

–SO₂–C₁₋₆ alkyl;

m is 0 or 1; and

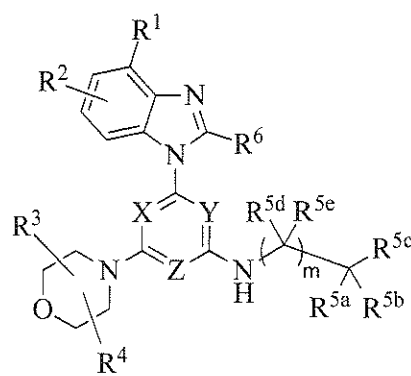
n is 0, 1, 2, 3, or 4;

wherein each alkyl, alkylene, heteroalkylene, alkenyl, alkenylene,

heteroalkenylene, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl in R¹, R², R³, R⁴, R⁶, R^X, R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, and R^{5g} is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q, wherein each substituent Q is independently selected from (a) oxo, cyano, halo, and nitro; (b) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; and (c) –C(O)R^a, –C(O)OR^a, –C(O)NR^bR^c, –C(NR^a)NR^bR^c, –OR^a, –OC(O)R^a, –OC(O)OR^a, –OC(O)NR^bR^c, –OC(=NR^a)NR^bR^c, –OS(O)R^a, –OS(O)₂R^a, –OS(O)NR^bR^c, –OS(O)₂NR^bR^c, –NR^bR^c, –NR^aC(O)R^d, –NR^aC(O)OR^d, –NR^aC(O)NR^bR^c, –NR^aC(=NR^d)NR^bR^c, –NR^aS(O)R^d, –NR^aS(O)₂R^d, –NR^aS(O)NR^bR^c, –NR^aS(O)₂NR^bR^c, –SR^a, –S(O)R^a, –S(O)₂R^a, –S(O)NR^bR^c, and –S(O)₂NR^bR^c, wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen; (ii) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl, each of which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; or (iii) R^b and R^c together with the N atom to which they are attached form heterocyclyl, which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a;

wherein each Q^a is independently selected from the group consisting of (a) oxo, cyano, halo, and nitro; (b) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, and heterocyclyl; and (c) –C(O)R^e, –C(O)OR^e, –C(O)NR^fR^g, –C(NR^e)NR^fR^g, –OR^e, –OC(O)R^e, –OC(O)OR^e, –OC(O)NR^fR^g, –OC(=NR^e)NR^fR^g, –OS(O)R^e, –OS(O)₂R^e, –OS(O)NR^fR^g, –OS(O)₂NR^fR^g, –NR^fR^g, –NR^eC(O)R^h, –NR^eC(O)OR^h, –NR^eC(O)NR^fR^g, –NR^eC(=NR^h)NR^fR^g, –NR^eS(O)R^h, –NR^eS(O)₂R^h, –NR^eS(O)NR^fR^g, –NR^eS(O)₂NR^fR^g, –SR^e, –S(O)R^e, –S(O)₂R^e, –S(O)NR^fR^g, and –S(O)₂NR^fR^g; wherein each R^e, R^f, R^g, and R^h is independently (i) hydrogen; (ii) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl; or (iii) R^f and R^g together with the N atom to which they are attached form heterocyclyl.

[0005a] In a first aspect, there is provided a compound of Formula I:



(I)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; wherein:

X, Y, and Z are each independently N or CR^X, with the proviso that at least two of X, Y, and Z are nitrogen atoms; where R^X is hydrogen or C₁₋₆ alkyl;

R¹ and R² are each independently (a) hydrogen, cyano, halo, or nitro; (b) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl; or (c) -C(O)R^{1a}, -C(O)OR^{1a}, -C(O)NR^{1b}R^{1c}, -C(NR^{1a})NR^{1b}R^{1c}, -OR^{1a}, -OC(O)R^{1a}, -OC(O)OR^{1a}, -OC(O)NR^{1b}R^{1c}, -OC(=NR^{1a})NR^{1b}R^{1c}, -OS(O)R^{1a}, -OS(O)₂R^{1a}, -OS(O)NR^{1b}R^{1c}, -OS(O)₂NR^{1b}R^{1c}, -NR^{1b}R^{1c}, -NR^{1a}C(O)R^{1d}, -NR^{1a}C(O)OR^{1d}, -NR^{1a}C(O)NR^{1b}R^{1c}, -NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}, -NR^{1a}S(O)R^{1d}, -NR^{1a}S(O)₂R^{1d}, -NR^{1a}S(O)NR^{1b}R^{1c}, -NR^{1a}S(O)₂NR^{1b}R^{1c}, -SR^{1a}, -S(O)R^{1a}, -S(O)₂R^{1a}, -S(O)NR^{1b}R^{1c}, or -S(O)₂NR^{1b}R^{1c}; wherein each R^{1a}, R^{1b}, R^{1c}, and R^{1d} is independently (i) hydrogen; (ii) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl; or (iii) R^{1b} and R^{1c} together with the N atom to which they are attached form heterocyclyl;

R³ and R⁴ are each independently hydrogen or C₁₋₆ alkyl; or R³ and R⁴ are linked together to form a bond, C₁₋₆ alkylene, C₁₋₆ heteroalkylene, C₂₋₆ alkenylene, or C₂₋₆ heteroalkenylene;

R^{5a} is (a) hydrogen or halo; (b) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl; or (c) -C(O)R^{1a}, -C(O)OR^{1a}, -C(O)NR^{1b}R^{1c}, -C(NR^{1a})NR^{1b}R^{1c}, -OR^{1a}, -OC(O)R^{1a}, -OC(O)OR^{1a}, -OC(O)NR^{1b}R^{1c}, -OC(=NR^{1a})NR^{1b}R^{1c}, -OS(O)R^{1a}, -OS(O)₂R^{1a}, -OS(O)NR^{1b}R^{1c},

wherein each alkyl, alkylene, heteroalkylene, alkenyl, alkenylene, heteroalkenylene, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl in R¹, R², R³, R⁴, R⁶, R^x, R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, and R^{5g} is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q, wherein each substituent Q is independently selected from (a) oxo, cyano, halo, and nitro; (b) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; and (c) -C(O)R^a, -C(O)OR^a, -C(O)NR^bR^c, -C(NR^a)NR^bR^c, -OR^a, -OC(O)R^a, -OC(O)OR^a, -OC(O)NR^bR^c, -OC(=NR^a)NR^bR^c, -OS(O)R^a, -OS(O)₂R^a, -OS(O)NR^bR^c, -OS(O)₂NR^bR^c, -NR^bR^c, -NR^aC(O)R^d, -NR^aC(O)OR^d, -NR^aC(O)NR^bR^c, -NR^aC(=NR^d)NR^bR^c, -NR^aS(O)R^d, -NR^aS(O)₂R^d, -NR^aS(O)NR^bR^c, -NR^aS(O)₂NR^bR^c, -SR^a, -S(O)R^a, -S(O)₂R^a, -S(O)NR^bR^c, and -S(O)₂NR^bR^c, wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen; (ii) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl, each of which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; or (iii) R^b and R^c together with the N atom to which they are attached form heterocyclyl, which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a;

wherein each Q^a is independently selected from the group consisting of (a) oxo, cyano, halo, and nitro; (b) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, and heterocyclyl; and (c) -C(O)R^e, -C(O)OR^e, -C(O)NR^fR^g, -C(NR^e)NR^fR^g, -OR^e, -OC(O)R^e, -OC(O)OR^e, -OC(O)NR^fR^g, -OC(=NR^e)NR^fR^g, -OS(O)R^e, -OS(O)₂R^e, -OS(O)NR^fR^g, -OS(O)₂NR^fR^g, -NR^fR^g, -NR^eC(O)R^h, -NR^eC(O)OR^h, -NR^eC(O)NR^fR^g, -NR^eC(=NR^h)NR^fR^g, -NR^eS(O)R^h, -NR^eS(O)₂R^h, -NR^eS(O)NR^fR^g, -NR^eS(O)₂NR^fR^g, -SR^e, -S(O)R^e, -S(O)₂R^e, -S(O)NR^fR^g, and -S(O)₂NR^fR^g; wherein each R^e, R^f, R^g, and R^h is independently (i) hydrogen; (ii) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl; or (iii) R^f and R^g together with the N atom to which they are attached form heterocyclyl.

[0006] In one embodiment, m is 0; and R^{5a} and R^{5b} are each independently (a) halo;

(b) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl; or (c) -C(O)R^{1a}, -C(O)OR^{1a}, -C(O)NR^{1b}R^{1c}, -C(NR^{1a})NR^{1b}R^{1c}, -OR^{1a}, -OC(O)R^{1a}, -OC(O)OR^{1a}, -OC(O)NR^{1b}R^{1c}, -OC(=NR^{1a})NR^{1b}R^{1c}, -OS(O)R^{1a}, -OS(O)₂R^{1a}, -OS(O)NR^{1b}R^{1c}, -OS(O)₂NR^{1b}R^{1c}, -NR^{1b}R^{1c}, -NR^{1a}C(O)R^{1d}, -NR^{1a}C(O)OR^{1d}, -NR^{1a}C(O)NR^{1b}R^{1c}, -NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}, -NR^{1a}S(O)R^{1d}, -NR^{1a}S(O)₂R^{1d}, -NR^{1a}S(O)NR^{1b}R^{1c}, -NR^{1a}S(O)₂NR^{1b}R^{1c}, -SR^{1a}, -S(O)R^{1a}, -S(O)₂R^{1a}, -S(O)NR^{1b}R^{1c}, or -S(O)₂NR^{1b}R^{1c}.

[0007] Also provided herein are pharmaceutical compositions comprising a compound disclosed herein, *e.g.*, a compound of Formula I, or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and one or more pharmaceutically acceptable excipients.

[0007a] In a second aspect, there is provided a pharmaceutical composition comprising the compound as defined above, or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate thereof; and one or more pharmaceutically acceptable excipients.

[0008] Furthermore, provided herein is a method for treating, preventing, or ameliorating one or more symptoms of a PI3K-mediated disorder, disease, or condition in a subject, comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, *e.g.*, a compound of Formula I, or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0009] Provided herein is a method for treating, preventing, or ameliorating one or more symptoms of a PI3Kδ-mediated disorder, disease, or condition in a subject, comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, *e.g.*, a compound of Formula I, or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0010] Provided herein is a method for treating, preventing, or ameliorating one or more symptoms of a proliferative disease in a subject, comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, *e.g.*, a compound of Formula I, or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0010a] In a third aspect, there is provided the use of a compound as defined above or the pharmaceutical composition as defined above in the manufacture of a medicament for the treatment, prevention, or amelioration of one or more symptoms of a PI3K-mediated disorder, disease, or condition in a subject.

[0011] Provided herein is a method for modulating PI3K activity, comprising contacting a PI3K with an effective amount of a compound disclosed herein, *e.g.*, a compound of Formula I, or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0012] Provided herein is a method for modulating PI3K δ activity, comprising contacting PI3K δ with an effective amount of a compound disclosed herein, *e.g.*, a compound of Formula I, or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0013] Provided herein is a method for selectively modulating PI3K δ activity, comprising contacting PI3K δ with an effective amount of a compound disclosed herein, *e.g.*, a compound of Formula I, or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0013a] In a fourth aspect, there is provided an *in vitro* method for modulating PI3K enzymatic activity, comprising contacting a PI3K enzyme with the compound as defined above or the pharmaceutical composition as defined above.

DETAILED DESCRIPTION

[0014] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below.

[0015] 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.

[0016] The term “subject” refers to an animal, including, but not limited to, a primate (*e.g.*, human), cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms “subject” and “patient” are used interchangeably herein in reference, for example, to a mammalian subject, such as a human subject, in one embodiment, a human.

[0017] The terms “treat,” “treating,” and “treatment” are meant to include alleviating or abrogating a disorder, disease, or condition, or one or more of the symptoms associated