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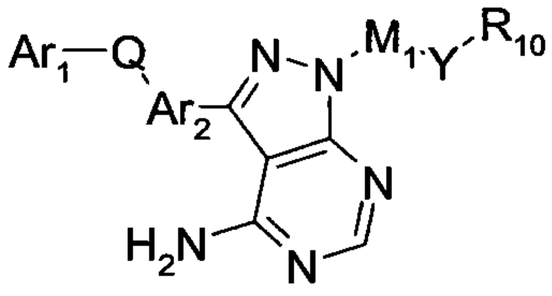
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CANADIAN PATENT APPLICATION

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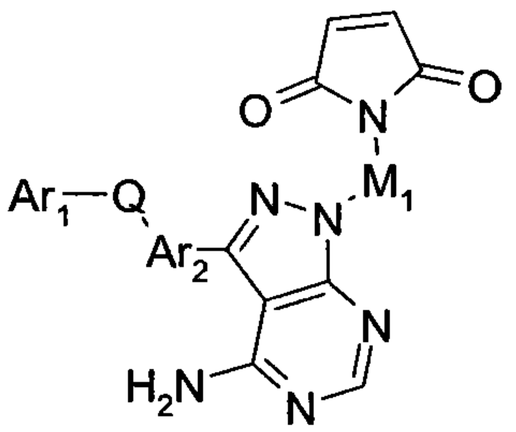
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C07F 5/04 (2006.01)

(54) **Titre : COMPOSES POLYFLUORES AGISSANT EN TANT QU'INHIBITEURS DE LA TYROSINE KINASE DE BRUTON**
(54) **Title: MULTI-FLUORO-SUBSTITUTED COMPOUND AS BRUTON'S TYROSINE KINASE (BTK) INHIBITOR**



(I)



(II)

(57) **Abrégé/Abstract:**
Provided are new polyfluoro-substituted pyrazolopyrimidine compounds or salts represented by formulae (I) to (IX), a preparation method therefor, and a method for using said compounds and a preparation thereof to treat and inhibit autoimmune diseases or disorders, heteroimmune diseases or disorders, inflammatory diseases and cancers or disorders.

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ABSTRACT

Provided herein are novel multi-fluoro-substituted pyrazolopyrimidine compounds or salts thereof, methods for preparing the same, and therapeutic methods by administering the compounds and formulation thereof to treat and inhibit autoimmune diseases or disorders, heteroimmune diseases or disorders, inflammatory diseases and cancers or disorders.

MULTI-FLUORO-SUBSTITUTED COMPOUND AS BRUTON'S TYROSINE KINASE (BTK) INHIBITOR

Field of the Invention

The present invention relates to a series of novel multi-fluoro-substituted pyrazolopyrimidine compounds and methods for preparing the same, as well as pharmaceutical compositions comprising the compounds described herein as an active component and the methods for inhibiting BTK activity by using the same. The present invention also relates to a series of novel multi-fluoro-substituted benzophenones and the corresponding borate, multi-fluoro-substituted phenoxybenzene and the corresponding borate, and methods for preparing the same.

Background

Bruton's tyrosine kinase (BTK) is a member of the Tec family, and is consisted of unique N-terminal domains, i.e., pleckstrin homology (PH) domain, Tec homology (TH) domain, Src homology 3 (SH3) domain, Srchomology 2 (SH2) domain, and catalytic domain which is also referred to Src homology 1/tyrosine kinase (SH1/TK) or kinase domain (Akinleye *et al*: Ibrutinib and novel BTK inhibitors in clinical development, *Journal of Hematology & Oncology,* **2013**, 6:59). In the normal development of B lymphocytes, the correct expression of a BTK gene in different protein regions plays a key role in the function of B cells and various signal transduction pathways.

There are a plurality of receptors downstream of BTK functions, including growth factors, B-cell antigen, chemokine, and innate immune receptors, so as to initiate a diverse range of cellular processes, such as cell proliferation, survival, differentiation, motility, angiogenesis, cytokine production, and antigen expression. Therefore, BTK plays an important role in many hematopoietic cell signaling pathways, and it is also crucial in B cell activation, development, survival and signaling (Kurosaki, Molecular mechanisms in B cell antigen receptor signaling. *Curr OP Imm*, **1997**, 9(3):309-18).

There are evidences to prove that B cells have immune regulatory effects on their immune responses and inflammatory responses. For example, CD20 antibody rituximab (rituxan) is a protein-based treatment agent consuming B cells and used for treating

autoimmune diseases, such as chronic lymphocytic leukemia and autoantibody-caused inflammatory diseases, such as rheumatoid arthritis. Therefore, protein kinase, which plays a key role in the activation of B cells, will be helpful for B cell related diseases.

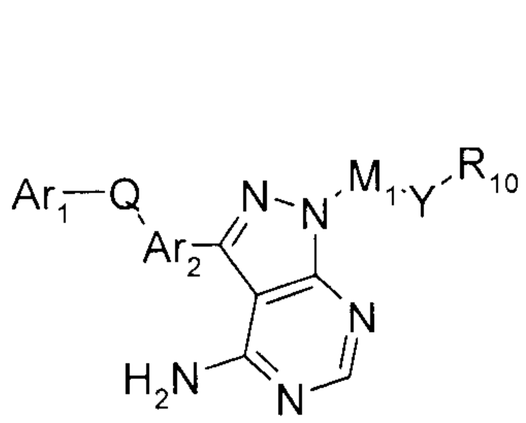
Evidences about the role of BTK in autoimmune diseases have been provided by a BTK-deficient mouse and a BTK-sufficient mouse model (Kil LP, *et al*: Bruton's tyrosine kinase mediated signaling enhances leukemogenesis in a mouse model for chronic lymphocytic leukemia. *Am J Blood Res* **2013**, 3(1):71–83.). In a mouse model of chronic lymphocytic leukemia (CLL), a BTK-deficient mouse completely abolishes chronic lymphocytic leukemia, BTK overexpression accelerates leukemia, and increases mortality.

The selectivity of a known BTK inhibitor is not ideal, due to inhibiting not only BTK but also various other kinases (such as ETK, EGF, BLK, FGR, HCK, YES, BRK and JAK3, and the like), thus which may cause more side effects. An inhibitor with better selectivity may result in less side effects.

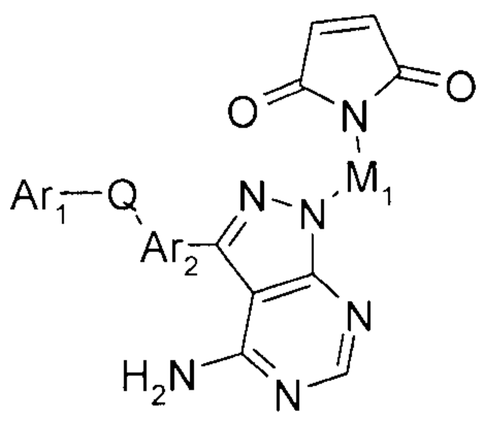
The known BTK inhibitors produce a variety of derivatives in vivo, which will affect the efficacy and result in side effects. The pharmacokinetics of the known BTK inhibitors can also be improved.

Summary

The present invention relates to the methods for treating or inhibiting autoimmune diseases, heteroimmune diseases, inflammatory diseases and cancers by using BTK inhibitors, including administering to a patient an effective amount of a compound represented by Formula (I) or (II), or pharmaceutically acceptable salts thereof.



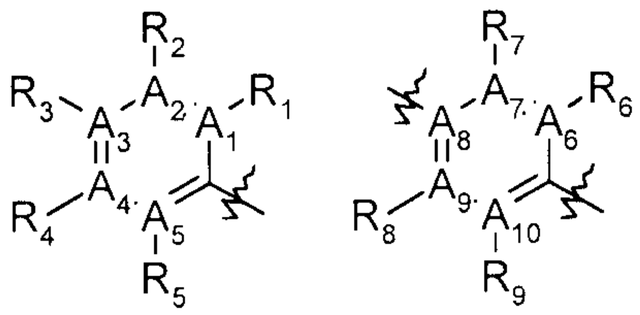
(I)



(II)

wherein:

Ar_1 and Ar_2 are independently represented by formula (III) or (IV):



(III)

(IV)

wherein:

A_1, A_2, A_3, A_4, A_5, A_6, A_7, A_8, A_9 and A_{10} are independently C or N, and when they are N, there is no substituent connected thereto;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9 are independent lyhydrogen, deuterium, amino, halogen, hydroxy, carbonyl, nitro, cyano, amide group, lower alkyl sulfonamide group, C_2-C_6 alkenyl, C_2-C_6 alkynyl, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_{10} cycloalkyl; wherein the alkyl, alkoxyl or cycloalkyl can be further optionally substituted with deuterium, halogen, amino, hydroxy, carbonyl, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxyl;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9 are preferably hydgrogen, deuterium, halogen, and more preferably hydgrogen, fluorine;

wherein,R_6, R_7, R_8, R_9, together with NH_2 of a pyrimidine ring, can form a 6 to 8 membered saturated or unsaturated heteroaromatic ring or heterocyclic ring;

Ar_1 is independently selected from benzoaryl and benzo-heteroaryl, wherein the substituent is independently selected from deuterium, amino, halogen, hydroxy, carbonyl, nitro, cyano, amide group, lower C_1-C_6 alkyl, C_1-C_6 alkoxyl; C_3-C_{10} cycloalkyl; wherein the alkyl, alkoxyl or cycloalkyl are each optionally substituted with deuterium, halogen, amino, hydroxy, carbonyl, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxyl,

Q is O, S or C(=O);

M_1 is a saturated or unsaturated C_1-C_8 carbon chain, C_6-C_{10} aryl, C_6-C_{10} aryl C_1-C_6 alkyl,alkylaryl, heteroaryl, heteroaryl alkyl, alkyl heteroaryl, cycloalkyl, cycloalkyl alkyl, alkyl cycloalkyl, heterocycloalkyl, heterocycloalkylalkyl, alkyl heterocycloalkyl; wherein hydrogen atoms on the carbon chain, aryl, heteroaryl, cycloalkyl and heterocycloalkyl can be

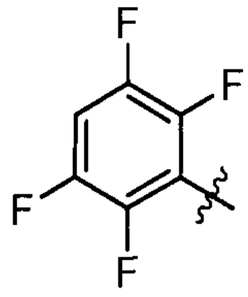
optionally substituted with alkyl, cycloalkyl,alkoxyl, cycloalkoxyl, amino, cyano, amide group or halogen;

Y is C(=O), $NR_{11}C(=O)$ or $S(=O)_2$;

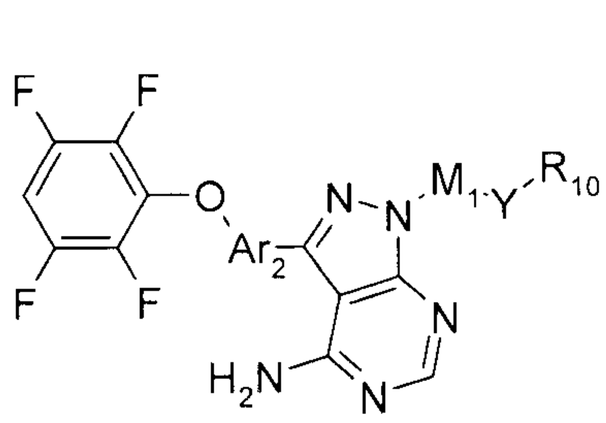
R_{10}, R_{11} can be independently represented by amino, cycloamino, aryl, heteroaryl, heterocycloalkyl, oxo-heterocyclyl, trifluoromethyl, trifluoromethoxy, trifluoroacetyl, amide group, acyl, guanidyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_1-C_6 alkoxyl, C_1-C_6 oxoalkyl; wherein the amino, amide group, acyl, C_2-C_6 alkenyl, alkyl, alkoxyl or cycloalkyl can be further optionally substituted with deuterium, halogen, amino, hydroxy, hydroxy alkyl, carbonyl, ester group, amide group, nitro, cyano, trifluoroacetyl, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_1-C_6 oxoalkyl, C_3-C_{10} cycloalkyl;

the hydrogen atoms connected to carbon or nitrogen on the aryl or a hetero-ring can be optionally substituted with alkyl, cycloalkyl, alkoxyl, cycloalkoxyl, amino, cyano, amide group and halogen.

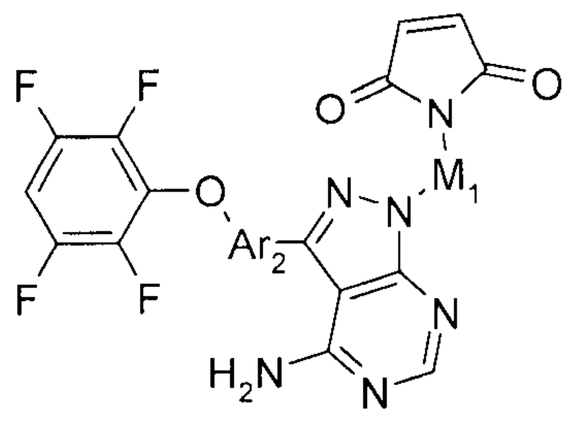
Ar_1 is preferably selected from below formula:



Q is preferably O to form Formulae (X) and (XI):



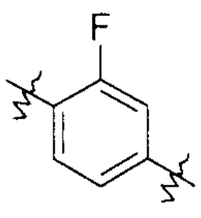
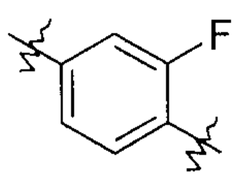
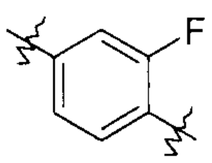
(X)



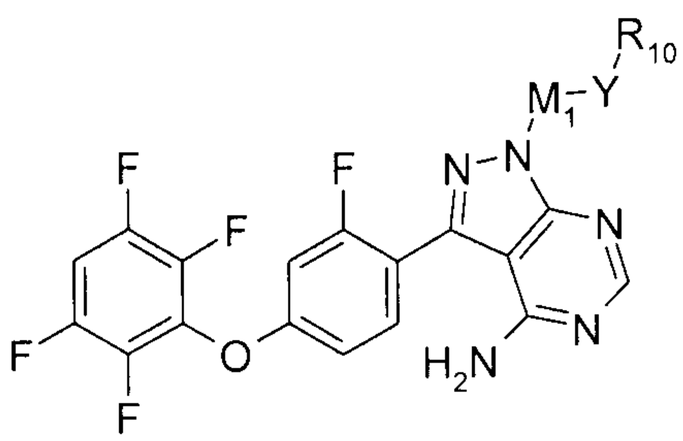
(XI)

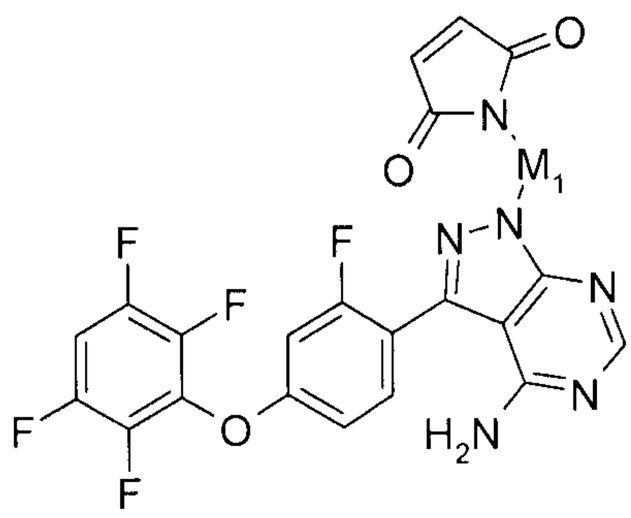
wherein, Ar_2, M_1, Y and R_{10} are defined as above.

wherein: Ar_2 is preferably substituted phenyl or heteroaryl, preferably substituted phenyl, and more preferably


or  , further preferably 

therefore to form formulae (XII) and (XIII):


（XII）


（XIII）

wherein, M_1 is a saturated or unsaturated C_1-C_8 carbon chain, aryl, arylalkyl, alkylaryl, alkylheteroaryl, cycloalkyl, cycloalkyl alkyl, alkyl cycloalkyl, heterocycloalkyl, heterocycloalkyl alkyl, alkyl heterocycloalkyl; wherein hydrogen atoms connected to the carbon or nitrogen atoms on the carbon chain, aryl, heteroaryl, cycloalkyl and heterocycloalkyl can be optionally substituted with alkyl, cycloalkyl, alkoxyl, amino, CN, amide group or halogen;

wherein, M_1 is preferably piperidinyl or pyrrolidinyl;

Y is C(=O), $NR_{11}C(=O)$ or $S(=O)_2$, preferably C(=O) or $NR_{11}C(=O)$, more preferably C(=O);

R_{10} is selected from amino, cycloamino, aryl, heteroaryl, heterocycloalkyl, oxo-heterocyclyl, trifluoromethyl, trifluoromethoxy, trifluoroacetyl, amide group, acyl, guanidyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_1-C_6 alkoxyl, C_1-C_6 oxoalkyl; wherein the amino, amide group, acyl, C_2-C_6 alkenyl, alkyl, alkoxyl or cycloalkyl can be further optionally substituted with deuterium, halogen, amino, hydroxy, hydroxy alkyl,

carbonyl, ester group, amide group, nitro, cyano, trifluoroacetyl, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_1-C_6 oxoalkyl, C_3-C_{10} cycloalkyl;

R_{10} is the most preferably vinyl.

Unless specified otherwise, as used herein, the terms "alkyl", "alkenyl" and "alkynyl" refer to a straight or branched alkyl containing 1 to 6 carbon atoms, or a straight or branched alkenyl and alkynyl containing 2 to 6 carbon atoms, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl; vinyl, propenyl, butenyl, pentenyl, or hexenyl; and isomers thereof.

The term "hydroxyl" refers to a group with -OH.

The term "halogen" or "halo" refers to fluoro, chloro, bromo or iodo.

The term "cycloalkyl" refers to a monocyclic or polycyclic carbon ring in which each ring has 3 to 10 carbon atoms and may contain one or more double or triple bonds. Examples of cycloalkyl includes, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term "cycloalkyl" also refers a tospiral ring system, in which the cycloalkyl rings share one common carbon atom.

The term "heterocycloalkyl" refers to a 5 to 6 membered non-aromatic heterocyclic ring that may contain one or more identical or different heteroatoms each selected from N, O and S (which can be oxidized). The heterocycloalkyl can be unsaturated or fused with a benzene ring, but does not include aza-bridged cyclic hydrocarbon. The heterocycloalkyl includes, but are not limited to, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, dihydrooxazolyl, tetrahydropyranyl, tetrahydrothiopyranyl, indolinyl, tetrahydroquinolyl, tetrahydroisoquinolyl and benzoxazinyl, preferably dihydrooxazolyl, oxadiazolanyl and tetrahydrofuranyl.

The term "cycloamino" refers to a 3 to 8 membered non-aromatic cyclic amine of a group defined by "heterocycloalkyl", which has at least one nitrogen atom and may have one or more different heteroatoms selected from nitrogen atom, oxygen atom, and sulphur atom (which can be oxidized), wherein at least one nitrogen atom is bonded. Although the "cycloamino" does not include aza-bridged cyclic hydrocarbon group, it may comprises, for example, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, thiomorpholinyl, piperazinyl.

The term “aryl” refers to an aromatic carbocyclic group, preferably an aryl having 6 to 10 carbon atoms, more preferably, phenyl, naphthyl and indenyl, most preferably phenyl.

The term “heteroaryl” refers to a monovalent 5 or 6 membered aromatic heterocyclic group having one or more identical or different heteroatoms selected from nitrogen atom, oxygen atom, and sulfur atom, and can be fused with a benzene ring. The “heteroaryl” may comprise, for example, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, thienyl, furyl, oxadiazolyl, thiadiazolyl, quinolinyl, isoquinolinyl, benzthiazolyl, benzoxazolyl, indolyl, indazolyl, quinoxalinyl, quinazolinyl, preferably pyridazinyl, pyridyl, pyrazinyl, thiazolyl, pyrazolyl and thiooxazolyl.

The term “bridged ring group” means “bridged cyclic hydrocarbon group” and “aza-bridged cyclic hydrocarbon group”.

The term "bridged cyclic hydrocarbon group" is a saturated or unsaturated, bridged bicyclic or polycyclic hydrocarbon group that has two or three cycloalkyl rings with 3 to 10 carbon atoms. Unbridged cycloalkyl are not included herein. Particularly preferred are bridged bicyclic or polycyclic hydrocarbon group having 4to 16 carbon atoms. The bridged cyclic hydrocarbon group may comprise, for example, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[4.3.1]decyl, bicyclo[3.3.1]nonyl, bornyl, norbornene group, norbornyl, norbornenyl, 6,6-dimethyl-bicyclo[3.1.1]heptyl, tricyclo butyl and adamantyl, preferably adamantyl or bicyclo [2.2.1] heptyl.

The term “nitro” refers to -NO_2 group.

The term “amine” refers to -NH_2 group, which may have one, two or three groups, such as, alkyl, alkenyl, alkynyl, aryl, or the like.

The term “cyano” refers to -CN group.

The term “alkoxy” refers to a alkyl connected with one oxygen atom, for example methoxyl, wherein the oxygen atom is bonded to other part of the molecule. Examples of alkoxy comprise methoxyl, ethoxyl, propoxyl, iso-propoxyl, n-butoxyl and tert-butoxyl.

The term “acyl” refers to -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, -C(=O)-cycloalkyl, -C(=O)-heterocycloalkyl, -C(=O)-aryl, -C(=O)-heteroaryl, carbamoyl, -C(=O)-C(=O)-alkyl, -C(=O)-C(=O)-NH-alkyl. The terms “alkyl”, “cycloalkyl”, “heterocycloalkyl”, “aryl” and “heteroaryl” herein have the same meaning as stated above.

The term “carboxyl” refers to -CO_2H group or salts thereof.

The term “trifloromethyl” refers to -CF_3 group.

The term “trifluoromethoxy” refers to -OCF_3 group.

The term “trifluoroacetyl” refers to $CF_3C(=O)$- group.

The term “alkyl sulfonamide” refers to -$NR'S(=O)_2R$ group, wherein, R is alkyl, R’ is hydrogen or C_1-C_6 alkyl which is defined as above.

The term “amide” refers to -C(=O)NHR or -NHC(=O)R group, wherein, R is alkyl which is defined as above.

The term “ester” refers to -C(=O)OR group, wherein, R is alkyl which is defined as above.

When two or more terms are used in combination, for example, “alkylaryl” or “arylakyl”, each term herein has the same meaning as defined above.

The term "pharmaceutically acceptable salt" refers to salts formed with acid or base, nonlimiting examples comprise (a) acid addition salts: salts of inorganic acid (e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and organic acid (e.g., acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, poly glutamic acid, oxybenzoic acid, and the like); (b) base addition salts, the formation of metal cations, such as zinc, calcium, sodium, potassium, and the like.

Synthesis Schemes

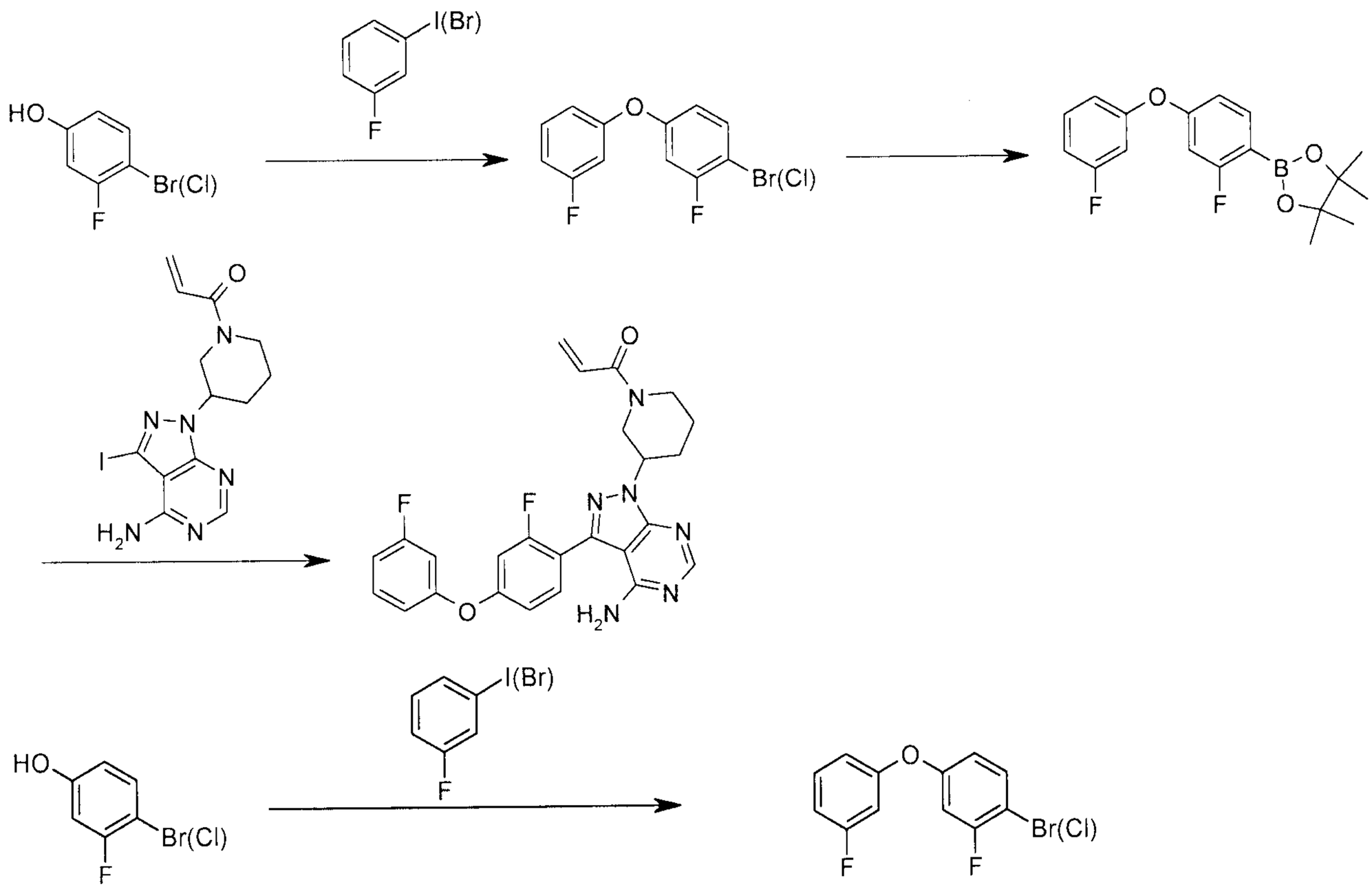
The present invention is exemplified through embodiments and the compounds disclosed herein. The particular compounds of the present invention are selected from the compounds of disclosed embodiments and their pharmaceutically acceptable salts and their individual diastereomers or salts.

The present invention has investigated the synthesis methods actively, excluded a variety of preparation schemes (see Schemes 1-3), and successfully developed novel methods for synthesizing pyrazolopyrimidine compounds (see Schemes 4-11 and the specific reaction examples).

The following reaction schemes illustrate the preparation pathways of the compounds according to the present invention.

Unless otherwise specified, in the following reaction schemes and discussion, A_1, A_2, A_3, A_4, A_5, A_6, A_7, A_8, A_9, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} have the same meaning as defined above.

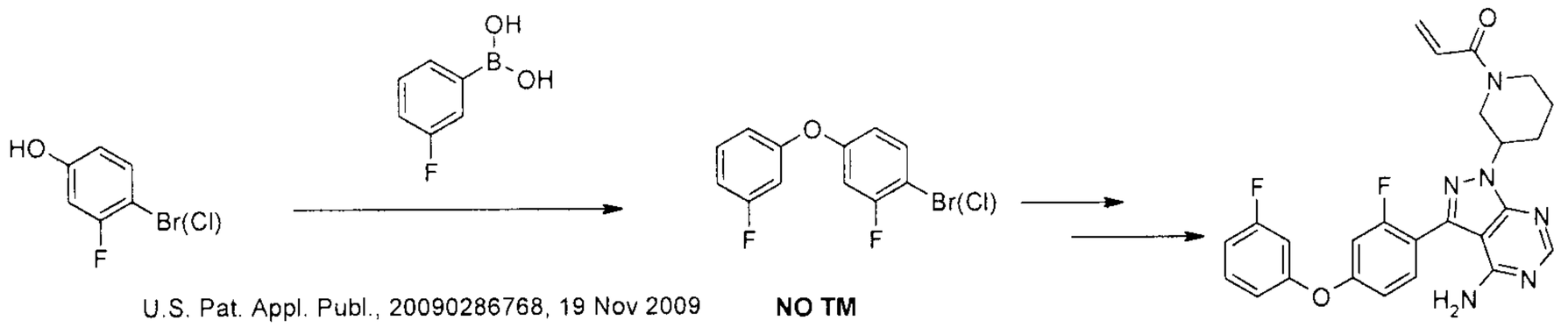
Scheme 1



Scheme 1 was designed based on the literature reported methods: 3-fluoro-4-bromo-phenol (or 3-fluoro-4-chloro-phenol) and 3-iodo-fluorobenzene (or 3-fluoro-bromophenyl) under a basic condition was catalyzied by a copper reagent to form 1-bromo-2-fluoro-4-(3-fluorophenoxy)benzene (or 1-chloro-2-fluoro-4-(3-fluorophenoxy)benzene), and then reacted with bis(pinacolato)borate in the presence of a suitable catalyst (e.g., [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium) to provide a corresponding boronate ester.

The resulting boronate ester reacted with a substituted 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine in the presence of a suitable catalyst (e.g., Pd-118) by Suzuki reaction to afford the target compound. Firstly, synthesize 1-bromo-2-fluoro-4-(3-fluorophenoxy)benzene (or 1-chloro-2-fluoro-4-(3-fluorophenoxy)benzene) according to literature reported methods, try different the reaction conditions, including different bases (e.g., potassium hydroxide, cesium carbonate), different copper catalysts (e.g., copper oxide, cuprous chloride, cuprous iodide) as well as different solvents (e.g., DMSO, N- methylpyrrolidone, 1,4-dioxane). No target compound was obtained by the above methods.

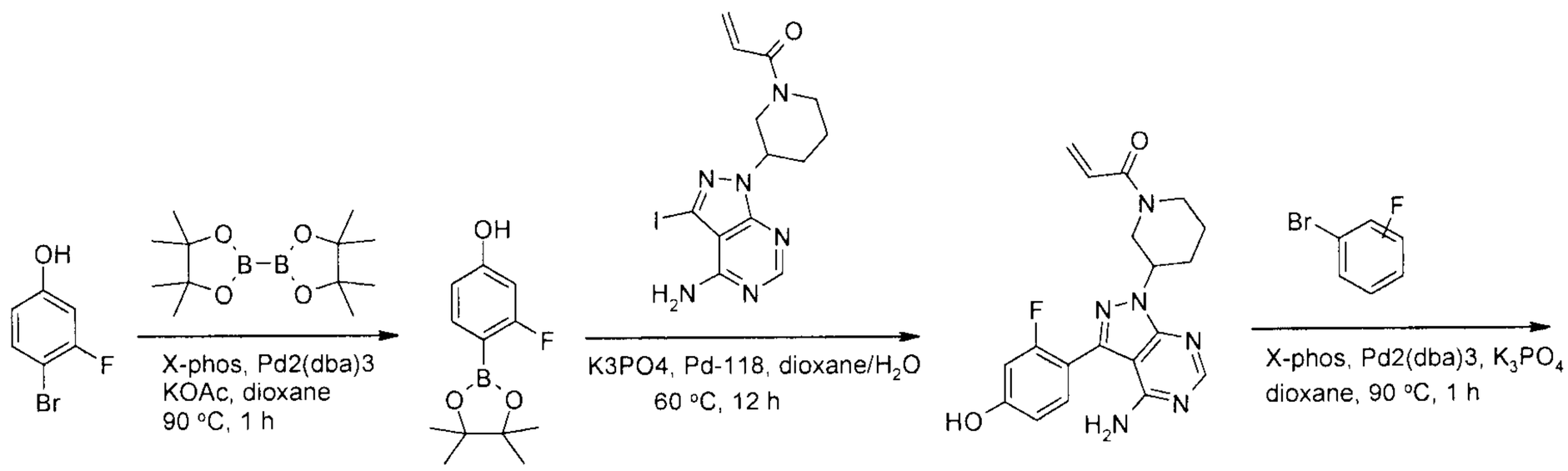
Scheme 2

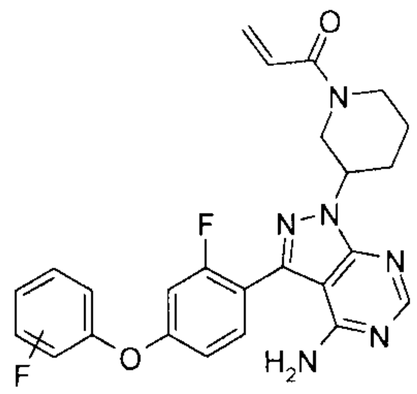


U.S. Pat. Appl. Publ., 20090286768, 19 Nov 2009 **NO TM**

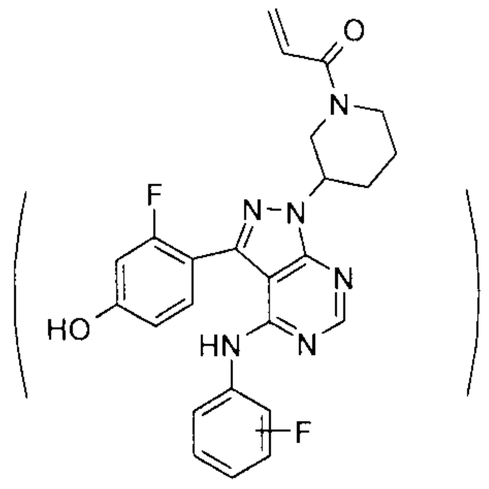
Scheme 2 was designed based on literature reported methods: 3-fluoro-4-bromo-phenol (or 3-fluoro-4-chloro-phenol) and 3-fluorophenyl boronic acid gave 1-bromo-2-fluoro-4-(3-fluorophenoxy)benzene (or l-chloro-2-fluoro-4-(3-fluorophenoxy)benzene), which then was converted to the corresponding boronate ester and then generated the target compound. Firstly, synthesized 1-bromo-2-fluoro-4-(3-fluorophenoxy)benzene (or 1-chloro-2-fluoro-4-(3-fluorophenoxy)benzene) according to literature reported methods, tried different bases (e.g., triethylamine), different catalysts (e.g., copper acetate) and different solvents (e.g., dichloromethane). No target compound was obtained by the above methods.

Scheme 3





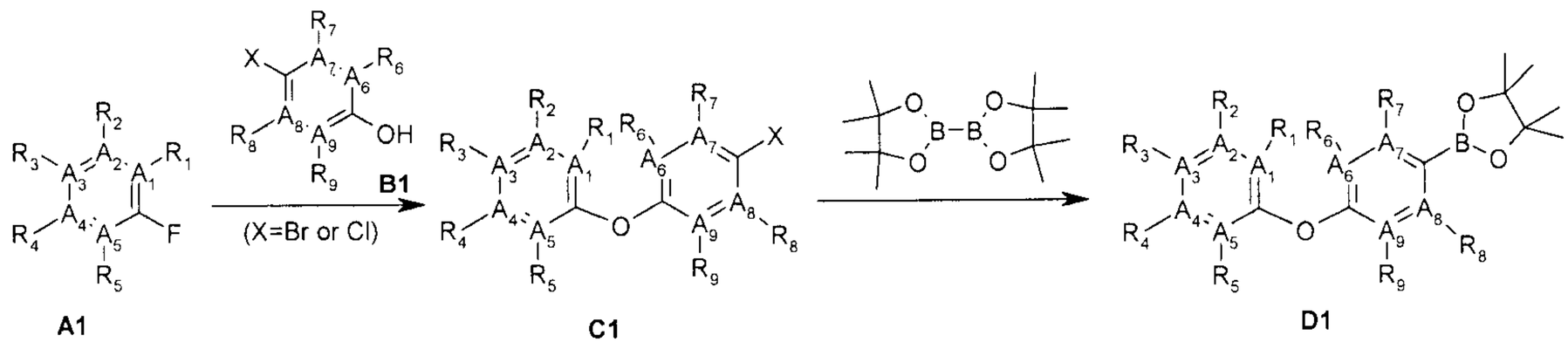
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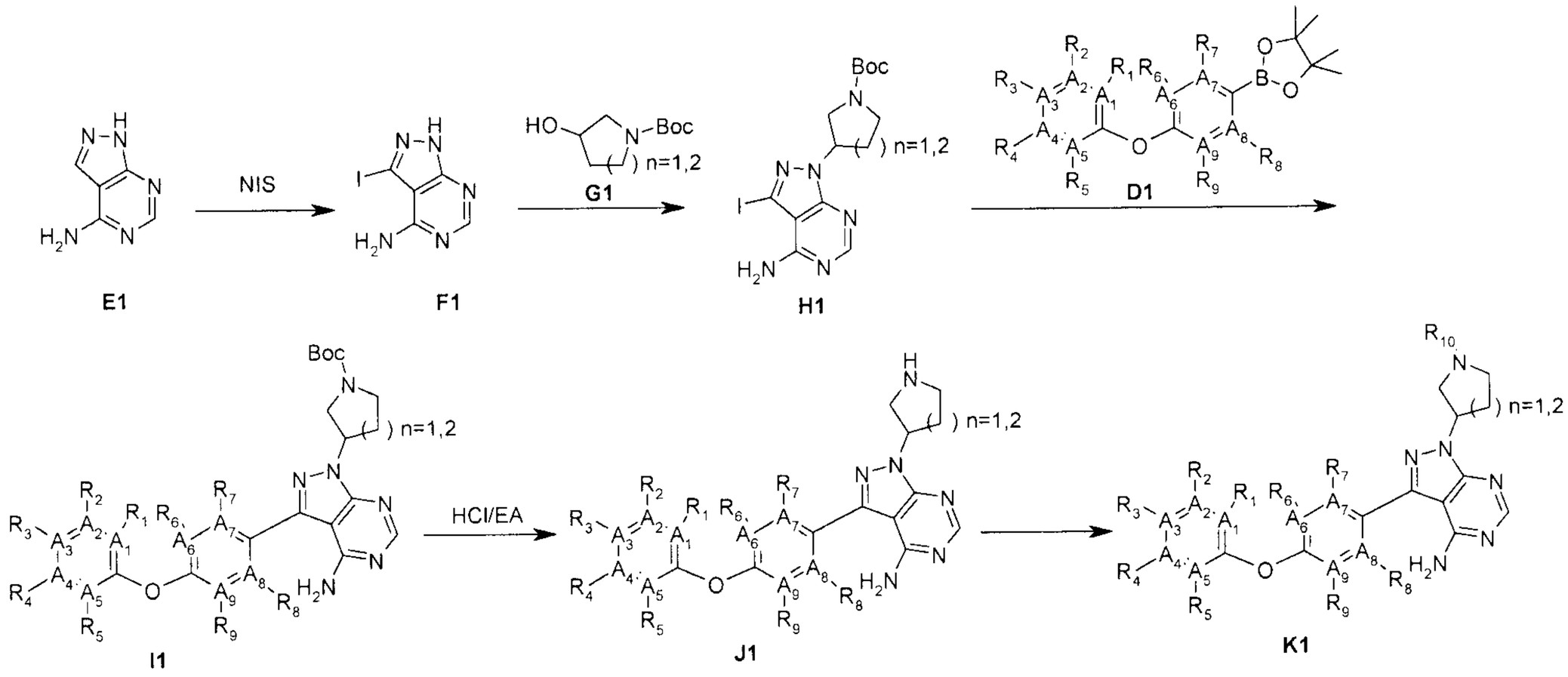


by-product was formed

Scheme 3 was designed based on the literature reported methods: 3- fluoro-4-bromo - phenol reacted with bis(pinacolato)diboron in the presence of a suitable catalyst (e.g., $Pd_2(dba)_3$) and a suitable ligand (e.g., X-phos) and gave the corresponding borate. The resulting borate reacted with a substituted 3-iodo-1H-pyrazolo[3,4-d] pyrimidin-4-amine in the presence of a suitable catalyst (e.g., Pd-118) by Suzuki reaction to afford substituted 3-fluorophenol, which reacted with 3-fluoro-bromobenzene (or 2-fluoro-bromobenzene) under a suitable condition to generate the target compound. NMR, LCMS and biological activity data demonstrate that the resulting compound is amino-alkylation product, rather than the target oxyalkylated product.

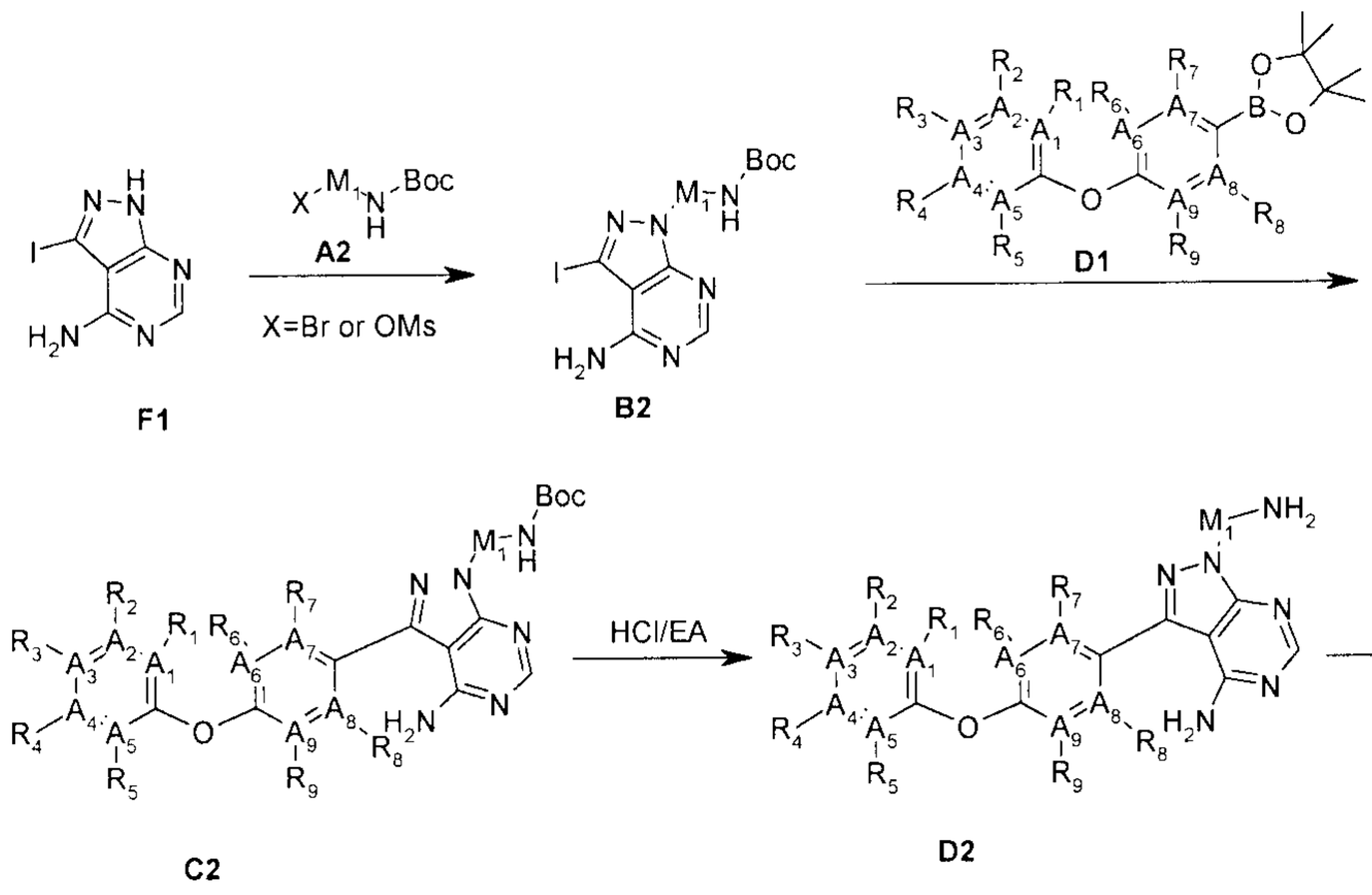
Scheme 4





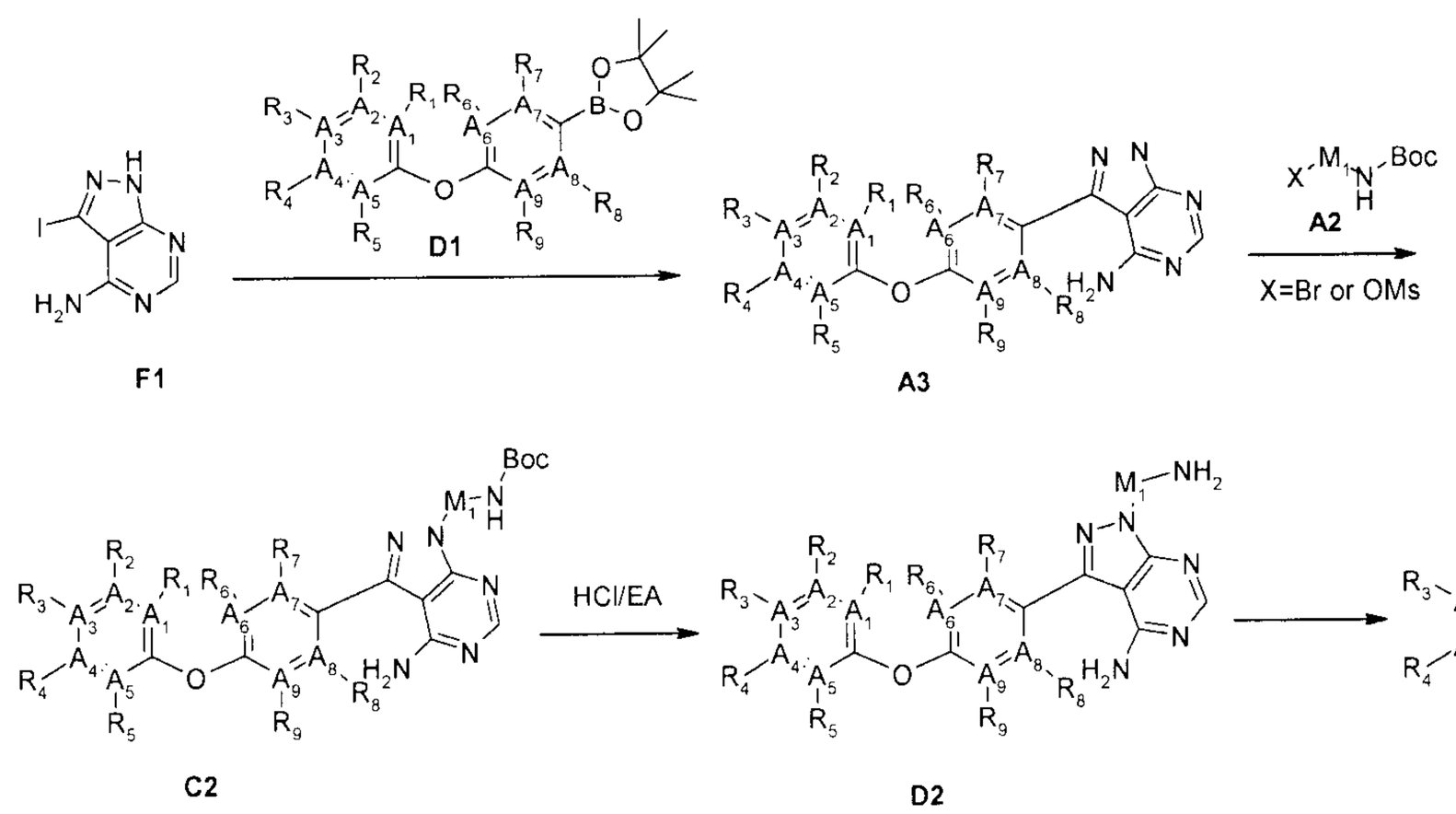
Fluoro-substituted starting material A1 reacted with substituted phenol B1 to generate intermediate C1 in the presence of base, e.g., potassium carbonate, in a suitable solvent, e.g., DMF. Intermediate C1 reacted with bis(pinacolato)diboron to give intermediate D1 in the presence of a suitable base, e.g., potassium acetate, and suitable solvent, e.g., 1,4-dioxane, under the effect of a suitable catalyst, e.g., [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium. 1H-pyrazolo[3,4-d]pyrimidin-4-amine reacted with NIS to obtain intermediate F1, then Mitsunobu reaction was carried out between intermediate F1 and alcohol G1 in a suitable condition to form intermediate H1. Intermediate H1 reacted with borate D1 to provide intermediate I1 in the presence of a suitable base, e.g., potassium phosphate, in a suitable solvent, e.g., 1,4-dioxane, under the effect of a suitable catalyst, e.g., Pd-118. In an acidic condition, the Boc group of intermediate I1 was removed to give amine J1, which was reacted with an electrophilic reagent to form product K1.

Scheme 5



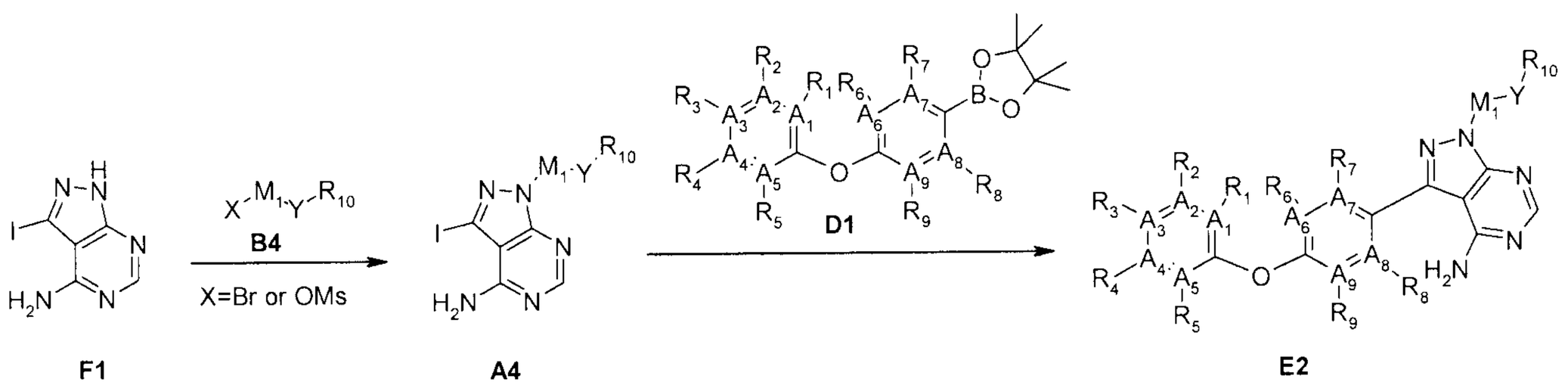
Intermediate F1 and Boc-protected bromo compound A2 (or mesylate) reacted to give intermediate B2 in the presence of a suitable base(e.g. potassium carbonate or cesium carbonate) in a suitable solvent (e.g.,DMF). Intermediate B2 then reacted with heterocyclic borate D1 to give intermediate C2 via Suzuki cross coupling reaction under the effect of a suitable catalyst (e.g., $Pd(PPh_3)_4$) in the presence of a suitable base (e.g., sodium carbonate) in a suitable solvent (e.g., 1,4-dioxane and H_2O). The Boc group can be removed from intermediate C2 to give amine D2 under acidic condition, and amine D2 can be reacted with an electrophilic reagent to obtain product E2.

Scheme 6



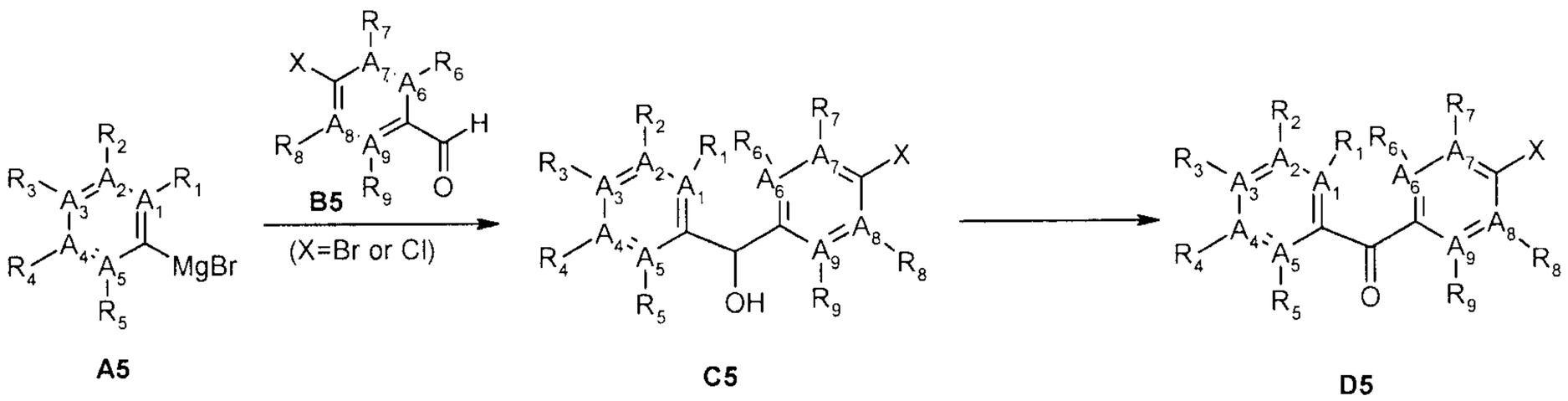
Suzuki cross coupling reaction can be carried out between Intermediate F1 and heterocyclic borate D1 to give intermediate A3 under the effect of a suitable catalyst (e.g., $Pd(PPh_3)_4$) in the presence of a suitable base (e.g., sodium carbonate) in a suitable solvent (e.g., 1,4-dioxane and H_2O). Intermediate F1 reacted with Boc-protected bromo compound A2 (or mesylate) to give intermediate C2 in the presence of a suitable base (e.g., sodium carbonate or cesium carbonate) in a suitable solvent (e.g., DMF). The Boc group can be removed from intermediate C2 to give amine D2 under acidic condition, which was reacted with an electrophilic reagent to obtain product E2.

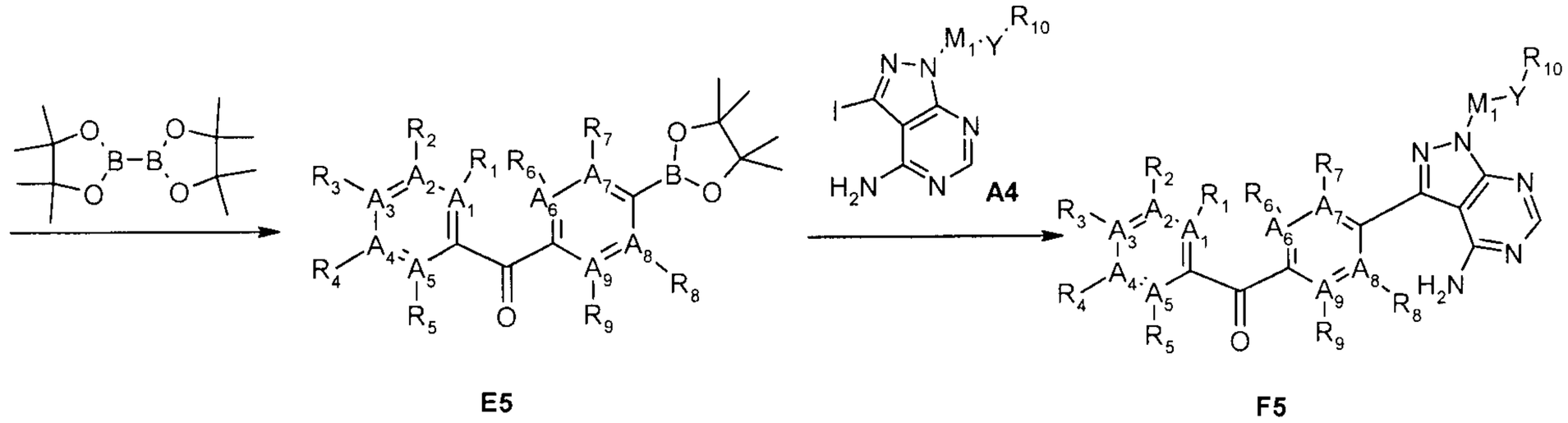
Scheme 7



Intermediate F1 reacted with Boc-protected bromo compound B4 (or mesylate) to give intermediate A4 in presence of a suitable base (e.g., potassium carbonate or cesium carbonate) in a suitable solvent (e.g., DMF). Suzuki cross coupling reaction can be carried out between Intermediate A4 and heterocyclic borate D1 to give product E2 in a suitable solvent (e.g., 1,4-dioxane and H_2O),in the presence fo a suitable base (e.g., sodium carbonate) under the effect of a suitable catalyst (e.g., $Pd(PPh_3)_4$).

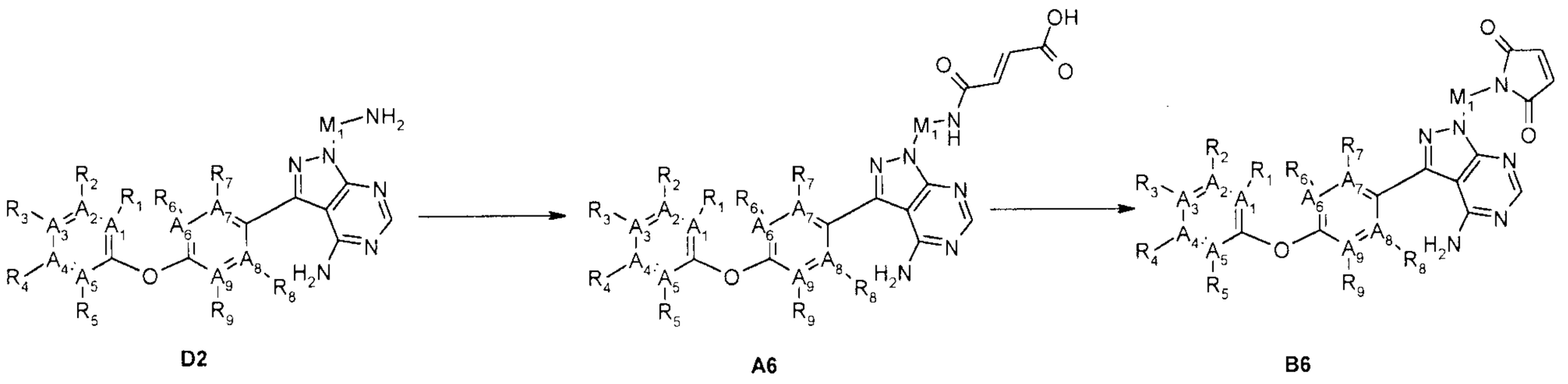
Scheme 8





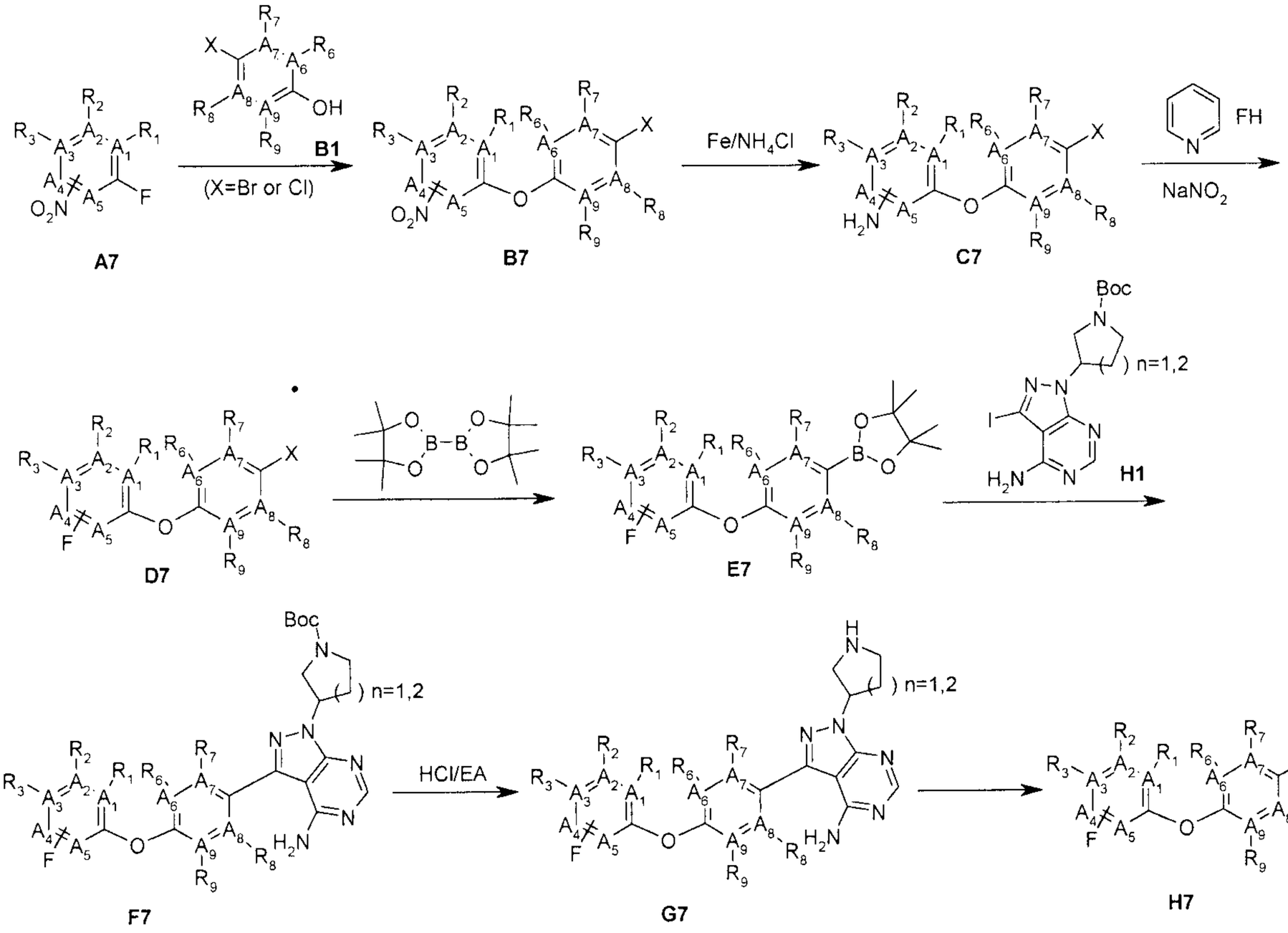
Starting material Grinard reagent A5 reacted with bromo (or chloro) aryl aldehyde to give intermediate C5 in a suitable solvent (e.g., tetrahydrofuran), which was then oxided to ketone D5 under the effect of a suitable oxidation reagents (e.g., tetrapropylammonium perruthenate and N-methyl morpholine oxide) in a suitable solvent (e.g., dichloromethane). Intermediate D5 then reacted with bis(pinacolato)diboron to give intermediate E5 under the effect of a suitable catalyst (e.g., [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)) in the presence of a suitable base (e.g., potassium acetate) in a suitable solvent (e.g., 1,4-dioxane). Suzuki cross coupling reaction was carried out between Intermediate A4 and heterocyclic borate E5 to give product F5 under the effect of a suitable catalyst (e.g., $Pd(PPh_3)_4$) in the presence of a suitable base (e.g., sodium carbonate) in a suitable solvent (e.g., 1,4-dioxane and H_2O).

Scheme 9



Compound D2 reacted with maleic anhydride to give intermediate A6 in the presence of a suitable base (e.g., triethylamine) in a suitable solvent (e.g., dichloromethane), which was then cyclized to form B6 at suitable temperature (e.g., 100 °C-110 °C) with polyphosphoric acid.

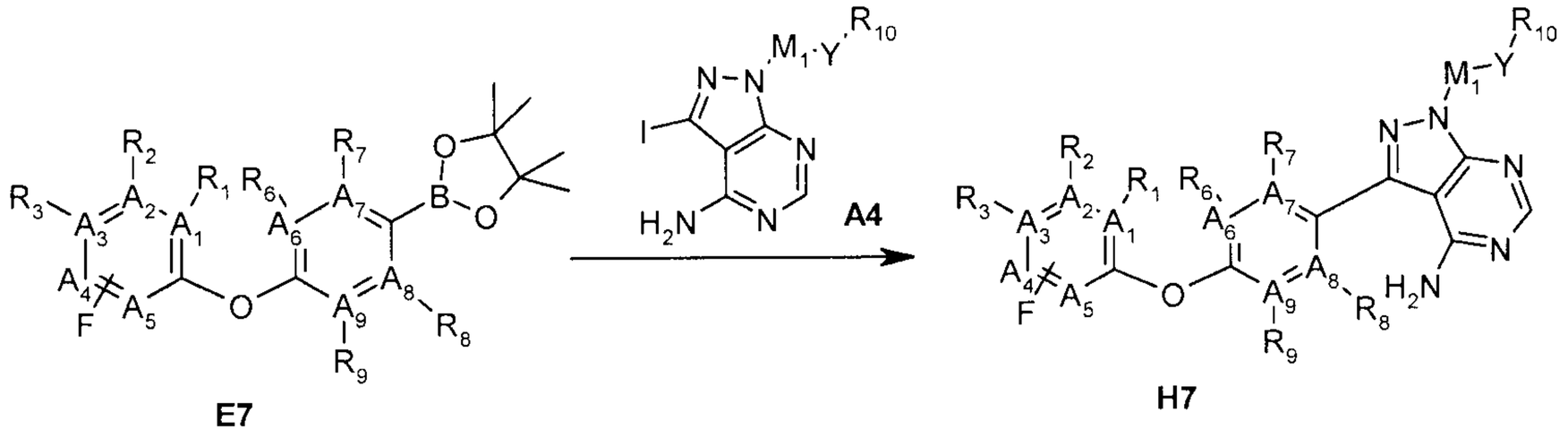
Scheme 10



Br-susbstituted starting material A7 reacted with substituted phenol B1 to give intermediate B7 in the presence of a base, e.g., potassium carbonate in a suitable solvent, e.g., DMF. Nitro compound B7 was reduced to amine C7 with appropriate reducing reagents, e.g., iron powder and ammonium chloride in appropriate solvents, e.g., ethanol and water, followed by treatment with sodium nitrite and hydrogen fluoride pyridine to generate F-substituted intermediate D7. Intermediate D7 then reacted with bis(pinacolato) diboron to give intermediate E7 under the effect of a suitable catalyst (e.g., [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II)) in the presence of a suitable base condition, e.g., potassium acetate, in a suitable solvent, e.g., 1,4-dioxane. Intermediate G1 reacted with borate E7 to give intermediate F7 under the effect of a suitable catalyst (e.g. Pd-

118) in the presence of a suitable base, e.g., potassium phosphate, in a suitable solvent, e.g., 1,4-dioxane. The Boc group can be removed from intermediate F7 to give amine G7 under acidic condition, which reacted with an electrophilic reagent to obtain product H7.

Scheme 11



Suzuki cross coupling reaction was carried out between Intermediate A4 and heterocyclic borate E7 to give product A8 under the effect of a suitable catalyst (e.g., $Pd(PPh_3)_4$) in the presence of a suitable base (e.g., sodium carbonate) in a suitable solvent (e.g., 1,4-dioxane and H_2O).

Activity data of the compounds of examples of the present invention in inhibiting BTK

Example	BTK IC50 (μM)	Example	BTK IC50 (μM)	Example	BTK IC50 (μM)
1	0.066	2	0.005	3	0.010
4	0.002	5	0.002	6	0.138
7	0.73	8	0.002	9	0.083
10	1.970	11	0.0008	12	0.002
13	0.001	14	0.009	15	0.003
16	0.003	17	0.004	18	0.003
19	0.067	20	0.004	21	0.005
22	0.050	23	0.003	24	1.020

25	0.017	26	0.034	27	0.223
28	0.007	29	0.026	30	0.024
31	0.015	32	7.222	33	0.002
34	0.023	35	0.081	36	0.593
37	0.099	38	0.379	39	0.022
40	1.640	41	0.017	42	0.038
43	0.131	44	0.374	45	0.0005
46	0.021	47	0.006	48	0.964
49	0.509	50	0.087	51	0.527
52	0.060	53	1.653	54	1.617
55	1.740	56	0.365	57	0.692
58	0.148	59	0.174	60	0.576
61	0.0008	62	0.207	63	0.454
64	0.006	65	0.119	66	0.729
67	0.586	68	0.279	69	0.052
70	0.017	71	0.006	72	0.001
73	0.006	74	0.003	75	0.003
76	0.027	77	0.201	78	1.900
79	1.658	80	1.278	81	2.237
82	0.025	83	0.075	84	0.016
85	0.017	86	0.008	87	0.008
88	0.011	89	0.025	90	0.015

91	0.003	92	2.398	93	2.648
94	0.001	95	0.005	96	0.013
97	0.006	98	0.002	99	0.002
100	0.002	101	0.525	102	1.599
103	0.546	104	0.107	105	0.589
106	0.003	107	0.101	108	0.436
109	1.282	110	5.272	111	0.043
112	0.107	113	0.207	114	0.050
115	0.013	116	0.001	117	0.712
118	0.057	119	0.083		

The present invention provides the compound of Formulae (I) to (XIII), an enantiomer thereof, a diastereomer thereof, or a pharmaceutically acceptable salt thereof.

The compound of Formulae (I) (XIII) comprises one or more stable isotopes or radio isotopes, wherein the isotopes include, but are not limited to, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, and so on.

The present invention first introduces ^{2}H, isotope of ^{1}H, into BTK inhibitor.

^{1}H, which is at the end of the double bond of the vinyl group in the compound of Formulae (I) to (XIII), can be replaced with ^{2}H to reduce the drug inactivation caused by the oxidation/reduction of double bond.

The present invention provides synthestic methods of the compound of Formulae (I) to (XIII), an enantiomer thereof and a diastereomer thereof.

The present invention provides the methods for regulating the activity of BTK, and treating or inhibiting diseases associated with the activity of BTK. It was confirmed that the compounds of the present invention inhibit the activity of BTK. The present invention provides a compound of Formula (I) to (XIII) as a pharmaceutical active component for the treatment and/or

prevention the following diseases, wherein these diseases caused by unfavorable cytokine signaling include, but are not limited to:

(1) Autoimmune diseases, such as chronic lymphocytic thyroiditis, hyperthyroidism, insulin-dependent diabetes mellitus, myasthenia gravis, chronic ulcerative colitis, pernicious anemia associated with chronic atrophic gastritis, goodpasture syndrome, pemphigus vulgaris, pemphigoid, primary biliary cirrhosis, multiple cerebrospinal sclerosis, acute idiopathic neuritis, systemic lupus erythematosus, rheumatoid arthritis, psoriasis, systemic vasculitis, scleroderma, pemphigus, mixed connective tissue disease, autoimmune hemolytic anemia, autoimmune thyroid disease, ulcerative colitis, and the like.

(2) Hypersensitivity diseases, such as serum sickness, asthma, allergic rhinitis, drug allergy, and the like.

(3) Inflammatory diseases, such as keratitis, rhinitis, stomatitis, mumps, pharyngitis, tonsillitis, tracheitis, bronchitis, pneumonia, myocarditis, gastritis, gastroenteritis, cholecystitis, appendicitis, and the like.

(4) Cancers include, but are not limited to various B-cell malignancies (including small lymphocytic lymphoma (SLL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), multiple myeloma and mantle cell lymphoma (MCL)) and other diseases benefiting from inhibition of BTK activity.

Other diseases benefiting from inhibition of BTK activity, include, but are not limited to: brain tumors, bladder cancer, stomach cancer, ovarian cancer, pancreatic cancer, breast cancer, head and neck cancer, cervical cancer, endometrial cancer, colorectal cancer, kidney cancer, esophageal cancer, prostate cancer, thyroid cancer, bone cancer, skin cancer, colon cancer, female reproductive tract tumors, lymphomas, multiple myeloma (MM), testicular cancer, and the like.

The method herein includes administering to a patient effective amount of the compound according to Claims 1 to 12.

According to standard pharmaceutical practice, the compounds (BTK inhibitors) of the present invention can be used alone in a combination with one or more additional drugs, wherin the pharmaceutical formulation comprising BTK inhibitors and the additional drugs may have the same or different administration routes, and the same or different administration

time. The additional drugs herein include (but are not limited to) tyrosine kinase inhibitors (e.g., Axitinib, Dasatinib, Icotinib), topoisomerase inhibitors (e.g., topotecan), protein kinase C inhibitors (e.g., AEB-071), sphingosine-1-phosphate receptor agonist (e.g., fingolimod, KRP-203, and the like), anti-T cell immunoglobulin (e.g., AtGam), anti-IL-2 receptor antibody (e.g., daclizumab), amides (CTX), ifosfamide (IFO), adriamycin (ADM), daunorubicin (DNR), vincristine (VCR), vinblastine (VBL), etoposide (VP16), vermeer (Vumon), carboplatin (CBP) and methotrexate (MTX) cyclosporin A, tacrolimus, sirolimus, everolimus, azathioprine, brequinar, leflunomide, LEA-29Y, anti-CD3 antibody (e.g. 0KT3), aspirin, B7-CD28 blocking molecules (e.g. belatacept, abatacept, and the like), CD40-CD154 blocking molecules (anti-CD40 antibodies, and the like), acetaminophen, ibuprofen, naproxen, piroxicam, and antiinflammatory steroids (e.g. prednisolone or dexamethasone)

Carriers, excipients and other additives commonly used for pharmaceutical preparations may be used to prepare pharmaceutical compositions comprising one or two or more compounds of formulae (I) to (XIII) or pharmaceutically acceptable salts thereof as active components.

The administration forms may be oral dosage forms, such as tablets, pills, capsules, granules, powders, emulsions, syrups, suspensions, liquid preparations, or non-oral dosage forms, such as intravenous injection or intramuscular injection, suppository, subcutaneous agent, transdermal agent, nasal agent, inhalation. Symptoms, age, sex, and the like of each patient should be considered in order to properly determine the dose of a compound. Generally, in the case of oral administration, daily dose for an adult patient of the compound is about 0.001 mg/kg to 100 mg/kg, a single dose or divided into 2 to 4 times daily. In the case of intravenous administration according to the patient symptoms, generally, daily dose for an adult patient is 0.0001 mg/kg to 10 mg/kg, once to more times daily. Further, in the case of using the inhalant administration, generally, daily dose for an adult patient is 0. 0001 mg/kg to l mg/kg, once to more times daily.

In the present invention, solid compositions for oral administration may be tablets, powders, granules and the like. In such solid compositions, one or more active substances and at least one inert excipient (e.g., lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, poly vinyl pyrrolidone, magnesium aluminum silicate, and

the like) were mixed. According to a conventional method, the composition may contain inert additives such as lubricants (e.g. magnesium stearate), disintegrating agents (e.g., sodium carboxymethyl starch) and dissolution aids. If necessary, tablets or pills may be coated with sugar coating or a gastric or enteric coating agent.

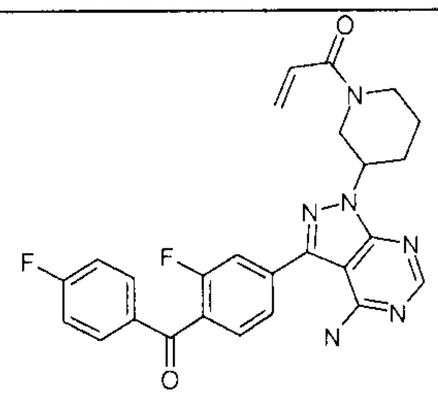
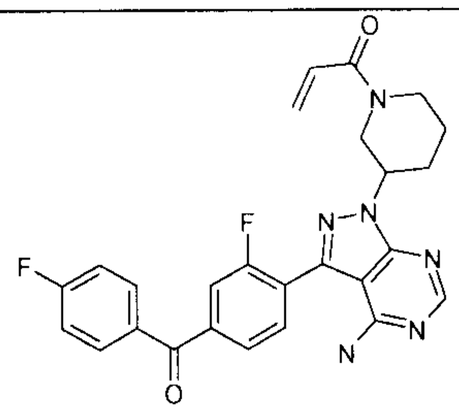
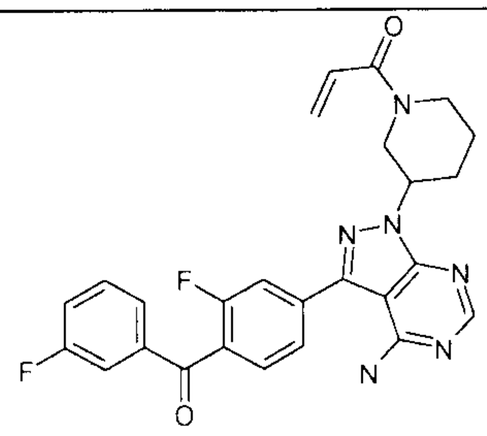
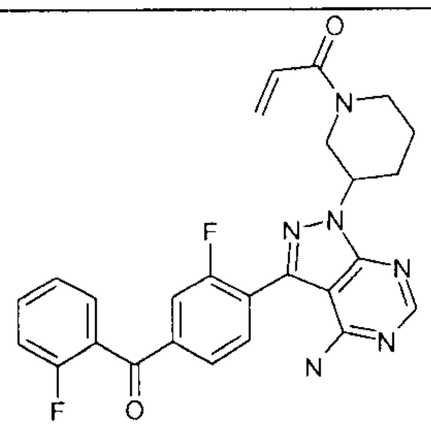
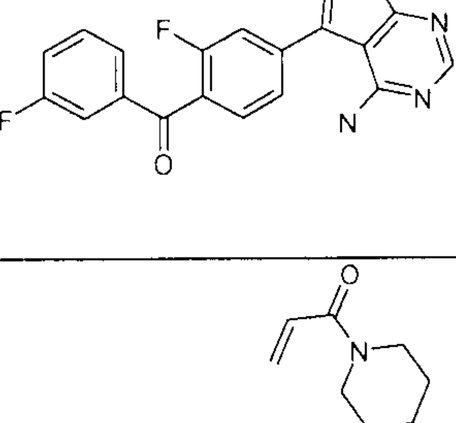
The liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs, and commenly used inert diluent (e.g., purified water, ethanol). In addition to the inert diluent, the composition may also contain additives such as solubilizing agents, wetting agents, suspending agents, and sweetener, flavoring agents, fragrance agents and preservatives.

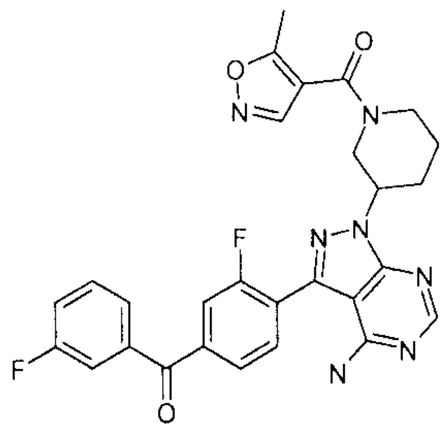
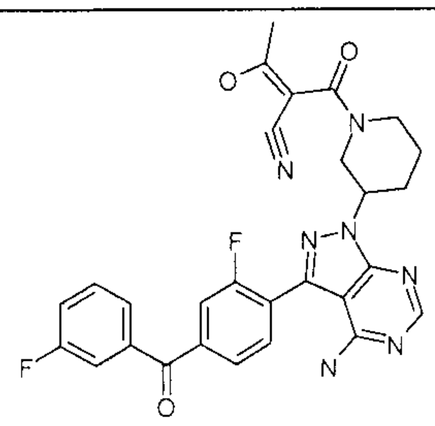
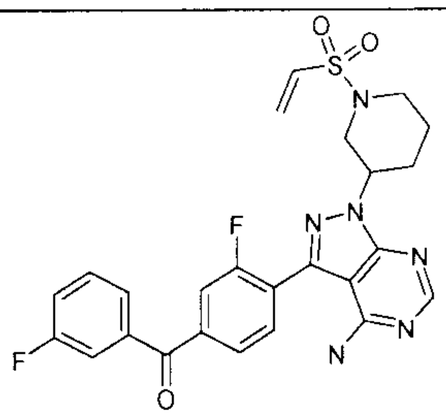
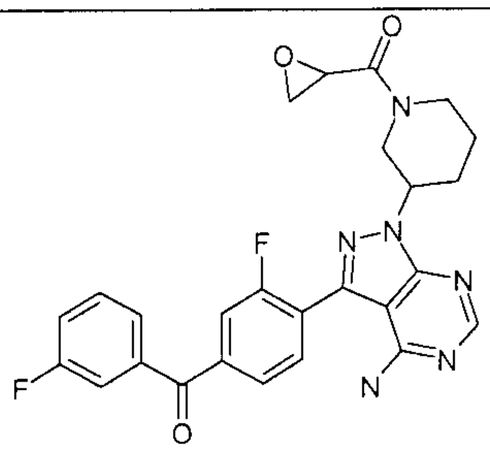
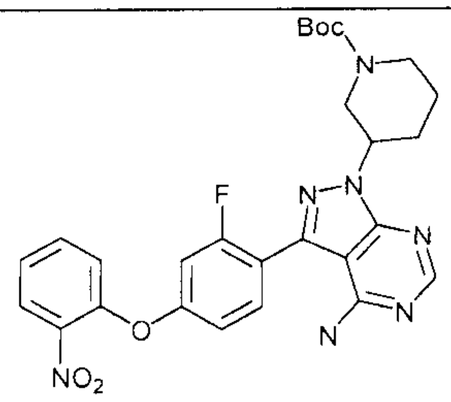
Injections for parenteral administration include sterile aqueous or non-aqueous liquid preparations, suspensions, and emulsions. Diluents for aqueous solution can comprise (for example) distilled water for injection and physiological saline. Diluents for non-aqueous solution can comprise (for example) propylene glycol, polyethylene glycol, vegetable oils (such as olive oil), alcohols (e.g. ethanol) and polysorbate 80. Such compositions may further comprise additives, such as isotonic agents, preservatives, wetting agents, emulsifying agents, dispersing agents, stabilizing agents, dissolving aids and the like. Methods, such as filtration through a bacteria retaining filter, adding bactericides or irradiation with light can be utilized to sterilize the composition. In addition, these compositions may be made sterile solid compositions, which can be dissolved or suspended with sterile water or a sterile solvent for injection prior to use.

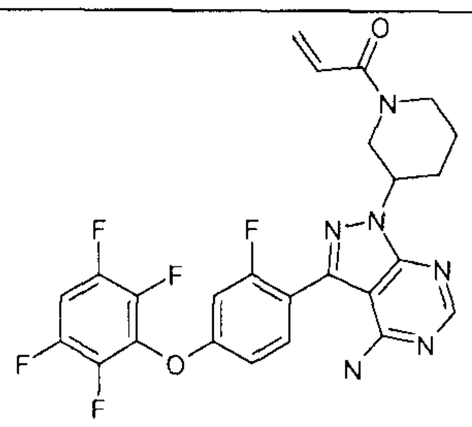
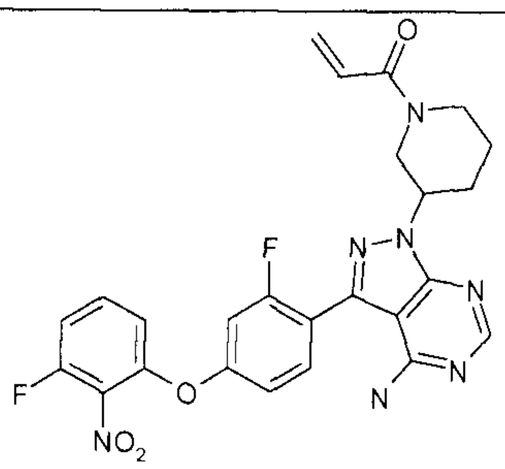
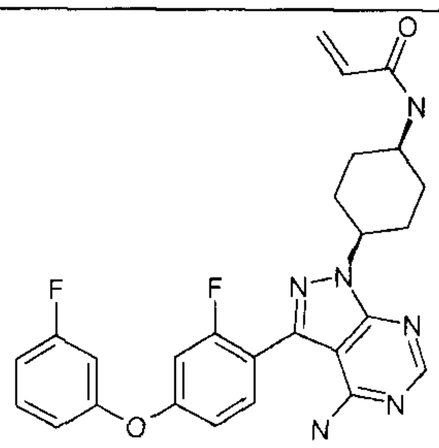
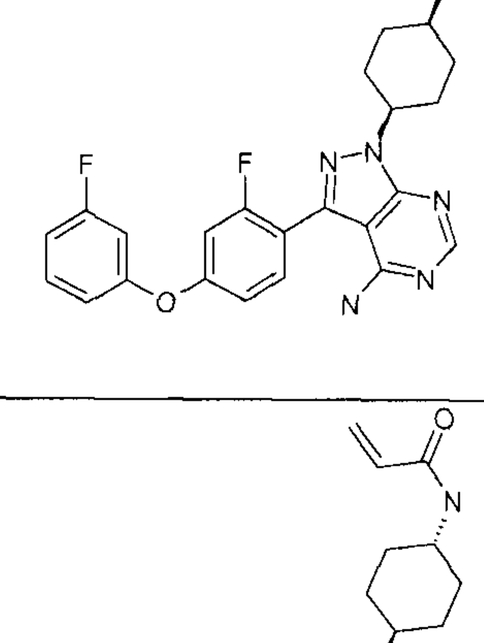
Transmucosal agents such as inhalations and nasal agents and the like, can be solid, liquid, or semi-solid state for use, and can be prepared in accordance with conventionally known methods. For example, an excipient may be added as needed (e.g., lactose and starch), pH adjusting agent, a preservative IJ, surfactants, lubricants IJ, stabilizing and thickening agents and the like. A suitable inhalation or insufflation device can be used for administration. For example, known devices, such as metered inhalation devices, and atomizers can be used, such that the compound alone or a formulated mixture powder of the compound is used to be administered. In addition, the compound may be combined with a pharmaceutically acceptable carrier, administered as a solution or suspension. The dry powder inhaler or the like may be used for a single dose or multiple doses, and dry powder

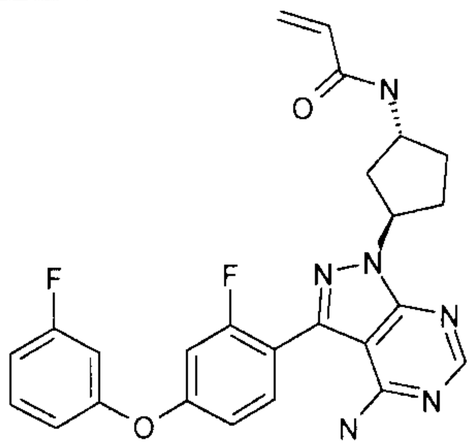
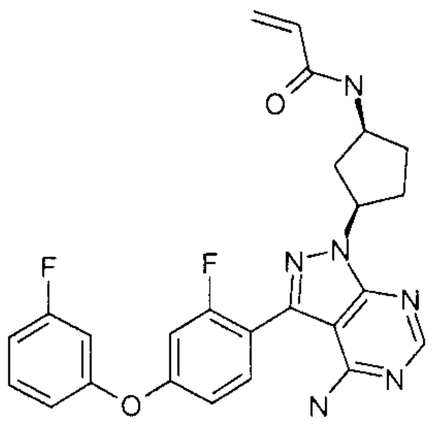
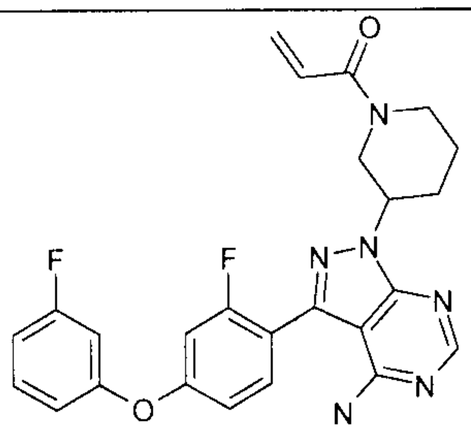
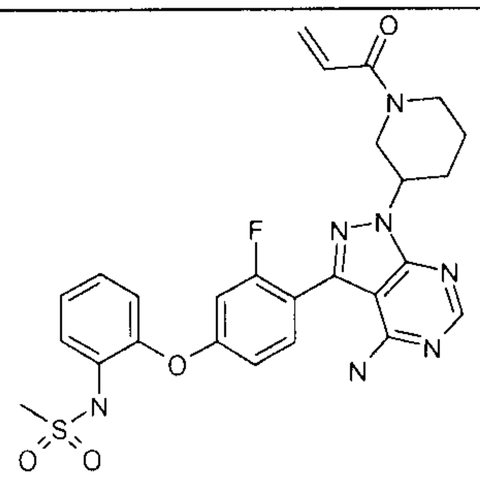
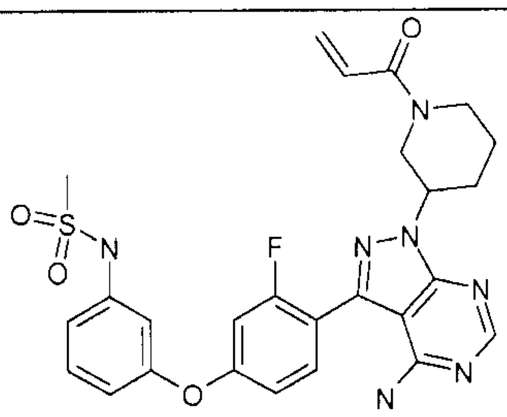
or a powder-containing capsule can used. Further, a pressurized aerosol spray can also be used for being administered by the use of a suitable propellant (e.g., chlorofluoroalkane, hydrofluoroalkane, or a suitable gas such as carbon dioxide).

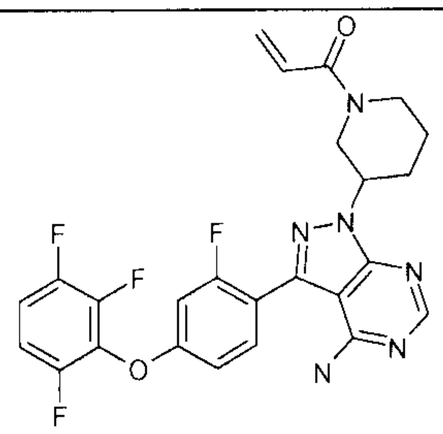
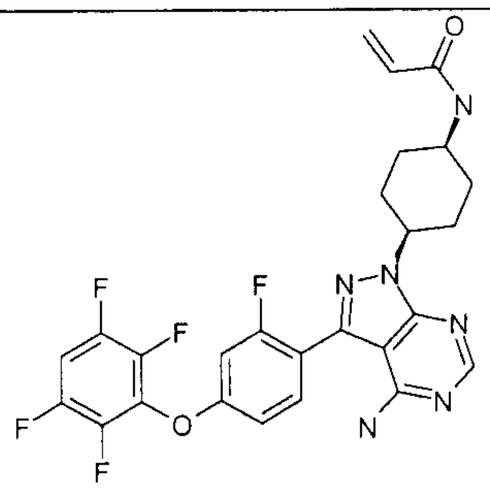
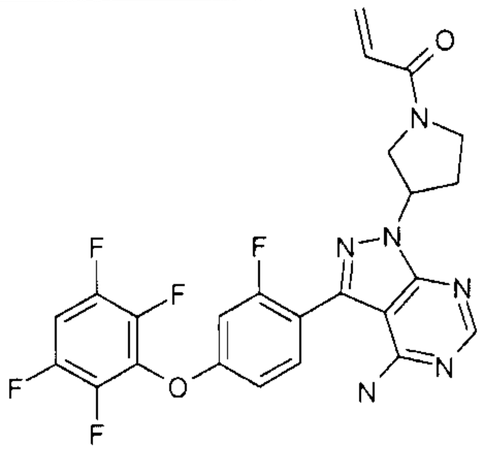
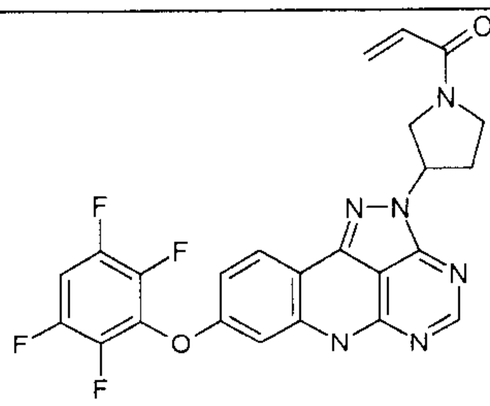
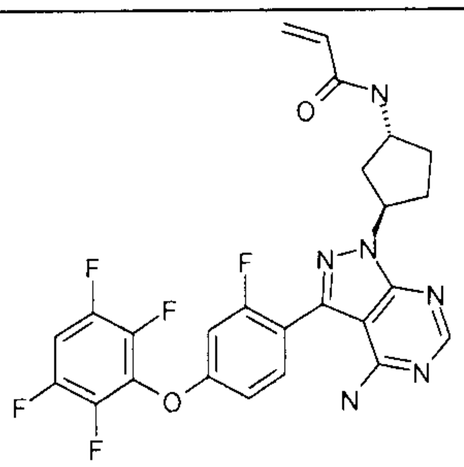
Compounds of BTK Inhibitors

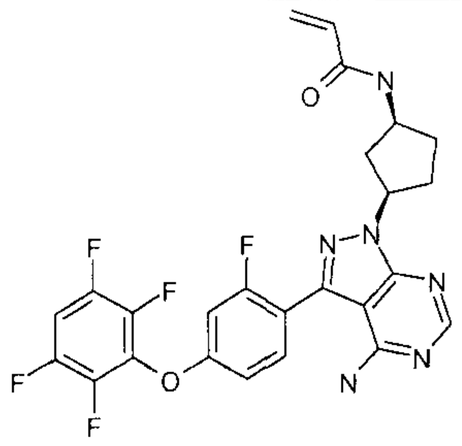
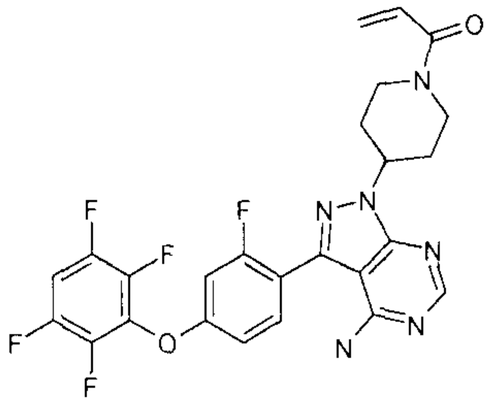
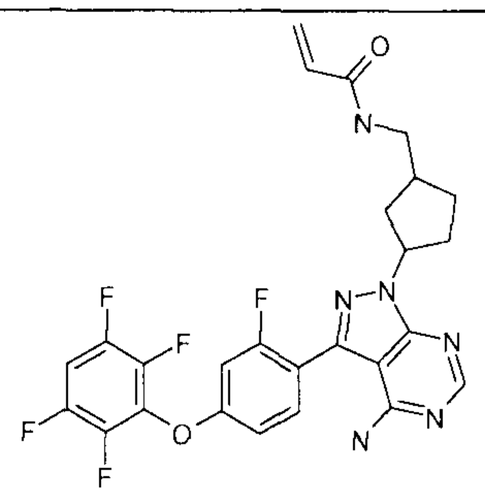
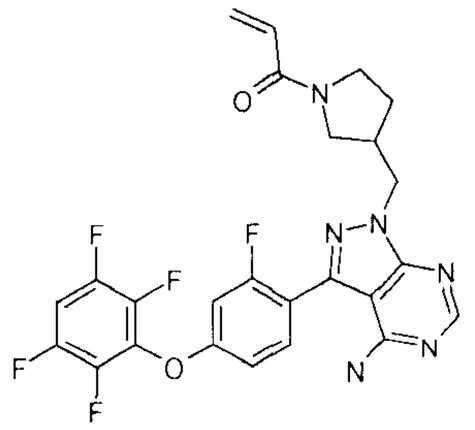
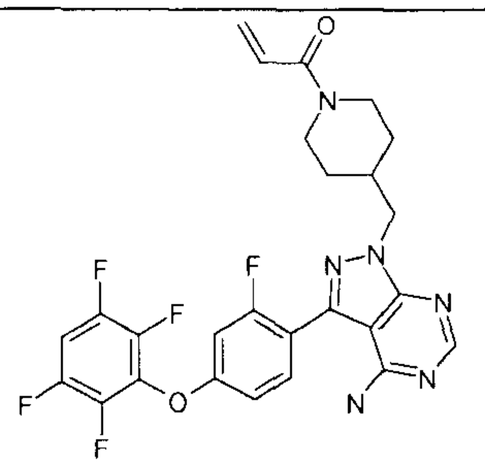
Example	Molecular structure	Name	M+1
1		1-(3-(4-amino-3-(3-fluoro-4-(4-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one	489
2		1-(3-(4-amino-3-(2-fluoro-4-(4-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one	489
3		1-(3-(4-amino-3-(3-fluoro-4-(3-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one	489
4		1-(3-(4-amino-3-(2-fluoro-4-(2-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one	489
5		1-(3-(4-amino-3-(2-fluoro-4-(3-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one	489

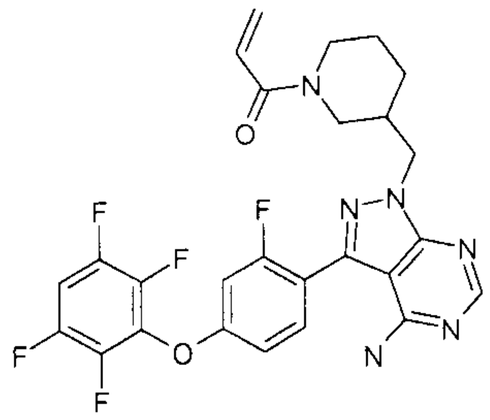
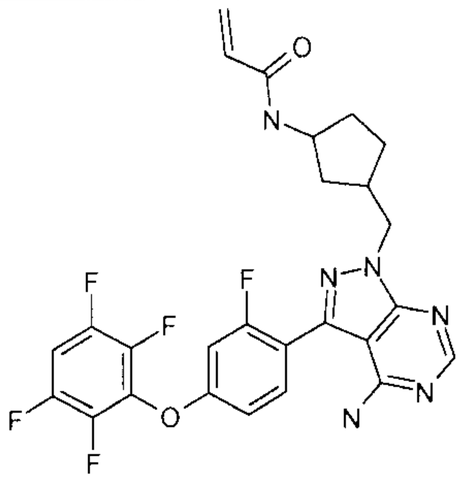
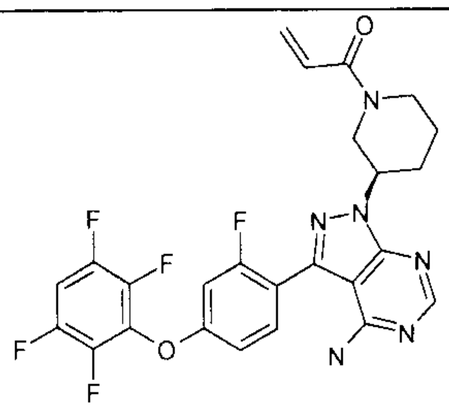
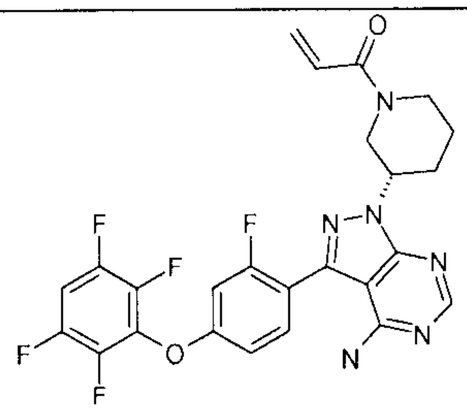
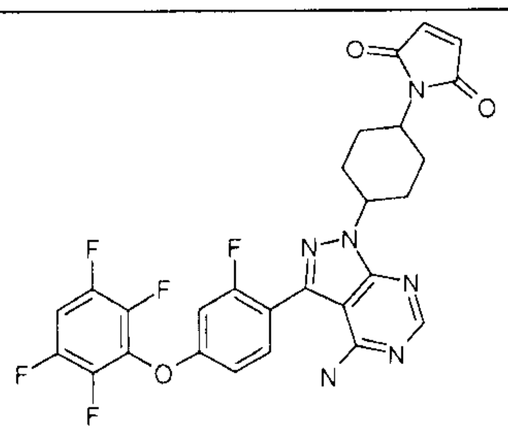
6		(3-(4-amino-3-(2-fluoro-4-(3-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)(5-methylisoxazol-4-yl)methanone	544
7		(E)-2-(3-(4-amino-3-(2-fluoro-4-(3-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-2-hydroxy-but-2-enenitrile	544
8		(4-(4-amino-1-(1-(vinylsulfonyl)piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenyl)(3-fluorophenyl)methanone	525
9		(3-(4-amino-3-(2-fluoro-4-(3-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)(oxiran-2-yl)methanone	505
10		tert-butyl 3-(4-amino-3-(2-fluoro-4-(2-nitrophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-formate	550

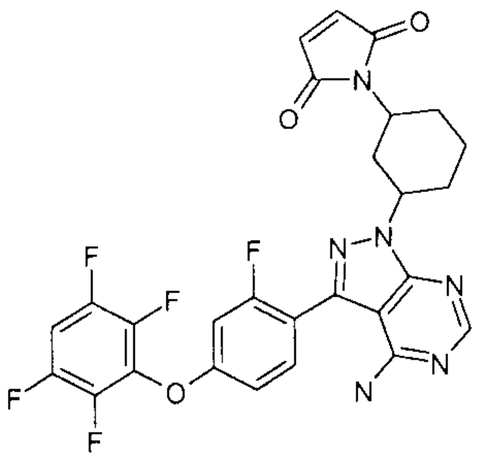
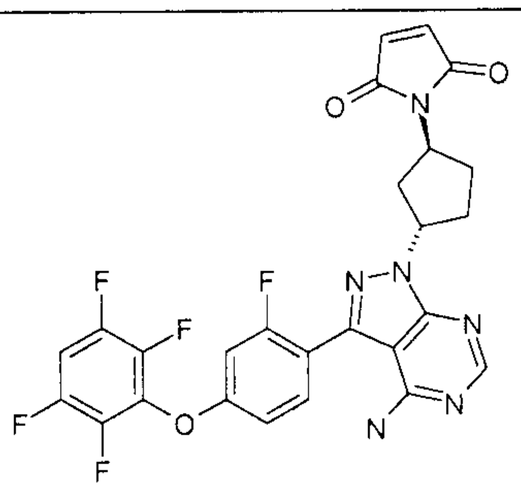
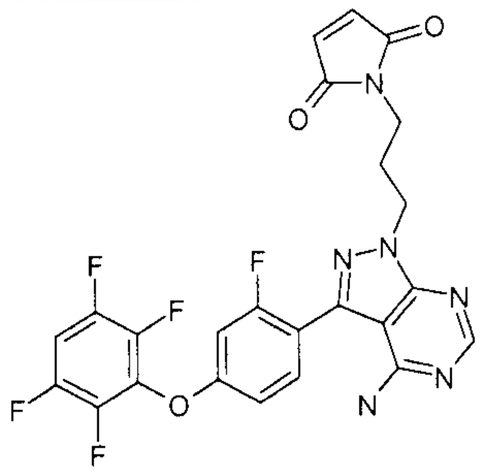
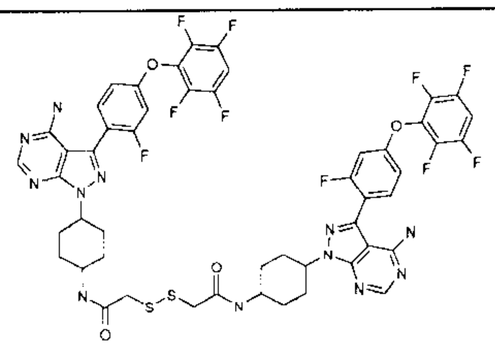
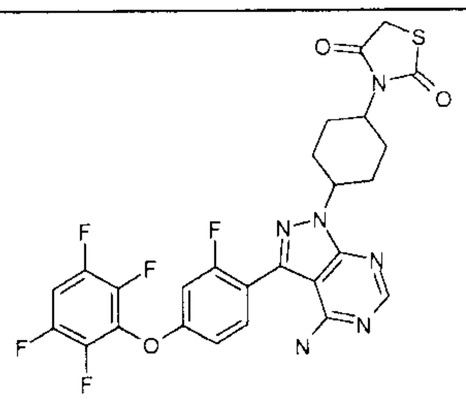
11		1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one	531
12		1-(3-(4-amino-3-(2-fluoro-4-(3-fluoro-2-nitrophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one	522
13		N-((1s,4s)-4-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)acrylamide	491
14		N-((1r,4r)-4-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)acrylamide	491
15		1-(3-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one	463

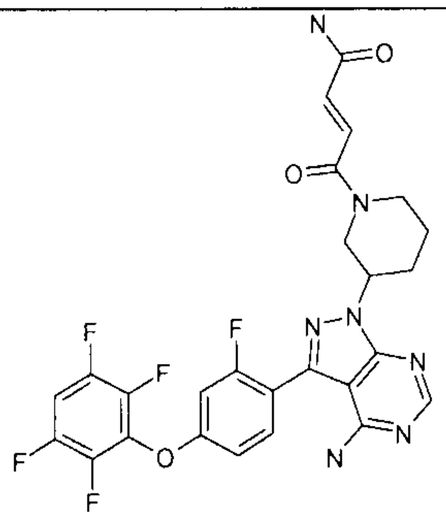
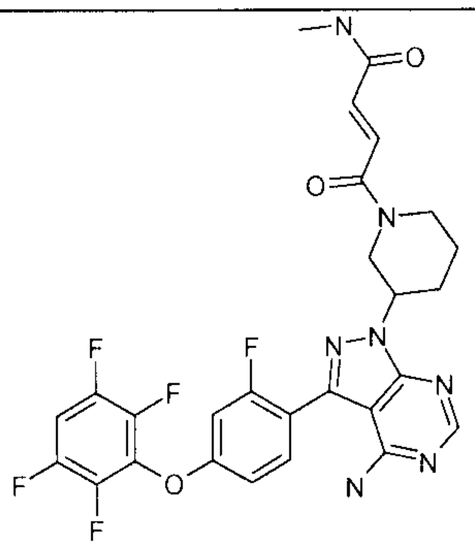
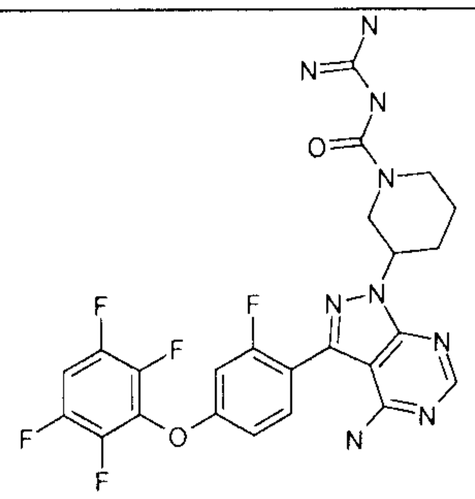
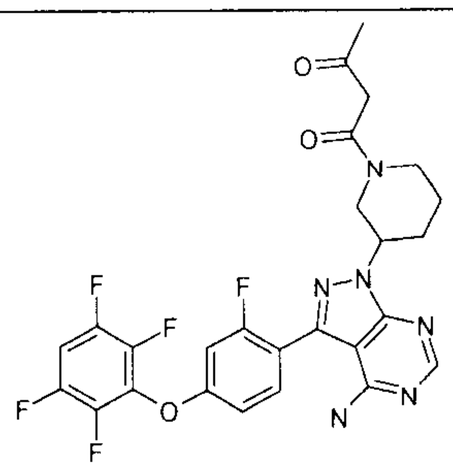
16		N-((1r,3r)-3-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentyl)acrylamide	476
17		N-((1s,3r)-3-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentyl)acrylamide	476
18		1-(3-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one	476
19		N-(2-(4-(1-(1-acryloylpiperidin-3-yl)-4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenoxy)phenyl)methanesulfonamide	552
20		N-(3-(4-(1-(1-acryloylpiperidin-3-yl)-4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenoxy)phenyl)methanesulfonamide	552

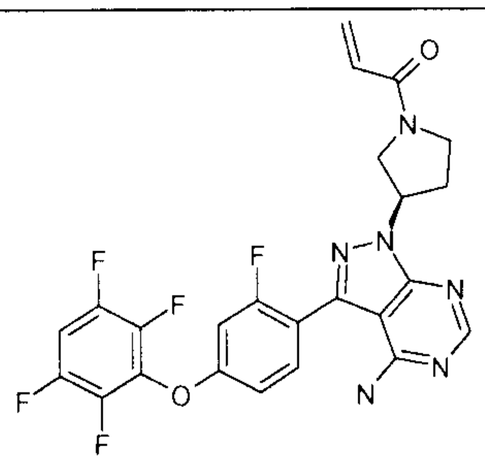
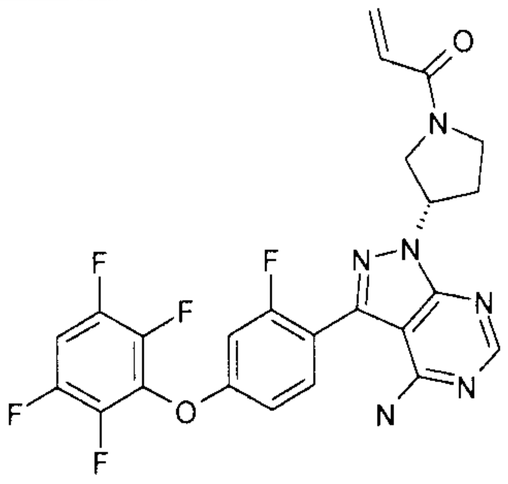
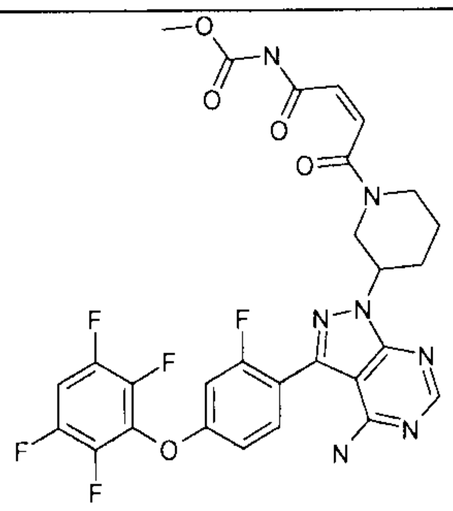
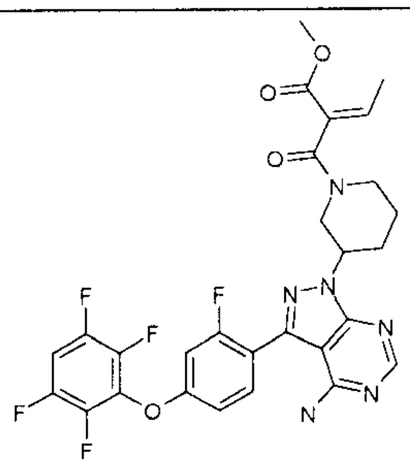
21		1-(3-(4-amino-3-(2-fluoro-4-(2,3,6-trifluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one	513
22		N-((1s,4s)-4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)acrylamide	545
23		1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one	517
24			497
25		N-((1r,3r)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentyl)acrylamide	531

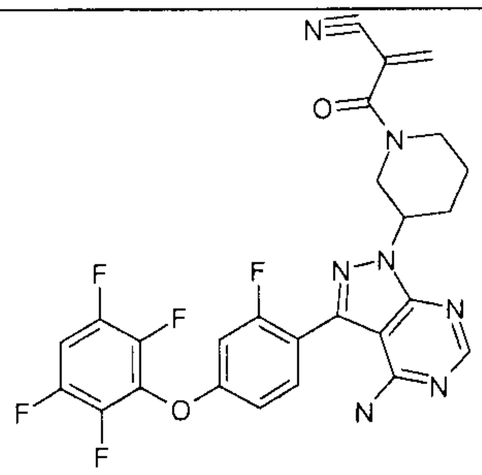
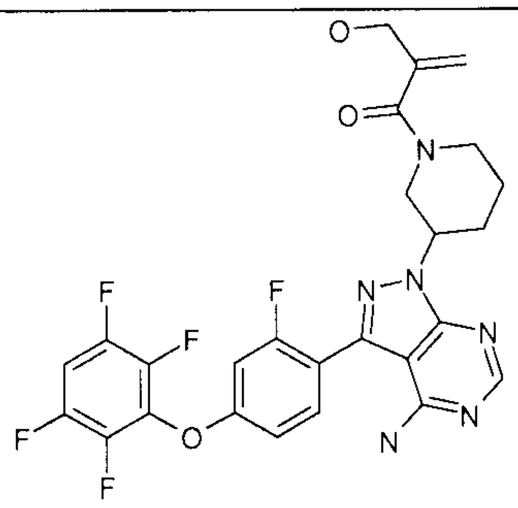
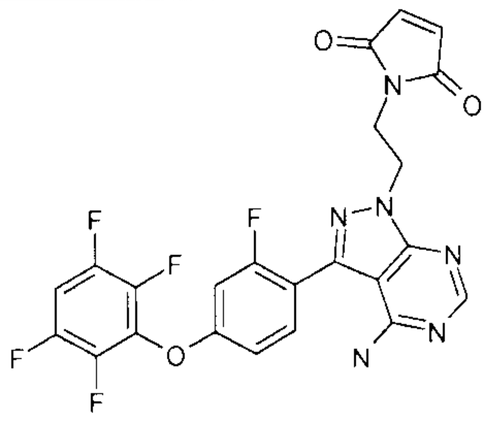
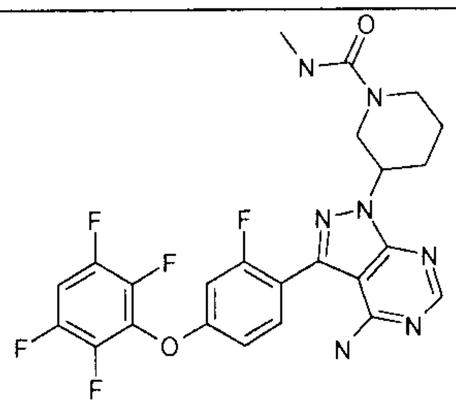
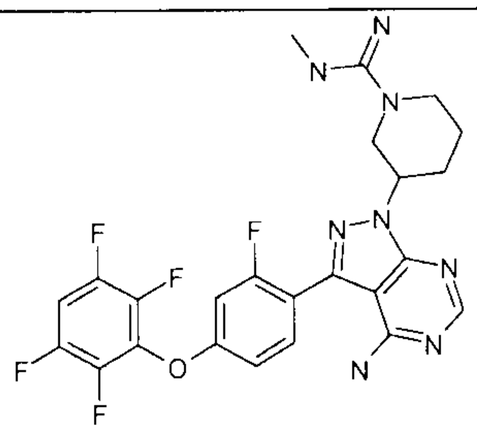
26		N-((1s,3r)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentyl)acrylamide	531
27		1-(4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one	531
28		N-((3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentyl)methyl)acrylamide	544
29		1-(3-((4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidin-1-yl)prop-2-en-1-one	531
30		1-(4-((4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)piperidin-1-yl)prop-2-en-1-one	545

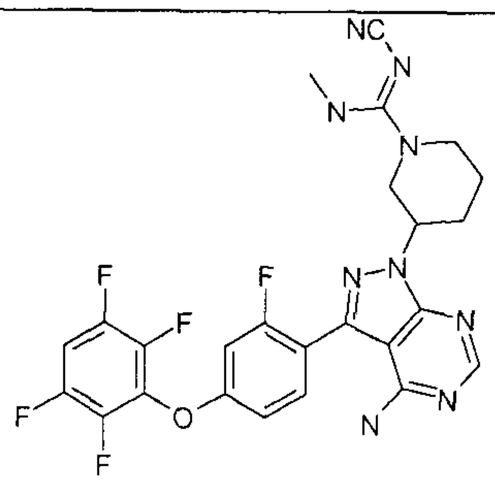
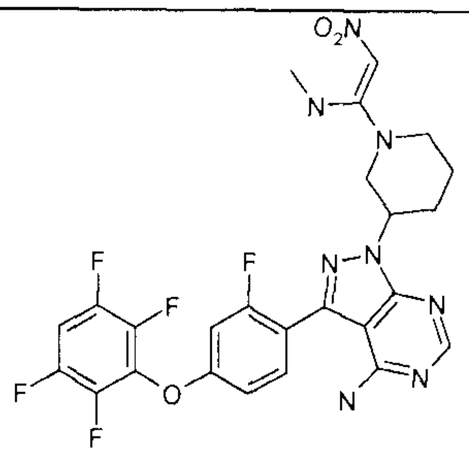
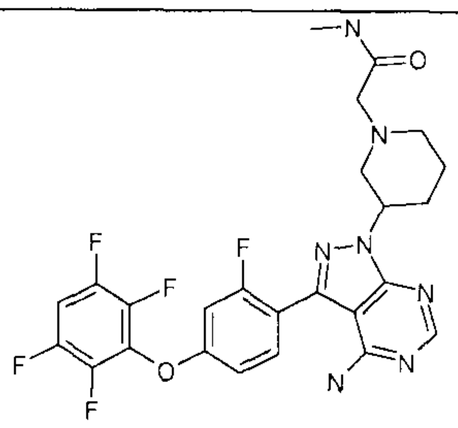
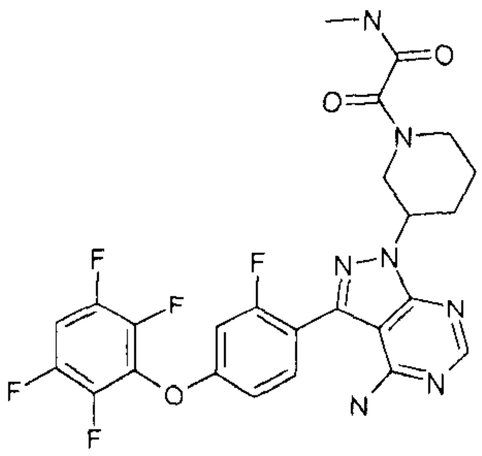
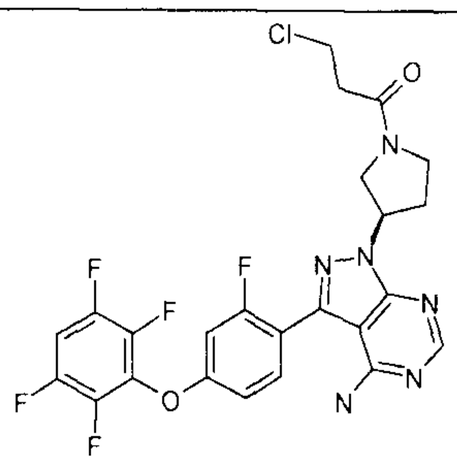
31		1-(3-((4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)piperidin-1-yl)prop-2-en-1-one	545
32		N-(3-((4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)cyclopentyl)acrylamide	545
33		1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one	531
34		1-((S)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one	531
35		1-(4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-1H-pyrrole-2,5-dione	571

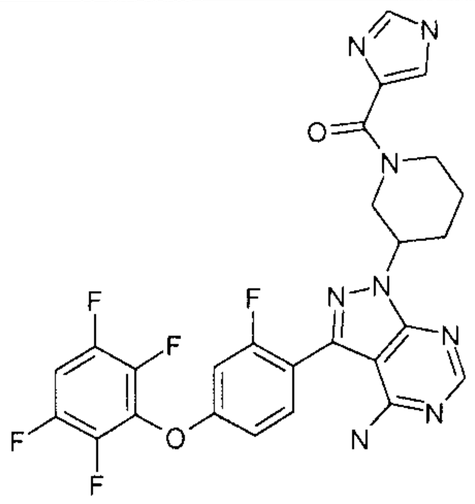
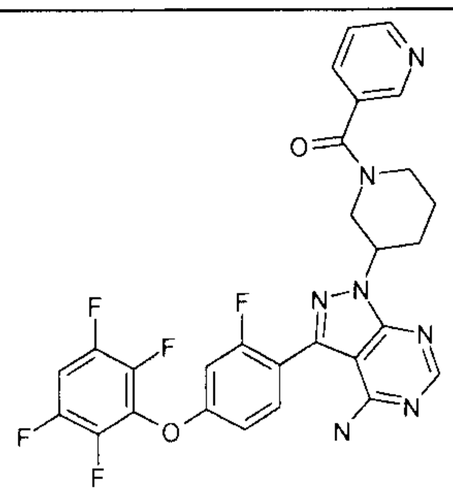
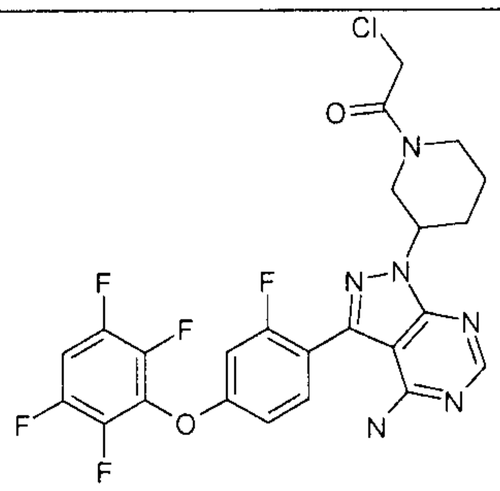
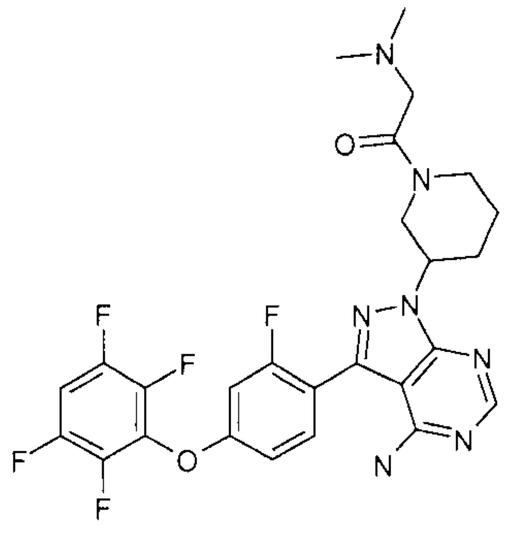
36		1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-1H-pyrrole-2,5-dione	571
37		1-((1S,3S)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentyl)-1H-pyrrole-2,5-dione	557
38		1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-1H-pyrrole-2,5-dione	531
39			1127
40		3-(4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)thiazolidine-2,4-dione	591

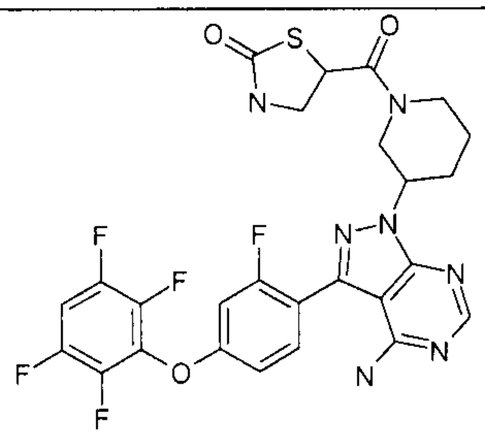
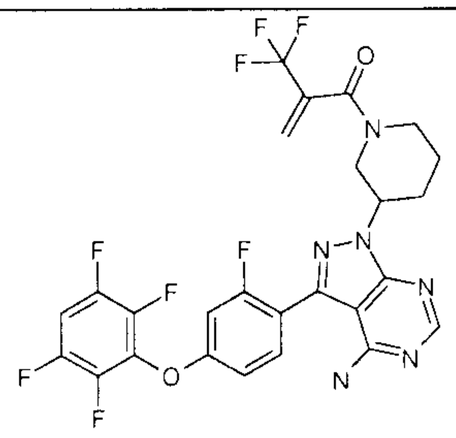
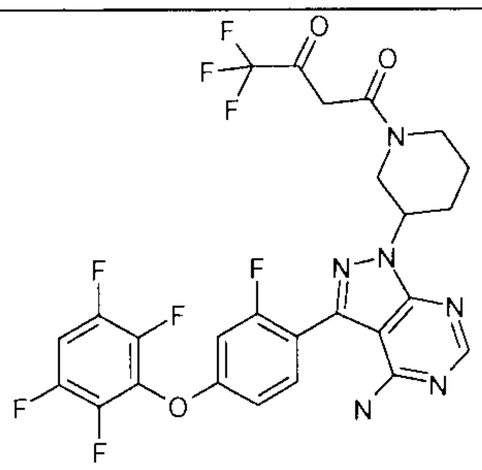
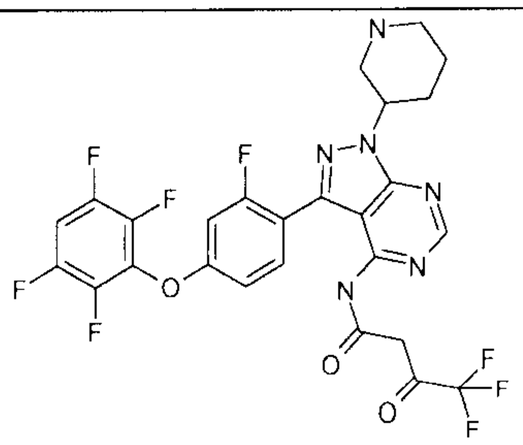
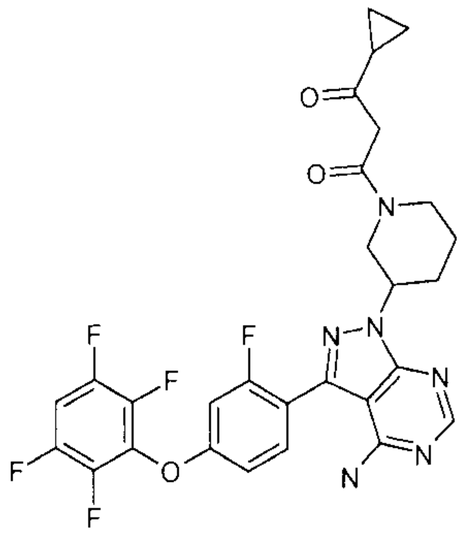
41		(E)-4-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4-oxo-but-2-enamide	574
42		(E)-4-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-N-methyl-4-oxo-but-2-enamide	588
43		N-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-trifluorophenoxy)phenyl]-1H-pyrazolo[3,4-d] pyrimidin-1-yl)piperidine-1-carbonyl) formamidine	562
44		1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)butane-1,3-dione	561

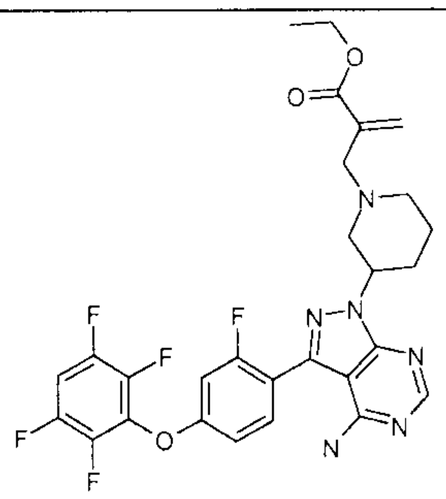
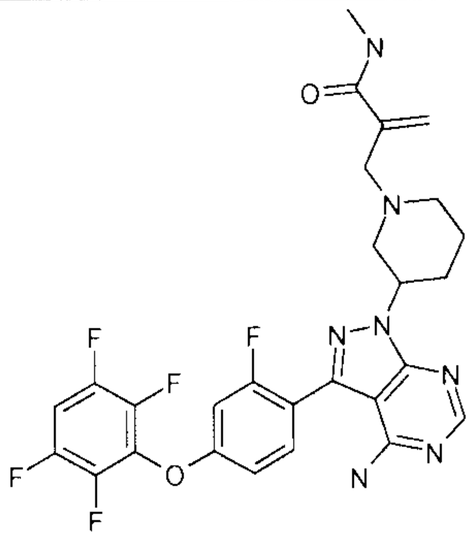
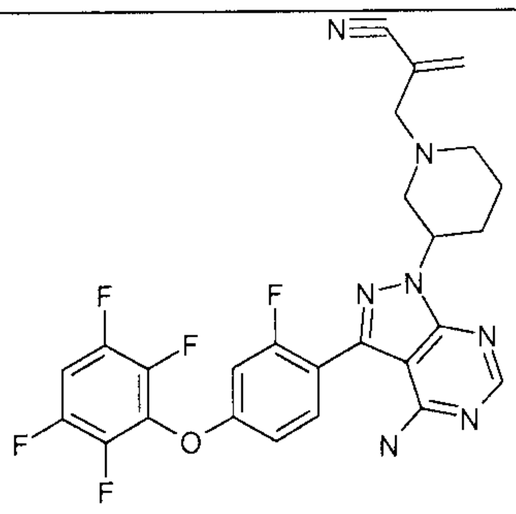
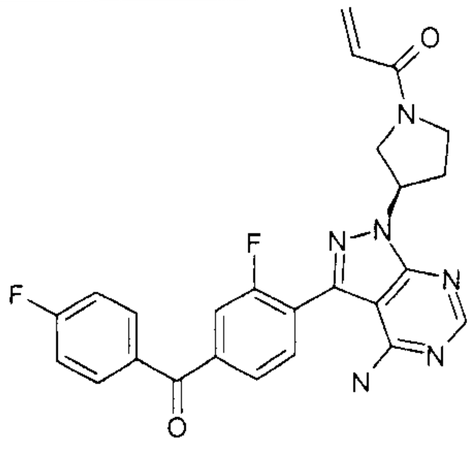
45		1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one	517
46		1-((S)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one	517
47		methyl 4-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4-oxo-but-2-enoylcarbamate	632
48		methyl 2-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)but-2-enoate	603

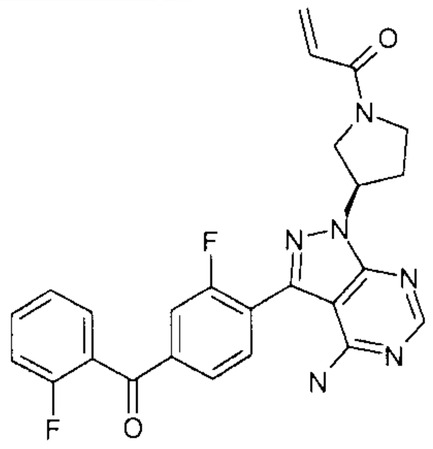
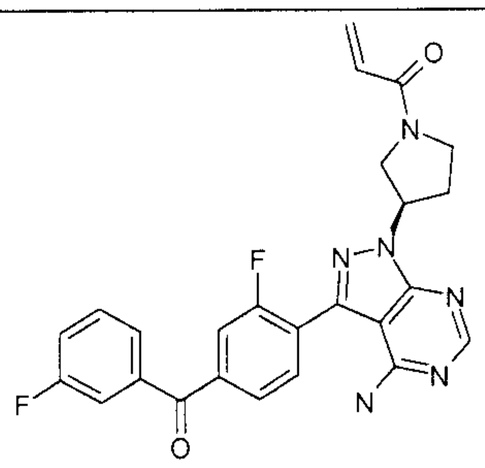
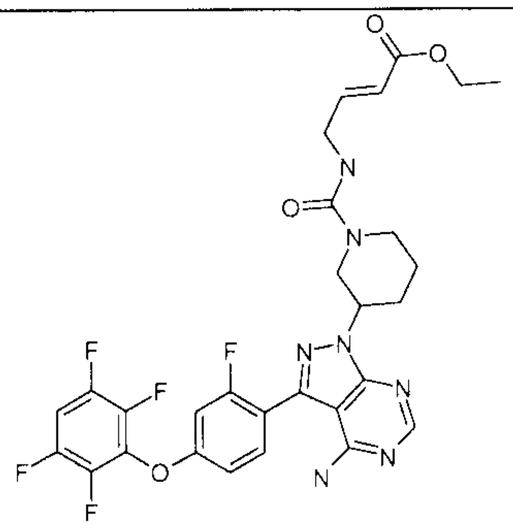
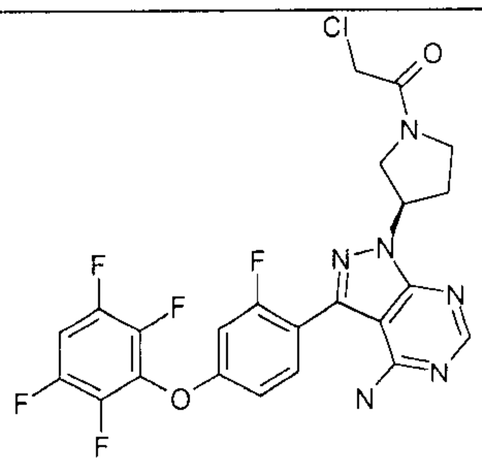
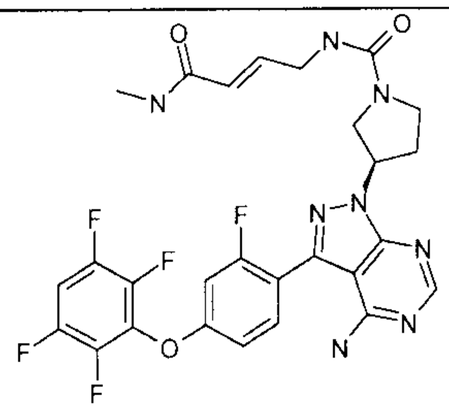
49		2-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)acrylonitrile	556
50		1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-(hydroxymethyl)prop-2-en-1-one	561
51		1-(2-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-1H-pyrrole-2,5-dione	517
52		3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-N-methylpiperidine-1-carboxamide	534
53		3-[4-amino-3-[2-fluoro-4-(2,3,5,6-fluorophenoxy)phenyl]-1H-pyrazolo[3,4-d]pyrimidine-1-yl]piperidine-1-formamidine	533

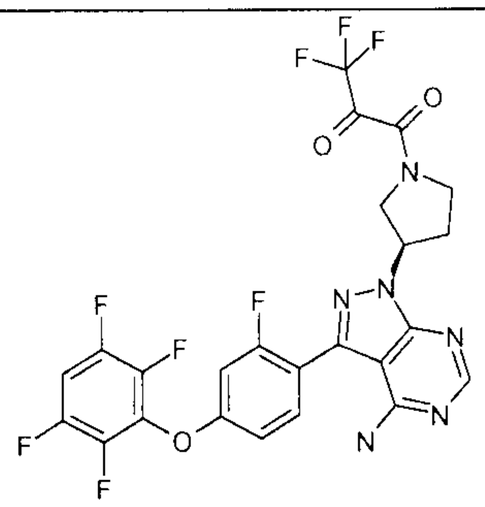
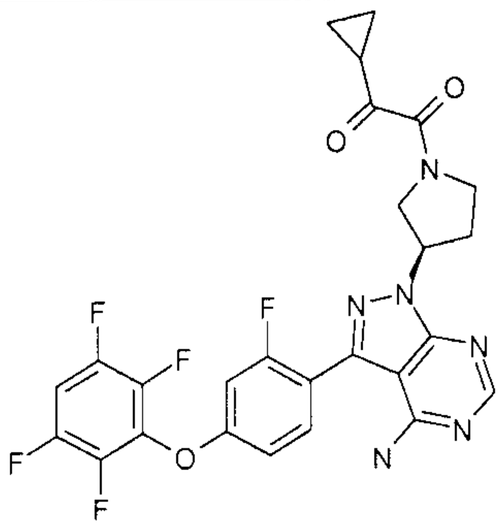
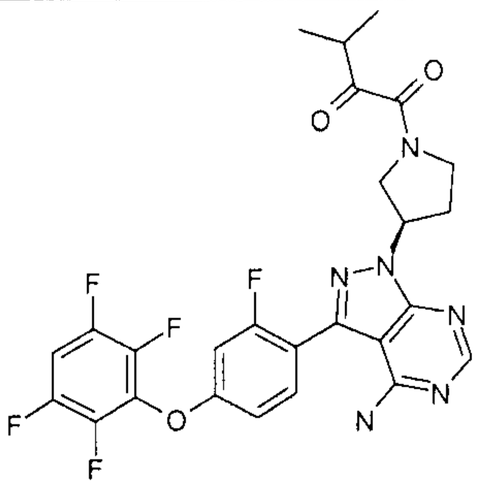
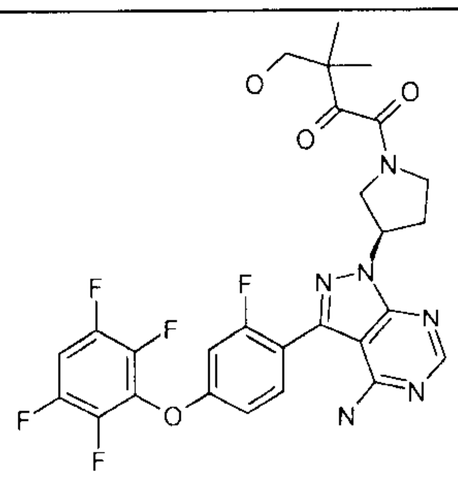
54		3-[4-amino-3-[2-fluoro-4-(2,3,5,6-fluorophenoxy)phenyl]-1H-pyrazolo[3,4-d] pyrimidine-1-yl]-N'-cyano-N-methyl-piperidine-1-formamidine	558
55		1-[3-[4-amino-3-[2-fluoro-4-(2,3,5,6-fluorophenoxy)phenyl]-1H-pyrazolo[3,4-d] pyrimidin-1-yl]-1-piperidinyl]-1-(methylamino)-2-nitro ethylene	578
56		2-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-N-methylacetamide	548
57		2-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-N-methyl-2-oxoacetamide	562
58		1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-3-chloro-propan-1-one	553

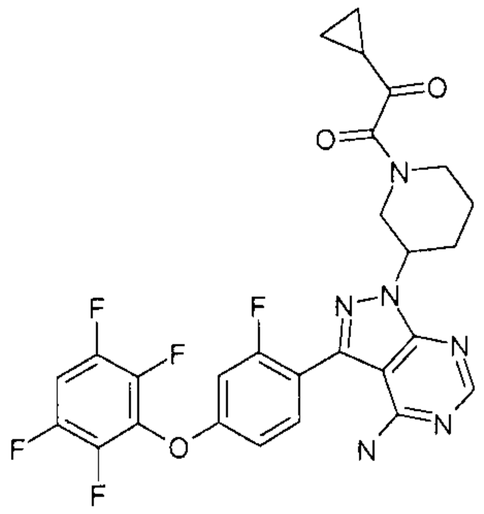
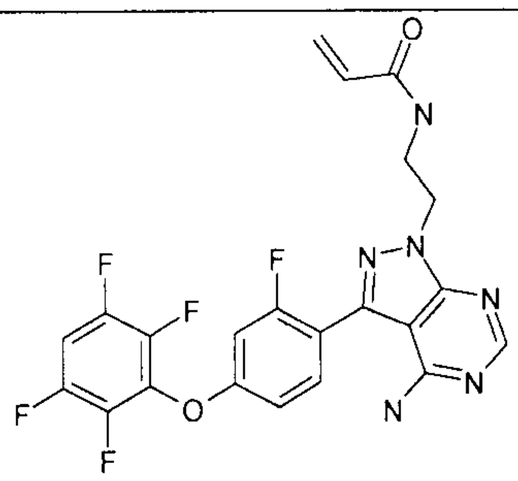
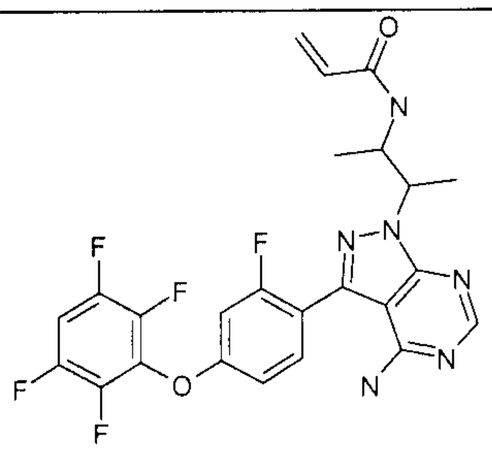
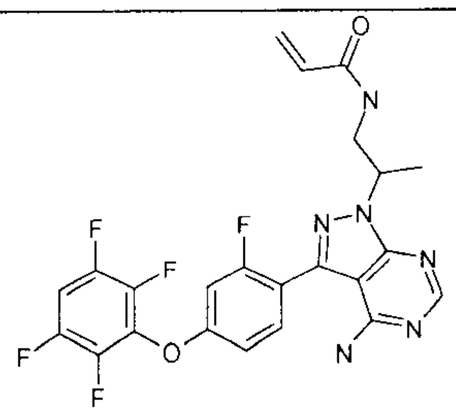
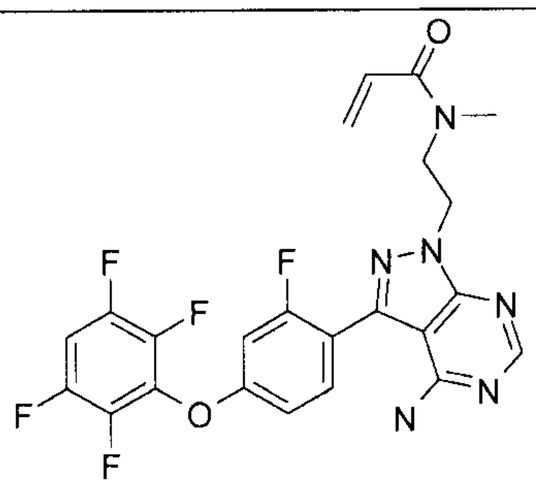
59		(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)(1H-imidazol-4-yl)methanone	571
60		(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)(pyridin-3-yl)methanone	582
61		1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-chloroethanone	553
62		1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-(dimethylamino)ethanone	562

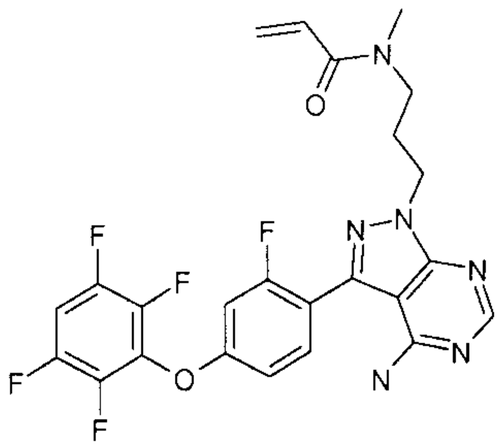
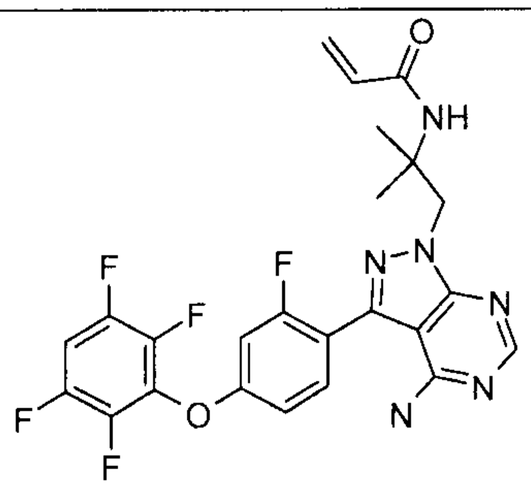
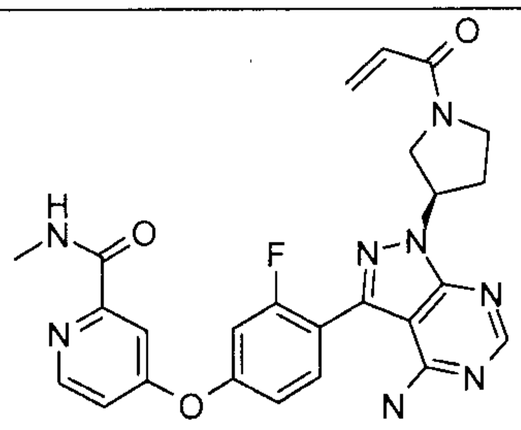
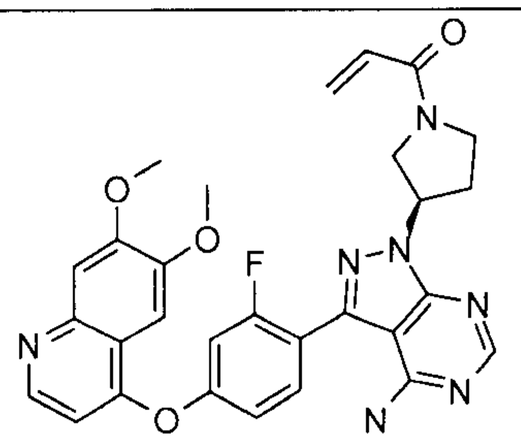
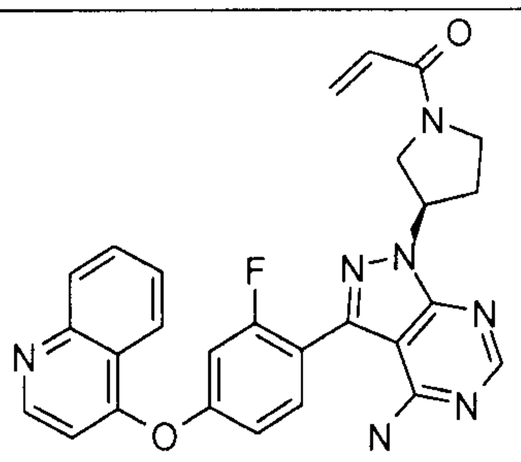
63		5-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)thiazoline-2-one	606
64		1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-(trifluoromethyl)prop-2-en-1-one	599
65		1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4,4,4-trifluorobutane-1,3-dione	615
66		4,4,4-trifluoro-N-(3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-3-oxobutanamide	615
67		1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-3-cyclopropylpropane-1,3-dione	587

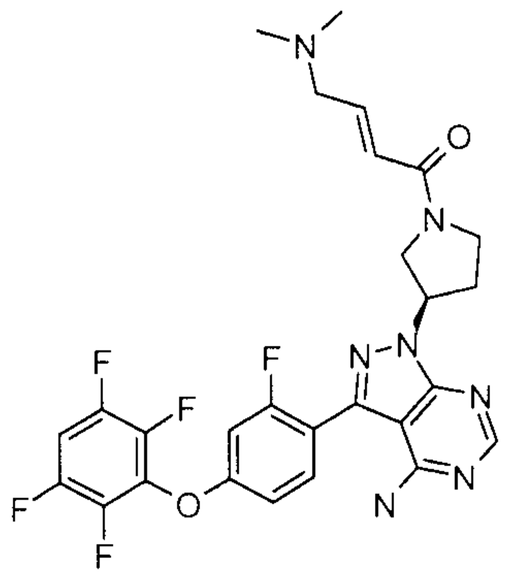
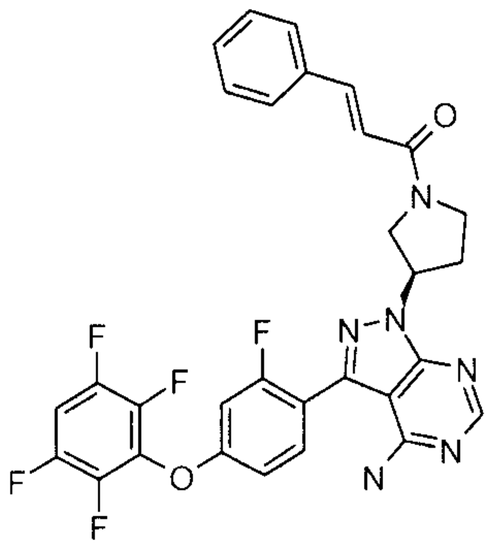
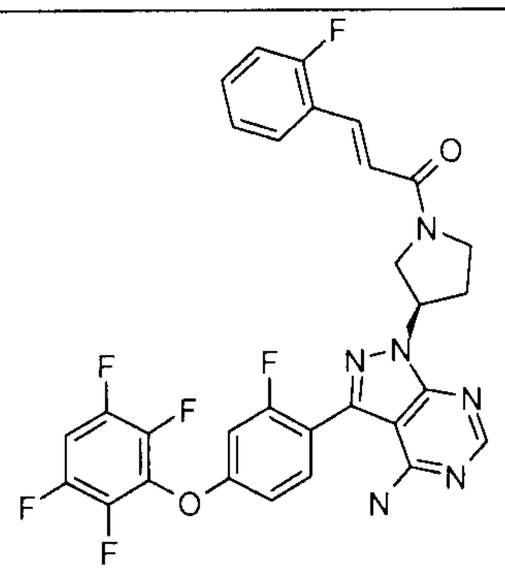
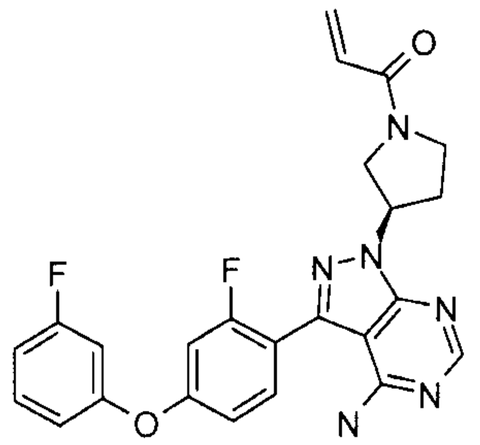
68		ethyl 2-((3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)methyl)acrylate	589
69		2-((3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)methyl)-N-methylacrylamide	574
70		2-((3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)methyl)acrylonitrile	542
71		1-((R)-3-(4-amino-3-(2-fluoro-4-(4-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one	474

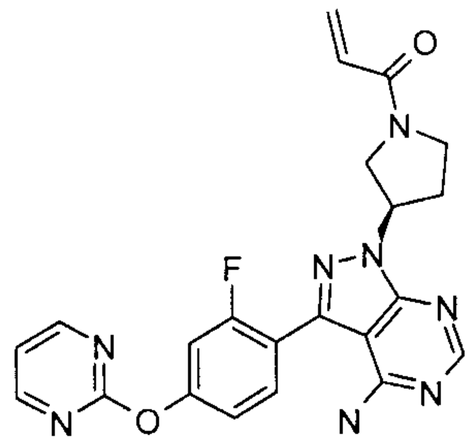
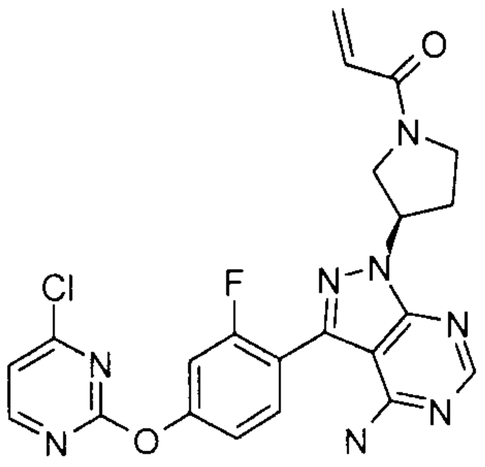
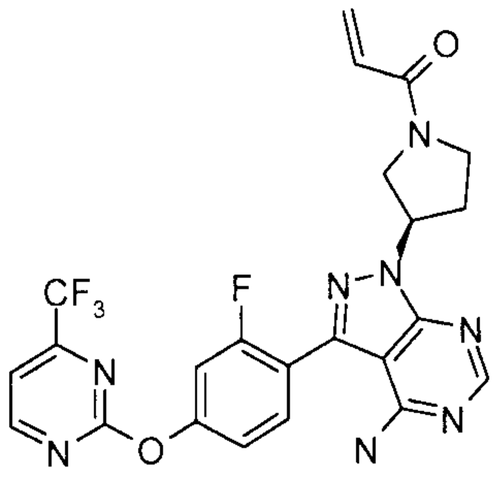
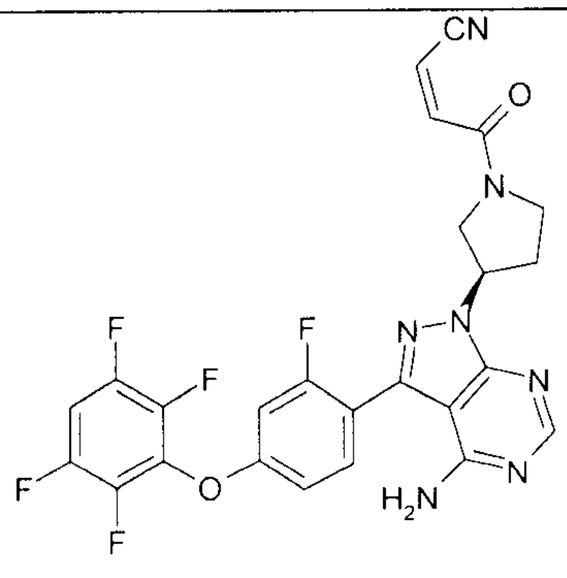
72		1-((R)-3-(4-amino-3-(2-fluoro-4-(2-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one	474
73		1-((R)-3-(4-amino-3-(2-fluoro-4-(3-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one	474
74		ethyl 4-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxamido)but-2-enoate	632
75		1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-chloroethanone	539
76		(3R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-N-(4-(methylamino)-4-oxo-but-2-enyl)pyrrolidine-1-formamide	603

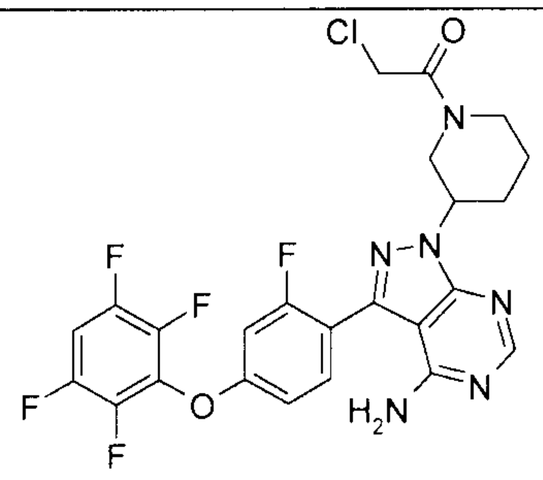
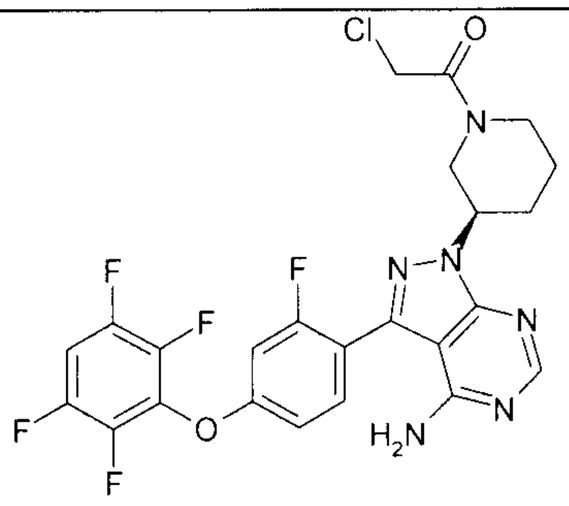
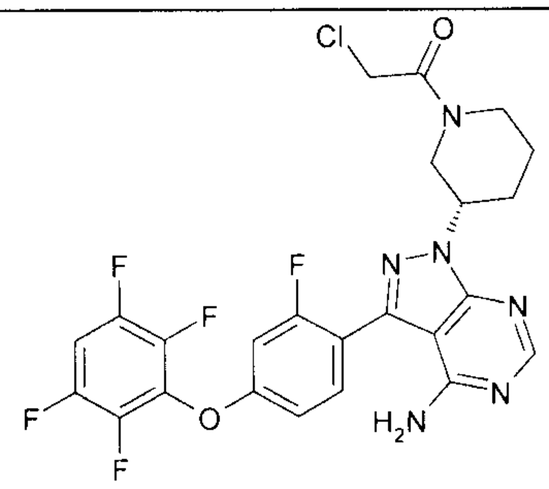
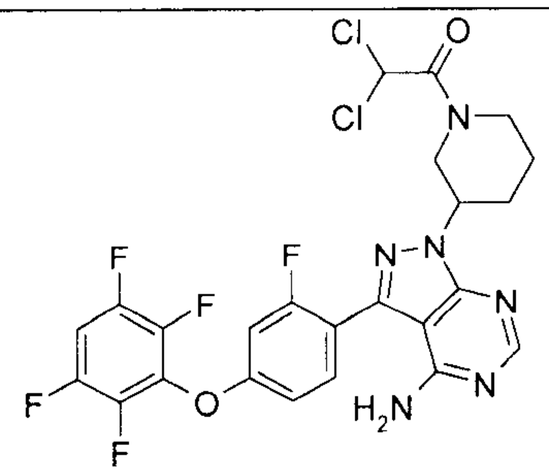
77		1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-3,3,3-trifluoropropane-1,2-dione	587
78		1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-cyclopropylethane-1,2-dione	559
79		1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-3-methylbutane-1,2-dione	561
80		1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-4-hydroxy-3,3-dimethylbutane-1,2-dione	591

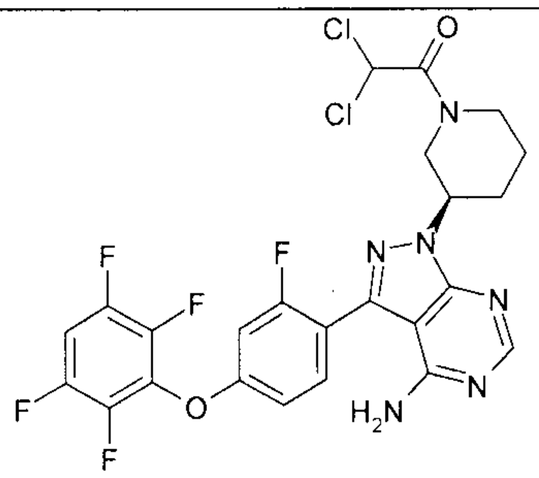
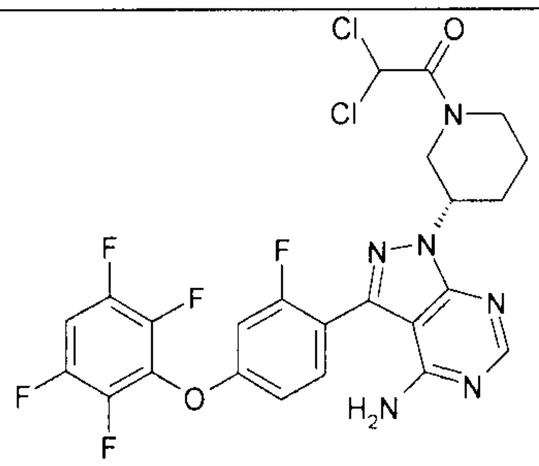
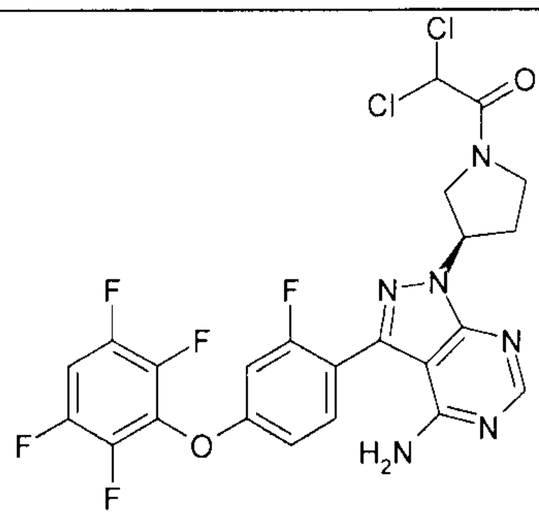
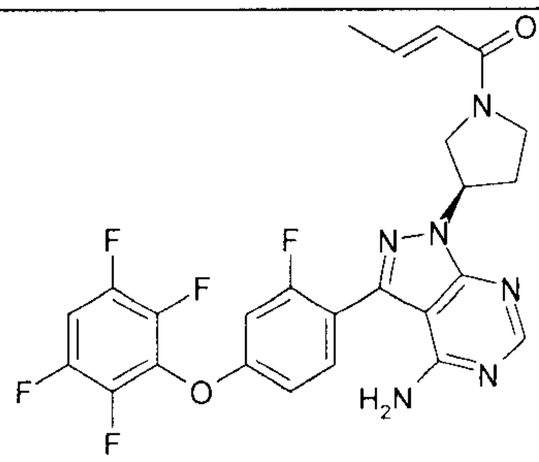
81		1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-cyclopropylethane-1,2-dione	573
82		N-(2-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)acrylamide	491
83		N-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)butan-2-yl)acrylamide	519
84		N-(2-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)acrylamide	505
85		N-(2-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-N-methylacrylamide	505

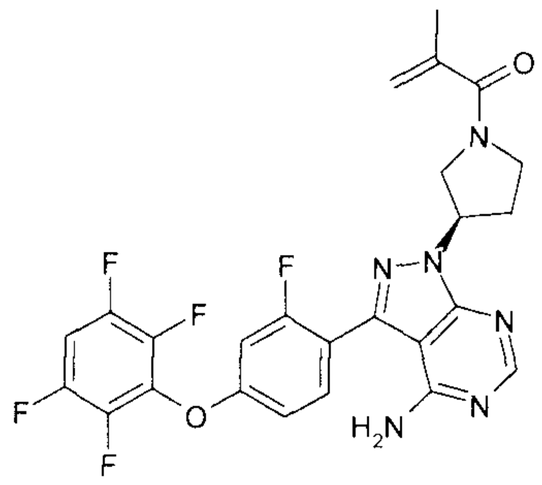
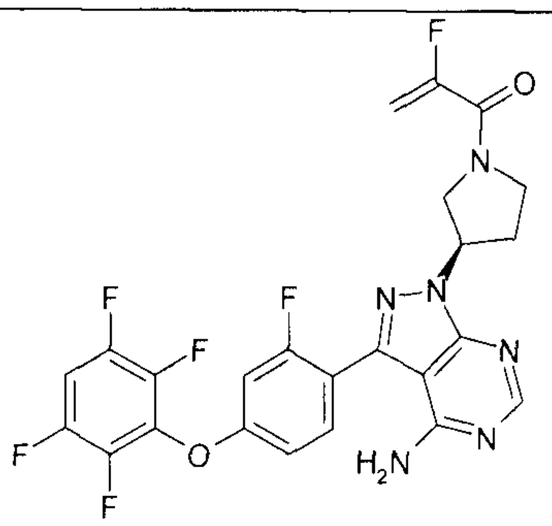
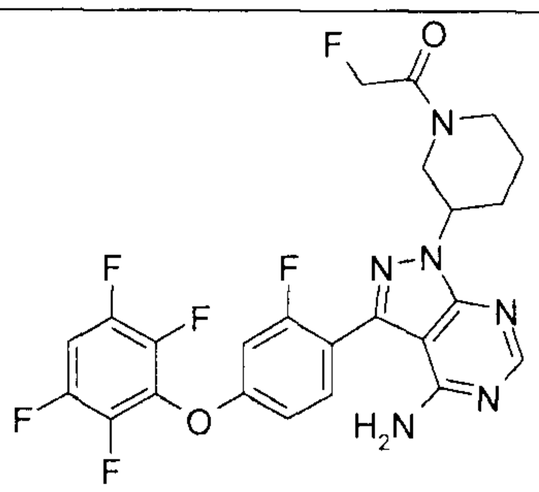
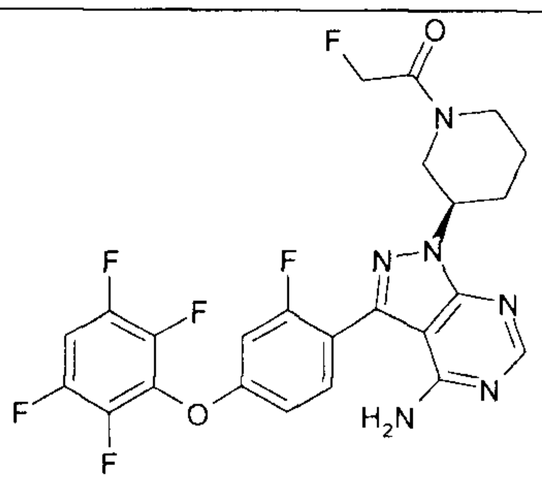
86		N-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-N-methylacrylamide	519
87		N-(1-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-methylpropan-2-yl)acrylamide	519
88		4-(4-(1-((R)-1-acryloylpyrrolidin-3-yl)-4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenoxy)-N-methylpicolinamide	503
89		1-((R)-3-(4-amino-3-(4-(6,7-dimethoxyquinolin-4-yloxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one	556
90		1-((R)-3-(4-amino-3-(2-fluoro-4-(quinolin-4-yloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one	495

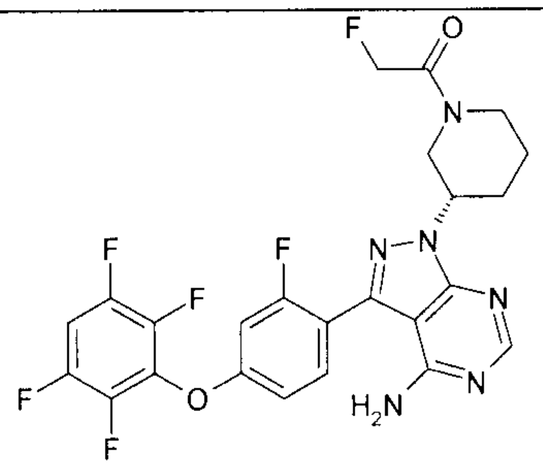
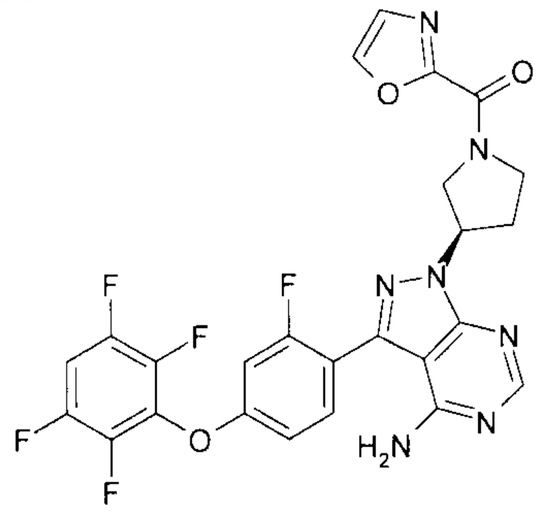
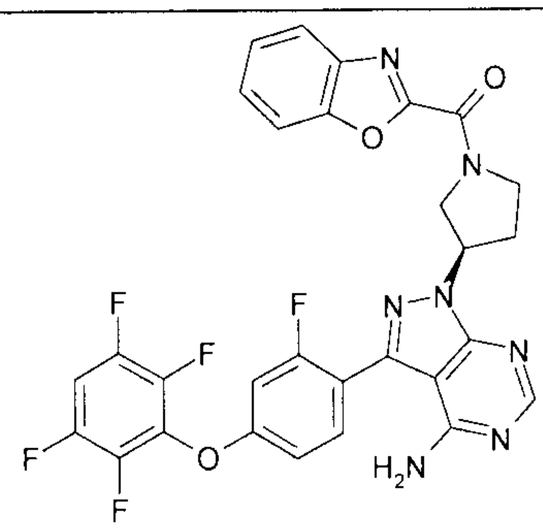
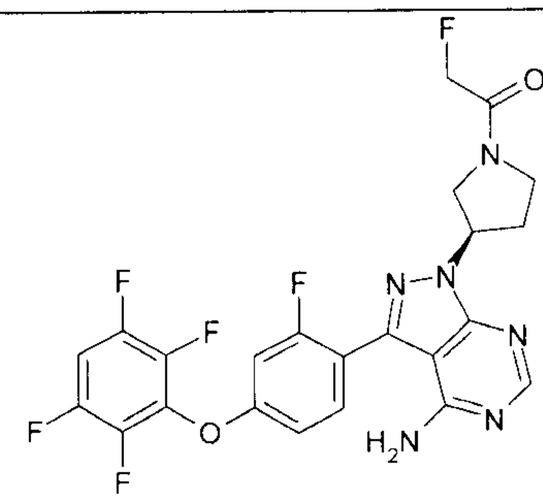
91		(E)-1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-4-(dimethylamino)but-2-en-1-one	574
92		(E)-1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-3-phenylprop-2-en-1-one	593
93		(E)-1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-3-(2-fluorophenyl)prop-2-en-1-one	611
94		1-((R)-3-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one	463

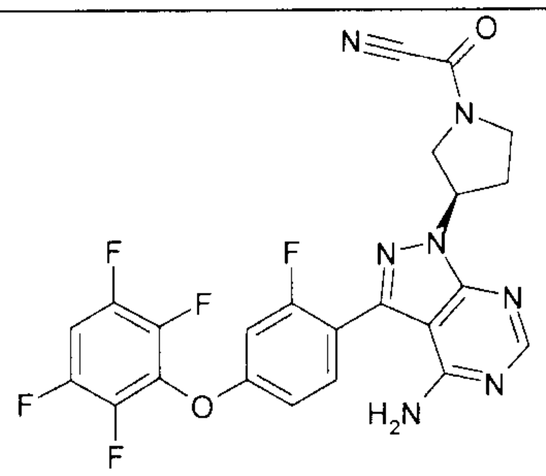
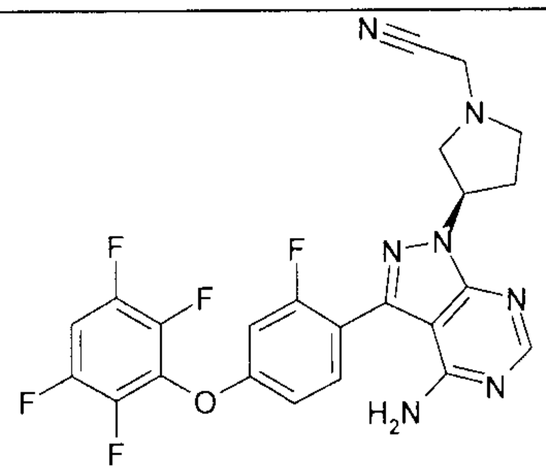
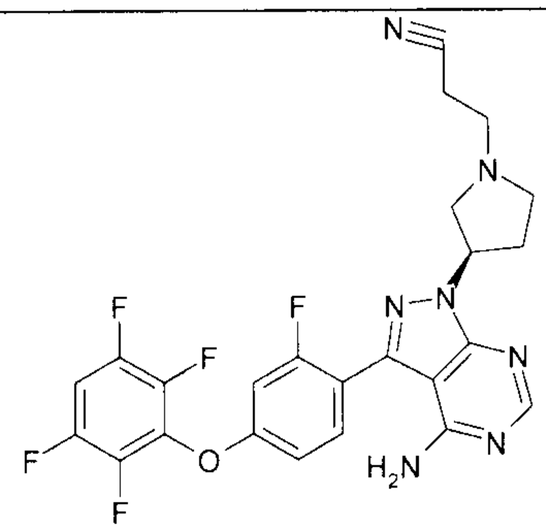
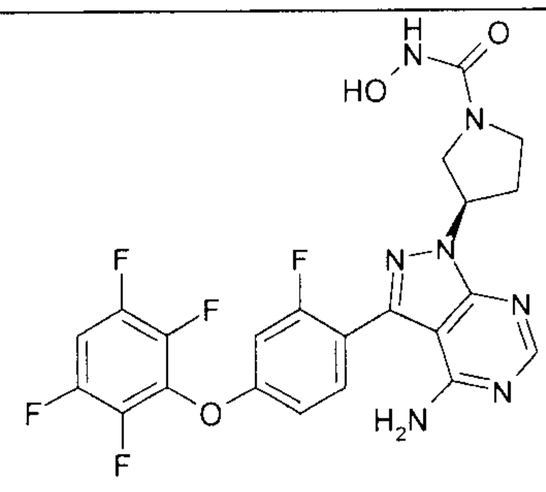
95		1-((R)-3-(4-amino-3-(2-fluoro-4-(pyrimidin-2-yloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one	447
96		1-((R)-3-(4-amino-3-(2-fluoro-4-(4-chloropyrimidin-2-yloxy)- 1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one	481
97		1-((R)-3-(4-amino-3-(2-fluoro-4-(4-(trifluoromethyl)pyrimidin-2-yloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one	515
98		(Z)-4-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-4-oxo-but-2-enenitrile	542

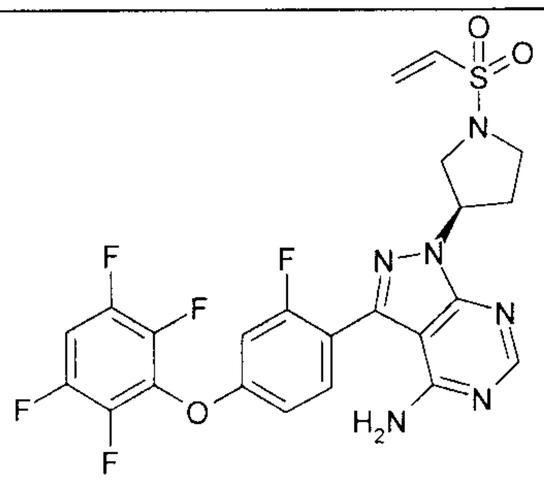
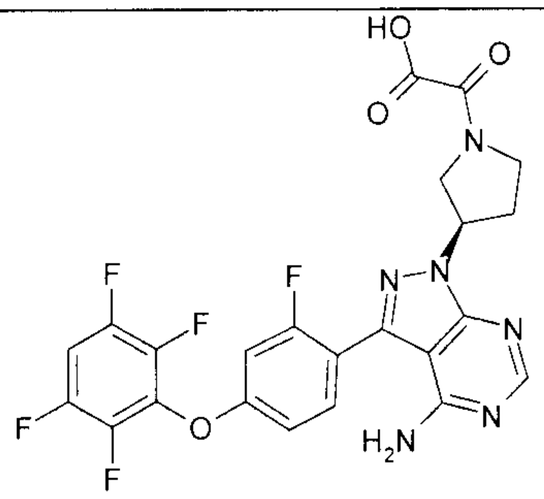
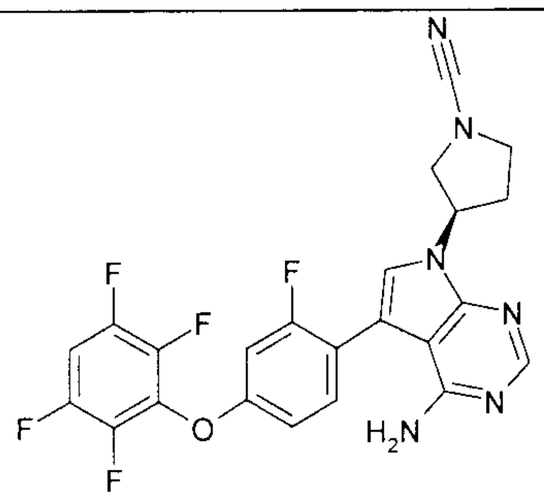
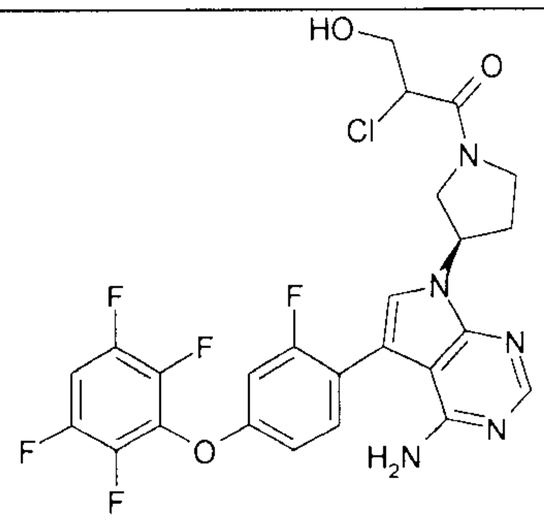
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99		1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-chloroethanone	553
100		1-((S)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-chloroethanone	553
101-A		1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2,2-dichloroethanone	587

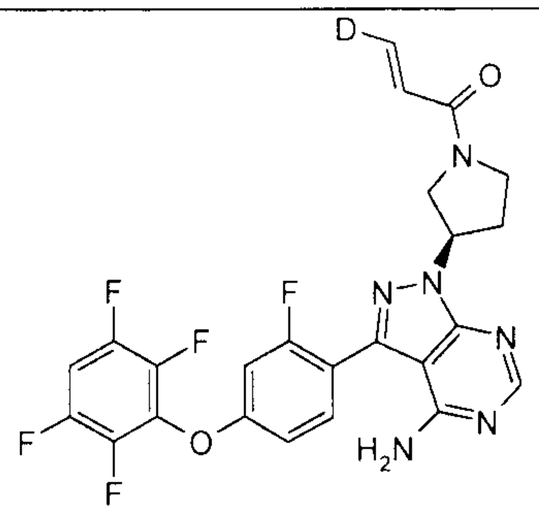
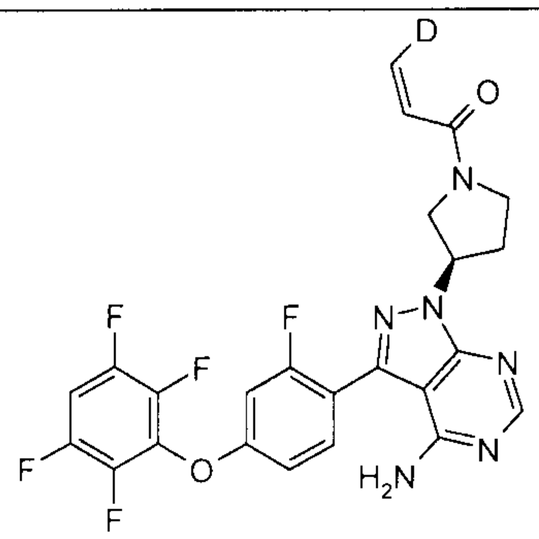
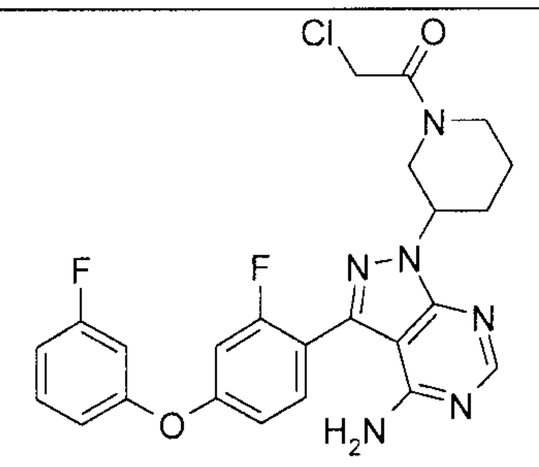
101		1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2,2-dichloroethanone	587
102		1-((S)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2,2-dichloroethanone	587
103		1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2,2-dichloroethanone	573
104		(E)-1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)but-2-en-1-one	531

105		1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-methylprop-2-en-1-one	531
106		1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-fluoroprop-2-en-1-one	535
107-A		1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-fluoroethanone	537
107		1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-fluoroethanone	537

108		1-((S)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-fluoroethanone	537
109		((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)(oxazol-2-yl)methanone	558
110		((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)(benzo[d]oxazol-2-yl)methanone	608
111		1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-fluoroethanone	523

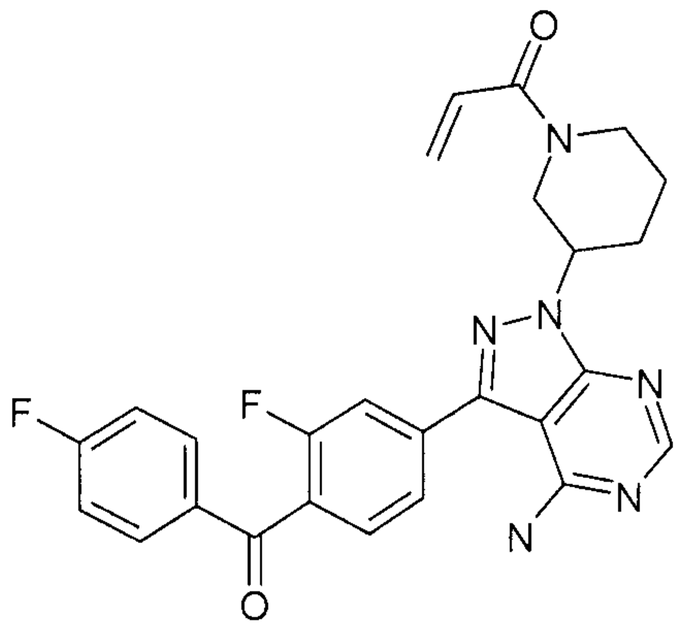
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113		2-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)acetonitrile	502
114		3-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)propanenitrile	516
115		(3R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-N-hydroxypyrrolidine-1-amide	522

116		3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-1-(vinylsulfonyl)pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine	553
117		2-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-oxoacetic acid	535
118		(3R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyrimidin-1-yl)pyrrolidine-1-carbonitrile	488
119		1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-chloro-3-hydroxypropan-1-one	569

120		(E)-1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyrimidin-1-yl)pyrrolidin-1-yl)-3-deuterium-prop-2-en-1-one	518
121		(Z)-1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyrimidin-1-yl)pyrrolidin-1-yl)-3-deuterium-prop-2-en-1-one	518
122		1-(3-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-chloroethanone	499

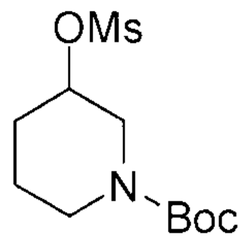
Note: If there are differences between the structure and name, the structure will prevail.

Example 1



1-(3-(4-amino-3-(3-fluoro-4-(4-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl) piperidin-1-yl)prop-2-en-1-one

Step A:

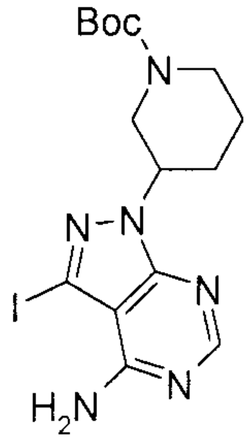


tert-butyl 3-(methylsulfonyloxy)piperidine-1-formate

Procedure:

Triethylamine (15 g, 150 mmol, 3.0 eq.) and methanesulfonyl chloride (6.3 g, 55 mmol, 1.1 eq.) were sequentially added dropwise to a solution of tert-butyl 3-hydroxypiperidine-1formate (10.0 g, 50 mmol, 1.0 eq.) in dichloromethane (100 mL) at 0 °C. The reaction mixture was stirred at 20 °C for1 hour, added with saturated $NaHCO_3$ (100 mL), and then extracted with dichloromethane (200 mL) 3 times. The organic phase was dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (13 g, yield: 95%).

Step B:

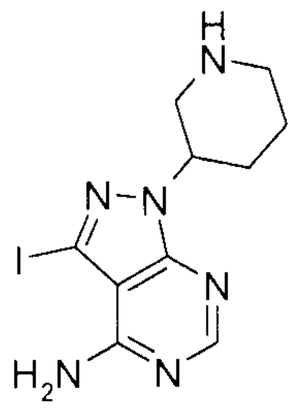


tert-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1- formate

Procedure:

Cesium carbonate (20.2 g, 62 mmol, 2.0 eq.) and tert-butyl 3-(methylsulfonyloxy)piperidine-1-formate (13 g, 46.5 mmol, 1.5 eq.) were added to a solution of 3-iodo-1H-pyrazolo[3,4-d]-pyrimidin-4-amine (8.1 g, 31 mmol, 1.0 eq.) in DMF (50 mL) at 0 °C. The reaction mixture was stirred at 80 °C overnight, filtered through celite, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: ethyl acetate) to give the target compound (5 g, yield: 25%) .

Step C:

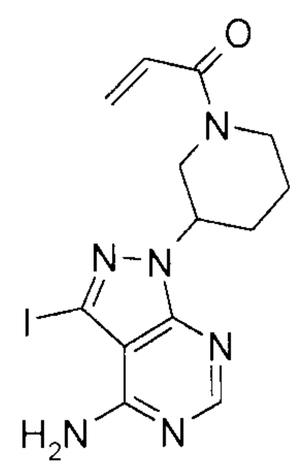


3-iodo-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

HCl/EA (20 mL, 4 mol/L) was added to a solution of tert-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-formate (5 g, 11.3 mmol) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred for 1 hour at room temperature, concentrated and spin-dried to give the hydrochloride of the target compound (4 g, yield: 94%).

Step D:

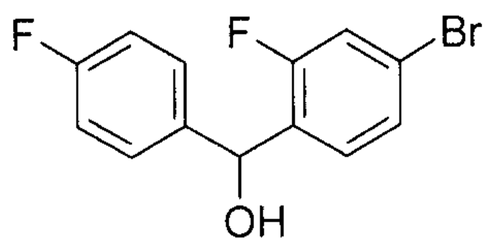


1-(3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one

Procedure:

Triethylamine (3.2 g, 31.5 mmol, 3.0 eq.) and acryloyl chloride (950 mg, 10.5 mmol, 1.0 eq.) were subsequently added to a solution of 3-iodo-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (4 g, 10.5 mmol, 1.0 eq.) in dichloromethane (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, and quenched with saturated sodium bicarbonate solution (30 mL). The aqueous phase was extracted with dichloromethane (50 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: ethyl acetate) to give the target compound (3.7 g, yield: 90%).

Step E:

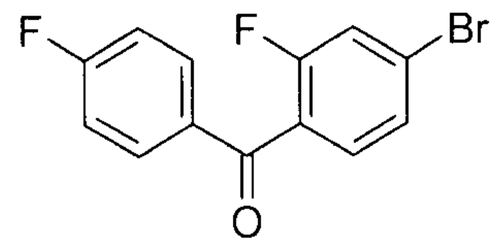


(2-fluoro-4-bromo-phenyl)(4-fluorophenyl)methanol

Procedure:

A solution of 4-fluorophenyl magnesium bromide in tetrahydrofuran (THF)(1 M, 6.0 mL, 6.0 mmol, 1.2 eq.) was added dropwise to a solution of 2-fluoro-4-bromo-benzaldehyde (1.0 g, 5.0 mmol, 1.0 eq.) in tetrahydrofuran (10 mL) at -78 °C. The reaction mixture was stirred at room temperature for 2 hours, then cooled to 0 °C and quenched with saturated ammonium chloride solution. The mixture was extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:0 to 1:1) to give the target compound (420 mg, yield: 30%).

Step F:

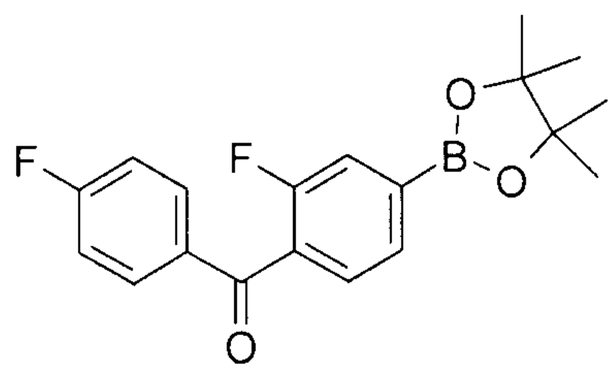


(2-fluoro-4-bromo-phenyl)(4-fluorophenyl)methanone

Procedure:

Tetrapropylammonium perruthenate (80 mg, 0.22 mmol, 0.15 eq.), N-methyl morpholine oxide (346 mg, 2.96 mmol, 2.0 eq.) and 4A molecular sieves (300 mg) were added to a solution of (2-fluoro-4-bromo-phenyl)(4-fluorophenyl)methanol (0.42 g, 1.48 mmol, 1.0 eq.) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 2 hours, then concentrated and spin-dried. The obtained crude product was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:0 to 1:1) to give the target compound (0.4 g, yield: 99%).

Step G:

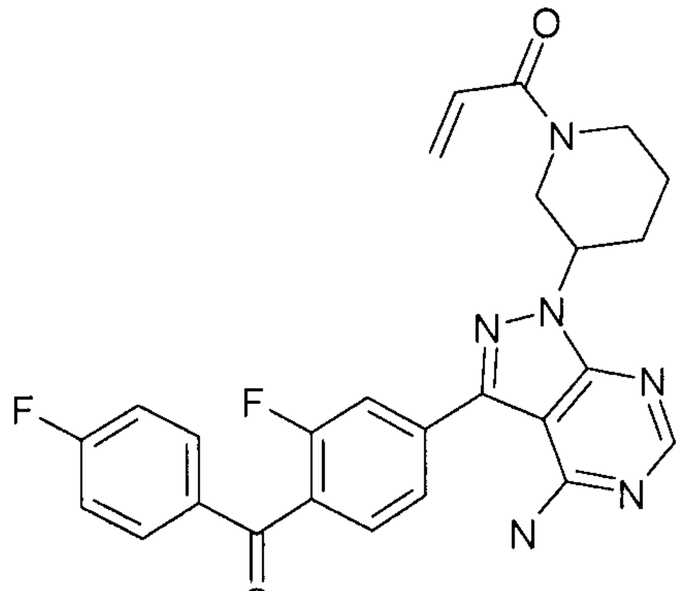


(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)(4-fluorophenyl)methanone

Procedure:

(2-fluoro-4-bromo-phenyl)(4-fluorophenyl)methanone (496 mg, 1.67 mmol, 1.0 eq.), bis(pinacolato)diboron (468 mg, 1.84 mmol, 1.1 eq.), potassium acetate (490 mg, 5.02 mmol, 3.0 eq.) and (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium (71 mg, 0.1 mmol, 0.058 eq.) were dissolved in 1,4-dioxane (3 mL), heated to 80 °C and then stirred under nitrogen for 4 hours. The reaction mixture was filtered through celite. The filtrate was spin-dried to give the crude product (574 mg, yield: 100%), which was used directly in the next step.

Step H:



1-(3-(4-amino-3-(3-fluoro-4-(4-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl) piperidin-1-yl)prop-2-en-1-one

Procedure:

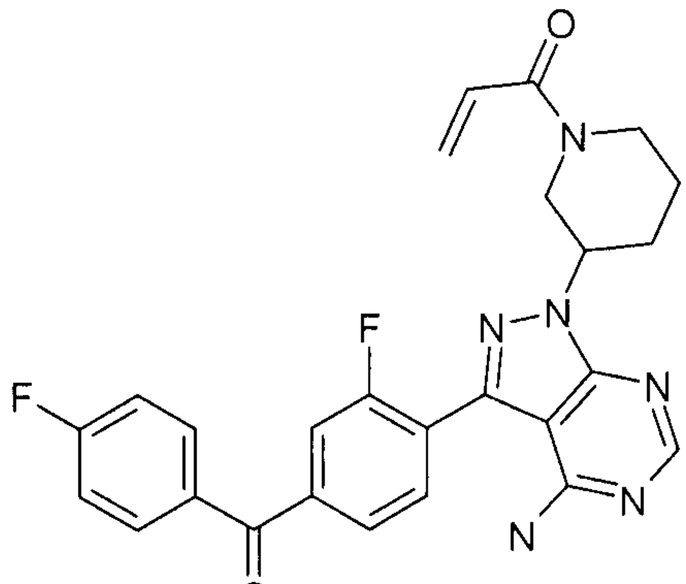
(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)(4-fluorophenyl)methanone (574 mg, 1.67 mmol, 1.0 eq.), 1-(3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (448 mg, 1.12 mmol, 1.0 eq.), sodium carbonate (356 mg, 3.36 mmol, 3.0 eq.) and $Pd(PPh_3)_4$ (127 mg, 0.11 mmol, 0.1 eq.) were dissolved in 1,4-dioxane/water (5 mL, 1/1, v/v). The reaction mixture was stirred at 85 °C for 30 min. under nitrogen atmosphere with microwave irradiation. The reaction mixture was diluted with water (10 mL), and then extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by thin layer chromatography (eluent: ethyl acetate) to give the target compound (70 mg, yield: 12%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 4.223 min; m/z = 489.2 $[M+H]^+$; Total running time: 7 min.

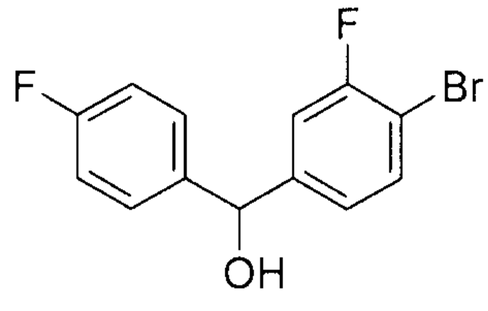
^{1}H NMR (400MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.00-7.97 (m, 2H), 7.73-7.55 (m, 3H),7.46-7.41 (m, 2H), 6.91-6.70 (m, 1H), 6.16-6.05 (m, 1H), 5.73-5.58 (m, 1H), 4.80-4.73 (m, 1H), 4.56-4.54 (m, 0.5H), 4.22-4.06 (m, 1.5H), 3.81-3.75 (m, 0.5H), 3.30-3.12 (m, 1.5H), 2.35-2.15 (m, 2H), 1.97-1.94 (m, 1H), 1.66-1.60 (m,1H).

Example 2



1-(3-(4-amino-3-(2-fluoro-4-(4-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl) piperidin-1-yl)prop-2-en-1-one

StepA:

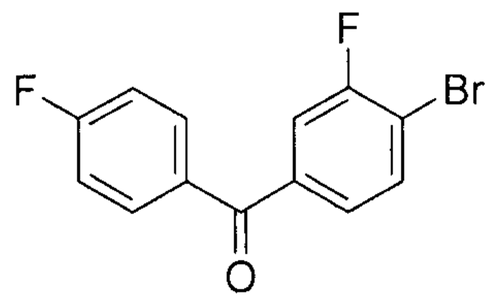


(3-fluoro-4-bromo-phenyl)(4-fluorophenyl)methanol

Procedure:

A solution of 4-fluorophenyl magnesium bromide in THF (1 M, 24.0 mL, 24.0 mmol, 1.2 eq.) was added dropwise to a solution of 3-fluoro-4-bromobenzaldehyde (4.06 g, 20.0 mmol, 1.0 eq.) in THF (20 mL) at -78 °C. The reaction mixture was reacted at room temperature for 2 hours, then cooled to 0 °C and quenched with saturated ammonium chloride solution. The mixture was extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:0 to 1:1) to give the target compound (5.3 g, yield: 89%).

Step B:

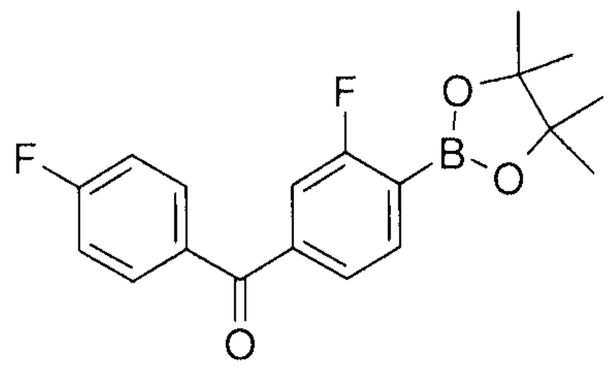


(3-fluoro-4-bromo-phenyl)(4-fluorophenyl)methanone

Procedure:

Tetrapropylammonium perruthenate (580 mg, 1.66 mmol, 0.15 eq.), N-methyl morpholine oxide (2.6 g, 22.0 mmol, 2.0 eq.) and 4A molecular sieves (1.0 g) were added to a solution of (3-fluoro-4-bromo-phenyl)(4-fluorophenyl)methanol (3.3 g, 11.0 mmol, 1.0 eq.) in dichloromethane (20 mL). The reaction mixture was reacted at room temperature for 2 hours, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:0 to 1:1) to give the target compound (3.0 g, yield: 92%).

Step C:

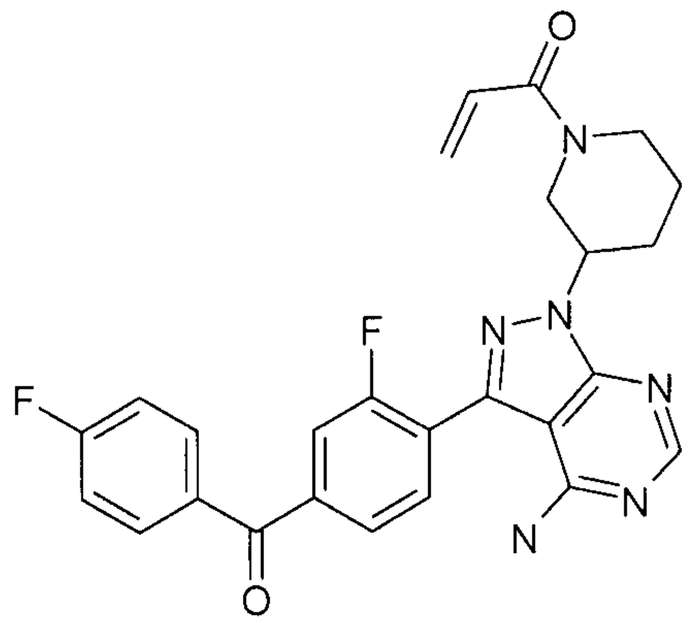


(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)(4-fluorophenyl)methanone

Procedure:

(3-fluoro-4-bromo-phenyl)(4-fluorophenyl)methanone (1.0 g, 3.5 mmol, 1.0 eq.), bis(pinacolato)diboron (980 mg, 3.9 mmol, 1.1 eq.), potassium acetate (1.2 g, 12.3 mmol, 3.5 eq.) and (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium (149 mg, 0.2 mmol, 0.058 eq.) were dissolved in 1,4-dioxane (10 mL), heated to 80 °C and stirred under nitrogen for 4 hours. The reaction mixture was filtered through celite. The filtrate was spin-dried to give the crude product (1.2 g, yield: 100%), which was used directly in the next step.

Step D:



1-(3-(4-amino-3-(2-fluoro-4-(4-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl) piperidin-1-yl)prop-2-en-1-one

Procedure:

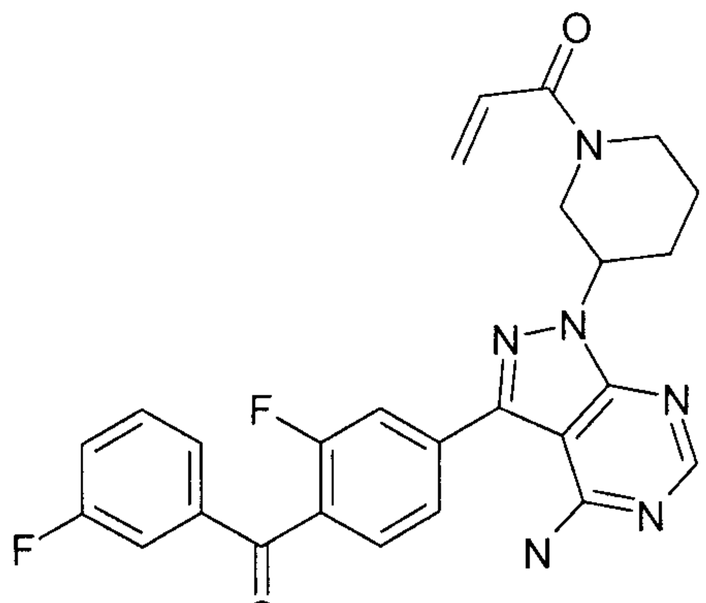
(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)(4-fluorophenyl)methanone (306 mg, 0.89 mmol, 1.0 eq.), 1-(3-(4-amino-3-iodo-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (355 mg, 1.12 mmol, 1.0 eq.), sodium carbonate (283 mg, 2.67 mmol, 3.0 eq.) and $Pd(PPh_3)_4$ (100 mg, 0.09 mmol, 0.1 eq.) were dissolved in 1,4-dioxane/water (10 mL, 1/1, v/v). The reaction mixture was reacted at 85 °C for 30 min. under nitrogen atmosphere with microwave irradiation. The reaction mixture was diluted with water (10 mL), and then extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was separated by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water, gradient 10% to 100% (volume ratio)) to give the target compound (42 mg, yield: 10%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 0.740 min; m/z = 488.9 $[M+H]^+$; Total running time: 2 min.

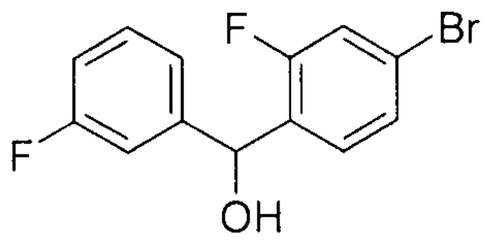
^1H NMR (400MHz, DMSO-d_6) δ 8.25 (s, 1H), 7.97-7.93 (m, 2H), 7.75-7.63 (m, 3H),7.45-7.41 (m, 2H), 6.88-6.71 (m, 1H), 6.14-6.02 (m, 1H), 5.74-5.56 (m, 1H), 4.73-4.54 (m, 1.5H), 4.19-4.04 (m, 1.5H), 3.71-3.65 (m, 0.5H), 3.23-3.15 (m, 1H), 3.02-2.97 (m, 0.5H), 2.31-2.07 (m, 2H), 1.97-1.90 (m, 1H), 1.60-1.52 (m,1H).

Example 3



1-(3-(4-amino-3-(3-fluoro-4-(3-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl) piperidin-1-yl)prop-2-en-1-one

Step A:

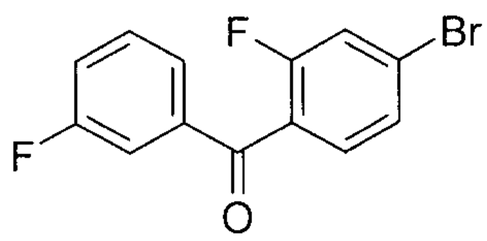


(2-fluoro-4-bromo-phenyl)(3-fluorophenyl)methanol

Procedure:

A solution of 3-fluorophenyl magnesium bromide in THF (1 M, 6.0 mL, 6.0 mmol, 1.2 eq.) was added dropwise to a solution of 2-fluoro- 4-bromobenzaldehyde (1.0 g, 5.0 mmol, 1.0 eq.) in THF (10 mL) at -78 °C. The reaction mixture was reacted at room temperature for 2 hours, then cooled to 0 °C and quenched with saturated ammonium chloride solution. The mixture was extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:0 to 1:1) to give the target compound (420 mg, yield: 30%).

Step B:

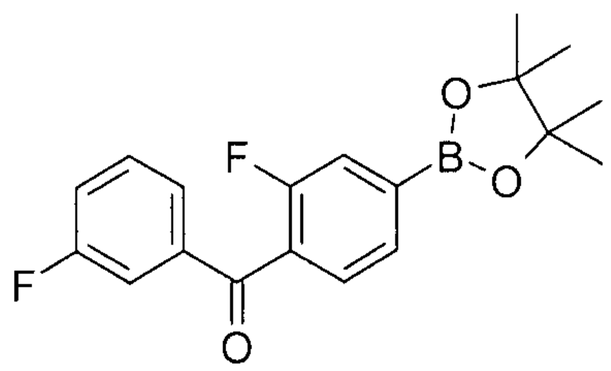


(2-fluoro-4-bromo-phenyl)(3-fluorophenyl)methanone

Procedure:

Tetrapropylammonium perruthenate (80 mg, 0.22 mmol, 0.15 eq.), N-methyl morpholine oxide (346 mg, 2.96 mmol, 2.0 eq.) and 4A molecular sieves (300 mg) were added to a solution of (2-fluoro-4-bromo-phenyl)(3-fluorophenyl)methanol (0.42 g, 1.48 mmol, 1.0 eq.) in dichloromethane (10 mL). The reaction mixture was reacted at room temperature for 2 hours, concentrated and spin-dried to give crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:0 to 1:1) to give the target compound (0.4 g, yield: 99%).

Step C:

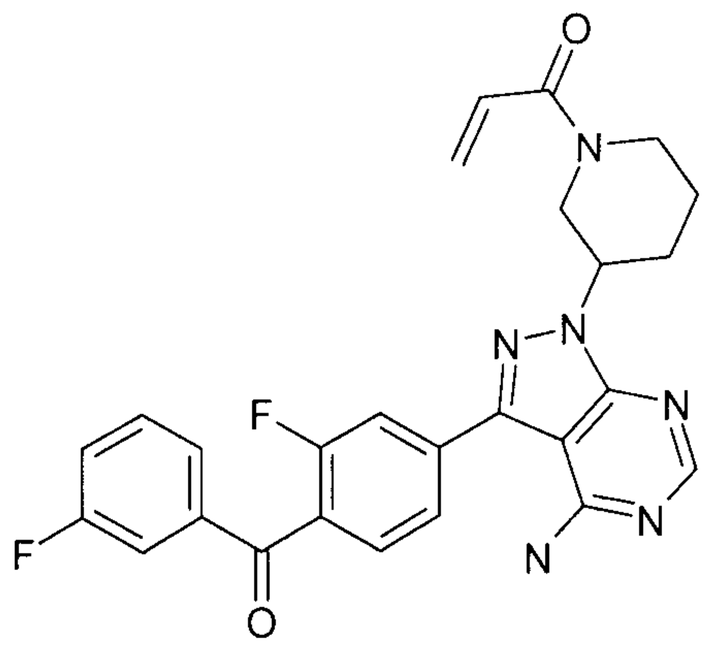


(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)(3-fluorophenyl)methanone

Procedure:

(2-fluoro-4-bromo-phenyl)(3-fluorophenyl)methanone (200 mg, 0.67 mmol, 1.0 eq.), bis(pinacolato)diboron (188 mg, 0.73 mmol, 1.1 eq.), potassium acetate (200 mg, 2.01 mmol, 3.0 eq.) and (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium (28 mg, 0.039 mmol, 0.058 eq.) were dissolved in 1,4-dioxane (10 mL), heated to 80 °C and stirred under nitrogen for 12 hours. The reaction mixture was filtered through celite. The filtrate was spin-dried to give the crude product (240 mg, yield: 100%), which was used directly in the next step.

Step D:



1-(3-(4-amino-3-(3-fluoro-4-(3-fluorobenzoyl)phenyl) -pyrazolo[3,4-d]pyrimidin-1-yl) piperidin-1-yl)prop-2-en-1-one

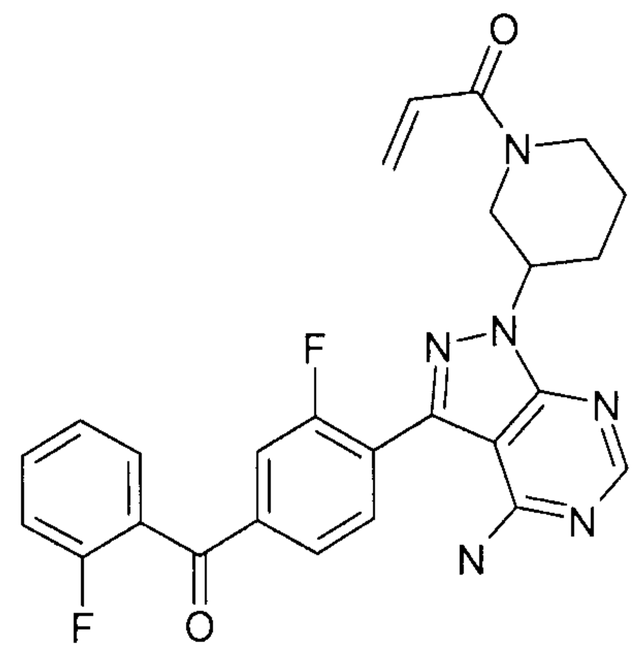
Procedure:

(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)(3-fluorophenyl)methanone (192 mg, 0.48 mmol, 1.0 eq.), 1-(3-(4-amino-3-iodo-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (300 mg, 0.87 mmol, 1.8 eq.), sodium carbonate (51 mg, 1.45 mmol, 3.0 eq.) and $Pd(PPh_3)_4$ (56 mg, 0.05 mmol, 0.1 eq.) were dissolved in 1,4-dioxane/water (10 mL, 1/1, v/v). The reaction mixture was reacted at 85 °C for 30 min. under nitrogen atmosphere with microwave irradiation. The reaction mixture was diluted with water (10 mL), and then extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient 10% to 100% (volume ratio)) to give the hydrochloride of the target compound (10 mg, yield: 4%).

Spectroscopy data:

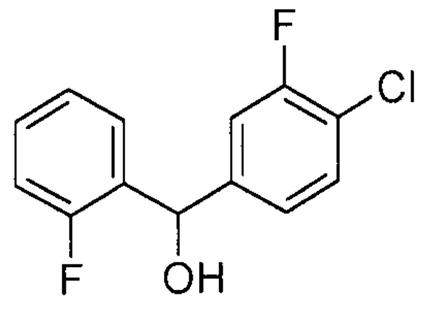
LC/MS (Method: UFLC): RT = 2.969 min; m/z = 489.1 $[M+H]^+$; Total running time: 7 min.

Example 4



1-(3-(4-amino-3-(2-fluoro-4-(2-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl) piperidin-1-yl)prop-2-en-1-one

Step A:

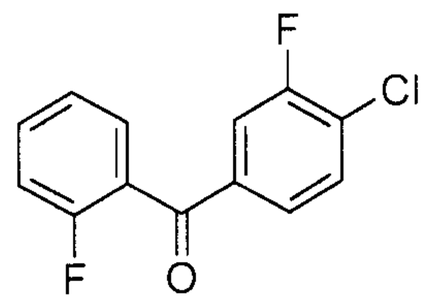


(3-fluoro-4-chlorophenyl)(2-fluorophenyl)methanol

Procedure:

A solution of 3-fluoro-4-chlorophenyl magnesium bromide in THF (2 M, 19.3 mL, 38.6 mmol, 1.2 eq.) was added dropwise to a solution of 2-fluorobenzaldehyde (3.6 g, 32.0 mmol, 1.0 eq.) in tetrahydrofuran (10 mL) at -78 °C. The reaction mixture was reacted at room temperature for 2 hours, then cooled to 0 °C and quenched with saturated ammonium chloride solution. The mixture was extracted with ethyl acetate (30 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:0 to 1:1) to give the target compound (2.2g, yield: 25%).

Step B:

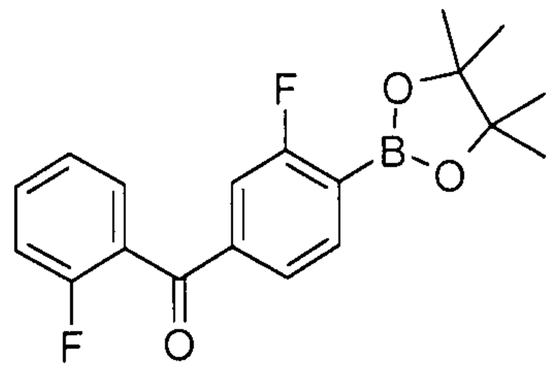


(3-fluoro-4-chlorophenyl)(2-fluorophenyl)methanone

Procedure:

Tetrapropylammonium perruthenate (455 mg, 1.3 mmol, 0.15 eq.), N-methyl morpholine oxide (2.0 g, 17.3 mmol, 2.0 eq.) and 4A molecular sieves (1.0 g) were added to a solution of (3-fluoro-4-chlorophenyl)(2-fluorophenyl)methanol (2.2 g, 8.66 mmol, 1.0 eq.) in dichloromethane (20 mL). The reaction mixture was stirred at room temperature for 2 hours, then concentrated and spin-dried to give crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:0 to 1:1) to give the target compound (2.0 g, yield: 92%).

Step C:

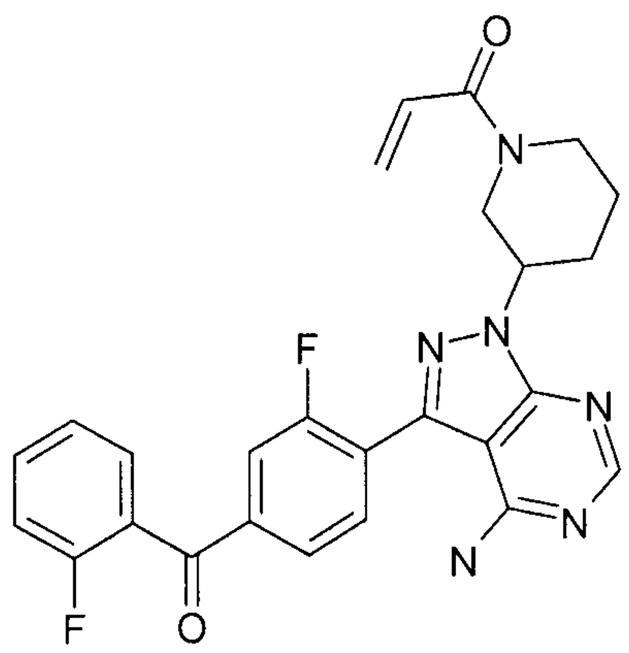


(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)(2-fluorophenyl)methanone

Procedure:

(3-fluoro-4-chlorophenyl)(2-fluorophenyl)methanone (1.5 g, 5.94 mmol, 1.0 eq.), bis(pinacolato)diboron (3.3 g, 13.08 mmol, 2.2 eq.), potassium acetate (1.74 g, 17.8 mmol, 3.0 eq.), tris(dibenzylideneacetone)dipalladium (540 mg, 0.59 mmol, 0.1 eq.) and 2-dicyclohexyl phosphino-2', 4', 6'-triisopropyl biphenyl (1.14 g, 2.37 mmol, 0.4 eq.) were dissolved in 1,4-dioxane (10 mL), and then stirred at 110 °C under microwave irradiation for 1 hours. The reaction mixture was filtered through celite. The filtrate was spin-dried to give the crude product (2.0 g, yield: 100%), which was used directly in the next step.

Step D:



1-(3-(4-amino-3-(2-fluoro-4-(2-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one

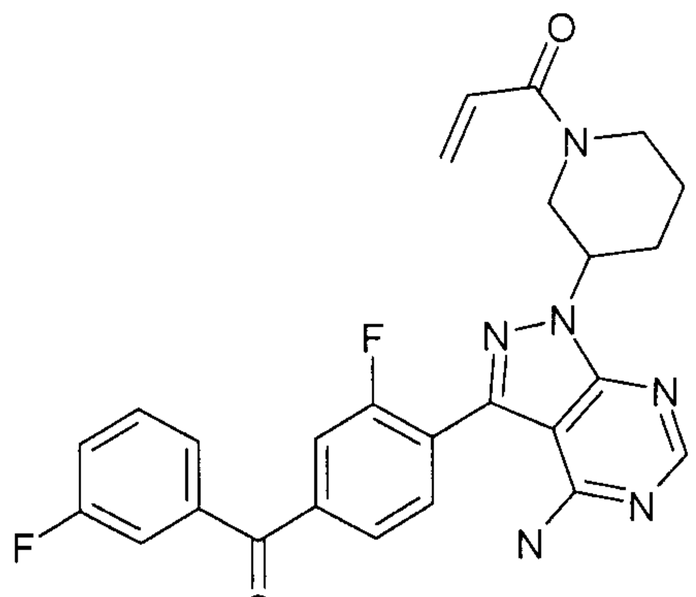
Procedure:

(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)(2-fluorophenyl)methanone (2.0 g, 5.81 mmol, 2.3 eq.), 1-(3-(4-amino-3-iodo-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (1.0 g, 2.51 mmol, 1.0 eq.), sodium carbonate (798 mg, 7.53 mmol, 3.0 eq.) and $Pd(PPh_3)_4$ (300 mg, 0.25 mmol, 0.1 eq.) were dissolved in 1,4-dioxane/water (20 mL, 1/1, v/v). The reaction mixture was stirred at 85 ^oC for 30 min. under nitrogen atmosphere with microwave irradiation. The reaction solution was diluted with water (20 mL), and then extracted with ethyl acetate (20 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient 10% to 100% (volume ratio)) to give the hydrochloride of the target compound (70 mg, yield: 6%).

Spectroscopy data:

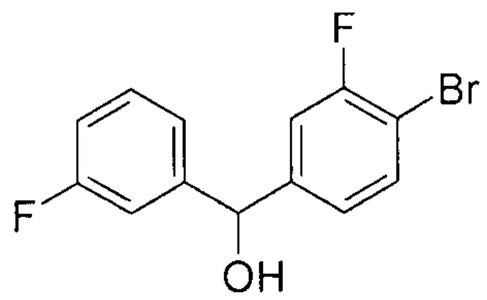
LC/MS (Method: UFLC): RT = 2.156 min; m/z = 489.2 $[M+H]^+$; Total running time: 4 min.

Example 5



1-(3-(4-amino-3-(2-fluoro-4-(3-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl) piperidin-1-yl)prop-2-en-1-one

Step A:

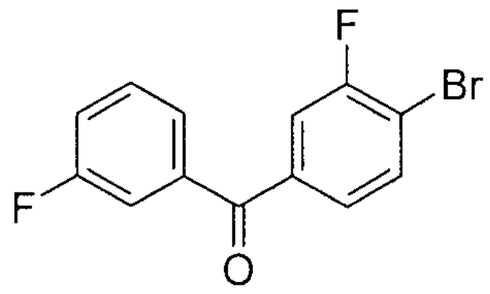


(3-fluoro-4-bromo-phenyl)(3-fluorophenyl)methanol

Procedure:

A solution of 3-fluorophenyl magnesium bromide in THF (1 M, 75 mL, 75 mmol, 1.5 eq.) was added dropwise to a solution of 3-fluoro-4-bromobenzaldehyde (10.0 g, 49.2 mmol, 1.0 eq.) in tetrahydrofuran (100 mL) at -78 °C. The reaction mixture was reacted at room temperature for 2 hours, then cooled to 0 °C and quenched with saturated ammonium chloride solution. The mixture was extracted with ethyl acetate (100 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:0 to 1:1) to give the target compound (2.0 g, yield: 13%).

Step B:

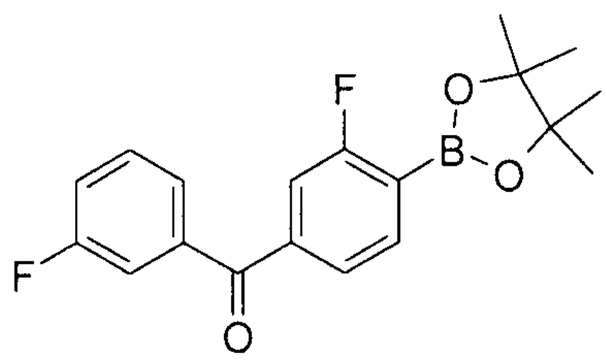


(3-fluoro-4-bromo-phenyl)(3-fluorophenyl)methanone

Procedure:

Tetrapropylammonium perruthenate (350mg, 1.0mmol, 0.15 eq.), N-methyl morpholine oxide (1.56 g, 13.4mmol, 2.0 eq.) and 4A molecular sieves (1.0 g) were added to a solution of (3-fluoro-4-bromo-phenyl)(3-fluorophenyl)methanol (2.0 g, 6.69 mmol, 1.0 eq.) in dichloromethane (20 mL). The reaction mixture was stirred at room temperature for 2 hours, then concentrated and spin-dried to give crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:0 to 1:1) to give the target compound (1.95 g, yield: 98%).

Step C:

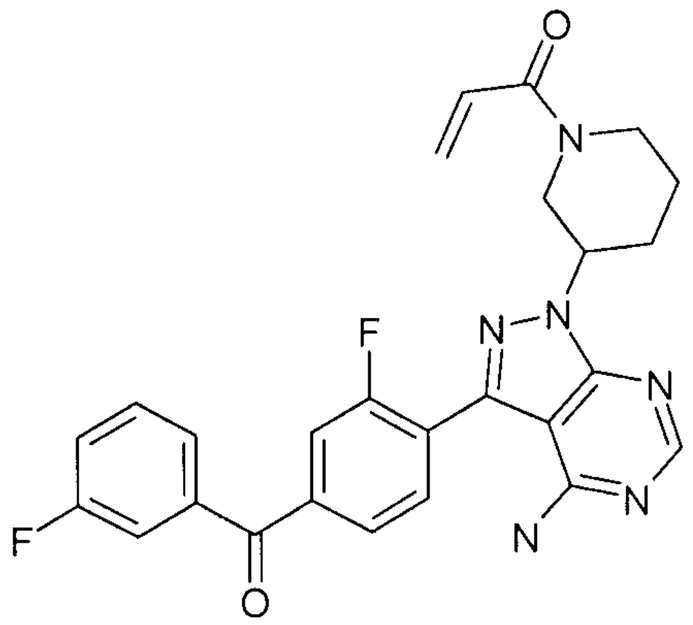


(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)(3-fluorophenyl)methanone

Procedure:

(3-fluoro-4-bromo-phenyl)(3-fluorophenyl)methanone (1.9 g, 6.4 mmol, 1.0 eq.), bis(pinacolato)diboron (2.1 g, 8.3 mmol, 1.2 eq.), potassium acetate (1.9 g, 19.2 mmol, 3.0 eq.), tris(dibenzylideneacetone)dipalladium (585 mg, 0.64 mmol, 0.1 eq.) and 2-dicyclohexyl phosphino-2',4',6'-triisopropyl biphenyl (1.21 g, 2.56 mmol, 0.4 eq.) were dissolved in 1,4-dioxane (10 mL), and then stirred at 110 °C under microwave irradiation for 1 hours. The reaction mixture was filtered through celite. The filtrate was spin-dried to give the crude product (2.2 g, yield: 100%), which was used directly in the next step.

Step D:



1-(3-(4-amino-3-(2-fluoro-4-(3-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl) piperidin-1-yl)prop-2-en-1-one

Procedure:

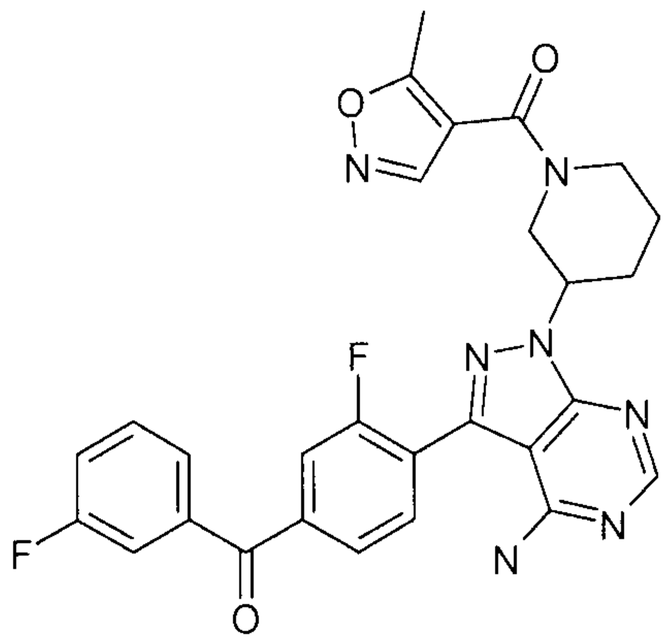
(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)(3-fluorophenyl)methanone (2.5 g, 7.3 mmol, 2.0 eq.), 1-(3-(4-amino-3-iodo-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (1.4 g, 3.6 mmol, 1.0 eq.), sodium carbonate (1.14g, 10.8 mmol, 3.0 eq.) and $Pd(PPh_3)_4$ (416 mg, 0.36 mmol, 0.1 eq.) were dissolved in 1,4-dioxane/water (20 mL, 1/1, v/v). The reaction mixture was stirred at 85 °C for 30 min. under nitrogen atmosphere with microwave irradiation. The reaction mixture was diluted with water (50 mL), and then extracted with ethyl acetate (50 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient 10% to 100% (volume ratio)) to give the hydrochloride of the target compound (150 mg, yield: 4%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 0.787 min; m/z = 489.1 $[M+H]^+$; Total running time: 1.5 min.

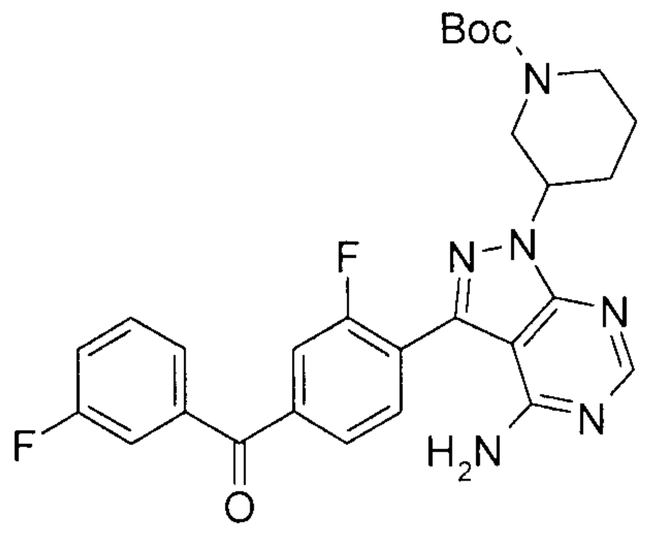
^1H NMR (400MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.78-7.73 (m, 3H), 7.65-7.53 (m, 3H), 7.35-7.25 (m, 1H), 6.64-6.57 (m, 1H), 6.35-6.28 (m, 1H), 5.76-5.66 (m, 1H), 5.48 (br, 2H), 4.99-4.90 (m, 1.5H), 4.60-4.56 (m, 0.5H), 4.25-4.22 (m, 0.5H), 4.07-4.05 (m, 0.5H), 3.81-3.77 (m, 0.5H), 3.45-3.41 (m, 0.5H), 3.28-3.20 (m, 0.5H), 2.99-2.94 (m, 0.5H), 2.44-2.32 (m, 2H), 2.06-2.01 (m, 1H), 1.80-1.76 (m, 1H).

Example 6



(3-(4-amino-3-(2-fluoro-4-(3-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)(5-methylisoxazol-4-yl)methanone

Step A:



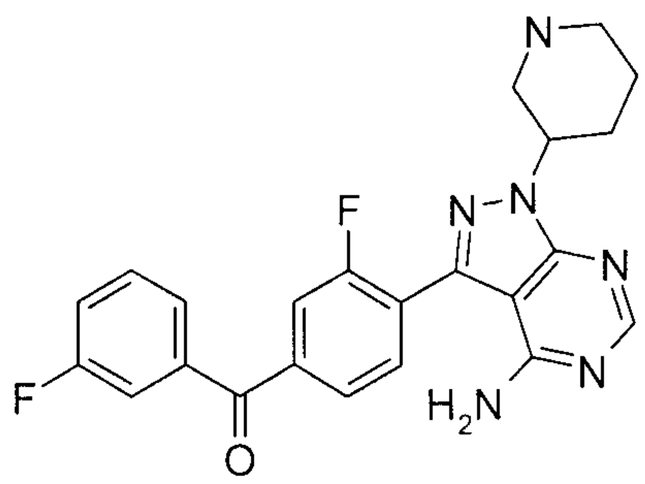
tert-butyl 3-(4-amino-3-(2-fluoro-4-(3-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-formate

Procedure:

(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)(3-fluorophenyl)methanone (1.16 g, 3.38 mmol, 2.0 eq.), tert-butyl 3-(4-amino-3-iodo-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-formate (0.75 g, 1.69 mmol, 1.0 eq.), sodium carbonate (358 mg, 3.38 mmol, 2.0 eq.) and $Pd(PPh_3)_4$ (196 mg, 0.17 mmol, 0.1 eq.) were dissolved in 1,4-dioxane (10 mL). The reaction mixture was stirred at 85 °C for 30 min. under nitrogen atmosphere with microwave irradiation. The reaction mixture was diluted with water (50 mL), and then extracted with ethyl acetate (50 mL) 3 times. The combined organic phases

were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: ethyl acetate : petroleum ether=1:1) to give the target compound (500 mg, yield: 55%).

Step B:

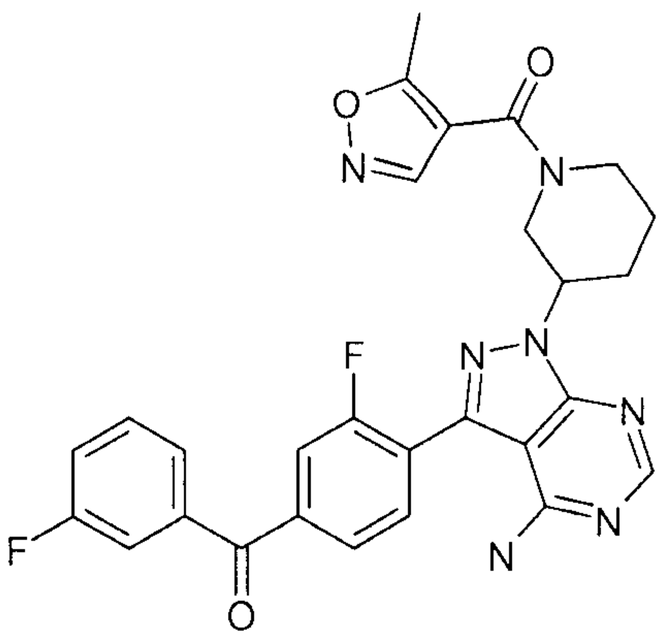


(4-(4-amino-1-(piperidin-3-yl)- pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenyl)(3-fluorophenyl)methanone

Procedure:

4M HCl/EA (5 mL) was added to a solution of tert-butyl 3-(4-amino-3-(2-fluoro-4-(3-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-formate (500 mg, 0.94 mol) in dicloromethane (5 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (440 mg, yield: 99%).

Step C:



(3-(4-amino-3-(2-fluoro-4-(3-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)(5-methylisoxazol-4-yl)methanone

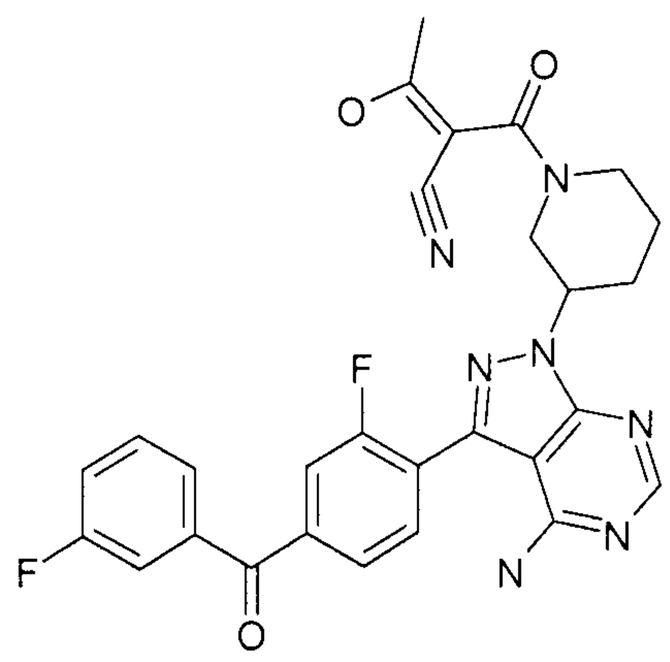
Procedure:

5-methylisoxazole-4-carboxylic acid (15 mg, 0.11 mmol, 1.1 eq.), HATU (60 mg, 0.15 mmol, 1.5 eq.) and DIPEA (38 mg, 0.3 mmol, 3.0 eq.) were added to a solution of (4-(4-amino-1-(piperidin-3-yl) -pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenyl)(3-fluorophenyl)methanone (45 mg, 0.1 mmol, 1.0 eq.) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 12 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, eluent gradient 10% to 100% (volume ratio)) to give the target compound hydrochloride (44 mg, yield: 81%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.976 min; m/z = 544.3 $[M+H]^+$; Total running time: 7 min.

Example 7



(E)-2-(3-(4-amino-3-(2-fluoro-4-(3-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)-2-hydroxy-but-2-enenitrile

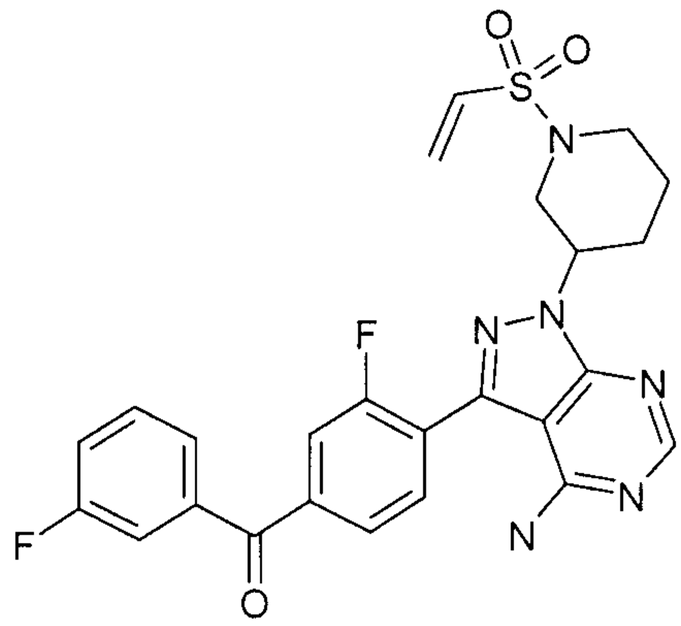
Procedure:

Triethylamine (17 mg, 0.16 mmol, 3.0 eq .) was added to a solution of (3-(4-amino-3-(2-fluoro-4-(3-fluorobenzoyl)phenyl) pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)(5-methylisoxazol-4-yl)methanone (30 mg, 0.055 mmol, 1.0 eq.) in tetrahydrofuran (10 mL). The reaction mixture was stirred at room temperature for 12 hours, concentrated and spin-dried to give the target compound (26 mg, yield: 83%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 1.089 min; m/z = 544.3 $[M+H]^+$; Total running time: 2 min.

Example 8



(4-(4-amino-1-(1-(vinylsulfonyl)piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenyl)(3-fluorophenyl)methanone

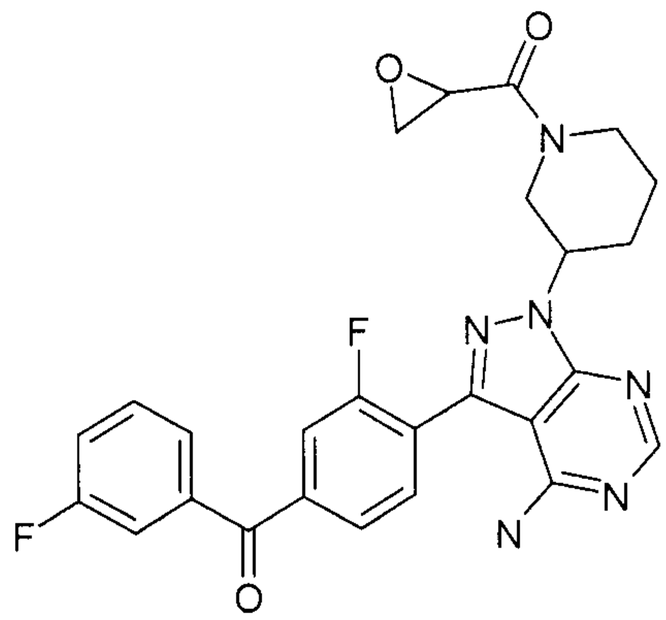
Procedure:

2-chloroethanesulfonyl chloride (16 mg, 0.1 mmol, 1.0 eq.) and triethylamine (50 mg, 0.5 mmol, 5.0 eq.) were added to a solution of (4-(4-amino-1-(piperidin-3-yl) -pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenyl)(3-fluorophenyl)methanone (45 mg, 0.1 mmol, 1.0 eq.) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 12 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water, eluent gradient 10% to 100% (volume ratio)), evaporated under a reduced pressure to remove volatile components, and lyophilized to give the target compound (2 mg, yield: 4%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.030 min; m/z = 525.1 $[M+H]^+$; Total running time: 3 min.

Example 9



(3-(4-amino-3-(2-fluoro-4-(3-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)(oxiran-2-yl)methanone

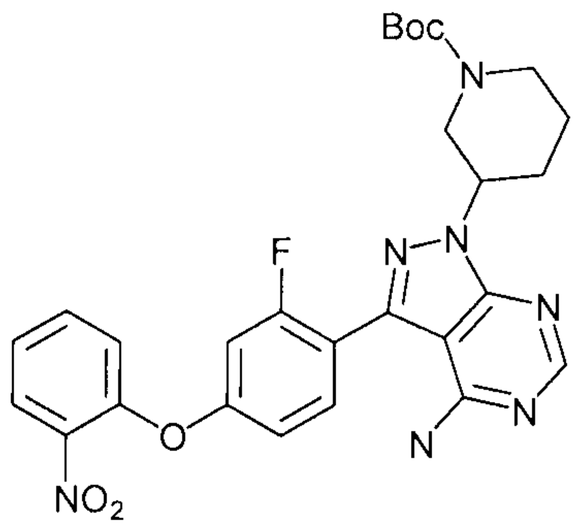
Procedure:

Potassium oxirane-2-formate (19 mg, 0.15 mmol, 1.0 eq.), PyBrop (84 mg, 0.18 mmol, 1.2 eq.) and DIPEA (38 mg, 0.3 mmol, 2.0 eq.) were added to a solution of (4-(4-amino-1-(piperidin-3-yl) pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenyl)(3-fluorophenyl)methanone (65 mg, 0.15 mmol, 1.0 eq.) in DMF (2 mL). The reaction was heated to 90 °C and stirred for 12 hours. After cooling to room temperature, the reaction mixture was diluted with saturated brine (10 mL) and extracted with ethyl acetate (10 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, eluent gradient 10% to 100% (volume ratio)), evaporated under a reduced pressure to remove volatile components, and lyophilized to give the hydrochloride of the target compound (38 mg, yield: 51%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 4.157 min; m/z = 505.2 $[M+H]^+$; Total running time: 7 min.

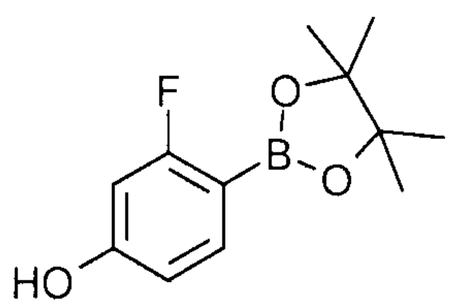
Example 10



tert-butyl 3-(4-amino-3-(2-fluoro-4-(2-nitrophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)

piperidine-1-formate

Step A:

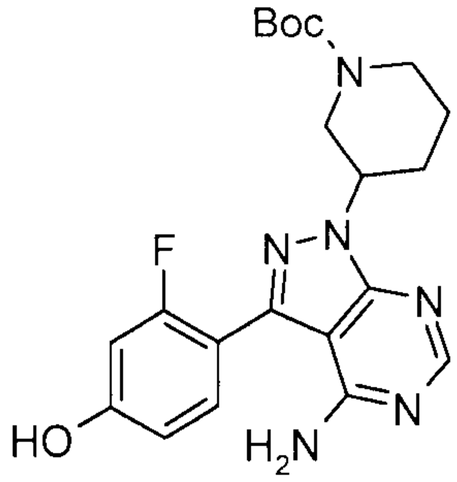


3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol

Procedure:

3-fluoro-4-bromophenol (0.5 g, 2.62 mmol, 1.0 eq.), bis(pinacolato)diboron (0.86 g, 3.41 mmol, 1.3 eq.), potassium acetate (490 mg, 5.02 mmol , 3.0 eq.), X-phos (125 mg, 0.26 mmol, 0.1 eq.) and $Pd_2(dba)_3$ (0.24 g, 0.26 mmol, 0.1 eq.) were dissolved in 1,4-dioxane (10 mL). The resulting mixture was heated to 90 °C and stirred under nitrogen for 1 hour. The reaction mixture was filtered through celite. The filtrate was spin-dried to give the crude product (0.62 g, yield: 99%), which was used directly in the next step.

Step B:



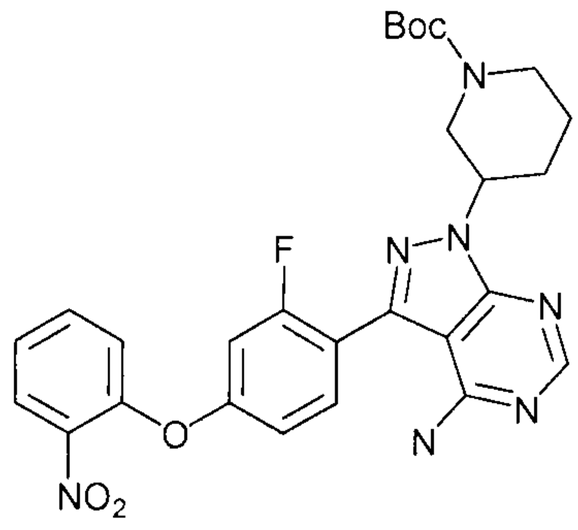
tert-butyl 3-(4-amino-3-(2-fluoro-4-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)

piperidine-1-formate

Procedure:

3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (268 mg, 1.13 mmol, 2.0 eq.), tert-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-formate (250 mg, 0.56 mmol, 1.0 eq.), potassium phosphate (239 mg, 1.13 mmol, 2.0 eq.) and Pd-118 (18 mg, 0.028 mmol, 0.05 eq.) were dissolved in 1,4-dioxane/water (11 mL, 10/1, v/v). The reaction mixture was stirred at 60 °C for 14 min. under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was diluted with ice-water (10 mL), and then extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by thin layer chromatography (eluent: ethyl acetate) to give the target compound (150 mg, yield: 62%).

Step C:



tert-butyl 3-(4-amino-3-(2-fluoro-4-(2-nitrophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)

piperidine-1-formate

Procedure:

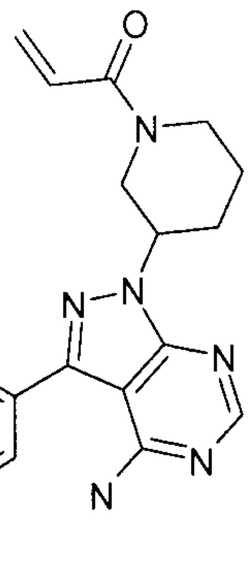
2-fluoro-nitrobenzene (20 mg, 0.14 mmol, 1.2 eq.) and potassium carbonate (32 mg, 0.233 mmol, 2.0 eq.) were added to a solution of tert-butyl 3-(4-amino-3-(2-fluoro-4-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-formate (50 mg, 0.117 mmol, 1.0 eq.) in DMF (2 mL). The reaction mixture was stirred at 100 °C for 14 hours. After cooling to room temperature, the mixture was filtered, and the filter cake was washed with ethyl acetate. The filtrate was concentrated and spin-dried to give the crude product, which was separated by HPLC with C18 reversed-phase column (mobile phase:

acetonitrile/water/0.7%NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated under a reduced pressure to remove volatile components, and lyophilized to give the target compound (8 mg, yield: 12%).

Spectroscopy data:

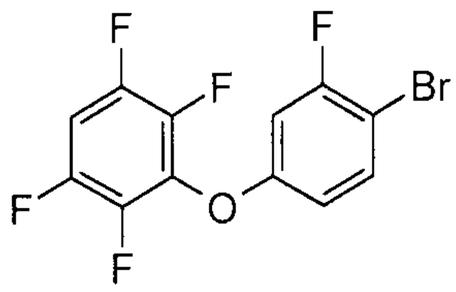
LC/MS (Method: UFLC): RT = 3.320 min; m/z = 550.4 $[M+H]^+$; Total running time: 7min.

Example 11



1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one

Step A:

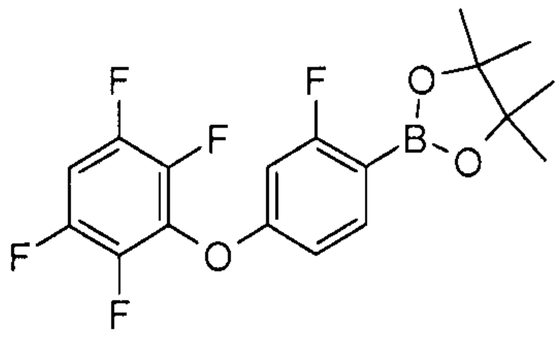


3-(3-fluoro-4-bromophenoxy)-1,2,4,5-tetrafluorobenzene

Procedure:

Potassium carbonate (68.0 g, 492.1 mmol, 2.0 eq.) and 1,2,3,4,5-pentafluorophenyl (49.6 g, 295.3 mmol, 1.2 eq.) were added to a solution of -3-fluoro-4-bromophenol (47.0 g, 246.1 mmol, 1.0 eq.) in DMF (500 mL). The reaction was stirred for 12 hours at 100 °C, and evaporated under a reduced pressure to remove the solvent. The residue was dissolved in ethyl acetate (300 mL), washed with water (100 mL) 2 times and saturated brine (100 mL) 1 time. The organic phase was dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (78 g, yield: 93%).

Step B:

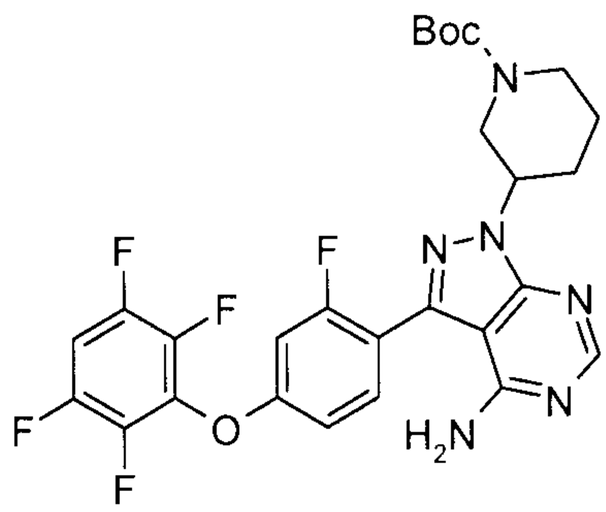


2-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

Procedure:

3-(3-fluoro-4-bromophenoxy)-1,2,4,5-tetrafluorobenzene (73 g, 215.3 mmol, 1.0 eq.), bis(pinacolato)diboron (65.6 g, 258.4 mmol, 1.2 eq.), potassium acetate (31.6 g, 322.9 mmol, 1.5 eq.) and (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium (9.4 g, 12.8 mmol, 0.06 eq.) were dissolved in 1,4-dioxane (1 L). The resulting mixture was at stirred 80 °C under nitrogen for 14 hours. After cooling to room temperature, the reaction mixture was filtered through celite. The filtrate was spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether) to give the target compound (60 g, yield: 72%).

Step C:

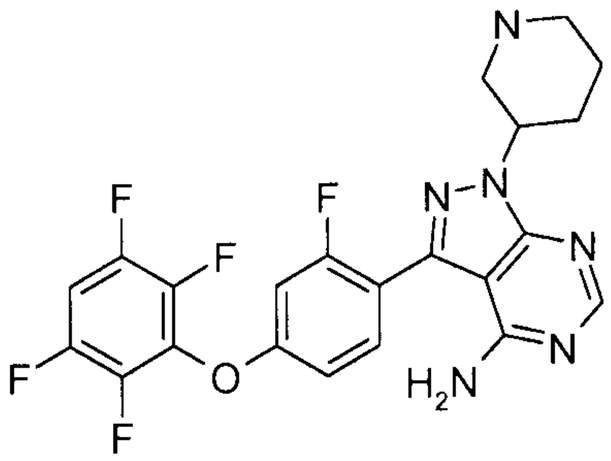


tert-butyl 3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-formate

Procedure:

tert-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-formate (7.6 g, 17.1 mmol, 1.0 eq.), 2-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (8.6 g, 22.3 mmol, 1.3 eq.), potassium phosphate (7.3 g, 34.2 mmol, 2.0 eq.) and Pd-118 (0.56 g, 0.855 mmol, 0.05 eq.) were dissolved in 1,4-dioxane/water (240 mL, 5/1, v/v). The reaction mixture was stirred at 60 °C for 12 hours under nitrogen atmosphere. The reaction mixture was poured into ice-water (300 mL) after cooling to room temperature, and then extracted with ethyl acetate (100 mL) 4 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: ethyl acetate) to give the target compound (6.8 g, yield: 69%).

Step D:

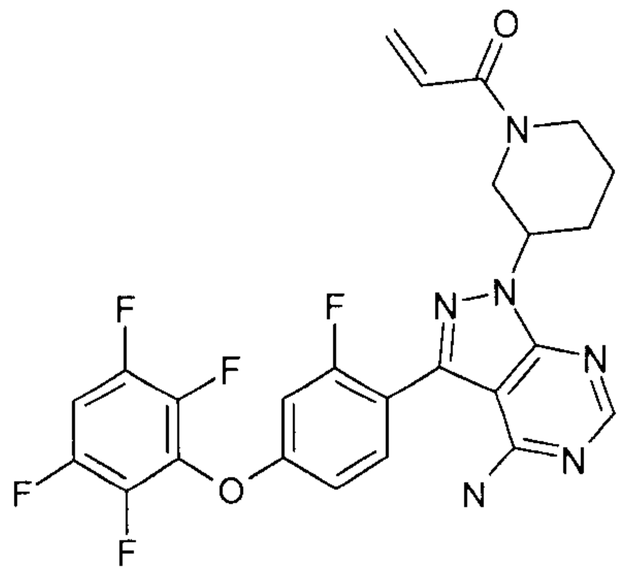


3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d] pyrimidin-4-amine

Procedure:

4M HCl/EA (20 mL) was added to a solution of tert-butyl 3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-formate (6.8 g, 11.8 mmol) in ethyl acetate (50 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (5.2 g, yield: 86%).

Step E:



1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one

Procedure:

Triethylamine (887 mg, 8.7 mmol, 3.0 eq.) and acryloyl chloride (0.26 g,2.9mmol, 1.0 eq.) were added subsequently to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (1.5 g, 2.9 mmol, 1.0 eq.) in

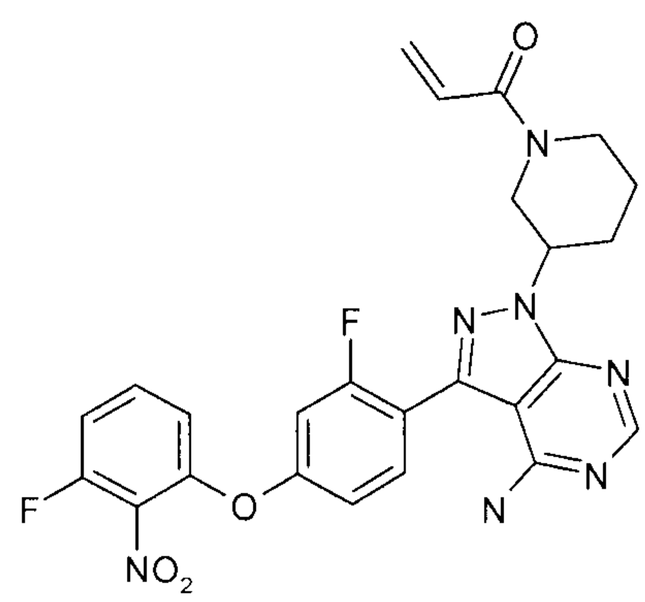
dichloromethane (10 mL). The reaction mixture was stirred at 0 °C for 1 hour, and then quenched with water (5 mL), diluted with dichloromethane (50 mL), washed with water (30 mL) 2 times and saturated brine (30 mL) 1 time. The organic phase was dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:0 to 1:1) to give the target compound (0.94 g, yield: 64%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 3.130 min; m/z = 531.1 $[M+H]^+$; Total running time: 7 min.

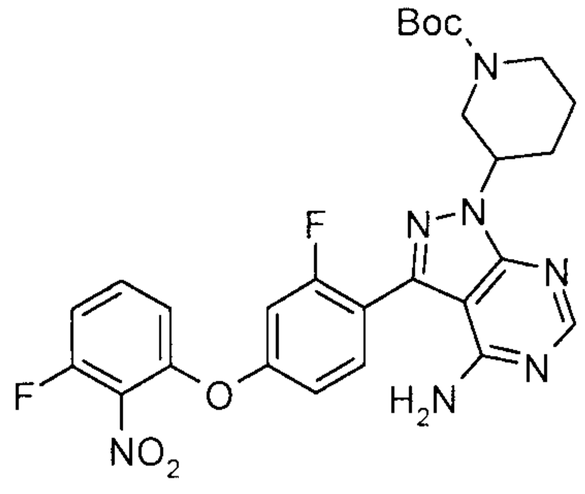
^{1}H NMR (400MHz, DMSO-d_6) δ 8.22 (s, 1H), 8.00-7.91 (m, 1H), 7.55-7.46 (m, 1H), 7.27 (dd, J = 2.4, 10.8 Hz, 1H), 7.12 (dd, J = 2.4, 8.8 Hz, 1H), 6.88-6.65 (m, 1H), 6.13-6.02 (m, 1H), 5.70-5.56 (m, 1H), 4.71-4.65 (m, 1H), 4.54-4.51 (m, 0.5H), 4.20-4.17 (m, 1H), 4.07-4.04 (m, 0.5H), 3.67-3.60 (m, 0.5H), 3.17-3.12 (m, 1H), 2.98-2.94 (m, 0.5H), 2.26-2.21 (m, 1H), 2.11-2.06 (m, 1H), 1.92-1.89 (m, 1H), 1.58-1.54 (m, 1H).

Example 12



1-(3-(4-amino-3-(2-fluoro-4-(3-fluoro-2-nitrophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one

Step A:

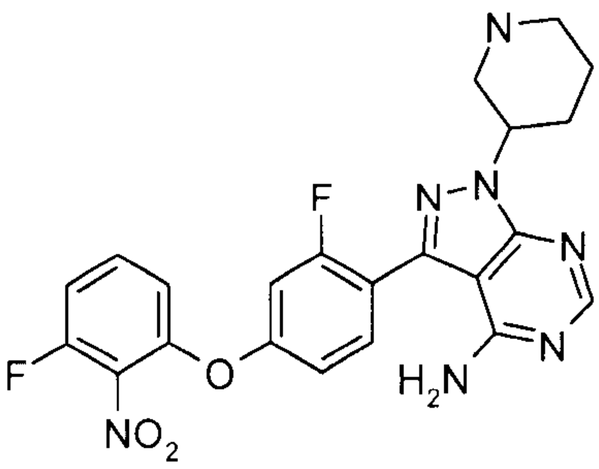


tert-butyl 3-(4-amino-3-(2-fluoro-4-(3-fluoro-2-nitrophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-formate

Procedure:

1,3-difluoro-2-nitrobenzene (222.8 mg, 1.4 mmol, 3.0 eq.) and potassium carbonate (96.8 mg, 0.7 mmol, 1.5 eq.) were added to a solution of tert-butyl 3-(4-amino-3-(2-fluoro-4-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-formate (200 mg, 0.467 mmol, 1.0 eq.) in acetonitrile (5 mL). The reaction mixture was stirred at 60 °C for 12 hours. After cooling to room temperature, the mixture was poured into water (10 mL), and then extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by thin layer chromatography (eluent: ethyl acetate) to give the target compound (90 mg, yield: 34%).

Step B:



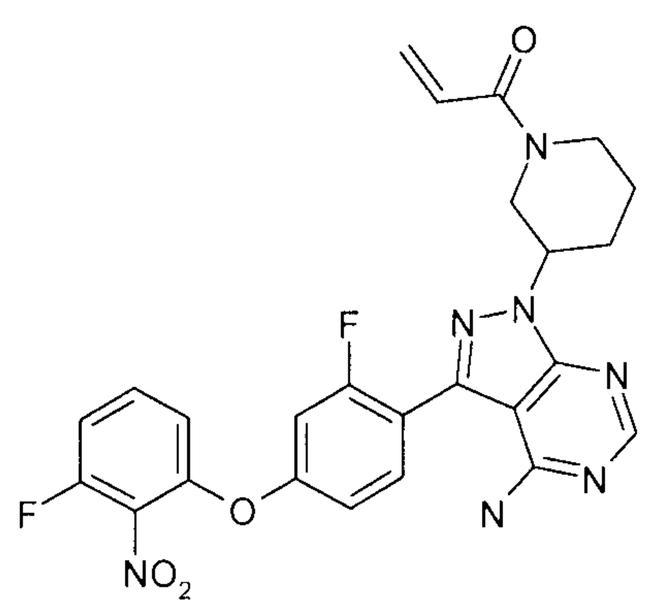
3-(2-fluoro-4-(3-fluoro-2-nitrophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EA (1 mL) was added to a solution of tert-butyl 3-(4-amino-3-(2-fluoro-4-(3-fluoro-2-nitrophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-formate (90 mg,

0.16 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (75 mg, yield: 94%).

Step C:



1-(3-(4-amino-3-(2-fluoro-4-(3-fluoro-2-nitrophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one

Procedure:

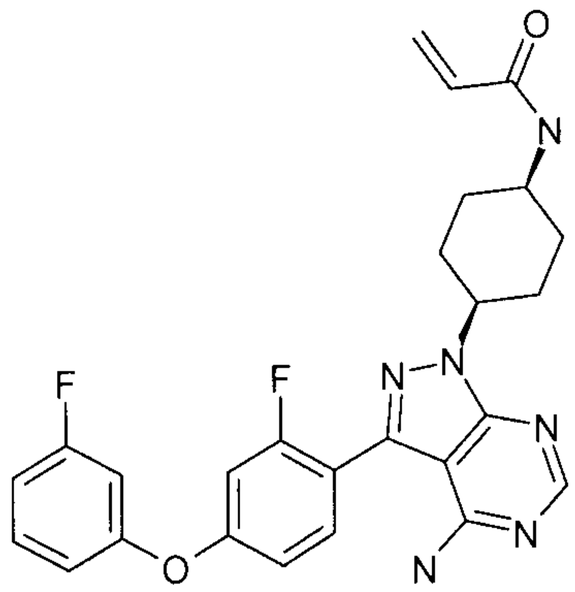
Triethylamine (45 mg, 0.45 mmol, 3.0 eq.) and acryloyl chloride (13 mg, 0.15mmol, 1.0 eq.) were added subsequently to a solution of 3-(2-fluoro-4-(3-fluoro-2-nitrophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (75 mg, 0.15 mmol, 1.0 eq.) in dichloromethane (2 mL). The reaction mixture was stirred at 0 °C for 1 hour, and then quenched with water (5 mL), diluted with dichloromethane (10 mL), washed with water (5 mL) 2 times and saturated brine (5 mL) 1 time. The organic phase was dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: dichloromethane: methanol=5:1) to give the target compound (19 mg, yield: 24%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.538 min; m/z = 522.3 $[M+H]^+$; Total running time: 7min.

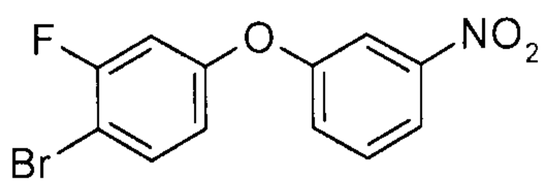
^{1}H NMR (400MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.71-7.55 (m, 2H), 7.43 (t, J = 9.2 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 7.2 Hz, 1H), 6.88-6.67 (m, 1H), 6.13-6.02 (m, 1H), 5.70-5.56 (m, 1H), 4.69-4.53 (m, 1.5H), 4.21-4.05 (m, 1.5H), 3.68-3.61 (m, 0.5H), 3.21-3.18 (m, 1H), 3.05-2.99 (m, 0.5H), 2.24-2.13 (m, 2H), 1.92-1.89 (m, 1H), 1.59-1.54 (m, 1H).

Example 13



N-((1s,4s)-4-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)acrylamide

Step A:

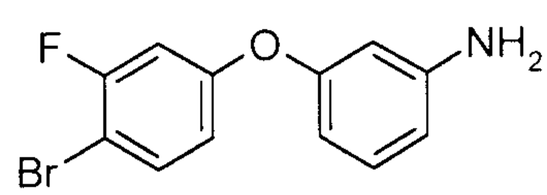


1-(3-fluoro-4-bromophenoxy)-3-nitrobenzene

Procedure:

Potassium carbonate (58 g, 420 mmol, 2.0 eq.) and 1-fluoro-3-nitrobenzene (29.6 g, 210 mmol, 1.0 eq.) were added to a solution of 3-fluoro-4-bromophenol (40 g, 210 mmol, 1.0 eq.) in DMF (400 mL). The reaction mixture was stirred for 12 hours at 90 °C, and evaporated to remove the solvent under reduced pressure. The residue was diluted withwater (300 mL), extrated with ethyl acetate (300 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (65 g, yield: 100%).

Step B:

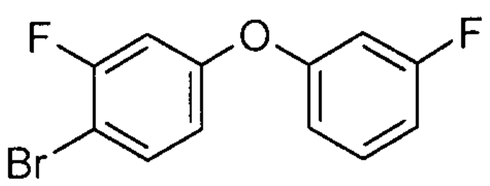


3-(3-fluoro-4-bromophenoxy)benzenamine

Procedure:

Chloride ammonium (28 g, 525 mmol, 2.5 eq.) and iron powder (58.8 g, 1.05 mol, 5.0 eq.) were added to a solution of 1-(3-fluoro-4-bromophenoxy)-3-nitrobenzene (65 g, 210 mmol, 1.0 eq.) in ethanol (300 mL) and water (60 mL). The reaction mixture was refluxed under nitrogen for 12 hours. After cooling to room temperature, the reaction was filtered through celite. The filtrate was concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column, (mobile phase: acetonitrile/water/0.7%NH_4HCO_3, gradient: 10% 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (19 g, yield: 23%).

Step C:

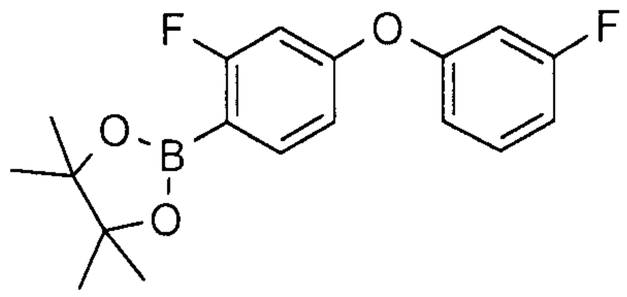


1-bromo-2-fluoro-4-(3-fluorophenoxy)benzene

Procedure:

3-(3-fluoro-4-bromophenoxy)aniline (9 g, 32 mmol, 1.0 eq.) was added portionwise to pyridine-hydrogen fluoride solution (30 mL) at -10 °C. The resulting reaction mixture was stirred at 0 °C for 30 min., and then sodium nitrite (2.42 g, 35 mmol, 1.1 eq.) was added portionwise at -10 °C. The reaction mixture was stirred at 20 °C for 30 min., then at 60 °C for 14 hours. After cooling to room temperature, the reaction solution was poured into ice-ethanol (50 mL), into which was added with a saturated solution of $NaHCO_3$ (50 mL), and then extracted with ethyl acetate (50 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether) to give the target compound (5.8 g, yield: 64%).

Step D:

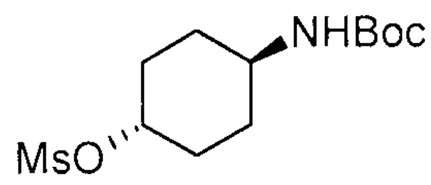


2-(2-fluoro-4-(3-fluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

Procedure:

1-bromo-2-fluoro-4-(3-fluorophenoxy)benzene (5.8 g, 20 mmol, 1.0 eq.), bis(pinacolato)diboron (6.1 g, 24 mmol, 1.2 eq.), potassium acetate (3.9 g, 40 mmol, 2.0 eq.) and (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium (0.89 g, 1.2 mmol, 0.06 eq.) were dissolved in 1,4-dioxane (100mL). The resulting mixture was stirred at 85 °C under nitrogen for 14 hours. After cooling to room temperature, the reaction mixture was filtered through celite. The filtrate was concentrated to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether) to give the target compound (6.5 g, yield: 100%).

Step E:

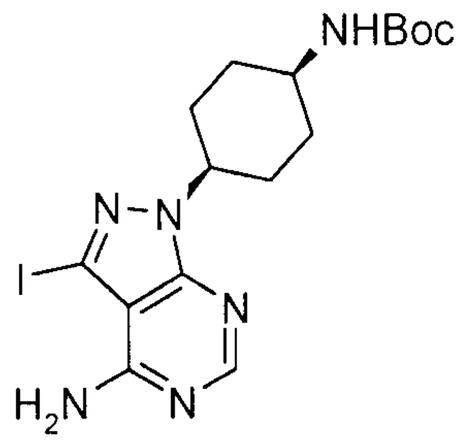


(1r,4r)-4-(tert-butoxycarbonyl)cyclohexyl methanesulfonate

Procedure:

Triethylamine (7 g, 70 mmol, 3.0 eq.) and methanesulfonyl chloride (2.9 g, 25.5 mmol, 1.1 eq.) were subsequently added to a solution of tert-butyl (1r,4r)-4-hydroxycyclohexylcarbamate (5.0 g, 23.2 mmol, 1.0 eq.) in dichloromethane (100 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 1 hour, quenched with saturated $NaHCO_3$ (100 mL), and then extracted with dichloromethane (200 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (6.0 g, yield: 88%).

Step F:

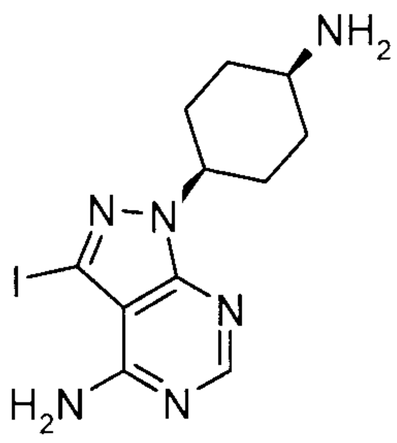


tert-butyl (1s,4s)-4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl) cyclohexylcarbamate

Procedure:

Cesium carbonate (8.8 g, 27.6 mmol, 2.0 eq.) and (1r,4r)-4-(tert-butoxycarbonyl)cyclohexyl methanesulfonate (6.0 g, 20.5 mmol, 1.5 eq.) were added to a solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (3.6 g, 13.6 mmol, 1.0 eq.) in DMF (50 mL) at 0 °C. The reaction mixture was stirred at 80 °C overnight, filtered through celite, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: ethyl acetate) to give the target compound (4 g, yield: 64%).

Step G:

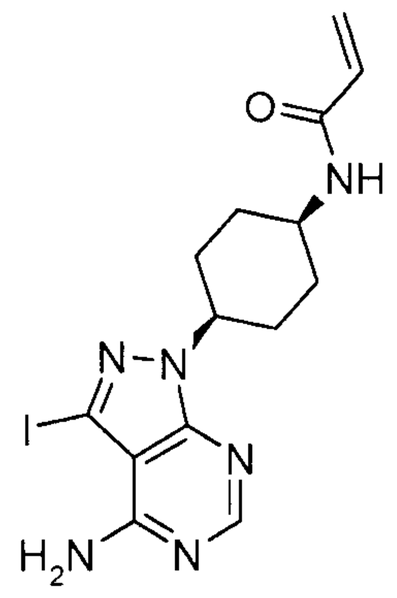


1-((1s,4s)-4-aminocyclohexyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EA (20 mL) was added to a solution of tert-butyl (1s,4s)-4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexylcarbamate (4 g, 8.73 mmol) in dichloromethane (20 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (2.5g, yield: 73%).

Step H:

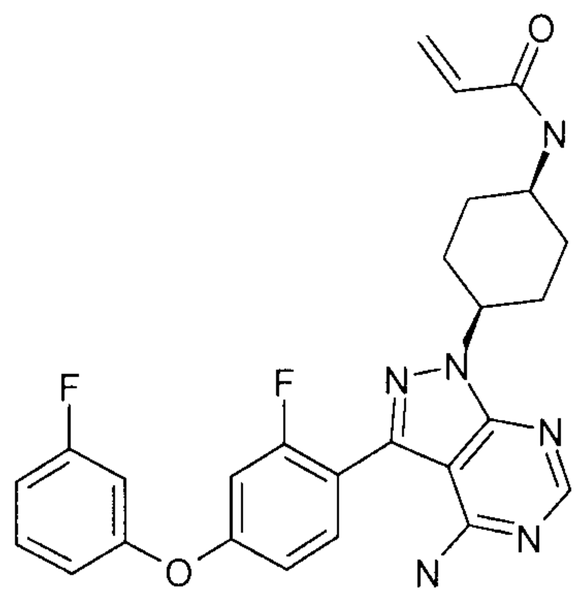


N-((1s,4s)-4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)acrylamide

Procedure:

Triethylamine (1.9 g, 19 mmol, 3.0 eq.) and acryloyl chloride (570 mg, 6.3 mmol, 1.0 eq.) were subsequently added to a solution of 1-((1s,4s)-4-aminocyclohexyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (2.5 g, 6.3 mmol, 1.0 eq.) in dichloromethane (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, and then quenched with saturated $NaHCO_3$ (30 mL). The aqueous phase was extracted with dichloromethane (50 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: ethyl acetate) to give the target compound (2.0g, yield: 77%).

Step I:



N-((1s,4s)-4-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)acrylamide

Procedure:

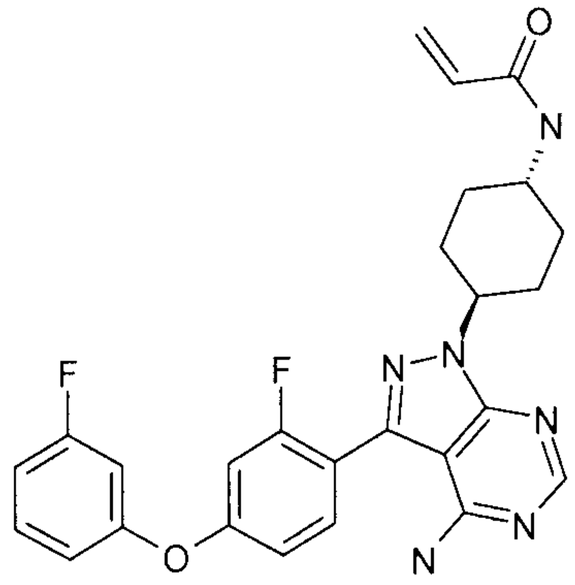
The compound N-((1s,4s)-4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)acrylamide (250 mg, 0.6 mmol, 1.0 eq.), 2-(2-fluoro-4-(3-fluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (400 mg, 1.2 mmol, 2.eq.), sodium carbonate (200 mg, 1.8 mmol, 3.0 eq.) and $Pd(PPh_3)_4$ (70 mg, 0.06 mmol, 0.1 eq.) were dissolved in 1,4-dioxane/water (10 mL, 1/1, v/v). The reaction mixture was stirred at 80 °C for 40 min. under nitrogen atmosphere with microwave irradiation. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by thin layer chromatography (eluent: ethyl acetate) to give the target compound (75 mg, yield: 23%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.856 min; m/z =491.3 $[M+H]^+$; Total running time: 7 min.

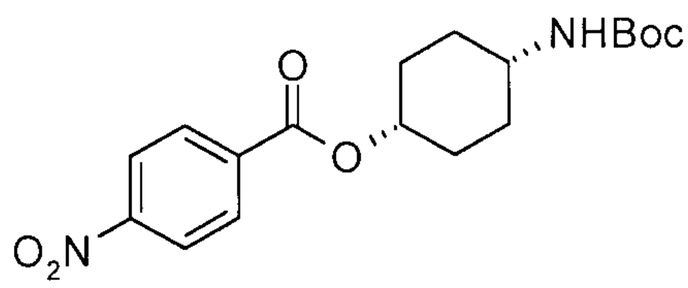
^{1}H NMR (400MHz, DMSO-d_6) δ 8.22 (s, 1H), 8.14 (d, 1H), 7.58-7.44 (m, 2H), 7.14-6.96 (m, 6H), 6.42-6.35 (m, 1H), 6.09-6.04 (m, 1H), 5.56-5.52 (m, 1H), 4.77-4.73 (m, 1H), 3.99-3.95 (m, 1H), 2.25-2.15 (m, 2H), 1.88-1.72 (m, 6H).

Example 14



N-((1r,4r)-4-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)acrylamide

Step A:



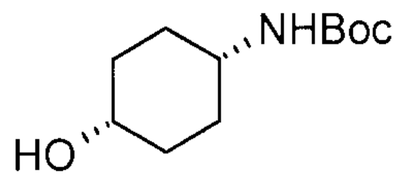
(1s,4s)-4-(tert-butoxycarbonyl)cyclohexyl 4-nitrobenzoate

Procedure:

Tert-butyl (1r,4r)-4-hydroxycyclohexylcarbamate (4.4 g, 20.4 mmol, 1.0 eq.), 4-nitrobenzoic acid (8.4 g, 50.3 mmol, 2.5 eq.) and triphenylphosphine (8.0 g, 30.5 mmol, 1.5 eq.) were dissolved in toluene (240 mL) and tetrahydrofuran (20 mL). Diethyl azodiformate (7.1 g, 40.8 mmol, 2.0 eq.) was added to the resulting mixture. The reaction mixture was stirred at room temperature for 12 hours under nitrogen atmosphere, evaporated to remove solvents under reduced pressure, into which was added with dichloromethane (500 mL) , stirred for 30 min., and then filtered. The filtrate was concentrated and spin-dried to give the crude product, which was purified by silica gel

column chromatography (eluent: petroleum ether: ethyl acetate=10:1 to 1:1) to give the target compound (4.0 g, yield: 54%).

Step B:

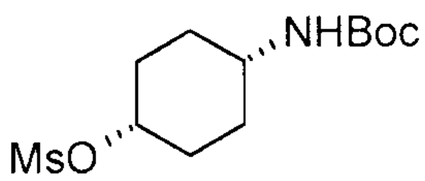


tert-butyl (1s,4s)-4-hydroxycyclohexylcarbamate

Procedure:

(1s,4s)-4-(tert-butoxycarbonyl)cyclohexyl 4-nitrobenzoate (4.0 g, 11.0 mmol) was dissolved in tetrahydrofuran (50 mL) and NaOH solution (2N, 100 mL), and then refluxed for 12 hours. The reaction mixture was diluted with water (50 mL), and extracted with methyl tert-butyl ether (50 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to to give the target compound (1.0 g, yield: 40%).

Step C:

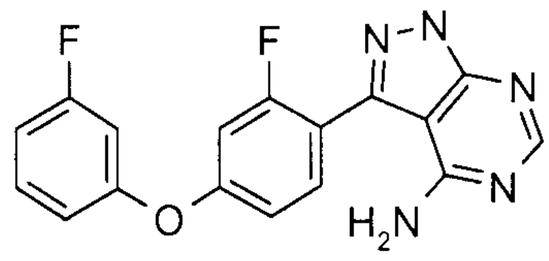


(1s,4s)-4-(tert-butoxycarbonyl)cyclohexyl methanesulfonate

Procedure:

Triethylamine (1.4 g, 14.0 mmol, 3.0 eq.) and methanesulfonyl chloride (0.8 g, 7.0 mmol, 1.5 eq.) were added sequentially to a solution oftert-butyl (1s,4s)-4-hydroxycyclohexylcarbamate (1.0 g, 4.6 mmol, 1.0 eq.) in dichloromethane (30 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, quenched with water (5 mL), washed with water (30 mL) 2 times and brine (30 mL) 1 time. The organic phase was dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (860 mg, yield: 64%).

Step D:

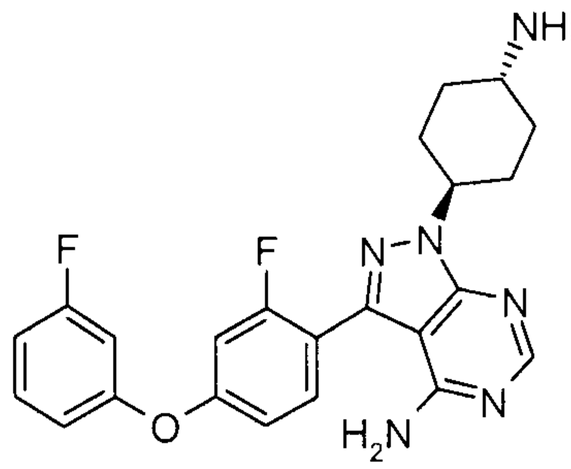


3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (2.3 g, 8.8 mmol, 1.0 eq.), 2-(2-fluoro-4-(3-fluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.8 g, 17.6 mmol, 2.0 eq.), potassium phosphate (3.7 g, 17.6 mmol, 2.0 eq.) and Pd-118 (570 mg, 0.88 mmol, 0.1 eq.) were dissolved in 1,4-dioxane/H_2O (40 mL, 1/1, v/v). The reaction mixture was stirred at 80 °C for 40 min. under nitrogen atmosphere with microwave irradiation. After colling to room temperature, the reaction mixture was extracted with ethyl acetate (50 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: ethyl acetate) to give the target compound (700 mg, yield: 23%).

Step E:



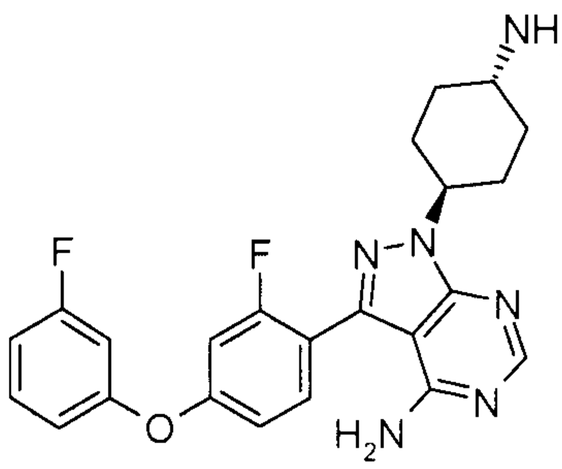
tert-butyl (1r,4r)-4-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexylcarbamate

Procedure:

Cesium carbonate (385 mg, 1.18 mmol, 2.0 eq.) and (1s,4s)-4-(tert-butoxycarbonyl)cyclohexyl methanesulfonate (346 mg, 1.18 mmol, 2.0 eq.) were added to a solution of 3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (200 mg, 0.59 mmol, 1.0 eq.) in DMF (10 mL). The reaction mixture was stirred at 80 °C for 12 hours, cooled to room temperatureand filtered. The filtrate was concentrated and spin-dired to give the crude product,

which was purified by thin layer chromatography (eluent: ethyl acetate) to give the target compound (70 mg, yield: 23%).

Step F:

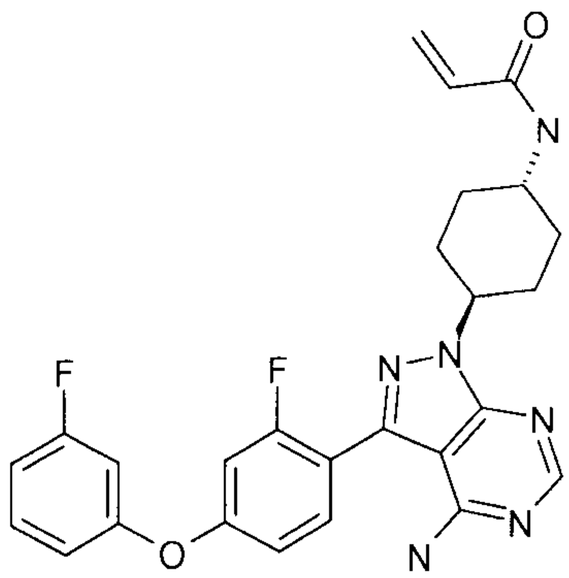


1-((1r,4r)-4-aminocyclohexyl)-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EA (1.0 mL) was added to a solution of tert-butyl (1r,4r)-4-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexylcarbamate (70 mg, 0.13 mmol) in ethyl acetate (10 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dired to give the hydrochloride of the target compound (61 mg, yield: 100%).

Step G:



N-((1r,4r)-4-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)acrylamide

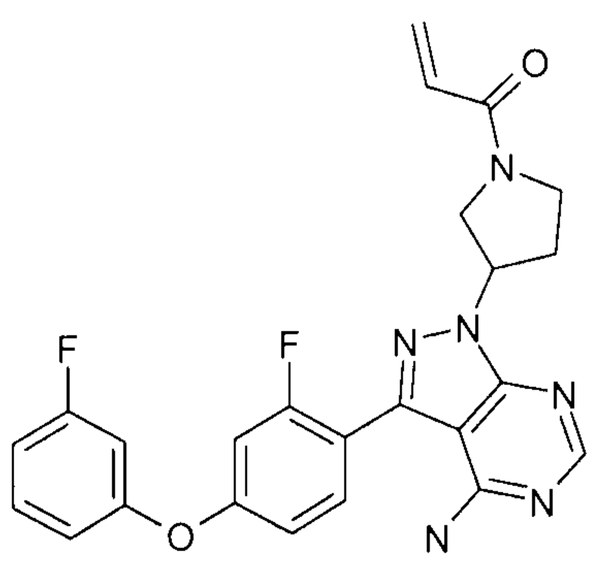
Procedure:

Triethylamine (40 mg, 0.39 mmol, 3.0 eq.) and acryloyl chloride (23 mg, 0.26 mmol, 2.0 eq.) were added subsequently to a solution of 1-((1r,4r)-4-aminocyclohexyl)-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (61.5 mg, 0.13 mmol, 1.0 eq.) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, and then quenched with water (5 mL), diluted with dichloromethane (10 mL), washed with water (5 mL) 2 times and brine (5 mL) 1 time. The organic phase was dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient: 10% to 100% (volume ratio)) to give the hydrochloride of the target compound (6.3 mg, yield: 10%).

Spectroscopy data:

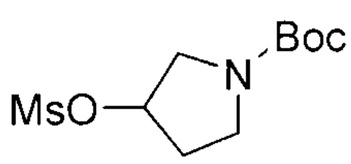
LC/MS (Method: UFLC): RT = 0.811 min; m/z = 491.1 $[M+H]^+$; Total running time: 1.5 min.

Example 15



1-(3-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Step A:



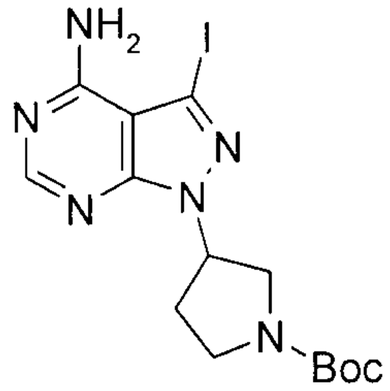
tert-butyl 3-(methylsulfonyloxy)pyrrolidine-1-formate

Procedure:

Triethylamine (35 g, 346 mmol, 2.1 eq.) and methanesulfonyl chloride (36.6 g, 321 mmol, 1.9 eq.) were added subsequently to a solution oftert-butyl 3-hydroxypyrrolidine-1-formate

(30.0 g, 163 mmol, 1.0 eq.) in dichloromethane (200 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 3 hours, quenched with water (20 mL), washed with water (100 mL) 2 times and brine (100 mL) 1 time. The organic phase was dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (45.6 g, yield: 100%).

Step B:

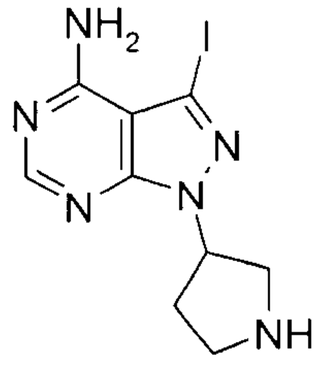


tert-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate

Procedure:

Cesium carbonate (37 g, 115 mmol, 3.0 eq.) and 3-iodo-1H-pyrazolo[3,4-d] pyrimidin-4-amine (10 g, 38 mmol, 1.0 eq.) were added to a solution of 3-(methylsulfonyloxy)pyrrolidine-1-formate (35 g, 134 mmol, 3.5 eq.) in DMF (300 mL). The reaction mixture was stirred at 85 °C for 12 hours, cooled to room temperature and filtered. The filtrate was concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (7.0 g, yield: 44%).

Step C:



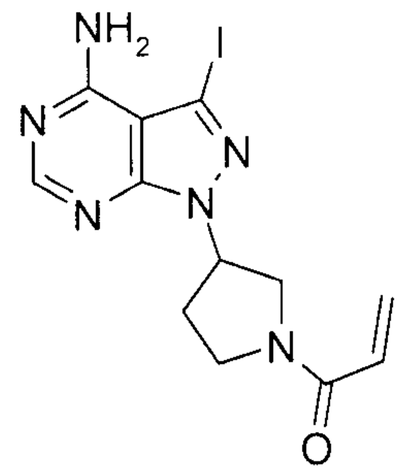
3-iodo-1-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EA (10.0 mL) was added to a solution of tert-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate (7.0 g, 16 mmol) in dichloromethane (100 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 hour,

concentrated and spin-dried to give the hydrochloride of the target compound (5.3 g, yield:100%).

Step D:

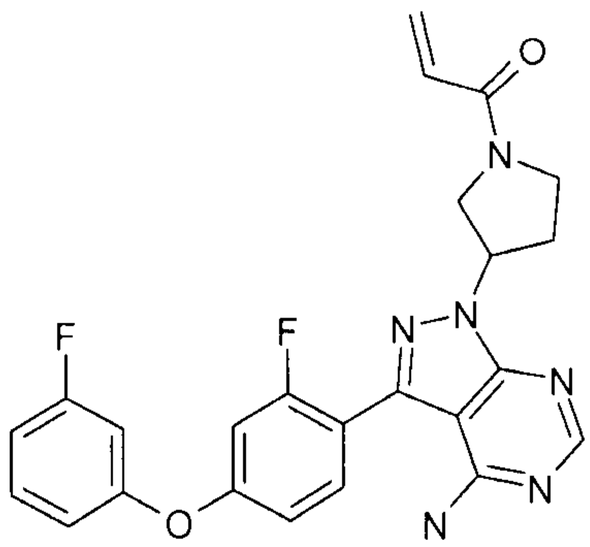


1-(3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Procedure:

Triethylamine (4.8 g, 48 mmol, 3.0 eq.) and acryloyl chloride (750 mg, 8.0 mmol, 0.5 eq.) were subsequently added to a solution of 3-iodo-1-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (5.3 g, 16 mmol, 1.0 eq.) in dichloromethane (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, and then quenched with saturated $NaHCO_3$ (10 mL), washed with water (30 mL) 2 times and brine (30 mL) 1 time. The organic phase was dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: ethyl acetate) to give the target compound (1.5 g, yield: 50%).

Step E:



1-(3-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Procedure:

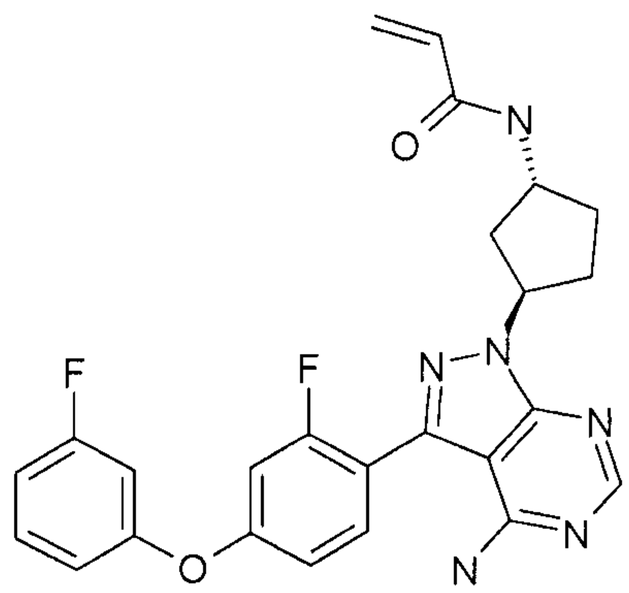
1-(3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one (250 mg, 0.65 mmol, 1.0 eq.), 2-(2-fluoro-4-(3-fluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (420 mg, 1.25 mmol, 2.eq.), sodium carbonate (200 mg, 1.88 mmol, 3.0 eq.) and $Pd(PPh_3)_4$ (72 mg, 0.06 mmol, 0.1 eq.) were dissolved in 1,4- dioxane/water (10 mL, 1/1, v/v). The reaction mixture was stirred at 85°C for 40 min. under nitrogen atmosphere with microwave irradiation. After cooling to room temperature, the reaction mixture was diluted with water (10 mL), and then extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: ethyl acetate) to give the target compound (65 mg, yield: 24%).

Spectroscopy data:

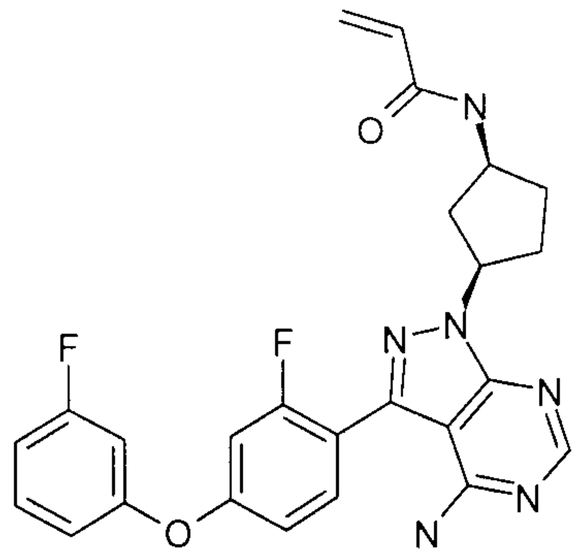
LC/MS (Method: UFLC): RT = 2.754 min; m/z = 463.3 $[M+H]^+$; Total running time: 7 min.

^1H NMR (400MHz, DMSO-d_6) δ 8.25 (s, 1H), 7.56-7.43 (m, 2H), 7.13-6.98 (m, 6H), 6.68-6.52 (m, 1H), 6.16-6.08 (m, 1H), 5.68-5.64 (m, 1H), 5.55-5.43 (m, 1H), 4.14-4.09 (m, 0.5H), 3.97-3.56 (m, 4.5H), 2.55-2.34 (m, 2H).

Examples 16 and 17

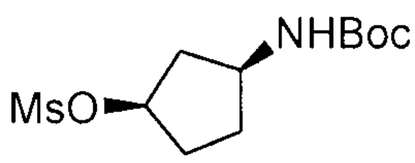


N-((1r,3r)-3-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentyl)acrylamide



N-((1s,3r)-3-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d] pyrimidin-1-yl)cyclopentyl)acrylamide

Step A:

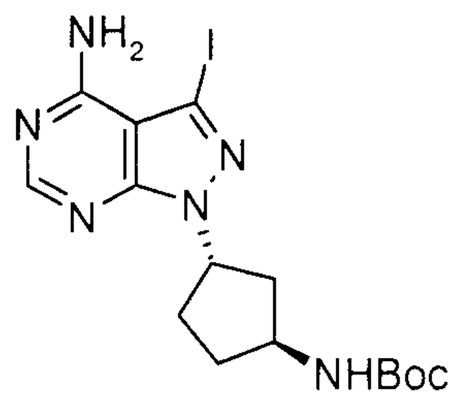


(1r,3s)-3-(tert-butoxycarbonyl)cyclopentyl methanesulfonate

Procedure:

Triethylamine (3.14 g, 31.05 mmol, 2.5 eq.) and methanesulfonyl chloride (3.5 g, 24.84 mmol, 1.2 eq.) were added sequentially to a solution of tert-butyl (1s,3r)-3-hydroxycyclopentylcarbamate (2.5 g, 12.42 mmol, 1.0 eq.) in dichloromethane (25 mL) at 0 °C. The reaction mixture was stirred at room temperature for 14 hours, quenched with water (20 mL), and then extracted with dichloromethane (25 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (2.5 g, yield: 72%).

Step B:

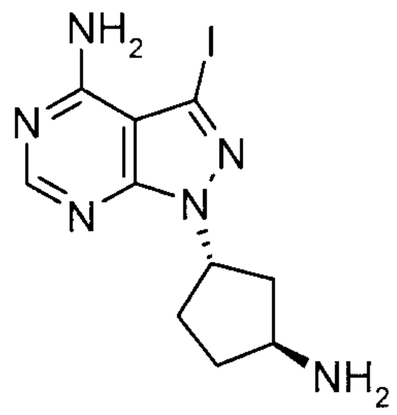


tert-butyl (1S,3S)-3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentylcarbamate

Procedure:

Cesium carbonate (8.75 g, 26.85 mmol, 3.0 eq.) and 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (1.87 g, 7.16 mmol, 0.8 eq.) were added to a solution of (1r,3s)-3-(tert-butoxycarbonyl)cyclopentyl methanesulfonate (2.5 g, 8.95 mmol, 1.0 eq.) in DMF (30 mL) at 0 °C. The reaction mixture was stirred at 85°C for 12 hours. After cooling to room temperature, the mixture was filtered. The filtrate was concentrated and spin-dried, and the residue was dissolved in ethyl acetate (100 mL), washed with water (50 mL) 2 times and brine (50 mL) 1 time. The organic phase was dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (500 mg, yield: 13%).

StepC:

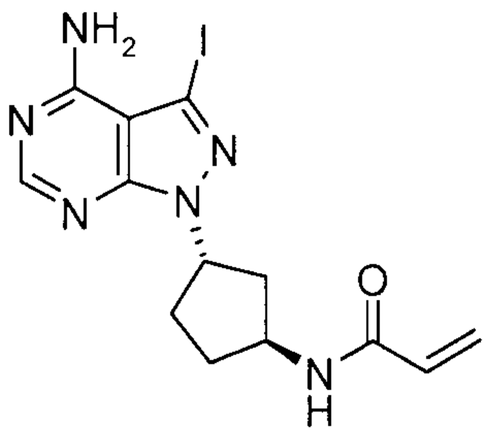


1-((1s,3s)-3-aminocyclopentyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EA (10.0 mL) was added to a solution of tert-butyl (1s,3s)-3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentylcarbamate (500 mg, 1.13 mmol) in ethyl acetate (20 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (500 mg, yield:100%).

StepD:

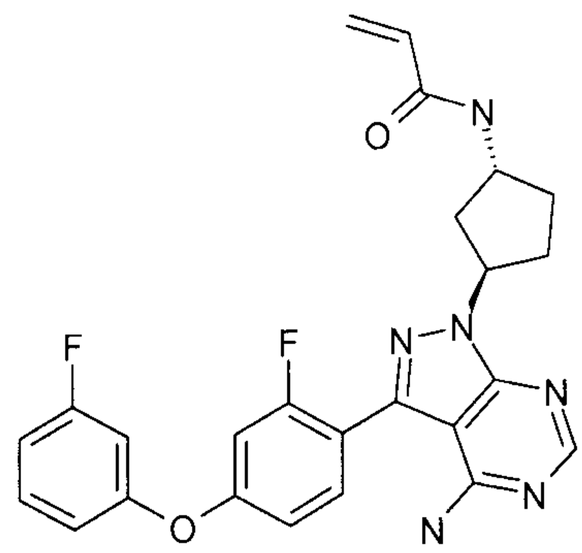


N-((1s,3s)-3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentyl)acrylamide

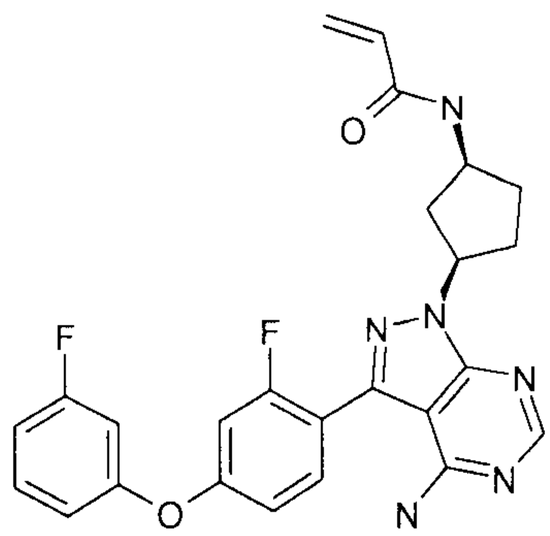
Procedure:

Triethylamine (170 mg, 1.7 mmol, 3.0 eq.) and acryloyl chloride (51 mg, 0.56 mmol, 1.1eq.) were added subsequently to a solution of 1-((1s,3s)-3-aminocyclopentyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (215 mg, 0.56 mmol, 1.0 eq.) in dichloromethane (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, and then quenched with saturated $NaHCO_3$ (10 mL). The organic phase was extracted with dichloromethane (5 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (100 mg, yield: 45%).

StepE:



N-((1s,3s)-3-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentyl)acrylamide



N-((1s,3r)-3-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentyl)acrylamide

Procedure:

N-((1s,3s)-3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentyl)acrylamide (70 mg, 0.175 mmol, 1.0 eq.), 2-(2-fluoro-4-(3-fluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (116.8 mg, 0.35 mmol, 1.1 eq.), sodium carbonate (93 mg, 0.875 mmol, 3.0 eq.) and $Pd(PPh_3)_4$ (20 mg, 0.017 mmol, 0.1 eq.) were dissolved in 1,4- dioxane/water (10 mL, 1/1, v/v). The reaction mixture was stirred at 85°C for 40 min. under nitrogen atmosphere with microwave irradiation. The reaction mixture was diluted with water (10 mL), and then extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient: 10% to 100% (volume ratio)) to give the hydrochloride of the compound of Example 16 (11 mg, yield: 5%) and the hydrochloride of the compound of Example 17 (3.8 mg, yield: 2%).

Spectroscopy data:

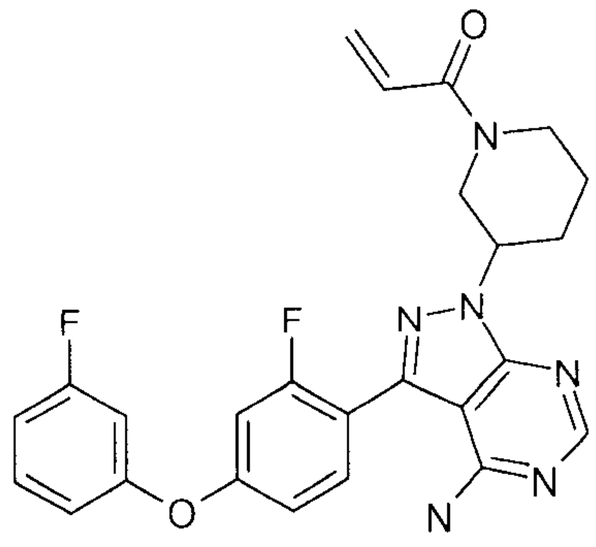
Example 16:

LC/MS (Method: UFLC): RT = 3.693 min; m/z = 477.1 $[M+H]^+$; Total running time: 7 min.

Example 17:

LC/MS (Method: UFLC): RT = 3.766 min; m/z = 477.1 $[M+H]^+$; Total running time: 7 min.

Example 18



1-(3-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one

Procedure:

1-(3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (250 mg, 0.63 mmol, 1.0 eq.), 2-(2-fluoro-4-(3-fluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (417 mg, 1.26 mmol, 2.0 eq.), sodium carbonate (200 mg, 1.88 mmol,

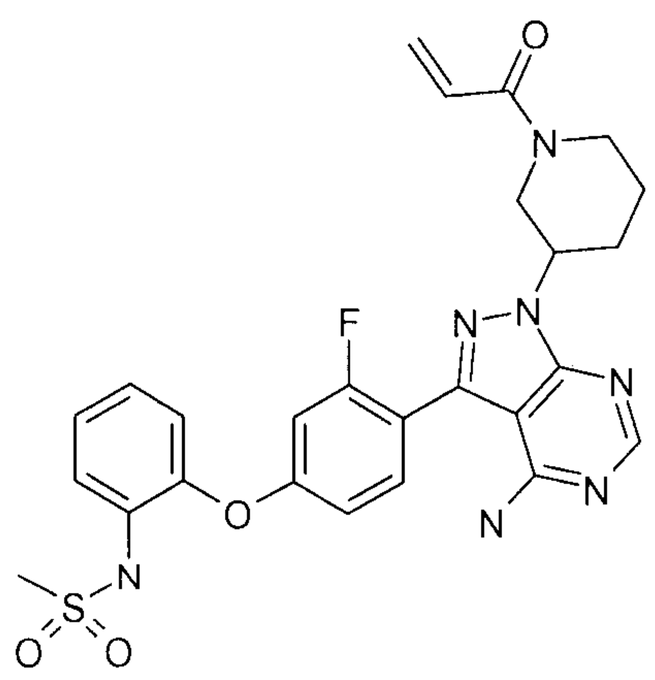
3.0 eq.) and $Pd(PPh_3)_4$ (37 mg, 0.032 mmol, 0.05 eq.) were dissolved in 1,4- dioxane/water (3 mL, 5:1, v/v). The reaction mixture was reacted at 85°C for 40 min. under nitrogen atmosphere with microwave irradiation. The reaction mixture was diluted with water (10 mL), and then extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by thin layer chromatography (eluent: ethyl acetate) to give the target compound (25 mg, yield: 4.3%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 3.693 min; m/z = 477.1 $[M+H]^+$; Total running time: 7 min.

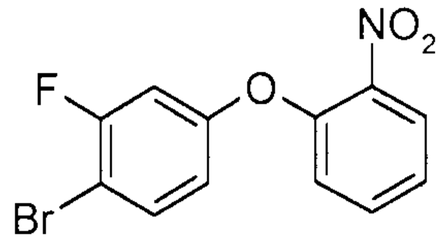
^1H NMR (400MHz, DMSO-d_6) δ 8.23 (s, 1H), 7.55-7.45 (m, 2H), 7.14-7.00 (m, 5H),6.85-6.69 (m, 2H), 6.09-6.02 (m, 1H), 6.13-6.02 (m, 1H), 5.70-5.56 (m, 1H), 4.69-4.53 (m, 1.5H), 4.21-4.04 (m, 1.5H), 3.69-3.66 (m, 0.5H), 3.20-3.14 (m, 1H), 2.99-2.94 (m, 0.5H), 2.27-2.12 (m, 2H), 1.92-1.89 (m, 1H), 1.59-1.53 (M,1H).

Example 19



N-(2-(4-(1-(1-acryloylpiperidin-3-yl)-4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenoxy)phenyl)methanesulfonamide

Step A:

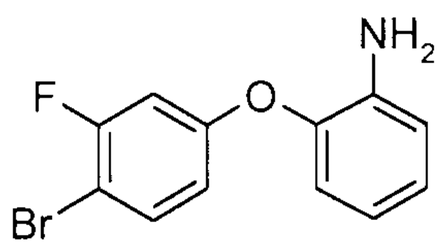


1-(3-fluoro-4-bromophenoxy)-2-nitrobenzene

Procedure:

2-fluoronitrobenzene (44.33 g, 314.14 mmol, 1.2 eq.) and potassium carbonate (72.36 g, 523.57 mmol, 2.0 eq.) were added to a solution of 3-fluoro-4-bromophenol (50 g, 261.78 mmol, 1.0 eq.) in DMF (500 mL). The reaction mixture was stirred at 110 °C for 14 hours. After cooling to room temperature, the mixture was filtered. The filter cake was sufficiently washed with ethyl acetate. The filtrate was concentrated and spin-dried to give the target compound (81.7 g, yield: 100%).

Step B:

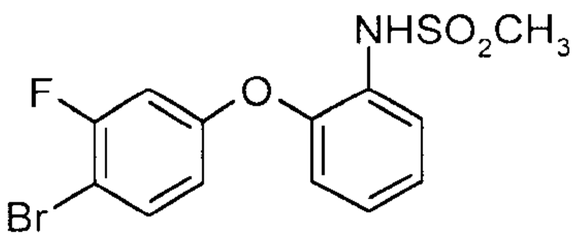


2-(3-fluoro-4-bromophenoxy)benzenamine

Procedure:

1-(3-fluoro-4-bromophenoxy)-2-nitrobenzene (40 g, 128.17 mmol, 1.0 eq.) was dissolved in ethanol (500 mL). The resulting mixture was degassed with nitrogen three times. 5% Pt/C (4 g, 10%, w/w) was added to the above solution, and then degassed with hydrogen three times. The reaction mixture was stirred under hydrogen (50 psi) at room temperature for 12 hours, then filtered through celite. The filtrate was concentrated and spin-dried to give the target compound (36 g, yield: 99%).

Step C:



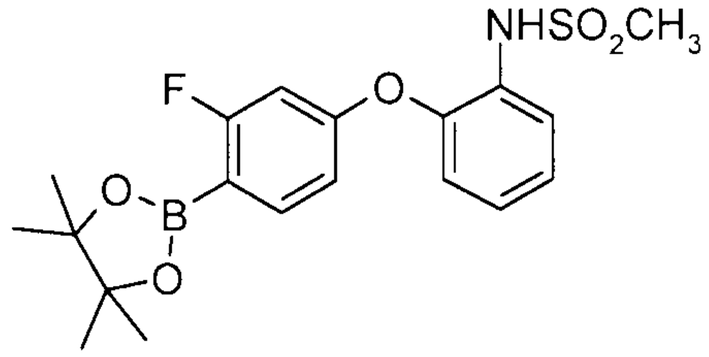
N-(2-(3-fluoro-4-bromophenoxy)phenyl)methanesulfonamide

Procedure:

Triethylamine (1.35 g , 13.29 mmol, 2.5 eq.) and methylsulfonyl chloride (1.22 g, 10.65 mmol, 1.0 eq.) were subsequently added to a solution of 2-(3-fluoro-4-bromophenoxy)aniline (1.5 g, 5.32 mmol, 1.0 eq.) in dichloromethane (25 mL) at 0 °C. The reaction was stirred at room temperature for 14 hours, quenched with water (20 mL) and then extracted with

dichloromethane (25 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate= 3:1) to give the target compound (1.0 g, yield : 52%).

Step D:

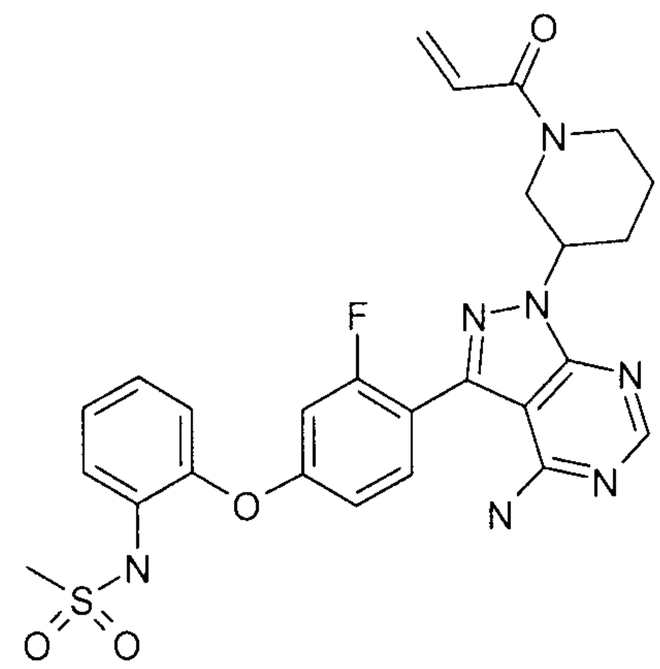


N-(2-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)phenyl)methanesulfonamide

Procedure:

N-(2-(4-bromo-3-fluorophenoxy)phenyl)methanesulfonamide (1.0 g, 2.78 mmol, 1.0 eq.), bis(pinacolato)diboron (0.85 g , 3.33 mmol, 1.2 eq.), potassium acetate (0.95 g, 9.72 mmol, 3.5 eq.) and (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium (121 mg, 0.16 mmol , 0.06 eq.) were dissolved in 1,4-dioxane (10 mL). The resulting mixture was heated to 80 °C and stirred for 12 hour under nitrogen atmosphere s. The reaction mixture was filtered through celite. The filtrate was concentrated and spin-dried to give the crude product (1.13 g, yield: 100%), which was used directly in the next step.

Step E:



N-(2-(4-(1-(1-acryloylpiperidin-3-yl)-4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenoxy)phenyl)methanesulfonamide

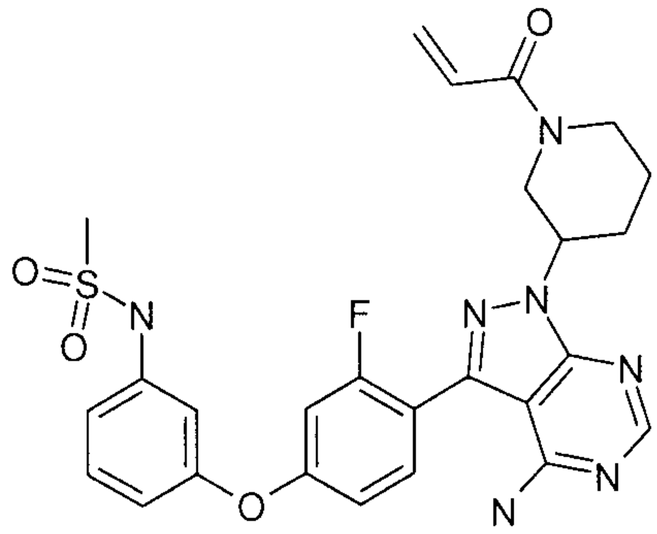
Procedure:

1-(3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (100 mg, 0.251 mmol, 1.0 eq.), N-(2-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)phenyl)methanesulfonamide (205 mg, 0.502 mmol, 2.0 eq.), sodium carbonate (2N, 0.25 mL, 0.502 mmol, 2.0 eq.) and $Pd(PPh_3)_4$ (29 mg, 0.025 mmol, 0.1 eq.) were dissolved in 1,4- dioxane (2 mL). The reaction mixture was stirred at 85°C for 40 min. under nitrogen atmosphere with microwave irradiation. The reaction mixture was diluted with water (10 mL), and then extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/7‰ NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (5 mg, yield: 4%).

Spectroscopy data:

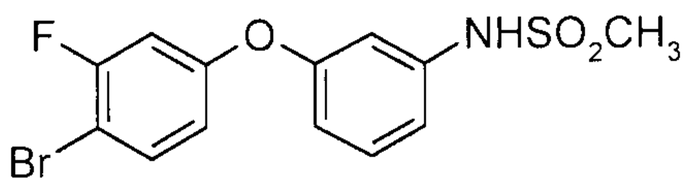
LC/MS (Method: UFLC): RT = 2.452 min; m/z = 552.4 $[M+H]^+$; Total running time: 7 min.

Example 20



N-(3-(4-(1-(1-acryloylpiperidin-3-yl)-4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenoxy)phenyl)methanesulfonamide

StepA:

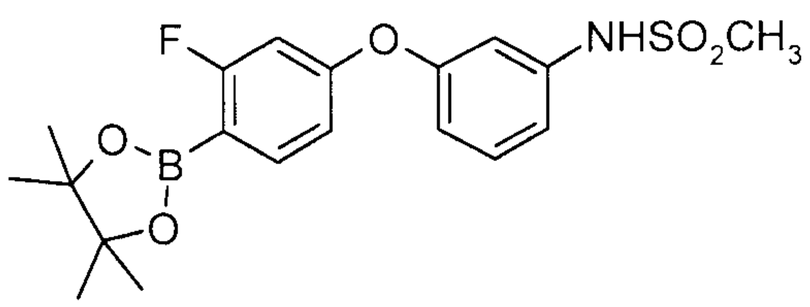


N-(3-(3-fluoro-4-bromophenoxy)phenyl)methanesulfonamide

Procedure:

Triethylamine (2.02 g, 20 mmol, 6.0 eq.) and methylsulfonyl chloride (1.2 g, 10.6 mmol, 3.0 eq.) were subsequently added to a solution of 3-(3-fluoro-4-bromophenoxy)aniline (1.0 g, 3.54 mmol, 1.0 eq.) in dichloromethane (25 mL) at 0 °C. The reaction mixturing was stirred at room temperature for 14 hours, quenched with water (20 mL) and then extracted with dichloromethane (25 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=10 : 1) to give the target compound (1.0 g, yield : 78%).

StepB:

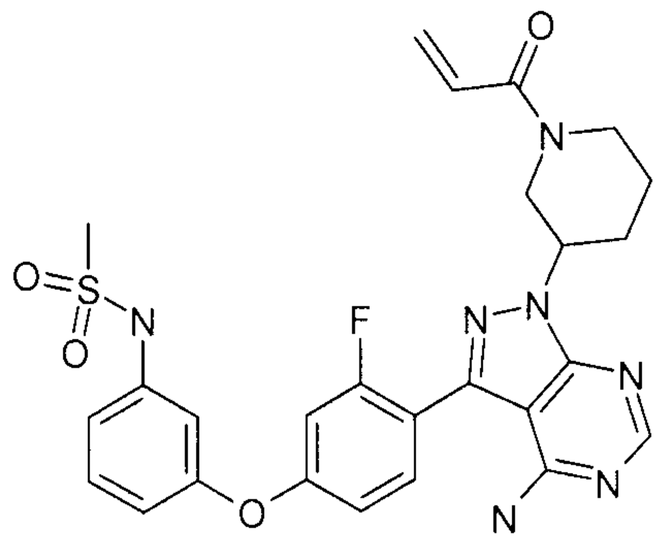


N-(3-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)phenyl)methanesulfonamide

Procedure:

N-(3-(3-fluoro-4-bromophenoxy)phenyl)methanesulfonamide (640 mg, 1.78 mmol, 1.0 eq.), bis(pinacolato)diboron (496 mg, 1.95 mmol, 1.1 eq.), potassium acetate (523 mg, 5.33 mmol, 3.0 eq.) and (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium (126 mg, 0.178 mmol, 0.1 eq.) were dissolved in 1,4-dioxane (10 mL). The resulting mixture was heated to 80 °C and stirred for 12 hours under nitrogen atmosphere. The reaction mixture was filtered through celite. The filtrate was concentrated and spin-dired to give the crude product (0.8 g, yield: 100%), which was used directly in the next step.

StepC:



N-(3-(4-(1-(1-acryloylpiperidin-3-yl)-4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenoxy)phenyl)methanesulfonamide

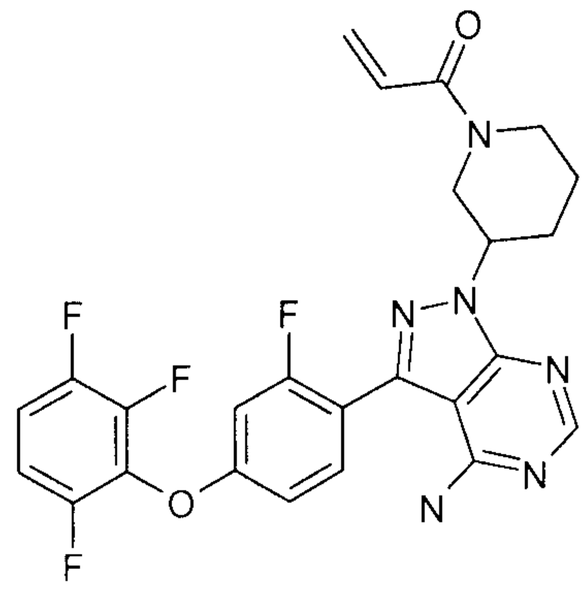
Procedure:

1-(3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (60 mg, 0.150 mmol, 1.0 eq.), N-(3-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)phenyl)methanesulfonamide (122 mg, 0.30 mmol, 2.0 eq.), sodium carbonate (64 mg, 0.6 mmol, 4.0 eq.) and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol, 0.1 eq.) were dissolved in 1,4-dioxane (6 mL, 1/1, v/v). The reaction mixture was reacted at 85°C for 40 min. under nitrogen atmosphere with microwave irradiation. The reaction mixture was diluted with water (10 mL), and then extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column, (mobile phase: acetonitrile/water/0.5%HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (16 mg, yield: 22%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 0.775 min; m/z = 552.1 $[M+H]^+$; Total running time: 1.5 min.

Example 21



1-(3-(4-amino-3-(2-fluoro-4-(2,3,6-trifluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one

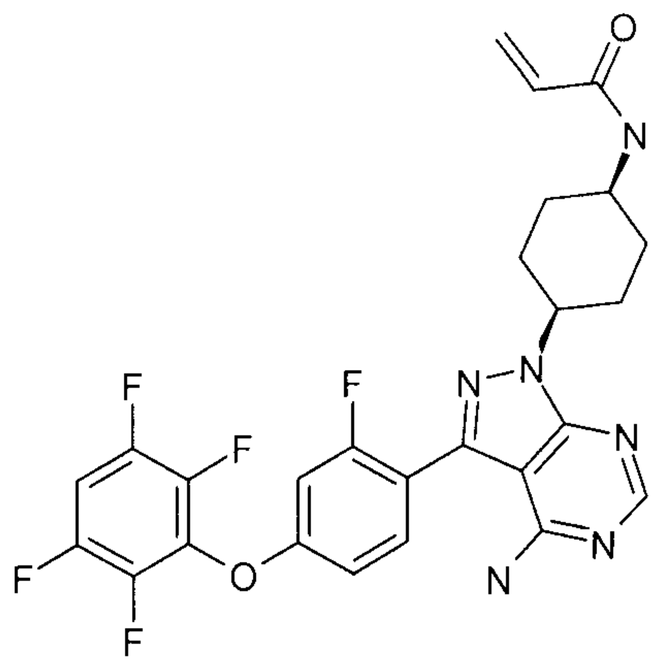
Procedure:

1,2,3,4-fluorobenzene (20 mg, 0.13 mmol, 1.0 eq.) and potassium carbonate (35 mg, 0.26 mmol, 2.0 eq.) were added to a solution of 1-(3-(4-amino-3-(2-fluoro-4-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (50 mg, 0.13 mmol, 1.0 eq.) in DMF (5 mL). The reaction mixture was heated to 100 °C and stirred for 4 hours. After cooling to room temperature, the reaction mixture was diluted with water (10 mL), and then extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (10 mg, yield: 15%).

Spectroscocy data:

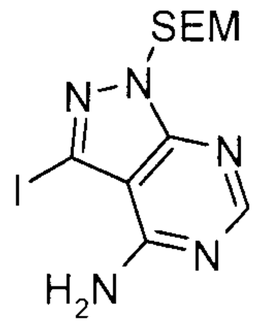
LC/MS (Method: UFLC): RT = 2.993 min; m/z = 513.2 $[M+H]^+$; Total running time: 7 min.

Example 22



N-((1s,4s)-4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)acrylamide

Step A:

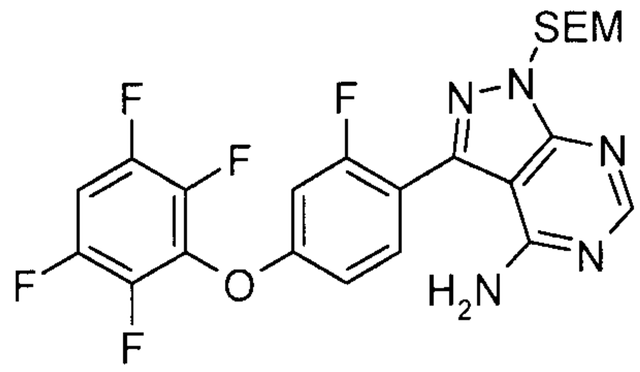


3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

NaH (13.8 g, 345 mmol, 1.5 eq.) was added to a solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 g, 230 mmol, 1.0 eq.) in DMF (1.24 L) and (180 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then SEMCl (42 g, 253 mmol, 1.1 eq.) was added. The reaction mixture was stirred overnight at room temperature, poured into ice water (500 mL) and extracted with ethyl acetate (500 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate= 10: 1 to 1:1) to give the target compound (10 g, yield: 44%).

Step B:

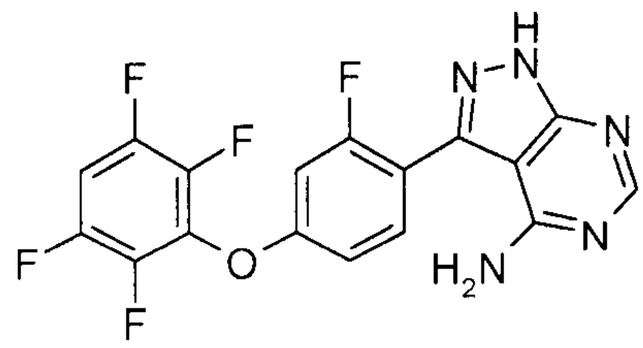


3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 g, 102 mmol, 1.0 eq.), 2-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (50 g, 129 mmol, 1.3 eq.), potassium phosphate (40 g, 189 mmol, 1.8 eq.) and Pd-118 (3.0 g, 5.0 mmol, 0.05 eq.) were dissolved in 1,4-dioxane/water (1400 mL, 5/1, v/v). The reaction solution was stirred at 60°C for 12 hours under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was filtered through celite. The filtrate was extracted with ethyl acetate (500 mL) 4 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate= 10: 1 to 1:1)to give the target compound (25 g, yield: 46%).

Step C:



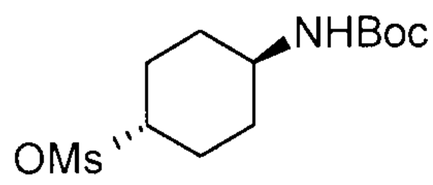
3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EtOAc (200 mL) was added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (25 g, 48 mmol, 1.0 eq.) in ethyl acetate (50 mL) at 0 °C. The reaction mixture was stirred at 60 °C for 14 hours, and then evaporated to remove the solvent under reduced pressure. Water (100 mL) and saturated $NaHCO_3$ (100 mL) were added to the

residue, and then the mixture was extracted with ethyl acetate (300 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (13 g, yield: 69%).

Step D:

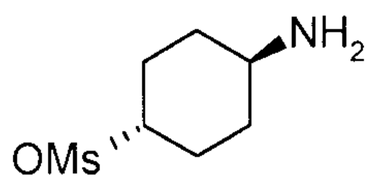


(1r,4r)-4-(tert-butoxycarbonyl)cyclohexyl methanesulfonate

Procedure:

Triethylamine (7.16 g, 70.7 mmol, 3.0 eq.) and methanesulfonyl chloride (5.4 g, 45 mmol, 2.05 eq.) were subsequently added to a solution of tert-butyl (1r,4r)-4-hydroxycyclohexylcarbamate (5.08 g, 23.6 mmol, 1.0 eq.) in dichloromethane (50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 14 hours, quenched with water (60 mL), and then extracted with dichloromethane (50 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (6.0 g, yield: 87%).

Step E:

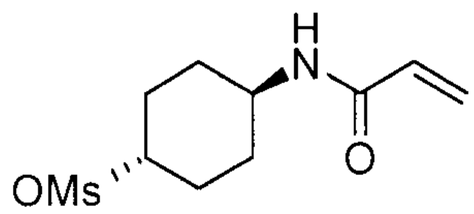


(1r,4r)-4-aminocyclohexyl methanesulfonate

Procedure:

4M HCl/EtOAc (10 mL) was added to a solution of (1r,4r)-4-(tert-butoxycarbonyl)cyclohexyl methanesulfonate (4 g, 13.63 mmol) in ethyl acetate (40 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, evaporated to remove the solvent to give the hydrochloride of the target compound (3.2g, yield: 100%).

Step F:

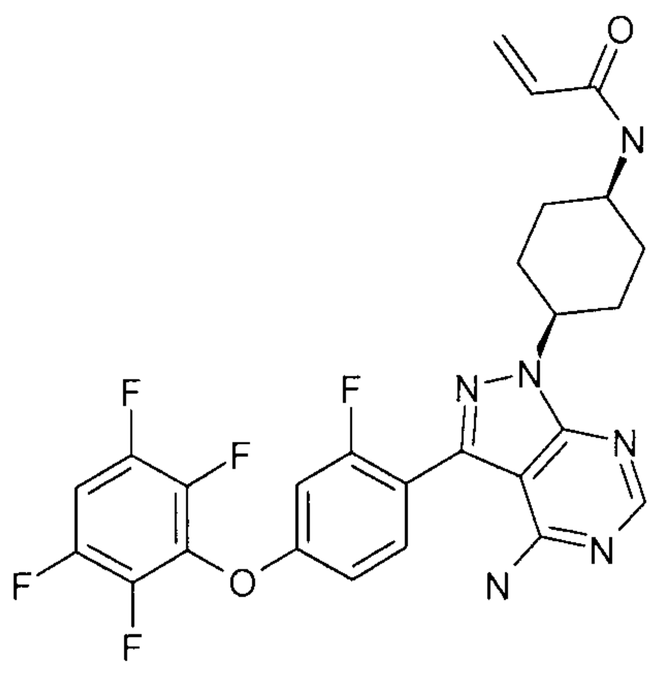


(1r,4r)-4-acrylamidocyclohexyl methanesulfonate

Procedure:

Triethylamine (1.03 g, 10.19 mmol, 3.0 eq.) and acryloyl chloride (307 mg, 3.4 mmol, 1.0 eq.) were subsequently added to a solution of (1r,4r)-4-aminocyclohexyl methanesulfonate (780 mg, 3.4 mmol, 1.0 eq.) in dichloromethane (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, and then quenched with saturated $NaHCO_3$ (10 mL). The aqueous phase was extracted with dichloromethane (5 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dired to give the target compound (780mg, yield: 93%).

Step G:



N-((1s,4s)-4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)acrylamide

Procedure:

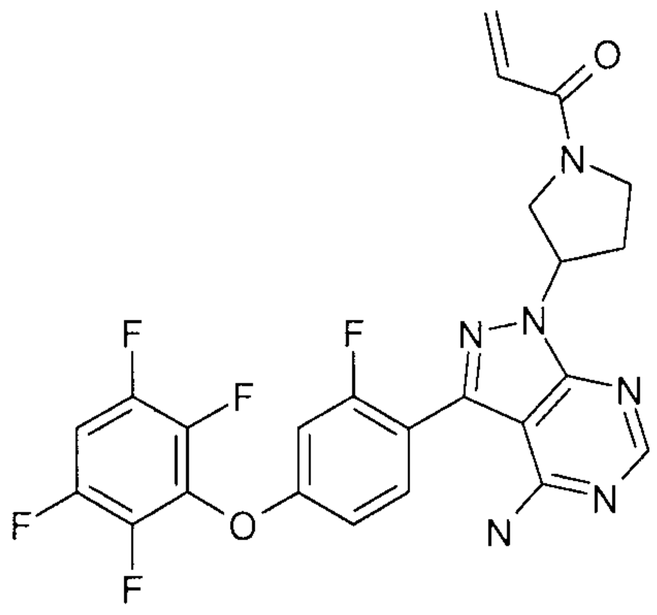
(1r,4r)-4-acrylamidocyclohexyl methanesulfonate (49 mg, 0.198 mmol, 1.3 eq.) and cesium carbonate (130.5 mg, 0.305 mmol, 2.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.152 mmol, 1.0 eq.) in DMF (2 mL). The reaction was stirred at 90 °C for 4 hours, diluted with water (10 mL) and extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over

anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (2 mg, yield: 2%).

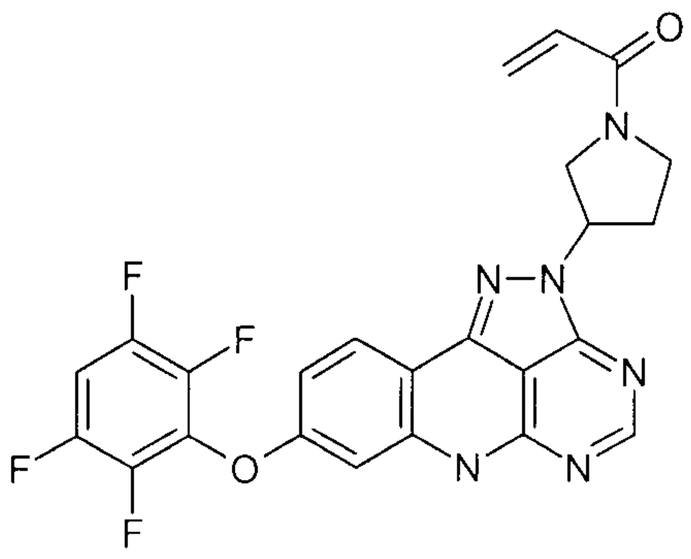
Spectroscopy data:

LC/MS (Method: UFLC): RT = 0.816 min; m/z = 544.9 $[M+H]^+$; Total running time: 1.5 min.

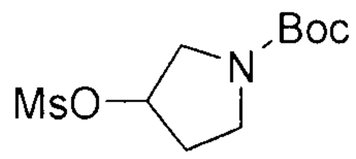
Examples 23 and 24



1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one



Step A:

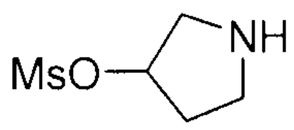


tert-butyl 3-(methylsulfonyloxy)pyrrolidine-1-formate

Procedure:

Triethylamine (4.8 g, 48 mmol, 3.0 eq.) and methanesulfonyl chloride (3.7 g, 32 mmol, 2.0 eq.) were subsequently added to a solution of tert-butyl 3-hydroxypyrrolidine-1-formate (3.0 g, 16 mmol, 1.0 eq.) in dichloromethane (50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours, quenched with water (60 mL), and then extracted with dichloromethane (50 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (4.0 g, yield: 95%).

Step B:

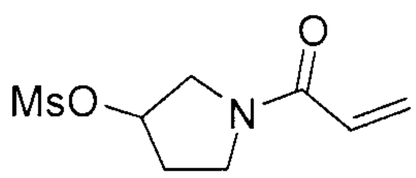


pyrrolidin-3-yl methanesulfonate

Procedure:

4M HCl/EtOAc (10 mL) was added to a solution of tert-butyl 3-(methylsulfonyloxy)pyrrolidine-1-formate (4.0 g, 15 mmol) in ethyl acetate (40 mL). The reaction mixture was stirred at room temperature for 1 hour, evaporated to remove the solvent under reduced pressure to give the hydrochloride of the target compound (2.5g, yield: 100%).

Step C:

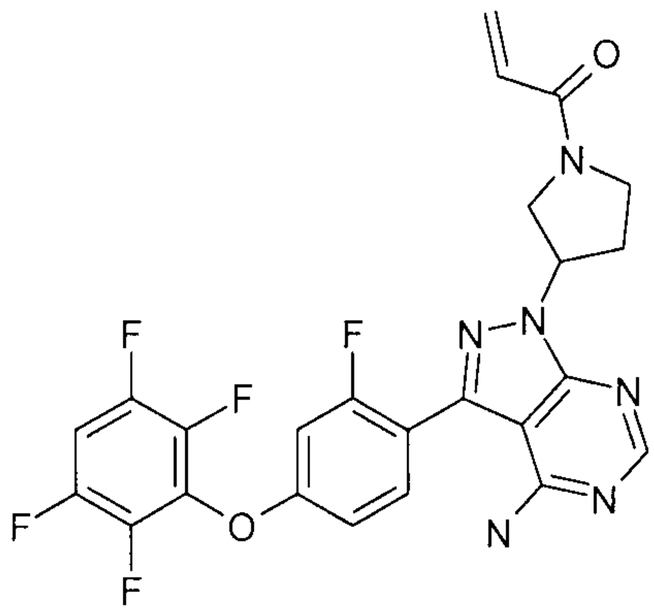


1-acryloylpyrrolidin-3-yl methanesulfonate

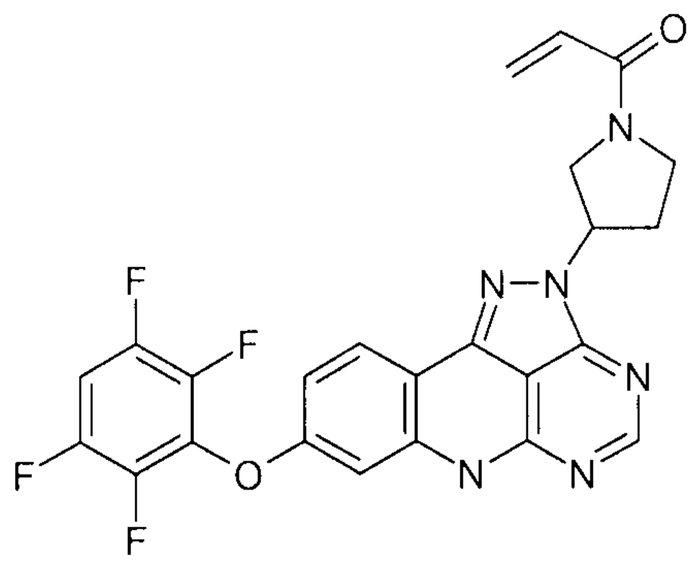
Procedure:

Triethylamine (4.5 g, 45 mmol, 3.0 eq.) and acryloyl chloride (1.01 g, 12 mmol, 0.8 eq.) were added subsequently to a solution of pyrrolidin-3-yl methanesulfonate (2.5 g, 15 mmol,1.0 eq.) in dichloromethane (30 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, and then quenched with saturated $NaHCO_3$ (10 mL). The aqueous phase was extracted with dichloromethane (5 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (2.5g, yield: 83%).

Step D:



1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one



Procedure:

1-acryloylpyrrolidin-3-yl methanesulfonate (62 mg, 0.306 mmol, 2.0 eq.) and cesium carbonate (149 mg, 0.459 mmol, 3.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.152 mmol, 1.0 eq.) in DMF (2 mL). The reaction mixture was stirred at 90 °C for 4 hours, diluted with water (10 mL) and extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water, gradient 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the compound of Example **23** (18 mg, yield: 11%) and the compound of Example **24** (3.5 mg, yield: 2%).

Spectroscopy data:

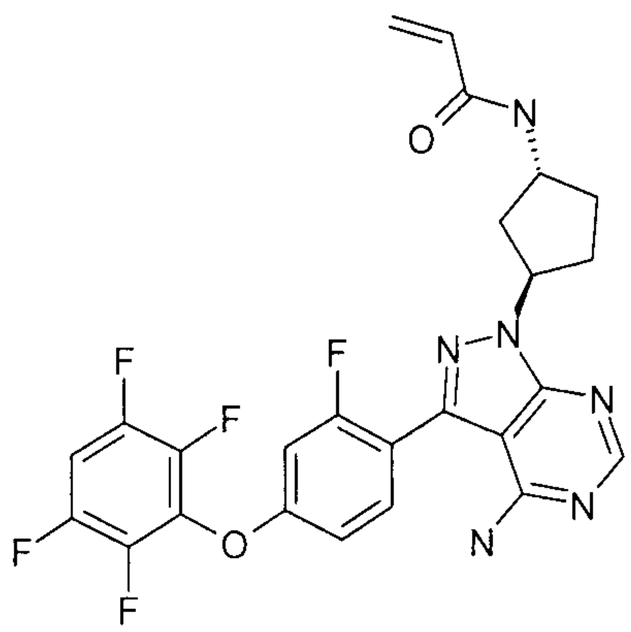
Example 23:

LC/MS (Method: UFLC): RT = 2.780 min; m/z = 517.1 $[M+H]^+$; Total running time: 7 min. ^1H NMR (400MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.55-7.48 (m, 1H), 7.10-7.03 (m, 1H), 6.93-6.88 (m, 2H), 6.43-6.39 (m, 1H), 5.73-5.57 (m, 2H), 5.47-5.43 (m, 1H), 4.15-3.96 (m, 3H), 3.82-3.73 (m, 1H), 2.70-2.42 (m, 2H).

Example 24:

LC/MS (Method: UFLC): RT = 0.813 min; m/z = 497.0 $[M+H]^+$; Total running time: 1.5 min.

Example 25



N-((1r,3r)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentyl)acrylamide

Procedure:

N-((1r,3r)-3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentyl)acrylamide (70 mg, 0.17 mmol, 1.0 eq.), 2-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (135 mg, 0.35 mmol, 2.0 eq.), sodium carbonate (56 mg, 0.52 mmol, 3.0 eq.) and $Pd(PPh_3)_4$ (20 mg, 0.0175 mmol, 0.1 eq) were dissolved in 1,4-dioxane (10 mL, 1/1, v/v). The reaction mixture was stirred at 85 °C for 40 min. with microwave irradiation under nitrogen atmosphere, diluted with water (10 mL) and extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product,which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove

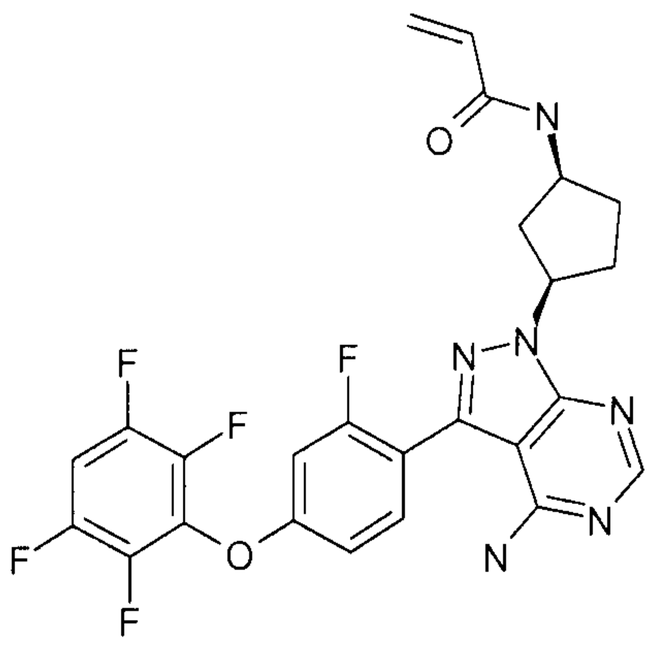
volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (4 mg, yield: 4%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 3.935 min; m/z = 531.1 $[M+H]^+$; Total running time: 7 min.

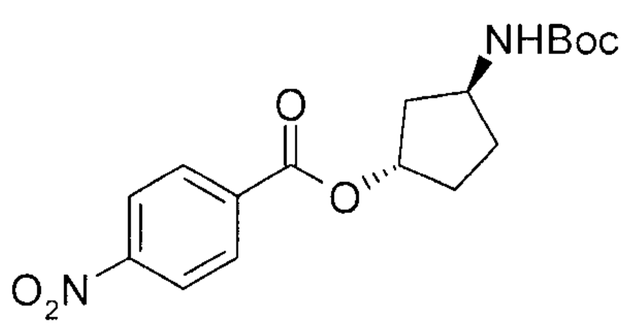
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (s, 1H), 8.30 (d, J = 7.2 Hz, 1H), 7.99-7.90 (m, 1H), 7.60 (t, J = 8.4 Hz, 1H), 7.30 (dd, J = 2.4, 10.8 Hz, 1H), 7.14 (dd, J = 2.8, 8.4 Hz, 1H), 6.21-6.17 (m, 1H), 6.08-6.04 (m, 1H), 5.58-5.55 (m, 1H), 5.49-5.41 (m, 1H), 4.47-4.42 (m, 1H), 2.34-2.25 (m, 3.5H), 2.04-1.96 (m, 1.5H), 1.62-1.59 (M,1H).

Example 26



N-((1s,3r)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentyl)acrylamide

Step A:



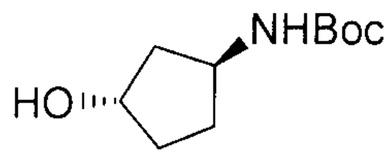
(1s,3s)-3-(tert-butoxycarbonyl)cyclopentyl 4-nitrobenzoate

Procedure:

Tert-butyl (1s,3r)-3-hydroxycyclopentylcarbamate (2.25 g, 11.2 mmol, 1.0 eq.), 4-nitrobenzoic acid (4.67 g, 28.0 mmol, 2.5 eq.) and triphenylphosphine (4.4 g, 16.8 mmol, 1.5 eq.) were dissolved in toluene (50 mL) and tetrahydrofuran (12 mL). Diethyl

azodiformate (3.0 g, 16.8 mmol, 1.5 eq.) was added to the resulting mixture. The reaction mixture was stirred at room temperature for 12 hours under nitrogen atmosphere, and evaporated to remove the solvent under reduced pressure. Dichloromethane (500 mL) was added to the residue, and stirred for 30 min., then filtered. The filtrate was concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=10: 1 to 1:1) to give the target compound (0.6 g, yield: 15%).

Step B:

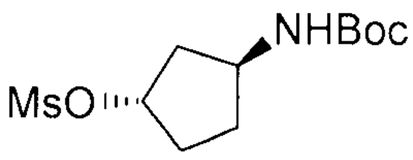


tert-butyl (1s,3s)-3-hydroxycyclopentylcarbamate

Procedure:

Potassium carbonate (177 mg, 1.28 mmol, 1.5 eq.) was added to a solution of (1s,3s)-3-(tert-butoxycarbonyl)cyclopentyl-4-nitrobenzoate (300 mg, 0.86 mmol) in methanol (5 mL). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with water (10 mL),and extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to to give the target compound (180mg, yield: 90%).

Step C:



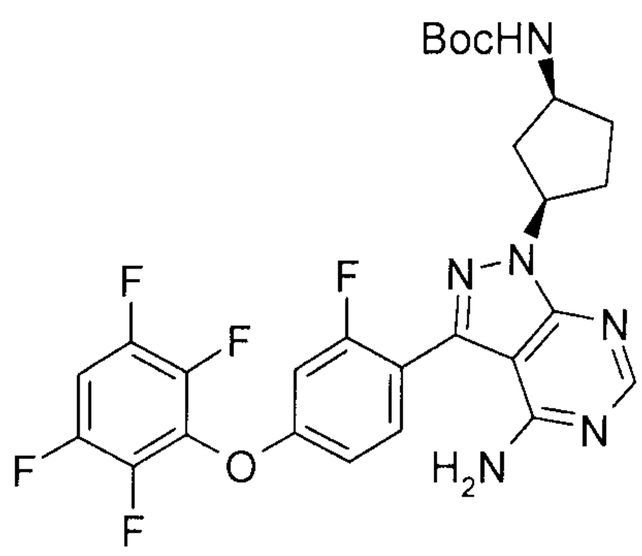
(1s,3s)-3-(tert-butoxycarbonyl)cyclopentyl methanesulfonate

Procedure:

Triethylamine (180 mg, 1.79 mmol, 2.0 eq.) and methanesulfonyl chloride (204 mg, 1.79 mmol, 2.0 eq.) were subsequently added to a solution of tert-butyl (1s,3s)-3-hydroxycyclopentylcarbamate (180 mg, 0.895 mmol, 1.0 eq.) in dichloromethane (3 mL) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1 hour, quenched with water (5 mL). The aqueous phase was extracted with dichloromethane (5 mL) 2 times. The combined organic

phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (200 mg, yield: 80%).

Step D:

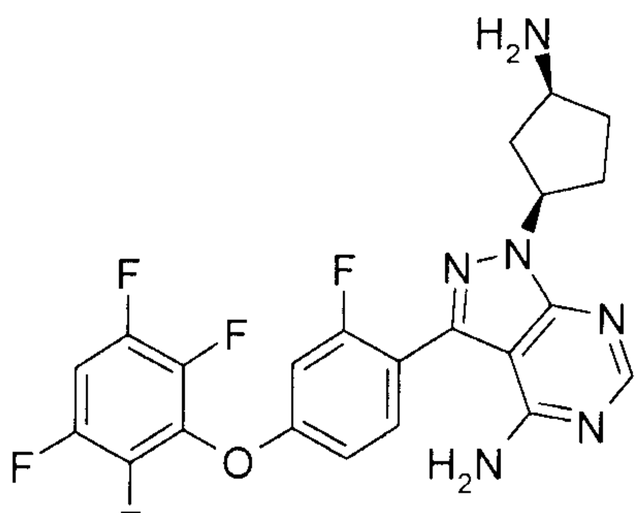


tert-butyl (1s,3r)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentylcarbamate

Procedure:

Cesium carbonate (66 mg, 0.202 mmol, 2.0 eq.) and 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.101 mmol, 1.0 eq.) were addedto a solution of (1s,3s)-3-(tert-butoxycarbonyl)cyclopentyl methanesulfonate (56 mg, 0.202 mmol, 2.0 eq.) in DMF (1 mL). The reaction mixture was stirred at 85 °C for 12 hours, cooled to room temperature and filtered. The filtrate was concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (9 mg, yield: 15%).

Step E:

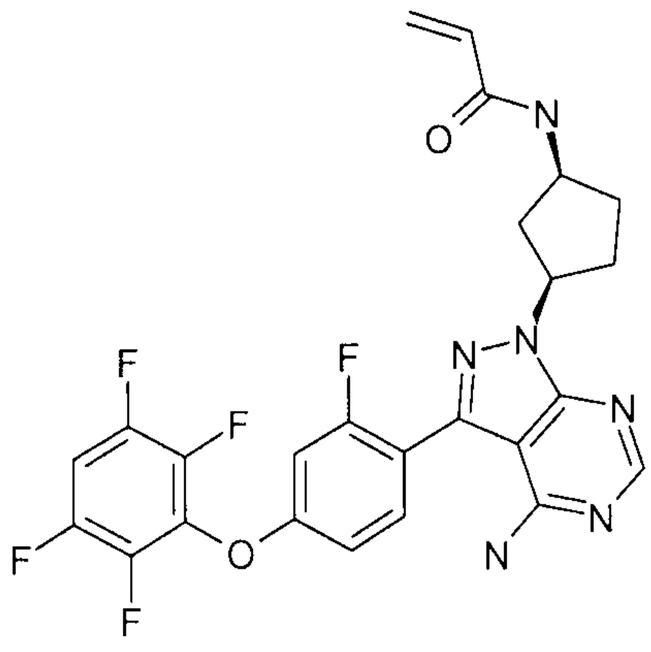


1-((1r,3s)-3-aminocyclopentyl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EA (1.0 mL) was added to a solution of tert-butyl (1s,3r)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexylcarbamate (9 mg, 0.015 mmol) in ethyl acetate (1 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (8 mg, yield:100%).

Step F:



N-((1s,3r)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentyl)acrylamide

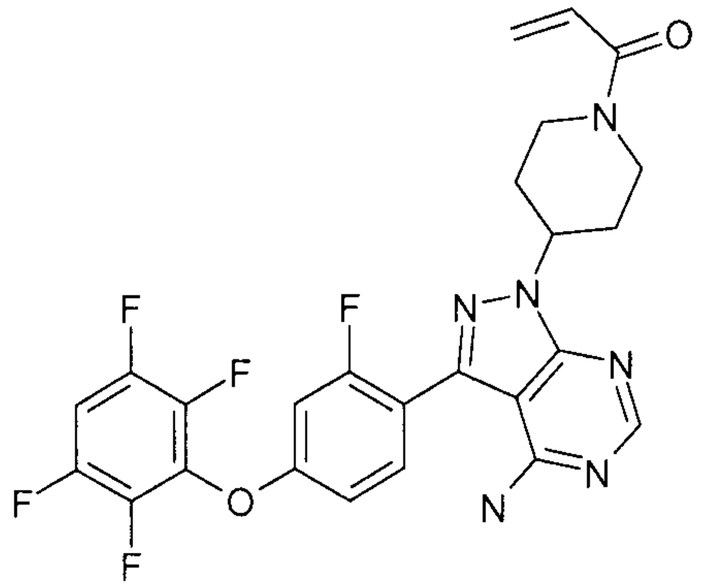
Procedure:

Triethylamine (3.0 mg, 0.03 mmol, 2.0 eq.) and acryloyl chloride (1.5 mg, 0.017 mmol, 1.1 eq.) were added dropwise to a solution of 1-((1r,3s)-3-aminocyclopentyl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (8 mg, 0.015 mmol, 1.0 eq.) in dichloromethane (1 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, quenched with water (5 mL), and then extracted with dichloromethane (5 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient: 10% to 100% (volume ratio)) to give the hydrochloride of the target compound (1.0 mg, yield: 12%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.424 min; m/z = 531.2 $[M+H]^+$; Total running time: 3min.

Example 27



1-(4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one

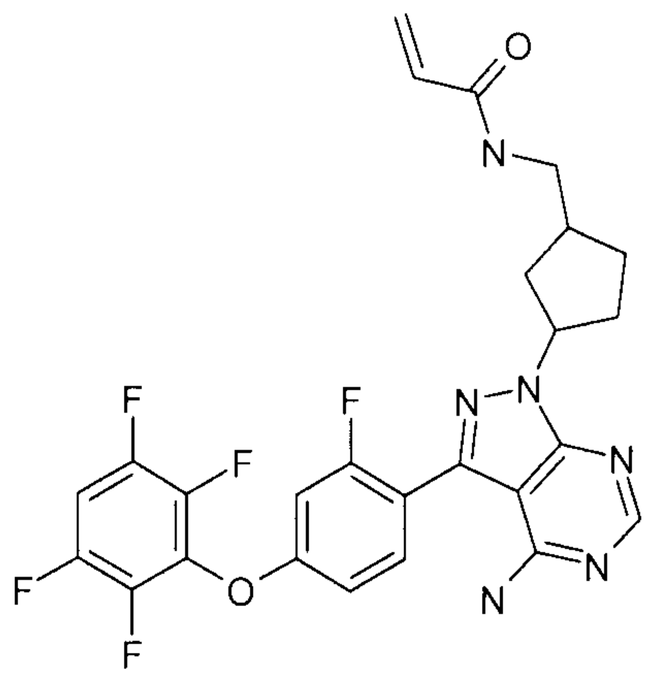
Procedure:

Potassium carbonate (42 mg, 0.304 mmol, 2.0 eq.) and 1-acryloylpiperidin-4-yl methanesulfonate (71 mg, 0.304 mmol, 2.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg , 0.152 mmol, 1.0 eq.) in DMF (1 mL). The reaction mixture was stirred at 85 °C for 3 hours, cooled to room temperature and filtered. The filtrate was concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient: 10% to 100% (volume ratio)) to give the hydrochloride of the target compound (1.1 mg, yield: 1.3%).

Spectroscopy data:

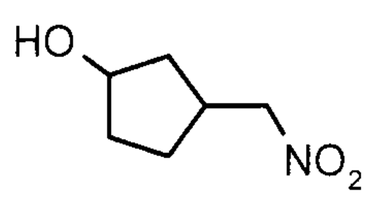
LC/MS (Method: UFLC): RT = 2.834 min; m/z = 531.1 [M+H]+; Total running time: 7 min.

Example 28



N-((3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentyl)methyl)acrylamide

Step A:

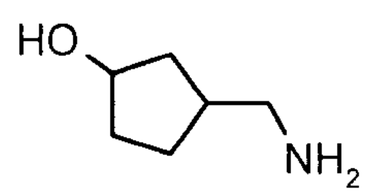


3-(nitromethyl)cyclopentanol

Procedure:

$NaBH_4$ (1.06 g, 27.94 mmol, 2.0eq.) was added to a solution of 3-(nitromethyl)cyclopentanone (2.0 g, 14.0 mmol, 1.0 eq.) in methanol (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours, quenched with water (2 mL), concentrated and spin-dried to give the target compound (2.0 g, yield: 98%).

Step B:



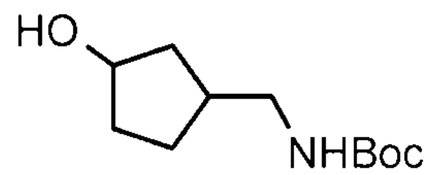
3-(aminomethyl)cyclopentanol

Procedure:

Raney nickel (200 mg, 10%) was added to a solution of 3-(nitromethyl)cyclopentanol (2.0 g, 13.8 mmol, 1.0 eq.) in ethanol (30 mL) under nitrogen atmosphere. The reaction mixture was degassed with hydrogen three times, and then stirred at 50 °C under hydrogen (50 psi)

for 12 hours. After cooling to room temperature, the reaction mixture was filtered through celite. The filtrate was concentrated and spin-dried to give the target compound (1.5 g, yield: 94%).

Step C:

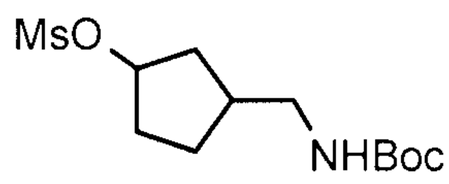


tert-butyl (3-hydroxycyclopentyl)methylcarbamate

Procedure:

$(Boc)_2O$ (3.1 g, 14.33 mmol, 1.1 eq.) and triethylamine (3.95 g, 39.07 mmol, 3.0 eq.) were added to a solution of 3-(aminomethyl)cyclopentanol (1.5 g, 13.0 mmol, 1.0 eq.) in dichloromethane (20 mL) . The reaction mixture was stirred for 12 hours at 20 °C, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1: 0 7: 3) to give the target compound (0.7 g, yield rate: 25%).

Step D:

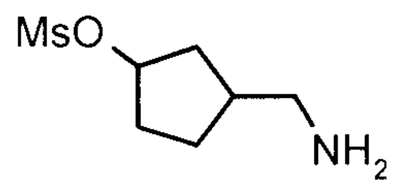


3-((tert-butoxycarbonyl)methyl)cyclopentyl methanesulfonate

Procedure:

Triethylamine (0.98 g , 9.75 mmol, 3.0 eq.) and methanesulfonyl chloride (0.74 g, 6.5 mmol, 2.0 eq.) were subsequently added to a solution of tert-butyl (3-hydroxycyclopentyl)methylcarbamate (0.7 g, 3.25 mmol, 1.0 eq.) in dichloromethane (25 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 14 hours, quenched with saturated $NaHCO_3$ (20 mL), then extracted with dichloromethane (20 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (0.76 g, yield: 80%).

Step E:

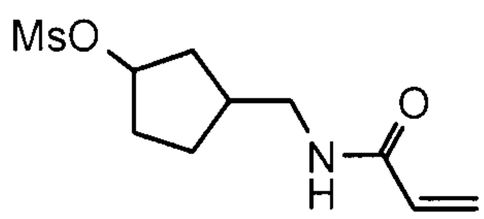


3-(aminomethyl)cyclopentyl methanesulfonate

Procedure:

4M HCl/EA (10 mL) was added to a solution of 3-((tert-butoxycarbonyl)methyl)cyclopentyl methanesulfonate (760 mg, 2.59 mmol) in dichloromethane (20 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (590 mg, yield:100%).

Step F:

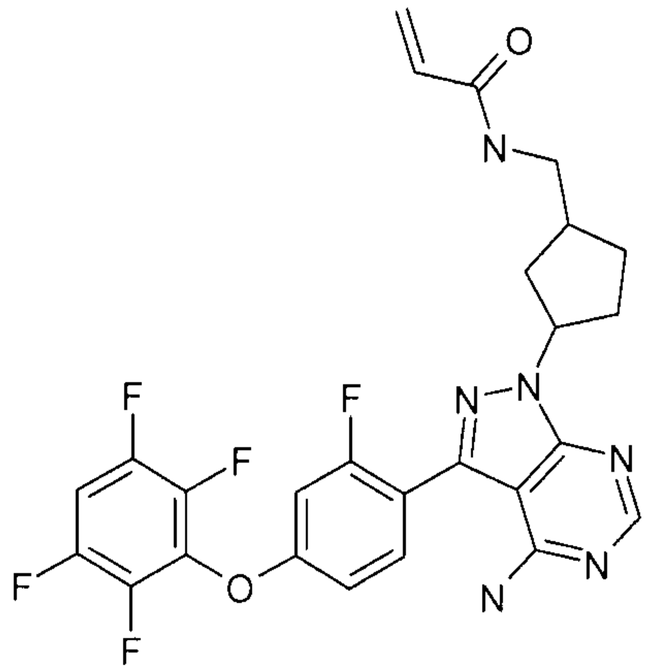


3-(acrylamidomethyl)cyclopentyl methanesulfonate

Procedure:

Triethylamine (530 mg, 5.3 mmol, 2.0 eq.) and acryloyl chloride (280 mg, 3.2 mmol, 1.2 eq.) were subsequently added to a solution of 3-(aminomethyl)cyclopentyl methanesulfonate (590 mg, 2.6 mmol, 1.0 eq.) in dichloromethane (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 hour, and then quenched with saturated $NaHCO_3$ (10 mL). The aqueous phase was extracted with dichloromethane (10 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and spin-dried to give the target compound (400 mg, yield: 60%).

Step G:



N-((3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentyl)methyl)acrylamide

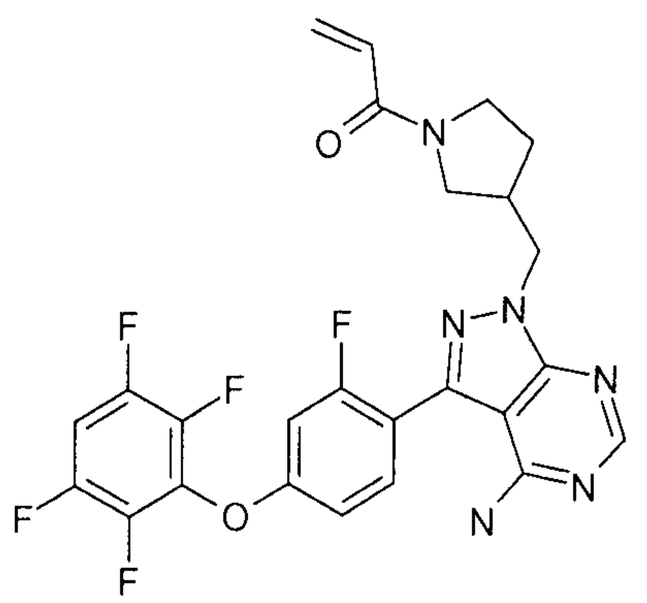
Procedure:

Potassium carbonate (98 mg, 0.712 mmol, 4.0 eq.) and 3-(acrylamidomethyl)cyclopentyl methanesulfonate (131 mg, 0.534 mmol, 3.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine(70 mg, 0.178 mmol, 1.0 eq.) in DMF (1 mL). The reaction mixture was stirred at 90°C for 12 hours, cooled to room temperatureand filtered. The filtrate was concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient: 10% to 100% (volume ratio)) to give the hydrochloride of the target compound (1.6 mg, yield: 0.6%).

Spectroscopy data:

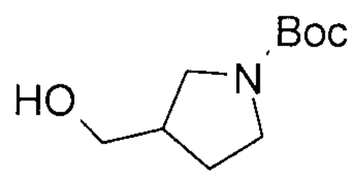
LC/MS (Method: UFLC): RT = 2.920 min; m/z = 545.1 [M+H]+; Total running time: 7 min.

Example 29



1-(3-((4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidin-1-yl)prop-2-en-1-one

Step A:

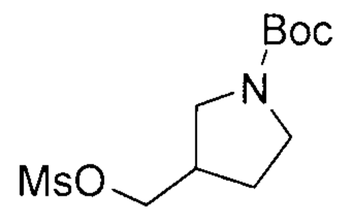


tert-butyl 3-(hydroxymethyl)pyrrolidine-1-formate

Procedure:

BH_3 (1 M, 90 mL, 90 mmol, 3.0 eq.) was dropwise added to a solution of 1-(tert-butoxycarbonyl)pyrrolidine-3-carboxylic acid (6.45 g, 30 mmol, 1.0 eq.) in tetrahydrofuran (30 mL) at 0 °C. After completion of the addition, the reaction mixture was allowed to warm to room temperature, heated to 45 °C and stirred for 2 hours. The reaction mixture was quenched with HCl (3N, 5 mL) at 0 °C, diluted with water (100 mL), and then extracted with ethyl acetate (200 mL) 2 times. The combined organic phases were washed with saturated $NaHCO_3$ (100 mL), dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (4.0 g, yield: 67%).

Step B:

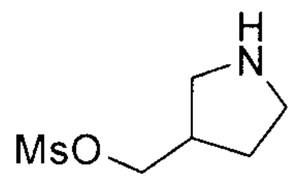


tert-butyl 3-((methylsulfonyloxy)methyl)pyrrolidine-1-formate

Procedure:

Triethylamine (3.02 g, 30.0 mmol, 3.0 eq.) and methanesulfonyl chloride (2.28 g, 20 mmol, 2.0 eq.) were subsequently added to a solution of tert-butyl 3-(hydroxymethyl)pyrrolidine-1-formate (0.7 g, 3.25 mmol, 1.0 eq.) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hours, quenched with water (20 mL), and separated, wherein the aqueous phase was extracted with dichloromethane (10 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (2.5 g, yield: 90%).

Step C:

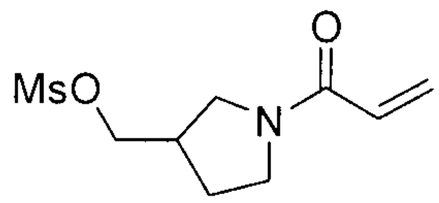


pyrrolidin-3-ylmethyl methanesulfonate

Procedure:

4M HCl/EA (10 mL) was added to a solution of tert-butyl 3-((methylsulfonyloxy)methyl)pyrrolidine-1-formate (2.5 g, 8.9 mmol) in ethyl acetate (40 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (1.9 g, yield:100%).

Step D:

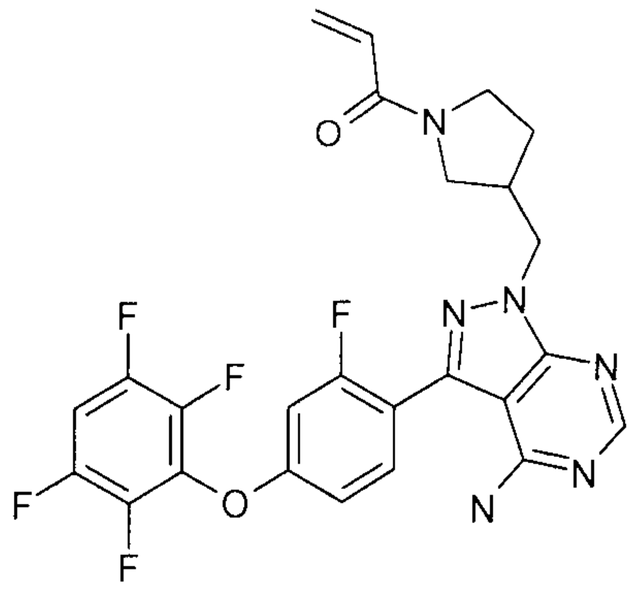


(1-acryloylpyrrolidin-3-yl)methyl methanesulfonate

Procedure:

Triethylamine (2.7 g, 26.7 mmol, 3.0 eq.) and acryloyl chloride (0.97 g, 10.7 mmol, 1.1 eq.) were subsequently added to a solution of pyrrolidin-3-ylmethyl methanesulfonate (1.9 g, 8.9 mmol, 1.0 eq.) in dichloromethane (30 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, and then quenched with saturated $NaHCO_3$ (10 mL), and separated, wherein the aqueous phase was extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (1.5 g, yield: 65%).

Step E:



1-(3-((4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)pyrrolidin-1-yl)prop-2-en-1-one

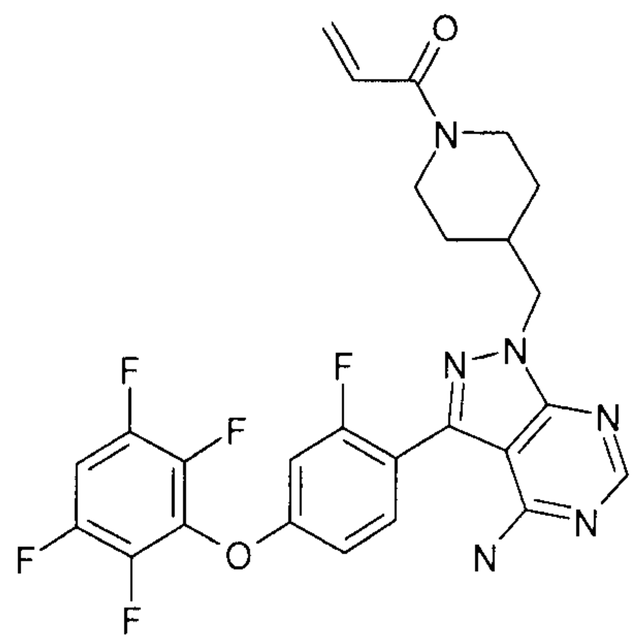
Procedure:

Potassium carbonate (42 mg, 0.305 mmol, 2.0 eq.) and 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.152 mmol, 1.0 eq.) were added to a solution of DEV-007-032-I5 (46 mg, 0.198 mmol, 1.3 eq.) in DMF (2 mL). The reaction mixture was stirred at 90 °C for 4 hours, cooled to room temperature and filtered. The filtrate was, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient: 10% to 100% (volume ratio)) to give the hydrochloride of the target compound (6 mg, yield: 7%).

Spectroscopy data:

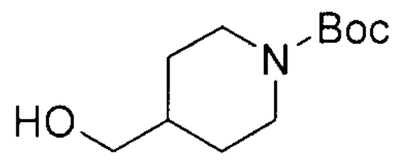
LC/MS (Method: UFLC): RT = 3.891 min; m/z = 531.2 [M+H]+; Total running time: 7 min.

Example 30



1-(4-((4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)piperidin-1-yl)prop-2-en-1-one

Step A:

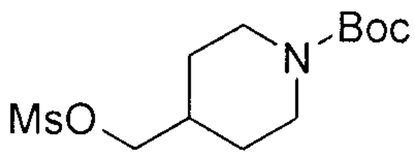


tert-butyl 4-(hydroxymethyl)piperidine-1-formate

Procedure:

A solution of $LiAlH_4$ (520 mg, 0.013 mmol, 0.7 eq.) in tetrahydrofuran (15 mL) was added dropwise to a solution of 1-tert-butyl 4-ethyl piperidine-1,4-diformate (5.0 g, 19.0 mmol, 1.0 eq.) in tetrahydrofuran (15 mL) at 0 °C. After completion of the addition, the reaction mixture was stirred at 0°C for 2 hours. The reaction mixture was quenched with water (1 mL), and then 15% NaOH (1 mL) was added. After stirring for 10 min, water (1 mL) was added to the resulting mixture, and dried over anhydrous magnesium sulfate for 30 min. The mixture was filtered through celite. The filtrate was concentrated and spin-dried to give the target compound (4.0 g, yield: 96%).

Step B:

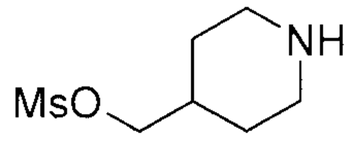


tert-butyl 4-((methylsulfonyloxy)methyl)piperidine-1-formate

Procedure:

Triethylamine (3.76 g, 37.2 mmol, 2.0 eq.) and methanesulfonyl chloride (3.19 g, 27.9 mmol, 1.5 eq.) were subsequently added to a solution of tert-butyl 4-(hydroxymethyl)piperidine-1-formate (4.0 g, 18.6 mmol, 1.0 eq.) in dichloromethane (25 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 14 hours, quenched with water (20 mL), then extracted with dichloromethane (50 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (4.5 g, yield: 83%).

Step C:

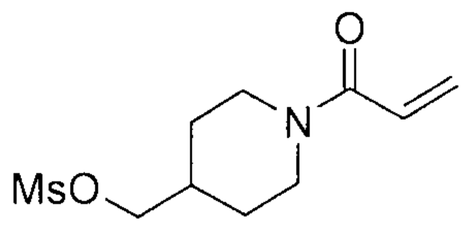


piperidin-4-ylmethyl methanesulfonate

Procedure:

4M HCl/EA (20 mL) was added to a solution of tert-butyl 4-((methylsulfonyloxy)methyl)piperidine-1-formate (4.5 g, 13.5 mmol) in dichloromethane (20 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dired to give the hydrochloride of the target compound (3.5 g, yield: 95%).

Step D:

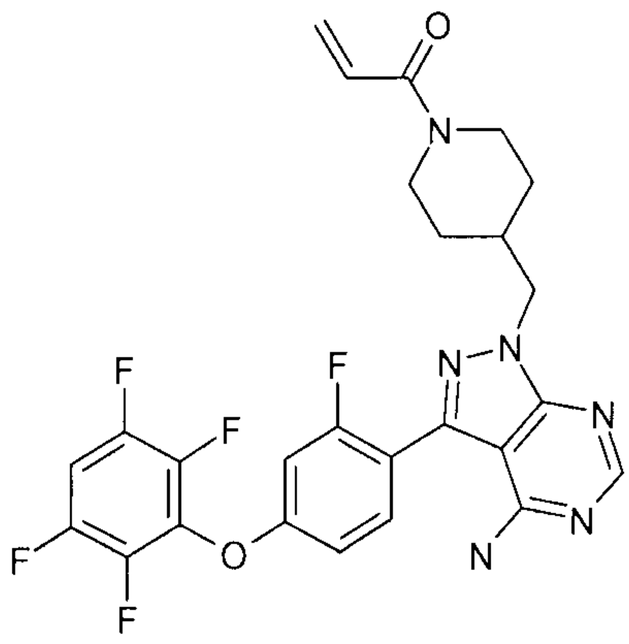


(1-acryloylpiperidin-4-yl)methyl methanesulfonate

Procedure:

Triethylamine (4.63 g, 45.7 mmol, 3.0 eq.) and acryloyl chloride (1.38 g, 15.2 mmol, 1.0 eq.) were subsequently added to a solution of piperidin-4-ylmethyl methanesulfonate (3.5 g, 15.2 mmol, 1.0 eq.) in dichloromethane (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 hour, and then quenched with water (60 mL). The aqueous layer was extracted with dichloromethane (100 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (2.5 g, yield: 66%).

Step E:



1-(4-((4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)piperidin-1-yl)prop-2-en-1-one

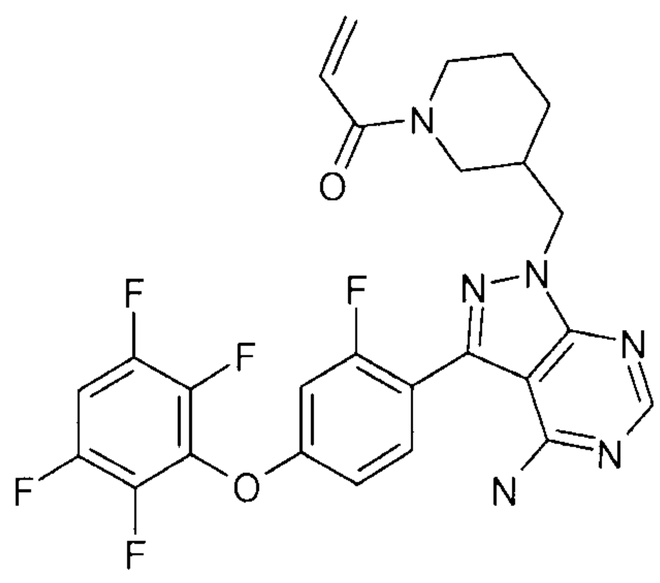
Procedure:

Potassium carbonate (42 mg, 0.304 mmol, 2.0 eq.) and 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine(60 mg, 0.152 mmol, 1.0 eq.) were added to a solution of (1-acryloylpiperidin-4-yl)methyl methanesulfonate (75 mg, 0.304 mmol, 2.0 eq.) in DMF (2 mL). The reaction mixture was stirred at 80 °C for 3 hours, cooled to room temperature and filtered. The filtrate was, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient: 10% to 100% (volume ratio)) to give the hydrochloride of the target compound (5 mg, yield: 6%).

Spectroscopy data:

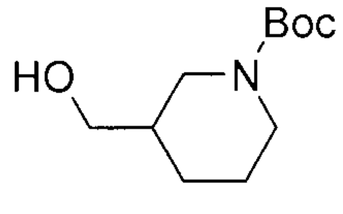
LC/MS (Method: UFLC): RT = 2.820 min; m/z = 545.1 [M+H]+; Total running time: 7 min.

Example 31



1-(3-((4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)piperidin-1-yl)prop-2-en-1-one

Step A:

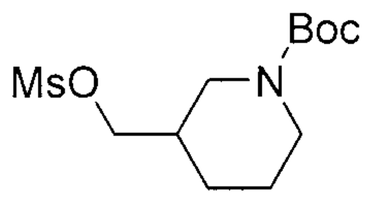


tert-butyl 3-(hydroxymethyl)piperidine-1-formate

Procedure:

$LiAlH_4$ (580 mg, 15.3 mmol, 0.7 eq.) was added to a solution of 1-(tert-butoxycarbonyl)piperidine-3-carboxylic acid (5.0 g, 21.8 mmol, 1.0 eq.) in tetrahydrofuran (30 mL) at 0 °C. After completion of the addition, the reaction mixture was stirred at 0 °C for 12 hours. The reaction was quenched with water (1 mL), and then 15% NaOH (1 mL) was added. After stirring for 10 min at room temperature, water (1 mL) was added to the resulting mixture, and the resulting mixture was dried over anhydrous megnesium sulfate, filtered through celite, concentrated and spin-dried to give the target compound (3.9 g, yield: 93%).

Step B:

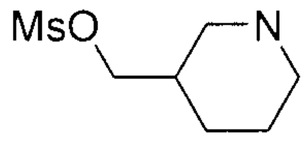


tert-butyl 3-((methylsulfonyloxy)methyl)piperidine-1-formate

Procedure:

Triethylamine (1.9 g, 18.6 mmol, 2.0 eq.) and methanesulfonyl chloride (2.12 g, 18.6 mmol, 2.0 eq.) were subsequently added to a solution of tert-butyl 3-(hydroxymethyl)piperidine-1-formate (2.0 g, 18.6 mmol, 1.0 eq.) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hours, quenched with water (20 mL), separated, and the aqueous phase was extracted with dichloromethane (10 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (2.5 g, yield: 92%).

Step C:

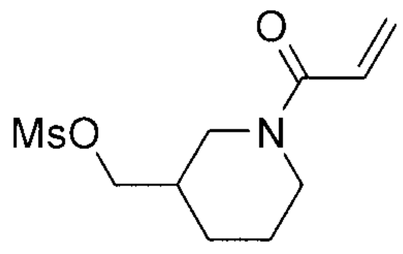


piperidin-3-ylmethyl methanesulfonate

Procedure:

4M HCl/EA (10 mL) was added to a solution of tert-butyl 3-((methylsulfonyloxy)methyl)piperidine-1-formate (2.5 g, 8.5 mmol) in ethyl acetate (40 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (1.93 g, yield: 98%).

Step D:

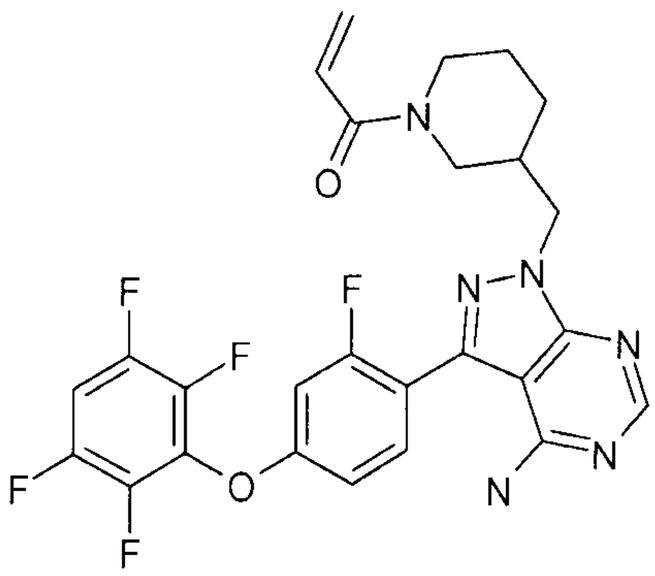


(1-acryloylpiperidin-3-yl)methyl methanesulfonate

Procedure:

Triethylamine (1.67 g, 16.6 mmol, 2.0 eq.) and acryloyl chloride (0.82 g, 9.1 mmol, 1.1 eq.) were subsequently added to a solution of piperidin-3-ylmethyl methanesulfonate (1.93 g, 8.3 mmol, 1.0 eq.) in dichloromethane (30 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, and then quenched with saturated $NaHCO_3$ (10 mL). The aqueous phase was extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (1.5 g, yield: 71%).

Step E:



1-(3-((4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)piperidin-1-yl)prop-2-en-1-one

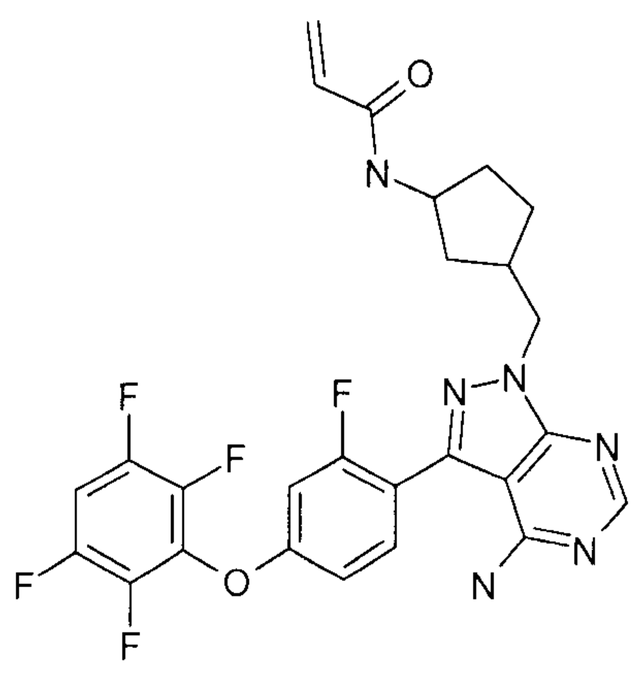
Procedure:

Cesium carbonate (99 mg, 0.304 mmol, 2.0 eq.) and 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine(60 mg, 0.152 mmol, 1.0 eq.) were added to a solution of (1-acryloylpiperidin-3-yl)methyl methanesulfonate (75 mg, 0.304 mmol, 2.0 eq.) in DMF (2 mL). The reaction mixture was stirred at 80 °C for 12 hours, cooled to room temperature and filtered. The filter cake washed with ethyl acetate. The filtrate was, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient: 10% to 100% (volume ratio)) to give the hydrochloride of the target compound (2 mg, yield: 2%).

Spectroscopy data:

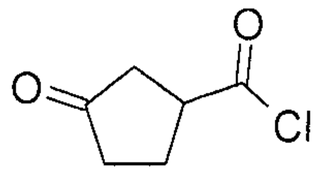
LC/MS (Method: UFLC): RT = 2.947 min; m/z = 545.1 $[M+H]^+$; Total running time: 7 min.

Example 32



N-(3-((4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)cyclopentyl)acrylamide

Step A:

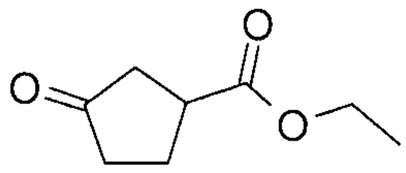


3-oxocyclopentanecarbonyl chloride

Procedure:

DMF (3 drops) and oxalyl chloride (3.8 g, 30 mmol, 3.0 eq.) was added dropwise to 3-oxo-1-cyclopentanecarboxylic acid (1.28 g, 10 mmol, 1.0 eq.) in dichloromethane (30 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours, concentrated and spin-dried to give the target compound (1.2 g, yield: 82%).

Step B:

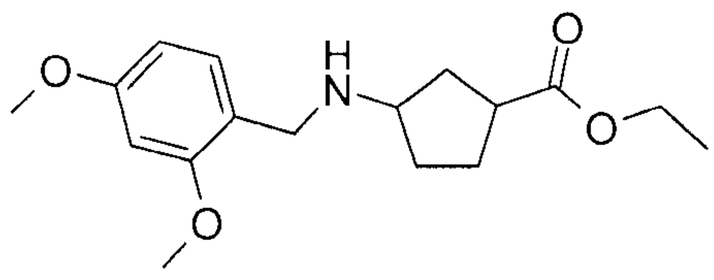


ethyl 3-oxocyclopentaneformate

Procedure:

Triethylamine (3.8 g, 30 mmol, 2.0 eq.) and ethanol (754 mg, 16.37 mmol, 2.0 eq.) were subsequently added dropwise to a solution of 3-oxocyclopentanecarbonyl chloride (1.28 g, 8.2 mmol, 1.0 eq.) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours, quenched with water (20 mL) and separated. The aqueous phase was extracted with dichloromethane (10 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (0.6 g, yield: 47%).

Step C:



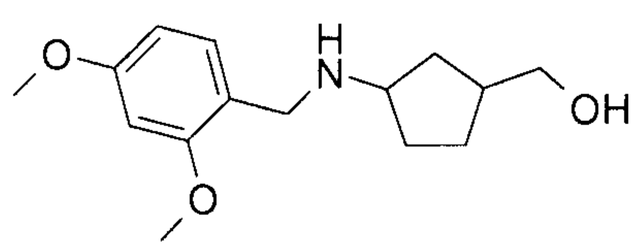
ethyl 3-(2,4-dimethoxybenzylamino)cyclopentaneformate

Procedure:

2,4-dimethoxybenzyl amine (556 mg, 4.66 mmol, 1.0 eq.), sodium triacetoxyborohydride (446 mg, 3.32 mmol, 1.4 eq.) and acetic acid (200 mg, 3.32 mmol, 1.0 eq.) were added to a solution of ethyl 3-oxocyclopentaneformate (520 mg, 3.32 mmol, 1.0 eq.) in tetrahydrofuran (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 14 hours,

quenched with saturated $NaHCO_3$ (10 mL) and separated. The aqueous phase was extracted with ethyl acetate (10 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (250 mg, yield: 44 %).

Step D:

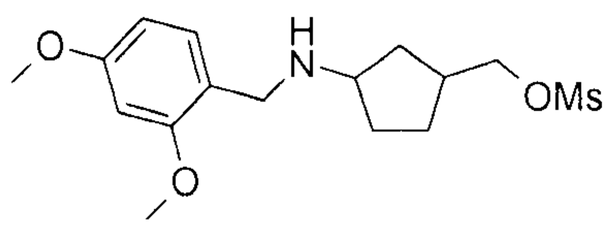


(3-(2,4-dimethoxybenzylamino)cyclopentyl)methanol

Procedure:

$LiAlH_4$ (17 mg, 0.445 mmol, 0.7 eq.) was added to a solution of ethyl 3-(2,4-dimethoxybenzylamino)cyclopentaneformate (200 mg, 0.65 mmol, 1.0 eq.) in tetrahydrofuran (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours, quenched with water (0.2 mL), and then 15% NaOH (0.2 mL) was added. After stirring for 10 min at room temperature, water (0.6 mL) was added to the resulting mixture. The resulting mixture was dried over anhydrous magnesium sulfate, then filtered through celite. The filtrate was concentrated and spin-dried to give the target compound (150 mg, yield: 87%).

Step E:



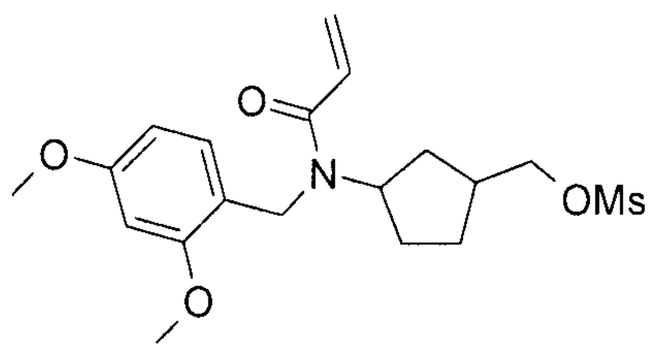
(3-(2,4-dimethoxybenzylamino)cyclopentyl)methyl methanesulfonate

Procedure:

Triethylamine (171 mg, 1.7 mmol, 3.0 eq.) and methanesulfonyl chloride (129 mg, 1.13 mmol, 2.0 eq.) were subsequently added to a solution of (3-(2,4-dimethoxybenzylamino)cyclopentyl)methanol (150 mg, 0.566 mmol, 1.0 eq.) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 14 hours, quenched with water (10 mL), and then extracted with dichloromethane (10 mL)

2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (194mg, yield: 100%).

Step F:

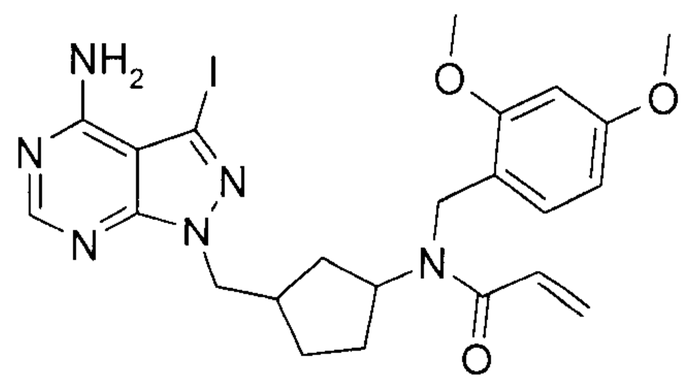


(3-(N-(2,4-dimethoxybenzyl)acrylamido)cyclopentyl)methyl methanesulfonate

Procedure:

Triethylamine (220 mg, 2.18 mmol, 3.0 eq.) and acryloyl chloride (79 mg, 0.873 mmol, 1.2 eq.) were subsequently added to a solution of (3-(2,4-dimethoxybenzylamino)cyclopentyl)methyl methanesulfonate (250 mg, 0.727 mmol, 1.0 eq.) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, and then quenched with saturated $NaHCO_3$ (10 mL) and separated. The aqueous phase was extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (200 mg, yield: 69%).

Step G:



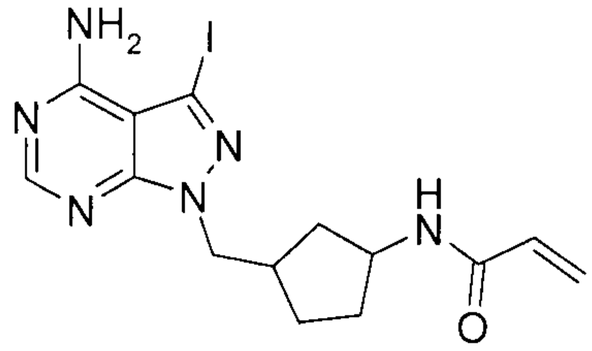
N-(2,4-dimethoxybenzyl)-N-(3-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)cyclopentyl)acrylamide

Procedure:

Potassium carbonate (79 mg, 0.57 mmol, 2.5 eq.) and 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.23 mmol, 1.0 eq.) were added to a solution of (3-(N-(2,4-dimethoxybenzyl)acrylamido)cyclopentyl)methyl methanesulfonate (137 mg, 0.34 mmol, 1.5 eq.) in DMF (5 mL) . The reaction mixture was stirred at 90 °C for 12 hours, cooled to room

temperature and filtered. The filter cake was washed with ethyl acetate. The filtrate was concentrated and spin-dried to give the crude product, which was purified by thin layer chromatography (eluent: petroleum ether: ethyl acetate=1:3) to give the target compound (60 mg, yield: 62%).

Step H:

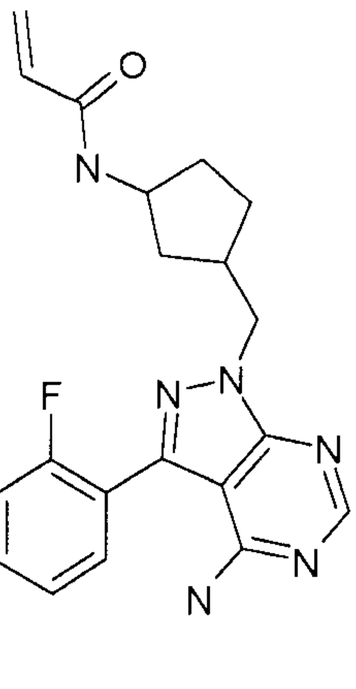


N-(3-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)cyclopentyl)acrylamide

Procedure:

Et_3SiH (0.5 mL) was added to a solution of N-(2,4-dimethoxybenzyl)-N-(3-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)cyclopentyl)acrylamide (60 mg, 0.14 mmol, 1.0 eq.) in trifluoroacetic acid (3 mL). The reaction mixture was refluxed and stirred for 3 hours, and then evaporated to remove the solvent under reduced pressure. The residue was dissolved in ethyl acetate (10 mL), washed with saturated NaHCO3 (10 mL) and brine (10 mL) respectively one time, dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by thin layer chromatography (eluent: petroleum ether: ethyl acetate=1:3) to give the target compound (15 mg, yield: 35%).

Step I:



N-(3-((4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]

pyrimidin-1-yl)methyl)cyclopentyl)acrylamide

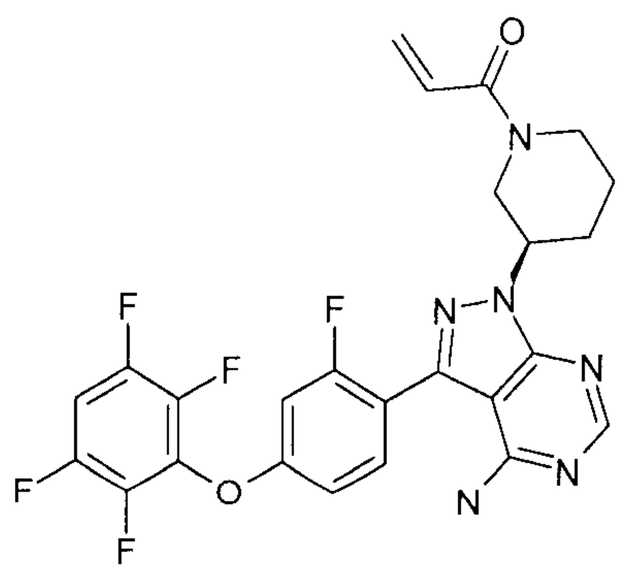
Procedure:

N-(3-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)cyclopentyl)acrylamide (15 mg, 0.036 mmol, 1.0 eq.), 2-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (21 mg, 0.054 mmol, 1.5 eq.), potassium carbonate (17 mg, 0.127 mmol, 3.0 eq.) and $Pd(PPh_3)_4$ (4 mg, 0.0036 mmol, 0.1 eq.) were dissolved in 1,4-dioxane (8 mL, 3/1, v/v). The reaction mixture was stirred at 85 °C for 30 min. with microwave irradiation under nitrogen atmosphere, diluted with water (10 mL) and extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried with anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by thin layer chromatography (eluent: petroleum ether: ethyl acetate=1:3) to give the target compound (5 mg, yield: 40%).

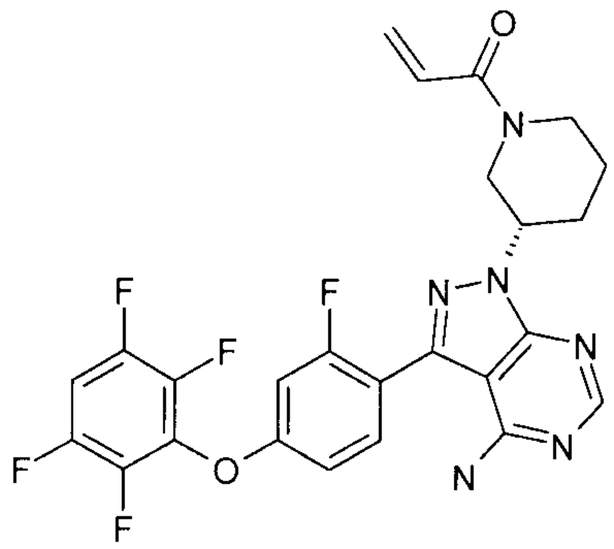
Spectroscopy data:

LC/MS (Method: UFLC): RT = 0.810 min; m/z = 545.0 $[M+H]^+$; Total running time: 1.5 min.

Examples 33 and 34



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one



1-((S)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one

Procedure:

1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (750 mg) was chirally separated by SFC (Chiralcel OJ, 20μm; Supercritical CO_2 :C_2H_5OH(0.2%DEA), v/v, 200ml/min) to give 1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (280 mg, ee: 100%) and 1-((S)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (330 mg, ee: 98%).

Spectroscopy data:

Example 33:

LC/MS (Method: UFLC): RT = 3.002 min; m/z = 531.1 $[M+H]^+$; Total running time: 7 min.

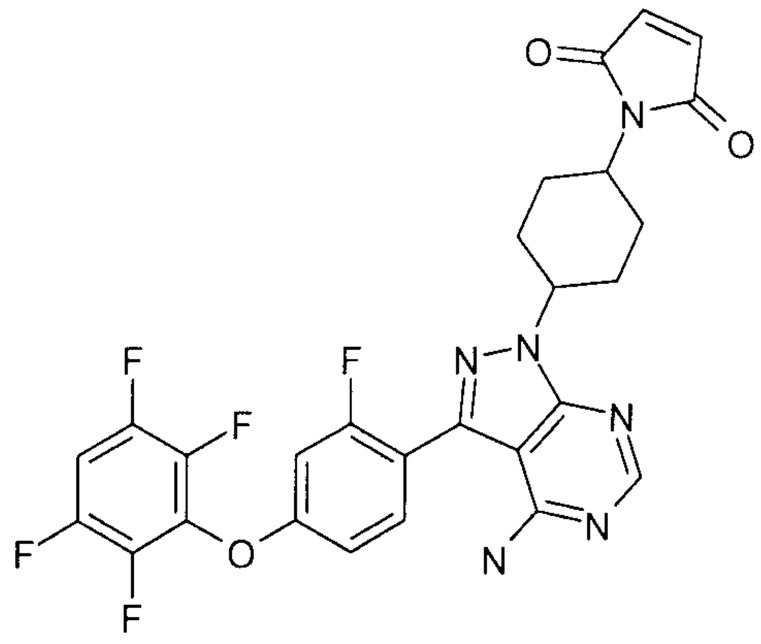
^1H NMR (400MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.58 (t, *J* = 8.4 Hz, 1H), 7.09-7.04 (m, 1H), 6.94-6.88 (m, 2H), 6.62-6.54 (m, 1H), 6.32-6.25 (m, 1H), 5.73-5.63 (m, 1H), 5.56-5.51 (m, 1H), 4.90-4.85 (m, 1.5H), 4.59-4.56 (m, 0.5H), 4.21-4.17 (m, 0.5H), 4.04-4.01 (m, 0.5H), 3.76-3.71 (m, 0.5H), 3.40-3.35 (m, 0.5H), 3.22-3.15 (m, 0.5H), 2.93-2.87 (m, 0.5H), 2.39-2.27 (m, 2H), 2.04-1.68 (m, 2H).

Example 34:

LC/MS (Method: UFLC): RT = 3.006 min; m/z = 531.1 $[M+H]^+$; Total running time: 7 min.

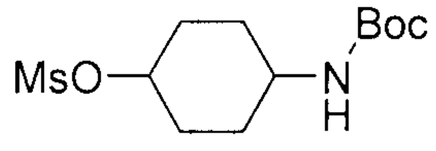
^1H NMR (400MHz, CD_3OD) δ 8.24 (s, 1H), 7.62 (t, J = 8.4 Hz, 1H), 7.50-7.45 (m, 1H), 7.09-7.01 (m, 2H), 6.85-6.63 (m, 1H), 6.21-6.09 (m, 1H), 5.77-5.61 (m, 1H), 4.63-4.59 (m, 1H), 4.23-4.07 (m, 1.5H), 3.90-3.85 (m, 0.5H), 3.51-3.45 (m, 0.5H), 3.34-3.17 (m, 1.5H), 2.40-2.23 (m, 2H), 2.08-2.05 (m, 1H), 1.75-1.71 (m, 1H).

Example 35



1-(4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-1H-pyrrole-2,5-dione

Step A:

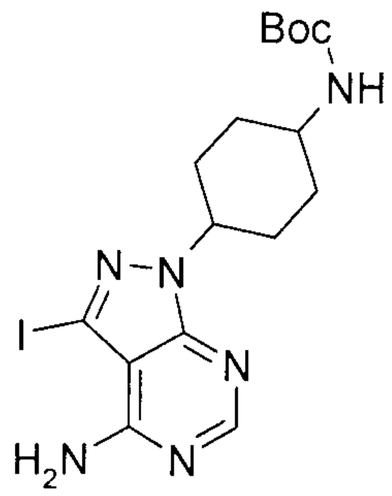


4-(tert-butoxycarbonyl)cyclohexyl methanesulfonate

Procedure:

Triethylamine (9.4 g, 92 mmol, 2.0 eq.) and methanesulfonyl chloride (10.5 g, 92 mmol, 2.0 eq.) were subsequently added to a solution of tert-butyl 4-hydroxycyclohexylcarbamate (10 g, 46 mmol, 1.0 eq.) in dichloromethane (100 mL) at 0 °C. The reaction mixture was stirred at room temperature for 14 hours, quenched with saturated $NaHCO_3$ (50 mL) and separated. The aqueous phase was extracted with dichloromethane (30 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (11 g, yield: 80%).

Step B:

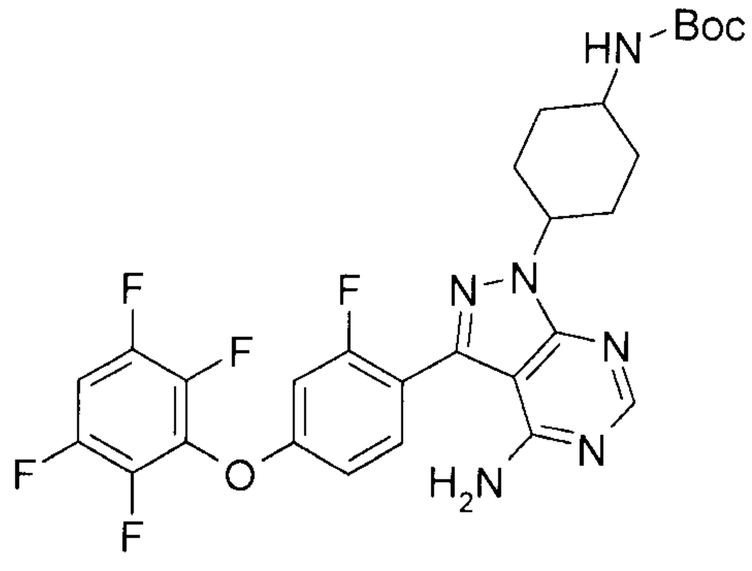


tert-butyl 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexylcarbamate

Procedure:

Cesium carbonate (5.0 g, 15.3 mmol, 2.0 eq) and 4-(tert-butoxycarbonyl)cyclohexyl methanesulfonate (4.5 g, 15.3 mmol, 2.0 eq) were added to a solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (2.0 g, 7.66 mmol, 1.0 eq.) in DMF (10 mL). The reaction mixture was stirred at 80 °C for 12 hours. After cooling to room temperature, the reaction mixture was filtered, and the filter cake was washed with ethyl acetate. The filtrate was concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (1.1 g, yield: 31%).

Step C:



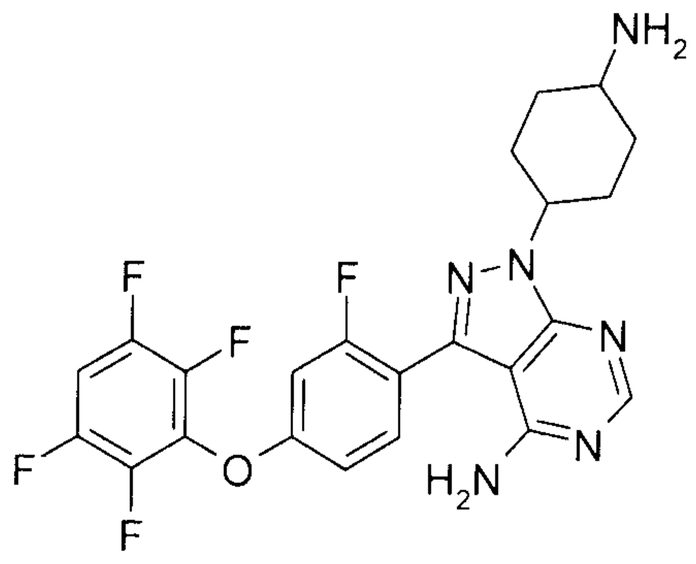
tert-butyl 4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexylcarbamate

Procedure:

Tert-butyl 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexylcarbamate (0.82 g, 1.79 mmol, 1.0 eq.), 2-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.0 g, 2.69 mmol, 1.5 eq.), potassium phosphate (0.76 g,

3.68 mmol, 2.0 eq.) and Pd-118 (58mg, 0.089 mmol, 0.05 eq.) were dissolved in 1,4-dioxane/water (10 mL, 5/1, v/v). The reaction mixture was stirred at 80 °C for 12 hours under nitrogen atmosphere. The reaction solution was diluted with water (10 mL) and extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by thinlayer chromatography (eluent: petroleum ether: ethyl acetate=1:3) to give the target compound (800 mg, yield: 80%).

Step D:

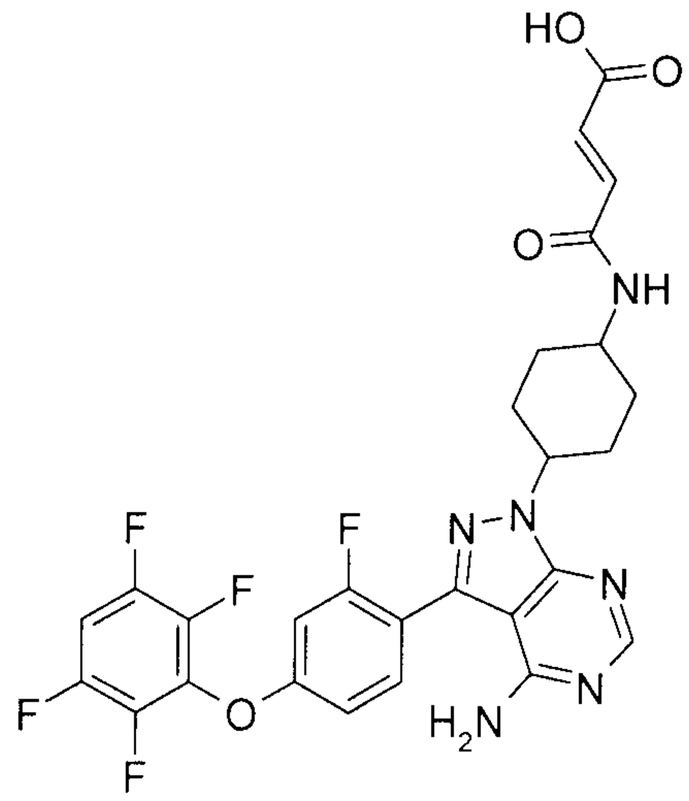


1-(4-aminocyclohexyl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EA (5 mL) was added to a solution of tert-butyl 4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexylcarbamate (800 mg, 1.35 mmol) in ethyl acetate (10 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (600 mg, yield:90%).

Step E:

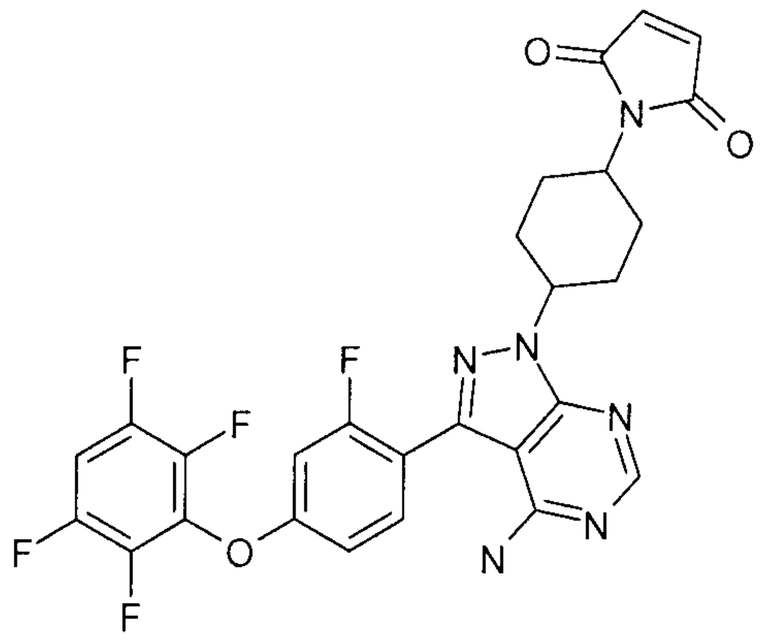


4-(4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexylamino)-4-oxo-but-2-enoic acid

Procedure:

A mixture of triethylamine (41 mg, 0.408 mmol, 2.0 eq.) and maleic anhydride (20 mg, 204 mmol, 1.0 eq.) in dichloromethane (0.2 mL) was added dropwise to a solution of 1-(4-aminocyclohexyl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.204 mmol, 1.0 eq.) in dichloromethane (1 mL) at 0 °C. The reaction mixture was stirred at room temperature for 14 hours, quenched with water (10 mL) and then extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (100 mg, yield: 83%).

Step F:



1-(4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-1H-pyrrole-2,5-dione

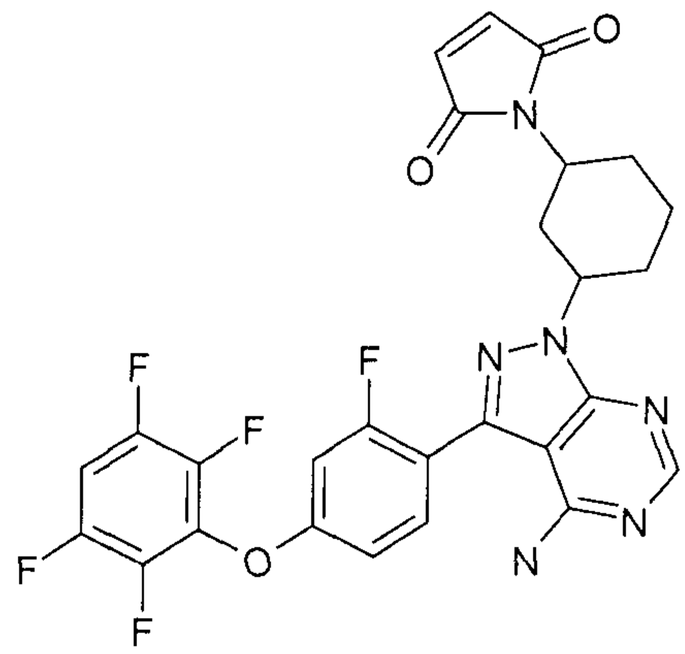
Procedure:

4-(4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexylamino)-4-oxo-but-2-enoic acid(50 mg, 0.085 mmol, 1.0 eq.) was dissolved in PPA (0.5 mL). The reaction mixture was stirred at 110 °C for 4 hours, and then poured into ice water (5 mL) to quench the reaction. The mixture was extracted with ethyl acetate (5 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient elution 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure to give the target compound (1.5 mg, yield: 3%).

Spectroscopy data:

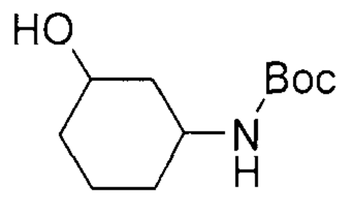
LC/MS (Method: UFLC): RT = 4.399 min; m/z = 571.1 $[M+H]^+$; Total running time: 7 min.

Example 36



1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-1H-pyrrole-2,5-dione

Step A:

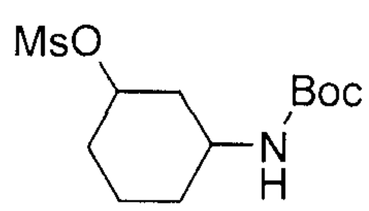


tert-butyl 3-hydroxycyclohexylcarbamate

Procedure:

Sodium borohydride (710 mg, 18.8 mmol, 2.0 eq.)was added to a solution of tert-butyl 3-oxocyclohexylcarbamate (2.0 g, 9.38 mmol, 1.0 eq.) in methanol (20 mL) at 0 °C. The reaction was stirred at room temperature for 14 hours, quenched with water (20 mL) and extracted with ethyl acetate (30 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, and concentrated to give the target compound (2.0 g, yield: 100%).

Step B:



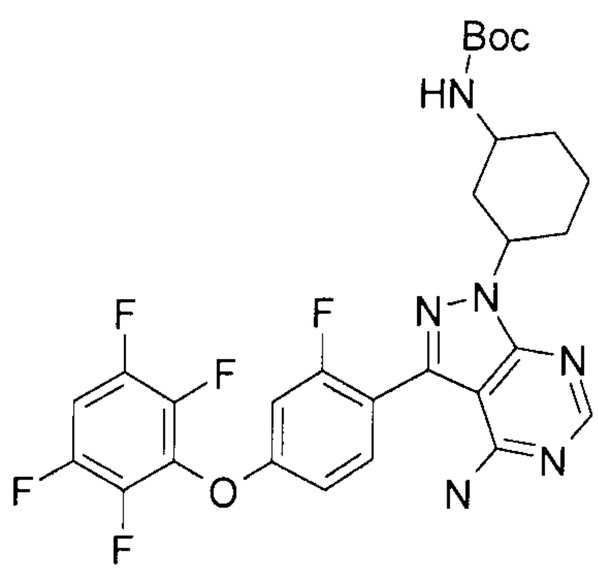
3-(tert-butoxycarbonyl)cyclohexyl methanesulfonate

Procedure:

Triethylamine (1.41g, 13.9 mmol, 3.0 eq.) and methanesulfonyl chloride (798 mg, 6.97 mmol, 1.5 eq.) were subsequently added to a solution of tert-butyl 3-

hydroxycyclohexylcarbamate (1.0 g, 4.64 mmol, 1.0 eq.) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 14 hours, quenched with saturated $NaHCO_3$ (10 mL), then extracted with dichloromethane (10 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (1.36 g, yield: 100%).

Step C:

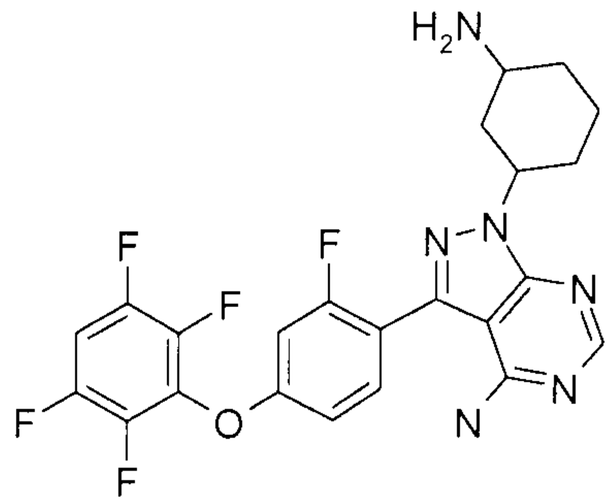


tert-butyl 3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexylcarbamate

Procedure:

Cesium carbonate (116 mg, 0.356 mmol, 2.0 eq) and 3-(tert-butoxycarbonyl)cyclohexyl methanesulfonate (105 mg, 0.356 mmol, 2.0 eq) were addedto a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (70 mg, 0.178 mmol, 1.0 eq.) in DMF (3 mL). The reaction mixture was stirred at 80 °C for 3 hours, cooled to room temperature and filtered. The filter cake washed with ethyl acetate. The filtrate was concentrated and spin-dried to give the crude product, which was purified by thin layer chromatography (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (35 mg, yield: 33%).

Step D:

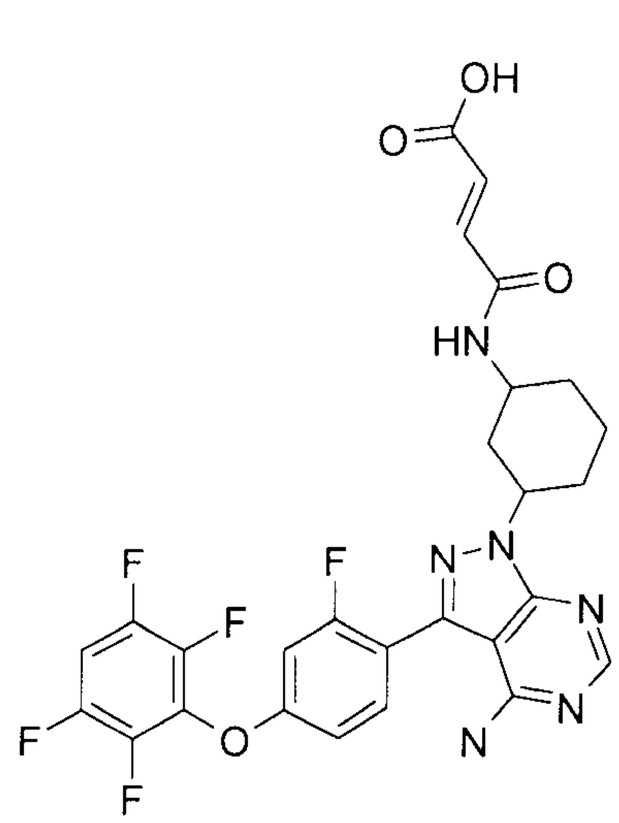


1-(3-aminocyclohexyl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EA (2 mL) was added to a solution of tert-butyl 3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexylcarbamate (34 mg, 0.058 mmol, 1.0 eq.) in ethyl acetate (5 mL) at 0°C. The reaction mixture was stirred at room temperature for 2 hours, concentrated and spin-dried to give the hydrochloride of the target compound (30 mg, yield: 100%).

Step E:



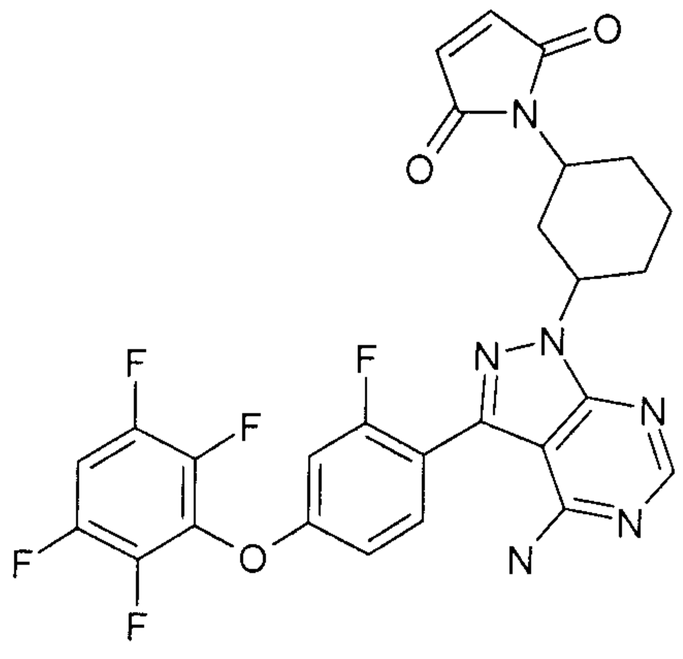
4-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexylamino)-4-oxo-but-2-enoic acid

Procedure:

A mixture of triethylamine (29.3 mg, 0.29 mmol, 5.0 eq.) and maleic anhydride (5.69 mg, 0.058 mmol, 1.0 eq.) in dichloromethane (0.2 mL) was added dropwise to a solution of 1-(3-

aminocyclohexyl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.058 mmol, 1.0 eq.) in dichloromethane (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 14 hours, quenched with water (10 mL) and then extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (16 mg, yield: 47%).

Step F:



1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-1H-pyrrole-2,5-dione

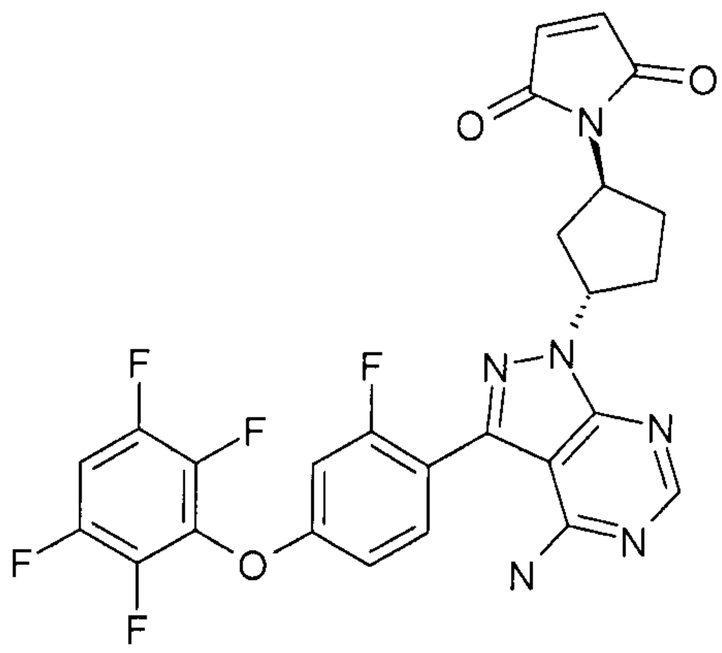
Procedure:

4-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexylamino)-4-oxo-but-2-enoic acid (16 mg, 0.028 mmol, 1.0 eq.) was dissolved in PPA (5mL). The reaction mixture was stirred at 110 °C for 16 hours, and then poured into ice water (10 mL) to quench the reaction. The mixture was extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18reversed-phase column (mobile phase: acetonitrile/water, gradient elution 10% to 100% (volume ratio)) to give the target compound (0.8 mg, yield: 5%).

Spectroscopy data:

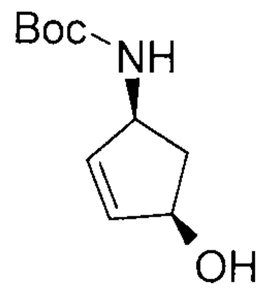
LC/MS (Method: UFLC): RT = 4.429 min; m/z = 571.1 $[M+H]^+$; Total running time: 7 min.

Example 37



1-((1s,3s)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentyl)-1H-pyrrole-2,5-dione

Step A:

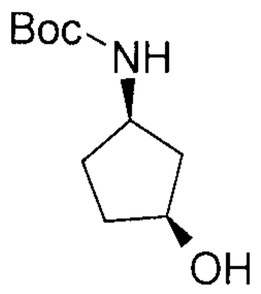


tert-butyl (1s,4r)-4-hydroxycyclopent-2-enylcarbamate

Procedure:

$Mo(Co)_6$ (1.6 g, 6.08 mmol, 1.0 eq.) was added to a solution of tert-butyl 3-oxa-2-aza-bicyclo[2.2.1]hept-5-ene-2-formate(6.0 g, 30.4 mmol, 5.0 eq.) in acetonitrile/water (10 mL, 20/1, v/v). Sodium borohydride (2.3 g, 60.8 mmol, 10.0 eq.) was added in one portion to the above solution at 30 °C. The reaction mixture was stirred at 60 °C for 12 hours, cooled to room temperature, and filtered through celite. The filtrate was concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1: 0 1:1) to give the target compound (2.0 g, yield: 33%)

Step B:

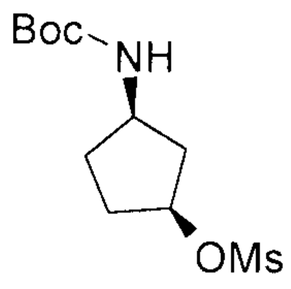


tert-butyl (1r,3s)-3-hydroxycyclopentylcarbamate

Procedure:

tert-butyl (1s,4r)-4-hydroxycyclopent-2-enylcarbamate (2.0 g, 10 mmol) was dissolved in methanol (20 mL), the reaction flask was degassed with nitrogen air three times. 10% Pd/C (0.2 g, 10%, w/w) was added to the above mixture, and then degassed with hydrogen three times. The reaction solution was stirred at room temperatureunder hydrogen atmosphere (1 atm) for 14 hours, and filtered through celite. The filtrate was concentrated to give the target compound (1.9 g, yield: 95%).

Step C:

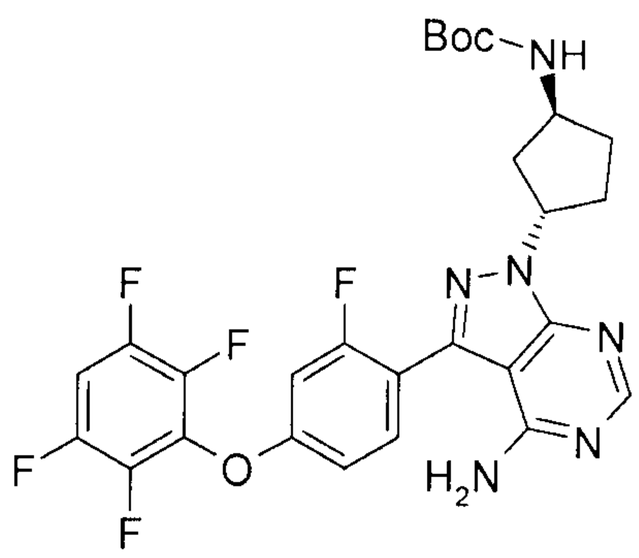


(1s,3r)-3-(tert-butoxycarbonyl)cyclopentyl methanesulfonate

Procedure:

Triethylamine (350 mg, 3.48 mmol, 2.0 eq.) and methanesulfonyl chloride (397 mg, 3.48 mmol, 2.0 eq.) were subsequently added to a solution of tert-butyl (1r,3s)-3-hydroxycyclopentylcarbamate (350 mg, 1.74 mmol, 1.0 eq.) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 14 hours, quenched with saturated $NaHCO_3$ (10 mL). The aqueous phase was extracted with dichloromethane (10 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (400 mg, yield: 83%).

Step D:

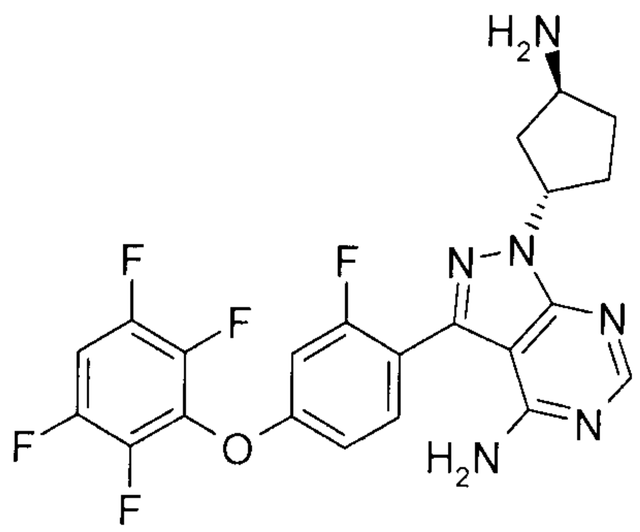


tert-butyl (1s,3s)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentylcarbamate

Procedure:

Cesium carbonate (160 mg, 0.508 mmol, 2.0 eq.) and (1s,3r)-3-(tert-butoxycarbonyl)cyclopentyl methanesulfonate (150 mg, 0.508 mmol, 2.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.254 mmol, 1.0 eq.) in DMF (3 mL). The reaction mixture was stirred at 80 °C for 12 hours, cooled to room temperature and filtered. The filter cake washed with ethyl acetate. The filtrate was concentrated and spin-dried to give the crude product, which was purified by thin layer chromatography (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (60 mg, yield: 41%).

Step E:

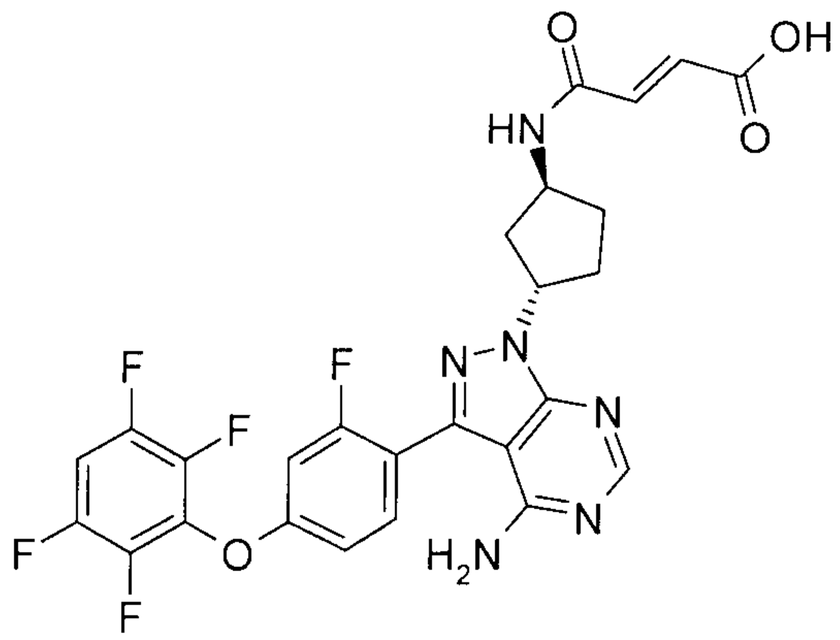


1-((1s,3s)-3-aminocyclopentyl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EA (2 mL) was added to a solution of tert-butyl (1s,3s)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentylcarbamate (60 mg, 0.104 mmol) in ethyl acetate (5 mL) at 0°C. The reaction mixture was stirred at room temperature for 0.5 hours, concentrated and spin-dried to give the hydrochloride of the target compound (41 mg, yield: 82%).

Step F:

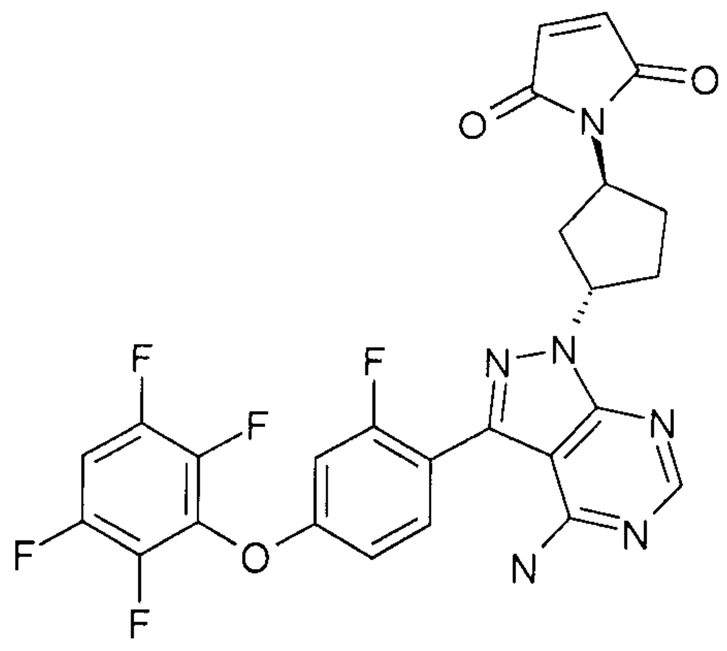


4-((1s,3s)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentylamino)-4-oxo-but-2-enoic acid

Procedure:

A mixture of triethylamine (16 mg, 0.16 mmol, 2.0 eq.) and maleic anhydride (8 mg, 0.08 mmol, 1.1 eq.) in dichloromethane (0.2 mL) was added dropwise to a solution of 1-((1s,3s)-3-aminocyclopentyl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (41 mg, 0.08 mmol, 1.0 eq.) in dichloromethane (0.5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 14 hours, quenched with water (10 mL) and then extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (40 mg, yield: 87%).

Step G:



1-((1s,3s)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentyl)-1H-pyrrole-2,5-dione

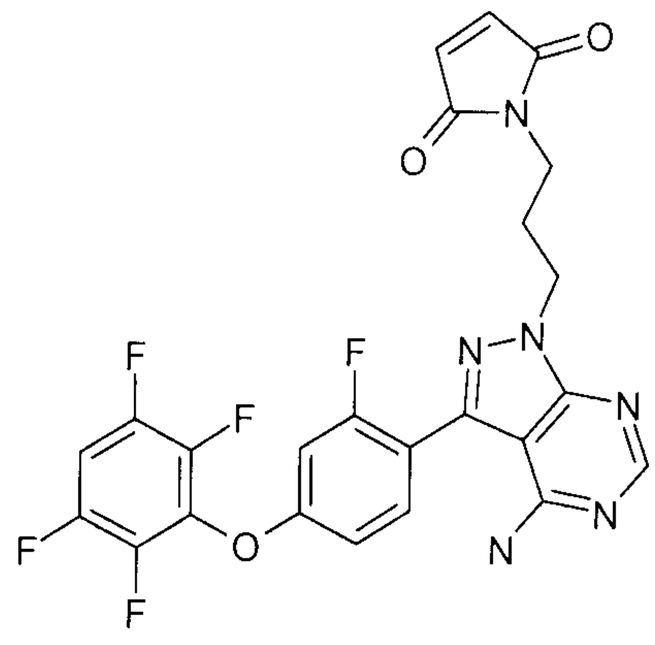
Procedure:

4-((1s,3s)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclopentylamino)-4-oxo-but-2-enoic acid(40 mg, 0.069 mmol, 1.0 eq.) was dissolved in PPA (0.5 mL). The reaction mixture was stirred at 110 °C for 4 hours, and then poured into ice water (10 mL) to quench the reaction. The mixture was extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient elution 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (0.7 mg, yield: 2%).

Spectroscopy data:

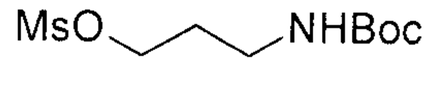
LC/MS (Method: UFLC): RT = 4.370 min; m/z = 557.1 $[M+H]^+$; Total running time: 7 min.

Example 38



1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-1H-pyrrole-2,5-dione

Step A:



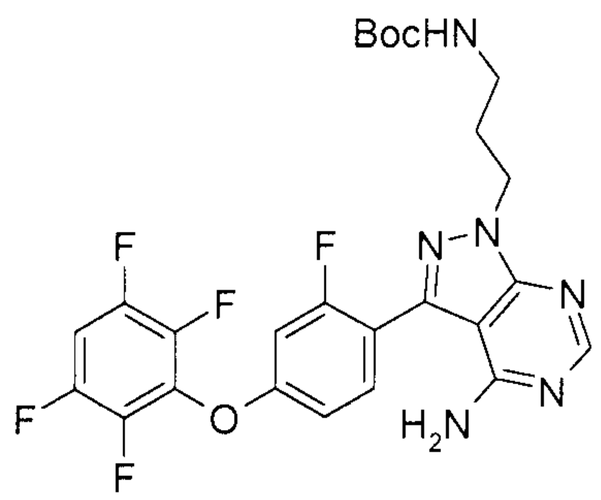
3-(tert-butoxycarbonyl)propyl methanesulfonate

Procedure:

Triethylamine (4.5 g, 44.6 mol, 3.0 eq.) and methanesulfonyl chloride (3.37 g, 29.6 mmol, 2.0 eq.) were subsequently added to a solution of 3-(tert-butoxycarbonyl)propyl methanesulfonate (2.6 g,

14.8 mmol, 1.0 eq.) in dichloromethane (30 mL) at 0 °C. The reaction mixture was stirred at room temperaturefor 14 hours, quenched with saturated $NaHCO_3$ (50 mL). The aqueous phase was extracted with dichloromethane (50 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (2.7 g, yield: 100%).

Step B:

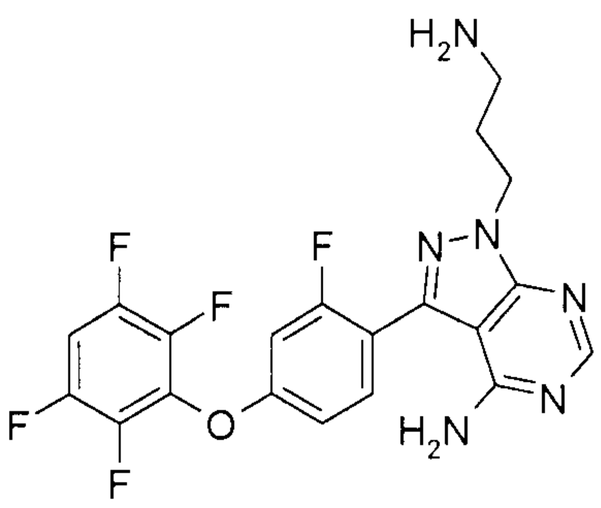


tert-butyl 3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propylcarbamate

Procedure:

Potassium carbonate (60 mg, 0.44 mmol, 3.0 eq.) and 3-(tert-butoxycarbonyl)propyl methanesulfonate (140 mg, 0.553 mmol, 3.6 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.153 mmol, 1.0 eq.) in DMF (3 mL). The reaction mixture was stirred at 90 °C for 12 hours, cooled to room temperature and filtered. The filter cake was washed with ethyl acetate. The filtrate was concentrated and spin-dried to give the crude product, which was purified by thin layer chromatography (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (50 mg, yield: 61%).

Step C:

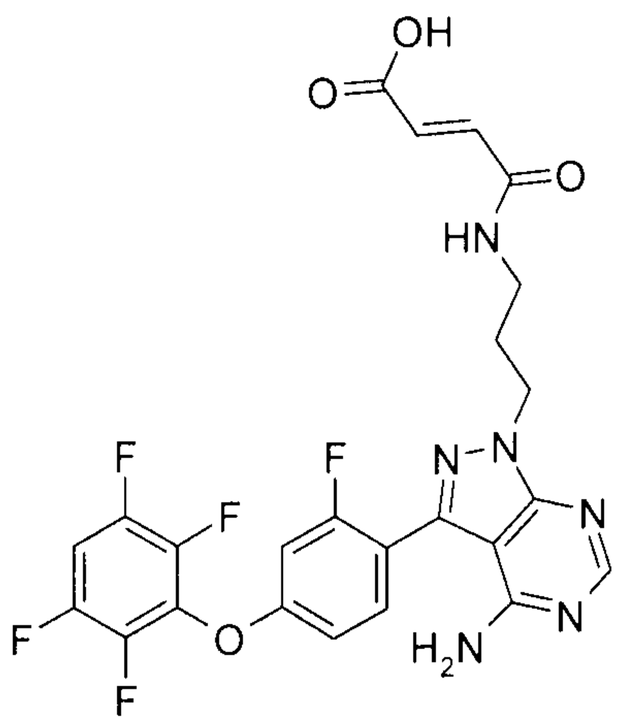


1-(3-aminopropyl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EA (2 mL) was added to a solution of tert-butyl 3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propylcarbamate (50 mg, 0.09 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 0.5 hours, concentrated and spin-dried to give the hydrochloride of the target compound (42 mg, yield: 100%).

Step D:

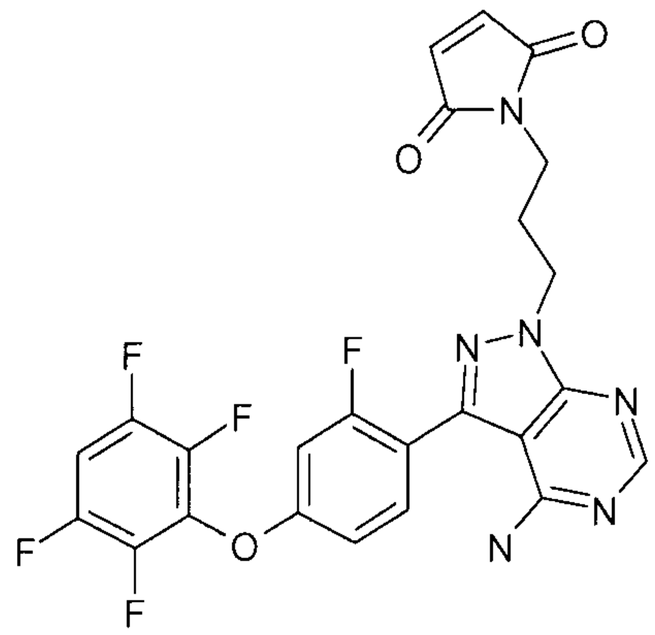


4-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propylamino)-4-oxo-but-2-enoic acid

Procedure:

A mixture of triethylamine (33 mg, 0.33 mmol, 3.0 eq.) and maleic anhydride (11 mg, 0.11 mmol, 1.0 eq.) in dichloromethane (0.2 mL) was added dropwise to a solution of 1-(3-aminopropyl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.11 mmol, 1.0 eq.) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 hours, quenched with water (10 mL) and then extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (60 mg, yield: 100%).

Step E:



1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-1H-pyrrole-2,5-dione

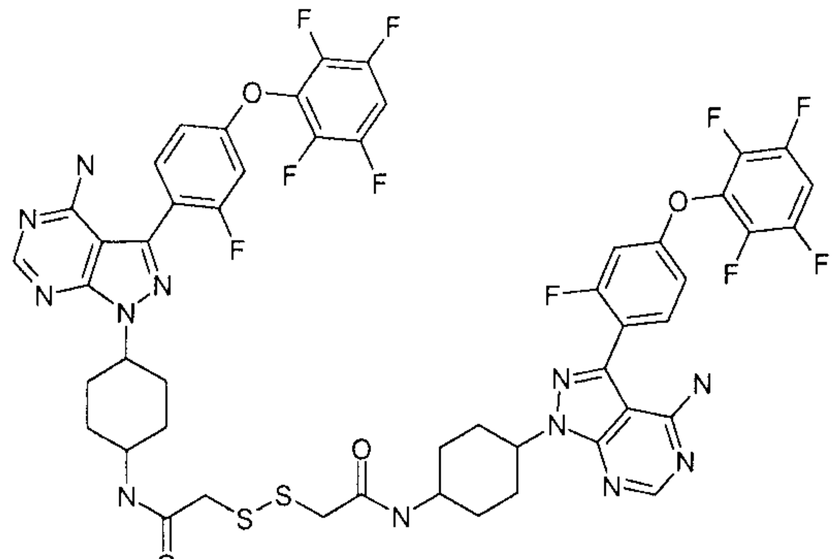
Procedure:

4-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propylamino)-4-oxo-but-2-enoic acid (450 mg, 1.28 mmol, 1.0 eq.) was dissolved in PPA (5 mL). The reaction mixture was stirred at 120 °C for 4 hours under nitregon, and then poured into ice water (10 mL) to quench the reaction. The mixture was extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient elution 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure to give the target compound (3.5 mg, yield: 6%).

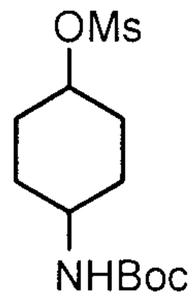
Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.902 min; m/z = 531.1 $[M+H]^+$; Total running time: 7 min.

Example 39



Step A:

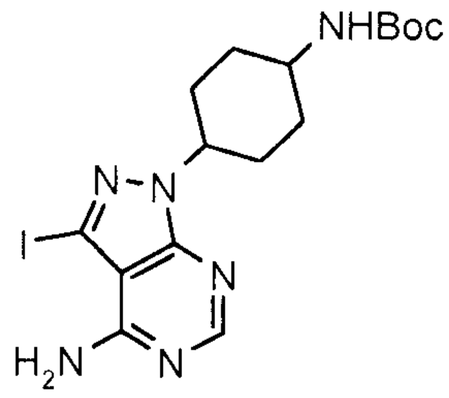


4-(tert-butoxycarbonyl)cyclohexyl methanesulfonate

Procedure:

Triethylamine (9.3 g, 92 mmol, 2.0 eq.) and methanesulfonyl chloride (10.5 g, 92 mmol, 2.0 eq.) were subsequently added to a solution of tert-butyl 4-hydroxycyclohexylcarbamate (10.0 g, 46 mmol, 1.0 eq.) in dichloromethane (100 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 14 hours, quenched with saturated $NaHCO_3$ (10 mL). The aqueous phase was extracted with dichloromethane (200 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (11 g, yield: 81%).

Step B:

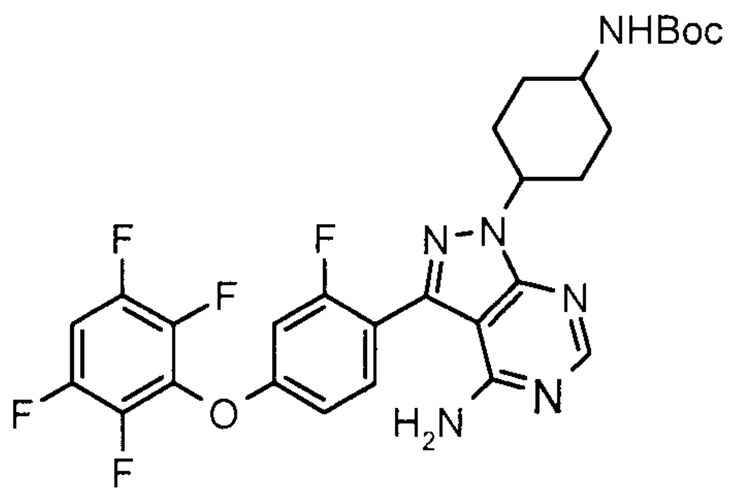


tert-butyl 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexylcarbamate

Procedure:

Cesium carbonate (4.9 g, 15.3 mmol, 2.0 eq.) and 4-(tert-butoxycarbonyl)cyclohexyl methanesulfonate (4.5 g, 15.3 mmol, 2.0 eq) were added to a solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (2.0 g, 7.66 mmol, 1.0 eq.) in DMF (10 mL). The reaction mixture was stirred at 80 °C for 12 hours, filtered through celite, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate = 4 : 1) to give the target compound (1.1 g, yield: 31%).

Step C:

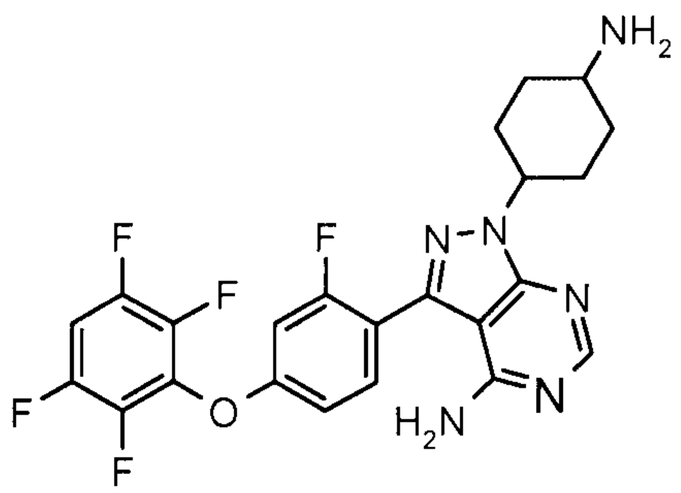


tert-butyl 4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexylcarbamate

Procedure:

Tert-butyl 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexylcarbamate (0.82 g, 1.79 mmol, 1.0 eq.), 2-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.0 g, 2.69 mmol, 1.5 eq.), potassium phosphate (0.76 g, 3.68 mmol, 2.0 eq.) and Pd-118 (58mg, 0.089 mmol, 0.05 eq.) were dissolved in 1,4-dioxane/water (9 mL, 5/1, v/v). The reaction mixture was stirred at 80 °C for 12 hours under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was poured into ice-water (10 mL) and extracted with ethyl acetate (10 mL) 4 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: ethyl acetate) to give the target compound (0.8 g, yield: 80%).

Step D:

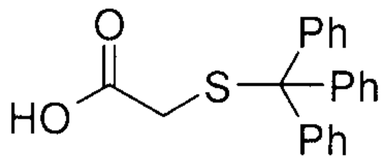


1-(4-aminocyclohexyl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EA (5 mL) was added to a solution of tert-butyl 4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexylcarbamate (800 mg, 1.35 mmol) in ethyl acetate (5 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (600 mg, yield:90%).

Step E:

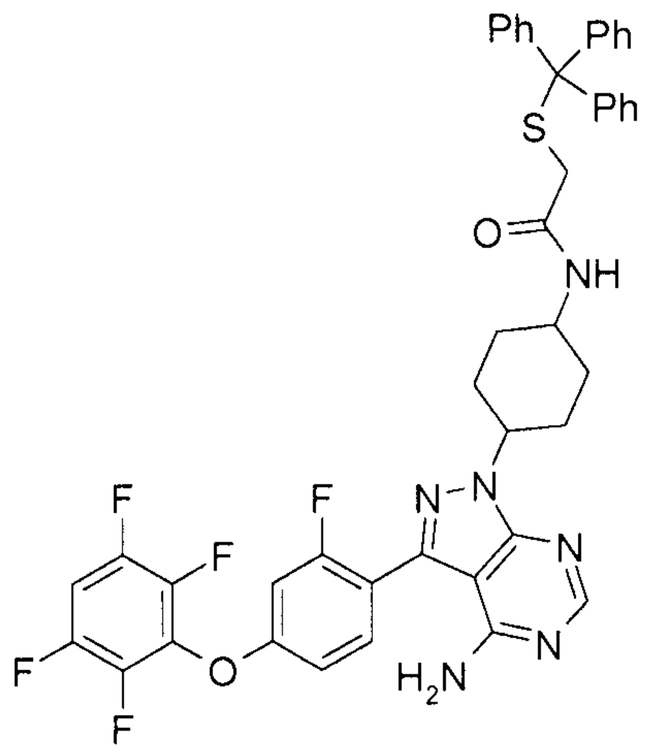


2-(tritylthio)acetic acid

Procedure:

Triphenylmethyl chloride (2.79 g, 10 mol, 1.0 eq.) and $BF_3 \cdot Et_2O$ (2 mL) was added dropwise to a solution of thioglycolic acid (0.92 g, 10 mmol, 1.0 eq.) in dichloromethane (30 mL) and acetic acid (6 mL). The reaction mixture was stirred at room temperature for 1 hour and evaporated to remove the solvent under reduced pressure. The residue was dissolved in ethyl acetate (30 mL), washed with water (20 mL) and brine (20 mL) respectively 1 time. The organic phase was dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (2.8 g, yield: 84%).

Step F:

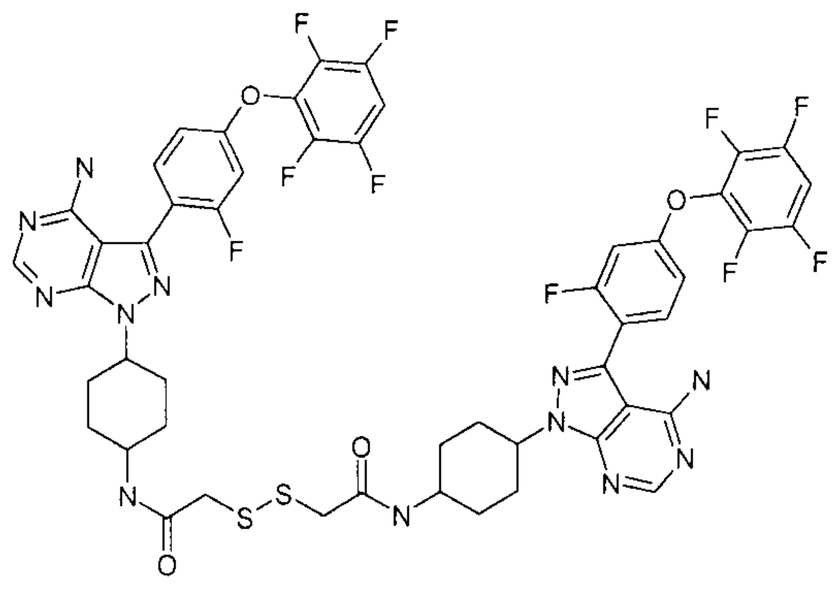


N-(4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-2-(tritylthio)acetamide

Procedure:

2-(tritylthio)acetic acid (65 mg, 0.195 mmol, 1.2 eq.), DIPEA (42 mg, 0.326 mmol, 2.0 eq.) and HATU (139 mg, 0.244 mmol, 1.5 eq.) were addedto a solution of 1-(4-aminocyclohexyl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (80 mg, 0.163 mmol, 1.0 eq.) in dichloromethane (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours, diluted with dichloromethane (30 mL), washed with water (20 mL) and brine (20 mL) respectively 1 time. The organic phase was dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (80 mg, yield: 62%).

Step G:



Procedure:

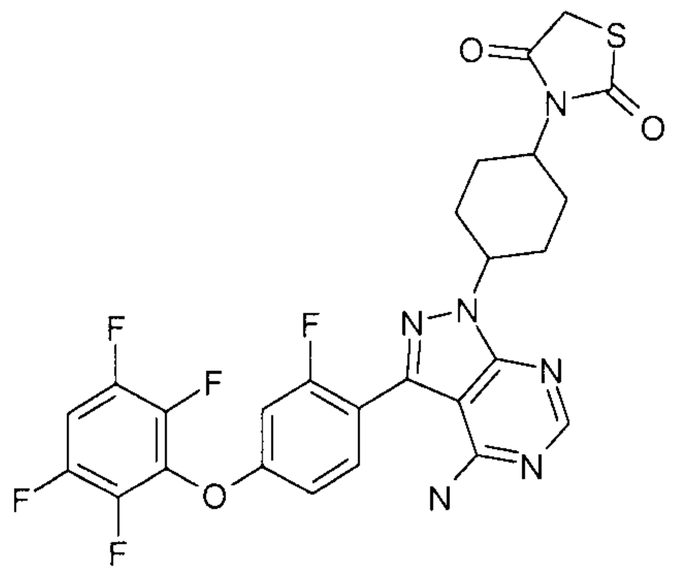
Et_3SiH (2 drops) was added to a solution of N-(4-(4-amino-3-(2-fluoro-4-(2,3,5,6-

tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-2-(tritylthio)acetamide (80 mg, 0.1 mmol) in TFA (0.5 mL). The reaction mixture was stirred at room temperature for 1 hour, quenched with water (10 mL), extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)) to give the target compound (5 mg, yield: 4%).

Spectroscopy data:

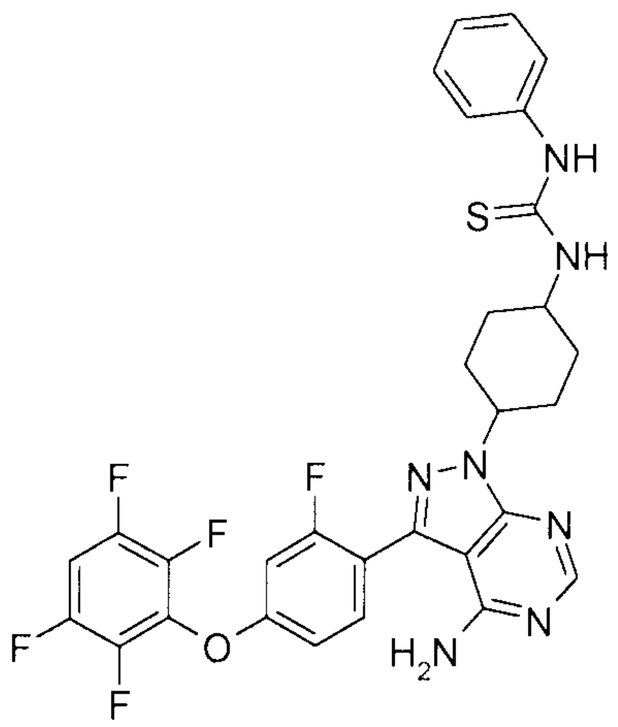
LC/MS (Method: UFLC): RT = 3.442 min; m/z = 564.5 $[M/2]^+$; Total running time: 7 min.

Example 40



3-(4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)thiazolidine-2,4-dione

Step A:

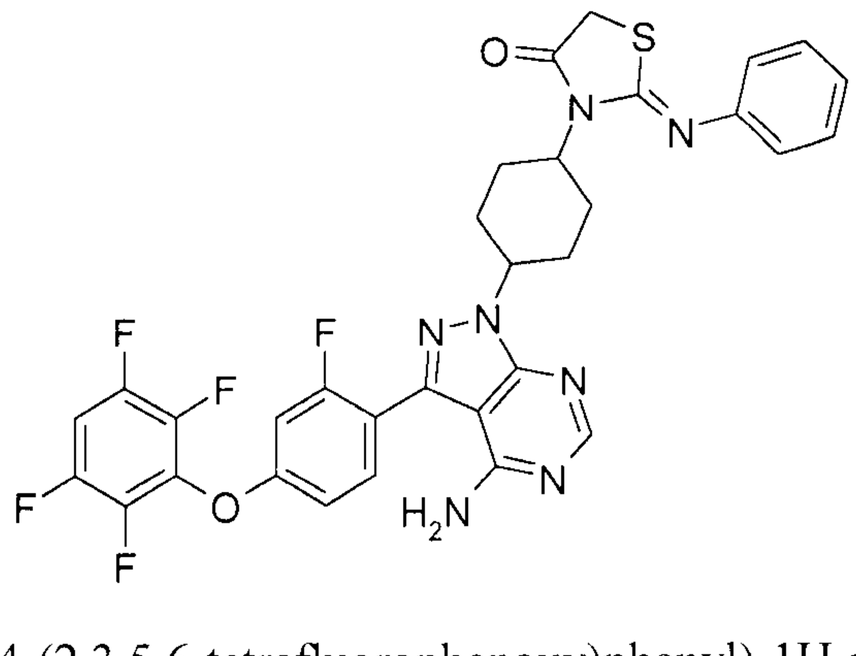


1-(4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-3-phenylthiourea

Procedure:

phenyl isothiocyanate (24.8 mg, 0.184 mmol, 0.9 eq.) was addedto a solution of 1-(4-aminocyclohexyl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.204 mmol, 1.0 eq.) in dichloromethane (3 mL). The reaction mixture was stirred at room temperature for 2 hours, concentrated and spin-dried to give the crude product, which was purified by thin layer chromatography (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (100 mg, yield: 79%).

Step B:

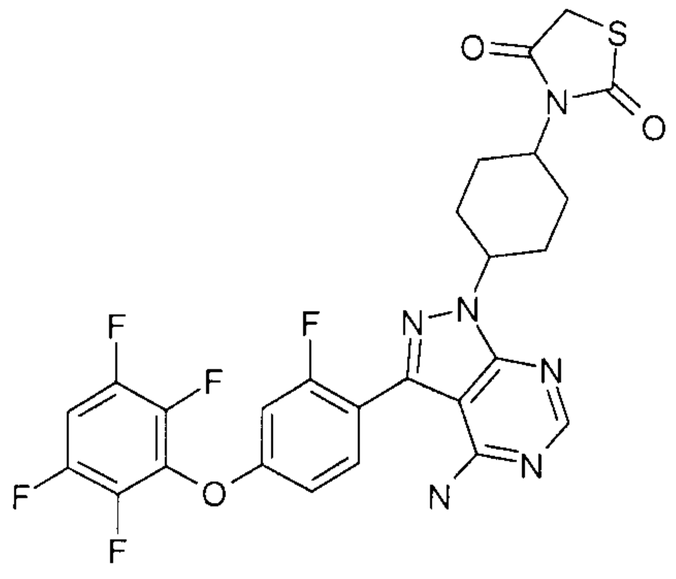


3-(4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-2-(phenylimino)thiazolidin-4-one

Procedure:

Chloroacetic acid (17.4 mg, 0.184 mmol, 2.3 eq.) and sodium acetate (3.94 mg, 0.048 mmol, 0.6 eq.) were added to a solution of 1-(4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-3-phenylthiourea (50 mg, 0.08 mmol, 1.0 eq.) in ethanol (3 mL). The reaction mixture was stirred at 110 °C 6 hours, cooled to room temperature, concentrated and spin-dried to give the crude product, which was purified by thin layer chromatography (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (20 mg, yield: 38%).

Step C:



3-(4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)thiazolidine-2,4-dione

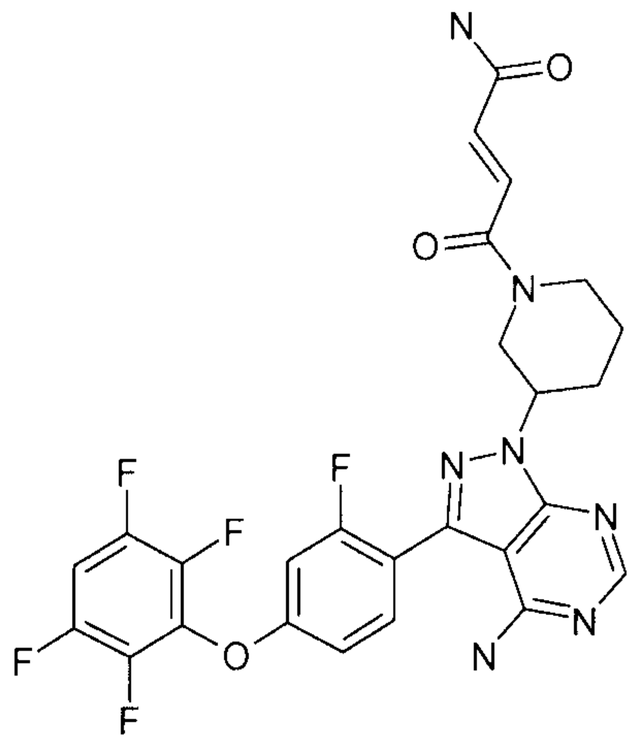
Procedure:

A solution of 3-(4-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-2-(phenylimino)thiazolidin-4-one (20 mg, 0.03 mmol) in concentrated HCl (5 mL) was stirred at 110 °C for 6 hours, cooled to room temperature, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (2 mg, yield: 12%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 3.794 min; m/z = 591.1 $[M+H]^+$; Total running time: 7 min.

Example 41



(E)-4-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4-oxo-but-2-enamide

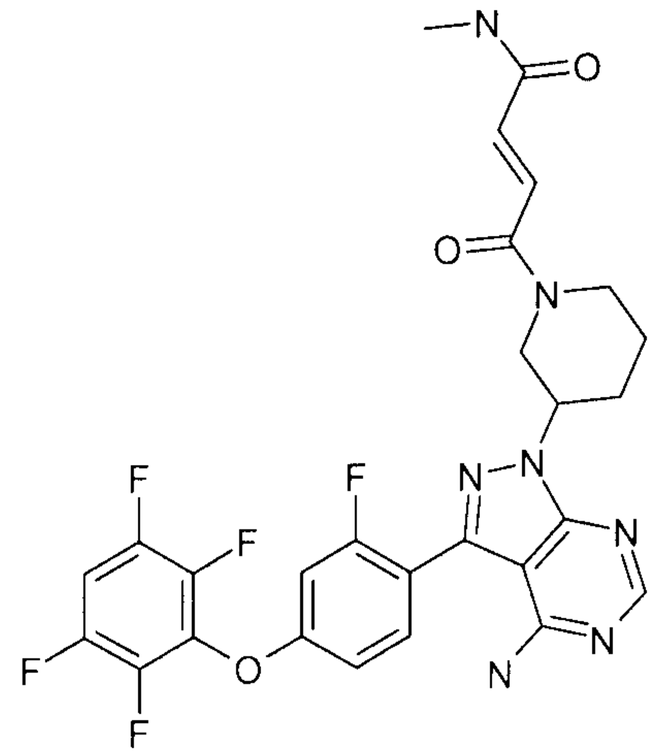
Procedure:

3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (48 mg, 0.1 mmol, 1.0 eq.), DIPEA (26 mg, 0.2 mmol, 2.0 eq.) and HATU (50 mg, 0.0.15 mmol, 1.5 eq.) were added to a solution of (E)-4-amino-4-oxo-but-2-enoic acid (15 mg, 0. 15 mmol, 1.5 eq.) in dichloromethane (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 16 hours, diluted with dichloromethane (30 mL), washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL) respectively 1 time. The organic phase was dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (5 mg, yield: 10%).

Spectroscopy data:

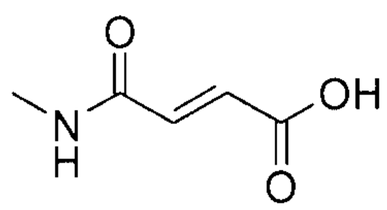
LC/MS (Method: UFLC): RT = 0.791 min; m/z = 574.0 $[M+H]^+$; Total running time: 1.5 min.

Example 42



(E)-4-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-N-methyl-4-oxo-but-2-enamide

Step A:

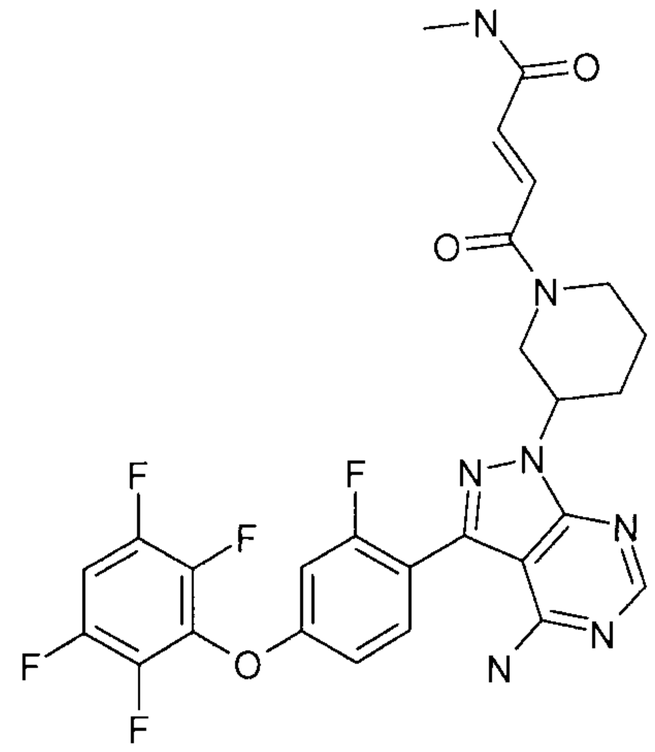


(E)-4-(methylamino)-4-oxo-but-2-enoic acid

Procedure:

A solution of maleic anhydride (500 mg, 5.1 mmol, 1.0 eq.) in methylamine (2 M tetrahydrofuran solution, 10 mL) was stirred at room temperature for 1 hour, concentrated and spin-dried to give the target compound (658 mg, yield: 100%).

Step B:



(E)-4-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-N-methyl-4-oxo-but-2-enamide

Procedure:

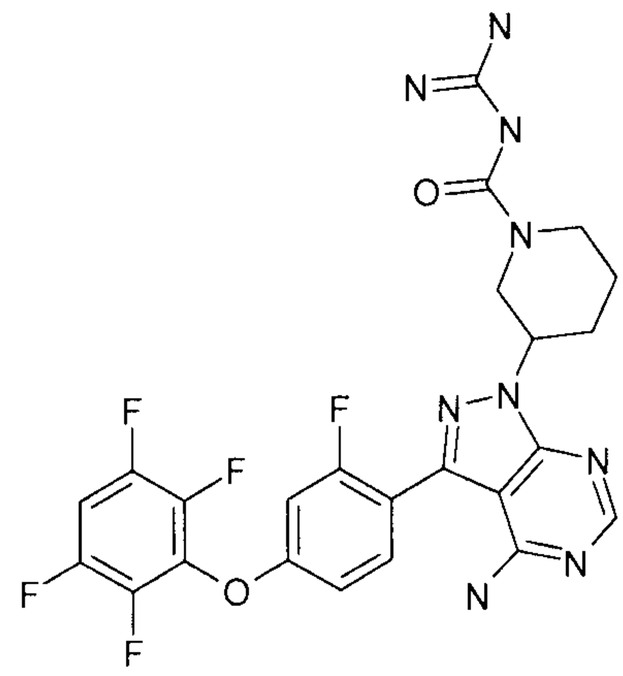
3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (150 mg, 0.315 mmol, 1.0 eq.), DIPEA (163 mg, 1.26 mmol, 4.0 eq.) and HATU (180 mg, 0.472 mmol, 1.5 eq.) were added to a solution of (E)-4-(methylamino)-4-oxo-but-2-enoic acid (40 mg, 0.315 mmol, 1.0 eq.) in dichloromethane (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 16 hours, diluted with dichloromethane (30 mL), washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL) respective 1 time. The organic phase was dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound hydrochloride (44 mg, yield: 24%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.723 min; m/z = 588.2 $[M+H]^+$; Total running time: 7 min.

^1H NMR (400MHz, DMSO-d_6) δ 8.59-8.53 (m, 1H), 8.25-8.20 (m, 1H), 7.97-7.92 (m, 1H), 7.65-7.57 (m, 1H), 7.34-7.31 (m, 1H), 7.16-7.12 (m, 1H), 6.41-6.28 (m, 1H), 6.06-5.95 (m, 1H), 5.00-4.80 (m, 1.5H), 4.61-4.58 (m, 0.5H), 4.35-4.32 (m, 0.5H), 3.90-3.87 (m, 1H), 3.69-3.66 (m, 0.5H), 3.52-3.49 (m, 0.5H), 3.15-3.09 (m, 1H), 2.66-2.64 (m, 3H), 2.53-2.47 (m, 2H), 2.16-2.12 (m, 1H), 1.75-1.71 (m, 1H).

Example 43



N-[3-[4-amino-3-[2-fluoro-4-(2,3,5,6-trifluorophenoxy)phenyl]-1H-pyrazolo[3,4-d] pyrimidin-1-yl]piperidine-1-carbonyl] formamidine

Procedure:

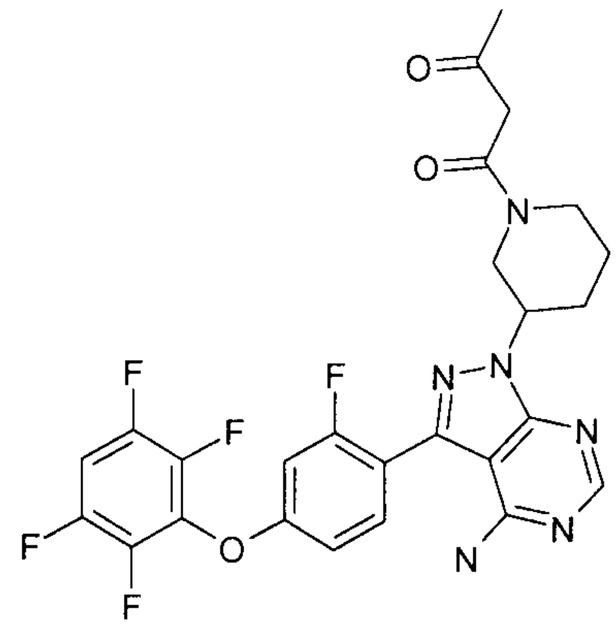
CDI (25 mg, 0.15 mmol, 1.5 eq.) was added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (48 mg, 0.1 mmol, 1.0 eq.) in DMF (5 mL). The reaction mixture was stirred at 70 °C for 2 hours, and then guanidine carbonate (11 mg, 0.06 mmol, 0.6 eq.) was added. The reaction mixture was stirred at 70 ° C for 3 hours. After cooling to room temperature, the raction mixture was concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (13 mg, yield: 23%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 0.749 min; m/z = 562.0 $[M+H]^+$; Total running time: 1.5 min.

^1H NMR (400MHz, CD_3OD) δ 8.44 (s, 1H), 7.72 (t, J = 8.4 Hz, 1H), 7.53-7.48 (m, 1H), 7.13-7.07 (m, 2H), 5.10-5.06 (m, 1H), 4.30-4.27 (m, 1H), 3.98-3.86 (m, 2H), 3.47-3.42 (m, 1H), 2.37-2.31 (m, 2H), 2.12-2.07 (m, 1H), 1.81-1.78 (m, 1H).

Example 44



1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)butane-1,3-dione

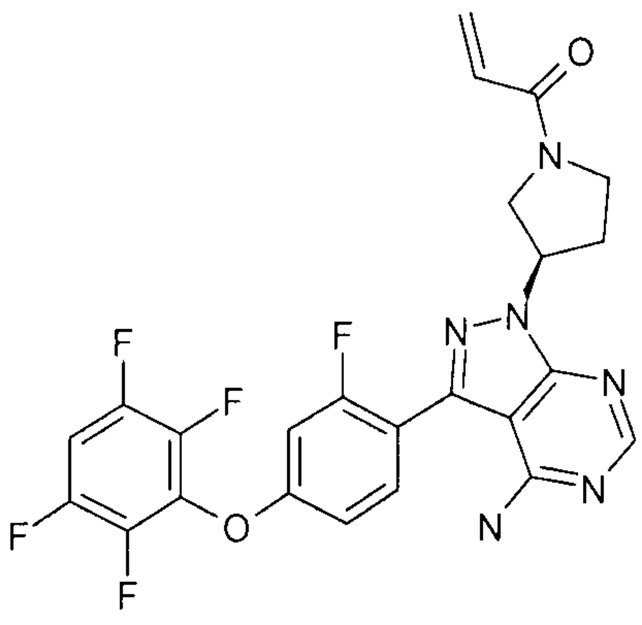
Procedure:

Tert-butyl acetoacetate (24 mg, 0.15 mmol, 1.5 eq.) and triethylamine (30 mg, 0.3 mmol, 3.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (48 mg, 0.1 mmol, 1.0 eq.) in toluene (3 mL). The reaction mixture was stirred at 90 °C for 16 hours. After cooling to room temperature, the mixture was concentrated spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (15 mg, yield: 27%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.778 min; m/z = 561.0 $[M+H]^+$; Total running time: 7 min.

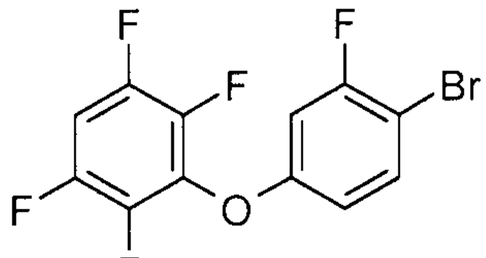
Example 45



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Method 1:

Step A:

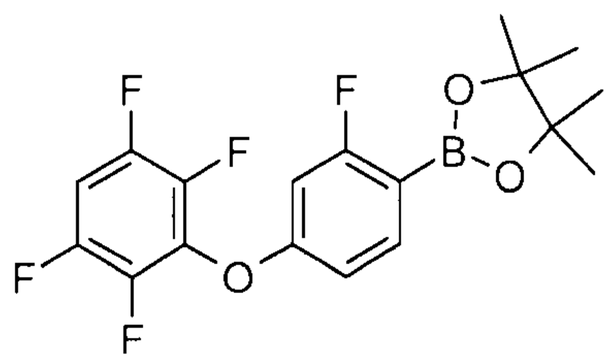


3-(3-fluoro-4-bromophenoxy)-1,2,4,5-tetrafluorobenzene

Procedure:

Potassium carbonate (34.0 g, 246 mmol, 2.0 eq.) and 1,2,3,4,5-pentafluorophenyl (24.8 g, 147 mmol, 1.2 eq.) were added to a solution of 4-bromo-3-fluorophenol (23.5 g, 123 mmol, 1.0 eq.) in DMF (250 mL). The reaction mixture was stirred at 100 °C overnight, evaporated to remove the solvent under reduced pressure. The residue was dissolved in ethyl acetate and water and separated. The aqueous phase was extracted with ethyl acetate (200 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (39 g, yield: 93%).

Step B:



2-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

Procedure:

3-(3-fluoro-4-bromophenoxy)-1,2,4,5-tetrafluorobenzene (36.5 g, 107.6 mmol, 1.0 eq.), bis(pinacolato)diboron (32.8 g, 129.2 mmol, 1.2 eq.), potassium acetate (37 g, 377 mmol, 3.5 eq.) and (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium (4.7 g, 6.45 mmol, 0.06 eq.) were dissolved in 1,4-dioxane (500 mL), and then stirred at 80 °C under nitrogen for 4 hours. The reaction mixture was filtered through celite. The filtrate was spin-dried to give the crude product,

which was purified by silica gel column chromatography (eluent: petroleum ether) to give the target compound (30 g, yield: 72%).

Step C:

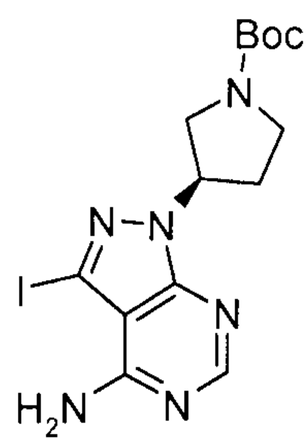


3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

NIS (250 g, 1.11 mol, 1.5 eq.) was added to a solution of 1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 g, 0.74 mol, 1.0 eq.) in DMF (800 mL) . The reaction mixture was stirred at 80 85°C for 16 hours under nitrogen atmosphere. The reaction mixture was filtered, and the filter cake was washed with ethanol (1000 mL) 3 times to give the target compound (184 g, yield: 95%).

Step D:



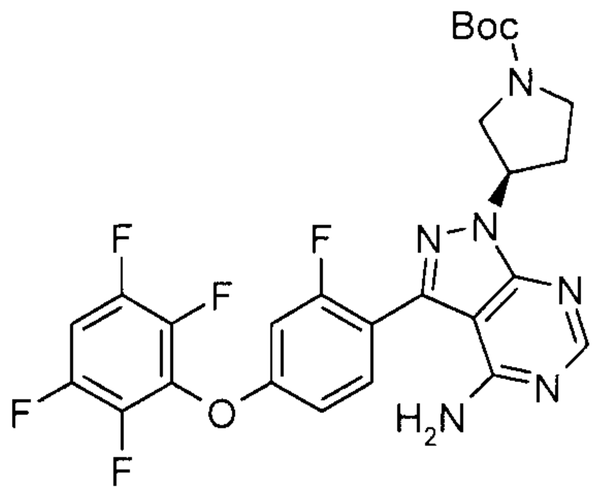
(R)-tert-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate

Procedure:

DIAD (27.6 g, 137.5 mmol, 1.5 eq.) was dropwise added to a solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (24 g, 92 mmol, 1.0 eq.), tert-butyl (3S)-3-hydroxycyclopentylcarbamate (26 g, 137.5 mmol, 1.5 eq) and PPh_3 (36 g, 137.5 mmol, 1.5 eq.) in tetrahydrofuran (720 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 1 hour at 0 °C, then stirred overnight at room temperature, evaporated to remove the solvent under reduced pressure, acetonitrile (200 mL) was added to the reaction flask, and then stirred at room temperature for 2 hours. The resulting mixture

was filtered, and the filter cake was washed with acetonitrile (20 mL) and dried to give the target compound (25 g, yield: 63%) .

Step E:

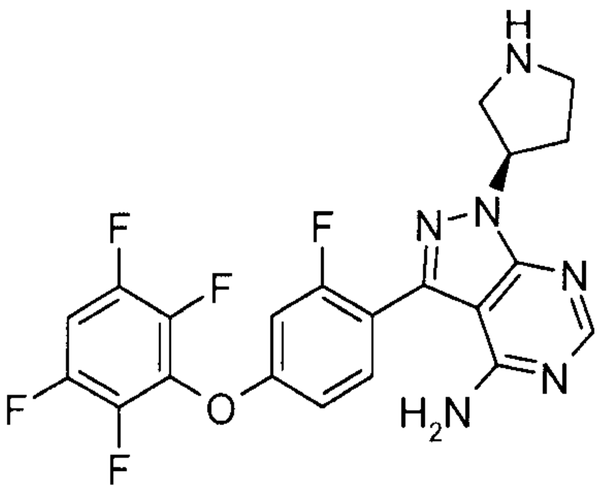


(3R)-tert-butyl 3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate

Procedure:

(R)-tert-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate (25 g, 58 mmol , 1.0 eq.), 2-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30 g, 75.4 mmol, 1.3 eq.), potassium phosphate (25 g, 116 mmol, 2.0 eq.) and Pd-118 (750 mg, 1.16 mmol, 0.02 eq.) were dissolved in 1,4-dioxane/water (600 mL, 5/1, v/v). The reaction mixture was stirred at 60°C overnight under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was filtered through celite. The filtrate was concentrated and spin-dried, water (300 mL) was added to the residue, and then extracted with ethyl acetate (300 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (60 g, crude).

Step F:

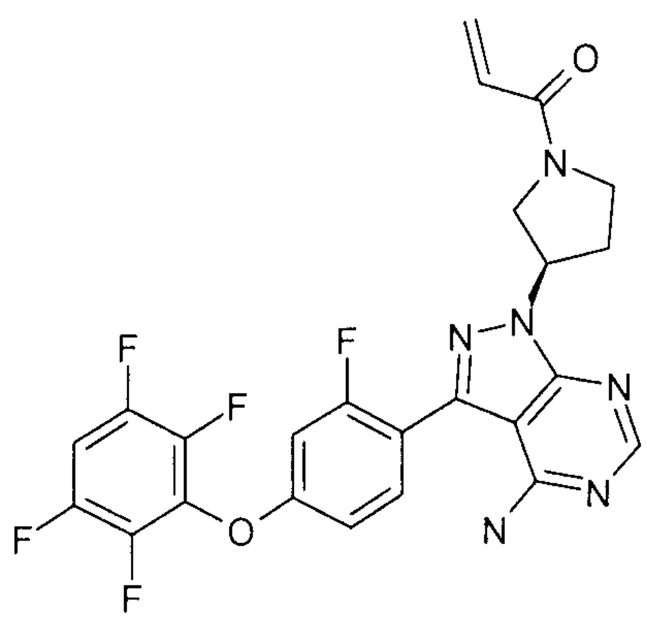


3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EA (100 mL) was added to a solution of (3R)-tert-butyl 3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate (60 g, crude) in ethyl acetate (100 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound. Water (500 mL) was added to the obtained product, and extracted with ethyl acetate (300 mL) 3 times. The aqueous phase was adjusted to pH=9 and extracted with ethyl acetate (300 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (24 g, 2-step yield: 90%).

Step G:



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Procedure:

NaOH (10%, 94 mL) was added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (23.5 g, 50.75 mmol, 1.0 eq.) in tetrahydrofuran (470 mL) at -5 °C, followed by dropwise addition of acryloyl chloride (5.97 g, 66 mmol, 1.3 eq.). The reaction mixture was stirred at -5 °C for 1 hour, quenched with saturated brine (100 mL), and extracted with ethyl acetate (200 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel

column chromatography (eluent: petroleum ether: ethyl acetate=1:3 to 1:1) to give the crude product, which was dissolved in methanol (500 mL) and filtered. Water (1500 mL) was added to the stirring filtrate, followed by stirring for 2 hours and filtered. The filter cake was dried under reduced pressure to give the target compound (16.5 g, yield: 63%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 3.764 min; m/z = 517.0 $[M+H]^+$; Total running time: 7 min.

^1H NMR (400MHz, CD_3OD) δ 8.45 (s, 1H), 7.70 (t, J = 8.4 Hz, 1H), 7.55-7.46 (m, 1H), 7.12-7.05 (m, 2H), 6.70-6.55 (m, 1H), 6.33-6.26 (m, 1H), 5.81-5.75 (m, 1H), 4.23-3.83 (m, 5H), 2.68-2.55 (m, 2H).

Method 2:

Procedure:

NaOH (216 mg, 5.40 mmol, 2.5 eq.) was added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (1.0 g, 2.16 mmol, 1.0 eq.) in tetrahydrofuran (50 mL) and water (10 mL) at 0 °C, followed by dropwise addition of a solution of chloropropionyl chloride (288 mg, 2.27 mmol, 1.05 eq.) in tetrahydrofuran (10 mL). The reaction mixture was stirred at 0 °C for 1 hour, and then stirred at 60 °C for 12 hours. After cooling to room temperature, saturated brine (100 mL) was added to the reaction mixture, and extracted with ethyl acetate (50 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:3 to 1:1) to give the target compound of Example 45 (0.8 g, yield: 71%).

Method 3:

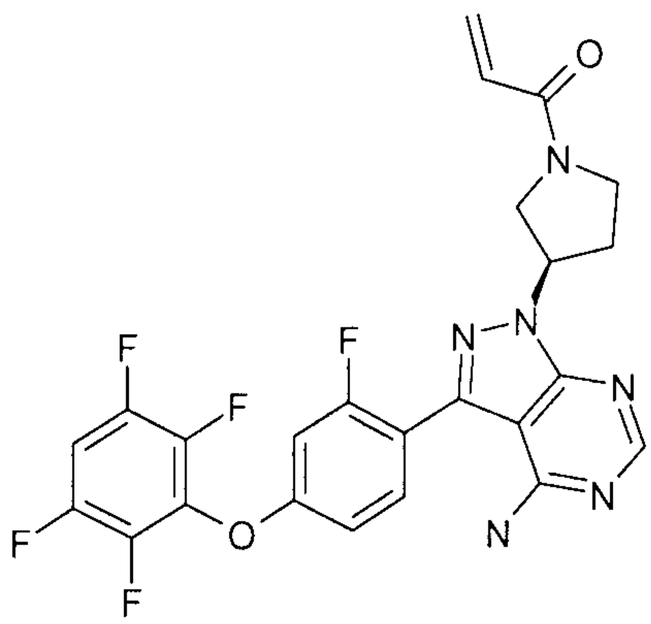
Procedure:

(R)-1-(3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one (100 g, 0.26 mmol, 1.0 eq.), 2-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (120 mg, 0.31 mmol, 1.2 eq.), sodium carbonate (55 mg, 0.52 mmol, 2.0 eq.) and $Pd(PPh_3)_4$ (30 mg, 0.026 mmol, 0.01 eq) were dissolved in 1,4-dioxane/water (5 mL, 1/1, v/v). The reaction mixture was stirred at 80 °C for 30 min. under microwave irradiation. After cooling to room temperature, the reaction mixture was filtered

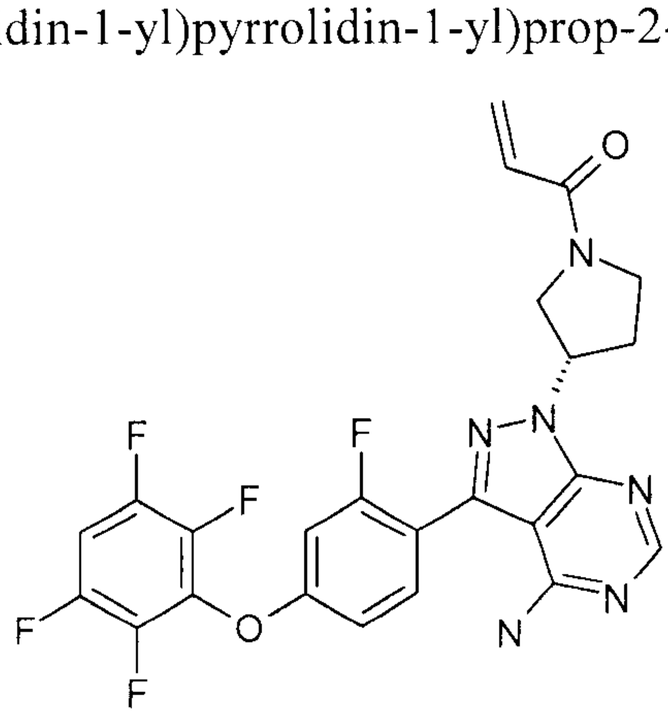
through celite. The filtrate was concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (38 mg, yield: 28%).

Method 4:

Example 45 and Example 46

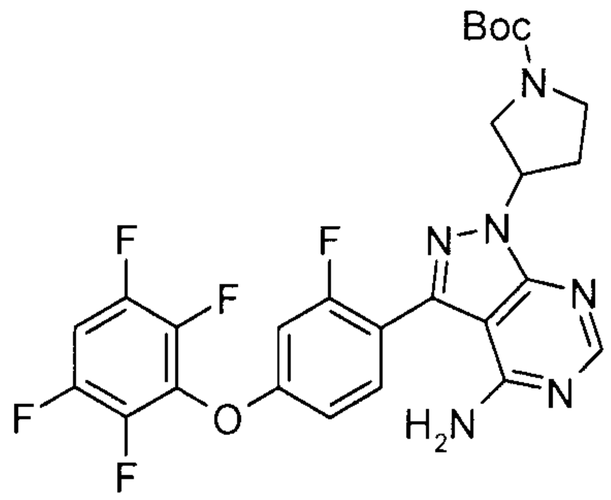


1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one



1-((S)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Step A:

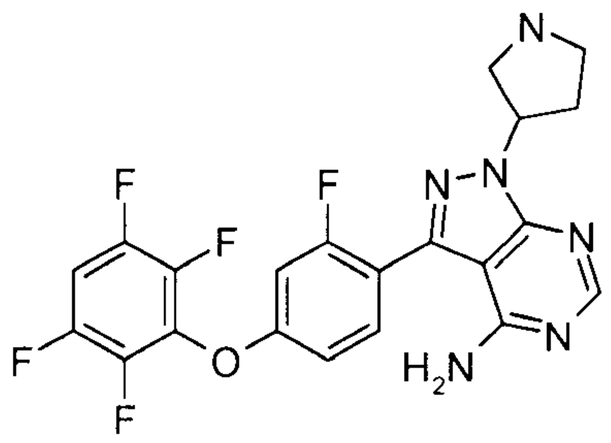


tert-butyl 3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate

Procedure:

tert-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate (8 g, 18 mmol, 1.0 eq.), 2-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10.7 g, 27 mmol, 1.5 eq.), potassium phosphate (7.6 g, 36 mmol, 2.0 eq.) and Pd-118 (1.2 g, 1.8 mmol, 0.1 eq.) was dissolved in 1,4-dioxane/water (180 mL, 5/1, v/v). The reaction mixture was stirred at 60 °C for 14 hours under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was poured into ice water (50 mL) and extracted with ethyl acetate (100 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: ethyl acetate: petroleum ether = 1:1) to give the target compound (2.5 g, yield : 25%).

Step B:



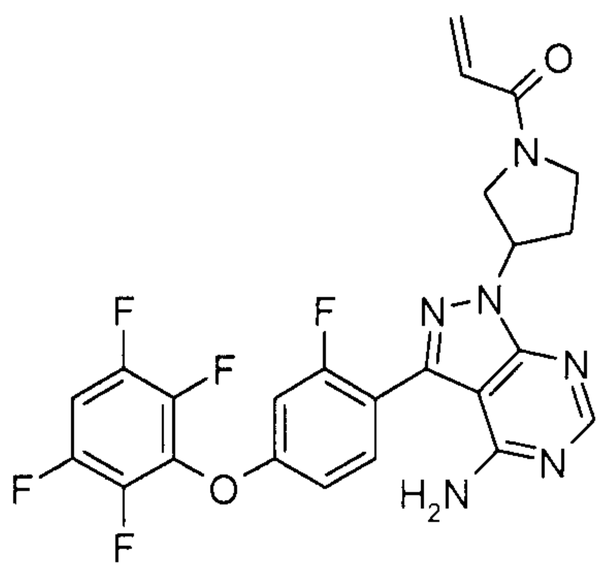
3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EA (20 mL) was added to a solution of tert-butyl 3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate (2.5 g,

4.4 mmol) in dichloromethane (20 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (2.2 g, yield:100%).

Step C:



1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

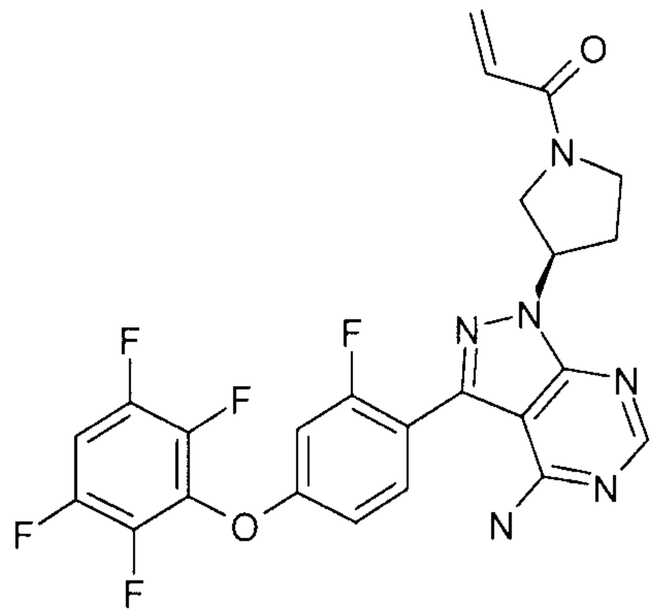
Procedure:

Triethylamine (1.4 g, 12.8 mmol, 3.0 eq.) and acryloyl chloride (0.38 g, 4.2 mmol, 0.95 eq.) were subsequently added dropwiseto a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (2.2 g, 4.4 mmol, 1.0 eq.) in dichloromethane (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for for 1 hour, and then quenched with water (30 mL) and separated. The aqueous phase was extracted with dichloromethane (30 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: ethyl acetate) to give the target compound (1.0 g, yield: 45%).

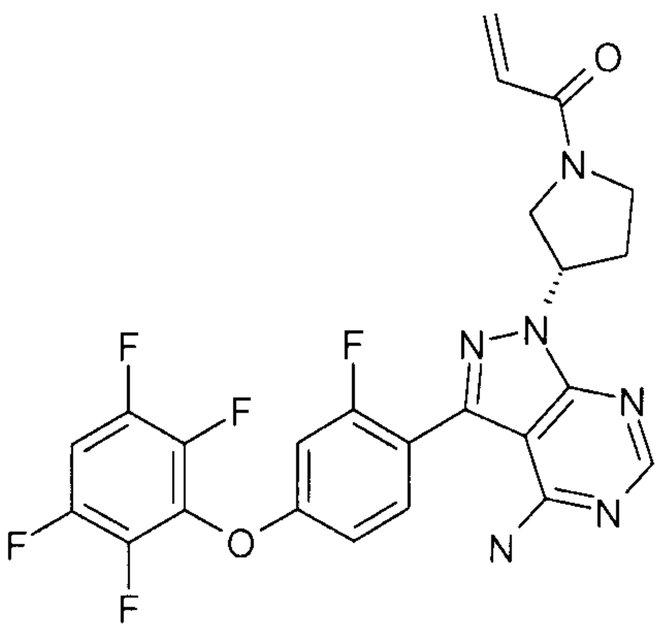
Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.810 min; m/z = 517.1 $[M+H]^+$; Total running time: 7 min.

Step D:



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one



1-((S)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

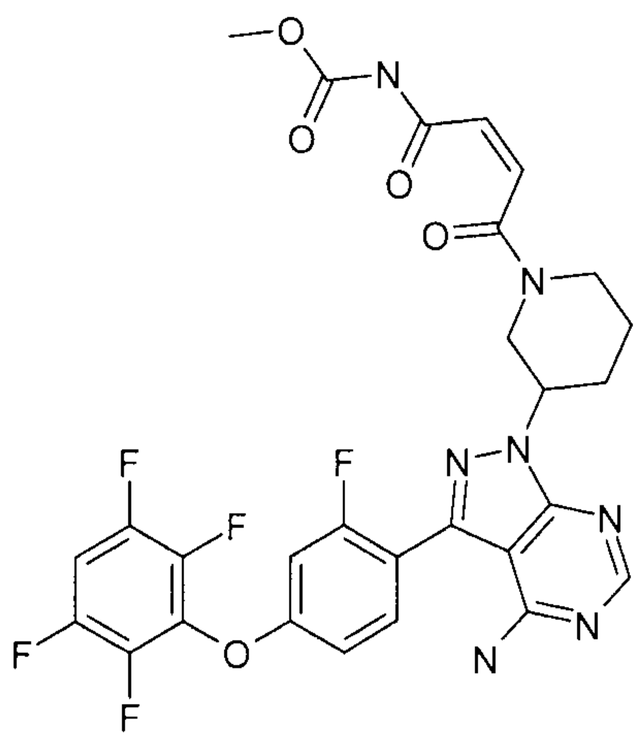
Procedure:

1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one was chirally separated by SFC to give the compound of Example 45(270 mg) and the compound of Example 46 (320 mg).

Example 46:

LC/MS (Method: UFLC): RT = 2.808 min; m/z = 517.1 $[M+H]^+$; Total running time: 7 min.

Example 47



methyl 4-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4-oxo-but-2-enoylcarbamate

Procedure:

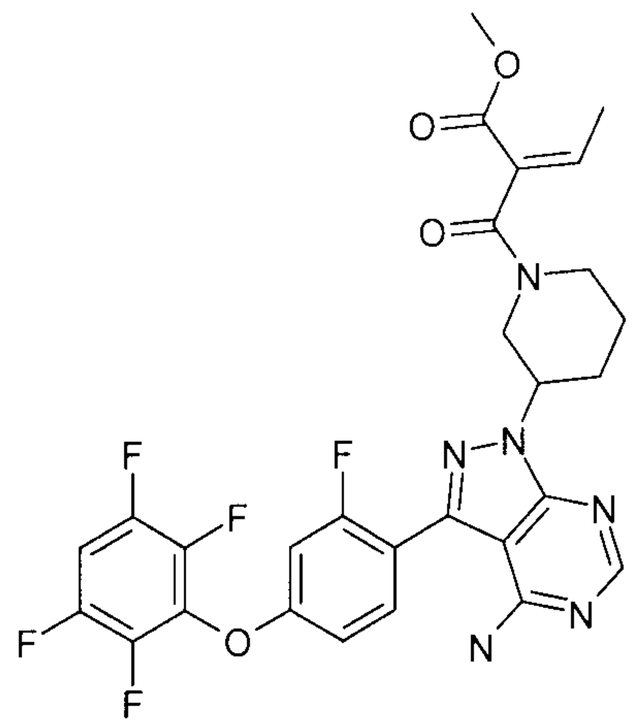
Methyl 2,5-dioxo-2H-pyrrole-1(5H)-carboxylate (17 mg, 0.11 mmol, 1.1 eq.) and sodium bicarbonate (17 mg, 0.2 mmol, 2.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (48 mg, 0.1 mmol, 1.0 eq.) in 1,4-dioxane/water (3 mL/1 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 2 hours, diluted with water (5 mL), and extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the drude product, which was purified by thin layer chromatography (eluent: petroleum ether: ethyl acetate=1:3) to give the target compound (40 mg, yield: 67%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 0.775 min; m/z = 632.1 $[M+H]^+$; Total running time: 1.5 min.

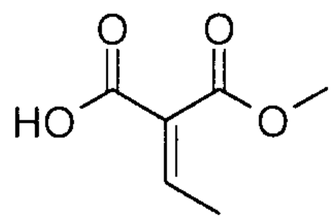
^{1}H NMR (400MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.58-7.54 (m, 1H), 7.15-7.06 (m, 1H), 6.96-6.90 (m, 2H), 6.77-6.73 (m, 1H), 6.65-6.55 (m, 1H), 4.63-4.59 (m, 1H), 4.99-4.94 (m, 1H), 4.85-4.80 (m, 0.5H), 4.57-4.54 (m, 0.5H), 4.04-4.00 (m, 0.5H), 3.88-3.77 (m, 4H), 3.50-3.44 (m, 0.5H), 3.26-3.22 (m, 0.5H), 2.98-2.95 (m, 0.5H), 2.34-2.26 (m, 1H), 2.03-1.96 (m, 2H), 1.85-1.81 (m, 1H).

Example 48



methyl 2-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)but-2-enoate

Step A:

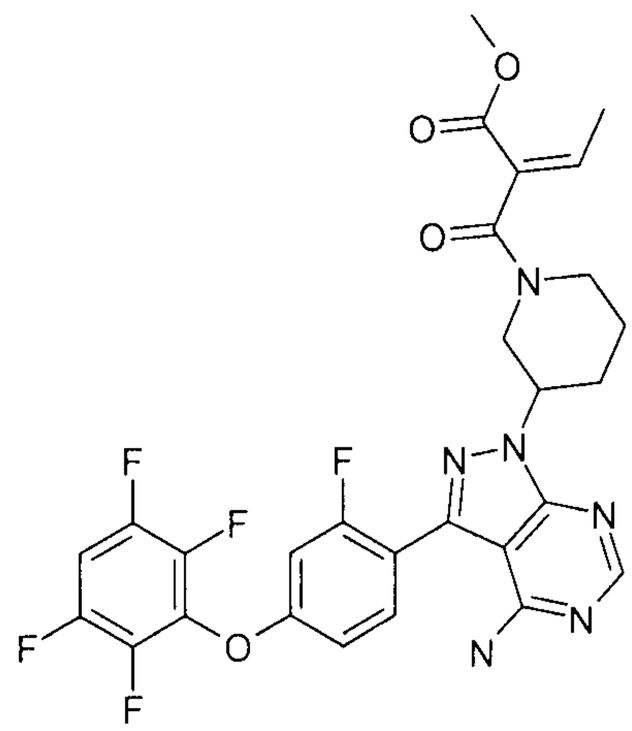


(Z)-2-(methoxycarbonyl)but-2-enoic acid

Procedure:

Lithium hydroxide monohydrate (0.265 g, 6.32 mmol, 1.0 eq.) was added to a solution of dimethyl 2-ethylidenemalonate (1.0 g, 6.32 mmol, 1.0 eq.) in tetrahydrofuran/water (20 mL, 1/1, v/v). The reaction mixture was stirred at room temperature for 14 hours, concentrated and spin-dried. The residue was dissolved in water (10 mL), adjusted with 2 N HCl to pH=1, and then extracted with ethyl acetate (20 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (0.6 g, yield: 63%).

Step B:



methyl 2-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)but-2-enoate

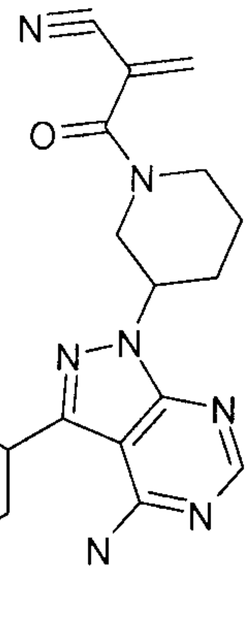
Procedure:

3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (48 mg, 0.1 mmol, 1.0 eq.), DIPEA (52 mg, 0.4 mmol, 4.0 eq.) and HATU (57 mg, 0.15 mmol, 1.5 eq.) were added to a solution of (Z)-2-(methoxycarbonyl)but-2-enoic acid (22 mg, 0.15 mmol, 1.5 eq.) in dichloromethane (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 16 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (2.4 mg, yield: 4%).

Spectroscopy data:

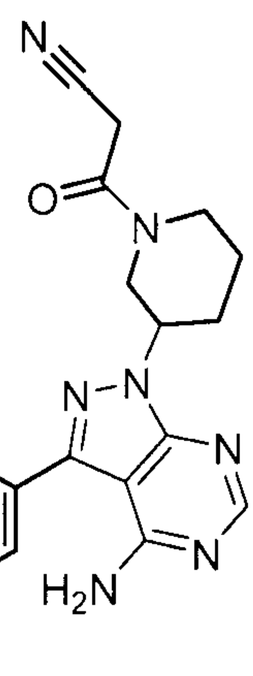
LC/MS (Method: UFLC): RT = 3.540 min; m/z = 603.2 $[M+H]^+$; Total running time: 7 min.

Example 49



2-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)acrylonitrile

Step A:

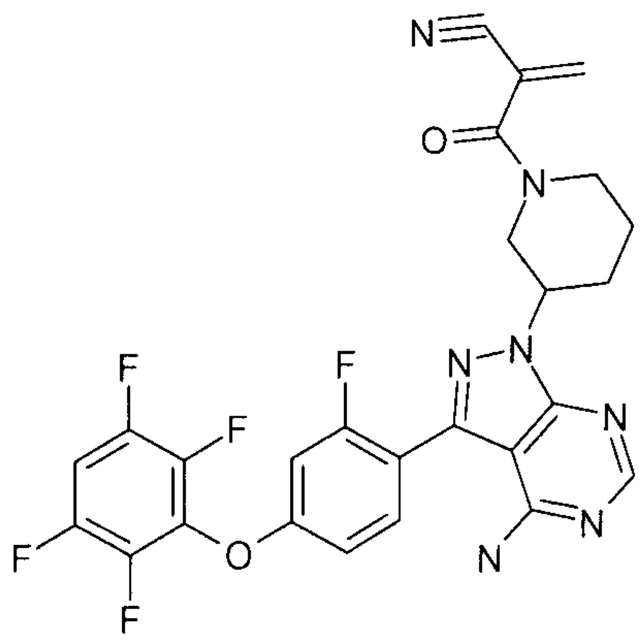


3-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-3-oxopropanenitrile

Procedure:

2-cyanoacetic acid (27 mg, 0.31 mmol, 1.5 eq.), DIPEA (108 mg, 0.84 mmol, 4.0 eq.) and HATU (120 mg, 0.31 mmol, 1.5 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.21 mmol, 1.0 eq.), in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 16 hours, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: ethyl acetate) to give the target compound (100 mg, yield: 88%).

Step B:

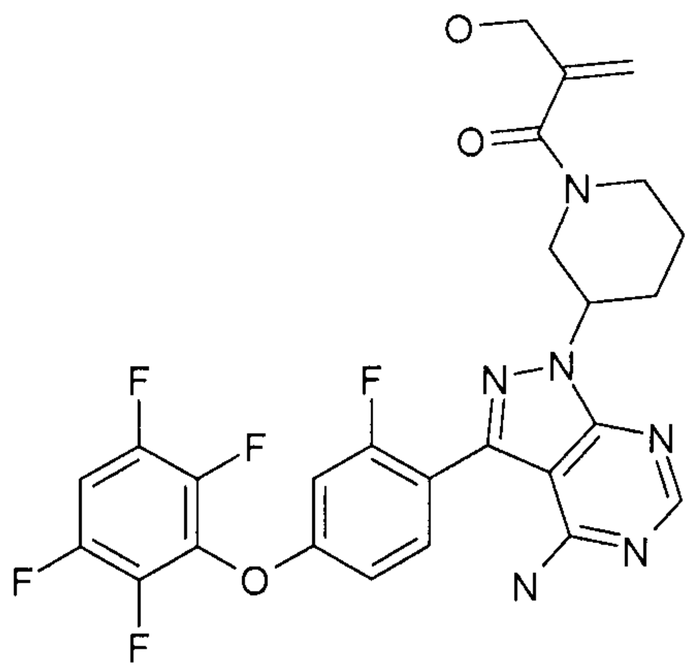


2-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)acrylonitrile

Procedure:

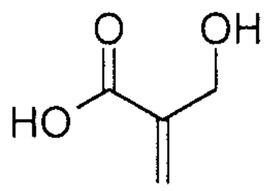
A mixture of paraformaldehyde (6 mg, 0.2 mmol, 2.0 eq.) and piperidine (0.2 mg, 0.002 mmol, 0.02 eq.) in methanol (10 mL) was refluxed for 1.5 hours, cooled to room temperature, and added with 3-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-3-oxopropanenitrile (54 mg, 0.1 mmol, 1.0 eq.), and then refluxed for 16 hours. After the removal of solvent under reduced pressure, toluene (10 mL) and p-toluenesulfonic acid monohydrate (0.2 mg, 0.001 mmol, 0.01 eq.) were added to the residue. The resulting mixture was refluxed for 3 hours. After cooling to room temperature, the mixture was concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (0.7 mg, yield: 1%).

Example 50



1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-(hydroxymethyl)prop-2-en-1-one

Step A:

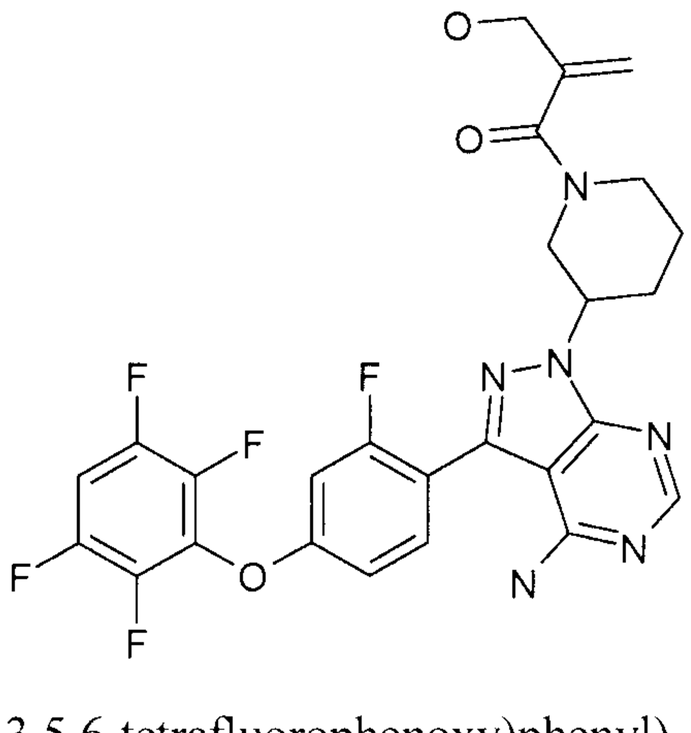


2-(hydroxymethyl)acrylic acid

Procedure:

Lithium hydroxide monohydrate (145 mg, 3.46 mmol, 5.0 eq.)was added to a solution of ethyl 2-(hydroxymethyl)acrylate (90 mg, 0.69 mmol, 1.0 eq.) in tetrahydrofuran/methanol/water (3 mL, 1/1/1, v/v/v). The reaction mixture was stirred at room temperature for 14 hours, and concentrated and spin-dried. The residue was dissolved in water (10 mL), adjusted with 2 N HCl to pH=5, and then extracted with ethyl acetate (20 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (70 mg, yield: 100%).

Step B:



1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-(hydroxymethyl)prop-2-en-1-one

Procedure:

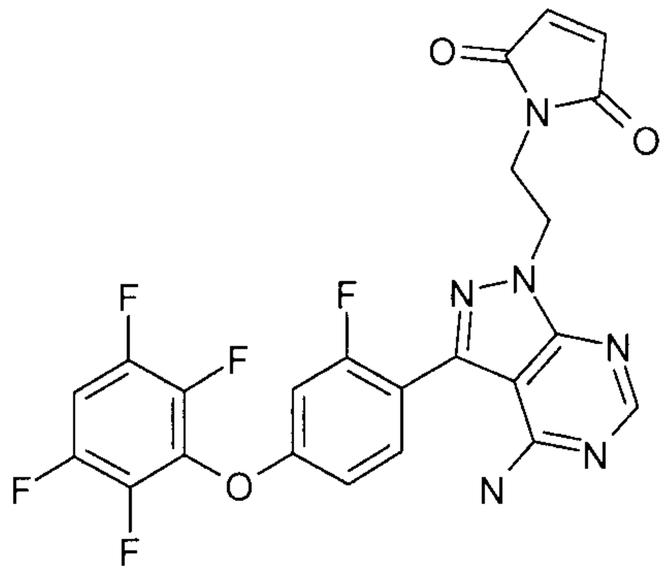
3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (257 mg, 0.54 mmol, 1.0 eq.), DIPEA (253 mg, 1.96 mmol, 4.0 eq.) and HATU (279 mg, 0.75 mmol, 1.5 eq.) were added to a solution of 2-(hydroxymethyl)acrylic acid (50 mg, 0.49 mmol, 1.0 eq.) in dichloromethane (3 mL) at 0 °C. The reaction mixturewas stirred at room temperature for 16 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (52 mg, yield: 20%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.799 min; m/z = 561.2 $[M+H]^+$; Total running time: 7 min.

^{1}H NMR (400MHz, DMSO-d_6) δ 9.51 (br, 1H), 8.62 (br, 2H), 7.98-7.95 (m, 1H), 7.62 (t, J = 8.4 Hz, 1H), 7.33-7.30 (m, 1H), 7.17-7.15 (m, 1H), 5.33-5.27 (m, 1H), 5.11-5.05 (m, 1H), 4.87-4.82 (m, 1H), 4.46-3.94 (m, 2H), 3.60-3.07 (m, 2H), 2.22-2.16 (m, 2H), 1.90-1.87 (m, 1H), 1.65-1.60 (m, 1H).

Example 51



1-(2-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-1H-pyrrole-2,5-dione

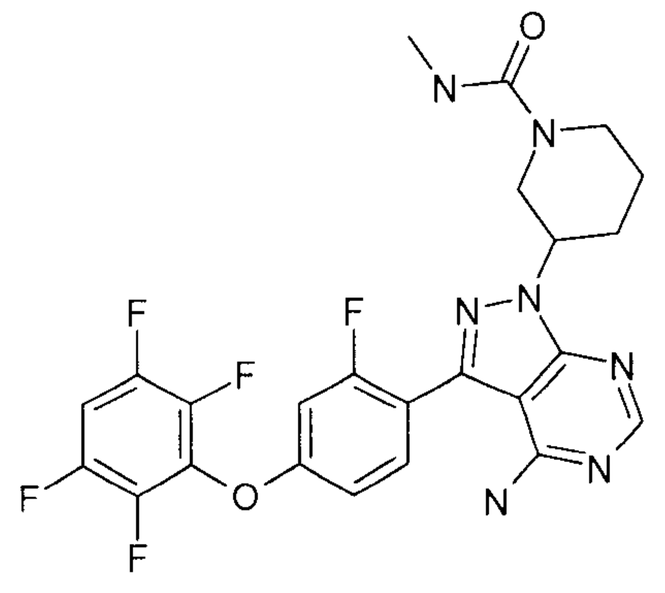
Procedure:

The compound was prepared by the above-mentioned method.

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.774 min; m/z = 517.1 $[M+H]^+$; Total running time: 7 min.

Example 52



3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-N-methylpiperidine-1-carboxamide

Procedure:

N, N'-carbonyldiimidazole (109 mg, 0.63 mmol, 2.0 eq.) was added to methylamine (0.16 mL, 0.31 mmol, 1.0 eq, 2.0 M solution in tetrahydrofuran) in tetrahydrofuran (2 mL). The reaction mixture was stirred at room temperature for 1 hour, followed by the addition of

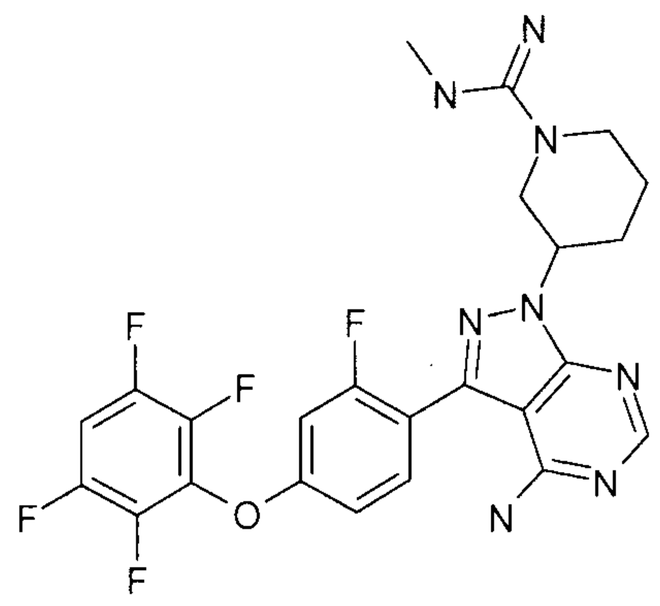
3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (150 mg, 0.31 mmol, 1.0 eq.). The reaction mixture was stirred for 16 hours at room temperature, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/7‰ NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (92 mg, yield: 55%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.724 min; m/z = 534.0 $[M+H]^+$; Total running time: 7 min.

^1H NMR (400MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.55 (t, J = 8.4 Hz, 1H), 7.27 (dd, J = 2.4, 8.8 Hz, 1H), 7.11 (dd, J = 2.4, 8.8 Hz, 1H), 6.50 (d, J = 4.4 Hz, 1H), 4.64-4.58 (m, 1H), 4.14-4.10 (m, 1H), 3.95-3.92 (m, 1H), 3.17-3.11 (m, 1H), 2.75-2.65 (m, 1H), 2.55-2.54 (m, 3H), 2.08-2.05 (m, 2H), 1.79-1.76 (m, 1H), 1.55-1.50 (m, 1H).

Example 53



3-[4-amino-3-[2-fluoro-4-(2,3,5,6-fluorophenoxy)phenyl]-1H-pyrazolo[3,4-d] pyrimidine-1-yl]piperidine-1-formamidine

Procedure:

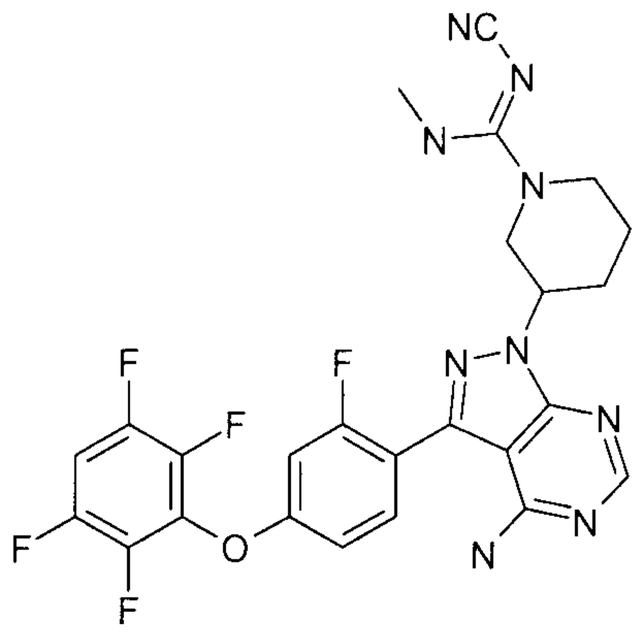
A mixture of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.1 mmol, 1.0 eq.), N-methyl-1-pyrazole formamidine (25 mg, 0.2 mmol, 2.0 eq.) and DIPEA (77 mg, 0.6 mmol , 6.0 eq.) in DMF (2 mL) was stirred at 150 °C for 20 min. under microwave irradiation. After cooling to room temperature, diluted with water (5 mL), extracted with ethyl acetate (5 mL) 3 times. The

combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (by volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (6 mg, yield: 13%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 0.781 min; m/z = 533.1 $[M+H]^+$; Total running time: 1.5 min.

Example 54



3-[4-amino-3-[2-fluoro-4-(2,3,5,6-fluorophenoxy)phenyl]-1H-pyrazolo[3,4-d] pyrimidine-1-yl]-N'-cyano-N-methyl-piperidine-1-formamidine

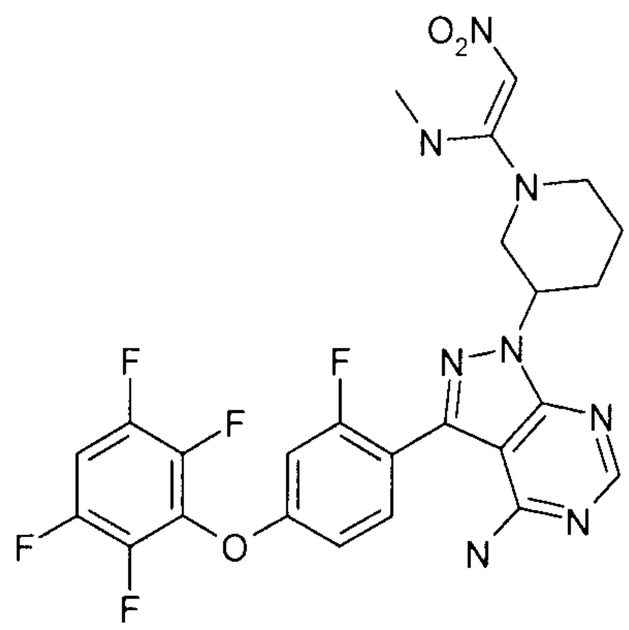
Procedure:

DIPEA (40 mg, 0.315 mmol, 3.0 eq.) and diphenyl N-cyanocarbonimidate (25 mg, 0.1 mmol, 1.0 eq.) were added to methylamine (2 M tetrahydrofuran solution, 0.05 mL, 0.1 mmol, 1.0 eq.) in DMF (2 mL). The reaction mixture was stirred at 20 °C for 1 hour and then 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50.0 mg, 0.105 mmol, 1.0 eq.) was added. The reaction mixture was stirred at 120 °C for 1 hour under microwave irradiation, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (4.5 mg, yield: 8%).

Spectroscopy data:

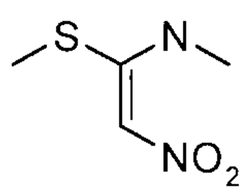
LC/MS (Method: UFLC): RT = 2.689 min; m/z = 558.0 $[M+H]^+$; Total running time: 7 min.

Example 55



1-[3-[4-amino-3-[2-fluoro-4-(2,3,5,6-three-fluorophenoxy)phenyl]-1H-pyrazolo[3,4-d] pyrimidin-1-yl]-1-piperidinyl]-1-(methylamino)-2-nitro ethylene

Step A:

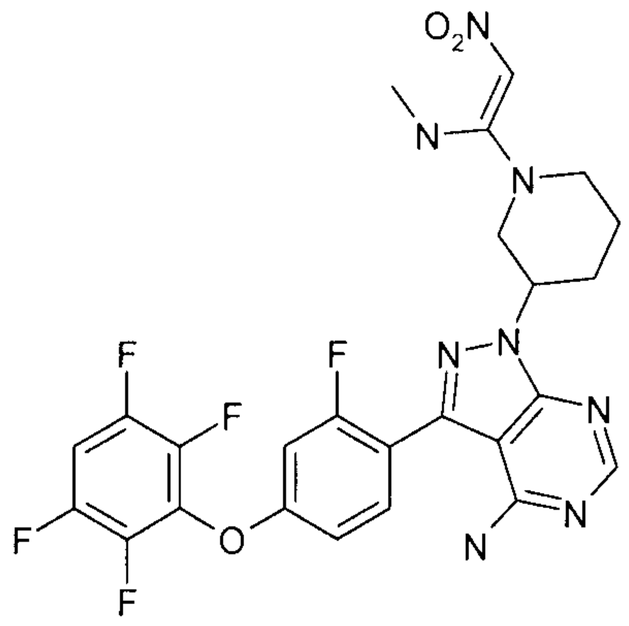


N-methyl-1-methylthio-2-nitroethyleneamine

Procedure:

Methylamine (31 mg, 2.0 mmol, 1.0 eq.) was added to a solution of 1,1-bis(methylthio)-2-nitroethene (330 mg, 2.0 mmol, 1.0 eq.) in ethanol (10 mL). The reaction mixture was stirred at 80 °C for 14 hours, cooled to room temperature, diluted with water (10 mL), and then extracted with dichloromethane (10 mL) 3 times. The combined organic phase was dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (200 mg, yield: 68%).

Step B:



1-[3-[4-amino-3-[2-fluoro-4-(2,3,5,6-three-fluorophenoxy)phenyl]-1H-pyrazolo[3,4-d] pyrimidin-1-yl]-1-piperidinyl]-1-(methylamino)-2-nitro ethylene

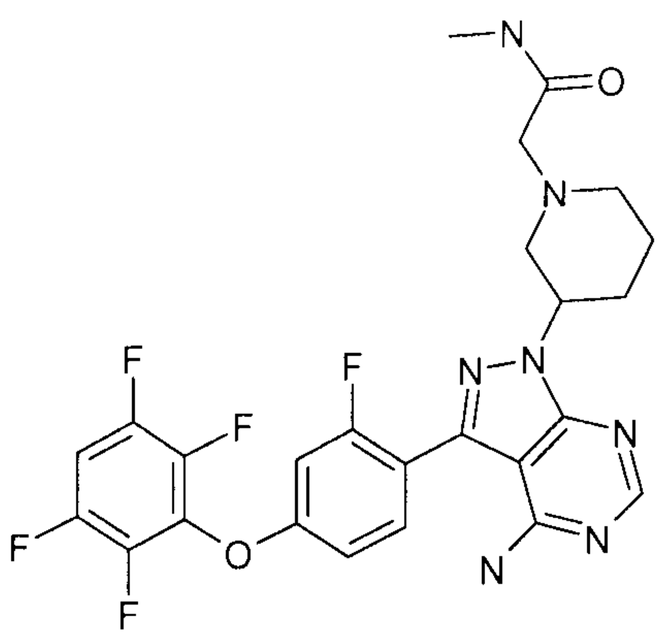
Procedure:

A mixture of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.13 mmol, 1.0 eq.) and N-methyl-1-methylthio-2-nitroethyleneamine (22 mg, 0.15 mmol, 1.2 eq.) in ethanol (10 mL) was refluxed for 14 hours. After cooling to room temperature, the reaction mixture was diluted with water (10 mL), then extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (by volume ratio)) to give the hydrochloride of the target compound (9.3 mg, yield: 13%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.343 min; m/z = 577.0 $[M+H]^+$; Total running time: 7 min.

Example 56



2-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-N-methylacetamide

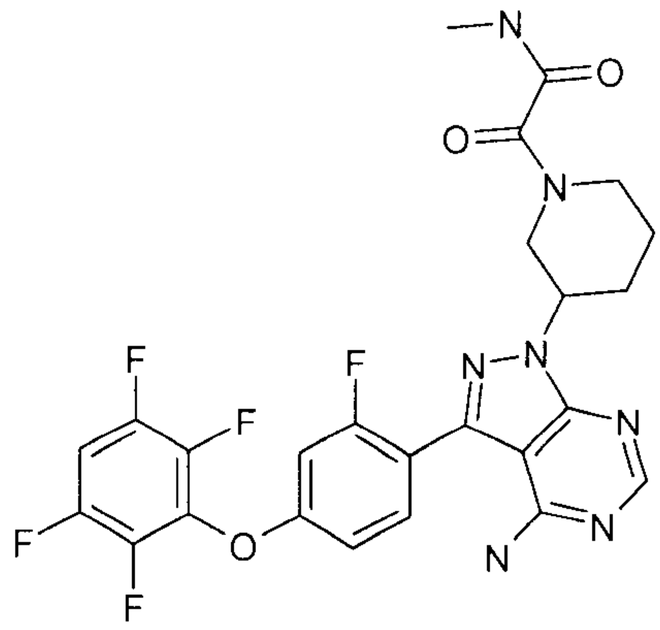
Procedure:

2-bromo-N-methyl-acetamide (32 mg, 0.21 mmol, 2.0 eq.), carbonate potassium (29 mg, 0.21 mmol, 2.0 eq.) and sodium iodide (2 mg, 0.01 mmol, 0.1 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.1 mmol, 1.0 eq.) in ethanol (2 mL). The reaction mixture was refluxed for 2 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.6%NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (4.5 mg, yield: 20%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.302 min; m/z = 548.1 $[M+H]^+$; Total running time: 7 min.

Example 57



2-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-N-methyl-2-oxoacetamide

Procedure:

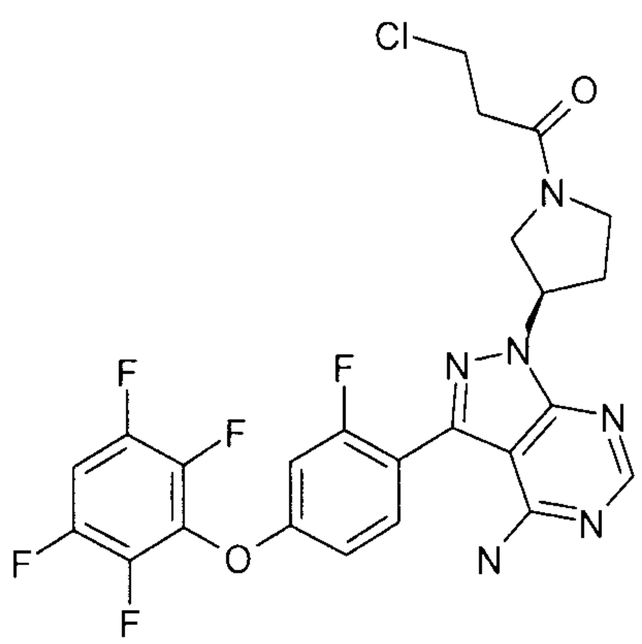
Triethylamine (38 mg, 0.38 mmol, 3.0 eq.) and oxalyl chloride (20 mg, 0.16 mmol, 1.25 eq.) was added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.13 mmol, 1.0 eq.) in dichloromethane

(2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min, and then methyl amine (6 mg, 0.19 mmol, 1.5 eq) was added. The reaction mixture was stirred at room temperature for 2 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (by volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (9.0 mg, yield: 6%).

Spectroscoy data:

LC/MS (Method: UFLC): RT = 2.748 min; m/z = 562.1 $[M+H]^+$; Total running time: 7 min.

Example 58



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-3-chloropropan-1-one

Procedure:

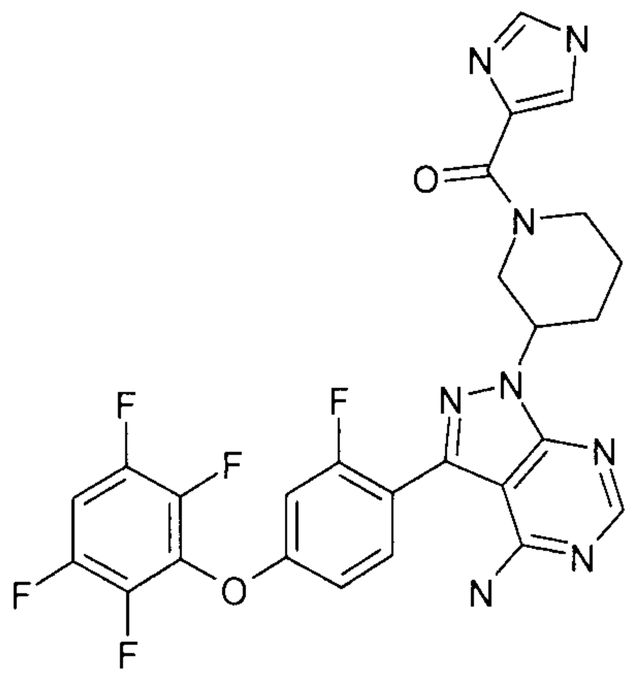
Triethylamine (66 mg, 0.649 mmol, 3.0 eq.) and chloropropionyl chloride (33 mg, 0.26 mmol, 1.2 eq.) were added dropwise to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.22 mmol, 1.0 eq.) in dichloromethane (3 mL) at -5 °C. The reaction mixture was stirred at 0 °C for 2 hours, quenched with water (10 mL), and extracted with dichloromethane (20 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (by volume ratio)) to give the hydrochloride of the target compound (4.0 mg, yield: 3%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 3.929 min; m/z = 553.1 $[M+H]^+$; Total running time: 7 min.

^1H NMR (400MHz, CD_3OD) δ 8.44 (s, 1H), 7.02 (t, J = 8.4 Hz, 1H), 7.51-7.48 (m, 1H), 7.10-7.03 (m, 2H), 5.74-5.67 (m, 1H), 4.13-4.11 (m, 1H), 4.00-3.97 (m, 2H), 3.82-3.78 (m, 3H), 2.90-2.84 (m, 2H), 2.62-2.53 (m, 2H).

Example 59



(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)(1H-imidazol-4-yl)methanone

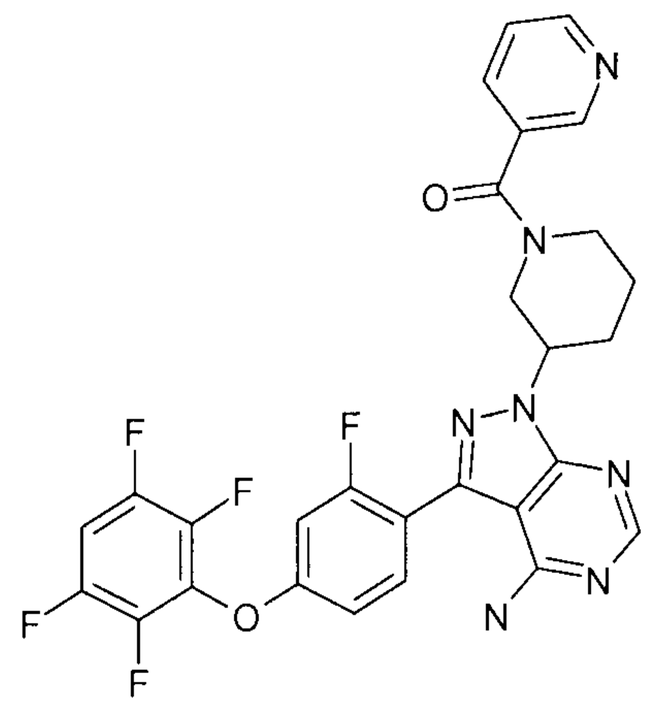
Procedure:

Imidazole-4-carboxylic acid (17 mg, 0.15 mmol, 1.2 eq.), DIPEA (49 mg, 0.38 mmol, 3.0 eq.) and HATU (53 mg, 0.14 mmol, 1.1 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.13 mmol, 1.0 eq.) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 30 min., concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (25.0 mg, yield: 35%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.368 min; m/z = 571.1 $[M+H]^+$; Total running time: 7 min.

Example 60



(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)(pyridin-3-yl)methanone

Procedure:

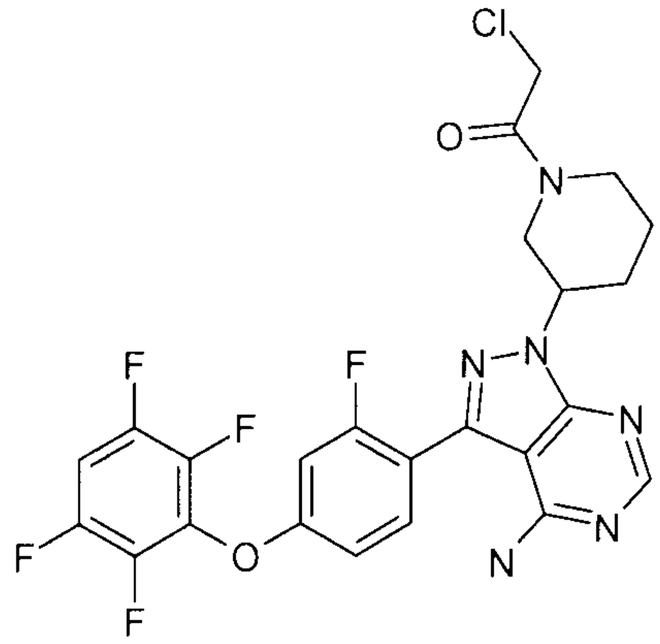
Nicotinic acid (19 mg, 0.15 mmol, 1.2 eq.), DIPEA (49 mg, 0.38 mmol, 3.0 eq.) and HATU (53 mg , 0.14 mmol, 1.1 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.13 mmol, 1.0 eq.) in dichloromethane (3 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 30 min., concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient: 10% to 100% (volume ratio)) to give the hydrochloride of the target compound (20 mg, yield: 27%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 3.672 min; m/z = 582.0 $[M+H]^+$; Total running time: 7 min.

^{1}H NMR (400MHz, CD_3OD) δ 9.06-8.93 (m, 2H), 8.69 (br, 1H), 8.50 (br, 1H), 8.18-8.10 (m, 1H), 7.77-7.71 (m, 1H), 7.53-7.48 (m, 1H), 7.15-7.08 (m, 2H), 5.34-5.23 (m, 1H), 4.61-4.58 (m, 0.5H), 4.43-4.40 (m, 0.5H), 3.99-3.68 (m, 2H), 3.48-3.46 (m, 1H), 2.42-2.37 (m, 2H), 2.15-2.09 (m, 1H), 1.95-1.87 (m, 1H).

Example 61



1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-chloroethanone

Procedure:

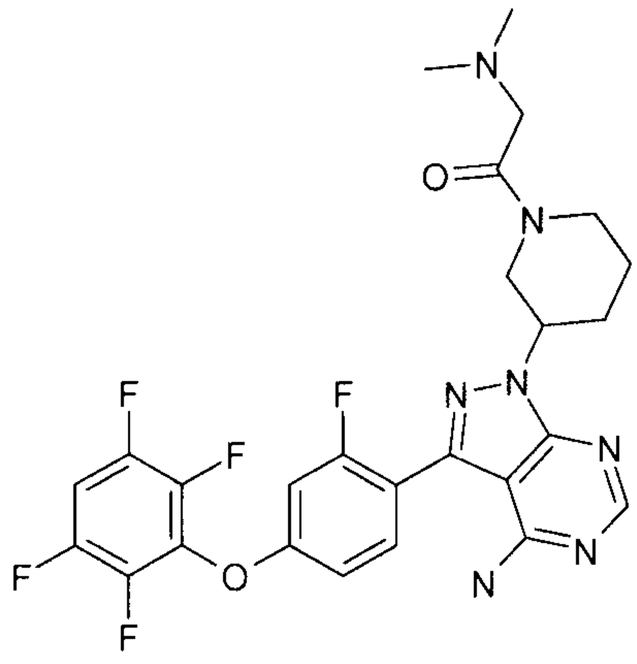
2-chloroacetic acid (14 mg, 0.13 mmol, 1.0 eq.), triethylamine (19 mg, 0.19 mmol, 1.5 eq.) and HATU (53 mg, 0.14 mmol, 1.1 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.13 mmol, 1.0 eq.) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 30 min., concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (16 mg, yield: 31%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 3.046 min; m/z = 553.1 $[M+H]^+$; Total running time: 7 min.

^{1}H NMR (400MHz, CD_3OD) δ 8.35 (s, 1H), 7.98-7.93 (m, 1H), 7.58-7.54 (m, 1H), 7.31 (dd, *J* = 2.4, 11.2 Hz, 1H), 7.15 (dd, *J* = 2.4, 8.8 Hz, 1H), 4.90-4.86 (m, 0.5H), 7-4.73-4.70 (m, 0.5H), 4.48-4.39 (m, 2H), 4.27-4.04 (m, 1.5H), 3.82-3.66 (m, 1H), 3.23-3.17 (m, 1H), 2.95-2.90 (m, 0.5H), 2.27-2.13 (m, 2H), 1.94-1.75 (m, 2H).

Example 62



1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-(dimethylamino)ethanone

Procedure:

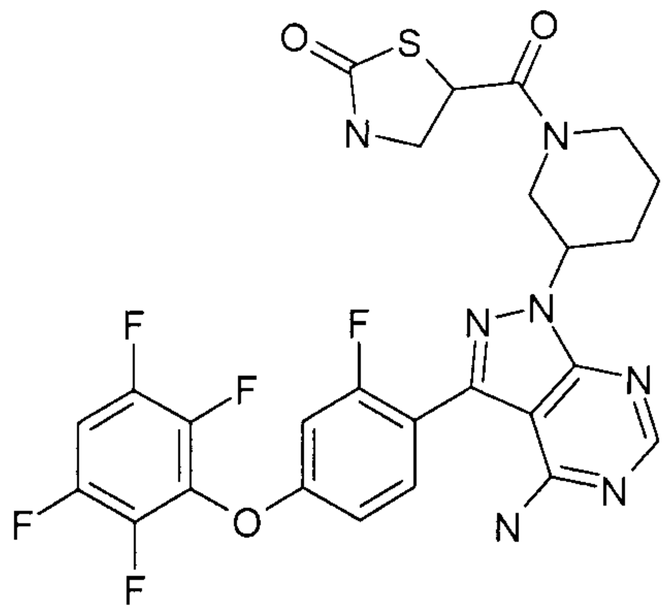
N,N-dimethylglycine (16 mg, 0.15 mmol, 1.2 eq.), DIPEA (49 mg, 0.38 mmol, 3.0 eq.) and HATU (53 mg, 0.14 mmol, 1.1 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.13 mmol, 1.0 eq.) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 30 min., concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.6%NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (30 mg, yield: 42%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.301 min; m/z = 562.1 $[M+H]^+$; Total running time: 7 min.

^1H NMR (400MHz, DMSO-d_6) δ 8.24-8.21 (m, 1H), 7.98-7.90 (m, 1H), 7.56-7.50 (m, 1H), 7.27-7.24 (m, 1H), 7.11-7.09 (m, 1H), 4.83-4.75 (m, 0.5H), 4.66-4.57 (m, 0.5H), 4.44-4.41 (m, 0.5H), 4.20-4.00 (m, 1.5H), 3.59-3.56 (m, 0.5H), 3.45-3.40 (m, 1H), 3.16-3.10 (m, 2H), 2.90-2.83 (m, 0.5H), 2.16-2.08 (m, 8H), 1.89-1.85 (m, 1H), 1.67-1.45 (m, 1H).

Example 63



5-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carbonyl)thiazolidin-2-one

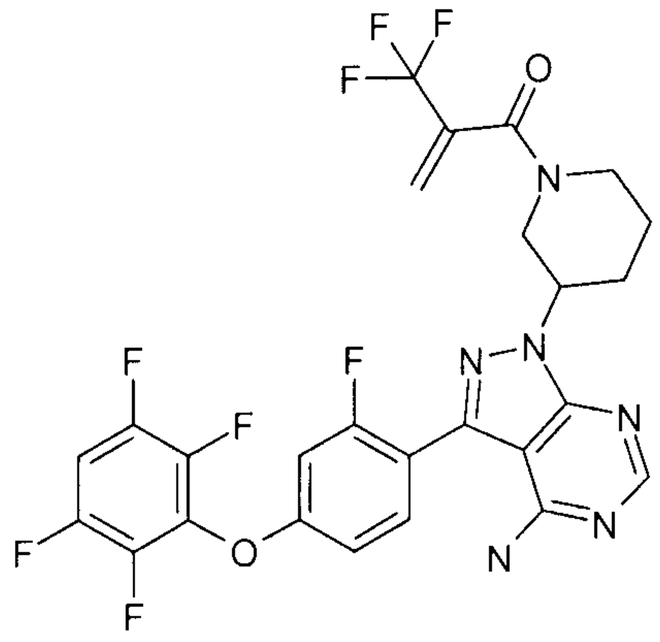
Procedure:

2-oxothiazolidine-5-carboxylic acid (26 mg, 0.19 mmol, 1.5 eq.), DIPEA (49 mg, 0.38 mmol, 3.0 eq.) and HATU (72 mg, 0.19 mmol, 1.5 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.13 mmol, 1.0 eq.) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 12 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.6%NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (4 mg, yield: 6%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.805 min; m/z = 606.1 $[M+H]^+$; Total running time: 7 min.

Example 64



1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-(trifluoromethyl)prop-2-en-1-one

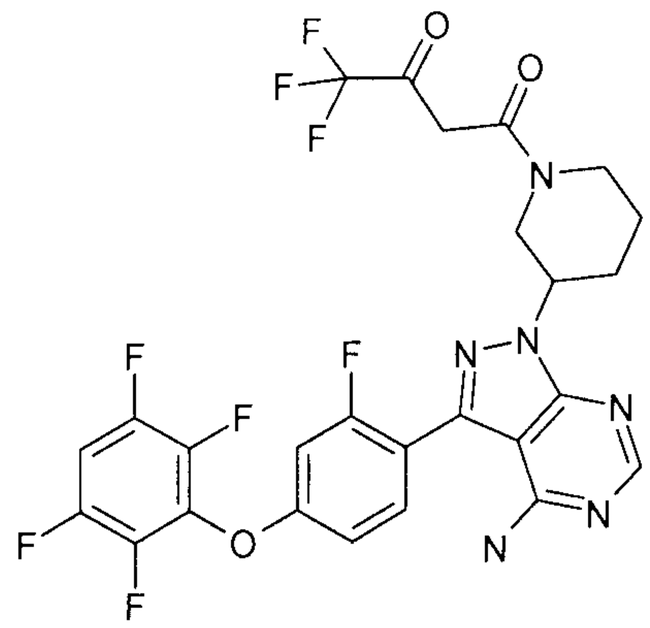
Procedure:

2-(trifluoromethyl)acrylic acid (26 mg, 0.19 mmol, 1.5 eq.), DIPEA (49 mg, 0.38 mmol, 3.0 eq.) and HATU (72 mg, 0.19 mmol, 1.5 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.13 mmol, 1.0 eq.) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 12 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.6%NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (2.9 mg, yield: 4%).

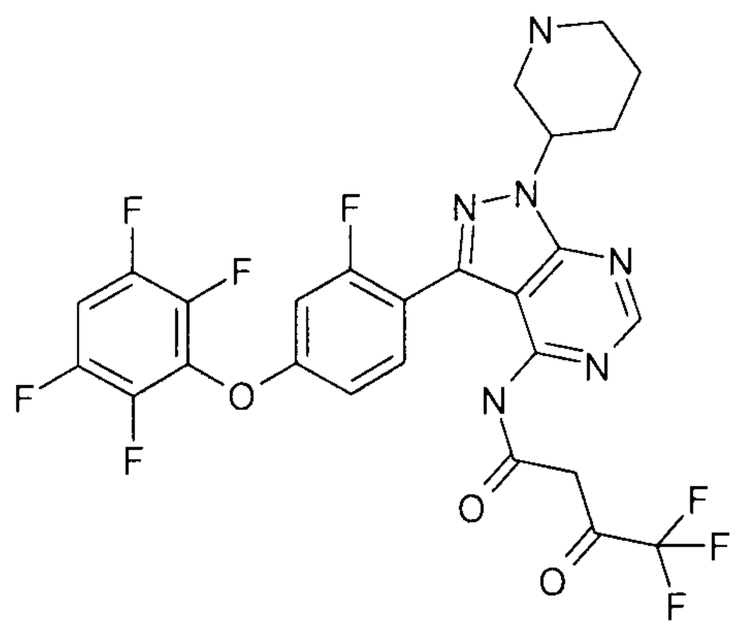
Spectroscopy data:

LC/MS (Method: UFLC): RT = 3.310 min; m/z = 599.1 $[M+H]^+$; Total running time: 7 min.

Examples 65 and 66



1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4,4,4-trifluorobutane-1,3-dione



4,4,4-trifluoro-N-(3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-3-oxo-butanamide

Procedure:

Ethyl 4,4,4-trifluoroacetoacetate (24 mg, 0.15 mmol, 1.2 eq.) and DIPEA (49 mg, 0.38 mmol, 3.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.13 mmol, 1.0 eq.) in toluene (2 mL). The reaction mixture was stirred at 20 °C for 0.5 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound 65 (5 mg, yield: 6%) and compound 66 (4 mg, yield: 5%).

Spectroscopy data:

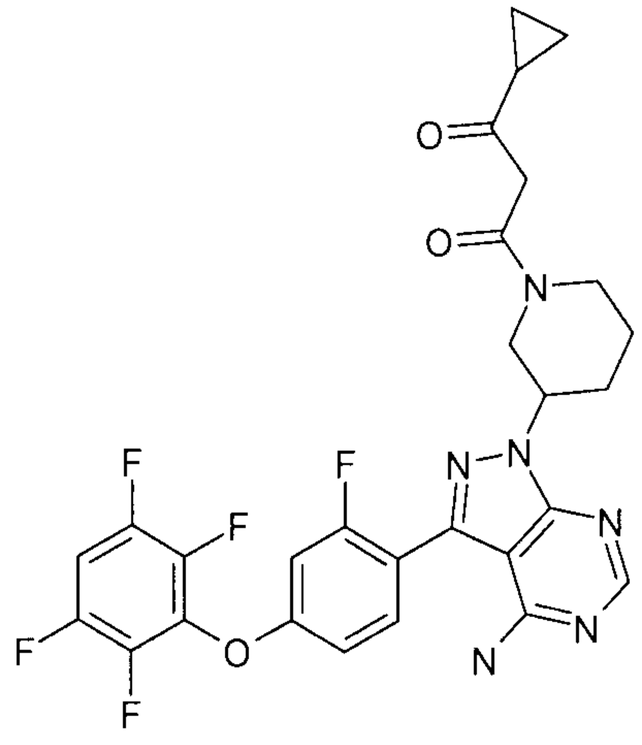
Example 65:

LC/MS (Method: UFLC): RT = 1.095 min; m/z = 615.1 $[M+H]^+$; Total running time: 2 min.

Example 66:

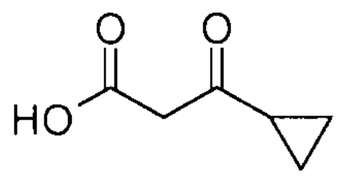
LC/MS (Method: UFLC): RT = 1.079 min; m/z = 615.1 $[M+H]^+$; Total running time: 2 min.

Example 67



1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-3-cyclopropylpropane-1,3-dione

Step A:

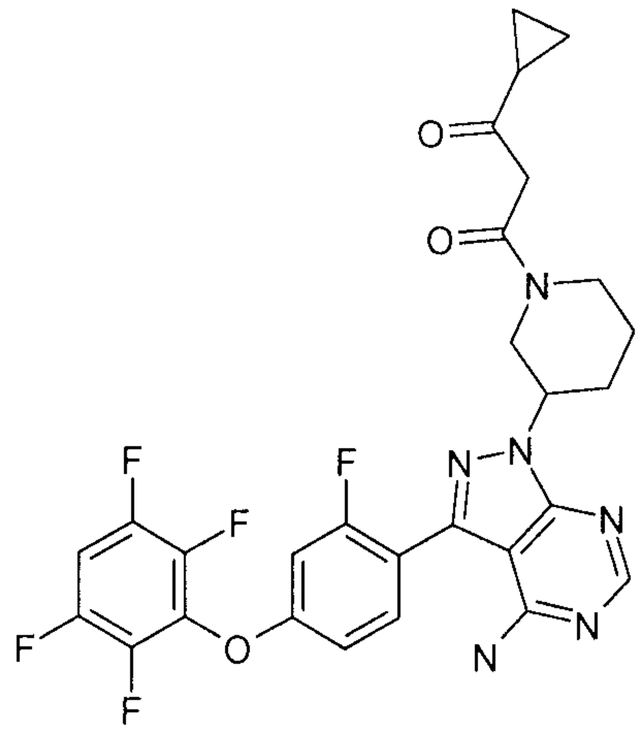


3-cyclopropyl-3-oxopropanoic acid

Procedure:

Lithium hydroxide monohydrate (0.59 g, 14.7 mmol, 2.0 eq.) was added to a solution of methyl 3-cyclopropyl-3-oxopropanoate (1.0 g, 7.03 mmol, 1.0 eq.) in tetrahydrofuran/water/methanol (15 mL, 1/1/1, v/v/v). The reaction mixture was stirred at 20 °C for 14 hours, and then evaporated to remove the solvent under reduced pressure. The residue was dissolved in water (10 mL), adjusted with 2 N HCl to pH=2, and then extracted with ethyl acetate (20 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (0.4 g, yield: 44%).

Step B:



1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-3-cyclopropylpropane-1,3-dione

Procedure:

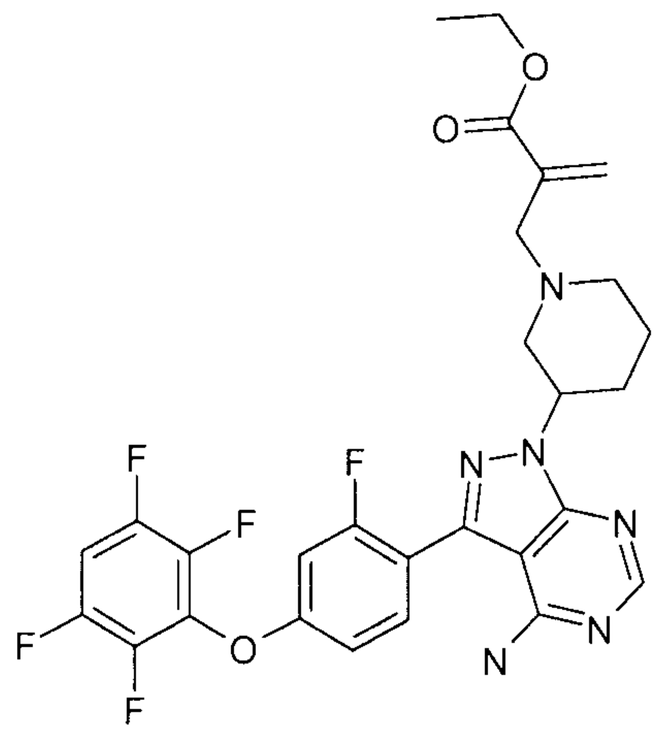
3-cyclopropyl-3-oxopropanoic acid (19 mg, 0.15 mmol, 1.2 eq.), DIPEA (49 mg, 0.38 mmol, 3.0 eq.) and HATU (72 mg, 0.19 mmol, 1.5 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.13 mmol, 1.0 eq.) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 12 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.6%NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (25 mg, yield: 34%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 3.003 min; m/z = 587.2 $[M+H]^+$; Total running time: 7 min.

^{1}H NMR (400MHz, DMSO-d_6) δ 8.24-8.23 (m, 1H), 7.99-7.93 (m, 1H), 7.59-7.54 (m, 1H), 7.29-7.26 (m, 1H), 7.13-7.11 (m, 1H), 4.79-4.63 (m, 1H), 4.53-4.50 (m, 0.5H), 4.28-4.25 (m, 0.5H), 3.86-3.70 (m, 3H), 3.15-3.08 (m, 1.5H), 2.85-2.79 (m, 0.5H), 2.24-1.96 (m, 2H), 1.90-1.85 (m, 1H), 1.65-1.53 (m, 1H), 0.93-0.84 (m, 4H).

Example 68



ethyl 2-((3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)methyl)acrylate

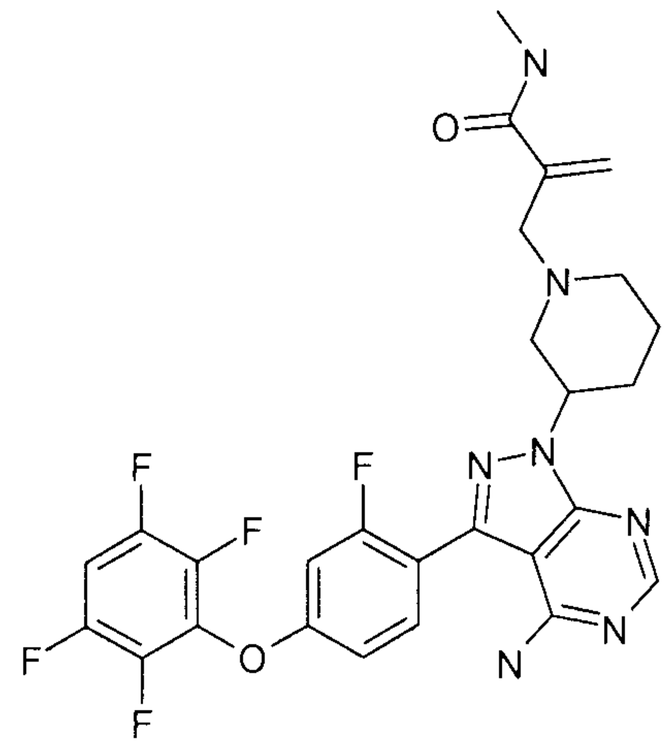
Procedure:

Ethyl 2-(bromomethyl) acrylate (53 mg, 0.28 mmol, 1.2 eq.) and potassium carbonate (63 mg, 0.46 mmol, 2.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (110 mg, 0.23 mmol, 1.0 eq.) in DMF (2 mL). The reaction mixture was stirred at 85 °C for 3 hours and filtered. The filter cake was washed with ethyl acetate. The filtrate was concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (38 mg, yield: 28%).

Spectroscopy data:

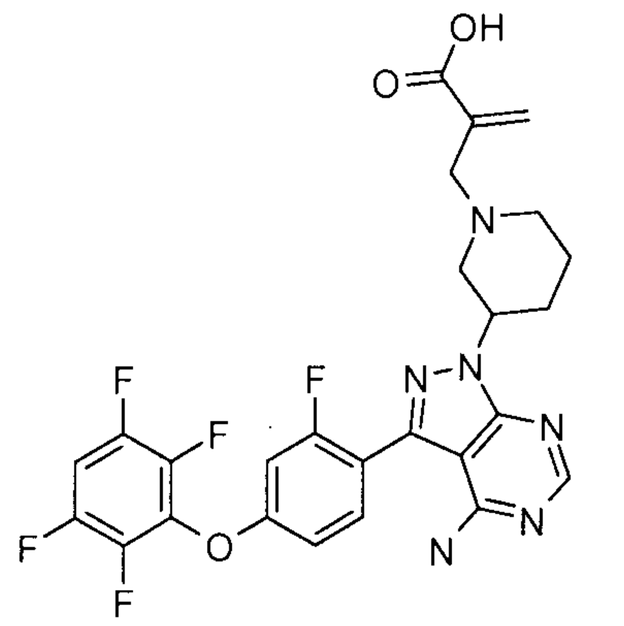
LC/MS (Method: UFLC): RT = 2.654 min; m/z = 589.2 $[M+H]^+$; Total running time: 7 min.

Example 69



2-((3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)methyl)-N-methylacrylamide

Step A:



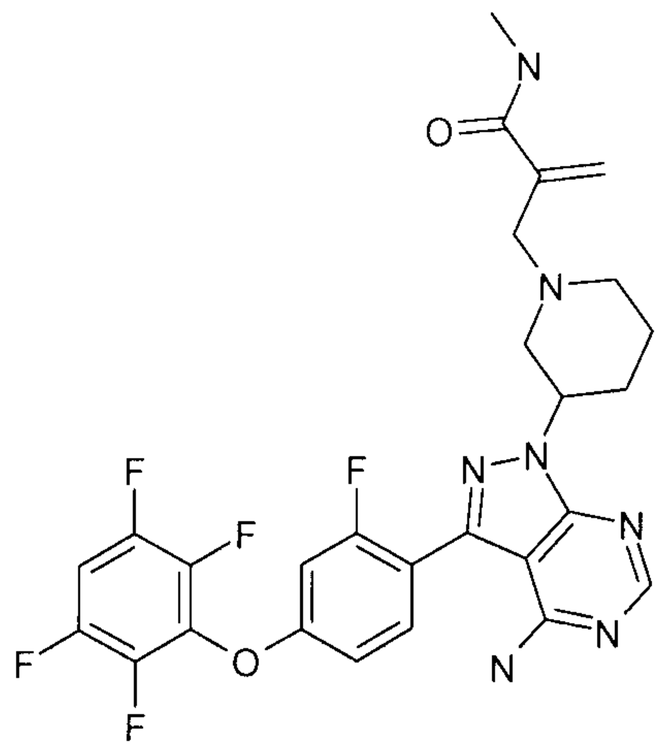
2-((3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)methyl)acrylic acid

Procedure:

Lithium hydroxide monohydrate (3 mg, 0.076 mmol, 1.5 eq.) was added to a solution of ethyl 2-((3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)methyl)acrylate (30 mg, 0.051 mmol, 1.0 eq.) in tetrahydrofuran/water/methanol (1.5 mL, 1/1/1, v/v/v). The reaction mixture was stirred at 20 °C for 14 hours, and then evaporated to remove solvent under reduced pressure. The residue was dissolved in water (5 mL), adjusted with 2 N HCl to pH=2, and then extracted with ethyl acetate (5 mL) 3 times. The combined

organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (20mg, yield: 86%).

Step B:



2-((3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)methyl)-N-methylacrylamide

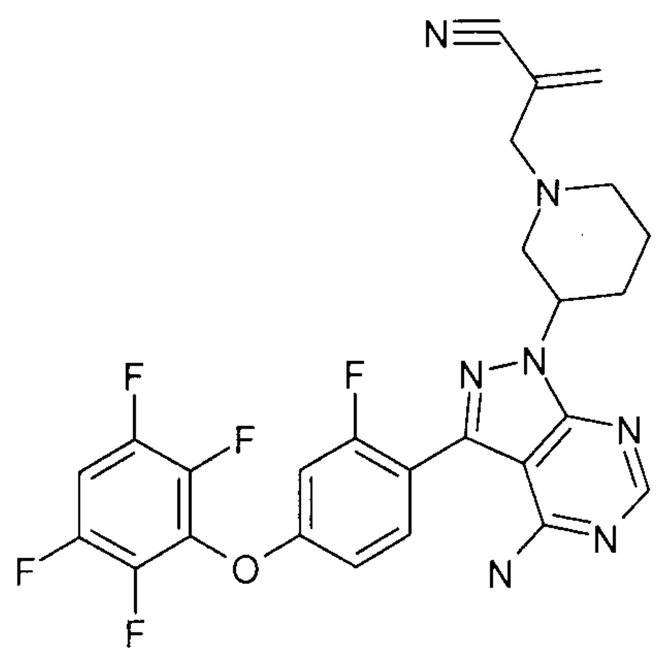
Procedure:

Methylamine (1M in THF, 0.072 mL, 0.072 mmol, 2.0 eq.), DIPEA (14 mg, 0.107 mmol, 3.0 eq.) and HATU (20 mg, 0.054 mmol, 1.5 eq.) were added to a solution of 2-((3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)methyl)acrylic acid (20 mg, 0.036 mmol, 1.0 eq.) in DMF (1 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 12 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)) to give the hydrochloride of the target compound (9 mg, yield: 40%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 3.262 min; m/z = 574.1 $[M+H]^+$; Total running time: 7 min.

Example 70



2-((3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)methyl)acrylonitrile

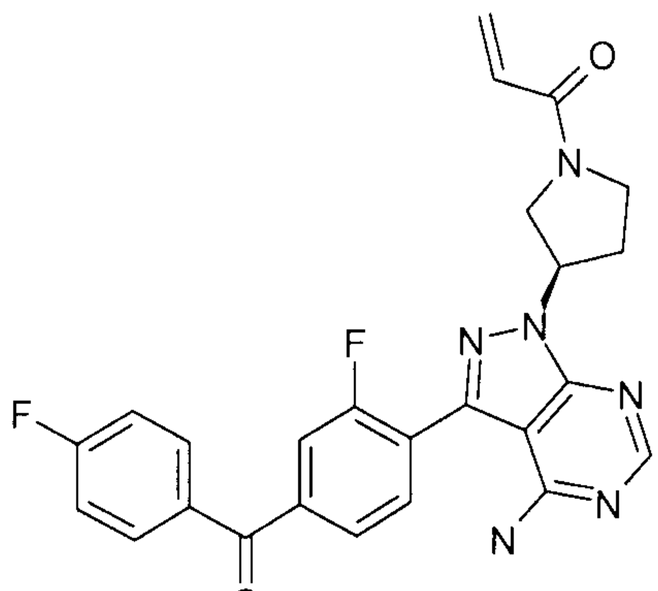
Procedure:

Cyanoacetic acid (10 mg, 0.12 mmol, 1.0 eq.) and formaldehyde (8.5 mg, 0.28 mmol , 2.4 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (56 mg, 0.12 mmol, 1.0 eq.) in toluene (3 mL). The resulting mixture was refluxed for 12 hours and concentrated to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.6‰NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound hydrochloride (3.7 mg, yield: 6%).

Spectroscopy data:

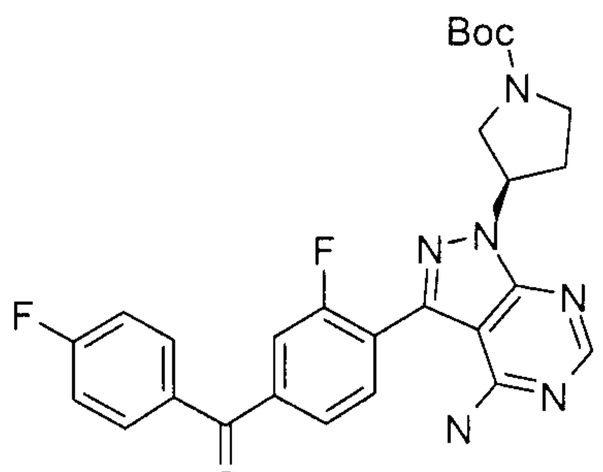
LC/MS (Method: UFLC): RT = 2.458 min; m/z = 542.1 $[M+H]^+$; Total running time: 7 min.

Example 71



1-((R)-3-(4-amino-3-(2-fluoro-4-(4-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Step A:

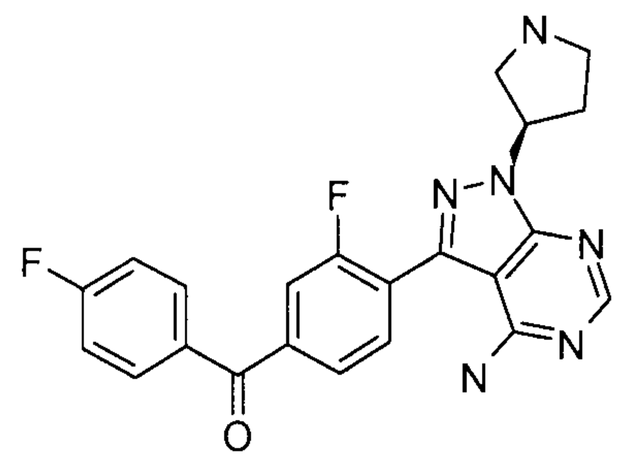


(3R)-tert-butyl 3-(4-amino-3-(2-fluoro-4-(4-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate

Procedure:

(R)-tert-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate (100 mg, 0.232 mmol, 1.0 eq.), (3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)(4-fluorophenyl)methanone (80 mg, 0.232 mmol, 1.0 eq.), potassiumcarbonate (96 mg, 0.696 mmol, 3.0 eq.) and $Pd(PPh_3)_4$ (26 mg, 0.023 mmol, 0.1 eq.) were dissolved in 1,4-dioxane/water (2.4 mL, 5/1, v/v). The reaction mixture was stirred at 90 °C for 30 min. under nitrogen atmosphere. After cooling to room temperature, the reaction was diluted with water (10 mL), and then extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by thin layer chromatography (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (20 mg, yield: 17%).

Step B:

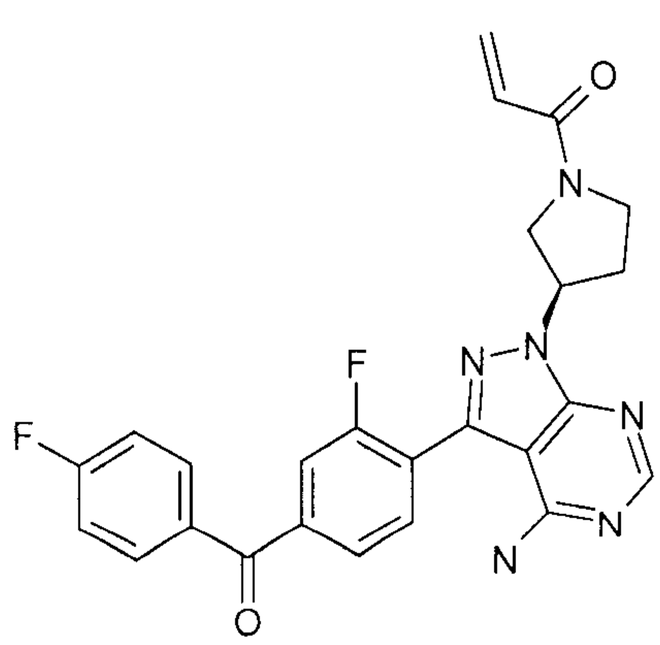


(4-(4-amino-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenyl)(4-fluorophenyl)methanone

Procedure:

4M HCl/EA (5 mL) was added to a solution of (3R)-tert-butyl 3-(4-amino-3-(2-fluoro-4-(4-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate (20 mg, 0.038 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (18 mg, yield: 100%).

Step C:



1-((R)-3-(4-amino-3-(2-fluoro-4-(4-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Procedure:

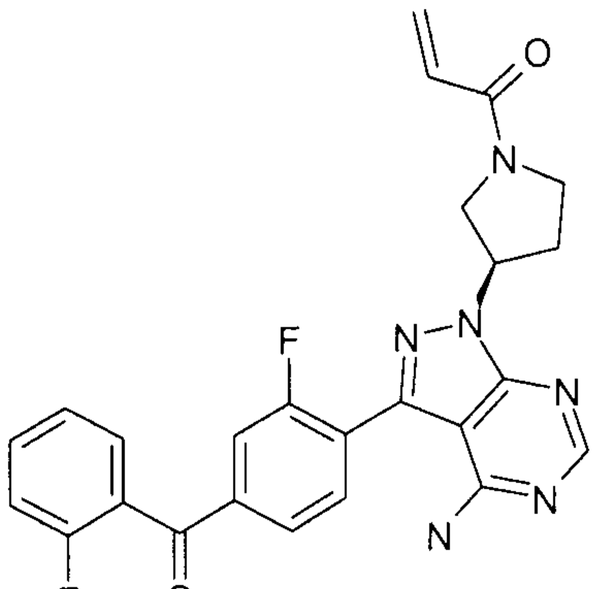
Triethylamine (12 mg, 0.115mmol, 3.0 eq.) and acrylic acid (3.4 mg, 0.038 mmol, 1.0 eq.) were subsequently added dropwise solution of (4-(4-amino-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenyl)(4-fluorophenyl)methanone (18 mg, 0.038 mmol, 1.0 eq.) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred at

0 °C for 1 hour, quenched with water (5 mL) and separated, and the aqueous phase was extracted with dichloromethane (5 mL) 3 times. The combined organic phase was dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient 10% to 100% (volume ratio)) to give the hydrochloride of the target compound (6.9 mg, yield: 38%).

Spectroscopy data:

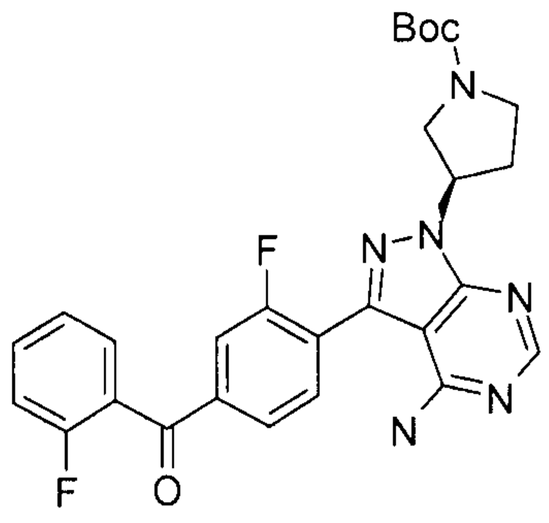
LC/MS (Method: UFLC): RT = 3.424 min; m/z = 475.1 $[M+H]^+$; Total running time: 7 min.

Example 72



1-((R)-3-(4-amino-3-(2-fluoro-4-(2-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Step A:



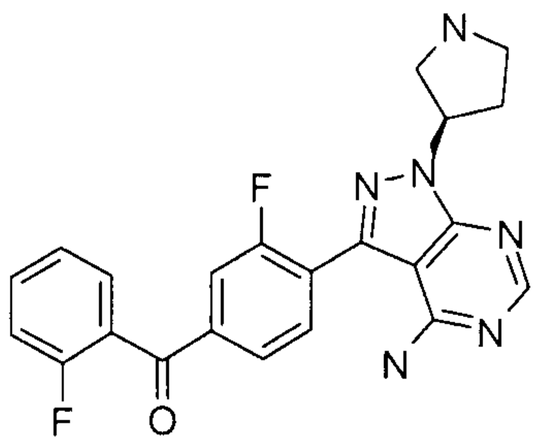
(3R)-tert-butyl 3-(4-amino-3-(2-fluoro-4-(2-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate

Procedure:

(R)-tert-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate

(100 mg, 0.232 mmol, 1.0 eq.), (3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)(2-fluorophenyl)methanone (144 mg, 0.418 mmol, 1.8 eq.), sodium carbonate (74 mg, 0.696 mmol, 3.0 eq.) and $Pd(PPh_3)_4$ (26 mg, 0.023 mmol, 0.1 eq.) were dissolved in 1,4-dioxane/water (2.4 mL, 5/1, v/v). The reaction mixture was stirred at 90 °C for 30 min. under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was diluted with water (10 mL), and then extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by thin layer chromatography (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (40 mg, yield: 33%).

Step B:

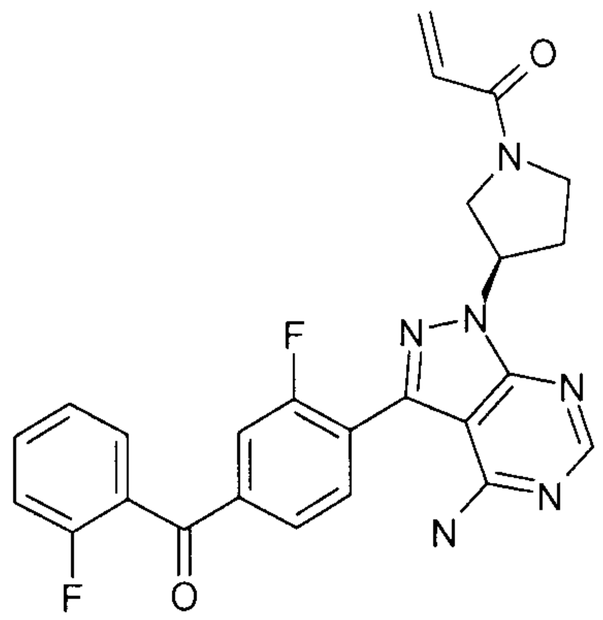


(4-(4-amino-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenyl)(2-fluorophenyl)methanone

Procedure:

4M HCl/EA (5 mL) was added to a solution of (3R)-tert-butyl 3-(4-amino-3-(2-fluoro-4-(2-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate (40 mg, 0.077 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (30 mg, yield: 93%).

Step C:



F O

1-((R)-3-(4-amino-3-(2-fluoro-4-(2-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Procedure:

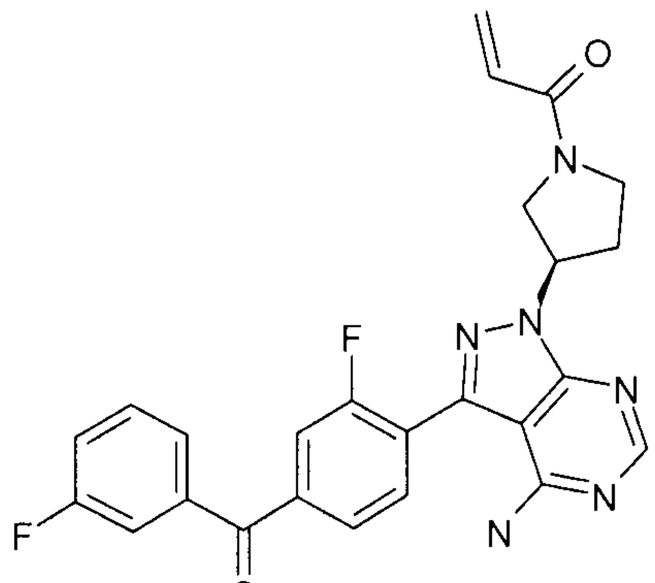
Triethylamine (14 mg, 0.14 mmol, 2.0 eq.) and acrylic acid (7.0 mg, 0.078 mmol, 1.1 eq.) were subsequently added dropwise to a solution of (4-(4-amino-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenyl)(2-fluorophenyl)methanone (30 mg, 0.071 mmol, 1.0 eq.) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, quenched with water (5 mL) and extracted with dichloromethane (5 mL) 3 times. The combined organic phase with anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.6% NH_4HCO_3, gradient 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (4 mg, yield: 15%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.359 min; m/z = 475.1 $[M+H]^+$; Total running time: 7 min.

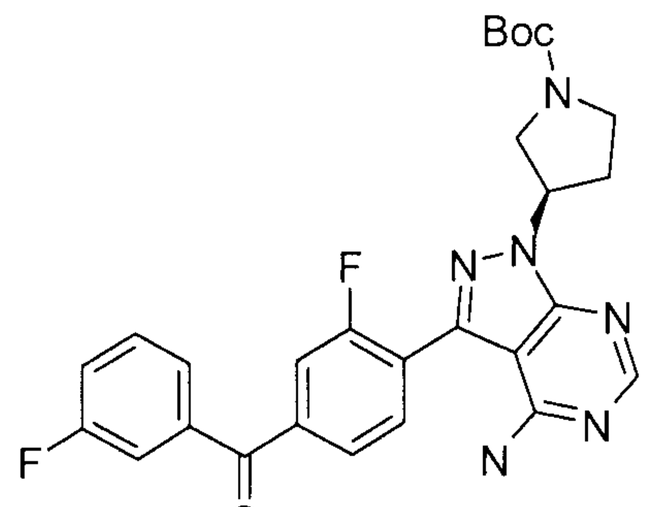
^1H NMR (400MHz, CD_3OD) δ 8.29 (s, 1H), 7.76-7.64 (m, 5H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.33 (t, *J* = 8.8 Hz, 1H), 6.70-6.55 (m, 1H), 6.32-6.28 (m, 1H), 5.79-5.76 (m, 1H), 5.65-5.56 (m, 1H), 4.20-4.04 (m, 2.5H), 3.93-3.85 (m, 1H), 3.76-3.73 (m, 0.5H), 2.64-2.49 (m, 2H).

Example 73



1-((R)-3-(4-amino-3-(2-fluoro-4-(3-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Step A:



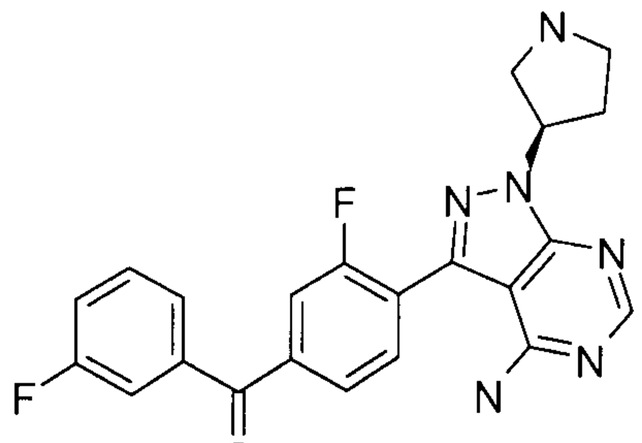
(3R)-tert-butyl 3-(4-amino-3-(2-fluoro-4-(3-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate

Procedure:

(R)-tert-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate (140 mg, 0.32 mmol, 1.0 eq.), (3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)(3-fluorophenyl)methanone (224 mg, 0.64 mmol, 2.0 eq.), sodium carbonate(101 mg, 0.96 mmol, 3.0 eq.) and $Pd(PPh_3)_4$ (34 mg, 0.03 mmol, 0.1 eq.) were dissolved in 1,4-dioxane/water (6 mL, 5/1, v/v). The reaction mixture was stirred at 90 °C for 30 min. under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was diluted with water (10 mL), and then extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by thin layer chromatography (eluent: petroleum ether: ethyl acetate=1:1) to give the

target compound (50 mg, yield: 23%).

Step B:

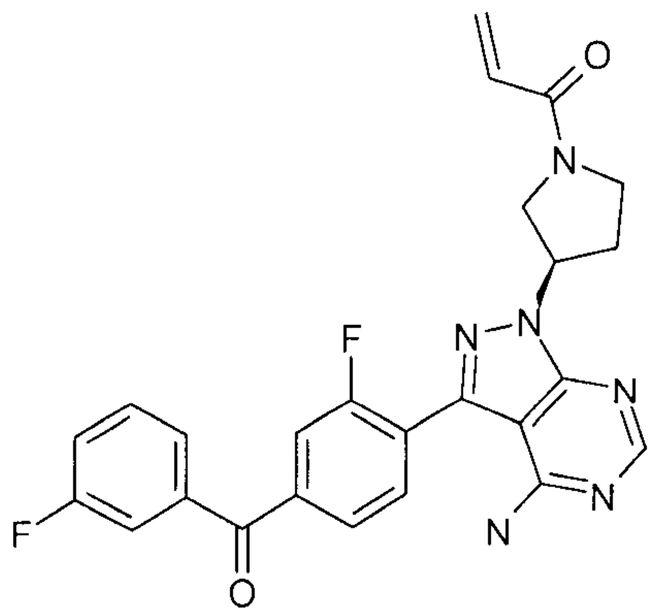


(4-(4-amino-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenyl)(3-fluorophenyl)methanone

Procedure:

4M HCl/EA (5 mL) was added to a solution of (3R)-tert-butyl 3-(4-amino-3-(2-fluoro-4-(3-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate (50 mg, 0.096 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (40 mg, yield: 99%).

Step C:



1-((R)-3-(4-amino-3-(2-fluoro-4-(3-fluorobenzoyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Procedure:

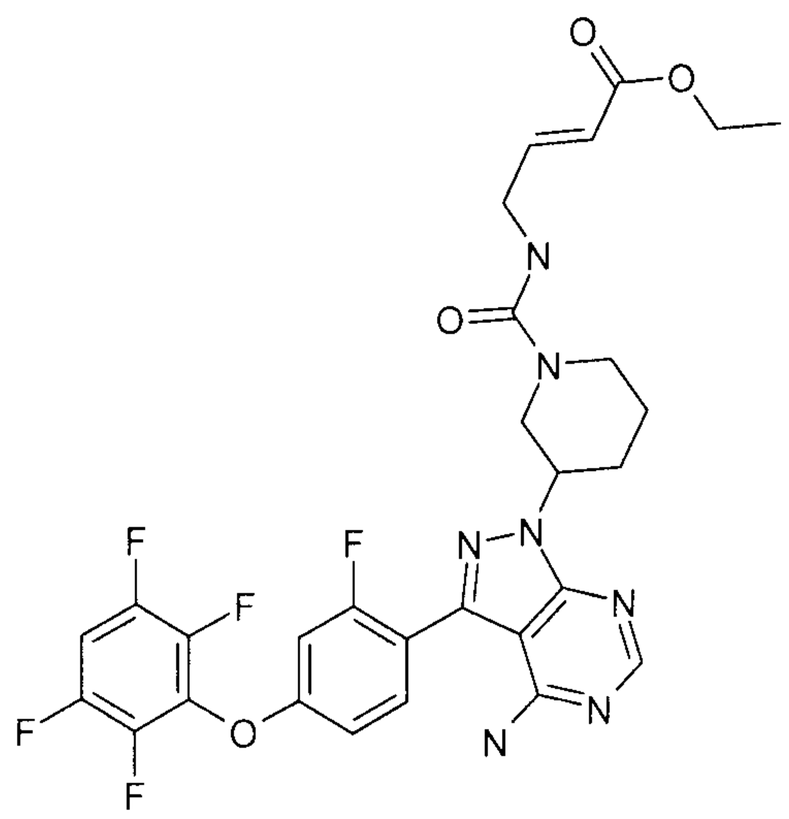
Triethylamine (19 mg, 0.19 mmol, 2.0 eq.) and acrylic acid (9.5 mg, 0.105 mmol, 1.1 eq.) were subsequently added dropwise to a solution of (4-(4-amino-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenyl)(3-fluorophenyl)methanone (40 mg, 0.096 mmol,

1.0 eq.) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, quenched with water (5 mL), separated and extracted with dichloromethane (5 mL) 3 times. The combined organic phase was dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (0.5 mg, yield: 1%).

Spectroscopy data:

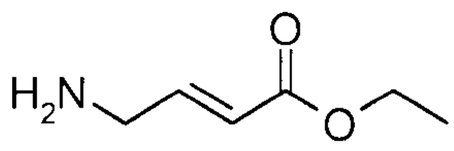
LC/MS (Method: UFLC): RT = 2.522 min; m/z = 475.1 $[M+H]^+$; Total running time: 7 min.

Example 74



ethyl 4-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxamido)but-2-enoate

Step A:

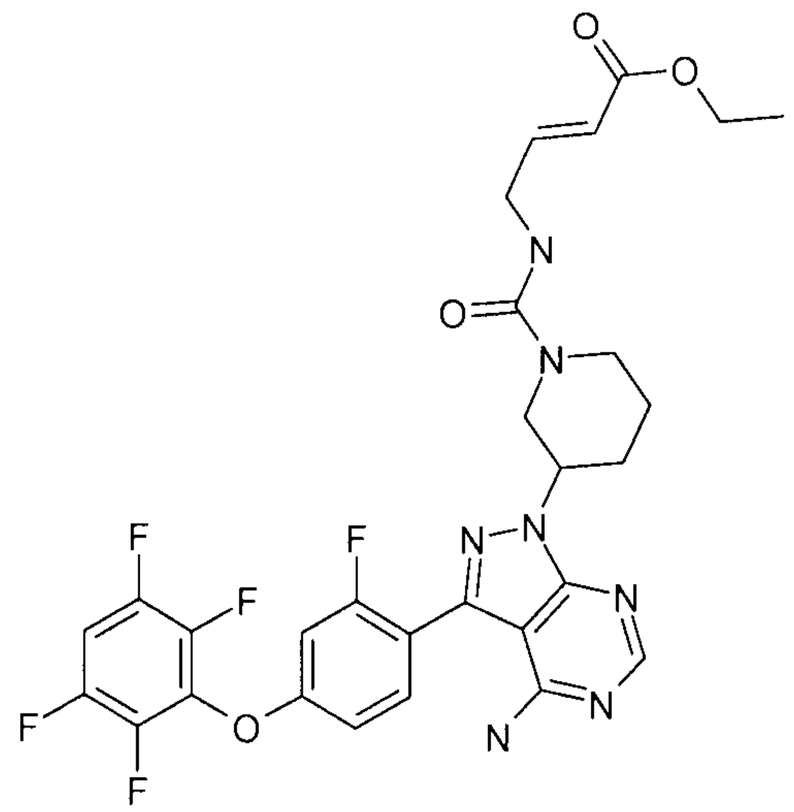


ethyl 4-aminobut-2-enoate

Procedure:

aqueous ammonia solution (10 mL) was added to a solution of ethyl 4-bromobut-2-enoate (1.0 g, 5.18 mmol, 1.0 eq.) in water (10 mL) . The reaction mixture was stirred at room temperature for 12 hours, concentrated and spin-dried to give the target compound (0.7 g, yield: 100%).

Step B:



ethyl 4-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxamido)but-2-enoate

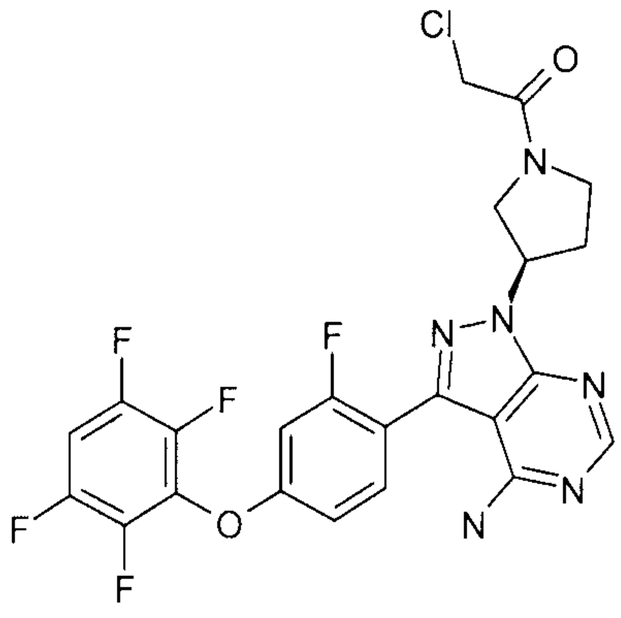
Procedure:

N, N'- carbonyldiimidazole (109 mg, 0.63 mmol, 2.0 eq.) was added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (48 mg, 0.1 mmol, 1.0 eq.) in DMF (3 mL). The reaction mixture was stirred at 90 °C for 1 hour, followed by addition of ethyl 4-aminobut-2-enoate (26 mg, 0.2 mmol, 2.0 eq.). The reaction mixture was stirred for 6 hours at 90 °C, cooled to room temperature, diluted with water (10 mL), and then extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by thin layer chromatography (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (15 mg, yield: 24 %).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 0.821 min; m/z = 632.1 $[M+H]^+$; Total running time: 1.5 min.

Example 75



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-chloroethanone

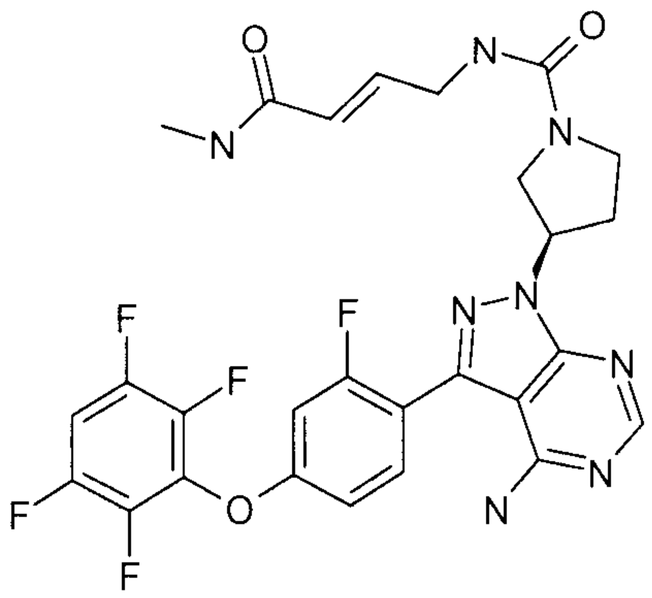
Procedure:

Triethylamine (44 mg, 0.43 mmol, 2.0 eq.) and chloroacetyl chloride (24 mg, 0.22 mmol, 1.0 eq.) were added dropwise to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.22 mmol, 1.0 eq.) in dichloromethane (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hours, quenched with water (5 mL), and extracted with dichloromethane (5 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulphate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/7‰ NH_4HCO_3, gradient: 10% to 100% (by volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (17 mg, yield: 14%).

Spectroscopy data:

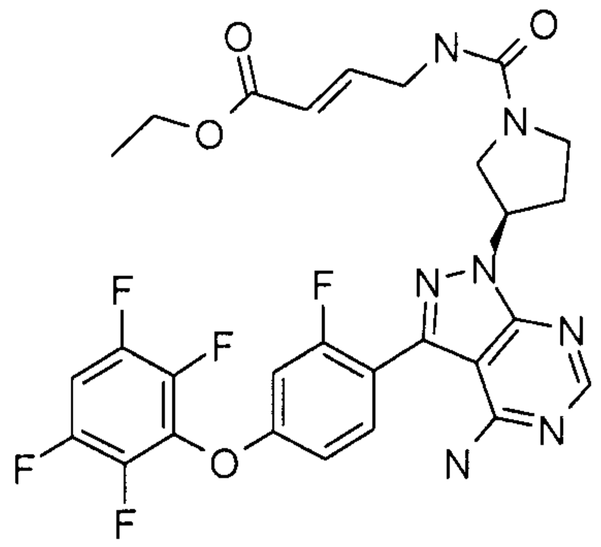
LC/MS (Method: UFLC): RT = 2.734 min; m/z = 539.0 $[M+H]^+$; Total running time: 7 min.

Example 76



(3R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-N-(4-(methylamino)-4-oxo-but-2-enyl)pyrrolidine-1-carboxamide

Step A:

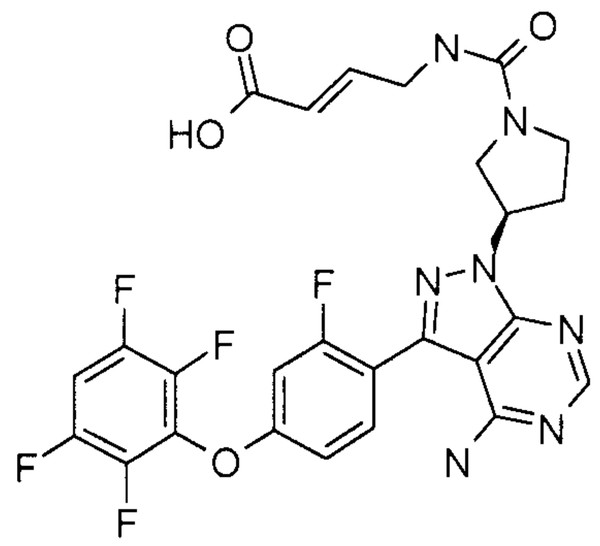


(E)-ethyl 4-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxamido)but-2-enoate

Procedure:

N, N'- carbonyldiimidazole (21 mg, 0.13 mmol, 1.0 eq.) was addedto a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.13 mmol, 1.0 eq.) in DMF (3 mL). The reaction mixture was stirred at 90 °C for 1 hour, followed by addition ofethyl 4-aminobut-2-enoate (34 mg, 0.26 mmol, 2.0 eq.). The reaction mixture was stirred for 6 hours at 90 °C, cooled to room temperature, diluted with water (10 mL), and then extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by thin layer chromatography (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (30 mg, yield: 37 %).

Step B:

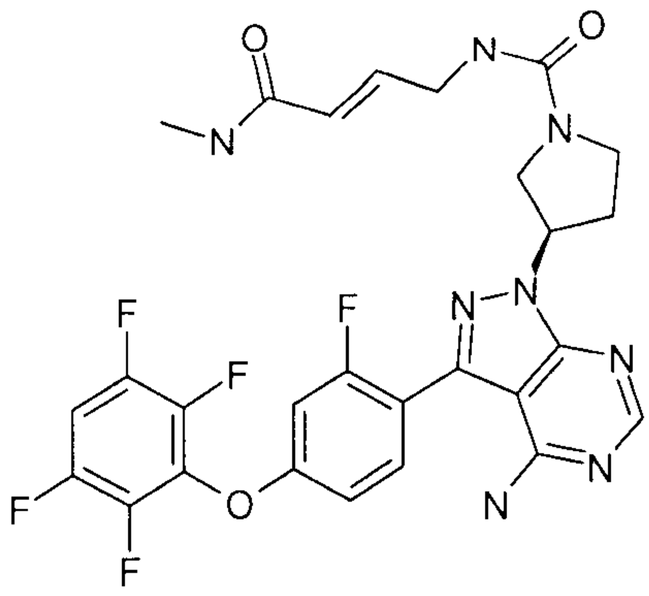


4-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxamido)but-2-enoic acid

Procedure:

Lithium hydroxide monohydrate (6 mg, 0.15 mmol, 3.0 eq.)was added to a solution of ethyl 4-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxamido)but-2-enoate (30 mg, 0.05 mmol, 1.0 eq.) in tetrahydrofuran/water/methanol (3 mL, 1/1/1, v/v/v). The reaction mixture was stirred at 20°C for 2 hours, and then evaporated to remove the solvent under reduced pressure. The residue was dissolved in water (10 mL), adjusted with 2 N HCl to pH=2, and then extracted with ethyl acetate (20 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (30mg, yield: 100%).

Step C:



(3R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-N-(4-(methylamino)-4-oxo-but-2-enyl)pyrrolidine-1-carboxamide

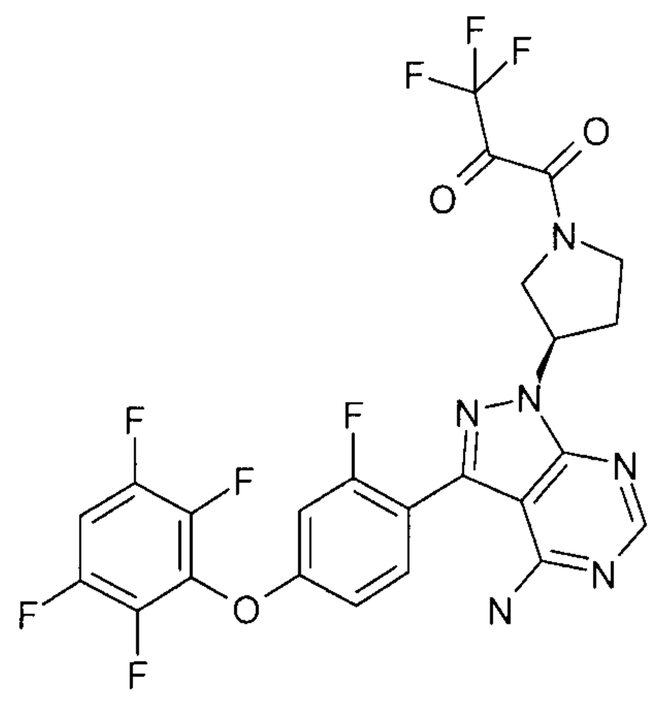
Procedure:

Methylamine (5 mg, 0.15 mmol, 3.0 eq.) and HATU (29 mg, 0.075 mmol, 1.5 eq.) were added to a solution of 4-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxamido)but-2-enoic acid (30 mg, 0.05 mmol, 1.0 eq.) in dichloromethane (3 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 3 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/7‰ NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (5 mg, yield: 16%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 0.854 min; m/z = 603.1 $[M+H]^+$; Total running time: 1.5 min.

Example 77



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-3,3,3-trifluoropropane-1,2-dione

Procedure:

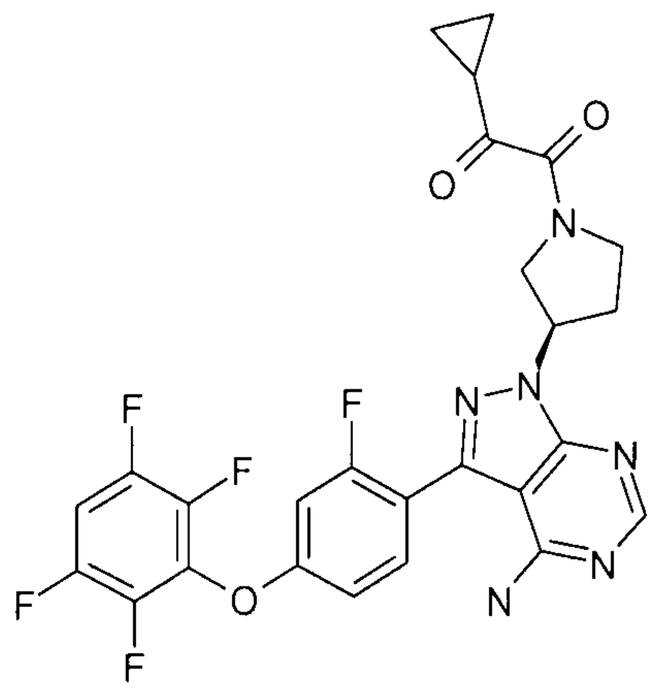
DIPEA (84 mg, 0.65 mmol, 3.0 eq.) and ethyl 4,4,4-trifluoroacetoacetate were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.216 mmol, 1.0 eq.) in toluene (3 mL) at 0 °C. The reaction mixture was stirred at 110 °C for 16 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient: 10% to 100% (volume ratio)), evaporated to

remove volatile components under reduced pressure, and lyophilized to give the target compound (6.7 mg, yield: 5.3%).

Spectroscopy data:

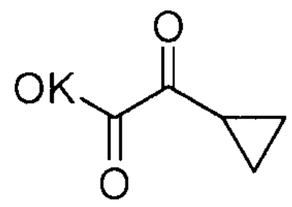
LC/MS (Method: UFLC): RT = 4.127 min; m/z = 588.9 $[M+H]^+$; Total running time: 7 min.

Example 78



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-cyclopropylethane-1,2-dione

Step A:

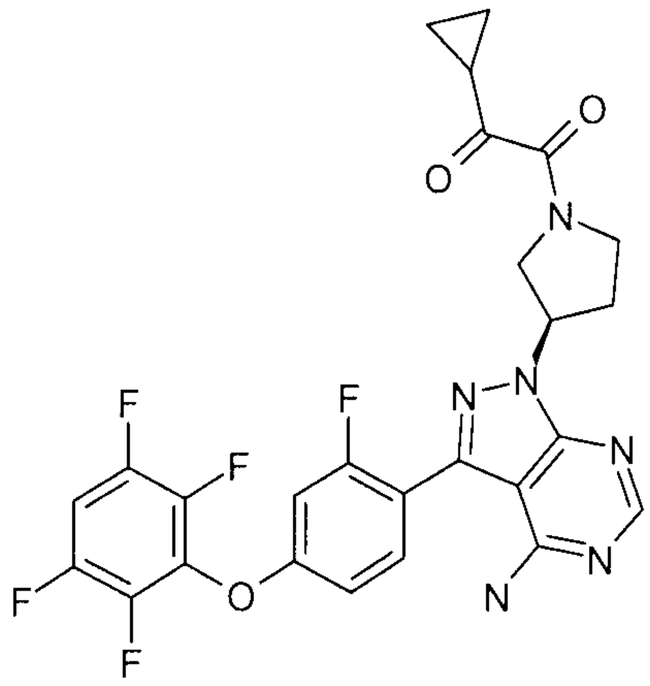


potassium 2-cyclopropyl-2-oxo acetate

Procedure:

1N Potassium hydroxide (0.7 mL, 0.70 mmol, 1.0 eq.) was addedto a solution of ethyl 2-cyclopropyl-2-oxoacetate (100 mg, 0.70 mmol, 1.0 eq.) in tetrahydrofuran/water (2 mL, 1/1, v / v). The reaction mixture was stirred at 20 °C for 2 hours, concentrated and spin-dried to give the target compound (85 mg, yield: 79%).

Step B:



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-cyclopropylethane-1,2-dione

Procedure:

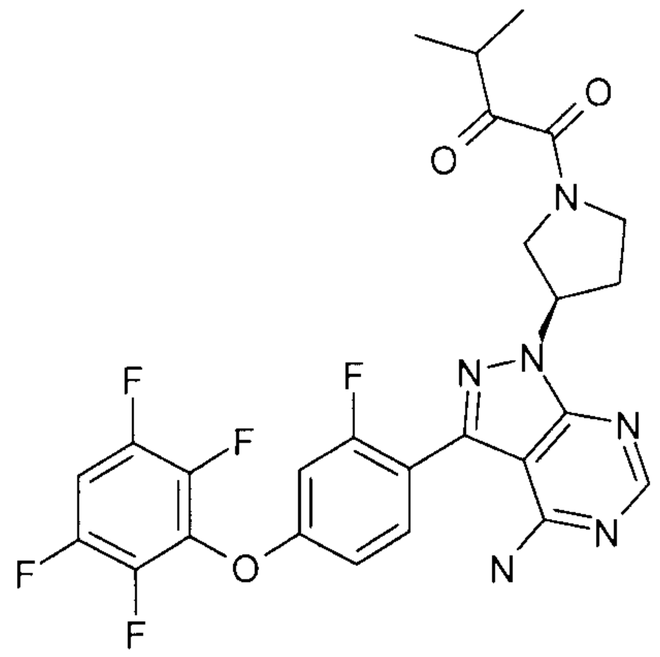
Potassium 2-cyclopropyl-2-oxo acetate (66 mg, 0.43 mmol, 2.0 eq.), DIPEA (84 mg, 0.65 mmol, 3.0 eq.) and PyBrop (12 mg, 0.24 mmol, 1.1 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.22 mmol, 1.0 eq.) in DMF (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/7‰ NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (53 mg, yield: 44%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.943 min; m/z = 559.1 $[M+H]^+$; Total running time: 7 min.

^1H NMR (400MHz, $CDCl_3$) δ 8.37-8.35 (m, 1H), 7.57 (t, J = 8.4 Hz, 1H), 7.10-7.05 (m, 1H), 6.95-6.89 (m, 2H), 5.60-5.54 (m, 1H), 4.21-3.88 (m, 3.5H), 3.80-3.72 (m, 0.5H), 2.73-2.48 (m, 3H), 1.25-1.05 (m, 4H).

Example 79



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-3-methylbutane-1,2-dione

Procedure:

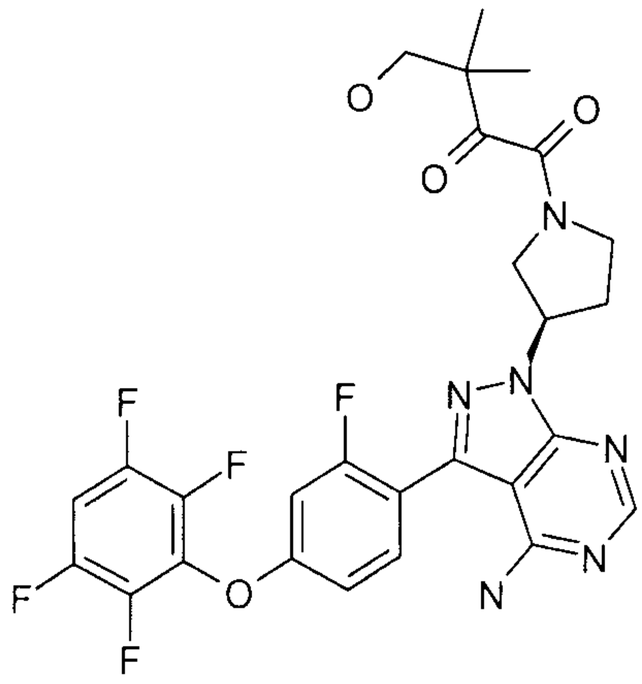
Sodium 3-methyl-2-oxo-butanoate(45 mg, 0.32 mmol, 1.5 eq.), DIPEA (84 mg, 0.65 mmol, 3.0 eq.) and PyBrop (100 mg， 0.22 mmol, 1.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.22 mmol, 1.0 eq.) in DMF (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/7‰ NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (51 mg, yield: 42%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 3.275 min; m/z = 561.0 $[M+H]^+$; Total running time: 7 min.

^1H NMR (400MHz, $CDCl_3$) δ 8.37-8.36 (m, 1H), 7.55-7.50 (m, 1H), 7.10-7.05 (m, 1H), 6.95-6.88 (m, 2H), 5.60-5.55 (m, 1H), 4.15-3.4 (m, 4H), 3.42-3.37 (m, 1H), 2.58-2.48 (m, 2H), 1.14-1.01 (m, 6H).

Example 80



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-4-hydroxy-3,3-dimethylbutane-1,2-dione

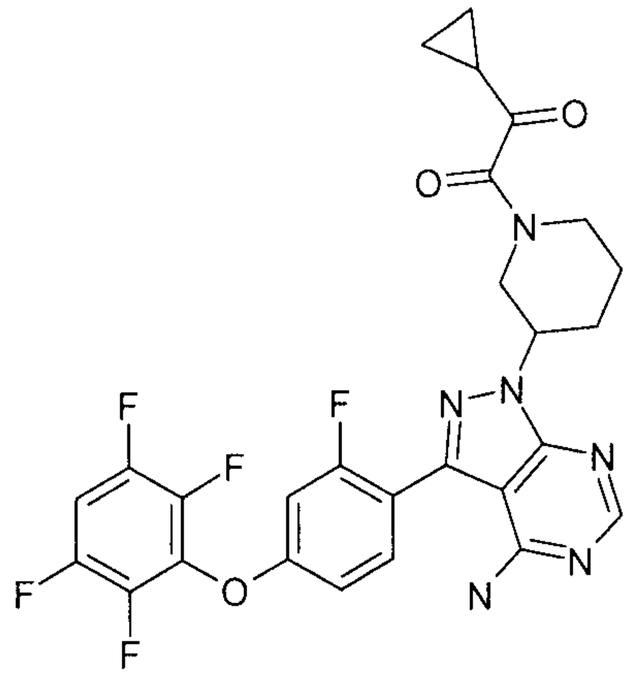
Procedure:

4,4-dimethyl-dihydrofuran-2,3-dione(15 mg, 0.12 mmol, 2.0 eq.) and DMAP (1.3 mg, 0.01 mmol, 0.1 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.11 mmol, 1.0 eq.) in tetrahydrofuran (3 mL). The reaction mixture was stirred at 70 °C for 3 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (0.8 mg, yield: 1.3%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 4.564min; m/z = 591.2 $[M+H]^+$; Total running time: 7min.

Example 81



1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-cyclopropylethane-1,2-dione

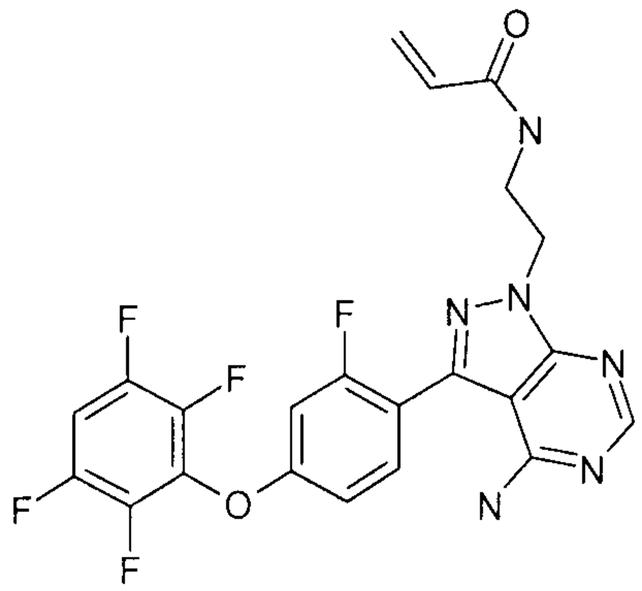
Procedure:

Potassium 2-cyclopropyl-2-oxo acetate (20 mg, 0.13 mmol, 1.1 eq.), DIPEA (51 mg, 0.39 mmol, 3.0 eq.) and PyBrop (56 mg, 0.12 mmol, 1.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.13 mmol, 1.0 eq.) in DMF (5 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 12 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.6‰NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (17 mg, yield: 6%).

Spectroscopy data:

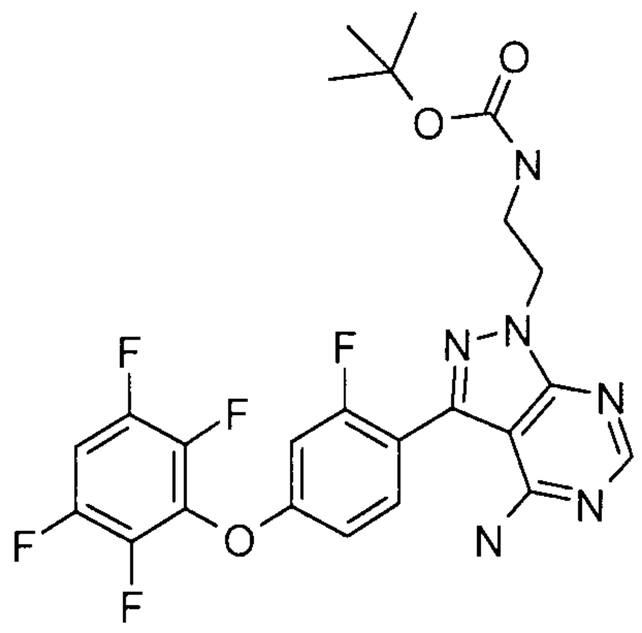
LC/MS (Method: UFLC): RT = 2.938 min; m/z = 573.5 $[M+H]^+$; Total running time: 7 min.

Example 82



N-(2-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)acrylamide

Step A:

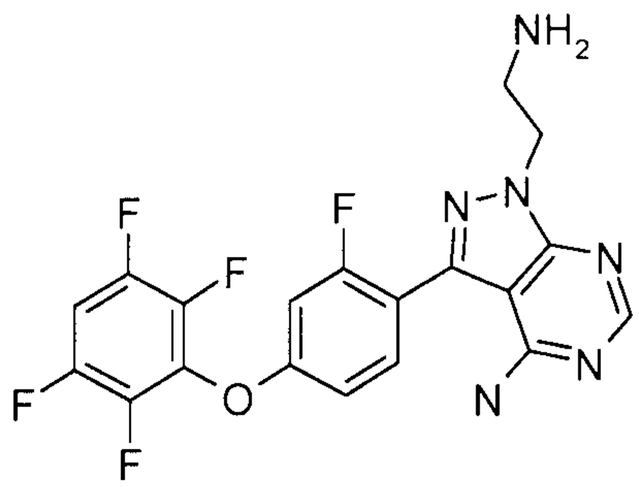


tert-butyl 2-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethylcarbamate

Procedure:

tert-butyl 2-bromoethylcarbamate (114 mg, 0.51 mmol, 2.0 eq.), potassium carbonate (70 mg, 0.51 mmol, 2.0 eq .) and sodium iodide (3.8 mg, 0.025 mmol, 0.1eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg , 0.25 mmol, 1.0 eq.) in DMF (2 mL). The reaction mixture was stirred at 80 °C for 14 hours and filtered. The filter cake was washed with ethyl acetate. The filtrate was concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: ethyl acetate) to give the target compound (50 mg, yield: 37%).

Step B:

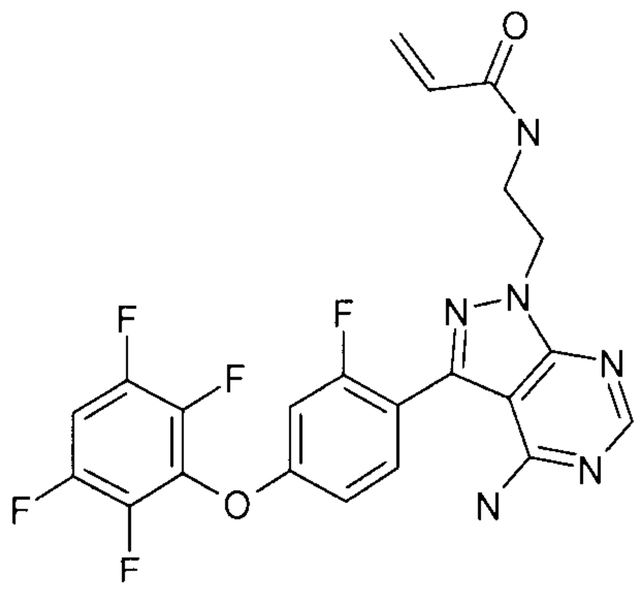


1-(2-aminoethyl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EA (2 mL) was added to a solution of tert-butyl 2-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethylcarbamate (50 mg, 0.093mmol) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (44 mg, yield:100%).

Step C:



N-(2-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)acrylamide

Procedure:

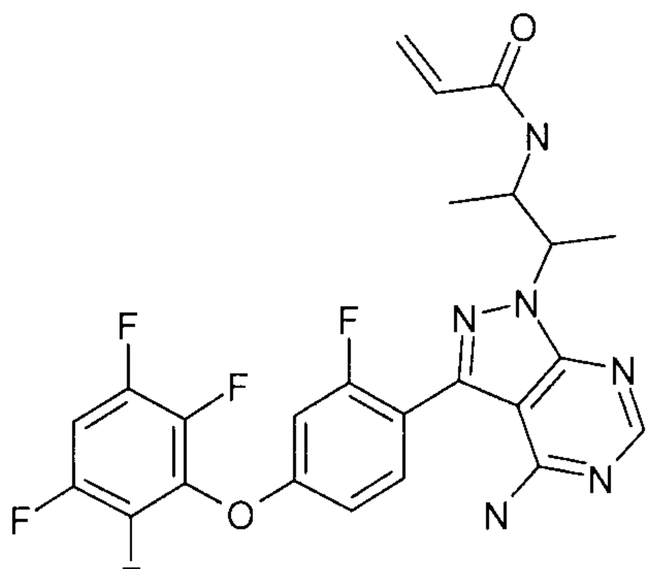
Triethylamine (28 mg, 0.28mmol, 3.0 eq.) and acryloyl chloride (8.4 mg, 0.093 mmol, 1.0 eq.) were subsequently added to a solution of 1-(2-aminoethyl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (44 mg, 0.093 mmol, 1.0 eq.) in dichloromethane (3 mL) at -15°C. The reaction mixture was stirred at -15 °C for 1 hour, and then quenched with water (5 mL) and separated. The aqueous phase was

extracted with dichloromethane (5 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (5 mg, yield: 11%).

Spectroscopy data:

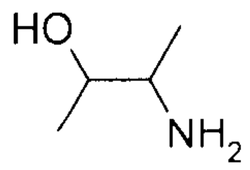
LC/MS (Method: UFLC): RT = 2.552 min; m/z = 491.0 $[M+H]^+$; Total running time: 7 min.

Example 83



N-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)butan-2-yl)acrylamide

Step A:

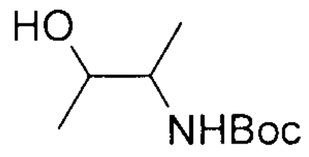


3-aminobutan-2-ol

Procedure:

Ammonium formate (10.8 g, 171.1 mmol, 6.8 eq.) and Pd/C (300 mg) were added to a solution of 3-nitrobutan-2-ol (3.0 g, 25.2 mmol, 1.0 eq.) in methanol (30 mL). The reaction mixture was stirred at room temperature for 18 hours and filtered through celite. The filtrate was concentrated and spin-dried to give compound the target compound (2.0 g, yield: 88%).

Step B:

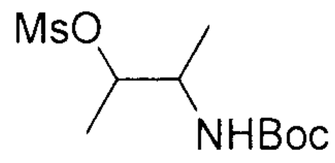


tert-butyl 3-hydroxybutan-2-ylcarbamate

Procedure:

Boc_2O (4.9 g, 22.5 mmol, 1.1 eq.) and triethylamine (4.54 g, 45.0 mmol, 2.0 eq.) were added to a solution of 3-aminobutan-2-ol (2.0 g, 22.5 mol, 1.0 eq.) in dichloromethane (20 mL). The reaction mixture was stirred at 20 °C for 16 hours and washed with water (20 mL) 2 times and brine (20 mL) 1 time. The organic phase was dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (600 mg, yield: 14%).

Step C:

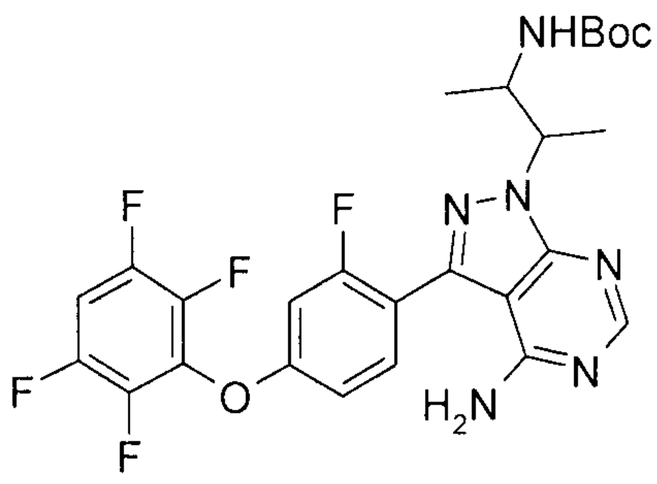


3-(tert-butoxycarbonyl)butan-2-yl methanesulfonate

Procedure:

Triethylamine (640 mg, 6.34 mmol, 2.0 eq.) and methanesulfonyl chloride (540 mg, 4.76 mmol, 1.5 eq.) were subsequently added to a solution of tert-butyl 3-hydroxybutan-2-ylcarbamate (600 mg, 3.17 mmol, 1.0 eq.) in dichloromethane (5 mL) at 0 °C. The reaction was stirred at 20 °C for 3 hours, quenched with saturated $NaHCO_3$ (20 mL), and then extracted with dichloromethane (20 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (500mg, yield: 59%).

Step D:



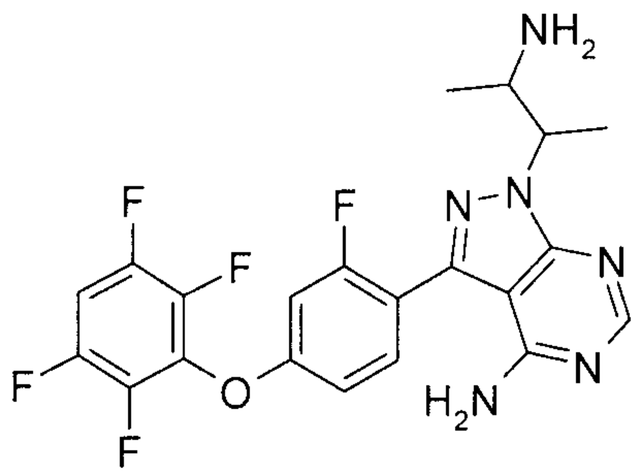
tert-butyl 3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-

d]pyrimidin-1-yl)butan-2-ylcarbamate

Procedure:

Cesium carbonate (165 mg, 0.51 mmol, 2.0 eq.) and 3-(tert-butoxycarbonyl)butan-2-yl methanesulfonate (136 mg, 0.51 mmol, 2.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine(100 mg, 0.25 mmol, 1.0 eq.) in DMF (2 mL). The reaction mixture was stirred at 85 °C for 3 hours, cooled to room temperature and filtered. The filter cake was washed with ethyl acetate. The filtrate was concentrated and spin-dried to give the crude product, which was purified by thin layer chromotagraphy (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (45 mg, yield: 31%).

Step E:

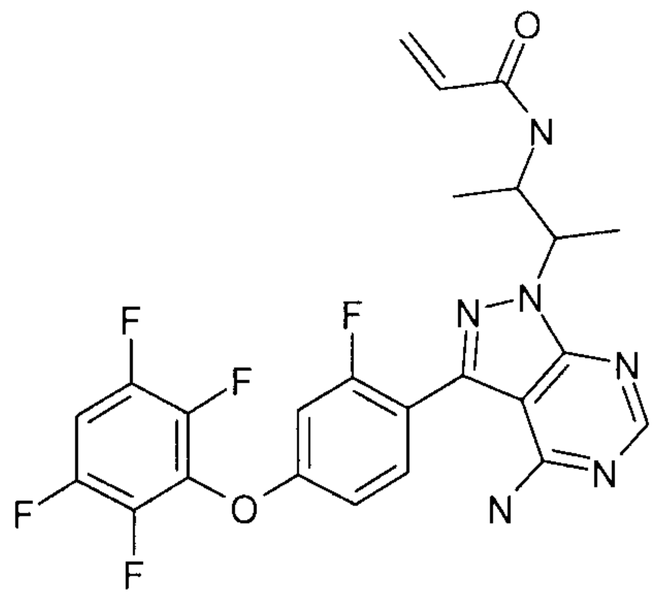


1-(3-aminobutan-2-yl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EA (5 mL) was added to a solution of tert-butyl 3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)butan-2-ylcarbamate (45 mg, 0.082 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (35 mg, yield: 85%).

Step F:



N-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)butan-2-yl)acrylamide

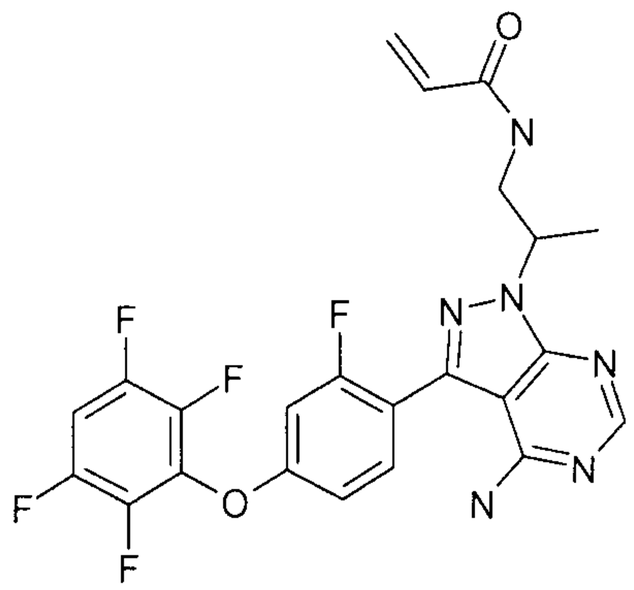
Procedure:

Triethylamine (15 mg, 0.15 mmol, 2.0 eq.) and acryloyl chloride (7 mg, 0.083 mmol, 1.1 eq.) were subsequently added dropwiseto a solution of 1-(3-aminobutan-2-yl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (35 mg, 0.075 mmol, 1.0 eq.) in dichloromethane (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for for 2 hour, and then quenched with water (5 mL). The aqueous phase was extracted with dichloromethane (5 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (3.0 mg, yield: 8%).

Spectroscopy data:

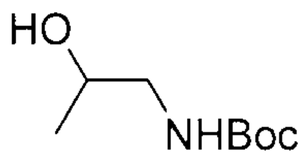
LC/MS (Method: UFLC): RT = 4.038 min; m/z = 519.1 $[M+H]^+$; Total running time: 7 min.

Example 84



N-(2-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)acrylamide

Step A:

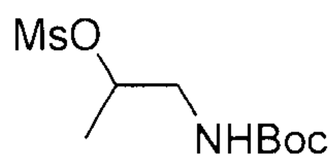


tert-butyl 2-hydroxypropylcarbamate

Procedure:

Boc_2O (29 g, 0.13 mol, 1.0 eq.) and triethylamine (37 mL, 0.27 mol, 2.0 eq.) were added to a solution of 1-amino-propan-2-ol (10 g, 0.13 mol, 1.0 eq.) in dichloromethane (200 mL). The reaction mixture was stirred at 20 °C for 16 hours and washed with water (100 mL) 2 times and brine (100 mL) 1 time. The organic phase was dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (20 g, yield: 87%).

Step B:

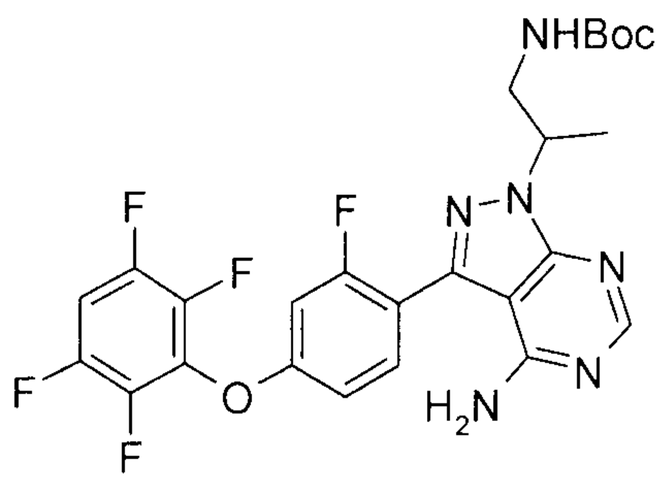


1-(tert-butoxycarbonyl)propan-2-yl methanesulfonate

Procedure:

Triethylamine (1.15 g, 11.4 mmol, 2.0 eq.) and methanesulfonyl chloride (0.98 g, 8.6 mmol, 1.5 eq.) were subsequently added to a solution of tert-butyl 2-hydroxypropylcarbamate (1.0 g, 5.7 mmol, 1.0 eq.) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 3 hours, quenched with saturated $NaHCO_3$ (20 mL) and separated. The aqueous phase was extracted with dichloromethane (10 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (0.8 g, yield: 69%).

Step C:

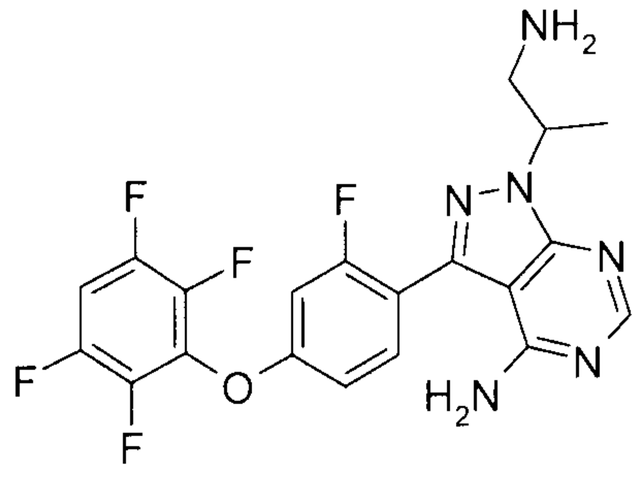


tert-butyl 2-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propylcarbamate

Procedure:

Cesium carbonate (165 mg, 0.51 mmol, 2.0 eq.) and 1-(tert-butoxycarbonyl)propan-2-yl methanesulfonate (128 mg, 0.51 mmol, 2.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.25 mmol, 1.0 eq.) in DMF (2 mL). The reaction mixture was stirred at 85 °C for 3 hours, cooled to room temperature and filtered. The filter cake was washed with ethyl acetate. The filtrate was concentrated and spin-dried to give the crude product, which was purified by silica gel column chromotagraphy (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (30 mg, yield: 21%).

Step D:

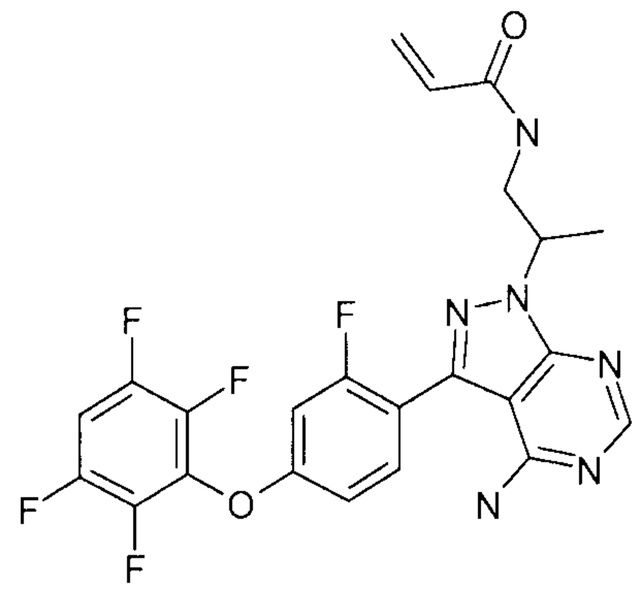


1-(1-aminopropan-2-yl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EA (5 mL) was added to a solution of tert-butyl 2-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propylcarbamate (30 mg, 0.054 mmol) in ethyl acetate (5 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (20 mg, yield:77%).

Step E:



N-(2-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)acrylamide

Procedure:

Triethylamine (8.4mg, 0.084mmol, 2.0 eq.) and acrylic anhydride (6.3mg, 0.05 mmol, 1.2 eq.) were subsequently added dropwiseto a solution of 1-(1-aminopropan-2-yl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20mg, 0.042 mmol, 1.0 eq.) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 hour, and then quenched with water (5 mL), and extracted with dichloromethane

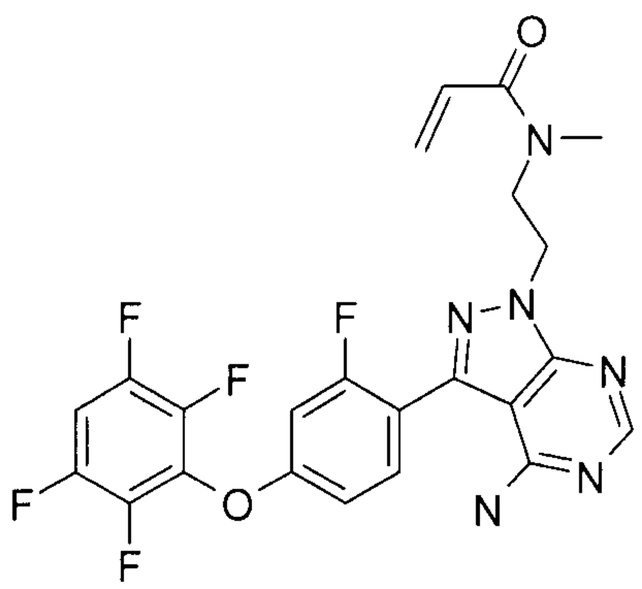
(5 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (5.0 mg, yield: 24%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 3.912 min; m/z = 505.0 $[M+H]^+$; Total running time: 7 min.

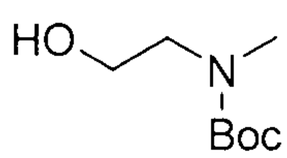
^{1}H NMR (400MHz, CD_3OD) δ 8.34 (s, 1H), 7.74 (t, J = 8.4 Hz, 1H), 7.55-7.48 (m, 1H), 7.13-7.06 (m, 2H), 6.10-6.08 (m, 2H), 5.60-5.57 (m, 1H), 5.27-5.24 (m, 1H), 3.82-3.73 (m, 2H), 1.66-1.64 (m, 3H).

Example 85



N-(2-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-N-methylacrylamide

Step A:



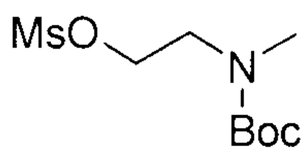
tert-butyl 2-hydroxyethyl(methyl)carbamate

Procedure:

Boc_2O (8.0 g, 36.6 mmol, 1.1 eq.) and triethylamine (6.75 g, 66.5 mmol, 2.0 eq.) were added to a solution of 2-(methylamino)ethanol (2.5 g, 33.3 mol, 1.0 eq.) in dichloromethane (50 mL). The reaction mixture was stirred at 20 °C for 16 hours and washed with water

(30 mL) 2 times and brine (30 mL) 1 time. The organic phase was dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (5.8 g, yield: 100%).

Step B:

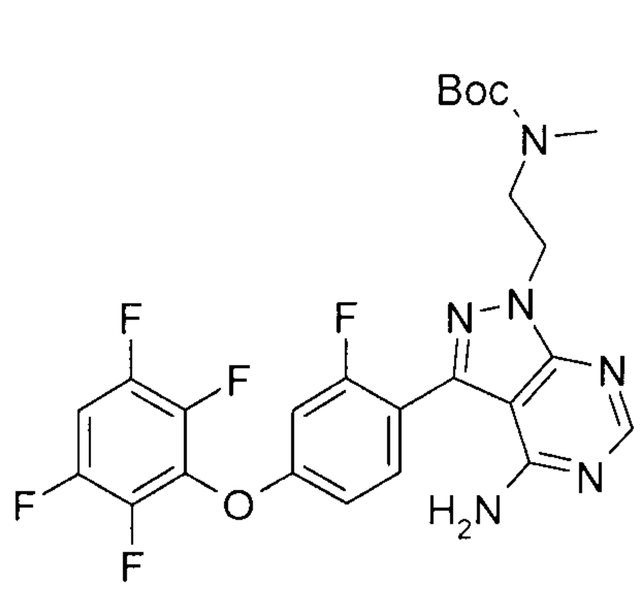


2-(tert-butoxycarbonyl)ethyl methanesulfonate

Procedure:

Triethylamine (2.31 g, 22.8 mmol, 2.0 eq.) and methanesulfonyl chloride (1.96 g, 17.7 mmol, 1.5 eq.) were subsequently added to a solution of tert-butyl 2-hydroxyethyl(methyl)carbamate (2.0 g, 11.4 mmol, 1.0 eq.) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 3 hours, quenched with saturated $NaHCO_3$ (20 mL) and separated. The aqueous phase was extracted with dichloromethane (20 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (2.8 g, yield: 100%).

Step C:



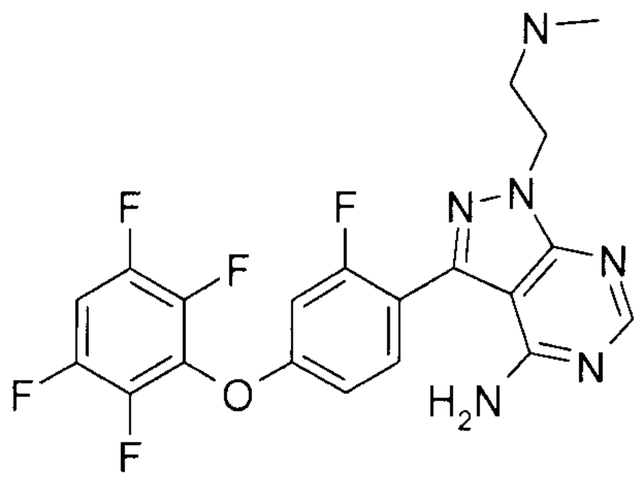
tert-butyl 2-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl(methyl)carbamate

Procedure:

Cesium carbonate (116 mg, 0.36 mmol, 2.0 eq.) and 2-(tert-butoxycarbonyl)ethyl methanesulfonate (90 mg, 0.36 mmol, 2.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (70 mg, 0.18 mmol, 1.0 eq.) in DMF (2 mL). The reaction mixture was stirred at 85 °C for 3 hours,

cooled to room temperature and filtered. The filter cake was washed with ethyl acetate. The filtrate was concentrated and spin-dried to give the crude product, which was purified by thin layer chromotagraphy (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (50 mg, yield: 52%).

Step D:

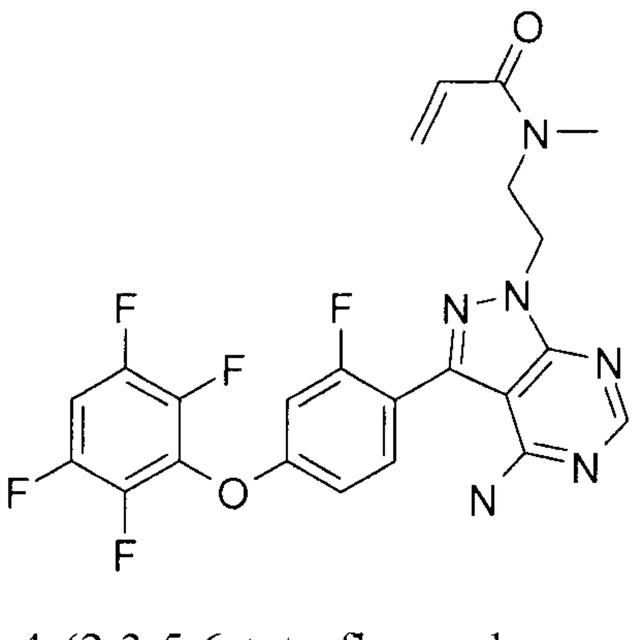


3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(2-(methylamino)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EA (5 mL) was added to a solution of tert-butyl 2-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl(methyl)carbamate (50 mg, 0.092 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (44 mg, yield: 100%).

Step E:



N-(2-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-N-methylacrylamide

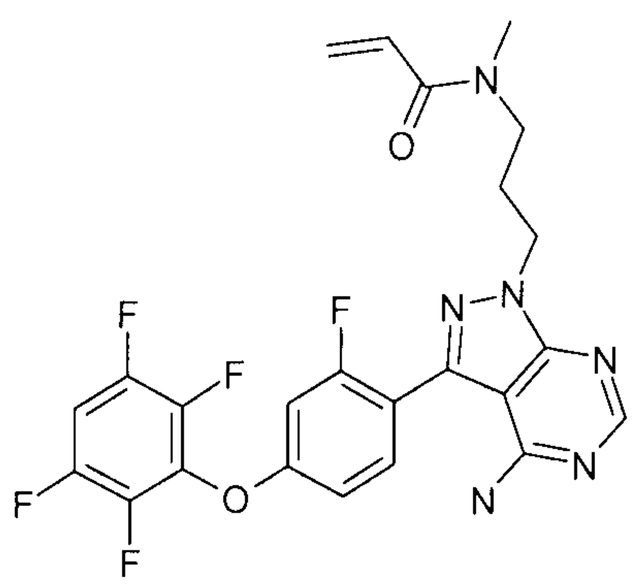
Procedure:

Triethylamine (28 mg, 0.28 mmol, 3.0 eq.) and acryloyl chloride (17 mg, 0.092 mmol, 1.0 eq.) were subsequently added dropwiseto a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(2-(methylamino)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.092 mmol, 1.0 eq.) in dichloromethane (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 hour, and then quenched with water (5 mL), extracted with dichloromethane (5 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (7.7 mg, yield: 16%).

Spectroscopy data:

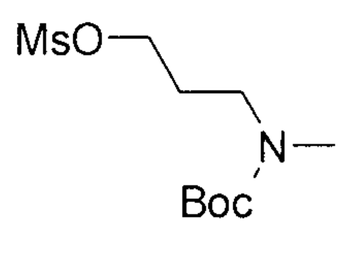
LC/MS (Method: UFLC): RT = 3.872 min; m/z = 505.0 $[M+H]^+$; Total running time: 7 min.

Example 86



N-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-N-methylacrylamide

Step A:

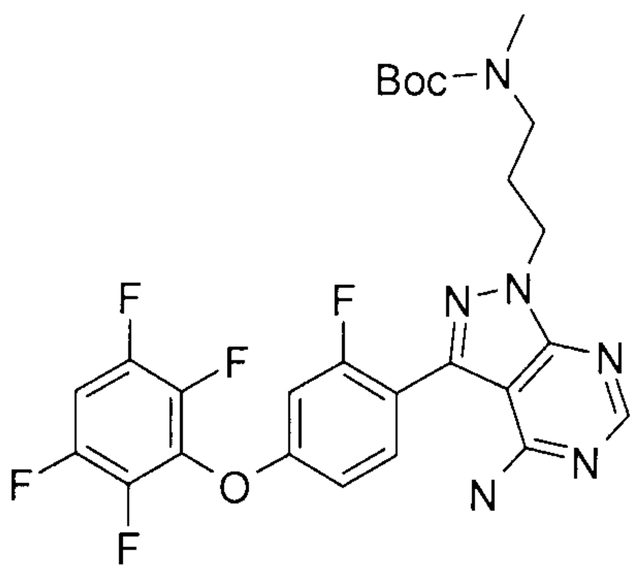


3-((tert-butoxycarbonyl)(methyl)amino)propyl methanesulfonate

Procedure:

Triethylamine (2.88 g, 28.5 mmol, 2.0 eq.) and methanesulfonyl chloride (1.64 g, 14.3 mmol, 1.0 eq.) were subsequently added to a solution of tert-butyl 3-hydroxypropyl(methyl)carbamate (1.8 g, 14.3 mmol, 1.0 eq.) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 3 hours, quenched with saturated $NaHCO_3$ (20 mL) and separated. The aqueous phase was extracted with dichloromethane (20 mL) 2 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (3.8 g, yield: 100%).

Step B:

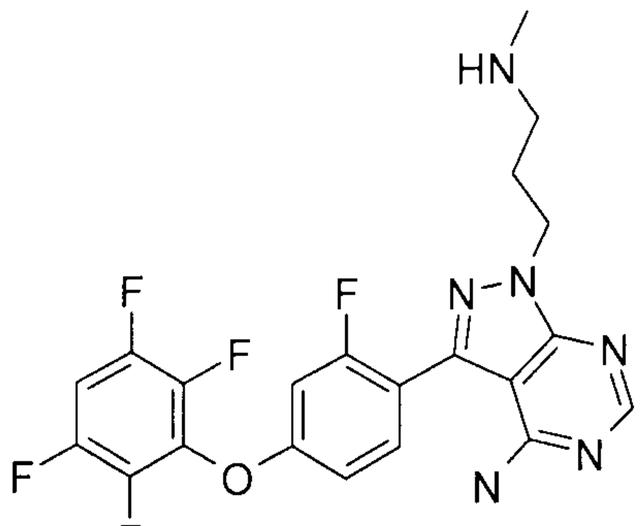


tert-butyl 3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl(methyl)carbamate

Procedure:

Cesium carbonate (331 mg, 1.02 mmol, 2.0 eq.) and 3-(tert-butoxycarbonyl)propyl methanesulfonate (272 mg, 1.02 mmol, 2.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine(200 mg, 0.51 mmol, 1.0 eq.) in DMF (2 mL). The reaction mixture was stirred at 85 °C for 3 hours, cooled to room temperature and filtered. The filter cake was washed with ethyl acetate. The filtrate was concentrated and spin-dried to give the crude product, which was purified by thin layer chromotagraphy (eluent: petroleum ether: ethyl acetate=1:1) to give the target compound (58 mg, yield: 20%).

Step C:

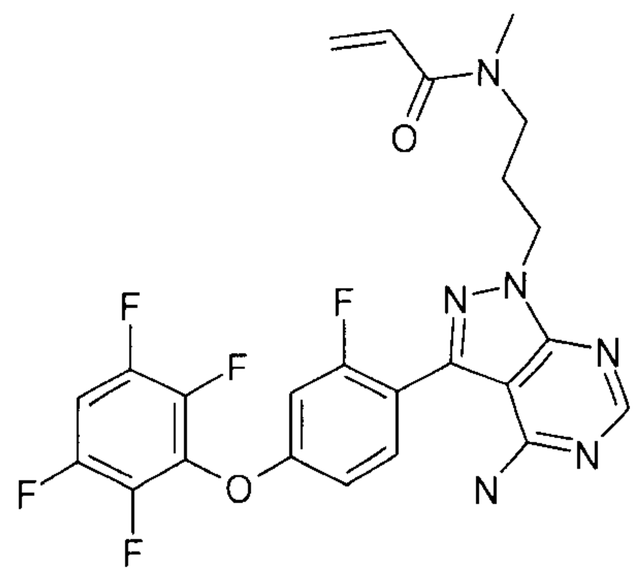


3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(3-(methylamino)propyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EA (5 mL) was added to a solution of tert-butyl 3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl(methyl)carbamate (50 mg, 0.089 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (45 mg, yield: 100%).

Step D:



N-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)propyl)-N-methylacrylamide

Procedure:

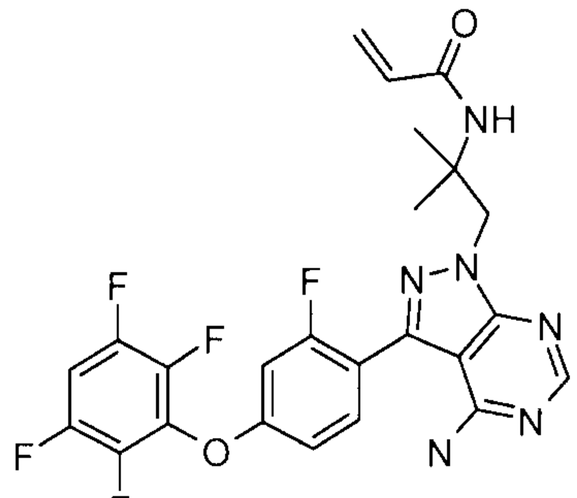
Triethylamine (27 mg, 0.27 mmol, 3.0 eq.) and acryloyl chloride (8 mg, 0.089 mmol, 1.0 eq.) were subsequently added dropwiseto a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(3-(methylamino)propyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

(45 mg, 0.089 mmol, 1.0 eq.) in dichloromethane (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours, and then quenched with water (5 mL), extracted with dichloromethane (5 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound hydrochloride (2.3 mg, yield: 5%).

Spectroscopy data:

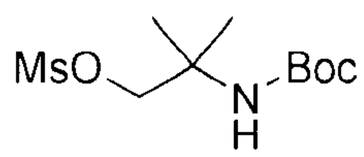
LC/MS (Method: UFLC): RT = 4.010 min; m/z = 519.2 $[M+H]^+$; Total running time: 7 min.

Example 87



N-(1-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-methylpropan-2-yl)acrylamide

Step A:



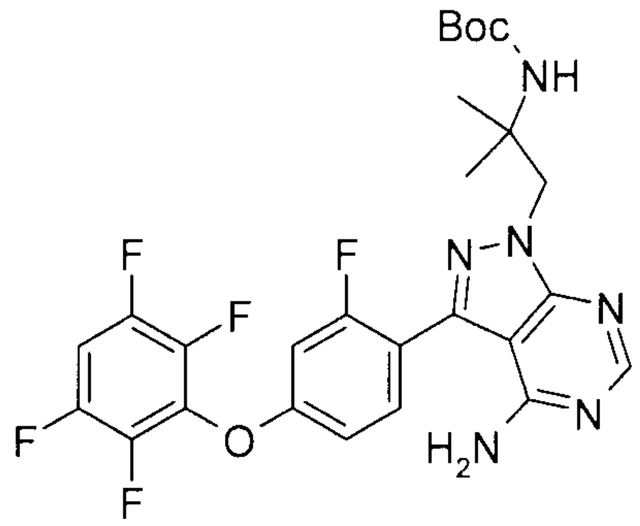
2-(tert-butoxycarbonyl)-2-methylpropyl methanesulfonate

Procedure:

Triethylamine (1.60 g, 15.9 mmol, 3.0 eq.) and methanesulfonyl chloride (908 mg, 7.93 mmol, 1.5 eq.) were subsequently added to a solution of tert-butyl 1-hydroxy-2-methylpropan-2-yl-carbamate (1.0 g, 5.28 mmol, 1.0 eq.) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 16 hours, quenched with saturated $NaHCO_3$ (20 mL), separated and then extracted with dichloromethane (20 mL) 2 times. The combined organic phases were dried over

anhydrous sodium sulfate, concentrated and spin-dried to give the target compound (0.4 g, yield: 28%).

Step B:

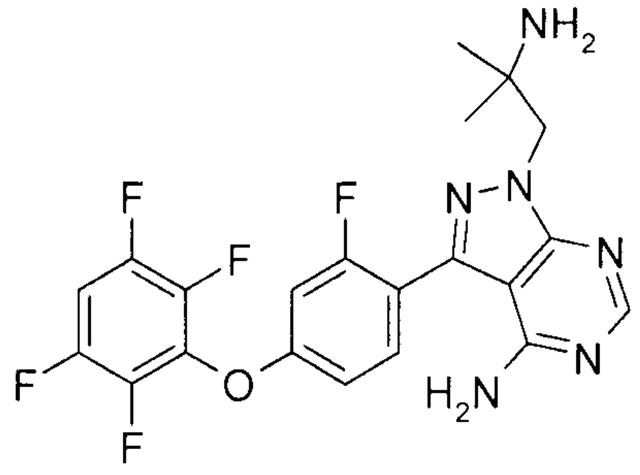


tert-butyl 1-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-methylpropan-2-ylcarbamate

Procedure:

Cesium carbonate (249 mg, 0.76 mmol, 2.0 eq.) and 2-(tert-butoxycarbonyl)-2-methylpropyl methanesulfonate (272 mg, 1.02 mmol, 2.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine(150 mg, 0.38 mmol, 1.0 eq.) in DMF (2 mL). The reaction mixture was stirred at 85°C for 3 hours, cooled to room temperature and filtered. The filter cake was washed with ethyl acetate. The filtrate was concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (50 mg, yield: 23%).

Step C:



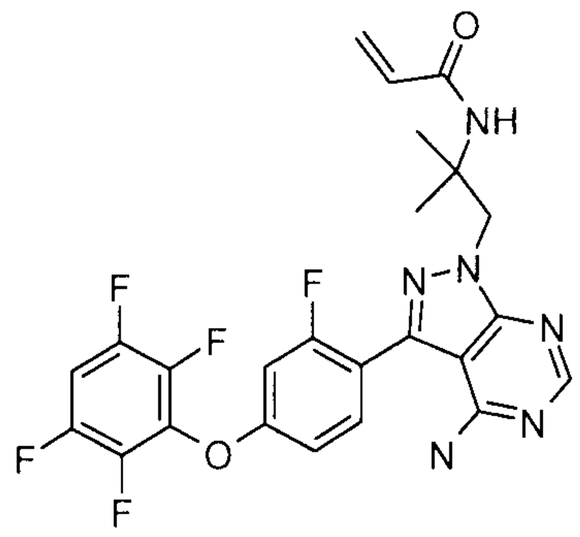
1-(2-amino-2-methylpropyl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-

d]pyrimidin-4-amine

Procedure:

4M HCl/EA (5 mL) was added to a solution of tert-butyl 1-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-methylpropan-2-ylcarbamate (20 mg, 0.035 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (18 mg, yield: 100%).

Step D:



N-(1-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-2-methylpropan-2-yl)acrylamide

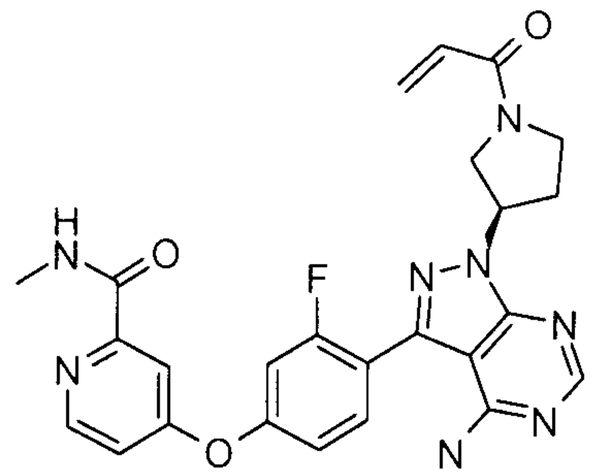
Procedure:

Triethylamine (12 mg, 0.12 mmol, 3.0 eq.) and acryloyl chloride (3.6 mg, 0.043 mmol, 1.0 eq.) were subsequently added dropwiseto a solution of 1-(2-amino-2-methylpropyl)-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.043 mmol, 1.0 eq.) in dichloromethane (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours, and then quenched with water (5 mL), extracted with dichloromethane (5 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound hydrochloride (0.8 mg, yield: 3.6%).

Spectroscopy data:

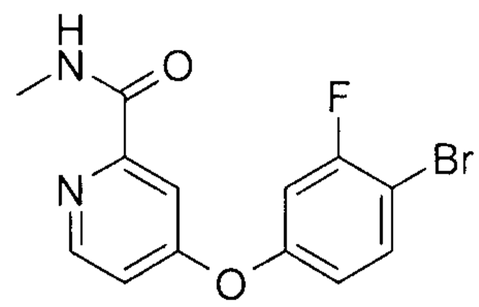
LC/MS (Method: UFLC): RT = 0.492 min; m/z = 519.1 $[M+H]^+$; Total running time: 1.5 min.

Example 88



4-(4-(1-((R)-1-acryloylpyrrolidin-3-yl)-4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenoxy)-N-methylpicolinamide

Step A:

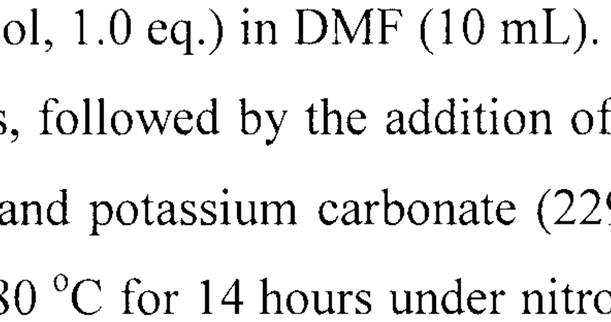


4-(3-fluoro-4-bromophenoxy)-N-methylpicolinamide

Procedure:

Potassium tert-butoxide (177 mg, 1.58 mmol, 1.0 eq.) was added to a solution of 4-bromo-3-fluorophenol (300 mg, 1.58 mmol, 1.0 eq.) in DMF (10 mL). The reaction mixture was stirred at room temperature for 2 hours, followed by the addition of 4-chloro-N-methylpicolinamide (282 mg, 1.66 mmol, 1.05 eq.) and potassium carbonate (229 mg, 1.66 mmol, 1.05 eq.). The reaction mixture was stirred at 80 °C for 14 hours under nitrogen atmosphere, cooled to room temperature and filtered. The filter cake was washed with ethyl acetate. The filtrate was concentrated and spin-dried to give the crude product by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (95 mg, yield: 19%).

Step B:



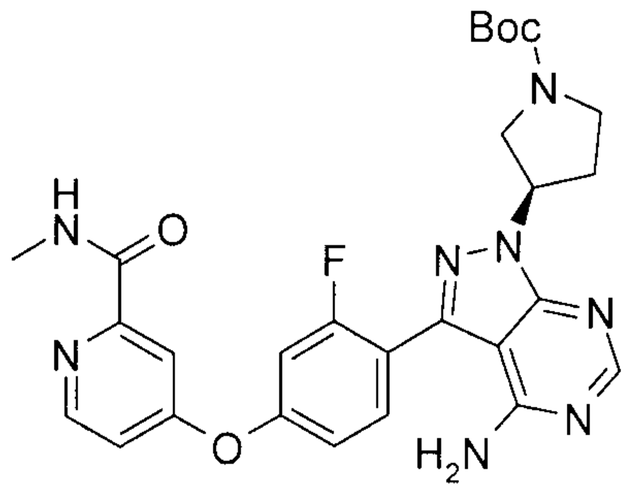
241

4-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-N-methylpicolinamide

Procedure:

4-(4-bromo-3-fluorophenoxy)-N-methylpyridine amide (95 mg, 0.29 mmol, 1.0 eq.), bis(pinacolato)diboron (88 mg, 0.35 mmol, 1.2 eq.), potassium acetate (86 mg, 0.87 mmol, 3.0 eq.) and (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium (13 mg, 0.017 mmol, 0.06 eq.) were dissolved in 1,4-dioxane (10 mL), and stirred for 12 hours at 80 °C under nitrogen atmosphere. The reaction mixture was filtered through celite. The filtrate was concentrated and spin-dried to give the crude product (100 mg, yield: 93%), which was used directly in the next step.

Step C:

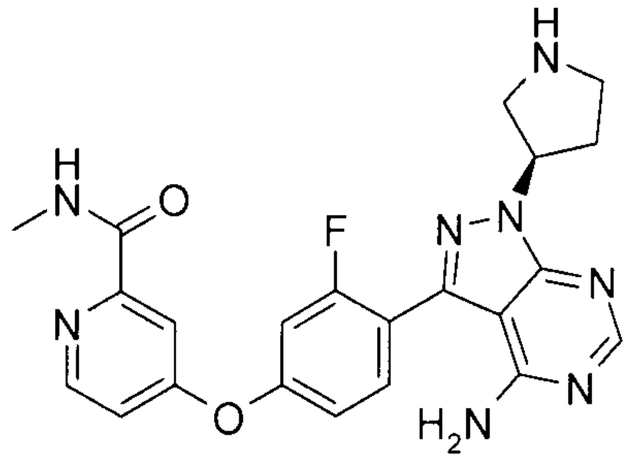


(3R)-tert-butyl 3-(4-amino-3-(2-fluoro-4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate

Procedure:

(R)-tert-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate (52 mg, 0.12 mmol, 1.0 eq.), 4-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-N-methylpicolinamide (45 mg, 0.12 mmol, 1.0 eq.), potassium phosphate (51 mg, 0.24 mmol, 2.0 eq.) and Pd-118 (8 mg, 0.012 mmol, 0.1 eq.) were dissolved in 1,4-dioxane/water (4 mL, 3/1, v/v). The reaction mixture was stirred at 80 °C for 40 min. under nitrogen atmosphere with microwave irradiation. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: ethyl acetate) to give the target compound (15 mg, yield: 24%).

Step D:

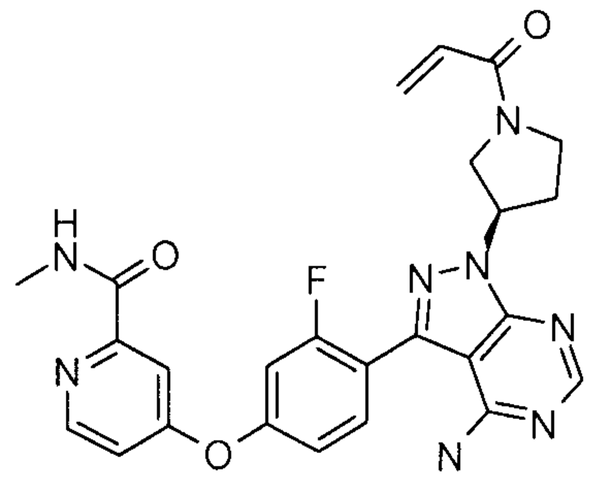


4-(4-(4-amino-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenoxy)-N-methylpicolinamide

Procedure:

4M HCl/EA (5 mL) was added to a solution of (3R)-tert-butyl 3-(4-amino-3-(2-fluoro-4-(2-(methylcarbamoyl)pyridin-4-yloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate (15 mg, 0.028 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (10 mg, yield: 81%).

Step E:



4-(4-(1-((R)-1-acryloylpyrrolidin-3-yl)-4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenoxy)-N-methylpicolinamide

Procedure:

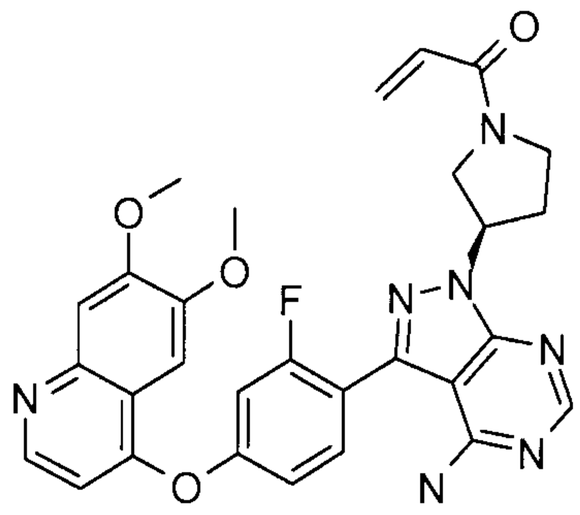
NaOH solution (2N, 0.4 mL) and acryloyl chloride (1.9 mg, 0.021 mmol, 1.0 eq.) were subsequently added dropwiseto a solution of 4-(4-(4-amino-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-fluorophenoxy)-N-methylpicolinamide (10 mg, 0.021 mmol, 1.0 eq.) in tetrahydrofuran (1 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours, and then quenched with water (5 mL), extracted with dichloromethane (5 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-

dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (6 mg, yield: 60%).

Spectroscopy data:

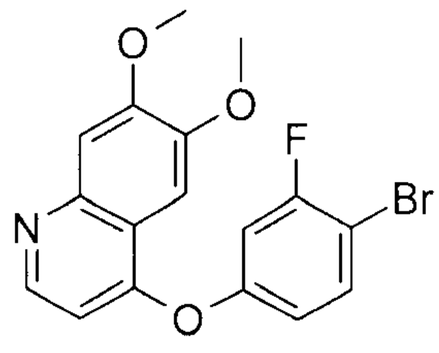
LC/MS (Method: UFLC): RT = 2.445 min; m/z = 489.1 $[M+H]^+$; Total running time: 7 min.

Example 89



1-((R)-3-(4-amino-3-(4-(6,7-dimethoxyquinolin-4-yloxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Step A:



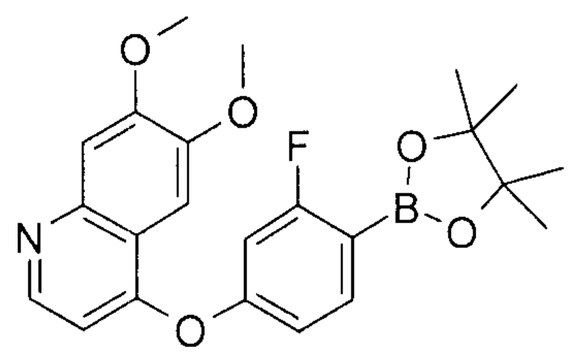
4-(4-bromo-3-fluorophenoxy)-6,7-dimethoxyquinoline

Procedure:

A solution of potassium tert-butoxide in THF (1N, 1.24 mL, 1.24 mmol, 1.05 eq.) was added to a solution of 3-fluoro-4-bromophenol (225 mg, 1.18 mmol, 1.0 eq.) in DMF (2 mL). The reaction mixture was stirred at 0 °C for 2 hours, followed by the addition of 4-chloro-6,7-dimethoxyquinoline (264 mg, 1.18 mmol, 1.0 eq.) and potassium carbonate (81 mg, 0.59 mmol,

0.5 eq.). The reaction mixture was stirred at 80 °C for 14 hours under nitrogen atmosphere, cooled to room temperature and filtered. The filter cake was washed with ethyl acetate. The filtrate was concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (100 mg, yield: 24%).

Step B:

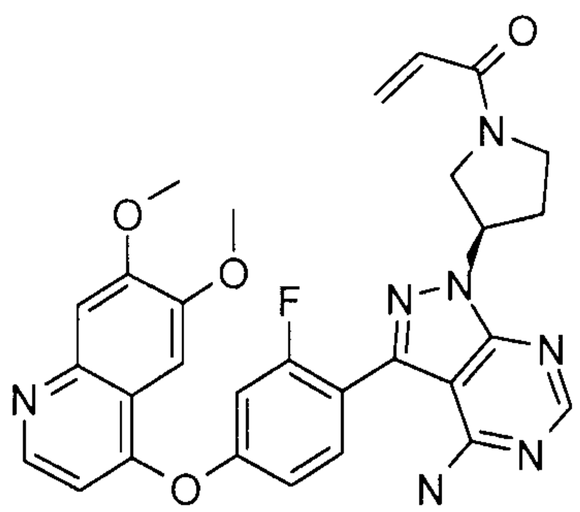


4-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-6,7-dimethoxyquinoline

Procedure:

4-(4-bromo-3-fluorophenoxy)-6,7-dimethoxyquinoline (100 mg, 0.26 mmol, 1.0 eq.), bis(pinacolato)diboron (101 mg, 0.39 mmol, 1.5 eq.), potassium acetate (78 mg, 0.79 mmol, 3.0 eq.) and (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium (25 mg, 0.026 mmol, 0.1 eq.) were dissolved in 1,4-dioxane (2 mL), and stirred at 85 °C for 12 hours under nitrogen atmosphere. The reaction mixture was filtered through celite. The filtrate was concentrated to give the crude product (110 mg, yield: 100%), which was used directly in the next step.

Step C:



1-((R)-3-(4-amino-3-(4-(6,7-dimethoxyquinolin-4-yloxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Procedure:

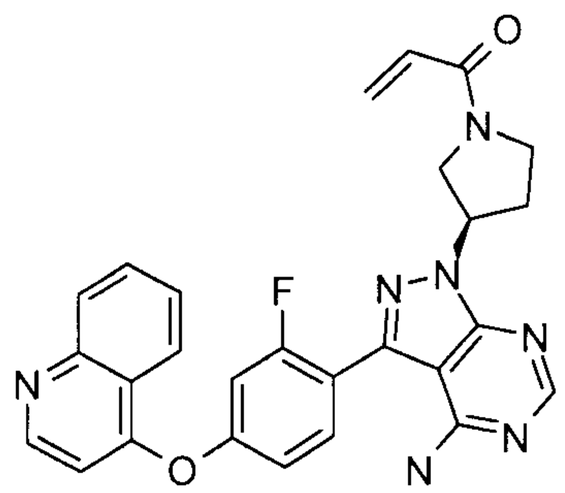
(R)-1-(3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one (100 mg, 0.26 mmol, 1.0 eq.), 4-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-6,7-dimethoxyquinoline (145 mg, 0.39 mmol, 1.5 eq), sodium carbonate (83 mg, 0.78 mmol, 3.0 eq) and $Pd(PPh_3)_4$ (30 mg, 0.026 mmol, 0.1 eq.) were dissolved in 1,4-dioxane/water (10 mL, 1/1, v/v). The reaction mixture was stirred at 85 °C for 30 min. under nitrogen atmosphere with microwave irradiation. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC reversed-phase column with mobile phase in C18: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (20 mg, yield: 12%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.717 min; m/z = 556.1 $[M+H]^+$; Total running time: 7 min.

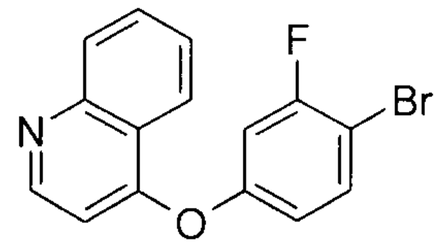
^1H NMR (400MHz, CD_3OD) δ 8.79 (br, 1H), 8.51 (s, 1H), 7.92-7.86 (m, 2H), 7.57-7.47 (m, 3H), 7.29 (br,1H), 6.74-6.60 (m, 1H), 6.34-6.29 (m, 1H), 5.82-5.76 (m, 2H), 4.27-4.23 (m, 0.5H), 4.15-4.10 (m, 8H), 3.97-3.82 (m, 1.5H), 2.67-2.59 (m, 2H).

Example 90



1-((R)-3-(4-amino-3-(2-fluoro-4-(quinolin-4-yloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Step A:

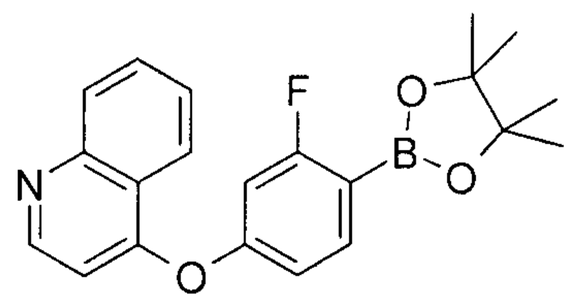


4-(4-bromo-3-fluorophenoxy)quinoline

Procedure:

4-chloro-quinoline (440 mg, 2.7 mmol, 1.0 eq.) was added to a solution of 3-fluoro-4-bromophenol (2.04 g, 10.8 mmol, 4.0 eq.) in chlorobenzene (5 mL). The reaction mixture was stirred at 100 °C for 12 hours and then sodium hydroxide solution (1 N, 10 mL) was added. The resulting mixture was extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, the filtrate was concentrated and spin-dried to give the crude product (800 mg, yield: 93%), which was used directly in the next step.

Step B:

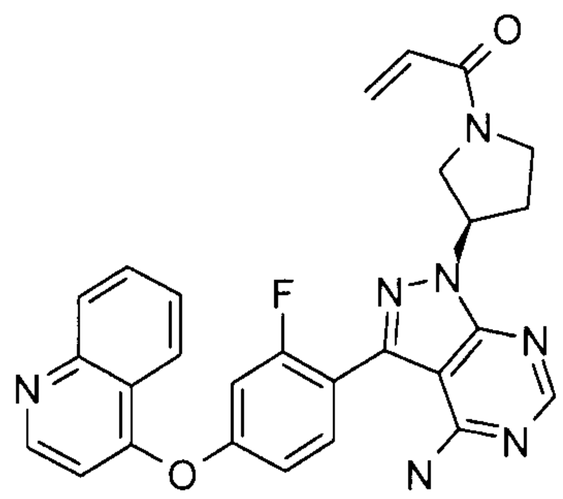


4-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)quinoline

Procedure:

4-(4-bromo-3-fluorophenoxy)quinoline (400 mg, 1.26 mmol, 1.0 eq.), bis(pinacolato)diboron (480 mg, 1.89 mmol, 1.5 eq.), potassium acetate (370 mg, 3.78 mmol, 3.0 eq.) and (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium (117 mg, 0.126 mmol, 0.1 eq.) were dissolved in 1,4-dioxane (4 mL), and stirred at 85 °C for 12 hours under nitrogen atmosphere. The reaction mixture was filtered through celite. The filtrate was concentrated and spin-dried to give the crude product (450 mg, yield: 98%), which was used directly in the next step.

Step C:



1-((R)-3-(4-amino-3-(2-fluoro-4-(quinolin-4-yloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Procedure:

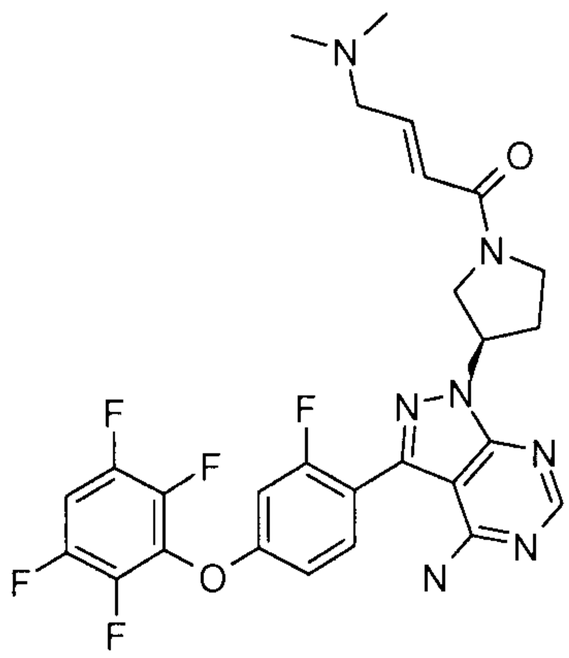
(R)-1-(3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one (100 mg, 0.26 mmol, 1.0 eq.), 4-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)quinoline (142 mg, 0.39 mmol, 1.5 eq), sodium carbonate (83 mg, 0.78 mmol, 3.0 eq) and $Pd(PPh_3)_4$ (30 mg, 0.026 mmol, 0.1 eq.) were dissolved in 1,4-dioxane/water (10 mL, 1/1, v/v). The reaction mixture was stirred at 85 °C for 40 min. under nitrogen atmosphere with microwave irradiation. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)) to give the hydrochloride of the target compound (15 mg, yield: 10%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.586 min; m/z = 496.1 $[M+H]^+$; Total running time: 7 min.

^1H NMR (400MHz, CD_3OD) δ 9.08 (d, J = 6.8 Hz, 1H), 8.72 (d, J = 8.4 Hz, 1H), 8.49 (s, 1H), 8.26-8.20 (m, 2H), 8.06 (br, 1H), 7.91 (d, J = 6.8 Hz, 1H), 7.56-7.44 (m, 3H), 6.71-6.57 (m, 1H), 6.31-6.27 (m, 1H), 5.80-5.74 (m, 2H), 4.27-3.92 (m, 4H), 2.70-2.55 (m, 2H).

Example 91



(E)-1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-4-(dimethylamino)but-2-en-1-one

Procedure:

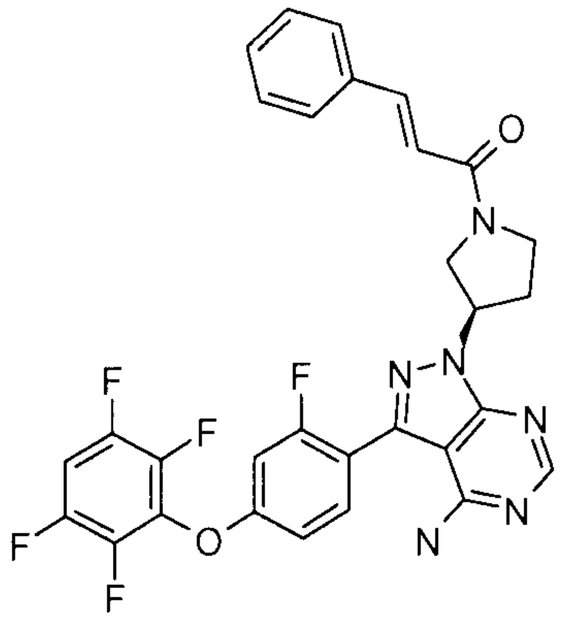
(E)-4-(dimethylamino)but-2-enoic acid hydrochloride (23 mg, 0.14 mmol, 1.1 eq.), DIPEA (50 mg, 0.39 mmol, 3.0 eq.) and HATU (54 mg, 0.14 mmol, 1.1 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.13 mmol, 1.0 eq.) in dichloromethane (3 mL). The reaction mixture was stirred at room temperature for 12 hours, and concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (29 mg, yield: 40%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 3.625 min; m/z = 574.1 $[M+H]^+$; Total running time: 7 min.

^{1}H NMR (400MHz, DMSO-d_6) δ 11.24 (br, 1H), 8.57 (s, 1H), 8.02-7.95 (m, 1H), 8.62 (t, J = 8.4 Hz, 1H), 7.33 (dd, J = 2.0, 10.8 Hz, 1H), 7.33 (dd, J = 2.0, 8.4 Hz, 1H), 6.76-6.68 (m, 2H), 5.65-5.56 (m, 1H), 4.22-4.16 (m, 0.5H), 4.04-3.87 (m, 4.5H), 3.69-3.58 (m, 1H), 2.71-2.68 (m, 6H), 2.54-2.37 (m, 2H).

Example 92



(E)-1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-3-phenylprop-2-en-1-one

Procedure:

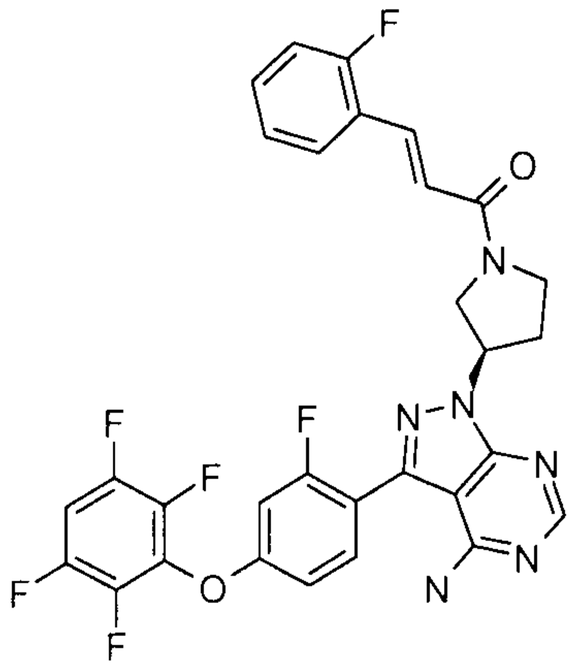
(E)-3-phenyl-2-acryloyl chloride (19.7 mg, 0.12 mmol, 1.1 eq.) and triethylaimne (22 mg, 0.22 mmol, 2.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.11 mmol, 1.0 eq.) in dichloromethane (3 mL). The reaction mixture was stirred at room temperature for 2 hours, quenched with water (5 mL) and extracted with dichloromethane (5 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5%HCl, gradient 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (16 mg, yield: 25%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 4.371 min; m/z = 593.1 $[M+H]^+$; Total running time: 7 min.

^1H NMR (400MHz, CD_3OD) δ 8.46 (s, 1H), 7.68-7.60 (m, 4H), 7.55-7.37 (m, 4H), 7.09-6.92 (m, 3H), 5.81-5.71 (m, 1H), 4.33-4.31 (m, 0.8H), 4.19-3.82 (m, 3.2H), 2.73-2.56 (m, 2H).

Example 93



(E)-1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-3-(2-fluorophenyl)prop-2-en-1-one

Procedure:

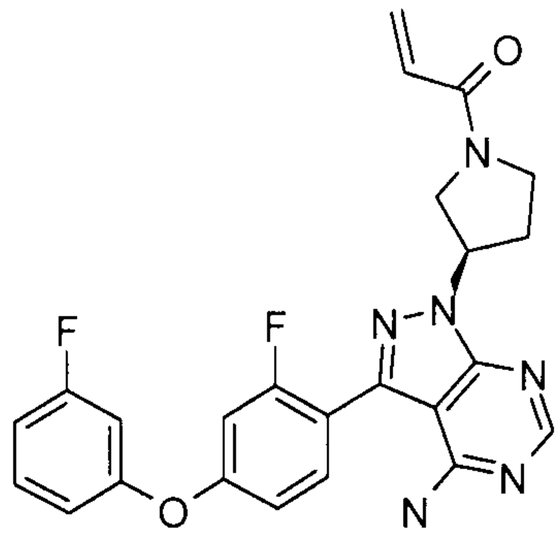
(E)-3-(2-fluorophenyl)acrylic acid (24 mg, 0.14 mmol, 1.1 eq.), DIPEA (50 mg, 0.39 mmol, 3.0 eq.) and HATU (54 mg, 0.14 mmol, 1.1 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.13 mmol, 1.0 eq.) in dichloromethane (3 mL). The reaction mixture was stirred at room temperature for 2 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)) to give the hydrochloride of the target compound (25 mg, yield: 31%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 5.220 min; m/z = 611.1 $[M+H]^+$; Total running time: 7 min.

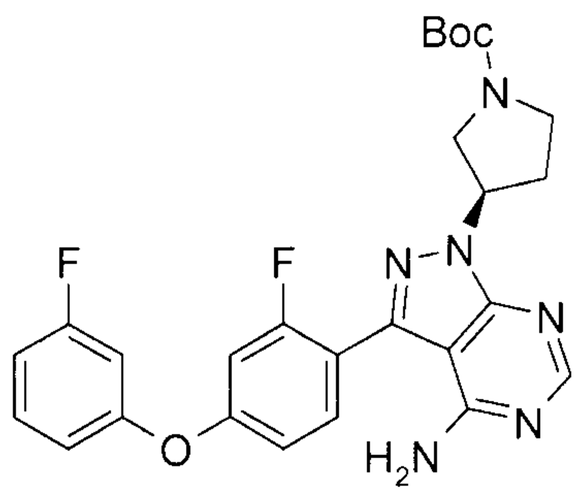
^{1}H NMR (400MHz, DMSO-d_6) δ 8.04 (s, 1H), 7.95-7.87 (m, 2H), 7.60-7.55 (m, 2H), 7.48-7.42 (m, 1H), 7.28-7.23 (m, 3H), 7.12-7.06 (m, 2H), 5.64-5.50 (m, 1H), 4.23-4.20 (m, 0.5H), 4.05-3.75 (m, 3.5H), 2.56-2.39 (m, 2H).

Example 94



1-((R)-3-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Step A:

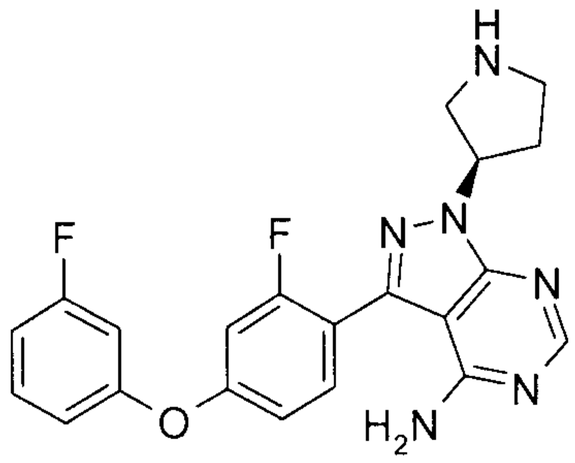


(3R)-tert-butyl 3-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate

Procedure:

tert-butyl 3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate (6.5 g, 15.0 mmol, 1.0 eq.), 2-(2-fluoro-4-(3-fluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.5 g, 19.6 mmol, 1.3 eq.), potassium phosphate (6.4 g, 30.1 mmol, 2.0 eq.) and Pd-118 (0.25 g, 0.39 mmol, 0.01 eq.) were dissolved in 1,4-dioxane/water (16 mL, 1/1, v/v). The reaction mixture was stirred at 85 °C for 12 hours under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was diluted with water (50 mL), and then extracted with ethyl acetate (100 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: ethyl acetate) to give the target compound (4.2 g, yield: 55%).

Step B:

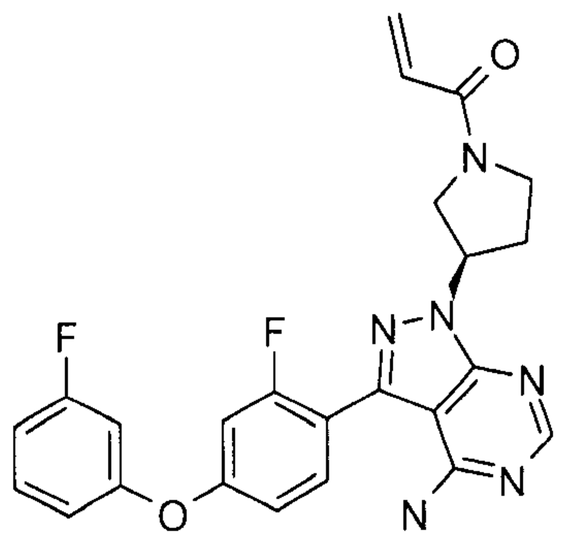


3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Procedure:

4M HCl/EA (10 mL) was added to a solution of (3R)-tert-butyl 3-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate (4.2 g, 8.27 mmol) in dichloromethane (15 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour, concentrated and spin-dried to give the hydrochloride of the target compound (3.7 g, yield: 92%).

Step C:



1-((R)-3-(4-amino-3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Procedure:

NaOH solution (10%, 15.3 mL) and acryloyl chloride (0.67 g, 7.44 mmol, 0.9 eq.) were subsequently added dropwiseto a solution of 3-(2-fluoro-4-(3-fluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (3.7 g, 8.27 mmol, 1.0 eq.) in tetrahydrofuran (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for

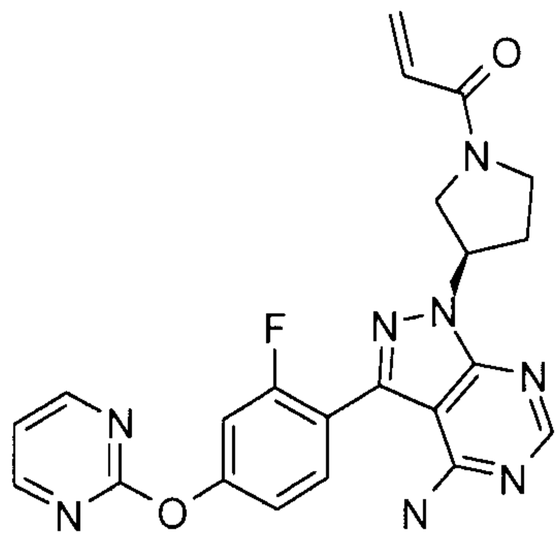
10 min, and then quenched with saturated $NaHCO_3$ (20 mL), extracted with dichloromethane (30 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (eluent: petroleum ether: ethyl acetate=1:0 to 1:1) to give the target compound (2.5 g, yield: 65%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 3.178 min; m/z = 463.0 $[M+H]^+$; Total running time: 7 min.

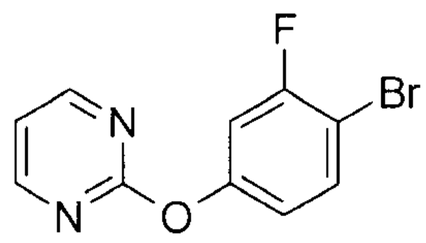
^1H NMR (400MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.53-7.49 (m, 1H), 7.40-7.35 (m, 1H), 6.95-6.81 (m, 4H), 6.41-6.39 (m, 2H), 5.69-5.55 (m, 3H), 4.14-3.98 (m, 3H), 3.78-3.72 (m, 1H), 2.71-2.54 (m, 2H).

Example 95



1-((R)-3-(4-amino-3-(2-fluoro-4-(pyrimidin-2-yloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Step A:



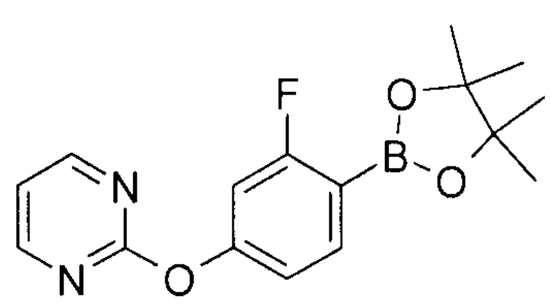
2-(4-bromo-3-fluorophenoxy)pyrimidine

Procedure:

2-chloropyrimidine (1.98 g, 17.3 mmol , 1.1 eq.) and potassium carbonate (2.6 g, 18.8 mmol, 1.2 eq) were added to a solution of 3-fluoro-4-bromophenol (3.0 g, 15.7 mmol, 1.0 eq.) in acetone (30 mL) and dimethyl sulfoxide (10 mL). The reaction mixture was stirred at 110 °C for 16 hours.

After cooling to room temperature, water (100 mL) was added, and then extracted with ethyl acetate (100 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 5: 1) to give the target compound (930 mg, yield: 22%).

Step B:

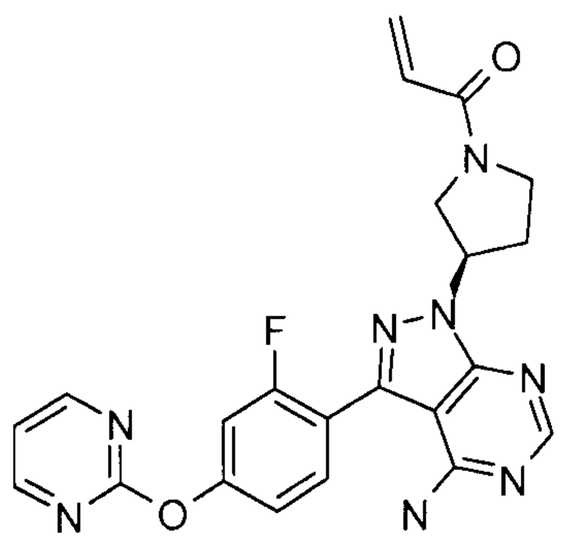


2-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pyrimidine

Procedure:

4-(4-bromo-3-fluorophenoxy)pyrimidine (300 mg, 1.11 mmol, 1.0 eq.), bis(pinacolato)diboron (425 mg, 1.67 mmol, 1.5 eq.), potassium acetate (328 mg, 3.34 mmol, 3.0 eq.) and (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium (89 mg, 0.11 mmol, 0.1 eq.) were dissolved in 1,4-dioxane (3 mL). The resulting mixture was heated to 85 °C and stirred for 12 hours under nitrogen atmosphere. The reaction mixture was filtered through celite. The filtrate was spin-dried to give the crude product (207 mg, yield: 59%), which was used directly in the next step.

Step C:



1-((R)-3-(4-amino-3-(2-fluoro-4-(pyrimidin-2-yloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

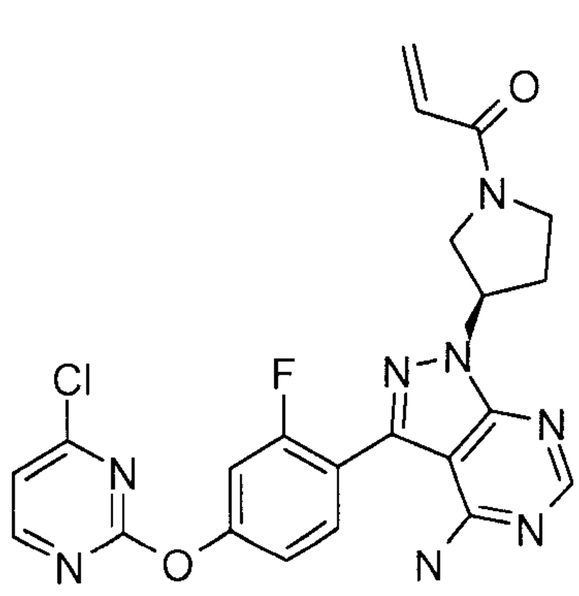
Procedure:

(R)-1-(3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one (80 mg, 0.21 mmol, 1.0 eq.), 2-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pyrimidine (132 mg, 0.42 mmol, 2.0 eq.), sodium carbonate (66 mg, 0.63 mmol, 3.0 eq.) and $Pd(PPh_3)_4$ (24 mg, 0.021 mmol, 0.1 eq.) were dissolved in 1,4-dioxane/water (2.4 mL, 5/1, v/v). The reaction mixture was stirred at 85 °C for 30 min. under nitrogen atmosphere with microwave irradiation. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (3.5 mg, yield: 3.7%).

Spectroscopy data:

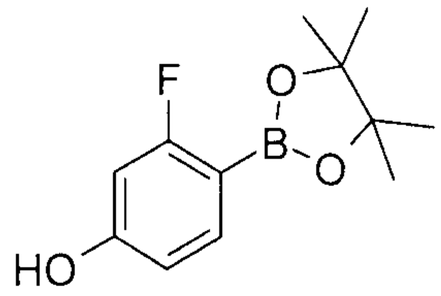
LC/MS (Method: UFLC): RT = 3.115 min; m/z = 447.0 $[M+H]^+$; Total running time: 7 min.

Example 96



1-((R)-3-(4-amino-3-(4-(4-chloropyrimidin-2-yloxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Step A:

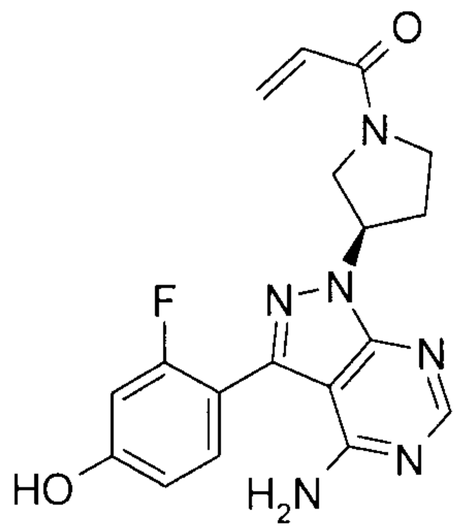


3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol

Procedure:

3-fluoro-4-bromophenol (3.0 g, 15.7 mmol, 1.0 eq.), bis(pinacolato)diboron (5.98 g, 23.6 mmol, 1.5 eq.), potassium acetate (4.62 g, 47.1 mmol, 3.0 eq.), $Pd_2(dba)_3$ (1.44 g, 1.57 mmol, 0.1 eq.) and x-phos (749 mg, 1.57 mmol, 0.1 eq.) were dissolved in 1,4-dioxane (30 mL), heated to 85 °C and stirred for 12 hours under nitrogen atmosphere. The reaction mixture was filtered through celite. The filtrate was concentrated and spin-dried to give the crude product (3.1 g, yield: 83%), which was used directly in the next step.

Step B:

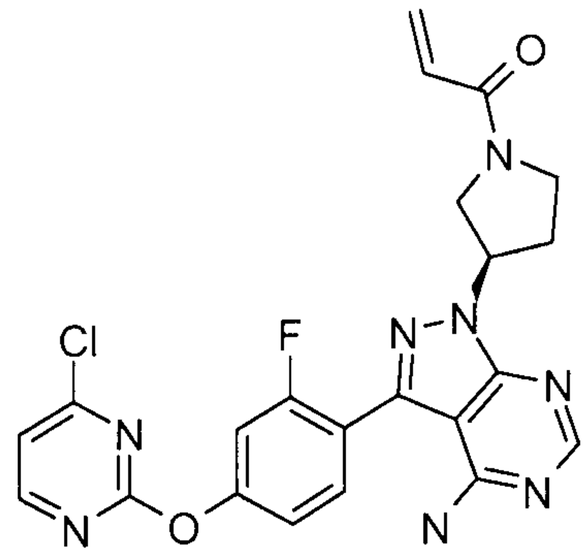


1-((R)-3-(4-amino-3-(2-fluoro-4-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Procedure:

(R)-1-(3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one (500 mg, 1.3 mmol, 1.0 eq.), 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (621 mg, 2.6 mmol, 2.0 eq.), sodium carbonate (415 mg, 3.9 mmol, 3.0 eq.) and $Pd(PPh_3)_4$ (150 mg, 0.13 mmol, 0.1 eq.) were dissolved in 1,4-dioxane/water (6 mL, 5/1, v/v). The reaction mixture was stirred at 85 °C for 30 min. under nitrogen atmosphere with microwave irradiation. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by silica gel column chromatography (petroleum ether: ethyl acetate=1:1), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (12 mg, yield: 2.5%).

Step C:



1-((R)-3-(4-amino-3-(4-(4-chloropyrimidin-2-yloxy)-2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

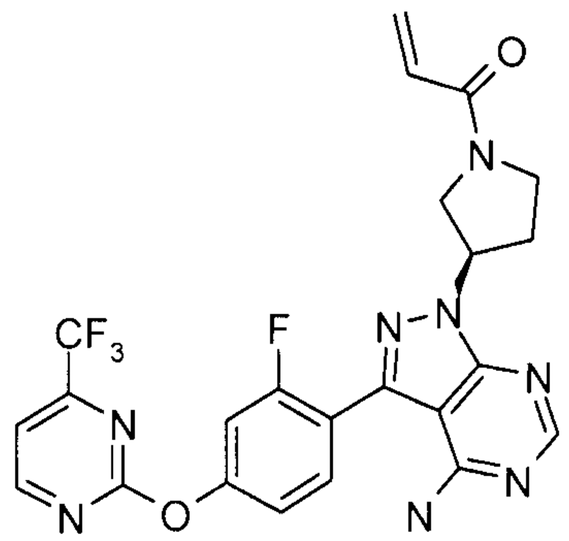
Procedure:

NaH (1.3 mg, 0.033 mmol, 1.0 eq.) was added to a solution of 1-((R)-3-(4-amino-3-(2-fluoro-4-hydroxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one (12 mg, 0.033 mmol, 1.0 eq.) in tetrahydrofuran (2 mL). The reaction mixture was stirred at 0 °C for 30 min. followed by the addition of 4-chloro-2-(methylsulfonyl)pyrimidine (6.3 mg, 0.033 mmol, 1.0 eq.). The reaction mixture was stirred overnight at room temperature, diluted with water (10 mL), and extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (4.1 mg, yield: 26%).

Spectroscopy data:

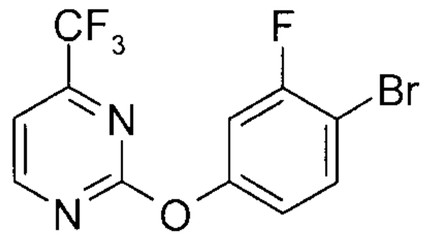
LC/MS (Method: UFLC): RT = 3.554 min; m/z = 481.0 $[M+H]^+$; Total running time: 7 min.

Example 97



1-((R)-3-(4-amino-3-(2-fluoro-4-(4-(trifluoromethyl)pyrimidin-2-yloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Step A:

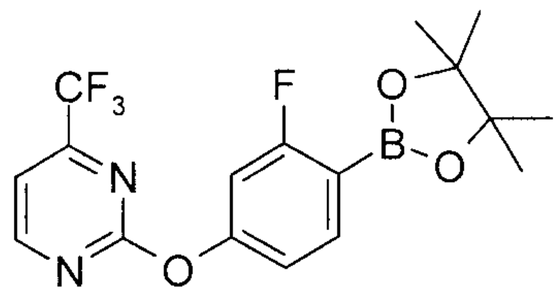


2-(4-bromo-3-fluorophenoxy)-4-(trifluoromethyl)pyrimidine

Procedure:

2-chloro-4-(trifluoromethyl)pyrimidine (4.2 g, 23.0 mmol, 1.1 eq.) and potassium carbonate (3.5 g, 25.1 mmol, 1.2 eq) were added to a solution of 3-fluoro-4-bromophenol (4.0 g, 20.9 mmol, 1.0 eq.) in butanone (15 mL) and dimethyl sulfoxide (5 mL). The reaction mixture was stirred at 100 °C for 12 hours. After cooling to room temperature, water (20 mL) was added, and then extracted with ethyl acetate (20 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, the filtrate was concentrated and spin–dried to give the crude product, which was isolated by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (500 mg, yield: 7%).

Step B:

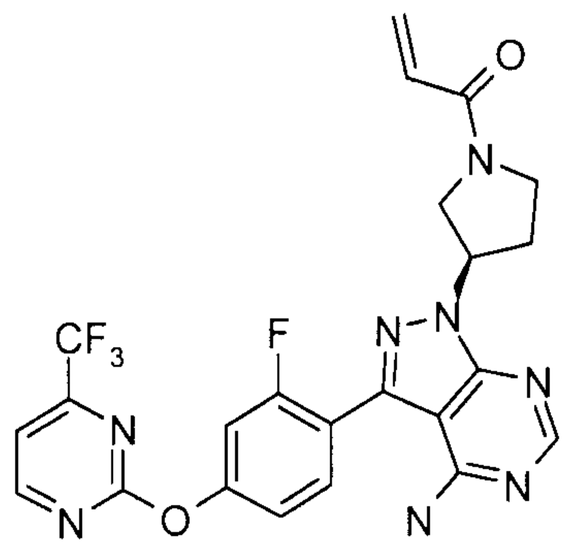


2-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-4-(trifluoromethyl)pyrimidine

Procedure:

2-(4-bromo-3-fluorophenoxy)-4-(trifluoromethyl)pyrimidine (300 mg, 0.89 mmol, 1.0 eq.), bis(pinacolato)diboron (452 mg, 1.78 mmol, 2.0 eq.), potassium acetate (272 mg, 2.78 mmol, 3.0 eq.) and (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium (40 mg, 0.05 mmol, 0.06 eq.) were dissolved in 1,4-dioxane (2 mL), heated to 85 °C and stirred for 12 hours under nitrogen atmosphere. The reaction mixture was filtered through celite. The filtrate was concentrated and spin-dried to give the crude product (340 mg, yield: 100%), which was used directly in the next step.

Step C:



1-((R)-3-(4-amino-3-(2-fluoro-4-(4-(trifluoromethyl)pyrimidin-2-yloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one

Procedure:

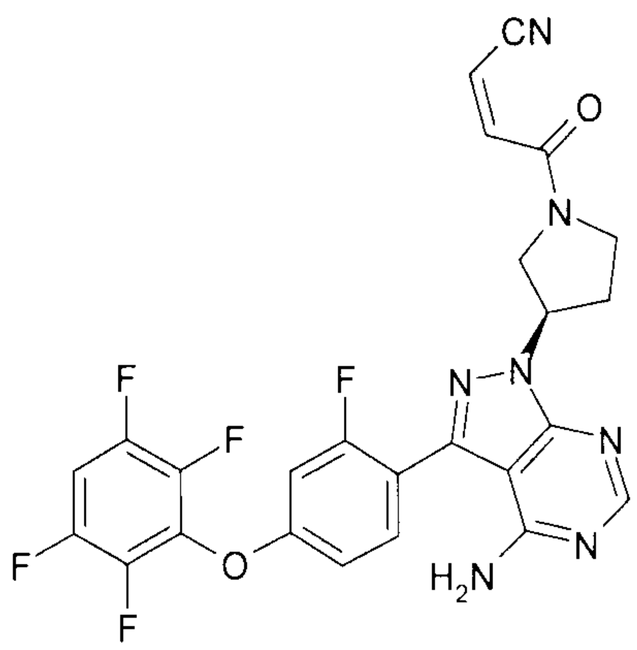
(R)-1-(3-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one (80 mg, 0.21 mmol, 1.0 eq.), 2-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-4-(trifluoromethyl)pyrimidine (160 mg, 0.42 mmol, 2.0 eq.), potassium carbonate (86 mg, 0.63 mmol, 3.0 eq.) and $Pd(PPh_3)_4$ (24 mg, 0.021 mmol, 0.1 eq.) were dissolved in 1,4-dioxane/water (10 mL, 1/1, v/v). The reaction mixture was stirred at 85 °C for 40 min. under nitrogen atmosphere with microwave irradiation. The reaction mixture was diluted with water

(10 mL) and extracted with ethyl acetate (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (14 mg, yield: 6%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.800 min; m/z = 515.0 $[M+H]^+$; Total running time: 7 min.

Example 98



(Z)-4-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-4-oxo-but-2-enenitrile

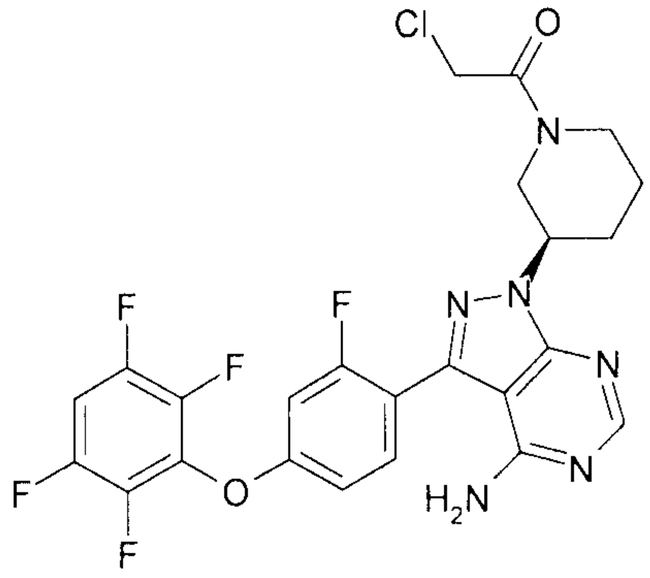
Procedure:

Potassium (Z)-3-cyanoacrylate (29 mg, 0.216 mmol, 2.0 eq.), PyBrop (60 mg, 0.130 mmol, 1.2 eq.), N, N- diisopropylethylamine (42 mg, 0.324 mmol, 3.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.108 mmol, 1.0 eq.) in DMF (3 mL). The reaction mixture was stirred at 0 °C for 5 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.7% NH_4HCO_3, gradient: 10% to 100% (by volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (14 mg, yield: 24%).

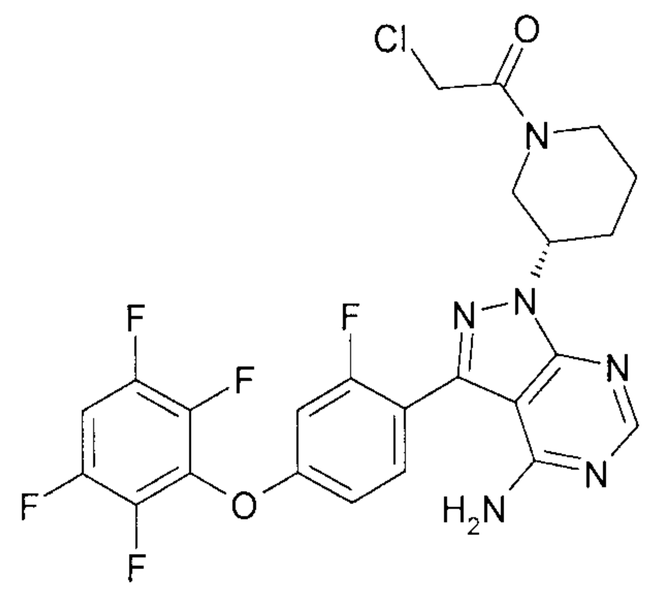
Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.545 min; m/z = 542.0 $[M+H]^+$; Total running time: 7 min.
^{1}H NMR (400MHz, CD_3OD) δ 8.24 (s, 1H), 7.61-7.58 (m, 1H), 7.48-7.43 (m, 1H), 7.19-7.01 (m, 3H), 6.08-6.01 (m, 1H), 5.62-5.56 (m, 1H), 4.16-4.14 (m, 1H), 4.05-3.98 (m, 1.5H), 3.88-3.83 (m, 1H), 3.75-3.70 (m, 0.5H), 2.61-2.51 (m, 2H).

Examples 99 and 100

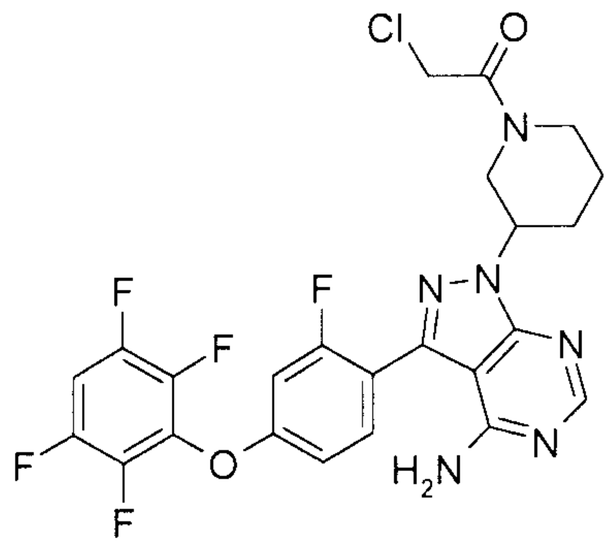


1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-chloroethanone



1-((S)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-chloroethanone

Step A:

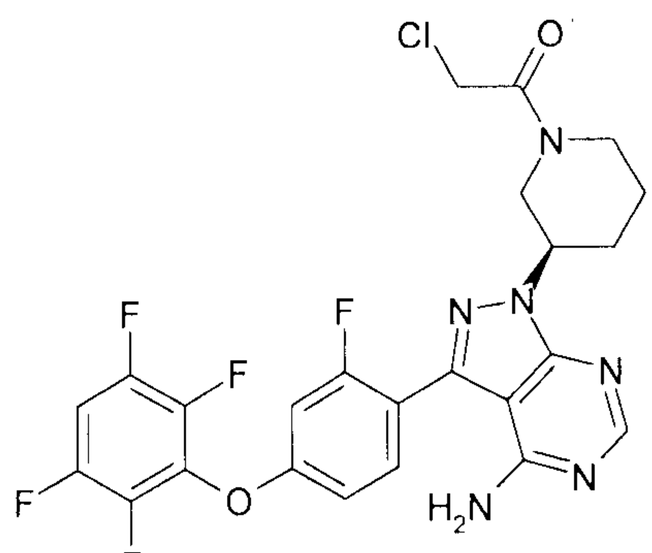


1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-chloroethanone

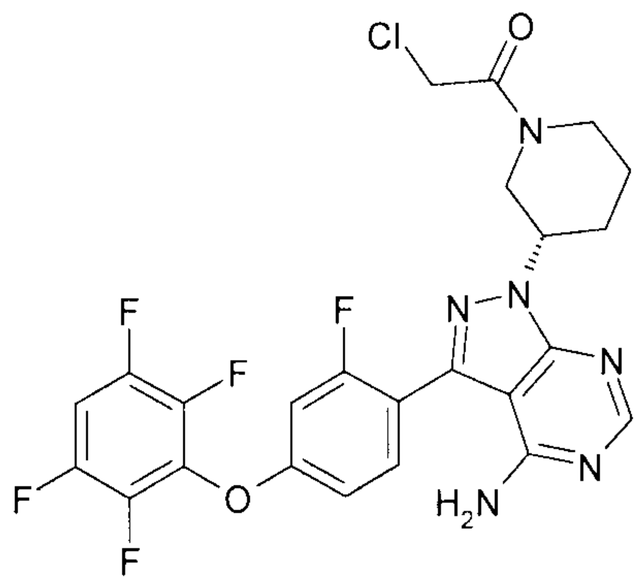
Procedure:

A solution of triethylamine (2 mL) and chloroacetyl chloride (21 mg, 0.19 mmol, 0.9 eq.) in dichloromethane (1 mL) was added dropwise to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.21 mmol, 1.0 eq.) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at room temperaturefor 2 hours, quenched with saturated $NaHCO_3$ (20 mL), and extracted with dichloromethane (30 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/7‰ NH_4HCO_3, gradient: 10% to 100% (by volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (80 mg, yield: 69%).

Step B:



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-chloroethanone



1-((S)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-chloroethanone

Procedure:

1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-chloroethanone was chirally separated by SFC to give the compound 99(20 mg, yield: 25%) and the compound of example 100 (35 mg, yield: 44%).

Spectroscopy data:

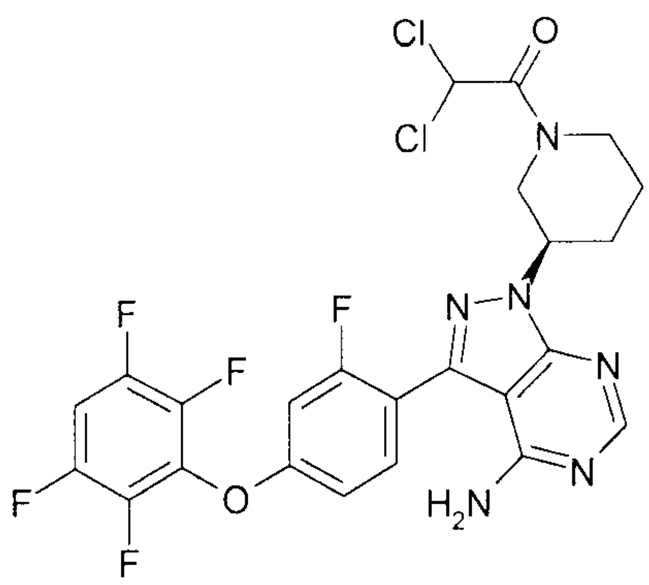
Example 99:

LC/MS (Method: UFLC): RT = 3.566 min; m/z = 552.9 $[M+H]^+$; Total running time: 7 min.

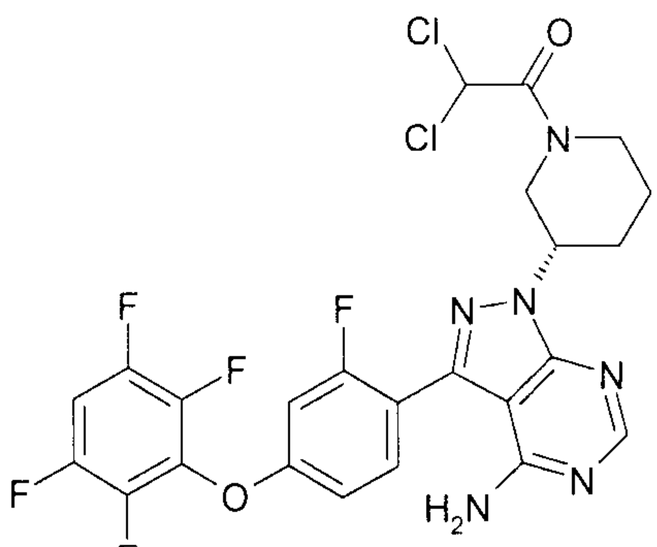
Example 100:

LC/MS (Method: UFLC): RT = 3.572 min; m/z = 552.9 $[M+H]^+$; Total running time: 7 min.

Examples 101 and 102

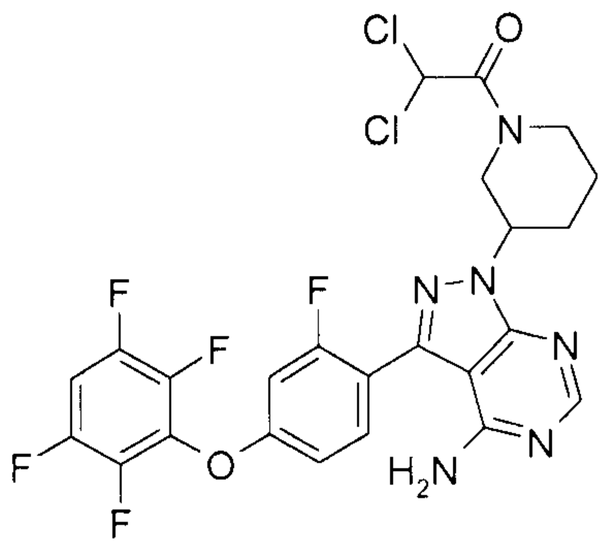


1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2,2-dichloroethanone



1-((S)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2,2-dichloroethanone

Step A:

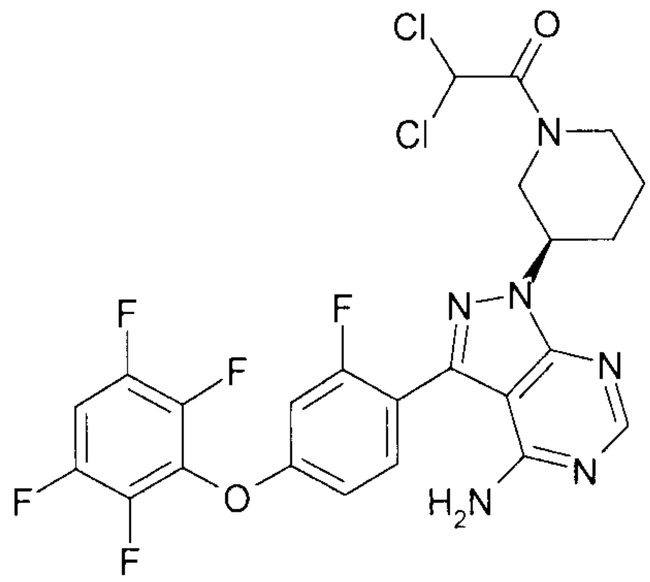


1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2,2-dichloroethanone

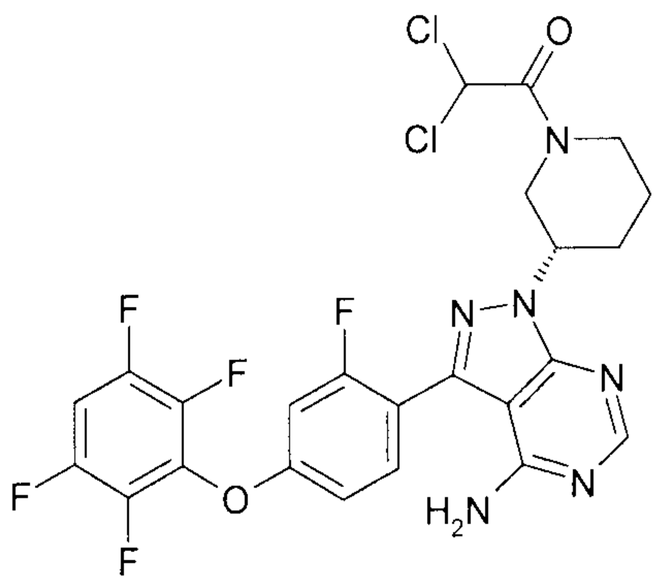
Procedure:

A solution of triethylamine (2 mL) and 2,2-dichloroacetyl chloride (28 mg, 0.19 mmol, 0.9 eq.) in dichloromethane (1 mL) were added dropwise to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-(piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.21 mmol, 1.0 eq.) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours, quenched with saturated $NaHCO_3$ (20 mL), and extracted with dichloromethane (30mL) 3 times. The combined organic phases were dried over anhydrous sodium sulphate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/7% NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (80 mg, yield: 65%).

Step B:



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2,2-dichloroethanone



1-((S)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2,2-dichloroethanone

Procedure:

1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2,2-dichloroethanone was chirally separated by SFC to give the compound of Example 101 (18 mg, yield: 23%) and the compound of Example 102 (30 mg, yield: 38%).

Spectroscopy data:

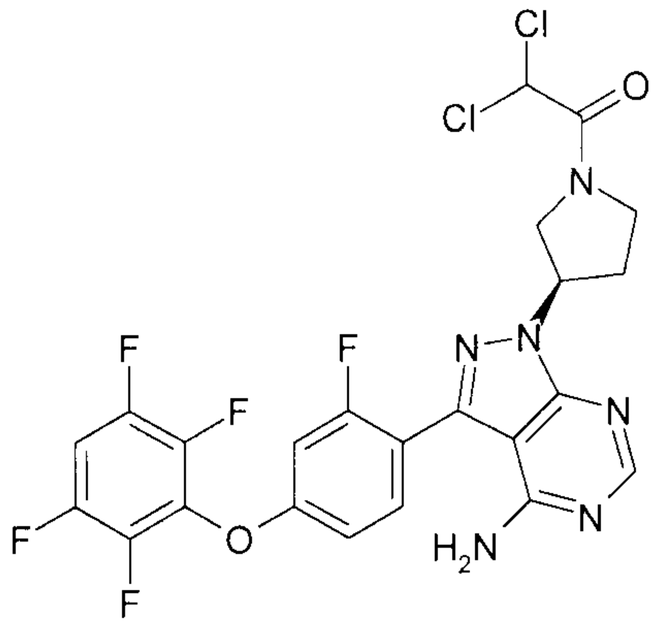
Example 101:

LC/MS (Method: UFLC): RT = 3.788 min; m/z = 586.9 $[M+H]^+$; Total running time: 7 min.

Example 102:

LC/MS (Method: UFLC): RT = 3.793 min; m/z = 586.9 $[M+H]^+$; Total running time: 7 min.

Example 103



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2,2-dichloroethanone

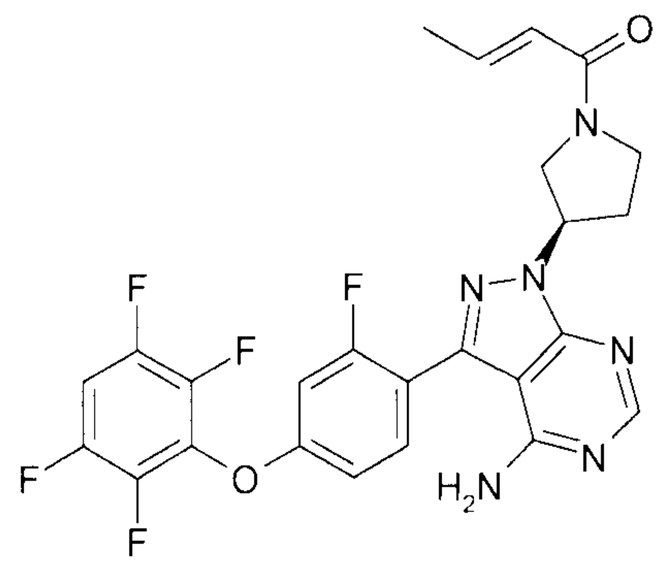
Procedure:

DIPEA (42 mg, 0.324 mmol, 3.0 eq.) and 2,2-dichloroacetyl chloride (34 mg, 0.162 mmol, 1.5 eq.) were sequentially added dropwise to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.108 mmol, 1.0 eq.) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred 0 °C for 5 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (26 mg, yield: 40%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 4.760 min; m/z = 572.9 $[M+H]^+$; Total running time: 7 min.

Example 104



(E)-1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)but-2-en-1-one

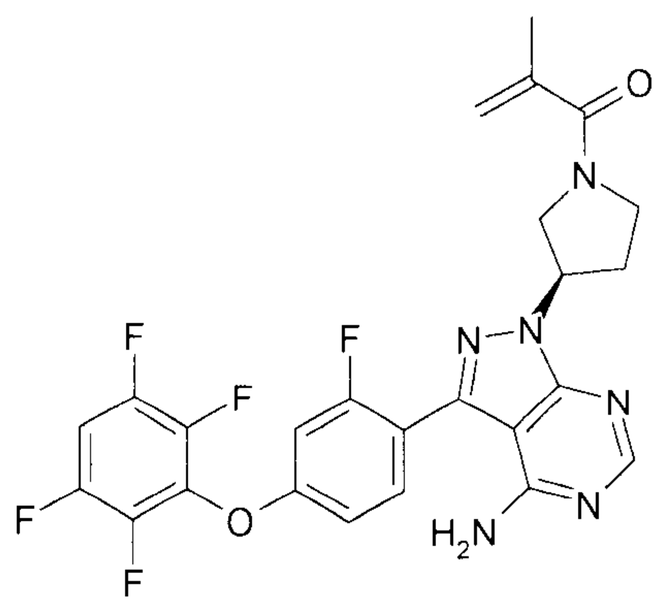
Procedure:

Triethylamine (30 mg, 0.3 mmol, 3.0 eq.) and (E)-but-2-enoyl chloride (10 mg, 0.1 mmol, 1.0 eq.) were added dropwise to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.1 mmol, 1.0 eq.) in dichloromethane (3 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight, diluted with water (10 mL), and extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulphate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (19 mg, yield: 36%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 3.854 min; m/z = 553.0 $[M+Na]^+$; Total running time: 7 min.

Example 105



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-methylprop-2-en-1-one

Procedure:

2-methacrylic acid (11 mg, 0.134 mmol, 1.2 eq.), HATU (53 mg, 0.140 mmol, 1.3 eq.) and N, N- diisopropylethylamine (42 mg, 0.324mmol, 1.0 eq.) were subsequently added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-

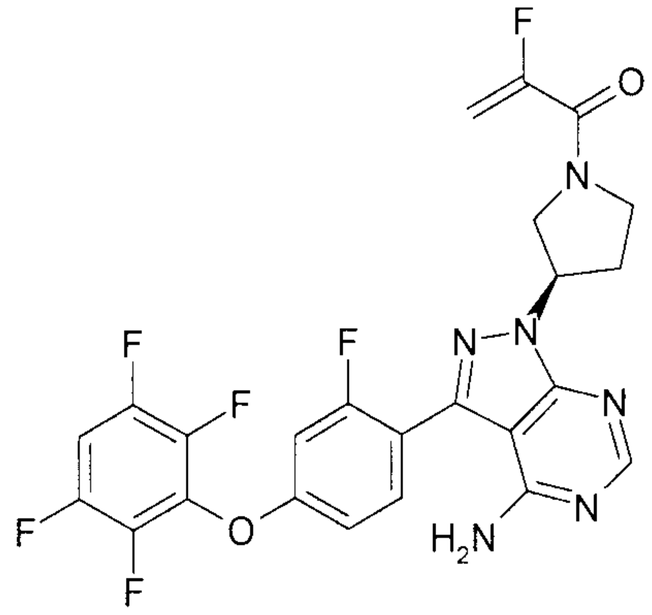
pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.108 mmol, 1.0 eq.) in dichloromethane (10 mL)a t 0 °C. The reaction mixture was stirred at room temperature for 5 hours, diluted with water (10 mL), and then extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was isolated by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (18 mg, yield: 32%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 4.557 min; m/z = 532.1 $[M+H]^+$; Total running time: 7 min.

^1H NMR (400MHz, CD_3OD) δ 8.44-8.43 (m, 1H), 7.71-7.65 (m, 1H), 7.53-7.47 (m, 1H), 7.13-7.06 (m, 2H), 5.76-5.65 (m, 1H), 5.36-5.32 (m, 1H), 5.24-5.21 (m, 1H), 4.21-3.99 (m, 2.5H), 3.88-3.80 (m, 1H), 3.70-3.65 (m, 0.5H), 2.59-2.52 (m, 2H), 1.94-1.89 (m, 3H).

Example 106



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-fluoroprop-2-en-1-one

Procedure:

2-fluoroacrylic acid (11 mg, 0.134 mmol , 1.2 eq.), HATU (53 mg, 0.140 mmol, 1.3 eq.) and N, N- diisopropylethylamine (42 mg, 0.324mmol, 1.0 eq.) were subsequently added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.108 mmol, 1.0 eq.) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 5 hours, diluted with water

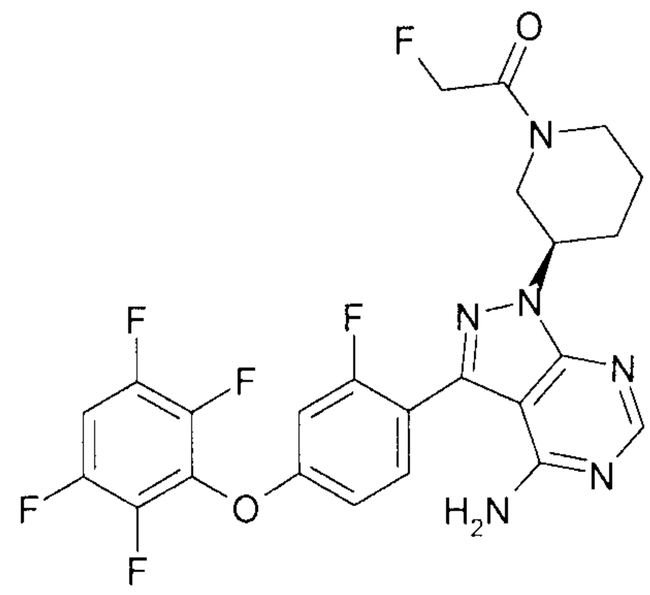
(10 mL), and then extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was isolated by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (10 mg, yield: 18%).

Spectroscopy data:

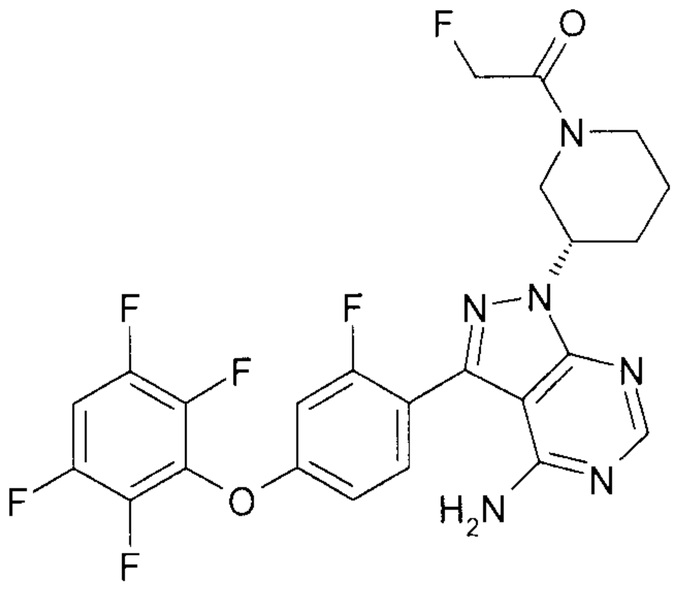
LC/MS (Method: UFLC): RT = 4.624 min; m/z = 535.0 $[M+H]^+$; Total running time: 7 min.

^1H NMR (400MHz, CD_3OD) δ 8.43-8.42 (m, 1H), 7.77-7.66 (m, 1H), 7.55-7.47 (m, 1H), 7.12-7.06 (m, 2H), 5.71-5.68 (m, 1H), 5.54-5.52 (m, 0.5H), 5.42-5.41 (m, 0.5H), 5.31-5.26 (m, 1H), 4.28-4.26 (m, 1H), 4.13-4.08 (m, 1.5H), 3.95-3.76 (m, 1.5H), 2.76-2.52 (m, 2H).

Examples 107 and 108

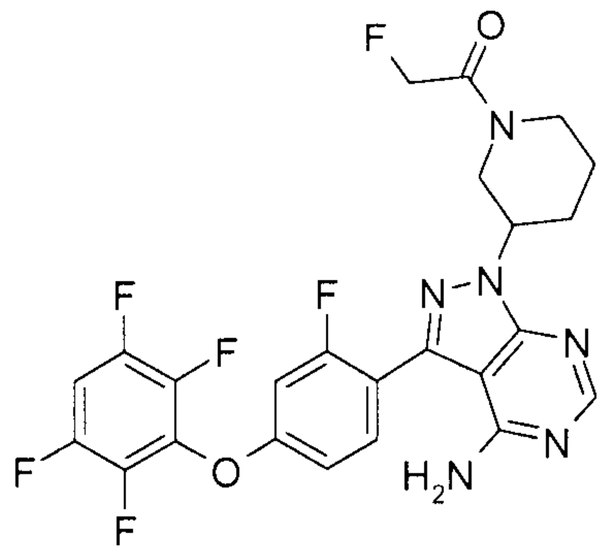


1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-fluoroethanone



1-((S)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-fluoroethanone

Step A:

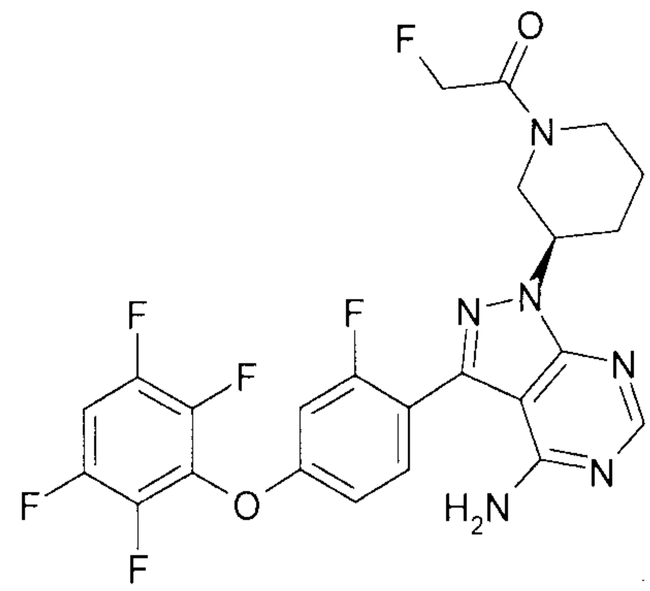


1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-fluoroethanone

Procedure:

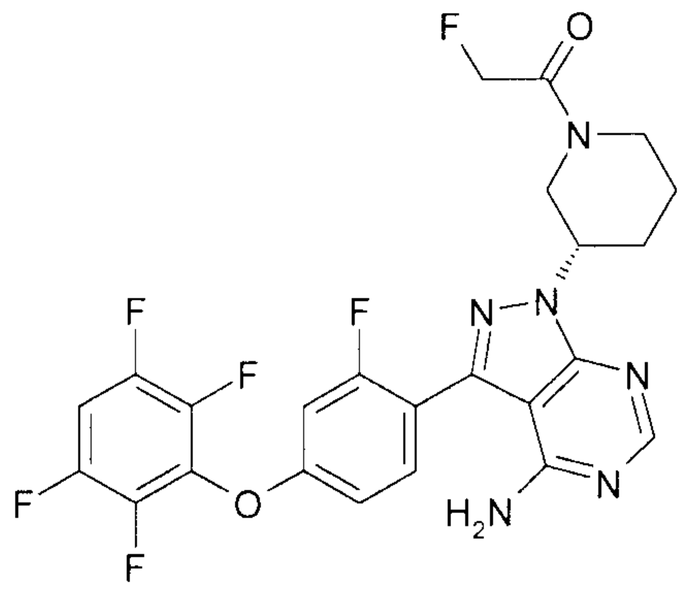
Triethylamine (2 mL) and 2-fluoroacetyl chloride (18 mg, 0.19 mmol, 0.9 eq.) were added dropwise to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-piperidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.21 mmol, 1.0 eq.) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours, and then quenched with saturated $NaHCO_3$ (20 mL), and extracted with dichloromethane (30 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.7% NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (30 mg, yield: 29%).

Step B:



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-

d]pyrimidin-1-yl)piperidin-1-yl)-2-fluoroethanone



1-((S)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-fluoroethanone

Procedure:

1-(3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-2-fluoroethanone was chirally separated by SFC to give the compound of Example 107 (13 mg, yield: 43%) and the compound of Example 108 (14 mg, yield: 47%).

Spectroscopy data:

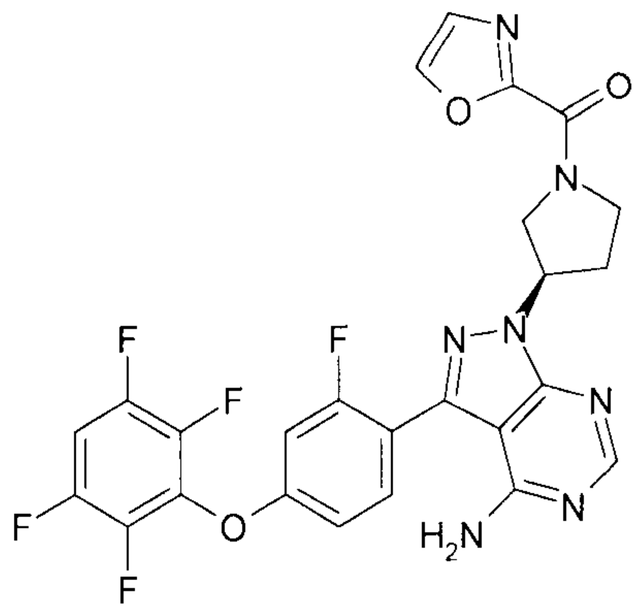
Example 107:

LC/MS (Method: UFLC): RT = 3.362 min; m/z = 537.1 $[M+H]^+$; Total running time: 7 min.

Example 108:

LC/MS (Method: UFLC): RT = 3.359 min; m/z = 537.1 $[M+H]^+$; Total running time: 7 min.

Example 109



((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)(oxazol-2-yl)methanone

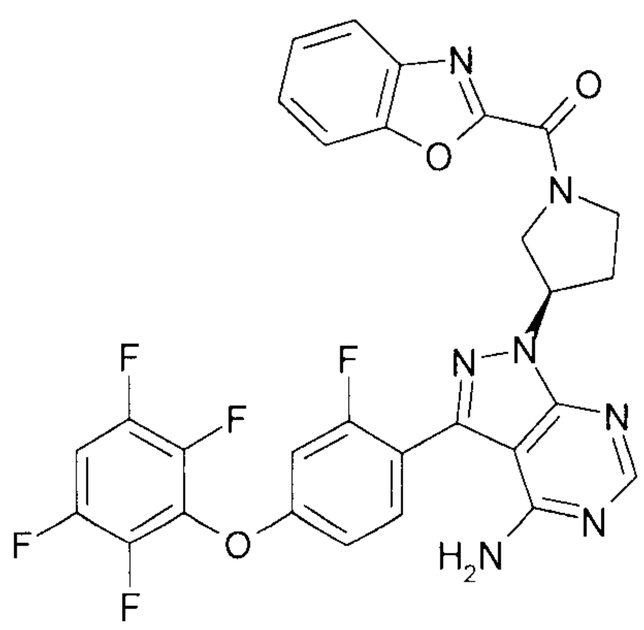
Procedure:

Oxazole-2-carboxylic acid (16 mg, 0.143 mmol, 1.1 eq.), HATU (54 mg, 0.143 mmol, 1.1 eq.) and N, N- diisopropylethylamine (50 mg, 0.389 mmol, 3.0 eq.) were subsequently added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (60 mg, 0.130 mmol, 1.0 eq.) in dichloromethane (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 5 hours, diluted with water (10 mL), and then extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (24 mg, yield: 33%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 4.417 min; m/z = 558.1 $[M+H]^+$; Total running time: 7 min.

Example 110



((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)(benzo[d]oxazol-2-yl)methanone

Procedure:

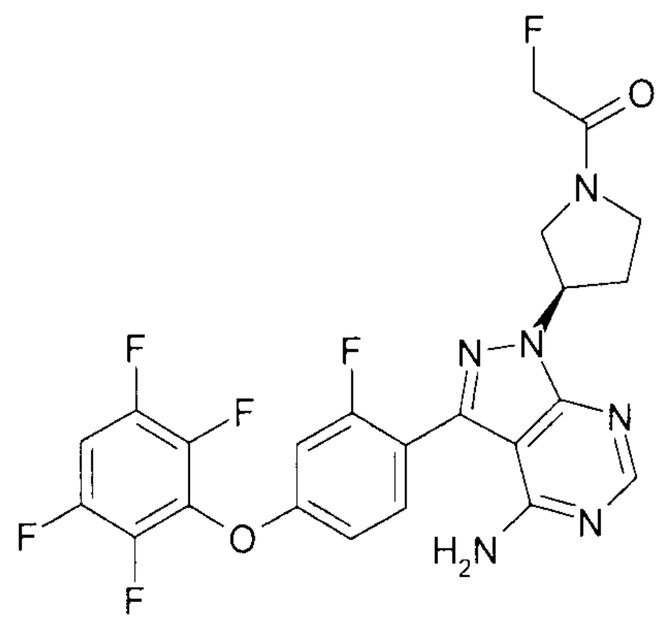
Benzo[*d*]oxazole-2-carboxylic acid (26 mg, 0.163 mmol, 1.5 eq.), HATU (45 mg, 0.119 mmol, 1.1 eq.) and N, N- diisopropylethylamine (42 mg, 0.324 mmol, 3.0 eq.) were subsequently added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-

pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.108 mmol, 1.0 eq.) in DMF (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 5 hours, diluted with water (10 mL), and then extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (8.7 mg, yield: 13%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 5.007 min; m/z = 608.1 $[M+H]^+$; Total running time: 7 min.

Example 111



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-fluoroethanone

Procedure:

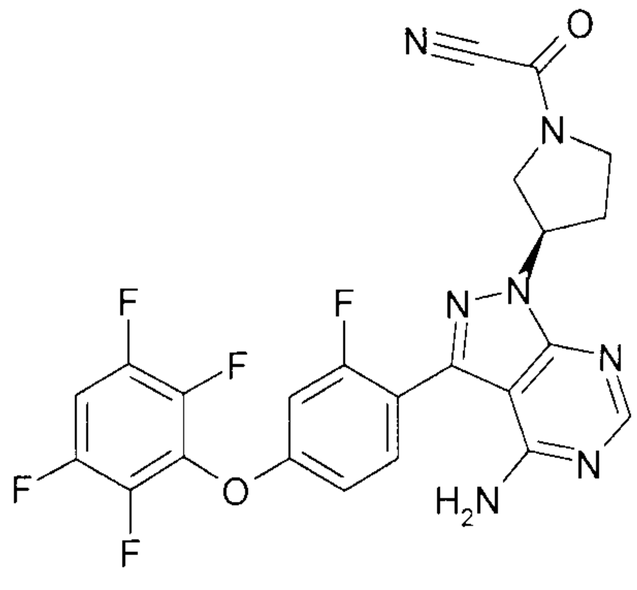
Triethylamine (30 mg, 0.6 mmol, 3.0 eq.) and 2-fluoroacetyl chloride (18 mg, 0.2 mmol, 2.0 eq.) were added dropwise to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine hydrochloride (100 mg, 0.10 mmol, 1.0 eq.) in dichloromethane (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 16 hours, diluted with water (10 mL), and then extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase:

acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound hydrochloride (9.5 mg, yield: 9%).

Spectroscopy data:

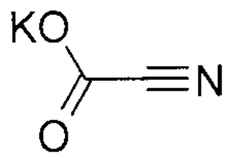
LC/MS (Method: UFLC): RT = 3.516 min; m/z = 523.3 $[M+H]^+$; Total running time: 7 min.

Example 112



2-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-oxoacetonitrile

Step A:

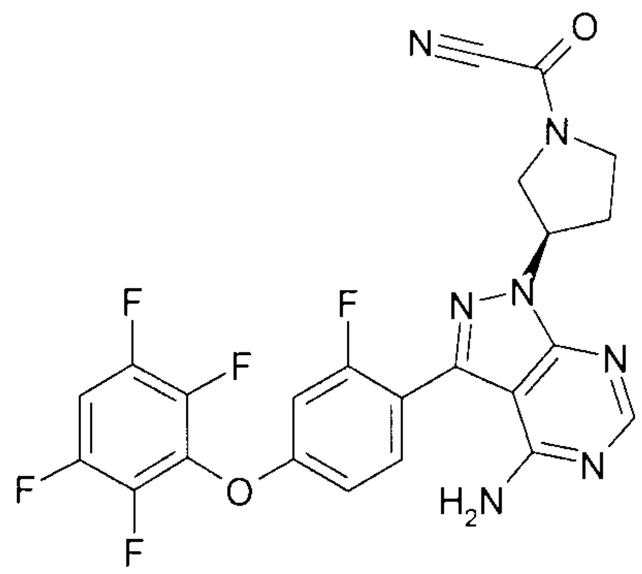


potassium cyanoformate

Procedure:

Potassium hydroxide (267 mg, 0.157 mmol, 1.0 eq.) was added to a solution of ethyl cyanoformate (300 mg, 0.157 mmol, 1.0 eq.) in tetrahydrofuran/water (10 mL/10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours, concentrated and spin-dried to give the target compound (570 mg, yield: 100%).

Step B:



2-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-oxoacetonitrile

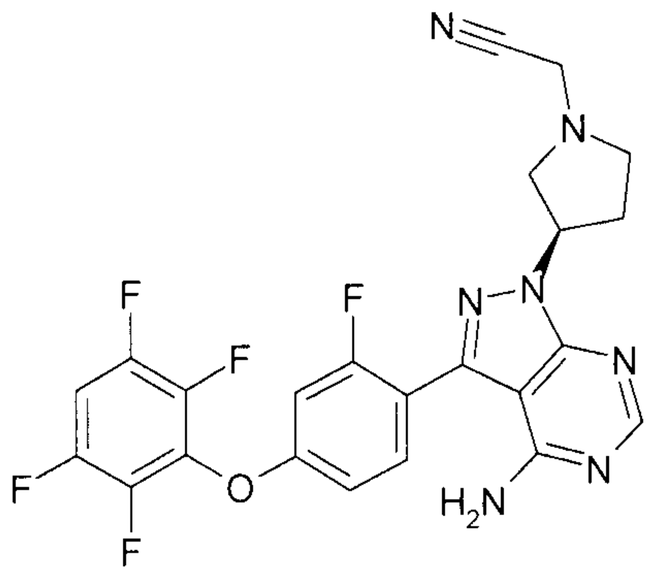
Procedure:

Potassium cyanoformate (28 mg, 0.26 mmol, 2.0 eq.), PyBrop (132 mg, 0.26 mmol, 2.0 eq.) and triethylamine (39 mg, 0.39 mmol, 3.0 eq.) were added dropwise to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine(60 mg, 0.13 mmol, 1.0 eq.) in DMF (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours, quenched with saturated $NaHCO_3$ (10 mL), and then extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.7% NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (10 mg, yield: 15%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.258 min; m/z = 515.5 $[M+H]^+$; Total running time: 7 min.

Example 113



2-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)acetonitrile

Procedure:

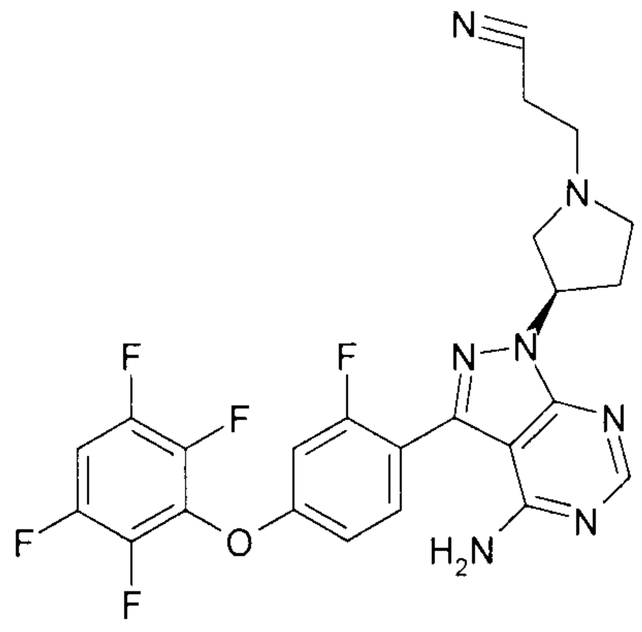
2-iodo acetonitrile (36 mg, 0.216 mmol, 2.0 eq.) and potassium carbonate (74 mg, 0.54 mmol, 5.0 eq.) was added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.108 mmol, 1.0 eq.) in DMF (0.5 mL). The reaction mixture was stirred at room temperature for 5 hours, quenched with saturated $NaHCO_3$ (10 mL), and then extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.7% NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (12 mg, yield: 22%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 4.350 min; m/z = 502.0 $[M+H]^+$; Total running time: 7 min.

^1H NMR (400MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.60 (t, J = 8.4 Hz, 1H), 7.09-7.02 (m, 1H), 6.94-6.88 (m, 2H), 5.63-5.56 (m, 1H), 3.74 (s, 2H), 3.30-3.25 (m, 1H), 3.19-3.12 (m, 2H), 2.97-2.90 (m, 1H), 2.56-2.52 (m, 2H).

Example 114



3-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)propanenitrile

Procedure:

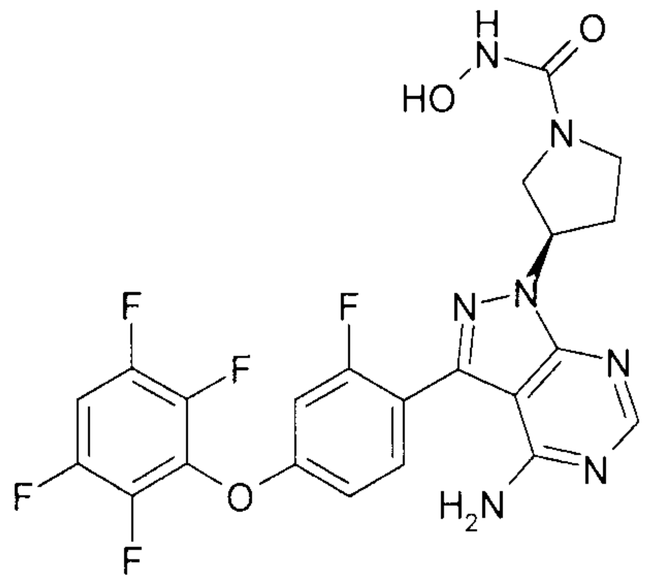
3-bromo-propionitrile (28 mg, 0.216 mmol, 2.0 eq.) and potassium carbonate (74 mg, 0.54 mmol, 5.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.108 mmol, 1.0 eq.) in DMF (0.5 mL). The reaction mixture was stirred at 80 °C for 12 hours, diluted with water (10 mL), and then extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.7% NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (6 mg, yield: 11%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 3.671 min; m/z = 516.0 $[M+H]^+$; Total running time: 7 min.

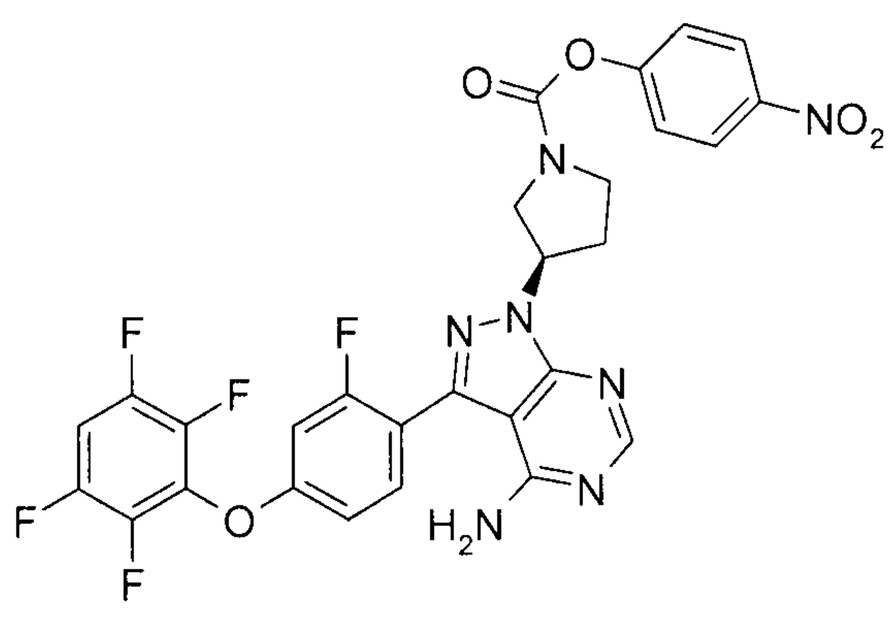
^1H NMR (400MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.59 (t, *J* = 8.4 Hz, 1H), 7.10-7.04 (m, 1H), 6.94-6.88 (m, 2H), 5.65-5.52 (m, 1H), 3.35-3.31 (m, 1H), 3.05-2.91 (m, 5H), 2.58-2.44 (m, 4H).

Example 115



(3R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-N-hydroxypyrrolidine-1-carboxamide

Step A:



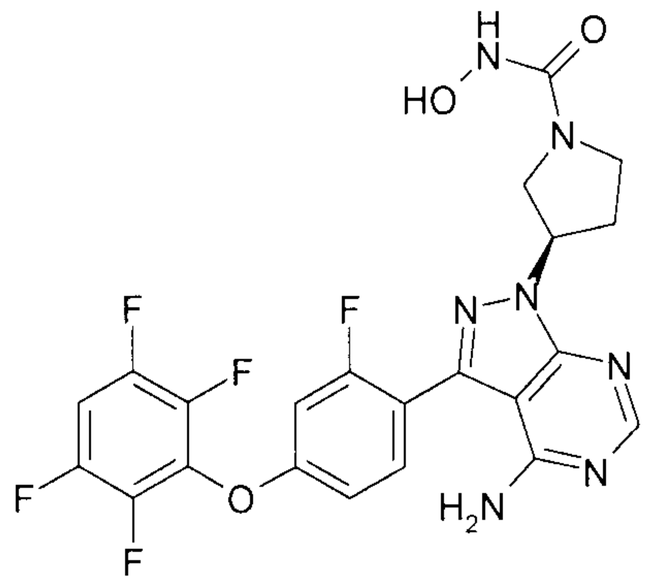
(3R)-4-nitrophenyl 3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-formate

Procedure:

Triethylamine (2 mL) and 4-nitrophenyl carbonochloridate (52 mg, 0.23 mmol, 1.1 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.21 mmol, 1.0 eq.) in dichloromethane (9 mL). The reaction mixture was stirred at room temperature for 12 hours, quenched with saturated $NaHCO_3$ (10 mL), and then extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.7% NH_4HCO_3, gradient: 10% to 100% (volume ratio)),

evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (80 mg, yield: 69%).

Step B:



(3R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-N-hydroxypyrrolidine-1-carboxamide

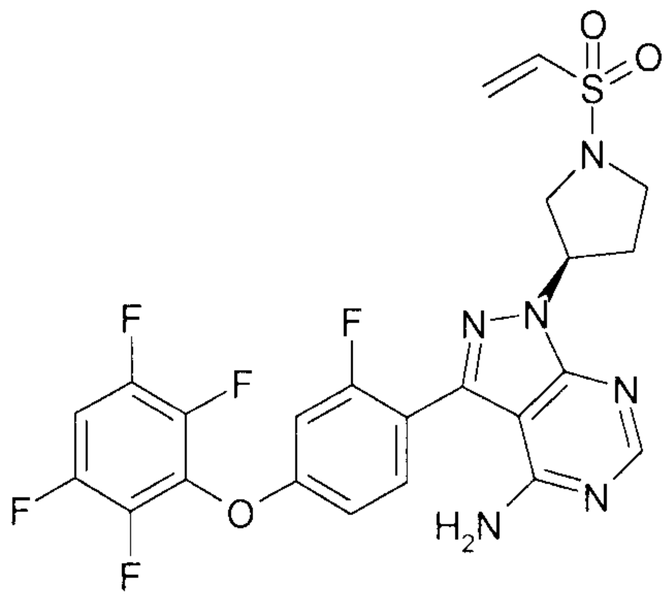
Procedure:

Hydroxylamine aqueous solution (50%, 0.5 mL, 0.254 mmol, 2 eq.) was added to a solution of (3R)-4-nitrophenyl 3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate (80 mg, 0.13 mmol, 1.0 eq.) in DMF (3 mL). The reaction mixture was stirred at 120 °C for 30 min., quenched with saturated $NaHCO_3$ (10 mL), and then extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column, mobile phase: acetonitrile/water/0.7% NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (5 mg, yield: 9%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.803 min; m/z = 522.1 $[M+H]^+$; Total running time: 7 min.

Example 116



3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-1-(vinylsulfonyl)pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

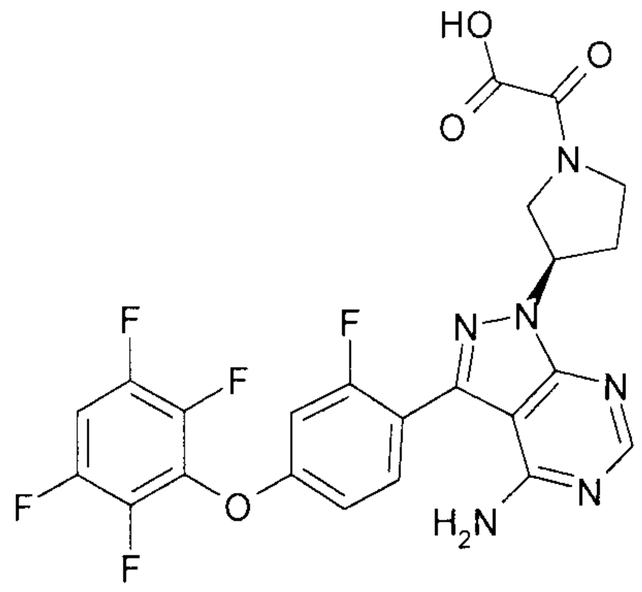
Procedure:

N, N- diisopropylethylamine (31 mg, 0.238 mmol, 2.2 eq.), DMAP (1.32 mg, 0.011 mmol, 0.1 eq.) and 2-chloroethyl sulfonyl chloride (21 mg, 0.130 mmol, 1.2 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.108 mmol, 1.0 eq.) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 12 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column, mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (6 mg, yield: 11%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 3.543 min; m/z = 552.9$[M+H]^+$; Total running time: 7 min.

Example 117



2-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-oxoacetic acid

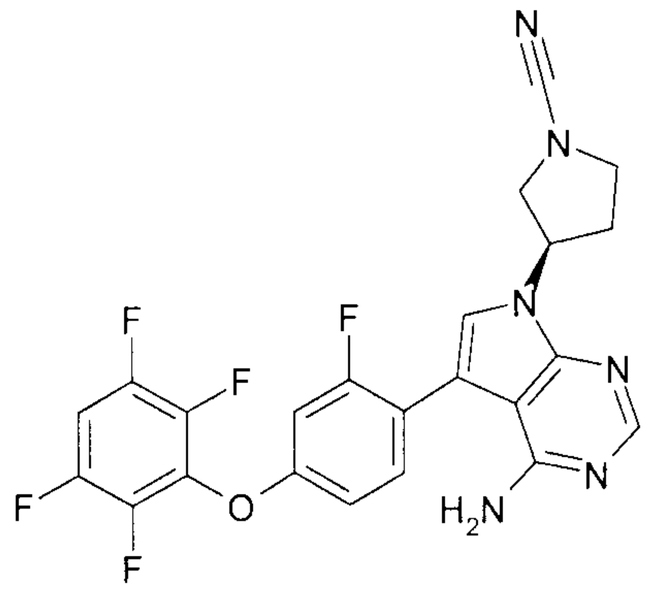
Procedure:

N, N- diisopropylethylamine (41 mg, 0.33 mmol, 3.0 eq.) and ethyl cyanoformate (13 mg, 0.13 mmol, 1.2 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.11 mmol, 1.0 eq.) in toluene (3 mL). The reaction mixture was stirred at room temperature for 12 hours, diluted with saturated $NaHCO_3$ (10 mL), and then extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.7% NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (5 mg, yield: 9%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 1.884 min; m/z = 535.1 $[M+H]^+$; Total running time: 3min.

Example 118



(3R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyrimidin-1-yl)pyrrolidine-1-carbonitrile

Procedure:

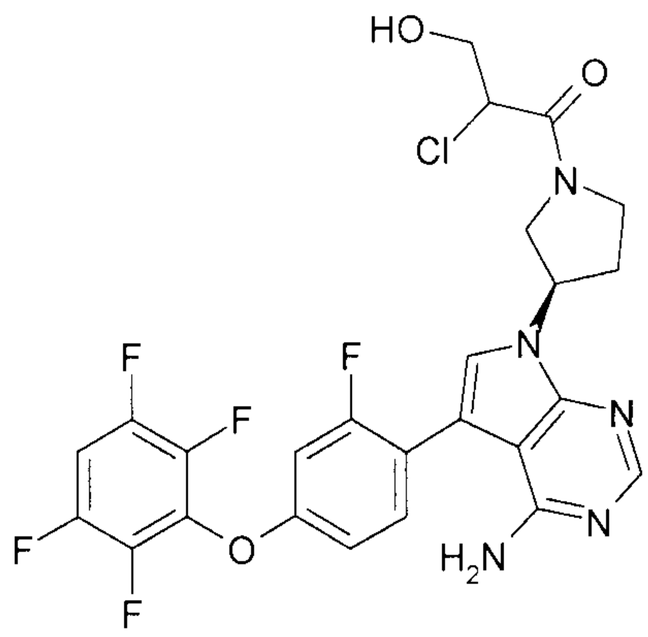
Bromine cyanide (23 mg, 0.216 mmol, 2.0 eq.) and sodium bicarbonate (27 mg, 0.324 mmol, 3.0 eq.) were added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.108 mmol, 1.0 eq.) in acetonitrile (2 mL). The reaction mixture was stirred at 20 °C for 12 hours, diluted with water (10 mL), and then extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.7% NH_4HCO_3, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the target compound (26 mg, yield: 49%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 3.338 min; m/z = 488.1 $[M+H]^+$; Total running time: 7 min.

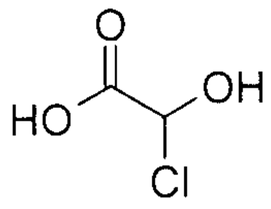
^1H NMR (400MHz, CD_3OD) δ 8.25 (s, 1H), 7.68 (t, J = 8.4 Hz, 1H), 7.52-7.45 (m, 1H), 7.10-7.02 (m, 2H), 5.57-5.52 (m, 1H), 4.01-3.96 (m, 1H), 3.86-3.80 (m, 2H), 3.69-3.65 (m, 1H), 2.52-2.46 (m, 2H).

Example 119



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-chloro-3-hydroxypropan-1-one

Step A:

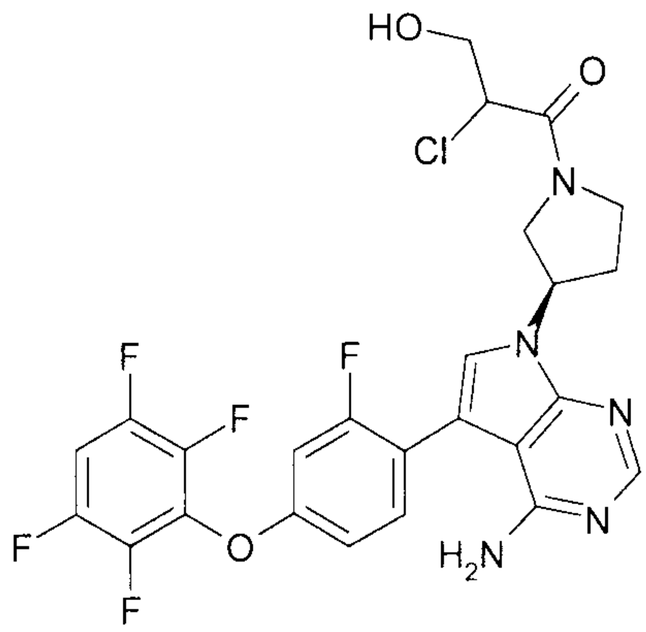


2-chloro-2-hydroxyacetic acid

Procedure:

Silver nitrate (620 mg, 3.669 mmol, 1.04 eq.) was added to a solution of sodium carbonate (530 mg, 6.386 mmol, 1.42 eq.) in water (3 mL). The resulting suspension was added dropwise to a solution of 2,2-dichloroacetic acid (500 mg, 3.521 mmol, 1.0 eq.) in water (3 mL). The reaction mixture was refluxed for 2 hours and filtered. The filtrate was refluxed for 2 hours and filtered. The filtrate was concentrated and spin-dried to give the target compound (326 mg, yield: 84%).

Step B:



1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyrimidin-1-yl)pyrrolidin-1-yl)-2-chloro-3-hydroxypropan-1-one

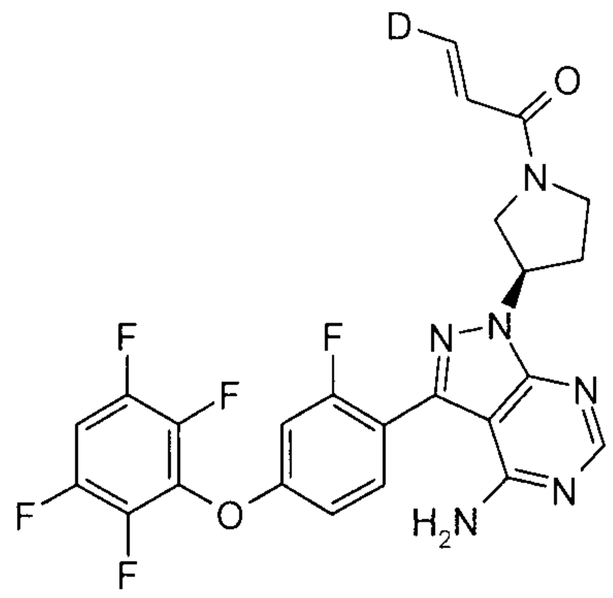
Procedure:

2-chloro-2-hydroxyacetic acid (15 mg, 0.163 mmol, 1.5 eq.), HATU (45 mg, 0.119 mmol, 1.1 eq.) and N, N- diisopropylethylamine (42 mg, 0.324 mmol, 3.0 eq.) were subsequently added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.108 mmol, 1.0 eq.) in dichloromethane (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours, quenched with saturated $NaHCO_3$ (10 mL), and then extracted with dichloromethane (10 mL) 3 times. The combined organic phases were dried over anhydrous sodium sulfate, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 10% to 100% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (3.4 mg, yield: 6%).

Spectroscopy data:

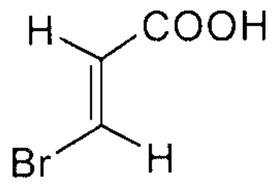
LC/MS (Method: UFLC): RT = 4.221 min; m/z = 569.0 $[M+H]^+$; Total running time: 7 min.

Example 120



(E)-1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyrimidin-1-yl)pyrrolidin-1-yl)-3-deuterium-prop-2-en-1-one

Step A:



(E)-3-bromoacrylic acid

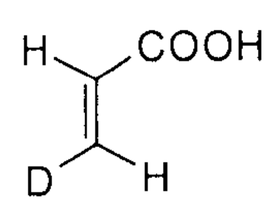
Procedure:

A mixture of propiolic acid (1 g, 14.28 mmol, 1.0 eq.) and HBr (40% aqueous solution, 1.7 mL, 0.88 eq.) was stirred overnight at 140 °C, and evaporated to remove the solvent under reduced pressure, the obtained crude product was crystallized from water (4 mL) three times to give the target compound (0.76 g, yield: 35%).

Spectroscopy data:

^{1}H NMR (400MHz, $CDCl_3$) δ 7.76 (d, J = 14 Hz, 1H), 6.55 (d, J = 14 Hz, 1H).

Step B:



(E)-3-deuterium acrylate

Procedure:

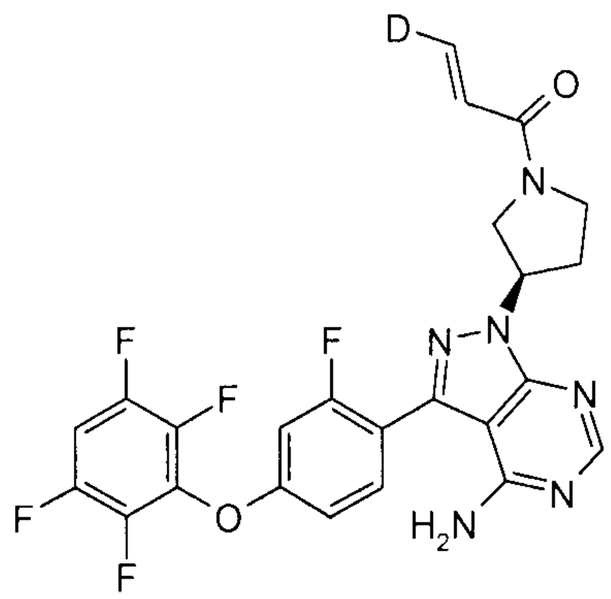
Na-Hg (6 g, 49.67mmol, 2.5 eq.) was added to a solution of (E)-3-bromoacrylic acid (3 g, 19.87 mmol, 1.0 eq.) in D_2O (30 mL) at 0 to 5 °C. The reaction mixture was stirred at room temperature for 36 hours and separated. The aqueous phase was adjusted to pH=5 with 1M

hydrochloric acid, and then extracted with diethyl ether (20 mL) 5 times. The combined organic phases were dried over anhydrous sodium sulfate, and evaporated to remove the solvent under reduced pressure, so as to give the target compound (0.52 g, yield: 36%).

Spectroscopy data:

^{1}H NMR (400MHz, $CDCl_3$) δ 7.76 (d, J = 17.2 Hz, 1H), 6.55 (d, J = 17.2 Hz, 1H).

Step C:



(E)-1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyrimidin-1-yl)pyrrolidin-1-yl)-3-deuterium-prop-2-en-1-one

Procedure:

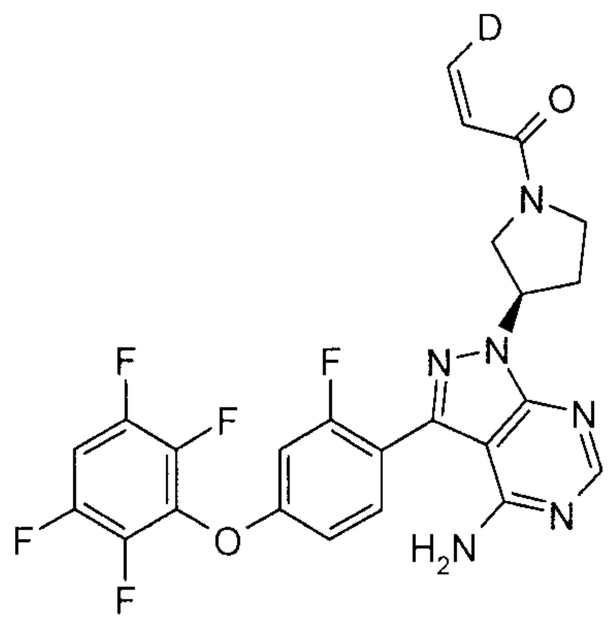
(E)-3-deuterium acrylate (76 mg, 1.08 mmol, 1.0 eq.), HATU (530 mg, 1.40 mmol, 1.3 eq.) and N,N-diisopropylethylamine (419 mg, 3.24 mmol, 3.0 eq.) were subsequently added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (500 mg, 1.08 mmol, 1.0 eq.) in dichloromethane (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 36% to 37% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (76 mg, yield: 13%).

Spectroscopy data:

LC/MS (Method: UFLC): RT = 2.765min; m/z = 518.1 $[M+H]^+$; Total running time: 7 min.

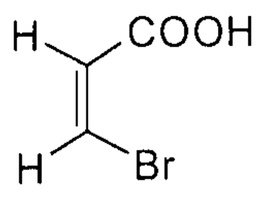
^{1}H NMR (400MHz, CD_3OD)δ 8.41 (s, 1H), 7.66 (t, J = 8.4 Hz, 1H), 7.51-7.44 (m, 1H), 7.09-7.01 (m, 2H), 6.66-6.56 (m, 1H), 6.28-6.23(m, 1H),5.75-5.66 (m, 1H), 4.19-4.16 (m, 1H), 4.06-4.02 (m, 1.5H), 3.89-3.85 (m, 1H), 3.78-3.72 (m, 0.5H), 2.63-2.49 (m, 2H).

Example 121



(Z)-1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyrimidin-1-yl)pyrrolidin-1-yl)-3-deuterium-prop-2-en-1-one

Step A:



(Z)-3-bromoacrylic acid

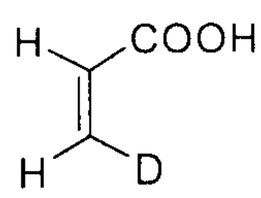
Procedure:

A mixture of propiolic acid (1 g, 14.28 mmol, 1.0 eq.) and HBr (40% aqueous solution, 1.7 mL, 0.88 eq.) was stirred overnight at 55 °C, and evaporated to remove the solvent under reduced pressure, the obtained crude product was crystallized from water (4 mL) three times to give the target compound (0.3 g, yield: 14%).

Spectroscopy data:

^{1}H NMR (400MHz, $CDCl_3$) δ 7.16 (d, J = 8.4 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H).

Step B:



(Z)-3-deuterium acrylate

Procedure:

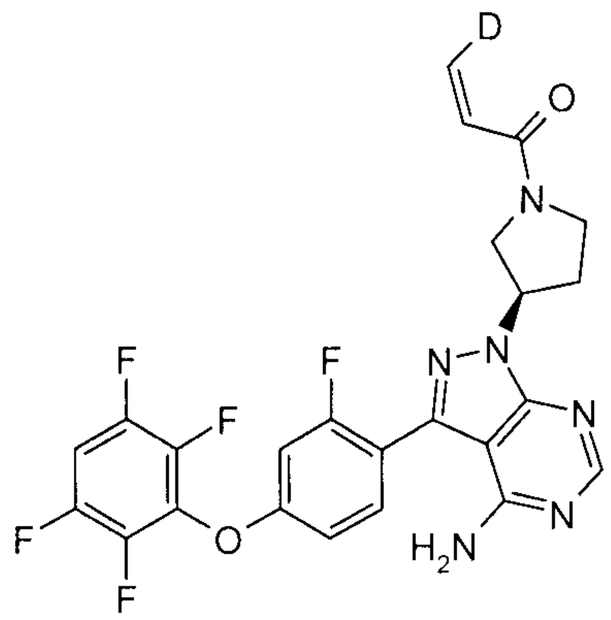
Na-Hg (6 g, 49.67mmol, 2.5 eq.) was added to a solution of (Z)-3-bromoacrylic acid (3 g, 19.87 mmol, 1.0 eq.) in D_2O (30 mL) at 0 to 5 °C. The reaction mixture was stirred at room

temperature for 36 hours and separated. The aqueous phase was adjusted to pH=5 with 1M hydrochloric acid, and then extracted with diethyl ether (20 mL) 5 times. The combined organic phases were dried over anhydrous sodium sulfate, and evaporated to remove the solvent under reduced pressure, so as to give the target compound (0.34 g, yield: 23%).

Spectroscopy data:

^{1}H NMR (400MHz, $CDCl_3$) δ 6.14 (d, J = 10.4 Hz, 1H), 5.96 (d, J = 10.4 Hz, 1H).

Step C:



(Z)-1-((R)-3-(4-amino-3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyrimidin-1-yl)pyrrolidin-1-yl)-3-deuterium-prop-2-en-1-one

Procedure:

(Z)-3-deuterium acrylate (151 mg, 2.16 mmol, 1.0 eq.), HATU (1.06 g, 2.80 mmol, 1.3 eq.) and N,N-diisopropylethylamine (838 mg, 6.48 mmol, 3.0 eq.) were subsequently added to a solution of 3-(2-fluoro-4-(2,3,5,6-tetrafluorophenoxy)phenyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (1.0 g, 2.16 mmol, 1.0 eq.) in dichloromethane (3 mL). The reaction mixture was stirred at room temperature for 12 hours, concentrated and spin-dried to give the crude product, which was purified by HPLC with C18 reversed-phase column (mobile phase: acetonitrile/water/0.5% HCl, gradient: 36%-37% (volume ratio)), evaporated to remove volatile components under reduced pressure, and lyophilized to give the hydrochloride of the target compound (228 mg, yield: 20%).

LC/MS (Method: UFLC): RT = 2.775min; m/z = 518.1 $[M+H]^+$; Total running time: 7 min.

^{1}H NMR (400MHz, CD_3OD) δ 8.45 (s, 1H), 7.70 (t, J = 8.4 Hz, 1H), 7.52-7.46 (m, 1H), 7.13-7.05 (m, 2H), 6.71-6.61 (m, 1H), 5.80-5.73 (m, 2H), 4.23-4.20 (m, 1H), 4.09-4.04 (m, 1.5H), 3.93-3.90 (m, 1H), 3.80-3.75 (m, 0.5H), 2.67-2.56 (m, 2H).

In Vitro Assay

Inhibition Assay of BTK Kinase Activity: The assay compound, the contrast compound or water (control) were added into a 50 mM HEPES (pH=7.5) buffer containing 1 nM BTK wild type, 1 μM biotin-TK1 peptide, and 30 μM ATP in a buffer. The mixture was incubated at room temperature for 60 min., and quenched by adding EDTA. Then, a 2 nM antibody and 62.5 nM XL665 were added to the inhibitors (5μl). The plates were incubated at room temperature for 60 min. and then the plate reader (Envision, Perkin Elmer) was used to measure the fluorescence intensity, then the readouts were transformed into kinase activity inhibition rate%.

In Vivo Assay

A pharmacokinetic study in male SD rats: Male SD rats for a 24-hour pharmacokinetic study were divided into two groups: intravenous administration and oral administration. Each group had three rats. For the intravenous administration group, blood samples were collected at 0.0833, 0.167, 0.5,1, 2, 4, 8, 24 hours pre-dose and post-dose; for oral administration group, blood samples were collected at 0.167, 0.5, 1, 2, 4, 8, 24 hours pre-dose and post-dose. After blood collection, HPLC-MS/MS was applied to determine plasma concentrations of the compound. The calculated pharmacokinetic parameters of intravenous group included mean plasma clearance (CLp), mean apparent volume of distribution at stead state (Vdss), 0-24 hours area under the curve (AUC), 0-24 hours mean residence time (MRT), the half-life (T1/2); The calculated pharmacokinetic parameters of oral group included mean peak concentration (Cmax), 0-24 hours area under the curve (AUC), 0-24 hours mean residence time (MRT); mean relative bioavailability for the study.

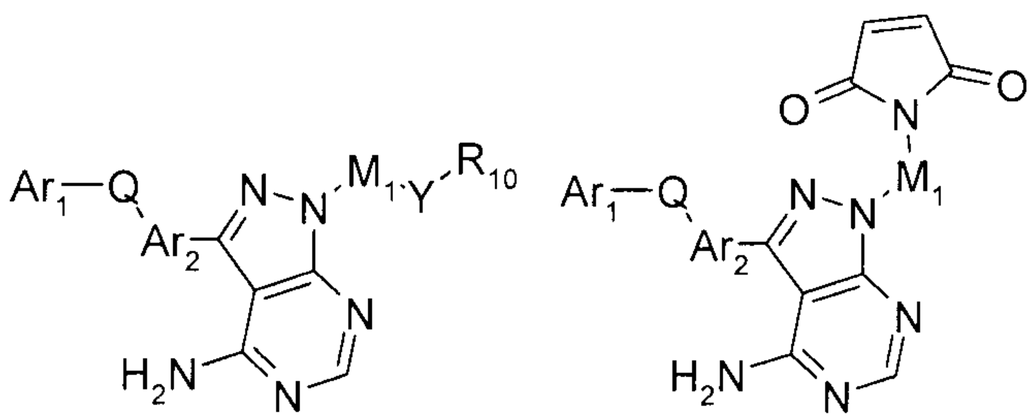
A pharmacokinetic study in Beagle dogs: Beagle dogs for 24-hour pharmacokinetic study were divided into two groups: intravenous administration (1 mg per kilogram) and oral administration (3 mg per kilogram). Each group had three dogs. For intravenous administration group, blood samples were collected at 0.033, 0.083, 0.25, 0.5, 1, 3, 6, 9, 24 hours pre-dose and post-dose; for oral administration group, blood samples were collected at 0.083, 0.25, 0.5, 1, 3, 6, 9, 24 hours pre-dose and post-dose. After blood collection, HPLC-MS/MS was applied to determine plasma concentrations of the compound. The calculated pharmacokinetic parameters of intravenous group included mean plasma clearance (CLp), mean apparent

volume of distribution at stead state (Vdss), 0-24 hours area under the curve (AUC), 0-24 hours mean residence time (MRT), the half-life (T1/2); The calculated pharmacokinetic parameters of oral group include mean peak concentration (Cmax), 0-24 hours area under the curve (AUC), 0-24 hours mean residence time (MRT); mean relative bioavailability for the study.

Inhibition study of tumor growth in vivo: SCID mice or nude mice (weighing about 18 g at the beginning of the experiment) were randomly divided into groups by the software in order to achieve close average weights among groups and control the deviations within an allowable range. The mice were injected with BTK cell lines for tumor formation. Inhibitors were administered orally once or twice daily, for a total of 7 days or 14 days. Body weights and tumor volume were recorded.

CLAIMS:

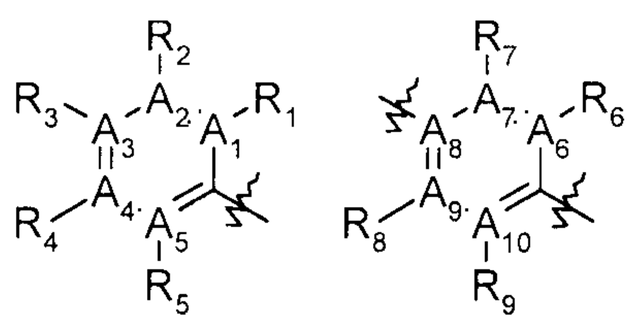
1. A compound of Formula (I) and (II), an enantiomer thereof, a diastereomer thereof, or a pharmaceutically acceptable salt thereof.



(I) (II)

wherein:

Ar_1 and Ar_2 are independently selected from (III) and (IV):



(III) (IV)

wherein:

A_1, A_2, A_3, A_4, A_5, A_6, A_7, A_8, A_9 and A_{10} are independently C or N (no substituent connected thereto);

R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9 are independently hydrogen, deuterium, amino, halogen, hydroxy, carbonyl, nitro, cyano, amide group, lower alkyl sulfonamide group, C_2-C_6 alkenyl, C_2-C_6 alkynyl, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_{10} cycloalkyl; wherein the alkyl, alkoxyl or cycloalkyl are each optionally substituted with deuterium, halogen, amino, hydroxy, carbonyl, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxyl;

wherein R_6, R_7, R_8, R_9, together with NH_2 from a pyrimidine ring, can form a 6 to 8 membered saturated or unsaturated heteroaromatic ring or heterocyclic ring;

Ar_1 is independently selected from benzoaryl and benzo-heteroaryl, wherein the substituent is independently selected from deuterium, amino, halogen, hydroxy, carbonyl, nitro, cyano,

amide group, lower C_1-C_6 alkyl, C_1-C_6 alkoxyl; C_3-C_{10} cycloalkyl; wherein the alkyl, alkoxyl or cycloalkyl are each optionally substituted with deuterium, halogen, amino, hydroxy, carbonyl, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxyl,

Q is O, S or C(=O);

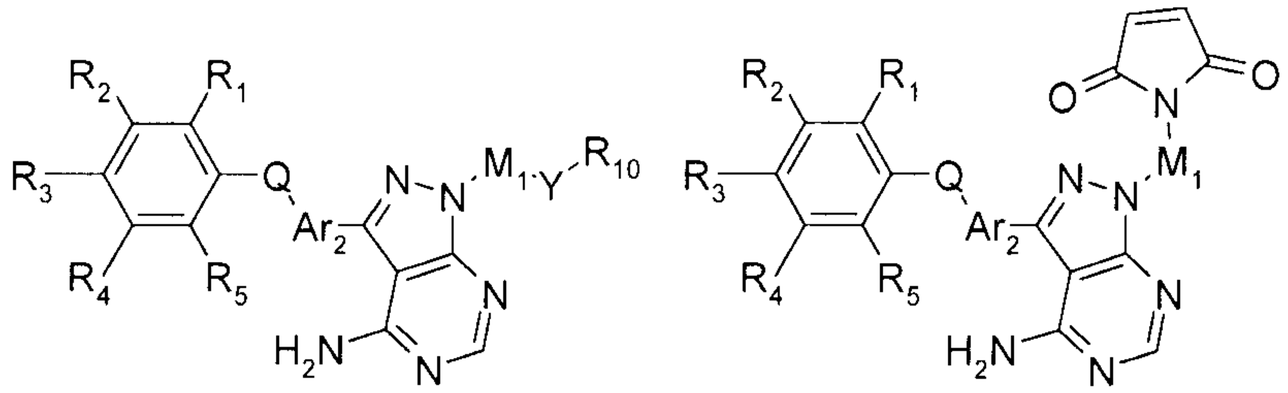
M_1 is a saturated or unsaturated C_1-C_8 carbon chain, C_6-C_{10} aryl, C_6-C_{10} aryl C_1-C_6 alkyl, alkylaryl, heteroaryl, heteroaryl alkyl, alkyl heteroaryl, cycloalkyl, cycloalkyl alkyl, alkyl cycloalkyl, heterocycloalkyl, heterocycloalkylalkyl, alkyl heterocycloalkyl; wherein hydrogen atoms on the carbon chain, aryl, heteroaryl, cycloalkyl and heterocycloalkyl can be optionally substituted with alkyl, cycloalkyl, alkoxyl, cycloalkoxyl, amino, cyano, amide group or halogen;

Y is C(=O), $NR_{11}C(=O)$ or $S(=O)_2$;

R_{10}, R_{11} can be independently selected from amino, cycloamino, aryl, heteroaryl, heterocycloalkyl, oxo-heterocyclyl, trifluoromethyl, trifluoromethoxy, trifluoroacetyl, amide group, acyl, guanidyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_1-C_6 alkoxyl, C_1-C_6 oxoalkyl; wherein the amino, amide group, acyl, C_2-C_6 alkenyl, alkyl, alkoxyl or cycloalkyl can be further optionally substituted with deuterium, halogen, amino, hydroxy, hydroxy alkyl, carbonyl, ester group, amide group, nitro, cyano, trifluoroacetyl, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_1-C_6 oxoalkyl, C_3-C_{10} cycloalkyl;

the hydrogen atoms connected to carbon or nitrogen on the the aryl or hetero-ring can be optionally substituted with alkyl, cycloalkyl, alkoxyl, cycloalkoxyl, amino, cyano, amide group and halogen.

2. The compound of Claim 1, which preferably is a compound of Formular (V) and (VI), an enantiomer thereof, a diastereomer thereof, or a pharmaceutically acceptable salts thereof;



(V) (VI)

wherein:

R_1, R_2, R_3, R_4, R_5, Q, Ar_2, M_1, Y and R_{10} are as defined in Claim 1.

3. The compound of any one of Claims 1-2, an enantiomer thereof, a diastereomer thereof, or a pharmaceutically acceptable salt thereof;

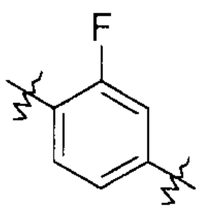
wherein: Ar_1 is a substutited or unsubstituted phenyl or heteroaryl, preferably substutited or unsubstituted phenyl, in which the substituents on the phenyl or heteroaryl are each independently are hydrogen, deuterium, amino, halogen, hydroxy, carbonyl, nitro, cyano, amide group, lower alkyl sulfonamide group, C_2-C_6 alkenyl, C_2-C_6 alkynyl, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_{10} cycloalkyl; wherein the alkyl, alkoxyl or cycloalkyl can be further substituted with deuterium, halogen, amino, hydroxy, carbonyl, nitro, cyano,C_1-C_6 alkyl, C_1-C_6 alkoxyl.

4. The compound of any one of Claims 1-3, an enantiomer thereof, a diastereomer thereof, or a pharmaceutically acceptable salt thereof,

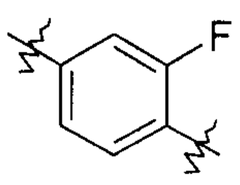
wherein: Q is O, S or C(=O), preferably O.

5. The compound of any one of Claims 1-4, an enantiomer thereof, a diastereomer thereof, or a pharmaceutically acceptable salt thereof,

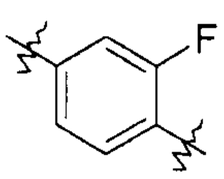
wherein: Ar_1 is phenyl or heteroaryl, preferably substituted phenyl, and more preferably



or



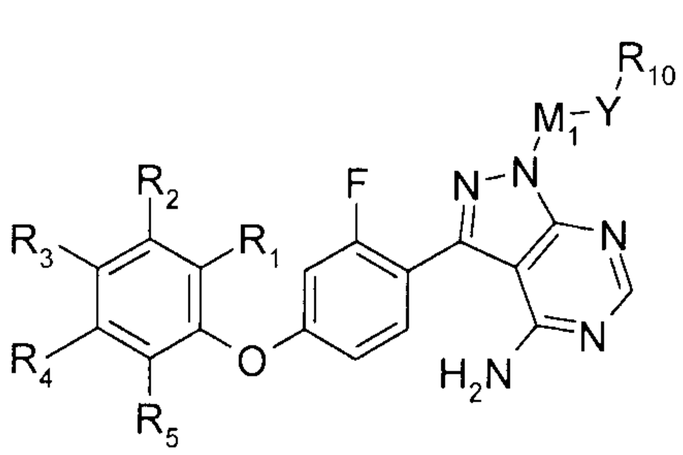
, more preferably



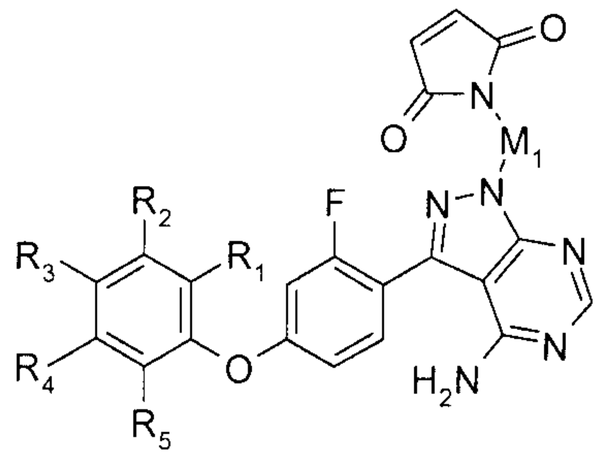
.

6. The compound of any one of Claims 1-5, an enantiomer thereof, a diastereomer thereof, or a pharmaceutically acceptable salt thereof,

wherein the compound has structures of Formula (VII) or (VIII):



(VII)



(VIII)

wherein:

R_1, R_2, R_3, R_4, R_5, M_1, Y and R_{10} are as defined in Claim 1.

7. The compound of any one of Claims 1-6, an enantiomer thereof, a diastereomer thereof, or a pharmaceutically acceptable salt thereof,

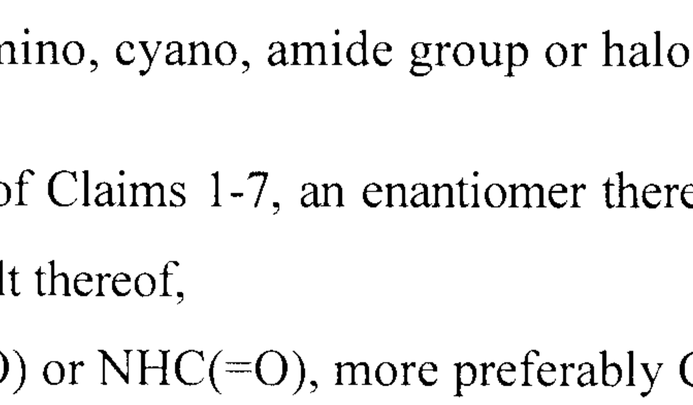
wherein: M_1 is preferably saturated or unsaturated C_1-C_8 alkyl, cycloalkyl, cycloalkyl alkyl, alkyl cycloalkyl, heterocycloalkyl, heterocycloalkyl alkyl,alkyl heterocycloalkyl; wherein a hydrogen connected to a carbon or nitrogen atom on the carbon chain, aryl, heteroaryl, cycloalkyl and heterocycloalkyl can be optionally substituted with deuterium, amino, halogen, hydroxyl, carboxyl, nitro, cyano, trifluoroacetyl, trifluoromethyl, trifluoromethoxy, alkyl, clycloalkyl, alkoxyl, amino, cyano, amide group or halogen.

8. The compound of any one of Claims 1-7, an enantiomer thereof, a diastereomer thereof, or a pharmaceutically acceptable salt thereof,

wherein: Y is preferably C(=O) or NHC(=O), more preferably C(=O).

9. The compound of any one of Claims 1-7, an enantiomer thereof, a diastereomer thereof, or a pharmaceutically acceptable salt thereof,

wherein the compound is represented by Formula (IX):



(IX)

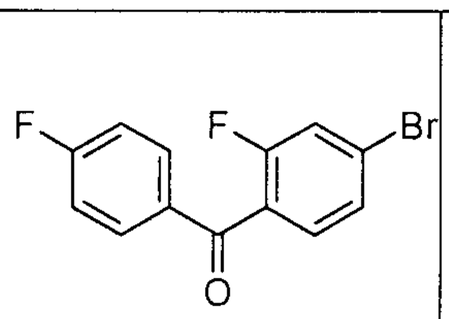
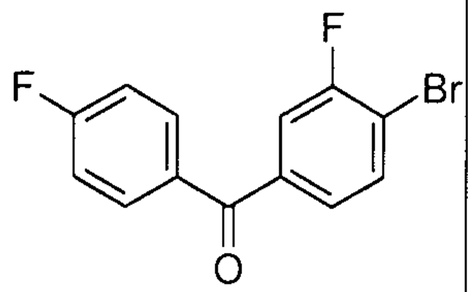
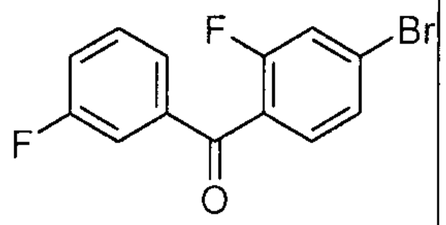
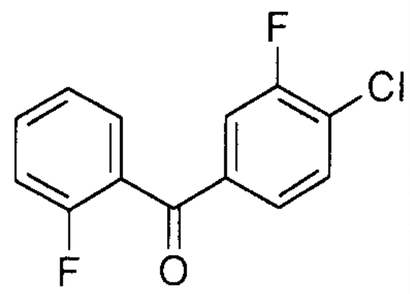
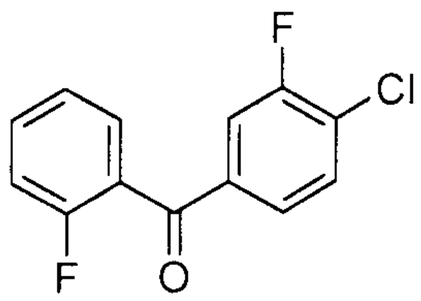
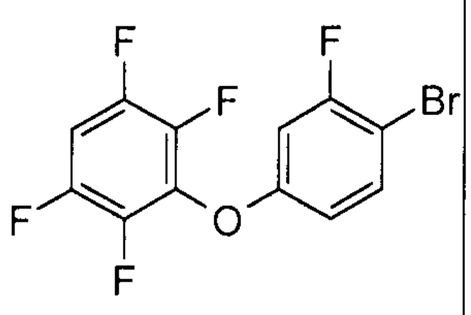
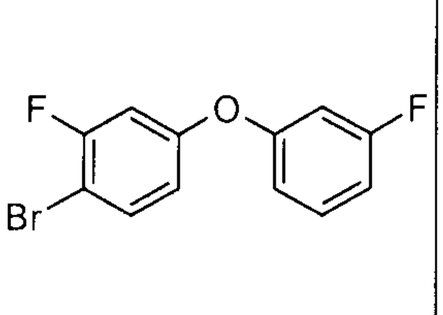
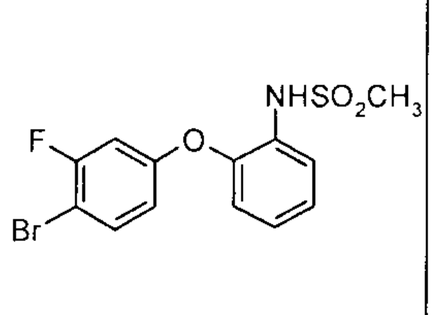
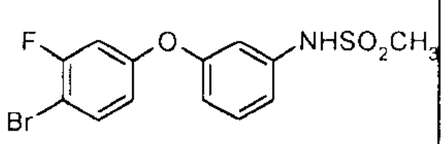
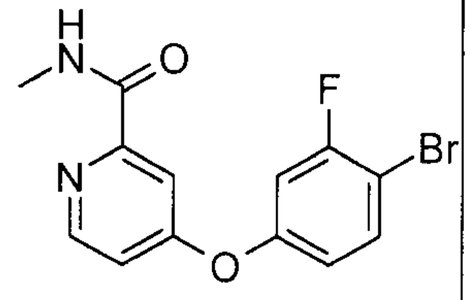
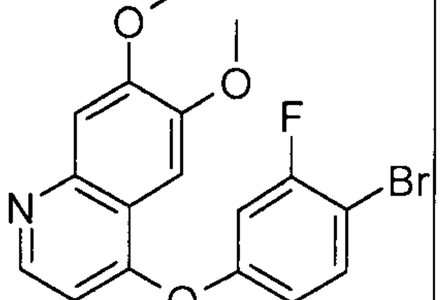
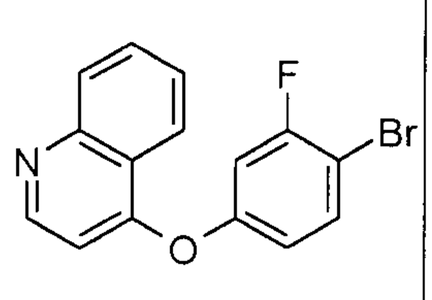
wherein: R_1, R_2, R_3, R_4, R_5, M_1 and R_{10} are as defined in Claim 1;

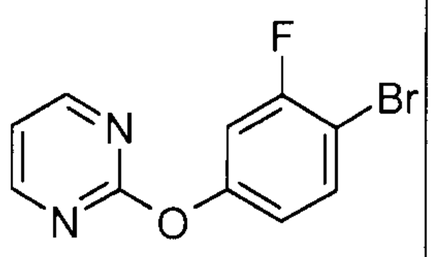
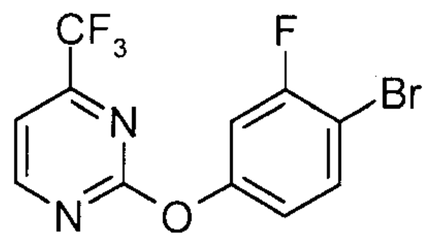
wherein: R_1, R_2, R_3, R_4 and R_5 each is preferably hydrogen, fluorine, chlorine, bromine, iodine; further preferably, R_1, R_2, R_4 and R_5 each is fluorine; further preferably, R_3 is hydrogen;

wherein: M_1 is preferably piperidinyl or pyrrolidinyl, more preferably pyrrolidinyl;

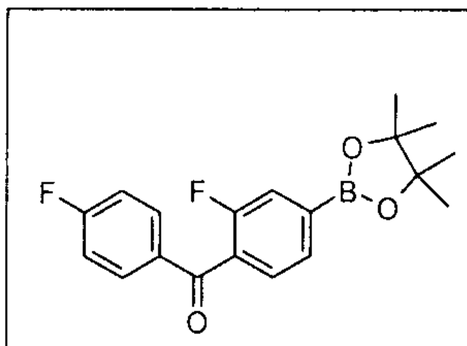
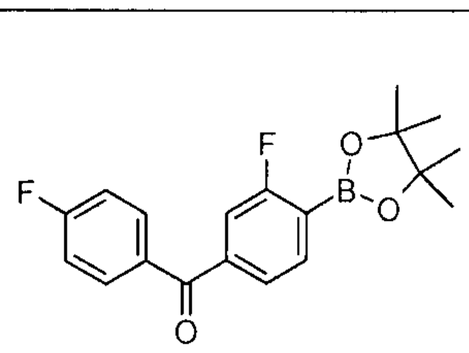
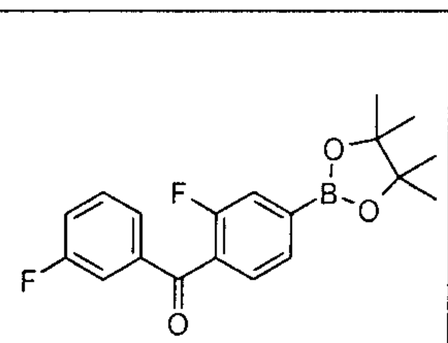
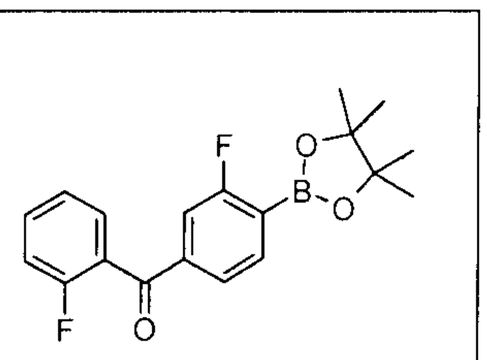
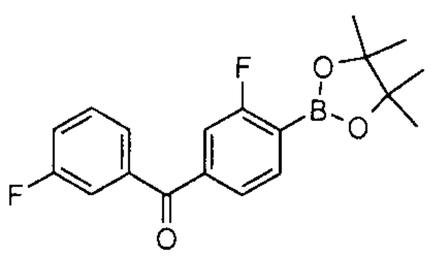
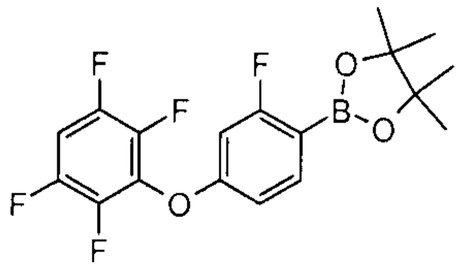
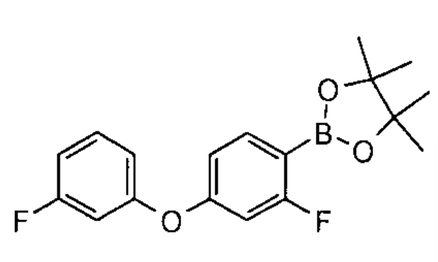
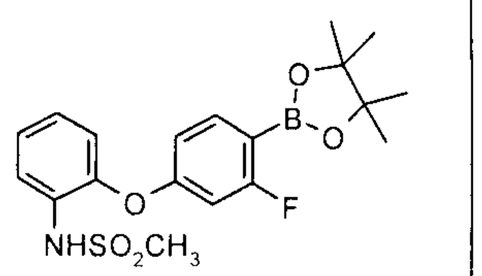
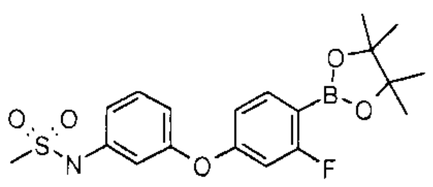
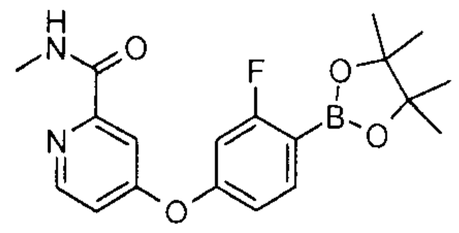
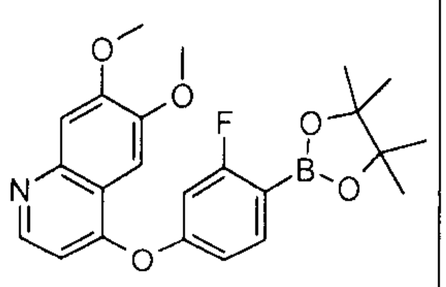
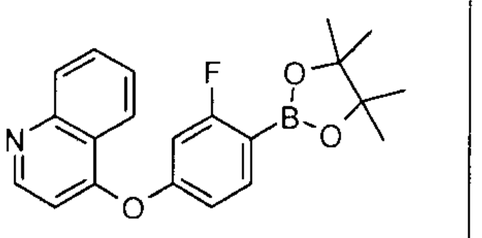
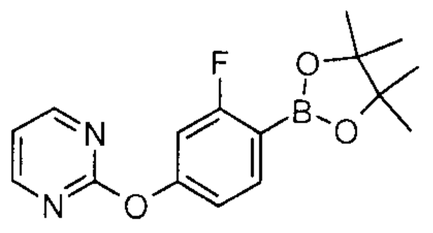
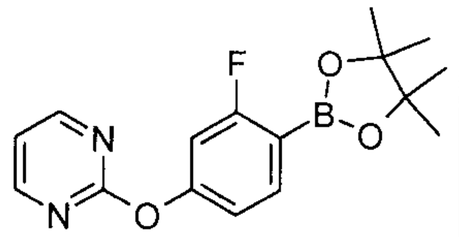
wherein: R_{10} is preferably C_2-C_6 alkenyl; wherein a hydrogen on the alkenyl can be independently substituted with deuterium, halogen, amino, cycloamino, hydroxy, hydroxy alkyl, carbonyl, ester group, amide group, nitro, cyano, trifluoroacetyl, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkyl, C_1-C_6 alkoxyl, C_3-C_{10} cycloalkyl.

10. A compound represented by the following formulae:

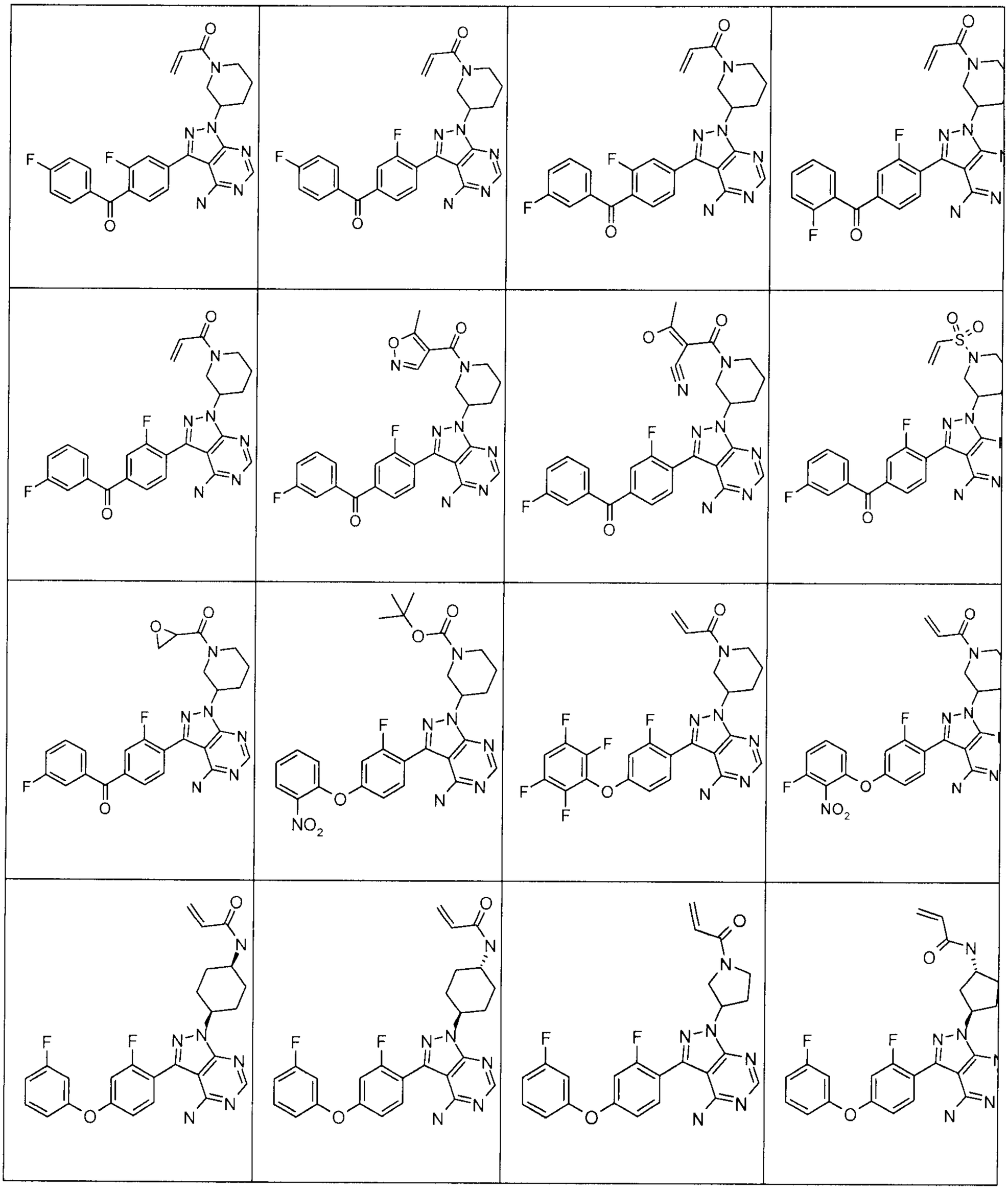
			
			
			

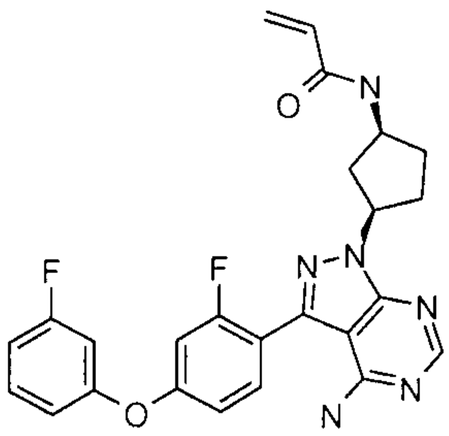
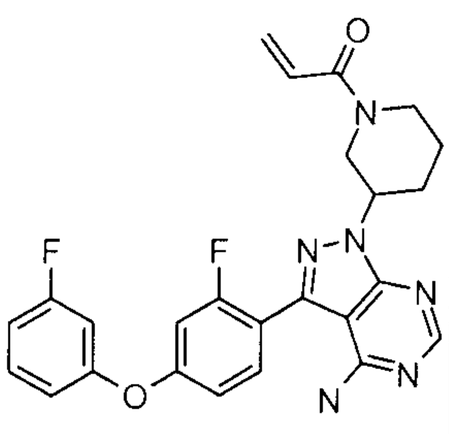
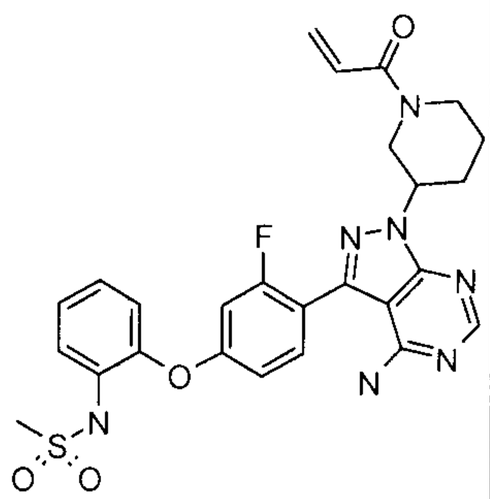
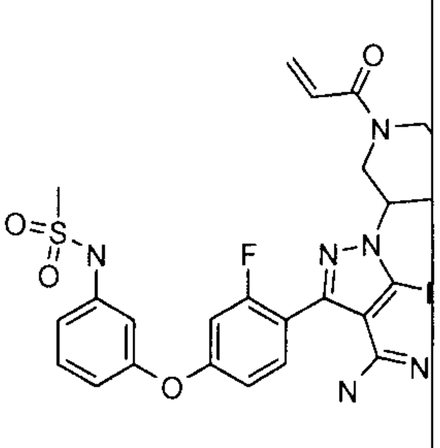
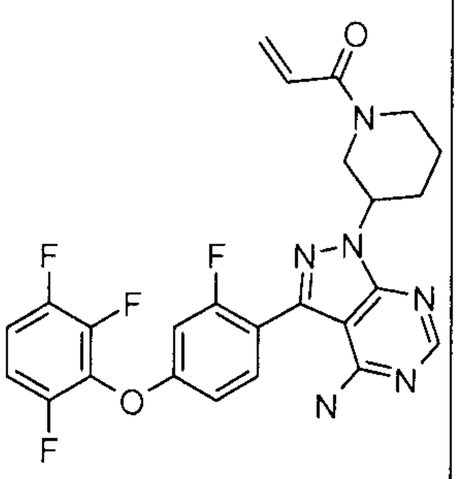
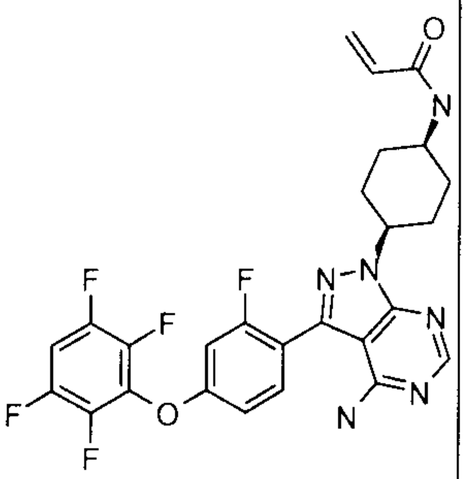
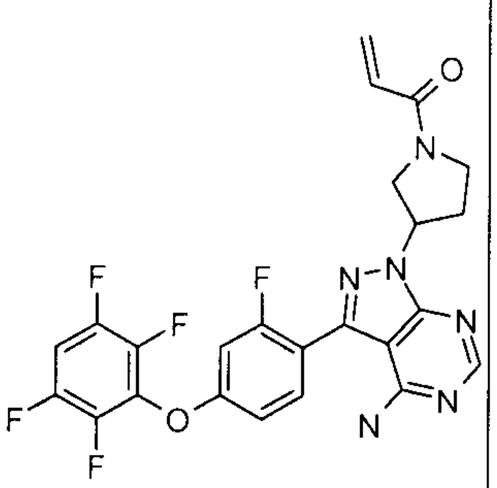
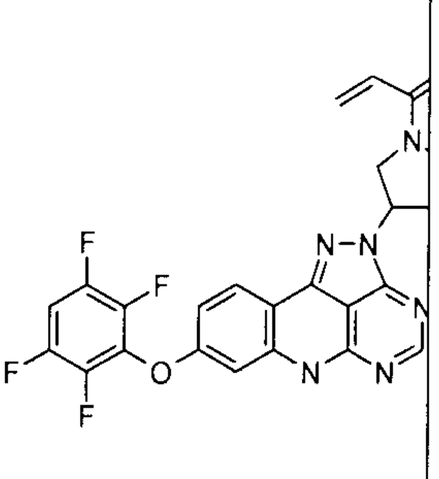
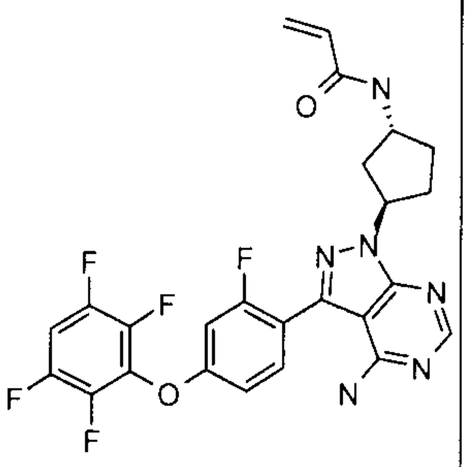
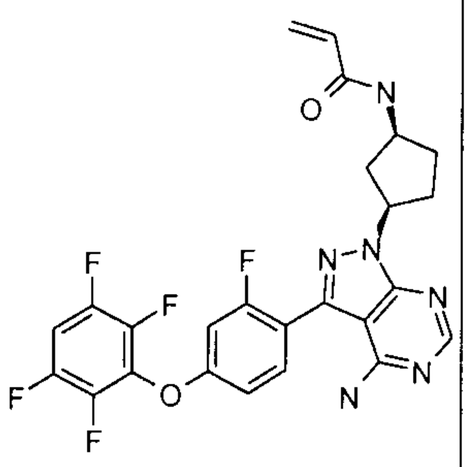
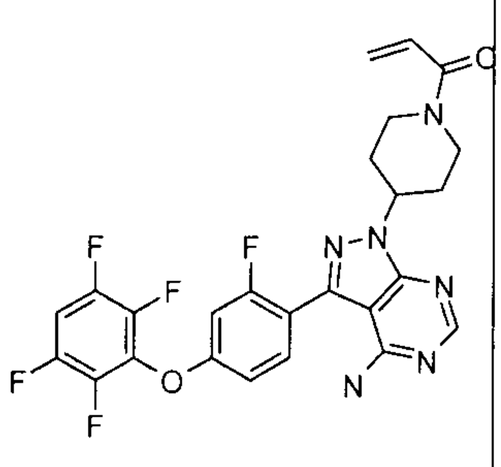
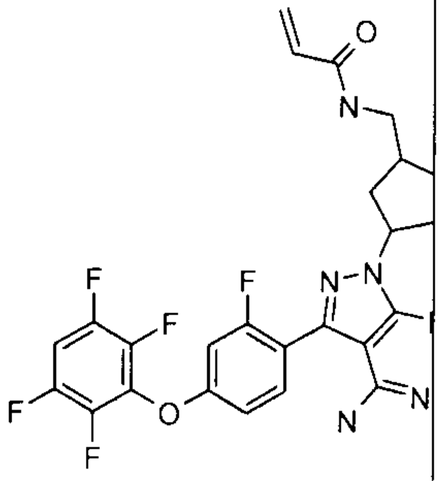
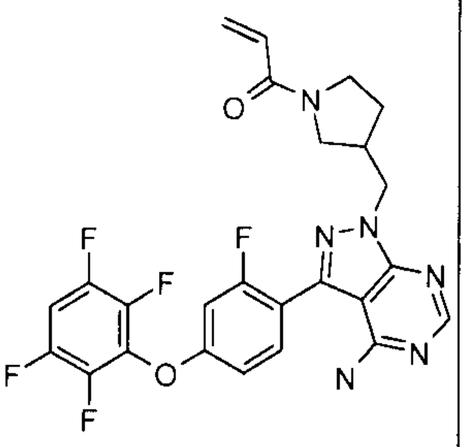
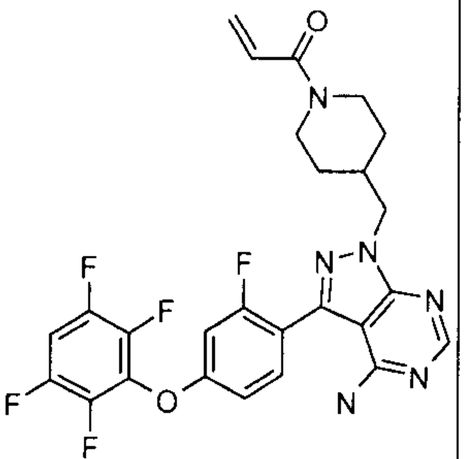
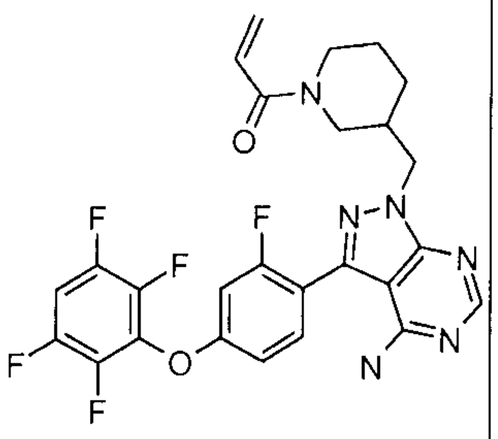
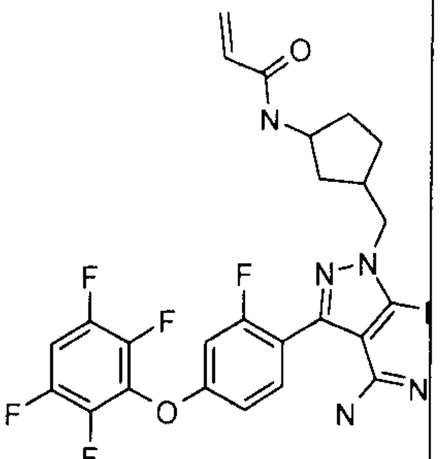
			

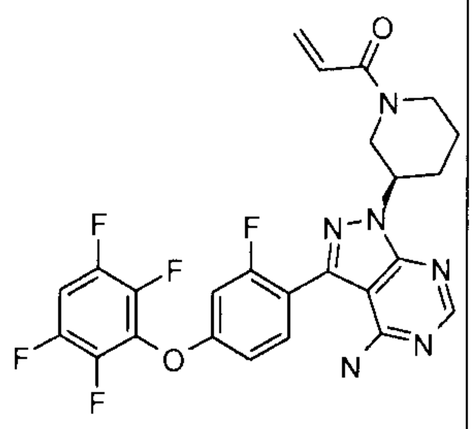
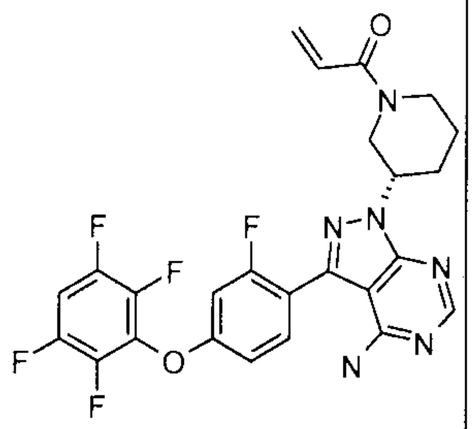
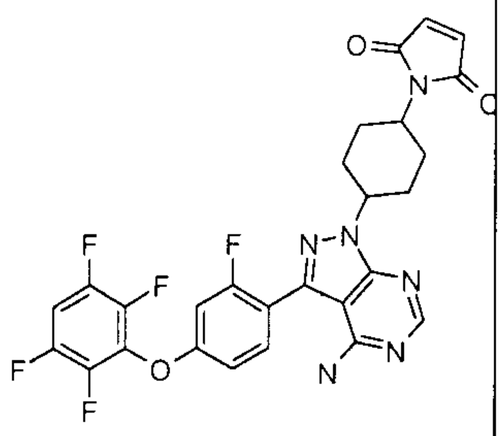
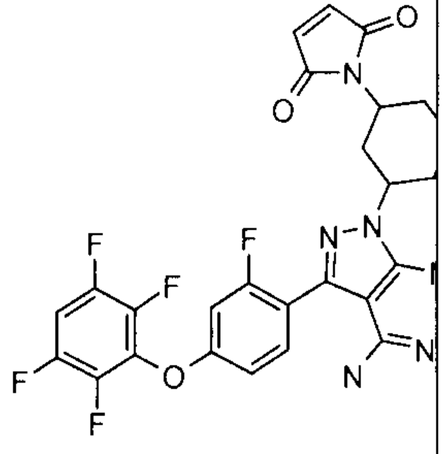
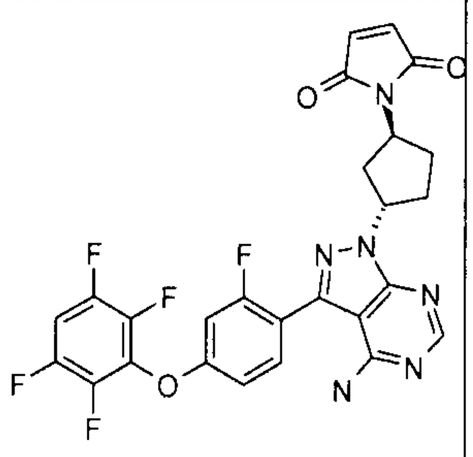
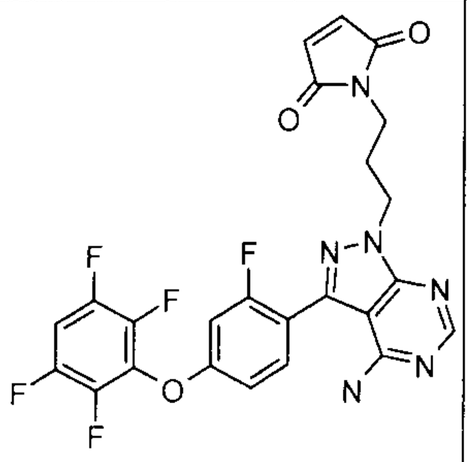
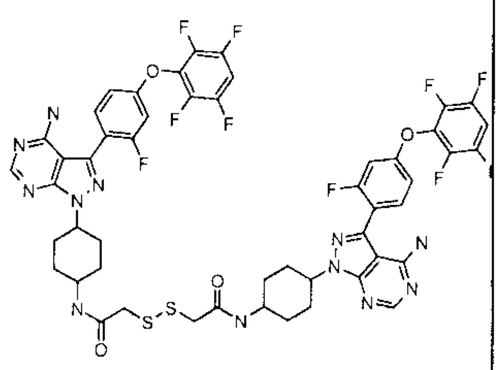
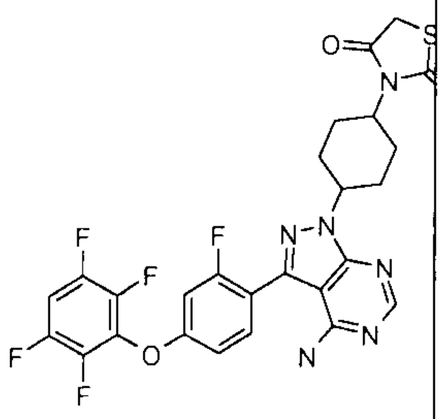
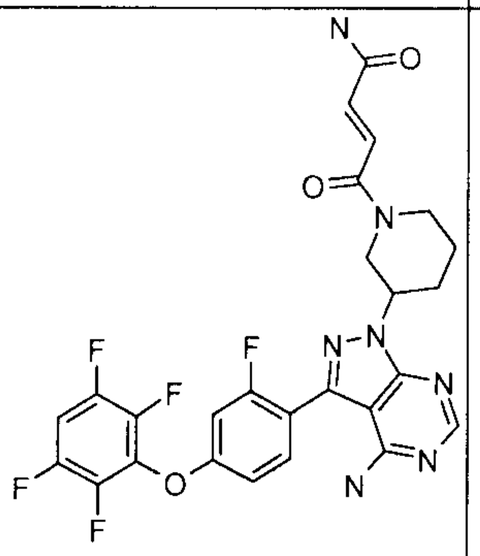
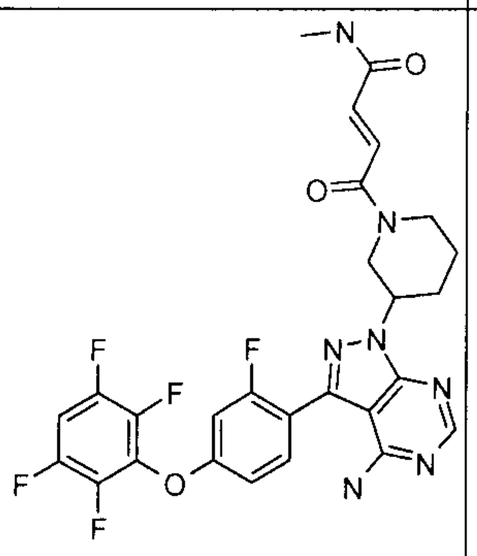
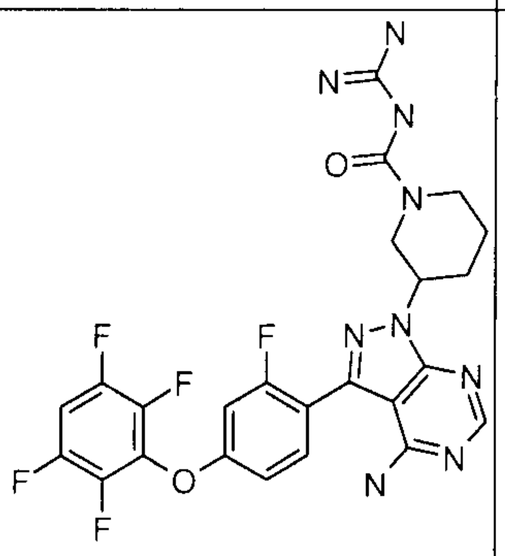
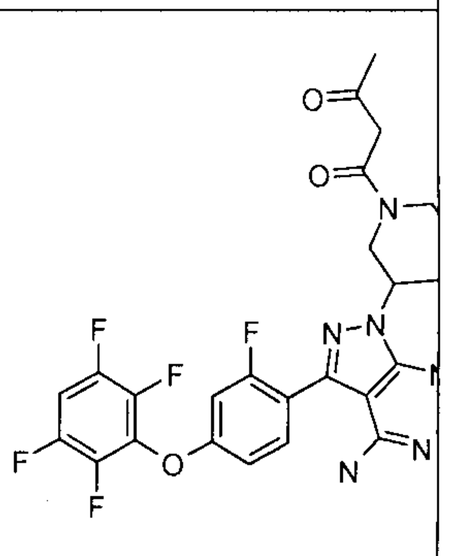
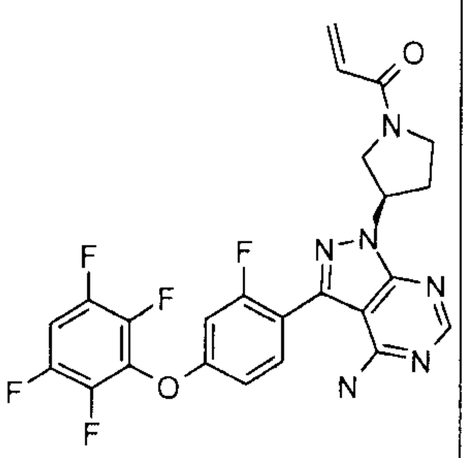
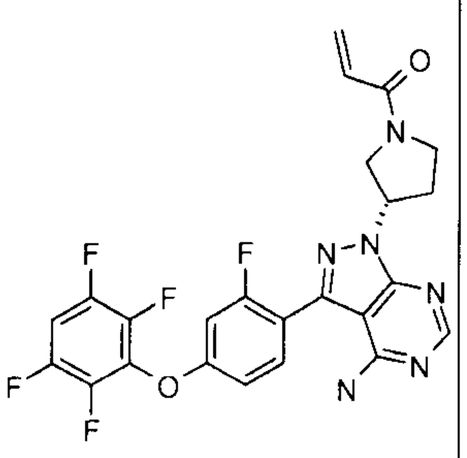
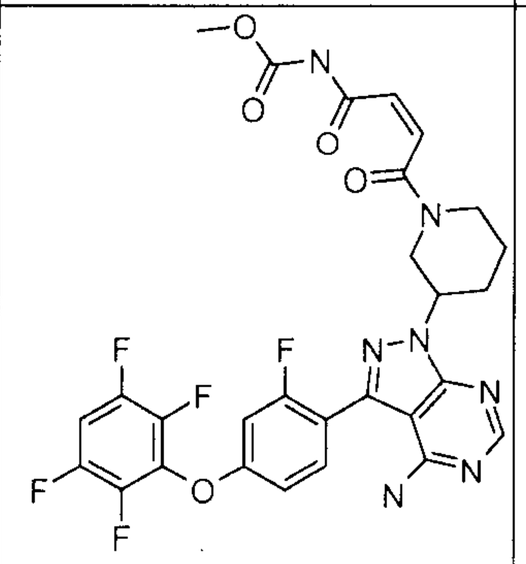
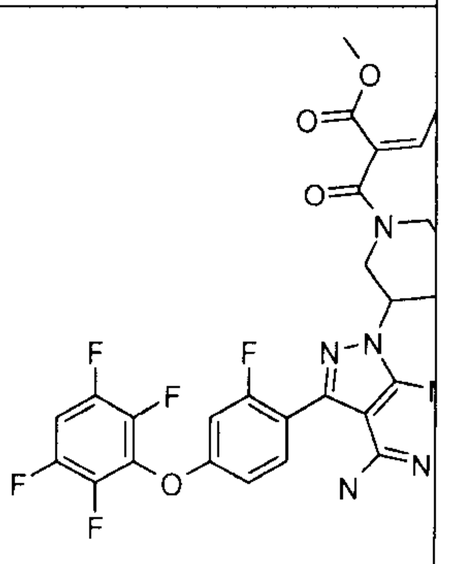
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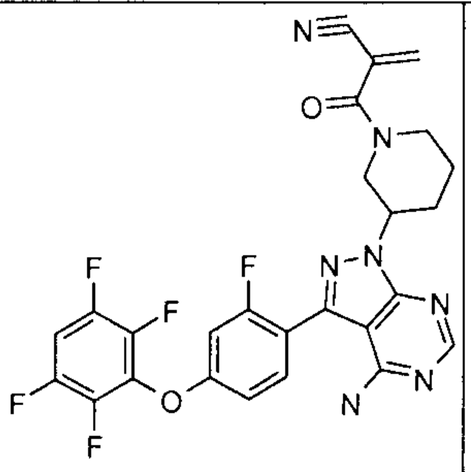
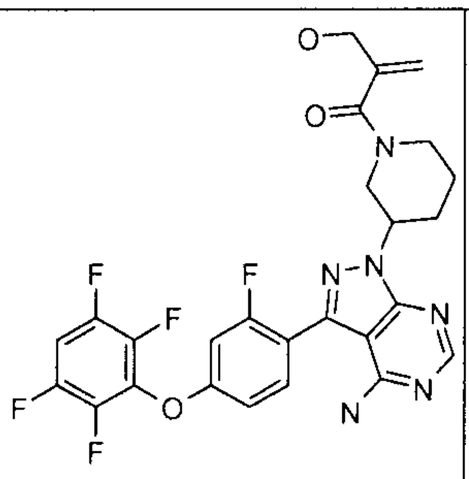
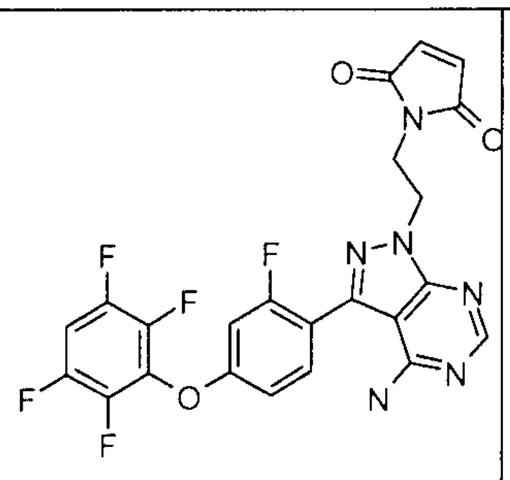
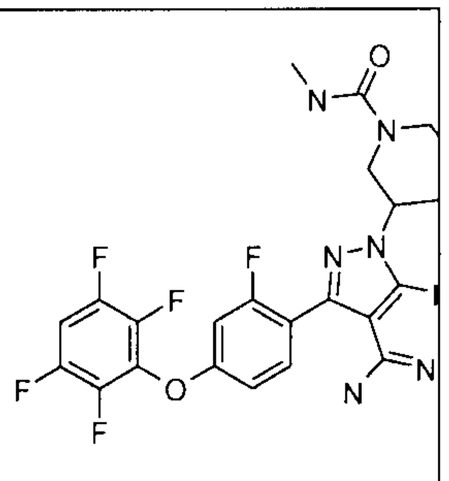
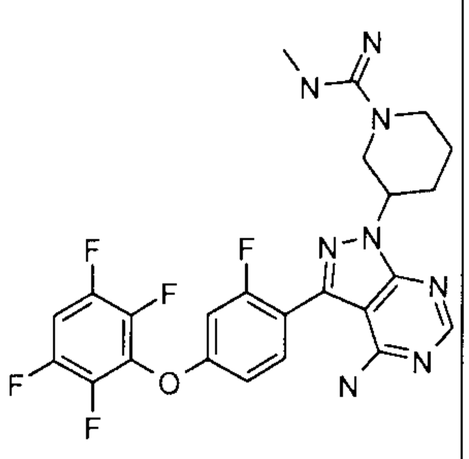
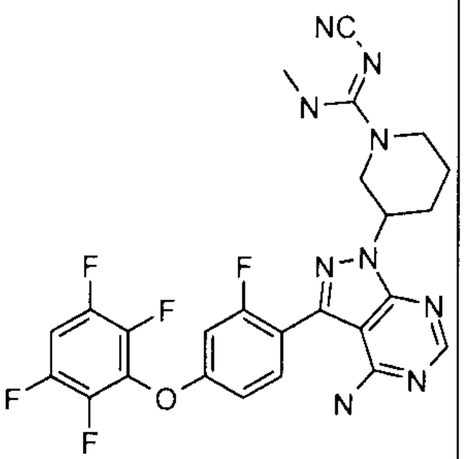
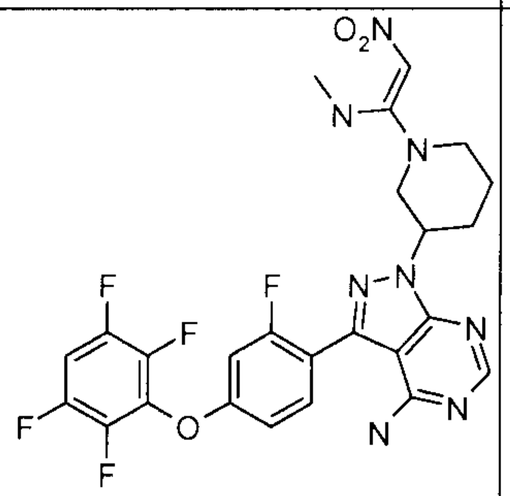
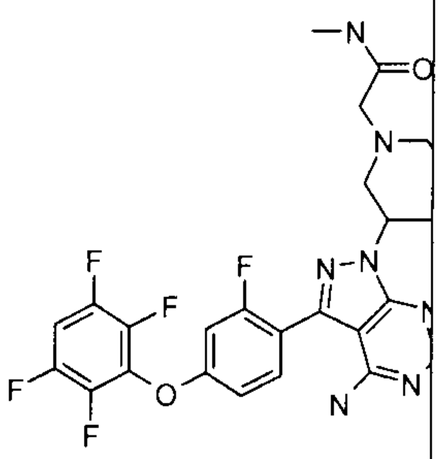
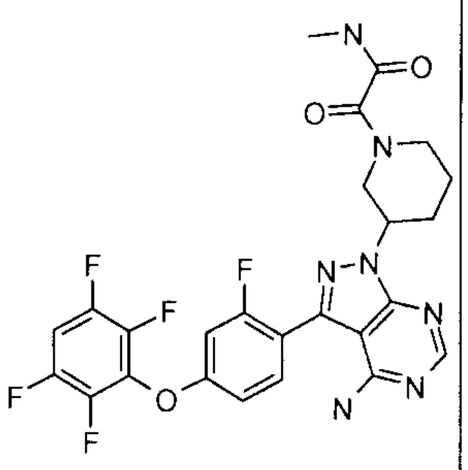
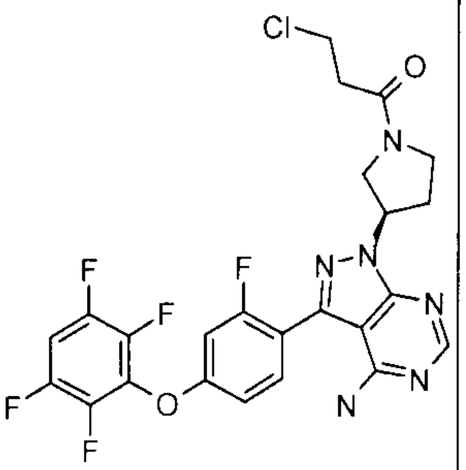
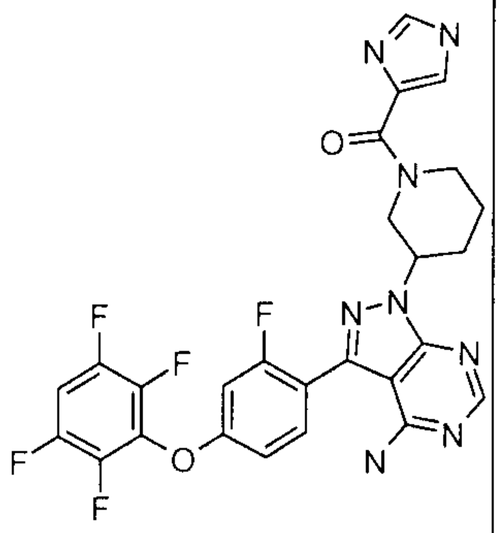
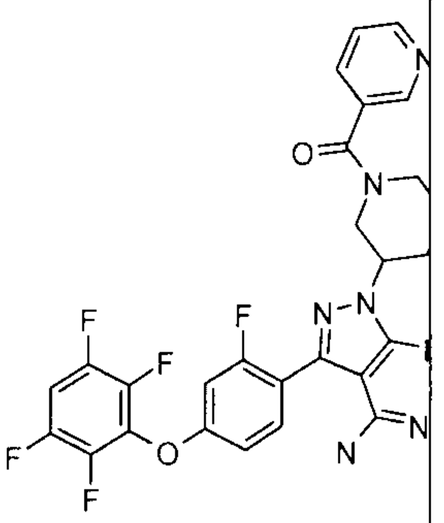
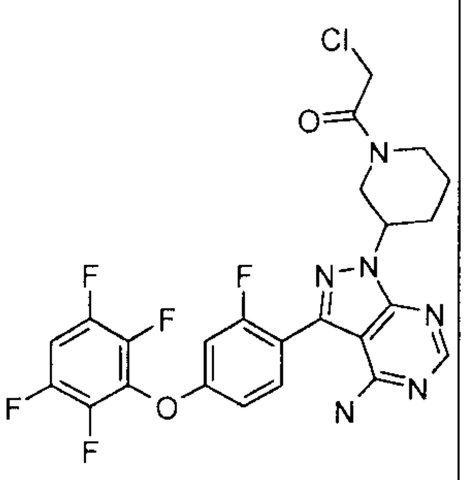
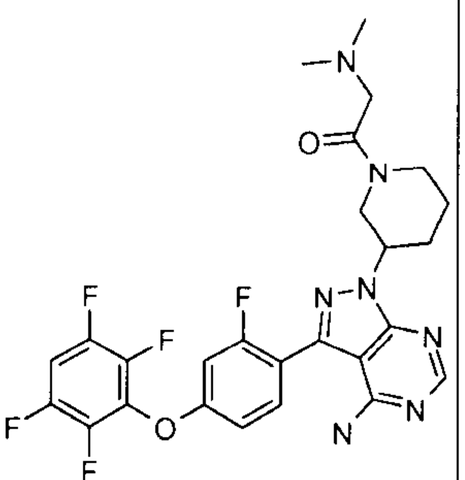
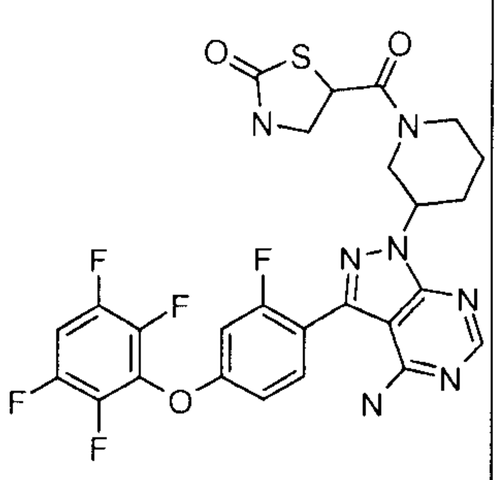
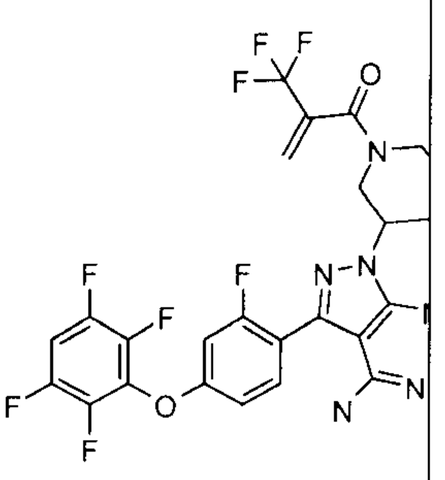
			
			
			
			

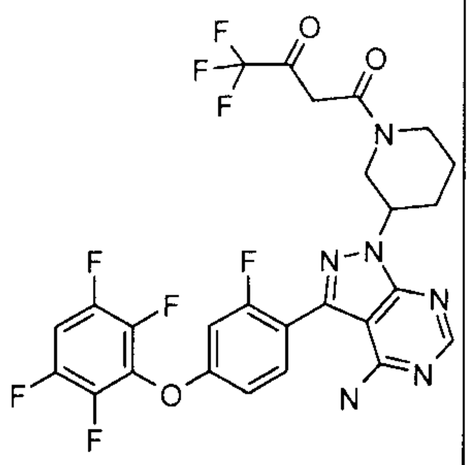
12. A compound represented by the following formulae, an enantiomer thereof, a diastereomer thereof, or a pharmaceutically acceptable salt thereof.

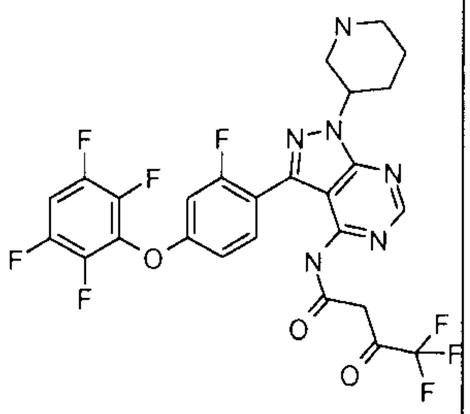


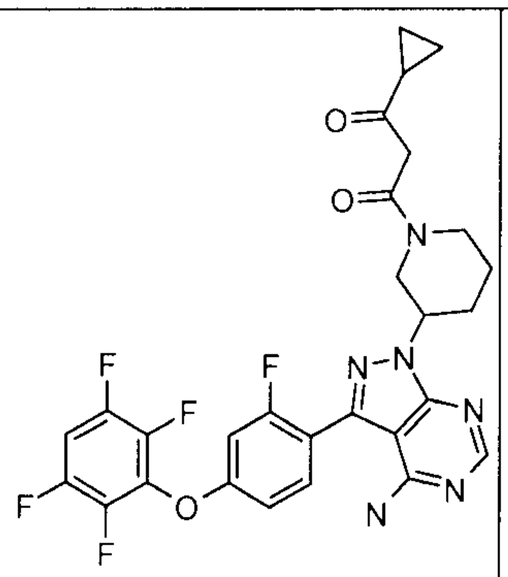
			
			
			
			

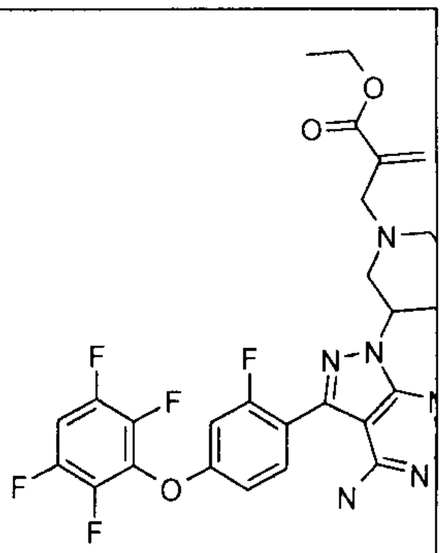
			
			
			
			

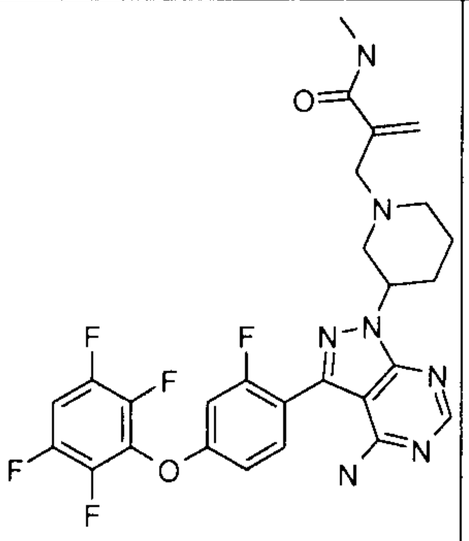
			
			
			
			

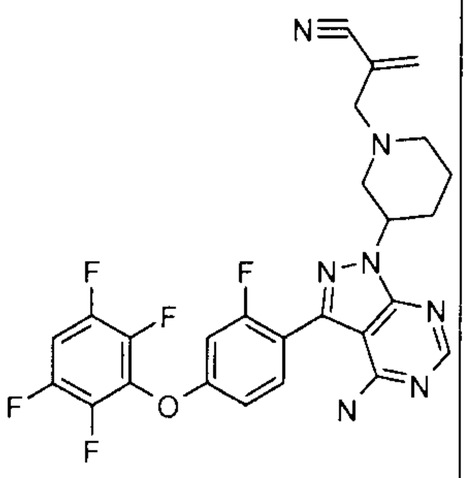


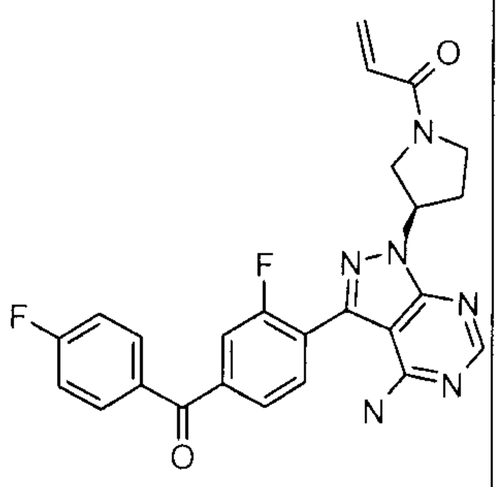


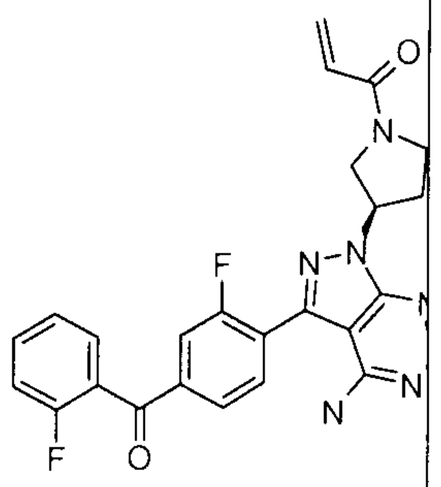


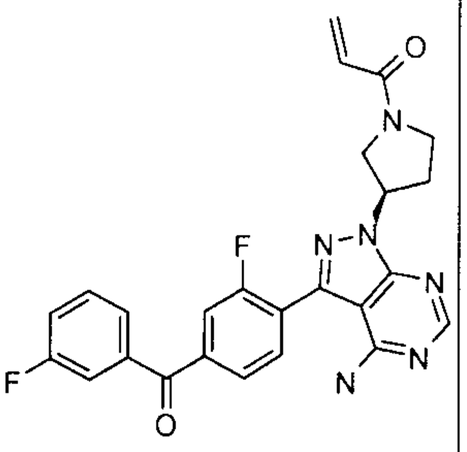


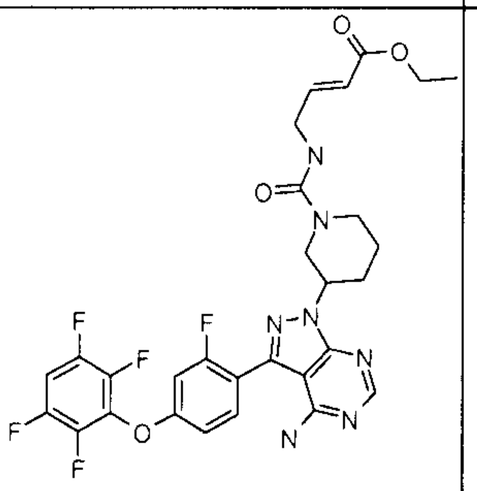


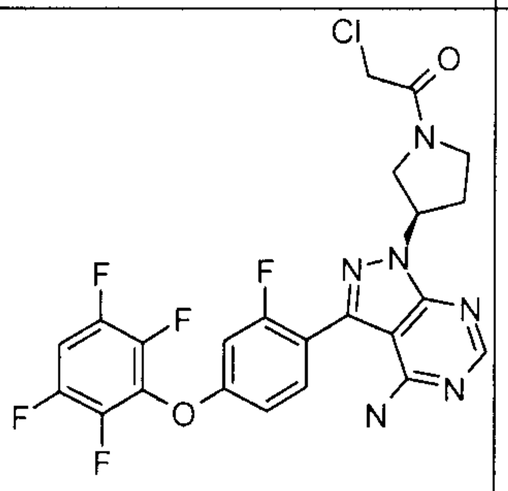


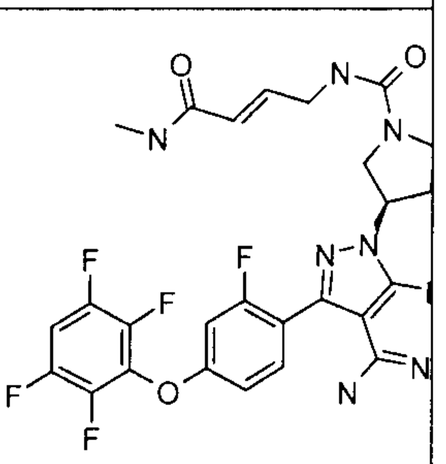


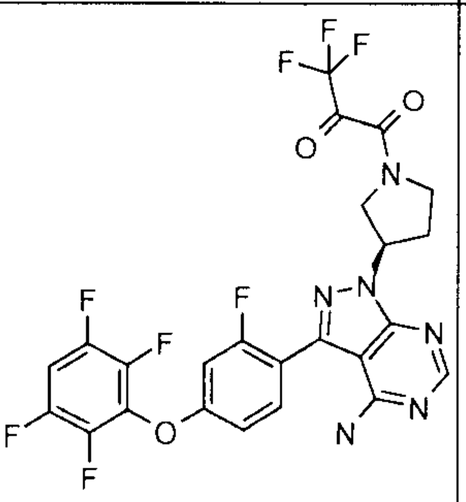


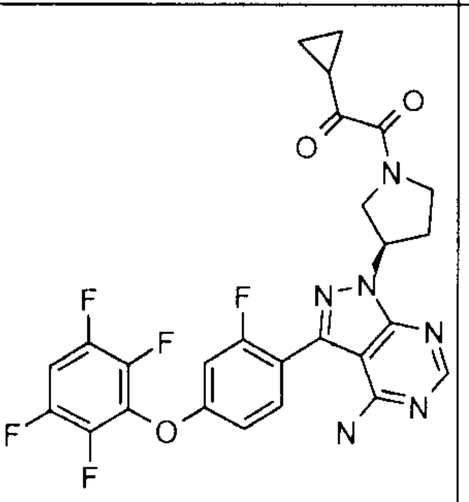


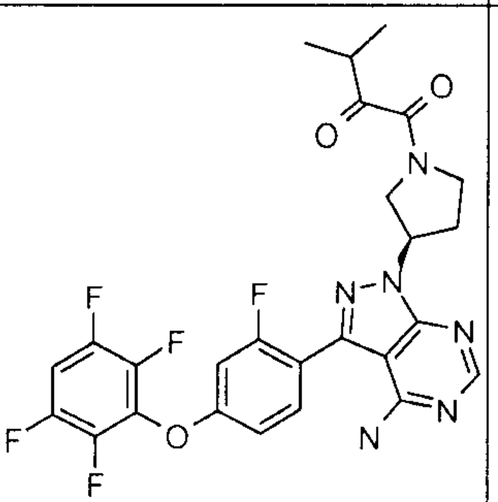


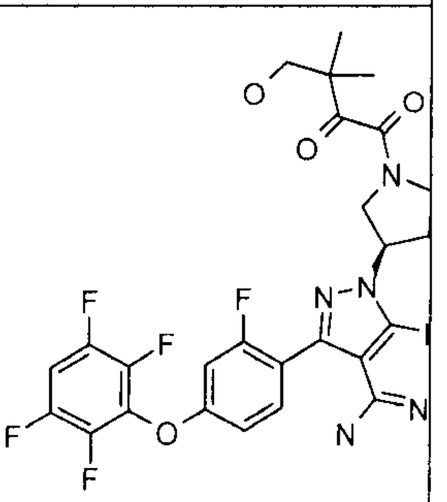


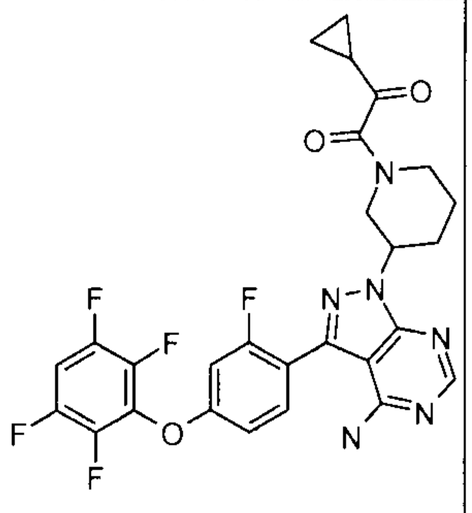
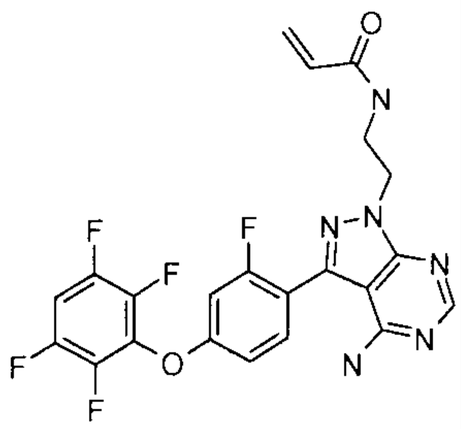
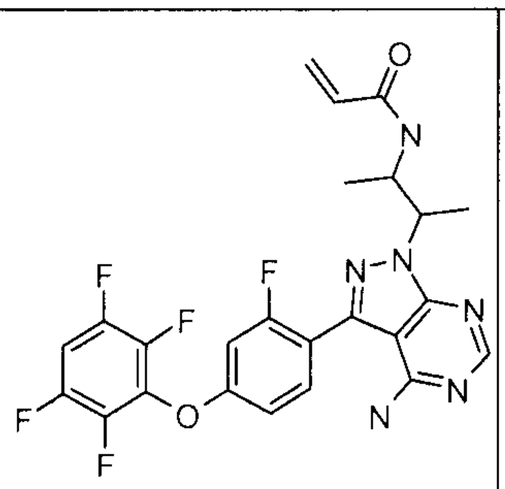
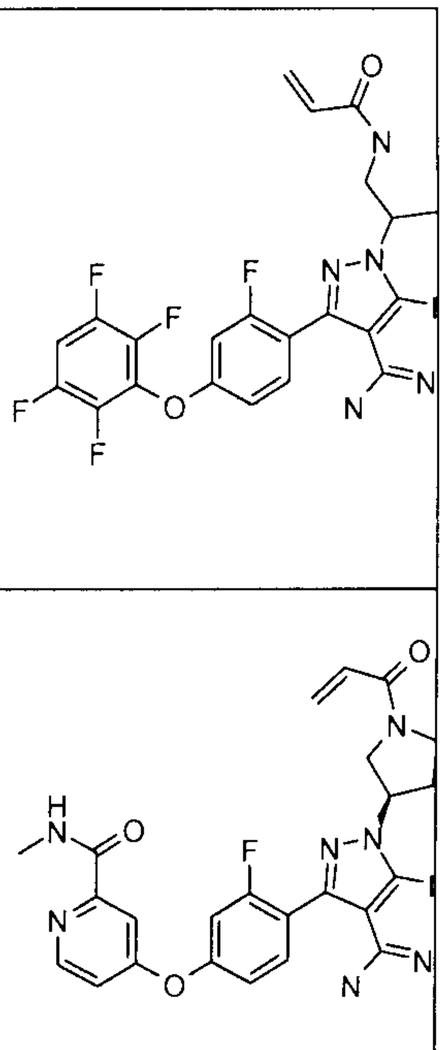
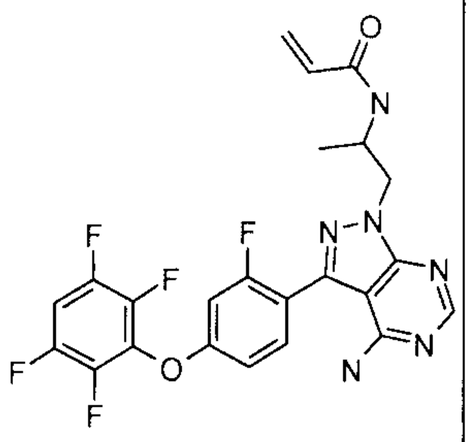
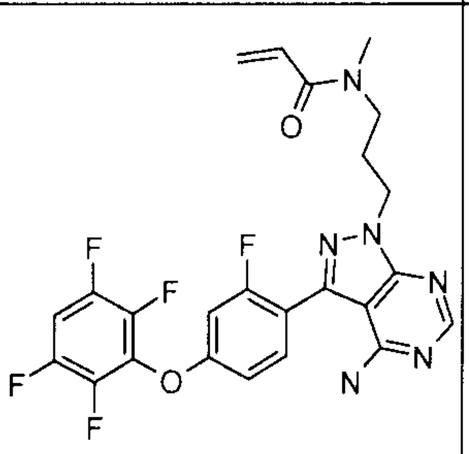
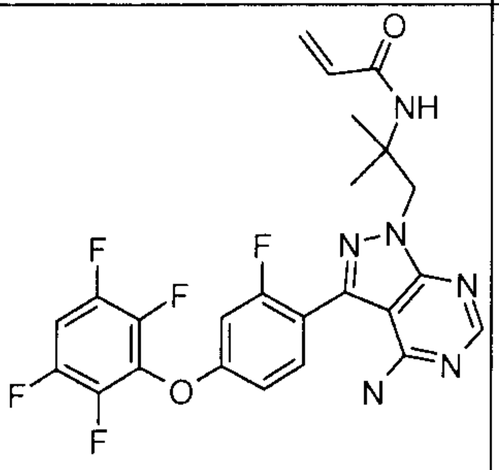
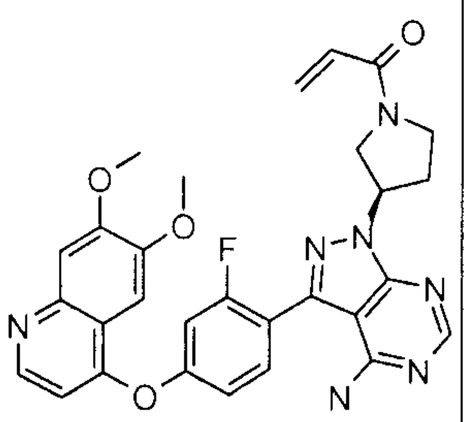
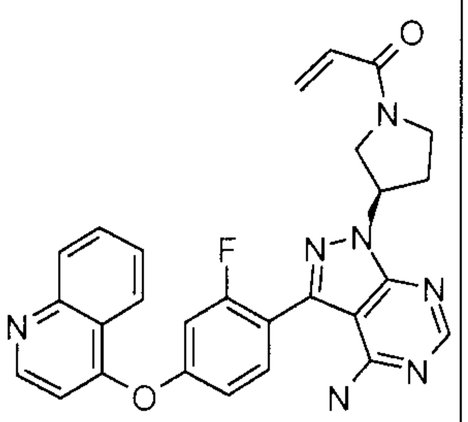
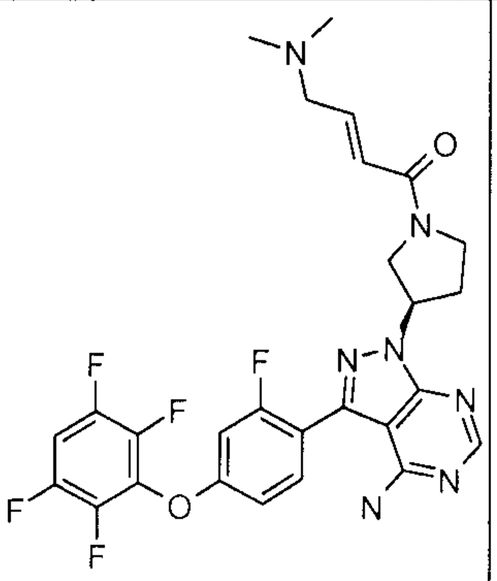
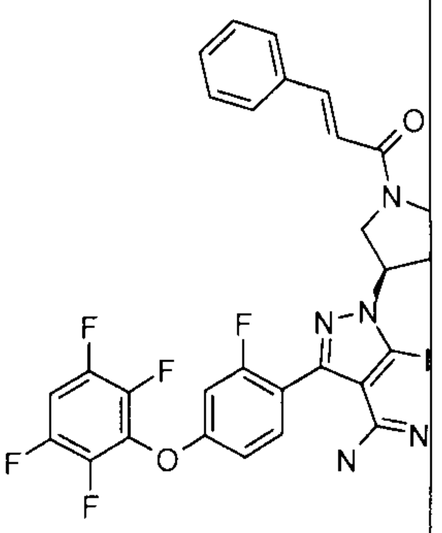
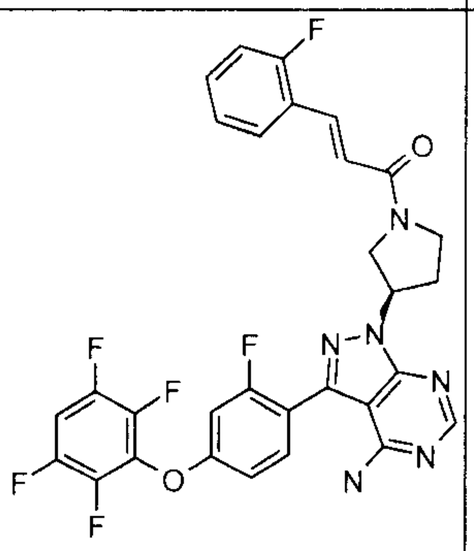
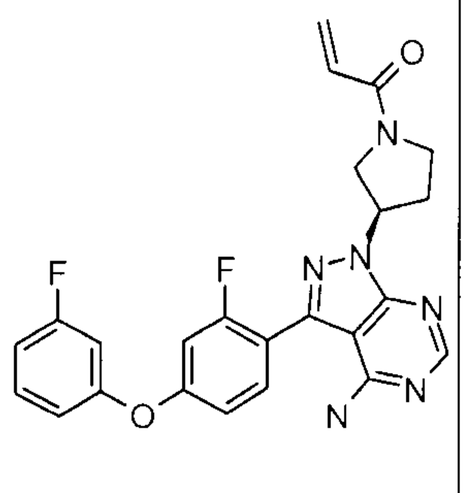
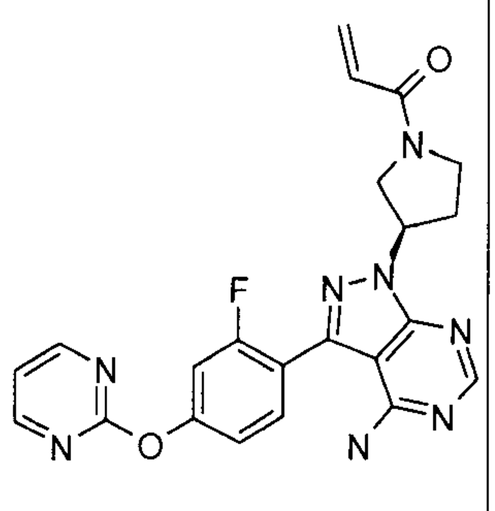
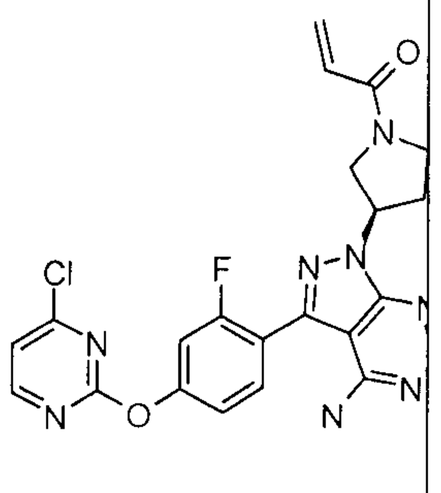


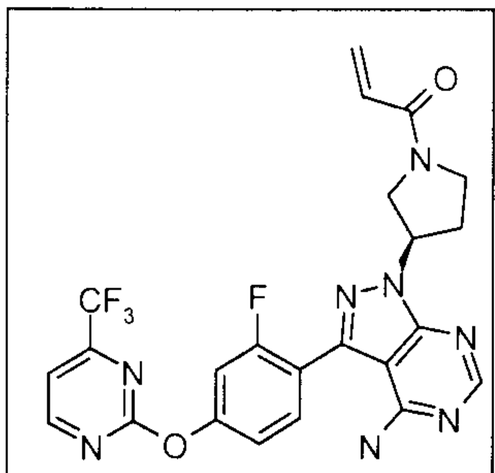


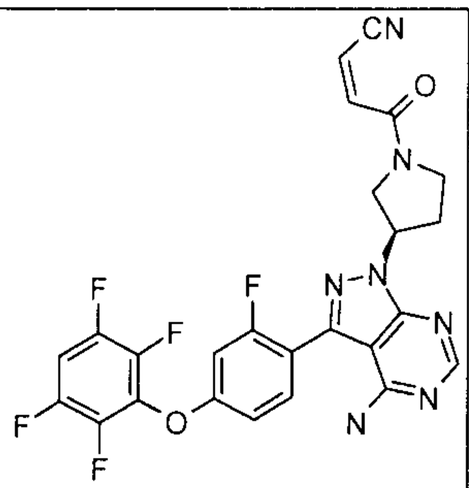


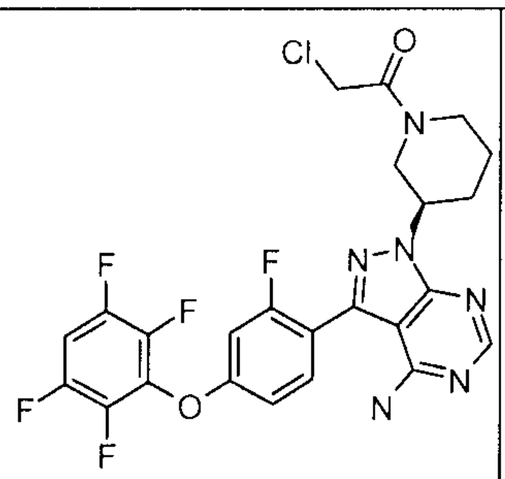


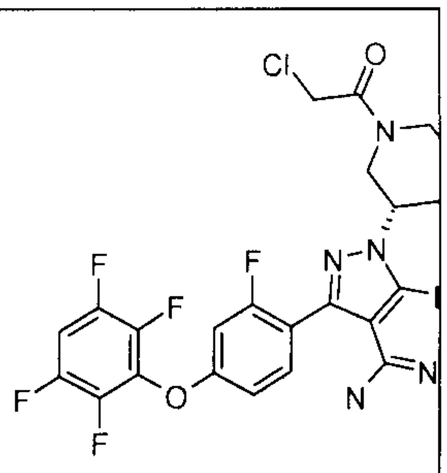


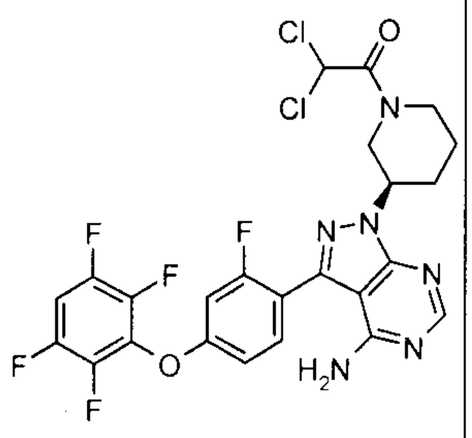
			
			
			
			

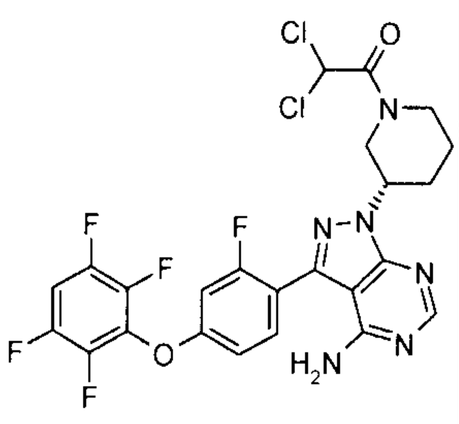


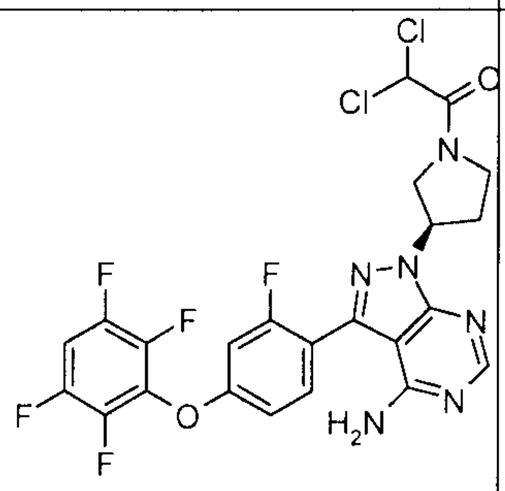


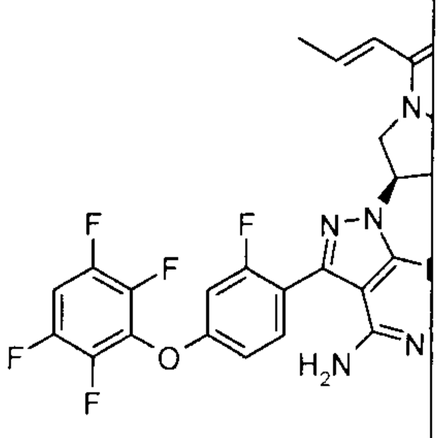


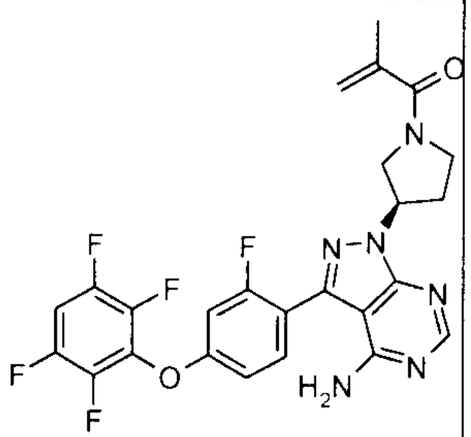


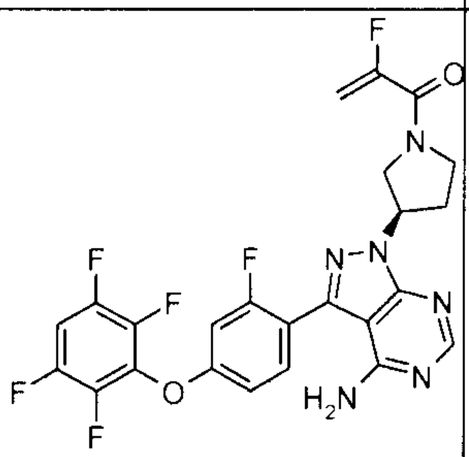


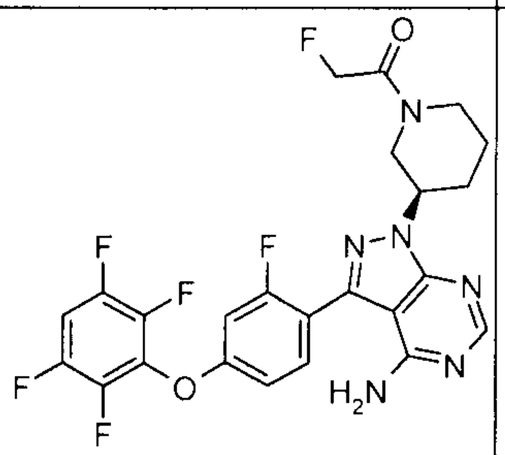


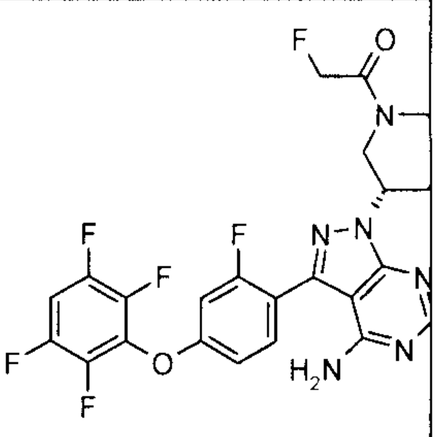


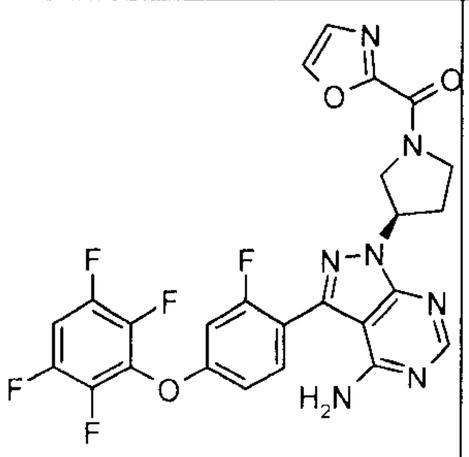


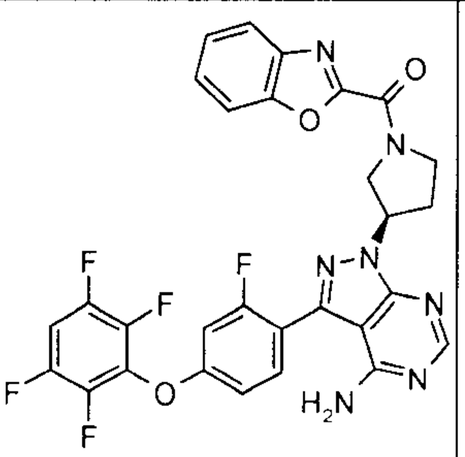


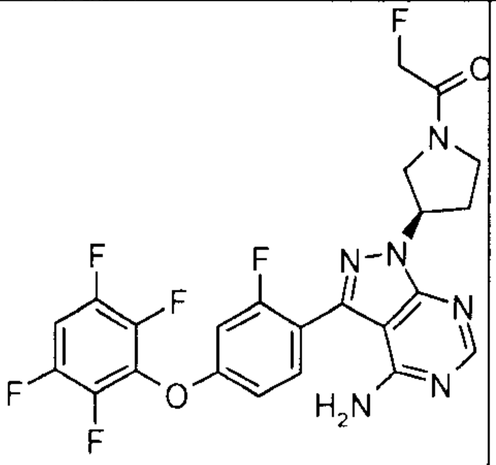


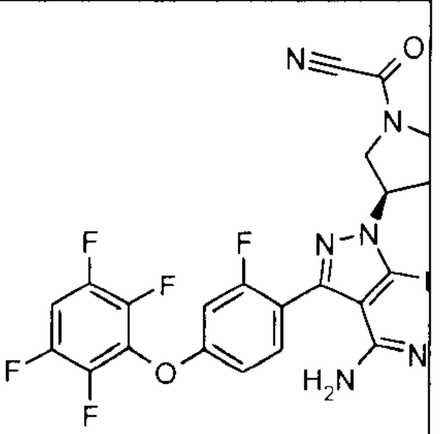


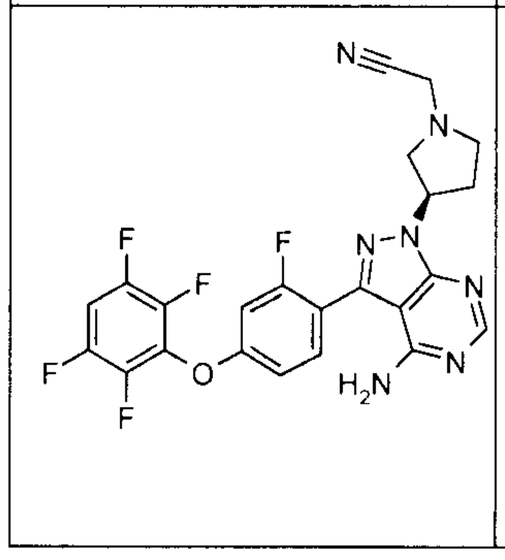


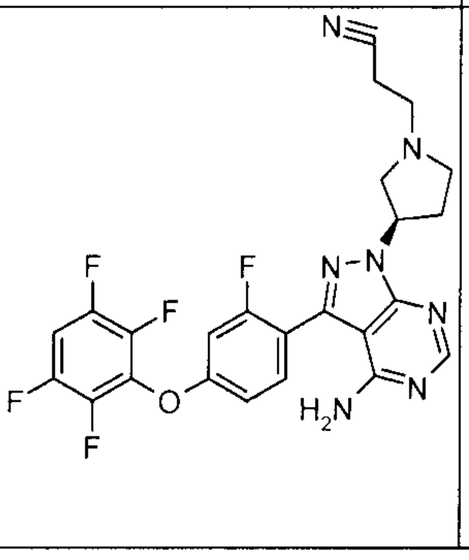


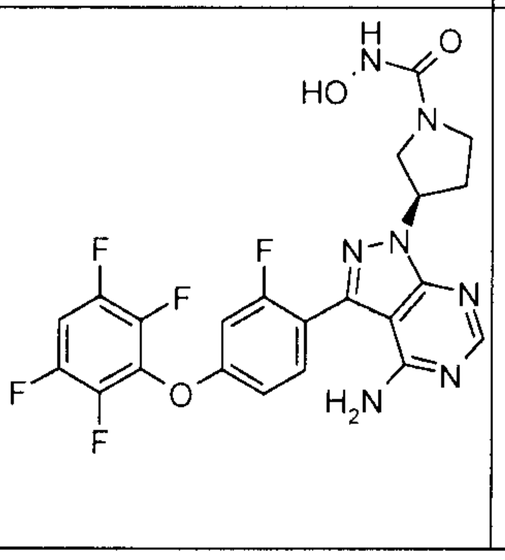


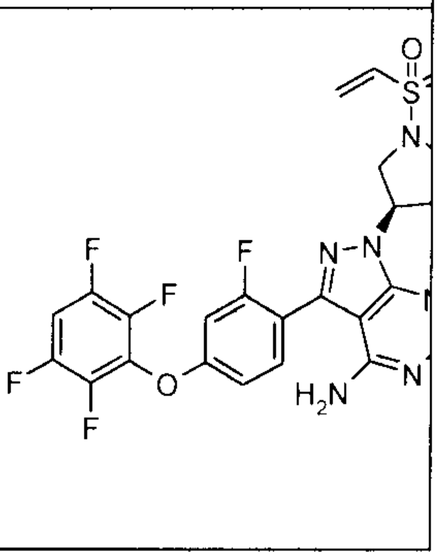


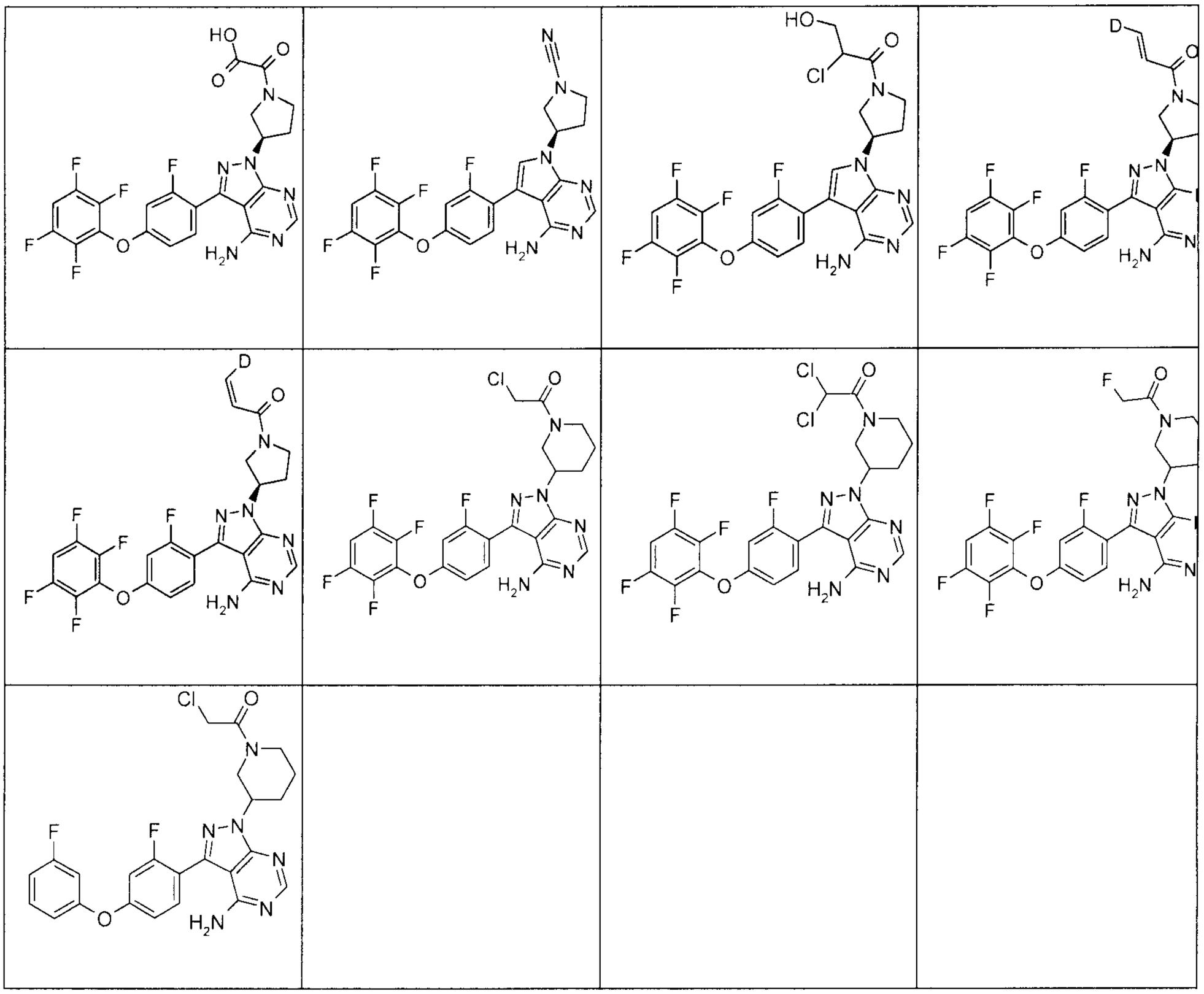












13. A pharmaceutical composition comprising an inert carrier and the compound of any one of Claims 1 to 12, preferably the compound of Claim 12.

14. A medicant comprising an inert carrier and the compound of any one of Claims 1 to 12 or a pharmaceutically acceptable salt thereof as an active component, preferably the compound of Claim 12.

15. A method for inhibiting BTK activity in a patient's body, comprising administering to the patient an effective amount of the compound of Claims 1 to 12.

16. A method for treating or inhibiting autoimmune disease or disorder, comprising administering to the patient an effective amount of the compound of Claims 1 to 12 or the

composition of Claim 13, wherein the autoimmune disease includes, but is not limited to, organ-specific autoimmune diseases, such as chronic lymphocytic thyroiditis, hyperthyroidism, insulin-dependent diabetes mellitus, myasthenia gravis, chronic ulcerative colitis, pernicious anemia associated with chronic atrophic gastritis, goodpasture syndrome, pemphigus vulgaris, pemphigoid, primary biliary cirrhosis, multiple cerebrospinal sclerosis, acute idiopathic neuritis; systemic autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, systemic vasculitis, scleroderma, pemphigus, mixed connective tissue disease, autoimmune hemolytic anemia, autoimmune thyroid disease, ulcerative colitis and so on.

17. A method for treating or inhibiting hypersensitivity diseases or disorders, comprising administering to a patient an effective amount of the compound of Claims 1 to 12 or the composition of Claim 13, wherein the hypersensitivity diseases include, but are not limited to, serum sickness, asthma, allergic rhinitis, drug allergy and so on.

18. A method for treating or inhibiting inflammatory diseases or disorders, including administering to a patient an effective amount of the compound of Claims 1 to 12 or the composition of Claim 13, wherein the inflammatory diseases include, but are not limited to, keratitis, rhinitis, stomatitis, mumps, pharyngitis, tonsillitis, tracheitis, bronchitis, pneumonia, myocarditis, gastritis, gastroenteritis, cholecystitis, appendicitis and so on.

19. A method for treating or inhibiting cancers or other diseases, comprising administering to a patient an effective amount of the compound of Claims 1 to 12 or the composition of Claim 13, wherein the cancers or other diseases include, but are not limited to, various B-cell malignancies (including small lymphocytic lymphoma (SLL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), Waldenstrom Macroglobulinemia (WM), follicular lymphoma (FL), mantle cell lymphoma (MCL)) and other diseases benefiting from inhibition of BTK activity.

20. Use of the compound of Claims 1 to 12 in preparing a medicant for treating or inhibiting autoimmune diseases , wherein the autoimmune diseases include, but are not limited to, organ-specific autoimmune diseases, such as chronic lymphocytic thyroiditis, hyperthyroidism, insulin-dependent diabetes mellitus, myasthenia gravis, chronic ulcerative colitis, pernicious anemia

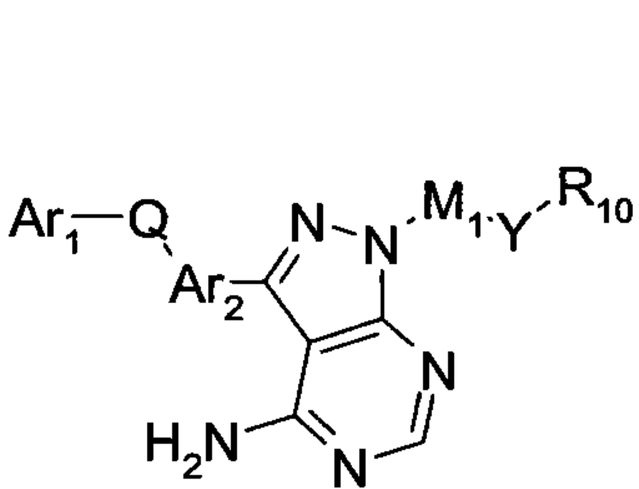
associated with chronic atrophic gastritis, goodpasture syndrome, pemphigus vulgaris, pemphigoid, primary biliary cirrhosis, multiple cerebrospinal sclerosis, acute idiopathic neuritis; systemic autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, systemic vasculitis, scleroderma, pemphigus, mixed connective tissue disease, autoimmune hemolytic anemia, autoimmune thyroid disease, ulcerative colitis and so on.

21. The use of the compound of Claims 1 to 12 in preparing a medicant for treating or inhibiting heterogeneous autoimmune diseases, wherein the heterogeneous autoimmune diseases include, but are not limited to, serum sickness, asthma, allergic rhinitis, and drug allergy and so on.

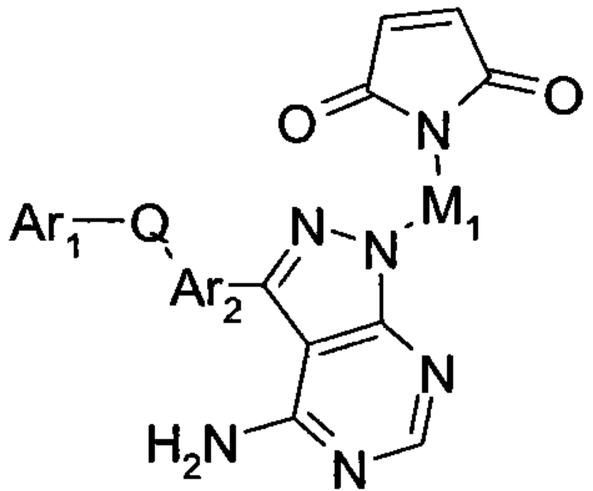
22. The use of the compound of Claims 1 to 12 in preparing a medicant for treating or inhibiting inflammatory diseases, wherein the inflammatory diseases include, but are not limited to, keratitis, rhinitis, stomatitis, mumps, pharyngitis, tonsillitis, tracheitis, bronchitis, pneumonia, myocarditis, gastritis, gastroenteritis, cholecystitis, appendicitis and so on.

23. The use of the compound of Claims 1 to 12 in preparing a medicant for treating or inhibiting cancers or other diseasess, wherein the cancers or other diseases include, but are not limited to, various B-cell malignancies (including small lymphocytic lymphoma (SLL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), Waldenstrom Macroglobulinemia (WM), follicular lymphoma (FL), mantle cell lymphoma (MCL)) and other diseases benefiting from inhibition of BTK activity.

24. The use of the compound of Claims 1 to 12 and various CD20 antibodies in treating or inhibiting cancers or other diseases, wherein the cancers or other diseases include, but are not limited to, various B-cell malignancies (including small lymphocytic lymphoma (SLL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), Waldenstrom Macroglobulinemia (WM), follicular lymphoma (FL), mantle cell lymphoma (MCL)) and other diseases benefiting from inhibition of BTK activity.



(I)



(II)