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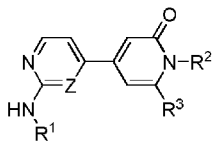
(54) Title: PYRIDINAMINE-PYRIDONE AND PYRIMIDINAMINE-PYRIDONE COMPOUNDS



(I)

(57) Abstract: The invention provides novel pyridinamine-pyridone and pyrimidinamine- pyridone compounds of formula (I), pharmaceutical compositions containing such compounds, and methods for using such compounds in treatment of diseases including cancer, type II diabetes, inflammatory disease, neurodegenerative disorders, cardiovascular disorders, autoimmune diseases and viral infections; (I) wherein R^1, R^2, R^3 and Z are as defined in the specification.

PYRIDINAMINE-PYRIDONE AND PYRIMIDINAMINE-PYRIDONE COMPOUNDS

FIELD OF THE INVENTION

The invention provides novel pyridinamine-pyridone and pyrimidinamine-pyridone compounds of formula (I), pharmaceutical compositions containing such compounds, and methods for using such compounds in treatment of diseases including cancer and type II diabetes.

BACKGROUND OF THE INVENTION

Enzymes belonging to the family of phosphatidylinositide 3-kinases (PI3K) are regulators of several important cellular events. The family consists of three classes, I, II and III and while the Class I group has been an interesting drug target for many years, Class II and III are less exploited. The PI3K Class III, vacuolar protein sorting 34 (Vps34, PIK3C3) forms a heterodimer with its regulatory subunit p150 (Vps15) and this dimer takes part in several complexes regulating vesicular trafficking events such as autophagy, endocytosis, exocytosis and micropinocytosis (Amaravadi et al. Clin Cancer Res. 2011, 17:654-666; Carpentier et al. 2013, Traffic). The enzyme is responsible for phosphorylation of phosphatidylinositol (PI) to phosphatidylinositol (3)-phosphate (PI3P). The ligand binding to PX and FYVE domains results in recruiting and delocalization of these effector proteins that lead to vesicular formation, elongation and movement (Backer et al. J Biochem. 2008, 410:1-17).

Autophagy is a catabolic process where cellular components are targeted for degradation by enclosing them in double-membrane vesicles, auto-phagosomes that are fused with the protease-containing lysosomes. This is a mean for the cell to handle damaged organelles and misfolded proteins and by that maintain cellular function. The pathway is also a way of recirculating cellular content into new building blocks (Boya et al, Nat Cell Biol 2013,

15;713–720). Autophagy is a cellular response to stressful conditions as nutrient deprivation, acidosis and hypoxia but also to drug treatment. Therefore, autophagy inhibition is a means to potentiate cancer drugs and resensitize drug resistant tumors (Nagelkerke et al, Semin Cancer Biol 2014, 31; 99-105). Most advanced tumors show a high upregulation of autophagic flux (Leone et al. Trends in Endocrin Metab 2013, 24; 209-217). An established marker for studying autophagic flux is the detection of autophagic puncta in the form of lipidated LC3 protein on the autophagosome. Inhibition of Vps34 results in the inhibition of autophagy as measured by LC3 redistribution into puncta (Dowdle et al., Nat Cell Biol 2014, 16; 1069-79).

As recently described, ablation of the regulatory subunit p150 leads to increased insulin sensitivity in vivo due to decreased insulin receptor internalization (Nemazanyy, Nature Commun., 2015, 6:8283). A kinase dead heterozygous animal model confirms this result with increased glucose tolerance and increased insulin sensitivity (WO2013076501).

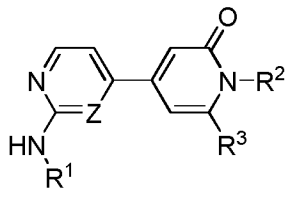
Several disease states could benefit from Vps34 inhibition including cancer, inflammatory diseases, neurodegenerative disorders, cardiovascular disorders, diabetes, such as type II diabetes, and viral infections (Reviewed in Rubinsztein et al, Nat Rev 2012, 11;709-730). Cancer forms that would benefit from Vps34 inhibition include, but are not limited to, breast cancer, such as triple negative breast cancer, bladder cancer, liver cancer, cervical cancer, pancreatic cancer, leukemia, lymphoma, renal cancer, colon cancer, glioma, prostate cancer, ovarian cancer, melanoma, and lung cancer as well as hypoxic tumors. There is thus a need for novel and potent inhibitors of Vps34.

Previous disclosures describing Vps34 inhibitors in use to affect diseases include WO2015150555; WO2015150557; WO2015108861; WO2015108881; WO2012085815; WO2012085244; WO2013190510; Farkas, J. Biol. Chem., 2011 286(45) 38904-12.

DESCRIPTION OF THE INVENTION

An object of the invention is to provide novel and potent inhibitors of Vps34. Another object of the invention is to provide novel and potent inhibitors of Vps34 that may be used for treating cancer and other diseases such as type II diabetes.

According to aspect 1 of the invention, there is provided a compound of Formula (I)



(I)

wherein

R^1 is phenyl or monocyclic 5-6 membered heteroaryl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_3-C_4cycloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, amino, N-C_1-C_3alkylamino and N,N-diC_1-C_3alkylamino;

R^2 is selected from hydrogen, C_1-C_3haloalkyl and C_1-C_3alkyl;

R^3 is selected from A, phenyl and monocyclic heteroaryl, said phenyl and said heteroaryl being each optionally substituted with one or more of R^4, R^5, R^6 and R^7;

R^4, R^5, R^6 and R^7 are independently selected from halogen, C_1-C_6alkyl, C_3-C_4cycloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, azetidine, amino, N-C_1-C_3alkylamino, N,N-diC_1-C_3alkylamino, $NHSO_2R^8$, SO_2R^9 and hydroxy;

R^8 is C_1-C_3haloalkyl or C_1-C_3alkyl;

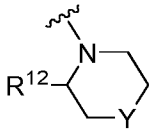
R^9 is selected from R^{10}, C_1-C_6alkyl, amino, N-C_1-C_3alkylamino, N,N-diC_1-C_3alkylamino and C_1-C_3alkoxyC_1-C_3alkyl, wherein said C_1-C_6alkyl and C_1-C_3alkoxyC_1-C_3alkyl being each optionally substituted with one R^{10} and/or one or more halogen;

R^{10} is selected from phenyl, benzyl, monocyclic heteroaryl, C_3-C_6cycloalkyl, heterocyclyl, each optionally substituted with one or more R^{11};

R^{11} is selected from halogen, C_1-C_3haloalkyl, C_3-C_4cycloalkyl, C_1-C_3alkyl,

amino, N-C_1-C_3alkylamino, N,N-diC_1-C_3alkylamino and C_1-C_3alkoxyC_1-C_3alkyl;

A is



R^{12} is selected from hydrogen, halogen, COR^{13}, C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_3alkoxyC_1-C_3alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_3cyanoalkyl, and C_1-C_3haloalkyl;

R^{13} is selected from C_1-C_3alkoxy, N-C_1-C_3alkylamino, N,N-diC_1-C_3alkylamino, 1-pyrrolidinyl, 1-piperidinyl and 1-azetidinyl;

Y is selected from CH_2, S, SO, SO_2, NR^{14}, $NCOR^9$, $NCOOR^{15}$, NSO_2R^9, $NCOCH_2R^9$, O, or a bond;

R^{14} is selected from H, C_1-C_3haloalkyl, C_1-C_3alkoxyC_1-C_3alkyl, C_1-C_3alkyl, and C_3-C_6cycloalkyl; and

R^{15} is selected from R^{10}, C_1-C_6alkyl and C_1-C_3alkoxyC_1-C_3alkyl, and wherein said C_1-C_6alkyl and C_1-C_3alkoxyC_1-C_3alkyl being each optionally substituted with one R^{10} and/or one or more halogen; and

Z is CH or N;

or a pharmaceutically acceptable salt thereof.

According to aspect 2 of the invention, there is provided a compound of Formula (I), such as according to aspect 1, wherein R^2 is hydrogen or C_1-C_3alkyl.

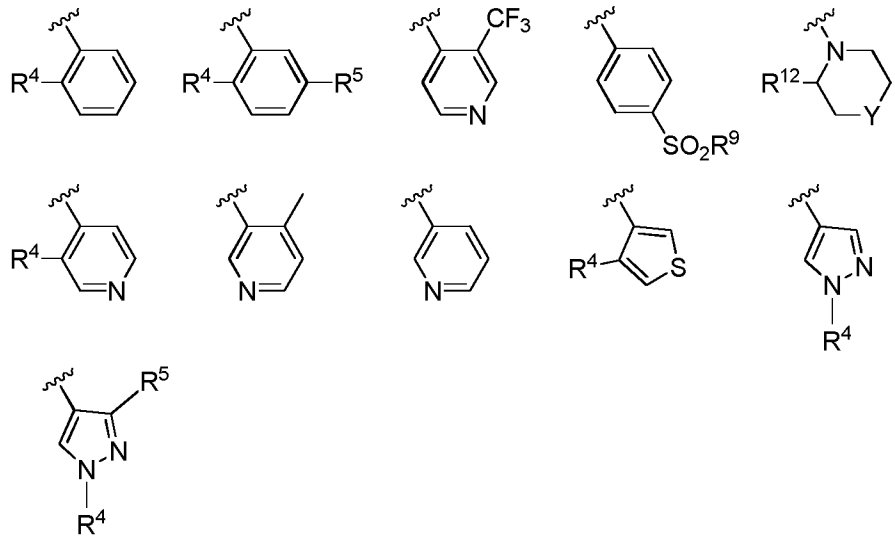
According to aspect 3 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 or 2, wherein R^2 is hydrogen.

According to aspect 4 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 3, wherein R^1 is phenyl or a monocyclic 5-6 membered heteroaryl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_3-

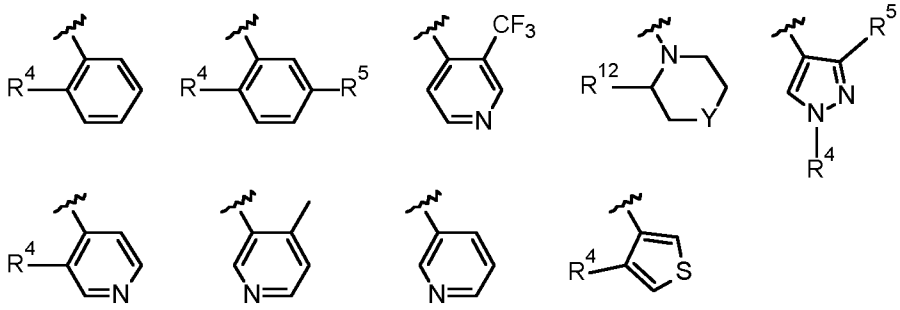
C_4cycloalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, amino, -N-C_1-C_3alkylamino, N,N-di-C_1-C_3alkylamino and halogen.

According to aspect 5 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 4, wherein R^1 is phenyl or a monocyclic 5-6 membered heteroaryl, each optionally substituted with one or more substituents selected from C_1-C_6alkyl, C_3-C_4cycloalkyl, and halogen.

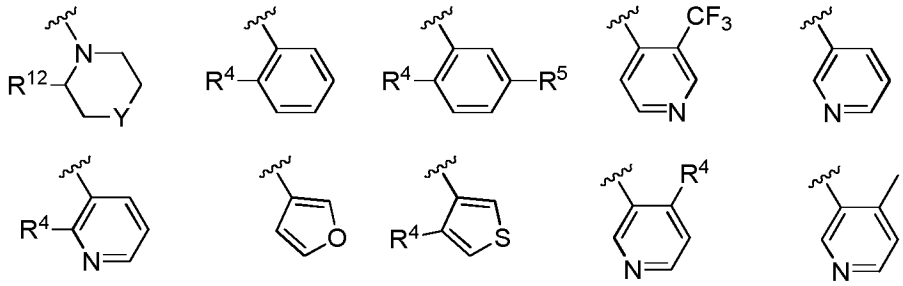
According to aspect 6 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 5, wherein R^3 is selected from



According to aspect 7 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 6, wherein R^3 is selected from



According to aspect 8 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 5, wherein R^3 is selected from



Y is selected from CH_2, NSO_2R^9, O and a bond;

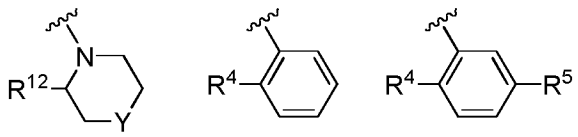
R^4 is selected from CF_3, fluoro, cyclopropyl and methyl;

R^5 is fluoro;

R^9 is selected from C_1-C_6alkyl, phenyl, and benzyl, each optionally substituted with one or more halogen; and

R^{12} is selected from hydrogen, methyl, cyclopropyl and CF_3.

According to aspect 9 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 7, wherein R^3 is selected from



Y is selected from NSO_2R^9, CH_2 and O;

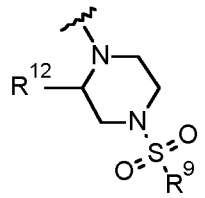
R^4 is selected from cyclopropyl, CF_3 and chloro;

R^5 is fluoro;

R^9 is selected from C_1-C_6alkyl, phenyl, and benzyl, each optionally substituted with one or more halogen; and

R^{12} is cyclopropyl or CF_3.

According to aspect 10 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 7, wherein R^3 is



R^9 is selected from C_1-C_6alkyl, phenyl, and benzyl, wherein said phenyl and benzyl group may optionally be substituted with one or more halogen, C_1-C_6alkyl, C_1-C_6haloalkyl and C_3-C_4cycloalkyl; and
R^{12} is selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl and C_3-C_4cycloalkyl.

According to aspect 11 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 10, wherein R^1 is selected from phenyl, pyrimidinyl, oxazolyl, imidazolyl, pyrazolyl and thiazolyl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_3-C_4cycloalkyl, and C_1-C_6haloalkyl.

According to aspect 12 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 11, wherein R^1 is selected from phenyl, pyrimidinyl, oxazolyl, imidazolyl, and thiazolyl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_3-C_4cycloalkyl, and C_1-C_6haloalkyl.

According to aspect 13 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 5, wherein R^3 is selected from A, phenyl, pyridyl, thienyl, furyl, pyrimidinyl and pyrazolyl, each optionally and independently substituted with one or more R^4 or R^5.

According to aspect 14 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 8, wherein R^3 is selected from A, phenyl and pyridyl, each optionally and independently substituted with one or more R^4 or R^5.

According to aspect 15 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 8, wherein R^3 is

selected from phenyl, pyridyl, morpholinyl, piperidyl, pyrrolidinyl, thienyl, and piperazinyl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl and C_3-C_4cycloalkyl.

According to aspect 16 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 7, wherein R^4, R^5, R^6 and R^7 are independently selected from fluoro, chloro, C_1-C_3alkyl, C_1-C_3fluoroalkyl, cyclopropyl and SO_2R^9.

According to aspect 17 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 8, aspect 13, aspect 14, or aspect 16, wherein Y is selected from CH_2, O and a bond.

According to aspect 18 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 7, or aspect 13, wherein R^{12} is selected from hydrogen, $CON(CH_3)_2$, C_1-C_3alkyl, CF_3 and cyclopropyl.

According to aspect 19 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 7, aspect 13, aspect 14, or aspect 16, wherein R^9 is selected from R^{10}, N,N-diC_1-C_3alkylamino and methoxyC_1-C_3alkyl, said C_1-C_3alkyl being optionally substituted with one R^{10}.

According to aspect 20 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 7, aspect 13, aspect 14, aspect 16, or aspect 19, wherein R^{10} is selected from phenyl, benzyl, pyridyl, imidazolyl, isoxazolyl, oxazolyl, cyclopropyl, cyclopentyl, pyrrolidinyl, and tetrahydrofuryl, each optionally substituted with one or more methyl and/or fluoro.

According to aspect 21 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 5, wherein R^3 is selected from phenyl, pyridyl, pyrrolidinyl and thienyl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl and C_3-C_4cycloalkyl; or A;

Y is CH_2, O, NSO_2-C_1-C_6alkyl or NSO_2-benzyl, wherein said benzyl is optionally substituted by one or more halogen; and
R^{12} is C_1-C_6alkyl or C_1-C_6haloalkyl.

According to aspect 22 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 3, wherein R^1 is phenyl or a monocyclic 5-6 membered heteroaryl each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_3-C_4cycloalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, amino, N-C_1-C_3alkylamino, N,N-di-C_1-C_3alkylamino and halogen;
R^2 is hydrogen;
R^3 is phenyl or monocyclic 5-6 membered heteroaryl each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl and C_3-C_4cycloalkyl.

According to aspect 23 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 7, wherein R^1 is phenyl or a monocyclic 5-6 membered heteroaryl each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_3-C_4cycloalkyl;
R^2 is hydrogen; and
R^3 is phenyl or monocyclic 5-6 membered heteroaryl each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl and C_3-C_4cycloalkyl.

According to aspect 24 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 5, wherein R^1 is selected from phenyl, pyrimidinyl, oxazolyl, imidazolyl, or thiazolyl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_3-C_4cycloalkyl;
R^2 is hydrogen;
R^3 is selected from phenyl, pyridyl, pyrazolyl pyrrolidinyl, and thienyl, each optionally substituted with one or more substituents selected from halogen,

C_1-C_6alkyl, C_1-C_6haloalkyl, C_3-C_4cycloalkyl; or A;
Y is CH_2, O, NSO_2-C_1-C_6alkyl or NSO_2-benzyl, wherein said benzyl is optionally substituted by one or more halogen; and
R^{12} is C_1-C_6alkyl or C_1-C_6haloalkyl.

According to aspect 25 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 7, wherein R^1 is selected from phenyl, 4-pyrimidinyl, 2-methylpyrimidin-4-yl, 2-cyclopropyl-pyrimidin-4-yl, 2 -oxazolyl, 1-methyl-imidazol-4-yl, 2-methyl-thiazol-4-yl, 3,5-difluorophenyl and 2-methylpyrazol-3-yl;
R^2 is hydrogen; and
R^3 is selected from 2-chlorophenyl, 3-pyridyl, 4-pyridyl, 4-morpholinyl, 3-(trifluoromethyl)morpholin-4-yl, 2-(trifluoromethyl)-piperidin-1-yl, 2-(trifluoromethyl)phenyl, 4-methyl-pyridin-3-yl, 2-(trifluoromethyl)-pyridin-3-yl, 1-ethyl-3-(trifluoromethyl)pyrazol-4-yl, 3-cyclopropyl-morpholin-4-yl, 4-[(4-fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazin-1-yl, 4-ethylsulfonyl-2-(trifluoromethyl)piperazin-1-yl, 2-(trifluoromethyl)-pyrrolidin-1-yl, 2-chloro-5-fluorophenyl, 3-(trifluoromethyl)-pyrazolin-4-yl, 2-(trifluoromethyl)-pyridin-3-yl, 3-methyl-thien-4-yl, 2-metylphenyl, 1-acetyl-3-trifluoromethyl-piperazin-4-yl , 2-methyl-piperidin-1-yl, 2-cyclopropyl-piperidin-1-yl, 2-methyl-morpholin-4-yl, 2-trifluoromethyl-morpholin-4-yl, and 2-cyclopropyl-morpholin-4-yl.

According to aspect 26 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 7, wherein R^1 is selected from phenyl, 4-pyrimidinyl, 2-methylpyrimidin-4-yl, 2-cyclopropyl-pyrimidin-4-yl, 2 -oxazolyl, 1-methyl-imidazol-4-yl, 2-methyl-thiazol-4-yl, and 3,5-difluorophenyl;
R^2 is hydrogen; and
R^3 is selected from 2-chlorophenyl, 3-pyridyl, 4-pyridyl, 4-morpholinyl, 3-(trifluoromethyl)morpholin-4-yl, 2-(trifluoromethyl)-piperidin-1-yl, 2-(trifluoromethyl)phenyl, 4-methyl-pyridin-3-yl, 2-(trifluoromethyl)-pyridin-3-yl, 1-ethyl-3-(trifluoromethyl)pyrazol-4-yl, 3-cyclopropyl-morpholin-4-yl, 4-[(4-fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazin-1-yl, 4-ethylsulfonyl-

2-(trifluoromethyl)piperazin-1-yl, 2-(trifluoromethyl)-pyrrolidin-1-yl, 2-chloro-5-fluorophenyl, 3-(trifluoromethyl)-pyrazolin-4-yl, 2-(trifluoromethyl)-pyridin-3-yl, 3-methyl-thien-4-yl, 2-metylphenyl, 1-acetyl-3-trifluoromethyl-piperazin-4-yl , 2-methyl-piperidin-1-yl, 2-cyclopropyl-piperidin-1-yl, 2-methyl-morpholin-4-yl, 2-trifluoromethyl-morpholin-4-yl, and 2-cyclopropyl-morpholin-4-yl.

According to aspect 27 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 7, wherein R^1 is phenyl or monocyclic 5-6 membered heteroaryl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_3-C_4cycloalkyl;
R^2 is hydrogen;
R^3 is phenyl or monocyclic 5-6 membered heteroaryl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_3-C_4cycloalkyl; and
Z is CH or N;
or a pharmaceutically acceptable salt thereof.

According to aspect 28 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 7, wherein R^1 is phenyl, or pyrimidinyl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_3-C_4cycloalkyl;
R^2 is hydrogen;
R^3 is selected from phenyl, pyridyl and pyrazolyl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_3-C_4cycloalkyl; or A;
Y is CH_2, O, NSO_2-C_1-C_6alkyl or NSO_2-benzyl, wherein said benzyl is optionally substituted by one or more halogen;
R^{12} is C_1-C_6alkyl or C_1-C_6haloalkyl; and
Z is CH or N;
or a pharmaceutically acceptable salt thereof.

According to aspect 29 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 7, wherein R^1 is phenyl, 3,5-diflurophenyl or 2-methylpyrimidin-4-yl;
R^2 is hydrogen;
R^3 is selected from 2-chlorophenyl, 3-pyridyl, 4-pyridyl, 1-morpholinyl, 2-(trifluoromethyl)-1-piperidyl, 3-(trifluoromethyl)morpholin-4-yl, 4-[(4-fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazin-1-yl, 4-ethylsulfonyl-2-(trifluoromethyl)piperazin-1-yl, 2-(trifluoromethyl)phenyl, 4-methyl-3-pyridyl, 2-(trifluoromethyl)-3-pyridyl, 1-ethyl-3-(trifluoromethyl)pyrazol-4-yl, and 3-cyclopropylmorpholin-4-yl; and
Z is CH or N;
or a pharmaceutically acceptable salt thereof.

According to aspect 30 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 7, wherein R^1 is phenyl or monocyclic 5-6 membered heteroaryl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_3-C_4cycloalkyl;
R^2 is hydrogen;
R^3 is phenyl or monocyclic 5-6 membered heteroaryl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_3-C_4cycloalkyl; and
Z is CH or N;
or a pharmaceutically acceptable salt thereof.

According to aspect 31 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 7, wherein R^1 is phenyl, or pyrimidinyl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_3-C_4cycloalkyl;
R^2 is hydrogen;
R^3 is selected from phenyl or pyridyl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_3-

C_4cycloalkyl; or A;
Y is CH_2, O, NSO_2-C_1-C_6alkyl or NSO_2-benzyl, wherein said benzyl is optionally substituted by one or more halogen;
R^{12} is C_1-C_6alkyl or C_1-C_6haloalkyl; and
Z is CH or N;
or a pharmaceutically acceptable salt thereof.

According to aspect 32 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 7, wherein R^1 is phenyl, 2-methylpyrimidin-4-yl, oxazol-2yl, 2-methylthiazol-4-yl, 2-methylpyrazol-3-yl, and 1-methylimidazol-4-yl;
R^2 is hydrogen;
R^3 is selected from 2-chlorophenyl, 3-pyridyl, 4-pyridyl, 1-morpholinyl, 2-(trifluoromethyl)-1-piperidyl, 3-(trifluoromethyl)morpholin-4-yl, 4-[(4-fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazin-1-yl, 4-ethylsulfonyl-2-(trifluoromethyl)piperazin-1-yl; 2-(trifluoromethyl)phenyl, 4-methyl-pyridin-3-yl, 2-(trifluoromethyl)-pyridin-3-yl and1-ethyl-3-(trifluoromethyl)pyrazol-4-yl; and
Z is CH or N;
or a pharmaceutically acceptable salt thereof.

According to aspect 33 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 7, wherein R^1 is phenyl, or 2-methylpyrimidin-4-yl;
R^2 is hydrogen;
R^3 is selected from 2-chlorophenyl, 3-pyridyl, 4-pyridyl, 1-morpholinyl, 2-(trifluoromethyl)-1-piperidyl, 3-(trifluoromethyl)morpholin-4-yl, 4-[(4-fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazin-1-yl, and 4-ethylsulfonyl-2-(trifluoromethyl)piperazin-1-yl; and
Z is CH or N;
or a pharmaceutically acceptable salt thereof.

According to aspect 34 of the invention, there is provided a compound

selected from:

4-(2-anilinopyrimidin-4-yl)-6-(2-chlorophenyl)-1H-pyridin-2-one;

4-(2-Anilinopyrimidin-4-yl)-6-(3-pyridyl)-1H-pyridin-2-one;

4-(2-Anilinopyrimidin-4-yl)-6-(4-pyridyl)-1H-pyridin-2-one

4-(2-anilinopyrimidin-4-yl)-6-morpholino-1H-pyridin-2-one;

4-[2-[(2-Methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)-1-piperidyl]-1H-pyridin-2-one;

4-(2-Anilinopyrimidin-4-yl)-6-[2-(trifluoromethyl)-1-piperidyl]-1H-pyridin-2-one;

4-[2-[(2-Methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one;

4-(2-Anilinopyrimidin-4-yl)-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one;

6-[4-[(4-Fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazin-1-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;

6-[4-Ethylsulfonyl-2-(trifluoromethyl)piperazin-1-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;

4-[2-(Oxazol-2-ylamino)-4-pyridyl]-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one;

4-[2-[(2-Methylthiazol-4-yl)amino]-4-pyridyl]-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one;

4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)¬phenyl]-1H-pyridin-2-one;

4-[2-[(2-Methylpyrazol-3-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)phenyl]-1H-pyridin-2-one;

4-[2-[(2-Methylthiazol-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)phenyl]-1H-pyridin-2-one;

6-(4-methyl-3-pyridyl)-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;

4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)-3-pyridyl]-1H-pyridin-2-one;

6-[1-ethyl-3-(trifluoromethyl)pyrazol-4-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;

4-[2-[(1-Methylimidazol-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)phenyl]-1H-pyridin-2-one; and
6-(2-chlorophenyl)-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one,
or a pharmaceutically acceptable salt thereof.

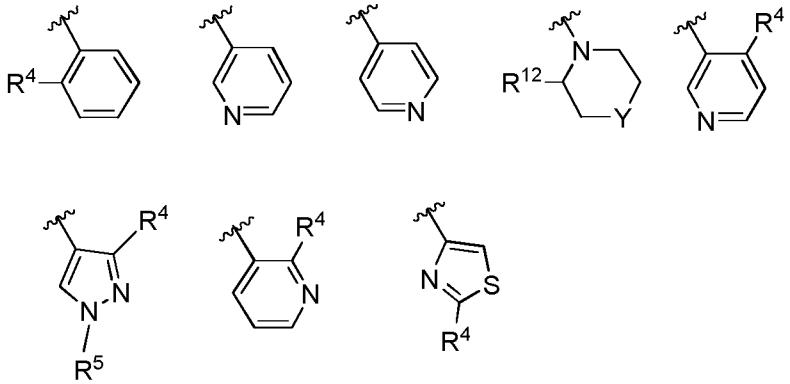
According to aspect 35 of the invention, there is provided a compound selected from:
4-(2-anilinopyrimidin-4-yl)-6-(2-chlorophenyl)-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-(3-pyridyl)-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-(4-pyridyl)-1H-pyridin-2-one
4-(2-anilinopyrimidin-4-yl)-6-morpholino-1H-pyridin-2-one;
4-[2-[(2-Methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)-1-piperidyl]-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-[2-(trifluoromethyl)-1-piperidyl]-1H-pyridin-2-one;
4-[2-[(2-Methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one;
6-[4-[(4-Fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazin-1-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;
6-[4-Ethylsulfonyl-2-(trifluoromethyl)piperazin-1-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;
4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)¬phenyl]-1H-pyridin-2-one;
6-(4-methyl-3-pyridyl)-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;
4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)-3-pyridyl]-1H-pyridin-2-one;
6-[1-ethyl-3-(trifluoromethyl)pyrazol-4-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;
6-(2-chlorophenyl)-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-

2-one; and
6-(3-cyclopropylmorpholin-4-yl)-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one,
or a pharmaceutically acceptable salt thereof.

According to aspect 36 of the invention, there is provided a compound selected from:
4-(2-anilinopyrimidin-4-yl)-6-(2-chlorophenyl)-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-(3-pyridyl)-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-(4-pyridyl)-1H-pyridin-2-one
4-(2-anilinopyrimidin-4-yl)-6-morpholino-1H-pyridin-2-one;
4-[2-[(2-Methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)-1-piperidyl]-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-[2-(trifluoromethyl)-1-piperidyl]-1H-pyridin-2-one;
4-[2-[(2-Methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one;
6-[4-[(4-Fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazin-1-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;
6-[4-Ethylsulfonyl-2-(trifluoromethyl)piperazin-1-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;
4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)¬phenyl]-1H-pyridin-2-one;
6-(4-methyl-3-pyridyl)-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;
4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)-3-pyridyl]-1H-pyridin-2-one;
6-[1-ethyl-3-(trifluoromethyl)pyrazol-4-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one; and
6-(2-chlorophenyl)-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one,

or a pharmaceutically acceptable salt thereof.

According to aspect 37 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 5, wherein R^3 is selected from



According to aspect 38 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 5, wherein R^4 is selected from chloro, CF_3 and methyl; R^5 is C_1-C_3alkyl, such as ethyl; and R^{12} is hydrogen or CF_3.

According to aspect 39 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 5, wherein Y is selected from CH2, O and NSO_2R^9.

According to aspect 40 of the invention, there is provided a compound of Formula (I), such as according to any one of aspects 1 to 5, wherein R^9 is selected from C_1-C_3alkyl and benzyl, said benzyl being meta-substituted with fluoro.

In one aspect of the invention, there is provided a compound according to the present invention, for use in the treatment or prophylaxis of a disease.

In one aspect of the invention, there is provided a compound according to the present invention, for use in treating cancer. Typically, said cancer is selected from breast cancer, such as triple negative breast cancer, bladder cancer, liver cancer, cervical cancer, pancreatic cancer, leukemia, lymphoma, renal

cancer, colon cancer, glioma, prostate cancer, ovarian cancer, melanoma and lung cancer, as well as hypoxic tumors.

In one aspect of the invention, there is provided a compound according to the present invention, for use in treating hypoxic tumors.

In one aspect of the invention, there is provided a compound according to the present invention, for use in treating type II diabetes.

In one aspect of the invention, there is provided a compound according to the present invention, for use in treating a disease selected from inflammatory diseases, neurodegenerative disorders, cardiovascular disorders, autoimmune diseases and viral infections.

In one aspect of the invention, there is provided use of a compound according to the present invention, in the preparation of a medicament for treating cancer. Typically said cancer is selected from breast cancer, such as triple negative breast cancer, bladder cancer, liver cancer, cervical cancer, pancreatic cancer, leukemia, lymphoma, renal cancer, colon cancer, glioma, prostate cancer, ovarian cancer, melanoma and lung cancer, as well as hypoxic tumors.

In one aspect of the invention, there is provided a compound according to the present invention, in the preparation of a medicament for treating hypoxic tumors.

In one aspect of the invention, there is provided use of a compound according to the present invention, in the preparation of a medicament for treating type II diabetes.

In one aspect of the invention, there is provided use of a compound according to the present invention, in the preparation of a medicament for treating a disease selected from inflammatory diseases, neurodegenerative disorders, cardiovascular disorders, autoimmune diseases and viral infections.

In one aspect of the invention, there is provided a method of treating cancer,

comprising administering a therapeutically effective amount of a compound according to the present invention, to a patient in need thereof. Typically, said cancer is selected from breast cancer, such as triple negative breast cancer, bladder cancer, liver cancer, cervical cancer, pancreatic cancer, leukemia, lymphoma, renal cancer, colon cancer, glioma, prostate cancer, ovarian cancer, melanoma and lung cancer, as well as hypoxic tumors.

In one aspect of the invention, there is provided a method of treating hypoxic tumors, comprising administering a therapeutically effective amount of a compound according to the present invention, to a patient in need thereof.

In one aspect of the invention, there is provided a compound according to the present invention, for use in treating cancer, wherein said cancer treatment further comprises radiation therapy.

In one aspect of the invention, there is provided a method of treating cancer, comprising administering a therapeutically effective amount of a compound according to the present invention, to a patient in need thereof, in conjunction with radiation therapy.

The compounds of the present invention may also be employed in cancer treatment in conjunction with radiation therapy and/or surgical intervention. Generally, the use of cytotoxic and/or cytostatic agents in combination with a compound or composition of the present invention will serve to:

(1) yield better efficacy in reducing the growth of a tumor or even eliminate the tumor as compared to administration of either agent alone,

(2) provide for the administration of lesser amounts of the administered chemotherapeutic agents,

(3) provide for a chemotherapeutic treatment that is well tolerated in the patient with fewer deleterious pharmacological complications than observed with single agent chemotherapies and certain other combined therapies,

(4) provide for treating a broader spectrum of different cancer types in

mammals, especially humans,

(5) provide for a higher response rate among treated patients,

(6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments,

(7) provide a longer time for tumor progression, and/or

(8) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other cancer agent combinations produce antagonistic effects.

In one aspect of the invention, there is provided a method of treating type II diabetes, comprising administering a therapeutically effective amount of a compound according to the present invention, to a patient in need thereof.

In one aspect of the invention, there is provided a method of treating a disease selected from inflammatory diseases, neurodegenerative disorders, autoimmune diseases and viral infections, comprising administering a therapeutically effective amount of a compound according to the present invention, to a patient in need thereof.

In one aspect of the invention, there is provided a pharmaceutical composition comprising a compound according to the present invention, and a pharmaceutically acceptable diluent, carrier and/or excipient.

In one aspect of the invention, there is provided a pharmaceutical composition, comprising a therapeutically effective amount of a compound according to the present invention and another anticancer agent selected from alkylating agents, antimetabolites, anticancer camptothecin derivatives, plant-derived anticancer agents, antibiotics, enzymes, platinum coordination complexes, tyrosine kinase inhibitors, hormones, hormone antagonists, monoclonal antibodies, interferons, and biological response modifiers.

As used herein, the term "C_1-C_6alkyl" means both linear and branched chain

saturated hydrocarbon groups with 1 to 6 carbon atoms. Examples of C_1-C_6alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, 4-methyl-butyl, n-hexyl, 2-ethyl-butyl groups. Among unbranched C_1-C_6alkyl groups, typical ones are methyl, ethyl, n-propyl, n-butyl, n-pentyl and n-hexyl groups. Among branched alkyl groups, there may be mentioned iso-propyl, iso-butyl, sec-butyl, t-butyl, 4-methyl-butyl and 2-ethyl-butyl groups.

As used herein, the term "C_1-C_3alkyl" means both linear and branched chain saturated hydrocarbon groups with 1 to 3 carbon atoms. Examples of C_1-C_3alkyl groups include methyl, ethyl, n-propyl and isopropyl groups.

As used herein, the term "C_1-C_6alkoxy" means the group O-C_1-C_6alkyl, where "C_1-C_6alkyl" is used as described above. Examples of C_1-C_6alkoxy groups include, but are not limited to, methoxy, ethoxy, isopropoxy, n-propoxy, n-butoxy, n-hexoxy, 3-methyl-butoxy groups.

As used herein, the term "C_1-C_3alkoxy" means the group O- C_1-C_3alkyl, where "C_1-C_3alkyl" is used as described above. Examples of C_1-C_3alkoxy groups include, but are not limited to, methoxy, ethoxy, isopropoxy and n-propoxy.

As used herein, the term "C_1-C_6haloalkyl" means both linear and branched chain saturated hydrocarbon groups, with 1 to 6 carbon atoms and with 1 to all hydrogens substituted by a halogen of different or same type. Examples of C_1-C_6haloalkyl groups include methyl substituted with 1 to 3 halogen atoms, ethyl substituted with 1 to 5 halogen atoms, n-propyl or iso-propyl substituted with 1 to 7 halogen atoms, n-butyl or iso-butyl substituted with 1 to 9 halogen atoms, and sec-butyl or t-butyl groups substituted with 1 to 9 halogen atoms.

As used herein, the term "C_1-C_3haloalkyl" means both linear and branched chain saturated hydrocarbon groups, with 1 to 3 carbon atoms and with 1 to all hydrogens substituted by a halogen of different or same type. Examples of C_1-C_3haloalkyl groups include methyl substituted with 1 to 3 halogen atoms, ethyl substituted with 1 to 5 halogen atoms, and n-propyl or iso-propyl

substituted with 1 to 7 halogen atoms.

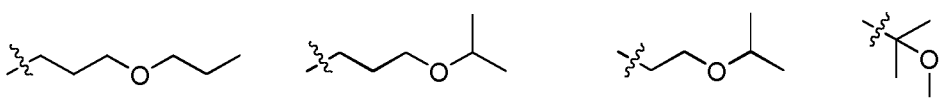
As used herein, the term "C_1-C_3haloalkoxy" means both linear and branched chain saturated alkoxy groups, with 1 to 3 carbon atoms and with 1 to all hydrogen atoms substituted by a halogen atom of different or same type. Examples of C_1-C_3haloalkoxy groups include methoxy substituted with 1 to 3 halogen atoms, ethoxy substituted with 1 to 5 halogen atoms, and n-propoxy or iso-propoxy substituted with 1 to 7 halogen atoms.

As used herein, the term "C_1-C_3fluorooalkyl" means both linear and branched chain saturated hydrocarbon groups, with 1 to 3 carbon atoms and with 1 to all hydrogen atoms substituted by a fluorine atom. Examples of C_1-C_3fluoroalkyl groups include methyl substituted with 1 to 3 fluorine atoms, ethyl substituted with 1 to 5 fluorine atoms, and n-propyl or iso-propyl substituted with 1 to 7 fluorine atoms.

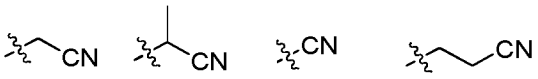
As used herein, the term "C_1-C_3fluorooalkoxy" means both linear and branched chain saturated alkoxy groups, with 1 to 3 carbon atoms and with 1 to all hydrogen atoms substituted by a fluorine atom. Examples of C_1-C_3fluoroalkoxy groups include methoxy substituted with 1 to 3 fluorine atoms, ethoxy substituted with 1 to 5 fluorine atoms, and n-propoxy or iso-propoxy substituted with 1 to 7 fluorine atoms.

As used herein, the term "C_3-C_6cycloalkyl" means a cyclic saturated hydrocarbon group, with 3 to 6 carbon atoms. Examples of C_3-C_6cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

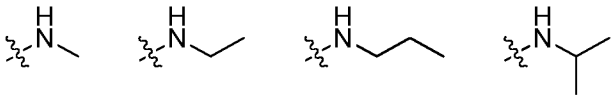
As used herein, the term "C_1-C_3alkoxyC_1-C_3alkyl" means both a linear and branched chain saturated hydrocarbon group, with 1 to 3 carbon atoms, substituted with an alkoxy group with 1 to 3 carbon atoms. Examples of C_1-C_3alkoxyC_1-C_3alkyl groups are drawn below.



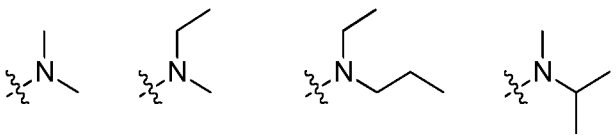
As used herein, the term "C_1-C_3cyanoalkyl" means both a linear and branched chain cyano (CN) derivative, with one to three carbon atoms including the carbon atom that is part of the cyano group. Examples of C_1-C_3cyanoalkyl groups are drawn below.



As used herein, the term N-C_1-C_3alkylamino means an amino substituent carrying one C_1-C_3alkyl group as defined supra. Examples of N-C_1-C_3alkylamino are drawn below.



As used herein, the term N,N-diC_1-C_3alkylamino means an amino substituent carrying two C_1-C_3alkyl groups as defined supra. Examples of N,N-diC_1-C_3alkylamino are drawn below.



As used herein, the term "halogen" means fluorine, chlorine, bromine or iodine. It is to be understood that when a substituent is halogen (or halo), it is always bound to a carbon atom.

As used herein, the term "aryl" means a monocyclic aromatic carbocyclic group. An examples of such group include phenyl.

As used herein, the term "monocyclic aryl" means a monocyclic aromatic carbocyclic group. Examples of monocyclic aryl groups include phenyl.

As used herein, the term "heteroaryl" means a monocyclic or bicyclic aromatic group of carbon atoms wherein from one to three of the carbon atoms is/are replaced by one or more heteroatoms independently selected from nitrogen, oxygen or sulfur. In a bicyclic aryl, one of the rings may be partially saturated.

Examples of such groups include indolinyl, dihydrobenzofuran and 1,3-benzodioxolyl.

As used herein, the term "monocyclic heteroaryl" means a monocyclic aromatic group of carbon atoms wherein from one to three of the carbon atoms is/are replaced by one or more heteroatoms independently selected from nitrogen, oxygen or sulfur.

Examples of monocyclic heteroaryl groups include, but are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazyl, isothiazolyl, isoxazolyl, pyrazinyl, pyrazolyl, and pyrimidinyl.

Examples of bicyclic heteroaryl groups include, but are not limited to, quinoxalinyl, quinazolinyl, pyridopyrazinyl, benzoxazolyl, benzothiophenyl, benzimidazolyl, naphthyridinyl, quinolinyl, benzofuryl, indolyl, indazolyl, benzothiazolyl, pyridopyrimidinyl, and isoquinolinyl.

As used herein, the term "heterocyclyl" means a cyclic group of carbon atoms wherein from one to three of the carbon atoms is/are replaced by one or more heteroatoms independently selected from nitrogen, oxygen and sulfur. Examples of heterocyclyl groups include, but are not limited to, tetrahydrofuryl, tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and dioxanyl.

Depending on the substituents present in compounds of the formula (I), the compounds may form salts which are within the scope of the present invention. Salts of compounds of formula (I), which are suitable for use in medicine are those wherein a counterion is pharmaceutically acceptable.

Suitable salts according to the invention include those formed with organic or inorganic acids or bases. In particular, suitable salts formed with acids according to the invention include those formed with mineral acids, strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, such

as saturated or unsaturated dicarboxylic acids, such as hydroxycarboxylic acids, such as amino acids, or with organic sulfonic acids, such as (C_1-C_4)alkyl or aryl sulfonic acids which are unsubstituted or substituted, for example by halogen. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, nitric, citric, tartaric, acetic, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, succinic, perchloric, fumaric, maleic, glycolic, lactic, salicylic, oxaloacetic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, benzenesulfonic, isethionic, ascorbic, malic, phthalic, aspartic, and glutamic acids, lysine and arginine.

Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts, for example those of potassium and sodium, alkaline earth metal salts, for example those of calcium and magnesium, and salts with organic bases, for example dicyclohexylamine, N-methyl-D-glucamine, morpholine, thiomorpholine, piperidine, pyrrolidine, a mono, di- or tri lower alkylamine, for example ethyl, tertbutyl, diethyl, diisopropyl, triethyl, tributyl or dimethylpropylamine, or a mono- ,di- or trihydroxy lower alkylamine, for example mono-, di- or triethanolamine. Corresponding internal salts may furthermore be formed.

The compounds of the invention may be used in the prophylaxis and/or treatment as such, or in a form of a pharmaceutical composition. While it is possible for the active ingredient to be administered alone, it is also possible for it to be present in a pharmaceutical composition. Accordingly, the invention provides a pharmaceutical composition comprising a compound of formula (I), and a pharmaceutically acceptable diluent, excipient and/or carrier. Pharmaceutical compositions of the invention may take the form of a pharmaceutical composition as described below.

Exemplary compositions for oral administration include suspensions which can contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity

enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which can contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate, calcium sulfate, sorbitol, glucose and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Disintegrators include without limitation starch, methylcellulose, agar, bentonite, xanthan gum and the like. The compounds of formula (I) can also be delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such compositions may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such compositions can also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g. Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. For oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like.

Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, pills or tablets each containing a predetermined amount of the active ingredient; as a powder or

granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid, for example as elixirs, tinctures, suspensions or syrups; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. The present compounds can, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release can be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The present compounds can also be administered liposomally.

Typical unit dosage compositions are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the compositions of this invention may include other agents conventional in the art having regard to the type of composition in question, for example those suitable for oral administration may include flavoring agents.

The compositions may be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Methods may include the step of bringing the active ingredient into association with the

carrier which constitutes one or more accessory ingredients. Compositions may be prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired composition.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, 1,2-dipalmitoylphosphatidylcholine, phosphatidyl ethanolamine (cephaline), phosphatidylserine, phosphatidylinositol, diphosphatidylglycerol (cardiolipin) or phosphatidylcholine (lecithin).

Compositions for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Exemplary compositions for parenteral administration include injectable solutions or suspensions which can contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as polyethylene glycol, ethanol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid, or Cremaphor.

Exemplary compositions for nasal, aerosol or inhalation administration include

solutions in saline, which can contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Compositions for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter, synthetic glyceride esters or polyethylene glycol. Such carriers are typically solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

Compositions for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavored basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerine or sucrose and acacia. Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

Compounds of formula (I) may be administered as the sole pharmaceutical agent or in combination with one or more additional therapeutic agents where the combination causes no unacceptable adverse effects. This pharmaceutical composition includes administration of a single pharmaceutical dosage composition which contains a compound of formula (I) and one or more additional therapeutic agents, as well as administration of the compound of formula (I) and each additional therapeutic agent in its own separate pharmaceutical dosage composition. For example, a compound of formula (I) and a therapeutic agent may be administered to the patient together in a single oral dosage composition such as a capsule or tablet, or each agent may be administered in compositions with separate dosage.

Where separate dosage compositions are used, the compound of formula (I) and one or more additional therapeutic agents may be administered at essentially the same time (e.g., concurrently) or at separately staggered times (e.g., sequentially).

The amount of active ingredient which is required to achieve a therapeutic

effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, including the type, species, age, weight, sex, and medical condition of the subject and the renal and hepatic function of the subject, and the particular disorder or disease being treated, as well as its severity. An ordinarily skilled physician, veterinarian or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 mg per kg of body weight per day (mg/kg/day) to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day, for adult humans. For oral administration, the compositions may be provided in the form of tablets or other forms of presentation provided in discrete units containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably from about 1 mg to about 100 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

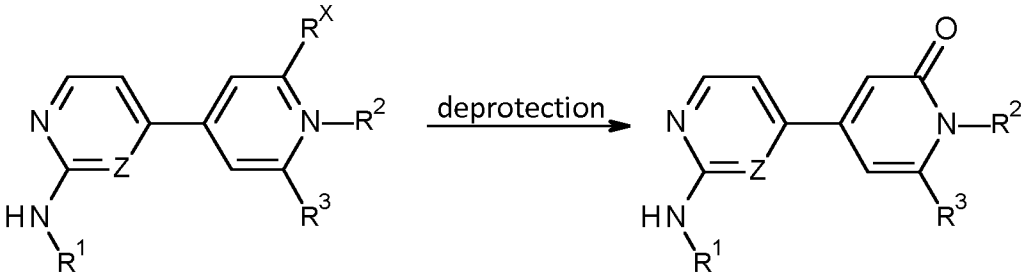
PREPARATION OF COMPOUNDS

The compounds in the present invention can be prepared as a free base or a pharmaceutically acceptable salt thereof by the process described below.

Throughout the following description of such processes it is understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are for example described in *Protective Groups in Organic Synthesis* by T.W. Greene, P.G.M Wutz, 4th Edition, Wiley-Interscience, New York, 2006. It is understood that microwaves can alternatively be used for the heating of reaction mixtures.

Another aspect of the present invention provides a process for preparing a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, and Zare, unless specified otherwise, as defined in herein. Said process comprises of:

(i) formation of a corresponding compound of formula (I)



(II) (I)

Scheme 1

A compound of formula (I) may be obtained (Scheme 1) by starting from, for example, a compound of formula (II), wherein R^X may be F, OCH_3, $OC(CH_3)_3$, or OSiR'R''R''' (wherein R', R'' and R''' are independently aryl (such as phenyl) or alkyl (such as methyl or *tert*-butyl)). If R^X is F the conversion into (I) may be carried out by for instance acidic hydrolysis using aqueous HCl. If R^X is OCH_3 the conversion into (I) may be carried out by reaction with for instance trimethylsilyl iodide in a suitable solvent such as chloroform or by reaction with HBr in a suitable solvent such as acetic acid or by reaction with

BBr_3 in a suitable solvent such as dichloromethane. If R^X is $OC(CH_3)_3$ the conversion into (I) may be carried out by reaction with for instance trifluoroacetic acid in a suitable solvent such as dichloromethane. If R^X is OSiR'R''R''' the conversion into (I) may be carried out by for instance HCl in a suitable solvent such as methanol or by using tetrabutyl ammonium fluoride in tetrahydrofuran. If enantiomerically pure or enriched compound (II) is used in this reaction, an enantiomerically pure or enantiomerically enriched compound (I) is obtained.

Compounds of formula (II) are commercially available compounds, or are known in the literature, or they are prepared by standard processes known in the art. A compound of formula (I) or (II) may be separated into its enantiomers by standard processes known in the art by for example chromatography on a chiral stationary phase.

GENERAL METHODS

All solvents used were of analytical grade and commercially available anhydrous solvents were routinely used for reactions. Starting materials were available from commercial sources, or prepared according to literature procedures. Room temperature refers to +20-25 °C. Solvent mixture compositions are given as volume percentages or volume ratios.
Microwave heating was performed in a Biotage Initiator microwave cavity producing continuous irradiation at 2.45 GHz. It is understood that microwaves may be used for the heating of reaction mixtures.
Straight phase chromatography was manually performed on Merck Silica gel 60 (0.040-0.063 mm), or automatically using an ISCO Combiflash® Companion ™ system using SiliaSep™ normal-phase flash columns using the solvent system indicated.
NMR spectra were recorded on a 400 MHz (or higher field) NMR spectrometer fitted with a probe of suitable configuration. Spectra were recorded at ambient temperature unless otherwise stated. Chemical shifts are given in ppm down- and upfield from TMS (0.00 ppm). The following

reference signals were used: the residual solvent signal of DMSO-d_6 δ 2.5, $CDCl_3$ δ 7.26 or Methanol-d_4 δ 3.31. Resonance multiplicities are denoted s, d, t, q, m and br for singlet, doublet, triplet, quartet, multiplet and broad, respectively.

High pressure liquid chromatography (HPLC) was performed on a reverse phase column. A linear gradient was applied using for example mobile phase A (aqueous 0.1% NH_3 or aqueous 0.1% acetic acid or aqueous 0.1% formic acid) and B (acetonitrile or methanol). Mass spectrometer (MS) analyses were performed in positive ion mode using electrospray ionization (ES+).

Preparative chromatography was run on a Gilson-PREP GX271 or GX281 with Trilution lc as software on a reverse phase column. A linear gradient was applied using for example mobile phase A (aqueous 0.1% NH_3 or aqueous 0.1% acetic acid or aqueous 0.1% formic acid) and B (acetonitrile or methanol).

Preparative chiral chromatography for separation of enantiomers was run on a Thar SFC using supercritical fluid chromatography on a chiral stationary phase. A linear gradient was applied using mobile phase A (carbon dioxide) and B (acetonitrile or methanol or ethanol or 2-propanol or any mixtures thereof). Additives (such as diethyl amine or isopropyl amine or ammonia or formic acid or TFA) may be used.

Compounds have been named using BIOVIA Draw 16.1.

ABBREVIATIONS

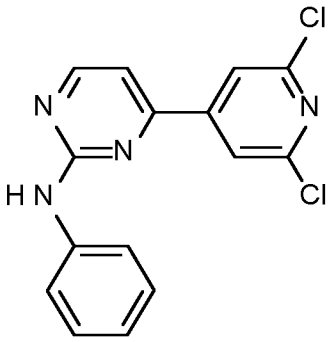
Amphos	(4-(N,N-Dimethylamino)phenyl)di-tert-butyl phosphine
anh.	anhydrous
aq.	aqueous
BuLi	butyl lithium
DCM	dichloromethane
DMAc	N,N-dimethyl acetamide
DME	1,2-Dimethoxyethane
DMF	N,N-dimethyl formamide
DMSO	dimethyl sulfoxide

EtOAc	ethyl acetate
EtOH	ethanol
h	hour(s)
HPLC	high pressure (or performance) liquid chromatography
KOtBu	potassium tert-butoxide
LCMS	liquid chromatography mass spectrometry
MeCN	acetonitrile
2-MeTHF	2-methyl tetrahydrofuran
MeOH	methanol
min.	minute(s)
NMR	nuclear magnetic resonance
Pd-118	Dichloro [1,1'- bis(di-tertbutylphosphino)ferrocene] palladium(II)
PEPPSI-iPr	1,3-Bis(2,6-Diisopropylphenyl)imidazol-2-ylidene](3chloro-pyridyl)palladium(II) dichloride
$Pd(OAc)_2$	palladium(II) acetate
$PdCl_2(dppf)$	[1,1′-Bis(diphenylphosphino)-ferrocene]-dichloro-palladium(II)
quant.	quantitative
rt	room temperature
sat.	saturated
TFA	trifluoroacetic acid
THF	tetrahydrofuran

EXAMPLES

Example 1

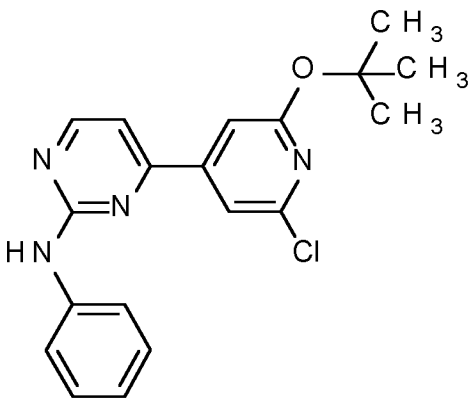
4-(2,6-Dichloro-4-pyridyl)-N-phenyl-pyrimidin-2-amine



2,6-Dichloropyridine-4-carboxylic acid (2.88 g, 15 mmol) was taken up in 1,4-Dioxane (75 ml) and oxalyl chloride (1.35 ml, 15.75 mmol) was added. The resulting mixture was stirred at 50 °C for 5 min then DMF (3 drop) was added and stirring continued for 45 min. When cooled to rt, $PdCl_2(PPh_3)_2$ (210 mg, 0.3 mmol), CuI (114 mg, 0.6 mmol), ethynyltrimethylsilane (2.12 ml, 15 mmol) and triethylamine (6.26 ml, 45 mmol) were added and the mixture stirred at rt for 30 min. Phenylguanidinium nitrate (2.97 g, 15 mmol), K_2CO_3 (5.18 g, 37.5 mmol) and 2-ethoxyethan-1-ol (15 ml) were added and the resulting mixture was refluxed overnight. When cooled to rt the mixture was filtered through a pad of silica gel eluted with DCM/MeOH/NH_3 (100:3:1) to give the product as a black gum. Recrystallization from MeOH gave the product as a solid (3.03 g, 64%). MS ES+ *m/z* 317 $[M+H]^+$.

Example 2

4-(2-Tert-butoxy-6-chloro-4-pyridyl)-N-phenyl-pyrimidin-2-amine

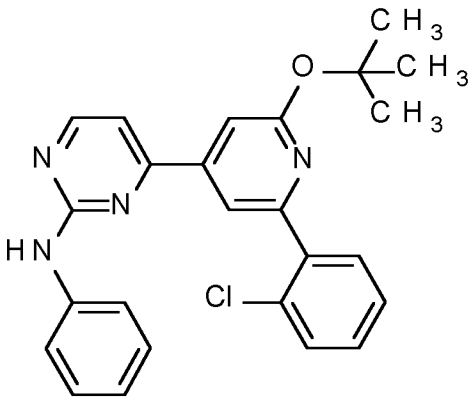


4-(2,6-Dichloropyridin-4-yl)-N-phenylpyrimidin-2-amine (3 g, 9.46 mmol), 4Å molecular sieves (3 g) and KOtBu (2.65 g, 23.65 mmol) were taken up in

Toluene (50 ml) and the resulting mixture was stirred at 90 °C for 3 h. When cooled to rt water (50 ml), aq. 2M HCl (20 ml) and EtOAc (50 ml) were added and the resulting precipitate was filtered off and discarded. The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 25 ml). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was taken up in DCM (50 ml) together with active charcoal and the mixture was stirred at rt for 15 min. Filtration through celite and concentration of the filtrate gave the product as a gum (1.5 g, 45%). MS ES+ *m/z* 355 $[M+H]^+$.

Example 3

4-[2-Tert-butoxy-6-(2-chlorophenyl)-4-pyridyl]-N-phenyl-pyrimidin-2-amine

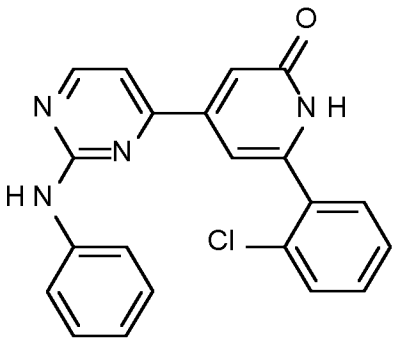


4-[2-(Tert-butoxy)-6-chloropyridin-4-yl]-N-phenylpyrimidin-2-amine (650 mg, 1.13 mmol), (2-chlorophenyl)boronic acid (344 mg, 2.2 mmol), Pd-118 (60 mg, 0.09 mmol) and K_2CO_3 (760 mg, 5.5 mmol) were taken up in DME:H_2O:EtOH (6:3:1, 15 ml) and the resulting mixture was stirred at 75 °C overnight. More (2-chlorophenyl)boronic acid (344 mg, 2.2 mmol) and Pd-118 (60 mg, 0.09 mmol) were added and the mixture stirred at 75 °C for 4 h. When cooled to rt the mixture was concentrated and the resulting residue was taken up in water (20 ml) and EtOAc (50 ml). The mixture was stirred at rt for 10 min and then filtered. To the filtrate was added EtOAc (20 ml) and the organic layer separated. The aqueous layer was extracted with EtOAc (2 x 10 ml) and the combined organics were washed with brine, dried over Na_2SO_4,

filtered, concentrated and purified on a silica gel column eluted with 0-50% EtOAc in Heptane, followed by preparative HPLC to give the product as a solid (140 mg, 18%). MS ES+ *m/z* 431 $[M+H]^+$.

Example 4

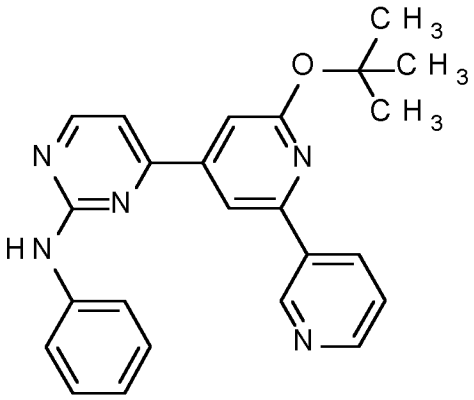
4-(2-anilinopyrimidin-4-yl)-6-(2-chlorophenyl)-1H-pyridin-2-one



TFA (0.1 ml, 1.35 mmol) was added to a solution of 4-[2-(tert-butoxy)-6-(2-chlorophenyl)pyridin-4-yl]-N-phenylpyrimidin-2-amine (130 mg, 0.3 mmol) in DCM (8 ml) at rt and the resulting mixture was stirred at rt for 2 h. More TFA (0.1 ml, 1.35 mmol) was added and stirring continued for 2 h. The mixture was concentrated and the resulting residue was taken up in MeOH (10 ml). NH_4OH (28%, 3 ml) was added and the mixture stirred at rt for 1 h. The precipitate was filtered off, washed with water, MeOH and dried. The solid was dissolved in boiling pyrdine (15 ml) and allowed to cool to rt. To the cloudy solution was added MeOH (10 ml), with stirring, and after 10 min at rt the mixture was cooled in refrigerator for 15 min. The resulting precipitate was filtered off, washed sequentially with MeOH and Pentane and dried to give the product as a solid (30 mg, 25%). ^1H NMR (500 MHz, DMSO-d6) δ ppm 12.15 (s, 1H), 9.77 (s, 1H), 8.62 (d, 1H), 7.79 (d, 2H), 7.69 – 7.56 (m, 2H), 7.51 (dq, 2H), 7.30 (q, 2H), 7.18 (s, 1H), 6.97 (t, 1H). MS ES+ *m/z* 375 $[M+H]^+$.

Example 5

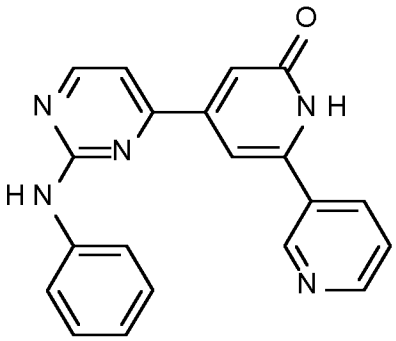
4-[2-Tert-butoxy-6-(3-pyridyl)-4-pyridyl]-N-phenyl-pyrimidin-2-amine



The title compound was prepared as described in Example 3, using (pyridin-3-yl)boronic acid, to give the product (435 mg, 97%). MS ES+ *m/z* 398 $[M+H]^+$.

Example 6

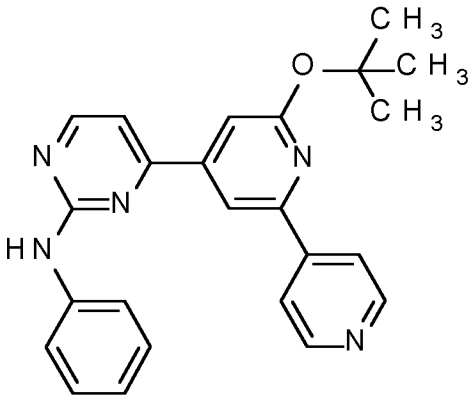
4-(2-Anilinopyrimidin-4-yl)-6-(3-pyridyl)-1H-pyridin-2-one,



The title compound was prepared as described in Example 4, recrystallized from 2-propanol, to give the product as a solid (14 mg, 14%). ^{1}H NMR (500 MHz, DMSO-d6) δ ppm 12.08 (s, 1H), 9.81 (s, 1H), 9.14 (s, 1H), 8.72 – 8.58 (m, 2H), 8.31 (d, 1H), 7.82 (d, 2H), 7.68 – 7.51 (m, 3H), 7.38 – 7.27 (m, 3H), 6.99 (t, 1H). MS ES+ *m/z* 342 $[M+H]^+$.

Example 7

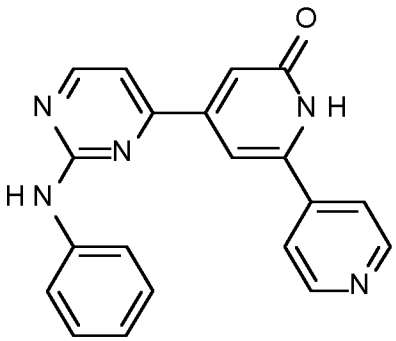
4-[2-Tert-butoxy-6-(4-pyridyl)-4-pyridyl]-N-phenyl-pyrimidin-2-amine



The title compound was prepared as described in Example 3, using (pyridin-4-yl)boronic acid, to give the product (100 mg, 64%). MS ES+ *m/z* 398 $[M+H]^+$.

Example 8

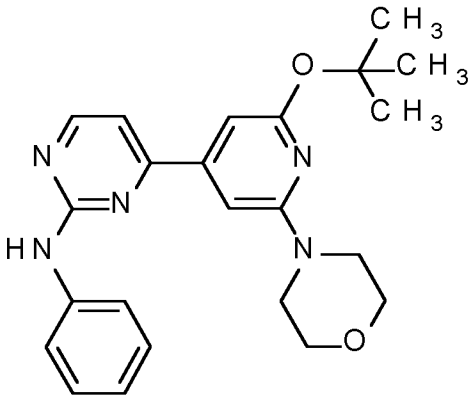
4-(2-Anilinopyrimidin-4-yl)-6-(4-pyridyl)-1H-pyridin-2-one



The title compound was prepared as described in Example 4, recrystallized from 2-propanol, to give the product as a solid (20 mg, 21%). ^{1}H NMR (500 MHz, DMSO-d6) δ ppm 11.85 (s, 1H), 9.83 (s, 1H), 8.76 (d, 2H), 8.67 (d, 1H), 7.98 (s, 2H), 7.82 (d, 2H), 7.62 (d, 1H), 7.44 – 7.24 (m, 3H), 7.00 (t, 1H). MS ES+ *m/z* 342 $[M+H]^+$.

Example 9

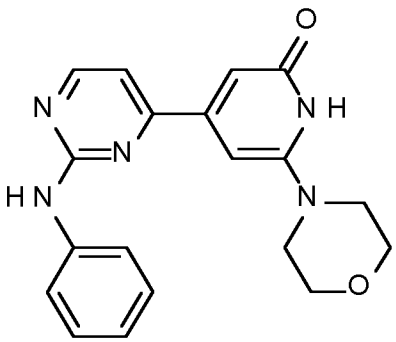
4-(2-Tert-butoxy-6-morpholino-4-pyridyl)-N-phenyl-pyrimidin-2-amine



4-(2-Tert-butoxy-6-chloro-4-pyridyl)-N-phenyl-pyrimidin-2-amine (190 mg, 0.54 mmol), $Pd(OAc)_2$ (8 mg, 0.04 mmol) and XantPhos (19 mg, 0.03 mmol) were dissolved in Toluene (6 ml). Morpholine (185 µl, 2.14 mmol) and KOtBu (180 mg, 1.61 mmol) were added and the resulting mixture was stirred at 100 °C overnight. When cooled to rt, EtOAc and brine were added, the organic layer separated and the aqueous layer extracted with EtOAc. The combined organics were washed with brine, dried over $MgSO_4$, filtered, concentrated and purified on a silica gel column eluted with 20% EtOAc in Heptane to give the product (60 mg, 28%). MS ES+ *m/z* 406 $[M+H]^+$.

Example 10

4-(2-anilinopyrimidin-4-yl)-6-morpholino-1H-pyridin-2-one

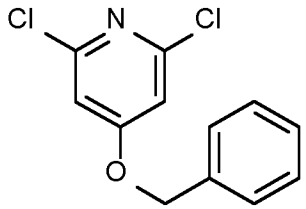


The title compound was prepared as described in Example 4 to give the product as a solid (26 mg, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.33 (s, 1 H) 3.47 (br. s., 4 H) 3.65 - 3.79 (m, 4 H) 6.62 (s, 1 H) 6.85 (br. s., 1 H)

6.97 (t, 1 H) 7.31 (t, 2 H) 7.42 (s, 1 H) 7.82 (d, 2 H) 8.58 (d, 1 H) 9.72 (s, 1 H). MS ES+ *m/z* 350 $[M+H]^+$.

Example 11

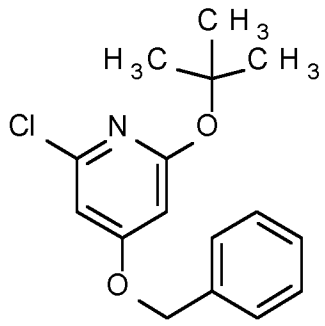
4-Benzyloxy-2,6-dichloro-pyridine



60% NaH (945mg, 24.7mmol) was added portion wise to a solution of 2,4,6-trichloropyridine (4.5 g, 24.7mmol) in DMF (25 ml) at 0°C. After 20 min phenylmethanol (2.7 g, 24.7mmol) was added dropwise and the mixture was stirred for 3h. Water (30 ml) was added and the precipitate was filtered off. The solid was dissolved in EtOAc, dried over $MgSO_4$, filtered and concentrated to give
the product as a solid (5 g, 80%). MS ES+ *m/z* 254 $[M+H]^+$.

Example 12

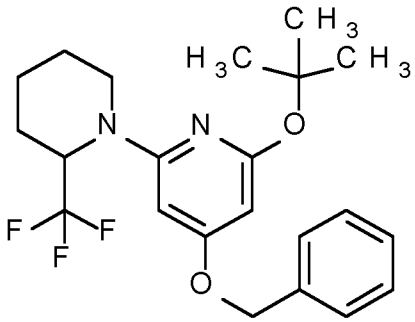
4-Benzyloxy-2-tert-butoxy-6-chloro-pyridine



4-Benzyloxy-2,6-dichloro-pyridine (5 g, 19.7mmol) and KOtBu (2.2 g, 19.7mmol) were dissolved in dry 2-MeTHF (25 ml) and the mixture was stirred at 70 °C for 2h. When cooled to rt the mixture was filtered, concentrated and purified on a silica gel column eluted with 30% EtOAc in Heptane to give the product (4 g, 70%). MS ES+ *m/z* 292 $[M+H]^+$.

Example 13

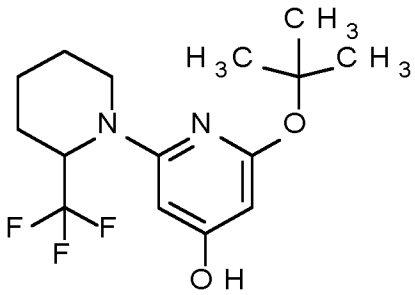
4-Benzyloxy-2-tert-butoxy-6-[2-(trifluoromethyl)-1-piperidyl]pyridine



4-Benzyloxy-2-tert-butoxy-6-chloro-pyridine (4 g, 13.7mmol), 2-(trifluoromethyl)piperidine (2.3 g, 15.1mmol), PEPPSI-iPr (146 mg, 1.37mmol) and KOtBu (3.85 g, 34.3mmol) were taken up in 1,4-Dioxane (30ml) and the mixture was stirred at 90 °C for 2h. When cooled to rt water and EtOAc weres added and the organic layer separated, filtered, concentrated and purified on silica gel column eluted with 30% EtOAc in Heptane to give the product (4.1 g, 73%). MS ES+ *m/z* 409 $[M+H]^+$.

Example 14

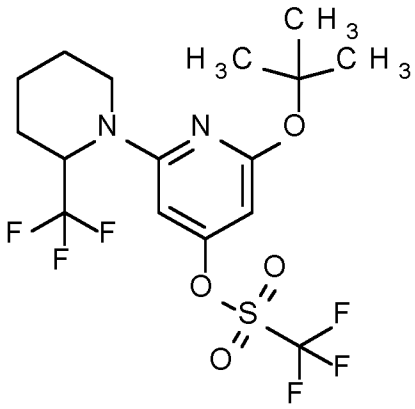
2-Tert-butoxy-6-[2-(trifluoromethyl)-1-piperidyl]pyridin-4-ol



A mixture of 4-benzyloxy-2-tert-butoxy-6-[2-(trifluoromethyl)-1-piperidyl]pyridine (3.5 g, 8.57mmol) and 10% Pd/C (600 mg, 0.56 mmol) in MeOH and EtOAc was hydrogenated (1.5 bar) at rt for 2 h. The mixture was filtered through celite and concentrated to give the product (2.7 g, quant.). MS ES+ *m/z* 319 $[M+H]^+$.

Example 15

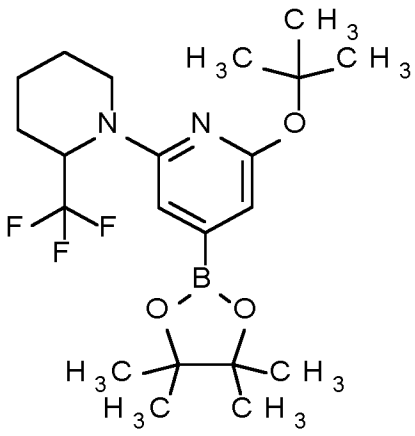
[2-Tert-butoxy-6-[2-(trifluoromethyl)-1-piperidyl]-4-pyridyl] trifluoromethanesulfonate



2-Tert-butoxy-6-[2-(trifluoromethyl)-1-piperidyl]pyridin-4-ol (2.7 g, 8.48mmol) and Et_3N (1.66 ml, 11.9 mmol) was taken up in DCM (20 mL) at 0°C. Trifluoromethylsulfonyl trifluoromethanesulfonate (2.54 ml, 11.9 mmol) was added dropwise over 5 minutes and stirred for 1 h. The mixture was washed with sat. aq. $NaHCO_3$ (2× 20 mL), concentrated and purified on silica gel column eluted with 20% EtOAc in Heptane to give the product (3.5 g, 92%). MS ES+ *m/z* 451 $[M+H]^+$.

Example 16

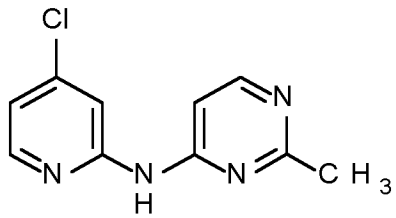
2-Tert-butoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-[2-(trifluoromethyl)-1-piperidyl]pyridine



4,4,5,5-Tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (2.96 g, 11.7mmol), [2-tert-butoxy-6-[2-(trifluoromethyl)-1-piperidyl]-4-pyridyl] trifluoromethanesulfonate (3.5 g, 7.77 mmol), KOAc (1.14 g, 11.7 mmol) and $PdCl_2$(dppf) (215 mg, 0.29 mmol) were taken up in Toluene (10 ml) and stirred at 90 °C for 5h. When cooled to rt the mixture was concentrated and the residue dissolved in EtOAc, washed with water, concentrated and purified on silica gel column eluted with 0-60% EtOAc in Heptane to give the product (2.15 g, 65%). MS ES+ *m/z* 347 $[M+H]^+$.

Example 17

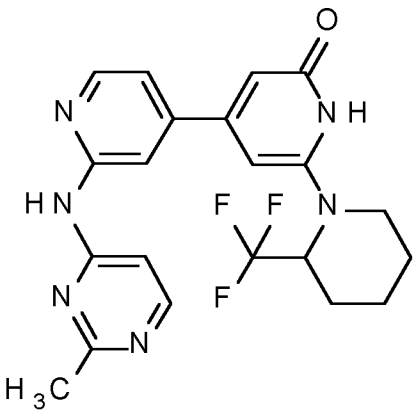
N-(4-chloro-2-pyridyl)-2-methyl-pyrimidin-4-amine



2-Bromo-4-chloro-pyridine (250 mg, 1.25 mmol), 2-methylpyrimidin-4-amine (107 mg, 0.9 mmol), $PdCl_2$(dppf) (14 mg, 0.015 mmol) and dppf (43 mg, 0.07 mmol) were taken up in Toluene. 1M KOtBu (167 mg, 1.4 mmol) in THF was added and the resulting mixture stirred at 110°C overnight. Work up and purification on a silica gel column chromatography gave the product as a solid (100 mg, 36%). MS ES+ *m/z* 221 $[M+H]^+$.

Example 18

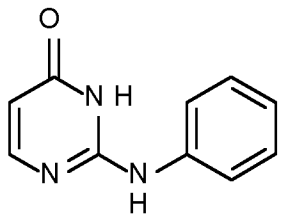
4-[2-[(2-Methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)-1-piperidyl]-1H-pyridin-2-one



1-[3-Tert-butoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-(trifluoromethyl)piperidine (100 mg, 0.23 mmol), K_2CO_3 (81 mg, 0.59 mmol), N-(4-chloro-2-pyridyl)-2-methyl-pyrimidin-4-amine (52 mg, 0.23 mmol) and $PdCl_2$(dppf) (15 mg, 0.02 mmol) were dissolved in 1,4-Dioxane (3 ml) and water (1 ml) and the resulting mixture was stirred at 90 °C for 2 h. When cooled to rt water and EtOAc were added and the organic layer separated and concentrated. The residue was dissolved in DCM (3 ml), TFA (0.5 ml, 6.7 mmol) was added and the mixture stirred at rt for 30 min. The mixture was concentrated, dissolved in MeOH, filtered and purified by preparative HPLC to give the product as a solid (7 mg, 6%). ^{1}H NMR (500 MHz, METHANOL-d4) δ ppm 1.17 - 1.33 (m, 1 H), 1.54 - 1.66 (m, 1 H), 1.68 - 1.77 (m, 2 H), 1.81 (br d, 3 H), 2.08 (br d, 1 H), 2.57 (s, 3 H), 3.15 - 3.29 (m, 1 H), 3.86 (br d, 1 H), 5.16 (br s, 1 H), 6.21 - 6.27 (m, 2 H), 7.17 (dd, 1 H), 7.38 (d, 1 H), 8.07 (br s, 1 H), 8.23 (d, 1 H), 8.32 (d, 1 H). MS ES+ *m/z* 431 $[M+H]^+$.

Example 19

2-Anilino-1H-pyrimidin-6-one

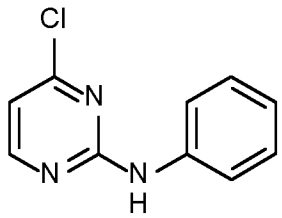


2-Methylsulfanyl-1H-pyrimidin-6-one (5 g, 35.21 mmol) and aniline (3.2 g, 35.21 mmol) were taken up in Diglyme (50 ml) and the resulting mixture was

stirred at 170 °C for 5 h. When cooled to rt water was added and the formed precipitate was filtered off, washed with water and dried to give the product as a solid (3 g, 46%). MS ES+ *m/z* 188 $[M+H]^+$.

Example 20

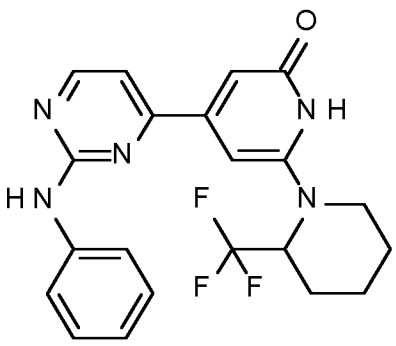
4-chloro-N-phenyl-pyrimidin-2-amine



PCl_5 (1 g, 5.34 mmol) was added portion wise to a solution of 2-Anilino-1H-pyrimidin-6-one (1.5 g, 5.34 mmol) in $POCl_3$ (5 ml) and the resulting mixture was stirred at 110 °C overnight. When cooled to rt ice/water were added and the mixture extracted with EtOAc. The combined organics were dried over Na_2SO_4, filtered, concentrated and purified on a silica gel column to give the product as a solid (840 mg, 76%). MS ES+ *m/z* 206 $[M+H]^+$.

Example 21

4-(2-Anilinopyrimidin-4-yl)-6-[2-(trifluoromethyl)-1-piperidyl]-1H-pyridin-2-one

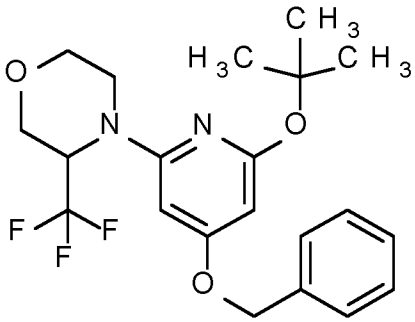


The title compound was prepared as described in Example 18, using 4-chloro-N-phenyl-pyrimidin-2-amine, to give the product as a solid (11 mg, 8%). ^{1}H NMR (500 MHz, DMSO-d6) δ ppm 1.52 (br s, 1 H), 1.70 (br s, 2 H), 1.78 (br d, 2 H), 2.02 (br d, 1 H), 3.09 (br t, 1 H), 4.22 (br s, 1 H), 5.54 (br s, 1

H), 6.65 (s, 1 H), 6.95 - 7.04 (m, 2 H), 7.31 (t, 2 H), 7.44 (d, 1 H), 7.83 (d, 2 H), 8.60 (d, 1 H), 9.72 (s, 1 H), 10.47 (br s, 1 H). MS ES+ *m/z* 416 $[M+H]^+$.

Example 22

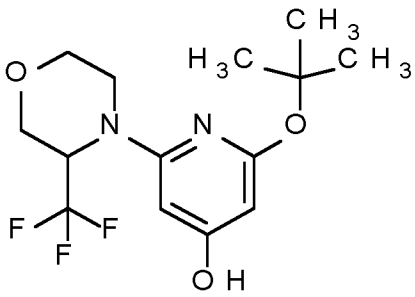
4-(4-Benzyloxy-6-tert-butoxy-2-pyridyl)-3-(trifluoromethyl)morpholine



The title compound was prepared as described in Example 13, using 3-(trifluoromethyl)morpholine, to give the product as an oil (1 g, 50%). MS ES+ *m/z* 411 $[M+H]^+$.

Example 23

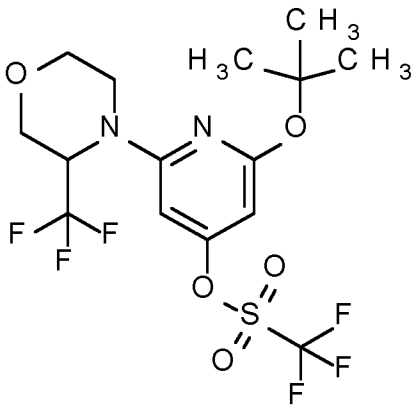
2-tert-Butoxy-6-[3-(trifluoromethyl)morpholin-4-yl]pyridin-4-ol



The title compound was prepared as described in Example 14 to give the product (780 mg, 99%). MS ES+ *m/z* 321 $[M+H]^+$.

Example 24

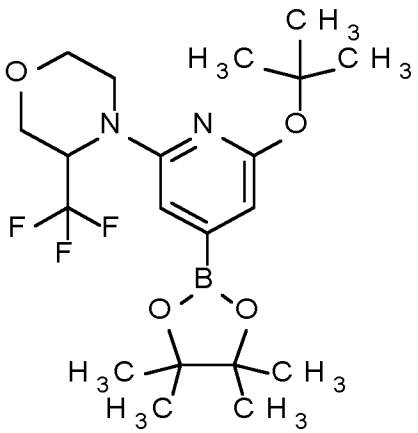
[2-tert-Butoxy-6-[3-(trifluoromethyl)morpholin-4-yl]-4-pyridyl] trifluoromethanesulfonate



The title compound was prepared as described in Example 15 to give the product as an oil (800 mg, 81%). MS ES+ *m/z* 453 $[M+H]^+$.

Example 25

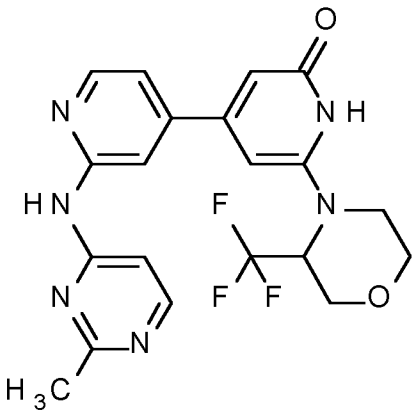
4-[6-tert-Bbutoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]-3-(trifluoromethyl)morpholine



The title compound was prepared as described in Example 16 to give the product (270 mg, 33%). MS ES+ *m/z* 431 $[M+H]^+$.

Example 26

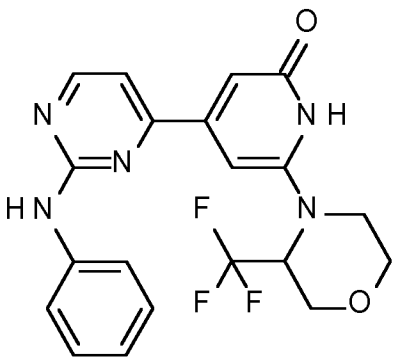
4-[2-[(2-Methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one



The title compound was prepared as described in Example 18, using 4-[6-tert-butoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]-3-(trifluoromethyl)morpholine, to give the product as a solid (6 mg, 6%). ^{1}H NMR (500 MHz, METHANOL-d_4) δ ppm 2.52 - 2.62 (m, 3 H), 3.50 - 3.69 (m, 2 H), 3.70 - 3.85 (m, 2 H), 4.04 (dd, 1 H), 4.30 (d, 1 H), 5.05 - 5.19 (m, 1 H), 6.34 (m, 2 H), 7.20 (dd, 1 H), 7.45 (d, 1 H), 8.04 (s, 1 H), 8.25 (d, 1 H), 8.30 - 8.40 (m, 1 H). MS ES+ *m/z* 433 $[M+H]^+$.

Example 27

4-(2-Anilinopyrimidin-4-yl)-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one

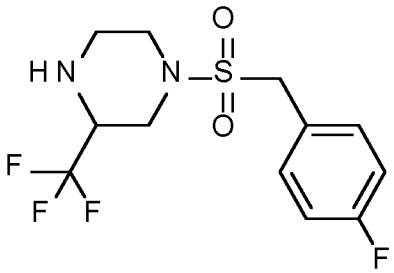


The title compound was prepared as described in Example 18, using 4-[6-tert-butoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]-3-(trifluoromethyl)morpholine and 4-chloro-N-phenyl-pyrimidin-2-amine, to give the product as a solid (15 mg, 17%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 3.33 - 3.38 (m, 1 H), 3.53 - 3.59 (m, 1 H), 3.77 (br d, 1 H), 4.00 (br dd, 2 H),

4.21 (d, 1 H), 5.29 (br dd, 1 H), 6.71 (s, 1 H), 6.96 (s, 1 H), 6.98 - 7.01 (m, 1 H), 7.32 (t, 2 H), 7.43 (d, 1 H), 7.84 (d, 2 H), 8.61 (d, 1 H), 9.72 (s, 1 H), 10.33 - 10.82 (m, 1 H). MS ES+ *m/z* 418 $[M+H]^+$.

Example 28

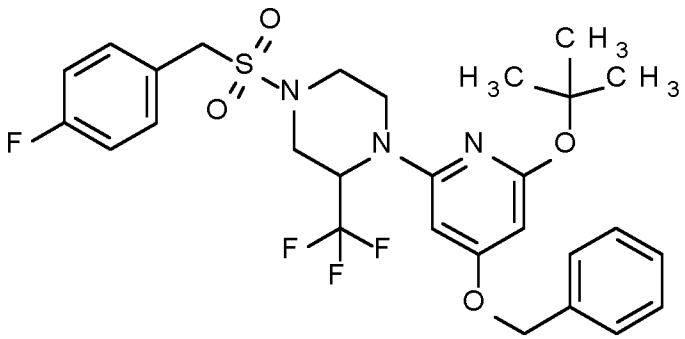
1-[(4-Fluorophenyl)methylsulfonyl]-3-(trifluoromethyl)piperazine



2-(Trifluoromethyl)-piperazine (2 g, 13 mmol) and TEA (2.17 ml, 15.6 mmol) were dissolved in DCM (30 ml). (4-fluorophenyl)methanesulfonyl chloride (2.71 g, 13 mmol) was added in small portions at 0 °C and the mixture was stirred at rt overnight. Water (45 ml) was added and the mixture extracted with DCM (2 x 80 ml). The combined organics were washed twice with brine, dried over Na_2SO_4, filtered and concentrated to give the product as a solid (3.5 g, 83%). MS ES+ *m/z* 327 $[M+H]^+$.

Example 29

1-(4-Benzyloxy-6-tert-butoxy-2-pyridyl)-4-[(4-fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazine

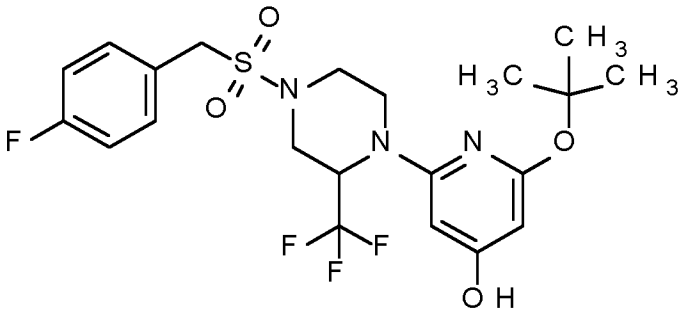


A mixture of 1-[(4-fluorophenyl)methylsulfonyl]-3-(trifluoromethyl)piperazine (1.2 g, 3.68 mmol), 4-benzyloxy-2-tert-butoxy-6-chloro-pyridine (1.34 g, 4.6

mmol), Cs_2CO_3 (2.4 g, 7.35 mmol), XantPhos (206 mg, 0.37 mmol) and $Pd(OAc)_2$ (83 mg, 0.37 mmol) in anh. degassed 1,4-dioxane (50 ml) was refluxed overnight under argon. Water was added and the mixture extracted with EtOAc. The combined organics were dried over Na_2SO_4, filtered, concentrated and purified on a silica gel column, eluted with 0-100% EtOAc in Heptane, to give the product (1.25 g, 58%). MS ES+ *m/z* 582 $[M+H]^+$.

Example 30

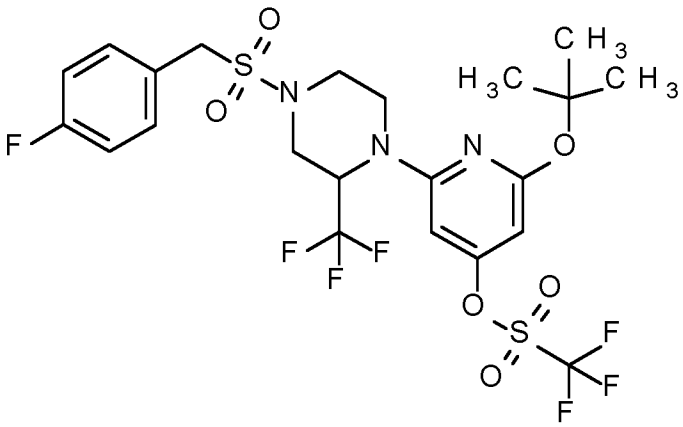
2-tert-Butoxy-6-[4-[(4-fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazin-1-yl]pyridin-4-ol



The title compound was prepared as described in Example 14 to give the product (1.22 g, 96%). MS ES+ *m/z* 492 $[M+H]^+$.

Example 31

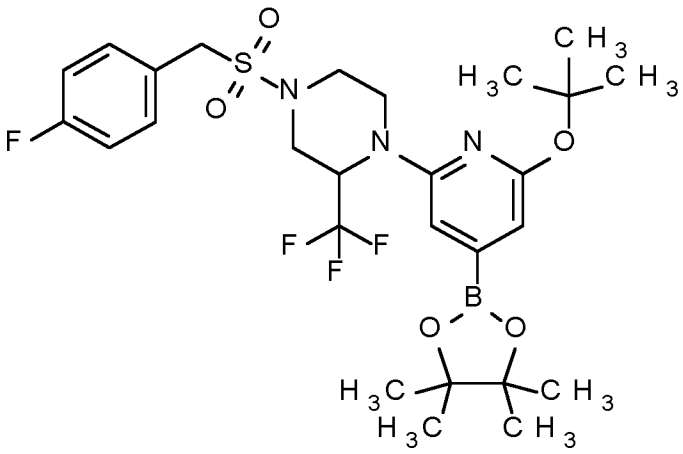
[2-tert-Butoxy-6-[4-[(4-fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazin-1-yl]-4-pyridyl] trifluoromethanesulfonate



The title compound was prepared as described in Example 15 to give the product (700 mg, 45%). MS ES+ *m/z* 624 $[M+H]^+$.

Example 32

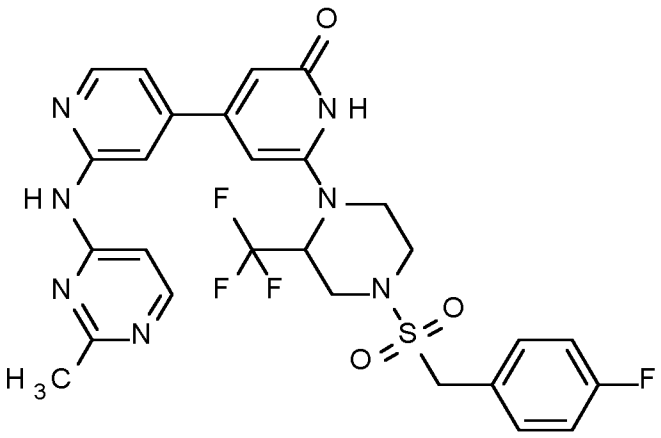
1-[6-tert-Butoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]-4-[(4-fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazine



The title compound was prepared as described in Example 16 to give the product (490 mg, 73%). MS ES+ *m/z* 602 $[M+H]^+$.

Example 33

6-[4-[(4-Fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazin-1-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one

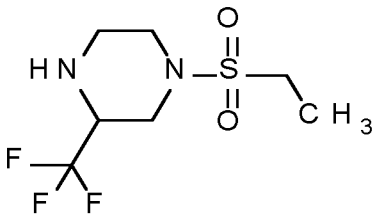


The title compound was prepared as described in Example 18, using 1-[6-tert-Butoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]-4-[(4-

fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazine, to give the product as a solid (14 mg, 14%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.85 - 2.94 (m, 1 H), 3.15 (br d, 1 H), 3.13 - 3.14 (m, 1 H), 3.17 - 3.18 (m, 1 H), 3.22 (br t, 1 H), 3.27 - 3.31 (m, 1 H), 3.62 (br d, 1 H), 3.89 (br d, 1 H), 4.33 (br d, 1 H), 4.52 (s, 2 H), 5.57 (br s, 1 H), 6.31 (s, 1 H), 6.65 (br s, 1 H), 7.24 (t, 2 H), 7.32 (dd, 1 H), 7.48 (dd, 2 H), 7.62 (br d, 1 H), 8.04 (s, 1 H), 8.35 (d, 1 H), 8.39 (d, 1 H), 10.23 (s, 1 H). MS ES+ *m/z* 604 $[M+H]^+$.

Example 34

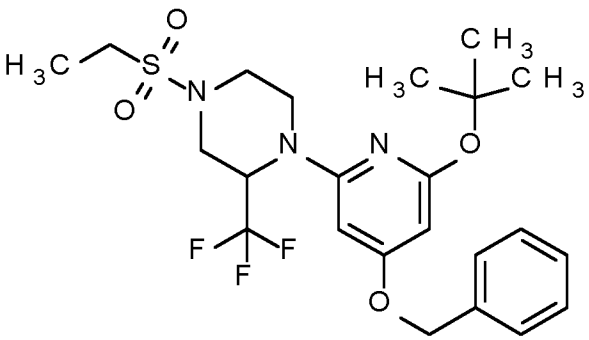
1-Ethylsulfonyl-3-(trifluoromethyl)piperazine



The title compound was prepared as described in Example 28, using ethanesulfonyl chloride, to give the product as a solid (3 g, 98%). MS ES+ *m/z* 247 $[M+H]^+$.

Example 35

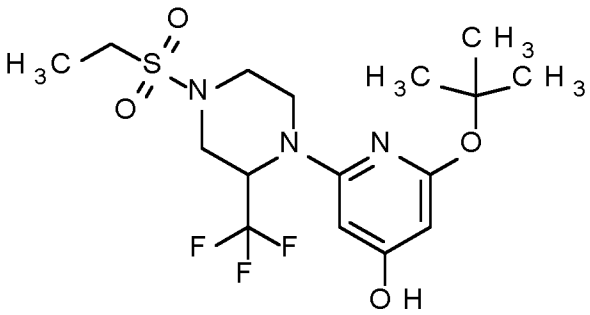
1-(4-Benzyloxy-6-tert-butoxy-2-pyridyl)-4-ethylsulfonyl-2-(trifluoromethyl)piperazine



The title compound was prepared as described in Example 29, using 1-ethylsulfonyl-3-(trifluoromethyl)piperazine, to give the product as a solid (2.53 g, 67%). MS ES+ *m/z* 502 $[M+H]^+$.

Example 36

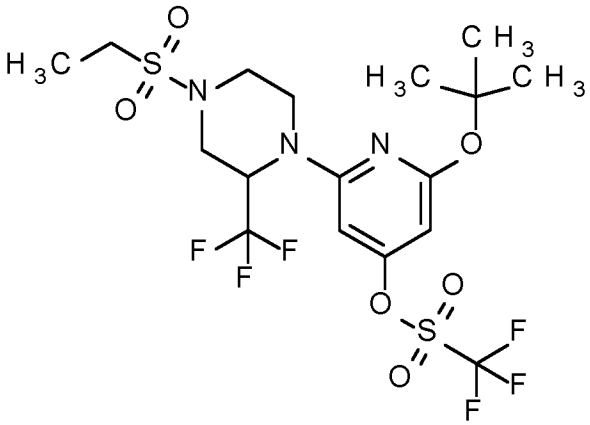
2-tert-Butoxy-6-[4-ethylsulfonyl-2-(trifluoromethyl)piperazin-1-yl]pyridin-4-ol



The title compound was prepared as described in Example 14 to give the product (1.94 g, 85%). MS ES+ *m/z* 412 $[M+H]^+$.

Example 37

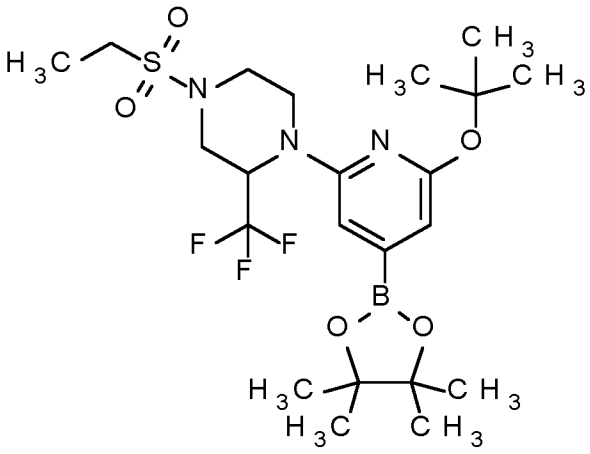
[2-tert-Butoxy-6-[4-ethylsulfonyl-2-(trifluoromethyl)piperazin-1-yl]-4-pyridyl] trifluoromethanesulfonate



The title compound was prepared as described in Example 15 to give the product (1.56 g, 62%). MS ES+ *m/z* 544 $[M+H]^+$.

Example 38

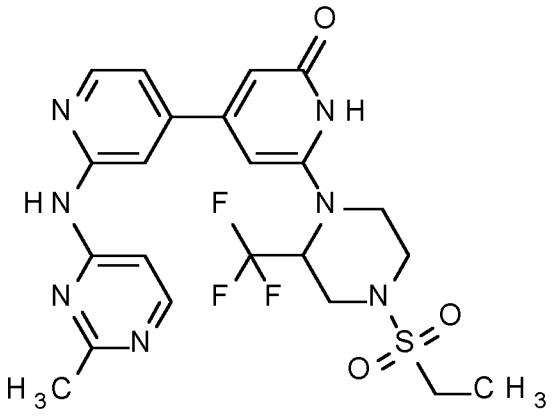
1-[6-tert-Butoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]-4-ethylsulfonyl-2-(trifluoromethyl)piperazine



The title compound was prepared as described in Example 16 to give the product (1.2 g, 86%). MS ES+ *m/z* 440 $[M+H]^+$ (boronic acid).

Example 39

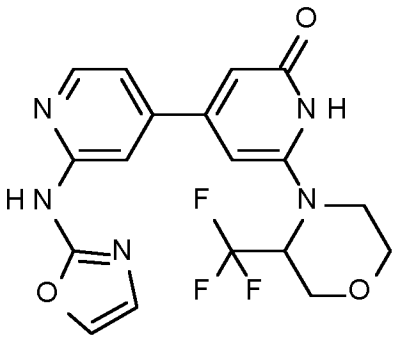
6-[4-Ethylsulfonyl-2-(trifluoromethyl)piperazin-1-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one



The title compound was prepared as described in Example 18, using 1-[6-tert-butoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]-4-ethylsulfonyl-2-(trifluoromethyl)piperazine, to give the product as a solid (7 mg, 7%). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ ppm 1.24 (t, 3 H), 2.50 (br s, 3 H), 2.97 - 3.05 (m, 1 H), 3.13 (q, 2 H), 3.23 - 3.30 (m, 2 H), 3.67 (br d, 1 H), 3.95 (br d, 1 H), 4.36 (br d, 1 H), 5.63 (br s, 1 H), 6.31 (s, 1 H), 6.67 (s, 1 H), 7.33 (dd, 1 H), 7.63 (d, 1 H), 8.04 (s, 1 H), 8.35 (d, 1 H), 8.39 (d, 1 H), 10.23 (s, 1 H), 10.66 (br s, 1 H). MS ES+ *m/z* 524 $[M+H]^+$.

Example 40

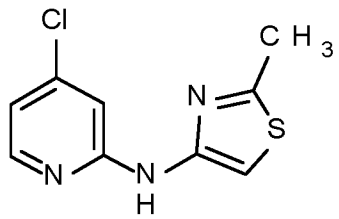
4-[2-(Oxazol-2-ylamino)-4-pyridyl]-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one



The title compound was prepared as described in Example 18, using 4-[6-tert-butoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]-3-(trifluoromethyl)morpholine and N-(4-chloro-2-pyridyl)oxazol-2-amine (*Tetrahedron Letters (2012), 53, (24), 3038-3043*), to give the product as a solid (5 mg, 5%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 3.23 - 3.31 (m, 1 H), 3.40 - 3.57 (m, 1 H), 3.75 (br d, 1 H), 3.94 - 4.04 (m, 2 H), 4.19 (d, 1 H), 5.28 - 5.35 (m, 1 H), 6.27 (s, 1 H), 6.57 (s, 1 H), 7.05 - 7.10 (m, 1 H), 7.29 (br d, 1 H), 7.73 (s, 1 H), 8.28 - 8.35 (m, 2 H), 10.84 (br s, 2 H). MS ES+ *m/z* 408 $[M+H]^+$.

Example 41

N-(4-chloro-2-pyridyl)-2-methyl-thiazol-4-amine

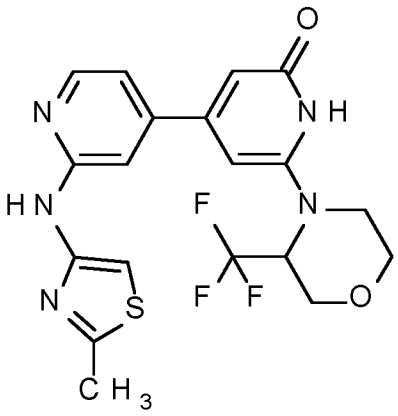


A mixture of 4-bromo-2-methyl-thiazole (1.5 g, 8.52 mmol), 4-chloropyridin-2-amine (1.3 g, 10.22 mmol) and Cs_2CO_3 (6.92 g, 21.3 mmol) in 1,4 dioxane (30 ml) was degassed with nitrogen for 20 min. $Pd_2(dba)_3$ (0.389 g, 0.42 mmol) and Xantphos (0.24 g, 0.42 mmol) were added and the resulting mixture was stirred at 90 °C for 16 h. When cooled to rt the mixture was

filtered through celite, concentrated and purified by preparative HPLC to give the product as a solid (600 mg, 31%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1 H), 8.15 (d, 1 H), 7.37 (s, 1 H), 7.03 (d, 1 H), 6.85-6.84 (m, 1 H), 2.61 (s, 3 H). MS ES+ *m/z* 226 $[M+H]^+$.

Example 42

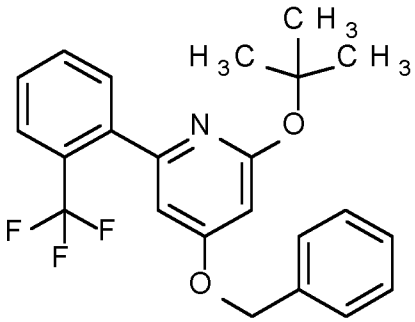
4-[2-[(2-Methylthiazol-4-yl)amino]-4-pyridyl]-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one



The title compound was prepared as described in Example 18, using 4-[6-tert-butoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]-3-(trifluoromethyl)morpholine and N-(4-chloro-2-pyridyl)-2-methyl-thiazol-4-amine, to give the product as a solid (20 mg, 21%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.62 - 2.65 (m, 3 H), 3.32 (br s, 1 H), 3.54 (td, 1 H), 3.71 - 3.80 (m, 1 H), 3.93 - 4.05 (m, 2 H), 4.20 (d, 1 H), 5.30 (br dd, 1 H), 6.22 (s, 1 H), 6.53 (s, 1 H), 7.08 (dd, 1 H), 7.23 (s, 1 H), 7.43 (s, 1 H), 8.27 (d, 1 H), 10.00 (s, 1 H), 10.57 (br s, 1 H). MS ES+ *m/z* 438 $[M+H]^+$.

Example 43

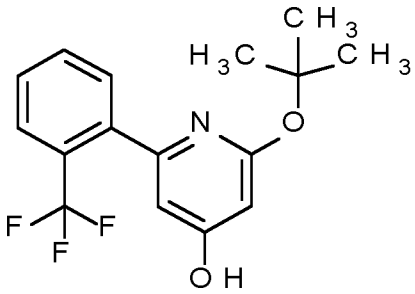
4-Benzyloxy-2-tert-butoxy-6-[2-(trifluoromethyl)phenyl]pyridine



4-Benzyloxy-2-tert-butoxy-6-chloro-pyridine (1.46 g, 5 mmol), [2-(trifluoromethyl)phenyl]boronic acid (950 mg, 5 mmol), K_2CO_3 (1.73 g, 12.5 mmol) and $PdCl_2$(dppf) (366 mg, 0.5 mmol) were dissolved in 1,4-dioxane (25 ml) and water (5 ml) and the resulting mixture was stirred at 90 °C for 2 h. When cooled to rt the mixture was diluted with water and EtOAc. The organic layer was separated and the aqueous layer extracted with EtOAc. The combined organics were filtered through celite, dried over Na_2SO_4, filtered, concentrated and purified on a silica gel column eluted with 0-80% EtOAc in heptane to give the product as a solid (1.58 g, 79%). MS ES+ *m/z* 402 $[M+H]^+$.

Example 44

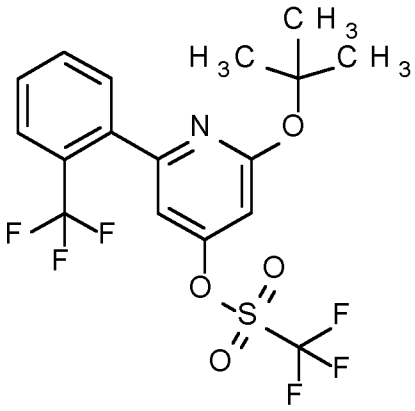
2-tert-Butoxy-6-[2-(trifluoromethyl)phenyl]pyridin-4-ol



The title compound was prepared as described in Example 14 to give the product (948 mg, 72%). MS ES+ *m/z* 312 $[M+H]^+$.

Example 45

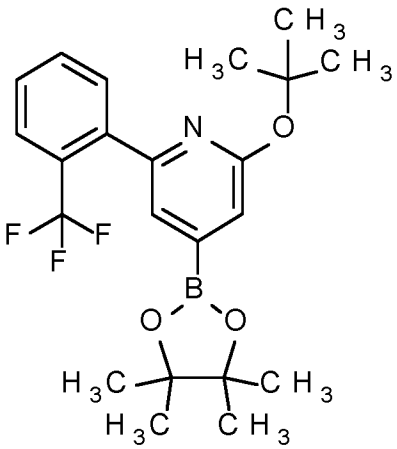
[2-tert-Butoxy-6-[2-(trifluoromethyl)phenyl]-4-pyridyl] trifluoromethanesulfonate



The title compound was prepared as described in Example 15 to give the product (720 mg, 54%). MS ES+ *m/z* 388 $[M\text{-}tBu]^+$.

Example 46

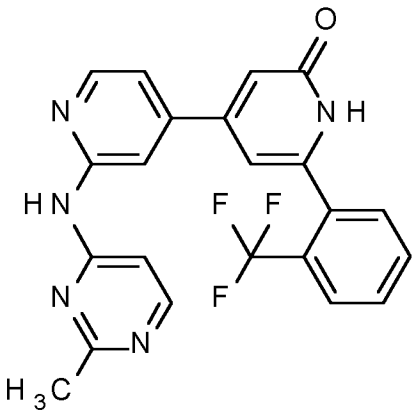
2-tert-Butoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-[2-(trifluoromethyl)phenyl]pyridine



The title compound was prepared as described in Example 16 to give the product (450 mg, 76%). MS ES+ *m/z* 340 $[M+H]^+$ (boronic acid).

Example 47

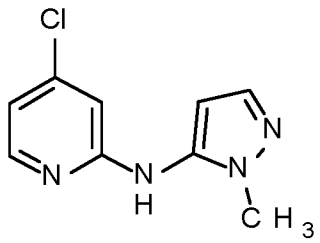
4-[2-[(2-Methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)phenyl]-1H-pyridin-2-one



The title compound was prepared as described in Example 18, using 2-tert-butoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-[2-(trifluoromethyl)phenyl]pyridine, to give the product as a solid (10 mg, 9%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.47 (s, 3 H), 6.46 - 6.63 (m, 1 H), 6.76 - 6.82 (m, 1 H), 7.30 - 7.37 (m, 1 H), 7.58 - 7.64 (m, 1 H), 7.65 - 7.68 (m, 1 H), 7.71 - 7.76 (m, 1 H), 7.78 - 7.84 (m, 1 H), 7.88 - 7.93 (m, 1 H), 8.03 - 8.10 (m, 1 H), 8.32 - 8.44 (m, 2 H), 10.18 - 10.31 (m, 1 H), 11.25 - 11.87 (m, 1 H). MS ES+ *m/z* 424 $[M+H]^+$.

Example 48

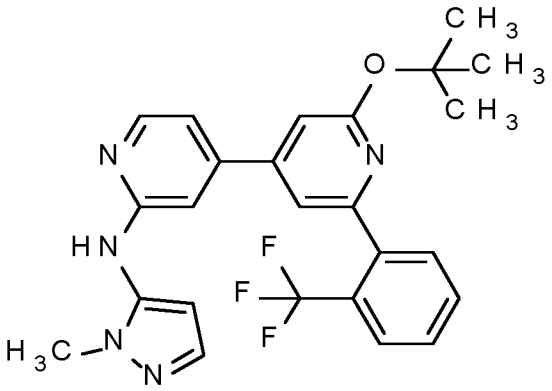
4-Chloro-N-(2-methylpyrazol-3-yl)pyridin-2-amine



The title compound was prepared as described in Example 41, using 2-methylpyrazol-3-amine and 2-bromo-4-chloro-pyridine. Purification on a silica gel column eluted with 0-5% MeOH in DCM gave the product as a solid (1.2 g, quant.). MS ES+ *m/z* 209 $[M+H]^+$.

Example 49

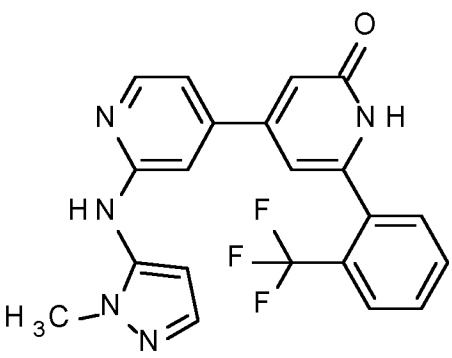
4-[2-tert-Butoxy-6-[2-(trifluoromethyl)phenyl]-4-pyridyl]-N-(2-methylpyrazol-3-yl)pyridin-2-amine



A mixture of 4-chloro-N-(2-methylpyrazol-3-yl)pyridin-2-amine (58 mg, 0.28 mmol), 2-tert-butoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-[2-(trifluoromethyl)phenyl]pyridine (117 mg, 0.28 mmol), K_2CO_3 (77 mg, 0.56 mmol) and $PdCl_2$(dppf) (20 mg, 0.03 mmol) in 1,4-dioxane (2 ml) and water (0.5 ml) was heated and stirred at 90 °C for 6 h. When cooled to rt the mixture was diluted with water and EtOAc. The organic layer was separated, and the aqueous layer extracted with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, filtered, concentrated and purified on a silica gel column eluted with 0-6% MeOH in DCM to give the product as a solid (94 mg, 51% yield, 70% purity). MS ES+ *m/z* 468 $[M+H]^+$.

Example 50

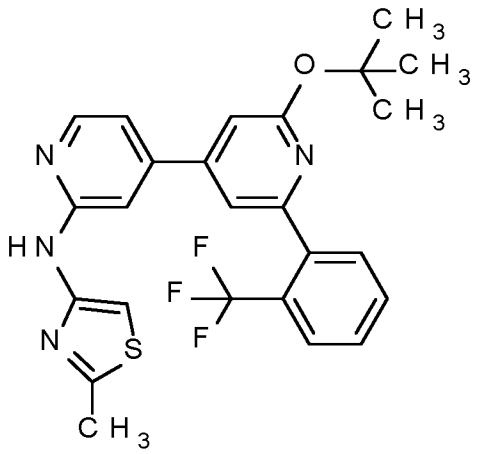
4-[2-[(2-Methylpyrazol-3-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)phenyl]-1H-pyridin-2-one



TFA (1.05 ml, 14.1 mmol) was added to a solution of 4-[2-tert-butoxy-6-[2-(trifluoromethyl)phenyl]-4-pyridyl]-N-(2-methylpyrazol-3-yl)pyridin-2-amine (94 mg, 0.14 mmol, 70%) in DCM (7 ml) at 0 °C and the resulting mixture was stirred at 0 °C for 1 h. The mixture was concentrated, chased with toluene and purified by preparative HPLC to give the product as a solid (11 mg, 19%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 3.68 (s, 3 H), 6.28 (d, 1 H), 6.51 (br s, 1 H), 6.72 (d, 1 H), 7.02 - 7.11 (m, 2 H), 7.34 (d, 1 H), 7.65 (d, 1 H), 7.71 - 7.82 (m, 2 H), 7.89 (d, 1 H), 8.20 (d, 1 H), 8.93 (s, 1 H), 12.03 (br s, 1 H). MS ES+ *m/z* 412 $[M+H]^+$.

Example 51

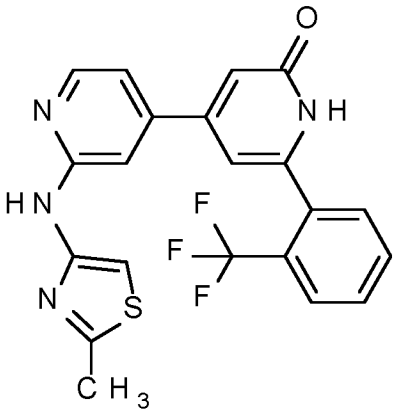
N-[4-[2-tert-butoxy-6-[2-(trifluoromethyl)phenyl]-4-pyridyl]-2-pyridyl]-2-methyl-thiazol-4-amine



The title compound was prepared as described in Example 49, using N-(4-chloro-2-pyridyl)-2-methyl-thiazol-4-amine, to give the product as a solid (145 mg, 60% yield, 80% purity). MS ES+ *m/z* 485 $[M+H]^+$.

Example 52

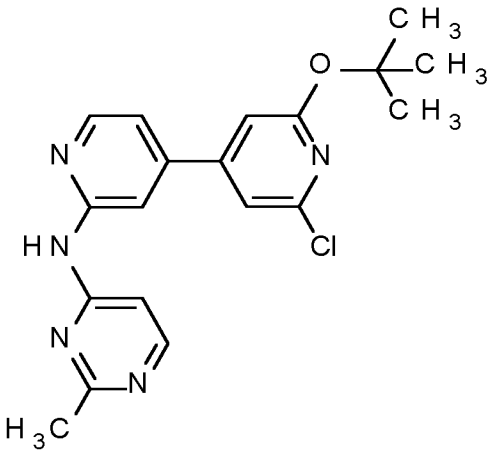
4-[2-[(2-Methylthiazol-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)phenyl]-1H-pyridin-2-one



The title compound was prepared as described in Example 50, to give the product as a solid (45 mg, 43%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.53 - 2.65 (m, 3 H), 6.48 (br s, 1 H), 6.63 - 6.79 (m, 1 H), 7.08 (dd, 1 H), 7.26 (s, 1 H), 7.43 (s, 1 H), 7.66 (d, 1 H), 7.72 - 7.83 (m, 2 H), 7.90 (d, 1 H), 8.28 (d, 1 H), 10.05 (s, 1 H), 12.02 (br s, 1 H). MS ES+ *m/z* 429 $[M+H]^+$.

Example 53

N-[4-(2-tert-butoxy-6-chloro-4-pyridyl)-2-pyridyl]-2-methyl-pyrimidin-4-amine

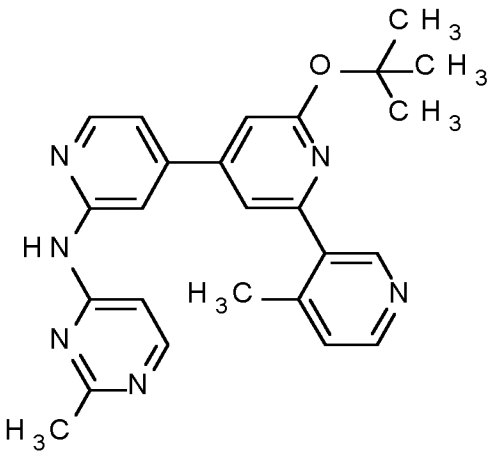


A mixture of N-(4-chloro-2-pyridyl)-2-methyl-pyrimidin-4-amine (1.08 g, 4.89 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.55 g, 6.12 mmol), KOAc (961 mg, 9.79 mmol) and $PdCl_2$(dppf) (358 mg, 0.49 mmol) in 1,4-dioxane (25 ml) was stirred at 100 °C overnight. When cooled to rt, 2-tert-butoxy-6-chloro-4-iodo-pyridine (*Bioorganic & Medicinal Chemistry Letters (2012), 22, (5), 1940-1943*, 1.53 g,

4.89 mmol), K_2CO_3 (1.35 g, 9.79 mmol), $PdCl_2$(dppf) (179 mg, 0.25 mmol) and water (6 ml) were added and the reaction was heated and stirred 85 °C for 2 h. When cooled to rt, water (25 ml) was added and the mixture was extracted with EtOAc. The combined organics were dried over Na_2SO_4, filtered, concentrated and purified on a silica gel column eluted with 25-100% EtOAc in heptane to give the product as a solid (1.61 g, 80% yield, 90% purity). MS ES+ *m/z* 370 $[M+H]^+$.

Example 54

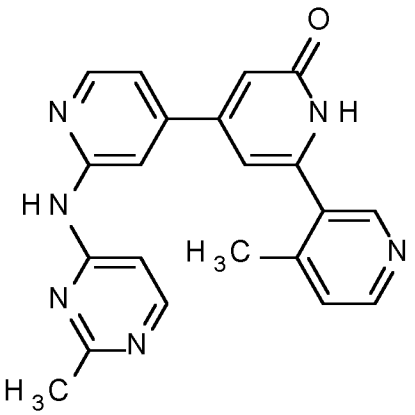
N-[4-[2-tert-butoxy-6-(4-methyl-3-pyridyl)-4-pyridyl]-2-pyridyl]-2-methyl-pyrimidin-4-amine



The title compound was prepared as described in Example 49, using N-[4-(2-tert-butoxy-6-chloro-4-pyridyl)-2-pyridyl]-2-methyl-pyrimidin-4-amine and (4-methyl-3-pyridyl)boronic acid (1.5 eq), to give the product as a solid (75 mg, 70%). MS ES+ *m/z* 427 $[M+H]^+$.

Example 55

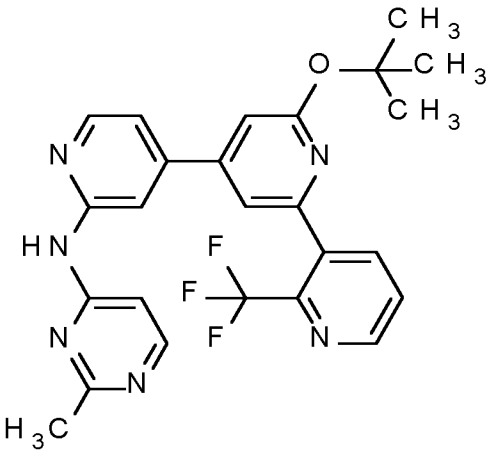
6-(4-Methyl-3-pyridyl)-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one



The title compound was prepared as described in Example 50, to give the product as a solid (55 mg, 58%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.36 - 2.41 (m, 3 H), 2.48 - 2.50 (m, 3 H), 6.62 (br s, 1 H), 6.74 (br s, 1 H), 7.37 - 7.42 (m, 2 H), 7.68 (d, 1 H), 8.05 (s, 1 H), 8.36 (d, 1 H), 8.40 (d, 1 H), 8.54 (d, 1 H), 8.57 (s, 1 H), 10.26 (s, 1 H), 12.06 (br s, 1 H). MS ES+ *m/z* 371 $[M+H]^+$.

Example 56

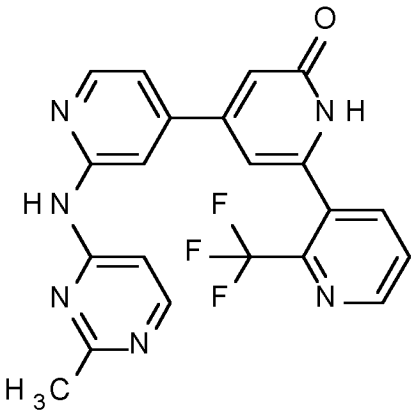
N-[4-[2-tert-butoxy-6-[2-(trifluoromethyl)-3-pyridyl]-4-pyridyl]-2-pyridyl]-2-methyl-pyrimidin-4-amine



The title compound was prepared as described in Example 49, using N-[4-(2-tert-butoxy-6-chloro-4-pyridyl)-2-pyridyl]-2-methyl-pyrimidin-4-amine and [2-(trifluoromethyl)-3-pyridyl]boronic acid (1.5 eq), to give the product as a solid (110 mg, 92%). MS ES+ *m/z* 481 $[M+H]^+$.

Example 57

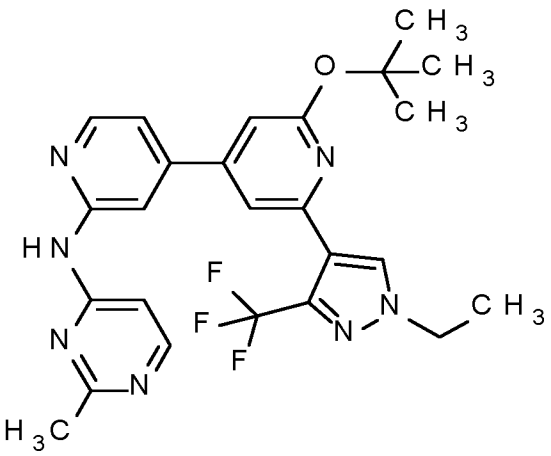
4-[2-[(2-Methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)-3-pyridyl]-1H-pyridin-2-one



The title compound was prepared as described in Example 50, to give the product as a solid (50 mg, 54%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.46 - 2.49 (m, 3 H), 6.68 (br s, 1 H), 6.83 (br s, 1 H), 7.35 (dd, 1 H), 7.62 (d, 1 H), 7.87 (dd, 1 H), 8.07 (s, 1 H), 8.19 (d, 1 H), 8.36 (d, 1 H), 8.41 (d, 1 H), 8.88 (d, 1 H), 10.29 (s, 1 H), 11.71 - 12.58 (m, 1 H). MS ES+ *m/z* 425 $[M+H]^+$.

Example 58

N-[4-[2-tert-butoxy-6-[1-ethyl-3-(trifluoromethyl)pyrazol-4-yl]-4-pyridyl]-2-pyridyl]-2-methyl-pyrimidin-4-amine

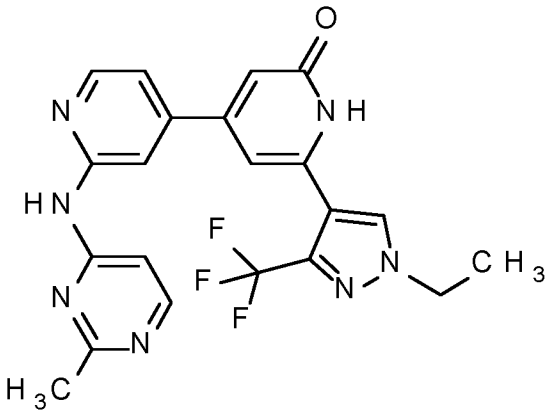


The title compound was prepared as described in Example 49, using N-[4-(2-tert-butoxy-6-chloro-4-pyridyl)-2-pyridyl]-2-methyl-pyrimidin-4-amine and 1-

ethyl-3-(trifluoromethyl)pyrazol-4-yl]boronic acid (1.2 eq), to give the product as a solid (194 mg, 66%). MS ES+ *m/z* 498 $[M+H]^+$.

Example 59

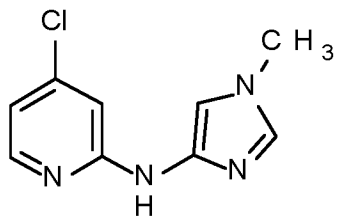
6-[1-Ethyl-3-(trifluoromethyl)pyrazol-4-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one



The title compound was prepared as described in Example 50, to give the product as a solid (2 mg, 1%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.42 - 1.46 (m, 3 H), 2.48 - 2.49 (m, 3 H), 4.24 - 4.31 (m, 2 H), 6.65 - 6.67 (m, 1 H), 6.66 - 6.74 (m, 1 H), 7.26 - 7.31 (m, 1 H), 7.61 - 7.67 (m, 1 H), 7.97 - 8.02 (m, 1 H), 8.35 (d, 1 H), 8.38 - 8.41 (m, 1 H), 8.41 - 8.45 (m, 1 H), 8.43 - 8.43 (m, 1 H), 10.31 - 10.36 (m, 1 H). MS ES+ *m/z* 442 $[M+H]^+$.

Example 60

4-Chloro-N-(1-methylimidazol-4-yl)pyridin-2-amine

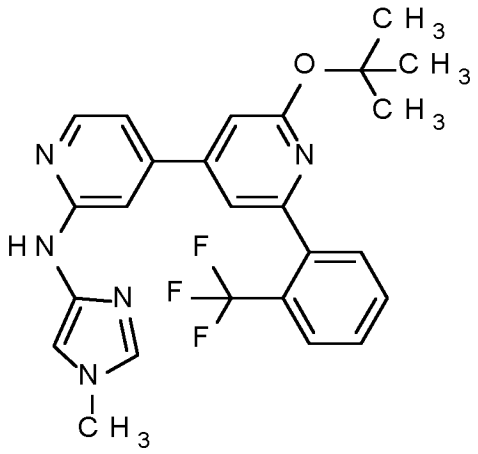


The title compound was prepared as described in Example 41, using 1-methylimidazol-4-amine and 2,4-dichloropyridine and heating the mixture in a microwave reactor at 160 °C for 1 h, to give the product as a solid (0.1 g,

12%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (s, 1 H), 8.59 (s, 1 H), 8.17 (d, 1 H), 7.48 (s, 1 H), 6.98-6.95 (m, 2 H), 3.80 (s, 3 H). MS ES+ *m/z* 209 $[M+H]^+$.

Example 61

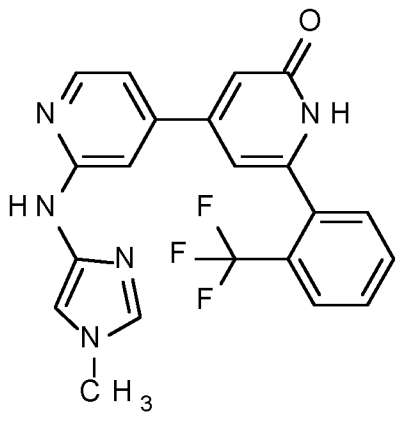
4-[2-tert-Butoxy-6-[2-(trifluoromethyl)phenyl]-4-pyridyl]-N-(1-methylimidazol-4-yl)pyridin-2-amine



The title compound was prepared as described in Example 49, using 4-chloro-N-(1-methylimidazol-4-yl)pyridin-2-amine, to give the product as a solid (50 mg, 21% yield, 80% purity). MS ES+ *m/z* 468 $[M+H]^+$.

Example 62

4-[2-[(1-Methylimidazol-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)phenyl]-1H-pyridin-2-one

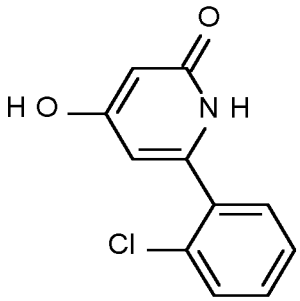


The title compound was prepared as described in Example 50, to give the product as a solid (18 mg, 37%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 3.63

(s, 3 H), 6.28 - 6.56 (m, 1 H), 6.67 (br s, 1 H), 6.93 (d, 1 H), 7.18 (s, 1 H), 7.28 (d, 1 H), 7.35 (s, 1 H), 7.65 (d, 1 H), 7.70 - 7.82 (m, 2 H), 7.89 (d, 1 H), 8.20 (d, 1 H), 9.27 (s, 1 H), 11.44 - 12.43 (m, 1 H). MS ES+ *m/z* 412 $[M+H]^+$.

Example 63

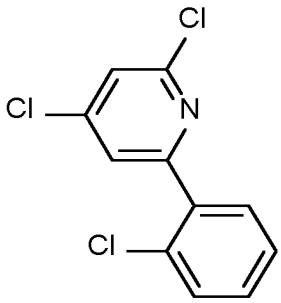
6-(2-Chlorophenyl)-4-hydroxy-1H-pyridin-2-one



Ethyl 3-oxobutanoate (6.33 ml, 50 mmol) was added dropwise to a suspension of 60% NaH (1.92 g, 50 mmol) in 2-MeTHF (60 ml) at -78 °C under a nitrogen atmosphere. After 5 min the cooling bath was removed and the mixture was stirred at rt for 20 min. The mixture was cooled back to - 78 °C and 1.6 M n-BuLi (31.25 ml, 50 mmol) was added slowly over 20 min. The resulting solution was stirred at -78 °C for 30 min. 2-Chlorobenzonitrile (6.88 g, 50 mmol) was added as a solid in one portion and the reaction mixture was stirred on the thawing cooling bath overnight. The mixture was cooled to 0 °C and MeOH (15 ml) was added slowly. The cooling bath was removed and the mixture stirred at rt for 30 min and then cooled to 0 °C again. The mixture was neutralized by slow addition of conc. HCl and the resulting precipitate was filtered off, washed with EtOH, pentane and dried to give the product as a solid (11.08 g, 87%). MS ES+ *m/z* 222 $[M+H]^+$.

Example 64

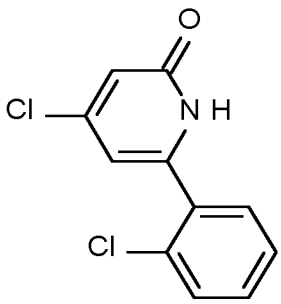
2,4-Dichloro-6-(2-chlorophenyl)pyridine



6-(2-Chlorophenyl)-4-hydroxy-1H-pyridin-2-one (5 g, 22.56 mmol) was taken up in $POCl_3$ (40 ml) and N,N-dimethylaniline (5.5 ml, 43.4 mmol) was added slowly. The resulting mixture was refluxed overnight. When cooled to rt the mixture was poured onto ice (600 ml) and stirred at rt for 30 min. The precipitate was filtered off and washed with water. The solid was dissolved in EtOAc (100 ml), dried over Na_2SO_4, filtered and concentrated to give the product as a solid (7 g, 83%). MS ES+ *m/z* 258 $[M+H]^+$.

Example 65

4-Chloro-6-(2-chlorophenyl)-1H-pyridin-2-one

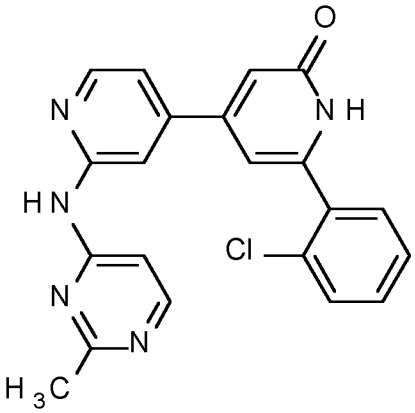


2,4-Dichloro-6-(2-chlorophenyl)pyridine (5.7 g, 22.05 mmol) and KOtBu (6.19 g, 55.12 mmol) were taken up in toluene (75 ml) and the resulting mixture was stirred at 100 °C for 2 h. When cooled to rt, water (40 ml) was added and the organic layer separated. The aqueous layer was made slightly acidic using conc. HCl and extracted with EtOAc (2 x 40 ml). The combined organics were washed with brine (50 ml), dried over Na_2SO_4, filtered and concentrated. The resulting residue was taken up in DCM (30 ml) and TFA (5 ml, 67.3 mmol) was added. The reaction mixture was stirred at rt for 1 h, concentrated and the resulting residue was taken up in MeOH (25 ml). 30% NH_4OH (20 ml) and water (20 ml) were added and the mixture was stirred at

rt overnight. The formed precipitate was filtered off, washed with water, EtOH, pentane and dried to give the product a solid (4.13 g, 78%). MS ES+ *m/z* 240 $[M+H]^+$.

Example 66

6-(2-Chlorophenyl)-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one



A mixture of N-(4-chloro-2-pyridyl)-2-methyl-pyrimidin-4-amine (132 mg, 0.6 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (190 mg, 0.75 mmol) and $PdCl_2$(dppf) (22 mg, 0.06 mmol) in 1,4-dioxane (1.5 ml) was stirred in a sealed tube at 100 °C for 15 h. When cooled to rt, 4-chloro-6-(2-chlorophenyl)-1H-pyridin-2-one (144 mg, 0.6 mmol), K_2CO_3 (83 mg, 0.6 mmol), $PdCl_2$(dppf) (11 mg, 0.03 mmol), 1,4-dioxane (1 ml) and water (0.5 ml) were added and the resulting mixture was flushed with argon, heated and stirred at 85 °C for 2 h. When cooled to rt, water (25 ml) was added and the mixture was extracted with DCM. The combined organics were dried over Na_2SO_4, filtered, concentrated and purified by preparative HPLC to give the product as a solid (20 mg, 9%). ^1H NMR (500 MHz, DMSO-d_6) δ ppm 2.48 - 2.50 (m, 3 H), 6.66 (br s, 1 H), 6.74 (s, 1 H), 7.37 (dd, 1 H), 7.46 - 7.56 (m, 2 H), 7.59 - 7.68 (m, 3 H), 8.05 (s, 1 H), 8.36 (d, 1 H), 8.40 (d, 1 H), 10.27 (s, 1 H), 11.57 - 12.34 (m, 1 H). MS ES+ *m/z* 390 $[M+H]^+$.

Example 67

The following compound is synthesized using suitible changes of starting material, and if necessary customizations of reaction conditions and the like.

- 6-(3-cyclopropylmorpholin-4-yl)-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one.

Example 68

Vps34 biochemical assay

Dilution series of compounds of the invention were prepared in DMSO at 100 times the final assay concentration ($n_1=n_0/3$ in 10 points). The compounds were further diluted to 4 times the assay concentration in assay buffer (Life technologies buffer Q, PV5125, diluted 5 times supplemented with 2 mM DTT and 2 mM $MnCl_2$). 2.5 µl of the diluted compounds were added to a 384 well assay plate followed by 2.5 µl of 16.5 nM Vps34 enzyme (Life technologies, PV5126). Enzyme and compounds were pre-incubated at rt for 15 min. Then 5 µl of substrate mix containing 20 µM ATP (Life technologies, PV3227) and 200 µM PI:PS substrate (Life technologies, PV5122) in assay buffer was added to the wells containing compound and enzyme. Mixing was performed by pipetting several times. The reaction was incubated at room temperature for 1 h. Then 5 µl stop-detection mix, prepared as described in the Adapta kinase assay kit instructions (Life technologies, PV5099) containing Adapta Eu-anti-ADP antibody (2.3 nM), Alexa Fluor 647 ADP tracer (9 nM) and EDTA (30 mM) in TR-FRET buffer, was added to quench the reaction. Mixing was performed by pipetting several times. The assay plate was then incubated at room temperature for 30 min and read with Artemis micro plate reader. Percent inhibition of the compounds as compared to DMSO treated control samples was calculated. By the use of Dotmatics software compound concentration versus percent inhibition was fitted to generate IC_{50} values. The example compounds effectively inhibited Vps34 and the results of the assay are shown in Table 1 (Median IC_{50} nM Adapta).

Table 1. Median IC_{50} values for the Vps34 assay

Example Compound	Median IC_{50} nM Adapta
4	<5
6	<5
8	6
10	<5
18	<5
21	<5
26	<5
27	<5
33	<5
39	<5
40	<5
42	13
47	<5
50	55
52	52
55	<5
57	<5
59	<5
62	12
66	<5

Example 69

High Content Screening Autophagy assay

Human osteosarcoma cells (HOS) stably expressing a Green Fluorescent Protein (GFP) tagged LC3 (GFP-LC3) were used to determine the inhibitory effect on autophagy of proprietary compounds. For that purpose, autophagy was activated by using the mTOR inhibitor KU-0063794 at 500 nM in the presence of Bafilomycin A1 (Sigma-Aldrich) at 5 nM. Shortly, cells were plated overnight in clear bottom 96-well plates in DMEM–High Modified media (Hi-Clone Cat # SH30285.01). At the start of the experiment, the media was removed and replaced with fresh media containing the mTOR inhibitor, Bafilomycin A1 and the vehicle or a test compound as indicated. After 6 hours the media was removed, cells were washed twice with ice-cold phosphate buffered saline (PBS) and fixed with 4% paraformaldehyde for 20 minutes at room temperature. Then the cells were washed twice with ice-cold PBS before adding Hoechst 33342 at 1 µg/ml in PBS for nuclear staining. After incubation overnight at 4°C, cells were washed once with PBS to remove the excess of dye and 100 µl of PBS was added to each well. Images were acquired at 20x magnification, 6 images per well, using the ImageXpress automated microscope (Molecular Devices Inc.) and analyzed with MetaXpress software to identify LC3-GFP foci. Foci area per cell values were used to generate dose response curves and IC50 values were calculated using the non-linear fitting analysis in GraphPad Prism software.

The tested example compounds effectively inhibited autophagy in HOS cells. The results of the assay are shown in Table 2 (Median IC_{50} µM HOS-LC3).

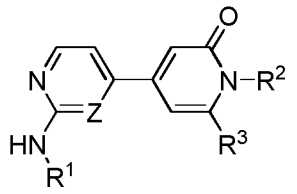
Table 2. Median IC_{50} values for the Vps34 assay and autophagy in HOS cells assay.

Example Compound	Median IC50 (μM) Cellular assay
6	0.054
8	0.066
10	0.019
26	0.010
27	0.020
33	0.003
39	0.002
40	0.029
47	0.003
50	0.254
55	0.099
57	0.006
59	0.005

5

CLAIMS

1. A compound of Formula (I)



(I)

wherein

R^1 is phenyl or monocyclic 5-6 membered heteroaryl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_3-C_4cycloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, amino, N-C_1-C_3alkylamino and N,N-diC_1-C_3alkylamino;

R^2 is selected from hydrogen, C_1-C_3haloalkyl and C_1-C_3alkyl;

R^3 is selected from A, phenyl and monocyclic heteroaryl, said phenyl and said heteroaryl being each optionally substituted with one or more of R^4, R^5, R^6 and R^7;

R^4, R^5, R^6 and R^7 are independently selected from halogen, C_1-C_6alkyl, C_3-C_4cycloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, azetidine, amino, N-C_1-C_3alkylamino, N,N-diC_1-C_3alkylamino, $NHSO_2R^8$, SO_2R^9 and hydroxy;

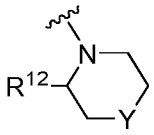
R^8 is C_1-C_3haloalkyl or C_1-C_3alkyl;

R^9 is selected from R^{10}, C_1-C_6alkyl, amino, N-C_1-C_3alkylamino, N,N-diC_1-C_3alkylamino and C_1-C_3alkoxyC_1-C_3alkyl, wherein said C_1-C_6alkyl and C_1-C_3alkoxyC_1-C_3alkyl being each optionally substituted with one R^{10} and/or one or more halogen;

R^{10} is selected from phenyl, benzyl, monocyclic heteroaryl, C_3-C_6cycloalkyl, heterocyclyl, each optionally substituted with one or more R^{11};

R^{11} is selected from halogen, C_1-C_3haloalkyl, C_3-C_4cycloalkyl, C_1-C_3alkyl, amino, N-C_1-C_3alkylamino, N,N-diC_1-C_3alkylamino and C_1-C_3alkoxyC_1-C_3alkyl;

A is



R^{12} is selected from hydrogen, halogen, COR^{13}, C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_3alkoxyC_1-C_3alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_3cyanoalkyl, and C_1-C_3haloalkyl;

R^{13} is selected from C_1-C_3alkoxy, N-C_1-C_3alkylamino, N,N-diC_1-C_3alkylamino, 1-pyrrolidinyl, 1-piperidinyl and 1-azetidinyl;

Y is selected from CH_2, S, SO, SO_2, NR^{14}, $NCOR^9$, $NCOOR^{15}$, NSO_2R^9, $NCOCH_2R^9$, O, or a bond;

R^{14} is selected from H, C_1-C_3haloalkyl, C_1-C_3alkoxyC_1-C_3alkyl, C_1-C_3alkyl, and C_3-C_6cycloalkyl;

R^{15} is selected from R^{10}, C_1-C_6alkyl and C_1-C_3alkoxyC_1-C_3alkyl, and wherein said C_1-C_6alkyl and C_1-C_3alkoxyC_1-C_3alkyl being each optionally substituted with one R^{10} and/or one or more halogen; and

Z is CH or N;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R^2 is hydrogen or C_1-C_3alkyl;

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or 2, wherein R^2 is hydrogen;

or a pharmaceutically acceptable salt thereof.

4. A compound according to any one of claims 1 to 3, wherein R^1 is phenyl or a monocyclic 5-6 membered heteroaryl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_3-C_4cycloalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, amino, -N-C_1-C_3alkylamino, N,N-di-C_1-C_3alkylamino and halogen;

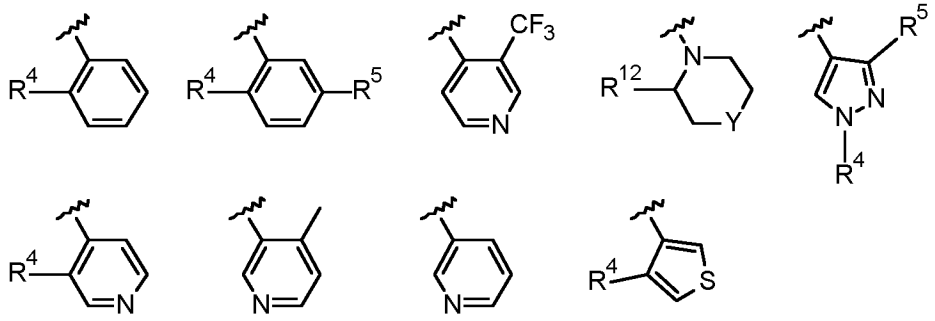
or a pharmaceutically acceptable salt thereof.

5. A compound according to any one of claims 1 to 4, wherein R^1 is phenyl or a monocyclic 5-6 membered heteroaryl, each optionally substituted

with one or more substituents selected from C_1-C_6alkyl, C_3-C_4cycloalkyl, and halogen;

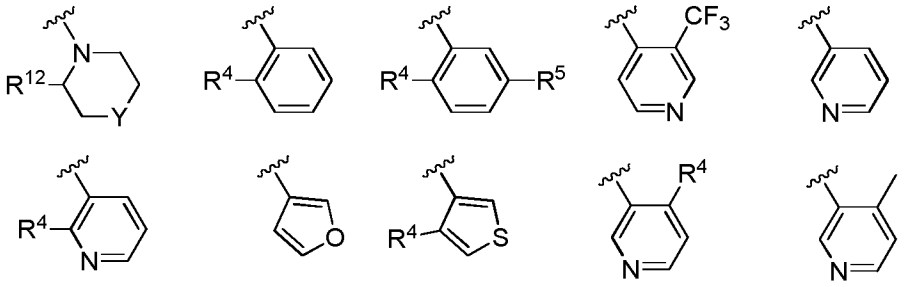
or a pharmaceutically acceptable salt thereof.

6. A compound according to any one of claims 1 to 5, wherein R^3 is selected from



or a pharmaceutically acceptable salt thereof.

7. A compound according to any one of claims 1 to 5, wherein R^3 is selected from



Y is selected from CH_2, NSO_2R^9, O and a bond;

R^4 is selected from CF_3, fluoro, cyclopropyl and methyl;

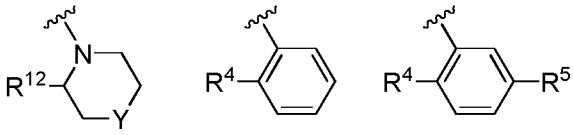
R^5 is fluoro;

R^9 is selected from C_1-C_6alkyl, phenyl, and benzyl, each optionally substituted with one or more halogen; and

R^{12} is selected from hydrogen, methyl, cyclopropyl and CF_3;

or a pharmaceutically acceptable salt thereof.

8. A compound according to any one of claims 1 to 6, wherein R^3 is selected from



Y is selected from NSO_2R^9, CH_2 and O;

R^4 is selected from cyclopropyl, CF_3 and chloro;

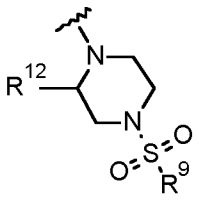
R^5 is fluoro;

R^9 is selected from C_1-C_6alkyl, phenyl, and benzyl, each optionally substituted with one or more halogen; and

R^{12} is cyclopropyl or CF_3;

or a pharmaceutically acceptable salt thereof.

9. A compound according to any one of claims 1 to 8, wherein R^3 is



R^9 is selected from C_1-C_6alkyl, phenyl, and benzyl, wherein said phenyl and benzyl group may optionally be substituted with one or more halogen, C_1-C_6alkyl, C_1-C_6haloalkyl and C_3-C_4cycloalkyl; and

R^{12} is selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl and C_3-C_4cycloalkyl;

or a pharmaceutically acceptable salt thereof.

10. A compound according to any one of claims 1 to 9, wherein R^1 is selected from phenyl, pyrimidinyl, oxazolyl, imidazolyl, pyrazolyl and thiazolyl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_3-C_4cycloalkyl, and C_1-C_6haloalkyl;

or a pharmaceutically acceptable salt thereof.

11. A compound according to any one of claims 1 to 5, wherein R^3 is selected from A, phenyl, pyridyl, thienyl, furyl, pyrimidinyl and pyrazolyl, each optionally and independently substituted with one or more R^4 or R^5;

or a pharmaceutically acceptable salt thereof.

12. A compound according to any one of claims 1 to 6, wherein R^3 is selected from A, phenyl and pyridyl, each optionally and independently substituted with one or more R^4 or R^5;
or a pharmaceutically acceptable salt thereof.

13. A compound according to any one of claims 1 to 6, wherein R^3 is selected from phenyl, pyridyl, morpholinyl, piperidyl, pyrrolidinyl, thienyl, and piperazinyl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl and C_3-C_4cycloalkyl;
or a pharmaceutically acceptable salt thereof.

14. A compound according to any one of claims 1 to 3, wherein R^4, R^5, R^6 and R^7 are independently selected from fluoro, chloro, C_1-C_3alkyl, C_1-C_3fluoroalkyl, cyclopropyl and SO_2R^9;
or a pharmaceutically acceptable salt thereof.

15. A compound according to any one of claims 1 to 7 or any one of claims 11 to 12, wherein Y is selected from CH_2, O and a bond;
or a pharmaceutically acceptable salt thereof.

16. A compound according to any one of claims 1 to 6 or claim 11, wherein R^{12} is selected from hydrogen, $CON(CH_3)_2$, C_1-C_3alkyl, CF_3 and cyclopropyl;
or a pharmaceutically acceptable salt thereof.

17. A compound according to any one of claims 1 to 6, any one of claims 11 to 12 or claim 14, wherein R^9 is selected from R^{10}, N,N-diC_1-C_3alkylamino and methoxyC_1-C_3alkyl, said C_1-C_3alkyl being optionally substituted with one R^{10};
or a pharmaceutically acceptable salt thereof.

18. A compound according to any one of claims 1 to 6, or claim 11, claim 12, claim 14, or claim 17, wherein R^{10} is selected from phenyl, benzyl, pyridyl, imidazolyl, isoxazolyl, oxazolyl, cyclopropyl, cyclopentyl, pyrrolidinyl, and tetrahydrofuryl, each optionally substituted with one or more methyl and/or

fluoro;
or a pharmaceutically acceptable salt thereof.

19. A compound according to any one of claims 1 to 6, wherein R^3 is selected from phenyl, pyridyl, pyrrolidinyl, and thienyl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl and C_3-C_4cycloalkyl; or A;
Y is CH_2, O, NSO_2-C_1-C_6alkyl or NSO_2-benzyl, wherein said benzyl is optionally substituted by one or more halogen; and
R^{12} is C_1-C_6alkyl or C_1-C_6haloalkyl;
or a pharmaceutically acceptable salt thereof.

20. A compound according to any one of claims 1 to 4, wherein R^1 is phenyl or a monocyclic 5-6 membered heteroaryl each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_3-C_4cycloalkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, amino, N-C_1-C_3alkylamino, N,N-di-C_1-C_3alkylamino and halogen;
R^2 is hydrogen; and
R^3 is phenyl or monocyclic 5-6 membered heteroaryl each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl and C_3-C_4cycloalkyl;
or a pharmaceutically acceptable salt thereof.

21. A compound according to any one of claims 1 to 6, wherein R^1 is phenyl or a monocyclic 5-6 membered heteroaryl each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_3-C_4cycloalkyl;
R^2 is hydrogen; and
R^3 is phenyl or monocyclic 5-6 membered heteroaryl each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl and C_3-C_4cycloalkyl;
or a pharmaceutically acceptable salt thereof.

22. A compound according to any one of claims 1 to 6, wherein R^1 is selected from phenyl, pyrimidinyl, oxazolyl, imidazolyl, or thiazolyl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_3-C_4cycloalkyl;
R^2 is hydrogen;
R^3 is selected from phenyl, pyridyl, pyrazolyl, pyrrolidinyl, and thienyl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_3-C_4cycloalkyl; or A;
Y is CH_2, O, NSO_2-C_1-C_6alkyl or NSO_2-benzyl, wherein said benzyl is optionally substituted by one or more halogen; and
R^{12} is C_1-C_6alkyl or C_1-C_6haloalkyl;
or a pharmaceutically acceptable salt thereof.

23. A compound according to any one of claims 1 to 6, wherein R^1 is selected from phenyl, 4-pyrimidinyl, 2-methylpyrimidin-4-yl, 2-cyclopropyl-pyrimidin-4-yl, 2-oxazolyl, 1-methyl-imidazol-4-yl, 2-methyl-thiazol-4-yl, 3,5-difluorophenyl and 2-methylpyrazol-3-yl;
R^2 is hydrogen; and
R^3 is selected from 2-chlorophenyl, 3-pyridyl, 4-pyridyl, 4-morpholinyl, 3-(trifluoromethyl)morpholin-4-yl, 2-(trifluoromethyl)-piperidin-1-yl, 2-(trifluoromethyl)phenyl, 4-methyl-pyridin-3-yl, 2-(trifluoromethyl)-pyridin-3-yl, 1-ethyl-3-(trifluoromethyl)pyrazol-4-yl, 3-cyclopropyl-morpholin-4-yl, 4-[(4-fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazin-1-yl, 4-ethylsulfonyl-2-(trifluoromethyl)piperazin-1-yl, 2-(trifluoromethyl)-pyrrolidin-1-yl, 2-chloro-5-fluorophenyl, 3-(trifluoromethyl)-pyrazolin-4-yl, 2-(trifluoromethyl)-pyridin-3-yl, 3-methyl-thien-4-yl, 2-metylphenyl, 1-acetyl-3-trifluoromethyl-piperazin-4-yl , 2-methyl-piperidin-1-yl, 2-cyclopropyl-piperidin-1-yl, 2-methyl-morpholin-4-yl, 2-trifluoromethyl-morpholin-4-yl, and 2-cyclopropyl-morpholin-4-yl;
or a pharmaceutically acceptable salt thereof.

24. A compound according to any one of claims 1 to 6, wherein R^1 is phenyl or monocyclic 5-6 membered heteroaryl, each optionally substituted

with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_3-C_4cycloalkyl;
R^2 is hydrogen;
R^3 is phenyl or monocyclic 5-6 membered heteroaryl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_3-C_4cycloalkyl; and
Z is CH or N;
or a pharmaceutically acceptable salt thereof.

25. A compound according to any one of claims 1 to 6, wherein R^1 is phenyl, or pyrimidinyl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_3-C_4cycloalkyl;
R^2 is hydrogen;
R^3 is selected from phenyl, pyridyl and pyrazolyl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_3-C_4cycloalkyl; or A;
Y is CH_2, O, NSO_2-C_1-C_6alkyl or NSO_2-benzyl, wherein said benzyl is optionally substituted by one or more halogen;
R^{12} is C_1-C_6alkyl or C_1-C_6haloalkyl; and
Z is CH or N;
or a pharmaceutically acceptable salt thereof.

26. A compound according to any one of claims 1 to 6, wherein R^1 is phenyl, 3,5-difluorophenyl or 2-methylpyrimidin-4-yl;
R^2 is hydrogen;
R^3 is selected from 2-chlorophenyl, 3-pyridyl, 4-pyridyl, 1-morpholinyl, 2-(trifluoromethyl)-1-piperidyl, 3-(trifluoromethyl)morpholin-4-yl, 4-[(4-fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazin-1-yl, 4-ethylsulfonyl-2-(trifluoromethyl)piperazin-1-yl, 2-(trifluoromethyl)phenyl, 4-methyl-3-pyridyl, 2-(trifluoromethyl)-3-pyridyl, 1-ethyl-3-(trifluoromethyl)pyrazol-4-yl, and 3-cyclopropylmorpholin-4-yl; and
Z is CH or N;

or a pharmaceutically acceptable salt thereof.

27. A compound according to any one of claims 1 to 6, wherein R^1 is phenyl, or pyrimidinyl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_3-C_4cycloalkyl;
R^2 is hydrogen;
R^3 is selected from phenyl or pyridyl, each optionally substituted with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, and C_3-C_4cycloalkyl; or A;
Y is CH_2, O, NSO_2-C_1-C_6alkyl or NSO_2-benzyl, wherein said benzyl is optionally substituted by one or more halogen;
R^{12} is C_1-C_6alkyl or C_1-C_6haloalkyl; and
Z is CH or N;
or a pharmaceutically acceptable salt thereof.

28. A compound according to claim 1, wherein R^1 is phenyl, 2-methylpyrimidin-4-yl, oxazol-2-yl, 2-methylthiazol-4-yl, 2-methylpyrazol-3-yl, and 1-methylimidazol-4-yl;
R^2 is hydrogen;
R^3 is selected from 2-chlorophenyl, 3-pyridyl, 4-pyridyl, 1-morpholinyl, 2-(trifluoromethyl)-1-piperidyl, 3-(trifluoromethyl)morpholin-4-yl, 4-[(4-fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazin-1-yl, 4-ethylsulfonyl-2-(trifluoromethyl)piperazin-1-yl; 2-(trifluoromethyl)phenyl, 4-methyl-pyridin-3-yl, 2-(trifluoromethyl)-pyridin-3-yl and 1-ethyl-3-(trifluoromethyl)pyrazol-4-yl; and
Z is CH or N;
or a pharmaceutically acceptable salt thereof.

29. A compound according to claim 1, wherein R^1 is phenyl, or 2-methylpyrimidin-4-yl;
R^2 is hydrogen;
R^3 is selected from 2-chlorophenyl, 3-pyridyl, 4-pyridyl, 1-morpholinyl, 2-(trifluoromethyl)-1-piperidyl, 3-(trifluoromethyl)morpholin-4-yl, 4-[(4-

fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazin-1-yl, and 4-ethylsulfonyl-2-(trifluoromethyl)piperazin-1-yl; and
Z is CH or N;
or a pharmaceutically acceptable salt thereof.

30. A compound according to claim 1, wherein the compound is selected from
4-(2-anilinopyrimidin-4-yl)-6-(2-chlorophenyl)-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-(3-pyridyl)-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-(4-pyridyl)-1H-pyridin-2-one
4-(2-anilinopyrimidin-4-yl)-6-morpholino-1H-pyridin-2-one;
4-[2-[(2-Methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)-1-piperidyl]-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-[2-(trifluoromethyl)-1-piperidyl]-1H-pyridin-2-one;
4-[2-[(2-Methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one;
6-[4-[(4-Fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazin-1-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;
6-[4-Ethylsulfonyl-2-(trifluoromethyl)piperazin-1-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;
4-[2-(Oxazol-2-ylamino)-4-pyridyl]-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one;
4-[2-[(2-Methylthiazol-4-yl)amino]-4-pyridyl]-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one;
4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)¬phenyl]-1H-pyridin-2-one;
4-[2-[(2-Methylpyrazol-3-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)phenyl]-1H-pyridin-2-one;
4-[2-[(2-Methylthiazol-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)phenyl]-1H-pyridin-2-one;
6-(4-methyl-3-pyridyl)-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-

pyridin-2-one;
4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)-3-pyridyl]-1H-pyridin-2-one;
6-[1-ethyl-3-(trifluoromethyl)pyrazol-4-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;
4-[2-[(1-Methylimidazol-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)phenyl]-1H-pyridin-2-one; and
6-(2-chlorophenyl)-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one,
or a pharmaceutically acceptable salt thereof.

31. A compound according to claim 1, wherein the compound is selected from
4-(2-anilinopyrimidin-4-yl)-6-(2-chlorophenyl)-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-(3-pyridyl)-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-(4-pyridyl)-1H-pyridin-2-one
4-(2-anilinopyrimidin-4-yl)-6-morpholino-1H-pyridin-2-one;
4-[2-[(2-Methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)-1-piperidyl]-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-[2-(trifluoromethyl)-1-piperidyl]-1H-pyridin-2-one;
4-[2-[(2-Methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one;
6-[4-[(4-Fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazin-1-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;
6-[4-Ethylsulfonyl-2-(trifluoromethyl)piperazin-1-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;
4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)¬phenyl]-1H-pyridin-2-one;
6-(4-methyl-3-pyridyl)-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;
4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)-3-pyridyl]-

1H-pyridin-2-one;
6-[1-ethyl-3-(trifluoromethyl)pyrazol-4-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;
6-(2-chlorophenyl)-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one; and
6-(3-cyclopropylmorpholin-4-yl)-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one,
or a pharmaceutically acceptable salt thereof.

32. A compound according to claim 1, wherein the compound is selected from
4-(2-anilinopyrimidin-4-yl)-6-(2-chlorophenyl)-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-(3-pyridyl)-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-(4-pyridyl)-1H-pyridin-2-one
4-(2-anilinopyrimidin-4-yl)-6-morpholino-1H-pyridin-2-one;
4-[2-[(2-Methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)-1-piperidyl]-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-[2-(trifluoromethyl)-1-piperidyl]-1H-pyridin-2-one;
4-[2-[(2-Methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one;
4-(2-Anilinopyrimidin-4-yl)-6-[3-(trifluoromethyl)morpholin-4-yl]-1H-pyridin-2-one;
6-[4-[(4-Fluorophenyl)methylsulfonyl]-2-(trifluoromethyl)piperazin-1-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;
6-[4-Ethylsulfonyl-2-(trifluoromethyl)piperazin-1-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;
4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)¬phenyl]-1H-pyridin-2-one;
6-(4-methyl-3-pyridyl)-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one;
4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-6-[2-(trifluoromethyl)-3-pyridyl]-1H-pyridin-2-one;
6-[1-ethyl-3-(trifluoromethyl)pyrazol-4-yl]-4-[2-[(2-methylpyrimidin-4-yl)amino]-

4-pyridyl]-1H-pyridin-2-one; and
6-(2-chlorophenyl)-4-[2-[(2-methylpyrimidin-4-yl)amino]-4-pyridyl]-1H-pyridin-2-one,
or a pharmaceutically acceptable salt thereof.

33. A compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of a disease.

34. A compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, for use in treating cancer.

35. A compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, for use in treating cancer, wherein said cancer is selected from breast cancer, such as triple negative breast cancer, bladder cancer, liver cancer, cervical cancer, pancreatic cancer, leukemia, lymphoma, renal cancer, colon cancer, glioma, prostate cancer, ovarian cancer, melanoma and lung cancer, as well as hypoxic tumors.

36. A compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, for use in treating hypoxic tumors.

37. A compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, for use in treating cancer, wherein said cancer treatment further comprises radiation therapy.

38. A compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, for use in treating type II diabetes.

39. A compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, for use in treating a disease selected from inflammatory diseases, neurodegenerative disorders, cardiovascular disorders, autoimmune diseases and viral infections.

40. Use of a compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating cancer.

41. Use of a compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating cancer, wherein said cancer is selected from breast cancer, such as triple negative breast cancer, bladder cancer, liver cancer, cervical cancer, pancreatic cancer, leukemia, lymphoma, renal cancer, colon cancer, glioma, prostate cancer, ovarian cancer, melanoma and lung cancer, as well as hypoxic tumors.

42. Use of a compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating hypoxic tumors.

43. Use of a compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating type II diabetes.

44. Use of a compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating a disease selected from inflammatory diseases, neurodegenerative disorders, cardiovascular disorders, autoimmune diseases and viral infections.

45. A method of treating cancer, comprising administering a therapeutically effective amount of a compound according any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

46. The method of claim 45, wherein said cancer is selected from breast cancer, such as triple negative breast cancer, bladder cancer, liver cancer, cervical cancer, pancreatic cancer, leukemia, lymphoma, renal cancer, colon cancer, glioma, prostate cancer, ovarian cancer, melanoma and lung cancer, as well as hypoxic tumors.

47. The method of claim 45, in conjunction with radiation therapy.

48. A method of treating hypoxic tumors, comprising administering a therapeutically effective amount of a compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

49. A method of treating type II diabetes, comprising administering a therapeutically effective amount of a compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

50. A method of treating a disease selected from inflammatory diseases, neurodegenerative disorders, autoimmune diseases and viral infections, comprising administering a therapeutically effective amount of a compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

51. A pharmaceutical composition comprising a compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent, carrier and/or excipient.

52. A pharmaceutical composition, comprising a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and another anticancer agent selected from alkylating agents, antimetabolites, anticancer camptothecin derivatives, plant-derived anticancer agents, antibiotics, enzymes, platinum coordination complexes, tyrosine kinase inhibitors, hormones, hormone antagonists, monoclonal antibodies, interferons, and biological response modifiers.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/072790

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D401/04 C07D498/14 A61K31/5377 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2015/108861 A1 (MILLENNIUM PHARM INC [US]) 23 July 2015 (2015-07-23) cited in the application Abstract; claims.	1-52
A	WO 2012/085815 A1 (NOVARTIS AG [CH]; CORNELLA TARACIDO IVAN [US]; HARRINGTON EDMUND MARTI) 28 June 2012 (2012-06-28) cited in the application Abstract; claims.	1-52
A,P	WO 2017/140841 A1 (SPRINT BIOSCIENCE AB [SE]) 24 August 2017 (2017-08-24) Abstract; claims.	1-52

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 September 2018	04/10/2018

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2018/072790

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