PI3Kδ inhibitor

Technical Field

The present invention involves in the technical field of pharmaceuticals, and specifically relates to PI3Kδ inhibitor, a pharmaceutically acceptable salt thereof, a stereoisomer thereof and a deuterated derivative thereof, a method for preparing the compounds, a pharmaceutical formulation and a pharmaceutical composition comprising the compound, and a use of the compounds, the pharmaceutically acceptable salt thereof or the stereoisomer thereof for the manufacture of a medicament for the treatment and/or prevention of diseases related to inflammatory disease and cancer.

Background art

Cancers occur when the body is subject to one or more of multiple tumorigenic factors, causing genetic changes, abnormal gene expression, and abnormal cell proliferation. Cancer cells lose their normal growth regulatory function, and will continue to multiply even when tumorigenic factors disappear. Cancer cells consume a large amount of the body's nutrients. If cancer is not diagnosed and treated early, the cancer cells will metastasize and transfer to other parts of the body, continue to grow, and release a variety of toxins, leading to weight loss, anemia, organ dysfunction and eventually death.

There are mainly three aspects in tumor treatment, drug therapy, surgery and radiotherapy. Due to surgery, radiotherapy is difficult to eradicate tumor, and the effect is not obvious for middle-late tumor patients, so the status of drug therapy is more and more obvious. Traditional antitumor drugs cannot distinguish tumor cells and normal tissue cells, and often cause serious side effects. Targeted drugs, as a specific target accurately in tumor, greatly improve the level of the treatment, and reduce the rate of adverse reactions, such as the the median survival time of late colorectal cancer increased by 66.7%, the treatment efficiency of advanced breast cancer increased by 71.3%.

Due to the acceleration of pharmaceutical companies for the development of targeted anti-tumor drugs, combined with the great market demand for this kind of antitumor drugs, molecular targeted drugs has become the fastest growing cells in global antitumor drugs market. The phosphoinositide 3-kinases (PI3Ks) signaling pathway is one of the most highly mutated

systems in human cancers. PI3K signaling is also a key factor in many other diseases in humans. PI3K signaling is involved in many disease states including allergic contact dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder, psoriasis, multiple sclerosis, asthma, disorders related to diabetic complications, and inflammatory complications of the cardiovascular system such as acute coronary syndrome.

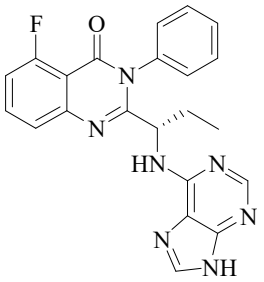
PI3Ks are members of a unique and conserved family of intracellular lipid kinases that phosphorylate the 3’-OH group on phosphatidylinositols or phosphoinositides. The PI3K family comprises 15 kinases that distinct substrate specificities, expression patterns, and modes of regulation. The class I PI3Ks (p110α, p110β, p110δ, p110r) are typically activated by tyrosine kinases or G-protein coupled receptors to generate PIP3, which engages downstream effectors such as those in the Akt/PDK1 pathway, mTOR, the Tec family kinases, and the Rho family GTPases. The class II and III PI3K-Ks play a key role in intracellular trafficking through the synthesis of PI (3) P and PI (3,4) P2. The PIKKs are protein kinases that control cell growth(mTORC1) or monitor genomic integrity(ATM, ATR, DNA-PK, and hSmg-1).

The delta (δ) isoform of class I PI3K has been implicated, in particular, in a number of diseases and biological processes. PI3Kδ is expressed primarily in hematopoietic cells including leukocytes such as T-cells, dendritic cells, neutrophils, mast cells, B-cells, and macrophages. PI3Kδ is integrally involved in mammalian immune system functions such as T-cell function, B-cell activation, mast cell activation, dendritic cell function, and neutrophil activity. Due to its integral role in immune system function, PI3Kδ is also involved in a number of diseases related to undesirable immune response such as allergic reactions, inflammatory diseases, inflammation mediated angiogenesis, rheumatoid arthritis, auto-immune diseases such as lupus, asthma, emphysema and other respiratory disease. Other class I PI3K involved in immune system function includes PI3Kr, which plays a role in leukocyte signaling and has been implicated in inflammation, rheumatoid arthritis, and autoimmune diseases such as lupus.

Downstream mediators of the PI3K signal transduction pathway include Akt and mammalian target of rapamycin (mTOR). Akt possesses a plckstrin homology (PH) domain that binds PIP3, leading to Akt kinase activation. Akt phosphorylates many substrates and is a

central downstream effector of PI3K for diverse cellular responses. One import function of Akt is to augment the activity of mTOR, through phosphorylation of TSC2 and other mechamisms. mTOR is a serine-threonine kinase related to the lipid kinases of the PI3K family. mTOR has been implicated in a wide range of bilological processes including cell growth, cell proliferation, cell motility and survival. Disregulaition of mTOR pathway has been reported in various types of cancer. mTOR is a multifunctional kinase that integrates growth factor and nutrient signals to regulate protein translation, nutrient uptake, autophagy, and mitochondrial function. As such, kinases, particularly PI3Ks are prime targets for drug development.

CAL-101 is an inhibitor of PI3Kδ and the original company is Calistoga. Calistoga was acquired by by Gilead in 2011. CAL-101 is first-in-class candidate of PI3Kδ inhibitors, currently in phase III clinical trials. The clinical indications are mainly chronic lymphocytic leukemia, non-hodgkin's lymphoma, acute myelogenous leukemia, allergic rhinitis and so on. Structure is as follows:



CAL-101

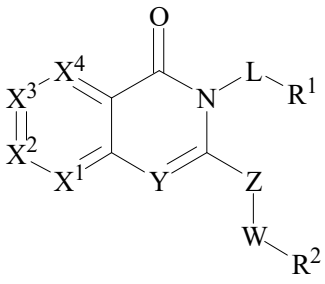
WO2009088990 (Intellikine) and US6667300 (Icos) both reported the efficacy of PI3Kδ inhibitors in the treatment of cancer and inflammation. At present, there are not any PI3Kδ inhibitor drugs in the market. So there remains a need for more PI3Kδ inhibitors structure type, choose better efficacy and safety of compound, used in the treatment of cancer and inflammation, in order to meet the clinical need.

Summary of the invention

Embodiments of the present application are as follows:

Embodiment 1

A compound shown by general formula (I), a pharmaceutically acceptable salt thereof, a stereoisomer thereof and a deuterated compounds thereof:



(I)

wherein,

X^1, X^2, X^3, X^4, Y are independently chosen from N or CR^3, R^3 is chosen from hydrogen, halogen, hydroxyl, carboxyl, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxy, -N(R^a)($R^{a'}$), cyano, C_{2-6}alkenyl, C_{2-6}alkynyl, aminocarbonyl, C_{1-6} alkylcarbonyl, aminosulfonyl, 3-14 membered cycloalkanes, 6-14 membered aryl, 3-14 membered heterocycle, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group;

L is covalent bond or -N(R^a)-;

When L is covalent bond, R^1 is benzoC_{3-8}cycloalkeny, benzoC_{4-8}cyclodienyl, bicyclic heteroaryl obtained by (phenyl or a 5-6 membered monocyclic heteroaryl) and (C_{3-8} cycloalkeny, C_{4-8} cyclodienyl or 3-8 membered heterocycloalkenyl) fused, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group, R^1 is chosen from optionally substituted by 1-3 R^b,

When L is -N(R^a)-, R^1 is C_{1-6} alkyl, C_{1-6}alkylcarbonyl, C_{1-6} alkylsulfonyl, 3-14 membered cycloalkanes, 6-14 membered aryl, 6-14 membered arylC_{1-4} alkyl, 3-14 membered heterocycle, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group, R^1 is chosen from optionally substituted by 1-3 R^b,

R^a, $R^{a'}$ are independently chosen from hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3-14 membered cycloalkanes, 6-14 membered aryl, 3-14 membered heterocycle, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group;

Z is -O-, -C($R^{4'}R^4$)- or -N(R^4)-;

W is -O-, -C($R^{5'}R^5$)- or -N(R^5)-;

R^4, $R^{4'}$, R^5, $R^{5'}$ are independently chosen from hydrogen, C_{1-6}alkyl or 3-14 membered cycloalkanes substituted or unsubstituted by at least one hydroxyl or halogen;

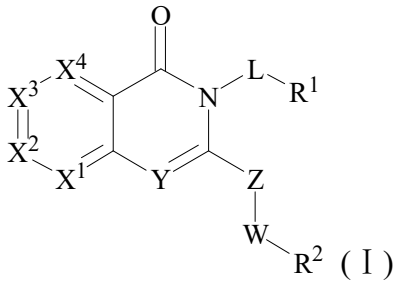
R^2 is 6-10 membered bicyclic heterocycloalkyl substituted or unsubstituted by at least one R^b, bicyclic heteroaryl obtained by (phenyl or a 5-6 membered monocyclic heteroaryl) and (5-6 membered monocyclic heteroaryl) fused, 7-12 membered spiro-ring group or 7-12 membered

bridged-ring group;

R^b is hydrogen, oxo, halogen, CN, hydroxyl, amino, C_{1-6} alkylamine, bio(C_{1-6} alkyl)amine, carboxyl, aminosulfonyl, aminocarbonyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted by halogen, C_{1-6} alkoxy substituted by halogen, hydroxyl C_{1-6}alkyl, aminoC_{1-6} alkoxy, carboxyl C_{1-6} alkyl, aminocarbonyl C_{1-6} alkyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkyl C(=O)-, C_{2-6} alkenyl, C_{2-6} alkynyl, 3-14 membered cycloalkanes, 3-14 membered cycloalkoxy, 6-14 membered aryl, 6-14 membered phenyloxy, 3-14 membered heterocycle, 3-14 membered heterocycloalkoxy, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group.

Embodiment 1a

A compound shown by general formula (I), a pharmaceutically acceptable salt thereof, a stereoisomer thereof and a deuterated compounds thereof:



(I)

wherein,

X^1,X^2,X^3,X^4,Y are independently chosen from N or CR^3, R^3 is chosen from hydrogen, halogen, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxy, -N(R^a)($R^{a'}$), cyano, C_{2-6}alkenyl, C_{2-6}alkynyl, 3-14 membered cycloalkanes, 6-14 membered aryl, 3-14 membered heterocycle, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group;

L is covalent bond or -N(R^a)-;

When L is covalent bond, R^1 is benzoC_{3-8}cycloalkeny, benzoC_{4-8}cyclodienyl, bicyclic heteroaryl obtained by (phenyl or a 5-6 membered monocyclic heteroaryl) and (C_{3-8} cycloalkeny, C_{4-8} cyclodienyl or 3-8 membered heterocycloalkenyl) fused, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group, R^1 is chosen from optionally substituted by 1-3 R^b,

When L is -N(R^a)-, R^1 is C_{1-6} alkyl, C_{1-6}alkylcarbonyl, C_{1-6} alkylsulfonyl, 3-14 membered cycloalkanes, 6-14 membered aryl, 6-14 membered arylC_{1-4} alkyl, 3-14 membered heterocycle, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group, R^1 is chosen from optionally substituted by 1-3 R^b,

R^a, $R^{a'}$ are independently chosen from hydrogen, C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3-14 membered cycloalkanes, 6-14 membered aryl, 3-14 membered heterocycle, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group;

Z is -O-,-C($R^{4'}R^4$)- or -N(R^4)-;

W is -O-,-C($R^{5'}R^5$)- or -N(R^5)-;

R^4, $R^{4'}$, R^5, $R^{5'}$ are independently chosen from hydrogen, C_{1-6}alkyl or 3-14 membered cycloalkanes substituted or unsubstituted by at least one hydroxyl or halogen;

R^2 is 6-10 membered Bicyclic heterocycloalkyl substituted or unsubstituted by at least one R^b ,bicyclic heteroaryl obtained by (phenyl or a 5-6 membered monocyclic heteroaryl) and (5-6 membered monocyclic heteroaryl) fused, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group;

R^b is hydrogen, oxo, halogen, CN, hydroxyl, amino, C_{1-6} alkylamine, bio(C_{1-6} alkyl) amine, carboxyl, aminosulfonyl, aminocarbonyl,C_{1-6} alkyl,C_{1-6} alkoxy, C_{1-6} alkyl substituted by halogen, C_{1-6} alkoxy substituted by halogen, hydroxyl C_{1-6}alkyl, aminoC_{1-6} alkoxy, carboxyl C_{1-6} alkyl, aminocarbonyl C_{1-6} alkyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkyl C(=O)-, C_{2-6} alkenyl, C_{2-6} alkynyl, 3-14 membered cycloalkanes, 3-14 membered cycloalkoxy, 6-14 membered aryl, 6-14 membered phenyloxy, 3-14 membered heterocycle, 3-14 membered heterocycloalkoxy, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group.

Embodiment 2

The compound, the pharmaceutically acceptable salt thereof, the stereoisomer thereof and the deuterated compounds thereof according to any one of embodiment 1a or embodiment 1:

Wherein:

X^1, X^2, X^3, X^4 are independently chosen from CR^3, R^3 is chosen from hydrogen, halogen, hydroxyl, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy, -N(R^a)($R^{a'}$), cyano, C_{2-6} alkenyl, C_{2-6} alkynyl, 3-8 membered monocycle cycloalkanes, phenyl or 3-8 membered monocycle heterocycle, 3-8 membered Heterocyclic alkenyl, 5-6 membered monocyclic heteroaryl;

Y is N;

When L is covalent bond, R^1 is benzoC_{3-8}cycloalkeny, benzoC_{4-8}cyclodienyl, bicyclic heteroaryl obtained by (phenyl or a 5-6 membered monocyclic heteroaryl) and (C_{3-8} cycloalkeny, C_{4-8} cyclodienyl or 3-8 membered heterocycloalkenyl) fused, 7-12 membered

spiro-ring group or 7-12 membered bridged-ring group, R^1 is chosen from optionally substituted by 1-3 R^b,

When L is -N(R^a)-, R^1 is C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6}alkylsulfonyl, 3-14 membered cycloalkanes, 6-14 membered aryl, 6-14 membered aryl C_{1-4} alkyl, 3-14 membered heterocycle, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group, R^1 is chosen from optionally substituted by 1-3 R^b,

R^a, $R^{a'}$ are independently chosen from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3-14 membered cycloalkanes, 6-14 membered aryl, 3-14 membered heterocycle, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group;

Z is -C($R^{4'}R^4$)-;

W is -N(R^5)-;

R^4, $R^{4'}$, R^5 are independently chosen from hydrogen, C_{1-6}alkyl or 3-14 membered cycloalkanes substituted or unsubstituted by at least one hydroxyl or halogen;

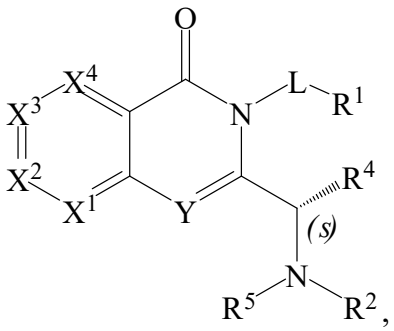
R^2 is 6-10 membered bicyclic heterocycloalkyl substituted or unsubstituted by at least one R^b, bicyclic heteroaryl obtained by (phenyl or a 5-6 membered monocyclic heteroaryl) and (5-6 membered monocyclic heteroaryl) fused, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group;

R^b is hydrogen, oxo, halogen, CN, hydroxyl, amino, C_{1-6} alkylamine, bio(C_{1-6} alkyl) amine, carboxyl, aminosulfonyl, aminocarbonyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl substituted by halogen, C_{1-6} alkoxy substituted by halogen, hydroxyl C_{1-6} alkyl, aminoC_{1-6} alkoxy, carboxyl C_{1-6}alkyl, alkylcarbonyl C_{1-6} alkyl, C_{1-6} alkylcarbonyloxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkyl C(=O)-, C_{2-6} alkenyl, C_{2-6} alkynyl, 3-8 membered cycloalkanes, 3-8 membered cycloalkoxy,phenyl, phenyl oxygen, 3-8 membered monocyclic heterocycloalkyl, 3-8 membered heterocyclic alkenyl, 5-6 membered monocyclic heteroaryl, 3-8 membered monocycle heterocycloalkoxy, 3-8 membered Heterocyclic alkenyloxy, 5-6 membered monocyclic heteroaryloxy.

Embodiment 3

The compound, the pharmaceutically acceptable salt thereof, the stereoisomer thereof and the deuterated compounds thereof according to any one of embodiment 1a or embodiment 1-2:

Wherein: at least one chemical entity chosen from a compound of Formula(Ⅰ):



X^1, X^2, X^3, X^4, Y, L, R^1, R^2, R^4 and R^5 have the meaning of embodiment 1, 1a or 2.

Embodiment 4

The compound, the pharmaceutically acceptable salt thereof, the stereoisomer thereof and the deuterated compounds thereof according to any one of embodiment 1a or embodiment 1-3:

Wherein:

X^1,X^2,X^3,X^4 are independently chosen from CR^3, R^3 is chosen from hydrogen, halogen, hydroxyl, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy or amino;

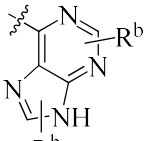
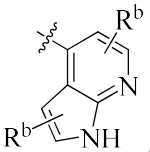
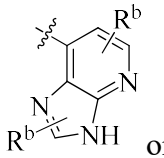
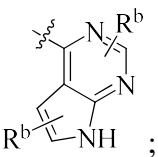
Y is N;

When L is covalent bond, R^1 is bicyclic heteroaryl obtained by (phenyl or a 5-6 membered monocyclic heteroaryl) and (C_{3-8} cycloalkeny, C_{4-8} cyclodienyl or a 3-8 membered heterocycloalkenyl) fused or 7-12 membered spiro heterocyclic group, R^1 is chosen from optionally substituted by 1-3 R^b,

Z is -CH(R^4)-;

W is -N(R^5)-;

R^4, R^5 are independently chosen from hydrogen, C_{1-3}alkyl or 3-5 membered cycloalkanes substituted or unsubstituted by at least one hydroxyl or halogen;

R^2 is  ,  ,  or  ;

R^b is hydrogen, oxo, halogen, CN, C_{1-3} alkyl, C_{1-3} alkoxy, trifluoromethyl, amino or 3-8 membered monocyclic heterocycloalkyl, 3-8 membered heterocyclic alkenyl, 5-6 membered monocyclic heteroaryl.

Embodiment 5

The compound, the pharmaceutically acceptable salt thereof, the stereoisomer thereof and the deuterated compounds thereof according to any one of embodiment 1a or embodiment 1-4:

Wherein:

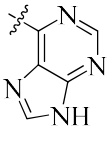
X^1, X^2, X^3, X^4 are independently chosen from CR^3, R^3 is chosen from hydrogen, fluorin, chlorin, trifluoromethyl or methyl;

Y is N;

When L is covalent bond, R^1 is bicyclic heteroaryl obtained by (phenyl or a 5-6 membered monocyclic heteroaryl) and (C_{5-6} cycloalkeny, C_{5-6} cyclodienyl or a 5-6 membered heterocycloalkenyl) fused or 7-12 membered spiro heterocyclic group, R^1 is chosen from optionally substituted by 1-3 R^b,

Z is -CH(R^4)-, R^4 is hydrogen, C_{1-3}alkyl or cyclopropyl substituted or unsubstituted by at least one hydroxyl or fluorin;

W is -N(R^5)-, R^5 are independently chosen from hydrogen or methyl;

R^2 is  ;

R^b is halogen.

Embodiment 6

The compound, the pharmaceutically acceptable salt thereof, the stereoisomer thereof and the deuterated compounds thereof according to any one of embodiment 1a or embodiment 1-5:

Wherein:

X^1, X^2, X^3, X^4 are independently chosen from CR^3, R^3 is chosen from hydrogen, halogen, hydroxyl, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy, -N(R^a)($R^{a'}$) or cyano;

Y is N;

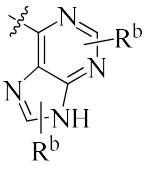
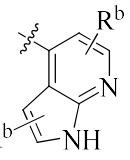
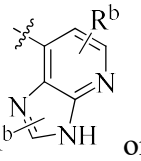
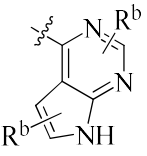
L is -N(R^a)-, R^1 is C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkylsulfonyl, 3-6 membered cycloalkanes, 6-14 membered aryl, 6-14 membered aryl C_{1-3} alkyl, 3-14 membered heterocycle, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group, R^1 is chosen from optionally substituted by 1-3 R^b,

R^a, $R^{a'}$ are independently chosen from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3-14 membered cycloalkanes, 6-14 membered aryl, 3-14 membered heterocycle, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group;

Z is -CH(R^4)-;

W is -N(R^5)-;

R^4, R^5 are independently chosen from hydrogen, C_{1-3}alkyl or 3-5 membered cycloalkanes substituted or unsubstituted by at least one hydroxyl or halogen;

R^2 is  ,  ,  or  ;

R^b is hydrogen, oxo, halogen, CN, hydroxyl, amino, C_{1-6} alkylamine, bio (C_{1-6} alkyl) amine, carboxyl, aminosulfonyl, aminocarbonyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkyl substituted by halogen, 3-6 membered cycloalkanes, 3-6 membered cycloalkoxy, 3-8 membered monocyclic heterocycloalkyl, 3-8 membered heterocyclic alkenyl, 5-6 membered monocyclic heteroaryl, 3-8 membered monocycle heterocycloalkoxy, 3-8 membered heterocyclic alkenyloxy, 5-6 membered monocyclic heteroaryloxy.

Embodiment 7

The compound, the pharmaceutically acceptable salt thereof, the stereoisomer thereof and the deuterated compounds thereof according to any one of embodiment 1a or embodiment 1-6:

Wherein:

X^1, X^2, X^3, X^4 are independently chosen from CR^3, R^3 is chosen from hydrogen, halogen, hydroxyl, trifluoromethyl, C_{1-6} alkyl or C_{1-6} alkoxy;

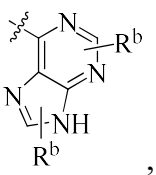
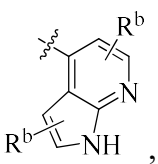
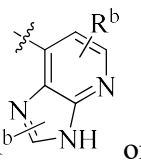
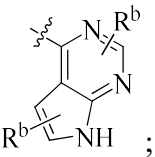
Y is N;

L is -N(R^a)-, R^1 is C_{1-3} alkyl, C_{1-3} alkylcarbonyl, C_{1-3} alkylsulfonyl, 3-6 membered cycloalkanes, 6-14 membered aryl, 6-14 membered aryl C_{1-3}alkyl, 5-6 membered monocycle heterocycle,5-6 membered heterocyclic alkenyl, 5-6 membered monocyclic heteroaryl,6-10 membered bicycle-heterocycle, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group, R^1 is chosen from optionally substituted by 1-3 R^b,

R^a is hydrogen, C_{1-6}alkyl, 3-14 membered cycloalkanes or 6-14 membered aryl;

Z is -CH(R^4)-, R^4 is hydrogen, C_{1-3}alkyl or cyclopropyl substituted or unsubstituted by at least one hydroxyl or halogen;

W is -N(R^5)-, R^5 is hydrogen or methyl;

R^2 is  ,  ,  or  ;

R^b is hydrogen, oxo, halogen, CN, hydroxyl, amino, C_{1-6} alkylamine, bio (C_{1-6}alkyl) amine, C_{1-6}alkoxy, C_{1-6} alkyl, C_{1-6} alkyl substituted by halogen, 3-6 membered cycloalkanes, 3-6 membered cycloalkoxy, 5-6 membered monocyclic heterocycloalkyl, 5-6 membered heterocyclic alkenyl, 5-6 membered monocyclic heteroaryl, 5-6 membered monocycle heterocycloalkoxy, 5-6 membered Heterocyclic alkenyloxy, 5-6 membered monocyclic heteroaryloxy.

Embodiment 8

The compound, the pharmaceutically acceptable salt thereof, the stereoisomer thereof and the deuterated compounds thereof according to any one of embodiment 1a or embodiment 1-7:

Wherein:

X^1, X^2, X^3, X^4 are independently chosen from CR^3, R^3 is chosen from hydrogen, fluorin, chlorin, hydroxyl, trifluoromethyl or methyl;

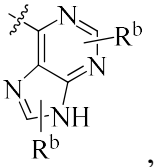
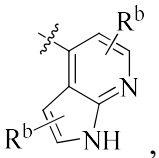
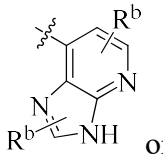
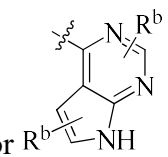
Y is N;

L is -N(R^a)-, R^1 is C_{1-3}alkyl, acetyl, methylsulfonyl, phenyl, pyridyl, pyrimidyl, furan, thienyl, pyrryl, thiazolyl, imidazole, pyrazolyl, imidazolidinyl, pyrazolidinyl, indolyl, indolyl, indazolyl, benzimidazolyl, pyridino-pyrazolyl, purine,piperazine, quinolyl, tetradydropyrane, piperidyl, morpholinyl, pyrazinyl, pyridine-2-keto, cyclohexyl, cyclopentyl or benzyl, R^1 is chosen from optionally substituted by 1-3 R^b,

R^a is hydrogen, C_{1-3} alkyl, 3-8 membered cycloalkanes or 6-14 membered aryl;

Z is -CH(R^4)-, R^4 is hydrogen, C_{1-3}alkyl or cyclopropyl substituted or unsubstituted by at least one hydroxyl or fluoro;

W is -N(R^5)-, R^5 is hydrogen or methyl;

R^2 is  ,  ,  or  ;

R^b is hydrogen, oxo, halogen, CN, hydroxyl, amino, C_{1-6} alkylamine, bio (C_{1-6}alkyl) amine, C_{1-6}alkoxy, C_{1-6} alkyl, C_{1-6} alkyl substituted by halogen, 3-6 membered cycloalkanes, 3-6 membered cycloalkoxy, 5-6 membered monocyclic heterocycloalkyl, 5-6 membered heterocyclic alkenyl, 5-6 membered monocyclic heteroaryl, 5-6 membered monocycle heterocycloalkoxy, 5-6 membered heterocyclic alkenyloxy, 5-6 membered monocyclic

heteroaryloxy.

Embodiment 9

The compound, the pharmaceutically acceptable salt thereof, the stereoisomer thereof and the deuterated compounds thereof according to any one of embodiment 1a or embodiment 1-8:

Wherein:

X1, X2, X3, X4 are independently chosen from CR^3, R^3 is chosen from hydrogen, fluorin, chlorin, hydroxyl, trifluoromethyl or methyl;

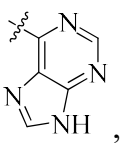
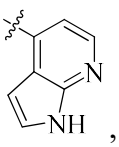
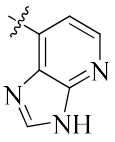
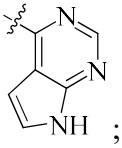
Y is N;

L is $-N(R^a)-$, R^1 is C_{1-3}alkyl, acetyl, methylsulfonyl, phenyl, pyridyl, pyridine-2- keto, cyclohexyl, cyclopentyl or benzyl, R^1 is chosen from optionally substituted by 1-3 R^b;

R^a is hydrogen, methyl, ethyl, cyclopropyl or phenyl;

Z is $-CH(R^4)-$, R^4 ishydrogen, C_{1-3}alkyl or cyclopropyl substituted or unsubstituted by at least one hydroxyl or fluoro;

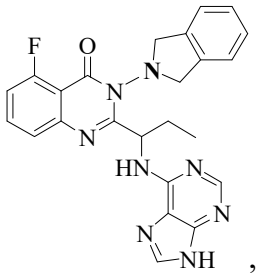
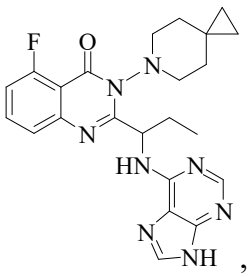
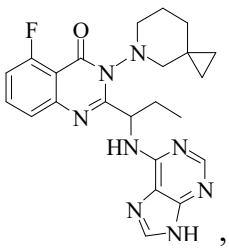
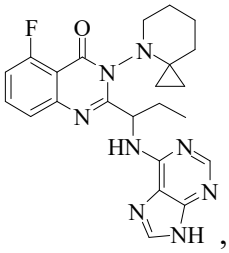
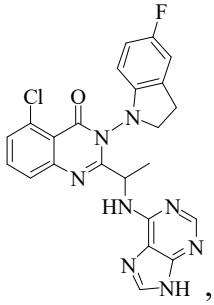
W is $-N(R^5)-$, R^5 is hydrogen or methyl;

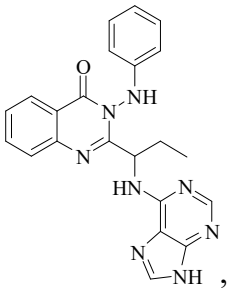
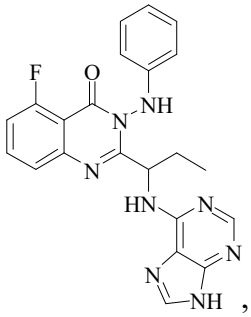
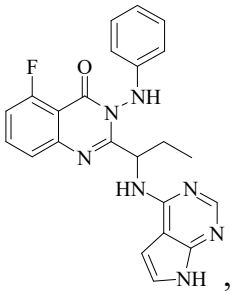
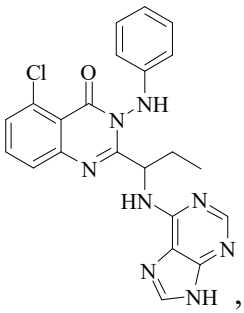
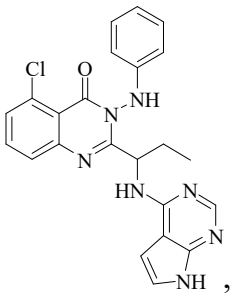
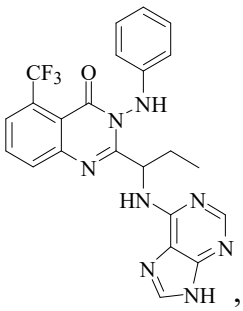
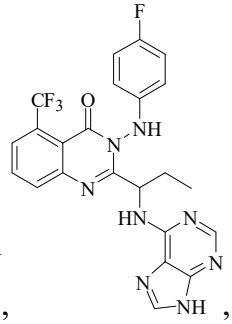
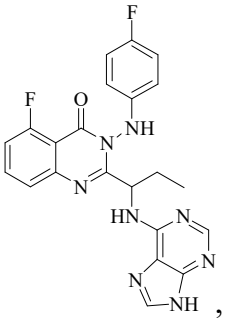
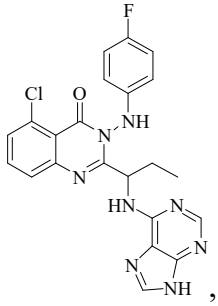
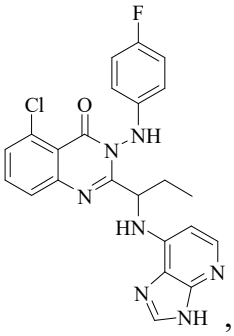
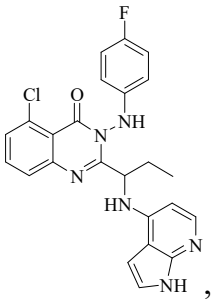
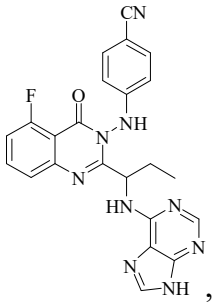
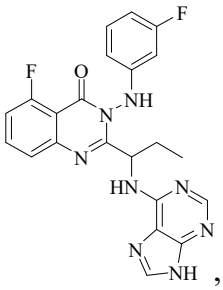
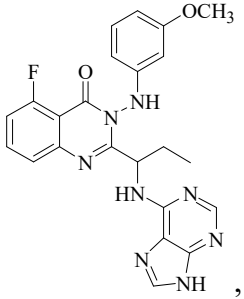
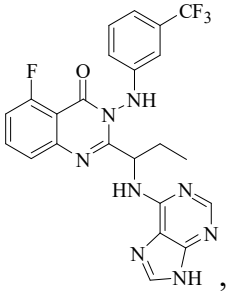
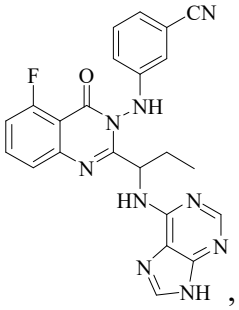
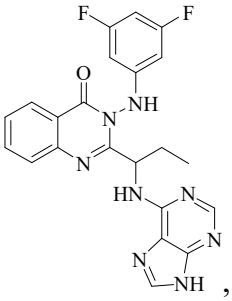
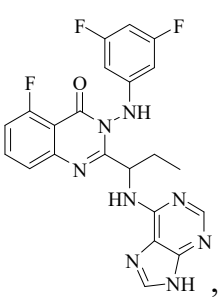
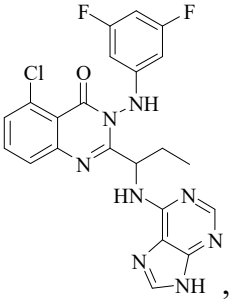
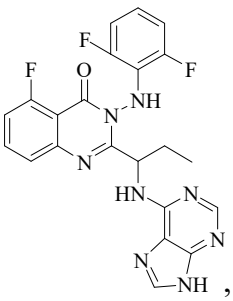
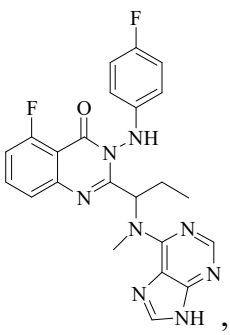
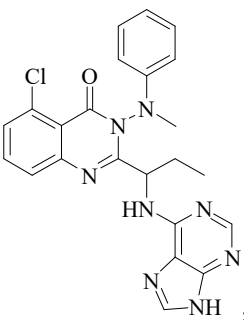
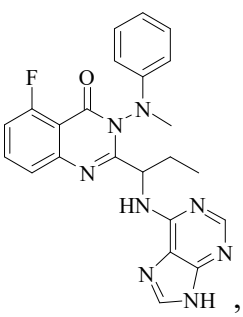
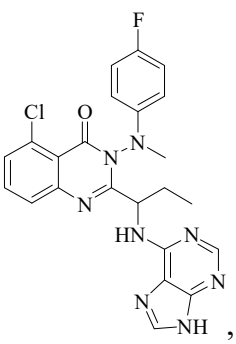
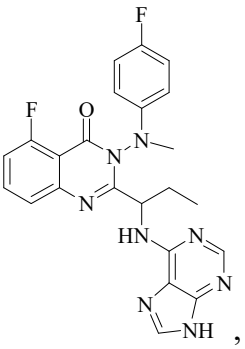
R^2 is  ,  ,  or  ;

R^b is hydrogen, oxo, halogen, CN, C_{1-3} alkyl, C_{1-3} alkoxy or trifluoromethyl.

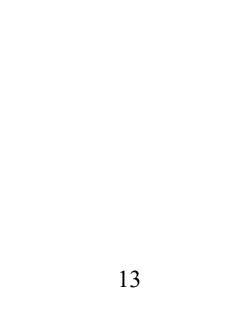
Embodiment 10

The compound, the pharmaceutically acceptable salt thereof, the stereoisomer thereof and the deuterated compounds thereof according to any one of embodiment 1a or embodiment 1-9, selected from the following compounds:

 ,  ,  ,  ,  ,

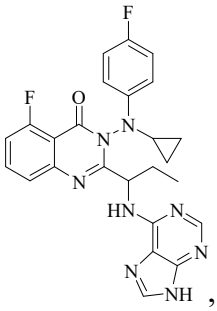
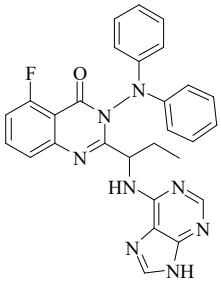
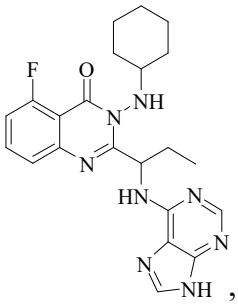
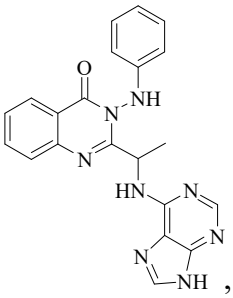
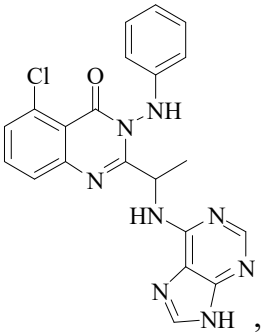
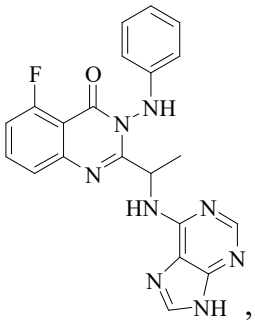
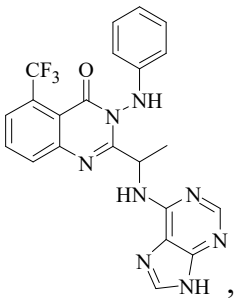
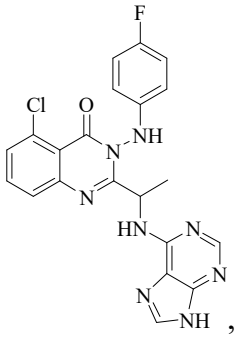
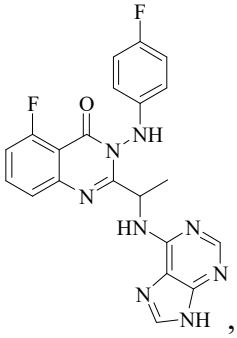
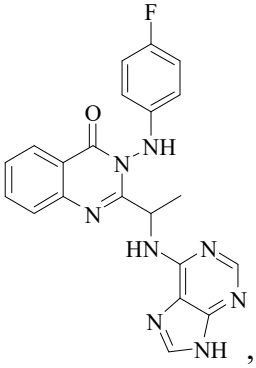
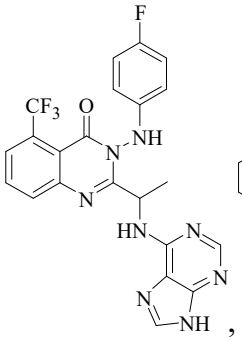
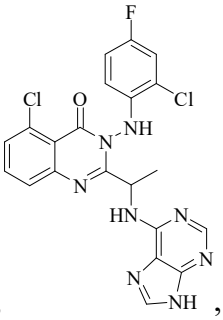
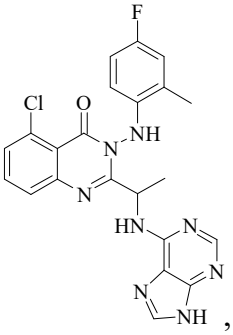
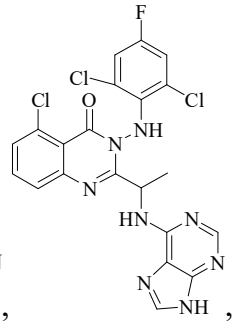
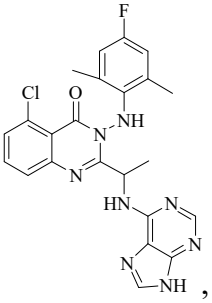
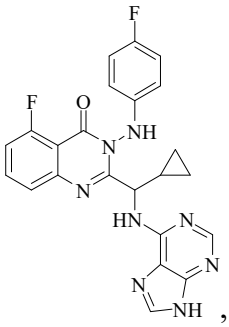
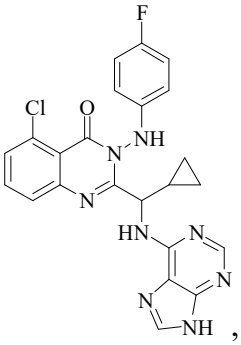
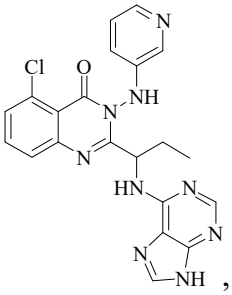
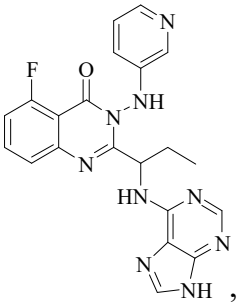
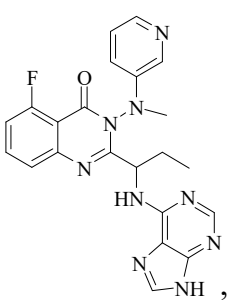
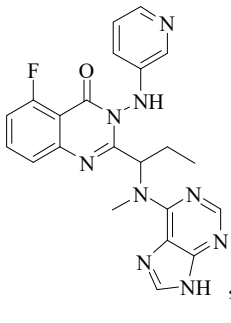
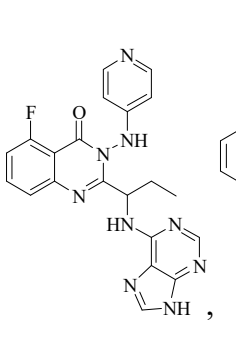
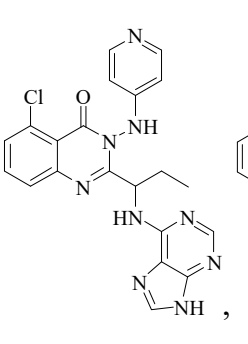
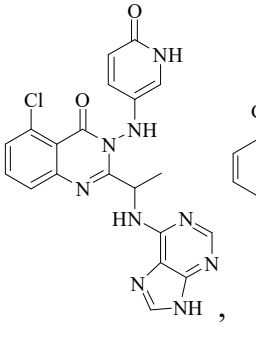
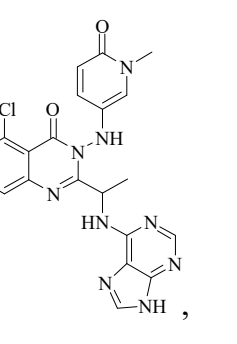

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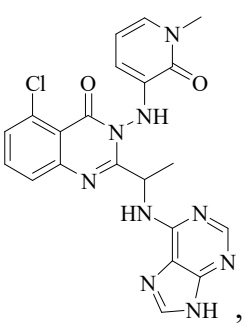
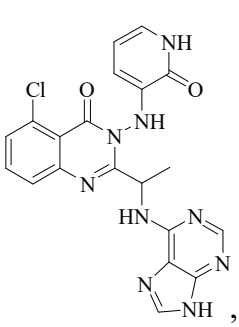
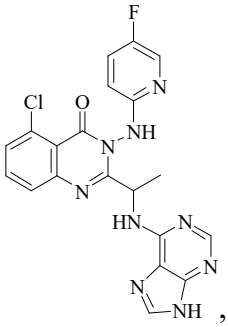
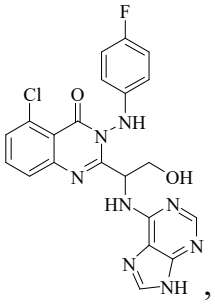
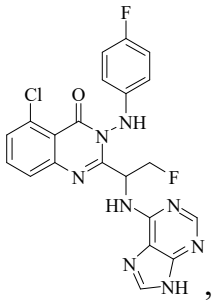
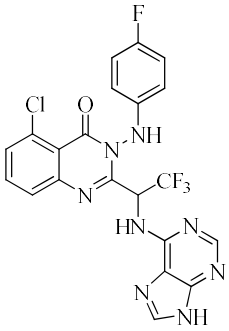
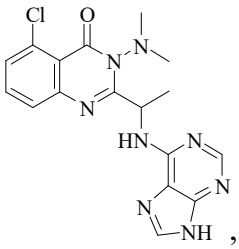
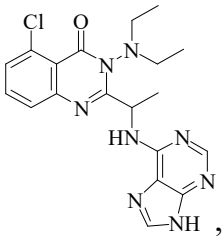
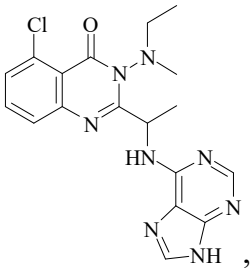
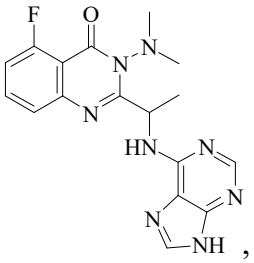
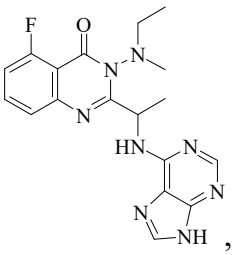
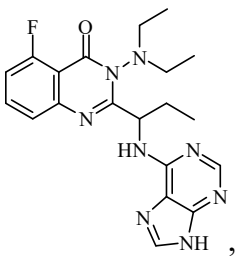
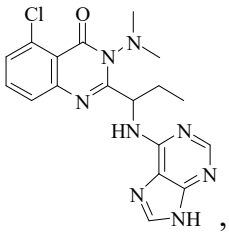
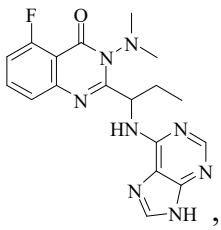
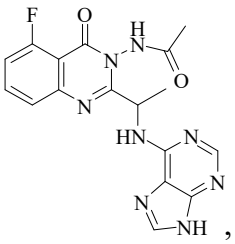
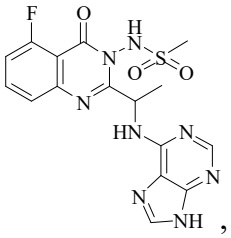
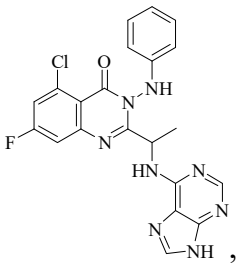
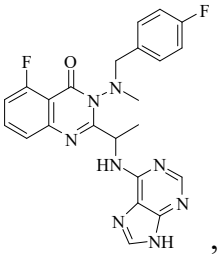
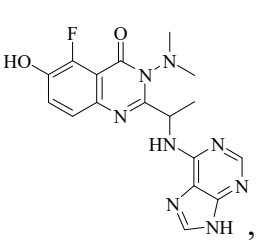
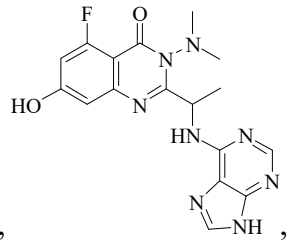
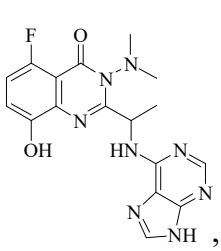
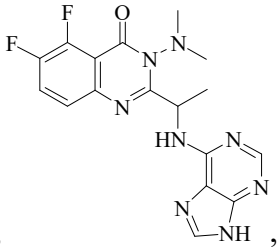
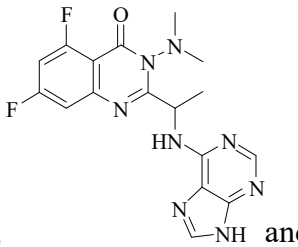
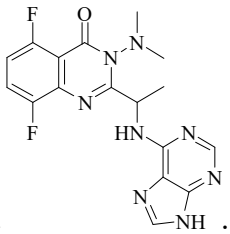
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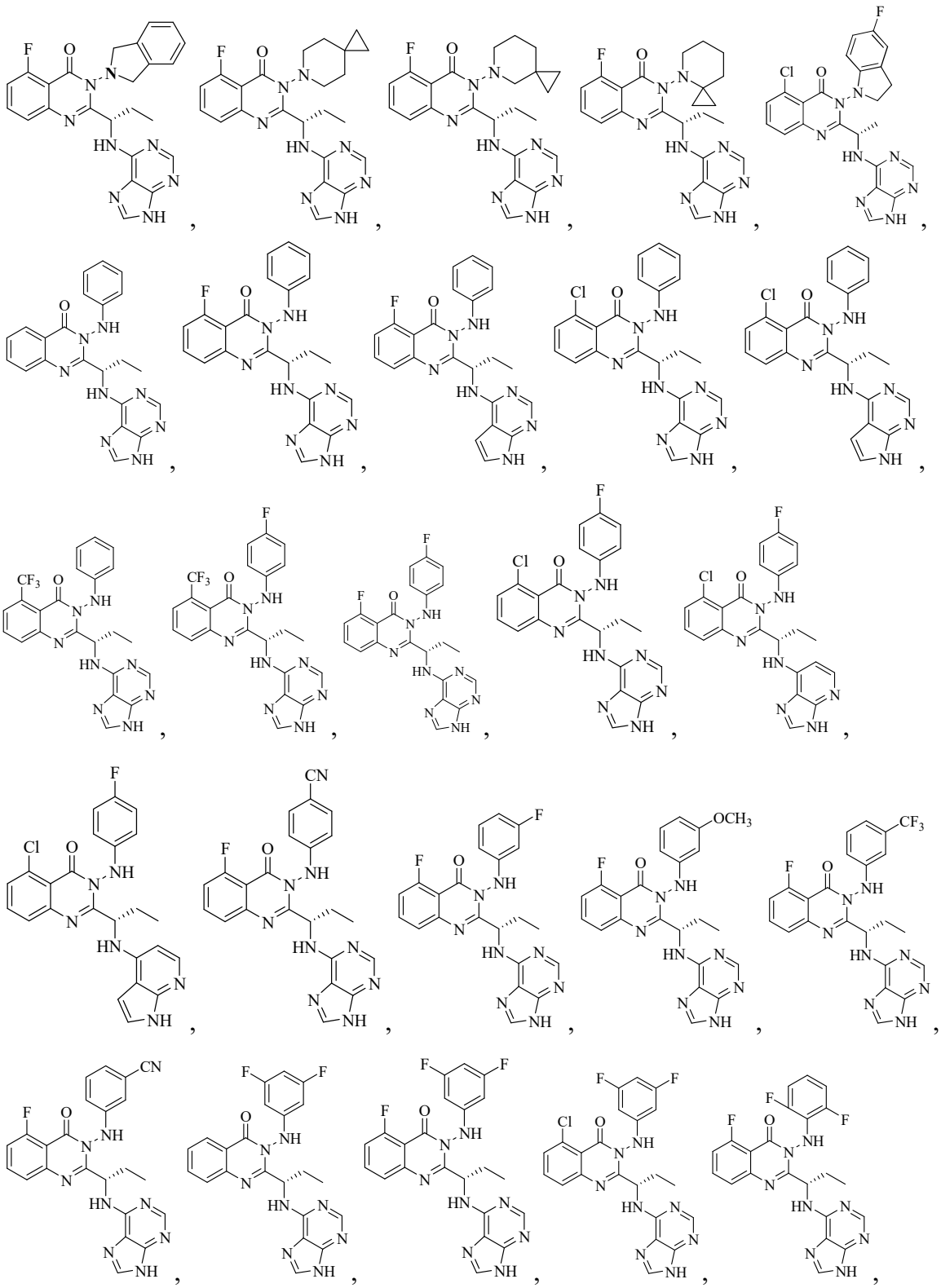
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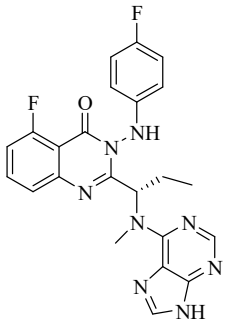
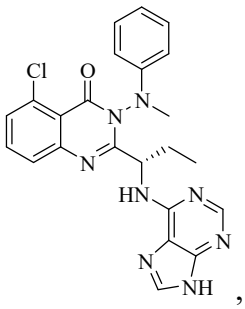
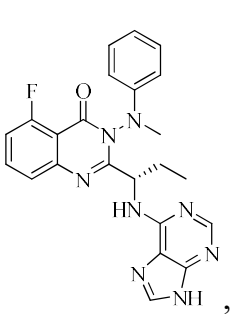
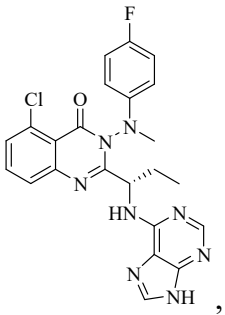
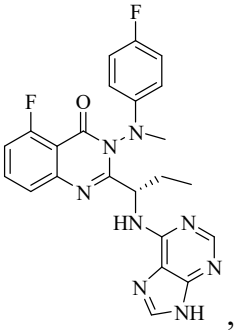
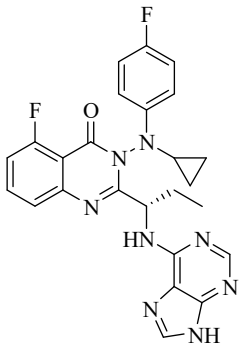
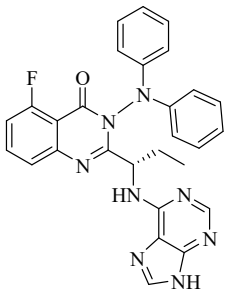
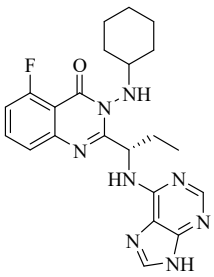
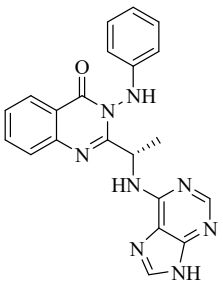
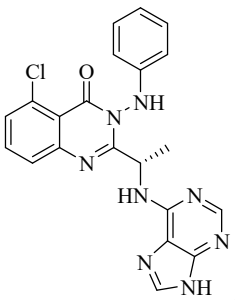
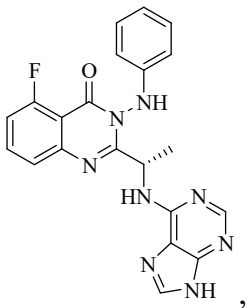
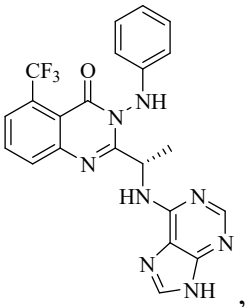
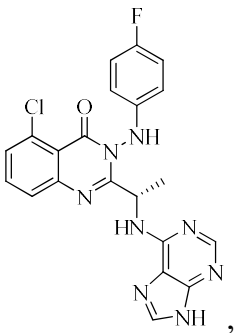
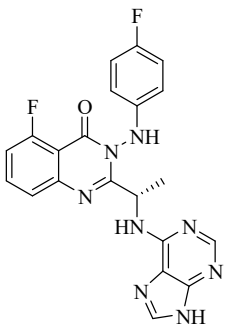
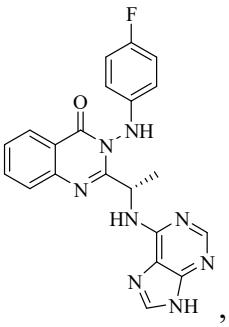
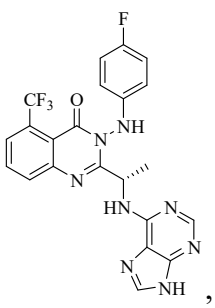
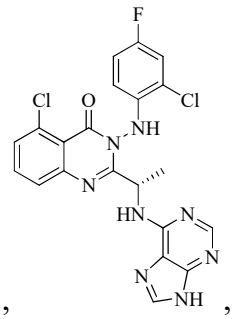
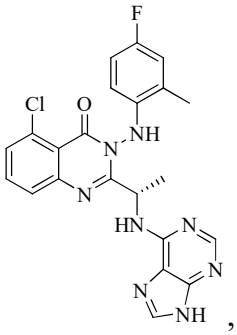
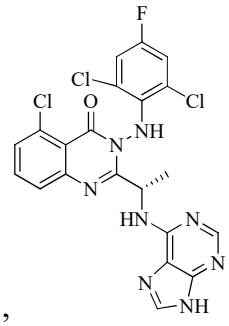
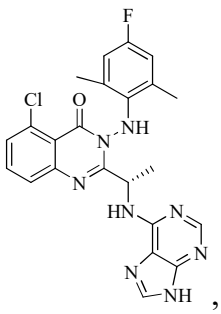
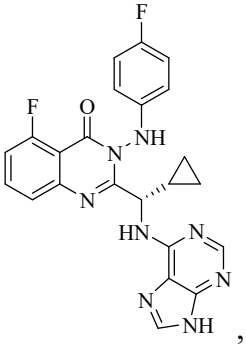
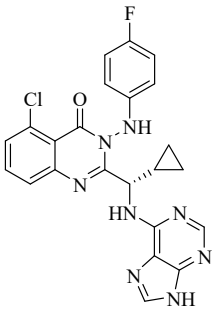
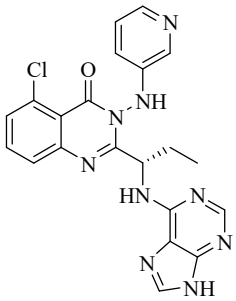
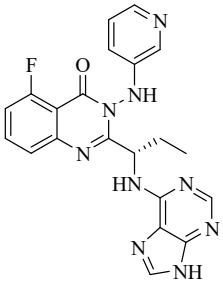
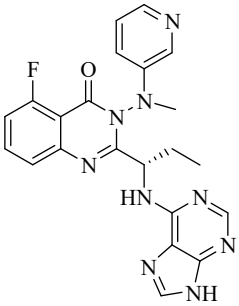
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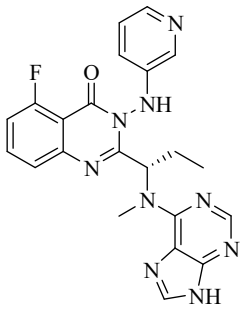
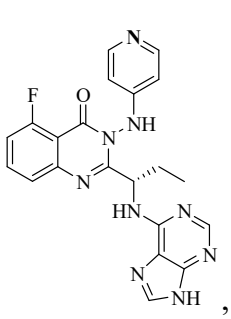
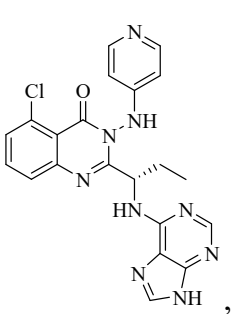
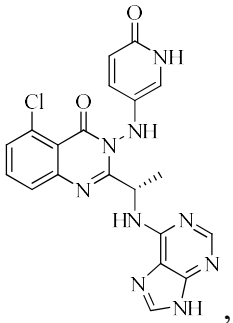
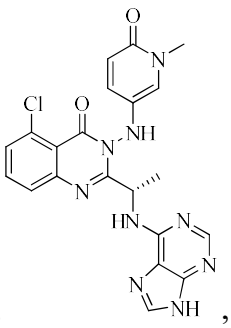
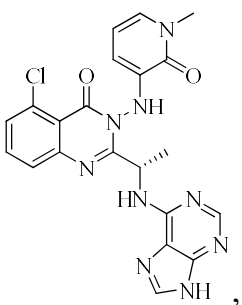
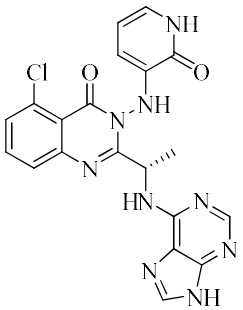
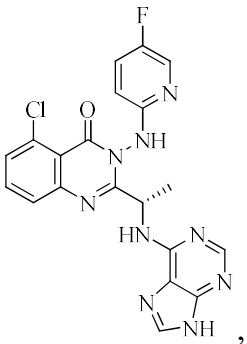
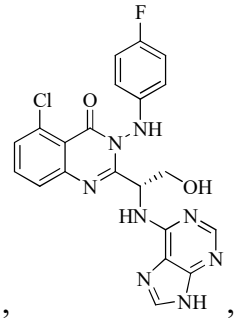
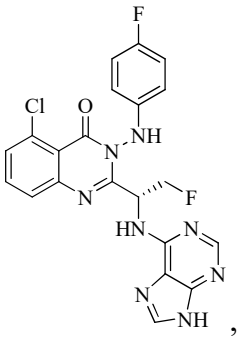
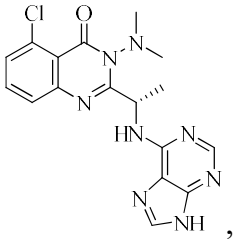
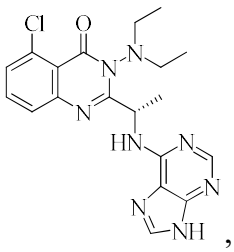
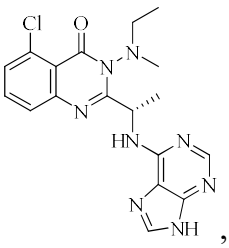
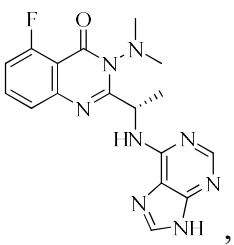
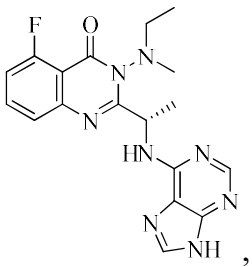
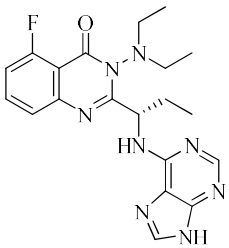
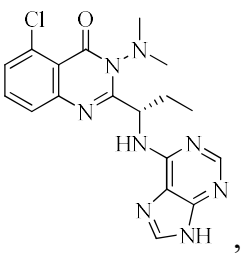
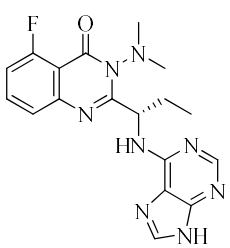
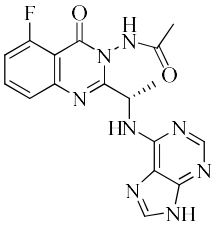
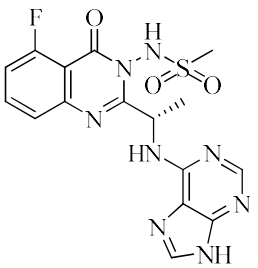
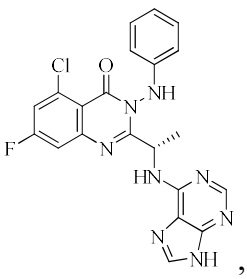
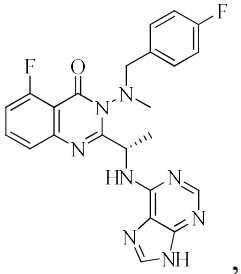
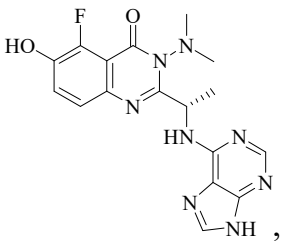
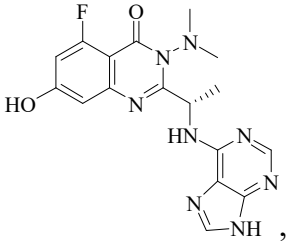
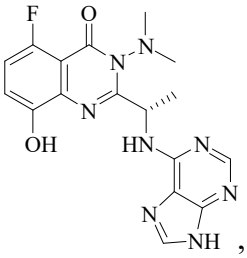
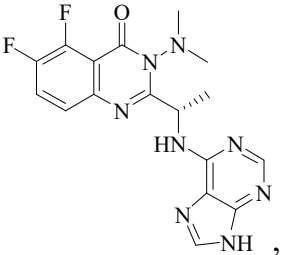
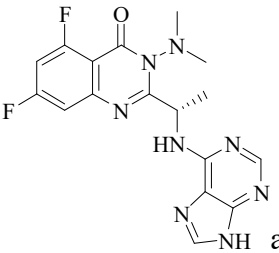
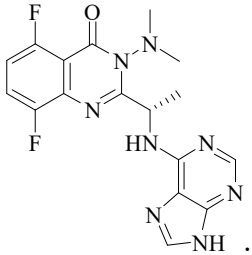

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Embodiment 11

The compound, the pharmaceutically acceptable salt thereof, the stereoisomer thereof and the deuterated compounds thereof according to any one of embodiment 1a or embodiment 1-10, selected from the following compounds:




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and

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Embodiment 12

A pharmaceutical formulation, comprising the compound, the pharmaceutically acceptable salt thereof, the stereoisomers thereof or the deuterated compounds thereof according to any one of embodiment 1a or embodiment 1-11 and one or more pharmaceutically acceptable carriers.

Embodiment 13

The compound, the pharmaceutically acceptable salt thereof, the stereoisomer thereof and the deuterated compounds thereof according to any one of embodiment 1a or embodiment 1-11 or the drug combination of embodiment 12 in the preparation of the compounds for the treatment and / or prevention of inflammatory diseases and / or tumor medicament.

Embodiment 14

A method for the treatment and / or prevention of inflammatory diseases and / or tumor, the method comprising administering to a subject in need thereof an effective amount of a therapeutic compound, the pharmaceutically acceptable salt thereof, the stereoisomer thereof and the deuterated compounds thereof according to any one of embodiment 1a or embodiment 1-11 or therapeutically effective amount of the composition of embodiment 12.

Embodiment 15

A use of the compound, the pharmaceutically acceptable salt thereof, the stereoisomers thereof or the deuterated compounds thereof according to any one of embodiment 1a or embodiment 1-11 for the manufacture of a medicament for the treatment and/or prevention of inflammatory disease and/or tumor.

Embodiment 16

In embodiment 13,14, and 15, wherein inflammatory disease selected from allergies, asthma, rheumatoid arthritis, osteoarthritis, allergic conjunctivitis, allergic keratitis, dry eyes, chronic obstructive pulmonary disease (COPD), lupus, psoriasis, multiple sclerosis and advanced kidney disease, and the described tumors are from leukemia, lymphoma, myeloproliferative disease, non-Hodgkin's lymphoma and chronic idiopathic myelofibrosis.

Mode of execution

Define

As used herein, the term “halogen atom” refers to fluorine atom, chlorine atom, bromine atom

or iodine atom.

As used herein, the term "alkyl" means a straight-chain or branched, having no double or triple bonds hydrocarbon group, including, e.g., “C_{1-6}-alkyl”, “C_{1-5}-alkyl”, “C_{1-4}-alkyl” and “C_{1-3}-alkyl”, each having 1 to 6 carbon atoms, 1 to 5 carbon atoms, 1 to 4 carbon atoms and 1 to 3 carbon atoms. Examples thereof including but not limited to, e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-methylpropyl, 1-methylpropyl, 1,1-dimethylethyl, n-pentyl, 3-methylbutyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, n-hexyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 2-ethylbutyl, 1,2-dimethylpropyl and the like.

As used herein, the term "cycloalkyl" refers to a hydrocarbon group having no double or triple bonds cyclic. From atoms, a cycloalkyl group having a ring formed of carbon atoms, the cycloalkyl groups include 3-14 membered cycloalkyl, 3-12 membered cycloalkyl, 3-10 membered cycloalkyl, 3-8 membered cycloalkyl, 3-6 membered cycloalkyl, 5-10 membered cycloalkyl, 5-8 membered cycloalkyl, and 4-6 membered cycloalkyl, each having 3 to 14 ring carbon atoms, 3-12 ring-forming carbon atoms, 3 to 10 ring carbon atoms, 3 to 8 ring carbon atoms, 3 to 6 ring carbon atoms, 5 to 10 ring carbon atoms, 5 to 8 ring carbon atoms and 4-6 ring-forming carbon atoms. From the ring number of the cycloalkyl group, the cycloalkyl group includes monocyclic cycloalkyl and fused cycloalkyl. Single ring group has only one ring. Cycloalkyl means a fused ring composed of two or more monocyclic cycloalkyl share two adjacent carbon atoms each formed group. Single ring groups include 3-8 membered monocyclic cycloalkyl, 3-6 membered monocyclic cycloalkyl, 5-8 membered monocyclic cycloalkyl, and 5-6 membered monocyclic cycloalkyl. Specific examples of monocyclic cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl group, and a cyclooctyloxy group. Monocyclic cycloalkyl groups may be further substituted by, e.g., C_{1-6} alkyl substituted by by 3-8 membered monocyclic cycloalkyl groups include, but are not limited to: methyl-cyclopropyl, dimethyl-cyclopropyl, methylcyclopropyl thietanyl, dimethyl cyclobutyl, methyl-cyclopentyl, dimethyl-cyclopentyl, methyl cyclohexyl, and dimethyl cyclohexane group. Fused cycloalkyl groups include 6-14 membered fused cycloalkyl, 6-12 membered fused cycloalkyl, 8-12 membered fused cycloalkyl, 7-10 membered fused cycloalkyl, such as 6-14 membered bicyclic cycloalkyl, 6-12 membered bicyclic cycloalkyl, 8-12 membered bicyclic cycloalkyl, 7-10 membered bicyclic ring group. Examples of fused

ring groups include, but are not limited to: bicyclo [3.1.0] hexanyl, bicyclo [4.1.0] heptanyl, bicyclo [2.2.0] hexanyl, bicyclo [3.2.0] heptanyl, bicyclo [4.2.0] octyl, octahydro-1H- indenyl, decahydronaphthalenyl, and fourteen hydrogen phenanthryl.

As used herein, the term "alkenyl" refers to a linear or branched alkenyl containing a double bond, including, e.g., "C_{2-4}-alkenyl", "C_{2-5}-alkenyl", "C_{2-4}-alkenyl", "C_{2-3}-alkenyl" and the like; examples thereof including but not limited to, e.g., ethenyl, 1-propenyl, 2-propenyl, 1-methylethenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-methyl-1-propenyl, 2-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-methyl-1-butenyl, 2-methyl-1-butenyl, 3-methyl-1-butenyl, 1-methyl-2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-methyl-3-butenyl, 2-methyl-3-butenyl, 3-methyl-3-butenyl, 1,1-dimethyl-2-propenyl, 1,2-dimethyl-1-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-1-propenyl, 1-ethyl-2-propenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-methyl-1-pentenyl, 2-methyl-1-pentenyl, 3-methyl-1-pentenyl, 4-methyl-1-pentenyl, 1-methyl-2-pentenyl, 2-methyl-2-pentenyl, 3-methyl-2-pentenyl, 4-methyl-2-pentenyl, 1-methyl-3-pentenyl, 2-methyl-3-pentenyl, 3-methyl-3-pentenyl, 4-methyl-3-pentenyl, 1-methyl-4-pentenyl, 2-methyl-4-pentenyl, 3-methyl-4-pentenyl, 4-methyl-4-pentenyl, 1,1-dimethyl-2-butenyl, 1,1-dimethyl-3-butenyl, 1,2-dimethyl-1-butenyl, 1,2-dimethyl-2-butenyl, 1,2-dimethyl-3-butenyl, 1,3-dimethyl-1-butenyl, 1,3-dimethyl-2-butenyl, 2,2-dimethyl-3-butenyl, 2,3-dimethyl-1-butenyl, 2,3-dimethyl-2-butenyl, 2,3-dimethyl-3-butenyl, 3,3-dimethyl-1-butenyl, 3,3-dimethyl-2-butenyl, 1-ethyl-1-butenyl, 1-ethyl-2-butenyl, 1-ethyl-3-butenyl, 2-ethyl-1-butenyl, 2-ethyl-2-butenyl, 2-ethyl-3-butenyl, 1,1,2-trimethyl-2-propenyl, 1-ethyl-1-methyl-2-propenyl, 1-ethyl-2-methyl-1-propenyl, 1-ethyl-2-methyl-2-propenyl, 1,3-butadiene, 1,3-pentadiene, 1,4-pentadiene, 1,4-hexadiene, and the like.

As used herein, the term "cycloalkenyl" refers to a cyclic hydrocarbon group having at least one double bond. Cycloalkenyl include C_{3-8}-cycloalkeny, C_{3-7}- cycloalkeny and C_{3-6}-cycloalkeny, having one double bond and each having 3 to 8 carbon atoms, 3 to 7 carbon atoms and 3 to 6 carbon atoms. Cycloalkenyl also include C_{4-8}- cyclodienyl, C_{4-7}- cyclodienyl and C_{4-6}- cyclodienyl, having two double bonds and each having 4 to 8 carbon atoms, 4 to 7 carbon atoms and 4 to 6 carbon atoms. Cycloalkenyl further include a cyclic hydrocarbon group having three double bonds or four double bonds. Examples thereof including but not limited to, e.g. cyclopropenyl, cyclobutenyl, cyclopentenyl, 1, 3-cyclopentadienyl, cyclohexenyl,

1,4-cyclohexadienyl and cyclooctatetraenyl.

As used herein, the term "alkynyl" refers to a linear or branched alkynyl containing a triple bond and include C_{2-6}- alkynyl, C_{2-5}- alkynyl, C_{2-4}-alkynyl and C_{2-3}-alkynyl each having 2 to 6 carbon atoms, 2 to 5 carbon atoms, 2 to 4 carbon atoms and 2 to 3 carbon atoms. Examples thereof including but not limited to, e.g., ethynyl, 2-propynyl, 2-butynyl, 3-butynyl, 1-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-methyl-2-butynyl, 1-methyl-3-butynyl, 2-methyl-3-butynyl, 1,1-dimethyl-2-propynyl, 1-ethyl-2-propynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-methyl-2-pentynyl, 1-methyl-3-pentynyl, 1-methyl-4-pentynyl, 2-methyl-3-pentynyl, 2-methyl-4-pentynyl, 3-methyl-4-pentynyl, 4-methyl-2-pentynyl, 1,1-dimethyl-2-butynyl, 1,1-dimethyl-3-butynyl, 1,2-dimethyl-3-butynyl, 2,2-dimethyl-3-butynyl, 1-ethyl-2-butynyl, 1-ethyl-3-butynyl, 2-ethyl-3-butynyl, 1-ethyl-1-methyl-2-propynyl, and the like.

As used herein, the term "alkoxy" refers to a group connected in a manner of "alkyl-O-", wherein "alkyl" is as defined above. Alkoxy include C_{1-6}-alkoxy, C_{1-5}-alkoxy, C_{1-4}-alkoxy and C_{1-3}-alkoxy each having 1 to 6 carbon atoms, 1 to 5 carbon atoms, 1 to 4 carbon atoms and 1 to 3 carbon atoms. Examples thereof including but not limited to, e.g., methoxyl, ethyoxyl, propoxy, isopropoxy, butoxyl, isobutoxy, tert-butoxy, 4-sec-butoxy, pentyloxy, neopentyloxy, hexyloxy, and the like.

As used herein, the term "aryl" refers to a cyclic aromatic group with all ring atoms being carbon atoms. According to the number of the ring carbon atoms, aryl include 6-14 membered aryl, 8-14 membered aryl, 6-10 membered aryl and 6-8 membered aryl each having 6 to 14 ring carbon atoms, 8 to 14 ring carbon atoms, 6 to 10 ring carbon atoms and 6 to 8 ring carbon atoms. From the number of rings of the aryl group, aryl include monocyclic aryl and condensed aryl. Monocyclic aryl refers to a completely unsaturated aryl, such as phenyl, cyclooctatetraenyl, and the like. Condensed aryl refers to a condensed ring group formed by two or more cyclic structures sharing two adjacent carbon atoms with each other, wherein at least one ring is an unsaturated aromatic ring, including unsaturated condensed aryl, such as naphthyl, phenanthryl, and the like, further including partially saturated condensed aryl, such as, benzo C_{3-8}-cycloalkyl, benzo C_{4-8}-cycloalkenyl, specific examples such as 2,3-dihydro-1*H*-indenyl, 1*H*-indenyl, 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl, and the like.

As used herein, the term "heterocyclyl" refers to a cyclic group containing at least one

heteroatom referring to N,O or S. Heterocyclyl may have 3 to 14 ring atoms (referred to 3-14 membered heterocyclyl, the same below), 3 to 10 ring-forming atoms, 3 to 8 ring atoms, 4 to 12 ring atoms, 5 to 10 ring atoms, 5 to 8 ring atoms, or 5-6 ring-forming atoms. Heterocyclyl include monocyclic heterocycloalkyl, bicyclic heterocycloalkyl, heterocycloalkenyl, monocyclic heteroaryl and bicyclic heteroaryl, and the like.

Monocyclic heterocycloalkyl refers to a monocyclic cycloalkyl, wherein the at least one carbon atom is replaced by a heteroatom selected from N, O and S. Monocyclic heterocycloalkyl group can have 3-8 ring-forming atoms (Acronym 3-8 membered monocyclic heterocycloalkyl, the same below), 3-6 ring atoms, 5-6 ring atoms, or 5-8 ring-forming atoms, and a monocyclic heterocycloalkyl group have 1 to 2,1 to 3 or 1 to 4 as a ring atom selected from N, O and S heteroatoms. 3-8 membered monocyclic heterocycloalkyl include but not limited to, e.g., aziridinyl, azetidinyl thietanyl, thietanyl, tetrahydrofuranyl, tetrahydro-pyrrolyl, imidazolidinyl, pyrazolidinyl, 1,4-dioxane, 1,3-dioxane group, a 1,3-dithiane group, piperidinyl, morpholinyl, piperazinyl, etc. further, CH_2 as ring atoms may be oxidized, in addition, monocyclic heterocycloalkyl group can be replaced by oxygen generations, e.g., piperidin-2-one , and the like.

Bicyclic heterocycloalkyl refers to two rings fused with cycloalkyl, wherein the at least one carbon atom is replaced by a heteroatom selected from N, O and S. Bicyclic heterocyclic groups include 6-10 membered bicyclic heteroaryl cycloalkyl group, which comprises 6-10 ring atoms, and 1 to 2,1 to 3 or 1 to 4 as a ring atom selected from N, O and S heteroatoms. 6-10 membered bicyclic heterocycle examples of alkyl groups include but not limited to, e.g., cyclobutane and tetrahydro-pyrrolyl (e.g. 3-azabicyclo [3.2.0] heptane), cyclopentane and tetrahydro-pyrrolyl (e.g. octahydro-cyclopenta [c] and pyrrole), and azetidine and imidazolidinyl (e.g. 2,4,6-azabicyclo [3.2.0] heptane) , and the like.

Heterocycloalkenyl refers to a cycloalkenyl group, wherein the at least one carbon atom is replaced by a heteroatom selected from N, O and S. Heterocyclenyl may have 3-8 ring atoms (referred to as a 3-8 membered heteroaryl cycloalkenyl group, the same below), 5 to 8 ring atoms, or a 5-6 ring atoms and have 1 to 2, 1 to 3 or 1 to 4 as a ring atom selected from N, O and S heteroatoms. 3-8 membered heterocyclenyl groups include but not limited to, e.g., 2,5-dihydro-thienyl, 4,5-dihydro-pyrazolyl, 1,2-dihydro-pyridyl, 3,4-hydrogen -2H- pyranyl, 5,6-dihydro-4H-1,3- oxazinyl, oxetane cycloheptatriene group, thietanyl cycloheptatriene group, aza cycloheptatrienyl, 1,3-diaza-cycloheptatrienyl, azocine alkenyl group. Further, heterocyclenyl may be oxo, such as pyridine-2-one and pyran-4-one, and the like.

Monocyclic heteroaryl group refers to a 5-6 membered monocyclic heteroaryl group, having aromatic character and include 5 to 6 ring atoms and 1 to 4 as a ring atom selected from N, O and S heteroatoms. Monocyclic heteroaryl groups but not limited to, e.g., furyl, thienyl, pyrrolyl, thiazolyl, thiadiazolyl, oxazolyl, oxadiazolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, 1,4-dioxinyl group, 2*H*-1,2-oxazinyl, 4*H*-1,2- oxazinyl, 6*H*-1,2- oxazinyl, 4*H*-1,3- oxazine yl, 6*H*-1,3- oxazinyl, 4*H*-1,4- oxazinyl, pyridazinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, and 1,2,4,5-tetrazinyl, and the like.

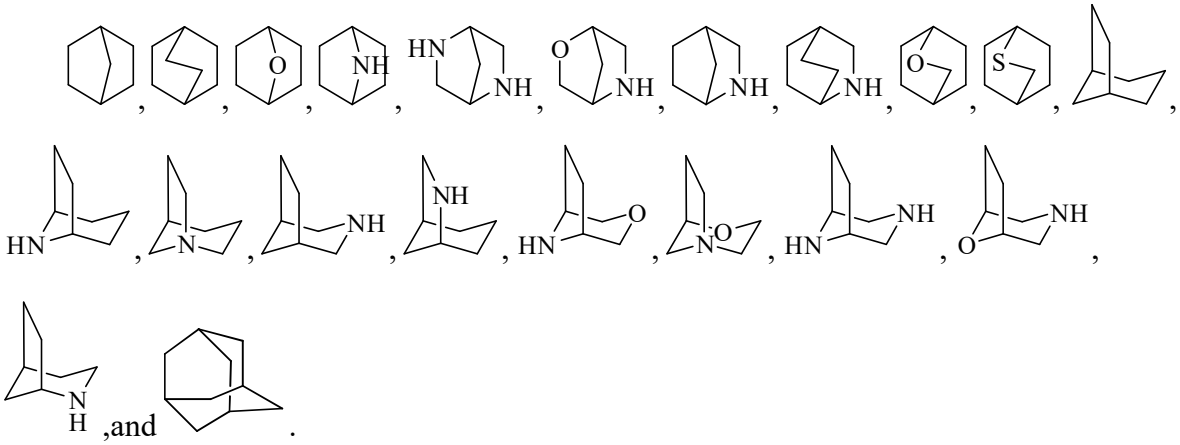
As used herein, bicyclic heteroaryl include bicyclic heteroaryl obtained by (phenyl or a 5-6 membered monocyclic heteroaryl) and (5-6 membered monocyclic heteroaryl) fused, and bicyclic heteroaryl obtained by (benzene group or a 5-6 membered monocyclic heteroaryl) and (C_{3-8} cycloalkeny, C_{4-8} cyclodienyl or a 3-8 membered heterocycloalkenyl) fused, for example, bicyclic heteroaryl obtained by (phenyl or a 5-6 membered monocyclic heteroaryl) and (C_{5-6} cycloalkeny, C_{5-6} cyclodienyl or a 5-6 membered heterocycloalkenyl) fused, and the like. Examples of bicyclic heteroaryl groups obtained by (phenyl or a 5-6 membered monocyclic heteroaryl) and (5-6 membered monocyclic heteroaryl) fused include: benzofuranyl, benzo iso furyl, benzothienyl, indolyl, benzoxazolyl, benzimidazolyl, indazolyl, benzotriazolyl, quinolyl, isoquinolyl, pyridyl and pyrazolyl, pyridyl and pyrrolyl, pyrimido pyrazolyl, pyrrolyl and pyrimidinyl, pyridazinyl and pyrazolyl, pyridazinyl and pyrrolyl, acridinyl, phenanthridinyl, benzo pyridazinyl, phthalazinyl, quinazolinyl, quinoxalinyl, pteridinyl, purinyl, and naphthyridinyl, and the like.

Examples of bicyclic heteroaryl obtained by (phenyl or a 5-6 membered monocyclic heteroaryl) and (C_{3-8} cycloalkeny, C_{4-8} cyclodienyl or a 3-8 membered heterocycloalkenyl) fused include: 1,3-Dihydro-benzofuranyl, benzo [d] [1.3] dioxol-yl, isoindoline-yl, indoline-yl, chromanyl, 1,2, 3,4-tetrahydro-pyrrolo [3,4-c] pyrrolyl, dihydro-pyrrolo pyridinyl, pyrimidinyl dihydro-pyrrolo, dihydropyrrolo pyridazinyl, tetrahydropyrrolo pyridinyl, pyrrolidine and pyrimidinyl, pyridazinyl tetrahydropyrrolo, and the like.

In the present invention, the term "bridged-ring group" refers to a cyclic group in which two rings share two ring atoms not directly connected. Ring atoms may be all carbon atoms or may contain the heteroatom selected from nitrogen, oxygen and sulfur. Bridged-ring group may contain an unsaturated bond. Examples of bridged-ring group include "7-12 membered bridged-ring group " or "7-12 membered bridged heterocyclic group" (referred to as 7-12 membered bridge (hetero) ring group), wherein 7-12 membered bridge (hetero) ring group

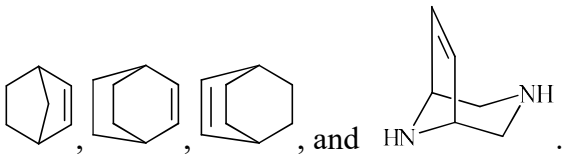
containing 7-12 ring atoms, wherein ring atoms may be all carbon atoms or may contain the heteroatom selected from nitrogen, oxygen and sulfur. The "7-12 membered bridge (hetero) ring group" includes "7-12 membered saturated bridge (hetero) ring group" and "7- 12 membered unsaturated bridge (hetero) ring group. "The 7-12 membered saturated bridge (hetero) ring group "means a bridge (hetero) cyclic group all rings are saturated cyclic group, wherein including, for example, "7-10 membered saturated bridge (hetero) ring group", and "7-8 membered saturated bridge (hetero) ring group" and the like. The "7-12 membered unsaturated bridge (hetero) ring group" refers to the bridge (hetero) cyclic group has at least one ring is an unsaturated cyclic group, including, for example, "7-10 membered unsaturated bridge (hetero) ring group", and "7-8 membered unsaturated bridge (hetero) ring group "and the like.

Examples of the 7-12 membered saturated bridge (hetero) ring group thereof including but not limited to, e.g.:



,and .

Examples of the 7-12 membered unsaturated bridge (hetero) ring group thereof including but not limited to, e.g.:

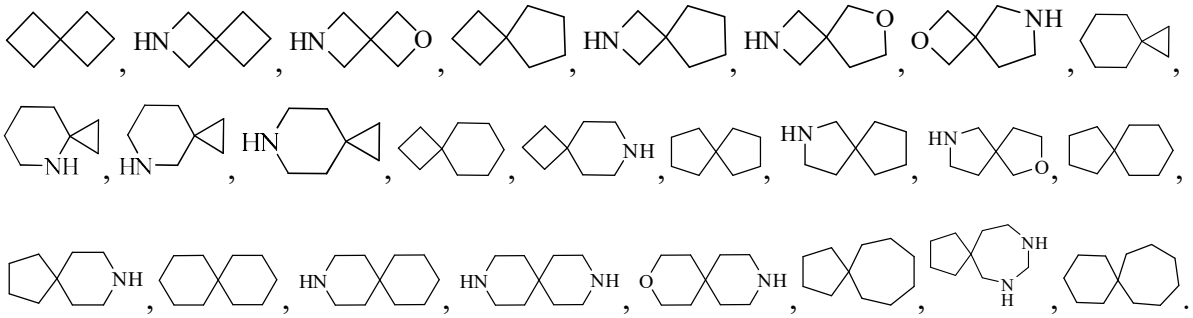


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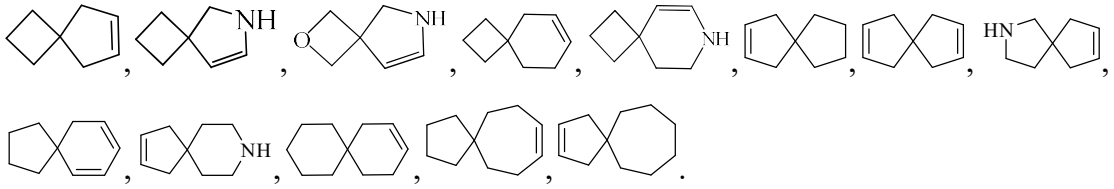
As used herein, the term " spiro-ring group " refers to a cyclic group, wherein at least two rings share a ring atom. Ring atoms may be all carbon atoms or a ring atoms may contain the heteroatom selected from nitrogen, oxygen and sulfur. spiro-ring group may contain an unsaturated bond. Examples include "7-12 membered spiro-ring group" and "7-12 membered spiro heterocyclic group" (referred to as 7- 12 membered spiro (hetero) ring group), which comprises 7-12 ring atoms, may be all carbon atoms or a ring atoms may contain the

heteroatom selected from nitrogen, oxygen and sulfur; "7-11 membered spiro (hetero) ring group", "8-11 membered spiro (hetero) ring group", and "9-10 membered spiro (hetero) ring group." The "7- 12 membered spiro (hetero) ring group "includes" 7-12 membered saturated spiro (hetero) ring group "and" 7-12 membered unsaturated spiro (hetero) ring group. "The" 7-12 membered saturated spiro (hetero) ring group "is refers to the spiro (hetero) cyclic group all rings are saturated cyclic group, including, for example, "7-11 membered saturated spiro (hetero) ring group", "8-11 membered saturated spiro (hetero) ring group "," 9-10 membered saturated spiro (hetero) ring group "and the like. The" 7-12 membered unsaturated spiro (hetero) cyclic group "refers to the spiro (hetero) cyclic group having at least one ring is unsaturated cyclic group, including, for example, "7-11 membered unsaturated spiro (hetero) ring group", "8-11 membered unsaturated spiro (hetero) ring group", "9-10 membered unsaturated spiro (hetero) ring group "and the like.

Examples of the 7-12 membered saturated spiro (hetero) ring group thereof including but not limited to, e.g.:



Examples of the 7-12 membered unsaturated spiro (hetero) ring group thereof including but not limited to, e.g.:



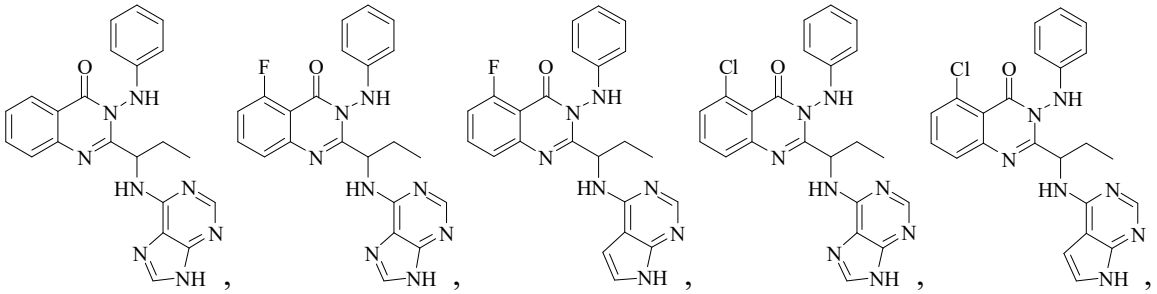
A pharmaceutically acceptable salt of any one of the above compounds of the present application includes alkali metal salts, such as sodium salt, potassium salt, lithium salt, and the like; alkaline-earth metal salts, such as calcium salt, magnesium salt, and the like; other metal salts, such as aluminium salt, iron salt, zinc salt, copper salt, nickel salt, cobalt salt, and the like; inorganic base salts, such as ammonium salt; organic base salts, such as tert-octyl amine

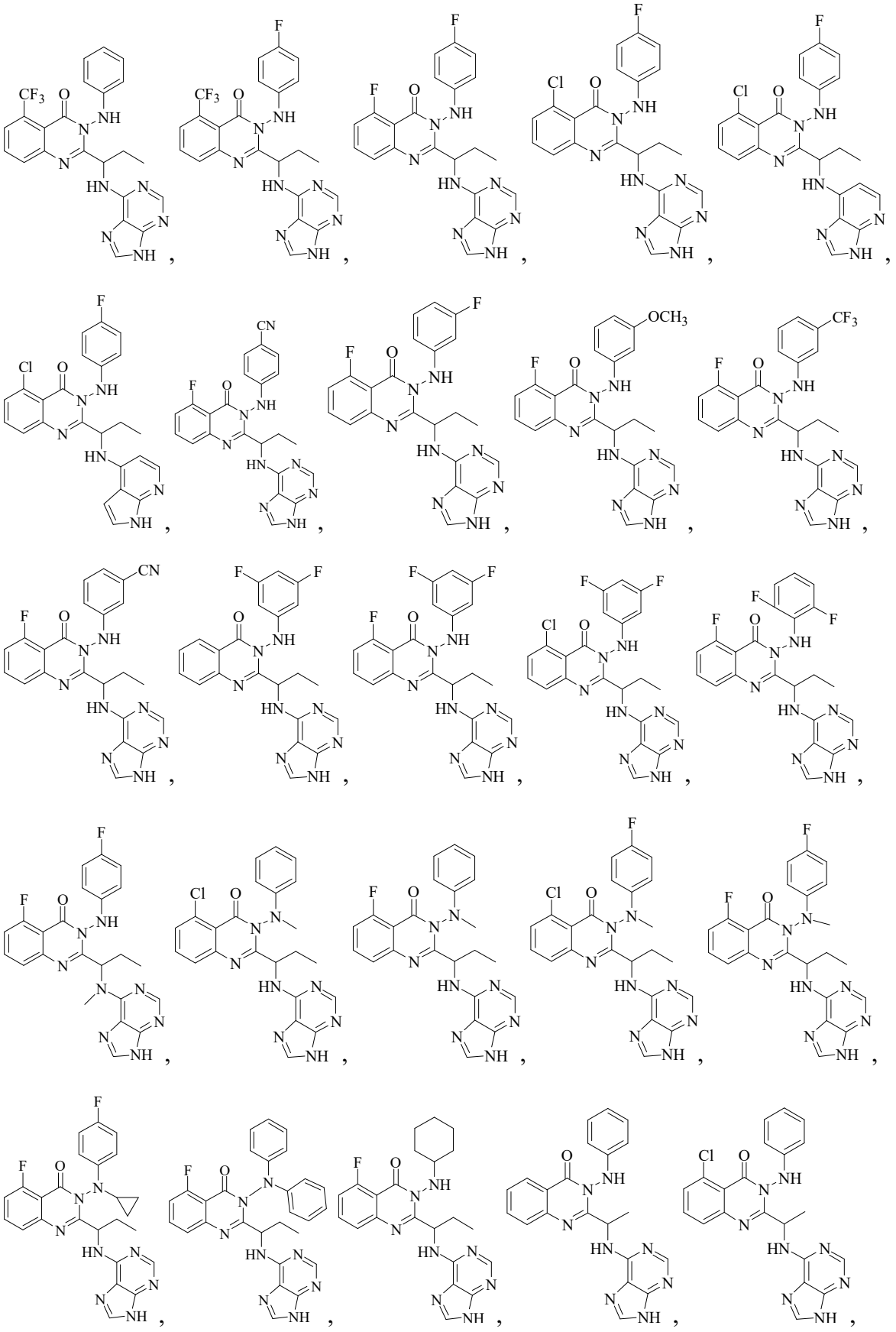
salt, dibenzylamine salt, morpholine salt, glucosamine salt, phenyl glycine-alkyl ester salt, ethylenediamine salt, N-methylglucosamine salt, guanidine salt, diethylamine salt, triethylamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, chloroprocaine salt, procaine salt, diethanolamine salt, N-benzyl-phenylethylamine salt, piperazine salt, tetramethylamine salt, tri(hydroxymethyl)aminomethane salt; when the compound of the present application is basic, a salt can be prepared from pharmaceutically acceptable non-toxic acids including inorganic acids and organic acids, such acid salts include: halogen acid salt, such as hydrofluoric acid salt, hydrochloric acid salt, hydrobromic acid salt, hydroiodic acid salt, and the like; inorganic acids salt, such as nitrate, perchlorate, sulfate, phosphate, and the like; lower alkyl sulfonates, such as methanesulfonate, trifluoromethanesulfonate, ethanesulfonate, and the like; arylsulfonates, such as benzenesulfonate, p-benzenesulfonate, and the like; organic acid salts, such as acetate, malate, fumarate, succinate, citrate, tartrate, oxalate, maleate, and the like; amino acid salts, such as glycine salt, trimethylglycine salt, arginine salt, ornithine salt, glutamine, aspartic acid salt, and the like.

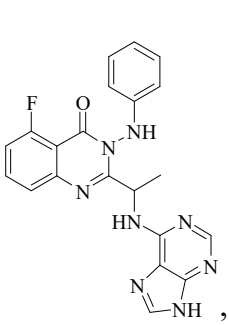
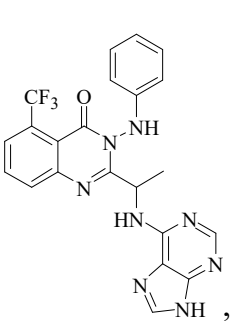
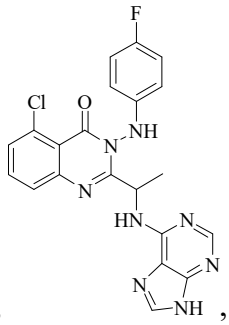
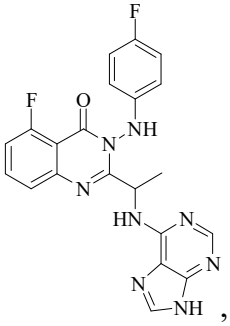
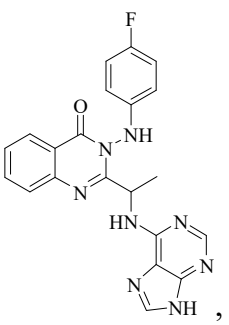
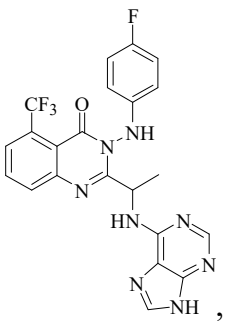
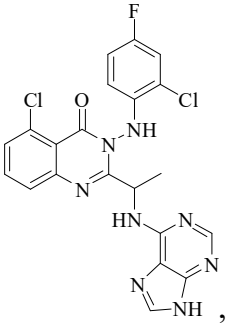
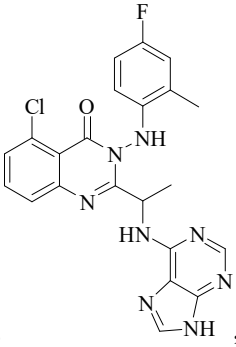
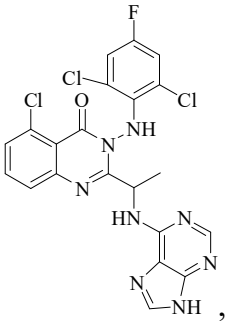
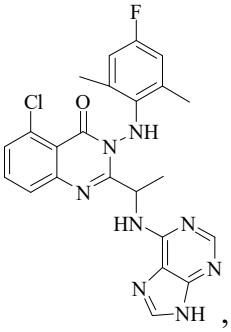
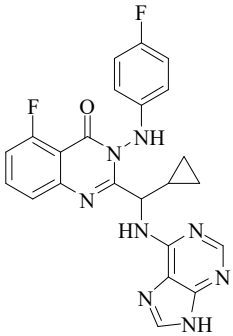
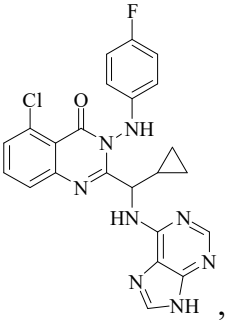
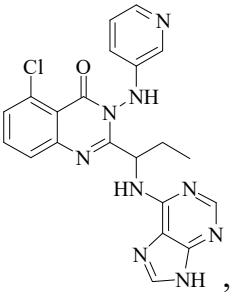
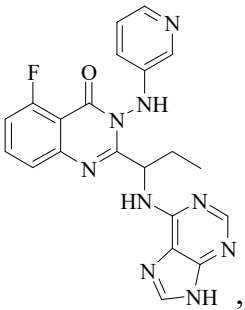
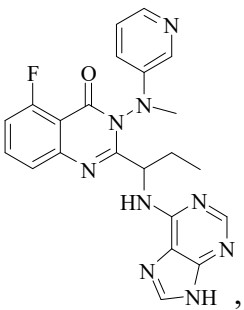
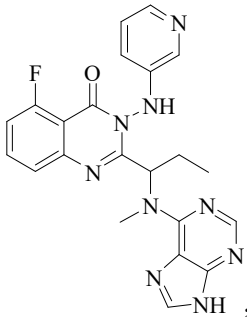
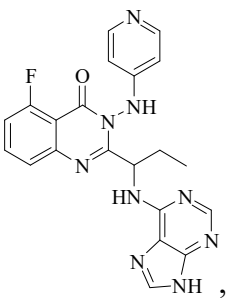
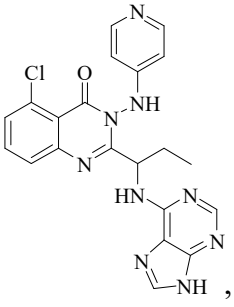
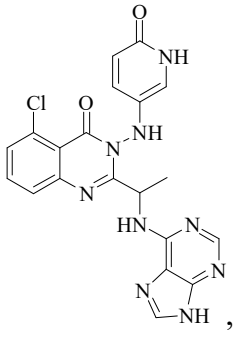
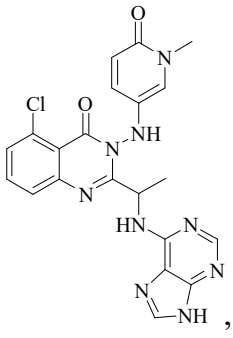
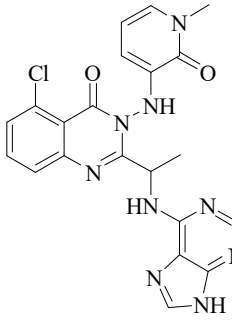
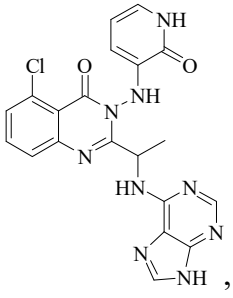
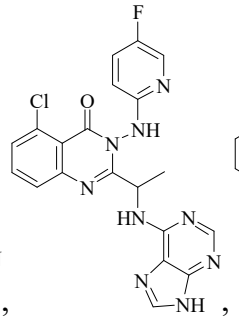
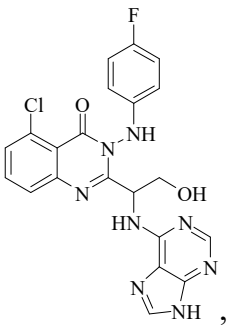
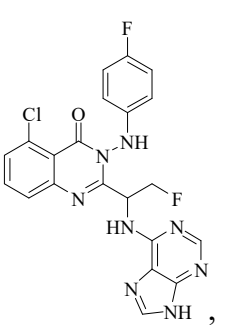
In the present invention, the compound further comprises thereof "stereoisomers." When the compound structure present in one or more asymmetric carbon atoms, enantiomers generated; when the compounds contain an alkenyl group or a cyclic structure, will produce cis / trans isomers; when there is a ketone or oxime compound, it will produce tautomers and the like. All such isomers and mixtures thereof are the scope of the present invention.

In the present invention, the compound further comprises thereof "deuterium content". The compounds of the hydrogen atoms of the isotope deuterium (symbol D) replacing some or all of its material generated also within the scope of the invention.

A compound shown by general formula (I), a pharmaceutically acceptable salt thereof and a stereoisomer thereof, wherein some preferable compounds are as follows:






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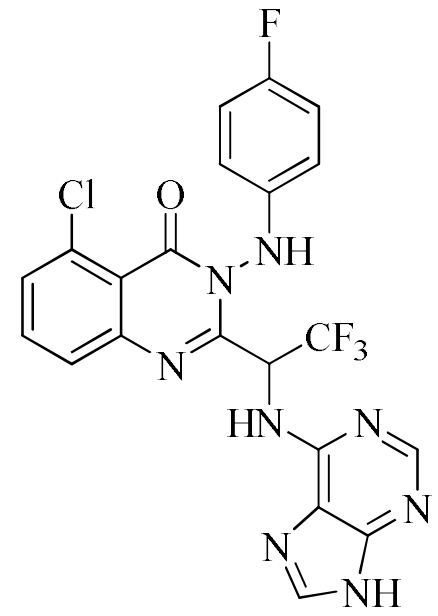
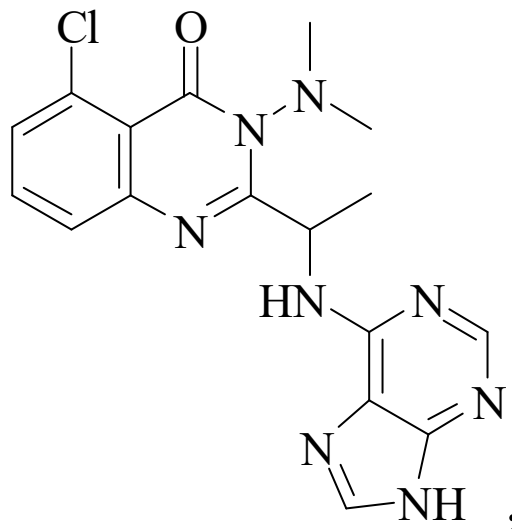
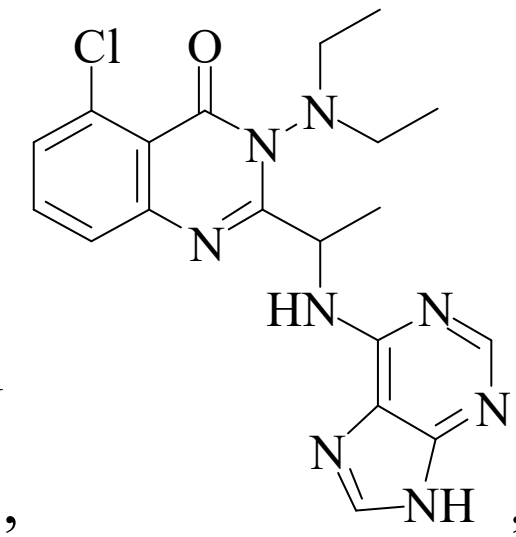
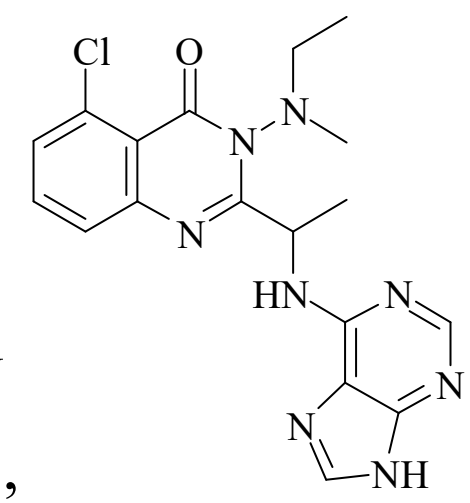
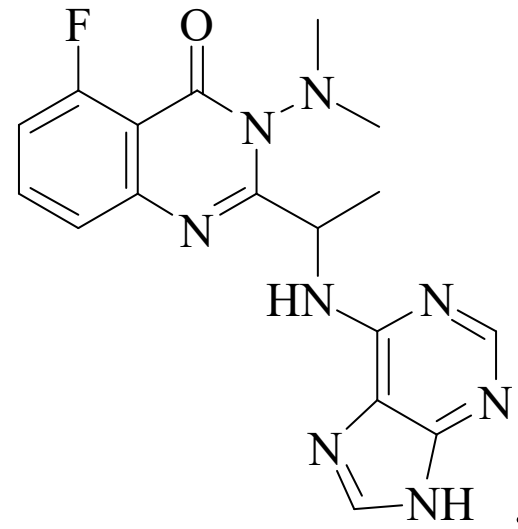
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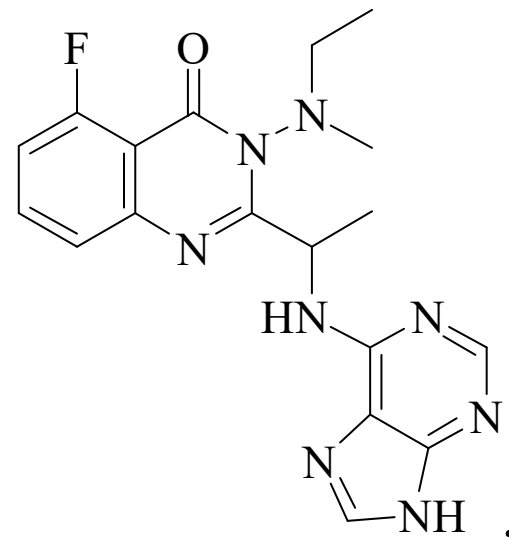
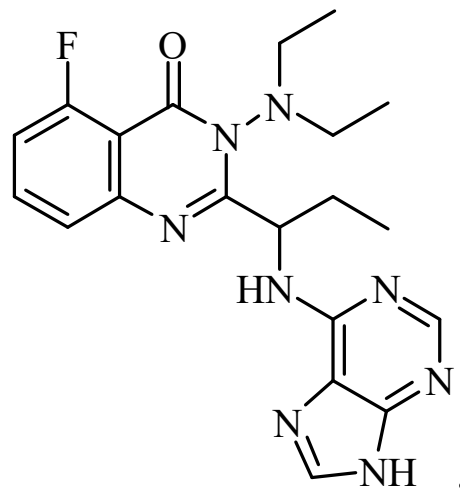
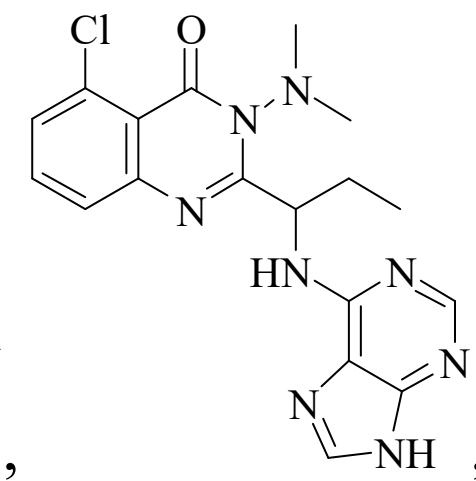
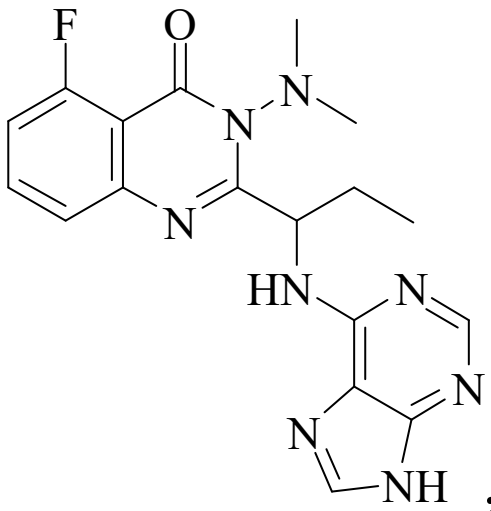
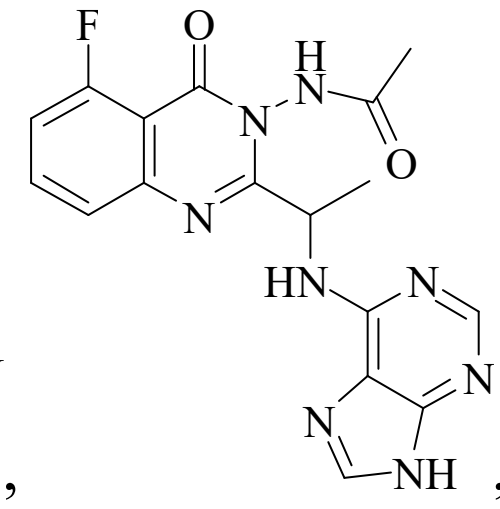
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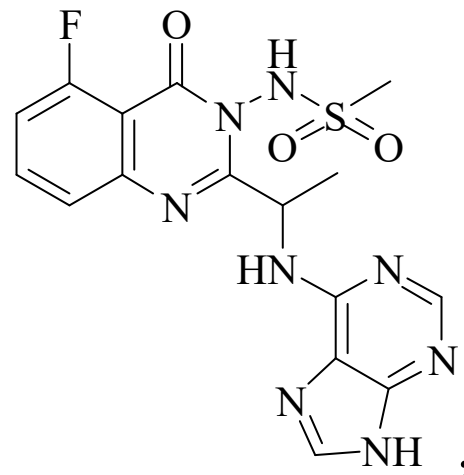
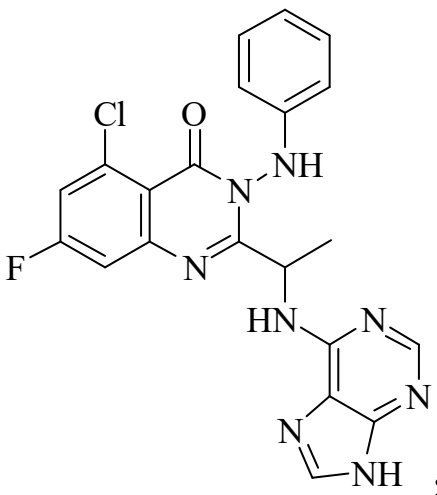
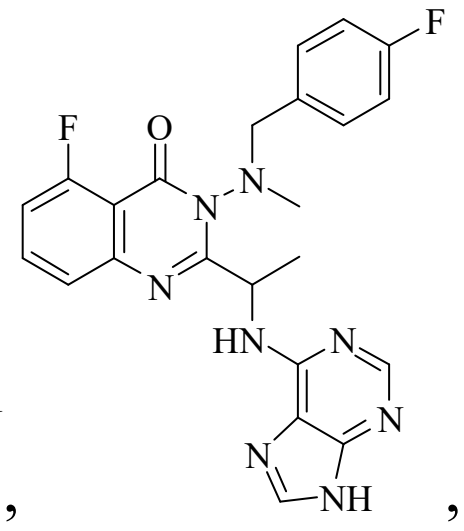
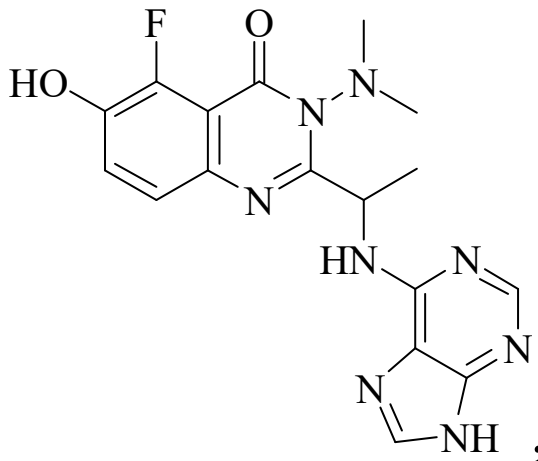
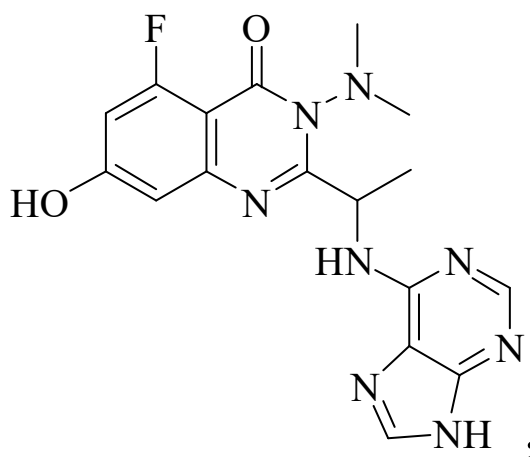
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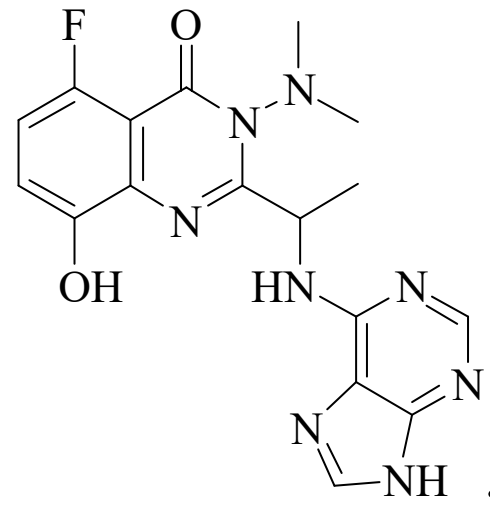
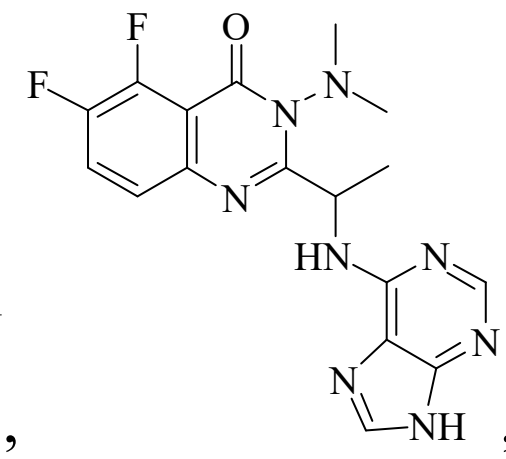
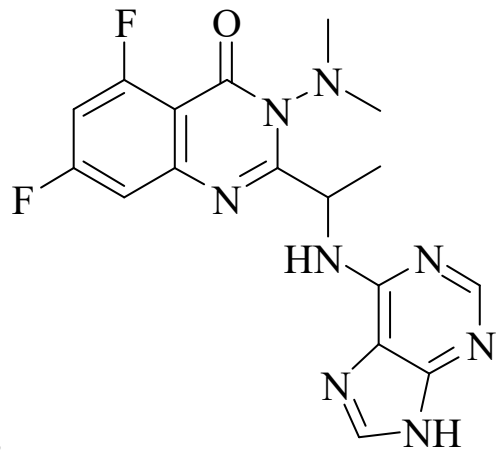
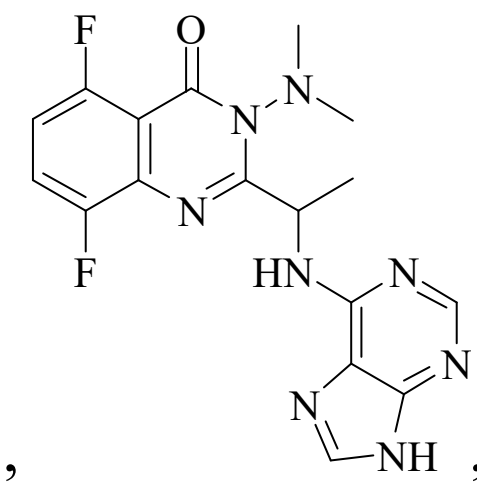
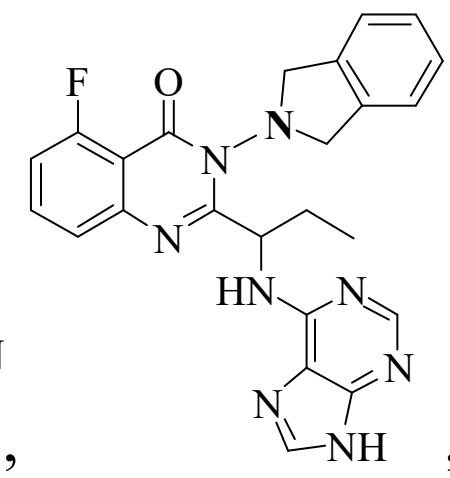
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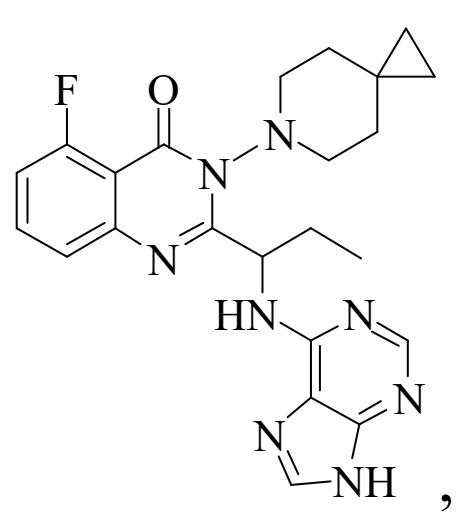
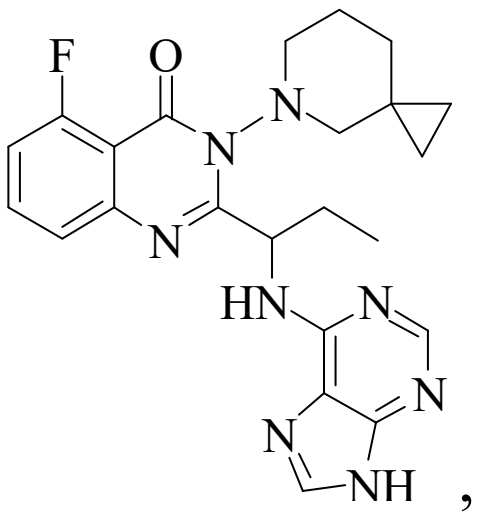
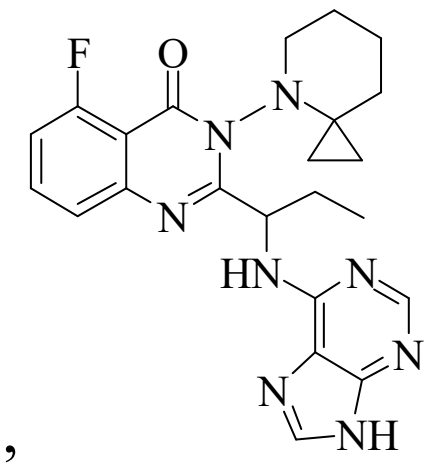
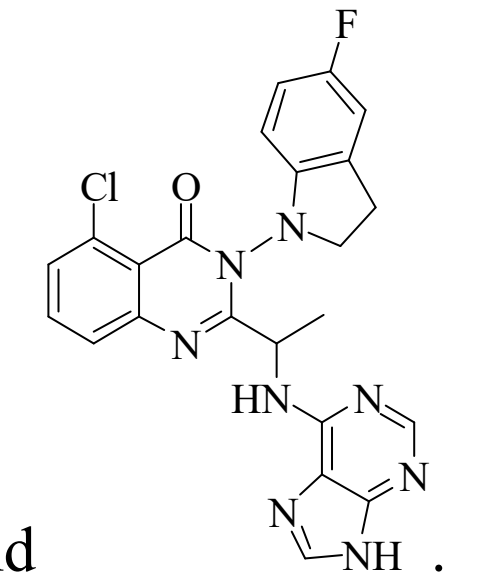
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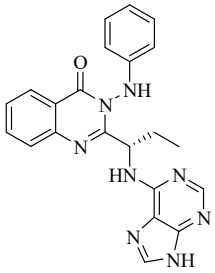
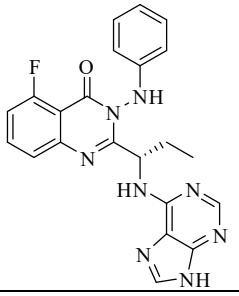
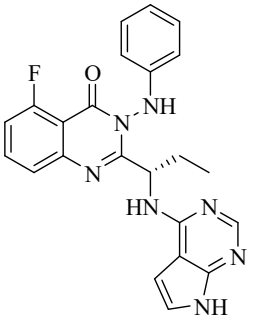
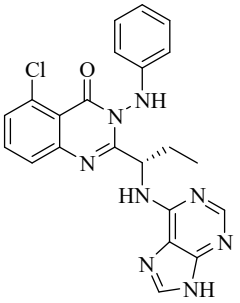
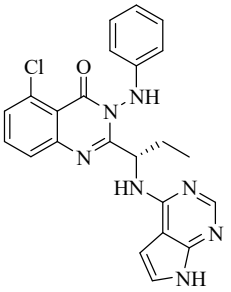
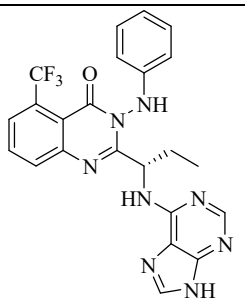
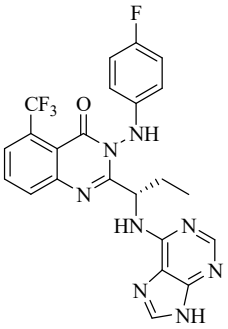
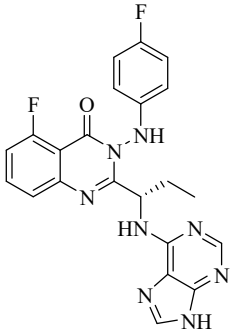
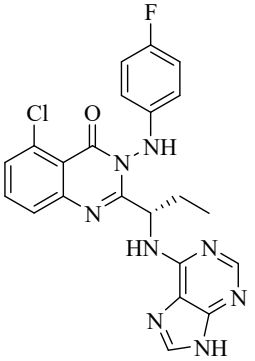
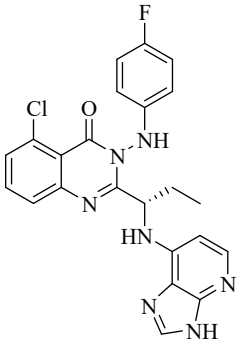
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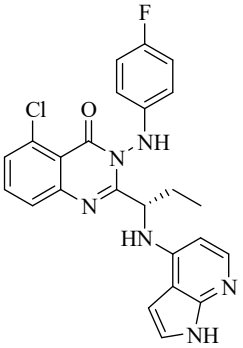
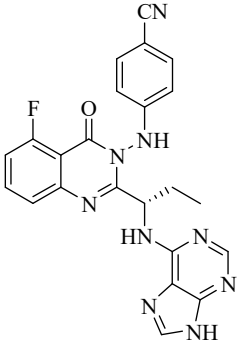
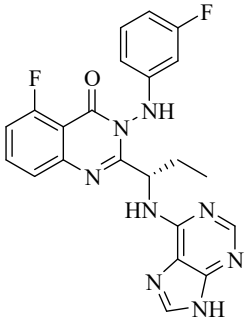
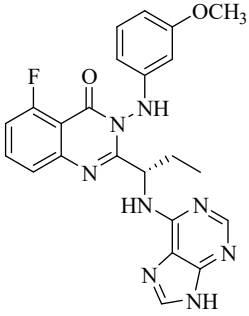
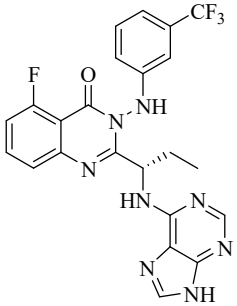
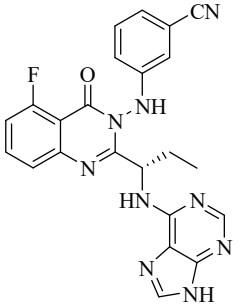
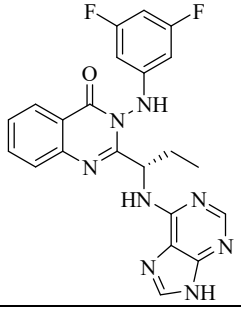
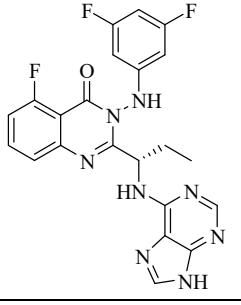
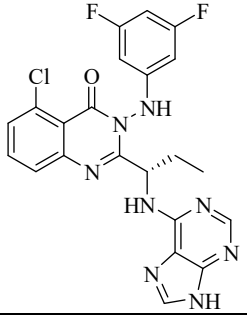
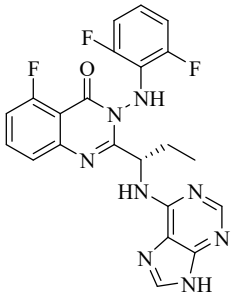
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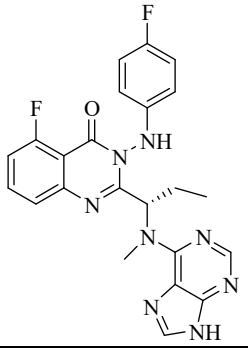
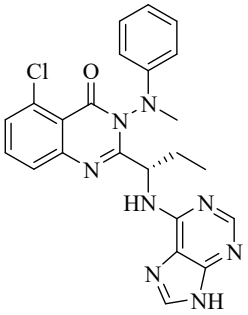
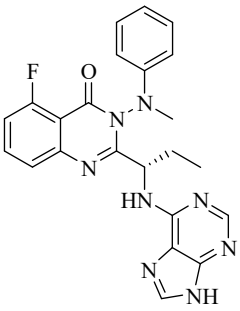
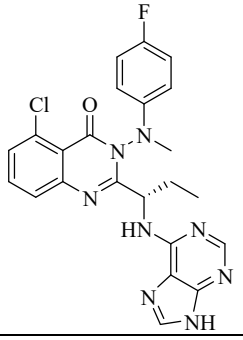
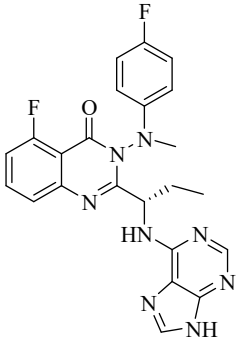
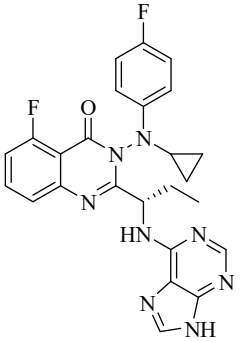
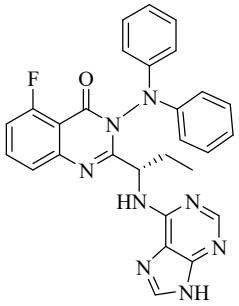
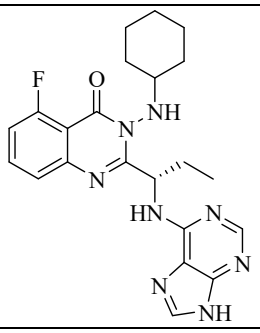
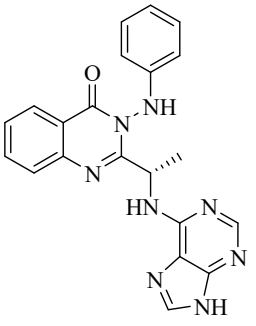
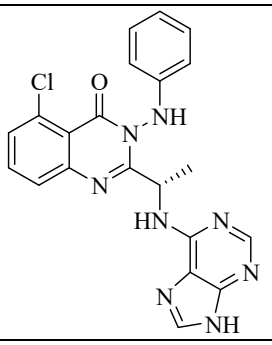
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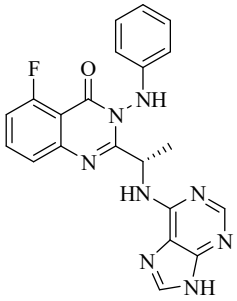
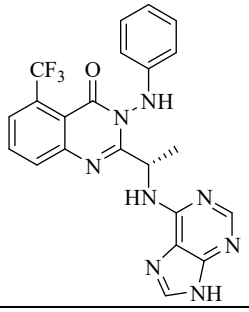
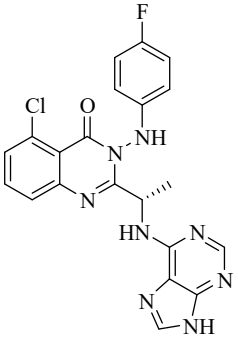
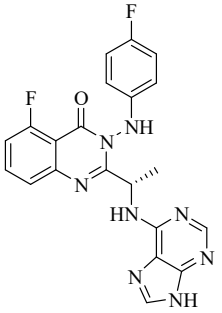
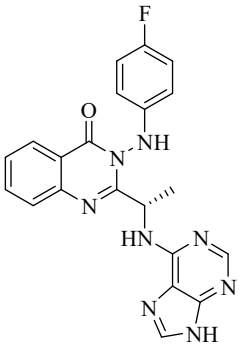
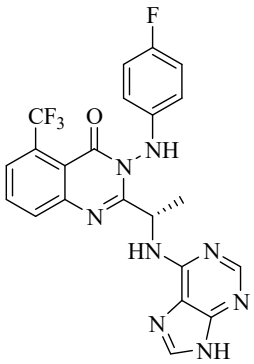
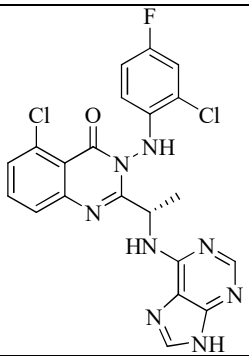
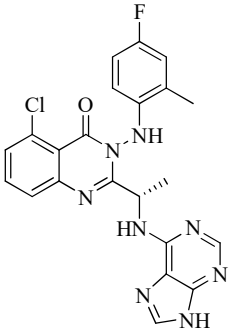
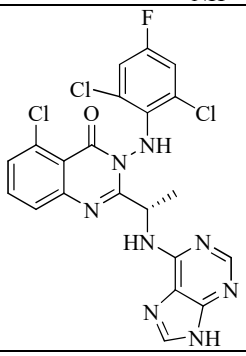
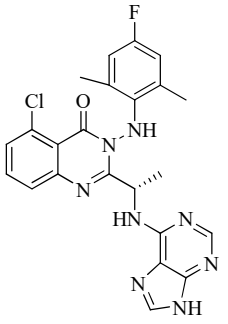
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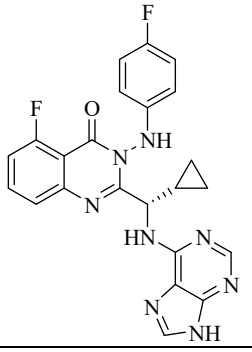
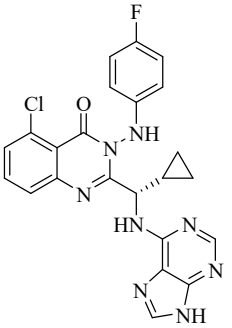
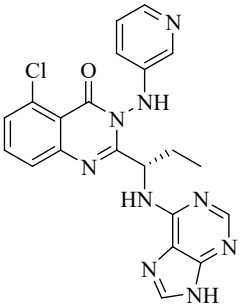
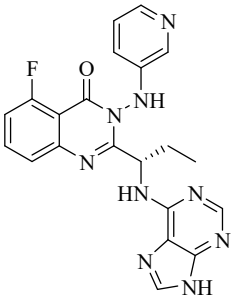
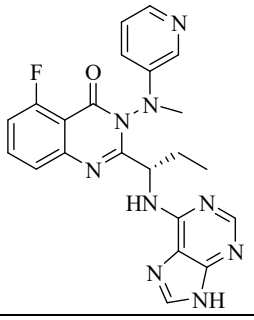
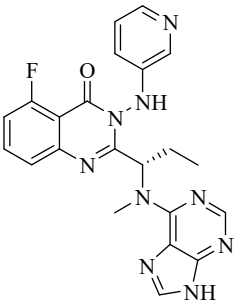
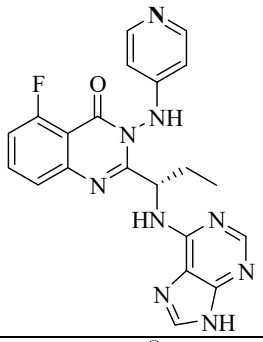
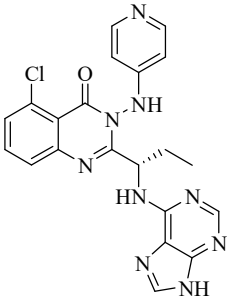
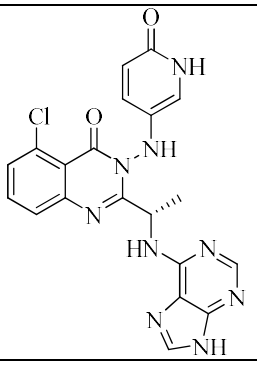
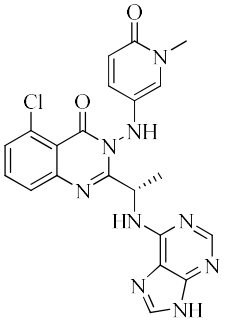
A compound shown by general formula (I), a pharmaceutically acceptable salt thereof and a stereoisomer thereof, wherein some preferable compounds are as follows:

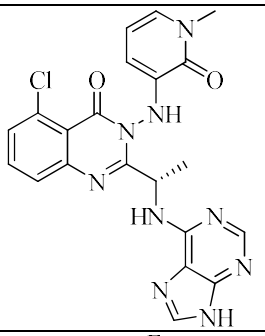
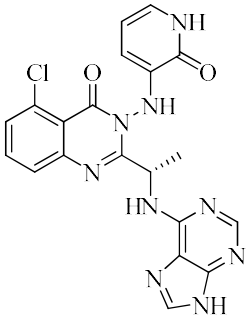
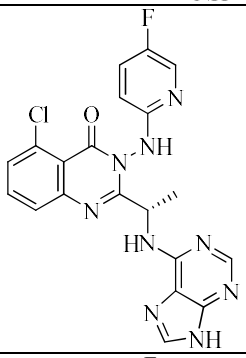
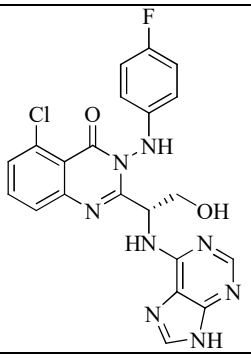
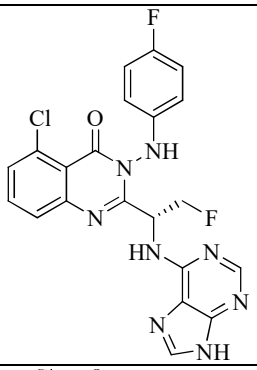
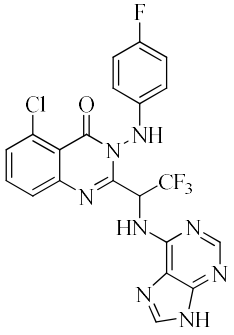
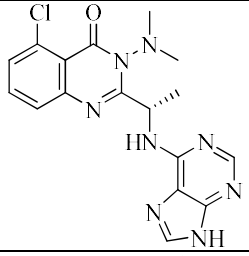
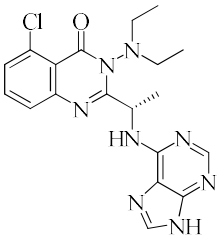
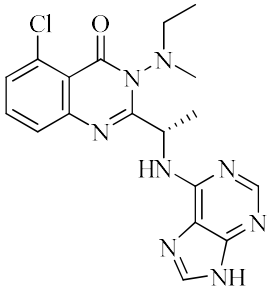
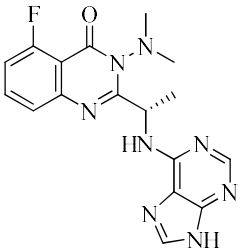
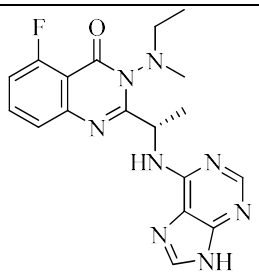
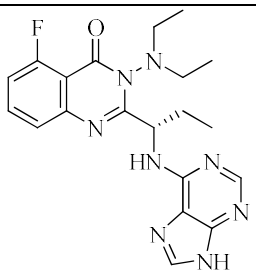
Compound	Structure	Compound	Structure
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5		6	
7		8	
9		10	

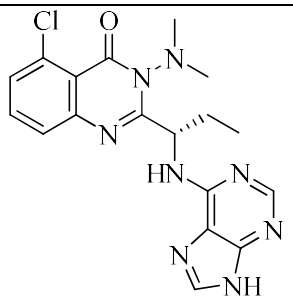
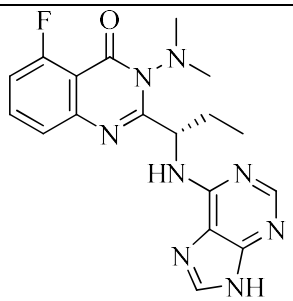
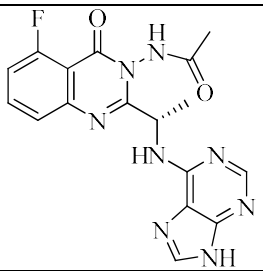
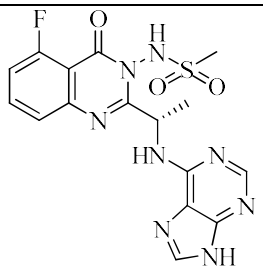
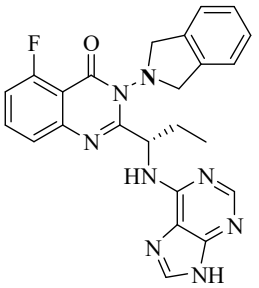
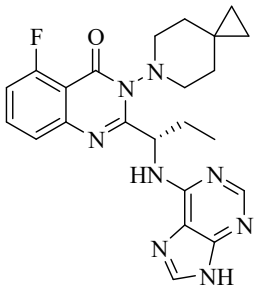
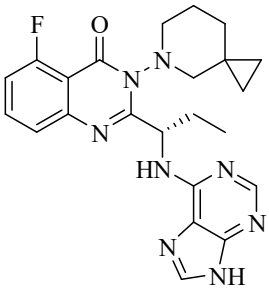
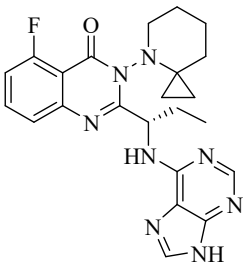
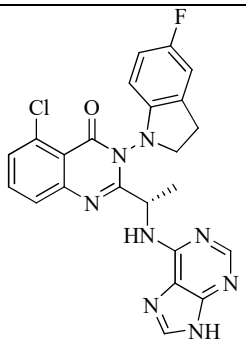
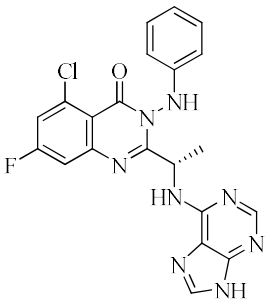
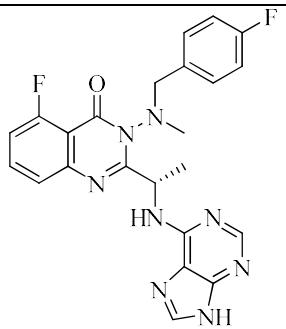
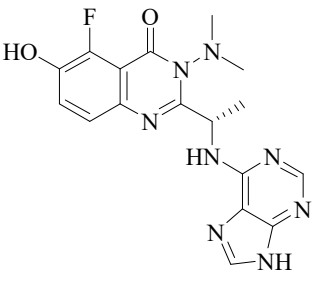
Compound	Structure	Compound	Structure
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13		14	
15		16	
17		18	
19		20	

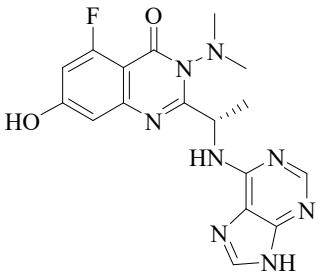
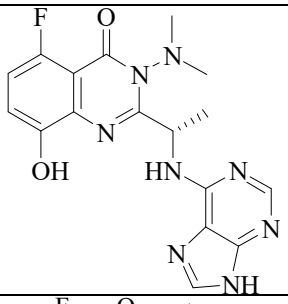
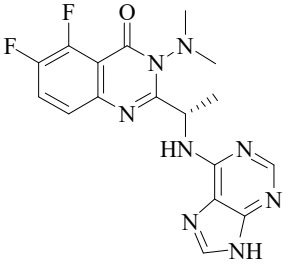
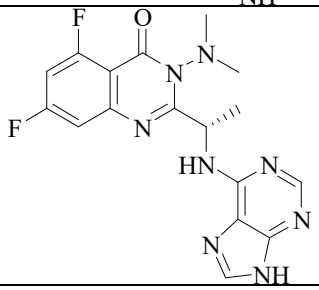
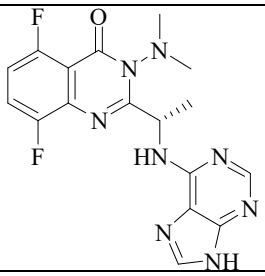
Compound	Structure	Compound	Structure
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23		24	
25		26	
27		28	
29		30	

Compound	Structure	Compound	Structure
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33		34	
35		36	
37		38	
39		40	

Compound	Structure	Compound	Structure
41		42	
43		44	
45		46	
47		48	
49		50	

Compound	Structure	Compound	Structure
51		52	
53		54	
55		56	
57		58	
59		60	
61		62	

Compound	Structure	Compound	Structure
63		64	
65		66	
67		68	
69		70	
71		72	
73		74	

Compound	Structure	Compound	Structure
75		76	
77		78	
79			

The present application also provides a pharmaceutical composition. The composition include the compound of formula (I) of the present application, a pharmaceutically acceptable salt thereof, a stereoisomer thereof and a deuterated compounds thereof, and one or more pharmaceutically acceptable carrier (e.g. excipient, binders, moisturizers, disintegrators, thickeners, etc.)

The compound of formula (I) of the present application, a pharmaceutically acceptable salt thereof, a stereoisomer thereof and a deuterated compounds thereof, can be formulated with one or more pharmaceutically acceptable carriers into a pharmaceutically acceptable pharmaceutical formulation, which is administered to a patient in need of such a treatment in a manner of orally, parenterally, and the like. Such as tablets, granules, capsules, powders, injections, inhalants, sublingual preparations , syrups, gels, ointments, suppositories, lotions, nasal drops, eye drops, sprays, transdermal preparations, etc. These preparations may be prepared by conventional methods, adding a pharmaceutically acceptable carrier such as excipient, binder, solubilizing humectants, disintegrating agents, thickeners, etc.

The present application also provides the compound of formula (I) of the present application, a pharmaceutically acceptable salt thereof, a stereoisomer thereof and a deuterated

compounds thereof, in preparation for the treatment of and/or prevention of inflammatory disease and/or tumor drug use. Wherein inflammatory disease selected from allergies, asthma, rheumatoid arthritis, osteoarthritis, allergic conjunctivitis, allergic keratitis, dry eyes, chronic obstructive pulmonary disease (COPD), lupus, psoriasis, multiple sclerosis and advanced kidney disease, and the described tumors are from leukemia, lymphoma, myeloproliferative disease, non-Hodgkin's lymphoma and chronic idiopathic myelofibrosis.

The invention also provides a preparation method of the compounds:

The preparation in the following, was used the following abbreviations:

DIEA: N,N-Diisopropylethylamine

HATU:o-(7-Azabenzotriazol-1-yl)-N,N,N',N'-te-tramethyluronium hexafluorophosphate

DMF: dimethylformamide

Et: ethyl

EtOH: ethanol;

Bu:butyl

BuOH: butanol

Boc: Tert butoxy carbonyl

DCM: dichloromethane

DMAP: 4-dimethylaminopyridine

TLC: thin-layer chromatography

TFA: trifluoroacetic acid

THF: tetrahydrofuran

Me:methyl

Py:pyridine

EA:ethyl acetate

PE:petroleum ether

Ac:acetyl

HOAc:acetic acid

LS-MS:liquid chromatograph mass spectrometer

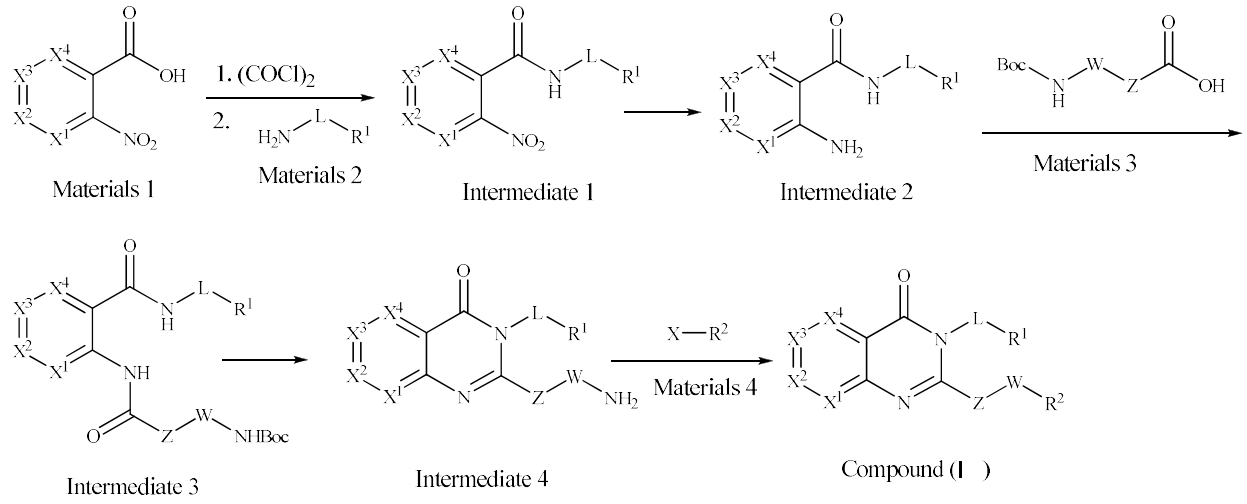
Ts:tosyl

TsCl:4-toluene sulfonyl chloride

THP:tetrahydropyran

Process 1

The compounds of the present invention (where Y was N) can refer to the following preparation method:



Procedure:

(1) Materials 1 (1 equivalent) was dissolved in dichloromethane, and a small amount of DMF was dropped, after that oxalyl chloride (1.1-1.5 equivalent) was dropped at 0℃.The solution was stirred for several hours and concentrated , and dissolved in 1,4-dioxane.the solution of materials 1 and $NaHCO_3$ in 1,4-dioxane and water was added at 0℃ and the mixture was stirred at rt. After the reaction was completed ,the mixture was extracted , concentrated and purified by column chromatography to give intermediate **1**

(2) A solution of intermediate 1was dissolved in solvent (e.g. MeOH or EtOH) .Pd/C was added and degassed with N_2 ,the mixture was stirred and filtered ,concentrated to give intermediate **2.**

(3) A mixture of intermediate (1 equiv.) , materials 3 ,(1.2 -2equiv.), tertiary amine(e.g.DIEA or triethylamine , 1.2 -2equiv.)and Condensation agent (HATU or EDCI, 1-1.2 equiv.) in DCM (DMF or DMA), was stirred at rt, After the reaction was completed ,the mixture was concentrated and purified by column chromatography to give intermediate **3**

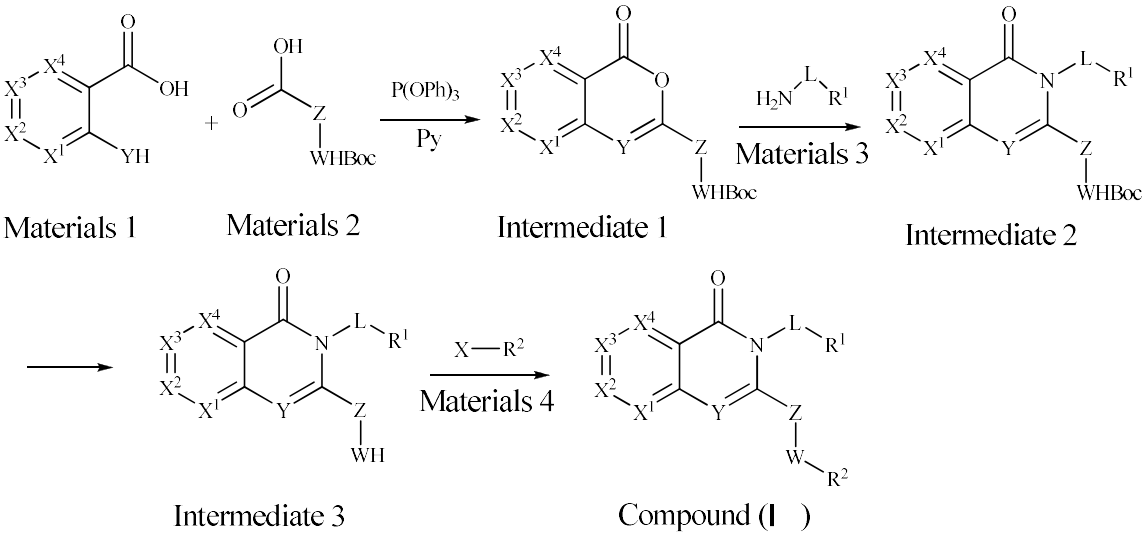
(4) A solution of intermediate **3** in an organic solvent(e.g ethanol) was kept at room temperature. To this solution was added Hydrochloric acid, or gaseous hydrogenchloride through bubbling, the mixture was heated for several hours until intermediate **3** can no

longer be detected. The reaction mixture was then concentrated to yield intermediate **4**.

(5) To a solution of intermediate **3** in an organic solvent, such as *tert*-butnaol, was added materials **4** (1-1.5 equiv.), and a base (2-5 equiv.), such as triethylamine, diisopropylethylamine. The resulting mixture was heated to and kept at reflux until intermediate **4** can no longer be detected. After cooled to room temperature, the reaction mixture was concentrated, and product the final compound (I) was isolated by silica gel column chromatography, or preparative HPLC.

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

Process 2



Procedure:

(1)To a solution of materials **1**(1 equiv.) in pyridine was added materials **2** (1-1.5 equiv), triphenoxyphosphine (1-1.5 equiv.). The resulting reaction mixture was heated to 45-85℃, and was stirred at this temperature for several hours to yield intermediate **1**, which was used directly for the next step.

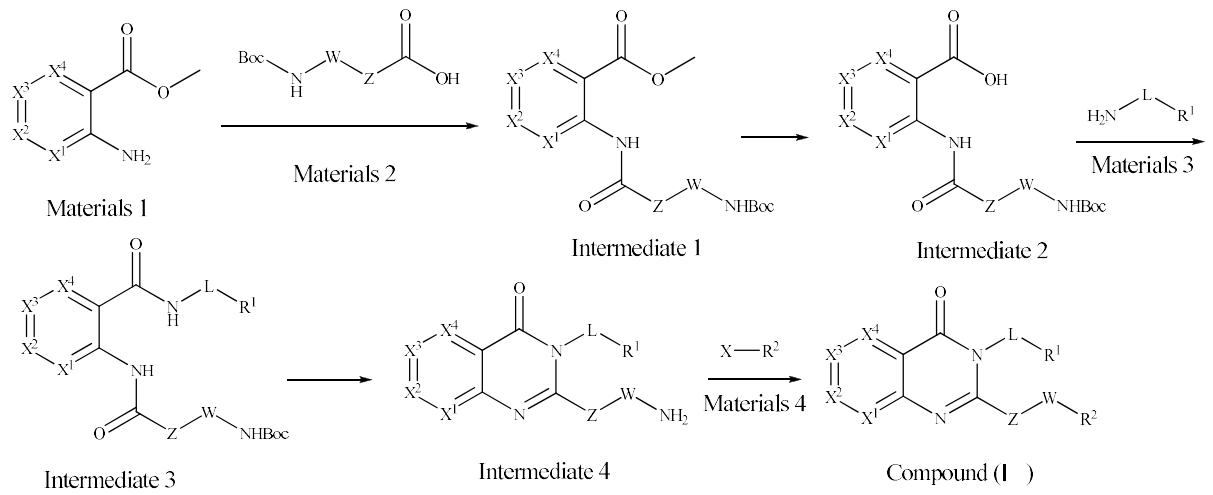
(2)To the reaction mixture of the previous stepcontaining intermediate **1** was added materials **3** (1-1.5 equiv.). The resulting mixture was heated to above 100℃, and was stirred at this temperature for several hours. After cooled to room temperature, the reaction mixture was concentrated, and the intermediate **2** was isolated by column chromatography.

(3)A solution of intermediate **2**(1-1.5 equiv.) in an organic solvent, such as dichloromethane, ethylether, or methanol, was kept at room temperature or cooled in an ice bath. To this solution was added trifluoroacetic acid, or gaseous hydrogenchloride through bubbling, until intermediate **2** can no longer be detected. The reaction mixture was then concentrated to yield intermediate **3**.

(4)To a solution of intermediate **3** in an organic solvent, such as *tert*-butnaol, was added materials **4**(1-1.5 equiv.), and a base (2-5 equiv.), such as triethylamine, diisopropylethylamine. The resulting mixture was heated to and kept at reflux until intermediate **3** can no longer be detected. After cooled to room temperature, the reaction mixture was concentrated, and product (I) was isolated by silica gel column chromatography, or preparative HPLC.

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

Process 3



Procedure:

(1)A mixture of materials1 (methyl or ethyl ester)(1 equiv.), materials 2 ,(1.2 -2equiv.), tertiary amine(e.g.DIEA or triethylamine , 1.5 -3 equiv.)and Condensation agent (HATU or EDCI, 1-1.2equiv.) in DCM (DMF or DMA), was stirred at rt, After the reaction was completed ,the mixture was extracted ,concentrated and purified by column chromatography to give intermediate **1**

(2)The intermediate 1 was hydrolyzed under alkaline conditions, the solution was usually added lithium hydroxide, sodium hydroxide or potassium hydroxide, in the solvent of tetrahydrofuran, methanol and water, after the reaction was end , adjusted pH to weak acid, filtered and aqueous phase was extracted , concentrated and combined to give intermediates 2.

(3) A mixture of intermediates 2 (1 equiv.), materials 3, (1-1.5 equiv.), tertiary amine(e.g.DIEA or triethylamine, 1.5-3 equiv.)and Condensation agent (HATU or EDCI, 1-1.2 equiv.) in DCM (DMF or DMA), was stirred at rt, After the reaction was completed ,the mixture was extracted ,concentrated and purified by column chromatography to give intermediate **3**

Procedure 4 and 5 was the same as procedure 4 and 5 in **Process 1.**

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

Specific Embodiments

The above-described present invention will be further described in detail by the following specific embodiments by way of example. However, this should not be understood that the scope of the above subject of the present invention is limited to the following embodiments. Where the present invention is based on the realization of the above technique are within the scope of the invention.

Biological activity tests

The following advantageous effects of the present invention is further illustrated by the biological activity of the compounds of the compounds of the present invention, experiments, other compounds of the present invention is exemplified with the test compounds of the invention have the same beneficial effect, but this should not be understood that the present invention is a compound having only the following advantageous effects.

Experiment 1 Inhibitory activity of the compounds of the present invention in vitro enzymatic assay

Test sample:This present invention compound was conducted as follow.

Experiment method:

1. Prepare 1mM of compound DMSO stock solution first. Dilute the compound to 100X of the final desired highest inhibitor concentration in reaction by 100% DMSO. The highest inhibitor concentration is 10μM. Serially dilute the compound by 100% DMSO and so forth for a total of 10 concentrations which are 2.5μM, 0.625μM, 0.156μM, 0.039μM, 0.009μM, 0.00244μM, 0.61nM, 0.15 nM, 0.04 nM;
2. Transfer 4 μl of compound from source plate to a 96-well plate as the intermediate plate;
3. Add 96 μl of 1x kinase buffer to each well of the intermediate plate. 1x kinase buffer: 50mM HEPES, pH 7.5; 3mM $MgCl_2$, 1mM EGTA, 100mM NaCl, 0.03% CHAPS, 2mM DTT;
4. Mix the compounds in intermediate plate for 10 minute;
5. Transfer 2.5 μl of each well from the 96-well intermediate plate to a 384-well plate in duplicates;
6. Add 2.5 μl of kinase solution to each well of the assay plate. Shake the plate. The final PI3Kδ kinase concentration is 5.7 nM;
7. Add 5 μl of substrate solution (PIP2 substrate and ATP) to each well of the assay plate to start reaction. Shake the plate;
8. Cover the assay plate and incubate at room temperature for 2 hour;
9. Add 10 μl of Kinase-Glo reagent to each well of the assay plate to stop the reaction, shaker for 15 minute before reading on a plate reader for luminescence Caliper reading.
10. IC_{50} calculate

Percent inhibition = (sample RLU - min)/(max-min)*100. or 100-(max- sample RLU)/(max-min)*100

“max” means the RLU of no enzyme control and “min” means the RLU of DMSO control. The curves fitted by XL fit and calculate IC_{50}. the compounds of the present application against CRTH2 receptor

Result:

Table 1 Inhibitory activity of the compounds in enzymatic assay

Compound	IC_{50} on PI3Kδ (nM)
Compound1	100
Compound2	52
Compound4	13
Compound5	86.52
Compound6	33.5
Compound7	26.2
Compound8	28.8
Compound9	14.3
Compound12	47.5
Compound13	86
Compound19	45
Compound22	16.8
Compound23	29
Compound24	11.58
Compound25	34.5
Compound28	36.7
Compound29	27.4
Compound30	5.4
Compound31	28
Compound32	13.6
Compound33	6.5
Compound34	7.2
Compound35	14.3
Compound36	10
Compound37	33
Compound38	27
Compound41	39
Compound42	11
Compound43	4.5
Compound44	85.92
Compound53	27
Compound57	9.3

Compound	IC_{50} on PI3Kδ (nM)
Compound59	3.3
Compound60	3.7
Compound61	4.5
Compound62	43
Compound63	8.3
Compound64	11
Compound65	44.6
Compound71	3.6

Conclusion: As shown in Table **1**, our compounds were potent inhibit PI3Kδ.

Experiment 2 Inhibitory activity of the compounds of the present invention in B cell lymphoma models.

Test sampel: The present invention compounds, synthesized by ourselves, its chemical name and the preparation of new compounds structured as shown in the synthetic example.

Experiment method:

1. Isolate Balb/c mice B cell

(1) Balb/c mice spleen was mashed in the MACS (Miltenyl Biotec) buffer, with 40 microns nylon mesh filter to get single cell suspension.

(2) Centrifuge cell suspension 5 minute at 400 g, 4°C. Discard the supernatant, resuspend the pellet thoroughly in 1ml Red Blood Cell Lysis Buffer. 2minute later, add precooling MACS buffer. 40 microns nylon mesh filter cell suspension. Centrifuge cell suspension 5 minute at 400 g, 4°C. Discard the supernatant.

(3) Add sufficient MACS buffer to the pellet to achieve a concentration of 10^7 cells/ml before add magnetic beads. Add 10μl biotinylated antibody mixture per 10^7 cells, mix and incubate 20 minute on ice. Add 30μl MACS buffer and 20μl biotinylated antibody magnetic beads per 10^7 cells and incubate 20 minute on ice. Add 500 μl MACS buffer to the pellet after centrifuge. Put the MACS separation column in the precooling MACS classifier. Add the cell suspension into MACS separation column. Collect shed not combined antibodies cell.

(4) Detect isolate before and after cell by PE anti-biotin antibody and CD45R(B220) antibody with flow cytometry analysis.

2. The cytotoxicity experiment and determination of IC50

(1) Count fresh isolated B cells with blood count chamber (steps 1-4). Detect cell survival rate by Trypanblue staining and the cell survival rate was more than 98%.

(2) Add medium to cell to achieve density of 3.89 x 10^5 cells/ml. Add 90 µl cell suspension into 96 - well plates by multichannel pipette and get the final cell density of 3.5 ×10^4 cells per well.

(3) The test compounds and reference compounds were dissolved in DMSO as stock solution. Add 10 µl different concentration sample solution in 96-well plate. Each concentration repeat three times. After 30 minutes 37℃ and 5% CO_2 incubation, add the 50µl B cell stimulate mixture: 3µg/ml LPS + 5 ng/ml recombination mice IL - 4 (final concentration)

(4) The cell plate was incubated at 37 ℃ and 5% CO_2 incubator for 72 hours then tested by CTG.

(5) Melt CTG reagent and balance to room temperature, add 50µl/well CTG reagent into 96 - well platewith multichannel pipette. After shake 2 minutes and dark 10 minutes, luminescent signals were detected in Envision

3．Statistical analysis

The curves fitted by Excel 2007and GraphPad Prism 5.0 and calculate IC_{50}. Cell survival rate was calculated using the following formula: V sample/V2 solvent control *100%. V is compound handle well read value, V2 solvent-solvent control is control holes (V2) read the average of the values.

Table 2 Inhibitory activity of the Compounds in B cell lymphoma models

Compound	B cell IC_{50}(µM)
Compound8	0.75
Compound9	0.65
Compound30	0.016
Compound33	0.034
Compound34	0.12
Compound53	0.111
Compound57	0.01
Compound60	0.032
Compound61	0.05
Compound63	0.04
Compound72	0.32

Conclusion: As shown in **Table 2**, our compounds were potent inhibit B cell.

Experiment 3　Activity of the compounds of the present invention in LPS induced TNFα assay

Test sample: The present invention compounds, synthesized by ourselves, its chemical name and the preparation of new compounds structured as shown in the synthetic example.

Experiment method:

BALB/C mice,male,22-25 g. 25 mice were divided into five groups:the model group receiving vehicle, Compound 30 group, Compound 33group, Compound 53 group,CAL-101 group　receiving correrspondingcompound 30 mg/kg. Mice were treated lipopolysaccharide(LPS,15mg/kg) by intraperitoneal injection 30 minute after the oral administration vehicle and compound, Blood samples were taken 1 h after the LPS via capillarity from eye. 500 μl blood sample was in the 1.5 ml of heparin anticoagulant one-time blending in the centrifuge tube, with 5424R eppendorf centrifuge 3500 rpm, 4℃ centrifuge for 10 minute, plasma preserved in - 80℃, the Mouse TNF alpha - Elisa Ready - set - go plasma content of TNF alpha in the kits.

Plasma TNF-α Inhibition rate=(Model group Mean value-Compound group Mean value)/ Model group Mean value×100%

Result and Conclusion:

Table3　Activity of the Compounds in LPS induced TNFα assay

Compound	TNFα Inhibition rate(%)
Compound30	52.4
Compound33	52.0
Compound53	51.7
CAL-101	41.2

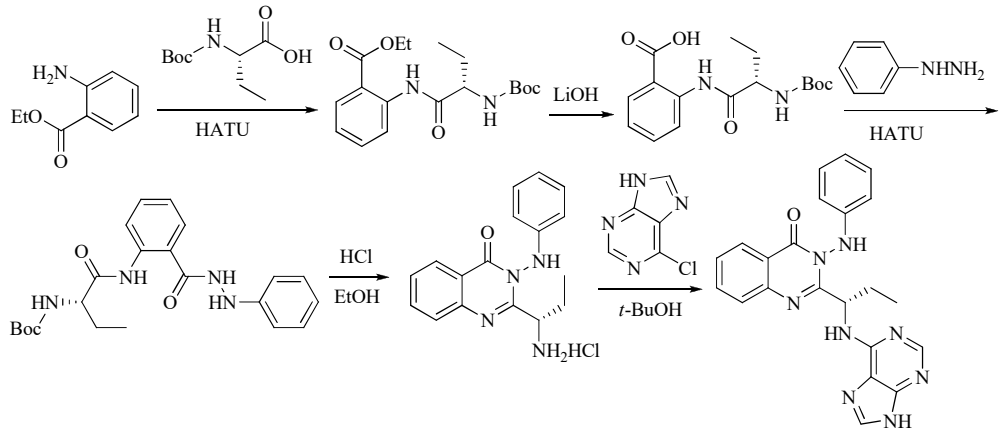
As shown in **Table3**, compared with Model group, CAL-101, Compound 30, Compound 33, Compound 53 inhibited TNF-α level significantly and the plasma TNF-α Inhibition rate was 41.2%($p<0.01$),52.0%($p<0.001$),52.4%($p<0.001$),51.7%($p<0.001$),respectively. Our compounds are more potent than CAL-101.

Synthesis Specific Embodiments

The materials are commercially available for preparation of compounds , for example, bought from Ji'nan qiguang Trading (Reagent) Co. Ltd., Shanghai drfinechem Co., Ltd., Shanghai

Jing Yan Chemical Technology Co.Ltd., Beijing J&K Scientific Co. Ltd, Shanghai demo chemical limited company, Alfa aesar (Tianjin) Chemical Co. Ltd., PharmaBlock (Nanjing) R&D Co. Ltd etc.

Example 1 : Preparation of (S)-2-(1-(9H-purin-6-ylamino)propyl)-3-(phenylamino)quinazolin-4(3H)-one (Compound 1)



(1) Preparation of (S)-ethyl- 2-(2-(tert-butoxycarbonylamino)butanamido) benzoate

A solution of (S)-2-((tert-butoxycarbonyl)amino)butanoic acid (18.33 g, 90.2 mmol), DIEA(31.3 mL,180 mmol),HATU(23 g, 60.5 mmol) in DCM(150mL) and DMF(2 mL) was stirred at rt for 30 min, and ethyl 2-aminobenzoate(10 g, 60.5 mmol) was added ,the mixture was left to stir at rt for 16 h. the mixture was evaporated and the residue was partitioned between EA and water ,the organic layer was separated washed with water, dried and concentrated in vacuo. The crude product was purified by silica column chromatography (PE:EA=4:1) to give the title compound as a white solid (12.5 g, yield: 59.0 %).

(2) Preparation of (S)-2-(2-((tert-butoxycarbonyl)amino)butanamido) benzoic acid.

To a solution of (S)-2-(2-((tert-butoxycarbonyl)amino)butanamido)-benzoate (2.94 g, 8.4 mmol) in MeOH(10mL),THF (10mL) and water(20mL) was added Lithium hydroxide monohydrate(0.806 g, 19.2 mmol),the mixture was stirred at rt overnight,evaporated and adjusted pH to 3-4, filtered to give the title compound as a white solid.(2.52 g, 9%).

(3) Preparation of tert-butyl (S)-(1-oxo-1-((2-(2-phenylhydrazine-1-carbonyl) phenyl) amino)butan-2-yl)carbamate.

A solution of (S)-2-(2-((tert-butoxycarbonyl)amino)butanamido) benzoic acid(2 g, 6.2 mmol), DIEA(3.24 mL, 18.6 mmol),HATU (2.61 g, 6.86 mmol) in DCM(40 mL) and DMF (2 mL)

was stirred for 30 min . Phenylhydrazine (0.675 g, 6.24 mmol) was added and the mixture was stirred at rt for 48 h, the mixture was evaporated and the residue was partitioned between EA and water ,the organic layer was separated, dried and concentrated in vacuo. The crude product was purified by silica column chromatography (PE:EA=51) to give the title compound as a white solid (1.18g, 6.1%).

(4) Preparation of (S)-2-(1-aminopropyl)-3-(phenylamino)quinazolin-4(3H) -one hydrochloride

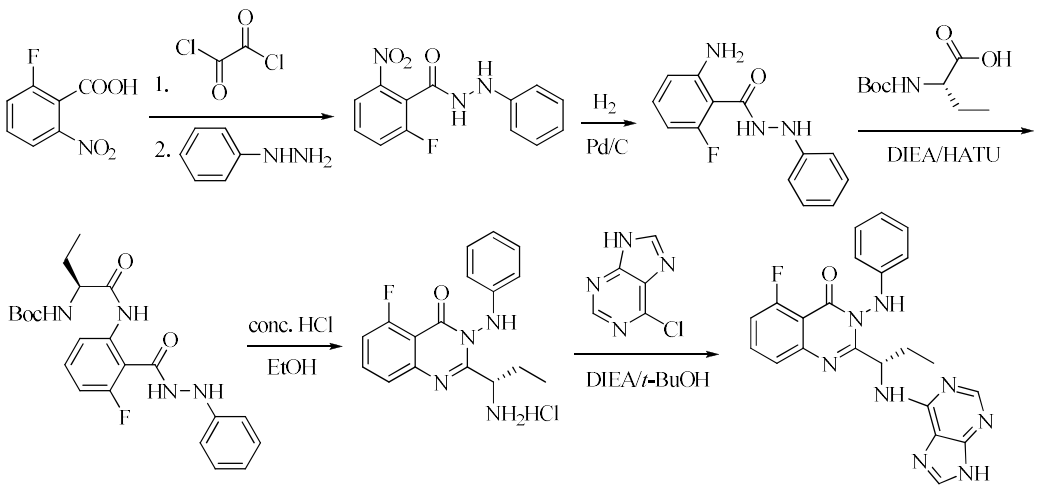
A solution of (*S*)-tert-butyl 1-(3-fluoro-2-(piperidin-1-ylcarbamoyl)phenyl -amino)-1-oxobutan-2-ylcarbamate(1.0 g, 2.42 mmol) in ethanol (40 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (4 mL). The reaction was stirred at room temperature for 30min, and then at 85ºC for 16 h. After cooled to room temperature, the reaction solution was concentrated, to give the title compound as a white solid for the next step.

(5) Preparation of (S)-2-(1-(9H-purin-6-ylamino)propyl)-3-(phenylamino) quinazolin-4(3H)-one

To a solution of (S)-2-(1-aminopropyl)-3-(phenylamino)quinazolin-4(3H) -one hydrochloride in tert-butanol (30 mL) was added DIEA (2.1 mL, 12.1 mmol). After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine (376 mg, 2.43 mmol) was added. The reaction was stirred at 85ºC for 6 h avoiding the light under N_2. After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by preparative HPLC, and the title compound (116mg, 11.6%) was isolated as a white solid.

MS(M+1): 413.2; ^{1}H-NMR(*d_6*-DMSO, 400 MHz): δ 12.9 (1H, br s), 9.10 (1H, s), 8.23-8.12 (1H, m), 8.11-8.02 (2H, m), 7.85-7.76 (1H, m), 7.76-7.68 (1H, m), 7.61 (1H, d), 7.50 (1H, t), 7.26-7.15 (2H, m), 6.94 (2H, d), 6.84 (1H, t), 5.53 (1H, m), 2.22-2.11 (1H, m), 2.05-1.92 (1H, m), 0.995 (3H, t).

Example 2 : Preparation of (S)-2-(1-(9H-purin-6-ylamino)propyl)-5-fluoro-3-(phenylamino)quinazolin-4(3H)-one (Compound 2)



(1) Preparation of 2-fluoro-6-nitro-N'-phenylbenzohydrazide

To a solution of 2-fluoro-6-nitrobenzoic acid(7.4 g, 40.0 mmol) in CH_2Cl_2 (50 mL)and DMF(0.4 mL) was added Oxalyl chloride(7.61 g, 60.0 mmol) dropwise, the mixture was stired for 30 min and concentrated .The residue was dissolved in 1,4-dioxane and added to a solution of benzohydrazide (4.32 g, 40.0 mmol), $NaHCO_3$ (6.72 g, 80.0 mmol) in 1,4-dioxane (20mL) and water (20 mL) drowrise ,the mixture was stirred for 30 min at rt and concentrated ,extracted with EA, dried by Anhydrous sodium sulfate ,filtered ,concentrated and purified by silica column chromatography (PE:EA=2:1) to give the title compound as a white solid (4.7g, 42.8%)

(2) Preparation of 2-amino-6-fluoro-N'-phenylbenzohydrazide

A solution of 2-fluoro-6-nitro-N'-phenylbenzohydrazide (1.5 g, 5.45 mmol) in methanol (20 mL) was carefully poured onto Pd/C (10%, 0.5 g), and the resulting reaction mixture was stirred under hydrogen atmosphere for 10 h. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound (1.3g, 97.2%).

(3) Preparation of (S)-tert-butyl 1-(3-fluoro-2-(2-phenylhydrazinecarbonyl) phenylamino)-1-oxobutan-2-ylcarbamate

A solution of 2-amino-6-fluoro-N'-phenylbenzohydrazide (0.1 mg, 0.408 mmol), (S)-2-(tert-butoxycarbonylamino)butanoic acid (166 mg, 0.817 mmol), DIEA (0.093mL,0.533 mmol),HATU(0.17 g, 0.448 mmo) in DCM(12mL) was stirred at rt for 48 h,. the mixture was partitioned between DCM and water ,the organic layer was separated washed with brine , dried and concentrated in vacuo. The crude product was purified by silica column chromatography (PE:EA=3:1) to give the title compound as a white solid (0.153 g , 87.0 %).

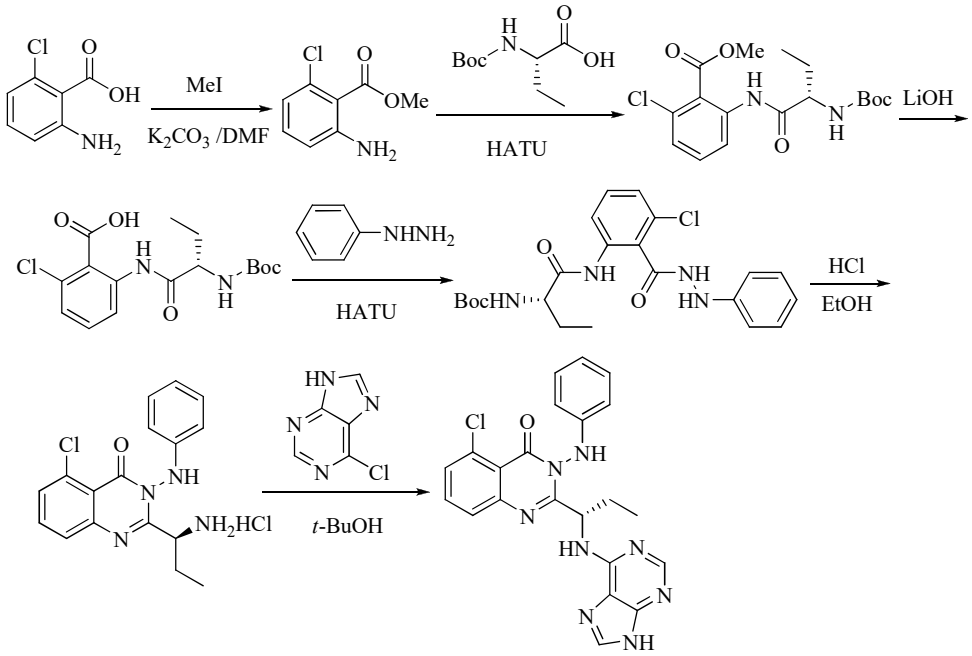
(4) Preparation of (S)-2-(1-aminopropyl)-3-(phenylamino) quinazolin-4(3H) -one hydrochloride

A solution of (S)-tert-butyl 1-(3-fluoro-2-(2-phenylhydrazinecarbonyl) phenylamino)-1-oxobutan-2-ylcarbamate (0.421g, 0.978 mmol) in ethanol 20 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (2 mL). The reaction was stirred at room temperature for 30min, and then at 85ºC for 16 hr. After cooled to room temperature, the reaction solution was concentrated, to give the title compound as a white solid for the next step.

(5) Preparation of (S)-2-(1-(9H-purin-6-ylamino)propyl)-5-fluoro-3-(phenylamino)quinazolin-4(3H)-one

To a solution of (S)-2-(1-aminopropyl)-3-(phenylamino) quinazolin-4(3H) -one hydrochloride in tert-butanol (20 mL) was added DIEA (0.68mL, 3.91mmol). After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine(0.152 g, 0.98 mmol)was added. The reaction was stirred at 85ºC for 6 h avoiding the light under N_2. After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by silica column chromatography (EA) to give the title compound as a white solid (0.178g, 42.3%) MS(M+1): 431; ^{1}H-NMR(*d*$_6$-DMSO, 400 MHz): δ 12.74 (1H, s), 8.86 (1H, s), 8.19-8.00 (2H, m), 7.83-7.74 (1H, m), 7.48 (1H, d), 7.29-7.13 (4H, m), 6.93-6.78 (3H, m), 5.78 (1H, s), 2.24-1.88 (2H, m), 1.03-0.91(3H, m).

Example 3 : Preparation of (S)-2-(1-(9H-purin-6-ylamino)propyl)-3-(phenylamino)quinazolin-4(3H)-one (Compound 4)



(1)Preparation of methyl 2-amino-6-chlorobenzoate

To a solution of 2-amino-6-chlorobenzoic acid(10 g, 58.3 mmol) and K_2CO_3(12 g, 86.8 mmol)) in DMF (120 mL) was added iodomethane(9.88 g, 69.6 mmol) at 0℃.The mixture was stirred overnight , concentrated and purified by silica column chromatography (PE:EA=4:1) to give the title compound as A colorless oil (10.3 g , yield: 95.2 %).

(2)Preparation of (S)-methyl 2-(2-(tert-butoxycarbonylamino)butanamido) -6-chlorobenzoate

A solution of (S)-2-((tert-butoxycarbonyl)amino)butanoic acid(18.0 g, 88.6 mmol), DIEA(12.6 mL, 72.4 mmol),HATU(23.3 g, 61.3 mmol) in DMF(100mL) was stirred at rt for 30 min, and methyl 2-amino-6-chlorobenzoate (10.3 g, 55.5 mmol) was added ,the mixture was left to stir at rt overnight. the mixture was evaporated and the residue was partitioned between EA and water ,the organic layer was separated washed with water , dried and concentrated in vacuo. The crude product was purified by silica column chromatography to give the title compound as a yellow oil (15.8 g , yield: 76.8 %).

(3) Preparation of (S)-2-(2-(tert-butoxycarbonylamino)butanamido)-6 -chlorobenzoic acid

To a solution of (S)-methyl 2-(2-(tert-butoxycarbonylamino)butanamido) -6-chlorobenzoate (15.7g, 42.3 mmol in MeOH(60mL),THF (2000mL) and water(200mL) was added Lithium hydroxide monohydrate(0.80 g, 0.2 mmol),the mixture was stirred at rt overnight, evaporated and adjusted pH to 3-4 ,extracted with EA to give the title compound as a yellow oil (15.0 g, 99.3%).

(4) Preparation of (S)-tert-butyl 1-(3-chloro-2-(2-phenylhydrazinecarbonyl)

phenylamino)-1-oxobutan-2-ylcarbamate.

A solution of ((S)-2-(2-(tert-butoxycarbonylamino)butanamido)-6 -chlorobenzoic acid (7.48 g, 21.0 mmol),DIEA(9.1 mL, 52.3 mmol),HATU(10.37 g, 27.3 mmol) in DCM(50 mL) and DMF (50 mL) was stirred for 30 min . Phenylhydrazine (4.48 g, 31.0 mmol) was added and the mixture was stirred at rt overnight, the mixture was evaporated and the residue was partitioned between EA and water ,the organic layer was separated, dried and concentrated in vacuo. The crude product was purified by silica column chromatography to give the title compound as a white solid (7.96g, 84.8%)

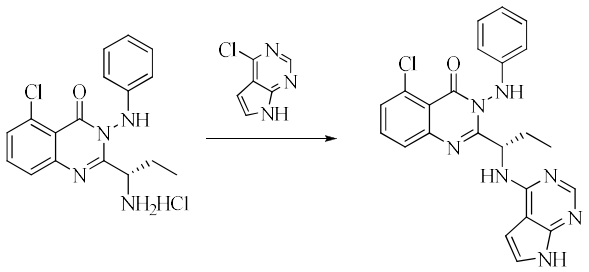
(5) Preparation of (S)-2-(1-aminopropyl)-5-chloro-3-(phenylamino)quinazolin-4- (3H)-one hydrochloride

A solution of (S)-tert-butyl 1-(3-chloro-2-(2-phenylhydrazinecarbonyl) phenylamino)-1-oxobutan-2-ylcarbamate. (0.5 g, 1.12 mmol) in ethanol (10 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (3 mL). The reaction was stirred at room temperature for 30min, and then at 85ºC overnight. After cooled to room temperature, the reaction solution was filtered to give the title compound as a white solid.(0.2 g, 48.8%)

(6) Preparation of (S)-2-(1-(9H-purin-6-ylamino)propyl)-5-chloro-3-(phenylamino) quinazolin-4(3H)-one

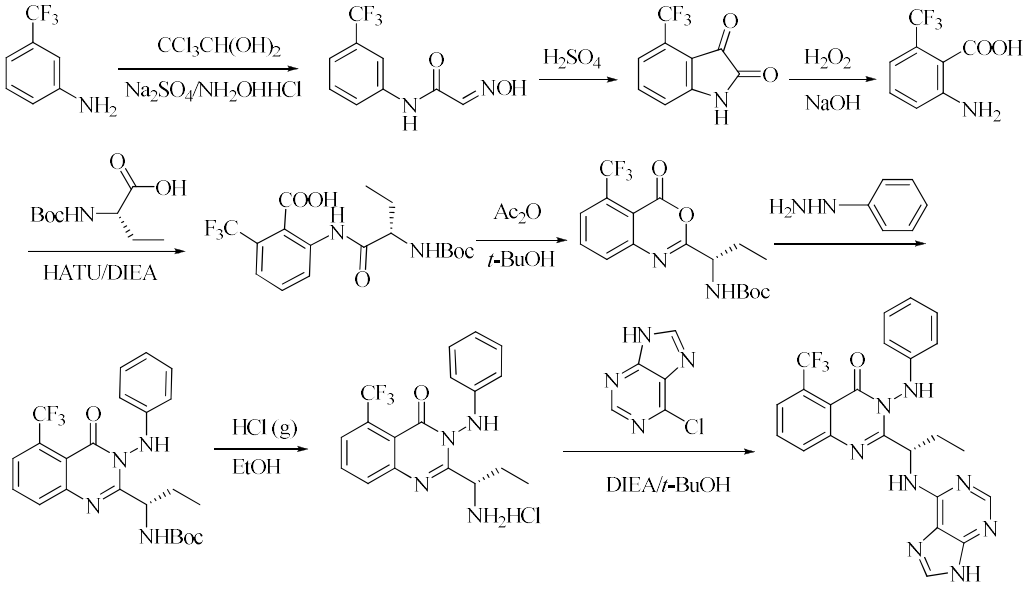
To a solution of (S)-2-(1-aminopropyl)-5-chloro-3-(phenylamino)quinazolin-4- (3H)-one hydrochloride(200mg, 0.547 mmol) in tert-butanol (13 mL) was added DIEA (2.1 mL, 12.1 mmol). After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine (113 mg, 0.73 mmol) was added. The reaction was stirred at 85ºC for 3 d. After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by silica column chromatography, and the title compound (116mg, 45.7%) was isolated as a white solid. MS(M+1): 447.2.^{1}H-NMR(d_6-DMSO, 400 MHz):δ 12.97 (1H, br s), 8.99 (1H, s), 8.22-8.12 (1H, m), 8.09 (1H, m), 7.80-7.61 (2H, m), 7.52 (2H, t), 7.28-7.15 (2H, m), 6.99 (2H, d), 6.71 (1H, d), 5.47 (1H, m), 2.21-2.10 (1H, m), 2.04-1.92 (1H, m), 0.999 (3H, t).

Example 4 : Preparation of (S)-2-(1-(7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)propyl)-5-chloro-3-(phenylamino)quinazolin-4(3H)-one (Compound 5)



To a solution of (S)-2-(1-aminopropyl)-5-chloro-3-(phenylamino)quinazolin-4- (3H)-one hydrochloride(600mg, 1.64mmol) in tert-butanol (10 mL) was added DIEA (0.8 mL, 4.59 mmol). After that4-chloro-7H-pyrrolo[2,3-d]pyrimidine (300 mg, 1.95 mmol) was added. The reaction was stirred at 85ºC for 7 d. After the mixture was cooled to room temperature, the reaction solution was concentrated, the crude product was purified by silica column chromatography, and the title compound (200mg, 27.3%) was isolated as a white solid. MS(M+1): 446.2.^{1}H-NMR(d_6-DMSO, 400 MHz):δ 11.51 (1H, s), 8.93 (1H, s), 7.98 (1H, s), 7.82 (1H, d), 7.66 (1H, t), 7.47 (2H, t), 7.27 (2H, t), 7.16-7.08 (2H, m), 6.87 (1H, t), 6.80-6.75 (1H, m), 6.74-6.65 (1H, m), 5.45-5.35 (1H, m), 2.20-2.08 (1H, m), 1.95-1.80 (1H, m), 1.06 (3H, t).

Example 5 : Preparation of (S)-2-(1-(9H-purin-6-ylamino)propyl)-3-(phenylamino)-5-(trifluoromethyl)quinazolin-4(3H)-one (Compound 6)



(1) Preparation of (E)-2-(hydroxyimino)-N-(3-(trifluoromethyl)phenyl)acetamide

A solution of chloral hydrate(100 g,0.605 mol) and anhydrous sodium sulfate (700 g,4.93 mol) in water (1.4 L) was stirred at 35℃ , 3-(trifluoromethyl)aniline (87 g,0.54 mol) in water (0.4 L)

and concentrated hydrochloric acid (56 mL) was added dropwise to keep the temperature at 35℃,after that a solution of hydroxylamine hydrochloride(135 g,1.94 mol) in water (0.2 L) was added ,the mixture was heated to 90 ℃ and stirred for 2 h .The mixture was cooled down to 50℃ ,filtered and dried to yield the title compound as a pale yellow solid (112 g, 89.3%).

(2)Preparation of 4-(trifluoromethyl)indoline-2,3-dione

To a stirring mixture of 86% sulfuric acid(430mL) was added 2-(hydroxyimino)-N -(3-(trifluoromethyl)phenyl)acetamide (100 g,431 mmol) in portions for 1h to keep the temperature below 65℃,after that the mixture was heated to 85℃ for 20 min, cooled down to rt. The mixture was poured into ice-water mixture and stirred for 30 min,filtered ,dried to yield the title compound as a yellow solid (20 g, 21.6%)

(3)Preparation of 2-amino-6-(trifluoromethyl)benzoic acid

To a mixture of 5% sodium hydroxide (220 mL ,275 mmol) and 30% hydrogen peroxide (220 mL) was added 4-(trifluoromethyl)indoline-2,3-dione (17 g, 79 mmol) in portions and the mixture was stirred at 50 ℃ for 1 h, After that the mixture was cooled down and filtered. The filtrate was adjusted Ph to 4, and filtered , dried to yield the title compound as a pale yellow solid (11 g, 67.8%)

(4)Preparation of

(S)-2-(2-((tert-butoxycarbonyl)amino)butanamido)-6-(trifluoromethyl)benzoic acid

A solution of (S)-2-((tert-butoxycarbonyl)amino)butanoic acid(5.2 g, 25.6 mmol), DIEA(3.44 g, 26.6 mmol), HATU(10.16 g,26.7 mmol) and 2-amino-6- (trifluoromethyl)benzoic acid (5.2 g, 25.3 mmol) in DMF(50 mL) was stirred at rt for 7 d ,the mixture was partitioned between DCM and water ,the organic layer was separated washed with water, dried and concentrated in vacuo. The crude product was purified by preparation HPLC to give the title compound as a white solid (2.6 g , yield: 26.3 %).

(5)Preparation of tert-butyl

(S)-(1-(4-oxo-5-(trifluoromethyl)-4H-benzo[d][1,3]oxazin-2-yl)propyl)carbamate

A solution of ((S)-2-(2-((tert-butoxycarbonyl)amino)butanamido)-6-(trifluoromethyl)benzoic acid (2.6 g, 6.66 mmol),Acetic anhydride(3.15 g, 30.9 mmol)in t-BuOH(50 mL) was reluxed overnight and evaporated in vacuo to give the title compound without retreatment for the next step.

(6)Preparation of tert-butyl
(S)-(1-(4-oxo-3-(phenylamino)-5-(trifluoromethyl)-3,4-dihydroquinazolin-2-yl)propyl)carbam ate

A miture of the last intermediate and phenylhydrazine (756 mg, 6.99 mmol)in pyridine(15 mL) was stirred at 100 ℃ for 8 h,the mixture was concentrated and purified by silica column chromatography to give the title compound as a pale yellow solid (1.5g, 48.7% two steps)

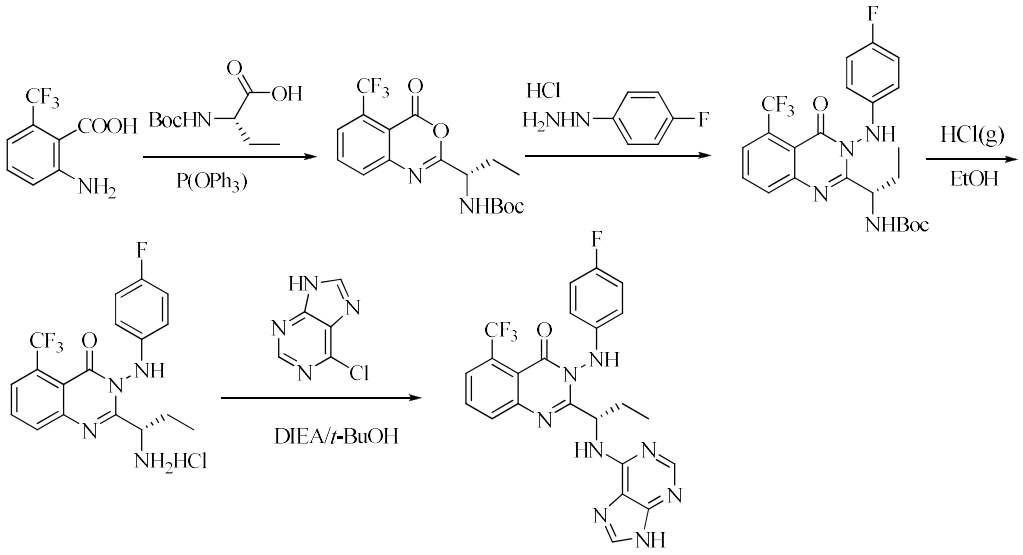
(7)Preparation of (S)-tert-butyl 1-(4-oxo-5-(trifluoromethyl)-4H-benzo [d][1,3]oxazin-2-yl)propylcarbamate

A solution of t tert-butyl
(S)-(1-(4-oxo-3-(phenylamino)-5-(trifluoromethyl)-3,4-dihydroquinazolin-2-yl)propyl)carbam ate(1.5 g, 3.24 mmol)in anhydrous ethanol(30mL) was stirred and bubbled with the hydrogen chloride gas until the reaction was completed ,and the mixture was concentrated to give give the title compound as a solid (1.2g, 92.9%)

(8)Preparation of (S)-2-(1-(9H-purin-6-ylamino)propyl)-3-(phenylamino)-5 -(trifluoromethyl)quinazolin-4(3H)-one

To a solution of
(S)-2-(1-aminopropyl)-3-(phenylamino)-5-(trifluoromethyl)quinazolin-4(3H)-one hydrochloride (800mg, 2.01mmol) in tert-butanol (30 mL) was added DIEA (1.4 mL, 8.04 mmol). After that 6-chloro-9H-purine (619 mg, 4.00 mmol) was added. The reaction was stirred at 85ºC for 24 h. After the mixture was cooled to room temperature, the reaction solution was concentrated, the crude product was purified by preparation HPLC and the title compound (194mg, 20.1%) was isolated as a white solid. MS(M+1): 481.2.^{1}H-NMR(d_6-DMSO, 400 MHz):12.92 (1H, br s), 9.13 (1H, s), 8.22-8.11 (1H, m), 8.10 (1H, s), 8.02-7.84 (3H, m), 7.84-7.63 (1H, m), 7.29-7.15 (2H, t), 6.99 (1H, d), 6.86 (1H, t), 6.69 (1H, d), 5.48 (1H, m), 2.25-2.10 (1H, m), 2.02-1.89 (1H, m), 1.01, 0.87 (3H, two triplets).

Example 6 : Preparation of (S)-2-(1-(9H-purin-6-ylamino)propyl)-3-(4-fluoro -phenylamino)-5-(trifluoromethyl)quinazolin-4(3H)-one (Compound 7)



(1) Preparation of (S)-tert-butyl 1-(4-oxo-5-(trifluoromethyl)-4H-benzo[d][1,3]oxazin-2-yl)propylcarbamate

To a stirred solution of 2-amino-6-(trifluoromethyl)benzoic acid (1.5 g, 7.31 mmol) in pyridine (50mL) was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (1.5 g, 7.38 mmol), and triphenylphosphinate (2.3 g, 7.41 mmol). The resulting reaction solution was stirred at 60ºC for 24 h, and then was used directly for the next step without working-up.

(2) Preparation of (S)-tert-butyl 1-(3-(4-fluorophenylamino)-4-oxo-5-(trifluoromethyl) -3,4-dihydroquinazolin-2-yl)propylcarbamate

To the stirred solution of (S)-tert-butyl 1-(4-oxo-5-(trifluoromethyl)-4H-benzo[d][1,3]oxazin-2-yl)propylcarbamate (crude reaction mixture) was added (4-fluorophenyl)hydrazine (1.5 g, 9.23 mmol), and the resulting reaction solution was stirred at 100ºC for 8 h. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to yield the title compound (1.5 g, 42.7% two steps) as a light yellow solid.

(3) Preparation of (S)-2-(1-aminopropyl)-3-((4-fluorophenyl)amino)-5-(trifluoromethyl)quinazolin-4(3H)-one hydrochloride

A stirred solution of (S)-tert-butyl-1-(3-(4-fluorophenylamino)-4-oxo-5-(trifluoromethyl)-3,4-dihydroquinazolin-2-yl)propylcarbamate (1.5 g, 3.12 mmol) in ethanol (30 mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was bubbled in HCl gas for 2 hr,. When the reaxtion was completed , the reaction solution was then

concentrated under reduced pressure to yield the crude product as a white solid (1.2 g, 92.3 %)

(4) Preparation of

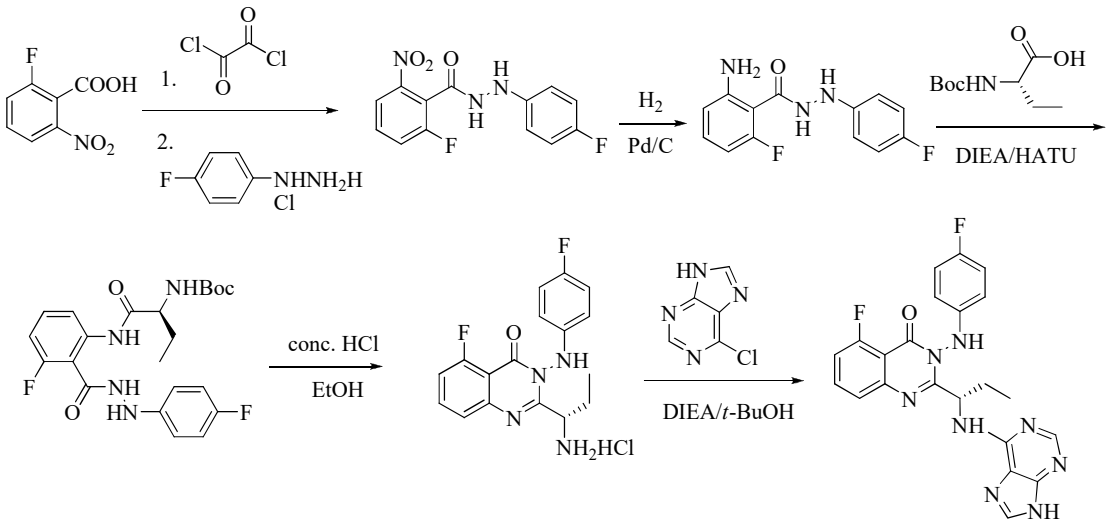
(S)-2-(1-(9H-purin-6-ylamino)propyl)-3-(4-fluorophenylamino)-5-(trifluoromethyl)quinazolin-4(3H)-one

To a stirred solution of the crude

(S)-2-(1-aminopropyl)-3-((4-fluorophenyl)amino)-5-(trifluoromethyl)quinazolin-4(3H)-one hydrochloride (1.0 g, 2.40 mmo) in *tert*-butanol (30 mL) in a dry round bottomed flask was added DIEA (2.0 mL, 11.5 mmol) and then 6-chloropurine (700 mg, 4.53 mmol) was added, and the reaction was stirred at 85ºC for 24 h. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by preparation HPLC to yield the title compound (600 mg, 50.0%) as a white solid.

MS(M+1): 499.2; ^{1}H-NMR(d_6-DMSO, 400 MHz):δ 12.98 (1H, s), 9.12 (1H, s), 8.22-8.10 (2H, m), 8.00-7.81 (4H, m), 7.16-7.00 (4H, m), 5.44 (1H, m), 2.21-1.80 (2H, m), 1.02 (3H, t).

Example 7 : Preparation of (S)-2-(1-(9H-purin-6-ylamino)propyl)-3-(4-fluoro -phenylamino)-5-(trifluoromethyl)quinazolin-4(3H)-one (Compound 8)



(1)Preparation of 2-fluoro-N'-(4-fluorophenyl)-6-nitrobenzohydrazide

To a solution of 2-fluoro-6-nitrobenzoic acid(5.5 g, 29.7 mmol) in CH_2Cl_2 (50 mL)and DMF(0.4 mL) was added Oxalyl chloride(5.66 g, 44.6 mmol) dropwise, the mixture was stired for 2 h and concentrated .The residue was dissolved in 1,4-dioxane and added to a solution of (4-fluorophenyl)hydrazine hydrochloride (4.829 g, 29.7 mmol), $NaHCO_3$ (6.72 g, 80.0 mmol) in 1,4-dioxane (20mL)and water (20 mL) drowrise ,the mixture was stirred for 30 min at rt and concentrated ,extracted with EA, dried by Anhydrous sodium sulfate, filtered,

concentrated and purified by silica column chromatography (PE:EA=2:1) to give the title compound as a white solid (4.4g, 50.5%).

(2) Preparation of 2-amino-6-fluoro-N'-(4-fluorophenyl)benzohydrazide

A solution of 2-fluoro-N'-(4-fluorophenyl)-6-nitrobenzohydrazide (4.4 g, 15.0 mmol) in methanol (60 mL) was carefully poured into Pd/C (10%, 0.5 g), and the resulting reaction mixture was stirred under hydrogen atmosphere for 36 h. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound (3.8g, 96.2%).

(3)Preparation of (S)-tert-butyl 1-(3-fluoro-2-(2-(4-fluorophenyl)hydrazinecarbonyl) phenylamino)-1-oxobutan-2-ylcarbamate

A solution of 2-amino-6-fluoro-N'-(4-fluorophenyl)benzohydrazide (3.8g, 14.4 mmol), (S)-2-(tert-butoxycarbonylamino)butanoic acid (5.8 g, 28.6mmol), DIEA (3.7 mL, 21.2 mmol,HATU(6.0 g,15.8 mmol) in DCM (200mL) was stirred at rt for 48 h,. the mixture was partitioned between DCM and water ,the organic layer was separated washed with brine , dried and concentrated in vacuo. The crude product was purified by preparation HPLC to give the title compound as a white solid (3.4 g , 52.6 %).

(4)Preparation of

(S)-2-(1-aminopropyl)-5-fluoro-3-(4-fluorophenylamino)quinazolin-4(3H)-one hydrochloride

A solution of (S)-tert-butyl 1-(3-fluoro-2-(2-(4-fluorophenyl)hydrazinecarbonyl) phenylamino)-1-oxobutan-2-ylcarbamate (3.4 g, 7.58 mmol) in ethanol (20 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (10 mL). The reaction was stirred at room temperature for 30min, and then at 85ºC for 16 hr. After cooled to room temperature, the reaction solution was concentrated and purified by preparation HPLC to give the title compound as a white solid (1.6 g , 57.5 %).

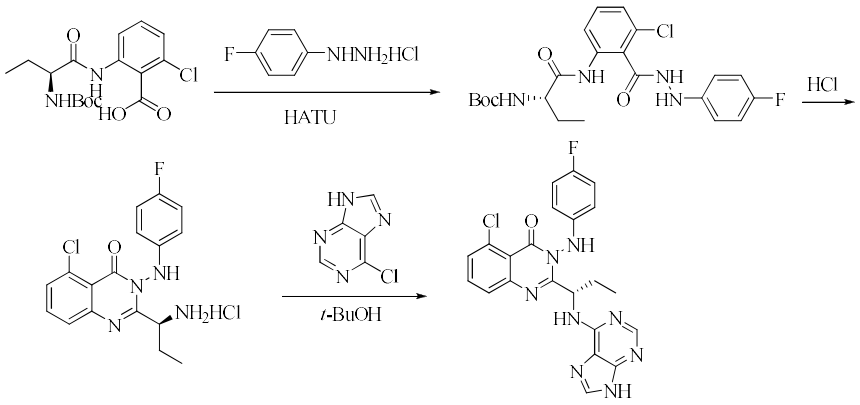
(5)Preparation of

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

To a solution of (S)-2-(1-aminopropyl)-5-fluoro-3-(4-fluorophenylamino) quinazolin-4(3H)-one hydrochloride (600 mg, 1.64 mmol) in tert-butanol (20 mL) was added DIEA (0.71 mL, 4.08 mmol). After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine (0.152 g, 0.98 mmol) was added. The reaction was stirred at 85ºC for 24 h ,After cooled to room temperature, the reaction solution was concentrated, the crude product

was purified by preparation HPLC to give the title compound as a white solid (140mg, 19.0%) MS(M+1): 449.2; ^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.96 (1H, br s), 8.99 (1H, s), 8.22-8.08 (2H, m), 7.66-7.47 (1H, m), 7.38 (1H, d), 7.24 (1H, t), 7.13-6.99 (4H, m), 6.78-6.69 (1H, m), 5.47 (1H, m), 2.20-2.07 (1H, m), 2.06-1.85 (1H, m), 1.01 (3H, t).

Example 8 : Preparation of (S)-2-(1-(9H-purin-6-ylamino)propyl)-5-chloro-3-(4-fluorophenylamino)quinazolin-4(3H)-one (Compound 9)



(1)Preparation of (S)-tert-butyl 1-(3-chloro-2-(2-(4-fluorophenyl)hydrazinecarbonyl)phenylamino)-1-oxobutan-2-ylcarbamate

A solution of (S)-2-(2-(tert-butoxycarbonylamino)butanamido)-6-chlorobenzoic acid (1.50 g ,4.20 mmol), (4-fluorophenyl)hydrazine hydrochloride (2.08 g,5.47 mmol)), DIEA (1.03 g ,6.33 mmol),HATU(2.08 g ,5.47 mmol) in DCM (20mL) and DMF (10 mL)was stirred at rt overnight. the mixture was partitioned between EA and water ,the organic layer was separated washed with brine, dried and concentrated in vacuo. The crude product was purified by silica column chromatography (PE/EA-3:1) to give the title compound as a pale yellow solid (1.95 g , 99.8%).

(2)Preparation of (S)-2-(1-aminopropyl)-5-chloro-3-(4-fluorophenylamino)quinazolin-4(3H)-one hydrochloride

A solution of (S)-2-(2-(tert-butoxycarbonylamino)butanamido)-6-chlorobenzoic acid (640 mg, 1.38 mmol) in ethanol (10 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (3 mL). The reaction was stirred at room temperature for 30min, and then at 85ºC overnight. After cooled to room temperature, filtered and washed with the mixture of ice-ethanol and ethyl ether as a white solid (0.2 g , 37.8 %).

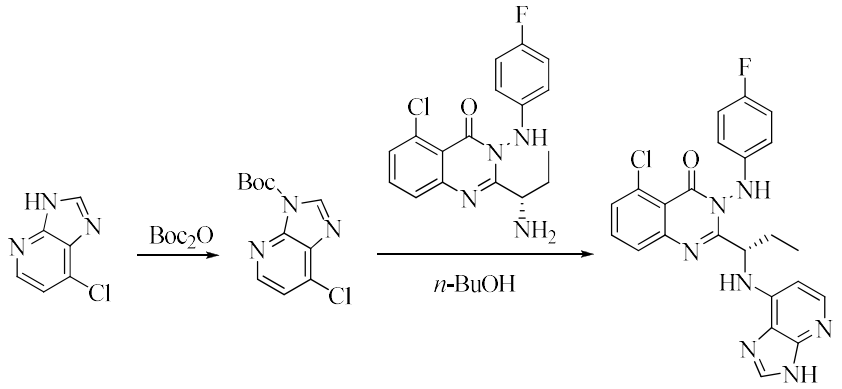
(3)Preparation of (S)-2-(1-(9H-purin-6-ylamino) propyl)-5-chloro-3-(4-fluorophenylamino)quinazolin-4(3H)-one

To a solution of

(S)-2-(1-aminopropyl)-5-chloro-3-(4-fluorophenylamino)quinazolin-4(3H)-one hydrochloride (200 mg, 0.522 mmol) in tert-butanol (15 mL) was added DIEA (2 mL,). After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine (0.155 g, 1.0 mmol) was added. The reaction was stirred at 85ºC for 3 d ,After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by silica column chromatography (PE/EA=1:1-1:3) to give the title compound as a white solid (200mg, 82.4%).

MS(M+1): 465.2; ^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.97 (1H, br s), 8.98 (1H, s), 8.30-8.08 (2H, m), 7.90-7.59 (2H, m), 7.57-7.46 (2H, m), 7.16-6.98 (4H, m), 5.44 (1H, m), 2.20-2.05 (1H, m), 2.05-1.92 (1H, m), 1.01 (3H, t).

Example 9 : Preparation of (S)-2-(1-((3H-imidazo[4,5-b]pyridin-7-yl)amino) propyl)-5-chloro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one (Compound 10)



(1) Preparation of tert-butyl 7-chloro-3H-imidazo[4,5-b]pyridine-3-carboxylate

A solution of 7-chloro-3H-imidazo[4,5-b]pyridine (1.34 g ,8.73 mmol) ,Boc_2O (2.85 g ,13.1 mmol) and DMAP (10 mg) was stirred for 1 h . When TLC showed that the reaction was completed ,the mixture was concentrated and purified by ilica column chromatography (PE/EA=10:1) to give the title compound as a white solid (1.8 g, 81.3%)

(2) Preparation of (S)-2-(1-((3H-imidazo[4,5-b]pyridin-7-yl)amino)propyl)-5-chloro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one

To a solution of

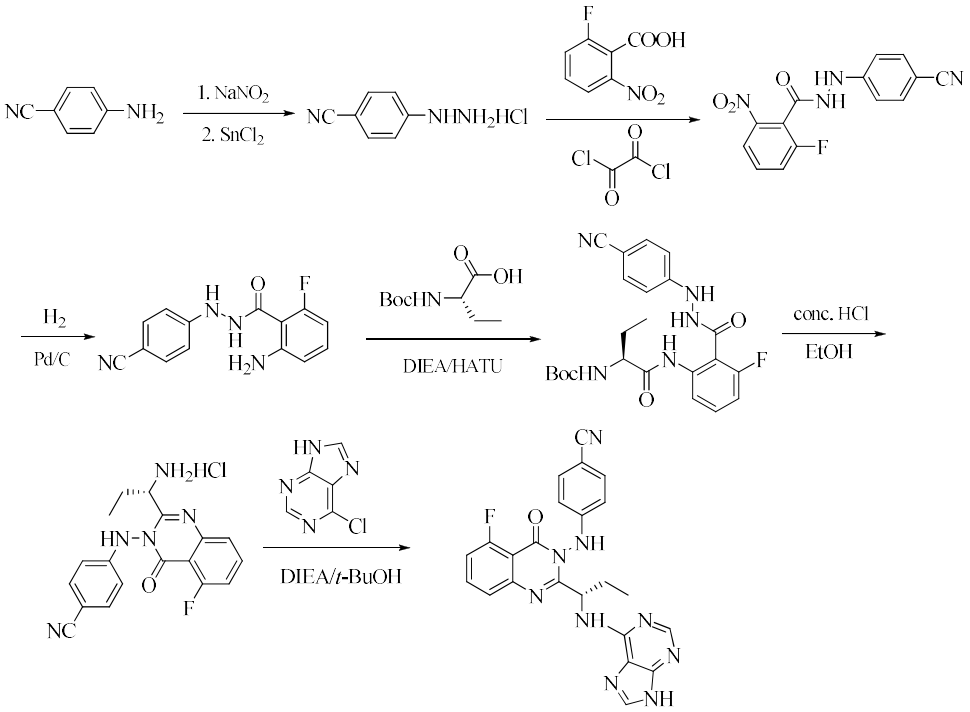
(S)-2-(1-aminopropyl)-5-chloro-3-(4-fluorophenylamino)quinazolin-4(3H)-one (1.40 g ,4.04 mmol) in tert-butanol (10 mL) was added DIEA (1.4 mL, 8.04 mmol). tert-butyl 7-chloro-3H-imidazo[4,5-b]pyridine-3-carboxylate

(1.8 g, 7.10 mmol) was added. The reaction was heated at 180℃ and kept this temperature

for 2 h by microwave ,After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by silica column chromatography (PE/EA=1:1-1:3) to give the title compound as a white solid (40mg, 2.1%).

MS(M+1): 464.0; ^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.60 (1H, br s), 9.32-8.93 (1H, m), 8.14-7.59 (5H, m), 7.18-6.91 (2H, m), 6.90-6.60 (4H, m), 5.46 (1H, m), 2.23-2.05 (1H, m), 2.05-1.80 (1H, m), 1.16 (3H, m).

Example 10 : Preparation of (S)-2-(1-((3H-imidazo[4,5-b]pyridin-7-yl)amino) propyl)-5-chloro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one (Compound 12)



(1) Preparation of 4-hydrazinylbenzonitrile hydrochloride

To a stirred solution of 4-aminobenzonitrile (25 g, 211 mmol) in concentrated hydrochloric acid (0.2 L) was added a solution of sodium nitrite (15.8 g, 229 mmol) in water (0.1 L) dropwise at -15 ℃,After that this mixture was added to a solution of hydrous stannous chloride (238 g, 1.05 mol) in concentrated hydrochloric acid (0.185 L) dropwise at -10 ℃.and the mixture was stirred for 15 min, and filtered ,washed with ethyl ether and dried to give the title compound as a white solid (28g, 78.2%).

(2) Preparation of N'-(4-cyanophenyl)-2-fluoro-6-nitrobenzohydrazide

To a solution of 2-fluoro-6-nitrobenzoic acid(5.55 g, 30.0mmol) in CH_2Cl_2 (50 mL)and DMF(0.3 mL) was added Oxalyl chloride(5.71 g, 45.0 mmol) dropwise, the mixture was stired

for 2 h and concentrated .The residue was dissolved in 1,4-dioxane and added to a solution of 4-hydrazinylbenzonitrile hydrochloride (5.09 g, 30.0 mmol),$NaHCO_3$ (7.56 g, 90.0 mmol) in 1,4-dioxane (15mL)and water (15 mL) drowrise ,the mixture was stirred for 30 min at rt and concentrated ,extracted with EA, dried by Anhydrous sodium sulfate ,filtered ,concentrated and purified by silica column chromatography (PE:EA=2:1) to give the title compound as a white solid (6.33g, 72.6%).

(3)Preparation of 2-amino-N'-(4-cyanophenyl)-6-fluorobenzohydrazide

A solution of N'-(4-cyanophenyl)-2-fluoro-6-nitrobenzohydrazide

(4.2 g, 14.0 mmol) in methanol (30 mL) was carefully poured into Pd/C (10%, 0.6 g), and the resulting reaction mixture was stirred under hydrogen atmosphere for 18 h. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound, for the next step.

(4)Preparation of tert-butyl

(S)-(1-((2-(2-(4-cyanophenyl)hydrazine-1-carbonyl)-3-fluorophenyl)amino)-1-oxobutan-2-yl) carbamate

A solution of 2-amino-N'-(4-cyanophenyl)-6-fluorobenzohydrazide (-14.0mmol), (S)-2-(tert-butoxycarbonylamino)butanoic acid (4.26 g, 21.0 mmol),DIEA (3.17 mL, 18.2 mmol) and HATU(6.38 g, 16.8 mmol) in DCM (40 mL) was stirred at rt for 64 h,. the mixture was partitioned between DCM and water ,the organic layer was separated washed with brine , dried and concentrated in vacuo. The crude product was purified by silica column chromatography (PE:EA:3:1) to give the title compound as a white solid (2.65g , 41.6% two steps).

(5)Preparation of (S)-4-((2-(1-aminopropyl)-5-fluoro-4-oxoquinazolin-3(4H)-yl)amino) benzonitrile hydrochloride

A solution of (S)-tert-butyl 1-(3-fluoro-2-(2-(4-fluorophenyl)hydrazinecarbonyl) phenylamino)-1-oxobutan-2-ylcarbamate (1.37 g, 3.0 mmol) in ethanol (30 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (3mL). The reaction was stirred at room temperature for 30min, and then at 85ºC for 24 hr. After cooled to room temperature, the reaction solution was concentrated to give the title compound as a white solid

(6)Preparation of

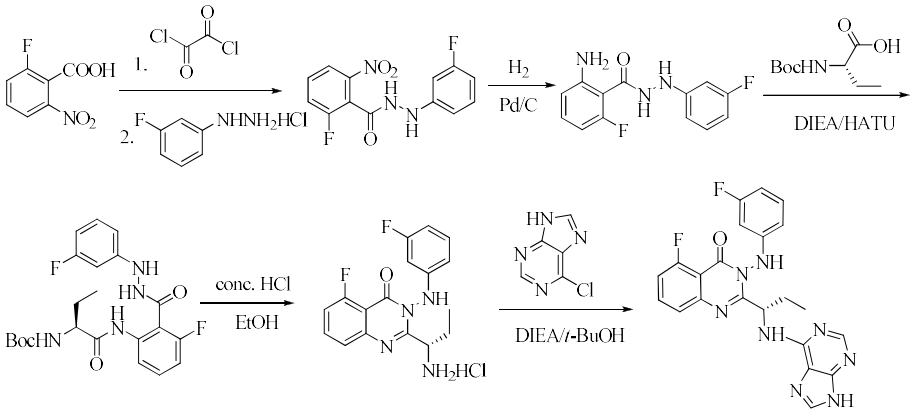
(S)-4-((2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-4-oxoquinazolin-3(4H)-yl)amino)benzonitrile

To a solution of

((S)-4-((2-(1-aminopropyl)-5-fluoro-4-oxoquinazolin-3(4H)-yl)amino)benzonitrile hydrochloride (3.0mmol) in tert-butanol (20 mL) was added DIEA(1.56 mL, 9.0 mmol), After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine (556 mg, 3.6 mmol) was added. The reaction was stirred at 85ºC for 36 h ,After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by preparation HPLC to give the title compound as a white solid (153mg, 11.2%) MS(M+1): 456.2; ^{1}H-NMR(*d_6*-DMSO, 400 MHz): ^{1}H-NMR(*d_6*-DMSO, 400 MHz):δ 12.94 (1H, s), 9.67 (1H, s), 8.28-8.03 (2H, m), 7.95-7.24 (6H, m), 7.08-6.28 (2H, m),.

Example 11 : Preparation of

(S)-2-(1-(9H-purin-6-ylamino)propyl)-5-fluoro-3-(3-fluorophenylamino)quinazolin-4(3H)-one (Compound 13)



(1) Preparation of 2-fluoro-N'-(3-fluorophenyl)-6-nitrobenzohydrazide

To a solution of 2-fluoro-6-nitrobenzoic acid(6.05g, 29.73 mmol) in CH_2Cl_2 (50 mL)and DMF(0.3 mL) was added Oxalyl chloride(5.71 g, 45.0 mmol) dropwise, the mixture was stired for 2 h and concentrated .The residue was dissolved in 1,4-dioxane and added to a solution of (3-fluorophenyl)hydrazine hydrochloride (4.8 g, 29.73 mmol),$NaHCO_3$ (5 g, 59.5 mmol) in 1,4-dioxane (15mL)and water (15 mL) dropwrise , the mixture was stirred for 30 min at rt and concentrated ,extracted with EA, dried by Anhydrous sodium sulfate ,filtered ,concentrated and filtered to give the title compound as a white solid (5.67g, 64.9%)

(2)Preparation of 2-amino-6-fluoro-N'-(3-fluorophenyl)benzohydrazide

A solution of 2-fluoro-N'-(3-fluorophenyl)-6-nitrobenzohydrazide (5.67 g, 19.3 mmol) in methanol (100 mL) was carefully poured into Pd/C (10%, 0.6 g), and the resulting reaction mixture was stirred under hydrogen atmosphere for 24 h. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound (4.8 g, 94.3%).

(3)Preparation of (S)-tert-butyl 1-(3-fluoro-2-(2-(3-fluorophenyl)hydrazinecarbonyl) phenylamino)-1-oxobutan-2-ylcarbamate

A solution of 2-amino-6-fluoro-N'-(3-fluorophenyl)benzohydrazide (3.8 g, 14.4 mmol), (S)-2-(tert-butoxycarbonylamino)butanoic acid (5.8 g, 28.5 mmol), DIEA (3.7 mL, 21.2 mmol)and HATU(6.0 g,15.8 mmol)in DMF (80 mL) was stirred at rt for 48h,. the mixture was partitioned between DCM and water ,the organic layer was separated washed with brine , dried and concentrated in vacuo. The crude product was purified by preparation HPLC to give the title compound as a white solid (3.6 g , 55.6%).

(4)Preparation of (S)-2-(1-aminopropyl)-5-fluoro-3-(3-fluorophenylamino) quinazolin-4(3H)-one hydrochloride

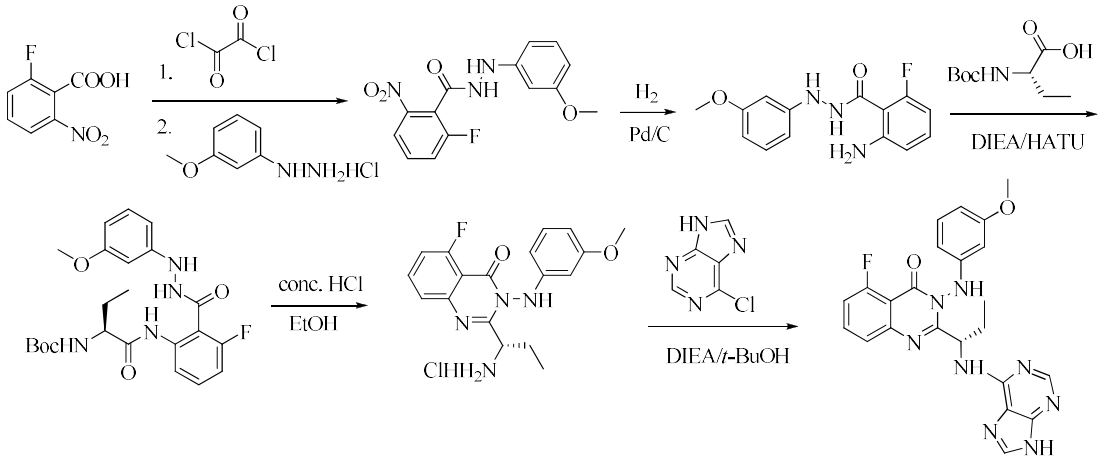
A solution of (S)-tert-butyl 1-(3-fluoro-2-(2-(3-fluorophenyl)hydrazinecarbonyl)phenylamino)-1-oxobutan-2-ylcarbamate (3.6 g, 8 mmol) in ethanol (40 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (5mL). The reaction was stirred at room temperature for 30min, and then at 85ºC for 4 d . After cooled to room temperature, the reaction solution was concentrated and purified by preparation HPLC to give the title compound as a white solid(0.65 g, 22.1%).

(5)Preparation of (S)-2-(1-(9H-purin-6-ylamino)propyl)-5-fluoro-3-(3-fluorophenylamino)quinazolin-4(3H)-one

To a solution of (S)-2-(1-aminopropyl)-5-fluoro-3-(3-fluorophenylamino)quinazolin-4(3H)-one hydrochloride (650 mg, 1.77 mmol) in tert-butanol (20 mL) was added DIEA(0.92 mL, 5.28 mmol), After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine (819 mg, 5.30 mmol) was added. The reaction was stirred at 85ºC for 24 h ,After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by silica column chromatography (EA) to give the title compound as a white solid (207mg, 26.1%) MS(M+1):

449.2; ^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.99 (1H, br s), 9.23 (1H, s), 8.22-8.11 (1H, m), 8.05 (1H, s), 7.95-7.70 (2H, m), 7.39 (1H, d), 7.31-7.19 (2H, m), 6.92-6.74 (2H, m), 6.70-6.61 (1H, m), 5.40 (1H, m), 2.17-2.05 (1H, m), 2.04-1.85 (1H, m), 1.02 (3H, t).

Example 12 : Preparation of (S)-2-(1-(9H-purin-6-ylamino)propyl)-5-fluoro-3-(3-methoxyphenylamino)quinazolin-4(3H)-one (Compound 14)



(1) Preparation of 2-fluoro-N'-(3-methoxyphenyl)-6-nitrobenzohydrazide

To a solution of 2-fluoro-6-nitrobenzoic acid(5.55 g, 30.0 mmol)in CH_2Cl_2 (50 mL)and DMF(0.3 mL) was added Oxalyl chloride(5.71 g, 45.0 mmol) dropwise, the mixture was stired for 2 h and concentrated .The residue was dissolved in 1,4-dioxane and added to a solution of (3-methoxyphenyl)hydrazine hydrochloride (5.23 g, 30.0 mmol),$NaHCO_3$ (7.56 g, 90.0 mmol) in 1,4-dioxane (15mL)and water (15 mL) dropwrise , the mixture was stirred for 30 min at rt and concentrated ,extracted with EA, dried by Anhydrous sodium sulfate ,filtered ,concentrated and purified by silica column chromatography (PE:EA=2:1) to give the title compound as a white solid (4.23g, 46.2%)

(2)Preparation of 2-amino-6-fluoro-N'-(3-methoxyphenyl)benzohydrazide

A solution of 2-fluoro-N'-(3-methoxyphenyl)-6-nitrobenzohydrazide (3.05 g,10.0 mmol) in methanol (30 mL) was carefully poured into Pd/C (10%, 0.5g), and the resulting reaction mixture was stirred under hydrogen atmosphere for 18 h. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound (2.7, 98.1%).

(3)Preparation of (S)-tert-butyl 1-(3-fluoro-2-(2-(3-methoxyphenyl)hydrazinecarbonyl)phenylamino)-1-oxobutan-2-ylcarbamate

A solution of 2-amino-6-fluoro-N'-(3-methoxyphenyl)benzohydrazide (2.7 g, 9.81 mmol),

(S)-2-(tert-butoxycarbonylamino)butanoic acid (3.0 g, 14.76 mmol),DIEA (2.3 mL, 13.3 mmol) and HATU(4.0 g, 10.5 mmol) in DCM (20 mL) was stirred at rt for 64h,. the mixture was partitioned between DCM and water ,the organic layer was separated washed with brine , dried and concentrated in vacuo. The crude product was purified purified by silica column chromatography (PE:EA=3:1) to give the title compound as a white solid (1.4g, 31.0%)

(4)Preparation of (S)-2-(1-aminopropyl)-5-fluoro-3-(3-methoxyphenylamino) quinazolin-4(3H)-one hydrochloride

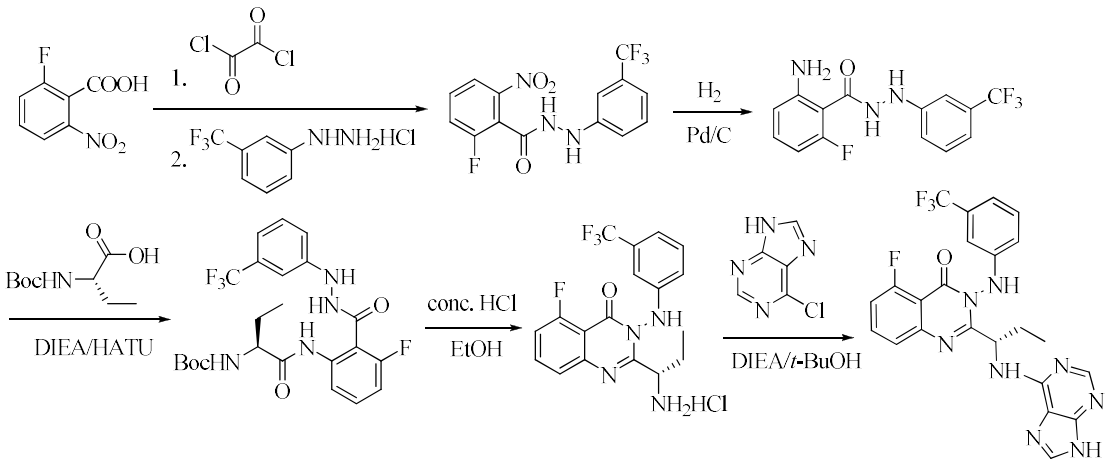
A solution of (S)-tert-butyl 1-(3-fluoro-2-(2-(3- methoxyphenyl)hydrazinecarbonyl) phenylamino)-1-oxobutan-2-ylcarbamate (600 mg, 1.31 mmol) in ethanol (20 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (2mL). The reaction was stirred at room temperature for 30min, and then at 85ºC for 24 hr. After cooled to room temperature, the reaction solution was concentrated to give the title compound as a white solid

(5)Preparation of (S)-2-(1-(9H-purin-6-ylamino)propyl)-5-fluoro-3-(3-methoxyphenylamino) quinazolin-4(3H)-one

To a solution of (S)-2-(1-aminopropyl)-5-fluoro-3-(3-methoxyphenylamino)quinazolin-4(3H)-one hydrochloride (1.31mmol) in tert-butanol (20 mL) was added DIEA(0.68 mL, 3.91 mmol), After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine (242 mg, 1.57 mmol)was added. The reaction was stirred at 85ºC for 36 h ,After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by silica column chromatography (EA) to give the title compound as a white solid (146mg, 24.2%).

MS(M+1): 461.2. ^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.97 (1H, s), 9.00 (1H, s), 8.22-8.05 (2H, m), 7.85-7.69 (2H, m), 7.40 (1H, d), 7.32-7.21 (1H, m), 7.17-7.05 (1H, m), 6.60-6.41 (3H, m), 5.47 (1H, s), 3.68 (3H, s), 2.20-2.08 (1H, m), 2.02-1.92 (1H, m), 0.998 (3H, t).

Example 13 : Preparation of (S)-2-(1-(9H-purin-6-ylamino)propyl)-5-fluoro-3-(3-methoxyphenylamino)quinazolin-4(3H)-one (Compound 15)



(1) Preparation of 2-fluoro-6-nitro-N'-(3-(trifluoromethyl)phenyl)benzohydrazide

To a solution of 2-fluoro-6-nitrobenzoic acid(6.32 g, 29.73 mmol)in CH_2Cl_2 (50 mL)and DMF(0.3 mL) was added Oxalyl chloride(5.71 g, 45.0 mmol) dropwise, the mixture was stired for 2 h and concentrated .The residue was dissolved in 1,4-dioxane and added to a solution of (3-(trifluoromethyl)phenyl)hydrazine hydrochloride (4.8 g, 29.73 mmol),$NaHCO_3$ (5 g, 59.5 mmol) in 1,4-dioxane (15mL)and water (15 mL) dropwrise , the mixture was stirred for 30 min at rt and concentrated ,extracted with EA, dried by Anhydrous sodium sulfate, filtered , concentrated and filtered to give the title compound as a white solid (5.3g, 51.8%)

(2)Preparation of 2-amino-6-fluoro-N'-(3-(trifluoromethyl)phenyl)benzohydrazide

A solution of 2-fluoro-6-nitro-N'-(3-(trifluoromethyl)phenyl)benzohydrazide (5.3 g, 15.4 mmol) in methanol (100 mL) was carefully poured into Pd/C (10%, 0.6 g), and the resulting reaction mixture was stirred under hydrogen atmosphere for 24 h. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound (4.76 g,98.7%).

(3)Preparation of tert-butyl (S)-(1-((3-fluoro-2-(2-(3-(trifluoromethyl)phenyl)hydrazine-1-carbonyl)phenyl)amino)-1-oxobutan-2-yl)carbamate

A solution of 2-amino-6-fluoro-N'-(3-(trifluoromethyl)phenyl)benzohydrazide (4.51 g, 14.4 mmol), (S)-2-(tert-butoxycarbonylamino)butanoic acid (5.8 g, 28.5 mmol),DIEA (3.7 mL, 21.2 mmol)and HATU(6.0 g,15.8 mmol)in DMF (80 mL) was stirred at rt for 48h,. the mixture was partitioned between DCM and water ,the organic layer was separated washed with brine, dried and concentrated in vacuo. The crude product was purified by preparation HPLC to give the title compound as a white solid (1.29g , 18.0%).

(4)Preparation of

(S)-2-(1-aminopropyl)-5-fluoro-3-((3-(trifluoromethyl)phenyl)amino)quinazolin-4(3H)-one hydrochloride

A solution of (tert-butyl

(S)-(1-((3-fluoro-2-(2-(3-(trifluoromethyl)phenyl)hydrazine-1-carbonyl)phenyl)amino)-1-oxobutan-2-yl)carbamate (1.29 g, 2.59 mmol) in ethanol (40 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (5mL). The reaction was stirred at room temperature for 30min, and then at 85ºC for 4 d . After cooled to room temperature, the reaction solution was concentrated and purified by preparation HPLC to give the title compound as a white solid(0.22 g, 20.4%).

(5)Preparation of

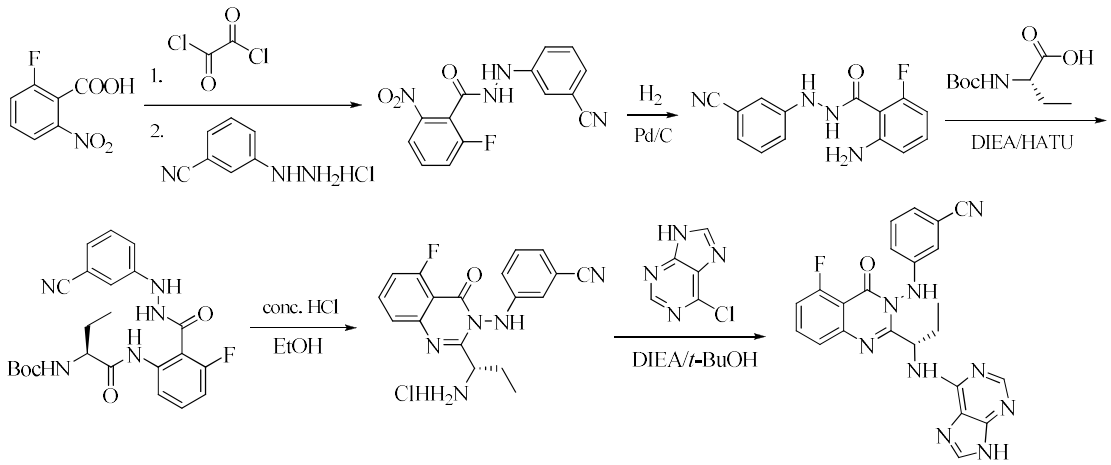
(S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-3-((3-(trifluoromethyl)phenyl)amino)quinazolin-4(3H)-one

To a solution of

(S)-2-(1-aminopropyl)-5-fluoro-3-((3-(trifluoromethyl)phenyl)amino)quinazolin-4(3H)-one hydrochloride (220 mg, 0.528 mmol) in tert-butanol (40 mL) was added DIEA(0.28 mL, 1.61 mmol), After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine (243 mg, 1.57 mmol) was added. The reaction was stirred at 85ºC for 24 h ,After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by silica column chromatography (EA) to give the title compound as a white solid (71mg, 27.0%) .MS(M+1): 499.2; ^{1}H-NMR(*d*$_6$-DMSO, 400 MHz): δ 12.96 (1H, br s), 9.38 (1H, s), 8.19-7.96 (2H, m), 7.92-7.64 (2H, m), 7.56-7.35 (2H, m), 7.31-7.13 (4H, m), 5.43 (1H, m), 2.21-2.06 (1H, m), 2.04-1.98 (1H, m), 1.02 (3H, t).

Example 14 : Preparation of

(S)-3-((2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-4-oxoquinazolin-3(4H)-yl)amino)benzonitrile (Compound 16)



(1) Preparation of N'-(3-cyanophenyl)-2-fluoro-6-nitrobenzohydrazide

To a solution of 2-fluoro-6-nitrobenzoic acid(5.55 g, 30.0 mmol)in CH_2Cl_2 (50 mL)and DMF(0.3 mL) was added Oxalyl chloride(5.71 g, 45.0 mmol) dropwise, the mixture was stired for 2 h and concentrated .The residue was dissolved in 1,4-dioxane and added to a solution of 3-hydrazinylbenzonitrile hydrochloride (5.09 g, 30.0 mmol),$NaHCO_3$ (7.56 g, 90.0 mmol) in 1,4-dioxane (15 mL)and water (15 mL) dropwrise , the mixture was stirred for 30 min at rt and concentrated ,extracted with EA, dried by Anhydrous sodium sulfate, filtered,concentrated and purified by silica column chromatography (PE:EA=2:1) to give the title compound as a white solid (7.2g, 80.0%).

(2)Preparation of 2-amino-N'-(3-cyanophenyl)-6-fluorobenzohydrazide

A solution of N'-(3-cyanophenyl)-2-fluoro-6-nitrobenzohydrazide (4.2 g, 14.0 mmol) in methanol (30 mL) was carefully poured into Pd/C (10%, 0.6g), and the resulting reaction mixture was stirred under hydrogen atmosphere for 18 h. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound for the next step.

(3)Preparation of tert-butyl (S)-(1-((2-(2-(3-cyanophenyl)hydrazine-1-carbonyl)-3-fluorophenyl)amino)-1-oxobutan-2-yl) carbamate

A solution of 2-amino-N'-(3-cyanophenyl)-6-fluorobenzohydrazide (-14 mmol), (S)-2-(tert-butoxycarbonylamino)butanoic acid (4.26 g, 21.0 mmol),DIEA (3.3 mL, 19 mmol) and HATU(6.38 g,16.8 mmol)in DCM (40 mL) was stirred at rt for 3 d . the mixture was partitioned between DCM and water ,the organic layer was separated washed with brine, dried and concentrated in vacuo. The crude product was purified purified by silica column

chromatography (PE:EA=3:1) to give the title compound as a white solid (2.9g, 45.5% two steps)

(4) Preparation of

(S)-3-((2-(1-aminopropyl)-5-fluoro-4-oxoquinazolin-3(4H)-yl)amino)benzonitrile hydrochloride

A solution of tert-butyl

(S)-(1-((2-(2-(3-cyanophenyl)hydrazine-1-carbonyl)-3-fluorophenyl)amino)-1-oxobutan-2-yl) carbamate (1.37 g, 3.0 mmol) in ethanol (30 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (3mL). The reaction was stirred at room temperature for 30min, and then at 85ºC for 24 hr. After cooled to room temperature, the reaction solution was concentrated to give the title compound as a white solid for the next step.

(5)Preparation of

(S)-3-((2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-4-oxoquinazolin-3(4H)-yl)amino)benzonitrile

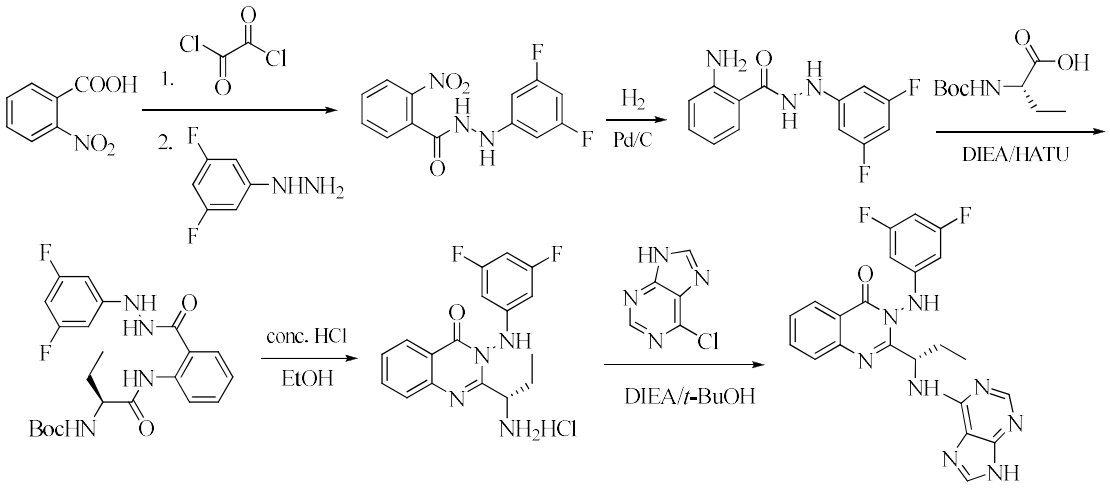
To a solution of

(S)-3-((2-(1-aminopropyl)-5-fluoro-4-oxoquinazolin-3(4H)-yl)amino)benzonitrile hydrochloride (3.0mmol) in tert-butanol (20 mL) was added DIEA(1.56 mL, 9.0 mmol), After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine(556 mg, 3.6 mmol) was added. The reaction was stirred at 85ºC for 36 h. After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by silica column chromatography (EA) to give the title compound as a white solid (168mg, 12.3%).

MS(M+1): 456.2.^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.95 (1H, s), 9.37 (1H, s), 8.20-8.07 (2H, m), 7.96-7.72 (2H, m), 7.47-7.20 (6H, m), 5.38 (1H, m), 2.18-1.85 (2H, m), 1.02 (3H, t).

Example 15 : Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)propyl)-3-((3,5-difluorophenyl)amino)quinazolin-4(3H)-one (Compound 17)



(1) Preparation of N'-(3,5-difluorophenyl)-2-nitrobenzohydrazide

To a solution of 2-nitrobenzoic acid (5 g,30 mmol)in CH_2Cl_2 (50 mL)and DMF(1 mL) was added Oxalyl chloride(5.71 g, 45.0 mmol) dropwise, the mixture was stired for 2 h and concentrated .The residue was dissolved in 1,4-dioxane and added to a solution of (3,5-difluorophenyl)hydrazine (5.23 g, 30.0 mmol),$NaHCO_3$ (10.08 g, 120 mmol) in 1,4-dioxane (20mL) and water (20 mL) dropwrise , the mixture was stirred for 30 min at rt and concentrated and poured into 50mL water, filtered and dried to give the title compound as a white solid (7.3g, 83.0%).

(2)Preparation of 2-amino-N'-(3,5-difluorophenyl)benzohydrazide

A solution of N'-(3,5-difluorophenyl)-2-nitrobenzohydrazide (7.3 g, 24.9 mmol)was carefully poured into Pd/C (10%, 0.8g), and the resulting reaction mixture was stirred under hydrogen atmosphere for 18 h. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound (6.4, 97.6%).

(3)Preparation of (tert-butyl (S)-(1-((2-(2-(3,5-difluorophenyl)hydrazine-1-carbonyl)phenyl) amino)-1-oxobutan-2-yl)carbamate

A solution of 2-amino-N'-(3,5-difluorophenyl)benzohydrazide (2.7 g, 9.81 mmol), (S)-2-(tert-butoxycarbonylamino)butanoic acid(3.09 g, 15.2 mmol),DIEA(7.86 mL, 45.1 mmol),HATU(6.34 g, 16.7 mmol) in DCM (80 mL) and DMF (2 mL) was stirred at rt for 72 h,. the mixture was partitioned between DCM and water ,the organic layer was separated washed with brine, dried and concentrated in vacuo. The crude product was purified purified by silica column chromatography to give the title compound as a white solid (1.2g, 17.6%).

(4) Preparation of (S)-2-(1-aminopropyl)-3-((3,5-difluorophenyl)amino)quinazolin-4(3H)-one

hydrochloride

A solution of tert-butyl (S)-(1-((2-(2-(3,5-difluorophenyl)hydrazine-1-carbonyl)phenyl) amino)-1-oxobutan-2-yl)carbamate(1.2 g, 2.68 mmol) in ethanol (50 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (5mL). The reaction was stirred at room temperature for 30min, and then at 85ºC for 16 hr. After cooled to room temperature, the reaction solution was concentrated to give the title compound as a white solid for the next step.

(5)Preparation of

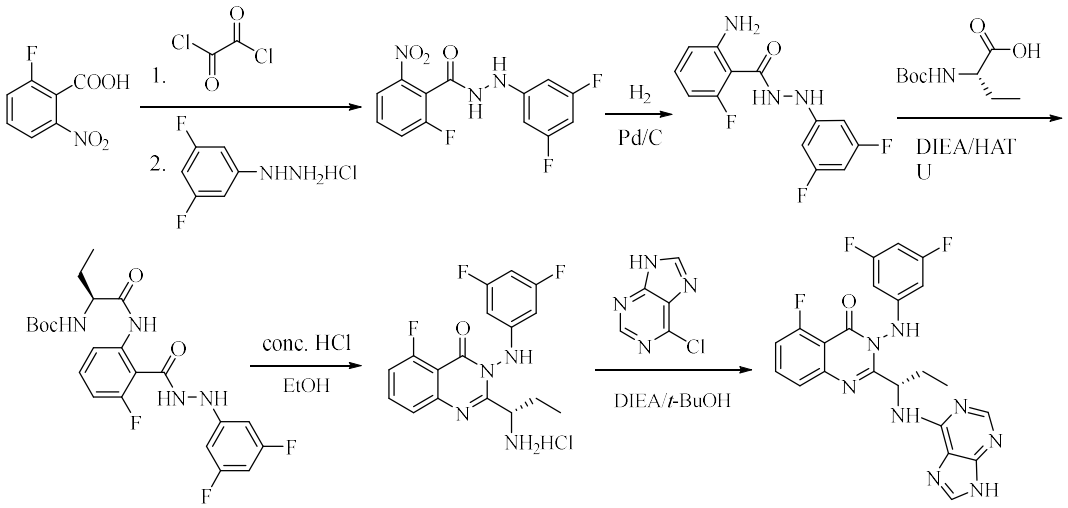
(S)-2-(1-((9H-purin-6-yl)amino)propyl)-3-((3,5-difluorophenyl)amino)quinazolin-4(3H)-one

To a solution of (S)-2-(1-aminopropyl)-3-((3,5-difluorophenyl)amino)quinazolin-4(3H)-one hydrochloride in tert-butanol (20 mL) was added DIEA(0.8 mL, 4.6 mmol). After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine (185 mg, 1.2 mmol) was added. The reaction was stirred at 85ºC for 5h under N_2 atmosphere. After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by preparation HPLC to give the title compound as a white solid (98mg, 8.2%).

MS(M+1): 449.2; ^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.95 (1H, br s), 9.50 (1H, s), 8.21-8.11 (1H, m), 8.07 (1H, d), 8.01 (1H, s), 7.98-7.85 (1H, m), 7.80 (1H, t), 7.59 (1H, d), 7.51 (1H, t), 6.75-6.55 (3H, m), 5.40 (1H, m), 2.17-2.07 (1H, m), 2.02-1.90 (1H, m), 1.03 (3H, t).

Example 16 : Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)propyl)-3-((3,5-difluorophenyl)amino)-5-fluoroquinazolin-4(3H)-one (Compound 18)



(1) Preparation of N'-(3,5-difluorophenyl)-2-fluoro-6-nitrobenzohydrazide

To a solution of 2-fluoro-6-nitrobenzoic acid(16.51 g, 89.2 mmol)in CH_2Cl_2 (100 mL)and DMF(0.5 mL) was added Oxalyl chloride(17 g, 134 mmol) dropwise, the mixture was stired for 2 h and concentrated .The residue was dissolved in 1,4-dioxane and added to a solution of (3,5-difluorophenyl)hydrazine hydrochloride (5.37 g, 29.73 mmol),$NaHCO_3$ (5 g, 59.5 mmol) in 1,4-dioxane (15mL)and water (15 mL) dropwrise , the mixture was stirred for 30 min at rt and concentrated ,extracted with EA, dried by Anhydrous sodium sulfate, filtered,concentrated and filtered to give the title compound as a white solid (5.8g,62.6%).

(2)Preparation of 2-amino-N'-(3,5-difluorophenyl)-6-fluorobenzohydrazide

A solution of N'-(3,5-difluorophenyl)-2-fluoro-6-nitrobenzohydrazide (5.8 g, 18.6 mmol)in methanol (100 mL) was carefully poured into Pd/C (10%, 0.6 g), and the resulting reaction mixture was stirred under hydrogen atmosphere for 24 h. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound (5.1 g,97.3%).

(3)Preparation of tert-butyl (S)-(1-((2-(2-(3,5-difluorophenyl)hydrazine-1-carbonyl)-3-fluorophenyl)amino)-1-oxobutan-2-yl)carbamate

A solution of 2-amino-N'-(3,5-difluorophenyl)-6-fluorobenzohydrazide (4.06 g, 14.4 mmol), (S)-2-(tert-butoxycarbonylamino)butanoic acid (5.8 g, 28.5 mmol), DIEA (3.7 mL, 21.2 mmol)and HATU(6.0 g,15.8 mmol)in DMF (80 mL) was stirred at rt for 48h,. the mixture was partitioned between DCM and water ,the organic layer was separated washed with brine, dried and concentrated in vacuo. The crude product was purified by preparation HPLC to give the title compound as a white solid (1.5g ,22.4%).

(4)Preparation of (S)-2-(1-aminopropyl)-3-((3,5-difluorophenyl)amino)-5-fluoroquinazolin-4(3H)-one hydrochloride

A solution of tert-butyl (S)-(1-((2-(2-(3,5-difluorophenyl)hydrazine-1-carbonyl)-3-fluorophenyl)amino)-1-oxobutan-2-yl)carbamate (1.5 g, 3.22 mmol) in ethanol (40 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (5mL). The reaction was stirred at room temperature for 30min, and then at 85ºC for 4 d. After cooled to room temperature, the reaction solution was concentrated and purified by preparation HPLC to give the title

compound as a white solid(0.44 g, 35.4%).

(5)Preparation of

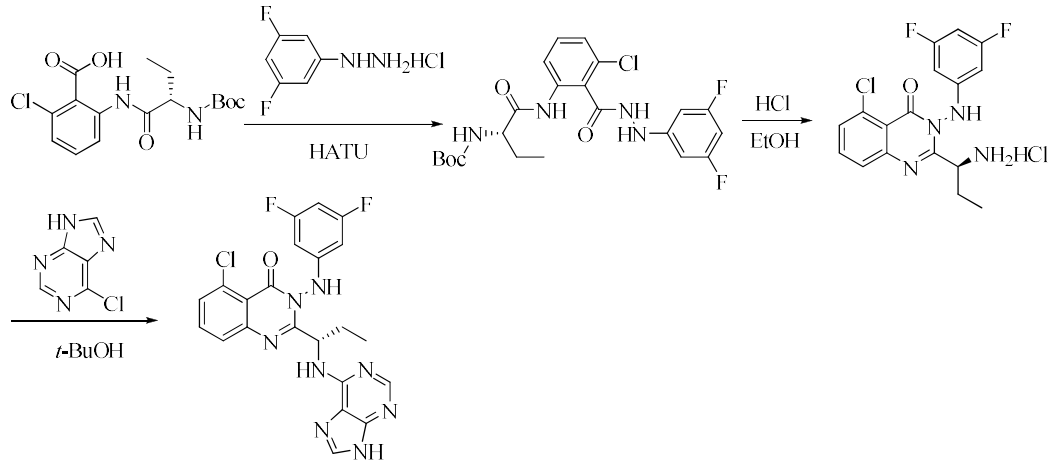
(S)-2-(1-((9H-purin-6-yl)amino)propyl)-3-((3,5-difluorophenyl)amino)-5-fluoroquinazolin-4(3H)-one

To a solution of

(S)-2-(1-aminopropyl)-3-((3,5-difluorophenyl)amino)-5-fluoroquinazolin-4(3H)-one hydrochloride(440 mg, 1.14 mmol)in tert-butanol (40 mL) was added DIEA(0.6 mL, 3.4 mmol), After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine (529 mg, 3.42 mmol) was added. The reaction was stirred at 85ºC for 24 h ,After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by silica column chromatography (EA) to give the title compound as a white solid (197mg, 37.0%). MS(M+1): 467.2; ^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.97 (1H, br s), 9.41 (1H, s), 8.30-7.90 (3H, m), 7.84-7.71 (1H, m), 7.39 (1H, d), 7.32-7.22 (1H, m), 6.80-6.67 (2H, m), 6.65-6.55 (1H, m), 5.36 (1H, m), 2.16-2.00 (1H, m), 1.96-1.82 (1H, m), 1.02 (3H, t).

Example 17 : Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-chloro-3-((3,5-difluorophenyl)amino)quinazolin-4(3H)-one (Compound 19)



(1)Preparation of tert-butyl

(S)-(1-((3-chloro-2-(2-(3,5-difluorophenyl)hydrazine-1-carbonyl)phenyl)amino)-1-oxobutan-2-yl)carbamate

A solution of (S)-2-(2-(tert-butoxycarbonylamino)butanamido)-6-chlorobenzoic acid(7.48 g ,21.0 mmol) ,(3,5-difluorophenyl)hydrazine hydrochloride (5.60 g, 31.0 mmol), DIEA

(9.1mL, 52.3 mmol),HATU(10.37g, 27.3 mmol) in DCM (50mL) and DMF (50 mL)was stirred at rt overnight. the mixture was partitioned between EA and water ,the organic layer was separated washed with brine, dried and concentrated in vacuo. The crude product was purified by silica column chromatography (PE/EA=3:1) to give the title compound as a pale yellow solid (7.23 g, 71.3%).

(2)Preparation of (S)-2-(1-aminopropyl)-5-chloro-3-((3,5-difluorophenyl)amino) quinazolin-4(3H)-one hydrochloride

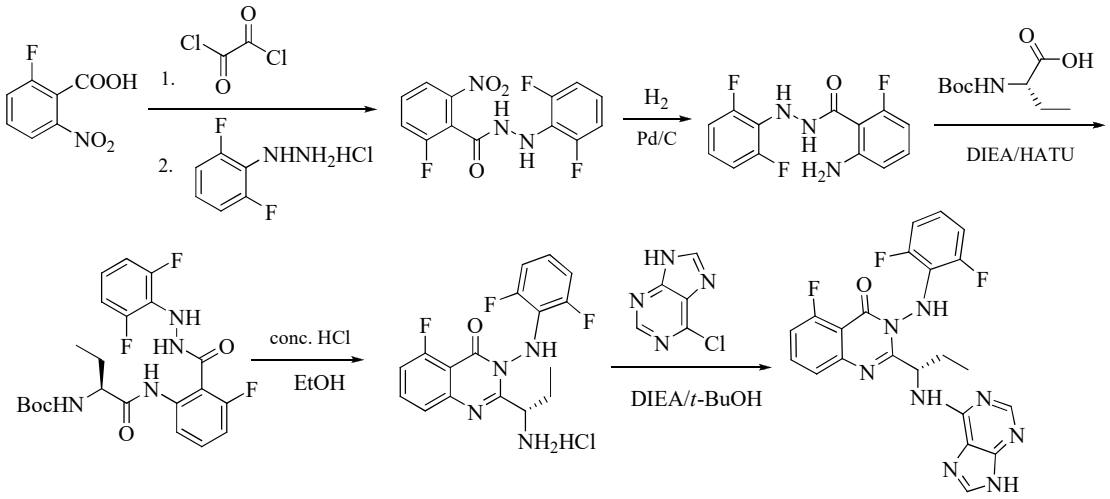
A solution of tert-butyl (S)-(1-((3-chloro-2-(2-(3,5-difluorophenyl)hydrazine-1-carbonyl) phenyl)amino)-1-oxobutan-2-yl)carbamate (900 mg, 1.86 mmol) in ethanol (10 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (3 mL). The reaction was stirred at room temperature for 30min, and then at 85ºC overnight. After cooled to room temperature, filtered and washed with the mixture of ice-ethanol and ethyl ether as a white solid (300mg, 40.2%).

(3)Preparation of (S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-chloro-3-((3,5-difluorophenyl) amino)quinazolin-4(3H)-one

To a solution of (S)-2-(1-aminopropyl)-5-chloro-3-((3,5-difluorophenyl)amino) quinazolin-4(3H)-one hydrochloride (300 mg, 0.748 mmol) in tert-butanol (15 mL) was added DIEA (2 mL). After the reaction was stirred at 0ºC for 30 min, 6-chloro-9*H*-purine (0.155 g, 1.0 mmol) was added. The reaction was stirred at 85ºC for 3 d ,After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by silica column chromatography (PE/EA=1:1-1:3) to give the title compound as a white solid (272mg, 75.3%).

MS(M+1): 483.1; ^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.96 (1H, br s), 9.39 (1H, s), 8.20-8.09 (1H, m), 8.02 (1H, s), 7.77-7.60 (2H, m), 7.57-7.48 (2H, m), 6.81-6.69 (2H, m), 6.67-6.56 (1H, m), 5.35 (1H, m), 2.15-1.92 (2H, m), 1.02 (3H, t).

Example 18 : Preparation of (S)-2-(1-((9H-purin-6-yl)amino)propyl)-3-((2,6-difluorophenyl)amino)-5-fluoroquinazolin -4(3H)-one (Compound 20)



(1) Preparation of N'-(2,6-difluorophenyl)-2-fluoro-6-nitrobenzohydrazide

To a solution of 2-fluoro-6-nitrobenzoic acid(5.5 g, 29.7 mmol)in CH_2Cl_2 (50 mL)and DMF(0.4 mL) was added Oxalyl chloride(5.66 g, 44.6 mmol) dropwise, the mixture was stired for 2 h and concentrated .The residue was dissolved in 1,4-dioxane and added to a solution of (2,6-difluorophenyl)hydrazine hydrochloride (5.0 g, 27.7 mmol), $NaHCO_3$ (6.72 g, 80.0 mmol) in 1,4-dioxane (20mL)and water (20 mL) dropwrise , the mixture was stirred for 30 min at rt and concentrated ,extracted with EA, dried by Anhydrous sodium sulfate, filtered, concentrated and filtered to give the title compound as a pale yellow solid (4.8g, 55.7%)

(2)Preparation of 2-amino-N'-(2,6-difluorophenyl)-6-fluorobenzohydrazide

A solution of N'-(2,6-difluorophenyl)-2-fluoro-6-nitrobenzohydrazide (4.8 g, 15.4 mmol)in methanol (60 mL) was carefully poured into Pd/C (10%, 0.5 g), and the resulting reaction mixture was stirred under hydrogen atmosphere for 36 h. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound (4.2 g, 97.0%).

(3)Preparation of tert-butyl (S)-(1-((2-(2-(2,6-difluorophenyl)hydrazine-1-carbonyl)-3-fluorophenyl)amino)-1-oxobutan-2-yl)carbamate

A solution of 2-amino-N'-(2,6-difluorophenyl)-6-fluorobenzohydrazide (4.2 g, 14.93 mmol), (S)-2-(tert-butoxycarbonylamino)butanoic acid (6.06 g, 29.8 mmol), DIEA (2.9 mL, 16.7 mmol)and HATU(6.25 g, 16.4 mmol)in DCM (200 mL) was stirred at rt for 48h, the mixture was partitioned between DCM and water, the organic layer was separated washed with brine, dried and concentrated in vacuo. The crude product was purified by preparation HPLC to give the title compound as a white solid (3.0g, 43.1%).

(4)Preparation of
(S)-2-(1-aminopropyl)-3-((2,6-difluorophenyl)amino)-5-fluoroquinazolin-4(3H)-one hydrochloride

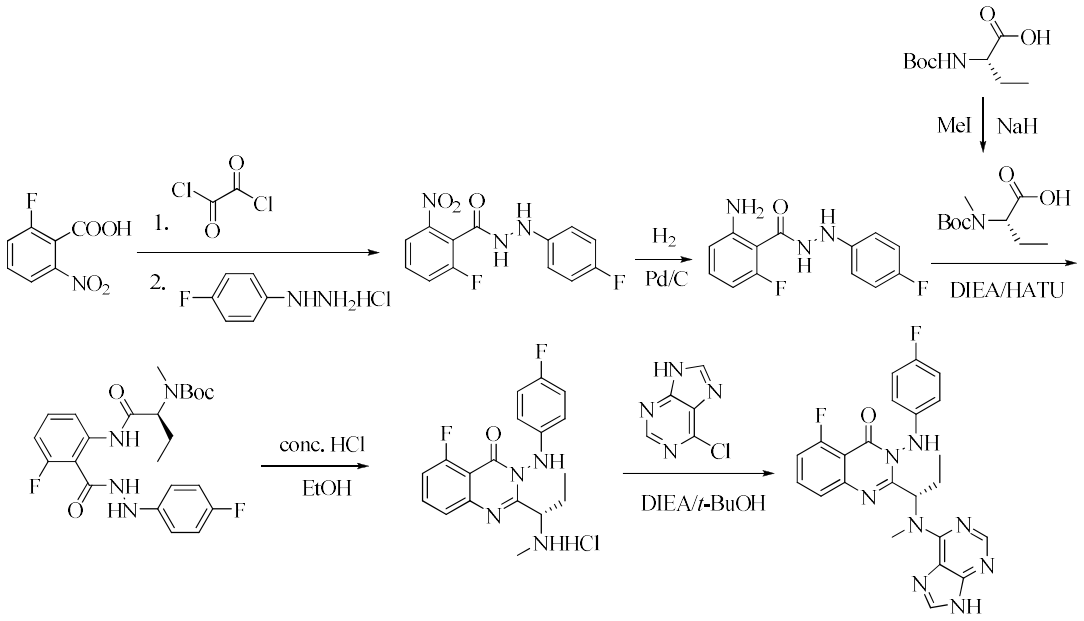
A solution of tert-butyl
(S)-(1-((2-(2-(2,6-difluorophenyl)hydrazine-1-carbonyl)-3-fluorophenyl)amino)-1-oxobutan-2-yl)carbamate(3.0 g, 6.43 mmol) in ethanol (60 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (5mL). The reaction was stirred at room temperature for 30min, and then at 85ºC for 4 d. After cooled to room temperature, the reaction solution was concentrated and purified by preparation HPLC to give the title compound as a white solid(1.3g, 52.5%).

(5)Preparation of (S)-2-(1-((9H-purin-6-yl)amino)propyl)-3-((2,6-difluorophenyl) amino)-5-fluoroquinazolin-4(3H)-one

To a solution of
(S)-2-(1-aminopropyl)-3-((2,6-difluorophenyl)amino)-5-fluoroquinazolin-4(3H)-one hydrochloride (1.3 g, 3.38 mmol) in tert-butanol (20 mL) was added DIEA (1.75 mL, 10 mmol), After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine (1.6 g, 10.4 mmol) was added. The reaction was stirred at 85ºC for 24 h, After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by silica column chromatography (EA) to give the title compound as a white solid (1.01g, 64.1%).

MS(M+1): 447.2; ^{1}H-NMR(d_6-DMSO, 400 MHz): δ 13.00 (1H, br s), 9.09 (1H, s), 8.25-8.05 (2H, m), 7.89-7.80 (1H, m), 7.57 (1H, d), 7.39-7.27 (2H, m), 7.06-6.85 (3H, m), 6.05 (1H, m), 2.26-2.12 (1H, m), 2.01-1.88 (1H, m), 0.92 (3H, t).

Example 19 : Preparation of
(S)-5-fluoro-3-((4-fluorophenyl)amino)-2-(1-(methyl(9H-purin-6-yl)amino)propyl)quinazolin-4(3H)-one (Compound 21)



(1)Preparation of 2-fluoro-N'-(4-fluorophenyl)-6-nitrobenzohydrazide

To a solution of 2-fluoro-6-nitrobenzoic acid (5.5 g, 29.7 mmol) in CH_2Cl_2 (50 mL)and DMF(0.4 mL) was added Oxalyl chloride(5.66 g, 44.6 mmol) dropwise, the mixture was stired for 2 h and concentrated .The residue was dissolved in 1,4-dioxane and added to a solution of (4-fluorophenyl)hydrazine hydrochloride (4.829 g, 29.7 mmol), $NaHCO_3$ (6.72 g, 80.0 mmol) in 1,4-dioxane (20mL)and water (20 mL) drowrise, the mixture was stirred for 30 min at rt and concentrated, extracted with EA, dried by Anhydrous sodium sulfate, filtered, concentrated and purified by silica column chromatography (PE:EA=2:1) to give the title compound as a white solid (4.4g, 50.5%).

(2)Preparation of 2-amino-6-fluoro-N'-(4-fluorophenyl)benzohydrazide

A solution of 2-fluoro-N'-(4-fluorophenyl)-6-nitrobenzohydrazide (4.4 g, 15.0 mmol) in methanol (60 mL) was carefully poured into Pd/C (10%, 0.5 g), and the resulting reaction mixture was stirred under hydrogen atmosphere for 36 h. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound (3.8g, 96.3%).

(3)Preparation of (S)-2-((tert-butoxycarbonyl)(methyl)amino)butanoic acid

To a solution of (S)-2-(tert-butoxycarbonylamino)butanoic acid (15.0 g, 73.8 mmol)in THF (600mL) was added 60%NaH(29.6 g, 740 mmol)at 0ºC, the mixture was stirred for 30 min, and iodomethane (104.92 g, 739 mmol)was added and this mixture was stirred at rt overnight. After the reaction was completed, the solution was evaporated and 200 mL water was added, the mixture was adjusted PH to 7 and extracted with EA, the organic layer was concentrated to

give the title compound (3.8 g, 68.6%).

(4)Preparation of tert-butyl (S)-(1-((3-fluoro-2-(2-(4-fluorophenyl)hydrazine-1-carbonyl)phenyl)amino)-1-oxobutan-2-yl)(methyl)carbamate

A solution of 2-amino-6-fluoro-N'-(4-fluorophenyl)benzohydrazide (3.8g, 14.4 mmol), (S)-2-(tert-butoxycarbonylamino)butanoic acid (5.8 g, 28.6mmol), DIEA (3.7 mL, 21.2 mmol,HATU(6.0 g,15.8 mmol) in DCM (200mL) was stirred at rt for 48 h, the mixture was partitioned between DCM and water, the organic layer was separated washed with brine, dried and concentrated in vacuo. The crude product was purified by preparation HPLC to give the title compound as a white solid (3.4 g, 52.6 %).

(5)Preparation of (S)-5-fluoro-3-((4-fluorophenyl)amino)-2-(1-(methylamino)propyl)quinazolin-4(3H)-one hydrochloride

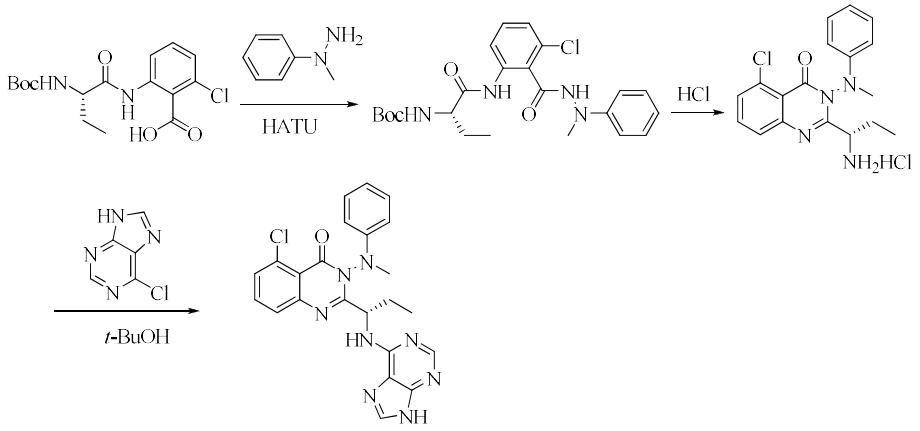
A solution of tert-butyl (S)-(1-((3-fluoro-2-(2-(4-fluorophenyl)hydrazine-1-carbonyl)phenyl)amino)-1-oxobutan-2-yl)(methyl)carbamate(2.6 g, 5.62 mmol) in ethanol (60 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (10 mL). The reaction was stirred at room temperature for 30min, and then at 85ºC for 64 h. After cooled to room temperature, the reaction solution was concentrated and purified by preparation HPLC to give the title compound as a white solid (0.4 g, 18.7 %).

(6)Preparation of (S)-5-fluoro-3-((4-fluorophenyl)amino)-2-(1-(methyl(9H-purin-6-yl)amino)propyl)quinazolin-4(3H)-one

To a solution of (S)-5-fluoro-3-((4-fluorophenyl)amino)-2-(1-(methylamino)propyl)quinazolin-4(3H)-one hydrochloride (300 mg, 0.788 mmol)in tert-butanol (10 mL) was added DIEA (0.45 mL, 2.58 mmol). After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine (241 mg, 1.56 mmol) was added. The reaction was stirred at 85ºC for 72 h, After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by preparation HPLC to give the title compound as a white solid (140mg, 38.4%).

MS(M+1): 463.1; ^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.82 (1H, s), 8.85-8.47 (2H, m), 8.15-7.46 (4H, m), 7.39-7.26 (1H, m), 7.10-6.86 (1H, m), 6.77-6.66 (1H, m), 6.62-6.51 (1H, m), 6.46-5.94 (1H, m), 3.66-2.94 (3H, d), 2.27-1.98 (2H, m), 0.93 (3H, t).

Example 20 : Preparation of (S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-chloro-3-(methyl(phenyl)amino)quinazolin-4(3H)-one (Compound 22)



(1)Preparation of tert-butyl (S)-(1-((3-chloro-2-(2-methyl-2-phenylhydrazine-1-carbonyl)phenyl)amino)-1-oxobutan-2-yl) carbamate

A solution of(S)-2-(2-((tert-butoxycarbonyl)amino)butanamido)-6-chlorobenzoic acid (1.50 g, 4.20 mmol), 1-methyl-1-phenylhydrazine (770 mg, 6.3 mmol) DIEA (1.47mL, 8.44 mmol), HATU(2.08 g, 5.47 mmol) in DCM (20mL) and DMF (10 mL)was stirred at rt overnight. the mixture was partitioned between EA and water, the organic layer was separated washed with brine, dried and concentrated in vacuo. The crude product was purified by silica column chromatography to give the title compound as a pale yellow solid (0.75 g , 38.8%).

(2)Preparation of (S)-2-(1-aminopropyl)-5-chloro-3-(methyl(phenyl)amino)quinazolin-4(3H)-one hydrochloride

A solution of tert-butyl (S)-(1-((3-chloro-2-(2-methyl-2-phenylhydrazine-1-carbonyl)phenyl)amino)-1-oxobutan-2-yl) carbamate (750mg, 1.63 mmol) in ethanol (10 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (3 mL). The reaction was stirred at room temperature for 30min, and then at 85ºC overnight. After cooled to room temperature, filtered and washed with the mixture of ice-ethanol and ethyl ether as a white solid (450mg, 73.0%).

(3)Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-chloro-3-(methyl(phenyl)amino)quinazolin-4(3H)-one

To a solution of (S)-2-(1-aminopropyl)-5-chloro-3-(methyl(phenyl)amino) quinazolin-4(3H)-one hydrochloride(450 mg, 1.19 mmol) in tert-butanol (15 mL) was added DIEA (2 mL). After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine (308 mg, 1.99 mmol) was added. The reaction was stirred at 85ºC for 2 d. After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by preparation HPLC to give the title compounds as white solid. The smaller retention time isomer in HPLC was yielded 100 mg, another isomer was 120mg in hand, the total yield 40.1%.

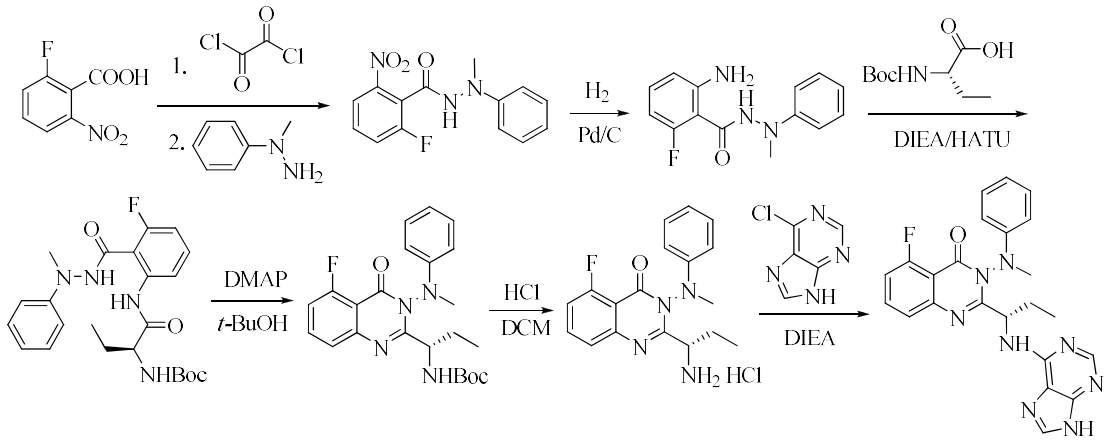
MS(M+1): 461.2;

The isomer 1(The retention time in HPLC was smaller)^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.90 (1H, br s), 8.20-7.99 (2H, m), 7.77-7.65 (2H, m), 7.62-7.48 (2H, m), 7.25-7.10 (2H, m), 6.92-6.70(3H, m), 5.44(1H, m), 3.45(3H, s), 2.20-2.07(1H, m), 2.07-1.90(1H, m), 1.01(3H, t).

The isomer 2^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.97 (1H, br s), 8.22-8.09 (2H, m), 7.94 (1H, m), 7.74 (1H, t), 7.61 (1H, d), 7.54 (1H, d), 7.24 (2H, t), 6.87 (1H, t), 6.66 (2H, d), 5.50 (1H, m), 3.39 (3H, s), 2.02-1.87 (2H, m), 0.886 (3H, t).

Example 21 : Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-3-(methyl(phenyl)amino)quinazolin-4(3H)-one (Compound 23)



(1) Preparation of 2-fluoro-N'-methyl-6-nitro-N'-phenylbenzohydrazide

To a solution of 2-fluoro-6-nitrobenzoic acid(3.7 g, 20.0 mmol)in CH_2Cl_2 (20 mL)and DMF(0.2 mL) was added Oxalyl chloride(3.87 g, 30.5 mmol) dropwise, the mixture was stired

for 2 h and concentrated .The residue was dissolved in 1,4-dioxane and added to a solution of 1-methyl-1-phenylhydrazine(2.4 g, 19.6 mmol), $NaHCO_3$ (3.36 g, 40.0 mmol) in 1,4-dioxane (10mL)and water (10mL) dropwrise, the mixture was stirred for 30 min at rt and concentrated, extracted with EA, dried by Anhydrous sodium sulfate, filtered, concentrated and purified by silica column chromatography (PE:EA=2:1) to give the title compound as a white solid(4.9g, 84.7%).

(2)Preparation of 2-amino-6-fluoro-N'-methyl-N'-phenylbenzohydrazide

A solution of 2-fluoro-N'-methyl-6-nitro-N'-phenylbenzohydrazide (4.9 g, 16.94 mmol)in methanol (30 mL) was carefully poured into Pd/C (10%, 0.5 g), and the resulting reaction mixture was stirred under hydrogen atmosphere for 36 h. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound (4.31 g,98.1%).

(3)Preparation of tert-butyl (S)-(1-((3-fluoro-2-(2-methyl-2-phenylhydrazine-1-carbonyl) phenyl)amino)-1-oxobutan-2-yl)carbamate

A solution of 2-amino-6-fluoro-N'-methyl-N'-phenylbenzohydrazide (4.31 g, 16.62 mmol), (S)-2-(tert-butoxycarbonylamino)butanoic acid(6.08 g, 29.92 mmol), DIEA (4.5 mL, 25.8 mmol) and HATU(8.36 g, 21.99 mmol) in DMF (30 mL) was stirred at rt for 48h, the mixture was partitioned between DCM and water, the organic layer was separated washed with brine, dried and concentrated in vacuo. The crude product was purified by silica column chromatography (PE:EA=3:1) to give the title compound as a white solid (3.2g , 43.3%).

(4)Preparation of tert-butyl (S)-(1-(5-fluoro-3-(methyl(phenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamat e

A solution of tert-butyl (S)-(1-((3-fluoro-2-(2-methyl-2-phenylhydrazine-1-carbonyl)phenyl) amino)-1-oxobutan-2-yl)carbamate(1.31 g, 2.95 mmol) and DMAP (0.38 g, 3.11 mmol) in in tert-butanol (30 mL) was stirred at room temperature for 64 h. After cooled to room temperature, the reaction solution was concentrated and purified by silica column chromatography (PE:EA=3:1) to give the title compound as a white solid (0.58g , 46.1%).

(5)Preparation of (S)-2-(1-aminopropyl)-5-fluoro-3-(methyl(phenyl)amino)quinazolin-4(3H)-one hydrochloride

A solution of tert-butyl

(S)-(1-(5-fluoro-3-(methyl(phenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate(0.58 g, 1.36 mmol) in ethanol (10 mL) and DCM(10 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (4 mL). The reaction was stirred at room temperature for 2h, and concentrated for the next step.

(6)Preparation of (S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-3-(methyl(phenyl)amino) quinazolin-4(3H)-one

To a solution of

(S)-2-(1-aminopropyl)-5-fluoro-3-(methyl(phenyl)amino)quinazolin-4(3H)-one hydrochloride (~1.36 mmol) in tert-butanol (20 mL) was added DIEA(0.3 mL, 1.72 mmol), After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine (210 mg, 1.36 mmol) was added. The reaction was stirred at 85ºC for 36 h. After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by preparation HPLC to give the title compounds as white solid. The smaller retention time isomer in HPLC was yielded 30 mg, another isomer was 95 mg in hand, the total yield 20.7%.

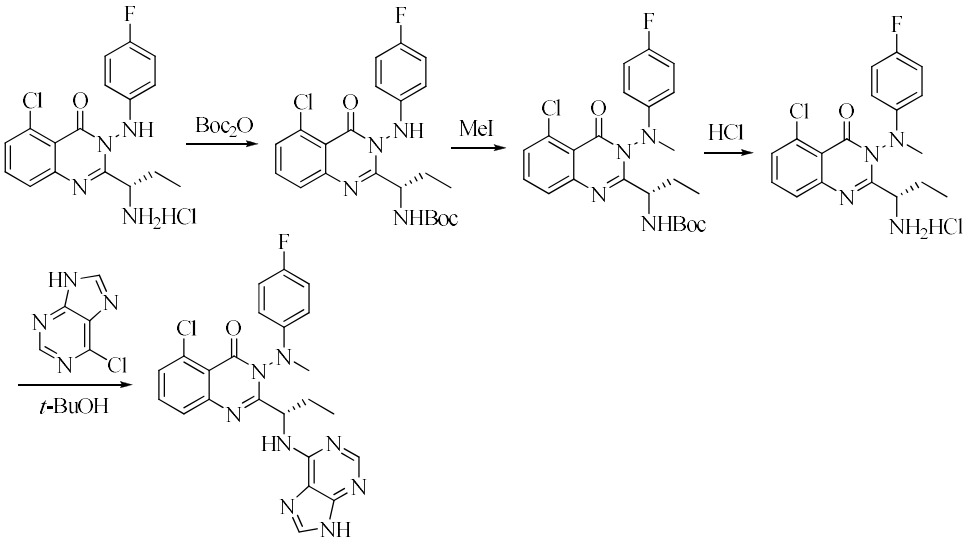
MS(M+1): 445.2;

The isomer 1(The retention time in HPLC was smaller)^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.90 (1H, br s), 8.20-7.90 (2H, m), 7.86-7.65 (2H, m), 7.47 (1H, m), 7.35-7.05 (3H, m), 6.95-6.60 (3H, m), 5.43 (1H, m), 3.45 (3H, s), 2.20-1.80 (2H, m), 1.02 (3H, t).

The isomer 2^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.98 (1H, br s), 8.22-8.10 (2H, m), 7.94 (1H, m), 7.86-7.77 (1H, m), 7.49 (1H, d), 7.32-7.20 (3H, m), 6.87 (1H, t), 6.75-6.62 (2H, m), 5.51 (1H, m), 3.40 (3H, s), 2.05-1.83 (2H, m), 0.882 (3H, t).

Example 22 : Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-chloro-3-((4-fluorophenyl)(methyl)amino)quinazolin-4(3H)-one (Compound 24)



(1) Preparation of tert-butyl (S)-(1-(5-chloro-3-((4-fluorophenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate

A mixture of (S)-2-(1-aminopropyl)-5-chloro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one hydrochloride(840 mg, 2.19 mmol), Et_3N(0.92 mL, 6.60 mmol), Boc_2O (720 mg, 3.30 mmol) and DMAP(20 mg, 0.16mmol) in DCM(20mL) was stirred overnight and concentrated and purified by silica column chromatography (PE:EA=3:1) to give the title compound as a white solid (0.800g , 81.7%).

(2) Preparation of tert-butyl (S)-(1-(5-chloro-3-((4-fluorophenyl)(methyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate

A mixture of tert-butyl (S)-(1-(5-chloro-3-((4-fluorophenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate(800 mg, 1.79 mmol), K_2CO_3(371 mg, 2.68 mmol) and CH_3I(381 mg, 2.68 mmol) in DMF(10 mL) was stirred overnight and concentrated and purified by silica column chromatography to give the title compound as a white solid (0.58g , 70.4%).

(3)Preparation of (S)-2-(1-aminopropyl)-5-chloro-3-((4-fluorophenyl)(methyl)amino)quinazolin-4(3H)-one hydrochloride

A solution of tert-butyl (S)-(1-((3-fluoro-2-(2-(4-fluorophenyl)hydrazine-1-carbonyl)phenyl)amino)-1-oxobutan-2-yl)(methyl)carbamate(2.6 g, 5.62 mmol) in DCM(15 mL) was cooled in an ice bath. To this

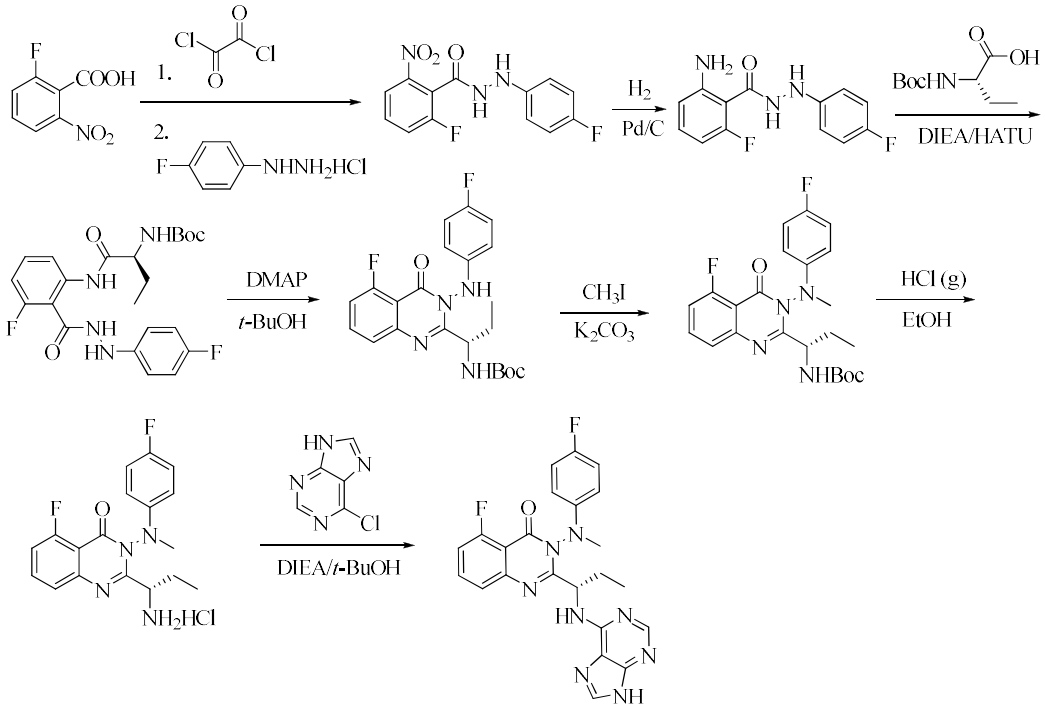
solution was bubbled with hydrogen chloride gas for 1 h, the reaction solution was concentrated to give the title compound as a white solid (0.53g).

(4)Preparation of (S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-chloro-3-((4-fluorophenyl)(methyl)amino)quinazolin-4(3H)-one

To a solution of (S)-2-(1-aminopropyl)-5-chloro-3-((4-fluorophenyl)(methyl)amino)quinazolin-4(3H)-one hydrochloride (0.53 mg) in tert-butanol (15 mL) was added DIEA (3mL). After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine(300 mg, 1.94 mmol) was added. The reaction was stirred at 85ºC for 2 d, After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by silica column chromatography to give the title compound as a white solid (370mg, 61.3% two steps).

MS(M+1): 479.2; ^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.94 (1H, d), 8.18-7.93 (2H, m), 7.85-7.66 (2H, m), 7.64-7.50 (2H, m), 7.11-6.95 (2H, m), 6.94-6.65 (2H, m), 5.55-5.35 (1H, m), 3.43-3.38 (3H, d), 2.20-1.85 (2H, m), 1.01-0.897 (3H, m).

Example 23 : Preparation of (S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-3-((4-fluorophenyl)(methyl)amino)quinazolin-4(3H)-one (Compound 25)



(1)Preparation of 2-fluoro-N'-(4-fluorophenyl)-6-nitrobenzohydrazide

To a solution of 2-fluoro-6-nitrobenzoic acid(5.5 g, 29.7 mmol) in CH_2Cl_2 (50 mL) and

DMF(0.4 mL) was added Oxalyl chloride(5.66 g, 44.6 mmol) dropwise, the mixture was stired for 2 h and concentrated. The residue was dissolved in 1,4-dioxane and added to a solution of (4-fluorophenyl)hydrazine hydrochloride (4.829 g, 29.7 mmol), $NaHCO_3$ (6.72 g, 80.0 mmol) in 1,4-dioxane (20mL) and water (20 mL) drowrise, the mixture was stirred for 30 min at rt and concentrated, extracted with EA, dried by Anhydrous sodium sulfate, filtered, concentrated and purified by silica column chromatography (PE:EA=2:1) to give the title compound as a white solid (4.4g, 50.5%).

(2)Preparation of 2-amino-6-fluoro-N'-(4-fluorophenyl)benzohydrazide

A solution of 2-fluoro-N'-(4-fluorophenyl)-6-nitrobenzohydrazide (4.4 g, 15.0 mmol) in methanol (60 mL) was carefully poured into Pd/C (10%, 0.5 g), and the resulting reaction mixture was stirred under hydrogen atmosphere for 36 h. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound (3.8g, 96.3%).

(3)Preparation of (S)-tert-butyl

1-(3-fluoro-2-(2-(4-fluorophenyl)hydrazinecarbonyl)phenylamino)-1-oxobutan-2-ylcarbamate

A solution of 2-amino-6-fluoro-N'-(4-fluorophenyl)benzohydrazide (3.8g, 14.4 mmol), (S)-2-(tert-butoxycarbonylamino)butanoic acid (5.8 g, 28.6mmol), DIEA (3.7 mL, 21.2 mmol,HATU(6.0 g,15.8 mmol) in DCM (200mL) was stirred at rt for 48 h, the mixture was partitioned between DCM and water, the organic layer was separated washed with brine, dried and concentrated in vacuo. The crude product was purified by preparation HPLC to give the title compound as a white solid (3.4 g , 52.6 %).

(4)Preparation of tert-butyl

(S)-(1-(5-fluoro-3-((4-fluorophenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate

A solution of tert-butyl

(S)-(1-((3-fluoro-2-(2-methyl-2-phenylhydrazine-1-carbonyl)phenyl)amino)-1-oxobutan-2-yl) carbamate(1.8 g, 4.01 mmol)and DMAP (0.54 g,4.42 mmol)in tert-butanol (60 mL) was stirred at room temperature for 24 h at 85℃. After cooled to room temperature, the reaction solution was concentrated to give the title compound as a white solid (1.1g , 63.7%).

(5) Preparation of tert-butyl

(S)-(1-(5-fluoro-3-((4-fluorophenyl)(methyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl) carbamate

A mixture of tert-butyl

(S)-(1-(5-fluoro-3-((4-fluorophenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate (1.1 g,2.56 mmol) , CH_3I (1.16 g,8.17 mmol), K_2CO_3 (0.70 g, 5.06 mmol) in DMF(20 mL) was stirred for 72 h and poured in ice-water (100 mL), extracted with EA and washed with brine, the organic layer was concentrated to give the title compound as a white solid (0.98g , 86.1%).

(6) Preparation of

(S)-2-(1-aminopropyl)-5-fluoro-3-((4-fluorophenyl)(methyl)amino)quinazolin-4(3H)-one hydrochloride

A solution of tert-butyl (tert-butyl

(S)-(1-(5-fluoro-3-((4-fluorophenyl)(methyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl) carbamate(2.6 g, 5.62 mmol) in ethanol (30 mL) was cooled in an ice bath. To this solution was bubbled with hydrogen chloride gas for 1 h, the reaction solution was concentrated to give the title compound as a white solid (0.800g, 95.5%).

(7)Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-3-((4-fluorophenyl)(methyl)amino)quinazolin-4(3H)-one

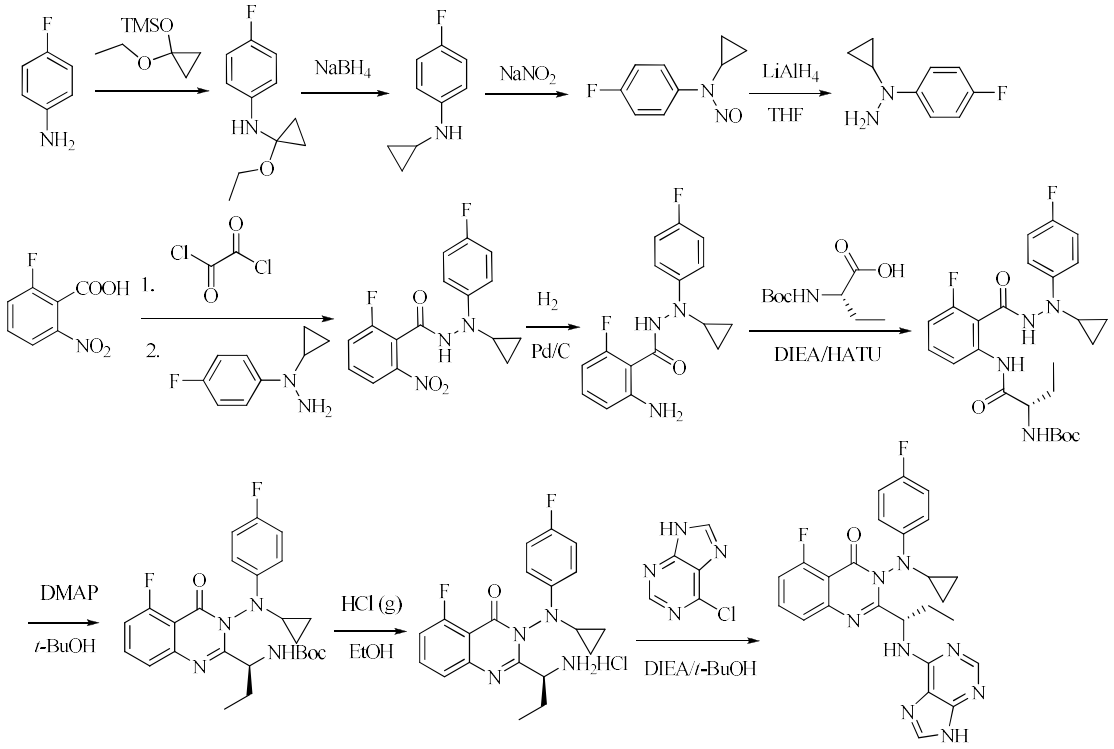
To a solution of

(S)-2-(1-aminopropyl)-5-fluoro-3-((4-fluorophenyl)(methyl)amino)quinazolin-4(3H)-one hydrochloride(623 mg, 1.64 mmol) in tert-butanol (30 mL) was added DIEA (0.71 mL, 4.08 mmol). After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine (378 mg, 2.45 mmol) was added. The reaction was stirred at 85ºC for 24 h. After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by preparation HPLC to give the title compound as a white solid (209mg, 27.6%).

MS(M+1): 463.2; ^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.88 (1H, br s), 8.19-8.03 (2H, m), 7.85-7.73 (2H, m), 7.51-7.40 (1H, m), 7.32-7.23 (1H, m), 7.11-6.94 (2H, m), 6.92-6.67 (2H, m), 5.45 (1H, m), 3.43 (3H, s), 2.18-1.84 (2H, m), 1.04 (3H, t).

Example 24 : Preparation of

(S)-2-(1-(9H-purin-6-ylamino)propyl)-5-fluoro-3-(3-methoxyphenylamino)quinazolin-4(3H)-one (Compound 26)



(1) Preparation of N-cyclopropyl-4-fluoroaniline

To a mixture of 4-fluoroaniline (11.1 g, 100 mmol)and some 4A molecular sieve in MeOH(250 mL) was added (1-ethoxycyclopropoxy) trimethylsilane(22.6 g, 130 mmol) and 50 mL acetic acid, the mixture was stirred for 2 h. After that Sodium borohydride (28 g, 740 mmol) was added in portions and reluxed overnight under N_2 atmosphere and cooled down to room temperature, flitered and poured into 100mL ice-water and adjusted PH to 7, the mixture was extracted with EA, washed with 2N NaOH solution and the organic layer was dried, concentrated to give the compound (6.8g ,45.0%).

(2) Preparation of N-cyclopropyl-N-(4-fluorophenyl)nitrous amide

To a solution of N-cyclopropyl-4-fluoroaniline (6.4 g, 42.3 mmol) in AcOH (35 mL) was added a solution of sodium nitrite(3.8 g, 55.1 mmol)in water (40mL) dropwise at 0ºC, the mixture was stirred for 2 h, and adjusted PH to 7 at 0ºC, extracted with EA, the combined organic phase was concentrated and purifird by column chromatography (PE:EA=5:1) to obtain the white solid 4.2 g, yield of 55.1%.

(3) Preparation of 1-cyclopropyl-1-(4-fluorophenyl)hydrazine

To a solution of N-cyclopropyl-N-(4-fluorophenyl)nitrous amide(4.0 g, 22.2 mmol) was added lithium aluminum hydride (1 M, 22.5 mL) slowly and dropwise, the mixture was stirred fou 30 min.and quenched with 30mL EA, after that 40% NaOH solution was added and extracted ,the

organic layer was dried to obtain the solid(2.6g ,70.5%).

(4) Preparation of N'-cyclopropyl-2-fluoro-N'-(4-fluorophenyl)-6-nitrobenzohydrazide

To a solution of 2-fluoro-6-nitrobenzoic acid(2.8 g, 15.1 mmol) in CH_2Cl_2 (30 mL)and DMF(0.4 mL) was added Oxalyl chloride(2.8 g, 22.1 mmol) dropwise, the mixture was stired for 2 h and concentrated. The residue was dissolved in 1,4-dioxane and added to a solution of 1-cyclopropyl-1-(4-fluorophenyl)hydrazine (2.5 g, 15.0 mmol) in 1,4-dioxane (10mL) dropwrise, the mixture was stirred for 30 min at rt and concentrated ,extracted with EA, dried by anhydrous sodium sulfate, filtered, concentrated to give the title compound as a pale yellow solid (2.4g, 48.0%).

(5)Preparation of 2-amino-N'-cyclopropyl-6-fluoro-N'-(4-fluorophenyl)benzohydrazide

A solution of N'-cyclopropyl-2-fluoro-N'-(4-fluorophenyl)-6-nitrobenzohydrazide (2.4 g, 7.2 mmol) in methanol (50 mL) was carefully poured into Pd/C (10%, 0.3 g), and the resulting reaction mixture was stirred under hydrogen atmosphere for 36 h. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound (2.0 g,91.6%).

(6)Preparation of tert-butyl (S)-(1-((2-(2-cyclopropyl-2-(4-fluorophenyl)hydrazine-1-carbonyl)-3-fluorophenyl)amino)-1-oxobutan-2-yl)carbamate

A solution of 2-amino-N'-cyclopropyl-6-fluoro-N'-(4-fluorophenyl)benzohydrazide (4.31 g, 16.62 mmol), (S)-2-(tert-butoxycarbonylamino)butanoic acid (2.0 g, 6.6 mmol), DIEA (1.3 mL, 7.5 mmol)and HATU HATU (2.77 g, 7.3 mmol) in DMF (50 mL) was stirred at rt for 48h, the mixture was partitioned between DCM and water, the organic layer was separated washed with brine, dried and concentrated in vacuo. The crude product was purified by preparation HPLC to give the title compound as a white solid (1.8g ,55.8%).

(7) Preparation of tert-butyl (S)-(1-(3-(cyclopropyl(4-fluorophenyl)amino)-5-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate

A solution of tert-butyl (S)-(1-((2-(2-cyclopropyl-2-(4-fluorophenyl)hydrazine-1-carbonyl)-3-fluorophenyl)amino)-1-oxobutan-2-yl)carbamate (1.8 g, 3.68 mmol)and DMAP (0.54 g, 4.42 mmol) in tert-butanol (30 mL) was refluxed for 24 h. After cooled to room temperature, the reaction solution was

concentrated to give the title compound as a white solid (1.1g , 63.5%).

(8)Preparation of

(S)-2-(1-aminopropyl)-3-(cyclopropyl(4-fluorophenyl)amino)-5-fluoroquinazolin-4(3H)-one hydrochloride

A solution of tert-butyl

(S)-(1-(3-(cyclopropyl(4-fluorophenyl)amino)-5-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate (1.1 g, 2.34 mmol) in ethanol (30 mL) was cooled in an ice bath. To this solution was bubbled with Hydrogen chloride gas The reaction was stirred at room temperature for 2h, and concentrated(0.7g) for the next step.

(9)Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-3-(methyl(phenyl)amino)quinazolin-4(3H)-one

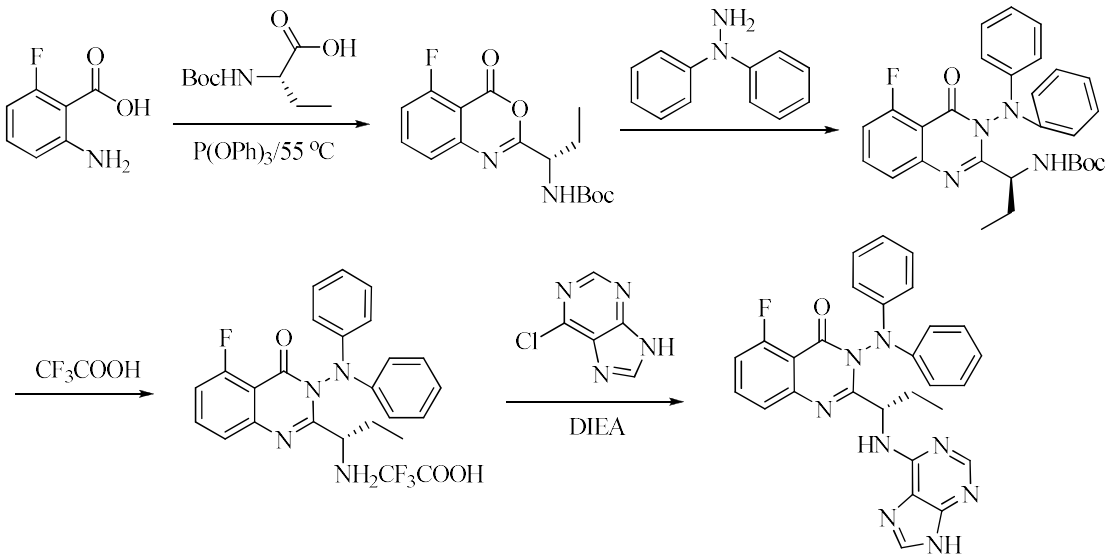
To a solution of

(S)-2-(1-aminopropyl)-3-(cyclopropyl(4-fluorophenyl)amino)-5-fluoroquinazolin-4(3H)-one hydrochloride(665 mg, 1.63 mmol) in tert-butanol (20 mL) was added (0.71 mL, 4.08 mmol) After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine (378 mg, 2.45 mmol) was added. The reaction was stirred at 85ºC for 24 h. After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by preparation HPLC to give the title compounds as white solid(135 mg, 17.0%).

MS(M+1): 489.2; ^{1}H-NMR(*d*$_6$-DMSO, 400 MHz): δ 12.66 (1H, s), 8.07-7.83 (3H, m), 7.63 (2H, t), 7.34 (1H, dd), 6.70-6.45 (4H, m), 5.67-5.56 (1H, m), 3.29-3.22 (1H, m), 2.26-2.12 (1H, m), 2.01-1.83 (1H, m), 1.46-1.35 (1H, s), 1.13-1.01 (1H, s), 0.97 (3H, t), 0.80-0.57 (2H, m).

Example 25 : Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)propyl)-3-(diphenylamino)-5-fluoroquinazolin-4(3H)-one (Compound 27)



(1) Preparation of tert-butyl

(S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)propyl)carbamate

To a stirred solution of 2-fluoro-6-aminobenzoic acid (1.00 g, 6.45 mmol)in pyridine (8mL) in a 100 mL flask was added (*S*)-2-(tert-butoxycarbonylamino) propanoic acid (1.571 g, 7.73 mmol), and triphenylphosphinate (2.00 g, 6.45 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr, and then was used directly for the next step without working-up.

(2) Preparation of tert-butyl

(S)-(1-(3-(diphenylamino)-5-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate

To the stirred solution of tert-butyl

(S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)propyl)carbamate (crude reaction mixture) was added 1,1-diphenylhydrazine (1.305 g, 7.08 mmol), and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography(PE:EA=6:1) to yield the title compound (2 g, 63.5% two steps) as a light yellow solid.

(3) Preparation of (S)-2-(1-aminopropyl)-3-(diphenylamino)-5-fluoroquinazolin-4(3H)-one trifluoroacetate.

A stirred solution of tert-butyl

(S)-(1-(3-(diphenylamino)-5-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate (1.00 g, 2.05 mmol) in chloromethane (20 mL) in a dry 100 mL round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid (10mL) at which time TLC showed

the disappearance of the starting material. The reaction solution was then concentrated under reduced pressure, and the crude product was used without further purification.

(4) Preparation of

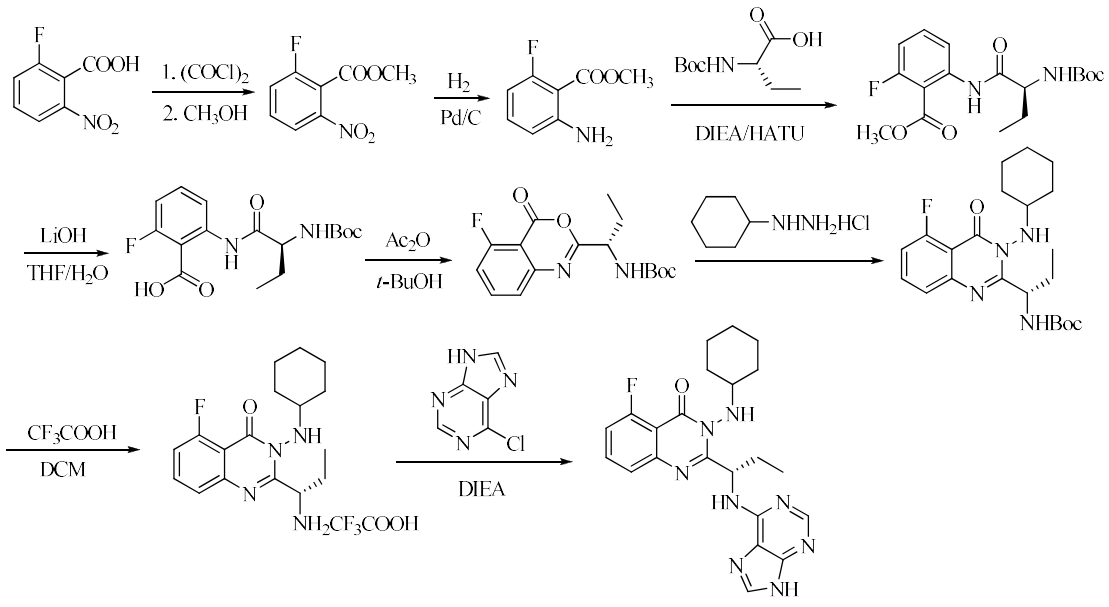
(S)-2-(1-((9H-purin-6-yl)amino)propyl)-3-(diphenylamino)-5-fluoroquinazolin-4(3H)-one

To a stirred solution of the crude

(S)-2-(1-aminopropyl)-3-(diphenylamino)-5-fluoroquinazolin-4(3H)-one trifluoroacetate (-2.55 mmol) in *tert*-butanol (10 mL) in a dry 100 mL round bottomed flask was added DIEA until the solution is basic, and then 6-chloropurine (0.380 g, 2.46 mmol) was added, and the reaction was stirred at 90ºC for 48 hr. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by praparation HPLC to yield the title compound (300 mg, 28.9% two steps) as a white solid. MS(M+1): 507.2; ^{1}H-NMR(d_6-DMSO, 400 MHz):δ 12.95 (1H, s), 8.17-8.04 (2H, m), 7.92-7.77 (2H, m), 7.53-7.42 (1H, m), 7.41-7.10 (11H, m), 5.65 (1H, m), 2.02-1.40 (2H, m), 0.74 (3H, t).

Example 26 : Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)propyl)-3-(cyclohexylamino)-5-fluoroquinazolin-4(3H)-one (Compound 28)



(1)Preparation of methyl 2-fluoro-6-nitrobenzoate

To a solution of 2-fluoro-6-nitrobenzoic acid(12.03 g, 65.0 mmol) in CH_2Cl_2 (50 mL)and DMF(0.3 mL) was added Oxalyl chloride(12.35 g, 97.3 mmol) dropwise, the mixture was

stired for 2 h and concentrated .The residue was dissolved in 1,4-dioxane and added MeOH (100mL),the mixture was stirred for 30 min at rt and concentrated ,extracted with EA, dried by Anhydrous sodium sulfate, filtered, concentrated and purified by silica column chromatography (PE:EA=2:1) to give the title compound as a white solid (12.7g, 98.1%).

(2)Preparation of methyl 2-amino-6-fluorobenzoate

A solution of methyl 2-fluoro-6-nitrobenzoate (12.70 g, 63.8 mmol)in methanol (60 mL) was carefully poured into Pd/C (10%, 0.065 g), and the resulting reaction mixture was stirred under hydrogen atmosphere for 36 h. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound (10.6g, 98.2%).

(3)Preparation of methyl (S)-2-(2-((tert-butoxycarbonyl)amino)butanamido)-6-fluorobenzoate

A solution of methyl 2-amino-6-fluorobenzoate(8.46 g, 50 mmol) DIEA(10.2 mL, 58.6 mmol), HATU(24.72 g, 65 mmol) (S)-2-((tert-butoxycarbonyl)amino)butanoic acid(12.19 g, 60 mmol) in DMF(100 mL) was stirred at rt for 64 h, the mixture was partitioned between DCM and water, the organic layer was separated washed with water, dried and concentrated in vacuo. The crude product was purified by silica column chromatography (PE:EA=3:1) to give the title compound as a white solid (12.14 g, yield: 68.5 %).

(4)Preparation of (S)-2-(2-((tert-butoxycarbonyl)amino)butanamido)-6-fluorobenzoic acid

To a solution of methyl

(S)-2-(2-((tert-butoxycarbonyl)amino)butanamido)-6-fluorobenzoate(12.14 g, 34.3 mmol) in THF (100mL) and water (50mL) was added lithium hydroxide monohydrate (4.31 g, 103 mmol) , the mixture was stirred for 4 h, after the reaction was completed by TLC, after was added and adjusted PH=3-4 with dilute hydrochloric acid ,filtered and dried to give the title compound as a white solid(10.22 g, 87.5 %).

(5)Preparation of (tert-butyl

(S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)propyl)carbamate

A solution of (S)-2-(2-((tert-butoxycarbonyl)amino)butanamido)-6-fluorobenzoic acid (3.4 g, 10 mmol),Acetic anhydride(4.1 g, 40.2 mmol) in t-BuOH(100 mL) was reluxed for 8 h and evaporated in vacuo to give the title compound (2.94 g, 91.2 %).

(6)Preparation of tert-butyl

(S)-(1-(3-(cyclohexylamino)-5-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate

A solution of tert-butyl (S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)propyl)carbamate(806 mg, 2.50 mmol) and cyclohexylhydrazine hydrochloride (452 mg, 3.0 mmol)in pyridine(30mL) was stirred at 100℃ for 8 h, the mixture was concentrated and purified by silica column chromatography (PE:EA=1:1) to give the title compound as a pale yellow solid (609mg, 58.2%).

(7)Preparation of (S)-2-(1-aminopropyl)-3-(cyclohexylamino)-5-fluoroquinazolin-4(3H)-one trifluoroacetate

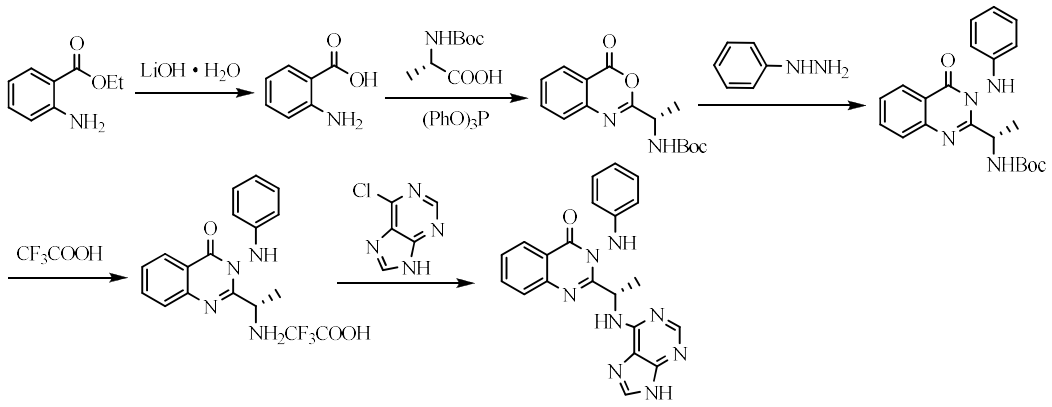
A solution of tert-butyl (S)-(1-(3-(cyclohexylamino)-5-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate (1.5 g, 3.24 mmol) and trifluoroacetic acid(6 mL) in DCM(20mL) was stirred for 2 h until the reaction was completed, and the mixture was concentrated to give the title compound as a solid.

(8)Preparation of (S)-2-(1-((9H-purin-6-yl)amino)propyl)-3-(cyclohexylamino)-5-fluoroquinazolin-4(3H)-one

To a solution of (S)-2-(1-aminopropyl)-3-(cyclohexylamino)-5-fluoroquinazolin-4(3H)-one trifluoroacetate (-1.46mmol) in tert-butanol (20 mL) was added DIEA (0.76 mL, 4.36 mmol) After that 6-chloro-9H-purine (271 mg, 1.75 mmol) was added. The reaction was stirred at 85ºC for 36 h. After the mixture was cooled to room temperature, the reaction solution was concentrated, the crude product was purified by silica column chromatography (EA) and the title compound (135mg, 21.2% two steps) was isolated as a white solid.

MS(M+1): 437.2; ^{1}H-NMR(*d*$_6$-DMSO, 400 MHz):δ 12.85 (1H, br s), 8.22-8.13 (2H, m), 7.82-7.69 (1H, m), 7.52-7.35 (2H, m), 7.26 (1H, t), 6.26 (1H, s), 5.98 (1H, m), 2.15-1.98 (1H, m), 1.92-1.48 (6H, m), 1.35-1.05 (6H, m), 0.945 (3H, m).

Example 27 : Preparation of (S)-2-(1-((9H-purin-6-yl)amino)ethyl)-3-(phenylamino)quinazolin-4(3H)-one (Compound 29)



(1) Preparation of 2-aminobenzoic acid

To a solution of ethyl-2-aminobenzoate (1.652 g, 10 mmol) in THF (30mL) was added lithium hydroxide monohydrate(1.68 g, 40 mmol), the mixture was stirred for 3 h, after the reaction was completed by TLC, the reaction was concentrated and partitioned with EA and water , the organic layer was dried and concentrated to give the title compound as a white solid(1.31g,95.6 %).

(2) Preparation of t tert-butyl (S)-(1-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate

To a stirred solution of 2-aminobenzoic acid (1.00 g, 7.29mmol) in pyridine (10mL) in a 100 mL flask was added (*S*)-2-(tert-butoxycarbonylamino) propanoic acid (1.52 g, 8.03 mmol), and triphenylphosphinate (2.492 g, 8.03 mmol). The resulting reaction solution was stirred at 55ºC for 12 hr, and then was used directly for the next step without working-up.

(3) Preparation of tert-butyl

(S)-(1-(3-(diphenylamino)-5-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate

To the stirred solution of t tert-butyl

(S)-(1-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate (crude reaction mixture) was added phenylhydrazine (0.868 g, 8.03 mmol), and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography(PE:EA=6:1) to yield the title compound (1.256 g, 45.3% two steps) as a white solid.

(4) Preparation of (S)-2-(1-aminoethyl)-3-(phenylamino)quinazolin-4(3H)-one trifluoroacetate.

A stirred solution of tert-butyl

(S)-(1-(3-(diphenylamino)-5-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate(0.761 g, 2.0 mmol) in chloromethane (5 mL) in a dry 100 mL round bottomed flask was cooled in an

ice-bath. To this solution was added trifluoroacetic acid (5mL) at which time TLC showed the disappearance of the starting material. The reaction solution was then concentrated under reduced pressure, and the crude product was obteined (0.758g, 96.1%).

(5) Preparation of

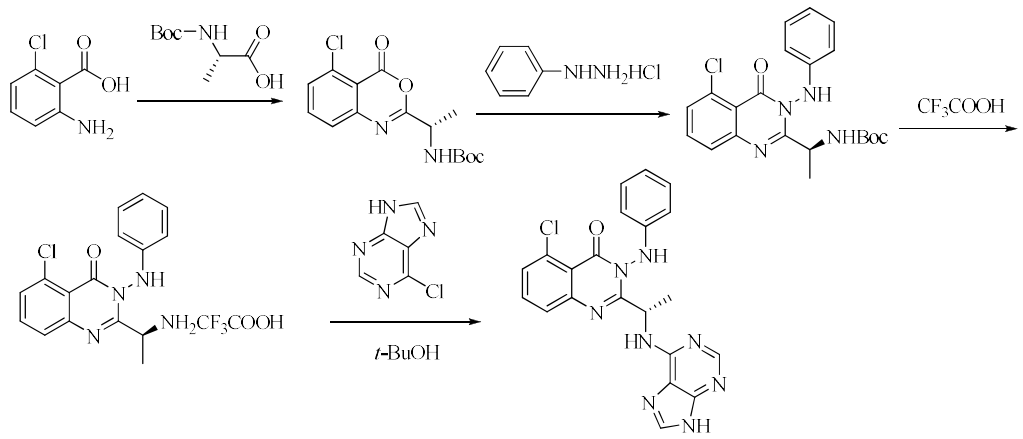
(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-3-(phenylamino)quinazolin-4(3H)-one

To a stirred solution of the crude (S)-2-(1-aminoethyl)-3-(phenylamino)quinazolin-4(3H)-one trifluoroacetate (0.758 g, 1.92 mmol) in *tert*-butanol (10 mL) in a dry 100 mL round bottomed flask was added DIEA(1.82 mL, 10.5 mmol)) until the solution is basic, and then 6-chloropurine (0.326 g, 2.11 mmol) was added, and the reaction was stirred at 90ºC for 12 h. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by praparation HPLC to yield the title compound (258 mg, 33.7% two steps) as a white solid.

MS(M+1): 399.2; ^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.99 (1H, s), 9.12 (1H, s), 8.22-8.03 (3H, m), 7.91-7.74 (2H, m), 7.61 (1H, d), 7.50 (1H, t), 7.30-7.15 (2H, m), 6.98 (2H, d), 6.85 (1H, t), 5.52 (1H, m), 1.66 (3H, d).

Example 28 : Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-3-(phenylamino)quinazolin-4(3H)-one (Compound 30)



(1) Preparation of tert-butyl

(S)-(1-(5-chloro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate

To a stirred solution of 2-fluoro-6-aminobenzoic acid (857 mg, 4.99 mmol) in pyridine (5mL) in a 100 mL flask was added (*S*)-2-(tert-butoxycarbonylamino) propanoic acid(1.13 g, 5.97 mmol) and triphenylphosphinate(1.86 g , 5.99 mmol) The resulting reaction solution was

stirred at 55ºC overnight, and then was used directly for the next step without working-up.

(2) Preparation of tert-butyl

(S)-(1-(5-chloro-4-oxo-3-(phenylamino)-3,4-dihydroquinazolin-2-yl)ethyl)carbamate

To the stirred solution of tert-butyl

(S)-(1-(5-chloro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate (crude reaction mixture) was added phenylhydrazine hydrochloride (867 mg, 6.0 mmol), and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography(PE:EA=5:1) to yield the title compound (2 g, 96.6% two steps) as a light yellow solid.

(3) Preparation of

(S)-2-(1-aminoethyl)-5-chloro-3-(phenylamino)quinazolin-4(3H)-onetrifluoroacetate.

A stirred solution of tert-butyl

(S)-(1-(5-chloro-4-oxo-3-(phenylamino)-3,4-dihydroquinazolin-2-yl)ethyl)carbamate (880 mg, 2.12 mmol) in chloromethane (6 mL) in a dry 100 mL round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid (3mL) at which time TLC showed the disappearance of the starting material. The reaction solution was then concentrated under reduced pressure, and the crude product was used without further purification.

(4) Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-3-(phenylamino)quinazolin-4(3H)-one

To a stirred solution of the crude

(S)-2-(1-aminoethyl)-5-chloro-3-(phenylamino)quinazolin-4(3H)-onetrifluoroacetate. (-2.12 mmol mmol) in *tert*-butanol (15mL) in a dry 100 mL round bottomed flask was added DIEA (2 mL, 11.5 mmol) until the solution is basic, and then 6-chloro-9H-purine (395 mg, 2.55 mmol) was added, and the reaction was stirred at 90ºC for 48 hr. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography(PE:EA=1:2) to yield the title compound (356 mg, 28.9% two steps) as a white solid.

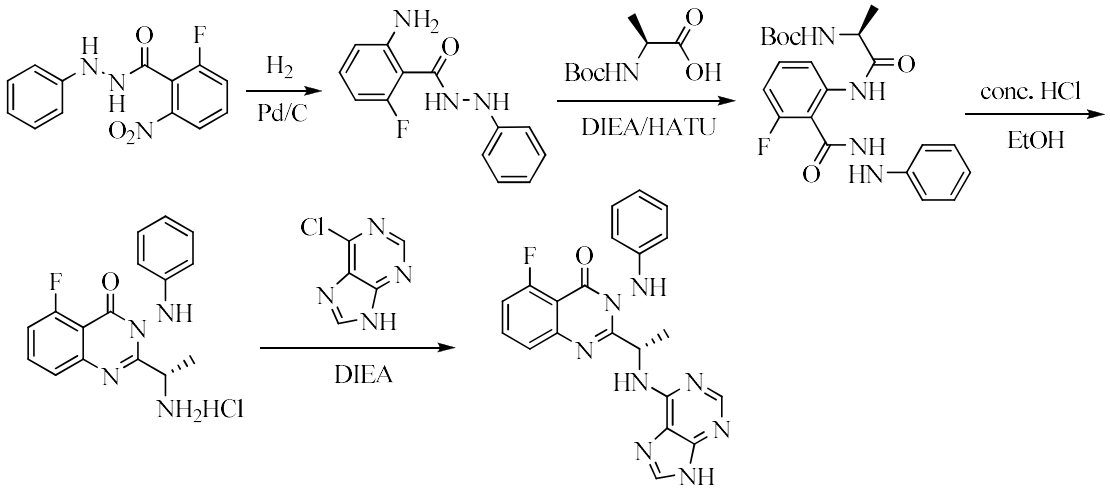
MS(M+1): 433.2; ^{1}H-NMR(d_6-DMSO, 400 MHz):δ 12.98 (1H, s), 9.01 (1H, s), 8.25-8.07 (2H, m), 7.90-7.60 (2H, m), 7.57-7.48 (2H, m), 7.25 (2H, t), 7.03 (2H, d), 6.86 (1H, t), 5.48 (1H, m),

1.65 (3H, d).

Example 29 : Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-fluoro-3-(phenylamino)quinazolin-4(3H)-one

(Compound 31)



(1) Preparation of 2-amino-6-fluoro-N'-phenylbenzohydrazide

A solution of 2-fluoro-6-nitro-N'-phenylbenzohydrazide (1.38 g, 5.01 mmol) in methanol (20 mL) was carefully poured into Pd/C (10%, 0.3 g), and the resulting reaction mixture was stirred under hydrogen atmosphere for 24 h. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound (1.2 g,97.7%).

(2)Preparation of tert-butyl

(S)-(1-((3-fluoro-2-(2-phenylhydrazine-1-carbonyl)phenyl)amino)-1-oxopropan-2-yl)carbamat

e

A solution of 2-amino-6-fluoro-N'-phenylbenzohydrazide (1.20 g, 4.89 mmol), (S)-2-(tert-butoxycarbonylamino)butanoic acid (1.11 g, 5.87 mmol), DIEA(1.3 mL, 7.47 mmol) and HATU(2.23 g, 5.86 mmol) in DCM (40 mL) was stirred at rt for 48h, the mixture was partitioned between DCM and water, the organic layer was separated washed with brine, dried and concentrated in vacuo. The crude product was purified by silica column chromatography (PE: EA =3:1) to give the title compound as a white solid (1.55g ,76.1%).

(3)Preparation of (S)-2-(1-aminoethyl)-5-fluoro-3-(phenylamino)quinazolin-4(3H)-one hydrochloride

A solution of tert-butyl

(S)-(1-((3-fluoro-2-(2-phenylhydrazine-1-carbonyl)phenyl)amino)-1-oxopropan-2-yl)carbamat

e EA in ethanol (30 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (3mL). The reaction was stirred at room temperature for 30min, and then at 85ºC for 16 h. After cooled to room temperature, the reaction solution was concentrated to give the title compound as a white solid for the next step.

(5)Preparation of

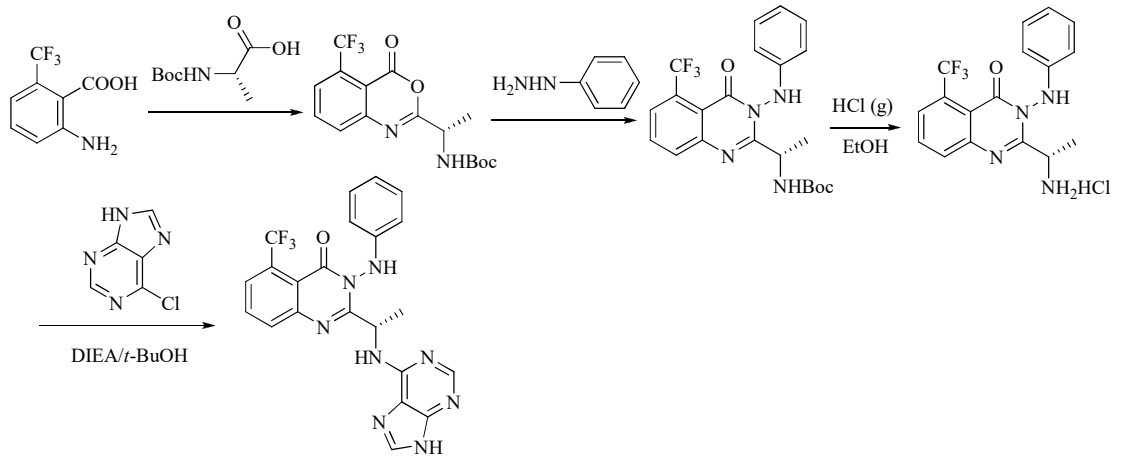
(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-fluoro-3-(phenylamino)quinazolin-4(3H)-one

To a solution of (S)-2-(1-aminoethyl)-5-fluoro-3-(phenylamino)quinazolin-4(3H)-one hydrochloride (3.72 mmol)in tert-butanol (20 mL) was added DIEA(1.95 mL, 11.2 mmol) After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine (575 mg, 3.72 mmol)was added. The reaction was stirred at 85ºC for 24 h. After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by silica column chromatography (EA) to give the title compound as a white solid (612mg, 39.5%).

MS(M+1): 417.2; ^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.98 (1H, s), 9.03 (1H, s), 8.25-8.06 (2H, m), 7.91-7.69 (2H, m), 7.54-7.15 (4H, m), 7.07-6.68 (3H, m), 5.51 (1H, m), 1.65 (3H, d).

Example 30 : Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-3-(phenylamino)-5-(trifluoromethyl)quinazolin-4(3H)-one (Compound 32)



(1) Preparation of tert-butyl

(S)-(1-(4-oxo-5-(trifluoromethyl)-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate

To a stirred solution of 2-amino-6-(trifluoromethyl)benzoic acid (1.5 g, 7.31 mmol)in pyridine (50mL) in a 100 mL flask was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (1.6 g, 8.46 mmol), and triphenylphosphinate(2.3 g, 7.41 mmol). The resulting reaction solution was stirred at 60ºC for 24 hr, and then was used directly for the next step without working-up.

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

To the stirred solution of tert-butyl
(S)-(1-(4-oxo-5-(trifluoromethyl)-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate (crude reaction mixture) was added phenylhydrazine (0.95 g, 8.78 mmol), and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE:EA=6:1)to yield the title compound (1.5 g, 45.8% two steps) as a light yellow solid.

(3) Preparation of tert-butyl
(S)-(1-(4-oxo-3-(phenylamino)-5-(trifluoromethyl)-3,4-dihydroquinazolin-2-yl)ethyl)carbamate

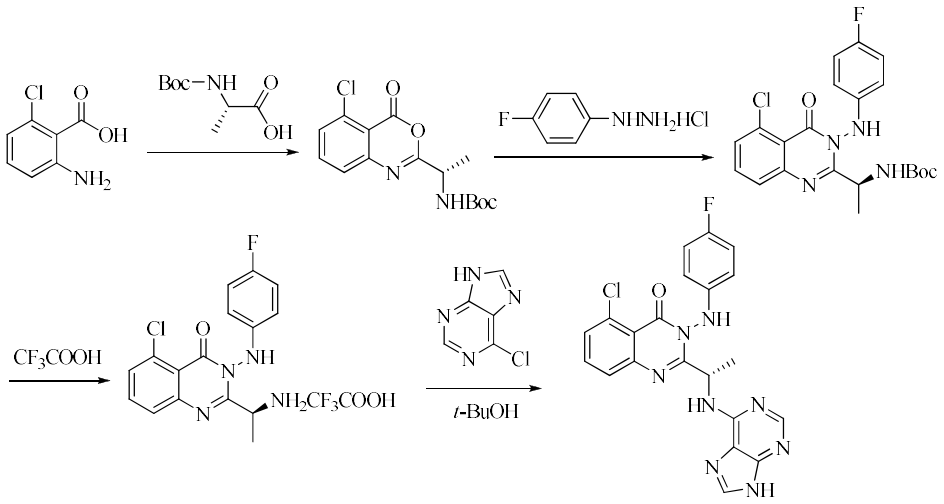
A stirred solution of (*S*)-tert-butyl
1-(5-fluoro-3-morpholino-4-oxo-3,4-dihydroquinazolin-2-yl)ethylcarbamate (1.5 g, 3.34 mmol)in ethanol (30 mL) in a dry 100 mL round bottomed flask was cooled in an ice-bath. To this solution was bubbled in HCl gas for 2 hr, at which time TLC showed the disappearance of the starting material. The reaction solution was then concentrated under reduced pressure, and the crude product (1.2g, 93.4%)was used without further purification.

(4) Preparation of
(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-3-(phenylamino)-5-(trifluoromethyl)quinazolin-4(3H)-one

To a stirred solution of the crude tert-butyl
(S)-(1-(4-oxo-3-(phenylamino)-5-(trifluoromethyl)-3,4-dihydroquinazolin-2-yl)ethyl)carbamate (1.0 g, 2.60 mmol) in *tert*-butanol (10 mL) in a dry 100 mL round bottomed flask was added DIEA(2.0 mL, 11.5 mmol) until the solution is basic, and then 6-chloropurine (700 mg, 4.53 mmol) was added, and the reaction was stirred at 85ºC for 24 hr. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography to yield the title compound (610 mg, 50.3%) as a white solid. MS(M+1): 467.2 ^{1}H-NMR(*d*$_6$-DMSO, 400 MHz):δ 12.99 (1H, s), 9.16 (1H, s), 8.16 (1H, d), 8.13 (1H, s), 8.01-7.84 (4H, m), 7.26 (2H, t), 7.03 (2H, d), 6.87 (1H, t), 5.49 (1H, m), 1.67 (3H, d).

Example 31 : Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one (Compound 33)



(1) Preparation of tert-butyl

(S)-(1-(4-oxo-5-(trifluoromethyl)-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate

To a stirred solution of 2-amino-6-(trifluoromethyl)benzoic acid (857 mg, 4.99 mmol) in pyridine (5mL) in a flask was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (1.13 g, 5.97 mmol), and triphenylphosphinate(1.86 g, 5.99 mmol). The resulting reaction solution was stirred at 55ºC for 24 hr, and then was used directly for the next step without working-up.

(2) Preparation of tert-butyl

(S)-(1-(5-chloro-3-((4-fluorophenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate

To the stirred solution of tert-butyl

(S)-(1-(4-oxo-5-(trifluoromethyl)-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate (crude reaction mixture) was added (4-fluorophenyl)hydrazine hydrochloride (975 mg, 6.0 mmol), and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE:EA=5:1)to yield the title compound (1.92 g, 89.0% two steps) as a white solid.

(3) Preparation of

(S)-2-(1-aminoethyl)-5-chloro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one trifluoroacetate

A stirred solution of tert-butyl (S)-(1-(5-chloro-3-((4-fluorophenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate (800 mg, 1.85 mmol) in DCM (6mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid(3 mL) The reaction was stirred for 30 min at 0ºC until the reaction was completed by TLC,concentrated under reduced pressure, and the crude product was used for the next step without further purification.

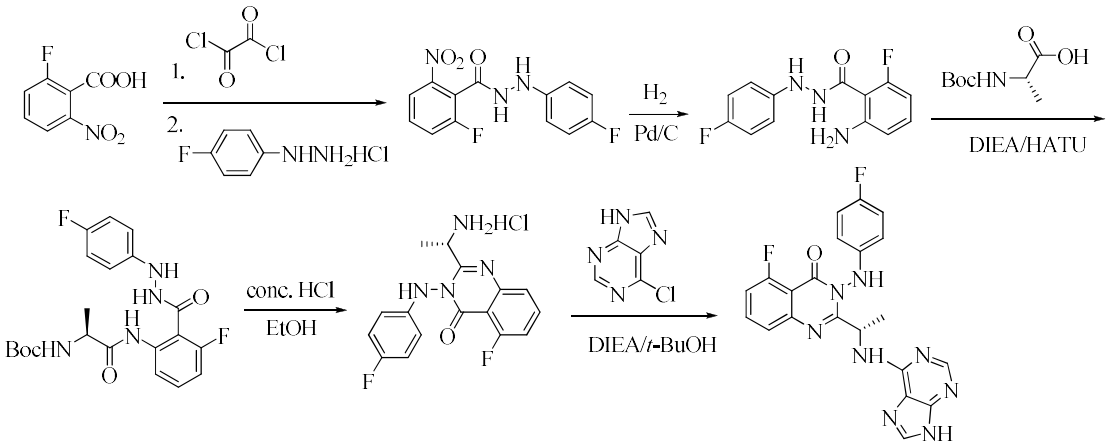
(4) Preparation of (S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one

To a stirred solution of the crude (S)-2-(1-aminoethyl)-5-chloro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one trifluoroacetate (1.85 mmol) in *tert*-butanol (15 mL) in a dry 100 mL round bottomed flask was added DIEA (2 mL, 11.5 mmol) until the solution is basic, and then 6-chloro-9H-purine (344 mg, 2.23 mmol) was added, and the reaction was stirred at 85ºC for 24 hr. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography to yield the title compound (390mg, 46.8% two steps) as a white solid.

Normal HPLC,was daicel chiral analytical column (OD-H, 5 m, 150 x 4.6 mm), the mobile phase was hexane: ethanol =90:10, flowing rate was 1 mL/min, temperature of column was 35 , the detection wavelength was 270 nm, sample concentration was 0.5 mg/mL (ethanol soluble), sample volume was 10μL, determination chiral purity was 73.9:26.1 (S:R).

MS(M+1): 451.2; ^{1}H-NMR(*d*$_6$-DMSO, 400 MHz):δ 12.97 (1H, s), 8.99 (1H, s), 8.30-8.09 (2H, m), 8.00-7.89 (1H, m), 7.77-7.60 (2H, m), 7.57-7.46 (2H, m), 7.16-7.00 (3H, m), 5.48 (1H, m), 1.65 (3H, d).

Example 32 : Preparation of (S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-fluoro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one (Compound 34)



(1)Preparation of 2-fluoro-N'-(4-fluorophenyl)-6-nitrobenzohydrazide

To a solution of 2-fluoro-6-nitrobenzoic acid(19.9 g, 107 mmol) in CH_2Cl_2 (150 mL) and DMF(2 mL) was added Oxalyl chloride(5.66 g, 44.6 mmol) dropwise, the mixture was stired for 2 h and concentrated. The residue was dissolved in 1,4-dioxane and added to a solution of (4-fluorophenyl)hydrazine hydrochloride(17.5 g, 107 mmol), $NaHCO_3$ (6.72 g, 80.0 mmol) in 1,4-dioxane (20mL) and water (20 mL) drowrise, the mixture was stirred for 30 min at rt and concentrated, extracted with EA, dried by Anhydrous sodium sulfate, filtered, concentrated and recrystallized from ether to give the title compound as a white solid (16.6g, 52.6%).

(2)Preparation of 2-amino-6-fluoro-N'-(4-fluorophenyl)benzohydrazide

A solution of 2-fluoro-N'-(4-fluorophenyl)-6-nitrobenzohydrazide (4.4 g, 15.0 mmol) in methanol (60 mL) was carefully poured into Pd/C (10%, 0.5 g), and the resulting reaction mixture was stirred under hydrogen atmosphere for 36 h. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound (3.8g, 96.2%).

(3)Preparation of tert-butyl (S)-(1-((3-fluoro-2-(2-(4-fluorophenyl)hydrazine-1-carbonyl)phenyl)amino)-1-oxopropan-2-yl)carbamate

A solution of 2-amino-6-fluoro-N'-(4-fluorophenyl)benzohydrazide (3.8g, 14.4 mmol), (tert-butoxycarbonyl)-L-alanine (4.25 g, 22.5 mmol), DIEA (3.39 mL, 19.5 mmol) and HATU(6.84 g,18.0 mmol) in DCM (200mL) was stirred at rt for 48 h, the mixture was partitioned between DCM and water, the organic layer was separated washed with brine, dried and concentrated in vacuo. The crude product was purified by silica column chromatography (PE:EA=2:1) to give the title compound as a white solid (3.9 g, 59.8 %).

(4)Preparation of

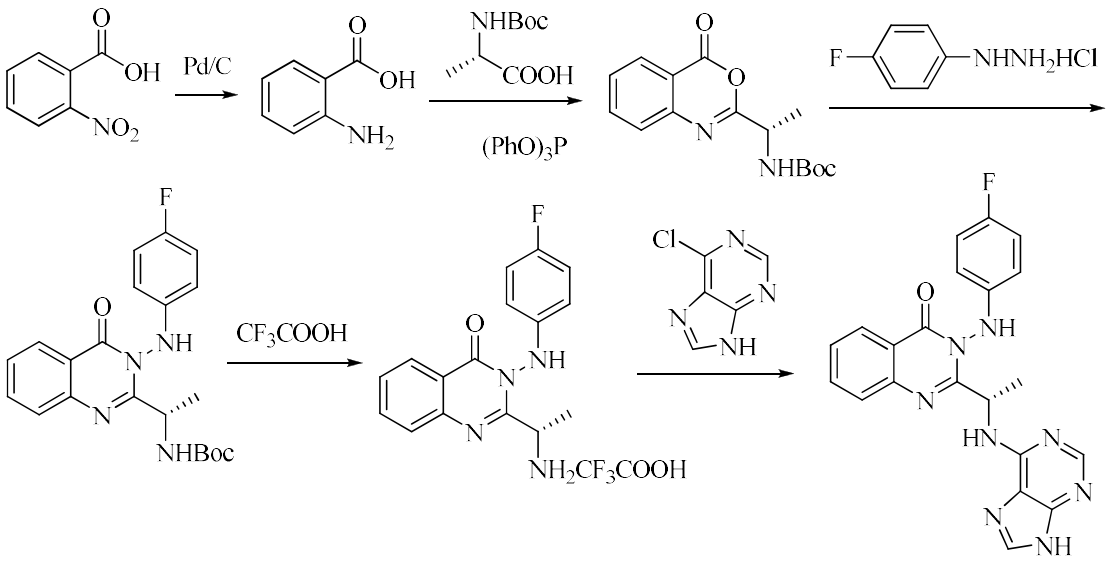
(S)-2-(1-aminoethyl)-5-fluoro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one hydrochloride

A solution of tert-butyl (S)-(1-((3-fluoro-2-(2-(4-fluorophenyl)hydrazine-1-carbonyl)phenyl)amino)-1-oxopropan-2-yl)carbamate (3.4 g, 7.8 mmol) in ethanol (50 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (5 mL). The reaction was stirred at room temperature for 30min, and then at 85ºC for 24 r. After cooled to room temperature, the reaction solution was concentrated to give the title compound as a white solid (2.56 g, 93.6 %).

(5)Preparation of (S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-fluoro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one

To a solution of (S)-2-(1-aminoethyl)-5-fluoro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one hydrochloride(1.05 g, 3.0 mmol) in tert-butanol (20 mL) was added DIEA(1.56 mL, 9.0 mmol), After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine (556 mg, 3.6 mmol) was added. The reaction was stirred at 85ºC for 36 h. After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by silica column chromatography (EA) to give the title compound as a white solid (282mg, 21.6%) MS(M+1): 435.2; ^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.99 (1H, s), 9.01 (1H, s), 8.16 (2H, m), 7.95 (1H, m), 7.84-7.69 (1H, m), 7.37 (1H, d), 7.24 (1H, t), 7.15-7.00 (4H, m), 5.51 (1H, m), 1.65 (3H, d).

Example 33 : Preparation of (S)-2-(1-((9H-purin-6-yl)amino)ethyl)-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one (Compound 35)



(1) Preparation of 2-aminobenzoic acid

A mixture of 2-nitrobenzoic acid (10 g, 59.8 mmol)and Pd/C(10%,0.5 g) in MeOH(200 mL) was stirred for 6 h under N_2 atmosphere. After that the reaction was filtered and concentrated to give the title compound as a pale yellow solid.(7.1, 86.6%)

(2) Preparation of tert-butyl (S)-(1-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate

To a stirred solution of 2-aminobenzoic acid (2 g, 14.6 mmol) in pyridine (5 mL) in a flask was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (3 g, 15.9 mmol) and triphenylphosphinate(5 g, 16.1 mmol). The resulting reaction solution was stirred at 55ºC for 12 hr, and then was used directly for the next step without working-up.

(3) Preparation of tert-butyl

(S)-(1-(3-((4-fluorophenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate

To the stirred solution of tert-butyl

(S)-(1-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate (crude reaction mixture) was added (4-fluorophenyl)hydrazine hydrochloride (2.6 g, 16.0 mmol), and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to yield the title compound (5g, 85.9% two steps) as a white solid.

(4) Preparation of

(S)-2-(1-aminoethyl)-3-((4-fluorophenyl)amino)quinazolin-4(3H)-onetrifluoroacetate

A stirred solution of tert-butyl

(S)-(1-(3-((4-fluorophenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate (2 g, 5

mmol) in DCM (10mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid(11 mL) The reaction was stirred for 3h until the reaction was completed by TLC, concentrated under reduced pressure, and the crude product(1.9g, 92.2%) was used for the next step without further purification.

(5) Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one

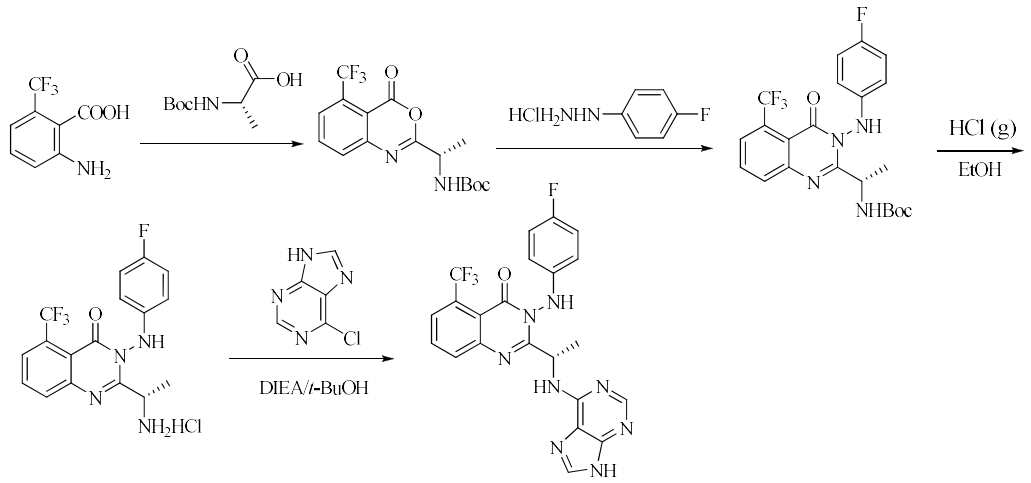
To a stirred solution of the crude

(S)-2-(1-aminoethyl)-3-((4-fluorophenyl)amino)quinazolin-4(3H)-onetrifluoroacetate (1.5 g, 3.64 mmol) in *tert*-butanol (10 mL) in a dry round bottomed flask was added DIEA (4.7 mL, 27 mmol) until the solution is basic, and then 6-chloro-9H-purine (0.93 g, 6 mmol)was added, and the reaction was stirred at 90ºC for 12 hr. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by praparation HPLC to yield the title compound (500mg, 33.0%) as a white solid.

MS(M+1): 417.2. ^{1}H-NMR(d_6-DMSO, 400 MHz):δ 12.98 (1H, s), 9.08 (1H, s), 8.23-8.02 (2H, m), 8.05 (1H, d), 7.98-7.66 (3H, m), 7.58 (1H, d), 7.49 (1H, t), 7.15-7.00 (3H, m), 5.53 (1H, m), 1.66 (3H, d).

Example 34 : Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-3-((4-fluorophenyl)amino)-5-(trifluoromethyl)quinazolin-4(3H)-one (Compound 36)



(1) Preparation of tert-butyl

(S)-(1-(4-oxo-5-(trifluoromethyl)-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate

To a stirred solution of 2-amino-6-(trifluoromethyl)benzoic acid (1.5 g, 7.31 mmol)in pyridine

(50mL) in a 100 mL flask was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (1.6 g, 8.46 mmol), and triphenylphosphinate(2.3 g, 7.41 mmol). The resulting reaction solution was stirred at 60ºC for 24 hr, and then was used directly for the next step without working-up.

(2) Preparation of tert-butyl (S)-(1-(3-((4-fluorophenyl)amino)-4-oxo-5-(trifluoromethyl)-3,4-dihydroquinazolin-2-yl)ethyl)carbamate

To the stirred solution of tert-butyl (S)-(1-(4-oxo-5-(trifluoromethyl)-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate (crude reaction mixture) was added (4-fluorophenyl)hydrazine hydrochloride (1.5 g, 9.23 mmol) and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE:EA=6:1)to yield the title compound (1.6 g, 46.9% two steps) as a light yellow solid.

(3) Preparation of (S)-2-(1-aminoethyl)-3-((4-fluorophenyl)amino)-5-(trifluoromethyl)quinazolin-4(3H)-one hydrochloride

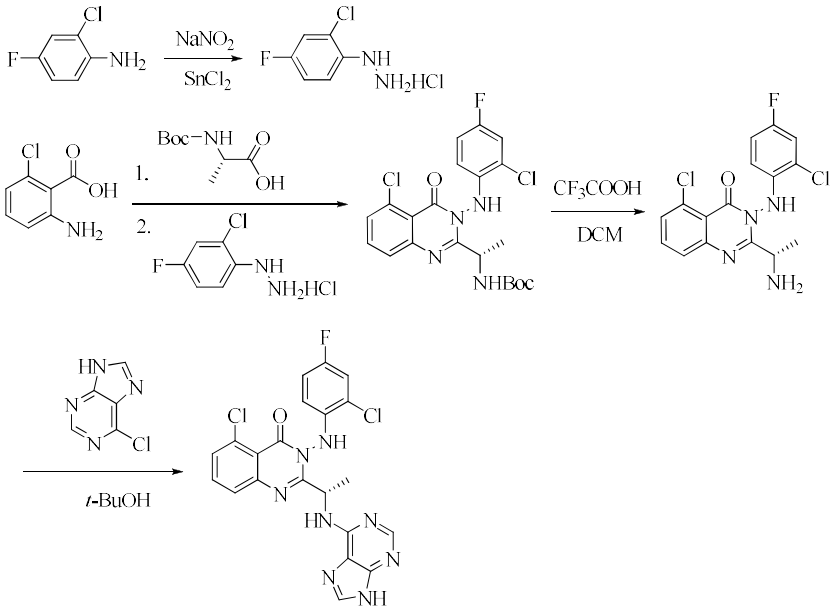
A stirred solution of tert-butyl (S)-(1-(3-((4-fluorophenyl)amino)-4-oxo-5-(trifluoromethyl)-3,4-dihydroquinazolin-2-yl)ethyl)carbamate (1.6 g, 3.43 mmol)in ethanol (30 mL) in a dry 100 mL round bottomed flask was cooled in an ice-bath. To this solution was bubbled in HCl gas for 2 hr, at which time TLC showed the disappearance of the starting material. The reaction solution was then concentrated under reduced pressure, and the crude product (1.3g, 94.1%)was used without further purification.

(4) Preparation of (S)-2-(1-((9H-purin-6-yl)amino)ethyl)-3-((4-fluorophenyl)amino)-5-(trifluoromethyl)quinazoli n-4(3H)-one

To a stirred solution of the crude (S)-2-(1-aminoethyl)-3-((4-fluorophenyl)amino)-5-(trifluoromethyl)quinazolin-4(3H)-one hydrochloride (1.0 g, 2.48 mmol) in *tert*-butanol (30 mL) in a dry round bottomed flask was added DIEA(2.0 mL, 11.5 mmol) until the solution is basic, and then 6-chloropurine (700 mg,

4.53 mmol) was added, and the reaction was stirred at 85ºC for 24 hr. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography to yield the title compound (500 mg, 41.6%) as a white solid. MS(M+1): 485.2 ^{1}H-NMR(d_6-DMSO, 400 MHz):δ 12.99 (1H, s), 9.13 (1H, s), 8.24-8.12 (2H, m), 8.07-7.78 (4H, m), 7.20-7.01 (4H, m), 5.49 (1H, m), 1.66 (3H, d).

Example 35 : Preparation of (S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-3-((2-chloro-4-fluorophenyl)amino)quinazolin-4(3H)-one (Compound 37)



(1) Preparation of (2-chloro-4-fluorophenyl)hydrazine hydrochloride

To a solution of trifluoroacetic acid (10mL) and concentrated hydrochloric acid(20 mL) was added 2-chloro-4-fluoroaniline(1.46 g,10 mmol)and a solution of sodium nitrite(0.828 mg, 12mmol) in water(6 mL), after that the mixture was stirred for 1 h, at 0ºC, and a solution of Tin(Ⅱ) chloride dihydrate (3.38g ,15mmol) in concentrated hydrochloric acid (15 mL) was added and the mixture was stirred overnight at rt. and then filtered and concentrated to give the title compound (1.10 g, 55.8% two steps) as a white solid.

(2) Preparation of tert-butyl (S)-(1-(5-chloro-3-((2-chloro-4-fluorophenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl) carbamate

To a stirred solution of 2-amino-6-chlorobenzoic acid (858 mg, 5.00 mmol) in pyridine (10mL)

in a flask was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (1.04 g, 5.50 mmol), and triphenylphosphinate(1.71 g, 5.52 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr, After that (2-chloro-4-fluorophenyl)hydrazine hydrochloride (1.10 g 5.58 mmol) was added and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE:EA=5:1)to yield the title compound (1.30 g, 55.6% two steps) as a white solid.

(3) Preparation of

(S)-2-(1-aminoethyl)-5-chloro-3-((2-chloro-4-fluorophenyl)amino)quinazolin-4(3H)-one

A stirred solution of tert-butyl

(S)-(1-(5-chloro-3-((2-chloro-4-fluorophenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl) carbamate(800 mg, 1.85 mmol) in DCM (10mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid(5mL) The reaction was stirred for 2h at 0ºC until the reaction was completed by TLC, concentrated under reduced pressure, and the crude product was used for the next step without further purification.

(4) Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-3-((2-chloro-4-fluorophenyl)amino)quinazolin -4(3H)-one

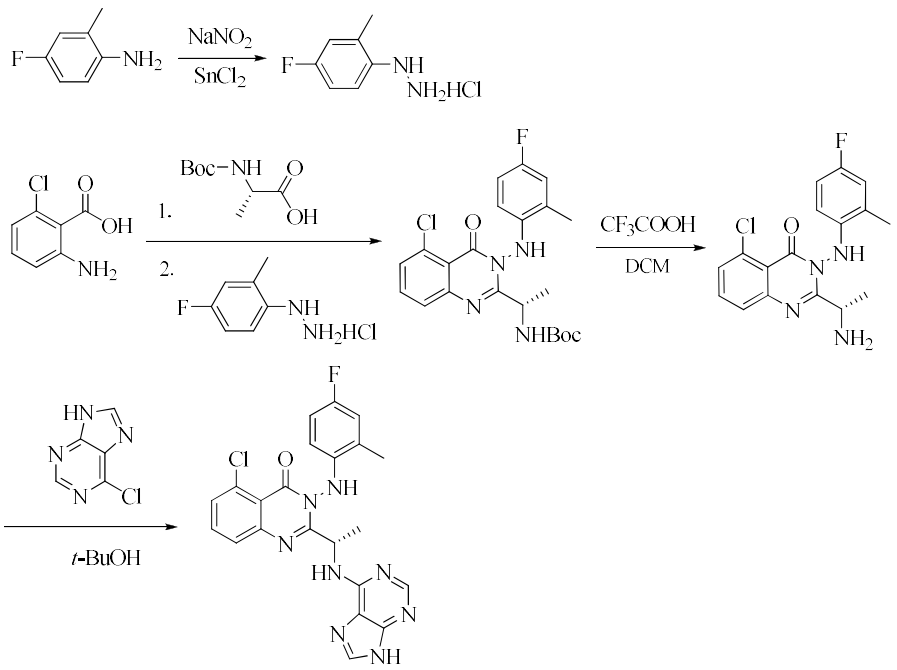
To a stirred solution of the crude

(S)-2-(1-aminoethyl)-5-chloro-3-((2-chloro-4-fluorophenyl)amino)quinazolin-4(3H)-one (2.78 mmol) in *tert*-butanol (15 mL) in a dry round bottomed flask was added DIEA (2 mL, 11.5 mmol) until the solution is basic, and then 6-chloro-9H-purine (474 mg ,3.07 mmol) was added, and the reaction was stirred at 85ºC for 48 hr. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (PE:EA=1:2)to yield the title compound (300mg, 22.3% two steps) as a white solid.

MS(M+1): 485.1. ^{1}H-NMR(d_6-DMSO, 400 MHz):12.95 (1H, s), 8.60 (1H, s), 8.14 (2H, s), 8.05-7.94 (1H, m), 7.70 (1H, t), 7.59-7.47 (2H, m), 7.43-7.35 (1H, m), 7.30-7.10 (2H, m), 5.44 (1H, s), 1.67 (3H, d).

Example 36 : Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-3-((4-fluoro-2-methylphenyl)amino)quinazolin-4(3H)-one (Compound 38)



(1) Preparation of (4-fluoro-2-methylphenyl)hydrazine hydrochloride

To a solution of concentrated hydrochloric acid(20 mL) was added 4-fluoro-2-methylaniline (1.00 g 8 mmol)and a solution of sodium nitrite(1.10 mg, 15.9mmol) in water(6 mL), after that the mixture was stirred for 1 h ,at 0ºC, and a solution of Tin(Ⅱ) chloride dihydrate (4.50g, 20mmol) in concentrated hydrochloric acid(15 mL) was added and the mixture was stirred overnight at rt. and then filtered washed with ethyl ether and concentrated to give the title compound (0.80 g, 56.6% two steps) as a white solid.

(2) Preparation of tert-butyl

(S)-(1-(5-chloro-3-((4-fluoro-2-methylphenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl) carbamate

To a stirred solution of 2-amino-6-chlorobenzoic acid (858 mg, 5.00 mmol) in pyridine (10mL) in a flask was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (1.04 g, 5.50 mmol), and triphenylphosphinate(1.71 g, 5.52 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr, After that (4-fluoro-2-methylphenyl)hydrazine hydrochloride (0.800 g 4.53mmol) was added and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE:EA=5:1)to yield the title compound (1.40 g, 69.1% two steps) as a white solid.

(3) Preparation of

(S)-2-(1-aminoethyl)-5-chloro-3-((4-fluoro-2-methylphenyl)amino)quinazolin-4(3H)-one

A stirred solution of tert-butyl

(S)-(1-(5-chloro-3-((4-fluoro-2-methylphenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl) carbamate (1.4 g, 3.13 mmol) in DCM (10mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid(5mL) The reaction was stirred for 2h at 0ºC until the reaction was completed by TLC,concentrated under reduced pressure, and the crude product was used for the next step without further purification.

(4) Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-3-((4-fluoro-2-methylphenyl)amino)quinazoli n-4(3H)-one

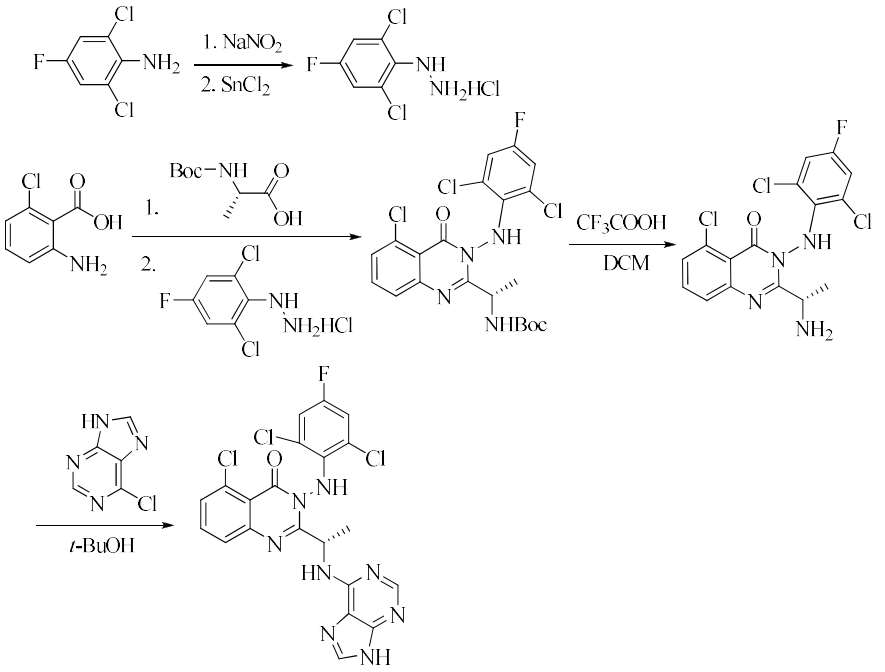
To a stirred solution of the crude

(S)-2-(1-aminoethyl)-5-chloro-3-((4-fluoro-2-methylphenyl)amino)quinazolin-4(3H)-one (3.13 mmol) in *tert*-butanol (20 mL) in a dry round bottomed flask was added DIEA (2 mL, 11.5 mmol) until the solution is basic, and then 6-chloro-9H-purine (534 mg ,3.45 mmol) was added, and the reaction was stirred at 85ºC for 48 hr. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (EA)to yield the title compound (700mg, 48.2% two steps) as a white solid.

MS(M+1): 465.2. ^{1}H-NMR(d_6-DMSO, 400 MHz):12.95 (1H, s), 8.28 (1H, s), 8.13 (2H, s), 7.95-7.84 (1H, s), 7.70 (1H, t), 7.59-7.47 (2H, m), 7.07-6.85 (2H, m), 5.48 (1H, m), 2.36 (3H, s), 1.73-1.63 (3H, m).

Example 37 : Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-3-((2,6-dichloro-4-fluorophenyl)amino)qu inazolin-4(3H)-one (Compound 39)



(1) Preparation of (2,6-dichloro-4-fluorophenyl)hydrazine hydrochloride

To a solution of concentrated hydrochloric acid(20 mL) and TFA(10 mL) was added 2,6-dichloro-4-fluoroaniline (1.80 g 10 mmol) and a solution of sodium nitrite (0.828 mg, 12.0mmol) in water(6 mL), after that the mixture was stirred for 1 h, at 0ºC, and a solution of Tin(Ⅱ) chloride dihydrate (3.35g, 15mmol) in concentrated hydrochloric acid(15 mL) was added and the mixture was stirred for 12 h at rt. and then filtered washed with ethyl ether and concentrated to give the title compound (1.70 g, 73.4% two steps) as a white solid.

(2) Preparation of tert-butyl (S)-(1-(5-chloro-3-((2,6-dichloro-4-fluorophenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate

To a stirred solution of 2-amino-6-chlorobenzoic acid (858 mg, 5.00 mmol) in pyridine (10mL) in a flask was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (1.04 g, 5.50 mmol), and triphenylphosphinate(1.71 g, 5.52 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr. After that (2,6-dichloro-4-fluorophenyl)hydrazine hydrochloride (1.27 g, 5.49mmol) was added and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE:EA=5:1) to yield the title compound (2.10 g, 83.7% two steps) as a white solid.

(3) Preparation of

(S)-2-(1-aminoethyl)-5-chloro-3-((2,6-dichloro-4-fluorophenyl)amino)quinazolin-4(3H)-one

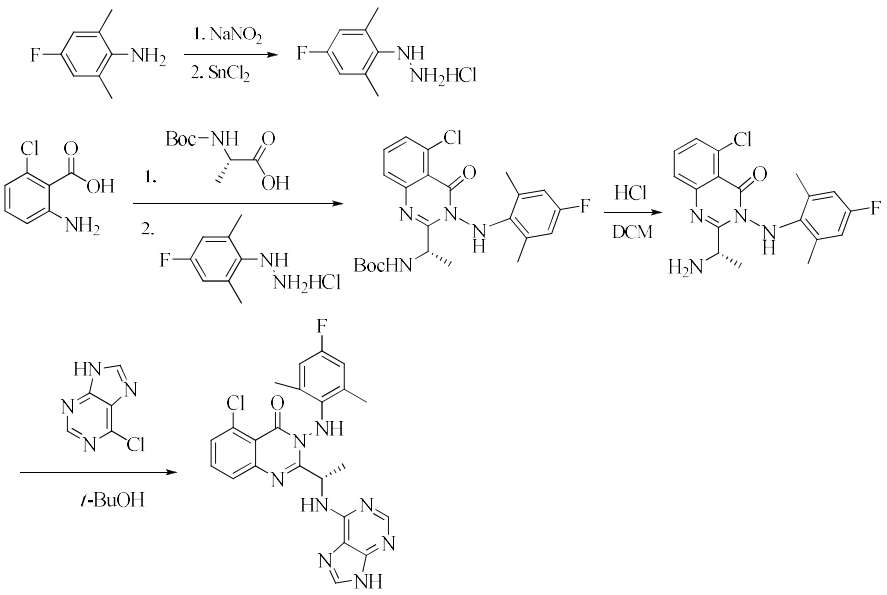
A stirred solution of tert-butyl (S)-(1-(5-chloro-3-((2,6-dichloro-4-fluorophenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate (2.10 g, 4.19 mmol) in DCM (10mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid(5mL) The reaction was stirred for 2h at 0ºC until the reaction was completed by TLC,concentrated under reduced pressure, and the crude product was used for the next step without further purification.

(4) Preparation of (S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-3-((2,6-dichloro-4-fluorophenyl)amino)quinazolin-4(3H)-one

To a stirred solution of the crude (S)-2-(1-aminoethyl)-5-chloro-3-((2,6-dichloro-4-fluorophenyl)amino)quinazolin-4(3H)-one (4.19 mmol) in *tert*-butanol (20 mL) in a dry round bottomed flask was added DIEA (2 mL, 11.5 mmol) until the solution is basic, and then 6-chloro-9H-purine (714 mg ,4.62 mmol) was added, and the reaction was stirred at 85ºC for 48 hr. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (PE:EA=1:1)to yield the title compound (700mg, 32.2% two steps) as a white solid.

MS(M+1): 419.1 ^{1}H-NMR(d_6-DMSO, 400 MHz): 13.04 (1H, s), 8.63 (1H, s), 8.17 (2H, d), 7.80 (1H, t), 7.77-7.71 (1H, m), 7.59 (1H, d), 7.57-7.49 (1H, m), 7.42-7.27 (2H, m), 6.18 (1H, m), 1.65 (3H, m).

Example 38 : Preparation of (S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-3-((4-fluoro-2,6-dimethylphenyl)amino)quinazolin-4(3H)-one (Compound 40)



(1) Preparation of (4-fluoro-2,6-dimethylphenyl) hydrazine hydrochloride

To a solution of concentrated hydrochloric acid (20 mL) and TFA(10 mL) was added 2,6-dichloro-4-fluoroaniline (1.39 g 10 mmol)and a solution of sodium nitrite(0.828 mg, 12.0mmol) in water(6 mL) ,after that the mixture was stirred for 1 h ,at 0ºC, and a solution of Tin(Ⅱ) chloride dihydrate (3.38g, 15mmol) in concentrated hydrochloric acid(15 mL) was added and the mixture was stirred for 12 h at rt. and then filtered washed with ethyl ether and concentrated to give the title compound (1.14 g, 59.8% two steps) as a white solid.

(2) Preparation of tert-butyl tert-butyl (S)-(1-(5-chloro-3-((4-fluoro-2,6-dimethylphenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate

To a stirred solution of 2-amino-6-chlorobenzoic acid (858 mg, 5.00 mmol) in pyridine (10mL) in a flask was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (1.04 g, 5.50 mmol), and triphenylphosphinate(1.71 g, 5.52 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr. After that (4-fluoro-2,6-dimethylphenyl)hydrazine hydrochloride (1.14 g 5.98mmol) was added and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE:EA=5:1)to yield the title compound (1.60 g, 69.4% two steps) as a white solid.

(3) Preparation of (S)-2-(1-aminoethyl)-5-chloro-3-((4-fluoro-2,6-dimethylphenyl)amino)quinazolin-4(3H)-one

hydrochloride

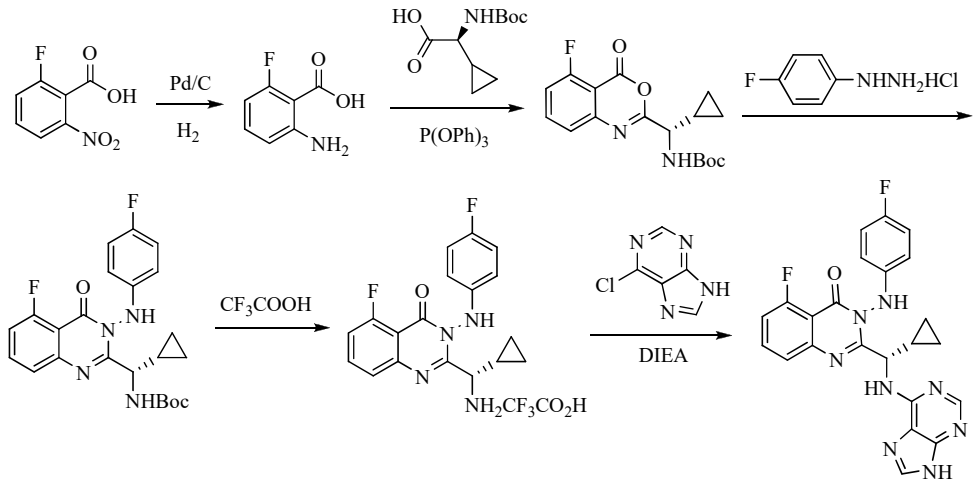
A stirred solution of tert-butyl (S)-(1-(5-chloro-3-((4-fluoro-2,6-dimethylphenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate (0.58g, 1.26 mmol) in DCM (10mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was bubbled with hydrogen chloride gas for 15 min at 0ºC until the reaction was completed by TLC, concentrated under reduced pressure, and the crude product was used for the next step without further purification.

(4) Preparation of (S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-3-((4-fluoro-2,6-dimethylphenyl)amino)quinazolin-4(3H)-one

To a stirred solution of the crude (S)-2-(1-aminoethyl)-5-chloro-3-((4-fluoro-2,6-dimethylphenyl)amino)quinazolin-4(3H)-one hydrochloride (1.26 mmol) in *tert*-butanol (20 mL) in a dry round bottomed flask was added DIEA (2 mL, 11.5 mmol) until the solution is basic, and then 6-chloro-9H-purine (232mg, 1.50mmol) was added, and the reaction was stirred at 85ºC for 48 hr. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by preparation HPLC to yield the title compound (300mg, 49.7% two steps) as a white solid.

MS(M+1): 479.2. ^{1}H-NMR(*d*$_6$-DMSO, 400 MHz):13.05 (1H, s), 8.19-8.15 (2H, m), 7.86 (1H, s), 7.77 (1H, t), 7.68 (1H, d), 7.56 (1H, dd), 7.45-7.35 (1H, m), 6.94-6.85 (1H, m), 6.74-6.63 (1H, m), 6.31 (1H, m), 2.38 (3H, s), 1.84 (3H, s), 1.67 (3H, d).

Example 39 : Preparation of (S)-2-(((9H-purin-6-yl)amino)(cyclopropyl)methyl)-5-fluoro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one (Compound 41)



(1) Preparation of 2-amino-6-fluorobenzoic acid

A mixture of 2-amino-6-fluorobenzoic acid (8.325 g, 45.0 mmol)and Pd/C(10%,0.9 g) in MeOH(200 mL) was stirred for 6 h under N_2 atmosphere. After that the reaction was filtered and concentrated to give the title compound as a pale yellow solid.(6.8, 97.3%).

(2) Preparation of tert-butyl

(S)-(cyclopropyl(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)methyl)carbamate

To a stirred solution of 2-amino-6-fluorobenzoic acid (1.085 g, 7.0 mmol) in pyridine (6mL) in a flask was added (S)-2-((tert-butoxycarbonyl)amino)-2-cyclopropylacetic acid (1.505 g, 7.0 mmol) and triphenylphosphinate(1.505 g, 7.0 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr, and then was used directly for the next step without working-up.

(3) Preparation of tert-butyl

(S)-(cyclopropyl(5-fluoro-3-((4-fluorophenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)carbamate

To the stirred solution of tert-butyl

(S)-(cyclopropyl(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)methyl)carbamate (crude reaction mixture) was added (4-fluorophenyl)hydrazine hydrochloride (1.138 g, 7.0 mmol), and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE:EA=6:1) to yield the title compound (2.13g, 68.7% two steps) as a white solid.

(4) Preparation of

(S)-2-(amino(cyclopropyl)methyl)-5-fluoro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one

trifluoroacetate

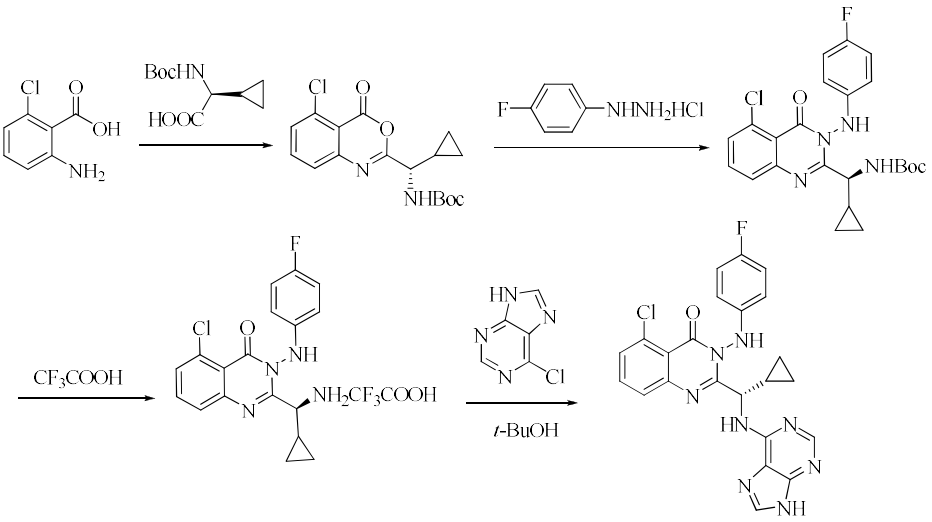
A stirred solution of tert-butyl (S)-(cyclopropyl(5-fluoro-3-((4-fluorophenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)carbamate(0.630 g, 1.42 mmol) in DCM (10mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid(6 mL) The reaction was stirred for 3h until the reaction was completed by TLC,concentrated under reduced pressure, and the crude product was used for the next step without further purification.

(5) Preparation of (S)-2-(((9H-purin-6-yl)amino)(cyclopropyl)methyl)-5-fluoro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one

To a stirred solution of the crude (S)-2-(amino(cyclopropyl)methyl)-5-fluoro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one trifluoroacetate in *tert*-butanol (20 mL) in a dry round bottomed flask was added DIEA until the solution is basic, and then 6-chloro-9H-purine (0.264 g, 1.71 mmol) was added, and the reaction was stirred at 90ºC for 48 hr. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by praparation HPLC to yield the title compound (0.311g,47.5%) as a white solid.

MS(M+1): 461.2 .^{1}H-NMR(d_6-DMSO, 400 MHz):δ 12.97 (1H, br s), 9.11 (1H, s), 8.22-8.00 (2H, m), 7.88-7.75 (1H, m), 7.60-7.45 (2H, m), 7.28 (1H, t), 7.06-6.84 (3H, m), 6.74-6.63 (1H, m), 5.49-5.27 (1H, m), 1.59-1.40 (1H, m), 0.75-0.30 (4H, m).

Example 40 : Preparation of (S)-2-(((9H-purin-6-yl)amino)(cyclopropyl)methyl)-5-chloro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one (Compound 42)



(1) Preparation of tert-butyl

(S)-((5-chloro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)(cyclopropyl)methyl) carbamate

To a stirred solution of 2-amino-6-chlorobenzoic acid (515 mg ,3.0 mmol) in pyridine (5mL) in a flask was added (S)-2-((tert-butoxycarbonyl)amino)-2-cyclopropylacetic acid (710 mg ,3.3 mmol) and triphenylphosphinate(1.02 g ,3.3 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr, and then was used directly for the next step without working-up.

(2) Preparation of tert-butyl

(S)-((5-chloro-3-((4-fluorophenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)carbamate

To the stirred solution of tert-butyl

(S)-((5-chloro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)(cyclopropyl)methyl)carbamate (crude reaction mixture) was added (4-fluorophenyl)hydrazine hydrochloride (536 mg ,3.3 mmol), and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE:EA=5:1) to yield the title compound (1.2g, 87.0% two steps) as a white solid.

(3) Preparation of

(S)-2-(amino(cyclopropyl)methyl)-5-chloro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one trifluoroacetate

A stirred solution of tert-butyl

(S)-((5-chloro-3-((4-fluorophenyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)(cyclopropyl)methyl)carbamate (1.2 g 2.61 mmol) in DCM (10mL) in a dry round bottomed flask was cooled in

an ice-bath. To this solution was added trifluoroacetic acid (5 mL) The reaction was stirred for 1h until the reaction was completed by TLC, concentrated under reduced pressure, and the crude product was used for the next step without further purification.

(4) Preparation of

(S)-2-(((9H-purin-6-yl)amino)(cyclopropyl)methyl)-5-chloro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one

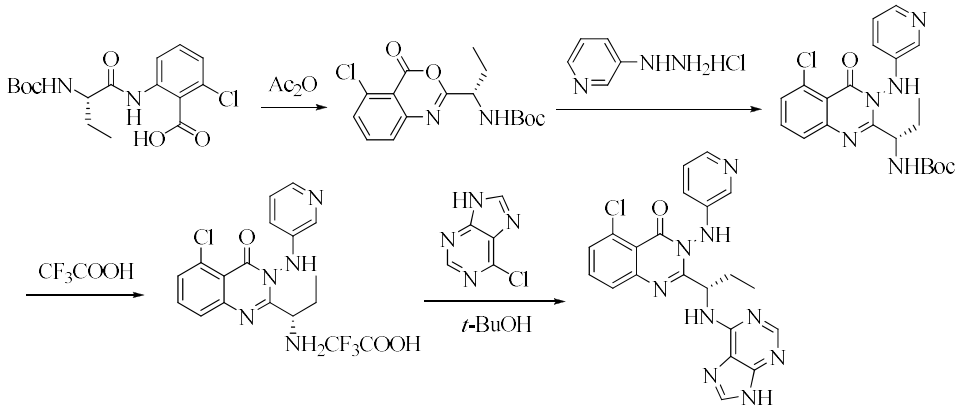
To a stirred solution of the crude

(S)-2-(amino(cyclopropyl)methyl)-5-chloro-3-((4-fluorophenyl)amino)quinazolin-4(3H)-one trifluoroacetate in *tert*-butanol (15 mL) in a dry round bottomed flask was added DIEA until the solution is basic, and then 6-chloro-9H-purine (445 mg, 2.88 mmol) was added, and the reaction was stirred at 90ºC for 48 hr. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (PE:EA=1:2) to yield the title compound (200mg, 16.1%) as a white solid.

MS(M+1): 477.2. ^{1}H-NMR(d_6-DMSO, 400 MHz):δ 12.98 (1H, s), 9.10 (1H, s), 8.29-8.02 (2H, m), 7.82-7.47 (4H, m), 7.06-6.84 (4H, m), 5.40 (1H, m), 1.59-1.41 (1H, m), 0.76-0.32 (4H, m).

Example 41 : Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-chloro-3-(pyridin-3-ylamino)quinazolin-4(3H)-one (Compound 43)



(1) Preparation of tert-butyl

(S)-(1-(5-chloro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)propyl)carbamate

To a stirred solution of (S)-2-(2-((tert-butoxycarbonyl)amino)butanamido)-6-chlorobenzoic acid (2.2 g ,6.17 mmol) in *tert*-butanol (25 mL) in a flask was added acetic anhydride 3.15 g

(30.8 mmol)The resulting reaction solution was refluxed overnight and then was used directly for the next step without working-up.

(2) Preparation of tert-butyl (S)-(1-(5-chloro-4-oxo-3-(pyridin-3-ylamino)-3,4-dihydroquinazolin-2-yl)propyl)carbamate

To the stirred solution of tert-butyl tert-butyl (S)-(1-(5-chloro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)propyl)carbamate (-3.09 mmol) in pyridine (5 mL) was added 3-hydrazinylpyridine hydrochloride (524 mg, 3.60 mmol), and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE:EA=1:1) to yield the title compound (630 mg, 47.6% two steps) as a white solid.

(3) Preparation of (S)-2-(1-aminopropyl)-5-chloro-3-(pyridin-3-ylamino)quinazolin-4(3H)-one trifluoroacetate

A stirred solution of tert-butyl (S)-(1-(5-chloro-4-oxo-3-(pyridin-3-ylamino)-3,4-dihydroquinazolin-2-yl)propyl)carbamate (630 mg, 1.47 mmol) in DCM (10mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid (5 mL) The reaction was stirred for 1h until the reaction was completed by TLC, concentrated under reduced pressure, and the crude product was used for the next step without further purification.

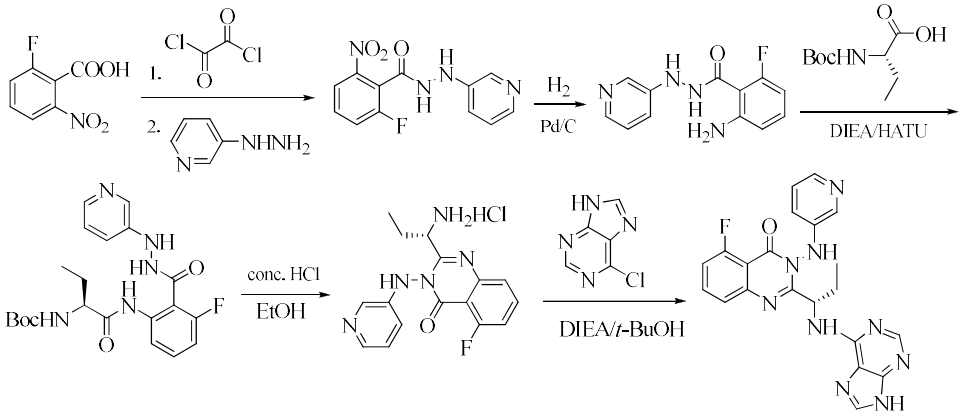
(4) Preparation of (S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-chloro-3-(pyridin-3-ylamino)quinazolin-4(3H)-one

To a stirred solution of the crude (S)-2-(1-aminopropyl)-5-chloro-3-(pyridin-3-ylamino)quinazolin-4(3H)-one trifluoroacetate (-1.47 mmol) in *tert*-butanol (20 mL) in a dry round bottomed flask was added DIEA (2 mL, 11.5 mmol) until the solution is basic, and then 6-chloro-9H-purine (340 mg ,2.20 mmol was added, and the reaction was stirred at 90ºC for 24 hr. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (EA) to yield the title compound (150mg,22.8%) as a white solid.

MS(M+1): 448.2 ^{1}H-NMR(d_6-DMSO, 400 MHz):δ 12.96 (1H, s), 9.27 (1H, s), 8.35 (1H, s),

8.21-8.01 (3H, m), 7.97-7.86 (1H, m), 7.79-7.60 (1H, m), 7.59-7.48 (2H, m), 7.45-7.34 (1H, m), 7.31-7.05 (1H, m), 5.45 (1H, m), 2.20-1.78 (2H, m), 1.02 (3H, t).

Example 42 : Preparation of (S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-3-(pyridin-3-ylamino)quinazolin-4(3H)-one (Compound 44)



(1) Preparation of 2-fluoro-6-nitro-N'-(pyridin-3-yl)benzohydrazide

To a solution of 2-fluoro-6-nitrobenzoic acid(12.03 g, 65.0 mmol) in CH_2Cl_2 (50 mL)and DMF(0.3 mL) was added Oxalyl chloride(12.347 g, 97.3 mmol) dropwise, the mixture was stired for 2 h and concentrated. The residue was dissolved in 1,4-dioxane and added to a solution of 3-hydrazinylpyridine (7.09 g, 65.0 mmol), $NaHCO_3$ (10.92 g, 130.0 mmol) in 1,4-dioxane (15mL)and water (15 mL) dropwrise, the mixture was stirred for 30 min at rt and concentrated ,extracted with EA, dried by Anhydrous sodium sulfate, filtered, concentrated and filtered to give the title compound as a white solid (14.65 g,81.5%).

(2)Preparation of 2-amino-6-fluoro-N'-(pyridin-3-yl)benzohydrazide

A solution of 2-fluoro-6-nitro-N'-(pyridin-3-yl)benzohydrazide (14.65 g, 53.0 mmol) in methanol (1030 mL) was carefully poured into Pd/C (10%, 1.5 g), and the resulting reaction mixture was stirred under hydrogen atmosphere for 24 h. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound for the next step.

(3) Preparation of tert-butyl (S)-(1-((3-fluoro-2-(2-(pyridin-3-yl)hydrazine-1-carbonyl)phenyl)amino)-1-oxobutan-2-yl)carbamate

A solution of 2-amino-6-fluoro-N'-(pyridin-3-yl)benzohydrazide (-53.0 mmol), (S)-2-(tert-butoxycarbonylamino)butanoic acid (12.93 g, 63.6 mmol), DIEA(10.2 mL, 58.5 mmol) and HATU(24.2 g, 63.7 mmol) in DMF (100 mL) was stirred at rt for 64h, the mixture

was partitioned between DCM and water, the organic layer was separated washed with brine, dried and concentrated in vacuo. The crude product was purified by silica gel column chromatography (PE:EA=3:1) to give the title compound as a white solid (6.52 g, 28.5% two steps).

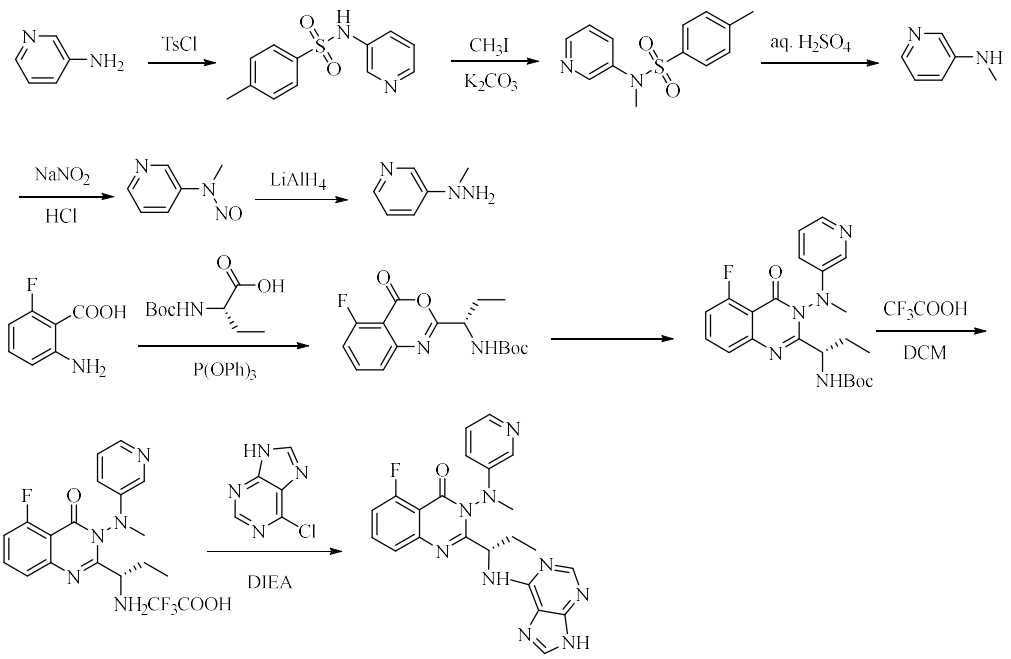
(4) Preparation of (S)-2-(1-aminopropyl)-5-fluoro-3-(pyridin-3-ylamino)quinazolin-4(3H)-one hydrochloride

A solution of tert-butyl (S)-(1-((3-fluoro-2-(2-(pyridin-3-yl)hydrazine-1-carbonyl)phenyl)amino)-1-oxobutan-2-yl)carbamate(6.52 g, 15.11 mmol) in ethanol (50 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (5mL). The reaction was stirred at room temperature for 30min, and then at 85ºC for 24 h. After cooled to room temperature, the reaction solution was concentrated and purified by preparation HPLC to give the title compound as a white solid(0.95 g, 18.0%).

(5) Preparation of (S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-3-(pyridin-3-ylamino)quinazolin-4(3H)-one

To a solution of (S)-2-(1-aminopropyl)-5-fluoro-3-(pyridin-3-ylamino)quinazolin-4(3H)-one hydrochloride (0.95 g, 2.72 mmol) in tert-butanol (20 mL) was added DIEA (0.6 mL, 3.44 mmol), After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine (562 mg, 3.64 mmol)was added. The reaction was stirred at 85ºC for 36h. After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by silica column chromatography (EA) to give the title compound as a white solid (93mg, 7.9%) MS(M+1): 432.2; ^{1}H-NMR(d_6-DMSO, 400 MHz): δ 12.96 (1H, s), 9.28 (1H, s), 8.37-8.30 (1H, m), 8.20-8.11 (1H, m), 8.11-8.02 (2H, m), 7.95-7.72 (2H, m), 7.45-7.34 (2H, m), 7.31-7.18 (2H, m), 5.46 (1H, m), 2.20-1.82 (2H, m), 1.02 (3H, t).

Example 43 : Preparation of (S)-2-(1-(9H-purin-6-ylamino)propyl)-5-fluoro-3-(3-methoxyphenylamino)quinazolin-4(3H)-one (Compound 45)



(1) Preparation of 4-methyl-N-(pyridin-3-yl)benzenesulfonamide

A solution of pyridin-3-amine(14.1 g, 0.15 mol),4-methylbenzenesulfonyl chloride (30 g, 0.157 mol)in pyridine was added at 100ºC for 2 h, cooled down and poured into ice-water, filtered and recrystallized from EtOH to give the title compound as a white solid (36 g, 96.7%).

(2) Preparation of N,4-dimethyl-N-(pyridin-3-yl)benzenesulfonamide

A solution of 4-methyl-N-(pyridin-3-yl)benzenesulfonamide(4.96 g, 20 mmol) and K_2CO_3 (5.52 g, 40 mmol)in acetone (40 mL) was refluxed and CH_3I(5.67 g, 40 mol) was added in 30 min.,and the mixture was refluxed foe 2h.and cooled down, filtered and washed with acetone to give the title compound as a brown oil(4.7 g,89.5%).

(3) Preparation of N-methylpyridin-3-amine

A solution of N,4-dimethyl-N-(pyridin-3-yl)benzenesulfonamide(4.96 g, 18.9 mmol) in 80% concentrated sulfuric acid (20 mL) was stirred at100ºC for 4 h, the mixture was cooled down and adjusted PH=9 with aqueous ammonia and extracted with EA, the organic layer was concentrated to give the title compound as a brown oil(1.86 g, 91.0%).

(4) Preparation of N-methyl-N-(pyridin-3-yl)nitrous amide

To a solution of N-methylpyridin-3-amine(1.86 g, 17.2 mmol) in 25 mL concentrated hydrochloric acid was added a solution of sodium nitrite (1.43 g, 20.7 mmol) in water (25 mL), after that the mixture was stirred at rt. for 1 h , and adjusted PH=9 with aqueous ammonia and extracted with EA, the organic layer was concentrated to give the title

compound as a brown oil(2.15 g,91.3%).

(5) Preparation of 3-(1-methylhydrazinyl) pyridine

To a solution of N-methyl-N-(pyridin-3-yl)nitrous amide (2.15 g, 15.7 mmol)in THF (20 mL) was added a solution of lithium aluminium hydride in THF (1N,17 mL) slowly, at 0 ºC, after that the mixture was stirred for 1 h, and 40% sodium hydroxide solution (10mL) was added and extracted with EA, the organic layer was concentrated give the title compound as a brown oil(1.73 g, 89.2%).

(6) Preparation of tert-butyl

(S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)propyl)(methyl)carbamate

To a stirred solution of 2-amino-6-fluorobenzoic acid (776 mg, 5.0 mmol)in pyridine (8mL) in a 100 mL flask was added (S)-2-((tert-butoxycarbonyl)amino)butanoic acid (1.22 g, 6.0 mmol), and triphenylphosphinate(1.55 g, 5.0 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr, and then was used directly for the next step without working-up.

(7) Preparation of tert-butyl

(S)-(1-(5-fluoro-3-(methyl(pyridin-3-yl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carb amate

To the stirred solution of tert-butyl

(S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)propyl)(methyl)carbamate (crude reaction mixture) was added 3-(1-methylhydrazinyl)pyridine (739 mg, 6.0 mmol) and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE:EA=1:1) to yield the title compound (0.603 g,28.2% two steps) as a light yellow solid.

(8) Preparation of

(S)-2-(1-aminopropyl)-5-fluoro-3-(methyl(pyridin-3-yl)amino)quinazolin-4(3H)-one

A stirred solution of tert-butyl (tert-butyl

(S)-(1-(5-fluoro-3-(methyl(pyridin-3-yl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carb amate (603 mg, 1.41 mmol)in DCM (30 mL) in a dry 100 mL round bottomed flask was cooled in an ice-bath. To this solution was added TFA (5 mL) and stirred for 2h at which time TLC showed the disappearance of the starting material. The reaction solution was then

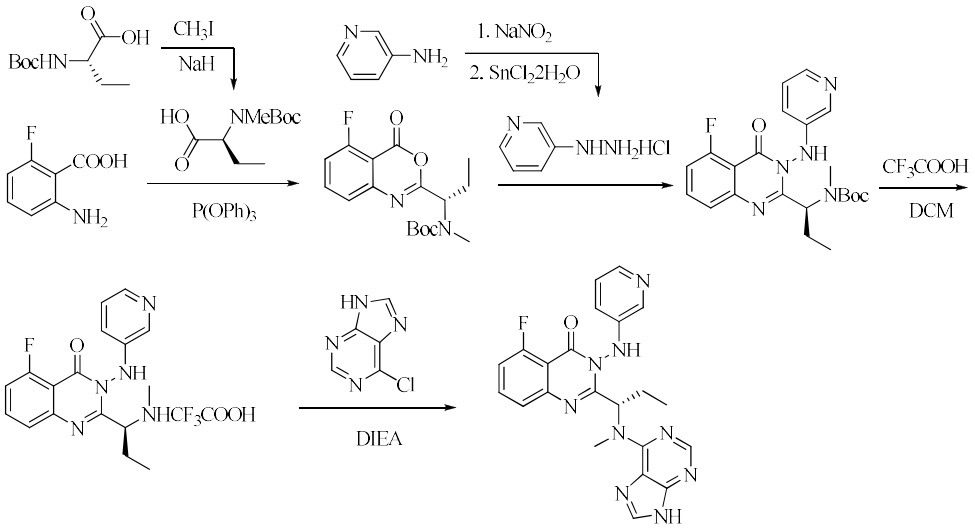
concentrated under reduced pressure, and the crude product was used without further purification.

(4) Preparation of (S)-2-(1-((9H-purin-6-yl)amino)ethyl)-3-((4-fluorophenyl)amino)-5-(trifluoromethyl)quinazolin-4(3H)-one

To a stirred solution of the crude (S)-2-(1-aminopropyl)-5-fluoro-3-(methyl(pyridin-3-yl)amino)quinazolin-4(3H)-one (-1.41 mmol) in *tert*-butanol (30 mL) in a dry round bottomed flask was added DIEA(0.74 mL, 4.24 mmol) until the solution is basic, and then 6-chloropurine(240 mg, 1.55 mmol)was added, and the reaction was stirred at 85ºC for 36 hr. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (EA) to yield the title compound (127 mg, 20.2%) as a white solid.

MS(M+1): 446.2. ^{1}H-NMR(*d*$_6$-DMSO, 400 MHz):δ 12.97 (1H, s), 8.28-7.77 (6H, m), 7.49 (1H, d), 7.34-7.07 (3H, m), 5.49 (1H, m), 3.50-3.41 (3H,m), 2.18-1.80 (2H, m), 1.30-0.82 (3H, m).

Example 44 : Preparation of (S)-5-fluoro-2-(1-(methyl(9H-purin-6-yl)amino)propyl)-3-(pyridin-3-ylamino)quinazolin-4(3H)-one (Compound 46)



(1) Preparation of (S)-2-((tert-butoxycarbonyl)(methyl)amino)butanoic acid

To a solution of (S)-2-((tert-butoxycarbonyl)amino)butanoic acid (20.32 g, 100 mmol)in THF (0.6 L) was added 60% sodium hydride (40 g, 1 mol) at ice-water bath, the mixture was stirred

for 30 min, and CH_3I (141.9 g, 1 mol) was added dropwise, the reaction solution was stirred overnight and extracted with EA, washed with brine. The organic layer was concentrated and recrystillized from PE to give the title compound (12.79 g,58.9 %) as a pale yellow solid.

(2) Preparation of 3-hydrazinylpyridine hydrochloride

To a solution of concentrated hydrochloric acid(200 mL) was added pyridin-3-amine (19.95 g, 212 mmol)and a solution of sodium nitrite(15.80 g, 229 mmol)in water(100 mL), after that the mixture was stirred for 1 h , at 0ºC , and a solution of Tin(Ⅱ) chloride dihydrate (58.7 g, 260 mmol) in concentrated hydrochloric acid(185 mL) was added and the mixture was stirred for 15 min at 0ºC and then filtered , washed with ethyl ether and dried to give the title compound (17.96 g 58.0 %) as a white solid.

(3) Preparation of tert-butyl

(S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)propyl)(methyl)carbamate

To a stirred solution of 2-amino-6-fluorobenzoic acid (776 mg,5.0 mmol) in pyridine (12mL) in a flask was added (S)-2-((tert-butoxycarbonyl)(methyl)amino)butanoic acid (1.31 g, 6.0 mmol) and triphenylphosphinate(1.55 g, 5.0 mmol). The resulting reaction solution was stirred at 55ºC for 10 h, and then was used directly for the next step without working-up.

(4) Preparation of tert-butyl

(S)-(1-(5-fluoro-3-(methyl(pyridin-3-yl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)(methyl) carbamate

To the stirred solution of tert-butyl

(S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)propyl)(methyl)carbamate (crude reaction mixture) was added3-hydrazinylpyridine hydrochloride (874 mg, 6.0 mmol) and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography(EA) to yield the title compound (624 mg, 29.2% two steps) as a brown solid.

(5) Preparation of

(S)-5-fluoro-2-(1-(methylamino)propyl)-3-(pyridin-3-ylamino)quinazolin-4(3H)-onetrifluoroacetate.

A stirred solution of tert-butyl

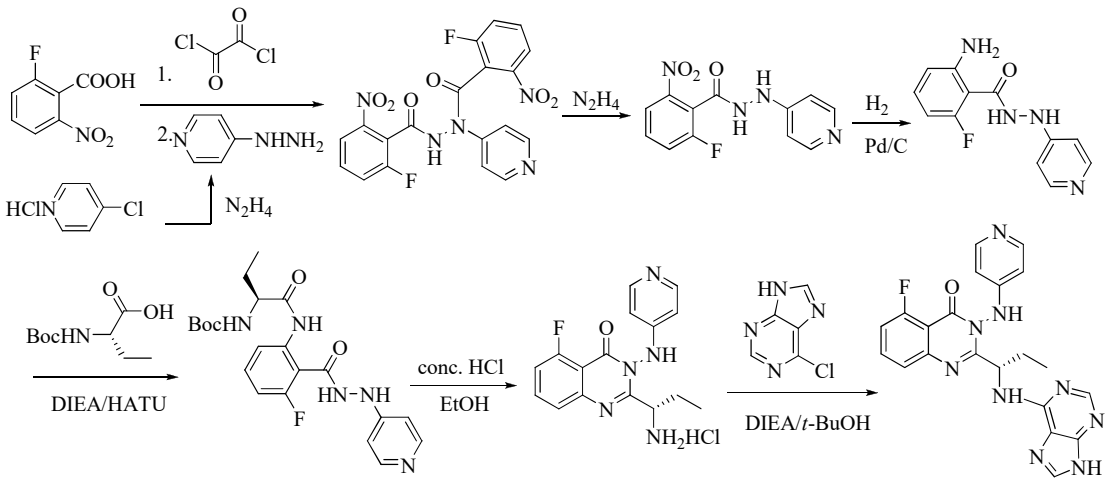
(S)-(1-(5-fluoro-3-(methyl(pyridin-3-yl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)(methyl)carbamate (624 mg, 1.46 mmol) in chloromethane (2 mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid (6mL) at which time TLC showed the disappearance of the starting material. The reaction solution was then concentrated under reduced pressure, and the crude product was used without further purification.

(6) Preparation of (S)-5-fluoro-2-(1-(methyl(9H-purin-6-yl)amino)propyl)-3-(pyridin-3-ylamino)quinazolin-4(3H)-one

To a stirred solution of the crude (S)-5-fluoro-2-(1-(methylamino)propyl)-3-(pyridin-3-ylamino)quinazolin-4(3H)-onetrifluoroacetate. (-1.46 mmol mmol) in *tert*-butanol (20mL) in a dry round bottomed flask was added DIEA (0.76 mL, 4.36 mmol) until the solution is basic, and then 6-chloro-9H-purine (395 mg, 2.55 mmol) was added, and the reaction was stirred at 90ºC for 48 hr. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography(EA) to yield the title compound (118 mg, 18.1% two steps) as a white solid.

MS(M+1): 446.2. ^{1}H-NMR(d_6-DMSO, 400 MHz):δ 12.82 (1H, s), 9.07, 8.81 (1H, two singlets), 8.11-7.78 (4H, m), 7.76-7.48 (2H, m), 7.40-7.05 (2H, m), 6.92-6.60 (1H, m), 5.31 (1H, m), 3.65, 2.94 (3H, two singlets), 2.25-1.92 (2H, m), 1.22 (3H, m).

Example 45 : Preparation of (S)-2-(1-(9H-purin-6-ylamino)propyl)-5-fluoro-3-(pyridin-4-ylamino)quinazolin-4(3H)-one (Compound 47)



(1) Preparation of 4-hydrazinylpyridine

A solution of 4-chloropyridine hydrochloride(25.3 g, 168.7 mmol),and 85% hydrazine hydrate (47 mL, 824 mmol) was refluxed for 1 h, the mixture was cooled down and filtered ,washed with isopropanol to give the title compound as a solid(16.1 g,87.5 %).

(2) Preparation of

2-fluoro-N'-(2-fluoro-6-nitro-benzoyl)-6-nitro-N'-(pyridin-4-yl)benzohydrazide

To a solution of 2-fluoro-6-nitrobenzoic acid(12.03 g, 65.0 mmol) in CH_2Cl_2 (50 mL)and DMF(0.3 mL) was added Oxalyl chloride(12.347 g, 97.3 mmol) dropwise, the mixture was stired for 30 min and concentrated.The residue was dissolved in 1,4-dioxane and added to a solution of 4-hydrazinylpyridine (7.09 g, 65.0 mmol),$NaHCO_3$ (10.92 g, 130 mmol) in 1,4-dioxane (30mL) and water (30 mL) drowrise ,the mixture was stirred for 30 min at rt and concentrated ,extracted with EA, dried by Anhydrous sodium sulfate, filtered, concentrated to give the title compound as a brown solid (14.66 g, 50.9 %).

(3) Preparation of 2-fluoro-6-nitro-N'-(pyridin-4-yl)benzohydrazide

To a solution of

2-fluoro-N'-(2-fluoro-6-nitro-benzoyl)-6-nitro-N'-(pyridin-4-yl)benzohydrazide (14.66 g, 33.1 mmol)in ethanol (20mL) was added 85% hydrazine hydrate (15 mL), the mixture was stirred for 2 h, evaporated most of the solvent and filtered and washed with PE to yield the title compound (8.45 g, 92.4 %).

(4) Preparation of 2-amino-6-fluoro-N'-(pyridin-4-yl)benzohydrazide

A solution of 2-fluoro-6-nitro-N'-(pyridin-4-yl)benzohydrazide (8.45 g, 30.6 mmol) in methanol (130 mL) was carefully poured onto Pd/C (10%, 1.5 g), and the resulting reaction

mixture was stirred under hydrogen atmosphere for 42 h. The Pd/C catalyst was filtered, and the organic solution was evaporated to yield the title compound for the next step.

(5)Preparation of (S)-tert-butyl 1-(3-fluoro-2-(2-(pyridin-4-yl)hydrazinecarbonyl)phenylamino)-1-oxobutan-2-ylcarbamate

A solution of 2-amino-6-fluoro-N'-(pyridin-4-yl)benzohydrazide (-30.6 mmol), (S)-2-(tert-butoxycarbonylamino)butanoic acid (9.33 g, 45.9 mmol), (6.4 mL, 36.75 mmol) and HATU(13.96 g,36.71 mmol) in DMF(80mL) was stirred at rt for 64 h, the mixture was partitioned between DCM and water, the organic layer was separated washed with brine, dried and concentrated in vacuo. The crude product was purified by silica column chromatography (PE:EA=3:1) to give the title compound as a white solid (3.76 g ,28.5 %).

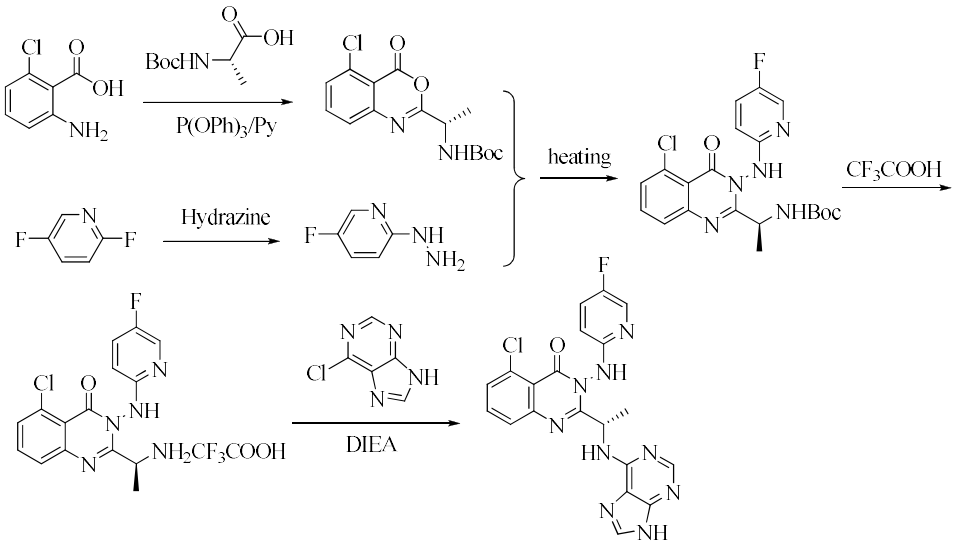
(6) Preparation of (S)-2-(1-aminopropyl)-5-fluoro-3-(pyridin-4-ylamino)quinazolin-4(3H)-one hydrochloride

A solution of (S)-tert-butyl 1-(3-fluoro-2-(2-(pyridin-4-yl)hydrazinecarbonyl)phenylamino)-1-oxobutan-2-ylcarbamate (3.76 g, 8.71 mmol) in ethanol (50 mL) was cooled in an ice bath. To this solution was added dropwise concentrated hydrochloric acid (5 mL). The reaction was stirred at room temperature for 30min, and then at 85ºC for 24 hr. After cooled to room temperature, and adjusted to PH =8 ,the reaction solution was concentrated to give the title compound as a white solid(0.95 g, 31.2 %).

(7) Preparation of (S)-2-(1-(9H-purin-6-ylamino)propyl)-5-fluoro-3-(pyridin-4-ylamino)quinazolin-4(3H)-one

To a (S)-2-(1-aminopropyl)-5-fluoro-3-(pyridin-4-ylamino)quinazolin-4(3H)-one hydrochloride (0.65 g, 1.86 mmol) in tert-butanol (20 mL) was added DIEA (0.6 mL, 3.44 mmol) , After the reaction was stirred at 0ºC for 30 min, 6-chloro-9H-purine(480 mg, 3.1 mmol) was added. The reaction was stirred at 85ºC for 36 h. After cooled to room temperature, the reaction solution was concentrated, the crude product was purified by silica column chromatography (EA) to give the title compound as a white solid (0.101g, 12.6%) MS(M+1): 432.2. ^{1}H-NMR(*d*$_6$-DMSO, 400 MHz): δ 9.78 (1H, d), 9.81-9.74 (1H, m), 9.72 (1H, d), 8.62 (1H, s), 8.31 (1H, s), 7.76 (1H, dd), 7.42 (1H, d), 7.36 (1H, d), 7.29 (1H, t), 7.15 (1H, d), 5.48 (1H, m), 2.27-2.14 (1H, m), 2.03-1.87 (1H, m), 1.06 (3H, t).

Example 46 : Preparation of ((S)-2-(1-(9H-purin-6-ylamino)ethyl)-5-chloro-3-(5-fluoropyridin-2-ylamino)quinazolin-4 (3H)-one (Compound 53)



(1) Preparation of 5-fluoro-2-hydrazinylpyridine

A mixture of 2,5-difluoropyridine (10 g, 59.8 mmol) in 85% hydrazine hydrate (0.90 mL, 13.7 mmol) was heated 120 ºC for 1 h by microwave. After that the reaction was cooled down to room temperature, filtered, washed with PE, and dried to give the title compound as a pale yellow solid.(525mg, 31.8%).

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

To a stirred solution of 2-amino-6-chlorobenzoic acid (515 mg,3.0 mmol) in pyridine (5 mL) in a flask was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (624 mg, 3.3 mmol) and triphenylphosphinate(1.10 g, 3.55 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr, and then was used directly for the next step without working-up.

(3) Preparation of (S)-tert-butyl 1-(5-chloro-3-(5-fluoropyridin-2-ylamino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethylcarbamate

To the stirred solution of (S)-tert-butyl 1-(5-chloro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethylcarbamate (crude reaction mixture) was added 5-fluoro-2-hydrazinylpyridine(420 mg, 3.3 mmol), and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography

(PE:EA=10:1) to yield the title compound (700mg,53.7% two steps) as a white solid.

(4) Preparation of

(S)-2-(1-aminoethyl)-5-chloro-3-(5-fluoropyridin-2-ylamino)quinazolin-4(3H)-one trifluoroacetate

A stirred solution of (S)-tert-butyl 1-(5-chloro-3-(5-fluoropyridin-2-ylamino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethylcarbamate (700 mg, 1.61 mmol) in DCM (20mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid(10 mL) The reaction was stirred until the reaction was completed by TLC,concentrated under reduced pressure, and the crude product was used for the next step without further purification.

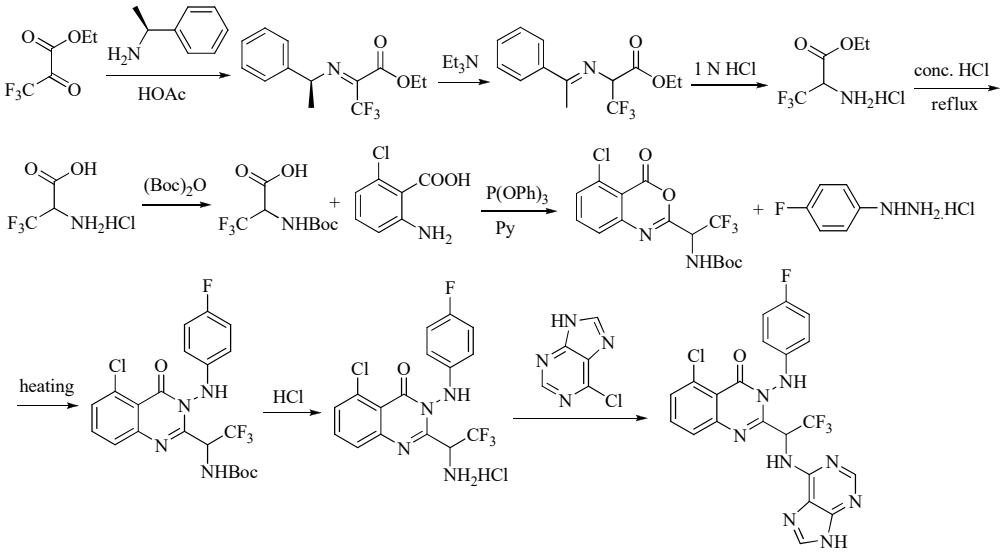
(5) Preparation of

(S)-2-(1-(9H-purin-6-ylamino)ethyl)-5-chloro-3-(5-fluoropyridin-2-ylamino)quinazolin-4(3H)-one

To a stirred solution of the crude (S)-2-(1-aminoethyl)-5-chloro-3-(5-fluoropyridin-2-ylamino)quinazolin-4(3H)-onetrifluoroacetate in *tert*-butanol (40 mL) in a dry round bottomed flask was added DIEA until the solution is basic, and then 6-chloro-9H-purine (308 mg, 1.99 mmol)was added, and the reaction was stirred at 90ºC for 48 h. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by praparation HPLC to yield the title compound (0.19g, 26.1%) as a white solid.

MS(M+1): 451.7. ^{1}H-NMR(d_6-DMSO, 400 MHz):δ 12.97 (1H, br s), 9.79, 9.64 (1H, two singlets), 8.19-8.07 (2H, m), 8.02-7.93 (1H, m), 7.81-7.58 (4H, m), 7.57-7.51 (1H, m), 7.06-6.95 (1H, m), 5.78, 5.56 (1H, two multiplets), 1.61, 1.44 (3H, two doublets).

Example 47 : Preparation of 2-(1-(9H-purin-6-ylamino)-2,2,2-trifluoroethyl)-5-chloro-3-(4-fluorophenylamino)quinazolin-4(3H)-one (Compound 56)



(1) Preparation of (S,Z)-ethyl 3,3,3-trifluoro-2-(1-phenylethylimino)propanoate

To a mixture of glacial acetic acid (4.2 g, 70 mmol) in chloroform (20 mL) was added (S)-1-phenylethanamine (8.47 g,70 mmol) and stirred fo 5 min, a solution of ethyl 3,3,3-trifluoro-2-oxopropanoate(10.88 g,64 mmol) in chloroform (20 mL) was added. The mixture was refluxed for 24 h, concentrated and purified by silica gel column chromatography (PE:EA=100:1)to yield the title compound (8.2 g, 46.7% two steps).

(2) Preparation of (E)-ethyl 3,3,3-trifluoro-2-(1-phenylethylideneamino)propanoate

A solution of (S,Z)-ethyl 3,3,3-trifluoro-2-(1-phenylethylimino)propanoate(8.2 g,30 mmol) in Et_3N(20 mL) was stirred for 16 h, and concentrated to yield the title compound for the next step.

(3) Preparation of ethyl 2-amino-3,3,3-trifluoropropanoate hydrochloride

To a mixture of crude (E)-ethyl 3,3,3-trifluoro-2-(1-phenylethylideneamino)propanoate in aether (20 mL) was added 1 N HCl(8 mL), the mixture was stirred for 16 h, and concentrated to yield the title compound(4 g).

(4) Preparation of 2-amino-3,3,3-trifluoropropanoic acid hydrochloride

A mixture of crude ethyl 2-amino-3,3,3-trifluoropropanoate hydrochloride(4 g) in concentrated hydrochloric acid (10 mL), the mixture was stirred at 90°C for 8 h,and concentrated to yield the title compound(2.9 g).

(5) Preparation of 2-(tert-butoxycarbonylamino)-3,3,3-trifluoropropanoic acid

To a solution of crude 2-amino-3,3,3-trifluoropropanoic acid hydrochloride(2.9 g) in THF (25 mL) and water (25 mL) was added Na_2CO_3(2.8 g,26.4 mmol) and Boc_2O(2.88 g,13.2 mmol),

The mixture was stirred for 16 h, and adjusted PH=2-3, extracted with EA,the organic layer was dried and concentrated to yield the title compound (1.95 g).

(6) Preparation of tert-butyl 1-(5-chloro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)-2,2,2-trifluoroethylcarbamate

To a stirred solution of 2-amino-6-chlorobenzoic acid (987 mg, 5.75 mmol) in pyridine (6mL) in a 100 mL flask was added 2-(tert-butoxycarbonylamino)-3,3,3-trifluoropropanoic acid (1.95 g, 8.0 mmol), and triphenylphosphinate(1.84 g, 5.9 mmol) The resulting reaction solution was stirred at 55ºC for 24 h, and then was used directly for the next step without working-up.

(7) Preparation of tert-butyl 1-(5-chloro-3-(4-fluorophenylamino)-4-oxo-3,4-dihydroquinazolin-2-yl)-2,2,2-trifluoroethylcarbamate

To the stirred solution of tert-butyl 1-(5-chloro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)-2,2,2-trifluoroethylcarbamate (crude reaction mixture) was added (4-fluorophenyl)hydrazine hydrochloride (1.07 g, 6.58 mmol)and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE:EA=10:1-4:1) to yield the title compound (0.33 g, 11.8% two steps) as a light yellow solid.

(8) Preparation of 2-(1-amino-2,2,2-trifluoroethyl)-5-chloro-3-(4-fluorophenylamino)quinazolin-4(3H)-one hydrochloride

A stirred solution of tert-butyl 1-(5-chloro-3-(4-fluorophenylamino)-4-oxo-3,4-dihydroquinazolin-2-yl)-2,2,2-trifluoroethylcarbamate (330 mg,0.68 mmol) in DCM(20 mL) in a dry 100 mL round bottomed flask was cooled in an ice-bath. To this solution was bubbled in HCl gas for 2 hr, at which time TLC showed the disappearance of the starting material. The reaction solution was then concentrated under reduced pressure, and the crude product (0.3 g)was used without further purification.

(9) Preparation of 2-(1-(9H-purin-6-ylamino)-2,2,2-trifluoroethyl)-5-chloro-3-(4-fluorophenylamino)quinazolin-4(3H)-one

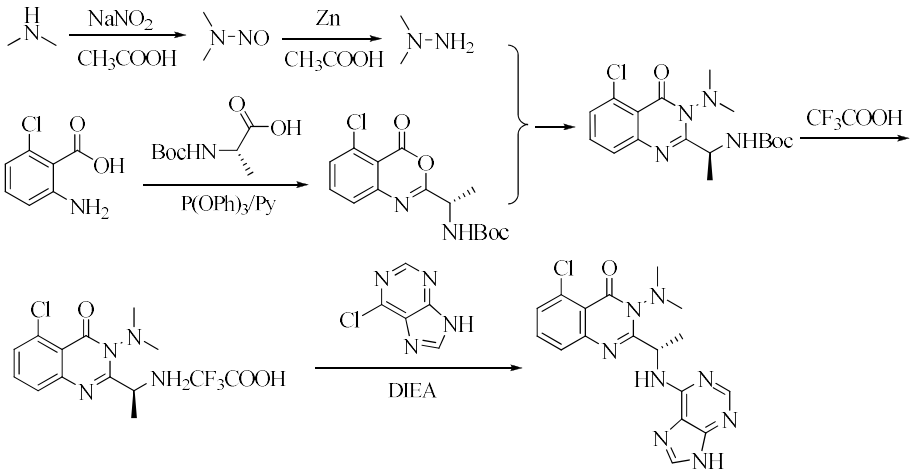
To a stirred solution of the crude

2-(1-amino-2,2,2-trifluoroethyl)-5-chloro-3-(4-fluorophenylamino)quinazolin-4(3H)-one hydrochloride (0.3 g) in *tert*-butanol (20 mL) in a dry round bottomed flask was added 5 drops of glacial acetic acid and then 6-chloropurine (195 mg,1.26 mmol)was added, and the reaction was stirred at 90ºC for 24 h. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (PE:EA=10:1-1:3)to yield the title compound (110 mg, 32.0%) as a white solid.

MS(M+1): 505.2. ^{1}H-NMR(*d*$_6$-DMSO, 400 MHz):δ 12.96 (1H, s), 8.92 (1H, s), 8.50-8.20 (1H, m), 8.18-8.05 (2H, m), 7.85 (1H, t), 7.78 (1H, d), 7.66 (1H, t), 7.25-6.95 (1H, m), 6.80-6.45 (4H, m).

Example 48 : Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-3-(dimethylamino)quinazolin-4(3H)-one (Compound 57)



(1) Preparation of N,N-dimethylnitrous amide

To a solution of dimethylamine hydrochloride (4.89 g, 60.0 mmol)in acetic acid (50 mL) was added a solution of sodium nitrite (5.38 g, 78.0 mmol)in water (40mL) dropwise at 0℃, and then the mixture was stirred overnight. The raw material was disappeared by LC-MS and the mixture was used for the next step without retreatment.

(2) Preparation of 1,1-dimethylhydrazine

To a solution of N,N-dimethylnitrous amide(the crude material) was added zinc powder(15.60 g, 239 mmol)in ice bath, the mixture was stirred at room temperature until the raw material

was disappeared by TLC, and filtered. The resulting filtrate was used directly for the fourth step reaction.

(3) Preparation of tert-butyl

(S)-(1-(5-chloro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate

To a stirred solution of 2-amino-6-chlorobenzoic acid(1.72 g, 10.0 mmol)in pyridine (10mL) in a flask was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (2.08 g, 11.0 mmol) and triphenylphosphinate(3.10 g, 10.0 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr, and then was used directly for the next step without working-up.

(4) Preparation of (tert-butyl

(S)-(1-(5-chloro-3-(dimethylamino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate

To the stirred solution of tert-butyl

(S)-(1-(5-chloro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate (crude reaction mixture) was added 1,1-dimethylhydrazine and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography(PE:EA=10:1)to yield the title compound (1.42 g, 38.7% two steps) as a pale yellow oil.

(5) Preparation of (S)-2-(1-aminoethyl)-5-chloro-3-(dimethylamino)quinazolin-4(3H)-one trifluoroacetate

A stirred solution of tert-butyl

(S)-(1-(5-chloro-3-(dimethylamino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate(0.710 g, 1.94 mmol) in DCM (20mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid(10 mL). The reaction was stirred until the reaction was completed by TLC,concentrated under reduced pressure, and the crude product was used for the next step without further purification.

(6) Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-3-(dimethylamino)quinazolin-4(3H)-one

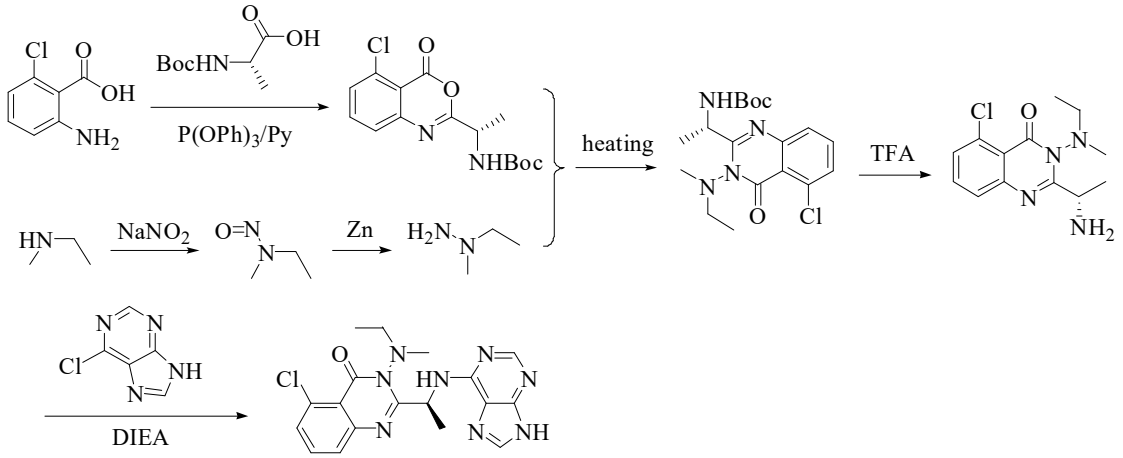
To a stirred solution of the crude

(S)-2-(1-aminoethyl)-5-chloro-3-(dimethylamino)quinazolin-4(3H)-one trifluoroacetate in *tert*-butanol (40 mL) in a dry round bottomed flask was added DIEA until the solution is basic, and then 6-chloro-9H-purine (0.330 g,2.13 mmol)was added, and the reaction was stirred at

90ºC for 48 h. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by praparation HPLC to yield the title compound (0.27g, 36.2% two steps) as a white solid.

MS(M+1): 384.8. ^{1}H-NMR(d_6-DMSO, 400 MHz):δ 12.96 (1H, s), 8.15 (2H, s), 7.86-7.77 (1H, m), 7.66 (1H, t), 7.52-7.45 (2H, m), 5.83 (1H, m), 3.09, 3.07 (6H, two singlets), 1.57 (3H, d).

Example 49 : Preparation of (S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-3-(ethyl(methyl)amino)quinazolin-4(3H)-one (Compound 59)



(1) Preparation of N-ethyl-N-methylnitrous amide

To a solution of N-methylethanamine (5.9 g, 100 mmol)in acetic acid (50 mL) was added a solution of sodium nitrite (9.0 g, 130mmol) in water (40mL) dropwise at 0℃, and then the mixture was stirred for 2h. The raw material was disappeared by LC-MS and the mixture was used for the next step without retreatment.

(2) Preparation of 1-ethyl-1-methylhydrazine

To a solution of N-ethyl-N-methylnitrous amide (the crude material) was added zinc powder(26 g, 400 mmol) in ice bath, the mixture was stirred at room temperature for 12 h until the raw material was disappeared by TLC, and filtered. The resulting filtrate was concentrated to give the title compound (5.8 g,78.3%) as a colorless oil.

(3) Preparation of tert-butyl (S)-(1-(5-chloro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate

To a stirred solution of 2-amino-6-chlorobenzoic acid(1.72 g, 10.0 mmol)in pyridine (10mL) in a flask was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (2.37 g,12.5 mmol) and triphenylphosphinate(3.40 g,11.0 mmol). The resulting reaction solution was stirred at 55ºC

for 10 hr, and then was used directly for the next step without working-up.

(4) Preparation of tert-butyl

(S)-(1-(5-chloro-3-(ethyl(methyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate

To the stirred solution of tert-butyl

(S)-(1-(5-chloro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate (crude reaction mixture) was added 1-ethyl-1-methylhydrazine(1.11 g, 15.0 mmol) and the resulting reaction solution was stirred at 100ºC for 12 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE:EA=1:1) to yield the title compound (1.48 g, 38.9% two steps) as a white solid.

(5) Preparation of

(S)-2-(1-aminoethyl)-5-chloro-3-(ethyl(methyl)amino)quinazolin-4(3H)-onetrifluoroacetate

A stirred solution of tert-butyl

(S)-(1-(5-chloro-3-(ethyl(methyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate(0.148 g,0.389 mmol) in DCM (10mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid(5 mL). The reaction was stirred until the reaction was completed by TLC,concentrated under reduced pressure, and the crude product was used for the next step without further purification.

(6) Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-3-(ethyl(methyl)amino)quinazolin-4(3H)-one

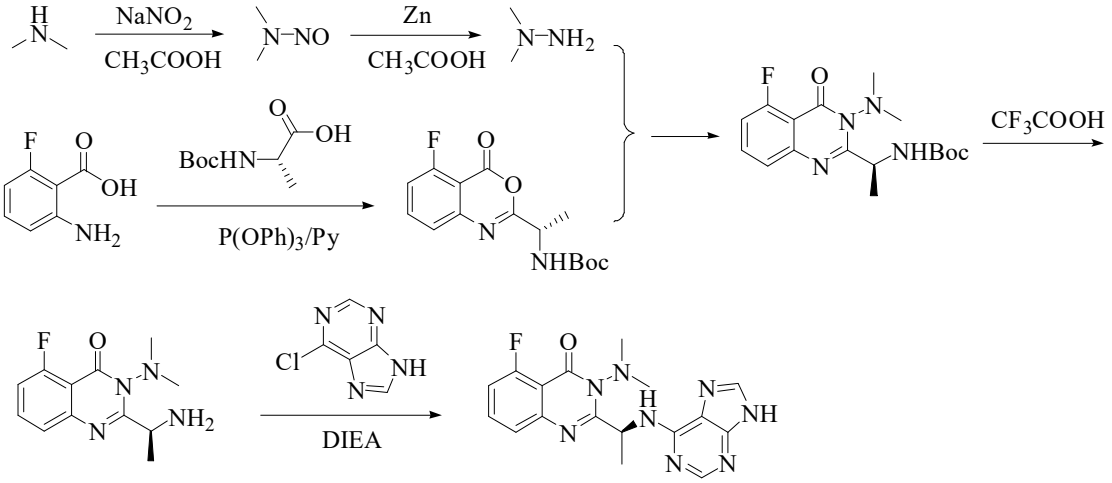
To a stirred solution of the crude

(S)-2-(1-aminoethyl)-5-chloro-3-(ethyl(methyl)amino)quinazolin-4(3H)-onetrifluoroacetate in *tert*-butanol (20 mL) in a dry round bottomed flask was added DIEA until the solution is basic, and then 6-chloro-9H-purine (60 mg, 0.39 mmol)was added, and the reaction was stirred at 90ºC for 48 h. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by praparation HPLC to yield the title compound (0.073g, 47.0% two steps) as a white solid.

MS(M+1): 399.2. ^{1}H-NMR(d_6-DMSO, 400 MHz):12.95 (1H, br s), 8.19-8.10 (2H, m), 7.89-7.80 (0.5H, m), 7.73-7.62 (1.5H, m), 7.55-7.45 (2H, m), 6.10-5.81 (1H, m), 3.60-3.37 (1.5H, m), 3.26-3.14 (0.5H, m), 3.04, 3.01 (3H, two singlets), 1.60-1.53 (3H, m), 1.06 (3H, q).

Example 50 : Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-fluoro-3-(dimethylamino)quinazolin-4(3H)-one (Compound 60)



(1) Preparation of N,N-dimethylnitrous amide

To a solution of dimethylamine hydrochloride (4.89 g, 60.0 mmol)in acetic acid (50 mL) was added a solution of sodium nitrite (5.38 g, 78.0 mmol)in water(40mL) dropwise at 0℃, and then the mixture was stirred overnight . The raw material was disappeared by LC-MS and the mixture was used for the next step without retreatment.

(2) Preparation of 1,1-dimethylhydrazine

To a solution of N,N-dimethylnitrous amide(the crude material) was added zinc powder(15.60 g, 239 mmol)in ice bath, the mixture was stirred at room temperature until the raw material was disappeared by TLC, and filtered. The resulting filtrate was used directly for the fourth step reaction.

(3) Preparation of tert-butyl

(S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate

To a stirred solution of 2-amino-6-fluorobenzoic acid (1.55 g, 10.0 mmol) in pyridine (10mL) in a flask was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (2.08 g, 11.0 mmol) and triphenylphosphinate(3.10 g, 10.0 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr, and then was used directly for the next step without working-up.

(4) Preparation of (tert-butyl

(S)-(1-(5-fluoro-3-(dimethylamino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate

To the stirred solution of tert-butyl

(S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate (crude reaction mixture)

was added 1,1-dimethylhydrazine and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography(PE:EA=10:1) to yield the title compound (2.42 g, 69.1% two steps) as a pale yellow oil.

(5) Preparation of (S)-2-(1-aminoethyl)-5-fluoro-3-(dimethylamino)quinazolin-4(3H)-one trifluoroacetate

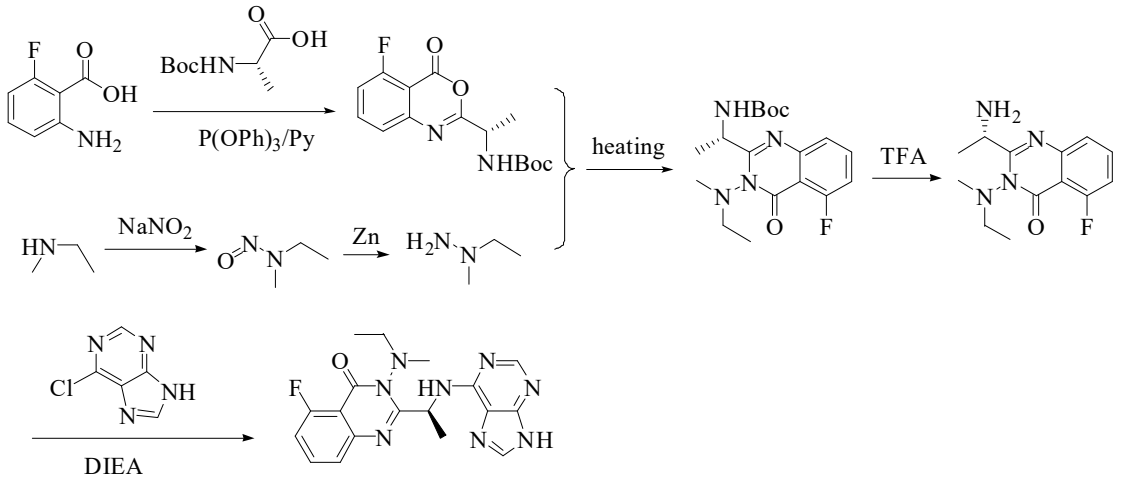
A stirred solution of tert-butyl (S)-(1-(5-fluoro-3-(dimethylamino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate(2.42 g,6.91 mmol) in DCM (20mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid (10 mL). The reaction was stirred until the reaction was completed by TLC,concentrated under reduced pressure, and the crude product was used for the next step without further purification.

(6) Preparation of (S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-fluoro-3-(dimethylamino)quinazolin-4(3H)-one

To a stirred solution of the crude (S)-2-(1-aminoethyl)-5-fluoro-3-(dimethylamino)quinazolin-4(3H)-one trifluoroacetate in *tert*-butanol (40 mL) in a dry round bottomed flask was added DIEA until the solution is basic, and then 6-chloro-9H-purine (0.80 g, 5.18 mmol)was added, and the reaction was stirred at 90ºC for 48 h. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by praparation HPLC to yield the title compound (0.26g, 10.2% two steps) as a white solid.

MS(M+1): 369.2^{1}H-NMR(d_6-DMSO, 400 MHz):δ 12.96 (1H, s), 8.15 (2H, s), 7.84-7.77 (1H, m), 7.72 (1H, dd), 7.36 (1H, d), 7.22 (1H, dd), 5.84 (1H, m), 3.09, 3.07 (6H, two singlets), 1.58 (3H, d).

Example 51 : Preparation of (S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-fluoro-3-(ethyl(methyl)amino)quinazolin-4(3H)-one (Compound 61)



(1) Preparation of N-ethyl-N-methylnitrous amide

To a solution of N-methylethanamine (5.9 g, 100 mmol)in acetic acid (50 mL) was added a solution of sodium nitrite (9.0 g, 130mmol) in water (40mL) dropwise at 0℃, and then the mixture was stirred for 2h. The raw material was disappeared by LC-MS and the mixture was used for the next step without retreatment.

(2) Preparation of 1-ethyl-1-methylhydrazine

To a solution of N-ethyl-N-methylnitrous amide (the crude material) was added zinc powder(26 g, 400 mmol) in ice bath, the mixture was stirred at room temperature for 12 h until the raw material was disappeared by TLC,and filtered. The resulting filtrate was concentrated to give the title compound(5.8 g,78.3%) as a colorless oil.

(3) Preparation of tert-butyl

(S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate

To a stirred solution of 2-amino-6-fluorobenzoic acid(4.2 g,27.1 mmol) in pyridine (42mL) in a flask was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (6.4 g, 33.8 mmol) and triphenylphosphinate(9.2 g, 29.7 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr, and then was used directly for the next step without working-up.

(4) Preparation of tert-butyl

(S)-(1-(5-fluoro-3-(ethyl(methyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate

To the stirred solution of tert-butyl

(S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate (crude reaction mixture) was added 1-ethyl-1-methylhydrazine(2.2 g, 29.7 mmol) and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated

under reduced pressure. The crude product was purified by silica gel column chromatography(PE:EA=1:1)to yield the title compound (3.5 g, 35.4% two steps) as a pale yellow oil.

(5) Preparation of (S)-2-(1-aminoethyl)-5-fluoro-3-(ethyl(methyl)amino)quinazolin-4(3H)-onetrifluoroacetate

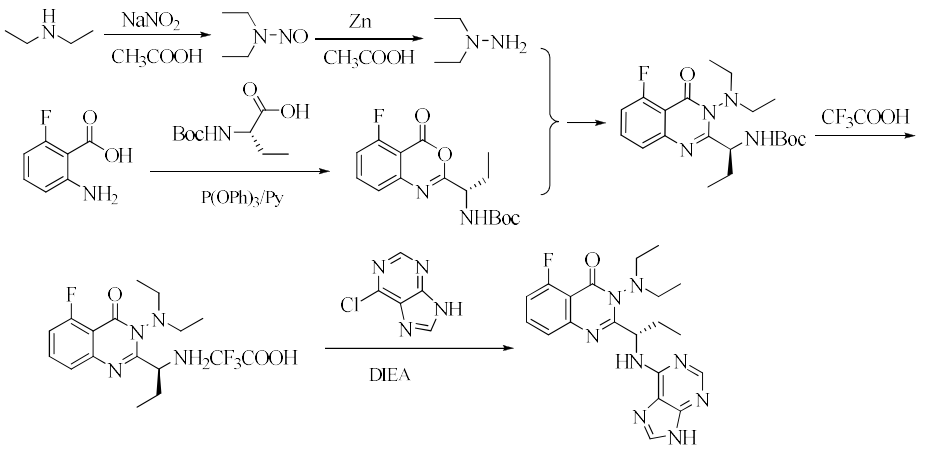
A stirred solution of tert-butyl (S)-(1-(5-fluoro-3-(ethyl(methyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate(1.0 g,2.74 mmol) in DCM (15mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid(5 mL) The reaction was stirred until the reaction was completed by TLC,concentrated under reduced pressure, and the crude product was used for the next step without further purification.

(6) Preparation of (S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-fluoro-3-(ethyl(methyl)amino)quinazolin-4(3H)-one

To a stirred solution of the crude (S)-2-(1-aminoethyl)-5-fluoro-3-(ethyl(methyl)amino)quinazolin-4(3H)-onetrifluoroacetate in *tert*-butanol (15mL) in a dry round bottomed flask was added DIEA until the solution is basic, and then 6-chloro-9H-purine (424 mg, 2.74 mmol)was added, and the reaction was stirred at 90ºC for 48 h. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by praparation HPLC to yield the title compound (0.080g, 7.7% two steps) as a white solid.

MS(M+1): 383.2 ^{1}H-NMR(*d*$_6$-DMSO, 400 MHz):δ 12.96 (1H, s) , 8.25-8.06 (2H, m), 7.90-7.58 (2H, m), 7.43-7.34 (1H, m), 7.27-7.17 (1H, m), 6.09-5.82 (1H, m), 3.61-3.37 (1.5H, m), 3.27-3.15 (0.5 H, m), 3.05, 3.01 (3H, two singlets), 1.61-1.52 (3H, m), 1.06 (3H, q).

Example 52 : Preparation of (S)-2-(1-((9H-purin-6-yl)amino)propyl)-3-(diethylamino)-5-fluoroquinazolin-4(3H)-one (Compound 62)



(1) Preparation of N,N-diethylnitrous amide

To a solution of diethylamine(10.95 g, 150.0 mmol)in acetic acid (120 mL) was added a solution of sodium nitrite (13.46 g, 195.0 mmol)in water(120mL) dropwise at 0℃, and then the mixture was stirred overnight. The raw material was disappeared by LC-MS and extracted with EA, the organic layer was concentrated and purified by silica gel column chromatography(PE:EA=10:1) to yield the title compound (13.31 g, 87.0 %) as a pale yellow oil.

(2) Preparation of 1,1-diethylhydrazine

To a solution of N,N-diethylnitrous amide (1.02 g, 10.0 mmol) was added zinc powder(2.60 g, 40.0 mmol)in ice bath, the mixture was stirred at room temperature until the raw material was disappeared by TLC, and filtered. The resulting filtrate was used directly for the fourth step reaction.

(3) Preparation of tert-butyl

(S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate

To a stirred solution of 2-amino-6-fluorobenzoic acid (0.50 g, 3.22mmol) in pyridine (8mL) in a flask was added (S)-2-((tert-butoxycarbonyl)amino)butanoic acid (0.787 g, 3.87 mmol) and triphenylphosphinate(3.10 g, 10.0 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr, and then was used directly for the next step without working-up.

(4) Preparation of tert-butyl

(S)-(1-(3-(diethylamino)-5-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate

To the stirred solution of tert-butyl

(S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate (crude reaction mixture) was added 1,1-diethylhydrazine and the resulting reaction solution was stirred at 100ºC for 8

hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography(PE:EA=10:1) to yield the title compound (0.71 g, 56.2% two steps) as a pale yellow oil.

(5) Preparation of (S)-2-(1-aminopropyl)-3-(diethylamino)-5-fluoroquinazolin-4(3H)-one trifluoroacetate

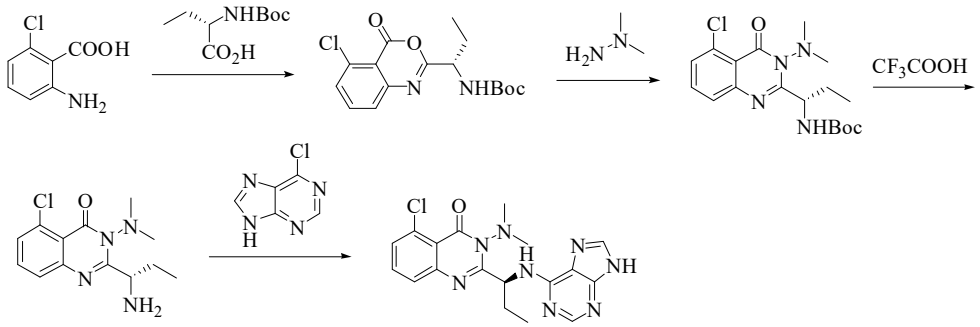
A stirred solution of tert-butyl (S)-(1-(3-(diethylamino)-5-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate(0.710 g, 1.81 mmol) in DCM (20mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid(10 mL). The reaction was stirred until the reaction was completed by TLC, concentrated under reduced pressure, and the crude product was used for the next step without further purification.

(6) Preparation of (S)-2-(1-((9H-purin-6-yl)amino)propyl)-3-(diethylamino)-5-fluoroquinazolin-4(3H)-one

To a stirred solution of the crude (S)-2-(1-aminopropyl)-3-(diethylamino)-5-fluoroquinazolin-4(3H)-onetrifluoroacetate in *tert*-butanol (40 mL) in a dry round bottomed flask was added DIEA until the solution is basic, and then 6-chloro-9H-purine (0.308 g, 1.99 mmol)was added, and the reaction was stirred at 90ºC for 48 h. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by praparation HPLC to yield the title compound (0.26 g, 35.0% two steps) as a white solid.

MS(M+1): 411.2^{1}H-NMR(*d*$_6$-DMSO, 400 MHz):δ 12.99 (1H, s), 8.25-8.13 (2H, m), 7.81-7.73 (1H, m), 7.50-7.38 (2H, m), 7.32-7.15 (1H, m), 6.12 (1H, m), 3.71-3.20 (4H, m), 2.16-1.80 (2H, m), 1.22 (3H, m), 1.05-0.92 (6H, m).

Example 53 : Preparation of (S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-chloro-3-(dimethylamino)quinazolin-4(3H)-one (Compound 63)



(1) Preparation of tert-butyl

(S)-(1-(5-chloro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate

To a stirred solution of 2-amino-6-chlorobenzoic acid(1.72 g, 10.0 mmol)in pyridine (10mL) in a flask was added (S)-2-((tert-butoxycarbonyl)amino)butanoic acid (2.23 g, 11.0 mmol) and triphenylphosphinate(3.10 g, 10.0 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr, and then was used directly for the next step without working-up.

(2) Preparation of tert-butyl

(S)-(1-(5-chloro-3-(dimethylamino)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate

To the stirred solution of tert-butyl

(S)-(1-(5-chloro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate (crude reaction mixture) was added 1,1-dimethylhydrazine(0.66 g, 11.0 mmol) and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography(PE:EA=5:1)to yield the title compound (2.50 g, 65.6% two steps) as a pale yellow oil.

(3) Preparation of (S)-2-(1-aminopropyl)-5-chloro-3-(dimethylamino)quinazolin-4(3H)-one trifluoroacetate

A stirred solution of tert-butyl

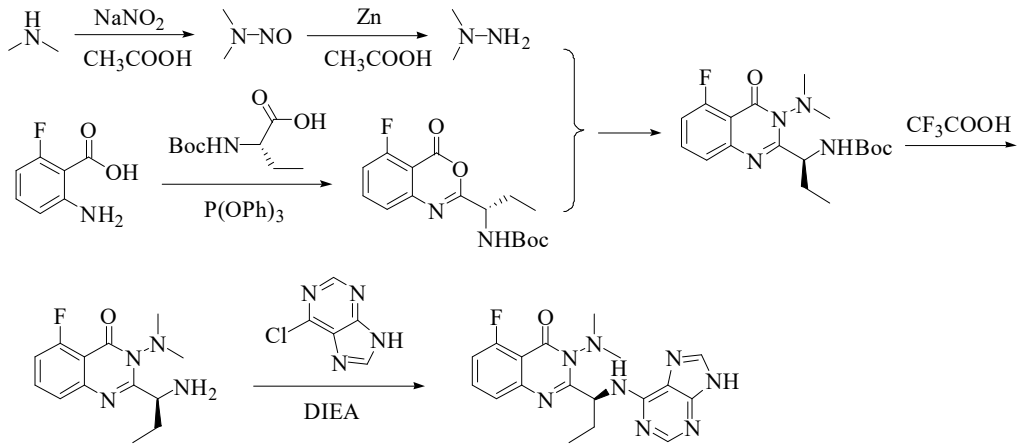
(S)-(1-(5-chloro-3-(dimethylamino)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate(2.5 g, 6.56 mmol) in DCM (20mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid(10 mL) The reaction was stirred until the reaction was completed by TLC, concentrated under reduced pressure, and the crude product was used for the next step without further purification.

(6) Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-chloro-3-(dimethylamino)quinazolin-4(3H)-one

To a stirred solution of the crude (S)-2-(1-aminopropyl)-5-chloro-3-(dimethylamino)quinazolin-4(3H)-one trifluoroacetate in *tert*-butanol (30 mL) in a dry round bottomed flask was added DIEA (3.25 mL, 18.7 mmol) until the solution is basic, and then 6-chloro-9H-purine (1.11 g, 7.18 mmol) was added, and the reaction was stirred at 90ºC for 48 h. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by praparation HPLC to yield the title compound (0.23g, 8.8% two steps) as a white solid. MS(M+1): 399.2 ^{1}H-NMR(d_6-DMSO, 400 MHz):δ 12.88 (1H, s), 8.15 (2H, s), 7.71-7.64 (1H, m), 7.64 (1H, t), 7.50-7.44 (2H, m), 5.78 (1H, m), 3.09, 3.06 (6H, two singlets), 2.05-1.86 (2H, m), 1.03 (3H, t).

Example 54 : Preparation of (S)-2-(1-((9H-purin-6-yl)amino)propyl)-3-(dimethylamino)-5-fluoroquinazolin-4(3H)-one (Compound 64)



(1) Preparation of N,N-dimethylnitrous amide

To a solution of dimethylamine hydrochloride (4.89 g, 60.0 mmol)in acetic acid (50 mL) was added a solution of sodium nitrite (5.38 g, 78.0 mmol)in water(40mL) dropwise at 0℃, and then the mixture was stirred overnight. The raw material was disappeared by LC-MS and the mixture was used for the next step without retreatment.

(2) Preparation of 1,1-dimethylhydrazine

To a solution of N,N-dimethylnitrous amide(the crude material) was added zinc powder(15.60 g, 239 mmol)in ice bath, the mixture was stirred at room temperature until the raw material was disappeared by TLC, and filtered. The resulting filtrate was used directly for the fourth step reaction.

(3) Preparation of tert-butyl

(S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)propyl)carbamate

To a stirred solution of 2-amino-6-fluorobenzoic acid (1.55 g, 10.0 mmol) in pyridine (10mL) in a flask was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (2.08 g, 11.0 mmol) and triphenylphosphinate(3.10 g, 10.0 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr, and then was used directly for the next step without working-up.

(4) Preparation of (tert-butyl

(S)-(1-(5-fluoro-3-(dimethylamino)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate

To the stirred solution of tert-butyl

(S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)propyl)carbamate (crude reaction mixture) was added 1,1-dimethylhydrazine and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography(PE:EA=10:1)to yield the title compound (2.12 g, 58.2% two steps) as a pale yellow oil.

(5) Preparation of (S)-2-(1-aminopropyl)-5-fluoro-3-(dimethylamino)quinazolin-4(3H)-one trifluoroacetate

A stirred solution of tert-butyl

(S)-(1-(5-fluoro-3-(dimethylamino)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate(2.12 g, 5.82 mmol) in DCM (20mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid(10 mL). The reaction was stirred until the reaction was completed by TLC, concentrated under reduced pressure, and the crude product was used for the next step without further purification.

(6) Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)propyl)-3-(dimethylamino)-5-fluoroquinazolin-4(3H)-one

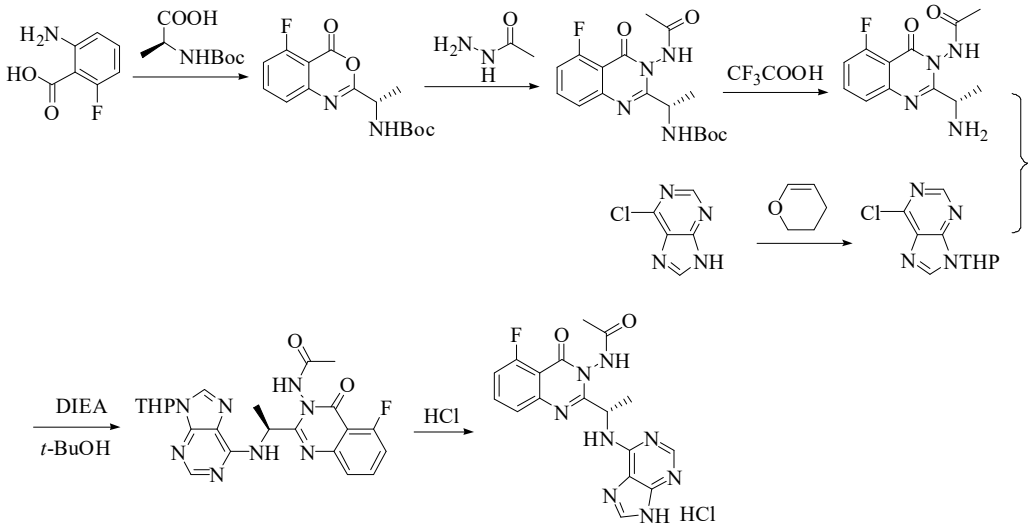
To a stirred solution of the crude

(S)-2-(1-aminopropyl)-5-fluoro-3-(dimethylamino)quinazolin-4(3H)-one trifluoroacetate in *tert*-butanol (40 mL) in a dry round bottomed flask was added DIEA until the solution is basic, and then 6-chloro-9H-purine (0.80 g, 5.18 mmol)was added, and the reaction was stirred at 90ºC for 48 h. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by praparation HPLC to yield the

title compound (0.23g, 10.3% two steps) as a white solid.

MS(M+1): 383.2^{1}H-NMR(d_6-DMSO, 400 MHz):δ 12.95 (1H, s), 8.15 (2H, s), 7.76-7.63 (2H, m), 7.35 (1H, d), 7.21 (1H, t), 5.80 (1H, m), 3.09, 3.07 (6H, two singlets), 2.06-1.88 (2H, m), 1.03 (3H, t).

Example 55 : Preparation of (S)-N-(2-(1-((9H-purin-6-yl)amino)ethyl)-5-fluoro-4-oxoquinazolin-3(4H)-yl)acetamide hydrochloride (Compound 65)



(1) Preparation of tert-butyl (S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate

To a stirred solution of 2-amino-6-fluorobenzoic acid (1.550 g, 10.0 mmol) in pyridine (10mL) in a flask was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (2.079 g, 11.0 mmol) and triphenylphosphinate(3.100 g, 10.0 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr, and then was used directly for the next step without working-up.

(2) Preparation of tert-butyl (S)-(1-(3-acetamido-5-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate

To the stirred solution of tert-butyl (S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate (crude reaction mixture) was added acetohydrazide(0.814 g, 11.0 mmol) and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography(PE:EA=2:1-100%EA)to yield the title compound (0.53 g, 14.5% two steps) as a pale yellow solid.

(3) Preparation of

(S)-N-(2-(1-aminoethyl)-5-fluoro-4-oxoquinazolin-3(4H)-yl)acetamidetrifluoroacetate

A stirred solution of tert-butyl

(S)-(1-(3-acetamido-5-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate(0.45 g, 1.23 mmol) in DCM (20mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid(5 mL). The reaction was stirred until the reaction was completed by TLC, concentrated under reduced pressure, and the crude product was used without further purification.

(4) Preparation of 6-chloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine

A solution of 6-chloro-9H-purine(25.36 g, 164 mmol), p-Toluenesulfonic acid monohydrate (0.565 g, 2.97 mmol) and 3,4-dihydro-2H-pyran (44.9 mL, 492 mmol) in a dry round bottomed flask was refluxed for 2 h at 90ºC, after the mixture was cooled down to room temperature, extracted with EA ,the organic layer was washed with brine, dried and concentrated to yield the title compound (36.1g, 92.1%) as a white solid.

(5) Preparation of

N-(5-fluoro-4-oxo-2-((1S)-1-((9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-yl)amino)ethyl)quinazolin-3(4H)-yl)acetamide

To a stirred solution of the crude

S)-N-(2-(1-aminoethyl)-5-fluoro-4-oxoquinazolin-3(4H)-yl)acetamidetrifluoroacetate in *n*-butanol (5 mL) in a dry round bottomed flask was added DIEA until the solution is basic, and then 6-chloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine (0.351 g, 1.47 mmol)was added, and the reaction was stirred at 110ºC for 4 h. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by preparation silica gel plate (DCM:MeOH=13:1)to yield the title compound (0.135 g, 23.5% two steps) as a pale yellow solid

(6) Preparation of

(*S*)-*N*-(2-(1-((9H-purin-6-yl)amino)ethyl)-5-fluoro-4-oxoquinazolin-3(4*H*)-yl)acetamide hydrochloride

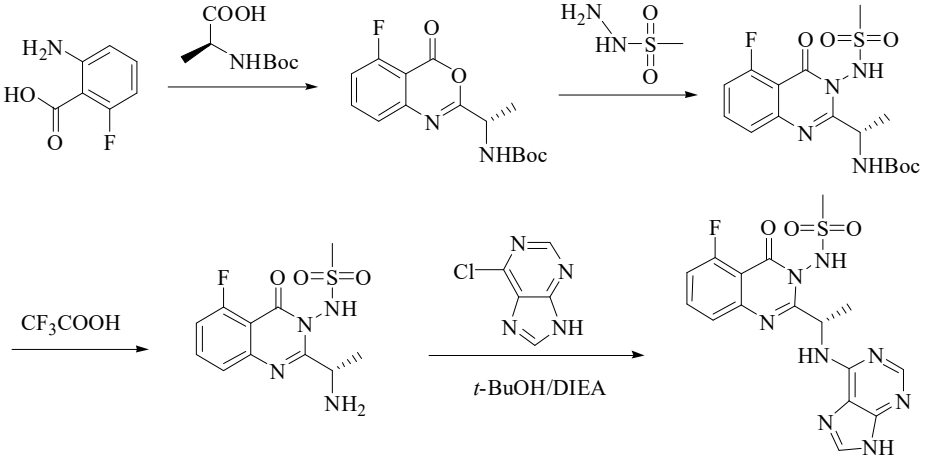
To a solution of

N-(5-fluoro-4-oxo-2-((1S)-1-((9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-yl)amino)ethyl)quina

zolin-3(4H)-yl)acetamide(0.13 g, 0.279 mmol) in MeOH (5mL) was added 2 drops of concentrated hydrochloric acid, the mixture was stirred for 2 h and concentrated to give the crude compound(0.13g). This crude compound was dissolved in MeOH(3 mL), and ether (10 mL) was added, filtered and dried to yield the title compound (0.057, 48.7%) as a pale yellow solid .

MS(M+1): 483.1. ^{1}H-NMR(d_6-DMSO, 400 MHz):δ 11.00 (1H, br s), 9.56-9.08 (1H, m), 8.65-8.51 (2H, m), 7.92-7.81 (1H, m), 7.62-7.51 (1H, m), 7.42-7.31 (1H, m), 5.77-5.55 (1H, m), 2.06, 2.02 (3H, two singlets), 1.62, 1.55 (3H, two doublets).

Example 56 : Preparation of (S)-N-(2-(1-((9H-purin-6-yl)amino)ethyl)-5-fluoro-4-oxoquinazolin-3(4H)-yl)methanesulfonamide (Compound 66)



(1) Preparation of tert-butyl (S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate

To a stirred solution of 2-amino-6-fluorobenzoic acid (1.550 g, 10.0 mmol) in pyridine (10mL) in a flask was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (2.079 g, 11.0 mmol) and triphenylphosphinate(3.100 g, 10.0 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr, and then was used directly for the next step without working-up.

(2) Preparation of tert-butyl (S)-(1-(5-fluoro-3-(methylsulfonamido)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate

To the stirred solution of tert-butyl (S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate (crude reaction mixture) was added methanesulfonohydrazide (1.22 g, 11.1 mmol)and the resulting reaction solution was stirred at 100ºC for 8 hr. After cooled to room temperature, the mixture was concentrated

under reduced pressure. The crude product was purified by silica gel column chromatography(PE:EA=4:1-2:1)to yield the title compound (1.10 g, 27.5% two steps) as a pale yellow solid.

(3) Preparation of (S)-N-(2-(1-aminoethyl)-5-fluoro-4-oxoquinazolin-3(4H)-yl)methanesulfonamide trifluoroacetate

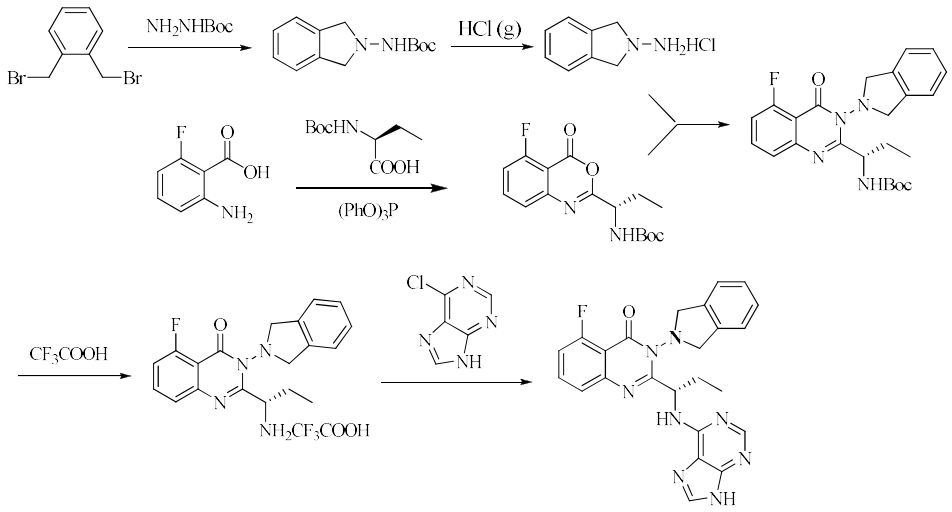
A stirred solution of tert-butyl (S)-(1-(5-fluoro-3-(methylsulfonamido)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate (0.52 g, 1.30 mmol) in DCM (20mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid(10 mL). The reaction was stirred until the reaction was completed by TLC, concentrated under reduced pressure, and the crude product was used for the next step without further purification.

(4) Preparation of (S)-N-(2-(1-((9H-purin-6-yl)amino)ethyl)-5-fluoro-4-oxoquinazolin-3(4H)-yl)methanesulfonamide

To a stirred solution of the crude (S)-N-(2-(1-aminoethyl)-5-fluoro-4-oxoquinazolin-3(4H)-yl)methanesulfonamide trifluoroacetate in *tert*-butanol (10 mL) in a dry round bottomed flask was added DIEA until the solution is basic, and then 6-chloro-9H-purine (0.239 g, 1.55 mmol)was added, and the reaction was stirred at 90ºC for 48 h. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by praparation HPLC to yield the title compound (0.152g, 27.9% two steps) as a white solid.

MS(M+1): 419.1. ^{1}H-NMR(d_6-DMSO, 400 MHz):δ 13.01 (1H, s), 11.12 (1H, br s), 8.24-8.10 (2H, m), 7.89-7.78 (2H, m), 7.48 (1H, d), 7.33 (1H, t), 5.83 (1H, m), 3.35 (3H, s), 1.59 (3H, m).

Example 57 : Preparation of (S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-3-(isoindolin-2-yl)quinazolin-4(3H)-one (Compound 67)



(1) Preparation of tert-butyl isoindolin-2-ylcarbamate

To a solution of 1,2-bis(bromomethyl)benzene(5.28 g, 20 mmol), tert-butyl hydrazinecarboxylate (2.64 g, 20 mmol) in dired DMF (10 mL) was added triethylamine (5.6 mL, 40.2 mmol) dropwise at 50℃, and then the mixture was stirred at room temperature for 3h. The mixture was extracted with EA and water, the organic layer was washed with water, dried and concentrated to give the crude compound (4.0 g, 85.4 %).

(2) Preparation of isoindolin-2-amine hydrochloride

To a solution of tert-butyl isoindolin-2-ylcarbamate (4.0 g, 17.1 mmol) in MeOH (10 mL) was bubbled with hydrogen chloride gas for 1 h, and filtered to yield the title compound (2.7g, 92.5%) as a white solid.

(3) Preparation of tert-butyl

(S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)propyl)carbamate

To a stirred solution of 2-amino-6-fluorobenzoic acid (1.0 g, 6.45 mmol) in pyridine (10mL) in a flask was added (S)-2-((tert-butoxycarbonyl)amino)butanoic acid(1.44 g, 7.09 mmol) and triphenylphosphinate(2.36 g, 7.61 mmol). The resulting reaction solution was stirred at 55ºC for 12 h, and then was used directly for the next step without working-up.

(4) Preparation of tert-butyl

(S)-(1-(5-fluoro-3-(isoindolin-2-yl)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate

To the stirred solution of tert-butyl

(S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)propyl)carbamate (crude reaction mixture) was added isoindolin-2-amine hydrochloride (1.21 g, 7.09 mmol) and the resulting reaction solution was stirred at 100ºC for 10 h. After cooled to room temperature, the mixture was

concentrated under reduced pressure. The crude product was purified by silica gel column chromatography(PE:EA=3:1)to yield the title compound (1.4 g, 49.5% two steps) as a white solid.

(5) Preparation of (S)-2-(1-aminopropyl)-5-fluoro-3-(isoindolin-2-yl)quinazolin-4(3H)-one trifluoroacetate

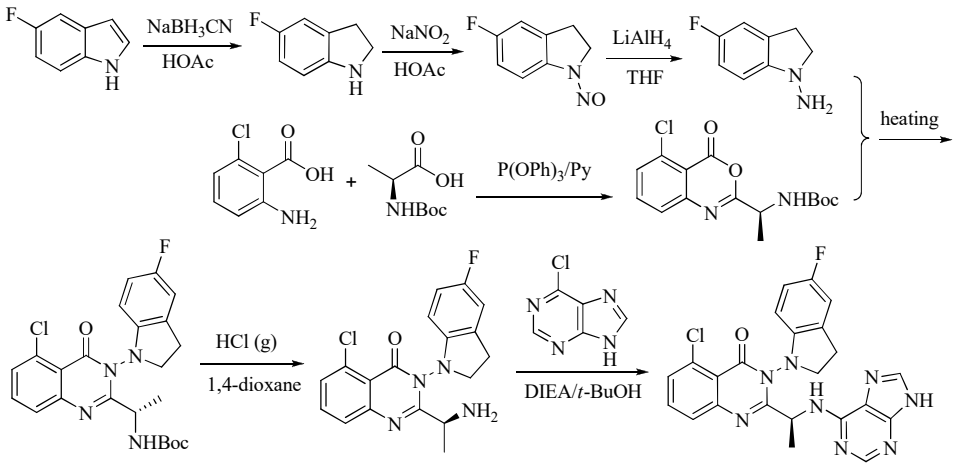
A stirred solution of tert-butyl (S)-(1-(5-fluoro-3-(isoindolin-2-yl)-4-oxo-3,4-dihydroquinazolin-2-yl)propyl)carbamate (0.65 g, 1.48 mmol) in DCM (5mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid(5 mL). The reaction was stirred until the reaction was completed by TLC, concentrated under reduced pressure, and the crude product (0.64 g, 95.6)was used for the next step without further purification.

(6) Preparation of (S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-3-(isoindolin-2-yl)quinazolin-4(3H)-one

To a stirred solution of the crude (S)-2-(1-aminopropyl)-5-fluoro-3-(isoindolin-2-yl)quinazolin-4(3H)-one trifluoroacetate (0.64 g, 1.41 mmol) in *tert*-butanol (10 mL) in a dry round bottomed flask was added DIEA(1.45 mL, 8.33 mmol) until the solution is basic, and then 6-chloro-9H-purine (0.26 g, 1.68 mmol)was added, and the reaction was stirred at 90ºC for 12 h. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by praparation HPLC to yield the title compound (0.29g, 45.1% two steps) as a white solid.

MS(M+1): 457.2. ^{1}H-NMR(d_6-DMSO, 400 MHz):δ 12.95 (1H, s), 8.15 (2H, s), 7.86-7.70 (2H, m), 7.42 (1H, d), 7.37-7.19 (5H, m), 5.95 (1H, m), 4.91 (1H, d), 4.82-4.69 (2H, m), 4.51 (1H, d), 2.13-1.92 (2H, m), 1.02 (3H, t).

Example 58 : Preparation of (S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-7-fluoro-3-(phenylamino)quinazolin-4(3H)-one (Compound 71)



(1) Preparation of 5-fluoroindoline

A solution of chloral hydrate(6.19 g, 37.4 mmol)and anhydrous sodium sulfate (53 g, 373 mmol)in water (100mL) was stirred at 35℃, 3-chloro-5-fluoroaniline (5.0 g, 34.3 mmol) in water (0.4 L) and concentrated hydrochloric acid (2.6mL) was added dropwise to keep the temperature at 35℃, after that a solution of hydroxylamine hydrochloride(7.3 g, 105 mmol) in water (30 mL) was added, the mixture was heated to 50℃ and stirred for 24 h .The mixture was cooled down to 50℃, filtered and dried to yield the title compound as a pale yellow solid (5.5g, 74.1%).

(2) Preparation of 4-chloro-6-fluoroindoline-2,3-dione

To a stirring mixture of 86% sulfuric acid(20mL) was added 2-(hydroxyimino)-N-(3-(trifluoromethyl)phenyl)acetamide (100 g,431 mmol) in portions for 1h to keep the temperature below 65℃, after that the mixture was heated to 85℃ for 20 min, cooled down to rt. The mixture was poured into ice-water mixture and stirred for 30 min, filtered, dried to yield the title compound as a yellow solid (1.7 g, 59.8%).

(3) Preparation of 2-amino-6-chloro-4-fluorobenzoic acid

To a mixture of 5% sodium hydroxide (42 mL) and 30% hydrogen peroxide (42 mL) was added 4-chloro-6-fluoroindoline-2,3-dione (3 g, 15 mmol) in portions and the mixture was stirred at 50 ℃ for 1 h. After that the mixture was cooled down and filtered. The filtrate was adjusted Ph to 4, and filtered, dried to yield the title compound as a pale yellow solid (1.7 g,59.8%).

(4) Preparation of tert-butyl

(S)-(1-(5-chloro-7-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate

To a stirred solution of 2-amino-6-chloro-4-fluorobenzoic acid (1.5 g, 7.91 mmol) in pyridine (10mL) in a flask was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (1.7 g, 8.99 mmol) and triphenylphosphinate(2.4 g, 7.73 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr, and then was used directly for the next step without working-up.

(5) Preparation of tert-butyl (S)-(1-(5-chloro-7-fluoro-4-oxo-3-(phenylamino)-3,4-dihydroquinazolin-2-yl)ethyl)carbamate

To the stirred solution of tert-butyl (S)-(1-(5-chloro-7-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate (crude reaction mixture) was added phenylhydrazine (1.27 g, 8.78 mmol)and the resulting reaction solution was stirred at 100ºC for 8 h. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by preparation HPLC to yield the title compound (2.0 g, 37.3% two steps) as a yellow solid.

(6) Preparation of (S)-2-(1-aminoethyl)-5-chloro-7-fluoro-3-(phenylamino)quinazolin-4(3H)-one hydrochloride

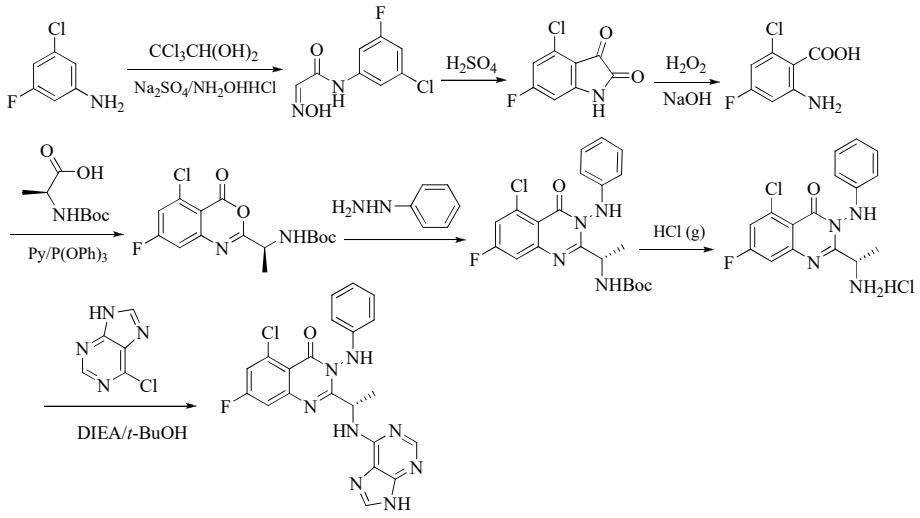
A stirred solution of (S)-2-(1-aminoethyl)-5-chloro-7-fluoro-3-(phenylamino)quinazolin-4(3H)-one hydrochloride(1 g, 2.2 mmol) in 1,4-dioxane(20mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was bubbled with hydrogen chloride gas. The reaction was stirred until the reaction was completed by TLC, concentrated under reduced pressure, and the crude product (0.86 g, 99%) was used for the next step .

(7) Preparation of (S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-7-fluoro-3-(phenylamino)quinazolin-4(3H)-one

To a stirred solution of the crude (S)-2-(1-aminoethyl)-5-chloro-7-fluoro-3-(phenylamino)quinazolin-4(3H)-one hydrochloride (0.2 g, 0.51 mmol) in *tert*-butanol (20 mL) in a dry round bottomed flask was added DIEA (0.261 g, 2.02 mmol) until the solution is basic, and then 6-chloro-9H-purine (86 mg, 0.56 mmol) was added, and the reaction was stirred at 90ºC for 18 h. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by praparation HPLC to yield the title compound (0.035g, 14.4%) as a pale yellow solid.

MS(M+1): 476.8. ^{1}H-NMR(d_6-DMSO, 400 MHz):δ 12.90 (1H, br s), 8.25-7.97 (3H, m), 7.76-7.64 (1H, m), 7.61-7.45 (2H, m), 7.07 (1H, d), 6.81 (1H, t), 6.63-6.52 (1H, m), 5.84 (1H, m), 4.17-4.03 (1H, m), 4.03-3.88 (1H, m), 3.24-3.13 (1H, m), 3.05-2.86 (1H, m), 1.55 (3H, d).

Example 59 : Preparation of (S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-7-fluoro-3-(phenylamino)quinazolin-4(3H)-one (Compound 72)



(1) Preparation of (Z)-N-(3-chloro-5-fluorophenyl)-2-(hydroxyimino)acetamide

To a solution of 5-fluoro-1H-indole(12 g, 88.8 mmol)in acetic acid (150 mL) was added sodium cyanoborohydride (11.2 g, 178 mmol)in portion, the mixture was stirred for 2.5 h until the reaction was completed by LC-MS. The mixture was poured into ice-water and adjusted PH=7 with 40% sodium hydroxide aqueous solution and extracted with DCM and the organic layer was dried and concentrated to give the title compound (11.4 g ,93.6%).

(2) Preparation of 4-chloro-6-fluoroindoline-2,3-dione

To a solution of (Z)-N-(3-chloro-5-fluorophenyl)-2-(hydroxyimino)acetamide(10 g,72.9 mmol) in acetic acid (75 mL) was added a solution of sodium nitrite (5.5 g,79.7 mmol)in water (80mL) dropwise at 0℃, and then the mixture was stirred for 3h. The raw material was disappeared by LC-MS and the mixture was adjusted PH=7 with 40% sodium hydroxide aqueous solution and extracted with EA and the organic layer was dried and concentrated and purified by silica gel column chromatography(PE:EA=10:1)to yield the title compound (10.5 g, 86.7% two steps) as a white solid.

(3) Preparation of 5-fluoroindolin-1-amine

To a solution of 4-chloro-6-fluoroindoline-2,3-dione (10 g, 60.2 mmol)in dried THF was

added 1M lithium aluminium hydride (90 mL) in ice bath under N_2 atmosphere, the mixture was stirred at 0ºC for 2 h until the raw material was disappeared by TLC, and quenched with EA. The mixture was extracted with EA and t purified by silica gel column chromatography(DCM:MeOH=20:1)to yield the title compound (6.3 g, 68.8%) as a brown solid.

(4) Preparation of tert-butyl

(S)-(1-(5-chloro-7-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate

To a stirred solution of 2-amino-6-chlorobenzoic acid(2.0 g, 11.7 mmol)in pyridine (20mL) in a flask was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (2.4 g, 12.7 mmol) and triphenylphosphinate(3.63 g, 11.7 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr, and then was used directly for the next step without working-up.

(5) Preparation of tert-butyl

(S)-(1-(5-chloro-7-fluoro-4-oxo-3-(phenylamino)-3,4-dihydroquinazolin-2-yl)ethyl)carbamate

To the stirred solution of tert-butyl

(S)-(1-(5-chloro-7-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate (crude reaction mixture) was added 5-fluoroindolin-1-amine (1.78 g,11.7 mmol) and the resulting reaction solution was stirred at 100ºC for 16 hr. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography(PE:EA=6:1)to yield the title compound (2.0 g, 58.4% two steps) as a yellow solid.

(6) Preparation of

(S)-2-(1-aminoethyl)-5-chloro-7-fluoro-3-(phenylamino)quinazolin-4(3H)-one hydrochloride

A stirred solution of tert-butyl

(S)-(1-(5-chloro-7-fluoro-4-oxo-3-(phenylamino)-3,4-dihydroquinazolin-2-yl)ethyl)carbamate (0.86 g, 2.0 mmol) in EA(20mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was bubbled with hydrogen chloride gas. The reaction was stirred until the reaction was completed by TLC, concentrated under reduced pressure, and the crude product (0.70 g, 95.0%) was used for the next step.

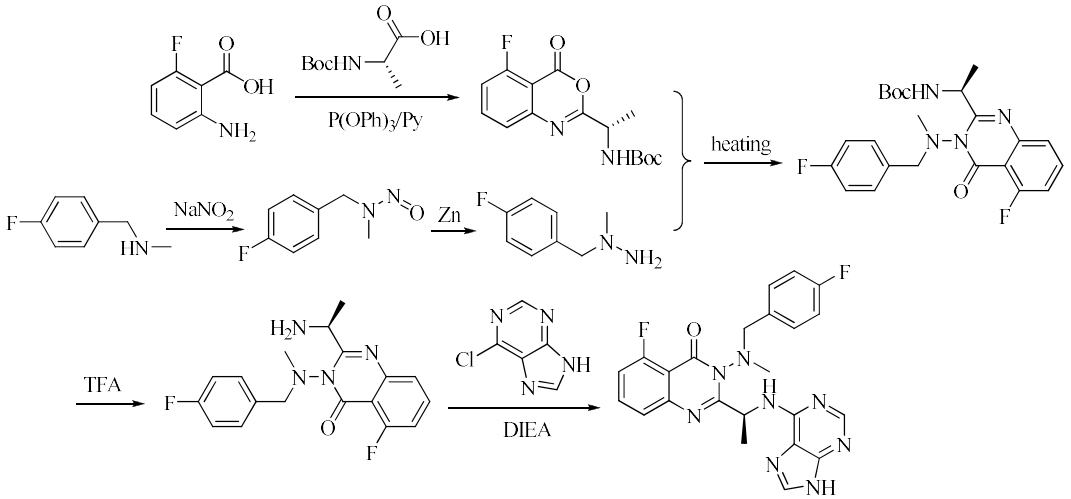
(7) Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-chloro-7-fluoro-3-(phenylamino)quinazolin-4(3H)-one

To a stirred solution of the crude (S)-2-(1-aminoethyl)-5-chloro-7-fluoro-3-(phenylamino)quinazolin-4(3H)-one hydrochloride (0.7 g, 1.9 mmol) in *tert*-butanol (30 mL) in a dry round bottomed flask was added DIEA (0.98 g, 7.6 mmol) until the solution is basic, and then 6-chloro-9H-purine (0.29 g, 1.9 mmol) was added, and the reaction was stirred at 90ºC for 2 d. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by praparation HPLC to yield the title compound (0.120g, 14.0%) as a pale yellow solid.

MS(M+1): 451.1^{1}H-NMR(d_6-DMSO, 400 MHz):δ 12.98 (1H, br s), 9.22, 9.02 (1H, two singlets), 8.25-8.08 (2H, m), 7.94-7.71 (1H, m), 7.61-7.51 (1H, m), 7.48-7.15 (3H, m), 7.10-6.71 (3H, m), 5.85, 5.49 (1H, two br s), 1.65, 1.46 (3H, two doublets).

Example 60 : Preparation of (S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-fluoro-3-((4-fluorobenzyl)(methyl)amino)quinazolin-4(3H)-one (Compound 73)



(1) Preparation of N-(4-fluorobenzyl)-N-methylnitrous amide

To a solution of 1-(4-fluorophenyl)-N-methylmethanamine (4.2 g, 30 mmol) in acetic acid (60 mL) was added a solution of sodium nitrite (9.0 g, 130 mmol) in water(40mL) dropwise at 0℃, and then the mixture was stirred for 2 h. The raw material was disappeared by LC-MS and the mixture was used for the next step without retreatment.

(2) Preparation of 1-(4-fluorobenzyl)-1-methylhydrazine

To a solution of N-(4-fluorobenzyl)-N-methylnitrous amide (the crude material) was added zinc powder(7.8 g, 119 mmol)in ice bath, the mixture was stirred at room temperature until the

raw material was disappeared by TLC, filtered and wahed with EA. The resulting filtrate wasconcentrated to yield the title compound (2.3 g, 49.7%) as a white solid.

(3) Preparation of tert-butyl

(S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate

To a stirred solution of 2-amino-6-fluorobenzoic acid (1.55 g, 10.0 mmol) in pyridine (10mL) in a flask was added (*S*)-2-(tert-butoxycarbonylamino)propanoic acid (2.37 g, 12.5 mmol) and triphenylphosphinate(3.40 g, 11.0 mmol). The resulting reaction solution was stirred at 55ºC for 10 hr, and then was used directly for the next step without working-up.

(4) Preparation of tert-butyl

(S)-(1-(5-fluoro-3-((4-fluorobenzyl)(methyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate

To the stirred solution of tert-butyl

(S)-(1-(5-fluoro-4-oxo-4H-benzo[d][1,3]oxazin-2-yl)ethyl)carbamate (crude reaction mixture) was added 1-(4-fluorobenzyl)-1-methylhydrazine (1.85 g, 12.0 mmol) and the resulting reaction solution was stirred at 100ºC for 12 h. After cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography(PE:EA=10:1)to yield the title compound (1.92 g, 43.2% two steps) as a white solid.

(5) Preparation of

(S)-2-(1-aminoethyl)-5-fluoro-3-((4-fluorobenzyl)(methyl)amino)quinazolin-4(3H)-one trifluoroacetate

A stirred solution of tert-butyl

(S)-(1-(5-fluoro-3-((4-fluorobenzyl)(methyl)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate(890 mg, 2.0 mmol) in DCM (7mL) in a dry round bottomed flask was cooled in an ice-bath. To this solution was added trifluoroacetic acid(3 mL). The reaction was stirred until the reaction was completed by TLC, concentrated under reduced pressure, and the crude product was used for the next step without further purification.

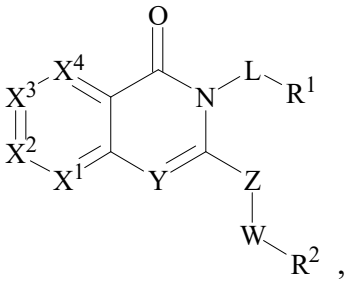
(6) Preparation of

(S)-2-(1-((9H-purin-6-yl)amino)ethyl)-5-fluoro-3-((4-fluorobenzyl)(methyl)amino)quinazolin-4(3H)-one

To a stirred solution of the crude (S)-2-(1-aminoethyl)-5-fluoro-3-((4-fluorobenzyl)(methyl)amino)quinazolin-4(3H)-onetrifluoroacetate in *tert*-butanol (20 mL) in a dry round bottomed flask was added DIEA until the solution is basic, and then 6-chloro-9H-purine (308 mg,2.0 mmol)was added, and the reaction was stirred at 90ºC for 24 h. After cooled to room temperature, the reaction solution was then concentrated under reduced pressure, and the crude product was purified by praparation HPLC to yield the title compound (0.260g, 28.1% two steps) as a white solid.
MS(M+1): 463.3. ^{1}H-NMR(*d*$_6$-DMSO, 400 MHz):δ 12.94 (1H, s) , 8.25-8.08 (2H, m), 7.97-7.60 (2H, m), 7.58-7.43 (2H, m), 7.39 (1H, t), 7.25 (1H, dd), 7.19 (1H, t), 7.06 (1H, t), 6.19-5.95 (1H, m), 4.72-4.41 (2H, m), 3.02-2.90 (3H, m), 1.54, 1.46 (3H, two doublets).

What is claimed is:

1. A compound of formula (I), a pharmaceutically acceptable salt thereof, a stereoisomer thereof and a deuterated compounds thereof:



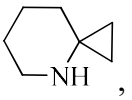
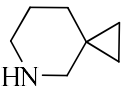
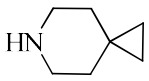
(I)

wherein,

X^1, X^2, X^3, and X^4 are independently CR^3, wherein R^3 is hydrogen, halogen, hydroxyl, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R^a)(R^{a'})$ or cyano;

Y is N;

L is a covalent bond or $-N(R^a)-$; wherein,

when L is a covalent bond, R^1 is bicyclic heteroaryl formed by fusing a phenyl with 5 membered heterocycloalkenyl having one N ring atom, or a spiro-ring consisting of a piperidinyl ring and a cyclopropyl ring, the spiro-ring selected from  ,  or  , wherein the nitrogen ring atom of the bicyclic ring and the spiro-ring is bonded to L, R^1 is an optionally substituted by 1-3 R^b,

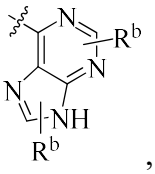
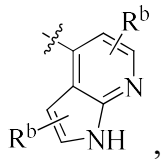
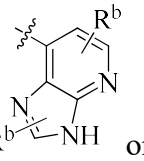
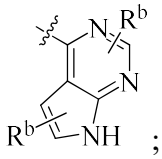
when L is $-N(R^a)-$, R^1 is C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkylsulfonyl, 3-6 membered cycloalkane, 6-14 membered aryl, 6-14 membered aryl C_{1-3} alkyl, 3-14 membered heterocycle, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group, wherein R^1 is optionally substituted by 1-3 R^b,

wherein R^a and $R^{a'}$ are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3-14 membered cycloalkanes, 6-14 membered aryl, 3-14 membered heterocycle, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group;

Z is $-CH(R^4)-$;

W is $-N(R^5)-$;

wherein R^4, and R^5 are independently hydrogen, C_{1-3} alkyl, or 3-5 membered cycloalkane unsubstituted or unsubstituted by at least one hydroxyl or halogen;

R^2 is  ,  ,  or  ; and

R^b is hydrogen, oxo, halogen, CN, hydroxyl, amino, C_{1-6} alkylamine, bio (C_{1-6} alkyl) amine, carboxyl, aminosulfonyl, aminocarbonyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkyl substituted by halogen, 3-6 membered cycloalkane, 3-6 membered cycloalkoxy, 3-8 membered monocyclic heterocycloalkyl, 3-8 membered heterocyclic alkenyl, 5-6 membered monocyclic heteroaryl, 3-8membered monocycle heterocycloalkoxy, 3-8 membered heterocyclic alkenyloxy, or 5-6 membered monocyclic heteroaryloxy.

2. The compound, the pharmaceutically acceptable salt thereof, the stereoisomer thereof and the deuterated derivative thereof according to claim 1, wherein

X^1, X^2, X^3, and X^4 are independently CR^3, wherein R^3 is hydrogen, halogen, hydroxyl, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(R^a)(R^{a'})$ or cyano;

Y is N;

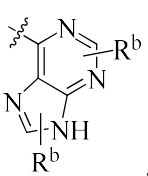
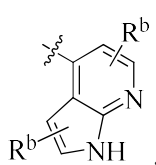
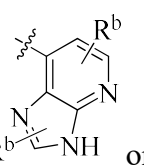
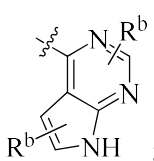
L is $-N(R^a)-$,R^1 is C_{1-6} alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkylsulfonyl, 3-6 membered cycloalkane, 6-14 membered aryl, 6-14 membered aryl C_{1-3} alkyl, 3-14 membered heterocycle, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group, wherein R^1 is optionally substituted by 1-3 R^b,

wherein R^a and $R^{a'}$ are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3-14 membered cycloalkanes, 6-14 membered aryl, 3-14 membered heterocycle, 7-12 membered spiro-ring group or 7-12 membered bridged-ring group;

Z is $-CH(R^4)-$;

W is $-N(R^5)-$;

wherein R^4, and R^5 are independently hydrogen, C_{1-3} alkyl, or 3-5 membered cycloalkane unsubstituted or unsubstituted by at least one hydroxyl or halogen;

R^2 is  ,  ,  or  ; and

R^b is hydrogen, oxo, halogen, CN, hydroxyl, amino, C_{1-6} alkylamine, bio (C_{1-6} alkyl) amine, carboxyl, aminosulfonyl, aminocarbonyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkyl substituted by halogen, 3-6 membered cycloalkane, 3-6 membered cycloalkoxy, 3-8 membered monocyclic heterocycloalkyl, 3-8 membered heterocyclic alkenyl, 5-6 membered monocyclic heteroaryl, 3-8membered monocycle heterocycloalkoxy, 3-8 membered heterocyclic alkenyloxy, or 5-6 membered monocyclic heteroaryloxy.

3. The compound, the pharmaceutically acceptable salt thereof, the stereoisomer thereof and the deuterated derivative thereof according to claim 1, wherein

X^1, X^2, X^3, and X^4 are independently CR^3, wherein R^3 is hydrogen, halogen, hydroxyl, trifluoromethyl, C_{1-6} alkyl or C_{1-6} alkoxy;

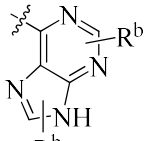
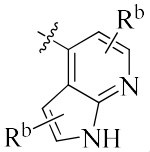
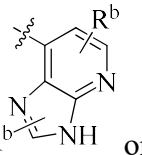
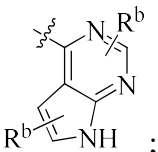
Y is N;

L is -N(R^a)-,R^1 is C_{1-3} alkyl, C_{1-3} alkylcarbonyl, C_{1-3} alkylsulfonyl, 3-6 membered cycloalkanes, 6-14 membered aryl, 6-14 membered aryl C_{1-3}alkyl, 5-6 membered monocycle heterocycle, 5-6 membered heterocyclic alkenyl, 5-6 membered monocyclic heteroaryl, 6-10 membered bicycle-heterocycle, 7-12 membered spiro-ring group, or 7-12 membered bridged-ring group, wherein R^1 is optionally substituted by 1-3 R^b,

wherein R^a is hydrogen, C_{1-6} alkyl, 3-14 membered cycloalkane or 6-14 membered aryl;

Z is -CH(R^4)-, wherein R^4 is hydrogen, C_{1-3}alkyl or cyclopropyl unsubstituted or substituted by at least one hydroxyl or halogen;

W is -N(R^5)-, wherein R^5 is hydrogen or methyl;

R^2 is  ,  ,  or  ; and

R^b is hydrogen, oxo, halogen, CN, hydroxyl, amino, C_{1-6} alkylamine, bio (C_{1-6}alkyl) amine, C_{1-6}alkoxy, C_{1-6} alkyl, C_{1-6} alkyl substituted by halogen, 3-6 membered cycloalkanes, 3-6 membered cycloalkoxy, 5-6 membered monocyclic heterocycloalkyl, 5-6 membered heterocyclic alkenyl, 5-6 membered monocyclic heteroaryl, 5-6 membered monocycle heterocycloalkoxy, 5-6 membered heterocyclic alkenyloxy, or 5-6 membered monocyclic heteroaryloxy.

4. The compound, pharmaceutically acceptable salt thereof, a stereoisomer thereof and a

deuterated derivative thereof according to claim 1, wherein:

X^1, X^2, X^3, and X^4 are independently CR^3, wherein R^3 is hydrogen, fluorin, chlorin, hydroxyl, trifluoromethyl or methyl;

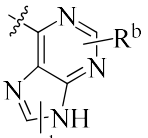
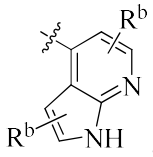
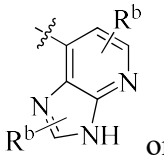
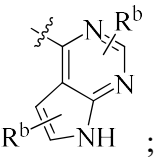
Y is N;

L is -N(R^a)-, R^1 is C_{1-3} alkyl, acetyl, methylsulfonyl, phenyl, pyridyl, pyrimidyl, furan, thienyl, pyrryl, thiazolyl, imidazole, pyrazolyl, imidazolidinyl, pyrazolidinyl, indolyl, indolyl, indazolyl, benzimidazolyl, pyridino-pyrazolyl, purine, piperazine, quinolyl, tetradydropyrane, piperidyl, morpholinyl, pyrazinyl, pyridine-2- keto, cyclohexyl, cyclopentyl, or benzyl, wherein R^1 is optionally substituted by 1-3 R^b,

R^a is hydrogen, C_{1-3} alkyl, 3-8 membered cycloalkanes or 6-14 membered aryl;

Z is -CH(R^4)-, wherein R^4 is hydrogen, C_{1-3}alkyl or cyclopropyl substituted or unsubstituted by at least one hydroxyl or fluoro;

W is -N(R^5)-, wherein R^5 is hydrogen or methyl;

R^2 is  ,  ,  or  ; and

R^b is hydrogen, oxo, halogen, CN, hydroxyl, amino, C_{1-6} alkylamine, bio (C_{1-6}alkyl) amine, C_{1-6}alkoxy, C_{1-6} alkyl, C_{1-6} alkyl substituted by halogen, 3-6 membered cycloalkanes, 3-6 membered cycloalkoxy, 5-6 membered monocyclic heterocycloalkyl, 5-6 membered heterocyclic alkenyl, 5-6 membered monocyclic heteroaryl, 5-6 membered monocycle heterocycloalkoxy, 5-6 membered heterocyclic alkenyloxy, or 5-6 membered monocyclic heteroaryloxy.

5. The compound, the pharmaceutically acceptable salt thereof, the stereoisomer thereof and the deuterated derivative thereof according to claim 1, wherein:

X^1, X^2, X^3, and X^4 are independently CR^3, wherein R^3 is hydrogen, fluorin, chlorin, hydroxyl, trifluoromethyl or methyl;

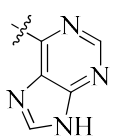
Y is N;

L is -N(R^a)-, R^1 is C_{1-3} alkyl, acetyl, methylsulfonyl, phenyl, pyridyl, pyridine-2-keto, cyclohexyl, cyclopentyl, or benzyl, wherein R^1 is chosen from optionally substituted by 1-3 R^b;

R^a is hydrogen, methyl, ethyl, cyclopropyl or phenyl;

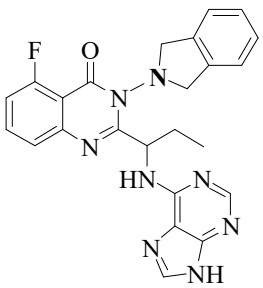
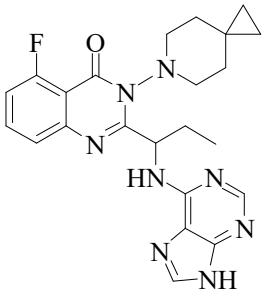
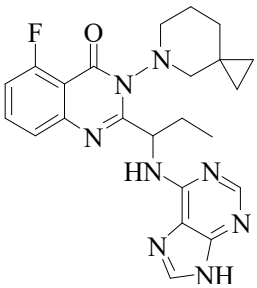
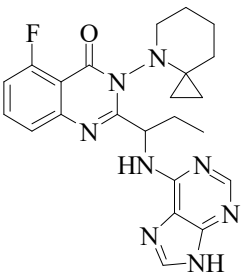
Z is -CH(R^4)-, R^4 is hydrogen, C_{1-3} alkyl or cyclopropyl unsubstituted or substituted by at least one hydroxyl or fluoro;

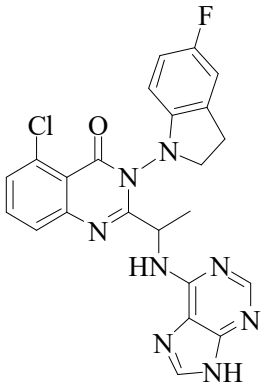
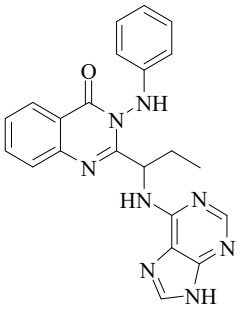
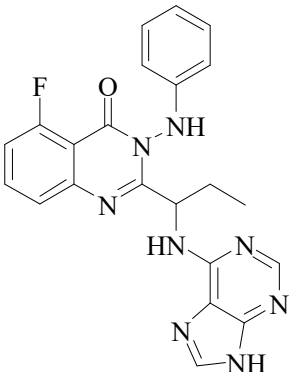
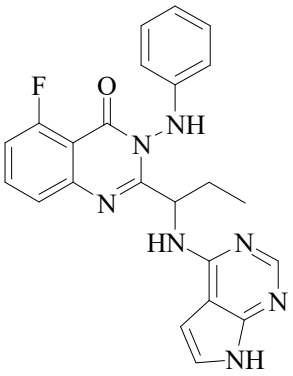
W is -N(R^5)-, wherein R^5 is hydrogen or methyl;

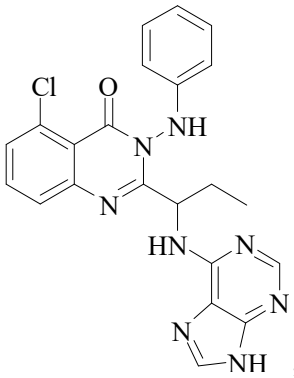
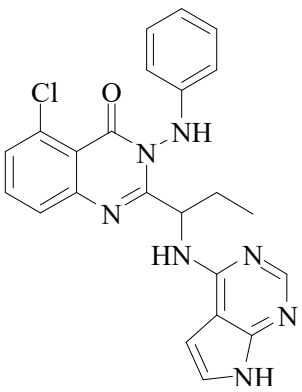
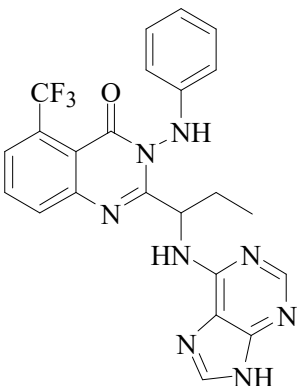
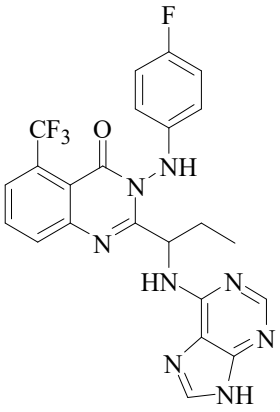
R^2 is  ; and

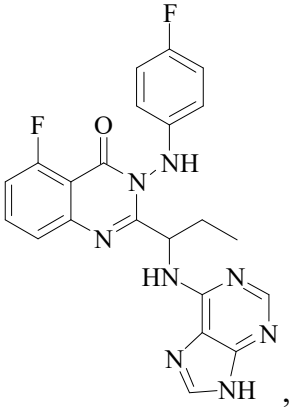
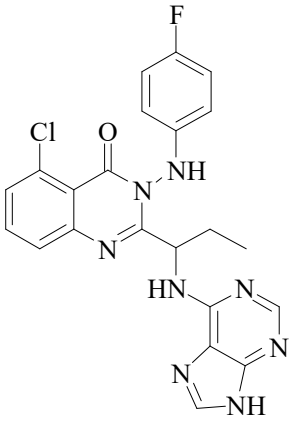
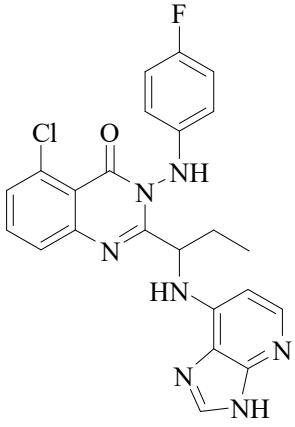
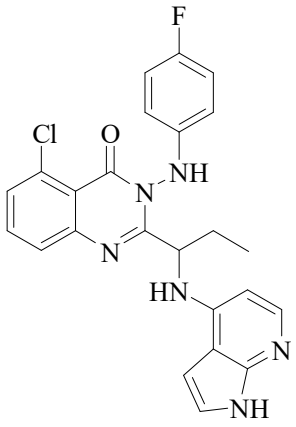
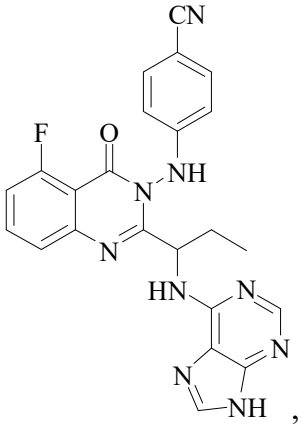
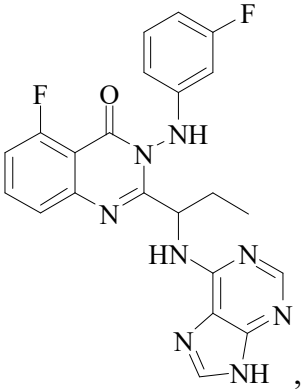
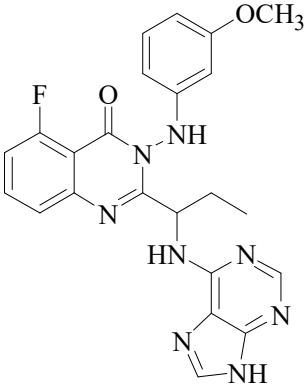
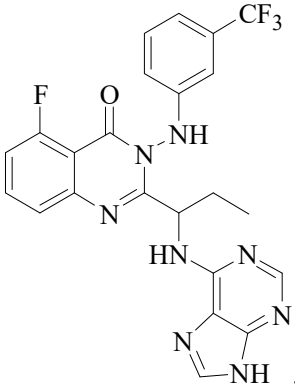
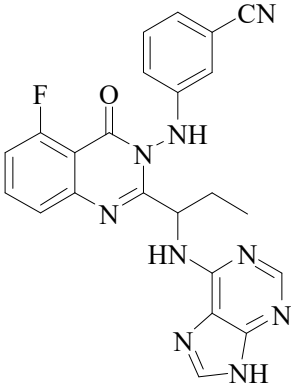
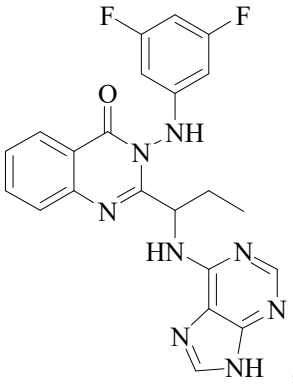
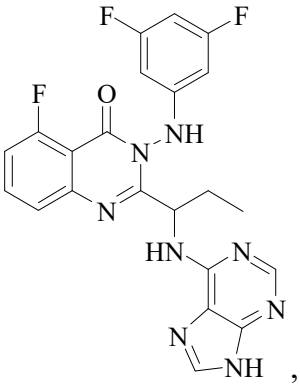
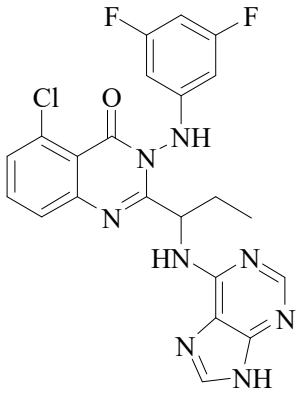
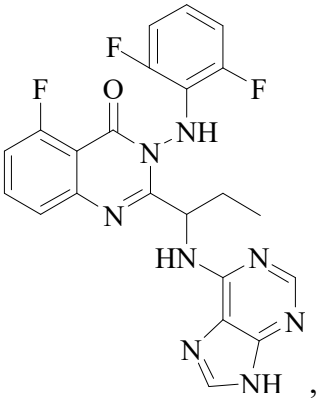
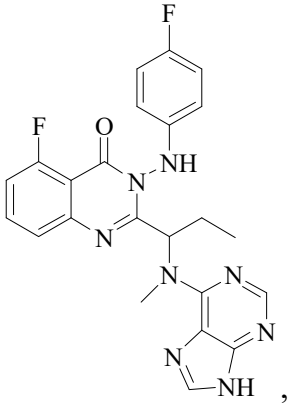
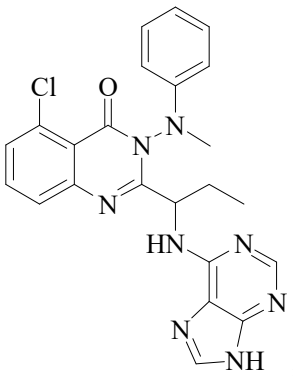
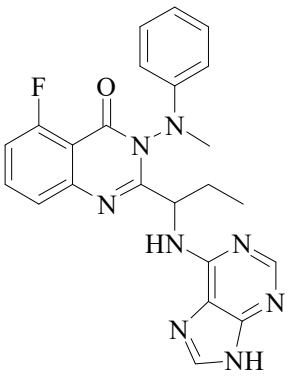
R^b is hydrogen, oxo, halogen, CN, C_{1-3} alkyl, C_{1-3} alkoxy, or trifluoromethyl.

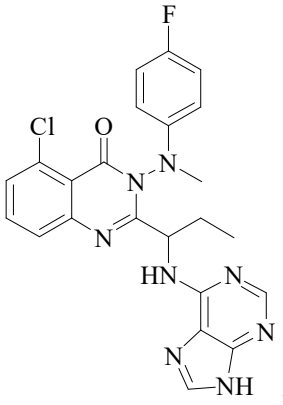
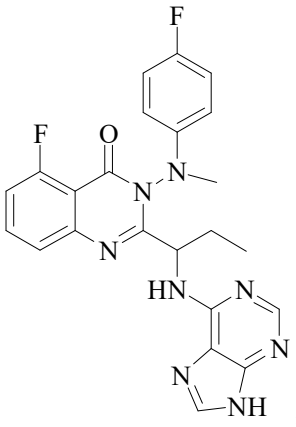
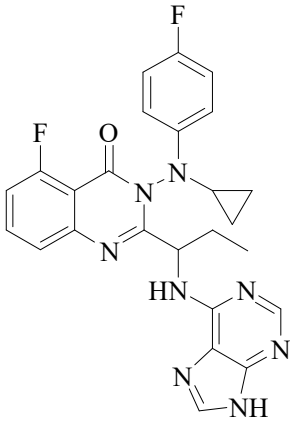
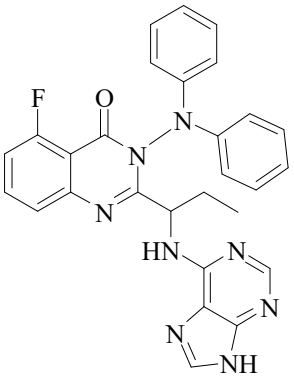
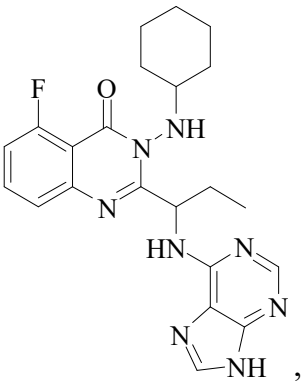
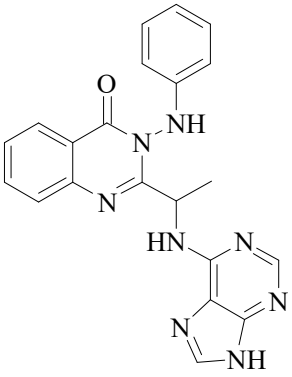
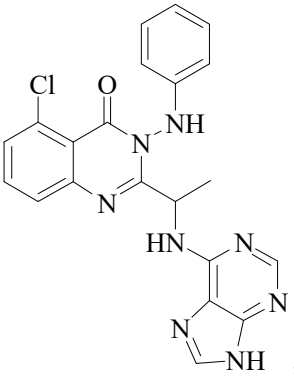
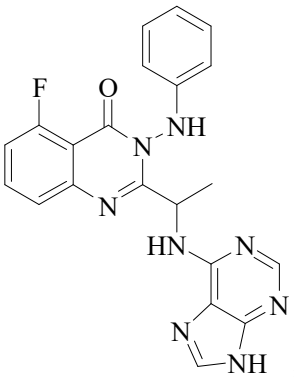
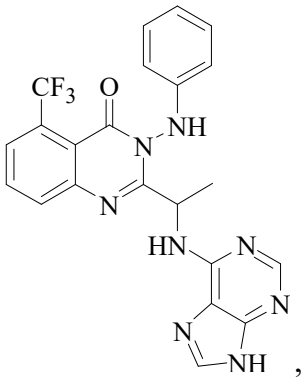
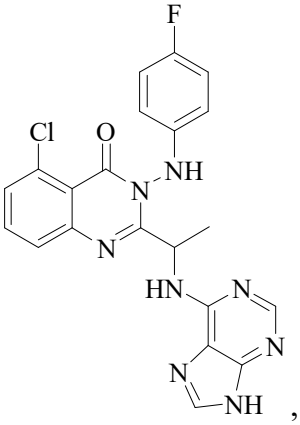
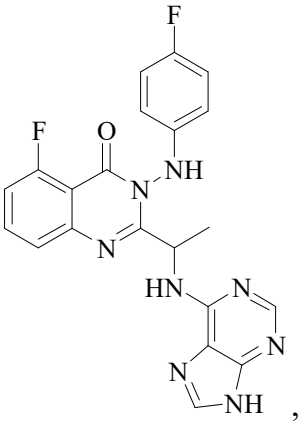
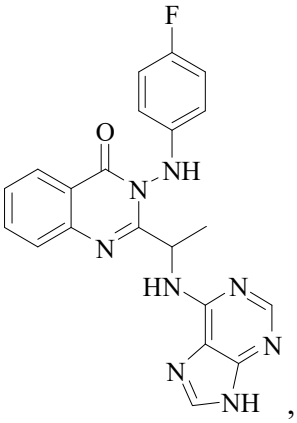
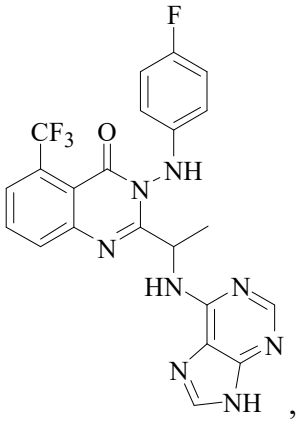
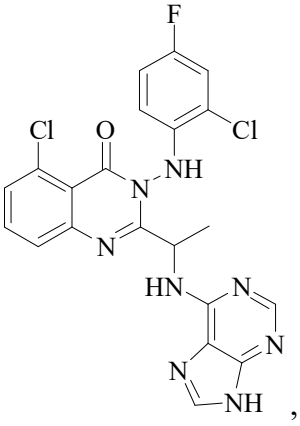
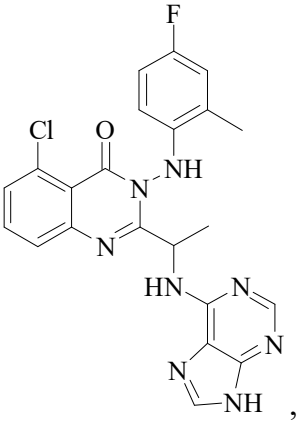
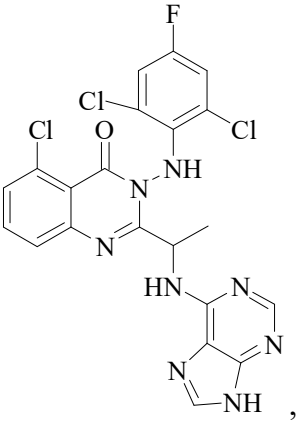
6. The compound, pharmaceutically acceptable salt thereof, a stereoisomer thereof and a deuterated derivative thereof according to claim 1, wherein the compound is:

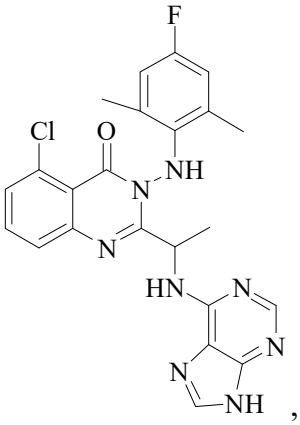
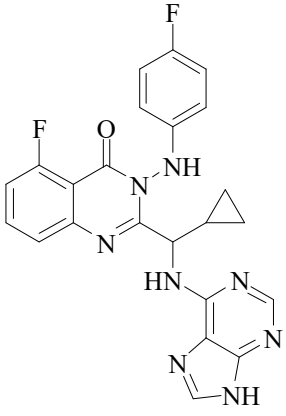
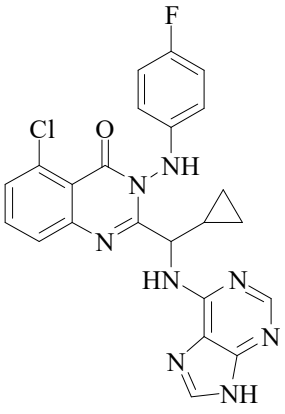
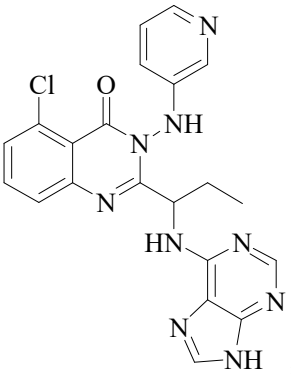
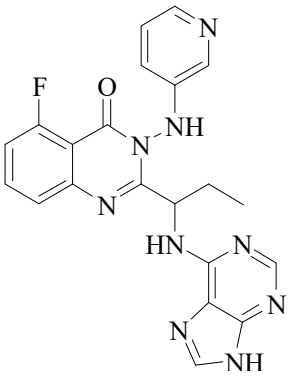
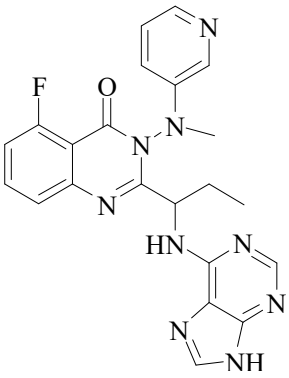
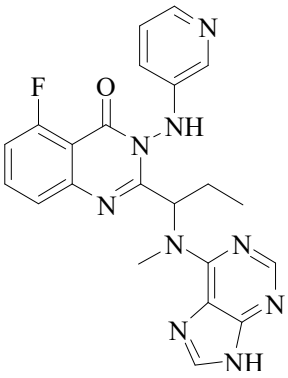
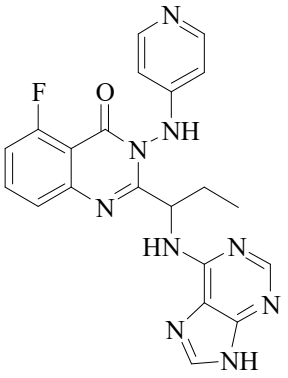
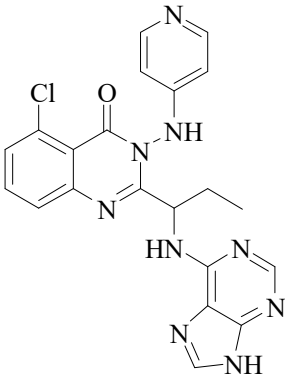
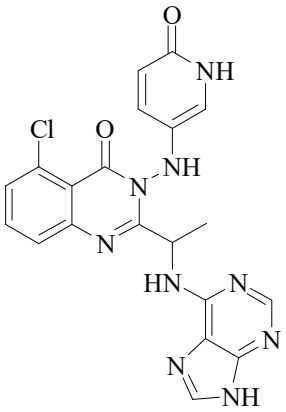
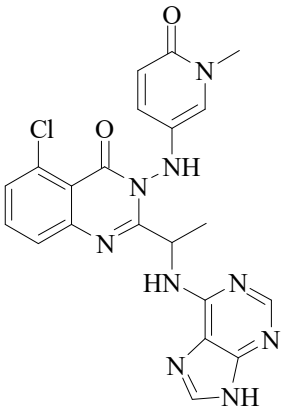
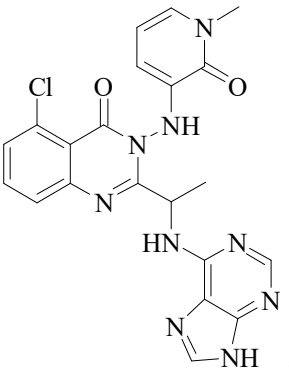
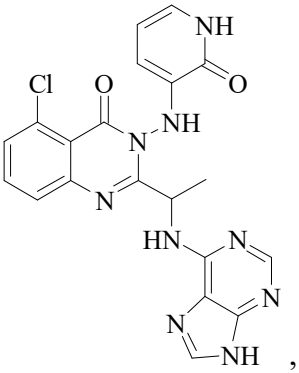
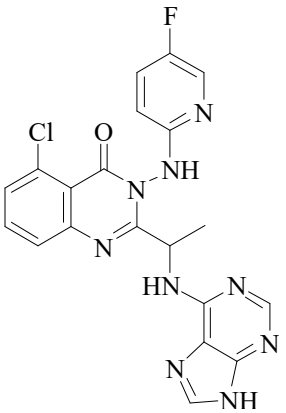
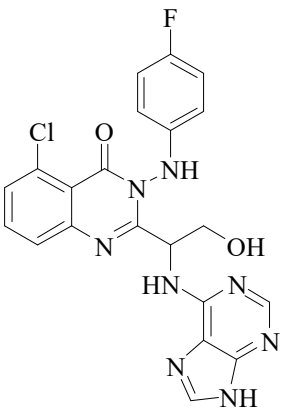
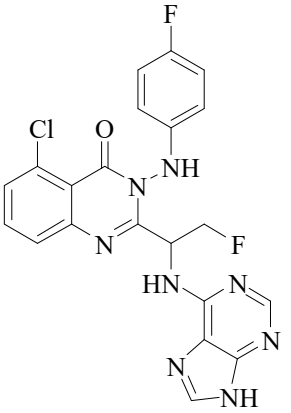
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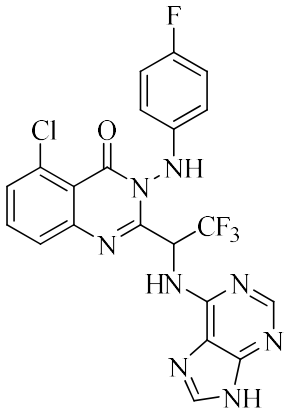
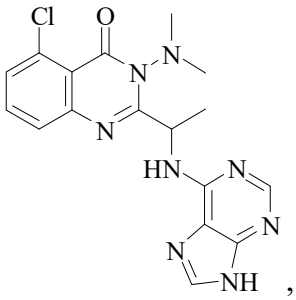
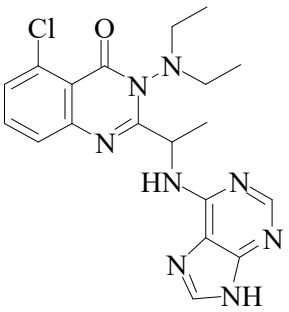
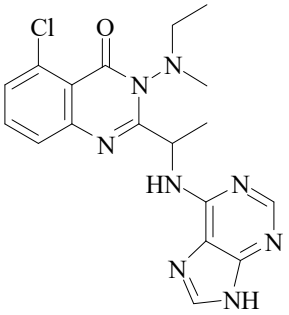
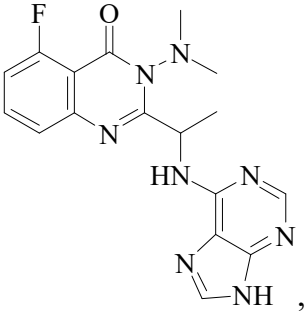
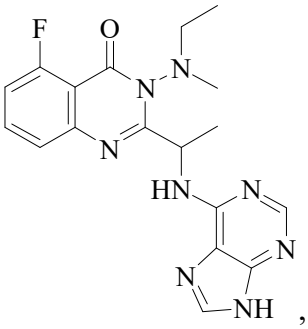
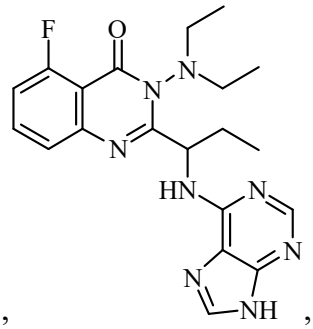
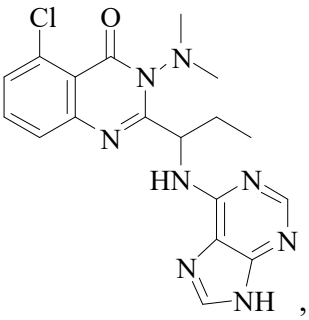
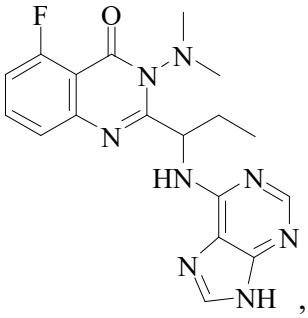
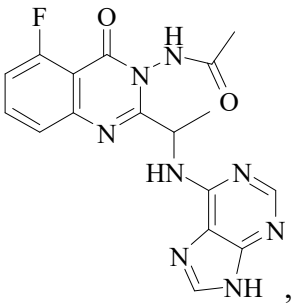
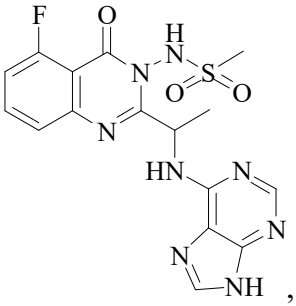
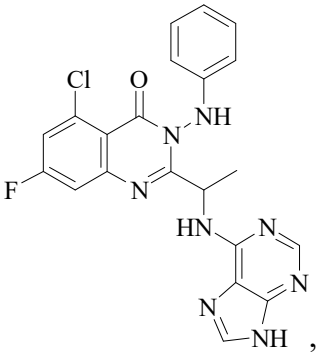
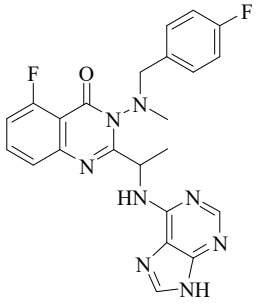
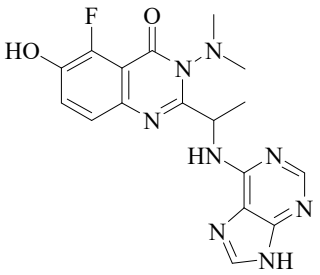
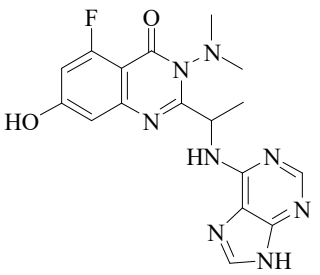
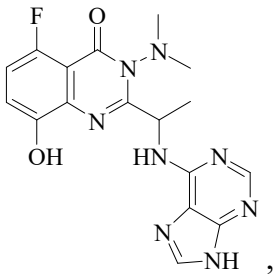
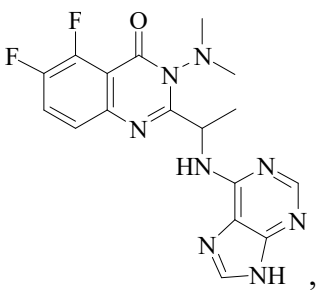
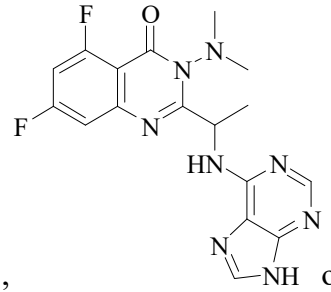
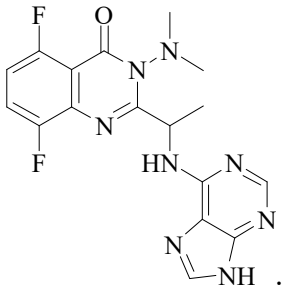

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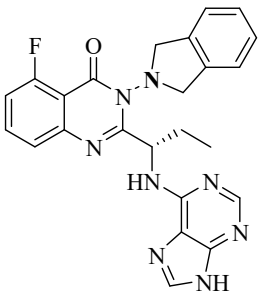
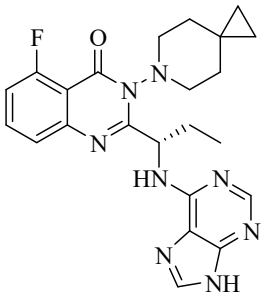
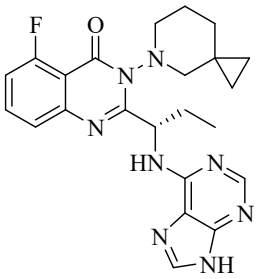
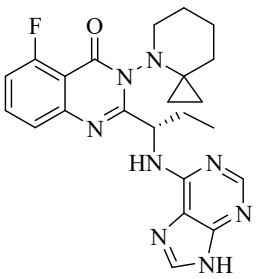
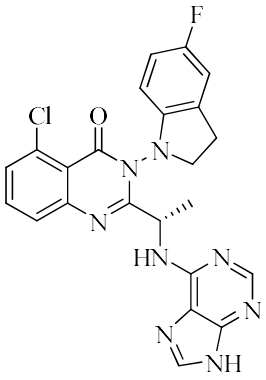
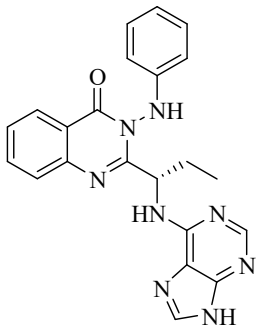
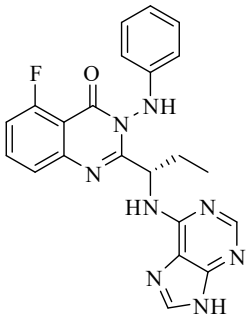
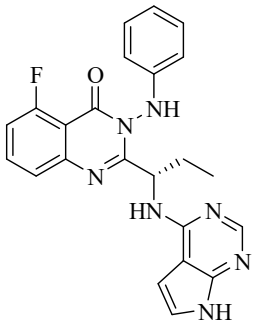
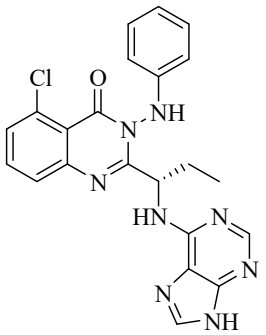
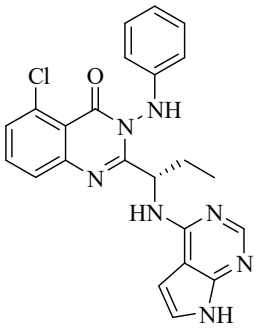
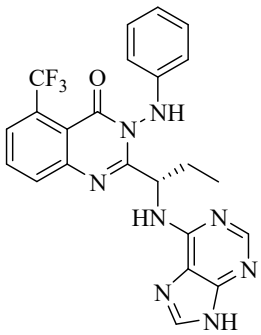
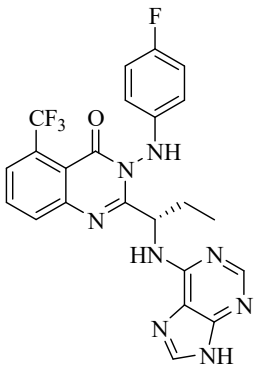
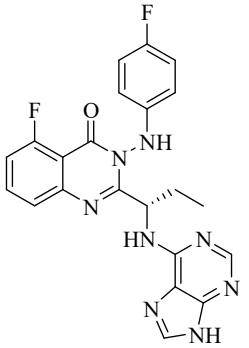
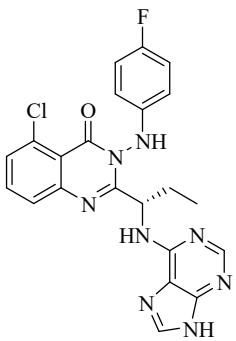
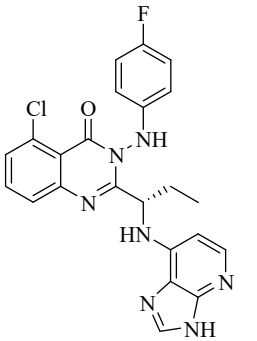
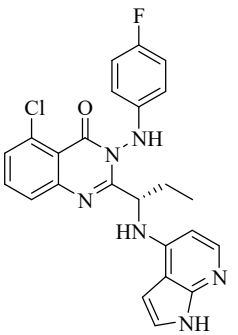
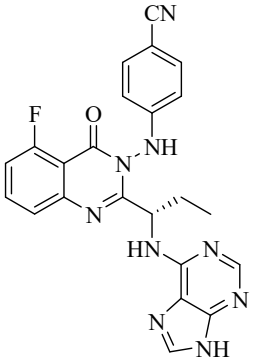
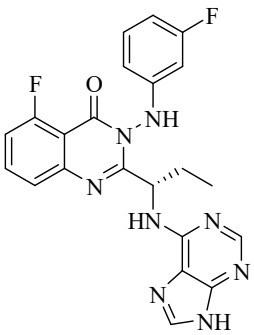
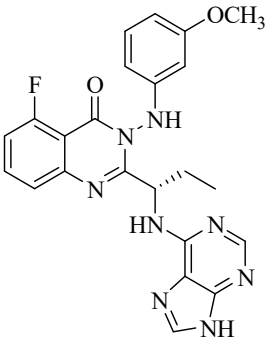
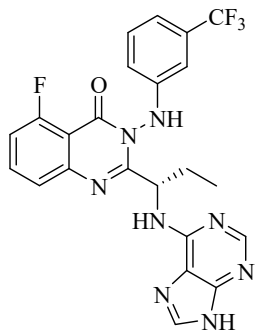
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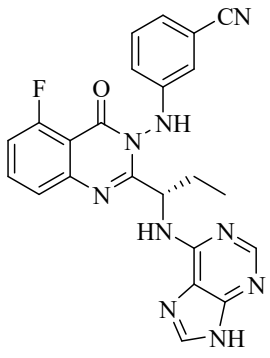
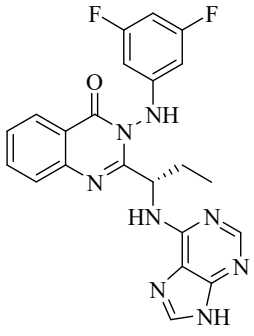
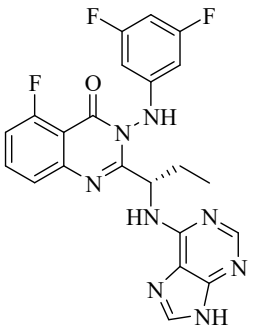
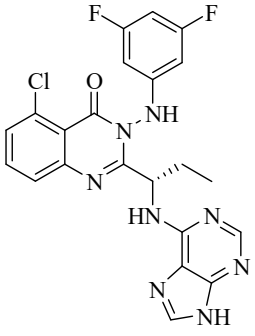
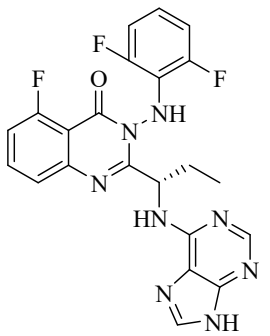
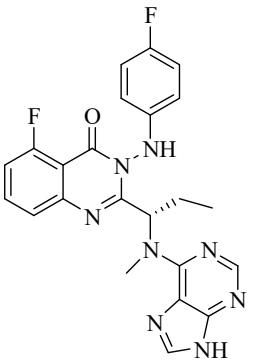
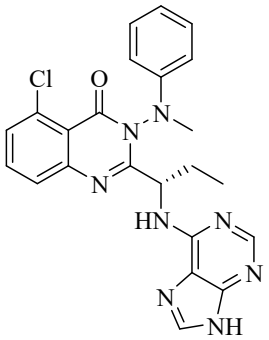
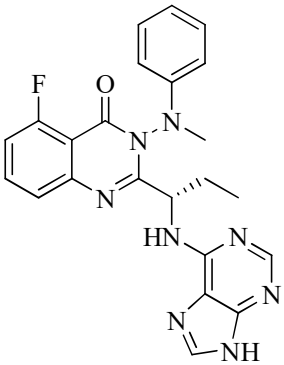
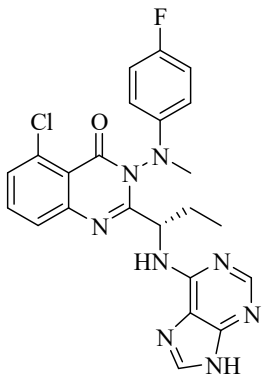
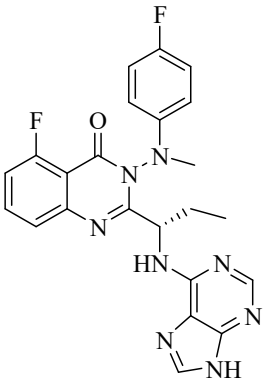
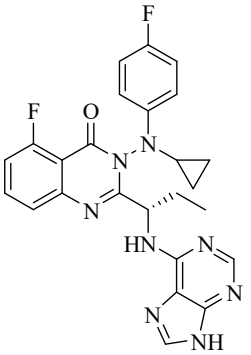
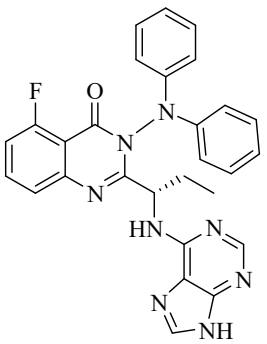
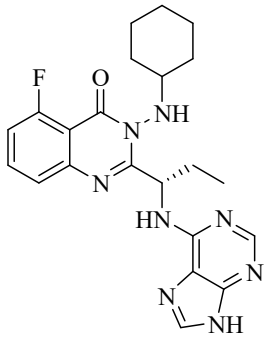
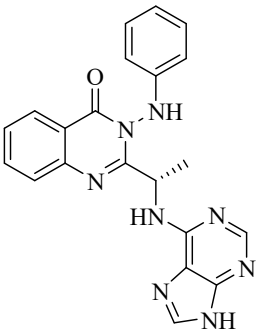
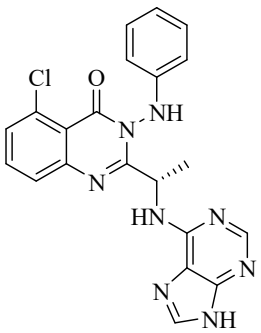
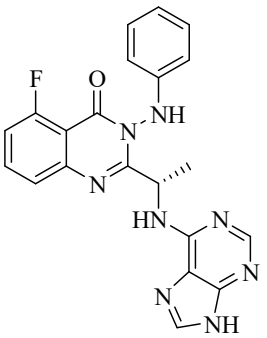
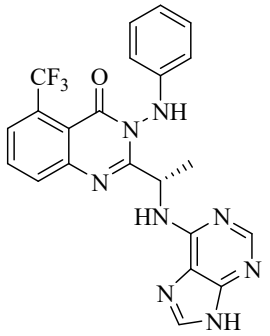
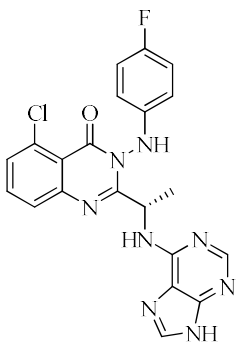
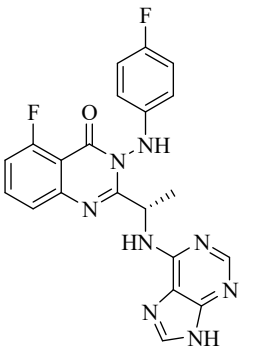
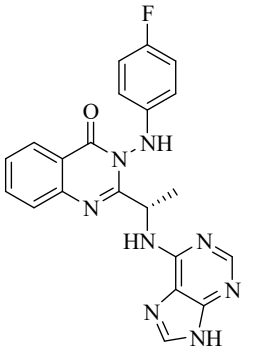
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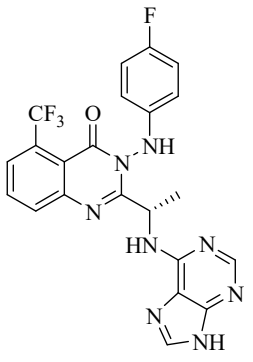
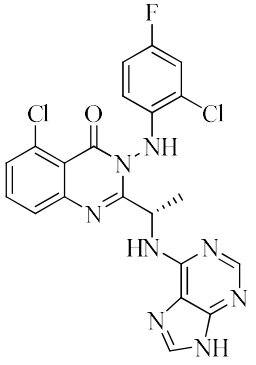
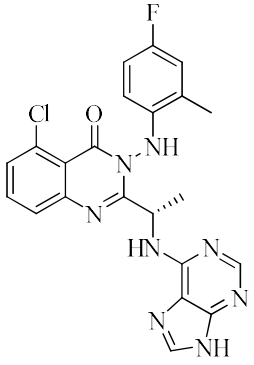
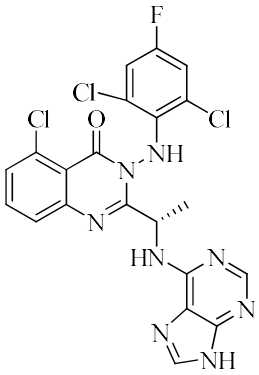
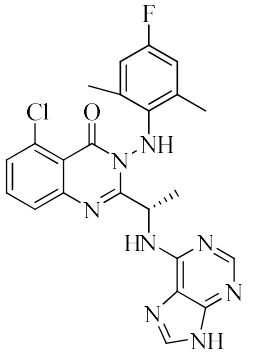
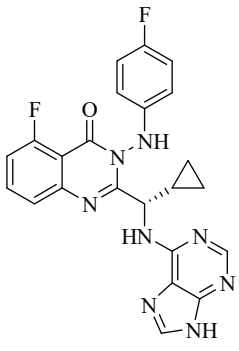
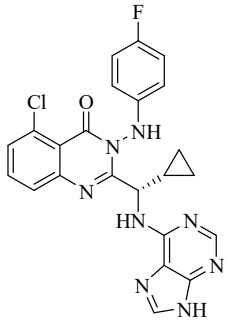
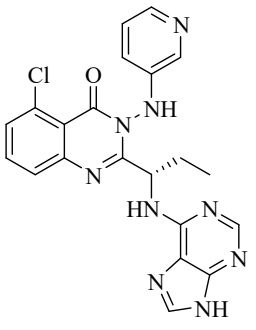
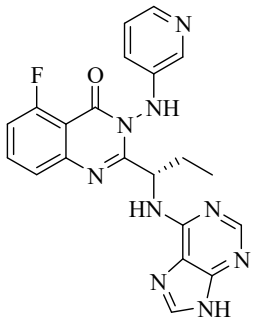
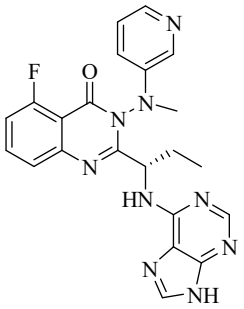
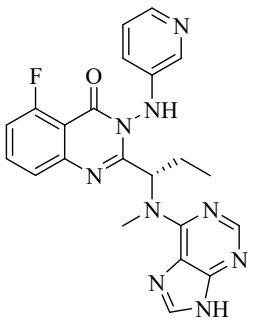
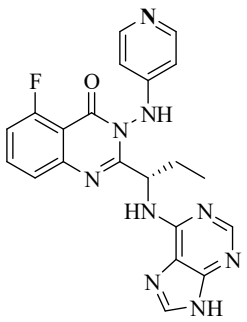
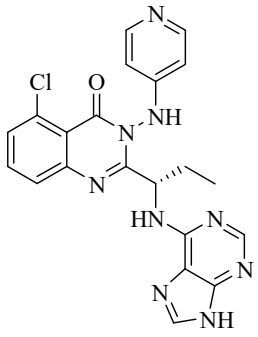
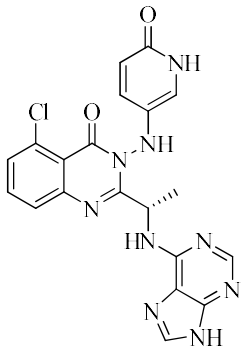
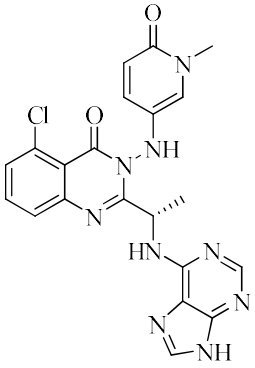
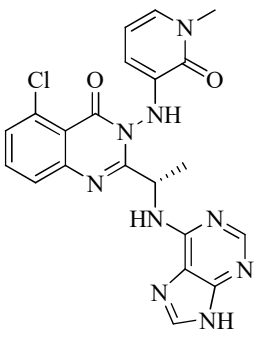
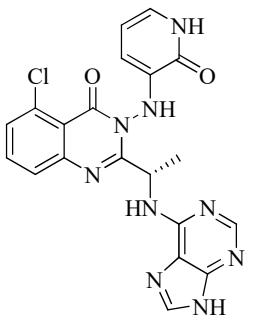
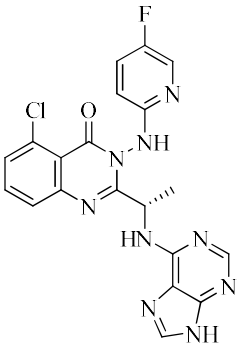
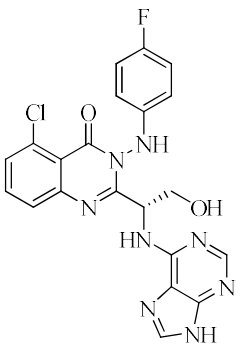
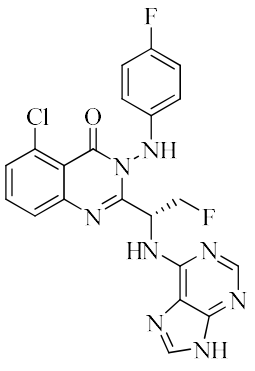
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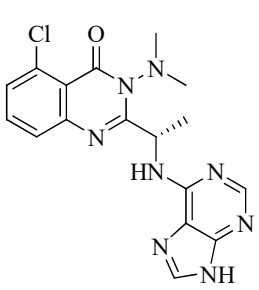
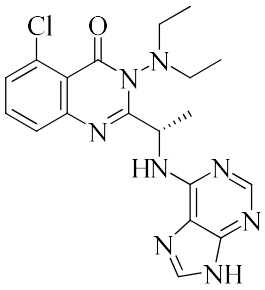
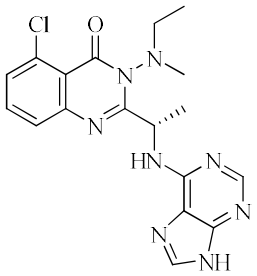
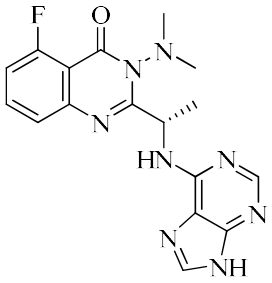
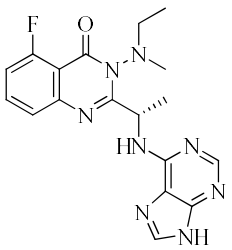
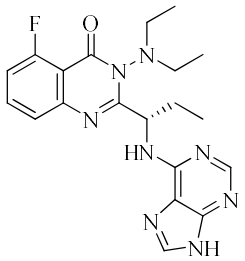
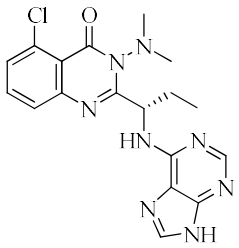
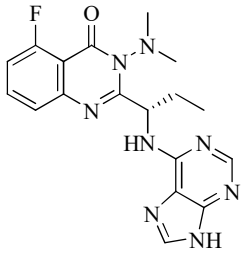
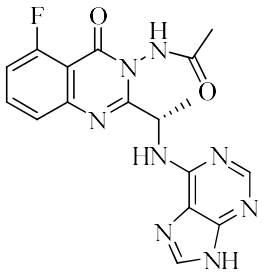
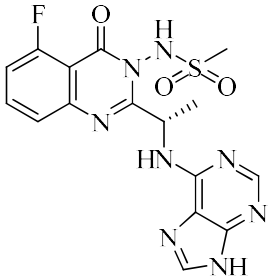
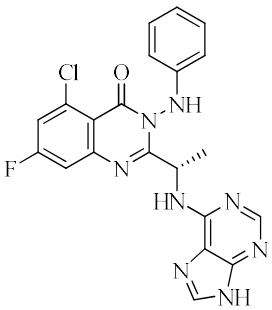
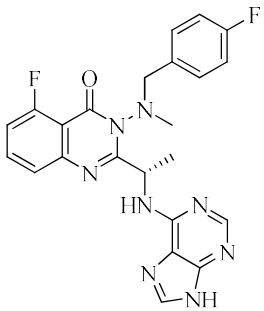
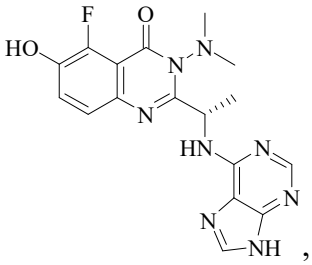
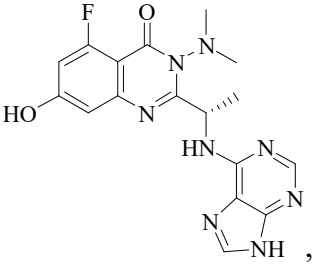
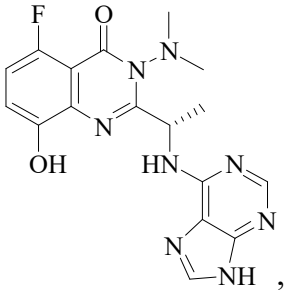
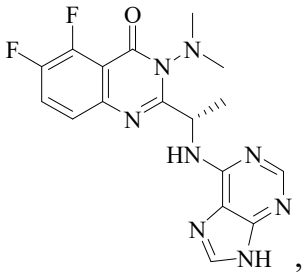
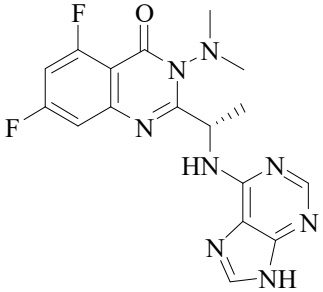
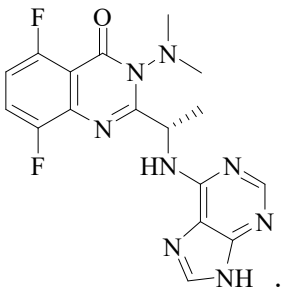

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7. The compound, pharmaceutically acceptable salt thereof, a stereoisomer thereof and a deuterated derivative thereof according to claim 1, wherein the compound is:


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or

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8. A pharmaceutical formulation, comprising the compound, the pharmaceutically acceptable salt thereof, the stereoisomer thereof or the deuterated derivative thereof according to any one of claims 1-7 and one or more pharmaceutically acceptable carriers.

9. A use of the compound, the pharmaceutically acceptable salt thereof, the stereoisomer thereof or the deuterated derivative thereof according to any one of claims 1-7 for the

manufacture of a medicament for the treatment or prevention of an inflammatory disease or tumor.

10. The use of claim 9, wherein inflammatory disease is selected from allergy, asthma, rheumatoid arthritis, osteoarthritis, allergic conjunctivitis, allergic keratitis, dry eyes, chronic obstructive pulmonary disease (COPD), lupus, psoriasis, multiple sclerosis and advanced kidney disease, and wherein the tumors are selected from leukemia, lymphoma, myeloproliferative disease, non-Hodgkin's lymphoma and chronic idiopathic myelofibrosis.