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本国际公布:
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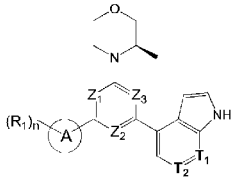
(54) **Title:** ATR INHIBITOR AND APPLICATION THEREOF

(54) **发明名称:** 一种ATR抑制剂及其应用



(I)

(57) **Abstract:** Disclosed are a compound as an ATR inhibitor and an application in preparing a drug as an ATR inhibitor. In particular, disclosed is a compound represented by formula (I) or an isomer or pharmaceutically acceptable salt thereof.

(57) **摘要:** 本发明公开了作为ATR抑制剂的一类化合物，以及在制备作为ATR抑制剂的药物中的应用。具体公开了式(Ⅰ)所示化合物、其异构体或其药学上可接受的盐。

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ATR INHIBITOR AND APPLICATION THEREOF

Cross Reference To Related Applications

The present application claims priority to the following applications:

Chinese Application No. 201810124494.2, filed on February 7, 2018.

Chinese Application No. 201811361512.5, filed on November 15, 2018.

Technical Field

Provided are compounds as ATR inhibitor and use thereof for the manufacture of ATR inhibitor and particularly, a compound of formula (I), an isomer or a pharmaceutically acceptable salt thereof.

Background

ATR (Ataxia Telangiectasia-mutated and Rad3-Related protein kinase) belongs to the PIKKs (phosphatidylinositol-3-kinase-related kinase) family and participates in DNA damage repair to maintain gene stability. ATR protein kinase has a synergistic response on DNA damage, replication stress and cell cycle disturbances. ATR and ATM belong to the PIKK family of serine/threonine protein kinases, and they are common component of the cell cycle and DNA damage repairing, and other members include Chkl, BRCAl, p53. ATR is mainly responsible for DNA replication stress (duplication fork arrest) and repair of single strand break.

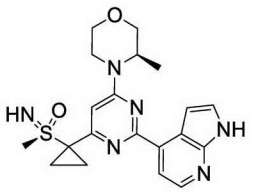
When the double-stranded DNA breaks and the replication fork arrests, ATR is activated by the single-stranded DNA structure. DNA polymerase stays in the process of DNA replication, and the replication helicase continues to unwind at the leading end of the DNA replication fork, resulting in the production of long single-stranded DNA (ssDNA), which is then bound by the single-stranded DNA and RPA (replication protein A). ATR/ATR acting protein complex is recruited by RPA upon replication stress or DNA damage to the damage site, RPA-single-stranded DNA complex activates the RAD17/rfc2-5 complex to bind to the damage site, DNA-ssDNA junction activates Rad9-HUS1-RAD1 (9-1-1) heterotrimer, 9-1-1 in turn recruits TopBP1 to activate ATR. Once ATR is activated, ATR promotes DNA repair through downstream targets, stabilizing and restarting arrested replication forks and transient cell cycle arrest. These functions are achieved by ATR via mediating the downstream target Chk1. ATR acts as checkpoint for DNA damage in the cell cycle during S phase. It can mediate the degradation of CDC25A through Chk1, thereby delaying the DNA replication process and providing time to repair the replication fork. ATR is also the main regulator of G2/M cell cycle checkpoint, preventing cells from entering mitosis prematurely before DNA replication is completed or DNA damage. This ATR-dependent G2/M cell cycle arrest is mainly mediated by two mechanisms: 1. Degradation of CDC25A; 2. Phosphorylation of Cdc25C by Chk1 to bind to 14-3-protein. The binding of Cdc25C to 14-3-3 protein promotes its export from the nucleus and cytoplasmic isolation, thereby inhibiting its ability to dephosphorylate and activate nuclear Cdc2, which in turn prevents entry into mitosis.

ATR gene mutations are very rare, and only few patients with Seckel syndrome have ATR gene mutations, which are characterized by stunting and microcephaly. Disruption of ATR-related pathways can lead to genome instability, and ATR protein is activated by most cancer chemotherapy. In addition, the

duplication of the ATR gene has been described as a risk factor for rhabdomyosarcoma.

ATR is essential for cell self-replication and is activated in the S phase to regulate the origin of replication and repair damaged replication forks. Damage to the replication forks can increase the sensitivity of cancer cells to platinum and hydroxyurea anticancer agents and reduce the resistance of cancer cells. Therefore, inhibiting ATR may be an effective method in cancer treatment in the future.

WO2011154737 discloses Compound AZD6738 as ATR inhibitor having the following structure:

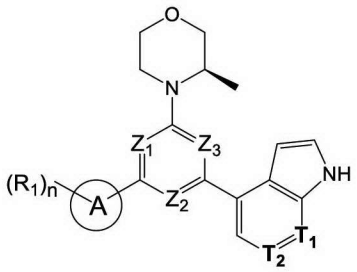


AZD6738

Any reference to or discussion of any document, act or item of knowledge in this specification is included solely for the purpose of providing a context for the present invention. It is not suggested or represented that any of these matters or any combination thereof formed at the priority date part of the common general knowledge, or was known to be relevant to an attempt to solve any problem with which this specification is concerned.

Summary

In a first aspect, provided is a compound of formula (I), or a tautomer or a pharmaceutically acceptable salt thereof,



(I)

wherein,

n is 1, 2, 3 or 4;

Z_1, Z_2, and Z_3 are each independently selected from the group consisting of CH and N, and at least one of Z_1, Z_2 and Z_3 is N;

T_1, and T_2 are each independently selected from the group consisting of $C(R_2)$ and N;

ring A is selected from the group consisting of 5-6 membered heteroaryl;

R_1 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, C_{1-6} alkyl, C_{1-6} alkoxy and C_{3-6} cycloalkyl, wherein the C_{1-6} alkyl, C_{1-6} alkoxy and C_{3-6} cycloalkyl are optionally substituted by 1, 2 or 3 R;

R_2 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, COOH and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by 1, 2 or 3 R;

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R is each independently selected from the group consisting of F, Cl, Br, I, OH, NH_2, C_{1-3} alkyl and C_{1-3} alkoxy, wherein the C_{1-3} alkyl and C_{1-3} alkoxy are optionally substituted by 1, 2 or 3 R';

R' is each independently selected from the group consisting of F, Cl, Br, I, OH and NH_2;

the 5-6 membered heteroaryl comprises 1, 2, 3 or 4 heteroatoms or heteroradicals independently selected from the group consisting of -NH-, -O-, -S- and N;

provided that the compound of formula (I) is not:

(3R)-3-methyl-4-[6-(pyridin-3-yl)-2-[1H-pyrrolo[2,3-b]pyridin-4-yl]pyrimidin-4-yl]morpholine,

(R)-4-(2-(1H-pyrrolo[2,3-b]pyridin-4-yl)-6-(6-(trifluoromethyl)pyridin-3-yl)pyrimidin-4-yl)-3-methylmorpholine, or

(R)-5-(6-(3-methylmorpholino)-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)pyrimidin-4-yl)pyridin-2-amine.

In some embodiments according to the present disclosure, R is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, CH_3, Et and -O-CH_3, and other variables are defined as herein.

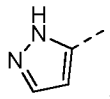
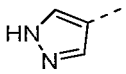
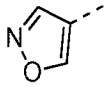
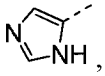
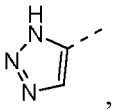
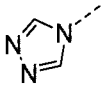
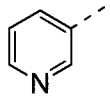
In some embodiments according to the present disclosure, R_1 is each independently selected from the

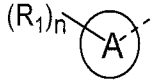
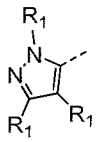
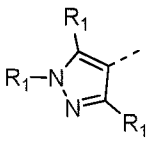
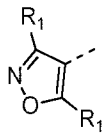
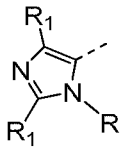
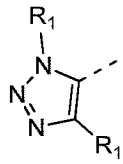
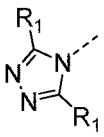
group consisting of H, F, Cl, Br, I, OH, NH_2, C_{1-3} alkyl, C_{1-3} alkoxy and cyclopropyl, wherein the C_{1-3} alkyl, C_{1-3} alkoxy and cyclopropyl are optionally substituted by 1, 2 or 3 R, and other variables are defined as herein.

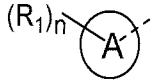
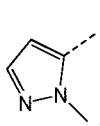
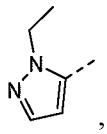
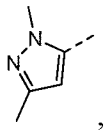
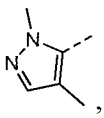
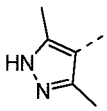
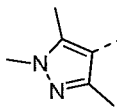
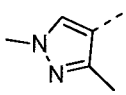
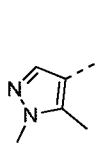
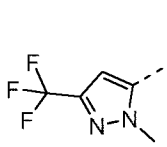
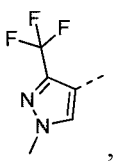
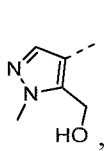
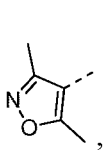
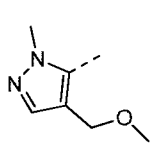
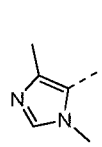
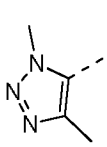
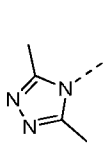
In some embodiments according to the present disclosure, R_1 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, CH_3, CH_2F, CHF_2, CF_3, Et, -CH_2OH, -O-CH_3,  and  , and other variables are defined as herein.

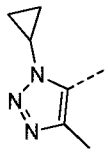
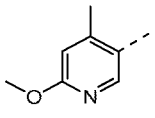
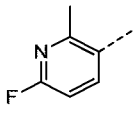
In some embodiments according to the present disclosure, R_2 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, COOH, CH_3, Et and -CH_2-OH, and other variables are defined as herein.

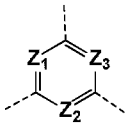
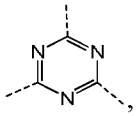
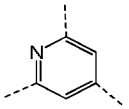
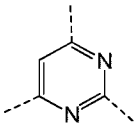
In some embodiments according to the present disclosure, ring A is selected from the group consisting of pyrazolyl, isoxazolyl, oxazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl and pyridyl, and other variables are defined as herein.

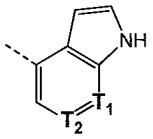
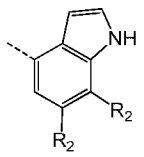
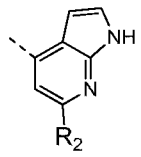
In some embodiments according to the present disclosure, ring A is selected from the group consisting of  ,  ,  ,  ,  ,  and  , and other variables are defined as herein.

In some embodiments according to the present disclosure, the structural unit  is selected from the group consisting of  ,  ,  ,  ,  ,  and  , and other variables are defined as herein.

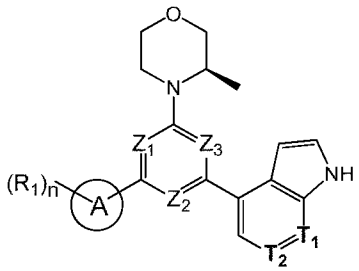
In some embodiments according to the present disclosure, the structural unit  is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

 ,  and  , and other variables are defined as herein.

In some embodiments according to the present disclosure, the structural unit  is selected from the group consisting of  ,  and  , and other variables are defined as herein.

In some embodiments according to the present disclosure, the structural unit  is selected from the group consisting of  and  , and other variables are defined as herein.

Provided is also a compound of formula (I) or an isomer or a pharmaceutically acceptable salt thereof,



(I)

wherein,

n is 1, 2, 3 or 4;

Z_1, Z_2, and Z_3 are each independently selected from the group consisting of CH and N, and at least one of Z_1, Z_2 and Z_3 is N;

T_1, and T_2 are each independently selected from the group consisting of $C(R_2)$ and N;

ring A is selected from the group consisting of 5-6 membered heteroaryl;

R_1 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, C_{1-6} alkyl, C_{1-6} alkoxy and C_{3-6} cycloalkyl, wherein the C_{1-6} alkyl, C_{1-6} alkoxy and C_{3-6} cycloalkyl are optionally substituted by 1, 2 or 3 R;

R_2 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2 and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by 1, 2 or 3 R;

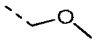
R is each independently selected from the group consisting of F, Cl, Br, I, OH, NH_2, C_{1-3} alkyl and C_{1-3} alkoxy, wherein the C_{1-3} alkyl and C_{1-3} alkoxy are optionally substituted by 1, 2 or 3 R';

R' is each independently selected from the group consisting of F, Cl, Br, I, OH and NH_2;

the 5-6 membered heteroaryl comprises 1, 2, 3 or 4 heteroatoms or heteroradicals independently selected from the group consisting of -NH-, -O-, -S- and N.

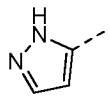
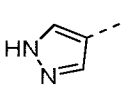
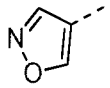
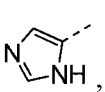
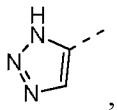
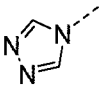
In some embodiments according to the present disclosure, R is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, CH_3, Et and -O-CH_3, and other variables are defined as herein.

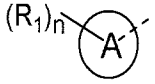
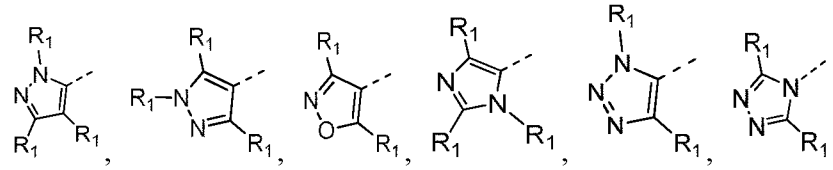
In some embodiments according to the present disclosure, R_1 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, C_{1-3} alkyl, C_{1-3} alkoxy and cyclopropyl, wherein the C_{1-3} alkyl, C_{1-3} alkoxy and cyclopropyl are optionally substituted by 1, 2 or 3 R, and other variables are defined as herein.

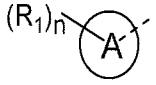
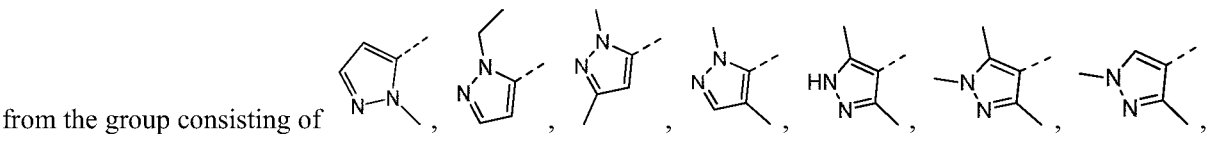
In some embodiments according to the present disclosure, R_1 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, CH_3, CH_2F, CHF_2, CF_3, Et, -CH_2OH, -O-CH_3,  and  , and other variables are defined as herein.

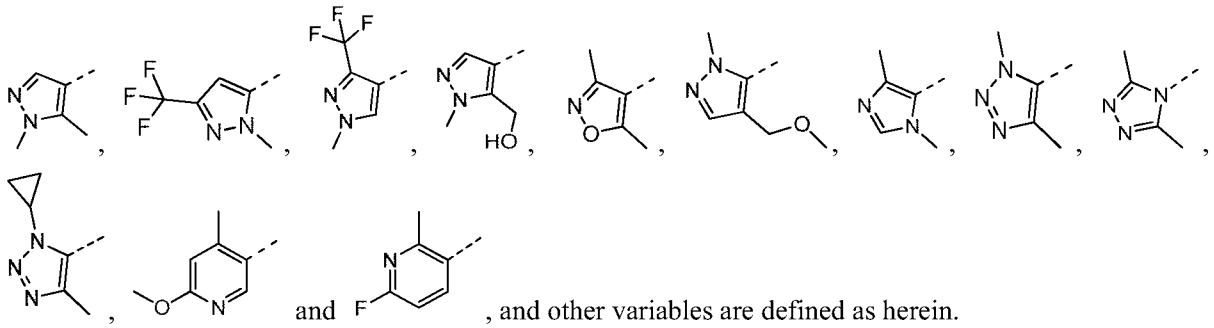
In some embodiments according to the present disclosure, R_2 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, CH_3, Et and -CH_2-OH, and other variables are defined as herein.

In some embodiments according to the present disclosure, ring A is selected from the group consisting of pyrazolyl, isoxazolyl, oxazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl and pyridyl, and other variables are defined as herein.

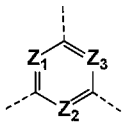
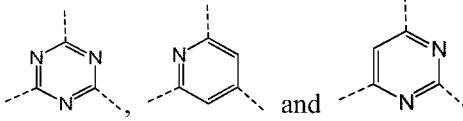
In some embodiments according to the present disclosure, ring A is selected from the group consisting of  ,  ,  ,  ,  ,  and  , and other variables are defined as herein.

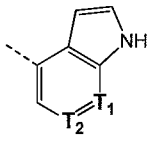
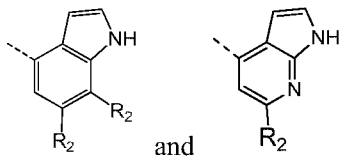
In some embodiments according to the present disclosure, the structural unit  is selected from the group consisting of  , and other variables are defined as herein.

In some embodiments according to the present disclosure, the structural unit  is selected from the group consisting of  , and other variables are defined as herein.

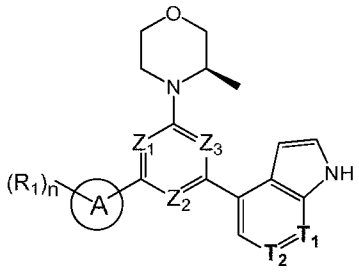


and , and other variables are defined as herein.

In some embodiments according to the present disclosure, the structural unit  is selected from the group consisting of  , and other variables are defined as herein.

In some embodiments according to the present disclosure, the structural unit  is selected from the group consisting of  and , and other variables are defined as herein.

Provided is further a compound of formula (I) or an isomer or a pharmaceutically acceptable salt thereof,



(I)

wherein,

n is 1, 2, 3 or 4;

Z_1, Z_2, and Z_3 are each independently selected from the group consisting of CH and N, and at least one of Z_1, Z_2 and Z_3 is N;

T_1, and T_2 are each independently selected from the group consisting of $C(R_2)$ and N;

ring A is selected from the group consisting of 5-6 membered heteroaryl;

R_1 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2 and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by 1, 2 or 3 R;

R_2 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2 and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by 1, 2 or 3 R;

R is each independently selected from the group consisting of F, Cl, Br, I, OH, NH_2 and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by 1, 2 or 3 R';

R' is each independently selected from the group consisting of F, Cl, Br, I, OH and NH_2;

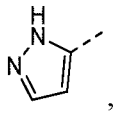
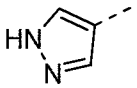
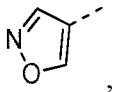
the 5-6 membered heteroaryl comprises 1, 2, 3 or 4 heteroatoms or heteroradicals independently selected from the group consisting of -NH-, -O-, -S- and N.

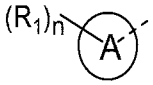
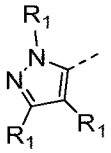
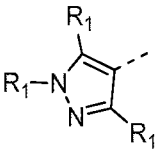
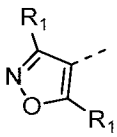
In some embodiments according to the present disclosure, R is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, CH_3 and Et, and other variables are defined as herein.

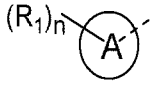
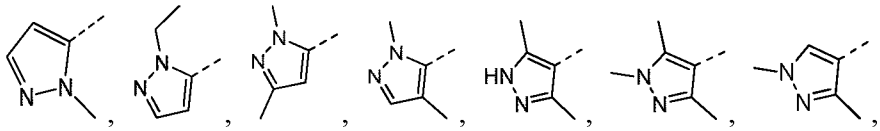
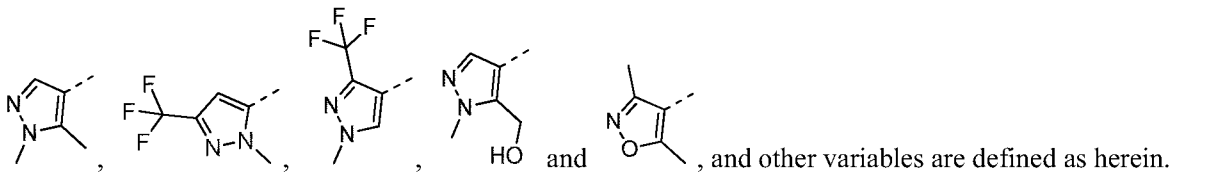
In some embodiments according to the present disclosure, R_1 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, CH_3, CH_2F, CHF_2, CF_3, Et and $-CH_2OH$, and other variables are defined as herein.

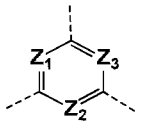
In some embodiments according to the present disclosure, R_2 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, CH_3 and Et, and other variables are defined as herein.

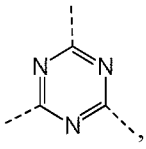
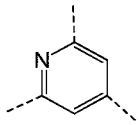
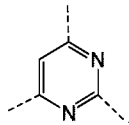
In some embodiments according to the present disclosure, ring A is selected from the group consisting of pyrazolyl, isoxazolyl, oxazolyl and imidazolyl, and other variables are defined as herein.

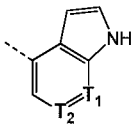
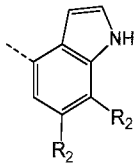
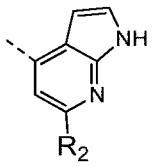
In some embodiments according to the present disclosure, ring A is selected from the group consisting of  ,  and  , and other variables are defined as herein.

In some embodiments according to the present disclosure, the structural unit  is selected from the group consisting of  ,  and  , and other variables are defined as herein.

In some embodiments according to the present disclosure, the structural unit  is selected from the group consisting of  ,  , , and , and other variables are defined as herein.

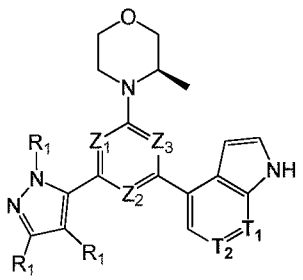
In some embodiments according to the present disclosure, the structural unit  is selected

from the group consisting of  ,  and  , and other variables are defined as herein.

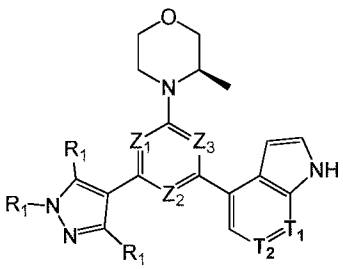
In some embodiments according to the present disclosure, the structural unit  is selected from the group consisting of  and  , and other variables are defined as herein.

Some embodiments of the present disclosure are derived from the combination of the above variables

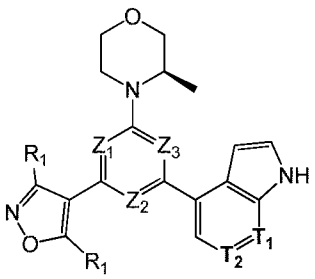
In some embodiments according to the present disclosure, provided is the above compound or the isomer thereof or the pharmaceutically acceptable salt, selected from



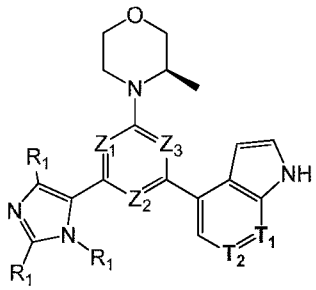
(II -1)



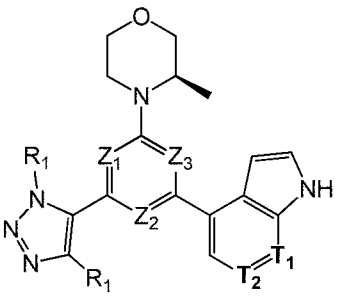
(II -2)



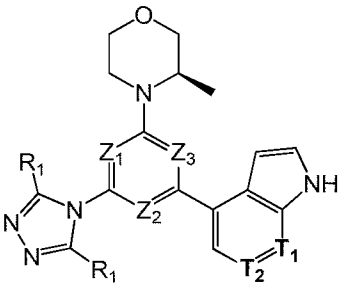
(II -3)



(II -4)

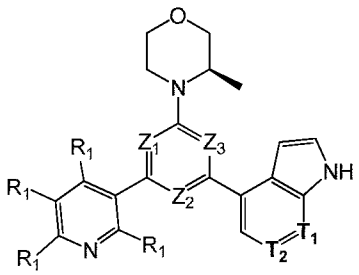


(II -5)



(II -6)

and



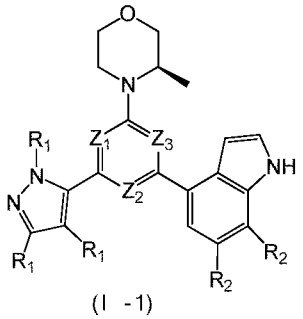
(II -7) ,

wherein,

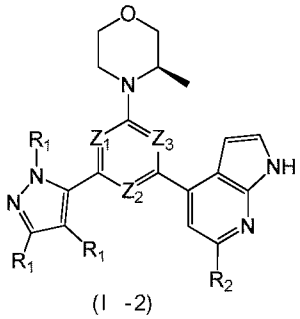
T_1, and T_2 are each independently selected from the group consisting of $C(R_2)$ and N;

R_1, R_2, Z_1, Z_2 and Z_3 are defined as herein.

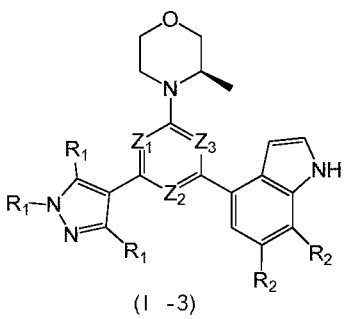
In some embodiments according to the present disclosure, provided is the above compound or the isomer thereof or the pharmaceutically acceptable salt, selected from



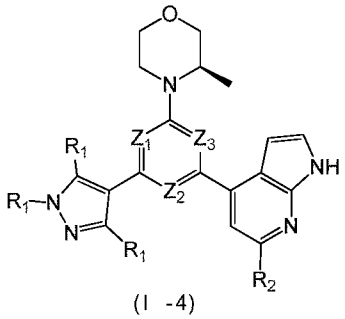
(I -1)



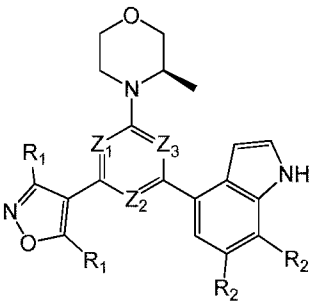
(I -2)



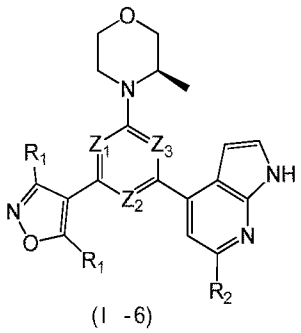
(I -3)



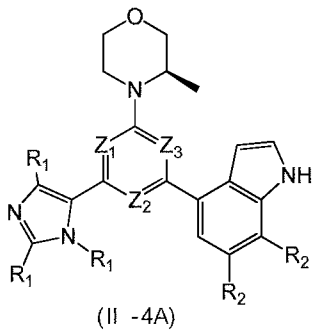
(I -4)



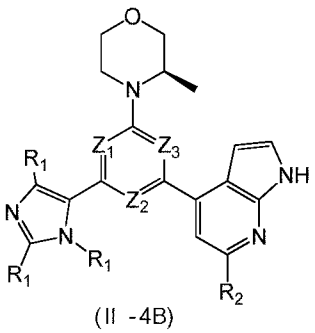
(I -5)



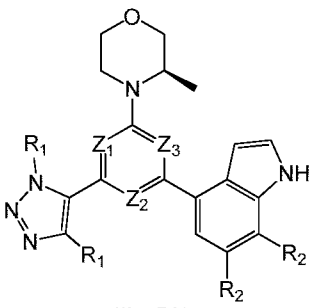
(I -6)



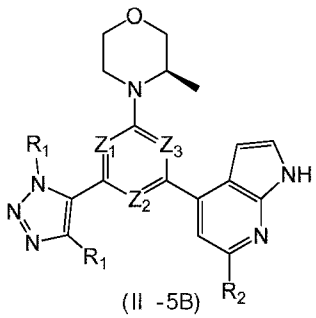
(II -4A)



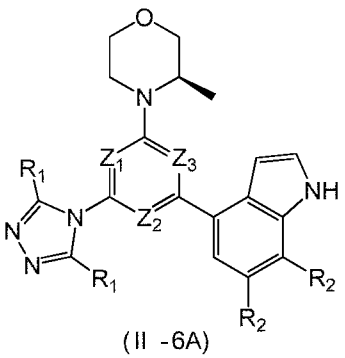
(II -4B)



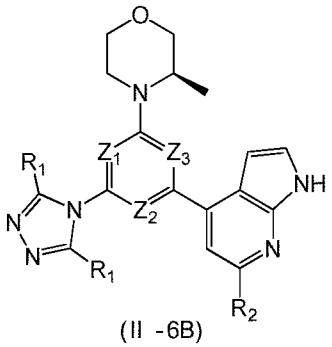
(II -5A)



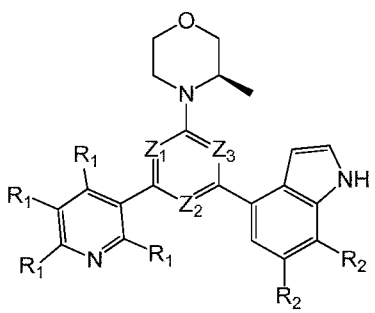
(II -5B)



(II -6A)

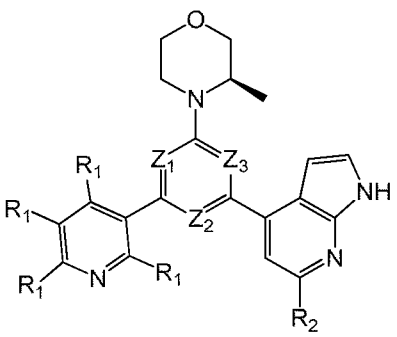


(II -6B)



(II -7A)

and



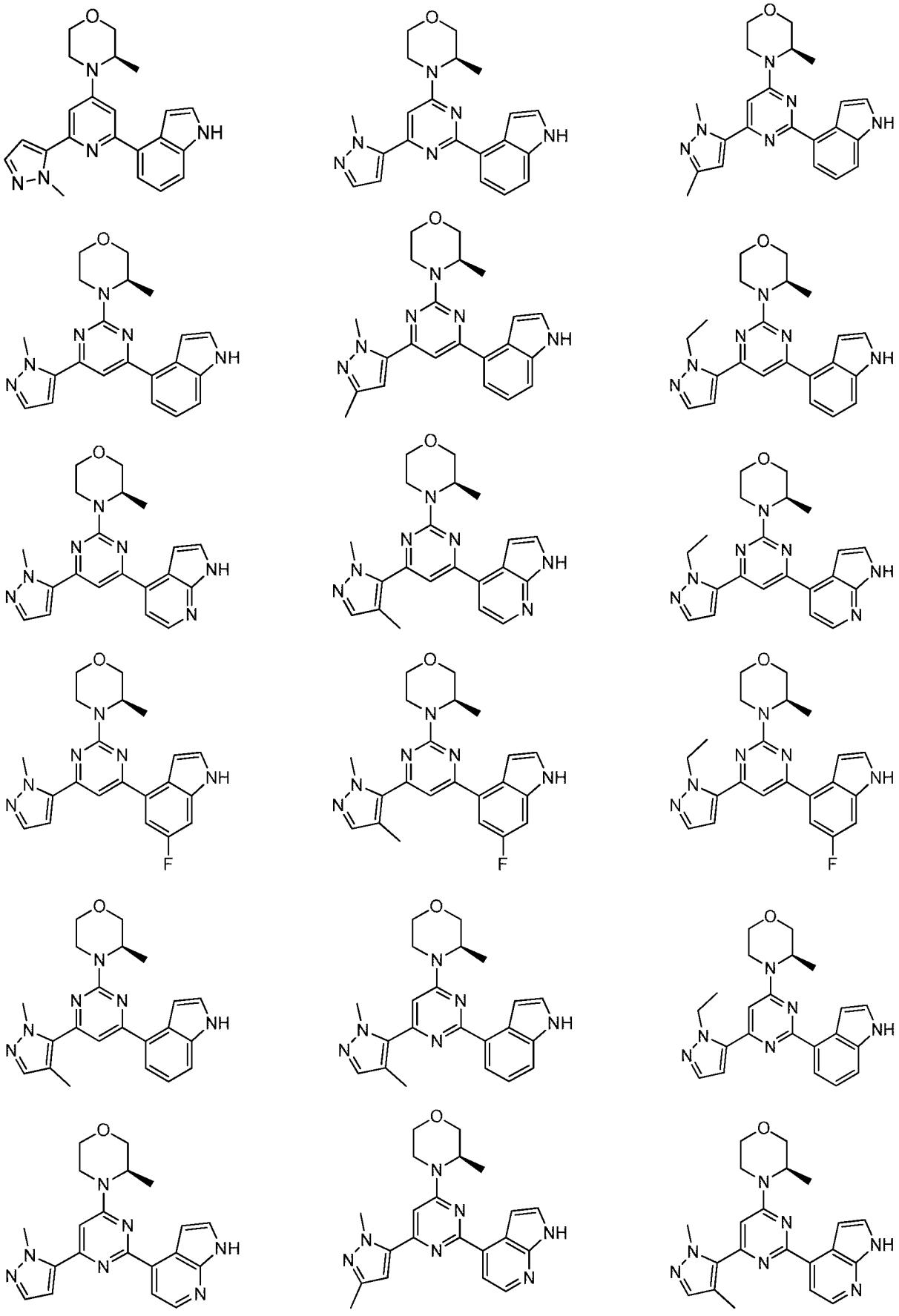
(II -7B)

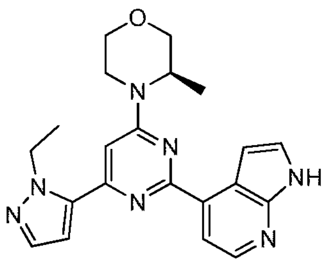
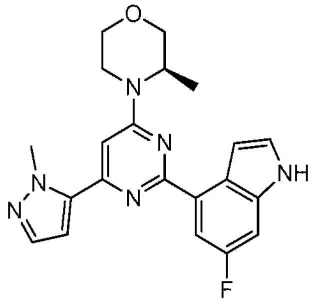
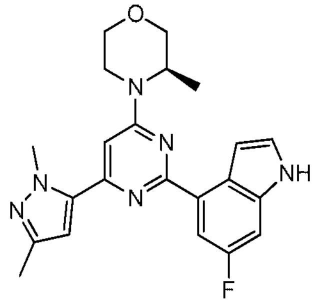
,

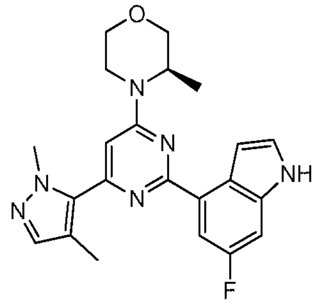
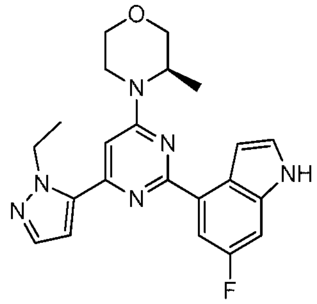
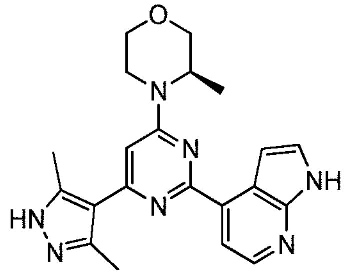
wherein,

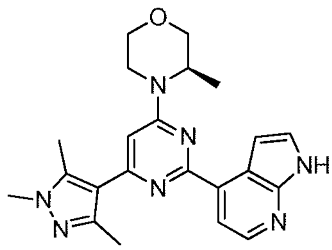
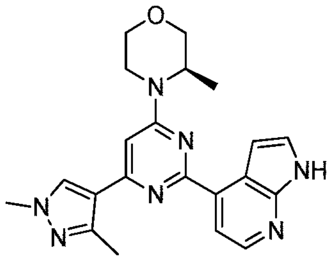
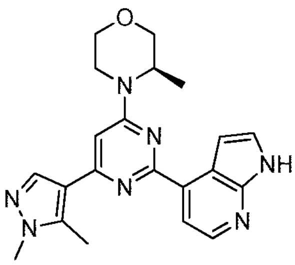
R_1, R_2, Z_1, Z_2 and Z_3 are defined as herein.

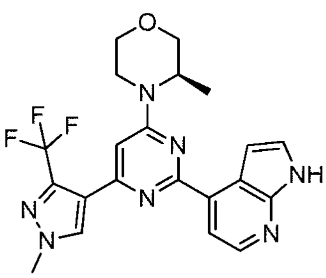
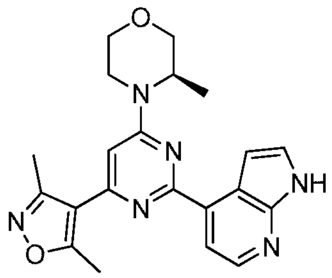
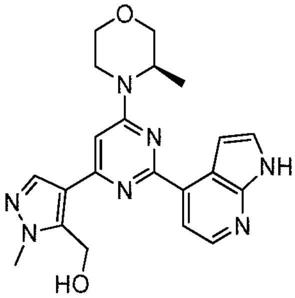
Provided is also the following compound or an isomer or a pharmaceutically acceptable salt thereof

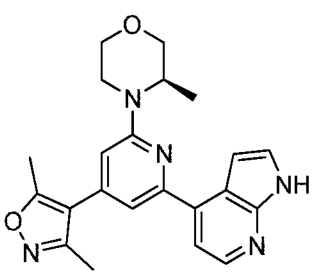
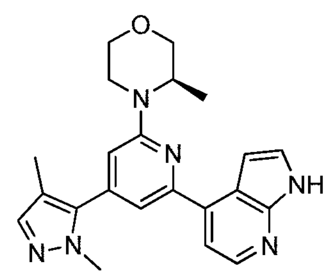
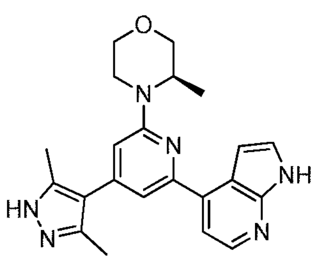


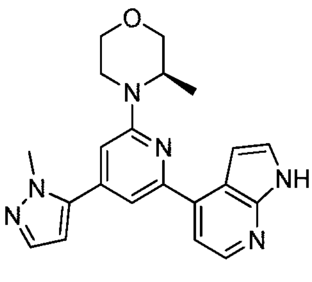
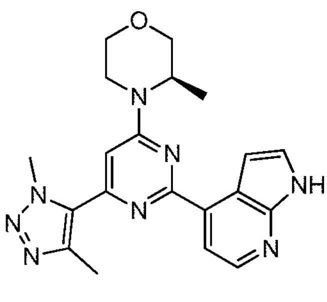
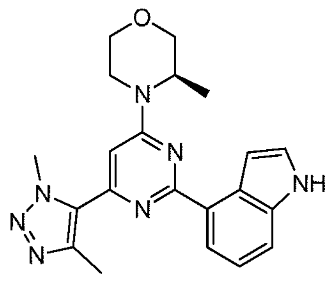




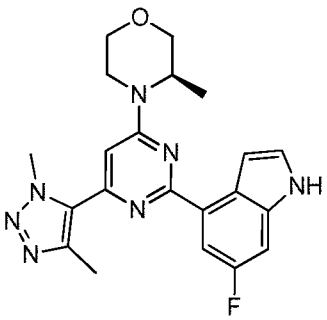
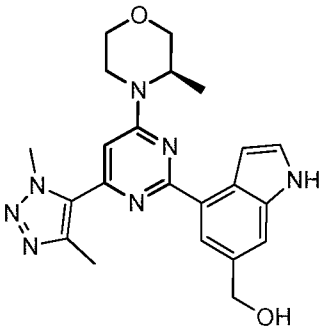
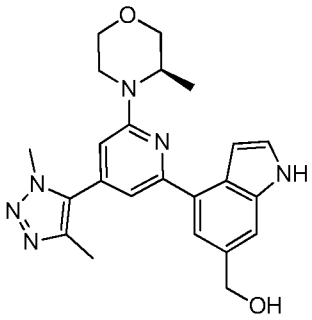
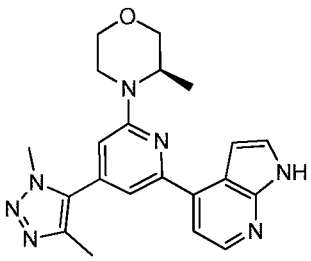
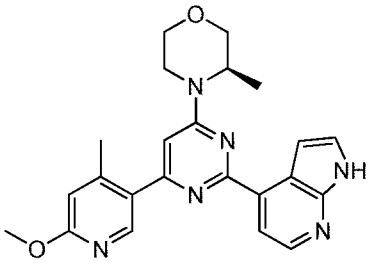
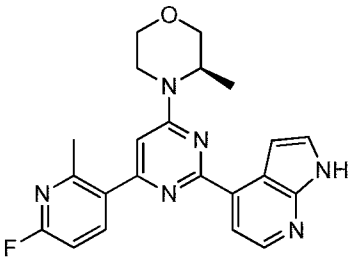
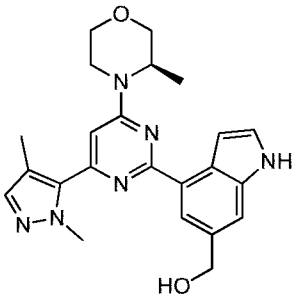
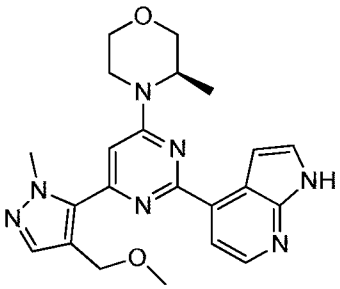
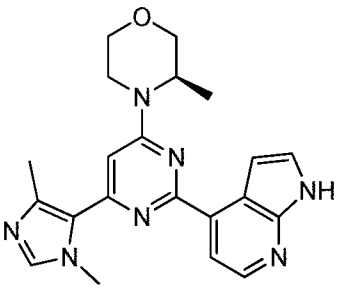
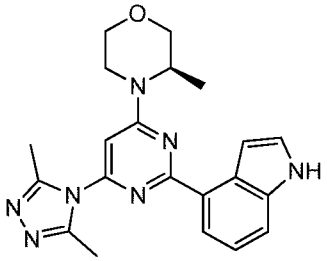
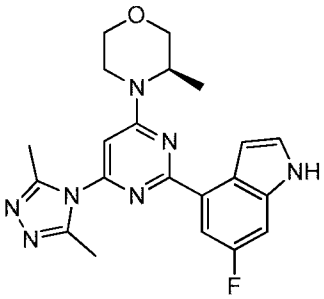
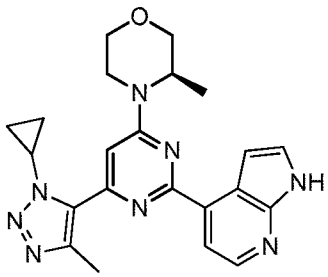
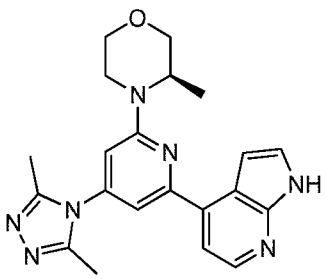
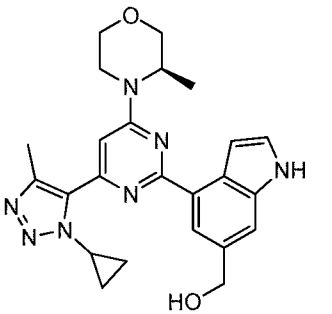
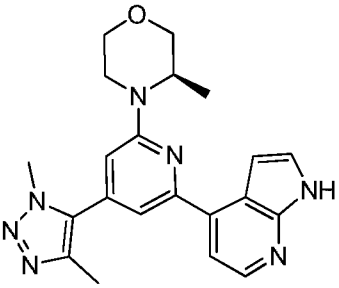




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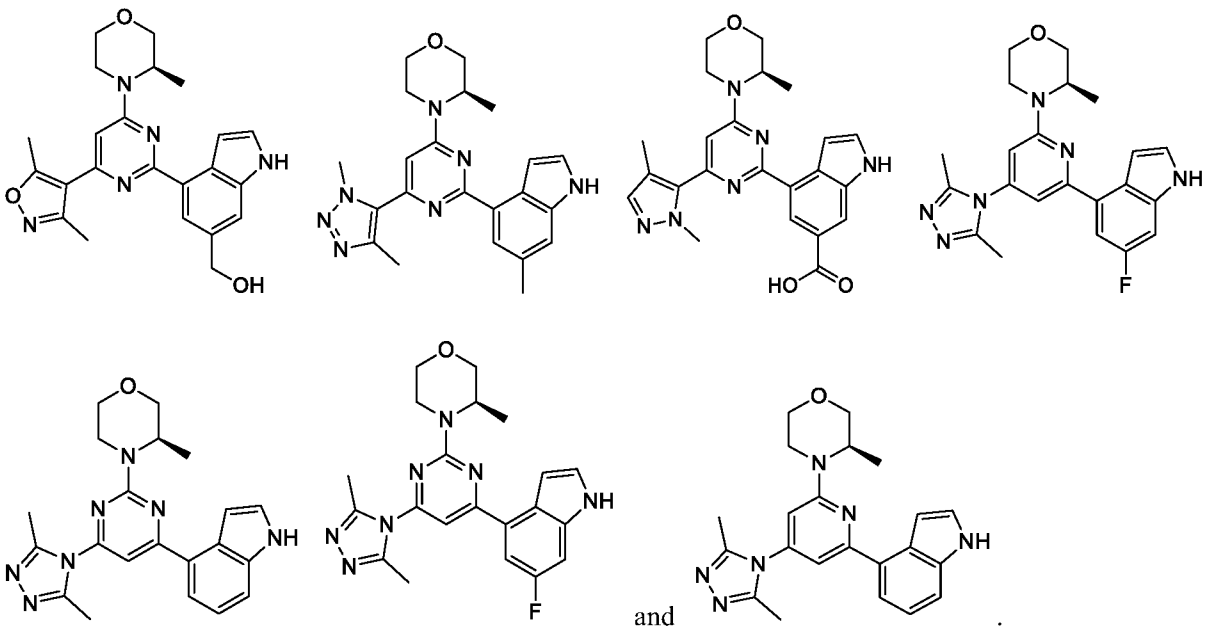

and .

In a second aspect, the present invention relates to a pharmaceutical composition comprising a compound of formula (I) or a tautomer or a pharmaceutically acceptable salt thereof according to the first aspect of the invention, and a pharmaceutically acceptable excipient.

In another aspect, provided is use of the above compound or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating an ATR associated disease.

In some embodiments according to the present disclosure, the medicament is used in treating solid tumor or hematologic tumor.

In another aspect, the present invention relates to use of the compound or a tautomer or a pharmaceutically acceptable salt thereof according to the first aspect of the invention or the pharmaceutical composition according to the second aspect of the invention for the manufacture of a medicament for treating an ATR associated disease; wherein the ATR associated disease is a solid tumor or a hematologic tumor.

In another aspect, the present invention relates to a method for treating an ATR associated disease, comprising administering the compound of formula (I) or the tautomer or the pharmaceutically acceptable salt thereof according to the first aspect of the invention, or the pharmaceutical composition according to the second aspect of the invention to a subject in need thereof; wherein the ATR associated disease is a solid tumor or a hematologic tumor.

Technical Effect

As a novel ATR inhibitor, the present compounds have good inhibitory activity against ATR kinase. Moreover, they show good tumor suppressing effects in animal models and have the potential as novel anti-tumor agents.

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Definition and description

Unless stated otherwise, the following terms and phrases have the following definitions. A specific term or phrase should not be considered as indefinite or unclear without specific definition and should be understood according to the normal meanings. A tradename used herein shall refer to the corresponding article or the active ingredient.

For the avoidance of doubt, in this specification, the terms 'comprises', 'comprising', 'includes', 'including', or similar terms are intended to mean a non-exclusive inclusion, such that a method, system or apparatus that comprises a list of elements does not include those elements solely, but may well include other elements not listed.

The term "pharmaceutically acceptable" means that, for the compounds, materials, compositions and/or dosage form, with reliable medical judgement, they are suitable for use in contact with tissues of humans and animals without excessive toxicity, irritation, allergic reaction or other problems or complications and commensurate with a reasonable benefit/risk ratio.

The term "pharmaceutically acceptable salt" refers to a salt of the compound of the present disclosure, which is prepared using a compound found in the present disclosure which has a specific substituent with a

relatively non-toxic acid or base. When the compound of the present disclosure contains a relatively acidic functional group, the base addition salt can be obtained by contacting the neutral form of such compound with a sufficient amount of base in a pure solution or a suitable inert solvent. Pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amine or magnesium salt or the like. When the compound of the present disclosure contains a relatively basic functional group, the acid addition salt can be obtained by contacting the neutral form of such compound with a sufficient amount of acid in a pure solution or a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include inorganic acid salts including, for example, hydrochloric acid, hydrobromic acid, nitric acid, carbonic acid, bicarbonate, phosphoric acid, monohydrogen phosphate, dihydrogen phosphate, sulfuric acid , hydrogen sulfate, hydroiodic acid, phosphorous acid, etc.; and organic acid salts including, for example, acetic acid, propionic acid, isobutyric acid, maleic acid, malonic acid, benzoic acid, succinic acid, suberic acid, fumaric acid, lactic acid, mandelic acid, phthalic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, citric acid, tartaric acid, methanesulfonic acid, etc.; and also includes salts of amino acids (such as arginine, etc.), and salts of organic acids such as glucuronic acid. Some specific compounds of the present disclosure contain basic and acidic functional groups, which can be converted to any base or acid addition salt.

The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound containing acid radicals or basic groups by conventional chemical processes. In general, the preparation process of such salts is: in water or an organic solvent or a mixture thereof, by reacting these compounds in free acid or base form with a stoichiometric amount of appropriate base or acid.

The compounds of the present disclosure may exist in specific geometric or stereoisomer forms. The present disclosure encompasses all such compounds, including cis and trans isomers, (-)- and (+)-enantiomers, (*R*)- and (*S*)-enantiomers, diastereomers, (*D*)-isomer, (*L*)-isomer, and their racemic mixtures and other mixtures, such as enantiomer or diastereomer-enriched mixtures. All of these mixtures are included within the scope of the present disclosure. There may be additional asymmetric carbon atoms in alkyl and other substituents. All these isomers and mixtures thereof are included in the scope of the present disclosure.

Unless stated otherwise, the term “enantiomer” or “optical isomer” refers to stereoisomers that are mirror images to each other.

Unless stated otherwise, the term “cis-trans isomer” or “geometric isomer” is caused by a double bond or a single bond of the ring-forming carbon atom which cannot rotate freely.

Unless stated otherwise, the term “diastereomer” refers to a stereoisomer in which the molecule has two or more chiral centers and there is a non-mirror relationship between the molecules.

Unless stated otherwise, “(*D*)” or “(+)” means right-handed, “(*L*)” or “(-)” means left-handed, and “(*DL*)” or “(±)” means racemic.

Unless stated otherwise, the wedge-shaped solid line bond () and the wedge-shaped dotted line bond () indicate the absolute configuration of a stereocenter; the straight solid line bond () and the straight dotted line bond () indicate the relative configuration of a stereocenter; and the wavy line () indicates a wedge-shaped solid line bond () or a wedge-shaped dotted line bond (), or a wavy line () indicates

a straight solid line bond () and a straight dotted line bond ().

The present compounds may be present in particular tautomeric forms. Unless stated otherwise, the term "tautomer" or "tautomeric form" means that at room temperature, different functional groups of an isomer are in dynamic equilibrium and can be transformed to each other quickly. If a tautomer is possible (e.g., in solution), the chemical equilibrium of tautomers can be achieved. For example, proton tautomer (also known as prototropic tautomer) includes interconversion through protolysis, such as ketone-enol isomerization and imine-enamine isomerization. The valence tautomer includes some recombination of bonding electrons for interconversion. A specific example of keto-enol tautomerization is the interconversion between two tautomers pentane-2,4-dione and 4-hydroxypent-3-en-2-one.

Unless stated otherwise, the term "enriched with an isomer", "isomer enriched", "enriched with an enantiomer" or "enantiomerically enriched" means that the content of an isomer or enantiomer is less than 100%, and the content of the isomer or enantiomer is 60% or more, or 70% or more, or 80% or more, or 90% or more, or 95% or more, or 96% or more, or 97% or more, or 98% or more, or 99% or more, or 99.5% or more, or 99.6% or more, or 99.7% or more, or 99.8% or more, or 99.9% or more.

Unless stated otherwise, the term "isomer excess" or "enantiomeric excess" refers to the difference between the relative percentages of two isomers or two enantiomers. For example, if the content of one isomer or enantiomer is 90% and the content of the other isomer or enantiomer is 10%, the excess of isomer or enantiomer (ee value) is 80%.

The optically active (*R*)- and (*S*)-isomers and *D* and *L* isomers can be prepared by chiral synthesis or chiral reagents or other conventional techniques. If an enantiomer of a compound of the present disclosure is desired, it can be prepared by asymmetric synthesis or derivatization with a chiral auxiliary, wherein the resulting mixture of diastereomers is separated and the auxiliary group is cleaved to provide pure and required enantiomer. Alternatively, when the molecule contains a basic functional group (such as amino) or an acidic functional group (such as, carboxyl group), a diastereomer salt is formed with an appropriate optically active acid or base, and the diastereomer resolution is performed by conventional processes known in the art, and then the pure enantiomer is recovered. In addition, the separation of enantiomers and diastereomers is usually accomplished by using chromatography, which employs a chiral stationary phase optionally with chemical derivatization processes (e.g., carbamate formation from amine). The present compounds may contain unnatural proportions of atomic isotopes at one or more of the atoms constituting the compound. For example, compounds can be labeled with radioactive isotopes, such as tritium (^{3}H), iodine-125 (^{125}I) or C-14 (^{14}C). As another example, hydrogen can be replaced by heavy hydrogen to form a deuterated drug. The bond formed by deuterium and carbon is stronger than that formed by ordinary hydrogen and carbon. Compared with non-deuterated drugs, the deuterated drugs have advantages such as less side effects, increased stability, improved efficacy, prolonged biological half-life and the like. Alternation of all the radioisotopes of the compound, either radioactive or not, is encompassed within the scope of the invention.

"Optional" or "optionally" means that the subsequently described event or condition may but does not necessarily occur, and the description includes the situation in which the event or condition occurs and the situation in which the event or condition does not occur.

The term "substituted" means any one or more hydrogen atoms on a specific atom are replaced by a

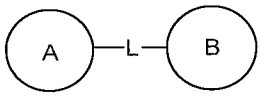
substituent, which may include heavy hydrogen and hydrogen variants, provided that the valence state of the specific atom is normal and the compound after substitution is stable. A substituent as oxygen (i.e. = O) means two hydrogen atoms are substituted. Oxygen substitution will not occur on an aromatic group. The term "optional substitution" or "optionally substituted" encompasses the cases that being unsubstituted or substituted. Unless stated otherwise, the type and number of substituents may be arbitrary given that they can be achieved chemically.

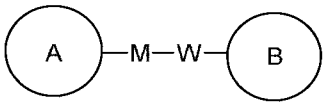
When any variable (e.g., R) appears more than once in the composition or structure of a compound, it is defined independently in each case. Thus, for example, if a group is substituted with 0-2 R, the group can be optionally substituted with at most two R, and R in each case has independent options. In addition, combinations of substituents and/or their variants are allowed provided that such combinations will produce stable compounds.

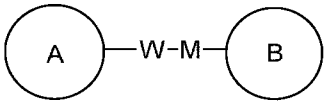
When the number of a linking group is 0, $-(CRR)_0-$, it means that the linking group is a single bond.

When one of the variables is selected from the group consists of single bonds, it means that the two groups connected thereby are directly connected. For example, when L represents a single bond in A-L-Z, the actual structure is A-Z.

When a substituent is absent, it means that the substituent does not exist. For example, when X is absent in A-X, it means that the actual structure is A. When the listed substituents do not indicate to which atom they are connected, such substituents can be bonded through any of the atoms. For example, pyridyl as a substituent can be attached to the substituted group through any carbon on the pyridine ring.

When the listed linking group does not indicate the connection direction, the connection direction is arbitrary. For example, the linking group L in 

is -MW-, in which -MW- can connect ring A and ring B in the same direction as the reading order from left to right to form 

, or can connect ring A and ring B in the opposite direction as the reading order from left to right to form 

. The combination of the linking group, substituents and/or variants thereof is allowed provided that such a combination will produce a stable compound.

Unless stated otherwise, the term "hetero" refers to heteroatom or heteroradical (i.e. a radical containing heteroatom), including atoms other than carbon (C) and hydrogen (H) and radicals containing such heteroatoms, including for example Oxygen (O), Nitrogen (N), Sulfur (S), Silicon (Si), Germanium (Ge), Aluminum (Al), Boron (B), -O-, -S-, , -C(=O)O-, -C(=O)-, -C(=S)-, -S(=O), $-S(=O)_2-$, and -C(=O)N(H)-, -N(H)-, -C(=NH)-, $-S(=O)_2N(H)-$ or -S(=O)N(H)-, which is optionally substituted.

Unless stated otherwise, "cyclo" refers to substituted or unsubstituted cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, cycloalkynyl, heterocycloalkynyl, aryl or heteroaryl. The ring includes single ring, and also includes bicyclic or polycyclic ring systems, such as spiro ring, fused ring, bridge ring or the like. The number of atoms in the ring is usually defined as the member number of the ring. For example, "5-7 membered ring" refers to 5-7 atoms which are arranged around. Unless stated otherwise, the ring

optionally contains 1-3 heteroatoms. Accordingly, "5-7 membered ring" includes for example phenyl, pyridyl and piperidinyl. In another aspect, the term "5-7 membered heterocycloalkyl" includes pyridyl and piperidinyl but does not include phenyl. The term "ring" also includes a ring system containing at least one ring, wherein each "ring" independently complies with the above definition.

Unless stated otherwise, the term "alkyl" refers to a linear or branched saturated hydrocarbon group. In some embodiments, the alkyl is C_{1-12} alkyl; in other embodiments, the alkyl is C_{1-6} alkyl; in other embodiments, the alkyl is C_{1-3} alkyl. The alkyl may be monosubstituted (such as, $-CH_2F$) or polysubstituted (such as, $-CF_3$), may be monovalent (such as, methyl), divalent (such as, methylene) or polyvalent (such as, methine). Examples of alkyl include but are not limited to methyl (Me), ethyl (Et), propyl (including *n*-propyl and isopropyl), butyl (including *n*-butyl, isobutyl, *s*-butyl and *t*-butyl), pentyl (including *n*-pentyl, isopentyl and neopentyl), hexyl or the like.

Unless stated otherwise, the term "C_{1-6} alkyl" refers to a linear or branched saturated hydrocarbon group composed of 1-6 carbon atoms. The C_{1-6} alkyl comprises C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-4}, C_6 and C_5 alkyl or the like. The alkyl may be monovalent (such as, methyl), divalent (such as, methylene) or polyvalent (such as, methine). Examples of C_{1-6} alkyl include but are not limited to methyl (Me), ethyl (Et), propyl (including *n*-propyl and isopropyl), butyl (including *n*-butyl, isobutyl, *s*-butyl and *t*-butyl), pentyl (including *n*-pentyl, isopentyl and neopentyl), hexyl or the like.

Unless stated otherwise, the term "C_{1-3} alkyl" refers to a linear or branched saturated hydrocarbon group composed of 1-3 carbon atoms. The C_{1-3} alkyl includes C_{1-2} and C_{2-3} alkyl or the like. The alkyl may be monovalent (such as, methyl), divalent (such as, methylene) or polyvalent (such as, methine). Examples of C_{1-3} alkyl include but are not limited to methyl (Me), ethyl (Et), propyl (including *n*-propyl and isopropyl), or the like.

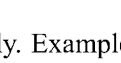
Unless stated otherwise, "alkenyl" refers to a linear or branched hydrocarbon group containing one or more carbon-carbon double bonds. The carbon-carbon double bond can be located at any position of the group. In some embodiments, the alkenyl is C_{2-8} alkenyl; in other embodiments, the alkenyl is C_{2-6} alkenyl; in other embodiments, the alkenyl is C_{2-4} alkenyl. The alkenyl may be monosubstituted or polysubstituted, and may be monovalent, divalent or polyvalent. Examples of alkenyl include but are not limited to ethenyl, propenyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, or the like.

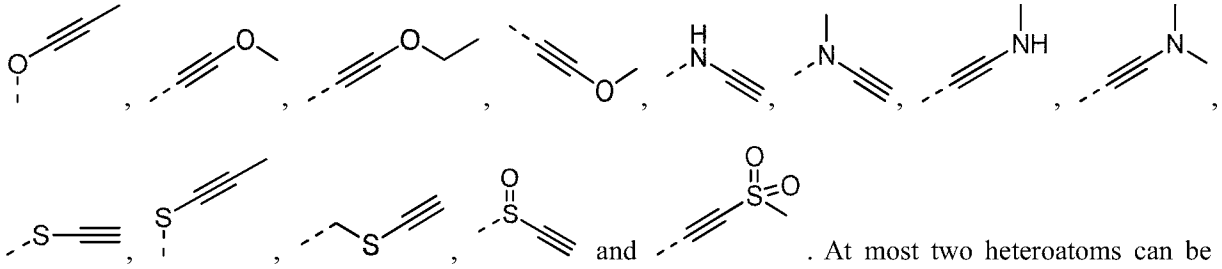
Unless stated otherwise, "alkynyl" refers to a linear or branched hydrocarbon group containing one or more carbon-carbon triple bonds. The carbon-carbon triple bond can be located at any position of the group. In some embodiments, the alkynyl is C_{2-8} alkynyl; in other embodiments, the alkynyl is C_{2-6} alkynyl; in other embodiments, the alkynyl is C_{2-4} alkynyl. The alkynyl may be monosubstituted or polysubstituted, and may be monovalent, divalent or polyvalent. Examples of alkynyl include but are not limited to ethynyl, propynyl, butynyl, pentynyl or the like.

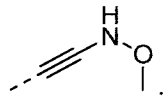
Unless stated otherwise, the term "heteroalkyl", alone or in combination with another term, refers to a stable linear or branched alkyl radical or composition thereof, which is composed of a certain number of carbon atoms and at least one heteroatom or heteroradical. In some embodiments, the heteroatom is selected from the group consisting of B, O, N and S, wherein the N and S atoms are optionally oxidized, the N heteroatom is optionally quaternarized. In some other embodiments, the heteroradical is selected from the group consisting of -C(=O)O-, -C(=O)-, -C(=S)-, -S(=O), $-S(=O)_2-$, -C(=O)N(H)-, -N(H)-, -C(=NH)-, -

$S(=O)_2N(H)$- and -S(=O)N(H)-. In some embodiments, the heteroalkyl is C_{1-6} heteroalkyl; in some other embodiments, the heteroalkyl is C_{1-3} heteroalkyl. The heteroatom or heteroradical can be located at any internal position of the heteroalkyl, including the connecting position of the alkyl to the rest of the molecule, but the terms "alkoxy", "alkylamino" and "alkylthio" (or thioalkoxy) are conventional expressions and refer to the alkyl groups which are connected to the rest of the molecule via an oxygen atom, an amino group or a sulfur atom, respectively. Examples of heteroalkyl include, but are not limited to $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$, $-OCH_2(CH_3)_2$, $-CH_2-CH_2-O-CH_3$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2CH_3$, $-N(CH_3)(CH_2CH_3)$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-SCH_3$, $-SCH_2CH_3$, $-SCH_2CH_2CH_3$, $-SCH_2(CH_3)_2$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2$, $-S(=O)-CH_3$, $-CH_2-CH_2-S(=O)_2-CH_3$, $-CH=CH-O-CH_3$, $-CH_2-CH=N-OCH_3$ and $-CH=CH-N(CH_3)-CH_3$. At most two heteroatoms can be continuous, for example $-CH_2-NH-OCH_3$.

Unless stated otherwise, the term "heteroalkenyl" alone or in combination with another term, refers to a stable linear or branched alkenyl radical or composition thereof, which is composed of a certain number of carbon atoms and at least one heteroatom or heteroradical. In some embodiments, the heteroatom is selected from the group consisting of B, O, N and S, wherein the N and S atoms are optionally oxidized, the N heteroatom is optionally quaternarized. In some other embodiments, the heteroradical is selected from the group consisting of -C(=O)O-, -C(=O)-, -C(=S)-, -S(=O), $-S(=O)_2-$, -C(=O)N(H)-, -N(H)-, -C(=NH)-, $-S(=O)_2N(H)-$ and -S(=O)N(H)-. In some embodiments, the heteroalkenyl is C_{2-6} heteroalkenyl; in some other embodiments, the heteroalkyl is C_{2-4} heteroalkenyl. The heteroatom or heteroradical can be located at any internal position of the heteroalkenyl, including the connecting position of the alkenyl to the rest of the molecule, but the terms "alkenyloxy", "alkenylamino" and "alkenylthio" are conventional expressions and refer to the alkenyl groups which are connected to the rest of the molecule via an oxygen atom, an amino group or a sulfur atom, respectively. Examples of heteroalkenyl include, but are not limited to $-O-CH=CH_2$, $-O-CH=CHCH_3$, $-O-CH=C(CH_3)_2$, $-CH=CH-O-CH_3$, $-O-CH=CHCH_2CH_3$, $-CH_2-CH=CH-OCH_3$, $-NH-CH=CH_2$, $-N(CH=CH_2)-CH_3$, $-CH=CH-NH-CH_3$, $-CH=CH-N(CH_3)_2$, -S-CH=CH2, $-S-CH=CHCH_3$, $-S-CH=C(CH_3)_2$, $-CH_2-S-CH=CH_2$, $-S(=O)-CH=CH_2$ and $-CH=CH-S(=O)_2-CH_3$. At most two heteroatoms can be continuous, for example $-CH=CH-NH-OCH_3$.

Unless stated otherwise, the term "heteroalkynyl", alone or in combination with another term, refers to a stable linear or branched alkynyl radical or composition thereof, which is composed of a certain number of carbon atoms and at least one heteroatom or heteroradical. In some embodiments, the heteroatom is selected from the group consisting of B, O, N and S, wherein the N and S atoms are optionally oxidized, the N heteroatom is optionally quaternarized. In some other embodiments, the heteroradical is selected from the group consisting of -C(=O)O-, -C(=O)-, -C(=S)-, -S(=O), $-S(=O)_2-$, -C(=O)N(H)-, -N(H)-, -C(=NH)-, $-S(=O)_2N(H)-$ and -S(=O)N(H)-. In some embodiments, the heteroalkynyl is C_{2-6} heteroalkynyl; in some other embodiments, the heteroalkyl is C_{2-4} heteroalkynyl. The heteroatom or heteroradical can be located at any internal position of the heteroalkynyl, including the connecting position of the alkynyl to the rest of the molecule, but the terms "alkynyloxy", "alkynylamino" and "alkynylthio" are conventional expressions and refer to the alkynyl groups which are connected to the rest of the molecule via an oxygen atom, an amino group or a sulfur atom, respectively. Examples of heteroalkynyl include, but are not limited to  ,



. At most two heteroatoms can be continuous, for example  .

Unless stated otherwise, "cycloalkyl" comprises any stable cyclic alkyl, including monocyclic, bicyclic or tricyclic systems, in which bicyclic and tricyclic systems include spiro ring, fused ring and bridge ring. In some embodiments, the cycloalkyl is C_{3-8} cycloalkyl. In some other embodiments, the cycloalkyl is C_{3-6} cycloalkyl. In some other embodiments, the cycloalkyl is C_{5-6} cycloalkyl. The cycloalkyl may be monosubstituted or polysubstituted, and may be monovalent, divalent or polyvalent. Examples of cycloalkyl include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl alkyl, [2.2.2]bicyclooctane, [4.4.0]bicyclodecane, or the like.

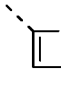
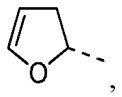
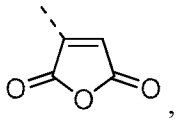
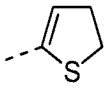
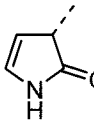
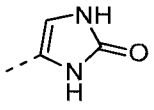
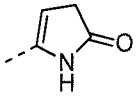
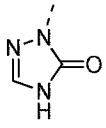
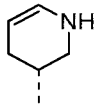
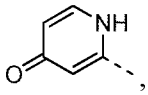
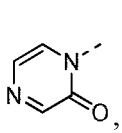
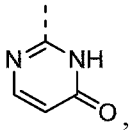
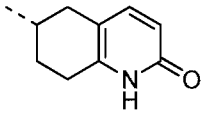
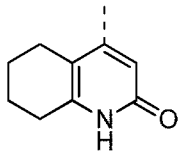
Unless stated otherwise, "C_{3-6} cycloalkyl" represents a saturated cyclic hydrocarbon group composed of 3-6 carbon atoms, which is a monocyclic and bicyclic system. The C_{3-6} cycloalkyl includes C_{3-5}, C_{4-5} and C_{5-6} cycloalkyl or the like. The cycloalkyl may be monovalent, divalent or polyvalent. Examples of C_{3-6} cycloalkyl include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or the like.

Unless stated otherwise, "cycloalkenyl" comprises any stable cyclic alkenyl containing one or more unsaturated carbon-carbon double bonds at any position, which includes monocyclic, bicyclic or tricyclic systems, wherein the bicyclic and tricyclic systems include spiro ring, fused ring and bridge ring, but all the rings in this system are non-aromatic. In some embodiments, the cycloalkenyl is C_{3-8} cycloalkenyl. In some other embodiments, the cycloalkenyl is C_{3-6} cycloalkenyl. In some other embodiments, the cycloalkenyl is C_{5-6} cycloalkenyl. The cycloalkenyl may be monovalent, divalent or polyvalent. Examples of cycloalkenyl include but are not limited to cyclopentenyl, cyclohexenyl, or the like.

Unless stated otherwise, "cycloalkynyl" comprises any stable cyclic alkynyl containing one or more carbon-carbon triple bonds at any position, which includes monocyclic, bicyclic or tricyclic system, wherein the bicyclic and tricyclic systems include spirocyclic, fused ring and bridge ring. The cycloalkynyl may be monosubstituted or polysubstituted, and may be monovalent, divalent or polyvalent.

Unless stated otherwise, the term "heterocycloalkyl", alone or in combination with another term, refers to cyclic "heteroalkyl", including monocyclic, bicyclic and tricyclic systems, wherein the bicyclic and tricyclic systems include spiro ring, fused ring and bridge ring. In addition, with respect to the "heterocycloalkyl", the heteroatom can occupy the connecting position of the heterocycloalkyl to the rest of the molecule. In some embodiments, the heterocycloalkyl is 4-6 membered heterocycloalkyl. In some other embodiments, the heterocycloalkyl is 5-6 membered heterocycloalkyl. Examples of heterocycloalkyl include, but are not limited to azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrothienyl (including tetrahydrothien-2-yl and tetrahydrothien-3-yl or the like), tetrahydrofuranyl (including tetrahydrofuran-2-yl or the like), tetrahydropyranyl, piperidinyl (including 1-piperidinyl, 2-

piperidinyl and 3-piperidinyl or the like), piperazinyl (including 1-piperazinyl and 2-piperazinyl or the like), morpholinyl (including 3-morpholinyl and 4-morpholinyl or the like), dioxanyl, dithianyl, isoxazolealkyl, isothiazolidinyl, 1,2-oxazinyl, 1,2-thiazinyl, hexahydropyridazinyl, homopiperazinyl, homopiperidinyl or oxepanyl.

Unless stated otherwise, the term "heterocycloalkenyl", alone or in combination with another term, refers to cyclic "heteroalkenyl", including monocyclic, bicyclic and tricyclic systems, wherein the bicyclic and tricyclic systems include spiro ring, fused ring and bridge ring, but all the rings in this system are non-aromatic. In addition, with respect to the "heterocycloalkenyl", the heteroatom can occupy the connecting position of the heterocycloalkenyl to the rest of the molecule. In some embodiments, the heterocycloalkenyl is 4-6 membered heterocycloalkenyl. In some other embodiments, the heterocycloalkenyl is 5-6 membered heterocycloalkenyl. Examples of heterocycloalkenyl include but are not limited to  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  .

Unless stated otherwise, the term "heterocycloalkynyl", alone or in combination with another term, refers to cyclic "heteroalkynyl", including monocyclic, bicyclic and tricyclic systems, wherein the bicyclic and tricyclic systems include spiro ring, fused ring and bridge ring. In addition, with respect to the "heterocycloalkynyl", the heteroatom can occupy the connecting position of the heterocycloalkynyl to the rest of the molecule. In some embodiments, the heterocycloalkynyl is 4-6 membered heterocycloalkynyl. In some other embodiments, the heterocycloalkynyl is 5-6 membered heterocycloalkynyl.

Unless stated otherwise, the term "halogen" or "halo", alone or as part of another substiutent, refers to F, Cl, Br or I atom. In addition, the term "haloalkyl" is intended to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" is intended to include but is not limited to trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, and 3-bromopropyl, or the like. Unless stated otherwise, examples of haloalkyl include, but are not limited to trifluoromethyl, trichloromethyl, pentafluoroethyl and pentachloroethyl.

"Alkoxy" refers to the above alkyl having a specific number of carbon atoms connected via an oxygen bridge. Unless stated otherwise, C_{1-6} alkoxy comprises C_1, C_2, C_3, C_4, C_5 and C_6 alkoxy. In some embodiments, the alkoxy is C_{1-3} alkoxy. Examples of alkoxy include but are not limited to methoxyl, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *sec*-butoxy, *tert*-butoxy, *n*-pentoxy and *S*-pentoxy.

Unless stated otherwise, the term "C_{1-6} alkoxy" refers to an alkyl group containing 1-6 carbon atoms connected to the rest of the molecule via an oxygen atom. The C_{1-6} alkoxy comprises C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-4}, C_6, C_5, C_4 and C_3 alkoxy or the like. Examples of C_{1-6} alkoxy include but are not limited to methoxyl, ethoxy, propoxy (including *n*-propoxy and isopropoxy), butoxy (including *n*-butoxy, isobutoxy, *s*-butoxy and *t*-butoxy), pentoxy (including *n*-pentoxy, isopentoxy and neopentoxy), hexyloxy, or the like.

Unless stated otherwise, the term "C_{1-3} alkoxy" refers to an alkyl group containing 1-3 carbon atoms connected to the rest of the molecule via an oxygen atom. The C_{1-3} alkoxy comprises C_{1-2}, C_{2-3}, C_3 和 C_2 alkoxy or the like. Examples of C_{1-3} alkoxy include but are not limited to methoxyl, ethoxy, propoxy (including *n*-propoxy and isopropoxy), or the like.

Unless stated otherwise, the terms "aromatic ring" and "aryl" can be used interchangeably herein. The term "aromatic ring" or "aryl" refers to a polyunsaturated carbocyclic system, which can be monocyclic, bicyclic or polycyclic system, wherein at least one ring is aromatic. Each ring in the bicyclic and polycyclic system are fused together. It may be mono- or poly-substituted, and may be monovalent, divalent or polyvalent. In some embodiments, the aryl is C_{6-12} aryl. In some other embodiments, the aryl is C_{6-10} aryl. Examples of aryl include but are not limited to phenyl, naphthyl (including 1-naphthyl and 2-naphthyl, or the like). The substituent of any one of the above aryl ring systems may be selected from the group consisting of acceptable substituents described herein.

Unless stated otherwise, the terms "heteroaromatic ring" and "heteroaryl" can be used interchangeably herein. The term "heteroaryl" refers to an aryl (or aromatic ring) containing 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of B, N, O and S, which may be monocyclic, bicyclic or tricyclic system, wherein the nitrogen atom can be substituted or unsubstituted (i.e., N or NR, where R is H or other substituents defined herein), and is optionally quaternarized; and nitrogen and sulfur heteroatoms can be optionally oxidized (i.e., NO and $S(O)_p$, p is 1 or 2). Heteroaryl can be connected to the rest of the molecule via heteroatom. In some embodiments, the heteroaryl is 5-10 membered heteroaryl. In some other embodiments, the heteroaryl is 5-6 membered heteroaryl. Examples of the heteroaryl include but are not limited to pyrrolyl (including *N*-pyrrolyl, 2-pyrrolyl and 3-pyrrolyl or the like), pyrazolyl (including 2-pyrazolyl and 3-pyrazolyl or the like), imidazolyl (including *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl and 5-imidazolyl or the like), oxazolyl (including 2-oxazolyl, 4-oxazolyl and 5-oxazolyl or the like), triazolyl (1*H*-1,2,3-triazolyl, 2*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl and 4*H*-1,2,4-triazolyl or the like), tetrazolyl, isoxazolyl (3-isoxazolyl, 4-isoxazolyl and 5-isoxazolyl or the like), thiazolyl (including 2-thiazolyl, 4-thiazolyl and 5-thiazolyl or the like), furyl (including 2-furyl and 3-furyl or the like), thienyl (including 2-thienyl and 3-thienyl or the like), pyridyl (including 2- pyridyl, 3-pyridyl and 4-pyridyl or the like), pyrazinyl, pyrimidinyl (including 2-pyrimidinyl and 4-pyrimidinyl or the like), benzothiazolyl (including 5-benzothiazolyl or the like), purinyl, benzimidazolyl (including 2-benzimidazolyl or the like), indolyl (including 5-indolyl or the like), isoquinolinyl (including 1-isoquinolinyl and 5-isoquinolinyl or the like), quinoxalinyl (including 2-quinoxalinyl and 5-quinoxalinyl or the like), quinolinyl (including 3-quinolinyl and 6-quinolinyl or the like), pyrazinyl, purinyl, benzoxazolyl. The substituent of any one of the above heteroaryl ring systems may be selected from the group consisting of acceptable substituents described herein.

Unless stated otherwise, the terms "5-6 membered heteroaromatic ring" and "5-6 membered heteroaryl" can be used interchangeably herein. The term "5-6 membered heteroaryl" refers to a monocyclic group composed of 5-6 ring atoms with a conjugated π electron system, wherein 1, 2, 3 or 4 ring atoms are heteroatoms independently selected from the group consisting of O, S and N, and the rest are carbon atoms, and wherein the nitrogen atom is optionally quaternarized, and the nitrogen and sulfur heteroatoms can be optionally oxidized (i.e., NO and $S(O)_p$, p is 1 or 2). The 5-6 membered heteroaryl can be connected to the rest of the molecule through heteroatom or carbon atom. The 5-6 membered heteroaryl comprises 5

membered and 6 membered heteroaryl. Examples of the 5-6 membered heteroaryl include but are not limited to pyrrolyl (including *N*-pyrrolyl, 2-pyrrolyl and 3-pyrrolyl or the like), pyrazolyl (including 2- pyrazolyl and 3-pyrazolyl or the like), imidazolyl (including *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl and 5-imidazolyl or the like), oxazolyl (including 2-oxazolyl, 4-oxazolyl and 5-oxazolyl or the like), triazolyl (1*H*-1,2,3-triazolyl, 2*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl and 4*H*-1,2,4-triazolyl or the like), tetrazolyl, isoxazolyl (3-isoxazolyl, 4-isoxazolyl and 5-isoxazolyl or the like), thiazolyl (including 2-thiazolyl, 4-thiazolyl and 5-thiazolyl or the like), furyl (including 2-furyl and 3-furyl or the like), thienyl (including 2-thienyl and 3-thienyl or the like), pyridyl (including 2-pyridyl, 3-pyridyl and 4-pyridyl or the like), pyrazinyl or pyrimidinyl (including 2-pyrimidinyl and 4-pyrimidinyl or the like).

Unless stated otherwise, the term "aralkyl" is intended to include those groups in which aryl is attached to the alkyl. In some embodiments, the aralkyl is C_{6-10} aryl-C_{1-4} alkyl. In some other embodiments, the aralkyl is C_{6-10} aryl-C_{1-2} alkyl. Examples of the aralkyl include but are not limited to benzyl, phenethyl, naphthylmethyl or the like. "Aryloxy" and "arylthio" refer to those groups in which a carbon atom (such as methyl) in aralkyl has been replaced by O or S atom. In some embodiments, the aryloxy is C_{6-10} aryl-O-C_{1-2} alkyl. In some other embodiments, the aryloxy is C_{6-10} aryl-C_{1-2} alkyl-O-. In some embodiments, the arylthiol is C_{6-10} aryl-S-C_{1-2} alkyl. In some other embodiments, the arylthiol is C_{6-10} aryl-C_{1-2} alkyl-S-. Examples of the aryloxy and arylthio include but are not limited to phenoxymethyl, 3-(1-naphthyloxy)propyl, phenylthiomethyl, or the like.

Unless stated otherwise, the term "heteroaralkyl" is intended to include those groups in which the heteroaryl is attached to the alkyl group. In some embodiments, the heteroaralkyl is 5-8 membered heteroaryl-C_{1-4} alkyl. In some other embodiments, the heteroaralkyl is 5-6 membered heteroaryl-C_{1-2} alkyl. Examples of the heteroaralkyl include but are not limited to pyrrolylmethyl, pyrazolylmethyl, pyridylmethyl, pyrimidinylmethyl or the like. "Heteroaryloxy" and "heteroarylthio" refer to those groups in which a carbon atom (such as methyl) in the heteroaralkyl group has been replaced by O or S atom. In some embodiments, the heteroaryloxy is 5-8 membered heteroaryl-O-C_{1-2} alkyl. In some other embodiments, the heteroaryloxy is 5-6 membered heteroaryl-C_{1-2} alkyl-O-. In some embodiments, the heteroarylthio is 5-8 membered heteroaryl-S-C_{1-2} alkyl. In some other embodiments, the heteroarylthio is 5-6 membered heteroaryl-C_{1-2} alkyl-S-. Examples of heteroaryloxy and heteroarylthio include but are not limited to pyrrolyloxymethyl, pyrazolyloxymethyl, 2-pyridyloxymethyl, pyrrolylthiomethyl, pyrazolylthiomethyl, 2-pyridylthiomethyl or the like.

Unless stated otherwise, C_{n-n+m} or C_n-C_{n+m} includes any specific case of n to n+m carbon. For example, C_{1-12} comprises C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, and C_{12} and also comprises any range within n to n+m, for example, C_{1-12} comprises C_{1-3}, C_{1-6}, C_{1-9}, C_{3-6}, C_{3-9}, C_{3-12}, C_{6-9}, C_{6-12}, and C_{9-12} or the like. Likewise, n membered to n+m membered means that the atom number in the ring is n to n+m, for example, 3-12 membered ring comprises 3 membered ring, 4 membered ring, 5 membered ring, 6 membered ring, 7 membered ring, 8 membered ring, 9 membered ring, 10 membered ring, 11 membered ring, and 12 membered ring, and also comprises any range within n to n+m, for example, 3-12 membered ring comprises 3-6 membered ring, 3-9 membered ring, 5-6 membered ring, 5-7 membered ring, 6-7 membered ring, 6-8 membered ring, and 6-10 membered ring or the like.

The term "leaving group" refers to a functional group or atom which can be replaced by another

functional group or atom through substitution reaction (e.g., affinity substitution reaction). For example, representative leaving groups include triflate; Cl, Br, I; sulfonate, such as mesylate, tosylate, p-bromobesylate, *p*-toluenesulfonate or the like; acyloxy, such as acetoxy, trifluoroacetoxy, or the like.

The term "protecting group" includes but are not limited to "amino protecting group", "hydroxyl protecting group" or "mercapto protecting group". The term "amino protecting group" refers to a protecting group suitable for preventing side reactions on the nitrogen position of an amino group. Representative amino protecting groups include but are not limited to formyl; acyl, such as alkanoyl (such as acetyl, trichloroacetyl or trifluoroacetyl); alkoxycarbonyl, such as *tert*-butoxycarbonyl (Boc); aryl methoxycarbonyl, such as benzyloxycarbonyl (Cbz) and 9-fluorene methoxycarbonyl (Fmoc); arylmethyl, such as benzyl (Bn), triphenylmethyl (Tr), 1,1-bis-(4'-methoxylphenyl)methyl; silyl, such as trimethylsilyl (TMS) and *tert*-butyldimethylsilyl (TBS), or the like. The term "hydroxyl protecting group" refers to a protecting group suitable for preventing hydroxyl side reactions. Representative hydroxyl protecting groups include but are not limited to alkyl, such as methyl, ethyl and *tert*-butyl; acyl, such as alkanoyl (such as acetyl); arylmethyl, such as benzyl (Bn), *p*-methoxylbenzyl (PMB), 9-fluorenylmethyl (Fm) and diphenylmethyl (benzhydryl, DPM); methylsilyl, such as trimethylsilyl (TMS) and *tert*-butyldimethylsilyl (TBS), or the like.

The present compounds can be prepared by various synthetic processes well-known to a person skilled in the art, including the specific embodiments listed below. The embodiments formed by the combination with other chemical synthesis processes and equivalence well-known to a person skilled in the art and preferable embodiments include but are not limited to Example herein.

The present compounds may have multiple applications or indications, including but not limited to those specifically listed herein.

The solvents used herein are commercially available. The following abbreviations are used herein: aq: water; HATU: O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethylurea hexafluorophosphate; EDC: *N*-(3-dimethylaminopropyl)-*N'*-ethyl carbodiimide hydrochloride; m-CPBA: 3-chloroperoxybenzoic acid; eq: equivalent, equivalence; CDI: carbonyldiimidazole; DCM: dichloromethane; PE: petroleum ether; DIAD: diisopropyl azodicarboxylate; DMF: *N,N*-dimethylformamide; DMSO: dimethyl sulfoxide; EtOAc: ethyl acetate; EtOH: ethanol; MeOH: methanol; CBz: benzyloxycarbonyl, an amine protecting group; BOC: *tert*-butoxycarbonyl, an amine protecting group; HOAc: acetic acid; $NaCNBH_3$: cyano sodium borohydride; r.t.: room temperature; O/N: overnight; THF: tetrahydrofuran ; Boc_2O: di-*tert*-butyl dicarbonate; TFA: trifluoroacetate; DIPEA: diisopropylethylamine; $SOCl_2$: thionyl chloride; CS_2: carbon disulfide; TsOH: *p*-toluenesulfonic acid; NFSI: *N*-fluoro-*N*-(benzenesulfonyl) benzenesulfonamide; NCS: *N*-chlorosuccinimide; *n*-Bu_4NF: tetrabutylammonium fluoride; *i*PrOH: 2-propanol; mp: melting point; LDA: lithium diisopropylamide.

The compounds are named manually or by ChemDraw® software. The compound names on catalog by the providers are used.

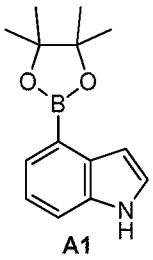
Brief Description of The Drawings

Figure 1: Tumor growth curve of human colorectal cancer LoVo cell subcutaneous xenograft model tumor-bearing mice after administration of the compound according the present disclosure.

Examples

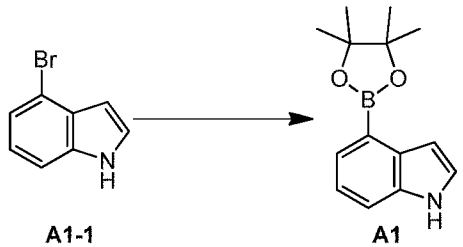
The present disclosure will be described in detail by the following Examples, which do not mean any limitation thereto. The present disclosure has been described in detail herein, which also discloses its specific embodiments. It will be apparent for a person skilled in the art that various changes and modifications can be made to specific embodiments of the present disclosure without departing from its spirit and scope.

Intermediate 1



A1

Synthesis Scheme:



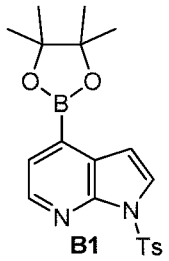
A1-1 **A1**

Step 1: Synthesis of Compound **A1**

To a solution of Compound **A1-1** (65 g, 331.56 mmol) in dimethyl sulfoxide (1 L) were added bispinacol borate (126.29 g, 497.34 mmol), 1,1-bis(diphenylphosphino)ferrocene palladium chloride (12.13 g, 16.58 mmol) and potassium acetate (113.89 g, 1.16 mol). The reaction solution was stirred under the protection of nitrogen at 90°C for 16 h. After the reaction solution was filtered through celite, the filtrate was extracted with 1 L of ethyl acetate (500 mL×2), and the organic phase was washed with 3 L of water (1L×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with silica gel column (petroleum ether/ethyl acetate=1:0,4:1) to give Compound **A1**.

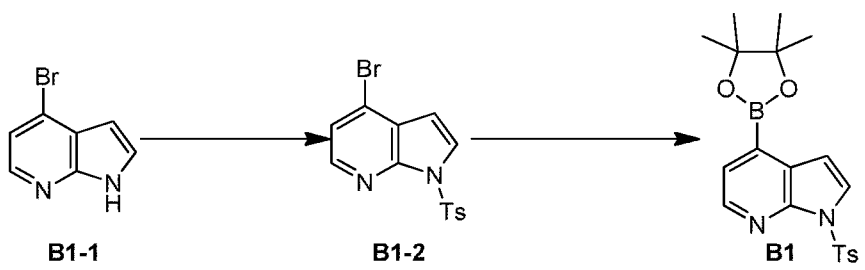
MS-ESI m/z:243.9 [M+H]+ .^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.42 (s, 13 H) 7.09 (t, J=2.13 Hz, 1 H) 7.21 - 7.25 (m, 1 H) 7.52 (d, J=8.03 Hz, 1 H) 7.67 (d, J=7.03 Hz, 1 H) 8.23 (br s, 1 H).

Intermediate 2



B1

Synthesis scheme:



B1-1 **B1-2** **B1**

Step 1: Synthesis of Compound **B1-2**

To a solution of Compound **B1-1** (90 g, 456.78 mmol) in dichloromethane (1L) were added sodium hydroxide solution (2 M, 685.17 mL) and tetrabutylammonium hydrogen sulfate (7.75 g, 22.84 mmol) and then added *p*-toluenesulfonyl chloride (174.17 g, 913.56 mmol) slowly. The reaction solution was stirred at 25°C for 15 h and extracted with 500 mL of dichloromethane (250 mL×2), and the organic phase was washed with 3L of water (1L×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with silica gel column (petroleum ether/ethyl acetate=1:0,1:0) to give Compound **B1-2**.

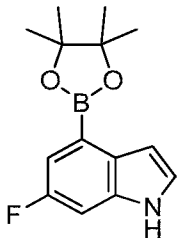
MS-ESI m/z: 352.9 [M+H]+.

Step 2: Synthesis of Compound **B1**

To a solution of Compound **B1-2** (25 g, 71.18 mmol) in *N,N*-dimethylformamide (500mL) were added bispinacol borate(36.15 g, 142.36 mmol), 1,1-bis(diphenylphosphino)ferrocene palladium chloride (5.21 g, 7.12 mmol) and potassium acetate (20.96 g, 213.54 mmol). The reaction solution was stirred under the protection of nitrogen at 90°C for 16 h. After the reaction solution was filtered through celite, the filtrate was extracted with 1 L of ethyl acetate (500mL×2), and the organic phase was washed with 3 L of water (1L×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with silica gel column (petroleum ether/ethyl acetate =1:0,4:1) to give Compound **B1**.

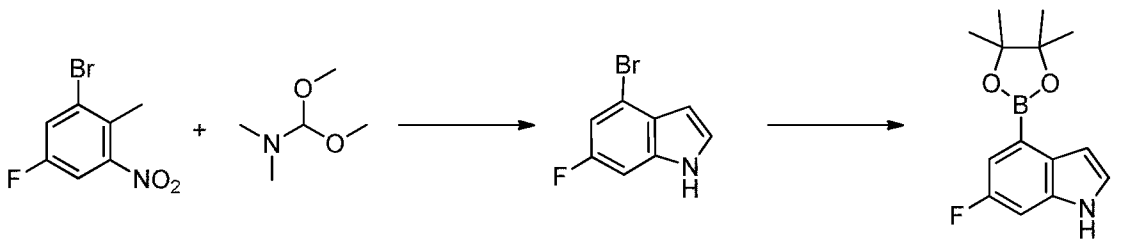
MS-ESI m/z:399.1 [M+H]+.^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.27 (d, J=2.76 Hz, 3 H) 1.32 - 1.39 (m, 1 H) 1.33 - 1.38 (m, 1 H) 1.36 (s, 10 H) 6.95 - 7.05 (m, 1 H) 7.02 (d, J=4.02 Hz, 1 H) 7.20 - 7.26 (m, 1 H) 7.24 (d, J=8.03 Hz, 1 H) 7.52 (d, J=4.77 Hz, 1 H) 7.72 - 7.78 (m, 1 H) 7.75 (d, J=3.76 Hz, 1 H) 8.02 - 8.04 (m, 2 H) 8.43 (d, J=4.77 Hz, 1 H).

Intermediate 3



C1

Synthesis scheme:



C1-1 **C1-2** **C1-3** **C1**

Step 1: Synthesis of Compound **C1-3**

At room temperature, to a solution of Compound **C1-1** (3.00 g, 12.82 mmol) in *N,N*-dimethylformamide (30.00 mL) was added **C1-2** (7.65 g, 64.23 mmol, 8.50 mL), which was stirred under nitrogen atmosphere at 160°C for 8 h. The reaction system was cooled, diluted with dichloromethane (50 mL), washed with water (20ml×5) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was

removed under reduced pressure to give the crude product. The crude product was dissolved with acetic acid (5ml) and was added dropwise to a boling solution of iron powder (7.16 g, 128.19 mmol) in acetic acid (5 mL). The reaction solution was refluxed for 40 min. The reaction solution was cooled to room temperature, adjusted to basic pH with saturated sodium carbonate solution and extracted with dichloromethane (30ml×3). The organic phases were combined, dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with column chromatography (petroleum ether/dichloromethane =3/1) to give Compound **C1-3**.

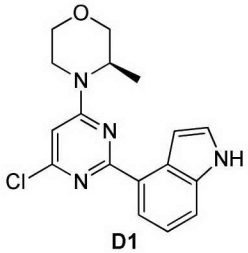
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 6.50 (t, *J*=2.26 Hz, 1 H) 6.96 - 7.00 (m, 1 H) 7.05 (dd, *J*=9.04, 2.01 Hz, 1 H) 7.16 (t, *J*=2.76 Hz, 1 H) 7.47 (dd, *J*=8.52, 5.52 Hz, 1 H) 8.20 (br s, 1 H).

Step 2: Synthesis of Compound **C1**

At room temperature, to a solution of Compound **C1-3** (1.00 g, 4.67 mmol) in 1,4-dioxane (15.00 mL) were added bispinacol borate(1.78 g, 7.00 mmol), 1,1-bis(diphenylphosphino)ferrocene palladium chloride (341.71 mg, 467.00 μmol), potassium acetate (1.37 g, 14.01 mmol), which was stirred under nitrogen atmosphere for 12 h. After cooling, the reaction system was diluted with ethyl acetate (40 mL) and filtered. The organic phase was washed with water (20 mL×2) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with column chromatography (petroleum ether/dichloromethane =3/1) to give Compound **C1**.

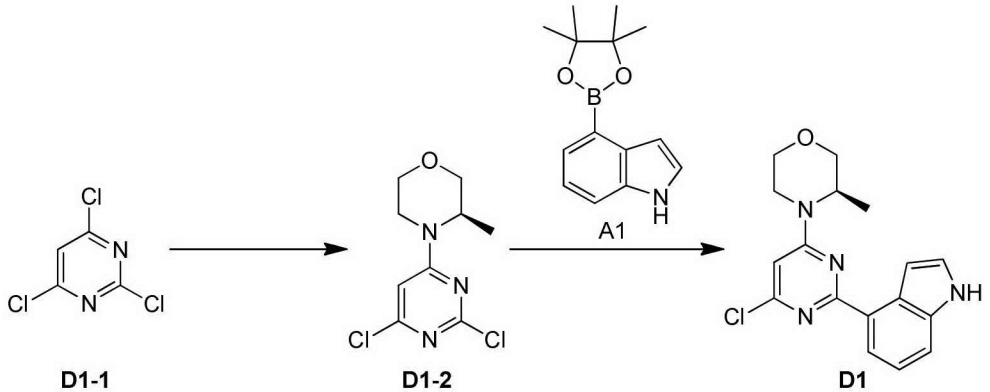
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 12 H) 6.74 (br s, 1 H) 7.12 (dd, *J*=10.04, 2.51 Hz, 1 H) 7.30 (dd, *J*=10.04, 2.01 Hz, 1 H) 7.38 (t, *J*=2.76 Hz, 1 H) 11.18 (br s, 1 H).

Intermediate 4



D1

Synthesis scheme:



D1-1 **D1-2** **D1**

Step 1: Synthesis of Compound **D1-2**

To a solution of Compound **D1-1** (2.00 g, 10.90 mmol, 1.25 mL) in dichloromethane (20mL) was added

triethylamine (3.15 g, 31.14 mmol, 4.32 mL), and added dropwise (*R*)-3-methylmorpholine slowly at -5°C. The reaction solution was warmed slowly to 15°C and stirred for 15 h. The compound was concentrated to dryness and the crude product was purified with silica gel column (petroleum ether/ethyl acetate =10:1,5:1) to give Compound **D1-2**.

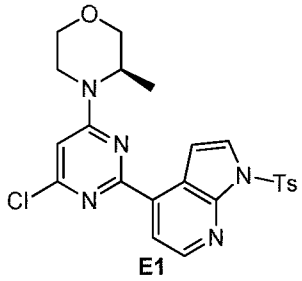
MS-ESI m/z: 247.9 [M+H]+.

Step 2: Synthesis of Compound **D1**

To a solution of Compound **D1-2** (1.5 g, 6.05 mmol) in 1,4-dioxane (40mL) were added **A1** (1.62 g, 6.65 mmol), bistriphenylphosphine palladium dichloride (424.35 mg, 604.57 μmol) and sodium carbonate (2 M, 9.07 mL). The reaction mixture was stirred under the protection of nitrogen at 110°C for 15 h. After the reaction solution was filtered through celite, the filtrate was extracted with 50mL of ethyl acetate (25mL×2). The organic phase was washed with 60 mL of water (20mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with silica gel column (petroleum ether/ethyl acetate =1:0,1:1) to give Compound **D1**.

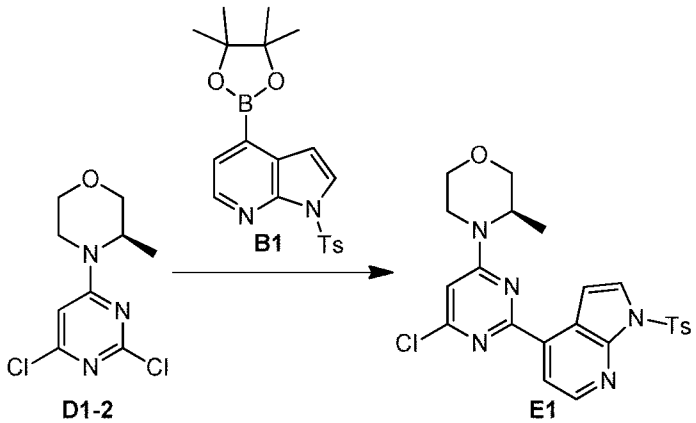
MS-ESI m/z: 328.9 [M+H]+.

Intermediate 5



E1

Synthesis scheme:

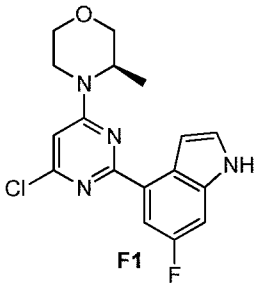


Step 1: Synthesis of Compound **E1**

To a solution of Compound **D1-2** (9.03 g, 36.41 mmol) in 1,4-dioxane(100mL) were added **B1** (14.5 g, 36.41 mmol), bistriphenylphosphine palladium dichloride (2.555 g, 3.641 mmol) and sodium carbonate (2 M, 54.61 mL). The reaction solution was stirred under the protection of nitrogen at 110°C for 15 h. After the reaction solution was filtered through celite, the filtrate was extracted with 600 mL of ethyl acetate (200mL×3). The organic phase was washed with 600 mL of water (200mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product,

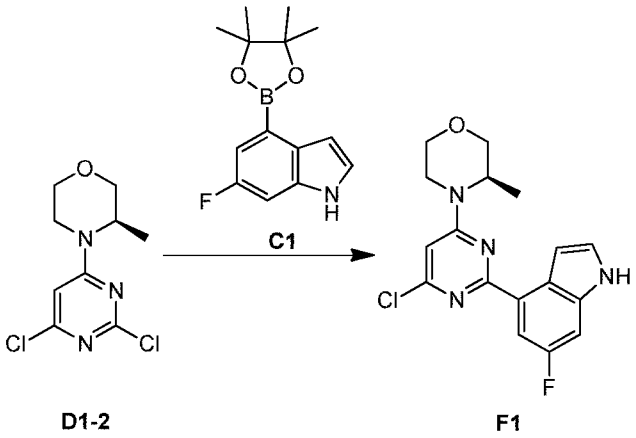
which was purified with silica gel column (petroleum ether/ethyl acetate =4:1,4:3) to give Compound **E1**. MS-ESI m/z:484.2 [M+H]+.

Intermediate 6



F1

Synthesis scheme:

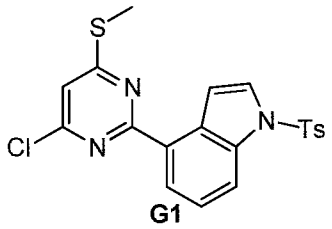


D1-2 **C1** **F1**

Step 1: Synthesis of Compound **F1**

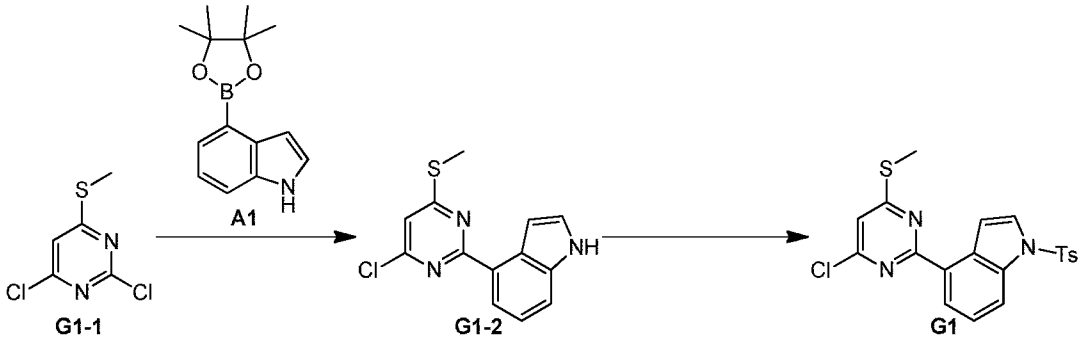
To a solution of Compound **D1-2** (0.5 g, 2.02 mmol) in 1,4-dioxane (10mL) were added **C1** (578.80 mg, 2.22 mmol), bistriphenylphosphine palladium dichloride (70.73 mg, 100.76 μmol) and sodium carbonate (2 M, 3.02 mL). The reaction mixture was stirred under the protection of nitrogen at 110°C for 15 h. After the reaction solution was filtered through celite, the filtrate was extracted with 60mL of ethyl acetate (20 mL×3). The organic phase was washed with 60 mL of water (20mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with silica gel column (petroleum ether/ethyl acetate =4:1,1:1) to give Compound **F1**. MS-ESI m/z:347.1[M+H]+.

Intermediate 7



G1

Synthesis scheme:



Step 1: Synthesis of Compound **G1-2**

To a solution of Compound **G1-1** (1 g, 5.13 mmol) in 1,4-dioxane(25mL) were added **A1** (1.37 g, 5.64 mmol), bistriphenylphosphine palladium dichloride (359.82 mg, 512.64 μmol) and sodium carbonate (2 M, 7.69 mL). The reaction mixture was stirred under the protection of nitrogen at 90°C for 15 h. After the reaction solution was filtered through celite, the filtrate was extracted with 90 mL of ethyl acetate (30mL×3). The organic phase was washed with 90mL of water (30mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with silica gel column (petroleum ether/ethyl acetate =1:0,4:1) to give Compound **G1-2**.

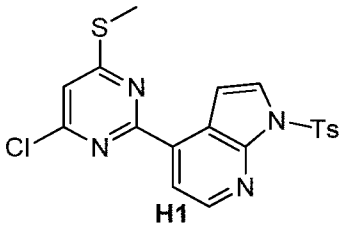
MS-ESI m/z:275.9 [M+H]+

Step 2: Synthesis of Compound **G1**

To a solution of Compound **G1-2** (1.09 g, 3.95 mmol) in dichloromethane (20mL) were added sodium hydroxide solution (2 M, 5.93 mL) and tetrabutylammonium hydrogen sulfate (671.36 mg, 1.98 mmol) and then added *p*-toluenesulfonyl chloride (1.13 g, 5.93 mmol) slowly. The reaction solution was stirred at 25°C for 15 h. The reaction solution was extracted with 90mL of dichloromethane (30mL×3). The organic phase was washed with 90mL of water (30mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with silica gel column (petroleum ether/ethyl acetate =1:0,4:1) to give Compound **G1**.

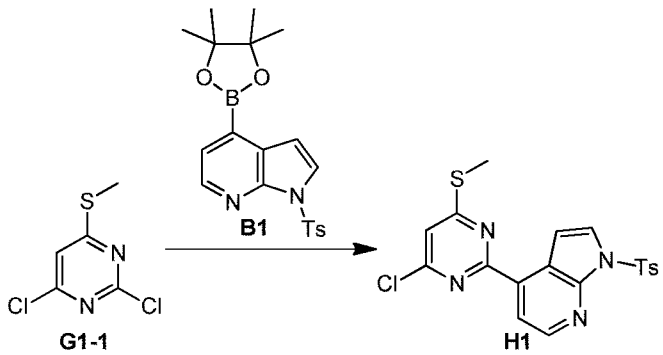
MS-ESI m/z:429.8[M+H]+.

Intermediate 8



H1

Synthesis scheme:

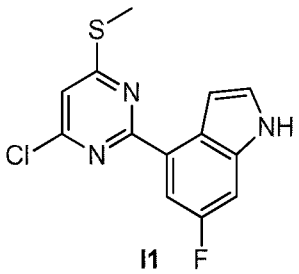


G1-1 **B1** **H1**

Step 1: Synthesis of Compound **H1**

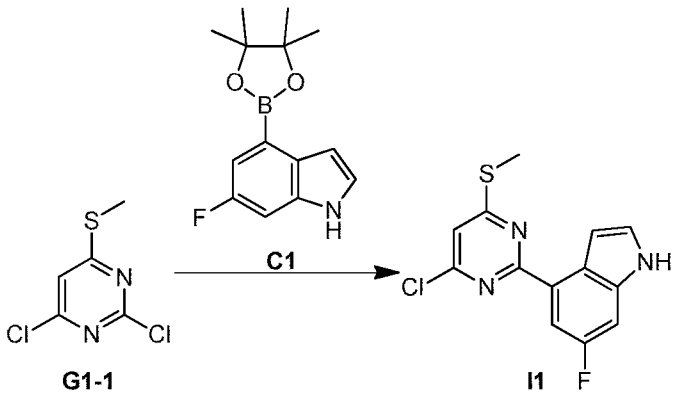
To a solution of Compound **G1-1** (487.08 mg, 2.50 mmol) in 1,4-dioxane(20mL) were added **B1** (1 g, 2.50 mmol), bistriphenylphosphine palladium dichloride (87.63 mg, 124.85 μmol) and sodium carbonate (2 M, 3.75 mL). The reaction mixture was stirred under the protection of nitrogen at 90°C for 15 h. After the reaction solution was filtered through celite, the filtrate was extracted with 90mL of ethyl acetate (30mL×3). The organic phase was washed with 90mL of water (30mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with silica gel column (petroleum ether/ethyl acetate =1:0,5:1) to give Compound **H1**. MS-ESI m/z:431.0 [M+H]+.

Intermediate 9



I1

Synthesis scheme:

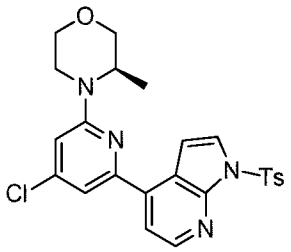


Step 1: Synthesis of Compound **I1**

To a solution of Compound **G1-1** (493.09 mg, 2.53 mmol) in 1,4-dioxane(20mL) were added **C1** (0.66 g, 2.53 mmol), bistriphenylphosphine palladium dichloride (88.71 mg, 126.39 μmol) and sodium carbonate (2 M, 3.79 mL). The reaction mixture was stirred under the protection of nitrogen at 90°C for 15 h. After the reaction solution was filtered through celite, the filtrate was extracted with 90mL of ethyl acetate (30mL×3). The organic phase was washed with 90mL of water (30mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with silica gel column (petroleum ether/ethyl acetate =1:0,5:1) to give Compound **I1**.

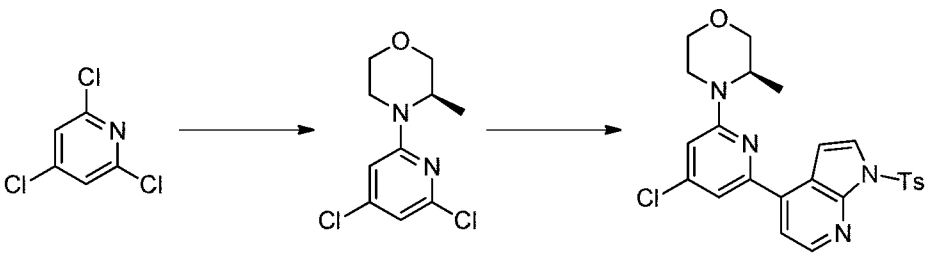
MS-ESI m/z:293.9 [M+H]+.

Intermediate 10



XX1

Synthesis scheme:



XX1-1 **XX1-2** **XX1**

Step 1: Synthesis of Compound **XX1-2**

At room temperature, to a solution of Compound **XX1-1** (500.00 mg, 2.74 mmol) in N,N-dimethylformamide (10.00 mL) were added (*R*)-3-methylmorpholine (304.87 mg, 3.01 mmol), potassium carbonate (946.74 mg, 6.85 mmol), which was stirred under nitrogen atmosphere at 100°C for 12 h. The reaction system was diluted with ethyl acetate (30 mL). The organic phase was washed with water (20 mL×3) and saturated brine (20 mL) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with column chromatography (petroleum

ether/ethyl acetate =10/1,5/1) to give Compound **XX1-2**.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.14 (d, *J*=6.53 Hz, 3 H) 3.09 (td, *J*=12.80, 3.51 Hz, 1 H) 3.44 (td, *J*=11.80, 3.01 Hz, 1 H) 3.56 - 3.62 (m, 1 H) 3.67 - 3.73 (m, 1 H) 3.82 - 3.96 (m, 2 H) 4.28 (br dd, *J*=6.52, 2.51 Hz, 1 H) 6.83 (d, *J*=1.00 Hz, 1 H) 6.87 (d, *J*=1.50 Hz, 1 H).

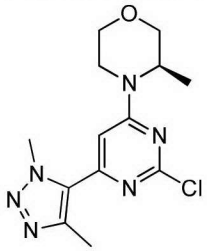
Step 2: Synthesis of Compound **XX1**

At room temperature, to a solution of Compound **XX1-2** (1.05 g, 4.25 mmol) in 1,4-dioxane (10.00 mL) were added Compound **B1** (1.69 g, 4.25 mmol), dichlorobis(triphenylphosphine) palladium (298.23 mg, 424.89 μmol), sodium carbonate solution (2 M, 6.37 mL), which was stirred under nitrogen atmosphere at 100°C for 9 h. The reaction system was diluted with 20 mL of water and extracted with ethyl acetate (30 mL). The organic phase was washed with water (20 mL) and saturated brine (20 mL) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with column chromatography (petroleum ether/ethyl acetate =3/1,1/1) to give Compound **XX1**.

MS *m/z*: 483.1 $[M+H]^+$

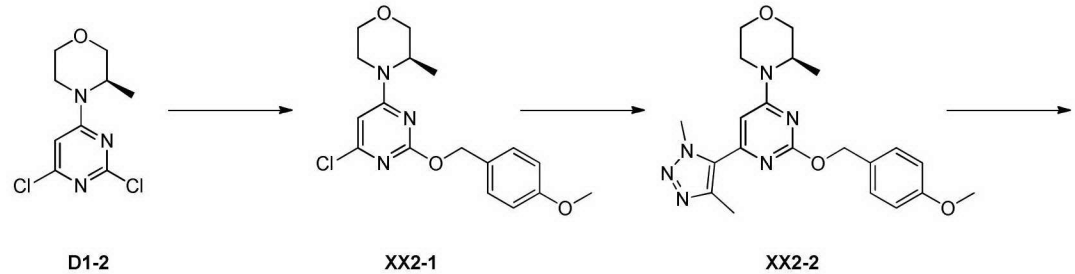
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.19 (d, *J*=6.78 Hz, 3 H) 2.34 (s, 3 H) 3.17 (td, *J*=12.74, 3.89 Hz, 1 H) 3.45 - 3.54 (m, 1 H) 3.62 - 3.67 (m, 1 H) 3.71 - 3.78 (m, 1 H) 3.92 - 3.99 (m, 2 H) 4.42 (br d, *J*=6.27 Hz, 1 H) 6.99 (d, *J*=1.00 Hz, 1 H) 7.23 (d, *J*=4.02 Hz, 1 H) 7.33 (d, *J*=1.25 Hz, 1 H) 7.43 (d, *J*=8.03 Hz, 2 H) 7.74 (d, *J*=5.27 Hz, 1 H) 7.99 (d, *J*=4.02 Hz, 1 H) 8.02 (d, *J*=8.53 Hz, 2 H) 8.44 (d, *J*=5.02 Hz, 1 H).

Intermediate 11

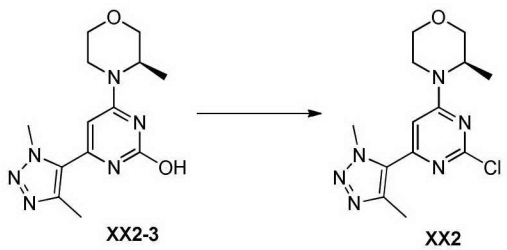


XX2

Synthesis scheme:



D1-2 **XX2-1** **XX2-2**



XX2-3 **XX2**

Step 1: Synthesis of Compound **XX2-1**

At 0°C, to a solution of 4-methoxylbenzyl alcohol (1.11 g, 8.06 mmol) in tetrahydrofuran (30 mL) was added sodium hydride (386.89 mg, 9.67 mmol, 60%) with stirring for 0.5 h. To the reaction solution was added **D1-2** (2 g, 8.09 mmol), which was purged with nitrogen three times. The reaction mixture was stirred at 20°C with heating for 12 h, quenched with water (30ml) and extracted with ethyl acetate (50ml). The organic phase was washed with saturated brine (30ml), dried over anhydrous sodium sulfate and filtered. The solution was concentrated to give the crude product, which was separated with column chromatography to give Compound **XX2-1**.

MS-ESI m/z: 350.2 [M+H]+.

Step 2: Synthesis of Compound **XX2-2**

To a solution of Compound **XX2-1** (4.5 g, 12.86 mmol) in N,N-dimethylformamide (50 mL) were added 1,4-dimethyltriazole (1.87 g, 19.30 mmol) bis(triphenylphosphine) palladium dichloride (451.46 mg, 643.2 μmol), and tetramethylammonium acetate (2.06 g, 15.44 mmol). The reaction mixture was stirred in a sealed tube at 130°C with heating for 12 h, and then diluted with ethyl acetate (200 mL), washed with water (80mL ×2) and saturated brine (80ml ×2), dried over anhydrous sodium sulfate, and filtered. The solution was concentrated to give the crude product, which was separated with column chromatography to give Compound **XX2-2**.

MS-ESI m/z:411.3 [M+H]+.

Step 3: Synthesis of Compound **XX2-3**

To a solution of Compound **XX2-2** (0.85 g, 2.07 mmol) in ethanol (20 mL) was added wet Pd/C(0.2 g, 2.07 mmol, 10%), which was purged with hydrogen three times. The reaction mixture was stirred at 30°C with heating for 12 h, and then filtered. The filtrate was concentrated to give crude Compound **XX2-3**.

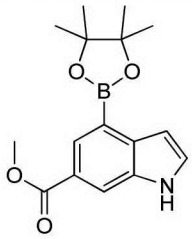
MS-ESI m/z: 291.2 [M+H]+.

Step 4: Synthesis of Compound **XX2**

To phosphorus oxychloride (20.35 g, 132.72 mmol) was added Compound **XX2-3** (0.6 g, 2.07 mmol) and the reaction mixture was stirred at 100°C for 1 h. The reaction solution was quenched with saturated sodium bicarbonate solution at 0°C, adjusted to pH 9, extracted with dichloromethane (100ml), washed with saturated brine (30ml), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to give crude Compound **XX2.**

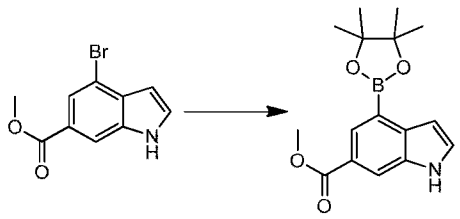
MS-ESI m/z: 309.1 [M+H]+.

Intermediate 12



XX3

Synthesis scheme:



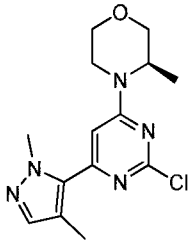
XX3-1 XX3

Step 1: Synthesis of Compound **XX3**

To a solution of Compound **XX3-1** (2 g, 7.87 mmol), bispinacol borate (4.00 g, 15.74 mmol) and ~~(14.72 mg, 12.74 μmol)~~ 1,1-bis(diphenylphosphino)ferrocene palladium chloride (0.3 g, 410.00 μmol) in 1,4-dioxane (25 mL) was added potassium acetate (2.32 g, 23.61 mmol), which was purged with nitrogen three times. The reaction mixture was stirred at 100°C with heating for 8 h and then filtered. The solution was concentrated to give the crude product, which was separated with column chromatography to give Compound **XX3**.

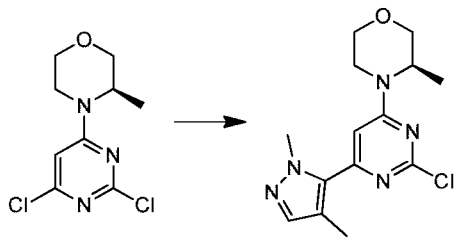
MS-ESI m/z: 302.1 [M+H]+.

Intermediate 13



XX4

Synthesis scheme:



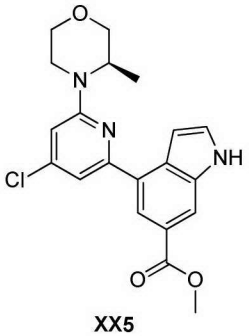
D1-2 XX4

Step 1: Synthesis of Compound **1**

To a solution of Compound **D1-2** (3.70 g, 14.91 mmol), 1,4-dimethylpyrazole-5-pinacol borate (3.31 g, 14.91 mmol) and bis(triphenylphosphine) palladium dichloride (523.36 mg, 745.64 μmol) in 1,4-dioxane (90 mL) was added 2M sodium carbonate (22.37 mL) aqueous solution, which was purged with nitrogen three times. The reaction mixture was stirred at 110°C with heating for 15 h and then filtered. The solution was concentrated to give the crude product, which was separated with column chromatography to give Compound **XX4**.

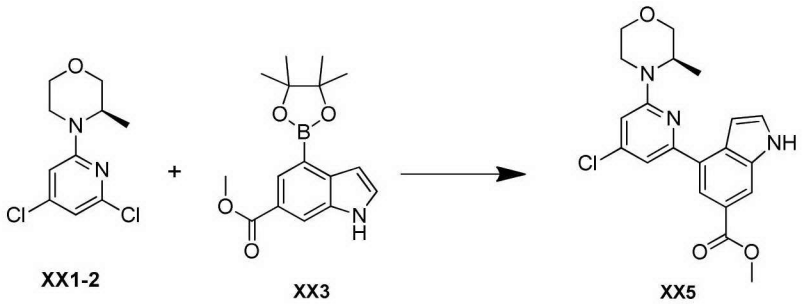
MS-ESI m/z: 308.2 [M+H]+.

Intermediate 14



XX5

Synthesis scheme:



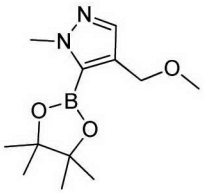
XX1-2 XX3 XX5

Step 1: Synthesis of Compound **XX5**

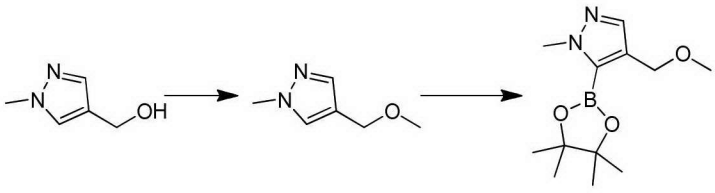
Except using corresponding raw materials, the procedures identical to those used for Compound **D1** in synthesis Example **Intermediate D1** were used to give Compound **XX5**.

MS-ESI m/z: 386.2 [M+H]+.

Intermediate 15



Synthesis scheme:



XX6-1 XX6-2 XX6

Step 1: Synthesis of Compound **XX6-2**

At 0°C, to a solution of Compound **XX6-1** (2 g, 17.84 mmol) in tetrahydrofuran (20 mL) was added sodium hydride (856.07 mg, 21.40 mmol, purity: 60%). The reaction mixture was stirred at 25°C for 1 h and then cooled to 0°C and added with methyl iodide (11.4 g, 80.32 mmol, 5.00 mL). The reaction mixture was stirred at 25°C for 10 h. The reaction was added with saturated brine (30 mL) and extracted with ethyl acetate (50 mL ×3). The organic phases were combined and successively washed with (70 mL) and brine (70 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced to give crude Compound **XX6-2**.

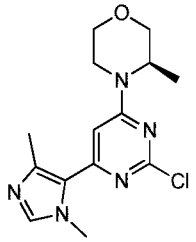
MS-ESI m/z: 253.1 [M+H]+.

Step 2: Synthesis of Compound **XX6**

At 0°C, to a solution of Compound **XX6-2** (0.5 g, 3.96 mmol) in tetrahydrofuran (15 mL) was added n-butyllithium (2.5 M, 4.76 mL). The reaction mixture was stirred at 25°C for 1h and then cooled to -78°C, and added with isopropanol pinacol borate (818.52 mg, 4.40 mmol). The reaction mixture was stirred at -78°C for 0.5 h and warmed to 0°C with stirring for 1 h. The reaction was quenched with saturated brine at 0-5°C, adjusted to pH=6-7 with 1 M hydrochloric acid and extracted with ethyl acetate (40 mL× 3). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated to give the crude product, which was separated with column chromatography to give Compound **XX6**.

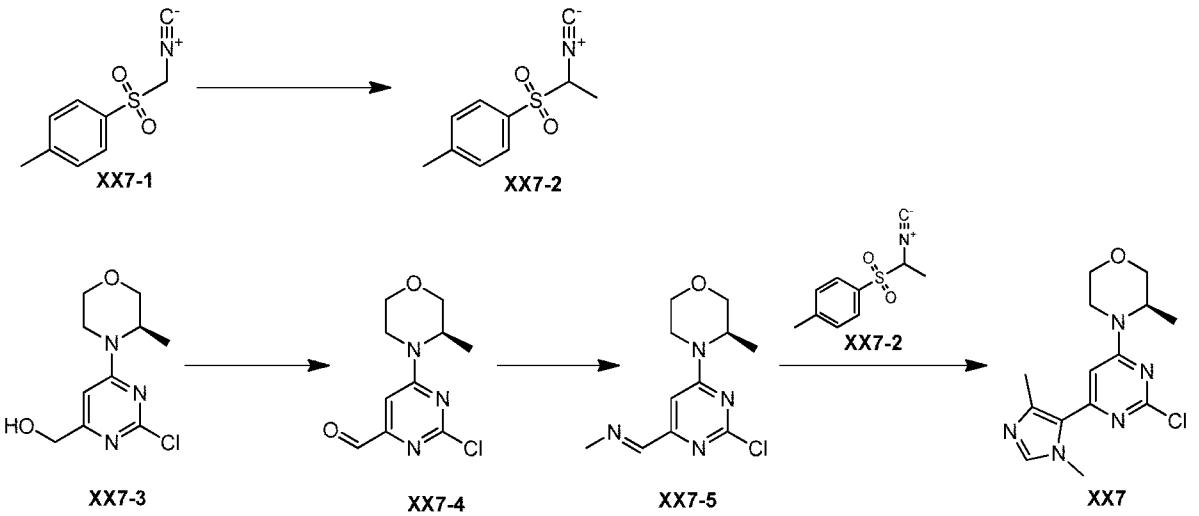
MS-ESI m/z: 127.0 [M+H]+.

Intermediate 16



XX7

Synthesis scheme:



Step 1: Synthesis of Compound **XX7-2**

At 0°C, to a solution of Compound **XX7-1**(1 g, 5.12 mmol) in dichloromethane (10 mL) were successively added benzyltriethyl ammonium chloride (233.33 mg, 1.02 mmol), methyl iodide (2.06 g, 14.51 mmol, 903.51 μL) and sodium hydroxide (10 mL) aqueous solution with the concentration of 30%. The reaction mixture was stirred at 0°C for 3 h and at 25°C for 2 h. The reaction was diluted with water (130 mL) and extracted with dichloromethane (75 mL×2). The organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product, which was separated with column chromatography to give Compound **XX7-2**.

^{1}H NMR (CHLOROFORM-d, 400MHz): δ = 7.90 (d, *J*=8.3 Hz, 2H), 7.46 (d, *J*=8.3 Hz, 2H), 4.61 (q, *J*=6.9 Hz, 1H), 2.52 (s, 3H), 1.77 ppm (d, *J*=6.8 Hz, 3H)

Step 2: Synthesis of Compound **XX7-4**

To a solution of Compound **XX7-3**(1 g, 4.10 mmol) in dichloromethane (20 mL) was added Dess-Martin periodiodine (2.61 g, 6.16 mmol). The reaction mixture was stirred at 30°C for 8 h, diluted with water (20 mL), extracted with dichloromethane (20 mL× 3). The organic phases were combined, washed with saturated brine (20 mL), filtered, and concentrated to give the crude product, which was separated with column chromatography to give Compound **XX7-4**.

MS-ESI m/z: 242.0 [M+H]+.

^{1}H NMR (CHLOROFORM-d, 400MHz): δ = 9.86 (s, 1H), 6.95 (s, 1H), 4.38 (br s, 1H), 4.06 (dd, *J*=11.8, 3.8 Hz, 1H), 4.14 (br d, *J*=7.5 Hz, 1H), 3.80-3.87 (m, 1H), 3.69-3.76 (m, 1H), 3.58 (td, *J*=12.0, 2.9 Hz, 1H), 3.37 (br t, *J*=11.8 Hz, 1H), 1.38 ppm (d, *J*=6.8 Hz, 3H).

Step 3: Synthesis of Compound **XX7-5**

To a solution of Compound **XX7-4**(0.51 g, 2.11 mmol) and methylamine hydrochloride (712.41 mg, 10.55 mmol) in toluene (20 mL) were successively added triethylamine (2.14 g, 21.10 mmol) and anhydrous sodium sulfate (4.50 g, 31.65 mmol). The reaction mixture was stirred at 50°C for 13 h, and the organic solvent was filtered and concentration to give crude Compound **XX7-5**.

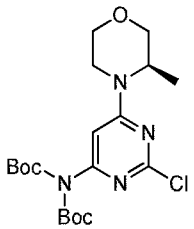
^{1}H NMR (CHLOROFORM-d, 400MHz): δ = 8.13 (d, *J*=1.8 Hz, 1H), 6.97 (s, 1H), 4.37 (br s, 1H), 4.08 (br s, 1H), 4.00 (dd, *J*=11.4, 3.6 Hz, 1H), 3.75-3.81 (m, 1H), 3.64-3.71 (m, 1H), 3.49-3.57 (m, 4H), 3.25-3.35 (m, 1H), 1.33 ppm (d, *J*=6.8 Hz, 3H)

Step 4: Synthesis of Compound **XX7**

To a solution of Compound **XX7-5** (0.535 g, 2.10 mmol) and **XX7-2** (439.54 mg, 2.10 mmol) in ethanol (25 mL) was added potassium carbonate (725.71 mg, 5.25 mmol). The reaction mixture was stirred at 25°C for 48 h and heated to 70°C with stirring for 12 h. The reaction solution was filtered and concentrated to give the crude product, which was separated with column chromatography to give Compound **XX7**.

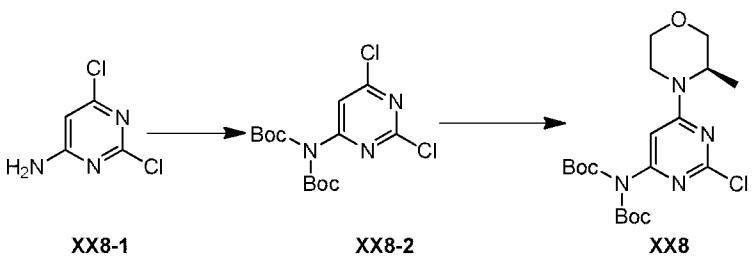
MS-ESI m/z: 308.1[M+H]+.

Intermediate 17



XX8

Synthesis scheme:



XX8-1 **XX8-2** **XX8**

Step 1: Synthesis of Compound **XX8-2**

At 0°C, to a solution of Compound **XX8-1**(10 g, 60.98 mmol) and 4-dimethylaminopyridine (744.96 mg, 6.10 mmol) in dichloromethane (100 mL) was slowly added di-*tert*-butyl decarbonate (29.28 g, 134.15 mmol). The reaction mixture was stirred at 30°C for 36 h and added with ice water (120 mL) and extracted with dichloromethane (150 mL×2). The organic phases were combined, washed with saturated brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to give the crude product, which was separated with column chromatography to give Compound **XX8-2**.

MS-ESI m/z: 364.1 [M+H]+.

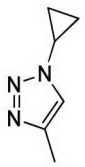
Step 2: Synthesis of Compound **XX8**

To a solution of Compound **XX8-2** (6 g, 16.47 mmol) and (R)-3-methylmorpholine (1.83 g, 18.12 mmol) in 1,4-dioxane (50 mL) was added N,N-diisopropylethylamine (2.13 g, 16.47 mmol). The reaction mixture was stirred at 50°C for 10 and then concentrated under reduced pressure to give the crude product, which was separated with column chromatography to give Compound **XX8**.

MS-ESI m/z: 429.3 [M+H]+.

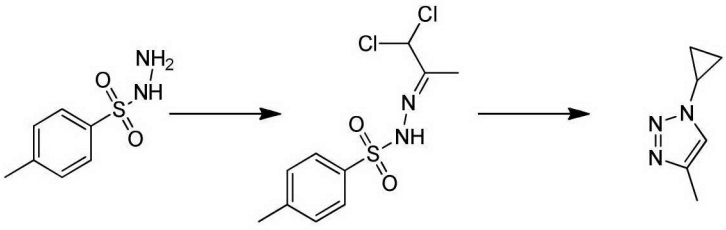
^{1}H NMR (CHLOROFORM-d, 400MHz): δ = 6.76 (s, 1H), 4.30 (br s, 1H), 3.99 (br dd, *J*=11.5, 3.5 Hz, 2H), 3.74-3.81 (m, 1H), 3.64-3.72 (m, 1H), 3.54 (td, *J*=11.9, 3.0 Hz, 1H), 3.28 (td, *J*=12.9, 3.9 Hz, 1H), 1.54 (s, 18H), 1.31 ppm (d, *J*=6.8 Hz, 3H).

Intermediate 18



XX9

Synthesis scheme:



XX9-1 **XX9-2** **XX9**

Step 1: Synthesis of Compound **XX9-2**

To as solution of Compound **XX9-1** (6.2 g, 33.29 mmol) in propionic acid (10 mL) was added 1,1-dichloroacetone (4.57 g, 35.96 mmol). The reaction mixture was stirred at 30°C for 14 h and filtered. The filter cake was washed with cyclohexane (100 mL) and the solid was rotated to remove the solvent to give crude Compound **XX9-2**.

^{1}H NMR (DMSO-d6, 400MHz): δ = 11.88 (br s, 1H), 9.19 (s, 1H), 7.80 (d, J=8.3 Hz, 2H), 7.43 (d, J=8.0 Hz, 2H), 2.39 (s, 3H), 1.84 ppm (s, 3H)

Step 2: Synthesis of Compound **XX9**

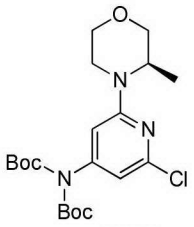
At 0°C, to a solution of compound cyclopropylamine (1.25 g, 21.89 mmol, 1.52 mL) in ethanol (50 mL) was added triethylamine (11.08 g, 109.45 mmol). The reaction mixture was stirred at 0°C for 10 h, then added with a solution of **XX9-2** (7.11 g, 24.08 mmol) in acetonitrile (50 mL) and heated to 30°C with stirring for

16 h. The reaction solution was concentrated to give the crude product, which was separated with column chromatography to give Compound **XX9**.

MS-ESI m/z: 124.0 [M+H]+.

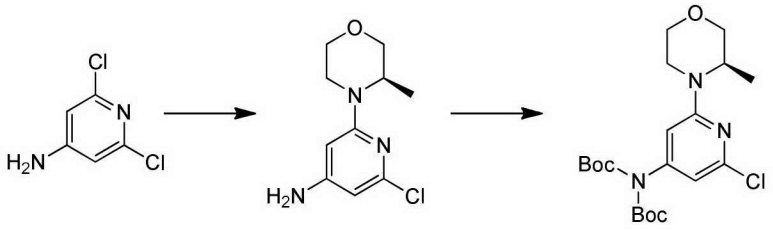
^{1}H NMR (CHLOROFORM-d, 400MHz): δ = 7.32 (s, 1H), 3.73 (m, 1H), 2.34 (s, 3H), 1.20-1.27 (m, 2H), 1.10-1.17 ppm (m, 2H).

Intermediate 19



XX10

Synthesis scheme:



XX10-1 **XX10-2** **XX10**

Step 1: Synthesis of Compound **XX10-2**

To a solution of Compound **XX10-1** (2 g, 12.27 mmol) and (*R*)-3-methylmorpholine (1.61 g, 15.95 mmol) 的 1-methyl-2-pyrrolidone (5 mL) was added N,N-diisopropylethylamine (1.74 g, 13.50 mmol). The reaction was heated with microwave at 180°C for 1 h and the reaction solution was concentrated to give the crude product, which was separated with column chromatography to give Compound **XX10-2**.

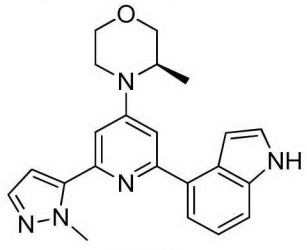
MS-ESI m/z: 228.0 M+H]+.

Step 2: Synthesis of Compound **XX10**

At 0-5°C, to a solution of Compound **XX10-2** (1.4 g, 6.15 mmol) and 4-dimethylaminopyridine (1 g, 8.19 mmol) in dichloromethane (30 mL) was slowly added di-*tert*-butyl decarbonate (4.03 g, 18.45 mmol). The reaction mixture was stirred at 30°C for 5 h, then added with water (30 mL) and extracted with dichloromethane (50 mL×3). The organic phases were combined, washed with saturated brine (70 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product, which was separated with column chromatography to give Compound **XX10**.

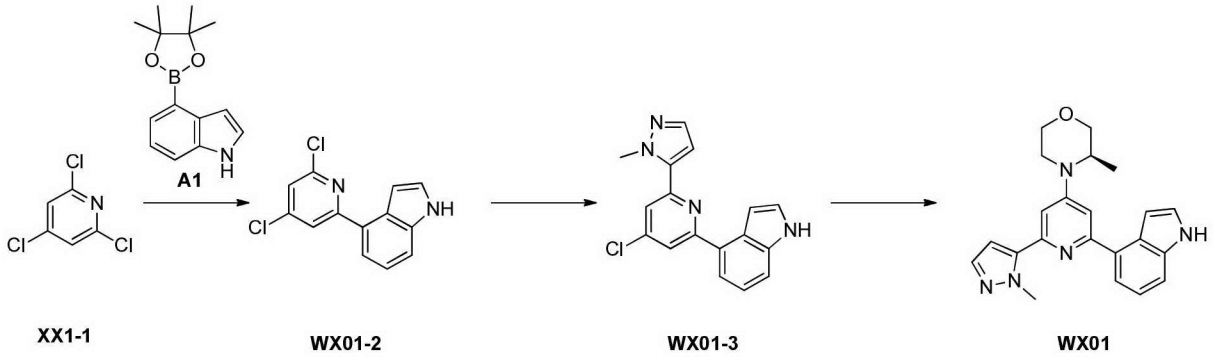
MS-ESI m/z: 428.6 M+H]+.

Example 1: Compound WX01



WX01

Synthesis scheme:



Step 1: Synthesis of Compound **WX01-2**

At room temperature, to as solution of Compound **A1** (300.00 mg, 1.64 mmol) in 1,4-dioxane (10.00 mL) were added Compound **XX1-1** (398.70 mg, 1.64 mmol), dichlorobis(triphenylphosphine) palladium (115.11 mg, 164.00 μmol), sodium carbonate solution (2 M, 2.46 mL), which was stirred at 90°C for 12 h. The reaction system was diluted with 20 mL of water and extracted with ethyl acetate (40 mL). The organic phase was washed with saturated brine (20 mL×2) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with column chromatography (petroleum ether/ethyl acetate =10/1,6/1) to give Compound **WX01-2**.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.03 (br s, 1 H) 7.23 (t, *J*=7.78 Hz, 1 H) 7.51 (t, *J*=2.76 Hz, 1 H) 7.57 (d, *J*=8.03 Hz, 1 H) 7.63 (d, *J*=7.53 Hz, 1 H) 7.71 (d, *J*=1.51 Hz, 1 H) 8.07 (d, *J*=1.51 Hz, 1 H) 11.41 (br s, 1 H).

Step 2: Synthesis of Compound **WX01-3**

At room temperature, to a solution of Compound **WX01-2** (100.00 mg, 380.05 μmol) in 1,4-dioxane (3.00 mL) were added 1-methyl-1H-pyrazole-5-boric acid (47.86 mg, 380.05 μmol), dichlorobis(triphenylphosphine) palladium (26.68 mg, 38.00 μmol) and sodium carbonate solution (2 M, 570.08 uL), which was stirred at 90°C for 12h. The reaction system was diluted with 20 mL of water and extracted with ethyl acetate (30 mL). The organic phase was washed with saturated brine (20 mL×2) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was separated and purified with silica gel plate (petroleum ether/ethyl acetate =2/1) to give Compound **WX01-3**.

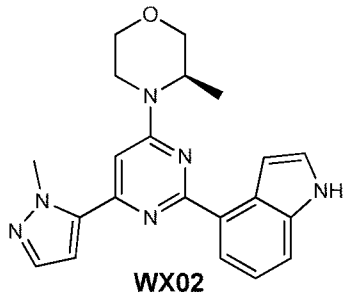
MS *m/z*: 308.9[M+H]$^+$

Step 3: Synthesis of Compound **WX01**

At room temperature, to a solution of Compound **WX01-3** (70.00 mg, 226.71 μmol) in 1,4-dioxane (3.00 mL) were added (*R*)-3-methylmorpholine (45.86 mg, 453.43 μmol), palladium acetate (26.68 mg, 38.00 μmol), 2-dicyclohexylphosphono-2,4,6-triisopropylbiphenyl (21.62 mg, 45.34 μmol), cesium carbonate (221.60 mg, 680.14 μmol), which was stirred at 100°C under nitrogen atmosphere for 12 h. The reaction system was diluted with 20 mL of water and extracted with ethyl acetate (25 mL). The organic phase was washed with saturated brine (15 mL×2) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was separated with preparative HPLC (neutral) to give Compound **WX01**.

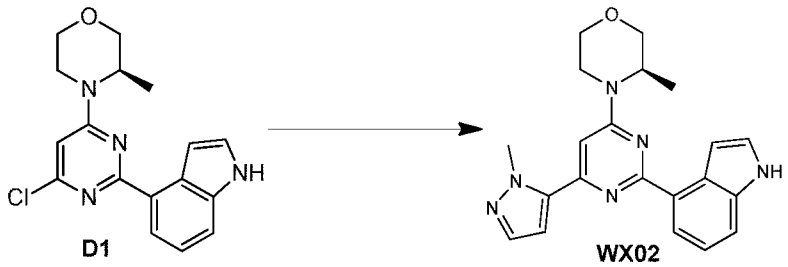
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.34 (d, *J*=6.52 Hz, 3 H) 3.31 - 3.38 (m, 1 H) 3.49 (br s, 1 H) 3.70 - 3.77 (m, 1 H) 3.88 (s, 2 H) 4.04 - 4.13 (m, 2 H) 4.32 (s, 3 H) 6.60 (d, *J*=2.00 Hz, 1 H) 6.93 (d, *J*=2.52 Hz, 1 H) 7.00 (br s, 1 H) 7.19 (d, *J*=2.00 Hz, 1 H) 7.31 - 7.36 (m, 2 H) 7.50 (d, *J*=8.52 Hz, 1 H) 7.53 (d, *J*=2.00 Hz, 1 H) 7.61 (d, *J*=7.52 Hz, 1 H) 8.33 (br s, 1 H).MS *m/z*: 374.0[M+H]$^+$.

Example 2: Compound WX02



WX02

Synthesis scheme:



D1 **WX02**

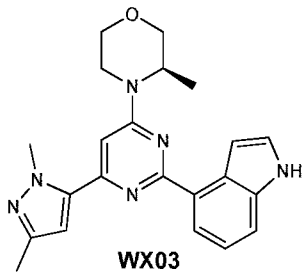
Step 1: Synthesis of Compound **WX02**

To a solution of Compound **D1** (0.08 g, 243.31 μmol) in 1,4-dioxane (5mL) were added 1-methylpyrazole-5-pinacol borate (75.94 mg, 364.97 μmol), bistriphenylphosphine palladium dichloride (17.08 mg, 24.33 μmol) and sodium carbonate (2 M, 364.97 uL). The reaction solution was stirred at 90°C under the protection of nitrogen for 15 h. The reaction solution was filtered through celite and the filtrate was extracted with 30 mL of ethyl acetate (10mL×3). The organic phase was washed with 30 mL of water (10mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was separated with preparative HPLC (neutral condition) to give Compound **WX02**.

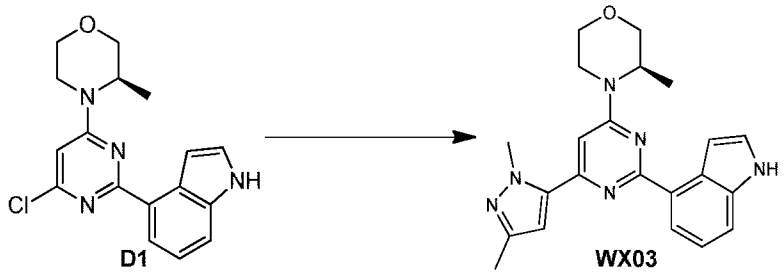
MS-ESI m/z: 375.0 [M+H]+.

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.30 (d, J=6.78 Hz, 3 H) 3.28 - 3.32 (m, 1 H) 3.31 (s, 1 H) 3.55 (td, J=11.80, 2.76 Hz, 1 H) 3.70 (dd, J=11.29, 2.76 Hz, 1 H) 3.79 - 3.86 (m, 1 H) 4.03 (dd, J=11.17, 3.14 Hz, 1 H) 4.29 (s, 4 H) 4.68 (br s, 1 H) 6.98 - 7.04 (m, 1 H) 7.01 (s, 1 H) 7.00 (d, J=2.01 Hz, 1 H) 7.22 (t, J=7.78 Hz, 1 H) 7.30 (br s, 1 H) 7.47 (t, J=2.64 Hz, 1 H) 7.52 - 7.57 (m, 2 H) 8.13 (d, J=7.28 Hz, 1 H) 11.22 - 11.34 (m, 1 H) 11.29 (br s, 1 H).

Example 3: Compound WX03



Synthesis scheme:



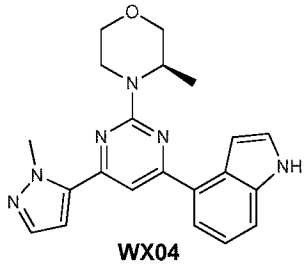
Step 1: Synthesis of Compound **WX03**

To a solution of Compound **D1** (0.08 g, 243.31 μmol) in 1,4-dioxane (5mL) were added 1,3-dimethylpyrazole-5-pinacol borate (54.04 mg, 243.31 μmol), bistriphenylphosphine palladium dichloride(17.08 mg, 24.33 μmol) and sodium carbonate (2 M, 364.97 uL). The reaction solution was stirred at 90°C under the protection of nitrogen for 15 h. The reaction solution was filtered through celite and the filtrate was extracted with 30mL of ethyl acetate (10 mL×3). The organic phase was washed with 30 mL of water (10 mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was separated with preparative HPLC (neutral condition) to give Compound **WX03**.

MS-ESI m/z:389.1 [M+H]+.

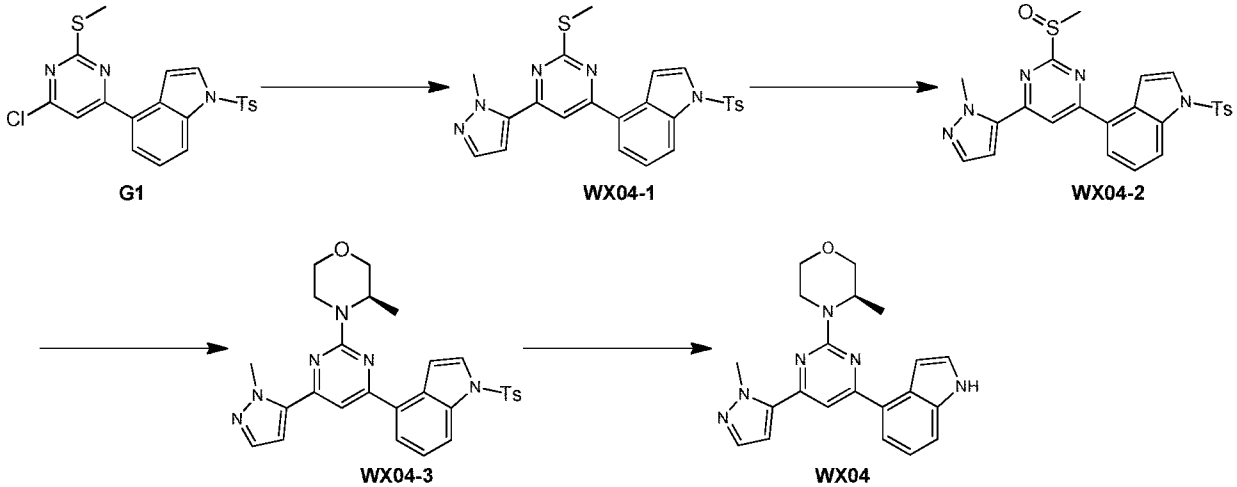
^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.29 (d, J=6.53 Hz, 3 H) 2.18 - 2.26 (m, 1 H) 2.21 (s, 1 H) 2.26 - 2.27 (m, 1 H) 3.23 - 3.30 (m, 1 H) 3.24 - 3.31 (m, 1 H) 3.48 - 3.59 (m, 1 H) 3.69 (dd, J=11.42, 2.64 Hz, 1 H) 3.77 - 3.88 (m, 1 H) 3.77 - 3.84 (m, 1 H) 4.02 (br dd, J=11.29, 3.01 Hz, 1 H) 4.20 (s, 2 H) 4.17 - 4.22 (m, 1 H) 4.26 (br d, J=13.55 Hz, 1 H) 4.54 - 4.80 (m, 1 H) 4.65 (br s, 1 H) 6.64 - 6.85 (m, 1 H) 6.69 - 6.83 (m, 1 H) 6.71 - 6.82 (m, 1 H) 6.78 (s, 1 H) 6.96 (s, 1 H) 6.92 - 7.03 (m, 1 H) 7.21 (t, J=7.78 Hz, 1 H) 7.27 - 7.33 (m, 1 H) 7.29 (br s, 1 H) 7.46 (t, J=2.64 Hz, 1 H) 7.55 (d, J=8.03 Hz, 1 H) 8.11 (d, J=7.28 Hz, 1 H) 11.27 (br s, 1 H).

Example 4: Compound WX04



WX04

Synthesis scheme:



Step 1: Synthesis of Compound **WX04-1**

To a solution of Compound **G1** (0.3 g, 697.77 μmol) in 1,4-dioxane (5mL) were added 1-methylpyrazole-5-pinacol borate (188.74 mg, 907.10 μmol), bistriphenylphosphine palladium dichloride (48.98 mg, 69.78 μmol) and sodium carbonate (2 M, 1.05 mL). The reaction solution was stirred at 90°C under the protection of nitrogen for 15 h. The reaction solution was filtered through celite and the filtrate was extracted with 60 mL of ethyl acetate (20mL×3). The organic phase was washed with 45mL of water (15 mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with silica gel column (petroleum ether/ethyl acetate =1:0,3:1) to give Compound **WX04-1**.

MS-ESI m/z: 476.1 [M+H]+.

Step 2: Synthesis of Compound **WX04-2**

To a solution of Compound **WX04-1** (0.205 g, 431.05 μmol) in dichloromethane (5mL) was added m-chloroperoxybenzoic acid (87.51 mg, 431.05 μmol). The reaction solution was stirred at 20°C for 15 h. The reaction solution was quenched at 20°C with 20 mL of saturated sodium sulfite solution and then extracted with 40mL of dichloromethane (20 mL×2). The organic phase was washed with 45mL of water (15mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give crude **WX04-2**.

MS-ESI m/z: 492.0 [M+H]+.

Step 3: Synthesis of Compound **WX04-3**

To a solution of Compound **WX04-2**(213.90 mg, 435.12 μmol) and (*R*)-3-methylmorpholine (220.06 mg, 2.18 mmol) in 1,4-dioxane (5mL) was added diisopropylethylamine (562.36 mg, 4.35 mmol). The reaction

solution was stirred at 100°C for 65 h. The reaction solution was extracted with 60 mL of ethyl acetate (20mL×3) and the organic phase was washed with 60mL of water (20mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give crude **WX04-3**.

MS-ESI m/z: 529.1 [M+H]+.

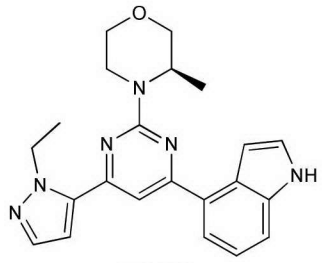
Step 4: Synthesis of Compound **WX04**

To a solution of Compound **WX04-3** (0.35 g, 662.10 μmol) in methanol (5 mL) was added sodium hydroxide (2 M, 993.14 μL). The reaction mixture was stirred at 60°C for 17 h. The reaction solution was extracted with 40mL of ethyl acetate (20mL×2) and the organic phase was washed with 60mL of water (20mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with preparative HPLC (neutral condition) to give Compound **WX04**.

MS-ESI m/z: 375.0 [M+H]+

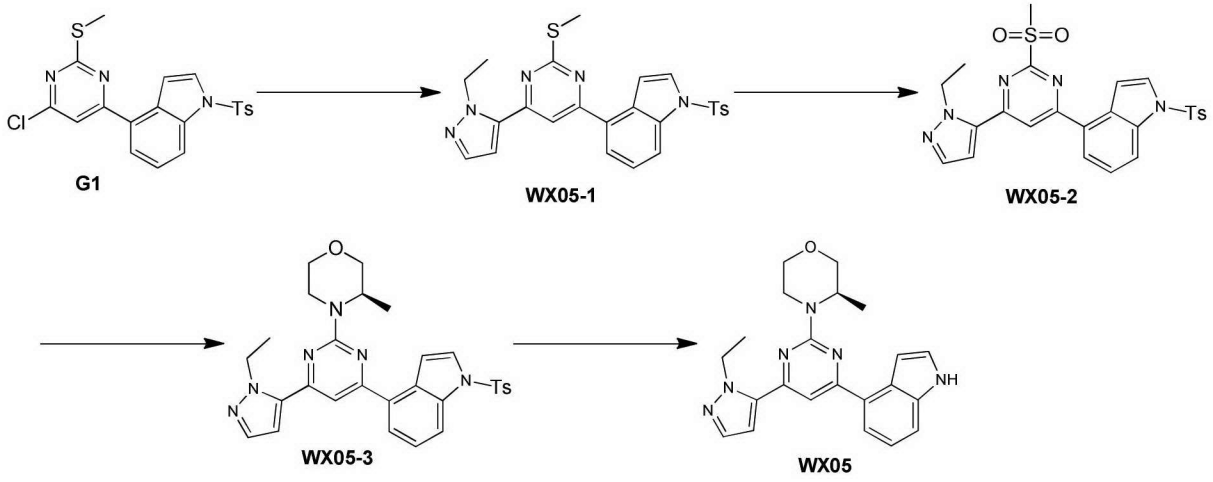
^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.43 (d, J=6.78 Hz, 3 H) 3.44 (td, J=12.99, 3.89 Hz, 1 H) 3.65 (td, J=11.86, 2.89 Hz, 1 H) 3.77 - 3.83 (m, 1 H) 3.84 - 3.89 (m, 1 H) 4.07 (dd, J=11.29, 3.51 Hz, 1 H) 4.35 (s, 3 H) 4.54 (br d, J=13.80 Hz, 1 H) 4.90 (br d, J=4.02 Hz, 1 H) 6.78 (d, J=2.01 Hz, 1 H) 7.16 (br s, 1 H) 7.30 - 7.35 (m, 1 H) 7.35 - 7.38 (m, 2 H) 7.52 - 7.57 (m, 2 H) 7.69 (d, J=7.53 Hz, 1 H) 8.35 (br s, 1 H)

Example 5: Compound WX05



WX05

Synthesis scheme:



Step 1: Synthesis of Compound **WX05-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX04-1** in synthesis Example **4** were used to give **WX05-1**.

MS-ESI m/z:490.1 [M+H]+.

Step 2: Synthesis of Compound **WX05-2**

To a solution of Compound **WX05-1** (0.193 g, 394.19 μmol) in dichloromethane (5mL) was added m-chloroperoxybenzoic acid (80.03 mg, 394.19 μmol). The reaction solution was stirred at 20°C for 15 h. The reaction solution was quenched with saturated sodium sulfite solution at 20°C and extracted with 40mL of dichloromethane (20mL×2). The organic phase was washed with 45mL of water (15mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give crude **WX05-2**.

MS-ESI m/z:522.1 [M+H]+.

Step 3: Synthesis of Compound **WX05-3**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX04-3** in synthesis Example **4** were used to give crude **WX05-3**.

MS-ESI m/z: 543.1 [M+H]+.

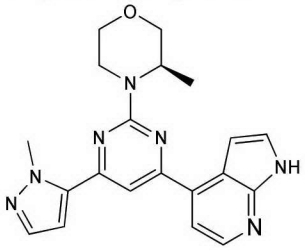
Step 4: Synthesis of Compound **WX05**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX04** in synthesis Example **4** were used to give Compound **WX05**.

MS-ESI m/z: 389.0 [M+H]+.

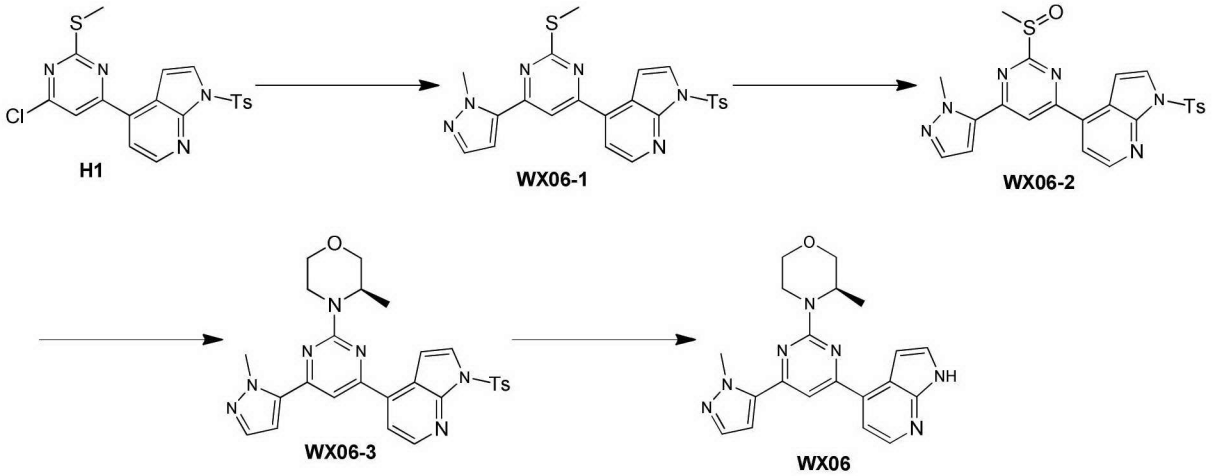
^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.42 (d, J=6.78 Hz, 3 H) 2.29 (s, 3 H) 3.43 (td, J=12.86, 3.39 Hz, 1 H) 3.59 - 3.69 (m, 1 H) 3.75 - 3.81 (m, 1 H) 3.83 - 3.88 (m, 1 H) 4.06 (br dd, J=11.04, 3.26 Hz, 1 H) 4.17 (br s, 1 H) 4.15 (s, 2 H) 4.56 (br d, J=12.05 Hz, 1 H) 4.92 (br d, J=5.02 Hz, 1 H) 7.17 (br s, 1 H) 7.20 (s, 1 H) 7.29 - 7.35 (m, 1 H) 7.37 (br s, 1 H) 7.40 (s, 1 H) 7.55 (d, J=8.03 Hz, 1 H) 7.68 (d, J=7.28 Hz, 1 H) 8.42 (br s, 1 H).

Example 6: Compound WX06



WX06

Synthesis scheme:



Step 1: Synthesis of Compound **WX06-1**

To a solution of Compound **H1**(200.46 mg, 465.18 μmol) in 1,4-dioxane(5mL) were added 1-methylpyrazole-5-pinacol borate (125.82 mg, 604.73 μmol), bistriphenylphosphine palladium dichloride (16.33 mg, 23.26 μmol) and sodium carbonate (2 M, 697.77 uL). The reaction solution was stirred under the protection of nitrogen at 90°C for 15 h. After the reaction solution was filtered through celite, the filtrate was extracted with 60 mL of ethyl acetate (20 mL×3), and the organic phase was washed with 45mL of water (15 mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with silica gel column (petroleum ether/ethyl acetate =1:0,3:1) to give Compound **WX06-1**.

MS-ESI m/z: 477.0 [M+H]+.

Step 2: Synthesis of Compound **WX06-2**

To a solution of Compound **WX06-1** (0.21 g, 440.65 μmol) in dichloromethane (5mL) was added m-chloroperoxybenzoic acid (89.46 mg, 440.65 μmol). The reaction solution was stirred at 20°C for 15 h. The reaction solution was quenched at 20°C with 20 mL of saturated sodium sulfite solution and then extracted with 40 mL of dichloromethane (20 mL×2). The organic phase was washed with 45 mL of water (15mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give crude **WX06-2**.

MS-ESI m/z: 493.0 [M+H]+.

Step 3: Synthesis of Compound **WX06-3**

To a solution of Compound **WX06-2** (226.45 mg, 459.74 μmol) and (*R*)-3-methylmorpholine (232.50 mg, 2.30 mmol) in 1,4-dioxane (5mL) was added diisopropylethylamine (594.17 mg, 4.60 mmol). The reaction solution was stirred at 100°C for 65 h. The reaction solution was extracted with 60 mL of ethyl acetate (20mL×3) and the organic phase was washed with 30mL of water (10mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give crude **WX06-3**.

MS-ESI m/z:530.1 [M+H]+.

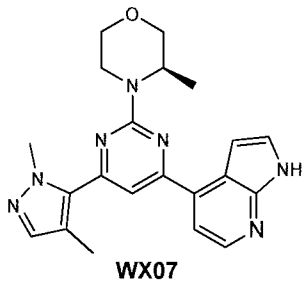
Step 4: Synthesis of Compound **WX06**

To a solution of Compound **WX06-3** (0.330 g, 623.10 μmol) in methanol (5 mL) was added sodium hydroxide (2 M, 934.65 uL). The reaction solution was stirred at 60°C for 17 h. The reaction solution was extracted with 60 mL of ethyl acetate (20mL×3) and the organic phase was washed with 45 mL of water (15 mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with preparative HPLC (neutral condition) to give Compound **WX06**.

MS-ESI m/z: 376.1[M+H]+.

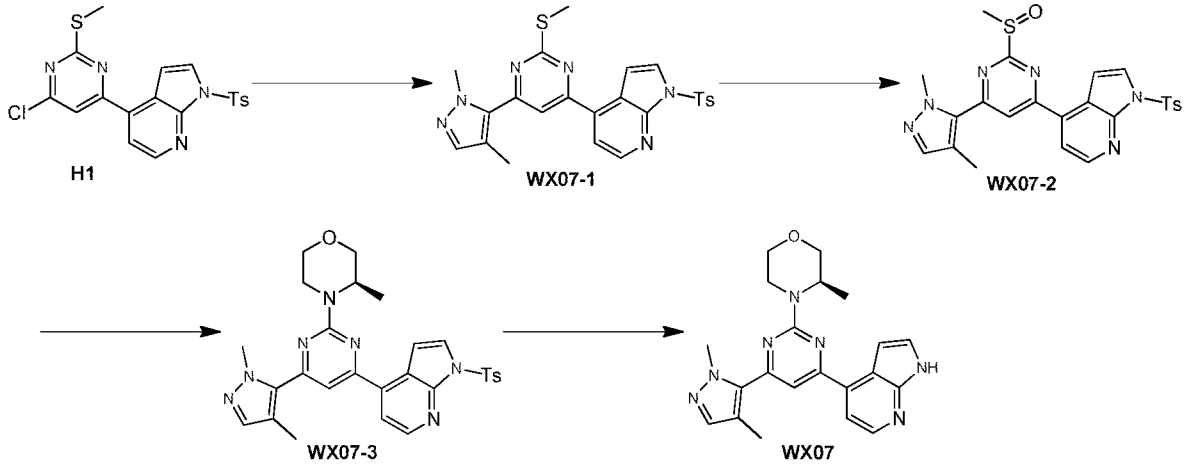
^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.43 (br d, J=6.78 Hz, 3 H) 3.37 - 3.53 (m, 1 H) 3.60 - 3.71 (m, 1 H) 3.78 - 3.84 (m, 1 H) 3.84 - 3.91 (m, 1 H) 4.09 (br d, J=9.04 Hz, 1 H) 4.35 (s, 3 H) 4.54 (br d, J=13.30 Hz, 1 H) 5.04 (s, 1 H) 4.88 (br d, J=4.52 Hz, 1 H) 6.75 - 6.88 (m, 1 H) 6.81 (s, 1 H) 6.98 - 7.13 (m, 1 H) 7.06 (br s, 1 H) 7.40 (s, 1 H) 7.50 (br s, 1 H) 7.56 (s, 1 H) 7.62 (br d, J=5.02 Hz, 1 H) 8.47 (br d, J=4.77 Hz, 1 H) 9.84 (br s, 1 H).

Example 7: Compound WX07



WX07

Synthesis scheme:



H1 WX07-1 WX07-2 WX07-3 WX07

Step 1: Synthesis of Compound **WX07-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX06-1** in synthesis Example **6** were used to give **WX07-1**.

MS-ESI m/z: 491.1 [M+H]+.

Step 2: Synthesis of Compound **WX07-2**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX06-2** in synthesis Example **6** were used to give crude **WX07-2**.

MS-ESI m/z: 507.1 [M+H]+.

Step 3: Synthesis of Compound **WX07-3**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX06-3** in synthesis Example **6** were used to give crude **WX07-3**.

MS-ESI m/z:544.2 [M+H]+.

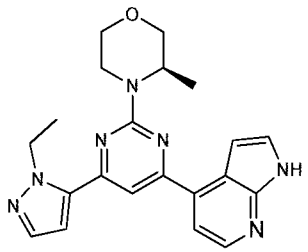
Step 4: Synthesis of Compound **WX07**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX06** in synthesis Example **6** were used to give Compound **WX07**.

MS-ESI m/z:390.0 [M+H]+.

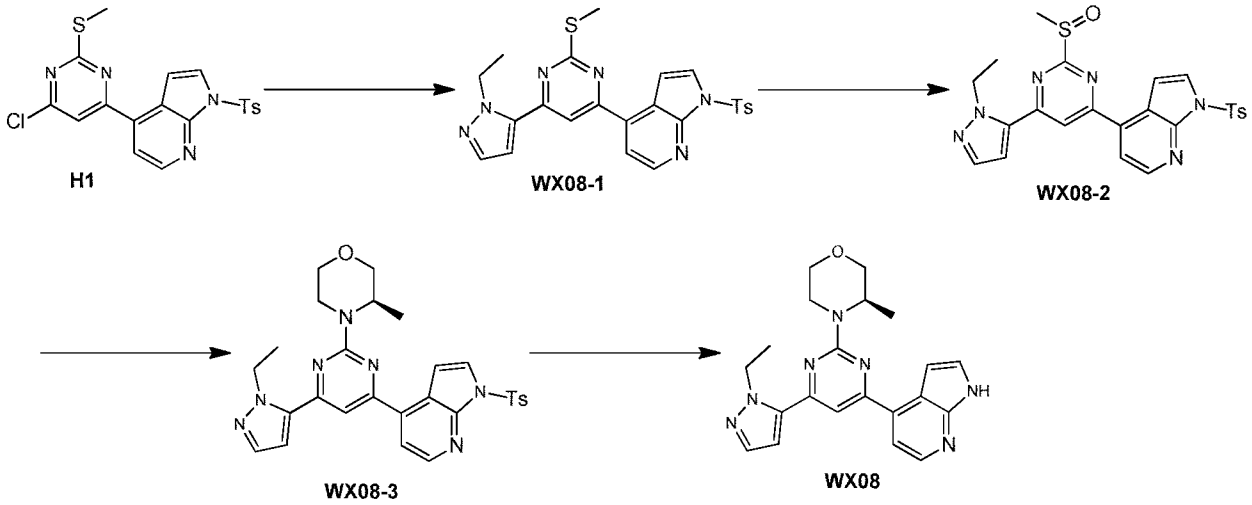
^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.43 (d, J=6.78 Hz, 3 H) 2.31 (s, 3 H) 3.44 (td, J=12.86, 3.64 Hz, 1 H) 3.64 (td, J=11.92, 3.01 Hz, 1 H) 3.77 - 3.82 (m, 1 H) 3.84 - 3.89 (m, 1 H) 4.07 (dd, J=11.54, 3.51 Hz, 1 H) 4.16 (s, 3 H) 4.55 (br d, J=13.30 Hz, 1 H) 4.90 (br d, J=4.77 Hz, 1 H) 7.06 (br s, 1 H) 7.24 (s, 1 H) 7.41 (s, 1 H) 7.48 (br s, 1 H) 7.59 - 7.66 (m, 1 H) 8.46 (br s, 1 H) 9.09 (br s, 1 H).

Example 8: Compound WX08



WX08

Synthesis scheme:



H1 WX08-1 WX08-2 WX08-3 WX08

Step 1: Synthesis of Compound **WX08-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX06-1** in synthesis Example **6** were used to give **WX08-1**.

MS-ESI m/z:491.3 [M+H]+.

Step 2: Synthesis of Compound **WX08-2**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX06-2** in synthesis Example **6** were used to give crude **WX08-2**.

MS-ESI m/z:507.1 [M+H]+.

Step 3: Synthesis of Compound **WX08-3**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX06-3** in synthesis Example **6** were used to give crude **WX08-3**.

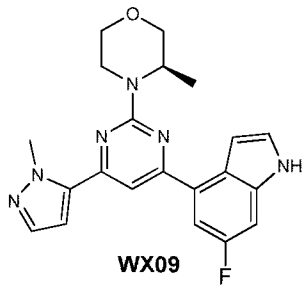
MS-ESI m/z:544.2 [M+H]+.

Step 4: Synthesis of Compound **WX08**

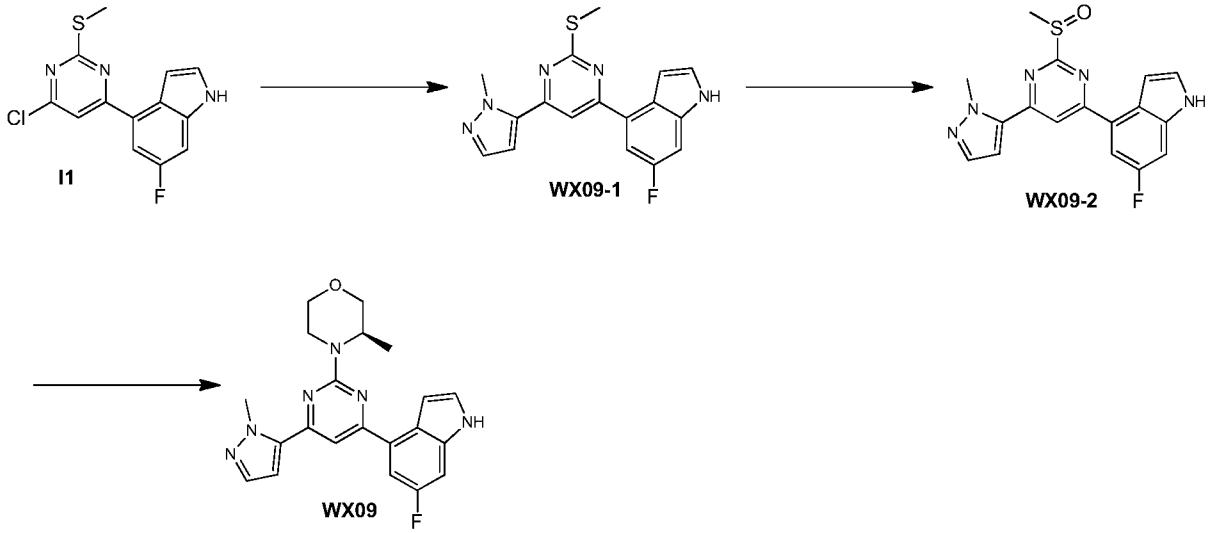
Except using corresponding raw materials, the procedures identical to those used for Compound **WX06** in synthesis Example **6** were used to give Compound **WX08**.

MS-ESI m/z:390.0 [M+H]+.^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.29 (br s, 3 H) 1.39 (br s, 3 H) 3.32 (br s, 1 H) 3.51 (br d, J=11.04 Hz, 1 H) 3.59 - 3.81 (m, 1 H) 3.71 (br d, J=16.56 Hz, 1 H) 3.95 (br d, J=9.79 Hz, 1 H) 4.39 (br d, J=11.80 Hz, 1 H) 4.72 (br s, 3 H) 6.66 (br s, 1 H) 6.93 (br s, 1 H) 7.13 (br s, 1 H) 7.32 - 7.74 (m, 3 H) 8.35 (br s, 1 H) 9.83 (br s, 1 H).

Example 9: Compound WX09



Synthesis scheme:



Step 1: Synthesis of Compound **WX09-1**

To a solution of Compound **I1** (0.1 g, 340.43 μmol) in 1,4-dioxane (5mL) were added 1-methylpyrazole-5-pinacol borate (92.08 mg, 442.56 μmol), bistriphenylphosphine palladium dichloride (11.95 mg, 17.02 μmol) and sodium carbonate (2 M, 510.64 μL). The reaction mixture was stirred under the protection of nitrogen at 90°C for 15 h. After the reaction solution was filtered through celite, the filtrate was extracted with 60 mL of ethyl acetate (20mL×3). The organic phase was washed with 45 mL of water (15 mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with silica gel column (petroleum ether/ethyl acetate =1:0,3:1) to give Compound **WX09-1**.

MS-ESI m/z:340.0[M+H]+.

Step 2: Synthesis of Compound **WX09-2**

To a solution of Compound **WX09-1** (102 mg, 300.54 μmol) in dichloromethane (5mL) was added m-chloroperoxybenzoic acid (61.02 mg, 300.54 μmol). The reaction solution was stirred at 20°C for 15 h. The reaction solution was quenched at 20°C with 20 mL of saturated sodium sulfite solution and then extracted with 40mL of dichloromethane (20 mL×2). The organic phase was washed with 45 mL of water (15mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give crude **WX09-2**.

MS-ESI m/z:356.0[M+H]+.

Step 3: Synthesis of Compound **WX09**

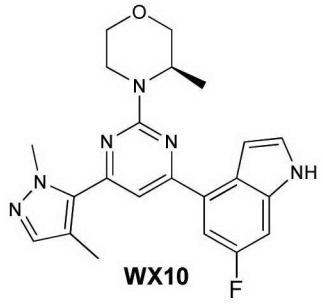
To a solution of Compound **WX09-2** (206 mg, 579.65 μmol) and (*R*)-3-methylmorpholine (293.15 mg, 2.90 mmol)的 1,4-dioxane (5mL) was added diisopropylethylamine(749.14 mg, 5.80 mmol). The reaction solution

was stirred at 100°C for 65 h. The reaction solution was extracted with 60mL of dichloromethane (20 mL×3). The organic phase was washed with 30mL of water (10mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with preparative HPLC (neutral condition) to give Compound **WX09**.

MS-ESI m/z:393.0 [M+H]+.

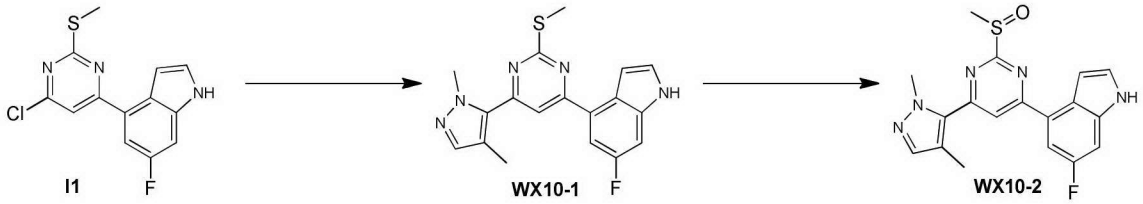
^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.42 (d, J=6.78 Hz, 3 H) 3.44 (td, J=12.86, 3.64 Hz, 1 H) 3.65 (td, J=11.80, 2.76 Hz, 1 H) 3.77 - 3.83 (m, 1 H) 3.84 - 3.89 (m, 1 H) 4.07 (dd, J=11.29, 3.51 Hz, 1 H) 4.35 (s, 3 H) 4.53 (br d, J=11.80 Hz, 1 H) 4.88 (br d, J=6.53 Hz, 1 H) 6.79 (d, J=1.76 Hz, 1 H) 7.08 (br s, 1 H) 7.23 (br d, J=8.78 Hz, 1 H) 7.32 - 7.36 (m, 2 H) 7.45 - 7.50 (m, 1 H) 7.48 (dd, J=10.67, 2.13 Hz, 1 H) 7.55 (d, J=2.01 Hz, 1 H) 8.36 (br s, 1 H).

Example 10: Compound WX10



WX10

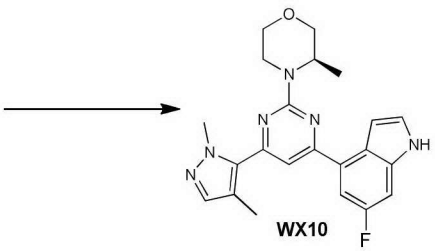
Synthesis scheme:



I1

WX10-1

WX10-2



WX10

Step 1: Synthesis of Compound **WX10-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX09-1** in synthesis Example **9** were used to give **WX10-1**.

MS-ESI m/z:353.9 [M+H]+

Step 2: Synthesis of Compound **WX10-2**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX09-2** in synthesis Example **9** were used to give crude **WX10-2**.

MS-ESI m/z:370.0[M+H]+.

Step 3: Synthesis of Compound **WX10**

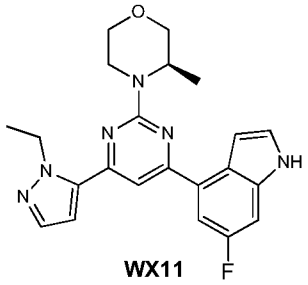
Except using corresponding raw materials, the procedures identical to those used for Compound **WX09** in

synthesis Example **9** were used to give Compound **WX10**.

MS-ESI m/z: 407.0 [M+H]+.

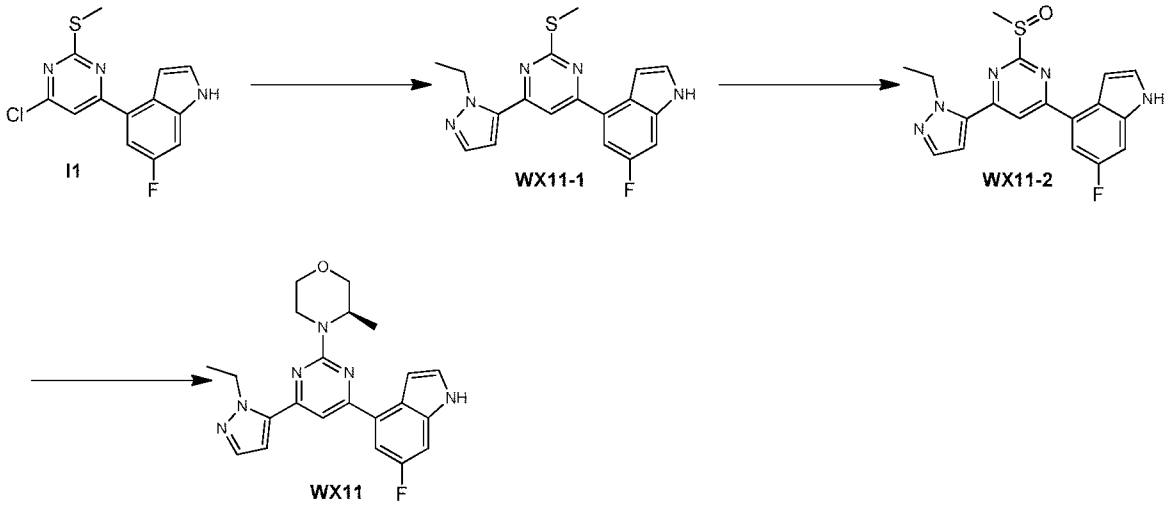
^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.42 (d, J=6.78 Hz, 3 H) 2.30 (s, 3 H) 3.43 (td, J=12.86, 3.64 Hz, 1 H) 3.61 - 3.69 (m, 1 H) 3.76 - 3.81 (m, 1 H) 3.83 - 3.88 (m, 1 H) 4.06 (dd, J=11.17, 3.39 Hz, 1 H) 4.15 (s, 3 H) 4.55 (br d, J=12.30 Hz, 1 H) 4.91 (br d, J=4.52 Hz, 1 H) 7.08 (br s, 1 H) 7.16 (s, 1 H) 7.23 (dd, J=8.78, 1.51 Hz, 1 H) 7.34 (t, J=2.76 Hz, 1 H) 7.40 (s, 1 H) 7.48 (dd, J=10.54, 2.26 Hz, 1 H) 8.50 (br s, 1 H).

Example 11: Compound WX11



WX11

Synthesis scheme:



Step 1: Synthesis of Compound **WX11-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX09-1** in synthesis Example **9** were used to give **WX11-1**.

MS-ESI m/z: 354.0 [M+H]+.

Step 2: Synthesis of Compound **WX11-2**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX09-2** in synthesis Example **9** were used to give crude **WX11-2**.

MS-ESI m/z:370.0[M+H]+.

Step 3: Synthesis of Compound **WX11**

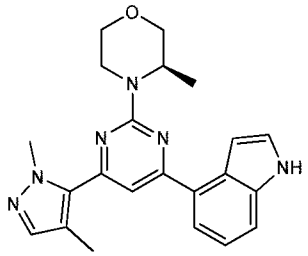
Except using corresponding raw materials, the procedures identical to those used for Compound **WX09** in synthesis Example **9** were used to give Compound **WX11**.

MS-ESI m/z: 407.0 [M+H]+.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.42 (d, J=6.78 Hz, 3 H) 1.52 (t, J=7.15 Hz, 3 H) 3.40 - 3.48 (m, 1 H) 3.64 - 3.69 (m, 1 H) 3.77 - 3.82 (m, 1 H) 3.83 - 3.89 (m, 1 H) 4.04 - 4.10 (m, 1 H) 4.53 (br d, J=13.05

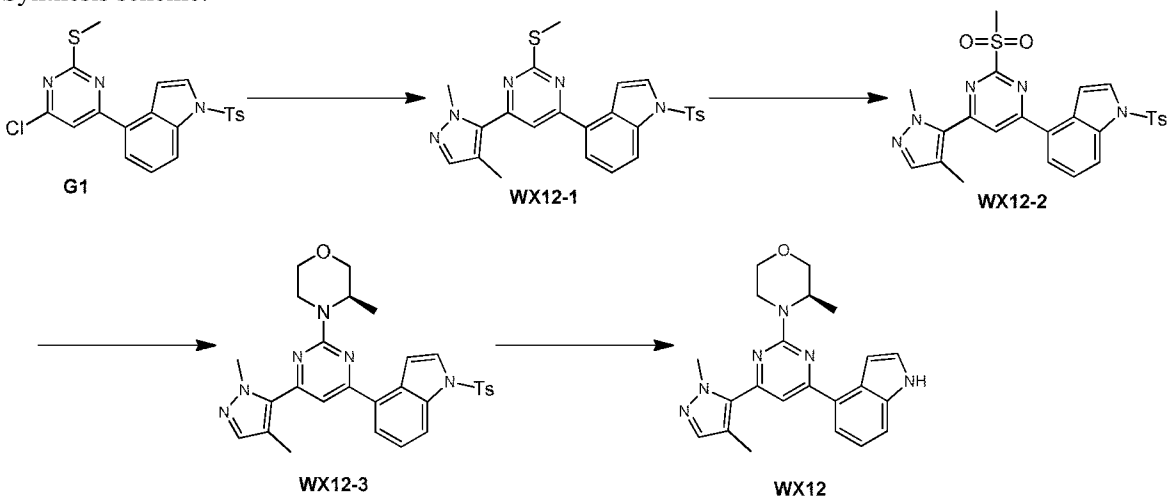
Hz, 1 H) 4.73 - 4.90 (m, 3 H) 6.77 (d, J=1.76 Hz, 1 H) 7.08 (br s, 1 H) 7.23 (br d, J=8.78 Hz, 1 H) 7.33 (s, 2 H) 7.48 (dd, J=10.67, 1.88 Hz, 1 H) 7.57 (d, J=1.51 Hz, 1 H) 8.42 (br s, 1 H).

Example 12: Compound WX12



WX12

Synthesis scheme:



Step 1: Synthesis of Compound **WX12-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX04-1** in synthesis Example **4** were used to give **WX12-1**.

MS-ESI m/z:490.1 [M+H]+.

Step 2: Synthesis of Compound **WX12-2**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX04-2** in synthesis Example **4** were used to give yellow crude **WX12-2**.

MS-ESI m/z:522.1 [M+H]+.

Step 3: Synthesis of Compound **WX12-3**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX04-3** in synthesis Example **4** were used to give crude **WX12-3**.

MS-ESI m/z: 543.1 [M+H]+.

Step 4: Synthesis of Compound **WX12**

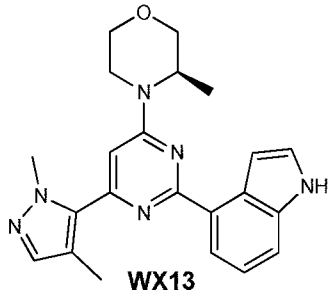
Except using corresponding raw materials, the procedures identical to those used for Compound **WX04** in synthesis Example **4** were used to give Compound **WX12**.

MS-ESI m/z: 389.0 [M+H]+.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.41 - 1.45 (m, 1 H) 1.43 (d, J=6.78 Hz, 2 H) 1.53 (t, J=7.15 Hz, 3 H) 3.45 (td, J=12.92, 3.51 Hz, 1 H) 3.66 (td, J=11.73, 2.64 Hz, 1 H) 3.77 - 3.83 (m, 1 H) 3.84 - 3.89 (m, 1 H) 4.07 (br dd, J=11.29, 3.01 Hz, 1 H) 4.55 (br d, J=13.55 Hz, 1 H) 4.74 - 4.86 (m, 2 H) 4.88 (br d,

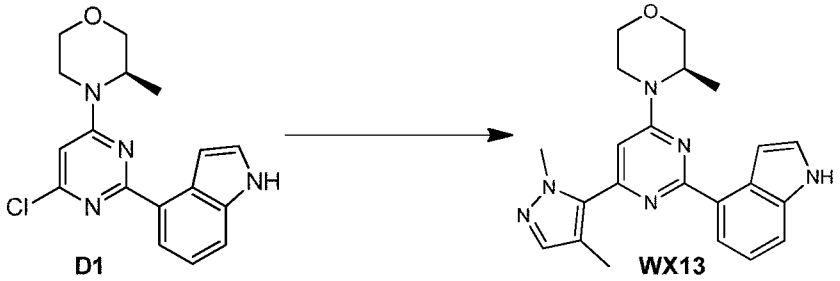
J=7.03 Hz, 1 H) 6.76 (d, J=1.51 Hz, 1 H) 7.16 (br s, 1 H) 7.30 - 7.35 (m, 1 H) 7.37 (s, 2 H) 7.52 - 7.58 (m, 2 H) 7.69 (d, J=7.28 Hz, 1 H) 8.41 (br s, 1 H).

Example 13: Compound WX13



WX13

Synthesis scheme:



D1 **WX13**

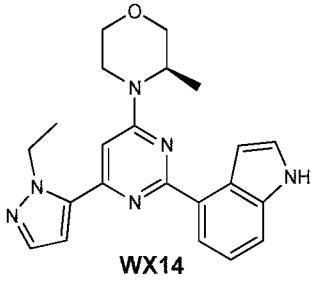
Step 1: Synthesis of Compound **WX13**

To a solution of Compound **D1** (0.075 g, 228.11μmol) in 1,4-dioxane (5mL) were added 1,4-dimethylpyrazole-5-pinacol borate (75.99 mg, 342.17 μmol), bistriphenylphosphine palladium dichloride (8.01 mg, 11.41 μmol) and sodium carbonate (2 M, 342.17 μL). The reaction solution was stirred under the protection of nitrogen at 90°C for 15 h. After the reaction solution was filtered through celite, the filtrate was extracted with 30 mL of ethyl acetate (10 mL×3), and the organic phase was washed with 30 mL of water (10 mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with preparative HPLC (neutral condition) to give Compound **WX13**.

MS-ESI m/z: 389.0 [M+H]+.

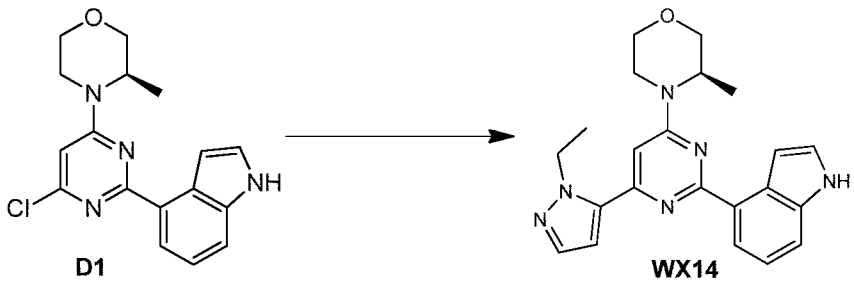
^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.43 (d, J=6.78 Hz, 3 H) 2.25 (s, 3 H) 3.43 (td, J=12.74, 3.89 Hz, 1 H) 3.69 (td, J=11.92, 3.01 Hz, 1 H) 3.80 - 3.85 (m, 1 H) 3.87 - 3.92 (m, 1 H) 4.12 (dd, J=11.29, 3.51 Hz, 1 H) 4.15 - 4.20 (m, 1 H) 4.16 (s, 2 H) 4.34 (s, 1 H) 4.27 (br d, J=13.30 Hz, 1 H) 4.51 (br d, J=4.02 Hz, 1 H) 6.41 - 6.56 (m, 1 H) 6.47 (s, 1 H) 7.29 - 7.36 (m, 1 H) 7.33 - 7.35 (m, 1 H) 7.41 (s, 1 H) 7.50 - 7.58 (m, 1 H) 7.52 - 7.56 (m, 1 H) 8.25 - 8.37 (m, 2 H).

Example 14: Compound WX14



WX14

Synthesis scheme:



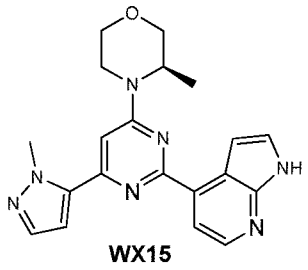
Step 1: Synthesis of Compound **WX14**

To a solution of Compound **D1**(0.075 g, 228.11 μmol) in 1,4-dioxane(5mL) were added 1-ethylpyrazole-5-pinacol borate (75.99 mg, 342.17 μmol), bistriphenylphosphine palladium dichloride (8.01 mg, 11.41 μmol) and sodium carbonate (2 M, 342.17 μL). The reaction mixture was stirred under the protection of nitrogen at 90°C for 15 h. After the reaction solution was filtered through celite, the filtrate was extracted with 30 mL of ethyl acetate (10 mL×3), and the organic phase was washed with 30 mL of water (10 mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with preparative HPLC (neutral condition) to give Compound **WX14**.

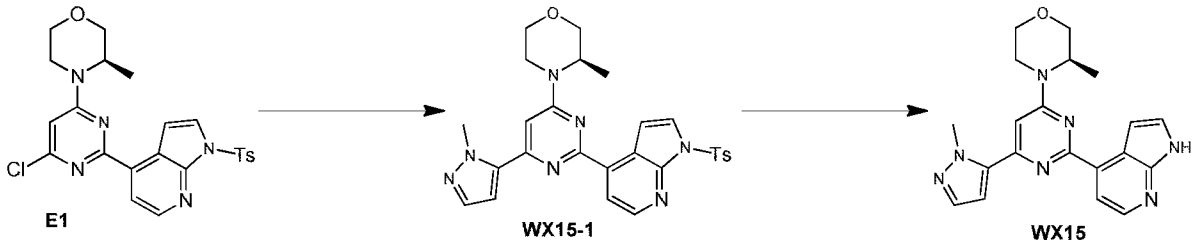
MS-ESI m/z:389.0 [M+H]+.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.43 (d, J=6.78 Hz, 3 H) 1.51 (t, J=7.15 Hz, 3 H) 3.44 (td, J=12.74, 3.89 Hz, 1 H) 3.68 (td, J=11.92, 3.01 Hz, 1 H) 3.79 - 3.86 (m, 1 H) 3.87 - 3.92 (m, 1 H) 4.11 (dd, J=11.42, 3.64 Hz, 1 H) 4.23 (br d, J=13.05 Hz, 1 H) 4.58 (br d, J=4.77 Hz, 1 H) 4.86 (q, J=7.03 Hz, 2 H) 6.63 (s, 1 H) 6.65 (d, J=2.01 Hz, 1 H) 7.30 - 7.36 (m, 2 H) 7.50 (br s, 1 H) 7.54 (d, J=8.03 Hz, 1 H) 7.57 (d, J=1.76 Hz, 1 H) 8.26 (d, J=7.53 Hz, 1 H) 8.35 (br s, 1 H).

Example 15: Compound WX15



Synthesis scheme:



Step 1: Synthesis of Compound **WX15-1**

To a solution of Compound **E1** (0.05 g, 103.31 μmol) in 1,4-dioxane(5mL) were added 1-methylpyrazole-5-pinacol borate (25.79 mg, 123.97 μmol), bistriphenylphosphine palladium dichloride (7.25 mg, 10.33 μmol) and sodium carbonate (2 M, 154.97 μL). The reaction mixture was stirred under the protection of nitrogen at 90°C for 15 h. After the reaction solution was filtered through celite, the filtrate was extracted with 30 mL of

ethyl acetate (10 mL×3), and the organic phase was washed with 45 mL of water (15 mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give crude **WX15-1**.

MS-ESI m/z: 530.2 [M+H]+.

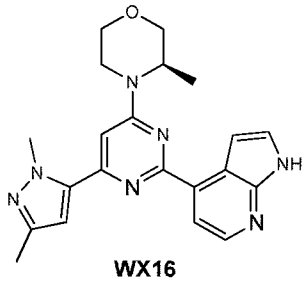
Step 2: Synthesis of Compound **WX15**

To a solution of Compound **WX15-1** (103 mg, 194.48 μmol) in methanol (2 mL) was added sodium hydroxide (2 M, 291.72 μL). The reaction mixture was stirred at 60°C for 15 h. The reaction solution was extracted with 60 mL of ethyl acetate (20 mL×3), and the organic phase was washed with 60 mL of water (20 mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with preparative HPLC (neutral condition) to give Compound **WX15**.

MS-ESI m/z: 376.0[M+H]+.

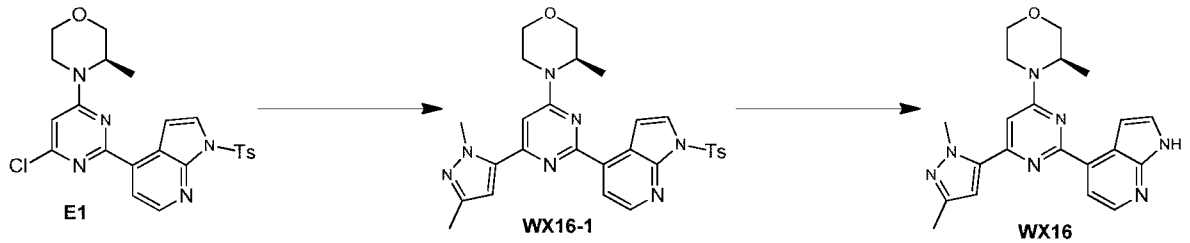
^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.44 (d, J=6.78 Hz, 3 H) 3.45 (td, J=12.74, 3.89 Hz, 1 H) 3.68 (td, J=11.92, 3.01 Hz, 1 H) 3.80 - 3.85 (m, 1 H) 3.88 - 3.94 (m, 1 H) 4.13 (dd, J=11.29, 3.51 Hz, 1 H) 4.22 (br d, J=13.05 Hz, 1 H) 4.38 (s, 3 H) 4.58 (br d, J=4.77 Hz, 1 H) 6.66 - 6.71 (m, 2 H) 7.37 (d, J=1.51 Hz, 1 H) 7.45 - 7.50 (m, 1 H) 7.56 (d, J=2.01 Hz, 1 H) 8.13 (d, J=5.02 Hz, 1 H) 8.47 (d, J=5.02 Hz, 1 H) 9.74 (br s, 1 H).

Example 16: Compound WX16



WX16

Synthesis scheme:



Step 1: Synthesis of Compound **WX16-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX15-1** in synthesis Example **15** were used to give crude **WX16-1**.

MS-ESI m/z: 544.1[M+H]+.

Step 2: Synthesis of Compound **WX16**

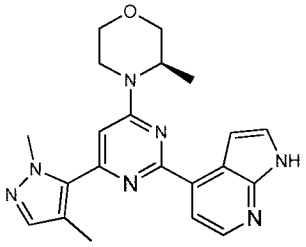
Except using corresponding raw materials, the procedures identical to those used for Compound **WX15** in synthesis Example **15** were used to give Compound **WX16**.

MS-ESI m/z: 390.0 [M+H]+

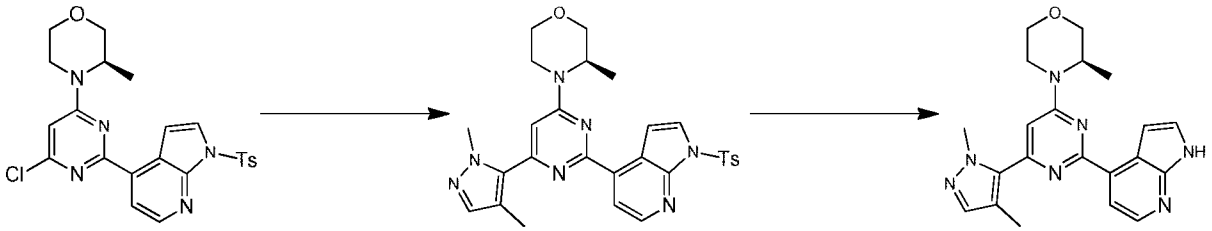
^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.43 (d, J=6.78 Hz, 3 H) 2.34 (s, 3 H) 3.44 (td, J=12.61, 3.89 Hz, 1 H) 3.67 (td, J=11.80, 3.01 Hz, 1 H) 3.78 - 3.85 (m, 1 H) 3.87 - 3.93 (m, 1 H) 4.12 (dd, J=11.29,

3.76 Hz, 1 H) 4.21 (br d, J=12.80 Hz, 1 H) 4.30 (s, 3 H) 4.56 (br d, J=4.52 Hz, 1 H) 6.47 (s, 1 H) 6.66 (s, 1 H) 7.3

Example 17: Compound WX17



WX17



E1 **WX17-1** **WX17**

Step 1: Synthesis of Compound **WX17-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX15-1** in synthesis Example **15** were used to give crude **WX17-1**.

MS-ESI m/z: 544.1[M+H]+.

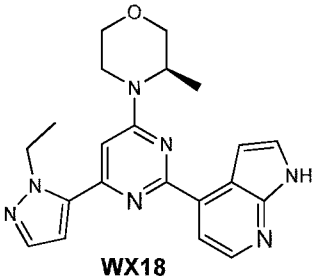
Step 2: Synthesis of Compound **WX17**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX15** in synthesis Example **15** were used to give Compound **WX17**.

MS-ESI m/z: 390.0 [M+H]+.

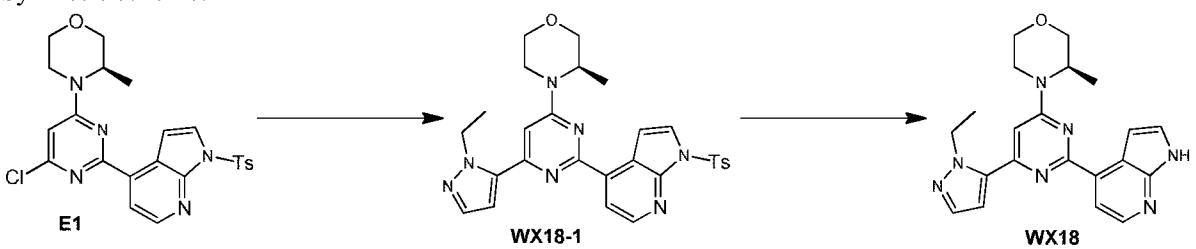
^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.45 (d, J=6.78 Hz, 3 H) 2.25 (s, 3 H) 3.45 (td, J=12.80, 3.76 Hz, 1 H) 3.69 (td, J=11.92, 2.76 Hz, 1 H) 3.80 - 3.86 (m, 1 H) 3.88 - 3.93 (m, 1 H) 4.11 - 4.17 (m, 4 H) 4.26 (br d, J=12.80 Hz, 1 H) 4.50 (br s, 1 H) 6.54 (s, 1 H) 7.38 - 7.44 (m, 2 H) 7.46 (br s, 1 H) 8.15 (br d, J=3.51 Hz, 1 H) 8.46 (br s, 1 H) 9.67 (br s, 1 H).

Example 18: Compound WX18



WX18

Synthesis scheme:



E1 **WX18-1** **WX18**

Step 1: Synthesis of Compound **WX18-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX15-1** in synthesis Example **15** were used to give crude **WX18-1** as white solid.

MS-ESI m/z: 544.2[M+H]+.

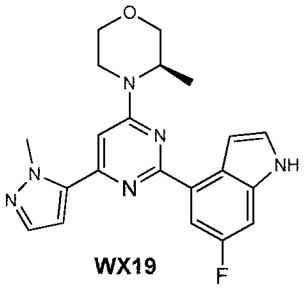
Step 2: Synthesis of Compound **WX18**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX15** in synthesis Example **15** were used to give Compound **WX18**.

MS-ESI m/z: 390.0 [M+H]+.

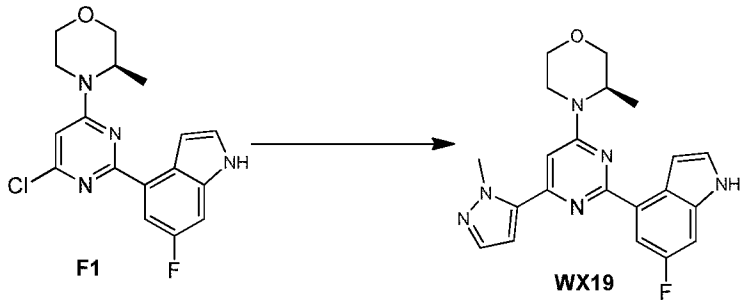
^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.46 (br d, J=6.53 Hz, 3 H) 1.51 (br t, J=6.90 Hz, 3 H) 3.42 - 3.55 (m, 1 H) 3.68 (br t, J=11.67 Hz, 1 H) 3.75 - 3.86 (m, 1 H) 3.89 - 3.97 (m, 1 H) 4.11 - 4.22 (m, 2 H) 4.54 (br s, 1 H) 4.69 - 4.82 (m, 2 H) 6.70 (s, 1 H) 6.78 (br s, 1 H) 7.51 - 7.60 (m, 1 H) 7.60 - 7.70 (m, 2 H) 8.38 (br d, J=18.32 Hz, 2 H) 12.42 (br s, 1 H).

Example 19: Compound WX19



WX19

Synthesis scheme:



F1 **WX19**

Step 1: Synthesis of Compound **WX19**

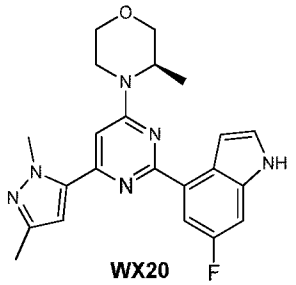
To a solution of Compound **F1** (50 mg, 144.18 μmol) in 1,4-dioxane(5mL) were added 1-methylpyrazole-5-pinacol borate (36.00 mg, 173.02 μmol), bistriphenylphosphine palladium dichloride (10.12 mg, 14.42 μmol) and sodium carbonate (2 M, 216.27 μL). The reaction solution was stirred under the protection of nitrogen at 9°C for 15 h. After the reaction solution was filtered through celite, the filtrate was extracted with 30 mL of ethyl acetate (10 mL×3), and the organic phase was washed with 45 mL of water (15 mL×3) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with preparative HPLC (neutral condition) to give Compound **WX19**.

MS-ESI m/z: 393.0 [M+H]+.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.43 (d, J=6.78 Hz, 3 H) 3.43 (td, J=12.61, 3.89 Hz, 1 H) 3.67 (td, J=11.80, 2.76 Hz, 1 H) 3.79 - 3.84 (m, 1 H) 3.87 - 3.92 (m, 1 H) 4.11 (dd, J=11.54, 3.51 Hz, 1 H) 4.22 (br d, J=13.05 Hz, 1 H) 4.36 (s, 3 H) 4.56 (br s, 1 H) 6.64 (s, 1 H) 6.62 - 6.65 (m, 1 H) 6.67 (d, J=1.76 Hz, 1 H) 7.23 (br d, J=7.78 Hz, 1 H) 7.32 (br s, 1 H) 7.48 (br s, 1 H) 7.55 (d, J=1.76 Hz, 1 H) 8.03 (dd,

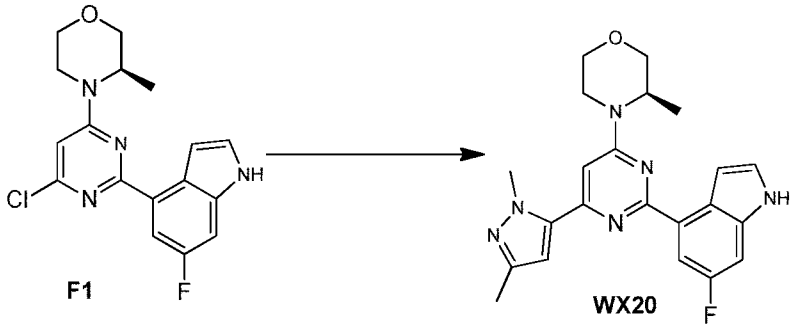
J=11.17, 1.88 Hz, 1 H) 8.34 (br s, 1 H).

Example 20: Compound WX20



WX20

Synthesis scheme:



F1 WX20

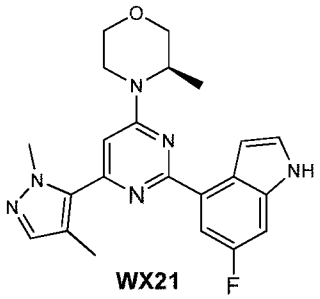
Step 1: Synthesis of Compound **WX20**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX19** in synthesis Example **19** were used to give Compound **WX20**.

MS-ESI m/z: 407.0 [M+H]+.

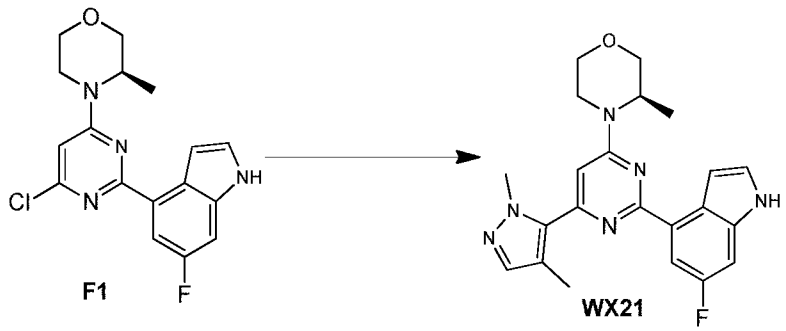
^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.42 (d, J=6.78 Hz, 3 H) 2.34 (s, 3 H) 3.42 (td, J=12.74, 3.64 Hz, 1 H) 3.66 (td, J=11.80, 2.76 Hz, 1 H) 3.78 - 3.83 (m, 1 H) 3.86 - 3.92 (m, 1 H) 4.11 (br dd, J=11.42, 3.39 Hz, 1 H) 4.21 (br d, J=13.30 Hz, 1 H) 4.28 (s, 3 H) 4.55 (br d, J=5.02 Hz, 1 H) 6.46 (s, 1 H) 6.61 (s, 1 H) 7.21 (br d, J=7.53 Hz, 1 H) 7.31 (br s, 1 H) 7.48 (br s, 1 H) 8.02 (dd, J=11.17, 1.63 Hz, 1 H) 8.41 (br s, 1 H).

Example 21: Compound WX21



WX21

Synthesis scheme:



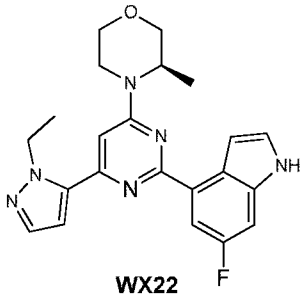
Step 1: Synthesis of Compound **WX21**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX19** in synthesis Example **19** were used to give Compound **WX21**.

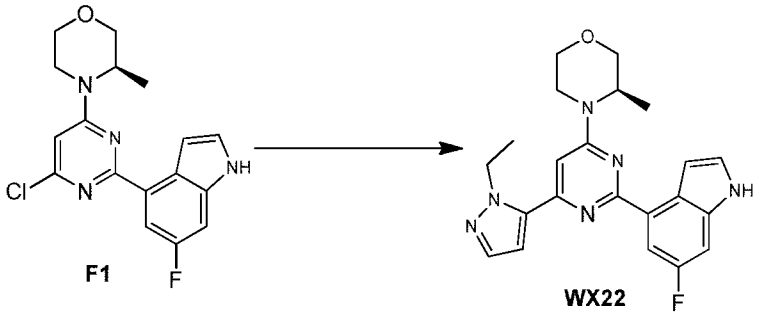
MS-ESI m/z: 407.0 [M+H]+.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.29 (d, J=6.78 Hz, 3 H) 2.10 (s, 3 H) 3.28 (td, J=12.74, 3.64 Hz, 1 H) 3.54 (td, J=11.86, 2.64 Hz, 1 H) 3.66 - 3.71 (m, 1 H) 3.73 - 3.77 (m, 1 H) 3.95 - 4.01 (m, 4 H) 4.11 (br d, J=12.30 Hz, 1 H) 4.34 (br s, 1 H) 6.34 (s, 1 H) 7.05 - 7.16 (m, 2 H) 7.36 (br s, 1 H) 7.90 (br d, J=10.54 Hz, 1 H) 8.35 (br s, 1 H).

Example 22: Compound WX22



Synthesis scheme:



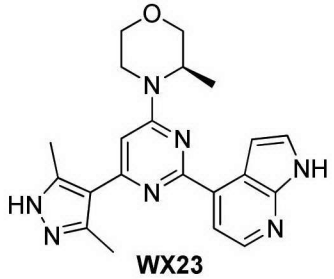
Step 1: Synthesis of Compound **WX22**

Except using corresponding raw materials, the procedures identical to those used for Compound **W19** in synthesis Example **19** were used to give Compound **WX22**.

MS-ESI m/z: 407.0 [M+H]+.

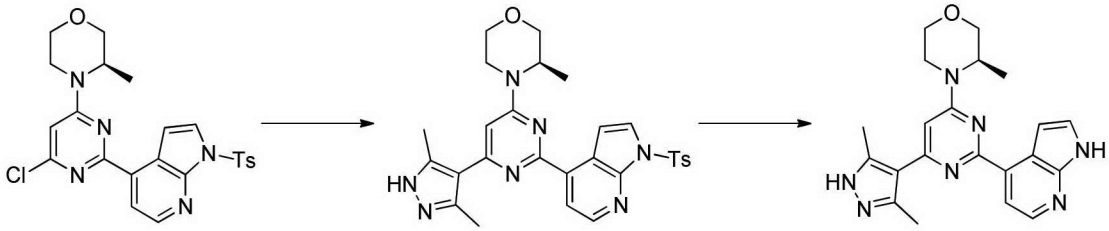
^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.43 (d, J=6.78 Hz, 3 H) 1.52 (t, J=7.15 Hz, 3 H) 3.43 (td, J=12.80, 3.76 Hz, 1 H) 3.67 (td, J=11.92, 2.76 Hz, 1 H) 3.78 - 3.84 (m, 1 H) 3.87 - 3.92 (m, 1 H) 4.11 (dd, J=11.54, 3.51 Hz, 1 H) 4.21 (br d, J=13.05 Hz, 1 H) 4.56 (br d, J=5.02 Hz, 1 H) 4.83 (q, J=7.03 Hz, 2 H) 6.62 - 6.66 (m, 2 H) 7.22 (dd, J=8.66, 1.88 Hz, 1 H) 7.31 (t, J=2.64 Hz, 1 H) 7.46 (br s, 1 H) 7.57 (d, J=1.76 Hz, 1 H) 8.01 (dd, J=11.42, 2.13 Hz, 1 H) 8.49 (br s, 1 H).

Example 23: Compound WX23



WX23

Synthesis scheme:



E1 **WX23-1** **WX23**

Step 1: Synthesis of Compound **WX23-1**

At room temperature, to a solution of Compound **E1** (0.16 g, 330.60 μmol) in 1,4-dioxane (2.00 mL) were added 3,5-dimethylpyrazole-4-boric acid pinacol ester (110.13 mg, 495.90 μmol), tris(dibenzylacetone) dipalladium (30.27 mg, 33.06 μmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (38.26 mg, 66.12 μmol), potassium phosphate (210.53 mg, 991.80 μmol), and water (0.2 mL), which was stirred at 120°C in a microwave instrument for 20 min. The reaction system was cooled and then diluted with ethyl acetate (50 mL). The organic phase was washed with water (30 mL) and saturated brine (30 mL) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with column chromatography (petroleum ether/ethyl acetate =4/1,2/1) to give Compound **WX23-1**.

MS *m/z*: 544.1[M+H]$^+$.

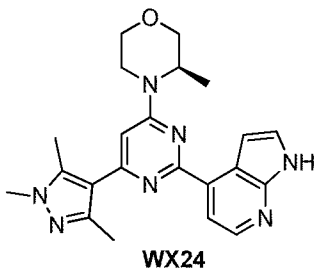
Step 2: Synthesis of Compound **WX23**

At room temperature, to a solution of Compound **WX23-1** (0.045 g, 82.78 μmol) in methanol (10.00 mL) was added sodium hydroxide solution (2 M, 206.94 μL), which was stirred at 30°C for 16 h. The reaction system was concentrated under reduced pressure at 45°C to give a mixture, which was dissolved with ethyl acetate (30 mL), washed with water (20 mL) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with column chromatography (dichloromethane /methanol=**100/1,10/1**) to give Compound **WX23**.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (br d, *J*=7.03 Hz, 3 H) 2.43 - 2.45 (m, 6 H) 3.37 - 3.42 (m, 1 H) 3.51 - 3.62 (m, 1 H) 3.71 (br d, *J*=11.54 Hz, 1 H) 3.82 (br d, *J*=11.54 Hz, 1 H) 4.03 (br d, *J*=10.04 Hz, 1 H) 4.21 (br d, *J*=12.55 Hz, 1 H) 4.60 (br s, 1 H) 6.67 (s, 1 H) 7.24 (br s, 1 H) 7.58 (br s, 1 H) 8.02 (d, *J*=4.77 Hz, 1 H) 8.34 (d, *J*=5.02 Hz, 1 H) 11.77 (br s, 1 H) 12.54 (br s, 1 H).

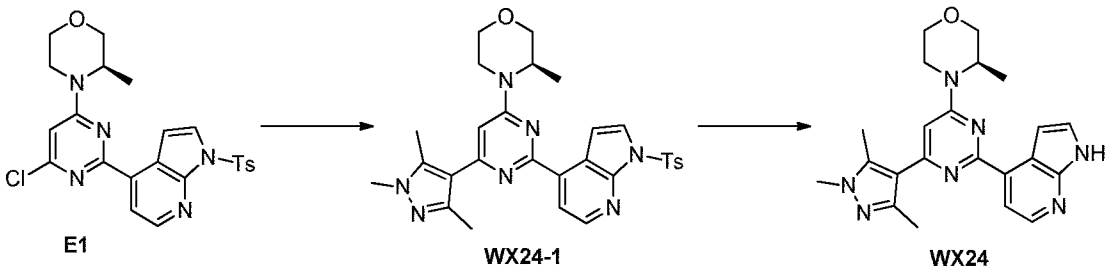
MS *m/z*: 390.0[M+H]$^+$.

Example 24: Compound WX24



WX24

Synthesis scheme:



E1 WX24-1 WX24

Step 1: Synthesis of Compound **WX24-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX23-1** in Example **23** were used to give the crude product, which was purified with column chromatography (petroleum ether: ethyl acetate =2/1,1/2) to give **WX24-1**.

MS *m/z*: 558.1[M+H]$^+$.

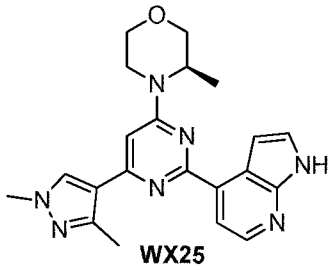
Step 2: Synthesis of Compound **WX24**

At room temperature, to a solution of Compound **WX24-1** (0.105 g, 188.28 μmol) in methanol (10.00 mL) was added sodium hydroxide solution (2 M, 941.42 μL), which was stirred at 30°C for 15 h. The reaction system was concentrated under reduced pressure at 45°C to give a mixture, which was dissolved with dichloromethane (30 mL), washed with water (20 mL) and saturated brine (20 mL), and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with column chromatography (dichloromethane /methanol=100/1,12/1) to give Compound **WX24**.

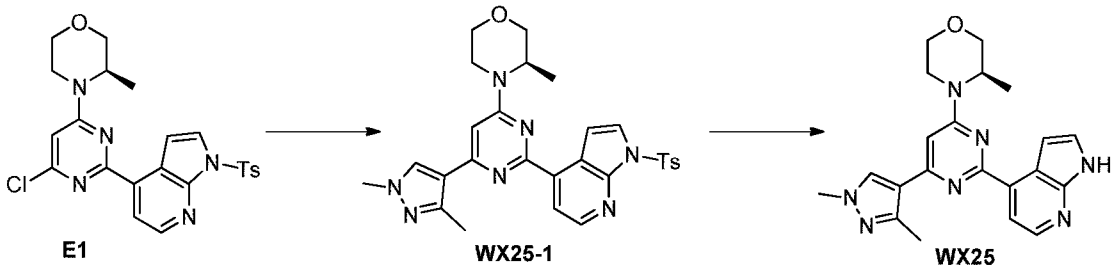
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.27 (d, *J*=6.53 Hz, 3 H) 2.36 (s, 3 H) 2.51 (br s, 3 H) 3.30 (br s, 1 H) 3.50 - 3.57 (m, 1 H) 3.68 (br d, *J*=8.53 Hz, 1 H) 3.73 (s, 3 H) 3.77 - 3.84 (m, 1 H) 4.01 (br d, *J*=8.53 Hz, 1 H) 4.20 (br d, *J*=11.29 Hz, 1 H) 4.55 (br s, 1 H) 6.63 (s, 1 H) 7.22 (dd, *J*=3.26, 2.01 Hz, 1 H) 7.56 (t, *J*=2.89 Hz, 1 H) 7.99 (d, *J*=5.02 Hz, 1 H) 8.32 (d, *J*=5.02 Hz, 1 H) 11.75 (br s, 1 H).

MS *m/z*: 404.0[M+H]$^+$.

Example 25: Compound WX25



Synthesis scheme:



Step 1: Synthesis of Compound **WX25-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX23-1** in Example **23** were used to give the crude product, which was purified with column chromatography (petroleum ether: ethyl acetate =2/1,1/2) to give Compound **WX25-1**.

MS *m/z*: 544.1[M+H]$^+$

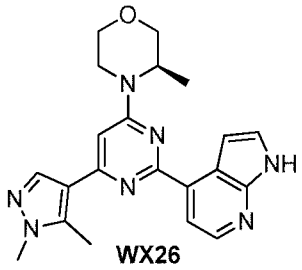
Step 2: Synthesis of Compound **WX25**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX23** in Example **23** were used to give the crude product, which was purified with column chromatography (dichloromethane: methanol=100/1,10/1) to give Compound **WX25**.

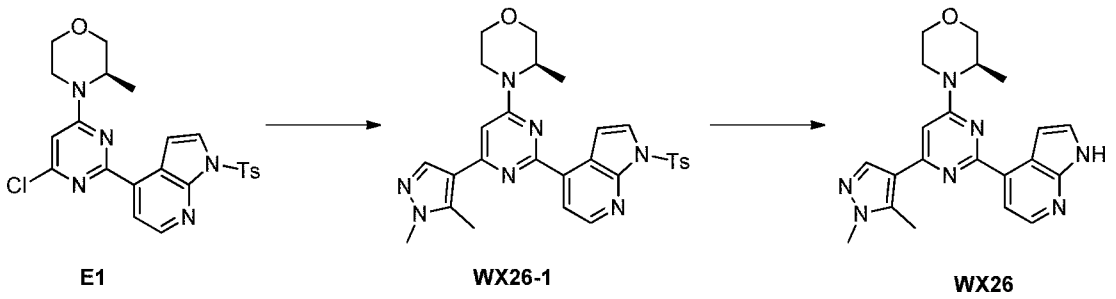
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.27 (d, *J*=6.78 Hz, 3 H) 2.55 (s, 3 H) 3.20 - 3.27 (m, 1 H) 3.49 - 3.58 (m, 1 H) 3.68 (dd, *J*=11.29, 2.76 Hz, 1 H) 3.78 - 3.85 (m, 4 H) 4.01 (br d, *J*=8.28 Hz, 1 H) 4.18 (br d, *J*=13.80 Hz, 1 H) 4.60 (br s, 1 H) 6.85 (s, 1 H) 7.23 (dd, *J*=3.26, 2.01 Hz, 1 H) 7.57 (t, *J*=2.89 Hz, 1 H) 8.02 (d, *J*=5.02 Hz, 1 H) 8.32 (d, *J*=5.02 Hz, 1 H) 8.40 (s, 1 H) 11.75 (br s, 1 H).

MS *m/z*: 390.0[M+H]$^+$.

Example 26: Compound WX26



Synthesis scheme:



Step 1: Synthesis of Compound **WX26-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX23-1** in Example **23** were used to give the crude product, which was purified with column chromatography (petroleum ether: ethyl acetate =2/1,1/2) to give Compound **WX26-1**.

MS *m/z*: 544.2[M+H]$^+$.

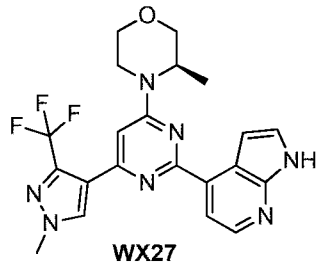
Step 2: Synthesis of Compound **WX26**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX23** in Example **23** were used to give the crude product, which was purified with column chromatography (dichloromethane: methanol=100/1,12/1) to give Compound **WX26**.

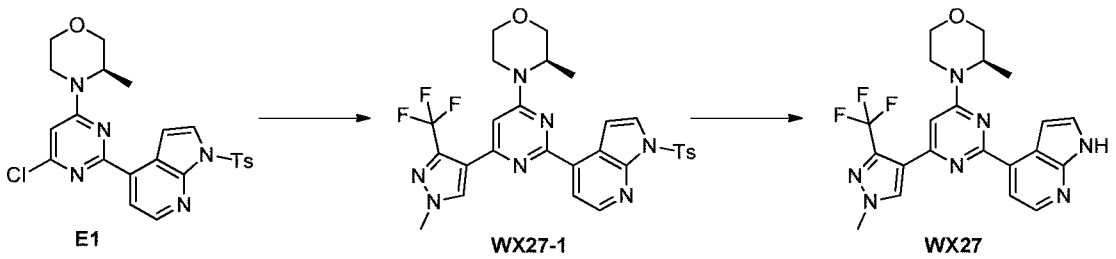
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.27 (d, *J*=6.78 Hz, 3 H) 2.74 (s, 3 H) 3.22 - 3.28 (m, 1 H) 3.48 - 3.57 (m, 1 H) 3.68 (dd, *J*=11.54, 2.76 Hz, 1 H) 3.78 - 3.84 (m, 4 H) 3.96 - 4.04 (m, 1 H) 4.21 (br d, *J*=12.55 Hz, 1 H) 4.65 (br s, 1 H) 6.92 (s, 1 H) 7.21 (dd, *J*=3.26, 2.01 Hz, 1 H) 7.55 - 7.59 (m, 1 H) 7.98 (d, *J*=5.02 Hz, 1 H) 8.11 (s, 1 H) 8.33 (d, *J*=5.02 Hz, 1 H) 11.76 (br s, 1 H).

MS *m/z*: 390.1[M+H]$^+$.

Example 27: Compound WX27



Synthesis scheme:



Step 1: Synthesis of Compound **WX27-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX23-1** in Example **23** were used to give the crude product, which was purified with column chromatography (petroleum ether: ethyl acetate =4/1,2/1) to give Compound **WX27-1**.

MS *m/z*: 598.1[M+H]$^+$.

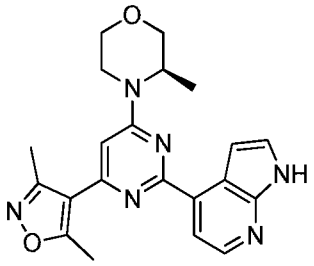
Step 2: Synthesis of Compound **WX27**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX23** in Example **23** were used to give the crude product, which was purified with column chromatography (dichloromethane: methanol=100/1,20/1) to give Compound **WX27**.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (d, J=6.76 Hz, 3 H) 3.25 - 3.30 (m, 1 H) 3.54 (td, J=11.84, 3.14 Hz, 1 H) 3.69 (dd, J=11.52, 2.76 Hz, 1 H) 3.82 (d, J=11.28 Hz, 1 H) 3.98 - 4.06 (m, 4 H) 4.19 (br d, J=11.52 Hz, 1 H) 4.56 (br s, 1 H) 6.95 (s, 1 H) 7.22 (dd, J=3.40, 1.88 Hz, 1 H) 7.55 - 7.59 (m, 1 H) 8.07 (d, J=5.28 Hz, 1 H) 8.32 (d, J=5.04 Hz, 1 H) 8.67 (s, 1 H) 11.77 (br s, 1 H).

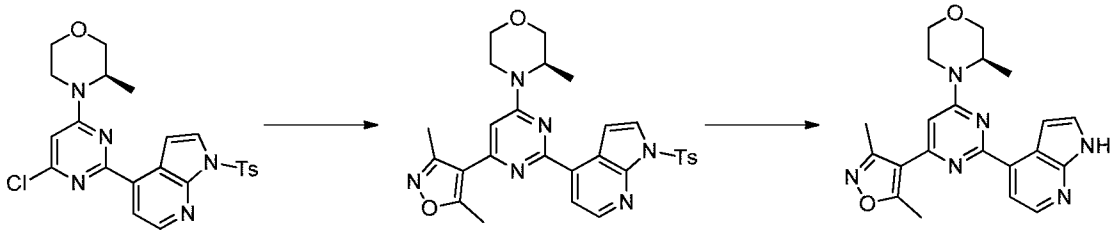
MS m/z: 444.0[M+H]$^+$.

Example 28: Compound WX28



WX-28

Synthesis scheme:



Step 1: Synthesis of Compound **WX28-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX23-1** in Example **23** were used to give the crude product, which was purified with column chromatography (petroleum ether: ethyl acetate =2/1,2/1) to give Compound **WX28-1**.

MS m/z: 545.1[M+H]$^+$

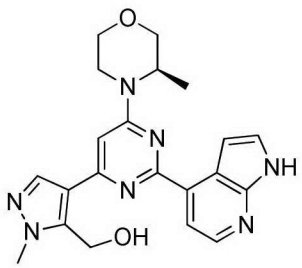
Step 2: Synthesis of Compound **WX28**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX23** in Example **23** were used to give the crude product, which was purified with column chromatography (dichloromethane: methanol=100/1,9/1) to give Compound **WX28**.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (br d, J=6.28 Hz, 3 H) 2.31 - 2.47 (m, 3 H) 2.70 (br s, 3 H) 3.56 (br t, J=11.16 Hz, 1 H) 3.71 (br d, J=11.28 Hz, 1 H) 3.79 - 3.89 (m, 1 H) 4.04 (br d, J=8.76 Hz, 1 H) 4.27 (br d, J=10.56 Hz, 1 H) 4.64 (br s, 1 H) 6.84 (br s, 1 H) 7.22 (br s, 1 H) 7.60 (br s, 1 H) 8.02 (br s, 1 H) 8.36 (br s, 1 H) 11.82 (br s, 1 H).

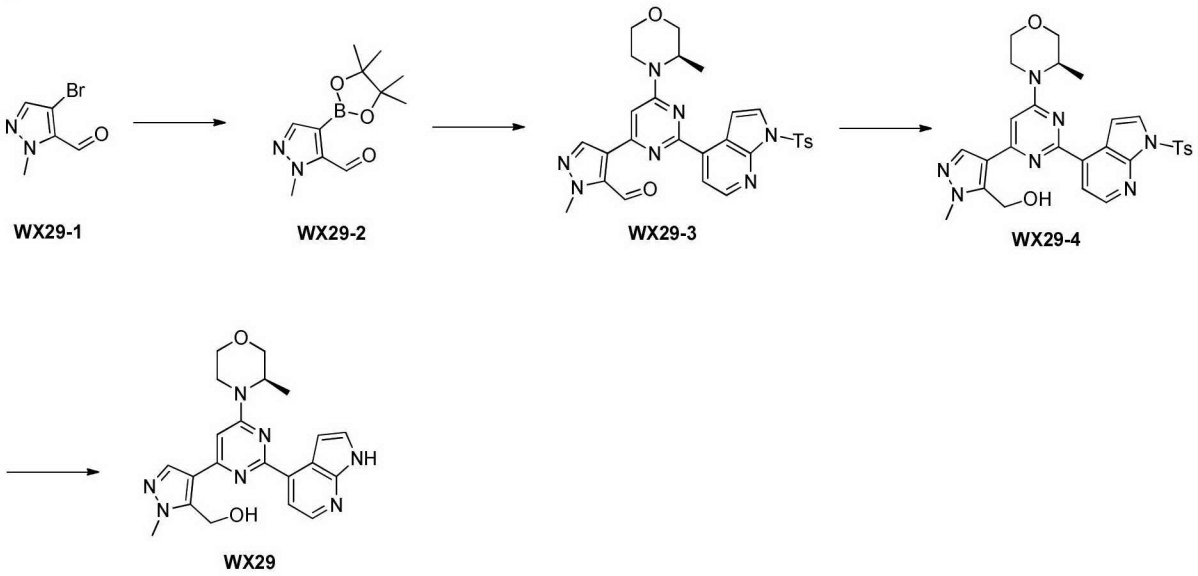
MS m/z: 391.0[M+H]$^+$.

Example 29: Compound WX29



WX29

Synthesis scheme:



Step 1: Synthesis of Compound **WX29-2**

At room temperature, to a solution of Compound **WX29-1** (0.3 g, 1.59 mmol) in 1,4-dioxane (8 mL) were added bispinacol borate (90.16 mg, 464.91 μmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium dichloride dichloromethane complex (64.81 mg, 79.36 μmol), and potassium acetate (467.32 mg, 4.76 mmol), which was stirred at 100°C in a microwave instrument for 1 h. The reaction system was cooled and then diluted with ethyl acetate (30 mL). After filtration, the solvent was removed under reduced pressure to give the crude product, which was purified with column chromatography (petroleum ether/ethyl acetate =10/1,5/1) to give Compound **WX29-2**.

MS *m/z*: 237.0[M+H]$^+$.

Step 2: Synthesis of Compound **WX29-3**

At room temperature, to a solution of Compound **E1** (0.15, 309.94 μmol) in 1,4-dioxane (2.00 mL) were added **WX29-2** (87.80 mg, 371.93 μmol), tris(dibenzylacetone) dipalladium (28.38 mg, 30.99 μmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (35.87 mg, 61.99 μmol), potassium phosphate (197.37 mg, 929.82 μmol), and water (0.2 mL), which was stirred at 120°C in a microwave instrument for 20 min. The reaction system was cooled and then diluted with ethyl acetate (30 mL). The organic phase was washed with water (30 mL) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with column chromatography (petroleum ether/ethyl acetate =2/1,1/2) to give Compound **WX29-3**.

MS *m/z*: 558.1[M+H]$^+$.

Step 3: Synthesis of Compound **WX29-4**

At room temperature, to a solution of Compound **WX29-3** (0.12 g, 215.20 μmol) in methanol (8.00 mL) was added sodium borohydride (16.28 mg, 430.40 μmol), which was stirred at 30°C for 4 h. The reaction system was concentrated under reduced pressure at 45°C to give a mixture, which was dissolved with ethyl acetate (30 mL), washed with water (20 mL) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give crude Compound **WX29-4.**

MS *m/z*: 560.1[M+H]$^+$.

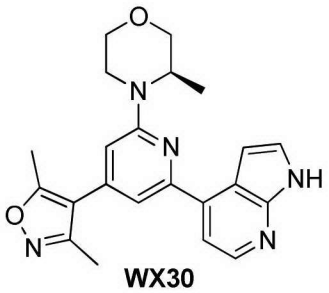
Step 4: Synthesis of Compound **WX29**

At room temperature, to a solution of Compound **WX29-4** (0.09 g, 150.60 μmol) in methanol (10.00 mL) was added sodium hydroxide solution (2 M, 753.00 μL), which was stirred at 30°C for 15 h. The reaction system was concentrated under reduced pressure at 45°C to give a mixture, which was dissolved with dichloromethane (30 mL), washed with saturated brine (20 mL) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with column chromatography (dichloromethane /methanol=100/1,15/1) to give Compound **WX29**.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (d, *J*=6.52 Hz, 3 H) 3.26 - 3.30 (m, 1 H) 3.51 - 3.60 (m, 1 H) 3.71 (br d, *J*=9.04 Hz, 1 H) 3.79 - 3.87 (m, 1 H) 3.93 (s, 3 H) 4.04 (br d, *J*=8.04 Hz, 1 H) 4.24 (br d, *J*=12.56 Hz, 1 H) 4.65 (br s, 1 H) 5.05 (br d, *J*=4.52 Hz, 2 H) 5.61 (br s, 1 H) 7.04 (s, 1 H) 7.23 (br s, 1 H) 7.60 (t, *J*=2.76 Hz, 1 H) 7.98 (d, *J*=4.76 Hz, 1 H) 8.15 (s, 1 H) 8.36 (d, *J*=5.04 Hz, 1 H) 11.79 (br s, 1 H) .

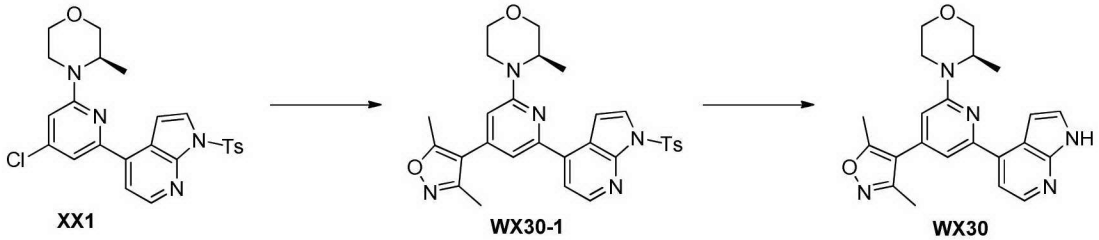
MS *m/z*: 406.0[M+H]$^+$.

Example 30: Compound WX30



WX30

Synthesis scheme:



Step 1: Synthesis of Compound **WX30-1**

At room temperature, to a solution of Compound **XX1** (0.1 g, 207.05 μmol) in 1,4-dioxane (10.00 mL) were added 3,5-dimethylisoxazole-4-boric acid pinacol ester (55.42 mg, 248.46 μmol), tris(dibenzylacetone) dipalladium (18.96 mg, 20.70 μmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (23.96 mg, 41.41μmol), potassium phosphate (131.85 mg, 621.14 μmol) and water (0.2 mL), which was stirred at 120°C in a microwave instrument for 20 min. The reaction system was cooled and then diluted with ethyl acetate (30 mL). The organic phase was washed with water (30 mL) and dried over anhydrous sodium sulfate. After

the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with column chromatography (petroleum ether/ethyl acetate =2/1,1/1) to give Compound **WX30-1**.

MS *m/z*: 566.1[M+Na]$^+$.

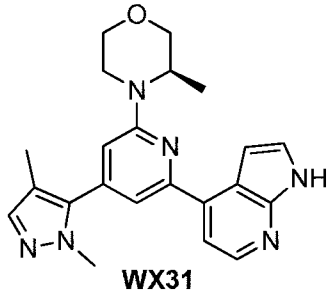
Step 2: Synthesis of Compound **WX30**

At room temperature, to a solution of Compound **WX30-1** (0.06 g, 110.37 μmol) in methanol (10.00 mL) was added sodium hydroxide solution (2 M, 551.84 uL), which was stirred at 40°C for 15 h. The reaction system was concentrated under reduced pressure at 45°C to give a mixture, which was dissolved with ethyl acetate (30 mL), washed with water (20 mL) and dried over anhydrous sodium sulfate. After the desiccant was filtered off, the solvent was removed under reduced pressure to give the crude product, which was purified with column chromatography (dichloromethane /methanol=40/1,20/1) to give Compound **WX30**.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.23 (d, *J*=6.53 Hz, 3 H) 2.34 (s, 3 H) 2.52 (br s, 3 H) 3.20 (td, *J*=12.67, 3.76 Hz, 1 H) 3.50 - 3.60 (m, 1 H) 3.66 - 3.73 (m, 1 H) 3.76 - 3.82 (m, 1 H) 4.00 (dd, *J*=11.04, 3.01 Hz, 1 H) 4.10 (br d, *J*=11.29 Hz, 1 H) 4.50 (br d, *J*=6.78 Hz, 1 H) 6.80 (s, 1 H) 6.93 (dd, *J*=3.39, 1.88 Hz, 1 H) 7.27 (s, 1 H) 7.55 - 7.60 (m, 2 H) 8.30 (d, *J*=5.02 Hz, 1 H) 11.79 (br s, 1 H) .

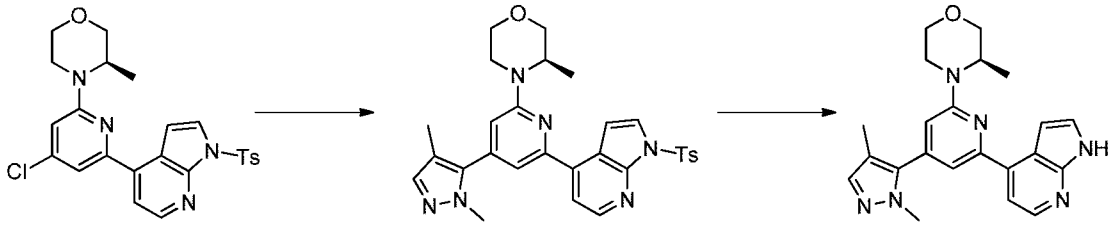
MS *m/z*: 390.2[M+H]$^+$.

Example 31: Compound WX31



WX31

Synthesis scheme:



XX1 **WX31-1** **WX31**

Step 1: Synthesis of Compound **WX31-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX30-1** in Example **30** were used to give the crude product, which was purified with column chromatography (dichloromethane: methanol=30/1,10/1) to give Compound **WX31-1**.

MS *m/z*: 543.1[M+H]$^+$.

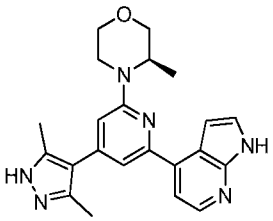
Step 2: Synthesis of Compound **WX31**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX30** in Example **30** were used to give the crude product, which was purified with column chromatography (dichloromethane: methanol=30/1,10/1) to give Compound **WX31**.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24 (d, J=6.53 Hz, 3 H) 2.08 (s, 3 H) 3.21 (td, J=12.61, 3.64 Hz, 1 H) 3.55 (td, J=11.73, 2.89 Hz, 1 H) 3.67 - 3.73 (m, 1 H) 3.76 - 3.81 (m, 1 H) 3.84 (s, 3 H) 3.97 - 4.02 (m, 1 H) 4.14 (br d, J=12.05 Hz, 1 H) 4.50 (br d, J=6.27 Hz, 1 H) 6.84 (s, 1 H) 6.93 (dd, J=3.39, 1.88 Hz, 1 H) 7.28 (s, 1 H) 7.39 (s, 1 H) 7.56 - 7.60 (m, 2 H) 8.30 (d, J=5.02 Hz, 1 H) 11.80 (br s, 1 H).

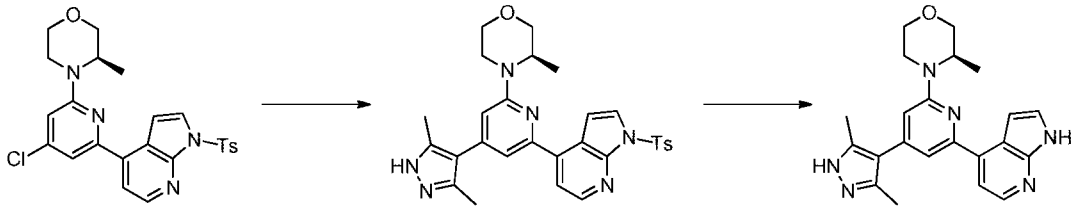
MS m/z: 389.2[M+H]$^+$.

Example 32: Compound WX32



WX32

Synthesis scheme:



XX1 **WX32-1** **WX32**

Step 1: Synthesis of Compound **WX32-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX30-1** in Example **30** were used to give the crude product, which was purified with column chromatography (dichloromethane: methanol=30/1,10/1) to give Compound **WX32-1**.

MS m/z: 543.1[M+H]$^+$.

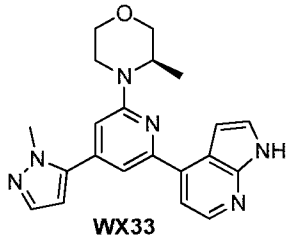
Step 2: Synthesis of Compound **WX32**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX30** in Example **30** were used to give the crude product, which was purified with column chromatography (dichloromethane: methanol=30/1,10/1) to give Compound **WX32**.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.22 (d, J=6.53 Hz, 3 H) 2.27 - 2.39 (m, 6 H) 3.18 (td, J=12.61, 3.64 Hz, 1 H) 3.50 - 3.59 (m, 1 H) 3.65 - 3.73 (m, 1 H) 3.75 - 3.81 (m, 1 H) 3.95 - 4.03 (m, 1 H) 4.07 (br d, J=11.54 Hz, 1 H) 4.47 (br d, J=5.27 Hz, 1 H) 6.68 (s, 1 H) 6.91 (dd, J=3.39, 1.88 Hz, 1 H) 7.21 (s, 1 H) 7.52 - 7.59 (m, 2 H) 8.29 (d, J=5.02 Hz, 1 H) 11.76 (br s, 1 H) 12.48 (br s, 1 H).

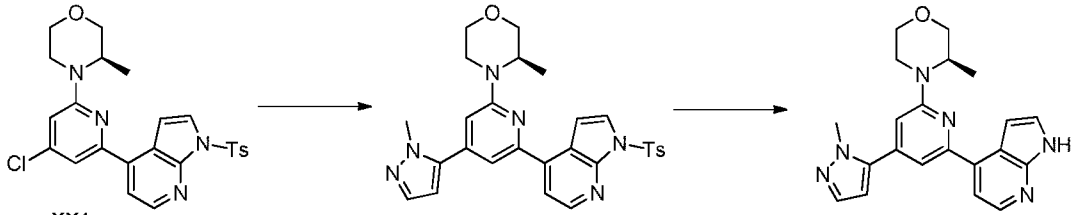
MS m/z: 389.2[M+H]$^+$.

Example 33: Compound WX33



WX33

Synthesis scheme:



XX1 **WX33-1** **WX33**

Step 1: Synthesis of Compound **WX33-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX30-1** in Example **30** were used to give the crude product, which was purified with column chromatography (dichloromethane: methanol=30/1,10/1) to give Compound **WX33-1**.

MS *m/z*: 529.1[M+H]$^+$.

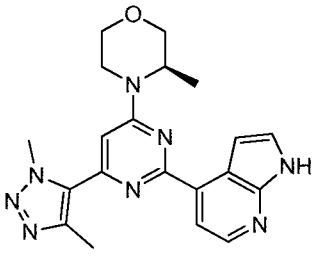
Step 2: Synthesis of Compound **WX33**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX30** in Example **30** were used to give the crude product, which was purified with column chromatography (dichloromethane: methanol=30/1,10/1) to give Compound **WX33**.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24 (d, *J*=6.53 Hz, 3 H) 3.22 (td, *J*=12.61, 3.64 Hz, 1 H) 3.55 (td, *J*=11.73, 2.64 Hz, 1 H) 3.67 - 3.74 (m, 1 H) 3.76 - 3.81 (m, 1 H) 3.99 (s, 4 H) 4.11 (br d, *J*=11.54 Hz, 1 H) 4.55 (br d, *J*=7.03 Hz, 1 H) 6.67 (d, *J*=1.76 Hz, 1 H) 6.89 - 7.01 (m, 2 H) 7.40 (s, 1 H) 7.54 (d, *J*=1.76 Hz, 1 H) 7.56 - 7.58 (m, 1 H) 7.60 (d, *J*=5.02 Hz, 1 H) 8.31 (d, *J*=5.02 Hz, 1 H) 11.79 (br s, 1 H)

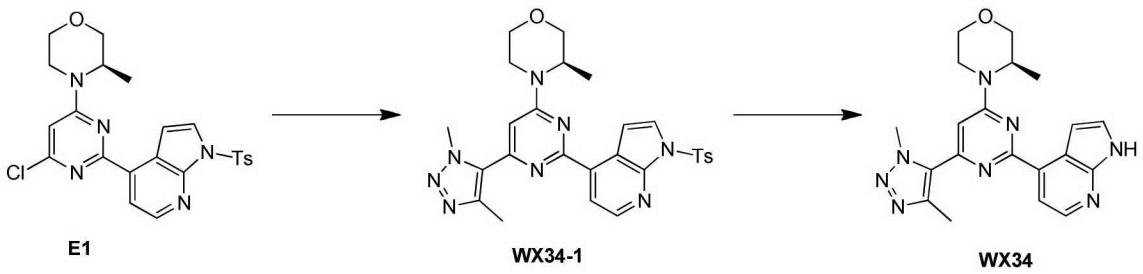
MS *m/z*: 375.2[M+H]$^+$.

Example 34



WX34

Synthesis scheme:



Step 1: Synthesis of Compound **WX34-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX15-1** in synthesis Example **15** were used to give the crude product, which was separated with column chromatography to give Compound **WX34-1.**

MS-ESI m/z: 545.4[M+H]+.

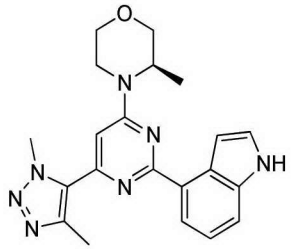
Step 2: Synthesis of Compound **34**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX15** in synthesis Example **15** were used to give Compound **WX34**.

MS-ESI m/z: 391.1 [M+H]+.

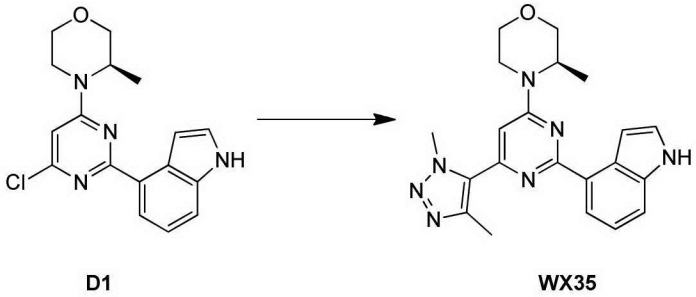
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (d, *J*=6.53 Hz, 3 H) 2.47 (s, 3 H) 3.37 (br d, *J*=3.51 Hz, 1 H) 3.56 (td, *J*=11.80, 2.76 Hz, 1 H) 3.71 (dd, *J*=11.42, 2.89 Hz, 1 H) 3.79 - 3.89 (m, 1 H) 4.04 (dd, *J*=11.17, 3.39 Hz, 1 H) 4.22 - 4.37 (m, 4 H) 4.65 (br s, 1 H) 6.99 (s, 1 H) 7.20 (dd, *J*=3.39, 1.88 Hz, 1 H) 7.61 (t, *J*=3.01 Hz, 1 H) 8.02 (d, *J*=5.02 Hz, 1 H) 8.36 (d, *J*=5.02 Hz, 1 H) 11.85 (br s, 1 H).

Example 35



WX35

Synthesis scheme:



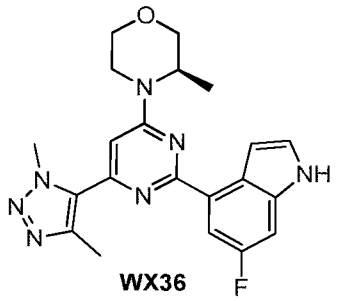
Step 1: Synthesis of Compound **WX35**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX13** in synthesis Example **13** were used to give Compound **WX35**.

MS-ESI m/z: 390.3 [M+H]+.

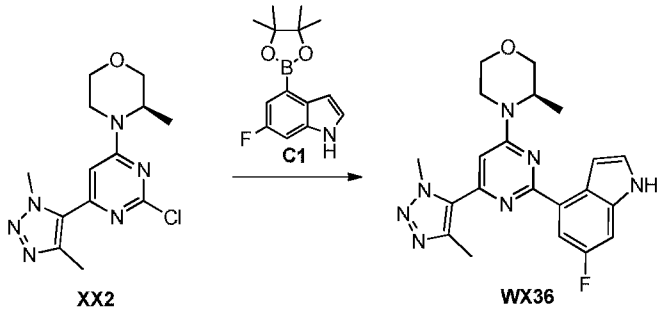
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.28 (s, 3 H) 2.58 (br s, 3 H) 3.49 (s, 1 H) 3.73 (s, 1 H) 3.91 (br s, 2 H) 4.14 (br s, 1 H) 4.29 (s, 1 H) 4.39 (br s, 3 H) 4.53 (s, 1 H) 6.52 (s, 1 H) 7.34 (br s, 1 H) 7.38 (br s, 1 H) 7.48 (br s, 1 H) 7.57 (s, 1 H) 8.27 (br d, *J*=7.53 Hz, 1 H) 8.37 (s, 1 H)

Example 36



WX36

Synthesis scheme:



XX2 **C1** **WX36**

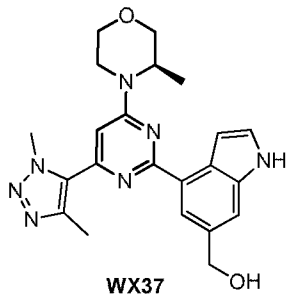
Step 1: Synthesis of Compound **WX36**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX13** in synthesis Example **13** were used to give Compound **WX36**.

MS-ESI m/z: 408.1 [M+H]+.

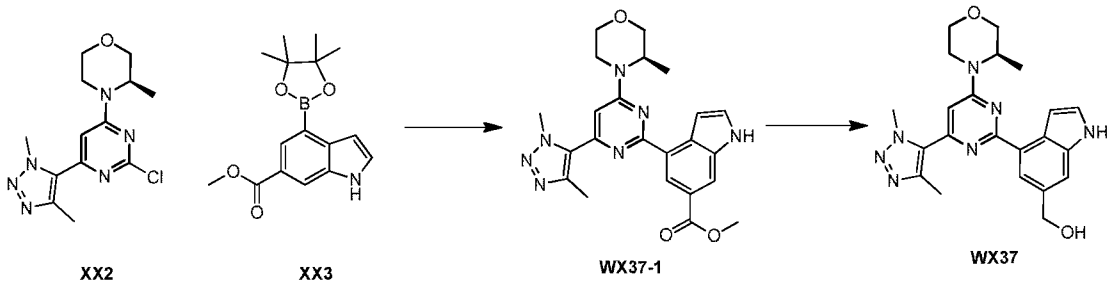
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (d, *J*=6.78 Hz, 3 H) 2.46 (s, 3 H) 3.36 (br d, *J*=4.27 Hz, 1 H) 3.50 - 3.62 (m, 1 H) 3.67 - 3.74 (m, 1 H) 3.79 - 3.86 (m, 1 H) 4.04 (dd, *J*=10.92, 3.14 Hz, 1 H) 4.25 (s, 3 H) 4.29 (br d, *J*=11.29 Hz, 1 H) 4.63 (br s, 1 H) 6.93 (s, 1 H) 7.29 (br s, 1 H) 7.36 (dd, *J*=9.29, 2.01 Hz, 1 H) 7.48 (t, *J*=2.64 Hz, 1 H) 7.90 (dd, *J*=11.29, 2.51 Hz, 1 H) 11.36 (br s, 1 H)

Example 37



WX37

Synthesis scheme:



Step 1: Synthesis of Compound **WX37-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX13** in synthesis Example **13** were used to give Compound **WX37-1**.

MS-ESI m/z: 411.3 [M+H]+.

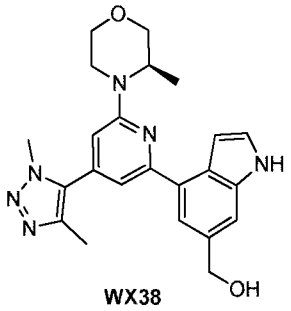
Step 2: Synthesis of Compound **WX37**

At 0°C, to a solution of Compound **WX37-1** (0.15 g, 335.20 μmol) in tetrahydrofuran (10 mL) was added lithium aluminum hydride (25.44 mg, 670.41 μmol), and the reaction mixture was stirred at 0°C for 0.5 h. At 0°C, the reaction solution was added with anhydrous sodium sulfate, quenched with water (1 ml) and filtered. The filtrate was concentrated to give the crude product, which was separated with column chromatography to give Compound **WX37**.

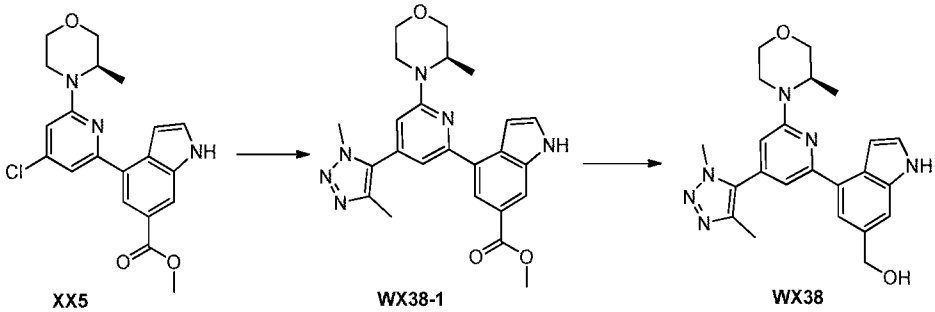
MS-ESI m/z: 420.3 [M+H]+.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (d, *J*=6.78 Hz, 3 H) 1.34 - 1.34 (m, 1 H) 2.46 (s, 3 H) 3.39 (br s, 1 H) 3.56 (td, *J*=11.92, 3.01 Hz, 1 H) 3.71 (dd, *J*=11.54, 2.76 Hz, 1 H) 3.83 (d, *J*=11.54 Hz, 1 H) 4.04 (br dd, *J*=11.42, 3.14 Hz, 1 H) 4.25 (s, 3 H) 4.30 (br d, *J*=12.80 Hz, 1 H) 4.65 (s, 3 H) 6.88 (s, 1 H) 7.24 (br s, 1 H) 7.43 (t, *J*=2.64 Hz, 1 H) 7.52 (s, 1 H) 8.10 (s, 1 H) 11.23 (br s, 1 H).

Example 38



Synthesis scheme:



Step 1: Synthesis of Compound **WX38-1**

To a solution of Compound **XX5** (0.28 g, 725.68 μmol) in N,N-dimethylformamide (5 mL) were added 1,4-dimethyl-1H-1,2,3-triazole (140.95 mg, 1.45 mmol), bis(triphenylphosphine) palladium dichloride (50.94

mg, 72.57 μmol), and tetramethylammonium acetate(115.98 mg, 870.82 μmol). The reaction mixture was stirred in a sealed tube at 140°C with heating for 4 h, and then diluted with ethyl acetate (50 mL), washed with water (20 mL) and saturated brine (20 ml), dried over anhydrous sodium sulfate, and filtered. The solution was concentrated to give the crude product, which was separated with column chromatography to give Compound **WX38-1**.

MS-ESI m/z: 447.3 [M+H]+.

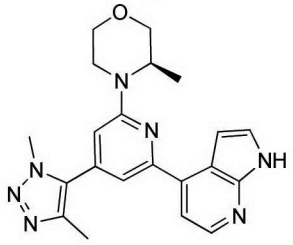
Step 2: Synthesis of Compound **WX38**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX37** in synthesis Example **WX37** were used to give Compound **WX38**.

MS-ESI m/z: 419.3 [M+H]+.

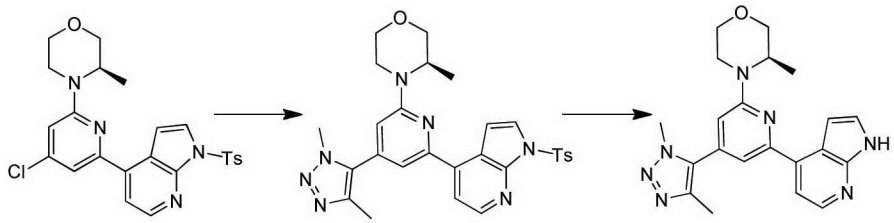
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.23 (br d, *J*=6.53 Hz, 3 H) 2.32 (s, 3 H) 3.16 - 3.23 (m, 1 H) 3.50 - 3.60 (m, 1 H) 3.67 - 3.73 (m, 1 H) 3.75 - 3.81 (m, 1 H) 4.00 (br d, *J*=8.28 Hz, 1 H) 4.05 (s, 3 H) 4.13 (br d, *J*=11.80 Hz, 1 H) 4.50 (br d, *J*=4.77 Hz, 1 H) 4.63 (d, *J*=5.52 Hz, 2 H) 5.13 (t, *J*=5.65 Hz, 1 H) 6.79 (s, 1 H) 6.88 (br s, 1 H) 7.16 (s, 1 H) 7.40 (br s, 1 H) 7.46 (d, *J*=11.80 Hz, 2 H) 11.21 (br s, 1 H)

Example 39



WX39

Synthesis scheme:



XX1 **WX39-1** **WX39**

Step 1: Synthesis of Compound **WX39-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX38-1** in synthesis Example **Intermediate WX38-1** were used to give Compound **WX39-1**.

MS-ESI m/z: 544.4 [M+H]+.

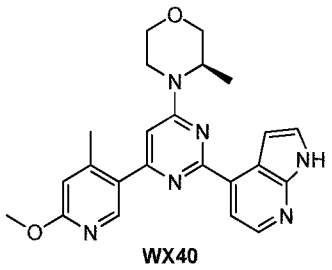
Step 2: Synthesis of Compound **WX39**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX15** in synthesis Example **15** were used to give Compound **WX39**.

MS-ESI m/z: 390.1 [M+H]+.

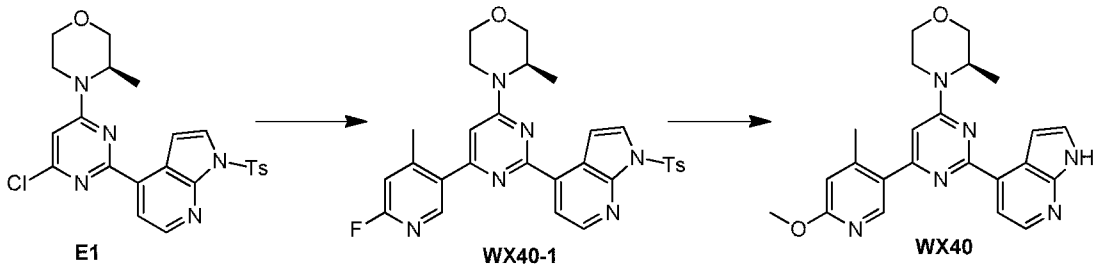
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24 (d, *J*=6.78 Hz, 3 H) 2.33 (s, 3 H) 3.18 - 3.26 (m, 1 H) 3.55 (td, *J*=11.86, 2.64 Hz, 1 H) 3.66 - 3.74 (m, 1 H) 3.76 - 3.82 (m, 1 H) 4.01 (dd, *J*=11.42, 3.14 Hz, 1 H) 4.06 (s, 3 H) 4.14 (br d, *J*=10.79 Hz, 1 H) 4.51 (br d, *J*=7.03 Hz, 1 H) 6.92 (s, 1 H) 6.95 (dd, *J*=3.51, 2.01 Hz, 1 H) 7.36 (s, 1 H) 7.57 - 7.61 (m, 2 H) 8.31 (d, *J*=5.02 Hz, 1 H) 11.80 (br s, 1 H)

Example 40



WX40

Synthesis scheme:



E1 **WX40-1** **WX40**

Step 1: Synthesis of Compound **WX40-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX15-1** in synthesis Example **Intermediate WX15-1** were used to give Compound **WX40-1**.

MS-ESI m/z: 559.1[M+H]+.

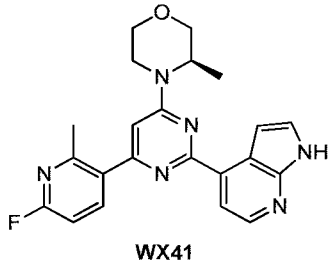
Step 2: Synthesis of Compound **WX40**

To a solution of Compound **WX40-1** (0.095 g, 170.06 μmol) in methanol (15 mL) was added 2M sodium hydroxide (2M, 1 mL). The reaction mixture was stirred at 15-20°C for 72 h, and then diluted with water (30 mL). The aqueous phase was extracted with dichloromethane (50mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate and filtered. The filtrate was rotated to dryness to give the crude product, which was separated with column chromatography to give Compound **WX40**.

MS-ESI m/z: 417.0 [M+H]+.

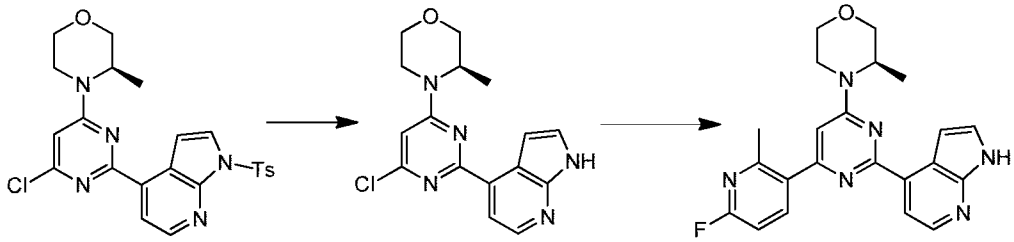
^{1}H NMR ($CDCl_3$, 400MHz): δ = 9.53 (br s, 1H), 8.44 (d, *J*=5.0 Hz, 1H), 8.27-8.34 (m, 1H), 8.14 (d, *J*=5.1 Hz, 1H), 7.37-7.47 (m, 2H), 6.72 (s, 1H), 6.55 (s, 1H), 4.62 (s, 1H), 4.53 (br s, 1H), 4.26 (br d, *J*=13.3 Hz, 1H), 3.97-4.02 (m, 3H), 3.87-3.94 (m, 1H), 3.79-3.86 (m, 1H), 3.69 (td, *J*=11.9, 3.1 Hz, 1H), 3.44 (td, *J*=12.8, 3.9 Hz, 1H), 2.54 (s, 3H), 1.44 ppm (d, *J*=6.9 Hz, 3H)

Example 41



WX41

Synthesis scheme:



E1 WX41-1 WX41

Step 1: Synthesis of Compound **WX41-1**

To a solution of Compound **E1** (2 g, 4.13 mmol) in ethanol (25 mL) was added 2M sodium hydroxide (10.33 mL) and the reaction mixture was stirred at 15-20°C for 14 h and then heated to 60°C with stirring for 5 h. The reaction solution was adjusted to pH 6-7 with 2M hydrochloric acid, diluted with water (40 mL) and extracted with ethyl acetate (60mL × 3). The organic phases were combined, washed with saturated brine (80 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was rotated to dryness to give crude Compound **WX41-1**.

MS-ESI m/z: 330.0 [M+H]+.

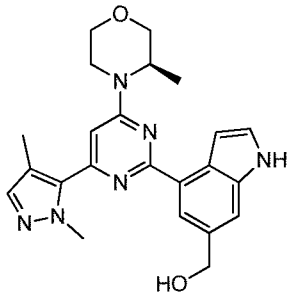
Step 2: Synthesis of Compound **WX41**

To a solution of Compound **WX41-1** (0.06 g, 181.94 μmol), 2-fluoro-6-methylpyridine-5-boric acid (42.28 mg, 272.91 μmol) and tetrakis (triphenylphosphine) palladium (14.72 mg, 12.74 μmol) in 1,4-dioxane(8 mL) was added 2M sodium carbonate (2M, 272.91 μL) aqueous solution, which was purged with nitrogen three times. The reaction mixture was stirred with heating at 95°C for 5 h and then filtered. The solution was concentrated to give the crude product, which was separated with column chromatography to give **WX41**.

MS-ESI m/z: 405.2 [M+H]+.

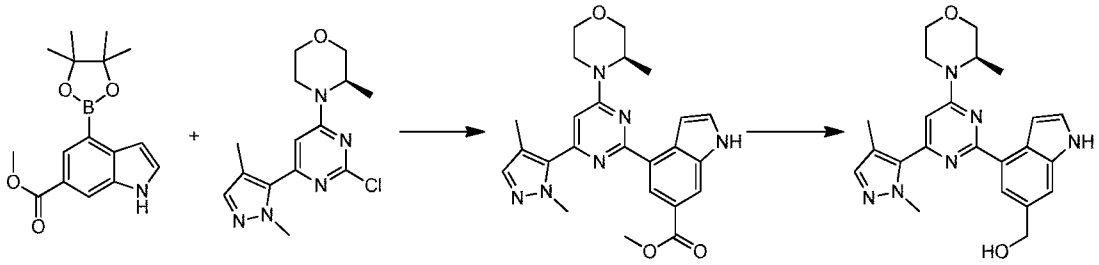
^{1}H NMR (CHLOROFORM-d, 400MHz): δ = 10.24 (br s, 1H), 8.47 (d, *J*=5.0 Hz, 1H), 8.15 (d, *J*=5.3 Hz, 1H), 7.98 (t, *J*=8.0 Hz, 1H), 7.45-7.57 (m, 1H), 7.36-7.41 (m, 1H), 6.91 (dd, *J*=8.3, 3.0 Hz, 1H), 6.55 (s, 1H), 4.54 (br s, 1H), 4.27 (br d, *J*=12.3 Hz, 1H), 4.13 (dd, *J*=11.5, 3.5 Hz, 1H), 3.88-3.96 (m, 1H), 3.78-3.86 (m, 1H), 3.69 (td, *J*=11.9, 3.0 Hz, 1H), 3.45 (td, *J*=12.8, 3.8 Hz, 1H), 2.71 (s, 3H), 1.45 ppm (d, *J*=6.8 Hz, 3H)

Example WX42



WX42

Synthesis scheme:



XX3 XX4 WX42-1 WX42

Step 1: Synthesis of Compound **WX42-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX37-1** in synthesis Example **WX37** were used to give Compound **WX42-1:**

To a solution of Compound **XX4** (0.11 g, 357.40 μmol), **XX3** (161.44 mg, 536.10 μmol) and tetrakis (triphenylphosphine) palladium (0.03 g, 25.96 μmol) in 1,4-dioxane(8 mL) was added 2M sodium carbonate (534.1 μL) aqueous solution, which was purged with nitrogen three times. The reaction mixture was stirred with heating at 100°C for 5 h and then filtered. The solution was concentrated to give the crude product, which was separated with column chromatography (ethyl acetate/petroleum ether: 20-55%) to give Compound **WX42-1**.

MS-ESI m/z: 447.1[M+H]+.

Step 2: Synthesis of Compound **WX42**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX37** in synthesis Example **WX37** were used to give Compound **WX42:**

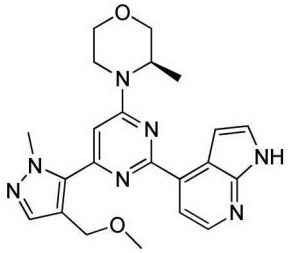
At the condition of 0-5°C, to a solution of Compound **WX42-1**(0.13 g, 291.15 μmol) in tetrahydrofuran (10 mL) was added lithium aluminum hydride (0.05 g, 1.32 mmol). The reaction mixture was stirred at 0-5°C for 1 h and then heated to 25°C with stirring for 2 h. At 0-5°C, to the reaction were successively added slowly one drop of water, two drops of 10% sodium hydroxide and three drops of water, which was then filtered. The filtrate was concentrated to give the crude product, which was separated with column chromatography (ethyl acetate/petroleum ether: 50-100%) to give Compound **WX42**.

MS-ESI m/z: 419.2 [M+H]+.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 8.44 (br s, 1H), 8.25 (s, 1H), 7.54 (s, 1H), 7.49 (br s, 1H), 7.41 (s, 1H), 7.32 (t, *J*=2.8 Hz, 1H), 6.47 (s, 1H), 4.87 (s, 2H), 4.48 (br d, *J*=4.5 Hz, 1H), 4.29 (br d, *J*=13.8 Hz, 1H), 4.14 (s,

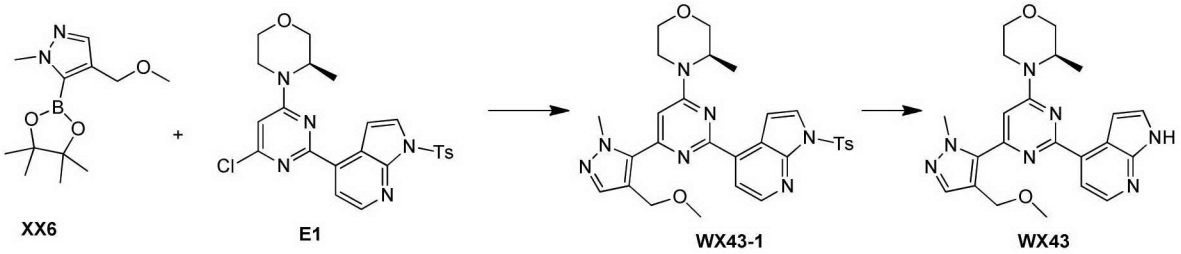
3H), 4.11 ((m, 1H), 3.86-3.94 (m, 1H), 3.79-3.86 (m, 1H), 3.69 (td, *J*=11.9, 3.1 Hz, 1H), 3.43 (td, *J*=12.7, 3.9 Hz, 1H), 2.24 (s, 3H), 1.70 (t, *J*=6.0 Hz, 1H), 1.43 ppm (d, *J*=6.8 Hz, 3H)

Example 43



WX43

Synthesis scheme:



Step 1: Synthesis of Compound **WX43-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX15-1** in synthesis Example **15** were used to give crude **WX43-1**.

MS-ESI m/z: 574.4 [M+H]+.

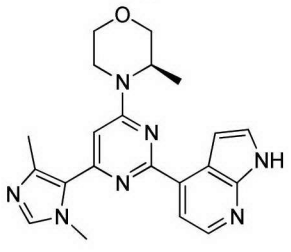
Step 2: Synthesis of Compound **WX43**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX15** in synthesis Example **15** were used to give Compound **WX43**.

MS-ESI m/z: 420.1 [M+H]+.

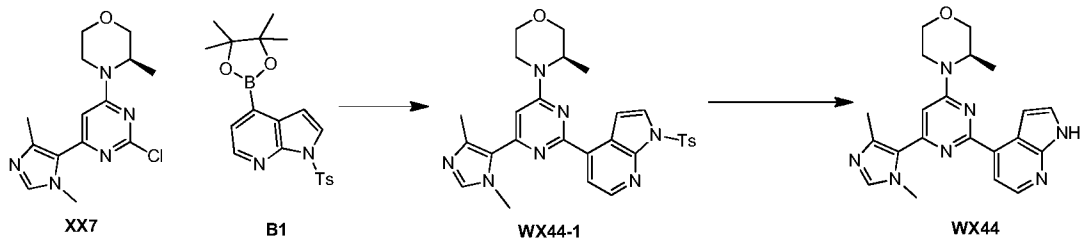
^{1}H NMR (CHLOROFORM-d, 400MHz): δ = 9.74 (br s, 1H), 8.46 (br s, 1H), 8.16 (br s, 1H), 7.60 (s, 1H), 7.48 (d, *J*=3.3 Hz, 1H), 7.40 (d, *J*=3.0 Hz, 1H), 7.09 (s, 1H), 4.53 (br s, 1H), 4.38 (s, 2H), 4.26 (s, 4H), 4.13 (dd, *J*=11.4, 3.6 Hz, 1H), 3.88-3.95 (m, 1H), 3.79-3.85 (m, 1H), 3.65-3.74 (m, 1H), 3.39-3.49 (m, 4H), 1.45 ppm (d, *J*=6.8 Hz, 3H).

Example 44



WX44

Synthesis scheme:



Step 1: Synthesis of Compound **WX44-1**

To a solution of Compound **XX7** (0.05 g, 162.45 μmol), **B1**(77.64 mg, 194.95 μmol) and tetrakis (triphenylphosphine) palladium(18.77 mg, 16.25 μmol) in 1,4-dioxane(5 mL) was added 2M sodium carbonate (2 M, 243.68 uL) aqueous solution, which was purged with nitrogen three times. The reaction mixture was stirred with heating at 100°C for 14 h and then filtered. The solution was concentrated to give the crude product, which was separated with column chromatography to give Compound **WX44-1**.

MS-ESI m/z: 544.4 [M+H]+.

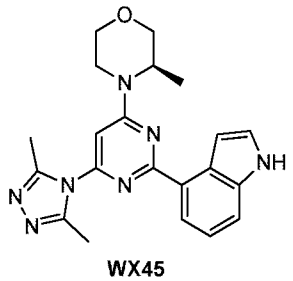
Step 2: Synthesis of Compound **WX44**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX15** in synthesis Example **15** were used to give Compound **WX44.**

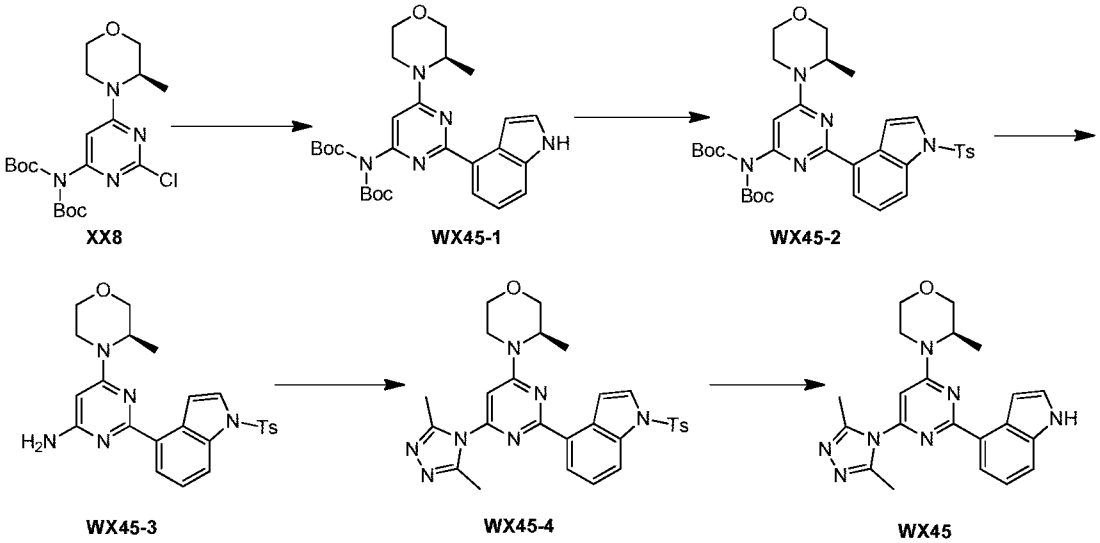
MS-ESI m/z: 390.3 [M+H]+.

^{1}H NMR (CHLOROFORM-d, 400MHz): δ = 9.09 (br s, 1H), 8.43 (d, *J*=5.0 Hz, 1H), 8.09 (d, *J*=5.0 Hz, 1H), 7.53 (br s, 1H), 7.44 (br s, 1H), 7.35 (d, *J*=2.3 Hz, 1H), 6.53 (s, 1H), 4.51 (br d, *J*=5.4 Hz, 1H), 4.23 (br d, *J*=12.6 Hz, 1H), 4.13 (dd, *J*=11.5, 3.5 Hz, 1H), 3.97 (s, 3H), 3.89-3.93 (m, 1H), 3.80-3.86 (m, 1H), 3.64-3.70 (m, 1H), 3.44 (td, *J*=12.7, 3.9 Hz, 1H), 2.48 (s, 3H), 1.44 ppm (d, *J*=6.8 Hz, 3H).

Example 45



Synthesis scheme:



Step 1: Synthesis of Compound **WX45-1**

To a solution of Compound **XX8** (1.6 g, 3.73 mmol), indole-4-boric acid pinacol ester (1.18 g, 4.85 mmol) and bis(triphenylphosphine) palladium dichloride(183.28 mg, 261.13 μmol) in 1,4-dioxane(20 mL) was added 2M sodium carbonate (2 M, 5.6 mL) aqueous solution, which was purged with nitrogen three times. The reaction mixture was stirred with heating at 95°C for 16 h and then filtered. The solution was concentrated to give the crude product, which was separated with column chromatography to give Compound **WX45-1**.

MS-ESI m/z: 510.8 [M+H]+.

Step 2: Synthesis of Compound **WX45-2**

At 0-5°C, to a solution of Compound **WX45-1** (1.25 g, 2.45 mmol) in *N'N*-dimethylformamide (10 mL) was added sodium hydride (127.54 mg, 3.19 mmol, purity: 60%). The reaction mixture was stirred at 0-5°C for 10 min, to which was added *p*-toluenesulfonyl chloride (561.17 mg, 2.94 mmol). The reaction mixture was stirred at 0-5°C for 50 min, quenched with water (30 mL) and extracted with ethyl acetate (40 mL × 3). The organic phases were combined and washed successively with water (30 mL × 2) and saturated brine (50 mL × 2). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give crude Compound **WX45-2**.

MS-ESI m/z: 664.5 [M+H]+.

Step 3: Synthesis of Compound **WX45-3**

To a solution of Compound **WX45-2** (1.7 g, 2.56 mmol) in 1,4-dioxane (10 mL) was added 4M hydrochloric acid/1,4-dioxane (4 M, 5 mL). The reaction mixture was stirred at 30°C for 2 h, adjusted to pH=7-8 with saturated sodium bicarbonate, diluted with water (30 mL) and extracted with ethyl acetate (40 mL × 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product, which was separated with column chromatography (ethyl acetate/petroleum ether: 25-75%) to give Compound **WX45-3**.

MS-ESI m/z: 464.7 [M+H]+.

Step 4: Synthesis of Compound **WX45-4**

To a solution of Compound **WX45-3** (0.3 g, 647.18 μmol), 2,5-dimethyl-1,3,4-oxadiazole (190.47 mg, 1.94 mmol) in 1-methyl-2-pyrrolidone (3 mL) was added anhydrous *p*-toluenesulfonic acid (111.45 mg, 647.18 μmol) and the reaction mixture was stirred at 200°C with microwave for 1.5 h. The reaction solution was diluted with water (20 mL) and extracted with dichloromethane (30 mL × 4). The organic phases were combined, washed with saturated brine (50 mL), and dried over anhydrous sodium sulfate. The filtered organic phase was concentrated to give the crude product, which was separated with column chromatography (methanol/dichloromethane: 0-10%) to give Compound **WX45-4**.

MS-ESI m/z: 544.4 [M+H]+.

Step 5: Synthesis of Compound **WX45**

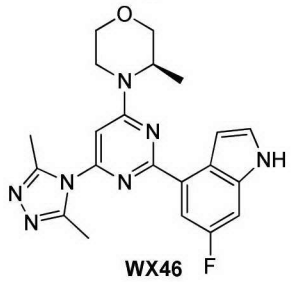
Except using corresponding raw materials, the procedures identical to those used for Compound **WX15** in synthesis Example **15** were used to give Compound **WX45**.

MS-ESI m/z: 390.3 [M+H]+.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 8.60 (br s, 1H), 8.26 (dd, *J*=7.5, 0.8 Hz, 1H), 7.58 (d, *J*=8.0 Hz, 1H), 7.45 (t, *J*=2.3 Hz, 1H), 7.36 (t, *J*=2.8 Hz, 1H), 7.31 (t, *J*=7.8 Hz, 1H), 6.20-6.25 (m, 1H), 4.49 (br s, 1H), 4.25 (br

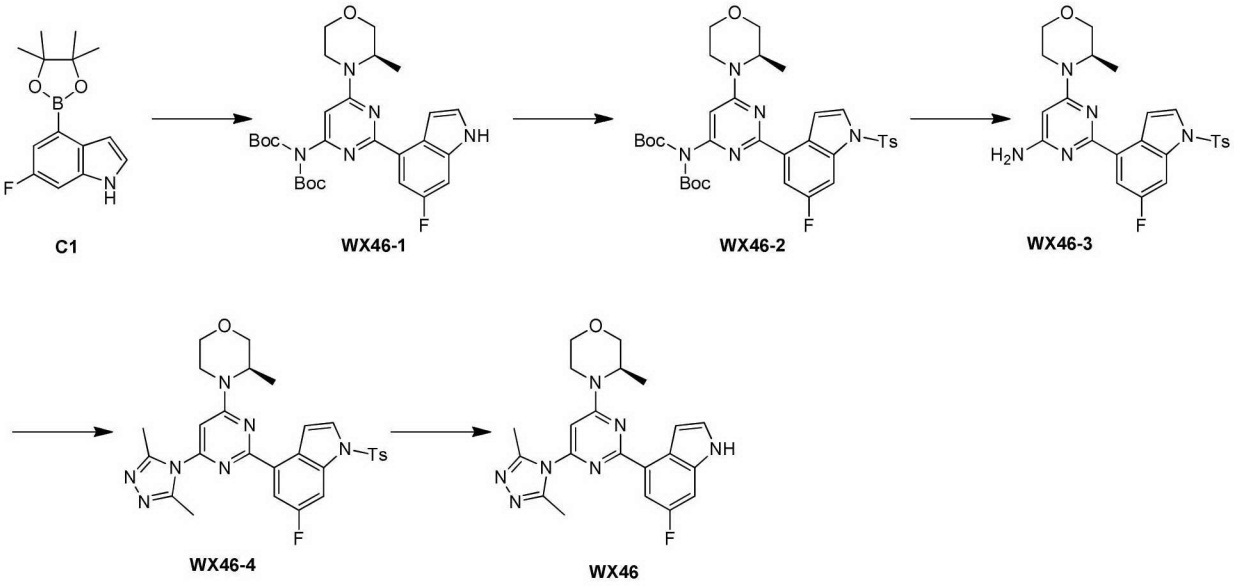
d, *J*=12.3 Hz, 1H), 4.13 (dd, *J*=11.5, 3.8 Hz, 1H), 3.88-3.96 (m, 1H), 3.80-3.87 (m, 1H), 3.68 (td, *J*=11.9, 3.1 Hz, 1H), 3.47 (td, *J*=12.8, 3.9 Hz, 1H), 2.54 (s, 6H), 1.45 ppm (d, *J*=6.8 Hz, 3H).

Example 46



WX46

Synthesis scheme:



Step 1: Synthesis of Compound **WX46-1**

To a solution of Compound **C1** (1.3 g, 3.03 mmol), **XX8** (830.95 mg, 3.18 mmol) and bis(triphenylphosphine) palladium dichloride(148.92 mg, 212.17 μmol) in 1,4-dioxane(20 mL) was added 2M sodium carbonate (2 M, 4.55 mL) aqueous solution, which was purged with nitrogen three times. The reaction mixture was stirred with heating at 85°C for 16 h and then filtered. The solution was concentrated to give the crude product, which was separated with column chromatography to give Compound **WX46-1**.

MS-ESI m/z: 528.4 [M+H]+.

Step 2: Synthesis of Compound **WX46-2**

At 0-5°C, to a solution of Compound **WX46-1** (1.35 g, 2.56 mmol) in N'N-dimethylformamide (10 mL) was added sodium hydride (133.06 mg, 3.33 mmol, 60% purity). The reaction mixture was stirred at 0-5°C for 10 min, to which was added *p*-toluenesulfonyl chloride (585.40 mg, 3.07 mmol). The reaction mixture was stirred at 0-5°C for 30 min, quenched with water (30 mL) and extracted with ethyl acetate (40 mL × 3). The organic phases were combined and washed successively with water (30 mL × 2) and saturated brine (50 mL × 2). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give crude Compound **WX46**-2.

MS-ESI m/z: 682.5 [M+H]+.

Step 3: Synthesis of Compound **WX46-3**

To a solution of Compound **WX46-2** (1.75 g, 2.56 mmol) in 1,4-dioxane (10 mL) was added 4M hydrochloric acid/1,4-dioxane (4 M, 10 mL). The reaction mixture was stirred at 30°C for 12 h, adjusted to pH=7-8 with saturated sodium bicarbonate, diluted with water (40 mL) and extracted with ethyl acetate (50 mL × 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product, which was separated with column chromatography to give Compound **WX46-3**.

MS-ESI m/z: 482.3 [M+H]+.

Step 4: Synthesis of Compound **WX46-4**

Except using corresponding raw materials, 以 synthesis Example **15** 中 Compound **WX15-1** 的方法相同. 得 Compound **WX46-4**.

MS-ESI m/z: 562.4 [M+H]+.

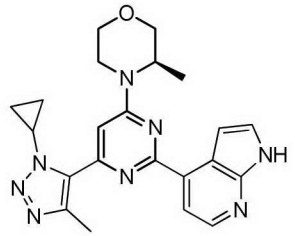
Step 5: Synthesis of Compound **WX46**

Except using corresponding raw materials, 以 synthesis Example **15** 中 Compound **WX15** 的方法相同. 得 Compound **WX46**.

MS-ESI m/z: 408.2 [M+H]+.

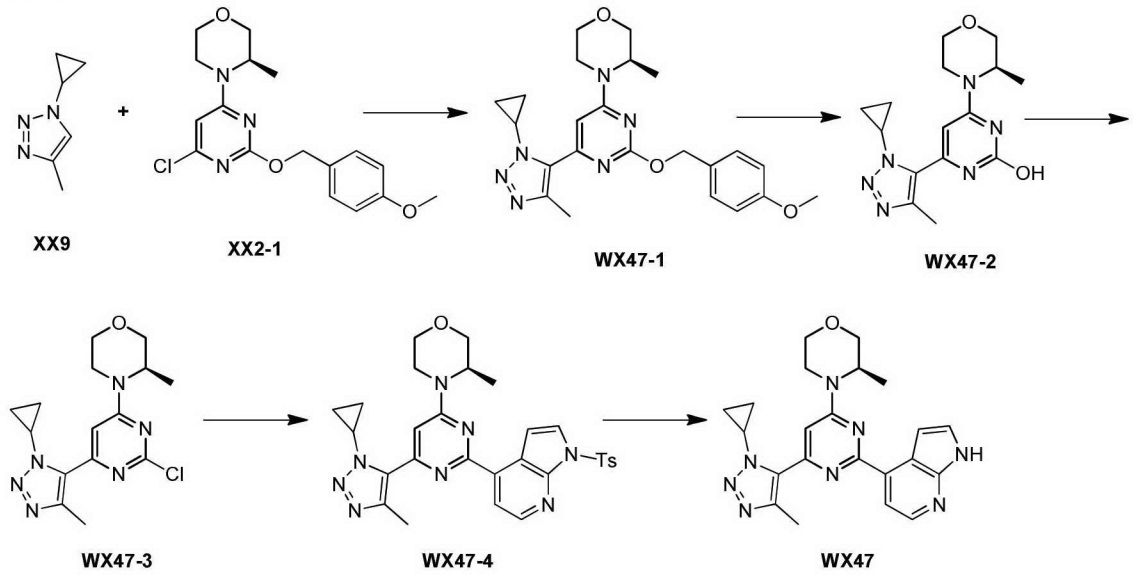
^{1}H NMR (CHLOROFORM-d, 400MHz): δ = 8.27-8.59 (m, 1H), 7.93-7.96 (m, 1H), 7.34 (t, *J*=2.3 Hz, 1H), 7.26 (t, *J*=2.8 Hz, 1H), 7.20 (br d, *J*=2.4 Hz, 1H), 6.16-6.22 (m, 1H), 4.40 (br s, 1H), 4.17 (br d, *J*=10.6 Hz, 1H), 4.06 (dd, *J*=11.6, 3.7 Hz, 1H), 3.79-3.87 (m, 1H), 3.72-3.78 (m, 1H), 3.61 (td, *J*=11.9, 3.0 Hz, 1H), 3.39 (td, *J*=12.8, 3.9 Hz, 1H), 2.46 (s, 6H), 1.37 ppm (d, *J*=6.8 Hz, 3H).

Example 47



WX47

Synthesis scheme:



Step 1: Synthesis of Compound **WX47-1**

To a solution of Compound **XX9** (0.3 g, 857.61 μmol), **XX2-1** (126.74 mg, 1.03 mmol), potassium carbonate (237.05 mg, 1.72 mmol), tricyclohexylphosphine (126.74 mg, 1.03 mmol) and trimethylacetic acid (17.52 mg, 171.52 μmol) in N,N-dimethylacetamide (2 mL) was added palladium acetate(19.25 mg, 85.76 μmol). The reaction was purged with nitrogen three times and stirred at 130-150°C for 18 h. The reaction solution was concentrated to give the crude product, which was separated with column chromatography to give Compound **WX47-1**.

MS-ESI m/z: 437.4 [M+H]+.

Step 2: Synthesis of Compound **WX47-2**

To a solution of Compound **WX47-1** (.45 g, 1.03 mmol) in ethanol (25 mL) was added Pd/C (0.1 g, 1.03 mmol, purity: 10%). The reaction was purged with hydrogen several times and stirred 16 h under hydrogen (15psi) at 30°C. The reaction solution was filtered through celite and the filtrate was concentrated to give crude Compound **WX47-2**.

MS-ESI m/z: 317.2 M+H]+.

Step 3: Synthesis of Compound **WX47-3**

To the solvent of phosphorus oxychloride (11.75 g, 76.63 mmol) was added **WX47-2** (0.33 g, 1.04 mmol) and the reaction was heated to 30°C and stirred under nitrogen atmosphere for 5 h. The reaction solution was concentrated and then diluted with dichloromethane (50 mL). The organic phase was adjusted to pH 8 with saturated sodium bicarbonate, extracted with dichloromethane (30 mL × 8). The organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated to give Compound **WX47-3**.

MS-ESI m/z: 335.2 M+H]+.

Step 4: Synthesis of Compound **WX47-4**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX15-1** in synthesis Example **15** were used to give Compound **WX47-4**.

MS-ESI m/z: 571.4 M+H]+.

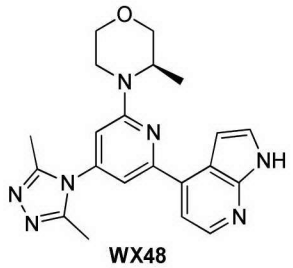
Step 5: Synthesis of Compound **WX47**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX15** in synthesis Example **15** were used to give Compound **WX47**.

MS-ESI m/z: 417.3 M+H]+.

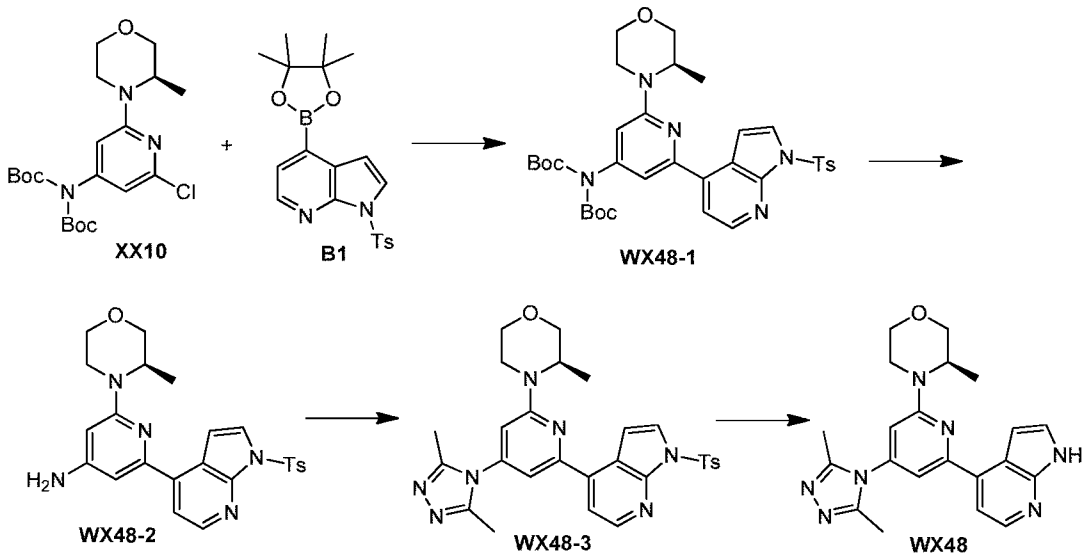
H NMR ($CDCl_3$, 400MHz): δ = 9.41 (br s, 1H), 8.45 (d, *J*=5.0 Hz, 1H), 8.13 (d, *J*=5.0 Hz, 1H), 7.45-7.51 (m, 1H), 7.39 (dd, *J*=3.5, 2.0 Hz, 1H), 6.62 (s, 1H), 4.52 (br s, 1H), 4.28-4.31 (m, 1H), 4.25 (tt, *J*=7.5, 3.8 Hz, 1H), 4.12-4.17 (m, 1H), 3.89-3.95 (m, 1H), 3.79-3.88 (m, 1H), 3.70 (td, *J*=11.9, 3.0 Hz, 1H), 3.47 (td, *J*=12.7, 3.8 Hz, 1H), 2.54 (s, 3H), 1.46 (d, *J*=6.8 Hz, 3H), 1.35-1.42 (m, 2H), 1.04-1.14 ppm (m, 2H).

Example 48



WX48

Synthesis scheme:



Step 1: Synthesis of Compound **WX48-1**

To a solution of Compound **XX10** (1.6 g, 3.74 mmol), **B1** (2.23 g, 5.61 mmol) and tetrakis (triphenylphosphine) palladium (18.77 mg, 16.25 μmol) in 1,4-dioxane (5 mL) was added 2M sodium carbonate (2 M, 4.67 mL) aqueous solution, which was purged with nitrogen three times. The reaction mixture was stirred with heating at 100°C for 20 h and then filtered. The solution was concentrated to give the crude product, which was separated with column chromatography to give Compound **WX48-1**.

MS-ESI m/z: 664.5 M+H]+.

Step 2: Synthesis of Compound **WX48-2**

To a solution of Compound **WX48-1** (2 g, 3.01 mmol) in 1,4-dioxane (10 mL) was added 4M hydrochloric acid/1,4-dioxane (4 M, 5 mL) solution. The reaction mixture was stirred at 30°C for 35 min, adjusted to pH=7-8 with saturated sodium bicarbonate, diluted with water (30 mL) and extracted with dichloromethane (40 mL × 3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product, which was separated with column chromatography to give Compound **WX48-2**.

MS-ESI m/z: 464.7 M+H]+.

Step 3: Synthesis of Compound **WX48-3**

To a solution of Compound **WX48-2** (0.3 g, 647.18 μmol), 2,5-dimethyl-1,3,4-oxadiazole(1240.00 mg, 2.45 mmol) in 1-methyl-2-pyrrolidone (2 mL) was added anhydrous *p*-toluenesulfonic acid (111.44 mg, 647.18 μmol) and the reaction mixture was stirred at 200°C with microwave for 1.5 h. The reaction was concentrated under reduced pressure to give the crude product, which was separated with column chromatography to give Compound **WX48-3**.

MS-ESI m/z: 544.1 M+H]+.

Step 4: Synthesis of Compound **WX48**

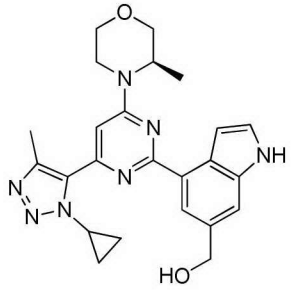
Except using corresponding raw materials, the procedures identical to those used for Compound **WX15** in synthesis Example **15** were used to give Compound **WX48**.

MS-ESI m/z: 390.3 M+H]+.

^{1}H NMR (CHLOROFORM-d, 400MHz): δ = 9.75 (br s, 1H), 8.44 (d, *J*=5.0 Hz, 1H), 7.56 (d, *J*=5.0 Hz, 1H), 7.42-7.51 (m, 1H), 7.06 (d, *J*=1.3 Hz, 1H), 6.94 (dd, *J*=3.4, 1.9 Hz, 1H), 6.38 (d, *J*=1.3 Hz, 1H), 4.39 (br d,

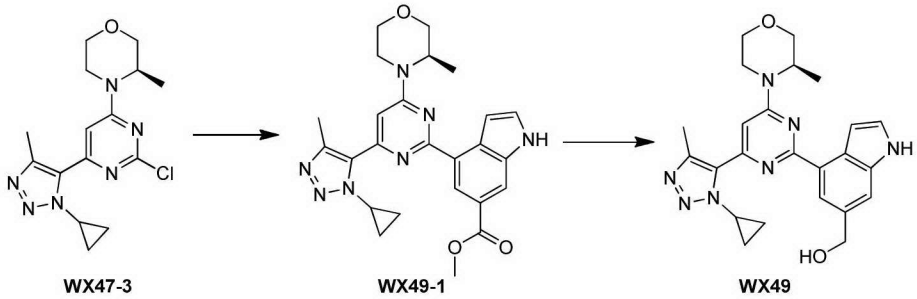
J=6.5 Hz, 1H), 4.04-4.21 (m, 2H), 3.87-3.95 (m, 1H), 3.78-3.86 (m, 1H), 3.69 (td, *J*=12.0, 3.1 Hz, 1H), 3.39 (td, *J*=12.6, 3.9 Hz, 1H), 2.41 (s, 6H), 1.39 ppm (d, *J*=6.8 Hz, 3H)

Example 49



WX49

Synthesis scheme:



WX47-3 **WX49-1** **WX49**

Step 1: Synthesis of Compound **WX49-1**

To a solution of Compound **WX47-3** (0.1 g, 298.68 μmol), **XX3**(125.93 mg, 418.16 μmol) and tetrakis (triphenylphosphine) palladium (24.16 mg, 20.91 μmol) in 1,4-dioxane(8 mL) was added 2M sodium carbonate (2 M, 448.02 μL) aqueous solution, which was purged with nitrogen three times. The reaction mixture was stirred with heating at 90°C for 16 h and then filtered. The solution was concentrated to give the crude product, which was separated with column chromatography to give Compound **WX49-1**.

MS-ESI m/z: 474.4 M+H]+.

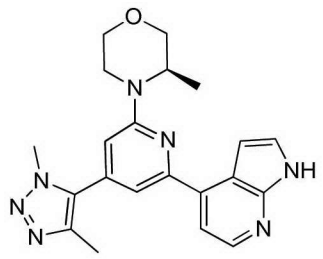
Step 2: Synthesis of Compound **WX49**

At the condition of 0-5°C, to a solution of Compound **WX49-1** (0.06 g, 126.71 μmol) in tetrahydrofuran (10 mL) was added lithium aluminum hydride (0.05 g, 1.32 mmol). The reaction was warmed to 30°C with stirring for 3 h. At 0-5°C, to the reaction were successively added slowly one drop of water, two drops of 10% sodium hydroxide and three drops of water, which was then filtered. The filtrate was concentrated to give the crude product, which was separated with column chromatography to give Compound **WX49**.

MS-ESI m/z: 446.1 M+H]+.

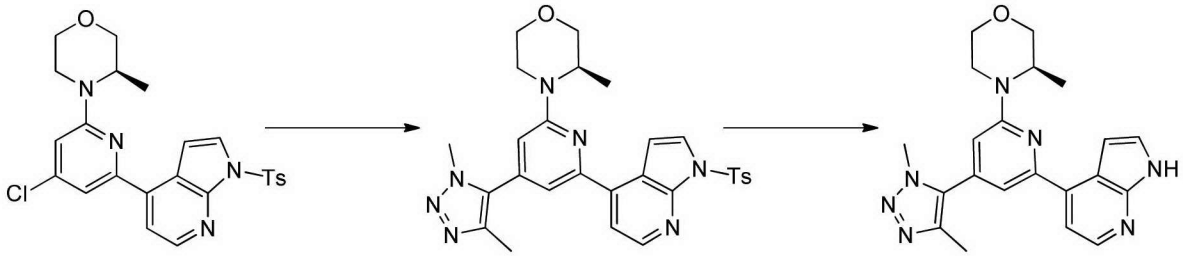
^{1}H NMR (CHLOROFORM-d, 400MHz): δ = 8.43 (br s, 1H), 8.27 (d, *J*=1.0 Hz, 1H), 7.57 (s, 1H), 7.50 (t, *J*=2.3 Hz, 1H), 7.34 (t, *J*=2.8 Hz, 1H), 6.54 (s, 1H), 4.88 (s, 2H), 4.50 (br d, *J*=4.5 Hz, 1H), 4.21-4.35 (m, 2H), 4.13 (dd, *J*=11.4, 3.6 Hz, 1H), 3.88-3.93 (m, 1H), 3.79-3.88 (m, 1H), 3.64-3.73 (m, 2H), 3.45 (td, *J*=12.8, 4.0 Hz, 1H), 2.52 (s, 3H), 1.44 (d, *J*=6.8 Hz, 3H), 1.33-1.40 (m, 2H), 1.02-1.11 ppm (m, 2H).

Example 50



WX50

Synthesis scheme:



XX1 WX50-1 WX50

Step 1: Synthesis of Compound **WX50-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX30-1** in Example **30** were used to give the crude product, which was separated with column chromatography (ethyl acetate/petroleum ether: 0-60%) to give **WX50-1**.

MS-ESI: 544.4 [M+H]+

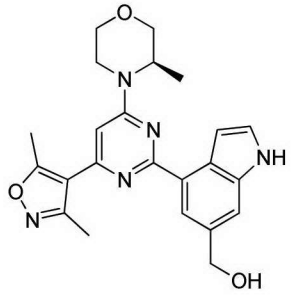
Step 2: Synthesis of Compound **WX50**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX30** in Example **30** were used to give the crude product, which was purified with column chromatography (dichloromethane : methanol=30/1,10/1) to give Compound **WX50**.

MS-ESI: 390.1 [M+H]+

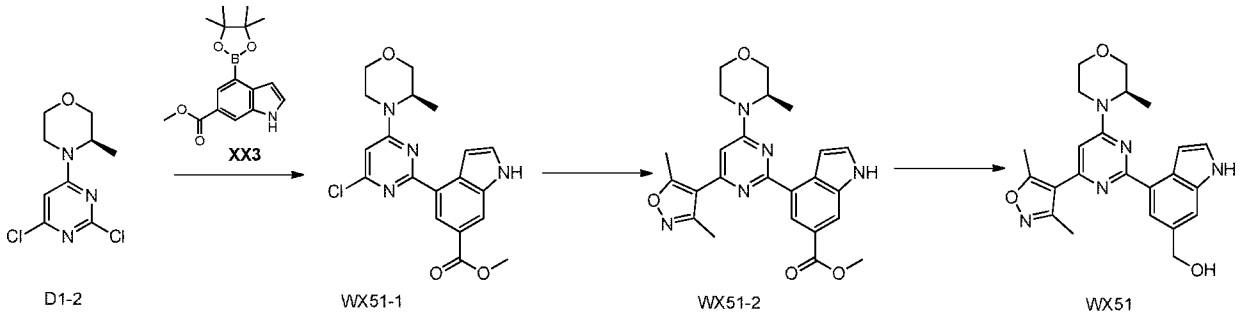
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24 (d, *J*=6.78 Hz, 3 H) 2.33 (s, 3 H) 3.22 (td, *J*=12.67, 4.02 Hz, 1 H) 3.37 - 3.42 (m, 1 H) 3.55 (td, *J*=11.86, 2.64 Hz, 1 H) 3.66 - 3.73 (m, 1 H) 3.76 - 3.83 (m, 1 H) 4.01 (dd, *J*=11.42, 3.14 Hz, 1 H) 4.06 (s, 3 H) 4.14 (br d, *J*=10.79 Hz, 1 H) 4.51 (br d, *J*=7.03 Hz, 1 H) 6.92 (s, 1 H) 6.95 (dd, *J*=3.51, 2.01 Hz, 1 H) 7.36 (s, 1 H) 7.57 - 7.61 (m, 2 H) 8.31 (d, *J*=5.02 Hz, 1 H) 11.80 (br s, 1 H)

Example 51



WX51

Synthesis scheme:



Step 1: Synthesis of Compound **WX51-1**

To a solution of Compound **D1-2** (4.51 g, 18.18 mmol), **XX3** (4.96 g, 16.47 mmol) and bis(triphenylphosphine) palladium dichloride (893.11 mg, 1.27 mmol) in 1,4-dioxane (60 mL) was added 2M sodium carbonate (27.27 mL) aqueous solution, which was purged with nitrogen three times. The reaction mixture was stirred at 110°C with heating for 15 h and then filtered. The solution was concentrated to give the crude product, which was separated with column chromatography (ethyl acetate/petroleum ether: 15-35%) to give **WX51-1**.

MS-ESI: 386.9[M+H]+

Step 2: Synthesis of Compound **WX51-2**

At room temperature, to a solution of Compound **WX51-1** (0.21 g, 542.87 μmol) in 1,4-dioxane (10 mL) were added 3,5-dimethylisoxazole-4-boric acid pinacol ester (181.65 mg, 814.31 μmol), tetrakis (triphenylphosphine) palladium(62.73 mg, 54.29 μmol), sodium carbonate (2 M, 814.31 μL), which was stirred at 100°C under nitrogen atmosphere for 12 h. The reaction system was cooled to room temperature, diluted with ethyl acetate (50mL), washed with water (20ml) and saturated brine (20ml), respectively, dried over anhydrous sodium sulfate and filtered. The solvent was removed under reduce pressure to give the crude product, which was purified with column chromatography (petroleum ether/ethyl acetate :33%~50%) to give Compound **WX51-2**.

MS-ESI: 448.3$[M+H]^+$

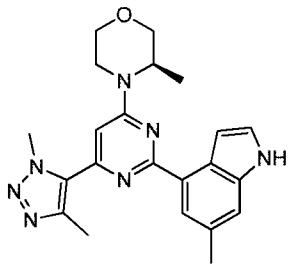
Step 3: Synthesis of Compound **WX51**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX37** in synthesis Example **WX37** were used to give Compound **WX50**.

MS-ESI m/z: 420.1 [M+H]+.

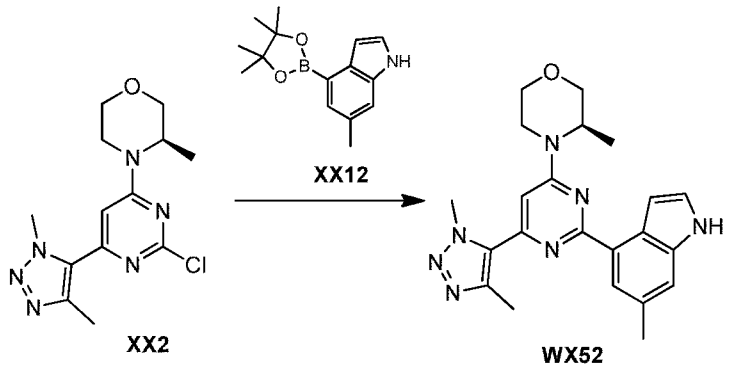
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (d, J=6.78 Hz, 3 H) 2.48 (s, 3 H) 2.68 (s, 3 H) 3.24 - 3.30 (m, 1 H) 3.51 - 3.61 (m, 1 H) 3.67 - 3.74 (m, 1 H) 3.79 - 3.86 (m, 1 H) 4.03 (br d, J=7.78 Hz, 1 H) 4.26 (br d, J=13.05 Hz, 1 H) 4.58 - 4.63 (m, 1 H) 4.65 (d, J=5.77 Hz, 2 H) 5.16 (t, J=5.77 Hz, 1 H) 5.76 (s, 1 H) 6.73 (s, 1 H) 7.25 (br s, 1 H) 7.41 (t, J=2.64 Hz, 1 H) 7.50 (s, 1 H) 8.09 (d, J=1.25 Hz, 1 H) 11.20 (br s, 1 H)

Example 52



WX52

Synthesis scheme:



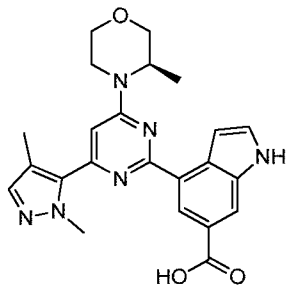
Step 1: Synthesis of Compound **WX52**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX13** in synthesis Example **13** were used to give Compound **WX52**.

MS-ESI m/z: 404.21 [M+H]+.

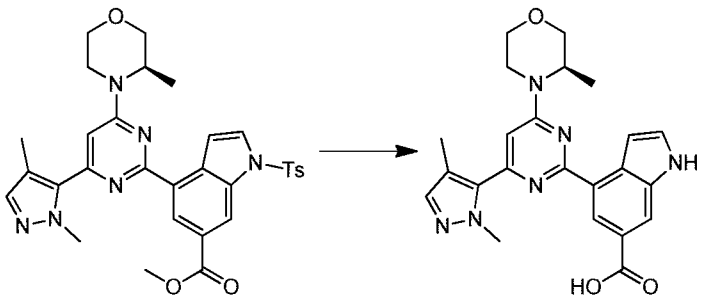
^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.15 (br s, 1H), 7.99 (s, 1H), 7.30 (t, *J*=2.3 Hz, 1H), 7.28 (s, 1H), 7.20 (br s, 1H), 6.41 (s, 1H), 4.44 (br s, 1H), 4.28 (s, 3H), 4.19 (br d, *J*=12.5 Hz, 1H), 4.05 (dd, *J*=3.6, 11.4 Hz, 1H), 3.85 - 3.80 (m, 1H), 3.77 - 3.72 (m, 1H), 3.61 (dt, *J*=3.0, 11.9 Hz, 1H), 3.36 (dt, *J*=4.0, 12.7 Hz, 1H), 2.48 (s, 3H), 2.47 (s, 3H), 1.36 (d, *J*=6.8 Hz, 3H)

Example 53



WX53

Synthesis scheme:



WX42-1 **WX53**

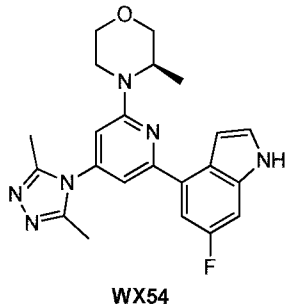
Step 1: Synthesis of Compound **WX53**

To a solution of Compound **WX42-1**(100 mg, 166.48 μmol) in 1,4-dioxane (2 mL) was added 2M sodium hydroxide aqueous solution (0.25 mL). The reaction mixture was stirred with heating at 80°C for 1.5 h, then adjusted to pH 5 with hydrochloric acid, and then extracted with dichloromethane and water. The organic phase was washed once with saturated brine, dried over anhydrous sodium sulfate, and concentrated to give the crude product, which was separated with pre-HPLC (neutral condition) to give Compound **2**.

MS-ESI m/z: 433.31 [M+H]+.

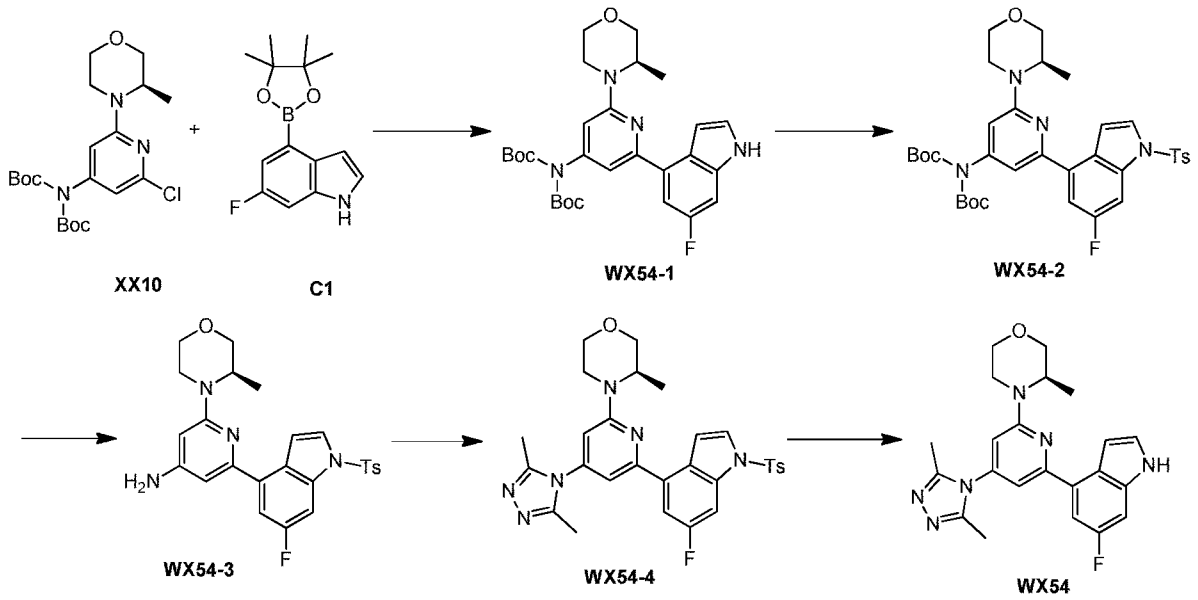
^{1}H NMR (400MHz, DMSO-d_6) δ = 11.65 (br s, 1H), 8.78 (d, *J*=1.5 Hz, 1H), 8.17 (s, 1H), 7.69 (t, *J*=2.8 Hz, 1H), 7.41 (s, 1H), 7.38 (br s, 1H), 6.82 (s, 1H), 4.60 (br s, 1H), 4.29 (br d, *J*=11.3 Hz, 1H), 4.05 (br s, 1H), 4.03 (s, 3H), 3.86 - 3.80 (m, 1H), 3.71 (br d, *J*=9.4 Hz, 1H), 3.61 - 3.53 (m, 1H), 3.28 (s, 1H), 2.20 (s, 3H), 1.32 (d, *J*=6.6 Hz, 3H).

Example 54



WX54

Synthesis scheme:



Step 1: Synthesis of Compound **WX54-1**

To a solution of Compound **XX10** (0.35 g, 817.91 μmol), **C1** (256.27 mg, 981.49 μmol) and tetrakis (triphenylphosphine) palladium ((66.16 mg, 57.25 μmol) of1,4-dioxane(8 mL)) was added 2M sodium carbonate (2 M, 1.02 mL) aqueous solution, which was purged with nitrogen three times. The reaction mixture was stirred with heating at 90°C for 36 h and then filtered. The solution was concentrated to give the crude product, which was separated with column chromatography (ethyl acetate/petroleum ether: 15-45%) to give Compound **WX54-1**.

MS-ESI m/z: 527.4 [M+H]+.

Step 2: Synthesis of Compound **WX54-2**

At 0-5°C, to a solution of Compound **WX54-1** (0.43 g, 816.56 mmol) in N'N-dimethylformamide (10 mL) was added sodium hydride (37.56 mg, 939.05 mmol, purity: 60%). The reaction mixture was stirred at 0-5°C for 15 min, to which was added *p*-toluenesulfonyl chloride (186.81 mg, 979.87 μmol). The reaction mixture was stirred at 0-5°C for 2 h, quenched with water (40 mL) at 0-5°C and extracted with ethyl acetate (50 mL * 3). The organic phases were combined, washed with saturated brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give **WX54-2**.

MS-ESI m/z: 681.5 [M+H]+.

Step 3: Synthesis of Compound **WX54-3**

To solution of Compound **WX54-2** (0.56 g, 822.58 mmol) in 1,4-dioxane (10 mL) was added 4M hydrochloric acid/1,4-dioxane (4 M, 4.67 mL). The reaction mixture was stirred at 30°C for 36 h, adjusted to pH=7-8 with saturated sodium bicarbonate, diluted with water (30 mL) and extracted with dichloromethane (40 mL*3). The organic phases were combined, washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product, which was separated with column chromatography(ethyl acetate/petroleum ether: 25-50%) to give Compound **WX54-3**.

MS-ESI m/z: 481.3$[M+H]^+$

Step 4: Synthesis of Compound **WX54-4**

To a solution of Compound **WX54-3** (0.12 g, 249.71 μmol), 2,5-dimethyl-1,3,4-oxadiazole (97.99 mg, 998.85 μmol) in 1-methyl-2-pyrrolidone (2 mL) was added anhydrous *p*-toluenesulfonic acid (43.00 mg,

249.71 umol), which was stirred at 220°C with microwave for 1.5 h. The reaction solution was concentrated to give the crude product, which was separated with column chromatography (methanol/dichloromethane: 2-8%) to give Compound **WX54-4**.

MS-ESI m/z: 561.4[M+H]$^+$

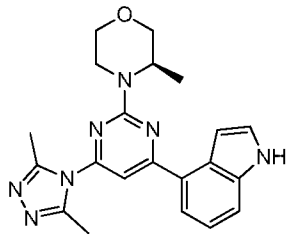
Step 5: Synthesis of Compound **WX54**

To a solution of Compound **WX54-4** (0.05 g, 89.18 μmol) in 1,4-dioxane (10 mL) was added 2M sodium hydroxide (2 M, 3 mL). The reaction mixture was stirred at 80°C for 12 h, adjusted to pH=7 with 1M hydrochloric acid, diluted with water (15 mL) and extracted with dichloromethane (25 mL*3). The organic phases were combined, washed with saturated brine (30 mL), and dried over anhydrous sodium sulfate. The filtered organic phase was concentrated to give the crude product, which was separated with column chromatography (methanol/dichloromethane: 10:1) to give Compound **WX54**.

MS-ESI m/z: 407.2 [M+H]$^+$

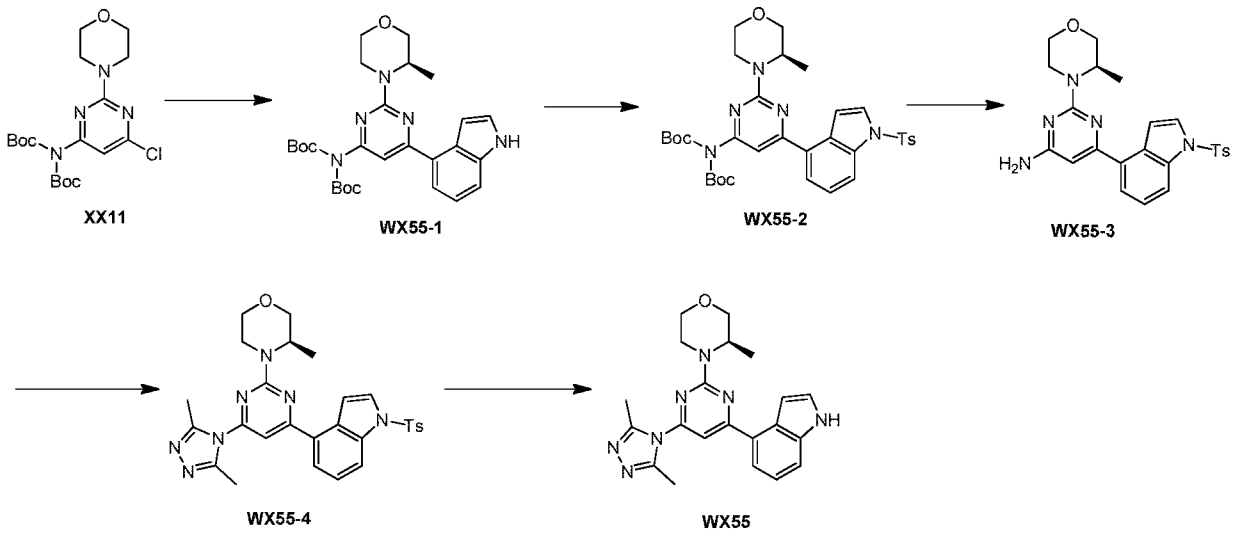
^{1}H NMR (CHLOROFORM-d, 400MHz): δ = 8.50 (br s, 1H), 7.32 (dd, *J*=10.5, 2.3 Hz, 1H), 7.25 (t, *J*=2.8 Hz, 1H), 7.12 (dd, *J*=8.9, 1.6 Hz, 1H), 6.88 (s, 1H), 6.85 (br s, 1H), 6.26 (s, 1H), 4.30 (br d, *J*=6.0 Hz, 1H), 3.97-4.08 (m, 2H), 3.72-3.83 (m, 2H), 3.60 (td, *J*=11.9, 3.1 Hz, 1H), 3.29 (td, *J*=12.7, 3.9 Hz, 1H), 2.34 (s, 6H), 1.30 ppm (d, *J*=6.8 Hz, 3H).

Example 55



WX55

Synthesis scheme:



Step 1: Synthesis of Compound **WX55-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX54-1** in synthesis Example **54** were used to give Compound **WX55-1**.

MS-ESI m/z: 510.4 [M+H]$^+$

Step 2: Synthesis of Compound **WX55-2**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX54-2** in synthesis Example **54** were used to give Compound **WX55-2**.

MS-ESI m/z: 664.5 $[M+H]^+$

Step 3: Synthesis of Compound **WX55-3**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX54-3** in synthesis Example **54** were used to give Compound **WX55-3**.

MS-ESI m/z: 464.3 $[M+H]^+$

Step 4: Synthesis of Compound **WX55-4**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX54-3** in synthesis Example **54** were used to give Compound **WX55-4**.

MS-ESI m/z: 544.4 $[M+H]^+$

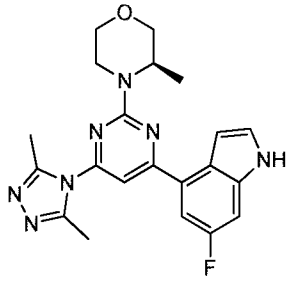
Step 5: Synthesis of Compound **WX55**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX54** in synthesis Example **54** were used to give Compound **WX55**.

MS-ESI m/z: 390.2 $[M+H]^+$

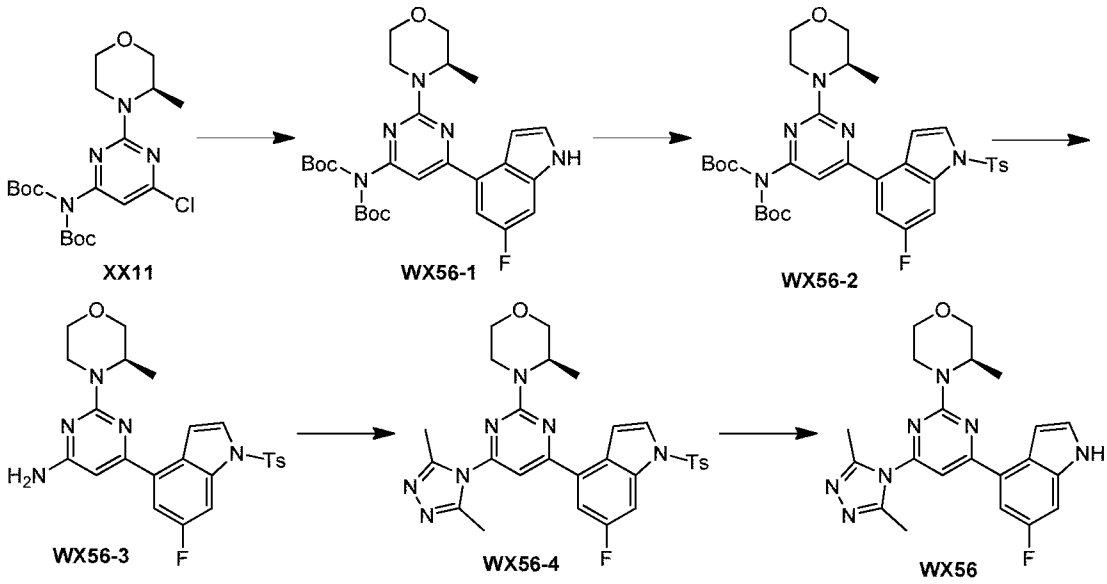
^1H NMR (CHLOROFORM-d, 400MHz): δ = 8.80 (br s, 1H), 7.68 (d, *J*=7.5 Hz, 1H), 7.62 (d, *J*=8.1 Hz, 1H), 7.41-7.45 (m, 1H), 7.34 (t, *J*=7.8 Hz, 1H), 7.13 (br s, 1H), 6.95 (s, 1H), 4.85 (br s, 1H), 4.54 (br d, *J*=12.8 Hz, 1H), 4.08 (dd, *J*=11.4, 3.1 Hz, 1H), 3.83-3.92 (m, 1H), 3.74-3.83 (m, 1H), 3.64 (td, *J*=11.9, 2.6 Hz, 1H), 3.45 (td, *J*=12.9, 3.4 Hz, 1H), 2.58 (s, 6H), 1.44 ppm (d, *J*=6.8 Hz, 3H)

Example 56



WX56

Synthesis scheme:



Step 1: Synthesis of Compound **WX56-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX54-1** in synthesis Example **54** were used to give Compound **WX56-1**.

MS-ESI m/z: 528.4 $[M+H]^+$

Step 2: Synthesis of Compound **WX56-2**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX54-2** in synthesis Example **54** were used to give Compound **WX56-2**.

MS-ESI m/z: 682.5 $[M+H]^+$

Step 3: Synthesis of Compound **WX56-3**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX54-3** in synthesis Example **54** were used to give Compound **WX56-3**.

MS-ESI m/z: 482.6 $[M+H]^+$

Step 4: Synthesis of Compound **WX56-4**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX54-3** in synthesis Example **54** were used to give Compound **WX564**.

MS-ESI m/z: 562.3 $[M+H]^+$

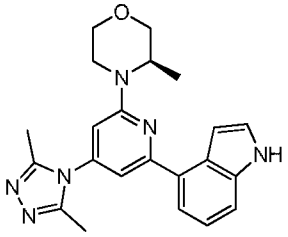
Step 5: Synthesis of Compound **WX56**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX54** in synthesis Example **54** were used to give Compound **WX56**.

MS-ESI m/z: 407.9 $[M+H]^+$

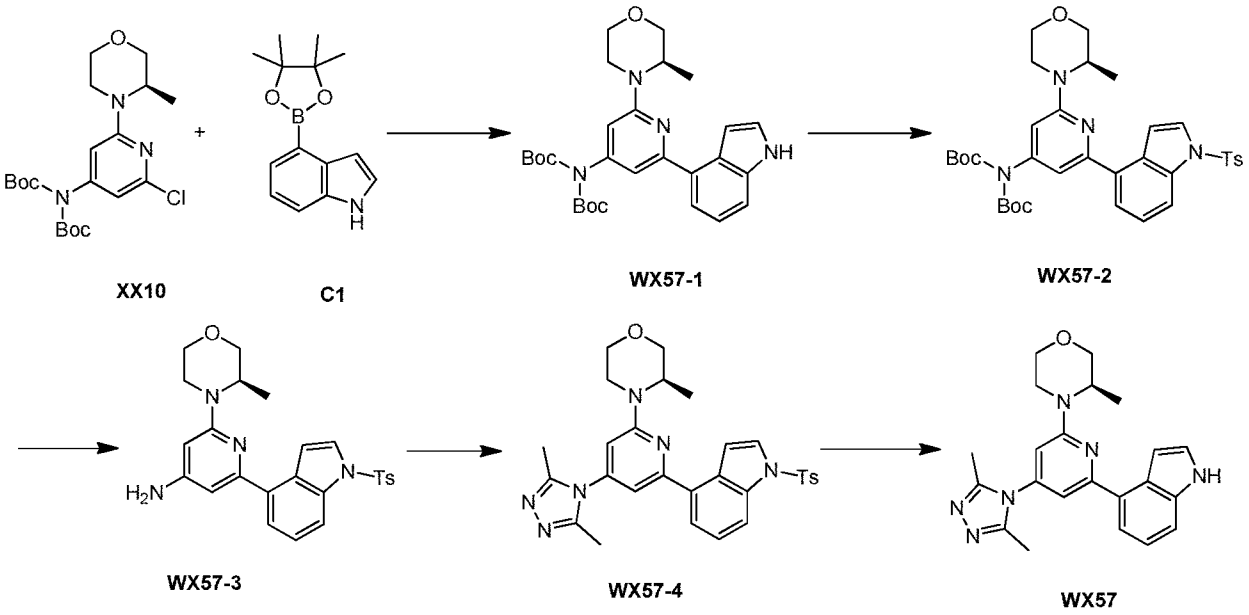
^1H NMR (400MHz, CHLOROFORM-d) δ = 8.47 (br s, 1H), 7.48 (br d, *J*=10.6 Hz, 1H), 7.39 (br s, 1H), 7.31 (s, 1H), 7.03 (br s, 1H), 6.92 (s, 1H), 4.84 (br s, 1H), 4.51 (br s, 1H), 4.08 (br d, *J*=10.4 Hz, 1H), 3.90 - 3.83 (m, 1H), 3.81 - 3.75 (m, 1H), 3.64 (br t, *J*=11.6 Hz, 1H), 3.50 - 3.39 (m, 1H), 2.58 (s, 6H), 1.44 (br d, *J*=6.5 Hz, 3H).

Example 57



WX57

Synthesis scheme:



Step 1: Synthesis of Compound **WX57-1**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX54-1** in synthesis Example **54** were used to give Compound **WX57-1**.

MS-ESI m/z: 509.4 [M+H]+.

Step 2: Synthesis of Compound **WX57-2**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX54-2** in synthesis Example **54** were used to give Compound **WX57-2**.

MS-ESI m/z: 663.5 [M+H]+.

Step 3: Synthesis of Compound **WX57-3**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX54-3** in synthesis Example **54** were used to give Compound **WX57-3**.

MS-ESI m/z: 463.3 $[M+H]^+$

Step 4: Synthesis of Compound **WX57-4**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX54-4** in synthesis Example **54** were used to give Compound **WX57-4**.

MS-ESI m/z: 542.9 $[M+H]^+$

Step 5: Synthesis of Compound **WX57**

Except using corresponding raw materials, the procedures identical to those used for Compound **WX54** in synthesis Example **54** were used to give Compound **WX57**.

MS-ESI m/z: 389.0 $[M+H]^+$

^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.38 (d, *J*=6.78 Hz, 3 H) 2.41 (s, 6 H) 3.37 (td, *J*=12.67, 4.02 Hz, 1 H) 3.68 (td, *J*=11.86, 3.14 Hz, 1 H) 3.80 - 3.89 (m, 2 H) 4.05 - 4.15 (m, 2 H) 4.39 (br d, *J*=6.78 Hz, 1 H) 6.28 (d, *J*=1.25 Hz, 1 H) 6.98 (d, *J*=1.00 Hz, 1 H) 7.01 (br s, 1 H) 7.28 - 7.33 (m, 1 H) 7.36 (t, *J*=2.89 Hz, 1 H) 7.52 (d, *J*=8.28 Hz, 1 H) 7.58 (d, *J*=7.28 Hz, 1 H) 8.69 (br s, 1 H)

Experimental Example 1: *In vitro* evaluation

IC_{50} values were determined to evaluate the inhibitory activity of the tested compounds on human ATR kinase.

ATR/ATRIP(h) was incubated in assay buffer containing 50nM GST-cMyc-p53 and Mg/ATP (according to concentration required). The reaction was initiated by adding Mg/ATP mixture. After incubating for 30 min at room temperature, a stop solution containing EDTA to was added to terminate the reaction. Finally, detecting buffer containing d^2-labeled anti-GST monoclonal antibody and europium-labeled anti-phospho Ser15 antibody against phosphorylated p^{53} were added. Then the plate was read in time-resolved fluorescence mode and homogeneous time resolution was performed.

The fluorescence (HTRF) signal was determined according to the formula HTRF = 10000×(Em665nm/Em620nm).

IC_{50} data was analyzed using XLFit version 5.3 (ID Business Solutions). Non-linear regression analysis was used to fit the sigmoidal dose response (variable slope) curve. The experimental results were shown in Table 1.

Table 1: *In vitro* screening test results of the present compounds

Compound	ATR average IC_{50}(nM)	Compound	ATR average IC_{50}(nM)
WX01	119	WX30	35
WX02	72	WX31	39
WX03	72	WX32	35
WX04	91	WX33	198
WX05	53	WX34	69
WX06	245	WX35	19
WX07	75	WX36	14
WX08	126	WX37	16
WX09	369	WX38	78
WX10	80	WX39	42
WX11	191	WX40	15
WX12	41	WX41	78
WX13	24	WX42	29
WX14	50	WX43	65
WX15	159	WX44	65

WX16	97	WX45	69
WX17	12	WX46	31
WX18	83	WX47	64
WX19	81	WX48	105
WX20	69	WX49	26
WX21	27	WX50	42
WX22	65	WX51	32
WX23	115	WX52	20
WX24	18	WX53	83
WX25	92	WX54	27
WX26	123	WX55	20
WX27	123	WX56	46
WX28	47	WX57	28
WX29	96		

Conclusion: The present compounds have good inhibitory activity against ATR.

Experimental Example 2: *In vitro* cell viability test

In this experiment, inhibitory effect of the compounds on cell proliferation was investigated by testing influence on cell viability *in vitro* in tumor cell line LoVo.

CellTiter-Glo Luminescence cell viability test

The following protocols were performed according to instruction of PromegaCellTiter-Glo Luminescence cell viability test Kit (Promega-G7573).

(1) Thawing CellTiter-Glo buffer and allowing it to acclimate to room temperature.

(2) Allowing CellTiter-Glo substrate to acclimate to room temperature.

(3) Adding CellTiter-Glo buffer to a bottle of CellTiter-Glo substrate to dissolve the substrate to prepare CellTiter-Glo working solution.

(4) Vortexing slowly to full dissolution.

(5) Removing the cell culture plate and balancing it to room temperature for 30 min.

(6) Adding 50 μL (equivalent to half volume of cell culture medium in each well) of CellTiter-Glo working solution to each well, wrapping the cell plate with aluminum foil to protect from light.

(7) Shaking the culture plate on an orbital shaker for 2 min to induce cell lysis.

(8) Placing the culture plate at room temperature for 10 min to stabilize the luminescence signal.

(9) Detecting the luminescence signal on SpectraMax i3x of Molecular Devices plate reader.

Data analysis

The following formula was used to calculate the inhibition rate of the test compound (Inhibition rate, IR): IR (%) = (1–(RLU Compound – RLU Blank control)/(RLU Vehicle control – RLU Blank control))*100%.

The inhibition rates of different concentrations of compounds were calculated in Excel, and GraphPad Prism software was used to make the inhibition curve and calculate relevant parameters, including the minimum

inhibition rate, the maximum inhibition rate and IC_{50}.

The experimental results were shown in Table 2.

Table 2: Results of LoVo cell proliferation inhibition *in vitro*

	AZD6738	WX15	WX42	WX45	WX46	WX47
IC50 (uM)	0.82	0.41	0.51	0.75	0.35	0.76

Conclusion: The present compounds have a good inhibitory effect on LoVo tumor cells with mutations in ATM signaling pathway.

Experimental Example 3: Study on pharmacokinetic properties *in vivo*

Testing samples: On the basis of the above experiments, some of the highly active compounds with representative structures were selected for further experiments.

Experimental method: The purpose of this study was to determine the pharmacokinetic parameters of the compounds and calculate the oral bioavailability in female Balb/c Nude mice.

The project involved 6 female Balb/c Nude mice. 3 mice were administered intravenously at a dose of 1 mg/kg, and plasma samples were collected at 0 h (before administration) and 0.0833, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h after administration, other 3 mice were given by oral gavage at a dose of 10 mg/kg or 25 mg/kg, and plasma samples were collected at 0 h (before dosing) and 0.5, 1, 2, 3, 4, 6, 8, 24 h after administration. Then LC/MS/MS analysis was performed for the collected samples and data was collected. The collected analysis data was calculated for relevant pharmacokinetic parameters with Phoenix WinNonlin 6.2.1 software.

The experimental results were shown in Table 3.1 and Table3.2.

3.1 Intravenous administration results

	WX15 (1mg/kg)	WX34 (1mg/kg IV)	WX42 (1mg/kg IV)	WX45 (1mg/kg IV)
C_0 (nM)	1962	1260	1955	1579
Cl (mL/min/kg)	47.0	53.9	34.3	48.3
V_{dss} (L/kg)	2.21	3.72	2.21	2.59
$T_{1/2}$ (h)	0.78	1.22	2.57	0.99
AUC_{0-t} (nM.h)	905	787	1087	880

3.2 Oral administration results

	WX15 (10 mg/kg)	WX34 (10 mg/kg)	WX42 (10 mg/kg)	WX45 (10 mg/kg)	WX46 (25 mg/kg)
Cmax (nM)	**4560**	**2863**	**6500**	**7717**	**10600**
$T_{1/2}$ (h)	**1.23**	**1.16**	**2.02**	**1.69**	**0.892**
AUC_{0-t} (nM.h)	**8747**	**5681**	**14983**	**10911**	**26206**
F (%)	**96.0**	**71.7**	**129.0**	**123.0**	**--**

Note: "--" indicates that no relevant test was done; C_0 (nM) is drug concentration at 0 min *in vivo*; Cl (mL/min/kg) is drug clearance rate *in vivo*; V_{dss} (L/kg) is distribution volume of drug *in vivo*; $T_{1/2}$ (h) is half-life; AUC_{0-t} (nM.h) is drug exposure *in vivo*; Cmax (nM) is highest concentration of drug *in vivo*.

Conclusion: The present compounds have good absorption and exposure at oral administration, and is suitable for oral administration.

Experimental Example 4: Study on *in vivo* efficacy in colorectal cancer LoVo CDX model

Purpose:

LoVo is a colorectal adenocarcinoma tumor cell line with MRE11A mutation (MRE11A is a key component of DNA double-strand break repairing ATM signaling pathway), which is sensitive to ATR inhibitor. In this experiment, the colorectal cancer LoVo CDX model was used to verify the inhibitory effect of ATR inhibitor as monotherapy on tumors with defect in ATM signaling pathway.

Procedures:

1. Laboratory animal

Species: mouse

Strain: BALB/c nude mice

Supplier: Beijing Vital River Laboratory Animal Technology Co., Ltd.

Weeks and weight: 6-8 weeks, weight 18-22 g

Gender: female

2. Cell culture

Human colorectal cancer LoVo cells (ECACC, CatLog: 87060101), *in vitro* monolayer culture, culture conditions: Ham's F-12 medium with 10% fetal bovine serum, 100 U/mL penicillin, 100 μg/mL streptomycin and 2 mM glutamine, 37°C, 5% CO_2 culture. General passage with trypsin-EDTA digestion was performed twice a week. When the cell saturation was 80%-90%, the cells were collected, counted, and inoculated. 0.1 mL (10 x 10^6) of LoVo cells were subcutaneously inoculated into the right back of each nude mouse. When the mean tumor volume reached 173 mm^3, grouping and administration were initiated.

3. Preparation and dose of testing substances

1) Compound WX15

25.51 mg of WX15 was weighed and dissolved in 0.500 mL of DMSO, which were added with 2.000 mL of propylene glycol and 2.500 mL of deionized water, vortexed for homogeneous mixing, adjusted to

PH=6.0, to obtain a clear solution. The preparing processes of Compound WX42, Compound WX45, Compound WX46 were referred to Compound WX15.

Dosage: All test compounds were administered orally at 25 mg/kg twice a day, with an interval of 8 h in a day.

4. Tumor measurement and experimental indicators

A vernier caliper was used to measure the tumor diameter twice a week. The formula for calculating the tumor volume: $V = 0.5a \times b^2$, a and b represent the long and short diameters of the tumor, respectively.

Antitumor efficacy of the compound was evaluated by TGI (%) or relative tumor proliferation rate T/C (%). Relative tumor proliferation rate T/C(%) = TRTV / CRTV × 100 % (TRTV: mean RTV value of treatment group; CRTV: mean RTV value of negative control group). The relative tumor volume (relative tumor volume, RTV) was calculated based on the tumor measurement results and the calculation formula was RTV = Vt / V0, where V0 is the tumor volume measured at grouping administration (i.e. D0), Vt is the tumor volume at a measurement, and data on the same day was used for TRTV and CRTV.

TGI (%) reflects the tumor growth inhibition rate. TGI(%)=[1-(mean tumor volume at the end of administration in a treatment group - mean tumor volume at the beginning of administration in this treatment group)/(mean tumor volume at the end of treatment in the solvent control group - mean tumor volume at the beginning of treatment in the solvent control group)] × 100%.

At the end of the experiment, the tumor weights were weighed, and the T/Cweight percentage was calculated. Tweight and Cweight represent the tumor weights of the administration group and the vehicle control group, respectively.

5. Experimental results

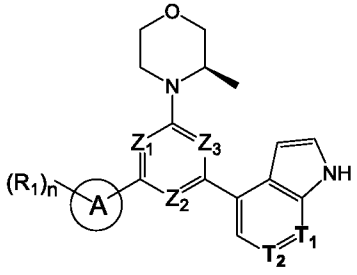
This experiment evaluated the efficacy of the compounds in human colorectal cancer xenograft model, with the solvent control group as reference. The tumor volumes of each group at different time points were shown in Figure 1. At day 17 of administration, T/C and TGI of WX42 (25 mg/kg) group were 27.8% and 90.7%, respectively, as compared with the vehicle control group; T/C and TGI of WX45 (25 mg/kg) group were 32.3% and 79.9% respectively, as compared with the vehicle control group; T/C and TGI of WX46 (25 mg/kg) group were 43.8% and 79.9% respectively, as compared with vehicle control group; T/C and TGI of WX15 (25 mg/kg) group were 46.7% and 66.8%, respectively, as compared with the vehicle control group.

6. Conclusion

In this experiment, the present compounds had inhibitory effect on growth of tumor-bearing mice of human colorectal cancer LoVo cell subcutaneous xenograft tumor model.

The claims defining the invention are as follows:

1. A compound of formula (I), or a tautomer or a pharmaceutically acceptable salt thereof,



(I)

wherein,

n is 1, 2, 3 or 4;

Z_1, Z_2, and Z_3 are each independently selected from the group consisting of CH and N, and at least one of Z_1, Z_2 and Z_3 is N;

T_1 and T_2 are each independently selected from the group consisting of $C(R_2)$ and N;

ring A is selected from the group consisting of 5-6 membered heteroaryl;

R_1 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, C_{1-6} alkyl, C_{1-6} alkoxy and C_{3-6} cycloalkyl, wherein the C_{1-6} alkyl, C_{1-6} alkoxy and C_{3-6} cycloalkyl are optionally substituted by 1, 2 or 3 R;

R_2 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, COOH and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by 1, 2 or 3 R;

R is each independently selected from the group consisting of F, Cl, Br, I, OH, NH_2, C_{1-3} alkyl and C_{1-3} alkoxy, wherein the C_{1-3} alkyl and C_{1-3} alkoxy are optionally substituted by 1, 2 or 3 R';

R' is each independently selected from the group consisting of F, Cl, Br, I, OH and NH_2;

the 5-6 membered heteroaryl comprises 1, 2, 3 or 4 heteroatoms or heteroradicals independently selected from the group consisting of -NH-, -O-, -S- and N;

provided that the compound of formula (I) is not:

(3R)-3-methyl-4-[6-(pyridin-3-yl)-2-[1H-pyrrolo[2,3-b]pyridin-4-yl]pyrimidin-4-yl]morpholine,

(R)-4-(2-(1H-pyrrolo[2,3-b]pyridin-4-yl)-6-(6-(trifluoromethyl)pyridin-3-yl)pyrimidin-4-yl)-3-methylmorpholine, or

(R)-5-(6-(3-methylmorpholino)-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)pyrimidin-4-yl)pyridin-2-amine.

2. The compound of formula (I) according to claim 1, or a tautomer or a pharmaceutically acceptable salt thereof,

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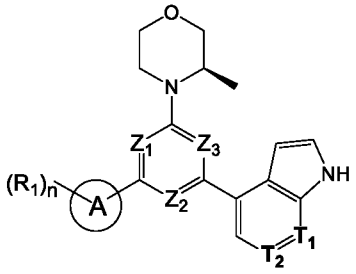


(I)

wherein,

n is 1, 2, 3 or 4;

Z_1, Z_2, and Z_3 are each independently selected from the group consisting of CH and N, and at least one of Z_1, Z_2 and Z_3 is N;

T_1 and T_2 are each independently selected from the group consisting of $C(R_2)$ and N;

R_2 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, COOH and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted by 1, 2 or 3 R;

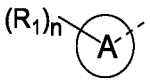
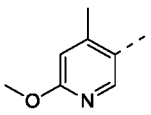
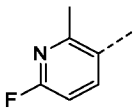
R is each independently selected from the group consisting of F, Cl, Br, I, OH, NH_2, C_{1-3} alkyl and C_{1-3} alkoxy, wherein the C_{1-3} alkyl and C_{1-3} alkoxy are optionally substituted by 1, 2 or 3 R';

R' is each independently selected from the group consisting of F, Cl, Br, I, OH and NH_2; and

(i) ring A is selected from the group consisting of pyrazolyl, isoxazolyl, oxazolyl, imidazolyl, 1,2,3-triazolyl and 1,2,4-triazolyl; and

R_1 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, C_{1-6} alkyl, C_{1-6} alkoxy and C_{3-6} cycloalkyl, wherein the C_{1-6} alkyl, C_{1-6} alkoxy and C_{3-6} cycloalkyl are optionally substituted by 1, 2 or 3 R;

or

(ii) the structural unit  is selected from the group consisting of  and  .

3. The compound according to claim 1 or 2, or the tautomer or the pharmaceutically acceptable salt thereof, wherein, R is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, CH_3, Et and -O-CH_3.

4. The compound according to claim 1 or 2, or the tautomer or the pharmaceutically acceptable salt thereof, wherein, R_1 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, C_{1-3} alkyl, C_{1-3} alkoxy and cyclopropyl, wherein the C_{1-3} alkyl, C_{1-3} alkoxy and cyclopropyl are optionally substituted by 1, 2 or 3 R.

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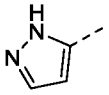
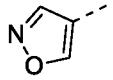
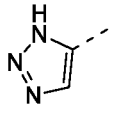
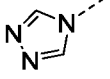
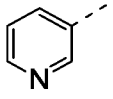
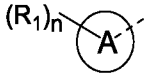
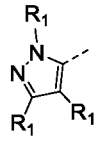
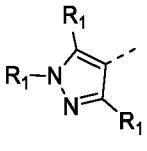
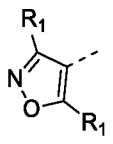
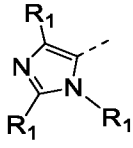
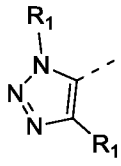
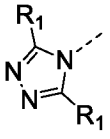
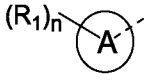
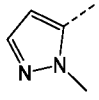
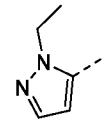
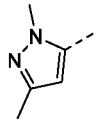
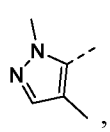
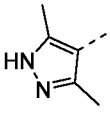
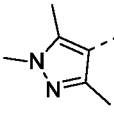
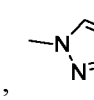
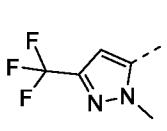
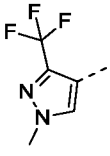
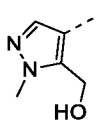
5. The compound according to claim 4, or the tautomer or the pharmaceutically acceptable salt thereof, wherein, R_1 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, CH_3, CH_2F, CHF_2, CF_3, Et, -CH_2OH, -O-CH_3,  and  .

6. The compound according to claim 1 or 2, or the tautomer or the pharmaceutically acceptable salt thereof, wherein, R_2 is each independently selected from the group consisting of H, F, Cl, Br, I, OH, NH_2, COOH, CH_3, Et and -CH_2-OH.

7. The compound according to claim 1, or the tautomer or the pharmaceutically acceptable salt thereof, wherein, ring A is selected from the group consisting of pyrazolyl, isoxazolyl, oxazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl and pyridyl.

8. The compound according to claim 1, or the tautomer or the pharmaceutically acceptable salt thereof, wherein, ring A is selected from the group consisting of  ,  ,  ,  ,  ,  and  .

9. The compound according to claim 1, or the tautomer or the pharmaceutically acceptable salt thereof, wherein, the structural unit  is selected from the group consisting of  ,  ,  ,  ,  ,  and  .

10. The compound according to claim 9, or the tautomer or the pharmaceutically acceptable salt thereof, wherein, the structural unit  is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

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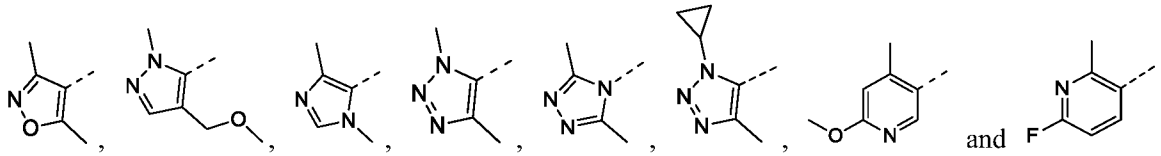
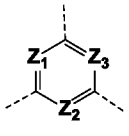
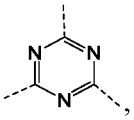
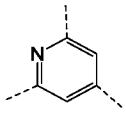
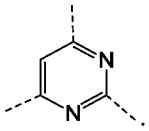
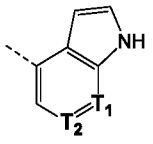
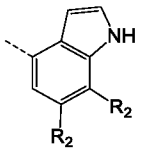
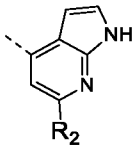


and .

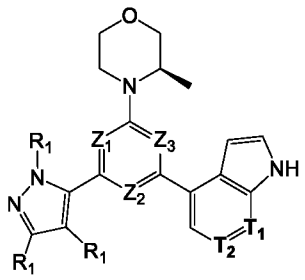
11. The compound according to claim 1 or 2, or the tautomer or the pharmaceutically acceptable salt thereof, wherein, the structural unit  is selected from the group consisting of  ,

 and  .

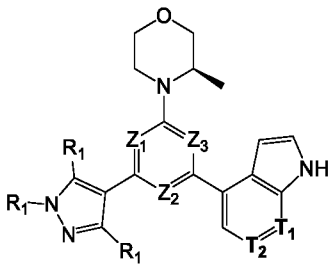
12. The compound according to claim 1 or 2, or the tautomer or the pharmaceutically acceptable salt thereof, wherein, the structural unit  is selected from the group consisting of 

and  .

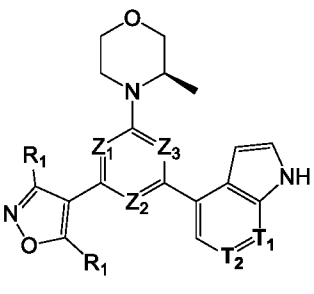
13. The compound according to any one of claims 1-9, or the tautomer or the pharmaceutically acceptable salt thereof, wherein the compound is selected from



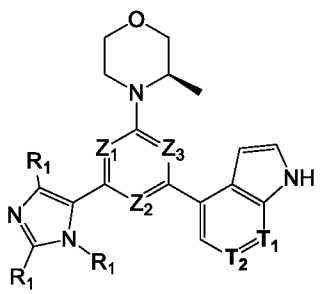
(II -1)



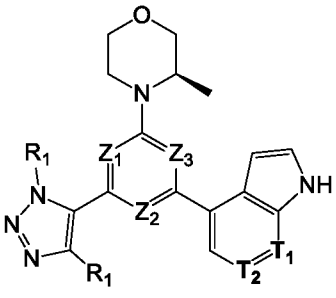
(II -2)



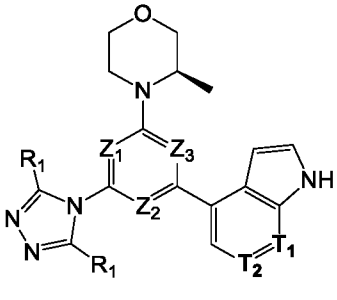
(II -3)



(II -4)



(II -5)



(II -6)

and

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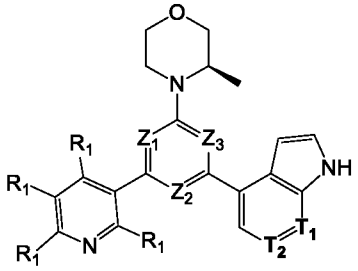


(II -7) ,

wherein,

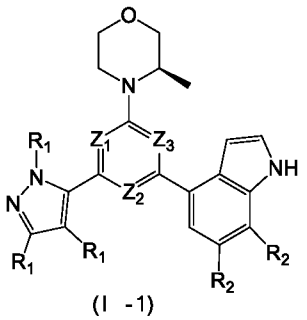
T_1, and T_2 are each independently selected from the group consisting of $C(R_2)$ and N;

Z_1, Z_2 and Z_3 are defined as in claim 1;

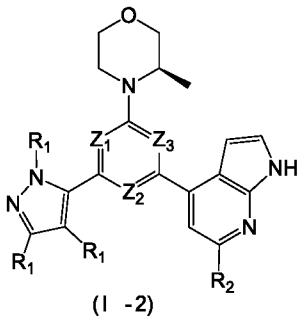
R_1 is defined as in any one of claims 1, 2, 4 or 5;

R_2 is defined as in claim 1, 2 or 6.

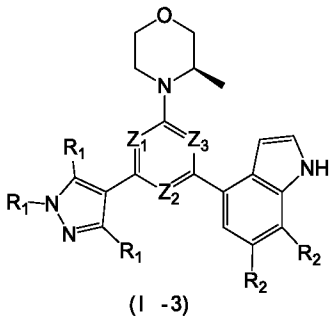
14. The compound according to claim 13, or the tautomer or the pharmaceutically acceptable salt thereof, wherein the compound is selected from



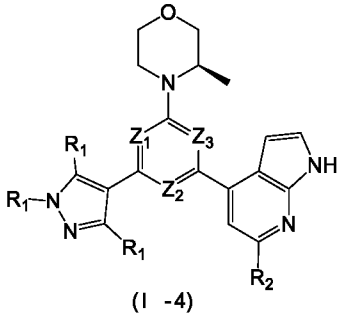
(I -1)



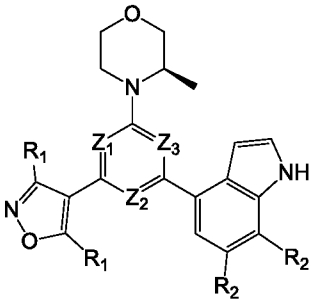
(I -2)



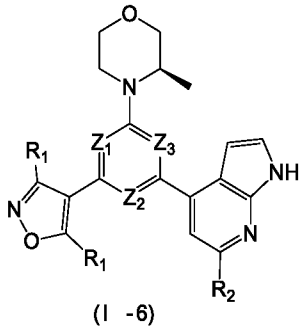
(I -3)



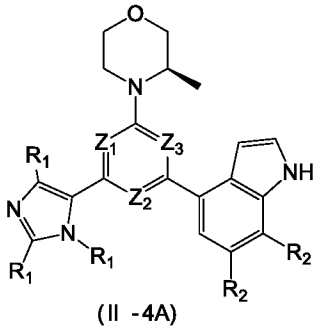
(I -4)



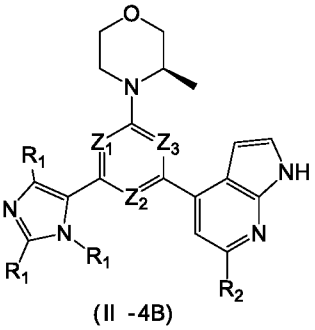
(I -5)



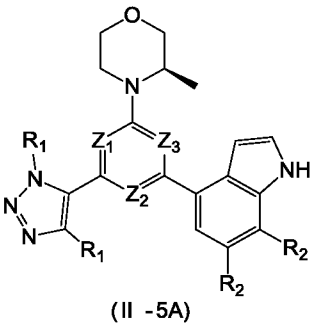
(I -6)



(II -4A)



(II -4B)



(II -5A)

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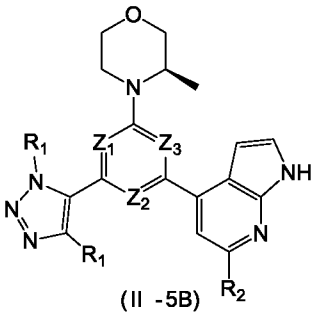
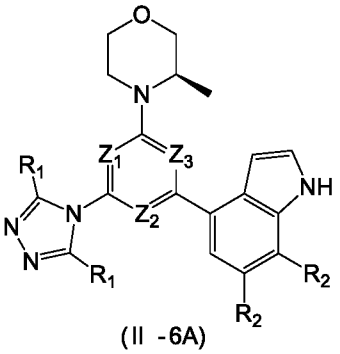
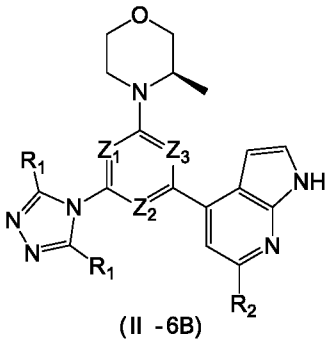


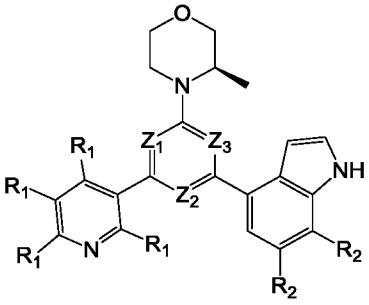
(II -5B)



(II -6A)

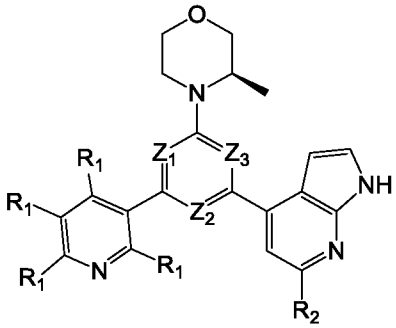


(II -6B)



(II -7A)

and



(II -7B)

,

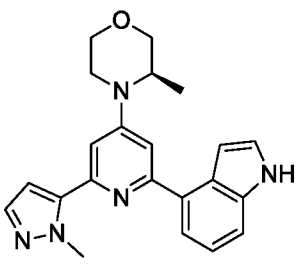
wherein,

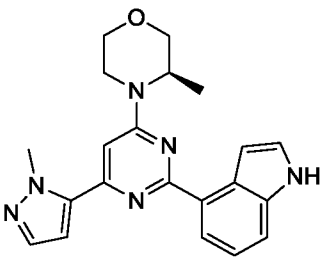
Z_1, Z_2, and Z_3 are defined as in claim 1;

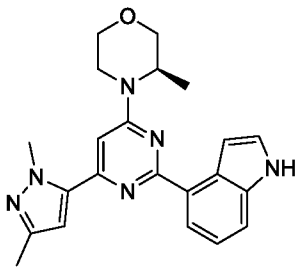
R_1 is defined as in any one of claim 1, 2, 4 or 5;

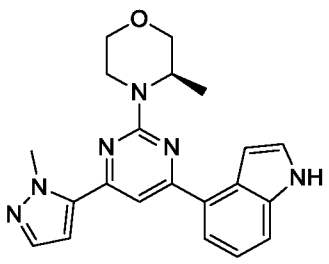
R_2 is defined as in claim 1 or 6.

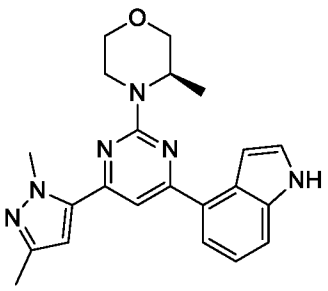
15. A compound or a tautomer or a pharmaceutically acceptable salt thereof, selected from

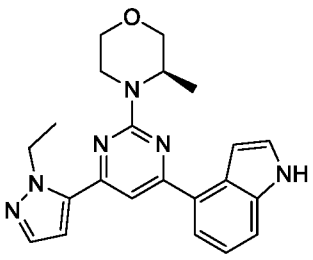












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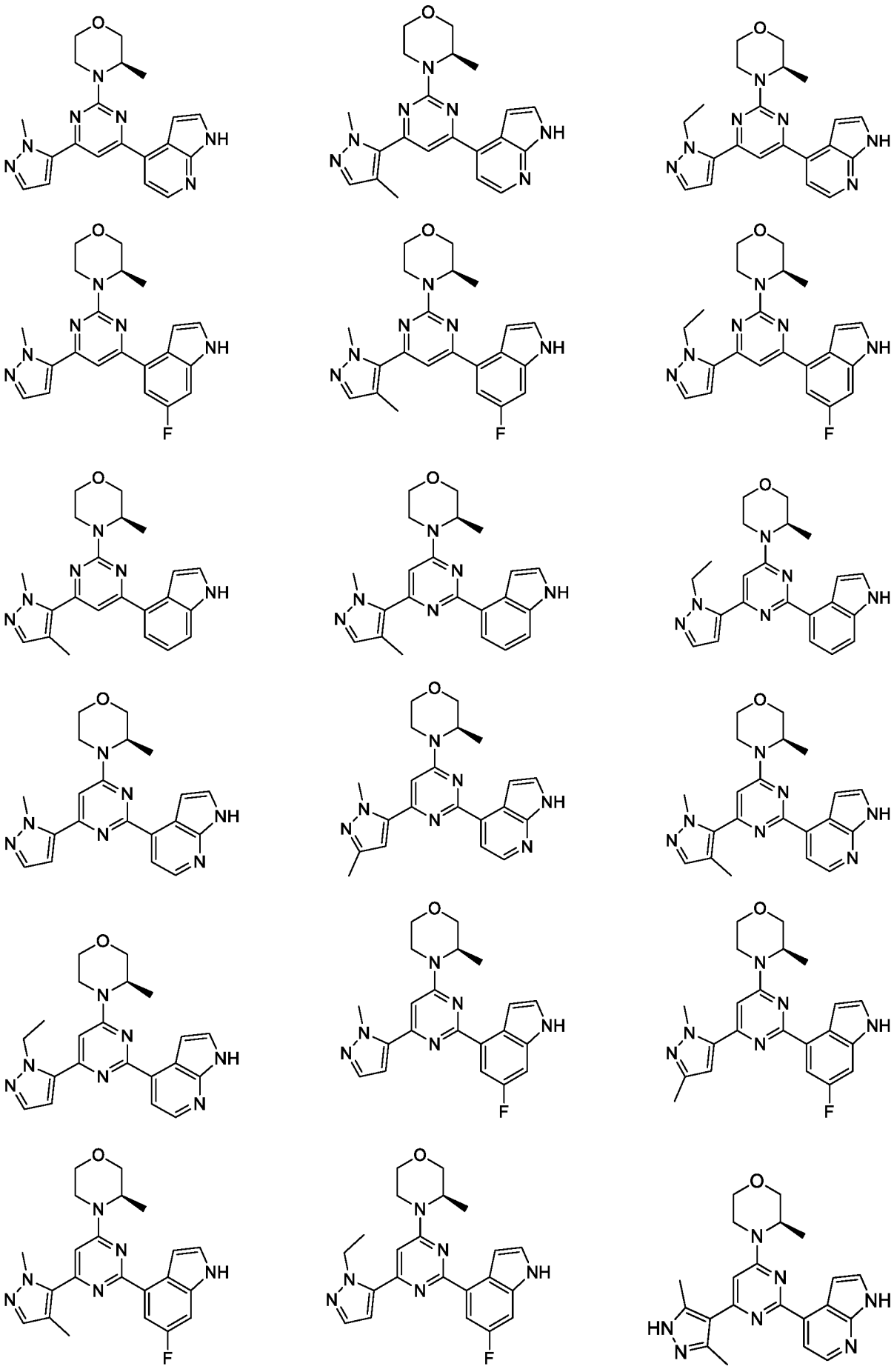

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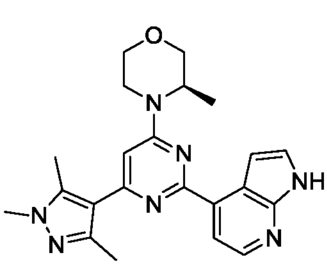

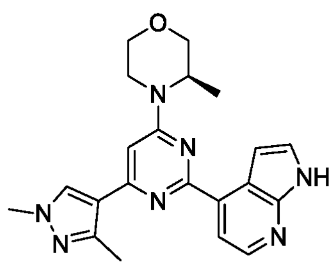

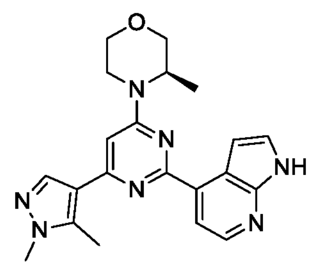

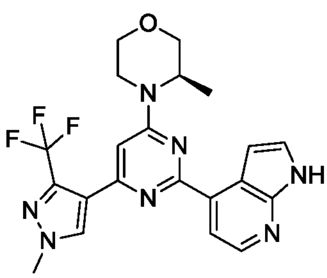

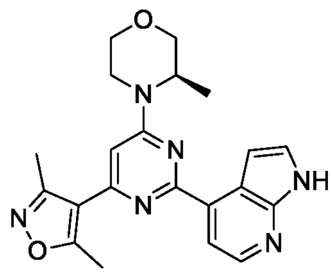

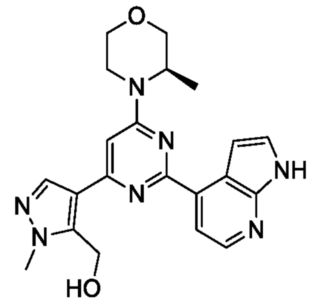

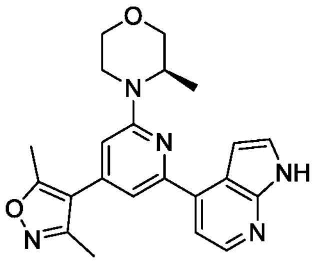

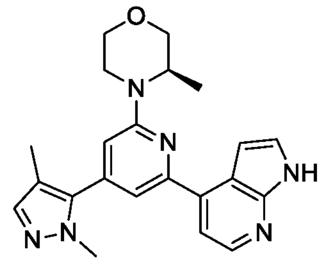

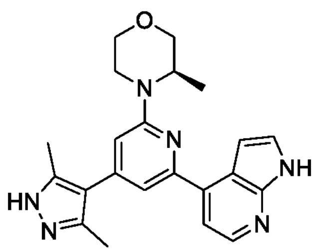

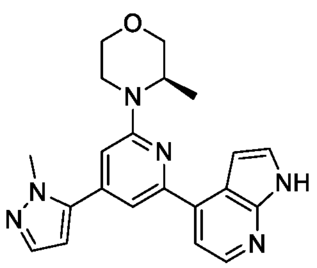

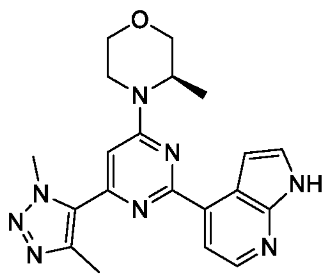

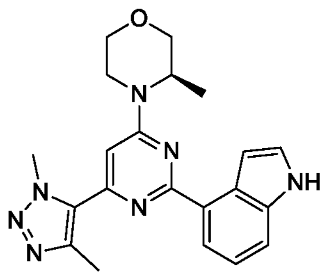

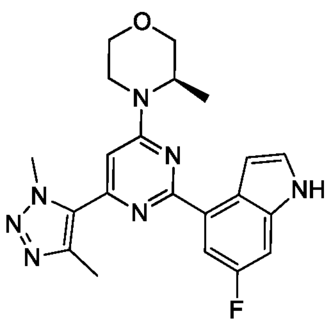

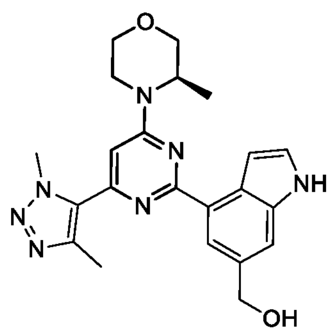

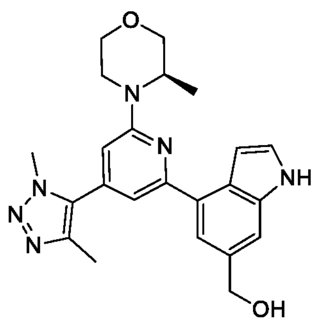

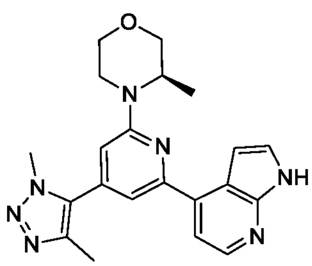

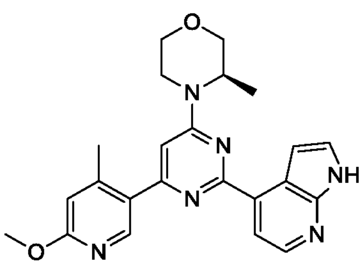

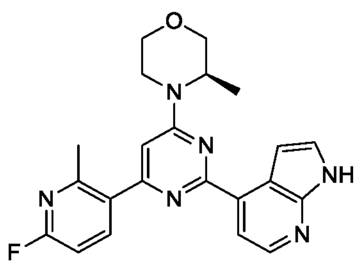

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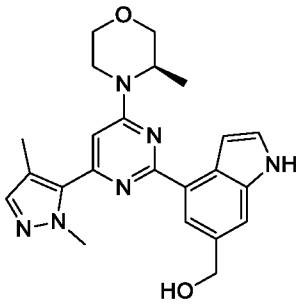
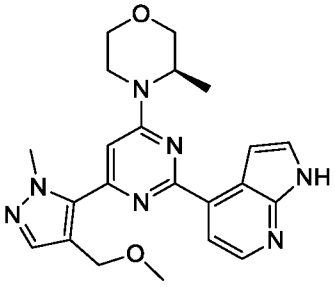
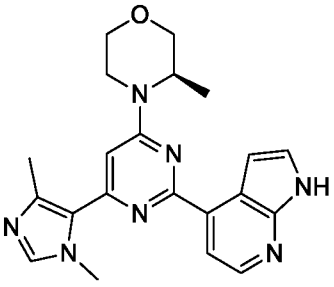
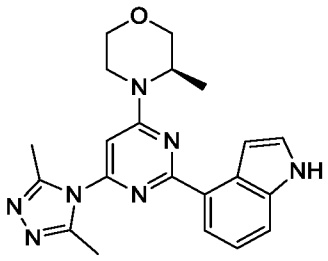
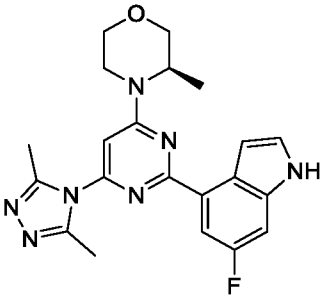
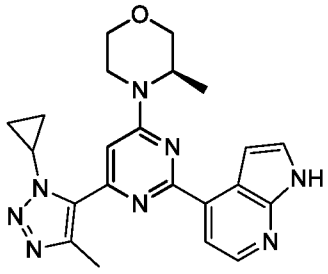
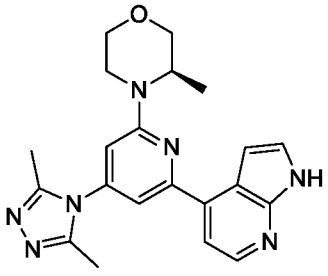
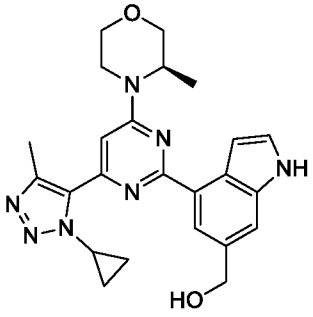
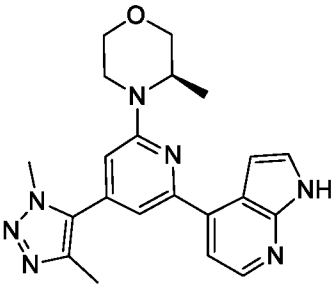
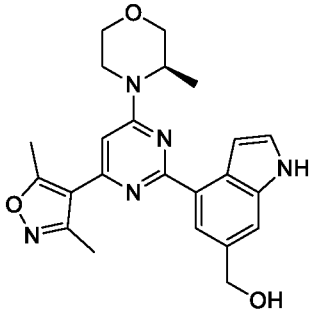
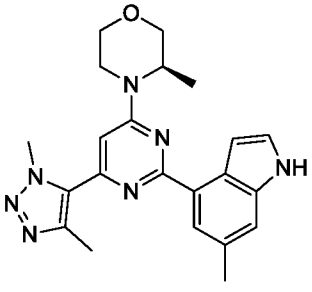
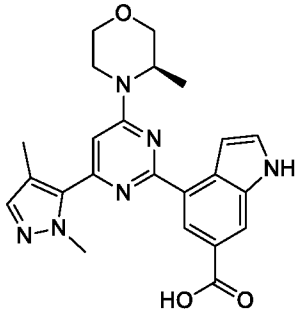
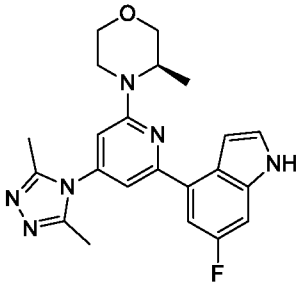
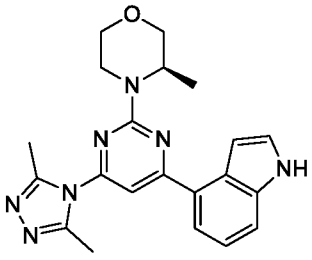
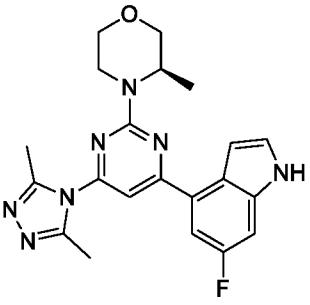

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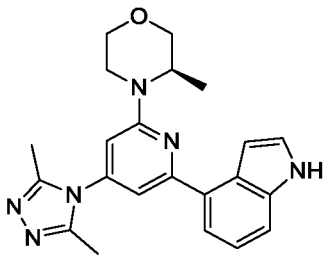

16. A pharmaceutical composition comprising the compound according to any one of claims 1-15, and a pharmaceutically acceptable excipient.

17. Use of the compound according to any one of claims 1-15 or the tautomer or the pharmaceutically acceptable salt thereof or the pharmaceutical composition of claim 16 for the manufacture of a medicament for treating an ATR associated disease; wherein the ATR associated disease is a solid tumor or a hematologic tumor.

18. A method for treating an ATR associated disease, comprising administering the compound of formula (I) according to any one of claims 1-15 or the tautomer or the pharmaceutically acceptable salt thereof or the pharmaceutical composition of claim 16 to a subject in need thereof; wherein the ATR associated disease is a solid tumor or a hematologic tumor.

Figures

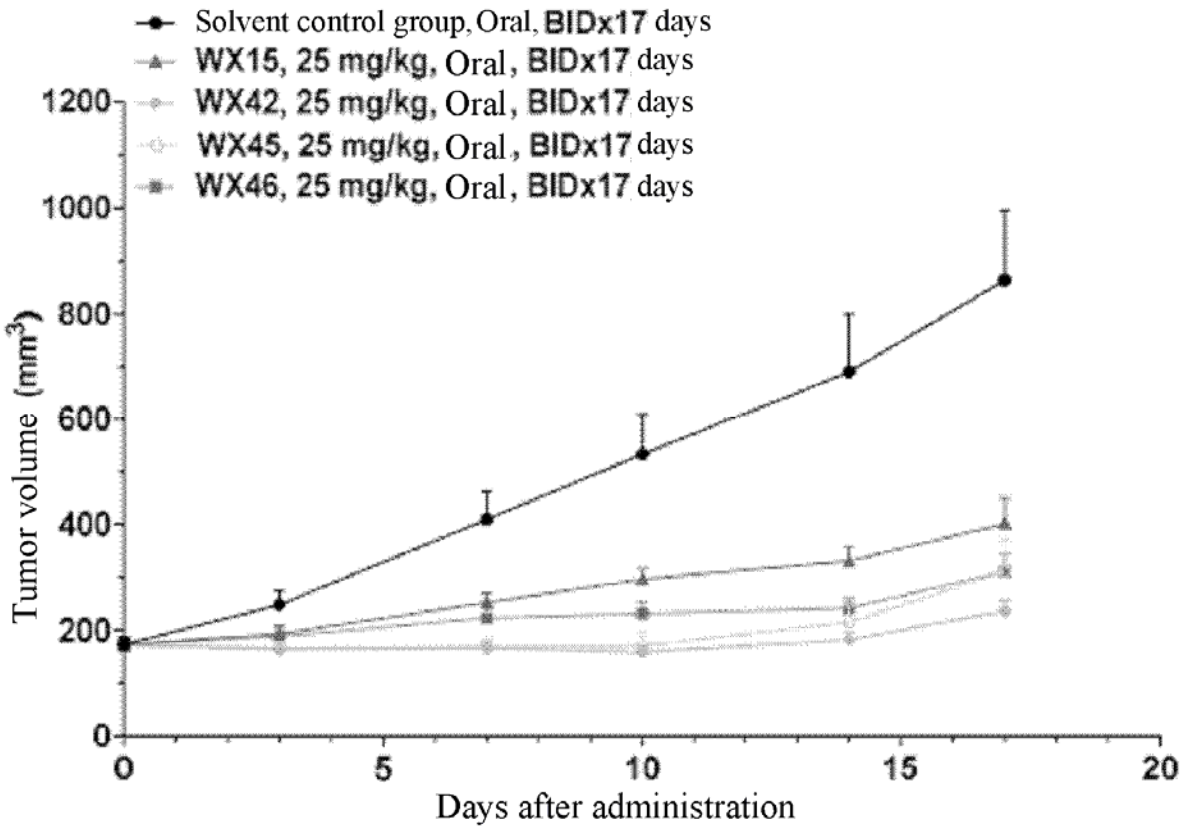

Figure 1