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Canadian Intellectual Property Office

CA 2909578 C 2021/07/06

(11)(21) 2 909 578

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2014/05/08
(87) Date publication PCT/PCT Publication Date: 2014/11/13
(45) Date de délivrance/Issue Date: 2021/07/06
(85) Entrée phase nationale/National Entry: 2015/10/14
(86) N° demande PCT/PCT Application No.: US 2014/037247
(87) N° publication PCT/PCT Publication No.: 2014/182873
(30) Priorité/Priority: 2013/05/08 (US61/820,853)

(51) Cl.Int./Int.Cl. *C07D 405/04* (2006.01),
A61K 31/506 (2006.01), *A61P 35/00* (2006.01),
C07D 405/14 (2006.01), *C07D 417/14* (2006.01)

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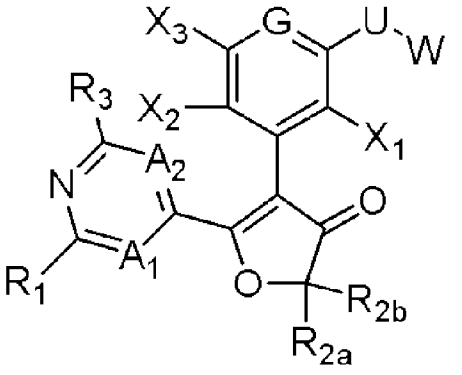
(54) Titre : COMPOSES DE FURANONE COMME INHIBITEURS DE KINASE
(54) Title: FURANONE COMPOUNDS AS KINASE INHIBITORS



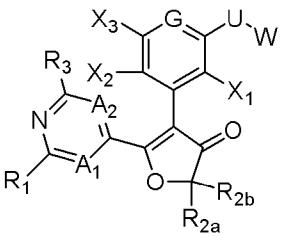
(I)

(57) Abrégé/Abstract:
The present disclosure provides novel furanone compounds of formula (I), or pharmaceutically acceptable salts, solvates or prodrugs thereof, as Raf kinase, especially BRAF kinase, inhibitors, which are useful therapeutic agents for treatment of Raf kinase related diseases or disorders, such as melanomas, cancers, and leukemia. The disclosure also provides methods and processes for preparing these novel furanone compounds, pharmaceutical compositions containing these furanone compounds, and methods of treatment using these furanone compounds.

(see formula I)

ABSTRACT

The present disclosure provides novel furanone compounds of formula (I), or pharmaceutically acceptable salts, solvates or prodrugs thereof, as Raf kinase, especially BRAF kinase, inhibitors, which are useful therapeutic agents for treatment of Raf kinase related diseases or disorders, such as melanomas, cancers, and leukemia. The disclosure also provides methods and processes for preparing these novel furanone compounds, pharmaceutical compositions containing these furanone compounds, and methods of treatment using these furanone compounds.



(I)

FURANONE COMPOUNDS AS KINASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 61/820,853, filed on May 8, 2013.

FIELD OF THE INVENTION

The present invention relates to novel furanone compounds, and compositions thereof, useful as kinase inhibitors useful for the treatment of hyperproliferative diseases, such as various cancers, melanomas and leukemia.

BACKGROUND OF THE INVENTION

Kinases are a superfamily of enzymes that transfer a phosphate group from ATP to target proteins. There are more than 518 kinases encoded in the human genome, including 90 tyrosine kinases, 388 serine/threnine kinases and 40 atypical kinases (Manning, G., et al., *Science*, 2002, 298(5600): 1912-1934). They play vital roles in cell activation, proliferation, differentiation, migration, vascular permeability, and so on. Dysfunction of kinases has been implicated in various diseases such as cancer, inflammation, cardiovascular diseases, diabetes, and neuronal disorders. Several kinase inhibitors have been developed for the treatment of cancers, including but not limited to imatinib, dasatinib, nilotinib, gefitinib, erlotinib, lapatinib, sunitinib, sorafenib, pazopanib, evrolimus, trastuzumab, cetuximab, panitumumab, and bevacizumab (Knight, Z. A., et al., *Nat. Rev. Cancer*, 2010, 10(2): 130-137).

BRAF is a member of the Raf kinase family of serine/threonine-specific protein kinases. BRAF plays an important role in regulating the MAPK/ERK signaling pathway, which affects cell division, proliferation, differentiation, and secretion. The RAS/RAF/MEK/ERK pathway acts as a signal transducer to send extracellular signals such as hormones, cytokines, and various growth factors into cell nucleus, directing a range of biochemical and physiological processes including cell differentiation, proliferation, growth, and apoptosis (McCubrey, J. A., et al., *Biochim. Biophys. Acta*, 2007, 1773 (8): 1263–84). The RAS/RAF/MEK/ERK pathway is frequently mutated in many human cancers (Downward, J., *Nat. Rev. Cancer*, 2003, 3 (1): 11–22). The finding that mutations in BRAF caused a wide range of human cancers and many of these tumors

Date Reçue/Date Received 2020-10-14

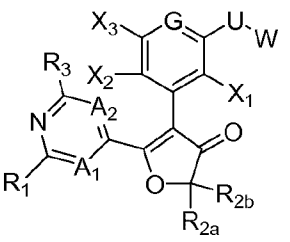
are dependent on the constitutive activation of BRAF/MEK/ERK pathway fueled drug discovery efforts in searching for small molecule inhibitors targeting BRAF mutants (especially the most common form of $BRAF^{V600E}$) (Davies, H., et al., *Nature*, 2002, 417: 949-954) (Flaherty, K.T., et al., *New Engl. J. Med.*, 2010, 363: 809-819). It was found that BRAF mutations are responsible for more than 50% of malignant melanomas, ~45% of papillary thyroid cancer, 10% of colorectal cancers, and had also been identified in ovarian, breast, and lung cancers (Cantwell-Dorris, E.R., et al., *Molecular Cancer Therapy*, 2011, 10: 385-394). Recently it was reported that almost all hairy-cell leukemia patients carry $BRAF^{V600E}$ mutation and inhibition of the enzyme caused significant remission of the disease (Sascha, D., et al., *New Engl. J. Med.*, 2012, 366:2038-2040). BRAF-specific inhibitors such as Vemurafenib (RG7204), PLX-4720, GDC-0879, and Dabrofenib (GSK2118436) have been reported to be efficacious in causing tumor regression in both preclinical and clinical studies (Flaherty, K.T., et al., *New Engl. J. Med.*, 2010, 363: 809-819; Kefford, R.A., et al., *J. Clin. Oncol.*, 2010, 28: 15s).

Accordingly, the identification and development of small-molecules that specifically modulate $BRAF^{V600E}$ kinase activity will serve as therapeutic approaches for successful treatment of a variety of $BRAF^{V600E}$ kinase-related diseases or disorders, such as cancers.

SUMMARY OF THE INVENTION

The present invention provides novel furanone compounds as useful therapeutic agents for the treatment of diseases or disorders associated with kinase activities, especially hyperproliferative diseases or disorder associated with $BRAF^{V600E}$ kinase activity, for example, melanomas, cancers, and leukemia.

In one aspect, the present disclosure provides compounds of formula (I):



(I),

or a pharmaceutically acceptable salt, solvate (in particular hydrate), or prodrug thereof, wherein:

A_1 and A_2 are independently selected from CH and N;

G is N or CX_4;

R_1 is selected from hydrogen, halogen, $NR_{11}R_{14}$, OR_{12}, and $S(O)_{0-2}R_{13}$;

R_{11} is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, and heteroaryl, each group except hydrogen optionally substituted;

R_{12}, R_{13}, and R_{14} are independently selected from hydrogen, alkyl and cycloalkyl;

R_{2a} and R_{2b} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, and heteroaryl; or R_{2a} and R_{2b} together with the carbon atom to which they are attached form a cyclic moiety selected from the group consisting of cycloalkyl, cycloalkenyl, and heterocyclyl, each optionally substituted;

R_3 is selected from hydrogen, halogen, hydroxyl, alkyl, alkoxy, and $NR_{31}R_{32}$;

R_{31} and R_{32} are independently selected from hydrogen and alkyl;

X_1 through X_4 are independently selected from hydrogen, halogen, cyano, nitro, hydroxyl, alkyl, alkoxy, and amino;

U is selected from –NH-, -NHC(O)-, $NHS(O)_n$-, NHC(O)O-, NHC(O)NH-, -O-, -C(O)-, -C(O)O-, -OC(O)NH-, -C(O)NH-, -S-, $-SO_2$-, and $-S(O)_nNH$-, wherein each n is independently 1 or 2; and

W is selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, and heteroaryl; each optionally substituted. In another aspect, the present invention provides pharmaceutical compositions containing any of these novel compounds, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable carrier.

In another aspect, the present invention provides methods of treating a hyperproliferative disease or disorder in a subject, the method comprising administering to the subject a therapeutically effective amount of any compound of the present invention, or a pharmaceutically acceptable salt, solvate or prodrug thereof. The compound of present invention is typically administered to a patient in a pharmaceutical formulation or dosage form that contains at least one pharmaceutically acceptable carrier.

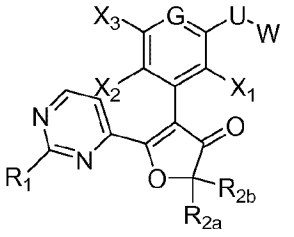
In another aspect, the present invention provides use of the novel furanone compounds, or pharmaceutically acceptable salt, solvate or prodrugs thereof, in the

manufacture of medicaments for treatment of a disease or disorder associated with a kinase activity.

Other aspects and embodiments of the present invention will be better appreciated through the following description, examples, and claims.

DETAILED DESCRIPTION OF THE INVENTION

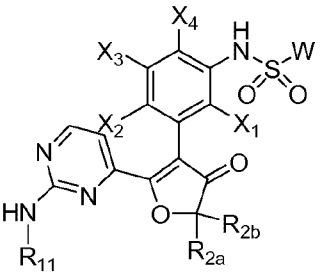
In one embodiment, the present disclosure provides compounds of formula (II):



(II),

or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R_1, R_{2a}, R_{2b}, X_{1-3}, G, U, W are as defined in formula I.

In another embodiment, the present disclosure provides a compound of formula (III):



(III),

or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein:

R_{2a}, R_{2b}, and X_1 through X_4 are as defined in formula I;

R_{11} is selected from hydrogen, alkyl optionally substituted by 1 to 3 groups independently selected from alkyl, aryl, heteroaryl, cyano, cycloalkyl, heterocyclyl, halogen, hydroxyl, $NR_{15}R_{16}$, OR_{17}, and $S(O)_{0-2}R_{18}$;

R_{15} is selected from hydrogen and optionally substituted alkyl , $C(O)R_{19}$, and $C(O)OR_{19}$;

R_{16} is selected from hydrogen and optionally substituted alkyl;

R_{17} is selected from alkyl, $C(O)R_{20}$, $C(O)NHR_{20}$;

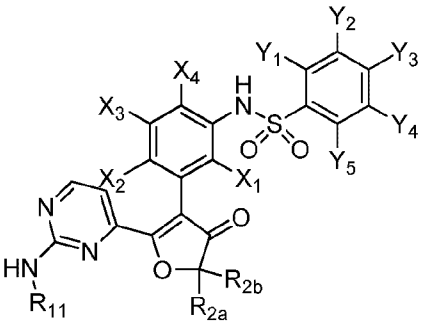
R_{18} is selected from alkyl, alkoxy, halogen, and hydroxyl;

R_{19} is optionally substituted alkyl;

R_{20} is selected from hydrogen and optionally substituted alkyl; and

W is selected from alkyl optionally substituted by 1 to 3 groups independently selected from hydroxyl, halogen, cyano, alkyl, alkoxy; and aryl optional substituted by 1 to 3 groups independently selected from hydroxyl, halogen, cyano, alkyl, alkoxy, amino, and nitro.

In another embodiment, the present invention relates to a compound of formula (IV):



(IV),

or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein:

R_{2a} and R_{2b} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, and heteroaryl; or R_{2a} and R_{2b} together with the carbon atom to which they are attached, form a cyclic moiety selected from the group consisting of cycloalkyl, cycloalkenyl, and heterocyclyl;

R_{11} is selected from hydrogen, alkyl optionally substituted by 1 to 3 groups independently selected from alkyl, aryl, heteroaryl, cyano, cycloalkyl, heterocyclyl, halogen, hydroxyl, $NR_{15}R_{16}$, OR_{17}, and $S(O)_{0-2}R_{18}$; wherein:

R_{15} is selected from hydrogen and optionally substituted alkyl and $C(O)OR_{19}$,

R_{16} is selected from hydrogen and optionally substituted alkyl;

R_{17} is selected from alkyl, $C(O)R_{20}$, and $C(O)NHR_{20}$;

R_{18} is selected from alkyl, alkoxy, halogen and hydroxyl;

R_{19} is optionally substituted alkyl;

R_{20} is selected from hydrogen and optionally substituted alkyl;

X_1 through X_4 are independently selected from hydrogen, halogen, cyano, nitro, hydroxyl, alkyl, alkoxy, and amino; and

Y_1 through Y_5 are independently selected from hydrogen, halogen, cyano, nitro, hydroxyl, alkyl, alkoxy, and amino.

In one preferred embodiment, X_2 and X_4 are hydrogen, and X_1 and X_3 are independently selected from fluorine (F) and chlorine (Cl).

In another preferred embodiment, Y_1 through Y_5 are independently selected from hydrogen and halogen; no more than two of Y_1 through Y_5 are halogens.

In another preferred embodiment, R_{2a} and R_{2b} are optionally substituted alkyl, or R_{2a} and R_{2b} together with the carbon atom to which they are attached form a cyclic moiety selected from the group consisting of cycloalkyl and heterocyclyl, each optionally substituted.

Yet other aspects and embodiments may be found in the description provided herein.

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.

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.

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.

Exemplary, non-limiting examples of formulations of the invention 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).

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.

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.

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.

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.

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.

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

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."

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 ($(CH_3)_3CO$-).

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.

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.

The term "cyano," as used herein, refers to -CN.

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.

The terms "halo" and "halogen," as used herein, refer to F, Cl, Br, or I.

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.

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-).

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.

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.

The terms "hydroxy" or "hydroxyl," as used herein, refers to -OH.

The term "nitro," as used herein, refers to $-NO_2$.

The term "oxo," as used herein, refers to "=O".

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.

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.

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.

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.

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.

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.

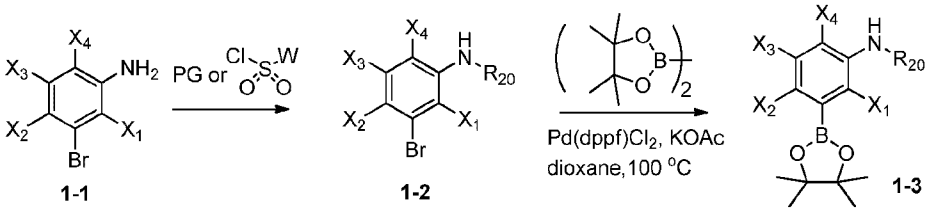
The term "patient" includes both human and other mammals.

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.

Synthetic Methods

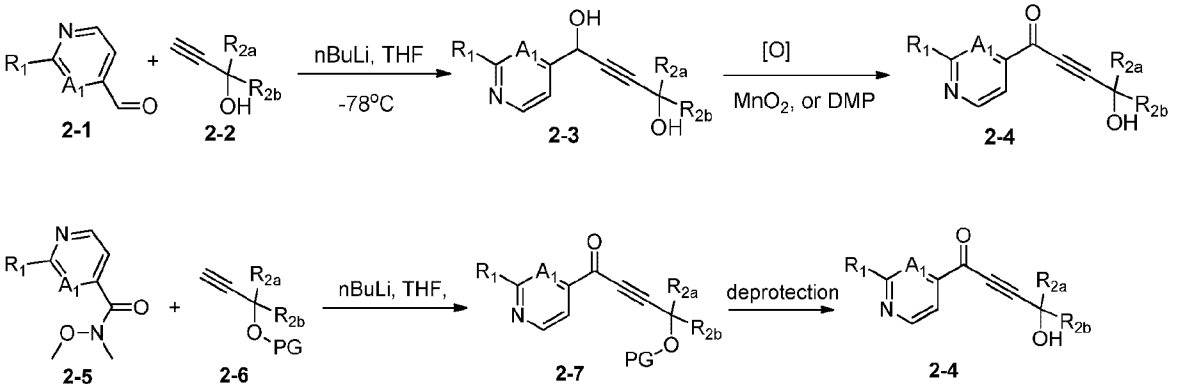
The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes that illustrate the methods by which the compounds of the invention may be prepared. Other reaction schemes could be readily devised by those skilled in the art based on the present disclosure.

Scheme 1



Amine **1-1** was purchased or prepared according to literature procedures. It was treated with sulfonyl chloride or protected by protecting group (Boc, Cbz, etc) to give **1-2**. Bromide **1-2** was converted to corresponding boronic ester **1-3** via standard conditions (Scheme 1).

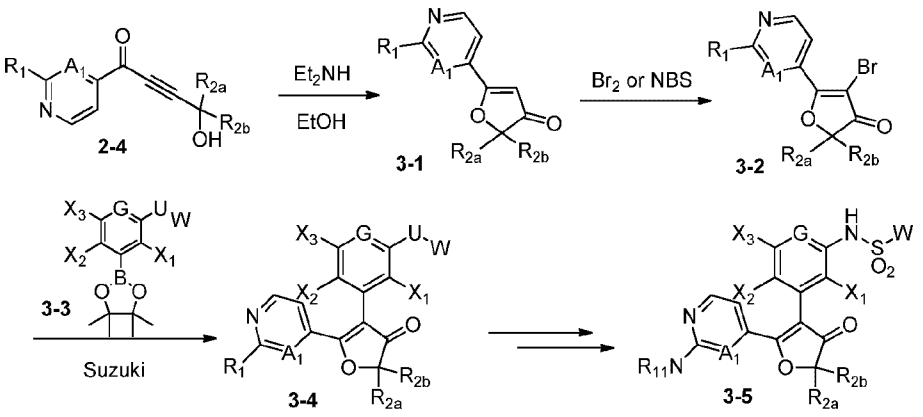
Scheme 2



Aldehyde **2-1** reacted with lithiated propynol **2-2** to afford alcohol **2-3**. Oxidation of **2-3** with MnO_2 or Dess-Martin periodinane gave ketone **2-4** (Scheme 2).

Alternately, protected propynol **2-6** was treated with nBuLi (or other strong bases), then reacted with methoxymethyl amide **2-5** to afford ketone **2-7**, which upon deprotection gave **2-4** (Scheme 2).

Scheme 3



Alcohol **2-4** was treated with Et_2NH to afford cyclized product **3-1**. Bromination with NBS or Br_2 gave bromide **3-2**, which reacted with bronic ester **3-3** under Suzuki reaction conditions to give **3-4**. Further modifications of R_1 and/or U-W gave **3-5**.

Abbreviations

The abbreviations used in the descriptions of the schemes and the examples that follow are:

DCM for dichloromethane;
DIEA or DIPEA for diisopropyl ethylamine;
DMAP for N,N-dimethylaminopyridine;
DME for ethylene glycol dimethyl ether;
DMF for *N,N*-dimethyl formamide;
DMP for Dess-Martin periodinane;
DMSO for dimethylsulfoxide;
EDCI or EDC for 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride;
ESI for electrospray ionization;
Et for ethyl;
EtOAc for ethyl acetate;
g for gram(s);
h for hour(s);
HATU for O-(7-Azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-phosphate;
HBTU for O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate;
HPLC for high-performance liquid chromatography;
mCPBA for 3-Chloroperbenzoic acid;
Me for methyl;
MeOH for methanol;
mg for milligram(s);
min for minute(s);
MS for mass spectrometry;
NBS for N-Bromosuccinimide
NMR for nuclear magnetic resonance;
$Pd(dppf)Cl_2$ for [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II);
PG for protecting groups;
Ph for phenyl;
PPh_3 for triphenylphosphine;
PTSA for p-Toluenesulfonic acid monohydrate
rt for room temperature;

TEA for triethyl amine;

TFA for trifluoroacetic acid;

THF for tetrahydrofuran;

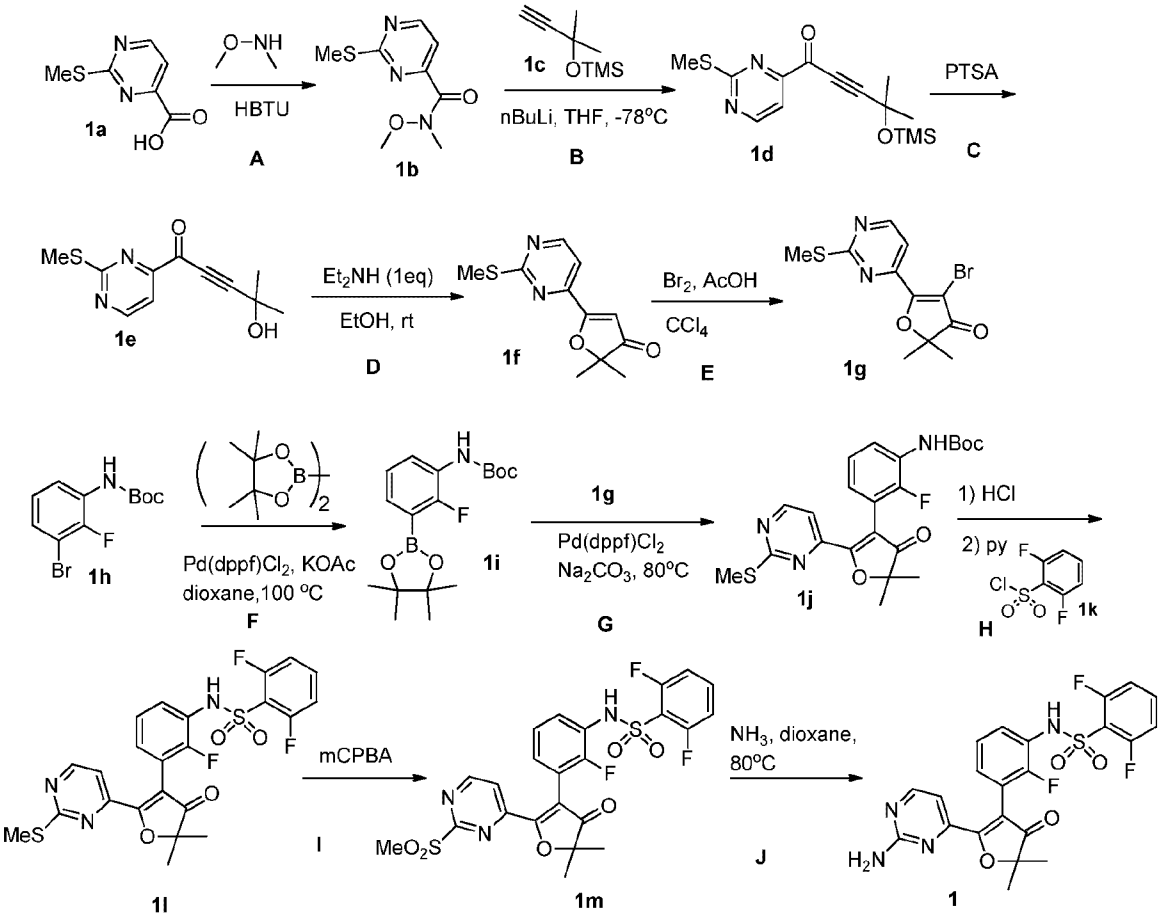
TLC for thin layer chromatography;

*t*BOC or Boc for *tert*-butyloxy carbonyl;

EXAMPLES

The compounds and processes of the present invention will be better understood in connection with the following illustrative, non-limiting examples

Example 1



Step 1A

A mixture of acid **1a** (300mg, 1.76mmol), N,O-dimethylhydroxylamine (257mg, 2.64mmol), DIPEA (0.95mL, 5.3mmol) and HBTU (0.80g, 2.1mmol) in CH_2Cl_2 (16 mL) was stirred at room temperature for 16h. Saturated $NaHCO_3$ solution was added, the resulting mixture was extracted with ethyl acetate three times. The organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to give colorless oil **1b** (330 mg, 88% yield).

Step 1B

To a solution of **1c** (290 μL, 1.5mmol) in THF (6mL) at -78 °C was added 2.5M nBuLi (0.6mL, 1.5mmol) dropwise. After stirred 45 min at -78 °C, the mixture was treated with a solution of **1b** (320mg, 1.5mmol) in THF (2mL). The reaction mixture was stirred at -78 °C for 3h, and quenched by saturated NH_4Cl solution. The aqueous solution was extracted with ethyl acetate three times. 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 yellow oil **1d** (250 mg, 54% yield [82% counting recovered **1b**]) plus recovered **1b** (110mg).

Step 1C

A mixture of *p*-toluenesulfonic acid monohydrate (200mg, 1.05mmol) and **1d** (250mg, 0.81mmol) in CH_2Cl_2 (8 mL) was stirred for 45 min at room temperature. The solution was diluted with CH_2Cl_2 and washed with water, saturated $NaHCO_3$ solution and water. The organic fraction was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to afford light brown oil **1e** (165 mg, 86% yield).

Step 1D

Et_2NH (0.11mL, 1.06mmol) was added dropwise to a solution of **1c** (0.25g, 1.06mmol) in EtOH (6mL). The resulting mixture was stirred at room temperature for 2h. EtOH was removed on rotovapor, and the residue was dissolved with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The

residue was purified by silica gel chromatography to give desired product **1f** (0.13g, 52% yield).

Step 1E

To a solution of **1f** (100 mg) in CCl_4 (10 ml) in ice bath were added AcOH (0.2 ml) and bromine (0.1 mL). The reaction mixture was stirred for 2h at 0-20 °C. $Na_2S_2O_5$ solution was added, and the resulting mixture was extracted with CH_2Cl_2 three times. The organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to give desired product **1g** (96 mg, 72% yield) MS (ESI): $m/z = 315[M+H]^+$

Step 1F

A mixture of **1h** (330 mg, 1.14 mmol), bis(pinacolato)diboron (450 mg), KOAc (330 mg),and $Pd(dppf)Cl_2$ (70 mg) in1,4-dioxane (6 ml) was stirred in a seal tube under N_2 at 100℃ for 18h. The reaction mixture was filtered through Celite®, and washed with EtOAc. The filtrate was concentrated and purified by silica gel chromatography to give desired product **1i** (320 mg, 82% yield).

Step 1G

A mixture of **1g** (25 mg), **1i** (32 mg), Na_2CO_3 (2M, 0.12mL), and $Pd(dppf)Cl_2$ (13 mg) in 1.4-dioxane(0.8 ml) was stirred in under N_2 at 80 °C for 2h. 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 yellow oil **1j** (35 mg). MS (ESI): m/z=446 $[M+H]^+$.

Step 1H

A mixture of **1j** (35 mg) and 4M HCl in dioxane (1mL) was stirred at room temperature for 2h. Solvents were removed, and the residue was dissolved in CH_2Cl_2. Pyridine (36 μL) and **1k** (20 μL) were added. The mixture was stirred overnight. Saturated $NaHCO_3$ solution was added to quench the reaction. The reaction mixture was extracted with CH_2Cl_2 three times. The organic extracts were dried over Na_2SO_4, filtered and

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concentrated. The residue was purified by silica gel chromatography to give yellow oil **1l** (27mg). MS (ESI): m/z=522 $[M+H]^+$.

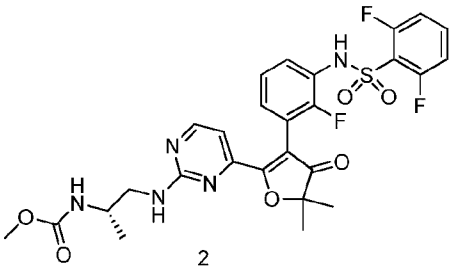
Step 1I

To a solution of **1l** (27 mg) in CH_2Cl_2 (1 ml) was added mCPBA (17 mg). The reaction mixture was stirred for 2h at room temperature. Sodium thiosulphate solution (1M) was added to quench the reaction. 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 desired product **1m** (22 mg). MS (ESI): m/z=554 $[M+H]^+$.

Step 1J

A mixture of **1m** (9 mg), and NH_4OH (0.4mL) in 1,4-dioxane (1.5mL) was stirred in a sealed tube for 4h at 80 °C. The reaction mixture was purified by reversed phase preparative HPLC to give title compound **1** (3 mg). MS (ESI): *m/z* = 491 $[M+H]^+$.

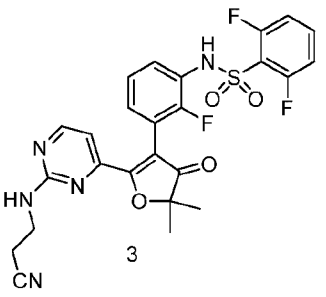
Example 2



2

A mixture of **1m** (13 mg), and (S)-methyl (1-aminopropan-2-yl)carbamate (10 µL, prepared according to the procedures described in WO 2011/25927) in NMP (0.8 mL) was stirred in a sealed vial for 18h at 90 °C. The reaction mixture was purified by reversed phase preparative HPLC to give title compound **2** (4 mg). MS (ESI): *m/z* = 606 $[M+H]^+$.

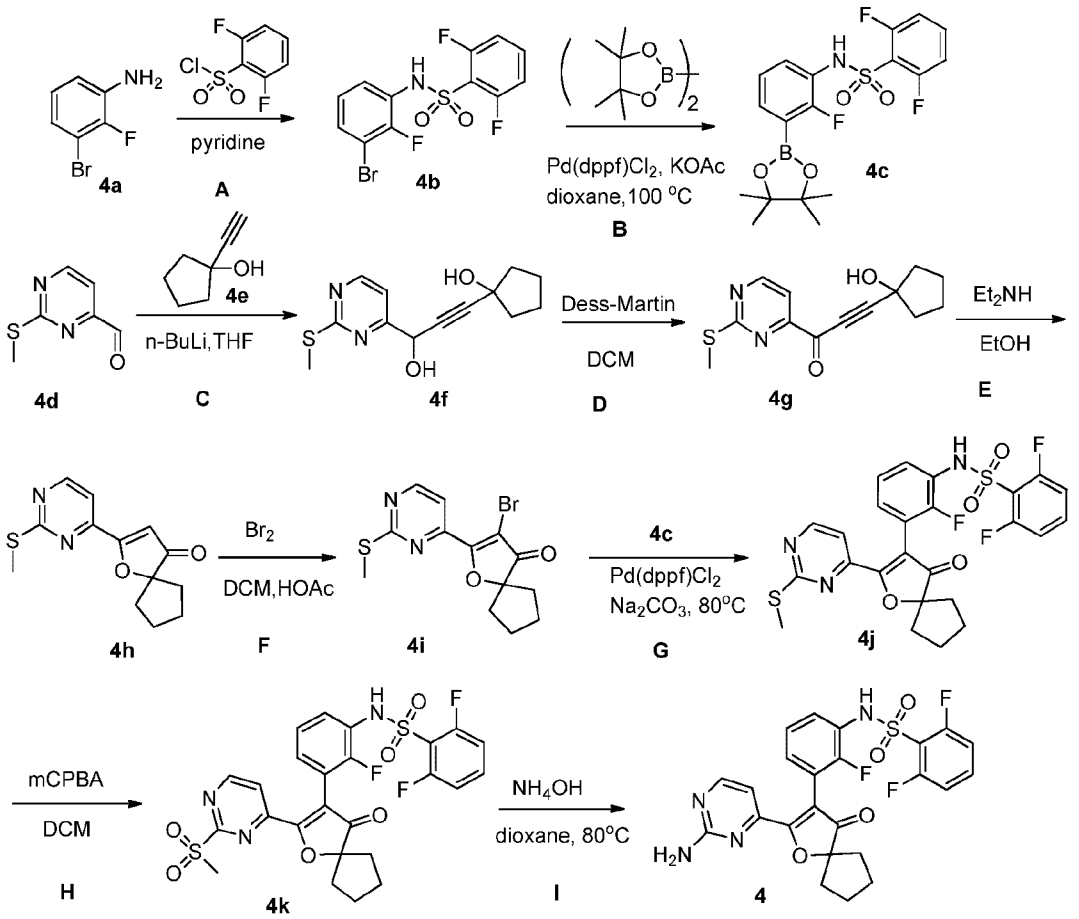
Example 3



3

Title compound **3** was prepared from **1m** and 3-aminopropionitrile using similar procedure as step 1J in example 1. MS (ESI): *m/z* = 544 $[M+H]^+$.

Example 4



Step 4A

To a solution of 3-bromo-2-fluoroaniline **4a** (228 mg) in DCM (5 ml) were added 2,6-difluorobenzene-1-sulfonyl chloride (280 mg), pyridine (120 mg) and DMAP (3 mg). The reaction mixture was stirred overnight at room temperature. 1N HCl was added to quench the reaction, and then the organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography to give desired product **4b** (200 mg 47% yield).

Step 4B

A mixture of **4b** (100 mg), Bis(pinacolato)diboron (83.7 mg), KOAc (53.7 mg), and Pd(dppf)Cl_2 (20 mg) in1,4-dioxane (3 mL) was stirred in microwave reactor under N_2 at 100°C for 1h. Water was added to quench the reaction. The mixture was extracted with EtOAc. The organic extracts were washed with brine and dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to give desired product **4c** (50 mg 39% yield). LC-MS m/z=412$[M-H]^-$.

Step 4C

A solution of 2-(methylthio)pyrimidine-4-carbaldehyde **4d** (600 mg, 3.90 mmol) in THF (5 mL) was stirred at -78°C for 10 min. n-BuLi (8.57 mmol) was added to the mixture at -78°C. The mixture was stirred at -78°C for 10 min followed by the addition of 1-ethynylcyclopentanol **4e**. The mixture was stirred at -78°C for 30 min. Saturated NH_4Cl solution was added to quench the reaction. The reaction mixture was extracted with EtOAc. The organic extracts were washed with brine, and dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel to give desired product **4f** (363 mg, 37% yield). MS (ESI): m/z = 265 $[M+H]^+$

Step 4D

To a solution of **4f** (363 mg, 30.2mmol) in DCM (10 ml) in ice bath was added Dess-Martin reagent (644 mg). The reaction mixture was stirred at room temperature for 1 h. It showed the complete conversion of **4f** to **4g** by LC- MS. Sodium thiosulphate

solution (1M) was added to quench the reaction. The reaction mixture was extracted with DCM. The organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel to give desired product **4g** (261 mg, 73% yield). MS (ESI): *m/z* = 263[M+H]$^+$

Step 4E

To a solution of **4g** (261 mg, 0.996mmol) in EtOH (5 ml) was added Et_2NH(77 mg) at room temperature. The reaction mixture was stirred over night at room temperature. After the complete conversion of **4g** to **4h,** the mixture was quenched with water, and then was extracted with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel to give desired product **4h** (160 mg 61% yield). MS (ESI): *m/z* = 263[M+H]$^+$

Step 4F

To a solution of **4h** (160 mg, 0.613mmol) in DCM (5 ml) in ice bath were added AcOH (0.2 ml) and bromine (102 mg). The reaction mixture was stirred for 2h at 0-5℃. Saturated $NaHCO_3$ solution was added to quench the reaction. The organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography to give desired product **4i** (180 mg 86% yield) MS (ESI): *m/z* = 341[M+H]$^+$

Step 4G

A mixture of **4i** (10 mg), **4c** (14.5 mg), Na_2CO_3 (5.6mg), $Pd(dppf)Cl_2$ (2.1 mg) and water (1 mL) in 1.4-dioxane(4 ml) was stirred in microwave under N_2 at 100 ℃ for 45min.Water was added to quench the reaction. 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 yellow product **4j** (12 mg 39% yield). LC-MS m/z=548[M+H]$^+$

Step 4H

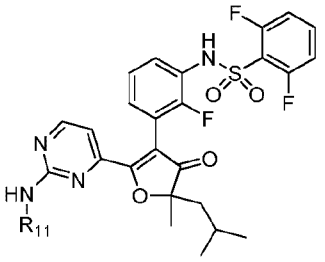
To a solution of **4j** (12 mg) in DCM (2 ml) were added mCPBA(13 mg). The reaction mixture was stirred for 2h at room temperature. Sodium thiosulphate solution (1M) was added to quench the reaction. The mixture was extracted with DCM. The organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to give desired product **4k** (12 mg 95% yield).

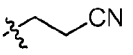
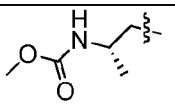
Step 4I

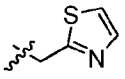
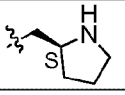
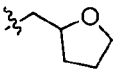
A mixture of **4k** (12 mg) and NH_4OH (2 ml) in 1, 4-dioxane was stirred for 12h at 90°C. Water and EtOAc were added to the mixture. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by reversed phase preparative HPLC to give title compound **4** (4 mg). MS (ESI): m/z = 517 $[M+H]^+$.

Examples 5 to **10** (Table 1) were made from 3,5-dimethylhex-1-yn-3-ol and corresponding amine via the similar conditions described in steps 1A~1J of Example 1.

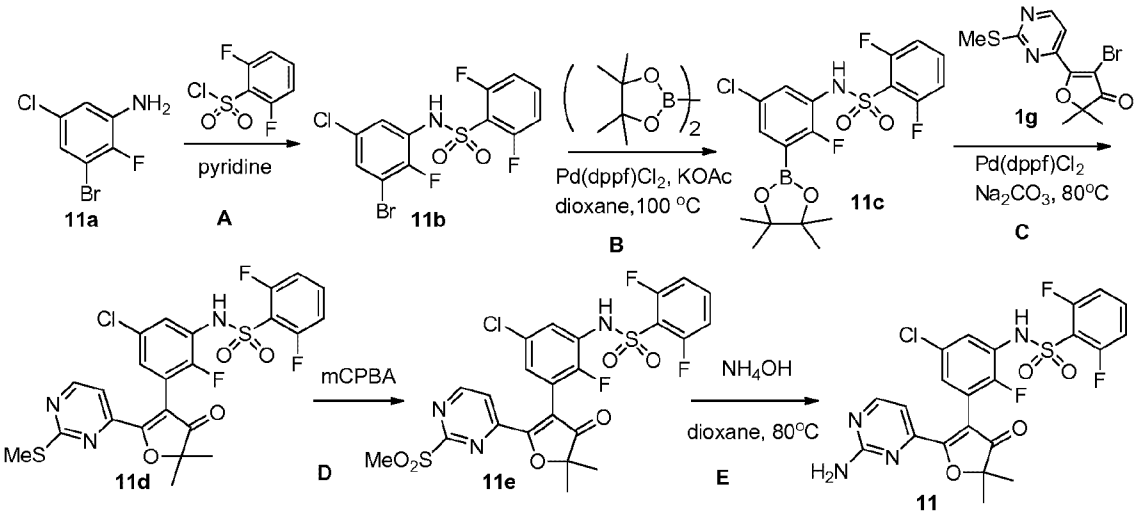
Table 1. Compounds of formula:



Example No.	R_{11}	MS(ESI) m/z [M+H]
5	H	533
6		586
7		648

8		630
9		616
10		617

Example 11



Step 11A

To a solution of **11a** (212 mg, 0.81 mmol) and pyridine (0.16 mL) in DCM (3 ml) was added 2,6-difluorobenzene-1-sulfonyl chloride (132 mg, 0.97mmol). The reaction mixture was stirred overnight at room temperature. The mixture was treated with water and 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 desired product **11b** (290 mg).

Step 11B

A mixture of the intermediate **11b** (180 mg), bis(pinacolato)diboron (170 mg), KOAc (130 mg), and Pd(dppf)Cl_2 (36 mg) in1,4-dioxane (8 mL) was stirred in a sealed

tube under N_2 at 100°C for 18h. Water was added to quench the reaction. The reaction mixture was filtered through Celite® and washed with EtOAc. The filtrate was concentrated and purified by silica gel chromatography to give desired product **11c** (150mg, 75% yield).

Step 11C

A mixture of **1g** (33 mg), **11c** (56 mg), Na_2CO_3 (2M in water, 0.2mL), $Pd(dppf)Cl_2$ (8 mg) in 1,4-dioxane(1.5 mL) was stirred under N_2 at 80 °C for 18 h. Water was added, 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 yellow oil **11d** (43 mg). MS (ESI): m/z=556 $[M+H]^+$.

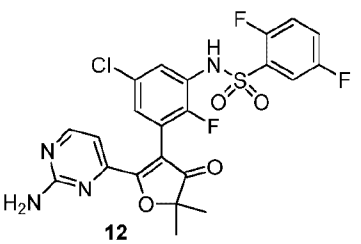
Step 11D

To a solution of **11d** (43 mg) in DCM (2 ml) were added mCPBA(30 mg). The reaction mixture was stirred for 2h at room temperature. Solvents were removed. The resulting residue was purified by silica gel chromatography to give desired product **11e** (25 mg).

Step 11E

A mixture of **11e** (25 mg) and NH_4OH (0.2 ml) in 1, 4-dioxane (1.5mL) was stirred for 4h at 78°C. Solvents were removed. The residue was purified by reversed phase preparative HPLC to give title compound **11** (20 mg). MS (ESI): m/z = 525 $[M+H]^+$.

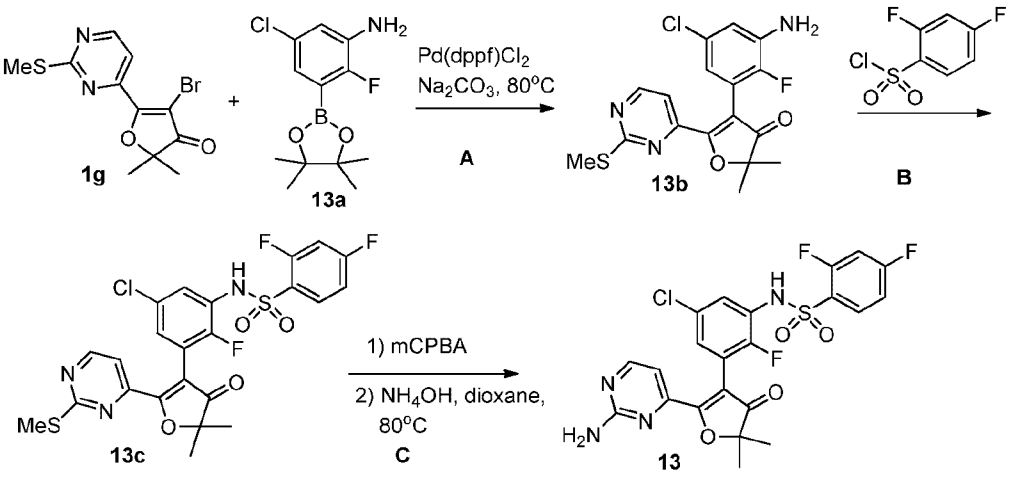
Example 12



12

The above compound was made from **11a** and 2,5-difluorobenzene-1-sulfonyl chloride using similar procedures described in example 11. MS (ESI): m/z = 525 $[M+H]^+$.

Example 13



Step 13A

A mixture of **1g** (27 mg), **13a** (28 mg), Na_2CO_3 (2M in water, 0.15 mL), $Pd(dppf)Cl_2$ (25 mg) in 1,4-dioxane (1.5 mL) was stirred under N_2 at 80 °C for 3h. 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 **13b** (15 mg). MS (ESI): m/z=380 $[M+H]^+$.

Step 13B

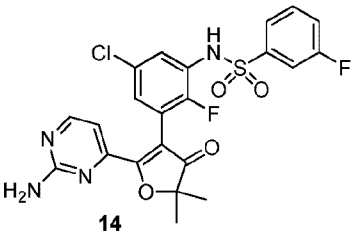
A mixture of **13b** (7 mg), pyridine (20 μL) and 2,4-difluorobenzene-1-sulfonyl chloride (12 μL) in DCM (0.7 mL) was stirred at rt for 18h. Solvents were removed by evaporation. The resulting residue was purified by silica gel chromatography to give desired product **13c** (7 mg). MS (ESI): m/z=556 $[M+H]^+$.

Step 13C

To a solution of **13c** (7 mg) in CH_2Cl_2 (1 ml) was added mCPBA (8 mg). The reaction mixture was stirred for 3 h at room temperature. Solvents were removed by evaporation. The resulting residue was purified by silica gel chromatography to give the oxidation product, which was stirred with NH_4OH (0.1 mL) and 1,4-dioxane (0.8 mL) in a

closed vial for 2h at 80 °C. The reaction mixture was purified by silica gel chromatography to give title compound **13** (4.8 mg). MS (ESI): *m/z* = 525 $[M+H]^+$.

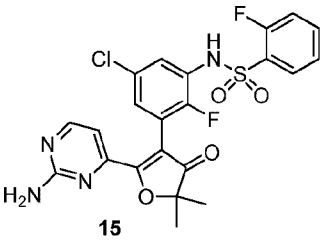
Example 14



14

The above compound was made from compound **13b** and 3-fluorobenzene-1-sulfonyl chloride following similar procedures to those described in Example 13. MS (ESI): m/z = 507 $[M+H]^+$.

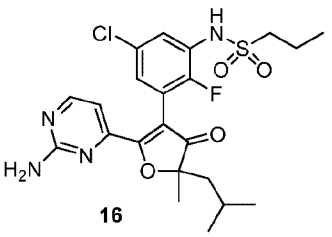
Example 15



15

The above compound was made from compound **13b** and 2-fluorobenzene-1-sulfonyl chloride following similar procedures to those described in Example 13. MS (ESI): m/z = 507 $[M+H]^+$.

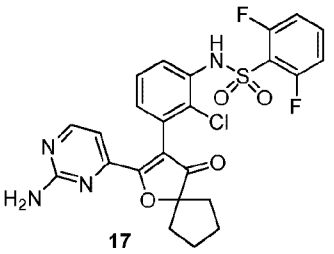
Example 16



16

The above compound was made by using similar procedures to those described in Examples 1 and 11. MS (ESI): m/z = 497 $[M+H]^+$.

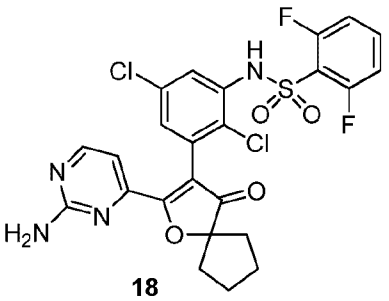
Example 17



17

The above compound was made from compound **4i** and 3-bromo-2-chloroaniline following similar procedures to those described in Example 4. MS (ESI): m/z = 533 $[M+H]^+$.

Example 18

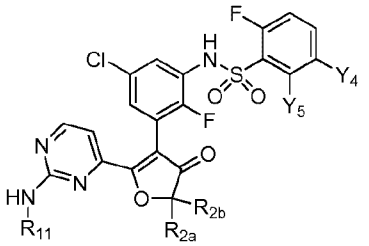


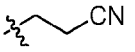
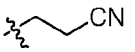
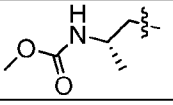
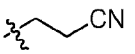
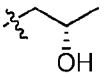
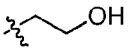
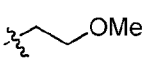
18

The above compound was made from compound **4i** and 2,5-dichloroaniline following similar procedures to those described in Example 4. MS (ESI): m/z = 567$[M+H]^+$.

Examples 19 to **29** (Table 2) were prepared by using similar procedures described to those described in Examples 1, 4 and 11.

Table 2. Compounds of formula:



Example No.	R_{2a}	R_{2b}	Y_4	Y_5	R_{11}	MS(ESI) m/z $[M+H]^+$
19	Me	*i*Bu	H	F	H	567
20	Me	*i*Bu	H	F		620
21	Me	Me	H	F		578
22	Me	Me	F	H		640
23	Me	Me	F	H		578
24	Me	Me	F	H		583
25	Me	Me	F	H		569
26	Me	Me	F	H		583
27	Me	Me	F	H	Et	553
28	$-(CH_2)_4-$		F	H	H	551
29	$-(CH_2)_4-$		H	F	H	551

BIOLOGICAL ASSAYS

$BRAF^{V600E}$ enzymatic activity assay: The $BRAF^{V600E}$ enzymatic assay was performed using a LanthaScreen kinase assay kit purchased from Life Technologies (Grand Island, NY). The assay was conducted according to the procedure provided in the assay kit. In brief, the enzyme reaction was carried out in the kinase reaction buffer containing $BRAF^{V600E}$ (20 ng/mL), ATP (2 μM), Fluorescein-MAP2K1 inactive substrate (0.4 μM), HEPES (50 mM, pH 7.5), 0.01% BRIJ-35, $MgCl_2$ (10mM), and EGTA (1mM) in the presence or absence of the tested compounds at various concentrations in a 384-well plate at room temperature (22 ± 1 °C) for 60 minutes. The final reaction volume for each

reaction was 10 μl. The reaction was stopped by addition of 10 μl of TR-FRET dilution buffer kinase supplemented with kinase quench buffer (10 mM final) and Tb-anti-pMAP2K1 (2 nM final). The plate was further incubated at room temperature for another 60 minutes, and the fluorescent signals were read on Victor 5 (Perkin Elmer) with excitation at 340 nM and emission at 495 and 520 nM. The assay signal was determined as a ratio of FRET-specific signal measured with emission filter at 520 nM to that of the signal measured with Tb-specific emission filter at 495 nM. IC_{50} value was calculated using appropriate programs in GraphPad Prism by plotting the logarithm of the concentration versus percent inhibition. The IC_{50} values for the example compounds are shown in Table 3.

Cell proliferation assay: A375, Colo-205, Calu-6, and SW-480 cells were purchased from American Type Culture Collection (USA). All cells were cultured in the recommended medium and serum concentration. Cells were maintained at 37 °C in a humidified atmosphere with 5% CO_2. For cell proliferation assay, cells were seeded in 96-well pates at a density of 1,000 to 5,000 cells per well and cultured overnight at 37 °C in a medium supplemented with 5-10% FBS. On the next day, the test articles at various concentrations or vehicle control (1% DMSO) were added into cell culture. After 3-day treatment, the growth of cells was assayed by the CellTiter-Glo® Luminestceaent Cell Viability Assay (Promega). IC_{50} value was calculated using GraphPad Prism by plotting the logarithm of the concentration versus percent inhibition of cell growth. The IC_{50} value for the example compounds is shown in Table 3.

Table 3. Biological Testing Results

Example No.	**$BRAF^{V600E}$ Lantha** IC_{50} (μM)	**A375 cell growth** IC_{50} (μM)
1	0.16	0.97
2	0.097	0.63
3	0.013	0.47
4	0.029	0.51
5	0.092	2.3

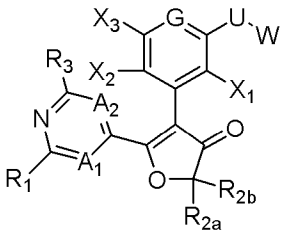
6	0.0096	12.0
7	0.027	0.87
8	0.26	27
9	2	-
10	0.75	-
11	0.0055	0.018
12	0.0006	0.0014
13	0.010	0.35
14	0.0012	0.12
15	0.0025	0.11
16	0.07	0.25
17	0.0037	0.15
18	0.0024	0.007
19	0.027	0.041
20	0.029	0.16
21	0.0025	0.20
22	0.050	0.18
23	0.013	0.051
24	0.024	0.41
25	0.011	0.16
26	0.050	0.26
27	0.0028	0.32
28	0.0026	0.011
29	0.0013	0.018

The foregoing preferred embodiments and examples are provided for illustration only and are not intended to limit the scope of the invention. Various changes and

modifications to the disclosed embodiments will be apparent to those skilled in the art based on the present disclosure, and such changes and modifications, including, without limitation, those relating to the chemical structures, substituents, derivatives, formulations and/or methods of preparation, may be made without departure from the spirit and scope of the present invention.

CLAIMS

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

A_1 is N; and A_2 is CH;

G is CX_4;

R_1 is selected from the group consisting of hydrogen, halogen, $-NR_{11}R_{14}$, $-OR_{12}$, and $-S(O)_{0-2}R_{13}$;

R_{11} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, and heteroaryl, wherein each group except hydrogen is optionally substituted;

R_{12}, R_{13}, and R_{14} are independently selected from the group consisting of hydrogen, alkyl and cycloalkyl;

R_{2a} and R_{2b} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, and heteroaryl; or alternatively R_{2a} and R_{2b} together with the carbon atom to which they are attached form a cyclic moiety selected from the group consisting of cycloalkyl, cycloalkenyl, and heterocyclyl, each optionally substituted;

R_3 is selected from the group consisting of hydrogen or halogen;

X_1 through X_4 are independently selected from the group consisting of hydrogen and halogen;

U is $-NHS(O)_2-$ or $-S(O)_2NH-$; and

W is alkyl or aryl, each optionally substituted.

2. The compound of claim 1, characterized by formula (II):

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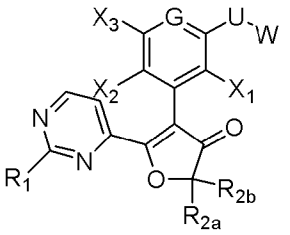


(II),

or a pharmaceutically acceptable salt or solvate thereof.

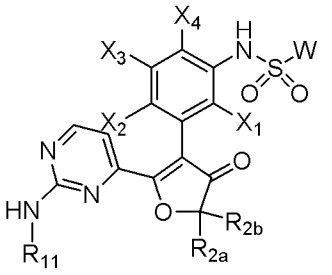
3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, wherein G is CH.

4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, wherein U is $-NHS(O)_2-$.

5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt or solvate thereof, wherein W is alkyl optionally substituted by 1 to 3 substituents independently selected from the group consisting of hydroxyl, halogen, cyano, and alkoxy; or aryl optionally substituted by 1 to 5 substituents independently selected from the group consisting of halogen, alkyl, alkoxy, haloalkyl, haloalkoxy, hydroxy, cyano, nitro, and amino.

6. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt or solvate thereof, wherein R_1 is $-NR_{11}R_{14}$.

7. The compound of claim 6, wherein R_{14} is hydrogen, characterized by formula (III):



(III),

or a pharmaceutically acceptable salt or solvate thereof.

8. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R_{11} is hydrogen or alkyl optionally substituted by 1 to 3 groups independently selected from the group consisting of aryl, heteroaryl, cyano, cycloalkyl, heterocyclyl, halogen, hydroxyl, $-NR_{15}R_{16}$, $-OR_{17}$, and $-S(O)_{0-2}R_{18}$;

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R_{15} is hydrogen, optionally substituted alkyl, $C(O)R_{19}$, or $-C(O)OR_{19}$;

R_{16} is hydrogen or optionally substituted alkyl;

R_{17} is alkyl, $-C(O)R_{20}$, or $-C(O)NHR_{20}$;

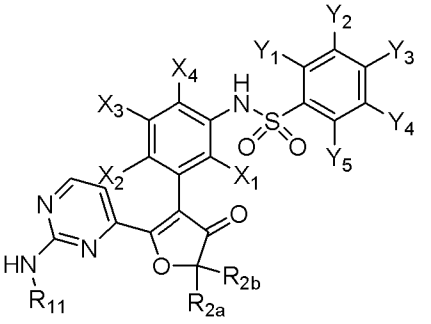
R_{18} is alkyl, alkoxy, halogen, or hydroxyl;

R_{19} is optionally substituted alkyl;

R_{20} is hydrogen or optionally substituted alkyl; and

W is C_6-C_{10} aryl optionally substituted by 1 to 5 substituents independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, hydroxy, cyano, nitro, and amino.

9. The compound of any one of claims 1 to 8, wherein W is optionally substituted phenyl, characterized by formula (IV):



(IV)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Y_1 through Y_5 are independently selected from the group consisting of hydrogen, halogen, cyano, nitro, hydroxyl, alkyl, alkoxy, and amino.

10. The compound of claim 9, or a pharmaceutically acceptable salt or solvate thereof, wherein Y_1, Y_2, Y_3, Y_4 and Y_5 are independently hydrogen or halogen.

11. The compound of claim 9, or a pharmaceutically acceptable salt or solvate thereof, wherein one, two or three of Y_1, Y_2, Y_3, Y_4 and Y_5 are halogen and the rest are hydrogen.

12. The compound of claim 11, or a pharmaceutically acceptable salt or solvate thereof, wherein one or two of Y_1, Y_2, Y_3, Y_4 and Y_5 are halogen and the rest are hydrogen.

13. The compound of any one of claims 9 to 12, or a pharmaceutically acceptable salt or solvate thereof, wherein any said halogen is fluorine (F) or chlorine (Cl).

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14. The compound of claim 13, or a pharmaceutically acceptable salt or solvate thereof, wherein said halogen is fluorine (F).

15. The compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt or solvate thereof, wherein X_1 through X_4 are independently hydrogen or halogen.

16. The compound of claim 15, or a pharmaceutically acceptable salt or solvate thereof, wherein X_2 and X_4 are hydrogen.

17. The compound of claim 15 or 16, or a pharmaceutically acceptable salt or solvate thereof, wherein X_1 and X_3 are independently hydrogen, fluorine (F) or chlorine (Cl).

18. The compound according to any one of claims 1 to 17, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{11} is hydrogen or C_1-C_6 alkyl optionally substituted by 1 to 3 groups independently selected from the group consisting of C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_8 cycloalkyl, 5- to 10-membered heterocyclyl, halogen, cyano, hydroxyl, $-NR_{15}R_{16}$, $-OR_{17}$, and $-S(O)_2R_{18}$;

R_{15} is hydrogen, C_1-C_4 alkyl, or $-C(O)OR_{19}$;

R_{16} is hydrogen or C_1-C_4 alkyl;

R_{17} is C_1-C_4 alkyl, $-C(O)R_{20}$, or $-C(O)NHR_{20}$;

R_{18} is alkyl, alkoxy, halogen, or hydroxyl;

R_{19} is C_1-C_4 alkyl; and

R_{20} is hydrogen or C_1-C_4 alkyl.

19. The compound according to any of claims 1 to 18, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{2a} and R_{2b} are independently selected from the group consisting of hydrogen, and optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, and heteroaryl.

20. The compound of claim 19, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{2a} and R_{2b} are independently C_1-C_6 alkyl.

21. The compound according to any of claims 1 to 18, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{2a} and R_{2b} together with the carbon atom to which they are attached form a cyclic moiety selected from the group consisting of optionally substituted cycloalkyl, cycloalkenyl, and heterocyclyl.

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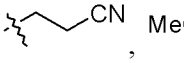
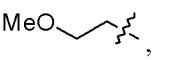
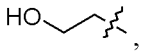
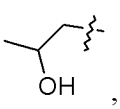
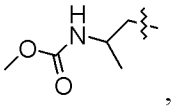
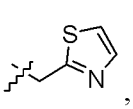
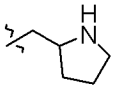
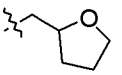
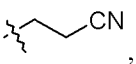
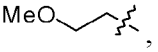
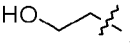
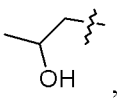
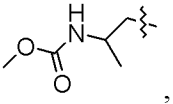
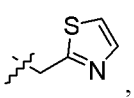
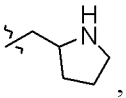
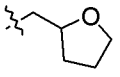
22. The compound of claim 21, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{2a} and R_{2b} together with the carbon atom to which they are attached form a C_3-C_8 cycloalkyl.

23. The compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt or solvate thereof, wherein R_{11} is hydrogen, C_1-C_6 alkyl,  ,  ,  ,  ,  ,  ,  , or  .

24. The compound of claim 9, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R_{11} is hydrogen, C_1-C_6 alkyl,  ,  ,  ,  ,  ,  ,  , or  ;

R_{2a} and R_{2b} are independently C_1-C_6 alkyl; or alternatively R_{2a} and R_{2b} together are -($CH_2CH_2CH_2CH_2$)- or -($CH_2CH_2CH_2CH_2CH_2$)-;

X_1 and X_3 are independently hydrogen, fluorine, or chlorine (Cl);

X_2 and X_4 are hydrogen; and

one or two of Y_1, Y_2, Y_3, Y_4, and Y_5 are fluorine, and the rest are hydrogen.

25. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of:

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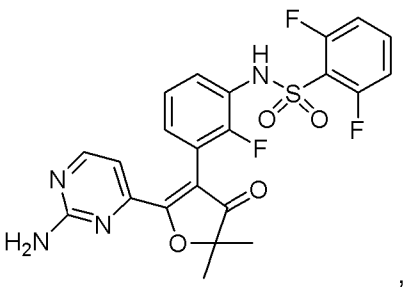
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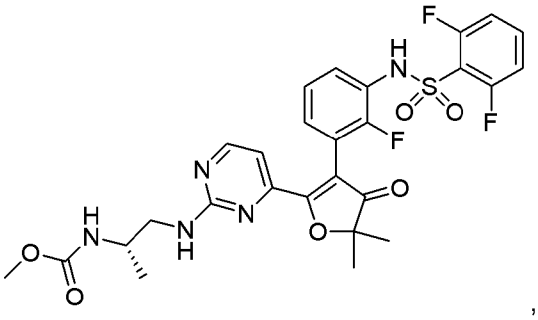
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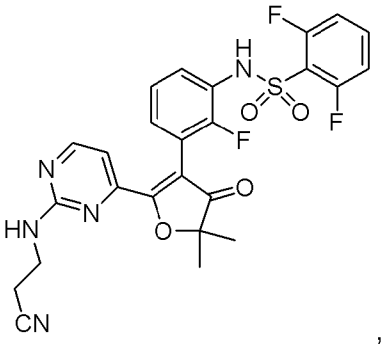
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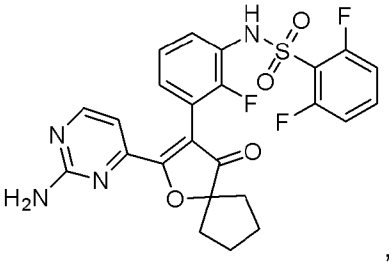
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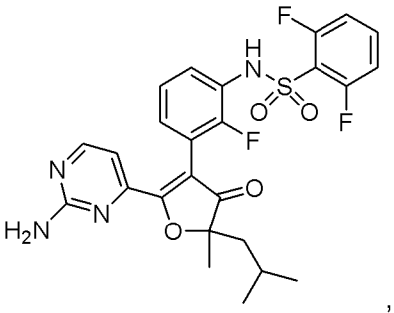
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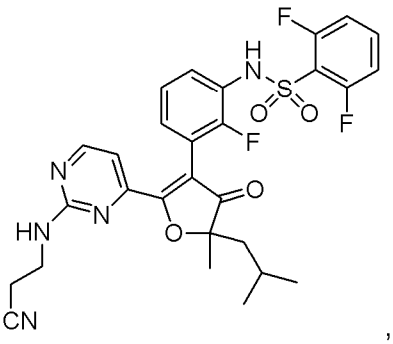
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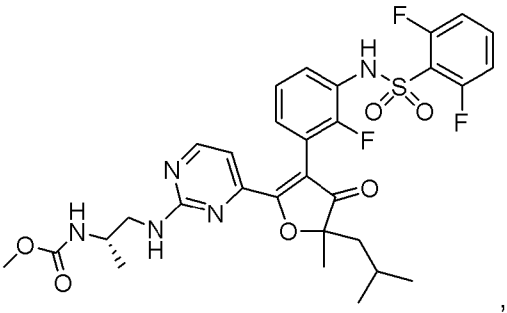
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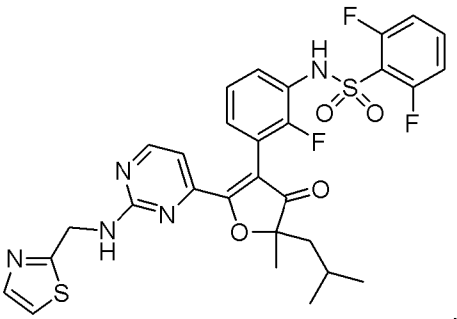
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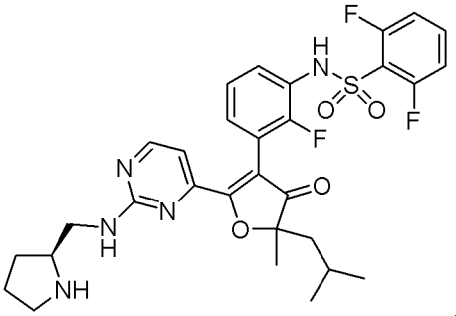
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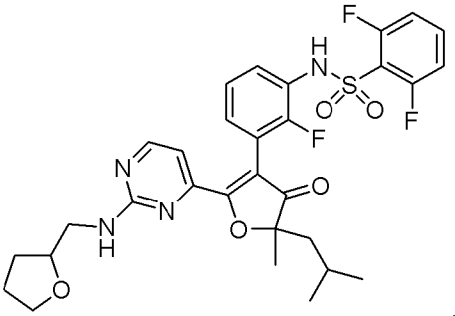
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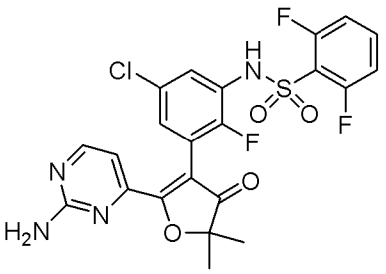
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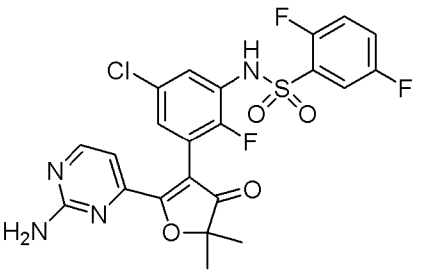
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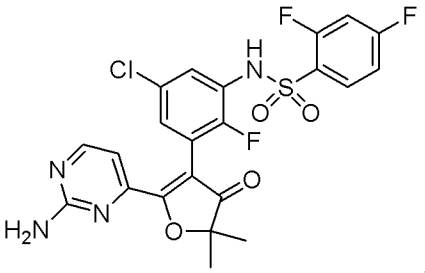
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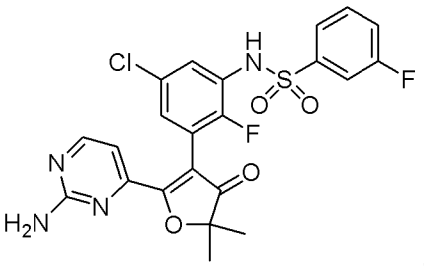
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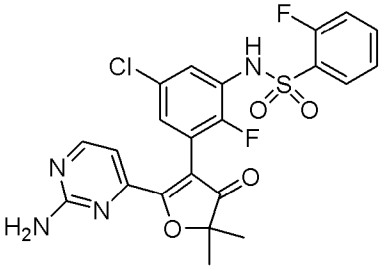
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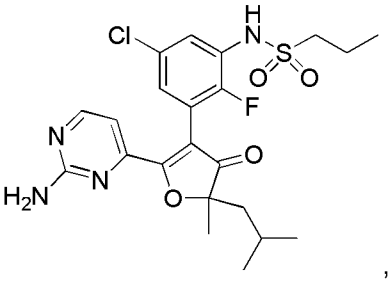
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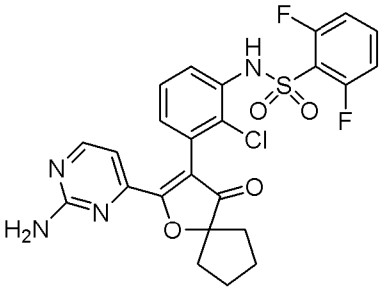
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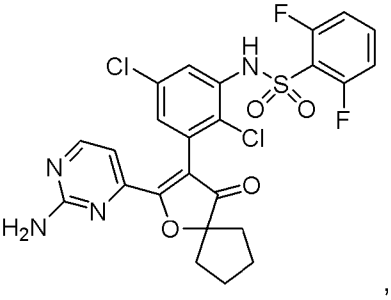
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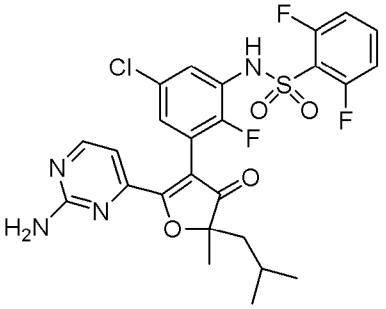
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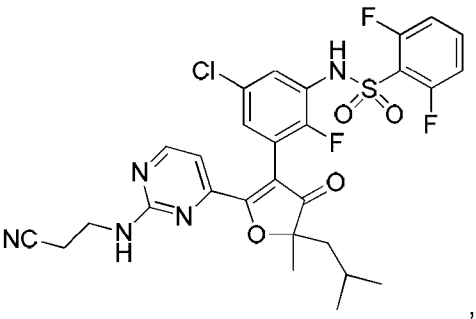
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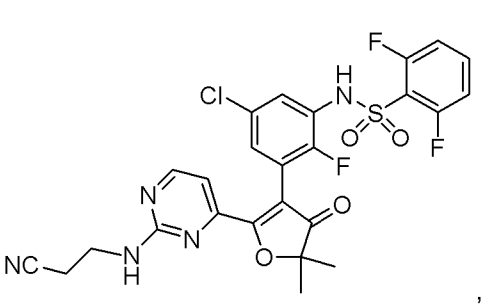
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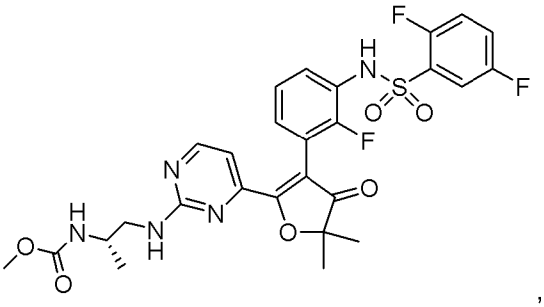
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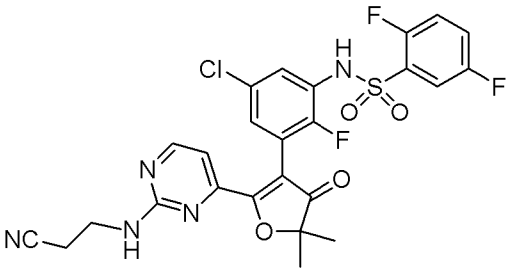
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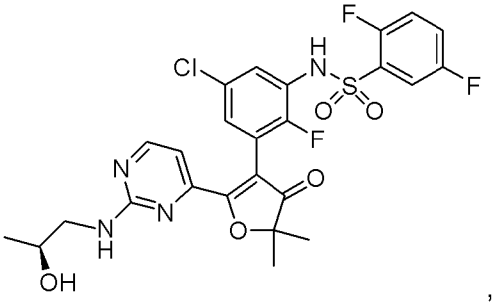
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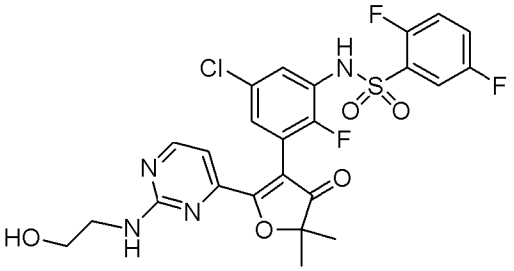
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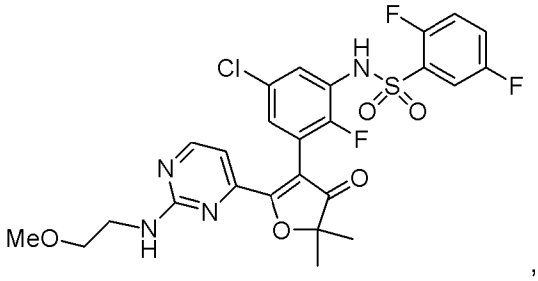
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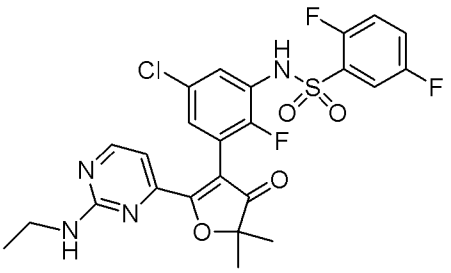
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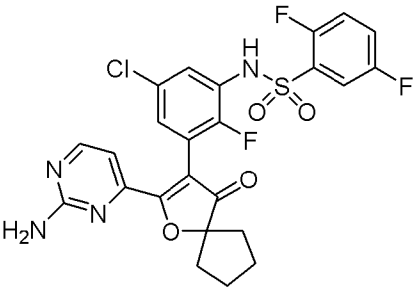
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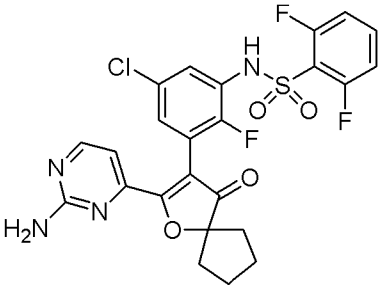
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26. A pharmaceutical composition comprising a compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

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27. Use of a compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of a hyperproliferative disease or disorder.

28. Use of a pharmaceutical composition of 26 in the manufacture of a medicament for the treatment of a hyperproliferative disease or disorder.

29. The use of claim 27 or 28, wherein the hyperproliferative disease or disorder is associated with $BRAF^{V600E}$ kinase activity.

30. The use of claim 27 or 28, wherein the hyperproliferative disease or disorder is a cancer.

31. The use of claim 27 or 28, wherein the hyperproliferative disease or disorder is selected from melanomas; papillary thyroid, colorectal, ovarian, breast, and lung cancers; and leukemia.

32. Use of a compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treatment of a disease or disorder associated with a kinase activity.

33. The use of claim 32, wherein said hyperproliferative disease or disorder is selected from the group consisting of melanomas; papillary thyroid, colorectal, ovarian, breast, and lung cancers; and leukemia.

34. A compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment of a disease or disorder associated with a BRAF kinase activity.

35. A pharmaceutical composition comprising a compound according to any one of claims 1 to 25, or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment of a disease or disorder associated with a BRAF kinase activity.

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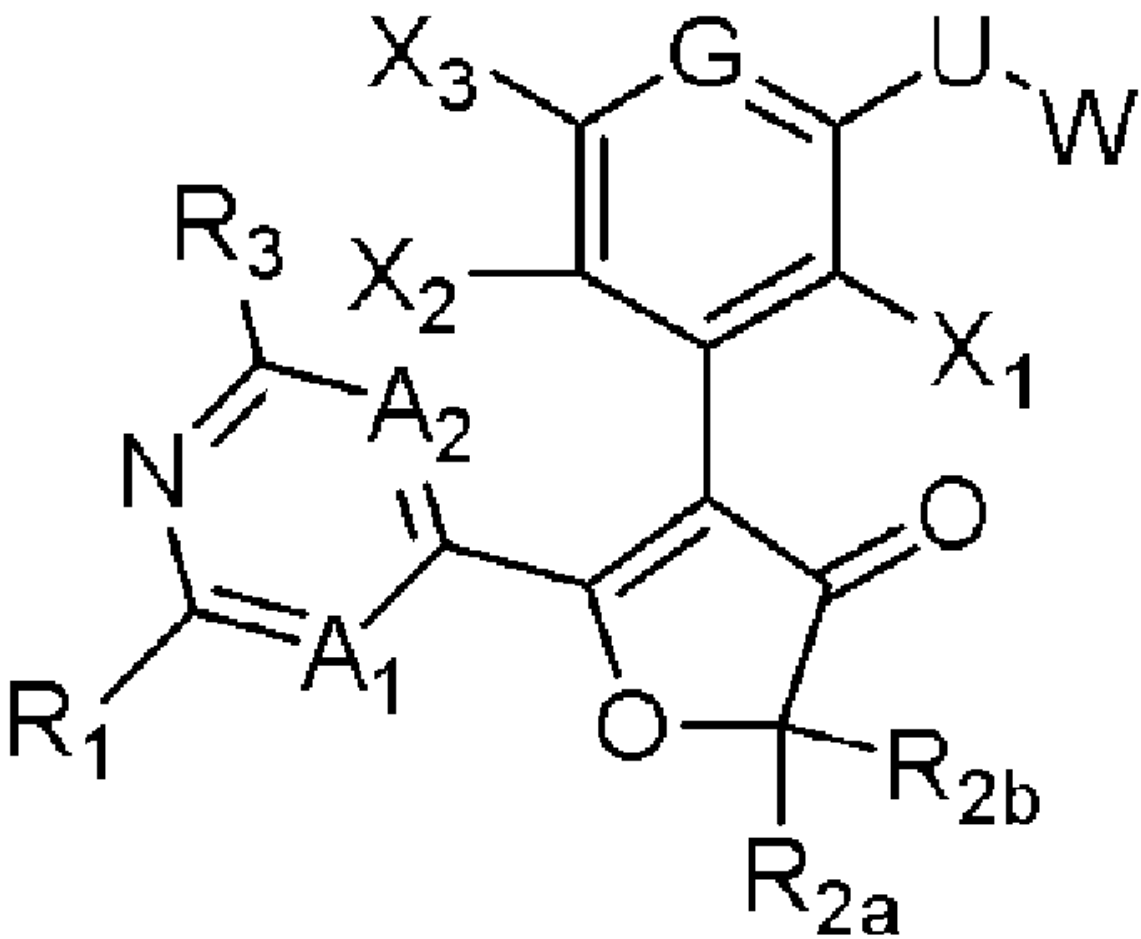

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