~~NOVEL KINASE MODULATORS~~ CHROMEN-4-ONE DERIVATIVES AS KINASE MODULATORS

[01] This application claims the benefit of Indian Provisional Patent Application Nos. 2690/CHE/2009 dated 5th November 2009, and 1429/CHE/2010 dated 24th May 2010, and U.S. Provisional Patent Application No. 61/364,661 dated 15th July, 2010, each of which is hereby incorporated by reference.

FIELD OF THE INVENTION

[02] The present invention provides PI3K protein kinase modulators, methods of preparing them, pharmaceutical compositions containing them and methods of treatment, prevention and/or amelioration of kinase mediated diseases or disorders with them.

BACKGROUND OF THE INVENTION

[03] In the recent past immense research has been dedicated to the discovery and understanding of the structure and functions of enzymes and bio-molecules associated with various diseases. One such important class of enzymes that has been the subject of extensive research is Protein Kinase.

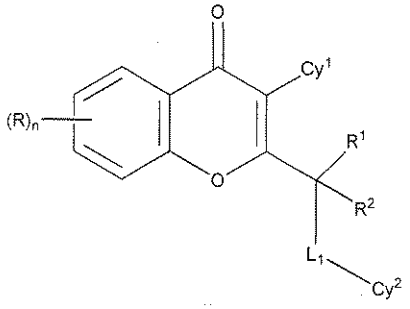
[04] In general, protein kinases represent a set of structurally related phosphoryl transferases having conserved structures and catalytic functions. These enzymes modify proteins by chemically adding phosphate groups (phosphorylation). Phosphorylation involves the removal of a phosphate group from ATP and covalently attaching it to amino acids that have a free hydroxyl group such as serine, threonine or tyrosine. Phosphorylation usually results in a functional change of the target protein (substrate) by altering enzyme activity, cellular localization or association with other proteins. Up to 30% of all proteins may be modified by kinase activity.

[05] This class of proteins are classified into subsets depending upon the substrate they act upon such as tyrosine kinase, serine/theronine kinase, histidine kinase and the like. These proteins can also be classified based on their localization into receptor tyrosine kinases (RTKs) or non-receptor tyrosine kinases.

[06] Receptor tyrosine kinases (RTKs) have an extracellular portion, a transmembrane domain, and an intracellular portion, while non-receptor tyrosine kinases are entirely intracellular. Receptor tyrosine kinase mediated signal transduction is typically

We claim:

1. A compound of formula



(I)

or a tautomer thereof, N-oxide thereof, pharmaceutically acceptable ester thereof, ~~prodrug thereof,~~ or pharmaceutically acceptable salt thereof, wherein

each occurrence of R is independently selected from hydrogen, halogen, $-OR^a$, CN, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, and substituted or unsubstituted heterocyclic group;

R^1 and R^2 may be the same or different and are independently selected from hydrogen, halogen, and substituted or unsubstituted C_{1-6} alkyl, or both R^1 and R^2 directly bound to a common atom, may be joined to form an oxo group (=O) or a substituted or unsubstituted saturated or unsaturated 3-10 member ring (including the carbon atom to which R^1 and R^2 are bound), which may optionally include one or more heteroatoms which may be the same or different and are selected from O, NR^a and S;

Cy^1 is a monocyclic group selected from substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

Cy^2 is selected from a substituted or unsubstituted heterocyclic group, ~~substituted or unsubstituted aryl~~ and substituted or unsubstituted heteroaryl;

L_1 is absent or -NH- ~~selected from $(CR^aR^b)_q$, O, $S(=O)_q$, NR^a or C(=Y)~~;

each occurrence of R^a and R^b may be the same or different and are independently selected from hydrogen, halogen, hydroxy, cyano, substituted or unsubstituted (C_{1-6})alkyl, $-NR^cR^d$ (wherein R^c and R^d are independently hydrogen, halogen, hydroxy, cyano, substituted or unsubstituted (C_{1-6})alkyl, and (C_{1-6})alkoxy) and $-OR^c$ (wherein R^c is substituted or unsubstituted (C_{1-6})alkyl) or when R^a and R^b are directly bound to a common atom, they may be joined to form an oxo group (=O) or form a substituted or unsubstituted saturated or unsaturated 3-10 member ring (including the common atom to which R^a and R^b are directly bound), which may optionally include one or more heteroatoms which may be the same or different and are selected from O, NR^d (wherein R^d is hydrogen or substituted or unsubstituted (C_{1-6})alkyl) or S;

Y is selected from O, S, and NR^a;

n is an integer from 1 to 4; and

q is 0, 1 or 2,

wherein the compound is not:

4',5,7-trihydroxy-2-piperidinomethylisoflavone,

4',5,7-trihydroxy-2-[(2-thiazolin-2-ylamino)methyl]isoflavone,

4',5,7-trihydroxy-2-[2-thiazolin-2-ylthio]methyl]isoflavone,

ethyl 3.3-(ethylenedioxy)-4-(7-methoxy-5-methyl-3-(3-methylisoxazol-5-yl)-4-oxo-4H-1-benzopyran-2·yl]butanoate,

2-benzoyl-3-[1,3]dioxan-2-yl-chromen-4-one,

3-[1,3]dioxan-2-yl-2-(2-[1,3]dioxan-2-yl-3-oxo-2,3-dihydro-benzofuran-2-ylmethyl)-chromen-4-one,

{2-[7-Methoxy-5-methyl-3-(3-methyl-isoxazol-5-yl)-4-oxo-4H-chromen-2-ylmethyl]-[1,3]dioxolan-2-yl}-acetic acid ethyl ester,

7-Methoxy-5-methyl-2-(2-methyl-[1,3]dioxolan-2-ylmethyl)-3-(3-methyl-isoxazol-5-yl)-chromen-4-one,

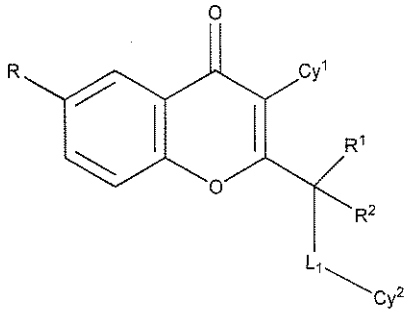
2-(((4,5-dihydrothiazol-2-yl)thio)methyl)-5,7-dihydroxy-3-(4-hydroxyphenyl)-4H-chromen-4-one,

2-(((4,5-dihydrothiazol-2-yl)amino)methyl)-5,7-dihydroxy-3-(4-hydroxyphenyl)-4H-chromen-4-one,

6-methyl-3-phenyl-4-oxo-N-(5-tetrazolyl)-4H-1-benzopyran-2-carboxamide, and

7-methoxy-3-phenyl-4-oxo-N-(5-tetrazolyl)-4H-1-benzopyran-2-carboxamide.

2. A compound of claim 1, wherein the compound has the formula:



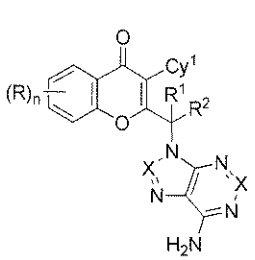
(I-A)

or a tautomer thereof, N-oxide thereof, pharmaceutically acceptable ester thereof, ~~prodrug thereof,~~ or pharmaceutically acceptable salt thereof, wherein

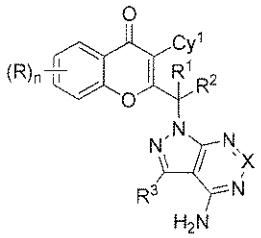
R, Cy^1, Cy^2, R^1, R^2, and L_1 are as defined in claim 1~~; and~~

~~Cy^2 is selected from substituted or unsubstituted heterocyclic group and substituted or unsubstituted heteroaryl~~.

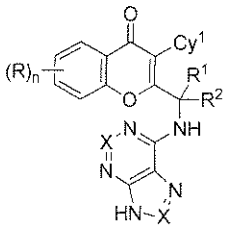
3. A compound of claim 1, wherein the compound has the formula **(IA-I)**, **(IA-II)**, or **(IA-III)**~~, or (IA-IV)~~:



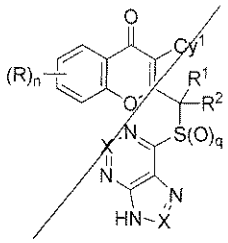
(IA-I)



(IA-II)



(IA-III)



~~**(IA-IV)**~~

or a tautomer thereof, N-oxide thereof, pharmaceutically acceptable ester thereof, ~~prodrug thereof,~~ or pharmaceutically acceptable salt thereof, wherein

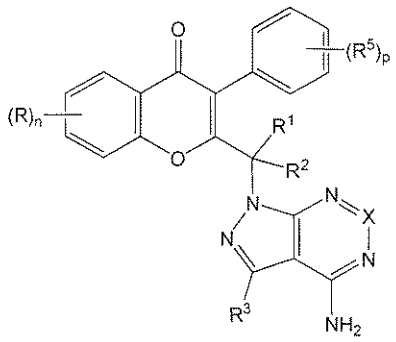
R, Cy^1, R^1, R^2, q and L_1 are as defined in claim 1;

each occurrence of X is independently selected from CR^3 or N; and

each occurrence of R^3 is independently selected from hydrogen, hydroxy, halogen, carboxyl, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenylalkyl substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted heterocyclylalkyl ring, substituted or unsubstituted guanidine, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^yR^z$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-(=N-N(R^x)R^y)$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y-$, $-NR^xC(S)R^y$ $-NR^xC(S)NR^yR^z$, $-SONR^xR^y-$, $-SO_2NR^xR^y-$, $-OR^x$, $-OR^xC(O)NR^yR^z$, $-OR^xC(O)OR^y-$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-R^xNR^yC(O)R^z$, $-R^xOR^y$, $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xC(O)R^x$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, and $-ONO_2$, wherein R^x, R^y and R^z in each of the above groups can be hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heteroaryl, substituted

or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl ring, or substituted or unsubstituted amino, or any two of R^x, R^y and R^z may be joined to form a substituted or unsubstituted saturated or unsaturated 3-10 membered ring, which may optionally include heteroatoms which may be the same or different and are selected from O, NR^x (e.g., R^x can be hydrogen or substituted or unsubstituted alkyl) or S.

4. A compound of claim 1, wherein the compound has the formula (IA-V)



(IA-V)

or a pharmaceutically acceptable salt thereof,

wherein

each occurrence of R is independently selected from hydrogen, halogen, $-OR^a$, CN, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, and substituted or unsubstituted heterocyclic group;

R^1 and R^2 may be the same or different and are independently selected from hydrogen, halogen, and substituted or unsubstituted C_{1-6} alkyl, or both R^1 and R^2 directly bound to a common atom, may be joined to form an oxo group (=O) or a substituted or unsubstituted saturated or unsaturated 3-10 member ring (including the carbon atom to which R^1 and R^2 are bound), which may optionally include one or more heteroatoms which may be the same or different and are selected from O, NR^a and S;

each occurrence of X is independently selected from CR^3 or N; and

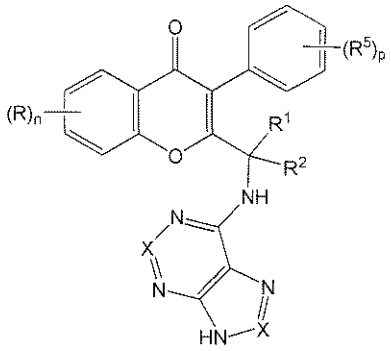
each occurrence of R^3 is independently selected from hydrogen, hydroxy, halogen, carboxyl, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenylalkyl substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted heterocyclylalkyl ring, substituted or unsubstituted guanidine, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^yR^z$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-(=N-N(R^x)R^y)$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y-$, $-NR^xC(S)R^y$ $-NR^xC(S)NR^yR^z$, $-SONR^xR^y-$, $-SO_2NR^xR^y-$, $-OR^x$, $-OR^xC(O)NR^yR^z$, $-OR^xC(O)OR^y-$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-R^xNR^yC(O)R^z$, $-R^xOR^y$, $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xC(O)R^x$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, and $-ONO_2$, wherein R^x, R^y and R^z in each of the above groups can be hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl ring, or substituted or unsubstituted amino, or any two of R^x, R^y and R^z may be joined to form a substituted or unsubstituted saturated or unsaturated 3-10 membered ring, which may optionally include heteroatoms which may be the same or different and are selected from O, NR^x (e.g., R^x can be hydrogen or substituted or unsubstituted alkyl) or S.

each occurrence of R^5 is hydrogen, C_{1-6} alkyl or halogen;

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

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

5. A compound of claim 1, wherein the compound has the formula (IA-VI):



(IA-VI)

or a pharmaceutically acceptable salt thereof, wherein

each occurrence of R is independently selected from hydrogen, halogen, -OR^a, CN, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, and substituted or unsubstituted heterocyclic group;

R^1 and R^2 may be the same or different and are independently selected from hydrogen, halogen, and substituted or unsubstituted C_{1-6} alkyl, or both R^1 and R^2 directly bound to a common atom, may be joined to form an oxo group (=O) or a substituted or unsubstituted saturated or unsaturated 3-10 member ring (including the carbon atom to which R^1 and R^2 are bound), which may optionally include one or more heteroatoms which may be the same or different and are selected from O, NR^a and S;

each occurrence of X is independently selected from CR^3 or N; and

each occurrence of R^3 is independently selected from hydrogen, hydroxy, halogen, carboxyl, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenylalkyl substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted heterocyclylalkyl ring, substituted or unsubstituted guanidine, –$COOR^x$, -$C(O)R^x$, -$C(S)R^x$, -$C(O)NR^xR^y$, -$C(O)ONR^xR^y$, -NR^yR^z, -$NR^xCONR^yR^z$, -$N(R^x)SOR^y$, -$N(R^x)SO_2R^y$, -(=N-$N(R^x)R^y$), - $NR^xC(O)OR^y$, -NR^xR^y, -$NR^xC(O)R^y$-, -$NR^xC(S)R^y$ -$NR^xC(S)NR^yR^z$, -$SONR^xR^y$-, -$SO_2NR^xR^y$-, -OR^x, -$OR^xC(O)NR^yR^z$, -

$OR^xC(O)OR^y$-, -$OC(O)R^x$, -$OC(O)NR^xR^y$, - $R^xNR^yC(O)R^z$, -R^xOR^y, -$R^xC(O)OR^y$, -$R^xC(O)NR^yR^z$, -$R^xC(O)R^x$, -$R^xOC(O)R^y$, -SR^x, -SOR^x, -SO_2R^x, and -ONO_2, wherein R^x, R^y and R^z in each of the above groups can be hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl ring, or substituted or unsubstituted amino, or any two of R^x, R^y and R^z may be joined to form a substituted or unsubstituted saturated or unsaturated 3-10 membered ring, which may optionally include heteroatoms which may be the same or different and are selected from O, NR^x (e.g., R^x can be hydrogen or substituted or unsubstituted alkyl) or S.

each occurrence of R^5 is hydrogen, C_{1-6} alkyl or halogen;

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

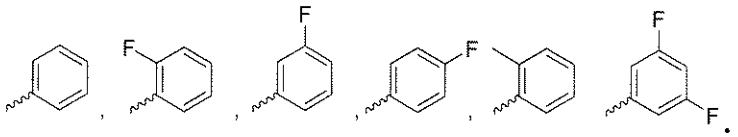
p is 0, 1, 2, 3, 4 or 5.

6. A compound of any one of claims 1-5, wherein R is hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl, or OR^a.

7. A compound of claim 6, wherein R^a is alkyl.

8. A compound of any one of claims 1-3, 6, and 7, wherein Cy^1 is substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl.

9. A compound of any one of claims 1-3, 6, and 7, wherein Cy^1 is selected from:



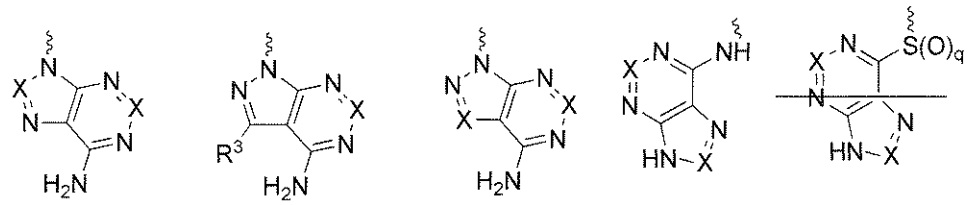
10. A compound of any one of claims 1-9, wherein R^1 and R^2 represent hydrogen or substituted or unsubstituted C_{1-6} alkyl.

~~11. A compound of any one of claims 1-3, 6-9, and 10, wherein L1 is selected from S(=O)q- or -NRa-.~~

~~12. A compound of any one of claims 11, wherein q is 0.~~

~~13. A compound of any one of claims 1-3, 6-9, and 10, wherein L1 is absent.~~

~~14~~11. A compound of claim 1, wherein Cy^2 is



a **b** **c** **d** ~~e~~

wherein

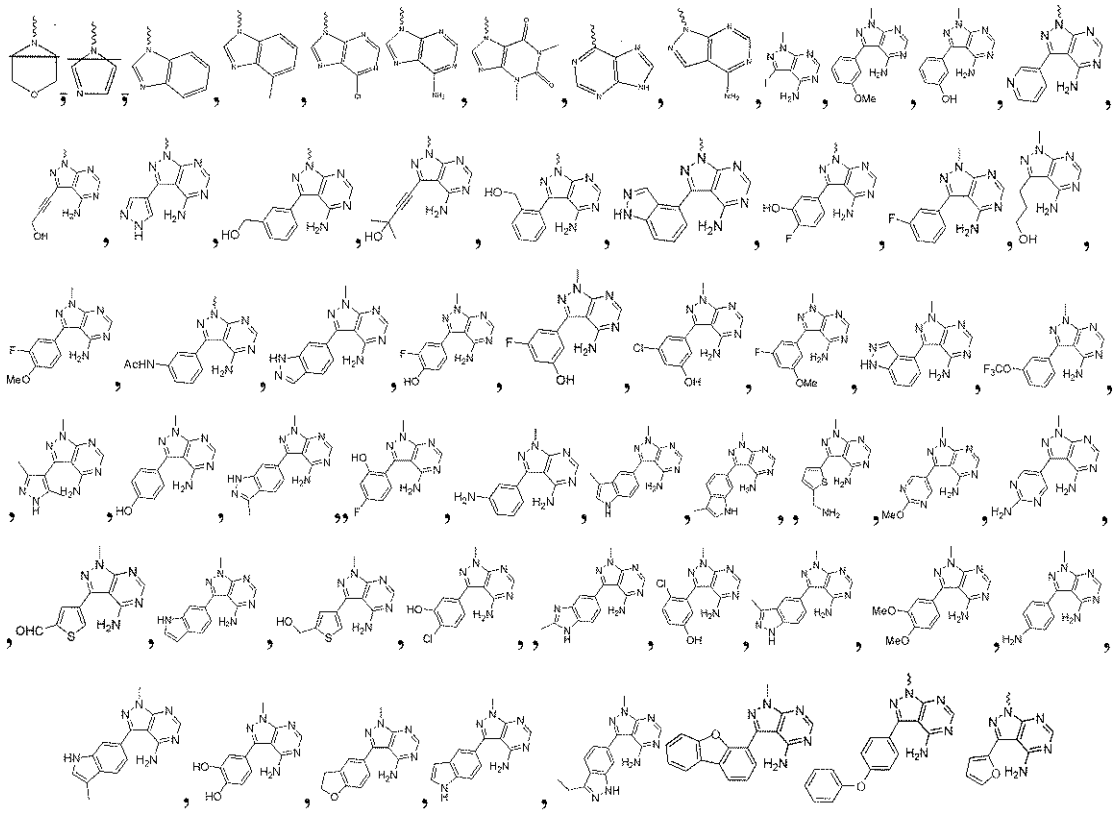
X is CR^3; ~~and~~

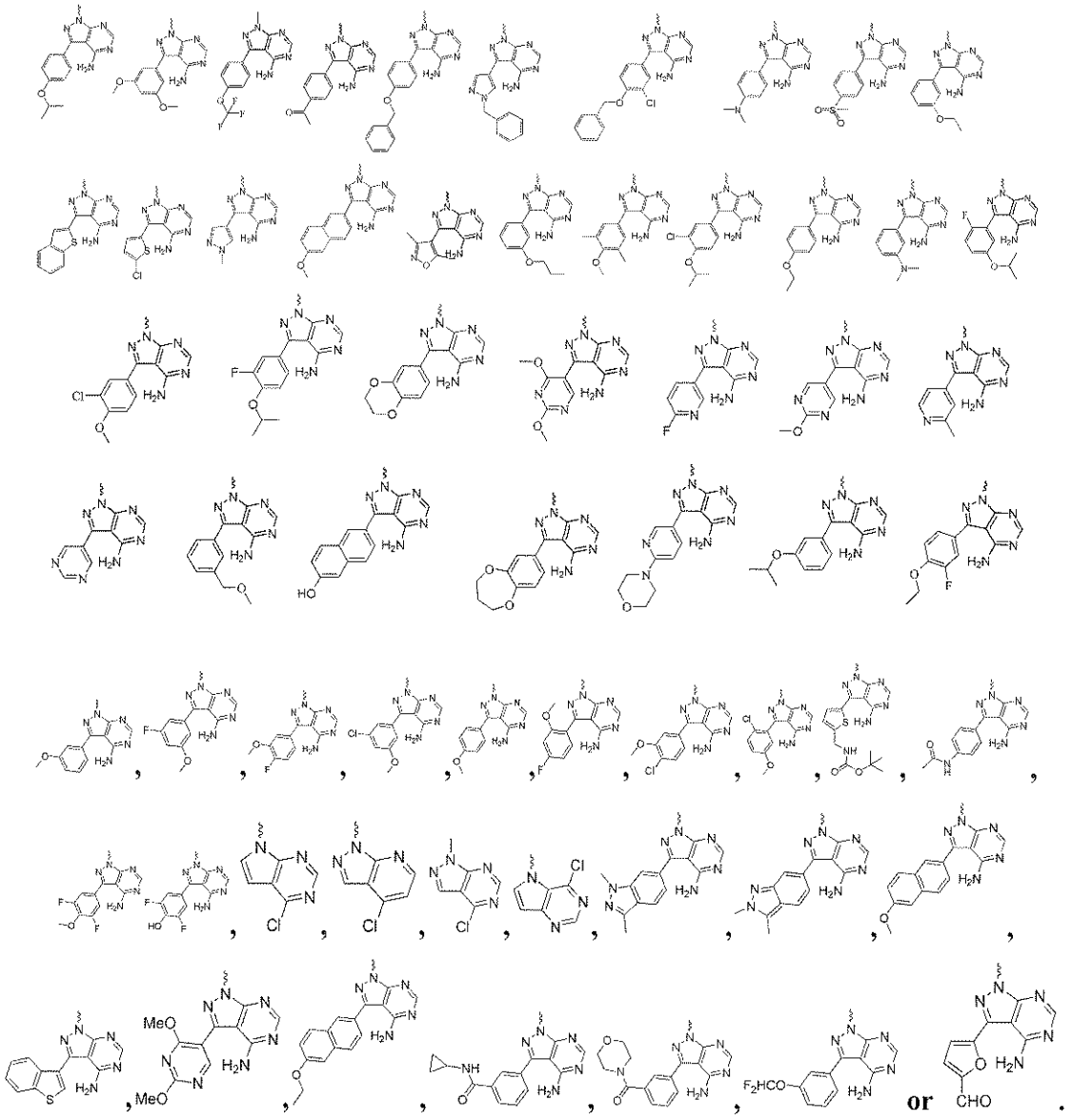
R^3 is independently selected from hydrogen, hydroxy, halogen, carboxyl, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted guanidine, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^yR^z$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-(=N-N(R^x)R^y)$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y-$, $-NR^xC(S)R^y$ $-NR^xC(S)NR^yR^z$, $-SONR^xR^y-$, $-SO_2NR^xR^y-$, $-OR^x$, $-OR^xC(O)NR^yR^z$, $-OR^xC(O)OR^y-$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-R^xNR^yC(O)R^z$, $-R^xOR^y$, $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xC(O)R^x$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-ONO_2$, wherein R^x, R^y and R^z in each of the above groups can be hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted

heteroaryl, substituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, or substituted or unsubstituted heterocyclic ring, or any two of R^x, R^y and R^z may be joined to form a substituted or unsubstituted saturated or unsaturated 3-10 membered ring, which may optionally include heteroatoms which may be the same or different and are selected from O, NR^X or S; and

q is 0, 1 or 2.

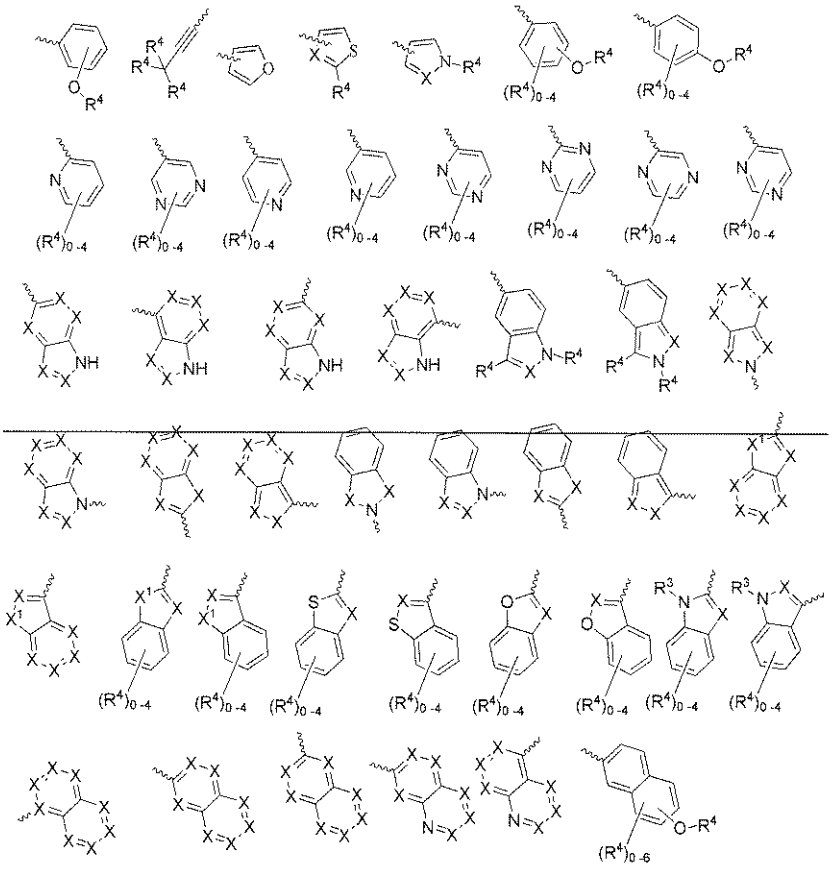
~~15~~12. A compound of claim 1, wherein Cy^2 is





~~16~~13. A compound of claim 3 or 4, wherein R^3 is iodo, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

~~17. A compound of claim 3, 4 or 16, wherein R^3 is~~



~~wherein~~

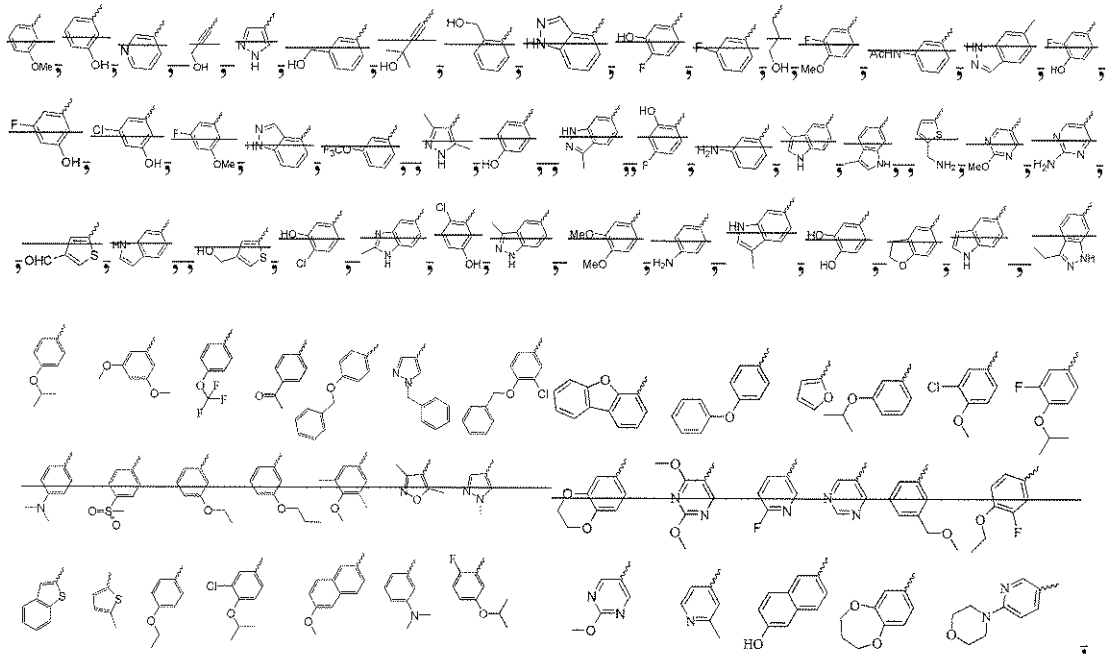
~~each occurrence of X is independently CR^4 or N;~~

~~X^1 is O, S, or NR^4; and~~

~~each occurrence of R^4 is independently selected from hydrogen, hydroxy, halogen, carboxyl, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenylalkyl substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted heterocyclylalkyl ring, substituted or unsubstituted guanidine, $COOR^x$, $C(O)R^x$, $C(S)R^x$, $C(O)NR^xR^y$, $C(O)ONR^xR^y$, NR^yR^z, $NR^xCONR^yR^z$, $N(R^x)SOR^y$, $N(R^x)SO_2R^y$, (=N-$N(R^x)R^y$), $NR^xC(O)OR^y$, NR^xR^y, $NR^xC(O)R^y$, $NR^xC(S)R^y$, $NR^xC(S)NR^yR^z$, $SONR^xR^y$, $SO_2NR^xR^y$, OR^x, $OR^xC(O)NR^yR^z$,~~

~~$OR^xC(O)OR^y$, $OC(O)R^x$, $OC(O)NR^xR^y$, $R^xNR^yC(O)R^z$, R^xOR^y, $R^xC(O)OR^y$, $R^xC(O)NR^yR^z$, $R^xC(O)R^x$, $R^xOC(O)R^y$, SR^x, SOR^x, SO_2R^x, and ONO_2, wherein R^x, R^y and R^z in each of the above groups can be hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl ring, or substituted or unsubstituted amino, or any two of R^x, R^y and R^z may be joined to form a substituted or unsubstituted saturated or unsaturated 3-10 membered ring, which may optionally include heteroatoms which may be the same or different and are selected from O, NR^x (e.g., R^x can be hydrogen or substituted or unsubstituted alkyl) or S.~~

~~18. A compound of claim 3, 4 or 16, wherein R^3 is selected from~~



~~19~~14. A compound of claim 3 or 5, wherein X is CR^3 and each occurrence of R^3 is independently hydrogen, halogen, hydroxyl or NH_2.

~~20~~15. A compound of claim ~~19~~14, wherein R^3 is hydrogen.

~~21~~16. A compound of claim 1, wherein the compound is selected from:

2-[(6-Amino-9H-purin-9-yl) methyl]-6-bromo-3-phenyl-4H-chromen-4-one;

6-Bromo-2-(morpholinomethyl)-3-phenyl-4H-chromen-4-one;

6-Bromo-2-(morpholinomethyl)-3-phenyl-4H-chromen-4-one hydrochloride;

2-[(6-Amino-9H-purin-9-yl) methyl]-3-phenyl-4H-chromen-4-one;

2-(Morpholinomethyl)-3-phenyl-4H-chromen-4-one;

2-(Morpholinomethyl)-3-phenyl-4H-chromen-4-one hydrochloride;

2-[(1H-Benzo[d]imidazol-1-yl) methyl]-6-bromo-3-phenyl-4H-chromen-4-one;

6-Bromo-2-[(4-methyl-1H-benzo[d]imidazol-1-yl) methyl]-3-phenyl-4H-chromen-4-one;

2-[(1H-benzo[d]imidazol-1-yl) methyl]-3-phenyl-4H-chromen-4-one;

2-[(4-methyl-1H-benzo[d]imidazol-1-yl)methyl]-3-phenyl-4H-chromen-4-one;

2-[(6-Chloro-9H-purin-9-yl)methyl]-3-phenyl-4H-chromen-4-one;

6-Bromo-2-[(6-chloro-9H-purin-9-yl)methyl]-3-phenyl-4H-chromen-4-one;

~~2-((9H-Purin-6-ylthio)methyl)-3-phenyl-4H-chromen-4-one;~~

2-[(1H-Imidazol-1-yl)methyl]-3-phenyl-4H-chromen-4-one ;

~~2-[(9H-Purin-6-ylthio)methyl]-6-bromo-3-phenyl-4H-chromen-4-one ;~~

2-((4-Amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-6-bromo-3-phenyl-4H-chromen-4-one ;

2-[(6-Amino-9H-purin-9-yl)methyl]-6-bromo-3-(4-fluorophenyl)-4H-chromen-4-one ;

2-[(6-Amino-9H-purin-9-yl)methyl]-3-(4-fluorophenyl)-4H-chromen-4-one ;

6-Bromo-3-(4-fluorophenyl)-2-(morpholinomethyl)-4H-chromen-4-one ;

6-Bromo-3-(4-fluorophenyl)-2-(morpholinomethyl)-4H-chromen-4-one hydro chloride;

3-(4-fluorophenyl)-2-(morpholinomethyl)-4H-chromen-4-one ;

3-(4-fluorophenyl)-2-(morpholinomethyl)-4H-chromen-4-one hydrochloride ;

2-[(6-Amino-9H-purin-9-yl)methyl]-6-bromo-3-o-tolyl-4H-chromen-4-one;

7-[(6-Bromo-4-oxo-3-phenyl-4H-chromen-2-yl)methyl]-1,3-dimethyl-1H-purine-2,6(3H,7H)-dione;

2-(1-(6-Amino-9H-purin-9-yl)ethyl)-6-bromo-3-phenyl-4H-chromen-4-one;

~~2-(1-(9H-Purin-6-ylthio)ethyl)-6-bromo-3-phenyl-4H-chromen-4-one;~~

2-(1-(6-Amino-9H-purin-9-yl)ethyl)-3-phenyl-4H-chromen-4-one;

(S)-2-(1-(9H-purin-6-ylamino)ethyl)-6-bromo-3-phenyl-4H-chromen-4-one ;

2-((9H-purin-6-ylamino)methyl)-6-bromo-3-phenyl-4H-chromen-4-one ;

2-(1-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-6-bromo-3-phenyl-4H-chromen-4-one ;

2-((6-Amino-9H-purin-9-yl)methyl)-6-methoxy-3-phenyl-4H-chromen-4-one;

2-(1-(6-Amino-9H-purin-9-yl)ethyl)-6-bromo-3-(2-fluorophenyl)-4H-chromen-4-one;

2-((6-Amino-9H-purin-9-yl)methyl)-6-bromo-3-(2-fluorophenyl)-4H-chromen-4-one ;

2-(1-(4-Amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-phenyl-4H-chromen-4-one ;

2-(1-(6-Amino-9H-purin-9-yl) propyl)-3-phenyl-4H-chromen-4-one;

2-(1-(6-Amino-9H-purin-9-yl)ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-((6-Amino-9H-purin-9-yl)methyl)-3-(2-fluorophenyl)-4H-chromen-4-one ;

2-(1-(6-Amino-9H-purin-9-yl)ethyl)-3-(2-fluorophenyl)-4H-chromen-4-one ;

2-(1-(6-Amino-9H-purin-9-yl)propyl)-3-(2-fluorophenyl)-4H-chromen-4-one;

2-(1-(6-amino-9H-purin-9-yl)propyl)-3-(3-fluorophenyl)-4H-chromen-4-one ;

2-(1-(6-Amino-9H-purin-9-yl)propyl)-3-(4-fluorophenyl)-4H-chromen-4-one ;

2-(1-(6-amino-9H-purin-9-yl)propyl)-6-fluoro-3-phenyl-4H-chromen-4-one;

2-(1-(6-Amino-9H-purin-9-yl)ethyl)-3-(4-fluorophenyl)-4H-chromen-4-one;

2-(1-(6-Amino-9H-purin-9-yl)ethyl)-6-fluoro-3-phenyl-4H-chromen-4-one;

2-(1-(4-Amino-3-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-phenyl-4H-chromen-4-one;

2-(1-(4-Amino-3-(3-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-phenyl-4H-chromen-4-one;

2-((9H-purin-6-ylamino)methyl)-3-phenyl-4H-chromen-4-one;

2-(1-(6-Amino-9H-purin-9-yl)ethyl)-3-o-tolyl-4H-chromen-4-one;

2-((9H-purin-6-ylamino)methyl)-3-(2-fluorophenyl)-4H-chromen-4-one;

2-((9H-purin-6-ylamino)methyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

(S)-2-(1-(9H-purin-6-ylamino)ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(6-amino-9H-purin-9-yl)ethyl)-6-fluoro-3-(2-fluorophenyl)-4H-chromen-4-one;

2-(1-(6-Amino-9H-purin-9-yl)ethyl)-3-(3,5-difluorophenyl)-4H-chromen-4-one;

2-(1-(6-amino-9H-purin-9-yl)ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-((4-Amino-3-(3-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-phenyl-4H-chromen-4-one;

2-((4-Amino-3-(3-hydroxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-phenyl-4H-chromen-4-one;

2-((4-amino-3-(3-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-((4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

(R)-2-(1-(9H-purin-6-ylamino) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

(S)-2-(1-(9H-purin-6-ylamino) ethyl)-6-fluoro-3-phenyl-4H-chromen-4-one;

2-((4-Amino-3-iodo-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-phenyl-4H-chromen-4-one;

2-(1-(4-amino-3-iodo-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-phenyl-4H-chromen-4-one;

2-(1-(4-amino-3-iodo-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-((4-amino-3-iodo-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-6-fluoro-3-phenyl-4H-chromen-4-one;

2-(1-(4-amino-3-iodo-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-6-fluoro-3-phenyl-4H-chromen-4-one;

2-(1-(4-amino-3-iodo-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-iodo-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) propyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-((4-amino-3-(pyridin-3-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-phenyl-4H-chromen-4-one;

2-((4-amino-3-(3-hydroxyprop-1-ynyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-phenyl-4H-chromen-4-one;

2-((4-amino-3-(1H-pyrazol-4-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-phenyl-4H-chromen-4-one;

2-((4-amino-3-(3-(hydroxymethyl) phenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-phenyl-4H-chromen-4-one;

2-((4-amino-3-(1H-indazol-4-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-phenyl-4H-chromen-4-one;

2-((4-amino-3-(3-fluorophenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-phenyl-4H-chromen-4-one

2-((4-amino-3-(3-hydroxypropyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-phenyl-4H-chromen-4-one;

N-(3-(4-amino-1-((4-oxo-3-phenyl-4H-chromen-2-yl) methyl)-1H-pyrazolo [3, 4-d] pyrimidin-3-yl) phenyl) acetamide;

2-((4-amino-3-(3-fluoro-5-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-phenyl-4H-chromen-4-one;

2-((4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-phenyl-4H-chromen-4-one;

2-((4-amino-3-(3-fluoro-5-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-((4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(1H-pyrazol-4-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-phenyl-4H-chromen-4-one;

2-(1-(4-amino-3-(1H-indazol-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-phenyl-4H-chromen-4-one;

2-(1-(4-amino-3-(3-hydroxy-3-methylbut-1-ynyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-phenyl-4H-chromen-4-one;

2-(1-(4-amino-3-(1H-pyrazol-4-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

(S)-2-(1-(9H-purin-6-ylamino) ethyl)-3-phenyl-4H-chromen-4-one;

(S)-2-(1-(9H-purin-6-ylamino) ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

2-((4-amino-3-(1H-indazol-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-phenyl-4H-chromen-4-one;

2-(1-(4-amino-3-(3-fluoro-5-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(1H-indazol-4-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3, 5-dimethyl-1H-pyrazol-4-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-methyl-1H-indazol-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(1H-indazol-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(2-(hydroxymethyl) phenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(4-fluoro-3-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(4-fluoro-3-hydroxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-hydroxyprop-1-ynyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-fluoro-4-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-fluoro-4-hydroxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-chloro-5-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-chloro-5-hydroxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-(trifluoromethoxy) phenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(4-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(4-hydroxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-((6-amino-9H-purin-9-yl) methyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(4-fluoro-2-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(4-fluoro-2-hydroxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-((4-amino-3-(3-aminophenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-phenyl-4H-chromen-4-one;

2-((4-amino-3-(3-methyl-1H-indazol-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-phenyl-4H-chromen-4-one;

2-(1-(4-amino-3-(2-aminopyrimidin-5-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(1H-indol-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(4-chloro-3-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(4-chloro-3-hydroxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(2-chloro-5-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(2-chloro-5-hydroxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3, 4-dimethoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3, 4-dihydroxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-((4-amino-3-(3-methyl-1H-indazol-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(1H-indol-5-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-Amino-3-(3-methyl-1H-indol-5-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

tert-butyl-(5-(4-amino-1-(1-(3-(3-fluorophenyl)-4-oxo-4H-chromen-2-yl) ethyl)-1H-pyrazolo [3, 4-d] pyrimidin-3-yl) thiophen-2-yl) methylcarbamate

2-(1-(4-amino-3-(5-(aminomethyl) thiophen-2-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-((4-amino-3-(3-methyl-1H-indazol-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-6-fluoro-3-phenyl-4H-chromen-4-one;

2-(1-(4-amino-3-(3-methyl-1H-indazol-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-phenyl-4H-chromen-4-one;

2-(1-(4-amino-3-(3-methyl-1H-indazol-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-6-fluoro-3-phenyl-4H-chromen-4-one;

2-(1-(4-amino-3-(3-methyl-1H-indazol-5-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

N-(4-(4-amino-1-(1-(3-(3-fluorophenyl)-4-oxo-4H-chromen-2-yl) ethyl)-1H-pyrazolo [3, 4-d] pyrimidin-3-yl) phenyl) acetamide;

2-(1-(4-amino-3-(4-aminophenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-methyl-1H-indazol-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(2, 3-dihydrobenzofuran-5-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-ethyl-1H-indazol-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-methyl-1H-indol-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(2-methoxypyrimidin-5-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

4-(4-amino-1-(1-(3-(3-fluorophenyl)-4-oxo-4H-chromen-2-yl) ethyl)-1H-pyrazolo [3, 4-d] pyrimidin-3-yl) thiophene-2-carbaldehyde;

2-(1-(4-amino-3-(5-(hydroxymethyl) thiophen-3-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(2-methyl-1H-benzo[d]imidazol-5-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-methyl-1H-indazol-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) propyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-methyl-1H-indol-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-((6-amino-9H-purin-9-yl) methyl)-6-fluoro-3-phenyl-4H-chromen-4-one;

2-((6-amino-9H-purin-9-yl) methyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

2-((4-amino-3-(3-fluoro-5-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

2-((4-amino-3-(3-fluoro-5-hydroxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-hydroxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

2-((9H-purin-6-ylamino) methyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

2-((9H-purin-6-ylamino) methyl)-6-fluoro-3-phenyl-4H-chromen-4-one;

(R)-2-(1-(9H-purin-6-ylamino) ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

2-((4-amino-3-(1H-pyrazol-4-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-6-fluoro-3-phenyl-4H-chromen-4-one;

2-(1-(4-amino-3-(3, 5-difluoro-4-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3, 5-difluoro-4-hydroxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-((4-amino-3-(3, 5-difluoro-4-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

2-((4-amino-3-(3, 5-difluoro-4-hydroxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) methyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

(+)-2-(1-(4-amino-3-(3-methyl-1H-indazol-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

(-)-2-(1-(4-amino-3-(3-methyl-1H-indazol-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3, 5-dimethoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(4-methoxy-3, 5-dimethylphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(2-fluoro-5-isopropoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(2, 3-dihydrobenzo[b] [1, 4] dioxin-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(1-benzyl-1H-pyrazol-4-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(2-methylpyridin-4-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3, 4-dihydro-2H-benzo[b] [1, 4] dioxepin-7-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(6-morpholinopyridin-3-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(dibenzo [b, d] furan-4-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(4-(benzyloxy)-3-chlorophenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-chloro-4-isopropoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-(dimethylamino) phenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(4-ethoxy-3-fluorophenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(4-isopropoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(4-(trifluoromethoxy) phenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(3-(4-acetylphenyl)-4-amino-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(4-(benzyloxy) phenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(4-(dimethylamino) phenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(4-(methylsulfonyl) phenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-ethoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(benzo[b]thiophen-2-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(5-chlorothiophen-2-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3, 5-dimethylisoxazol-4-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-propoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(furan-2-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(4-ethoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-chloro-4-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(6-fluoropyridin-3-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(pyrimidin-5-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-(methoxymethyl) phenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(6-hydroxynaphthalen-2-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-isopropoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

6-Fluoro-3-(3-fluorophenyl)-2-(1-(4-methoxyphenylamino) ethyl)-4H-chromen-4-one;

2-(1-(4-Chloro-7H-pyrrolo [2, 3-d] pyrimidin-7-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-Chloro-1H-pyrazolo [3, 4-b] pyridin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-Chloro-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-Chloro-5H-pyrrolo [3, 2-d] pyrimidin-5-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(1, 3-dimethyl-1H-indazol-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(2, 3-dimethyl-2H-indazol-6-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(6-methoxynaphthalen-2-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(benzo[b]thiophen-3-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(2, 4-dimethoxypyrimidin-5-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(6-ethoxynaphthalen-2-yl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

3-(4-amino-1-(1-(3-(3-fluorophenyl)-4-oxo-4H-chromen-2-yl) ethyl)-1H-pyrazolo [3, 4-d] pyrimidin-3-yl)-N-cyclopropylbenzamide;

2-(1-(4-amino-3-(3-(morpholine-4-carbonyl) phenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-(4-amino-3-(3-(difluoromethoxy) phenyl)-1H-pyrazolo [3, 4-d] pyrimidin-1-yl) ethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

5-(4-amino-1-(1-(3-(3-fluorophenyl)-4-oxo-4H-chromen-2-yl) ethyl)-1H-pyrazolo [3, 4-d] pyrimidin-3-yl) furan-2-carbaldehyde

and pharmaceutically acceptable salts thereof.

~~22~~17. A pharmaceutical composition, comprising a compound of any one of claims ~~1-21~~ 1-16 and a pharmaceutically acceptable carrier.

~~23~~18. The pharmaceutical composition of claim ~~22~~17, further comprising one or more additional therapeutic agents selected from anti-cancer agents, anti-inflammatory agents, immunosuppressive agents, steroids, non-steroidal anti-inflammatory agents, antihistamines, analgesics, and mixtures thereof.

~~24~~19. Use of a compound of any one of claims 1-16~~1-21~~ in the manufacture of a medicament for the treatment of a disease, disorder, or condition ~~that would benefit from inhibiting catalytic activity of a kinase~~ selected from inflammation, glomerulonephritis, uveitis, hepatic diseases or disorders, renal diseases or disorders, chronic obstructive pulmonary disease, rheumatoid arthritis, inflammatory bowel disease, vasculitis, dermatitis, osteoarthritis, inflammatory muscle disease, allergic rhinitis, vaginitis, interstitial cystitis, scleroderma, osteoporosis, eczema, allogeneic or xenogeneic transplantation, graft rejection, graft-versus-host disease, lupus erythematosus, pulmonary fibrosis, dermatomyositis, thyroiditis, myasthenia gravis, autoimmune hemolytic anemia, cystic fibrosis, chronic relapsing hepatitis, primary biliary cirrhosis, allergic conjunctivitis, hepatitis, atopic dermatitis, asthma, Sjogren's syndrome, organ transplant rejection, multiple sclerosis, Guillain-Barre, autoimmune uveitis, autoimmune hemolytic anemia, pernicious anemia, autoimmune thrombocytopenia, temporal arteritis, anti-phospholipid syndrome, vasculitides such as Wegener's granulomatosis, Behcet's disease, psoriasis, dermatitis herpetiformis, pemphigus vulgaris, vitiligo, Crohn's disease, colitis, ulcerative colitis, primary biliary cirrhosis, autoimmune hepatitis, Type 1 or immune-mediated diabetes mellitus, Grave's disease, Hashimoto's thyroiditis, autoimmune oophoritis and orchitis, autoimmune disorder of the adrenal gland, systemic lupus erythematosus, polymyositis, dermatomyositis, ankylosing spondylitis, transplant rejection, skin graft rejection, arthritis, bone diseases associated with increased bone resorption, ileitis, Barrett's syndrome, adult respiratory distress syndrome, chronic obstructive airway disease; corneal dystrophy, trachoma, onchocerciasis, sympathetic ophthalmitis, endophthalmitis; gingivitis, periodontitis; tuberculosis; leprosy; uremic complications, nephrosis; scleroderma titis, psoriasis, chronic

demyelinating diseases of the nervous system, AIDS-related neurodegeneration, Alzheimer's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis viral or autoimmune encephalitis; autoimmune disorders, immune-complex vasculitis, systemic lupus and erythematodes; systemic lupus erythematosus (SLE); cardiomyopathy, ischemic heart disease hypercholesterolemia, atherosclerosis, preeclampsia; chronic liver failure, brain and spinal cord trauma, cancer, hematopoietic tumors of lymphoid lineage, leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, acute myelogenous leukemias, chronic myelogenous leukemias, myelodysplastic syndrome, promyelocytic leukemia; carcinoma of the bladder, carcinoma of the breast, carcinoma of the colon, carcinoma of the kidney, carcinoma of the liver, carcinoma of the lung, small cell lung cancer, esophageal cancer, gall bladdercancer, ovarian cancer, pancreatic cancer, stomach cancer, cervical cancer, thyroidcancer, prostatecancer, skincancer, squamous cell carcinoma; tumors of mesenchymal origin, fibrosarcoma, rhabdomyosarcoma; tumors of the central and peripheral nervous system, astrocytoma, neuroblastoma, glioma, schwannoma; melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer, Kaposi's sarcoma, chronic lymphocytic leukemia, multiple myelomas which includes smoldering multiple myeloma, nonsecretory myeloma, osteosclerotic myeloma, plasma cell leukemia, solitary plasmacytoma, extramedullary plasmacytoma, Chronic Lymphocytic Leukemia (CLL); Lymphoma Non-Hodgkin (NHL); Acute Myeloid Leukemia (AML); Multiple Myeloma (MM), Small Lymphocytic Lymphoma (SLL), or Indolent Non-Hodgkin's Lymphoma (I-NHL).

~~25. The use of claim 24, wherein the inhibition takes place in a subject suffering from a disease or disorder which is cancer, bone disorder, inflammatory disease, immune disease, nervous system disease, metabolic disease, respiratory disease, thrombosis, or cardiac disease.~~

~~26. Use of a compound of claim 24, wherein the kinase is PI3 kinase.~~

~~27. Use of an effective amount of compound of any one of claims 1-21 in the manufacture of a medicament for the treatment of a PI3K associated disease or disorder, wherein said medicament is to be administered to a subject in need thereof.~~

~~28~~20. The use of claim 19 ~~27~~, wherein the medicament is administered to a subject in need thereof simultaneously or sequentially with at least one other anti-cancer agent, anti-inflammatory agent, immunosuppressive agent, steroid, non-steroidal anti-inflammatory agent, antihistamine, analgesic, or a mixture thereof.

~~29. The use of claim 27 or 28, wherein the PI3K-associated disease, disorder or condition is an immune system-related disease, a disease or disorder involving inflammation, cancer or other proliferative disease, a hepatic disease or disorder, or a renal disease or disorder.~~

30. The use of claim 27 or 28, wherein the PI3K associated disease, disorder or condition is selected frominflammation, glomerulonephritis, uveitis, hepatic diseases or disorders, renal diseases or disorders, chronic obstructive pulmonary disease, rheumatoid arthritis, inflammatory bowel disease, vasculitis, dermatitis, osteoarthritis, inflammatory muscle disease, allergic rhinitis, vaginitis, interstitial cystitis, scleroderma, osteoporosis, eczema, allogeneic or xenogeneic transplantation, graft rejection, graft-versus-host disease, lupus erythematosus, pulmonary fibrosis, dermatomyositis, thyroiditis, myasthenia gravis, autoimmune hemolytic anemia, cystic fibrosis, chronic relapsing hepatitis, primary biliary cirrhosis, allergic conjunctivitis, hepatitis, atopic dermatitis, asthm , Sjogren's syndrome, organ transplant rejection, multiple sclerosis, Guillain-Barre, autoimmune uveitis, autoimmune hemolytic anemia, pernicious anemia, autoimmune thrombocytopenia, temporal arteritis, anti-phospholipid syndrome, vasculitides such as Wegener's granulomatosis, Behcet's disease, psoriasis, dermatitis herpetiformis, pemphigus vulgaris, vitiligo, Crohn's disease, colitis, ulcerative colitis, primary biliary cirrhosis, autoimmune hepatitis, Type 1 or immune-mediated diabetes mellitus, Grave's disease. Hashimoto's thyroiditis, autoimmune oophoritis and orchitis, autoimmune disorder of the adrenal gland, systemic lupus erythematosus, polymyositis, dermatomyositis, ankylosing spondylitis, transplant rejection, skin graft rejection, arthritis, bone diseases associated with increased bone resorption;, ileitis, Barrett's syndrome, adult respiratory distress syndrome, chronic obstructive airway disease; corneal dystrophy, trachoma, onchocerciasis, sympathetic ophthalmitis, endophthalmitis; gingivitis, periodontitis; tuberculosis; leprosy; uremic complications, nephrosis; sclerodermatitis, psoriasis, chronic demyelinating diseases of the nervous system, AIDS-related neurodegeneration, Alzheimer's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis viral or autoimmune encephalitis; autoimmune disorders, immune-complex vasculitis, systemic lupus and erythematodes; systemic lupus erythematosus (SLE); cardiomyopathy, ischemic heart disease hypercholesterolemia, atherosclerosis, preeclampsia; chronic liver failure, brain and spinal cord trauma, and cancer.

31. The use of claim 27 or 28, wherein the PI3K associated disease, disorder or condition is selected from hematopoietic tumors of lymphoid lineage, leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, acute myelogenous leukemias, chronic

~~myelogenous leukemias, myelodysplastic syndrome, promyelocytic leukemia; carcinoma of the bladder, carcinoma of the breast, carcinoma of the colon, carcinoma of the kidney, carcinoma of the liver, carcinoma of the lung, small cell lung cancer, esophageal cancer, gall bladdercancer, ovarian cancer, pancreatic cancer, stomachcancer, cervical cancer, thyroidcancer, prostatecancer, skincancer, squamous cell carcinoma; tumors of mesenchymal origin, fibrosarcoma, rhabdomyosarcoma; tumors of the central and peripheral nervous system, astrocytoma, neuroblastoma, glioma, schwannoma; melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.~~

~~32. The use of claim 30, wherein the PI3K associated disease, disorder or condition is selected from chronic obstructive pulmonary disease, asthma, rheumatoid arthritis, chronic bronchitis, inflammatory bowel disease, allergic rhinitis, lupus erythematosus and ulcerative colitis.~~

~~33. The use of claim 31, wherein the PI3K associated disease, disorder or condition is selected from hematopoietic tumors of lymphoid lineage, leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkins lymphoma, chronic lymphocytic leukemia, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, acute myelogenous leukemias, chronic myelogenous leukemias, myelodysplastic syndrome, promyelocytic leukemia or multiple myelomas which includes smoldering multiple myeloma, nonsecretory myeloma, osteosclerotic myeloma, plasma cell leukemia, solitary plasmacytoma, and extramedullary plasmacytoma.~~

~~34. The use of claim 31 or 33, wherein the PI3K associated disease, disorder or condition is Chronic Lymphocytic Leukemia (CLL); Lymphoma Non-Hodgkin (NHL); Acute Myeloid Leukemia (AML); Multiple Myeloma (MM), Small Lymphocytic Lymphoma (SLL), or Indolent Non-Hodgkin's Lymphoma (I-NHL).~~

~~35. A compound selected from:~~

~~6-Bromo-2-methyl-3-phenyl-4H-chromen-4-one;~~

~~6-Bromo-2-(bromomethyl)-3-phenyl-4H-chromen-4-one;~~

2-(Bromomethyl)-3-phenyl-4H-chromen-4-one;

1-(5-Bromo-2-hydroxyphenyl)-2-(4-fluorophenyl) ethanone;

6-Bromo-3-(4-fluorophenyl)-2-methyl-4H-chromen-4-one;

6-Bromo-2-(bromomethyl)-3-(4-fluorophenyl)-4H-chromen-4-one;

3-(4-Fluorophenyl)-2-methyl-4H-chromen-4-one;

2-(Bromomethyl)-3-(4-fluorophenyl)-4H-chromen-4-one;

1-(5-bromo-2-hydroxyphenyl)-2-o-tolylethanone;

6-bromo-2-methyl-3-o-tolyl-4H-chromen-4-one;

6-Bromo-2-(bromomethyl)-3-o-tolyl-4H-chromen-4-one;

6-Bromo-2-ethyl-3-phenyl-4H-chromen-4-one;

6-Bromo-2-(1-bromoethyl)-3-phenyl-4H-chromen-4-one;

(S)-tert-butyl 1-(6-bromo-4-oxo-3-phenyl-4H-chromen-2-yl) ethylcarbamate;

(S)-2-(1-aminoethyl)-6-bromo-3-phenyl-4H-chromen-4-one;

tert-Butyl (6-bromo-4-oxo-3-phenyl-4H-chromen-2-yl) methylcarbamate;

2-(Amino methyl)-6-bromo-3-phenyl-4H-chromen-4-one;

2-(Bromomethyl)-6-methoxy-3-phenyl-4H-chromen-4-one;

1-(5-Bromo-2-hydroxyphenyl)-2-(2-fluorophenyl) ethanone;

6-Bromo-2-ethyl-3-(2-fluorophenyl)-4H-chromen-4-one;

6-Bromo-2-(1-bromoethyl)-3-(2-fluorophenyl)-4H-chromen-4-one;

6-Bromo-3-(2-fluorophenyl)-2-methyl-4H-chromen-4-one;

6-Bromo-2-(bromomethyl)-3-(2-fluorophenyl)-4H-chromen-4-one;

2-(1-Bromoethyl)-3-phenyl-4H-chromen-4-one;

6-Bromo-3-phenyl-2-propyl-4H-chromen-4-one;

3-Phenyl-2-propyl-4H-chromen-4-one;

2-(1-Bromopropyl)-3-phenyl-4H-chromen-4-one;

1-(5-Bromo-2-hydroxyphenyl)-2-(3-fluorophenyl) ethanone;

6-Bromo-2-ethyl-3-(3-fluorophenyl)-4H-chromen-4-one;

2-Ethyl-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-Bromoethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

3-(2-Fluorophenyl)-2-methyl-4H-chromen-4-one;

2-(Bromomethyl)-3-(2-fluorophenyl)-4H-chromen-4-one;

2-Ethyl-3-(2-fluorophenyl)-4H-chromen-4-one;

2-(1-Bromoethyl)-3-(2-fluorophenyl)-4H-chromen-4-one;

6-Bromo-3-(2-fluorophenyl)-2-propyl-4H-chromen-4-one;

3-(2-Fluorophenyl)-2-propyl-4H-chromen-4-one;

2-(1-Bromopropyl)-3-(2-fluorophenyl)-4H-chromen-4-one;

6-Bromo-3-(3-fluorophenyl)-2-propyl-4H-chromen-4-one;

3-(3-Fluorophenyl)-2-propyl-4H-chromen-4-one;

2-(1-Bromopropyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

6-Bromo-3-(4-fluorophenyl)-2-propyl-4H-chromen-4-one;

3-(4-Fuorophenyl)-2-propyl-4H-chromen-4-one;

2-(1-Bromopropyl)-3-(4-fluorophenyl)-4H-chromen-4-one;

6-Fluoro-3-phenyl-2-propyl-4H-chromen-4-one;

2-(1-Bromopropyl)-6-fluoro-3-phenyl-4H-chromen-4-one;

6-Bromo-2-ethyl-3-(4-fluorophenyl)-4H-chromen-4-one;

2-Ethyl-3-(4-fluorophenyl)-4H-chromen-4-one;

2-(1-Bromoethyl)-3-(4-fluorophenyl)-4H-chromen-4-one;

2-Ethyl-6-fluoro-3-phenyl-4H-chromen-4-one;

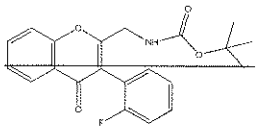
2-(1-Bromoethyl)-6-fluoro-3-phenyl-4H-chromen-4-one;

6-Bromo-2-ethyl-3-o-tolyl-4H-chromen-4-one;

2-Ethyl-3-o-tolyl-4H-chromen-4-one;

2-(2-Fluorophenyl)-1-(2-hydroxyphenyl) ethanone;

tert-butyl (3-(2-fluorophenyl)-4-oxo-4H-chromen-2-yl) methyl carbamate;



2-(Amino methyl)-3-(2-fluorophenyl)-4H-chromen-4-one;

2-(3-Fluorophenyl)-1-(2-hydroxyphenyl) ethanone;

1-(5-Fluoro-2-hydroxyphenyl)-2-(2-fluorophenyl) ethanone;

2-Ethyl-6-fluoro-3-(2-fluorophenyl)-4H-chromen-4-one;

2-(1-bromoethyl)-6-fluoro-3-(2-fluorophenyl)-4H-chromen-4-one;

1-(5-bromo-2-hydroxyphenyl)-2-(3, 5-difluorophenyl) ethanone;

2-(3, 5-Difluorophenyl)-1-(2-hydroxyphenyl) ethanone;

3-(3, 5-Difluorophenyl)-2-ethyl-4H-chromen-4-one;

2-(1-Bromoethyl)-3-(3, 5-difluorophenyl)-4H-chromen-4-one;

1-(5-Fluoro-2-hydroxyphenyl)-2-(3-fluorophenyl) ethanone;

2-Ethyl-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

2-(1-Bromoethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

3-(3-fluorophenyl)-2-methyl-4H-chromen-4-one;

2-(bromomethyl)-3-(3-fluorophenyl)-4H-chromen-4-one;

3-(3-fluorophenyl)-1H-pyrazolo [3, 4-d] pyrimidin-4-amine;

3-(4-Fluoro-3-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-4-amine;

3-(3-fluoro-4-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-4-amine;

3-(3-chloro-5-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-4-amine;

3-(3-(trifluoromethoxy) phenyl)-1H-pyrazolo [3, 4-d] pyrimidin-4-amine;

3-(4-fluoro-2-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-4-amine;

3-(4-chloro-3-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-4-amine;

3-(2-chloro-5-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidin-4-amine;

6-fluoro-2-methyl-3-phenyl-4H-chromen-4-one;

2-(bromomethyl)-6-fluoro-3-phenyl-4H-chromen-4-one;

6-fluoro-3-(3-fluorophenyl)-2-methyl-4H-chromen-4-one;

2-(bromomethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one;

tert-butyl 6-bromo-3-methyl-1H-indazole-1-carboxylate;

tert-butyl 3-methyl-6-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1H-indazole-1-carboxylate;

tert-butyl 6-bromo-3-ethyl-1H-indazole-1-carboxylate;

3-methyl-6-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1H-indole;

~~3-(2, 3-dihydrobenzofuran-5-yl)-1H-pyrazolo [3, 4-d] pyrimidin-4-amine;~~

~~tert-butyl 2-methyl-6-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1H-benzo[d]imidazole-1-carboxylate; and~~

~~salts thereof.~~

21~~37~~. An in vitro method for inhibiting a catalytic activity of a PI3 kinase present in a cell, comprising contacting the cell with an effective amount of a compound of any one of claims 1 to 16~~1 to 21~~.

CHROMEN-4-ONE DERIVATIVES AS KINASE MODULATORS

ABSTRACT

The present invention provides PI3K protein kinase modulators, methods of preparing them, pharmaceutical compositions containing them and methods of treatment, prevention and/or amelioration of kinase mediated diseases or disorders with them.