsewhere. Resulting hygromycin-resistant embryonic stem clones were evaluated for transgene integration via PCR. Then, transgene-positive embryonic stem clones were injected into C57BL/6 blastocysts, and the resulting chimeras were mated with BALB/c WT mice to determine germline transmission of the TLCS transgene. Progeny of TL, TD and TLCS mice were genotyped by PCR of tail DNA.

The TL and TD mice were fed a doxycycline diet at 6 weeks of age to induce EGFR TL or TD expression, respectively. The TLCS mice were intranasally instilled with Ad-Cre (University of Iowa viral vector core) at 6 weeks of age to excise the loxP sites, activating EGFR TLCS expression.

All care of experimental animals was in accordance with Harvard Medical School/Dana-Farber Cancer Institute (DFCI) institutional animal care and use committee (IACUC) guidelines. All mice were housed in a pathogen-free environment at a DFCI animal facility and handled in strict accordance with Good Animal Practice as defined by the Office of Laboratory Animal Welfare.

In vivo treatment and MRI tumor volume quantification

The TL, TD and TLCS mice were monitored by MRI to quantify lung tumor burden before being assigned to various treatment study cohorts. All the treatment mice had equal amount initial tumor burden. A compound of the present application was dissolved in 10% NMP (10% 1-methyl-2-pyrrolidinone: 90% PEG-300), and was dosed at 60 mg/kg daily by oral gavage. Cetuximab was administrated at 1 mg/mouse every three days by intraperitoneal injection. MRI evaluation was repeated every 2 weeks during the treatment. The animals were imaged with a rapid acquisition with relaxation enhancement sequence (TR = 2000 ms, TE effect = 25 ms) in the coronal and axial planes with a 1-mm slice thickness gating with respiratory rates. The detailed procedure for MRI scanning has been previously described (Li *et al.*, 2007).

The tumor burden volumes were quantified using 3-dimensional Slicer software.

Example 6: Additional/Alternative Biochemical/Biological Studies

Cell viability assays

H3255GR cells were treated with increasing concentrations of inhibitors for 72 hours and growth or the inhibition of growth was assessed by MTS assay according to previously established methods (Engelman *et al.*, 2006; Ercan *et al.*, 2015; Zhou *et al.*, 2009). All experimental points were set up in six technical replicates and all experiments were repeated at least three times.

Western blotting

To assess the effect of compounds on EGFR and its downstream pathways, NIH-3T3, H1975, H3255GR cells were treated for 4 hours before cells were lysed with NP40 lysis buffer, supplemented with protease and phosphatase inhibitors, followed by protein quantification.

µg of lysates were used for Western Blotting analyses. For experiments that examine the effect of an allosteric EGFR inhibitor in the presence of EGF, cells were treated with 10 ng/ml of EGF for 15 minutes before they were treated with drugs for 4 hours followed by lysis and protein quantification as described above. All experiments were done at least three times.

5 *Biotinylated drug pull down assay*

For *in vitro* pull down assays, cells were treated with dose-escalated WZ-4002, an ATP-competitive EGFR inhibitor for two hours before they were subjected to lysis and protein quantification. 15-20 µg of proteins lysates were aliquoted and loaded at the same time as the pull down assay to ensure the presence of EGFR protein, phospho-EGFR activity. Tubulin
10 expression was assessed to ensure even loading of gels. 500 µg of protein was incubated with either biotinylated-linker (control) or with biotinylated allosteric EGFR inhibitor for two hours before 50 % NeutrAvidin agarose beads (Thermo Fisher Scientific) slurry was added for an hour to precipitate the EGFR that was associated to the biotinylated allosteric inhibitor. The beads were then washed three times with PBS containing 1 % IGEPAL and an insulin syringe was used
15 to remove extraneous buffer before the samples were suspended in 2X SDS sample preparation buffer for Western blotting analyses. All experiments were performed at least three times.

ENU mutagenesis

N-ethyl-*N*-nitrosourea (ENU) was purchased from Sigma Aldrich and mutagenesis studies were carried as previously described (Ercan et al., 2015). Briefly, 1 x10⁶ cells/ml of
20 L858R and L858R/T790M Ba/F3 cells were treated with 50 µg/ml of ENU for 24 hours before the cells were washed three times in RPMI media and expanded for 3 days. 1x10⁴ cells per well were plated in 96 wells and 5 plates were plated per condition. These cells were treated continuously with either DMSO, 1 µM gefitinib, 1 µM of an ATP-competitive EGFR inhibitor, 10 µM of an allosteric EGFR inhibitor alone or with gefitinib/allosteric EGFR inhibitor or ATP-
25 competitive EGFR inhibitor/allosteric EGFR inhibitor drug combinations for 4 weeks with media and drug change once a week. Cell growth was monitored and number of resistant clones were counted and expanded.

IncuCyte studies

For cell confluency studies, H3255GR cells were treated with different inhibitors and
30 monitored by the automated microscopy using the IncuCyte Live-Cell Imaging system (Essen Bioscience). Confluency was measured by averaging the percentage of area that the cells

occupied from three images of a given well every two hours for 72 hours. For apoptosis studies, cells were treated with inhibitors incubated in media containing the CellEvent™ Caspase 3/7 Green ReadyProbes® reagent (Thermo Fisher Scientific) and monitored for change in green fluorescence activity using the aforementioned imaging system. The average number of objects
5 that were stained with green from three images per well was counted as positive for Caspase 3/7, indicating apoptosis, and recorded every two hours for 72 hours. All experimental conditions were set up in at least six replicates and all experiments were performed at least three times.

In vivo studies

All breeding, mouse husbandry, and *in vivo* experiments were performed with the
10 approval of the Dana-Farber Cancer Institute (Boston, MA) Animal Care and Use Committee.

For the H1975 xenograft study, Nu/Nu mice were purchased from Charles River Laboratories International Inc. H1975 cells were detected as pathogen free at Charles River Laboratories International Inc. and were resuspended in serum-free medium mixed with an equal amount of Matrigel (BD Biosciences). Mice were injected at 2 locations per mouse in the flanks
15 with 2 million cells per shot. The mice were randomly grouped, and treatment started when tumor size reached 100 to 200 mm³. Each cohort included at least 5 mice. Tumor sizes were monitored weekly, and volumes were calculated using the following formula: (mm³) = length × width × width × 0.5.

To assess EGFR activity in the mice after the study was performed, tumors were taken 3
20 hours after the last dose for pharmacodynamic (PD) studies. Tumors were flash frozen in liquid nitrogen to preserve tissue integrity and homogenized in RIPA buffer supplemented with protease and phosphatase inhibitors. The protein was quantified and 20 µg of lysates were used for Western Blotting analyses.

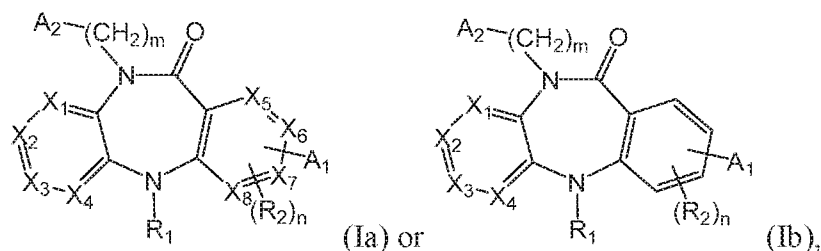
In the H1975 xenograft study, an allosteric EGFR inhibitor was dissolved in 5 % NMP (5
25 % 1-methyl-2-pyrrolidinone; 95 % PEG-300). An allosteric EGFR inhibitor was dosed at 100 mg/kg once daily orally. An ATP-competitive EGFR inhibitor was dissolved in 0.5 % HMPC (0.5 % Hydroxypropyl methylcellulose; 99.5 % 0.05N hydrogen chloride). Mice received 25 mg/kg ATP-competitive EGFR inhibitor once daily orally.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific embodiments described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

CLAIMS

1. A compound of Formula Ia or Ib:



or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein:

5 A₁ is phenyl or heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl or heteroaryl is substituted with one or more R_{A1}; each R_{A1} is independently C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, halogen, CN, phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-
10 membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, and halogen, or

two R_{A1}, together with the adjacent atoms to which they are attached, form phenyl, C₃-C₆
15 cycloalkyl, or a 5- or 6-membered heteroaryl or heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, and halogen;

n is 0, 1, 2, or 3;

20 each R₂ is independently C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, halogen, or CN;

each m is independently 0, 1, 2, or 3;

A₂ is phenyl or heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl or heteroaryl is optionally substituted with one or
25 more R_{A2};

each R_{A2} is independently C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, halogen, CN, phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring

and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, and halogen,
 5 or

two R_{A2}, together with the adjacent atoms to which they are attached, form phenyl, C₃-C₆ cycloalkyl, or a 5- or 6-membered heteroaryl or heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, and halogen;
 10

R₁ is H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, halogen, CN, or (CH₂)_m-A₃;

A₃ is phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, halogen, and W;
 15

X₁, X₂, X₃, and X₄ are each independently N or CR_X, provided that at least two of X₁, X₂, X₃, and X₄ are CR_X;

20 X₅, X₆, X₇, and X₈ are each independently N or CR_X;

each R_X is independently W, H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, halogen, CN, phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, and halogen;
 25

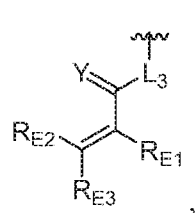
R₃ is H or C₁-C₄ alkyl;

R₄ is C₁-C₄ alkyl substituted with one or more R₅ or C₂-C₄ alkenyl optionally substituted with one or more R₅;
 30

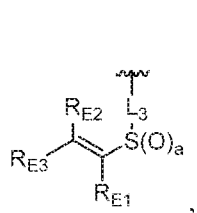
each R₅ is independently halogen or NR_{n1}R_{n2};

each R_{N1} and each R_{N2} are independently H or C₁-C₄ alkyl;

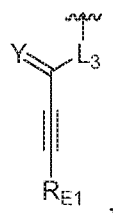
W is $NR_3C(O)R_4$, $C(O)R_4$, or is of formula:



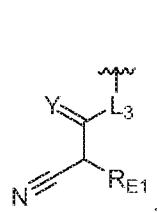
(i-1)



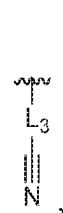
(i-2)



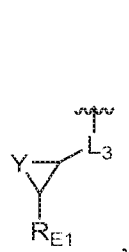
(i-3)



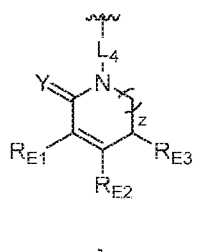
(i-4)



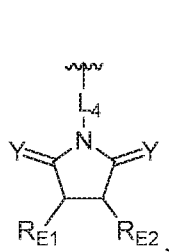
(i-5)



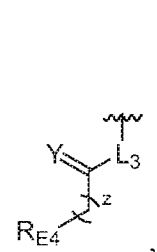
(i-6)



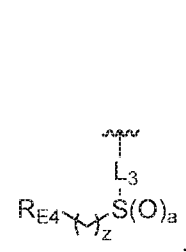
(i-7)



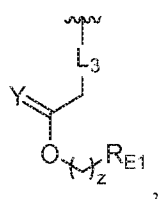
(i-8)



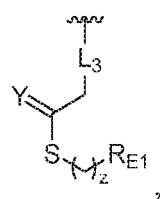
(i-9)



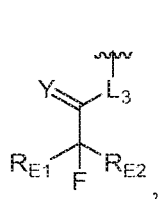
(i-10)



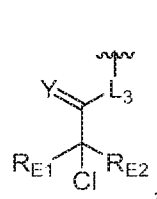
(i-11)



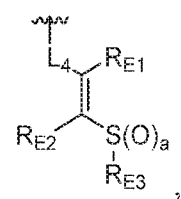
(i-12)



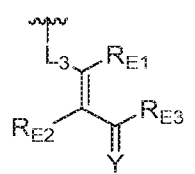
(i-13)



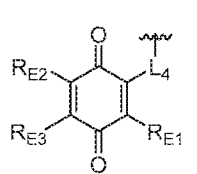
(i-14)



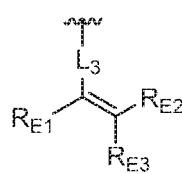
(i-15)



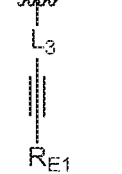
(i-16)



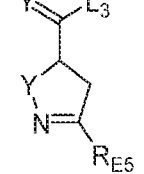
(i-17)



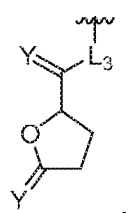
(i-18)



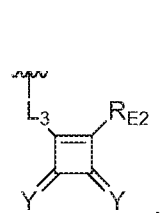
(i-19)



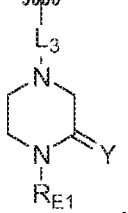
(i-20)



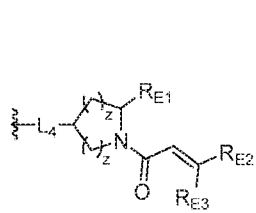
(i-21)



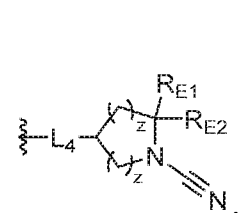
(i-22)



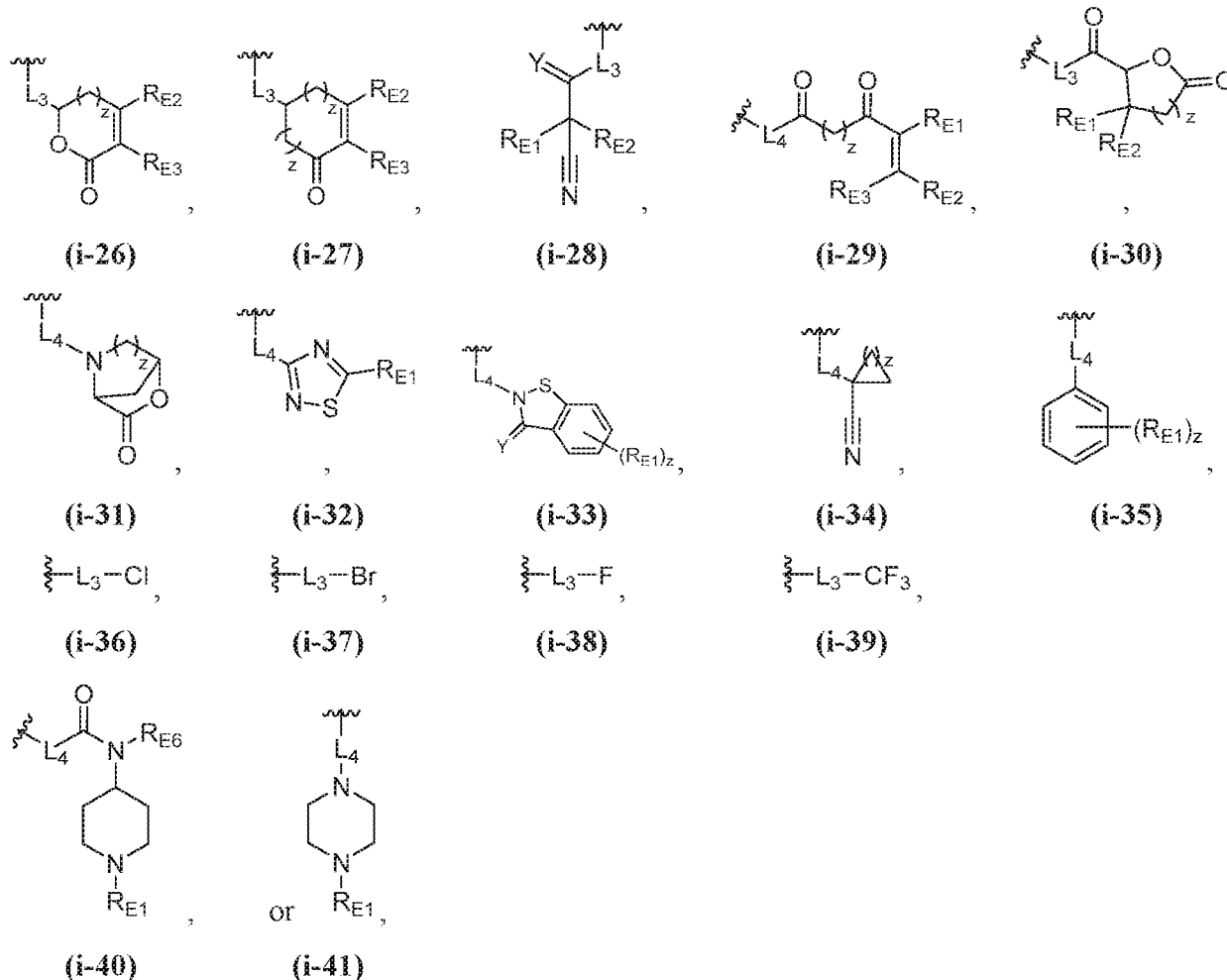
(i-23)



(i-24)



(i-25)



L₃ is a bond or an optionally substituted C₁-C₄ hydrocarbon chain, optionally wherein one or more carbon units of the hydrocarbon chain are independently replaced with -C=O-, -O-, -S-, -NR_{L3a}-, -NR_{L3a}C(=O)-, -C(=O)NR_{L3a}-, -SC(=O)-, -C(=O)S-, -OC(=O)-, -C(=O)O-, -NR_{L3a}C(=S)-, -C(=S)NR_{L3a}-, *trans*-CRL_{3b}=CRL_{3b}-, *cis*-CRL_{3b}=CRL_{3b}-, -C≡C-, -S(=O)-, -S(=O)O-, -OS(=O)-, -S(=O)NR_{L3a}-, -NR_{L3a}S(=O)-, -S(=O)₂-, -S(=O)₂O-, -OS(=O)₂-, -S(=O)₂NR_{L3a}-, or -NR_{L3a}S(=O)₂-;

R_{L3a} is H, optionally substituted C₁-C₆ alkyl, or a nitrogen protecting group;

each R_{L3b} is independently H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S, optionally substituted C₆-C₁₀ aryl, or optionally substituted heteroaryl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S, or two R_{L3b} groups are joined to form an optionally substituted C₃-C₈

carbocycle or optionally substituted 4- to 7-membered heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S;

L₄ is a bond or an optionally substituted C₁-C₆ hydrocarbon chain;

each of R_{E1}, R_{E2}, and R_{E3} is independently H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S, optionally substituted C₆-C₁₀ aryl, or optionally substituted heteroaryl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S, CN, CH₂OR_{EE}, CH₂N(R_{EE})₂, CH₂SR_{EE}, OR_{EE}, N(R_{EE})₂, Si(R_{EE})₃, or SR_{EE}, or R_{E1} and R_{E3}, or R_{E2} and R_{E3}, or R_{E1} and R_{E2} are joined to form an optionally substituted C₃-C₈ carbocycle or optionally substituted 4- to 7-membered heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S;

R_{E4} is halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S, optionally substituted C₆-C₁₀ aryl, or optionally substituted heteroaryl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S, CN, CH₂OR_{EE}, CH₂N(R_{EE})₂, CH₂SR_{EE}, OR_{EE}, N(R_{EE})₂, Si(R_{EE})₃, or SR_{EE};

each R_{EE} is independently H, optionally substituted C₁-C₆ alkyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted heterocyclyl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S, optionally substituted C₆-C₁₀ aryl, or optionally substituted heteroaryl comprising one or two 5- or 6-membered rings and 1-4 heteroatoms selected from N, O, and S, or two R_{EE} are joined to form an optionally substituted 4- to 7-membered heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S;

R_{E5} is halogen;

R_{E6} is H, optionally substituted C₁-C₆ alkyl, or a nitrogen protecting group;

each Y is independently O, S, or NR_{E7};

R_{E7} is H, optionally substituted C₁-C₆ alkyl, or a nitrogen protecting group;

a is 1 or 2; and

each z is independently 0, 1, 2, 3, 4, 5, or 6,

provided that at least one of R_X and R_1 is a moiety comprising W, and not both of R_X and R_1 are a moiety comprising W.

2. The compound of claim 1, wherein A_1 is phenyl.

3. The compound of claim 1, wherein A_1 is heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S.

4. The compound of any one of claims 1-3, wherein at least one R_{A1} is C_1 - C_4 straight-chain or C_3 - C_4 branched alkyl, C_1 - C_4 straight-chain or C_3 - C_4 branched haloalkyl, C_1 - C_4 straight-chain or C_3 - C_4 branched alkoxy, C_1 - C_4 straight-chain or C_3 - C_4 branched haloalkoxy, OH, halogen, or CN.

5. The compound of any one of claims 1-3, wherein at least one R_{A1} is phenyl, C_3 - C_6 cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, OH, and halogen.

6. The compound of any one of claims 1-3, wherein two R_{A1} , together with the adjacent atoms to which they are attached, form phenyl, C_3 - C_6 cycloalkyl, or a 5- or 6-membered heteroaryl or heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, OH, and halogen.

7. The compound of any one of claims 1-6, wherein n is 0, 1, or 2.

8. The compound of any one of claims 1-7, wherein n is 0 or 1.

9. The compound of any one of claims 1-8, wherein n is 0.

10. The compound of any one of claims 1-9, wherein at least one R₂ is C₁-C₆ straight-chain or C₃-C₆ branched alkyl, C₁-C₆ straight-chain or C₃-C₆ branched haloalkyl, C₁-C₆ straight-chain or C₃-C₆ branched alkoxy, C₁-C₆ straight-chain or C₃-C₆ branched haloalkoxy, OH, halogen, or CN.

11. The compound of any one of claims 1-10, wherein A₂ is unsubstituted phenyl.

12. The compound of any one of claims 1-10, wherein A₂ is phenyl substituted with one or more R_{A2}.

13. The compound of any one of claims 1-10, wherein A₂ is unsubstituted heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S.

14. The compound of any one of claims 1-10, wherein A₂ is heteroaryl comprising one 5-membered ring and 1-3 heteroatoms selected from N, O, and S, and is optionally substituted with one or more R_{A2}.

15. The compound of any one of claims 1-14, wherein at least one R_{A2} is C₁-C₄ straight-chain or C₃-C₄ branched alkyl, C₁-C₄ straight-chain or C₃-C₄ branched haloalkyl, C₁-C₄ straight-chain or C₃-C₄ branched alkoxy, C₁-C₄ straight-chain or C₃-C₄ branched haloalkoxy, OH, halogen, or CN.

16. The compound of any one of claims 1-14, wherein at least one R_{A2} is phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, OH, and halogen.

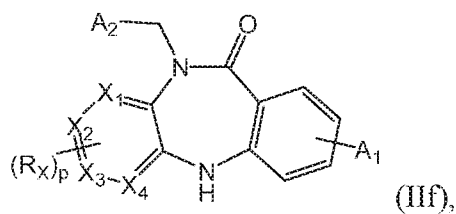
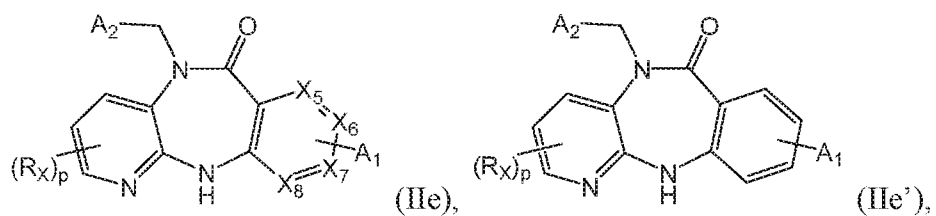
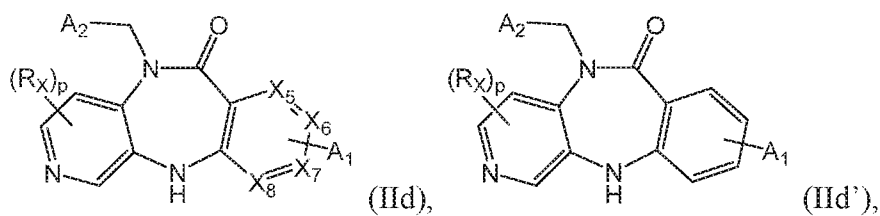
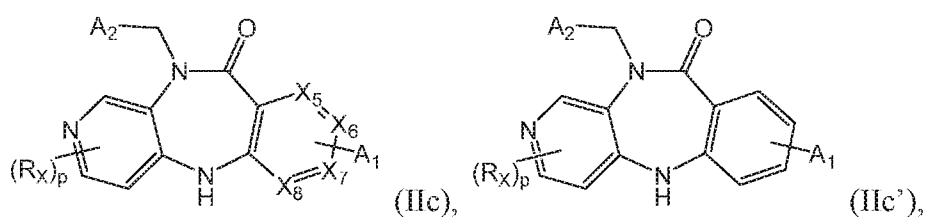
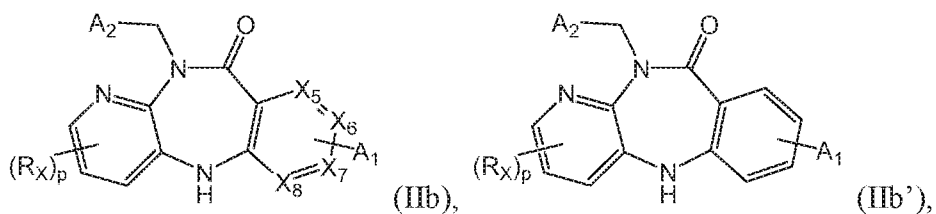
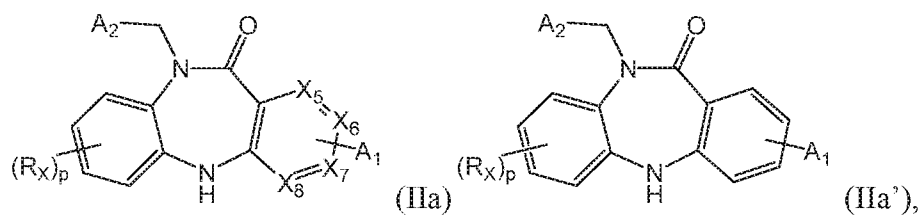
17. The compound of any one of claims 1-14, wherein two R_{A2} , together with the adjacent atoms to which they are attached, form phenyl, C_3 - C_6 cycloalkyl, or a 5- or 6-membered heteroaryl or heterocyclyl ring comprising 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, OH, and halogen.
18. The compound of any one of claims 1-17, wherein each m is independently 0, 1, or 2.
19. The compound of any one of claims 1-17, wherein each m is independently 0 or 1.
20. The compound of any one of claims 1-19, wherein R_1 is H.
21. The compound of any one of claims 1-19, wherein R_1 is C_1 - C_6 straight-chain or C_3 - C_6 branched alkyl, C_1 - C_6 straight-chain or C_3 - C_6 branched haloalkyl, C_1 - C_6 straight-chain or C_3 - C_6 branched alkoxy, C_1 - C_6 straight-chain or C_3 - C_6 branched haloalkoxy, OH, halogen, or CN.
22. The compound of any one of claims 1-19, wherein R_1 is $(CH_2)_m-A_3$.
23. The compound of any one of claims 1-19 and 22, wherein A_3 is phenyl, C_3 - C_6 cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with one or more substituents independently selected from C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, OH, and halogen.
24. The compound of any one of claims 1-19 and 22, wherein A_3 is phenyl, C_3 - C_6 cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted with W.

25. The compound of any one of claims 1-24, wherein X_1 , X_2 , X_3 , and X_4 are each CR_X .
26. The compound of any one of claims 1-24, wherein one of X_1 , X_2 , X_3 , and X_4 is N, and the
5 remainder of X_1 , X_2 , X_3 , and X_4 are each CR_X .
27. The compound of any one of claims 1-24, wherein two of X_1 , X_2 , X_3 , and X_4 are N, and the remainder of X_1 , X_2 , X_3 , and X_4 are each CR_X .
- 10 28. The compound of any one of claims 1-27, wherein X_5 , X_6 , X_7 , and X_8 are each CR_X .
29. The compound of any one of claims 1-27, wherein one of X_5 , X_6 , X_7 , and X_8 is N, and the remainder of X_5 , X_6 , X_7 , and X_8 are each CR_X .
- 15 30. The compound of any one of claims 1-27, wherein two of X_5 , X_6 , X_7 , and X_8 are N, and the remainder of X_5 , X_6 , X_7 , and X_8 are each CR_X .
31. The compound of any one of claims 1-23 and 25-30, wherein one of R_X is W, and the remaining one or more R_X are each independently H, $NR_{n1}R_{n2}$, $NR_3C(O)R_4$, C₁-C₆ straight-chain
20 or C₃-C₆ branched alkyl, C₁-C₆ straight-chain or C₃-C₆ branched haloalkyl, C₁-C₆ straight-chain or C₃-C₆ branched alkoxy, C₁-C₆ straight-chain or C₃-C₆ branched haloalkoxy, OH, halogen, or CN.
32. The compound of any one of claims 1-23 and 25-30, wherein one of R_X is W, and the
25 remaining one or more R_X are each independently H, phenyl, C₃-C₆ cycloalkyl, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, or heterocyclyl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S, wherein the phenyl, cycloalkyl, heteroaryl, or heterocyclyl is optionally substituted.
- 30 33. The compound of any one of claims 1-23 and 25-32, wherein one of R_X is W, and the remaining one or more R_X are each H.

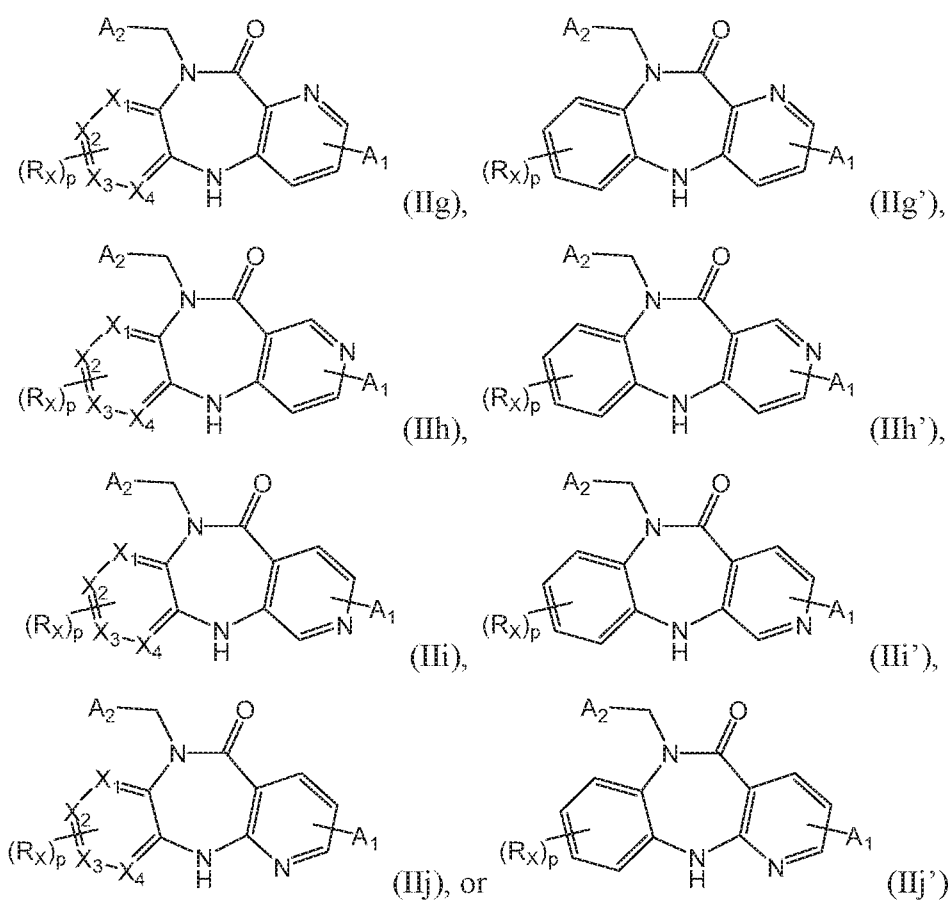
34. The compound of any one of claims 1-33, wherein W is $\text{NR}_3\text{C}(\text{O})\text{R}_4$ or $\text{C}(\text{O})\text{R}_4$.

35. The compound of claim 1, of Formula IIa, IIa', IIb, IIb', IIc, IIc', IId, IId', IIe, IIe', IIg,

5 IIg', IIh, IIh', IIf, IIf', IIj, or IIj':

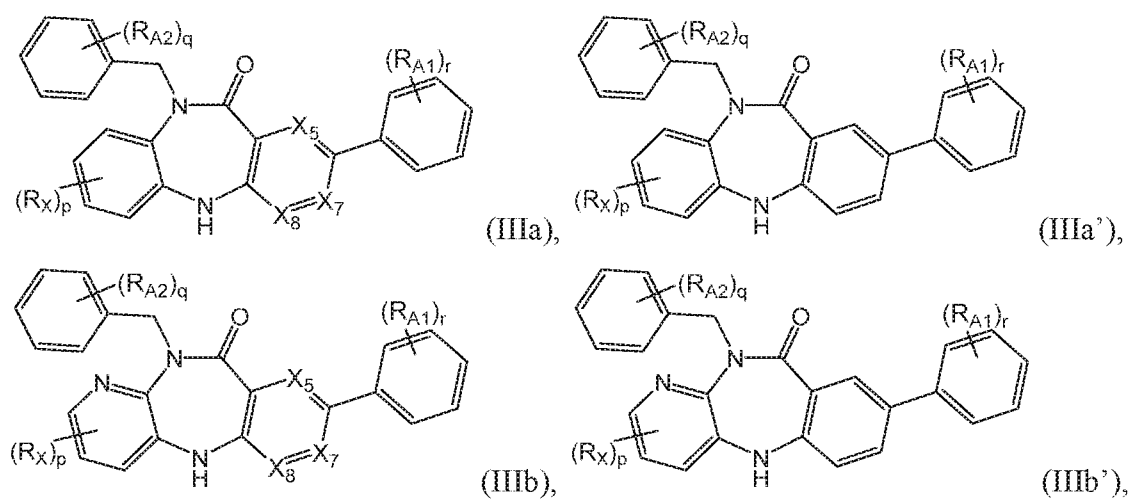


10

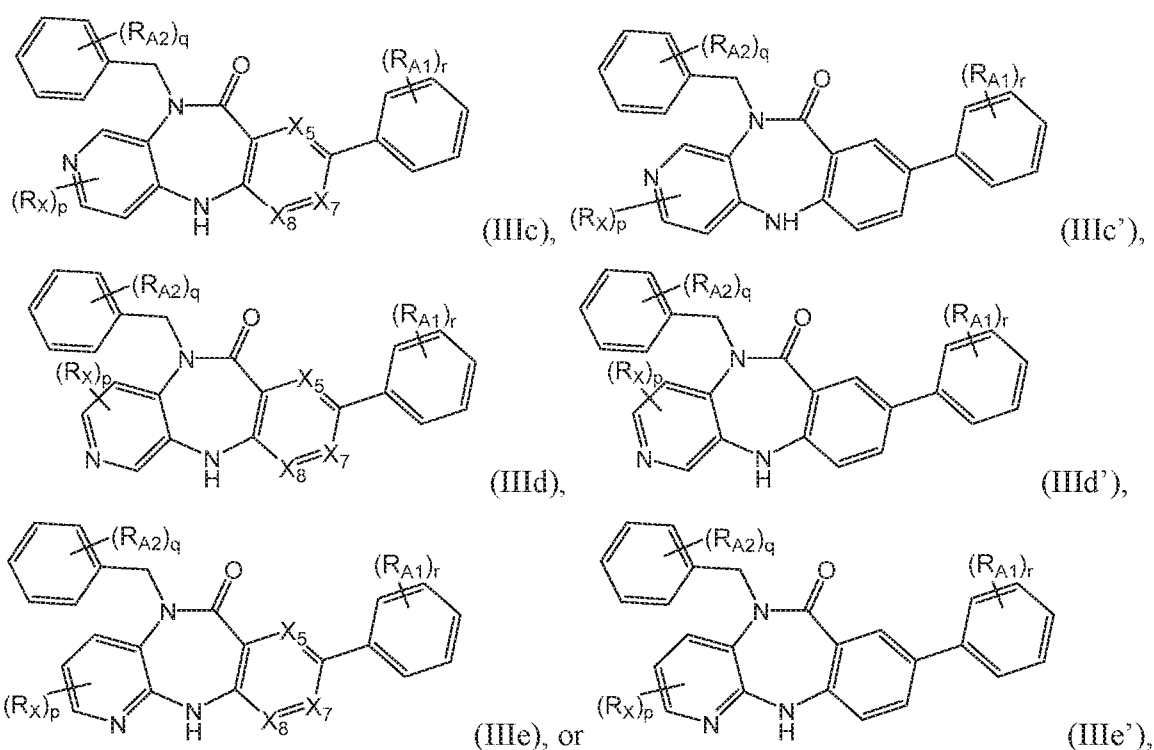


5 or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein p is 0, 1, 2, or 3.

36. The compound of claim 1, of Formula IIIa, IIIa', IIIb, IIIb', IIIc, IIIc', IIId, IIId', IIIe, or IIIe':



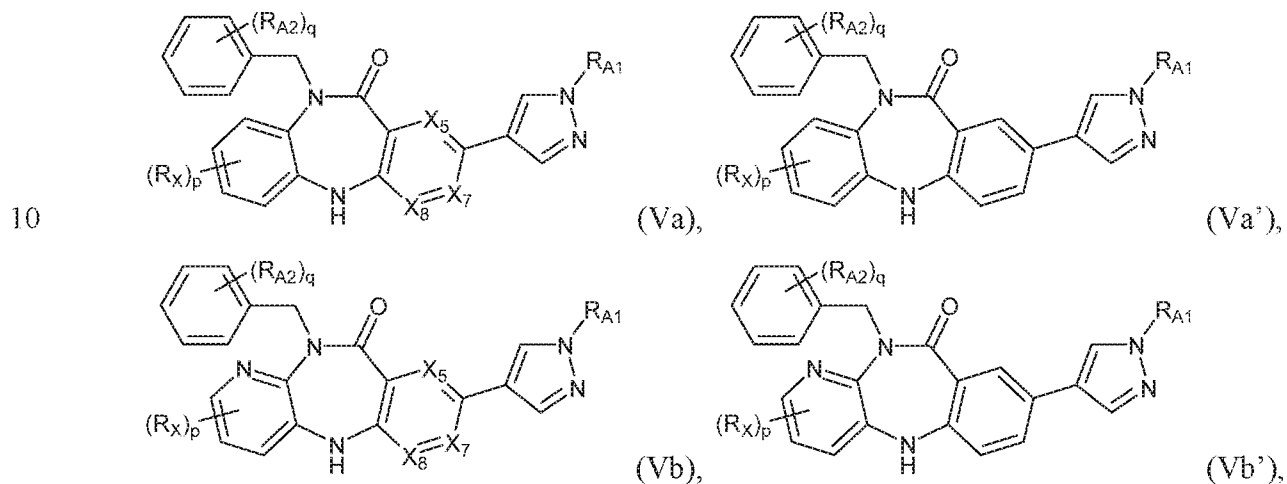
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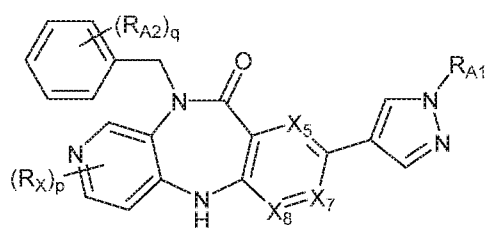


or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein:

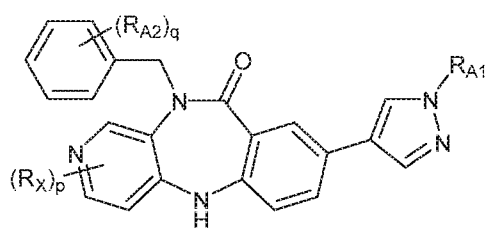
- 5 p is 0, 1, 2, or 3;
 q is 0, 1, 2, 3, 4, or 5; and
 r is 0, 1, 2, 3, 4, or 5.

37. The compound of claim 1, of Formula Va, Va', Vb, Vb', Vc, Vc', Vd, Vd', Ve or Ve':

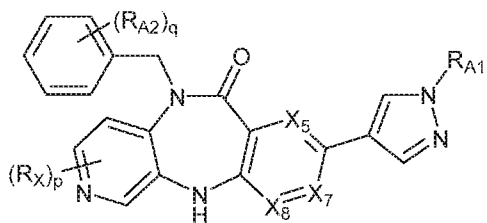




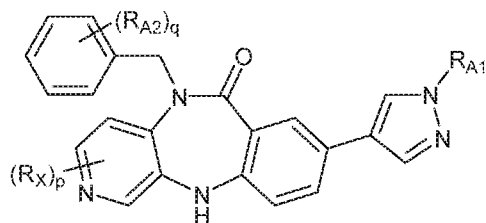
(Vc),



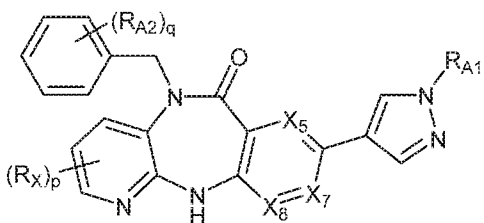
(Vc'),



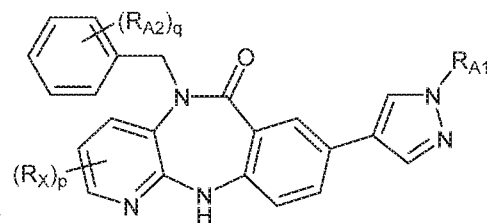
(Vd),



(Vd'),



(Ve), or



(Ve'),

or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein:

- 5 p is 0, 1, 2, or 3; and
 q is 0, 1, 2, 3, 4, or 5.

38. The compound of claim 1, selected from Table A.

- 10 39. A pharmaceutical composition comprising a compound of any one of claims 1-38, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and a pharmaceutically acceptable carrier, optionally further comprising a second agent that prevents EGFR dimer formation, and a pharmaceutically acceptable carrier.

- 15 40. A kit comprising a compound of any one of claims 1-38, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, optionally further comprising a second agent that prevents EGFR dimer formation, and a pharmaceutically acceptable carrier.

- 20 41. A method of inhibiting a kinase, comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-38, or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

42. A method of treating or preventing a disease, a disease resistant to an EGFR targeted therapy, cancer wherein the cell of the cancer comprises an activated EGFR or an activated ERBB2, or cancer in a subject wherein the subject is identified as being in need of EGFR inhibition or ERBB2 inhibition for the treatment or prevention of cancer, comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-38, or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

43. The method of claim 41 or 42, further comprising administering a second agent that prevents EGFR dimer formation, and a pharmaceutically acceptable carrier.

44. A compound of any one of claims 1-38, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for use in the manufacture of a medicament for
inhibiting a kinase in a subject in need thereof,
treating or preventing a disease in a subject in need thereof,
treating or preventing a disease resistant to an EGFR targeted therapy in a subject in need thereof,
treating or preventing cancer in a subject in need thereof, wherein the cell of the cancer comprises an activated EGFR or an activated ERBB2, or
treating or preventing cancer in a subject, wherein the subject is identified as being in need of EGFR inhibition or ERBB2 inhibition for the treatment or prevention of cancer.

45. A compound of any one of claims 1-38, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and a second agent that prevents EGFR dimer formation, for use in the manufacture of a medicament for
inhibiting a kinase in a subject in need thereof,
treating or preventing a disease in a subject in need thereof,
treating or preventing a disease resistant to an EGFR targeted therapy in a subject in need thereof,
treating or preventing cancer in a subject in need thereof, wherein the cell of the cancer comprises an activated EGFR or an activated ERBB2, or

treating or preventing cancer in a subject, wherein the subject is identified as being in need of EGFR inhibition or ERBB2 inhibition for the treatment or prevention of cancer.

46. A compound of any one of claims 1-38, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for

inhibiting a kinase in a subject in need thereof,

treating or preventing a disease in a subject in need thereof,

treating or preventing a disease resistant to an EGFR targeted therapy in a subject in need thereof,

treating or preventing cancer in a subject in need thereof, wherein the cell of the cancer comprises an activated EGFR or an activated ERBB2, or

treating or preventing cancer in a subject, wherein the subject is identified as being in need of EGFR inhibition or ERBB2 inhibition for the treatment or prevention of cancer.

47. A compound of any one of claims 1-38, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and a second agent that prevents EGFR dimer formation, for

inhibiting a kinase in a subject in need thereof,

treating or preventing a disease in a subject in need thereof,

treating or preventing a disease resistant to an EGFR targeted therapy in a subject in need thereof,

treating or preventing cancer in a subject in need thereof, wherein the cell of the cancer comprises an activated EGFR or an activated ERBB2, or

treating or preventing cancer in a subject, wherein the subject is identified as being in need of EGFR inhibition or ERBB2 inhibition for the treatment or prevention of cancer.

48. Use of a compound of any one of claims 1-38, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, in the manufacture of a medicament for

inhibiting a kinase in a subject in need thereof,

treating or preventing a disease in a subject in need thereof,

treating or preventing a disease resistant to an EGFR targeted therapy in a subject in need thereof,

treating or preventing cancer in a subject in need thereof, wherein the cell of the cancer comprises an activated EGFR or an activated ERBB2, or

treating or preventing cancer in a subject, wherein the subject is identified as being in need of EGFR inhibition or ERBB2 inhibition for the treatment or prevention of cancer.

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49. Use of a compound of any one of claims 1-38, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and a second agent that prevents EGFR dimer formation, in the manufacture of a medicament for

inhibiting a kinase in a subject in need thereof,

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treating or preventing a disease in a subject in need thereof,

treating or preventing a disease resistant to an EGFR targeted therapy in a subject in need thereof,

treating or preventing cancer in a subject in need thereof, wherein the cell of the cancer comprises an activated EGFR or an activated ERBB2, or

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treating or preventing cancer in a subject, wherein the subject is identified as being in need of EGFR inhibition or ERBB2 inhibition for the treatment or prevention of cancer.

50. Use of a compound of any one of claims 1-38, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for

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inhibiting a kinase in a subject in need thereof,

treating or preventing a disease in a subject in need thereof,

treating or preventing a disease resistant to an EGFR targeted therapy in a subject in need thereof,

treating or preventing cancer in a subject in need thereof, wherein the cell of the cancer

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comprises an activated EGFR or an activated ERBB2, or

treating or preventing cancer in a subject, wherein the subject is identified as being in need of EGFR inhibition or ERBB2 inhibition for the treatment or prevention of cancer.

51. Use of a compound of any one of claims 1-38, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and a second agent that prevents EGFR dimer formation, for

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inhibiting a kinase in a subject in need thereof,

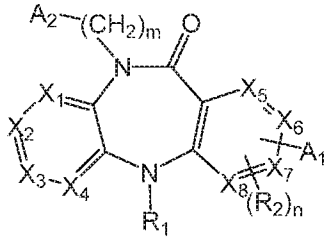
treating or preventing a disease in a subject in need thereof,

treating or preventing a disease resistant to an EGFR targeted therapy in a subject in need thereof,

treating or preventing cancer in a subject in need thereof, wherein the cell of the cancer comprises an activated EGFR or an activated ERBB2, or

5 treating or preventing cancer in a subject, wherein the subject is identified as being in need of EGFR inhibition or ERBB2 inhibition for the treatment or prevention of cancer.

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(Ia) or

