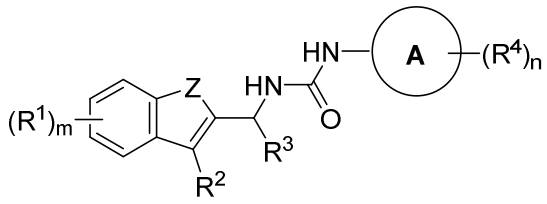
## SUMMARY

Some examples provide a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

Z is O or $NR^x$;

$R^x$ is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

each $R^1$ is independently selected from halogen, hydroxyl, cyano, C1-C6 alkyl optionally substituted with hydroxyl, and C3-C6 cycloalkyl;

m is 0, 1, 2, or 3;

$R^2$ is halogen, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

$R^3$ is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl;

Ring A is a 6-10 membered aryl, a C3-C8 cycloalkyl, a 5-10 membered heteroaryl, or a 4-10 membered heterocyclyl;

each $R^4$ is independently selected from the group consisting of:

(i) halogen,

(ii) C1-C6 alkyl optionally substituted with 1 or 2 hydroxyl or $-NR^AR^B$,

(iii) C1-C6 alkoxy optionally substituted with 1-2 substituents independently selected from hydroxyl and C3-C6 cycloalkyl,

(iv) C1-C6 haloalkyl,

(v) hydroxyl,

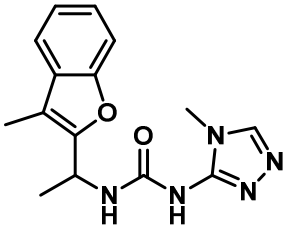
(vi) cyano,

(vii) $-CO_2H$,

(viii) $-NR^AR^B$,

(ix) $=NR^{A2}$,

(x) $-C(=O)NR^CR^D$,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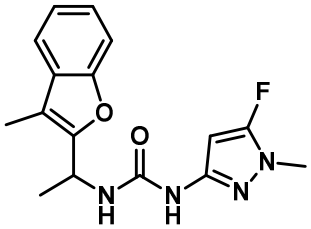
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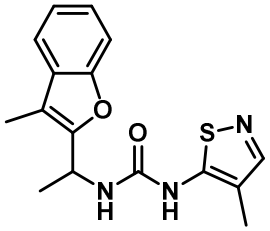
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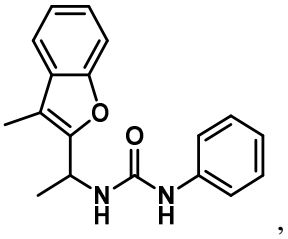
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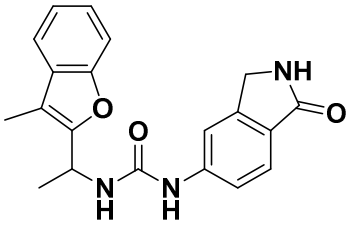
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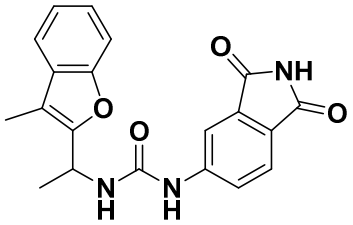
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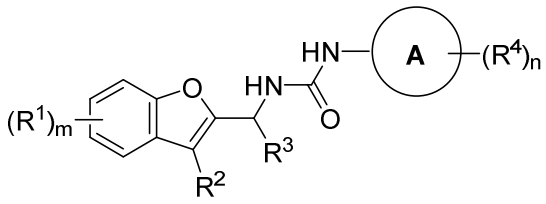
Some examples provide a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

each $R^1$ is independently selected from halogen, hydroxyl, cyano, C1-C6 alkyl optionally substituted with hydroxyl, and C3-C6 cycloalkyl;

m is 0, 1, 2, or 3;

$R^2$ is halogen, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

$R^3$ is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl;

Ring A is a 6-10 membered aryl, a C3-C8 cycloalkyl, a 5-10 membered heteroaryl, or a 4-10 membered heterocyclyl;

each $R^4$ is independently selected from the group consisting of:

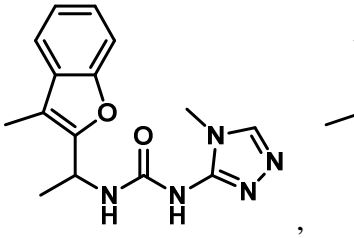
(i) halogen,

(ii) C1-C6 alkyl optionally substituted with 1 or 2 hydroxyl or $-NR^AR^B$,

(iii) C1-C6 alkoxy optionally substituted with 1-2 substituents independently selected from hydroxyl and C3-C6 cycloalkyl,

(iv) C1-C6 haloalkyl,

(v) hydroxyl,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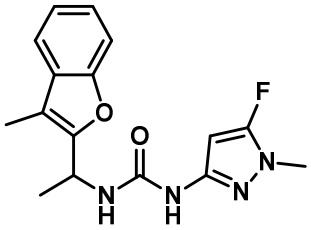
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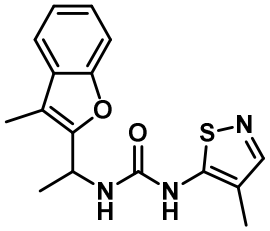
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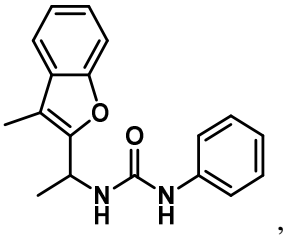
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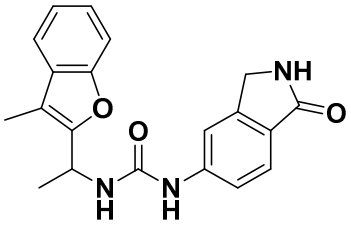
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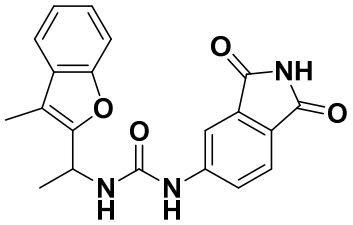
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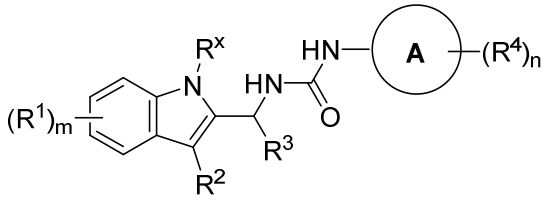
Some examples provide a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

each $R^1$ is independently selected from halogen, hydroxyl, cyano, C1-C6 alkyl optionally substituted with hydroxyl, and C3-C6 cycloalkyl;

m is 0, 1, 2, or 3;

$R^2$ is halogen, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

$R^3$ is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl;

Ring A is a 6-10 membered aryl, a C3-C8 cycloalkyl, a 5-10 membered heteroaryl, or a 4-10 membered heterocyclyl;

each $R^4$ is independently selected from the group consisting of:

(i) halogen,

(ii) C1-C6 alkyl optionally substituted with 1 or 2 hydroxyl or $-NR^AR^B$,

(iii) C1-C6 alkoxy optionally substituted with 1-2 substituents independently selected from hydroxyl and C3-C6 cycloalkyl,

(iv) C1-C6 haloalkyl,

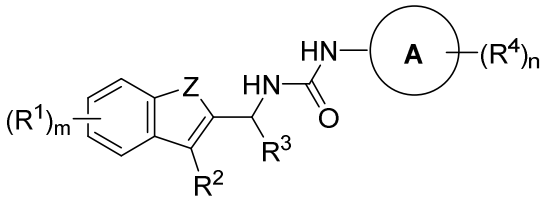
(v) hydroxyl,

hydroxyl, halogen, -C(=O)$NR^{B1}R^{C1}$, -$SO_2$(C1-C6 alkyl), -$CO_2H$, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 alkoxy, and C1-C6 haloalkoxy;

each $R^{A2}$, $R^{B2}$, and $R^{C2}$ is independently hydrogen or C1-C6 alkyl;

each $R^G$ is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 alkoxy, -$NR^{A1}R^{B1}$, =$NR^{A2}$, -C(=O)$NR^{C1}R^{D1}$, -$CO_2$(C1-C6 alkyl), C1-C6 haloalkyl, C3-C6 cycloalkyl, C1-C6 haloalkoxy, -$SO_2$(C1-C6 alkyl), and -$CO_2H$.

Some examples provide compounds of Formula (I), having Formula (X):




(X)

or a pharmaceutically acceptable salt thereof, wherein:

Z is O or $NR^x$;

$R^x$ is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

each $R^1$ is an independently selected halogen;

m is 0, 1, 2, or 3;

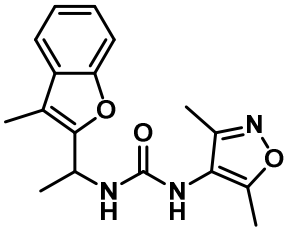
$R^2$ is halogen, C1-C6 alkyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

$R^3$ is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

Ring A is a 6-10 membered aryl, a C3-C8 cycloalkyl, a 5-10 membered heteroaryl, or a 4-10 membered heterocyclyl;

each $R^4$ is independently selected from the group consisting of: halogen, C1-C6 alkyl optionally substituted with 1 or 2 hydroxyl or -$NR^AR^B$, C1-C6 alkoxy, C1-C6 haloalkyl, hydroxyl, cyano, -$CO_2H$, -$NR^AR^B$, -C(=O)$NR^CR^D$, -$SO_2$($NR^ER^F$), -$SO_2$(C1-C6 alkyl), -S(=O)(=NH)(C1-C6 alkyl), -C(=O)(C1-C6 alkyl), -$CO_2$(C1-C6 alkyl), 5-6 membered heteroaryl, and a 3-6 membered heterocyclyl or 3-6 membered cycloalkyl each optionally substituted with 1 or 2 independently selected $R^G$;

n is 0, 1, or 2;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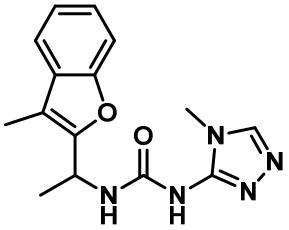
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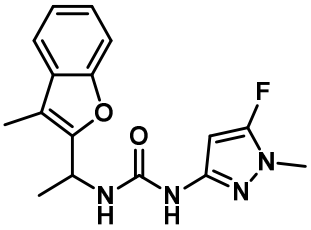
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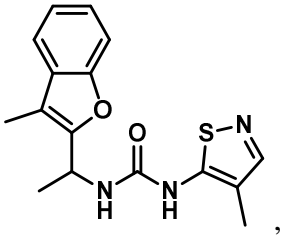
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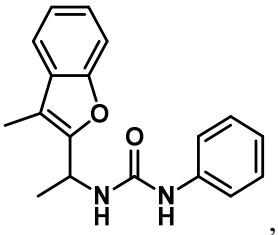
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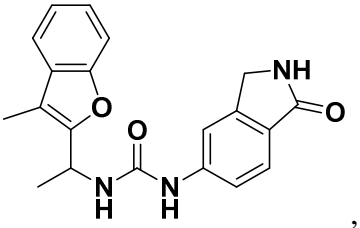
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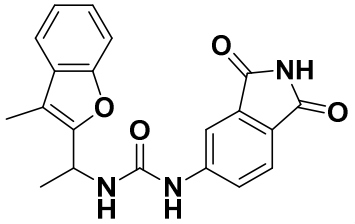
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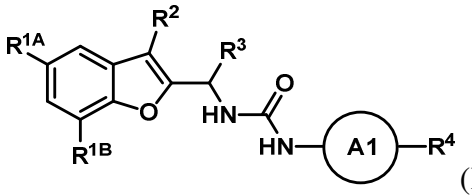
In one aspect, the present disclosure refers to a compound of Formula (I-A):


(I-A)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A1 is pyrimidinyl or pyridyl;

$R^{1A}$ is halogen;

$R^{1B}$ is halogen or absent;

$R^2$ is a C1-C6 alkyl or a C1-C6 haloalkyl;

$R^3$ is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 substituents independently selected from fluoro and C1-C6 alkyl;

$R^4$ is independently selected from the group consisting of: C1-C6 alkyl optionally substituted with $-NR^AR^B$, C1-C6 alkoxy, C1-C6 haloalkyl, hydroxyl, cyano, $-CO_2H$, $-NR^AR^B$, $-C(=O)NR^CR^D$, $-SO_2(NR^ER^F)$, $-SO_2$(C1-C6 alkyl), $-S(=O)(=NH)$(C1-C6 alkyl), $-C(=O)$(C1-C6 alkyl), $-CO_2$(C1-C6 alkyl), 5-6 membered heteroaryl optionally substituted with C1-C6 alkyl, 3-6 membered heterocyclyl optionally substituted with 1 or 2 independently selected $R^G$, and 3-6 membered cycloalkyl optionally substituted with 1 or 2 independently selected $R^G$;

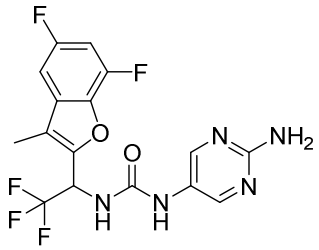
each $R^A$, $R^{A1}$, $R^B$, $R^{B1}$, $R^C$, $R^{C1}$, $R^D$, $R^{D1}$, $R^E$, and $R^F$ is independently hydrogen, 4-6 membered heterocyclyl, C1-C6 haloalkyl, 3-6 membered cycloalkyl optionally substituted with hydroxyl, or C1-C6 alkyl optionally substituted with 1-2 substituents independently selected from hydroxyl, 3-6 membered cycloalkyl, $-SO_2$(C1-C6 alkyl), and $-SO_2(NH_2)$; or

$R^C$ and $R^D$, together with the nitrogen atom to which they are attached form a 4-6 membered heterocyclyl; and

each $R^G$ is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkoxy, $-NR^{A1}R^{B1}$, $-C(=O)NR^{C1}R^{D1}$, $-CO_2$(C1-C6 alkyl), C1-C6 haloalkyl, C3-C6 cycloalkyl, $-CO_2H$, and C1-C6 alkyl optionally substituted with hydroxyl.

In one aspect, the present disclosure refers to a compound selected from the group consisting of the compounds in Table A, Table B, and Table C, Table D, or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure refers to a compound which is 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt thereof, having the structure:



or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

Also provided herein is a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

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), 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 disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition disclosed herein 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 a *PIK3CA* gene, a PI3Kα protein, 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), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

Provided herein is a method of treating a PI3Kα-associated disease or disorder in a subject, the method comprising administering to a subject identified or diagnosed as having a PI3Kα-associated disease or disorder a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

This disclosure also provides a method of treating a PI3Kα-associated disease or disorder in a subject, the method comprising: determining that the cancer in the subject is a PI3Kα-associated disease or disorder; and administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

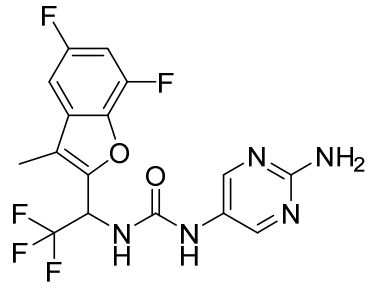
Further provided herein is a method of treating a PI3Kα-associated cancer in a subject, the

method comprising administering to a subject identified or diagnosed as having a PI3Kα-associated cancer a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

This disclosure also provides a method of treating a PI3Kα-associated cancer in a subject, the method comprising: determining that the cancer in the subject is a PI3Kα-associated cancer; and administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

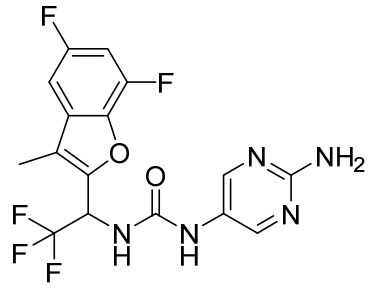
Provided herein is a method of treating a subject, the method comprising administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein, to a subject having a clinical record that indicates that the subject has a dysregulation of a *PIK3CA* gene, a PI3Kα protein, or expression or activity or level of any of the same.

In one aspect, the present disclosure refers to use of a compound in the manufacture of a medicament for treating a solid tumor, wherein the solid tumor has one or more mutations in PI3Kα, and wherein the compound is 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt thereof, having the structure:



or a pharmaceutically acceptable salt thereof.

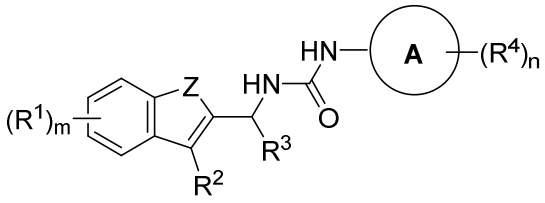
In one aspect, the present disclosure refers to use of a compound in the manufacture of a medicament for treating cancer, wherein the cancer has one or more mutations in PI3Kα, wherein in the cancer is selected from breast cancer, endometrial cancer, bladder cancer, head and neck cancer, and wherein the compound is 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt thereof, having the structure:



or a pharmaceutically acceptable salt thereof.

This disclosure also provides a method for inhibiting PI3Kα in a mammalian cell, the method comprising contacting the mammalian cell with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Some examples of the methods and composition described herein include compounds of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein:

Z is O or $NR^x$;

$R^x$ is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

each $R^1$ is an independently selected halogen;

m is 0, 1, 2, or 3;

$R^2$ is a C1-C6 alkyl or a C1-C6 haloalkyl;

$R^3$ is a C1-C6 alkyl, a C1-C6 haloalkyl, or a C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;

Ring A is a 6-10 membered aryl, a C3-C8 cycloalkyl, a 5-10 membered heteroaryl, or a 4-10 membered heterocyclyl;

acceptable salt thereof, or a pharmaceutical composition as provided herein.

Provided herein is a method of treating a PI3Kα-associated disease or disorder in a subject, the method comprising administering to a subject identified or diagnosed as having a PI3Kα-associated disease or disorder a therapeutically effective amount of a compound of Formula (II), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

This disclosure also provides a method of treating a PI3Kα-associated disease or disorder in a subject, the method comprising: determining that the cancer in the subject is a PI3Kα-associated disease or disorder; and administering to the subject a therapeutically effective amount of a compound of Formula (II), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

Further provided herein is a method of treating a PI3Kα-associated cancer in a subject, the method comprising administering to a subject identified or diagnosed as having a PI3Kα-associated cancer a therapeutically effective amount of a compound of Formula (II), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

This disclosure also provides a method of treating a PI3Kα-associated cancer in a subject, the method comprising: determining that the cancer in the subject is a PI3Kα-associated cancer; and administering to the subject a therapeutically effective amount of a compound of Formula (II), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as provided herein.

Provided herein is a method of treating a subject, the method comprising administering a therapeutically effective amount of a compound of Formula (II), 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 a *PIK3CA* gene, a PI3Kα protein, or expression or activity or level of any of the same.

This disclosure also provides a method for inhibiting PI3Kα in a mammalian cell, the method comprising contacting the mammalian cell with an effective amount of a compound of Formula (II), 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 “about” when referring to a number or a numerical range means that the number or numerical range referred to is an approximation, for example, within experimental variability and/or statistical experimental error, and thus the number or numerical range may vary up to ±10% of the stated number or numerical range.

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.

The term "inhibit" or "inhibition of" means to reduce by a measurable amount, or to prevent entirely (e.g., 100% inhibition).

“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 “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

The term “pharmaceutical composition” refers to a mixture of a compound described herein with other chemical components (referred to collectively herein as “pharmaceutically acceptable excipients”), such as carriers, stabilizers, diluents, dispersing agents, suspending agents, and/or thickening agents. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to: rectal, oral, intravenous, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

As used herein, the terms "subject," "individual," or "patient," are used interchangeably, refers to any animal, including mammals such as primates (e.g., humans), mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, and humans. In some examples, the subject is a human. In some examples, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented.

As used herein, terms "treat" or "treatment" refer to therapeutic or palliative measures. Beneficial or desired clinical results include, but are not limited to, alleviation, in whole or in part, of symptoms associated with a disease or disorder or condition, diminishment of the extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state (e.g., one or more symptoms of the disease), and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

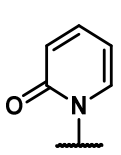
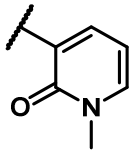
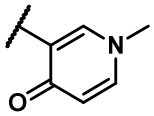
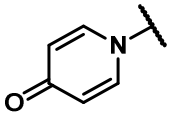
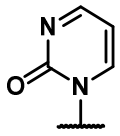
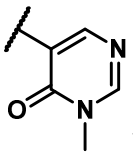
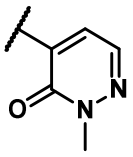
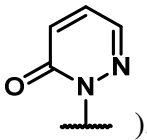
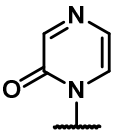
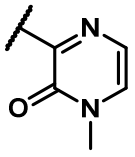
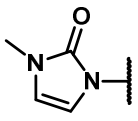
The term "halo" refers to fluoro (F), chloro (Cl), bromo (Br), or iodo (I).

The term “oxo” refers to a divalent doubly bonded oxygen atom (i.e., “=O”). As used herein, oxo groups are attached to carbon atoms to form carbonyls.

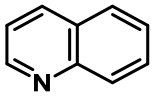
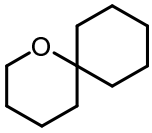
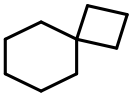
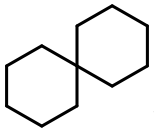
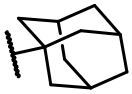
The term "hydroxyl" refers to an -OH radical.

The term "cyano" refers to a -CN radical.

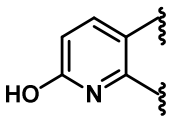
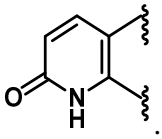
The term "alkyl" refers to a saturated acyclic hydrocarbon radical that may be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, $C_{1\text{-}10}$ indicates that the group may have from 1 to 10 (inclusive) carbon atoms in it. Alkyl groups can either be unsubstituted or substituted with one or more substituents. Non-limiting examples include methyl, ethyl, *iso*-propyl, *tert*-butyl, *n*-hexyl. The term “saturated” as used in this context means only single bonds present between constituent carbon atoms and other available valences occupied by hydrogen and/or other substituents as defined herein.

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 (e.g.,  or ), pyrazinone (e.g.,  or ), and imidazolone (e.g., ), wherein each ring nitrogen adjacent to a carbonyl is tertiary (i.e., the oxo group (i.e., "=O") herein is a constituent part of the heteroaryl ring).

The term "heterocyclyl" refers to a mono-, bi-, tri-, or polycyclic saturated or partially unsaturated ring system with 3-16 ring atoms (e.g., 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system) having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic or polycyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein one or more ring atoms may be substituted by 1-3 oxo (forming, e.g., a lactam) and one or more N or S atoms may be substituted by 1-2 oxido (forming, e.g., an N-oxide, an S-oxide, or an S,S-dioxide), valence permitting; and wherein 0, 1, 2 or 3 atoms

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

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

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

The compounds provided herein may encompass various stereochemical forms. The compounds also encompass enantiomers (e.g., R and S isomers), diastereomers, as well as mixtures of enantiomers (e.g., R and S isomers) including racemic mixtures and mixtures of diastereomers, 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 (e.g., a "flat"

structure) and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound. Likewise, unless otherwise indicated, when a disclosed compound is named or depicted by a structure that specifies the stereochemistry (e.g., a structure with "wedge" and/or "dashed" bonds) and has one or more chiral centers, it is understood to represent the indicated stereoisomer of the compound.

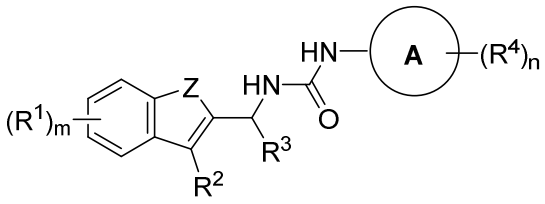
The details of one or more examples of this disclosure are set forth in the accompanying drawings and the description below. Other features and advantages of the present disclosure will be apparent from the description and drawings, and from the claims.

## DETAILED DESCRIPTION

This disclosure provides compounds of Formula (I), Formula (II), and pharmaceutically acceptable salts thereof, that inhibit phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K) isoform alpha (PI3Kα). These chemical entities are useful, e.g., for treating a condition, disease or disorder in which increased (e.g., excessive) PI3Kα 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.

### Formulae (I) Compounds

Some embodiments provide a compound of Formula (I):




(I)

or a pharmaceutically acceptable salt thereof, wherein:

Z is O or $NR^x$;

$R^x$ is hydrogen, C1-C6 alkyl, or C3-C6 cycloalkyl;

each $R^1$ is independently selected from halogen, hydroxyl, cyano, C1-C6 alkyl optionally substituted with hydroxyl, and C3-C6 cycloalkyl;

m is 0, 1, 2, or 3;

$R^2$ is halogen, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 haloalkyl, C3-C6 cycloalkyl optionally substituted with 1 or 2 fluoro;