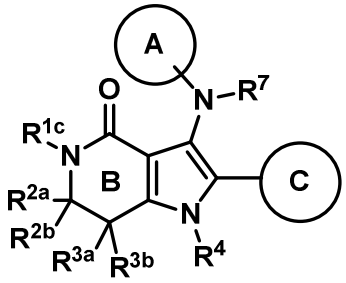
SUMMARY

This disclosure provides chemical entities (e.g., a compound or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination of the compound) that inhibit epidermal growth factor receptor (EGFR, ERBB1) and/or Human epidermal growth factor receptor 2 (HER2, ERBB2). These chemical entities are useful, e.g., for treating a condition, disease or disorder in which increased (e.g., excessive) EGFR and/or HER2 activation contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g., cancer) in a subject (e.g., a human). This disclosure also provides compositions containing the same as well as methods of using and making the same.

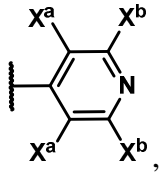
In one example, this disclosure features compounds of Formula **(I)**:



Formula **(I)**

or a pharmaceutically acceptable salt thereof, wherein:

Ring C is selected from the group consisting of:

- 

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

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

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

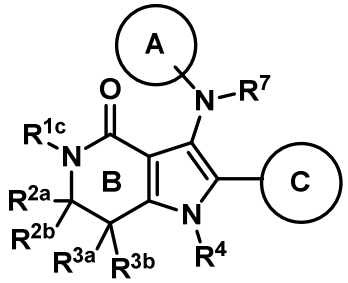
each **g** is independently 1, 2, or 3;

each $\mathbf{R^{g2}}$ is a divalent $\mathbf{R^g}$ group;

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

each occurrence of $\mathbf{R^N}$ is independently H, C_{1-3} alkyl, or C_{3-6} cycloalkyl.

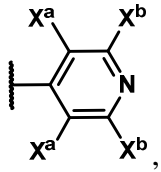
In one aspect, the present disclosure refers to a compound of Formula **(I)**:



Formula **(I)**

or a pharmaceutically acceptable salt thereof, wherein:

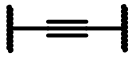
Ring C is selected from the group consisting of:

- , wherein:
  - each $\mathbf{X^b}$ is independently $\mathbf{X^1}$, $\mathbf{R^c}$, or H; and
  - each $\mathbf{X^a}$ is independently selected from the group consisting of: H, halo; cyano; $C_{1\text{-}10}$ alkyl which is optionally substituted with from 1-6 independently selected $\mathbf{R^a}$; $C_{2\text{-}6}$ alkenyl; $-S(O)_{1\text{-}2}(C_{1\text{-}4}$ alkyl); $-S(O)(=NH)(C_{1\text{-}4}$ alkyl); $-N\mathbf{R^eR^f}$; –OH; $-S(O)_{1\text{-}2}N\mathbf{R'R''}$; $-C_{1\text{-}4}$ thioalkoxy; $-NO_2$; $-C(=O)(C_{1\text{-}10}$ alkyl); $-C(=O)O(C_{1\text{-}4}$ alkyl); $-C(=O)OH$; $-C(=O)N\mathbf{R'R''}$; and $–SF_5$;
- 2-pyridyl or 3-pyridyl, each optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;
- 2-pyridonyl or 4-pyridonyl, each optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$, wherein the ring nitrogen atom is optionally substituted with $\mathbf{R^d}$;
- heteroaryl including 6 ring atoms, wherein from 2-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), and N($\mathbf{R^d}$), and wherein the heteroaryl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;
- heteroaryl including 5 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0\text{-}2}$, and wherein the heteroaryl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;
- bicyclic heteroaryl including 7-10 ring atoms, wherein from 1-4 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0\text{-}2}$, and wherein the heteroaryl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- $C_{3\text{-}10}$ cycloalkyl or $C_{3\text{-}10}$ cycloalkenyl, each of which is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$;
- heterocyclyl or heterocycloalkenyl including from 3-10 ring atoms, wherein from 1-3 ring atoms are heteroatoms, each independently selected from the group consisting of N, N(H), N($\mathbf{R^d}$), O, and $S(O)_{0\text{-}2}$, and wherein the heterocyclyl or heterocycloalkenyl is optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo and $\mathbf{R^c}$; and

- C_{6-10} aryl optionally substituted with $\mathbf{X^1}$ and further optionally substituted with from 1-4 $\mathbf{R^c}$;

$\mathbf{X^1}$ is $-(\mathbf{X^2})_{\mathbf{m}}\text{-}\mathbf{L^1}\text{-}\mathbf{R^5}$, wherein: **m** is 0 or 1;

$\mathbf{X^2}$ is selected from the group consisting of:

- -O-, -N($\mathbf{R^N}$)-, or $-S(O)_{0-2}$;
- ;
- $-C_{2-6}$ alkenylene optionally substituted with from 1-3 $\mathbf{R^a}$;
- -C(=O)O-*, -C(=O)N($\mathbf{R^N}$)-*, or $-S(O)_{1-2}N(\mathbf{R^N})$-*;
- -OC(=O)-*, -N($\mathbf{R^N}$)C(=O)-*, or $-N(\mathbf{R^N})S(O)_{1-2}$-*; and
- -OC(=O)N($\mathbf{R^N}$)-*, -N($\mathbf{R^N}$)C(=O)O-*, -N($\mathbf{R^N}$)C(=O)N($\mathbf{R^N}$)-*, or $-N(\mathbf{R^N})S(O)_{1-2}N(\mathbf{R^N})$-*,

wherein the asterisk represents point of attachment to $\mathbf{L^1}$;

$\mathbf{L^1}$ is selected from the group consisting of: a bond and C_{1-10} alkylene optionally substituted with from 1-6 $\mathbf{R^a}$;

$\mathbf{R^5}$ is selected from the group consisting of:

- H;
- halo;
- -OH;
- -N$\mathbf{R^e}\mathbf{R^f}$;
- $-C_{1-6}$ alkoxy or $-S(O)_{0-2}(C_{1-6}$ alkyl), each optionally substituted with from 1-6 $\mathbf{R^a}$;
- -$\mathbf{R^g}$;
- -$\mathbf{L^5}$-$\mathbf{R^g}$;
- -$\mathbf{R^{g2}}$-$\mathbf{R^W}$ or -$\mathbf{R^{g2}}$-$\mathbf{R^Y}$; and
- -$\mathbf{L^5}$-$\mathbf{R^{g2}}$-$\mathbf{R^W}$ or –$\mathbf{L^5}$-$\mathbf{R^{g2}}$-$\mathbf{R^Y}$;

provided that:

when $\mathbf{L^1}$ is a bond, then $\mathbf{R^5}$ is selected from the group consisting of: H, -$\mathbf{R^g}$, -$\mathbf{R^{g2}}$-$\mathbf{R^W}$, and -$\mathbf{R^{g2}}$-$\mathbf{R^Y}$; and

$\mathbf{X^1}$ is other than H, -OH, or NH_2;

$\mathbf{L^5}$ is selected from the group consisting of: –O-, $-S(O)_{0-2}$, -NH-, and -N($\mathbf{R^d}$)-;

$\mathbf{R^W}$ is $-\mathbf{L^W}\text{-}\mathbf{W}$,

wherein $\mathbf{L^W}$ is C(=O), $S(O)_{1-2}$, OC(=O)*, NHC(=O)*, N$\mathbf{R^d}$C(=O)*, $NHS(O)_{1-2}$*, or $N\mathbf{R^d}S(O)_{1-2}$*, wherein the asterisk represents point of attachment to **W**, and

W is selected from the group consisting of:

- C_{2-6} alkenyl; C_{2-6} alkynyl; or C_{3-10} allenyl, each of which is optionally substituted with from 1-3 $\mathbf{R^a}$ and further optionally substituted with $\mathbf{R^g}$, wherein **W** is attached to $\mathbf{L^W}$ via an sp^2 or sp hybridized carbon atom, thereby providing an α, β-unsaturated system; and
- bicyclo[**x**.**y**.0]cycloalkyl optionally substituted with from 1-2 $\mathbf{R^c}$, wherein **x** is 1 or 2; and **y** is an integer from 1 to 6;

$\mathbf{R^Y}$ is selected from the group consisting of: -$\mathbf{R^g}$ and -$\mathbf{(L^g)}_g$-$\mathbf{R^g}$;

each of $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$ is independently selected from the group consisting of: H; halo; -OH; -C(O)OH or –$C(O)NH_2$; -CN; -$\mathbf{R^b}$; -$\mathbf{L^b}$-$\mathbf{R^b}$; -N$\mathbf{R^e R^f}$; -$\mathbf{R^g}$; -$\mathbf{(L^g)}_g$-$\mathbf{R^g}$; -$\mathbf{(L^g)}_g$-$\mathbf{R^W}$; -$\mathbf{(L^g)}_g$-$\mathbf{R^{g2}}$-$\mathbf{R^W}$; and -C_{1-6} alkoxy or -C_{1-6} thioalkoxy, each optionally substituted with from 1-6 $\mathbf{R^a}$; provided that $\mathbf{R^{1c}}$ is other than halo, –CN, or –C(O)OH; or

two of variables $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$, together with the **Ring B** ring atoms to which each is attached, form a fused saturated or unsaturated ring of 3-12 ring atoms;

- wherein from 0-2 of the ring atoms are each an independently selected heteroatom (in addition to –N($\mathbf{R^{1c}}$)- when –N($\mathbf{R^{1c}}$)- forms part of the fused saturated or unsaturated ring), wherein each of the independently selected heteroatoms is selected from the group consisting of N, NH, N($\mathbf{R^d}$), O, and $S(O)_{0-2}$; and
- wherein the fused saturated or unsaturated ring of 3-12 ring atoms is optionally substituted with from 1-4 substituents independently selected from the group consisting of oxo, $\mathbf{R^c}$, and $\mathbf{R^W}$; or

one of $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ and one of $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ combine to form a double bond between the **Ring B** atoms to which each is attached;

Ring A is $\mathbf{R^g}$;

$\mathbf{R^4}$ and $\mathbf{R^7}$ are independently H or $\mathbf{R^d}$;

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

each occurrence of $\mathbf{R^b}$ is independently C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, each of which is optionally substituted with from 1-6 $\mathbf{R^a}$;

each occurrence of $\mathbf{L^b}$ is independently C(=O); C(=O)O; $S(O)_{1-2}$; C(=O)NH*; C(=O)N$\mathbf{R^d}$*; $S(O)_{1-2}$NH*; or $S(O)_{1-2}$N($\mathbf{R^d}$)*, wherein the asterisk represents point of attachment to $\mathbf{R^b}$;

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

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

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

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

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

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

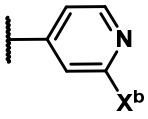
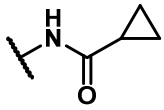
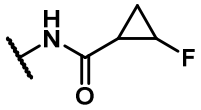
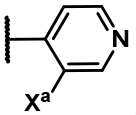
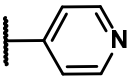
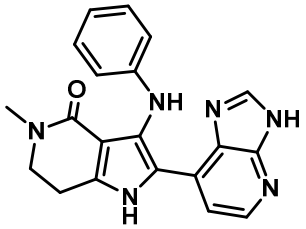
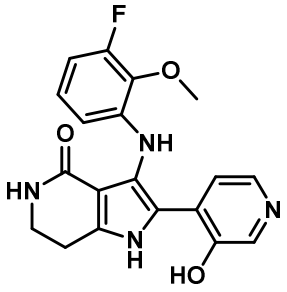
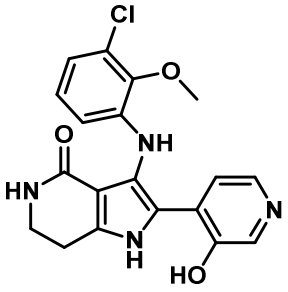
each **g** is independently 1, 2, or 3;

each $\mathbf{R^{g2}}$ is a divalent $\mathbf{R^g}$ group;

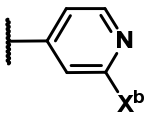
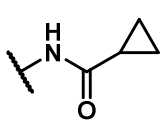
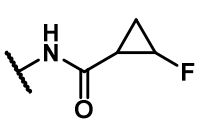
each occurrence of **R'** and **R''** is independently selected from the group consisting of: H; -OH; and C_{1-4} alkyl; and

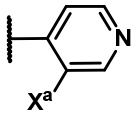
each occurrence of $\mathbf{R^N}$ is independently H, $C_{1\text{-}3}$ alkyl, or $C_{3\text{-}6}$ cycloalkyl,

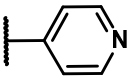
provided that one or more of the following applies:

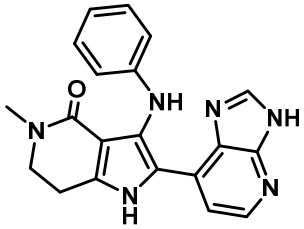
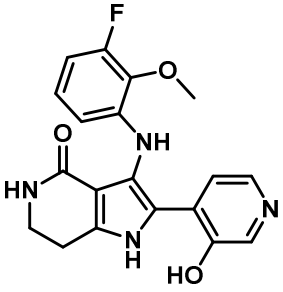
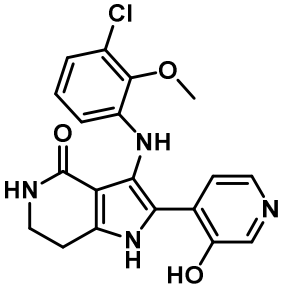
- when $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are H or methyl; $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ are H; **Ring C** is  ; and $\mathbf{X^b}$ is H, methyl, NH_2, NHC(=O)Me, NHC(=O)iPr, NHC(=O)NHEt,  ,  , then **Ring A** is other than unsubstituted phenyl;
- when $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$ are each H; **Ring C** is  ; and $\mathbf{X^a}$ is methyl or F, then **Ring A** is other than unsubstituted phenyl;
- when $\mathbf{R^{1c}}$, $\mathbf{R^{2a}}$, $\mathbf{R^{2b}}$, $\mathbf{R^{3a}}$, and $\mathbf{R^{3b}}$ are each H; **Ring C** is  , then **Ring A** is other than 4-fluorophenyl; and
- the compound is other than:  ,  , or  .

In some examples, it is provided that one or more of the following applies:

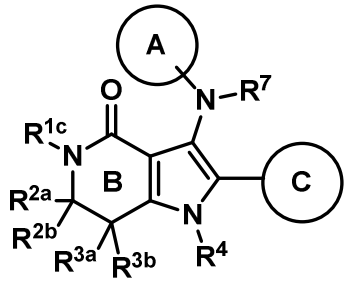
- when $\mathbf{R^{2a}}$ and $\mathbf{R^{2b}}$ are H or methyl; $\mathbf{R^{3a}}$ and $\mathbf{R^{3b}}$ are H; **Ring C** is  ; and $\mathbf{X^b}$ is H, methyl, NH_2, NHC(=O)Me, NHC(=O)iPr, NHC(=O)NHEt,  ,  , then **Ring A** is other than unsubstituted phenyl;

- when **R^{2a}**, **R^{2b}**, **R^{3a}**, and **R^{3b}** are each H; **Ring C** is  ; and **X^{a}** is methyl or F, then **Ring A** is other than unsubstituted phenyl;

- when **R^{1c}**, **R^{2a}**, **R^{2b}**, **R^{3a}**, and **R^{3b}** are each H; **Ring C** is , then **Ring A** is other than 4-fluorophenyl; and

- the compound is other than: , , or .

In one example, the disclosure features A compound of Formula **(I)**:



Formula **(I)**

or a pharmaceutically acceptable salt thereof, wherein:

Ring C is selected from the group consisting of:

Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as provided herein, or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable diluent or carrier.

In one aspect, the present disclosure refers to a compound as provided herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

Provided herein is a method for treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein. In one aspect, the present disclosure refers to use of a compound as provided herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer.

Also provided herein is a method for treating cancer in a subject in need thereof, the method comprising (a) determining that the cancer is associated with a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same; and (b) administering to the subject a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein. In one aspect, the present disclosure refers to use of a compound as provided herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer, wherein the cancer is associated with a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same.

Provided herein is a method of treating an EGFR-associated disease or disorder in a subject, the method comprising administering to a subject identified or diagnosed as having an EGFR-associated disease or disorder a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

This disclosure also provides a method of treating an EGFR-associated disease or disorder in a subject, the method comprising: determining that the cancer in the subject is an EGFR-associated disease or disorder; and administering to the subject a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein. Further provided herein is a method of treating an EGFR-associated cancer in a subject, the method comprising administering to a subject identified or diagnosed as having an EGFR-associated cancer a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or

a pharmaceutical composition as provided herein.

This disclosure also provides a method of treating an EGFR-associated cancer in a subject, the method comprising: determining that the cancer in the subject is an EGFR-associated cancer; and administering to the subject a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein. In one aspect, the present disclosure refers to use of a compound as provided herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an EGFR-associated cancer.

Provided herein is a method of treating a subject, the method comprising administering a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein, to a subject having a clinical record that indicates that the subject has a dysregulation of an *EGFR* gene, an EGFR kinase, or expression or activity or level of any of the same.

In one aspect, the present disclosure refers to use of a compound as provided herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an EGFR-associated cancer that has one or more EGFR inhibitor resistance mutations.

Also provided herein is a method of treating a subject having a cancer, wherein the method comprises:

(a) administering one or more doses of a first EGFR inhibitor to the subject for a period of time;

(b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one EGFR inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first EGFR inhibitor of step (a); and

(c) administering a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has been determined to have a cancer cell that has at least one EGFR inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with the first EGFR inhibitor of step (a); or

(d) administering additional doses of the first EGFR inhibitor of step (a) to the subject if the subject has not been determined to have a cancer cell that has at least one

Further provided herein is a method of treating a subject having a cancer, wherein the method comprises:

(a) determining that a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first EGFR inhibitor does not have one or more EGFR inhibitor resistance mutations that confer increased resistance to a cancer cell or tumor to treatment with the first EGFR inhibitor that was previously administered to the subject; and

(b) administering additional doses of the first EGFR inhibitor to the subject.

This disclosure also provides a method for inhibiting EGFR in a mammalian cell, the method comprising contacting the mammalian cell with an effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure refers to a method for modulating EGFR in a mammalian cell, the method comprising contacting the mammalian cell with an effective amount of a compound as provided herein, or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure refers to use of a compound as provided herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer associated with a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same.

Also provided herein is a method for treating cancer in a subject in need thereof, the method comprising (a) determining that the cancer is associated with a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same; and (b) administering to the subject a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

Further provided herein is a method of treating a HER2-associated cancer in a subject, the method comprising administering to a subject identified or diagnosed as having a HER2-associated cancer a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

This disclosure also provides a method of treating a HER2-associated cancer in a subject, the method comprising: determining that the cancer in the subject is a HER2-associated cancer; and administering to the subject a therapeutically effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

of the same and a dysregulation of a *HER2* gene, a HER2 kinase, or expression or activity or level of any of the same.

This disclosure also provides a method for inhibiting EGFR and HER2 in a mammalian cell, the method comprising contacting the mammalian cell with an effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof.

In addition to the above, provided herein is a method for inhibiting a BUB (budding uninhibited by benzimidazole, BUB1-3) kinase. In some examples, the methods provided herein include methods for inhibiting BUB11. For example, a method for inhibiting BUB1 in a mammalian cell, the method comprising contacting the mammalian cell with an effective amount of a compound of Formula (**I**) (e.g., Formula **(I-a)**, **(I-b)**, **(I-c)**, **(I-d)**, **(I-e)**, **(I-f)**, **(I-g)**, **(I-h)**, **(I-i)**, **(I-j)**, **or (I-k)**), or a pharmaceutically acceptable salt thereof.

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

Additional Definitions

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

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

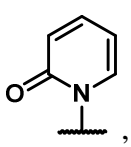
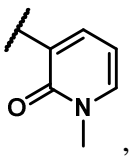
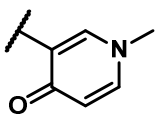
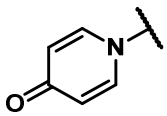
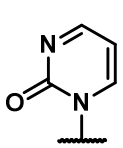
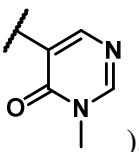
“API” refers to an active pharmaceutical ingredient.

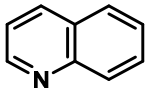
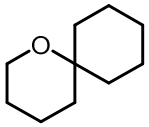
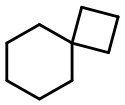
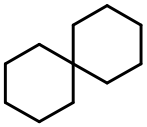
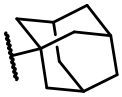
The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of a chemical entity being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation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

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

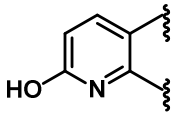
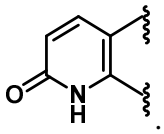
The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In certain instances, pharmaceutically acceptable salts are obtained by reacting a compound described herein, with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. In some instances, pharmaceutically acceptable salts are obtained by reacting a compound having acidic group described herein with a base to form

As partially unsaturated cyclic hydrocarbon groups, cycloalkenyl groups may have any degree of unsaturation provided that one or more double bonds is present in the ring, none of the rings in the ring system are aromatic, and the cycloalkenyl group is not fully saturated overall. Cycloalkenyl may include multiple fused and/or bridged and/or spirocyclic rings.

The term "heteroaryl", as used herein, means a mono-, bi-, tri- or polycyclic group having 5 to 20 ring atoms, alternatively 5, 6, 9, 10, or 14 ring atoms; wherein at least one ring in the system contains one or more heteroatoms independently selected from the group consisting of N, O, and S and at least one ring in the system is aromatic (but does not have to be a ring which contains a heteroatom, e.g. tetrahydroisoquinolinyl, e.g., tetrahydroquinolinyl). Heteroaryl groups can either be unsubstituted or substituted with one or more substituents. Examples of heteroaryl include thienyl, pyridinyl, furyl, oxazolyl, oxadiazolyl, pyrrolyl, imidazolyl, triazolyl, thiodiazolyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thiazolyl benzothienyl, benzoxadiazolyl, benzofuranyl, benzimidazolyl, benzotriazolyl, cinnolinyl, indazolyl, indolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, purinyl, thienopyridinyl, pyrido[2,3-*d*]pyrimidinyl, pyrrolo[2,3-*b*]pyridinyl, quinazolinyl, quinolinyl, thieno[2,3-*c*]pyridinyl, pyrazolo[3,4-*b*]pyridinyl, pyrazolo[3,4-*c*]pyridinyl, pyrazolo[4,3-*c*]pyridine, pyrazolo[4,3-*b*]pyridinyl, tetrazolyl, chromane, 2,3-dihydrobenzo[*b*][1,4]dioxine, benzo[*d*][1,3]dioxole, 2,3-dihydrobenzofuran, tetrahydroquinoline, 2,3-dihydrobenzo[*b*][1,4]oxathiine, isoindoline, and others. In some examples, the heteroaryl is selected from thienyl, pyridinyl, furyl, pyrazolyl, imidazolyl, isoindolinyl, pyranyl, pyrazinyl, and pyrimidinyl. For purposes of clarification, heteroaryl also includes aromatic lactams, aromatic cyclic ureas, or vinylogous analogs thereof, in which each ring nitrogen adjacent to a carbonyl is tertiary (i.e., all three valences are occupied by non-hydrogen substituents), such as one or more of pyridone (e.g., , , , or ), pyrimidone (e.g.,  or ), pyridazinone

and the like described herein) containing a sufficient number of ring atoms to form bicyclic or higher order ring systems (e.g., tricyclic, polycyclic ring systems), it is understood that such rings and cyclic groups encompass those having fused rings, including those in which the points of fusion are located (i) on adjacent ring atoms (e.g., [x.x.0] ring systems, in which 0 represents a zero atom bridge (e.g., )); (ii) a single ring atom (spiro-fused ring systems) (e.g., , , or ), or (iii) a contiguous array of ring atoms (bridged ring systems having all bridge lengths > 0) (e.g., , , or ).

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

In addition, the compounds generically or specifically disclosed herein are intended to include all tautomeric forms. Thus, by way of example, a compound containing the moiety:  encompasses the tautomeric form containing the moiety: . Similarly, a pyridinyl or pyrimidinyl moiety that is described to be optionally substituted with hydroxyl encompasses pyridone or pyrimidone tautomeric forms.

The compounds provided herein may encompass various stereochemical forms. The compounds also encompass diastereomers as well as optical isomers, e.g., mixtures of enantiomers including racemic mixtures, as well as individual enantiomers and

diastereomers, which arise as a consequence of structural asymmetry in certain compounds. Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

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

DETAILED DESCRIPTION

This disclosure provides chemical entities (e.g., a compound or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination of the compound) that inhibit epidermal growth factor receptor (EGFR, ERBB1) and/or Human epidermal growth factor receptor 2 (HER2, ERBB2). These chemical entities are useful, e.g., for treating a condition, disease or disorder in which increased (e.g., excessive) EGFR and/or HER2 activation contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g., cancer) in a subject (e.g., a human). In some embodiments, the chemical entities provided herein can inhibit an EGFR kinase and/or a HER2 kinase that has an exon 20 mutation (e.g., any of the exon 20 mutations described herein). Exon 20 mutations can confer intrinsic resistance to EGFR and/or HER2 inhibitors, and there are currently only limited targeted therapies that have been approved for subjects with these mutations. This disclosure also provides compositions containing the chemical entities provided herein as well as methods of using and making the same.

Formulae (I) Compounds

In one aspect, this disclosure features compounds of Formula **(I)**:

