# Nitrogen Containing Heterocyclic PI3Kδ Inhibitors

## 1. FIELD OF THE INVENTION

The present invention belongs to pharmacetical field, and specifically relates to nitrogen atom containing heterocyclic compounds useful as inhibitors of phosphoinositide 3-kinase delta (PI3Kδ) isoform, or pharmaceutically acceptable salts; or stereoisomers and deuterated derivatives thereof; The invention is also directed to the preparation of these compounds, pharmaceutical compositions comprising these compounds and the use of these compounds in the manufacture of a medicament for the prevention or treatment of inflammatory disorders and cancers.

## 2. BACKGROUND OF THE INVENTION

Cancers are abnormal new growth in a body, triggered by carcinogenic factors, which causes changes in genetic material at cellular level, and leads to abnormal expression of genes. Cancer cells cannot be regulated as normal cells in host bodies, and are self-promoting, even after withdraw of carcinogenic factors. Cancer cells consume a large amount of nutrients in host bodies. If it were not diagnosed and treated in time, cancer metastasis might happen, and cancer cells would continue to grow in other parts of host bodies, and releasing toxins during the process, causing weight-loss, anemia, organ failure, and finally death of the patient.

There are three mainstream treatments for cancer patients, chemotherapy, radiotherapy, and surgery. Usually, radiotherapy and surgery cannot completely eliminate all cancer cells, and they are especially less effective for late stage cancer patients. Chemotherapy, on the other hand, is getting important in cancer patient treatment. Most of the traditional anticancer drugs cannot distinguish cancer cells from normal tissue cells, and therefore, have severe side effects. Newer generation anticancer drugs target specific cancer cell markers, and therefore, can act specifically on cancer cells. As a result, they usually have enhanced efficacy, and reduced side effects. For example, the median life-span of late stage colon cancer patients has increased by 66.7%, and the efficacy of late stage breast cancer treatment has increased by 71.3%.

Because of the large investment of pharmaceutical industry on target specific anticancer research and development, plus the rapidly increase of market demand for this class of anticancer drugs, molecular target specific anticancer is becoming the fastest growing secter of the worldwide anticancer drug market.

The phosphoinositide 3-kinase delta (PI3Kδ) signaling pathway is one of themost highly

mutated systems in human cancers. PI3Ksignaling is involved in many disease states including allergic contact dermatitis, rheumatoid arthritis, osteoarthritis, inflmammatory bowel diseases, chronic obstructive pulmonary disorder, psoriasis, multiple sclerosis, asthma, disorders related to diabetic complications, and inflammatory complications of the cardiovascular system such as acute coronary syndrome.

PI3Ks are members of a unique and conserved family of intracellular lipid kinases that phosphorylate the 3'-OH group on phosphatidylinositols or phosphoinositides. The PI3K family comprises 15 kinases with distinct substrate specificities, expression patterns, and modes of regulation. The class I PI3Ks (p110α, p110β, p110δ, and p110γ) are typically activated by tyrosine kinases or G-protein couples receptors to generate PIP3, which engages downstream effectors such as those in the Akt/PDK1 pathway, mTOR, the Tec family kinases, and the Pho family GTPases.The class II and II PI3Ks play a key role in intracellular trafficking through the synthesis of PI(3)P and PI(3,4)P2. The PIKKs are protein kinases that control cell growth (mTORC1) or monitor genomic integrity (ATM, ATE, DNA-PK, and hSmg-1).

The delta (δ) isoform of class I PI3K has been implicated, in particular, in a number of diseases and biological processes. PI3Kδ is expressed primarily in hematopoietic cells including leukocytes such as T-cells, dendritic cells, neutorphils, mast cells, B-cells, and macrophages. PI3Kδ is integrally involved in mammalian immune system functions such as T-cell function, B-cell activation, mast cell activation, dendritic cell function, and neutrophil activity. Due to its integral role in immune system function, PI3Kδ is also involved in a number of diseases related to undesirable immune response such as allergic reactions, inflammatory diseases, inflammation mediated angiogenesis, rheumatoid arthritis, auto-immune diseases such as lupus, asthma, emphysema and other respiratory diseases.

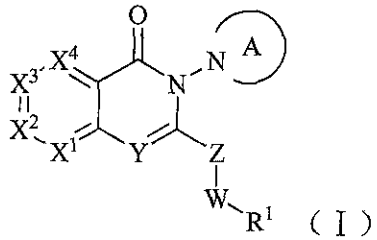
Downstream mediators of the PI3K signal transduction pathway include Akt and mammalian target of rapamycin (mTOR). Akt possesses a plckstrin homology (PH) domain that binds PIP3, leading to Akt kinase activation. Akt phosphorylates many substrates and is a central downstream effector of PI3K for diverse cellular responses. One important function of Akt is to augment the activity of mTOR, through phosphorylation of TSC2 and other mechanisms. mTOR is a serine-threonine kinase related to the lipid kinases of the PI3K family. mTOR has been implicated in a wide reange of biological processes including cell growth, cell proliferation, cell motility and survival. Disregulation of the mTOR pathway has been reported in various types of cacer. mTOR is

a multifunctional kinase that integrates growth factor and nutrient signals to regulate protein translation, nutrient uptake, autophagy, and mitochondrial function.

As such, kinases, particulatly PI3Ks are prime targets for durg development. Patent WO2009088990 of Intelikine and US 6667300 of Icos have described the invention of PI3Kδ inhibitors for the treatment of cancer and inflammation, but no drugs of PI3Kδ inhibitors have reached market to date. There remains a need for PI3Kδ inhibitors that are selective, safe, and efficacious, suitable for drug development.

## 3. DETAILED DESCRIPTION OF THE INVENTION

Compounds of the present invention are described by structural formula (I), or pharmaceutically acceptable salts and stereoisomers thereof; or deuterated derivatives thereof:



( I )

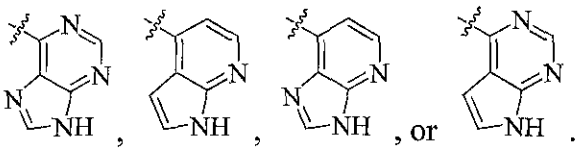
Wherein, $X^1$, $X^2$, $X^3$, and $X^4$ are independently $CR^2$; $R^2$ are independently selected from the group consisting hydrogen, halogen, $C_{1\text{-}6}$alkyl, halogenated $C_{1\text{-}6}$alkyl, and $C_{1\text{-}6}$alkoxy;

Yare N;

A are independently selected from the group consisting azacyclopropyl, azacyclobutyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyridinyl, morpholino, and piperazinyl; and A can be further substituted by 1 to 3 $R^b$, $R^b$ are independently selected from the group consisting hydrogen, halogen, hydroxy, cyano, amino, $C_{1\text{-}6}$alkylamino, $C_{1\text{-}6}$dialkylamino, $C_{1\text{-}6}$alkoxy, $C_{1\text{-}6}$alkyl, and trifluoromethyl;

Z are $-CH(R^3)-$, and $R^3$ are independently selected from the group consisting hydrogen, and $C_{1\text{-}3}$alkyl unsubstituted or substituted with at least one hydroxyl or fluorine, cylcopropylunsubstituted or substituted with at least one hydroxyl or fluorine;

W are $-N(R^4)-$, $R^4$ are independently selected from the group consisting hydrogen, and methyl;

$R^1$ are .

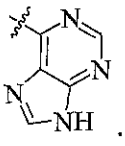
In one embodiment of the compounds of the present invention, $X^1$, $X^2$, $X^3$, and $X^4$ are independently $CR^2$; $R^2$ are independently selected from the group consisting hydrogen, fluorine, chlorine, methyl, and trifluoromethyl;

Y are N;

A are independently selected from the group consisting azacyclopropyl, azacyclobutyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyridinyl, morpholino, and piperazinyl; and A can be further substituted by 1 to 3 $R^b$, $R^b$ are independently selected from the group consisting hydrogen, halogen, hydroxy, cyano, $C_{1\text{-}3}$alkyl, $C_{1\text{-}3}$alkoxy, and trifluoromethyl;

Z are $-CH(R^3)-$, and $R^3$ are independently selected from the group consisting hydrogen, and $C_{1\text{-}3}$alkyl unsubstituted or substituted with at least one hydroxyl or fluorine; cylcopropylunsubstituted or substituted with at least one hydroxyl or fluorine;

W are $-N(R^4)-$, $R^4$ are independently selected from the group consisting hydrogen and methyl;

$R^1$is .

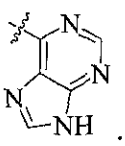
In a second embodiment of the compounds of the present invention, $X^1$, $X^2$, $X^3$, and $X^4$ are independently $CR^2$; $R^2$ are independently selected from the group consisting hydrogen, fluorine, chlorine, methyl, and trifluoromethyl;

Y are N;

A are independently selected from the group consisting azacyclopropyl, azacyclobutyl, pyrrolidinyl, piperidinyl, and morpholino; and A can be further substituted by 1 to 3 $R^b$, $R^b$ are independently selected from the group consisting hydrogen, fluorine, chlorine, hydroxy, and $C_{1\text{-}3}$alkyl;

Z are $-CH(R^3)-$, and $R^3$ are independently selected from the group consisting hydrogen, and $C_{1\text{-}3}$alkyl;

W are $-N(R^4)-$, $R^4$ are independently selected from the group consisting hydrogen and methyl;

$R^1$is .

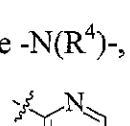
In a third embodiment of the compounds of the present invention, $X^1$, $X^2$, $X^3$, and $X^4$ are independently $CR^2$; $R^2$ are independently selected from the group consisting hydrogen, fluorine, chlorine, and methyl;

Y are N;

A are independently selected from the group consisting azacyclobutyl, piperidinyl, and morpholino; and A can be further substituted by 1 to 3 $R^b$, $R^b$ are independently selected from the group consisting hydrogen, fluorine, hydroxy, and methyl;

Z are $-CH(R^3)-$, and $R^3$ are independently selected from the group consisting hydrogen and $C_{1-3}$alkyl;

W are $-N(R^4)-$, $R^4$ are independently selected from the group consisting hydrogen and methyl;

$R^1$is  .

As used herein the following definitions are applicable.

The term "Halogen" refers to fluorine, chlorine, bromine and iodine.

The term "$C_{1-6}$Alkyl" refers carbon chains of 1 to 6 carbon atoms, which may be linear or branched, and combinations thereof, including $C_{1-5}$alkyl, $C_{1-4}$alkyl, $C_{1-3}$alkyl, and the like. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, 2-methylpropyl, 1-methylpropyl, 1,1-dimethylethyl, pentyl, 3-methylbutyl, 2-methylbutyl, 1-menthylbutyl, 1-ethylpropyl, hexyl, 4-methylpentyl, 3-methylpentyl, 2-methylperntyl, 1-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethybutyl, 2-ethylbutyl, 1,2-dimethylpropyl, and the like. The terms "$C_{1-5}$alkyl", "$C_{1-4}$alkyl", and "$C_{1-3}$alkyl" refer to examples containing 1-5 carbon atoms, 1-4 carbon atoms, and 1-3 carbon atoms, respectively.

The term " $C_{2-6}$Alkenyl" refers carbon chains containing one or more carbon-carbon double bonds and 2 to 6 carbon atoms, which may be linear or branched, and combinations thereof, unless the carbon chain is defined otherwise, including $C_{2-5}$Alkenyl, $C_{2-4}$Alkenyl, $C_{2-3}$Alkenyl, $C_{3-6}$Alkenyl, and the like. Examples of alkenyl groups include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 1-methylethenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-methyl-1-propenyl, 2-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 1-pentenyl, 2-pentenyl,

3-pentenyl, 4-pentenyl, 1-methyl-1-butenyl, 2-methyl-1-butenyl, 3-methyl-1-butenyl, 1-methyl-2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-methyl-3-butenyl, 2-methyl-3-butenyl, 3-methyl-3-butenyl, 1,1-dimethyl-2-propenyl, 1,2-dimethyl-1-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-1-propenyl, 1-ethyl-2-propenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-methyl-1-pentenyl, 2-methyl-1-pentenyl, 3-methyl-1-pentenyl, 4-methyl-1-pentenyl, 1-methyl-2-pentenyl, 2-methyl-2-pentenyl, 3-methyl-2-pentenyl, 4-methyl-2-pentenyl, 1-methyl-3-pentenyl, 2-methyl-3-pentenyl, 3-methyl-3-pentenyl, 4-methyl-3-pentenyl, 1-methyl-4-pentenyl, 2-methyl-4-pentenyl, 3-methyl-4-pentenyl, 4-methyl-4-pentenyl, 1,1-dimethyl-2-butenyl, 1,1-dimethyl-3-butenyl, 1,2-dimethyl-1-butenyl, 1,2-dimethyl-2-butenyl, 1,2-dimethyl-3-butenyl, 1,3-dimethyl-1-butenyl, 1,3-dimethyl-2-butenyl, 2,2-dimethyl-3-butenyl, 2,3-dimethyl-1-butenyl, 2,3-dimethyl-2-butenyl, 2,3-dimethyl-3-butenyl, 3,3-dimethyl-1-butenyl, 3,3-dimethyl-2-butenyl, 1-ethyl-1-buenyl, 1-ethyl-2-butenyl, 1-ethyl-3-butenyl, 2-ethyl-1-butenyl, 2-ethyl-2-butenyl, 2-ethyl-3-butenyl, 1,1,2-trimethyl-2-propenyl, 1-ethyl-1-methyl-2-propenyl, 1-ethyl-2-methyl-1-propenyl, 1-ethyl-2-methyl-2-propenyl, 1,3-butadienyl, 1,3-pentadienyl, 1,4-pentadienyl, 1,4-hexadienyl, and the like. Examples of"$C_{3-6}$cycloalkenyl" include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, 1,3-cyclopentadienyl, cyclohexenyl, 1,4-cyclohexadienyl, and the like.

The term " $C_{2-6}$Alkynyl" refers carbon chains containing one or more carbon-carbon triple bonds and 2 to 6 carbon atoms, which may be linear or branched, and combinations thereof, unless the carbon chain is defined otherwise, including $C_{2-5}$Alkynyl, $C_{2-4}$Alkynyl, $C_{2-3}$Alkynyl, and the like. Examples of alkynyl groups include, but are not limited to, ethynyl, 1-propynyl, 2-propenyl, 2-butynyl, 3-butynyl, 1-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-methyl-2-butynyl, 1-methyl-3-butynyl, 2-methyl-3-butynyl, 1,1-dimethyl-2-propynyl, 1-ethyl-2-propynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-methyl-2-pentynyl, 1-methyl-3-pentynyl, 1-methyl-4-pentynyl, 2-methyl-3-pentynyl, 2-methyl-4-pentynyl, 3-methyl-4-pentynyl, 4-methyl-2-pentynyl, 1,1-dimethyl-2-butynyl, 1,1-dimethyl-3-butynyl, 1,2-dimethyl-3-butynyl, 2,2-dimethyl-3-butynyl, 1-ethyl-2-butynyl, 1-ethyl-3-butynyl, 2-ethyl-3-butynyl, 1-ethyl-1-methyl-2-propynyl, and the like.

The term "$C_{1-6}$alkoxy" refers to straight or branched chain alkoxides of the number of 1-6 carbon atoms, or any number within this range, including $C_{1-5}$alkoxy, $C_{1-4}$alkoxy, $C_{1-3}$alkoxy, and the like. Examples of alkoxy groups include, but are not limited to, methoxy (MeO-), ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, *tert*-butoxy, *sec*-butoxy, pentoxy, *neo*-pentoxy, hexanoxy,

and the like.

"3-14 membered Cycloalkyl" is a subset of alkyl and means a saturated carbocyclic structure having a specified number of carbon atoms, including 3-12 membered cycloalkyl, 3-10 memberedcycloalkyl, 3-8 memberedcycloalkyl, 3-6 memberedcycloalkyl, 3-5 memberedcycloalkyl, 5-10 memberedcycloalkyl, 5-8 membered cycloalkyl, 5-6 membered cycloalkyl, 4-6 membered cycloalkyl, and the like. Also included in the group are 3-8 membered monocycloalkyl and 6-14 membered polycycloalkyl.

The term "3-8 membered monocycloalkyl" refers to a saturated carbocyclic structure of a single ring with 3-8 carbon atoms, including 3-6 membered monocycloalkyl, 3-5 membered monocycloalkyl, 5-8 membered monocycloalkyl, 5-6 membered monocycloalkyl, and the like. Examples of 3-8 membered monocycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. "3-8 membered monocycloalkyl" can be further substituted by $C_{1-6}$ alkyl, including, but are not limited to, methylcyclopropyl, dimethylcyclopropyl, methylcyclobutyl, dimethylcyclobutyl, methylcyclopentyl, dimethylcyclopentyl, methylcyclohexyl, dimethylcyclohexyl, and the like.

The term "6-14 membered polycycloalkyl" refers to a carbocyclic structure of two or more fused rings with 6-14 carbon atoms, including 6-12 membered bicycloalkyl, 8-12 membered bicycloalkyl, 7-10 membered bicycloalkyl, and the like. Examples of 6-14 membered polycycloalkyl groups include, but are not limited to, [3.1.0]bicyclohexyl, [4.1.0]bicycloheptyl, [2.2.0]bicyclohexyl, [3.2.0]bicycloheptyl, [4.2.0]bicyclooctyl, tetrahydrocyclopentadienyl, decahydronaphthalenyl, tetradecahydrophenanthrenyl, and the like.

The term "6-14 membered aryl" refers to a mono- or polycyclic aromatic ring system having 6 to 14 carbon atoms, including 6-10 membered aryl, 6-8 membered monoaryl, 8-14 membered fused aryl, and the like.

Examples of 6-8 membered monoaryl groups include, but are not limited to, phenyl, cyclooctatetraene, and the like.

The term "8-14 membered fused aryl" refers to a carbocyclic structure of two or more fused rings, of which at least one is aromatic, with 8-14 carbon atoms, including 10-14 membered aromatic groups, such as naphthalenyl and phenanthrenyl, and 8-14 membered partially aromatic fused ring structures, such as $C_{3-8}$benzocycloalkyl, $C_{3-6}$benzocycloalkenyl. Examples include, but are not limited to, 2,3-dihydro-1*H*-cyclopentadienyl, 1*H*-cyclopentadienyl, 1,4-dihydronaphthalenyl,

and the like.

The term "3-14 membered Heterocyclyl" refers to saturated or unsaturated rings or ring systems containing at least one heteroatom on the ring, including 3-10 membered heterocyclyl, 4-12 membered heterocyclyl, 3-8 membered heterocyclyl, 3-6 membered heterocyclyl, 5-10 membered heterocyclyl, 5-8 membered heterocyclyl, 5-6 membered heterocyclyl, and the like. Also included in this group are 3-8 membered heteromonocyclyl and 6-14 membered heteropolycyclyl. Heteroatoms indenpendently selected from O, S and N, further including the oxidized forms of carbonyl or sulfur, namely SO and $SO_2$.

The term "3-8 membered heteromonocyclyl" refers to a saturated or unsaturated single ring structure of 3-8 atoms and containing at least one heteroatom on the ring, including 5-8 membered heteromonocyclyl, 5-6 membered heteromonocyclyl, and the like. Examples of saturated 3-8 membered heteromonocyclyls include, but are not limited to, aziridinyl, azetidinyl, thiacyclobutanyl, tetrahydrofuryl (THF), pyrrolidinyl, imidazolidinyl, pyrazolidinyl, 1,4-dioxanyl, 1,3-dioxanyl, 1,3-dithianyl, piperidinyl, morpholinyl, piperazinyl, and the like. The $CH_2$'s on the ring can be further substituted by O, such as piperidin-2-onyl. Examples of unsaturated 3-8 membered heteromonocyclyls include, but are not limited to, 2,5-dihydrothiophenyl, 4,5-dihydropyrazolyl, 1,2-dihydropydinyl, 3,4-dihydro-2*H*-pyran, 5,6-dihydro-4H-1,3-oxazinyl, 1,2,3,4-tetrahydropydinyl, 1,2,3,6-tetrahydropydinyl, furyl, thienyl, thiazolyl, thiadiazolyl, oxazolyl, oxadiazolyl, imidazolyl, pyridinyl, pyrimidinyl, 1,4-dioxinyl, 2*H*-1,2-oxazinyl, 4*H*-1,2- oxazinyl, 6*H*-1,2- oxazinyl, 4*H*-1,3-oxazinyl, 6*H*-1,3- oxazinyl, 4*H*-1,4- oxazinyl, pyridazinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4- triazinyl, 1,3,5- triazinyl, 1,2,4,5-tetrazinyl, oxepinyl, thiepinyl, 1*H*-azepinyl, azocinyl, and the like. The $CH_2$'s on the ring can be further substituted by O, such as pyridin-2-onyl, and pyran-4-onyl.

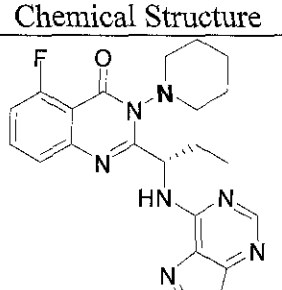
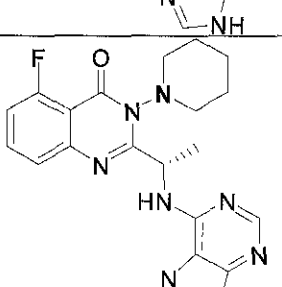
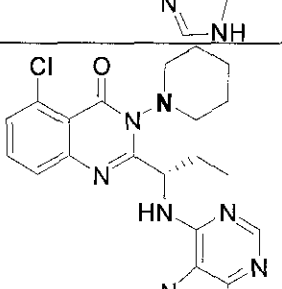
The term "6-14 membered heteropolycyclyl" refers to a ring sytems of 6-14 atoms in which one heteromonocyclyl group is fused with one or more rings of cycloalkyl, aryl, heterrocyclyl, and heteroaryl, including 8-12 membered heteropolycyclyl, 7-10 membered heteropolycyclyl, 9-10 membered heteropolycyclyl, 9-12 membered heteropolycyclyl, 6-10 membered heteropolycyclyl, 8-14 membered heteropolycyclyl and the like.

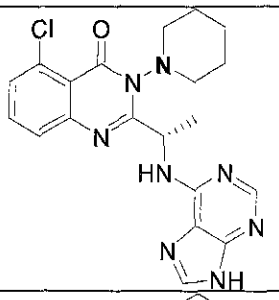
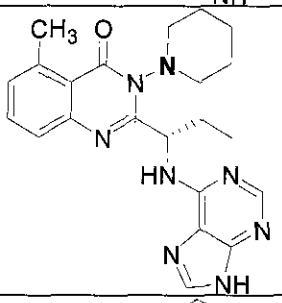
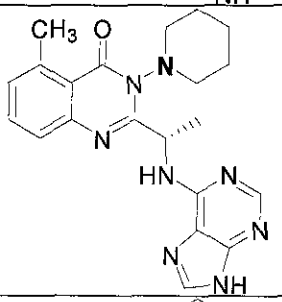
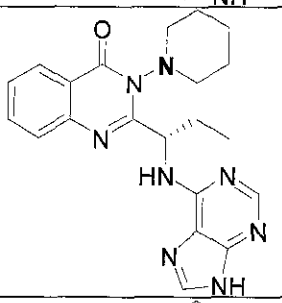
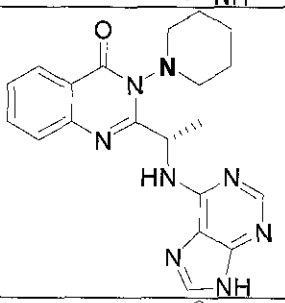
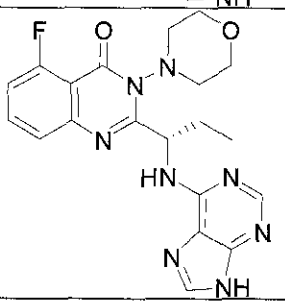
Examples of saturated 6-10 membered heteropolycyclyls include, but are not limited to, cyclobutane fused pyrrolidinyl, cyclopentane fused pyrrolidinyl, azetidine fused imidazolidinyl, and the like. Examples of unsaturated 6-10 membered heteropolycyclyls include, but are not limited to, 1,3-dihydrobenzofuran, benzo[d][1.3]dioxacyclopentenyl, isoindolinyl, indolinyl, chromanyl,

pyrrolidino[3,4-c]pyrrolyl, dihydropyrrolopyridinyl, dihydropyrrolopyrimidinyl, dihydropyrrolopyridazinyl, pyrrolidinopyridinyl, pyrrolidinopyrimidinyl, pyrrolidinopyridazinyl, and the like.

The term "8-14 membered heteropolyaryl" refers to a heteroaromatic ring system that contains at least one ring heteroatom selected from O, S and N, such as 8-12 membered heteropolyaryl, 9-10 membered heteropolyaryl, and 10-14 membered heteropolyaryl. Examples of heterpolyaryl groups include, but are not limited to: benzofuranyl, benzothiophenyl, indolyl, benzoxazolyl, benzimidazolyl, indazolyl, benzotriazolyl, quinolyl, isoquinolyl, pyridinopyrrazolyl, pyridinopyrrolyl, pyrimidinopyrrazolyl, pyirmidinopyrrolyl, pyrazinopyrrazolyl, pyridazinopyrrolyl, acridinyl, phenanthridinyl, benzopyridazinyl, phthalazinyl, quinazolinyl, phenazinyl, pteridinyl, guanyl, naphthyridinyl, and the like.

Representative compounds of the present invention:

| Compound No. | Chemical Structure |
|---|---|
| 1 |  |
| 2 |  |
| 3 |  |

| Compound No. | Chemical Structure |
|---|---|
| 4 |  |
| 5 |  |
| 6 |  |
| 7 |  |
| 8 |  |
| 9 |  |

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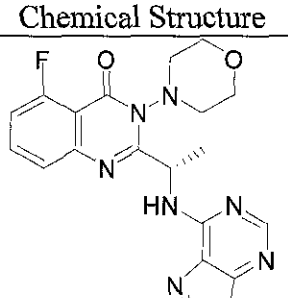
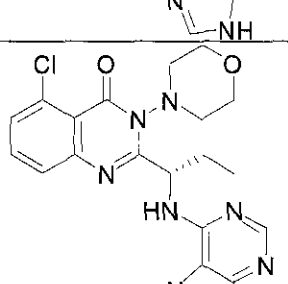
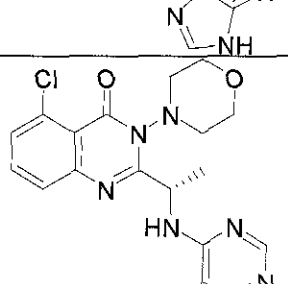
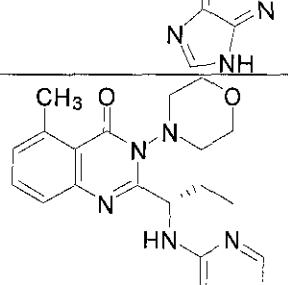
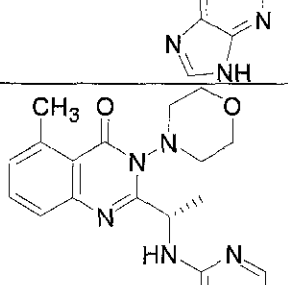
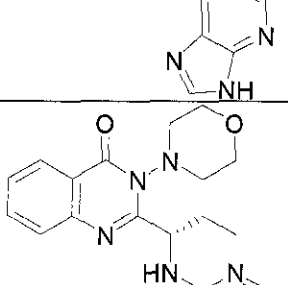
| 10 |  |
| 11 |  |
| 12 |  |
| 13 |  |
| 14 |  |
| 15 |  |

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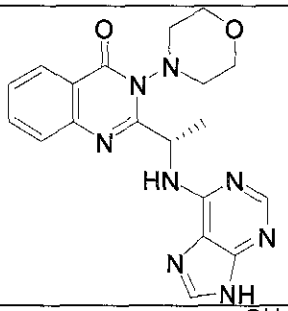
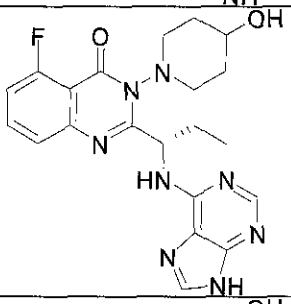
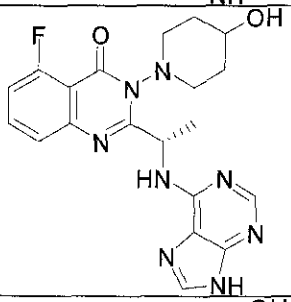
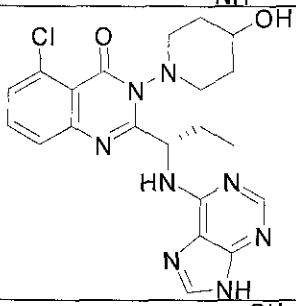
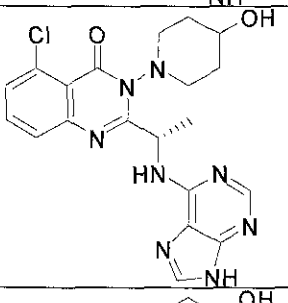
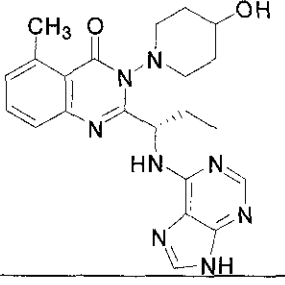
| 16 |  |
| 17 |  |
| 18 |  |
| 19 |  |
| 20 |  |
| 21 |  |

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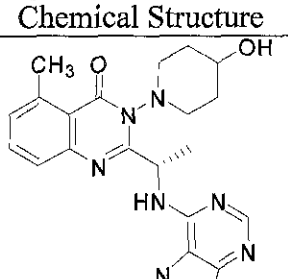
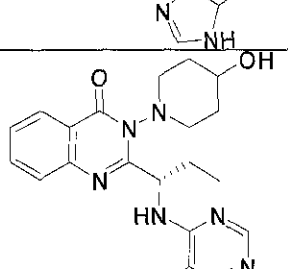
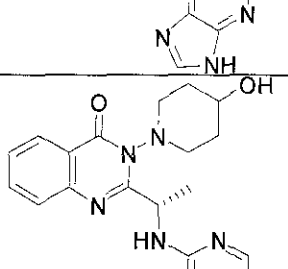
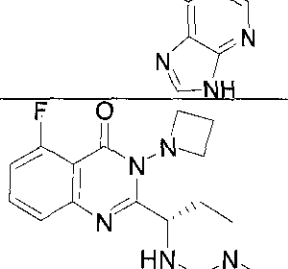
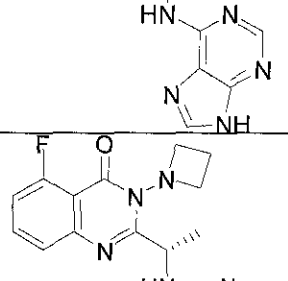
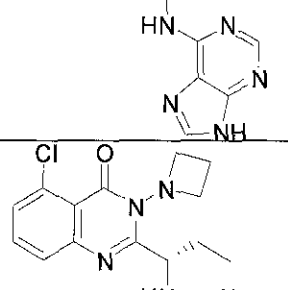
| 22 |  |
| 23 |  |
| 24 |  |
| 25 |  |
| 26 |  |
| 27 |  |

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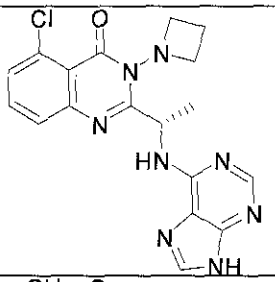
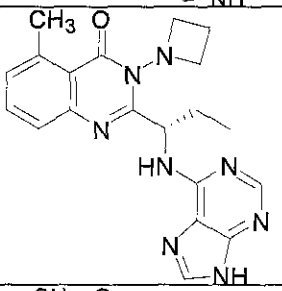
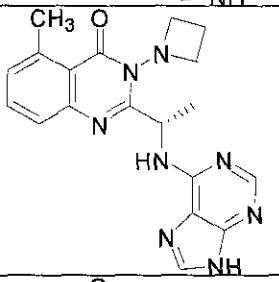
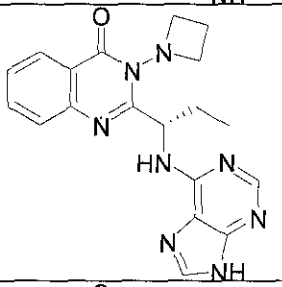
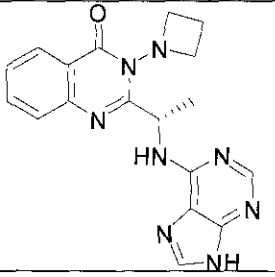
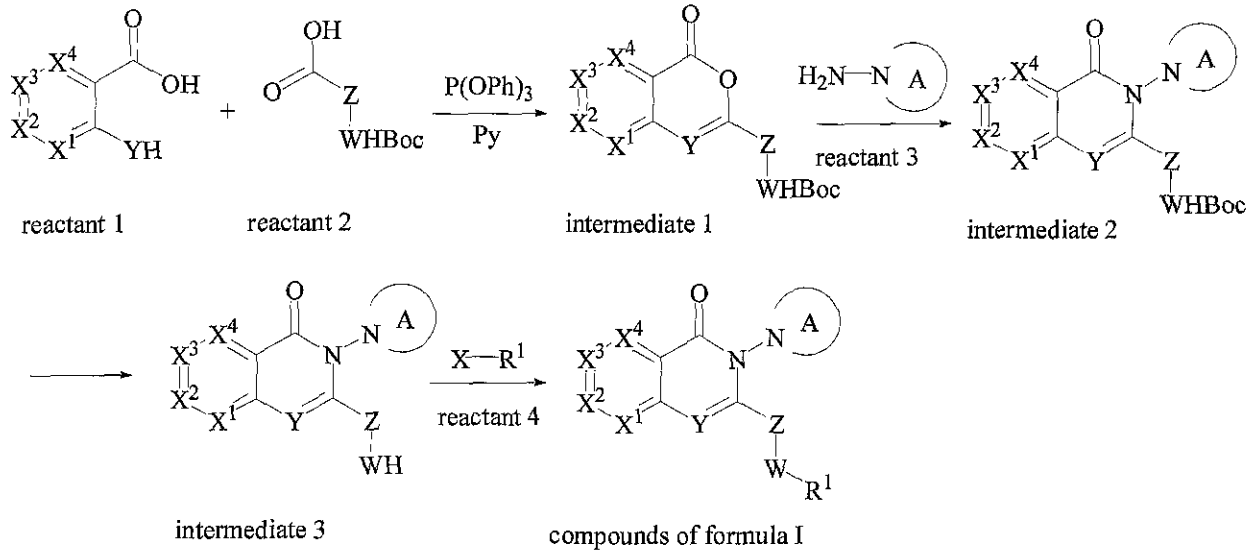
| 28 |  |
| 29 |  |
| 30 |  |
| 31 |  |
| 32 |  |

The compounds of the present invention can be prepared by the procedures described below:

Scheme 1.




General Procedure:

1. To a solution of reactant **1** (1 equiv.) in pyridine was added reactant **2** (1-1.5 equiv), triphenoxyphosphine (1-1.5 equiv.). The resulting reaction mixture was heated to 45-85 ℃, and was stirred at this temperature for several hours to yield intermediate **1**, which was used directly for the next step.
2. To the reaction mixture of the previous stepcontaining intermediate **1** was added reactant **3** (1-1.5 equiv.). The resulting mixture was heated to above 100 ℃, and was stirred at this temperature for several hours. After cooled to room temperature, the reaction mixture was concentrated, and the intermediate **2** was isolated by column chromatography.
3. A solution of intermediate **2** (1-1.5 equiv.) in an organic solvent, such as dichloromethane, ethylether, or methanol, was kept at room temperature or cooled in an ice bath. To this solution was added trifluoroacetic acid, or gaseous hydrogenchloride through bubbling, until intermediate **2** can no longer be detected. The reaction mixture was then concentrated to yield intermediate **3**.
4. To a solution of intermediate **3** in an organic solvent, such as *tert*-butnaol, was added reactant **4** (1-1.5 equiv.), and a base (2-5 equiv.), such as triethylamine, diisopropylethylamine. The resulting mixture was heated to and kept at reflux until intermediate **3** can no longer be detected. After cooled to room temperature, the reaction mixture was concentrated, and compounds of formula (I) was isolated by silica gel column chromatography, or preparative HPLC.

In the reaction scheme 1, $X^1$, $X^2$, $X^3$, $X^4$, Y, Z, W, A, and $R^1$ are defined in the previous section. For reaction 4, X is a halogen, such as chlorine, bromine, or iodine. If necessary, common protecting groups were used to protect interfering functional groups, and those protecting groups were removed later by commonly used methods. Reactants that were not commercially available were prepared via standard methods.

The compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Representative salts of the present invention include, but are not limited to, the following: salts derived from inorganic bases, such as aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, mangamous, potassium, sodium, zinc, copper, nickel, cobalt, and the like; salts derived from organic bases, such as *tert*-pentylamine, dibenzylamine, morpholine, glucosamine, phenylalanine alkylester, ethylenediamine, *N*-methylglucamine, guanidine, diethylamine, triethylamine, dicyclohexylamine, *N,N'*-dibenzylethylenediamine, ChloroProcaine, Procaine, hydroxyethylamine, *N*-benzylphenethylamine, piperazine, tetramethylammonium, tri(hydroxymethyl)methylammonium, and the like; salts derived from inorganic acids, such as fluoride, chloride, bromide, iodide, nitrate, perchlorate, sulfate, bisulfate, phosphate, hydrogenphosphate, dihydrogenphosphate, carbonate, bicarbonate, borate, and the like; salts derived from organic acids, such as methanesulfonate, trifluoromethanesulfonate, ethanesulfonate, benzenesulfonate, toluenesulfonate, acetate, malate, fumarate, succinate, citrate, formate, tartrate, maleate, glycine, trimethylglycine, arginine, ornithine, glutamate, aspartate, and the like.

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds.

Some of the compounds described herein contain olefinic double bonds, and unless specified

otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist as tautomers, which have different points of attachment of hydrogen accompanied by one or more double bond shifts. For example, a ketone and its enol form are keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of the present invention.

The compounds described herein are meant to include unnatural proportions of deuterium (chemical symbol D) isotope at one or more of hydrogen atoms that constitute such compounds. All deuterium isotopic varations of the compounds of the present invention are encompassed within the scope of the present invention.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier, such as excipient, adhesive, humidizer, disintegrating agent, thickening agent, and the like.

Compounds of the present invention described by structural formula I, or pharmaceutically acceptable salts and solvates thereof; or deuterium substituted isotopic isomers thereof; can be made into pharmaceutical compsitions for clinical applications by admixing one or more pharmaceuticaly acceptable carriers, including commonly used formulations, such as tablets, granules, capsules, powders, injectables, inhalers, sublingual agents, syrups, gels, ointment, supporsitories, lotion, nasal drop, aerosol spray, subcutaneous transdermal, and the like.

Compounds of the present invention described by structural formula I, or pharmaceutically acceptable salts and solvates thereof; or deuterium substituted isotopic isomers thereof; or acceptable pharmaceutical compsitions thereof, are useful in a method for the prevention or treatment of the following diseases, disorders and conditions, including, not are not limited to inflammatory disorders ofallergy, asthma, rheumatoid arthritis, osteoarthritis, allergic conjunctivitis, allergic keratitis, xerophthalmia, chronic obstructive pulmonary disease (COPD), lupus erythematosus, psoriasis, multiple sclerosis, and late stage kidney disease; and the cancers of leukemia, lymphoma, bone marrow hyperplasia, non-Hodgkin's lymphoma, and chronic idiopathic myelofibrosis, and the like.

The utility of the compounds in accordance with the present invention is further demonstrated

by their in vitro ezyme acitivities. Other compounds of the present invention should have similar biological activities, and therefore similar utility. It is to be understood that the scope of the present invention is not limted in any way by the scope of the following examples.

EXAMPLES OF IN VITRO EZYMETIC ACTIVITIES

Samples: Compounds of present invention, prepared as described.

Method:

1. A sample was dissolved in DMSO to make a stock solution of 1 mM. An aliquot of the stock solution was diluted with DMSO to 10 μM, followed by a serial diluation to 10 different concentrations with a dilution factor of 4: 10 μM, 2.5 μM, 0.625 μM, 0.156 μM, 0.039 μM, 0.009 μM, 0.00244 μM, 0.61 nM, 0.15 nM, 0.04 nM;
2. To a 96-well plate was added 4 μL each of these serial solutions;
3. To this 96-well plate was added 1 μL of 1x kinase buffer. 1x kinase buffer: 50 mM HEPES, pH 7.5; 3 mM MgCl2, 1 mM EGTA, 100 mM NaCL, 0.03%CHAPS, 2 mM DTT;
4. The serial solutions step 2 were well mixed with kinase buffer of step 3, and incubated for 10 min.;
5. To a 384-well plate was add aliguots of 2.5 μL of mixtures of step 4. Two copies were made on the same plate and set aside;
6. To this 384-well plate was added 2.5 μL of a solution of PI3Kα and PI3Kδ, and shaked well. The final concentrations of PI3Kα and PI3Kδ were 1.65 nM and 5.7 nM, respectively;
7. To this 384-well plate was added 5 μL of a solution of the substrate ($PIP_2$), ATP reaction buffer, and shaked well;
8. PI3Kα and PI3Kδ were incubated at room temperature for 1h and 2 h;
9. To this plate was added 10μL of a reaction solution to quench to reaction, and plate was read by Caliper;
10. To determine $IC_{50}$, the following equation was applied:

    % inhibition = 100 – (maxium conversion – observed conversion)/(maxium conversion – minimum conversion) x 100

    The $IC_{50}$'s were determined with non-linear regression using XL Fit software.

Experimental Data:

**Table 1 in vitro Activities of Representative Compounds**

| Sample | PI3Kδ Inhibition $IC_{50}$ (nM) | PI3Kα Inhibition $IC_{50}$ (nM) |
|---|---|---|
| Compound 1 | 2.885 | - |
| Compound 10 | 5.3 | 1825 |
| Compound 18 | 4.1 | 244 |
| Compound 26 | 5.2 | 833 |

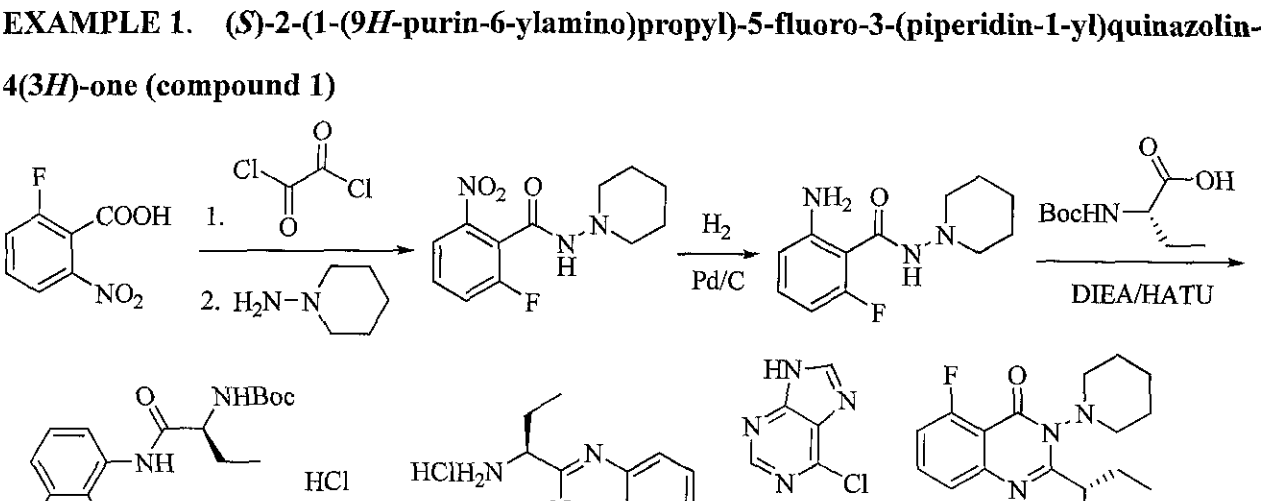
Note: " - " undetermined

Based on the data shown in Table 1, the compounds of present invention are highly potent inhibitors of PI3Kδ, and highly selective relative to PI3Kα.

## 4. DETAILED EXPERIMENTAL PROCEDURES

It is to be understood that the scope of the present invention is not limted in any way by the scope of the following examples.

**EXAMPLE 1. (*S*)-2-(1-(9*H*-purin-6-ylamino)propyl)-5-fluoro-3-(piperidin-1-yl)quinazolin-4(3*H*)-one (compound 1)**




(1) 2-Fluoro-6-nitro-*N*-(piperidin-1-yl)benzamide

To a stirred solution of 2-fluoro-6-nitrobenzoic acid (5.50 g, 29.7 mmol) in dicloromethane (50 mL) and DMF (0.4 mL) was added dropwise oxalyl chloride (5.66 g, 44.6 mmol). The resulting reaction solution was stirred at room temperature for 2 hr, concentrated, and then was taken up into dioxane (8 mL). The resulting solution was added dropwise to a stirred solution *N*-amino-piperidine

(2.976 g, 29.7 mmol) in dioxane (20 mL) and water (20 mL) with cooling, and the resulting reaction solution was stirred at room temperature for 30 min. The reaction solution was concentrated under reduced pressure to 1/3 of the original volume, extracted with ethyl acetate. The combined organice solution was washed, dried with sodiumsulfate, filtered, and evaporated to yield the title compound (3.80 g, 47.8%) as a light yellow solid.

(2) 2-Amino-6-fluoro-*N*-(piperidin-1-yl)benzamide

A solution of 2-fluoro-6-nitro-*N*-(piperidin-1-yl)benzamide (3.80 g, 14.2 mmol) in methanol (60 mL) was carefully poured onto Pd/C (10%, 0.4 g), and the resulting reaction mixture was stirred under hydrogen atmosphere for 10 hr. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound (3.0 g, 88.7%).

(3) (*S*)-tert-butyl 1-(3-fluoro-2-(piperidin-1-ylcarbamoyl)phenylamino)-1-oxobutan-2-ylcarbamate

To a solution of 2-amino-6-fluoro-*N*-(piperidin-1-yl)benzamide (3.0 g, 12.6 mmol) in DMF (50 mL) was added *N*-Boc-2-(*S*)-aminobutanoic acid (3.8 g, 18.7 mmol), DIEA (3.7 mL, 21.2 mmol) and HATU (6.0 g, 15.8 mmol). The reaction was stirred at room temperature for 48 hr, and then was quenched with water, extracted with dichloromethane. The combined organice phase was washed with water and brine, dried with sodiumsulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography, and the title compound (1.8 g, 33.8%) was isolated as a white solid.

(4) (*S*)-2-(1-aminopropyl)-5-fluoro-3-(piperidin-1-yl)quinazolin-4(3*H*)-one hydrochloride

A solution of (*S*)-tert-butyl 1-(3-fluoro-2-(piperidin-1-ylcarbamoyl)phenyl-amino)-1-oxobutan-2-ylcarbamate (1.8 g, 4.26 mmol) in ethanol (60 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (8 mL). The reaction was stirred at room temperature for 30 min, and then at 85 °C for 16 hr. After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by preparative HPLC, and the title compound (0.8 g, 55.2%) was isolated as white solid.

(5) (*S*)-2-(1-(9*H*-purin-6-ylamino)propyl)-5-fluoro-3-(piperidin-1-yl)quinazolin-4(3*H*)-one

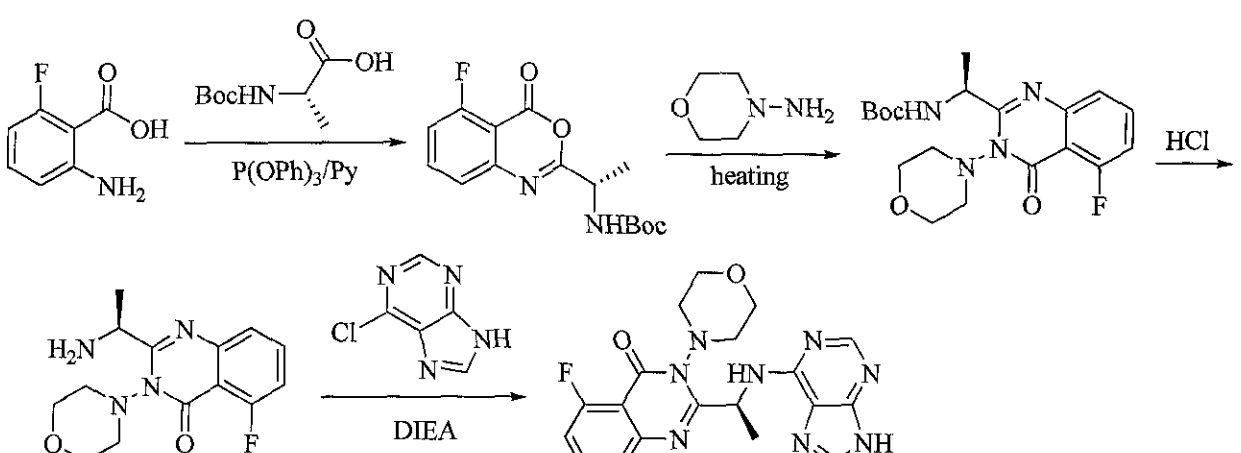
To a solution of (*S*)-2-(1-aminopropyl)-5-fluoro-3-(piperidin-1-yl)quinazolin-4(3*H*)-one hydrochloride (0.8 g, 2.35 mmol) in tert-butanol (30 mL) was added DIEA (0.71 mL, 4.08 mmol). After the reaction was stirred at 0 °C for 30 min, 6-chloro-9H-purine (378 mg, 2.45 mmol) was added. The reaction was stirred at 85 °C for 24 hr. After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by preparative HPLC, and the title

compound (140 mg, 14.1%) was isolated as a white solid.

MS(M+1): 423.2;

$^1$H-NMR($d_6$-DMSO, 400 MHz): δ 12.90 (1H, s), 8.21-8.09 (2H, m), 7.81-7.64 (2H, m), 7.33 (1H, d), 7.19 (1H, t), 5.80 (1H, m), 4.36 (1H, m), 3.87 (1H, t), 3.72 (1H, t), 3.46-3.39 (1H, m), 3.02 (1H, m), 2.01-1.86 (2H, m), 1.80-1.65 (3H, m), 1.65-1.50 (2H, m), 1.11-1.00 (3H, m).

**EXAMPLE 2. (*S*)-2-(1-(9*H*-purin-6-ylamino)ethyl)-5-fluoro-3-morpholino quinazolin-4(3*H*) -one (compound 10)**




(1) (*S*)-tert-butyl 1-(5-fluoro-4-oxo-4*H*-benzo[d][1,3]oxazin-2-yl)ethylcarbamate

To a stirred solution of 2-fluoro-6-aminobenzoic acid (3.1 g, 20.0 mmol) in pyridine (20 mL) in a 100 mL flask was added (*S*)-2-(*N*-tBoc)aminopropionic acid (4.16 g, 22.0 mmol), and triphenylphosphinate (6.2 g, 20.0 mmol). The resulting reaction solution was stirred at 55 °C for 15 hr, and then was used directly for the next step without working-up.

(2) (*S*)-tert-butyl 1-(5-fluoro-3-morpholino-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl carbamate

To the stirred solution of (*S*)-tert-butyl 1-(5-fluoro-4-oxo-4*H*-benzo[d][1,3]oxazin-2-yl)ethylcarbamate (crude reaction mixture) was added *N*-aminomorpholine (2.24 g, 22.0 mmol), and the resulting reaction solution was stirred at 100 °C for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to yield the title compound (2 g, 25.5% two steps) as a light yellow solid.

(3) (*S*)-2-(1-aminoethyl)-5-fluoro-3-morpholinoquinazolin-4(3*H*)-one hydrochloride

A stirred solution of (*S*)-tert-butyl

1-(5-fluoro-3-morpholino-4-oxo-3,4-dihydroquinazolin-2-yl)ethylcarbamate (1.0 g, 2.55 mmol) in chloromethane (20 mL) in a dry 100 mL round bottomed flask was cooled in an ice-bath. To this solution was bubbled in HCl gas for 2 hr, at which time TLC showed the disappearance of the starting material. The reaction solution was then concentrated under reduced pressure, and the crude product was used without further purification.

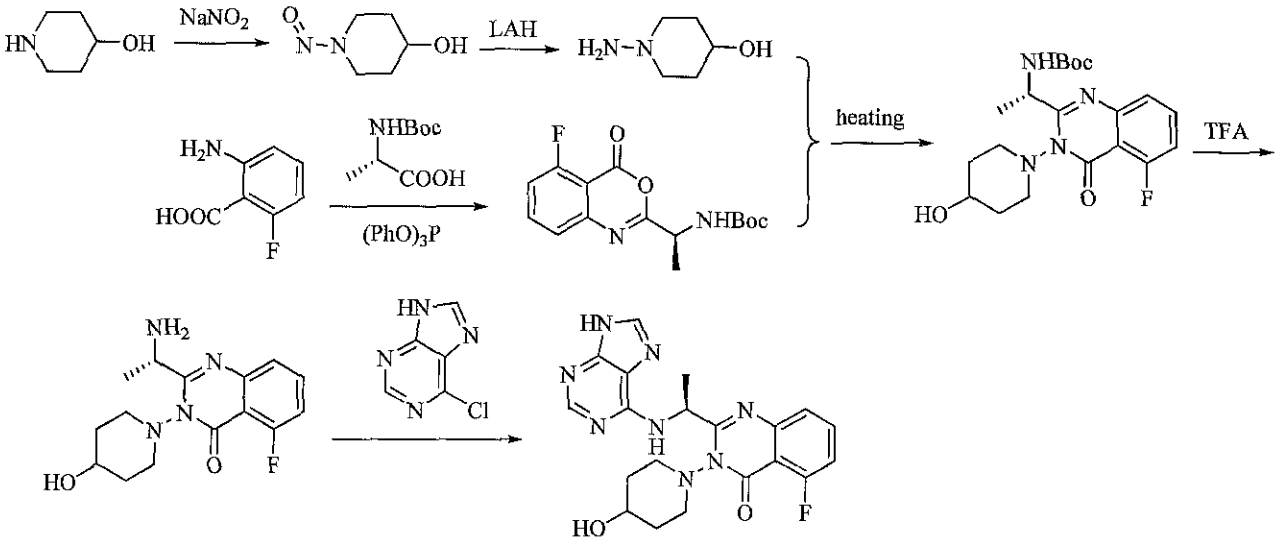
(4) (*S*)-2-(1-(9*H*-purin-6-ylamino)ethyl)-5-fluoro-3-morpholinoquinazolin-4(3*H*)-one

To a stirred solution of the crude (*S*)-2-(1-aminoethyl)-5-fluoro-3-morpholino quinazolin-4(3*H*)-one hydrochloride (~2.55 mmol) in *tert*-butanol (10 mL) in a dry 100 mL round bottomed flask was added DIEA until the solution is basic, and then 6-chloropurine (394 mg, 2.55 mmol) was added, and the reaction was stirred at 90 °C for 24 hr. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography to yield the title compound (500 mg, 47.8% two steps) as a white solid.

MS(M+1): 410.6;

$^1$H-NMR($d_6$-DMSO, 400 MHz): δ 12.94 (1H, s), 8.22-7.93 (3H, m), 7.79-7.68 (1H, m), 7.38 (1H, d), 7.24 (1H, t), 5.92 (1H, m), 4.07-3.79 (3H, m), 3.76-3.67 (1H, m), 3.65-3.50 (1H, m), 3.26-3.17 (2H, m), 3.03-2.95 (1H, m), 1.58 (1H, d).

**EXAMPLE 3. (*S*)-2-(1-(9*H*-purin-6-ylamino)ethyl)-5-fluoro-3-(4-hydroxy piperidin-1-yl) quinazolin-4(3*H*)-one (compound 18)**




(1) (*N*)-Nitroso-piperidin-4-ol

A stirred solution of piperidin-4-ol (10.108 g, 100.0 mmol) in water (20 mL) was cooled in an

ice-bath. To this solution was added a solution of sodium nitrite (13.8 g, 200 mmol) in water (40 mL). After 5 min, glacier acetic acid (8.6 mL, 150 mmol) was added dropwise, and the resulting reaction solution was stirred at 0 °C for 30 min, and room temperature for 6 hr. The reaction was carefully quenched by addition of sodium carbonate (15.9 g, 150 mL) in small portions and the neutralized reaction solution was extracted with ethyl acetate. The combined organic solution was washed with water and brine, dried with sodium sulfate, filtered and evaporated to yield the title compound (12.58 g, 96.6%) as a yellow oil.

(2) (*N*)-Amino-piperidin-4-ol

To the stirred solution of (*N*)-Nitroso-piperidin-4-ol (3.9 g, 30 mmol) in THF (100 mL) under nitrogen atmosphere and cooled in an ice bath was carefully added a 2.5 M solution LAH (21 mL, 52.5 mmol) in THF. After the completion of the addition, the reaction was stirred at reflux for 3 hr. After cooled in an ice-bath, the reaction was quenched very carefully with slow addition of water (15 mL). The ice-bath was then removed, and the mixture was allowed to warm up to room temperature, filtered, and washed with THF. The solution was filtered the second time, dried with sodium sulfate, and concentrated to yield the title compound (3.12 g, 89.7%) as a yellow oil.

(3) (*S*)-tert-butyl 1-(5-fluoro-4-oxo-4*H*-benzo[d][1,3]oxazin-2-yl)ethylcarbamate

To a stirred solution of 2-fluoro-6-aminobenzoic acid (1.132 g, 7.3 mmol) in pyridine (20mL) in a round bottomed flask was added (*S*)-2-(*N*-tBoc)aminopropionic acid (1.52 g, 8.03 mmol), and triphenylphosphinate (2.49 g, 8.03 mmol). The resulting reaction solution was stirred at 55°C for 12 hr, and then was used directly for the next step without working-up.

(4) (*S*)-tert-butyl 1-(5-fluoro-3-(4-hydroxypiperidin-1-yl)-4-oxo-3,4-dihydro quinazolin-2-yl)ethylcarbamate

To the stirred solution of (*S*)-tert-butyl 1-(5-fluoro-4-oxo-4*H*-benzo[d][1,3]oxazin-2-yl)ethylcarbamate (crude reaction mixture) was added *N*-aminopiperidin-4-ol (0.933 g, 8.03 mmol), and the resulting reaction solution was stirred at 100 °C for 12 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to yield the title compound (1.38 g, 46.4% two steps) as a white solid.

(5) (*S*)-2-(1-aminoethyl)-5-fluoro-3-(4-hydroxypiperidin-1-yl)quinazolin-4(3*H*)-one

To a stirred solution of (*S*)-tert-butyl 1-(5-fluoro-3-(4-hydroxypiperidin-1-yl)-4-oxo-3,4-dihydroquinazolin-2-yl)ethylcarbamate (1.38 g,

3.39 mmol) in chloromethane (10 mL) in a dry flask was added TFA ( 10 mL). The reaction solution was stirred at room temperature for 3 hr. and then was concentrated under reduced pressure to yield the title compound (1.354 g, 95%) as a white solid.

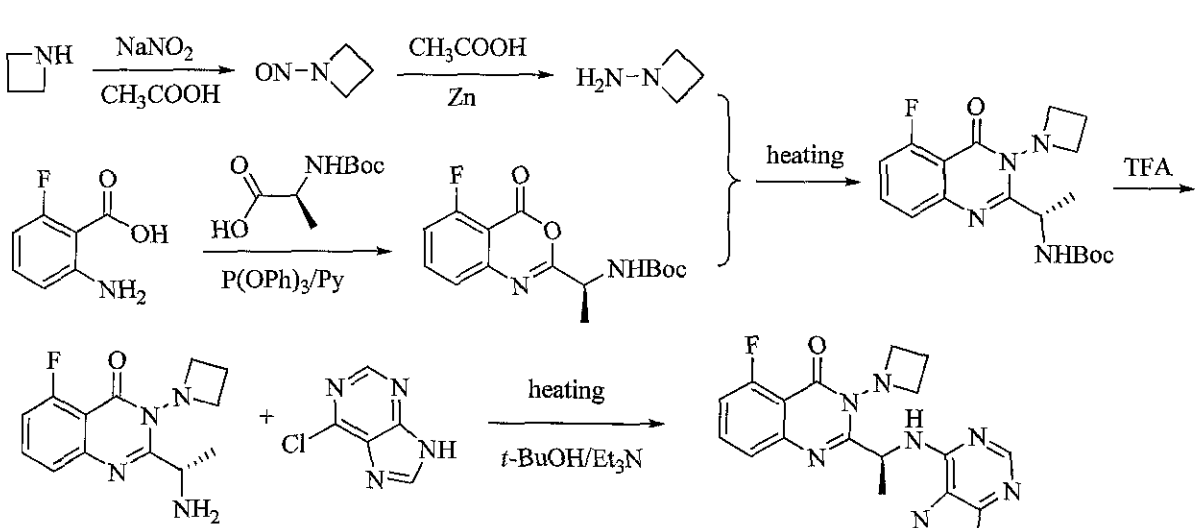
(6) (*S*)-2-(1-(9*H*-purin-6-ylamino)ethyl)-5-fluoro-3-(4-hydroxypiperidin-1-yl)quinazolin-4(3*H*)-one

To a stirred solution of (*S*)-2-(1-aminoethyl)-5-fluoro-3-(4-hydroxypiperidin-1-yl)quinazolin-4(3*H*)-one (1.354 g, 3.22 mmol) in *tert*-butanol (20 mL) in a dry flask was added DIEA (2.79 mL, 16 mmol), and then 6-chloropurine (597 mg, 3.86 mmol). The reaction was stirred at 90 °C for 12 hr. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by prep HPLC to yield the title compound (632 mg, 46.3%) as a white solid.

MS(M+1): 424.6;

$^1$H-NMR($d_6$-DMSO, 400 MHz): δ 12.95 (1H, s), 8.21-8.08 (2H, m), 7.90-7.79 (1H, m), 7.72 (1H, dd), 7.36 (1H, d), 7.21 (1H, t), 5.86 (1H, m), 4.76, 4.49 (1H, two singlet), 4.30-4.06 (1H, m), 3.95-3.70 (2H, m), 3.53-3.41 (1H, m), 3.08-2.96 (1H, m), 1.93-1.65 (2H, m), 1.63-1.52 (1H, m), 1.57 (3H, d), 1.46-1.31 (1H, m).

**EXAMPLE 4. (*S*)-2-(1-(9*H*-purin-6-ylamino)ethyl)-3-(azetidin-1-yl)-5-fluoro quinazolin-4(3*H*)-one (compound 26)**




(1) (*N*)-Nitroso-azetidine

A stirred solution of azetidine (3.0 g, 52.5 mmol) in glacier acetic acid (50 mL) was cooled in an ice-bath. To this solution was added a solution of sodium nitrite (5.45 g, 79 mmol) in water (40

mL) with stirring. The reaction solution was stirred at room temperature overnight, at which time the starting material could no longer be detected by LCMS. The reaction was quenched, extracted with dichloromethane. The combined organic solution was dried with sodium sulfate, filtered and evaporated. The crude product was purified by silica gel column chromatography to yield the title compound (1.8 g, 39.8%) as a slightly yellowed liquid.

(2) (*N*)-Amino-azetidine

To the stirred solution of (*N*)-Nitroso-azetidine (1.8 g, 20.9 mmol) in glacier acetic acid (20 mL) under nitrogen atmosphere and cooled in an ice bath was carefully added zinc powder (5.44 g, 83.2 mmol) in small portions. After the completion of the addition, the reaction was stirred at room temperature until the starting material could no longer be detected by TLC. Excess zinc powder was filtered, and the filtrate was concentrated to yield a crude product of the title compound as a yellow oil, which was used in the next reaction without further treatment.

(3) (*S*)-tert-butyl 1-(5-fluoro-4-oxo-4*H*-benzo[d][1,3]oxazin-2-yl)ethylcarbamate

To a stirred solution of 2-fluoro-6-aminobenzoic acid (2.0 g, 12.9 mmol) in pyridine (80 mL) in a round bottomed flask was added (*S*)-2-(*N*-tBoc)-aminopropionic acid (2.68 g, 14.2 mmol), and triphenylphosphinate (4.40 g, 14.2 mmol). The resulting reaction solution was stirred at 55 °C for 8 hr, and then was used directly for the next step without working-up.

(4) (*S*)-tert-butyl 1-(3-(azetidin-1-yl)-5-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl carbamate

To the stirred solution of (*S*)-tert-butyl 1-(5-fluoro-4-oxo-4*H*-benzo[d][1,3] oxazin-2-yl)ethylcarbamate (crude reaction mixture from step 3) was added the solution *N*-aminoazetidine in pyridine (from step 1), and the resulting reaction solution was stirred at 100 °C for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to yield the title compound (3.05 g, 65.3% two steps) as a light yellow liquid.

(5) (*S*)-2-(1-aminoethyl)-3-(azetidin-1-yl)-5-fluoroquinazolin-4(3*H*)-one

A stirred solution of (*S*)-tert-butyl 1-(3-(azetidin-1-yl)-5-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)ethylcarbamate (3.05 g, 8.42 mmol) in chloromethane (30 mL) in a dry flask was cooled in an ice-bath. To this solution was added dropwise TFA ( 15 mL). The reaction solution was stirred at room temperature until starting material could no longer be detected by TLC, and then was concentrated under reduced pressure to yield the title compound, which was used without further treatment.

(6) (*S*)-2-(1-(9*H*-purin-6-ylamino)ethyl)-3-(azetidin-1-yl)-5-fluoroquinazolin-4(3*H*)-one

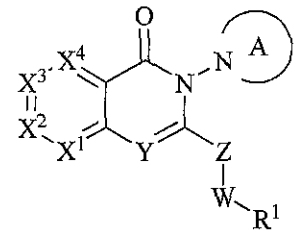
To a stirred solution of (*S*)-2-(1-aminoethyl)-3-(azetidin-1-yl)-5-fluoroquinazolin-4(3*H*)-one (crude product from step 5) in *tert*-butanol (50 mL) in a dry flask was added triethylamine until the pH is basic, and then 6-chloropurine (1.43 g, 9.25 mmol). The reaction was stirred at 90 °C for 12 hr. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by prep HPLC to yield the title compound (345 mg, 10.8% two steps) as a white solid.

MS(M+1): 381.5;

$^1$H-NMR($d_6$-DMSO, 400 MHz): δ 12.95 (1H, s), 8.24-8.09 (2H, m), 7.80-7.65 (2H, m), 7.45-7.34 (1H, m), 7.24 (1H, t), 5.96 (1H, m), 4.82-3.73 (4H, br s), 2.24-2.08 (2H, m), 1.55 (3H, d).

CLAIMS

1. Compounds of general formula (I), or pharmaceutically acceptable salts, stereoisomers or deuterated derivatives thereof:



( I )

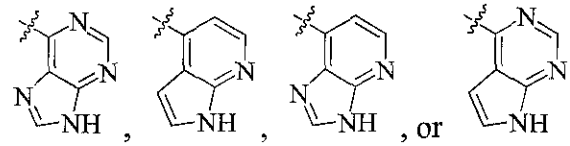
wherein, $X^1$, $X^2$, $X^3$, and $X^4$ are independently $CR^2$; $R^2$ are independently selected from the group consisting hydrogen, halogen, $C_{1-6}$alkyl, halogenated $C_{1-6}$alkyl, and $C_{1-6}$alkoxy;

Y are N;

A are independently selected from the group consisting azacyclopropyl, azacyclobutyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyridinyl, morpholino, and piperazinyl; and A can be further substituted by 1 to 3 $R^b$, $R^b$ are independently selected from the group consisting hydrogen, halogen, hydroxy, cyano, amino, $C_{1-6}$alkylamino, $C_{1-6}$dialkylamino, $C_{1-6}$alkoxy, $C_{1-6}$alkyl, and trifluoromethyl;

Z are -CH($R^3$)-, and $R^3$ are independently selected from the group consisting hydrogen, and $C_{1-3}$alkyl unsubstituted or substituted with at least one hydroxyl or fluorine, cylcopropyl unsubstituted or substituted with at least one hydroxyl or fluorine;

W are -N($R^4$)-, $R^4$ are independently selected from the group consisting hydrogen, and methyl;

$R^1$ are .

2. The compound of Claim 1, or pharmaceutically acceptable salts, stereoisomers or deuterated derivatives thereof:

wherein, $X^1$, $X^2$, $X^3$, and $X^4$ are independently $CR^2$; $R^2$ are independently selected from the group consisting hydrogen, fluorine, chlorine, methyl, and trifluoromethyl;

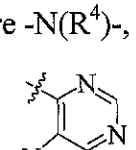
Y are N;

A are independently selected from the group consisting azacyclopropyl, azacyclobutyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyridinyl, morpholino, and piperazinyl; and A can be further substituted by 1 to 3 $R^b$, $R^b$ are independently selected from the

group consisting hydrogen, halogen, hydroxy, cyano, $C_{1-3}$alkyl, $C_{1-3}$alkoxy, and trifluoromethyl;

Z are -CH($R^3$)-, and $R^3$ are independently selected from the group consisting hydrogen, and $C_{1-3}$alkyl unsubstituted or substituted with at least one hydroxyl or fluorine; cylcopropylunsubstituted or substituted with at least one hydroxyl or fluorine;

W are -N($R^4$)-, $R^4$ are independently selected from the group consisting hydrogen and methyl;

$R^1$ is .

3. The compound of Claim 2, or pharmaceutically acceptable salts, stereoisomers or deuterated derivatives thereof:

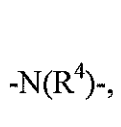
wherein, $X^1$, $X^2$, $X^3$, and $X^4$ are independently $CR^2$; $R^2$ are independently selected from the group consisting hydrogen, fluorine, chlorine, methyl, and trifluoromethyl;

Y are N;

A are independently selected from the group consisting azacyclopropyl, azacyclobutyl, pyrrolidinyl, piperidinyl, and morpholino; and A can be further substituted by 1 to 3 $R^b$, $R^b$ are independently selected from the group consisting hydrogen, fluorine, chlorine, hydroxy, and $C_{1-3}$alkyl;

Z are -CH($R^3$)-, and $R^3$ are independently selected from the group consisting hydrogen, and $C_{1-3}$alkyl;

W are -N($R^4$)-, $R^4$ are independently selected from the group consisting hydrogen and methyl;

$R^1$ is .

4. The compound of Claim 3, or pharmaceutically acceptable salts, stereoisomers or deuterated derivatives thereof:

wherein, $X^1$, $X^2$, $X^3$, and $X^4$ are independently $CR^2$; $R^2$ are independently selected from the group consisting hydrogen, fluorine, chlorine, and methyl;

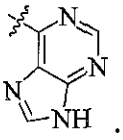
Y are N;

A are independently selected from the group consisting azacyclobutyl, piperidinyl, and morpholino; and A can be further substituted by 1 to 3 $R^b$, $R^b$ are independently selected from the group consisting hydrogen, fluorine, hydroxy, and methyl;

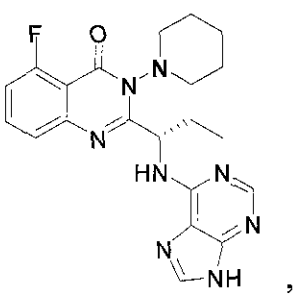
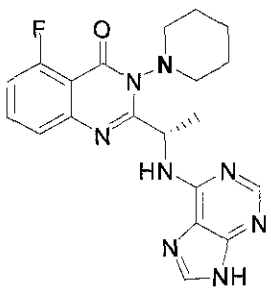
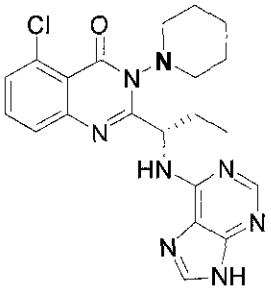
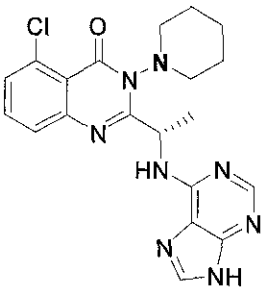
Z are -CH($R^3$)-, and $R^3$ are independently selected from the group consisting hydrogen and

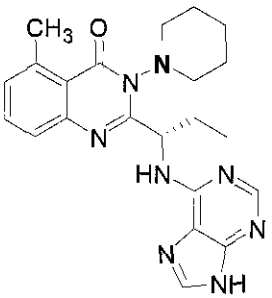
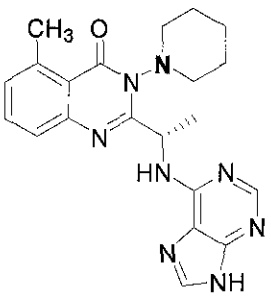
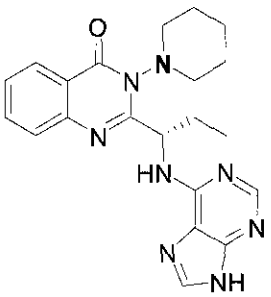
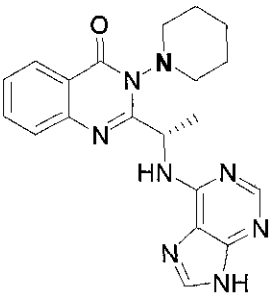
$C_{1-3}$alkyl;

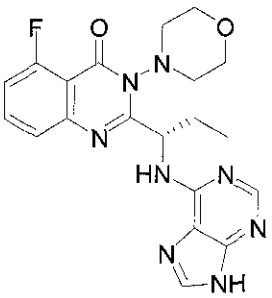
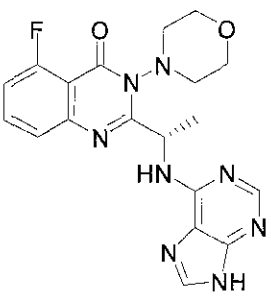
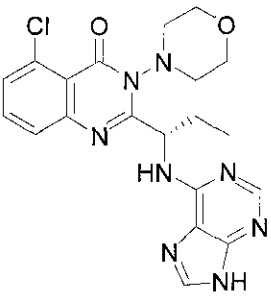
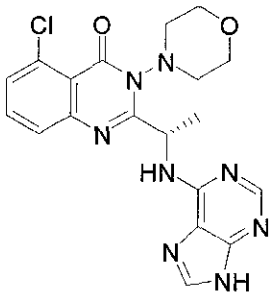
W are -N($R^4$)-, $R^4$ are independently selected from the group consisting hydrogen and methyl;

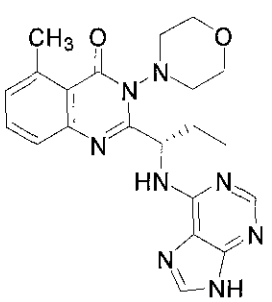
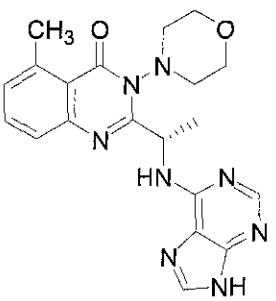
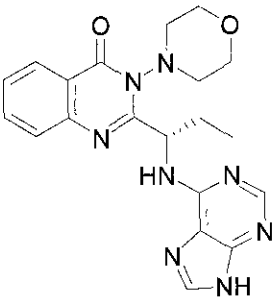
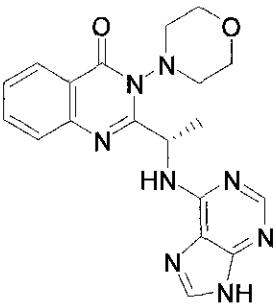
$R^1$ is  .

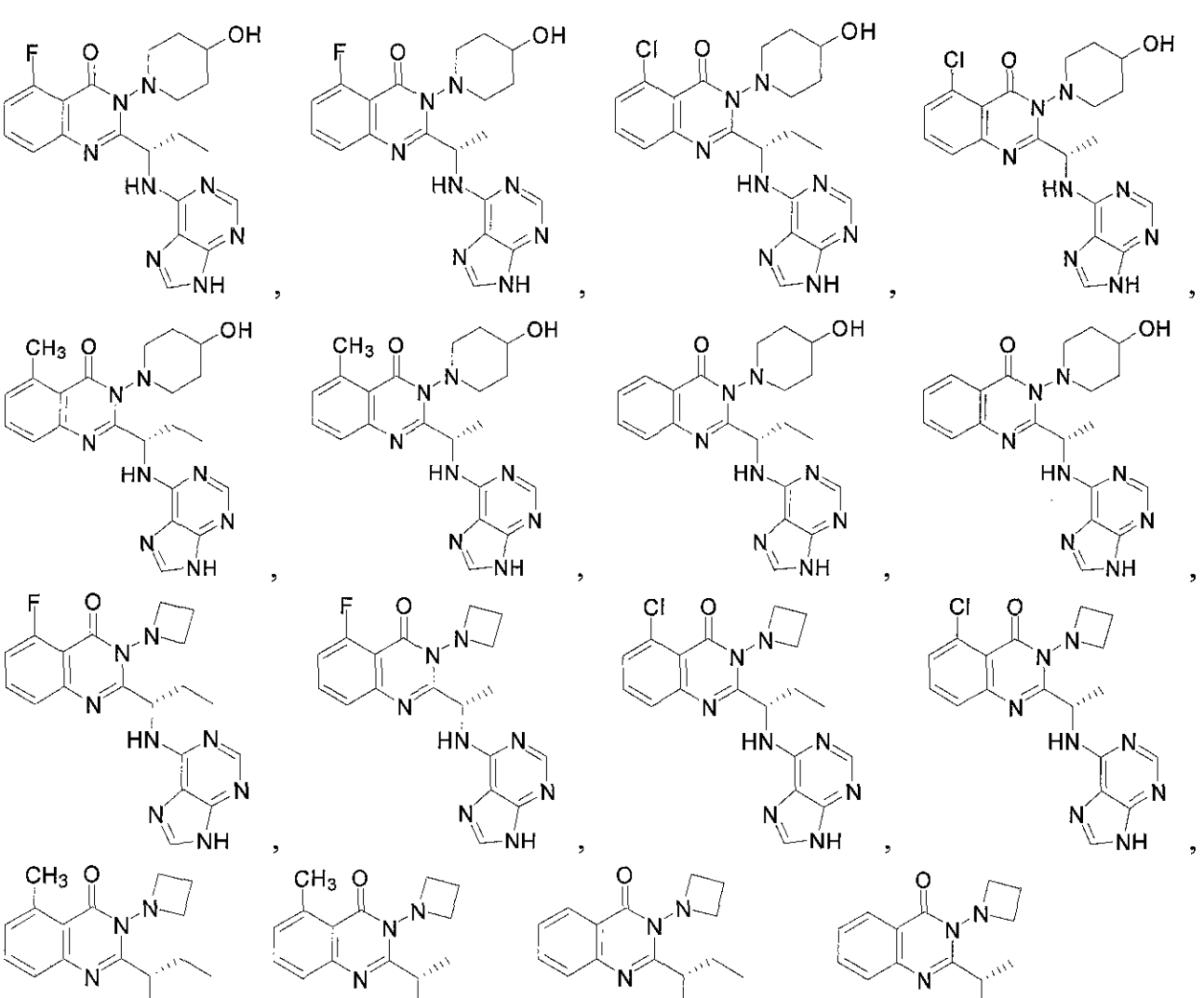
5. The compound of Claim 4, or pharmaceutically acceptable salts, stereoisomers or deuterated derivatives thereof:

, , , ,

, , , ,

, , , ,

, , , ,



6. A pharmaceutical composition comprising a compound of any of Claim 1 to 5, or pharmaceutically acceptable salts, stereoisomers or deuterated derivatives thereof; and one or more pharmaceutically acceptable carriers.

7. The use of these compounds of any of Claim 1 to 5, or pharmaceutically acceptable salts, stereoisomers or deuterated derivatives thereof; and the pharmaceutical composition of Claim 9, in manufacture of a medicament for the prevention and/or treatment of inflammatory disorders and cancers.

8. The use of Claim 7, the prevention and/or treatment of inflammatory disorders of allergy, asthma, rheumatoid arthritis, osteoarthritis, allergic conjunctivitis, allergic keratitis, xerophthalmia, chronic obstructive pulmonary disease (COPD), lupus erythematosus, psoriasis, multiple sclerosis, and late stage kidney disease; and the cancers of leukemia, lymphoma, bone marrow hyperplasia, non-Hodgkin's lymphoma, and chronic idiopathic myelofibrosis.