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(54) Title: COMBINATION OF A JAK INHIBITOR AND A BROMODOMAIN INHIBITOR FOR TREATING CANCER

(57) Abstract: Provided herein are methods and pharmaceutical compositions for the treatment of cancer comprising filgotinib and a BET inhibitor.



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COMBINATION OF A JAK INHIBITOR AND A BROMODOMAIN INHIBITOR FOR TREATING CANCER

CROSS REFERENCE TO RELATED APPLICATIONS

5 This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 62/269,075, filed December 17, 2015, the entirety of which is incorporated herein by reference.

BACKGROUND

10 Janus kinase (JAK) is a family of intracellular, nonreceptor tyrosine kinases that transduce cytokine-mediated signals via the JAK-STAT pathway. Filgotinib is a JAK1 selective inhibitor.

15 BET (Bromodomain and Extra-Terminal motif) inhibitors are a class of drugs with anti-cancer, immunosuppressive, and other effects. They reversibly bind the BET proteins BRD2, BRD3, BRD4 and BRDT, and prevent protein-protein interactions between BET proteins and acetylated histones and transcription factors.

SUMMARY

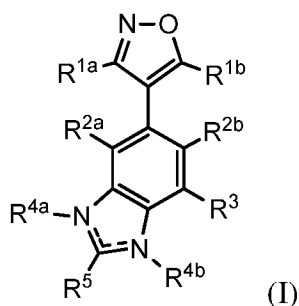
Described herein are methods of treating cancers comprising administering filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, and a BET inhibitor, to a patient in need thereof.

20 In some embodiments, provided herein is a method of treating cancer in a human in need thereof, comprising administering to the human:

(i) a therapeutically effective amount of filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof; and

(ii) a therapeutically effective amount of a BET inhibitor.

25 In some embodiments, the BET inhibitor is a compound of the formula:



wherein:

one --- is a single bond and the other --- is a double bond;

R^{1a} and R^{1b} are each independently C_{1-6} alkyl optionally substituted with from 1 to 5 R^{20} groups;

5 R^{2a} and R^{2b} are each independently H or halo;

R^3 is $-\text{B}(\text{OH})_2$, $-\text{B}(\text{OR}^a)_2$, halo, $-\text{C}(\text{O})\text{OR}^a$, $-\text{NHC}(\text{O})\text{OR}^a$, $-\text{NHS}(\text{O})_2\text{R}^a$, $-\text{S}(\text{O})_2\text{NR}^a\text{R}^b$, C_{1-10} alkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl,

10 wherein each of C_{1-10} alkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl is optionally substituted with from 1 to 5 R^{20} groups;

one of R^{4a} and R^{4b} is selected from the group consisting of H and C_{1-6} alkyl optionally substituted with from 1 to 5 R^{20} groups, and the other is absent;

15 R^5 is $-\text{C}(\text{O})\text{OR}^a$, $-\text{NHC}(\text{O})\text{OR}^a$, $-\text{NHS}(\text{O})_2\text{R}^a$, or $-\text{S}(\text{O})_2\text{NR}^a\text{R}^b$, H, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl,

wherein each of C_{1-10} alkyl, C_{1-10} haloalkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl is optionally substituted with from 1 to 5 R^{20} groups;

each R^a and R^b is independently selected from the group consisting of H, C_{1-10} alkyl, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; and

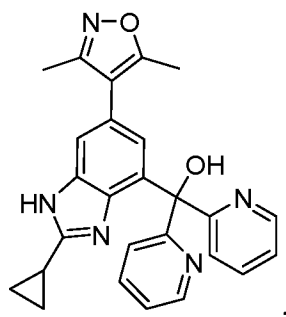
each R^{20} is independently selected from the group consisting of acyl, C_{1-10} alkyl, C_{1-10} alkoxy, amino, amido, amidino, C_{5-10} aryl, C_{6-20} arylalkyl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, guanidino, halo, C_{1-10} haloalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, C_{6-20} heteroarylalkyl, hydroxy, hydrazino, imino, oxo, nitro, sulfinyl, sulfonic acid, sulfonyl, thiocyanate, thiol, and thione,

or a pharmaceutically acceptable salt thereof.

In another embodiment, this disclosure provides a method for treating cancer in a human in need thereof, comprising administering to the human:

(i) a therapeutically effective amount of filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof; and

(ii) a therapeutically effective amount of



or a pharmaceutically acceptable salt thereof.

In another embodiment, this disclosure provides a co-formulation comprising:

(i) filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof; and

(ii) a BET inhibitor.

In some embodiments, this disclosure provides a composition for use in the treatment of cancer, the composition comprising:

filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof; and

5 a BET inhibitor.

DETAILED DESCRIPTION

The following description sets forth exemplary embodiments of the present technology. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary
10 embodiments.

Definitions

As used in the present specification, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

15 Recitation of numeric ranges of values throughout the specification is intended to serve as a shorthand notation of referring individually to each separate value falling within the range inclusive of the values defining the range, and each separate value is incorporated in the specification as it were individually recited herein.

20 The compound names provided herein are named using ChemBioDraw Ultra 12.0. One skilled in the art understands that the compound may be named or identified using various commonly recognized nomenclature systems and symbols. By way of example, the compound may be named or identified with common names, systematic or non-systematic names. The nomenclature systems and symbols that are commonly recognized in the art of chemistry include, for example, Chemical Abstract Service (CAS), ChemBioDraw Ultra, and International
25 Union of Pure and Applied Chemistry (IUPAC).

Also provided herein are isotopically labeled forms of compounds detailed herein. Isotopically labeled compounds have structures depicted by the formulas given herein except that

one or more atoms are replaced by an atom having a selected atomic mass or mass number.

Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as, but not limited to ^2H (deuterium, D), ^3H (tritium), ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}F , ^{31}P , ^{32}P , ^{35}S , ^{36}Cl and

5 ^{125}I . Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as ^3H , ^{13}C and ^{14}C are incorporated, are provided. Such isotopically labeled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays
10 or in radioactive treatment of subjects (*e.g.* humans). Also provided for isotopically labeled compounds described herein are any pharmaceutically acceptable salts, or hydrates, as the case may be.

In some variations, the compounds disclosed herein may be varied such that from 1 to n hydrogens attached to a carbon atom is/are replaced by deuterium, in which n is the number of
15 hydrogens in the molecule. Such compounds may exhibit increased resistance to metabolism and are thus useful for increasing the half life of the compound when administered to a mammal. See, for example, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism", Trends Pharmacol. Sci. 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogens
20 have been replaced by deuterium.

Deuterium labeled or substituted therapeutic compounds of the disclosure may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to absorption, distribution, metabolism and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability,
25 for example increased *in vivo* half-life, reduced dosage requirements and/or an improvement in therapeutic index. An ^{18}F labeled compound may be useful for PET or SPECT studies.

Isotopically labeled compounds of this disclosure can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled

reagent. It is understood that deuterium in this context is regarded as a substituent in the compounds provided herein.

The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not specifically
5 designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as “H” or “hydrogen”, the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium.

10 A dash at the front or end of a chemical group is a matter of convenience; chemical groups may be depicted with or without one or more dashes without losing their ordinary meaning. A wavy line drawn through a line in a structure indicates a point of attachment of a group. A dashed line indicates an optional bond. Unless chemically or structurally required, no directionality is indicated or implied by the order in which a chemical group is written. For
15 instance, the group “-SO₂CH₂-” is equivalent to “-CH₂SO₂-” and both may be connected in either direction. The prefix “C_{u-v}” indicates that the following group has from u to v carbon atoms, one or more of which, in certain groups (e.g. heteroalkyl, heteroaryl, heteroarylalkyl, etc.), may be replaced with one or more heteroatoms or heteroatomic groups. For example, “C₁₋₆ alkyl” indicates that the alkyl group has from 1 to 6 carbon atoms.

20 Also, certain commonly used alternative chemical names may or may not be used. For example, a divalent group such as a divalent “alkyl” group, a divalent “aryl” group, etc., may also be referred to as an “alkylene” group or an “alkylenyl” group, an “arylene” group or an “arylenyl” group, respectively.

25 “Alkyl” refers to any aliphatic hydrocarbon group, i.e. any linear, branched, cyclic, or spiro nonaromatic hydrocarbon group or an isomer or combination thereof. As used herein, the term “alkyl” includes terms used in the art to describe saturated and unsaturated aliphatic hydrocarbon groups with one or more points of attachment, including alkenyl (an aliphatic group containing at least one carbon-carbon double bond), alkylene (a divalent aliphatic group), alkynyl (an aliphatic group containing at least one carbon-carbon triple bond), cycloalkyl (a

cyclic aliphatic group), alkylcycloalkyl (a linear or branched aliphatic group attached to a cyclic aliphatic group), and the like. Alkyl groups include, but are not limited to, methyl; ethyl; propyls such as propan-1-yl, propan-2-yl (iso-propyl), and cyclopropyls such as cyclopropan-1-yl, etc.; butyls such as butan-1-yl, butan-2-yl (sec-butyl), 2-methyl-propan-1-yl (iso-butyl), 2-methyl-
5 propan-2-yl (t-butyl), cyclobutan-1-yl; butenes (e.g. (E)-but-2-ene, (Z)-but-2-ene); pentyls; pentenes; hexyls; hexenes; octyls; decyls; cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylecyclohexyl, spiro[2.4]heptyl, and the like. An alkyl group comprises from 1 to about 10 carbon atoms, e.g., from 1 to 6 carbon atoms. In some embodiments, alkyl is a monovalent, linear or branched, saturated aliphatic hydrocarbon group comprising from 1 to about 10 carbon
10 atoms, e.g., from 1 to 6 carbon atoms.

“Alkenyl” is a subset of “alkyl” and refers to an aliphatic group containing at least one carbon-carbon double bond and having from 2 to about 10 carbon atoms, e.g., from 2 to 6 carbon atoms or 2 to 4 carbon atoms and having at least one site of vinyl unsaturation ($>C=C<$). Alkenyl groups include ethenyl, propenyl, 1,3-butadienyl, and the like. Alkynyl may have from
15 2 to about 10 carbon atoms, e.g. from 2 to 6 carbon atoms or 2 to 4 carbon atoms.

“Alkynyl” is a subset of “alkyl” and refers to an aliphatic group containing at least one carbon-carbon triple bond. The term “alkynyl” is also meant to include those groups having one triple bond and one double bond.

“Alkoxy” refers to the group -O-alkyl, wherein the alkyl group may be optionally
20 substituted. Alkoxy includes, by way of example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy, sec-butoxy, and n-pentoxy.

“Acyl” refers to a group $-C(=O)R$, where R is hydrogen, alkyl, cycloalkyl, cycloheteroalkyl, aryl, arylalkyl, heteroalkyl, heteroaryl or heteroarylalkyl as defined herein, each of which may be optionally substituted, as defined herein. Representative examples
25 include, but are not limited to formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethyl-carbonyl, benzoyl, benzyloxycarbonyl and the like.

“Amido” refers to both a “C-amido” group which refers to the group $-C(=O)NRyRz$ and an “N-amido” group which refers to the group $-NRyC(=O)Rz$, wherein Ry and Rz are

independently selected from the group consisting of hydrogen, alkyl, aryl, heteralkyl, heteroaryl (each of which may be optionally substituted), and where Ry and Rz are optionally joined together with the nitrogen or carbon bound thereto to form an optionally substituted heterocycloalkyl.

5 “Amino” refers to the group -NRyRz wherein Ry and Rz are independently selected from the group consisting of hydrogen, alkyl, aryl, heteralkyl, heteroaryl (each of which may be optionally substituted), and where Ry and Rz are optionally joined together with the nitrogen bound thereto to form a heterocycloalkyl or heteroaryl heteroaryl (each of which may be optionally substituted).

10 “Amidino” refers to the group -C(=NRx)NRyRz where Rx, Ry, and Rz are independently selected from the group consisting of hydrogen, alkyl, aryl, heteralkyl, heteroaryl (each of which may be optionally substituted), and where Ry and Rz are optionally joined together with the nitrogen bound thereto to form a heterocycloalkyl or heteroaryl (each of which may be optionally substituted).

15 “Aryl” refers to a group with one or more aromatic rings. It may be a single aromatic ring or multiple aromatic rings which are fused together, linked covalently, or linked via one or more such as a methylene or ethylene moiety. Aryl groups include, but are not limited to, those groups derived from acenaphthylene, anthracene, azulene, benzene, biphenyl, chrysene, cyclopentadienyl anion, diphenylmethyl, fluoranthene, fluorene, indane, indene, naphthalene, perylene, phenalene, phenanthrene, pyrene, triphenylene, and the like. An aryl group comprises
20 from 5 to about 20 carbon atoms, e.g., from 5 to 20 carbon atoms, e.g. from 5 to 10 carbon atoms. In some embodiments, aryl is a a single aromatic ring or multiple aromatic rings which are fused together.

 “Arylalkyl” (also “aralkyl”) refers to an aryl group attached to an alkyl group. Arylalkyl
25 groups include, but are not limited to, benzyl, tolyl, dimethylphenyl, 2-phenylethan-1-yl, 2-naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, phenylvinyl, diphenylmethyl, and the like. For example, the “arylalkyl” may be attached to the rest of the compound of formula (I) through the aryl group. Alternatively, the “arylalkyl” may be attached to the rest of the compound of formula (I) through the alkyl group. Where specific alkyl moieties are intended, the

nomenclature arylalkanyl, arylalkenyl and/or arylalkynyl may be used. An arylalkyl group comprises from 6 to about 30 carbon atoms, e.g. the alkyl portion of the arylalkyl group can comprise from 1 to about 10 carbon atoms and the aryl portion of the arylalkyl group can comprise from 5 to about 20 carbon atoms. In some instances an arylalkyl group comprises from 5 to about 20 carbon atoms, e.g. the alkyl portion of the arylalkyl group can comprise from 1 to about 10 carbon atoms and the aryl portion of the arylalkyl group can comprise from 5 to about 10 carbon atoms.

“Aryloxy” refers to the group -O-aryl, including by way of example, phenoxy and naphthoxy.

“Azido” refers to the group -N₃.

“Boronic acid” refers to the group -B(OH)₂.

“Boronic acid ester” refers to an ester derivative of a boronic acid compound. Suitable boronic acid ester derivatives include those of the formula -B(OR)₂ where R is hydrogen, alkyl, aryl, arylalkyl, heteroalkyl, or heteroaryl, each of which may be optionally substituted. For example, boronic acid ester may be pinacol ester or catechol ester.

“Carbamoyl” refers to the group -C(O)NR^yR^z where R^y and R^z are defined as in “amino” above.

“Carbonyl” refers to the divalent group -C(O)- which is equivalent to -C(=O)-.

“Carboxyl” or “carboxy” refers to -COOH or salts thereof.

“Carboxyl ester” or “carboxy ester” refers to the groups -C(O)OR, wherein R is hydrogen, alkyl, aryl, arylalkyl, heteroalkyl, or heteroaryl, each of which may be optionally substituted. In one embodiment, R is alkyl, aryl, arylalkyl, heteroalkyl, or heteroaryl, each of which may be optionally substituted.

“Cyano” or “carbonitrile” refers to the group -CN.

“Cycloalkyl” is a subset of “alkyl” and refers to a saturated or partially saturated cyclic group of from 3 to about 10 carbon atoms and no ring heteroatoms and having a single ring or multiple rings including fused, bridged, and spiro ring systems. For multiple ring systems having aromatic and non-aromatic rings that have no ring heteroatoms, the term “cycloalkyl” applies when the point of attachment is at a non-aromatic carbon atom (e.g., 5,6,7,8,-tetrahydronaphthalene-5-yl). The term “cycloalkyl” includes cycloalkenyl groups. Examples of cycloalkyl groups include, for instance, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and cyclohexenyl.

“Guanidino” refers to the group -NHC(=NH)NH_2 .

“Halo” or “halogen” refers to fluoro, chloro, bromo and iodo.

“Haloalkyl” refers to substitution of alkyl groups with 1 to 5 or, in some embodiments, 1 to 3 halo groups, e.g., $\text{-CH}_2\text{Cl}$, $\text{-CH}_2\text{F}$, $\text{-CH}_2\text{Br}$, -CFClBr , $\text{-CH}_2\text{CH}_2\text{Cl}$, $\text{-CH}_2\text{CH}_2\text{F}$, -CF_3 , $\text{-CH}_2\text{CF}_3$, $\text{-CH}_2\text{CCl}_3$, and the like, and further includes those alkyl groups such as perfluoroalkyl in which all hydrogen atoms are replaced by fluorine atoms.

“Haloaryl” refers to aryl groups with one or more halo or halogen substituents. For example, haloaryl groups include phenyl groups in which from 1 to 5 hydrogens are replaced with a halogen. Haloaryl groups include, for example, fluorophenyl, difluorophenyl, trifluorophenyl, chlorophenyl, chlorofluorophenyl, and the like.

“Heteroalkyl” refers to an alkyl group in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatom or heteroatomic group. For example, heteroalkyl may include 1, 2 or 3 heteroatomic groups, e.g. 1 heteroatomic group. Heteroatoms include, but are not limited to, N, P, O, S, etc. Heteroatomic groups include, but are not limited to, -NR- , -O- , -S- , -PH- , $\text{-P(O)}_2\text{-}$, -S(O)- , $\text{-S(O)}_2\text{-}$, and the like, where R is H, alkyl, aryl, cycloalkyl, heteroalkyl, heteroaryl or cycloheteroalkyl. The term “heteroalkyl” includes heterocycloalkyl (a cyclic heteroalkyl group), alkyl-heterocycloalkyl (a linear or branched aliphatic group attached to a cyclic heteroalkyl group), and the like. Heteroalkyl groups include, but are not limited to, -OCH_3 , $\text{-CH}_2\text{OCH}_3$, -SCH_3 , $\text{-CH}_2\text{SCH}_3$, -NRCH_3 , $\text{-CH}_2\text{NRCH}_3$, and the like, where R is hydrogen, alkyl, aryl,

arylalkyl, heteroalkyl, or heteroaryl, each of which may be optionally substituted. A heteroalkyl group comprises from 1 to about 10 carbon and hetero atoms, e.g., from 1 to 6 carbon and hetero atoms.

“Heteroaryl” refers to an aryl group in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatoms, as defined above. For example, heteroaryl may include 1, 2 or 3 heteroatomic groups, e.g. 1 heteroatomic group. Heteroaryl groups include, but are not limited to, groups derived from acridine, benzoimidazole, benzothiophene, benzofuran, benzoxazole, benzothiazole, carbazole, carboline, cinnoline, furan, imidazole, imidazopyridine, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like. A heteroaryl group comprises from 5 to about 20 carbon and hetero atoms in the ring or rings, e.g., from 5 to 20 carbon and hetero atoms, e.g. from 5 to 10 carbon and hetero atoms.

“Heteroarylalkyl” refers to an arylalkyl group in which one or more carbon atoms (and any associated hydrogen atoms) are independently replaced with the same or different heteroatoms, as defined above. For example, heteroarylalkyl may include 1, 2 or 3 heteroatomic groups. Heteroarylalkyl groups include, but are not limited to, groups derived from heteroaryl groups with alkyl substituents (e.g. methylpyridine, dimethylisoxazole, etc.), hydrogenated heteroaryl groups (dihydroquinolines, e.g. 3,4-dihydroquinoline, dihydroisoquinolines, e.g. 1,2-dihydroisoquinoline, dihydroimidazole, tetrahydroimidazole, etc.), isoindoline, isoindolones (e.g. isoindolin-1-one), dihydrophthalazine, quinolinone, spiro[cyclopropane-1,1'-isoindolin]-3'-one, di(pyridin-2-yl)methyl, di(pyridin-3-yl)methyl, di(pyridin-4-yl)methyl, and the like. A heteroarylalkyl group comprises from 6 to about 30 carbon and hetero atoms, for example from 6 to about 20 carbon and hetero atoms.

“Heterocycloalkyl” is a subset of “heteroalkyl” and refers to a saturated or unsaturated cycloalkyl group in which one or more carbon atoms (and any associated hydrogen atoms) are

independently replaced with the same or different heteroatom. Heteroatoms include, but are not limited to, N, P, O, S, etc. A heterocycloalkyl group may also contain a charged heteroatom or group, e.g., a quaternized ammonium group such as $-N^+(R)_2-$ wherein R is alkyl, e.g., methyl, ethyl, etc. Heterocycloalkyl groups include, but are not limited to, groups derived from epoxide, imidazolidine, morpholine, piperazine, piperidine, pyrazolidine, pyrrolidine, pyrrolidinone, tetrahydrofuran, tetrahydrothiophene, dihydropyridine, tetrahydropyridine, quinuclidine, N-bromopyrrolidine, N-bromopiperidine, N-chloropyrrolidine, N-chloropiperidine, an N,N-dialkylpyrrolidinium, such as N,N-dimethylpyrrolidinium, a N,N-dialkylpiperidinium such as N,N-dimethylpiperidinium, and the like. The heterocycloalkyl group comprises from 3 to about 10 carbon and hetero atoms in the ring or rings. In some embodiments, heterocycloalkyl includes 1, 2 or 3 heteroatomic groups.

“Hydrazino” refers to the group $-NHNH_2$.

“Hydroxy” or “hydroxyl” refers to the group $-OH$.

“Imino” refers to the group $-C(=NR)-$ wherein R is hydrogen, alkyl, aryl, arylalkyl, heteroalkyl, or heteroaryl, each of which may be optionally substituted.

“Nitro” refers to the group $-NO_2$.

The terms “optional” or “optionally” mean that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

“Oxide” refers to products resulting from the oxidation of one or more heteroatoms. Examples include N-oxides, sulfoxides, and sulfones.

“Oxo” refers to a double-bonded oxygen ($=O$). In compounds where an oxo group is bound to an sp^2 nitrogen atom, an N-oxide is indicated.

The term “solvate” refers to an association or complex of one or more solvent molecules and a compound of the disclosure. Examples of solvents that form solvates may include water, isopropanol, ethanol, methanol, dimethylsulfoxide, ethylacetate, acetic acid and ethanolamine.

The term “hydrate” refers to the complex formed by the combining of a compound described herein and water.

The term “prodrug” refers to compounds disclosed herein that include chemical groups which, *in vivo*, can be converted and/or can be split off from the remainder of the molecule to provide for the active drug, a pharmaceutically acceptable salt thereof, or a biologically active metabolite thereof.

“Racemates” refers to a mixture of enantiomers.

“Stereoisomer” or “stereoisomers” refer to compounds that differ in the chirality of one or more stereocenters. Stereoisomers include enantiomers and diastereomers. The compounds may exist in stereoisomeric form if they possess one or more asymmetric centers or a double bond with asymmetric substitution and, therefore, can be produced as individual stereoisomers or as mixtures. Unless otherwise indicated, the description is intended to include individual stereoisomers as well as mixtures. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see, e.g., Chapter 4 of Advanced Organic Chemistry, 4th ed., J. March, John Wiley and Sons, New York, 1992).

“Substituted” (as in, e.g., “substituted alkyl”) refers to a group wherein one or more hydrogens have been independently replaced with one or more substituents including, but not limited to, alkyl, alkenyl, alkynyl, alkoxy, acyl, amino, amido, amidino, aryl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, guanidino, halo, haloalkyl, heteroalkyl, heteroaryl, heterocycloalkyl, hydroxy, hydrazino, hydroxyl, imino, oxo, nitro, sulfinyl, sulfonic acid, sulfonyl, thiocyanate, thiol, thione, or combinations thereof. Polymers or similar indefinite structures arrived at by defining substituents with further substituents appended ad infinitum (e.g., a substituted aryl having a substituted alkyl which is itself substituted with a substituted aryl group, which is further substituted by a substituted heteroalkyl group, etc.) are not intended for inclusion herein. Unless otherwise noted, the maximum number of serial substitutions in compounds described herein is three. For example, serial substitutions of substituted aryl groups with two other substituted aryl groups are limited to -substituted aryl-(substituted aryl)-substituted aryl. For example, in some embodiments, when a group described above as being “optionally substituted” is substituted, that substituent is itself unsubstituted. Similarly, it is

understood that the above definitions are not intended to include impermissible substitution patterns (e.g., methyl substituted with 5 fluoro groups or heteroaryl groups having two adjacent oxygen ring atoms). Such impermissible substitution patterns are well known to the skilled artisan. When used to modify a chemical group, the term “substituted” may describe other chemical groups defined herein. For example, the term “substituted aryl” includes, but is not limited to, “arylalkyl.” Generally, substituted groups will have 1 to 5 substituents, 1 to 3 substituents, 1 or 2 substituents or 1 substituent. Alternatively, the optionally substituted groups of the invention may be unsubstituted.

“Sulfonyl” refers to the divalent group $-S(O)_2-$.

“Tautomer” refers to alternate forms of a compound that differ in the position of a proton, such as enol-keto and imine-enamine tautomers, or the tautomeric forms of heteroaryl groups containing a ring atom attached to both a ring $-NH-$ moiety and a ring $=N-$ moiety such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles.

“Thiocyanate” refers to the group $-SCN$.

“Thiol” refers to the group $-SH$.

“Thione” refers to a thioketone ($=S$) group.

“Pharmaceutically acceptable” refers to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

“Pharmaceutically acceptable salt” refers to a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, lactic acid, maleic acid, malonic acid, mandelic acid, methanesulfonic acid, 2-naphthalenesulfonic acid, oleic acid, palmitic acid, propionic acid,

stearic acid, succinic acid, tartaric acid, p-toluenesulfonic acid, trimethylacetic acid, and the like, and salts formed when an acidic proton present in the parent compound is replaced by either a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as diethanolamine, triethanolamine, N-methylglucamine and the like. Also
5 included in this definition are ammonium and substituted or quaternized ammonium salts.

Representative non-limiting lists of pharmaceutically acceptable salts can be found in S.M. Berge et al., J. Pharma Sci., 66(1), 1-19 (1977), and Remington: The Science and Practice of Pharmacy, R. Hendrickson, ed., 21st edition, Lippincott, Williams & Wilkins, Philadelphia, PA, (2005), at p. 732, Table 38-5, both of which are hereby incorporated by reference herein.

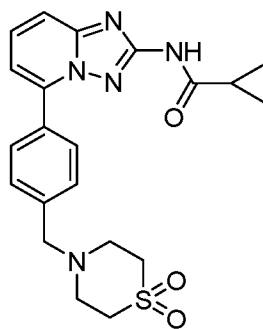
10 It is understood that combinations of chemical groups may be used and will be recognized by persons of ordinary skill in the art. For instance, the group "hydroxyalkyl" would refer to a hydroxyl group attached to an alkyl group. A great number of such combinations may be readily envisaged.

Provided are also compounds in which from 1 to n hydrogen atoms attached to a carbon
15 atom may be replaced by a deuterium atom or D, in which n is the number of hydrogen atoms in the molecule. As known in the art, the deuterium atom is a non-radioactive isotope of the hydrogen atom. Such compounds exhibit may increase resistance to metabolism, and thus may be useful for increasing the half-life of the compounds when administered to a mammal. See, e.g., Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism", Trends Pharmacol.
20 Sci., 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogen atoms have been replaced by deuterium.

Compounds

Filgotinib

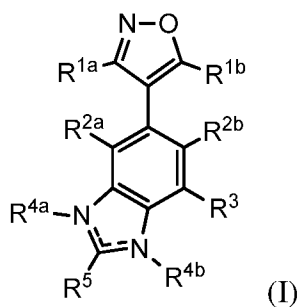
25 Filgotinib, also known as GLPG0634, is described in U.S. Patent No. 8,563,545, and has the following structure:



Solvates and polymorphs of filgotinib are described in International Application Publication No. WO 2015/117981. A metabolite of filgotinib is described in U.S. Patent No. 9,284,311. One specific pharmaceutically acceptable salt of filgotinib that may be used in the methods and compositions disclosed herein is the maleate salt of filgotinib.

BET inhibitors

In some embodiments, the BET inhibitor is a compound of Formula (I):



wherein:

one --- is a single bond and the other --- is a double bond;

R^{1a} and R^{1b} are each independently C₁₋₆ alkyl optionally substituted with from 1 to 5 R²⁰ groups;

R^{2a} and R^{2b} are each independently H or halo;

R³ is -B(OH)₂, -B(OR^a)₂, halo, -C(O)OR^a, -NHC(O)OR^a, -NHS(O)₂R^a, -S(O)₂NR^aR^b, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, amino, C₅₋₁₀ aryl, C₆₋₂₀ arylalkyl, C₁₋₁₀ heteroalkyl, C₅₋₁₀ heteroaryl, or C₆₋₂₀ heteroarylalkyl,

wherein each of C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, amino, C₅₋₁₀ aryl, C₆₋₂₀ arylalkyl, C₁₋₁₀ heteroalkyl, C₅₋₁₀ heteroaryl, or C₆₋₂₀ heteroarylalkyl is optionally substituted with from 1 to 5 R²⁰ groups;

one of R^{4a} and R^{4b} is selected from the group consisting of H and C₁₋₆ alkyl optionally substituted with from 1 to 5 R²⁰ groups, and the other is absent;

R⁵ is -C(O)OR^a, -NHC(O)OR^a, -NHS(O)₂R^a, or -S(O)₂NR^aR^b, H, C₁₋₁₀ alkyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ alkoxy, amino, C₅₋₁₀ aryl, C₆₋₂₀ arylalkyl, C₁₋₁₀ heteroalkyl, C₅₋₁₀ heteroaryl, or C₆₋₂₀ heteroarylalkyl,

wherein each of C₁₋₁₀ alkyl, C₁₋₁₀ haloalkyl, C₁₋₁₀ alkoxy, amino, C₅₋₁₀ aryl, C₆₋₂₀ arylalkyl, C₁₋₁₀ heteroalkyl, C₅₋₁₀ heteroaryl, and C₆₋₂₀ heteroarylalkyl is optionally substituted with from 1 to 5 R²⁰ groups;

each R^a and R^b is independently selected from the group consisting of H, C₁₋₁₀ alkyl, C₅₋₁₀ aryl, C₆₋₂₀ arylalkyl, C₁₋₁₀ heteroalkyl, C₅₋₁₀ heteroaryl, and C₆₋₂₀ heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R²⁰ groups; and

each R²⁰ is independently selected from the group consisting of acyl, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, amino, amido, amidino, C₅₋₁₀ aryl, C₆₋₂₀ arylalkyl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, guanidino, halo, C₁₋₁₀ haloalkyl, C₁₋₁₀ heteroalkyl, C₅₋₁₀ heteroaryl, C₆₋₂₀ heteroarylalkyl, hydroxy, hydrazino, imino, oxo, nitro, sulfinyl, sulfonic acid, sulfonyl, thiocyanate, thiol, and thione,

or a pharmaceutically acceptable salt thereof.

Compounds of Formula (I) (which include compounds of any of Formulae (Ia), (Ib), (Ic), (Id) and (Ie), described below) can include, independently, one or more of the following features. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments.

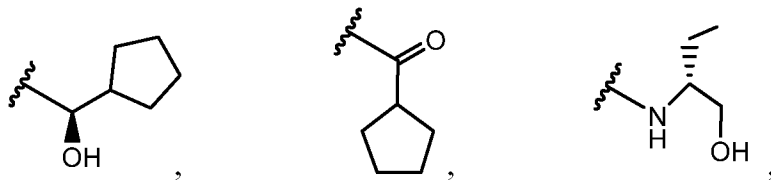
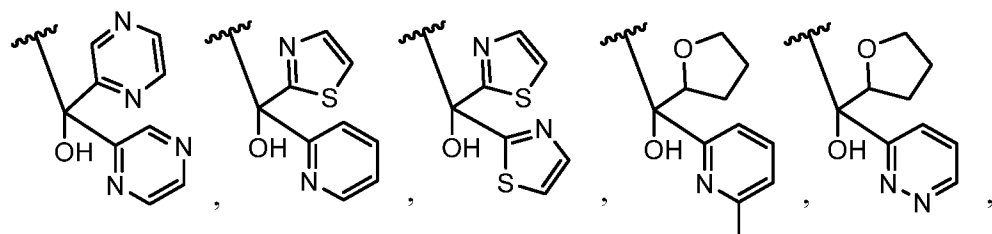
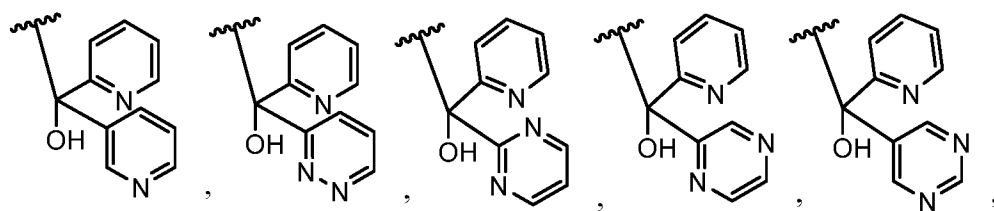
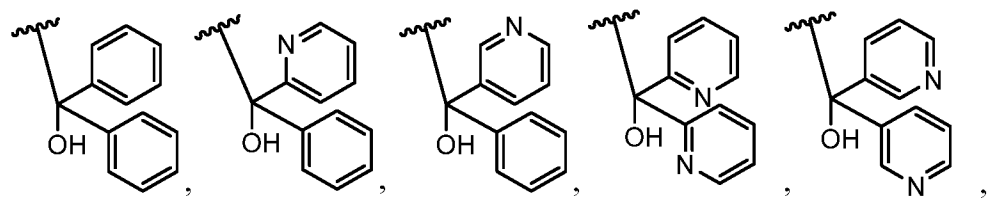
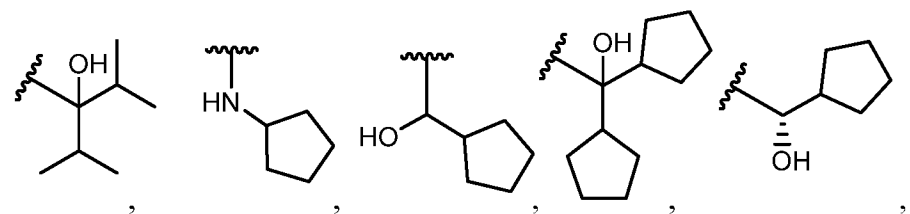
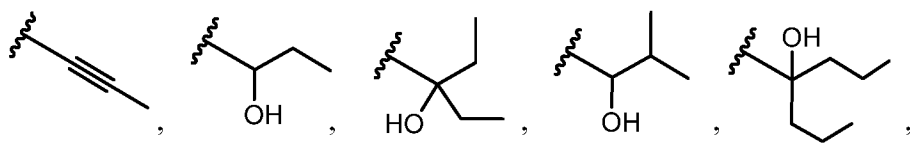
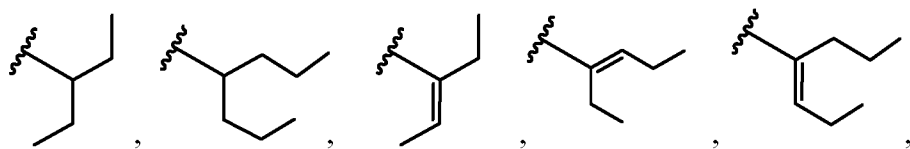
In some embodiments, R^{1a} and R^{1b} are each independently C₁₋₆ alkyl. In some embodiments, R^{1a} and R^{1b} are different, and in other compounds R^{1a} and R^{1b} are the same. In some compounds, R^{1a} and R^{1b} are each independently a C₁₋₆ alkyl optionally substituted with 1-5

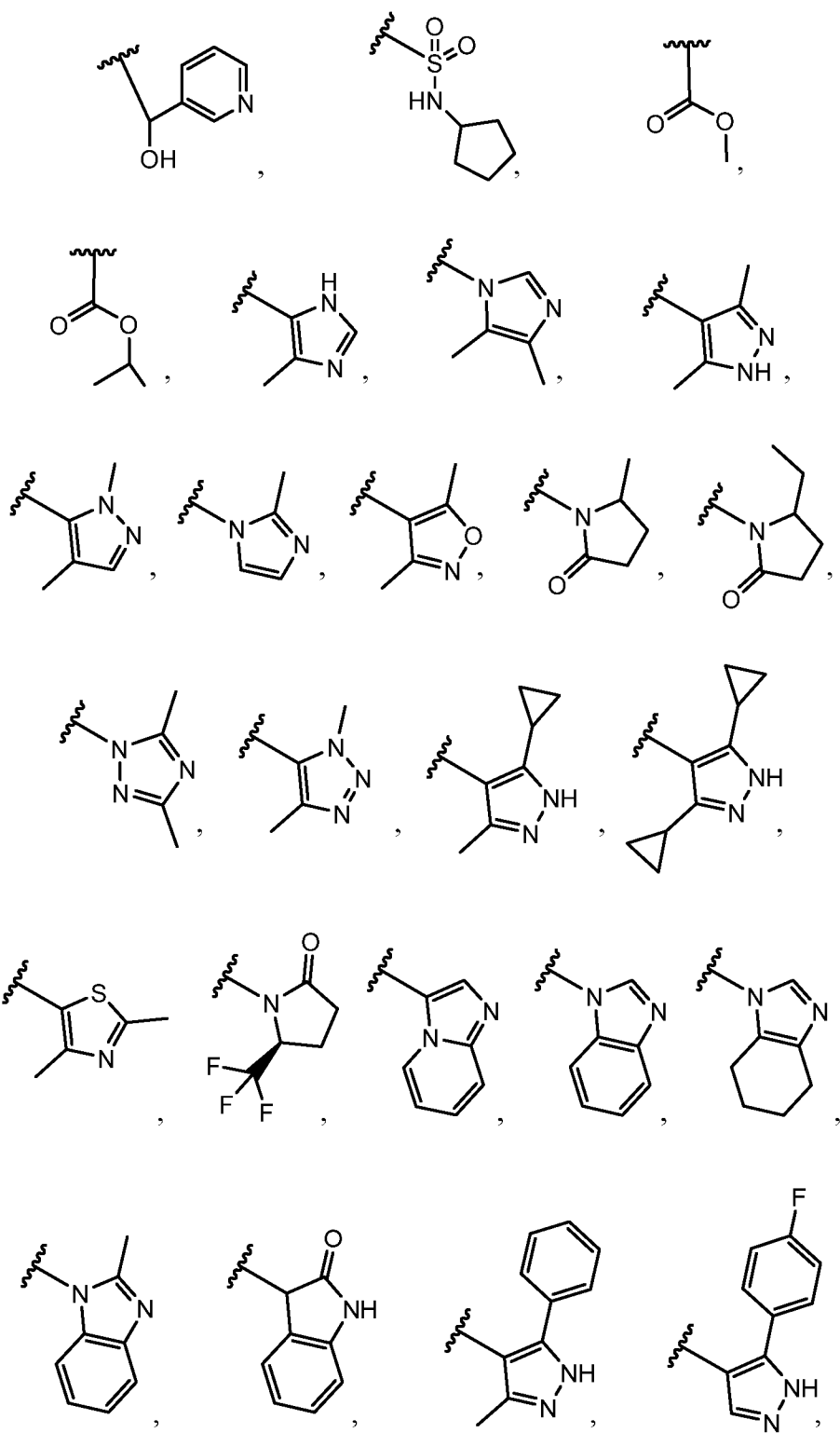
R^{20} groups. In some embodiments, R^{1a} and R^{1b} are both methyl. In some embodiments, one of R^{1a} and R^{1b} is a methyl and the other is a methyl substituted with a hydroxy. In some embodiments, R^{1a} and R^{1b} are both methyl substituted with a hydroxy. In some embodiments, one of R^{1a} and R^{1b} is a methyl and the other is a methyl substituted with an amine. In some compounds, R^{1a} and R^{1b} are both methyl substituted with an amine.

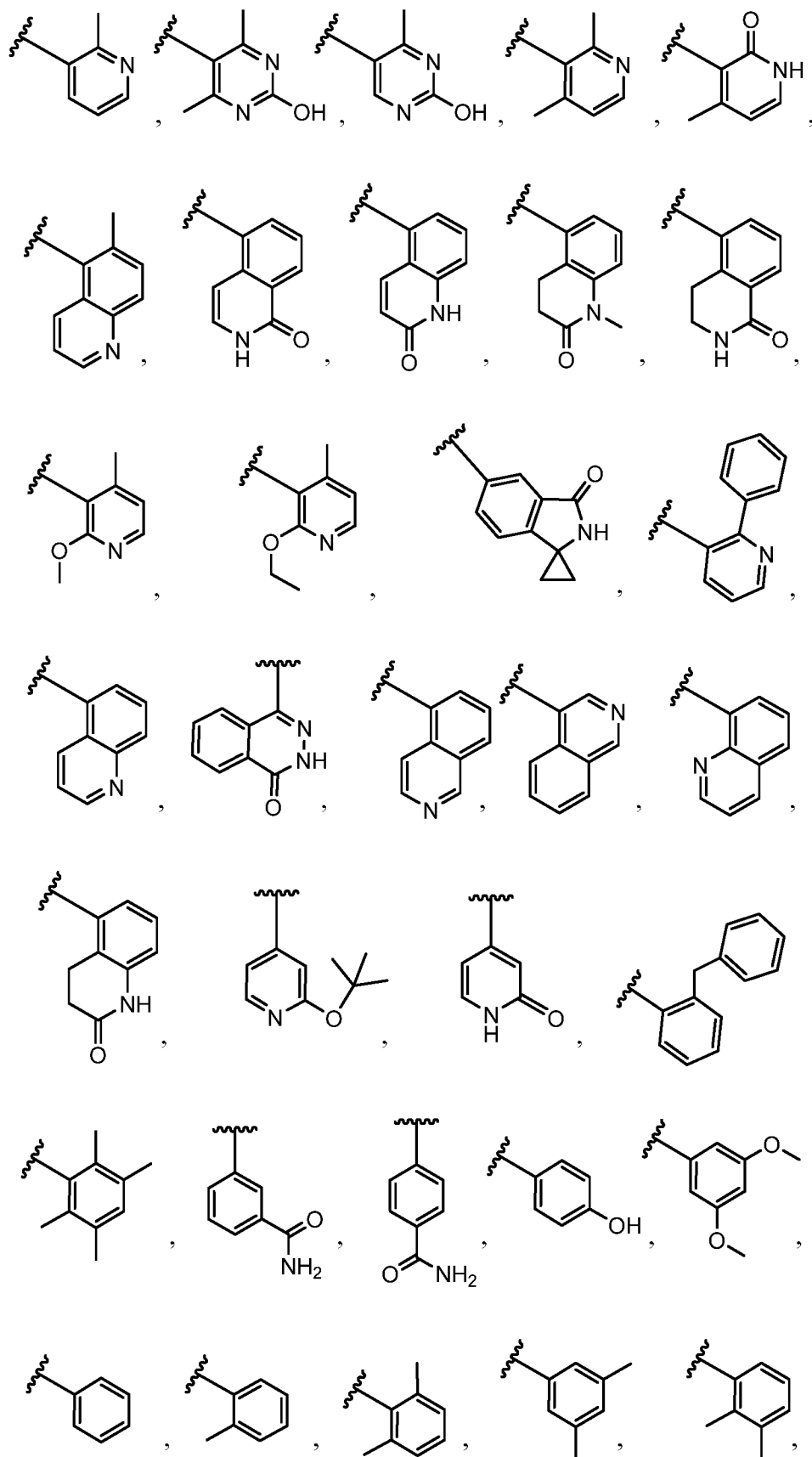
In some embodiments, R^{2a} and R^{2b} are both H. In some embodiments, R^{2a} and R^{2b} are both halo. In some embodiments, one of R^{2a} and R^{2b} is H and the other is halo. In some embodiments, the halo is -F or -Cl.

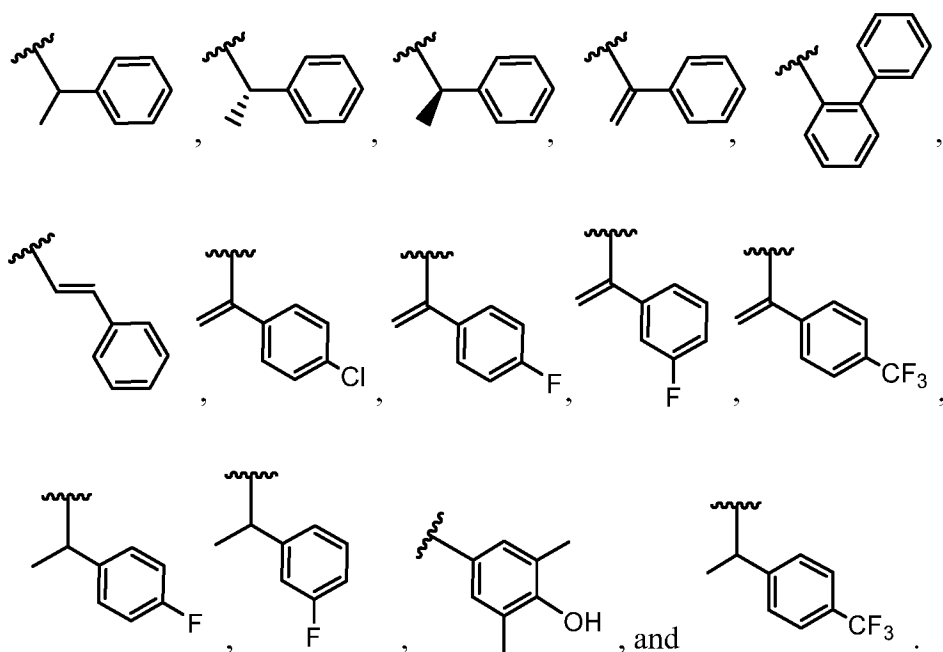
In some embodiments, R^3 is $-B(OH)_2$, $-B(OR^a)_2$, or halo. In some compounds, R^3 is -
 $C(O)OR^a$, $-NHC(O)OR^a$, $-NHS(O)_2R^a$, or $-S(O)_2NR^aR^b$ wherein R^a and R^b are described above.
 In some compounds, R^3 is $-C(O)OR^a$, $-NHC(O)OR^a$, $-NHS(O)_2R^a$, or
 $-S(O)_2NR^aR^b$, wherein each R^a and R^b is independently C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} heteroalkyl or
 C_{5-10} heteroaryl, each of which may be optionally substituted as described above. For example,
 in some embodiments, R^3 is $-C(O)OR^a$, $-NHC(O)OR^a$, $-NHS(O)_2R^a$, or $-S(O)_2NR^aR^b$, wherein
 each R^a and R^b is independently C_{5-10} aryl or C_{5-10} heteroaryl. In some embodiments, R^3 is
 selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl,
 C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl, each of which is optionally
 substituted with from 1 to 5 R^{20} groups, wherein R^{20} is described above. In some embodiments,
 R^3 is C_{1-10} alkyl, C_{1-10} alkoxy, or C_{1-10} heteroalkyl, each of which may be optionally substituted as
 described above. In some embodiments, the heteroalkyl is a heterocycloalkyl. In other
 embodiments, R^3 is C_{6-20} arylalkyl or C_{6-20} heteroarylalkyl, each of which may be optionally
 substituted as described above. In other embodiments, R^3 is C_{5-10} aryl, C_{6-20} arylalkyl, C_{5-10}
 heteroaryl, or C_{6-20} heteroarylalkyl, each of which may be optionally substituted as described
 above. In some embodiments, R^3 is amino optionally substituted as described above. For
 example, in some embodiments, R^3 is $-NH_2$, and in other embodiments, R^3 is $-NR^yR^z$, wherein R^y
 and R^z together with the nitrogen to which they are bonded form a C_{1-10} heteroalkyl or C_{5-10}
 heteroaryl, each of which may be optionally substituted as described above.

Other non-limiting examples of R^3 include the following:









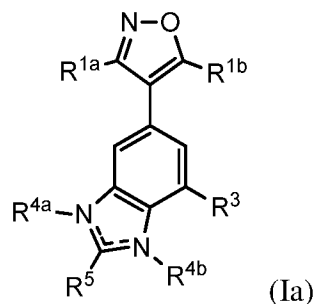
In some embodiments, one of R^{4a} or R^{4b} is H and the other is absent, that is, in some
 5 compounds R^{4a} is H and R^{4b} is absent, and in other compounds R^{4a} is absent and R^{4b} is H. In
 other embodiments, one of R^{4a} and R^{4b} is alkyl and the other is absent, that is, in some
 compounds R^{4a} is alkyl and R^{4b} is absent, and in other compounds R^{4a} is absent and R^{4b} is alkyl.
 In some embodiments, the alkyl is methyl.

In some embodiments, R^5 is $-C(O)OR^a$, $-NHC(O)OR^a$, $-NHS(O)_2R^a$, or $-S(O)_2NR^aR^b$,
 10 wherein R^a and R^b are described above. In some embodiments, R^5 is $-C(O)OR^a$, $-NHC(O)OR^a$, $-$
 $NHS(O)_2R^a$, or $-S(O)_2NR^aR^b$, wherein each R^a and R^b is independently C_{1-10} alkyl or C_{5-10} aryl,
 each of which may be optionally substituted as described above. For example, in some
 embodiments, R^5 is $-NHC(O)OR^a$, wherein R^a is methyl. In some embodiments, R^5 is $-$
 $NHS(O)_2R^a$, wherein R^a is C_{1-10} alkyl or C_{5-10} aryl, each of which may be optionally substituted
 15 as described above. For example, in some embodiments, R^5 is $-NHS(O)_2R^a$, wherein R^a is
 cyclopropyl. In some embodiments, R^5 is selected from the group consisting of H, C_{1-10} alkyl,
 C_{1-10} haloalkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl,
 and C_{6-20} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups,
 wherein R^{20} is described above. In some embodiments, R^5 is C_{1-10} alkyl optionally substituted as
 20 described above. In some compounds the C_{1-10} alkyl is a C_{1-10} cycloalkyl, e.g. cyclopropyl. In
 other embodiments, R^5 is amino optionally substituted as described above. For example, in some

embodiments, R^5 is $-NH_2$, and in other embodiments, R^5 is $-NR^yR^z$, wherein R^y is H and R^z is alkyl, e.g. cyclopropyl. In other embodiments, R^5 is alkoxy, e.g. methoxy.

In some embodiments, R^{1a} , R^{1b} , R^3 , R^{4a} , R^{4b} and R^5 are optionally substituted with from 1 to 5 (i.e. 1, 2, 3, 4 or 5) R^{20} groups as described above. In some embodiments, R^{1a} , R^{1b} , R^3 , R^{4a} , R^{4b} and R^5 are optionally substituted with 1, 2, or 3 R^{20} groups. In some embodiments, each R^{20} is independently selected from the group consisting of alkyl, alkoxy, amino, cyano, halo, haloalkyl, heteroalkyl, hydroxy, and sulfonyl. In some embodiments, each R^{20} is independently selected from the group consisting of aryl, alkylaryl, heteroaryl, and heteroalkylaryl. In some embodiments, R^{1a} , R^{1b} , R^3 , R^{4a} , R^{4b} and R^5 are not substituted. In some compounds, R^{20} is not substituted.

One subset of compounds of Formula (I) relates to compounds of Formula (Ia):



wherein:

--- is a single bond or a double bond;

R^{1a} and R^{1b} are each independently C_{1-6} alkyl optionally substituted with from 1 to 5 R^{20} groups;

R^3 is boronic acid, boronic acid ester, halo, $-C(O)OR^a$, $-NHC(O)OR^a$, $-NHS(O)_2R^a$, $-S(O)_2NR^aR^b$, C_{1-10} alkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl,

wherein each of C_{1-10} alkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl is optionally substituted with from 1 to 5 R^{20} groups;

one of R^{4a} and R^{4b} is selected from the group consisting of H and C_{1-6} alkyl optionally substituted with from 1 to 5 R^{20} groups, and the other is absent;

R^5 is $-C(O)OR^a$, $-NHC(O)OR^a$, $-NHS(O)_2R^a$, or $-S(O)_2NR^aR^b$, H, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, or

5 C_{6-20} heteroarylalkyl,

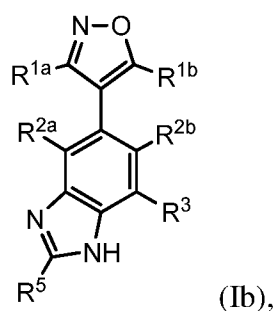
wherein each of C_{1-10} alkyl, C_{1-10} haloalkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl is optionally substituted with from 1 to 5 R^{20} groups;

each R^a and R^b is independently selected from the group consisting of H, C_{1-10} alkyl, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; and

each R^{20} is independently selected from the group consisting of acyl, C_{1-10} alkyl, C_{1-10} alkoxy, amino, amido, amidino, C_{5-10} aryl, C_{6-20} arylalkyl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, guanidino, halo, C_{1-10} haloalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, C_{6-20} heteroarylalkyl, hydroxy, hydrazino, imino, oxo, nitro, sulfinyl, sulfonic acid, sulfonyl, thiocyanate, thiol, and thione,

or a pharmaceutically acceptable salt thereof.

Another subset of compounds of Formula (I) relates to compounds of Formula (Ib):



20 wherein:

R^{1a} and R^{1b} are each independently C_{1-6} alkyl optionally substituted with from 1 to 5 R^{20} groups;

R^3 is $-B(OH)_2$, $-B(OR^a)_2$, halo, $-C(O)OR^a$, $-NHC(O)OR^a$, $-NHS(O)_2R^a$, $-S(O)_2NR^aR^b$, C_{1-10} alkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl,

wherein each of C_{1-10} alkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl is optionally substituted with from 1 to 5 R^{20} groups;

R^5 is $-C(O)OR^a$, $-NHC(O)OR^a$, $-NHS(O)_2R^a$, or $-S(O)_2NR^aR^b$, H, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl,

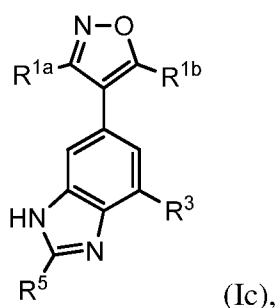
wherein each of C_{1-10} alkyl, C_{1-10} haloalkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl is optionally substituted with from 1 to 5 R^{20} groups;

each R^a and R^b is independently selected from the group consisting of H, C_{1-10} alkyl, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; and

each R^{20} is independently selected from the group consisting of acyl, C_{1-10} alkyl, C_{1-10} alkoxy, amino, amido, amidino, C_{5-10} aryl, C_{6-20} arylalkyl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, guanidino, halo, C_{1-10} haloalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, C_{6-20} heteroarylalkyl, hydroxy, hydrazino, imino, oxo, nitro, sulfinyl, sulfonic acid, sulfonyl, thiocyanate, thiol, and thione,

or a pharmaceutically acceptable salt thereof.

Another subset of compounds of Formula (I) relates to compounds of Formula (Ic):



wherein:

R^{1a} and R^{1b} are each independently C_{1-6} alkyl optionally substituted with from 1 to 5 R^{20} groups;

5 R^3 is $-B(OH)_2$, $-B(OR^a)_2$, halo, $-C(O)OR^a$, $-NHC(O)OR^a$, $-NHS(O)_2R^a$, $-S(O)_2NR^aR^b$, C_{1-10} alkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl,

10 wherein each of C_{1-10} alkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl is optionally substituted with from 1 to 5 R^{20} groups;

R^5 is $-C(O)OR^a$, $-NHC(O)OR^a$, $-NHS(O)_2R^a$, or $-S(O)_2NR^aR^b$, H, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl,

15 wherein each of C_{1-10} alkyl, C_{1-10} haloalkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl is optionally substituted with from 1 to 5 R^{20} groups;

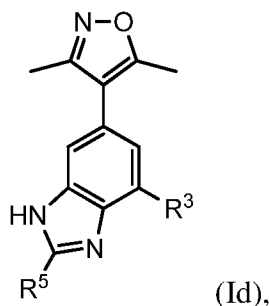
each R^a and R^b is independently selected from the group consisting of H, C_{1-10} alkyl, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; and

20 each R^{20} is independently selected from the group consisting of acyl, C_{1-10} alkyl, C_{1-10} alkoxy, amino, amido, amidino, C_{5-10} aryl, C_{6-20} arylalkyl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, guanidino, halo, C_{1-10} haloalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, C_{6-20}

heteroarylalkyl, hydroxy, hydrazino, imino, oxo, nitro, sulfinyl, sulfonic acid, sulfonyl, thiocyanate, thiol, and thione,

or a pharmaceutically acceptable salt thereof.

Another subset of compounds of Formula (I) relates to compounds of Formula (Id):



wherein:

R^3 is $-B(OH)_2$, $-B(OR^a)_2$, halo, $-C(O)OR^a$, $-NHC(O)OR^a$, $-NHS(O)_2R^a$, $-S(O)_2NR^aR^b$, C_{1-10} alkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl,

wherein each of C_{1-10} alkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl is optionally substituted with from 1 to 5 R^{20} groups;

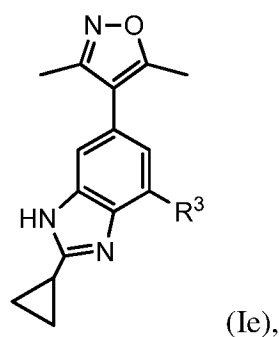
R^5 is $-C(O)OR^a$, $-NHC(O)OR^a$, $-NHS(O)_2R^a$, or $-S(O)_2NR^aR^b$, H, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl,

wherein each of C_{1-10} alkyl, C_{1-10} haloalkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl is optionally substituted with from 1 to 5 R^{20} groups;

each R^a and R^b is independently selected from the group consisting of H, C_{1-10} alkyl, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; and

each R^{20} is independently selected from the group consisting of acyl, C_{1-10} alkyl, C_{1-10} alkoxy, amino, amido, amidino, C_{5-10} aryl, C_{6-20} arylalkyl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, guanidino, halo, C_{1-10} haloalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, C_{6-20} heteroarylalkyl, hydroxy, hydrazino, imino, oxo, nitro, sulfinyl, sulfonic acid, sulfonyl, thiocyanate, thiol, and thione, or a pharmaceutically acceptable salt thereof.

Another subset of compounds of Formula (I) relates to compounds of Formula (Ie):



wherein:

R^3 is $-B(OH)_2$, $-B(OR^a)_2$, halo, $-C(O)OR^a$, $-NHC(O)OR^a$, $-NHS(O)_2R^a$, $-S(O)_2NR^aR^b$, C_{1-10} alkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl,

wherein each of C_{1-10} alkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl is optionally substituted with from 1 to 5 R^{20} groups;

each R^a and R^b is independently selected from the group consisting of H, C_{1-10} alkyl, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; and

each R^{20} is independently selected from the group consisting of acyl, C_{1-10} alkyl, C_{1-10} alkoxy, amino, amido, amidino, C_{5-10} aryl, C_{6-20} arylalkyl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, guanidino, halo, C_{1-10} haloalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, C_{6-20}

heteroarylalkyl, hydroxy, hydrazino, imino, oxo, nitro, sulfinyl, sulfonic acid, sulfonyl, thiocyanate, thiol, and thione,

or a pharmaceutically acceptable salt thereof.

5 In separate embodiments within each of the compounds described for Formulas I, Ia, Ib, and Ic, there is another embodiment comprising a compound in which R^{1a} and R^{1b} are each independently C_{1-6} alkyl, or a pharmaceutically acceptable salt thereof.

10 In separate embodiments within each of the compounds described for Formulas I, Ia, Ib, Ic, Id, and Ie, there is another embodiment comprising a compound in which R^3 is C_{1-10} alkyl, C_{1-10} alkoxy, or C_{1-10} heteroalkyl, each of which may be optionally substituted with from 1 to 5 R^{20} groups, or a pharmaceutically acceptable salt thereof.

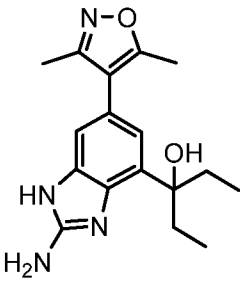
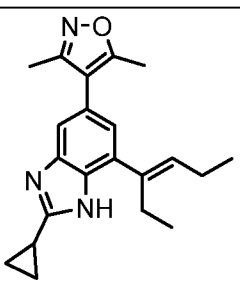
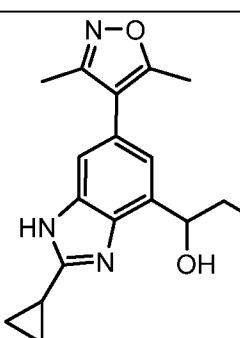
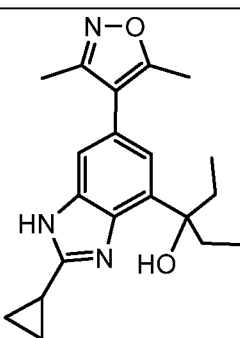
In separate embodiments within each of the compounds described for Formulas I, Ia, Ib, Ic, Id, and Ie, there is another embodiment comprising a compound in which R^3 is C_{5-10} aryl, C_{6-20} arylalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl, each of which may be optionally substituted with from 1 to 5 R^{20} groups, or a pharmaceutically acceptable salt thereof.

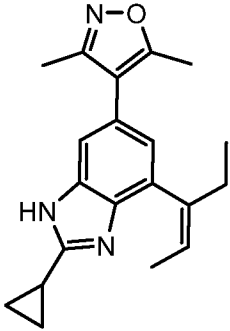
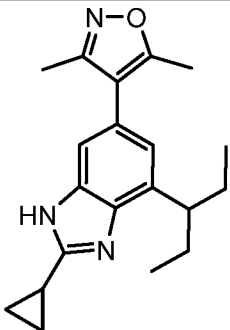
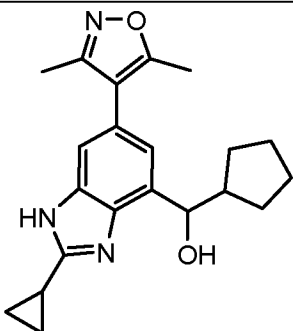
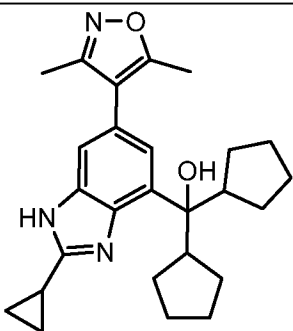
15 In separate embodiments within each of the compounds described for Formulas I, Ia, Ib, Ic, and Id, there is another embodiment comprising a compound in which R^5 is C_{1-10} alkyl, or a pharmaceutically acceptable salt thereof.

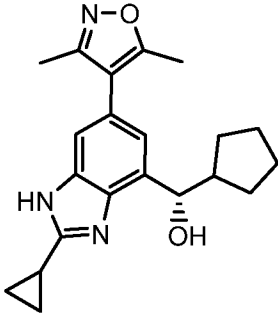
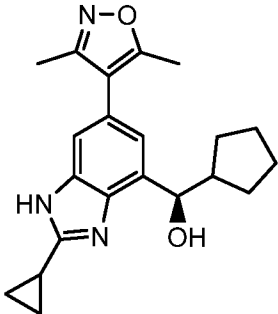
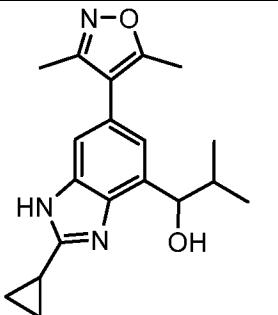
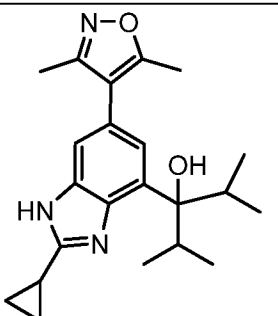
20 A separate embodiment comprises a compound of Formula Ie, as defined above, wherein R^3 is C_{1-10} alkyl, C_{1-10} alkoxy, or C_{1-10} heteroalkyl, each of which may be optionally substituted with from 1 to 5 R^{20} groups, or a pharmaceutically acceptable salt thereof.

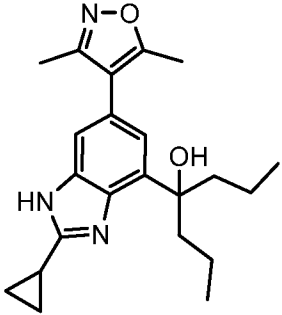
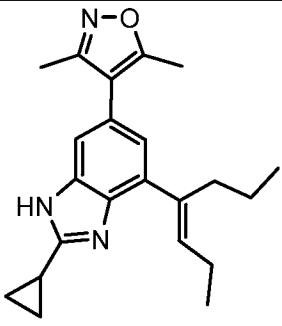
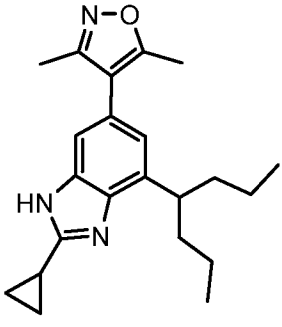
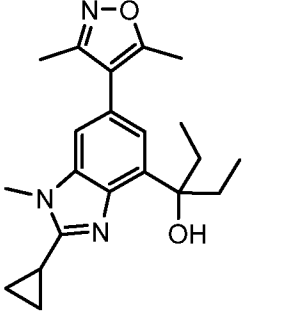
There is also provided a separate embodiment with each of the embodiments described herein comprising a compound of Formula Ie, further in which R^3 is C_{5-10} aryl, C_{6-20} arylalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl, each of which may be optionally substituted with from 1 to 5 R^{20} groups, or a pharmaceutically acceptable salt thereof.

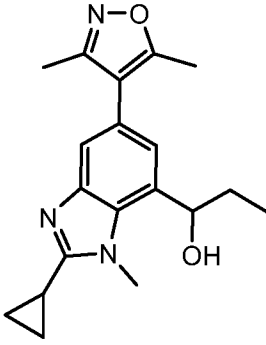
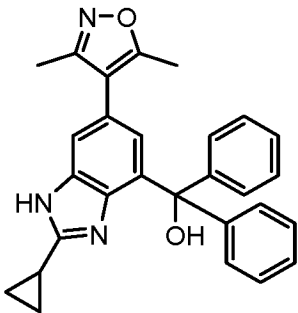
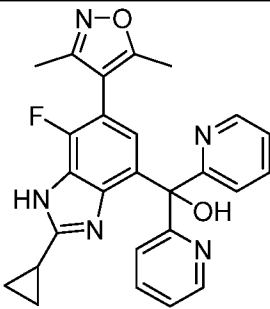
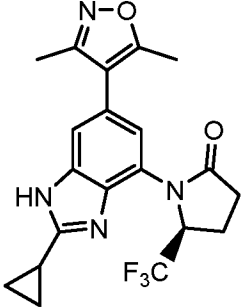
25 In some embodiments, the BET inhibitor is a compound selected from the table below, or a pharmaceutically acceptable salt thereof.

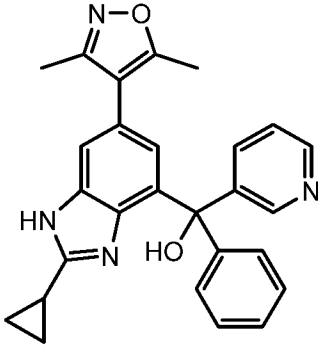
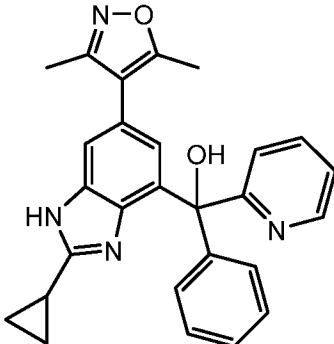
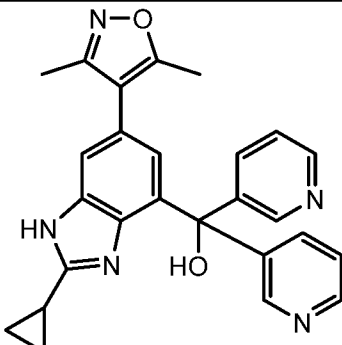
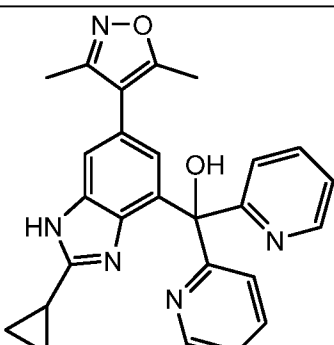
Compound #	Structure	Chemical Name
1		3-(2-amino-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)pentan-3-ol
2		(E)-4-(2-cyclopropyl-7-(hex-3-en-3-yl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
3		1-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)propan-1-ol
4		3-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)pentan-3-ol

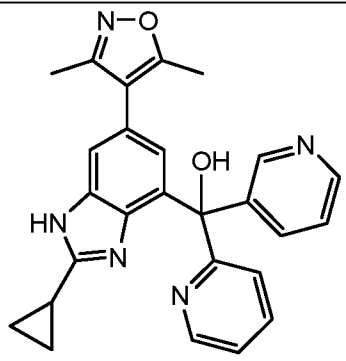
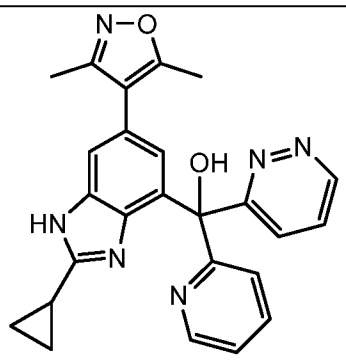
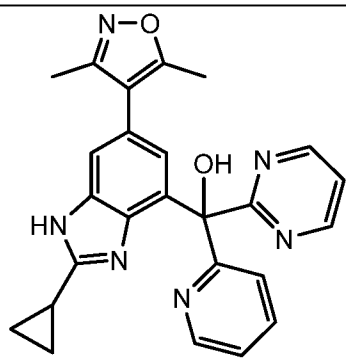
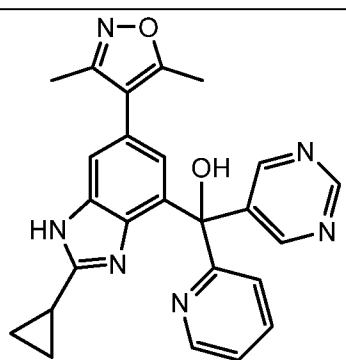
5		(Z)-4-(2-cyclopropyl-4-(pent-2-en-3-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
6		4-(2-cyclopropyl-4-(pentan-3-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
7		cyclopentyl(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)methanol
8		dicyclopentyl(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)methanol

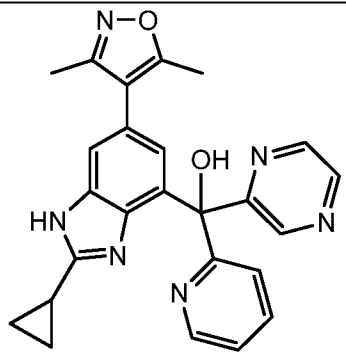
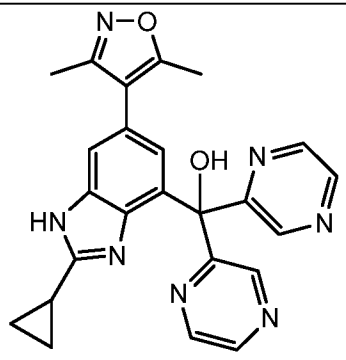
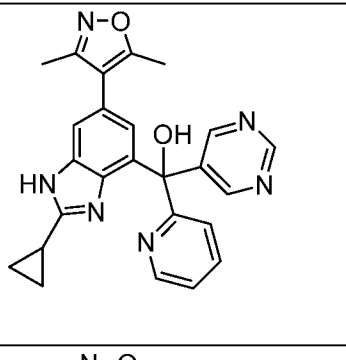
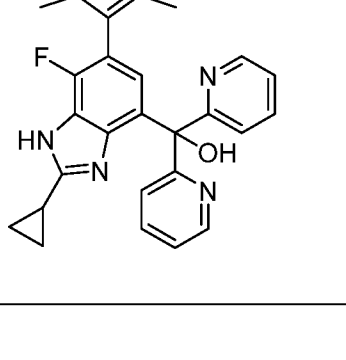
9		(S)-cyclopentyl(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)methanol
10		(R)-cyclopentyl(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)methanol
11		1-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)-2-methylpropan-1-ol
12		3-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)-2,4-dimethylpentan-3-ol

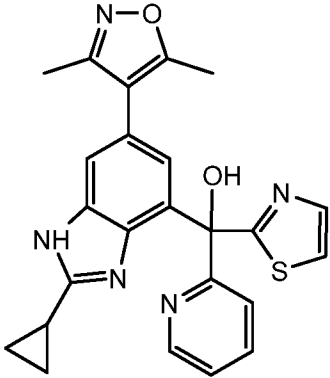
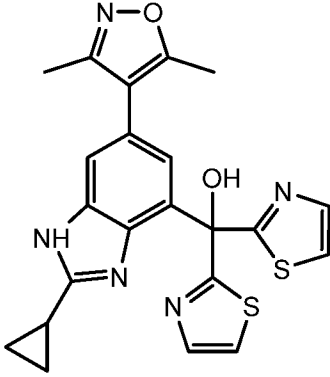
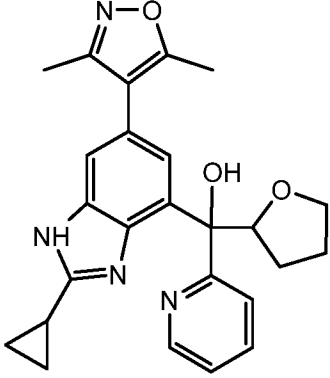
13		4-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)heptan-4-ol
14		(E)-4-(2-cyclopropyl-4-(hept-3-en-1-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
15		4-(2-cyclopropyl-4-(heptan-4-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
16		3-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-4-yl)pentan-3-ol

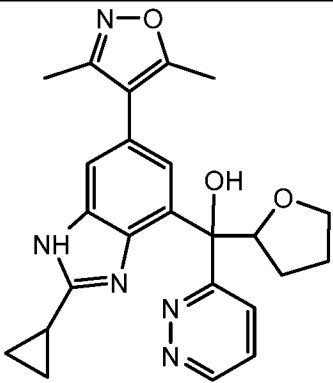
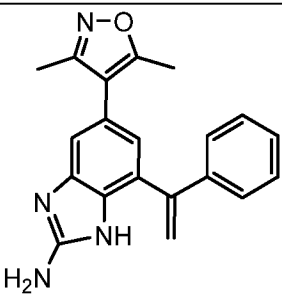
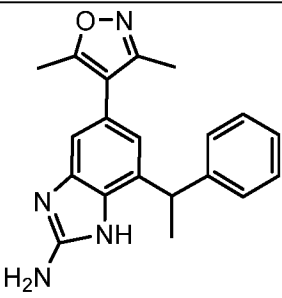
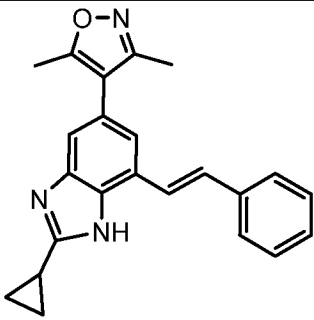
17		1-(2-cyclopropyl-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-7-yl)propan-1-ol
18		(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)diphenylmethanol
19		(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-7-fluoro-1H-benzo[d]imidazol-4-yl)di(pyridin-2-yl)methanol
20		(S)-1-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)-5-(trifluoromethyl)pyrrolidin-2-one

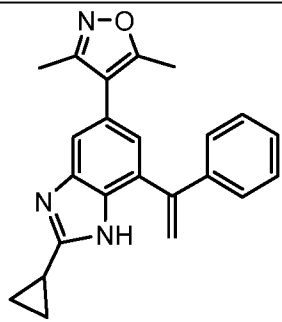
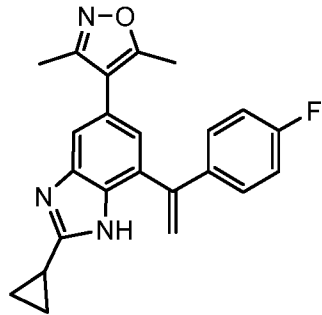
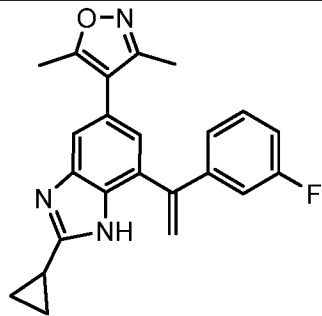
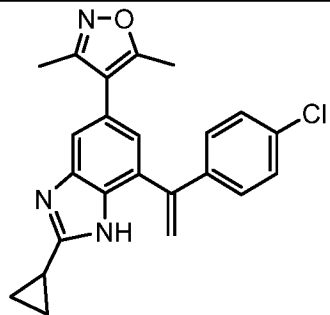
21		(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)(phenyl)(pyridin-3-yl)methanol
22		(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)(phenyl)(pyridin-2-yl)methanol
23		(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)di(pyridin-3-yl)methanol
24		(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)di(pyridin-2-yl)methanol

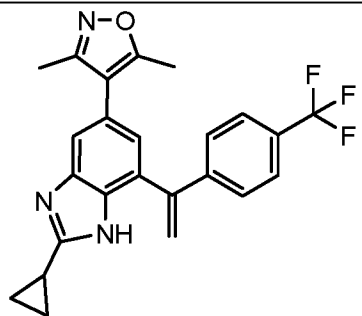
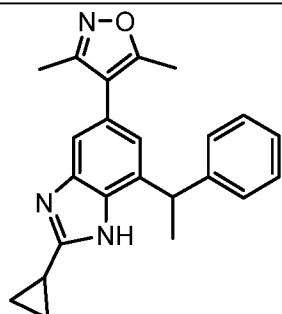
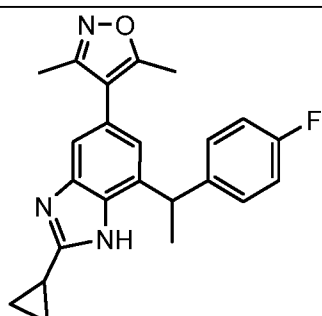
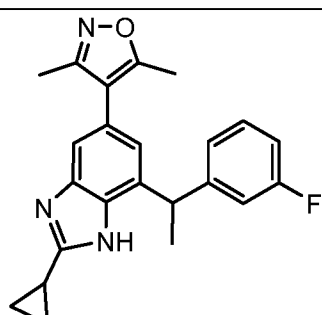
25		(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)(pyridin-3-yl)methanol
26		(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)(pyridazin-3-yl)(pyridin-2-yl)methanol
27		(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)(pyrimidin-2-yl)methanol
28		(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)(pyrimidin-5-yl)methanol

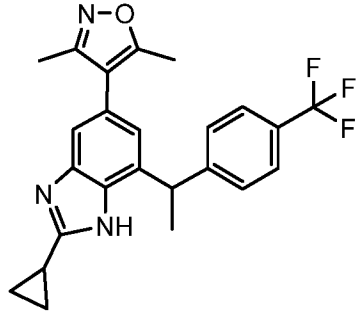
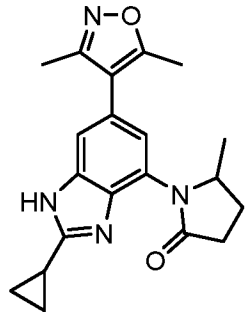
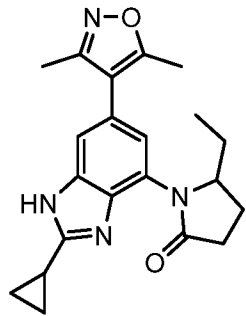
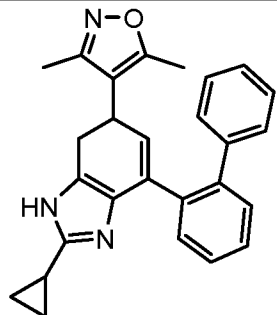
29		(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)methanol
30		(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)di(pyridin-2-yl)methanol
31		(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)(pyrimidin-5-yl)methanol
32		(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-7-fluoro-1H-benzo[d]imidazol-4-yl)di(pyridin-2-yl)methanol

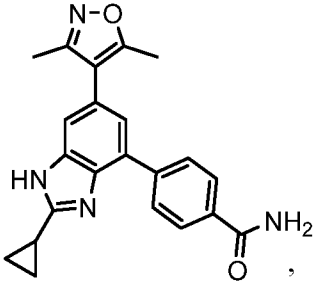
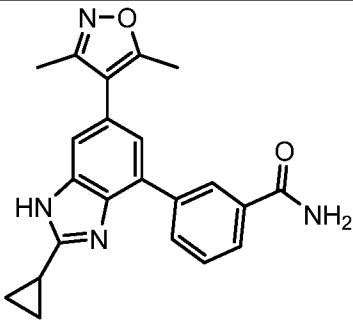
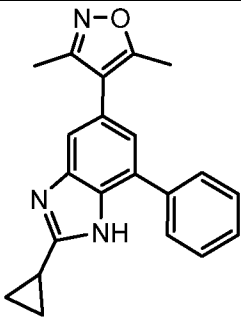
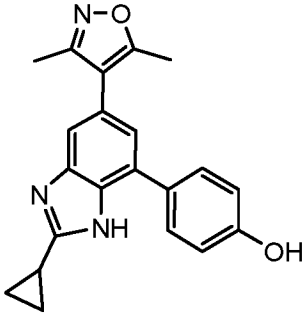
33		(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)(thiazol-2-yl)methanol
34		(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)di(thiazol-2-yl)methanol
35		(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)(6-methylpyridin-2-yl)(tetrahydrofuran-2-yl)methanol

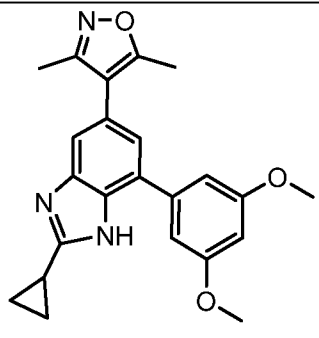
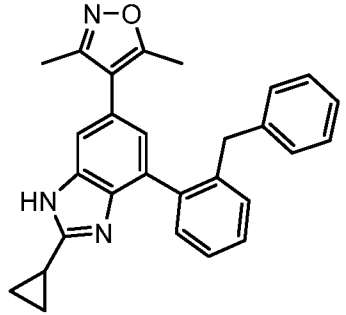
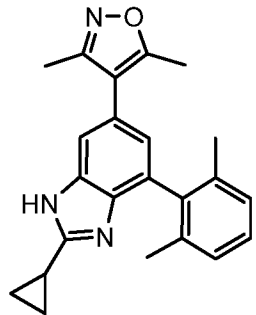
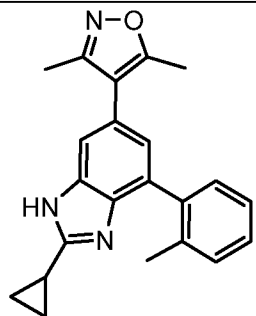
36		(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)(pyridazin-3-yl)(tetrahydrofuran-2-yl)methanol
37		5-(3,5-dimethylisoxazol-4-yl)-7-(1-phenylvinyl)-1H-benzo[d]imidazol-2-amine
38		5-(3,5-dimethylisoxazol-4-yl)-7-(1-phenylethyl)-1H-benzo[d]imidazol-2-amine
39		(E)-4-(2-cyclopropyl-7-styryl-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole

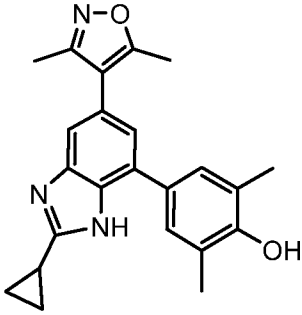
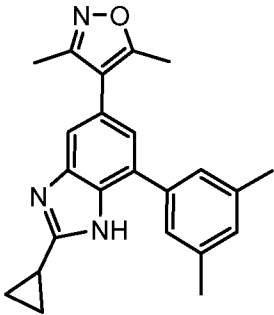
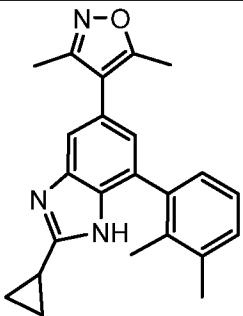
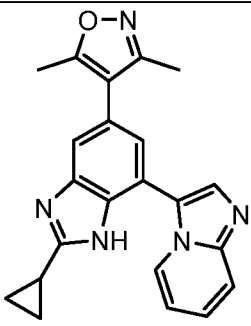
40		4-(2-cyclopropyl-7-(1-phenylvinyl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
41		4-(2-cyclopropyl-7-(1-(4-fluorophenyl)vinyl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
42		4-(2-cyclopropyl-7-(1-(3-fluorophenyl)vinyl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
43		4-(7-(1-(4-chlorophenyl)vinyl)-2-cyclopropyl-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole

44		4-(2-cyclopropyl-7-(1-(4-(trifluoromethyl)phenyl)vinyl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
45		4-(2-cyclopropyl-7-(1-phenylethyl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
46		4-(2-cyclopropyl-7-(1-(4-fluorophenyl)ethyl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
47		4-(2-cyclopropyl-7-(1-(3-fluorophenyl)ethyl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole

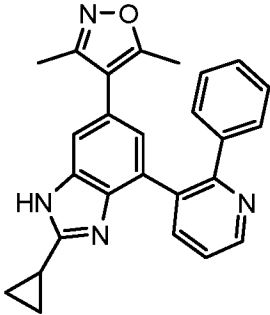
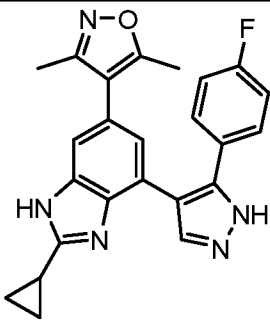
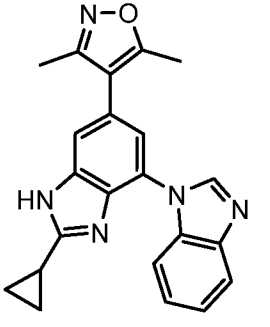
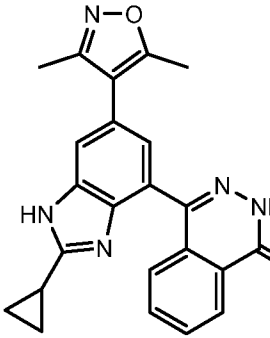
48		4-(2-cyclopropyl-7-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
49		1-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)-5-methylpyrrolidin-2-one
50		1-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)-5-ethylpyrrolidin-2-one
51		4-(4-([1,1'-biphenyl]-2-yl)-2-cyclopropyl-6,7-dihydro-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole

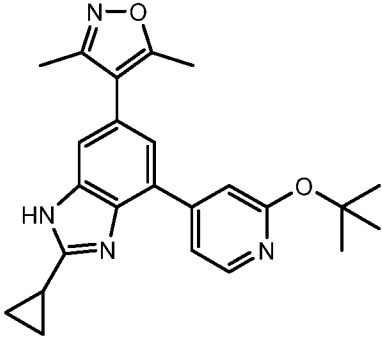
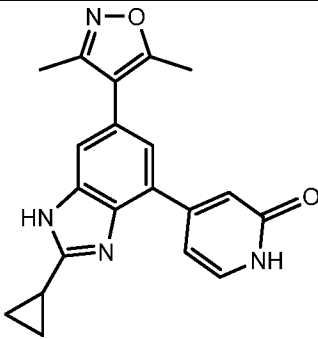
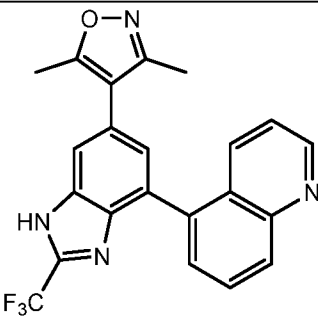
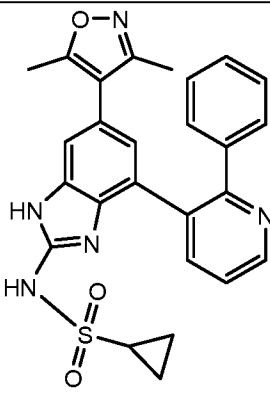
52		4-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)benzamide
53		3-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)benzamide
54		4-(2-cyclopropyl-7-phenyl-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
55		4-(2-cyclopropyl-5-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-7-yl)phenol

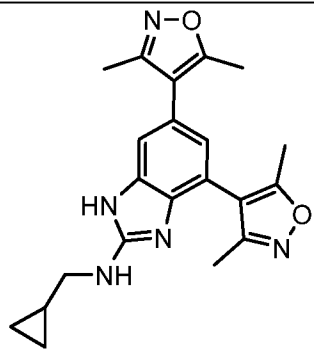
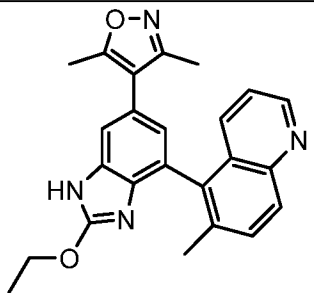
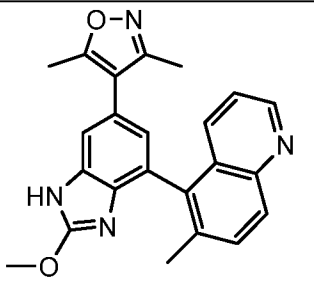
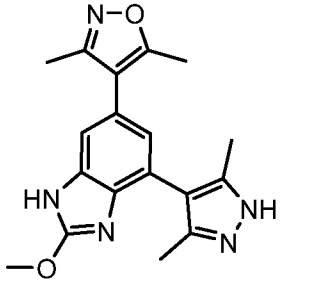
56	 Chemical structure of 4-(2-cyclopropyl-7-(3,5-dimethoxyphenyl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole. The structure features a 3,5-dimethylisoxazole ring connected at its 4-position to the 5-position of a 1H-benzo[d]imidazole ring. The 2-position of the benzimidazole ring is substituted with a cyclopropyl group, and the 7-position is substituted with a 3,5-dimethoxyphenyl group.	4-(2-cyclopropyl-7-(3,5-dimethoxyphenyl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
57	 Chemical structure of 4-(4-(2-benzylphenyl)-2-cyclopropyl-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole. The structure features a 3,5-dimethylisoxazole ring connected at its 4-position to the 6-position of a 1H-benzo[d]imidazole ring. The 2-position of the benzimidazole ring is substituted with a cyclopropyl group, and the 4-position is substituted with a 2-benzylphenyl group.	4-(4-(2-benzylphenyl)-2-cyclopropyl-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
58	 Chemical structure of 4-(2-cyclopropyl-4-(2,6-dimethylphenyl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole. The structure features a 3,5-dimethylisoxazole ring connected at its 4-position to the 6-position of a 1H-benzo[d]imidazole ring. The 2-position of the benzimidazole ring is substituted with a cyclopropyl group, and the 4-position is substituted with a 2,6-dimethylphenyl group.	4-(2-cyclopropyl-4-(2,6-dimethylphenyl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
59	 Chemical structure of 4-(2-cyclopropyl-4-(o-tolyl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole. The structure features a 3,5-dimethylisoxazole ring connected at its 4-position to the 6-position of a 1H-benzo[d]imidazole ring. The 2-position of the benzimidazole ring is substituted with a cyclopropyl group, and the 4-position is substituted with an o-tolyl group.	4-(2-cyclopropyl-4-(o-tolyl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole

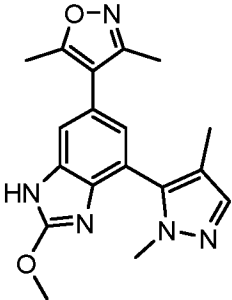
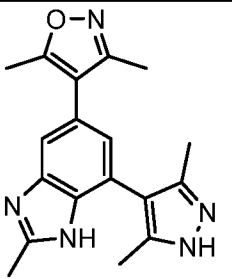
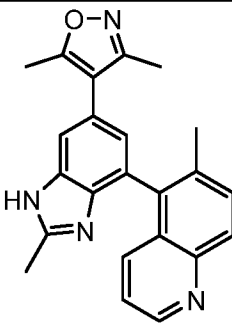
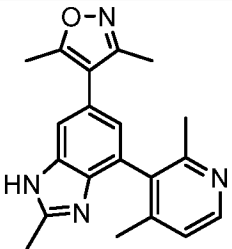
60		4-(2-cyclopropyl-5-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-7-yl)-2,6-dimethylphenol
61		4-(2-cyclopropyl-7-(3,5-dimethylphenyl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
62		4-(2-cyclopropyl-7-(2,3-dimethylphenyl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
63		4-(2-cyclopropyl-7-(imidazo[1,2-a]pyridin-3-yl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole

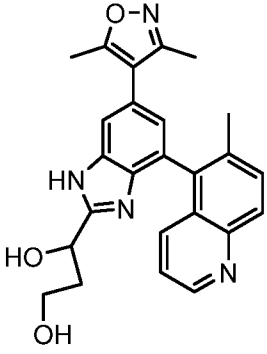
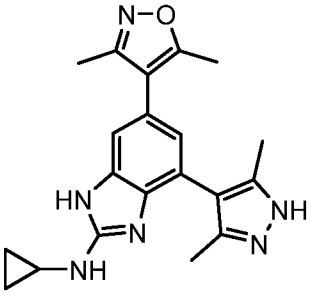
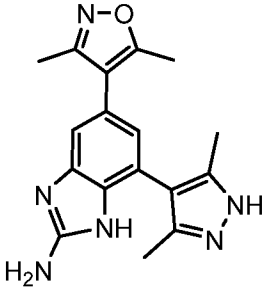
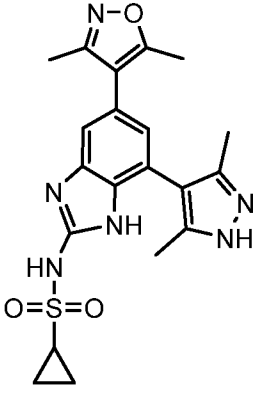
64		4-(2-cyclopropyl-7-(quinolin-8-yl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
65		4-(2-cyclopropyl-7-(quinolin-5-yl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
66		4-(2-cyclopropyl-7-(isoquinolin-5-yl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
67		4-(2-cyclopropyl-7-(isoquinolin-4-yl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole

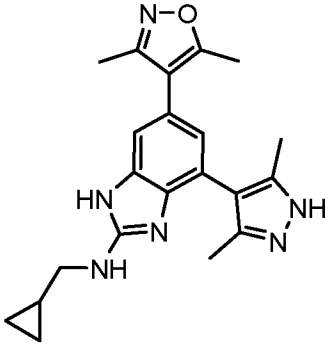
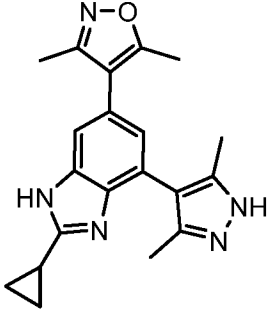
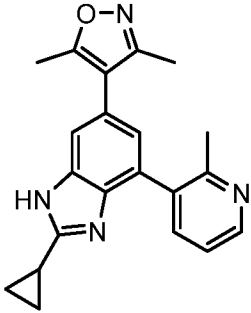
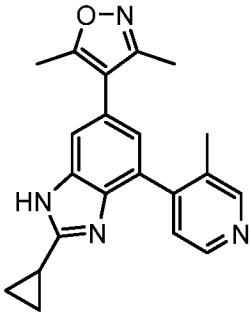
68		4-(2-cyclopropyl-4-(2-phenylpyridin-3-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
69		4-(2-cyclopropyl-4-(5-(4-fluorophenyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
70		4-(2'-cyclopropyl-1'H-[1,4'-bibenzo[d]imidazol]-6'-yl)-3,5-dimethylisoxazole
71		4-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)phthalazin-1(2H)-one

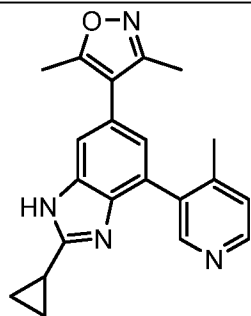
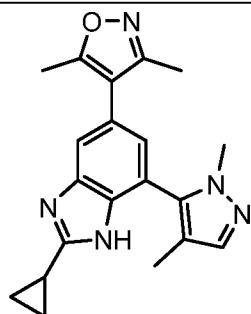
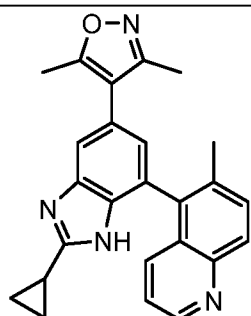
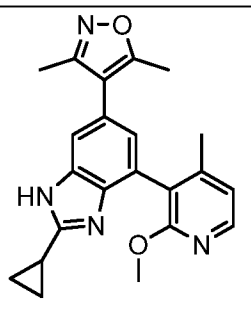
72		4-(4-(2-(tert-butoxy)pyridin-4-yl)-2-cyclopropyl-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
73		4-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)pyridin-2(1H)-one
74		3,5-dimethyl-4-(4-(quinolin-5-yl)-2-(trifluoromethyl)-1H-benzo[d]imidazol-6-yl)isoxazole
75		N-(6-(3,5-dimethylisoxazol-4-yl)-4-(2-phenylpyridin-3-yl)-1H-benzo[d]imidazol-2-yl)cyclopropanesulfonamide

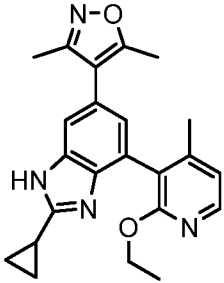
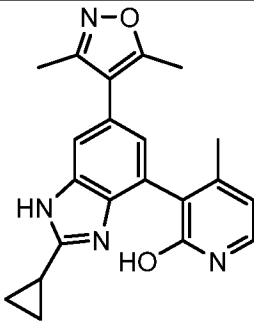
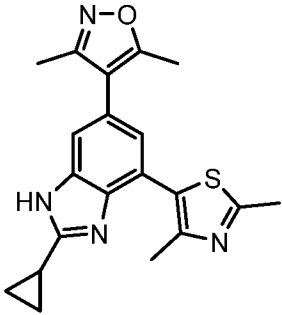
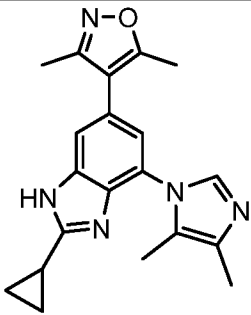
76		N-(cyclopropylmethyl)-4,6-bis(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2-amine
77		4-(2-ethoxy-4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
78		4-(2-methoxy-4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
79		4-(4-(3,5-dimethyl-1H-pyrazol-4-yl)-2-methoxy-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole

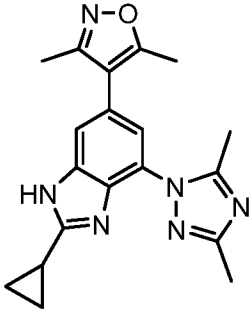
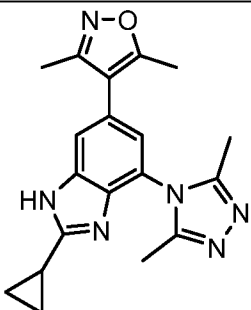
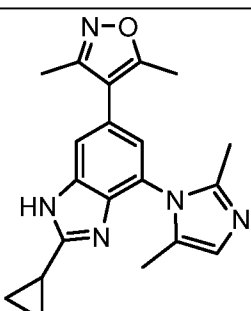
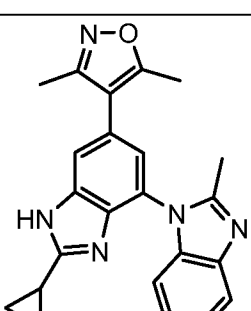
80		4-(4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-methoxy-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
81		4-(7-(3,5-dimethyl-1H-pyrazol-4-yl)-2-methyl-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
82		3,5-dimethyl-4-(2-methyl-4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-6-yl)isoxazole
83		4-(4-(2,4-dimethylpyridin-3-yl)-2-methyl-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole

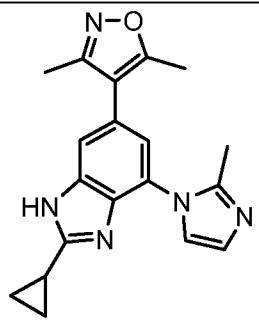
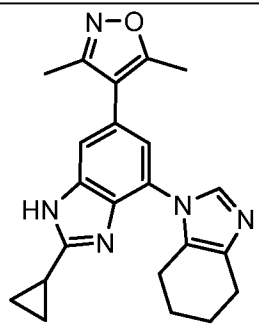
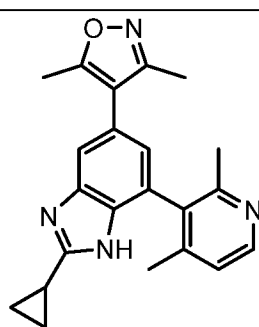
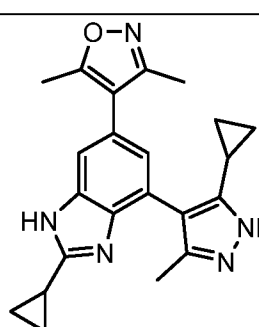
84		1-(6-(3,5-dimethylisoxazol-4-yl)-4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2-yl)propane-1,3-diol
85		N-cyclopropyl-4-(3,5-dimethyl-1H-pyrazol-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2-amine
86		7-(3,5-dimethyl-1H-pyrazol-4-yl)-5-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2-amine
87		N-(7-(3,5-dimethyl-1H-pyrazol-4-yl)-5-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2-yl)cyclopropanesulfonamide

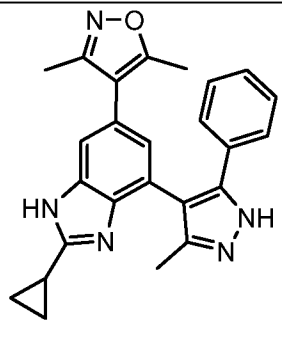
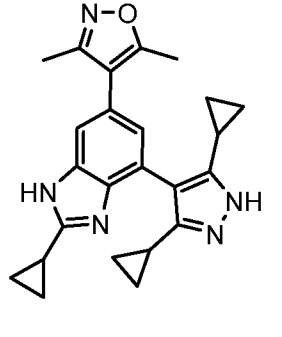
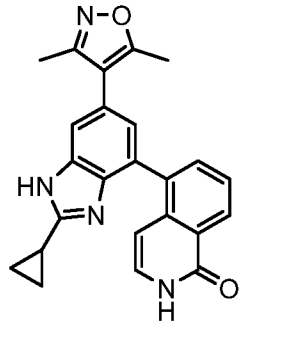
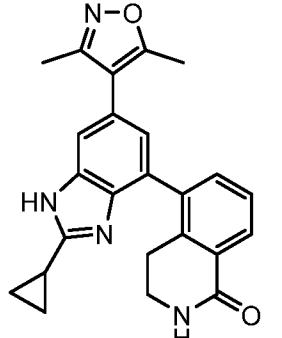
88		N-(cyclopropylmethyl)-4-(3,5-dimethyl-1H-pyrazol-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2-amine
89		4-(2-cyclopropyl-4-(3,5-dimethyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
90		4-(2-cyclopropyl-4-(2-methylpyridin-3-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
91		4-(2-cyclopropyl-4-(3-methylpyridin-4-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole

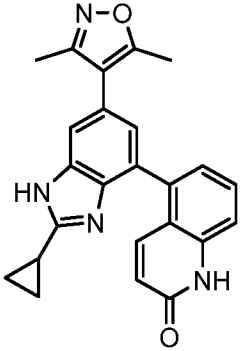
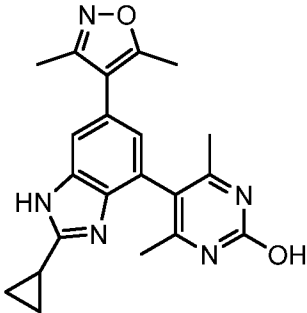
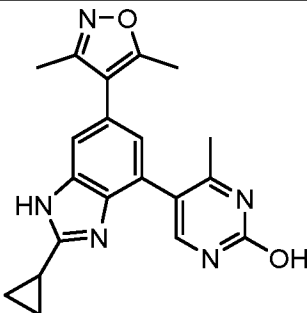
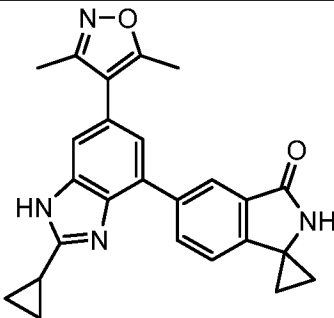
92	 Chemical structure of 4-(2-cyclopropyl-4-(4-methylpyridin-3-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole. The structure features a central benzene ring substituted with a 3,5-dimethylisoxazole-4-yl group at the top, a 4-methylpyridin-3-yl group at the right, and a 2-cyclopropyl-1H-imidazol-5-yl group at the bottom.	4-(2-cyclopropyl-4-(4-methylpyridin-3-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
93	 Chemical structure of 4-(2-cyclopropyl-7-(1,4-dimethyl-1H-pyrazol-5-yl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole. The structure features a central benzene ring substituted with a 3,5-dimethylisoxazole-4-yl group at the top, a 1,4-dimethyl-1H-pyrazol-5-yl group at the right, and a 2-cyclopropyl-1H-imidazol-5-yl group at the bottom.	4-(2-cyclopropyl-7-(1,4-dimethyl-1H-pyrazol-5-yl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
94	 Chemical structure of 4-(2-cyclopropyl-7-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole. The structure features a central benzene ring substituted with a 3,5-dimethylisoxazole-4-yl group at the top, a 6-methylquinolin-5-yl group at the right, and a 2-cyclopropyl-1H-imidazol-5-yl group at the bottom.	4-(2-cyclopropyl-7-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
95	 Chemical structure of 4-(2-cyclopropyl-4-(2-methoxy-4-methylpyridin-3-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole. The structure features a central benzene ring substituted with a 3,5-dimethylisoxazole-4-yl group at the top, a 2-methoxy-4-methylpyridin-3-yl group at the right, and a 2-cyclopropyl-1H-imidazol-5-yl group at the bottom.	4-(2-cyclopropyl-4-(2-methoxy-4-methylpyridin-3-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole

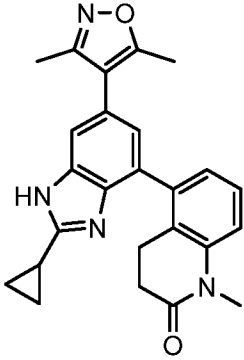
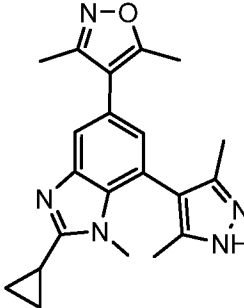
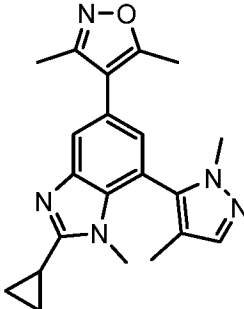
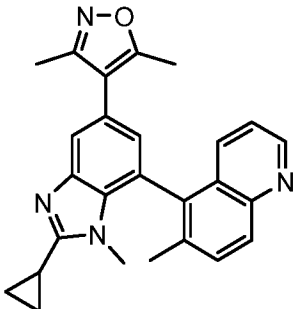
96		4-(2-cyclopropyl-4-(2-ethoxy-4-methylpyridin-3-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
97		3-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)-4-methylpyridin-2-ol
98		4-(2-cyclopropyl-4-(2,4-dimethylthiazol-5-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
99		4-(2-cyclopropyl-4-(4,5-dimethyl-1H-imidazol-1-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole

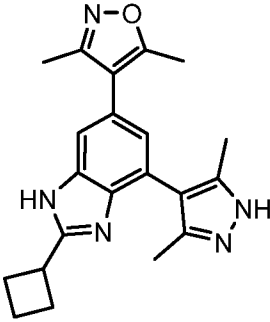
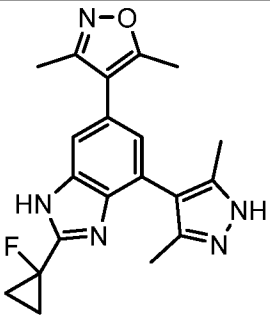
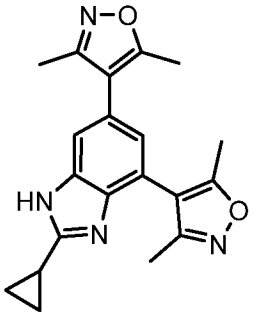
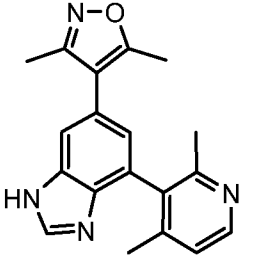
100		4-(2-cyclopropyl-4-(3,5-dimethyl-1H-1,2,4-triazol-1-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
101		4-(2-cyclopropyl-4-(3,5-dimethyl-4H-1,2,4-triazol-4-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
102		4-(2-cyclopropyl-4-(2,5-dimethyl-1H-imidazol-1-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
103		4-(2'-cyclopropyl-2-methyl-1'H-[1,4'-bibenzo[d]imidazol]-6'-yl)-3,5-dimethylisoxazole

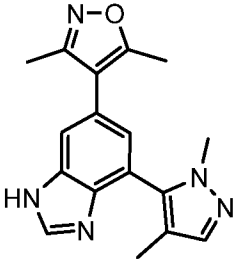
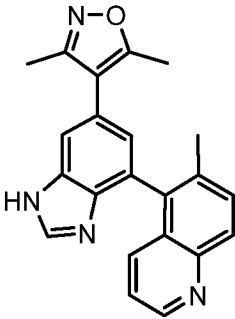
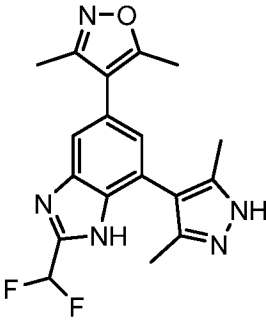
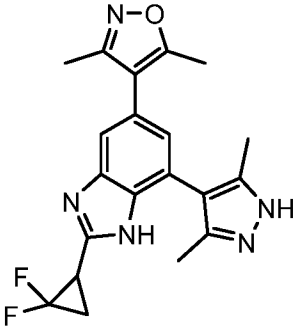
104		4-(2-cyclopropyl-4-(2-methyl-1H-imidazol-1-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
105		4-(2'-cyclopropyl-4,5,6,7-tetrahydro-1'H-[1,4'-bibenzo[d]imidazol]-6'-yl)-3,5-dimethylisoxazole
106		4-(2-cyclopropyl-7-(2,4-dimethylpyridin-3-yl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
107		4-(2-cyclopropyl-4-(5-cyclopropyl-3-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole

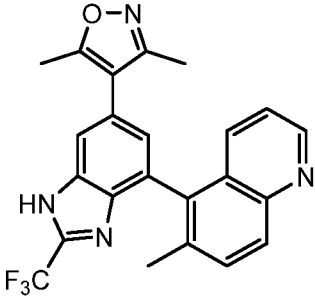
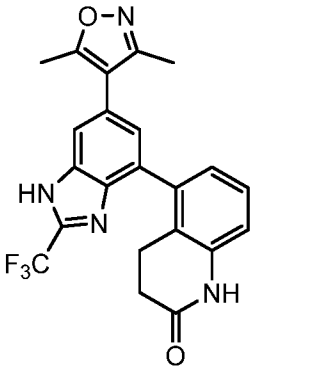
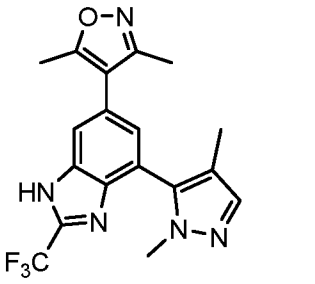
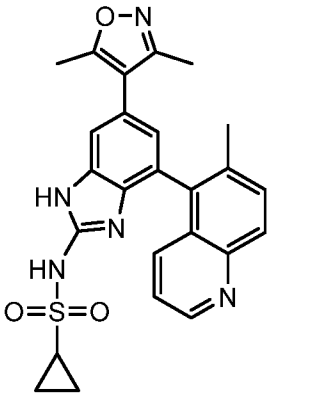
108		4-(2-cyclopropyl-4-(3-methyl-5-phenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
109		4-(2-cyclopropyl-4-(3,5-dicyclopropyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
110		5-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)isoquinolin-1(2H)-one
111		5-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)-3,4-dihydroisoquinolin-1(2H)-one

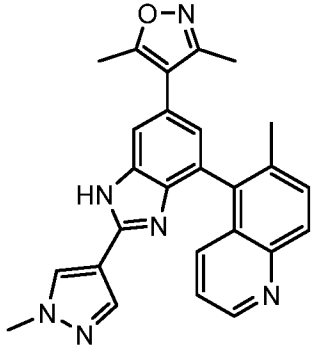
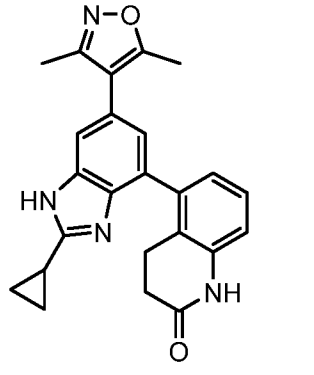
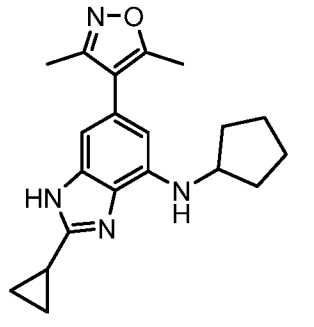
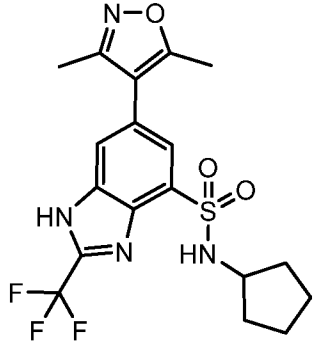
112		5-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)quinolin-2(1H)-one
113		5-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)-4,6-dimethylpyrimidin-2-ol
114		5-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)-4-methylpyrimidin-2-ol
115		5'-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)spiro[cyclopropane-1,1'-isoindolin]-3'-one

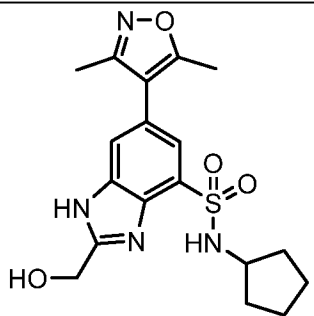
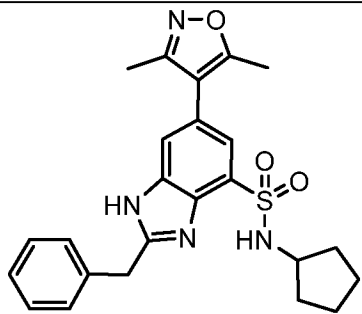
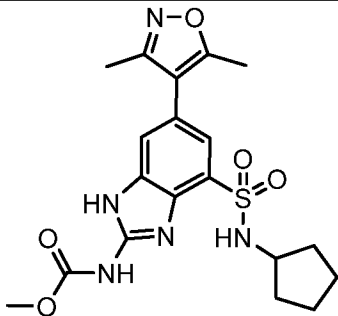
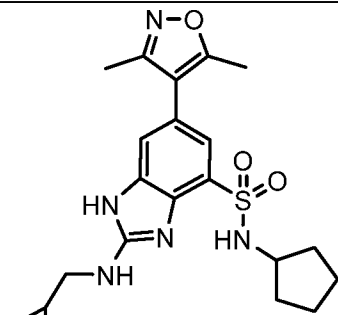
116		5-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)-1-methyl-3,4-dihydroquinolin-2(1H)-one
117		4-(2-cyclopropyl-7-(3,5-dimethyl-1H-pyrazol-4-yl)-1-methyl-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
118		4-(2-cyclopropyl-7-(1,4-dimethyl-1H-pyrazol-5-yl)-1-methyl-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
119		4-(2-cyclopropyl-1-methyl-7-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole

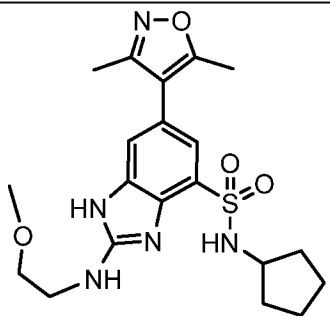
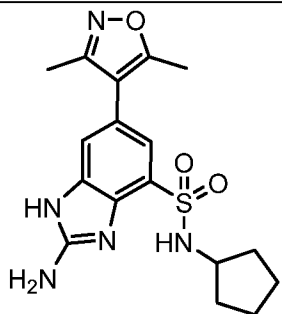
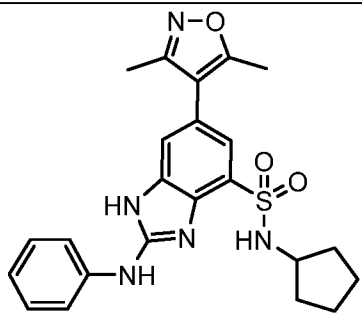
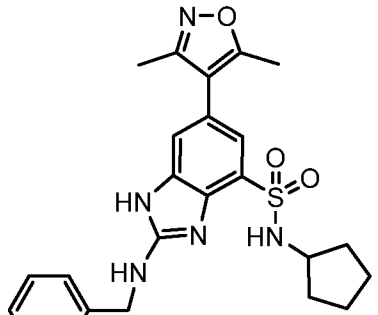
120		4-(2-cyclobutyl-4-(3,5-dimethyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
121		4-(4-(3,5-dimethyl-1H-pyrazol-4-yl)-2-(1-fluorocyclopropyl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
122		4,4'-(2-cyclopropyl-1H-benzo[d]imidazole-4,6-diyl)bis(3,5-dimethylisoxazole)
123		4-(4-(2,4-dimethylpyridin-3-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole

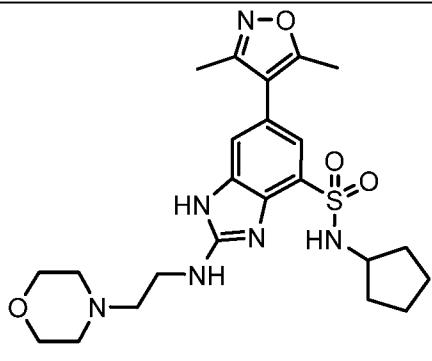
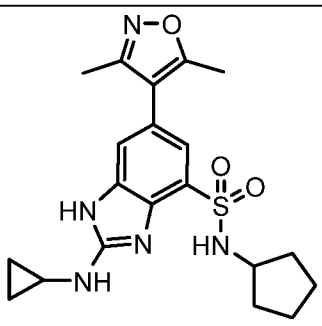
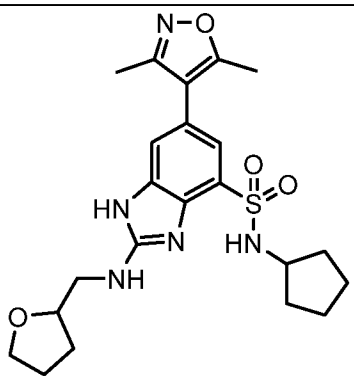
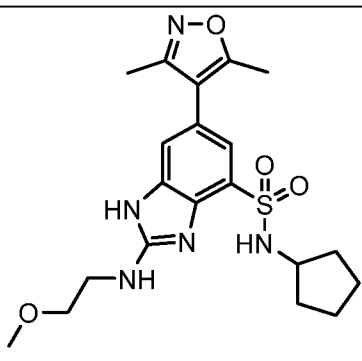
124		4-(4-(1,4-dimethyl-1H-pyrazol-5-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
125		3,5-dimethyl-4-(4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-6-yl)isoxazole
126		4-(2-(difluoromethyl)-7-(3,5-dimethyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole
127		4-(2-(2,2-difluorocyclopropyl)-7-(3,5-dimethyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole

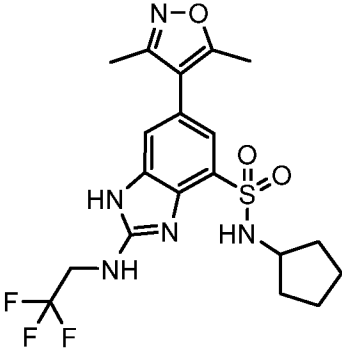
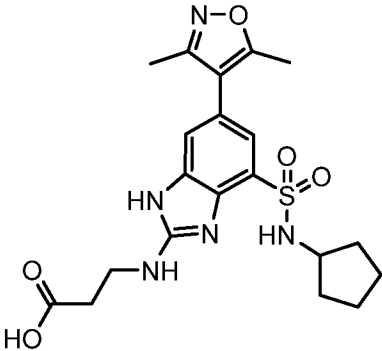
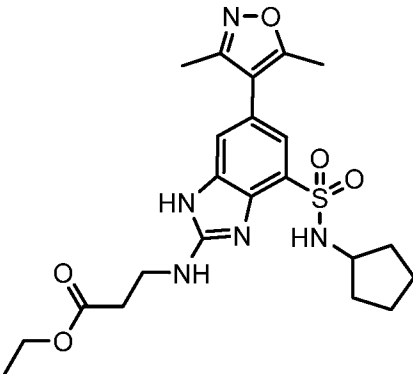
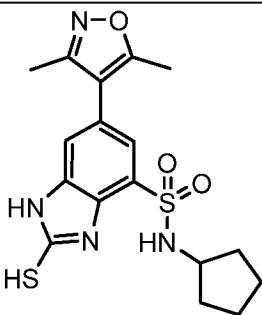
128		3,5-dimethyl-4-(4-(6-methylquinolin-5-yl)-2-(trifluoromethyl)-1H-benzo[d]imidazol-6-yl)isoxazole
129		5-(6-(3,5-dimethylisoxazol-4-yl)-2-(trifluoromethyl)-1H-benzo[d]imidazol-4-yl)-3,4-dihydroquinolin-2(1H)-one
130		4-(4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-(trifluoromethyl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole
131		N-(6-(3,5-dimethylisoxazol-4-yl)-4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2-yl)cyclopropanesulfonamide

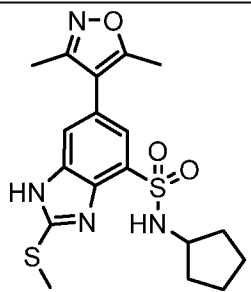
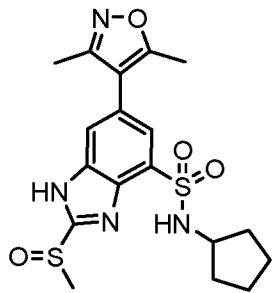
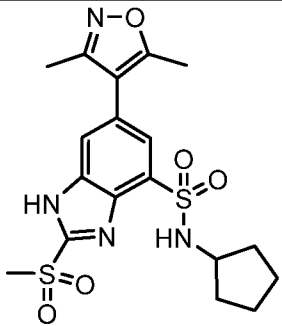
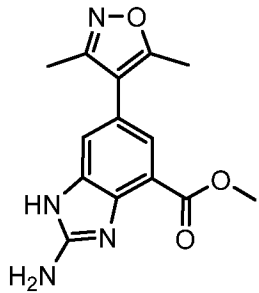
132		3,5-dimethyl-4-(2-(1-methyl-1H-pyrazol-4-yl)-4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-6-yl)isoxazole
133		5-(2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)-3,4-dihydroquinolin-2(1H)-one
134		N-cyclopentyl-2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-amine
135		N-cyclopentyl-6-(3,5-dimethylisoxazol-4-yl)-2-(trifluoromethyl)-1H-benzo[d]imidazole-4-sulfonamide

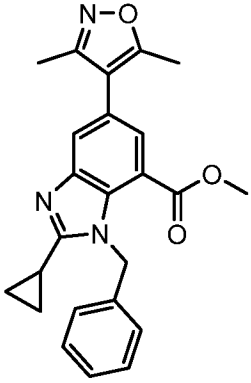
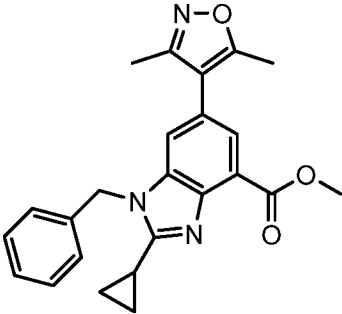
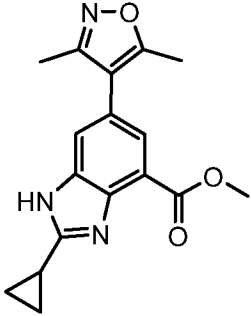
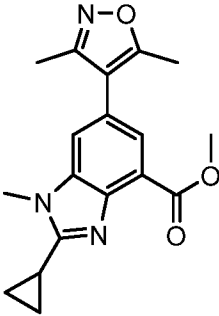
136		N-cyclopentyl-6-(3,5-dimethylisoxazol-4-yl)-2-(hydroxymethyl)-1H-benzo[d]imidazole-4-sulfonamide
137		2-benzyl-N-cyclopentyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazole-4-sulfonamide
138		methyl (4-(N-cyclopentylsulfamoyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2-yl)carbamate
139		N-cyclopentyl-2-((cyclopropylmethyl)amino)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazole-4-sulfonamide

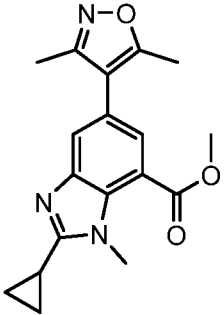
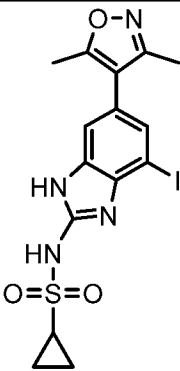
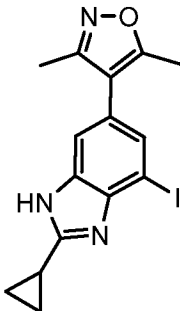
140		N-cyclopentyl-6-(3,5-dimethylisoxazol-4-yl)-2-((2-methoxyethyl)amino)-1H-benzo[d]imidazole-4-sulfonamide
141		2-amino-N-cyclopentyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazole-4-sulfonamide
142		N-cyclopentyl-6-(3,5-dimethylisoxazol-4-yl)-2-(phenylamino)-1H-benzo[d]imidazole-4-sulfonamide
143		2-(benzylamino)-N-cyclopentyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazole-4-sulfonamide

144		N-cyclopentyl-6-(3,5-dimethylisoxazol-4-yl)-2-((2-morpholinoethyl)amino)-1H-benzo[d]imidazole-4-sulfonamide
145		N-cyclopentyl-2-(cyclopropylamino)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazole-4-sulfonamide
146		N-cyclopentyl-6-(3,5-dimethylisoxazol-4-yl)-2-(((tetrahydrofuran-2-yl)methyl)amino)-1H-benzo[d]imidazole-4-sulfonamide
147		N-cyclopentyl-6-(3,5-dimethylisoxazol-4-yl)-2-((2-methoxyethyl)amino)-1H-benzo[d]imidazole-4-sulfonamide

148		N-cyclopentyl-6-(3,5-dimethylisoxazol-4-yl)-2-((2,2,2-trifluoroethyl)amino)-1H-benzo[d]imidazole-4-sulfonamide
149		3-((4-(N-cyclopentylsulfamoyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2-yl)amino)propanoic acid
150		ethyl 3-((4-(N-cyclopentylsulfamoyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2-yl)amino)propanoate
151		N-cyclopentyl-6-(3,5-dimethylisoxazol-4-yl)-2-mercapto-1H-benzo[d]imidazole-4-sulfonamide

152		N-cyclopentyl-6-(3,5-dimethylisoxazol-4-yl)-2-(methylthio)-1H-benzo[d]imidazole-4-sulfonamide
153		N-cyclopentyl-6-(3,5-dimethylisoxazol-4-yl)-2-(methylsulfinyl)-1H-benzo[d]imidazole-4-sulfonamide
154		N-cyclopentyl-6-(3,5-dimethylisoxazol-4-yl)-2-(methylsulfonyl)-1H-benzo[d]imidazole-4-sulfonamide
155		methyl 2-amino-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazole-4-carboxylate

156		methyl 1-benzyl-2-cyclopropyl-5-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazole-7-carboxylate
157		methyl 1-benzyl-2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazole-4-carboxylate
158		methyl 2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazole-4-carboxylate
159		methyl 2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazole-4-carboxylate

160		methyl 2-cyclopropyl-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazole-7-carboxylate
161		N-(6-(3,5-dimethylisoxazol-4-yl)-4-iodo-1H-benzo[d]imidazol-2-yl)cyclopropanesulfonamide
162		4-(2-cyclopropyl-4-iodo-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole

It is understood that separate, single embodiments comprise the methods, regimens, kits, and articles of manufacture in which the BET inhibitor is each separate compound listed in the table above. For instance, in one embodiment of each of the methods, regimens and kits discussed herein, there is an embodiment in which the BET inhibitor is, (2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)di(pyridin-2-yl)methanol, or a pharmaceutically acceptable salt thereof. In separate other embodiments for each of the methods, regimens, kits, and articles of manufacture discussed herein, there is an embodiment in which the BET inhibitor is (2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-

4-yl)di(pyrazin-2-yl)methanol, or a pharmaceutically acceptable salt thereof. There are also
embodiments in which the BET inhibitor is (2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-
benzo[d]imidazol-4-yl)(pyridin-2-yl)(pyrimidin-5-yl)methanol, or a pharmaceutically acceptable
salt thereof. There are also embodiments in which the BET inhibitor is (2-cyclopropyl-6-(3,5-
5 dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)(pyrimidin-5-yl)methanol, or a
pharmaceutically acceptable salt thereof. There are also embodiments in which the BET
inhibitor is (2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)(pyridin-2-
yl)(pyrimidin-2-yl)methanol, or a pharmaceutically acceptable salt thereof. There are also
embodiments in which the BET inhibitor is (2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-
10 benzo[d]imidazol-4-yl)di(pyridin-3-yl)methanol, or a pharmaceutically acceptable salt
thereof. There are also embodiments in which the BET inhibitor is (2-cyclopropyl-6-(3,5-
dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-yl)(phenyl)(pyridin-2-yl)methanol, or a
pharmaceutically acceptable salt thereof. There are also embodiments in which the BET
inhibitor is (2-cyclopropyl-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-4-
15 yl)(phenyl)(pyridin-3-yl)methanol, or a pharmaceutically acceptable salt thereof. There are also
embodiments in which the BET inhibitor is 4-(2-cyclopropyl-7-(6-methylquinolin-5-yl)-1H-
benzo[d]imidazol-5-yl)-3,5-dimethylisoxazole or a pharmaceutically acceptable salt thereof.

The BET inhibitors described above may be prepared by methods disclosed in U.S.
Patent Application Publication No. 2014/0336190.

20 Pharmaceutically acceptable salts, esters, stereoisomers, tautomers, prodrugs, solvates,
and deuterated forms of the compounds disclosed herein may be used in the methods and
compositions disclosed herein.

Treatment Methods and Uses

Reference to the word “comprise” and variations thereof, such as, “comprises” and
25 “comprising” are to be construed in an open, inclusive sense, that is, as “including, but not
limited to.” Further, the singular forms “a,” “an,” and “the” include plural references unless the
context clearly dictates otherwise. Thus, reference to “the compound” includes a plurality of
such compounds, and reference to “the assay” includes reference to one or more assays and
equivalents thereof known to those skilled in the art.

Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter *per se*. The term “about X” thus includes description of “X”. In certain embodiments, the term “about” includes the indicated amount $\pm 10\%$. In other embodiments, the term “about” includes the indicated amount $\pm 5\%$. In certain other
5 embodiments, the term “about” includes the indicated amount $\pm 1\%$.

“Effective amount” or “therapeutically effective amount” means the amount of a compound described herein that may be effective to elicit the desired biological or medical response. These terms include the amount of a compound that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. The effective amount
10 will vary depending on the compound, the disease and its severity and the age, weight, etc., of the subject to be treated.

“Subject” and “subjects” refers to humans, domestic animals (e.g., dogs and cats), farm animals (e.g., cattle, horses, sheep, goats and pigs), laboratory animals (e.g., mice, rats, hamsters, guinea pigs, pigs, rabbits, dogs, and monkeys), and the like.

“Treating” and “treatment” of a disease include the following: (1) preventing or reducing the risk of developing the disease, i.e., causing the clinical symptoms of the disease not to develop in a subject that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease, (2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms, and (3) relieving the disease,
15 i.e., causing regression of the disease or its clinical symptoms.
20 i.e., causing regression of the disease or its clinical symptoms.

The methods described herein may be applied to cell populations *in vivo* or *ex vivo*. “*In vivo*” means within a living individual, as within an animal or human. In this context, the methods described herein may be used therapeutically in an individual. “*Ex vivo*” means outside of a living individual. Examples of *ex vivo* cell populations include *in vitro* cell cultures and
25 biological samples including fluid or tissue samples obtained from individuals. Such samples may be obtained by methods well known in the art. Exemplary biological fluid samples include blood, cerebrospinal fluid, urine, and saliva. In this context, the compounds and compositions described herein may be used for a variety of purposes, including therapeutic and experimental purposes. For example, the compounds and compositions described herein may be used *ex vivo*

to determine the optimal schedule and/or dosing of administration of a compound of the present disclosure for a given indication, cell type, individual, and other parameters. Information gleaned from such use may be used for experimental purposes or in the clinic to set protocols for *in vivo* treatment. Other *ex vivo* uses for which the compounds and compositions described herein may be suited are described below or will become apparent to those skilled in the art. The selected compounds may be further characterized to examine the safety or tolerance dosage in human or non-human subjects. Such properties may be examined using commonly known methods to those skilled in the art.

“The terms “synergy” and “synergistic effect” encompass a more than additive effect of two or more agents compared to their individual effects. In certain embodiments, synergy or synergistic effect refers to an advantageous effect of using two or more agents in combination, e.g., in a pharmaceutical composition, or in a method of treatment. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g. in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e. serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together. As used herein, the synergistic anti-cancer effect of the combination of filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, and a BET inhibitor is greater than the predicted purely additive effects of the individual compounds of the combination.

The present disclosure, in one embodiment, provides a method for treating cancer in a human in need thereof, comprising administering to the human a therapeutically effective amount of filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, and a therapeutically effective amount of a BET inhibitor.

In another aspect, the methods comprising combination of filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, and a BET inhibitor,

provide synergy. In some embodiments, the amount or dosage of filgotinib, or pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, the BET inhibitor, or both, used in combination, does not exceed the level at which each agent is used individually, e.g., as a monotherapy. In certain embodiments, the amount or dosage of filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, or the BET inhibitor, or both, used in combination, is lower (e.g., at least 20%, at least 30%, at least 40%, or at least 50% lower) than the amount or dosage of each agent used individually, e.g., as a monotherapy. In other embodiments, the amount or dosage of filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, the BET inhibitor, or both, used in combination that results in treatment of cancer is lower (e.g., at least 20%, at least 30%, at least 40%, or at least 50% lower) than the amount or dosage of each agent used individually, e.g., as a monotherapy.

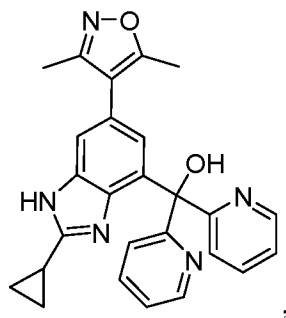
In one embodiment, filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, is administered intravenously, intramuscularly, parenterally, nasally or orally. In another embodiment, the BET inhibitor is administered intravenously, intramuscularly, parenterally, nasally or orally. In another embodiment, filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, is administered prior, after or concurrently with the BET inhibitor.

The present disclosure, in one embodiment, provides a method for treating cancer in a human in need thereof, comprising administering to the human a therapeutically effective amount of filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, and a therapeutically effective amount of a BET inhibitor, wherein the BET inhibitor is a compound of the Formula (I) as disclosed herein, wherein the cancer is carcinoma, sarcoma, melanoma, lymphoma or leukemia.

In one embodiment, this disclosure provides a method for treating cancer in a human in need thereof, comprising administering to the human:

(i) a therapeutically effective amount of filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof; and

(ii) a therapeutically effective amount of



or a pharmaceutically acceptable salt thereof.

In a further embodiment, the cancer is carcinoma, sarcoma, melanoma, lymphoma or leukemia. In another embodiment, filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof is administered intravenously, intramuscularly, parenterally, nasally or orally. In another embodiment, the compound in step (ii) is administered intravenously, intramuscularly, parenterally, nasally or orally. In another embodiment, filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof is administered prior, after or concurrently with compound in step (ii).

10 Cancer

In some embodiments, the cancer is carcinoma, sarcoma, melanoma, lymphoma or leukemia. In other embodiments, the cancer is a hematologic malignancy. In some embodiments, the cancer is leukemia (*e.g.*, chronic lymphocytic leukemia), lymphoma (*e.g.*, non-Hodgkin's lymphoma), or multiple myeloma. In other embodiments, the cancer is a solid tumor.

In some variations, the cancer is small lymphocytic lymphoma, non-Hodgkin's lymphoma, indolent non-Hodgkin's lymphoma (iNHL), refractory iNHL, mantle cell lymphoma, follicular lymphoma, lymphoplasmacytic lymphoma, marginal zone lymphoma, immunoblastic large cell lymphoma, lymphoblastic lymphoma, Splenic marginal zone B-cell lymphoma (+/- villous lymphocytes), nodal marginal zone lymphoma (+/- monocytoid B-cells), extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type, cutaneous T-cell lymphoma, extranodal T-cell lymphoma, anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma, mycosis fungoides, B-cell lymphoma, diffuse large B-cell lymphoma, Mediastinal large B-cell lymphoma, Intravascular large B-cell lymphoma, Primary effusion

lymphoma, small non-cleaved cell lymphoma, Burkitt's lymphoma, multiple myeloma, plasmacytoma, acute lymphocytic leukemia, T-cell acute lymphoblastic leukemia, B-cell acute lymphoblastic leukemia, B-cell prolymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, juvenile myelomonocytic leukemia, minimal residual disease, hairy cell
5 leukemia, primary myelofibrosis, secondary myelofibrosis, chronic myeloid leukemia, myelodysplastic syndrome, myeloproliferative disease, or Waldstrom's macroglobulinemia.

In other variations, the cancer is pancreatic cancer, urological cancer, bladder cancer, colorectal cancer, colon cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, thyroid cancer, gall bladder cancer, lung cancer (*e.g.* non-small cell lung cancer, small-
10 cell lung cancer), ovarian cancer, cervical cancer, gastric cancer, endometrial cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancer, CNS cancer, brain tumors (*e.g.*, glioma, anaplastic oligodendroglioma, adult glioblastoma multiforme, and adult anaplastic astrocytoma), bone cancer, soft tissue sarcoma, retinoblastomas, neuroblastomas, peritoneal effusions, malignant pleural effusions, mesotheliomas, Wilms tumors, trophoblastic neoplasms,
15 hemangiopericytomas, Kaposi's sarcomas, myxoid carcinoma, round cell carcinoma, squamous cell carcinomas, esophageal squamous cell carcinomas, oral carcinomas, cancers of the adrenal cortex, or ACTH-producing tumors.

Subject

The human in need thereof may be an individual who has or is suspected of having a
20 cancer. In some of variations, the human is at risk of developing a cancer (*e.g.*, a human who is genetically or otherwise predisposed to developing a cancer) and who has or has not been diagnosed with the cancer. As used herein, an "at risk" subject is a subject who is at risk of developing cancer (*e.g.*, a hematologic malignancy). The subject may or may not have detectable disease, and may or may not have displayed detectable disease prior to the treatment
25 methods described herein. An at risk subject may have one or more so-called risk factors, which are measurable parameters that correlate with development of cancer, such as described herein. A subject having one or more of these risk factors has a higher probability of developing cancer than an individual without these risk factor(s).

These risk factors may include, for example, age, sex, race, diet, history of previous disease, presence of precursor disease, genetic (*e.g.*, hereditary) considerations, and environmental exposure. In some embodiments, a human at risk for cancer includes, for example, a human whose relatives have experienced this disease, and those whose risk is
5 determined by analysis of genetic or biochemical markers. Prior history of having cancer may also be a risk factor for instances of cancer recurrence.

In some embodiments, provided herein is a method for treating a human who exhibits one or more symptoms associated with cancer (*e.g.*, a hematologic malignancy). In some
10 embodiments, the human is at an early stage of cancer. In other embodiments, the human is at an advanced stage of cancer.

In some embodiments, provided herein is a method for treating a human who is undergoing one or more standard therapies for treating cancer (*e.g.*, a hematologic malignancy), such as chemotherapy, radiotherapy, immunotherapy, and/or surgery. Thus, in some foregoing
15 embodiments, the combination of filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, and a BET inhibitor may be administered before, during, or after administration of chemotherapy, radiotherapy, immunotherapy, and/or surgery.

In another aspect, provided herein is a method for treating a human who is “refractory” to a cancer treatment or who is in “relapse” after treatment for cancer (*e.g.*, a hematologic malignancy). A subject “refractory” to an anti-cancer therapy means they do not respond to the
20 particular treatment, also referred to as resistant. The cancer may be resistant to treatment from the beginning of treatment, or may become resistant during the course of treatment, for example after the treatment has shown some effect on the cancer, but not enough to be considered a remission or partial remission. A subject in “relapse” means that the cancer has returned or the signs and symptoms of cancer have returned after a period of improvement, *e.g.* after a treatment
25 has shown effective reduction in the cancer, such as after a subject is in remission or partial remission.

In some variations, the human is (i) refractory to at least one anti-cancer therapy, or (ii) in relapse after treatment with at least one anti-cancer therapy, or both (i) and (ii). In some of

embodiments, the human is refractory to at least two, at least three, or at least four anti-cancer therapies (including, for example, standard or experimental chemotherapies).

In another aspect, provided is a method for sensitizing a human who is (i) refractory to at least one chemotherapy treatment, or (ii) in relapse after treatment with chemotherapy, or both (i) and (ii), wherein the method comprises administering a filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, in combination with a BET inhibitor, to the human. A human who is sensitized is a human who is responsive to the treatment involving administration of filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, in combination with a BET inhibitor or who has not developed resistance to such treatment.

For chronic lymphocytic leukemia the prior treatments a human may have received include regimens of:

- fludarabine (Fludara®);
- rituximab (Rituxan®);
- rituximab (Rituxan®) combined with fludarabine (sometimes abbreviated as FR);
- cyclophosphamide (Cytosan®) combined with fludarabine; cyclophosphamide combined with rituximab and fludarabine (sometimes abbreviated as FCR);
- cyclophosphamide combined with vincristine and prednisone (sometimes abbreviated as CVP);
- cyclophosphamide combined with vincristine, prednisone, and rituximab;
- combination of cyclophosphamide, doxorubicin, vincristine (Oncovin), and prednisone (sometimes referred to as CHOP);
- Chlorambucil combined with prednisone, rituximab, obinutuzumab, or ofatumumab
- pentostatin combined with cyclophosphamide and rituximab (sometimes abbreviated as PCR);
- bendamustine (Treanda®) combined with rituximab ((sometimes abbreviated as BR);

alemtuzumab (Campath®);

fludarabine plus cyclophosphamide, bendamustine, or chlorambucil; and

fludarabine plus cyclophosphamide, bendamustine, or chlorambucil, combined with an anti-CD20 antibody, such as rituximab, ofatumumab, or obinutuzumab.

- 5 In another aspect, provided herein is a methods for treating a human for a cancer, with comorbidity, wherein the treatment is also effective in treating the comorbidity. A “comorbidity” to cancer is a disease that occurs at the same time as the cancer.

Kits

- Compositions (including, for example, formulations and unit dosages) comprising
10 filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, and compositions comprising a BET inhibitor can be prepared and placed in an appropriate container, and labeled for treatment of an indicated condition. Accordingly, provided is also an article of manufacture, such as a container comprising a unit dosage form of filgotinib, or a
pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, and a unit dosage
15 form of a BET inhibitor, and a label containing instructions for use of the compounds. In some embodiments, the article of manufacture is a container comprising (i) a unit dosage form of filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, and one or more pharmaceutically acceptable carriers, adjuvants or excipients; and (ii) a unit dosage
form of a BET inhibitor, and one or more pharmaceutically acceptable carriers, adjuvants or
20 excipients. In one embodiment, the unit dosage form for both filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, and the BET inhibitor, is a tablet.

- Kits also are contemplated. For example, a kit can comprise unit dosage forms of
filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, and
compositions comprising a BET inhibitor, and a package insert containing instructions for use of
25 the composition in treatment of a medical condition. In some embodiments, the kits comprises (i) a unit dosage form of filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, and one or more pharmaceutically acceptable carriers, adjuvants or excipients; and (ii) a unit dosage form of a BET inhibitor, and one or more pharmaceutically acceptable carriers, adjuvants or excipients. In one embodiment, the unit dosage form for both

filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, and the BET inhibitor, is a tablet.

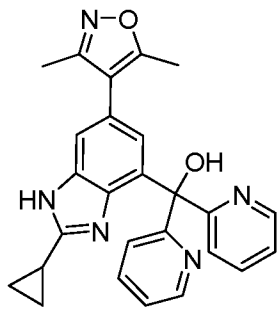
The instructions for use in the kit may be for treating a cancer, including, for example, a hematologic malignancy, as further described herein.

5 In one embodiment, this disclosure provides a kit comprising (i) a pharmaceutical composition comprising filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof; (ii) a pharmaceutical composition comprising a BET inhibitor; and (iii) instructions for use of filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof and the BET inhibitor in treating cancer.

10 In one embodiment, this disclosure provides a kit comprising:

(i) a pharmaceutical composition comprising filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof;

(ii) a pharmaceutical composition comprising:



15 or a pharmaceutically acceptable salt thereof; and

(iii) instructions for use in treating cancer.

Pharmaceutical Compositions and Modes of Administration

In one embodiment, this disclosure provides a pharmaceutical composition comprising filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, and a

BET inhibitor, and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition exhibits synergy in treating cancer.

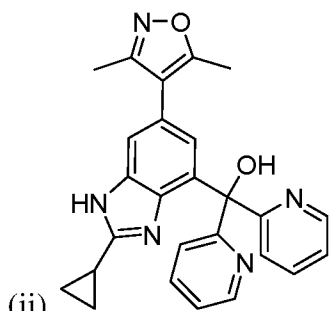
In another embodiment, this disclosure provides a pharmaceutical composition comprising filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof and a BET inhibitor, such as a compound of Formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In another embodiment, the pharmaceutical composition exhibits synergy in treating cancer.

In another embodiment, this disclosure provides a co-formulation comprising filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof; a BET inhibitor; and a pharmaceutically acceptable carrier. In some embodiments, the co-formulation exhibits synergy in treating cancer.

In another embodiment, this disclosure provides a co-formulation comprising filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof; and a therapeutically effective amount of a BET inhibitor, such as a compound of Formula (I) or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier. In some embodiments, the co-formulation exhibits synergy in treating cancer.

In another embodiment, this disclosure provides a co-formulation comprising:

- (i) filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof; and



- (ii) or a pharmaceutically acceptable salt thereof.

In another embodiment, this disclosure provides combination therapy for treating cancer, wherein separate compositions comprising filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, and a BET inhibitor are used. For example, a

composition comprising filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof and a composition comprising a BET inhibitor, such as a compound of Formula (I) or a pharmaceutically acceptable salt thereof are used separately for the combination therapy.

5 The pharmaceutical compositions and/or co-formulations may be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, for example as described in those patents and patent applications incorporated by reference, including rectal, buccal, intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically,
10 as an inhalant, or via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer.

 In one aspect, the compounds described herein may be administered orally. Oral administration may be via, for example, capsule or enteric coated tablets. In making the pharmaceutical compositions that include at least one compound of Formula (I), or a
15 pharmaceutically acceptable salt thereof, the active ingredient is usually diluted by an excipient and/or enclosed within such a carrier that can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be in the form of a solid, semi-solid, or liquid material (as above), which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets,
20 elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

 Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium
25 silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

The compositions can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the subject by employing procedures known in the art. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations. Another formulation for use in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Dosing

The dosing regimen of filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, and a BET inhibiting compound disclosed herein (*e.g.* a compound of Formula (I) or a pharmaceutically acceptable salt thereof) in the methods provided herein may vary depending upon the indication, route of administration, and severity of the condition. For instance, depending on the route of administration, a suitable dose can be calculated according to body weight, body surface area, or organ size. The final dosing regimen is determined by the attending physician in view of good medical practice, considering various factors that modify the action of drugs, *e.g.*, the specific activity of the compound, the identity and severity of the disease state, the responsiveness of the subject, the age, condition, body weight, sex, and diet of the subject, and the severity of any infection. Additional factors that can be taken into account include time and frequency of administration, drug combinations, reaction sensitivities, and tolerance/response to therapy. Further refinement of the doses appropriate for treatment involving any of the formulations mentioned herein is done routinely by the skilled practitioner without undue experimentation, especially in light of the dosing information and assays disclosed, as well as the pharmacokinetic data observed in human clinical trials. Appropriate doses can be ascertained through use of established assays for determining concentration of the agent in a body fluid or other sample together with dose response data.

As indicated above, the dose and frequency of dosing may depend on pharmacokinetic and pharmacodynamic, as well as toxicity and therapeutic efficiency data. For example, pharmacokinetic and pharmacodynamic information about filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof; and the BET inhibiting compounds disclosed herein (*e.g.* a compound of Formula (I) or a pharmaceutically acceptable salt thereof) can be collected through preclinical *in vitro* and *in vivo* studies, later confirmed in humans during the course of clinical trials. Thus, for filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, and the BET inhibitors disclosed herein, a therapeutically effective dose can be estimated initially from biochemical and/or cell-based assays. The dosage can then be formulated in animal models to achieve a desirable circulating concentration range that modulates BET activity. As human studies are conducted further information will emerge regarding the appropriate dosage levels and duration of treatment for various diseases and conditions.

Toxicity and therapeutic efficacy of filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, or a compound of Formula (I) or a pharmaceutically acceptable salt thereof, can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the “therapeutic index”, which typically is expressed as the ratio LD₅₀/ED₅₀. Compounds that exhibit large therapeutic indices, *i.e.*, the toxic dose is substantially higher than the effective dose, are preferred. The data obtained from such cell culture assays and additional animal studies can be used in formulating a range of dosage for human use. The doses of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity.

Accordingly, the formulation, route of administration, dosage and dosing frequency of filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, or a compound of Formula (I) or a pharmaceutically acceptable salt thereof, may be based on one or more factors disclosed herein, and tailored to the individual subject, the nature of the condition to be treated in the subject, and generally, the judgment of the attending practitioner.

In some embodiments, a therapeutically effective amount or a pharmaceutically effective amount refers to an amount that is sufficient to effect treatment, when administered to a subject (*e.g.*, a human) in need of such treatment. In one embodiment, a therapeutically effective amount of filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, is an amount sufficient to modulate JAK expression, and thereby treat a human suffering an indication, or to ameliorate or alleviate the existing symptoms of the indication. In another embodiment, a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, is an amount sufficient to modulate activity of bromodomain-containing proteins, and thereby treat a human suffering an indication, or to ameliorate or alleviate the existing symptoms of the indication.

In some embodiments, the therapeutically effective amount of any of the compounds disclosed herein may be determined based on data obtained from assays known in the art, including for example, an apoptosis assay.

The therapeutically effective amount of any of the compounds disclosed herein may be provided in a single dose or multiple doses to achieve the desired treatment endpoint. As used herein, “dose” refers to the total amount of an active ingredient (*e.g.*, filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof or a compound of Formula (I) or a pharmaceutically acceptable salt thereof) to be taken each time by a subject (*e.g.*, a human).

The dose administered of any of the compounds disclosed herein may be administered once daily (QD), twice daily (BID), three times daily, four times daily, or more than four times daily using any suitable mode described herein (*e.g.*, oral administration). In some embodiments, the dose of any of the compounds disclosed herein is administered once daily. In some embodiments, the dose of any of the compounds disclosed herein is administered twice daily.

Moreover, administration or treatment with the compounds disclosed herein may be continued for a number of days; for example, treatment may continue for at least 7 days, 14 days, or 28 days, for one cycle of treatment. Treatment cycles are well known, and are frequently alternated with resting periods of about 1 to 28 days, commonly about 7 days or about 14 days, between cycles. The treatment cycles, in other embodiments, may also be continuous.

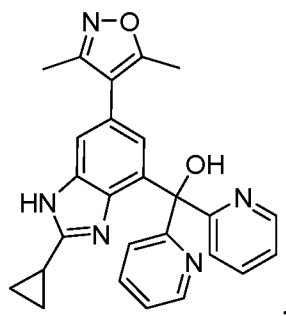
In some embodiments, filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, is administered to a human at a dose between 40 mg and 1200 mg, between 40 mg and 800 mg, between 40 mg and 600 mg, or between 40 mg and 400 mg. In some embodiments, the therapeutically effective amount of filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, is administered to a human at a dose of from about 1 mg to about 200 mg, about 10 mg to about 200 mg, about 100 mg to about 200 mg, about 50 mg to about 175 mg, about 50 mg to about 200 mg, about 20 mg to about 160 mg, about 20 mg to about 150 mg, about 10 mg to about 100 mg, or about 75 mg to about 100 mg. In some embodiments, filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, is administered to a human at a dose between about 50 mg to about 200 mg.

In one embodiment, filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, is administered to a human subject once, twice, three times, or four times daily. In some embodiments, about 50-200 mg of filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, is administered to a human subject once, twice, three times, or four times daily. In some embodiments, about 50-200 mg of filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, is administered to a human subject once daily.

In some embodiments, exemplary doses of the BET inhibitor, such as a compound of Formula (I) or a pharmaceutically acceptable salt thereof, for a human subject may be from about 0.1 mg to about 200 mg per day. In some embodiments, about 0.2 mg, about 1 mg, about 5 mg, about 10 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 180 mg, about 190 mg, about 200 mg. In some embodiments, the BET inhibitor, such as a compound of Formula (I) or a pharmaceutically acceptable salt thereof, is administered to a human at a dose between about 0.1 mg to about 50 mg.

In one embodiment, the BET inhibitor, such as a compound of Formula (I) or a pharmaceutically acceptable salt thereof, is administered to a human subject once, twice, three times, or four times daily. In some embodiments, about 0.2 mg, about 1 mg, about 10 mg, about

25 mg, about 50 mg, about 75 mg, about 100 mg of the BET inhibitor, such as a compound of Formula (I) or a pharmaceutically acceptable salt thereof, is administered to a human subject once, twice, three times, or four times daily. In some embodiments, about 25 mg of the BET inhibitor, such as a compound of Formula (I) or a pharmaceutically acceptable salt thereof, is administered to a human subject once daily. In some embodiments, about 25 mg of the BET inhibitor:



or a pharmaceutically acceptable salt thereof, is administered to a human subject once daily.

The compositions may, in some embodiments, be formulated in a unit dosage form. The term “unit dosage forms” refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient (*e.g.*, a tablet, capsule, ampoule). The compounds are generally administered in a pharmaceutically effective amount. In some embodiments, for oral administration, each dosage unit contains from about 0.1 mg to about 200 mg of a compound disclosed herein, for example about 0.2 mg, about 1 mg, about 10 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg or about 200 mg. In other embodiments, for parenteral administration, each dosage unit contains from 0.1 to 200 mg of a compound disclosed herein. It will be understood, however, that the amount of the compound actually administered usually will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual subject, and the severity of the subject’s symptoms.

For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical excipient to form a solid preformulation composition containing a

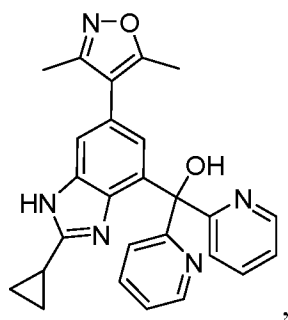
homogeneous mixture of a compound of Formula (I), or a pharmaceutically acceptable salt thereof or filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof. When referring to these preformulation compositions as homogeneous, the active ingredient may be dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

The tablets or pills of the compounds disclosed herein may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

In certain embodiments, filgotinib, or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof, is formulated as a capsule or a tablet. In certain embodiments, the capsule or tablet comprises about 10 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, or about 500 mg of filgotinib. In certain embodiments, the capsule or tablet comprises from about 50 mg to about 200 mg of filgotinib. In certain embodiments, the capsule or tablet comprises about 50 mg, about 100 mg, about 125 mg or about 200 mg of filgotinib.

In certain embodiments, the BET inhibitor (e.g. a compound of Formula (I), or a pharmaceutically acceptable salt thereof) is formulated as a capsule or a tablet. In certain embodiments, the capsule or tablet comprises about 0.2 mg, about 1 mg, about 5 mg, about 10 mg, about 25 mg, about 50 mg, about 75 mg or about 100 mg of the BET inhibitor. In certain embodiments, the capsule or tablet comprises from about 0.2 mg to about 50 mg of the BET inhibitor. In certain embodiments, the capsule or tablet comprises about 0.2 mg, about 1 mg, about 10 mg, about 25 mg or about 50 mg of the BET inhibitor.

In certain embodiments, the BET inhibitor:



or a pharmaceutically acceptable salt thereof, is formulated as a capsule or a tablet. In certain
embodiments, the capsule or tablet comprises about 0.1 mg, 0.2 mg, about 0.5 mg, about 1 mg,
about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg or
5 about 100 mg of the BET inhibitor. In certain embodiments, the capsule or tablet comprises
from about 0.1 mg to about 50 mg of the BET inhibitor. In certain embodiments, the capsule or
tablet comprises about 0.2 mg, about 1 mg, about 10 mg or about 25 mg of the BET inhibitor.

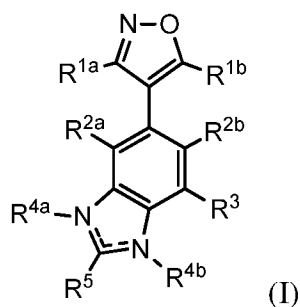
CLAIMS

1. A method of treating cancer in a human in need thereof, comprising administering to the human:

(i) a therapeutically effective amount of filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof; and

(ii) a therapeutically effective amount of a BET inhibitor.

2. The method of claim 1, wherein the BET inhibitor is a compound of the formula:



or a pharmaceutically acceptable salt thereof,

10 wherein:

one --- is a single bond and the other --- is a double bond;

R^{1a} and R^{1b} are each independently C_{1-6} alkyl optionally substituted with from 1 to 5 R^{20} groups;

R^{2a} and R^{2b} are each independently H or halo;

R^3 is $-B(OH)_2$, $-B(OR^a)_2$, halo, $-C(O)OR^a$, $-NHC(O)OR^a$, $-NHS(O)_2R^a$,

15 $-S(O)_2NR^aR^b$, C_{1-10} alkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl,

wherein each of C_{1-10} alkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10}

heteroalkyl, C_{5-10} heteroaryl, or C_{6-20} heteroarylalkyl is optionally substituted with from 1 to 5 R^{20} groups;

one of R^{4a} and R^{4b} is selected from the group consisting of H and C_{1-6} alkyl optionally substituted with from 1 to 5 R^{20} groups, and the other is absent;

R^5 is $-C(O)OR^a$, $-NHC(O)OR^a$, $-NHS(O)_2R^a$, or $-S(O)_2NR^aR^b$, H, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, or

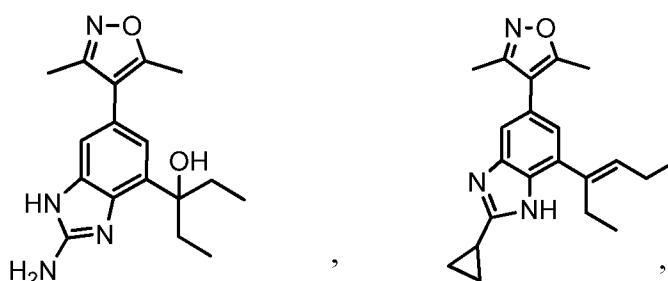
5 C_{6-20} heteroarylalkyl,

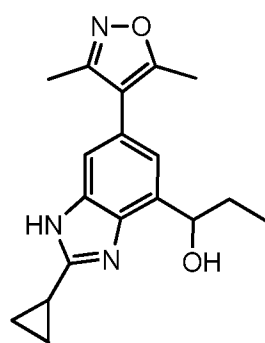
wherein each of C_{1-10} alkyl, C_{1-10} haloalkyl, C_{1-10} alkoxy, amino, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl is optionally substituted with from 1 to 5 R^{20} groups;

each R^a and R^b is independently selected from the group consisting of H, C_{1-10} alkyl, C_{5-10} aryl, C_{6-20} arylalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, and C_{6-20} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; and

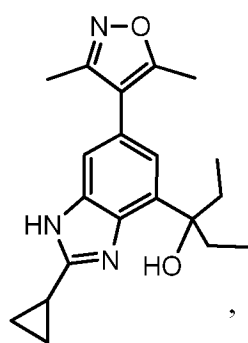
each R^{20} is independently selected from the group consisting of acyl, C_{1-10} alkyl, C_{1-10} alkoxy, amino, amido, amidino, C_{5-10} aryl, C_{6-20} arylalkyl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, guanidino, halo, C_{1-10} haloalkyl, C_{1-10} heteroalkyl, C_{5-10} heteroaryl, C_{6-20} heteroarylalkyl, hydroxy, hydrazino, imino, oxo, nitro, sulfinyl, sulfonic acid, sulfonyl, thiocyanate, thiol, and thione.

3. The method of claim 1, wherein the BET inhibitor is:

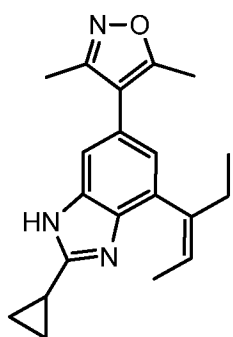




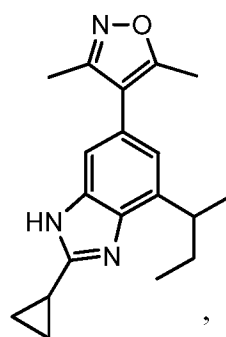
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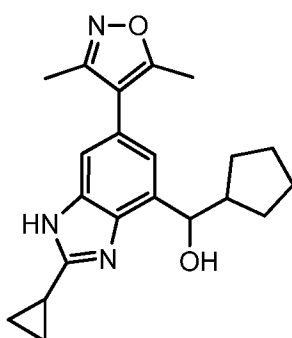
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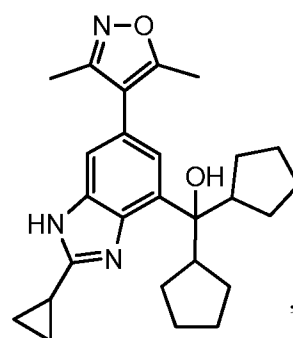
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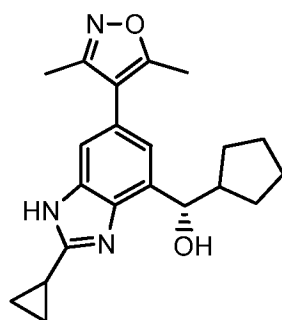
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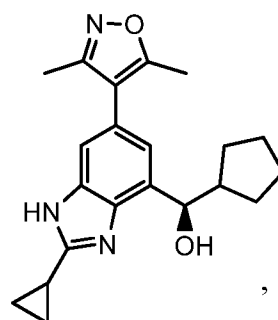
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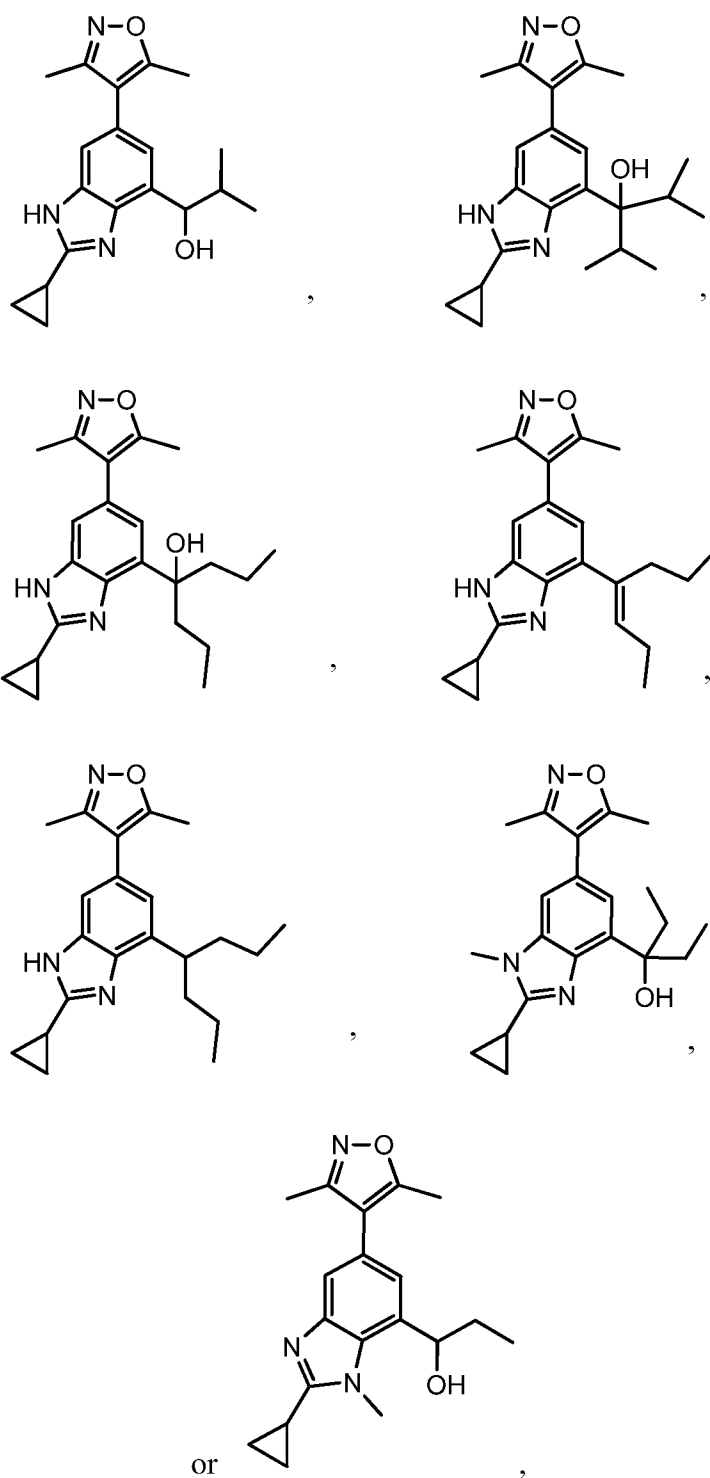
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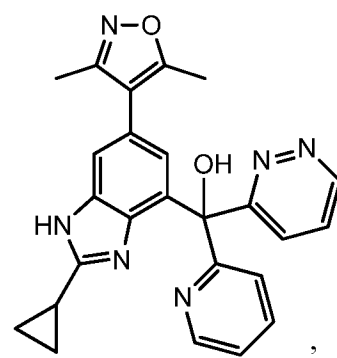
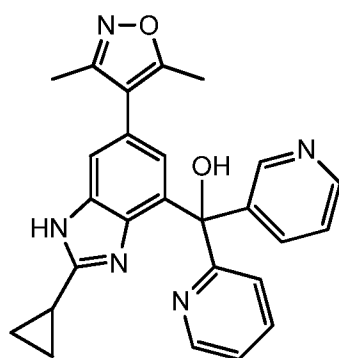
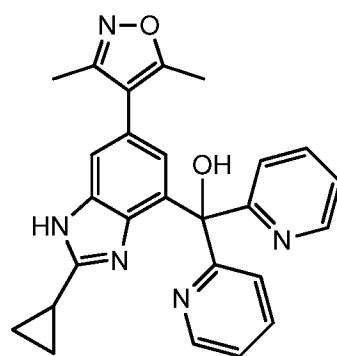
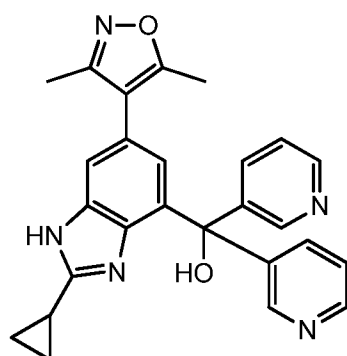
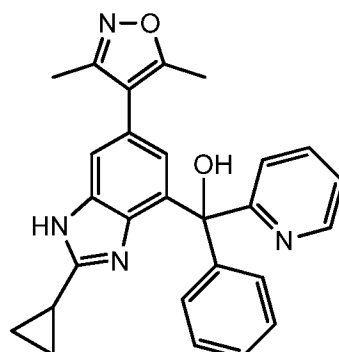
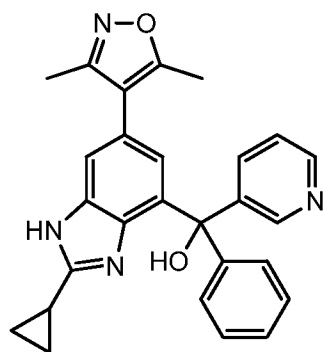
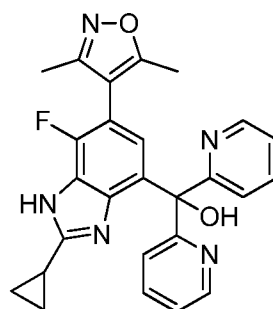
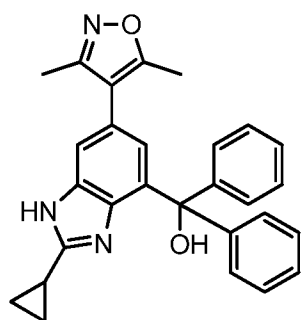


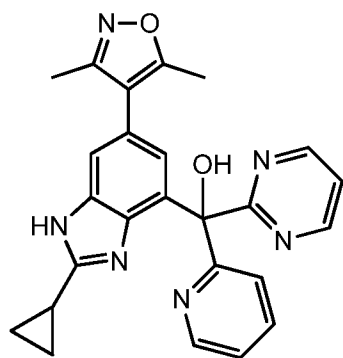
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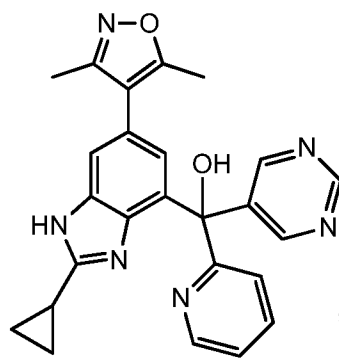
5 or a pharmaceutically acceptable salt thereof.

4. The method of claim 1, wherein the BET inhibitor is:

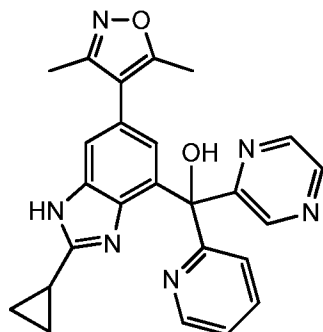




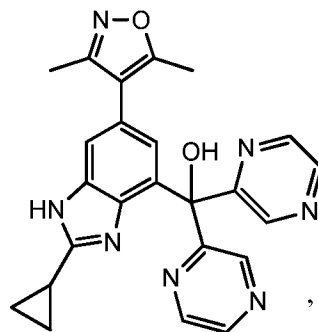
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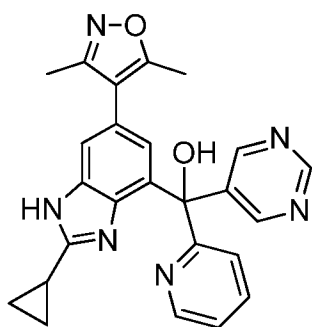
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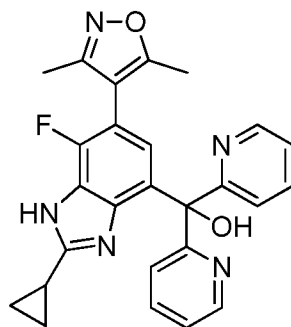
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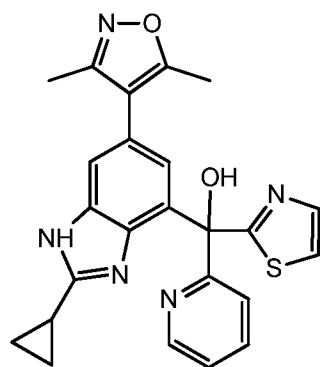
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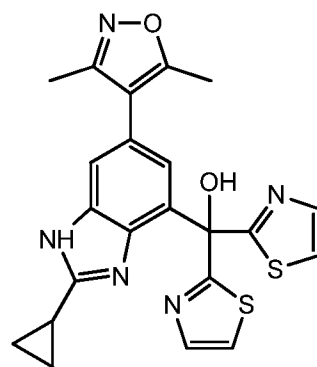
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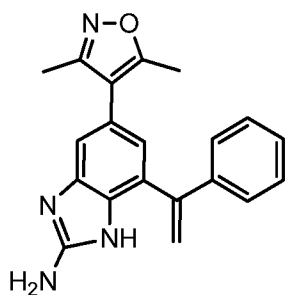
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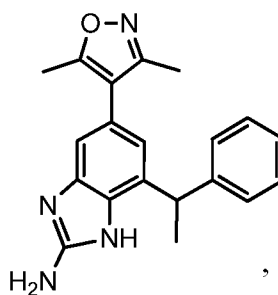
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5 or a pharmaceutically acceptable salt thereof.

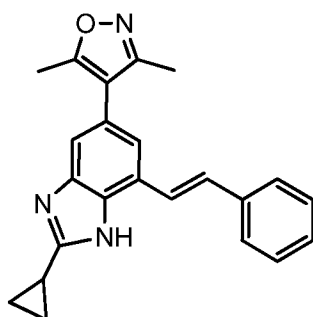
5. The method of claim 1, wherein the BET inhibitor is:



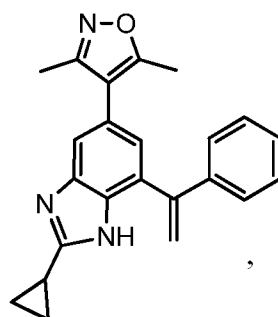
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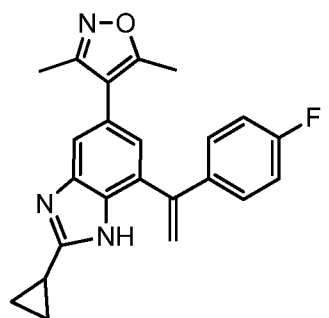
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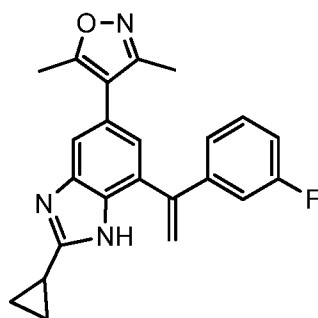
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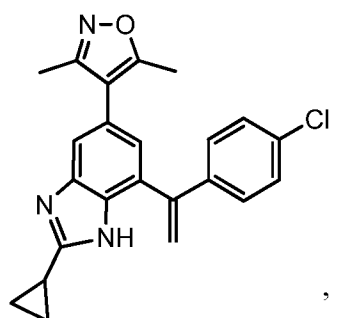
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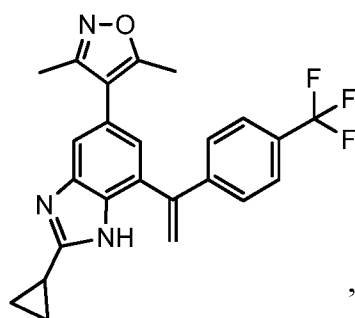
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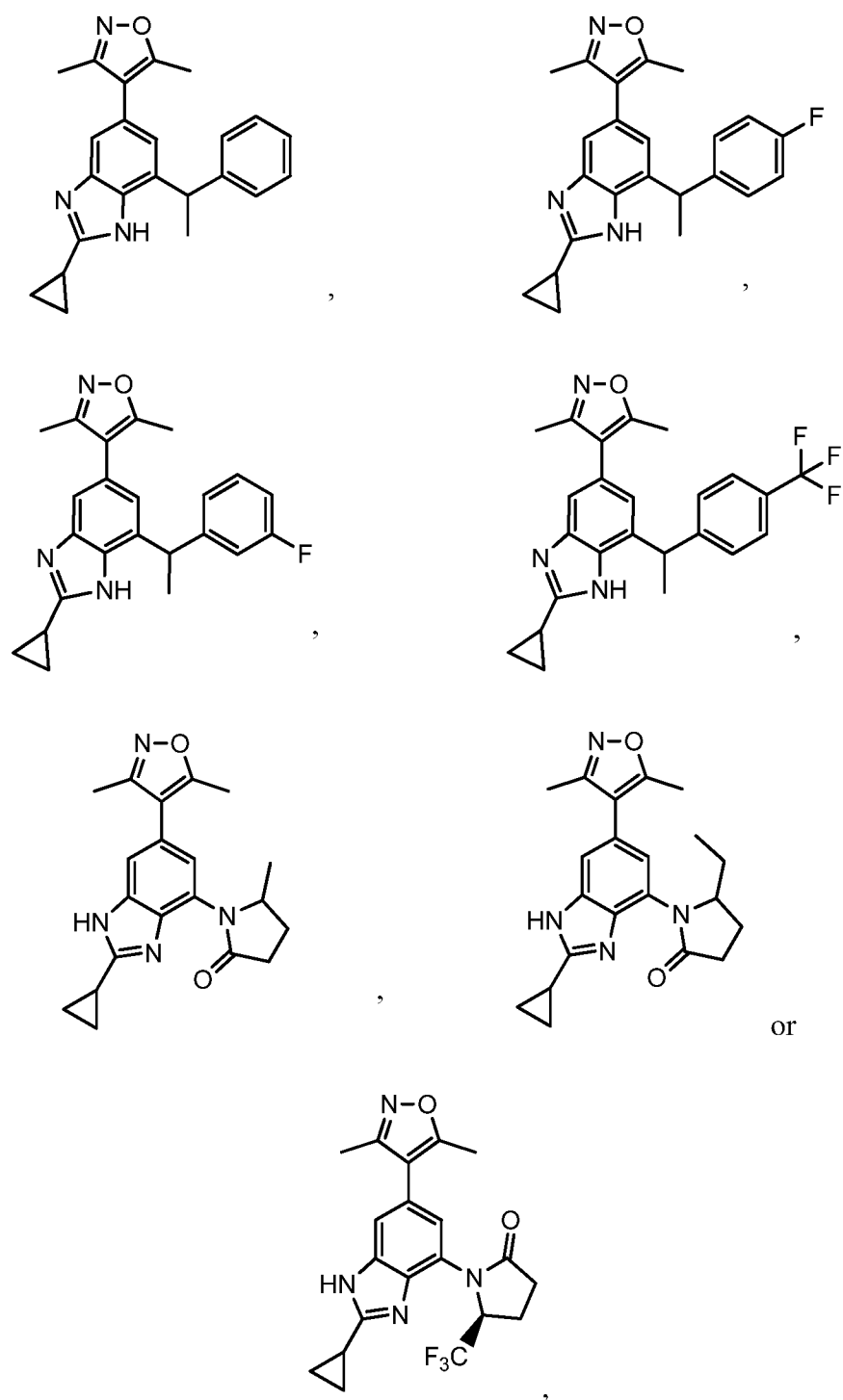
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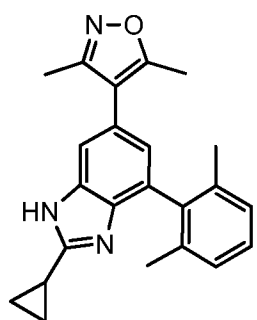
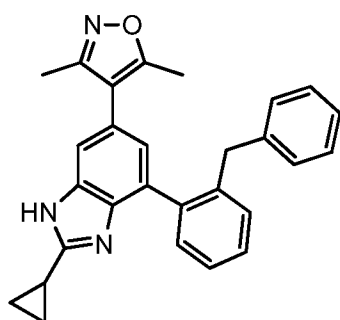
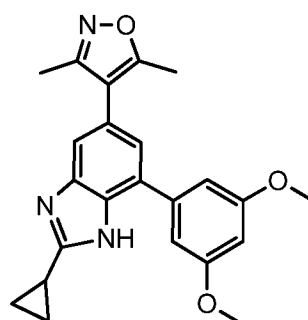
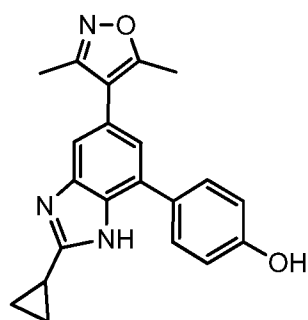
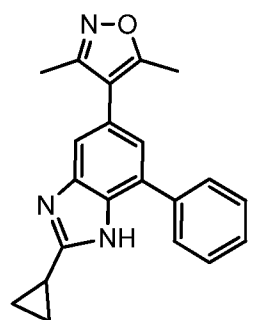
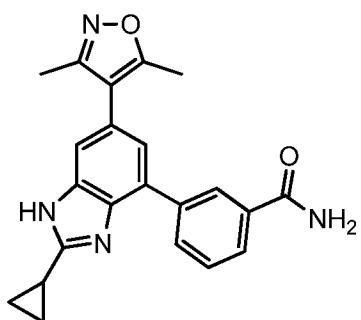
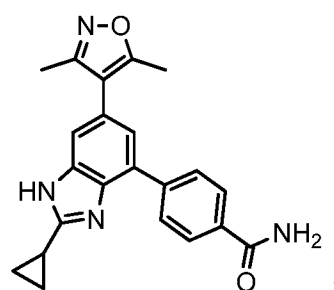
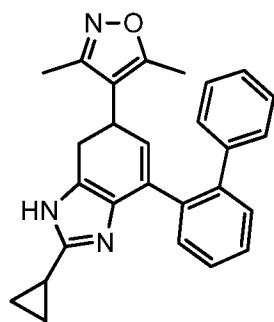


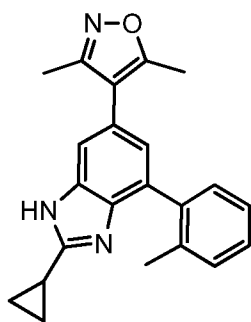
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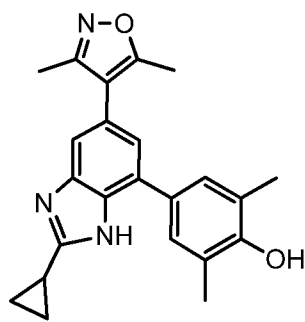
5 or a pharmaceutically acceptable salt thereof.

6. The method of claim 1, wherein the BET inhibitor is:

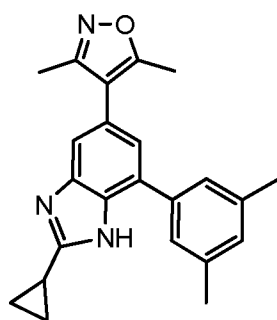




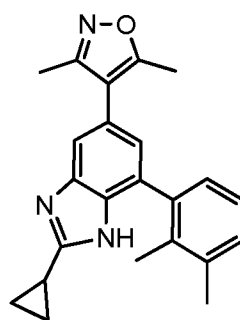
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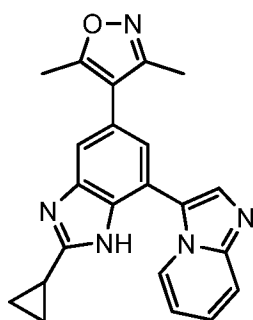
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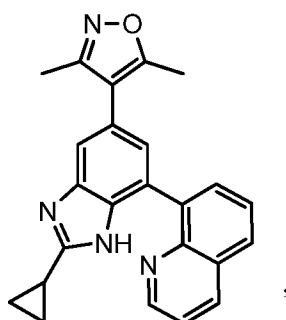
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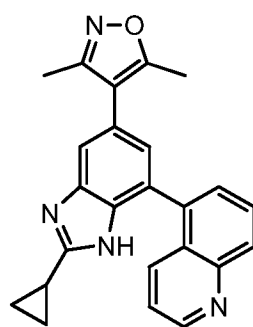
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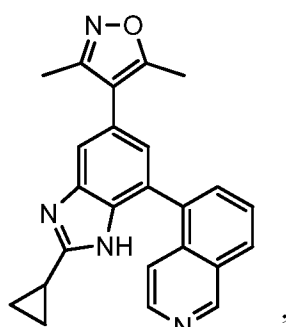
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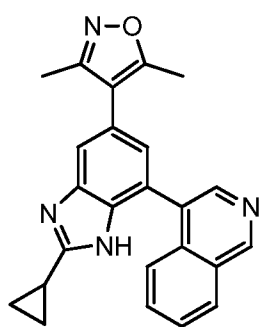
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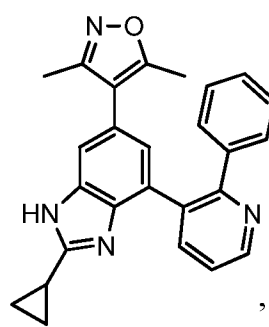
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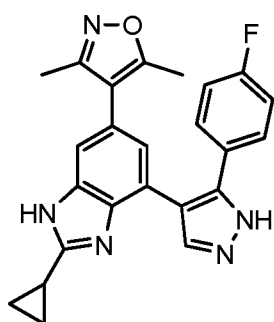
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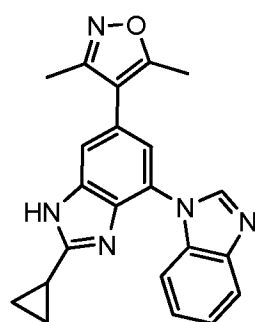
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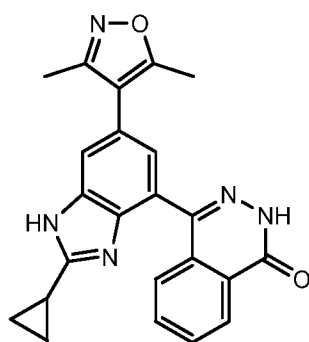
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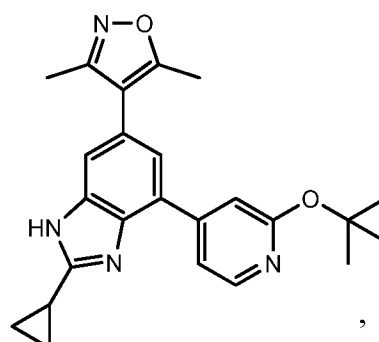
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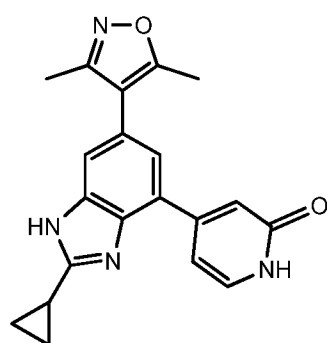
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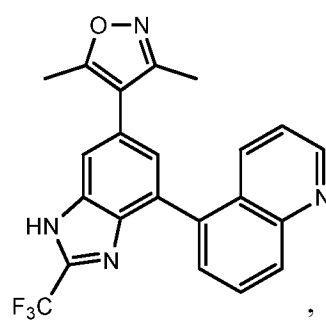
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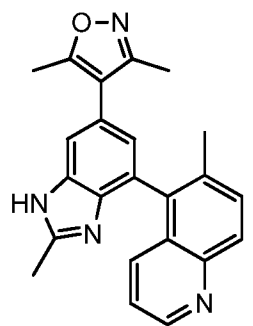
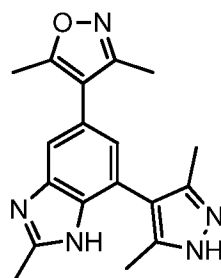
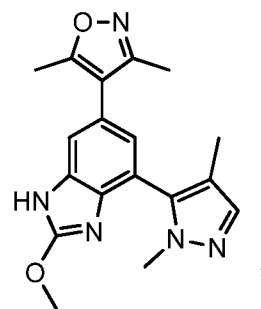
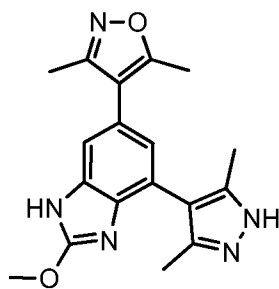
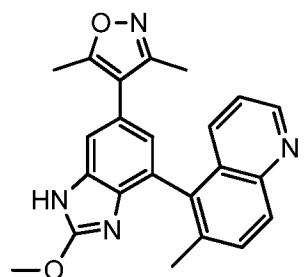
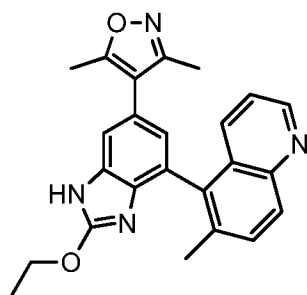
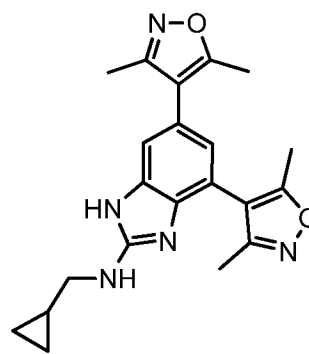
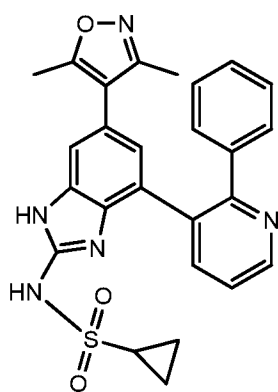
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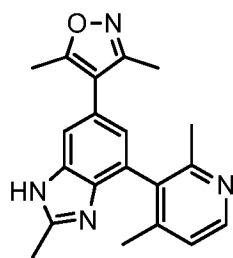


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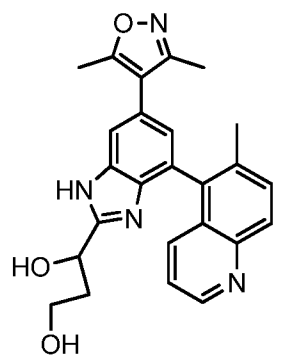


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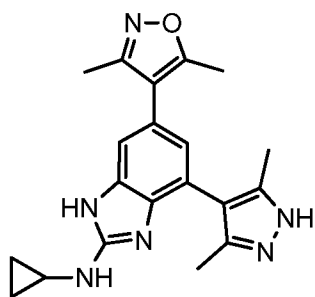




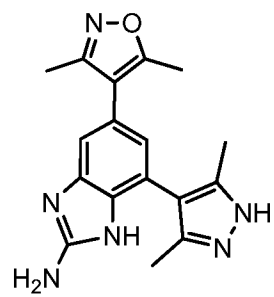
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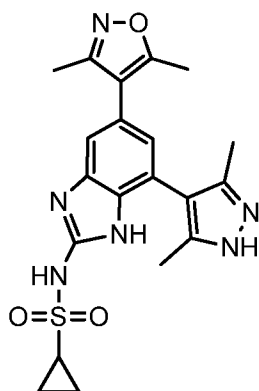
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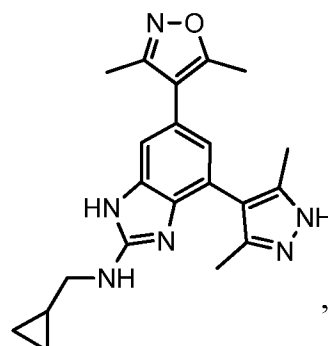
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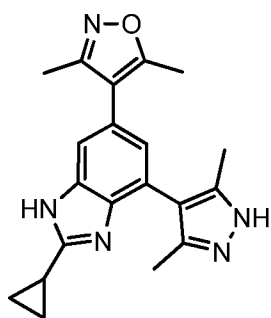
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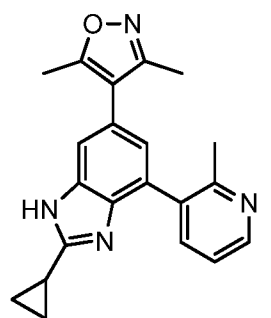
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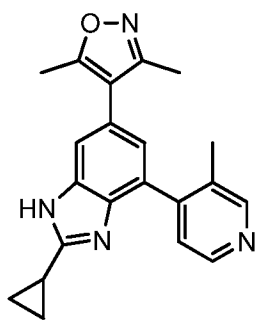
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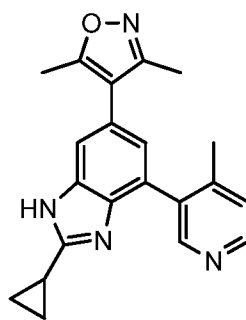
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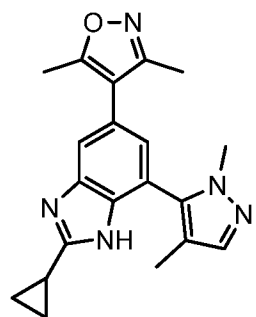
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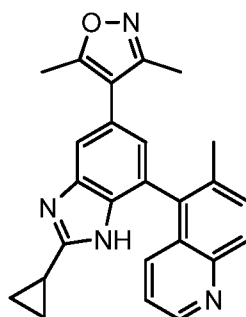
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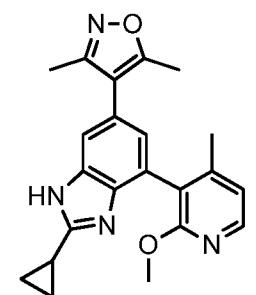
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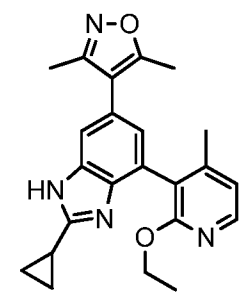
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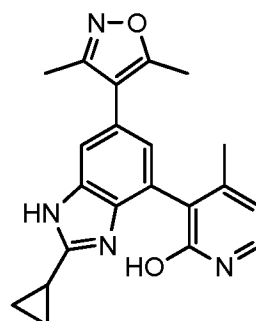
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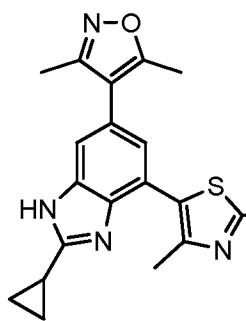
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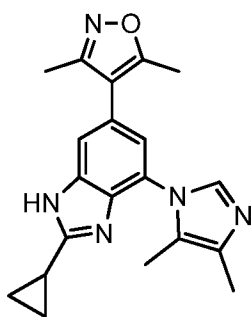
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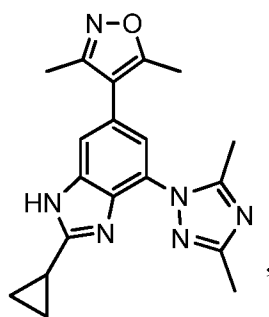
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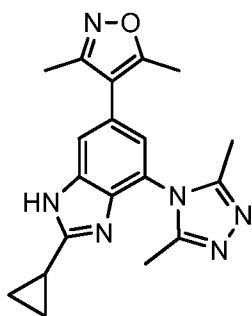
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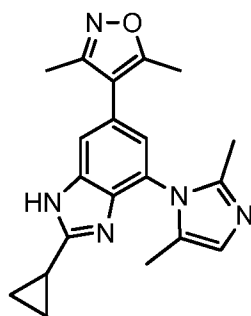
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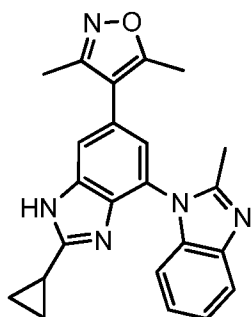
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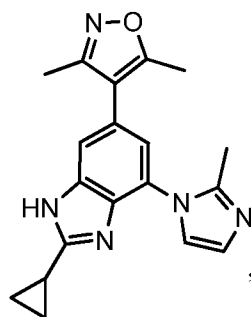
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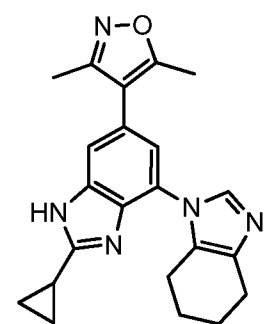
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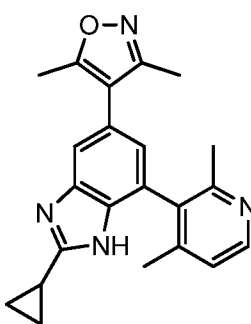
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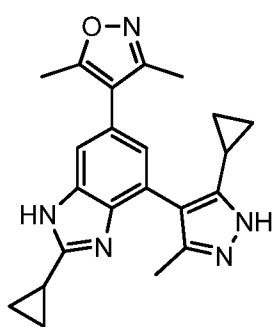
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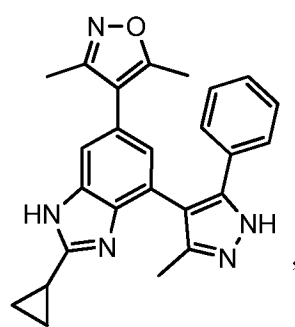
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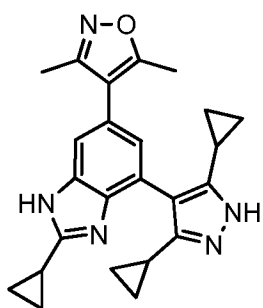
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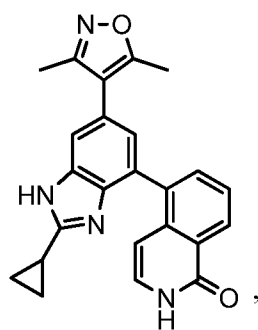
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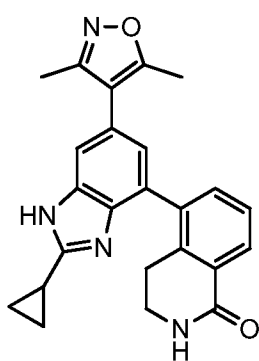
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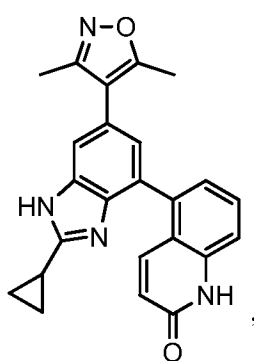
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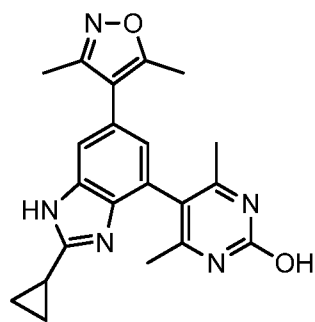
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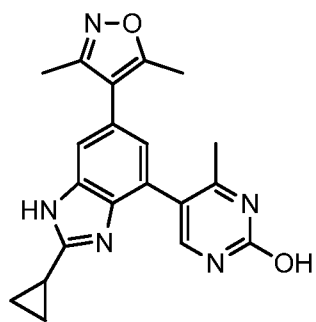
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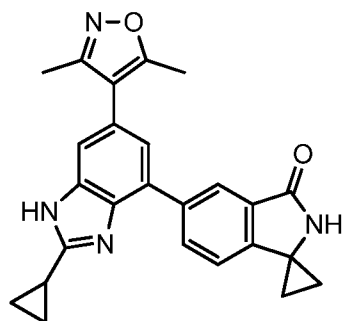
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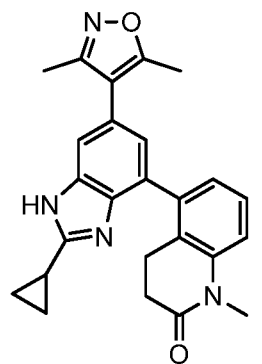
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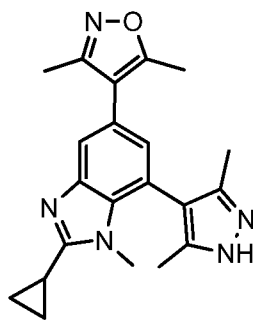
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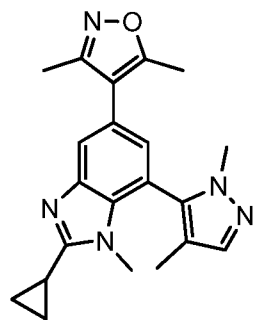
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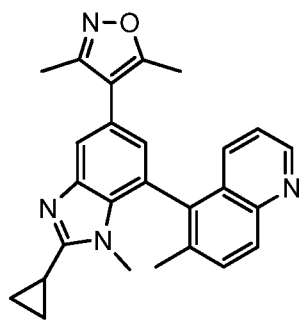
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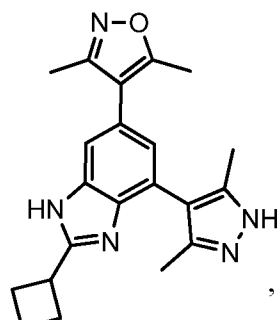
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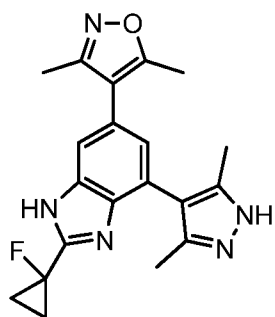
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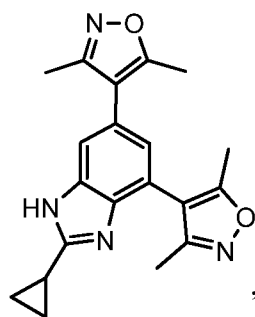
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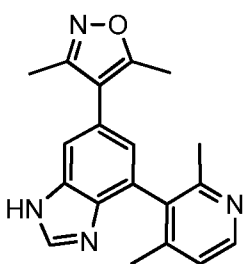
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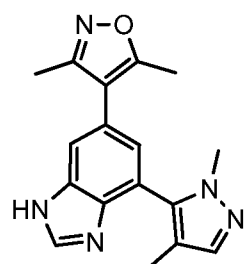
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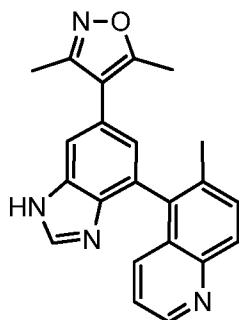
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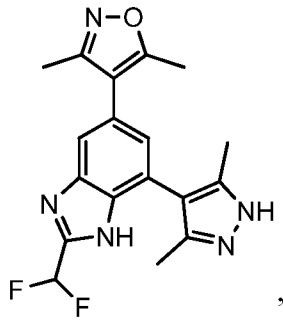
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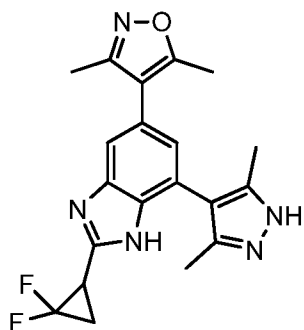
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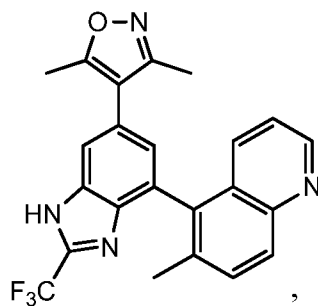
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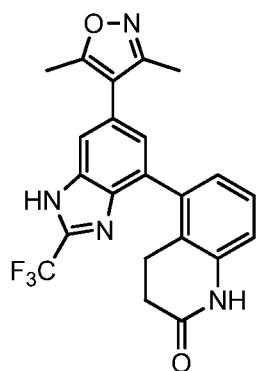
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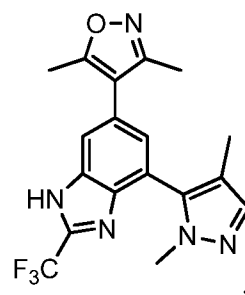
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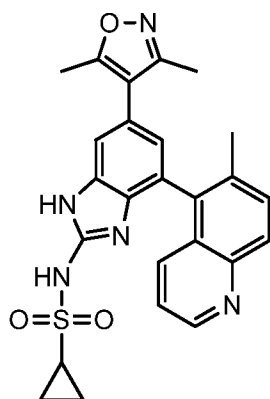
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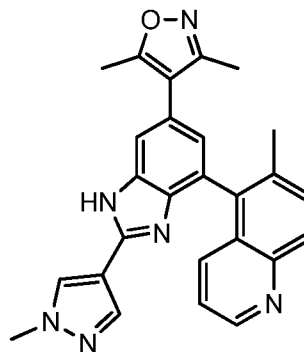
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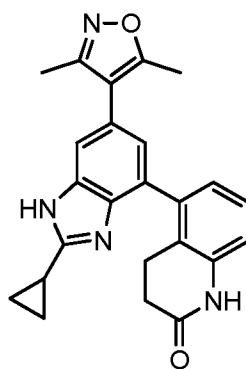
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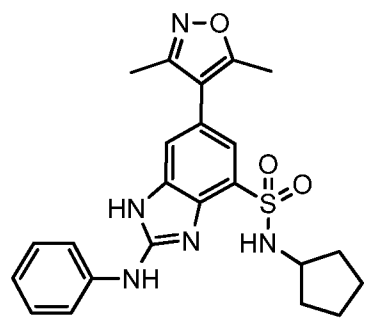
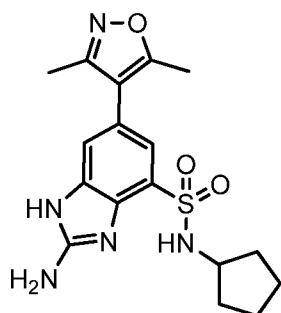
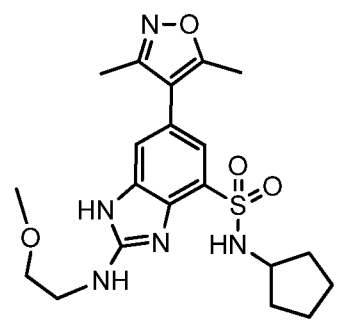
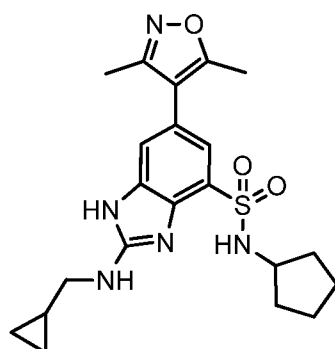
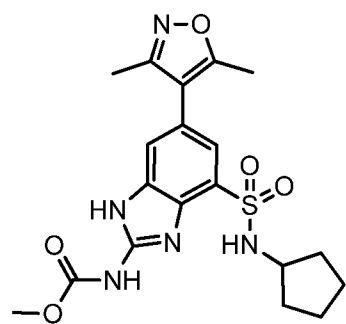
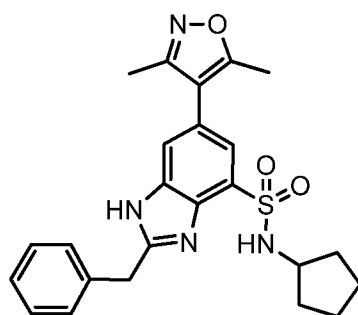
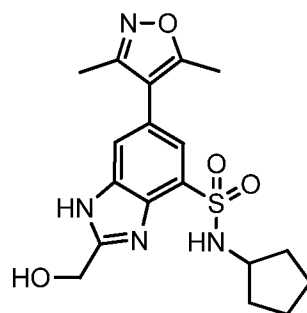
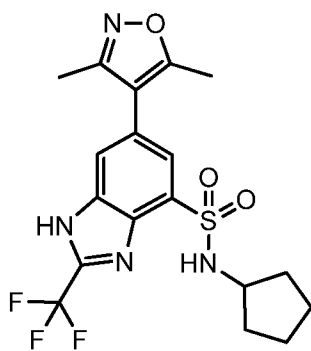


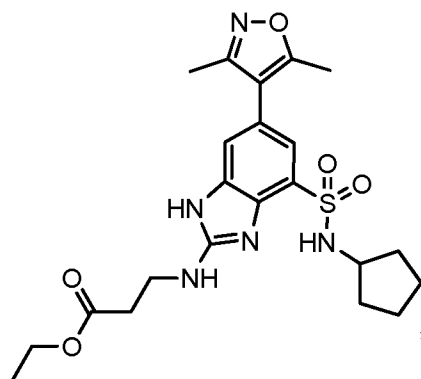
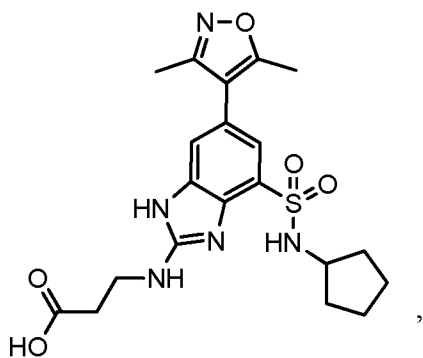
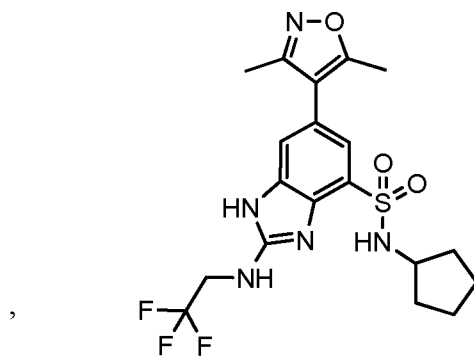
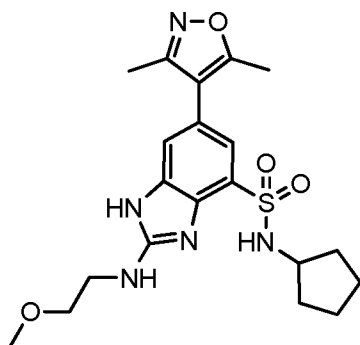
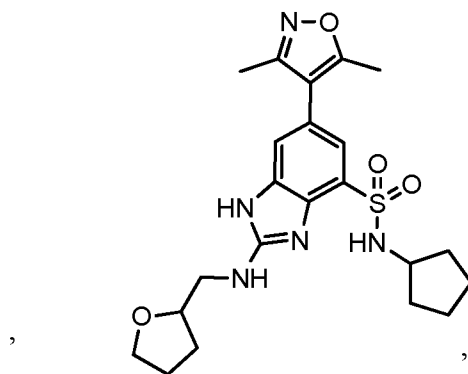
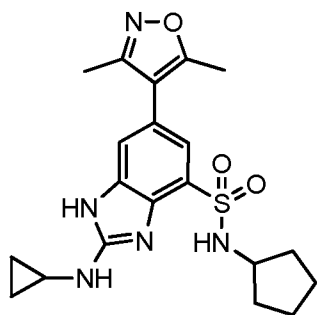
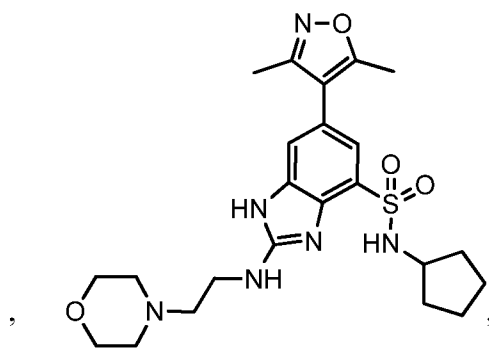
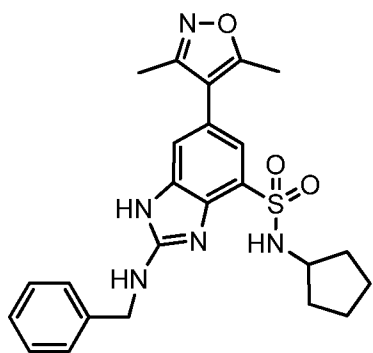
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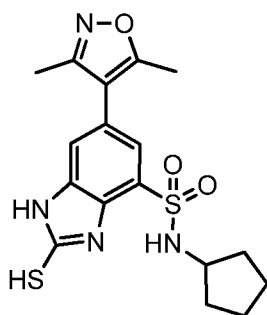
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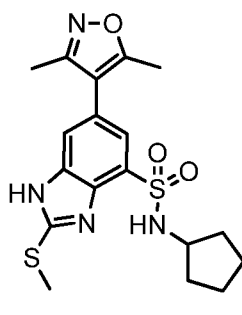
- 5 7. The method of claim 1, wherein the BET inhibitor is:



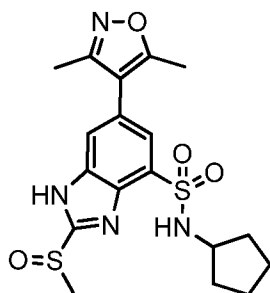




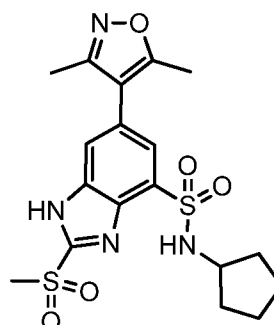
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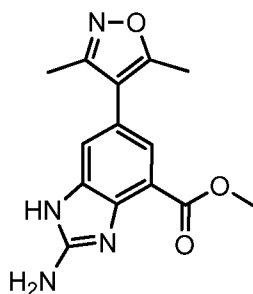
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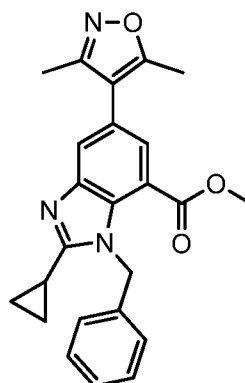
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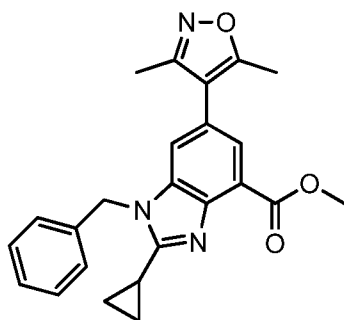
8. The method of claim 1, wherein the BET inhibitor is:



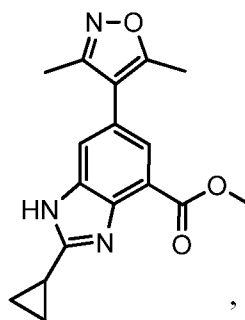
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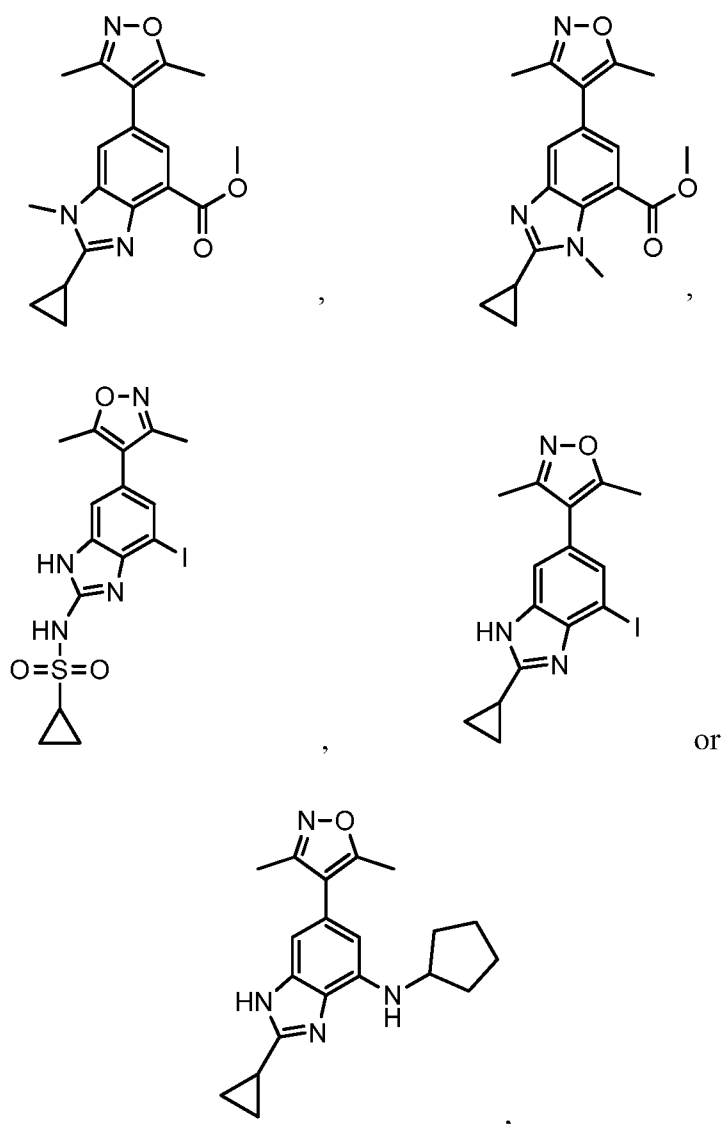
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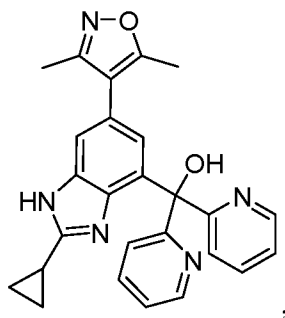


or a pharmaceutically acceptable salt thereof.

- 5 9. A method of treating cancer in a human in need thereof, comprising administering to the human:

(i) a therapeutically effective amount of filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof; and

(ii) a therapeutically effective amount of



or a pharmaceutically acceptable salt thereof.

10. The method of any one of the preceding claims, wherein the cancer is carcinoma, sarcoma, melanoma, lymphoma or leukemia.

5 11. The method of any one of the preceding claims, wherein (i) is administered intravenously, intramuscularly, parenterally, nasally or orally.

12. The method of any one of the preceding claims, wherein (ii) is administered intravenously, intramuscularly, parenterally, nasally or orally.

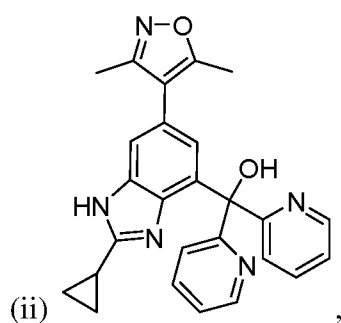
10 13. The method of any one of the preceding claims, wherein (i) is administered prior, after or concurrently with (ii).

14. The method of claim 1 or 9, wherein the method comprises administering a co-formulation of (i) and (ii).

15. The method of claim 14, wherein the method comprises administering the co-formulation intravenously, intramuscularly, parenterally, nasally or orally.

15 16. A co-formulation comprising:

(i) filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite thereof; and



or a pharmaceutically acceptable salt thereof.

17. A composition for use in the treatment of cancer, the composition comprising:

filgotinib or a pharmaceutically acceptable salt, solvate, polymorph, or metabolite

5 thereof; and

a BET inhibitor.

18. The composition of claim 17, wherein the cancer is carcinoma, sarcoma, melanoma, lymphoma or leukemia.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2016/067039

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/00 A61K45/06 A61K31/422 A61K31/427 A61K31/4439
 A61K31/444 A61K31/4709 A61K31/497 A61K31/501 A61K31/502
 A61K31/506 A61K31/5355 A61K31/541 A61P35/00 A61P35/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, INSPEC, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2014/336190 A1 (AKTOUDIANAKIS EVANGELOS [US] ET AL) 13 November 2014 (2014-11-13) cited in the application abstract paragraph [0005] - paragraph [0034] paragraph [0186] - paragraph [0187] paragraph [0189] - paragraph [0198] Examples, especially Example 104 claims 1-24 ----- -/-	1-18



Further documents are listed in the continuation of Box C.



See patent family annex.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/067039

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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Information on patent family members

International application No

PCT/US2016/067039

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