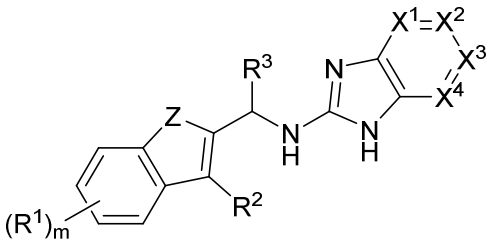
p110α, p110β and p110δ catalytic subunits produced from different genes (*PIK3CA, PIK3CB and PIK3CD*, respectively), while p110γ produced by *PIK3CG* represents the only catalytic subunit in class IB PI3K. *PIK3CA*, the gene encoding the p110α subunit, is frequently mutated or amplified in many human cancers, such as breast cancer, colon cancer, gastric cancer, cervical cancer, prostate cancer, and lung cancer. (*See,* Samuels Y, et al. High frequency of mutations of the *PIK3CA* gene in human cancers. Science. 2004;304:554.)

However, the development of PI3K inhibitors has been problematic for several reasons including (i) adaptive molecular mechanisms upon therapeutic inhibition of PI3K, (ii) inability to specifically inhibit signaling by PIK3CA mutations while sparing endogenous p110α, (iii) the limited use of these therapies in rational combinations, including those informed with strong mechanistic support, and (iv) dose-limiting toxicities that prevent sustained PI3K pathway suppression. (*See*, Hanker et al., *Challenges for the Clinical Development of PI3K Inhibitors: strategies to Improve Their Impact in solid Tumors,* Cancer Discovery, April 2019;9: 482-491.) Additionally, there are other factors and compensatory pathways derived from both clinical and in vitro lab studies, which affect PI3K signaling, such as HRAS and KRAS mutations, which reduce susceptibility to PI3K inhibitors (and knockdown of these has shown to improve sensitivity to PI3K inhibitors). (*See,* Misrha, R.; PI3K *Inhibitors in Cancer: Clinical Implications and Adverse Effects.* Int. J. Mol. Sci. 2021, 22, 3464.)

Domain deletions in *PIK3CA* can activate PI3K signaling significantly and also enhance the sensitivity to PI3K inhibitors. (*See,* Croessmann, S. et al., Clin. Cancer Res. 2018, 24, 1426–1435). Thus, targeting PI3Kα represents an approach for the treatment of proliferative disorders such as cancer.

SUMMARY

Some examples provide compounds 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 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;

X^1, X^2, X^3, and X^4 are each independently N, CH, or CR^4, wherein no more than two of X^1, X^2, X^3, and X^4 can be N;

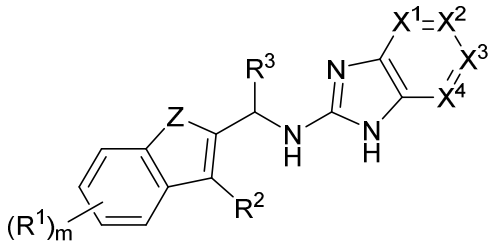
each R^4 is independently selected from the group consisting of: halogen, C1-C6 alkyl optionally substituted with $-NR^AR^B$, C1-C6 alkoxy, C1-C6 haloalkyl, hydroxyl, cyano, $-CO_2H$, $-NR^AR^B$, $-C(=O)NR^CR^D$, $-SO_2(NR^ER^F)$, $-SO_2$(C1-C6 alkyl), -S(=O)(=NH)(C1-C6 alkyl), -C(=O)(C1-C6 alkyl), $-CO_2$(C1-C6 alkyl), phenyl, 5-6 membered heteroaryl, and a 3-6 membered heterocyclyl or a 3-6 cycloalkyl each 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, C1-C6 alkyl optionally substituted with R^G, C1-C6 haloalkyl, -C(=O)(C1-C6 alkyl), or $-SO_2$(C1-C6 alkyl); 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, hydroxyl, cyano, C1-C6 alkyl, C1-C6 alkoxy, $-NR^{A1}R^{B1}$, $-C(=O)NR^{C1}R^{D1}$, and $-CO_2H$.

In one aspect, the present disclosure refers to 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 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;

X^1, X^2, X^3, and X^4 are each independently N, CH, or CR^4, wherein no more than two of X^1, X^2, X^3, and X^4 can be N;

each R^4 is independently selected from the group consisting of: halogen, 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), phenyl, 5-6 membered heteroaryl, and a 3-6 membered heterocyclyl or a 3-6 cycloalkyl each 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, C1-C6 alkyl optionally substituted with R^G, C1-C6 haloalkyl, -C(=O)(C1-C6 alkyl), or $-SO_2$(C1-C6 alkyl); 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, hydroxyl, cyano, C1-C6 alkyl, C1-C6 alkoxy, $-NR^{A1}R^{B1}$, $-C(=O)NR^{C1}R^{D1}$, and $-CO_2H$.

Also provided herein is a pharmaceutical composition comprising a compound of Formula (I), 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 of disclosed herein, or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable diluent or carrier.

In one aspect, the present disclosure refers to use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cancer has one or more mutations in PI3Kα.

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.

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.

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.

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).

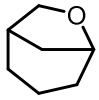
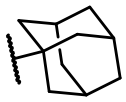
"API" refers to an active pharmaceutical ingredient.

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.

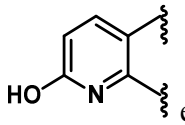
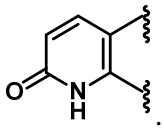
The term "excipient" or "pharmaceutically acceptable excipient" means a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, carrier, solvent, or encapsulating material. In one example, each component is "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a

The term "cycloalkyl" as used herein refers to cyclic saturated hydrocarbon groups having, e.g., 3 to 20 ring carbons, preferably 3 to 16 ring carbons, and more preferably 3 to 12 ring carbons or 3-10 ring carbons or 3-6 ring carbons, wherein the cycloalkyl group may be optionally substituted. Examples of cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Cycloalkyl may include multiple fused and/or bridged rings. Non-limiting examples of fused/bridged cycloalkyl includes: bicyclo[1.1.0]butane, bicyclo[2.1.0]pentane, bicyclo[1.1.1]pentane, bicyclo[3.1.0]hexane, bicyclo[2.1.1]hexane, bicyclo[3.2.0]heptane, bicyclo[4.1.0]heptane, bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane, bicyclo[4.2.0]octane, bicyclo[3.2.1]octane, bicyclo[2.2.2]octane, and the like. Cycloalkyl also includes spirocyclic rings (e.g., spirocyclic bicycle wherein two rings are connected through just one atom). Non-limiting examples of spirocyclic cycloalkyls include spiro[2.2]pentane, spiro[2.5]octane, spiro[3.5]nonane, spiro[3.5]nonane, spiro[3.5]nonane, spiro[4.4]nonane, spiro[2.6]nonane, spiro[4.5]decane, spiro[3.6]decane, spiro[5.5]undecane, and the like. The term “saturated” as used in this context means only single bonds present between constituent carbon atoms.

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

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.

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), and pharmaceutically acceptable salts thereof, that inhibit phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K) isoform alpha (PI3Kα).