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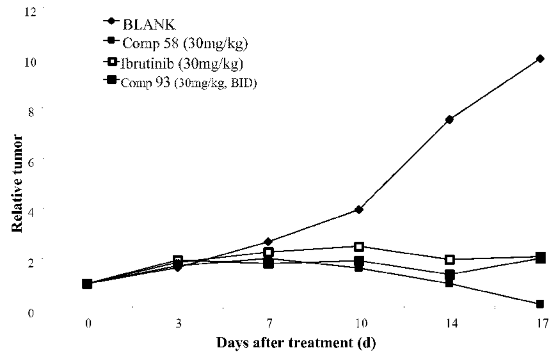
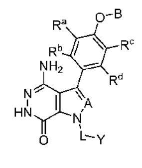
(54) Title: AMINOPYRIDAZINONE COMPOUNDS AS PROTEIN KINASE INHIBITORS

(57) Abstract: The present disclosure provides a compound of formula (I) and the use thereof for the therapeutic treatment of human cancers including B-cell lymphoma and autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis.

Fig. 1.





(I)

AMINOPYRIDAZINONE COMPOUNDS AS PROTEIN KINASE INHIBITORS

TECHNICAL FIELD

[0001] The present invention describes a series of new compounds that display potent inhibition against Bruton's tyrosine kinase and, therefore, may provide a potential therapeutic approach to treating human cancers including B-cell lymphoma and autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis.

BACKGROUND

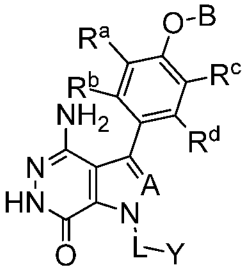
[0002] Bruton's tyrosine kinase (Btk) is a non-receptor cytoplasmic tyrosine kinase belonging to the Tec family of kinases, members of which also include Tec, Itk, Txk, and Bmx. Most of these kinases are predominantly expressed in hematopoietic cells and play important roles in relaying signal transductions from cell surface receptors to direct cell development, differentiation, and other functions (Berg JJ et al. Annual Review of Immunology, 2005; 23:549-600). Btk is critical for B cell development, differentiation, maturation, and signaling (Mohamed AJ et al. Immunological Reviews, 2009; 228:58-73). Loss-of-function mutations of Btk cause X linked agammaglobulinemia (XLA) in humans and X linked immunodeficiency in mice (Thomas JD et al. Science 1993; 261:355-358). Patients with XLA have normal pre-B cell populations in their bone marrow but these cells fail to mature and enter the circulation. Therefore, these patients essentially have no circulating B cells and are incapable of producing antibodies.

[0003] BTK plays pivotal roles in B cell proliferation and activation mediated by B cell receptor (BCR). Upon BCR activation, Btk is translocated to the plasma membrane where it is phosphorylated and subsequently initiates a cascade of signaling events including activation of phospholipase Cγ2 (PLCγ2) and eventually leading to calcium mobilization and transcriptional regulation involving nuclear factor kappa B (NF κB) (Mohamed AJ et al. Immunological Reviews 2009; 228:58-73). Because of the indispensable roles in BCR signaling pathway, it is believed that the kinase activity of Btk is critical for development and maintenance of a wide variety of B cell malignancies, including chronic lymphocytic leukemia (CLL) and a number of non-Hodgkin's lymphoma (NHL) subtypes, mantle cell lymphoma (MCL), and diffuse large B cell lymphoma (DLBCL) (Ponader S. et al. Blood 2012, 119:1182-1189; Honigberg LA et al.

Proceedings of the National Academy of Sciences, 2010, 107:13075-13080). In addition, the role of B cell in the pathogenesis of rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and other immune disorders has been clinically demonstrated (Edwards JC et al. The New England Journal of Medicine, 2004, 350:2572-2581; Favas C et al. Nature Review Rheumatology, 2009, 5:711-716; Hauset SL et al. The New England Journal of Medicine, 2008, 358:676-688). Therefore, targeting Btk with small molecule inhibitors may provide therapeutic benefit for the treatment of B cell malignancies and autoimmune diseases.

SUMMARY

[0004] In one aspect, compounds are of formula (I), or pharmaceutically acceptable salts, solvates, hydrates, metabolites, or prodrugs thereof:



I .

wherein:

A is selected from the group consisting of CR^1 and N; and wherein R^1 is selected from the group consisting of hydrogen, halogen, and unsubstituted or substituted alkyl;

R^a, R^b, R^c and R^d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, unsubstituted or substituted alkyl, and unsubstituted or substituted alkoxyl;

B is selected from the group consisting of hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl;

L is unsubstituted or substituted alkyl, or absent; and

Y is selected from the group consisting of unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl.

BRIEF DESCRIPTION OF THE DRAWINGS

[0005] Fig. 1 illustrates effect of Btk inhibitors on tumor growth in TMD-8 xenograft model.

[0006] Fig. 2 illustrates effect of Btk inhibitors on tumor growth in TMD-8 xenograft model (final tumor weight).

DETAILED DESCRIPTION

[0007] This disclosure relates generally to compounds that modulate protein tyrosine kinase activity, methods of synthesizing, and using such compounds in therapeutic methods.

Definitions

[0008] Any terms in the present application, unless specifically defined, will take the ordinary meanings as understood by a person of ordinary skill in the art.

[0009] As used herein, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise.

[0010] Unless stated otherwise, all aryl, cycloalkyl, heteroaryl, and heterocyclyl groups of the present disclosure may be substituted as described in each of their respective definitions. For example, the aryl part of an arylalkyl group, such as benzyl, may be substituted as described in the definition of the term “aryl.”

[0011] The term “alkoxy,” as used herein, refers to a C_1-C_{10}, preferably C_1-C_6, alkyl group attached to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy group include, but are not limited to, methoxy (CH_3O-), ethoxy (CH_3CH_2O-), and t-butoxy ($(CH_3)_3CO$-).

[0012] The term “alkyl,” as used herein, refers to a group derived from a straight or branched chain saturated hydrocarbon by removal of a hydrogen from one of the saturated carbons. The alkyl group preferably contains from one to ten carbon atoms, more preferably one to six carbon atoms. Representative examples of alkyl group include, but are not limited to, methyl, ethyl, isopropyl, and tert-butyl.

[0013] The term “aryl,” as used herein, refers to a group derived from a C_6-C_{12}, preferably C_6-C_{10}, aromatic carbocycle by removal of a hydrogen atom from an aromatic ring. The aryl group can be monocyclic, bicyclic or polycyclic. Preferred examples of aryl groups include phenyl and naphthyl.

[0014] The term “cyano,” as used herein, refers to -CN.

[0015] The term “cycloalkyl,” as used herein, refers to a group derived from a monocyclic saturated carbocycle, having preferably three to eight, more preferably three to six, carbon atoms, by removal of a hydrogen atom from the saturated carbocycle. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclopentyl, and cyclohexyl. When a cycloalkyl group contains one or more double bond(s) in the ring, yet not aromatic, it forms a “cycloalkenyl” group.

[0016] The terms “halo” and “halogen,” as used herein, refer to F, Cl, Br, or I.

[0017] The term “haloalkoxy,” as used herein, refers to a C_1-C_6, preferably C_1-C_4, haloalkyl group attached to the parent molecular moiety through an oxygen atom.

[0018] The term “haloalkyl,” as used herein, refers to a C_1-C_{10}, preferably C_1-C_6, more preferably C_1-C_4, alkyl group substituted by at least one halogen atom. The haloalkyl group can be an alkyl group of which all hydrogen atoms are substituted by halogens. Representative examples of haloalkyl include, but are not limited to, trifluoromethyl (CF_3-), 1-chloroethyl ($ClCH_2CH_2$-), and 2,2,2-trifluoroethyl (CF_3CH_2-).

[0019] The term “heteroaryl,” as used herein, refers to a 5- to 10-membered, monocyclic or bicyclic aromatic group comprising one or more, preferably one to three, heteroatoms independently selected from nitrogen, oxygen, and sulfur in the aromatic ring(s). As is well known to those skilled in the art, heteroaryl rings have less aromatic character than their all-carbon counterparts. Thus, for the purposes of the invention, a heteroaryl group need only have some degree of aromatic character. Illustrative examples of heteroaryl groups include, but are not limited to, pyridyl, pyridazinyl, pyrimidyl, pyrazyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, pyrimidinyl, furyl, thienyl, isoxazolyl, thiazolyl, isoxazolyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, benzisoxazolyl, benzothiazolyl, and benzothienyl.

[0020] The term “heterocyclyl,” as used herein, refers to a 3- to 10-membered monocyclic or bicyclic nonaromatic group comprising one or more, preferably one to three, heteroatoms independently selected from nitrogen, oxygen, and sulfur in the nonaromatic ring(s). The heterocyclyl groups of the present disclosure can be attached to the parent molecular moiety through a carbon atom or a nitrogen atom in the group. A heterocylcyl group can be saturated or unsaturated, for example, containing one or more double bond(s) in the ring. Examples of heterocyclyl groups include, but are not limited to, morpholinyl, oxazolidinyl, piperazinyl, piperidinyl, pyrrolidinyl, tetrahydrofuryl, thiomorpholinyl, and indolinyl, or the like.

[0021] The terms “hydroxy” or “hydroxyl,” as used herein, refers to -OH.

[0022] The term “nitro,” as used herein, refers to $-NO_2$.

[0023] The term “oxo,” as used herein, refers to “=O”.

[0024] When any group, for example, alkyl, alkenyl, “cycloalkyl,” “aryl,” “heterocyclyl,” or “heteroaryl”, is said to be “optionally substituted,” unless specifically defined, it means that the group is or is not substituted by from one to five, preferably one to three, substituents independently selected from halogen, alkyl, alkoxy, haloalkyl, haloalkoxy, hydroxy, oxo, acyl, cyano, nitro, and amino group, or the like, provided that such substitution would not violate the conventional bonding principles known to a person of ordinary skill in the art. When the phrase “optionally substituted” is used before a list of groups, it means that each one of the groups listed may be optionally substituted.

[0025] The compounds of the present disclosure can exist as pharmaceutically acceptable salts or solvates. The term “pharmaceutically acceptable salt,” as used herein, means any non-toxic salt that, upon administration to a recipient, is capable of providing the compounds or the prodrugs of a compound of this invention. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting a suitable nitrogen atom with a suitable acid. Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, hydrogen bisulfide as well as organic acids, such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucuronic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, *para*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid acid, and related inorganic and organic acids.

[0026] Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of pharmaceutically acceptable salts include, but are not limited to, lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, and N-methylmorpholine.

[0027] The term “solvate,” as used herein, means a physical association of a compound of this invention with one or more, preferably one to three, solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more, preferably one to three, solvent molecules are incorporated in the crystal lattice of the crystalline solid. Exemplary solvates include, but are not limited to, hydrates, ethanolates, methanolates, and isopropanolates. Methods of solvation are generally known in the art.

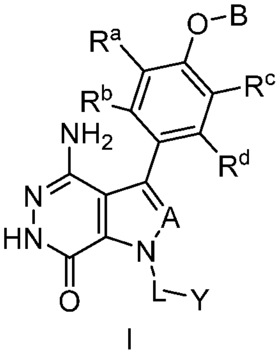
[0028] The term “therapeutically effective amount,” as used herein, refers to the total amount of each active component that is sufficient to show a meaningful patient benefit, e.g., a sustained reduction in viral load. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially, or simultaneously.

[0029] The term “pharmaceutically acceptable,” as used herein, refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[0030] The term “patient” includes both human and other mammals.

[0031] The term “treating” refers to: (i) preventing a disease, disorder or condition from occurring in a patient that may be predisposed to the disease, disorder, and/or condition but has not yet been diagnosed as having it; (ii) inhibiting the disease, disorder, or condition, i.e., arresting its development; and (iii) relieving the disease, disorder, or condition, i.e., causing regression of the disease, disorder, and/or condition.

[0032] In one embodiment, compounds are of formula (I), or pharmaceutically acceptable salts, solvates, hydrates, metabolites, or prodrugs thereof: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wherein:

A is selected from the group consisting of CR^1 and N; and wherein R^1 is selected from the group consisting of hydrogen, halogen, and unsubstituted or substituted alkyl;

R^a, R^b, R^c and R^d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, unsubstituted or substituted alkyl, and unsubstituted or substituted alkoxyl;

B is selected from the group consisting of hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl;

L is unsubstituted or substituted alkyl, or absent; and

Y is selected from the group consisting of unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl.

[0033] In some embodiments, A is selected from the group consisting CH, CF, CCl and N.

[0034] In some embodiments, at least one of R^a, R^b, R^c and R^d is selected from the group consisting of hydrogen, F, Cl, and methoxyl. In some embodiments, R^a, R^b, R^c and R^d are hydrogen. In some embodiments, R^a is F, Cl, or methoxyl. In some embodiments, R^d is F, Cl, or methoxyl.

[0035] In some embodiments, B is unsubstituted or substituted C_1-C_6 alkylln some embodiments, B is unsubstituted or substituted aryl. In some embodiments, B is unsubstituted or substituted phenyl. In some embodiments, B is phenyl. In some embodiments, B is phenyl substituted with at least one member selected from the group consisting of halogen, cyano, nitro, hydroxyl, unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy, $-NR^1R^2$, $-C(O)R^3$, $-C(O)OR^4$,

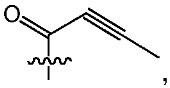
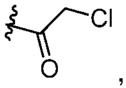
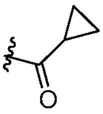
-C(O)NHR^5, and -S(O)$_2$R^6. R^1 and R^2 are independently selected from the group consisting of hydrogen, unsubstituted or substituted alkyl, -C(O)R^7, -C(O)OR^8, -C(O)NHR^9, -S(O)$_2$R^{10}; and wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl.

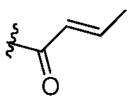
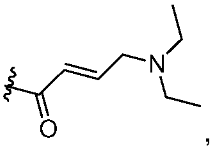
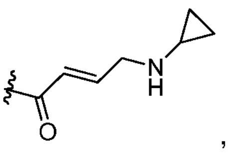
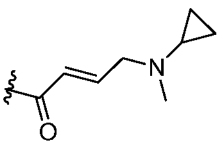
[0036] In some embodiments, B is phenyl substituted with at least one member selected from the group consisting of F, Cl, and methoxyl. In some embodiments, B is phenyl substituted with two F. In some embodiments, B is phenyl substituted with two Cl. In some embodiments, B is phenyl substituted with one Cl and one methoxyl.

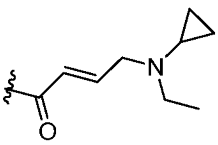
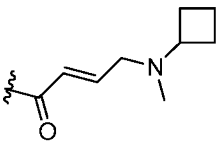
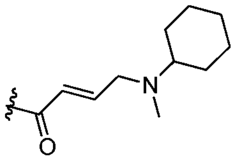
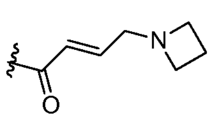
[0037] In some embodiments, L is absent. In some embodiments, L is methylene.

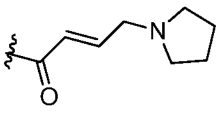
[0038] In some embodiments, Y is selected from the group consisting of unsubstituted or substituted piperidinyl, unsubstituted or substituted phenyl, unsubstituted or substituted bicyclo[3.2.1]octanyl, unsubstituted or substituted azetidinyl, and unsubstituted or substituted pyrrolidinyl. In some embodiments, Y is substituted with at least one member selected from the group consisting of halogen, -CN, -C(O)R^{11}, -NHC(O)R^{12}, -S(O)$_2$R^{13}, and -NHS(O)$_2$R^{14}; and wherein R^{11}, R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted cycloalkenyl, and unsubstituted or substituted alkynyl.

[0039] In some embodiments, Y is substituted with at least one member selected from the group consisting of F, CN,-C(O)CH=CH$_2$, -C(O)CH=CHCH$_2$N(CH$_3$)$_2$, -NHC(O)CH=CH$_2$, -NHC(O)CH=CHCH$_2$N(CH$_3$)$_2$, -C(O)CH=CHCH$_2$N(CH$_3$)(COOC(CH$_3$)$_3$; -C(O)CH=CHCH$_2$NH(CH$_3$),

-C(O)CH$_2$CH$_3$, -C(O)CH$_2$CH$_2$CH$_3$, , , ,

-C(O)CH$_2$CN, , , , , ,

, , , ,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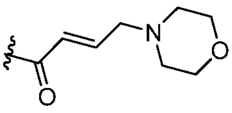
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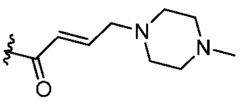
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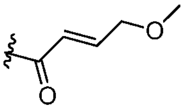
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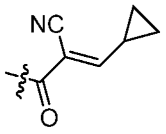
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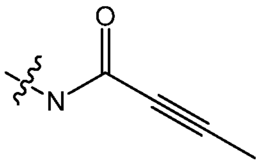
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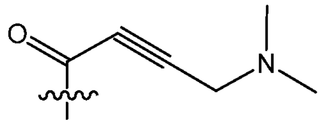
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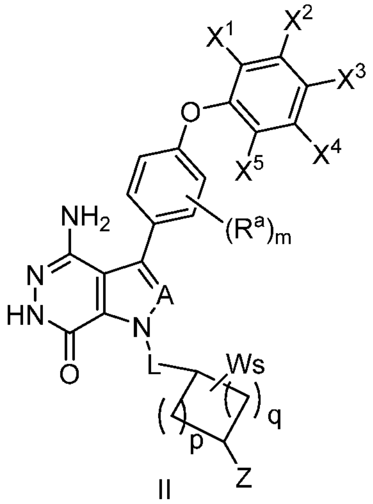
[0040] In some embodiments, the compound has both S-form and R-form. In some embodiments, the compound has more R-form than S-form. In some embodiments, the compound has more S-form than R-form.

[0041] In some embodiments, the compound has a structure of formula (II):



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where R^a, A, and L are defined as in formula (I);

X^1, X^2, X^3, X^4, and X^5 are independently selected from the group consisting of hydrogen, halogen, cyano, nitro, hydroxyl, unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy, $-NR^1R^2$, $-C(O)R^3$, $-C(O)OR^4$, $-C(O)NHR^5$, and $-S(O)_2R^6$;

wherein R^1 and R^2 are independently selected from the group consisting of hydrogen, unsubstituted or substituted alkyl, $-C(O)R^7$, $-C(O)OR^8$, $-C(O)NHR^9$, $-S(O)_2R^{10}$; and wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl;

W is selected from the group consisting of halogen, hydroxyl, unsubstituted or substituted alkyl, and unsubstituted or substituted alkoxyl; wherein two W may combine with an atom or atoms to which they are attached to form unsubstituted or substituted C_{3-12} cycloalkyl, unsubstituted or substituted 3- to 12- membered heterocyclic, unsubstituted or substituted C_{6-12} aryl, or unsubstituted or substituted 5- to 12- membered heteroaryl;

m = 0, 1, 2, or 3;

p = 1, 2, or 3;

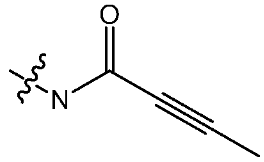
q = 0, 1, or 2;

s = 0, 1, 2, or 3; and

Z is selected from the group consisting of $-NHC(O)R^{12}$, and $-NHS(O)_2R^{14}$; and wherein R^{12}, and R^{14} are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted cycloalkenyl, and unsubstituted or substituted alkynyl.

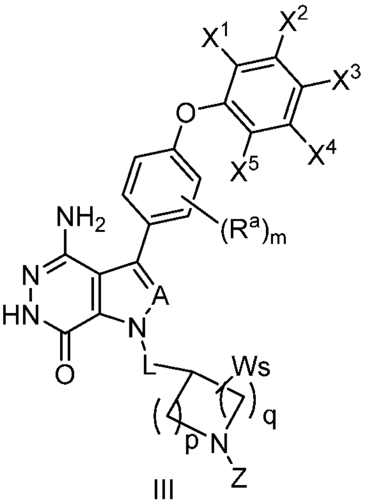
[0042] In some embodiments, A is N, CH, CF or CCl. In some embodiments, L is absent or $-CH_2-$. In some embodiments, p and q are independently 1 or 2. In some embodiments, s is 1 or 2.

[0043] In some embodiments, Z is selected from the group consisting of $-NHC(O)CH=CH_2$, $-NHC(O)CH=CHCH_2N(CH_3)_2$,



and .

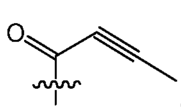
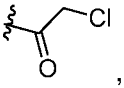
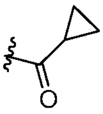
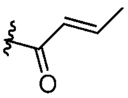
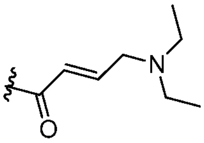
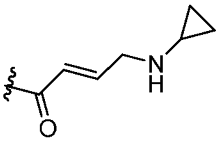
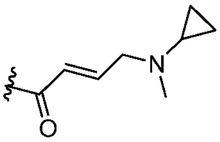
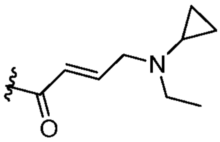
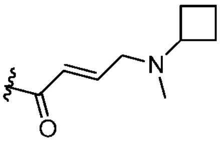
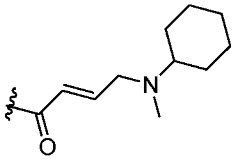
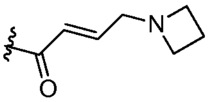
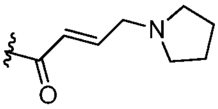
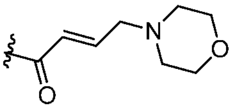
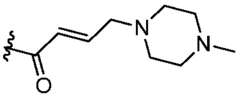
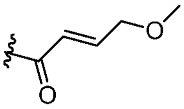
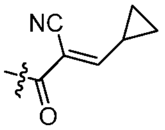
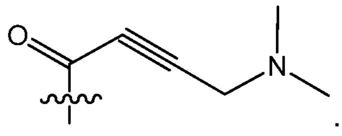
[0044] In some embodiments, the compound has a structure of formula (III):



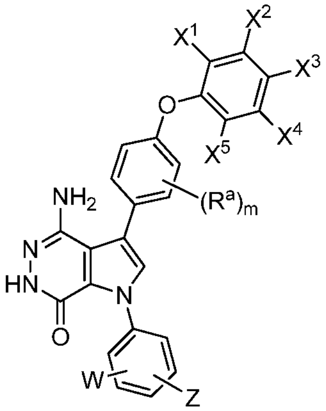
III

where R^a, A, L, X^1, X^2, X^3, X^4, X^5, W, p, q, s and m are defined as above.

Z is selected from -CN, -C(O)R^{11} and -$S(O)_2R^{13}$; and wherein R^{11} and R^{13} are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted cycloalkenyl, and unsubstituted or substituted alkynyl.

[0045] In some embodiments, Z is selected from the group consisting of CN,-$C(O)CH=CH_2$, -$C(O)CH=CHCH_2N(CH_3)_2$, -$C(O)CH=CHCH_2N(CH_3)(COOC(CH_3)_3$; -$C(O)CH=CHCH_2NH(CH_3)$, -$C(O)CH_2CH_3$, -$C(O)CH_2CH_2CH_3$, , , , -$C(O)CH_2CN$, , , , , , , , , , , , , , , , and .

[0046] In some embodiments, the compound has formula (IV):

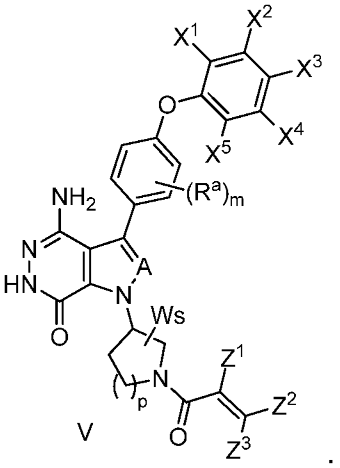


IV

where R^a, X^1, X^2, X^3, X^4, X^5, W, Z, and m are defined as above.

[0047] In some embodiments, Z is selected from the group consisting of $-NHC(O)R^{12}$ and $-NHS(O)_2R^{14}$.

[0048] In some embodiments, the compound has formula (V):



V

where R^a, A, X^1, X^2, X^3, X^4, X^5, W, s, and m are defined as above;

Z^1 is selected from the group consisting of hydrogen, halogen, cyano, and unsubstituted or substituted alkyl; and

Z^2 and Z^3 are independently selected from the group consisting of hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, $-CH_2OR^{15}$, and $-CH_2NR^{16}R^{17}$;

R^{15} and R^{16} are independently selected from the group consisting of hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, and unsubstituted or substituted heterocycloalkyl; R^{17} is selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl, $-C(O)R^{18}$, $-C(O)OR^{19}$, and $-S(O)_2R^{20}$; wherein R^{18}, R^{19} and R^{20} are independently selected from the group consisting of unsubstituted or substituted alkyl, and unsubstituted or substituted cycloalkyl;

R^{16} and R^{17} combine with N to which they are attached to form unsubstituted or substituted 3- to 12- membered heterocyclic, or unsubstituted or substituted 5- to 12- membered heteroaryl; and

Z^1 and Z^2 can join together to form a bond or combine with atoms to which they are attached to form unsubstituted or substituted C_{5-12} cycloalkenyl, unsubstituted or substituted 5- to 12- membered heterocyclic, unsubstituted or substituted C_{6-12} aryl, or unsubstituted or substituted 5- to 12- membered heteroaryl.

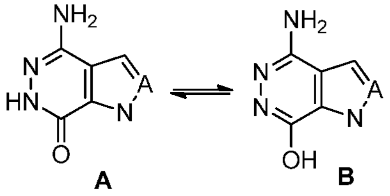
[0049] In some embodiments, A is selected from the group consisting of CH, CF and CCl.

[0050] In some embodiments, Z^1, Z^2 and Z^3 are H. In some embodiments, Z^1 and Z^2 join together to form a bond . In some embodiments, Z^1 and Z^3 are hydrogen, Z^2 is -$CH_2NR^{16}R^{17}$.

[0051] In some embodiments, 3 or less than 3 of X^1, X^2, X^3, X^4, and X^5 are halogen. In some embodiments, X^1 is F. In some embodiments, X^2, X^3, and X^4 are hydrogen. In some embodiments, X^5 is selected from the group consisting of H, F and Cl.

[0052] Although all of the above structure formulas were drawn as certain isomers for convenience, the present invention may include all isomers, such as, tautomers, rotamers, geometric isomers, diastereomers, racemates, and enantiomers.

[0053] Tautomers are constitutional isomers of organic compounds that readily interconvert by a chemical reaction called tautomerization. This reaction commonly results in the formal migration of a hydrogen atom or proton, accompanied by a switch of a single bond and adjacent double bond. A couple of the common tautomeric pairs are: ketone - enol, lactam - lactim. An example of lactam - lactim equilibria is between A and B as shown below.



[0054] All the compounds in the present disclosure can be drawn as either form A or form B. All tautomeric forms are included in the scope of the invention. The naming of the compounds does not exclude any tautomers.

[0055] Pharmaceutical compositions or formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. Regardless of the route of administration selected, the active ingredient(s) are formulated into pharmaceutically acceptable dosage forms by methods known to those of skill in the art.

[0056] The amount of the active ingredient(s) which will be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration and all of the other factors described above. The amount of the active ingredient(s) which will be combined with a carrier material to produce a single dosage form will generally be that amount of the active ingredient(s) which is the lowest dose effective to produce a therapeutic effect.

[0057] Methods of preparing pharmaceutical formulations or compositions include the step of bringing the active ingredient(s) into association with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly mixing the active ingredient(s) into liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0058] Exemplary, non-limiting examples of formulations of the disclosure suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or nonaqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of the active ingredient(s).

[0059] In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the prodrug(s), active ingredient(s) (in their micronized form) is/are mixed with one or more pharmaceutically-acceptable carriers known to those of skill in the art. Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size, and by the use of surfactants.

[0060] These compositions may also contain adjuvants such as wetting agents, emulsifying agents and dispersing agents. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like in the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[0061] In some cases, in order to prolong the effect of the active ingredient(s), it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the active ingredient(s) then depends upon its/their rate of dissolution which, in turn, may depend upon crystal size and crystalline form.

[0062] The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a lyophilized condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions maybe prepared from sterile powders, granules and tablets of the type described above.

[0063] The present disclosure includes a method of modulating protein tyrosine kinase activity, comprising contacting a cell with an effective amount of any compound of formulae (I)-(V) or the pharmaceutically acceptable salt thereof.

[0064] The present disclosure includes a method of treating a condition or a disease mediated by protein tyrosine kinase, comprising administering to a subject a therapeutically effective amount of any compound of formulae (I)-(V), or the pharmaceutically acceptable salt thereof. In some embodiments, the condition or the disease is cancer or autoimmune diseases. In some embodiments, the cancer is B-cell malignancies. In some embodiments, the cancer is chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), multiple myeloma (MM), follicular lymphoma (FL), armginal zone lymphoma and waldenström's macroglobulinemia (WM). In some embodiments, the autoimmune disease is rheumatoid arthritis. In some embodiments, the autoimmune disease is systemic lupus erythematosus.

Synthetic Methods

Abbreviations

[0065] Abbreviations which have been used in the descriptions of the schemes and the examples that follow are:

[0066] Cy for cyclohexane

[0067] DAST for diethylaminosulfur trifluoride;

[0068] DCM for dichloromethane;

[0069] DIEA or DIPEA for diisopropyl ethylamine;

[0070] DMAP for N,N-dimethylaminopyridine;

[0071] DME for ethylene glycol dimethyl ether;

[0072] DMF for *N,N*-dimethyl formamide;

[0073] DMSO for dimethylsulfoxide;

[0074] DPPA for diphenoxyphosphoryl azide;

[0075] EDCI or EDC for 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride;

[0076] ESI for electrospray ionization;

[0077] Et for ethyl;

[0078] EtOAc for ethyl acetate;

[0079] g for gram(s);

[0080] h for hour(s);

[0081] HATU for O-(7-Azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-phosphate;

[0082] HBTU for O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate;

[0083] HPLC for high-performance liquid chromatography;

[0084] mCPBA for 3-Chloroperbenzoic acid;

[0085] Me for methyl;

[0086] MeOH for methanol;

[0087] mg for milligram(s);

[0088] min for minute(s);

[0089] MS for mass spectrometry;

[0090] NBS for N-Bromosuccinimide;

[0091] NCS for N-Chlorosuccinimide;

[0092] NMR for nuclear magnetic resonance;

[0093] $Pd(dppf)Cl_2$ for [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II);

[0094] $Pd_2(dba)_3$ for Tris(dibenzylideneacetone)dipalladium(0);

[0095] PG for protecting groups;

[0096] Ph for phenyl;

[0097] PPh_3 for triphenylphosphine;

[0098] rt for room temperature;

[0099] TEA for triethyl amine;

[00100] TFA for trifluoroacetic acid;

[00101] THF for tetrahydrofuran;

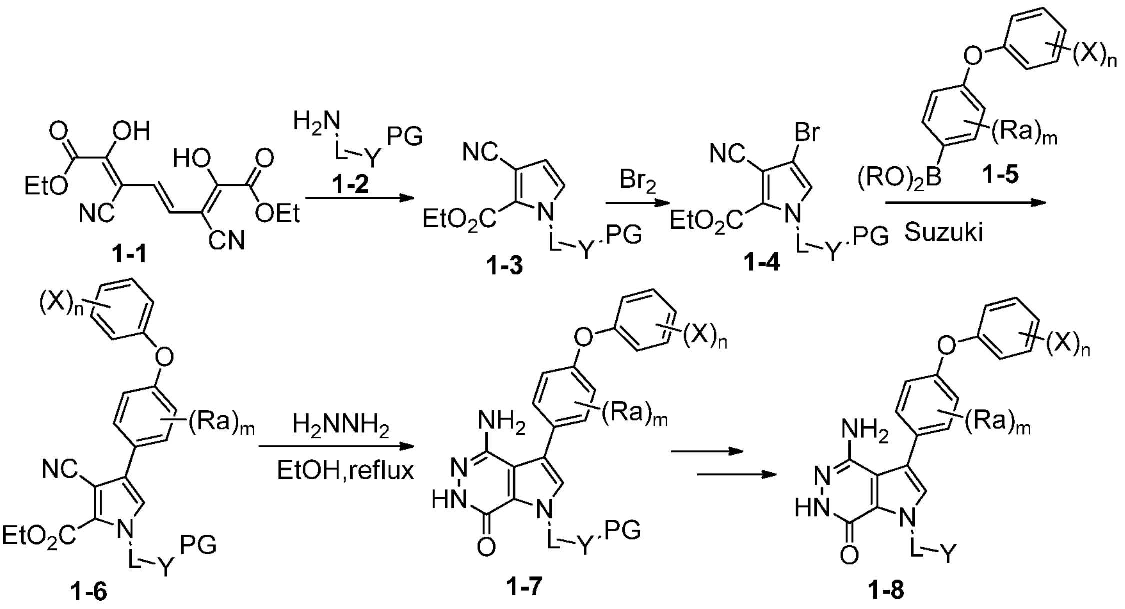
[00102] TLC for thin layer chromatography; and

[00103] *t*BOC or Boc for *tert*-butyloxy carbonyl.

[00104] The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes that illustrate the methods by which the compounds of the invention may be prepared. Other reaction

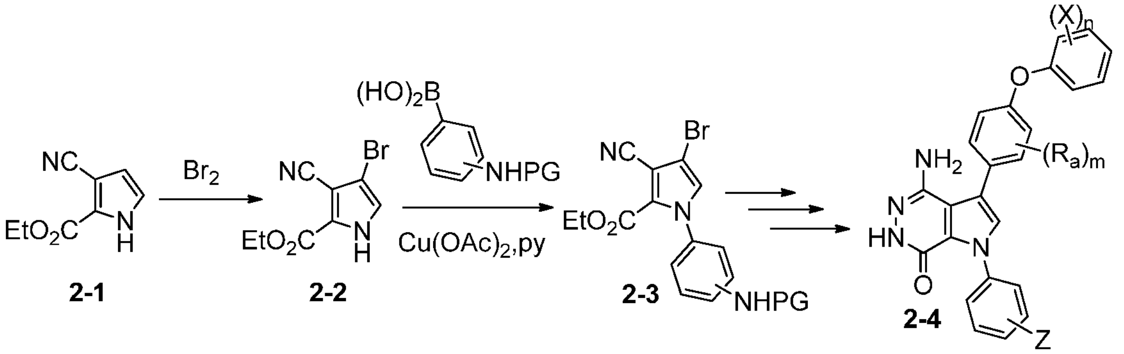
schemes could be readily devised by those skilled in the art.

Scheme 1



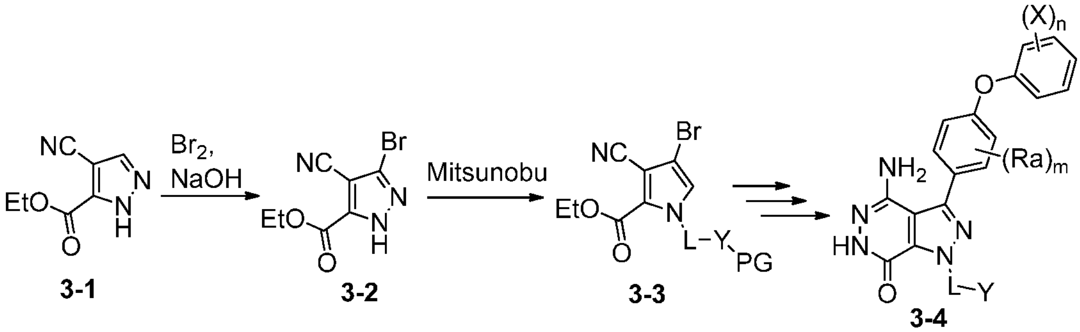
[00105] Triene **1-1** and amine **1-2** stirred in organic solvents (e.g. EtOAc) at elevated temperature to afford pyrrole **1-3**. Bromination with Br_2 or other proper reagents gave bromide **1-4**, which reacted with readily available bronic acid or bronic ester **1-5** under Suzuki reaction conditions to give **1-6**. Ester **1-6** and hydrazine refluxed in EtOH gave key intermediate **1-7**. Deprotection and Z installation yielded **1-8**.

Scheme 2



[00106] Alternatively, pyrrole **2-1** without N substitute was prepared, followed by bromination to afford bromide **2-2.** The aromatic ring was installed via copper catalyzed C–N cross-coupling reactions. The resulting intermediate **2-3** was transformed to final compound **2-4** via similar sequences illustrated in Scheme 1.

Scheme 3

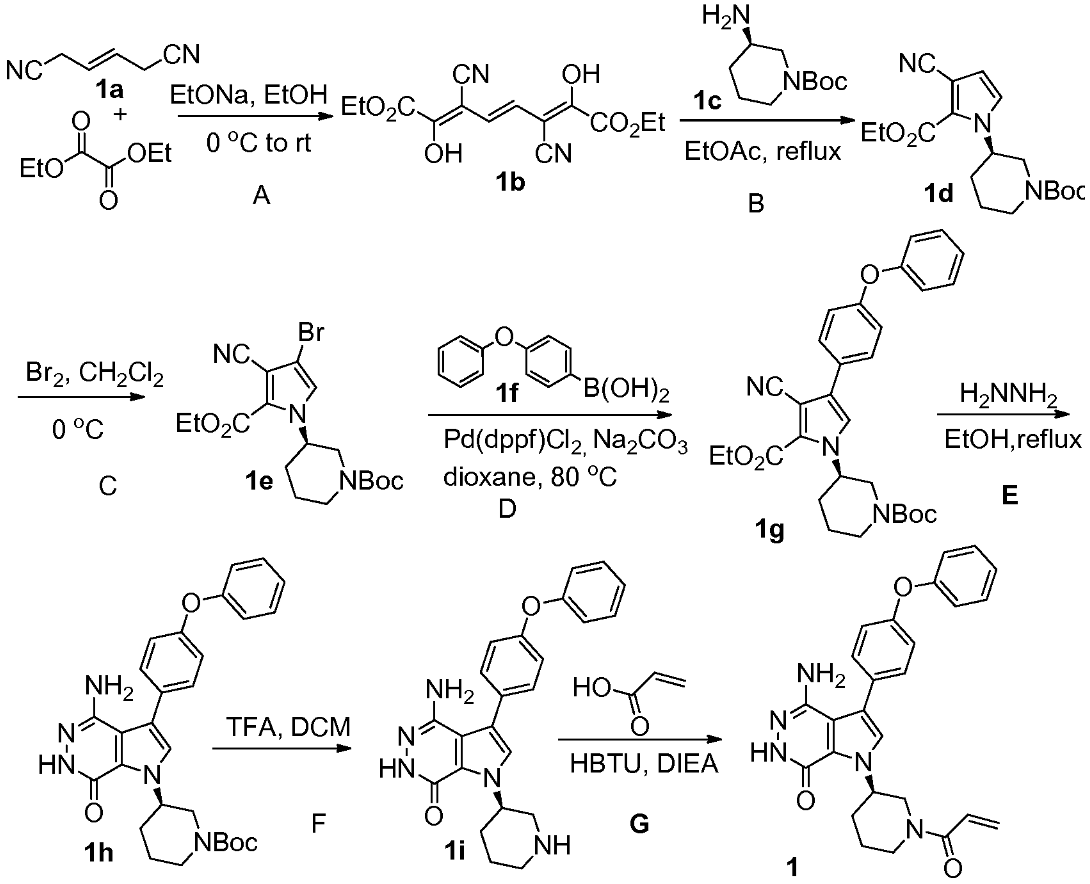


[00107] Pyrazole **3-1** reacted with Br_2 under basic conditions gave bromide **3-2**. Y group was installed via Mitsunobu reactions. **3-3** was converted to **3-4** following similar sequences illustrated in Scheme 1.

EXAMPLES

[00108] The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an illustration only and not limiting of the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and modifications including, without limitation, relating to the chemical structures, substituents, derivatives, formulations and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

[00109] **Example 1.** (R)-1-(1-acryloylpiperidin-3-yl)-4-amino-3-(4-phenoxyphenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



Step 1A

[00110] To a solution of EtONa (160 ml, solution of 21% in EtOH, 0.49 mmol) in EtOH (110 ml) in ice bath was added diethyl oxalate (64 ml, 0.47 mol). The mixture was stirred for 30 min. A solution of **1a** (16 g, 0.15 mmol) in EtOH (30 ml) was added. The resulting mixture was stirred overnight at room temperature. After cooled in ice bath, the suspension was filtered. The solid was washed with small amount EtOH and then dissolved in water (380 ml). The solution was acidified by HCl to pH ~4. Large amount solid appeared, filtered, washed with water, dried gave **1b** (11.9 g) as yellow solid.

Step 1B

[00111] To a solution of **1b** (2.3 g, 7.5 mmol) in EtOAc (120 ml) at 60°C was added dropwise a solution of **1c** (2.3 g, 11.4 mmol) in EtOAc (32 ml). The mixture was refluxed for 4 h. After cooled to room temperature, the solvents were removed. The residue was purified by silica gel chromatography to afford light yellow oil **1d** (1.09 g).

Step 1C

[00112] To a solution of **1d** (1.09 g) in DCM (200 ml) was added slowly a solution of Br_2 (6.15g) in DCM (7 ml) over 30 min. The mixture was stirred for 30 min, and then quenched with a solution of 10% $Na_2S_2O_3$ and saturated solution of $NaHCO_3$. The two phases were separated; the aqueous phase was extracted with DCM. The combined organic extracts were treated with excess Boc_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to give **1e** (0.8 g) and **1d** (0.3 g).

Step 1D

[00113] A mixture of **1e** (0.8 g), **1f** (1.2 g), Na_2CO_3 (2 M, 5 ml), and Pd(dppf)Cl_2 (0.3 g) in 1.4-dioxane(50 ml) was stirred in under N_2 at 80 °C for 20 h. After cooled to room temperature, the solvents were removed. The residue was purified by silica gel chromatography to give colorless oil **1g** (0.8 g). MS (ESI): m/z=516 $[M+H]^+$.

Step 1E

[00114] A mixture of **1g** (0.8 g) and N_2H_4 (8 ml) in EtOH (80 ml) was refluxed for 28h. After cooled to room temperature, the solvents were removed. The residue was purified by silica gel chromatography to give colorless oil **1h** (0.327 g). MS (ESI): m/z=502 $[M+H]^+$.

Step 1F

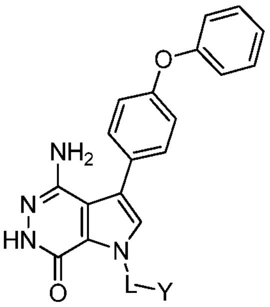
[00115] To a solution of **1 h** (0.327 g) in DCM (15 ml) was added TFA (1.5 ml). The mixture was stirred at rt for 30 min and concentrated to give **1i** which was used directly in next step.

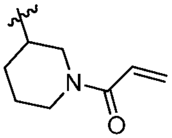
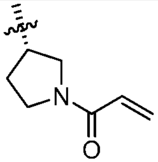
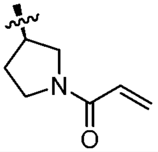
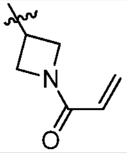
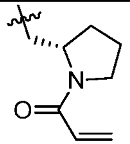
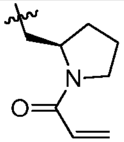
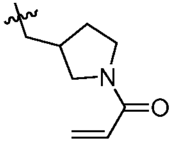
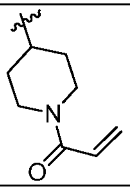
Step 1G

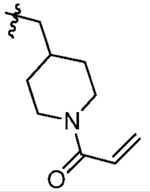
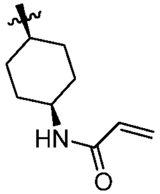
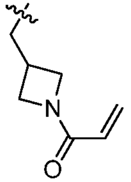
[00116] To a solution of **1i** (10.6 mg, 0.026 mmol) in DCM (2 ml) were added Et_3N (0.1 ml), acrylic acid (5 mg, 0.067 mmol) and HBTU (19 mg, 0.05 mmol). The resulting mixture was stirred at room temperature for 0.5 h and purified by reversed phase preparative HPLC to give title compound **1** (3.5 mg) as white solid. MS (ESI): *m/z* = 456 $[M+H]^+$.

[00117] **Examples 2** to **12** (Table 1) were made from **1b** and corresponding amines (commercially available) via the similar conditions described in steps 1B~1G of Example 1.

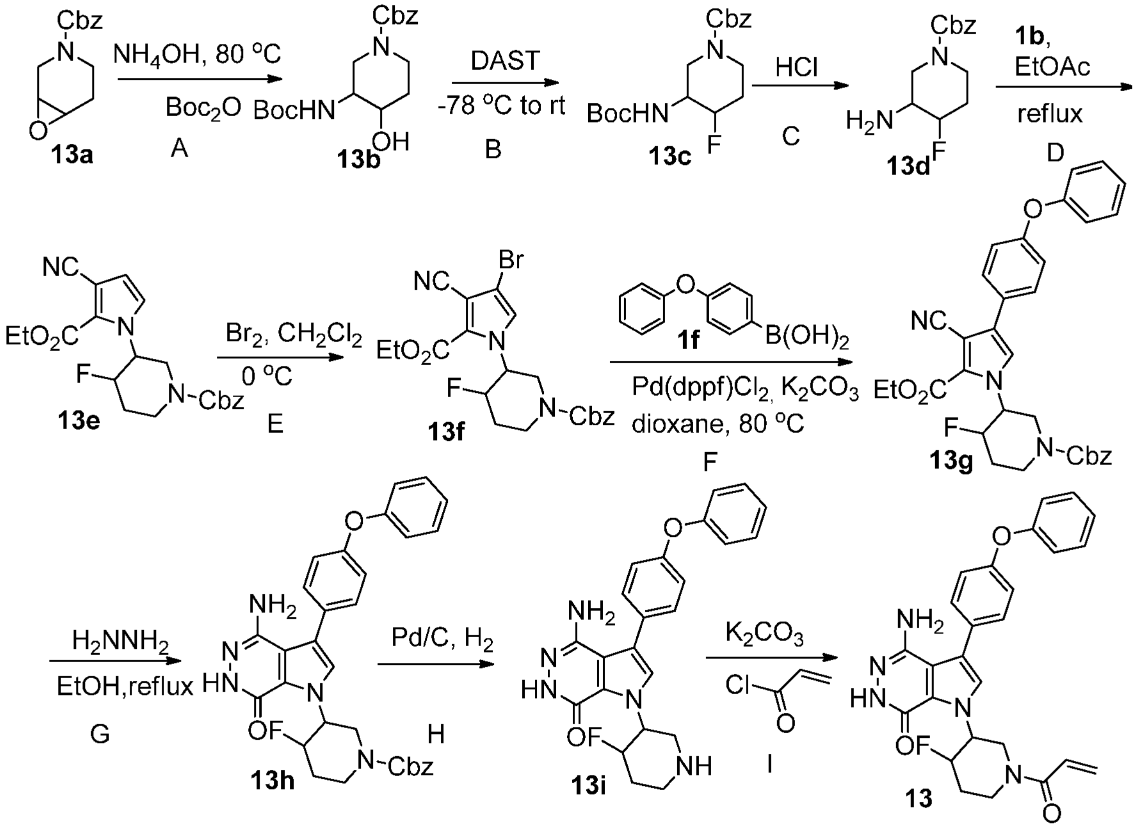
[00118] **Table 1**. Compounds of formula:



Example	L-Y	Name	MS(ESI) m/z $[M+H]^+$
2		4-amino-3-(4-phenoxyphenyl)-1-(1-prop-2-enoyl-3-piperidyl)-6H-pyrazolo[3,4-d]pyridazin-7-one	456
3		4-amino-3-(4-phenoxyphenyl)-1-[(3S)-1-prop-2-enoylpyrrolidin-3-yl]-6H-pyrrolo[2,3-d]pyridazin-7-one	442
4		4-amino-3-(4-phenoxyphenyl)-1-[(3R)-1-prop-2-enoylpyrrolidin-3-yl]-6H-pyrrolo[2,3-d]pyridazin-7-one	442
5		4-amino-3-(4-phenoxyphenyl)-1-(1-prop-2-enoylazetidin-3-yl)-6H-pyrrolo[2,3-d]pyridazin-7-one	428
6		4-amino-3-(4-phenoxyphenyl)-1-[[(2S)-1-prop-2-enoylpyrrolidin-2-yl]methyl]-6H-pyrrolo[2,3-d]pyridazin-7-one	456
7		4-amino-3-(4-phenoxyphenyl)-1-[[(2R)-1-prop-2-enoylpyrrolidin-2-yl]methyl]-6H-pyrrolo[2,3-d]pyridazin-7-one	456
8		4-amino-3-(4-phenoxyphenyl)-1-[(1-prop-2-enoylpyrrolidin-3-yl)methyl]-6H-pyrrolo[2,3-d]pyridazin-7-one	456
9		4-amino-3-(4-phenoxyphenyl)-1-(1-prop-2-enoyl-4-piperidyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	456

Example	L-Y	Name	MS(ESI) m/z $[M+H]^+$
10		4-amino-3-(4-phenoxyphenyl)-1-[(1-prop-2-enoyl-4-piperidyl)methyl]-6H-pyrrolo[2,3-d]pyridazin-7-one	470
11		N-((1s,4s)-4-(4-amino-7-oxo-3-(4-phenoxyphenyl)-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-yl)cyclohexyl)acrylamide	470
12		4-amino-3-(4-phenoxyphenyl)-1-[(1-prop-2-enoylazetidin-3-yl)methyl]-6H-pyrrolo[2,3-d]pyridazin-7-one	442

[00119] **Example 13.** 1-(1-acryloyl-4-fluoropiperidin-3-yl)-4-amino-3-(4-phenoxyphenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



Step 13A

[00120] A mixture of **13a** (2.2 g) and NH_4OH (14 mL) in EtOH (33 mL) was stirred in

seal tube at 80°C for 18 h. The solvents were removed; the residue was dissolved in THF (30 mL) and EtOH (30 mL) and charged with Boc_2O (2.46 g). The mixture was stirred at room temperature for 20h. The crude product was purified by silica gel chromatography to give white solid **13b** (1.02 g) and undesired region isomer (1.7 g).

Step 13B

[00121] DAST (0.28 mL, 2.14 mmol) was added dropwise to a solution of **13b** (0.68g, 1.94 mmol) in DCM (20 mL) at -78°C. The mixture was allowed to warm to room temperature overnight. It was quenched with saturated $NaHCO_3$ solution, extracted with DCM. The organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to give colorless oil **13c** (0.31 g).

Step 13C

[00122] A mixture of **13c** (0.31 g) and HCl (4 M in dioxane) was stirred for 2h. The solvents were removed, the residue was suspended in EtOAc, 2M K_2CO_3 solution was added to adjust pH over 9. The aqueous layer was extracted with EtOAc three times. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to give light yellow oil **13d** (0.18 g).

Step 13D

[00123] To a solution of **13d** (140 mg) in EtOAc (12 ml) at 60°C was added dropwise a solution of **1b** (140 mg) in EtOAc (3 ml). The mixture was refluxed for 18h. After cooled to room temperature, the solvents were removed. The residue was purified by silica gel chromatography to afford yellow oil **13e** (40 mg).

Step 13E

[00124] To a solution of **13e** (40 mg) and AcOH (40 μl) in DCM (3 ml) at 0°C was added Br_2 (40 mg) slowly. The mixture was allowed to warm to rt and stirred for 5 h, and then quenched with a solution of 10% $Na_2S_2O_3$ and saturated solution of $NaHCO_3$. The two phases were separated; the aqueous phase was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to give **13f** (18 mg).

Step 13F

[00125] A mixture of **13f** (22 mg), **1f** (25 mg), K_2CO_3 (2 M, 0.1 ml), and $Pd(dppf)Cl_2$

(13 mg) in 1.4-dioxane(1 ml) was stirred in under N_2 at 80 °C for 20 h. After cooled to room temperature, the solvents were removed. The residue was purified by silica gel chromatography to give colorless oil **13g** (28 mg). MS (ESI): m/z=568 $[M+H]^+$.

Step 13G

[00126] A mixture of **13g** (28 mg) and N_2H_4 (0.2 ml) in EtOH (2 ml) was refluxed for two days. After cooled to room temperature, the solvents were removed. The residue was purified by silica gel chromatography to give **13h** (15mg). MS (ESI): m/z=554 $[M+H]^+$.

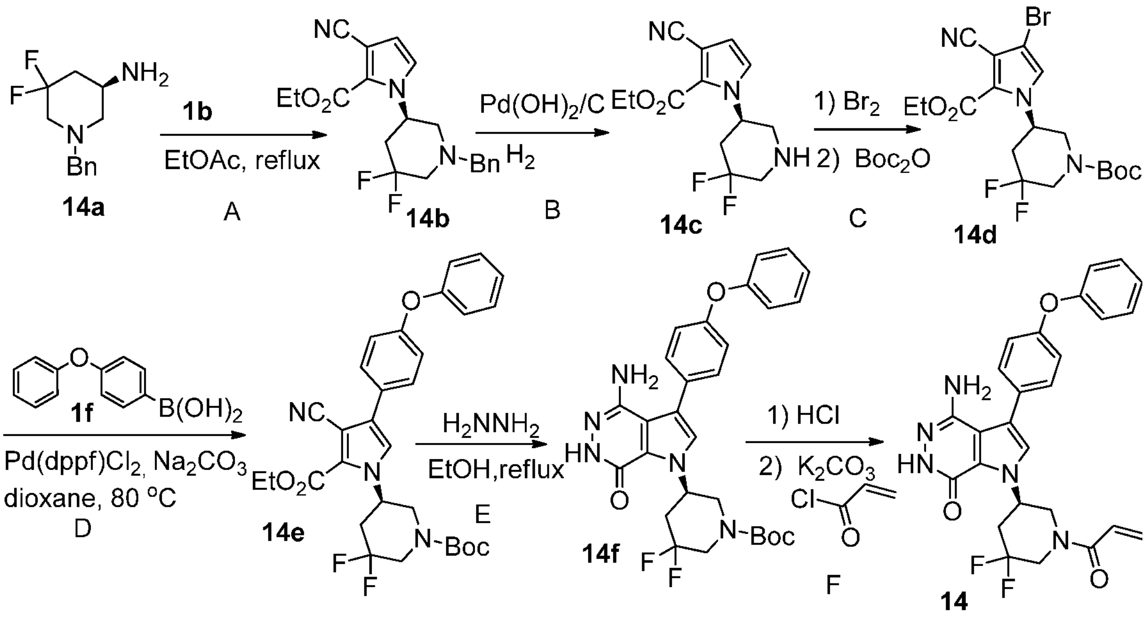
Step 13H

[00127] A mixture of **13h** (15 mg) and Pd/C (10wt%, 9 mg) in MeOH (1 ml) was stirred under H_2 balloon for 3 h. The reaction mixture was filtered through a pad of celite, washed with EtOAc/MeOH and concentrated to give white solid **13i** (10mg).

Step 13I

[00128] To a mixture of **13i** (5.3 mg) and K_2CO_3 (2M, 30 μl) in THF (0.8 ml) at 0°C was added a solution of acryloyl chloride (1.4 mg) in THF. The resulting mixture was stirred at 0°C for 0.5 h and purified by reversed phase preparative HPLC to give title compound **13** (3 mg) as off white solid. MS (ESI): *m/z* = 474 $[M+H]^+$.

[00129] **Example 14.** (R)-1-(1-acryloyl-5,5-difluoropiperidin-3-yl)-4-amino-3-(4-phenoxyphenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



Step 14A

[00130] To a solution of **1b** (271 mg) in EtOAc (12 ml) at 60°C was added dropwise a solution of **14a** (223 mg, the compound was prepared following procedures described in *Organic Letters, 2011, vol. 13, p.4442-4445* Anne Cochi *et al.*) in EtOAc (2 ml). The mixture was refluxed for 18 h. After cooled to room temperature, the solvents were removed. The residue was purified by silica gel chromatography to afford light yellow oil **14b** (76 mg).

Step 14B

[00131] A mixture of **14b** (65 mg) and $Pd(OH)_2/C$ (10wt%, 50 mg) in MeOH/THF (3/1 ml) was stirred under H_2 balloon for 20 h. The reaction mixture was filtered through a pad of celite, washed with EtOAc/MeOH and concentrated. The residue was purified by silica gel chromatography to afford white solid **14c** (38 mg).

Step 14C

[00132] To a solution of **14c** (38 mg) in DCM (3 ml) at 0°C was added Br_2 (15 μl) slowly. The mixture was stirred at rt for 18 h. Excess TEA and Boc_2O were added. The resulting mixture was stirred at rt for 24 h. Water was added, and the mixture was extracted with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to give **14d** (20 mg).

Step 14D

[00133] A mixture of **14d** (20 mg), **1f** (19 mg), K_2CO_3 (2M, 0.1 ml), and $Pd(dppf)Cl_2$ (7 mg) in 1.4-dioxane(1.5 ml) was stirred in under N_2 at 80 °C for 3 h. After cooled to room temperature, the solvents were removed. The residue was purified by silica gel chromatography to give colorless oil **14e** (30 mg). MS (ESI): m/z=552 $[M+H]^+$.

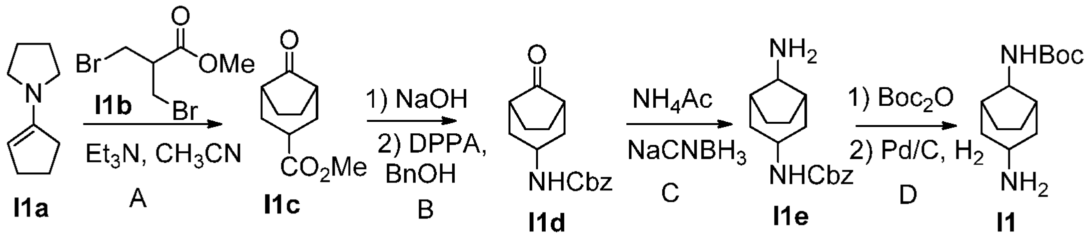
Step 14E

[00134] A mixture of **14e** (30 mg) and N_2H_4 (0.25 ml) in EtOH (2.5 ml) was refluxed for 20 h. After cooled to room temperature, the solvents were removed. The residue was purified by silica gel chromatography to give white solid **14f** (15mg). MS (ESI): m/z=538 $[M+H]^+$.

Step 14F

[00135] A mixture of **14f** (15 mg) and HCl solution (1 ml, 4M in dioxane) was stirred at rt for 2h and concentrated to give **14g** (22 mg)which was used directly in next step without further purification. To a mixture of **14g** (13 mg) and K_2CO_3 (2 M, 40 µl) in THF (1 ml) at 0°C was added a solution of acryloyl chloride (4 mg) in THF. The resulting mixture was stirred at 0°C for 20 min and purified by reversed phase preparative HPLC to give title compound **14** (3.3 mg) as white solid. MS (ESI): *m/z* = 492 $[M+H]^+$.

[00136] **Intermediate 1.** tert-butyl (3-aminobicyclo[3.2.1]octan-8-yl)carbamate



Step I1A

[00137] Methyl 3-bromo-2-(bromomethyl)propanoate **I1b** (2.61 g) was added dropwise to a solution of 1-(cyclopent-1-en-1-yl)pyrrolidine **I1a** (1.44 g), Et_3N(1.46 ml) in CH_3CN (10 ml). The mixture was refluxed for 20 h. A solution of 5% AcOH in water (1ml) was added. The mixture was refluxed for 1.5 h. After cooled to room temperature, EtOAc (15 ml) was added. The suspension was filtered. The resulting filtrate was treated with water, extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to afford **I1c** (1.0 g).

Step I1B

[00138] A mixture of **I1c** (1.0 g), 2M NaOH (10 ml) and MeOH (5 ml) was stirred at room temperature for 1.5 h. The mixture was acidified and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting oil was dissolved in toluene (14 ml) followed by adding DPPA(1.7 g) and Et_3N (0.84 ml). The mixture was stirred at room temperature for 1.5h and heated to 110°C for 2h. After addition of BnOH (5.7 ml), the mixture was stirred at 110°C for 2 days. The mixture was diluted with EtOAc and washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to afford **I1d** (3.0 g).

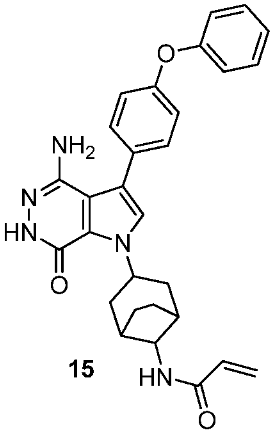
Step I1C

[00139] To a solution of **I1d** (0.5 g), NH_4OAc (0.7 g) in CH_3OH (5 ml) was added $NaCNBH_3$ (0.23 g). The mixture was stirred at rt for 2 h. It was quenched with saturated $NaHCO_3$ solution, extracted with DCM. The organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to give **I1e** (45mg).

Step I1D

[00140] A mixture of **I1e** (0.24 g) and Boc_2O (1.2 g) in DCM (10 ml) was stirred at rt for 20 h. After evaporation of solvents under reduced pressure, the residue was purified by silica gel chromatography to give 0.14 g colorless oil. The oil was dissolved in MeOH (15 ml) and charged with Pd/C. The mixture was stirred under H_2 balloon for 20 h, filter through a pad of celite and concentrated to give **I1** (66mg). MS (ESI): *m/z* = 241 $[M+H]^+$.

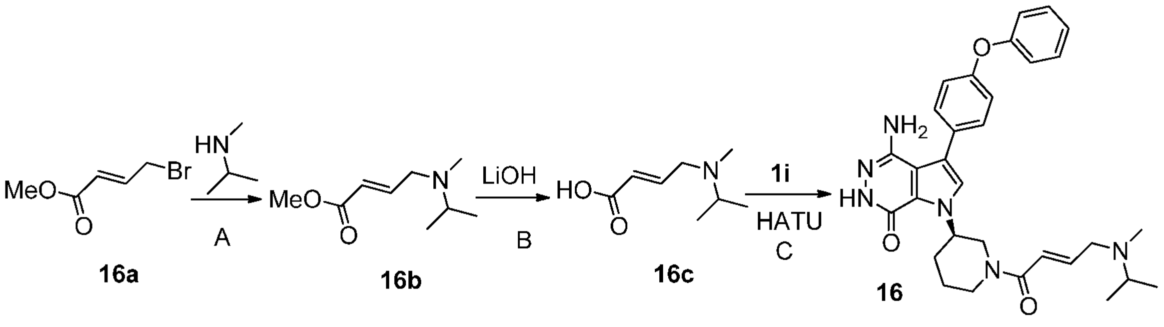
[00141] **Example 15.** N-(3-(4-amino-7-oxo-3-(4-phenoxyphenyl)-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-yl)bicyclo[3.2.1]octan-8-yl)acrylamide



15

[00142] Title compound **15** (light yellow solid, 4.8 mg) was made from **1b** and **I1** via the similar conditions described in steps 1B~1G of Example 1. MS (ESI): *m/z* = 496 $[M+H]^+$.

[00143] **Example 16.** 4-amino-1-[(3R)-1-[(E)-4-[isopropyl(methyl)amino]but-2-enoyl]-3-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one



Step 16A

[00144] A mixture of **16a** (225 mg) and N-methylpropan-2-amine (190 mg) in THF (3 ml) was stirred at rt for two days. Saturated NaCl solution was added, the mixture was extracted with EtOAc twice. The organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give **16b** (200 mg).

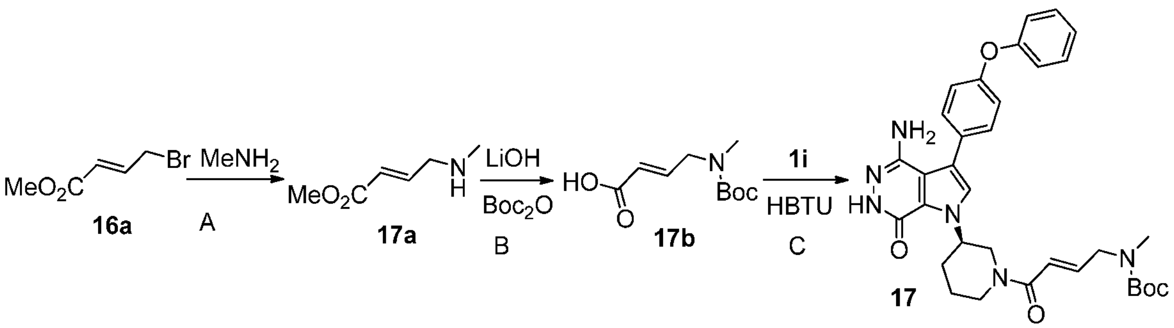
Step 16B

[00145] To a solution of **16b** (195 mg) in THF (5 ml) was added LiOH (1M solution, 2.5 ml). The mixture was stirred at rt for 2 h. 2M HCl solution was added to pH <5, concentrated to give **16c** (500 mg).

Step 16C

[00146] To a solution of **1i** (11 mg) in DMF (1 ml) was added DIEA (0.05 ml), acid **16c** (15 mg) and HATU (20 mg). The resulting mixture was stirred at room temperature for 1.5 h. The solvents were removed, and the residue was purified by reversed phase preparative HPLC to give title compound **16** (4 mg). MS (ESI): *m/z* = 541 $[M+H]^+$.

[00147] **Example 17.** tert-butyl N-[(E)-4-[(3R)-3-[4-amino-7-oxo-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-1-yl]-1-piperidyl]-4-oxo-but-2-enyl]-N-methyl-carbamate



Step 17A

[00148] To a mixture of **16a** (0.43 g) in THF at -60 °C was added dropwise a solution of 2M methylamine in THF (3 ml). The mixture was stirred at -60 °C for 2 h and concentrated. The residue was purified by silica gel chromatography to give **17a** (0.146 g).

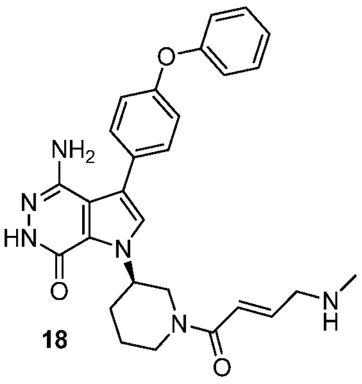
Step 17B

[00149] To a solution of **17a** (145 mg) in THF (5 ml) was added NaOH (2 M solution, 2ml) and MeOH(0.5 ml). The mixture was stirred at rt for 35 min. 1M HCl solution was added to pH <5, concentrated. The crude product was dissolved in DCM/MeOH and treated with Boc_2O (0.5 g). The mixture was stirred at rt for 2 h and concentrated. The residue was purified by silica gel chromatography to give **17b** (0.11 g).

Step 17C

[00150] To a solution of **1i** (10 mg) in DCM (2 ml) were added Et_3N (0.1 ml), acid **17b** (7 mg) and HBTU (18 mg). The resulting mixture was stirred at room temperature for 0.5 h and purified by silica gel chromatography to give title compound **17** (10 mg) as off white solid. MS (ESI): $m/z = 599$ $[M+H]^+$.

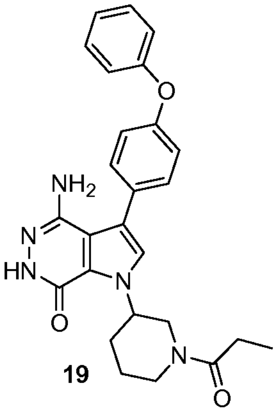
[00151] **Example 18.** 4-amino-1-[(3R)-1-[(E)-4-(methylamino)but-2-enoyl]-3-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one



18

[00152] To a solution of compound **17** (6 mg) in DCM (1.6 ml) was added TFA (0.2ml). The mixture was stirred at rt for 30 min and concentrated. The residue was purified by reversed phase preparative HPLC to give title compound **18** (2.4 mg) as white solid. MS (ESI): $m/z = 499$ $[M+H]^+$.

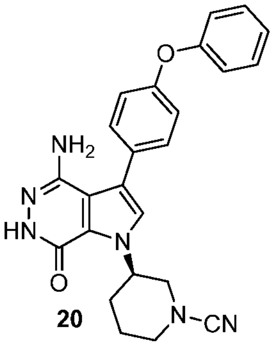
[00153] **Example 19.** 4-amino-3-(4-phenoxyphenyl)-1-(1-propionylpiperidin-3-yl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



19

[00154] A mixture of compound **2** (5 mg) and Pd/C (10wt%, 5 mg) in MeOH (5 ml) was stirred under H_2 balloon for 3h. The reaction mixture was filtered through a pad of celite, washed with EtOAc/MeOH and concentrated to give title compound **19** (2.7 mg) as white solid. MS (ESI): *m/z* = 458 $[M+H]^+$.

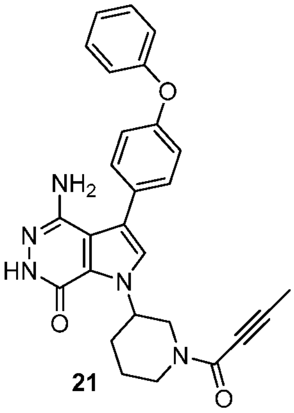
[00155] **Example 20.** (R)-3-(4-amino-7-oxo-3-(4-phenoxyphenyl)-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-yl)piperidine-1-carbonitrile



20

[00156] To a mixture of **1i** (3.5 mg) and K_2CO_3 (2M, 15 µl) in acetone (3 ml) was added BrCN (1 mg). The mixture was stirred at rt for 2 h and concentrated. The residue was purified by reversed phase preparative HPLC to give title compound **20** (1.6 mg) as white solid. MS (ESI): *m/z* = 427 $[M+H]^+$.

[00157] **Example 21.** 4-amino-1-(1-(but-2-ynoyl)piperidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one

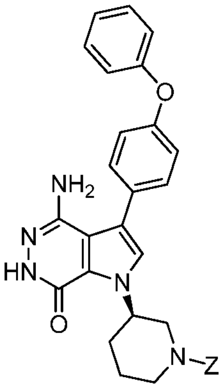


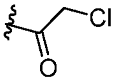
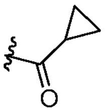
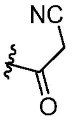
21

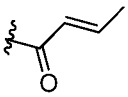
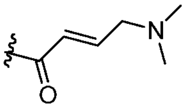
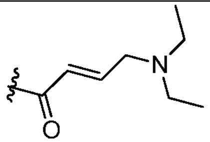
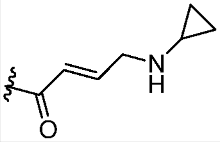
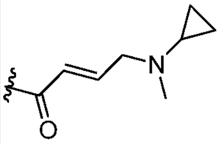
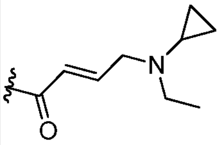
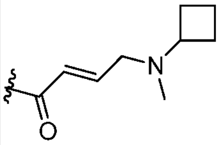
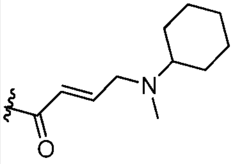
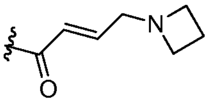
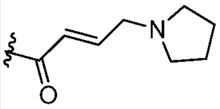
[00158] The title compound was made from racemic **1i** and but-2-ynoic acid via the similar conditions described in step 1G of Example 1. MS (ESI): *m/z* = 468 $[M+H]^+$.

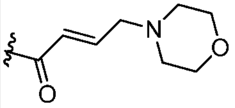
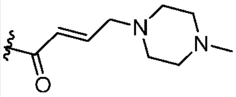
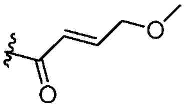
[00159] **Examples 22** to **37** (Table 2) were made from **1i** and corresponding acids (commercially available or easily prepared) via the similar conditions described in Examples 16, 17, 18.

[00160] **Table 2**. Compounds of formula:



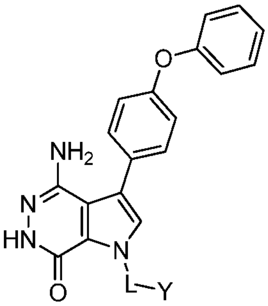
Example	Z	Name	MS(ESI) m/z [M+H]
22		4-amino-1-[(3R)-1-(2-chloroacetyl)-3-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	478
23		4-amino-1-[(3R)-1-(cyclopropanecarbonyl)-3-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	470
24		3-[(3R)-3-[4-amino-7-oxo-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-1-yl]-1-piperidyl]-3-oxo-propanenitrile	469

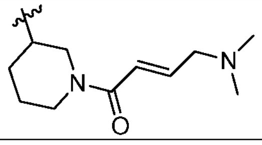
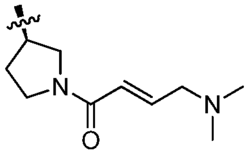
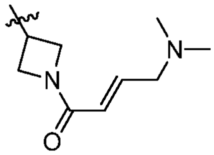
Example	Z	Name	MS(ESI) m/z [M+H]
25		4-amino-1-[(3R)-1-[(E)-but-2-enoyl]-3-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	470
26		4-amino-1-[(3R)-1-[(E)-4-(dimethylamino)but-2-enoyl]-3-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	513
27		4-amino-1-[(3R)-1-[(E)-4-(diethylamino)but-2-enoyl]-3-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	541
28		4-amino-1-[(3R)-1-[(E)-4-(cyclopropylamino)but-2-enoyl]-3-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	525
29		4-amino-1-[(3R)-1-[(E)-4-(cyclopropyl(methyl)amino)but-2-enoyl]-3-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	539
30		4-amino-1-[(3R)-1-[(E)-4-[cyclopropyl(ethyl)amino]but-2-enoyl]-3-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	553
31		4-amino-1-[(3R)-1-[(E)-4-[cyclobutyl(methyl)amino]but-2-enoyl]-3-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	553
32		4-amino-1-[(3R)-1-[(E)-4-[cyclohexyl(methyl)amino]but-2-enoyl]-3-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	581
33		4-amino-1-[(3R)-1-[(E)-4-(azetidin-1-yl)but-2-enoyl]-3-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	525
34		4-amino-3-(4-phenoxyphenyl)-1-[(3R)-1-[(E)-4-pyrrolidin-1-ylbut-2-enoyl]-3-piperidyl]-6H-pyrrolo[2,3-d]pyridazin-7-one	539

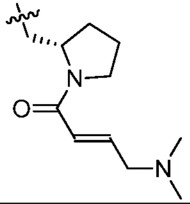
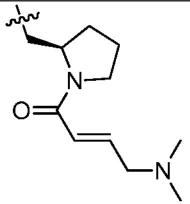
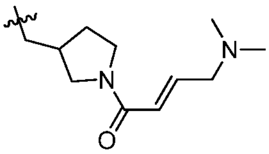
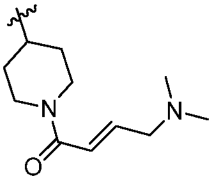
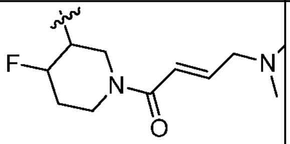
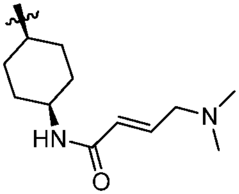
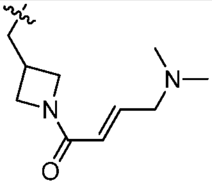
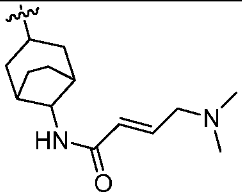
Example	Z	Name	MS(ESI) m/z [M+H]
35		4-amino-1-[(3R)-1-[(E)-4-morpholinobut-2-enoyl]-3-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	555
36		4-amino-1-[(3R)-1-[(E)-4-(4-methylpiperazin-1-yl)but-2-enoyl]-3-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	568
37		4-amino-1-[(3R)-1-[(E)-4-methoxybut-2-enoyl]-3-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	500

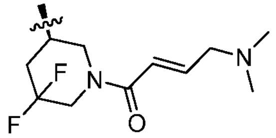
[00161] **Examples 38** to **49** (Table 3) were made from (E)-4-(dimethylamino)but-2-enoic acid and corresponding amines (precursors of previous examples) via the similar conditions described in step 16C of Example 16.

[00162] **Table 3**. Compounds of formula:

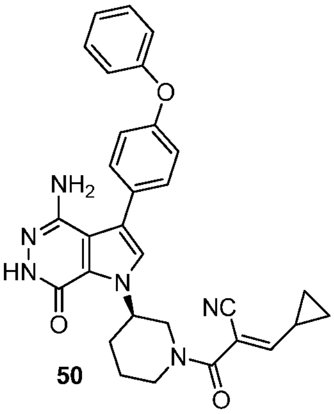


Example	L-Y	Name	MS(ESI) m/z [M+H]+
38		4-amino-1-[1-[(E)-4-(dimethylamino)but-2-enoyl]-3-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	513
39		4-amino-1-[(3R)-1-[(E)-4-(dimethylamino)but-2-enoyl]pyrrolidin-3-yl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	499
40		4-amino-1-[1-[(E)-4-(dimethylamino)but-2-enoyl]azetidin-3-yl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	485

Example	L-Y	Name	MS(ESI) m/z [M+H]+
41		4-amino-1-[[(2S)-1-[(E)-4-(dimethylamino)but-2-enoyl]pyrrolidin-2-yl]methyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	513
42		4-amino-1-[[(2R)-1-[(E)-4-(dimethylamino)but-2-enoyl]pyrrolidin-2-yl]methyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	513
43		4-amino-1-[[1-[(E)-4-(dimethylamino)but-2-enoyl]pyrrolidin-3-yl]methyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	513
44		4-amino-1-[1-[(E)-4-(dimethylamino)but-2-enoyl]-4-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	513
45		4-amino-1-[1-[(E)-4-(dimethylamino)but-2-enoyl]-4-fluoro-3-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	531
46		(E)-N-[4-[4-amino-7-oxo-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-1-yl]cyclohexyl]-4-(dimethylamino)but-2-enamide	527
47		4-amino-1-[[1-[(E)-4-(dimethylamino)but-2-enoyl]azetidin-3-yl]methyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	499
48		(E)-N-[3-[4-amino-7-oxo-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-1-yl]-8-bicyclo[3.2.1]octanyl]-4-(dimethylamino)but-2-enamide	553

Example	L-Y	Name	MS(ESI) m/z [M+H]+
49		4-amino-1-[(3R)-1-[(E)-4-(dimethylamino)but-2-enoyl]-5,5-difluoro-3-piperidyl]-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one	549

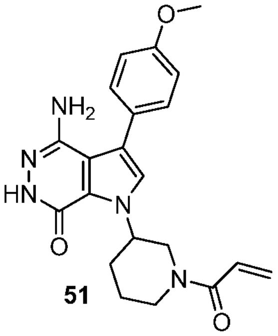
[00163] **Example 50.** (E)-2-[(3R)-3-[4-amino-7-oxo-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-1-yl]piperidine-1-carbonyl]-3-cyclopropyl-prop-2-enenitrile



50

[00164] To a mixture of compound **24** (9 mg) and piperidine (2 mg) in MeOH (1 ml) was added cyclopropanecarbaldehyde (2.1 mg). The mixture was stirred at rt for 20h and concentrated. The residue was purified by reversed phase preparative HPLC to give title compound **50** (2.7 mg) as white solid. MS (ESI): *m/z* = 521 $[M+H]^+$.

[00165] **Example 51.** 1-(1-acryloylpiperidin-3-yl)-4-amino-3-(4-methoxyphenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one

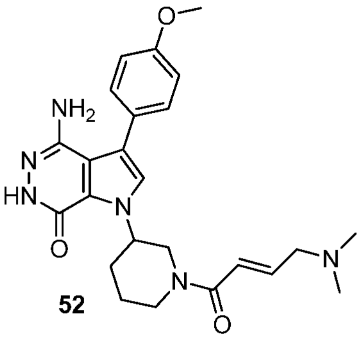


51

[00166] The title compound was made was made from racemic **1e** and (4-methoxyphenyl)boronic acid via the similar conditions described in steps 1D~1G of Example 1. MS (ESI): *m/z* = 394 $[M+H]^+$.

[00167] **Example 52.** 4-amino-1-[1-[(E)-4-(dimethylamino)but-2-enoyl]-3-piperidyl]-3-

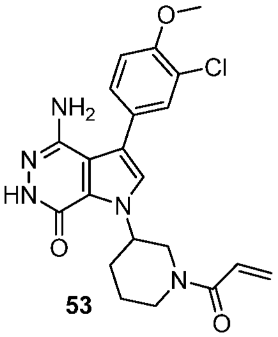
(4-methoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one



52

[00168] The title compound was made from (E)-4-(dimethylamino)but-2-enoic acid and corresponding amine (precursor of example 51) via the similar conditions described in step 16C of Example 16. MS (ESI): *m/z* = 451 $[M+H]^+$.

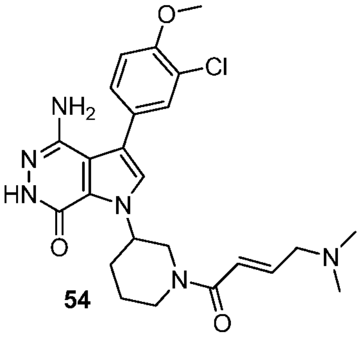
[00169] **Example 53.** 1-(1-acryloylpiperidin-3-yl)-4-amino-3-(3-chloro-4-methoxyphenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



53

[00170] The title compound was made was made from racemic **1e** and (3-chloro-4-methoxyphenyl)boronic acid via the similar conditions described in steps 1D~1G of Example 1. MS (ESI): *m/z* = 428 $[M+H]^+$.

[00171] **Example 54.** 4-amino-3-(3-chloro-4-methoxy-phenyl)-1-[1-[(E)-4-(dimethylamino)but-2-enoyl]-3-piperidyl]-6H-pyrrolo[2,3-d]pyridazin-7-one

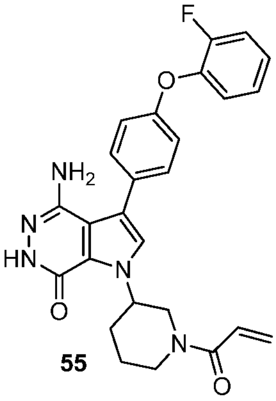


54

[00172] The title compound was made from (E)-4-(dimethylamino)but-2-enoic acid and corresponding amine (precursor of example 53) via the similar conditions described

in step 16C of Example 16. MS (ESI): *m/z* = 485 $[M+H]^+$.

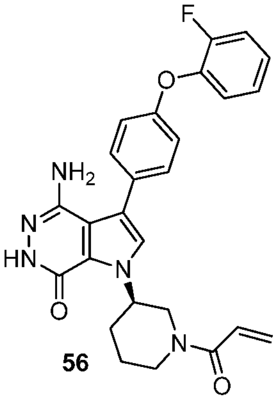
[00173] **Example 55.** 1-(1-acryloylpiperidin-3-yl)-4-amino-3-(4-(2-fluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



55

[00174] The title compound was made from racemic **1e** and ((4-(2-fluorophenoxy)phenyl)boronic acid via the similar conditions described in steps 1D~1G of Example 1. MS (ESI): *m/z* = 474 $[M+H]^+$.

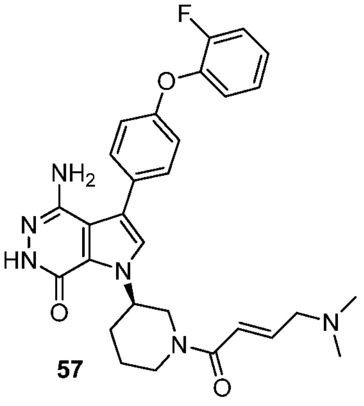
[00175] **Example 56.** (R)-1-(1-acryloylpiperidin-3-yl)-4-amino-3-(4-(2-fluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



56

[00176] The title compound was made was made from **1e** and ((4-(2-fluorophenoxy)phenyl)boronic acid via the similar conditions described in steps 1D~1G of Example 1. MS (ESI): *m/z* = 474 $[M+H]^+$.

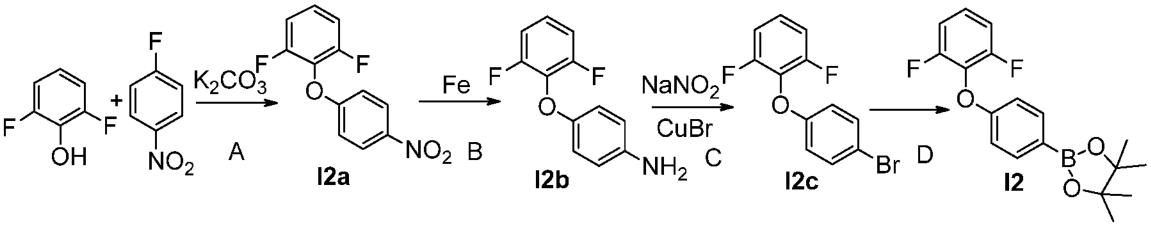
[00177] **Example 57.** 4-amino-1-[(3R)-1-[(E)-4-(dimethylamino)but-2-enoyl]-3-piperidyl]-3-[4-(2-fluorophenoxy)phenyl]-6H-pyrrolo[2,3-d]pyridazin-7-one



57

[00178] The title compound was made from (E)-4-(dimethylamino)but-2-enoic acid and corresponding amine (precursor of example 56) via the similar conditions described in step 16C of Example 16. MS (ESI): *m/z* = 531 $[M+H]^+$.

[00179] **Intermediate 2.**



Step I2A

[00180] A mixture of 2,6-difluorophenol (3.0 g, 21.3 mmol), 1-fluoro-4-nitrobenzene (3.04 g, 23.4 mmol) and K_2CO_3 (4.4 g, 32 mmol) in CH_3CN (50 ml) was refluxed 16 h. After cooled to room temperature, the solvents were removed. Water was added, the mixture was extracted with EtOAc three times. The organic extracts were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated to give oil **I2a** (4.9 g).

Step I2B

[00181] A mixture of 1,3-difluoro-2-(4-nitrophenoxy)benzene **I2a** (4.9 g, 19.5 mmol), saturated NH_4Cl solution (5 ml) and iron powder (5.5 g, 97.5 mmol) in MeOH(40 mL) was refluxed for 3 h. The mixture was filtered. Water was added to the filtrate, extracted with EtOAc three times. The organic extracts were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated to give light yellow oil **I2b** (4.1g). MS (ESI): m/z=222.1 $[M+H]^+$.

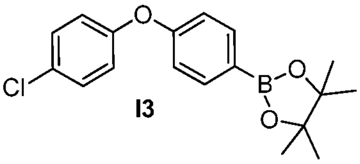
Step I2C

[00182] To a mixture of 4-(2,6-difluorophenoxy)aniline **I2b** (4.1 g, 18.5 mmol) in 2M H_2SO_4 solution (50 ml) at 0 °C was added a solution of $NaNO_2$(6.4 g, 92.7 mmol) in water (20 ml). The mixture was stirred at 0 °C for 40min and charged with CuBr (5.3 g, 37 mmol). The resulting mixture was refluxed for 16 h, cooled to rt, extracted with EtOAc three times. The organic extracts were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated to give colorless oil **I2c** (1.6 g).

Step I2D

[00183] A mixture of 2-(4-bromophenoxy)-1,3-difluorobenzene **I2c** (1.6 g, 3.6 mmol), bis(pinacolato)-diboron (1.71 g, 6.7 mmol), KOAc (830 mg, 8.4 mmol) and $Pd(PPh_3)_2Cl_2$(126 mg, 0.18 mmol) in 1,4-dioxane (40 ml) was stirred in under N_2 at 80 °C for 16h. After cooled to room temperature, the solvents were removed. The residue was purified by silica gel chromatography to give colorless oil **I2** (1.6 g).

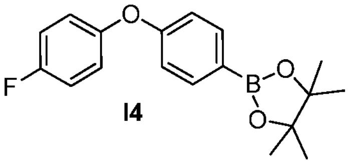
[00184] **Intermediate 3.** 2-(4-(4-chlorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



I3

[00185] A mixture of 1-chloro-4-(4-iodophenoxy)benzene (330 mg), bis(pinacolato)diboron (508 mg), KOAc (300 mg) and $Pd(PPh_3)_2Cl_2$(82 mg) in 1,4-dioxane (10 ml) was stirred in seal tube under N_2 at 100 °C for 16h. After cooled to room temperature, filtered off solids, the filtrate was concentrated. The residue was purified by silica gel chromatography to give yellow oil **I3** (150 mg).

[00186] **Intermediate 4.** 2-(4-(4-fluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

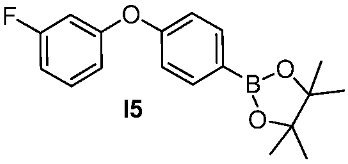


I4

[00187] The title compound was made was made from 1-fluoro-4-(4-iodophenoxy)benzene via the similar conditions described in Intermediate 3.

[00188] **Intermediate 5.** 2-(4-(3-fluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-

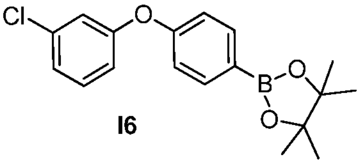
dioxaborolane



I5

[00189] A mixture of (3-fluorophenyl)boronic acid (0.71 g), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (1.02 g), $Cu(OAc)_2$ (1.0 g), TEA (1.3ml), and molecular sieve 4A (3 g) in DCM (20 ml) was stirred at rt for 24h. The reaction mixture was filtered through a pad of celite, washed with DCM and concentrated. The residue was purified by silica gel chromatography to give colorless oil **I5** (60 mg).

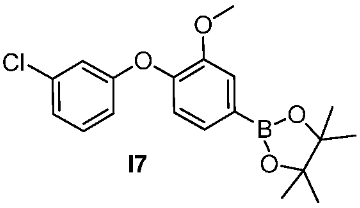
[00190] **Intermediate 6.** 2-(4-(3-chlorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



I6

[00191] The title compound was made was made from (3-chlorophenyl)boronic acid via the similar conditions described in Intermediate 5.

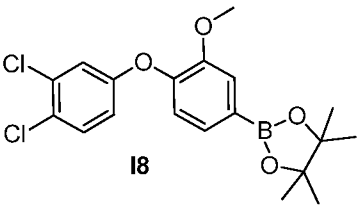
[00192] **Intermediate 7.** 2-(4-(3-chlorophenoxy)-3-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



I7

[00193] The title compound was made was made from 3-chlorophenol and 1-fluoro-2-methoxy-4-nitrobenzene via the similar conditions described in Intermediate 2.

[00194] **Intermediate 8.** 2-(4-(3,4-dichlorophenoxy)-3-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

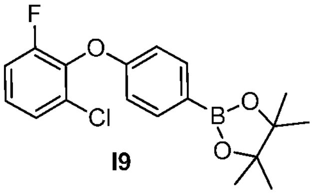


I8

[00195] The title compound was made was made from 3,4-dichlorophenol and 1-

fluoro-2-methoxy-4-nitrobenzene via the similar conditions described in Intermediate 2.

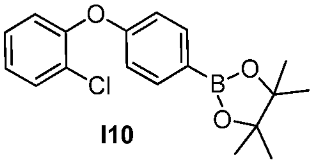
[00196] **Intermediate 9.** 2-(4-(2-chloro-6-fluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



I9

[00197] The title compound was made was made from 2-chloro-6-fluorophenol and 1-fluoro-4-nitrobenzene via the similar conditions described in Intermediate 2.

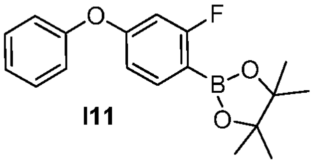
[00198] **Intermediate 10.** 2-(4-(2-chlorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



I10

[00199] The title compound was made was made from 2-chlorophenol and 1-fluoro-4-nitrobenzene via the similar conditions described in Intermediate 2.

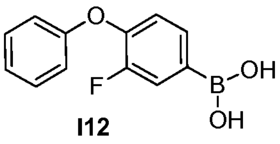
[00200] **Intermediate 11.** 2-(2-fluoro-4-phenoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



I11

[00201] The title compound was made was made from phenol and 2,4-difluoro-1-nitrobenzene via the similar conditions described in Intermediate 2.

[00202] **Intermediate 12.** (3-fluoro-4-phenoxyphenyl)boronic acid

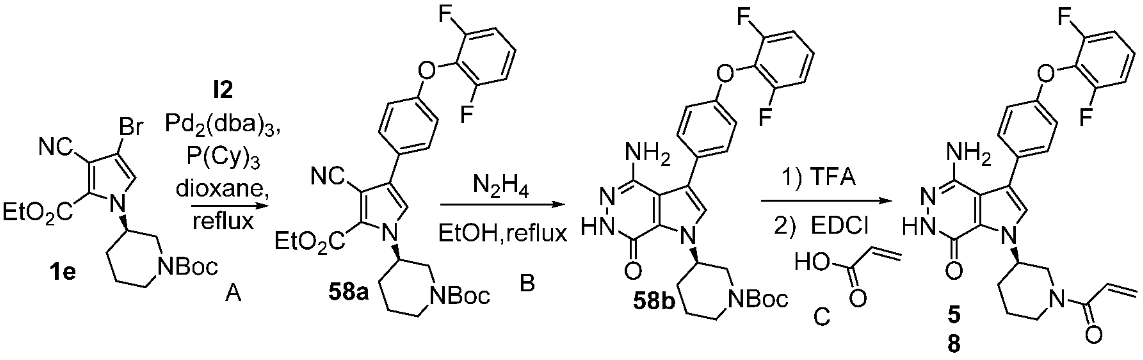


I12

[00203] To a solution of 4-bromo-2-fluoro-1-phenoxybenzene (0.5 g, 3.6 mmol) in THF (20 ml) at -78 °C was added dropwise a solution of n-BuLi (2.5 M in hexane, 2.16 ml, 5.4 mmol). After 30min, triisopropyl borate (1.15 ml, 5.4 mmol) was added dropwise. The mixture was stirred -78 °C for 1 h. The reaction was quenched with water, extracted with

EtOAc three times. The combined organic extracts were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated to give light yellow oil **I12** (0.18 g).

[00204] **Example 58.** (R)-1-(1-acryloylpiperidin-3-yl)-4-amino-3-(4-(2,6-difluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



Step 58A

[00205] A mixture of **1e** (2.8 g, 6.6 mol), **I2** (2.2 g, 6.6 mol) and $K_3PO_4 \cdot 3H_2O$ (2.6g, 9.9 mol) in 1.4-dioxane/water (10 ml/1 ml) was degassed with N_2. Next was added $Pd_2(dba)_3$ (300mg, 0.33 mmol) and $P(Cy)_3$ (185 mg, 0.66 mmol). The resulting mixture was refluxed under N_2 for 16h. After cooled to room temperature, the solid was filtered off, the filtrate was concentrated. The residue was purified by silica gel chromatography to give white solid **58a** (1.2 g). MS (ESI): m/z=552 $[M+H]^+$.

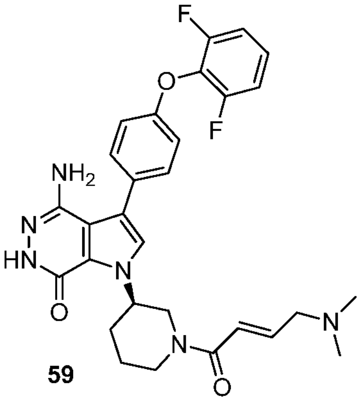
Step 58B

[00206] A mixture of **58a** (1.2 g) and $N_2H_4 \cdot H_2O$ (1 mL) in EtOH (5 ml) was refluxed for 16h. After cooled to room temperature, the solvents were removed. The residue was purified by silica gel chromatography to give white solid **58b** (0.66 g). MS (ESI): m/z=538 $[M+H]^+$.

Step 58C

[00207] To a solution of **58b** (880 mg, 1.63 mol) in DCM (5 ml) was added TFA (1 ml). The mixture was stirred at rt for 3 h and concentrated to give oil **58c** (940 mg). To a solution of **58c** (940 mg) in DCM (5 ml) was added acrylic acid (210 mg, 2.5 mol), EDCI (627 mg, 3.3 mmol) and TEA (340 mg, 3.3 mmol). The resulting mixture was stirred at room temperature for 18 h and concentrated. The residue was purified by silica gel chromatography to give the title compound **58** (450 mg) as white solid. MS (ESI): *m/z* = 492 $[M+H]^+$.

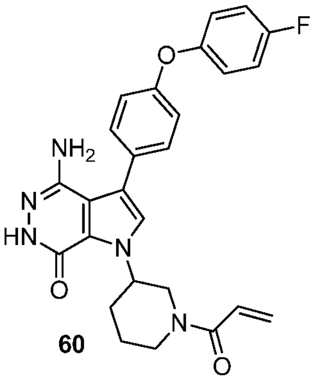
[00208] **Example 59.** 4-amino-3-[4-(2,6-difluorophenoxy)phenyl]-1-[(3R)-1-[(E)-4-(dimethylamino)but-2-enoyl]-3-piperidyl]-6H-pyrrolo[2,3-d]pyridazin-7-one



59

[00209] The title compound was made from (E)-4-(dimethylamino)but-2-enoic acid and amine **58c** via the similar conditions described in step 16C of Example 16. MS (ESI): *m/z* = 549 $[M+H]^+$.

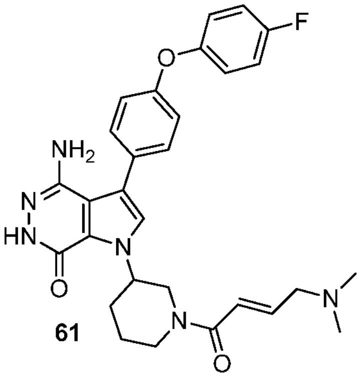
[00210] **Example 60.** 1-(1-acryloylpiperidin-3-yl)-4-amino-3-(4-(4-fluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



60

[00211] The title compound was made was made from racemic **1e** and intermediate 4 via the similar conditions described in steps 1D~1G of Example 1. MS (ESI): *m/z* = 474 $[M+H]^+$.

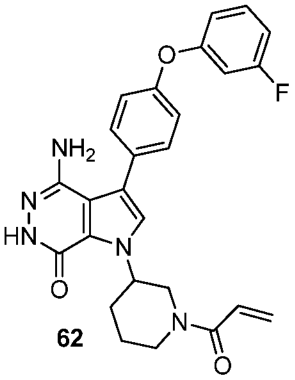
[00212] **Example 61.** 4-amino-1-[1-[(E)-4-(dimethylamino)but-2-enoyl]-3-piperidyl]-3-[4-(4-fluorophenoxy)phenyl]-6H-pyrrolo[2,3-d]pyridazin-7-one



61

[00213] The title compound was made from (E)-4-(dimethylamino)but-2-enoic acid and corresponding amine (precursor of example 60) via the similar conditions described in step 16C of Example 16. MS (ESI): *m/z* = 531 $[M+H]^+$.

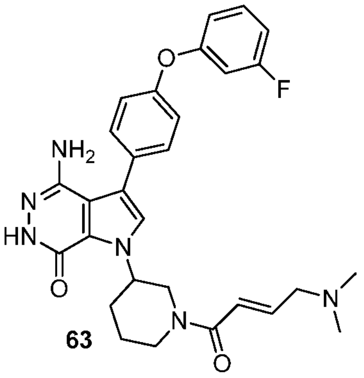
[00214] **Example 62.** 1-(1-acryloylpiperidin-3-yl)-4-amino-3-(4-(3-fluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



62

[00215] The title compound was made was made from racemic **1e** and intermediate 5 via the similar conditions described in steps 1D~1G of Example 1. MS (ESI): *m/z* = 474 $[M+H]^+$.

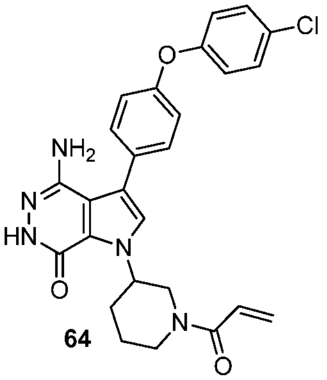
[00216] **Example 63.** 4-amino-1-[1-[(E)-4-(dimethylamino)but-2-enoyl]-3-piperidyl]-3-[4-(3-fluorophenoxy)phenyl]-6H-pyrrolo[2,3-d]pyridazin-7-one



63

[00217] The title compound was made from (E)-4-(dimethylamino)but-2-enoic acid and corresponding amine (precursor of example 62) via the similar conditions described in step 16C of Example 16. MS (ESI): *m/z* = 531 $[M+H]^+$.

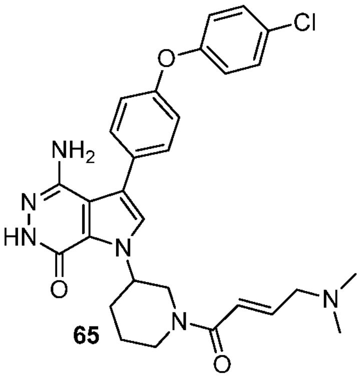
[00218] **Example 64.** 1-(1-acryloylpiperidin-3-yl)-4-amino-3-(4-(4-chlorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



64

[00219] The title compound was made was made from racemic **1e** and intermediate 3 via the similar conditions described in steps 1D~1G of Example 1. MS (ESI): *m/z* =490 $[M+H]^+$.

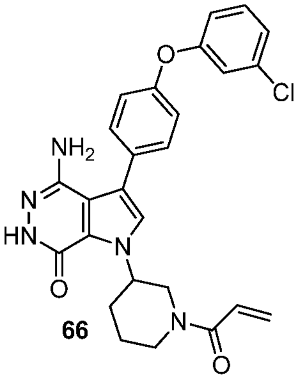
[00220] **Example 65.** 4-amino-3-[4-(4-chlorophenoxy)phenyl]-1-[1-[(E)-4-(dimethylamino)but-2-enoyl]-3-piperidyl]-6H-pyrrolo[2,3-d]pyridazin-7-one



65

[00221] The title compound was made from (E)-4-(dimethylamino)but-2-enoic acid and corresponding amine (precursor of example 64) via the similar conditions described in step 16C of Example 16. MS (ESI): *m/z* = 547 $[M+H]^+$.

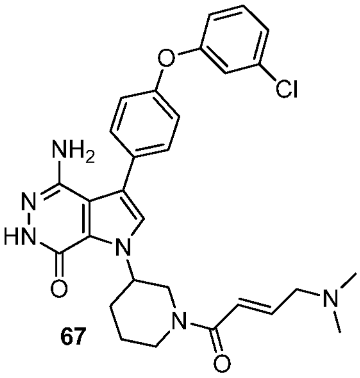
[00222] **Example 66.** 1-(1-acryloylpiperidin-3-yl)-4-amino-3-(4-(3-chlorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



66

[00223] The title compound was made was made from racemic **1e** and intermediate 6 via the similar conditions described in steps 1D~1G of Example 1. MS (ESI): *m/z* = 490 $[M+H]^+$.

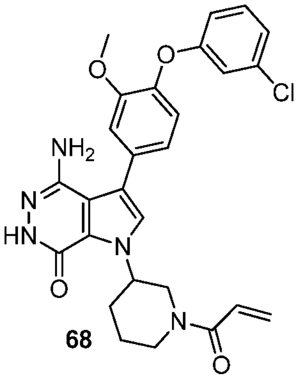
[00224] **Example 67.** 4-amino-3-[4-(3-chlorophenoxy)phenyl]-1-[1-[(E)-4-(dimethylamino)but-2-enoyl]-3-piperidyl]-6H-pyrrolo[2,3-d]pyridazin-7-one



67

[00225] The title compound was made from (E)-4-(dimethylamino)but-2-enoic acid and corresponding amine (precursor of example 66) via the similar conditions described in step 16C of Example 16. MS (ESI): *m/z* = 547 $[M+H]^+$.

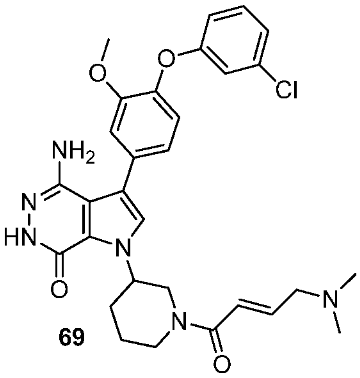
[00226] **Example 68.** 1-(1-acryloylpiperidin-3-yl)-4-amino-3-(4-(3-chlorophenoxy)-3-methoxyphenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



68

[00227] The title compound was made was made from racemic **1e** and intermediate 7 via the similar conditions described in steps 1D~1G of Example 1. MS (ESI): *m/z* = 520 $[M+H]^+$.

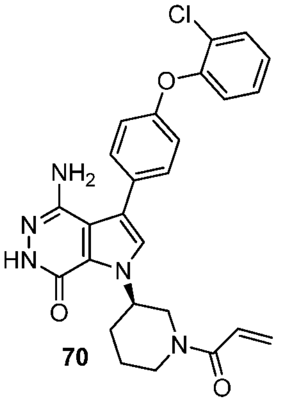
[00228] **Example 69.** 4-amino-3-[4-(3-chlorophenoxy)-3-methoxy-phenyl]-1-[1-[(E)-4-(dimethylamino)but-2-enoyl]-3-piperidyl]-6H-pyrrolo[2,3-d]pyridazin-7-one



69

[00229] The title compound was made from (E)-4-(dimethylamino)but-2-enoic acid and corresponding amine (precursor of example 68) via the similar conditions described in step 16C of Example 16. MS (ESI): *m/z* = 577 $[M+H]^+$.

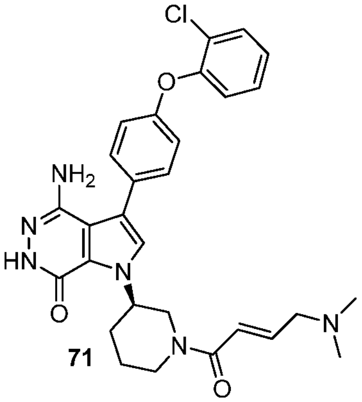
[00230] **Example 70.** (R)-1-(1-acryloylpiperidin-3-yl)-4-amino-3-(4-(2-chlorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



70

[00231] The title compound was made was made from **1e** and intermediate 10 via the similar conditions described in Example 58. MS (ESI): *m/z* = 490 $[M+H]^+$.

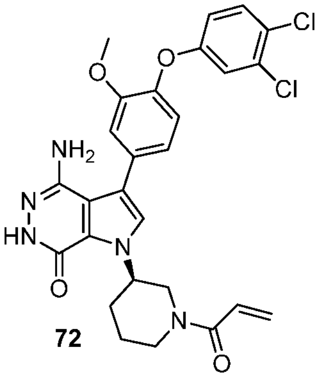
[00232] **Example 71.** 4-amino-3-[4-(2-chlorophenoxy)phenyl]-1-[(3R)-1-[(E)-4-(dimethylamino)but-2-enoyl]-3-piperidyl]-6H-pyrrolo[2,3-d]pyridazin-7-one



71

[00233] The title compound was made from (E)-4-(dimethylamino)but-2-enoic acid and corresponding amine (precursor of example 70) via the similar conditions described in step 16C of Example 16. MS (ESI): *m/z* = 547 $[M+H]^+$.

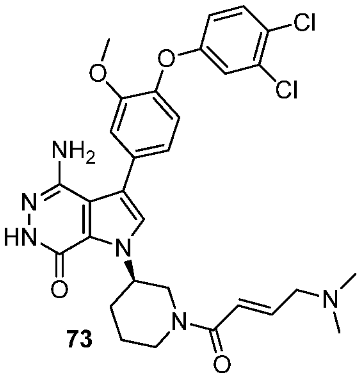
[00234] **Example 72.** (R)-1-(1-acryloylpiperidin-3-yl)-4-amino-3-(4-(3,4-dichlorophenoxy)-3-methoxyphenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



72

[00235] The title compound was made was made from **1e** and intermediate 8 via the similar conditions described in Example 58. MS (ESI): *m/z* = 554 $[M+H]^+$.

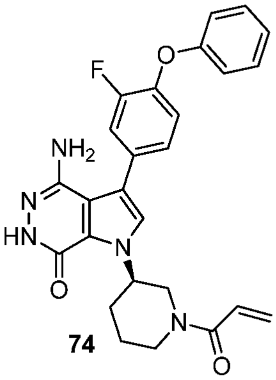
[00236] **Example 73.** 4-amino-3-[4-(3,4-dichlorophenoxy)-3-methoxy-phenyl]-1-[(3R)-1-[(E)-4-(dimethylamino)but-2-enoyl]-3-piperidyl]-6H-pyrrolo[2,3-d]pyridazin-7-one



73

[00237] The title compound was made from (E)-4-(dimethylamino)but-2-enoic acid and corresponding amine (precursor of example 72) via the similar conditions described in step 16C of Example 16. MS (ESI): *m/z* = 611 $[M+H]^+$.

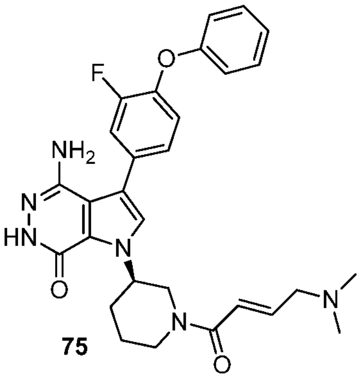
[00238] **Example 74.** (R)-1-(1-acryloylpiperidin-3-yl)-4-amino-3-(3-fluoro-4-phenoxyphenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



74

[00239] The title compound was made from **1e** and intermediate 12 via the similar conditions described in Example 58. MS (ESI): *m/z* = 474 $[M+H]^+$.

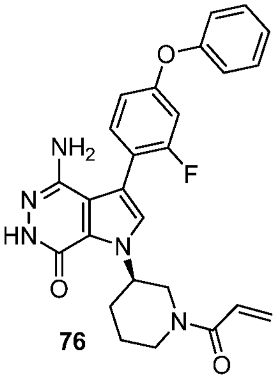
[00240] **Example 75.** 4-amino-1-[(3R)-1-[(E)-4-(dimethylamino)but-2-enoyl]-3-piperidyl]-3-(3-fluoro-4-phenoxy-phenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one



75

[00241] The title compound was made from (E)-4-(dimethylamino) but-2-enoic acid and corresponding amine (precursor of example 74) via the similar conditions described in step 16C of Example 16. MS (ESI): *m/z* = 531 $[M+H]^+$.

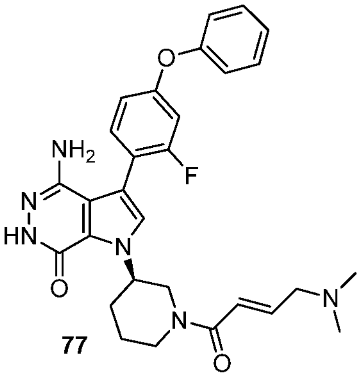
[00242] **Example 76.** (R)-1-(1-acryloylpiperidin-3-yl)-4-amino-3-(2-fluoro-4-phenoxyphenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



76

[00243] The title compound was made from **1e** and intermediate 11 via the similar conditions described in Example 58. MS (ESI): *m/z* = 474 $[M+H]^+$.

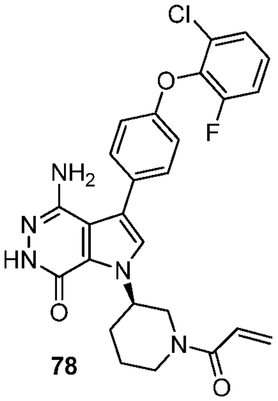
[00244] **Example 77.** 4-amino-1-[(3R)-1-[(E)-4-(dimethylamino)but-2-enoyl]-3-piperidyl]-3-(2-fluoro-4-phenoxy-phenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one



77

[00245] The title compound was made from (E)-4-(dimethylamino)but-2-enoic acid and corresponding amine (precursor of example 76) via the similar conditions described in step 16C of Example 16. MS (ESI): *m/z* = 531 $[M+H]^+$.

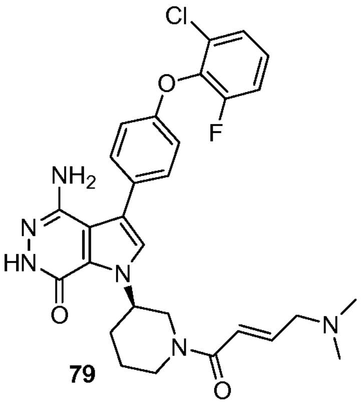
[00246] **Example 78.** (R)-1-(1-acryloylpiperidin-3-yl)-4-amino-3-(4-(2-chloro-6-fluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



78

[00247] The title compound was made from **1e** and intermediate 9 via the similar conditions described in Example 58. MS (ESI): *m/z* = 508 $[M+H]^+$.

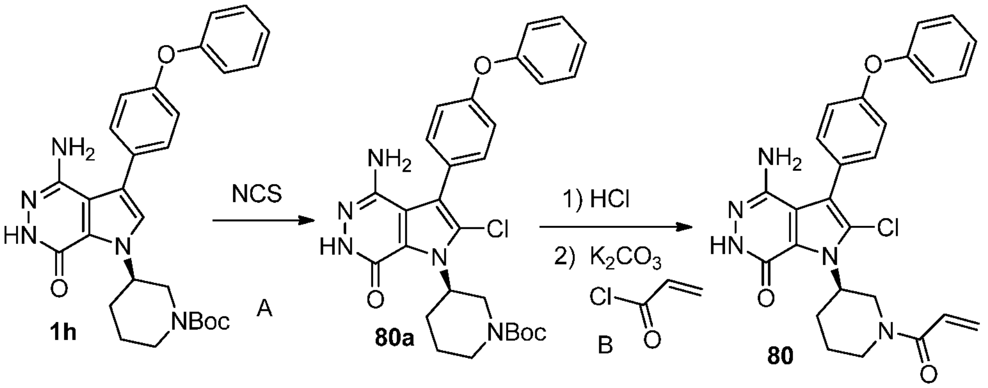
[00248] **Example 79.** 4-amino-3-[4-(2-chloro-6-fluoro-phenoxy)phenyl]-1-[(3R)-1-[(E)-4-(dimethylamino)but-2-enoyl]-3-piperidyl]-6H-pyrrolo[2,3-d]pyridazin-7-one



79

[00249] The title compound was made from (E)-4-(dimethylamino)but-2-enoic acid and corresponding amine (precursor of example 78) via the similar conditions described in step 16C of Example 16. MS (ESI): *m/z* = 565 $[M+H]^+$.

[00250] **Example 80.** (R)-1-(1-acryloylpiperidin-3-yl)-4-amino-2-chloro-3-(4-phenoxyphenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



Step 80A

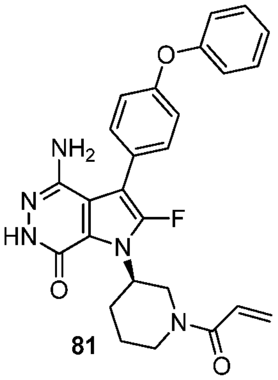
[00251] A mixture of **1h** (23 mg) and NCS (15 mg) in DCM (1.5 ml) was stirred at rt for 20 h and concentrated. The residue was purified by silica gel chromatography to afford beige solid **80a** (13 mg). MS (ESI): *m/z* = 536 $[M+H]^+$.

Step 80B

[00252] A mixture of **80a** (13 mg) and HCl solution (0.2 ml, 4M in dioxane) in DCM (1 ml) was stirred at rt for 0.5 h and concentrated. The crude product was dissolved in THF

and cooled in ice bath. To the mixture was added K_2CO_3 (2 M, 30 μl) and a solution of acryloyl chloride (5 mg) in THF. The resulting mixture was stirred at 0°C for 30 min and purified by reversed phase preparative HPLC to give title compound **80** (2.1 mg) as off white solid. MS (ESI): *m/z* = 490 $[M+H]^+$.

[00253] **Example 81.** (R)-1-(1-acryloylpiperidin-3-yl)-4-amino-2-fluoro-3-(4-phenoxyphenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one

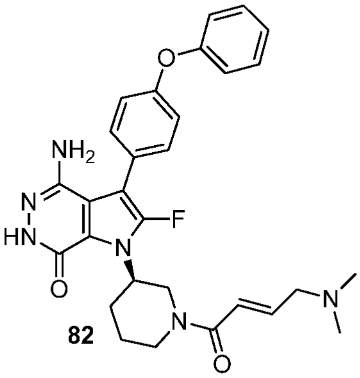


81

[00254] A mixture of **1g** (120 mg, 0.23 mmol) and selectflour (98.9 mg, 0.28 mmol) in CH_3CN (10 ml) was refluxed for 10h. After cooled to room temperature, the solvents were removed. Water was added, the mixture was extracted with EtOAc three times. The combined organic extracts were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated to give oil **81a** (71 mg). MS (ESI): *m/z* = 534 $[M+H]^+$.

[00255] The title compound was made from **81a** and via the similar conditions described in steps 1E~1G of Example 1. MS (ESI): *m/z* = 474 $[M+H]^+$.

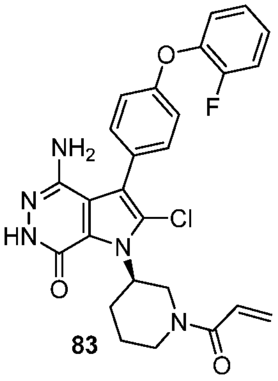
[00256] **Example 82.** 4-amino-1-[(3R)-1-[(E)-4-(dimethylamino)but-2-enoyl]-3-piperidyl]-2-fluoro-3-(4-phenoxyphenyl)-6H-pyrrolo[2,3-d]pyridazin-7-one



82

[00257] The title compound was made from (E)-4-(dimethylamino)but-2-enoic acid and corresponding amine (precursor of example 81) via the similar conditions described in step 16C of Example 16. MS (ESI): *m/z* = 531 $[M+H]^+$.

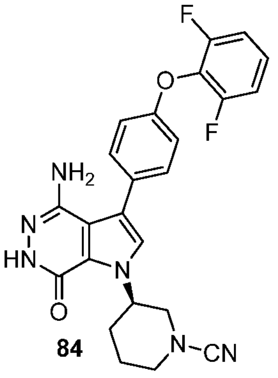
[00258] **Example 83.** (R)-1-(1-acryloylpiperidin-3-yl)-4-amino-2-chloro-3-(4-(2-fluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



83

[00259] The title compound was prepared via the similar conditions described in Example 80. MS (ESI): m/z=508 $[M+H]^+$.

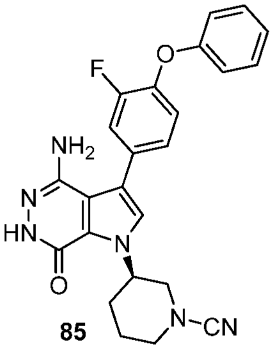
[00260] **Example 84.** (R)-3-(4-amino-3-(4-(2,6-difluorophenoxy)phenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-yl)piperidine-1-carbonitrile



84

[00261] The title compound was prepared via the similar conditions described in Example 20. MS (ESI): m/z=463 $[M+H]^+$.

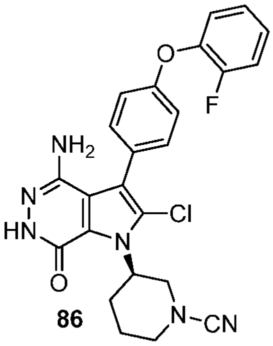
[00262] **Example 85.** (R)-3-(4-amino-3-(3-fluoro-4-phenoxyphenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-yl)piperidine-1-carbonitrile



85

[00263] The title compound was prepared via the similar conditions described in Example 20. MS (ESI): m/z=445 $[M+H]^+$.

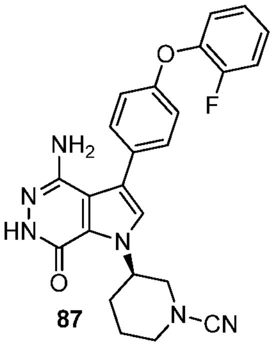
[00264] **Example 86.** (R)-3-(4-amino-2-chloro-3-(4-(2-fluorophenoxy)phenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-yl)piperidine-1-carbonitrile



86

[00265] The title compound was prepared via the similar conditions described in Example 20, 80. MS (ESI): m/z=479 $[M+H]^+$.

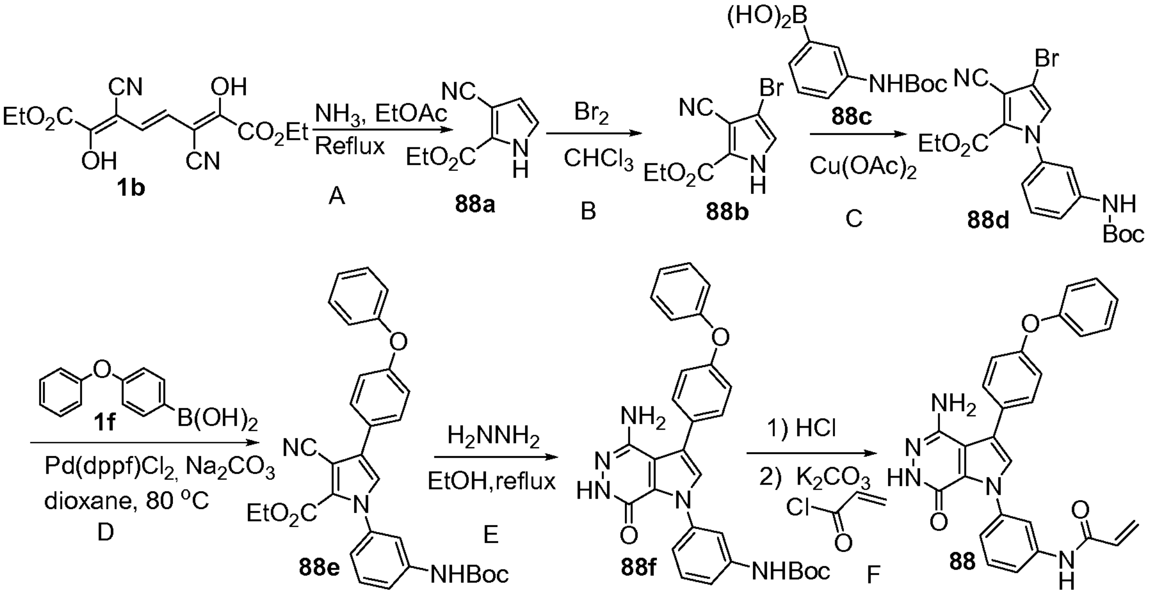
[00266] **Example 87.** (R)-3-(4-amino-3-(4-(2-fluorophenoxy)phenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-yl)piperidine-1-carbonitrile



87

[00267] The title compound was prepared via the similar conditions described in Example 20. MS (ESI): m/z=445 $[M+H]^+$.

[00268] **Example 88.** N-(3-(4-amino-7-oxo-3-(4-phenoxyphenyl)-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-yl)phenyl)acrylamide



Step 88A

[00269] To a solution of **1b** (1.62 g) in EtOAc (30 ml) at 60°C was added dropwise a solution of 0.5 M NH_3 in dioxane (22 ml). The mixture was refluxed for 18 h. After cooled to room temperature, the solvents were removed. The residue was purified by silica gel chromatography to afford light yellow solid **88a** (0.37 g).

Step 88B

[00270] To a solution of **88a** (320 mg) in $CHCl_3$ (17 ml) at -20°C was added dropwise a solution of Br_2 (350 mg) in $CHCl_3$ (3 ml). The mixture was stirred at lower than 10°C for 5 h, and then quenched with a solution of 10% $Na_2S_2O_3$ and saturated solution of $NaHCO_3$. The two phases were separated; the aqueous phase was extracted with DCM three times. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to give **88b** (400 mg).

Step 88C

[00271] To a mixture of **88b** (200 mg, 0.82 mmol), **88c** (390 mg, 1.64 mmol) in DCM (10 ml) at 0°C was added $Cu(OAc)_2$ (224 mg, 1.23 mmol) and pyridine (185 μl). The mixture stirred at rt for 20h. Water was added, extracted with EtOAc twice. The organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography to give **88d** (360 mg).

Step 88D

[00272] A mixture of **88d** (133 mg, 0.306 mmol), **1f** (131 mg, 0.612 mmol), K_2CO_3 (2M, 0.5 ml), and Pd(dppf)Cl_2 (49 mg, 0.06 mmol) in 1.4-dioxane(8 ml) was stirred in under N_2 at 80°C for 18 h. Water was added, extracted with EtOAc twice. The organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography to give colorless oil **88e** (135 mg). MS (ESI): m/z=524 $[M+H]^+$.

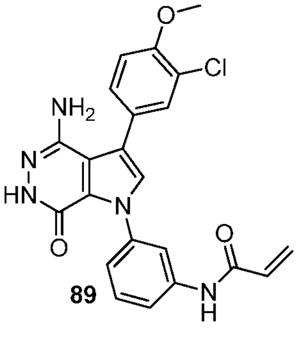
Step 88E

[00273] A mixture of **88e** (130 mg) and N_2H_4 (1.2 ml) in EtOH (10 ml) was refluxed for 24 h. After cooled to room temperature, the solvents were removed. The residue was purified by silica gel chromatography to give white solid **88f** (38 mg). MS (ESI): m/z=510 $[M+H]^+$.

Step 88F

[00274] A mixture of **88f** (18 mg) and HCl solution (1 ml, 4 M in dioxane) was stirred at rt for 1 h and concentrated. The crude product was dissolved in THF and cooled in ice bath. To the mixture was added K_2CO_3 (2 M, 40 µl) and a solution of acryloyl chloride (4 mg) in THF. The resulting mixture was stirred at 0°C for 20 min and purified by reversed phase preparative HPLC to give title compound **88** (7.2 mg) as white solid. MS (ESI): *m/z* = 464 $[M+H]^+$.

[00275] **Example 89.** N-(3-(4-amino-3-(3-chloro-4-methoxyphenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-yl)phenyl)acrylamide

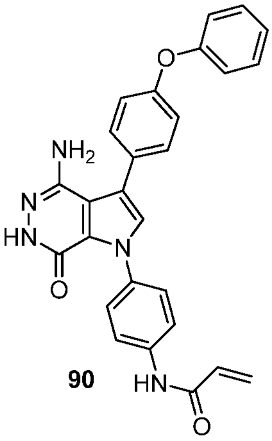


89

[00276] The title compound was made from **88d** and (3-chloro-4-methoxyphenyl)boronic acid via the similar conditions described in steps 88D~88F of Example 88. MS (ESI): *m/z* = 436 $[M+H]^+$.

[00277] **Example 90.** N-(4-(4-amino-7-oxo-3-(4-phenoxyphenyl)-6,7-dihydro-1H-

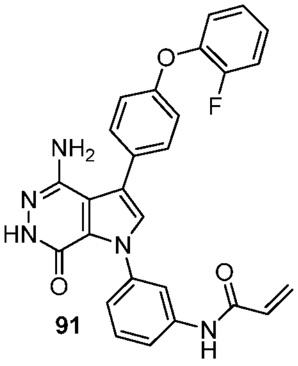
pyrrolo[2,3-d]pyridazin-1-yl)phenyl)acrylamide



90

[00278] The title compound was made from **88b** and (4-((tert-butoxycarbonyl)amino)phenyl)boronic acid via the similar conditions described in steps 88C~88F of Example 88. MS (ESI): *m/z* = 464 $[M+H]^+$.

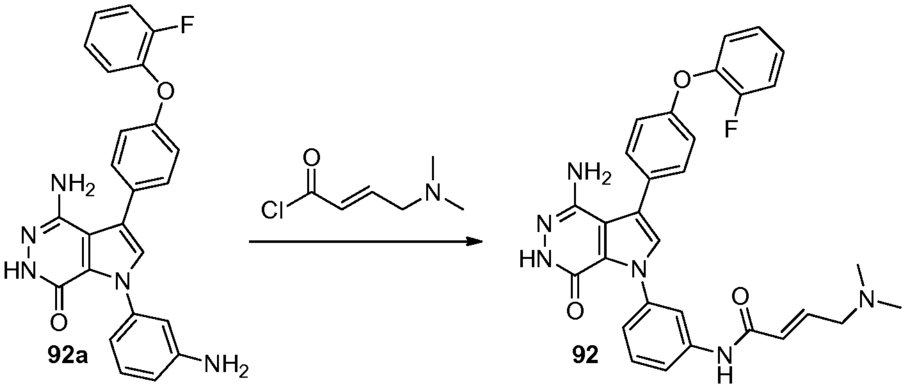
[00279] **Example 91.** N-(3-(4-amino-3-(4-(2-fluorophenoxy)phenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-yl)phenyl)acrylamide



91

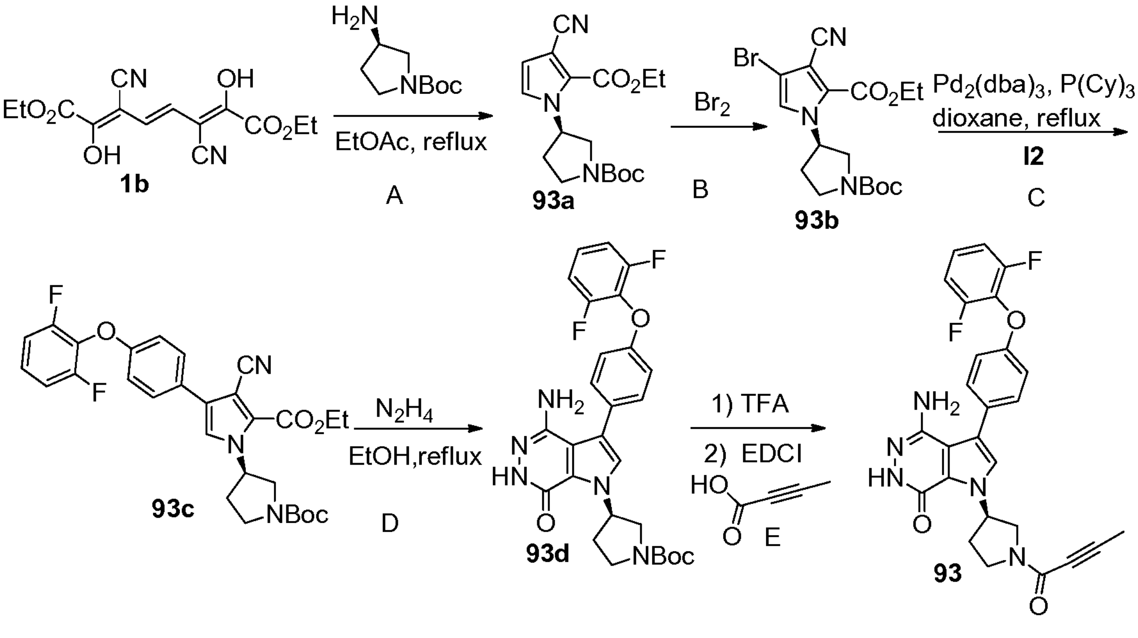
[00280] The title compound was made from **88d** and (4-(2-fluorophenoxy)phenyl)boronic acid via the similar conditions described in steps 88D~88F of Example 88. MS (ESI): *m/z* = 482 $[M+H]^+$.

[00281] **Example 92.** (E)-N-[3-[4-amino-3-[4-(2-fluorophenoxy)phenyl]-7-oxo-6H-pyrrolo[2,3-d]pyridazin-1-yl]phenyl]-4-(dimethylamino)but-2-enamide



[00282] To a solution of **92a** (10mg) in DCM at 0°C was added fresh prepared (E)-4-(dimethylamino)but-2-enoyl chloride. The resulting mixture was stirred at 0°C for 0.5 h and purified by reversed phase preparative HPLC to give title compound **92** (1 mg). MS (ESI): *m/z* = 539 $[M+H]^+$.

[00283] **Example 93.** (R)-4-amino-1-(1-(but-2-ynoyl)pyrrolidin-3-yl)-3-(4-(2,6-difluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



Step 93A

[00284] To a solution of **1b** (1.5 g) in EtOAc (84 ml) at 60°C was added dropwise a solution of (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (1.41 g) in EtOAc (21 ml). The mixture was refluxed for 4 h. After cooled to room temperature, the solvents were removed. The residue was purified by silica gel chromatography to afford **93a** (0.686 g).

Step 93B

[00285] To a solution of **93a** (0.686 g) in DCM (120 ml) at 0°C was added slowly a solution of Br_2 (3.7 g) in DCM (5 ml). The mixture was stirred for 1.5 h, and then quenched with a solution of 10% $Na_2S_2O_3$ and saturated solution of $NaHCO_3$. The two phases were separated; the aqueous phase was extracted with DCM. The combined organic extracts were treated with excess Boc_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to give **93b** (0.342 g).

Step 93C

[00286] A mixture of **93b** (198 mg, 0.48 mmol), **I2** (160 mg, 0.48 mmol) and $K_3PO_4{\cdot}3H_2O$ (188 mg, 0.72 mmol) in 1.4-dioxane/water (10 ml/1 ml) was degassed with N_2. Next was added $Pd_2(dba)_3$ (22 mg, 0.024 mmol) and $P(Cy)_3$ (14 mg, 0.048 mmol). The resulting mixture was refluxed under N_2 for 16 h. After cooled to room temperature, the solid was filtered off, the filtrate was concentrated. The residue was purified by silica gel chromatography to give white solid **93c** (59 mg). MS (ESI): m/z=538 $[M+H]^+$.

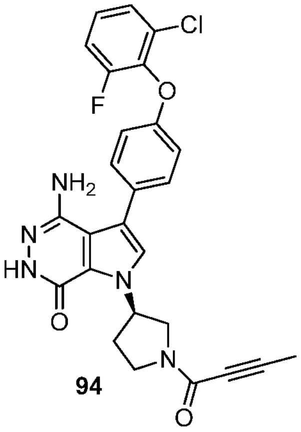
Step 93D

[00287] A mixture of **93c** (72 mg, 0.13 mmol) and $N_2H_4{\cdot}H_2O$ (1 mL) in EtOH (5 ml) was refluxed for 16 h. After cooled to room temperature, the solvents were removed. The residue was purified by silica gel chromatography to give white solid **93d** (24 mg). MS (ESI): m/z=524 $[M+H]^+$.

Step 93E

[00288] To a solution of **93d** (40 mg, 0.08 mmol) in DCM (5 ml) was added TFA (1 ml). The mixture was stirred at rt for 3 h and concentrated to give oil **93e** (49 mg). To a solution of **93e** (49 mg) in DCM (5 ml) was added but-2-ynoic acid (13 mg, 0.16 mmol), EDCI (31 mg, 0.16 mmol) and TEA (17 mg, 0.16 mmol). The resulting mixture was stirred at room temperature for 18 h and concentrated. The residue was purified by silica gel chromatography to give the title compound **93** (20 mg) as white solid. MS (ESI): m/z = 490 $[M+H]^+$.

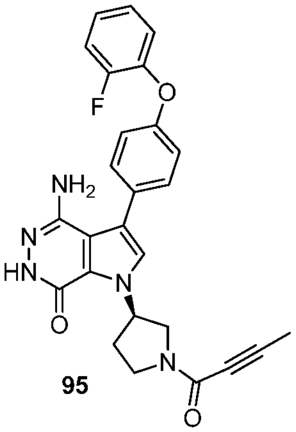
[00289] **Example 94.** (R)-4-amino-1-(1-(but-2-ynoyl)pyrrolidin-3-yl)-3-(4-(2-chloro-6-fluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



94

[00290] The title compound was made from **93b** and intermediate 9 via the similar conditions described in steps 93C~93E of Example 93. MS (ESI): *m/z* = 506 $[M+H]^+$.

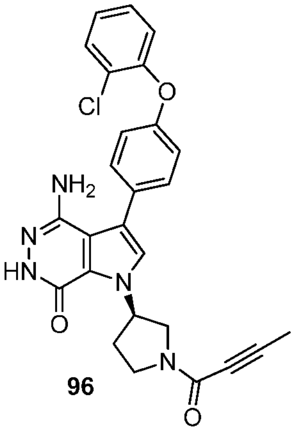
[00291] **Example 95.** (R)-4-amino-1-(1-(but-2-ynoyl)pyrrolidin-3-yl)-3-(4-(2-fluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



95

[00292] The title compound was made from **93b** and ((4-(2-fluorophenoxy)phenyl)boronic acid via the similar conditions described in steps 93C~93E of Example 93. MS (ESI): *m/z* = 472 $[M+H]^+$.

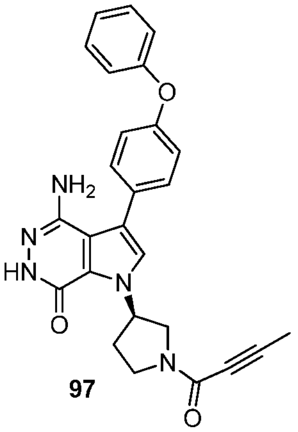
[00293] **Example 96.** (R)-4-amino-1-(1-(but-2-ynoyl)pyrrolidin-3-yl)-3-(4-(2-chlorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



96

[00294] The title compound was made from **93b** and intermediate 10 via the similar conditions described in steps 93C~93E of Example 93. MS (ESI): *m/z* = 488 $[M+H]^+$.

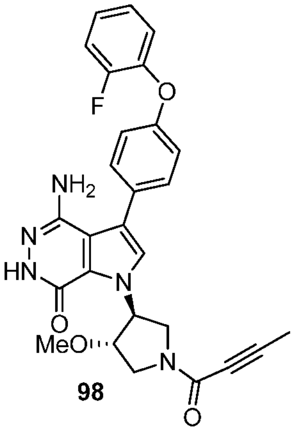
[00295] **Example 97.** (R)-4-amino-1-(1-(but-2-ynoyl)pyrrolidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



97

[00296] The title compound was made from **93b** and (4-phenoxyphenyl)boronic acid via the similar conditions described in steps 93C~93E of Example 93. MS (ESI): *m/z* = 454 $[M+H]^+$.

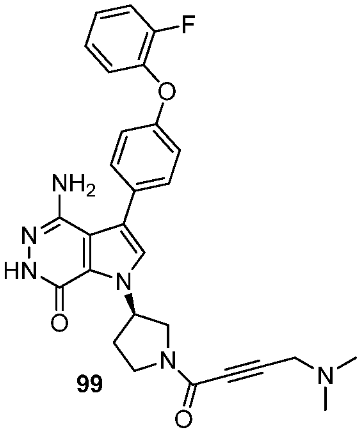
[00297] **Example 98.** 4-amino-1-((3S,4S)-1-(but-2-ynoyl)-4-methoxypyrrolidin-3-yl)-3-(4-(2-fluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one and enantiomer



98

[00298] The title compound was made from trans-tert-butyl 3-amino-4-methoxypyrrolidine-1-carboxylate via the similar conditions described in Example 1. MS (ESI): m/z=502 $[M+H]^+$.

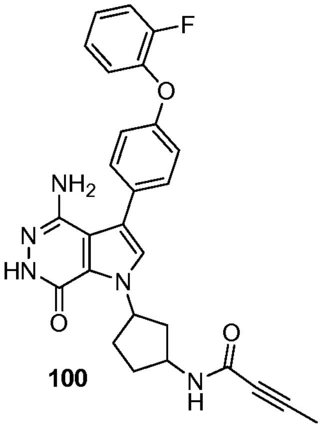
[00299] **Example 99.** (R)-4-amino-1-(1-(4-(dimethylamino)but-2-ynoyl)pyrrolidin-3-yl)-3-(4-(2-fluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



99

[00300] The title compound was prepared via the similar procedures described in Example 93. MS (ESI): m/z=515 $[M+H]^+$.

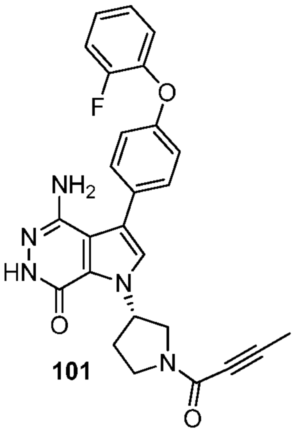
[00301] **Example 100.** N-(3-(4-amino-3-(4-(2-fluorophenoxy)phenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-yl)cyclopentyl)but-2-ynamide



100

[00302] The title compound was prepared via the similar procedures described in Example 93. MS (ESI): m/z=486 $[M+H]^+$.

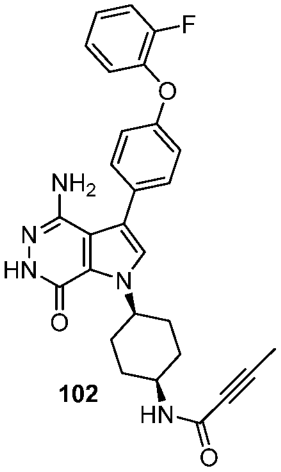
[00303] **Example 101.** (S)-4-amino-1-(1-(but-2-ynoyl)pyrrolidin-3-yl)-3-(4-(2-fluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



101

[00304] The title compound was prepared via the similar procedures described in Example 93. MS (ESI): m/z=472 $[M+H]^+$.

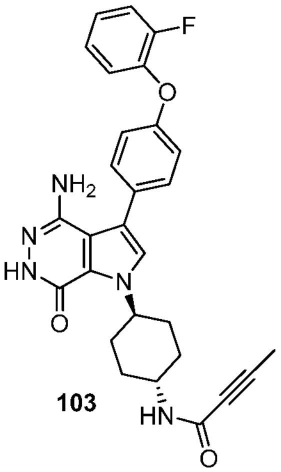
[00305] **Example 102.** N-((1s,4s)-4-(4-amino-3-(4-(2-fluorophenoxy)phenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-yl)cyclohexyl)but-2-ynamide



102

[00306] The title compound was prepared via the similar procedures described in Example 1. MS (ESI): m/z=500 $[M+H]^+$.

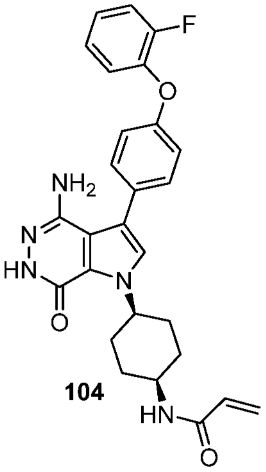
[00307] **Example 103.** N-((1r,4r)-4-(4-amino-3-(4-(2-fluorophenoxy)phenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-yl)cyclohexyl)but-2-ynamide



103

[00308] The title compound was prepared via the similar procedures described in Example 1. MS (ESI): m/z=500 $[M+H]^+$.

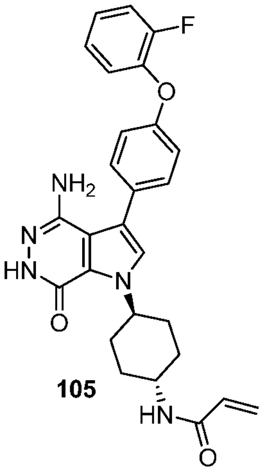
[00309] **Example 104.** N-((1s,4s)-4-(4-amino-3-(4-(2-fluorophenoxy)phenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-yl)cyclohexyl)acrylamide



104

[00310] The title compound was prepared via the similar procedures described in Example 1. MS (ESI): m/z=488 $[M+H]^+$.

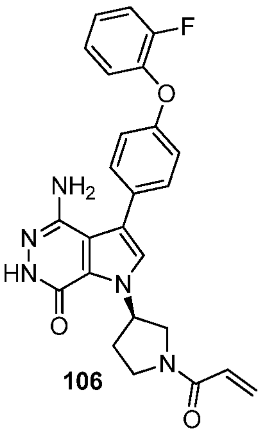
[00311] **Example 105.** N-((1r,4r)-4-(4-amino-3-(4-(2-fluorophenoxy)phenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-yl)cyclohexyl)acrylamide



105

[00312] The title compound was prepared via the similar procedures described in Example 1. MS (ESI): m/z=488 $[M+H]^+$.

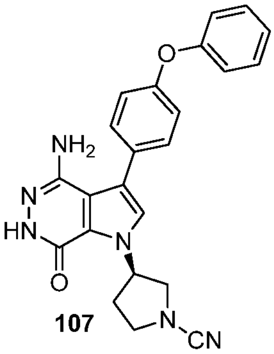
[00313] **Example 106.** (R)-1-(1-acryloylpyrrolidin-3-yl)-4-amino-3-(4-(2-fluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



106

[00314] The title compound was prepared via the similar procedures described in Example 1. MS (ESI): m/z=460 $[M+H]^+$.

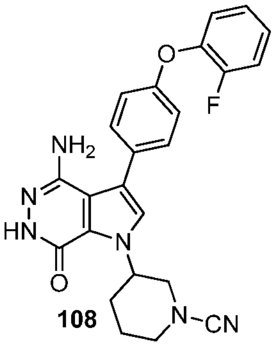
[00315] **Example 107.** (R)-3-(4-amino-7-oxo-3-(4-phenoxyphenyl)-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-yl)pyrrolidine-1-carbonitrile



107

[00316] The title compound was prepared via the similar conditions described in Example 20. MS (ESI): m/z=413 $[M+H]^+$.

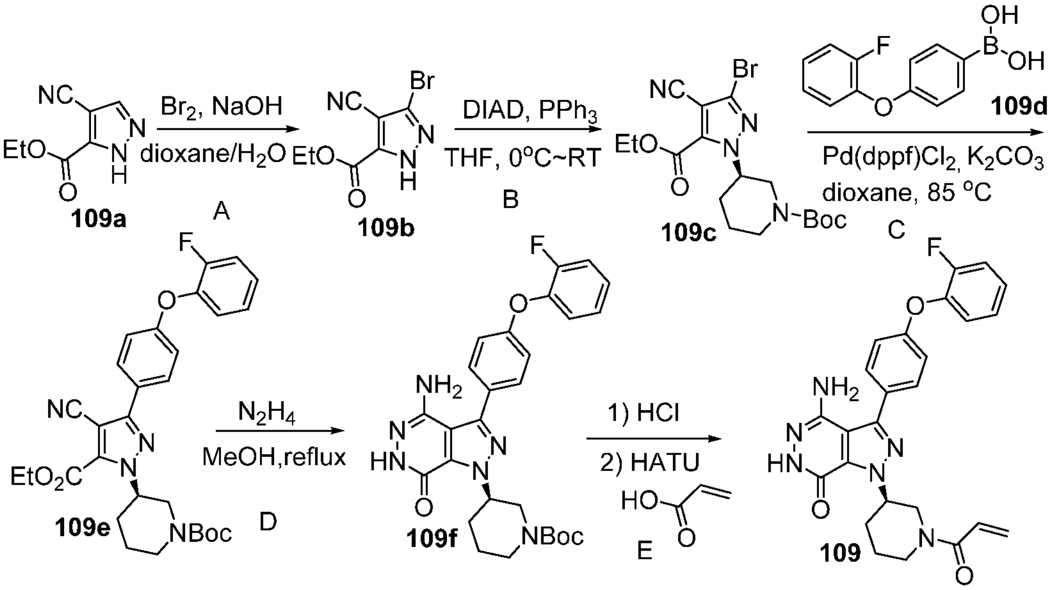
[00317] **Example 108.** 3-(4-amino-3-(4-(2-fluorophenoxy)phenyl)-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-d]pyridazin-1-yl)piperidine-1-carbonitrile



108

[00318] The title compound was prepared via the similar conditions described in Example 20. MS (ESI): m/z=445 $[M+H]^+$.

[00319] **Example 109.** (R)-1-(1-acryloylpiperidin-3-yl)-4-amino-3-(4-(2-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyridazin-7(6H)-one



Step 109A

[00320] To a mixture of **109a** (200 mg) and NaOH (2 M, 1.2 ml) in dioxane (4 ml) at 0°C was added a solution of Br_2 (380 mg) in dioxane (2 ml). The mixture was stirred at rt for 1 h and concentrated. The residue was purified by silica gel chromatography to give **109b** (340 mg).

Step 109B

[00321] To a solution of **109b** (50 mg), (S)-tert-butyl 3-hydroxypiperidine-1-carboxylate (80 mg) and PPh_3 (100 mg) in THF (5 ml) at 0°C was added DIAD (80 mg). The mixture was stirred at rt for 18 h and concentrated. The residue was purified by silica gel chromatography to give **109c** (76 mg).

Step 109C

[00322] A mixture of **109c** (70 mg), **109d** (114 mg), K_2CO_3 (113 mg), and $Pd(dppf)Cl_2$ (66 mg) in dioxane/water(5 ml/0.5 ml) was stirred in under N_2 at 85 °C for 3 h. After cooled to room temperature, the solvents were removed. The residue was purified by silica gel chromatography to give **109e** (100 mg). MS (ESI): m/z=535 $[M+H]^+$.

Step 109D

[00323] A mixture of **109e** (100 mg) and N_2H_4 (2.5 ml) in MeOH (5 ml) was refluxed for

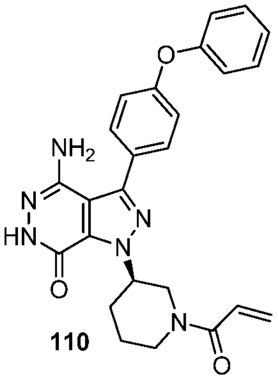
3 h. After cooled to room temperature, the solvents were removed. The residue was purified by silica gel chromatography to give **109f** (70 mg). MS (ESI): m/z=521 $[M+H]^+$.

Step 109E

[00324] A mixture of **109f** (70 mg) and HCl solution (4 ml, 4M in dioxane) was stirred at rt for 0.5h and concentrated to give **109g** (100 mg) which was used directly in next step.

[00325] To a solution of **109g** (9 mg) in DMF (1 ml) was added DIEA (13 mg), acid (6 mg) and HATU (18 mg). The resulting mixture was stirred at room temperature for 0.5 h and purified by reversed phase preparative HPLC to give title compound **109** (3.1 mg). MS (ESI): *m/z* = 475 [M+H].

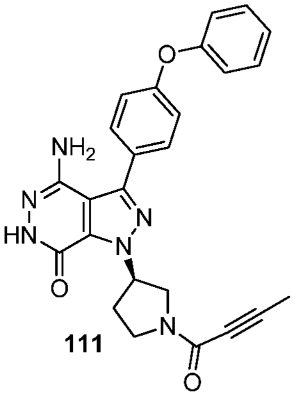
[00326] **Example 110.** (R)-1-(1-acryloylpiperidin-3-yl)-4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyridazin-7(6H)-one



110

[00327] The title compound was made was made from **109c** and (4-phenoxyphenyl)boronic acid via the similar conditions described in steps 109C~109E of Example 109. MS (ESI): *m/z* = 457 $[M+H]^+$.

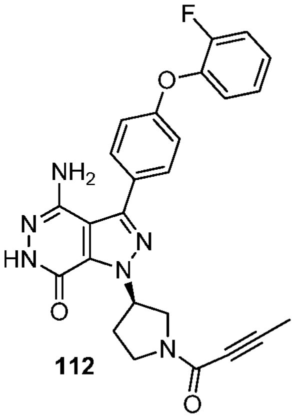
[00328] **Example 111.** (R)-4-amino-1-(1-(but-2-ynoyl)pyrrolidin-3-yl)-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyridazin-7(6H)-one



111

[00329] The title compound was made was made from **109b** and proper reagents via the similar conditions described in steps 109B~109E of Example 109. MS (ESI): *m/z* = 455 $[M+H]^+$.

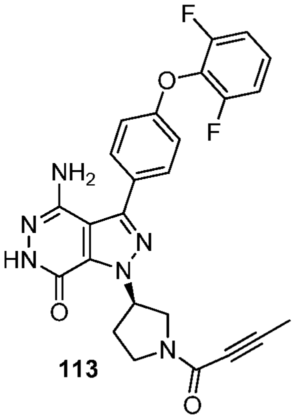
[00330] **Example 112.** (R)-4-amino-1-(1-(but-2-ynoyl)pyrrolidin-3-yl)-3-(4-(2-fluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyridazin-7(6H)-one



112

[00331] The title compound was made was made from **109b** and proper reagents via the similar conditions described in steps 109B~109E of Example 109. MS (ESI): *m/z* = 473 $[M+H]^+$.

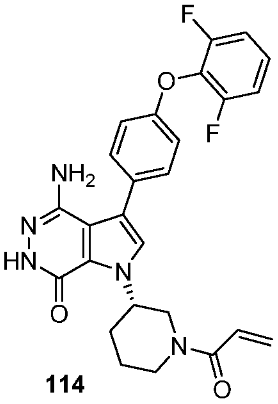
[00332] **Example 113.** (R)-4-amino-1-(1-(but-2-ynoyl)pyrrolidin-3-yl)-3-(4-(2,6-difluorophenoxy)phenyl)-1H-pyrazolo[3,4-d]pyridazin-7(6H)-one



113

[00333] The title compound was made was made from **109b** and proper reagents via the similar conditions described in steps 109B~109E of Example 109. MS (ESI): *m/z* = 491 $[M+H]^+$.

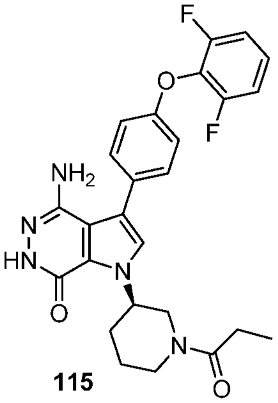
[00334] **Example 114.** (S)-1-(1-acryloylpiperidin-3-yl)-4-amino-3-(4-(2,6-difluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



114

[00335] The title compound was prepared via the similar conditions described in Example 58. MS (ESI): *m/z* = 492 $[M+H]^+$.

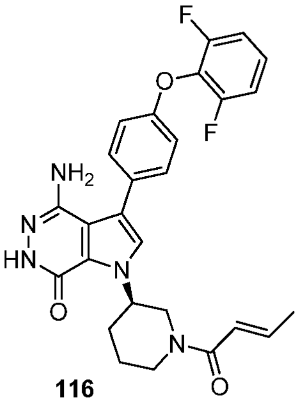
[00336] **Example 115.** (R)-4-amino-3-(4-(2,6-difluorophenoxy)phenyl)-1-(1-propionylpiperidin-3-yl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



115

[00337] The title compound was prepared from compound **58** via the similar conditions described in Example 19. MS (ESI): *m/z* = 494 $[M+H]^+$.

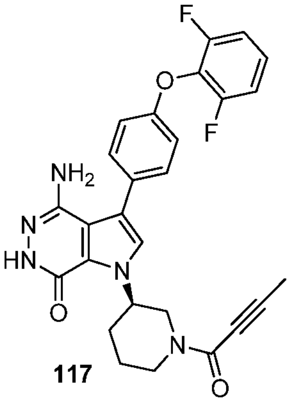
[00338] **Example 116.** 4-amino-3-[4-(2,6-difluorophenoxy)phenyl]-1-[(3R)-1-[(E)-but-2-enoyl]-3-piperidyl]-6H-pyrrolo[2,3-d]pyridazin-7-one



116

[00339] The title compound was made from (E)-but-2-enoic acid and amine **58c** via the similar conditions described in step 58C of Example 58. MS (ESI): *m/z* = 506 $[M+H]^+$.

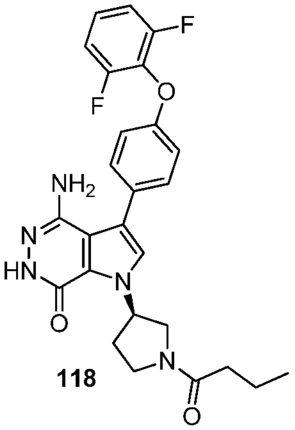
[00340] **Example 117.** (R)-4-amino-1-(1-(but-2-ynoyl)piperidin-3-yl)-3-(4-(2,6-difluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



117

[00341] The title compound was made from but-2-ynoic acid and amine **58c** via the similar conditions described in step 58C of Example 58. MS (ESI): *m/z* = 504 $[M+H]^+$.

[00342] **Example 118.** (R)-4-amino-1-(1-butyrylpyrrolidin-3-yl)-3-(4-(2,6-difluorophenoxy)phenyl)-1H-pyrrolo[2,3-d]pyridazin-7(6H)-one



118

[00343] The title compound was prepared compound **93** via the similar conditions described in Example 19. MS (ESI): *m/z* = 494 $[M+H]^+$.

[00344] **Example 119**. Evaluation of BTK activity

[00345] Methods for biochemical and cell-based assays:

[00346] **Btk kinase assay** - The Btk kinase assay was performed using a ADP-Glo Btk kinase assay kit purchased from Promega (Madison, WI). The assay was conducted according to the protocols provided in the assay kit. In brief, the enzyme reaction was

carried out in the kinase reaction buffer containing Btk (2 ng/μl), ATP (1.2 μM), poly GT peptide (0.3 μM), DTT (40 nM), MnCl2 (1.4 mM), and 1×kinase buffer (included in the kit) in the presence or absence of the tested articles at various concentrations in 384-well plate at room temperature (22 ± 1 °C) for 60 minutes. The final reaction volume for each reaction was 10 μl. Then, 4 μl of ADP-Glo reagent (included in the kit) was added into the reaction and the plate was further incubated for another 40 minutes to terminate the reaction and deplete the remaining ATP. Finally, 10 μl of the kinase detection reagent was added into each reaction to simultaneously convert ADP to ATP and allow the newly synthesized ATP to be measured by a plate-reading luminometer (Victor X5 2030 multilabel reader, PerkinElmer). IC50 value was calculated using appropriate programs in GraphPad Prism by plotting the logarithm of the concentration versus percent inhibition as compared with a vehicle (DMSO) control. The IC50 values for the example compounds are shown in Table 4.

[00347] **Cell proliferation assay:** TMD-8 and SU-DHL-1 cells were maintained at 37°C in a humidified atmosphere with 5% CO_2 in the recommended medium and serum concentrations. For cell proliferation assay, cells were seeded in 96-well pates at a density of 5,000 to 10,000 cells per well and cultured overnight at 37°C in recommended medium supplemented with 5-10% FBS. On the next day, the test articles at various concentrations or vehicle control (0.5% DMSO) were added into cell culture. After 5-day treatment, the growth of cells was assayed by the CellTiter-Glo® Luminestceaent Cell Viability Assay (Promega). IC$_{50}$ values were calculated using GraphPad Prism by plotting the logarithm of the concentration versus percent inhibition of cell growth as compared with the vehicle control. The IC$_{50}$ values for the example compounds are shown in Table 4.

Table 4. Biological Testing Results

[00348] A ≤0.01 μM; 0.01 μM < B ≤1 μM ; 1 μM < C < 100 μM

Example	BTK enzyme IC$_{50}$ (μM)	TMD8 cells growth IC$_{50}$ (μM)
1	A	A
2	A	A
3	B	B
4	B	B
5	B	B
6	B	A
7	C	-

Example	BTK enzyme IC_{50} (µM)	TMD8 cells growth IC_{50} (µM)
8	B	B
9	C	-
10	B	B
11	B	A
12	B	A
13	A	A
14	A	A
15	B	A
16	A	B
17	B	B
18	A	A
19	B	B
20	B	A
21	C	-
22	B	B
23	B	B
24	B	B
25	B	B
26	A	A
27	A	A
28	A	A
29	B	A
30	B	B
31	A	B
32	B	B
33	A	A
34	A	A
35	A	A
36	A	B
37	C	-
38	A	A
39	A	A
40	B	B
41	B	B
42	C	-
43	B	B
44	B	B
45	A	A
46	B	B
47	A	A
48	B	B
49	B	B
50	B	B
51	A	B
52	A	C
53	A	B
54	A	B

Example	BTK enzyme IC_{50} (µM)	TMD8 cells growth IC_{50} (µM)
55	A	A
56	A	A
57	A	A
58	A	A
59	B	A
60	B	B
61	B	B
62	B	A
63	A	A
64	B	A
65	B	B
66	B	A
67	A	B
68	B	A
69	A	A
70	B	A
71	A	A
72	B	B
73	B	B
74	B	A
75	A	B
76	B	A
77	A	A
78	A	A
79	A	A
80	B	B
81	B	A
82	A	A
83	C	-
84	B	A
85	B	A
86	C	-
87	A	A
88	A	A
89	B	B
90	B	A
91	B	A
92	B	A
93	B	A
94	B	A
95	B	A
96	B	B
97	B	A
98	B	B
99	A	B
100	B	A
101	C	-

Example	BTK enzyme IC_{50} (µM)	TMD8 cells growth IC_{50} (µM)
102	B	A
103	B	A
104	B	A
105	B	B
106	B	A
107	A	C
108	A	A
109	B	A
110	B	A
111	A	A
112	B	A
113	B	A
114	B	A
115	B	B
116	B	B
117	B	B
118	C	-

[00349] **Pharmacokinetic tests**: The tested articles were given to Sprague-Dawley rats or Beagle dogs by intravenous and oral administration. Plasma samples were prepared from blood samples which were collected at various time points. The plasma concentrations of the tested articles were determined by specific LC-MS/MS analytical methods. Pharmacokinetic parameters were calculated with WinNonlin®. The pharmacokinetic test results for the example compounds are shown in Table 5 (rat) and Table 6 (dog) below.

Table 5. Rat PK parameters of selected examples.

Example	58		93	
Dose	IV(0.5mg/kg)	PO (5mg/kg)	IV (0.5mg/kg)	PO (5mg/kg)
Cmax(ng/ml)	1509	1297	710	914
AUC 0-t (ng/ml*h)	1511	6837	395	2290
t1/2(h)	0.64	4.09	0.63	4.62
CLz/F (ml/min/kg)	5.45	11.0	22.9	39.2
Vz/F(ml/kg)	301	3827	1371	15421
F%	-	51.9%	-	58.1%

Table 6. Dog PK parameters of selected examples.

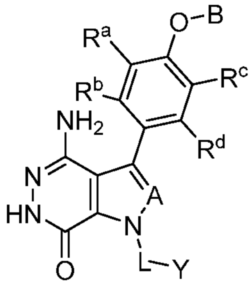
Example	58		93	
Dose	IV(0.2mg/kg)	PO (2mg/kg)	IV (0.5mg/kg)	PO (2mg/kg)
Cmax(ng/ml)	145	656	212	315

AUC 0-t (ng/ml*h)	94.4	1094	525	1290
t1/2(h)	0.43	0.66	1.5	1.78
CLz/F (ml/min/kg)	35.4	31.1	15.9	26.3
Vz/F(ml/kg)	1281	1753	2050	4010
F%	-	114%	-	61.6%

[00350] ***In vivo* efficacy study**: The *in vivo* antitumor activity was assessed with TMD-8 xenograft model. In brief, TMD-8 cells were implanted into NOD-SCID nude mice and allowed to grow to the designated size (c.a. 100-200 mm^3) before treatment. The tested articles were given orally at various dose levels once daily (QD) or twice a day (BID) for 14 consecutive days. Tumor and body weight were measured during the experiments, and tumor volumes were estimated from the formula [length/2] x [$width^2$]. Established tumors in each animal were individually normalized to their size at the start of the experiment, and the data were calculated as the change in tumor volume relative to the day 0 volume by the use of the relative tumor volume (RTV) formula, $RTV=TV_x/TV_0$, where TV_x is the tumor volume on any day and TV_0 is the tumor volume at the initiation of dosing. Significant suppression of tumor growth was observed with examples 58 (98% tumor growth inhibition rate) and 93(80% tumor growth inhibition rate).

What is claimed is:

1. A compound of formula (I), including all isomers, such as, tautomers, rotamers, geometric isomers, diastereomers, racemates, and enantiomers, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof,



I

wherein A is selected from the group consisting of CR^1 and N; and wherein R^1 is selected from the group consisting of hydrogen, halogen, and unsubstituted or substituted alkyl;

R^a, R^b, R^c and R^d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, unsubstituted or substituted alkyl, and unsubstituted or substituted alkoxyl;

B is selected from the group consisting of hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl;

L is unsubstituted or substituted alkyl, or absent; and

Y is selected from the group consisting of unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl.

2. The compound of claim 1, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein A is selected from the group consisting CH, CF, CCl and N.

3. The compound of claim 1 or 2, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein at least one of R^a, R^b, R^c and R^d is

selected from the group consisting of hydrogen, F, Cl, and methoxyl.

4. The compound of claim 1 or 2, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein R^a, R^b, R^c and R^d are hydrogen.

5. The compound of claim 1 or 2, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein B is unsubstituted or substituted C_1-C_6 alkyl.

6. The compound of claim 1 or 2, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein B is unsubstituted or substituted aryl.

7. The compound of claim 1 or 2, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein B is unsubstituted or substituted phenyl.

8. The compound of claim 1 or 2, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein B is phenyl substituted with at least one member selected from the group consisting of halogen, cyano, nitro, hydroxyl, unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy, $-NR^1R^2$, $-C(O)R^3$, $-C(O)OR^4$, $-C(O)NHR^5$, and $-S(O)_2R^6$;

wherein R^1 and R^2 are independently selected from the group consisting of hydrogen, unsubstituted or substituted alkyl, $-C(O)R^7$, $-C(O)OR^8$, $-C(O)NHR^9$, $-S(O)_2R^{10}$; and wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl.

9. The compound of claim 8, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein B is phenyl substituted with at least one member selected from the group consisting of F, Cl, and methoxyl.

10. The compound of claim 8, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein B is phenyl substituted with two F.

11. The compound of claim 8, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein B is phenyl substituted with two Cl.

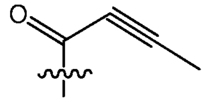
12. The compound of claim 8, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein B is phenyl substituted with one Cl and one F.

13. The compound of claim 1 or 2, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein L is absent.

14. The compound of claim 1 or 2, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein L is methylene.

15. The compound of claim 1 or 2, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein Y is selected from the group consisting of unsubstituted or substituted piperidinyl, unsubstituted or substituted phenyl, unsubstituted or substituted bicyclo[3.2.1]octanyl, unsubstituted or substituted azetidinyl, and unsubstituted or substituted pyrrolidinyl.

16. The compound of claim 15, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein Y is substituted with at least one member selected from the group consisting of halogen, -CN, $-C(O)R^{11}$, $-NHC(O)R^{12}$, $-S(O)_2R^{13}$, and $-NHS(O)_2R^{14}$; and wherein R^{11}, R^{12}, R^{13}, and R^{14} are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted cycloalkenyl, and unsubstituted or substituted alkynyl.

17. The compound of claim 15, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein Y is substituted with at least one member selected from the group consisting of F, CN,$-C(O)CH=CH_2$, $-C(O)CH=CHCH_2N(CH_3)_2$, $-NHC(O)CH=CH_2$, $-C(O)CH=CHCH_2N(CH_3)(COOC(CH_3)_3$; $-C(O)CH=CHCH_2NH(CH_3)$, $-C(O)CH_2CH_3$, $-C(O)CH_2CH_2CH_3$, 

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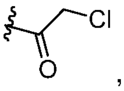
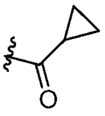
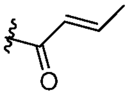
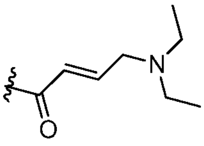
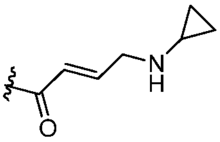
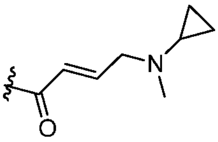
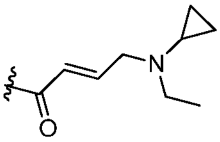
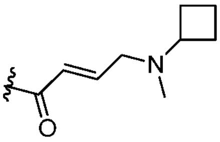
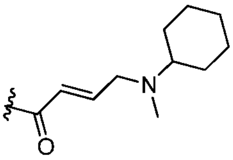
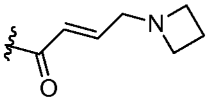
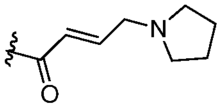
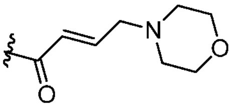
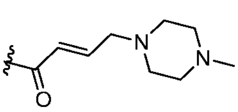
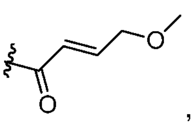
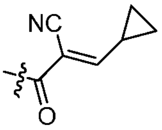
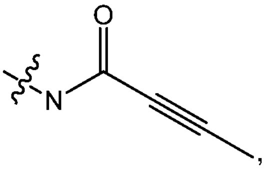
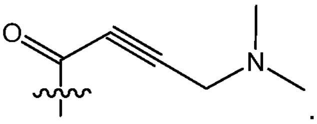
-C(O)CH2CH2Cl, , , -C(O)CH2CN, , , ,

, , , ,

, , , ,

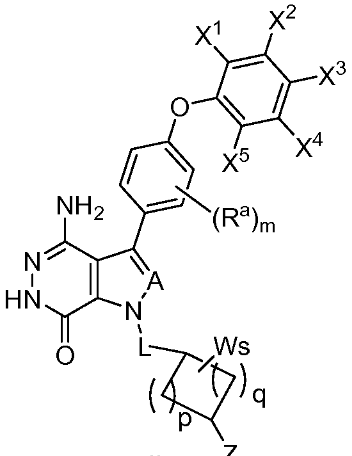
, , , , and

.

18. The compound of claim 1 or 2, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein the compound has more R-form than S-form.

19. The compound of claim 1 or 2, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein the compound has more S-form than R-form.

20. The compound of claim 1 or 2, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein the compound is of formula (II):



II

wherein X^1, X^2, X^3, X^4, and X^5 are independently selected from the group consisting of hydrogen, halogen, cyano, nitro, hydroxyl, unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy, $-NR^1R^2$, $-C(O)R^3$, $-C(O)OR^4$, $-C(O)NHR^5$, and $-S(O)_2R^6$;

R^1 and R^2 are independently selected from the group consisting of hydrogen, unsubstituted or substituted alkyl, $-C(O)R^7$, $-C(O)OR^8$, $-C(O)NHR^9$, $-S(O)_2R^{10}$; and wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl;

R^a is selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, unsubstituted or substituted alkyl, and unsubstituted or substituted alkoxyl;

W is selected from the group consisting of halogen, hydroxyl, unsubstituted or substituted alkyl, and unsubstituted or substituted alkoxyl; wherein two W may combine with an atom or atoms to which they are attached to form unsubstituted or substituted C_{3-12} cycloalkyl, unsubstituted or substituted 3- to 12- membered heterocyclic, unsubstituted or substituted C_{6-12} aryl, or unsubstituted or substituted 5- to 12- membered heteroaryl;

m = 0, 1, 2, or 3;

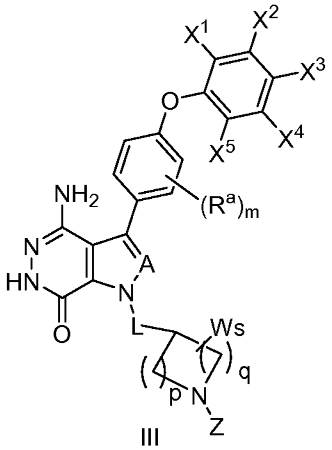
p = 1, 2, or 3;

q = 0, 1, or 2;

s = 0, 1, 2, or 3; and

Z is selected from the group consisting of -NHC(O)$R^{12}$and -NHS$(O)_2R^{14}$; and wherein R^{12} and R^{14} are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted cycloalkenyl, and unsubstituted or substituted alkynyl.

21. The compound of claim 1 or 2, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein the compound is of formula (III):



III

wherein X^1, X^2, X^3, X^4, and X^5 are independently selected from the group consisting of hydrogen, halogen, cyano, nitro, hydroxyl, unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy, -NR^1R^2, -C(O)R^3, -C(O)OR^4, -C(O)NHR^5, and -S$(O)_2R^6$;

R^1 and R^2 are independently selected from the group consisting of hydrogen, unsubstituted or substituted alkyl, -C(O)R^7, -C(O)OR^8, -C(O)NHR^9, -S$(O)_2R^{10}$; and wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl;

R^a is selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, unsubstituted or substituted alkyl, and unsubstituted or substituted alkoxyl;

W is selected from the group consisting of halogen, hydroxyl, unsubstituted or substituted alkyl, and unsubstituted or substituted alkoxyl; wherein two W may combine with an atom or atoms to which they are attached to form unsubstituted or substituted C_{3-12} cycloalkyl, unsubstituted or substituted 3- to 12- membered heterocyclic, unsubstituted or substituted C_{6-12} aryl, or unsubstituted or substituted 5- to 12-membered heteroaryl;

m = 0, 1, 2, or 3;

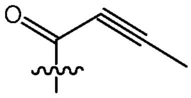
p = 1, 2, or 3;

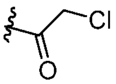
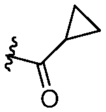
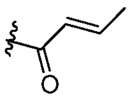
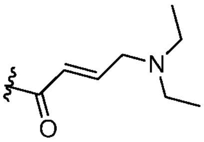
q = 0, 1, or 2;

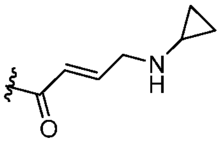
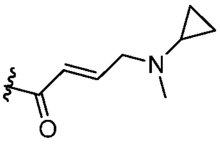
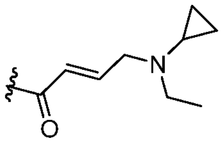
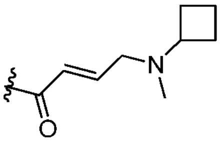
s = 0, 1, 2, or 3; and

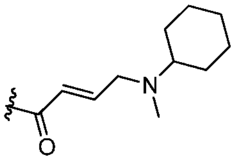
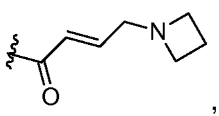
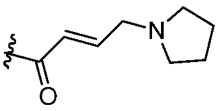
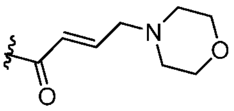
Z is selected from the group consisting of CN, -C(O)R^{11}, and -S(O)$_2$R^{13}; and wherein R^{11}, and R^{13} are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted cycloalkenyl, and unsubstituted or substituted alkynyl.

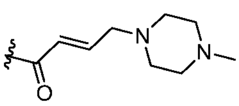
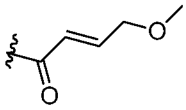
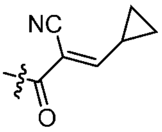
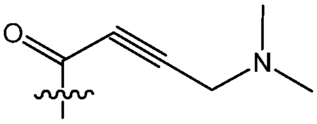
22. The compound of claim 21, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein Z is from the group consisting of CN,-C(O)CH=CH$_2$, -C(O)CH=CHCH$_2$N(CH$_3$)$_2$, -C(O)CH=CHCH$_2$N(CH$_3$)(COOC(CH$_3$)$_3$;

-C(O)CH=CHCH$_2$NH(CH$_3$), -C(O)CH$_2$CH$_3$, -C(O)CH$_2$CH$_2$CH$_3$, ,

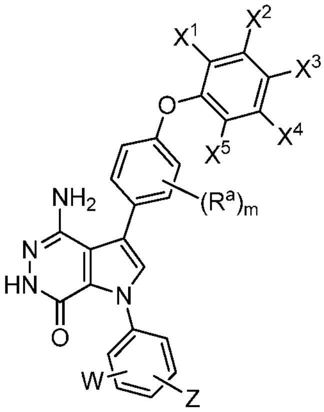
-C(O)CH$_2$CH$_2$Cl, , , -C(O)CH$_2$CN, , , ,

, , , ,

, , , ,

, , , and .

23. The compound of claim 1 or 2, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein the compound is of formula (IV):



IV

wherein X^1, X^2, X^3, X^4, and X^5 are independently selected from the group consisting of hydrogen, halogen, cyano, nitro, hydroxyl, unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy, $-NR^1R^2$, $-C(O)R^3$, $-C(O)OR^4$, $-C(O)NHR^5$, and $-S(O)_2R^6$;

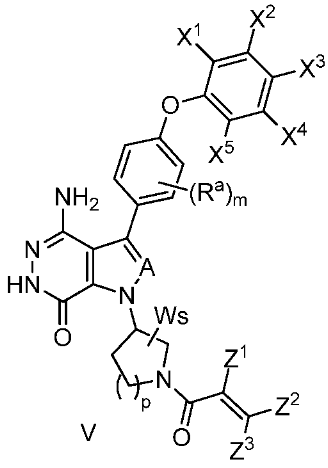
R^1 and R^2 are independently selected from the group consisting of hydrogen, unsubstituted or substituted alkyl, $-C(O)R^7$, $-C(O)OR^8$, $-C(O)NHR^9$, $-S(O)_2R^{10}$; and wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl;

W is selected from the group consisting of halogen, hydroxyl, cyano, unsubstituted or substituted alkyl, and unsubstituted or substituted alkoxyl;

$m = 0, 1, 2, \text{or } 3$; and

Z is selected from the group consisting of $-NHC(O)R^{12}$, and $-NHS(O)_2R^{14}$; and wherein R^{12}, and R^{14} are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted cycloalkenyl, and unsubstituted or substituted alkynyl.

24. The compound of claim 1 or 2, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein the compound is of formula (V):



V

wherein X^1, X^2, X^3, X^4, and X^5 are independently selected from the group consisting of hydrogen, halogen, cyano, nitro, hydroxyl, unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy, $-NR^1R^2$, $-C(O)R^3$, $-C(O)OR^4$, $-C(O)NHR^5$, and $-S(O)_2R^6$;

R^1 and R^2 are independently selected from the group consisting of hydrogen, unsubstituted or substituted alkyl, $-C(O)R^7$, $-C(O)OR^8$, $-C(O)NHR^9$, $-S(O)_2R^{10}$; and wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl;

R^a is selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, cyano, unsubstituted or substituted alkyl, and unsubstituted or substituted alkoxyl;

W is selected from the group consisting of halogen, hydroxyl, cyano, unsubstituted or substituted alkyl, and unsubstituted or substituted alkoxyl;

$m = 0, 1, 2, \text{ or } 3$;

$p = 1 \text{ or } 2$;

Z^1 is selected from the group consisting of hydrogen, halogen, cyano, and unsubstituted or substituted alkyl; and

Z^2 and Z^3 are independently selected from the group consisting of hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocycloalkyl, $-CH_2OR^{15}$, $-CH_2NR^{16}R^{17}$;

wherein R^{15} and R^{16} are independently selected from the group consisting of hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, and unsubstituted or substituted heterocycloalkyl; R^{17} is selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl,$-C(O)R^{18}$, $-C(O)OR^{19}$, and $-S(O)_2R^{20}$; wherein R^{18}, R^{19} and R^{20} are independently selected from the group consisting of unsubstituted or substituted alkyl, and unsubstituted or substituted cycloalkyl;

wherein R^{16} and R^{17} combine with N to which they are attached to form unsubstituted or substituted 3- to 12- membered heterocyclic, or unsubstituted or substituted 5- to 12- membered heteroaryl; and

wherein Z^1 and Z^2 can join together to form a bond or combine with atoms to which they are attached to form unsubstituted or substituted C_{5-12} cycloalkenyl, unsubstituted or substituted 5- to 12- membered heterocyclic, unsubstituted or substituted C_{6-12} aryl, or unsubstituted or substituted 5- to 12- membered heteroaryl.

25. The compound of claim 24, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein A is N.

26. The compound of claim 24, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein A is selected from the group consisting of CH, CF and CCl.

27. The compound of claim 24, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein Z^1, Z^2 and Z^3 are H.

28. The compound of claim 24, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein Z^1 and Z^3 are H, Z^2 is $-CH_2NR^{16}R^{17}$.

29. The compound of claim 24, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein Z^1 and Z^2 join together to form a bond.

30. The compound of claim 24, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein 3 or less than 3 of X^1, X^2, X^3, X^4, and X^5 are halogen.

31. The compound of claim 24, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein X^1 is F.

32. The compound of claim 24, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein X^2, X^3, and X^4 are hydrogen.

33. The compound of claim 24, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein X^5 is selected from the group consisting of H, F and Cl.

34. A pharmaceutical composition comprising the compound of claim 1 or 2, and a pharmaceutically acceptable carrier.

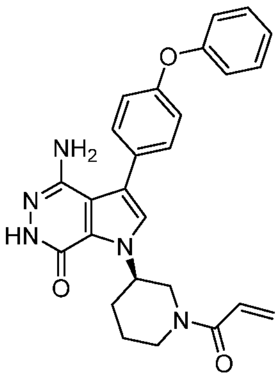
35. A method of modulating protein tyrosine kinase activity, comprising contacting a cell with an effective amount of the compound of claim 1 or 2, or the pharmaceutically acceptable salt thereof.

36. A method of treating a condition or a disease mediated by protein tyrosine kinase, comprising administering to a subject a therapeutically effective amount of the compound of claim 1 or 2, or the pharmaceutically acceptable salt thereof.

37. The method of claim 36, wherein the condition or the disease is cancer or autoimmune diseases.

38. The method of claim 37, wherein the cancer is B-cell malignancies, selected from the group consisting of chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), multiple myeloma (MM), follicular lymphoma (FL), marginal zone lymphoma, and waldenström’s macroglobulinemia (WM).

39. A compound, a tautomer, a pharmaceutically acceptable salt, a solvate, a hydrate, a metabolite, or a prodrug thereof, wherein the compound is selected from the group consisting of: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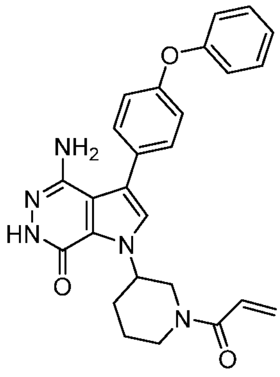
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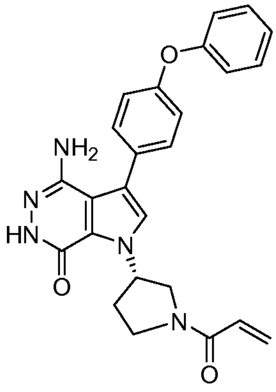
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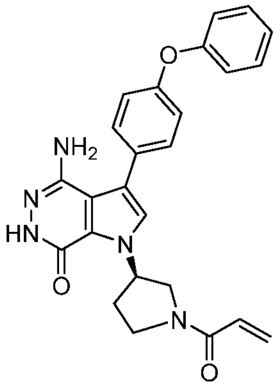
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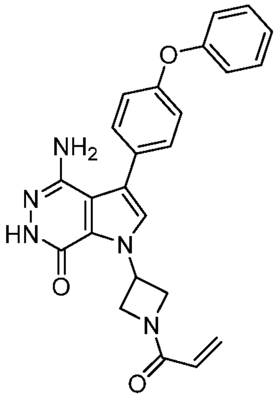
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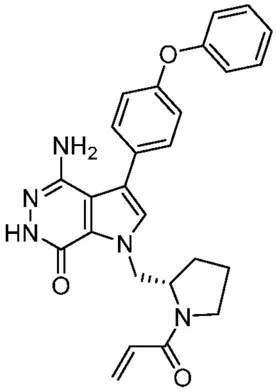
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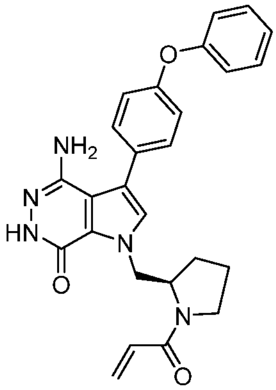
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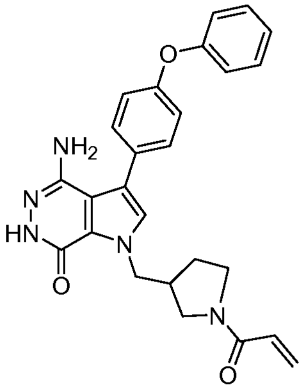
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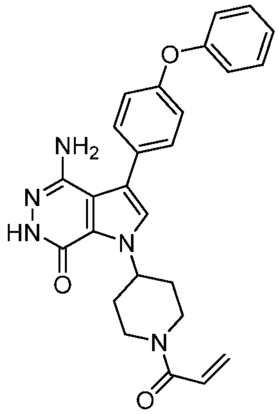
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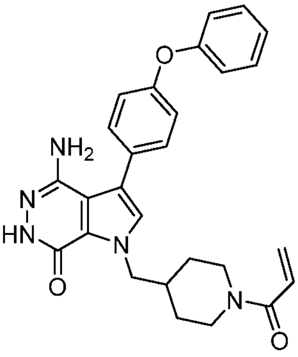
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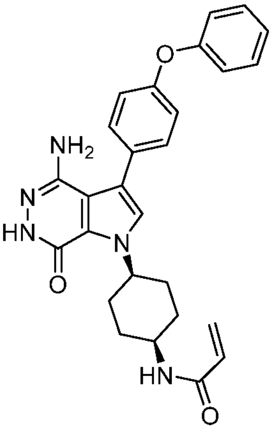
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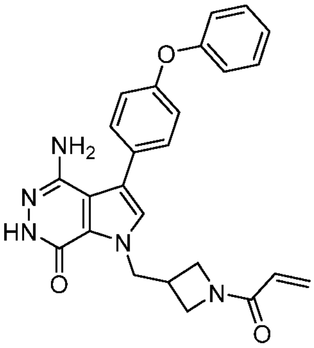
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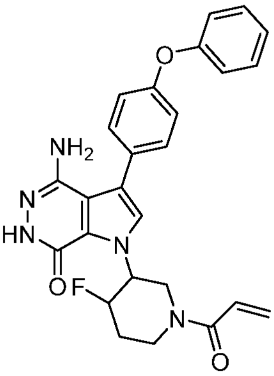
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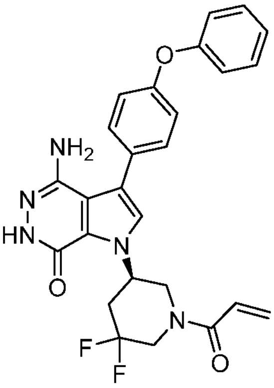
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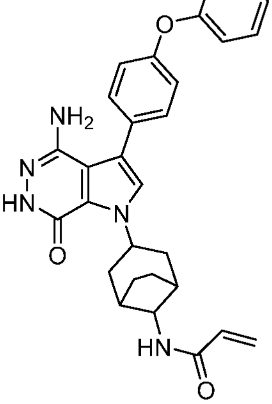
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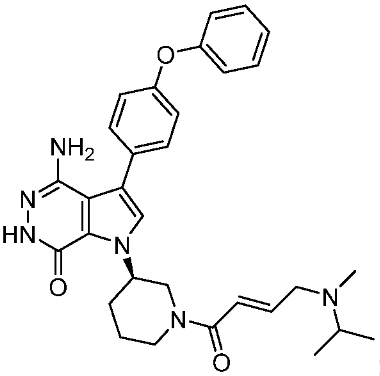
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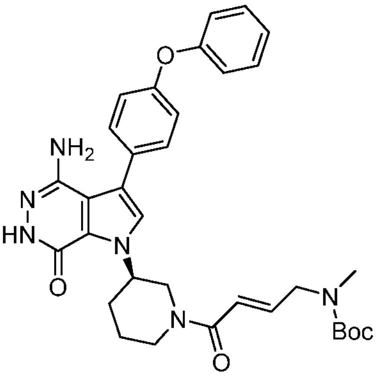
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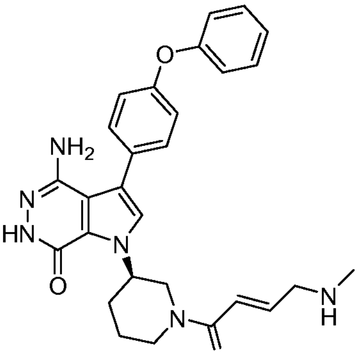
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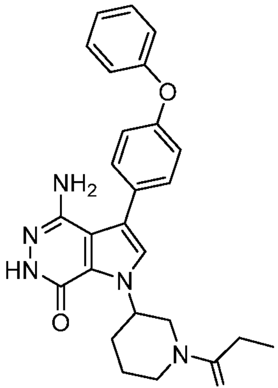
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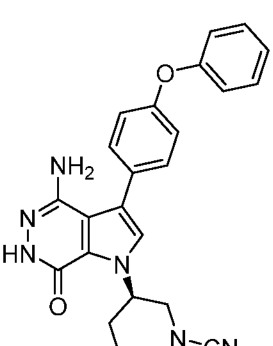
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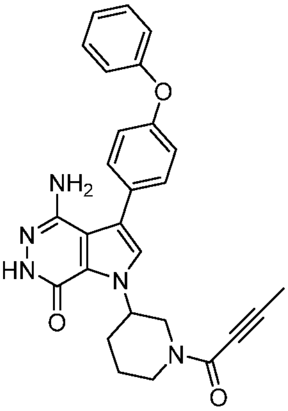
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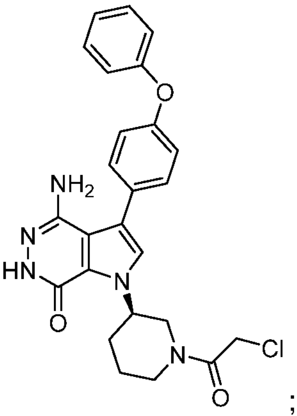
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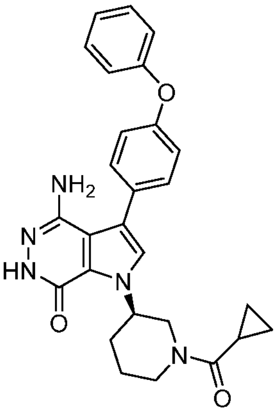
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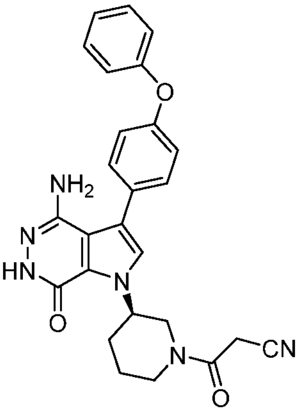
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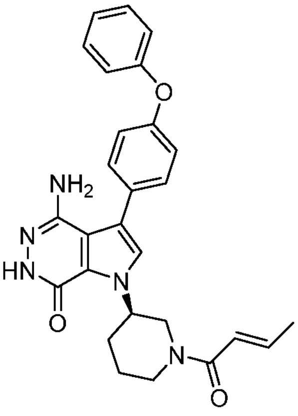
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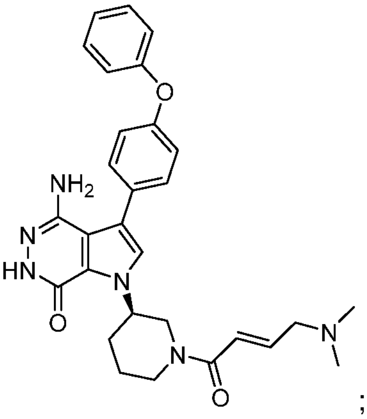
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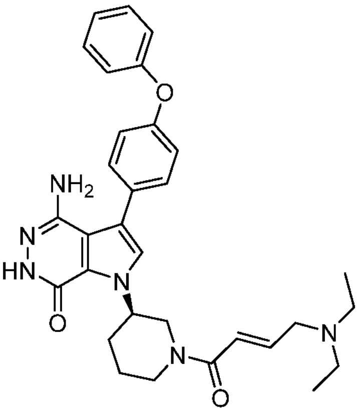
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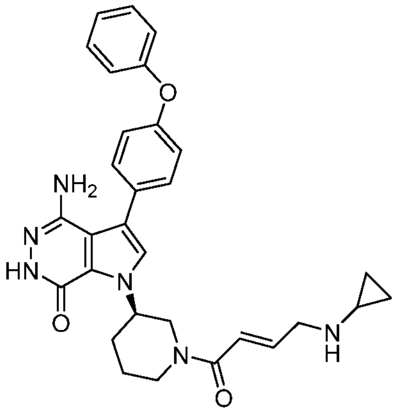
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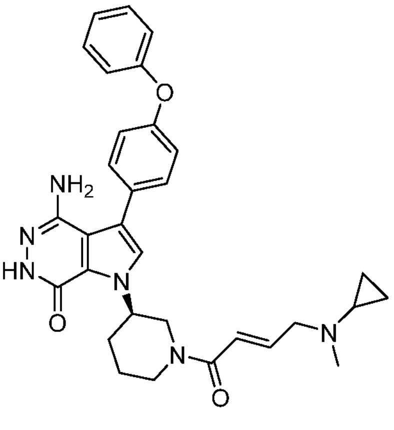
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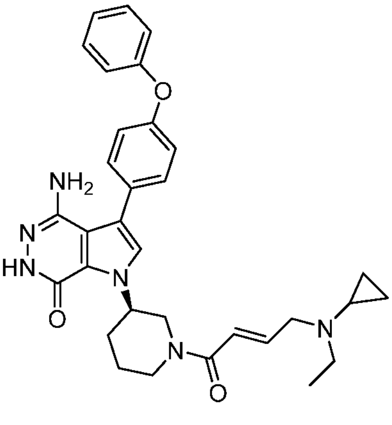
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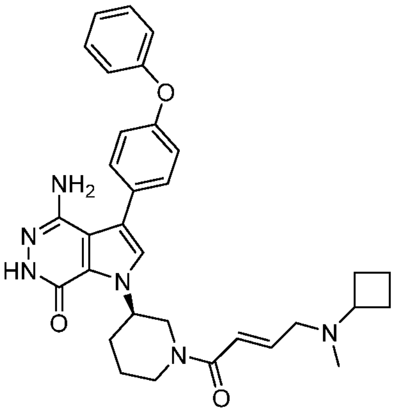

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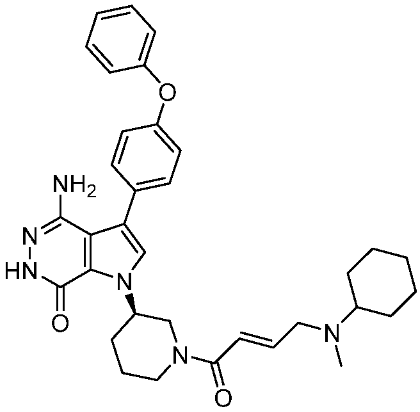

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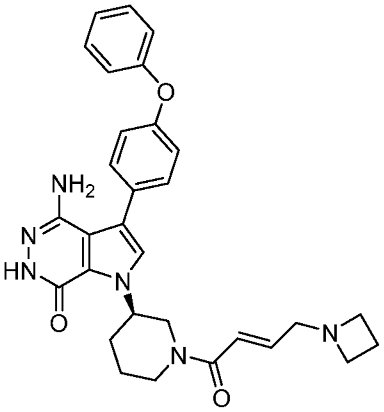

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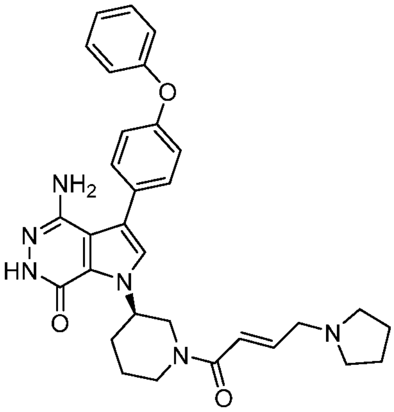

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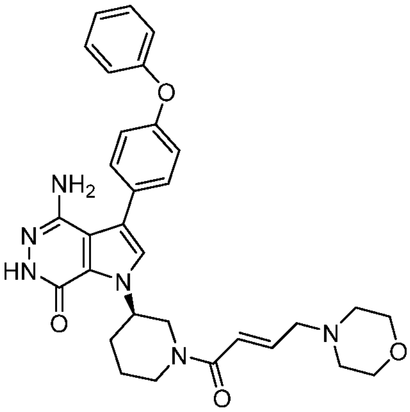

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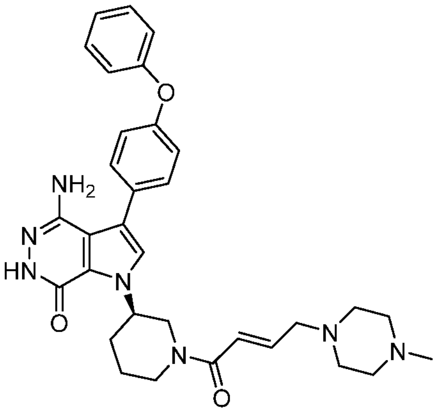

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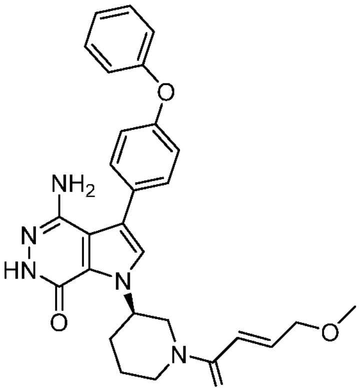

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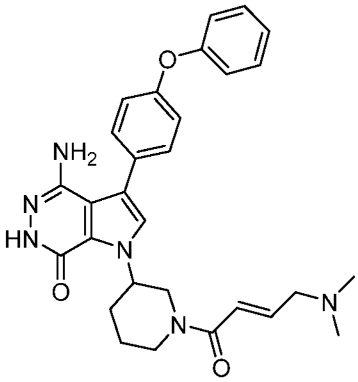

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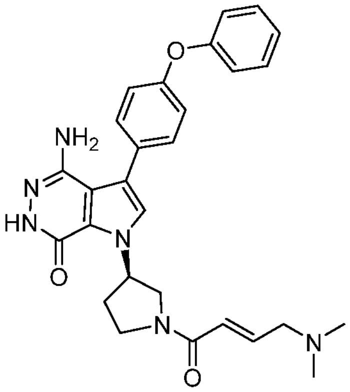

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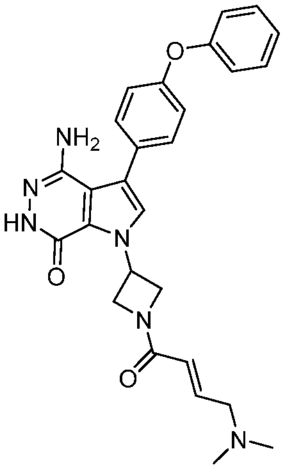
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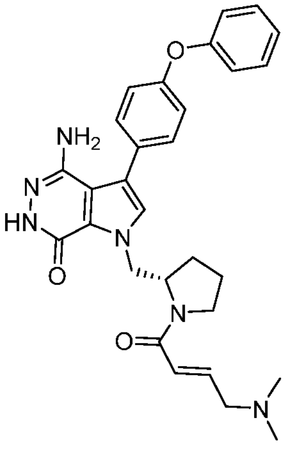
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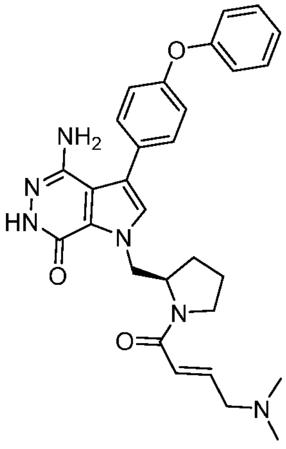
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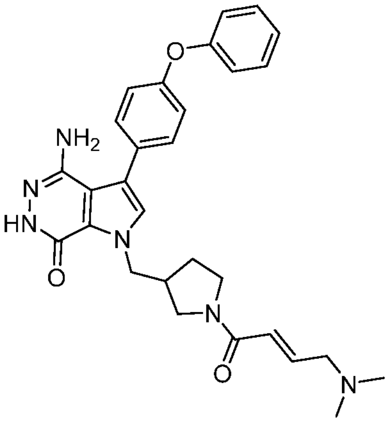
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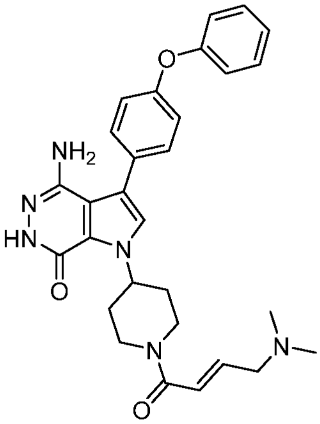
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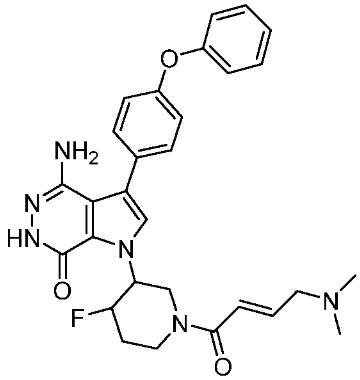
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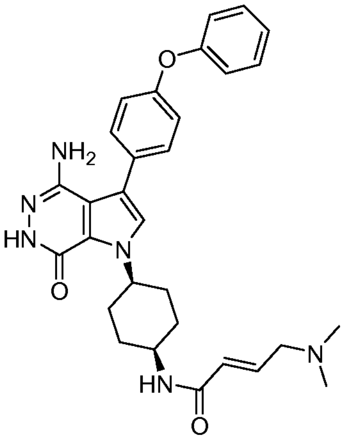
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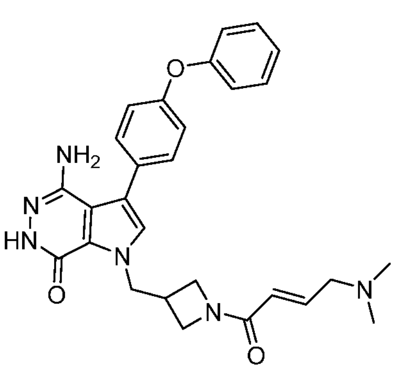
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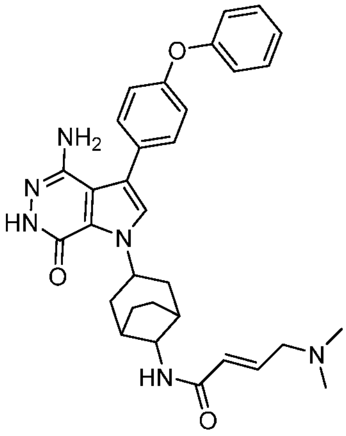
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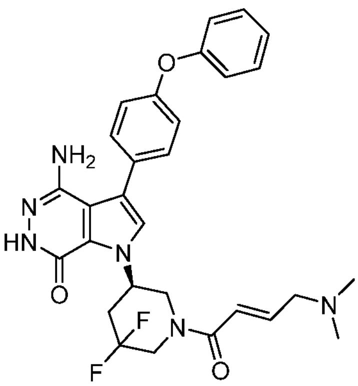
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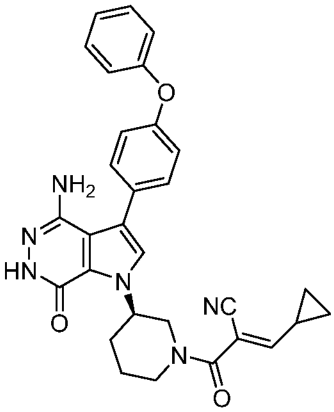
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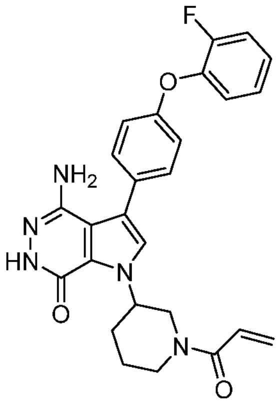
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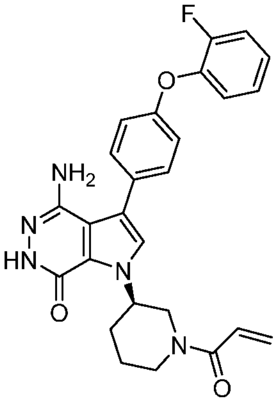
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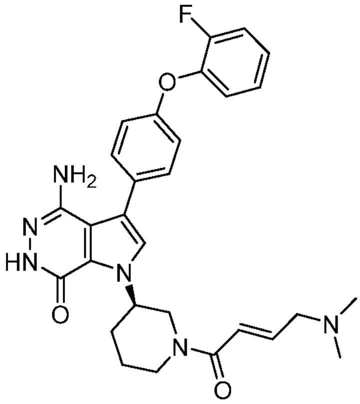
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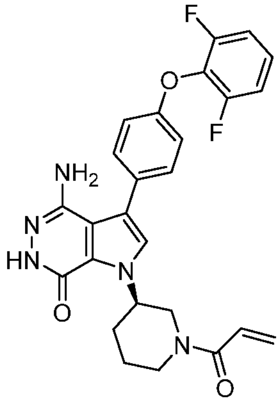
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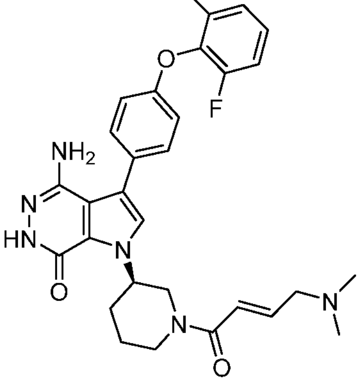
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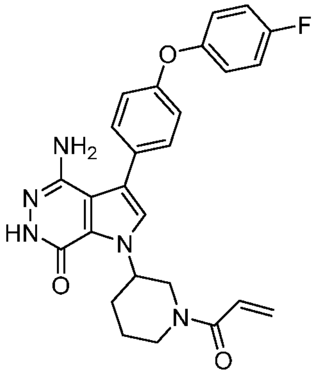
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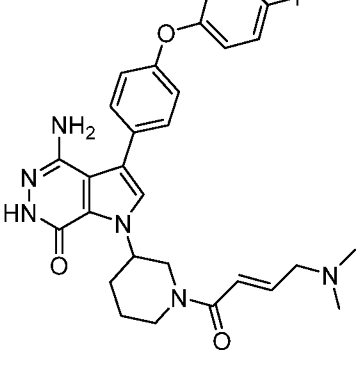
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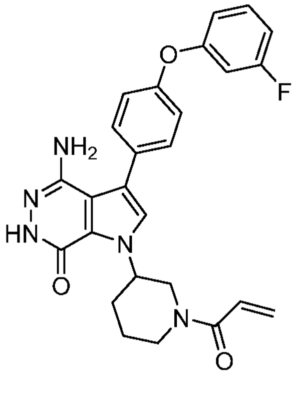
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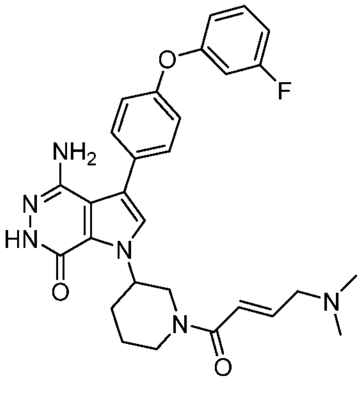
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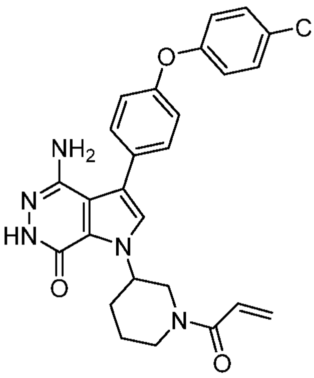
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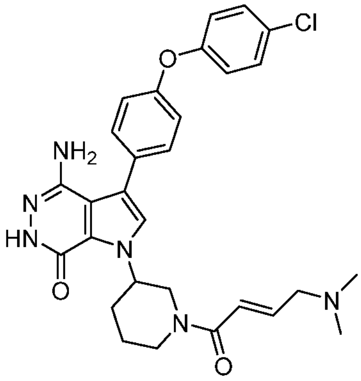
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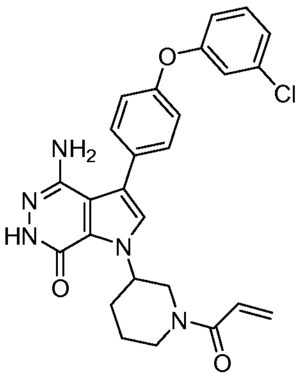
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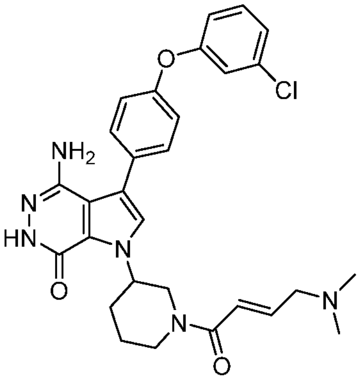
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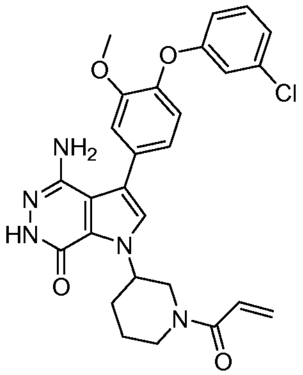
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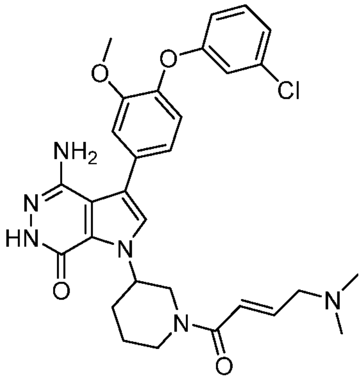
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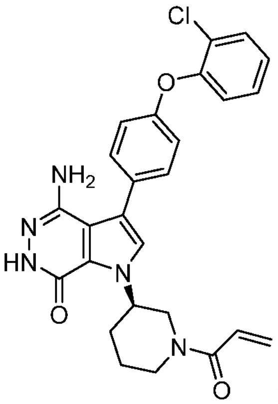
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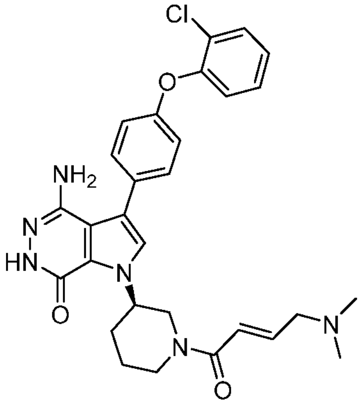
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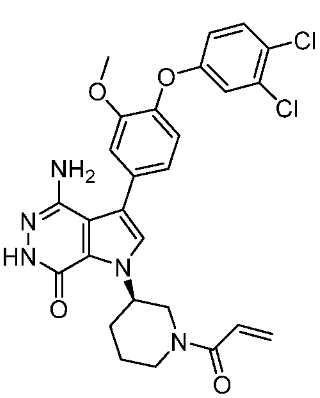
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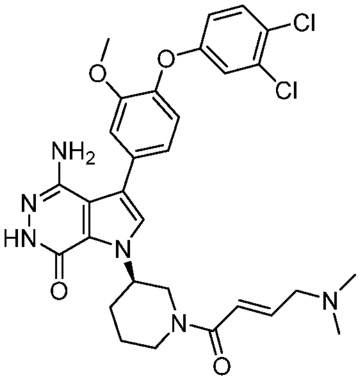
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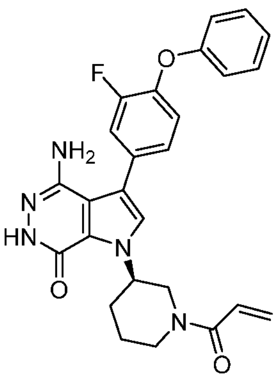
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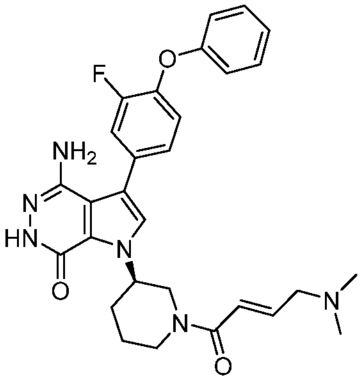
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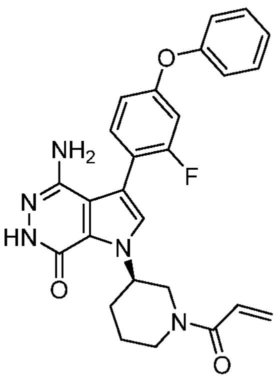
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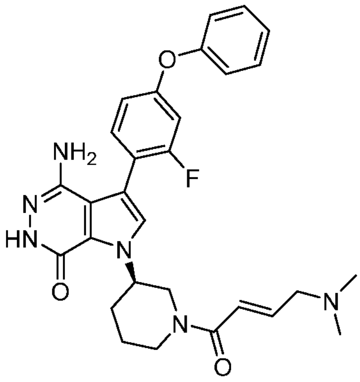
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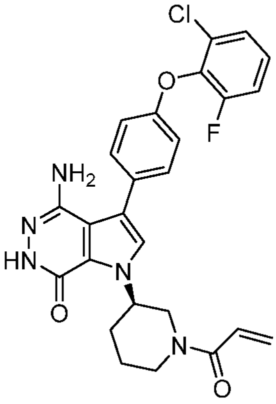
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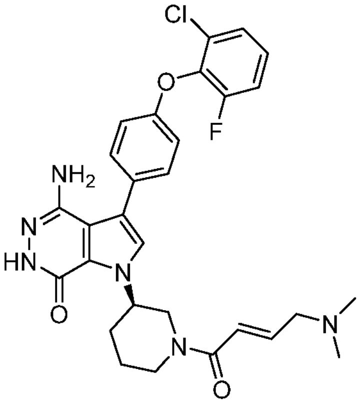
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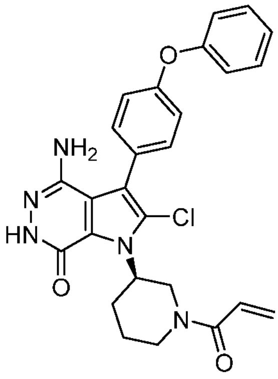
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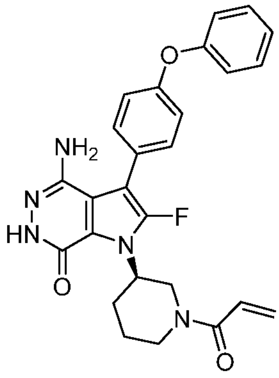
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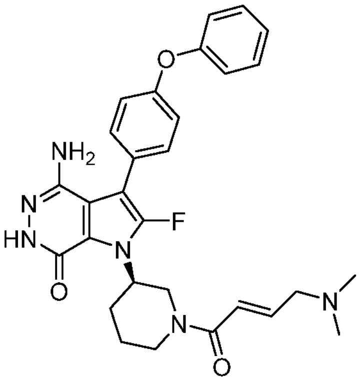
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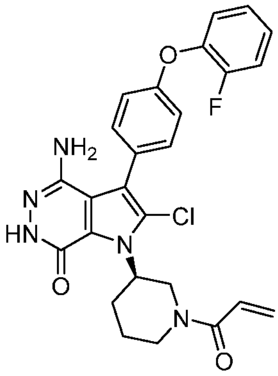
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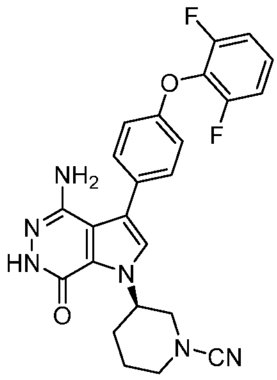
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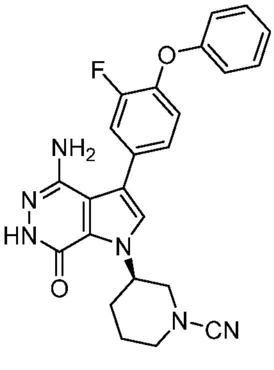
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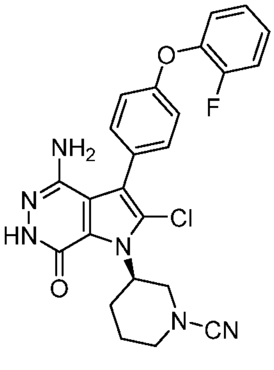
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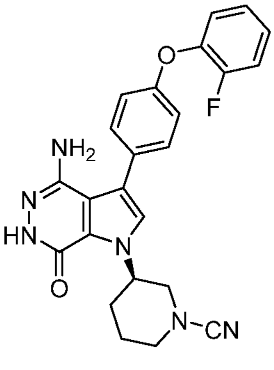
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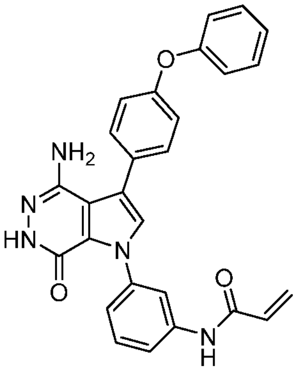
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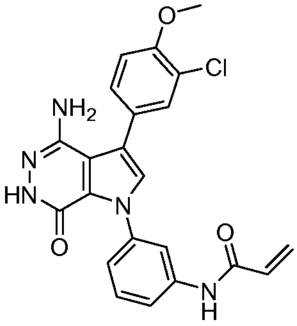
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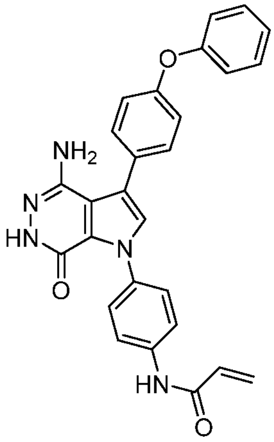
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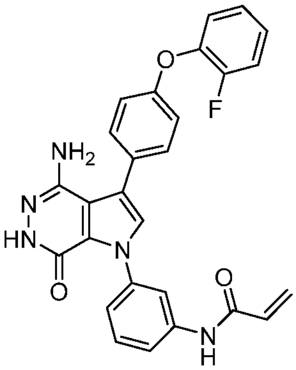
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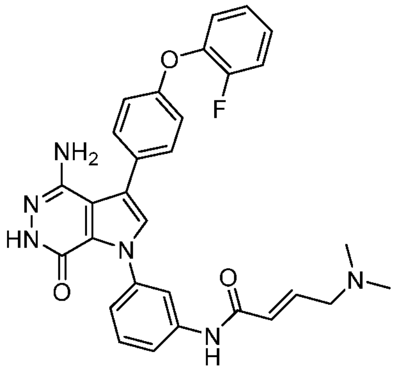
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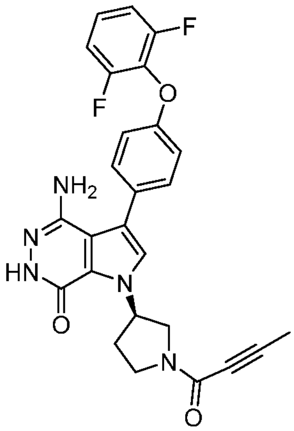
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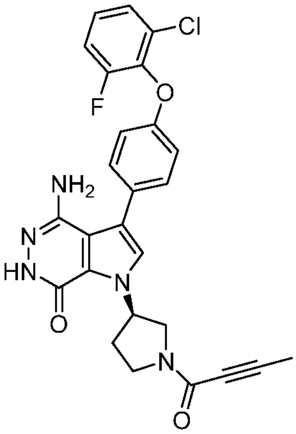
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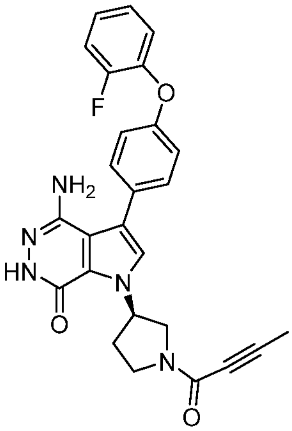
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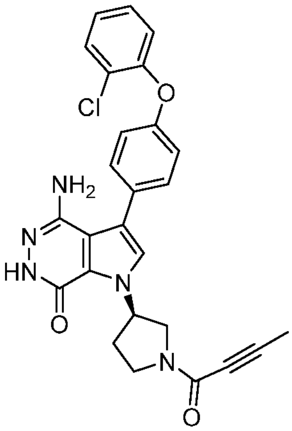
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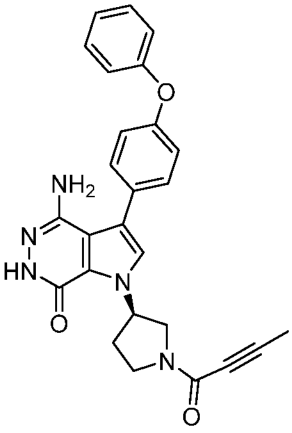
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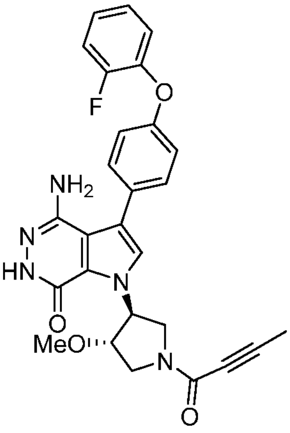
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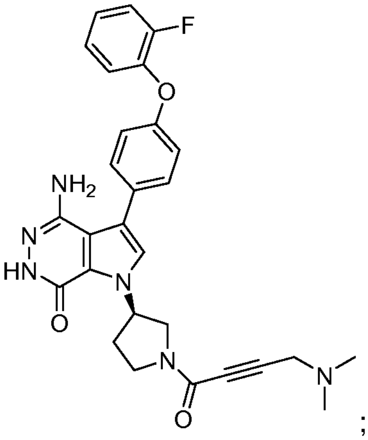
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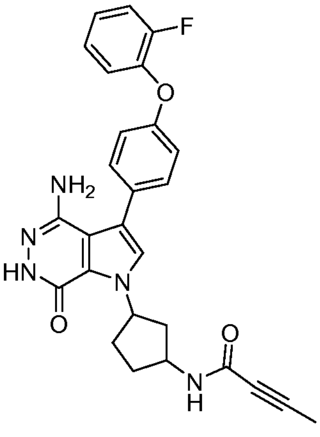
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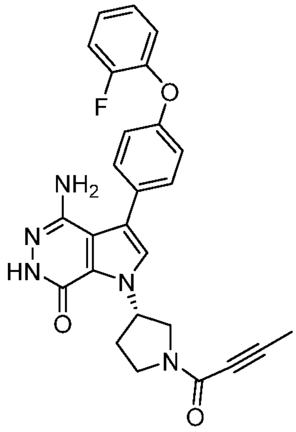
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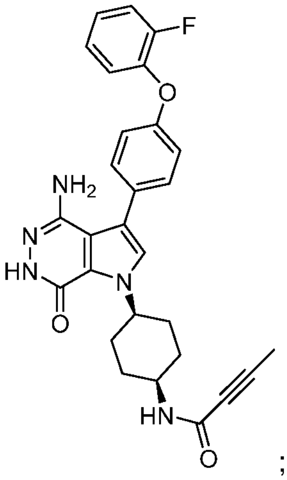
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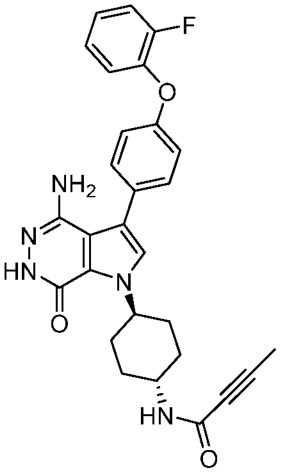
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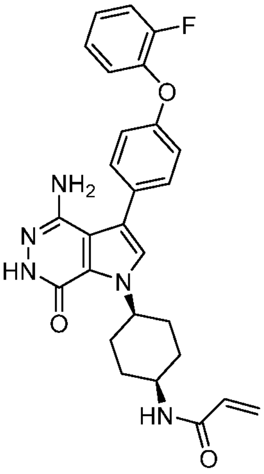
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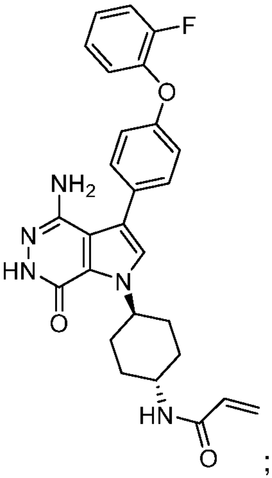
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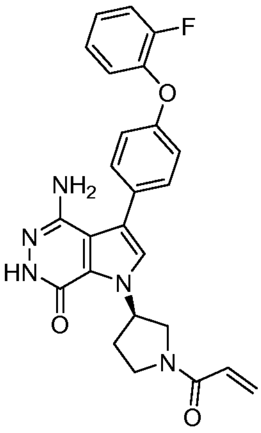
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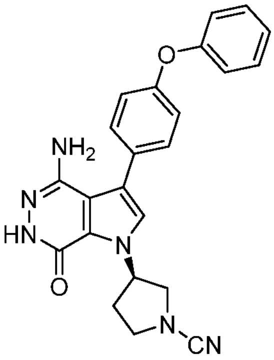
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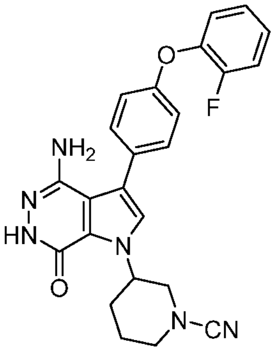
HN
O
N
N
CN

;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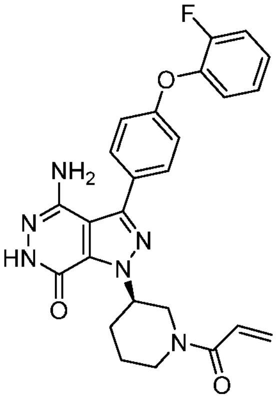
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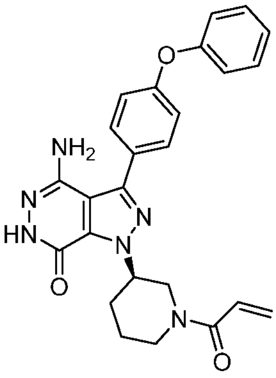
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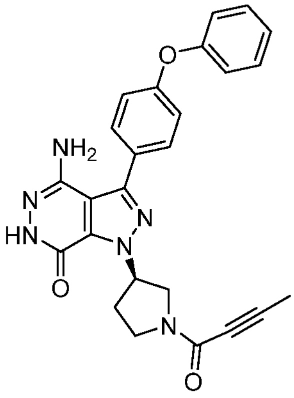
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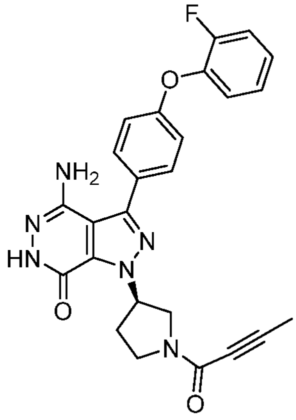
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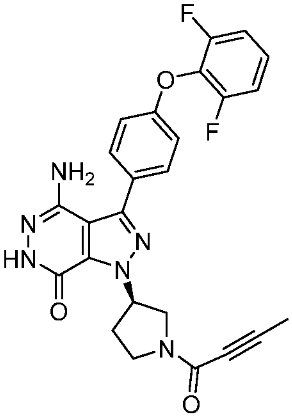
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O

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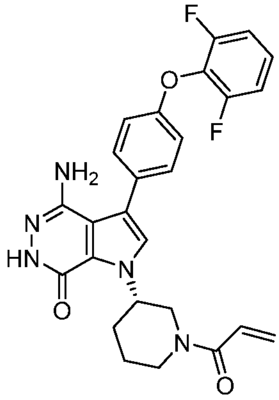
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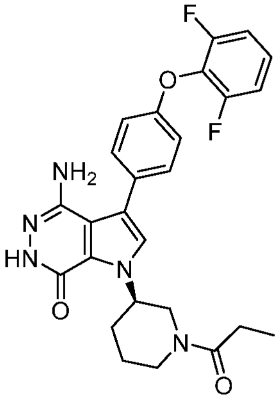
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HN
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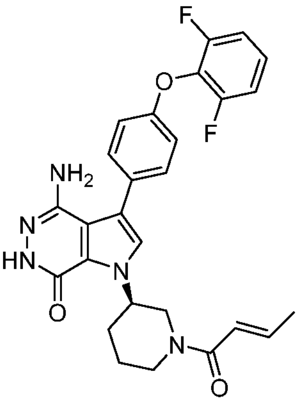

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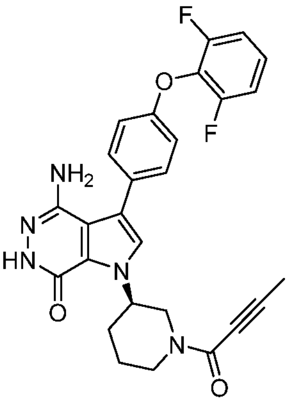

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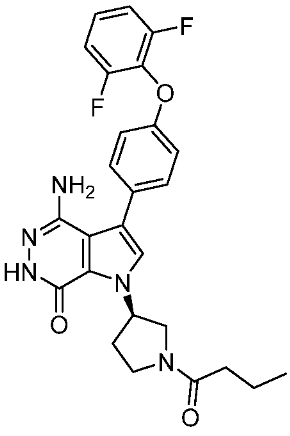

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Fig. 1.

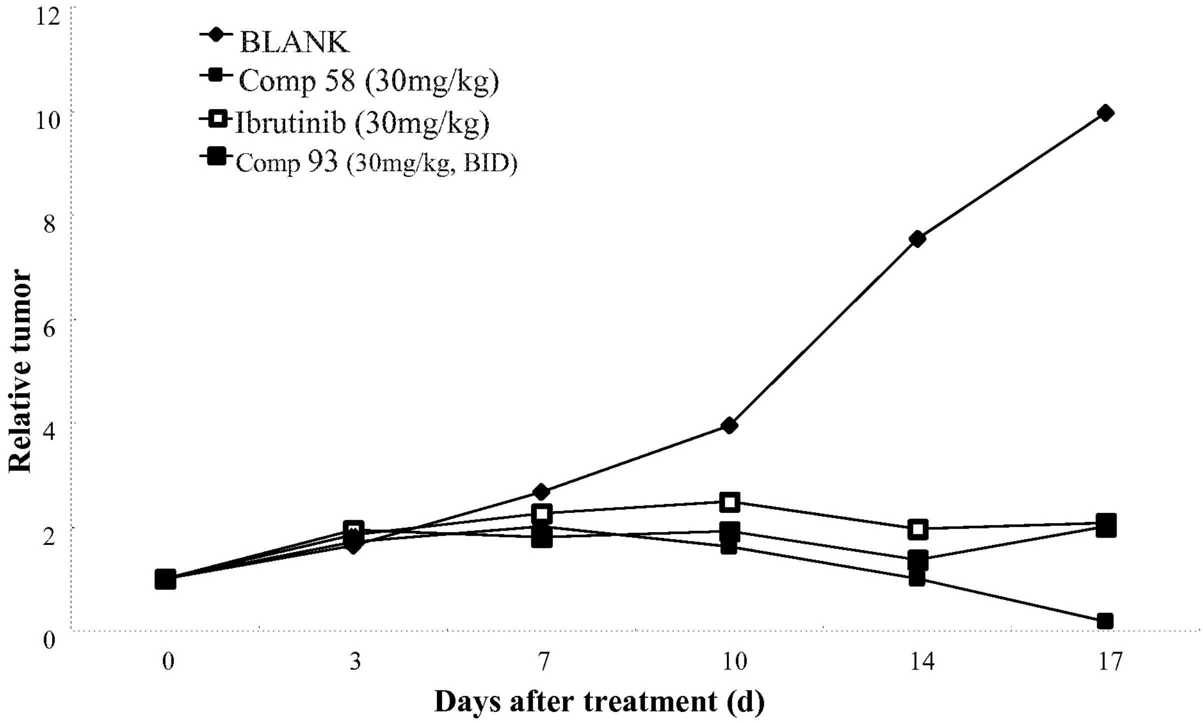
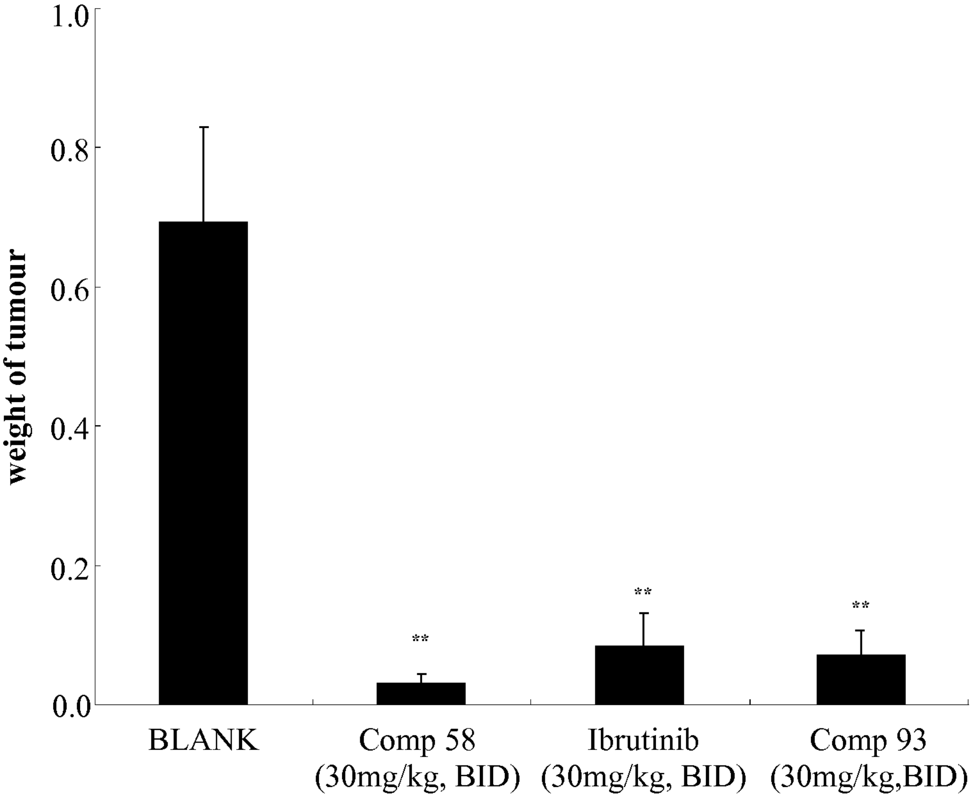

BLANK
Comp 58 (30mg/kg)
Ibrutinib (30mg/kg)
Comp 93 (30mg/kg, BID)
Relative tumor
0
2
4
6
8
10
12
Days after treatment (d)
0
3
7
10
14
17

Fig. 2.



**: p<0.01,vs blank.