Fused Heterocyclic Compound, Preparation Method Therefor, Pharmaceutical Composition, And Uses Thereof

The application claims priority to CN Patent Application CN20131048520.6 filed on October 16, 2013, which is hereby incorporated herein by reference in its entirety.

Field of the invention

The present invention especially relates to a fused heterocyclic compound, preparation method therefor, pharmaceutical composition, and uses thereof.

Prior arts

Phosphatidylinositol 3-kinase (PI3K) is a type of intracellular phosphatidylinositol kinase that can catalyze the phosphorylation of the 3-hydroxy of phosphatidylinositol. The PI3K can be divided into type I kinase, type II kinase, and type III kinase, and the most extensively investigated one is the type I PI3Ks that can be activated by cell surface receptors. Type I PI3Ks in mammalian cells are further divided into two groups based on their structures and receptors, class Ia and class Ib, which transmits signals from tyrosine kinase-coupled receptors and G protein-coupled receptors, respectively. Class Ia PI3Ks include PI3Kα, PI3Kβ and PI3Kδ, class Ib PI3Ks include PI3K γ (*Trends Biochem. Sci.,* **1997**, *22*, 267-272). Class Ia PI3Ks are dimers of a catalytic subunit, p110, and a regulatory subunit, p85, having dual activity of lipid kinases and protein kinases (*Nat.Rev.Cancer* **2002**, 2, 489-501), which are considered to be related to the cell proliferation, developing of cancers, immunological diseases and inflammation-relating diseases.

Existing technologies have disclosed a number of compounds as PI3K inhibitors, such as: WO2008064093, WO2007044729, WO2008127594, WO2007127183, WO2007129161, US20040266780, WO2007072163, WO2009147187, WO2009147190, WO2010120987, WO2010120994, WO2010091808, WO2011101429, WO2011041399, WO2012040634, WO2012037226, WO2012032065, WO2012007493, WO2012135160 etc.

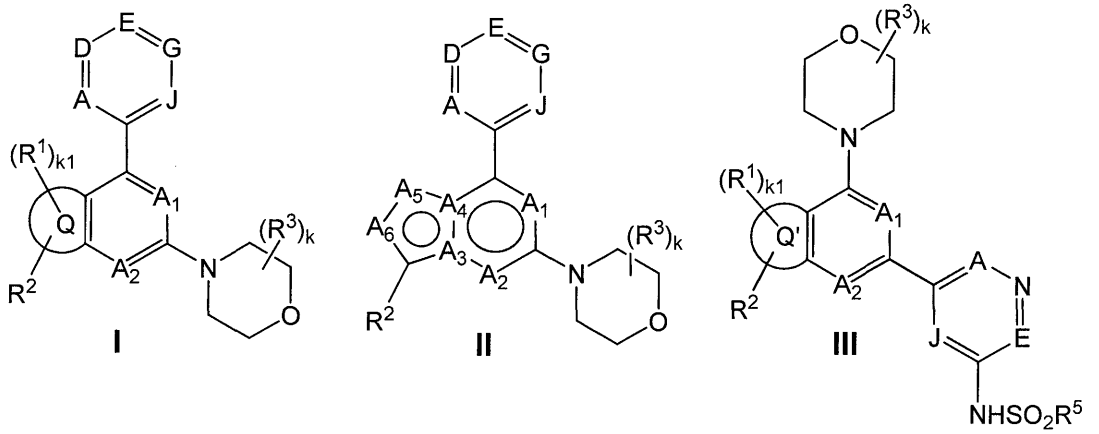
So far there is no small molecular PI3K inhibitor in market. Therefore, it is urgent to develop an efficient medicament of the PI3K δ inhibitor with selectivity for treating cancers, infection, inflammation and cell proliferation diseases such as autoimmune diseases.

Content of the present invention

The problem to be solved by the present invention is to provide a fused heterocyclic compound, preparation method therefor, pharmaceutical composition, and uses thereof which is totally different from the prior art. The fused heterocyclic compound of the

invention as an inhibitor with selectivity against PI3K δ can be used to prepare a medicament for treating cancers, infection, inflammation or cell proliferation diseases such as autoimmune diseases.

The present invention provides a fused heterocyclic compound represented by formula I, formula II or formula III, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof,



Wherein,

A_1 is N or CH;

A_2 is N or CH;

A_3 is N or C;

A_4 is N or C;

A_5 is O, S, N, CR^{1a} or NR^{5a};

A_6 is O, S, N, CR^{1b} or NR^{5b};

When A_5 is O or S, A_6 is N;

When A_6 is O or S, A_5 is N;

R^{1a} and R^{1b} are each independently a hydrogen, a deuterium, a halogen, an alkyl, an alkoxy, an alkenyl, an alkynyl, a cycloalkyl, a heterocycloalkyl or CN;

R^2 is $-(CR^8R^9)_mNR^5R^6$, $-(CR^8R^9)_mNR^7C(=Y)R^5$, $-(CR^8R^9)_mNR^7S(O)_2R^5$, $-(CR^8R^9)_mOR^5$, $-(CR^8R^9)_mS(O)_2R^5$, $-(CR^8R^9)_mS(O)_2NR^5R^6$, $-C(OR^5)R^6R^8$, $-C(=Y)R^5$, $-C(=Y)OR^5$, $-C(=Y)NR^5R^6$, $-C(=Y)NR^7OR^5$, $-C(=O)NR^7S(O)_2R^5$, $-C(=O)NR^7(CR^8R^9)_mNR^5R^6$, $-NR^7C(=Y)R^6$, $-NR^7C(=Y)OR^6$, $-NR^7C(=Y)NR^5R^6$, $-NR^7S(O)_2R^5$, $-NR^7S(O)_2NR^5R^6$, $-SR^5$, $-S(O)_2R^5$, $-S(O)_2NR^5R^6$, $-SC(=Y)R^5$, $-SC(=Y)OR^5$, $-O(CR^8R^9)_mCR^5R^6$, $-O(CR^8R^9)_mNR^5R^6$, a C_{1-12} alkyl, a C_{2-8} alkenyl, a C_{2-8} alkynyl, a C_{3-12} carbocyclic group, a C_{2-20} heterocyclic group, a C_{6-20} aryl or a C_{1-20} heteroaryl;

$(R^3)_k$ represents that the hydrogens attached to the morpholine ring are substituted by 0-k occurrences of R^3, at each occurrence the R^3 is the same or different from each other, and is independently a hydrogen, a deuterium, a halogen, a C_{1-6} alkyl, or any two of the R^3 are linked by a single bond, a C_{1-6} alkylene or a C_{1-6} alkylene substituted by one or two heteroatoms to form a ring structure, the heteroatom is O, N, or S;

A is N or CR^{4a};

D is N or CR^{4d};

E is N or CR^{4e};

G is N or CR^{4g};

J is N or CR^{4j};

A, D, E, G and J are not N at the same time;

R^{4a}, R^{4d}, R^{4e}, R^{4g} and R^{4j} are each independently a hydrogen, a halogen, -CN, an alkyl, an alkoxy, an alkenyl, an alkynyl, a cycloalkyl, a heterocycloalkyl, $-NR^5R^6$, $-OR^5$, $-SR^5$, $-C(O)R^5$, $-NR^5C(O)R^6$, $-N(C(O)R^6)_2$, $-NR^5C(O)NR^{5'}R^6$, $-NR^7S(O)_2R^5$, $-C(=O)OR^5$ or $-C(=O)NR^5R^6$, or R^{4j} and R^{4g}, together with the atoms to which they are attached form a saturated, unsaturated or partially unsaturated 5-membered or 6-membered heterocycle, the 5-membered or 6-membered heterocycle is fused to the 6-membered ring containing A, D, E, G and J;

Ring Q and ring Q' are benzene, a 5- to 9-membered alicyclic ring, a 5- to 9-membered heteroalicyclic ring, or a 5- to 6-membered heterocyclic ring; ring Q is not a thiophene or a furan; $(R^1)_{k1}$ represents that the hydrogens attached to the ring Q or ring Q' are substituted by 0-k1 occurrences of R^1, at each occurrence the R^1 is the same or different from each other, and is each independently a halogen, -CN, an alkyl, an alkoxy, an alkenyl, an alkynyl, a cycloalkyl, a heterocycloalkyl, $-NR^5R^6$, $-OR^5$, $-SR^5$, $-C(O)R^5$, $-NR^5C(O)R^6$, $-N(C(O)R^6)_2$, $-NR^5C(O)NR^{5'}R^6$, $-NR^7S(O)_2R^5$, $-C(=O)OR^5$ or $-C(=O)NR^5R^6$;

R^5, $R^{5'}$, R^{5a}, R^{5b}, R^6, R^7 and $R^{7'}$ are each independently a hydrogen, a C_{1-12} alkyl, $-(CH_2)_{2-3}NH_2$, a C_{2-8} alkenyl, a C_{2-8} alkynyl, a C_{3-12} carbocyclic group, a C_{2-20} heterocyclic group, a C_{6-20} aryl or a C_{1-20} heteroaryl, or R^5, R^6 together with the nitrogen or carbon atoms to which they are directly attached form a heterocyclic ring or a cycloalkyl, or R^7, $R^{7'}$ together with the nitrogen atom to which R^7 is directly attached form a heterocyclic ring; the heterocyclic ring or the cycloalkyl may be optionally substituted by the substituent selected from the group consisting of: oxo, $-(CH_2)_mOR^7$, $-NR^7R^{7'}$, $-CF_3$, a halogen, $-SO_2R^7$, $-C(=O)R^7$, $-NR^7C(=Y)R^{7'}$, $-NR^7S(O)_2R^{7'}$, $-C(=Y)NR^7R^{7'}$, a C_{1-12} alkyl, a C_{2-8} alkenyl, a C_{2-8} alkynyl, a C_{3-12} carbocyclic group, a C_{2-20} heterocyclic group, a C_{6-20} aryl or a C_{1-20} heteroaryl;

$(CR^8R^9)_m$ represents that 0 to m (CR^8R^9) are linked with each other, R^8 and R^9 are the substituents attached to the formed carbon chain, wherein each R^8 and R^9 are the same or different from each other, and are each independently a hydrogen, a deuterium, a

halogen, -CN, a hydroxyl, an alkoxy, a C_{1-12} alkyl, a C_{2-12} alkenyl, a C_{2-12} alkynyl, a C_{3-12} cycloalkyl, a C_{6-12} aryl, a 3- to 12-membered heterocycloalkyl or a 5- to 12-membered heteroaryl; or R^8, R^9 together with the atoms to which they are attached form a saturated or partially unsaturated C_{3-12} carbon ring or C_{2-20} heterocyclic ring;

wherein the alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, carbocyclic ring, heterocyclic ring, heterocyclylalkyl, aryl, or heterocyclic group can be optionally substituted by the substituent selected from the group consisting of: a halogen, a hydroxyl, -CN, $-CF_3$, $-NO_2$, oxo, R^5, $-C(=Y)R^5$, $-C(=Y)OR^5$, $-C(=Y)NR^5R^6$, $-(CR^8R^9)_mNR^5R^6$, $-(CR^8R^9)_mOR^5$, $-NR^5R^6$, $-NR^7C(=Y)R^5$, $-NR^7C(=Y)OR^6$, $-NR^7C(=Y)NR^5R^6$, $-(CR^8R^9)_mNR^7SO_2R^5$, $=NR^7$, OR^5, $-OC(=Y)R^5$, $-OC(=Y)OR^5$, $-OC(=Y)NR^5R^6$, $-OS(O)_2(OR^5)$, $-OP(=Y)(OR^5)(OR^6)$, $-OP(OR^5)(OR^6)$, $-SR^5$, $-S(O)R^5$, $-S(O)_2R^5$, $-S(O)_2NR^5R^6$, $-S(O)(OR^5)$, $-S(O)_2(OR^5)$, $-SC(=Y)R^5$, $-SC(=Y)OR^5$, $-SC(=Y)NR^5R^6$, a C_{1-12} alkyl, a C_{2-8} alkenyl, a C_{2-8} alkynyl, a C_{3-12} carbocyclic group, a C_{2-20} heterocyclic group, a C_{6-20} aryl or a C_{1-20} heteroaryl;

Y is O, S or NR^7;

m, k or k1 is independently 0, 1, 2, 3, 4, 5 or 6.

In the formula I,

A_1 is preferably N;

A_2 is preferably N;

R^2 is preferably $-(CR^8R^9)_mNR^5R^6$, $-O(CR^8R^9)_mCR^5R^6$ or $-O(CR^8R^9)_mNR^5R^6$;

R^3 is preferably a hydrogen, a deuterium, a halogen or a C_{1-3} alkyl;

A is preferably CR^{4a}; R^{4a} is preferably a hydrogen, a halogen or a C_{1-3} alkyl;

D is preferably N or CR^{4d}; R^{4d} is preferably $-NR^7S(O)_2R^5$;

E is preferably CR^{4e}; R^{4e} is preferably a hydrogen, a C_{1-3} alkoxy or $-NR^5R^6$;

G is preferably N or CR^{4g}; R^{4g} is preferably $-NR^7S(O)_2R^5$;

J is preferably CR^{4j}; R^{4j} is preferably a hydrogen, a halogen or a C_{1-3} alkyl;

or, R^{4j} and R^{4g}, together with the atoms to which they are attached form a saturated, unsaturated or partially unsaturated 5- to 6-membered heterocyclic ring, the 5- to 6-membered heterocyclic ring is fused to the 6-membered ring containing A, D, E, G and J; the 5-membered heterocyclic ring is preferably a 5-membered nitrogen-containing heterocyclic ring; the 5-membered nitrogen-containing heterocyclic ring is preferably a pyrazole or a pyrrole;

A, D, E, G and J are not N at the same time;

ring Q is preferably a benzene;

$(R^1)_{k1}$ represents that the hydrogens to which attached to the ring Q are substituted by 0-k1 occurrences of R^1, at each occurrence the R^1 is the same or different from each other, and is each preferably independently a halogen;

R^5, R^6 and R^7 are each preferably independently a hydrogen, $-(CH_2)_{2-3}NH_2$ or a C_{1-6} alkyl, or R^5, R^6 together with the nitrogen or carbon atoms to which they are directly attached form a heterocyclic ring or a cycloalkyl, the heterocyclic ring or the cycloalkyl may optionally be substituted by the substituent selected from the group consisting of: $-(CH_2)_mOR^7$, $-SO_2R^7$, $-C(=O)R^7$, a C_{1-3} alkyl, a C_{3-6} carbocyclic group and a C_{2-5} heterocyclic group; wherein the heterocyclic ring is preferably a nitrogen-containing or an oxygen-containing 4- to 6-memebered heteroalicyclic ring, the cycloalkyl is preferably a 4- to 6-membered cycloalkyl; wherein the nitrogen-containing 6-membered heteroalicyclic ring is preferably a piperidine or a piperazidine, the oxygen-containing 6-membered heteroalicyclic ring is preferably a tetrahydropyran, the oxygen-containing 5-membered heteroalicyclic ring is preferably a tetrahydrofuran, the nitrogen-containing 5-membered heteroalicyclic ring is preferably a tetrahydropyrrole;

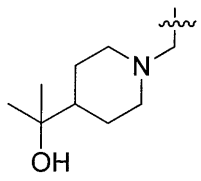
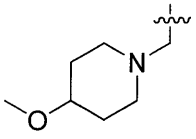
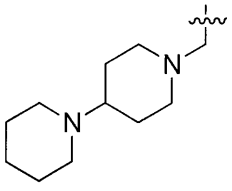
R^8 is preferably a hydrogen, a deuterium, a halogen or a C_{1-3} alkyl;

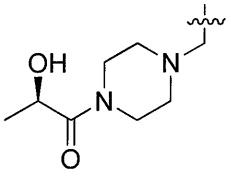
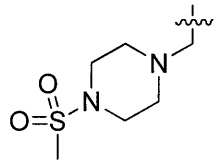
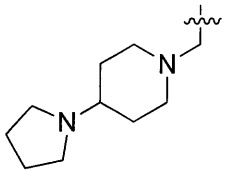
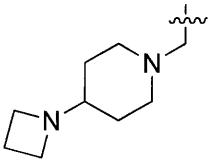
$(CR^8R^9)_m$ represents that 0 to m (CR^8R^9) are linked, R^8 and R^9 are the substituents attached to the formed carbon chain, wherein each R^8 and R^9 are the same or different from each other, and are each preferably independently a hydrogen, a deuterium, a halogen or a C_{1-3} alkyl;

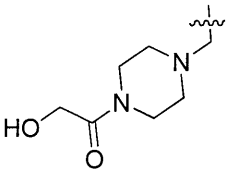
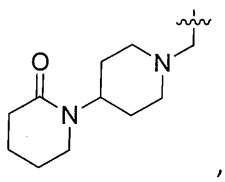
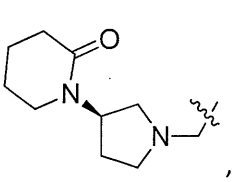
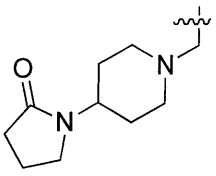
m, k or k1 is preferably independently 0 or 1.

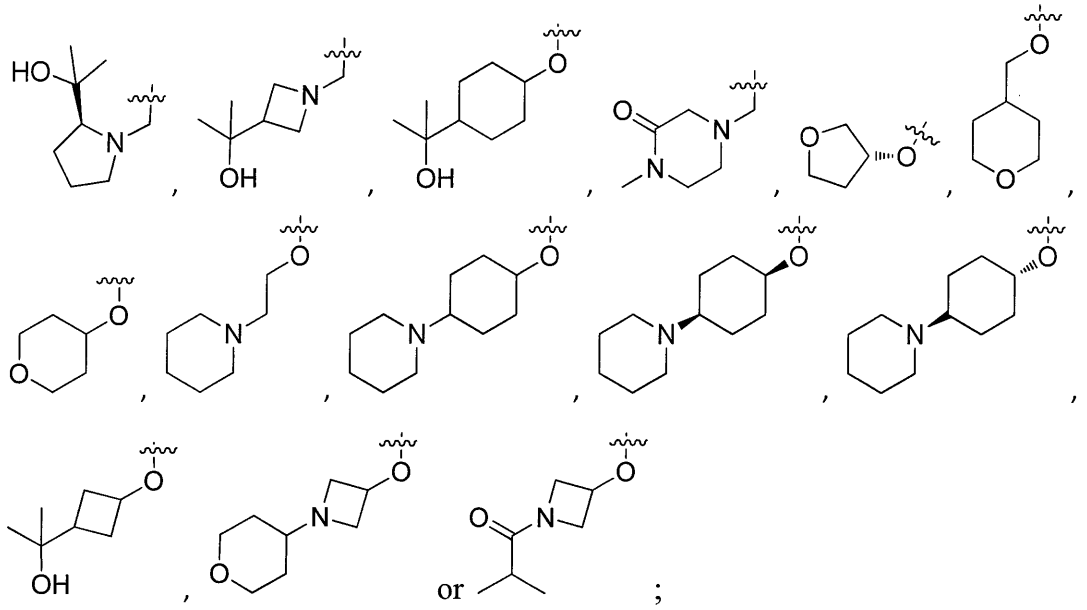
In the formula I,

more preferably, A_1 and A_2 are N at the same time;

more preferably, R^2 is  ,  ,  ,

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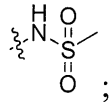


more preferably, R^3 is a hydrogen;

more preferably, A is CR^{4a}; R^{4a} is more preferably a hydrogen;

more preferably, D is N;

more preferably, E is CR^{4e}; R^{4e} is more preferably a hydrogen, a methoxy or $-NH_2$;

more preferably, G is N or CR^{4g}; R^{4g} is more preferably  ;

more preferably, J is CR^{4j}; R^{4j} is more preferably a hydrogen;

or, R^{4j} and R^{4g}, together with the atoms to which they are attached form a saturated, unsaturated or partially unsaturated 5- or 6-membered heterocyclic ring, the 5- or 6-membered heterocyclic ring is fused to the 6-memebered ring containing A, D, E, G and J; the 5- or 6-membered heterocyclic ring is more preferably a pyrazole or a pyrrole;

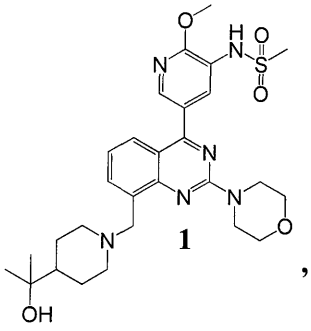
A, D, E, G and J are not N at the same time;

Ring Q is more preferably a benzene;

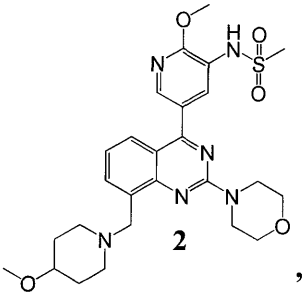
$(R^1)_{k1}$ represents that the hydrogens attached to the ring Q are substituted by 0-k1 occurrences of R^1, at each occurrence the R^1 is the same or different from each other, and is each more preferably independently fluorine;

more preferably, m, k or k1 is independently 0 or 1.

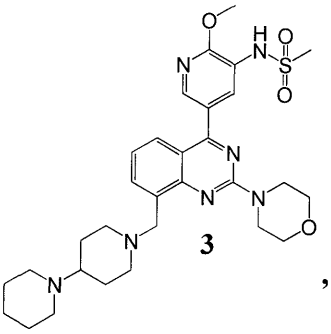
The formula I is preferably a compound selected from the group consisting of:



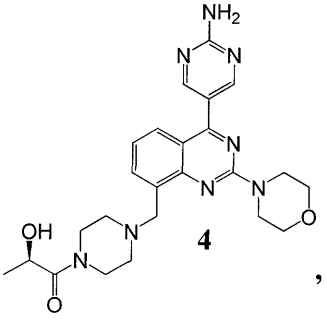
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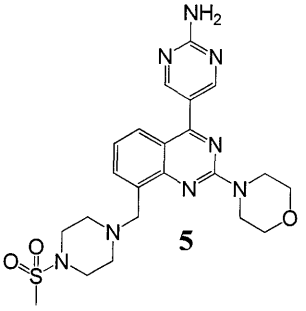
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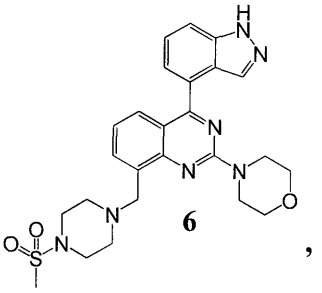
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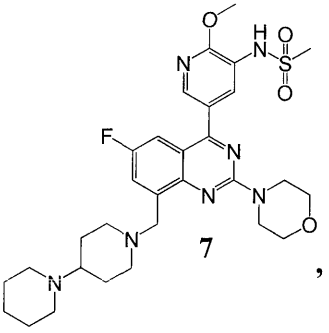
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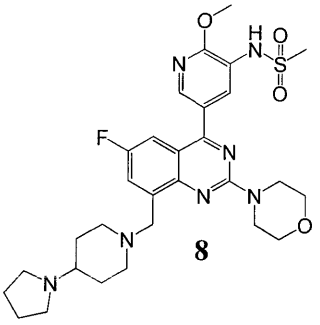
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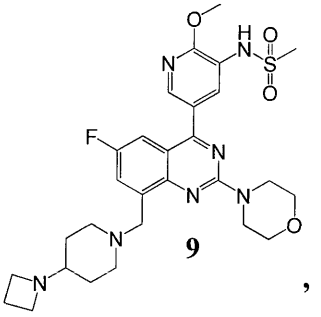
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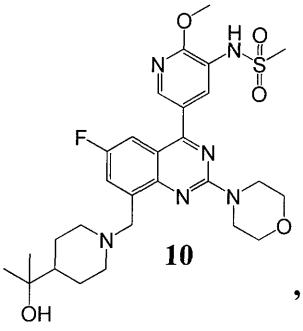
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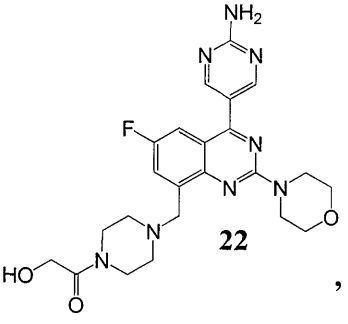
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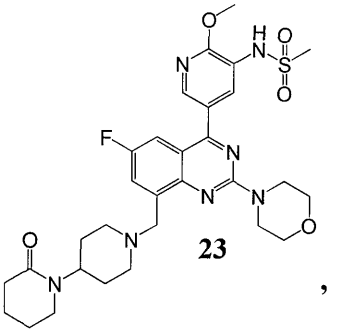
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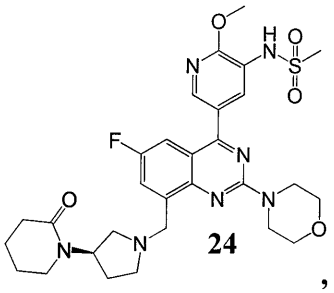
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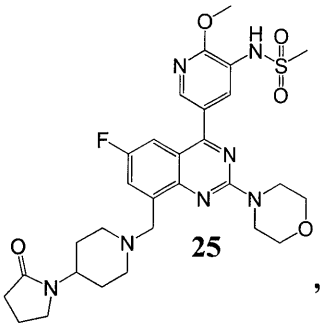
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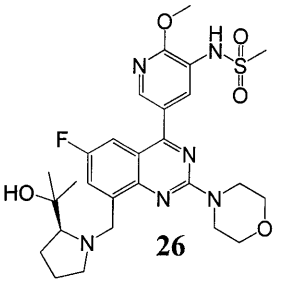
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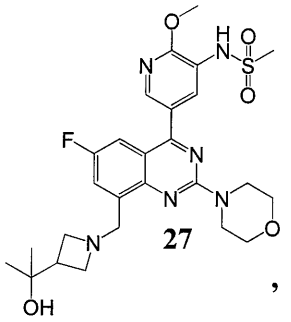
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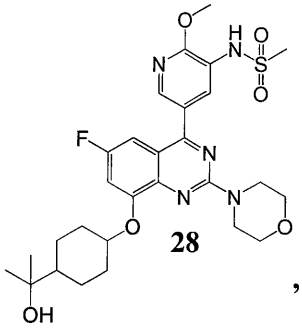
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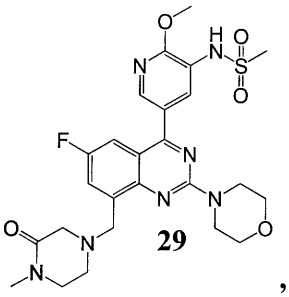
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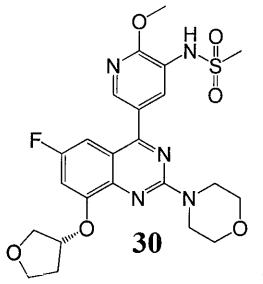
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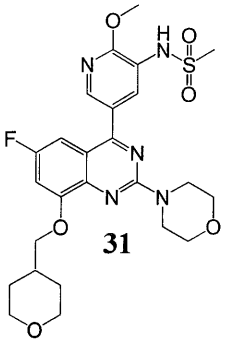
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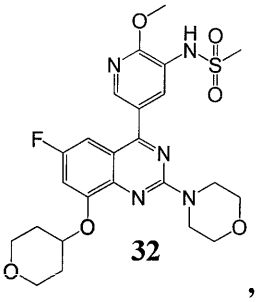
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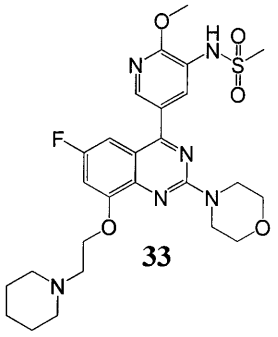
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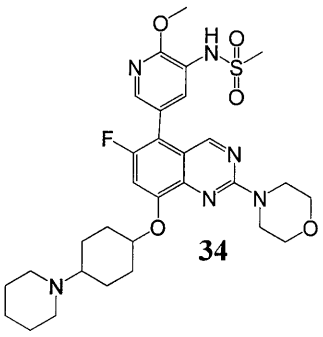
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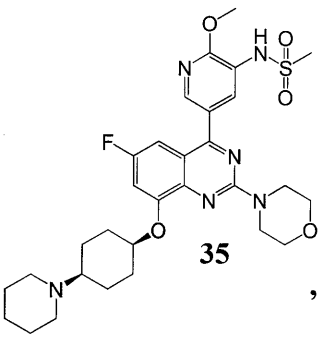
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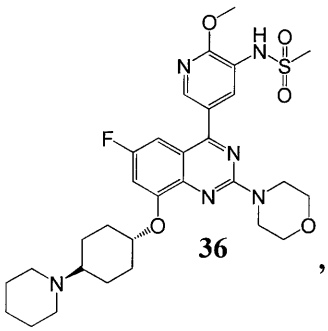
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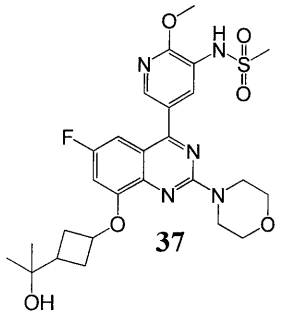
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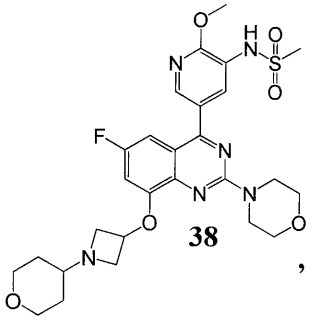
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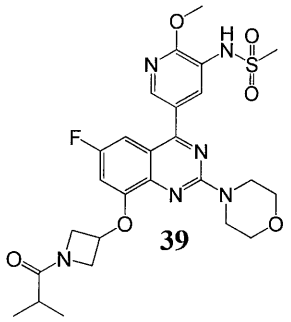
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In the formula II,

A_1 is preferably N or CH;

A_2 is preferably N or CH;

A_3 is preferably N or C;

A_4 is preferably N or C;

A_5 is preferably N;

A_6 is preferably CR^{1b}; R^{1b} is preferably a hydrogen or a deuterium;

R^2 is preferably $-(CR^8R^9)_mNR^5R^6$;

$(R^3)_k$ represents that the hydrogens attached to the morpholine ring are substituted by 0-k occurrences of R^3, at each occurrence the R^3 is the same or different from each other, and is each independently a hydrogen, a deuterium, a halogen, a C_{1-3} alkyl;

A is preferably CR^{4a}; R^{4a} is preferably a hydrogen, a halogen or a C_{1-3} alkyl;

D is preferably N or CR^{4d}; R^{4d} is preferably a hydrogen, a halogen or a C_{1-3} alkyl;

E is preferably CR^{4e}; R^{4e} is preferably a hydrogen, a halogen or a C_{1-3} alkyl;

G is preferably CR^{4g}; R^{4g} is preferably $-NR^7S(O)_2R^5$;

J is preferably CR^{4j}; R^{4j} is preferably a hydrogen;

or, R^{4j} and R^{4g}, together with the atoms to which they are attached form a saturated, unsaturated or partially unsaturated 5-membered heterocyclic ring, the 5-membered heterocyclic ring is fused to the 6-membered ring containing A, D, E, G and J; wherein the 5-membered heterocyclic ring is preferably a 5-membered nitrogen-

containing heterocyclic ring; the 5-membered nitrogen-containing heterocyclic ring is preferably a pyrazole or a pyrrole;

R^5, R^6 and R^7 are each preferably independently a hydrogen, a C_{1-6} alkyl, $-(CH_2)_{2-3}NH_2$, a C_{2-4} alkenyl or a C_{2-4} alkynyl, or R^5, R^6 together with the nitrogen atom to which they are directly attached form a heterocyclic ring which may be optionally substituted by substituent selected from the group consisting of: oxo, $-(CH_2)_mOR^7$, $-CF_3$, a halogen, $-SO_2R^7$, $-C(=O)R^7$, a C_{1-3} alkyl, a C_{3-6} carbocyclic group or a C_{2-5} heterocyclic group; wherein the heterocyclic ring formed by R^5, R^6 and the nitrogen atom to which they are directly attached is preferably a nitrogen-containing 6-membered heteroalicyclic ring, the nitrogen-containing 6-membered heteroalicyclic ring is preferably a piperidine or a piperazidine;

$(CR^8R^9)_m$ represents that 0 to m (CR^8R^9) are linked, R^8 and R^9 are the substituents attached to the formed carbon chain, wherein each R^8 and R^9 are the same or different from each other, and are each preferably independently a hydrogen, a deuterium, a halogen, -CN, a hydroxyl or a C_{1-3} alkyl;

wherein the alkyl, alkenyl, alkynyl, carbocyclic group, heterocyclic ring or heterocyclic group may optionally be substituted by the substituent selected from the group consisting of: a halogen, a hydroxyl, -CN, $-CF_3$, $-NO_2$ or oxo;

m or k is preferably independently 0 or 1.

In the formula II,

more preferably, A_1, A_3 and A_5, or, A_2, A_4 and A_5 are N at the same time;

when A_1, A_3 and A_5 are N, A_2, A_4 and A_6 are CH at the same time;

when A_2, A_4 and A_5 are N, A_1, A_3 and A_6 are CH at the same time;

more preferably, R^2 is $-(CR^8R^9)_mNR^5R^6$;

$(R^3)_k$ represents that the hydrogens attached to the morpholine ring are substituted by 0-k occurrences of R^3, at each occurrence the R^3 is the same or different from each other, and is each preferably independently a hydrogen or a deuterium;

A is more preferably CR^{4a}; R^{4a} is more preferably a hydrogen;

D is more preferably N or CR^{4d}; R^{4d} is more preferably a hydrogen;

E is more preferably CR^{4e}; R^{4e} is more preferably a hydrogen;

G is more preferably CR^{4g}; R^{4g} is more preferably $-NR^7S(O)_2R^5$;

J is more preferably CR^{4j}; R^{4j} is more preferably a hydrogen;

or, R^{4j} and R^{4g}, together with the atoms to which they are attached form a saturated, unsaturated or partially unsaturated 5-membered nitrogen-containing heterocyclic ring, the 5-membered nitrogen-containing heterocyclic ring is fused to the 6-

membered ring containing A, D, E, G and J; wherein the 5-membered nitrogen-containing heterocyclic ring is more preferably a pyrazole or a pyrrole;

R^5, R^6 and R^7 are each more preferably independently a hydrogen, a C_{1-3} alkyl, -$(CH_2)_2NH_2$, or R^5, R^6 and the nitrogen atom to which they are directly attached form a heterocyclic ring which may optionally be substituted by the substituent selected from the group consisting of: -SO_2R^7 or a C_{1-3} alkyl; wherein the heterocyclic ring formed by R^5, R^6 and the nitrogen atom to which they are directly attached is more preferably a nitrogen-containing 6-membered heteroalicyclic ring, the nitrogen-containing 6-membered heteroalicyclic ring is preferably a piperidine or a piperazidine;

$(CR^8R^9)_m$ represents that 0 to m (CR^8R^9) are linked, R^8 and R^9 are the substituents attached to the formed carbon chain, wherein each R^8 and R^9 are the same or different from each other, and are each preferably independently a hydrogen or a deuterium;

wherein the alkyl, heterocyclic ring or heterocyclic group may optionally be substituted by the substituent selected from the group consisting of: a halogen, a hydroxyl, -CN, -CF_3, -NO_2 or oxo;

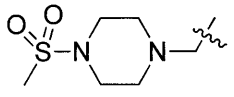
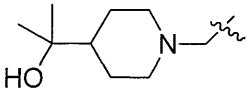
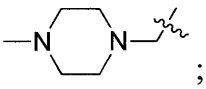
m or k is more preferably independently 0 or 1.

In the formula II, preferably,

A_1, A_3 and A_5, or, A_2, A_4 and A_5 are N at the same time;

when A_1, A_3 and A_5 are N, A_2, A_4 and A_6 are CH at the same time;

when A_2, A_4 and A_5 are N, A_1, A_3 and A_6 are CH at the same time;

R^2 is , , or ;

$(R^3)_k$ represents that the hydrogens attached to the morpholine ring are substituted by 0-k occurrences of R^3, at each occurrence the R^3 is the same or different from each other, and is each independently a hydrogen or a deuterium;

A is CR^{4a}; R^{4a} is a hydrogen;

D is N or CR^{4d}; R^{4d} is a hydrogen;

E is CR^{4e}; R^{4e} is a hydrogen;

G is CR^{4g}; R^{4g} is -$NR^7S(O)_2R^5$;

J is CR^{4j}; R^{4j} is a hydrogen;

or, R^{4j} and R^{4g}, together with the atoms to which they are attached form a saturated, unsaturated or partially unsaturated 5-membered nitrogen-containing heterocyclic ring, the 5-membered nitrogen-containing heterocyclic ring is fused to the 6-membered ring containing A, D, E, G and J; wherein the 5-membered nitrogen-

containing heterocyclic ring is a pyrazole or a pyrrole;

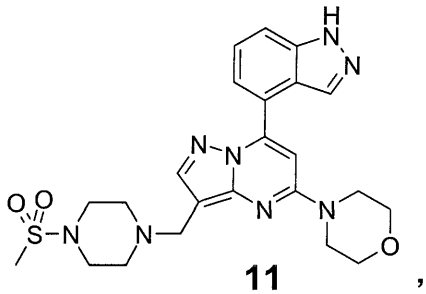
R^5 and R^7 are each independently a hydrogen or a C_{1-3} alkyl;

$(CR^8R^9)_m$ represents that 0 to m (CR^8R^9) are linked, R^8 and R^9 are the substituents attached to the formed carbon chain, wherein each R^8 and R^9 are the same or different from each other, and are each independently a hydrogen or a deuterium;

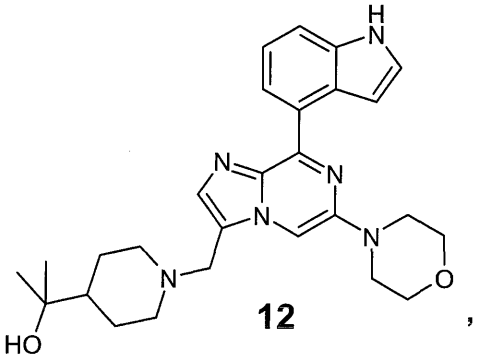
wherein the alkyl is substituted by a hydroxyl;

m or k is independently 0 or 1.

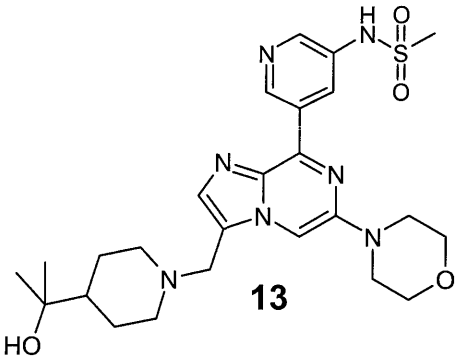
The formula II is a compound selected from the group consisting of:



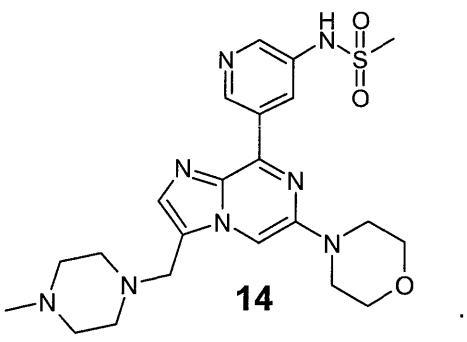
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In the formula III,

A_1 is preferably N;

A_2 is preferably N;

R^2 is preferably $-(CR^8R^9)_mNR^5R^6$ or $-(CR^8R^9)_mOR^5$;

$(R^3)_k$ represents that the hydrogens attached to the morpholine ring are substituted by 0-k occurrences of R^3, at each occurrence the R^3 is the same or different from each other, and is each preferably independently a hydrogen, a deuterium, a halogen or a C_{1-3} alkyl;

A is preferably CR^{4a}; R^{4a} is preferably a hydrogen, a halogen or a C_{1-3} alkyl;

E is preferably CR^{4e}; R^{4e} is preferably a C_{1-6} alkoxy;

J is preferably CR^{4j}; R^{4j} is preferably a hydrogen;

ring Q' is preferably a benzene or a 5-memebered heterocyclic ring; $(R^1)_{k1}$ represents that the hydrogens attached to the ring Q' are substituted by 0-k1 occurrences of R^1, at each occurrence the R^1 is the same or different from each other, and is each preferably independently a halogen, -CN or a C_{1-12} alkyl;

R^5, R^6, R^7 and $R^{7'}$ are each preferably independently a hydrogen, a C_{1-6} alkyl, $-(CH_2)_{2-3}NH_2$, a C_{3-6} carbocyclic group or a C_{2-5} heterocyclic group, or R^5, R^6 and the nitrogen atom to which they are directly attached form a heterocyclic ring which may optionally be substituted by the substituent selected from the group consisting of: $-NR^7R^{7'}$, a C_{1-3} alkyl, a C_{3-6} carbocyclic group or a C_{2-5} heterocyclic group;

$(CR^8R^9)_m$ represents that 0 to m (CR^8R^9) are linked, R^8 and R^9 are the substituents attached to the formed carbon chain, wherein each R^8 and R^9 are the same or different from each other, and are each independently preferably a hydrogen, a deuterium or a C_{1-3} alkyl;

m, k or k1 is preferably independently 0 or 1.

In the formula III,

A_1 is more preferably N;

A_2 is more preferably N;

R^2 is more preferably $-(CR^8R^9)_mNR^5R^6$ or $-(CR^8R^9)_mOR^5$;

$(R^3)_k$ represents that the hydrogens attached to the morpholine ring are substituted by 0-k occurrences of R^3, at each occurrence the R^3 is the same or different from each other, and is each more preferably independently a hydrogen or a deuterium;

A is more preferably CR^{4a}; R^{4a} is more preferably a hydrogen;

E is more preferably CR^{4e}; R^{4e} is more preferably a C_{1-3} alkoxy;

J is more preferably CR^{4j}; R^{4j} is more preferably a hydrogen;

ring Q' is more preferably a benzene or a 5-membered heterocyclic ring, the 5-membered heterocyclic ring is preferably a thiophene or an imidazole;

$(R^1)_{k1}$ represents that the hydrogens attached to the ring Q' are substituted by 0-k1 occurrences of R^1, at each occurrence the R^1 is the same or different from each other, and is each more preferably independently a C_{1-3} alkyl;

R^5, R^6, R^7 and $R^{7'}$ are each more preferably independently a hydrogen, a C_{1-3} alkyl, $-(CH_2)_{2-3}NH_2$, a C_{3-6} carbocyclic group or a C_{2-5} heterocyclic group, or R^5, R^6 and the nitrogen atom to which they are directly attached form a heterocyclic ring which may optionally be substituted by the substituent selected from the group consisting of: $-NR^7R^{7'}$, a C_{1-3} alkyl, a C_{3-6} carbocyclic group or a C_{2-5} heterocyclic group; the C_{2-5} heterocyclic group is preferably a piperidine, a pyran, a tetrahydropyrrole or an

oxetane;

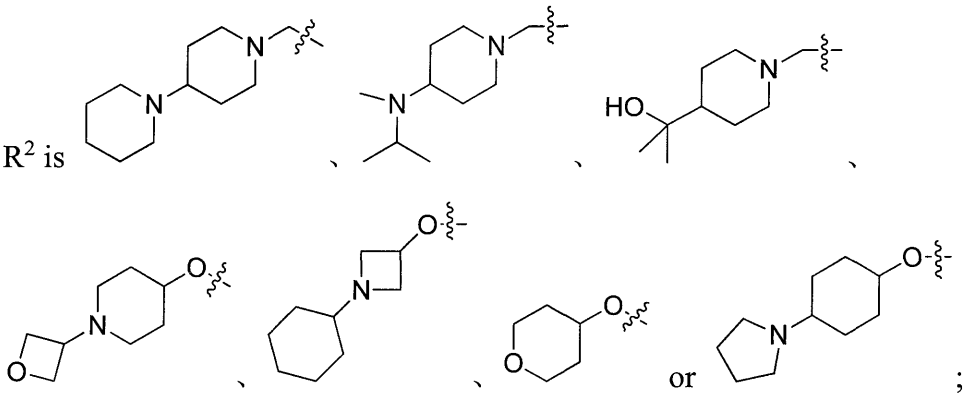
$(CR^8R^9)_m$ represents that 0 to m (CR^8R^9) are linked, R^8 and R^9 are the substituents attached to the formed carbon chain, wherein each R^8 and R^9 are the same or different from each other, and are each more preferably independently a hydrogen or a deuterium;

m, k or k1 is preferably independently 0 or 1.

In the formula III, preferably,

A_1 is N;

A_2 is N;

R^2 is 

or ;

$(R^3)_k$ represents that the hydrogens attached to the morpholine ring are substituted by 0-k occurrences of R^3, at each occurrence the R^3 is the same or different from each other, and is each independently a hydrogen or a deuterium;

A is CR^{4a}; R^{4a} is a hydrogen;

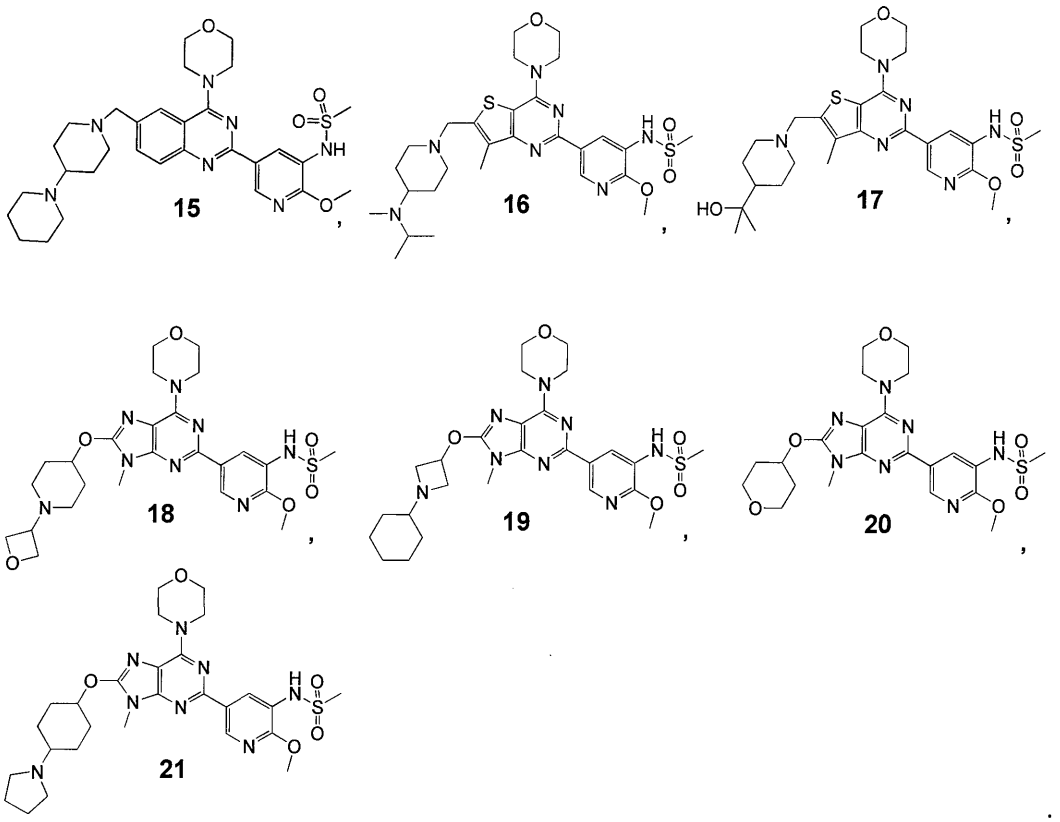
E is CR^{4e}; R^{4e} is a methoxy;

J is CR^{4j}; R^{4j} is a hydrogen;

ring Q' is a benzene or a 5-membered heterocyclic ring, the 5-membered heterocyclic ring is a thiophene or an imidazole; $(R^1)_{k1}$ represents that the hydrogens attached to the ring Q' are substituted by 0-k1 occurrences of R^1, at each occurrence the R^1 is the same or different from each other, and is each independently a methyl;

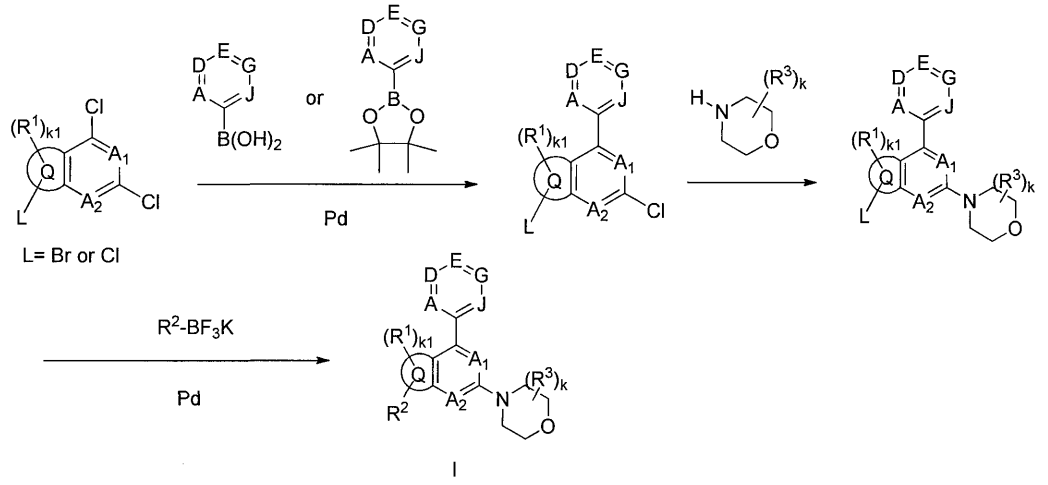
m, k or k1 is independently 0 or 1.

The formula III is more preferably a compound selected from the group consisting of:

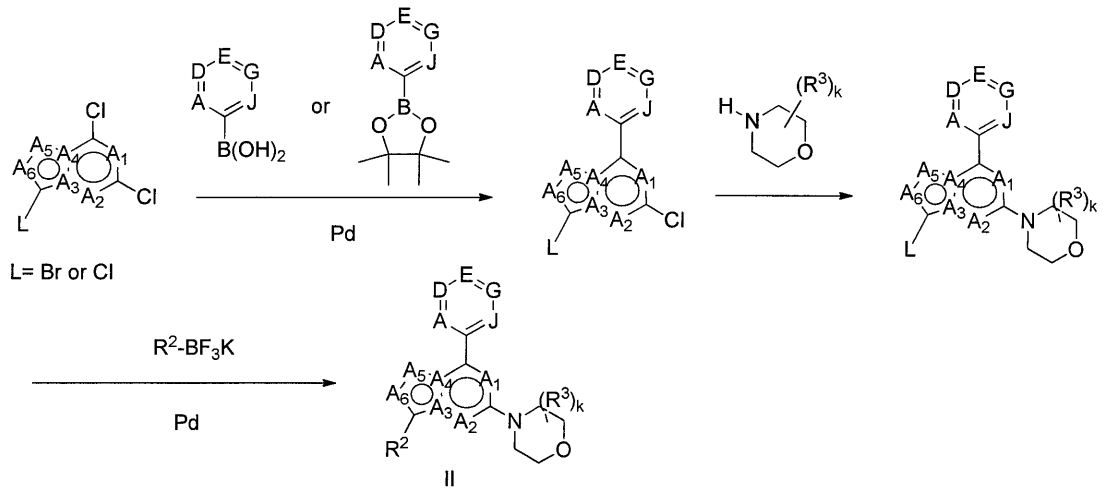


The present invention also provides a process for preparing the fused heterocyclic compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof, which may use commercially available raw materials, known methods in the art in combination with the contents disclosed in the present invention. Specific routes are as following:

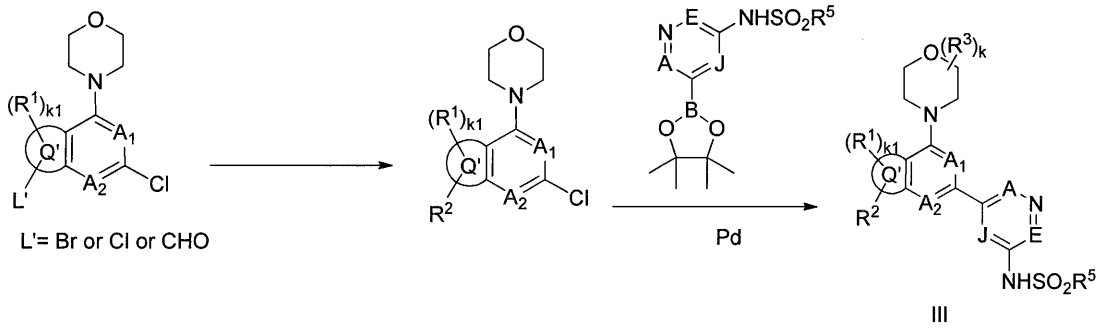
Reaction route I comprises the following steps:



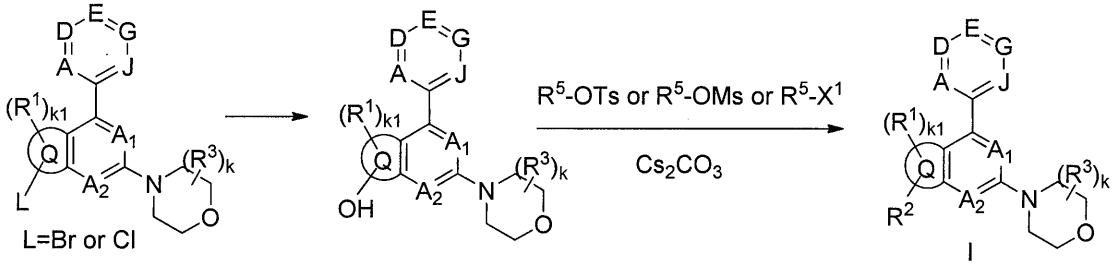
Reaction route II comprises the following steps:



Reaction route III comprises the following steps:



Reaction route IV comprises the following steps:

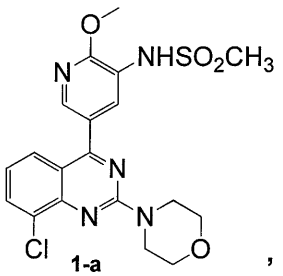


wherein the substituents are each defined as above, and when R^2 is $-O(CR^8R^9)_mCR^5R^6$ or $-O(CR^8R^9)_mNR^5R^6$ in the formula I, the reaction route IV is utilized to synthesis. When R^2 is not $-O(CR^8R^9)_mCR^5R^6$ or $-O(CR^8R^9)_mNR^5R^6$ in the formula I, the reaction route I is utilized to synthesis; X^1 is Cl, Br or I.

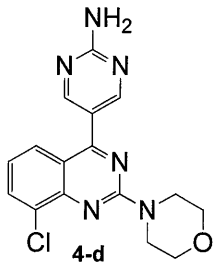
The conditions and steps utilized in the chemical reactions involved in the four reaction routes above can all be performed by reference to those commonly used in the art, and particularly can refer to the following references: J. Org. Chem. 2011, 76, 2762–2769; R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd ED., John Wiley and Sons (1999); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette(edit), Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995) and its

subsequent editions. In addition, the compounds obtained according to the methods above can be further modified in peripheral positions to give other target compounds of the present invention according to the relevant methods disclosed in the above references.

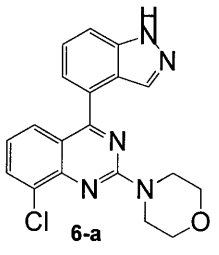
The present invention also provides a compound represented by the structure selected from the group consisting of:



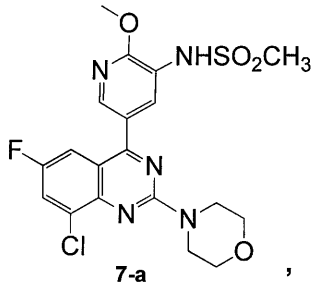
1-a ,



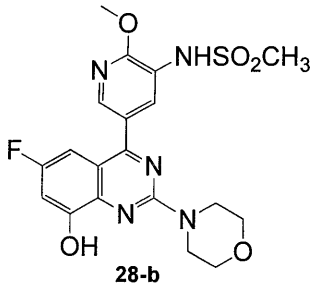
4-d ,



6-a ,



7-a ,



28-b .

At least one of the fused heterocyclic compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof prepared by the above routes can be purified by column chromatograph, HPLC, crystallization or other proper conditions.

The conditions and steps used in the purification method such as column chromatograph, HPLC and crystallization can refer to conventional conditions and steps in the art.

The above fused heterocyclic compound provided in the present invention can exhibit tautomerism, structural isomerism and stereoisomerism. The present invention includes any tautomer, structural isomer or stereo isomer of the compound and their mixtures, they have the ability of regulating the activity of the kinase and this ability is not limited to any isomer or the form of its mixture.

The present invention also provides a use of the fused heterocyclic compound represented by formula I, formula II or formula III, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof in manufacturing an inhibitor of kinase.

The present invention also provides a use of the fused heterocyclic compound represented by formula I, formula II or formula III, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof in manufacturing a medicament for treating and/or preventing a disease related to the kinase.

In the present invention, the kinase is preferably PI3 kinase (PI3K), more preferably p110 δ subtype of PI3K (PI3K).

The present invention also provides a pharmaceutical composition, which comprises a therapeutically effective dosage of one or more of the fused heterocyclic compounds represented by formula I, formula II or formula III, pharmaceutically acceptable salt, hydrate, solvate, polymorph and pro-drug thereof, and a pharmaceutically acceptable carrier.

In the present invention, the term "therapeutically effective dosage" means (i) the amount of the compound of the present invention required for preventing or treating the specific disease or disorder described in the application; (ii) the amount of the compound of the present invention required for attenuating, ameliorating or eliminating one or more symptoms of the specific disease or disorder described in the application; or (iii) the amount of the compound of the present invention required for preventing or delaying the onset of one or more symptoms of the specific disease or disorder described in the application. The dosage for treating human patients may range from 0.0001 mg/kg to 50 mg/kg, most typically 0.001 mg/kg to 10 mg/kg body weight, e.g. within the range from 0.01 mg/kg to 1 mg/kg. Such a dosage may be administered, for example 1-5 times a day.

Depending on the purpose of therapy, the pharmaceutical composition can be prepared into a variety of unit dose formulations, such as tablets, pills, powder, liquid, suspensions, emulsions, granules, capsules, suppositories and injections (solutions and suspensions) and so on, and preferably liquids, suspensions, emulsions, suppositories and injections (solutions and suspensions) etc.

In order to make the pharmaceutical composition form a tablet preparation, any known and widely used excipient in the art can be used. For example, carriers (such as lactose, sugar, sodium chloride, glucose, carbamide, starch, calcium carbonate, kaolin, crystalline cellulose and silicic acid etc.), adhesive (such as water, ethanol, propanol, ordinary syrup, glucose solution, starch solution, gelatin solution , carboxymethyl cellulose, lac, methyl cellulose and potassium phosphate, Polyvinylpyrrolidone, etc.), disintegrant (such as dry starch, sodium alginate, agar powder and kelp powder, sodium bicarbonate, calcium carbonate, the polyethylene sorbitan fatty acid ester, sodium dodecyl sulfate, stearic acid monoglyceride, starch and lactose, etc.), disintegration inhibitor (such as sugar, glyceryl tristearate, coconut oil and hydrogenated oil), adsorption accelerant (such as quaternary amine base and sodium dodecyl sulfate, etc.), wetting agent (such as glycerin, starch, etc.), sorbent (such as starch, lactose, kaolin, bentonite and colloid silicic acid, etc.) and lubricant (such as pure talc, stearate, boric acid powder and polyethyleneglycol, etc.). Common coating materials can also be used according to the requirements to form sugar-coated tablets, gelatin-coated tablets, enteric coated tablets, film-coated tablets, double film coated tablets and multiple film coated tablets.

In order to make the pharmaceutical composition form a pill preparation, any known

and widely used excipient in the art can be used, for example, carriers (such as lactose, starch, coconut oil, hydrogenated vegetable oil, kaolin and talc powder, etc.), adhesive (such as acacia powder, tragacanth gum powder, gelatin and ethanol, etc.), disintegrant (such as agar and kelp powder, etc.).

In order to make the pharmaceutical composition form a suppository preparation, any known and widely used excipient in the art can be used, for example, polyethyleneglycol, coconut oil, higher alcohols, higher alcohol esters, gelatin and semisynthetic glyceride, etc.

In order to make the pharmaceutical composition form an injection preparation, the solution or suspension (preferably adding a proper amount of sodium chloride, glucose or glycerin, etc.) can be sterilized, and then with which prepare the injection preparation having isosmotic pressure with the blood. In the process for preparing the injection preparation, any commonly used carriers in the art can also be used. For instance, water, ethanol, propanediol, ethoxylated isostearyl alcohol, polyoxy isostearyl alcohol and the polyethylene sorbitan fatty acid ester, etc. Besides, conventional solvents, buffer and analgetic and the like can also be added.

In the present invention, the administration of the pharmaceutical composition do not have special requirements. Various preparation for administration is selected according to the age, gender, other condition and symptoms of patients. For instance, tablets, pills, solutions, suspensions, emulsions, granules or capsules for oral administration; injection preparations can be administered individually, or mixed with an injectable conveying liquid (such as glucose solution and amino acid solution) and transvenously injected; the suppository is administered rectally.

The present invention also provides a use of the pharmaceutical composition in manufacturing a kinase inhibitor.

The present invention also provides a use of the pharmaceutical composition in manufacturing a medicament for treating and/or preventing a disease related to kinase.

The kinase is preferably PI3 kinase.

In the present invention, the "disease related to kinase" includes, but is not limited to, the disease selected from the group consisting of cancer, immunological diseases, metabolic and/or endocrine dysfunction, angiocardiopathy, virus infections and inflammation, and nerve diseases, preferably cancer and/or immunological diseases. The immunological diseases include but are not limited to the disease selected from the group consisting of rheumatoid arthritis, psoriasis, ulcerative colitis, Crohn disease and systemic lupus erythematosus. The angiocardiopathy includes but is not limited to neoplastic hematologic disorder. The virus infections and inflammation include but are not limited to asthma and/or atopic dermatitis.

Unless otherwise indicated, the following terms used in the descriptions and the claims of the present invention have the following meanings:

As used herein, the term "alkyl" (used alone or as a part of other groups) refers to a saturated linear or branched-chain aliphatic hydrocarbyl containing 1 to 20 carbon atoms, preferably 1 to 12 carbon atoms, more preferably 1 to 6 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, isobutyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, 4,4-dimethylpentyl, 2,2,4-trimethylpentyl, undecyl, dodecyl, and the various isomers thereof etc.; as well as the alkyl groups containing 1 to 4 substituents selected from the group consisting of: a deuterium, a halogen (preferred F, Br, Cl or I), an alkyl, an alkoxy, an aryl, an aryloxy, an aryl or a diaryl substituted by an aryl, an arylalkyl, an arylalkoxy, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, a cycloalkyl alkyl, a cycloalkyl alkoxy, amino, optionally substituted amino (such as amino sunstituted by one to two C_1-C_3 alkyl groups, or $-NR^7C(=Y)R^5$ mentioned above), a hydroxyl, a hydroxylalkyl, an acyl, an aldehyde group, a heteroaryl, a heteroaryloxy, a heterocycloalkyl, a heterocycloalkoxy, an arylheteroaryl, an arylalkoxycarbonyl, a heteroarylalkyl, a heteroarylalkoxy, an aryloxyalkyl, an aryloxyaryl, an alkylamino, an acylamino, an arylcarbonylamino, a $C_{2\text{-}20}$ heterocyclic group, a nitro, a cyano, a thiol, a haloalkyl, a trihaloalkyl (such as a trifluoromethyl) and/or an alkylthio. "C_{x1}-C_{y1}" alkyl (x1 and y1 are integer) described in the present invention with the range of the number of carbon atoms specified, such as "a C_1-C_{12} alkyl", except that the range of the number of carbon atoms differs from the range of the number of carbon atoms of "alkyl" defined in this paragraph, has the same definition as the term "alkyl".

As used herein, the term "alkylene" (used alone or as a part of other groups) refers to a subsaturated linear or branched-chain aliphatic hydrocarbyl containing 1 to 20 carbon atoms, preferably 1 to 12 carbon atoms, more preferably 1 to 6 carbon atoms, such as a methylene, an ethylene, a *n*-propylene, an isopropylene, a *n*-butylene, a *tert*-butylene, an isobutylene, a pentylene, a hexylene, a heptylene, an octylene, a nonylene, a decylene, 4,4-dimethylpentylene, 2,2,4-trimethylpentylene, an undecylene, a dodecylene, and the various isomers thereof etc.; as well as the alkylene containing 1 to 4 substituents selected from the group consisting of: a deuterium, a halogen (preferably selected from F, Br, Cl or I), an alkyl, an alkoxy, an aryl, an aryloxy, an aryl or a diaryl substituted by an aryl, an arylalkyl, an arylalkoxy, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, a cycloalkyl alkyl, a cycloalkyl alkoxy, an amino, optionally substituted amino (such as amino sunstituted by one to two C_1-C_3 alkyl groups), a hydroxyl, a hydroxylalkyl, an acyl, an aldehyde group, a heteroaryl, a heteroaryloxy, a heterocycloalkyl, a heterocycloalkoxy, an arylheteroaryl, an arylalkoxycarbonyl, a heteroarylalkyl, a heteroarylalkoxy, an aryloxyalkyl, an aryloxyaryl, an alkylamino, an acylamino, an arylcarbonylamino, a nitro, a cyano, a thiol, a haloalkyl, a trihaloalkyl (such as trifluoromethyl), and/or an alkylthio; the substituents selected from the group mentioned above may also form a ring together with the alkylene group, thereby forming a spiro ring or a fused ring.

The term "alicyclic ring", "carbocyclic group" or "cycloalkyl" (used alone or as a part of other groups) includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclic alkyl,

bicyclic alkyl or tricyclic alkyl exhibited in the form of a fused ring or a bridge ring containing 3 to 20 ring-forming carbon atoms, preferably 3 to 12 carbon atoms, for example: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl; the cycloalkyl may be optionally substituted by 1 to 4 substituents selected from the group consisting of: a deuterium, a halogen, an alkyl, an alkoxy, a hydroxyl, an aryl, an aryloxy, an arylalkyl, a cycloalkyl, an alkylamino, an acylamino, oxo, an acyl, an arylcarbonylamino, an amino, a nitro, a cyano, a thiol and/or an alkylthio and/or any alkyl substituents. In addition, any cycloalkyl ring may be fused to a cycloalkyl, an aryl, a heteroaryl or a heterocycloalkyl ring to form a fused ring, a bridge ring or a spiro ring.

The term "alkoxy" refers to a cyclic or non-cyclic alkyl group containing the indicated number of carbon atoms and having a connection through an oxygen bridge. Thus, "alkoxy" includes the definitions of "alkyl" and "cycloalkyl" mentioned above.

The term "alkenyl" refers to a straight-chain, branched-chain or cyclic non-aromatic hydrocarbyl having the indicated number of carbon atoms and at least one carbon-carbon double bond. Preferably, there is one carbon-carbon double bond, and may have up to four non-aromatic carbon-carbon double bonds. Thus, "C_2-C_{12} alkenyl" refers to an alkenyl group having 2 to 12 carbon atoms. "C_2-C_6 alkenyl" refers to an alkenyl group having 2 to 6 carbon atoms, including vinyl, propenyl, butenyl, 2-methyl-butenyl and cyclohexenyl. A double bond may locate at the straight-chain, branched or cyclic portion of the alkenyl group and, where specified, the alkenyl group may be substituted.

The term "alkynyl" refers to a straight-chain, branched-chain or cyclic hydrocarbyl having the indicated number of carbon atoms and at least one carbon-carbon triple bond. It may have up to three carbon-carbon triple bonds. Thus, "C_2-C_{12} alkynyl" refers to an alkynyl group having 2 to 12 carbon atoms. "C_2-C_6 alkynyl" refers to an alkynyl group having 2 to 6 carbon atoms, including an ethynyl, a propynyl, a butynyl and 3-methyl-1-butynyl and the like.

As used herein, the term "aryl" refers to any stable monocyclic or bicyclic carbocyclic ring containing up to 7 atoms in each ring, wherein at least one ring is an aromatic ring. Examples of the above-mentioned aryl group include phenyl, naphthyl, tetrahydronaphthyl, 2,3-indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl. It can be understood that if an aryl substituent is a bicyclic ring having one non-aromatic ring, then the connection is through the aromatic ring. It also includes the aryl optionally substituted by the substituents selected from the group consisting of: a deuterium, a halogen (F, Br, Cl or I), an alkyl, an alkoxy, an aryl, an aryloxy, an aryl or a diaryl substituted by an aryl, an arylalkyl, an arylalkoxy, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, a cycloalkylalkyl, a cycloalkylalkoxy, optionally substituted amino, a hydroxyl, a hydroxylalkyl, an acyl, an aldehyde group, a heteroaryl, a heteroaryloxy, a heterocycloalkyl, a heterocycloalkyloxy, an arylheteroaryl, an arylalkoxycarbonyl, a heteroarylalkyl, a heteroarylalkoxy, an aryloxyalkyl, an aryloxyaryl, an alkylamino, an acylamino, an arylcarbonylamino, a

nitro, a cyano, a thiol, a haloalkyl, a trihaloalkyl and/or an alkylthio.

The term "alkylthio" refers to a cyclic or non-cyclic alkyl group containing the indicated number of carbon atoms and having a connection through a sulfur atom. Thus, "alkylthio" includes the definition of "alkyl" and "cycloalkyl".

The term "halogen" refers to fluorine, chlorine, bromine, iodine, or astatine.

The term "haloalkyl" refers to an alkyl group substituted by halogen at optionally position. Thus, "haloalkyl" includes the definition of "halogen" and "alkyl".

The term "haloalkoxy" refers to an alkoxy group substituted by halogen at optionally position. Thus, the "haloalkoxy" includes the definition of "halogen" and "alkoxy".

The term "aryloxy" refers to an aryl group containing the indicated number of carbon atoms and having a connection through an oxygen bridge. Thus, "aryloxy" includes the definition of "aryl".

As used herein, the term "arylhetero" or "heteroaryl" refers to any stable monocyclic or bicyclic ring containing up to 7 atoms in each ring, wherein at least one ring is an aromatic ring containing 1 to 4 heteroatoms selected from the group consisting of O, N, and S. Heteroaryl groups within the scope of this definition include, but are not limited to, acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrazolyl, imidazolyl, indolyl, indazolyl, triazolyl, tetrazolyl, benzotriazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzoisoxazolyl, benzisothiazolyl, guanine group, furyl, thienyl, thiazolyl, benzothienyl, benzofuranyl, quinolyl, isoquinolyl, oxazolyl, oxadiazolyl, isoxazolyl, triazinyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, tetrahydroquinolinyl. As the heterocycle defined below, "heteroaryl" should also be understood to include the N-oxide derivative of any nitrogen-containing heteroaromatic group. It can be understood that if a heteroaryl substituent is a bicyclic ring having one non-aromatic ring or one ring without heteroatom, then the connection is through the aromatic ring or the heteroatom contained in the ring. Heteroaryl groups are optionally substituted by 1 to 4 substituents selected from the group consisting of a deuterium, a halogen, an alkyl, an alkoxy, a hydroxyl, an aryl, an aryloxy, an arylalkyl, a cycloalkyl, an alkylamino, an acylamino, an acyl, an arylcarbonylamino, an amino, a nitro, a cyano, a thiol and/or an alkylthio and/or any alkyl substituents.

As used herein, the term "heterocyclic ring" or "heterocyclic group" refers to 5 to 10 membered aromatic or non-aromatic heterocyclic ring having 1 to 4 heteroatoms selected from the group consisting of O, N, and S, and bicyclic groups are also included. Therefore, the "heterocyclic group" includes the above heteroaryl groups, as well as their dihydro or tetrahydro analogs. Other examples of "heterocyclic group" include, but are not limited to, benzimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothienyl, benzoxazolyl, carbazyl, carbolinyl, cinnolinyl, furyl, imidazolyl, dihydroindolyl, indolyl, indazolyl, isobenzofuranyl, pseudoindolyl, isoquinoline, isothiazolyl, isoxazolyl, naphthalene pyrimidinyl,

oxadiazolyl, oxazolyl, oxazolinyl, isoxazolinyl, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydrodiazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thio-morpholinyl, dihydro-benzimidazolyl, dihydro-benzofuranyl, dihydro-benzothienyl, dihydro-benzoxazolyl, dihydro-furyl, dihydro-imidazolyl dihydro-indolyl, dihydro-isoxazolyl, dihydro-isothiazolyl, dihydro-oxadiazolyl, dihydro-oxazolyl, dihydro-pyrazinyl, dihydro-pyrazolyl, dihydropyridyl, dihydro-pyrimidinyl, dihydro-pyrrolyl, dihydro-quinolyl, dihydro-tetrazolyl, dihydro-thiadiazolyl, dihydro-thiazolyl, dihydro-thienyl, dihydro-triazolyl, dihydro-azetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl and tetrahydrothienyl and N-oxides thereof. A heterocyclic group can be linked with other groups through a carbon atom or a heteroatom. As the heterocyclic group can be substituted by substituents selected from the group consisting of: a halogen, -CN, $-CF_3$, $-NO_2$, oxo, R^5, $-C(=Y)R^5$, $-C(=Y)OR^5$, $-C(=Y)NR^5R^6$, $-(CR^8R^9)_nNR^5R^6$, $-(CR^8R^9)_nOR^5$, $-NR^5R^6$, $-NR^7C(=Y)R^5$, $-NR^7C(=Y)OR^6$, $-NR^7C(=Y)NR^5R^6$, $-(CR^8R^9)_mNR^7SO_2R^5$, $=NR^7$, OR^5, $-OC(=Y)R^5$, $-OC(=Y)OR^5$, $-OC(=Y)NR^5R^6$, $-OS(O)_2(OR^5)$, $-OP(=Y)(OR^5)(OR^6)$, $-OP(OR^5)(OR^6)$, $-SR^5$, $-S(O)R^5$, $-S(O)_2R^5$, $-S(O)_2NR^5R^6$, $-S(O)(OR^5)$, $-S(O)_2(OR^5)$, $-SC(=Y)R^5$, $-SC(=Y)OR^5$, $-SC(=Y)NR^5R^6$, a C_{1-12} alkyl (such as substituted or unsubstituted C_{1-6} alkyl, preferably substituted or unsubstituted C_{1-3} alkyl, whose substituent is preferably a hydroxyl, e.g., together with alkyl forming hydroxylethyl, or α-hydroxy isopropyl), C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-12} carbocyclic group, C_{2-20} heterocyclic group, C_{6-20} aryl or C_{1-20} heteroaryl; other groups and letters have the meanings given above. The C_{2-20} heterocyclic group is preferably a C_{2-8} saturated heterocyclic group, further preferably a C_{4-5} saturated heterocyclic group, wherein the heteroatom is N, O or S, more preferably a C_{4-5} saturated heterocyclic group containing two heteroatoms, such as piperazinyl or piperidyl. Where the C_{2-20} heterocyclic group has one heteroatom, the substituted position of which is preferably on a carbon atom or a heteroatom; where the C_{2-20} heterocyclic group has two or more heteroatoms, the substituted position of which is preferably on the heteroatom.

The term "heteroalicyclic ring" or "heterocycloalkyl" used herein alone or as a part of other groups refers to a 4 to 12 membered saturated or partially unsaturated ring containing 1 to 4 heteroatoms (such as nitrogen, oxygen and/or sulphur). The heterocycloalkyl groups may include at least one substituents, such as alkyl, halogen, oxo and/or any alkyl substituents set out above. In addition, any heterocycloalkyl rings can be fused to a cycloalkyl, aryl, heteroaryl or heterocycloalkyl ring, thereby to form a fused ring, a bridge ring or a spiro ring. A heterocycloalkyl substituent can be linked with other groups through a carbon atom or a heteroatom therein.

Without departing from common sense of the art, all the above preferred conditions can be combined in any way to provide the preferred embodiments of the present invention.

The materials and reagents used in the present invention are all commercially

available.

The room temperature in the present application refers to an environmental temperature which ranges from 10℃ to 35℃.

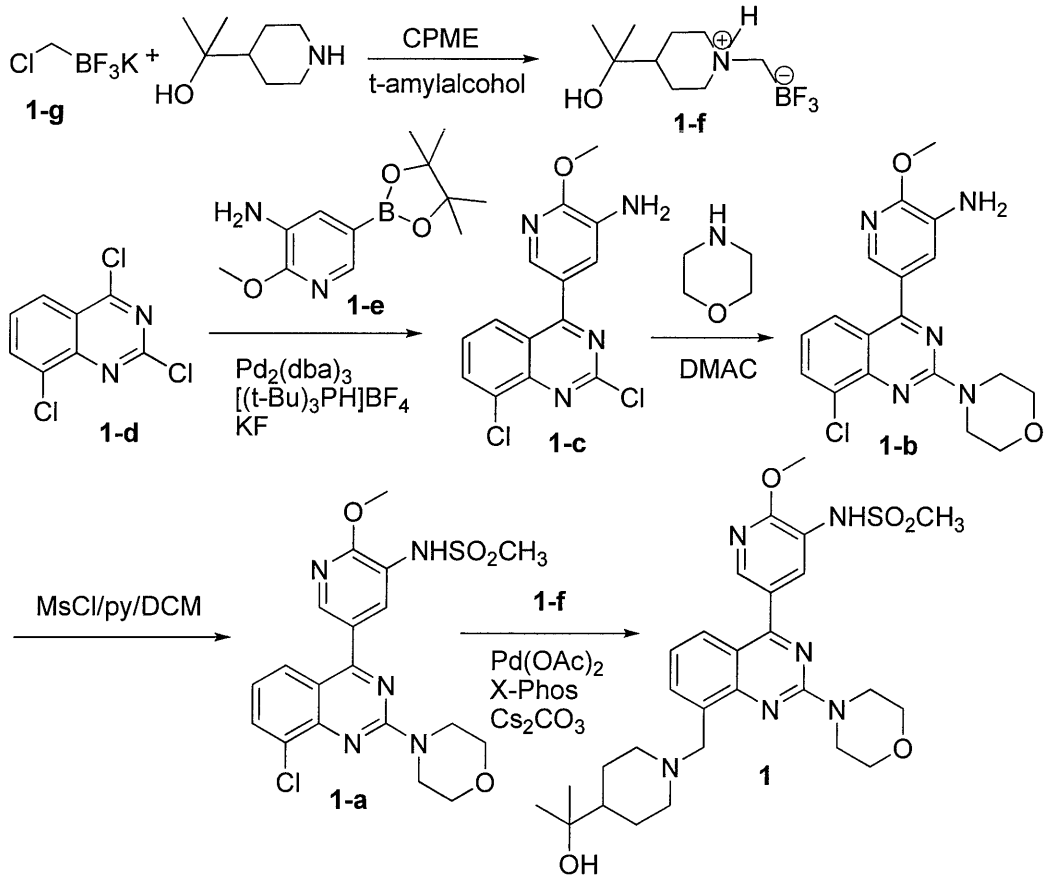
The positive effect of the present invention is that: the fused heterocyclic compound represented by formula I, II or III in the present invention is an efficient PI3 kinase (especially PI3K δ -selective) inhibitor which can be used for manufacturing a medicament for preventing and/or treating cell proliferation diseases such as cancer, infections, inflammation and autoimmune diseases.

Detailed description of the preferred embodiment

Below in conjunction with specific embodiments, the present invention is further elaborated. But the present invention is not therefore limited within the scope of the embodiments. The following embodiment does not indicate the specific conditions of the experiment, usually in accordance with conventional methods and conditions, or product manual.

Example 1 Synthesis of compound 1

Synthesis route of compound 1



Synthesis of compound **1-f**

To a reaction tube were added compound **1-g** (prepared according to the method disclosed in J. Org. Chem. 2011, 76, 2762 - 2769) (0.5 g, 3.2 mmol), 2-(4-piperidyl)-2-propanol (0.46 g, 3.23 mmol), cyclopentyl methyl ether (CPME) (2.1 mL) and tertiary amyl alcohol (0.7 mL). Under nitrogen gas atmosphere, the mixture was stirred overnight at 110℃. The reaction solution was cooled and concentrated under reduced pressure. Acetone (6 mL) was added into the residue and refluxed, ether (10 mL) was added slowly to precipitate, and another portion of ether (90 mL) was added. Cool to room temperature, filtrate, and the filter cake was dried to give compound 1-f (0.77 g, yield 100%). ^{1}H NMR (500 MHz, DMSO-d_6) : δ 9.19 (s, 1H), 4.25 (s, 1H), 3.38 (d, J = 12.5 Hz, 2H), 2.67 (t, J = 12.5 Hz, 2H), 1.90 (d, J = 5.0 Hz, 2H), 1.74 (d, J = 13.5 Hz, 2H), 1.44-1.57 (m, 2H), 1.36 (t, J = 12.0 Hz, 1H), 1.02 (s, 6H).

Synthesis of compound **1-c**

A mixture of compound **1-d** (prepared according to the method disclosed in Heterocycles, 2012 , pages 1417 – 1426) (480 mg, 2.068 mmol), compound 1-e (prepared according to the method disclosed in WO 2009/147187 A1) (510 mg, 2.068 mmol), $Pd_2(dba)_3$ (42 mg, 0.046 mmol), $[(t\text{-}Bu)_3PH]BF_4$ (60 mg, 0.207 mmol), patassium flouride (470 mg, 8.276 mmol), tetrahydrofuran (15 mL) and water (1.5 mL) was heated to 50℃ under nitrogen gas atomsphere and stirred for 7 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by column chromotograph (elution system: dichloromethane/ethanol=20/1) to give compound **1-c** (260 mg，39%). LC-MS (ESI): m/z = 321.0 $(M+H)^+$

Synthesis of compound **1-b**

A mixture of compound **1-c** (260 mg), morpholine (160 mg) and N, N-dimethylacetamide (4 mL) was heated to 90℃ and reacted for 1 hour. The reactant was cooled to room temperature, and concentrated under reduced pressure. The residue was diluted by ethyl acetate, and washed with saturated saline. The separated organic layer was dried over anhydrous sodium sulphate, and concentrated under reduced pressure to give crude compound **1-b** (260 mg). LC-MS (ESI): m/z = 372.1 $(M+H)^+$.

Synthesis of compound **1-a**

A solution of compound **1-b** (260 mg), pyridine (2 mL) and methylsulfonyl chloride (300 mg) in dichloromethane (10 mL) was stirred overnight at room temperature. The reaction solution was concentrated under reduced pressure. The redisdue was purified by silica column chromatograph (elution system: dichloromethane/ethanol=30/1) to give compound **1-a** (150 mg，total yield for two steps is 41%). LC-MS (ESI): m/z = 449.9 $(M+H)^+$.

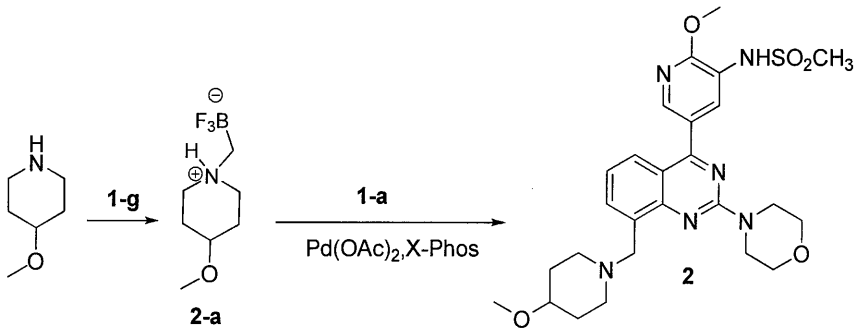
Synthesis of compound **1**

A suspension of compound **1-a** (150 mg, 0.305 mmol), compound **1-f** (176 mg, 0.672 mmol), palladium acetate (10 mg, 0.045 mmol), x-Phos (20 mg, 0.045 mmol), cesium carbonate (365 mg, 1.120 mmol), tetrahydrofuran (15 mL) and water (1.5 mL) was

heated to 72℃ under nitrogen atomsphere and stirred overnight. The reaction solution was cooled, then sodium hydroxide (80 mg) and methanol (10 mL) were added, and stirred for another 2 hours at room temperature. The reaction solution was neutralized with 1N hydrocholoride, and concentrated under reduced pressure. The residue was separated and purified by silica preparative plate chromatograph (developing system: dichloromethane/methanol=8/1) to give compond **1** (70 mg, 55%). LC-MS (ESI): m/z = 571.2 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD): δ8.15 (d, J = 2.4 Hz, 1H), 7.99 (d, J = 2.4 Hz, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.62 (d, J = 6.0 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 3.97 (s, 5H), 3.81 (t, J = 4.8 Hz, 4H), 3.66 (t, J = 4.8 Hz, 4H), 3.03 (d, J = 12.0 Hz, 2H), 2.92 (s, 3H), 2.12 (t, J = 12.0 Hz, 2H), 1.64 (d, J = 12.0 Hz, 2H), 1.14-1.37 (m, 3H), 1.01 (s, 6H).

Example 2 Synthesis of compound **2**

Synthesis route of compound **2**



Synthesis of compound **2-a**

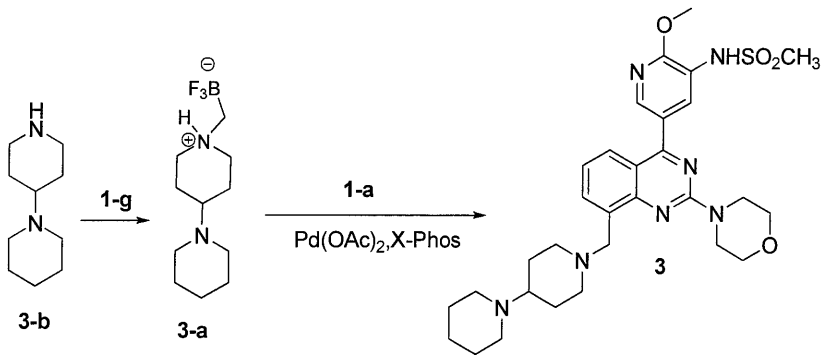
According to the process for preparing compound **1-f**, commercially available 4-methoxy piperidine was used to give compound **2-a** (800 mg, 78%) which was white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H), 3.23 (s, 6H), 2.48 (s, 1H), 2.12 (s, 1H), 1.92 (d, J = 4.9Hz, 4H), 1.86 (s, 2H).

Synthesis of compound **2**

According to the process for preparing compound **1**, compound **2-a** was used to give compound **2** (10 mg, 21%). LC-MS (ESI): m/z = 543.2 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$): δ8.28 (d, J = 2.0 Hz, 1H), 8.11 (d, J = 2.0 Hz, 1H), 7.74 (d, J = 6.8 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.13 (t, J = 7.2 Hz, 1H), 4.04 (s, 3H), 3.98 (s, 2H), 3.89-3.91 (m, 4H), 3.74-3.77 (m, 4H), 3.27 (s, 3H), 3.15-3.21 (m, 1H), 2.99 (s, 3H), 2.80-2.83 (m, 2H), 2.24-2.29 (m, 2H), 1.86-1.88 (m, 2H), 1.54-1.63 (m, 2H).

Example 3 Synthesis of compound **3**

Synthesis route of compound **3**



Synthesis of compound **3-a**

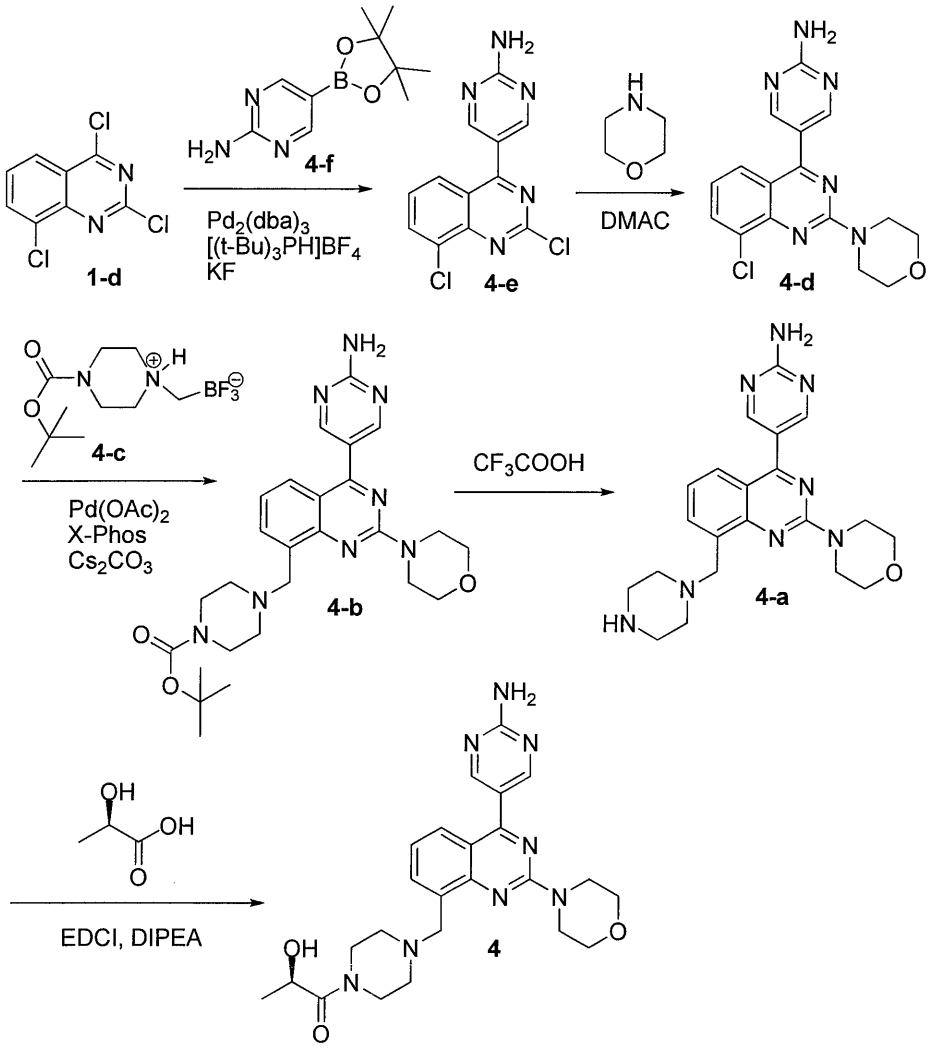
According to the process for preparing compound **1-f**, commercially available compound **3-b** was used to give compound **3-a** (700 mg, 89%) which was white solid.

Synthesis of compound **3**

According to the process for preparing compound **1**, compound **3-a** was used to give compound **3** (48 mg, 72%). LC-MS (ESI): m/z = 596.3 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35(d, *J*=2.0 Hz, 1H), 8.18(d, *J*=2.0 Hz, 1H), 7.74-7.80(m, 2H), 7.19(t, *J*=7.2 Hz, 1H), 4.11(s, 3H), 4.03(s, 2H), 3.96-3.98(m, 4H), 3.82-3.84(m, 4H), 3.06-3.10(m, 5H), 2.53-2.55(m, 4H), 2.30-2.37(m, 1H), 2.12-2.18(m, 2H), 1.79-1.82(m, 2H), 1.57-1.72(m, 6H), 1.43-1.45(m, 2H).

Example 4 Synthesis of compound **4**

Synthesis route of compound **4**



Synthesis of compound **4-e**

According to the process for preparing compound **1-c**, commercially available compound **4-f** was used to give compound **4-e** (0.69 g, 56%). LC-MS (ESI): m/z = 293 $(M+H)^+$.

Synthesis of compound **4-d**

A mixture of compound 4-e (0.68 g), morpholine (4 mL) and N, N-dimethylacetamide (40 mL) was heated to 90℃ and reacted for 1 hour. The reactant was cooled to room temperatrue, and filtrated to collect precipitate to give compound **4-d** (623 mg, 78%). LC-MS (ESI): m/z = 343.1 $(M+H)^+$.

Synthesis of compound **4-b**

According to the process for preparing compound **1**, compound **4-d** and compound **4-c** (prepared according to the method disclosed in J. Org. Chem. 2011, 76, 2762–2769) were used to give compound **4-b** (140 mg, 94%). LC-MS (ESI): m/z = 507.3 $(M+H)^+$.

Synthesis of compound **4-a**

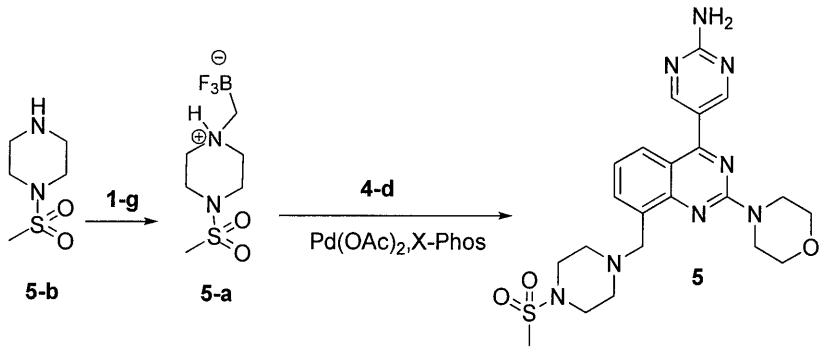
A solution of compound **4-b** (140 mg, 0.276 mmol) in dichloromethane/trifloroacetic acid (v/v, 2/1, 15 mL) was stirred at room temperature for half an hour. The reaction solution was concentrated under reduced pressure. The residue was dissolved in 5 mL methanol, and then neutralized to alkality by adding an excess amount of solid potassium carbonate, and diluted with 10 mL dichloromethane. The mixture was filtrated by a short silica cholumn, and eluted with a mixed solution of dichloromethane/methanol (v/v, 10/1). The filtrate was concentrated under reduced pressure to give crude compound **4-a** (110 mg, 98%). LC-MS (ESI): m/z = 407.3 $(M+H)^+$.

Synthesis of compound **4**

To a mixed solution of compound **4-a** (110 mg, 0.278 mmol), D-lactic acid (25 mg, 0.278 mmol), diisopropylethylamine (0.1 mL) and N, N-dimethylacetamide (2 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (52 mg, 0.271 mmol), and stirred for 2 hours at room temperature. The reaction solution was filtered. The filtrate was purified by Preparative HPLC to give compond 4 (30 mg, 23%). LC-MS (ESI): m/z = 479.3 $(M+H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68(s, 2H), 7.69-7.73(m, 2H), 7.14(t, *J*=8.0 Hz, 1H), 5.54(s, 2H), 4.37-4.40(m, 1H), 4.00(s, 2H), 3.88-3.91(m, 5H), 3.75-3.77(m, 4H), 3.54-3.74(m, 2H), 3.34-3.42(m, 2H), 2.50-2.58(m, 4H), 1.25(d, *J*=6.4 Hz, 3H).

Example 5 Synthesis of compound **5**

Synthesis route of compound **5**



Synthesis of compound **5-a**

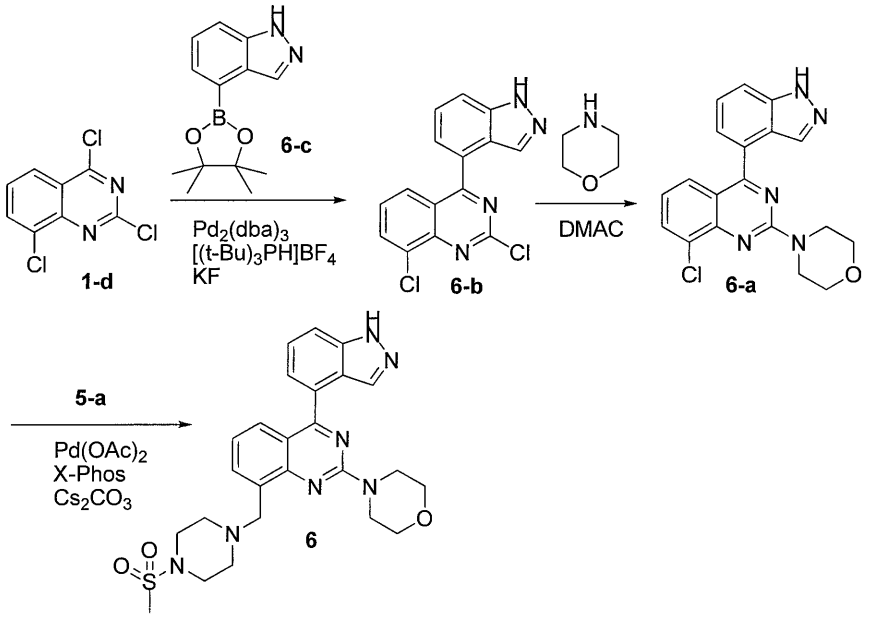
According to the process for preparing compound **1-f**, commercially purchased compound **5-b** was used to give compound **5-a** (7 g, yield 62%). ^{1}H NMR (500 MHz, DMSO-d_6) : δ 8.94 (1H, brs), 3.51-3.69 (2H, m), 3.37-3.50 (2H, m), 3.06-3.22 (2H, m), 2.89-3.04 (2H, m), 2.97 (3H ,s), 2.03 (2H, q, *J* = 5.0 Hz).

Synthesis of compound **5**

According to the process for preparing compound **1**, compound **4-d** and compound **5-a** were used to give compound **5** (15 mg, 10%). LC-MS (ESI): m/z = 485.2 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.67(s, 2H), 7.69-7.71(m, 2H), 7.13(t, *J*=8.0 Hz, 1H), 5.43(s, 2H), 4.02(s, 2H), 3.89-3.92(m, 4H), 3.75-3.78(m, 4H), 3.20-3.23(m, 4H), 2.72(s, 3H), 2.63-2.66(m, 4H).

Example 6 Synthesis of compound **6**

Synthesis route of compound **6**



Synthesis of compound **6-b**

According to the process for preparing compound **1-c**, commercially purchased compound **6-c** was used to give compound **6-b** (0.56 g, 43%). LC-MS (ESI): m/z = 316 $(M+H)^+$.

Synthesis of compound **6-a**

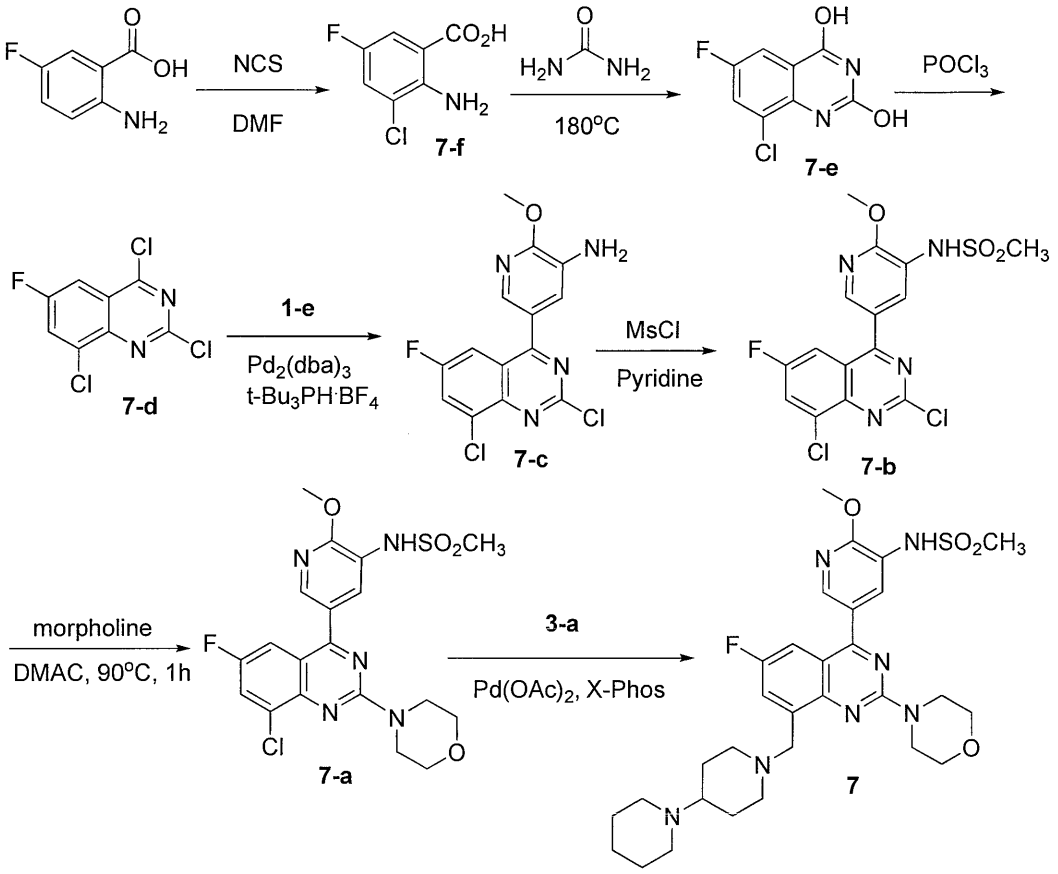
A mixture of compound **6-b** (190 mg), morpholine (0.4 mL) and N, N-dimethylacetamide (10 mL) was heated to 80℃ and reacted for 1 hour. The reactant was cooled to room temperature, and concentrated under reduced pressure. The residue was separated and purified by silica column chromatograph (elution system: dichloromethane/methanol=10/1) to give compound **6-a** (140 mg, 64%). LC-MS (ESI): m/z = 366.1 $(M+H)^+$.

Synthesis of compound **6**

According to the process for preparing compound **1**, compound **6-a** and compound **5-a** were used to give compound **6** (21 mg, 26%). LC-MS (ESI): m/z = 508.2 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.04(s, 1H), 7.69-7.72(m, 2H), 7.60(d, *J*=8.4 Hz, 1H), 7.48(t, *J*=8.0 Hz, 1H), 7.41(d ,*J*=6.8 Hz, 1H), 7.07(t, *J*=8.0 Hz, 1H), 4.07(s, 2H), 3.92-3.94(m, 4H), 3.76-3.79(m, 4H), 3.23-3.25(m, 4H), 2.69-2.72(m, 7H).

Example 7 Synthesis of compound **7**

Synthesis route of compound **7**



Synthesis of compound **7-f**

A mixture of 2-amino-5-fluorobenoic acid (5.0 g, 32.26 mmol), NCS (4.39 g, 32.9 mmol) and DMF (30 mL) was stirred at room temperature for 16 hours. The reaction solution was diluted with water (100 mL) and extracted with ethyl acetate (3x100 mL). The organic layer was combined, washed with saturated saline, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The residue was stirred with dichloromethane (100 mL) for 10 minutes, and filtrated to give compound **7-f** (3.4 g, yield 56%), which was grey solid. LC-MS (ESI): m/z = 190.0 $(M+H)^+$.

Synthesis of compound **7-e**

A mixture of compound **7-f** (3.4 g, 18 mmol) and carbamide (10.8 g, 180 mmol) was stirred at 180℃ for 3 hours. The reaction mixture was cooled, and the precipitated solid was washed with water, and dried to give compound **7-e** (3.8 g, 99%) which was grey solid powder. LC-MS (ESI): m/z = 215.0 $(M+H)^+$.

Synthesis of compound **7-d**

A mixture of compound **7-e** (3.1 g, 14.5 mmol) and phosphorus oxychloride (30 mL) was stirred at 110℃ for 16 hours. The reaction mixture was cooled and concentrated under reduced pressure. The residue was added with ice water and extracted with dichloromethane (3x100 mL). The organic layer was combined and washed with saturated saline, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The residue was separated and purified by silica column chromotograph (elution system: petroleum ether/ethyl acetate=50/1) to give compound **7-d** (1.8 g, 50%) which was white solid. LC-MS (ESI): m/z = 251.1 $(M+H)^+$.

Synthesis of compound **7-c**

A solution of compound **7-d** (400 mg, 1.6 mmol), compound 1-e (400 mg, 1.6 mmol), $Pd_2(dba)_3$ (30 mg, 0.032 mmol), *t*-$Bu_3PH{\cdot}BF_4$(24 mg, 0.08 mmol), potassium fluoride (372 mg, 6.4 mmol) and a mixture of THF and water (10/1, v/v, 25 mL) was stirred at 50℃ for 2 hours under nitrogen gas atomsphere. The reaction mixture was concentrated under reduced pressure. The residue was added with dichloromethane (50 mL), washed in sequence with water and saturated saline, dried over anhydrous sodium sulphate, and concentrated under reduced prssure. The residue was separated and purified by silica column chromotograph (elution system: petroleum ether/ethyl acetate = 25/1 to 10/1) to give compound **7-c** (150 mg, 28%) which was yellow solid. LC-MS (ESI): m/z = 339.0 $(M+H)^+$.

Synthesis of compound **7-b**

To a mixture of compound 7-c (150 mg, 0.44 mmol), pyridine (4 mL) and dichloromethane (30 mL) was added dropwise methylsulfonyl chloride (254 mg, 2.22 mmol), and stirred for 16 hours at room temperature. The reaction solution was concentrated under reduced pressure. The residue was added with dichloromethane (50 mL), washed in sequence with water and saturated saline, dried over anhydrous sodium sulphate, and concentrated under reduced prssure. The residue was separated and purified with silica column chromatograph (elution system: petroleum ether/ethyl acetate = 1/1) to give compound **7-b** (50 mg, 27%), which was yellow solid. LC-MS (ESI): m/z = 417.0 $(M+H)^+$.

Synthesis of compound **7-a**

A mixture of compound **7-b** (50 mg, 0.12 mmol), morpholine (52 mg, 0.60 mmol) and N, N-dimethylacetamide (2 mL) was stirred at 90℃ for 1 hour. The reaction mixture was diluted with ethyl actate (20 mL), washed in sequence with water and saturated saline, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to give compound **7-a** (55 mg, 98%) which was yellow solid. LC-MS (ESI): m/z = 468.1 $(M+H)^+$.

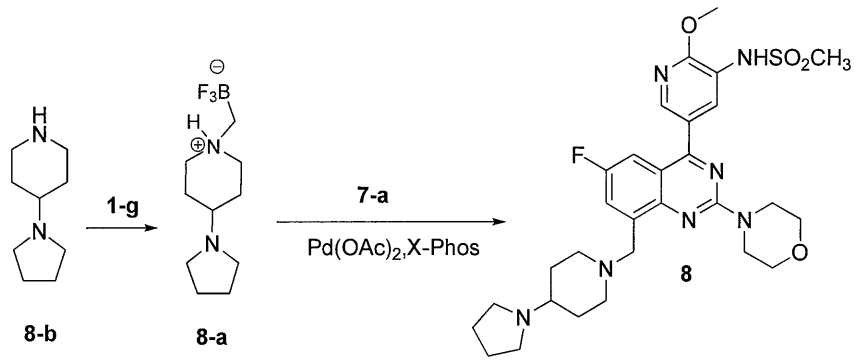
Synthesis of compound **7**

According to the process for preparing compound **1**, compound **7-a** and compound **3-a** were used to give compound **7** (40 mg, 61%). LC-MS (ESI): m/z = 614.2 $(M+H)^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (1H, d, J = 2.0 Hz), 8.16 (1H, d, J = 2.0 Hz), 7.66-7.62 (1H, m), 7.38-7.34 (1H, m), 4.11 (3H, s), 4.00 (2H, s), 3.93 (4H, t, J = 4.4 Hz), 3.82 (4H, t, J = 4.4 Hz), 3.07-3.04 (5H, m), 2.64-2.61 (4H, m), 2.48-2.42 (2H, m), 2.21-2.15 (2H, m), 1.91-1.87 (2H, m), 1.76-1.67 (6 H, m), 1.48-1.46 (2H, m).

Example 8 Synthesis of compund **8**

Synthesis route of compound **8**



Synthesis of compound **8-a**

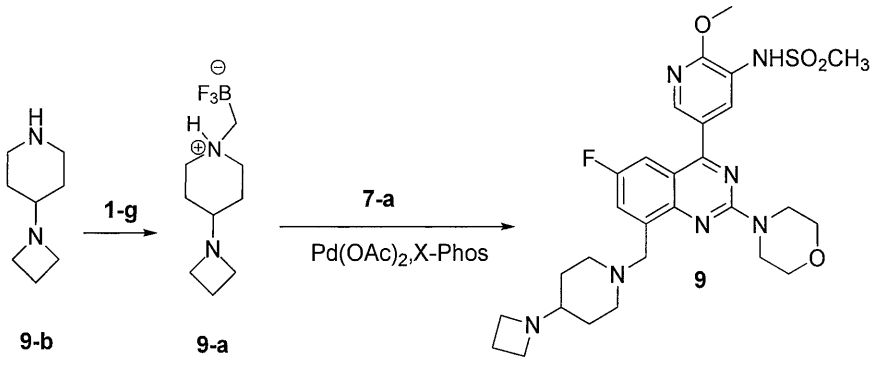
According to the process for preparing compound **1-f**, commercially purchased compound **8-b** was used to give compound **8-a** (500 mg, 68%) which was white solid.

Synthesis of compound **8**

According to the process for preparing compound **1**, compound **8-a** and compound **7-a** were used to give compound **8** (30 mg, 36%). LC-MS (ESI): m/z = 600.3 $(M+H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (1H, d, J = 2.4 Hz), 8.16 (1H, d, J = 2.4 Hz), 7.68-7.65 (1H, m), 7.38-7.34 (1H, m), 4.12 (3H, s), 4.02 (2H, s), 3.94-3.91 (4H, m), 3.82 (4H, t, J = 4.4 Hz), 3.07-3.02 (5H, m), 2.90-2.88 (3H, m), 2.47-2.45 (2H, m), 2.25-2.19 (2H, m), 2.01-1.81 (8H, m).

Example 9 Synthesis of compound **9**

Synthesis route of compound **9**



Synthesis of compound **9-a**

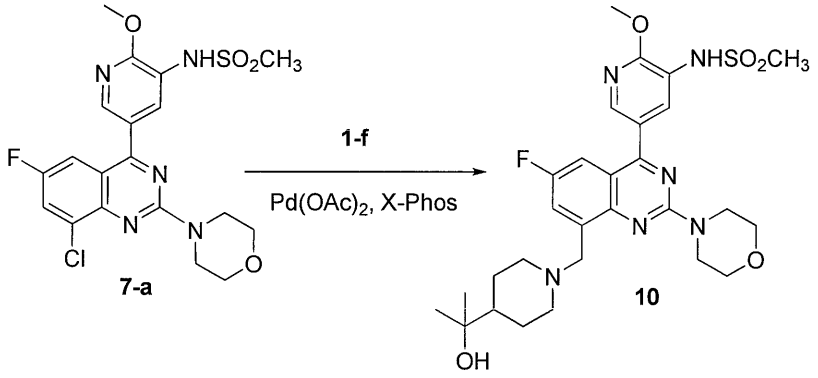
According to the process for preparing compound **1-f**, commercially purchased compound **9-b** was used to give compound **9-a** (180 mg, 62%) which was white solid.

Synthesis of compound **9**

According to the process for preparing compound **1**, compound **9-a** and compound **7-a** were used to give compound **9** (20 mg, 36%). LC-MS (ESI): m/z = 586.3 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (1H, d, J = 2.0 Hz), 8.16 (1H, d, J = 2.0 Hz), 7.67-7.65 (1H, m), 7.40-7.34 (1H, m), 4.12 (3H, s), 4.03 (2H, s), 3.93 (4H, t, J = 4.4 Hz), 3.82 (4H, t, J = 4.4 Hz), 3.70 (1H, s), 3.37-3.35 (3H, m), 3.07 (3H, s), 2.99-2.95 (2H, m), 2.25-2.14 (5H, m), 1.78-1.75 (2H, m), 1.55-1.47 (2H, m).

Example 10 Synthesis of compound **10**

Synthesis route of compound **10**

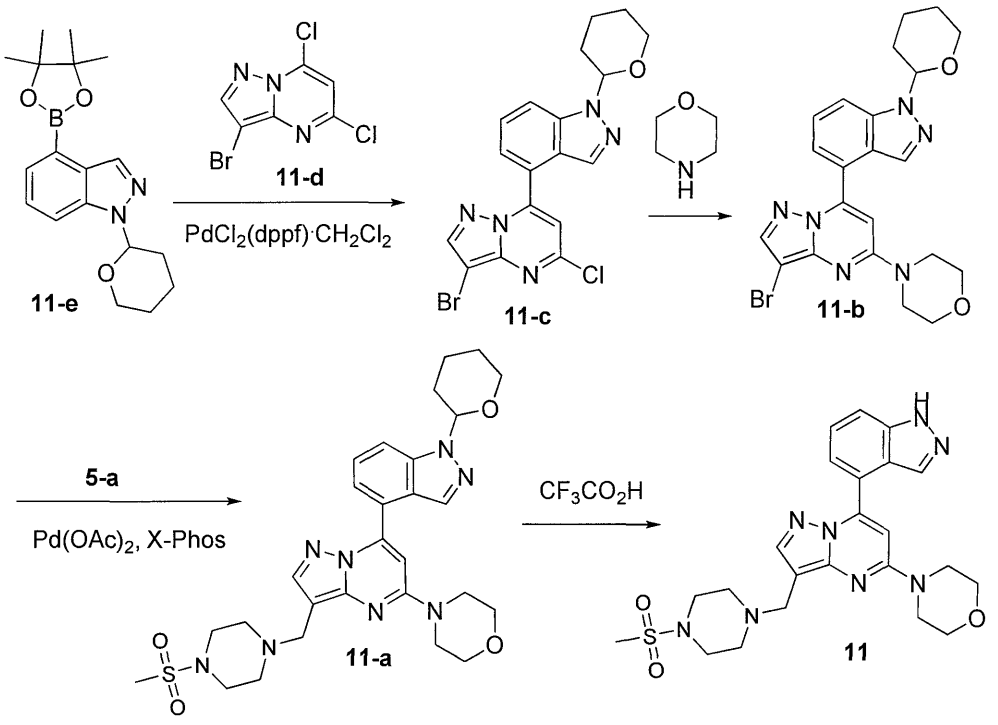


Synthesis of compound **10**

According to the process for preparing compound **1**, compound **7-a** was used to give compound **10** (19 mg, 61.3%). LC-MS (ESI): m/z = 589.2 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (1H, d, J = 2.0 Hz), 8.17 (1H, d, J = 2.4 Hz), 7.70-7.68 (1H, m), 7.38-7.35 (1H, m), 4.12 (3H, s), 4.03 (2H, s), 3.95 (4H, t, J = 4.4 Hz), 3.83 (4H, t, J = 4.4 Hz), 3.11-3.05 (5H, m), 2.16 (2H, t, J = 10.8 Hz), 1.77 (2H, d, J = 12.4 Hz), 1.51-1.45 (2H, m), 1.37-1.34 (1 H, m), 1.21 (6H, s).

Example 11 Synthesis of compound **11**

Synthesis route of compound **11**



Synthesis of compound **11-c**

A mixture of compound **11-d** (prepared according to the method disclosed in WO 2004/087707A1) (300 mg, 1.12 mmol), **11-e** (prepared according to the method disclosed in Synlett 2009, No. 4, 615–619) (367 mg, 1.12 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (90 mg, 0.112 mmol), 2N aqueous solution of sodium carbonate (4.48 mL , 8.96 mmol) and dimethoxyethane (12 mL) was stirred overnight at 85℃ under nitrogen gas atmosphere. The reaction mixture was filtrated through celite, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatograph (elution system: petroleum ether/ethyl acetate = 4/1) to give compound **11-c** (261 mg, 54%). LC-MS (ESI): m/z = 432 $(M+H)^+$.

Synthesis of compound **11-b**

According to the process for preparing compound **6-a**, compound **11-c** was used to give compound **11-b** (256 mg, 88%). LC-MS (ESI): m/z = 505 $(M+Na)^+$.

Synthesis of compound **11-a**

According to the process for preparing compound **1**, compound **11-b** and compound **5-a** were used to give compound **11-a** (30 mg, 28%). LC-MS (ESI): m/z = 581 $(M+H)^+$.

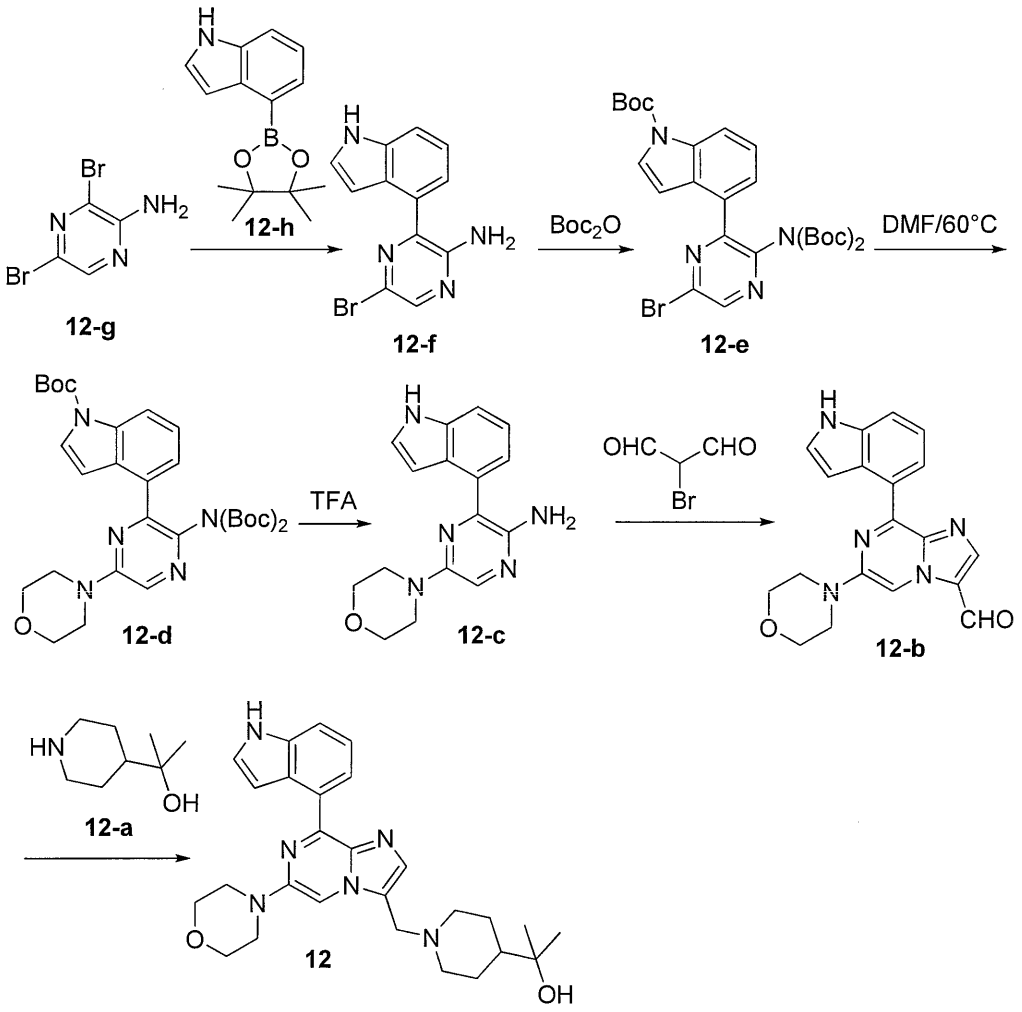
Synthesis of compound **11**

To a solution of compound **11-a** (30 mg, 0.052 mmol) in dichloromethane (2.0 mL) was added slowly dropwise trifluoroacetic acid (0.076 mL,1.04 mmol), and stirred for 3 hours at room temperature. The reaction solution was deluted with ethyl acetate (15 mL), washed with aqueous ammonia (2x10 mL). The organic phase was

separated, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to give compound **11** (26 mg, 100%). LC-MS (ESI): m/z = 497 $(M+H)^+$; ^1H NMR (500MHz, $CDCl_3$) δ7.88 (1H, s), 7.28 (1H, s), 7.60(1H, d, *J* = 7.0 Hz), 7.56(1H, d, *J* = 8.0 Hz), 7.44(1H, t, *J* = 7.5Hz), 6.45 (1H, s), 3.77(4H, t, *J* = 5.0 Hz),3.71 (2H, s), 3.64(4H, t, *J* = 5.0 Hz), 3.21(4H, s), 2.70(3H, s), 2.64(4H, s).

Example 12 Synthesis of compound **12**

Synthesis route of compound **12**



Synthesis of compound **12-f**

A mixture of compound **12-g** (1 g, 3.35 mmol), compound **12-h** (1.05 g, 4.11 mmol), triphenylphosphine (0.21 g, 0.80 mmol), palladium acetate (0.09 g, 0.40 mmol), THF (50 mL) and saturated aqueous solution of sodium bicarbonate (5 mL) was stirred overnight at 90℃ under nitrogen gas atmosphere. The reaction solution was diluted with THF, filtrated through celite, and the filter cake was washed with THF. The filtrate was concentrated under reduced pressure. The residue was separated and purified with silica column chromatograph (elution system:

dichloromethane/methanol =10/1) to give compound **12-f** (0.68 g, 60%). LC-MS (ESI): m/z = 289.0 $(M+H)^+$.

Synthesis of compound **12-e**

A mixed solution of Boc_2O (1.25 mmol), 4-dimethylaminopyridine (10 mg), compound 12-f (90 mg, 0.25 mmol) and THF (20 mL) was stirred overnight at room temperatrue. The reaction soluiton was concentrated under reduced pressure, and the residue was separated and purified with silica column chromatograph (petroleum ehter/ethyl acetate = 5/1 to 2/1) to give compound **12-e** (0.91 g, 75%) which was white solid.

Synthesis of compound **12-d**

To a solution of compound **12-e** (886 mg, 1.50 mmol) in DMF (20 mL) was added morpholine (0.7 mL, 7.95 mmol), and the reaction solution was stirred at 60℃ overnight. Water (10 mL) was added into the reaction mixture and the mixture was filtrated. The filter cake was washed with water, dried, and then purified by silica column chromatograph to give compound **12-d** (875 mg, 98%).

Synthesis of compound **12-c**

To a solution of compound **12-d** (900 mg, 0.19 mmol) in dichloromethane (4 mL) was added dropwise trifluoroacetic acid (3 mL), and the reaction solution was stirred for 1 hour at room temperature. The reaction solution was concentrated under reduced pressure. The residue was adjusted to alkalinity with saturated aqueous solution of sodium carbonate, and extracted with ethyl acetate. The organic layers were combined, washed in sequence with water and saturated sodium chloride, dried with anhydrous sodium suphate, and concentrated under reduced pressure to give compound **12-c** (370 mg, 83%) which was yellow solid.

Synthesis of compound **12-b**

A mixture of compound **12-c** (170 mg, 0.58 mmol), 2-bromomalonaldehyde (102 mg, 0.68 mmol) and acetonitrile (10 mL) was stirred at 50℃ overnight. The reaction solution was adjusted to pH >8 with saturated aqueous solution of sodium bicarbonate, and extracted with ethyl acetate. The organic layers were combined, washed with saturated sodium chloride, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to give compound **12-b**, which was used directly in the next reaction.

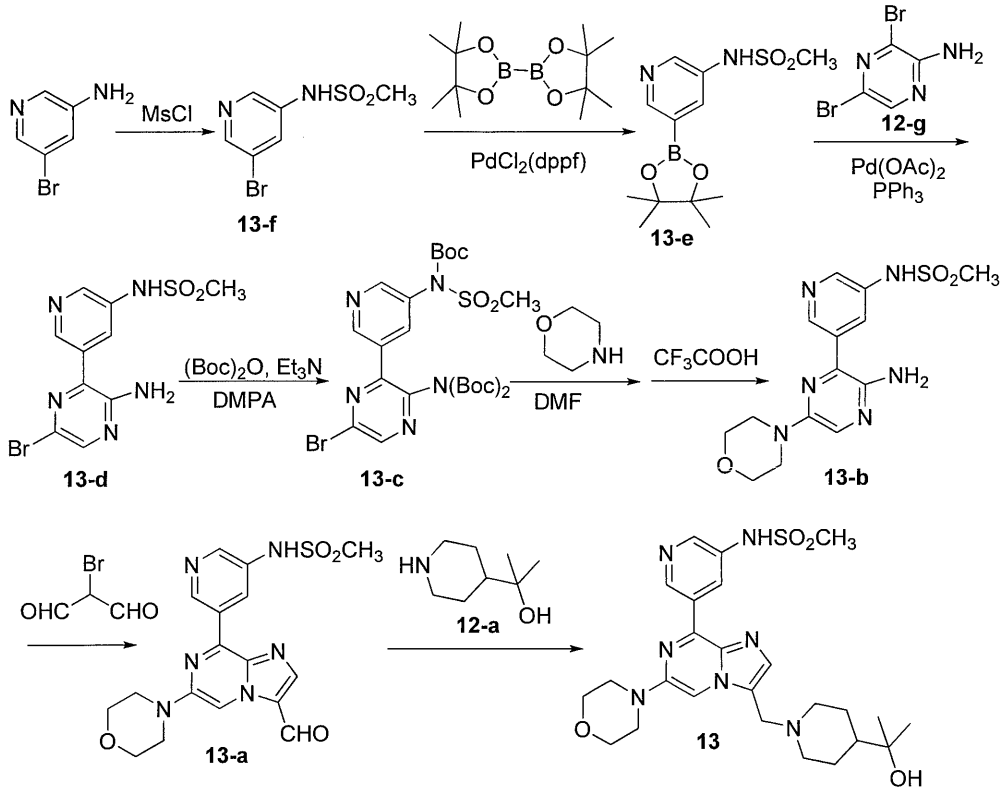
Synthesis of compound **12**

To the solution of compound **12-b** (230 mg, 0.58 mmol) obtained from the previous step in 1,2-dichloroethane (3 mL) were added compound **12-a** (107 mg, 0.75 mmol), sodium cyanoborohydride (109 mg, 1.73 mmol) and acetic acid (1 drop), and the reaction solution was stirred at 25℃ overnight. The reaction solution was diluted with saturated aqueous solution of sodium bicarbonate (10 mL), and extracted with dichloromethane. The organic layers were combined, washed with water and

saturated aqueous solution of sodium chloride in sequence, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The residue was separated and purified by Preparative TLC to give compound **12** (8 mg, two steps 3%). LC-MS (ESI): m/z = 475.3$(M+H)^+$. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.33-8.48 (2H, m), 7.62 (1H, s), 7.61 (1H, s), 7.51 (1H, d, *J* = 8.0 Hz), 7.36 (1H, t, *J* = 8.0 Hz), 7.30 (1H, t, *J* = 2.8 Hz), 7.12 (1H, t, *J* = 2.0 Hz), 3.94 (4H, t, *J* = 4.8 Hz), 3.81 (2H, s), 3.46 (4H, t, *J* = 4.8 Hz), 2.97 (2H, d, *J* = 11.2 Hz), 2.02 (2H, t, *J* = 10.8 Hz), 1.72-1.83 (2H, m), 1.28-1.39 (3H, m), 1.18 (6H ,s).

Example 13 Synthesis of compound **13**

Synthesis route of compound **13**



Synthesis of compound **13-f**

5-Bromo-3-aminopyridine (2.12 g, 11.84 mmol) was dissolved in dichloromethane (100.0 mL) and pyridine (20.0 mL). The solution was cooled with an ice bath, to which was slowly added dropwise methylsufonyl chloride (0.9 mL, 11.84 mmol). The reaction solution was stirred overnight at room temperature, and then partitioned between water and dichloromethane. The organic layer was separated, dried over anhydrous sodium sulphate, and concentrated under reduce pressure to give compound **13-f** (2.9 g, 97.3%). LC-MS (ESI): m/z = 250.9 $(M+H)^+$.

Synthesis of compound **13-e**

To a reaction flask were added compund **31-f** (867 mg, 3.44 mmol), $PdCl_2$(dppf) (126 mg, 0.172 mmol), bis(pinacolato)diboron (961 g, 3.78 mmol), potassium acetate (1.01 g, 10.32 mmol) and 1,4-dioxane (87 mL). The mixture was stirred overnight at 115℃ under nitrogen gas atmosphere, and then concentrated under reduced pressure. The residue was dissolved in ethyl acetate (250 mL), and filtrated through celite. The filtrate was concentrated under reduced pressure to give **13-e** (1.6 g) and the crude product was used in the next step without purification. LC-MS (ESI): m/z = 299$(M+H)^+$.

Synthesis of compound **13-d**

According to the process for preparing compound **12-f**, compound **13-e** was used to give compound **13-d** (571 mg, 42%) which was white solid. LC-MS (ESI): m/z = 344.9 $(M+H)^+$.

Synthesis of compound **13-c**

According to the process for preparing compound **12-e**, compound **13-d** was used to give compound **13-c** (693 mg, 65%) which was white solid. LC-MS (ESI): m/z = 644.0 $(M+H)^+$.

Synthesis of compound **13-b**

To a solution of compound **13-c** (693 mg, 1.1 mmol) in DMF (15 mL) was added morpholine (0.39 mL, 4.4 mmol), and the reaction solution was stirred overnight at 60℃. The reaction mixture was added with water (30 mL), and extracted with ethyl acetate. The organic layers were combined, washed with water and saturated aqueous solution of sodium chloride in sequence, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The residue was dissolved in dichloromethane (6 mL), added with trifluoroacetic acid (3 mL), and stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure. The residue was adjusted to alkalinity with saturated aqueous solution of sodium carbonate, and extracted with ethyl acetate. The organice layers were combined, washed with water and saturated aqueous solution of sodium chloride in sequence, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to give compound **13-b** (234 mg, 60.8%) which was yellow solid. LC-MS (ESI): m/z = 351 $(M+H)^+$.

Synthesis of compound **13-a**

According to the process for preparing compound **12-b**, compound **13-b** was used to give compound **13-a** (50 mg, 29%) which was yellow solid. LC-MS (ESI): m/z = 403.0 $(M+H)^+$.

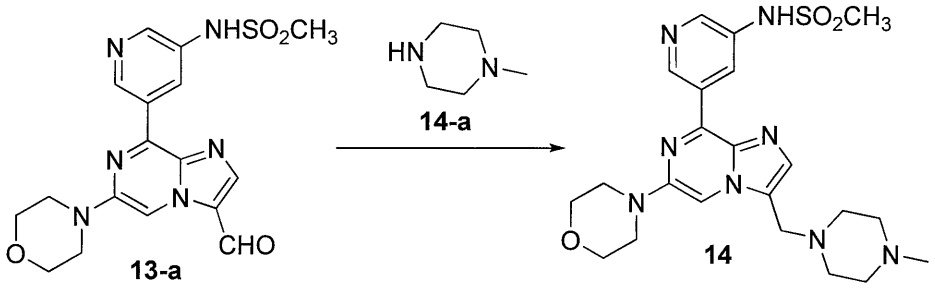
Synthesis of compound **13**

According to the process for preparing compound **12**, compound **13-a** was used to give compound **13** (8 mg, 15%) which was yellow solid. LC-MS (ESI): m/z = 530.0

$(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.42 (d, 1H, J = 1.6 Hz), 8.91 (s, 1H), 8.39 (d, 1H, J = 2.4 Hz), 7.72 (s, 1H), 7.67 (s, 1H), 3.94 (t, 4H, J = 4.4 Hz), 3.85 (s, 2H), 3.43 (t, 4H, J = 4.4 Hz), 3.13 (s, 3H), 2.97 (d, 2H, J = 9.2 Hz), 2.07 (t, 2H, J = 8.0 Hz), 1.78 (d, 2H, J = 8.8 Hz), 1.39-1.40 (m, 1H), 1.34 (s, 2H), 1.18 (s, 6H).

Example 14 Synthesis of compound **14**

Synthesis route of compound **14**

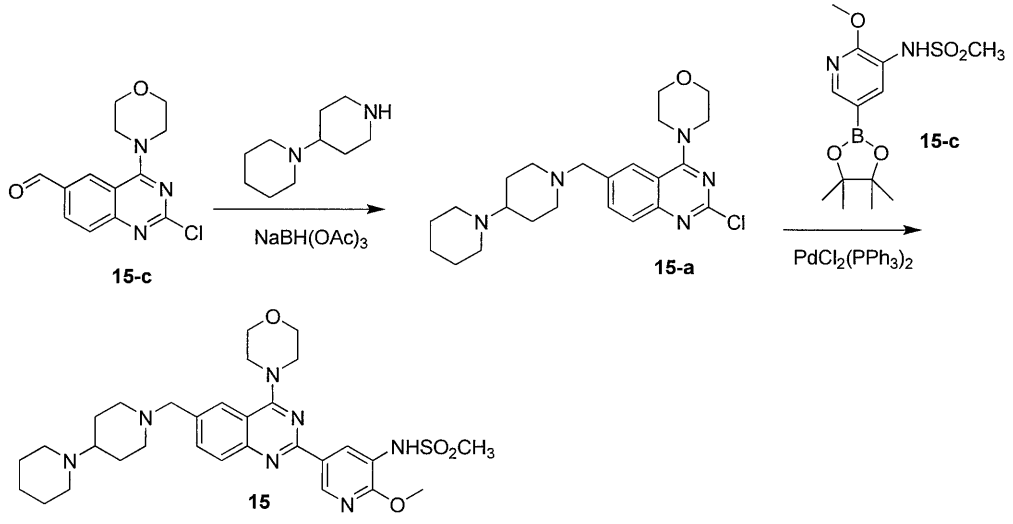


Synthesis of compound **14**

According to the process for preparing compound **12**, compound **13-a** and compound **14-a** were used to give compound **14** (8 mg, 18%) which was yellow solid. LC-MS (ESI): m/z = 487.2 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.47 (d, 1H, J = 1.6 Hz), 8.97 (d, 1H, J = 1.6 Hz), 8.47 (d, 1H, J = 2.4 Hz), 7.67 (s, 1H), 7.62 (s, 1H), 3.96 (t, 4H, J = 4.4 Hz), 3.88 (s, 2H), 3.44 (t, 4H, J = 4.4 Hz), 3.13 (s, 3H), 2.62 (brs, 8H), 2.42 (s, 3H).

Example 15 Synthesis of compound **15**

Synthesis route of compound **15**



Synthesis of compound **15-a**

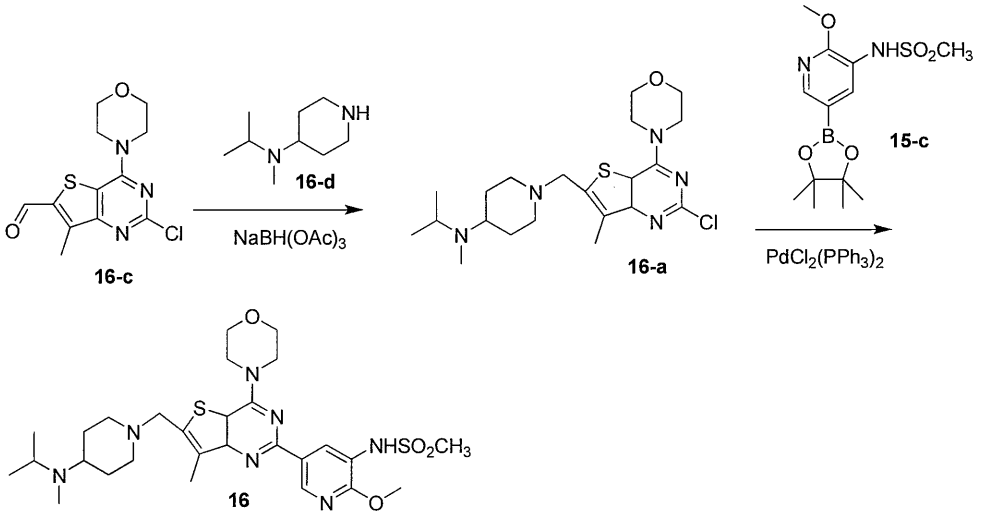
To a solution of compound **15-c** (prepared according to the method disclosed in WO 2008/152387 A1) and 4-piperidyl piperidine (360 mg, 2.166 mmol) in dichloroethane (10 mL) was added acetic acid (0.1 mL), stirred for half an hour at room temperature, followed by adding sodium triacetoxyborohydride (459 mg, 2.166 mmol), and then stirred at room temperature overnight. The reaction solution was concentrated under reduced pressure, and the residue was purified with silica column chromatograph (elution system: dichloromethane/methanol = 20/1) to give compound **15-a** (80 mg, 34%). LC-MS (ESI): m/z = 430.1 $(M+H)^+$.

Synthesis of compound **15**

A suspension of compound **15-a** (95 mg, 0.221 mmol), compound **15-c** (prepared according to the method disclosed in WO 2012/032067 A1) (90 mg, 0.274 mmol), sodium carbonate (60 mg, 0.566 mmol), dichlorobis(triphenylphosphine) palladium (12 mg, 0.017 mmol) in methylbenzene/ethanol/water (5 mL, 4/2/1) was heated to 125℃ by microwave under nitrogen gas atmosphere and stirred for 1 hour. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica Preparative plate chromatograph (developing system: dichloromethane/methanol = 20/1) to give product **15** (36 mg, 27%). LC-MS (ESI): m/z = 596.3 $(M+H)^+$. ^1H NMR (400MHz, $CDCl_3$) δ 9.03(d, J=2.0 Hz, 1H), 9.78(d, J=2.0 Hz, 1H), 7.83(d, J=8.4 Hz, 1H), 7.71(s, 1H), 7.64(dd, J_1=2.0 Hz, J_2=8.4 Hz, 1H), 4.02(s, 3H), 3.85-3.87(m, 4H), 3.76-3.79(m, 4H), 3.54(s, 2H), 3.00(s, 3H), 2.86-2.89(m, 2H), 2.42-2.44(m, 4H), 2.16-2.24(m, 1H), 1.92-1.97(m, 2H), 1.70-1.74(m, 2H), 1.48-1.57(m, 6H), 1.35-1.37(m, 2H).

Example 16 Synthesis of compound **16**

Synthesis route of compound **16**



Synthesis of compound **16-a**

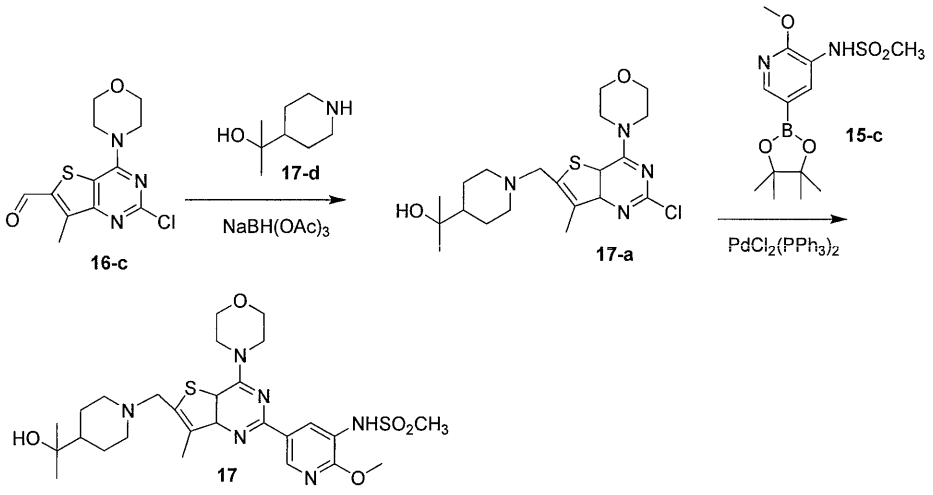
According to the process for preparing compound **15-a**, compound **16-c** (prepared according to the method disclosed in Journal of Medicinal Chemistry, 2011, No. 4, 615–619) and compound **16-d** were used to give compound **16-a** (82 mg, 56%) which was yellow solid. LC-MS (ESI): m/z = 440.2 $(M+H)^+$.

Synthesis of compound **16**

According to the process for preparing compound **15**, compound **16-a** was used to give compound **16** (45 mg, 42%) which was yellow solid. LC-MS (ESI): m/z = 604.3 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.09 (d, 1H, J = 2.0 Hz), 8.83 (d, 1H, J = 2.0 Hz), 4.08 (s, 3H), 4.04 (t, 4H, J = 4.4 Hz), 3.88 (t, 4H, J = 4.4 Hz), 3.77 (s, 2H), 3.03 (s, 6H), 2.50-2.47 (m, 1H), 2.41 (s, 3H), 2.23 (s, 3H), 2.12 (t, 2H, J = 9.6 Hz), 1.80 (d, 2H, J = 11.2 Hz), 1.70 (dd, 2H, J = 20.8, 11.2 Hz), 1.07 (d, 6H, J = 6.4 Hz).

Example 17 Synthesis of compound **17**

Synthesis route of compound **17**



Synthesis of compound **17-a**

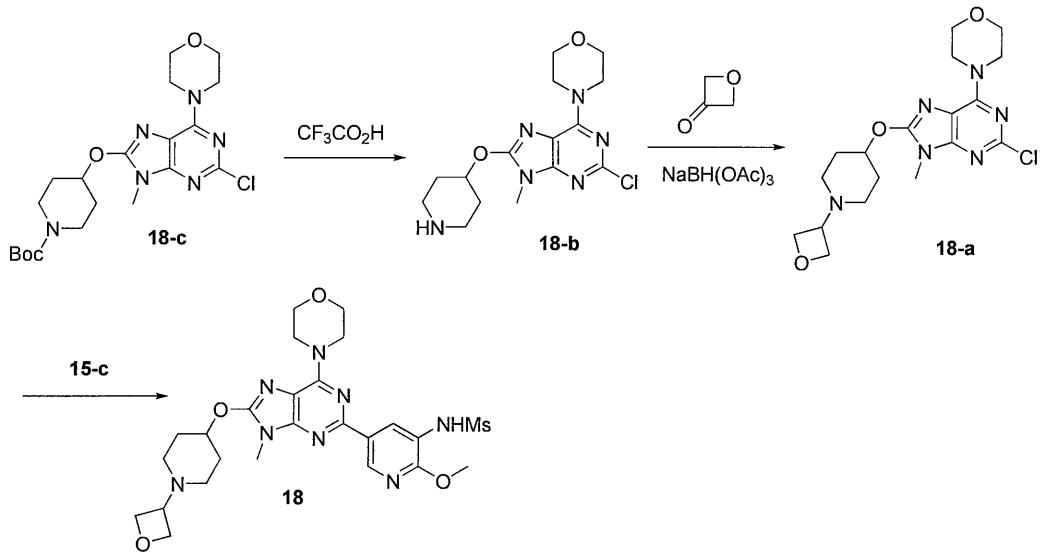
According to the process for preparing compound **15-a**, compound **16-c** and compound **17-d** were used to give compound **17-a** (450 mg, 74%) which was yellow solid. LC-MS (ESI): m/z = 425.2 $(M+H)^+$.

Synthesis of compound **17**

According to the process for preparing compound **15**, compound **17-a** was used to give compound **17** (52 mg, 34%). LC-MS (ESI): m/z = 591.3 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.09 (d, 1H, J = 2.0 Hz), 8.83 (d, 1H, J = 2.0 Hz), 6.71 (s, 1H), 4.08 (s, 3H), 4.04 (t, 4H, J = 4.4 Hz), 3.88 (t, 4H, J = 4.4 Hz), 3.78 (s, 2H), 3.08 (bs, 2H), 3.03 (s, 3H), 2.43 (s, 3H), 2.05 (bs, 2H), 1.77 (d, 2H, J = 12.0 Hz), 1.45 (bs, 2H), 1.35-1.31 (m, 1H), 1.24 (s, 1H), 1.20 (s, 6H).

Example 18 Synthesis of compound **18**

Synthesis route of compound **18**



Synthesis of compound **18-b**

To a solution of compound **18-c** (prepared according to the method disclosed in US 2012/015931A1) (120 mg, 0.27 mmol) in dichloromethane (7 mL) was added dropwise trifluoroacetic acid (7 mL), and reacted for 3 hours at room temperature. The reaction solution was concentrated under reduced pressure, and the residue was partitioned between water and ethyl acetate. The organic layer was concentrated under reduced pressure to give compound **18-b** (93 mg, 100%). LC-MS (ESI): m/z = 353.1$(M+H)^+$.

Synthesis of compound **18-a**

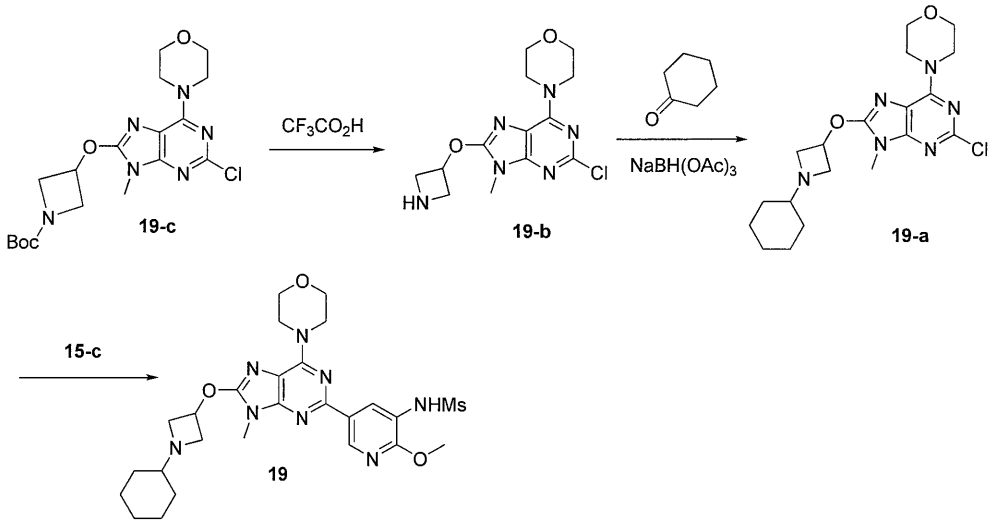
To a solution of compound **18-b** (93 mg, 0.26 mmol) and 3-oxetanone (19 mg, 0.26 mmol) in dichloroethane (10 mL) was added acetic acid (0.05 mL), stirred for 10 minutes at room temperature, followed by adding sodium triacetoxyborohydride (275 mg, 1.3 mmol), and stirred overnight at room temperature. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica column chromatograph (elution system: petroleum ether/ethyl acetate = 20/1) to give compound **18-a** (82 mg, 76.6%). LC-MS (ESI): m/z = 409.2 $(M+H)^+$.

Synthesis of compound **18**

According to the process for preparing compound **15**, compound **18-a** was used to give compound **18** (52 mg, 65.4%). LC-MS (ESI): m/z = 575.2 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (1H, d, J = 1.6 Hz), 8.74 (1H, d, J = 2.0 Hz), 6.71 (1H, s),5.15 (1H, t, J = 3.6 Hz), 4.71-4.63 (4H, m), 4.21 (4H, d, J = 4.0 Hz), 4.08 (3H, s), 3.84 (4H, t, J = 4.4 Hz), 3.59 (3H, s), 3.57-3.52 (1H, m), 3.03 (3H, s), 2.56 (2H, s), 2.28 (2H, d, J = 8.0 Hz), 2.17-2.12 (2H, m), 2.02-1.96 (2H, m).

Example 19 Synthesis of compound **19**

Synthesis route of compound **19**



Synthesis of compound **19-b**

According to the process for preparing compound **19-b**, compound **19-c** (prepared according to the method disclosed in US 2012/015931A1) was used to give compound **19-b** (456 mg, 95%). LC-MS (ESI): m/z = 325.1 $(M+H)^+$.

Synthesis of compound **19-a**

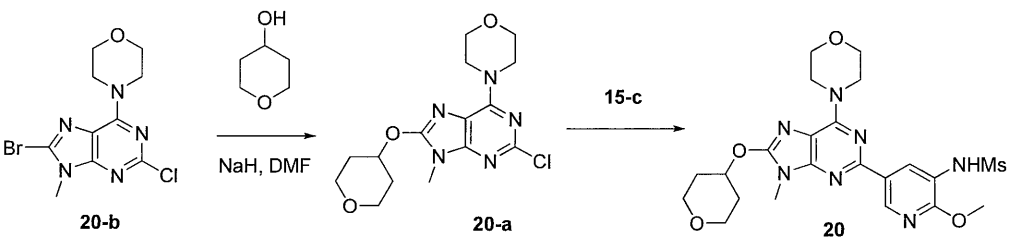
According to the process for preparing compound **18-a**, compound **19-b** and cyclohexanone were used to give compound **19-a** (115 mg, 92%). LC-MS (ESI): m/z = 407.2 $(M+H)^+$.

Synthesis of compound **19**

According to the process for preparing compound **15**, compound **19-a** was used to give compound **19** (20 mg, 17.4%). LC-MS (ESI): m/z = 573.2 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.98 (1H, d, J = 2.0 Hz), 8.74 (1H, d, J = 2.0 Hz), 5.36 (1H, t, J = 5.6 Hz), 4.21 (4H, d, J = 4.0 Hz), 4.07 (3H, s), 3.84-3.81 (6H, m), 3.61 (3H, s), 3.21-3.17 (2H, m), 3.03 (3H, s), 2.11-2.05 (1H, m), 1.79-1.73 (6H, m), 1.31-1.25 (4H, m).

Example 20 Synthesis of compound **20**

Synthesisi route of compound **20**



Synthesis of compound **20-a**

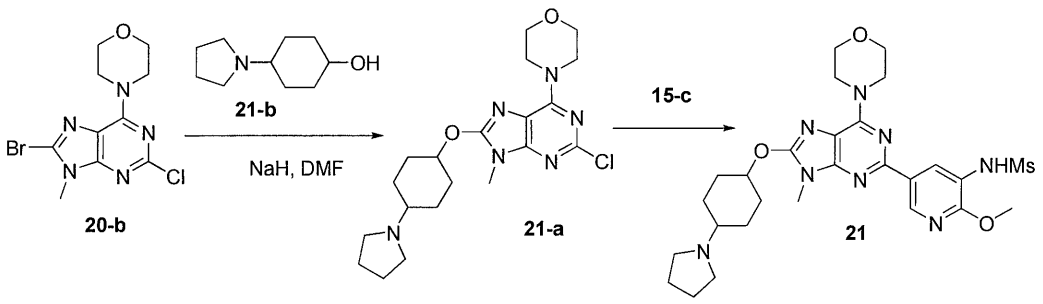
To a suspention of 60% sodium hydride (60 mg, 1.5 mmol) in THF (10 mL) was added dropwise a solution of 4-hydroxytetrahydropyran (45 mg, 0.36 mmol) in DMF (15 mL), stirred at room temperature for 1 hour, followed by adding dropwise a solution of compound **20-b** (prepared according to the method in US 2012/015931A1) (100 mg, 0.30 mmol) in DMF (15 mL), and stirred overnight at room temperature. The reaction mixture was quenched with water, and extracted with ethyl acetate (3x40 mL). The organic layers were combined, and concentrated under reduced pressure. The residue was separated and purified with silica column chromatograph (elution system: dichloromethane/methanol =30/1) to give compound **20-a** (85 mg, 80.1 %). LC-MS (ESI):m/z = 354.1$(M+H)^+$.

Synthesis of compound **20**

According to the process for preparing compound **15**, compound **20-a** was used to give compound **20** (30 mg, 24%). LC-MS (ESI): m/z = 520.2 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (1H, d, J = 2.0 Hz), 8.75 (1H, d, J = 2.0 Hz), 6.71 (1H, s), 5.26 (1H, t, J = 4.0 Hz), 4.22 (4H, t, J = 4.8 Hz), 4.08 (3H, s), 4.03-3.98 (2H, m), 3.85 (4H, t, J = 4.8 Hz), 3.69-3.63 (2H, m), 3.61 (3H, s), 3.03 (3H, s), 2.19-2.14 (2H, m), 1.94-1.89 (2H, m).

Example 21 Synthesis of compound **21**

Synthesis route of compound **21**



Synthesis of compound **21-a**

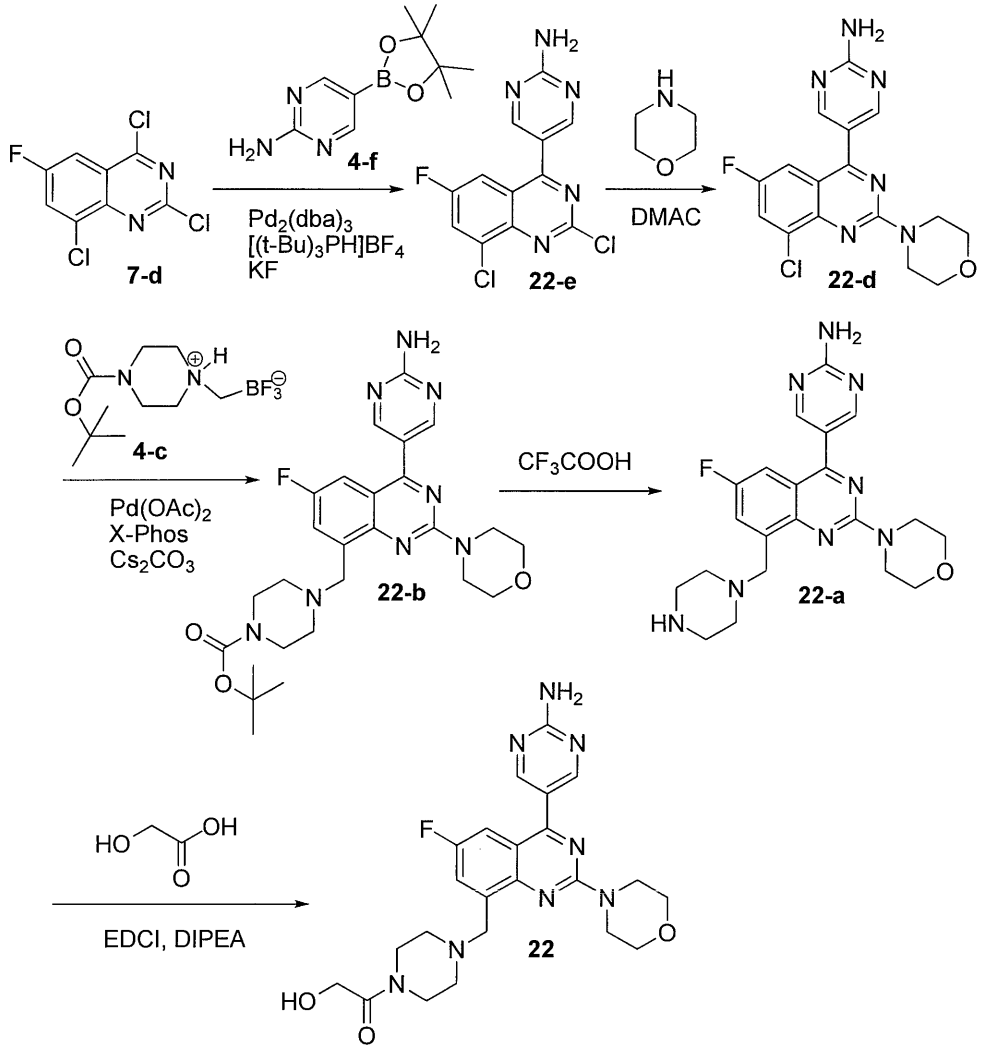
According to the process for preparing compound **20-a**, compound **21-b** was used to give compound **21-a** (20 mg, 24%). LC-MS (ESI): m/z = 421.2 $(M+H)^+$.

Synthesis of compound **21**

According to the process for preparing compound **15**, compound **21-a** was used to give compound **21** (10 mg, 16%). LC-MS (ESI): m/z = 587.3 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (1H, d, J = 2.0 Hz), 8.73 (1H, d, J = 2.0 Hz), 6.71 (1H, s), 5.34 (1H, s), 4.21 (4H, t, J = 4.8 Hz), 4.08 (3H, s), 3.83 (5H, t, J = 4.8 Hz), 3.72 (3H, s), 3.04 (3H, s), 2.44-2.13 (12H, m), 1.90-1.88 (1H, m), 1.30-1.26 (3H, m).

Example 22 Synthesis of compound **22**

Synthesis route of compound **22**



Synthesis of compound **22-e**

According to the process for preparing compound **1-c**, compound **7-d** and commercially purchased compound **4-f** were used to give compound **22-e** (0.24 g, 49%). LC-MS (ESI): m/z = 310.0 $(M+H)^+$.

Synthesis of compound **22-d**

According to the process for preparing compound **4-d**, compound **22-e** was used to give compound **22-d** (0.27 g, 97%). LC-MS (ESI): m/z = 361.1 $(M+H)^+$.

Synthesis of compound **22-b**

According to the process for preparing compound **1**, compound **22-d** and compound **4-c** were used to give compound **22-b** (195 mg, 71%). LC-MS (ESI): m/z = 525.3 $(M+H)^+$.

Synthesis of compound **22-a**

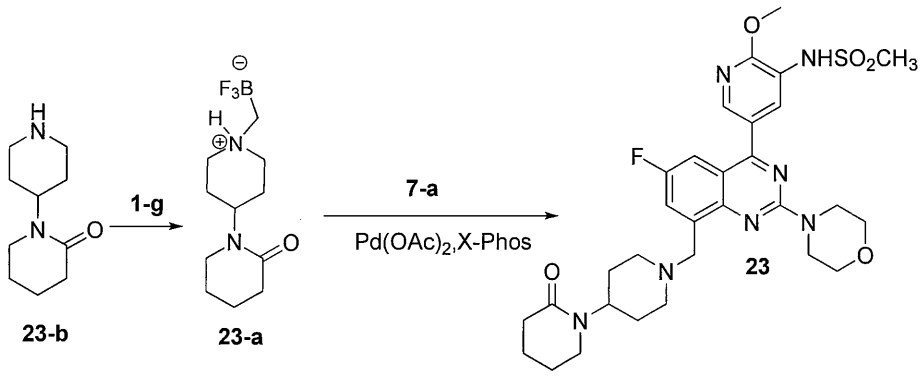
According to the process for preparing compound **4-a**, compound **22-b** was used to give compound **22-a** (150 mg, 95%). LC-MS (ESI): m/z = 425.2 $(M+H)^+$.

Synthesis of compound **22**

According to the process for preparing compound **4**, compound **22-a** and glycolic acid were used to give compound **22** (25 mg, 44%). LC-MS (ESI): m/z = 483.1 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ8.73 (2H, s), 7.67-7.64 (1H, m), 7.41-7.37 (1H, m), 5.38 (2H, s), 4.10 (2H, d, J = 3.6 Hz), 4.06 (2H, s), 3.95-3.91 (4H, m), 3.84-3.81 (4H, m), 3.75-3.72 (2H, m), 3.64 (1H, t, J = 4.8 Hz), 3.63-3.58 (4H, m).

Example 23 Synthesis of compound **23**

Synthesis route of compound **23**



Synthesis of compound **23-a**

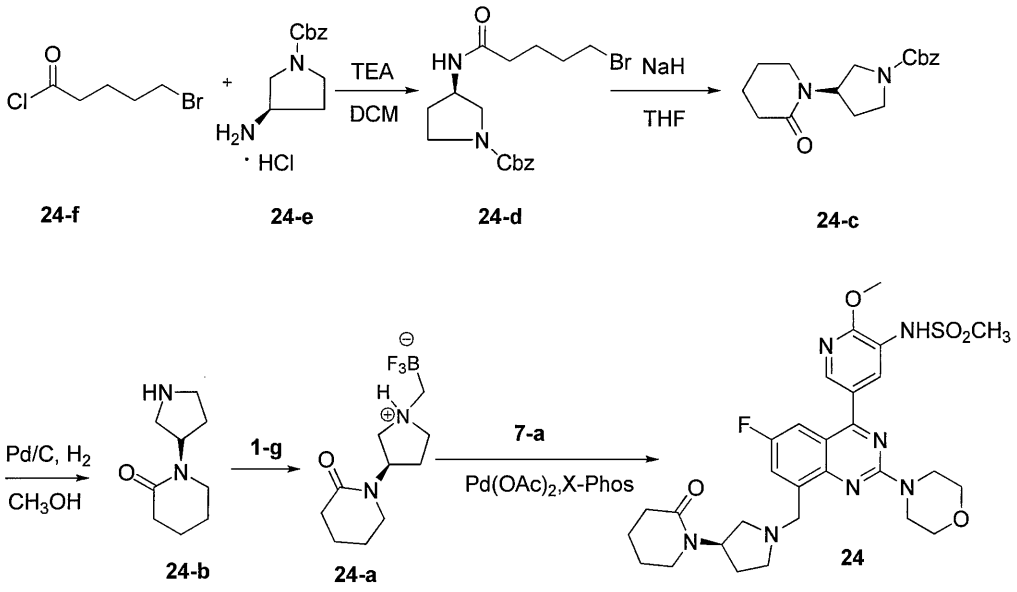
According to the process for preparing compound **1-f**, comercially purchased compound **23-b** was used to give compound **23-a** (420 mg, 76%) which was white solid.

Synthesis of compound **23**

According to the process for preparing compound **1**, compound **23-a** and compound **7-a** were used to give compound **23** (34 mg, 50.7%). LC-MS (ESI): m/z = 628.1 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 2.0 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.36-7.39 (m, 1H), 4.58-4.64 (m, 1H), 4.12 (s, 3H), 4.02 (s, 2H), 3.93-3.98 (m, 4H), 3.82-3.85 (m, 4H), 3.22-3.25 (m, 2H), 3.03-3.07 (m, 5H), 2.40-2.43 (m, 2H), 2.34 (t, J = 11.6 Hz, 2H), 1.76-1.87 (m, 6H), 1.55-1.71 (m, 2H).

Example 24 Synthesis of compound **24**

Synthesis route of compound **24**



24-f 24-e 24-d 24-c

24-b 24-a 24

Synthesis of compound **24-d**

To a solution of commercially purchased compound **24-e** (2.0 g, 7.8 mmol) and triethylamine (2.37 g, 23.4 mmol) in dichloromethane (150 mL) was added slowly commercially purchased compound **24-f** (1.556 g, 7.8 mmol), and the reaction solution was stirred overnight at room temperature. To the solution was added water (50 mL), followed by washing the orgaic phase with 5% citric acid (80 mL×2). The organic layer was dried over anhydrous sodium sulphate, filtrated, and concentrated to give crude product **24-d** (2.8 g, 93.8%), and the crude product was used directly for the next reaction without purification. LC-MS (ESI): m/z = 383.1$(M+H)^+$.

Synthesis of compound **24-c**

A solution of compound **24-d** (2.8 g, 7.8 mmol) in THF (30 mL) was cooled with an ice bath, followed by slowly adding NaH (936 mg, 23.4 mmol). The reaction solution was stirred overnight at 80℃ under reflux. The reaction solution was diluted with water (60 mL), and the aqueous phase was extracted with ethyl acetate (80 mL×2). The organic layers were combined, dried over anhydrous sodium sulphate, filtrated, concentrated to give crude product, and then separated with silica plate chromatograph (CH_2Cl_2/CH_3OH = 30:1) to give compound **24-c** (1.85 g, 83.3%).

Synthesis of compound **24-b**

To a solution of compound **24-c** (1.0 g, 3.30 mmol) in methanol (35 mL) was added slowly Pd/C (200 mg), and the reaction solution was stirred overnight under hydrogen gas atmosphere at room temperature. The reaction solution was diluted with ethyl acetate (60 mL), and filtrated to remove Pd/C. The filtrate was concentrated to give crude product **24-b** (554 mg, 100%) which was used directly for the next reaction without purification.

Synthesis of compound **24-a**

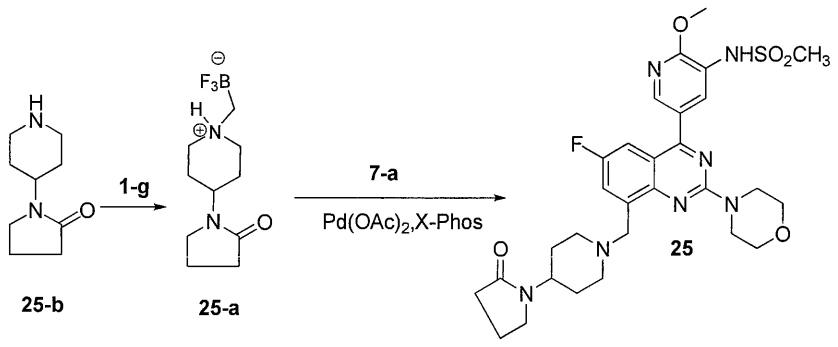
According to the process for preparing compound **1-f**, compound **24-b** was used to give compound **24-a** (850 mg, 73%).

Synthesis of compound **24**

According to the process for preparing compound **1**, compound **24-a** and compound **7-a** were used to give compound **24** (35 mg, 53.4%). LC-MS (ESI): m/z = 614.2 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 2.0 Hz, 1H), 8.10 (d, J = 2.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.31(d, J = 8.8 Hz, 1H), 5.33 (s, 1H), 4.05 (brs, 5H), 3.92-3.94 (m, 4H), 3.75-3.77 (m, 4H), 3.32-3.42 (m, 2H), 2.91-3.01 (m, 4H), 2.72-2.77 (m, 1H), 2.57-2.62 (m, 1H), 2.34(t, J = 6.4 Hz, 3H), 2.10-2.16 (m, 1H), 1.64-1.74 (m, 5H), 1.55(brs, 1H).

Example 25 Synthesis of compound **25**

Synthesis route of compound **25**



Synthesis of compound **25-a**

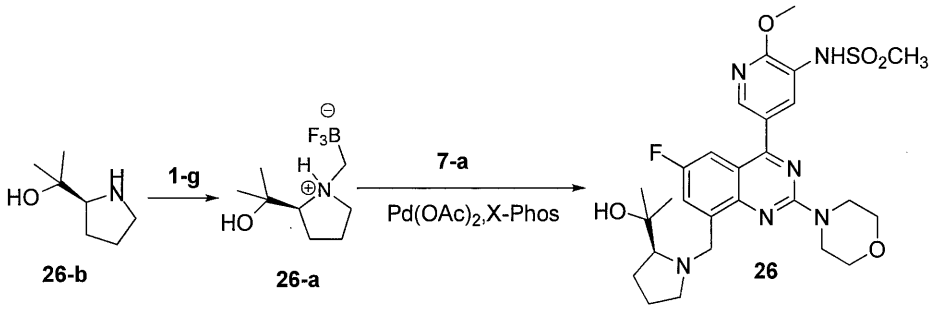
According to the process for preparing compound **1-f**, commercially purchased compound **25-b** was used to give compound **25-a** (180 mg, 65%).

Synthesis of compound **25**

According to the process for preparing compound **1**, commercially purchased compound **25-a** and compound **7-a** were used to give compound **25** (22 mg, 37.4%). LC-MS (ESI): m/z = 613.7 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.17 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.35-7.38 (m, 1H), 5.50 (d, J = 7.6 Hz, 1H), 4.12 (s, 3H), 4.01 (s, 2H), 3.87-3.94 (m, 4H), 3.71-3.84 (m, 4H), 3.07 (s, 3H), 2.94 (d, J = 11.2 Hz, 2H), 2.33 (t, J = 11.6Hz, 2H), 1.98 (d, J = 11.2 Hz, 2H), 1.48-1.66 (m, 4H), 1.26-1.34 (m, 1H), 0.96-0.97 (m, 2H), 0.72-0.75 (m, 2H).

Example 26 Synthesis of compound **26**

Synthesis route of compound **26**



Synthesis of compound **26-a**

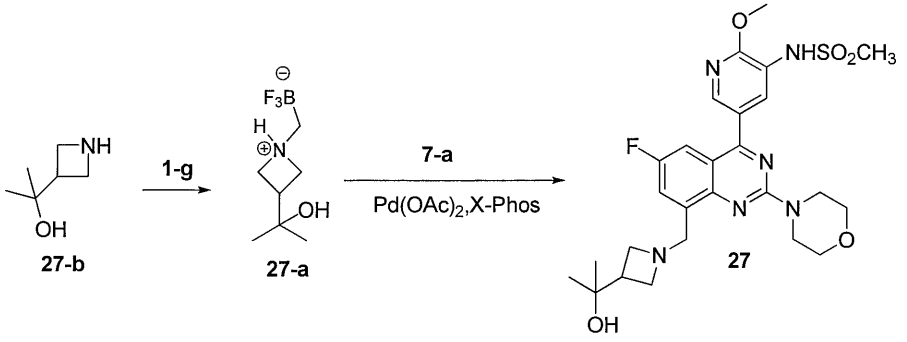
According to the process for preparing compound **1-f**, commercially purchased compound **26-b** was used to give compound **26-a** (880 mg, 67%).

Synthesis of compound **26**

According to the process for preparing compound **1**, compound **26-a** and compound **7-a** were used to give compound **26** (22 mg, 36.1%). LC-MS (ESI): m/z = 575.1 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 2.0 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 4.44-4.48 (m, 1H), 4.25-4.30 (m, 1H), 4.12 (s, 3H), 3.90-4.00 (m, 4H), 3.71-3.84 (m, 4H), 2.97-3.08 (m, 5H), 2.48 (s, 1H), 1.95-2.01(m, 1H), 1.78 (s, 3H), 1.17-1.26 (m, 6H).

Example 27 Synthesis of compound **27**

Synthesis route of compound **27**



Synthesis of compound **27-a**

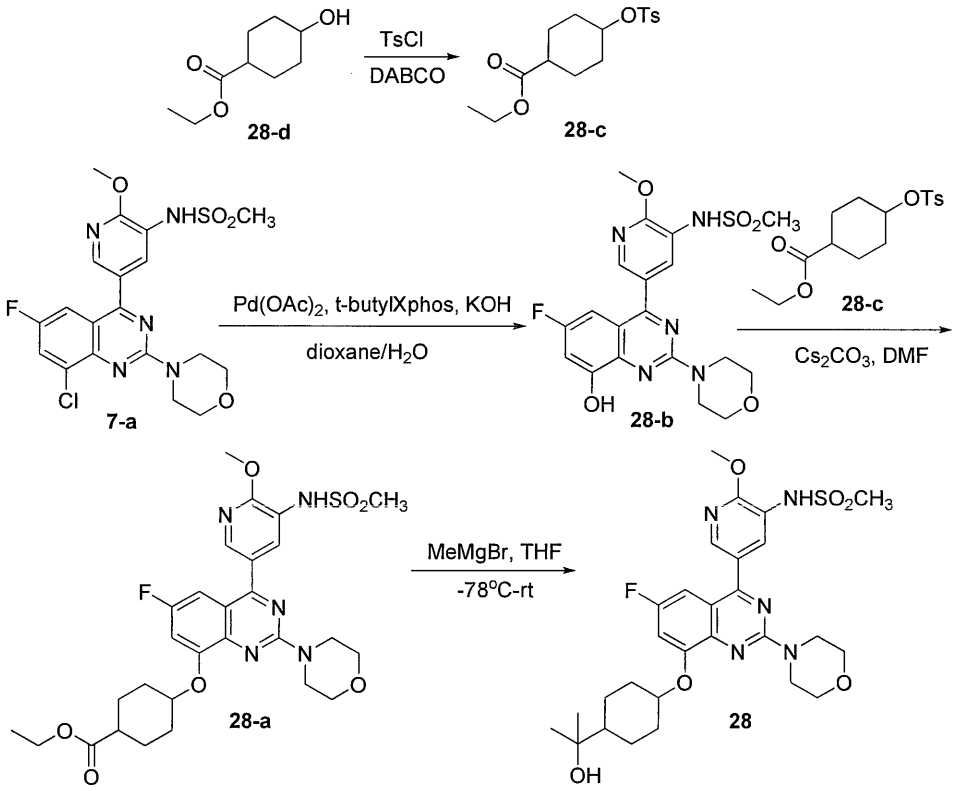
According to the process for preparing compound **1-f**, commercially purchased compound **27-b** was used to give compound **27-a** (176 mg, 75%).

Synthesis of compound **27**

According to the process for preparing compound **1**, compound **27-a** and compound **7-a** were used to give compound **27** (42 mg, 58%). LC-MS (ESI): m/z = 561.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.53 (s, 1H), 8.37 (d, 1H, J = 2.0 Hz), 7.98 (d, 1H, J = 2.4 Hz), 7.57 (dd, 1H, J = 9.2, 2.4 Hz), 7.44 (dd, 1H, J = 9.2, 2.8 Hz), 4.35 (s, 1H), 4.04 (s, 2H), 4.02 (s, 3H), 3.87 (t, 4H, J = 4.8 Hz), 3.74 (t, 4H, J = 5.2 Hz), 3.40 (t, 2H, J = 7.2 Hz), 3.23 (t, 2H, J = 7.2 Hz), 3.17 (d, 1H, J = 4.8 Hz), 3.08 (s, 3H), 1.03 (s, 6H).

Example 28 Synthesis of compound **28**

Synthesis route of compound **28**



Synthesis of compound **28-c**

In an ice bath, to a solution of commercially purchased compound 28-d (1.72 g, 10 mmol) and DABCO (2.24 g, 20 mmol) in dichloromethane (30 mL) was added slowly TsCl (2.86 g, 15 mmol). The reaction solution was warmed to normal temperatrue and stirred for about 1 hour, followed by washing with 2N HCl solution (30 mL), water (30 mL) and saturated solution of sodium bicarbonate (30 mL) in sequence. The organic phase was dried over anhydrous sodium sulphate and concentrated. The crude product was purified with silica column chromatograph (petroleum ether/ethyl acetate = 10/1-3/1) to give **28-c** (2.94 g, 90%) which was white solid. LC-MS (ESI): m/z = 344.1 $(M+NH_4)^+$.

Synthesis of compound **28-b**

To a microwave tube were added compound **7-a** (200 mg, 0.43 mmol), $Pd_2(dba)_3$ (31 mg, 0.043 mmol), *t*-butylXPhos (78 mg, 0.185 mmol), potassium hydroxide (1.04 g, 18.5 mmol), 1,4-dioxane (8 mL) and water (5 mL), and stirred at 100℃ overnight under nitrogen gas atomsphere. The reaction solution was cooled to room temperature, acified with 1N HCl solution, followed by neutralizing to pH>7 with saturated sodium bicarbonate solution. The mixture was extracted with dichloromethane (50*3 mL). The organic phases were combined, dried over anhydrous sodium sulphate, filtrated and concentrated. The crude product was separated and purified with silica column chromatograph (DCM/MeOH = 10/1) to give compound **28-b** (164 mg, 85%) which was yellow solid. LC-MS (ESI): m/z = 450.0 $(M+H)^+$.

Synthesis of compound **28-a**

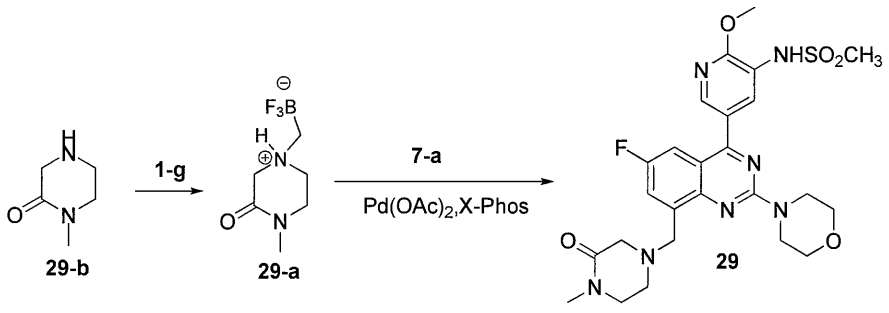
A solution of compound 28-c (89 mg, 0.275 mmol) and cesium carbonate (122 mg, 0.375 mmol) in DMF (4 mL) was stirred for 10 minutes at 80℃, followed by adding compound **28-b** (112 mg, 0.25 mmol). The reaction solution was stirred overnight at 80℃. The reaction solution was quenched with water (20 mL), extracted with ethyl acetate (20 mL), and washed with saturated saline (3*20 mL). The organic phase was dried over anhydrous sodium sulphate, and concentrated. The crude product was separated and purified with silica Preparative plate chromatograph (DCM/MeOH =10/1) to give compound **28-a** (94 mg, 57%) which was yellow solid. LC-MS (ESI): m/z = 604.1 $(M+H)^+$.

Synthesis of compound **28**

At -78℃, to a solution of compound **28-a** (94 mg, 0.16 mmol) in THF (4 mL) was added slowly 3.0 M methylmagnesium bromide (160 μL, 0.48 mmol). The reaction solution was warmed to normal temperature and stirred for about 2 hours. The reaction solution was quenched with saturated aqueous solution of ammonium chloride (5 mL), adjusted to pH>7 with saturated aqueous solution of sodium bicarbonate, and extracted with dichloromethane (3*10 mL). The organic phases were combined, washed with saturated saline (20 mL), dried over anhydrous sodium sulphate, filtrated, and concentrated. The crude product was separated and purified with silica Preparative plate thin layer chromatograph (DCM/MeOH = 10/1) to give compound **28** (60 mg, 66%) which was yellow solid. LC-MS (ESI): m/z = 590.2 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (t, 1H, J = 2.0 Hz), 8.17 (d, 1H, J = 2.0 Hz), 7.11-7.05 (m, 1H), 6.96-6.89 (m, 2H), 4.82-4.36 (m, 1H), 4.11 (s, 3H), 3.96 (t, 4H, J = 4.4 Hz), 3.83-3.78 (m, 4H), 3.07 (s, 3H), 2.37 (d, 1H, J = 10.4 Hz), 2.29 (d, 1H, J = 14.0 Hz), 2.01 (d, 1H, J = 12.8 Hz), 1.71-1.65 (m, 2H), 1.65-1.59 (m, 2H), 1.44-1.38 (m, 2H), 1.21 (s, 6H).

Example 29 Synthesis of compound **29**

Synthesis route of compound **29**



Synthesis of compound **29-a**

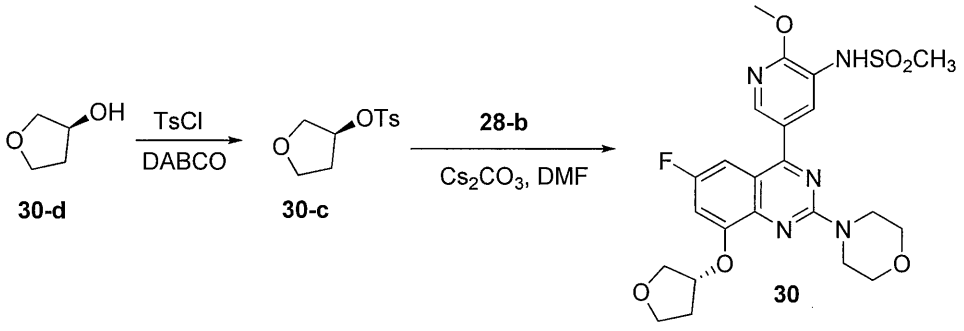
According to the process for preparing compound **1-f**, commercially purchased compound **29-b** was used to give compound **29-a** (436 mg, 95%).

Synthesis of compound **29**

According to the process for preparing compound **1**, compound **29-a** and compound **7-a** were used to give compound **29** (85 mg, 70%). LC-MS (ESI): m/z = 560.2 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, 1H, J = 2.0 Hz), 8.17 (d, 1H, J = 2.0 Hz), 7.64 (dd, 1H, J = 9.2, 2.8 Hz), 7.42 (dd, 1H, J = 8.8, 3.2 Hz), 7.28 (s, 1H), 7.03 (s, 1H), 4.12 (s, 3H), 4.08 (s, 2H), 3.95 (t, 4H, J = 5.2 Hz), 3.84 (t, 4H, J = 5.2 Hz), 3.39 (t, 2H, J = 5.2 Hz), 3.30 (s, 2H), 3.08 (s, 3H), 2.98 (s, 3H), 2.86 (t, 2H, J = 5.2 Hz).

Example 30 Synthesis of compound **30**

Synthesis route of compound **30**



Synthesis of compound **30-c**

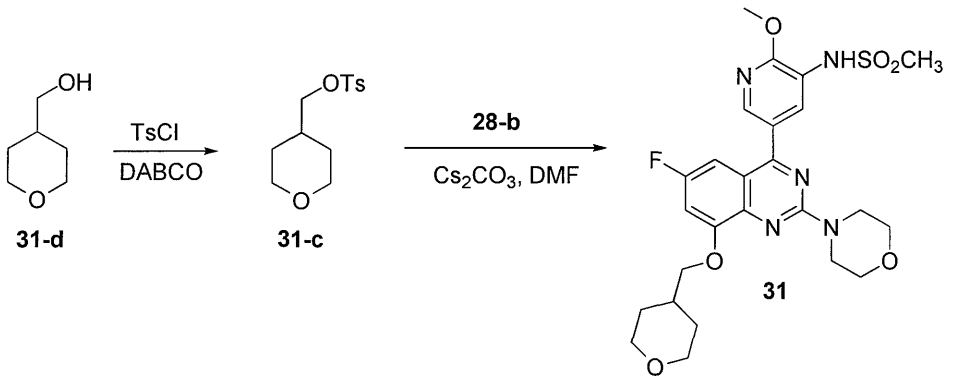
According to the process for preparing compound **28-c**, commercially purchased compound **30-d** was used to give compound **30-c** (236 mg, 85%). LC-MS (ESI): m/z = 260.0 $(M+NH_4)^+$.

Synthesis of compound **30**

According to the process for preparing compound **28-a**, compound **30-c** was used to give compound **30** (25 mg, 22%). LC-MS (ESI): m/z = 520.1 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, 1H, J = 2.4 Hz), 8.18 (d, 1H, J = 2.0 Hz), 7.14 (dd, 1H, J = 9.2, 2.8 Hz), 6.86 (dd, 2H, J = 10.4, 3.2 Hz), 5.18-5.17 (m, 1H), 4.18-4.07 (m, 6H), 3.99-3.94 (m, 5H), 3.83 (t, 4H, J = 5.2 Hz), 3.07 (s, 3H), 2.33-2.28 (m, 2H).

Example 31 Synthesis of compound **31**

Synthesis route of compound **31**



31-d **31-c** **31**

Synthesis of compound **31-c**

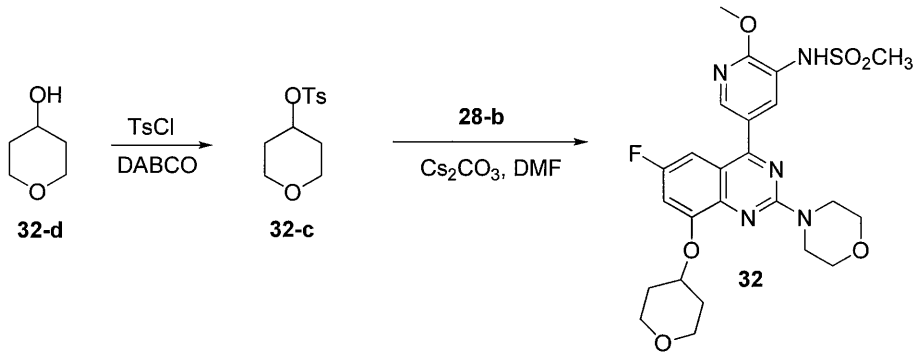
According to the process for preparing compound **28-c**, commercially purchased compound **31-d** was used to give compound **31-c** (1.9 g, 91%). LC-MS (ESI): m/z = 288.1 $(M+NH_4)^+$.

Synthesis of compound **31**

According to the process for preparing compound **28-a**, compound **31-c** was used to give compound **31** (65 mg, 54%). LC-MS (ESI): m/z = 548.0 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, 1H, J = 2.4 Hz), 8.18 (d, 1H, J = 2.0 Hz), 7.09 (dd, 1H, J = 9.2, 2.4 Hz), 6.90 (s, 1H), 6.88 (dd, 1H, J = 10.0, 2.4 Hz), 4.11 (s, 3H), 4.08 (dd, 2H, J = 11.2, 3.2 Hz), 3.99 (d, 2H, J = 6.4 Hz), 3.96 (t, 4H, J = 4.0 Hz), 3.83 (t, 4H, J = 4.4 Hz), 3.53-3.47 (m, 2H), 3.07 (s, 3H), 2.32-2.26 (m, 1H), 1.90 (d, 2H, J = 12.8 Hz), 1.60-1.50 (m, 2H).

Example 32 Synthesis of compound **32**

Synthesis route of compound **32**



32-d **32-c** **32**

Synthesis of compound **32-c**

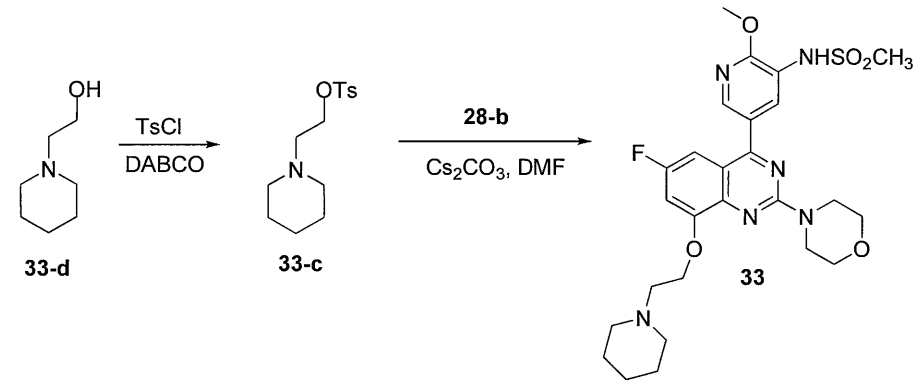
According to the process for preparing compound **28-c**, commercially purchased compound **32-d** was used to give compound **32-c** (2.5 g, 98%). LC-MS (ESI): m/z = 274.0 $(M+NH_4)^+$.

Synthesis of compound **32**

According to the process for preparing compound **28-a**, compound **32-c** was used to give compound **32** (60 mg, 51%). LC-MS (ESI): m/z = 534.0 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, 1H, J = 1.6 Hz), 8.18 (d, 1H, J = 2.4 Hz), 7.14 (dd, 1H, J = 9.2, 2.4 Hz), 6.98 (dd, 1H, J = 10.0, 2.4 Hz), 6.89 (s, 1H), 4.80-4.76 (m, 1H), 4.12 (s, 3H), 4.10-4.06 (m, 2H), 3.97 (t, 4H, J = 4.4 Hz), 3.84 (t, 4H, J = 4.0 Hz), 3.66-3.61 (m, 2H), 3.07 (s, 3H), 2.13-2.07 (m, 2H), 2.01-1.94 (m, 2H).

Example 33 Synthesis of compound **33**

Synthesis route of compound **33**



33-d **33-c** **33**

Synthesis of compound **33-c**

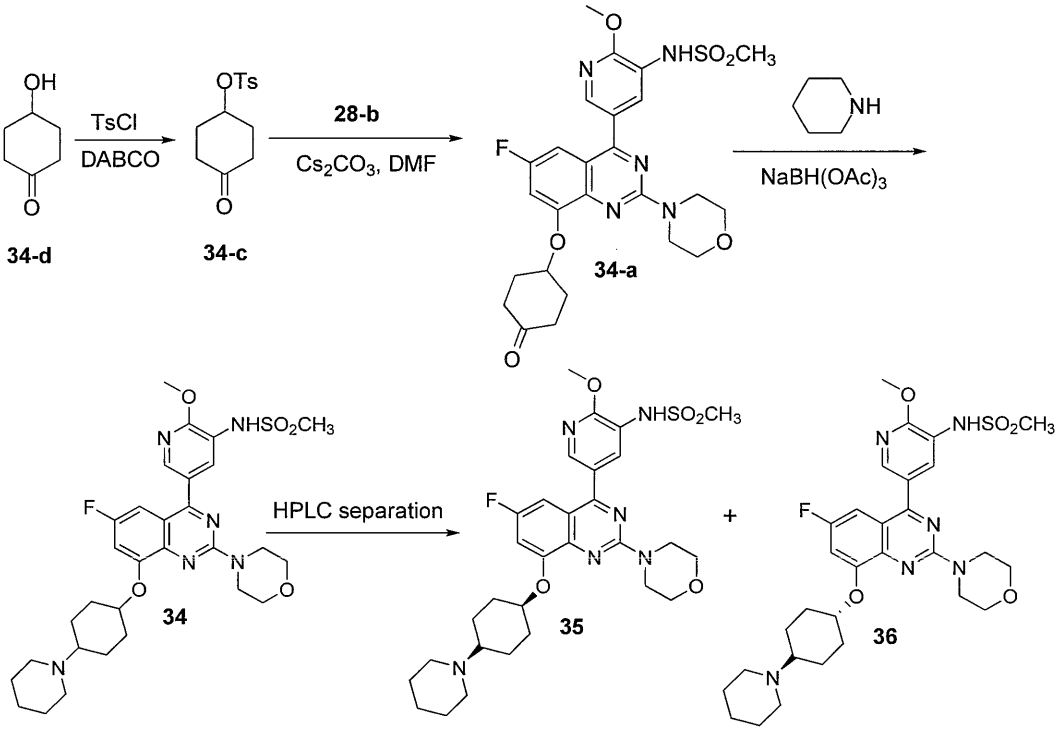
According to the process for preparing compound **28-c**, commercially purchased compound **33-d** was used to give compound **33-c** (176 mg, 16%). LC-MS (ESI): m/z = 284.1 $(M+H)^+$.

Synthesis of compound **33**

According to the process for preparing compound **28-a**, compound **33-c** was used to give compound **33** (25 mg, 22%). LC-MS (ESI): m/z = 561.1 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$): δ8.34 (d, 1H, J= 2.0 Hz), 8.18 (d, 1H, J= 2.4 Hz), 7.09 (dd, 1H, J= 9.2, 2.4 Hz), 6.89 (dd, 1H, J= 10.0, 2.4 Hz), 4.29 (t, 2H, J= 6.0 Hz), 4.11 (s, 3H), 3.96 (t, 4H, J= 4.4 Hz), 3.83 (t, 4H, J= 4.4 Hz), 3.07 (s, 3H), 2.98 (t, 2H, J= 5.6 Hz), 2.64 (bs, 4H), 1.66-1.60 (m, 4H), 1.48-1.46 (m, 2H).

Example 34 Synthesis of compounds **34, 35, 36**

Synthesis route of compounds **34, 35, 36**



Synthesis of compound **34-c**

According to the process for preparing compound **28-c**, commercially purchased compound **34-d** was used to give compound **34-c** (581mg, 95%). LC-MS (ESI): m/z = 286.0 $(M+H)^+$.

Synthesis of compound **34-a**

According to the process for preparing compound **28-a**, compound **34-c** was used to give compound **34-a** (460 mg, 95%). LC-MS (ESI): m/z = 546.3 $(M+H)^+$.

Synthesis of compound **34**

To a flask were added compound **34-a** (460 mg, 0.84 mmol), piperidine (718 mg, 8.4 mmol), $NaBH(OAc)_3$ (1.78 g, 8.4 mmol), glacial acetic acid (5 mg，0.084mmol) and 1,2-dichloroethane (20 mL). The mixture was stirred overnight at 40℃, followed by adding water (15 mL) and extracted with dichloromethane (20 mL) for 3 times. The

organic phases were combined, dried, and concentrated. The residue was purified with silica column chromatograph (CH_2Cl_2/CH_3OH = 60/1 to 10/1) to give compound 34 (210 mg, 40.5%). LC-MS (ESI): m/z = 615.1 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$): 8.34 (t, J = 2.4 Hz, 1H), 8.17 (d, J = 2.1 Hz, 1H), 7.10 (m, 1H), 6.97 – 6.89 (m, 1H), 4.78 (s, 0.7H), 4.38 (dd, J = 9.6, 5.4 Hz, 0.3H), 4.12 (s, 3H), 3.95 (dd, J = 9.0, 3.8 Hz, 4H), 3.82 (dd, J = 9.5, 4.6 Hz, 4H), 3.07 (s, 3H), 2.72 – 2.45 (m, 5H), 2.29 (d, J = 14.9 Hz, 2H), 2.00 (t, J = 12.8 Hz, 2H), 1.81 – 1.54 (m, 8H), 1.47 (dd, J = 13.0, 7.8 Hz, 3H).

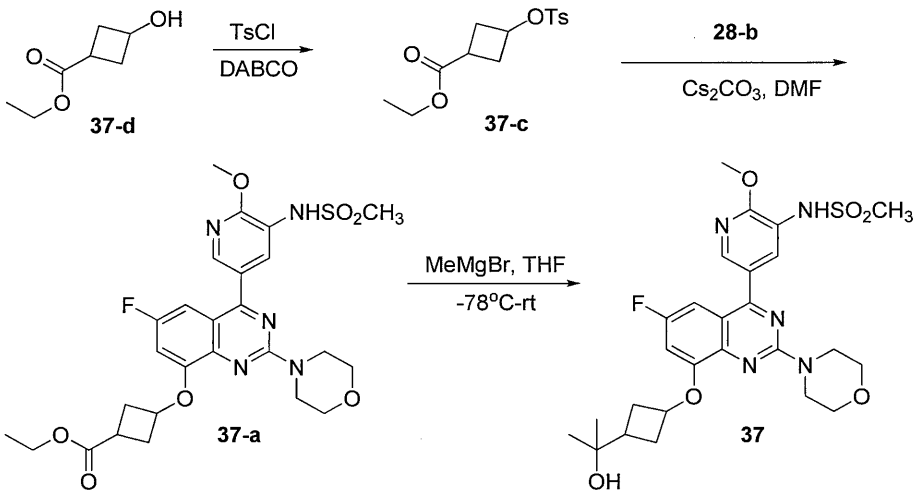
The *cis/trans* mixture of compound **34** was separated with preparative supercritical fluid chromatography (apparatus: SFC-80 (Thar, Waters); column: RegisCell, 30*250mm, 5 μm; mobile phase: CO_2/Methanol (0.1%NH_4OH) = 65/35; flow rate: 80 g/min; Back pressure: 100 bar) to give compound **35** (with a relatively short retention time) and compound **36** (with a relatively long retention time). The isomers were characterized by 1H-NMR.

Compound **35**: LC-MS (ESI): m/z = 615.3 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$): 8.34 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 2.1 Hz, 1H), 7.08 (dd, J = 9.2, 2.6 Hz, 1H), 6.92 (dd, J = 10.4, 2.6 Hz, 1H), 4.77 (s, 1H), 4.12 (s, 3H), 4.00 – 3.92 (m, 4H), 3.85 – 3.79 (m, 4H), 3.07 (s, 3H), 2.63 – 2.55 (m, 4H), 2.50 (s, 1H), 2.27 (d, J = 14.7 Hz, 2H), 1.97 (dd, J = 11.0, 8.4 Hz, 2H), 1.70 (d, J = 10.3 Hz, 2H), 1.60 (dd, J = 14.8, 9.7 Hz, 6H), 1.46 (d, J = 5.2 Hz, 2H).

Compound **36**: LC-MS (ESI): m/z = 615.3 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$): 8.34 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 2.0 Hz, 1H), 7.10 (dd, J = 9.2, 2.5 Hz, 1H), 6.94 (dd, J = 10.2, 2.5 Hz, 1H), 4.37 (dd, J = 9.6, 5.4 Hz, 1H), 4.12 (s, 3H), 3.97 – 3.91 (m, 4H), 3.85 – 3.79 (m, 4H), 3.07 (s, 3H), 2.57 (s, 4H), 2.43 (d, J = 11.3 Hz, 1H), 2.34 (d, J = 11.5 Hz, 2H), 2.10 – 1.99 (m, 2H), 1.64 (dd, J = 15.8, 9.6 Hz, 6H), 1.46 (t, J = 11.4 Hz, 4H).

Example 35 Synthesis of compounds **37**

Synthesis route of compounds **37**



Synthesis of compound **37-c**

According to the process for preparing compound **28-c**, commercially purchased compound **37-d** was used to give compound **37-c** (619 mg, 99%). LC-MS (ESI): m/z = 316.0 $(M+H)^+$.

Synthesis of compound **37-a**

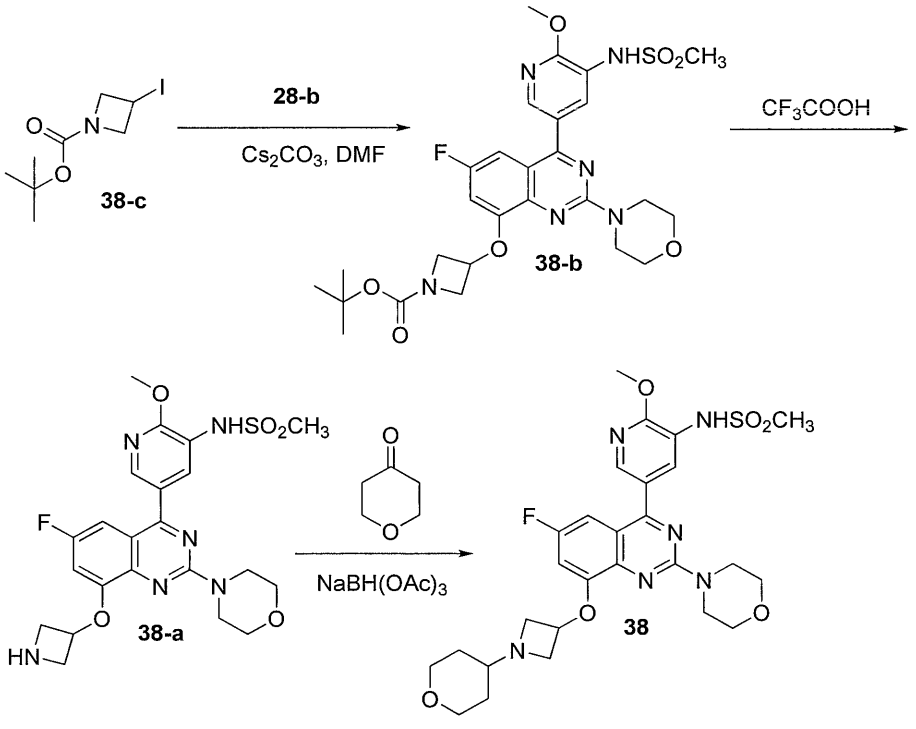
According to the process for preparing compound **28-a**, compound **37-c** was used to give compound **37-a** (121 mg, 66%). LC-MS (ESI): m/z = 576.0 $(M+H)^+$.

Synthesis of compound **37**

According to the process for preparing compound **28**, compound **37-a** was used to give compound **37** (7 mg, 6%). LC-MS (ESI): m/z = 562.0 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, J = 2.1 Hz, 1H), 8.19 (d, J = 2.1 Hz, 1H), 7.06 (dd, J = 9.2, 2.5 Hz, 1H), 6.80 (s, 1H), 6.65 (dd, J = 10.4, 2.5 Hz, 1H), 4.85 (s, 1H), 4.12 (s, 3H), 4.01 – 3.95 (m, 4H), 3.87 – 3.81 (m, 4H), 3.07 (s, 3H), 2.59 – 2.45 (m, 5H), 1.27 (s, 1H), 1.24 (s, 6H).

Example 36 Synthesis of compounds **38**

Synthesis route of compounds **38**



Synthesis of compound **38-b**

According to the process for preparing compound **28-a**, commercially purchased compound **38-c** was used to give compound **38-b** (270 mg, 90.9%). LC-MS (ESI): m/z = 605.0 $(M+H)^+$.

Synthesis of compound **38-a**

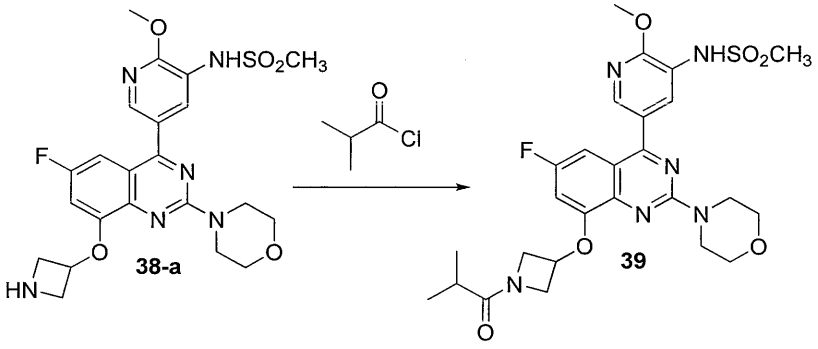
According to the process for preparing compound **4-a**, compound **38-b** was used to give compound **38-a** (260 mg, 100%). LC-MS (ESI): m/z = 505.0 $(M+H)^+$.

Synthesis of compound **38**

To a flask were added compound 38-a (67 mg, 0.13 mmol), tetrahydrofuran-4-one (26 mg, 0.26 mmol), $NaBH(OAc)_3$ (137 mg, 0.65 mmol), glacial acetic acid (0.5 mg) and 1,2-dichloroethane (30 mL). The mixture was stirred overnight at room temperature, followed by adding water (15 mL) and then extracted with dichloromethane (20 mL) for 3 times. The organic phases were combined, dried, and concentrated. The residue was separated and purified by Prep-HPLC to give compound **38** (10 mg, 12.3%). LC-MS (ESI): m/z = 589.1 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (1H, d, J = 1.6 Hz), 8.18 (1H, d, J = 2.4 Hz), 7.12-7.09 (1H, m), 6.67-6.64 (1H, m), 4.98 (1H, t, J = 6.0 Hz), 4.12 (3H, s), 4.01-3.93 (8H, m), 3.83 (4H, t, J = 4.4 Hz), 3.44-3.37 (2H, m), 3.32-3.29 (2H, m), 3.07 (3H, s), 2.44-2.39 (1H, m), 1.73-1.70 (2H, m), 1.45-1.35 (2H, m).

Example 37 Synthesis of compounds **39**

Synthesis route of compounds **39**



Synthesis of compound **39**

Compound **38-a** (60 mg, 0.12 mmol) was dissolved in 20 mL dichloromethane, followed by adding triethylamine (37 mg, 0.36 mmol) and isobutyryl chloride (12 mg, 0.12 mmol). The reaction mixture was stirred for 30 minutes at room temperature, followed by adding water (15 mL) and then extracted with dichloromethane (20 mL) for 3 times. The organic phases were combined, dried, and concentrated. The residue was separated and purified by Prep-HPLC to give compound **39** (35 mg, 51.4%). LC-MS (ESI): m/z = 575.0 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$): $\delta\delta$ 8.35 (1H, d, J = 2.4 Hz), 8.18(1H, d, J = 2.4 Hz), 7.18-7.15 (1H, m), 6.83 (1H, s), 6.60-6.57 (1H, m), 5.16-5.13 (1H, m), 4.65-4.61 (1H, m), 4.50-4.46 (1H, m), 4.42-4.39(1H, m), 4.29-4.25 (1H, m), 4.13 (3H, s), 3.98 (4H, t, J = 4.8 Hz), 3.83 (4H, t, J = 4.8 Hz), 3.08 (3H, s), 2.53-2.46 (1H, m), 1.15-1.13 (6H, m).

Effect example 1 PI3Kα, PI3Kδ, PI3Kβ and PI3Kγ enzymatic inhibitory activity IC50 assay

1. Buffer preparation: 50 mM HEPES, pH 7.5, 3 mM $MgCl_2$, 1 mM EGTA, 100 mM NaCl, 0.03% CHAPS.

2. The compound was formulated in 100% DMSO in a concentration gradient, and deposited to a 384-well plate with a final DMSO concentration of 1%.

3. PI3Kα, PI3Kδ, PI3Kβ and PI3Kγ enzymes (purchased from EMD Millipore) were diluted to the optimal concentration with the following buffer: 50 mM HEPES, pH 7.5, 3 mM $MgCl_2$, 1 mM EGTA, 100 mM NaCl, 0.03% CHAPS, 2 mM DTT, transferred to a 384-well plate and incubated with the compound for a certain time.

4. The substrate was diluted to an optimal concentration with the following buffer: 50 mM HEPES, pH 7.5, 3 mM $MgCl_2$, 1 mM EGTA, 100 mM NaCl, 0.03% CHAPS, 2 mM DTT, 50 μM PIP2, 25 μM ATP and added to the 384-well plate to initiate the reaction. PI3Kα, PI3Kβ and PI3Kγ were allowed to react for 1h at room temperature, and PI3Kδ reacted for 2 hours at room temperature. Another 10 μL ADP-Glo Detection Reagent also needed to be added for PI3Kβ and PI3Kγ, and then equilibrated at room temperature for 30 minutes.

5. Luminescense was read by using Flexstation, and the inhibition rate was calculated as the average value of two tests.

Table 1 shows the IC_{50} values against PI3Kδ of the compounds in the present invention and the ratio of IC_{50} values aganist PI3Kα to PI3Kδ (referred to as α/δ). Table 2 shows the ratio of IC_{50} values against PI3Kβ to PI3Kδ of partial compounds (referred to as β/δ) and the ratio of IC_{50} values against PI3Kγ to PI3Kδ (referred to as γ/δ).

Table 1

Compound No.	PI3Kδ IC50 (nM)	α/δ	Compound No.	PI3Kδ IC50 (nM)	α/δ
1	7.6	341	**2**	17	368
3	31	119	**4**	45	2
5	58.6	1	**6**	457	2.4
7	31	130	**8**	9.8	292
9	19	233	**10**	6.4	320
11	606	2.3	**12**	241	>41

13	239	>42	**14**	1035	>9
15	345	23	**16**	15	42
17	3.4	38	**18**	4.2	11
19	5	88	**20**	4.6	15
21	15.3	91	**22**	31	2
23	16	79	**24**	21	45
25	28	28	**26**	87	32
27	24	83	**28**	77	63
29	19	22	**30**	41	15
31	27	24	**32**	38	23
33	47.1	113	**34**	18.2	202
35	20	227	**36**	17	239
37	117	42	**38**	15.8	28
39	22	58			

Table 2

Compound No.	**β/δ**	**γ/δ**	**Compound No.**	**β/δ**	**γ/δ**
7	166	>322	**10**	31	>1000
15	>29	>29	**16**	341	>650
23	40	>625	**28**	>129	>129
34	360	>549	**35**	322	>500
36	366	>588	**37**	>85	>85

Effect example 2 Assay for screening the drugs for inhibiting human Raji cell TNF-α generation induced by human IgM

1. Raji cell line (human Burkitt's lymphoma origin) (ATCC, Cat# CCL-86) was used.

2. Raji cells were applied onto the 96-well plate with 1×10^5/well.

3. The compounds to be screened were diluted to the corresponding test concentration, and added to the cell culture system 30 minutes prior to IgM stimulation.

4. 10 μg/ml IgM monoclonal antibody (JACKSON, Cat# 109-006-129) was added to the cell culture system in order to stimulate the cells generating TNF-α.

5. After 24 hours, the amount of TNF-α produced by the cell line was determined by ELISA.

6. The inhibition rates at each concentration of the compound were calculated and plotted to calculate 50% inhibition rate (IC50), and the specific results were shown in table 3.

Table 3 IC50 against TNF-α of partial compounds

Compound No.	TNF-α IC50 (nM)	Compound No.	TNF-α IC50 (nM)
1	29.1	**2**	92.7
3	31.7	**7**	34.8
8	28.4	**10**	66.0
16	20.1	**18**	15.2
23	88.7	**27**	230.1
30	351.8	**33**	260.0
34	66.0	**35**	105.1
36	27.0	**38**	32.0
39	107.5		

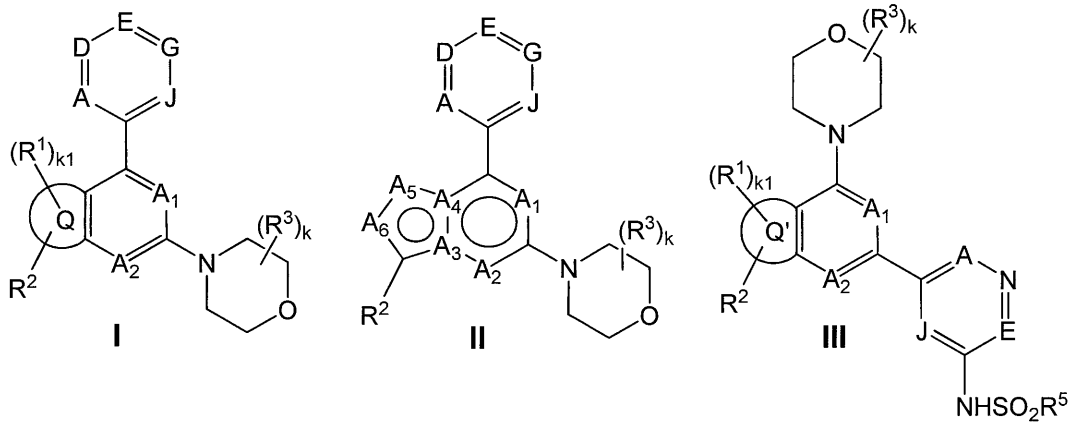
From the test results above it can be determined that, the compounds of the present invention have an excellent selective inhibition against PI3Kδ and are a type of selective inhibitor which possesses stronger inhibitory activity aganist PI3Kδ than that

against PI3Kα, PI3Kβ or PI3Kγ and can be an excellent immunosuppressant, and can be an agent useful for treating or preventing rejection responses in a variety of organ transplantation, allergic diseases (asthma, atopic dermatitis etc.), autoimmune diseases (rheumatoid arthritis, psoriasis, ulcerative colitis, Crohn's disease, systemic lupus erythematosus etc.), and neoplastic hematologic disorder and so on.

Though the embodiments of the present invention are described above, a person skilled in the art should understand that these embodiments are just illustrated for explaination, without departing from the principle and substance of the present invention, a variety of modifications and alterations can be made to these embodiments. Therefore, the protection scope of the present invention is defined by the attached claims.

What is claimed is:

1. A fused heterocyclic compound represented by formula I, formula II or formula III, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof,



Wherein,

A_1 is N or CH;

A_2 is N or CH;

A_3 is N or C;

A_4 is N or C;

A_5 is O, S, N, CR^{1a} or NR^{5a};

A_6 is O, S, N, CR^{1b} or NR^{5b};

When A_5 is O or S, A_6 is N;

When A_6 is O or S, A_5 is N;

R^{1a} and R^{1b} are each independently a hydrogen, a deuterium, a halogen, an alkyl, an alkoxy, an alkenyl, an alkynyl, a cycloalkyl, a heterocycloalkyl or CN;

R^2 is $-(CR^8R^9)_mNR^5R^6$, $-(CR^8R^9)_mNR^7C(=Y)R^5$, $-(CR^8R^9)_mNR^7S(O)_2R^5$, $-(CR^8R^9)_mOR^5$, $-(CR^8R^9)_mS(O)_2R^5$, $-(CR^8R^9)_mS(O)_2NR^5R^6$, $-C(OR^5)R^6R^8$, $-C(=Y)R^5$, $-C(=Y)OR^5$, $-C(=Y)NR^5R^6$, $-C(=Y)NR^7OR^5$, $-C(=O)NR^7S(O)_2R^5$, $-C(=O)NR^7(CR^8R^9)_mNR^5R^6$, $-NR^7C(=Y)R^6$, $-NR^7C(=Y)OR^6$, $-NR^7C(=Y)NR^5R^6$, $-NR^7S(O)_2R^5$, $-NR^7S(O)_2NR^5R^6$, $-SR^5$, $-S(O)_2R^5$, $-S(O)_2NR^5R^6$, $-SC(=Y)R^5$, $-SC(=Y)OR^5$, $-O(CR^8R^9)_mCR^5R^6$, $-O(CR^8R^9)_mNR^5R^6$, a C_{1-12} alkyl, a C_{2-8} alkenyl, a C_{2-8} alkynyl, a C_{3-12} carbocyclic group, a C_{2-20} heterocyclic group, a C_{6-20} aryl or a C_{1-20} heteroaryl;

$(R^3)_k$ represents that the hydrogens attached to the morpholine ring are substituted by 0-k occurrences of R^3, at each occurrence the R^3 is the same or different from each other, and is independently a hydrogen, a deuterium, a halogen, a C_{1-6} alkyl, or any

two of the R^3 are linked by a single bond, a C_{1-6} alkylene or a C_{1-6} alkylene substituted by one or two heteroatoms to form a ring structure, the heteroatom is O, N, or S;

A is N or CR^{4a};

D is N or CR^{4d};

E is N or CR^{4e};

G is N or CR^{4g};

J is N or CR^{4j};

A, D, E, G and J are not N at the same time;

R^{4a}, R^{4d}, R^{4e}, R^{4g} and R^{4j} are each independently a hydrogen, a halogen, -CN, an alkyl, an alkoxy, an alkenyl, an alkynyl, a cycloalkyl, a heterocycloalkyl, $-NR^5R^6$, $-OR^5$, $-SR^5$, $-C(O)R^5$, $-NR^5C(O)R^6$, $-N(C(O)R^6)_2$, $-NR^5C(O)NR^{5'}R^6$, $-NR^7S(O)_2R^5$, $-C(=O)OR^5$ or $-C(=O)NR^5R^6$, or R^{4j} and R^{4g}, together with the atoms to which they are attached form a saturated, unsaturated or partially unsaturated 5-membered or 6-membered heterocycle, the 5-membered or 6-membered heterocycle is fused to the 6-membered ring containing A, D, E, G and J;

Ring Q and ring Q' are benzene, a 5- to 9-membered alicyclic ring, a 5- to 9-membered heteroalicyclic ring, or a 5- to 6-membered heterocyclic ring; ring Q is not a thiophene or a furan; $(R^1)_{k1}$ represents that the hydrogens attached to the ring Q or ring Q' are substituted by 0-k1 occurrences of R^1, at each occurrence the R^1 is the same or different from each other, and is each independently a halogen, -CN, an alkyl, an alkoxy, an alkenyl, an alkynyl, a cycloalkyl, a heterocycloalkyl, $-NR^5R^6$, $-OR^5$, $-SR^5$, $-C(O)R^5$, $-NR^5C(O)R^6$, $-N(C(O)R^6)_2$, $-NR^5C(O)NR^{5'}R^6$, $-NR^7S(O)_2R^5$, $-C(=O)OR^5$ or $-C(=O)NR^5R^6$;

R^5, $R^{5'}$, R^{5a}, R^{5b}, R^6, R^7 and $R^{7'}$ are each independently a hydrogen, a C_{1-12} alkyl, $-(CH_2)_{2-3}NH_2$, a C_{2-8} alkenyl, a C_{2-8} alkynyl, a C_{3-12} carbocyclic group, a C_{2-20} heterocyclic group, a C_{6-20} aryl or a C_{1-20} heteroaryl, or R^5, R^6 together with the nitrogen or carbon atoms to which they are directly attached form a heterocyclic ring or a cycloalkyl, or R^7, $R^{7'}$ together with the nitrogen atom to which R^7 is directly attached form a heterocyclic ring; the heterocyclic ring or the cycloalkyl is preferably optionally substituted by the substituent selected from the group consisting of: oxo, $-(CH_2)_mOR^7$, $-NR^7R^{7'}$, $-CF_3$, a halogen, $-SO_2R^7$, $-C(=O)R^7$, $-NR^7C(=Y)R^{7'}$, $-NR^7S(O)_2R^{7'}$, $-C(=Y)NR^7R^{7'}$, a C_{1-12} alkyl, a C_{2-8} alkenyl, a C_{2-8} alkynyl, a C_{3-12} carbocyclic group, a C_{2-20} heterocyclic group, a C_{6-20} aryl or a C_{1-20} heteroaryl;

$(CR^8R^9)_m$ represents that 0 to m (CR^8R^9) are linked with each other, R^8 and R^9 are the substituents attached to the formed carbon chain, wherein each R^8 and R^9 are the same or different from each other, and are each independently a hydrogen, a deuterium, a halogen, -CN, a hydroxyl, an alkoxy, a C_{1-12} alkyl, a C_{2-12} alkenyl, a C_{2-12} alkynyl, a C_{3-12} cycloalkyl, a C_{6-12} aryl, a 3- to 12-membered heterocycloalkyl or a 5- to 12-membered heteroaryl; or R^8, R^9 together with the atoms to which they are attached

form a saturated or partially unsaturated C_{3-12} carbon ring or C_{2-20} heterocyclic ring;

wherein the alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, carbocyclic ring, heterocyclic ring, heterocycloalkyl, aryl, or heterocyclic group can be optionally substituted by the substituent selected from the group consisting of: a halogen, a hydroxyl, -CN, $-CF_3$, $-NO_2$, oxo, R^5, $-C(=Y)R^5$, $-C(=Y)OR^5$, $-C(=Y)NR^5R^6$, $-(CR^8R^9)_mNR^5R^6$, $-(CR^8R^9)_mOR^5$, $-NR^5R^6$, $-NR^7C(=Y)R^5$, $-NR^7C(=Y)OR^6$, $-NR^7C(=Y)NR^5R^6$, $-(CR^8R^9)_mNR^7SO_2R^5$, $=NR^7$, OR^5, $-OC(=Y)R^5$, $-OC(=Y)OR^5$, $-OC(=Y)NR^5R^6$, $-OS(O)_2(OR^5)$, $-OP(=Y)(OR^5)(OR^6)$, $-OP(OR^5)(OR^6)$, $-SR^5$, $-S(O)R^5$, $-S(O)_2R^5$, $-S(O)_2NR^5R^6$, $-S(O)(OR^5)$, $-S(O)_2(OR^5)$, $-SC(=Y)R^5$, $-SC(=Y)OR^5$, $-SC(=Y)NR^5R^6$, a C_{1-12} alkyl, a C_{2-8} alkenyl, a C_{2-8} alkynyl, a C_{3-12} carbocyclic group, a C_{2-20} heterocyclic group, a C_{6-20} aryl or a C_{1-20} heteroaryl;

Y is O, S or NR^7;

m, k or k1 is independently 0, 1, 2, 3, 4, 5 or 6.

2. The fused heterocyclic compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof as defined in claim 1, wherein in the formula I,

A_1 is N;

A_2 is N;

R^2 is $-(CR^8R^9)_mNR^5R^6$, $-O(CR^8R^9)_mCR^5R^6$ or $-O(CR^8R^9)_mNR^5R^6$;

R^3 is a hydrogen, a deuterium, a halogen or a C_{1-3} alkyl;

A is CR^{4a}; R^{4a} is a hydrogen, a halogen or a C_{1-3} alkyl;

D is N or CR^{4d}; R^{4d} is $-NR^7S(O)_2R^5$;

E is CR^{4e}; R^{4e} is a hydrogen, a C_{1-3} alkoxy or $-NR^5R^6$;

G is N or CR^{4g}; R^{4g} is $-NR^7S(O)_2R^5$;

J is CR^{4j}; R^{4j} is a hydrogen, a halogen or a C_{1-3} alkyl;

or, R^{4j} and R^{4g}, together with the atoms to which they are attached form a saturated, unsaturated or partially unsaturated 5- or 6-membered heterocyclic ring, the 5- or 6-membered heterocyclic ring is fused to the 6-membered ring containing A, D, E, G and J; the 5-membered heterocyclic ring is a 5-membered nitrogen-containing heterocyclic ring;

A, D, E, G and J are not N at the same time;

ring Q is a benzene;

$(R^1)_{k1}$ represents that the hydrogens to which attached to the ring Q are substituted by 0-k1 occurrences of R^1, at each occurrence the R^1 is the same or different from each

other, and is each independently a halogen;

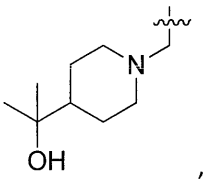
R^5, R^6 and R^7 are each independently a hydrogen, $-(CH_2)_{2-3}NH_2$ or a C_{1-6} alkyl, or R^5, R^6 together with the nitrogen or carbon atoms to which they are directly attached form a heterocyclic ring or a cycloalkyl, the heterocyclic ring or the cycloalkyl is preferably optionally substituted by the substituent selected from the group consisting of: $-(CH_2)_mOR^7$, $-SO_2R^7$, $-C(=O)R^7$, a C_{1-3} alkyl, a C_{3-6} carbocyclic group and a C_{2-5} heterocyclic group; wherein the heterocyclic ring is a nitrogen-containing or an oxygen-containing 4- to 6-memebered heteroalicyclic ring, the cycloalkyl is a 4- to 6-membered cycloalkyl;

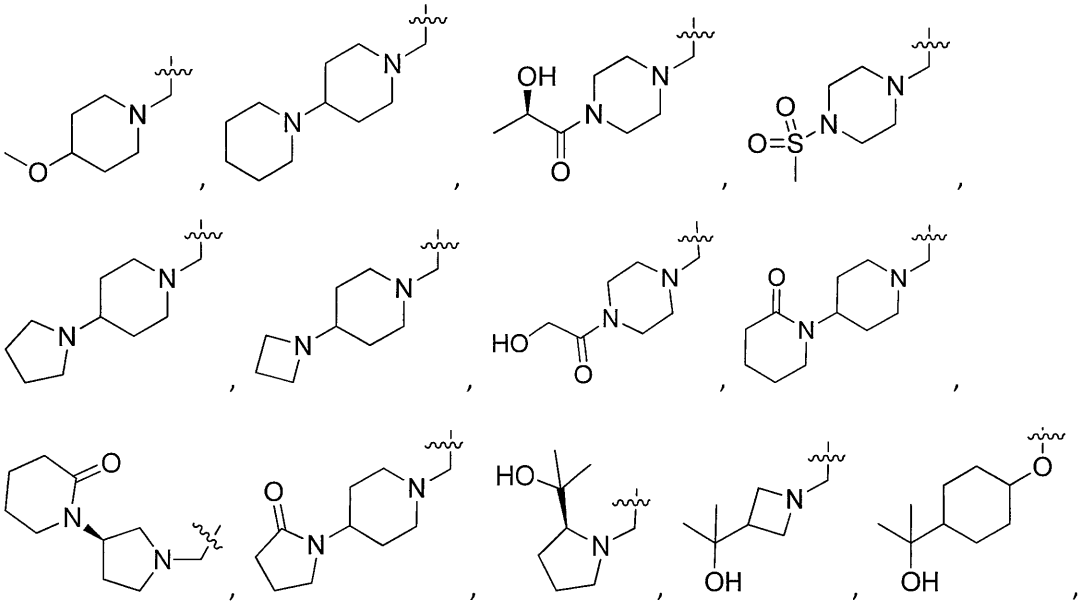
$(CR^8R^9)_m$ represents that 0 to m (CR^8R^9) are linked, R^8 and R^9 are the substituents attached to the formed carbon chain, wherein each R^8 and R^9 are the same or different from each other, and are each independently a hydrogen, a deuterium, a halogen or a C_{1-3} alkyl;

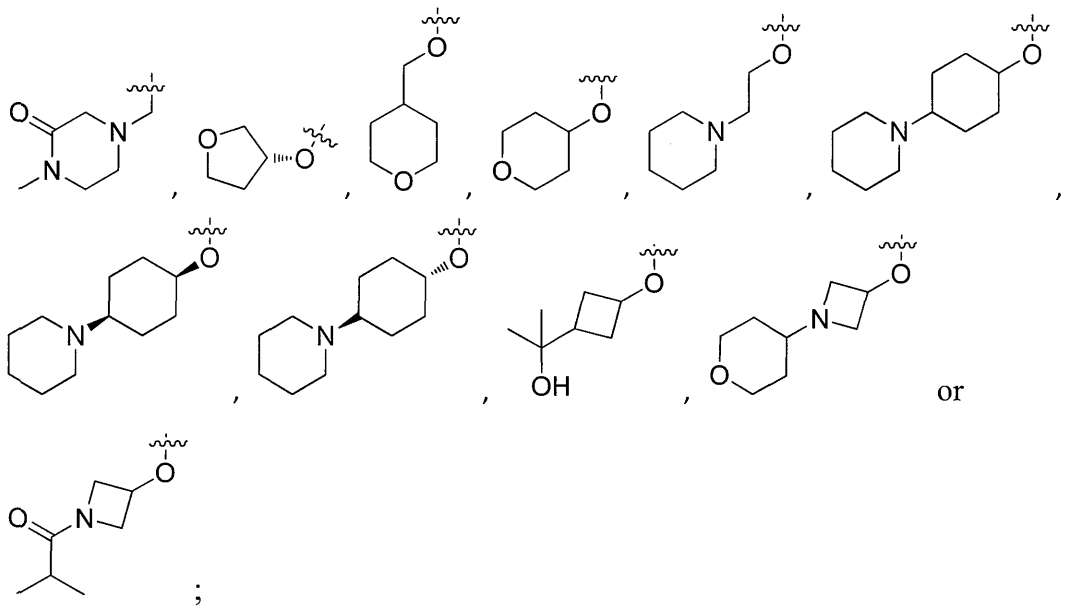
m, k or k1 is independently 0 or 1.

3. The fused heterocyclic compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof as defined in claim 1, wherein in the formula I,

A_1 and A_2 are N at the same time;

R^2 has a structure selected from the group consisting of ,





or

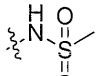
;

R^3 is a hydrogen;

A is CR^{4a}; R^{4a} is a hydrogen;

D is N;

E is CR^{4e}; R^{4e} is a hydrogen, a methoxy or $-NH_2$;

G is N or CR^{4g}; R^{4g} is ;

J is CR^{4j}; R^{4j} is a hydrogen;

or, R^{4j} and R^{4g}, together with the atoms to which they are attached form a saturated, unsaturated or partially unsaturated 5- or 6-membered heterocyclic ring, the 5- or 6-membered heterocyclic ring is fused to the 6-memebered ring containing A, D, E, G and J;

A, D, E, G and J are not N at the same time;

ring Q is a benzene;

$(R^1)_{k1}$ represents that the hydrogens attached to the ring Q are substituted by 0-k1 occurrences of R^1, at each occurrence the R^1 is the same or different from each other, and is each independently fluorine;

m, k or k1 is independently 0 or 1.

4. The fused heterocyclic compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof as defined in claim 2, wherein in the formula I,

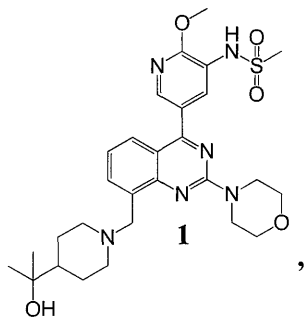
R^{4j} and R^{4g}, together with the atoms to which they are attached form a saturated, undaturated or partially saturated 5-membered heterocyclic ring, the 5-membered

heterocyclic ring is fused to the 6-membered ring containing A, D, E, G and J; the 5-membered heterocyclic ring is 5-membered nitrogen-containing heterocyclic ring; the 5-membered nitrogen-containing heterocyclic ring is a pyrazole or a pyrrole;

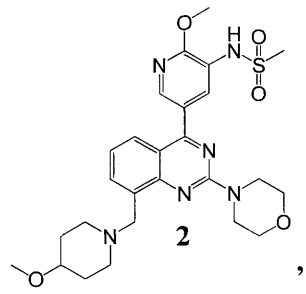
the heterocyclic ring fomed by R^5, R^6, with the nitrogen atom to which they are directly attached is a nitrogen-containing 6-membered heteroalicyclic ring; the nitrogen-containing 6-membered heteroalicyclic ring is a piperidine or a piperazidine.

5. The fused heterocyclic compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof as defined in claim 1, wherein

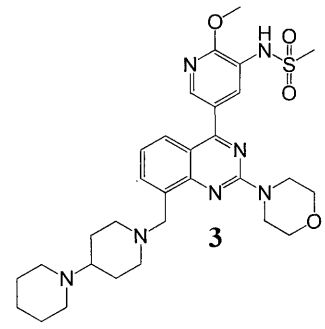
formula I is a compound selected from the group consisting of:



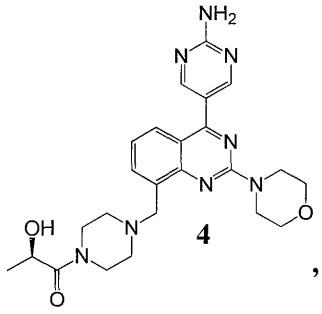
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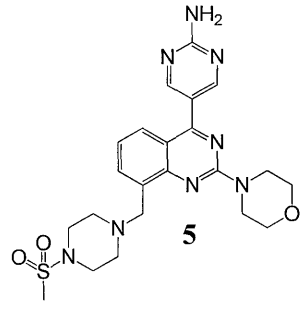
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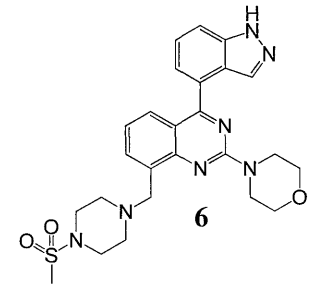
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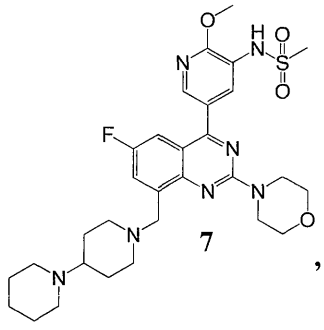
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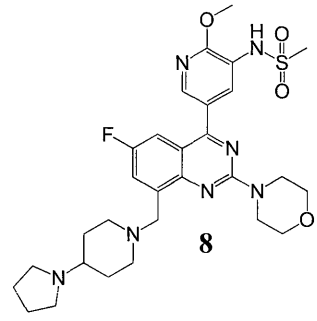
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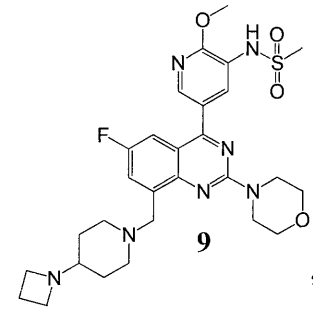
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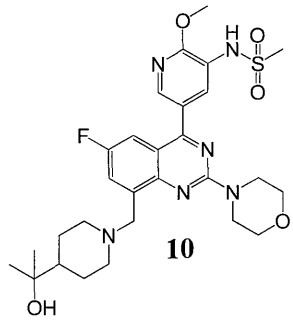
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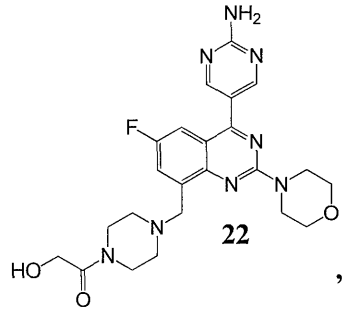
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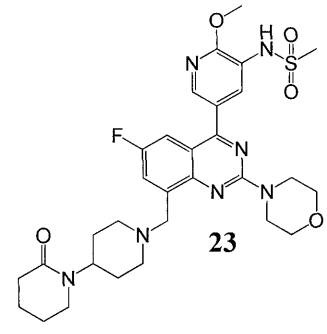
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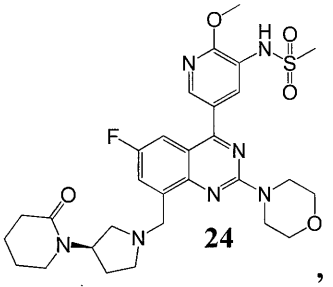
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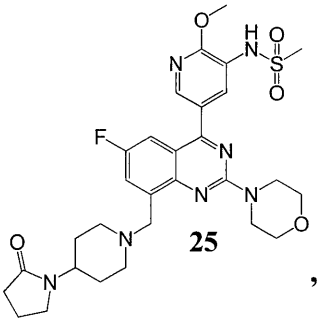
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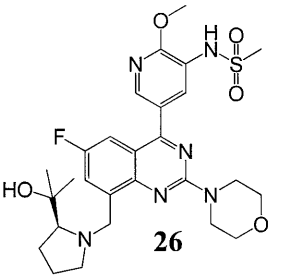
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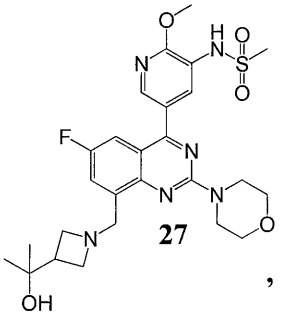
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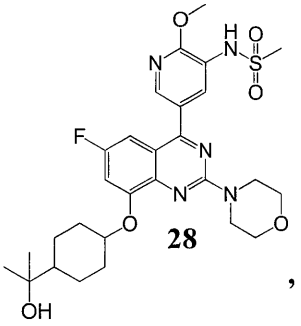
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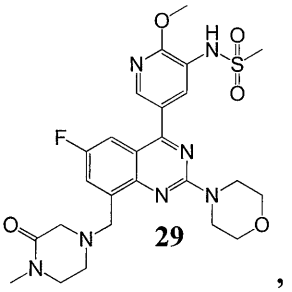
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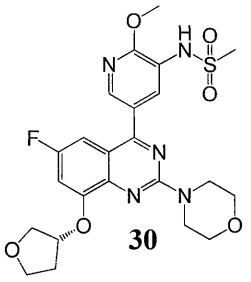
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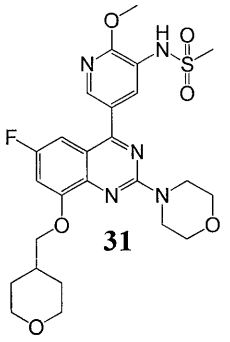
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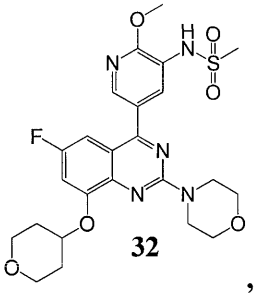
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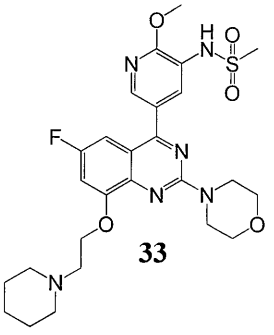
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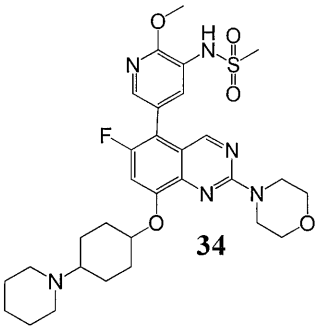
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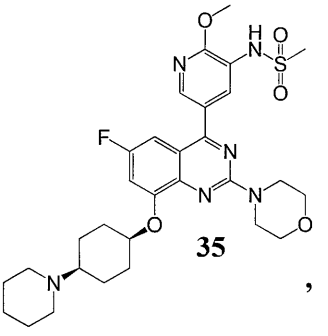
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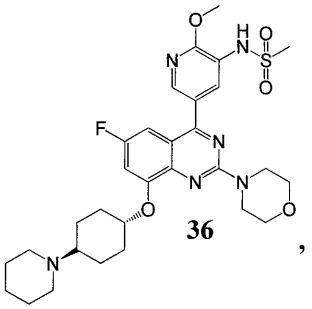
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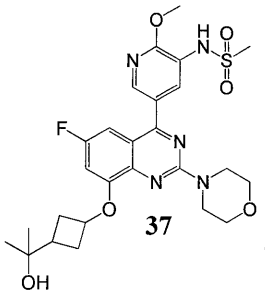


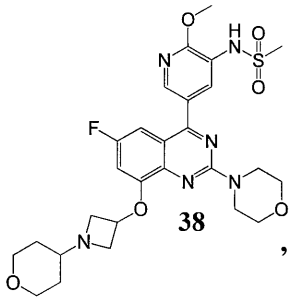
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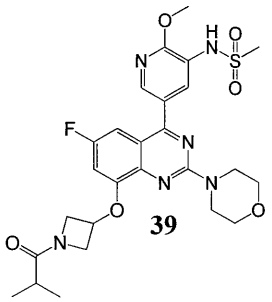


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6. The fused heterocyclic compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof as defined in claim 1, wherein in the formula II,

A_1 is N or CH;

A_2 is N or CH;

A_3 is N or C;

A_4 is N or C;

A_5 is N;

A_6 is CR^{1b}; R^{1b} is a hydrogen or a deuterium;

R^2 is $-(CR^8R^9)_mNR^5R^6$;

$(R^3)_k$ represents that the hydrogens attached to the morpholine ring are substituted by 0-k occurrences of R^3, at each occurrence the R^3 is the same or different from each other, and is each independently a hydrogen, a deuterium, a halogen, or a C_{1-3} alkyl;

A is CR^{4a}; R^{4a} is a hydrogen, a halogen or a C_{1-3} alkyl;

D is N or CR^{4d}; R^{4d} is a hydrogen, a halogen or a C_{1-3} alkyl;

E is CR^{4e}; R^{4e} is a hydrogen, a halogen or a C_{1-3} alkyl;

G is CR^{4g}; R^{4g} is $-NR^7S(O)_2R^5$;

J is CR^{4j}; R^{4j} is a hydrogen;

or, R^{4j} and R^{4g}, together with the atoms to which they are attached form a saturated, unsaturated or partially unsaturated 5-membered heterocyclic ring, the 5-membered heterocyclic ring is fused to the 6-membered ring containing A, D, E, G and J;

wherein the 5-membered heterocyclic ring is a 5-membered nitrogen-containing heterocyclic ring;

R^5, R^6 and R^7 are each independently a hydrogen, a C_{1-6} alkyl, $-(CH_2)_{2-3}NH_2$, a C_{2-4} alkenyl or a C_{2-4} alkynyl, or R^5, R^6 with the nitrogen atom to which they are attached form a heterocyclic ring which is preferably optionally substituted by the substituent selected from the group consisting of: oxo, $-(CH_2)_mOR^7$, $-CF_3$, a halogen, $-SO_2R^7$, $-C(=O)R^7$, a C_{1-3} alkyl, a C_{3-6} carbocyclic group or a C_{2-5} heterocyclic group; wherein the heterocyclic ring formed by R^5, R^6 and with the nitrogen atom to which they are attached is a nitrogen-containing 6-membered heteroalicyclic ring;

$(CR^8R^9)_m$ represents that 0 to m (CR^8R^9) are linked, R^8 and R^9 are the substituents attached to the formed carbon chain, wherein each R^8 and R^9 are the same or different from each other, and are each independently a hydrogen, a deuterium, a halogen, -CN, a hydroxyl or a C_{1-3} alkyl;

wherein the alkyl, alkenyl, alkynyl, carbocyclic group, heterocyclic ring or heterocyclic group is preferably optionally substituted by the substituent selected from the group consisting of: a halogen, a hydroxyl, -CN, $-CF_3$, $-NO_2$ or oxo;

m or k is independently 0 or 1.

7. The fused heterocyclic compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof as defined in claim 6, wherein in the formula II,

A_1, A_3 and A_5, or, A_2, A_4 and A_5 are N at the same time;

when A_1, A_3 and A_5 are N, A_2, A_4 and A_6 are CH at the same time;

when A_2, A_4 and A_5 are N, A_1, A_3 and A_6 are CH at the same time;

R^2 is $-(CR^8R^9)_mNR^5R^6$;

$(R^3)_k$ represents that the hydrogens attached to the morpholine ring are substituted by 0-k occurrences of R^3, at each occurrence the R^3 is the same or different from each other, and is each independently a hydrogen or a deuterium;

A is CR^{4a}; R^{4a} is a hydrogen;

D is N or CR^{4d}; R^{4d} is a hydrogen;

E is CR^{4e}; R^{4e} is a hydrogen;

G is CR^{4g}; R^{4g} is $-NR^7S(O)_2R^5$;

J is CR^{4j}; R^{4j} is a hydrogen;

or, R^{4j} and R^{4g}, together with the atoms to which they are attached form a saturated, unsaturated or partially unsaturated 5-membered nitrogen-containing heterocyclic ring, the 5-membered nitrogen-containing heterocyclic ring is fused to the 6-membered ring containing A, D, E, G and J; wherein the 5-membered nitrogen-

containing heterocyclic ring is a pyrazole or a pyrrole;

R^5, R^6 and R^7 are each independently a hydrogen, a C_{1-3} alkyl, $-(CH_2)_2NH_2$, or R^5, R^6 and with the nitrogen atom to which they are directly attached form a heterocyclic ring which is preferably optionally substituted by the group consisting of: $-SO_2R^7$ or a C_{1-3} alkyl; wherein the heterocyclic ring formed by R^5, R^6 and with the nitrogen atom to which they are directly attached is a nitrogen-containing 6-membered heteroalicyclic ring, the nitrogen-containing 6-membered heteroalicyclic ring is a piperidine or a piperazidine;

$(CR^8R^9)_m$ represents that 0 to m (CR^8R^9) are linked, R^8 and R^9 are the substituents attached to the formed carbon chain, wherein each R^8 and R^9 are the same or different from each other, and are each independently a hydrogen or a deuterium;

wherein the alkyl, heterocyclic ring or heterocyclic group is preferably optionally substituted by the substituent selected from the group consisting of: a halogen, a hydroxyl, -CN, $-CF_3$, $-NO_2$ or oxo;

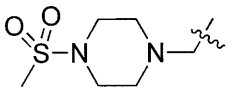
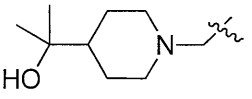
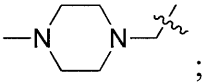
m or k is independently 0 or 1.

8. The fused heterocyclic compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof as defined in claim 7, wherein in the formula II,

A_1, A_3 and A_5, or, A_2, A_4 and A_5 are N at the same time;

when A_1, A_3 and A_5 are N, A_2, A_4 and A_6 are CH at the same time;

when A_2, A_4 and A_5 are N, A_1, A_3 and A_6 are CH at the same time;

R^2 is , , or ;

$(R^3)_k$ represents that the hydrogens attached to the morpholine ring are substituted by 0-k occurrences of R^3, at each occurrence the R^3 is the same or different from each other, and is each independently a hydrogen or a deuterium;

A is CR^{4a}; R^{4a} is a hydrogen;

D is N or CR^{4d}; R^{4d} is a hydrogen;

E is CR^{4e}; R^{4e} is a hydrogen;

G is CR^{4g}; R^{4g} is $-NR^7S(O)_2R^5$;

J is CR^{4j}; R^{4j} is a hydrogen;

or, R^{4j} and R^{4g}, together with the atoms to which they are attached form a saturated, unsaturated or partially unsaturated 5-membered nitrogen-containing heterocyclic ring, the 5-membered nitrogen-containing heterocyclic ring is fused to the 6-membered ring containing A, D, E, G and J; wherein the 5-membered nitrogen-

containing heterocyclic ring is a pyrazole or a pyrrole;

R^5 and R^7 are each independently a hydrogen or a C_{1-3} alkyl;

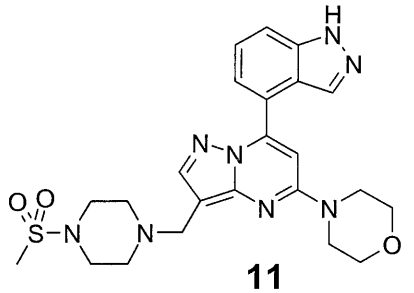
$(CR^8R^9)_m$ represents that 0 to m (CR^8R^9) are linked, R^8 and R^9 are the substituents attached to the formed carbon chain, wherein each R^8 and R^9 are the same or different from each other, and independently a hydrogen or a deuterium;

wherein the alkyl is substituted by a hydroxyl;

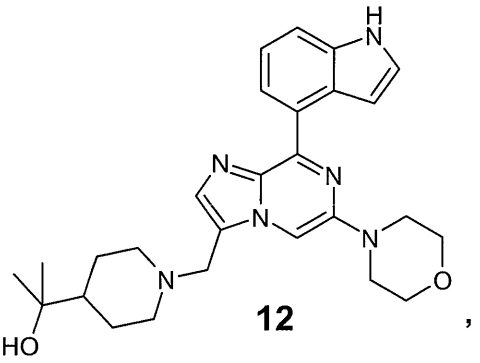
m or k is independently 0 or 1.

9. The fused heterocyclic compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof as defined in claim 1, wherein

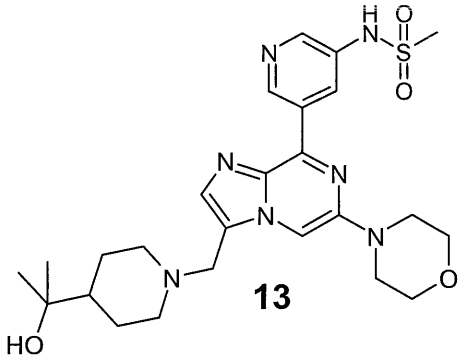
formula II is a compound selected from the group consisting of:



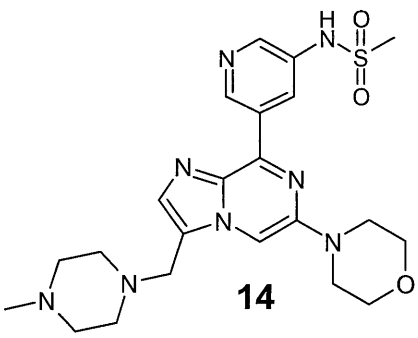
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10. The fused heterocyclic compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof as defined in claim 1, wherein in the formula III,

A_1 is N;

A_2 is N;

R^2 is $-(CR^8R^9)_mNR^5R^6$ or $-(CR^8R^9)_mOR^5$;

$(R^3)_k$ represents that the hydrogens attached to the morpholine ring are substituted by 0-k occurrences of R^3, at each occurrence the R^3 is the same or different from each other, and is each independently a hydrogen, a deuterium, a halogen or a C_{1-3} alkyl;

A is CR^{4a}; R^{4a} is a hydrogen, a halogen or a C_{1-3} alkyl;

E is CR^{4e}; R^{4e} is a C_{1-6} alkoxy;

J is CR^{4j}; R^{4j} is a hydrogen;

ring Q' is a benzene or a 5-memebered heterocyclic ring; $(R^1)_{k1}$ represents that the hydrogens attached to the ring Q' are substituted by 0-k1 occurrences of R^1, at each occurrence the R^1 is the same or different from each other, and is each independently a halogen, -CN or a C_{1-12} alkyl;

R^5, R^6, R^7 and $R^{7'}$ are are each independently a hydrogen, a C_{1-6} alkyl, $-(CH_2)_{2-3}NH_2$, a C_{3-6} carbocyclic group or a C_{2-5} heterocyclic group, or R^5, R^6 and the nitrogen atom to which they are directly attached form a heterocyclic ring which is preferably optionally substituted by the substituent selected from the group consisting of: $-NR^7R^{7'}$, a C_{1-3} alkyl, a C_{3-6} carbocyclic group or a C_{2-5} heterocyclic group;

$(CR^8R^9)_m$ represents that 0 to m (CR^8R^9) are linked, R^8 and R^9 are the substituents attached to the formed carbon chain, wherein each R^8 and R^9 are the same or different from each other, and are each independently a hydrogen, a deuterium or a C_{1-3} alkyl;

m, k or k1 is independently 0 or 1.

11. The fused heterocyclic compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof as defined in claim 10, wherein in the formula III,

A_1 is N;

A_2 is N;

R^2 is $-(CR^8R^9)_mNR^5R^6$ or $-(CR^8R^9)_mOR^5$;

$(R^3)_k$ represents that the hydrogens attached to the morpholine ring are substituted by 0-k occurrences of R^3, at each occurrence the R^3 is the same or different from each other, and is each independently a hydrogen or a deuterium;

A is CR^{4a}; R^{4a} is a hydrogen;

E is CR^{4e}; R^{4e} is a C_{1-3} alkoxy;

J is CR^{4j}; R^{4j} is a hydrogen;

ring Q' is a benzene or a 5-membered heterocyclic ring, the 5-membered heterocyclic ring is a thiophene or an imidazole;

$(R^1)_{k1}$ represents that the hydrogens attached to the ring Q' are substituted by 0-k1 occurrences of R^1, at each occurrence the R^1 is the same or different from each other, and is each independently a C_{1-3} alkyl;

R^5, R^6, R^7 and $R^{7'}$ are each independently a hydrogen, a C_{1-3} alkyl, $-(CH_2)_{2-3}NH_2$, a

C_{3-6} carbocyclic group or a C_{2-5} heterocyclic group, or R^5, R^6 and the nitrogen atom to which they are directly attached form a heterocyclic ring which is preferably optionally substituted by the substituent selected from the group consisting of: -$NR^7R^{7'}$, a C_{1-3} alkyl, a C_{3-6} carbocyclic group or a C_{2-5} heterocyclic group; the C_{2-5} heterocyclic group is a piperidine, a pyran, a tetrahydropyrrole or an oxetane;

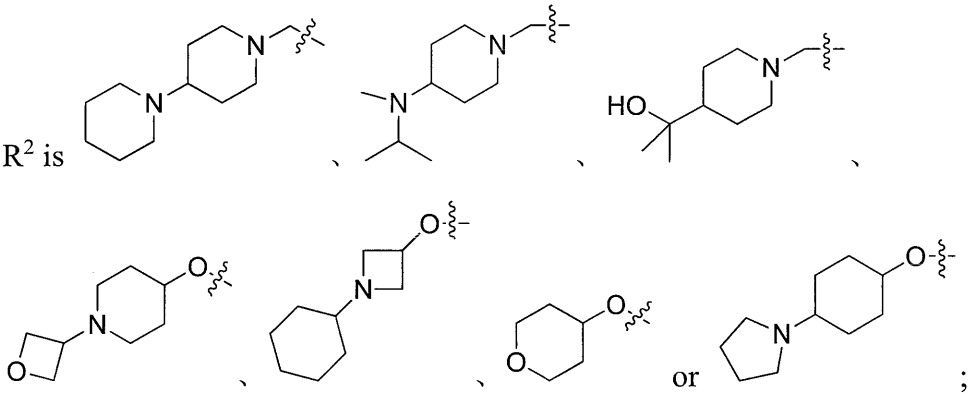
$(CR^8R^9)_m$ represents that 0 to m (CR^8R^9) are linked, R^8 and R^9 are the substituents attached to the formed carbon chain, wherein each R^8 and R^9 are the same or different from each other, and are each independently a hydrogen or a deuterium;

m, k or k1 is independently 0 or 1.

12. The fused heterocyclic compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof as defined in claim 11, wherein in the formula III,

A_1 is N;

A_2 is N;

R^2 is 

;

$(R^3)_k$ represents that the hydrogens attached to the morpholine ring are substituted by 0-k occurrences of R^3, at each occurrence the R^3 is the same or different from each other, and is each independently a hydrogen or a deuterium;

A is CR^{4a}; R^{4a} is a hydrogen;

E is CR^{4e}; R^{4e} is a methoxy;

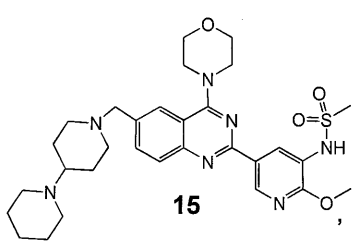
J is CR^{4j}; R^{4j} is a hydrogen;

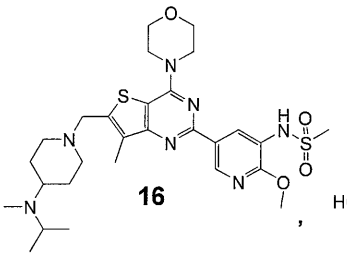
ring Q' is a benzene or a 5-membered heterocyclic ring, the 5-membered heterocyclic ring is a thiophene or an imidazole; $(R^1)_{k1}$ represents that the hydrogens attached to the ring Q' are substituted by 0-k1 occurrences of R^1, at each occurrence the R^1 is the same or different from each other, and is each independently a methyl;

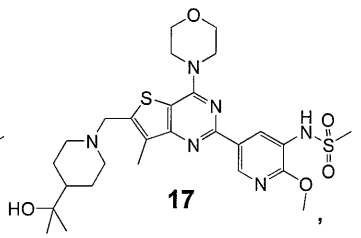
m, k or k1 is independently 0 or 1.

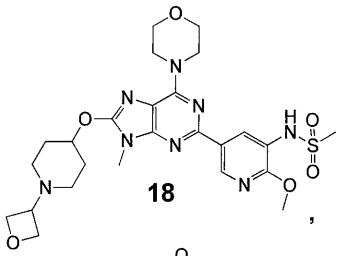
13. The fused heterocyclic compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof as defined in claim 1, wherein

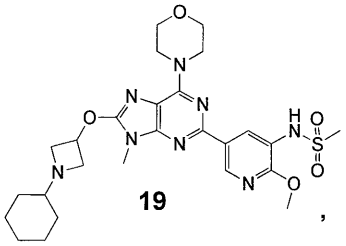
formula III is a compound selected from the group consisting of:

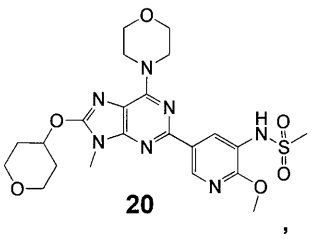

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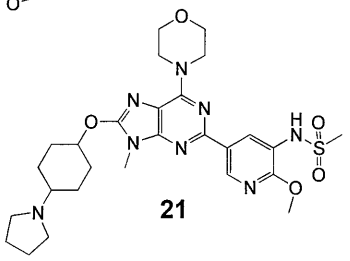

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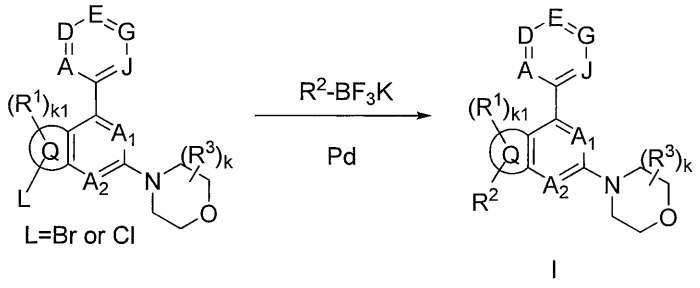

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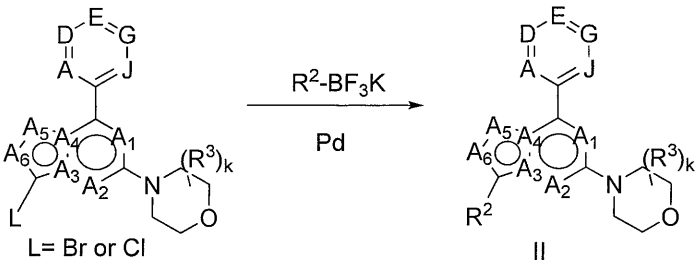

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14. A process for preparing the fused heterocyclic compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof as defined in any one of claims 1-13, wherein

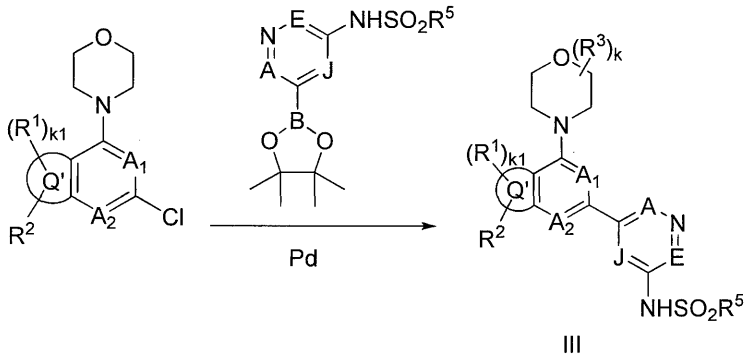
reaction route I comprises the following steps:



reaction route II comprises the following steps:

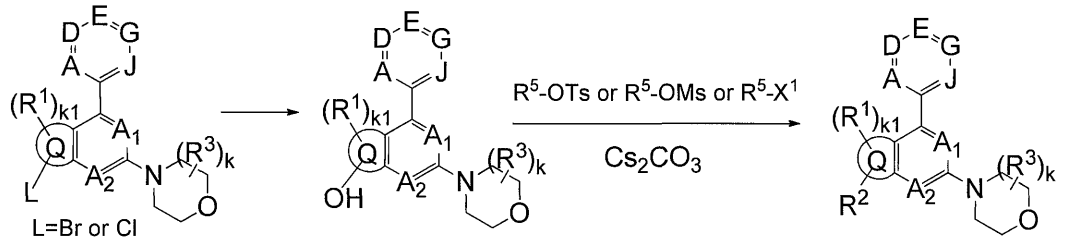


reaction route III comprises the following steps:



III

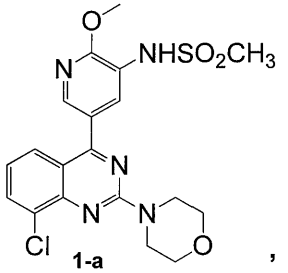
reaction route IV comprises the following steps:

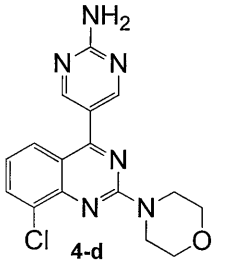


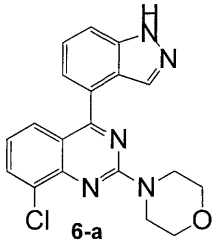
I

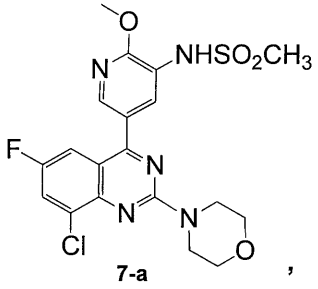
Wherein, when R^2 is $-O(CR^8R^9)_mCR^5R^6$ or $-O(CR^8R^9)_mNR^5R^6$ in the formula I, the reaction route IV is utilized to synthesis, when R^2 is not $-O(CR^8R^9)_mCR^5R^6$ or $-O(CR^8R^9)_mNR^5R^6$ in the formula I, the reaction route I is utilized to synthesis; X^1 is Cl, Br or I.

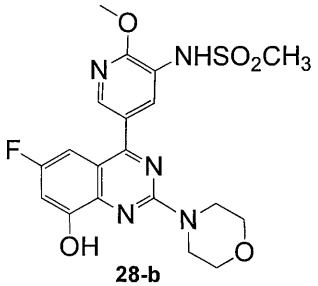
15. A compound as shown below:


1-a ,


4-d ,


6-a ,


7-a ,


28-b .

16. A pharmaceutical composition comprising a therapeutically effective dosage of the fused heterocyclic compound, pharmaceutically acceptable salt, hydrate, solvate,

polymorph and pro-drug thereof as defined in any one of claims 1 to 13, and a pharmaceutically acceptable carrier.

17. A use of the fused heterocyclic compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof as defined in any one of the claims 1 to 13, or the pharmaceutical composition as defined in claim 16 in manufacturing an inhibitor of kinase.

18. The use as defined in claim 17, wherein the kinase is PI3 kinase.

19. The use as defined in claim 18, wherein the kinase is p110 δ subtype of PI3 kinase.

20. A use of the fused heterocyclic compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph or pro-drug thereof as defined in any one of the claims 1 to 13, or the pharmaceutical composition as defined in claim 16 in manufacturing a medicament for treating and/or preventing a disease related to kinase.

21. The use as defined in claim 20, wherein the kinase is PI3 kinase.

22. The use as defined in claim 21, wherein the kinase is p110 δ subtype of PI3 kinase.

23. The use as defined in claim 20, wherein the "disease related to kinase" is a disease selected from the group consisting of cancer, immunological diseases, metabolic and/or endocrine dysfunction, angiocardiopathy, virus infections and inflammation, and nerve diseases.

24. The use as defined in claim 23, wherein the immunological disease is a disease selected from the group consisting of rheumatoid arthritis, psoriasis, ulcerative colitis, Crohn's disease and systemic lupus erythematosus; the angiocardiopathy is neoplastic hematologic disorder; the virus infection and inflammation is asthma and/or atopic dermatitis.