Substituted 7-Aza-benzothiophene Compounds as Lipid Kinase Inhibitors

1. Field of The Invention

The present invention relates to substituted 7-aza-benzothiophene compounds and the pharmaceutically acceptable salts and prodrugs thereof, such compounds are lipid kinase inhibitors especially PI3K and/or mTOR inhibitors. The invention also relates to methods and processes for preparation of such compounds, to pharmaceutical compositions containing the compounds, and to the method of using the above compounds to treat and/or to prevent lipid kinase and/or PI3-kinase related lipid kinase (especially PI3-kinase and/or mTOR) activity mediated proliferative diseases such as cancer, inflammatory diseases such as asthma, and disorders commonly occurring in connection with transplantation.

2. Background of The Invention

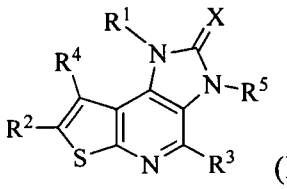
Phosphoinositide-3-kinases (PI3Ks) are a group of lipid kinases, which phosphorylate the 3-hydroxyl of phosphoinositides. They are classified into many classes and sub-classes. PI3Ks play key regulatory roles in many cellular processes such as cell survival, proliferation and differentiation. For example, p110a plays a specific role in cancer growth, p110b in thrombus formation, p110g in inflammation, rheumatoid arthritis and other chronic inflammation states. PI3Ks transducer signals from various growth factors and cytokines into intracellular messages by generating phospholipids, which activate the serine-threonine protein kinase AKT and other downstream effector pathway.

mTOR plays a crucial part in the regulation of cell growth and proliferation by monitoring nutrient availability, cellular energy levels, oxygen levels and mitogenic signals. It belongs to a group of seine-threonine protein kinases of the PI3K superfamily, referred to as class IV PI3Ks. mTOR exists in two distinct complexes – mTORC1 and mTORC2. The discovery of the association of mTORC1 with the bipartite complex TSC1 and TSC2 of tumor suppressor proteins provided a molecular link between mTOR and cancer. Activation of mTOR may provide tumor cells with a growth advantage by promoting protein synthesis.

It has been demonstrated that inhibition of PI3Ks and/or mTOR will inhibit tumor growth and reduce inflammatory responses. Thus, PI3Ks and mTOR are interesting targets for drug intervention.

3. Disclosure of the Invention

The present invention provides compounds of inhibitors of PI3K and/or mTOR. According to a first aspect, the present invention provides a compound of general formula (I) or its pharmaceutically acceptable salt or its stereoisomers thereof:



(I)

Wherein

X is O, S, or NH;

R^1 is hydrogen, or C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} alkenyl, C_{3-8} alkynyl, aryl, heterocyclyl, that is optionally substituted by at least one R^6;

R^2 is hydrogen, or C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heterocyclyl, which is optionally substituted at least with one R^6;

R^3 is hydrogen, cyano, hydroxyl, carboxyl, $-(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nC(O)R^8$, $-(CH_2)_nS(O)_mR^8$, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, $-(CH_2)_nC(O)(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nOC(O)R^8$, $-(CH_2)_nC(O)OR^8$, $-(CH_2)_nNR^{7a}C(O)R^8$, $-(CH_2)_nNR^{7a}C(O)NR^{7a}R^{7b}$, or C_{1-6} alkyl, C_{1-6} alkoxy which is optionally substituted by at least one substituent selected from halogen, hydroxyl, carboxyl;

R^4 is hydrogen, halogen, cyano, hydroxyl, carboxyl, $-(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nC(O)R^8$, $-(CH_2)_nS(O)_mR^8$, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, $-(CH_2)_nC(O)(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nOC(O)R^8$, $-(CH_2)_nC(O)OR^8$, $-(CH_2)_nNR^{7a}C(O)R^8$, $-(CH_2)_nNR^{7a}C(O)NR^{7a}R^{7b}$, or C_{1-6} alkyl, C_{1-6} alkoxy which is optionally substituted by at least one substituent selected from halogen, hydroxyl, carboxyl and cyano;

R^5 is hydrogen, $-(CH_2)_nS(O)_mR^8$, or C_{1-6} alkyl which is optionally substituted by at least one R^6;

R^6 is hydroxyl, halogen, cyano, carboxyl, $-(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nC(O)R^8$, $-(CH_2)_nS(O)_mR^8$, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, $-(CH_2)_nC(O)(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nOC(O)R^8$, $-(CH_2)_nC(O)OR^8$, $-(CH_2)_nNR^{7a}C(O)R^8$, $-(CH_2)_nNR^{7a}C(O)NR^{7a}R^{7b}$, or C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-6} alkoxy, C_{3-8} cyclo alkyl, aryl, heterocyclyl which is optionally substituted by at least one R^9;

R^{7a} and R^{7b} are independently hydrogen, or C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heterocyclyl

which is optionally substituted at least one R^9;

R^8 is C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, aryl, heterocyclyl which is optionally substituted by at least one R^9;

R^9 is hydroxyl, halogen, cyano, trifluoromethyl, C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, aryl, heterocyclic, $-(CH_2)_nNR^{10a}R^{10b}$, $-(CH_2)_nC(O)R^{11}$, $-(CH_2)_nC(O)NR^{10a}R^{10b}$, $-(CH_2)_nS(O)_mR^{11}$, $-(CH_2)_nS(O)_mNR^{10a}R^{10b}$, $-(CH_2)_nNR^{10a}S(O)_mR^{11}$, $-(CH_2)_nOC(O)R^{11}$, $-(CH_2)_nNR^{10a}C(O)R^{11}$, or $-(CH_2)_nNR^{10a}C(O)NR^{10a}R^{10b}$;

R^{10a} and R^{10b} are independently hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, or heterocyclic;

R_{11} is C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, or heterocyclic;

m is 1 or 2;

n is 0 to 4.

In another preferred embodiment, wherein

X is O;

R^1 is C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, 4-10 membered heterocyclyl, that is optionally substituted by at least one R^6;

R^2 is hydrogen, or C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heterocyclyl, which is optionally substituted at least with one R^6;

R^3 is hydrogen, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, or C_{1-6} alkyl, C_{1-6} alkoxy which is optionally substituted by at least one substituent selected from halogen, hydroxyl, carboxyl;

R^4 is hydrogen, halogen, cyano, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, or C_{1-6} alkyl, C_{1-6} alkoxy which is optionally substituted by at least one substituent selected from halogen, hydroxyl, carboxyl;

R^5 is hydrogen, or C_{1-6} alkyl which is optionally substituted by at least one R^6;

R^6 is hydroxyl, halogen, $-(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nC(O)R^8$, $-(CH_2)_nS(O)_mR^8$, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, $-(CH_2)_nC(O)(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nOC(O)R^8$, $-(CH_2)_nC(O)OR^8$, $-(CH_2)_nNR^{7a}C(O)R^8$, $-(CH_2)_nNR^{7a}C(O)NR^{7a}R^{7b}$, or C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cyclo alkyl, aryl, 4-10 membered heterocyclyl which is optionally substituted by at least one R^9;

R^{7a} and R^{7b} are independently hydrogen, or C_{1-6} alkyl which is optionally substituted by at least one R^9;

R^8 is C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, aryl, 4-10 membered heterocyclyl which is optionally substituted by at least one R^9;

R^9 is hydroxyl, halogen, cyano, trifluoromethyl, C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, aryl, 4-10 membered heterocyclic, $-(CH_2)_nNR^{10a}R^{10}$;

R^{10a} and R^{10b} are independently hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, or 4-10 membered heterocyclic;

m is 1 or 2;

n is 0 to 4.

In another preferred embodiment, wherein

X is O;

R^1 is C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl, naphthyl, 5-10 membered heterocyclyl, that is optionally substituted by at least one R^6;

R^2 is phenyl, naphthyl, 5-10 membered heterocyclyl, which is optionally substituted by at least one R^6;

R^3 and R^4 are hydrogen;

R^5 is hydrogen, or C_{1-6} alkyl which is optionally substituted by at least one R^6;

R^6 is hydroxyl, halogen, $-(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nC(O)R^8$, $-(CH_2)_nS(O)_mR^8$, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, $-(CH_2)_nC(O)(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nOC(O)R^8$, $-(CH_2)_nC(O)OR^8$, $-(CH_2)_nNR^{7a}C(O)R^8$, $-(CH_2)_nNR^{7a}C(O)NR^{7a}R^{7b}$, or C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-7} cyclo alkyl, phenyl, 5-10 membered heterocyclyl which is optionally substituted by at least one R^9;

R^{7a} and R^{7b} are independently hydrogen, or C_{1-6} alkyl which is optionally substituted by at least one R^9;

R^8 is C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl, phenyl, 5-10 membered heterocyclyl, which is optionally substituted by at least one R^9;

R^9 is hydroxyl, fluorine, cyano, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl, phenyl, 5-10 membered heterocyclic, or $-(CH_2)_nNR^{10a}R^{10}$;

R^{10a} and R^{10b} are independently hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl, or 5-10 membered heterocyclic;

m is 1 or 2;

n is 0 to 3.

In another preferred embodiment, wherein

X is O;

R^1 is cyclopentyl, cyclohexyl, piperidinyl, piperazinyl, imidazolidinyl, pyrazolyl alkyl, tetrahydrofuran base, phenyl, naphthyl, pyridyl, pyrimidinyl , pyrazolyl, indazole-based, quinolyl, indolyl, pyrazolpyridyl, which is optionally substituted by at least on R^6;

R^2 is phenyl, pyridyl, pyrimidinyl, pyrazolyl, indazolyl, quinolyl, indolyl, pyrazolpyridyl, which is optionally substituted by at least on R^6;

R^3 and R^4 are hydrogen;

R^5 is hydrogen, or C1-6 alkyl, which is optionally substituted by at least on R^6;

R^6 is hydroxyl, halogen, $-(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nC(O)R^8$, $-(CH_2)_nS(O)_mR^8$, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, $-(CH_2)_nC(O)(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nOC(O)R^8$, $-(CH_2)_nC(O)OR^8$, $-(CH_2)_nNR^{7a}C(O)R^8$, $-(CH_2)_nNR^{7a}C(O)NR^{7a}R^{7b}$, or C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cyclo alkyl, 5-7 membered heterocyclyl, which is optionally substituted by at least one R^9;

R^{7a} and R^{7b} are independently for hydrogen, methyl, or ethyl;

R^8 is C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, phenyl, 5-7 membered heterocyclyl, which is optionally substituted by at least one R^9;

R^9 is hydroxyl, cyano, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy, or $-(CH_2)_nNR^{10a}R^{10}$;

R^{10a} and R^{10b} are independently hydrogen, methyl, or ethyl;

m is 1 or 2;

n is 0 to 3.

In another preferred embodiment, wherein

X is O;

R^1 is cyclopentyl, cyclohexyl, piperidinyl, piperazinyl, phenyl, naphthyl, pyridyl, pyrimidinyl, pyrazolyl, indazole base, quinolinyl , indole, pyrazolpyridine, which is optionally substituted by at least on R^6;

R^2 is phenyl, pyridyl, pyrimidinyl, pyrazolyl, indazolyl, quinolyl, indolyl, pyrazolylpyridyl, which is optionally substituted by at least on R^6;

R^3 and R^4 are hydrogen;

R^5 is hydrogen, methyl, ethyl or propyl;

R^6 is hydroxyl, fluorine, chlorine, $-(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nC(O)R^8$, $-(CH_2)_nS(O)_mR^8$, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, $-(CH_2)_nC(O)(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nOC(O)R^8$, $-(CH_2)_nC(O)OR^8$, $-(CH_2)_nNR^{7a}C(O)R^8$, $-(CH_2)_nNR^{7a}C(O)NR^{7a}R^{7b}$, or C1-6 alkyl, C1-6 alkoxy, C3-6 cycloalkyl, piperazinyl, imidazolyl, pyrazolyl, triazolyl, which is optionally substituted by at least one R^9;

R^{7a} and R^{7b} are independently for hydrogen, methyl, or ethyl;

R^8 is C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, phenyl, which is optionally substituted by at least one R^9;

R^9 is hydroxyl, cyano, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy, or $-(CH_2)_nNR^{10a}R^{10}$;

R^{10a} and R^{10b} are independently hydrogen, methyl, or ethyl;

m is 1 or 2;

n is 0 to 3.

In a further preferred embodiment, wherein

X is O;

R^1 is cyclopentyl, cyclohexyl, piperidinyl, phenyl, pyridyl, pyrimidine, indazolyl, quinolyl, indolyl, pyrazolylpyridyl, which is optionally substituted by at least on R^6;

R^2 is pyridyl, pyrimidine, indazolyl, quinolyl, indolyl, pyrazolyl and pyridyl, which is optionally substituted by at least on R^6;

R^3 and R^4 are hydrogen;

R^5 is hydrogen, methyl, ethyl or propyl;

R^6 is hydroxyl, fluorine, chlorine, $-(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nC(O)R^8$, $-(CH_2)_nS(O)_mR^8$, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, $-(CH_2)_nC(O)(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nOC(O)R^8$, $-(CH_2)_nC(O)OR^8$, $-(CH_2)_nNR^{7a}C(O)R^8$, $-(CH_2)_nNR^{7a}C(O)NR^{7a}R^{7b}$, or C1-3 alkyl, C1-2 alkoxy, C3-6 cycloalkyl, piperazinyl, imidazolyl, pyrazolyl, which is optionally substituted by at least one R^9;

R^{7a} and R^{7b} are independently hydrogen, methyl or ethyl;

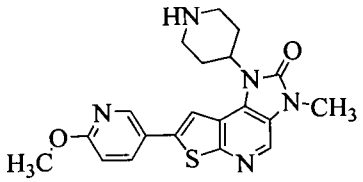
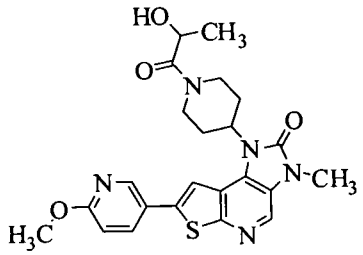
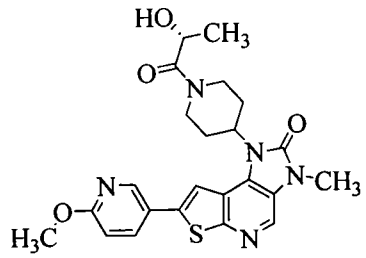
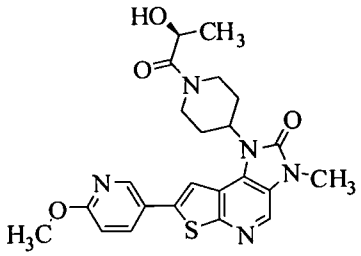
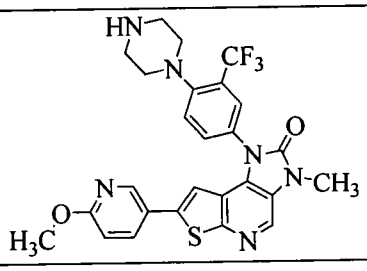
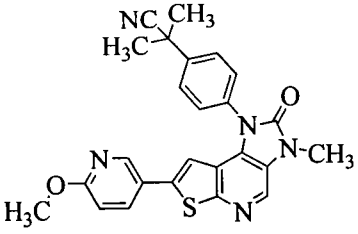
R^8 is C_{1-4} alkyl, C_{1-3} alkoxy, phenyl, which is optionally substituted by at least one R^9;

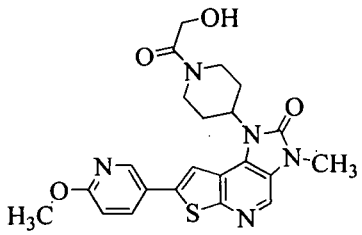
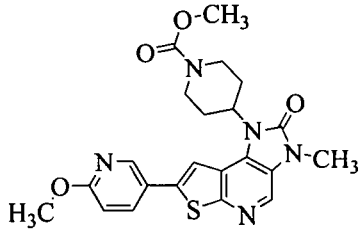
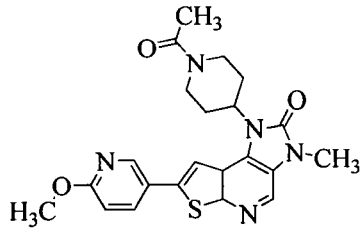
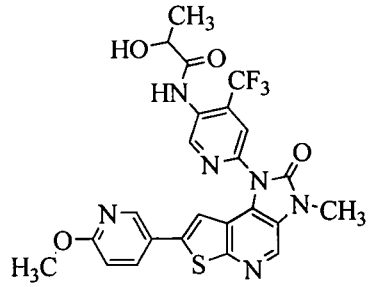
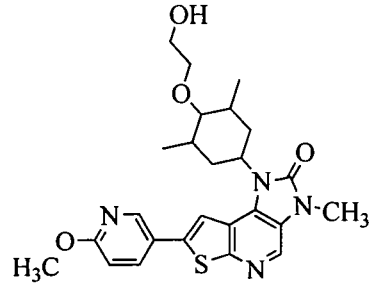
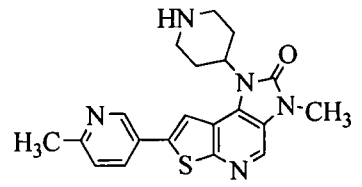
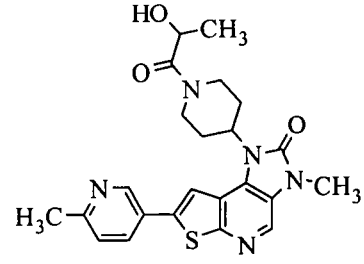
R^9 is hydroxyl, cyano, trifluoromethyl, methyl, ethyl, isopropyl, methoxy, or ethoxy;

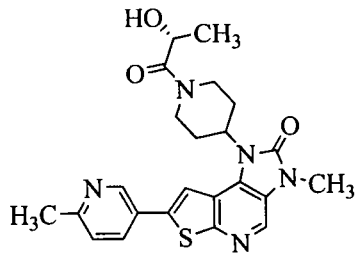
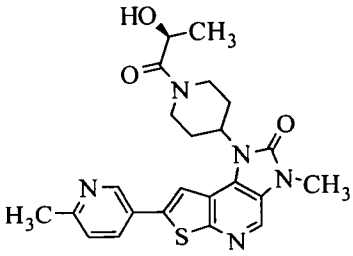
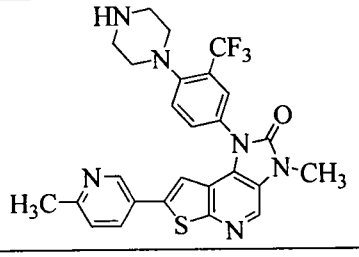
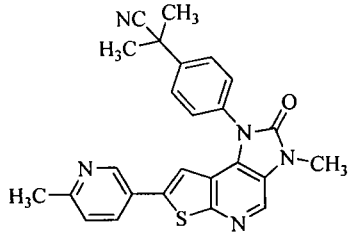
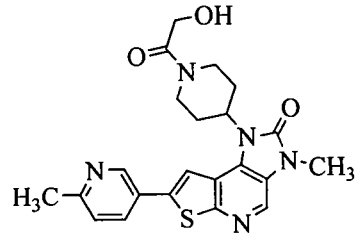
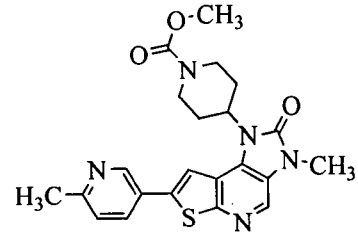
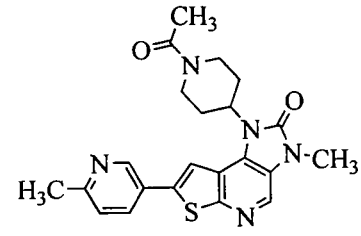
m is 1 or 2;

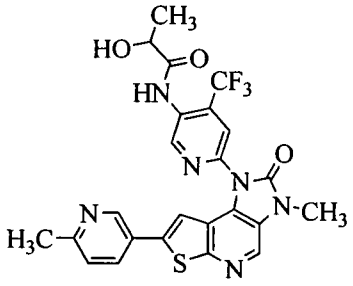
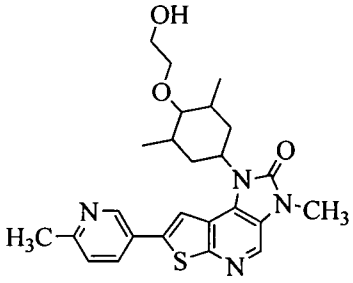
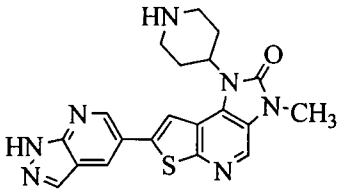
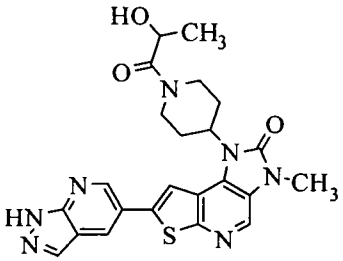
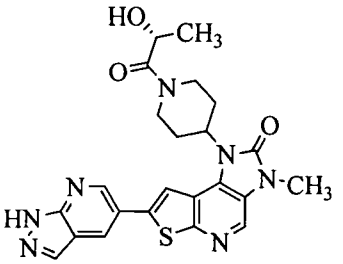
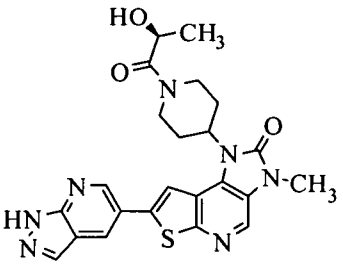
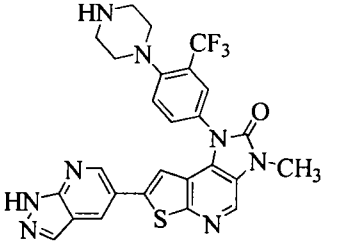
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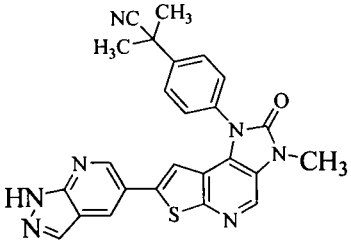
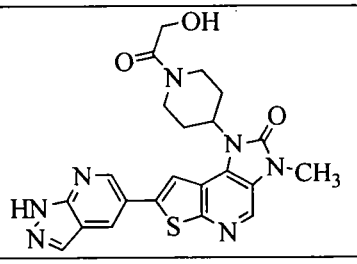
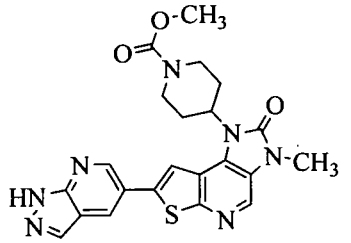
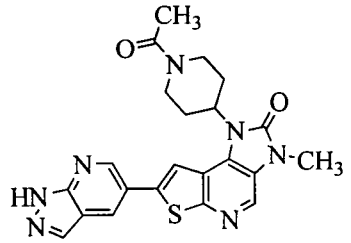
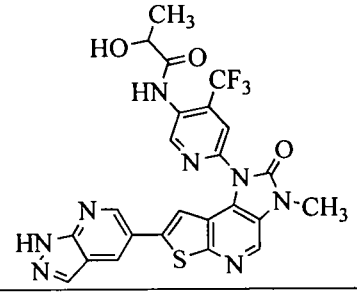
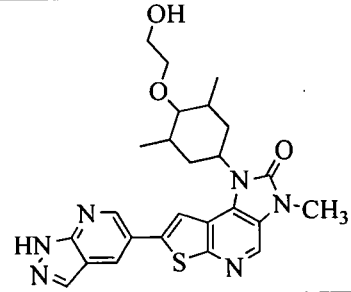
Examples of the present invention are listed below:

Compound	Structure	Chemical Name
1		7-(6-Methoxypyridin-3-yl)-3-methyl-1-(piperidin-4-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
2		1-(1-(2-hydroxypropanoyl)piperidin-4-yl)-7-(6-methoxypyridin-3-yl)-3-methyl-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
2-a		(*R*)-1-(1-(2-Hydroxypropanoyl)piperidin-4-yl)-7-(6-methoxypyridin-3-yl)-3-methyl-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
2-b		(*S*)-1-(1-(2-hydroxypropanoyl)piperidin-4-yl)-7-(6-methoxypyridin-3-yl)-3-methyl-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
3		7-(6-Methoxypyridin-3-yl)-3-methyl-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
4		2-(4-(7-(6-Methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)phenyl)-2-methylpropanenitrile

5		1-(1-(2-Hydroxyacetyl)piperidin-4-yl)-7-(6-methoxypyridin-3-yl)-3-methyl-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
6		Methyl 4-(7-(6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate
7		1-(1-Acetylpiperidin-4-yl)-7-(6-methoxypyridin-3-yl)-3-methyl-5a,8a-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
8		2-Hydroxy-N-(6-(7-(6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)-4-(trifluoromethyl)pyridin-3-yl)propanamide
9		1-(4-(2-Hydroxyethoxy)-3,5-dimethylcyclohexyl)-7-(6-methoxypyridin-3-yl)-3-methyl-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
10		3-Methyl-7-(6-methylpyridin-3-yl)-1-(piperidin-4-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
11		1-(1-(2-hydroxypropanoyl)piperidin-4-yl)-3-methyl-7-(6-methylpyridin-3-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one

11-a		(*R*)-1-(1-(2-Hydroxypropanoyl)piperidin-4-yl)-3-methyl-7-(6-methylpyridin-3-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
11-b		(*S*)-1-(1-(2-hydroxypropanoyl)piperidin-4-yl)-3-methyl-7-(6-methylpyridin-3-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
12		3-Methyl-7-(6-methylpyridin-3-yl)-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
13		2-Methyl-2-(4-(3-methyl-7-(6-methylpyridin-3-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)phenyl)propanenitrile
14		1-(1-(2-Hydroxyacetyl)piperidin-4-yl)-3-methyl-7-(6-methylpyridin-3-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
15		Methyl 4-(3-methyl-7-(6-methylpyridin-3-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate
16		1-(1-Acetylpiperidin-4-yl)-3-methyl-7-(6-methylpyridin-3-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one

17		2-Hydroxy-N-(6-(3-methyl-7-(6-methylpyridin-3-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)-4-(trifluoromethyl)pyridin-3-yl)propanamide
18		1-(4-(2-Hydroxyethoxy)-3,5-dimethylcyclohexyl)-3-methyl-7-(6-methylpyridin-3-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
19		3-Methyl-1-(piperidin-4-yl)-7-(1H-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
20		1-(1-(2-hydroxypropanoyl)piperidin-4-yl)-3-methyl-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
20-a		(*R*)-1-(1-(2-Hydroxypropanoyl)piperidin-4-yl)-3-methyl-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
20-b		(*S*)-1-(1-(2-hydroxypropanoyl)piperidin-4-yl)-3-methyl-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
21		3-Methyl-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one

22		2-Methyl-2-(4-(3-methyl-2-oxo-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)phenyl)propanenitrile
23		1-(1-(2-Hydroxyacetyl)piperidin-4-yl)-3-methyl-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
24		Methyl 4-(3-methyl-2-oxo-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate
25		1-(1-Acetylpiperidin-4-yl)-3-methyl-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one
26		2-Hydroxy-N-(6-(3-methyl-2-oxo-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)-4-(trifluoromethyl)pyridin-3-yl)propanamide
27		1-(4-(2-Hydroxyethoxy)-3,5-dimethylcyclohexyl)-3-methyl-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one

The following are definitions of terms used in this specification of the present invention.

Unless indicated otherwise, the term "halogen" refers fluorine, chlorine, bromine, iodine. The term "C_{1-6} alkyl" refers straight or branched chain containing 1-6 carbon atom alkyl, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl,

2-methylbutyl, neopentyl, 1-ethyl-propyl, n-hexyl-based, alien base, 4-methyl pentyl, 3-methyl-pentyl, 2-methyl-pentyl, 1-methyl pentyl, 3,3-dimethyl butyl, 2,2-dimethyl butyl, 1,1-dimethyl butyl, 1,2-dimethyl butyl, 1,3-dimethyl butyl, 2,3-dimethyl butyl, 2-ethyl butyl, 1-methyl-2-methylpropyl and so on.

The terms "C_{1-4} alkyl" and "C_{1-3} alkyl" refer respectively1-4 carbon atom alkyl and 1-3 carbon atom alkyl in above-mentioned examples.

The term "C_{3-8} cycloalkyl" refers to the cycloalkanes of 3-8 carbon atom membered size, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctanyl and so on. The terms "C_{3-7} cycloalkyl" and "C_{3-6} cycloalkyl" refer respectively 3-7 carbon and 3-6 carbon atom cycloalkane in above-mentioned examples.

The term "C_{2-8} alkenyl" refers straight or branched chain or cyclic alkenyl containing 2-8 carbon atom with double bond(s), such as vinyl, 1-propenyl, 2-propylenyl, 1-butenyl, 2-butenyl, 1,3-butadienyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 1,3-pentadienyl, 1,4-pentadiene, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1,4-hexadiene, cyclopentenyl, 1,3-cyclopentadienyl, cyclohexenyl, 1,4-cyclohexadienyl, cycloheptenyl, 1,4-cycloheptadienyl, cyclooctenyl, 1,5-cyclooctadienyl and so on.

The invention "C_{3-8} alkenyl" refers 3 to 8 carbon atoms with double bond in above-mentioned specific examples.

The term "C_{2-8} alkynyl" refers straight or branched chain containing 2-8 carbon atom with triple bond(s), such as acetylene, propynyl, 2-butynyl, 2-pentynyl, 3-pentynyl, 4-methyl-2-pentynyl, 2-hexynyl, 3-hexynyl, 5-methyl-2-hexynyl, 2-heptynyl, 5-methyl-2-heptynyl, 2-octynyl, 3-octynyl and so on.

The term "C_{3-8} alkynyl" refers 3 to 8 carbon atoms with triple bond in above-mentioned specific examples.

The term "C_{1-6} alkoxy" refers to the term "C_{1-6} alkyl" structure through the oxygen atom connected with other groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, secondary butoxy, pentyloxy, isopentyloxy, hexyloxy and so on.

The terms "C_{1-3} alkoxy" and "C_{1-2} alkoxy" refer respectively to in above-mentioned specific examples 1-3 and 1-2 carbon atoms.

The term "aryl" refers to aromatic rings such as phenyl, substituted phenyl (e.g., benzyl, phenylethyl), and fused aromatic rings (for example, naphthalene, phenanthrene) and so The

term, "heterocycle" refers 3 to 14 membered cyclic group containing one or more heteroatom where heteroatom means nitrogen, oxygen, sulfur atom and so on.

"Heterocycle" includes mono heterocycle and fused heterocycle.

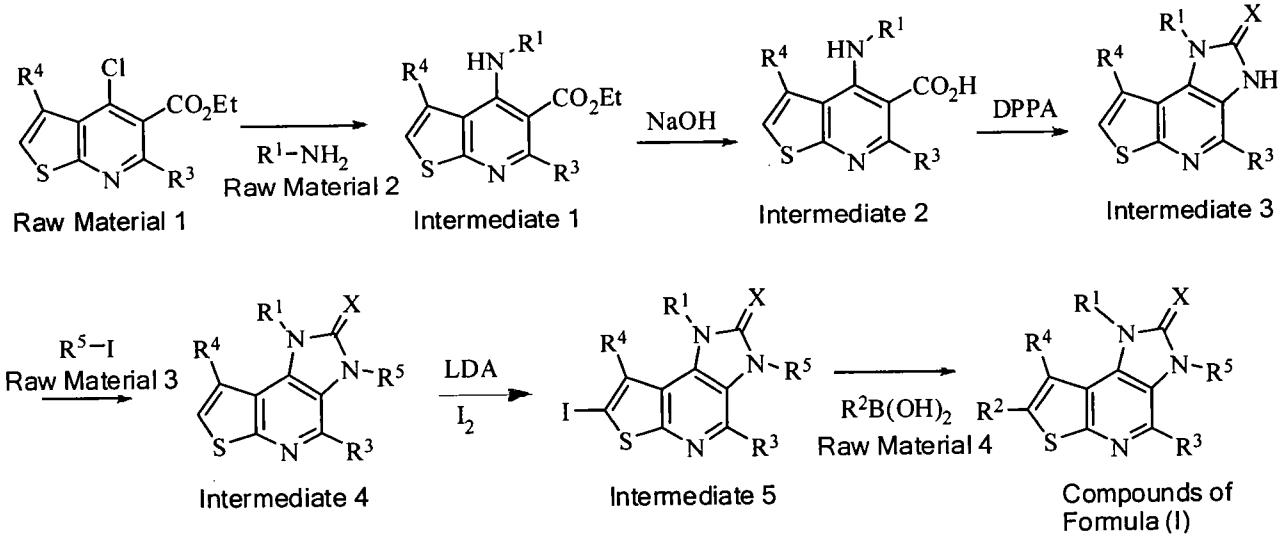
The examples of "mono heterocycle" are: aziridine, 2H-aziridine, diaziridine, 3H-diazirine, azetidine, 1,2-diazetidine, azete, 1,2-diazete, pyrrole, dihydro-pyrrole, pyrrolidine, imidazole, 4,5-dihydro-imidazole, alkyl imidazole, pyrazole, 4,5-dihydro-pyrazole, alkyl pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, 2-pyridone, 4-pyridone, piperidine, pyridazine, pyrimidine, pyrazine, piperazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, aza-cycloheptatriene, 1,2-diaza-cycloheptatriene, 1,3-diaza-cycloheptatriene, 1,4-diaza cycloheptatriene, aza-cyclooctatetraene, 1,4-dihydro-1,4-diaza cyclooctatriene, oxirane, cyclopropane dioxide, thiirene, oxitane, 1,2-dioxitane, thietane, 1,2-dithietane, furan, tetrahydrofuran, thiophene, 2,5-dihydro-thiophene, tetrahydrothiophene, 1,3-dioxolane, 1,3-dioxolane-2-ketone, 1,2-dithiole, 1,3-dithiolane, 2H-pyran, 2H-pyran-2-ketone, 3,4-dihydro-2H-pyran, 4H-pyran, tetrahydropyran, 4H-pyran-4-ketone, 1,4-dioxine 1,4-dithioxine, 1,4-oxathioxine, 1,4-dioxane, 1,3-dioxane, 1,3-thiooxane, oxepine, thiepine, 1,4-dioxoctatriene, oxaziridine, oxazoline, 4,5-dihydro-oxazole, isoxazole, 4,5-dihydro isoxazole, 2,3-dihydro isoxazole, 1,2,3-oxadiazole, 1,2,5-oxadiazole, thiazole, 4,5-dihydro-thiazole, isothiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, 2H-1,2-oxazine, 4H-1,2-oxazine, 6H-1,2-oxazine, 2H-1,3-oxazine, 4H-1,3-oxazine, 5,6-dihydro-4H-1,3-oxazine, 6H-1,3-oxazine, 2H-1,4-oxazine, 4H-1,4-oxazine, 2H-1,3-thiazine, 4H-1,3-thiazine, 5,6-dihydro-4H-1,3-thiazine, 6H-1,3-thiazine, 2H-1,4-thiazine, 4H-1,4-thiazine, morpholine and so on.

The examples of "fused heterocycle" are: indole, isoindole, carbazole, benzimidazole, indazole, benzotriazole, tetrahydro-imidazo [4,5-c] pyridine, quinoline, isoquinoline, 2-quinolinone, 4-quinolinone, 1-isoquinolone, acridine, phenanthridine, bass phenanthroline, phthalazine, quinazoline, 3,4-dihydro-quinazoline, quinoxaline, 1,2-dihydro-quinoxaline, 1,8-naphthyridine, 1,7-naphthyridine, 1,6-naphthyridine, 1,5-naphthyridine, 2,7-naphthyridine, 2,6-naphthyridine, purine, pteridine, phenazine, benzo [b] furan, benzo different [b] furan, dibenzo [b] furan, benzo [b] thiophene, benzo [c] thiophene, Benzo [d] [1,3] dioxol, 3-oxo-1,3-dihydro-isobenzofuran, 2H-chromene, 2H-chromene-2-one, 4H-chromene, 4H-chromene-4-one, chroman, benzoxazole, benzothiazole, 4H-1,3-benzoxazine, phenazine,

phenothiazine, 4,6-dihydro-1H-furo [3,4-d] imidazole, 3a, 4,6,6 a-tetrahydro-1H-furo [3,4-d] imidazole, 4,6-dihydro-1H-thieno [3 ,4-d] imidazole, 4,6-dihydro-1H-pyrrolo [3,4-d] imidazole, 4,5,6,7-tetrahydro-1H-benzo [d] imidazole and so on.

The terms of the "4-10 membered heterocycle", "5-10 membered heterocycle" and "5-7 member heterocycle" refers respectively heterocycles 4-10, 5-10 and 5-7 atom ring size in above-mentioned examples.

The aforementioned compounds of the present invention can be prepared by any methods obvious to one skilled in the art, including but not limited to the methods described in the scheme below:



Reaction Procedures:

(1) Preparation of intermediate 1

To an alcohol solution of raw material 1 was added raw material 2 and heated to reflux. After the completion of reaction, the reaction mixture was evaporated to dryness and purified by column chromatography to afford intermediate 1.

(2) Preparation of Intermediate 2

To an alcohol/THF solution of intermediate 1 was added an aqueous NaOH (or LiOH) solution and stirred at ambient temperature. After completion of the reaction, the PH was adjusted to 2-3, and the reaction mixture was filtered to afford the crude product that was rinsed with small amount of alcohol to afford intermediate 2.

(3) Preparation of intermediate 3

To a stirring DMF suspension of intermediate 2 was added a tertiary amine (such as triethylamine) at ambient temperature followed by addition of DPPA. After completion of the reaction it was cooled, and the precipitated solid was filtered and washed with small amount of MeOH to afford intermediate 3 after drying.

(4) Preparation of intermediate 4

To an anhydrous DMSO solution of intermediate 3 was added K_2CO_3 and raw material 3 successively and stirred overnight at ambient temperature. The reaction mixture was poured into water, and the precipitate was filtered, rinsed, and dried to afford intermediate 4.

(5) Preparation of intermediate 5

To an anhydrous THF solution of intermediate 4 at low temperature was added fresh prepared LDA and slowly warmed up with stirring. It was then cooled again and added a THF solution of iodine and then allowed to warm to ambient temperature and stirred overnight. Water was added to quench the reaction, and the reaction mixture was extracted with EtOAc, dried and purified by column chromatography to afford intermediate 5.

(6) Preparation of compounds of formula (I)

To a mixture of organic solvent (including but not limited to dioxane, DMSO, DMF, toluene) and small amount of water was added intermediate 5, raw material 4, Pd catalyst (including but not limited to $Pd(PPh_3)_4$, $Pd(dppf)_2Cl_2$, $Pd(PPh_3)_2Cl_2$), and base (including but not limited to KOAC, K_3PO4, K_2CO_3) successively. The reaction mixture was placed in a seal tube and was heated under nitrogen. After completion of the reaction, water was added to quench. The reaction mixture was extracted, dried, and purified by column chromatography to afford compounds of formula (I).

R^1, R^2, R^3, R^4, R^5 and X in the reaction scheme are as previously defined. When R^5 = H, step 4 (preparation of intermediate 4) can be skipped.

During the course of the reaction the functional group of raw materials / intermediates that should not participate in the reaction can exist in either unprotected form or in a protected form and de-protected partially or fully afterwards with conventional method. For example, acidic protons within amine functional groups can be protected with common "amine protecting groups". Such "amine protecting groups" include but are not limited to: methyl, ethyl, cyclopropylmethyl, 1-methyl-1-cyclopropylmethyl, diisopropylmethyl, 9-fluorenylmethyl, 9-(2-thio) fluorenylmethyl, 2-furanylmethyl, 2,2,2-trichloromethyl, 2-halomethyl, 2-iodoethyl, 2-trimethylsilylethyl, 2-methylthioethyl, 2-methylsulfonylethyl, 2-(p-toluenesulfonyl)ethyl, 2-phosphonioethyl, 1,1-dimethyl-3(N,N-dimethyl-formamido)propyl, 1,1-diphenyl-3-(N,N-diethylamimo)propyl, 1-methyl-1-(adamantanyl)ethyl, 1-methyl-1-phenyethyl, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1-(4-biphenyl)ethyl, 1-methyl-1-(p-phenylazophenyl)ethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1,1-dimethyl-2-cyanoethyl, isobutyl, t-butyl, t-pentyl, cyclobutyl, 1-methylcyclobutyl, cyclopentyl, cyclohexyl, 1-methylcyclohexyl, 1-adamantly, isobornyl, vinyl, allyl, cinnamyl, phenyl, 2,4,6-tri-t-butylphenyl, m-nitrophenyl, S-phenyl,

8-quinolyl, N'-hydroxypiperidinyl, 4-(1,4-dimethylpiperdinyl), 4,5-diphenyl-3-oxazolin-2-one, benzyl, 2,4,6-trimethylbenzyl, p-methoxybenzyl, p-methoxybenzyloxycarbonyl, 3,5-dimethoxybenzyl, p-decyloxybenzyl, p-nitro-benzyl, p-nitrobenzyloxycarbonyl, o-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, p-bromobenzyl, chlorobenzyl, 2,4-dichlorobenzyl, p-cyanobenzyl, o-(N,N-dimethyl-formamido)benzyl, m-chloro-p-acyloxybenzyl, p-(dihydroxyboryl)-benzyl, p-(phenylazo)benzyl, *p*-(*p*-methoxyphenylazo)benzyl, 5-benzoisoxazolylmethyl, 9-anthrylmethyl, diphenylmethyl, phenyl(o-nitrophenyl)methyl, di(2-pyridyl)methyl, 1-methyl-1-(4-pyridyl)ethyl, isonicotinyl, S-benzyl, N'-piperidinylcarbonyl, carbamate of N'-p-toluenesulfonylaminocarbonyl and N'-phenylaminothiocarbonyl; formyl, acetyl, acetyl-pyridinium, (N'-dithiobenzyloxycarbonylamino)acetyl, 3-phenylpropionyl, 3-(p-hydroxyphenyl)propionyl, 3-(o-nitrophenyl)propionyl, 2-methyl-2-(o-nitrophenoxy)-propionyl, 2-methyl-2-(o-phenylazophenoxy)propionyl, 4-chlorobutyryl, isobutyryl, o-nitrocinnamoyl, pyridylformyl, N'-acetylmethionyl, N'-benzoyl-phenylalkyl, benzoyl, p-phenybenzoyl, p-methoxybenzoyl, o-nitrobenzoyl, amide of o-(benzoyloxymethyl)benzoyl and p-P-benzoyl; the cyclic imides of phthaloyl, 2,3-diphenylmaleoyl and dithiosuccinoyl; t-butoxycarbonyl, allyl, allyloxycarbonyl, phenacyl, 3-acetoxypropyl, 4-nitro-1-cyclohexyl-2-oxo-3-pyrrolidin-3-yl, quaternary ammonium salts, methoxymethyl, 2-chloroethoxymethyl, benzyloxymethyl, pivaloylmethyl, [1-(alkoxycarbonylamino)]-2,2,2,trifluoroethyl, [1-trifluoromethyl-1-(p-chlorophenoxymethoxy)-2,2,2-trifluoro]ethyl, 2-tetrahydro-pyranyl, 2,4-dinitrophenyl, benzyl, 3,4-dimethoxybenzyl, o-nitrobenzyl, di(p-methoxyphenyl)methyl, triphenylmethyl, (p-methoxyphenyl)diphenylmethyl, diphenyl-4-pyridylmethyl, 2-pyridylmethyl-N'-oxide, 5-diphenylpropylsuberyl, N',N'-dimethylaminomethylene, N'-isopropylidene, benzylidene, p-methoxy-benzylidene, p-nitrobenzylidene, salicylidene, 5-chlorosalicylidene, diphenylmethylene, (5-chloro-2-hydroxyphenyl)phenylmethylene, acylvinyl, 5,6-dimethyl-3-oxo-1-cyclohexenyl, borane, [phenyl(pentacarbonylchromium)]carbonyl or [phenyl(pentacarbonyltungsten)]carbonyl, copper or zinc chelate, nitro, nitroso, oxide, diphenylphosphino, dimethylthiophosphinyl, diphenylthiophosphinyl, diethyl phosphoryl, dibenzyl phosphoryl, diphenyl phosphoryl, phosphoryl, trimethylsilyl, benzenesulfanyl, o-nitrobenzenesulfanyl, 2,4-dinitrobenzenesulfanyl, 2-nitro-4-methoxybenzenesulfanyl, triphenylmethylsulfanyl, benzenesulfonyl, p-methoxybenzenesulfonyl,

2,4,6-trimethylbenzenesulfonyl, methylsulfonyl, phenylmesyl, p-toluenemesyl, trifluoromethylsulfonyl, phenacylsulfonyl, etc.

Pharmaceutically acceptable salts of the compounds of formula (I) refers to the salts formed between the basic nitrogen of compounds of formula (I) and inorganic and organic acids.

The term "stereoisomers" as used herein, refers to all epimeric, enantiomeric, diastereomeric and tautomeric forms. When a bond is drawn as a wedge, this indicates that in three dimensions the bond would be coming out of the paper and when a bond is hatched, this indicates that in three dimensions the bond would be going back into the paper. The compounds of the formulae (I) may contain a number of stereo centers.

Another embodiment of this invention pertains to a pharmaceutical composition comprising any compound of formulae (I), pharmaceutically acceptable salts thereof, hydrolysable esters thereof, isomers thereof, hydrates thereof, hydrates of esters or salts thereof and other pharmaceutically active ingredients.

Another embodiment of this invention pertains to a pharmaceutical composition comprising any compounds of formula (I), pharmaceutically acceptable salts thereof, hydrolysable esters thereof, or isomers thereof and one or more pharmaceutical carrier(s) and/or diluent(s). Methods known in the art can be applied to formulate any clinically or pharmaceutically acceptable dosage forms, preferably oral or injectable formations, comprising a compound of formula (I) in a physiologically effective amount ranging from 0.01 to 10 g, *e.g.* 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.04 g, 0.05 g, 0.1 g, 0.125 g, 0.2 g、0.25 g, 0.3 g, 0.4 g, 0.5 g, 0.6 g, 0.75 g, 1 g, 1.25 g, 1.5 g, 1.75 g, 2 g, 2.5 g, 3 g, 4 g, 5 g, 6 g, 7 g, 8 g, 9 g, 10 g *etc*

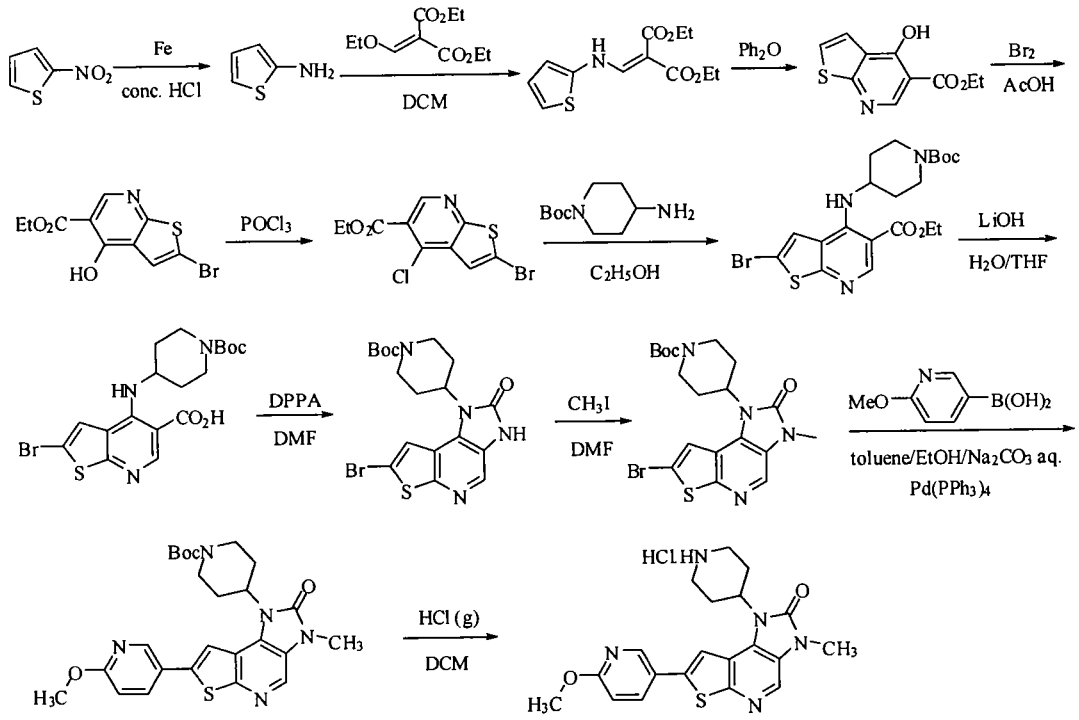
Another embodiment of this invention pertains to the method of using the compounds of the formulae (I) or pharmaceutically acceptable salts thereof, hydrolysable esters thereof, stereoisomers thereof, hydrate thereof or hydrates of esters and salts thereof, used alone or in combination with other active ingredients, to treat and/or to prevent lipid kinase and/or PI3-kinase related lipid kinase (especially PI3-kinase and/or mTOR) activity mediated proliferative diseases such as cancer, inflammatory diseases such as asthma, and disorders commonly occurring in connection with transplantation. The proliferative diseases include all type of tumors.

4. Examples

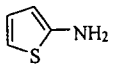
The present invention will be further illustrated with the following examples. However the scope of this invention is not limited in any way to these examples. Any variations and modifications obvious to one skilled in the art are intended to be included within the scope of the present invention.

Example 1. Preparation of

7-(6-methoxypyridin-3-yl)-3-methyl-1-(piperidin-4-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one (Compound 1)

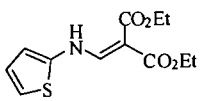


(1) Preparation of thiophen-2-amine



To a concentrated HCl (30 mL) solution of 2-nitrothiophene (5.16 g, 40 mmol) was added iron powder (4.46 g, 80 mmol) and reacted at 50 °C for 1 h. The reaction was then cooled, treated with 1 M NaOH to reach a PH of 7-8, and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, concentrated and used directly for the next step.

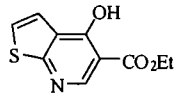
(2) Preparation of diethyl 2-((thiophen-2-ylamino)methylene)malonate



To CH_2Cl_2 (200 mL) was added thiophene-2-amine prepared above and diethyl 2-(ethoxymethylene)malonate (6.5 g, 30 mmol) and refluxed for 6 h. The reaction was cooled,

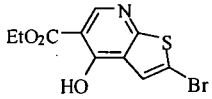
concentrated, and purified by column chromatography (silica gel, petroleum ether / ethyl acetate = 50 / 1) to afford the product as a light yellow solid (2.6 g, 26.1% yield over 2 steps based on 40 mmol of 2-nitrothiophene).

(3) Preparation of ethyl 4-hydroxythieno[2,3-*b*]pyridine-5-carboxylate



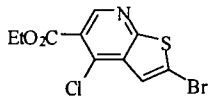
To diphenylether (60 mL) was added diethyl 2-((thiophen-2-ylamino)methylene)malonate and refluxed 45 min under N_2. TLC (ethyl acetate / petroleum ether = 50 / 1) showed complete consumption of starting material. The reaction was cooled and purified by column chromatography (silica gel, petroleum ether / ethyl acetate = 50 / 1) to afford the product as white solid (3.5 g, 70.4 % yield).

(4) Preparation of ethyl 2-bromo-4-hydroxythieno[2,3-*b*]pyridine-5-carboxylate



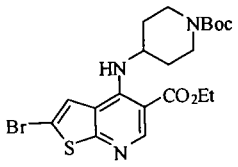
To an acetic acid (30 mL) solution of ethyl 4-hydroxythieno[2,3-b]pyridine-5-carboxylate (3.5 g, 15.7 mmol) was added bromine (1.6 mL, 31.4 mmol) portion-wise and reacted at 80 °C for 6 h under light-free conditions. The reaction was cooled and filtered. The cake was rinsed 2 times with acetic acid and water and dried under vacuum to afford the product as light yellow solid (3.8 g, 80.0% yield).

(5) Preparation of ethyl 2-bromo-4-chlorothieno[2,3-*b*]pyridine-5-carboxylate



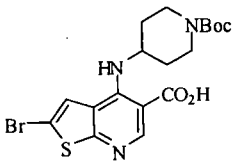
To ethyl 2-bromo-4-hydroxythieno[2,3-b]pyridine-5-carboxylate (3.7 g, 12.3 mmol) and *N*,*N*-dimethylphenylamine (2 mL) was added $POCl_3$ (30 mL) and refluxed for 1 h and then cooled. Extra $POCl_3$ was removed by vacuum distillation, and the leftover was poured into ice-water. The PH was adjusted to ~ 8, and the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated to afford the product as light yellow solid (3.15 g, 80.6% yield).

(6) Preparation of ethyl 2-bromo-4-(1-(*tert*-butoxycarbonyl)piperidin-4-ylamino) thieno[2,3-*b*]pyridine-5-carboxylate



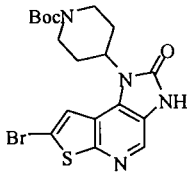
To an ethanol (30 mL) solution of *tert*-butyl 4-aminopiperidine-1-carboxylate (2.3 g, 11.5 mmol) and ethyl 2-bromo-4-chlorothieno[2,3-*b*]pyridine-5-carboxylate (3.1 g, 9.67 mmol) was added Et_3N (19.3 g, 19.1 mmol) and refluxed for 24 h. The reaction was cooled and concentrated to afford the product as a light yellow solid (3.9 g, 83.3% yield).

(7) Preparation of 2-bromo-4-(1-(*tert*-butoxycarbonyl)piperidin-4-ylamino) thieno[2,3-*b*]pyridine-5-carboxylic acid



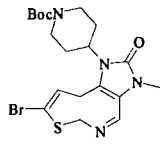
To a mixture of THF (30 mL) and H_2O (30 mL) was added ethyl 2-bromo-4-(1-(*tert*-butoxycarbonyl)piperidin-4-ylamino)thieno[2,3-*b*]pyridine-5-carboxylate (3.9 g, 8.05 mmol) and $LiOH.H_2O$ (1.0 g, 23.8 mmol) and stirred at ambient temperature for 18 h. After EtOH was evaporated, H_2O (50 mL) was added, and PH was adjusted to ~ 4 with 2 N HCl. The resulting precipitate was filtered and dried to afford the product as a light yellow solid (2.8 g, 77.0% yield).

(8) Preparation of *tert*-butyl 4-(7-bromo-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*] thieno[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



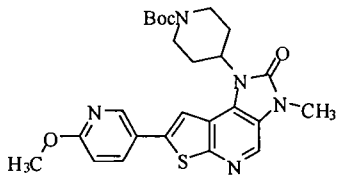
To 2-bromo-4-(1-(*tert*-butoxycarbonyl)piperidin-4-ylamino)thieno[2,3-*b*] pyridine-5-carboxylic acid (2.8 g, 6.2 mmol) in DMF (50 mL) was added Et_3N (1.3 g, 12.8 mmol) till everything dissolved. The reaction was stirred at ambient temperature for 30 min, added DPPA (3.5 g, 12.7 mmol), and reacted 2 h at 60 °C till the reaction was complete. The reaction mixture was poured into ice-water to form the white solid precipitate that was filtered and dried under vacuum to afford the product (2.4 g, 85.3% yield).

(9) Preparation of *tert*-butyl 4-(7-bromo-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo [4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



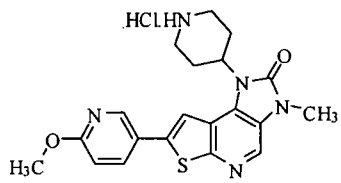
tert-Butyl 4-(7-bromo-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin -1-yl)piperidine-1-carboxylate (2.0 g, 4.4 mmol) was dissolved in DMF (20 mL) under ice-bath, and to this solution was added NaH (60wt% in mineral oil, 0.265 g, 6.6 mmol), stirred 30 min at ambient temperature, and added CH_3I (0.8 g, 5.6 mmol). After the reaction was complete, it was poured into ice-water to form the white solid precipitate that was filtered and dried under vacuum to afford the product (1.6 g, 77.3% yield).

(10) Preparation of *tert*-butyl 4-(7-(6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



tert-Butyl 4-(7-bromo-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3 -*b*]pyridin-1-yl)piperidine-1-carboxylate and 6-methoxypyridin-3-ylboronic acid (160 mg, 1.05 mmol) were dissolved in a mixture of toluene (15 mL) and EtOH (5 mL), and to this solution was added $(Ph_3P)_4Pd$ (50 mg) and 2 N Na_2CO_3 solution (1.3 mL) and refluxed 5 h under N_2. The reaction was cooled to ambient temperature and filtered, and the organic phase was concentrated and then dissolved in CH_2Cl_2, washed with water and brine, dried over Na_2SO_4, concentrated, and purified by column chromatography (silica gel, ethyl acetate / petroleum ether = 1 /1) to afford the product (280 mg, 65.7% yield).

(11) Preparation of 7-(6-methoxypyridin-3-yl)-3-methyl-1-(piperidin-4-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one hydrochloride



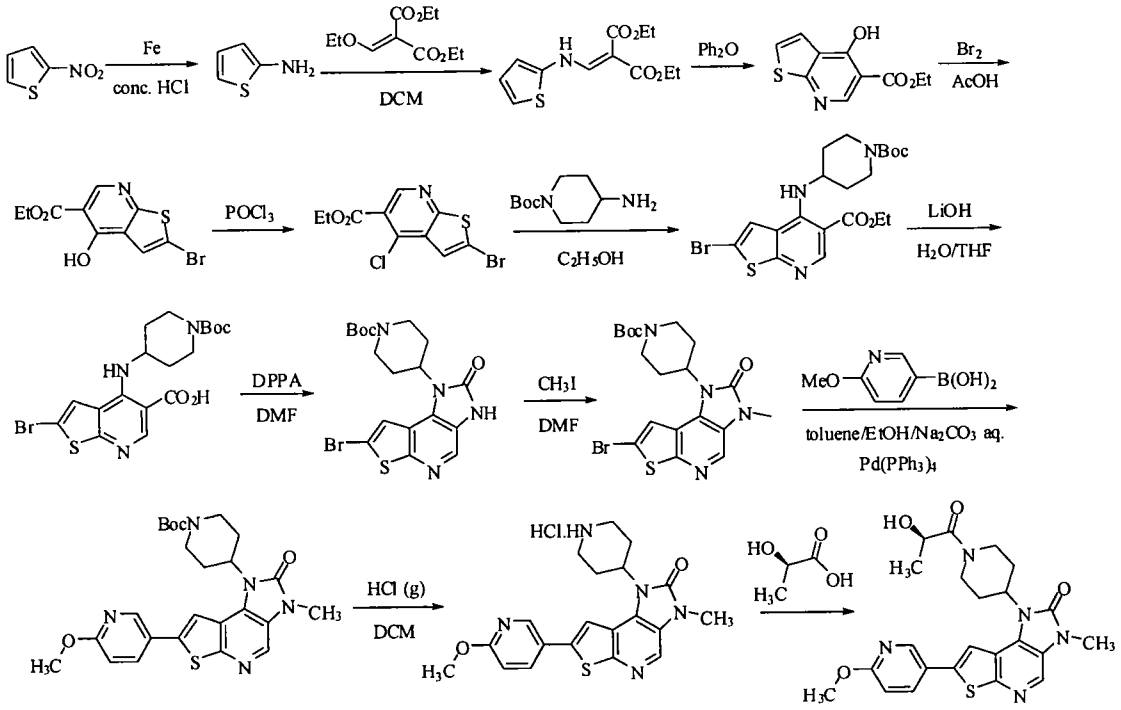
To a CH_2Cl_2 (10 mL) solution of *tert*-butyl 4-(7-(6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylat e (100 mg, 0.20 mmol) was bubbled HCl gas for 30 min. The resulting precipitate was filtered, rinsed with CH_2Cl_2 and ether, and recrystallized from ethyl acetate to afford the product as a

HCl salt (37 mg, 42.8% yield).

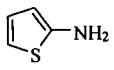
Molecular Formula: $C_{20}H_{21}N_5O_2S$ Molecular Weight: 395.48 Mass(M+H): 396.1

^{1}H-NMR(D_2O, 400 MHz) δ 7.98 (1H, s), 7.86 (1H, s), 7.70 (1H, d), 7.23 (1H, s), 6.58 (1H, d), 4.65-4.52 (1H, m), 3.73 (3H, s), 3.59 (2H, d), 3.36 (2H, t), 3.20 (3H, s), 2.77 (2H, dd), 2.14 (2H, d).

Example 2 Preparation of (*R*)-1-(1-(2-hydroxypropanoyl)piperidin-4-yl)-7-(6-methoxypyridin-3-yl)-3-methyl-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one (Compound 2-a)

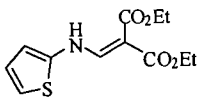


(1) Preparation of thiophen-2-amine



To a concentrated HCl (30 mL) solution of 2-nitrothiophene (5.16 g, 40 mmol) was added iron powder (4.46 g, 80 mmol) and reacted at 50 °C for 1 h. The reaction was then cooled, treated with 1 M NaOH to reach a PH of 7-8, and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, concentrated and used directly for the next step.

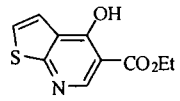
(2) Preparation of diethyl 2-((thiophen-2-ylamino)methylene)malonate



To CH_2Cl_2 (200 mL) was added thiophene-2-amine prepared above and diethyl 2-(ethoxymethylene)malonate (6.5 g, 30 mmol) and refluxed for 6 h. The reaction was cooled,

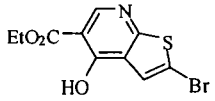
concentrated, and purified by column chromatography (silica gel, petroleum ether / ethyl acetate = 50 / 1) to afford the product as a light yellow solid (2.6 g, 26.1% yield over 2 steps based on 40 mmol of 2-nitrothiophene).

(3) Preparation of ethyl 4-hydroxythieno[2,3-*b*]pyridine-5-carboxylate



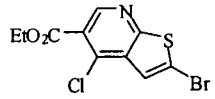
To diphenylether (60 mL) was added diethyl 2-((thiophen-2-ylamino)methylene)malonate and refluxed 45 min under N_2. TLC (ethyl acetate / petroleum ether = 50 / 1) showed complete consumption of starting material. The reaction was cooled and purified by column chromatography (silica gel, petroleum ether / ethyl acetate = 50 / 1) to afford the product as white solid (3.5 g, 70.4 % yield).

(4) Preparation of ethyl 2-bromo-4-hydroxythieno[2,3-*b*]pyridine-5-carboxylate



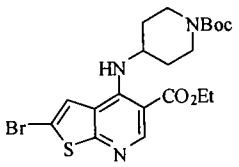
To an acetic acid (30 mL) solution of ethyl 4-hydroxythieno[2,3-b]pyridine-5-carboxylate (3.5 g, 15.7 mmol) was added bromine (1.6 mL, 31.4 mmol) portion-wise and reacted at 80 °C for 6 h under light-free conditions. The reaction was cooled and filtered. The cake was rinsed 2 times with acetic acid and water and dried under vacuum to afford the product as light yellow solid (3.8 g, 80.0% yield).

(5) Preparation of ethyl 2-bromo-4-chlorothieno[2,3-*b*]pyridine-5-carboxylate



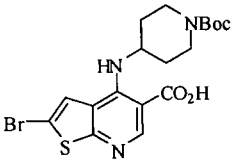
To ethyl 2-bromo-4-hydroxythieno[2,3-b]pyridine-5-carboxylate (3.7 g, 12.3 mmol) and *N*,*N*-dimethylphenylamine (2 mL) was added $POCl_3$ (30 mL) and refluxed for 1 h and then cooled. Extra $POCl_3$ was removed by vacuum distillation, and the leftover was poured into ice-water. The PH was adjusted to ~ 8, and the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated to afford the product as light yellow solid (3.15 g, 80.6% yield).

(6) Preparation of ethyl 2-bromo-4-(1-(*tert*-butoxycarbonyl)piperidin-4-ylamino) thieno[2,3-*b*]pyridine-5-carboxylate



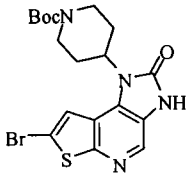
To an ethanol (30 mL) solution of *tert*-butyl 4-aminopiperidine-1-carboxylate (2.3 g, 11.5 mmol) and ethyl 2-bromo-4-chlorothieno[2,3-*b*]pyridine-5-carboxylate (3.1 g, 9.67 mmol) was added Et_3N (19.3 g, 19.1 mmol) and refluxed for 24 h. The reaction was cooled and concentrated to afford the product as a light yellow solid (3.9 g, 83.3% yield).

(7) Preparation of 2-bromo-4-(1-(*tert*-butoxycarbonyl)piperidin-4-ylamino) thieno[2,3-*b*]pyridine-5-carboxylic acid



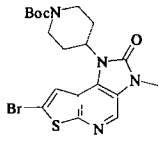
To a mixture of THF (30 mL) and H_2O (30 mL) was added ethyl 2-bromo-4-(1-(*tert*-butoxycarbonyl)piperidin-4-ylamino)thieno[2,3-*b*]pyridine-5-carboxylate (3.9 g, 8.05 mmol) and $LiOH.H_2O$ (1.0 g, 23.8 mmol) and stirred at ambient temperature for 18 h. After EtOH was evaporated, H_2O (50 mL) was added, and PH was adjusted to ~ 4 with 2 N HCl. The resulting precipitate was filtered and dried to afford the product as a light yellow solid (2.8 g, 77.0% yield).

(8) Preparation of *tert*-butyl 4-(7-bromo-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*] thieno[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



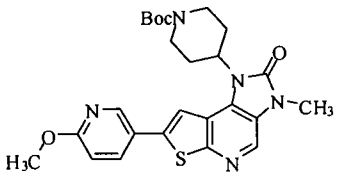
To 2-bromo-4-(1-(*tert*-butoxycarbonyl)piperidin-4-ylamino)thieno[2,3-*b*] pyridine-5-carboxylic acid (2.8 g, 6.2 mmol) in DMF (50 mL) was added Et_3N (1.3 g, 12.8 mmol) till everything dissolved. The reaction was stirred at ambient temperature for 30 min, added DPPA (3.5 g, 12.7 mmol), and reacted 2 h at 60 °C till the reaction was complete. The reaction mixture was poured into ice-water to form the white solid precipitate that was filtered and dried under vacuum to afford the product (2.4 g, 85.3% yield).

(9) Preparation of *tert*-butyl 4-(7-bromo-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo [4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



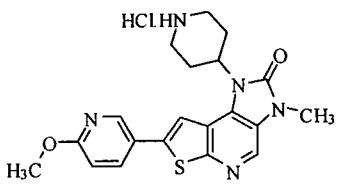
tert-Butyl 4-(7-bromo-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate (2.0 g, 4.4 mmol) was dissolved in DMF (20 mL) under ice-bath, and to this solution was added NaH (60wt% in mineral oil, 0.265 g, 6.6 mmol), stirred 30 min at ambient temperature, and added CH_3I (0.8 g, 5.6 mmol). After the reaction was complete, it was poured into ice-water to form the white solid precipitate that was filtered and dried under vacuum to afford the product (1.6 g, 77.3% yield).

(10) Preparation of *tert*-butyl 4-(7-(6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate



tert-Butyl 4-(7-bromo-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate and 6-methoxypyridin-3-ylboronic acid (160 mg, 1.05 mmol) were dissolved in a mixture of toluene (15 mL) and EtOH (5 mL), and to this solution was added $(Ph_3P)_4Pd$ (50 mg) and 2 N Na_2CO_3 solution (1.3 mL) and refluxed 5 h under N_2. The reaction was cooled to ambient temperature and filtered, and the organic phase was concentrated and then dissolved in CH_2Cl_2, washed with water and brine, dried over Na_2SO_4, concentrated, and purified by column chromatography (silica gel, ethyl acetate / petroleum ether = 1 /1) to afford the product (280 mg, 65.7% yield).

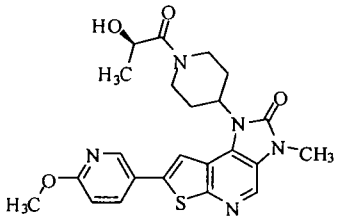
(11) Preparation of 7-(6-methoxypyridin-3-yl)-3-methyl-1-(piperidin-4-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one hydrochloride



To a CH_2Cl_2 (10 mL) solution of *tert*-butyl 4-(7-(6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate (100 mg, 0.20 mmol) was bubbled HCl gas for 30 min. The resulting precipitate was filtered, rinsed with CH_2Cl_2 and ether, and recrystallized from ethyl acetate to afford the

product as a HCl salt (37 mg, 42.8% yield).

(12) Preparation of (*R*)-1-(1-(2-hydroxypropanoyl)piperidin-4-yl)-7-(6-methoxypyridin-3-yl)-3-methyl-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one

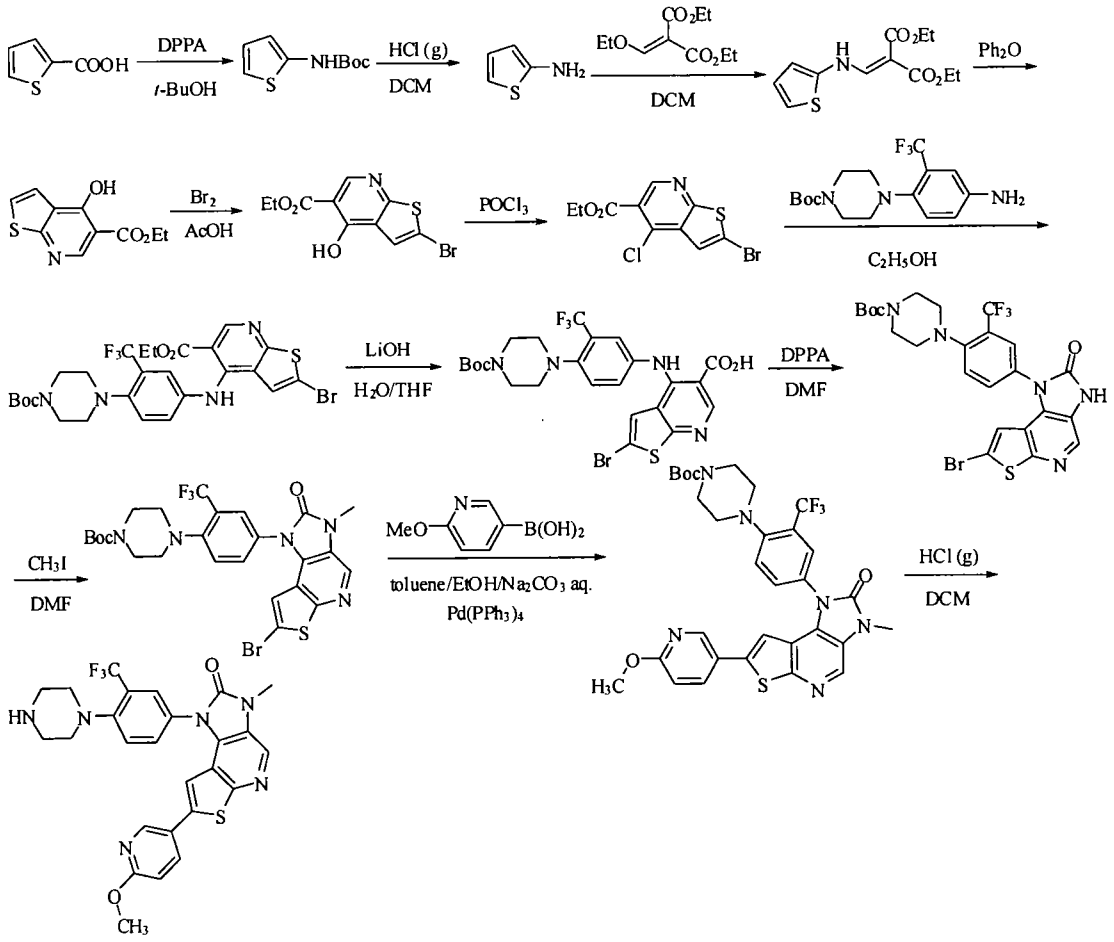


To a CH_2Cl_2 (20 mL) solution of Preparation of 7-(6-methoxypyridin-3-yl)-3-methyl-1-(piperidin-4-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one hydrochloride (100 mg, 0.23 mmol) was added Et3N (0.05 mL), (R)-lactic acid (26.7 mg, 0.296 mmol), HOBT (37.8 mg, 0.280 mmol), and EDC (70.8 mg, 0.37 mmol) and stirred at ambient temperature for 2 h when TLC monitoring (CH_2Cl_2 / MeOH = 10 / 1) showed complete reaction. The reaction mixture was washed with saturated Na_2CO_3 solution, water, and brine in such order, and the organic phase was dried over Na_2SO_4, concentrated, and purified by column chromatography and crystallization (EA / MeOH = 1 /1) to afford the product as a white solid (48 mg, 44.6% yield).

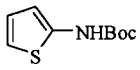
Molecular Formula: $C_{23}H_{25}N_5O_4S$ Molecular Weight: 467.54 Mass(M+H): 468.1

^{1}H-NMR($CDCl_3$, 400 MHz) δ 8.52 (1H, d), 8.27 (1H, s), 7.85 (1H, d), 7.43 (1H, s), 6.87 (1H, d), 5.10-4.72 (2H, m), 4.67-4.50 (1H, m), 4.10-3.92 (1H, m), 4.01 (3H, s), 3.91-3.78 (1H, m), 3.55 (3H, s), 3.42-3.17 (1H, m), 2.89 (1H, t), 2.79-2.53 (2H, m), 2.15-1.93 (2H, br s), 1.41 (3H, d).

Example 3 Preparation of 7-(6-methoxypyridin-3-yl)-3-methyl-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one (Compound 3)

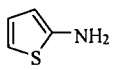


(1) Preparation of *tert*-butyl thiophen-2-ylcarbamate



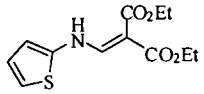
To *tert*-butanol (150 mL) was added thiophene-2-carboxylic acid (10 g, 78 mmol), DPPA (20.2 mL, 93.6 mmol) and Et_3N (17.4 mL, 125 mmol) and refluxed for 6 h. The reaction was cooled and concentrated, and the residue was poured into saturated $NaHCO_3$ solution to afford a light yellow precipitate that was filtered, washed 3 times with water and dried 8 h under vaccum at 45 °C. The crude product was used directly for the next step without further purification.

(2) Preparation of thiophene-2-amine



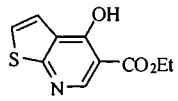
To a CH_2Cl_2 (200 mL) solution of the crude product from the above step (12 g, 60 mmol) under ice-water bath was bubbled HCl gas for 2 h. After TLC minotoring (petroleum ether / ethyl acetate = 5 /1) showed complete reaction, the solution was concentrated, and the crude product was used directly for the next step without further purification.

(3) Preparation of diethyl 2-((thiophen-2-ylamino)methylene)malonate



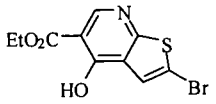
To CH_2Cl_2 (200 mL) was added thiophene-2-amine prepared above and diethyl 2-(ethoxymethylene)malonate (21.8 g, 100 mmol) and refluxed for 6 h. The reaction was cooled, concentrated, and purified by column chromatography (silica gel, petroleum ether / ethyl acetate = 50 / 1) to afford the product as a light yellow solid (9.4 g, 44.7% yield over 3 steps).

(4) Preparation of ethyl 4-hydroxythieno[2,3-*b*]pyridine-5-carboxylate



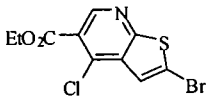
To diphenylether (60 mL) was added diethyl 2-((thiophen-2-ylamino)methylene)malonate and refluxed 45 min under N_2. TLC (ethyl acetate / petroleum ether = 50 / 1) showed complete consumption of starting material. The reaction was cooled and purified by column chromatography (silica gel, petroleum ether / ethyl acetate = 50 / 1) to afford the product as white solid (3.5 g, 70.4 % yield).

(5) Preparation of ethyl 2-bromo-4-hydroxythieno[2,3-*b*]pyridine-5-carboxylate



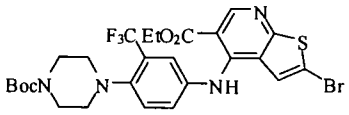
To an acetic acid (30 mL) solution of ethyl 4-hydroxythieno[2,3-b]pyridine-5-carboxylate (3.5 g, 15.7 mmol) was added bromine (1.6 mL, 31.4 mmol) portion-wise and reacted at 80 °C for 6 h under light-free conditions. The reaction was cooled and filtered. The cake was rinsed 2 times with acetic acid and water and dried under vacuum to afford the product as light yellow solid (3.8 g, 80.0% yield).

(6) Preparation of ethyl 2-bromo-4-chlorothieno[2,3-*b*]pyridine-5-carboxylate



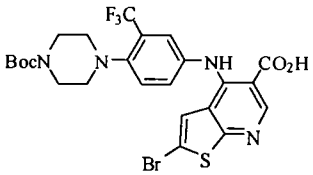
To ethyl 2-bromo-4-hydroxythieno[2,3-b]pyridine-5-carboxylate (3.7 g, 12.3 mmol) and *N*,*N*-dimethylphenylamine (2 mL) was added $POCl_3$ (30 mL) and refluxed for 1 h and then cooled. Extra $POCl_3$ was removed by vacuum distillation, and the leftover was poured into ice-water. The PH was adjusted to ~ 8, and the mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated to afford the product as light yellow solid (3.15 g, 80.6% yield).

(7) Preparation of ethyl 2-bromo-4-(4-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-3-(trifluoromethyl)phenylamino)thieno[2,3-*b*]pyridine-5-carboxylate



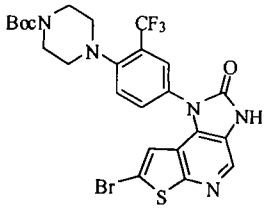
To an EtOH (10 mL) solution of ethyl 2-bromo-4-chlorothieno[2,3-*b*]pyridine-5-carboxylate (0.50 g, 1.56 mmol) and *tert*-butyl 4-(4-amino-2-(trifluoromethyl)phenyl) piperazine-1-carboxylate (0.64 g, 1.85 mmol) was added Et_3N (0.47 g, 4.65 mmol) and refluxed for 24 h. The reaction was cooled and concentrated to afford the crude product as a light yellow solid (0.70 g, 71.2% yield).

(8) Preparation of 2-bromo-4-(4-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-3-(trifluoromethyl)phenylamino)thieno[2,3-*b*]pyridine-5-carboxylic acid



To a mixture of THF (5 mL) and H2O (5 mL) was added ethyl 2-bromo-4-(4-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-3-(trifluoromethyl)phenylamino)thieno[2,3-*b*]pyridine-5-carboxylate (0.70 g, 1.11 mmol) and $LiOH.H_2O$ (0.233 g, 5.55 mmol) and stirred at ambient temperature for 18 h. After removing THF by evaporation, H_2O (10 mL) was added, and the PH was adjusted to 4 with 2 N HCl. The resulting precipitate was filtered and dried to afford the product as a light yellow solid (0.50 g, 74.8% yield).

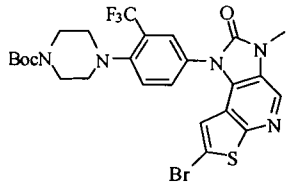
(9) Preparation of *tert*-butyl 4-(4-(7-bromo-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)-2-(trifluoromethyl)phenyl)piperazine-1-carboxylate



To DMF (8 mL) was added 2-bromo-4-(4-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-3-(trifluoromethyl)phenylamino)thieno[2,3-*b*]pyridine-5-carboxylic acid (0.5 g, 0.83 mmol) followed by Et_3N (0.21 g, 2.1 mmol) until everything dissolves. After stirring at ambient temperature for 30 min, DPPA (0.46 g, 1.67 mmol) was added, and the reaction was brought to 60 °C and reacted for 2 h until the completion of reaction. Afterwards the reaction mixture was

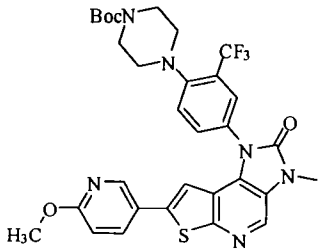
poured into ice-water to form the light yellow precipitate that was filtered and dried under vacuum to afford the product (0.40 g, 80.7% yield).

(10) Preparation of *tert*-butyl 4-(4-(7-bromo-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)-2-(trifluoromethyl)phenyl)piperazine-1-carboxylate



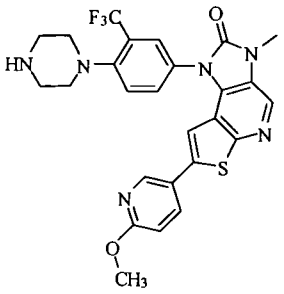
To a DMF (5 mL) solution of *tert*-butyl 4-(4-(7-bromo-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)-2-(trifluoromethyl)phenyl)piperazine-1-carboxylate (0.40 g, 0.67 mmol) under ice-water bath was added NaH (60wt% in mineral oil, 0.04 g, 1.00 mmol) and stirred at ambient temperature for 30 min followed by addition of CH_3I (0.117 g, 0.82 mmol). After the completion of reaction, the mixture was poured into ice-water to form the white precipitate that was filtered and dried under vacuum to afford the product (0.30 g, 73.1% yield).

(11) Preparation of *tert*-butyl 4-(4-(7-(6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)-2-(trifluoromethyl)phenyl)piperazine-1-carboxylate



To a toluene (9 mL) and EtOH (3 mL) solution of *tert*-butyl 4-(4-(7-bromo-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)-2-(trifluoromethyl)phenyl)piperazine-1-carboxylate (300 mg, 0.49 mmol) and 6-methoxypyridin-3-ylboronic acid (160 mg, 1.05 mmol) was added $Pd(PPh_3)_4$ (30 mg) and 2 N Na_2CO_3 solution (9 mL) and refluxed under N_2 for 5 h. The reaction was cooled to ambient temperature and filtered, and the organic phase was concentrated and dissolved in CH_2Cl_2 and washed with H_2O and brine in such order, dried over Na_2SO_4, concentrated, and purified by column chromatography (silica gel, EA / PE = 1 /1) to afford the product (160 mg, 51.0% yield)

(12) Preparation of 7-(6-methoxypyridin-3-yl)-3-methyl-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one



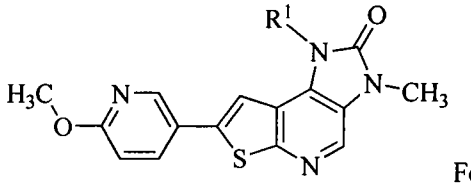
To a CH_2Cl_2 (10 mL) solution of *tert*-butyl 4-(4-(7-(6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)-2-(trifluoromethyl)phenyl)piperazine-1-carboxylate (160 mg, 0.25 mmol) was bubbled HCl gas for 30 min. The resulting precipitate was filtered, rinsed with CH_2Cl_2 and Et_2O in such order, and purified by prep-HPLC to afford the product as a white solid (49 mg, 36.3% yield).

Molecular Formula: $C_{26}H_{23}F_3N_6O_2S$ Molecular Weight: 540.56 Mass(M+H): 541.2

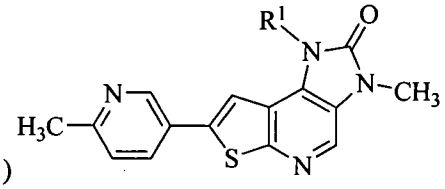
^{1}H-NMR(d_6-DMSO, 400 MHz) δ 8.58 (1H, s), 8.39 (1H, s), 8.01 (1H, s), 7.97(1H, d), 7.89-7.79 (2H, m), 6.92 (1H, d), 6.75 (1H, s), 3.88 (3H, s), 3.53 (3H, s), 3.24-3.15 (8H, m).

Compounds 4~10, 12~19, 21~27 within the present invention can be prepared using the methods described above.

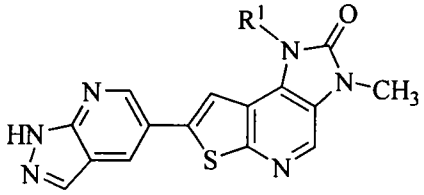
The following compounds can also be prepared using the methods described above:



Formula(I-1)

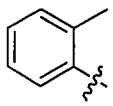
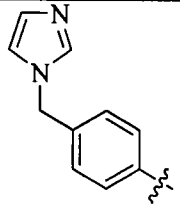
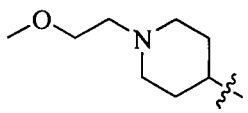


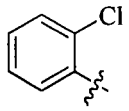
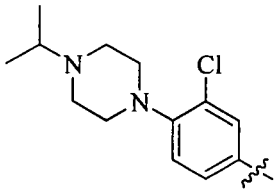
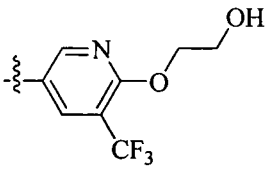
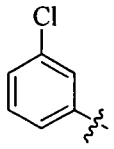
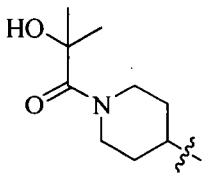
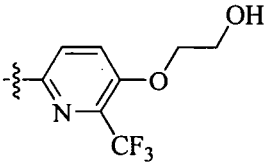
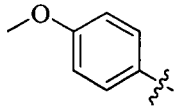
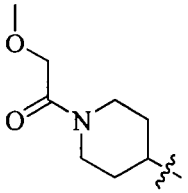
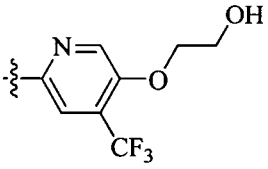
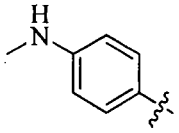
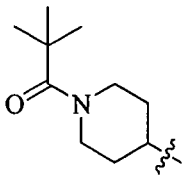
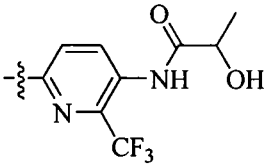
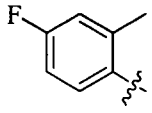
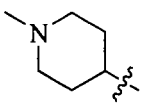
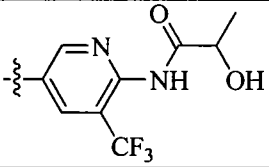
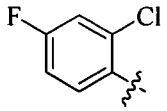
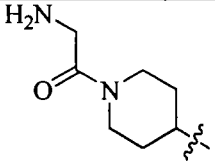
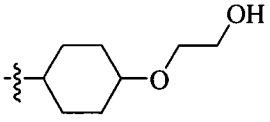
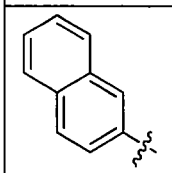
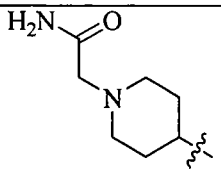
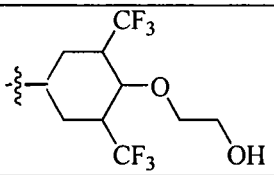
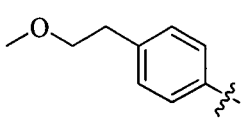
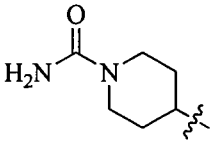
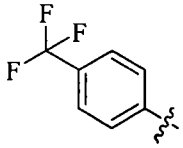
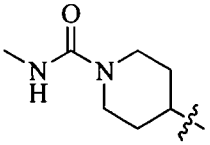
Formula(I-2)

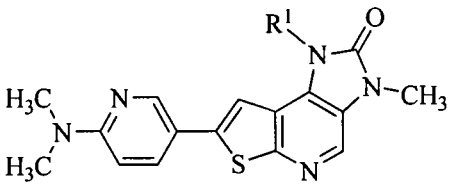


Formula(I-3)

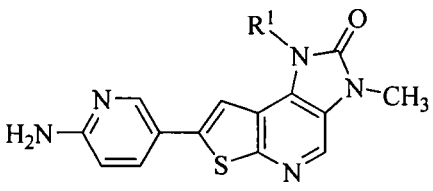
The substituents R^1 of the formulas (I-1), (I-2), and (I-3) described above are the following groups, :

R^1	R^1	R^1
		

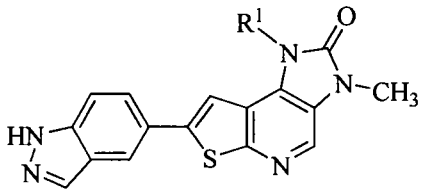
R^1	R^1	R^1
		
		
		
		
		
		
		
		
		



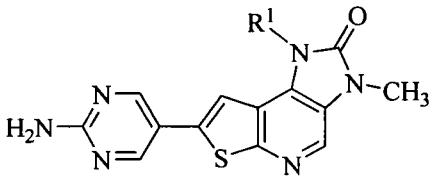
Formula(I-4)



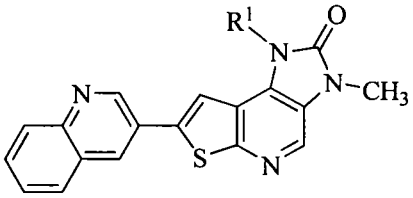
Formula(I-5)



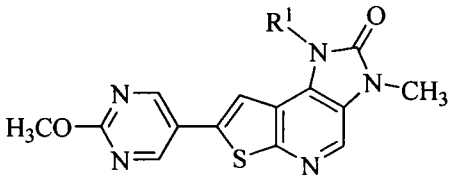
Formula(I-6)



Formula(I-7)

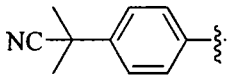
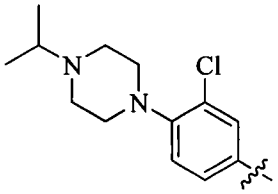
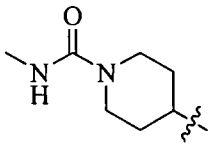
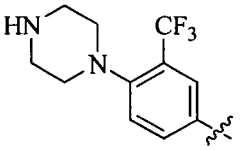
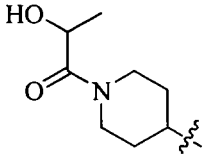
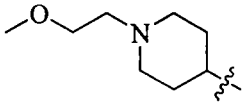
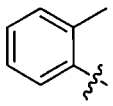
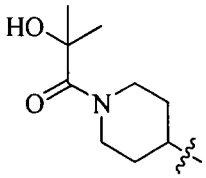
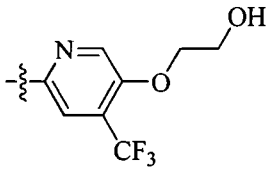
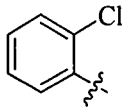
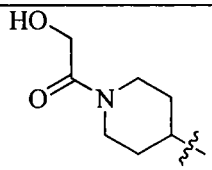
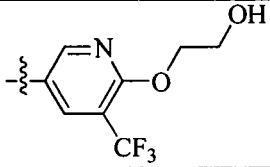
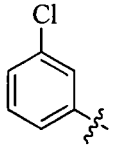
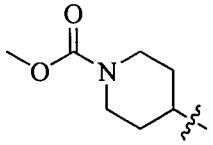
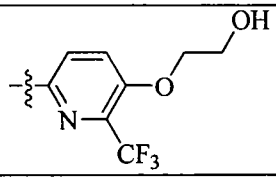
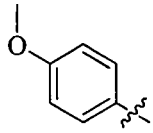
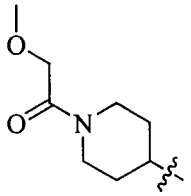
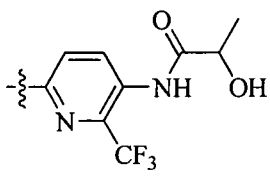
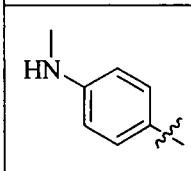
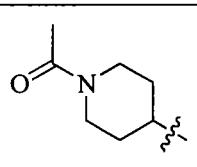
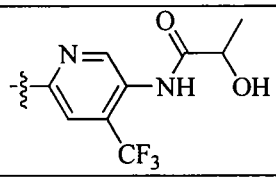


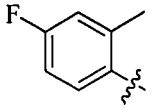
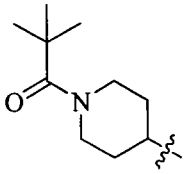
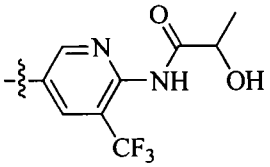
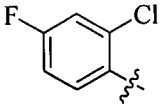
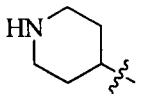
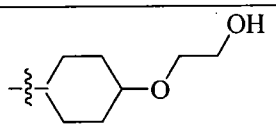
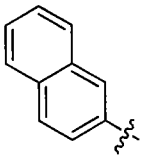
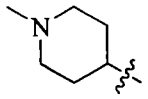
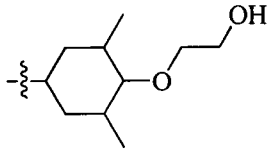
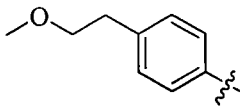
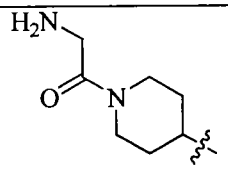
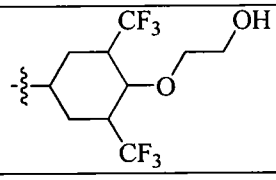
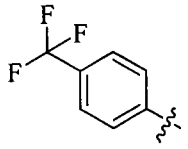
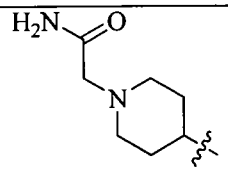
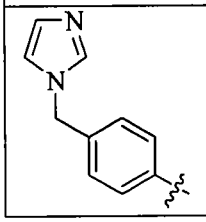
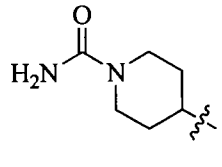
Formula(I-8)



Formula(I-9)

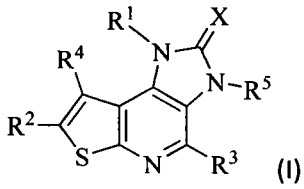
The substituents R^1 of the formulas (I-4), (I-5), (I-6), (I-7), (I-8), and (I-9) described above are the following groups:

R^1	**R^1**	**R^1**
		
		
		
		
		
		
		

R^1	R^1	R^1
		
		
		
		
		
		

CLAIMS

1 Compounds of general formula (I) or a pharmaceutically acceptable salt or its stereoisomers thereof:



(I)

Wherein

X is O, S, or NH;

R^1 is hydrogen, or C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} alkenyl, C_{3-8} alkynyl, aryl, heterocyclyl, that is optionally substituted by at least one R^6;

R^2 is hydrogen, or C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heterocyclyl, which is optionally substituted at least with one R^6;

R^3 is hydrogen, cyano, hydroxyl, carboxyl, $-(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nC(O)R^8$, $-(CH_2)_nS(O)_mR^8$, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, $-(CH_2)_nC(O)(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nOC(O)R^8$, $-(CH_2)_nC(O)OR^8$, $-(CH_2)_nNR^{7a}C(O)R^8$, $-(CH_2)_nNR^{7a}C(O)NR^{7a}R^{7b}$, or C_{1-6} alkyl, C_{1-6} alkoxy which is optionally substituted by at least one substituent selected from halogen, hydroxyl, carboxyl;

R^4 is hydrogen, halogen, cyano, hydroxyl, carboxyl, $-(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nC(O)R^8$, $-(CH_2)_nS(O)_mR^8$, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, $-(CH_2)_nC(O)(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nOC(O)R^8$, $-(CH_2)_nC(O)OR^8$, $-(CH_2)_nNR^{7a}C(O)R^8$, $-(CH_2)_nNR^{7a}C(O)NR^{7a}R^{7b}$, or C_{1-6} alkyl, C_{1-6} alkoxy which is optionally substituted by at least one substituent selected from halogen, hydroxyl, carboxyl and cyano;

R^5 is hydrogen, $-(CH_2)_nS(O)_mR^8$, or C_{1-6} alkyl which is optionally substituted by at least one R^6;

R^6 is hydroxyl, halogen, cyano, carboxyl, $-(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nC(O)R^8$, $-(CH_2)_nS(O)_mR^8$, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, $-(CH_2)_nC(O)(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nOC(O)R^8$, $-(CH_2)_nC(O)OR^8$, $-(CH_2)_nNR^{7a}C(O)R^8$, $-(CH_2)_nNR^{7a}C(O)NR^{7a}R^{7b}$, or C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-6} alkoxy, C_{3-8} cyclo alkyl, aryl, heterocyclyl which is optionally substituted by at least one R^9;

R^{7a} and R^{7b} are independently hydrogen, or C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, heterocyclyl

which is optionally substituted at least one R^9;

R^8 is C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, aryl, heterocyclyl which is optionally substituted by at least one R^9;

R^9 is hydroxyl, halogen, cyano, trifluoromethyl, C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, aryl, heterocyclic, $-(CH_2)_nNR^{10a}R^{10b}$, $-(CH_2)_nC(O)R^{11}$, $-(CH_2)_nC(O)NR^{10a}R^{10b}$, $-(CH_2)_nS(O)_mR^{11}$, $-(CH_2)_nS(O)_mNR^{10a}R^{10b}$, $-(CH_2)_nNR^{10a}S(O)_mR^{11}$, $-(CH_2)_nOC(O)R^{11}$, $-(CH_2)_nNR^{10a}C(O)R^{11}$, or $-(CH_2)_nNR^{10a}C(O)NR^{10a}R^{10b}$;

R^{10a} and R^{10b} are independently hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, or heterocyclic;

R_{11} is C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, or heterocyclic;

m is 1 or 2;

n is 0 to 4.

2. A compound claimed in claim 1, or its pharmaceutically acceptable salt or its stereoisomers:

Wherein

X is O;

R^1 is C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, 4-10 membered heterocyclyl, that is optionally substituted by at least one R^6;

R^2 is hydrogen, or C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, heterocyclyl, which is optionally substituted at least with one R^6;

R^3 is hydrogen, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, or C_{1-6} alkyl, C_{1-6} alkoxy which is optionally substituted by at least one substituent selected from halogen, hydroxyl, carboxyl;

R^4 is hydrogen, halogen, cyano, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, or C_{1-6} alkyl, C_{1-6} alkoxy which is optionally substituted by at least one substituent selected from halogen, hydroxyl, carboxyl;

R^5 is hydrogen, or C_{1-6} alkyl which is optionally substituted by at least one R^6;

R^6 is hydroxyl, halogen, $-(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nC(O)R^8$, $-(CH_2)_nS(O)_mR^8$, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, $-(CH_2)_nC(O)(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nOC(O)R^8$, $-(CH_2)_nC(O)OR^8$, $-(CH_2)_nNR^{7a}C(O)R^8$, $-(CH_2)_nNR^{7a}C(O)NR^{7a}R^{7b}$,

or C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cyclo alkyl, aryl, 4-10 membered heterocyclyl which is optionally substituted by at least one R^9;

R^{7a} and R^{7b} are independently hydrogen, or C_{1-6} alkyl which is optionally substituted by at least one R^9;

R^8 is C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, aryl, 4-10 membered heterocyclyl which is optionally substituted by at least one R^9;

R^9 is hydroxyl, halogen, cyano, trifluoromethyl, C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, aryl, 4-10 membered heterocyclic, $-(CH_2)_nNR^{10a}R^{10}$;

R^{10a} and R^{10b} are independently hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, aryl, or 4-10 membered heterocyclic;

m is 1 or 2;

n is 0 to 4.

3. A compound claimed in claim 2, or its pharmaceutically acceptable salt or its stereoisomers:

Wherein

X is O;

R^1 is C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl, naphthyl, 5-10 membered heterocyclyl, that is optionally substituted by at least one R^6;

R^2 is phenyl, naphthyl, 5-10 membered heterocyclyl, which is optionally substituted by at least one R^6;

R^3 and R^4 are hydrogen;

R^5 is hydrogen, or C_{1-6} alkyl which is optionally substituted by at least one R^6;

R^6 is hydroxyl, halogen, $-(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nC(O)R^8$, $-(CH_2)_nS(O)_mR^8$, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, $-(CH_2)_nC(O)(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nOC(O)R^8$, $-(CH_2)_nC(O)OR^8$, $-(CH_2)_nNR^{7a}C(O)R^8$, $-(CH_2)_nNR^{7a}C(O)NR^{7a}R^{7b}$, or C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-7} cyclo alkyl, phenyl, 5-10 membered heterocyclyl which is optionally substituted by at least one R^9;

R^{7a} and R^{7b} are independently hydrogen, or C_{1-6} alkyl which is optionally substituted by at least one R^9;

R^8 is C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl, phenyl, 5-10 membered heterocyclyl,

which is optionally substituted by at least one R^9;

R^9 is hydroxyl, fluorine, cyano, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl, phenyl, 5-10 membered heterocyclic, or $-(CH_2)_nNR^{10a}R^{10}$;

R^{10a} and R^{10b} are independently hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl, or 5-10 membered heterocyclic;

m is 1 or 2;

n is 0 to 3.

4. A compound claimed in claim 3, or its pharmaceutically acceptable salt or its stereoisomers:

wherein

X is O;

R^1 is cyclopentyl, cyclohexyl, piperidinyl, piperazinyl, imidazolidinyl, pyrazolyl alkyl, tetrahydrofuran base, phenyl, naphthyl, pyridyl, pyrimidinyl , pyrazolyl, indazole-based, quinolyl, indolyl, pyrazolpyridyl, which is optionally substituted by at least on R^6;

R^2 is phenyl, pyridyl, pyrimidinyl, pyrazolyl, indazolyl, quinolyl, indolyl, pyrazolpyridyl, which is optionally substituted by at least on R^6;

R^3 and R^4 are hydrogen;

R^5 is hydrogen, or C1-6 alkyl, which is optionally substituted by at least on R^6;

R^6 is hydroxyl, halogen, $-(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nC(O)R^8$, $-(CH_2)_nS(O)_mR^8$, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, $-(CH_2)_nC(O)(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nOC(O)R^8$, $-(CH_2)_nC(O)OR^8$, $-(CH_2)_nNR^{7a}C(O)R^8$, $-(CH_2)_nNR^{7a}C(O)NR^{7a}R^{7b}$, or C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cyclo alkyl, 5-7 membered heterocyclyl, which is optionally substituted by at least one R^9;

R^{7a} and R^{7b} are independently for hydrogen, methyl, or ethyl;

R^8 is C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, phenyl, 5-7 membered heterocyclyl, which is optionally substituted by at least one R^9;

R^9 is hydroxyl, cyano, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy, or $-(CH_2)_nNR^{10a}R^{10}$;

R^{10a} and R^{10b} are independently hydrogen, methyl, or ethyl;

m is 1 or 2;

n is 0 to 3.

5. A compound claimed in claim 4, or its pharmaceutically acceptable salt or its stereoisomers:

wherein

X is O;

R^1 is cyclopentyl, cyclohexyl, piperidinyl, piperazinyl, phenyl, naphthyl, pyridyl, pyrimidinyl, pyrazolyl, indazole base, quinolinyl , indole, pyrazolpyridine, which is optionally substituted by at least on R^6;

R^2 is phenyl, pyridyl, pyrimidinyl, pyrazolyl, indazolyl, quinolyl, indolyl, pyrazolylpyridyl, which is optionally substituted by at least on R^6;

R^3 and R^4 are hydrogen;

R^5 is hydrogen, methyl, ethyl or propyl;;

R^6 is hydroxyl, fluorine, chlorine, $-(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nC(O)R^8$, $-(CH_2)_nS(O)_mR^8$, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, $-(CH_2)_nC(O)(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nOC(O)R^8$, $-(CH_2)_nC(O)OR^8$, $-(CH_2)_nNR^{7a}C(O)R^8$, $-(CH_2)_nNR^{7a}C(O)NR^{7a}R^{7b}$, or C1-6 alkyl, C1-6 alkoxy, C3-6 cycloalkyl, piperazinyl, imidazolyl, pyrazolyl, triazolyl, which is optionally substituted by at least one R^9;

R^{7a} and R^{7b} are independently for hydrogen, methyl, or ethyl;

R^8 is C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, phenyl, which is optionally substituted by at least one R^9;

R^9 is hydroxyl, cyano, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy, or $-(CH_2)_nNR^{10a}R^{10}$;

R^{10a} and R^{10b} are independently hydrogen, methyl, or ethyl;

m is 1 or 2;

n is 0 to 3.

6 . A compound claimed in claim 5, or its pharmaceutically acceptable salt or its stereoisomers:

Which

X is O;

R^1 is cyclopentyl, cyclohexyl, piperidinyl, phenyl, pyridyl, pyrimidine, indazolyl, quinolyl, indolyl, pyrazolylpyridyl, which is optionally substituted by at least on R^6;

R^2 is pyridyl, pyrimidine, indazolyl, quinolyl, indolyl, pyrazolyl and pyridyl, which is optionally substituted by at least on R^6;

R^3 and R^4 are hydrogen;

R^5 is hydrogen, methyl, ethyl or propyl;

R^6 is hydroxyl, fluorine, chlorine, $-(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nC(O)R^8$, $-(CH_2)_nS(O)_mR^8$, $-(CH_2)_nS(O)_mNR^{7a}R^{7b}$, $-(CH_2)_nNR^{7a}S(O)_mR^8$, $-(CH_2)_nC(O)(CH_2)_nNR^{7a}R^{7b}$, $-(CH_2)_nOC(O)R^8$, $-(CH_2)_nC(O)OR^8$, $-(CH_2)_nNR^{7a}C(O)R^8$, $-(CH_2)_nNR^{7a}C(O)NR^{7a}R^{7b}$, or C1-3 alkyl, C1-2 alkoxy, C3-6 cycloalkyl, piperazinyl, imidazolyl, pyrazolyl, which is optionally substituted by at least one R^9;

R^{7a} and R^{7b} are independently hydrogen, methyl or ethyl;

R^8 is C_{1-4} alkyl, C_{1-3} alkoxy, phenyl, which is optionally substituted by at least one R^9;

R^9 is hydroxyl, cyano, trifluoromethyl, methyl, ethyl, isopropyl, methoxy, or ethoxy;

m is 1 or 2;

n is 0 to 2.

7. A compound claimed in claim 6, or its pharmaceutically acceptable salt or its stereoisomers and selected from the following compounds:

7-(6-Methoxypyridin-3-yl)-3-methyl-1-(piperidin-4-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

1-(1-(2-hydroxypropanoyl)piperidin-4-yl)-7-(6-methoxypyridin-3-yl)-3-methyl-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

(*R*)-1-(1-(2-Hydroxypropanoyl)piperidin-4-yl)-7-(6-methoxypyridin-3-yl)-3-methyl-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

(*S*)-1-(1-(2-hydroxypropanoyl)piperidin-4-yl)-7-(6-methoxypyridin-3-yl)-3-methyl-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

7-(6-Methoxypyridin-3-yl)-3-methyl-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

2-(4-(7-(6-Methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)phenyl)-2-methylpropanenitrile ,

1-(1-(2-Hydroxyacetyl)piperidin-4-yl)-7-(6-methoxypyridin-3-yl)-3-methyl-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

Methyl 4-(7-(6-methoxypyridin-3-yl)-3-methyl-2-oxo

-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate ,

1-(1-Acetylpiperidin-4-yl)-7-(6-methoxypyridin-3-yl)-3-methyl-5a,8a-dihydro-1*H*-imid

azo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

2-Hydroxy-N-(6-(7-(6-methoxypyridin-3-yl)-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)-4-(trifluoromethyl)pyridin-3-yl)propanamide ,

1-(4-(2-Hydroxyethoxy)-3,5-dimethylcyclohexyl)-7-(6-methoxypyridin-3-yl)-3-methyl-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

3-Methyl-7-(6-methylpyridin-3-yl)-1-(piperidin-4-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

1-(1-(2-hydroxypropanoyl)piperidin-4-yl)-3-methyl-7-(6-methylpyridin-3-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

(*R*)-1-(1-(2-Hydroxypropanoyl)piperidin-4-yl)-3-methyl-7-(6-methylpyridin-3-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

(*S*)-1-(1-(2-hydroxypropanoyl)piperidin-4-yl)-3-methyl-7-(6-methylpyridin-3-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

3-Methyl-7-(6-methylpyridin-3-yl)-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

2-Methyl-2-(4-(3-methyl-7-(6-methylpyridin-3-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)phenyl)propanenitrile ,

1-(1-(2-Hydroxyacetyl)piperidin-4-yl)-3-methyl-7-(6-methylpyridin-3-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

Methyl 4-(3-methyl-7-(6-methylpyridin-3-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate ,

1-(1-Acetylpiperidin-4-yl)-3-methyl-7-(6-methylpyridin-3-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

2-Hydroxy-N-(6-(3-methyl-7-(6-methylpyridin-3-yl)-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)-4-(trifluoromethyl)pyridin-3-yl)propanamide ,

1-(4-(2-Hydroxyethoxy)-3,5-dimethylcyclohexyl)-3-methyl-7-(6-methylpyridin-3-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

3-Methyl-1-(piperidin-4-yl)-7-(1H-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

1-(1-(2-hydroxypropanoyl)piperidin-4-yl)-3-methyl-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

(*R*)-1-(1-(2-Hydroxypropanoyl)piperidin-4-yl)-3-methyl-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

(*S*)-1-(1-(2-hydroxypropanoyl)piperidin-4-yl)-3-methyl-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

3-Methyl-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

2-Methyl-2-(4-(3-methyl-2-oxo-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)phenyl)propanenitrile ,

1-(1-(2-Hydroxyacetyl)piperidin-4-yl)-3-methyl-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

Methyl 4-(3-methyl-2-oxo-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)piperidine-1-carboxylate ,

1-(1-Acetylpiperidin-4-yl)-3-methyl-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one ,

2-Hydroxy-N-(6-(3-methyl-2-oxo-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-2,3-dihydro-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-1-yl)-4-(trifluoromethyl)pyridin-3-yl)propanamide ,

1-(4-(2-Hydroxyethoxy)-3,5-dimethylcyclohexyl)-3-methyl-7-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-1*H*-imidazo[4,5-*d*]thieno[2,3-*b*]pyridin-2(3*H*)-one .

8. A pharmaceutical composition of any compound in the claims 1-7 or its pharmaceutically acceptable salts thereof, hydrolysable esters thereof, isomers thereof, hydrates thereof, hydrates of esters or salts thereof and other pharmaceutically active ingredients.

9. A pharmaceutical composition comprising any compound in the claims 1-7 or its pharmaceutically acceptable salts thereof, hydrolysable esters thereof, or isomers thereof and one or more pharmaceutical carrier(s) and/or diluent(s).

10. A method of using any compound in claims 1-7, or its pharmaceutically acceptable salts thereof, hydrolysable esters thereof, stereoisomers thereof, hydrate thereof or hydrates of esters and salts thereof, used alone or in combination with other active ingredients, to treat and/or to prevent lipid kinase and/or PI3-kinase related lipid kinase (especially PI3-kinase and/or mTOR) activity mediated proliferative diseases.